SPRINGER
REFERENCE

ARTHUR ZIMMERMANN

Tumors and Tumor-Like Lesions of the Hepatobiliary Tract

General and Surgical Pathology

Springer

Tumors and Tumor-Like Lesions of the Hepatobiliary Tract

Arthur Zimmermann

Tumors and Tumor-Like Lesions of the Hepatobiliary Tract

General and Surgical Pathology

With 880 Figures and 199 Tables

Springer

Arthur Zimmermann
Emeritus Professor of Pathology
University of Bern
Bern, Switzerland

ISBN 978-3-319-26954-2 ISBN 978-3-319-26956-6 (eBook)
ISBN 978-3-319-26955-9 (print and electronic bundle)
DOI 10.1007/978-3-319-26956-6

Library of Congress Control Number: 2016948216

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

I dedicate this textbook to my wife, Geneviève, who for many years of preparatory work endured much and offered continued interest, help, and compassion while I was creating this work. She accompanied me with great loyalty in this endeavor. I also dedicate this book to my children, Laxmi and Tristan, who have given so much meaning to my life, and to my venerated late teacher in pathology, Professor Hans Cottier.

Preface

This textbook is designed to be a comprehensive assessment of current knowledge regarding the surgical and general pathology of hepatobiliary tumors and tumor-like lesions. The scope of the book is broad and provides an up-to-date source for the wide-ranging tumor pathology of the entire hepatobiliary tract. In the planning phase of this work, the question had arisen as to the purpose and need of such a book, in the light of numerous excellent monographs and textbooks that have been published in this field during the last years, but a major justification for a new book relates to the rapid change in the role of pathology in the investigation of hepatobiliary tumors and related lesions. Therefore, an update of the dramatic changes that have taken place in the discovery and application of several lines of knowledge referring to hepatobiliary tumor pathology in a broader sense was regarded a worthwhile task. Notwithstanding the impressive increase in diagnostic precision of modern imaging and other, in particular various molecular, methods, tumor biopsy and its morphological interpretation based on complex techniques is still a central diagnostic instrument that serves refined diagnosis and classification, risk stratification, and therapy planning, also in the light of future personalized treatment strategies. A combined approach by using conventional, fine structural, immunohistochemical and hybridization morphological studies, and molecular techniques generated a new concept of the tight correlation between structure and function in tumor pathology, contributing to advanced modes of diagnosis. Apart from information on a given diagnostic tumor entity, differential diagnosis is discussed in depth as a most critical issue.

The main reason for integrating several important issues of general pathology is based on the rapidly evolving and continued changes that are occurring in the disciplines of tumor biology, genomics, and associated molecular features that characterize tumors. The concept of the present work in fact aims at concentrating detailed aspects of surgical pathology needed for diagnosis and the pathogenic mechanisms behind disease in one source with ample color illustrations and a detailed reference corpus.

In the light of refined imaging techniques and other modern diagnostic approaches that can uncover a host of previously undetectable hepatobiliary lesions, a significant part of the textbook is dedicated to an extensive range of tumor-like lesions, pathologies that may, in a clinical-radiological setting, be confounded with true hepatobiliary neoplasms. Part of the tumor-like lesions, including mass-forming infections and infestations, are common entities

world-wide, while others may appear as unexpected or incidental findings, or rare and "exotic" disorders.

This text has been planned to serve hepatopathologists, hepatologists, and others interested and involved in this field, and it is the author's hope that the book is a comprehensive account on the surgical and general pathology of hepatobiliary tumors and their tumor-like mimics. The book is also hoped to be a useful source of information for basic scientists active in the field of liver pathophysiology.

To provide a systematic review of the immense field of hepatobiliary tumors and tumor-like lesions, the textbook has been divided into 39 parts, each covering one to several chapters, in order to assist the reader in locating topics of interest. In what follows, brief overviews on the contents of each chapter are presented.

Part 1 starts off with a series of chapters that supply comprehensive information on tumors characterized by a hepatocyte-derived lineage and its precursors. Chapter ▶ 1 deals with the role of hepatic stem and progenitor cells in hepatocarcinogenic pathways. Hepatocytes were perceived to represent the major cells of origin for numerous neoplasms of the liver, but stem and progenitor cells have been identified as important sources. The chapter addresses issues of hepatic stem cell niches, types of stem/progenitor cells found in these niches, interactions of stem cells with other cells, changes of their microenvironment, and mechanisms involved in a stem cell-cancer sequence. As cancer initiating cells and cancer-associated stem cells can circulate in blood, the significance of cycling clonogenic cells with longevity and remote spread for tumor progression is discussed. Chapter ▶ 2 provides an in-depth description of ordinary hepatocellular carcinoma (HCC), including classification of gross phenotypes, macroscopic growth patterns, pertinent histologic and diagnostic features, and tumor grading. In Chap. ▶ 3, the numerous immunohistochemical features characterizing ordinary HCC are discussed in detail. Chapter ▶ 4 focuses on invasion and metastatic patterns of ordinary HCC. Patterns of macrovascular and microvascular invasion and the features of intrahepatic and remote metastasis are explained and illustrated. This part also provides information on risk factors for metastasis and on the presentation and frequency of extrahepatic organ metastases. In Chap. ▶ 5, secondary changes that develop in HCCs, and in particular the interesting phenomenon of spontaneous tumor regression, are highlighted. Progression and recurrence of HCC are major elements of the tumor's biology of disease. Numerous prognostic factors for the natural course of HCC have been delineated, discussed in detail in Chap. ▶ 6. The issues of Chap. ▶ 7 are the various types of HCC precursor lesions that can develop in cirrhotic livers, including small and large cell change, dysplastic foci, and dysplastic nodules. There is a group of ordinary HCCs characterized by small size at the time point of diagnosis, lesions that are more frequently diagnosed due to improved imaging techniques. These intriguing lesions, specifically their morphology, classification, biology, and relationship to early cancer are dealt with in Chap. ▶ 8. The chapters on neoplasms of the hepatocyte lineage are considerably extended to reflect the growing importance of special types of liver cell cancers in the setting of clinical presentation, detectability by modern imaging techniques,

molecular features, and biology of disease (Chaps. ▶ 9, ▶ 10, ▶ 11, ▶ 12, and ▶ 13). Chapter ▶ 9 deals with clear cell HCC, a group of neoplasms that belong to a growing spectrum of epithelial clear cell tumors of the alimentary tract with a distinct biology of disease. A heterogeneous group of HCCs is characterized by the accumulation of neutral fat, including steatotic HCC and its inflammatory variant, steatohepatitic HCC, tumors that also develop in the setting of nonalcoholic and alcoholic fatty liver disease. Part of these tumors are rich in Mallory-Denk bodies (Chap. ▶ 10). A rare group of HCCs is characterized by the presence of an abundant desmoplastic stroma, similar to cholangiocarcinoma (sclerosing and scirrhous HCCs; Chap. ▶ 11). A further unusual subset of HCCs shows dense infiltrates of mononuclear leukocytes (inflammatory HCCs). One variant of these neoplasms reflects a morphology similar to lymphoepithelial carcinoma, with or without association with EBV virus infection, and another rare variant exhibits a plasmacellular infiltrate and signs of regression (medullary HCC; Chap. ▶ 12). Very rare forms of HCCs are characterized by peliotic change, multinucleated giant cells, chromophobe cells, oxyophilic/oncocytic cells, or cells with a Dubin-Johnson-like pigment (Chap. ▶ 13). An interesting group of liver cell tumors displays the presence of progenitor cells or stem-like cells. Part of these HCCs with progenitor cell features express cytokeratin 19, a feature conferring a more aggressive course (Chap. ▶ 14). A clinically and radiologically intriguing situation is produced by HCCs arising in an ectopic, extrahepatic location (Chap. ▶ 15). HCCs also occur in infancy and childhood (pediatric HCC). It is not yet clarified whether these unusual malignancies are the same or different from their adult counterparts (Chap. ▶ 16). A neoplasm that in several respects mimics HCC is hepatoid carcinoma, which can develop in numerous organs, but is usually manifest in the liver in the form of metastases (Chap. ▶ 17). An intriguing variant of HCC is fibrolamellar HCC, a tumor mainly occurring in younger individuals, showing a biology similar to that of ordinary HCC, and associated with a typical recurrent chimeric transcript (Chap. ▶ 18). A rare group of neoplasms composed of immature hepatocyte progenitors (embryonal and fetal hepatocytes) is formed by the various types and subtypes of hepatoblastoma and related neoplasms (Chap. ▶ 19). The majority of these cancers develops in children younger than 5 years, but rarely also develop in adults. Unusual variants of hepatoblastoma with aberrant differentiation patterns are treated in Chap. ▶ 20, including tumors with a bile duct cell differentiation. The focus of Chap. ▶ 21 relates to the biology and prognostic factors of heptoblastoma, while Chap. ▶ 22 treats risk factors and pathogenic pathways of neoplasms of the hepatoblastoma tumor family. An intriguing neoplasm related to hepatoblastoma and associated with an interesting clinical presentation and unique molecular features, nested stromal epithelial tumor, is the theme of Chap. ▶ 23. A benign tumor of the hepatocyte lineage is hepatocellular adenoma, which has recently been subdivided into several molecular subtypes associated with distinct morphologic patterns. The discussion of this important hepatic tumor and its variants is found in Chaps. ▶ 24 and ▶ 25. A rare group of neoplasms containing hepatocyte-like cells is combined hepatocellular-cholangiocarcinoma, malignancies that display a biphenotypic histologic picture. In contrast to HCC, these highly aggressive

neoplasms occur in cirrhotic and noncirrhotic livers with almost the same frequency (Chap. ▶ 26).

Part 2 of the textbook relates to benign and malignant neoplasms of the cholangiocyte lineage. Cholangiocarcinomas (CC) are divided into two major groups, extrahepatic and intrahepatic bile duct cancers. Among the former, hilar and perihilar CC form a distinct clinicopathologic entity different from CC originating in the mid-region and distal parts of the large bile duct. Intrahepatic CC is a malignancy that can present in three major gross growth patterns and originates from both small or large intrahepatic bile ducts. CC are malignancies of adult patients, but very rarely also develop in the pediatric age group (Chaps. ▶ 27, ▶ 28, ▶ 29, ▶ 30, ▶ 31, and ▶ 32). A distinct group of bile duct neoplasms is formed by intraductal neoplasms, tumors that resemble their pancreatic counterparts. They display a phase of intraluminal, often papillary noninvasive growth and a later high risk of transition into invasive CC (Chap. ▶ 33). In addition to classical forms of CC, there are tumors developing in the setting of hepatobiliary cystic disease, or exhibit distinct differentiation patterns different from those observed in ordinary CC (Chaps. ▶ 34, ▶ 35, ▶ 36, ▶ 37, and ▶ 38). A rare subset of bile duct tumors is characterized by cysts lined by a mucin-producing epithelium, frequently associated with a subepithelial ovarian-like stroma and expression of sex steroid receptors. These mucinous cystic neoplasms (MCN) can undergo a dysplasia-carcinoma sequence (Chap. ▶ 39). Both the intrahepatic and extrahepatic biliary tree can be the site of several types of benign epithelial neoplasms and hamartomas, including tubular and papillary adenomas, peribiliary gland hamartomas, biliary microhamartoma, and neoplasms and hyperplasias of peribiliary glands (Chaps. ▶ 40 and ▶ 41).

Part 3 covers a heterogeneous group of liver tumors derived from other epithelial lineages. Some hepatobiliary carcinomas are characterized by varying proportions of squamous epithelial cells, including squamous cell carcinoma, adenosquamous carcinoma, and mucoepidermoid carcinoma, or acinar cell and adenoid cystic components (Chaps. ▶ 42 and ▶ 43). Rare carcinomas of the biliary tract are undifferentiated neoplasms, such as nonendocrine small cell and spindle cell carcinomas, and carcinomas with rhabdoid features (Chap. ▶ 44). In a small group of hepatobiliary neoplasms, the cells of origin are not yet fully clarified. These lesions mainly comprise hepatic adrenal rest tumor and progenitor cell neoplasms (Chap. ▶ 45).

Part 4 of the textbook refers to mixed epithelial-mesenchymal tumors of the hepatobiliary tract. Chapter ▶ 46 highlights an intriguing group of hepatobiliary malignancies that are composed of a complex mixture of various neoplastic tissue types. These tumors are classified as carcinosarcomas and carcinomas with sarcomatoid features. Few primary hepatic tumors are characterized by the presence of multinucleated, osteoclast-like giant cells with a macrophage/histiocyte lineage (Chap. ▶ 47). Apart from carcinosarcomas, rare hepatic tumors present a mixed cellular phenotype that is still difficult to classify, including malignant mixed tumors, adenosarcomas, stromal tumors, and adult-type mixed hepatoblastomas (Chap. ▶ 48).

Part 5 focuses on the predominant group of hepatobiliary mesenchymal tumors, i.e., vascular tumors. The most important type of primary hepatic

vascular neoplasm is cavernous hemangioma with its various phenotypes and associations with extrahepatic vascular tumors (Chap. ▶ 49). Less common hepatic vascular tumors include several forms of hemangiomatosis, hemangioblastoma, epithelioid hemangioendothelioma, infantile hepatic hemangioma/hemangioendothelioma, kaposiform hemangioendothelioma, angiosarcoma, Kaposi's sarcoma, glomus tumors, myopericytoma, and glomangiopericytoma (Chaps. ▶ 50, ▶ 51, ▶ 52, ▶ 53, ▶ 54, ▶ 55, ▶ 56, and ▶ 57). Unusual vascular malformations, which may be part of complex inborn syndromes, can mimic true vascular neoplasms, such as Klippel-Trenaunay syndrome (Chap. ▶ 58). A second group of reactive vascular lesions that can cause tumor-like hepatic manifestations include bacillary angiomatosis and peliosis hepatis (Chap. ▶ 59).

Part 6 refers to tumors and tumor-like lesions of lymph vessels. In the hepatobiliary tract, these are very rare conditions which include cystic and noncystic lymphangioma, capillary lymphangioma, lymphangiomatosis, hepatic lymphangiectasis, and lymphocele (Chap. ▶ 60).

Part 7 is exclusively dedicated to solitary fibrous tumor and tumors with a hemangiopericytoma-like pattern. These lesions now include at least part of the former hemangiopericytomas and are characterized by a distinct somatic fusion of two genes, NAB2 and STAT6 (Chap. ▶ 61).

Part 8 discusses the complex spectrum of nonvascular mesenchymal tumors of the hepatobiliary tract. All these neoplasm are rare lesions and include fibroblastoid and myofibroblastoid neoplasms, leiomyoma and leiomyosarcomas, rhabdomyosarcomas, lipoma, liposarcoma, myelolipoma, hibernoma, tumors with osteosarcomatous and chondrosarcomatous components, gastrointestinal stromal tumors, benign and malignant nerve sheath tumors, granular cell tumors, synovial sarcoma, and undifferentiated high-grade pleomorphic sarcomas (Chaps. ▶ 62, ▶ 63, ▶ 64, ▶ 65, ▶ 66, ▶ 67, ▶ 68, ▶ 69, ▶ 70, and ▶ 71).

Part 9 summarizes tumors with a mesothelial cell lineage. Primary mesotheliomas of the liver are very rare, but characteristic neoplasms mimic mesothelial tumors in other locations. A unique mesothelial tumor occurring also in the liver is adenomatoid tumor (Chap. ▶ 72).

The theme of Part 10 is a heterogeneous group of neoplasms that are derived from, or related to, perivascular epithelioid cells. The liver is the primary site of various perivascular epithelioid cell tumors or PEComas, all with complex cellular compositions. They include PEComa proper, angiomyolipoma with its various subtypes, clear cell myomelanocytic tumors, clear cell and sugar tumors, and lymphangiomyomatosis (Chap. ▶ 73).

Part 11 presents hepatobiliary tumors of neuroendocrine lineages. Chapter ▶ 74 provides pertinent information regarding extraadrenal paraganglioma, neoplasms that also in the liver range in biology from a benign to frankly malignant behavior. In Chap. ▶ 75, the various types and subtypes of hepatobiliary neuroendocrine tumors are treated, emphasis being placed on novel classifications and grading systems.

In Part 12, a rare group of small tumors that also originate in the liver are discussed. The lesions comprise various small cell blue tumors, such as primitive neuroectodermal tumors (PNET), desmoplastic small round cell tumor, NUT midline carcinoma, and hepatic neuroblastoma (Chap. ▶ 76).

Part 13 refers to the interesting group of primary and secondary melanotic tumors of the hepatobiliary tract. Emphasis is placed on primary and metastatic melanoma, in particular also metastatic ocular melanoma, melanotic progonoma, and manifestations of melanoma of soft parts (Chap. ▶ 77).

Part 14 focuses on hepatic tumors with a rhabdoid cell lineage. Liver and bile duct tumors with rhabdoid cell components are, at least in part, associated with absence of the chromatin remodeling factor SRF5/INI1 and include malignant rhabdoid tumor proper, carcinomas with rhabdoid features, and a subset of small cell hepatoblastoma (Chap. ▶ 78).

In Part 15, primary and metastatic germ cell tumors are treated. Most germ cell tumors occurring in the gonads can occur as primary lesions in the liver, but teratomas, yolk sac tumor, and choriocarcinoma prevail, also in the pediatric age group. The liver is a well-known site of metastatic germ cell tumors and can be the site of growing teratoma syndrome (Chap. ▶ 79).

Part 16 summarizes the pathology of hepatic manifestations of myeloid neoplasms. With the exception of granulocytic sarcomas, these neoplasms cause diffuse infiltration of the liver substance. The conditions discussed comprise polycythemia vera, several types of myeloproliferative syndrome, chronic eosinophilic leukemia and idiopathic hypereosinophilia, mast cell neoplasms, acute leukemias, myeloid neoplasms with a monocytoid lineage, and blastic plasmacytoid dendritic cell neoplasms (Chaps. ▶ 80, ▶ 81, ▶ 82, ▶ 83, ▶ 84, ▶ 85, ▶ 86, and ▶ 87).

Part 17 refers to the complex pathology of hepatobiliary Hodgkin's disease. This disorder causes, on the one hand, tumorous hepatic lesions that can clinically be confounded with liver cancer, but on the other hand also reveals associations with paraneoplastic changes, including vanishing bile duct syndrome (Chap. ▶ 88).

Part 18 covers the large field of hepatobiliary non-Hodgkin's lymphomas, other lymphoproliferative disorders, and neoplasms of dendritic and histiocytic cell systems. Major groups comprise B-cell and T-cell neoplasms that occur in numerous extrahepatic sites, but pseudolymphomas, neoplasms of the Langerhans cell and histiocytic systems, dendritic cell neoplasms, and reactive histiocytic syndromes (such as Rosai-Dorfman syndrome) are also discussed (Chaps. ▶ 89, ▶ 90, ▶ 91, ▶ 92, ▶ 93, ▶ 94, ▶ 95, ▶ 96, ▶ 97, ▶ 98, ▶ 99, ▶ 100, ▶ 101, ▶ 102, and ▶ 103).

Part 19 treats mesenchymal hamartoma of the liver and related neoplasms. Mesenchymal hamartoma and undifferentiated embryonal sarcoma of the liver are typical pediatric hepatic neoplasms, but they have rare counterparts in adult patients (Chaps. ▶ 104 and ▶ 105).

Part 20 is a large complex of chapters that relates to the very important issue of metastatic liver disease. The chapters discuss in detail aspects of gross and microscopic pathology of liver metastases in general, a specific chapter on colorectal cancer metastases, other common and rare metastatic cancers, secondary changes that frequently develop in hepatic metastases, secondary spread of metastatic disease into locoregional lymph nodes, associated liver lesions, growth and regrowth of metastases, and pathogenic features of liver metastasis (Chaps. ▶ 106, ▶ 107, ▶ 108, ▶ 109, ▶ 110, ▶ 111, ▶ 112, ▶ 113, ▶ 114, and ▶ 115).

In Part 21, a small theme of liver tumor pathology is addressed, tumors and tumor-like lesions of hepatic ligaments. Falciform and round hepatic ligaments are the site of rare primary benign and malignant neoplasms, metastases, and various types of cysts (Chap. ▶ 116).

Part 22 contains chapters on reactive nodular hyperplastic hepatocyte lesions of the liver. Focal nodular hyperplasia (FNH) of the liver is an important mass-forming regenerative condition that often develops secondary to localized vascular and circulatory abnormalities of the liver. After hemangiomas, FNH is the second most common benign hepatic tumorous lesion (Chap. ▶ 117). A second important regenerative condition of the liver is nodular regenerative hyperplasia, which is associated with a broad array of causative factors (Chap. ▶ 118).

In Part 23, pseudotumors of the hepatobiliary tract are discussed. Pseudotumors and inflammatory pseudotumors form a heterogeneous group of lesions that share spindle cell proliferations and inflammatory infiltrates of variable density. Inflammatory myofibroblastic tumors is a lesion that contains a subset with neoplastic features and aberrant ALK expression (Chap. ▶ 119).

Part 24 relates to nonneoplastic tumor-like lesions of the liver. The liver is the site of tumor-like ectopias and heterotopias, mass-forming malformations, solitary necrotic nodule, various types of dust-induced nodular lesions, tumor-like lesions caused by gallstones and foreign bodies, pseudotumors consisting of reactive proliferations of hematopoietic cells and macrophages, pyogenic liver abscesses mimicking cancer, numerous hepatic bacterial, fungal, and protozoal infections causing tumor-like hepatic masses (tuberculosis, syphilis, brucellosis, and amebiasis representing prominent examples), tumor-like parasitic lesions (mainly echinococcosis), and liver infarcts (Chaps. ▶ 120, ▶ 121, ▶ 122, ▶ 123, ▶ 124, ▶ 125, ▶ 126, ▶ 127, ▶ 128, ▶ 129, ▶ 130, ▶ 131, ▶ 132, ▶ 133, ▶ 134, ▶ 135, ▶ 136, and ▶ 137).

Part 25 refers to reactive cystic lesions of the liver that may mimic cystic neoplasms. They include simple nonparasitic cysts, ciliated foregut cyst, pancreatitic pseudocysts, and cerebrospinal fluid pseudocysts (Chap. ▶ 138).

Part 26 provides information related to hepatic mass lesions caused by noninfectious granulomas. The main disorder is sarcoidosis that can also cause a complex form of sclerosing bile duct disease with bile duct loss. Blau syndrome and complex inflammatory disorders in part involving deregulated inflammasome function are also discussed (Chap. ▶ 139). A small chapter refers to chronic granulomatous disease (Chap. ▶ 140).

Part 27 presents the hepatic pathology of interesting fibrosclerotic disorders. The conditions include idiopathic retroperitoneal fibrosis and its variants, and the complex spectrum of IgG4-associated systemic sclerosing disease (Chap. ▶ 141).

In Part 28, numerous reactive bile duct alterations that can mimic biliary neoplasms are discussed. Intrahepatic and extrahepatic bile ducts can be involved with inflammatory stenosing polyps, granulomatous cholangitis, follicular cholangitis, oriental cholangitis, xanthogranulomatous cholangitis, bile duct cholesterolosis, sclerosing eosinophilic cholangitis, mechanical and anatomical bile duct alterations, bile duct stenosis caused by congenital

anomalies and acquired disorders of the splanchnic arterial tree and the portal vein, and postcholecystectomy changes (Chaps. ▶ 142, ▶ 143, ▶ 144, ▶ 145, and ▶ 146).

Part 29 addresses the important issue of gallbladder cancer and other tumors and tumor-like lesions of this organ. Ordinary gallbladder carcinoma usually develops in a gallbladder that has undergone secondary changes related to longstanding cholelithiasis and associated inflammations. This neoplasm, an adenocarcinoma, can be associated with epithelial precursor lesions and presents in the form of distinct growth patterns (Chap. ▶ 147). Biology of disease, prognosticators, staging, risk factors, and pathogenic pathways of gallbladder carcinoma are treated in more detail in Chaps. ▶ 148 and ▶ 149. Apart from the common ordinary adenocarcinoma of the gallbladder, several rare variants with other differentiation patterns are recognized, including mucinous, signet ring cell, and squamous cell carcinomas (Chaps. ▶ 150 and ▶ 151). The gallbladder is also the site of rare cystic and mixed neoplasms, such as cystadenoma and cystadenocarcinoma (Chap. ▶ 152). As outlined in Chap. ▶ 153, the gallbladder can give rise to a spectrum of adenomatous, borderline, and dysplastic lesions. Of differential diagnostic importance is the observation of various types of hyperplastic and metaplastic lesions in the gallbladder mucosa (Chap. ▶ 154). Similar to the bile duct system and liver, the gallbladder is a well-known origin of diverse types of neuroendocrine tumors, mesenchymal neoplasms, malignant melanoma, and a wide spectrum of other, however very rare, neoplasms (Chaps. ▶ 155, ▶ 156, and ▶ 157). A broad array of reactive, inflammatory, and noninflammatory alterations of the gallbladder can result in mass lesions that mimic neoplasms, and in particular gallbladder cancer (Chaps. ▶ 158, ▶ 159, ▶ 160, and ▶ 161). A rare group of malignant and benign tumors takes its origin in the cystic duct (Chap. ▶ 162).

Part 30 refers to a heterogeneous group of tumorous and tumor-like peritoneal lesions that may involve the liver surface. They include several primary carcinomas and other malignancies, pseudomyxoma peritonei, gliomatosis peritonei, and various forms of metaplasia, granulomas, endometriosis, and deciduosis (Chap. ▶ 163).

Part 31 is the first part of the textbook referring to aspects of general pathology of hepatobiliary tumors, specifically etiology and pathogenesis of hepatocellular carcinoma (HCC). A first chapter discusses in depth inflammatory and toxic causes, in particular the role of hepatitis virus infections, fatty liver and steatohepatitis, and nutritional and other toxins in hepatocarcinogenic pathways (Chap. ▶ 164). The following chapter (Chap. ▶ 165) discusses HCC that arises in the setting of inborn errors of metabolism, in particular various forms of chronic hepatic iron overload. Chapter ▶ 166 focuses on chromosomal alterations, oncogenes, tumor suppressors, and associated signaling networks that are involved in tumorigenesis, while Chap. ▶ 167 puts emphasis on the roles of transcription factors, regulators of growth and apoptosis, and telomere homeostasis. Finally, Chap. ▶ 168 is an overview on the etiologic and pathogenic significance of epigenetic mechanisms in hepatocarcinogenesis (the epigenome).

Part 32 contains an important chapter on the general pathology of structural and functional nuclear changes in hepatobiliary cancer. In Chap. ▶ 169,

relevant diagnostic and theoretical aspects of nuclear and nucleolar abnormalities, anaplasia, and chromatin alterations are addressed. Numerous types of structural abnormalities of cancer cell nuclei are directly associated with functional disorders of nuclear homeostasis, DNA replication, cell division, and organization of chromatin superstructures during interphase. Abnormal heterochromatin generation, a deranged production of euchromatin strings, malposition of interphase chromosomes, and anomalies of intranuclear chromosome movements are hallmarks of nuclear function failure in cancer cells (Chap. ▶ 170).

Part 33 addresses mitochondrial structure and function in normal and malignant neoplastic cells. Apart from their central role in energy production, mitochondria play a significant role within carcinogenic pathways involving abnormal stress responses and deregulation of cell death pathways. This role has led to the "mitochondrial malignancy theory." Mitochondria hold a central position in apoptosis induction, but they also modulate cell shape and engage in complex interactions with other organelles. Cancer cells exhibit various types of structural abnormalities of mitochondria and may show changes in mitochondrial number, mitochondrial fission, and elimination of this organelle. Part of these alterations are associated with losses and mutations of mitochondrial DNA (Chap. ▶ 171).

The contents of Part 34 pertain to tumor growth and its regulation. Uncontrolled, progressive growth is a key feature of cancers. Net mass increase of tumors not only depends on cell proliferation, but also on cell loss caused by various forms of apoptosis and necrosis and the contribution of nonneoplastic tissues and cells accompanying neoplasms, in particular stroma, blood vessels, and leukocytes. Cell proliferation in liver cell cancer reflects features of normal liver regeneration which is therefore discussed in some detail. The aberrant proliferation of liver cancer cells is related to deranged functions of factors orchestrating cell division, checkpoint regulators, proteins involved in DNA synthesis, proteins of the mitotic apparatus, and the numerous components of the cytoskeleton. Similar to the regenerating liver, growth of liver neoplasm is regulated by numerous growth factors and their receptors, including factors produced by platelets and antagonists of proliferation. Furthermore, hepatobiliary cancers reveal abnormal expression patterns of proteins that control entry into and passage through the cell division cycle, including cyclins and cyclin-dependent kinases. Finally, regulation of tumor growth strongly depends on various epigenetic mechanisms, specifically on complex expression patterns of microRNAs and other RNA classes (Chaps. ▶ 172, ▶ 173, ▶ 174, and ▶ 175).

Part 35 informs the reader about important aspects of the necrobiology of hepatobiliary cancer. An intricate process to control tumor cell mass is apoptosis, a complex form of tightly controlled cell death. Growth caused by proliferation is also counteracted by necrosis which, in contrast to traditional views, is a controlled process rather than a passive phenomenon. In liver cancer, apoptosis can be assessed by immunohistochemical and molecular methods. In addition to classical apoptosis, necrobiologic processes active in cancer also include various forms of cell death related to, but not identical with, apoptosis. These pathways may play a significant role for future novel

therapies (Chaps. ▶ 176 and ▶ 177). A special chapter is dedicated to the pathophysiology of classical (passive) necrosis in comparison with regulated necrosis (necroptosis). The latter involves a complex signaling platform, the necrosome, a molecular machine that senses ATP depletion and transmits this signal into kinase execution switches (Chap. ▶ 178). An important role in cancer cell biology is played by autophagy, a process involved in the maintenance of cell and tissue homeostasis, control of the protein composition of cells, aging, senescence, and neoplastic transformation. Autophagy is the instrument to eliminate altered proteins, damaged or superfluous organelles, and pathogens, and is a complex system connected with inflammasome function, inflammation, immunogenic cell death, and cell senescence. Special forms of autophagy in cancer cells include mitophagy and nucleophagy (Chap. ▶ 179).

Part 36 covers several important aspects of cancer invasion and metastasis. Invasion and metastatic spread of cancer cells involve a highly complex sequence of events that comprise tumor cell individualization, tumor cell polarization, migration, and the acquisition of a secretory phenotype, with release of histolytic enzymes. It is not yet fully known how these features are acquired by cancer cells in a seemingly concerted fashion. For being able to locomote, cancer cells, similar to leukocytes, must be able to undergo shape change and polarization, a process that requires numerous cytoskeletal components and specific polarity proteins. The invasive process strongly depends on the generation of invadosomes, including podosomes and invadopodia, matrix-degrading adhesive, and actin-dependent dynamic cellular structures or "organelles" that can also extend through endothelial linings and mediate extravasation of tumor cells. An important role for the invasion of carcinomas is the distinct tumor stroma. Stroma is composed of cancer-associated fibroblasts/CAFs, myofibroblasts, mesenchymal stem cells, stellate cells, blood vessel cells, extracellular matrix, and several classes of infiltrating leukocytes. The interaction of stromal cells with cancer cells affects invasive functions and modulates epithelial-mesenchymal transition (Chaps. ▶ 180, ▶ 181, ▶ 182, and ▶ 183). Metastatic spread of cancer cells, preceded by invasion, is a process that depends on the construction of premetastatic niches, the expression of distinct prometastatic genes and metastasis suppressors, on numerous microRNAs, and on the exchange of cellular information through exosomes and other vehicles that transfer signal cargo and extracellular nucleic acids (Chap. ▶ 184).

Part 37 is reserved for a distinct tumor tissue that affects numerous biologic functions of neoplasms, i.e., tumor stroma. Stroma forms a specific microenvironment that critically regulates the development and behavior of malignant neoplasms. Stromal cells interact with tumor cells directly, in part through cell fusion, and via molecular signals, resulting in a complex signal platform that expands in parallel with tumor growth. Stroma regulates tumor growth, differentiation, invasion, and metastatic spread. The various types of leukocytes present in stroma, in particular tumor-associated macrophages, myeloid-derived suppressor cells, lymphocytes, and neutrophils, create a unique inflammatory microenvironment which, through chemokines and other signal substances, significantly affects tumor biology (Chap. ▶ 185).

Part 38 shows how tumor angiogenesis functions and how it is an essential process in many aspects of liver tumor invasion and progression. Angiogenesis, the formation of new tumor blood vessels, is a critical mechanism for the development and progression of hepatobiliary tumors, which are often highly vascular lesions. In contrast to normal tissues, tumor blood vessels often form highly atypical branching patterns, with irregular diameters and abrupt changes from large to small diameters. The cells mediating tumor angiogenesis are endothelial cells and auxiliary cells that modulate the biology of endothelial cells, in particular perivascular cells, stromal cells, and tumor-associated macrophages and other leukocytes. As in normal tissue, initiation and progression of angiogenesis in tumors involve the action of numerous angiogenic factors, but neoplasms also produce several antiangiogenic factors. Tumor angiogenesis is modulated by epigenetic mechanisms, mainly microRNAs expressed by tumor cells and stromal cells (Chap. ▶ 186). This chapter is supplemented by a chapter that addresses basic questions of vasculogenesis, angiogenesis, and lymphangiogenesis (Chap. ▶ 187).

The last part of the present book, Part 39, provides a summary of current systems of tumor staging. As with other cancers, staging of hepatobiliary cancers is critical for prognostication and optimal treatment planning. Staging is a complex task that depends on multiple factors. In recent years, several staging systems have been developed and markedly improved the methods to arrive at optimal risk stratification procedures. Apart from hepatocellular carcinoma, highly reproducible staging systems have been developed for extrahepatic and intrahepatic cholangiocarcinoma and for hepatoblastoma (Chap. ▶ 188).

Arthur Zimmermann
Bern, Switzerland

Acknowledgments

It is both a great honor and pleasure to thank all those who encouraged me to be involved in this endeavor and offered me continuous advice, support, and help. In fact, the present textbook could only be created thanks to numerous persons who have contributed in several ways to make this work possible. First of all, I express my deep gratitude to my former and venerated teacher in pathology, the late Professor Hans Cottier of the Berne University who, when I was still a beginner in surgical pathology and research, inspired me and filled his young disciple with enthusiasm to engage in a mode of thinking that was strongly based on science. Specifically, it was he who so clearly showed me the uppermost significance of basic science in pathology and, by doing this, kindled my strong desire to follow this path of thinking and acting. Later in my professional life as a pathologist I had the privilege to chair the Berne Institute of Pathology together with an outstanding partner, Professor Thomas Schaffner, whose critical mind in science and the highly stimulating interaction with him as a really good friend will remain unforgettable and irreplaceable. In regard to my early and continued interest in hepatology, I am indebted to all those who uncovered this fascinating field for me, in particular Professors Preisig, Reichen, Lauterburg, and Dufour of the Berne University. In the field of surgery, I have profited a lot from intense contacts with Professors Blumgart and Büchler, with whom I had the great chance to cooperate in various scientific projects and who converted me to bring hepatobiliary pathology to the bedside. In the field of pediatric hepatobiliary oncology, I would like to acknowledge the stimulating influence and help of all my professional friends of the international SIOPEL study group, with whom I had a very fruitful interaction for so many years. Having had access to large numbers of hepatobiliary tumor specimens deserves special thanks for the enthusiasm and tireless work of the laboratory crew of the Berne pathology institute, in particular I remain indebted to the wonderful support I have received from the histopathology staff with its chief, Mary Economou. A hearty thanks also goes to all who so often served me with special methods in diagnostic pathology, particularly Andreas Kappeler and his crew. A central place in the project of this book is held by my outstanding scientific secretary, Erna Kramel. I am highly grateful for the excellent secretarial help and the skillful illustration work performed by Erna, who spared no effort in seeing the preparatory work being completed. I also deeply acknowledge the outstanding librarian work of Sibylle Graf and Irene Marconi who, during many years, competently

provided me with large numbers of scientific articles and books and performed literature search with great motivation and innovation. I extend my appreciation to Alexander Grossniklaus for his continued help in matters of informatics. The significance of the contributions of all these persons cannot be overestimated. The author has been fortunate in having a continued and outstanding relationship with his publisher and his Springer partners associated with and enthusiastically accompanying him in this fascinating project, in particular Daniela Graf who offered continued excellent support and advice. Finally, the creation of this work would have been inconceivable without the continued interest, help, and compassion of my wife, Geneviève, who endured much in all these years of hard work and who accompanied me with great loyalty in this endeavor.

Contents

Volume 1

About the Author

Professor Arthur Zimmermann is an internationally known specialist in hepatobiliary tumor pathology. Following his training as MD and pathologist at the University of Berne, Switzerland, he worked in basic research for several years, focusing on tumor cell growth regulation, tumor cell locomotion, and cell cycle mutants of cancer cells. In surgical pathology, he analyzed more than 20,000 liver specimens, described new tumor entities, and was an author or coauthor of more than 500 publications in his field of interest. As chapter author, he participated in several well-known books on liver and biliary tract disease, including the 2010 edition of the *WHO Classification of Tumors of the Digestive System*, and was one of the editors of the book, *Pediatric Liver Tumors* (Pediatric Oncology Series, Springer). Professor Zimmermann developed the pathology review center for the multinational SIOPEL pediatric liver cancer treatment studies and was involved in the formulation of the new classification of pediatric liver tumors.

Part I

Tumors of the Hepatocyte Lineage and Its Precursors

Liver Cancer: Stem and Progenitor Cells 1

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_1

Abstract

Stem cells are involved in hepatocarcinogenic pathways. In the normal liver, hepatic stem cells are self-renewing cells dwelling in distinct compartments termed stem cell niches. These niches are distinct microenvironments which maintain the balance of slow self-renewal of quiescent stem cells and their priming to become hepatocytes and other differentiated cells. Hepatic stem cells possess plasticity, allowing them to undergo lineage diversification. In hepatocarcinogenesis, tumor stem cells mimick certain features of their normal counterparts. Tumor stem cells in hepatocellular carcinoma (HCC) can act as tumor-initiating cells and tumor-propagating cells that express hepatic stem cell markers and show distinct gene expression profiles. Apart from their role in carcinogenic pathways, cancer stem cells in HCC are considered to play an important role in tumor recurrence and metastasis. The expression of stemness-related markers in HCC confers an aggressive phenotype in these neoplasms. Tumor stem cells in HCC modulate several processes, including maintenance of slowly cycling clonogenic cells having longevity, induction of distinct growth features, and tumor progression. Following removal of HCC and other liver cancers, tumor stem cells can remain in the liver and enter the bloodstream to settle in new stem cell niches, including metastatic niches.

Introduction

Stem cells participate in tumorigenic pathways of numerous neoplasms and have therefore anticipated to be involved in hepatocarcinogenesis. Tumor stem cells (cancer stem cells, CSCs) in hepatocellular carcinoma (HCC) drive carcinogenic pathways and maintain a growing cell population in addition to proliferating nonstem cancer cells, but stem cells are also considered to play a significant role in HCC metastasis and recurrence. Furthermore, and similar to normal stem cells, CSCs exhibit the features of plasticity in regard to their lineage fating, an element that plays an important role in tumor heterogeneity and progressive phenotypic change, e.g., in metastases (reviews: Meacham and Morrison 2013; Sukowati and Tiribelli 2013). Recent research on liver cancer stem cells has also been undertaken with the aim of shedding light on novel treatment directions (reviews: Lee et al. 2009; Pang and Poon 2012). Generally, it is proposed that the expression of stemness-related markers in HCC confers an aggressive phenotype to these neoplasms. As in other organs and tissues, hepatic stem cells are self-renewing cells that dwell in distinct compartments termed stem cell niches, specific microenvironments which provide conditions for maintaining a balance of slow self-renewal of the mostly quiescent stem cells and their priming to become differentiated cell lineages. It is assumed that, following removal of HCC and other malignancies, stem cells involved in maintenance of a neoplastic phenotype remain in the liver and can enter the bloodstream to settle in new stem cell niches, including metastatic niches.

Selected References Sell (1993), Alison and Lovell (2005), Shupe and Petersen (2005), Wu and Chen (2006), Kitisin et al. (2007), Dan and Yeoh (2008), Sell and Leffert (2008), Zou (2008), Alison et al. (2009), Chiba et al. (2009), Lee et al. (2009), Mishra et al. (2009), Yao and Mishra (2009), Darwiche and Petersen (2010), Marquardt and Thorgeirsson (2010), Oliva et al. (2010), Teufel and Galle (2010), Lau et al. (2011), Liu et al., (2011a), Tong et al. (2011), Wang and Jacob (2011), Alisi and Baffet (2012), Ji and Wang (2012), Rountree et al. (2012), Shen and Cao (2012), Yoon (2012), Blechacz and Mishra (2013), Dong et al. (2013), Jia et al. (2013), Oishi et al. (2014), Sainz and Heeschen (2013), Yamashita and Wang (2013), Yamashita and Kaneko (2014).

Stem Cells and Progenitor Cells in the Normal Liver: Pacemakers of Hepatic Ontogeny and Regeneration in the Injured Liver

Stem cells are critically involved in liver ontogenesis (reviews: Kamiya et al. 2006; Navarro-Alvarez et al. 2010). After fating of primordial endodermal cells to become liver, hepatic specification produces bipotential hepatic stem cells or hepatoblasts which can differentiate into either hepatocytes or cholangiocytes (reviews: Sangan and Tosh 2010; Parveen et al. 2011; Shin and Monga 2013; Kamiya and Inagaki 2015). Hepatic specification is a highly complex process that not only depends on fated endodermal cells but also on an interaction of several cell types located to endoderm, including the endothelial cell niche which promotes hepatic endoderm expansion and is directly required for liver speciation (Han et al. 2011b). In regard to regeneration of hepatocytes, the liver is in a special situation insofar as most of the cells that repopulate undamaged parenchyma after cell loss (e.g., resection) are the mature hepatocytes themselves, and not stem/progenitor cells, as hepatocytes are in a G0 phase of cycle and can be rapidly recruited into a cell division cycle. Stem cells play a significant role in regeneration of the liver in case of hepatocyte damage, i.e., when metabolic injury and decreased viability precludes a regenerative response of hepatocytes. Two types of hepatic stem cells have been defined, viz. fetal hepatic stem cells and stem cells of the adult liver (oval cells; progenitor cells). Fetal hepatic stem cells can maintain their self-renewal capability in the developing liver (Zheng and Taniguchi 2003). In adult livers, hepatic progenitor cells are present in small numbers and are quiescent stem cells with a low proliferative rate, representing a reserve or "emergency" compartment that is activated in case of marked hepatocyte damage or massive hepatocyte loss (Sharma et al. 2006; Gaudio et al. 2009; "ghosts in the machine"; Darwiche and Petersen 2010). In the normal adult, liver stem cells mainly reside in peripheral parts of portal tracts, in the compartment of canals of von Hering, and ductules (Vessey and de la Hall 2001), but a subset of liver progenitor cells originates from HNF1beta(+) biliary duct cells (Rodrigo-Torres et al. 2014). The progenitor cell response comes in four components, viz. activation/priming, proliferation, migration, and differentiation. In the course of stem cell-mediated regeneration, primed stem cells and their progeny, oval cells in rodents and progenitor cells in humans, form ductular profiles (ductular reaction) that deeply invade the damaged parenchyma and differentiate into focally arranged cell clusters that will generate hepatocytes (reviews: Fausto and Campbell 2003; Vestentoft 2013; Katoonizadeh et al. 2014). These clusters can also form narrow intraparenchymal ductular structures which have been termed parenchymal ductules. The cells forming these ductules have the same immunophenotype as resting stem cells (Papp et al. 2014). Stem cells isolated from fetal liver have the capacity to repopulate up to 10 % of normal liver, while progenitor cell lines from embryonal and adult liver have no significant repopulation activity (review: Dabeva and Shafritz 2003).

Extrahepatic Stem Cells Home to Liver and Liver Cancer and Regulate the Respective Cell Biologies

In addition to resident hepatic stem and progenitor cells, stem cells acting in the liver can also be recruited from extrahepatic organs and tissues. Induced pluripotent stem cells (iPSCs) develop through reprogramming of somatic cells to a pluripotent state by a complex induction process. iPSCs resemble embryonic stem cells/ESCs in several aspects (review: Chiang et al. 2013). iPSCs can, e.g., originate from mesenchymal cells (including mesenchymal stem cells), fibroblasts, adipocytes, and several types of bone marrow derived cells. As iPSCs can undergo tridermal priming/fating and differentiation, they can give rise to several types of hepatic cells. Embryonal

fibroblasts can be reprogrammed by hepatocyte nuclear factor 1 alpha and Foxa3 to bipotential hepatic stem cells (Yu et al. 2013b). Circulating bone marrow and/or adipose tissue-derived hematopoietic and mesenchymal stem cells (MSC) are capable to give rise to hepatic cells enabled to act in hepatic regeneration (Petersen et al. 1999; Grompe 2005; Oh et al. 2007; Guest et al. 2010; Ishikawa et al. 2010; Gong et al. (2013a, b); Stock et al. 2014). MSCs form a heterogeneous population of fibroblastoid cells surrounding blood vessels and are concentrated in the bone marrow and in adipose tissue, from where they can emigrate, circulate in the blood, and home to diverse tissues. Both hematopoietic stem cells and MSCs can home to the liver after hepatocyte loss, populate the remaining liver, and give rise to cells that can regenerate liver. MSCs can also home to tumors, including HCCs, where they exert diverse functions, including contribution to tumor cell development and expansion, generation of metastatic niches, neovascularization, and immunosuppression (review: Reagan and Kaplan 2011). Human fetal hepatic stem/progenitor cells are distinct from, but closely related to, hematopoietic stem cells (Chen et al. 2013d). Bone marrow-derived MSCs homing to liver tumors can, through interaction with tumor cells, increase tumor cell apoptosis and inhibit metastatic spread (Hang and Xia 2014). Homing of hematopoietic stem cells to the liver after hepatectomy requires hepatocyte growth factor (HGF) and stroma-derived factor-1 (SDF-1) (Lehwald et al. 2014), and hepatic differentiation of human adipose tissue-derived stem cells is promoted by distinct microRNAs (Davoodian et al. 2014).

Identification of Liver Tumor Stem Cells: Morphology, Stem Cell Markers, and Their Characteristics

Morphology

In the normal and regenerating liver, at least part of the stem or progenitor cells can morphologically be identified (Alison et al. 2001; Forbes et al. 2002; Fausto and Campbell 2003; Strain et al. 2003; Zheng and Taniguchi 2003; Kuhlmann and Peschke 2006; Bird et al. 2008). Stem cells, which in part are located in the lining of bile ductules, from where they can be recruited and mobilized, have morphological features of oval cells, small basophil cells, and transition cells between cholangiocytes and hepatocytes. Recently, it was reported that also ballooned cells forming Mallory-Denk bodies may have features of progenitor cells (French et al. 2013). Numerous investigations provided strong evidence that hepatic cancer stem cells (CSC) can be isolated from HCC (Chiba et al. 2006; Ma et al. 2007; Kamohara et al. 2008; Sell 2008; Sell and Leffert 2008; Lingala et al. 2010; Tomuleasa et al. 2010; review: Ji and Wang 2012).

Markers of Stem/Progenitor Cells

CSC are characterized by several markers, including CD13, CD24, CD44, CD90, CD133, EpCam (CD326), OV6 (Terris et al. 2010), and numerous others (Table 1).

Stem cells or stem-like cells can also be isolated from HCC cell lines in vitro via isolation of the side population (SP) cells, a cell population

Table 1 Markers for hepatocellular carcinoma-related cancer stem cells

CD133 (prominin-1)
OV6
EpCAM (epithelial cell adhesion molecule)
CD24
CD90
CD133
CD176
SALL4 (Sal-like protein 4)
c-Kit
ICAM-1 (intercellular adhesion molecule-1)
NCAM (neural cell adhesion molecule)
Delta-like protein 1
Nestin
Granulin-epithelin precursor (GEP)
BMI1 polycomb product
Doublecortin
CaM kinase-like-1
ABCB5
Tudor domain-containing protein 4

capable to exclude Hoechst 33343 dye owing to the capacity of these cells with sufficient ATP-binding cassettes to transport the Hoechst dye out of the cell, while non-SP cells cannot. Due to this difference, tumor SP cells can then be separated from the other cell populations by use of cell sorting, and the resulting SP cells tested for typical stem cell features. Results of such analyses showed that SP cells contain a CSC cell population (review: Sell and Leffert 2008). However, not all cells of side population cell fractions have the characteristic features of CSCs (Nakayama et al. 2014). HCC-CSCs can also be identified by their molecular makeup. Stem cell features of HCC cells are associated with well-established gene alterations conferring an abnormal growth and apoptosis behavior in HCC, such as TP53 mutations (Woo et al. 2011).

CD133: Prominin 1 is a Crucial Molecule in HCC-CSC Biology

CD133 (prominin 1; PROM1) is a well-known stem cell marker (Mizrak et al. 2008; Wu and Wu 2009; Li 2013) which is involved in cell differentiation and polarity (Fargeas et al. 2011), organ morphogenesis (Anderson et al. 2011), cell surface dynamics (Mak et al. 2011), iron homeostasis of various cells (Bourseau-Guilmain et al. 2011), and interactions between cancer cells and stromal cells (Moriyama et al. 2010; Akita et al. 2013a, b). CD133 is expressed in subsets of liver stem cells (Rountree et al. 2011). These cells display a greater colony-forming efficiency and a higher proliferative output (Ma et al. 2007). Expression of CD133 also characterized part of HCC stem cells (Suetsugu et al. 2006; Ma et al. 2008; Song et al. 2008; Yoshikawa et al. 2009; Suetsugu et al. 2010; Zhang et al. 2011; Tsai et al. 2012; Ma 2013), and CD133+/CD44+ cells in HCC are considered to be true cancer stem/progenitor cells that are involved in tumor maintenance and chemoradioresistance (Zhu et al. 2010; Piao et al. 2012). There is evidence that the presence of CD133+ stem cells in HCCs is related to the etiology of HCC. In an area endemic for HBV virus (Taiwan), CD133 expression in HCC was negatively associated with the presence of HBsAg, implicating a non-HBV viral origin of CD133+ HCC (Yeh et al. 2009). In HCC cell lines, expression of CD133 markedly affects the biological features of the tumor cells. Silencing of CD133 expression impaired in vitro HCC cell proliferation, formation of tumor spheres, colony formation, and in vivo tumorigenicity in immunodeficient mice. In addition, knockdown of CD133 reduced cells in G0/G1 and increased tumor cell apoptosis through modulation of Bcl-2 and Bax (Lan et al. 2013). CD133 expression predicted poor disease-free survival independently of p53 expression (Yeh et al. 2009). Expression of CD133 in HCC cells is a predictor of the effectiveness of S1+ pegylated interferon alpha-2b therapy (Hagiwara et al. 2011). CD133 is also expressed in cholangiocarcinoma and gallbladder carcinoma cells (Shi et al. 2010; Fan et al. 2011; Iwahashi et al. 2013), and this expression is correlated with positive tumor margin status and lymph node metastasis (Leelawat et al. 2011).

Other Stem Cell Markers

A well-known second hepatic stem cell marker, OV6, is also present in HCC-associated CSC. OV6+ HCC stem cells are tumor-initiating cells that possess a high capacity to form tumor spheroids in vitro and give rise to tumors in severe combined immunodeficient (SCID) mice (Yang et al. 2012). CD90 characterizes a stem cell lineage in liver cancer, and cells expressing CD90 express several hundred other genes, including glypican-3 (Ho et al. 2012). A further protein expressed in part of stem and progenitor cells is c-Kit (CD117). In one investigation, c-Kit expression was detected in only 2.3 % of HCC, suggesting that c-Kit is not significantly overexpressed in HCC cells (Becker et al. 2007). In another study, immunoreactivity for c-Kit was detectable in 70 % of HCC with different degrees of intensity, illustrating highly variable results in regard to the expression of this stem cell marker in HCC. However, c-Kit reactivity was also found in 90 % of peritumoral cirrhotic and noncirrhotic liver tissue. Similarly, c-Kit

mRNA was identified in 83 % of HCC and 90–100 % of surrounding tissue (Mansuroglu et al. 2009). Sal-like protein 4/SALL4, a member of a family of zinc finger transcription factors, modifier of somatic cells and regulator of organogenesis and pluripotency, is a stem cell marker. SALL4 is expressed in normal human hepatic stem cells, hepatoblasts, HCC, cholangiocarcinoma, and mixed cholangiocarcinoma but is silenced in the normal adult liver. Its expression correlates with cell and tumor growth and an aggressive HCC phenotype (Yong et al. 2013), whereas its suppression results in slowed tumor growth and tumor cell differentiation (Oikawa et al. 2013). SALL4 is a marker for a progenitor subclass of HCC with an aggressive phenotype (Yong et al. 2013). Epithelial cell adhesion molecule (EpCAM) is expressed in several cancer and HCC stem cells and in tumor-initiating cells (TIC) (Yamashita et al. 2009; Terris et al. 2010; Imrich et al. 2012). In subsets of HCC stem cells, EpCAM is coexpressed with another stem cell marker, CD133, and cells with this phenotype represent tumor-initiating cells (TIC; Chen et al. 2012). In a recent investigation, it was shown that the two CSC markers of HCC, EpCAM and CD90, are independently expressed, in that EpCAM positivity characterized epithelial CSC, while CD90+ CSC had features of vascular endothelial cells, suggesting that more than one type of hepatic CSC may occur together and fulfill different functions (Yamashita et al. 2013). Liver cancer stem cells are also characterized by positivity for the Thomsen-Friedenreich core-1 protein, CD176 (Lin et al. 2011). Stemness features of HCC cells were analyzed by analysis of two stem cell characteristics, low proteasome activity and low intracellular reactive oxygen species/ROS. Isolated HCC with these two features demonstrated asymmetric divisions, tumorigenicity and a metastatic phenotype in immunodeficient mice, upregulated chemokine-related genes, and facilitation of macrophage migration in vitro (Muramatsu et al. 2013), suggesting that HCC stem cells not only affect tumorigenesis as such but also features of spread and interactions with tumor-associated cells such as macrophages. In HCC tumor cell lines kept in culture, a minor cell population expresses intercellular adhesion molecule 1 (ICAM-1). These ICAM-1-positive cells, which were also detected in human HCC and as circulating tumor cells in HCC patients, have greater sphere-forming and tumorigenic properties and represent tumor stem cells (Liu et al. 2013a). A second molecule involved in the regulation of cell adhesion is dysadherin. Dysadherin expression in liver cells characterizes a stem-like cell phenotype (Park et al. 2011). Part of HCC progenitor/stem cells are reactive for the 140 kDa isoform of neural cell adhesion molecule (NCAM) (Tsuchiya et al. 2011). A novel HCC stem cell marker is Delta-like 1 protein (Dlk-1), a surface protein expressed on fetal hepatic stem/progenitor cells but absent from mature hepatocytes in neonatal and adult rodent livers (Yanai et al. 2010). Overall, Dlk-1 is expressed in 20 % of all HCC but is even more frequently detectable in HCC diagnosed in young patients (Nishina 2012). Granulin-epithelin precursor (GEP) is a hepatic oncofetal protein expressed in fetal livers, but not in normal adult livers. Fetal liver cells containing GEP coexpress the stem cell-related signaling molecules beta-catenin, Oct4, Nanog, Sox2, and Dlk-1 and the CSC markers CD133, EpCAM, and ABCB5 (Cheung et al. 2011). The polycomb gene product BMI1 is critically involved in the self-renewal of somatic stem cells and participates in several types of tumorigenesis. BMI1 is expressed in subpopulations of HCC stem cells and plays a role in the maintenance of TICs in HCC (Chiba et al. 2008). HCV virus-induced CSC have a molecular signature containing doublecortin and CaM kinase-like-1 (Ali et al. 2011). A stemness-related molecule in HCC is cytokeratin-19 (CK19) (Lee et al. 2012a). Expression of CK19 in HCC confers increased EMT-related protein and mRNA expression and an invasive, aggressive phenotype (Kim et al. 2011; Lee et al. 2012).

HCC-Associated Stem Cells: Self-Renewing Cells with Various Biological Functions

HCC-associated stem cells promote tumor maintenance and progression.

HCCs can possess various self-renewing tumorigenic cell types, including CSCs sensu strictiori. These cells act as tumor-initiating cells (TICs) and tumor-propagating cells that express numerous morphologic and phenotypic features and distinct gene expression profiles (Colombo et al. 2011). CSCs of HCC express typical hepatic stem cell markers, such as CD133 and CD90, and their priming manifests in the expression of HCC lineage markers, as CD90(+) HCC-CSCs can also express glypican-3 (Ho et al. 2012). HCC-associated CSCs or stem-like cells are present in the tumors themselves, but they also occur in increased numbers in chronic liver disease, e.g., HCV-related liver cirrhosis (Behnke et al. 2013). A distinct property characterizing HCC stem cells is that they can initiate tumor growth in syngeneic or immunocompromised recipients. It is, however, difficult to judge whether such tumor-initiating cells are true CSC or non-CSC tumor cells that can give rise to growing tumors after cell transplantation (review: Sell and Leffert 2008). HCC-associated CSCs differ in several respects from other stem cells. In mouse HCC models, HCC progenitor cells give rise to fully developed cancer only when introduced into a liver showing chronic damage and compensatory hepatocyte regeneration, and tumor growth depends on cytokine stimulation, e.g., IL-6 signaling (He et al. 2013). CSCs occurring in HCC affect and modulate several biological functions, including maintenance of clonogenic cells with low proliferative activity but longevity, induction of distinct growth features (also in vitro; sphere formation, colony formation, anchorage-independent growth), and tumor spread and progression. There is also growing evidence that CSC are involved in the process of hepatocarcinogenesis itself, hepatic progenitor cells exposed to carcinogens progressively accumulating genetic alterations and genomic instability, in part acquiring the features of tumor-initiating cells, and finally showing a stably transformed phenotype (Xu et al. 2010; Kim et al. 2014; Machida et al. 2015). CSCs make part of a hierarchic cancer stem cell model for solid tumors such as HCC (review: Tong et al. 2011).

HCC-associated CSCs are not only involved in the initiation and maintenance of a given tumor but are also operational in HCC recurrence (HCC recurrence-associated stem cells, RASCs), the programming and establishment of metastatic niches (niche-associated stem cells, NASCs), and growth of metastases (metastasis-associated stem cells, MASCs). The pathways leading from the expression of stem cell markers to specific cancer cell behaviors are only partially elucidated. For example, expression of the stem cell marker, CD133, in HCC cells is associated with high capacity for tumorigenicity (Suetsugu et al. 2006; Yin et al. 2007) and confers an aggressive and invasive phenotype to HCC cells through the expression of metalloproteinase-1 (MMP-1) and a disintegrin and metalloproteinase (ADAM9; Kohga et al. (2010). Cytoplasmic expression of CD133 is an important risk factor for overall survival in HCC, specifically for stage III and IVA lesions (Sasaki et al. 2010).

HCC stem cells program epithelial-mesenchymal transition (EMT), a process critical for invasion and spread.

Epithelial-mesenchymal transition (EMT) is a process that occurs in many epithelial lineages and tumors derived thereof, characterized by the acquisition of a mesenchymal phenotype. The reverse process, mesenchymal-epithelial transition (MET) is less well known. EMT is driven by a distinct set of non-tissue-specific master transcriptional regulators (review: Cicchini et al. 2014). HCC stem cells are involved in the programming of EMT, a phenomenon which is crucial to invasion and spread of cancer cells and their interactions with the tissue microenvironment. On the other hand EMT creates a niche in which CSCs can settle and undergo differentiation. In this niche, with its features as an inflammatory microenvironment, mesenchymal stem cells can settle and accelerate HCC metastasis via induction of EMT (Jing et al. 2012). In cancers, EMT is chiefly characterized by disruption of intercellular contacts and connections leading to individualization of cells, enhancement of cell motility, and achievement of a primitive cell type capable to integrate into novel microenvironments (Guarino et al. 2007). In human HCC stem-like cells, the EMT promoter Twist2 induces self-renewal of these cells in a CD24-dependent manner (Liu et al. 2014). An EMT phenotype is

induced in hepatic oval cells by downregulation of microRNA-200a via targeting the beta-catenin signaling pathway (Liu et al. 2013b), which in turn affects the expression of cadherin, an important modulator of EMT. MicroRNA-200 upregulates vasohibin2 which in turn induced EMT and promotes HCC transformation (Xue et al. 2014). HCC cells that express the stem cell marker CD133 display more invasive characteristics by upregulation of invasion-associated genes and EMT-associated genes (Na et al. 2011). The relationship between EMT and a more invasive phenotype of cancers is linked to a distinct E-cadherin adhesion molecule repressor interactome in EMT (Hugo et al. 2011). Loss of E-cadherin, a typical feature of EMT, is associated with the acquisition of stem cell signatures and of cell with increased invasiveness (Nakagawa et al. 2014). NANOG, a major transcription factor essential for stem cell self-renewal, regulates self-renewal of CSC through the insulin-like growth factor pathway in human HCC (Shan et al. 2012) and promotes HCC invasion by inducing MEM, via activation of NODAL and CRIPTO-1 to promote SMAD3 phosphorylation and SNAIL expression. Interestingly, NANOG is preferentially expressed at the tumor edge, where invasion is most active (Sun et al. 2013a), suggesting that tumor stem cells may not be randomly distributed in liver cancer, but may rather populate distinct tumor areas. EMT can also be induced by hepatocyte growth factor secreted by hepatic stellate cells (HSCs), associated with upregulation of cancer stem cell-like properties in HCC cells (Yu et al. 2013a). The function of stem cell in the setting of EMT is modulated by tumor-associated macrophages (TAMs). In HCCs, TAMs promote cancer stem cell-like properties through TGF-beta1-induced EMT (Fan et al. 2014).

Stem Cells in HCC: Significance for Invasion, Spread, Stroma Formation, and Angiogenesis

A meta-analysis of HCC demonstrated that the presence of cancer stem cells was significantly associated with poor histological grade and elevated serum AFP levels, but there was no correlation between the presence of cancer stem cells and tumor size, tumor stage, or chronic liver disease/cirrhosis. Cancer stem cells in HCC were significantly associated with poor survival, including overall survival and disease-free survival, suggesting that the analysis of stem cells has an impact on the prognostication of HCC biology (Ma et al. 2013). HCC harboring CD133+ cells showed an aggressive, invasive phenotype, complicated by bile duct tumor invasion and thrombi (Yu et al. 2011). The reason why CSCs in HCC can significantly affect tumor biology and prognosis is related to several CSC-modulated mechanisms involved in tumor growth, invasion spread, and generation of a tumor-specific microenvironment. CSCs interact with and modulate the function of bone marrow-derived stromal stem cells (BMSCs), stem cells that are recruited to form tumor stroma and that are prone to undergo progressive changes similar to that of their cancerous partner cells, including telomere attrition due to telomerase failure (review: Saeed and Iqtedar 2013). CSCs contribute to neovascularization and angiogenesis through the production of proangiogenic factors, transdifferentiation of CSCs into endothelial and myoid cells, and formation of non-endothelium-lined channels called vasculogenic mimicry (reviews: Yu et al. 2010a, b; Barajas et al. 2007; Ping and Bian 2011; Zhu et al. 2012a, b). High expression levels of hepatic stem cell markers are related to tumor angiogenesis and poor prognosis in HCC. HCC with higher levels of CSC displayed higher levels of vascular endothelial growth factor and had an angiogenic pattern characteristic for aggressive tumors (Ho et al. 2006; Yang et al. 2010). Part of angiogenic effects exerted by hepatic CSC are linked to the angiogenic effects of CD133 (Akita et al. 2013a). Expression of CD133 in liver tumor-initiating cells (TIC) promotes tumor angiogenesis, growth, and cell renewal via a neurotensin / interleukin-8/CXCL1 signaling pathway, causing activation of p-ERK1/2 and RAF-1, components of the mitogen-activated protein kinase/MAPK pathway (Tang et al. 2012). A second stem cell factor that affects invasive properties of HCC cells is EpCAM. There is evidence that HCC growth

and invasiveness is dependent on a subset of EpCAM+ stem cells (Terris et al. 2010). In addition to the proangiogenic effect of CSCs, neovascularization /angiogenesis in malignant neoplasms is also accomplished by homing of angiogenic circulating progenitor cells to tumors. These cells are either angiogenic stem cells already primed for endothelial differentiation or homing MSCs that will upon their settling in the tumor be fated to become angiogenic cells (review: Melero-Martin and Dudley 2011). On the other hand, endothelial progenitor cells, through their angiogenic modulation of the tumor niche, affect HCC progression. These cells promote HCC intrahepatic metastasis via monocyte chemotactic protein-1 induction of microRNA-21 (Shih et al. 2014).

Cancer Stem Cells and Vasculogenic Mimicry

Vasculogenic mimicry (VM) was described in 1999 based on the detection of vascular channel formation by human melanoma cells (Maniotis et al. 1999). The term, VM, denotes a phenotype resembling the pattern of embryonic vasculogenic networks and describes the plasticity of cancer cells and their precursors forming de novo vessel-like channels lined by cancerous cells, whereby these channels contribute to perfusion and transport fluid from leaky vessels (Frenkel et al. 2008). Like this, the pseudovascular structures in VM contribute to neovascularization of rapidly growing malignancies in a mode that is independent of classical angiogenesis and vasculogenesis. The development of fluid-transporting spaces in VM facilitates metastatic spread (reviews: Folberg et al. 2000; Folberg and Maniotis 2004; Ping and Bian 2011; Kirschmann et al. 2012; Liu et al. 2012; Seftor et al. 2012). In cancers, two main patterns of VM are recognized, i.e., tubular VM and patterned matrix VM. In tubular VM, fluid-containing spaces are surrounded by tumor cells, while in patterned matrix VM laminin-reactive loops with PAS-positive laminas surrounding packets of tumor cells are seen (laminin-rich looping VM). Mainly in patterned matrix VM epithelial-mesenchymal transition (EMT) induced by Twist1 plays a significant pathogenic role whereby cancer cells can acquire a mesenchyme-like phenotype and may even become endothelial-like cells. In EMT-induced VM, CSCs are important actors, whereby EMT itself is potent for the acquisition and maintenance of stem-like features of cancer cells (Fan et al. 2013). Twist1 involved in EMT can stimulate cancer cell migration (Matsuo et al. 2009) and via this effect facilitates VM which requires tumor cell movements. In hypoxia-induced VM, Bcl-2 can induce a major endothelial adhesion molecule in tumor cells, i.e., VE-cadherin (Zhao et al. 2012). However, VM is resistant to antiangiogenic therapies (Fan and Sun 2010). Apart from factors regulating EMT, several other molecules are active in the promotion of VM, including the PI3-K signaling pathway, matrix metalloproteinases, laminin-5-gamma chain, protein tyrosine kinases, epithelial cell kinase (ECK), focal adhesion kinase, Eph receptors, Nodal, Notch4, hypoxia-inducible factor, galectin-3, bone morphogenetic proteins, cAMP signaling, cyclooxygenase-2, inhibitor of DNA binding 2/Id2, autophagy-related proteins, and VEGF (Hess et al. 2001; Hess et al. 2007; Sun et al. 2007; Lissitzky et al. 2009; Su et al. 2009; Fan and Sun 2010; Hardy et al. 2010; McAllister et al. 2010; Paulis et al. 2010; Che et al. 2011; Han et al. 2011a; Sun et al. 2012; Vartanian et al. 2013; Ding et al. 2014).

Both tubular and patterned matrix VM occur in HCC and is correlated with aggressiveness and poor clinical prognosis (Sun et al. 2006; Zhao et al. 2006; Guzman et al. 2007). Patterned matrix VM in HCC was associated with larger tumor, vascular invasion, high tumor grade, and late stage (Liu et al. 2011b). Similar to other cancers, VM induced by HCC cells is related to the induction of EMT, in that HCC cells in VM express the EMT inducer, Twist1 (Sun et al. 2010). Via EMT, Twist1 directly induces VM in hypoxic HCC cells (Ma et al. 2011) and promotes a metastatic phenotype (Lee et al. 2006). EMT-associated VM induced by Twist1 is stimulated by Bcl-2, which binds to and activates Twist1 under hypoxic conditions (Sun et al. 2011). Various factors present in EMT microenvironments are involved in

VM. The extracellular protease ADAMTS1 is a critical enzyme for cancer cells to acquire endothelial-like properties (Casal et al. 2010), and VM in HCCs is associated with the expression of osteopontin and matrix metalloproteinase-2 (Liu et al. 2011d). In the course of EMT-induced VM, poorly differentiated HCC cells can become CD31 positive and therefore phenotypically resemble endothelial cells (Zhao et al. 2007).

HCC-associated CSCs play a role VM. In the process of VM, a stem cell-like phenotype is involved, whereby cells forming the vascular channels express stemness markers, including CD133 (Yao et al. 2011; Lai et al. 2012; Valyi-Nagy et al. 2012). VM channel formation in HCCs is associated with EMT, dedifferentiation of tumor cells, and increased expression of stemness genes (Lirdprapamongkol et al. 2012). Stem cell-induced VM is particularly prevalent in EMT that develops in hypoxia. Expression of Slug, a potent inducer of EMT, in HCCs promotes the biogenesis and maintenance of a CSC subpopulation that is capable to produce VM (Sun et al. 2013b). EMT itself promotes the formation of HCC cells with stem-like properties via Twist1-Bmi1 signaling, Bmi1 belonging to the polycomb repressive complex 1 (Wu and Yang 2011), and this connection may favor EMT-induced VM mediated by cancer stem cells.

CSCs in Tumor Recurrence and Metastatic Spread: RASCs, NASCs, and MASCs

Tumor recurrence is traditionally viewed as a process that originates from remaining cancer cells that have not been radically removed and/or were resistant to chemo- or radiotherapy. However, within the population of recurrent HCC cells, cells with stem-like features were identified (Yi and Nan 2008; Xu et al. 2010a, b), and it is assumed that such cells contribute to recurrence and significantly modify the recurrence phenotype and pattern. For hepatic recurrence, recurrence-associated stem cells (RASCs) may either represent (a) surviving HCC-CSCs capable to resume growth following therapy, (b) novel stem cell species arising from the recurrent tumor, or (c) stem cells derived from an extrahepatic site and homing to the recurrent tumor with its new microenvironment. Tumor stem cells and their fully malignant offspring play a critical role in the biogenesis of metastatic niches. In human HCCs, expression of the two stem cell markers CD90 and EpCAM was higher in the early recurrence group (Guo et al. 2014). As niche-associated stem cells (NASCs), CSCs undergo a complex crosstalk with normal cells in the prometastatic niche, in that they secrete factors that affect stromagenesis, recruitment of tumor-associated macrophages (TAMs) and tumor-associated endothelial cells (TECs), and angiogenesis (Gupta et al. 2014). These factors include the TGF-beta/Smad system, PDGF, VEGF, and IL-6. Similar to the complex function of the portal fibroblast, which provided a niche for controlled cholangiocyte turnover (Wells 2014), prometastatic niches contain a fibroblastoid population that interacts with NASCs, with a mutual regulation of the cells involved. Part of fibroblastoid cells and angiogenic cells constituting the prometastatic niche are derived from mesenchymal stem cells (MSCs) that circulate in the blood and home to the tumor microenvironment (Wang and Chen 2013), where they interact with tumor cells and NASCs. The mode of this interaction is not yet well known, but MSCs rarely fuse with HCC cells in murine models (Li et al. 2013). HCC cells and their stromal component themselves modulate the migratory behavior of MSCs (Garcia et al. 2011). As the tumor microenvironment is often hypoxic and/or deficient in nutrients, niche-associated tumor cells have developed strategies to circumvent this stress situation. CD133(+) HCC-CSCs showed higher survival, less apoptosis, and higher clonogenicity under hypoxic and nutrient deprivation stress, in part associated with increased autophagy (Song et al. 2013). CD133 is involved in the regulation of autophagy and glucose uptake (Chen et al. 2013d). Following their exit from a primary or recurrent tumor, or a metastatic niche, RASCS and NASCs enter circulation and can become metastasis-associated stem cells or MASCs. There is evidence that circulating HCC stem cell-like cells capable to generate metastatic recurrence (MASCs) express certain markers that allow their identification, such as the stem cell marker CD90 (Yamashita et al. 2013), the oncofetal

marker Lin28B (Cheng et al. 2013), and the G protein-coupled receptor 87/GPR87 (Yan et al. 2013). Expression of CD133 in liver CSC plays a critical role in hematogenous metastasis of HCC (Hou et al. 2012; Chow et al. 2013). CD133-positive CSCs play a role in repeated pulmonary recurrence of HCC (Toshima et al. 2013). In regard to prognostication, the various HCC stem cell markers differ in several respects. While expression of CD133 was more frequently found in small tumors in cirrhotic livers and early stage disease, expression of EpCAM characterized small tumors and poor differentiation and was an independent prognosticator at all stages (Chan et al. 2014). Can circulating CSCs rehome to primary cancers or metastatic niches and modulate the features of their tumor of origin?

Tumor Stem Cells in Nontumorous Liver Tissue

CSC are readily detectable in HCC tissue itself by means of their distinct marker profile, but cells with similar or the same features also occur in the nonneoplastic parenchyma of livers harboring HCC. Cell lines producing colonies in soft agar and showing anchorage-independent growth were isolated form liver resections with HCC, and these cells revealed the marker profile of CSC (Zhang et al. 2010).

Cells with Stem Cell-Like Features in Special Variants of Hepatocellular Carcinoma and in Precursor Lesions

Tumor stem cells seem to be involved in pathogenesis of scirrhous HCC. In this variant of HCC, small neoplastic cells were reactive for cytokeratin 7 and ATP-binding cassette transporter G2. Part of these cells (termed type 1 cells) stained for cytokeratin 19, neural cell adhesion molecule (NCAM), and epithelial cell adhesion molecule, while another subset (termed type 2 cells) did not show this immunophenotype. In type 3 scirrhous HCC, no small tumor cells with stem cell features were present. It was suggested that type 1 and type 2 cells in scirrhous HCC correspond to a side population of cultured cells (Fujii et al. 2008). Apart from conventional HCC, features of stemness are also present in dysplastic hepatocytes (Lingala et al. 2010), fibrolamellar hepatocellular carcinoma (Zenali et al. 2010), and hepatoblastomas (Akita et al. 2013).

Stem Cells in Hepatoblastomas

Hepatoblastomas (HBs) have been shown to contain cells with stem-like features. Hepatoblasts, a putative normal counterpart of HB, show a pattern of proteins shared by hepatic stem cells, i.e., CK19, human epithelial antigen-125/HEA-125, and OV-6 (Crosby et al. 1998). This has in particular been observed in HBs of low differentiation, such as small cell undifferentiated HB (see the respective chapter). In subsets of HB, expression of CK19, Oct-3/4, and EpCAM was observed (Yun et al. 2013). HB cells can express proteins that are present in human fetal liver, including delta-like protein/DLK, a membrane protein of unknown function (Dezso et al. 2008; Yun et al. 2013).

Biogenesis of HCC-Associated Stem Cells

Mechanisms of Stem Cell Formation in the Liver and Liver Neoplasms

Recent findings showed that several mechanisms can elicit tumor stem cells and stem cell signatures in normal liver, regenerating liver, and HCCs. They comprise the expression of transcription factors (Sox2, c-Myc, LIN28, NANOG), several signaling pathways (TGF-beta, Wnt/beta-catenin signaling), factors modulating the cancer microenvironment (Notch signaling), microRNAs, and differential DNA methylation patterns (reviews: Zheng et al. 2013; Bogaerts et al. 2014; Dang et al. 2014). Expression of transforming growth factor beta play an important role in signaling pathways taking place in hepatic and intestinal stem cell niches (review: Majumdar et al. 2012).

Chronic and constant TGF-beta stimulation results in the generation of hepatoma-initiating cells derived from hepatic progenitor cells (Wu et al. 2012), and TGF-beta secreted by HCC cells mediates the crosstalk between cancer cells and the tumor microenvironment (Gupta et al. 2014).

How are the distinct growth and survival features of CSCs regulated, in particular their critical capacity for self-renewal? Overall, the expression of stemness-related proteins by HCC cells is related to increased telomere lengths, increased expression of hTERT and shelterin complex proteins, and increased chromosomal/genomic instability in comparison with conventional HCC (Idrissi et al. 2013). Maintenance of telomeres is compromised in HCCs, and it is expected that a derangement of the telomere platform may be an early event in hepatocarcinogenesis, eventually already involving CSCs (Ye et al. 2010). Specifically, there is evidence that abnormal stem cells may lack telomerase, an enzyme responsible for telomere extension (reviews: Gardano et al. 2013; Saeed and Iqtedar 2013). Telomeres are the terminal elements at the ends of linear chromosomes and are critically involved in the prevention of exonucleolytic degradation, inter- and intrachromosomal fusion, and subsequent chromosomal instability (Ye et al. 2010; Calado and Dumitriu 2013). Telomere integrity is critically required for the unlimited replicative potential of cancer cells. The stability of telomeres depends on the binding of the six-protein subunit complex shelterin to telomeric repetitive DNA sequences (Palm and de Lange 2008; Xin et al. 2008). Further proteins playing a role in telomere stability are the sirtuins (Rodriguez et al. 2013). Telomerase elongates telomeres and is recruited by homeobox telomere-bending protein1/HOT1 (Kappel et al. 2013). Furthermore, the subunit telomerase reverse transcriptase (TERT) has additional functions, including transcriptional regulation and metabolic reprogramming (Low and Tergaonkar 2013). All telomeric proteins involved in telomere function form, together with the telomere proper, the telosome (Liu et al. 2004; Folini et al. 2009).

Epigenetic mechanisms play a central role in the generation of hepatic stem cells and side population cells occurring in HCC. Side population cells of HCC have a high rate of DNA hypermethylation as compared with their corresponding non-side population cells, and the differentially methylated genes in side population cells were involved in numerous signaling pathways (Zhai et al. 2013). Among stem cell molecules regulated by epigenetic mechanisms is CD133, this regulation pathway involving TGF-beta1 which inhibits DNA methyltransferase 1 and DNA methyltransferase 3beta expression and subsequent demethylation of promoter-1 (You et al. 2010). CD133 expression is also promoted by hypoxia, in that hypoxia-inducible factors activate CD133 promoter via ETS family transcription factors (Ohnishi et al. 2013). Certain transcription factors and transcription repressors are preferentially active in stem and progenitor cells and affect epigenetic mechanisms. BORIS (brother of regulator of imprinted sites) is a protein encoded by the CTCFL gene, is a paralog of the transcription suppressor CTCF (Tiffen et al. 2013), and is an ubiquitous 11-zinc finger protein with highly versatile functions, including transcriptional silencing and organization of epigenetically controlled chromatin insulators that regulate imprinted genes in the soma both in normal and cancerous tissues (Klenova et al. 2002; Loukinov et al. 2002; Rosa-Garrido et al. 2012). As BORIS expression in HCC is correlated with expression of the stem cell marker CD90, BORIS may itself be a property of hepatic and HCC-associated stem cells (Chen et al. 2013b).

Pathways from Primed Stem Cells to Differentiated Cells

In parallel to normal stem cells it may be anticipated that CSC can undergo priming to more differentiated neoplastic cells. This is an important study field, because it potentially opens pathways for novel treatment strategies. One factor involved in the switch turning CSC to differentiated cells is the Hippo pathway. Hippo signaling

has a dual regulation of Hippo in liver tumor suppression as well as a transition of oval stem cells to fully differentiated hepatocytes and hepatocyte-like cells in tumors (Zheng et al. 2011). A second crucial pathway involved in the phenotypic shift of CSC to a more differentiated offspring is the WNT/beta-catenin-signaling pathway (Yang and Poon 2008). Expression of beta-catenin is pertinent in hepatic oval cell activation and differentiation (Nejak-Bowen and Monga 2011), and it is expected that the same mechanism is operational in HCC and related neoplasms. As discussed in the respective chapter, immature cells forming undifferentiated clusters in hepatoblastomas are markedly reactive for beta-catenin and seem to give rise to more differentiated but rapidly proliferating offspring surrounding the stem-like cell clusters (Zimmermann 2005).

Regulation of Stem Cells by microRNAs and Other Noncoding RNAs

The function of HCC-associated stem cells is itself regulated by several factors and signaling pathways, including microRNAs (reviews: Chai and Ma 2013; Qi et al. 2013; Chen and Verfaillie 2014). In HCCs and HCC cell lines several and in part specific microRNAs have been identified (Xu et al. 2013). miRNA-130b was shown to promote liver tumor-initiating cell growth and self-renewal through induction of nuclear protein 1 by tumor p53 (Ma et al. 2010). In isolated subsets of side population cells, silencing of microRNA-21 reduced migration and invasion of cancer cells, while overexpression of mRNA-21 drastically inhibited the expression of PTEN, RECK, and PDCD4 proteins (Zhou et al. 2013). MicroRNA-142-3p regulates the expression of the functional hepatic cancer stem cell marker CD133 (Chai et al. 2014). microRNA-181 is highly expressed in embryonic liver tissue and in isolated hepatic stem cells. Specifically, inhibition of microRNA-181 resulted in reduction in EpCAM+ HCC cells and tumor-initiating capacity (Ji et al. 2009). microRNA-150 inhibits human CD133+ liver cancer stem cells through negative regulation of the transcription factor cMyb, associated with downregulation of the cell cycle regulator cyclin D1 and the cell survival regulator Bcl-2 (Zhang et al. 2012). micro-612 suppresses the stemness of HCC CSCs via the Wnt/beta-catenin-signaling pathway (Tang et al. 2014). The tumorigenicity of cancer stem-like cells derived from HCC is regulated by microRNA-145, probably through modulation of the downstream target, the stem cell-related gene Oct4 (Jia et al. 2012; Wang et al. 2013). microRNA-148a inhibits EMT and several CSC properties and by this impairs metastasis of HCC (Yan et al. 2013). Lin-41, a stem cell-specific E3 ligase and a target of the tumor suppressor microRNA let-7 mediates ubiquitinylation and degradation of the microRNA pathway protein Ago2. Lin-41 is overexpressed in HCC, where it is involved in growth control through regulating the RISC complex proteins Ago1 and Ago2 to inhibit microRNA-mediated gene silencing and promoting the expression of oncogenic proteins (Chen et al. 2013a). Lin-41 expression in HCC confers an aggressive phenotype associated with early recurrence and poor survival, suggesting that Li41 is involved in HCC CSC. Hepatic stem cell biology is also affected by long noncoding RNAs. Oncofetal long noncoding RNA PVT1 promotes proliferation and stem cell-like properties of HCC cells by stabilizing NOP2 (Wang et al. 2014).

Modulation of Stem Cell Biogenesis and Function by Microvesicles and Exosomes: Can Cancer Stem Cells "Infect" Other Cells and Transmit Them a Malignant Phenotype?

Mesenchymal stem cells (MSC) as a potential source of hepatic cells possess a complex stem cell secretome that can be transferred to other cell systems through exosomal pathways (Bruno et al. 2013; Kupcova 2013; Xiong et al. 2013). Microvesicles of MSC can serve as trophic shuttles for diverse cell types, including stem cells (Aliotta et al. 2012; Mokarizadeh et al. 2013) and act as a complex paracrine information system within cell interactomes (Quesenberry and

Aliotta 2010), e.g., in regeneration and tissue repair (Camussi et al. 2010; Anthony and Shiels 2013) and the induction of epithelial-mesenchymal transition (Garnier et al. 2013). Via this mechanism, stem cell properties are maintained, while loss of the pathway may result in differentiation of stem cells (Bauer et al. 2011). Specifically, microvesicles released from stem cells confer a stem cell-like phenotype to other stem cells and damaged cells, evoking stem cell maintenance and self-regenerative programs (Herrera et al. 2010; Quesenberry et al. 2012; Camussi et al. 2013), but they may also transfer stem cell-like features to neoplastic cells being in close contact with them (Muralidharan-Chari et al. 2010; Lee et al. 2011; Pap 2011).

A critical property of stem cell microvesicles and exosomes is their genetic information cargo, i.e., they are loaded with microRNAs and mRNAs, genetic information that can be transferred among cells through microvesicle release (Yuan et al. 2009; Deregibus et al. 2010; Lee et al. 2012b). The molecular mechanisms by which genetic information such as microRNAs are loaded into microvesicles/exosomes are not yet well known, but distinct RNA-related zipcode-like sequences seem to act as sentinel sequences for these processes (Bolukbasi et al. 2012). Multipotent mesenchymal stem cells can affect and modulate their partners and other cells through CD133/prominin-1, contained in lipid rafts of these cells, by release of microvesicles. Similarly, cancer cells possess exosomes containing CD133 and numerous other proteins and microRNAs that are involved in metastatic pathways (Rappa et al. 2013). Human liver stem cell-derived microvesicles inhibit HCC growth in immunodeficient mice by releasing antitumor microRNAs (Fonsato et al. 2012). Informational cargo transported and transmitted by exosomes also modulates processes that are associated with and required by stem cell-driven cancer growth and spread. Endothelial progenitor cells located within tumors produce microvesicles that activate an angiogenic program in endothelial cells by horizontal transfer of specific mRNAs (Deregibus et al. 2007).

Systemic and Hepatic Mesenchymal Stem Cells and Stem-Like Cells: Modulation of HCC Biology

In murine models, there is evidence that HCC may originate from genetically mutated MSCs (Gong et al. 2013). MSC interact with HCC cells and modulate their behavior and affect interactions of HCC cells with stromal and vascular cells. In the nude mouse tumor transplantation model, BMSCs could promote the growth of small vessels and increased microvascular density (Gong et al. 2013a, b; Kupcova 2013), and in another murine HCC model, hematogenic MSC could modulate their microenvironment via secreted cytokines that promoted tumor initiation, growth, and homing to tumor sites (Gong et al. 2013). Hepatic stellate cells (HSC) and their precursors are specific mesenchymal cells of the liver that exert a profound impact on growth, differentiation, and morphogenesis of several other hepatic cell systems and neoplasms derived thereof (review: Yin et al. 2013).

Dormant Cancer Stem Cells

Dormant cancer stem cells (D-CSC) are defined as cells that remain intact after apparent eradication of cancer, including HCC, and are capable to maintain a transformed phenotype and to generate recurrent cancer. In one study, such D-CSC were detected in human HCC cell population grown in immunodeficient murine hosts after chemotherapy in the form of human AFP+/CD13+/PCNA cells (Martin-Padura et al. 2012).

References

Akita M, Tanaka K, Matsumoto S, Komatsu K, Fujita K (2013a) Detection of the hematopoietic stem and progenitor cell marker CD133 during angiogenesis in three-dimensional collagen gel culture. Stem Cells Int 2013:10

Akita M, Tanaka K, Murai N, Matsumoto S, Fujita K, Takaki T, Nishiyama H (2013b) Detection of CD133 (prominin-1) in a human hepatoblastoma cell line (HuH-6 clone 5). Microsc Res Tech 76:844–852

Ali N, Allam H, May R, Sureban SM, Bronze MS, Bader T, Umar S, Anant S, Houchen CW (2011) Hepatitis C virus-induced cancer stem cell-like signatures in cell culture and murine tumor xenografts. J Virol 85:12292–12303

Aliotta JM, Lee D, Puente N, Faradyan S, Sears EH, Amaral A, Goldberg L, Dooner MS et al (2012) Progenitor/stem cell fate determination: interactive dynamics of cell cycle and microvesicles. Stem Cells 21:1627–1638

Alisi A, Baffet G (2012) Self-renewal of tumor-initiating cells: what's new about hepatocellular carcinoma ? Gastroenterology 142:1414–1416

Alison MR, Poulsom R, Forbes SJ (2001) Update on hepatic stem cells. Liver 21:367–373

Alison MR, Lovell MJ (2005) Liver cancer: the role of stem cells. Cell Prolif 38:407–421

Alison MR, Islam S, Lim S (2009) Stem cells in liver regeneration, fibrosis and cancer: the good, the bad and the ugly. J Pathol 217:282–298

Anderson LH, Boulanger CA, Smith GH, Carmeliet P, Watson CJ (2011) Stem cell marker prominin-1 regulates branching morphogenesis, but not regenerative capacity, in the mammary gland. Dev Dyn 240:674–681

Anthony DF, Shiels PG (2013) Exploiting paracrine mechanisms of tissue regeneration to repair damaged organs. Transplant Res 2(1):10

Barajas M, Franchi F, Clavel C, Aranguren XL, Kramer MG, Abizanda G, Merino J et al (2007) Multipotent adult progenitor cells (MAPC) contribute to hepatocarcinoma neovasculature. Biochem Biophys Res Commun 364:92–99

Bauer N, Wilsch-Bräuninger M, Karbanova J, Fonseca AV, Strauss D, Freund D, Thiele C et al (2011) Haematopoietic stem cell differentiation promotes the release of prominin-1/containing membrane vesicles-a role of the endocytic-exocytic pathway. EMBO Mol Med 3:398–409

Becker G, Schmitt-Graeff A, Ertelt V, Blum HE, Allgaier HP (2007) CD177 (c-kit) expression in human hepatocellular carcinoma. Clin Oncol (R Coll Radiol) 19:204–208

Behnke MK, Reimers M, Fisher RA (2013) Stem cell and hepatocyte proliferation in hepatitis C cirrhosis and hepatocellular carcinoma: transplant implications. Ann Hepatol 13:45–53

Bird TG, Lorenzini S, Forbes SJ (2008) Activation of stem cells in hepatic diseases. Cell Tissue Res 331:283–300

Blechacz B, Mishra L (2013) Hepatocellular carcinoma biology. Recent Results Cancer Res 190:1–20

Bogaerts E, Heindryckx F, Vandewynckel YP, Van Grunsven LA, Van Vlierberghe H (2014) The roles of transforming growth factor-b, Wnt. Notch and hypoxia on liver progenitor cells in primary liver tumours (review). Int J Oncol 44:1015–1022

Bolukbasi MF, Mizrak A, Ozdener GB, Madlener S, Ströbel T, Erkan EP, Fan JB et al (2012) miR-1289 and "zipcode"-like sequence enrich mRNAs in microvesicles. Mol Ther Nucleic Acids 1:e10

Bourseau-Guilmain E, Griveau A, Benoit JP, Garcion E (2011) The importance of the stem cell marker prominin-1/CD133 in the uptake of transferrin and in iron metabolism in human colon cancer Caco-2 cells. PLoS One 6, e25515

Bruno S, Collino F, Deregibus MC, Grange C, Tetta C, Camussi G (2013) Microvesicles derived from human bone marrow mesenchymal stem cells inhibit tumor growth. Stem Cells Dev 22:758–771

Calado RT, Dumitriu B (2013) Telomere dynamics in mice and humans. Semin Hematol 50:165–174

Camussi G, Deregibus MC, Bruno S, Cantaluppi V, Biancone L (2010) Exosomes/microvesicles as a mechanism of cell-to-cell communication. Kidney Int 78:838–848

Camussi G, Deregibus MC, Cantaluppi V (2013) Role of stem-cell-derived microvesicles in the paracrine action of stem cells. Biochem Soc Trans 41:283–287

Casal C, Torres-Collado AX, Plaza-Calonge MC, Martino-Echarri E, Ramon Y, Cajal S et al (2010) ADAMTS1 contributes to the acquisition of an endothelial-like phenotype in plastic tumor cells. Cancer Res 70:4676–4686

Chai S, Ma S (2013) Clinical implications of miRNAs in liver cancer stem cells. Chin J Cancer 32:419–426

Chai S, Tong M, Ng KY, Kwan PS, Chan YP, Fung TM, Lee TK, Wong N, Xie D, Yuan YF, Guan XY et al (2014) Regulatory role of miR-142-3p on the functional hepatic cancer stem cell marker CD133. Oncotarget 5:5725–5735

Chan AW, Tong JH, Chan SL, Lai PB, To KF (2014) Expression of stemness markers (CD133 ad EpCAM) in prognostication of hepatocellular carcinoma. Histopathology 64:935–950

Che N, Zhao XL, Sun T, Zhao XM, Gu Q, Dong XY, Zhao N, Liu YR, Yao Z, Sun BC (2011) The role of Twist1 in hepatocellular carcinoma angiogenesis: a clinical study. Hum Pathol 42:840–847

Chen Y, Yu D, Zhang H, He H, Zhang C, Zhao W, Shao RG (2012) CD133(+)EpCAM(+) phenotype possesses more characteristics of tumor initiating cells in hepatocellular carcinoma Huh7 cells. Int J Biol Sci 8:992–1004

Chen YL, Yuan RH, Yang WC, Hsu HC, Jeng YM (2013a) The stem cell E3-ligase Lin-41 promotes liver cancer progression through inhibition of microRNA-mediated gene silencing. J Pathol 229:486–496

Chen K, Huang W, Huang B, Wie Y, Li B, Ge Y, Qin Y (2013b) BORIS, brother of the regulator of imprinted sites, is aberrantly expressed in hepatocellular carcinoma. Genet Test Mol Biomarkers 17:160–165

Chen Q, Khoury M, Limmon G, Choolani M, Chan JK, Chen J (2013c) Human fetal hepatic progenitor cells are distinct from, but closely related to, hematopoietic stem/progenitor cells. Stem Cells 31:1160–1169

Chen H, Luo Z, Dong L, Tan Y, Yang J, Feng G, Wu M, Li Z, Wang H (2013d) Cd133+/prominin-1-mediated autophagy and glucose uptake beneficial for hepatoma cell survival. PLoS One 8, e56878

Chen Y, Verfaillie CM (2014) MicroRNAs: the fine modulators of liver development and function. Liver Int 34(7):976–990. doi:10.1111/liv.12496

Cheng SW, Tsai HW, Lin YJ, Cheng PN, Chang YC, Yen CJ, Huang HP, Chuang YP et al (2013) Lin28B is an oncofetal circulating cancer stem cell-like marker associated with recurrence of hepatocellular carcinoma. PLoS One 8, e80053

Cheung PF, Cheng CK, Wong NC, Ho JC, Yip CW, Liu VC, Cheung AN, Fan ST et al (2011) Granulin-epithelin precursor is an oncofetal protein defining hepatic cancer stem cells. PLoS One 6, e28246

Chiang CH, Huo TI, Sun CC, Hsieh JH, Chien Y, Lu KH, Lee SD (2013) Induced pluripotent stem cells and hepatic differentiation. J Chin Med Assoc 76:599–605

Chiba T, Kita K, Zheng YW, Yokosuka O, Saisho H, Iwama A, Nakauchi H, Taniguchi H (2006) Side population purified from hepatocellular carcinoma cells harbors cancer stem cell-like properties. Hepatology 44:240–251

Chiba T, Miyagi S, Saraya A, Aoki R, Seki A, Morita Y, Yonemitsu Y, Yokosuka O et al (2008) The polycomb gene product BMI1 contributes to the maintenance of tumor-initiating side population cells in hepatocellular carcinoma. Cancer Res 8:7742–7749

Chiba T, Kamiya A, Yokosuka O, Iwama A (2009) Cancer stem cells in hepatocellular carcinoma: recent progress and perspective. Cancer Lett 286:145–153

Chow AK, Ng L, Lam CS, Wong SK, Wan TM, Cheng NS, Yau TC, Poon RT, Pang RW (2013) The enhanced metastatic potential of hepatocellular carcinoma (HCC) cells with sorafenib resistance. PLoS One 8, e78675

Cicchini C, Amicone L, Alonzi T, Marchetti A, Mancone C, Tripodi M (2014) Molecular mechanisms controlling the phenotype and the EMT/MET dynamics of hepatocyte. Liver Int 35(2):302–310. doi:10.1111/liv.12577

Colombo F, Baldan F, Mazzucchelli S, Martin-Padura I, Marighetti P, Cattaneo A, Foglieni B et al (2011) Evidence of distinct tumour-promoting cell populations with different properties in primary human hepatocellular carcinoma. PLoS One 6, e21369

Crosby HA, Hubscher SG, Joplin RE, Kelly DA, Strain AJ (1998) Immunolocalization of OV-6, a putative progenitor cell marker in human fetal and diseased pediatric liver. Hepatology 28:980–985

Dabeva MD, Shafritz DA (2003) Hepatic stem cells and liver repopulation. Semin Liver Dis 23:349–362

Dan YY, Yeoh GC (2008) Liver stem cells: a scientific and clinical perspective. J Gastroenterol Hepatol 23:687–698

Dang HT, Budhu A, Wang XW (2014) The origin of cancer stem cells. J Hepatol 60(6):1304–1305. doi:10.1016/j.hep.2014.03.001

Darwiche H, Petersen BE (2010) Biology of the adult hepatic progenitor cell: "ghosts in the machine". Prog Mol Biol Transl Sci 97:229–249

Davoodian N, Lotfi AS, Soleimani M, Mola J (2014) MicroRNA-122 overexpression promotes hepatic differentiation of human adipose tissue-derived stem cells. J Cell Biochem 115(9):1582–1593. doi:10.1002/jcb.24822

Deregibus MC, Cantalupi V, Calogero R, Lo IM, Tetta C, Biancone L, Bruno S et al (2007) Endothelial progenitor cell derived microvesicles activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA. Blood 110:2440–2448

Deregibus MC, Tetta C, Camussi G (2010) The dynamic stem cell microenvironment is orchestrated by microvesicle-mediated transfer of genetic information. Histol Histopathol 25:397–404

Dezso K, Halasz J, Bisgaard HC, Paku S, Turanyi E, Schaff Z, Nagy P (2008) Delta-like protein (DLK) is a novel immunohistochemical marker for human hepatoblastoma. Virchows Arch 452:443–448

Ding YP, Yang XD, Wu Y, Xing CG (2014) Autophagy promotes the survival and development of tumors by participating in the formation of vasculogenic mimicry. Oncol Rep 31:2321–2327

Dong HH, Xiang S, Liang HF, Li CH, Zhang ZW, Chen XP (2013) The niche of hepatic cancer stem cell and cancer recurrence. Med Hypotheses 80:666–668

Fan YZ, Sun W (2010) Molecular regulation of vasculogenic mimicry in tumors and potential tumor-target therapy. World J Gastrointest Surg 2:117–127

Fan L, He F, Liu H, Zhu J, Liu Y, Yin Z, Wang L, Guo Y, Wang Z, Yan Q, Huang G (2011) CD133: a potential indicator for differentiation and prognosis of human cholangiocarcinoma. BMC Cancer 11:320

Fan YL, Zheng M, Tang YL, Liang XH (2013) A new perspective of vasculogenic mimicry: EMT and cancer stem cells (review). Oncol Lett 6(5):1174–1180

Fan QM, Jing YY, Yu GF, Kou XR, Ye F, Gao L, Li R, Zhao QD, Yang Y, Lu ZH, Wei LX (2014) Tumor-associated macrophages promote cancer stem cell-like properties via transforming growth factor-beta1-induced epithelial-mesenchymal transition in hepatocellular carcinoma. Cancer Lett 352:160–168

Fargeas CA, Karbanova J, Jaszai J, Corbeil D (2011) CD133 and membrane microdomains: old facets for future hypotheses. World J Gastroenterol 17:4149–4152

Fausto N, Campbell JS (2003) The role of hepatocytes and oval cells in liver regeneration and repopulation. Mech Dev 120:117–130

Folberg R, Hendrix MJ, Maniotis J (2000) Vasculogenic mimicry and tumor angiogenesis. Am J Pathol 156:361–381

Folberg R, Maniotis AJ (2004) Vasculogenic mimicry. APMIS 112:508–525

Folini M, Gandellini P, Zaffaroni N (2009) Targeting the telosome: therapeutic implications. Biochim Biophys Acta 1792:309–316

Fonsato V, Collino F, Herrera MB, Cavallari C, Deregibus MC, Cisterna B, Bruno S et al (2012) Human liver stem cell-derived microvesicles inhibit hepatoma growth in SCID mice by delivering antitumor microRNAs. Stem Cells 30:1985–1998

Forbes S, Vig P, Poulsom R, Thomas H, Alison M (2002) Hepatic stem cells. J Pathol 197:510–518

French SW, Vitocruz E, French BA (2013) Balloon liver cells forming Mallory-Denk-bodies are progenitor cells. Exp Mol Pathol 95:117–120

Frenkel S, Barzel I, Levy J, Lin AY, Bartsch DU, Majumdar D, Folberg R, Pe'er J (2008) Demonstrating circulation in vasculogenic mimicry patterns of uveal melanoma by confocal indocyanine green angiography. Eye (Lond) 22:948–952

Fujii T, Zen Y, Harada K, Niwa H, Masuda S, Kaizaki Y, Watanabe K, Kawashima A et al (2008) Participation of liver cancer stem/progenitor cells in tumorigenesis of scirrhous hepatocellular carcinoma-human and cell culture study. Hum Pathol 39:1185–1196

Garcia MG, Bayo J, Bolontrade MF, Sganga L, Malvicini M, Alaniz L, Aquino JB, Fiore E et al (2011) Hepatocellular carcinoma cells and their fibrotic microenvironment modulate bone marrow-derived mesenchymal stromal cell migration in vitro and in vivo. Mol Pharm 8:1538–1548

Gardano L, Pucci F, Christian L, Le Bihan T, Harrington L (2013) Telomeres, a busy platform for cell signaling. Front Oncol 3:146

Garnier D, Magnus N, Meehan B, Kislinger T, Rak J (2013) Qualitative changes in the proteome of extracellular vesicles accompanying cancer cell transition to mesenchymal state. Exp Cell Res 319:2747–2757

Gaudio E, Carpino G, Cardinale V, Franchitto A, Onori P, Alvaro D (2009) New insights into liver stem cells. Dig Liver Dis 41:455–462

Gong P, Wang Y, Zhang J, Wang Z (2013a) Bone marrow mesenchymal stem cells in hepatocellular carcinoma. Front Biosc 18:811–819

Gong P, Wang Y, Wang Y, Jin S, Luo H, Zhang J, Bao H, Wang Z (2013b) Effect of bone marrow mesenchymal stem cells on hepatocellular carcinoma in microcirculation. Tumour Biol 34:2161–2168

Grompe M (2005) Bone marrow-derived hepatocytes. Novartis Found Symp 265:20–27

Guarino M, Rubino B, Ballabio G (2007) The role of epithelial-mesenchymal transition in cancer pathology. Pathology 39:305–318

Guest I, Ilic Z, Ma J, Grant D, Glinsky G, Sell S (2010) Direct and indirect contribution of bone marrow derived cells to cancer. Int J Cancer 126:2308–2318

Guo Z, Li LQ, Jiang JH, Ou C, Zeng LX, Xiang BD (2014) Cancer stem cell markers correlate with early recurrence and survival in hepatocellular carcinoma. World J Gastroenterol 20:2098–2106

Gupta DK, Singh N, Sahu DK (2014) TGF-b mediated crosstalk between malignant hepatocyte and tumor microenvironment in hepatocellular carcinoma. Cancer Growth Metastasis 7:1–8

Guzman G, Cotler SJ, Lin AY, Maniotis AJ, Folberg R (2007) A pilot study of vasculogenic mimicry immunohistochemical expression in hepatocellular carcinoma. Arch Pathol Lab Med 131:1776–1781

Hagiwara S, Kudo M, Ueshima K, Chung H, Yamaguchi M, Takita M, Haji S, Kimura M et al (2011) The cancer stem cell marker CD133 is a predictor of the effectiveness of S1+ pegylated interferon a-2b therapy against advanced hepatocellular carcinoma. J Gastroenterol 46:212–221

Han C, Sun B, Wang W, Cai W, Lou D, Sun Y, Zhao X (2011a) Overexpression of microtubule-associated protein-1 light chain 3 is associated with melanoma metastasis and vasculogenic mimicry. Tohoku J Exp Med 223:243–251

Han S, Dziedzic N, Gadue P, Keller GM, Gouon-Evans V (2011b) An endothelial cell niche induces hepatic specification through dual repression of Wnt and Notch signaling. Stem Cells 29:217–228

Hang HL, Xia Q (2014) Role of BMSCs in liver regeneration and metastasis after hepatectomy. World J Gastroenterol 20:126–132

Hardy KM, Kirschmann DA, Seftor EA, Margaryan NV, Postovit LM, Strizzi L, Hendrix MJ (2010) Regulation of the embryonic morphogen Nodal by Notch4 facilitates manifestation of the aggressive melanoma phenotype. Cancer Res 70:10340–10350

He G, Dhar D, Nakagawa H, Font-Burgada J, Ogata H, Jiang Y, Shalapour S, Seki E et al (2013) Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. Cell 155:384–396

Herrera MB, Fonsato V, Gatti S, Deregibus MC, Sordi A, Cantarella D, Calogero R et al (2010) Human liver stem cell-derived microvesicles accelerate hepatic regeneration in hepatectomized rats. J Cell Mol Med 14:1605–1618

Hess AR, Seftor EA, Gardner LM, Carles-Kinch K, Schneider GB, Seftor RE, Kinch MS et al (2001) Molecular regulation of tumor cell vasculogenic mimicry by tyrosine phosphorylation: role of epithelial cell kinase (Eck/EphA2). Cancer Res 61:3250–3255

Hess AR, Margarayan NV, Seftor EA, Hendrix MJ (2007) Deciphering the signaling events that promote melanoma tumor cell vasculogenic mimicry and their link to embryonic vasculogenesis: role of the Eph receptors. Dev Dyn 236:3283–3296

Ho JW, Pang RW, Lau C, Sun CK, Yu WC, Fan ST, Poon RT (2006) Significance of circulating endothelial progenitor cells in hepatocellular carcinoma. Hepatology 44:836–843

Ho DW, Yang ZF, Yi K, Lam CT, Ng MN, Yu WC, Lau J, Wan T, Wang X, Yan Z et al (2012) Gene expression profiling of liver cancer stem cells by RNA-sequencing. PLoS One 7, e37159

Hou Y, Zou Q, Ge R, Shen F, Wang Y (2012) The critical role of CD133(+)CD44(+/high) tumor cells in hematogenous metastasis of liver cancers. Cell Res 22:259–272

Hugo HJ, Kokkinos MI, Blick T, Ackland ML, Thompson EW, Newgreen DF (2011) Defining the E-cadherin repressor interactome in epithelial-mesenchymal

transition: the PMC42 model as a case study. Cells Tissues Organs 193:23–40
Idrissi ME, Hervieu V, Merle P, Mortreux F, Wattel E (2013) Cause-specific telomere factors deregulation in hepatocellular carcinoma. J Exp Clin Cancer Res 32:64
Imrich S, Hachmeister M, Gires O (2012) EpCAM and its potential role in tumor-initiating cells. Cell Adh Migr 6:30–38
Ishikawa T, Banas A, Hagiwara K, Iwaguro H, Ochiya T (2010) Stem cells for hepatic regeneration: the role of adipose tissue derived mesenchymal stem cells. Curr Stem Cell Res Ther 5:182–189
Iwahashi S, Utsunomiya T, Shimada M, Saito Y, Morine Y, Imura S, Ikemoto T, Mori H et al (2013) High expression of cancer stem cell markers in cholangiocellular carcinoma. Surg Today 43:654–660
Ji J, Yamashita T, Budhu A, Forgues M, Jia HL, Li C, Deng C, Wauthier E, Reid LM et al (2009) Identification of microRNA-181 by genome-wide screening as a critical player in EpCAM-positive hepatic cancer stem cells. Hepatology 50:472–480
Ji J, Wang XW (2012) Clinical implications of cancer stem cell biology in hepatocellular carcinoma. Semin Oncol 39:461–472
Jia Y, Liu H, Zhuang Q, Xu S, Yang Z, Li J, Lou J, Zhang W (2012) Tumorigenicity of cancer stem-like cells derived from hepatocarcinoma is regulated by microRNA-145. Oncol Rep 27:1865–1872
Jia SQ, Ren JJ, Dong PD, Meng XK (2013) Probing the hepatic progenitor cell in human hepatocellular carcinoma. Gastroenterol Res Pract. doi:10.1155/2013/145253
Jing Y, Han Z, Liu Y, Sun K, Zhang S, Jiang G, Li R, Gao L, Zhao X, Wu D, Cai X et al (2012) Mesenchymal stem cells in inflammation microenvironment accelerates hepatocellular carcinoma metastasis by inducing epithelial-mesenchymal transition. PLoS One 7, e43372
Kamiya A, Gonzalez FJ, Nakauchi H (2006) Identification and differentiation of hepatic stem cells during liver development. Front Biosci 11:1302–1310
Kamiya A, Inagaki Y (2015) Stem and progenitor cell systems in liver development and regeneration. Hepatol Res 45(1):29–37. doi:10.1111/hepr.12349
Kamohara Y, Haraguchi N, Mimori K, Tanaka F, Inoue H, Mori M, Kanematsu T (2008) The search for cancer stem cells in hepatocellular carcinoma. Surgery 144:119–124
Kappel D, Butter F, Benda C, Scheibe M, Draskovic I, Stevense M, Novo CL, Basquin C et al (2013) HOT1 is a mammalian direct telomere repeat-binding protein contributing to telomerase recruitment. EMBO J 32:1681–1701
Katoonizadeh A, Poustchi H, Malekzadeh R (2014) Hepatic progenitor cells in liver regeneration: current advances and clinical perspectives. Liver Int 34(10): 1464–1472. doi:10.1111/liv.12573
Kim H, Choi GH, Na DC, Ahn EY, Kim GI, Lee JE, Cho JY, Yoo JE, Choi JS et al (2011) Human hepatocellular carcinoms with "stemness"-related marker expression: keratin 19 expression and a poor prognosis. Hepatology 54:1707–1717
Kim SK, Nasu A, Komori J, Shimizu T, Matsumoto Y, Minaki Y, Kohno K, Shimizu K et al (2014) A model of liver carcinogenesis originating from hepatic progenitor cells with accumulation of genetic alterations. Int J Cancer 134:1067–1076
Kirschmann DA, Seftor EA, Hardy KM, Seftor RE, Hendrix MJ (2012) Molecular pathways: vasculogenic mimicry in tumor cells: diagnostic and therapeutic implications. Clin Cancer Res 18:2726–2732
Kitisin K, Pishvaian MJ, Johnson LB, Mishra L (2007) Liver stem cells and molecular signaling pathways in hepatocellular carcinoma. Gastrointest Cancer Res 1(suppl 2):S13–S21
Klenova et al. (2002) Pub Med PMID 12191639
Kohga K, Tasumi T, Takehara T, Tsunematsu H, Shimizu S, Yamamoto M, Sasakawa A et al (2010) Expression of CD133 confers malignant potential by regulating metalloproteinases in human hepatocellular carcinoma. J Hepatol 52:872–879
Kuhlmann WD, Peschke P (2006) Hepatic progenitor cells, stem cells, and AFP expression in models of liver injury. Int J Exp Pathol 87:343–359
Kupcova SH (2013) Proteomic techniques for characterization of mesenchymal stem cell secretome. Biochimie 95:2196–2211
Lai CY, Schwartz BE, Hsu MY (2012) CD133+ melanoma subpopulations contribute to perivascular niche morphogenesis and tumorigenicity through vasculogenic mimicry. Cancer Res 72:5111–5118
Lan X, Wu YZ, Wang Y, Wu FR, Zang CB, Tang C, Cao S, Li SL (2013) CD133 silencing inhibits stemness properties and enhances chemoradiosensitivity in CD133-positive liver cancer stem cells. Int J Mol Med 31:315–324
Lau CK, Yang ZF, Fan ST (2011) Role of stem cells in normal liver and cancer. Anticancer Agents Med Chem 11:522–528
Lee TK, Poon RT, Yuen AP, Ling MT, Kwok WK, Wang XH, Wong YC, Guan XY et al (2006) Twist overexpression correlates with hepatocellular carcinoma metastasis through induction of epithelial-mesenchymal transition. Clin Cancer Res 12:5369–5376
Lee TK, Castilho A, Ma S, Ng IO (2009) Liver cancer stem cells: implications for a new therapeutic target. Liver Int 29:955–965
Lee TH, D'Asti E, Magnus N, Al-Nedawi K, Meehan B, Rak J (2011) Microvesicles as mediators of intracellular communication in cancer-the emerging science of cellular 'debris'. Semin Immunopathol 33:455–467
Lee JI, Lee JW, Kim JM, Kim JK, Chung HJ, Kim YS (2012a) Prognosis of hepatocellular carcinoma expression cytokeratin 19: comparison with other liver cancers. World J Gastroenterol 18:4751–4757
Lee Y, El Andaloussi S, Wood MJ (2012b) Exosomes and microvesicles: extracellular vesicles for genetic

information transfer and gene therapy. Hum Mol Genet 21:R125–R134

Leelawat K, Tongtawee T, Narong S, Subwongcharoen S, Treepongkaruna SA (2011) Strong expression of CD133 is associated with increased cholangiocarcinoma. World J Gastroenterol 17:1192–1198

Lehwald N, Duhme C, Wildner M, Kuhn S, Fürst G, Forbes SJ, Jonas S, Robson SC et al (2014) HGF and SDF-1-mediated mobilization of CD133+ BMSC for hepatic regeneration following extensive liver resection. Liver Int 34:89–101

Li Z (2013) CD133: a stem cell biomarker and beyond. Exp Hematol Oncol 2:17

Li GC, Ye QH, Dong QZ, Ren N, Jia HL, Qin LX (2013) Mesenchymal stem cells seldomly fuse with hepatocellular carcinoma cells and are mainly distributed in the tumor stroma in mouse models. Oncol Rep 29:713–719

Lidprapamomgkol K, Chiablaem K, Sila-Asna M, Surarit R, Bunyaratvej A, Svasti J (2012) Exploring stemness gene expression and vasculogenic mimicry capacity in well- and poorly-differentiated hepatocellular carcinoma cell lines. Biochem Biophys Res Commun 422:429–435

Lin WM, Karsten U, Goletz S, Cheng RC, Cao Y (2011) Expression of CD176 (Thomsen-Friedenreich antigen) on lung, breast and liver cancer-initiating cells. Int J Exp Pathol 92:97–105

Lingala S, Cui YY, Chen X, Ruebner BH, Qian XF, Zern MA, Wu J (2010) Immunohistochemical staining of cancer stem cell markers in hepatocellular carcinoma. Exp Mol Pathol 89:27–35

Lirdprapamongkol K, Chiablaem K, Sila-Asna M, Surarit R, Bunyaratvej A, Svasti J (2012) Exploring stemness gene expression and vasculogenic mimicry capacity in well-and poorly-differentiated hepatocellular carcinoma cell lines. Biochem Biophys Res Commun 422:429–435

Lissitzky JC, Parriaux D, Ristorcelli E, Vérine A, Lombardo D, Verrando P (2009) Cyclic AMP signaling as a mediator of vasculogenic mimicry in aggressive human melanoma cells in vitro. Cancer Res 69:802–809

Liu D, O'Connor MS, Qin J, Songyang Z (2004) Telosome, a mammalian telomere-associated complex formed by multiple telomeric proteins. J Biol Chem 279:51338–51342

Liu LL, Fu D, Ma Y, Shen XZ (2011a) The power and the promise of liver cancer stem cell markers. Stem Cells Dev 20:2023–2030

Liu WB, Xu GL, Jia WD, Li JS, Ma JL, Chen K, Wang ZH, Ge YS, Ren WH et al (2011b) Prognostic significance and mechanisms of patterened matrix vasculogenic mimicry in hepatocellular carcinoma. Med Oncol 28 (suppl 1):S228–S238

Liu W, Xu G, Ma J, Jia W, Li J, Chen K, Wang W, Hao C, Wang Y, Wang X (2011c) Osteopontin as a key mediator for vasculogenic mimicry in hepatocellular carcinoma. Tohoku J Exp Med 224:29–39

Liu J, Huang J, Yao WY, Ben QW, Chen DF, He XY, Li L, Yuan YZ (2012) The origins of vascularization in tumors. Front Biosci 17:2559–2565

Liu S, Li N, Yu X, Xiao X, Cheng K, Hu J, Wang J, Zhang D, Cheng S, Liu S (2013a) Expression of intercellular adhesion molecule 1 by hepatocellular carcinoma stem cells and circulating tumor cells. Gastroenterology 144:1031–1041

Liu J, Ruan B, You N, Huang Q, Liu W, Dang Z, Xu W, Zhou T, Ji R, Cao Y, Li X et al (2013b) Downregulation of miR-200a induces EMT phenotypes and CSC-like signatures through targeting the b-catenin pathway in hepatic oval cells. PLoS One 8, e79409

Liu AY, Cai Y, Mao Y, Lin Y, Zheng H, Wu T, Huang Y, Fang X, Lin S, Feng Q, Huang Z et al (2014) Twist2 promotes self-renewal of liver cancer stem-like cells by regulating CD24. Carcinogenesis 35:537–545

Low KC, Tergaonkar V (2013) Telomerase: central regulator of all of the hallmarks of cancer. Trends Biochem Sci 38:426–434

Loukinov et al. (2002) Pub Med PMID 12011441

Ma S, Chan KW, Hu L, Lee TK, Wo JY, Ng IO, Zheng BJ, Guan XY (2007) Identification and characterization of tumorigenic liver cancer stem/progenitor cells. Gastroenterology 132:2542–2556

Ma S, Lee TK, Zheng BJ, Chan KW, Guan XY (2008) CD133+ HCC cancer stem cells confer chemoresistance by preferential expression of the Akt/PKB survival pathway. Oncogene 27:1749–1758

Ma S, Tang KH, Chan YP, Lee TK, Kwan PS, Castilho A, Ng I, Man K, Wong N et al (2010) miR-130b promotes CD133(+) liver tumor-initiating cell growth and self-renewal via tumor protein 53-induced nuclear protein 1. Cell Stem Cell 7:694–707

Ma JL, Han SX, Zhu Q, Zhao J, Zhang D, Wang L, Lv Y (2011) Role of twist in vasculogenic mimicry formation in hypoxic hepatocellular carcinoma cells in vitro. Biochem Biophys Res Commun 408:686–691

Ma S (2013) Biology and clinical implications of CD133(+) liver cancer stem cells. Exp Cell Res 319:126–132

Ma YC, Yang JY, Yan LN (2013) Relevant markers of cancer stem cells indicate a poor prognosis in hepatocellular carcinoma patients: a meta-analysis. Eur J Gastroenterol Hepatol 25:1007–1016

Machida K, Feldman DE, Tsukamoto H (2015) TLR4-dependent tumor-initiating stem cell-like cells (TICs) in alcohol-associated hepatocellular carcinogenesis. Adv Exp Med Biol 815:131–144

Majumdar A, Curley SA, Wu X, Brown P, Hwang JP, Shetty K, Yao ZX, He AR et al (2012) Hepatic stem cells and transforming growth factor b in hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 9:530–538

Mak AB, Blakely KM, Williams RA, Penttilä PA, Shukalyuk AI, Osman KT, Kasimer D et al (2011) CD133 protein N-glycosylation processing contributes to cell surface recognition of the primitive cell marker AC133 epitope. J Biol Chem 286:41046–41056

Maniotis AJ, Folberg R, Hess A, Seftor EA, Gardner LM, Pe'er J, Trent JM, Meltzer PS et al (1999) Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry. Am J Pathol 155:739–752

Mansuroglu T, Baumhoer D, Dudas J, Haller F, Cameron S, Lorf T, Füzesi L, Ramadori G (2009) Expression of stem cell factor receptor c-kit in human nontumoral and tumoral hepatic cells. Eur J Gastroenterol Hepatol 21:1206–1211

Marquardt JU, Thorgeirsson SS (2010) Stem cells in hepatocarcinogenesis: evidence from genomic data. Semin Liver Dis 30:26–34

Martin-Padura I, Marighetti P, Agliano A, Colombo F, Larzabal L, Redrado M, Bleau AM et al (2012) Residual dormant cancer stem-cell foci are responsible for tumor relapse after antiangiogenic metronomic therapy in hepatocellular carcinoma xenografts. Lab Invest 92:952–966

Matsuo N, Shiraha H, Fujikawa T, Takaoka N, Ueda N, Tanaka S, Nishina S, Nakanishi Y et al (2009) Twist expression promotes migration and invasion in hepatocellular carcinoma. BMC Cancer 9:240

McAllister JC, Zhan Q, Weishaupt C, Hsu MY, Murphy GF (2010) The embryonic morphogen, Nodal, is associated with channel-like structures in human malignant melanoma xenografts. J Cutan Pathol 37(Suppl1): 19–25

Meacham C.E. and Morrison S.J. (2013). Tumour heterogeneity and cancer cell plasticity.Nature 501, 328–337

Melero-Martin JM, Dudley AC (2011) Concise review: vascular stem cells and tumor angiogenesis. Stem Cells 29:163–168

Mishra L, Banker T, Murray J, Byers S, Thenappan A, He AR, Shetty K, Johnson L et al (2009) Liver stem cells and hepatocellular carcinoma. Hepatology 49:318–329

Mizrak D, Brittan M, Allison MR (2008) CD133: molecule of the moment. J Pathol 214:3–9

Mokarizadeh A, Rezvanfar MA, Dorostkar A, Abdollahi M (2013) Mesenchymal stem cell derived microvesicles: trophic shuttles for enhancement of sperm quality parameters. Reprod Toxicol 42C:78–84

Moriyama T, Ohuchida K, Mizumoto K, Cui L, Ikenaga N, Sato N, Tanaka M (2010) Enhanced cell migration and invasion of CD133+ pancreatic cancer cells cocultured with pancreatic stromal cells. Cancer 116:3357–3368

Muralidharan-Chari V, Clancy JW, Sedgwik A, D'Souza-Schorey C (2010) Microvesicles: mediators of extracellular communication during cancer progression. J Cell Sci 123:1603–1611

Muramatsu S, Tanaka S, Mogushi K, Adikrisna R, Aihara A, Ban D, Ochiai T, Irie T et al (2013) Visualization of stem cell features in human hepatocellular carcinoma reveals in vivo significance of tumor-host interaction and clinical course. Hepatology 58:218–228

Na DC, Lee JE, Yoo JE, Oh BK, Choi GH, Park YN (2011) Invasion and EMT-associated genes are up-regulated in B viral hepatocellular carcinoma with high expression of CD133-human and cell culture study. Exp Mol Pathol 90:66–73

Nakagawa H, Hikiba Y, Hirata Y, Font-Burgada J, Sakamoto K, Hayakawa Y, Taniguchi K et al (2014) Loss of liver E-cadherin induces sclerosing cholangitis and promotes carcinogenesis. Proc Natl Acad Sci U S A 111:1090–1095

Nakayama M, Ogasawara S, Akiba J, Ueda K, Koura K, Todoroki K, Kinoshita H, Yano H (2014) Side population cell fractions from hepatocellular carcinoma cell lines increased with tumor dedifferentiation, but lack characteristic features of cancer stem cells. J Gastroenterol Hepatol 29:1092–1101

Navarro-Alvarez N, Soto-Gutierrez A, Kobayashi N (2010) Hepatic stem cells and liver development. Methods Mol Biol 640:181–236

Nejak-Bowen KN, Monga SP (2011) Beta-catenin signaling, liver regeneration and hepatocellular cancer: sorting the good from the bad. Semin Cancer Biol 21:44–58

Nishina H (2012) hDlk-1: a cell surface marker common to normal hepatic stem/progenitor cells and carcinomas. J Biochem 152:121–123

Oh SH, Witek RP, Bae SH, Zheng D, Jung Y, Piscaglia AC, Petersen BE (2007) Bone marrow-derived hepatic oval cells differentiate into hepatocytes in 2-acetylfluorene/partial hepatectomy-induced liver regeneration. Gastroenterology 132:1077–1087

Ohnishi S, Maehara O, Nakagawa K, Kameya A, Otaki K, Fujita H, Higashi R, Takagi K et al (2013) Hypoxia-inducible factors activate CD133 promoter through ETS family transcription factors. PLoS One 8, e66255

Oikawa T, Kamiya A, Zeniya M, Chikada H, Hyuck AD, Yamazaki Y, Wauthier E, Tajiri H et al (2013) Sal-like protein 4 (SALL4), a stem cell biomarker in liver cancers. Hepatology 57:1469–1483

Oishi N, Yamashita T, Kaneko S (2014) Molecular biology of liver cancer stem cells. Liver Cancer 3:71–84

Oliva J, French BA, Qing X, French SW (2010) The identification of stem cells in human liver diseases and hepatocellular carcinoma. Exp Mol Pathol 88:331–340

Palm W, de Lange T (2008) How shelterin protects mammalian telomeres. Annu Rev Genet 42:301–334

Pang RW, Poon RT (2012) Cancer stem cell as a potential therapeutic target in hepatocellular carcinoma. Curr Cancer Drug Targets 12:1081–1094

Pap E (2011) The role of microvesicles in malignancies. Adv Exp Med Biol 714:183–199

Papp V, Rokusz A, Dezsö K, Bugyik E, Szabo V, Pavai Z, Paku S, Nagy P (2014) Expansion of hepatic stem cell compartment boosts liver regeneration. Stem Cells Dev 23:56–65

Park JR, Kim RJ, Lee YK, Kim SR, Roh KJ, Oh SH, Kong G, Kang KS, Nam JS (2011) Dysadherin can enhance tumorigenesis by conferring properties of stem-like cells to hepatocellular carcinoma cells. J Hepatol 54:122–131

Parveen N, Aleem AK, Habeeb MA, Habibullah CM (2011) An update on hepatic stem cells: bench to bedside. Curr Pharm Biotechnol 12:226–230

Paulis YW, Soetekouw PM, Verheul HM, Tjan-heijnen VC, Griffoen AW (2010) Signalling pathways in vasculogenic mimicry. Biochim Biophys Acta 1806:18–28

Petersen BE, Bowen WC, Patrene KD, Mars WM, Sullivan AK, Murase N, Boggs SS et al (1999) Bone marrow as a potential source of hepatic oval cells. Science 284:1168–1170

Piao LS, Hur W, Kim TK, Hong SW, Kim SW, Choi JE, Sung PS, Song MJ, Lee BC et al (2012) CD133(+) liver cancer stem cells modulate radioresistance in human hepatocellular carcinoma. Cancer Lett 315:129–137

Ping YF, Bian XW (2011) Concise review: contribution of cancer stem cells to neovascularization. Stem Cells 29:888–894

Qi W, Liang W, Jiang H, Miuyee WM (2013) The function of miRNA in hepatic cancer stem cell. Biomed Res Int 2013:358902

Quesenberry PJ, Aliotta JM (2010) Cellular phenotype switching and microvesicles. Adv Drug Deliv Rev 62:1141–1148

Quesenberry PJ, Dooner MS, Goldberg LR, Aliotta JM, Pereira M, Amaral A, Del Tatto MM et al (2012) A new stem cell biology: the continuum and microvesicles. Trans Am Clin Climatol Assoc 123:152–166

Rappa G, Mercapide J, Anzanello F, Pope RM, Lorico A (2013) Biochemical and biological characterization of exosomes containing prominin-1/CD133. Mol Cancer 12:62

Reagan MR, Kaplan DL (2011) Concise review: mesenchymal stem cell tumor-homing: detection methods in disease model systems. Stem Cells 29:920–927

Rodrigo-Torres D, Affo S, Coll M, Morales-Ibanez O, Millan C, Blaya D, Alvarez-Guaita A et al (2014) The biliary epithelium gives rise to liver progenitor cells. Hepatology 60(4):1367–1377. doi:10.1002/hep.27078

Rodriguez RM, Fernandez AF, Fraga MF (2013) Role of sirtuins in stem cell differentiation. Genes Cancer 4:105–111

Rosa-Garrido M, Ceballos L, Alonso-Lecue P, Abraira C, Delgado MD, Gandarillas A (2012) A cell cycle role for the epigenetic factor CTCF-L/BORIS. PLoS One 7, e39371

Rountree CB, Ding W, Dang H, Vankirk C, Crooks GM (2011) Isolation of CD133+ liver stem cells for clonal expansion. J Vis Exp 56:3183

Rountree CB, Mishra L, Willenbring H (2012) Stem cells in liver diseases and cancer: recent advances on the path to new therapies. Hepatology 55:298–306

Saeed H, Iqtedar M (2013) Stem cell function and maintenance – ends that matter: role of telomeres and telomerase. J Biosc 38:641–649

Sainz B, Heeschen C (2013) Standing out from the crowd: cancer stem cells in hepatocellular carcinoma. Cancer Cell 23:431–433, Cancer Lett 275:185–193

Sangan CB, Tosh D (2010) Hepatic progenitor cells. Cell Tissue Res 342:131–137

Sasaki A, Kamiyama T, Yokoo H, Nakanishi K, Kubota K, Haga H, Matsushita M, Ozaki M et al (2010) Cytoplasmic expression of CD133 is an important risk factor for overall survival in hepatocellular carcinoma. Oncol Rep 24:537–546

Seftor RE, Hess AR, Seftor EA, Kirschmann DA, Hardy KM, Margaryan NV, Hendrix MJ (2012) Tumor cell vasculogenic mimicry: from controversy to therapeutic promise. Am J Pathol 181:1115–1125

Sell S (1993) The role of determined stem-cells in the cellular lineage of hepatocellular carcinoma. Int J Dev Biol 37:189–201

Sell S (2008) Alpha-fetoprotein, stem cells and cancer: how study of the production of alpha-fetoprotein during chemical hepatocarcinogenesis led to reaffirmation of the stem cell theory of cancer. Tumour Biol 29:161–180

Sell S, Leffert HL (2008) Liver cancer stem cells. J Clin Oncol 26:2800–2805

Shan J, Shen J, Liu L, Xia F, Xu C, Duan G, Xu Y, Ma Q, Yang Z, Zhang Q, Ma L et al (2012) Nanog regulates self-renewal of cancer stem cells through the insulin-like growth factor pathway in human hepatocellular carcinoma. Hepatology 56:1004–1014

Sharma AD, Cantz T, Manns MP, Ott M (2006) The role of stem cells in physiology, pathophysiology, and therapy of the liver. Stem Cell Rev 2:51–58

Shen Y, Cao D (2012) Hepatocellular carcinoma stem cells: origins and roles in hepatocarcinogenesis and disease progression. Front Biosc (Elide Ed) 4:1157–1169

Shi C, Tian R, Wang M, Wang X, Jiang J, Zhang Z, Li X, He Z, Gong W, Qin R (2010) CD44+ CD133+ population exhibits cancer stem cell-like characteristics in human gallbladder carcinoma. Cancer Biol Ther 10:1182–1190

Shih YT, Wang MC, Zhou J, Peng HH, Lee DY, Chiu JJ (2014) Endothelial progenitors promote hepatocarcinoma intrahepatic metastasis through monocyte chemotactic protein-1 induction of microRNA-21. Gut 64(7):1132–1147. doi:10.1136/gutjnl-2013-306302

Shin D, Monga SP (2013) Cellular and molecular basis of liver development. Comp Physiol 3:799–815

Shupe T, Petersen BE (2005) Evidence regarding a stem cell origin of hepatocellular carcinoma. Stem Cell Rev 1:261–264

Song W, Li H, Tao K, Li R, Song Z, Zhao Q, Zhang F, Dou K (2008) Expression and clinical significance of the stem cell marker CD133 in hepatocellular carcinoma. Int J Clin Pract 62:1212–1218

Song YJ, Zhang SS, Guo XL, Sun K, Han ZP, Li R, Zhao QD, Deng WJ, Xie XQ et al (2013) Autophagy contributes to the survival of CD133+ liver cancer stem cells in the hypoxic and nutrient-deprived tumor microenvironment. Cancer Lett 339:70–81

Stock P, Brückner S, Winkler S, Dollinger MM, Christ B (2014) Human bone marrow mesenchymal stem cell-derived hepatocytes improve the mouse liver after acute acetaminophen intoxication by preventing progress of injury. Int J Mol Sci 15:7004–7028

Strain AJ, Crosby HA, Nijar S, Kelly DA, Hubscher SG (2003) Human liver-derived stem cells. Semin Liver Dis 23:373–384

Su F, Li B, Wang J, Xu X, Ren R, Li L, Gao F, Liu X (2009) Molecular regulation of vasculogenic mimicry in human uveal melanoma cells: role of helix-loop-helix ld2 (inhibitor of DANN binding 2). Graefes Arch Clin Exp Ophthalmol 247:411–419

Suetsugu A, Nagaki M, Aoki H, Motohashi T, Kunisada T, Moriwaki H (2006) Characterization of CD133+ hepatocellular carcinoma cells as cancer stem/progenitor cells. Biochem Biophys Res Commun 351:820–824

Suetsugu A, Osawa Y, Nagaki M, Moriwaki H, Saji S, Bouvet M, Hoffman RM (2010) Simultaneous color-coded imaging to distinguish cancer "stem-like" and non-stem cells in the same tumor. J Cell Biochem 111:1035–1041

Sukowati CH, Tiribelli C (2013) The biological implication of cancer stem cells in hepatocellular carcinoma: a possible target for future therapy. Expert Rev Gastroenterol Hepatol 7:749–757

Sun B, Zhang S, Zhang D, Du J, Guo H, Zhao X, Zhang W, Hao X (2006) Vasculogenic mimicry is associated with high tumor grade, invasion and metastasis, and short survival in patients with hepatocellular carcinoma. Oncol Rep 16:693–698

Sun B, Zhang D, Zhang S, Zhang W, Guo H, Zhao X (2007) Hypoxia influences vasculogenic mimicry channel formation and tumor invasion-related expression in melanoma. Cancer Lett 249:188–197

Sun T, Zhao N, Zhao XL, Gu Q, Zhang SW, Che N, Wang XH, Du J, Liu YX, Sun BC (2010) Expression and functional significance of Twist1 in hepatocellular carcinoma: its role in vasculogenic mimicry. Hepatology 51:545–556

Sun T, Sun BC, Zhao XL, Zhao N, Dong XY, Che N, Yao Z, Ma YM, Gu Q, Zong WK et al (2011) Promotion of tumor cell metastasis and vasculogenic mimicry by way of transcription coactivation by Bcl-2 and Twist1: a study of hepatocellular carcinoma. Hepatology 54:1690–1706

Sun XT, Yuan XW, Zhu HT, Deng ZM, Yu DC, Zhou X, Ding YT (2012) Endothelial precursor cells promote angiogenesis in hepatocellular carcinoma. World J Gastroenterol 18:4925–4933

Sun C, Sun L, Jiang K, Gao DM, Kang XN, Wang C, Zhang S, Huang S, Qin X, Li Y et al (2013a) NANOG promotes liver cancer cell invasion by inducing epithelial-mesenchymal transition through NODAL/SMAD3 signaling pathway. Int J Biochem Cell Biol 45:1099–1108

Sun D, Sun B, Liu T, Zhao X, Che N, Gu Q, Dong X, Yao Z, Li R, Li J, Chi J, Sun R (2013b) Slug promoted vasculogenic mimicry in hepatocellular carcinoma. J Cell Mol Med 17:1038–1047

Tang KH, Ma S, Lee TK, Chan YP, Kwan PS, Tong CM, Ng IO, Man K, To KF et al (2012) CD133(+) liver tumor-initiating cells promote tumor angiogenesis, growth, and self-renewal through neurotensin/interleukin-8/CXCL1 signaling. Hepatology 55:807–820

Tang J, Tao ZH, Wen D, Wan JL, Liu DL, Zhang S, Cui JF, Sun HC, Wang L, Zhou J et al (2014) miR-612 suppresses the stemness of liver cancer via Wnt/b-catenin signaling. Biochem Biophys Res Commun 447:210–215

Terris B, Cavard C, Perret C (2010) EpCAM, a new marker for cancer stem cells in hepatocellular carcinoma. J Hepatol 52:280–281

Teufel A, Galle PR (2010) Collecting evidence for a stem cell hypothesis in HCC. Gut 59:870–871

Tiffen JC, Bailey CG, Marshall AD, Metierre C, Feng Y, Wang Q, Watson SL, Holst J et al (2013) The cancer-testis antigen BORIS phenocopies the tumor suppressor CTCF in normal and neoplastic cells. Int J Cancer 133:1603–1613

Tomuleasa C, Soritau O, Rus-Ciuca D, Pop T, Todea D, Mosteanu O, Pintea B, Foris V et al (2010) Isolation and characterization of hepatic cancer cells with stem-like properties from hepatocellular carcinoma. J Gastrointestin Liver Dis 19:61–67

Tong CM, Ma S, Guan XY (2011) Biology of hepatic cancer stem cells. J Gastroenterol Hepatol 26:1229–1237

Toshima T, Yoshizumi T, Uchiyama H, Ikegami T, Soejima Y, Ikeda T, Kawanaka H et al (2013) Effect of Cd133-positive stem cells in repeated recurrence of hepatocellular carcinoma after liver transplantation: a case report. Fukuoka Igaku Zasshi 104:383–388

Tsai ST, Tsou CC, Mao WY, Chang WC, Han HY, Hsu WL, Li CL, Shen CN et al (2012) Label-free quantitative proteomics of CD133-positive liver cancer stem cells. Proteome Sci 10:69

Tsuchiya A, Kamimura H, Tamura Y, Takamura M, Yamagiwa S, Suda T, Nomoto M et al (2011) Hepatocellular carcinoma with progenitor cell features distinguishable by the hepatic stem/progenitor cell marker NCAM. Cancer Lett 309:95–103

Valyi-Nagy K, Kormos B, Ali M, Shukla D, Valyi-Nagy T (2012) Stem cell marker CD271 is expressed by vasculogenic mimicry-forming uveal melanoma cells in three-dimensional cultures. Mol Vis 18:588–592

Vartanian A, Gatsina G, Grigorieva I, Solomko E, Dombrovsky V, Baryshnikov A, Stepanova E (2013) The involvement of Notch signaling in melanoma vasculogenic mimicry. Clin Exp Med 13:201–209

Vessey CJ, de la Hall PM (2001) Hepatic stem cells: a review. Pathology 33:130–141

Vestentoft PS (2013) Development and molecular composition of the hepatic progenitor cell niche. Dan Med J 60:B4640

Wang B, Jacob ST (2011) Role of cancer stem cells in hepatocarcino-genesis. Genome Med 3:11

Wang H, Chen L (2013) Tumor microenvironment and hepatocellular carcinoma metastasis. J Gastroenterol Hepatol 28(suppl 1):43–48

Wang L, Guo ZY, Zhang R, Xin B, Chen R, Zhao J, Wang T, Wen WH, Jia LT, Yao LB et al (2013)

Pseudogene OCT4-pg4 functions as a natural micro RNA sponge to regulate OCT4 expression by competing for miR-145 in hepatocellular carcinoma. Carcinogenesis 34:773–781

Wang F, Yuan JH, Wang SB, Yang F, Yuan SX, Ye C, Yang N, Zhou WP, Li WL, Li W, Sun SH (2014) Oncofetal long noncoding RNA PVT1 promotes proliferation and stem cell-like property of hepatocellular carcinoma cells by stabilizing NOP2. Hepatology 60:1278–1290

Wells RG (2014) The portal fibroblast – Not just a poor man's stellate cell. Gastroenterology 147(1):41–47. doi:10.1053/j.gastro.2014.05.001

Woo HG, Wang XW, Budhu A, Kim YH, Kwon SM, Tang ZY, Sun Z, Harris CC et al (2011) Association of TP53 mutations with stem cell-like gene expression and survival of patients with hepatocellular carcinoma. Gastroenterology 140:1063–1070

Wu XZ, Chen D (2006) Origin of hepatocellular carcinoma: role of stem cells. J Gastroenterol Hepatol 21:1093–1098

Wu Y, Wu PY (2009) CD133 as a marker for cancer stem cells: progresses and concerns. Stem Cells Dev 18:1127–1134

Wu KJ, Yang MH (2011) Epithelial-mesenchymal transition and cancer stemness: the Twist1-Bmi1 connection. Biosci Rep 31:449–455

Wu K, Ding J, Chen C, Sun W, Ning BF, Wen W, Huang L, Han T, Yang W, Wang C et al (2012) Hepatic transforming growth factor beta gives rise to tumor-initiating cells and promotes liver cancer development. Hepatology 56:2255–2267

Xin H, Liu D, Songyang Z (2008) The telosome/shelterin complex and its functions. Genome Biol 9:232

Xiong W, Sun LP, Chen XM, Li HY, Huang SA, Jie SH (2013) Comparison of microRNA expression profiles in HCC-derived microvesicles and the parental cells and evaluation of their roles in HCC. J Huazhong Univ Sci Technolog Med Sci 33:346–352

Xu XL, Xing BC, Han HB, Zhao W, Hu MH, Xu ZL, Li JY, Xie Y, Gu J, Wang Y et al (2010a) The properties of tumor-initiating cells from a hepatocellular carcinoma patient's primary and recurrent tumor. Carcinogenesis 31:167–174

Xu X, Xing B, Hu M, Xu Z, Xie Y, Dai G, Gu J, Wang Y, Zhang Z (2010b) Recurrent hepatocellular carcinoma cells with stem cell-like properties: possible targets for immunotherapy. Cytotherapy 12:190–200

Xu Y, Xie Y, Wang X, Chen X, Liu Q, Ying M, Zheng Q (2013) Identification of cancer stem cells from hepatocellular carcinoma cell lines and their related microRNAs. Oncol Rep 30:2056–2062

Xue X, Zhang Y, Zhi Q, Tu M, Xu Y, Sun J, Wei J, Lu Z, Miao Y, Gao W (2014) MiR200-upregulated vasohibin 2 promotes the malignant transformation of tumors by inducing epithelial-mesenchymal transition in hepatocellular carcinoma. Cell Commun Signal 12:62

Yamashita T, Ji J, Budhu A, Forgues M, Yang W, Wang HY, Jia H, Ye Q, Qin LX et al (2009) EpCAM-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/progenitor cell features. Gastroenterology 136:1012–1024

Yamashita T, Wang XW (2013) Cancer stem cells in the development of liver cancer. J Clin Invest 123:1911–1918

Yamashita T, Honda M, Nakamoto Y, Baba M, Nio K, Hara Y, Zeng SS, Hayashi T et al (2013) Discrete nature of EpCAM+ and CD90+ cancer stem cells in human hepatocellular carcinoma. Hepatology 57:1484–1497

Yamashita T, Kaneko S (2014) Orchestration of hepatocellular carcinoma development by diverse liver cancer stem cells. J Gastroenterol 49:1105–1110

Yan H, Dong X, Zhong X, Ye J, Zhou Y, Yang X, Shen J, Zhang J (2013) Inhibitions of epithelial to mesenchymal transition and cancer stem cells-like properties are involved in miR-148a-mediated anti-metastasis of hepatocellular carcinoma. Mol Carcinog 53(12): 960–969. doi:10.1002/mc.22064

Yanai H, Nakamura K, Hijoka S, Kamei A, Ikari T, Ishikawa Y, Shinozaki E, Mizunuma N et al (2010) Dlk-1, a cell surface antigen on fetal hepatic stem/progenitor cells, is expressed in hepatocellular, colon, pancreas and breast carcinomas at a high frequency. J Biochem 148:85–92

Yang W, Yan HX, Chen L, Liu Q, He YQ, Yu LX, Zhang SH, Huang DD, Tang L et al (2008) Wnt/beta-catenin signaling contributes to activation of normal and tumorigenic liver progenitor cells. Cancer Res 68:4287–4295

Yang ZF, Poon RT (2008) Vascular changes in hepatocellular carcinoma. Anat Rec (Hoboken) 291:721–734

Yang XR, Xu Y, Yu B, Zhou J, Qiu SJ, Shi GM, Zhang BH, Wu WZ, Shi YH, Wu B et al (2010) High expression levels of putative hepatic stem/progenitor cell biomarkers related to tumour angiogenesis and poor prognosis of hepatocellular carcinoma. Gut 59:953–962

Yang W, Wang C, Lin Y, Liu Q, Yu LX, Tang L, Yan HX, Fu J, Chen Y, Zhang HL et al (2012) OV6+ tumor-initiating cells contribute to tumor progression and invasion in human hepatocellular carcinoma. J Hepatol 57:613–620

Yao Z, Mishra L (2009) Cancer stem cells and hepatocellular carcinoma. Cancer Biol Ther 8:1691–1698

Yao XH, Ping YF, Bian XW (2011) Contribution of cancer stem cells to tumor vasculogenic mimicry. Protein Cell 2:266–272

Ye J, Wu Y, Gilson E (2010) Dynamics of telomeric chromatin at the crossroads of aging and cancer. Essays Biochem 48:147–164

Yeh CT, Kuo CJ, Lai MW, Chen TC, Lin CY, Yeh TS, Lee WC (2009) CD133-positive hepatocellular carcinoma in an area endemic for hepatitis B virus infection. BMC Cancer 9:324

Yi SY, Nan KJ (2008) Tumor-initiating stem cells in liver cancer. Cancer Biol Ther 7:325–330

Yin S, Li J, Hu C, Chen X, Yao M, Yan M, Jiang G, Ge C, Xie H, Wan D, Yang S et al (2007) CD133 positive

hepatocellular carcinoma cells possess high capacity for tumorigenicity. Int J Cancer 120:1444–1450
Yin C, Evason KJ, Asahina K, Stainier DY (2013) Hepatic stellate cells in liver development, regeneration, and cancer. J Clin Invest 123:1902–1910
Yong KJ, Gao C, Lim JS, Yan B, Yang H, Dimitrov T, Kawasaki A, Ong CW, Wong KF et al (2013) Oncofetal gene SALL4 in aggressive hepatocellular carcinoma. N Engl J Med 368:2266–2276
Yoon SK (2012) The biology of cancer stem cells and its clinical implication in hepatocellular carcinoma. Gut Liver 6:29–40
Yoshikawa S, Zen Y, Fukii T, Sato Y, Ohta T, Aoyagi Y, Nakanuma Y (2009) Characterization of CD133+ parenchymal cells in the liver: histology and culture. World J Gastroenterol 15:4896–4906
You H, Ding W, Rountree CB (2010) Epigenetic regulation of cancer stem cell marker CD133 by transforming growth factor-beta. Hepatology 51:1635–1644
Yu DC, Chen J, Sun XT, Zhuang LY, Jiang CP, Ding YT (2010a) Mechanism of endothelial progenitor cell recruitment into neo-vessels in adjacent non-tumor tissues in hepatocellular carcinoma. BMC Cancer 10:435
Yu DC, Chen J, Ding YT (2010b) Hypoxic and highly angiogenic non-tumor tissues surrounding hepatocellular carcinoma: the 'niche' of endothelial progenitor cells. Int J Mol Sci 11:2901–2909
Yu XH, Xu LB, Liu C, Zhang R, Wang J (2011) Clinicopathologic characteristics of 20 cases of hepatocellular carcinoma with bile duct tumor thrombi. Dig Dis Sci 56:252–259
Yu G, Jing Y, Kou X, Ye F, Gao L, Fan Q, Yang Y, Zhao Q, Li R, Wu M, Wei L (2013a) Hepatic stellate cells secreted hepatocyte growth factor contributes to the chemoresistance of hepatocellular carcinoma. PLoS One 8, e73312
Yu B, He ZY, You P, Han QW, Xiang D, Chen F, Wang MJ, Liu CC, Lin XW, Borjigin U et al (2013b) Reprogramming fibroblasts into bipotential hepatic stem cells by defined factors. Cell Stem Cell 13:328–340
Yuan A, Farber EL, Rapoport AL, Tejada D, Deniskin R, Akhmeddov NB, Farber DB (2009) Transfer of microRNAs by embryonic stem cell microvesicles. PLoS One 4, e4722
Yun WJ, Shin E, Lee K, Jung HY, Kim SH, Park YN, Yu E, Jang JJ (2013) Clinicopathologic implication of hepatic progenitor cell marker expression in hepatoblastoma. Pathol Res Pract 209:568–573
Zenali MJ, Tan D, Li W, Dhingra S, Brown RE (2010) Stemness characteristics of fibrolamellar hepatocellular carcinoma: immunohistochemical analysis with comparisons to comparisons to conventional hepatocellular carcinoma. Ann Clin Lab Sci 40:126–134
Zhai JM, Yin XY, Hou X, Hao XY, Cai P, Liang LJ, Zhang LJ (2013) Analysis of the genome-wide DNA methylation profile of side population cells in hepatocellular carcinoma. Dig Dis Sci 58:1934–1947
Zhang A, London R, Schulz FM, Giguère-Simmonds PW, Delriviere L, Chandraratana H et al (2010) Human liver progenitor cell lines are readily established from non-tumorous tissue adjacent to hepatocellular carcinoma. Stem Cells Dev 19:1277–1284
Zhang J, Luo N, Luo Y, Peng Z, Zhang T, Li S (2012) microRNA-150 inhibits human CD133-positive liver cancer stem cells through negative regulation of the transcription factor c-Myb. Int J Oncol 40:747–756
Zhang C, Xu Y, Zhao J, Fan L, Jiang G, Li R, Ling Y, Wu M, Wie L (2011) Elevated expression of the stem cell marker CD133 associated with Line-1 demethylation in hepatocellular carcinoma. Ann Surg Oncol 18:2373–2380
Zhao XL, Du J, Zhang SW, Liu XY, Wang X, Sun BC (2006) A study on vasculogenic mimicry in hepatocellular carcinoma (in Chinese). Zhonghua Gan Zang Bing Za Zhi 14:41–44
Zhao J, Huang JS, Yang AJ, Wang CY, Liu W, Li M (2007) Three-dimension cell culture and histology of vasculogenic mimicry in hepatocellular carcinoma (in Chinese). Ai Zheng 26:123–126
Zhao N, Sun BC, Sun T, Ma YM, Zhao XL, Liu ZY, Dong XY, Che N, Mo J, Gu Q (2012) Hypoxia-induced vasculogenic mimicry formation via VE-cadherin regulation by Bcl-2. Med Oncol 29:3599–3607
Zheng YW, Taniguchi H (2003) Diversity of hepatic stem cells in the fetal and adult liver. Semin Liver Dis 23:337–348
Zheng T, Wang J, Jiang H, Liu L (2011) Hippo signaling in oval cells and hepatocercinogenesis. Cancer Lett 302:91–99
Zheng YW, Nie YZ, Taniguchi H (2013) Cellular reprogramming and hepatocellular carcinoma development. World J Gastroenterol 19:8850–8860
Zhou L, Yang ZX, Song WJ, Li QJ, Yang F, Wang DS, Zhang N, Dou KF (2013) MicroRNA-21 regulates the migration and invasion of a stem-like population in hepatocellular carcinoma. Int J Oncol 43:661–669
Zhu Z, Hao X, Yan M, Yao M, Ge C, Gu J, Li J (2010) Cancer stem/progenitor cells are highly enriched in CD133+ CD44+ population in hepatocellular carcinoma. Int J Cancer 126:2067–2078
Zhu H, Shao Q, Sun X, Deng Z, Yuan X, Yu D, Zhou X, Ding Y (2012a) The mobilization, recruitment and contribution of bone marrow-derived endothelial progenitor cells to the tumor neovascularization occur at an early stage and throughout the entire process of hepatocellular carcinoma growth. Oncol Rep 28:1217–1224
Zhu H, Shao Q, Sun X, Deng Z, Yuan X, Zhou X, Ding Y (2012b) Bone marrow cells: important role on neovascularization of hepatocellular carcinoma. J Gastroenterol Hepatol 27:1241–1251
Zimmermann A (2005) The emerging family of hepatoblastoma tumours: from ontogenesis to oncogenesis. Eur J Cancer 41:1503–1514
Zou GM (2008) Cancer initiating cells or cancer stem cells in the gastrointestinal tract and liver. J Cell Physiol 217:598–604

Hepatocellular Carcinoma (Ordinary Hepatocellular Carcinoma)

2

ICD-O code 8170/3

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_2

Abstract

Hepatocellular carcinoma (HCC) is a malignant neoplasm composed of cells with a hepatocellular differentiation. Most HCCs exhibit a trabecular and/or acinar histologic pattern (ordinary or classical HCC), but there also exist numerous variants with a different morphology and a fibrolamellar variant treated in a separate chapter. HCC is a frequent malignancy and is estimated to be the fifth most common malignancy in males worldwide. Most of the tumors arise in patients with liver cirrhosis caused by various etiologies, hepatitis virus infections, and toxic agents playing a central role. HCC displays specific macroscopic growth patterns. Eggel divided the neoplasms in nodular, massive, and diffuse types, nodular HCC being the most common. This classification has subsequently been extended and refined. HCC frequently invades large and small hepatic vessels and bile ducts, causing distinct clinical disorders. Histologically, hepatocyte-like cells arranged in large plates with an abnormal reticulin pattern and loss of Kupffer cells are the hallmarks of trabecular HCC, whereas pseudoglandular structures are found in other tumors. The grading of HCC has been standardized and is an important prognosticator. Morphological classifications of HCC are currently extended by the use of molecular signatures of these neoplasms.

Introduction

Hepatocellular carcinoma (HCC) is a malignant neoplasm composed of cells with a hepatocellular differentiation. The majority of HCC shows trabecular and/or pseudoglandular/acinar patterns that consist of a hepatocyte-like cell lineage (ordinary, "classical," or "standard" HCC). In addition, there exist numerous variants of ordinary HCC and a distinct entity, fibrolamellar hepatocellular carcinoma, treated in separate chapters.

Eggel (1901) was the first to clearly state that primary liver cell cancer is derived from hepatocytes. Apart from the morphologic resemblance between hepatocytes and hepatoid cells in moderately to well-differentiated HCC, a crucial argument of Eggel was his discovery of bile depositions in 6 of the 117 histologically examined tumors that he compiled from the literature, by adding a case of his own. Identification of bile in and between tumor cells still is a hallmark for the diagnosis of HCC.

Epidemiology

Liver cancer is a frequent malignancy worldwide with an incidence that is particularly high in all low-resource regions of the world, except Northern Africa and Western Asia. It is estimated that 82 % of HCC occur in developing countries (Leong and Leong 2005; Chuang et al. 2009). Estimates from the year 2004 show that HCC is the fifth most common malignancy in males and the eighth in females worldwide (Table 1).

About 564,000 new cases are diagnosed per year, with 398,000 in men and 166,000 in females, illustrating that HCC is two to four times more common in men than in women (reviews: Bosch et al. 2004, 2005). The yearly incidence comprises between 2.5 % and 7 % of patients with liver cirrhosis (Montalto et al. 2002). The highest reported incidence of 100 cases per 100,000 of population annually had been reported from Mozambique, due to high prevalence of HBV infection followed by cirrhosis, aflatoxin

Table 1 Age-adjusted incidence of HCC per 100,000 inhabitants (Llovet et al. 2003; modified)

Area	Age-adjusted incidence (males/females)
Worldwide	14.9/5.5
East Asia	35.4/12.6
Middle Africa	24.2/12.9
Southeast Asia	18.3/5.7
Southern Europe	9.8/3.4
Western Europe	5.8/1.6
South America	4.8/3.6
North America	4.1/1.6
Northern Europe	2.6/1.3

and alcohol toxicity, and possible iron overload. The peak age of onset of HCC is continuously rising worldwide, and there is evidence that the clinical features in the elderly differ from those in younger individuals. In a study of 622 patients with HCC, including 91 patients 70 years old or older, the proportion of females increased, and tumor sizes at diagnosis were smaller in the elderly than in younger patients, whereas clinical stage taking liver function into consideration was similar in the two age groups (Nomura et al. 1994). Whereas an increase in incidence has been noted in certain regions, the incidence of HCC has, e.g., been static over recent decades in the Asia Pacific region (Yuen et al. 2009).

HCC is closely associated with liver cirrhosis (Siegenbeek van Heukelom 1894; Kew and Popper 1984; Gall 1960; Fattovich et al. 2004), the main causes of this chronic liver disease being hepatitis virus infections, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD). The development of HCC in a background of cirrhosis varies as a function of underlying disease. Particularly high incidences of HCC in cirrhotic liver are found in HCV infection and hereditary hemochromatosis. HCV infection was found to have the highest HCC incidence in cirrhotic patients, with a 5-year cumulative incidence of 17 % in Western countries and 30 % in Japan. In the cirrhotic stage of hemochromatosis, the 5-year cumulative incidence was 21 %. Lower values are observed in other important causes of cirrhosis, i.e., HBV infection, alcoholic liver disease, and various forms of biliary cirrhosis. In high endemic areas of HBV infection, the 5-year cumulative incidence of HCC is 15 %, while it is 10 % in Western countries. Overall, alcoholic liver cirrhosis has a 5-year cumulative HCC risk of 8 % (review: Fattovich et al. 2004). Male gender and age more than 50 years are risk factors for HCC in cirrhotic patients. A subset of HCC develops in the absence of cirrhosis (Tabarin et al. 1987; Giarelli et al. 1991). In an autopsy study from Japan, non-cirrhotic cases among 618 HCC patients amounted to 10.7 % (Okuda et al. 1989). In Western countries, HCC in non-fibrotic livers was associated with younger age and female sex (Bège et al. 2007).

It seems that the earliest true primary HCC was a case reported in Frerich's series in 1861, followed by a bona fide example of HCC in a cirrhotic liver with invasion of the inferior vena cava, reported in 1876 (Weigert 1876). It is striking to note that in early works on the incidence of HCC in Europe, relatively few cases were found in a clinical setting or in autopsy series in comparison with metastatic liver disease. In his work on liver tumors, Thöle (1913) cites that von Hansemann (a pathologist, assistant of Virchow, who formulated the concept of anaplasia) found 225 metastases and 6 HCC among 258 malignancies observed until 1889 and that Ahlenstiel detected 95 hepatic malignancies in 6,000 autopsies, of which 90 were metastases and 5 primary liver cancer. Similarly, Mau identified, in 1901, 246 hepatic malignancies among 8,587 autopsies performed in Hamburg, Germany, including 242 metastases and 4 primary liver cancers. Riesenfeld (1868) diagnosed liver cancer in 2.3 % of autopsies performed in Berlin between 1864 and 1868. Among 24,400 consecutive autopsies performed at Bellevue Hospital, New York, from 1906 to 1936, 62 cases of primary hepatic carcinoma were identified (Gustafson 1937). Between 1850 and 1950, many publications were written on single cases and small series, and numerous later studies and reviews have then addressed issues of occurrence patterns and epidemiology of HCC.

Selected References Anthony 1973; Sabourin 1881; Okuda et al. 1985; Okuda 1990; Dominguez-Malagon and Gaytan-Graham 2001; El-Serag 2002; Llovet et al. 2003; Bosch et al. 2004, 2005; Srivatanakul et al. 2004; Lee et al. 2009; McGlynn and London 2011.

Clinical Features

General Features

In early HCC, many patients are asymptomatic. In the absence of distinct complications, symptoms and signs in symptomatic patients are nonspecific and in part related to underlying chronic liver

disease, in particular hepatic cirrhosis. They include upper abdominal discomfort or pain, effects of hepatomegaly, malaise, anorexia, weight loss, and anemia (Berman 1959). In one European study, malaise (85 %), weight loss (78 %), anorexia (67 %), and hepatomegaly (84 %) were common findings at presentation (Kaczynski et al. 2005). In advanced disease, signs of hepatic failure and jaundice may ensue. In patients with underlying cirrhosis, sequelae of portal hypertension are often the leading clinical signs. Serologically, several markers for HCC and HCC recurrence have been identified, but AFP and its variants remains the most frequently used tumor marker for the diagnosis of HCC (Vogel et al. 1974; Gonzalez and Keeffe 2011; Nakao and Ichikawa 2013). However, a significant proportion of HCC patients do not show elevated serum AFP levels (low-AFP HCC; Carr et al. 2010). Serum AFP is employed for monitoring patients' response to therapy. Specifically, monitoring of *Lens culinaris* agglutinin-reactive AFP (AFP-L3, the fucosylated variant of AFP) is useful for early detection of recurrent HCC (Okuda 2000; Giannelli and Antonaci 2006). Elevated serum AFP is not only a bystander, but the protein exerts distinct functions. HCC patients with high or very high AFP serum levels show a higher mortality rate, probably related to a tumor growth-promoting activity of AFP (Li et al. 2011). It was earlier reported that AFP has immunosuppressive properties and induces spontaneous T and B lymphocyte responses in HCC patients. These responses are related to distinct immunogenic epitopes of the AFP molecule (review: Bei and Mizejewski 2011). AFP is also capable to activate monocytes and to augment phagocytic capacity of both monocytes and granulocytes (Kong et al. 2012), but abolishes the activation of natural killer cells by inhibiting the function of dendritic cells (Yamamoto et al. 2011).

Assessment of des-gamma-carboxy prothrombin (PIVKA-II), an abnormal prothrombin secreted by HCC, by sensitive assays has an important place in the diagnosis and follow-up of HCC (Takikawa et al. 1992; Bertino et al. 2012). In one study of 116 HCC, PIVKA-II was detected in serum in 54.3 % of patients and the concentration showed a positive correlation with tumor size (Takikawa et al. 1992). Further serum markers for HCC include glypican-3 and Golgi protein 73 (Giannelli and Antonaci 2006; Tian et al. 2011). Serum carcinoembryonic antigen (CEA) is raised in part of HCC patients (Macnab et al. 1978). For small or early HCC, reliable serum markers have not yet been established (Talwalkar and Gores 2004).

Paraneoplastic Syndromes

Hepatocellular carcinomas can be associated with a wide array of paraneoplastic syndromes (Table 2).

Complications

HCC may cause several types of complications. Rupture of HCC is a particularly severe

Table 2 Paraneoplastic syndromes associated with hepatocellular carcinoma

Hematologic paraneoplastic syndromes
Erythrocytosis (polyglobulism, erythremia)
Thrombocytosis
Leukemoid reactions (paraneoplastic neutrocytosis)
Peripheral hypereosinophilia
Paraneoplastic dermatological syndromes (paraneoplastic dermadromes)
Prurigo
Papuloerythroderma
Lichen planus
Lichen myxedematosus
Psoriasiform dermatoses (psoriasis guttata)
Pemphigus-like disorders
Lupus erythematosus-like syndromes
Acanthosis nigricans
Acquired perforating dermatoses
Papuloerythroderma of Ofuji
Acrokeratosis paraneoplastica (Bazex syndrome)
Disseminated porokeratosis
Pityriasis rotunda
Acquired porphyria

(*continued*)

Table 2 (continued)

Neurological paraneoplastic syndromes
Necrotizing leukoencephalopathy
Demyelinating polyradiculoneuropathy
Encephaloradiculopathy
Cerebellar ataxia
Necrotizing myelopathy
Demyelinating polyneuropathy
Peripheral neuropathy
Retinopathy
Autoimmune paraneoplastic syndromes
Dermatomyositis/polymyositis
Autoimmune arthritis/polyarthritis
Myasthenia gravis and other muscle weaknesses
Autoimmune thyroid disease
Behçet's disease
Metabolic disorders
Hypoglycemia
Hypercalcemia
Hypophosphatemia
Paraneoplastic hyperlipidemia and hypercholesterolemia
Hormonal syndromes
Paraneoplastic hyperthyroxinemia
Inappropriate ADH secretion
Coagulation disorders
Acquired von Willebrand disease
Cryofibrinogenemia
Combined paraneoplastic syndromes
Fever of unknown origin (FUO)

complication of this neoplasm and bears a high mortality. Rupture may occur spontaneously or following blunt abdominal trauma (Ong and Taw 1972; Chearanai et al. 1983; Van Landingham et al. (1985); Clarkston et al. (1988); Kanematsu et al. (1992); Chen et al. (1996); Castells et al. (2001); Chedid et al. 2001; Polat et al. 2005; Lai and Lau 2006; Kim et al. 2008). Spontaneous rupture of HCC can also occur in pediatric HCC (Nejmeddine et al. 2010). Localization of tumor to the left lobe and expansion of HCC outside the liver surface are risk factors for tumor rupture (Chen et al. 1995). Spontaneous rupture of HCC with hemoperitoneum is a rare condition in Western countries (Pombo et al. 1991; Chedid et al. 2001), while over 10 % of patients with HCC may experience tumor rupture in certain regions of Africa and Asia (Nagasue and Inokushi 1979). Spontaneous rupture of HCC was found to be the cause of death in only 3 % of patients in one study of 530 HCC patients (Kaczynski et al. 2005). Disruption of the tumor surface and a tear in a parasitic feeding artery are typical causes of HCC rupture (Chen et al. 1995; Kim et al. 2008). Vascular injuries that favor spontaneous rupture include degradation of collagen in the vascular wall (Zhu et al. 2001, 2002) and immune complex-induced damage of elastic lamellae (Zhu et al. 2004, 2006). Risk factors for HCC rupture included underlying disease such as hypertension and cirrhosis, a tumor size exceeding 5 cm, tumor protrusion from the liver surface, vascular thrombus, and extrahepatic invasion (Miyoshi et al. 2011; Zhu et al. 2012). HCC rupture can cause massive hemoperitoneum (Gibbons and Bell 1963). Parts of HCC present with jaundice, which is a negative prognosticator. In a minority of jaundiced patients, hyperbilirubinemia is due to biliary obstruction caused by the tumor, a situation outlined in more detail below. In the majority of patients, however, jaundice is caused by hepatic insufficiency caused by tumor and/or associated liver cirrhosis. Among 530 HCC patients with clinically detectable jaundice, 481 had jaundice due to hepatic insufficiency and 49 patients had obstructive jaundice. Patients with hepatic insufficiency had extremely poor prognosis, and 90 % of them died within 10 weeks of first presentation (Lau et al. 1997).

Imaging Features

Imaging features of HCC have been described in detail in numerous publications and are not specifically dealt with in this chapter (Okuda 1980a; Vermess et al. 1985; Stevens et al. 1996; Lee et al. 2011). Diagnostic imaging of HCC has recently undergone marked progress, mainly due to the introduction of the ultrasound contrast agent Sonazoid used in contrast-enhanced US (CEUS) and MR techniques employing a liver-specific gadolinium MR contrast agent (Ogawa et al. 2006; Xu et al. 2011; Tanaka et al. 2014; review: Kudo 2011).

Pathology

Introduction

As outlined in the paragraph on classification, HCCs are characterized by several distinct macroscopic patterns. The preparation and documentation of specimens for the identification of gross features has been standardized (Ruby 2000), as has the reporting of tissues removed (Dabbs et al. 2004; Association of Directors of Anatomic and Surgical Pathology 2005). Similarly, the definitions and nomenclature of nodular liver cell lesions has been standardized in a consensus panel (International Working Party 1995). In this paragraph, the morphology of advanced HCC is discussed, while the pathology of early and small HCC (Wanless 2007) is discussed in a separate chapter.

Selected References Rindfleisch 1878; Eggel 1901; Wegelin 1905; Rosenberg and Ochsner 1948; Edmondson and Steiner 1954; Edmondson 1955; Berman 1959; Patton and Horn 1964; Foster and Berman 1977; Mori et al. 1980; Anthony 1999; Kai et al. 2012.

Both the macroscopic growth patterns and the histopathologic presentation of HCC vary as a function of geography and genetic background, and between individual patients (Okuda et al. 1984; Okuda 1997). There are certain geographic specificities in regard to the presentation of diffuse and other variants of HCC and the type of underlying liver disease. This issue has been outlined by Okuda (1997) who emphasized that there are significant global variations of clinicopathologic features of HCCs, based on comparative studies of patients from Japan, Los Angeles, and Pretoria in South Africa (Okuda et al. 1984). For example, most patients from Japan show HCCs growing in an expanding fashion, with formation of a fibrous capsule, while capsule formation was very uncommon in South African Blacks. Depending on its gross growth patterns, primary HCC can involve one liver lobe or both liver lobes, whereby bilobar involvement had been found more frequently in HCC not associated with cirrhosis (Ho et al. 1981).

Classifications

Clinical Classifications

Several classifications of HCC are based on clinical and staging data (Llovet et al. 2003; review: Llovet 2007). The Barcelona Clinic Liver Cancer (BCLC) classification is an important classification for the clinical management of HCC and design of trials, endorsed by EASL and AASLD guidelines. It links stage stratification with a recommended therapy strategy. Other systems include the Cancer of the Liver Italian Program (CLIP) investigators, the Chinese University Prognostic Index (CUPI), and French staging systems, forming scoring systems predicting outcome in patients with advanced-stage disease.

Classifications Based on Macroscopic Presentation and Growth Patterns

Virchow separated primary from secondary liver cancer. However, in the thesis of Riesenfeld performed under Virchow's guidance (1868), gallbladder cancer was still regarded as a primary liver cancer. A fundamental step into the direction of modern pathology classifications of HCCs was the work of Eggel (1901) who divided liver cancers into nodular, massive, and diffuse forms. This and subsequent classifications are discussed in detail in the paragraph on tumor macroscopy.

Originally, primary HCC was divided into two major macroscopic groups, i.e., nodular carcinoma formed of discrete nodules of varying size and massive carcinoma, consisting of one large tumor mass. Hanot and Gilbert (1888) divided HCCs into three forms, i.e., nodular cancer ("cancer nodulaire," several to numerous nodules of varying size), massive cancer ("cancer massif," one large tumor mass), and cancer with cirrhosis, i.e., they proposed a classification based on tumor morphology on the one hand and underlying liver disease on the other hand. This system had

intrinsic inconsistencies of logic and was, therefore, applicable only with difficulty or not at all, because also nodular and massive cancers of course develop in cirrhotic livers. Already Eggel (1901) put his finger on the fact that Hanot and Gilbert themselves allocated one cancer in cirrhosis each to a nodular and a massive tumor.

A major step ahead is based on the novel classification of Eggel (1901), as further outlined below. Early comments on this classification were reviewed by Wegelin (1905). Today we know that HCCs show a characteristic spectrum of macroscopic growth patterns, comprising usual and unusual gross appearances (review: Kai et al. 2012). The macroscopic growth of HCCs can be classified according to several criteria (Table 3).

Table 3 Classification of HCC growth patterns

Eggel's classification (1901):
Nodular HCC
Massive HCC
Diffuse HCC
Kaufmann's classification (1958)
Large massive node
HCC in cirrhotic liver
(a) Multiple nodules
(b) Diffuse growth
(c) Combination of nodules and growth
Okuda classification (1984)
Expanding
Spreading
Multifocal
Surgical classification:
Invading lesions ("invaders")
Expanding lesions ("pushers")
Pedunculated lesions ("hangers")
Classification of the Liver Cancer Study Group of Japan (LCSGJ):
Nodular HCC (distinctly nodular type)
Simple nodular (SN) type
Simple nodular type with extranodular growth (SNEG)
Confluent multinodular type (CMN)
Nodular HCC
Small nodular type with indistinct margins (vaguely nodular type)
Classification according to size:
Small HCC
Solitary large HCC

In Eggel's investigations, nodular HCCs accounted for 64.6 %, massive for 23 %, and diffuse cancers for 12.4 %. Herxheimer in Germany (1930) arrived at similar figures (65 %, 28 %, and 7 %, respectively). In rare instances, a mixture of all three patterns is present. Eggel noted that mainly the massive form of HCC resulted in marked hepatomegaly, but hepatomegaly was in fact found in most of Eggel's original cases. He described a patient with a liver weight of 7 kg, but Herxheimer (1930) cites an observation by Bruzelius and Schwink reporting a liver cancer causing a liver weight of 14 kg. In some of the cases, the macroscopic presentation is dominated by liver cirrhosis, and tumor is only detectable on cut sections.

Eggel (1901) divided HCCs into two histologic groups (carcinoma solidum and carcinoma adenomatosum) and classified the macroscopic growth patterns, also based on the concepts of Hanot and Gilbert, into three patterns, i.e., nodular, massive, and diffuse. Eggel's classification of HCCs, proposed more than 100 years ago (Eggel 1901), was widely used, however, mainly for autopsy studies and less for surgical cases. The nodular type is grossly characterized by single or multiple discrete nodular neoplasms with a clear demarcation. Massive HCCs present as a large mass that almost completely replaces the left or right liver lobe. The diffuse type of HCC is characterized by a diffuse infiltration of the liver by numerous small to minute cancer nodules that macroscopically somewhat resemble cirrhotic nodules. The nodular form is the most common and is, based on data in the literature, present in 64.6 % of cases, while the massive form was found in 23 % and the diffuse form in 12.4 %. The nodular category of Eggel is sometimes applicable to surgical specimens with some difficulties only. For the adequate classification of HCC in hepatectomy specimens, the Liver Cancer Study Group of Japan proposed to divide nodular HCCs in subclasses. In 1984, Okuda and coworkers proposed a simple classification based on gross anatomical features of HCC from three disparate geographic areas, common major patterns being expanding, spreading, and multifocal (Okuda et al. 1984). Growth patterns were used as a stage

classification, e.g., the expansive-invasive-disseminative growth staging classification (Zhu et al. 2013).

Molecular Classifications

Based on the continuously growing recognition of distinct molecular signatures found in HCC, attempts to classify HCC according to molecular features have been and are undertaken (Boyault et al. 2007; Katoh et al. 2007). Katoh and coworkers (2007) found that HCC is composed of several genetically homogeneous subclasses, each having characteristic genetic alterations. Molecular signatures are associated with distinct macroscopic growth patterns. For example, EpCAM was predominantly expressed in the confluent multinodular (CM) type of HCC which is an aggressive phenotype with poor outcome (Murakata et al. 2011). In the setting of an integrative transcriptome analysis, three robust HCC subclasses termed S1, S2, and S3 have been identified, and each of these molecular subclasses correlated with clinical parameters, including tumor size, extent of cellular differentiation, and serum AFP levels. The S1 subclass reflected aberrant activation of the WNT signaling pathway, S2 proliferation, as well as MYC and AKT activation, and S3 was associated with hepatocyte differentiation (Hoshida et al. 2009).

Macroscopic Pathology of Main Gross Patterns of HCC

Size of Hepatocellular Carcinoma

The size of HCC at diagnosis varies markedly, ranging from tumors defined as early or small HCC (see the respective chapter) to very large lesions exceeding 20 cm in diameter and replacing most of the liver. Multinodular tumors with a liver weight exceeding 10 kg have been reported (Cooper et al. 1935), suggesting that, similar to other organs, HCC can grow to enormous size without leading to death through metastatic disease. HCC occurring in normal livers were, at least in part of analyses, significantly larger in average tumor size than those occurring in cirrhotic livers (Kishi et al. 1983).

Nodular HCCs

Nodular cancer in HCCs forms well-circumscribed, more or less spherical masses, mostly in a cirrhotic liver. These nodules most commonly either form simple and firm to friable masses of variable color or are closely grouped or form irregular nodular masses (Berman 1959). The color as seen on cut sections is yellowish, yellow-green, frankly green (in tumors with marked bile accumulation; "green hepatomas"), or gray to reddish. The green color of bile-rich lesions typically becomes more strong after formalin fixation. In cases where nodular cancers form groups or clusters of nodules, the color may vary from one nodule to the other, reflecting variations in differentiation (e.g., bile production) caused by progressive genomic instability or variations in regressive phenomena. Such differences can sometimes be found within one and the same nodule. Frequently, bile-storing green HCC nodules stand out against the non-bile-stained background of the cirrhotic liver. Large nodules can contains extensive hemorrhage, sometimes leaving a dark red-blue nodular lesion resembling a hemangioma (Figs. 1, 2, 3, 4, 5, 6, 7, 8, and 9). Clustered lesions form HCCs of the confluent multinodular type. In some cases, numerous nodules are present, and this presentation may be difficult to distinguish from multiple intrahepatic metastatic spread (Fig. 10). Small nodules are usually more firm than large one. The variable consistency depends on the ratio between preserved or necrotic epithelial cells versus stroma, the latter inducing firmness of the lesions when present in significant amounts. Large nodules are often soft and friable, whereby the centers are softer than the periphery owing to central necrosis. When cutting through large nodules, a creamy matter of necrotic tissue typically sticks to the blade of the knife. Macroscopically, nodular lesions tend to show an expanding growth pattern and therefore display a sharp border, but there also

Fig. 1 Nodular hepatocellular carcinoma in a cirrhotic liver. The tumor mass displays an expanding growth pattern and shows a rather homogeneous cut surface (formalin-fixed resection specimen)

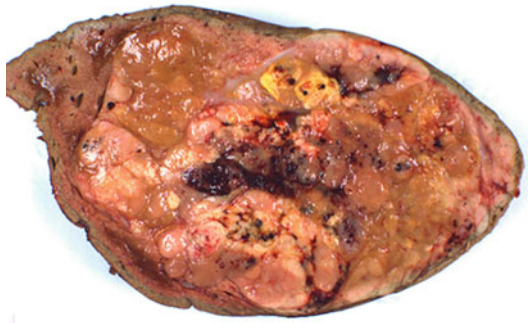

Fig. 2 Nodular hepatocellular carcinoma with an expanding growth pattern in a non-cirrhotic liver. The heterogeneous cut surface shows central hemorrhage and few *yellow* areas with necrosis and fatty change

lesions with a blurred border due to a macroscopically invasive phenotype. Mainly in large tumors, central necrosis, sometimes with cyst formation, is often impressive.

Small HCCs with a diameter of less than about 2 cm are classified into two major types, i.e., small nodular type with indistinct margins (SN-IM, vaguely nodular type) and the distinctly nodular type (SN-DN; Kojiro and Nakashima 1999). SN-IM may, due to its blurred margins, be difficult to distinguish from surrounding cirrhotic nodules and/or nodular precursor lesions. SN-IM are histologically often well-differentiated lesions with so-called replacing growth at the periphery. The tumors can contain portal tracts in markedly reduced numbers. These portal tracts are deformed by invasive growth of HCC, the so-called stromal

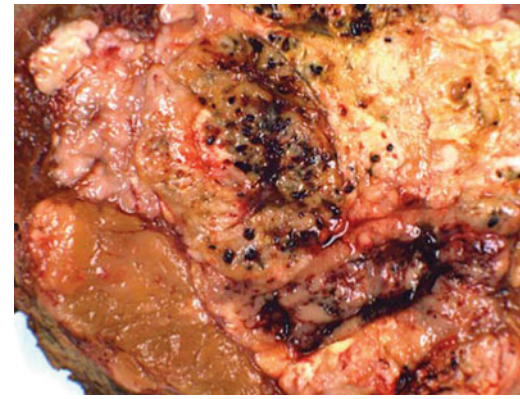

Fig. 3 Cut surface of a nodular hepatocellular carcinoma at higher magnification. This tumor is highly heterogeneous: the *greenish* part to the *left lower corner* exhibits bile accumulation, while the *whitish-pink* parts showed less differentiated neoplastic tissue. This tumor heterogeneity can cause bioptic sampling errors in regard to typing and grading. Extensive necrosis and hemorrhage are observed (*center* and *upper right corner*)

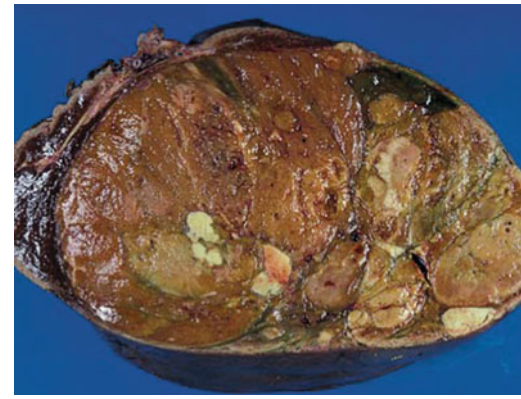

Fig. 4 Large hepatocellular carcinoma, nodular type with multinodular interior composition. The cut surface is characterized by *brown* and *greenish* areas (bile accumulation) and several *white* necrotic foci. In this non-fixed specimen, tumor tissue bulges from the cut surface

invasion, which is a very important diagnostic element. In some studies, these lesions have been termed, early HCC (Kojiro 2007), a lesion further discussed in a separate chapter.

As seen in Table 3, Japanese investigators have subdivided nodular HCCs into three subcategories, in order to cope with imaging findings surgically resected HCCs (The Liver Cancer Study Group of Japan (LCSGJ) 2003). In this

Fig. 5 Nodular hepatocellular carcinoma with an expanding growth pattern and marked bile accumulation. The *green* discoloration of bile-storing HCC becomes more intense in formalin-fixed specimens, as in the present case

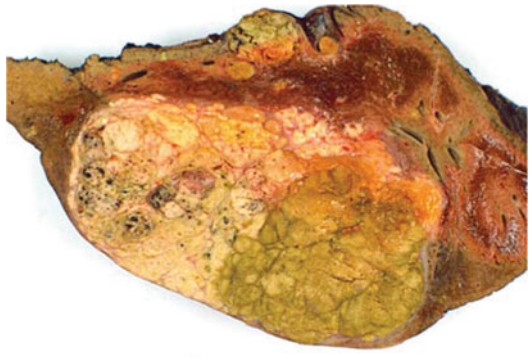

Fig. 6 This nodular hepatocellular carcinoma exhibits a striking pattern on the cut surface, with a *green* part rich in bile being well-separated from a *whitish* part histologically less differentiated and showing necrosis and hemorrhage. Several satellite nodules are present

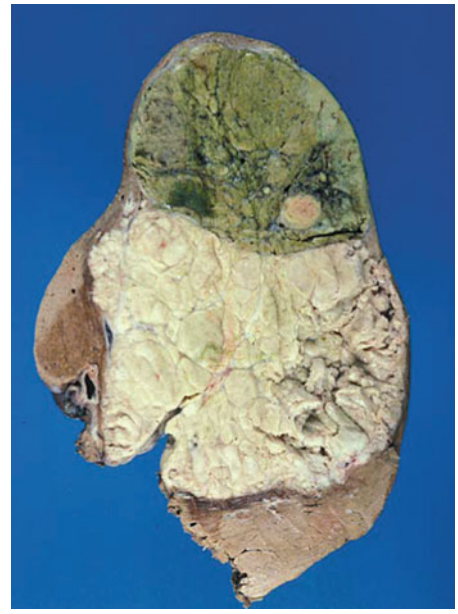

Fig. 7 In this hepatocellular carcinoma, the presence of three separate subunits showing different colors is striking. The *dark-green* part was a well-differentiated HCC with marked bile accumulation, while the *whitish* part revealed moderately differentiated HCC with necrosis. Within this part, a nodule with poor differentiation emerged, suggesting clonal evolution in the setting of progressive genomic instability

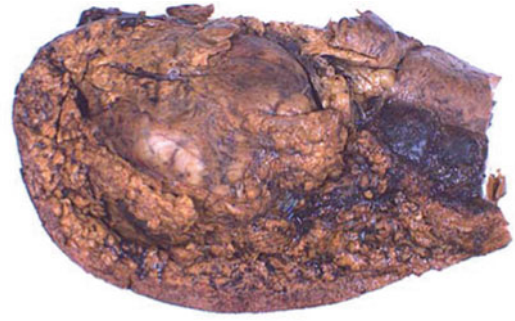

Fig. 8 Nodular hepatocellular carcinoma in cirrhotic liver, resection margin. The expanding lesion is situated close to the margin, but exterior surface appears intact (fixed resection specimen)

classification system, SN-DN is further subdivided into three subtypes, namely, the simple nodular type (SN), the simple nodular type with extranodular growth (SNEG), and the confluent multinodular type (CMN). This subclassification has an impact on prognosis. Based on 65 resected HCCs with a diameter of less than 5 cm, the median time to recurrence and duration of disease-free survival were significantly shorter for CMN lesions than in the other two groups (Hui et al. 2000). SN is characterized by a sharply

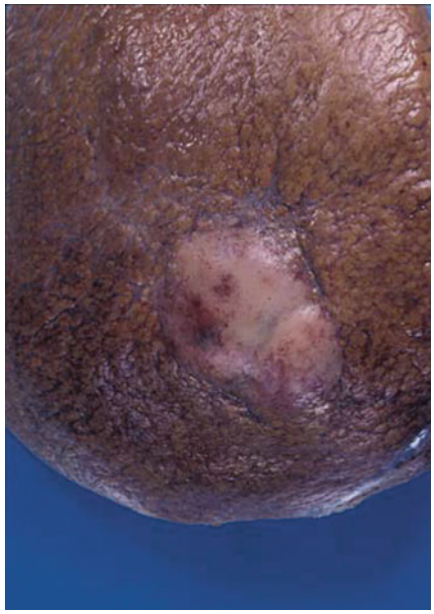

Fig. 9 Nodular hepatocellular carcinoma in a cirrhotic liver. This tumor reaches to the capsular surface of the liver, resulting in slight bulging. The *red-brown* speckles on the tumor are tiny hemorrhages

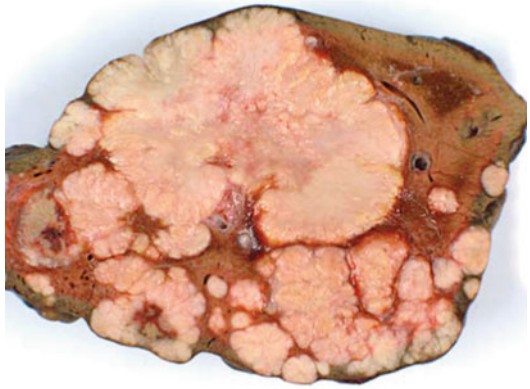

Fig. 10 Hepatocellular carcinoma with a multinodular growth pattern in a non-cirrhotic liver. In situations with a dominant larger tumor associated with several smaller nodules, intrahepatic metastasis has also to be considered

delineated, more or less spherical nodules, often well differentiated and encapsulated, with no macroscopic evidence of extranodular growth or vascular invasion. SNEG nodules include those with extranodular HCC foci, growing beyond the capsule of the principal nodule, nodules showing vascular invasion, and/or small metastases near

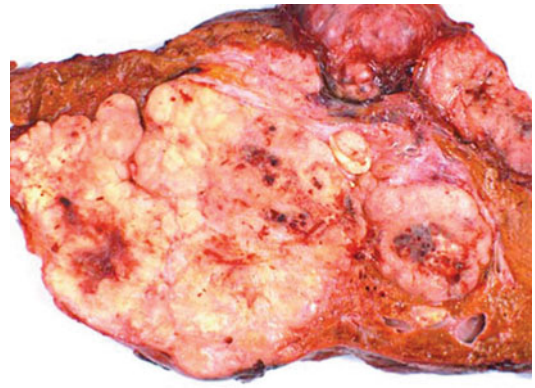

Fig. 11 Hepatocellular carcinoma with a massive growth pattern. The liver is extensively infiltrated by in part confluent tumor nodules that show necrosis and multiple hemorrhages

the main nodule. CMN HCCs result from joining together of few to multiple small tumor nodules. CMN is not encapsulated. Portal tracts are entrapped between the clustered nodules. Vascular invasion and/or intrahepatic metastasis are more common than in the simple subtype.

Massive Hepatocellular Carcinoma

Massive HCC is often found in a markedly enlarged liver that is deformed by large, irregularly shaped tumor masses (Fig. 11). On sections, the involved liver lobe may be almost completely occupied by a usually whitish mass with numerous necroses and hemorrhages, associated with secondary or satellite lesions and gross vascular invasion (Goldberg and Wallerstein 1934; Berman 1959). In part of the tumors, the distinction between a nodular pattern with confluence and massive-type HCC may be difficult. In principle, nodular HCC with multiple nodules and occupying an entire liver lobe becomes a massive-type HCC (Kojiro 2006).

Diffuse Hepatocellular Carcinoma

The diffuse type of HCC is a rare growth variant of this cancer (Okuda et al. 1981). Diffuse HCC is macroscopically characterized by a liver that is

studded with numerous minute, uniformly sized nodules, with homogeneous involvement of the organ. HCC presenting with this patterns is usually poorly differentiated. As diffuse HCC usually develops in cirrhotic livers, the small tumor nodules may macroscopically be confounded with cirrhosis nodules or other small regenerative nodules. In some cases of diffuse-type HCC, the cancer nests can only be detected histologically. The tumor often invaded large portal vein branches and displays invasion of numerous small intrahepatic vessels, suggesting vascular spread as a pathogenic mechanism of the diffuse growth pattern. A prominent clinical feature of diffuse HCC was rapid deterioration of patients' general condition, associated with rapid enlargement of liver size and terminating in hepatic failure (Okuda et al. 1981).

Pedunculated Hepatocellular Carcinoma

Pedunculated hepatocellular carcinoma (P-HCC) is defined as a form of HCC protruding from the liver as a roughly polypoid or spherical mass with or without a clearly delineated vascular pedicle (Anthony and James 1987; Kohno et al. 1987; Nakashima and Kojiro 1987; Tsoulidis et al. 2007; Zhang et al. 2011). Baer and coworkers (1995) defined HCC as pedunculated if they showed a real pedicle with pedicle vessels and as dependent HCC if over 50 % of their surface growth was located extrahepatically. The term dependent was coined by us to describe, in a clinical-surgical setting, tumors that grow with a base adjacent to the free liver edge and hanging in their entirety, rendering these lesions relatively easy to resect (Baer et al. 1989). P-HCC does not differ significantly from other growth patterns with respect to associated liver disease (Yeh et al. 2002a). P-HCC; (HCC with extrahepatic growth; clinically-surgically a "hanging lesion" or "hanger"; Baer et al. 1995) was first described at the end of the nineteenth century (Roux 1897), followed by a report in 1934 (Goldberg and Wallerstein 1934). The term pedunculated HCC was coined in 1954 (Edmondson and Steiner 1954). These authors regarded P-HCC connected with liver and showing extrahepatic growth with a pedicle as an exception, and relatively few cases were reported in the Western literature until recently, but numerous cases of P-HCC have been published from Japan. Okuda reported ten cases of P-HCC among 4,031 cases of HCC observed in Japan (Okuda 1980b). Until 1981, 20 cases were reported from Japan and several other followed (Nishizaki et al. 1993; Yan et al. 2009). In Japan, P-HCC accounts for only 0.24–4.2 % of all HCC (Okuda 1980; Horie et al. 1983; Yeh et al. 2002). It is estimated that P-HCC overall accounts for 0.24–3.0 % of all HCC (Horie et al. 1983).

Macroscopically, P-HCCs are in most cases solitary neoplasms that sometimes grow to a very large size, e.g., having a diameter of 23 cm (Baer et al. 1995). P-HCC is sometimes subclassified into a subtype I with a pedicle and a subtype II lacking a clearly visible pedicle (Figs. 12, 13, 14, 15, 16, and 17; Nakashima et al. 1983). P-HCC is more often observed in the right liver lobe (Nishizaki et al. 1993), and many tumors arise from the hepatic inferior surface or hepatic rim (Horie et al. 1983). Markedly pedunculated subtype I lesions manifest as polypoid masses that freely hang in abdominal cavity, most often the right cavity, large or giant tumors sometimes extending into the right iliac fossa (Karatzas et al. 2011). The size of P-HCC varies considerably, and also nodules having a diameter

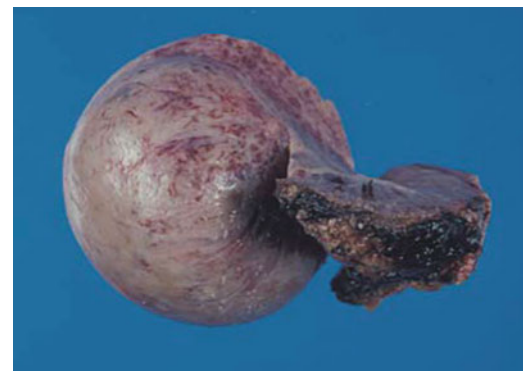

Fig. 12 Extrahepatic hepatocellular carcinoma connected to the liver by a thin vascular pedicle (pedunculated hepatocellular carcinoma, type 1)

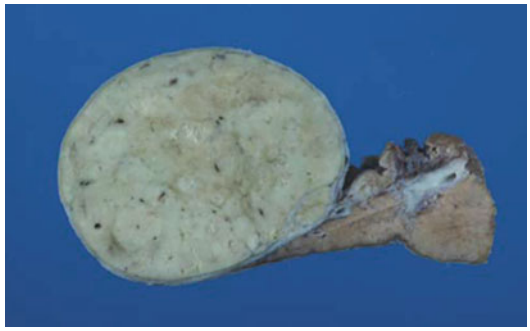

Fig. 13 Cut surface of a pedunculated hepatocellular carcinoma (type 1). The well-delineated, encapsulated tumor nodule is connected to the liver through a stalk or pedicle containing blood vessels

Fig. 14 Hepatocellular carcinoma situated at the anterior margin of the liver, to the left of the gallbladder. Part of the tumor mass is situated outside the cirrhotic liver substance, however, without a vascular pedicle. Such lesions have been termed type 2 pedunculated HCC

of 3 cm can produce an extrahepatic growth, but larger tumors are more common, some reported examples exceeding a diameter of 20 cm. The spherical or dome-shaped tumors are covered by the liver capsule which is smooth and in most cases devoid of adhesions of inflammatory changes, although adhesions to the transverse colon have been found in some cases (Horie et al. 1983). In the subcapsular tissue, dilated veins may be noted, sometimes forming a prominent network of congested vessels. Mainly in cases with well-developed pedicles (subtype I lesions), gross invasion of the liver substance is lacking.

Histologically, P-HCCs share the morphology of other ordinary HCCs. Rarely, the histologic presentation deviates from ordinary HCC, e.g.,

Fig. 15 A large part of this nodular hepatocellular carcinoma in a cirrhotic liver has grown out of the liver substance. A rim of cirrhotic tissue forms a thin collar around the tumor, in the absence of a pedicle. Note the abnormal dilated blood vessels on the tumor convexity

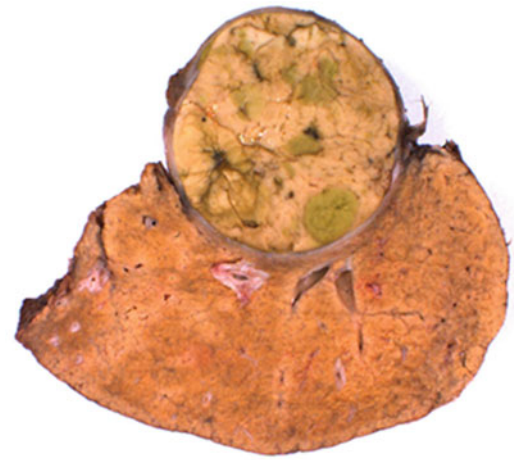

Fig. 16 Cut surface of type 2 pedunculated hepatocellular carcinoma. This tumor is demarcated from the liver substance by a thin pseudocapsule. The *greenish* nodules within tumor are areas with marked bile accumulation

showing a sarcomatoid component or presenting as a combined hepato-cholangiocarcinoma (Noh et al. 2012). In one patient, a giant P-HCC was synchronously associated with a hemangioma interposed between HCC and the liver capsule (Karatzas et al. 2011). P-HCCs were shown to have a more favorable biology of disease in comparison with other growth patterns, in part related

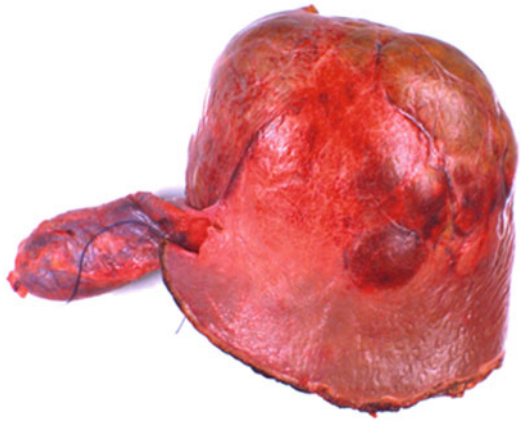

Fig. 17 Some type 2 pedunculated hepatocellular carcinomas reveal a morphology resembling exophytically growing focal nodular hyperplasia. The present tumor developed close to the insertion of the *round* hepatic ligament

to the higher proportion of well-differentiated tumors in the P-HCC group (61 %), the presence of a more prominent capsule, and the relative ease to obtain a wide resection margin (Yeh et al. 2002).

The pathogenesis of P-HCC has not yet been clarified. It has been proposed that this variant of HCC might arise from congenitally displaced lobules situated in Glisson's capsule (Goldberg and Wallerstein 1934). Other authors suggested an origin from accessory liver lobes (Gyotoku et al. 1980), as such lobes are often located to the right liver lobe and to its inferior surface. One theory proposed that some, or perhaps most, of right-sided P-HCCs represent fusion of the right liver lobe and para-adrenal or adrenal metastatic HCC, eventually based on vascular connections caused by adrenohepatic fusion (Okuda et al. 1998). In fact, extrahepatically growing HCC was fed by the adrenal arteries in two patients (Yoshimura et al. 1989; Kaneko et al. 1992). A pedunculated or dependent phenotype not only exists for HCC, but is also encountered with hepatic metastases and certain benign tumors and tumor-like lesions, e.g., focal nodular hyperplasia and giant hemangiomas (Baer et al. 1995).

Satellite Lesions

A series of 149 resected HCC showed satellite lesions in 19 % of cases. HCC with a single nodular type with extranodular growth and the confluent multinodular type more often displayed satellite lesions than the single nodular type or early HCC, and satellite lesions prevailed in tumors with poor differentiation. Most lesions (50 %) were located at 0.6–1.0 cm from the main tumor, whereas 33 % were 0.5 cm or less, and 17 % at 1.1–2.0 cm (Okusaka et al. 2002).

Bile Duct Invasion (Icteric-Type HCC)

A subset of HCC is characterized by bile duct invasion. In part of these patients, obstructive jaundice is a leading sign, but the condition is uncommon, with a reported incidence of 0.5–13 % in patients with HCC. Intrabiliary growth was found in 5.1 % of 257 HCC patients (Ikeda et al. 1997), while in another series of 549 HCC patients, gross evidence of bile duct invasion was present in only ten cases (Wang et al. 1999). Even small or very small HCC can cause intraductal growth (Lee et al. 2001). In case this intraductal tumor extends to the confluence region and/or the choledochus, obstructive jaundice ensues ("icteric-type HCC"; Lin et al. 1975; Lee et al. 2001; Huang et al. 2002).

Selected References Kojiro et al. 1982; Sastry et al. 1996; Yeh et al. 2004; Esaki et al. 2005; Huang et al. 2006; Ikenaga et al. 2009; Liu et al. 2011a; Yu et al. 2011; Paradis 2013b.

Mechanisms of obstructive jaundice comprise either the forming of a growing intraluminal tumor tissue plug, tumor tissue fragments admixed with bile and exudate, or intraductal accumulation of blood or coagulated blood masses derived from necrotic and hemorrhagic intraluminal tumor. Parts of intrabiliary tumors can detach and dislocated to more distal parts (Lam et al. 2009). This is mainly due to the loose texture of the tumors and their tendency to undergo necrosis. Acute tumor bleeding may

favor the detachment of fragments which are then transported along the biliary tract. In case the blood coagulates, tumor fragments are caught in this mass and either decay or continue with their growth, which however requires induction of a new vascular support. Macroscopically, these neoplasms appear as nodular lesions in close associated with a tumor mass located within the lumen of an often dilated intrahepatic bile duct. These intraluminal masses are sometimes called "bile duct thrombi," which is a misnomer. Small nodular or pluglike lesions are usually situated in one or two intrahepatic ducts, while large lesions may present as extensive biliary duct casts that obstruct large parts of ducts and also the biliary confluence. As intraductal tumors tend to further grow along the lumen, without significant infiltration of the duct wall (Yu et al. 2011), the involved segment of the duct is often enlarged into a fusiform shape. The intraductal tumors are usually hypervascular, with a distinct array of feeding vessels and a characteristic imaging presentation, with an early enhancement pattern on contrast-enhanced CT and MR images. In the course of dissection of a specimen, a continuum between the main tumor and its intraductal manifestation is detected in the majority of cases. However, there are few cases of intraductal HCC in which no extraductal tumor could be identified (Makino et al. 2006; Long et al. 2010; Abe et al. 2012). Intrabiliary growth is a risk factor for poor outcome in part of patients (Ueda et al. 1994), but in one investigation there was no significant difference in survival rates between patients with and without bile duct thrombi, although the rate of stage IV or portal vein invasion was significantly higher in patients with biliary tract invasion (Satoh et al. 2000). Even if HCC tumor "thrombus" is detected in major branches of bile ducts, outcome following surgery may be satisfactory in part of patients (Tantawi et al. 1996; Qin and Tang 2003; Qin et al. 2004; Esaki et al. 2005; Ebara et al. 2013; Moon et al. 2013). Intraductal HCC "thrombi" may present in a manner similar to polypoid cholangiocarcinomas. Intraductal ultrasonography can serve to separate these two lesions sharing an intraluminal growth pattern (Tamada et al. 2001). Intraductal HCC may also be mimicked by intraductal clots resulting from hemobilia (Casagrande et al. 1985). HCC invading large bile ducts has to be distinguished from the rare instances of ectopic HCC primarily developing in bile ducts (Hasegawa et al. 2002), and from HCC exerting compression of large duct followed by obstructive jaundice (Lee et al. 1988), or causing extrinsic stricture (Dusenberg 1997).

Histopathology

Introduction

Histologically, HCC presents with a wide array of phenotypes reflecting a complex histogenesis and varying as a function of early versus advanced disease The general or most common histologic features have been described and reviewed in numerous reports (Yamagiwa 1911; Lapis and Johannessen 1979; Schirmacher et al. 2001; Schlageter et al. 2014). In the present chapter, histologic features of classic, conventional, or "standard" HCC are discussed, whereas specific histologic phenotypes are treated in separate chapters. Main histologic and cytologic features of ordinary HCC are compiled in Table 4.

Selected References Hansemann 1897; Cunningham 1943/1944; Kaufmann 1958; Anthony 1979; Klatskin and Conn 1993; Okuda et al. 1993; Okuda 1997; Suriawinata and Thung 2002; Hytiroglou 2004; Wanless 2004, 2007; Kojiro 2005; Ferrell and Kakar 2007; International Consensus Group 2009; Roskams and Kojiro 2010; Gonzalez and Keeffe 2011; Salomao et al. 2012a; Mitchell 2013; Paradis 2013a.

Histology of Well-Differentiated and Moderately Differentiated Hepatocellular Carcinomas

Well-differentiated HCC often grows in the form of liver cell plates that minimally deviate from the normal situation, i.e., having essentially a normotrabecular arrangement or having

Table 4 Histologic and cytologic features of ordinary hepatocellular carcinoma

Growth patterns
Expanding ("pushing" tumors)
Infiltrative ("invaders")
Diffuse/dissociative
Histologic structures
Trabecular structures (cell plates, macrotrabecular structures)
Acinar structures (pseudoglandular structures)
Cell nests
Medullary growth
Stroma formation
Stroma-poor tumors
Desmoplastic tumors
Sclerosing tumors
General tumor cell morphology
Hepatocyte-like
Amphophilic cells
Oxyphilic cells
Giant cells (multinucleated)
Pleomorphic cells
Small and anaplastic cells
Nuclear morphology
Hepatocyte-like vesicular nuclei (mainly G1 and G2 HCC)
Pleomorphic nuclei
Small round nuclei
Cytoplasmic inclusions and distinct structures
Hyaline globular inclusions (PAS-positive or PAS-negative)
Pale bodies
Ground-glass inclusions
Mallory-Denk bodies
Bile droplets
Fat droplets (tumor cell steatosis)

trabecules two to three cells thick, or present as macrotrabecular structures with a width sometimes exceeding ten cells. In such situations, criteria that result in a diagnosis of well-differentiated HCC include nuclear crowding, cytoplasmic amphophilia or increased cytoplasmic basophilia, and microacinar formation (Kondo et al. 1989). Apart from cell plates, gyriform to cerebriform structures (Adelheim's gyriform structures), or solid cell nests, can occur. In HCCs, tumor cell plates often anastomose, and there are cell plates with slits, showing exterior palisading. In addition to plates and variant thereof, acinar (pseudoglandular) structures are often seen, the cells lining acini sometimes, but not often being prismatic (Kondo and Nakajima 1987). The lumina of the acini may contain bile, bile-stained fluid, or proteinaceous material. Mixed trabecular-acinar components are often encountered, and some acinar profiles can result in microcystic structures. Cell plates and acini are almost never separated by stromal tissue (Figs. 18, 19, 20, 21, 22, 23, and 24).

Well-differentiated HCC and part of moderately differentiated HCC are characterized by cells that closely resemble normal hepatocytes and by a trabecular growth pattern (Fischer 1903; Oertel 1905; Von Albertini 1974). The size of the cells of ordinary HCC are about the size of normal hepatocytes, sometimes slightly larger or smaller. Cells in the center of nodules may be smaller than those at the periphery. In contrast to normal or regenerating hepatocytes, HCC cells are more often slightly amphophilic, and also pale cells are encountered (Wegelin 1905). Such HCC are the most difficult to diagnose in biopsies, but can also be diagnosed by means of fine-needle aspiration biopsies.

Selected References Jacobsen et al. 1983; Bell et al. 1986; Huang et al. 1996; Soyuer et al. 2003; Wee and Nilsson 2003; Chhieng 2004; Yang et al. 2004; Wee 2005, 2011, 2013.

The morphology of the tumor cells together with a sometimes normotrabecular pattern may render diagnosis of malignancy difficult, and the detection of an infiltrative growth is crucial, as emphasized by Masson in 1956. A high level of differentiation occurs in both advanced and small/early HCC (Tomizawa et al. 1995). Tumor cell nuclei generally retain the basic morphology of hepatocyte nuclei, but they are often enlarged and more vesicular, the chromatin is more coarse, heterochromatin at the nuclear membrane is more prominent, and nucleoli are larger. HCCs display an increased number of binucleated cells and of polyploidy nuclei, whereas well-differentiated HCCs, in contrast to HCCs with a

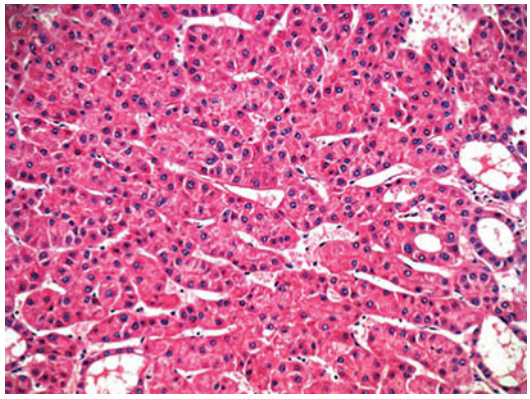

Fig. 18 Hepatocellular carcinoma, predominantly trabecular type. In this well-differentiated neoplasm, tumor cell plates show an abnormal width, although parts of the plates are rather slender. Few acinar/pseudoglandular structures are present (to the *right* and *bottom*). The cell plates are separated by sinusoid-like vascular channels (hematoxylin and eosin stain)

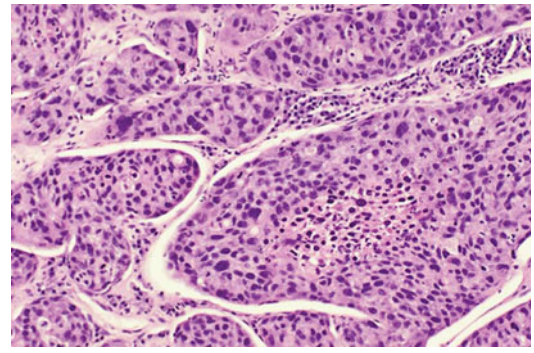

Fig. 20 In trabecular hepatocellular carcinoma with a macrotrabecular pattern, cells in inner parts of the plates may suffer from hypoxia due to a large distance to the next vascular channel, causing focal ischemic necrosis with karyopyknosis and karyorrhexis (to the *right* of the *middle*, hematoxylin and eosin stain)

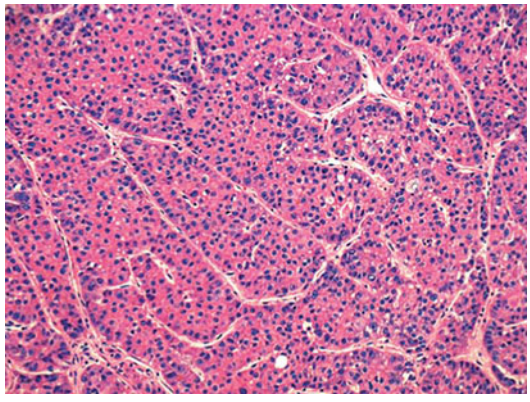

Fig. 19 In this trabecular hepatocellular carcinoma, tumor cell plates are large, sometimes exceeding a thickness of ten cells (macrotrabecular pattern). The neoplastic cells are hepatocyte-like and well differentiated (hematoxylin and eosin stain)

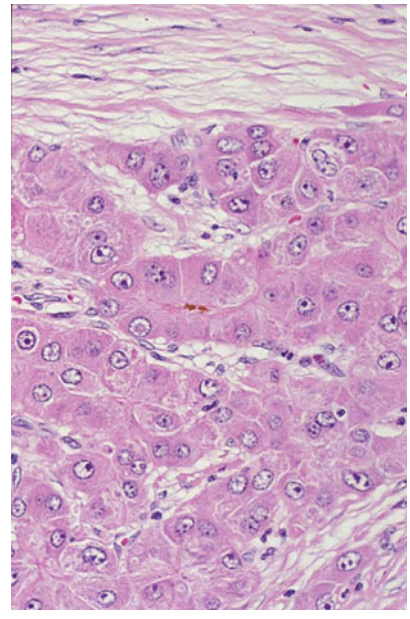

Fig. 21 This well-differentiated trabecular hepatocellular carcinoma with hepatocyte-like cells and abnormally enlarged nuclei shows deposition of *brown-yellow* bile in canaliculus-like structures (close to center of figure, hematoxylin and eosin stain)

grade 3, only rarely show multinucleated cells. Multinucleated cells in HCCs were described in early works on these tumors already (Nazari 1905). Nucleoli are prominent, and two to three of them may be observed (Smetana et al. 1972). Mitotic figures are usually not common in well-differentiated tumors; they are, e.g., less frequently present than in regenerating liver.

Morphometry disclosed that cell size in normotrabecular HCC is slightly reduced in comparison with normal hepatocytes or regenerative hepatocytes (Kondo et al. 1988; Nagato et al. 1991). The tumors may show a slight decrease in the density of the reticulin network,

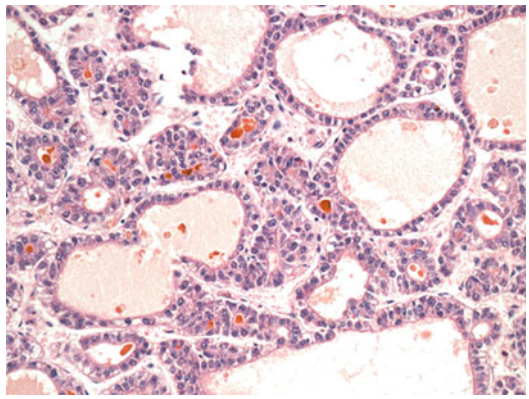

Fig. 22 Hepatocellular carcinoma, acinar/pseudoglandular type. The neoplastic cells form spherical spaces that may contain bile and/or a proteinaceous fluid (hematoxylin and eosin stain)

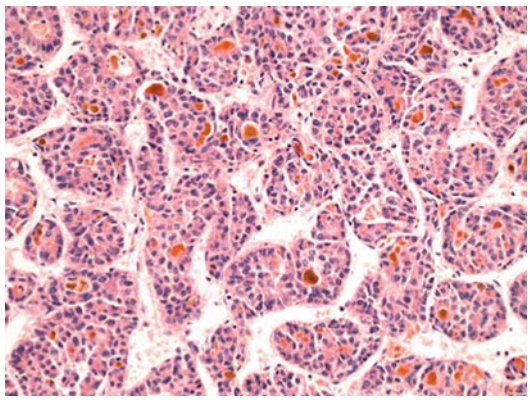

Fig. 23 Hepatocellular carcinoma with incomplete acinus formation. There is marked bile accumulation within dilated canaliculi and protoacini. A prominent sinusoidal vascular network is present (hematoxylin and eosin stain)

irrespective of the absence of macrotrabecular structures. Useful cytology features for well-differentiated HCC included small tumor cell size with an increased nuclear/cytoplasmic ratio; striking similarity of tumor cells to hepatocytes; a monotonous aspect of atypia; the presence of tumor giant cells, intracytoplasmic vacuoles, bile production, acinar formation, and narrow cell plates; a tendency for cell dissociation; and the presence of sinusoidal endothelial cells. In contrast, poorly differentiated HCC were characterized by cell dehiscence, large cells with ovoid nuclei, dyshesive pleomorphic cells, a thickened

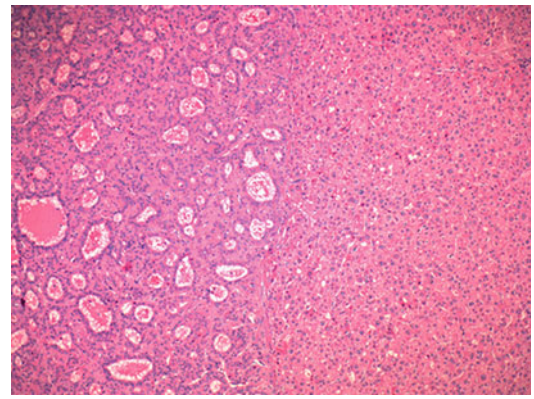

Fig. 24 Mixed acinar and trabecular/solid hepatocellular carcinoma. An acinar area (*left*) exhibits an abrupt transition into a non-acinar area (*right*, hematoxylin and eosin stain)

nuclear membrane, and one or more prominent nucleoli (Wee et al. 1991, 1994). A high level of differentiation sometimes includes large HCC in their entirety, but well-differentiated tumors may with time switch to components of lesser differentiation. This heterogeneity as to differentiation causes a bias in the interpretation of needle biopsies and fine-needle aspirates, due to sampling errors. A differentiation switch may already occur in small lesions. When well-differentiated small/early HCC reach a diameter of 1.0–1.5 cm, areas of lesser differentiation with increased proliferative activity may evolve (Kojiro and Nakashima 1999). It must be emphasized that many if not most advanced HCC are heterogeneous with respect to growth patterns, cellular differentiation, and grade, an observation that was already made by well-known authors of earlier literature (Von Albertini 1974).

Histology of Poorly Differentiated Hepatocellular Carcinoma

In contrast to well-differentiated or moderately differentiated HCC, high-grade HCCs with poor differentiation are less capable to form trabecular structures or plates, and usually no acinar profiles, the neoplastic cells having lost polarity and the junctional apparatus to generate more complex patterns. The cells are heterogeneous as to the

size, shape, and structure. Some tumors consist of small "basophilic" cells and resemble any anaplastic carcinoma, while others have medium-sized cells with an amphophilic cytoplasm, no longer of the hepatocyte type. A minority of tumors show pleomorphic or giant cells with highly atypical nuclei, with prominent nucleoli and numerous, in part abnormal mitotic figures. Poorly differentiated liver cancers may be difficult to classify as hepatocyte cancers, and only immunohistochemistry will solve the problem.

Cytologic Features

Cell Polarity

Well-differentiated and moderately differentiated HCC consists of neoplastic cells that recapitulate, at least in part, the polarized phenotype of normal hepatocytes (Zegers and Hoekstra 1998; Treyer and Münsch 2013). Subsets of tumor cells are oriented with a basolateral domain toward sinusoidal channels, whereas a canalicular-like domain can face the lumen of acinar structures.

Pleomorphism and Giant Cells

The presence of multinucleated or pleomorphic giant cells was already described and depicted in detail in the textbook of Ewing (1922). As outlined below (paragraph on grading), grade 3 HCCs often show enlarged cells with several nuclei. These cells have to be distinguished from the multinucleated and highly abnormal, pleomorphic cells that occur in part of poorly differentiated HCCs.

Tumor Cell Inclusions

Part of HCC cells harbor cytoplasmic globules or inclusions (Figs. 25 and 26). They comprise eosinophilic globules that are either PAS-positive or PAS-negative, hyaline globules, and pale bodies (Keeley et al. 1972; Underwood 1972; Grimelius et al. 1977; An et al. 1983; Wang and Liu 1986; MacDonald and Bedard 1990; Fukunaga et al. 1996; Nayar et al. 2000). These inclusions have to be distinguished from Mallory-Denk bodies (Pappenheimer and Hawthorne 1936). In one study, hyaline intracytoplasmic globules were detected in 15.2 % of HCC cases, mainly in male patients with a mean age in the fifth decade. HCC with hyaline globules more often showed tumor necrosis in comparison with HCC lacking globules (Cohen 1976), but the presence of hyaline globules was not related to tumor differentiation (Nayar et al. 2000). It was assumed

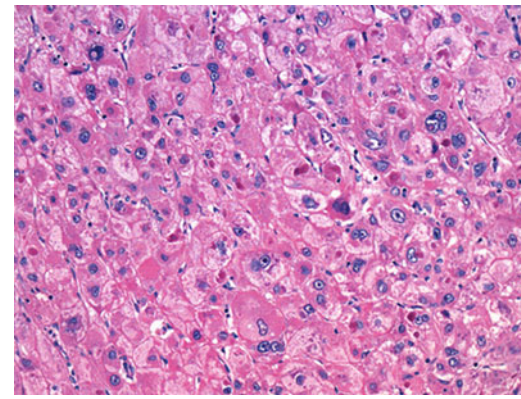

Fig. 25 Trabecular hepatocellular carcinoma with several types of cytoplasmic inclusions. Apart from pale eosinophilic inclusions, several Mallory-Denk bodies are observed. The latter appear as dark and homogeneous, dense eosinophilic bodies with irregular shape (hematoxylin and eosin stain)

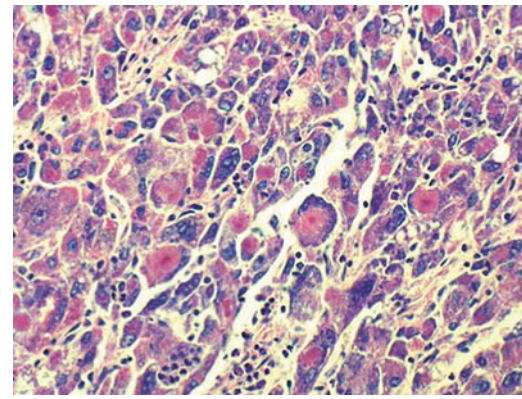

Fig. 26 Hepatocellular carcinoma with numerous eosinophilic inclusions showing a radiated structure (hematoxylin and eosin stain)

that hyaline globules may represent, at least in part, giant lysosomes. Ultrastructurally, hyaline inclusions appeared in two forms, i.e., one form consisting of a lamellar ultrastructure compatible with hyperplastic smooth endoplasmic reticulum and the other consisting of globular non-membrane-limited areas with a fibrillar material. These inclusions can contain p62 protein, a phosphotyrosine-independent ligand of p56lck kinase, similar to Mallory-Denk bodies (Stumptner et al. 1999a, b; Zatloukal et al. 2002). Parts of inclusions in HCC cells have a fibrillar structures and were termed globoid fibrillar inclusions (Huntrakoon and Bhatia 1984) or cytoplasmic fibrillar bodies (Smetana et al. 1972).

A further type of cytoplasmic inclusions or "bodies" are pale bodies which were described in fibrolamellar hepatocellular carcinoma (Craig et al. 1980), but also occur in ordinary HCC. Pale bodies are characterized as a pale amorphous, PAS-negative substance with a distinct margin and occupying a large part of the cytoplasm (Nakashima et al. 1992; Moon et al. 2000). They were detectable in up to 5.7 % of resected HCC (Nakashima et al. 1992). In one study, where these bodies were detectable in 5.5 % of HCC, the pale inclusion was sometime slightly eosinophilic, rarely resembling ground-glass inclusions found in HBV infection. In fact, part of pale inclusions may be caused by deposition of HBsAG, which is detectable in some HCC in HBV-positive patients (Péquignot et al. 1974; Wu and Lam 1979; Stromeyer et al. 1980). Nuclei of tumor cells with pale bodies were often displaced to the periphery of inclusions, leaving only a rime of cytoplasm. Cells with pale bodies may be clustered to small nodules (Moon et al. 2000). Ultrastructurally, pale bodies show a granular or fibrillar material surrounded by a limiting membrane, suggesting a relationship with the rough endoplasmic reticulum (Nakashima et al. 1992; Moon et al. 2000). A variant of pale eosinophilic inclusion in HCC achieve a diameter of about 14 μm and closely resemble ground-glass cells. These inclusions are thought to represent deposition of secretory proteinaceous material (Nakanuma et al. 1982). Various types of globular inclusions are also detectable in metastatic HCC (Haratake et al. 1990). HCC cells can contain bona fide Mallory-Denk bodies, sometimes associated with cell ballooning similar to that seen in alcohol toxicity (Hoso and Nakanuma 1990). In some subsets of HCC, Mallory-Denk bodies are very common; this variant of nonstandard liver cancer is treated in a separate paragraph. Part of HCC developed in the setting of alpha-1-antitrypsin deficiency can contain cytoplasmic PAS-positive globules similar to those found in nonneoplastic hepatocytes (see below). In contrast, the cytoplasmic hepatocyte inclusions seen in porphyria cutanea tarda are not present in the cells of HCC arising in this condition (Fakan et al. 1998).

Bile Accumulation

Depending on cell differentiation and the expression of bilirubin and bile acid transporters, HCC can extract bile components from blood, accumulate it in cytoplasm, and eventually secrete bile into the cavities of canaliculi and acini. Bile is seen as a yellow to green homogeneous material, droplets in the cytoplasm, and plugs in lumina of canaliculi. Older bile depositions in acini appear as a golden or brown matter. The identification of bile in a given tumor is diagnostic, or at least a very strong argument for HCC. Accumulation of bile is also found in part of HCC metastases (Nappi et al. 1992; Yu et al. 2013).

Accumulation of Neutral Fat (Fatty Change, Steatotic Change) and Other Cytoplasmic Changes

Part of HCC accumulate neutral fat (triglycerides) in their cytoplasm, visualized as small to large fat droplets ("fatty HCC"; fatty metamorphosis of HCC; steatotic HCC; Itai et al. 1987; Yoshikawa et al. 1988; Ueda et al. 1989; Kutami et al. 2000). In part of these neoplasms, steatosis of tumor cells is associated with inflammatory changes similar to those encountered in nonalcoholic or alcoholic steatohepatitis (steatohepatitic HCC, SH-HCC;

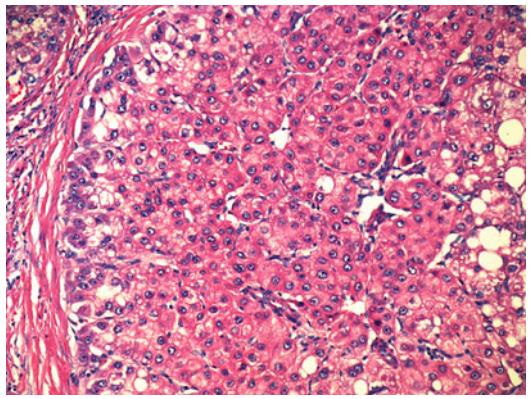

Fig. 27 At the interface between tumor and adjacent liver, HCC cells may show a morphology different from that in central tumor parts, i.e., with a clear cell change in this case (*left* part of figure, hematoxylin and eosin stain)

Salomao et al. 2010, 2012b). These tumors are further discussed in a separate chapter. HCC can show a focal clear cell change, not to be confounded with clear cell HCC which is a distinct variant (Fig. 27).

Reticulin Fiber Patterns

The production of a reticulin network is a characteristic feature of most non-squamous cell carcinomas. This feature was formerly summarized under the term reticulum (review: Tureen and Seelig 1933) and was first shown to consist of distinct fibrils by Henle in 1859. The demonstration of the reticulin fiber network by use of silver stains has proved useful in the differential diagnosis between HCC, in particular trabecular types, and benign hepatocellular nodules (Ferrell et al. 1992; Stahl and Voyvodic 2000; Wee and Nilsson 2003; Yao et al. 2013). The demonstration of a reticulin framework reliably allows to estimate the thickness of liver cell plates, which are normally two to three cells wide, while in HCC plates exceed a thickness of three cells (Ferrell et al.1993). Several studies arrived at the conclusion that, in contrast to normal or cirrhotic liver, well-differentiated HCC has either absent or markedly reduced reticulin, or an abnormal reticulin staining pattern with increased distances between mature reticulin fibers, the presence of

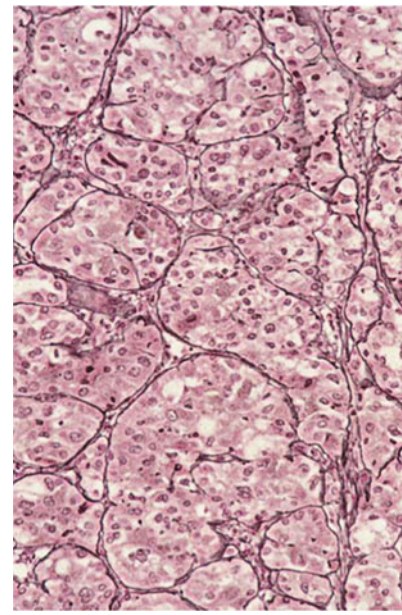

Fig. 28 Reticulin stain of a trabecular hepatocellular carcinoma. In contrast to normal liver tissue, the reticulin fibers are widely spaced due to macrotrabecular plates. By the use of the reticulin stain, the abnormal patterns of HCCs are readily visualized, this stain therefore being a very helpful method in diagnosis and differential diagnosis (Gomori *silver stain*)

abnormally short reticulin fibers, or an increased amount of very fine and loosely arranged fibers (Fig. 28).

There are rare exceptions in which HCC show a preserved reticulin framework (Wilkens et al. 2006; Hong et al. 2011). In the cases reported by Hong and coworkers (2011), a preserved reticulin framework was found to surrounding groups of neoplastic cells or individual neoplastic hepatocytes, a finding which is atypical both for HCC and benign liver cells tumors.

Reticulin loss is seen in early HCC undergoing stromal invasion (Kondo 2009, 2011), the invading cell cords not being accompanied by a typical reticulin framework (Miyao et al. 1999), and a lack of a reticulin framework distinguishes small HCC from macroregenerative nodules in cirrhotic livers (Ferrell et al. 1992). Reticulin loss also characterizes fine-needle aspirates of HCC (Gagliano 1995; Bergman et al. 1997; Wee and Nilsson 2003, Yang et al. 2004). It is thought that the phenomenon of loss of the reticulin framework is either due

to a "true" loss of reticulin fibers in the course of growth of HCC cells and the generation of abnormal sinusoid-like channels that are not surrounded by a normal, reticulin-containing perisinusoidal space or to an apparent reticulin loss due to the wider spacing of reticulin fibers owing to the presence of large tumor cell plates. Reticulin loss (defined as a loss similar to that seen in HCC) was also detected in benign fatty liver. For mild steatosis, reticulin loss was rare; however, loss increased for moderate steatosis and was most prominent in marked steatosis. An almost identical situation was found in cases of nonalcoholic steatohepatitis (NASH). In liver cell adenomas, reticulin loss was only seen in areas of steatosis (Singhi et al. 2012).

Loss of Kupffer Cells (Hepatic Macrophages) in Hepatocellular Carcinoma

Kupffer cells are reduced in HCC and display an altered intrasinusoidal distribution (Kranz et al. 1980; He et al. 2002; Liu et al. 2003). In contrast, Kupffer cells are present in liver cell adenoma, although their number may be less than in surrounding normal liver (Goodman et al. 1987). It has been claimed that loss of Kupffer cells is a general feature of HCC. However, there is a relationship between intratumoral Kupffer cell numbers and the differentiation grade and stage of tumors. By the use of the CD68 immunostain, it was found that the average number of Kupffer cells in well-differentiated HCC tissues less than 1 cm in diameter was not statistically different from that in noncancerous liver tissue, whereas the number of Kupffer cells decreased in HCC as tumor size increased and the histologic grade decreased (Tanaka et al. 1996). In an investigation on 48 cases, the number of Kupffer cells decreased as tumor size increased, and the lowest values were found in poorly differentiated neoplasms (Liu et al. 2003). CD68-reactive Kupffer cells were observed in early HCC, but were absent in advanced HCC (Wakasa et al. 1997). A loss of Kupffer cells in HCC was also found electron microscopically (Tabarin et al. 1986). In cytology smears, the presence of vimentin-positive, spider-shaped Kupffer cells is helpful in distinguishing HCC from other carcinomas (Wu et al. 1996). A reduced set of Kupffer cells in HCC is a substrate for the efficiency of modern imaging techniques, such as superparamagnetic iron oxide-enhanced MR, which reflects Kupffer cell numbers in hepatic tumors (Imai et al. 2000; Asahina et al. 2003; Shimofusa et al. 2010). Superparamagnetic iron oxide particles are sequestered by Kupffer cells under normal conditions, but are not retained in lesions lacking Kupffer cells such as HCC (Wang 2011).

It has been suggested that depletion of Kupffer cells as a distinct population of hepatic macrophages is linked to decreased hepatic immune surveillance favoring carcinogenic pathways (Manifold et al. 1983). Kupffer cells which are the differentiated offspring of bone marrow-derived monocytes are important in several host defense mechanisms, including clearance of microorganisms transported from gastrointestinal tract to liver and antitumor activities (Chen et al. 2001). Kupffer cells are thought to execute tumor cell control through increased production of chemokines and cytokines, specifically TNF-alpha and interferon-gamma, and via pathways involving nitric oxide. By these macrophage-derived factors, apoptosis of tumor precursor cells and cancer cells is induced (Zhu et al. 2000). A disordered defense milieu is already present in cirrhotic livers, as the number of Kupffer cells is reduced in hepatic cirrhosis. In addition, the ischemic-hypoxic situation present in sinusoids of cirrhotic nodules may incite Kupffer cells to produce and secrete, like tumor-associated macrophages (TAMs), cytokines that may promote tumor growth and metastasis (Liu et al. 2011b).

Grading of Hepatocellular Carcinoma

Previous histologic descriptions of HCC already related to various forms of differentiation, resulting in the terms trabecular carcinoma (carcinoma hepatocellular trabeculare, often grade

Table 5 Differentiation grades of hepatocellular carcinoma (grading, based on the Edmondson and Steiner grading system, 1954, modified and extended)

Grade I
Grade I is reserved for those areas in HCC of grade II where the difference between neoplastic cells and normal or hyperplastic hepatocytes is so minor that a diagnosis of HCC rests upon the demonstration of more aggressive growth in other parts of the tumor
Grade II
In grade HCC, the cells display marked resemblance to normal hepatocytes. However, the nuclei are larger and more hyperchromatic than normal, but the cytoplasm is abundant and eosinophilic; the cell borders are often sharp and clear-cut. Acini (pseudoglandular structures) are frequent; their lumina vary in size from tiny canaliculi to large thyroid-like spaces. The lumina of the acini are often filled with bile or a proteinaceous material
Grade III
In grade III HCC, the nuclei are usually larger and more hyperchromatic than in grade II cells. These nuclei occupy a relatively greater proportion of the cell (the nuclear-to-cytoplasm is increased). The cytoplasm is granular and eosinophilic as in grade II, but usually less so. Sometimes there is segregation of the granular cytoplasm toward the end of the cell bordering a lumen that usually does not contain bile. Acini are less common and less often contain bile or proteinaceous material. Tumor giant cells are most numerous in this grade
Grade IV
In grade III HCC, the nuclei are intensely hyperchromatic and occupy the greater part of the cell (markedly elevated nuclear-to-cytoplasm ratio). The cytoplasm is variable in amount, is often scanty, and contains fewer granules. The growth pattern is medullary in character, trabecules are difficult to find, and cell masses seem to lie loosely without cohesion between or in vascular channels. Only rare acini are found. Giant cells are not conspicuous. Spindle cell areas are seen in some of the tumors. Short plump cell forms, resembling oat cell carcinoma of the lung, are seen in some grade IV tumors

1 or 2), vesicular carcinoma (carcinoma hepatocellular vesiculare, now acinar HCC), and anaplastic carcinoma (carcinoma hepatocellulare anaplasticum, grade 4; Von Albertini 1974). A major breakthrough for HCC grading arrived when Edmondson and Steiner proposed their four-level grading system, which is now generally termed Edmondson-Steiner grading (Edmondson and Steiner 1954). Grading can be performed by the use of fine-needle aspiration biopsies (Ali et al. 1986). The grading includes nuclear and cytoplasmic features and growth patterns. Definitions of tumor grades are compiled in Table 5.

Most HCC are either grade 2 or grade 3, grade 2 being more common than grade 3, while grade 1 is less common, and grade 4 is the least common (Chapel et al. 1996). It is still difficult to judge what forms of HCC are "true" grade I neoplasms, and whether "pure" grade I HCCs exist, as grade I makes part of grade II lesions in the Edmondson-Steiner system. There are examples of well-differentiated small or early HCC that seem to consists exclusively of a grade I pattern, and there are also large solitary HCC with these features. Grade III HCC is relatively easy to recognize, owing to the typical presence of multinucleated tumor giant cells, that are however not pleomorphic. Due to the scant cytoplasm, which may be amphophilic or even slightly basophilic, the high or very high nucleus-to-cytoplasm ratio, the associated nuclear crowding, and the medullary-like growth pattern with effacement of plates and prominent sinusoid-like vessels, grade IV HCC resemble anaplastic carcinomas and may, without immunohistochemistry, sometimes be difficult to diagnose as HCC (Sasaki et al. 2014; Figs. 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38).

Stroma Formation (Desmoplasia) in Hepatocellular Carcinoma

Stroma is formed in HCC to variable degrees, with some variants being markedly desmoplastic (scirrhous HCC). However, apart from special forms of HCC, desmoplasia is usually less prominent than in many cholangiocarcinomas. Stromagenesis in hepatic malignancies is a distinct biologic feature affecting growth and spread (Sivridis et al. 2004), that is discussed in a separate chapter in more detail. Specifically, tumor stroma, even in cases where it is sparsely developed, displays a distinct gene expression signature that has a marked impact on growth, differentiation, and invasive properties of cancer cells embedded or migrating in it (Gao et al. 2011). Stromal cells engage in complex interaction with epithelial tumors cells that affect cancer cell behavior (review: Shtilbas

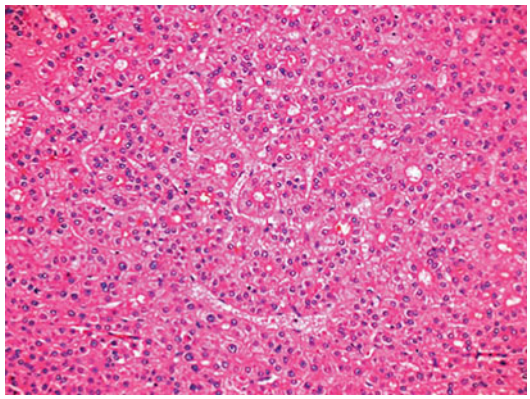

Fig. 29 Grading of hepatocellular carcinoma. This mixed trabecular and acinar neoplasm reveals a homogeneous population of hepatocyte-like cells and is grade 1 (hematoxylin and eosin stain)

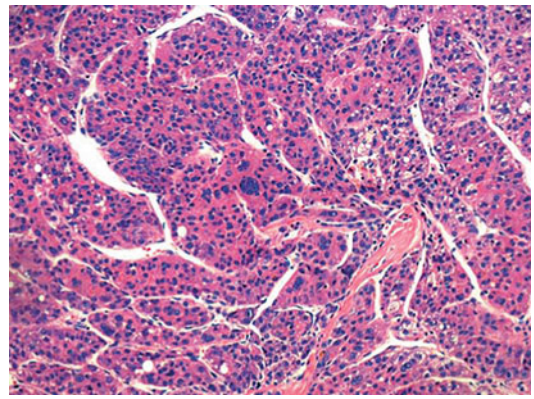

Fig. 31 Trabecular hepatocellular carcinoma with an increased proportion of atypical hepatoid cells and presence of multinucleated tumor cells, corresponding to grade 3 (hematoxylin and eosin stain)

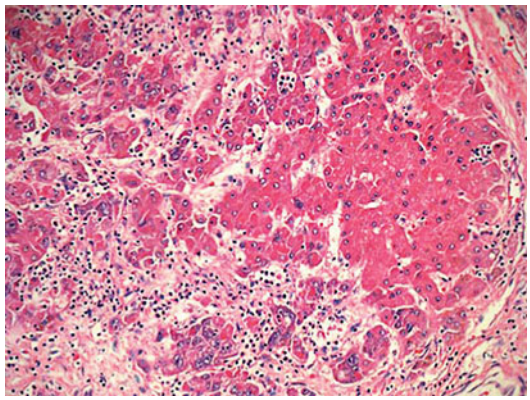

Fig. 30 Trabecular hepatocellular carcinoma of mixed grade, G1 and G2. The large hepatocyte-like cells to the *right* show only minor deviation from normal and are G1, while the neoplastic cells to the *left* exhibit increased nucleus-to-cytoplasm ratio and more pronounced nuclear atypia, representing G2 (hematoxylin and eosin stain)

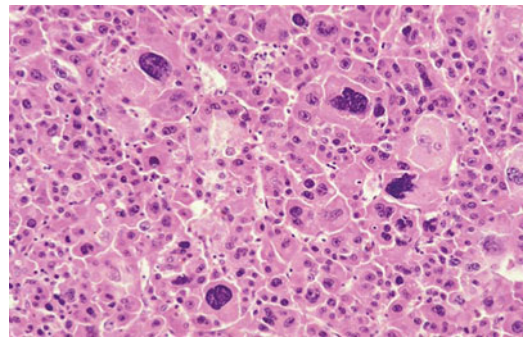

Fig. 32 In some hepatocellular carcinomas with otherwise grade 2 or grade 3 morphology, highly atypical and pleomorphic tumor cells can occur (hematoxylin and eosin stain)

2013). The tissue space between cancer cell plates and endothelia of intervening vascular channels is occupied by stromal spindle cells that have, on the one hand, the features of fibroblasts (stromal fibroblasts, review Li et al. 2012), while on the other hand a significant fraction of these spindle cells are reactive for alpha-smooth muscle actin and, less often, vimentin, but negative for desmin. These stromal cells therefore have the features of myofibroblasts (Enzan et al. 1994; Terada et al. 1996; review: Hinz 2010).

Vascular Patterns (Angioarchitecture) of Hepatocellular Carcinoma

HCCs are highly vascular tumors that possess a distinct angioarchitecture that in part mimics the microvascular system of normal liver, i.e., a sinusoid-like vessel pattern. In the course of

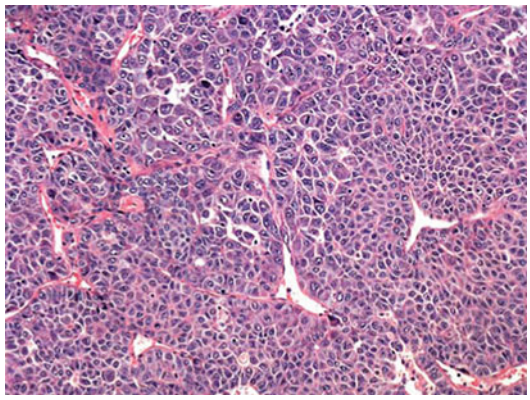

Fig. 33 In this trabecular hepatocellular carcinoma, almost all neoplastic cells display a markedly increased nucleus-to-cytoplasm ratio, resulting in a "blue cellular tumor," a feature typical for poorly differentiated HCCs (grade 4, hematoxylin and eosin stain)

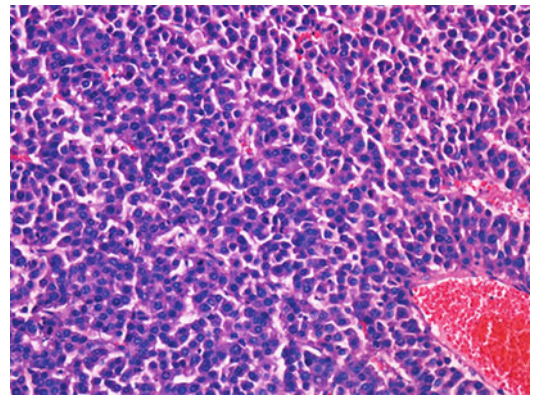

Fig. 35 Grade 4 hepatocellular carcinoma with predominance of small cells and diffuse growth pattern. Such "anaplastic" neoplasms are difficult to diagnose, requiring immunohistochemical and/or molecular methods (hematoxylin and eosin stain)

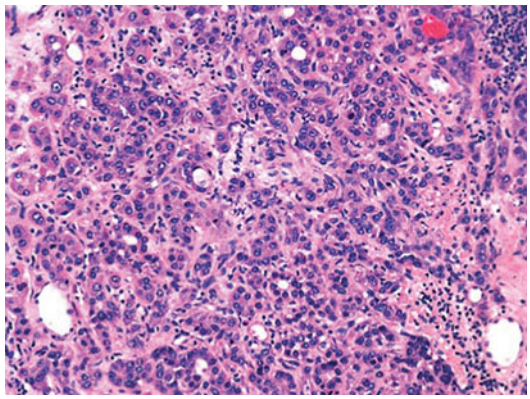

Fig. 34 Poorly differentiated grade 4 hepatocellular carcinoma may be dominated by clusters of medium-sized to small cells in the absence of a trabecular or acinar pattern, rendering diagnosis of HCC difficult without immunohistochemistry (hematoxylin and eosin stain)

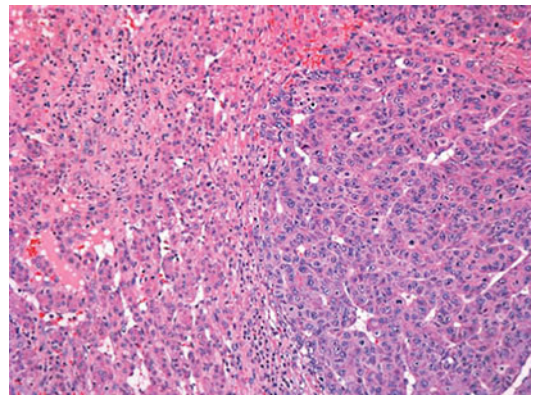

Fig. 36 Trabecular hepatocellular carcinoma of mixed differentiation. Some HCCs exhibit heterogeneity in regard to differentiation. In the present tumor, well-differentiated components (G1 and G2, *left*) are separated from a focus showing G3 and G4 (hematoxylin and eosin stain)

growth an invasion, this vascular system is continuously constructed in the setting of tumor angiogenesis, outlined in a separate chapter. HCCs show two predominant patterns of microvessels, capillary-like and sinusoid-like microvessels, these two patterns having an impact on tumor biology (see above; Chen et al. 2011). A fraction of HCC contain abnormal/aberrant arteries and display a lack of portal tracts with hepatic artery and portal vein branches. On CT images during arterial portography and CT during hepatic arteriography, these abnormal vascular patterns can be visualized in vivo. In the course of hepatocarcinogenesis in cirrhotic livers, abnormal arteries (intranodal arterial supply through newly formed abnormal arteries) gradually increase (Hayashi et al. 2002; Matsui 2004). However, the number of arteries in HCC varies as a function

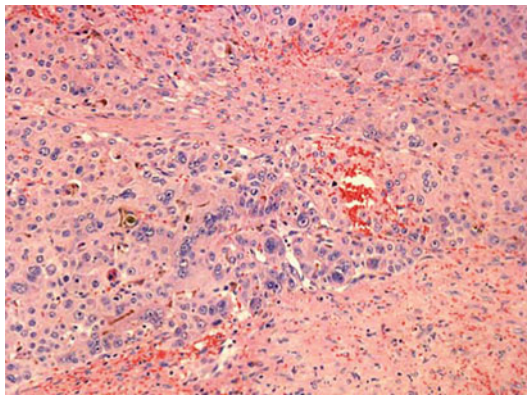

Fig. 37 Trabecular hepatocellular carcinoma of mixed differentiation. On a background of grade 2 tumor tissue, one focus is characterized by increased nuclear atypia and multinuclearity, being grade 3 (hematoxylin and eosin stain)

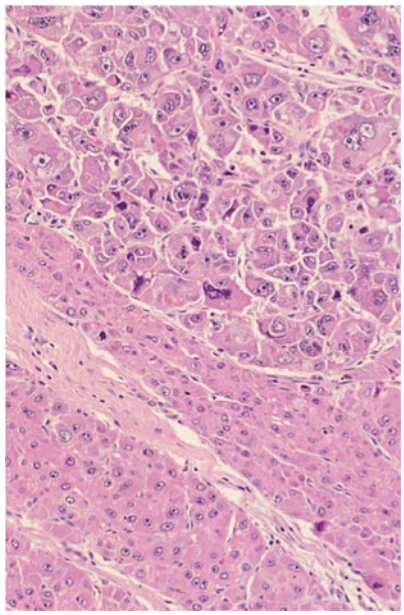

Fig. 38 Trabecular hepatocellular carcinoma of mixed differentiation. Well-differentiated HCC (G1/2) can contain poorly differentiated and pleomorphic components, reflecting tumor heterogeneity also observed at a macroscopic level (hematoxylin and eosin stain)

of tumor differentiation. There is a low-arterial vessel group of HCC with moderate differentiation and a more aggressive course (Fujita et al. 2010).

Encapsulation (Pseudocapsule or Capsule Formation)

Introduction

The formation of an incomplete or complete pseudocapsule (often termed capsule or encapsulation) has predominantly been found in non-small HCCs showing a nodular growth pattern. The reported prevalence of a pseudocapsule in nodular HCCs ranges from 10.3 % to 86.4 %, depending on geographic factors, diagnostic criteria used, and size and type of tumors studied (Okuda et al. 1977; Nakashima et al. 1982; Hsu et al. 1985; Tanaka et al. 1985; Kemeny et al. 1989; Fekete et al. 1990; Ng et al. 1992). Encapsulation of HCC may be more often observed in Japan in comparison with tumors studied in Western countries (Nakashima et al. 1983), but this was not confirmed by a later investigation (Kemeny et al. 1989). In a Japanese autopsy study on 26 cases of encapsulated HCCs, the mean age of the patients at diagnosis was 64.1 years, which was significantly older compared with that of 143 cases of nonencapsulated HCCs (Okuda et al. 1977). In an analysis of 154 HCC with adequate histology, encapsulation was identified in 46.8 %, the thickness of the capsule ranging from 0.13 to 3.09 mm (mean: 0.87 mm). Tumors with a capsule showed a much lower incidence of liver invasion, tumor microsatellites, and venous invasion (Ng et al. 1992). In an investigation of patient survival in HCC in relation to age, younger patients (<50 years of age) had less often pseudocapsules and a more advanced tumor stage (Ng et al. 1996). The incidence of tumor pseudocapsules did not increase or decrease with tumor size (Ng et al. 1992), but pseudocapsules are more common in pedunculated HCCs (Yeh et al. 2002) and are also found in early HCCs and small HCCs (Hsu et al. 1985; Kojiro 1998; Zheng et al. 2007). In one study, small nodular HCCs with distinct margins had thin fibrous pseudocapsules in more than half of the cases (Kojiro 1998). There seems to be a relation between the presence or absence of cirrhosis and tumor encapsulation. In a study of 74 cases of

non-cirrhotic HCC, only 50 % of the tumors were encapsulated (Liu et al. 2013).

Pathology

When strongly developed, tumor pseudocapsules are grossly visualized as a whitish to gray-white rim surrounding an expansively growing tumor, either complete, incomplete, or fragmented (Fig. 39).

A fragmented encapsulation is more often found in grossly invasive neoplasms that invade the liver substance. The whitish rim of a capsule is particularly well observable in pedunculated HCC. The liver parenchyma adjacent to the pseudocapsule may by atrophic, this atrophy zone sometimes reaching a thickness of more than 10 mm. This zone is slightly reddish, and on sections through a fresh specimen, the zone is often sunken with respect to more distant parts of parenchyma. Beneath the pseudocapsule, calcifications may develop, visualized as ring calcification on CT images (Fukuya et al. 1999).

Histologically, the pseudocapsule consists of a dense connective tissue that contains spindle cells (fibroblasts and myofibroblasts) and collagen fiber bundles (Fig. 40).

In contrast to tumor stroma, capsular tissue usually does not have a matrix rich in glycosaminoglycans and is therefore slightly eosinophilic. The capsule is strongly stained with the Van Gieson and trichrome stains and may be slightly PAS-positive, depending on the amount of glycoproteins such as fibronectin and laminin. The capsule is vascularized, whereby younger capsules usually contain more blood vessels than old, sclerosed ones. The fibrous tissue of pseudocapsules is traversed by few S100-positive nerve fibers in contact with blood vessels (Terada and Matsunaga 2001). The pseudocapsule may be invaded by HCC cells, which tend to follow perivascular spaces to reach the adjacent hepatic parenchyma. Immunohistochemically, many of the capsular spindle cells are reactive for alpha-smooth muscle actin (SMA) and therefore represent myofibroblasts that may have been recruited from local hepatic stellate cells, which are known to also occur in tumor stroma.

Fig. 39 Encapsulated hepatocellular carcinoma. The small tumor is sharply demarcated from cirrhotic liver tissue by a fibrous pseudocapsule

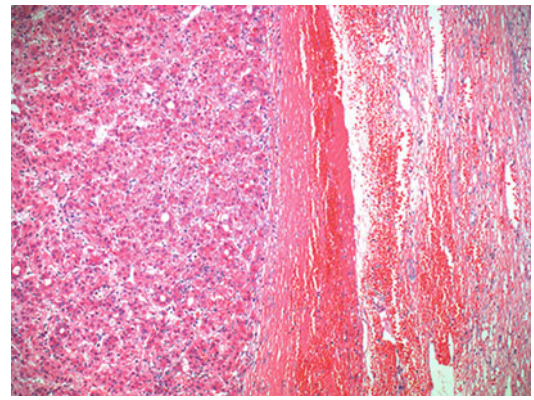

Fig. 40 Encapsulated hepatocellular carcinoma. The well-differentiated neoplasm is surrounded by a sheath of collagenous, hypocellular connective tissue (hematoxylin and eosin stain)

Biologic Significance of HCC Pseudocapsules

The presence of a pseudocapsule in HCC is one of the factors exerting a positive influence on outcome (Okuda et al. 1977; Ng et al. 1992; Iguchi

et al. 2009; Lin et al. 2010; review; Qin and Tang 2002; Lu et al. 2013). It has been suggested that the pseudocapsule acts as barrier or barricade preventing the spread of cancer cells, although this may be a mechanistic view that not adequately describes the function of a complex pseudocapsule. In a study of 189 surgically resected HCCs, 46.8 % of the cases had tumor encapsulation. Tumors with such a pseudocapsule showed a much lower incidence of direct liver invasion, tumor microsatellites, and venous permeation when compared with HCCs without pseudocapsule. Disease-free and actuarial survival times were significantly better in patients with encapsulated tumors (Ng et al. 1992). In a multivariate analysis of patients having undergone curative resection of HCC, only the presence of a tumor pseudocapsule was significantly associated with long-term survival without recurrence (Tsai et al. 2000). The absence of a complete tumor pseudocapsule is correlated with several high-risk prognostic factors in HCC. The lack of an intact tumor pseudocapsule was correlated with bile duct tumor thrombi, a lesion conferring an extremely dismal prognosis (Yu et al. 2011). The biological significance of tumor cells invading liver tissue beyond the pseudocapsule has been studied in detail. A study on 88 HCCs with a diameter of 5 cm or less compared an extracapsular infiltrating type, in which HCC cells infiltrated outside the pseudocapsule and touched the extratumoral liver parenchyma, and an intracapsular infiltrating type, in which the infiltrating HCC cells stayed inside the pseudocapsule. The analysis showed that the former type revealed a poorer outcome for the overall survival and disease-free survival, and this type was an independent prognostic factor for disease-free survival (Iguchi et al. 2008).

Pathogenesis of Pseudocapsules

Most HCCs develop in livers with cirrhotic change, but the development of a fibrous tumor pseudocapsule does not seem to be directly related to cirrhosis, as such pseudocapsules also arise around HCCs in non-cirrhotic livers (Fekete et al. 1990). The cellular source of pseudocapsules are mainly fibroblasts and myofibroblasts (Kojima et al. 1999; Ishizaki et al. 2001). The pseudocapsule of HCCs contains numerous stromal spindle cells expressing high molecular weight caldesmon, a highly specific marker for smooth muscle cells (Nakayama et al. 2004). Alpha-SMA-positive myofibroblasts are also observed in fibrous capsules around hepatic metastases, e.g., of colorectal carcinoma (Lunevicius et al. 2001; Gulubova and Vlaykova 2006). Procollagen alpha1(I) mRNA colocalized to alpha-SMA-positive stellate cells/myofibroblasts within regions of increased collagen deposition in HCC pseudocapsules, suggesting that hepatic stellate cells differentiated into myofibroblasts are responsible for pseudocapsular matrix production (Ooi et al. 1997). The fact that the CD34-negative cells of HCC's tumor stroma also express SMA and are myofibroblasts (Enzan et al. 1994; Terada et al. 1996; Faouzi et al. 1999) suggests that the stroma may participate in the morphogenesis of a pseudocapsule.

Differential Diagnosis of Ordinary Hepatocellular Carcinoma

Both radiologically and pathologically, HCC with its diverse differentiation patterns and grades has to be distinguished from other nodular hepatocellular lesions, specifically liver cell adenoma, several types of nodular hepatic precursor lesions, and focal nodular hyperplasia (Hytiroglou and Theise 1998). Unusual nodular hepatocyte lesions with large cell change and formation liver cell rosettes occur in primary biliary cirrhosis and may be confounded with well-differentiated HCC (Nakanuma and Hirata 1993).

References

Abe T, Kajiyama K, Harimoto N, Gion T, Shirabe K, Nagaie T (2012) Intrahepatic bile duct recurrence of hepatocellular without a detectable liver tumor. Int J Surg Case Rep 3:275–278

Ali MA, Akhtar M, Mattingly RC (1986) Morphologic spectrum of hepatocellular carcinoma in fine needle aspiration biopsies. Acta Cytol 30:294–302

An T, Ghatak N, Kastner R, Kay S, Lee HM (1983) Hyaline globules and intracellular lumina in a hepatocellular carcinoma. Am J Clin Pathol 79:392–396

Anthony PP (1973) Primary carcinoma of the liver: a study of 282 cases in Ugandan Africans. J Pathol 110:37–48

Anthony PP (1979) Hepatic neoplasms. In: Macsween RN, Anthony PP, Scheuer PJ (eds) Pathology of the liver. Churchill Livingstone, Edinburgh, pp 387–413

Anthony RR (1999) Hepatocellular carcinoma. Adv Liver Pathol 32:297–298

Anthony PP, James K (1987) Pedunculated hepatocellular carcinoma. Is it an entity? Histopathology 11:403–414

Asahina Y, Izumi N, Uchihara M, Noguchi O, Ueda K, Inoue K, Nishimura Y, Tsuchiya K et al (2003) Assessment of Kupffer cells by ferumoxides-enhanced MR imaging is beneficial for diagnosis of hepatocellular carcinoma: comparison of pathological diagnosis and perfusion patterns assessed by CT hepatic arteriography and CT arterioportography. Hepatol Res 27:196–204

Association of Directors of Anatomic and Surgical Pathology (2005) Recommendations for the reporting of tissues removed as part of the surgical treatment of malignant liver tumors. Am J Clin Pathol 123:494–498

Baer HU, Gertsch P, Matthews JB, Schweizer W, Triller J, Zimmermann A, Blumgart LH (1989) Resectability of large focal liver lesions. Br J Surg 76:1042–1045

Baer HU, Holzinger F, Dennison AR, Zimmermann A (1995) Diagnosis and surgical therapy of dependent and pedunculated hepatic tumours. Dig Surg 12:228–234

Bège T, Le Treut YP, Hardwigsen J, Ananian P, Richa H, Campan P, Garcia S (2007) Prognostic factors after resection for hepatocellular carcinoma in nonfibrotic or moderately fibrotic liver. A 116-case European series. J Gastrointest Surg 11:619–625

Bei R, Mizejewski GJ (2011) Alpha fetoprotein is more than a hepatocellular cancer biomarker: from spontaneous immune response in cancer patients to the development of an AFP-based cancer vaccine. Curr Mol Med 11:564–581

Bell DA, Carr CP, Szyfelbein WM (1986) Fine needle aspiration cytology of focal liver lesions. Results obtained with examination of both cytologic and histologic preparations. Acta Cytol 30:397–402

Bergman S, Graeme-Cook F, Pitman MB (1997) The usefulness of the reticulin stain in the differential diagnosis of liver nodules on fine-needle aspiration biopsy cell block preparations. Mod Pathol 10:1258–1264

Berman C (1959) Primary carcinoma of the liver. Bull N Y Acad Med 35:275–292

Bertino G, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS (2012) Hepatocellular carcinoma serum markers. Semin Oncol 39:410–433

Bosch FX, Ribes J, Diaz M, Cléries R (2004) Primary liver cancer: worldwide incidence and trends. Gastroenterology 127(Suppl 1):S5–S16

Bosch FX, Ribes J, Cléries R, Diaz M (2005) Epidemiology of hepatocellular carcinoma. Clin Liver Dis 9:191–211

Boyault et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17187432

Carr BI, Pancoska P, Branch RA (2010) Low alpha-fetoprotein hepatocellular carcinoma. J Gastroenterol Hepatol 25:1543–1549

Casagrande A, Liscidini P, Pepoli R (1985) Obstructive icterus caused by a biliary thrombus due to hemobilia caused by a hepatocarcinoma. Case observation (in Italian). Minerva Chir 40:571–576

Castells L, Moreiras M, Quiroga S, Alvarez-Castells A, Segarra A, Estaban R, Guardia J (2001) Hemoperitoneum as a first manifestation of hepatocellular carcinoma in western patients with liver cirrhosis: effectiveness of emergency treatment with transcatheter arterial embolization. Dig Dis Sci 46:555–562

Chapel F, Guettier C, Chastang C, Rached AA, Mathieu D, Tepper M, Beaugrand M, Trinchet JC (1996) Needle biopsy of hepatocellular carcinoma: assessment of prognostic contribution of histologic parameters including proliferating cell nuclear antigen labeling and correlations with clinical outcomes. Group d'Etude et de Traitement du Carcinoma Hépatocellulaire. Cancer 77:864–871

Chearanai O, Plengvanit U, Asavanich C et al (1983) Spontaneous rupture of primary hepatoma: report of 63 cases with particular reference to the pathogenesis and rationale treatment by hepatic artery ligation. Cancer 51:1532–1536

Chedid AD, Klein PW, Tiburi MF, Villwock MM, Bassani LE, Chedid MF (2001) Spontaneous rupture of hepatocellular carcinoma with haemoperitoneum: a rare condition in Western countries. HPB 3:227–230

Chen CY, Lin XZ, Shin JS, Lin CY, Leow TC, Chen CY, Chang TT (1995) Spontaneous rupture of hepatocellular carcinoma. A review of 141 Taiwanese cases and comparison with nonrupture cases. J Clin Gastroenterol 21:238–242

Chen TZ, Wu JC, Chan CY, Sheng WY, Yen FS, Chiang JH, Chau GY, Liu WY et al (1996) Ruptured hepatocellular carcinoma: treatment strategy and prognostic factor analysis. Zhonghua Yi Xue Za Zhi (Taipei) 57:322–328

Chen GG, Lau WY, Lai PB, Chun YS, Chak EC, Leung BC, Lam IK, Lee JF, Chui AK (2001) Activation of Kupffer cells inhibits tumor growth in a murine model system. Int J Cancer 99:713–720

Chen et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21488945

Chhieng DC (2004) Fine needle aspiration biopsy of liver – an update. World J Surg Oncol 2:5

Chuang et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19091458

Clarkston W, Inciardi M, Kirkpatrick S, MsEwen G, Ediger S, Schubert T (1988) Acute hemoperitoneum from rupture of a hepatocellular carcinoma. J Clin Gastroenterol 10:221–225

Cohen C (1976) Intracytoplasmic hyaline globules in hepatocellular carcinomas. Cancer 37:1754–1758

Cooper CE, Rogers SO, Norwich AC, Lougheed GW (1935) Primary carcinoma of the liver of unusually massive proportions. Can Med Assoc J 32:420–422

Craig JR, Peters RL, Edmondson HA, Omata M (1980) Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinicopathologic features. Cancer 46:372–379

Cunningham RM (1943/44) Primary carcinoma of the liver. A clinical-pathologic report of 14 cases at the University Hospital from 1927 to 1943. Bull School Med Univ Maryland 28:61–79

Dabbs DJ, Geisinger KR, Ruggiero F, Raab SS, Nalesnik M, Silverman JF, Association of Directors of Anatomic and Surgical Pathology (2004) Recommendations for the reporting of tissues removed as part of the surgical treatment of malignant liver tumors. Hum Pathol 35:1315–1323

Dominguez-Malagon H, Gaytan-Graham S (2001) Hepatocellular carcinoma: an update. Ultrastruct Pathol 25:497–516

Dusenbery D (1997) Biliary stricture due to hepatocellular carcinoma: diagnosis by bile duct brushing cytology. Diagn Cytopathol 16:55–56

Ebara C, Yamazaki S, Moriguchi M, Mitsuka Y, Funada T, Higaki T, Takayama T (2013) Complete remission by transarterial infusion with cisplatin for recurrent bile duct tumor thrombus of hepatocellular carcinoma: report of a case. World J Surg Oncol 11:78

Edmondson HA (1955) Pathology of cancer of the liver in the United States of America. Schweiz Z Pathol Bakteriol 18:653–656

Edmondson HA, Steiner PE (1954) Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 7:462–503

Eggel H (1901) Über das primäre Carcinom der Leber. Beitr Pathol Anat Allg Pathol 30:506

El-Serag HB (2002) Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 35(5 Suppl 2): S72–S78

Enzan H, Himeno H, Iwamura S, Onishi S, Saibara T, Yamamoto Y, Hara H (1994) Alpha-smooth muscle actin-positive perisinusoidal stromal cells in human hepatocellular carcinoma. Hepatology 19:895–903

Esaki M, Shimada K, Sano T, Sakamoto Y, Kosuge T, Ojima H (2005) Surgical results for hepatocellular carcinoma with bile duct invasion: a clinicopathologic comparison between macroscopic and microscopic tumor thrombus. J Surg Oncol 90:226–232

Ewing J (1922) Neoplastic diseases; a treatise on tumors. W.B. Saunders, Philadelphia and London, 2nd ed

Fakan F, Chlumska A, Krijt J, Kocova L (1998) Cytoplasmic liver cell inclusions – a typical feature of porphyria cutanea tarda – are absent in porphyria-related hepatic neoplasias. Neoplasma 45:102–106

Faouzi S, Le Bail B, Neaud V, Boussarie L, Saric J, Bioulac-Sage P, Balabaud C, Rosenbaum J (1999) Myofibroblasts are responsible for collagen synthesis in the stroma of human hepatocellular carcinoma: an in vivo and in vitro study. J Hepatol 30:275–284

Fattovich G, Stroffolini T, Zagni I, Donato F (2004) Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 127(5 Suppl 1):S35–S50

Fekete F, Belghiti J, Flejou JF, Panis Y, Molas G (1990) Hepatocellular carcinoma arising in the normal liver. A clinical study and long-term prognosis after surgical resection in 12 patients (in French). Chirurgie 116:730–734

Ferrell L, Kakar S (2007) Tumors of the liver, gallbladder, and biliary tree. In: Fletcher CDM (ed) Diagnostic histopathology of tumors, vol 1, 3rd edn. Churchill Livingstone/Elsevier, Philadelphia, pp 417–462

Ferrell L, Wright T, Lake J, Roberts J, Ascher N (1992) Incidence and diagnostic features of macroregenerative nodules vs. small hepatocellular carcinoma in cirrhotic livers. Hepatology 16:1372–1381

Ferrell LD, Crawford JM, Dhillon AP, Scheuer PJ, Nakanuma Y (1993) Proposal for standardized criteria for the diagnosis of benign, borderline, and malignant hepatocellular lesions arising in chronic advanced liver disease. Am J Surg Pathol 17:1113–1123

Fischer B (1903) XXVII. Über Gallengangskarzinome sowie über Adenom und primären Krebs der Leberzellen. Virchows Arch Pathol Anat Physiol Klin Med 174:544–563

Foster JH, Berman MM (1977) Solid liver tumors. In: Ebert PA (ed) Series major problems in clinical surgery, vol XXII. W.B. Saunders, Philadelphia

Fujita N, Aishima S, Iguchi T, Nishihara Y, Yamamoto H, Taketomi A, Oda Y, Honda H et al (2010) Down-regulation of artery in moderately differentiated hepatocellular carcinoma related to tumor development. Hum Pathol 41:838–847

Fukunaga N, Fujioka A, Tanaka K, Toyama R (1996) Oncocytic hepatocellular carcinoma with numerous globular hyaline bodies. Pathol Int 46:286–291

Fukuya et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10593291

Gagliano EF (1995) Reticulin stain in the fine needle aspiration differential diagnosis of liver nodules. Acta Cytol 39:596–598

Gall EA (1960) Primary and metastatic carcinoma of the liver – relationship to hepatic cirrhosis. Arch Pathol 70:226–232

Gao Q, Wang XY, Qiu SJ, Zhou J, Shi YH, Zhang BH, Fan J (2011) Tumor stroma reaction-related gene signature predicts clinical outcome in human hepatocellular carcinoma. Cancer Sci 102:1522–1531

Giannelli G, Antonaci S (2006) New frontiers in biomarkers for hepatocellular carcinoma. Dig Liver Dis 38:854–859

Giarelli L, Melato M, Zanconati F, Musse MM, Laurino L, Okuda K, Kojiro M (1991) Primary liver cancer in non-cirrhotic liver. Epidemiological study based on autopsies performed in Trieste, Italy, and Kurume. Jpn J Gastroenterol Hepatol 6:278–282

Gibbons GE, Bell JW (1963) Massive spontaneous hemoperitoneum, a complication of primary liver carcinoma. West J Surg Obstet Gynecol 71:26–29

Goldberg S, Wallerstein H (1934) Primary massive liver-cell carcinoma. Rev Gastroenterol 1:305–313

Gonzalez SA, Keeffe EB (2011) Diagnosis of hepatocellular carcinoma: role of tumor markers and liver biopsy. Clin Liver Dis 15:297–306

Goodman ZD, Mikel UV, Lubbers PR, Ros PR, Langloss JM, Ishak KG (1987) Kupffer cells in hepatocellular adenomas. Am J Surg Pathol 11:191–196

Grimelius L, Stenram U, Westman J, Westman-Naeser S (1977) Hyaline cytoplasmic inclusions in human hepatoma. A case report. Acta Cytol 21:469–476

Gulubova MV, Vlaykova TI (2006) Significance of tenascin-C, fibronectin, laminin, collagen IV, alpha5beta1 and alpha9beta1 integrins and fibrotic capsule formation around liver metastases originating from cancers of the digestive tract. Neoplasma 53:372–383

Gustafson EG (1937) An analysis of 62 cases of primary carcinoma of the liver based on 24,40 necropsies at Bellevue hospital. Ann Intern Med 11:889–900

Gyotoku Y, Sugihara H, Amagasaki T, Mori I, Kinoshita I (1980) An autopsy case of pedunculated liver cell carcinoma and its review. Jpn J Cancer Clin 26:92–96

Hanot VC, Gilbert A (1888) Etudes sur les maladies du foie: cancer (épitheliome); sarcome; mélanomes; kystes non parasitaires; angiomes. Asselin and Houzeau, Paris

Hansemann D (1897) Die mikroskopische Diagnose der bösartigen Geschwülste. Verlag von August Hirschwald, Berlin

Haratake J, Horie A, Setojima M (1990) Globular cytoplasmic inclusion bodies in a metastatic hepatocellular carcinoma of the iliac bone. Ultrastruct Pathol 14:283–288

Hasegawa K, Kubota K, Mori M, Midorikawa Y, Takayama T, Makuuchi M (2002) Hepatocellular carcinoma originating from intramural cells in the bile duct. Hepatogastroenterology 49:1688–1691

Hayashi M, Matsui O, Ueda K, Kawamori Y, Gabata T, Kadoya M (2002) Progression to hypervascular hepatocellular carcinoma: correlation with intranodular blood supply evaluated with CT during intraarterial injection of contrast material. Radiology 225:143–149

He X, Liu K, Zhao L, Zhou S, Liu L, Liu C (2002) Localization and distribution of Kupffer cells in hepatocellular carcinoma (in Chinese). Zhonghua Gan Zang Bing Za Zhi 10:177

Herxheimer G (1930) Lebergewächse. In: Henke F, Lubarsch O (eds) Verdauungsdrüsen, erster Teil: Leber, vol 5, Handbuch der speziellen pathologischen Anatomie und Histologie. Verlag von Julius Springer, Berlin, pp 797–987

Hinz B (2010) The myofibroblast: paradigm for a mechanically active cell. J Biomech 43:146–155

Ho J, Wu PC, Kung TM (1981) An autopsy study of hepatocellular carcinoma in Hong Kong. Pathology 13:409–416

Hong H, Patonay B, Finley J (2011) Unusual reticulin staining pattern in well-differentiated hepatocellular carcinoma. Diagn Pathol 6:15

Horie Y, Katoh S, Yoshida H, Imaoka T, Suou T, Hirayama C (1983) Pedunculated hepatocellular carcinoma: report of three cases and review of literature. Cancer 51:746–751

Hoshida Y, Nijman SMB, Kobayashi M, Chan JA, Brunet JP, Chiang DY, Villanueva A et al (2009) Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. Cancer Res 69:7385–7392

Hoso M, Nakanuma Y (1990) Clinicopathological characteristics of hepatocellular carcinoma bearing Mallory bodies: an autopsy study. Liver 10:264–268

Hsu HC, Sheu JC, Lin YH, Chen DS, Lee CS, Hwang LY, Beasley RP (1985) Prognostic histologic features of resected small hepatocellular carcinoma (HCC) in Taiwan. A comparison with resected large HCC. Cancer 56:672–680

Huang et al. 1996. http://www.ncbi.nlm.nih.gov/pubmed/8895013

Huang JF, Wang LY, Lin ZY, Chen SC, Hsieh MY, Chuang WL, Yu MY, Lu SN et al (2002) Incidence and clinical outcome of icteric type hepatocellular carcinoma. J Gastroenterol Hepatol 17:190–195

Huang JF, Chen SC, Wang LY, Yu ML, Dai CY, Chuang WL, Chang WY (2006) Diagnosis of icteric-type hepatocellular carcinoma by fine needle aspiration: a case report. Acta Cytol 50:531–533

Hui AM, Takayama T, Sano K, Kubota K, Akahane M, Ohtomo K, Makuuchi M (2000) Predictive value of gross classification of hepatocellular carcinoma on recurrence and survival after hepatectomy. J Hepatol 33:975–979

Huntrakoon M, Bhatia P (1984) Globoid fibrillar inclusions in hepatocellular carcinoma. Ultrastruct Pathol 6:265–268

Hytiroglou P (2004) Morphological changes of early human hepatocarcinogenesis. Semin Liver Dis 24:65–75

Hytiroglou P, Theise ND (1998) Differential diagnosis of hepatocellular nodular lesions. Semin Diagn Pathol 15:285–299

Iguchi T, Aishima S, Taketomi A, Nishihara Y, Fujita N, Sanefuji K, Maehara Y et al (2008) Extracapsular penetration is a new prognostic factor in human hepatocellular carcinoma. Am J Surg Pathol 32:1675–1682

Iguchi T, Aishima S, Sanefuji K, Fujita N, Sugimachi K, Gion T, Taketomi A, Shirabe K et al (2009) Both fibrous capsule formation and extracapsular penetration are powerful predictors of poor survival in human hepatocellular carcinoma: a histological

assessment of 365 patients in Japan. Ann Surg Oncol 16:2539–2546
Ikeda Y, Matsumata T, Adachi E, Hayashi H, Takenaka K, Sugimachi K (1997) Hepatocellular carcinoma of the intrabiliary growth type. Int Surg 82:76–78
Ikenaga N, Chijiwa K, Otani K, Ohuchida J, Uchiyama S, Kondo K (2009) Clinicopathologic characteristics of hepatocellular carcinoma with bile duct invasion. J Gastrointest Surg 13:492–497
Imai Y, Murakami T, Yoshida S, Nishikawa M, Ohsawa M, Tokunaga K, Murata M et al (2000) Superparamagnetic iron oxide-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading. Hepatology 32:205–212
International Consensus Group for Hepatocellular Neoplasia (2009) Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology 49:658–664
International Working Party (1995) Terminology of nodular hepatocellular lesions. Int Work Party Hepatol 22:983–993
Ishizaki M, Ashida K, Higashi T, Nakatsukasa H, Kaneyoshi T, Fujiwara K, Nouso K et al (2001) The formation of capsule and septum in human hepatocellular carcinoma. Virchows Arch 438:574–580
Itai Y, Ohtomo K, Kokubo T, Makita K, Okada Y, Machida T, Yashiro N (1987) CT and MR imaging of fatty tumors of the liver. J Comput Assist Tomogr 11:253–257
Jacobsen et al. 1983. http://www.ncbi.nlm.nih.gov/pubmed/6573086
Kaczynski J, Hansson G, Wallerstedt S (2005) Clinical features in hepatocellular carcinoma and the impact of autopsy on diagnosis. A study of 530 cases from a low-endemicity area. Hepatogastroenterology 52:1798–1802
Kai K, Miyoshi A, Kitahara K, Miyazaki K, Noshiro H, Tokunaga O (2012) Usual and unusual gross appearance of hepatocellular carcinomas. In: Lau JWY (ed) Hepatocellular carcinoma – clinical research. InTech, http://www.intechopen.com/books/hepatocellular-carcinoma-clinical-research/usual-and-unsual-gross-appearance-of-hepatocellular-carcinomas
Kaneko T, Terabe K, Ito K et al (1992) A case of extrahepatically growing hepatocellular carcinoma fed by the right middle adrenal artery. Jpn J Gastroenterol Surg 25:132–135
Kanematsu M, Imaeda T, Yamawaki Y, Seki M, Goto H, Sone Y, Iinuma G, Mochizki R et al (1992) Rupture of hepatocellular carcinoma: predictive value of CT findings. AJR Am J Roentgenol 158:1247–1250
Karatzas T, Smirnis A, Dimitroulis D, Patsouras D, Evaggelou K, Kykalos S, Kouraklis G (2011) Giant pedunculated hepatocellular carcinoma with hemangioma mimicking intestinal obstruction. BMC Gastroenterol 11:99
Katoh H, Ojima H, Kokubu A, Saito S, Kondo T, Kosuge T, Hosoda F, Imoto I, Inazawa J et al (2007) Genetically distinct and clinically relevant classification of hepatocellular carcinoma: putative therapeutic targets. Gastroenterology 133:1475–1486
Kaufmann E (1958) In: Staemmler M (ed) Lehrbuch der speziellen pathologischen Anatomie, Vol.2, part 2, 11 and 12th edn. Walter de Gruyter, Berlin, pp 1214–1222
Keeley AF, Iseri OA, Gottlieb LS (1972) Ultrastructure of hyaline cytoplasmic inclusions in a human hepatoma: relationship to Mallory's alcoholic hyaline. Gastroenterology 62:280–293
Kemeny F, Vadrot J, Wu A, Smadja C, Meakins JL, Franco D (1989) Morphological and histological features of resected hepatocellular carcinoma in cirrhotic patients in the West. Hepatology 9:253–257
Kew MC, Popper H (1984) Relationship between hepatocellular carcinoma and cirrhosis. Semin Liver Dis 4:136–146
Kim HC, Yang DM, Jin W, Park SJ (2008) The various manifestations of ruptured hepatocellular carcinoma: CT imaging findings. Abdom Imaging 33:633–642
Kishi K, Shikata T, Hirohashi S, Hasegawa H, Yamazaki S, Makuuchi M (1983) Hepatocellular carcinoma. A clinical and pathologic analysis of 57 hepatectomy cases. Cancer 51:542–548
Klatskin G, Conn HO (1993) Chapter 25. Neoplasms of the liver and intrahepatic bile ducts, vol 1, Histopathology of the liver. Oxford University Press, New York, pp 367–395
Kohno H, Koga S, Taniura H, Hayashi H, Hayashi T, Yaita A, Nakamura T (1987) A case report of pedunculated hepatocellular carcinoma diagnosed before surgery. Jpn J Gastroenterol Surg 20:98–101
Kojima A, Kaneda K, Ueda M, Maki A, Takabayashi A, Fukushima S, Sakurai M, Nagai R et al (1999) Induction of smooth muscle cells in the fibrous capsule of human hepatocellular carcinoma but not in the septa of hepatic cirrhosis. Virchows Arch 434:413–422
Kojiro M (1998) Pathology of early hepatocellular carcinoma: progression from early to advanced. Hepatogastroenterology 45(Suppl 3):1203–1205
Kojiro M (2005) Histopathology of liver cancers. Best Pract Res Clin Gastroenterol 19:39–62
Kojiro M (2006) Pathology of hepatocellular carcinoma. Wiley-Blackwell Publishers
Kojiro M (2007) Pathology of hepatocellular carcinoma. Blackwell Publishing, Oxford
Kojiro M, Nakashima O (1999) Histopathologic evaluation of hepatocellular carcinoma with special reference to small early stage tumors. Semin Liver Dis 19:287–296
Kojiro M, Kawabata K, Kawano Y, Shirai F, Takmoto N, Nakashima T (1982) Hepatocellular carcinoma presenting as intrabile duct tumor growth: a clinicopathologic study of 24 cases. Cancer 49:2144–2147
Kondo F (2009) Histological features of early hepatocellular carcinomas and their developmental process: for daily practical clinical application: hepatocellular carcinoma. Hepatol Int 3:283–293

Kondo F (2011) Assessment of stromal invasion for correct histological diagnosis of early hepatocellular carcinoma. Int J Hepatol 2011:241652

Kondo Y, Nakajima T (1987) Pseudoglandular hepatocellular carcinoma. A morphogenetic study. Cancer 60:1032–1037

Kondo F, Wada K, Kondo Y (1988) Morphometric analysis of hepatocellular carcinoma. Virchows Arch A Pathol Anat Histopathol 413:425–430

Kondo F, Wada K, Nagato Y, Nakajima T, Kondo Y, Hirooka N, Ebara M, Ohto M, Okuda K (1989) Biopsy diagnosis of well-differentiated hepatocellular carcinoma based on new morphologic criteria. Hepatology 9:751–755

Kong M, Tian S, Shi H, Zhao J, Feng X, Zheng S, Duan Z, Chen Y (2012) The effect of alpha-fetoprotein on the activation and phagocytosis of granulocytes and monocytes. Hepatogastroenterology 59:2385–2388

Kranz et al. 1980. http://www.ncbi.nlm.nih.gov/pubmed/7445804

Kudo M (2011) Diagnostic imaging of hepatocellular carcinoma: recent progress. Oncology 81(Suppl 1):73–85

Kutami R, Nakashima Y, Nakashima O, Shiota K, Kojiro M (2000) Pathomorphologic study on the mechanism of fatty change in small hepatocellular carcinoma in humans. J Hepatol 33:282–289

Lai and Lau 2006. http://www.ncbi.nlm.nih.gov/pubmed/16490898

Lam HD, Hauters P, Ilioaje C, Nakad A, Renard N, Malvaux P, Landenne J (2009) Hepatocellular carcinoma with distant double bile duct tumoral thrombus: a case report. Acta Chir Belg 109:769–771

Lapis K, Johannessen JV (1979) Pathology of primary liver cancer. J Toxicol Environ Health 5:315–355

Lau W, Leung K, Leung TW, Liew CT, Chan MS, Yu SC, Li AK (1997) A logical approach to hepatocellular carcinoma presenting with jaundice. Ann Surg 225:281–285

Lee KC, Sakai K, Kinoshita H, Hirohashi K, Tsuji Y, Kubo S, Iwasa R (1988) Resection of hepatocellular carcinoma with obstructive jaundice caused by compression of the common hepatic duct. J Surg Oncol 39:201–205

Lee YC, Wang HP, Huang SP, Chang YT, Wu CT, Yang CS, Wu MS, Lin JT (2001) Obstructive jaundice caused by hepatocellular carcinoma: detection by endoscopic sonography. J Clin Ultrasound 29:363–366

Lee LT, Huang HY, Huang KC, Chen CY, Lee WC (2009) Age-period-cohort analysis of hepatocellular carcinoma mortality in Taiwan, 1976–2005. Ann Epidemiol 19(5):323–328

Lee JM, Trevisani F, Vilgrain V, Wald C (2011) Imaging diagnosis and staging of hepatocellular carcinoma. Liver Transpl 17(Suppl 2):S34–S43

Leong TY, Leong AS (2005) Epidemiology and carcinogenesis of hepatocellular carcinoma. HPB (Oxford) 7:5–15

Li P, Wang SS, Liu H, McNutt MA, Li G, Ding HG (2011) Elevated serum alpha fetoprotein levels promote pathological progression of hepatocellular carcinoma. World J Gastroenterol 17:4563–4571

Li S, Liu Y, Shen Z (2012a) Characterization of somatostatin receptor 2 and 5 expression in operable hepatocellular carcinomas. Hepatogastroenterology 59:2054–2058

Li J, Chen L, Qin Z (2012b) Multifaceted tumor stromal fibroblasts. Cancer Microenviron 5:187–193

Lin et al. 1975. http://www.ncbi.nlm.nih.gov/pubmed/173942

Lin M, Guo LM, Liu H, Du J, Yang J, Zhang LJ, Zhang B (2010) Nuclear accumulation of glioma-associated oncogene 2 protein and enhanced expression of forkhead-box transcription factor M1 protein in human hepatocellular carcinoma. Histol Histopathol 25:1269–1275

Liu K, He X, Lei XZ, Zhao LS, Tang H, Liu L, Lei BJ (2003) Pathomorphological study on location and distribution of Kupffer cells in hepatocellular carcinoma. World J Gastroenterol 9:1946–1949

Liu QY, Lai DM, Liu C, Zhang L, Zhang WD, Li HG, Gao M (2011a) A special recurrent pattern in small hepatocellular carcinoma after treatment: bile duct tumor thrombus formation. World J Gastroenterol 17:4817–4824

Liu QY, Zhang WD, Chen JY, Li HG, Liu C, Liang BL (2011b) Hepatocellular carcinoma with bile duct tumor thrombus: dynamic computed tomography findings and histopathologic correlation. J Comput Assist Tomogr 35:187–194

Liu Q, Zhang A, Xu W, Dong J (2011c) A new view of the roles of blood flow dynamics and Kupffer cell in intrahepatic metastasis of hepatocellular carcinoma. Med Hypotheses 77:87–90

Liu T, Gao JF, Yi YX, Ding H, Liu W (2013) Misdiagnosis of left supraclavicular lymph node metastasis of hepatocellular carcinoma: a case report. World J Gastroenterol 19:960–963

Liver Cancer Study Group of Japan (2003) General rules for the clinical and pathological study of primary liver cancer, 2nd edn. Kanehara, Tokyo

Llovet JM (2007) Clinical and molecular classification of hepatocellular carcinoma. Liver Transpl 13:S13–S16

Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. Lancet 362:1907–1917

Long XY, Li YX, Wu W, Li L, Cao J (2010) Diagnosis of bile duct hepatocellular carcinoma thrombus without obvious intrahepatic mass. World J Gastroenterol 16:4998–5004

Lu et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23280814

Lunevicius R, Nakanishi H, Ito S, Kozaki K, Kato T, Tatematsu M, Yasui K (2001) Clinicopathological significance of fibrotic capsule formation around liver metastasis from colorectal cancer. J Cancer Res Clin Oncol 127:193–199

MacDonald K, Bedard YC (1990) Cytologic, ultrastructural and immunologic features of intracytoplasmic hyaline bodies in fine needle aspirates of hepatocellular carcinoma. Acta Cytol 34:197–200

Macnab GM, Urbanowicz JM, Kew MC (1978) Carcinoembryonic antigen in hepatocellular cancer. Br J Cancer 38:51–54

Makino T, Nakamori S, Kashiwazaki M, Masuda N, Ikenaga M, Hirao M, Fujitani K et al (2006) An icteric type hepatocellular carcinoma with no detectable tumor in the liver: report of a case. Surg Today 36:633–637

Manifold IH, Triger DR, Underwood JC (1983) Kupffer-cell depletion in chronic liver disease: implications for hepatic carcinogenesis. Lancet 2:431–433

Matsui O (2004) Imaging of multistep human hepatocarcinogenesis by CT during intra-arterial contrast injection. Intervirology 47:271–276

McGlynn KA, London WT (2011) The global epidemiology of hepatocellular carcinoma: present and future. Clin Liver Dis 15:223–243

Mitchell KA (2013) Hepatocellular carcinoma: histologic considerations: pure, mixed, and motley. J Clin Gastroenterol 47(Suppl):S20–S26

Miyao Y, Ozaki D, Nagao T, Kondo Y (1999) Interstitial invasion of well-differentiated hepatocellular carcinoma and subsequent tumor growth. Pathol Int 49:208–213

Miyoshi A, Kitahara K, Kohya N, Noshiro H, Miyazaki K (2011) Outcomes of patients with spontaneous rupture of hepatocellular carcinoma. Hepatogastroenterology 58:99–102

Montalto G, Cervello M, Giannitrapani L, Dantona F, Terranova A, Castagnetta LA (2002) Epidemiology, risk factors, and natural history of hepatocellular carcinoma. Ann N Y Acad Sci 963:13–20

Moon WS, Yu HC, Chung MJ, Kang MJ, Lee DG (2000) Pale bodies in hepatocellular carcinoma. J Korean Med Sci 15:516–520

Moon DB, Hwang S, Wang HJ, Yun SS, Kim KS, Lee YJ, Kim KH, Park YK, Xu W et al (2013) Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: a Korean multicenter study. World J Surg 37:443–451

Mori W, Machinami R, Tanaka K (1980) Pathology of hepatocellular carcinoma. Pathol Res Pract 169:4–20

Murakata et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21233610

Nagasue and Inokuohi 1979. http://www.ncbi.nlm.nih.gov/pubmed/222390

Nagato Y, Kondo F, Kondo Y, Ebara M, Ohto M (1991) Histological and morphometrical indicators for a biopsy diagnosis of well-differentiated hepatocellular carcinoma. Hepatology 14:473–478

Nakamura Y, Kono N, Ohta G, Shirasaki S, Takeshita H, Watanabe K, Tsuda S, Yoshizawa H (1982) Pale eosinophilic inclusions simulating ground-glass appearance of cells of hepatocellular carcinoma. Acta Pathol Jpn 32:71–81

Nakanuma and Hirata 1993. http://www.ncbi.nlm.nih.gov/pubmed/8382391

Nakao K, Ichikawa T (2013) Recent topics on α−fetoprotein. Hepatol Res 43:820–825

Nakashima T, Kojiro M (1987) Pedunculated hepatocellular carcinoma. In: Nakashima T, Kojiro M (eds) Hepatocellular carcinoma: an atlas of its pathology. Springer, Tokoyo, pp 7–8

Nakashima T, Kojiro M, Kawano Y, Shirai F, Takemoto N, Tomimatsu Y, Kawasaki H et al (1982) Histologic growth pattern of hepatocellular carcinoma: relationship to orcein (hepatitis B surface antigen)-positive cells in cancer tissue. Hum Pathol 13:563–568

Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K, Ikari T (1983) Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. Cancer 51:863–877

Nakashima O, Sugihara S, Eguchi A, Taguchi J, Watanabe J, Kojiro M (1992) Pathomorphologic study of pale bodies in hepatocellular carcinoma. Acta Pathol Jpn 42:414–418

Nakayama H, Enzan H, Yamamoto M, Miyazaki E, Yasui W (2004) High molecular weight caldesmon positive stromal cells in the capsule of hepatocellular carcinomas. J Clin Pathol 57:776–777

Nappi O, Ferrara G, Ianniello G, Wick MR (1992) Metastatic hepatocellular carcinoma of the breast, simulating gynecomastia: diagnosis by fine-needle aspiration biopsy. Diagn Cytopathol 8:588–592

Nayar R, Bourtsos E, DeFrias DV (2000) Hyaline globules in renal cell carcinoma and hepatocellular carcinoma. A clue or a diagnostic pitfall on fine-needle aspiration? Am J Clin Pathol 114:576–582

Nazari G (1905) Contributo allo studio delle neoformazioni epitheliali associate a cirrosi del fegato. Il Policlinico 12:301

Nejmeddine A, Bassem A, Salah B, Issam BM (2010) Spontaneous rupture of hepatocellular carcinoma in children. Afr J Paediatr Surg 7:188–190

Ng IO, Lai EC, Ng MM, Fan ST (1992) Tumor encapsulation in hepatocellular carcinoma. A pathologic study of 189 cases. Cancer 70:45–49

Ng IO, Ng MM, Lai EC, Fan ST (1996) Pathologic features and patient survival in hepatocellular carcinoma in relation to age. J Surg Oncol 61:134–137

Nishizaki T, Matsumata T, Adachi E, Hayashi H, Sugimachi K (1993) Pedunculated hepatocellular carcinoma and surgical treatment. Br J Cancer 67:115–118

Noh SJ, Lee HK, Yu HC, Moon WS (2012) Exophytic combined hepatocellular carcinoma and cholangiocarcinoma. CMH Clin Mol Hepatol 18:416–419

Nomura F, Ohnishi K, Honda M, Satomura Y, Nakai T, Okuda K (1994) Clinical features of hepatocellular carcinoma in the elderly: a study of 91 patients older than 70 years. Br J Cancer 70:690–693

Oertel H (1905) XXVI. Der primäre Leberkrebs. Virchows Arch Pathol Anat Physiol Klin Med 180:499–515

Ogawa S, Kumada T, Toyoda H, Ichikawa H, Kawachi T, Otobe K, Hibi T, Takeshima K et al (2006) Evaluation of pathological features of hepatocellular carcinoma by contrast-enhanced ultrasonography: comparison with pathology on resected specimen. Eur J Radiol 59:74–81

Okuda K (1980a) Radiological diagnosis of hepatocellular carcinoma. Ann Acad Med Singapore 9:222–227
Okuda K (1980b) The liver cancers in Japan. Cancer 45:2663–2669
Okuda K (1990) Geographic heterogeneity of hepatocellular carcinoma. Gastroenterol Jpn 25:787–792
Okuda K (1997) Hepatocellular carcinoma: clinicopathological aspects. J Gastroenterol Hepatol 12:S314–S318
Okuda et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9925921
Okuda K (2000) Hepatocellular carcinoma. J Hepatol 32(Suppl 1):225–237
Okuda K, Musha H, Nakajima Y, Kubo Y, Shimokawa Y, Nagasaki Y, Sawa Y, Jinnouchi S et al (1977) Clinicopathologic features of encapsulated hepatocellular carcinoma: a study of 26 cases. Cancer 40:1240–1245
Okuda K, Noguchi T, Kubo Y, Shimokawa Y, Kojiro M, Nakashima T (1981) A clinical and pathological study of diffuse type hepatocellular carcinoma. Liver 1:280–289
Okuda K, Peters RL, Simson IW (1984) Gross anatomic features of hepatocellular carcinoma from three disparate geographic areas. Proposal of new classification. Cancer 54:2165–2173
Okuda K, Ohtsuki T, Obata H, Tamimatsu M, Okazaki N, Hasegawa H et al (1985) Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 56:918–928
Okuda K, Nakashima T, Kojiro M, Kondo Y, Wada K (1989) Hepatocellular carcinoma without cirrhosis in Japanese patients. Gastroenterology 97:140–146
Okuda K, Kojiro M, Okuda H (1993) 44. Neoplasms of the liver. In: Schiff L, Schiff ER (eds) Diseases of the liver, vol 2. J.B. Lippincott, Philadelphia, pp 1236–1296
Okusaka T, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, Kosuge T, Yamasaki S et al (2002) Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. Cancer 95:1931–1937
Ong GB, Taw JL (1972) Spontaneous rupture of hepatocellular carcinoma. Br Med J 4:146–149
Ooi LP, Crawford DH, Gotley DC, Clouston AD, Strong RW, Gob GC, Halliday JW et al (1997) Evidence that "myofibroblast-like" cells are the cellular source of capsular collagen in hepatocellular carcinoma. J Hepatol 26:798–807
Pappenheimer AM, Hawthorne JJ (1936) Certain cytoplasmic inclusions of liver cells. Am J Pathol 12:625–634
Paradis V (2013a) Histopathology of hepatocellular carcinoma. Recent Results Cancer Res 190:21–32
Paradis V (2013b) Histopathology of hepatocellular carcinoma. In: Vauthey JN, Brouquet A (eds) Multidisciplinary treatment of hepatocellular carcinoma. recent results in cancer research. Springer, Heidelberg, pp 22–29
Patton and Hom 1964. http://www.ncbi.nlm.nih.gov/pubmed/14176989
Péquignot H, Abelanet R, Deslignières S, Christoforov B (1974) Australia antigen. Hepatocytes with "ground-glass" cytoplasm. Apropos of a hepatoma in cirrhosis with Australia antigen and "ground-glass" hepatocytes (in French). Ann Med Interne (Paris) 125:567–569
Polat KY, Akçay MN, Aydinli B, Erdogan F, Kantarci M, Oztürk G, Peker K (2005) Spontaneous rupture of hepatocellular carcinoma: a case report and review of literature. Int J Clin Pract Suppl (147):103–105
Pombo F, Arrojo L, Perez-Fontan J (1991) Hemoperitoneum secondary to spontaneous rupture of hepatocellular carcinoma: CT diagnosis. Clin Radiol 43:321–322
Qin LX, Tang ZY (2002) The prognostic molecular markers in hepatocellular carcinoma. World J Gastroenterol 8:385–392
Qin and Tang 2003. http://www.ncbi.nlm.nih.gov/pubmed/12632482
Qin LX, Ma ZC, Wu ZQ, Fan J, Zhou XD, Sun HC, Ye QH, Wang L, Tang ZY (2004) Diagnosis and surgical treatments of hepatocellular carcinoma with tumor thrombosis in bile duct: experience of 34 patients. World J Gastroenterol 10:1397–1401
Riesenfeld B (1868) Über 69 im pathologischen Institut zu Berlin in der Zeit von 1864 bis zum 15. Juli 1868 vorgekommenen Fälle von Krebs der Leber. Inaugural-Dissertation, Berlin
Rindfleisch GE Von (1878) Lehrbuch der pathologischen gewebe lehre mit einschluss einer pathologischen anatomie in kurz ge fassten krankheits bildern, von Eduard Rindfleisch. W. Engelmann, Leipzig, 5th ed
Rosenberg DM, Ochsner A (1948) Primary carcinoma of the liver; an analysis of 55 autopsied cases, the record of a case with resection, and a review of the recent literature. Surgery 24:1036–1068
Roskams T, Kojiro M (2010) Pathology of early hepatocellular carcinoma: conventional and molecular diagnosis. Semin Liver Dis 30:17–25
Roux C (1897) Un cas de cancer primitif du foie avec pericholecystitis calculeuse, perforation intestinale. Hémostase hépatique. Rev Méd Suisse Rom 17:114–119
Ruby SG (2000) Protocol for the examination of specimens from patients with hepatocellular carcinoma and cholangiocarcinoma, including intrahepatic bile ducts. Cancer Committee of the College of American Pathologists. Arch Pathol Lab Med 124:41–45
Sabourin C (1881) Contribution à l'étude des lesions du parenchyme hépatique dans la cirrhose; essai sur l'adénome du foie (contribution to the study of liver parenchyma in cirrhosis; essay on liver adenoma). Editions A. Parent, Paris
Salomao M, Yu WM, Brown RS, Emond JC, Lefkowitch JH (2010) Steatohepatitic hepatocellular carcinoma (SH-HCC): a distinctive histological variant of HCC in hepatitis C virus-related cirrhosis with associated NAFLD/NASH. Am J Surg Pathol 34:1630–1636
Salomao M, McMillen E, Lefkowitch JH (2012a) Recent advances in the classification of hepatocellular carcinoma. Diagn Histopathol 18:37–45

Salomao M, Remotti H, Vaughan R, Siegel AB, Lefkowitch JH, Moreira RK (2012b) The steatohepatitic variant of hepatocellular carcinoma and its association with underlying steatohepatitis. Hum Pathol 43:737–746

Sasaki K, Matsuda M, Ohkuda Y, Kawamura Y, Inoue M, Hashimoto M, Ikeda K, Kumada H et al (2014) In hepatocellular carcinomas, any proportion of poorly differentiated components is associated with poor prognosis after hepatectomy. World J. Surg 38:1147–1153

Sastry RA, Raju GS, Kumar YR (1996) Icterus due to tumor emboli – a rare presentation of hepatoma. Indian J Gastroenterol 15:24–25

Satoh S, Ikai I, Honda G, Okabe H, Takeyama O, Yamamoto Y, Yamamoto N, Iimuro Y et al (2000) Clinicopathologic evaluation of hepatocellular carcinoma with bile duct thrombi. Surgery 128:779–783

Schirmacher P, Prange W, Dries V, Dienes HP (2001) Hochdifferenzierte hepatozellulare Tumoren. Konzepte, Kriterien und Differenzialdiagnose. Pathologe 22:407–416

Schlageter M, Terracciano LM, D'Angelo S, Sorrentino P (2014) Histopathology of hepatocellular carcinoma. World J Gastroenterol 20:15955–15964

Shimofusa R, Ueda T, Kishimoto T, Nakajima M, Yoshikawa M, Kondo F, Ito H (2010) Magnetic resonance imaging of hepatocellular carcinoma: a pictorial review of novel insights into pathophysiological features revealed by magnetic resonance imaging. J Hepatobiliary Pancreat Sci 17:583–589

Shtilbas 2013. http://www.ncbi.nlm.nih.gov/pubmed/23430817

Siegenbeek van Heukelom F (1894) Das Adenokarzinom der Leber mit Cirrhose. Zieglers Beitr Pathol Anat 16:341

Singhi AD, Jain D, Kakar S, Wu TT, Yeh MM, Torbenson M (2012) Reticulin loss in benign fatty liver: an important diagnostic pitfall when considering a diagnosis of hepatocellular carcinoma. Am J Surg Pathol 36:710–715

Sivridis E, Giatromanolaki A, Koukourakis MI (2004) "Stromatogenesis" and tumor progression. Int J Surg Pathol 12:1–9

Smetana K, Gyorkey F, Gyorkey P, Busch H (1972) Studies on nucleoli and cytoplasmic fibrillar bodies of human hepatocellular carcinomas. Cancer Res 32:925–932

Soyuer I, Ekinci C, Kaya M, Genc Y, Bahar K (2003) Diagnosis of hepatocellular carcinoma by fine needle aspiration cytology. Cellular features. Acta Cytol 47:581–589

Srivatanakul P, Sriplung H, Deerasamee S (2004) Epidemiology of liver cancer: an overview. Asian Pac J Cancer Prev 5:118–125

Stahl J, Voyvodic F (2000) Biopsy diagnosis of malignant versus benign liver "nodules": new helpful markers. An update. Adv Anat Pathol 7:230–239

Stevens WR, Gulino SP, Batts KP, Stephens DH, Johnson CD (1996) Mosaic pattern of hepatocellular carcinoma: histologic basis for a characteristic CT appearance. J Comput Assist Tomogr 20:337–342

Stromeyer FW, Ishak KG, Gerber MA, Mathew T (1980) Ground-glass cells in hepatocellular carcinoma. Am J Clin Pathol 74:254–258

Stumptner C, Heid C, Fuchsbichler A, Hauser H, Mischinger HJ, Taloukal K, Denk H (1999a) Analysis of intracytoplasmic hyaline bodies in a hepatocellular carcinoma. Demonstration of p62 as major constituent. Am J Pathol 154:1701–1710

Stumptner C, Heid H, Zatloukal K, Fuchsbichler A, Hauser H, Denk H (1999b) Identification of p62, a phosphotyrosine independent ligand of p56lck kinase, as a major component of intracytoplasmic hyaline bodies in hepatocellular carcinoma. Verh Dtsch Ges Pathol 83:254–259

Suriawinata AA, Thung SN (2002) Malignant liver tumors. Clin Liver Dis 6:527–554

Tabarin A, Bioulac-Sage P, Merlio JP, Lamouliatte H, Saric J, Balabaud C (1986) Sinusoids ultrastructure of human hepatocellular carcinoma. J Submiscroc Cytol 18:171–176

Tabarin A, Bioulac-Sage P, Boussarie L, Balabaud C, de Mascarel A, Grimaud JA (1987) Hepatocellular carcinoma developed on noncirrhotic livers. Sinusoids in hepatocellular carcinoma. Arch Pathol Lab Med 111:174–180

Takikawa Y, Suzuki K, Yamazaki K, Goto T, Madarame T, Miura Y, Yoshida T, Kashiwabara T et al (1992) Plasma abnormal prothrombin (PIVKA-II): a new and reliable marker for the detection of hepatocellular carcinoma. J Gastroenterol Hepatol 7:1–6

Talwalkar JA, Gores GJ (2004) Diagnosis and staging of hepatocellular carcinoma. Gastroenterology 127: S126–S132

Tamada K, Isoda N, Wada S, Tomiyama T, Ohashi A, Satoh Y, Ito K, Sugano K (2001) Intraductal ultrasonography for hepatocellular carcinoma with tumor thrombi in the bile duct: comparison with polypoid cholangiocarcinoma. J Gastroenterol Hepatol 16:801–805

Tanaka N, Okamoto E, Toyosaka A, Fujiwara S (1985) Pathological evaluation of hepatic dearterialization in encapsulated hepatocellular carcinoma. J Surg Oncol 29:256–260

Tanaka M, Nakashima O, Wada Y, Kage M, Kojiro M (1996) Pathomorphological study of Kupffer cells in hepatocellular carcinoma and hyperplastic nodular lesions in the liver. Hepatology 24:807–812

Tanaka H, Iijima H, Higashiura A, Yoh K, Ishii A, Takashima T, Sakai Y, Aizawa N et al (2014) New malignant grading system for hepatocellular carcinoma using the Sonazoid contrast agent for ultrasonography. J Gastroenterol 49:755–763

Tantawi B, Cherqui D, Tran van Nhieu J, Kracht M, Fagniez PL (1996) Surgery for biliary obstruction by tumour thrombus in primary liver cancer. Br J Surg 83:1522–1525

Terada T, Matsunaga Y (2001) S-100-positive nerve fibers in hepatocellular carcinoma and intrahepatic

cholangiocarcinoma: an immunohistochemical study. Pathol Int 51:89–93
Terada T, Makimoto K, Terayama N, Suzuki Y, Nakanuma Y (1996) Alpha-smooth muscle actin-positive stromal cells in cholangiocarcinoma, hepatocellular carcinomas and metastatic liver carcinomas. J Hepatol 24:706–712
Thöle F (1913) Chirurgie der Lebergeschwülste. In: von Bruns P (ed) Neue Deutsche Chirurg, vol 7. Verlag von Ferdinand Enke, Stuttgart
Tian L, Wang Y, Xu D, Gui J, Jia X, Tong H, Wen X, Dong Z, Tian Y (2011) Serological AFP/Golgi protein 73 could be a new diagnostic parameter of hepatic diseases. Int J Cancer 129:1923–1931
Tomizawa M, Kondo F, Kondo Y (1995) Growth patterns and interstitial invasion of small hepatocellular carcinoma. Pathol Int 45:352–358
Treyer A, Münsch A (2013) Hepatocyte polarity. Compr Physiol 3:243–287
Tsai HP, Lee WC, Jeng LB, Chen MF (2000) Clinicopathologic factors influencing long-term survival after resection for hepatocellular carcinoma. Chang Gung Med J 23:529–535
Tsoulidis L, Hulin SJ, Shaw I, Rees M (2007) Image of the month – pedunculated hepatocellular carcinoma. Arch Surg 142:95
Tureen LL, Seelig MG (1933) Reticulum in tumors. Arch Pathol 15:498–508
Ueda E, Hirota S, Fujii M, Tanaka K, Shimizu M, Kono M, Hase M, Sako M (1989) Three cases of hepatocellular carcinoma with remarkable fatty metamorphosis (in Japanese). Ronsho Hoshasen 34:921–924
Ueda M, Takeuchi T, Takayasu T, Takahashi K, Okamoto S, Tanaka A, Morimoto T, Mori K, Yamaoka Y (1994) Classification and surgical treatment of hepatocellular carcinoma (HCC) with bile duct thrombi. Hepatogastroenterology 41:349–354
Underwood JC (1972) Light and electron microscopy of globular hyaline inclusions in liver cells. J Clin Pathol 25:821–826
Van Landingham SB, Hendricks JC, Roberts JW (1985) Spontaneous rupture of hepatocellular carcinoma. J Surg Oncol 29:129–131
Vermess M, Leung AW, Bydder GM, Steiner RE, Blumgart LH, Young IR (1985) MR imaging of the liver in primary hepatocellular carcinoma. J Comput Assist Tomogr 9:749–754
Vogel CL, Primack A, McIntire KR, Carbone PP, Anthony PP (1974) Serum alpha-fetoprotein in 184 Ugandan patients with hepatocellular carcinoma. Clinical. laboratory, and histopathologic correlations. Cancer 33:959–964
Von Albertini A (1974) Histologische Geschwulstdiagnostik. Systematische Morphologie der menschlichen Geschwülste als Grundlage für die klinische Beurteilung, 2nd edn. Georg Thieme Verlag, Stuttgart, pp 134–147
Wakasa K, Haba T, Hamada T, Sasaki M, Sakurai M (1997) Early hepatocellular carcinoma macroscopically resembling adenomatous hyperplasia: pathological resemblance to carcinoma-in-situ. Pathol Int 47:54–59
Wang YX (2011) Superparamagnetic iron oxide based MRI contrast agents: current status of clinical application. Quant Imaging Med Surg 1:35–40
Wang WL, Liu J (1986) Ultrastructural study on cytoplasmic inclusions in human hepatocellular carcinoma (in Chinese). Zhonghua Yi Xue Za Zhi 66:160–162. Carcinoma. An approach to grading. Chin Med J (Engl) 99:576–580
Wang HJ, Kim JH, Kim JH, Kim WH, Kim MW (1999) Hepatocellular carcinoma with tumor thrombi in the bile duct. Hepatogastroenterology 46:2495–2499
Wanless IR (2004) Pathology and nomenclature of early hepatocellular neoplasia. J Gastroenterol Hepatol 19:S361–S363
Wanless IR (2007) International consensus on histologic diagnosis of early hepatocellular carcinoma. Hepatol Res 37(Suppl):S139–S141
Wee and Nilsson 2003. http://www.ncbi.nlm.nih.gov/pubmed/1258026
Wee 2005. http://www.ncbi.nlm.nih.gov/pubmed/15941489
Wee A (2011) Fine-needle aspiration biopsy of hepatocellular carcinoma and related hepatocellular nodular lesions in cirrhosis: controversies, challenges, and expectations. Pathol Res Int 2011:281930
Wee A (2013) Fine needle aspiration biopsy of malignant mass lesions in the liver: a revisit of diagnostic profiles and challenges. J Gastrointest Oncol 4:5–7
Wee A, Nilsson B, Chan-Wilde C, Yap I (1991) Fine needle aspiration biopsy of hepatocellular carcinoma. Some unusual features. Acta Cytol 35:661–670
Wee A, Nilsson B, Tan LK, Yap I (1994) Fine needle aspiration biopsy of hepatocellular carcinoma. Diagnostic dilemma at the ends of the spectrum. Acta Cytol 38:347–354
Wegelin K (1905) Über das Adenokarzinom und Adenom der Leber. Virchows Arch Pathol Anat Physiol Klin Med 179:95–153
Weigert C (1876) Onkologische Beiträge.II.Ueber primäres Lebercarcinom. Virchows Arch Path Anat 67:492–522
Wilkens L, Becker T, Schlegelberger B, Kreipe HH, Flemming P (2006) Preserved reticulin network in a case of hepatocellular carcinoma. Histopathology 48:876–878
Wu PC, Lam KC (1979) Cytoplasmic hepatitis B surface antigen and the ground-glass appearance in hepatocellular carcinoma. Am J Clin Pathol 71:229–234
Wu HH, Tao LC, Cramer HM (1996) Vimentin-positive spider-shaped Kupffer cells. A new clue to cytologic diagnosis of primary and metastatic hepatocellular carcinoma by fine-needle aspiration biopsy. Am J Clin Pathol 106:517–521
Xu JF, Liu HY, Shi Y, Wei ZH, Wu Y (2011) Evaluation of hepatocellular carcinoma by contrast-enhanced

sonography: correlation with pathologic differentiation. J Ultrasound Med 30:625–633
Yamagiwa K (1911) XXIII. Zur Kenntnis des primären parenchymatösen Leberkarzinoms ("Hepatoma"). Arch Pathol Anat Physiol Klin Med 206:437–467
Yamamoto M, Tatsumi T, Miyagi T, Tsunematsu H, Aketa H, Hosui A, Kanto T, Hiramatsu N et al (2011) α-fetoprotein impairs activation of natural killer cells by inhibiting the function of dendritic cells. Clin Exp Immunol 165:211–219
Yan et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19891029
Yang GC, Yang GY, Tao LC (2004) Cytologic features and histologic correlations of microacinar and microtrabecular types of well-differentiated hepatocellular carcinoma in fine-needle aspiration biopsy. Cancer 102:27–33
Yao et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23686365
Yeh CN, Lee WC, Jeng LB, Chen MF (2002a) Pedunculated hepatocellular carcinoma: clinicopathologic study of 18 surgically resected cases. World J Surg 26:1133–1138
Yeh CN, Lee WC, Jeng LB, Cehn MF, Yu MC (2002b) Spontaneous tumour rupture and prognosis in patients with hepatocellular carcinoma. Br J Surg 89:1125–1129
Yeh CN, Chen HM, Chen MF, Chao TC (2002c) Peritoneal implanted hepatocellular carcinoma with rupture after TACE presented as acute appendicitis. Hepatogastroenterology 49:938–940
Yeh CN, Jan YY, Lee WC, Chen MF (2004) Hepatic resection for hepatocellular carcinoma with obstructive jaundice due to biliary tumor thrombi. World J Surg 28:471–475
Yoshikawa J, Matsui O, Takashima T, Ida M, Takanaka T, Kawamura I, Kakuda K et al (1988) Fatty metamorphosis in hepatocellular carcinoma: radiologic features in 10 cases. AJR Am J Roentgenol 151:717–720
Yoshimura K, Tomooka Y, Saiki S, Kuroda M, Miki T, Usami M, Kotake T (1989) A case of exohepatic pedunculated hepatocellular carcinoma suspected of adrenal tumor (in Japanese). Hinyokika Kiyo 35:2131–2133
Yu XH, Xu LB, Liu C, Zhang R, Wang J (2011) Clinicopathological characteristics of 20 cases of hepatocellular carcinoma with bile duct tumor thrombi. Dig Dis Sci 56:252–259
Yu J, Ren X, Chen Y, Liu P, Wei X, Li H, Ying G, Chen K, Winkler H, Hao X (2013) Dysfunctional activation of neurotensin/IL-8 pathway in hepatocellular carcinoma is associated with increased inflammatory response in microenvironment, more epithelial mesenchymal transition in cancer and worse prognosis in patients. PLoS One 8:e56069
Yuen MF, Hou JL, Chutaputti A, Asia Pacific Working Party on prevention of Hepatocellular Carcinoma (2009) Hepatocellular carcinoma in the Asia pacific region. J Gastroenterol Hepatol 24:346–353
Zatloukal K, Stumptner C, Fuchsbichler A, Heid H, Schnoelzer M, Kenner L, Kleinert R et al (2002) p62 is a common component of cytoplasmic inclusions in protein aggregation diseases. Am J Pathol 160:255–263
Zegers MM, Hoekstra D (1998) Mechanisms and functional features of polarized membrane traffic in epithelial and hepatic cells. Biochem J 336:257–269
Zhang J, Ni J, Zheng B (2011) Giant pedunculated sarcomatoid hepatocellular carcinoma: a case report. The Chinese-German. J Clin Oncol 10:669–671
Zheng KG, Shen JX, Wang GS, Xu DS (2007) Small hepatocellular carcinoma with peripheral enhancement: pathological correlation with dual phase images by helical CT. Chin Med J (Engl) 120:1583–1586
Zhu LX, Geng XP, Fan ST (2001) Spontaneous rupture of hepatocellular carcinoma and vascular injury. Arch Surg 136:682–687
Zhu LX, Liu Y, Fan ST (2002) Ultrastructural study of the vascular endothelium of patients with spontaneous rupture of hepatocellular carcinoma. Asian J Surg 25:157–162
Zhu LX, Geng XP, Fan SD (2004) Mechanism of spontaneous rupture of hepatocellular carcinoma (in Chinese). Zhonghua Wai Ke Za Zhi 42:1036–1039
Zhu LX, Geng XP, Fan SD (2006) Ultrastructure study on patients with spontaneous rupture of hepatocellular carcinoma (in Chinese). Zhonghua Wai Ke Za Zhi 44:161–164
Zhu Q, Li J, Yan JJ, Huang L, Wu MC, Yan YQ (2012) Predictors and clinical outcomes for spontaneous rupture of hepatocellular carcinoma. World J Gastroenterol 18:7302–7307
Zhu CH, Liu XH, Cao R, Wu XZ (2013) Proposal of new classification for postoperative patients with hepatocellular carcinoma based on tumor growth characteristics. World J Gastroenterol 19:5534–5541
Zu HZ, Ruan YB, Wu ZB, Zhang CM (2000) Kupffer cell and apoptosis in experimental HCC. World J Gastroenterol 6:1504–1513

Immunohistochemistry of Hepatocellular Carcinoma

3

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_3

Abstract

Although the histological and cytological features of differentiated hepatocellular carcinomas (HCC) usually allow a reliable diagnosis, poorly differentiated HCCs and tumors found in small samples require immunohistochemical confirmation. Generally, cells of HCCs share with normal hepatocytes a rather wide array of lineage markers. These include Hep Par1, arginase 1, and glutamine synthetase, which are expressed in many, but not all, HCCs. A majority of HCCs are positive for the heparan sulfate proteoglycan, glypican-3. Many HCCs express and secrete typical export proteins, of which alpha-fetoprotein is the best-known example. Part of HCCs show reactivity for the canalicular domain markers, polyclonal CEA and CD10. The tumors share with hepatocytes the expression of cytokeratins 8 and 18, and sometimes 19, the latter defining a tumor subset with poor prognosis. In addition, HCCs express, however in a variable manner, markers of cellular differentiation, cell adhesion molecules, oncogenes, tumor suppressors, and a host of other markers related to various biochemical and metabolic functions.

Introduction

Immunohistochemistry has an important role in the diagnostic approach to HCC and for tumor monitoring (Varma and Cohen 2004; Wee 2006; Lo and Ng 2011; Masuda and Miyoshi 2011; Minguez and Lachenmayer 2011). The field of HCC markers is very active and the number of markers is steadily growing (Marrero and Lok 2004). The most important markers are compiled in the Table 1.

Hepatocyte Lineage Markers

As part of HCC consists of cells that are similar to normal or hyperplastic hepatocytes, immunohistochemical methods are useful for the diagnosis of these neoplasms (reviews: Varma and Cohen

Table 1 Markers for hepatocellular carcinoma

Hepatocyte/HCC cell lineage markers
Hep Par1
Arginase 1
Glutamine synthetase
Heparan sulfate proteoglycan expressed by hepatocytes/HCC cells
Glypican-3
Hepatocyte/HCC-typical export proteins
Alpha fetoprotein (AFP)
Alpha-1-antitrypsin (AAT)
Ferritin
Abnormal prothrombins (PIVKA-II)
Canalicular domain markers
CD10
Polyclonal CEA (pCEA)
Intermediate filaments
Cytokeratin 8
Cytokeratin 18
Cytokeratin 19
Wnt/beta-catenin signaling pathway
Beta-catenin
Markers of proliferative activity
PCNA
Ki-67
Cyclin D1
Markers of cellular differentiation
DEC1 (in part of HCCs)
MUC1 (in part of HCCs)
Squamous cell carcinoma antigen (SCCA; in part of HCCs)
Cell adhesion molecules and cytoskeletal proteins
CD44
N-cadherin (in part of HCCs)
EpCAM (epithelial cell adhesion molecule; in part of HCCs)
NCAM (neural cell adhesion molecule; in part of HCCs)
Clathrin heavy chain
Oncogenes and tumor suppressor genes
p53
p73
Other markers (expressed in part of HCCs)
Heat shock protein 70 (HSP70)
HCC-specific gamma-glutamyltransferase
Kazal type 1 proteinase inhibitor (SPINK1)
CD147 (EMMPRIN)
SALL4
Osteopontin
Osteonectin/SPARC
Importin-alpha1
Aldo-keto reductase 1

2004; Wee 2006). There are several markers of the hepatocyte cell lineage that can be employed in HCC diagnosis, including antibodies directed against hepatocyte antigens and proteins exclusively expressed in hepatocytes (review: Roncalli et al. 2011).

HepPar1

Hep Par1 is a reliable hepatocyte lineage marker and is also regarded as a potent tool in the differential diagnosis of hepatocellular tumors (Leong et al. 1998; Zimmermann et al. 2001; Chu et al. 2002; Siddiqui et al. 2002; Lamps and Folpe 2003; Saad et al. 2004; Varma and Cohen 2004; Wang et al. 2006; Karabork et al. 2010; Al-Muhannadi et al. 2011; Shibuya et al. 2011). The antigen for Hep Par1 was reported to be the hepatocytic urea cycle enzyme, carbamoyl phosphate synthetase 1 located in mitochondria (Butler et al. 2008). Hep Par1 has a sensitivity for HCC of around 80–100 % and generally reflects hepatocyte-like differentiation in tumors. The reactivity manifests as a diffuse cytoplasmic granular staining pattern in normal and neoplastic hepatocytes (Figs. 1 and 2).

The frequency of Hep Par1 positivity depends on the tumor's grade. In an analysis of 96 cases of HCC, all 50 cases of nuclear grade 1 and nuclear grade 2 HCC were positive for Hep Par1, while only 84 % with grade 3 and 50 % with grade 4 were positive, and a positive result was more common in HCC with a trabecular, pseudoacinar, or scirrhous growth pattern than in those with a compact pattern (Chu et al. 2002). Apart from differences related to grade, not all HCC show uniform Hep Par1 staining. Tumors containing steatotic, clear cell, or oncocytic components show reduced or lacking reactivity in these areas. Hep Par1 reactivity is also detectable in metastases of HCC and seems to be a prognostic factor (Mondada et al. 2006). As Hep Par1 is expressed in hepatoid adenocarcinoma and it metastases (Pitman et al. 2004), and hepatoid carcinomas histologically are more or less identical to HCC, Hep Par1 will not serve to distinguish these two entities. However, not all HCC stain uniformly, and not all Hep Par1-positive tumors are of hepatocyte lineage or arise in the liver (review; Wee 2006). In one analysis, 3/19 HCCs showed <5 % Hep Par1 immunostaining, and variable Hep Par1 positivity was detected in part of gastric carcinoma, cholangiocarcinoma, colorectal carcinoma, lung carcinomas, ovarian carcinomas, and adrenocortical carcinomas (Fan et al. 2003), but also in reactive lesions such as intestinal metaplasia (Chu et al. 2003).

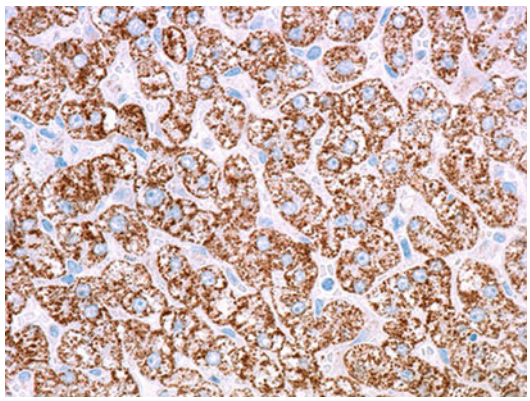

Fig. 1 Well-differentiated hepatocellular carcinoma with expression of Hep Par1 in a cytoplasmic granular pattern (Hep Par1 immunostain)

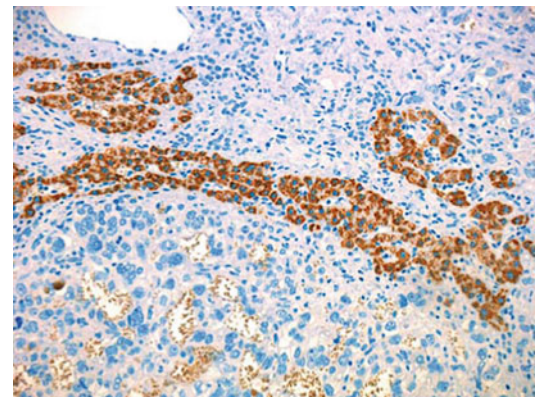

Fig. 2 Poorly differentiated hepatocellular carcinoma may downregulate expression of Hep Par1. In the present case, pleomorphic HCC cells (lower half of figure) are Hep Par1-negative, in contrast to compressed and partially atrophic hepatocytes (Hep Par1 immunostain)

Arginase-1

An important marker of the hepatocyte enzyme category comprises arginase-1 which is reactive in HCC (Yokoyama et al. 2004; Yan et al. 2010; Radwan and Ahmed 2012). Arginase-1 reactivity was demonstrated as a reliable marker of HCC in fine needle aspirates (McKnight et al. 2012) and was found to be superior in sensitivity to Hep Par1 and glypican-3 (Fujiwara et al. 2012). Arginase-1 reactivity was also useful in the diagnosis of scirrhous HCC (Krings et al. 2013). However, expression of arginase-1 is not restricted to hepatocytes and hepatocytic neoplasms, as this enzyme is expressed in myelocytes/metamyelocytes and localized in gelatinase granules of human neutrophils (Jacobsen et al. 2007).

Glutamine Synthetase

Expression of glutamine synthetase (GS) is an early marker for HCC based on immunohistochemical and proteomic analyses (Matsuno and Goto 1992; Dal Bello et al. 2010; Long et al. 2010; Shin et al. 2011) and is expressed in most of these neoplasms. GS expression is regulated by ubiquitin-dependent proteolysis (Osada et al. 1999). GS immunostaining is characterized by diffuse reactivity of the cytoplasm. GS showed an increased expression and phosphorylation in well-differentiated HCC, GS-positive cells sometimes growing in nodule-in-nodule manner (Kuramitsu et al. 2006). GS staining was correlated with large tumors, low histologic grade, formation of pseudoacini, bile deposition, and reduced specific and overall mortality (Del Bello et al. 2010). On the other hand, there is evidence that GS expression may enhance the metastatic potential in HCC (Osada et al. 1999, 2000). GS immunostaining is also present in focal nodular hyperplasia/FNH, regardless of size or a steatotic component. However, the staining pattern is different from that of HCC in that it is not diffuse, but characteristically anastomosed in a map-like cytoplasmic pattern (Bioulac-Sage et al. 2009).

Glypican-3

Glypican-3 is a valuable marker for hepatocyte-derived malignancies, including HCC and hepatoblastoma (Zhu et al. 2001; Coston et al. 2008; Wang et al. 2012b; Filmus and Capurro 2013; Krings et al. 2013; Witjes et al. 2013) but also for several other malignancies. Immunostaining for GPC3 can distinguish HCC from benign liver cell neoplasms, preneoplastic lesions, cholangiocarcinoma, metastases, and hyperplastic cells of cirrhosis. That enhanced GPC expression differentiates the majority of HCCs from non-HCC lesions has been shown by us in 2001 (Zhu et al. 2001) and has since been confirmed several times (Nakatsura et al. 2003; Filmus and Capurro 2004; Man et al. 2005; Liu et al. 2010; Suzuki et al. 2010; Yan et al. 2011; Yorita et al. 2011; review: Kandil and Cooper 2009; Fig. 3).

In contrast to HCCs, which show an upregulation of GPC3 in the majority of cases, GPC3 is downregulated in cholangiocarcinomas (Man et al. 2005) and nonmalignant hepatocellular lesions (Enan et al. 2013). Expression of GPC3 is a valuable diagnostic element in early HCC (Chen et al. 2014) and in HCC that are negative for AFP (Li et al. 2013). Immunohistochemically,

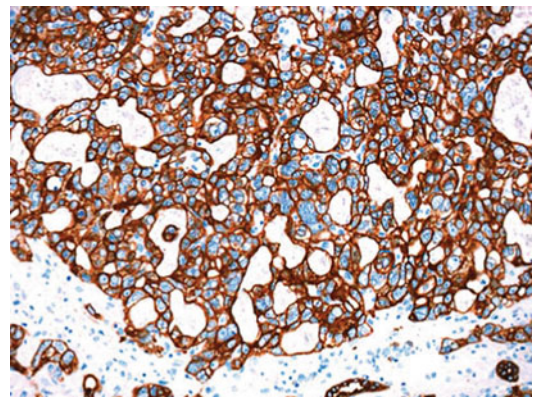

Fig. 3 Glypican-3 expression by HCC cells (glypican-3 immunostain)

GPC3 is visualized as a more or less diffuse cytoplasmic staining of cells in moderately and well-differentiated HCCs. In poorly differentiated HCC, membranous GPC3 immunostaining is seen, and membranous staining is also prevalent in metastatic lesions of HCC when compared with the primary tumors (Suzuki et al. 2010). HCC patients with circumferential cell surface GPC3 immunostaining revealed worse prognosis of their tumor disease (Yorita et al. 2011). This immunophenotype of HCCs is also visualized in needle biopsies (Kandil et al. 2007). The yield of GPC3 positivity in HCCs may exceed 85 % (Wang et al. 2006). In a microarray study of 54 HCCs and adjacent liver tissue, GPC3 staining was observed in 90 % of 21 HCC cases with cirrhosis and in 64 % of 28 HCC cases associated with non-cirrhotic liver. In cases with adenomas, only malignant foci were positive. Among 94 macronodules, GPC3 immunostaining was noted in 48 % of high-grade dysplastic nodules or early HCCs and in only 3 % of benign or low-grade dysplastic nodules (Wang et al. 2006).

Similar to classical HCC, fibrolamellar hepatocellular carcinoma (FL-HCC) can express GPC3 (Shafizadeh et al. 2008; Abdul-Al et al. 2010; Ward et al. 2010; Ward and Waxman 2011). In a comparative immunohistochemical study of 26 cases of FL-HCC and 62 classical HCCs, 39 % of HCC and 59 % of FL-HCC cases were positive for GPC3 (Ward et al. 2010). In contrast to this study, another investigation found that GPC3 was more often and more strongly expressed in HCCs (72 %) than in FL-HCCs (17 %) (Abdul-Al et al. 2010). Immunoreactivity for GPC3, together with that of Hep Par1, was detected in lymphoepithelioma-like hepatocellular carcinoma (Nemolato et al. 2008). GPC3 is also involved in the biology of hepatic cells other than hepatocytes and neoplasm derived thereof. M2-polarized tumor-associated macrophages which promote the progression and metastasis of HCC are recruited by CCL5, CCL3, and CSF1 under involvement of GPC3 (Takai et al. 2009).

Glypican-3 (GPC3) is a member of the membrane-anchored heparan sulfate proteoglycan glypican family. Glypicans are linked to the cell surface membrane by a glycosylphosphatidylinositol (GPI) anchor. So far, six members of this family (GPC1 – GPC6) have been identified in mammals, and two in *Drosophila*. All glypicans share the same basic structure, characterized by a core domain, an N-terminal secretory signal peptide, and a hydrophobic domain required for the addition of the GPI anchor (review: Filmus and Selleck 2001). Glypican-type heparan sulfate proteoglycans are coordinators of several cell functions (reviews: David and Bernfield 1998; Tumova et al. 2000; De Cat and David 2001; Fransson 2003), represent important mediators of developmental processes, and play distinctive roles in carcinogenic pathways. GPC3 has an important role in several developmental processes. Loss of GPC3 function causes growth factor-dependent defect in cardiogenesis (Ng et al. 2009), and loss-of-function mutations of the GPC3 gene (localized to chromosome Xq26) are the cause of Simpson-Golabi-Behmel syndrome type 1 (SGBS1; OMIM 312870, synonyms: Bulldog syndrome, Golabi-Rosen syndrome, Simpson dysmorphia syndrome; dysplasia gigantism syndrome, X-linked). Silencing of the glypican-3 gene regulates invasion and migration of human HCC cells (Qi et al. 2014). GPC3 is normally expressed in fetal tissues, including fetal liver and placenta, but not in the normal adult human liver. In the postnatal liver, GPC3 mRNA is repressed by the transcription factor, zinc fingers, and homeoboxes 2 (Zhx2) (Morford et al. 2007). In the liver, GPC3 is involved in hepatocyte proliferation and regeneration. GPC3 mainly operates in pathways regulating cell proliferation and the function of the cytoskeleton. The expression of GPC3 itself is regulated by the action of specific microRNAs (miRs; Maurel et al. 2013). miR-96, belonging to the miR-182/183 cluster, downregulates GPC3 expression by targeting its mRNA 3′-untranslated region and interacting with the predicted site.

Glypican-3 is also the source of a potential peptide vaccine (Sawada et al. 2012, 2013) and for recombinant humanized antibodies to treat HCC (Zhu et al. 2013). Glypican-3 is particularly useful in the diagnosis of well-differentiated

HCC (Sakamoto et al. 2008; Shafizadeh and Kakar 2011). In HCC patients, glypican-3 can circulate in the blood, and it is comparable to AFP as a serum marker for the diagnosis of HCC (Liu et al. 2013; Xu et al. 2013; Yao et al. 2013b) or for monitoring tumor recurrence (Fu et al. 2013). GPC3 has been considered as a potential target for the antibody therapy of liver cancer (reviews: Ho 2011; Feng and Ho 2014). By use of RNA interference it was shown that suppression of GPC3 in cultured HCC cells inhibited cell proliferation with cell cycle arrest at the G1 phase, associated with upregulation of TGF-beta2 (Sun et al. 2011). GPC3 can be targeted to HCC cells using multifunctional nanoparticles (Park et al. 2011) or liposomes containing GPC-3-targeting peptide ligands (Lee et al. 2011).

Heat Shock Protein 70

Expression of heat shock protein 70/HSP70 has proven to be a reliable marker for HCC (Di Tommaso et al. 2009). In one series, HSP70 was found in 71.9 % of HCC (Shin et al. 2011). HSP70 can synchronously be co-expressed with AFP in HCC cells (Wang et al. 2007).

Alpha-Fetoprotein (AFP) and Other Proteins Secreted by Hepatocytes

Alpha fetoprotein (AFP), an embryonal/fetal type of albumin, is produced and secreted by the majority of HCC (Fig. 4). AFP can be visualized in HCC cells both by immunofluorescence and immunohistochemistry methods (Purtilo and Yunis 1971; Nishioka et al. 1972; Thung et al. 1979; Espinoza et al. 1984; Imoto et al. 1985; Roncalli et al. 1985; Okushin et al. 1987; Brumm et al. 1989; Hurlimann and Gardiol 1991).

Also AFP messenger RNA is detectable in human HCC expressing the AFP gene (Di Bisceglie et al. 1986). In cases with AFP positivity, AFP is not present in distinct cell populations but rather shows a randomly heterogeneous distribution (Kinoyama et al. 1986). By use of immune-electron microscopy, intracellular AFP was mainly found in perinuclear space, cisternae of the rough endoplasmic reticulum, Golgi complex, and secretory vesicles (Okada et al. 1987). It was reported that the number of positive cells and the intensity of cytoplasmic AFP staining was roughly proportional to serum AFP levels in most cases (Kojiro et al. 1981), but depending on the preservation status of tissue and antibodies used, this phenomenon is not always observed. Expression patterns for AFP may be related to tumor grade, although reported percentages of positivity per a given grade vary considerably. In small HCC with a diameter of <3 cm, AFP immunoreactivity was less frequent than that of vitamin K absence or antagonist II/PIVKA-II. There is evidence that AFP-positive HCC are biologically more malignant than those neoplasms that are AFP-negative or PIVKA-II-positive (Fujioka et al. 2001).

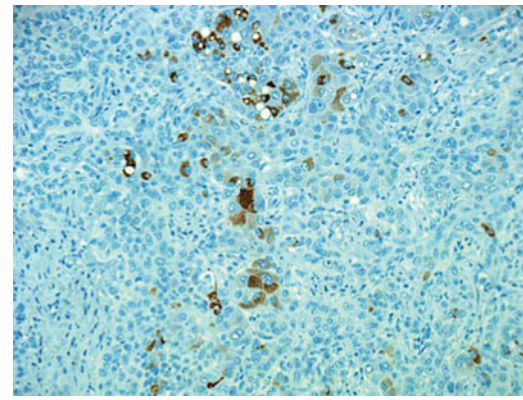

Fig. 4 A subset of hepatocellular carcinoma cells are reactive for alpha-fetoprotein (*AFP*) in a highly variable pattern (AFP immunostain)

Part of HCC cells are reactive for alpha-1-antitrypsin (AAT; Palmer and Wolfe 1976; Thung et al. 1979; Cohen et al. 1982; Nakopoulou et al. 1982; Fernandez-Izquierdo and llombart-Bosch 1987). In a series of 63 HCC cases, AAT reactivity of cancer cells was found in 82.5 % (Busachi et al. 1986). Some HCC showed atypical PAS-positive diastase-resistant globules resembling those in Z-gene AAT deficiency, and these globules were in part reactive for AAT (Palmer

and Wolfe 1976; Palmer et al. 1977; Reintoft and Hägerstrand 1979). In one investigation, atypical AAT-positive globules were found in 5.4 % of HCC, whereas a diffuse fine granular pattern of AAT distribution was detected in 31 % of HCC cases (Nakopoulou et al. 1982). A second study described AAT positivity in tumor cells in a finely granular pattern in 73 % of cases (Thung et al. 1979). In contrast to globules in normal hepatocytes in inherited AAT deficiency, where the inclusions are round and regular and show a ringlike AAT immunoreactivity, AAT inclusions in HCC were both intracellularly and extracellularly as round, but often distorted and less uniform globules (Palmer et al. 1980). However, other studies failed to detect AAT globules in HCC cells in patients with AAT deficiency who had inclusions in normal hepatocytes (Blenkinsopp and Haffenden 1977).

HCC cells are capable to synthesize and secrete ferritin. Serum ferritin concentrations are elevated in up to 100 % of patients with HCC. In part of these cases, ferritin can immunohistochemically be demonstrated in tumor tissue (Cohen et al. 1984). However, high serum ferritin in patients with HCC can also be caused by associated hepatic iron overload. Immunohistochemically, reactivity for ferritin was found in up to 70 % of cases, but predominantly in well-differentiated neoplasms (Imoto et al. 1985). HCC show an upregulated expression of transferrin receptors (Sakurai et al. 2014). PIVKA-II, an abnormal prothrombin, is secreted by part of HCC and serves as a serum marker for this neoplasm. About half of HCC showed cytoplasmic reactivity for PIVKA-II (Koda et al. 1993).

HCC-Specific Gamma-Glutamyltransferase

HCC cells can express a tumor-specific form of gamma-glutamyltransferase (GGT; hepatoma-specific GGT; HS-GGT; Yao et al. 2004). Analysis of HS-GGT bands in serum can serve as a diagnostic means for HCC (Yao et al. 1998). Overexpression of HS-GGT in HCC may be related to an altered methylation status of the HS-GGT gene (hypomethylation of CCGG sites; Yao et al. 2000).

Canalicular Domain Markers and Organelle Markers

CD10 (other names : neprilysin, CALLA/common acute lymphoblastic leukemia antigen, atriopeptidase, endopeptidase 24.11, enkephalinase, fibroblast metalloelastase, kidney-brush-border neutral peptidase, membrane metalloproteinase A, neutral endopeptidase; MEROPS peptidase code M13.001) is thermolysin-like zinc metalloendopeptidase of the neprilysin/NEP family that can also act as a secretase and plays an important role in tuning off peptide signaling events at the surface of several cell types, targets including enkephalins, tachykinins, chemotactic peptides, natriuretic peptide, and Alzheimer beta-amyloid peptide (Turner et al. 2001; Xiao et al. 2001). The canalicular domain, which is usually present in well-differentiated HCC, is immunoreactive for CD10 (CD1can), similar to polyclonal CEA antibody (Borscheri et al. 2001; Wee 2006). CD10 was detectable in 52 % of HCC cases (Chu et al. 2002), and is more often expressed by moderately to well-differentiated HCC cells than poorly differentiated HCC cells (Dragovic et al. 1997; Lau et al. 2002; Ahuja et al. 2008). Reactivity for CD10 is suitable to distinguish HCC from metastatic carcinomas resembling liver cancer (Ahuja et al. 2008). Expression of CD10can (but not its cytoplasmic counterpart, CD10cyt) in HCC was found to be a favorable prognostic factor (Mondada et al. 2006). Similar to CD10, polyclonal CEA antibody (pCEA) stains the canalicular domain of moderately to well-differentiated HCC (Varma and Cohen 2004), and reactivity was found in up to more than 80 % of cases (Wee and Nilsson 1997; Morrison et al. 2002; Al-Muhannadi et al. 2011). pCEA expression is related to tumor grade, in that canalicular staining becomes infrequent and irregularly distributed with increasing anaplasia. However, pCEA immunostaining did not separate

malignant, dysplastic, or benign hepatocytes (Wee and Nilsson 1997).

Intermediate Filament Expression Patterns

HCC cells can be distinguished from normal hepatocytes by differing patterns of organellogenesis, including mitochondria (Fig. 5).

Cytokeratins

Cytokeratins 8 and 18

HCC cells are strongly and consistently stained by CAM 5.2, which reacts with keratins of molecular weights 50, and 43, corresponding to cytokeratins 8 and 18 (Fig. 6; Hurlimann and Gardiol 1991; Wee 2006). Fifty-five percent of pure, classical HCC expressed cytokeratins of the hepatocyte lineage (D'Errico et al. 1996). In one study, intensity and extent of CMA 5.2 immunostaining did not correlate with the histologic grade of HCC (Johnson et al. 1988). In contrast to the strong expression of lineage-typical cytokeratins, most HCC do not show reactivity for vimentin, but vimentin may be positive in poorly differentiated HCC with ambiguous cell lineages. In HCC cells, the vimentin gene is aberrantly methylated (Kitamura et al. 2011), causing silenced expression via an epigenetic mechanism.

Cytokeratin 19

Part of HCC are reactive for cholangiocyte markers, including CK7 and CK19, a phenomenon probably related to transdifferentiation (Van Eyken et al. 1988; Shibuya et al. 2011). Expression of CK19 can also be found among morphologically pure HCC (D'Errico et al. 1996). Expression of CK19 in HCC as a stemness feature associated with high-risk biology (HCC of progenitor cell type). Expression of cytokeratin 19 (CK19; Keratin 19) is a feature typical for many adenocarcinomas, in particular also cholangiocarcinomas, while it was formerly held that CK19 is not a feature characterizing hepatocellular carcinomas (HCC). A subset of HCCs is characterized by the expression of stemness-related markers, including CK19 (Kamohara et al. 2008) and ezrin (Okamura et al. 2008). Such tumors have been termed, "dual-phenotype HCC/DPHHCC" (Lu et al. 2011). However, expression of CK19 in HCCs not only represents

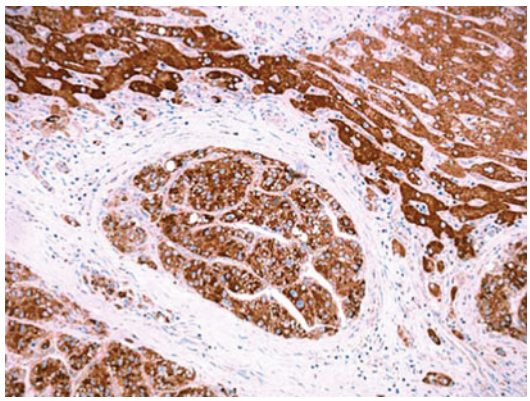

Fig. 5 Similar to normal hepatocytes, HCC cells contain variable amounts of mitochondria and are therefore reactive for a mitochondrial antigen (tumor focus in the center of the figure). The adjacent, strongly positive hepatocytes exhibit perifocal atrophy (mitochondrial antigen immunostain)

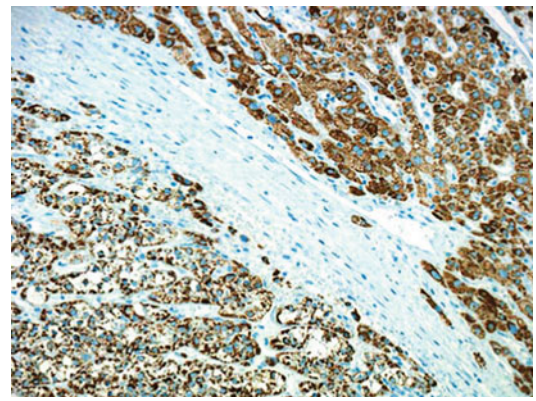

Fig. 6 Hepatocellular carcinoma cells (*left bottom corner*) show strong positivity for cytokeratins 8 and 18, but the granular reaction product is less compact than that of normal hepatocytes seen to the right and top (CAM 5.2 immunostain)

the acquisition of a biliary phenotype but is also related to stemness features. It has been proposed that HCC expressing a cholangiocyte phenotype is a novel subtype of HCC with a highly aggressive behavior. CK19 expression predicts accelerated progression of HCC and poorer survival (Uenishi et al. 2003; Yang et al. 2008; Yamada et al. 2011; van Malenstein et al. 2012; Wang et al. 2012a; Greenhill 2013; Lee et al. 2013; review: Izumi 2012). Among 155 HCCs, tumors with CK19 expression accounted for 10.1 %, and patients with this type of neoplasm a significantly lower overall survival and recurrence-free survival (Lu et al. 2011). 35.7 % of 210 surgically resected HCCs were CK19-positive, and this feature predicted early tumor recurrence and poor prognosis (Yuan et al. 2011). CK19-expressing HCCs with stemness-related marker expression demonstrated more frequent large vessel invasion, increased tumor size, microvessel invasion, poor tumor encapsulation, and poor survival (Kim et al. 2011). The adverse effect of CK 19 on prognosis, with early tumor recurrence, has also been found in small HCC after curative resection (Zhou et al. 2010), and particularly small HCCs (diameter <3 cm) additionally expressing mucin as an indicator for biliary differentiation form a high-risk group (Aishima et al. 2007). CK19-positivity in HCCs is an independent risk factor for developing lymph node metastasis (Ding et al. 2004; Zhuang et al. 2008). Part of HCCs expressing CK19 and showing aggressive behavior coexpress other stemness-related markers, such as CD133, nestin, CD44, and ATP-binding cassette subfamily G member 2/ABCG2 (Yang et al. 2010). In one investigation, CK19 was most frequently expressed in combination with at least one other stemness-related marker, such as CD133, EpCAM, and c-kit. HCC expressing CK19 in part also expressed Yes-associated protein 1, a potential oncogene known to promote stem cell proliferation (Kim et al. 2013). Expression of CK19 was also significantly associated with expression of proteins characterizing epithelial to mesenchymal transition (EMT), including vimentin, S100A4, uPAR, and ezrin (Kim et al. 2011). There is a significant inverse correlation between the expression of the organic anion transporter peptides (OATP) 1B1 and 1B3 and of CK7 and CK19, in that all HCCs expressing OATP 1B1/1B3 were CK7/CK19 negative (Vasuri et al. 2011). One stemness-related marker, epithelial cell adhesion molecule (EpCAM), is highly expressed in premalignant hepatic tissues and in a subset of HCCs (De Boer et al. 1999). EpCAM-positive HCCs display a distinct molecular signature with features of hepatic progenitor cells (Yamashita et al. 2008). The aggressive phenotype of EpCAM-positive HCCs may be related to the observation that expression of EpCAM shifts the state of cadherin-mediated adhesions from strong to weak (Winter et al. 2003). The reason why expression of CK19 is associated with higher aggressivity of HCCs is not yet known. From other tumor models there is evidence that CK19 and other intermediate filaments play an important role in tumor cell migration, invasion, and metastasis (Hendrix et al. 1996). Keratin 19-positive HCC highly expressed invasion-related/metastasis-related markers and showed expression of members of the miRNA 200 family. Furthermore, primary human keratin 19-positive HCC showed increased invasiveness in vitro (Govaere et al. 2014). HCC expressing "stemness"-related proteins were characterized by increased telomere length, augmented expression hTERT, and shelterin complex proteins, associated with increased chromosome instability, alterations favoring an aggressive tumor phenotype (Kim et al. 2013).

Proliferative Activity

Proliferative activity of HCC cells is usually assessed by means of determination of the mitotic index or immunohistochemical assessment using PCNA or Ki-67 (MIB1) staining (Figs. 7 and 8; Grigioni et al. 1989; Ojanguren et al. 1993; Ng et al. 1995). The proliferative activity of HCC assessed through PCNA and MIB1 labeling is significantly related to tumor differentiation (Ng et al. 1995). Whereas PCNA immunostaining of normal and regenerative livers showed no or only a minimal proliferative activity, even well-differentiated HCC exhibited a labeling index

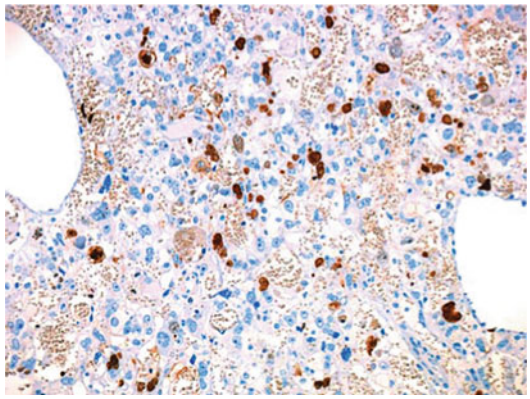

Fig. 7 Hepatocellular carcinoma, grade 3. There is increased proliferative activity (MIB1 immunostain)

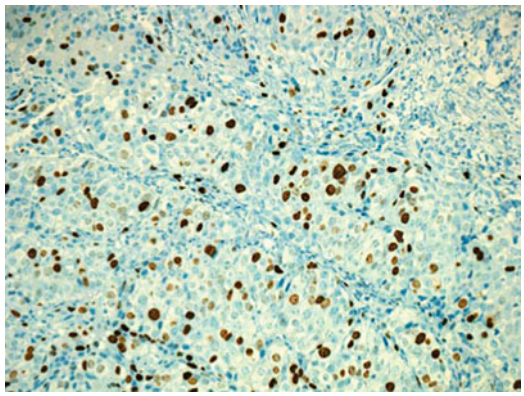

Fig. 8 This hepatocellular carcinoma with a diffuse growth pattern and grade 4 differentiation exhibits a markedly increased proliferative activity (MIB1 immunostain)

exceeding 15 % (Ojanguren et al. 1993). Ojanguren and coworkers (1993) classified PCNA labeling into several categories, i.e., absent; minimal, <5 % positive nuclei; grade 1, 1.5–25 % positive nuclei; grade 2, 26–50 % positive nuclei; grade 3, 51–75 % positive nuclei; and grade 4, 76–100 % positive nuclei. These categories are now known as Ojanguren grades. In cirrhotic liver harboring HCC, the PCNA labeling index was higher in perineoplastic cirrhotic liver than in perineoplastic non-cirrhotic liver (Mun et al. 2006). Based on Ki-67 immunostaining, HCC had a proliferative index ranging from 15 % to 50 %, dependent on Edmondson-Steiner grade (Grigioni et al. 1989). HCC express factors involved in the promotion of cell proliferation, such as cyclin D1 (expression associated with tumor progression), other cyclins (Choi et al. 2001), and S100A6 (Hua et al. 2011).

Markers of Cellular Differentiation

Apart from the synthesis and secretion of certain distinct proteins, such as AFP, other proteins produced by HCC cells reflect variable grades of differentiation and lineage features. The protein, differentiated embryo chondrocyte 1/DEC1, is expressed in the cytoplasm of hepatocytes and HCC, but well-differentiated HCC cells also display nuclear reactivity of DEC1, while low DEC1 expression indicates poor histologic differentiation (Shin et al. 2011). A subset of HCC expresses mucin core protein 1 (MUC1). In one study, MUC1 immunoreactivity was demonstrated in 85/186 HCCs, and MUC1 positivity in HCC was significantly associated with serum AFP concentrations, tumor differentiation, bile duct invasion, lymph node metastasis, cytokeratin 19 expression, and higher rate of first recurrence, suggesting that MUC1-expressing HCC form a high-risk group of neoplasms (Ichikawa et al. 2006). HCC express the squamous cell carcinoma antigen (SCCA) or variants/isoforms thereof, a protein that is also secreted into serum (Pontisso et al. 2004; Guido et al. 2008; Schmilovitz-Weiss et al. 2011). Immunohistochemically, the antigen is expressed in the cytoplasm of HCC cells, with an uneven distribution of positive tumor cells within HCC nodules, either scattered or in irregular clusters (Guido et al. 2008). A further expression pattern reflecting cell differentiation is the production of intercellular junctions and the associated proteins. Tight junctions are involved in numerous important processes in hepatocytes and cholangiocytes (reviews: Lee and Luk 2010; Lee 2012). In the course of carcinogenesis, including hepatocarcinogenesis, tight junction components undergo marked alterations which allow cancer cells to individualize and to dissociate, prerequisites for invasion (Swift et al. 1983). While occludin and ZO-1, two typical tight junction components, are

strongly expressed in canalicular domains of normal hepatocytes, they are not expressed in HCC cells. As colorectal metastases show strong occluding and ZO-1 expression, analysis of these two proteins may be diagnostically helpful (Orban et al. 2008). Tight junction proteins can be used in differential diagnostic approaches. Claudins have a complex role in liver cell function and play a role in HCV biology. Claudins are members of the tetraspanin family of proteins. During HCV infection, claudin-1 is highly expressed in liver and is required for HCV entry (Ahmad et al. 2011). Claudin-1 and claudin-4 are highly expressed in colorectal cancer metastasis, but claudin-1 has low expression in HCC and claudin-4 is virtually absent (Holczbauer et al. 2013). Lack of claudin-4 expression in HCC and high expression in cholangiocarcinoma has been described in another analysis (Lodi et al. 2006). Conversely, claudin-7 was expressed in HCC cells (Brokalaki et al. 2012). High expression of claudin-10 in HCC determined by molecular methods was associated with tumor recurrence (Cheung et al. 2005). Claudin-5 is expressed in sinusoidal endothelial cells, portal vein, and arteries, but not central veins, while it is downregulated in tumor vessels of HCC (Sakaguchi et al. 2008). Claudins play a role in acquisition of an invasive phenotype. For example, claudin-1 acts through a c-Abl-protein kinase C delta signaling pathway to promote cell invasion (Yoon et al. 2010).

Markers Related to Adhesion Molecules, Cytoskeletal Structures, and Tumor Cell Organelles

HCC express diverse cell adhesion molecules in differential patterns. Normal hepatocytes express E-cadherin but are only weakly stained for alpha-catenin, whereas bile duct cells show high-level expression of alpha-catenin. Conversely, E-cadherin and alpha-catenin expression is often reduced in HCC (Kozyraki et al. 1996; Zhao and Zimmermann 1998). Loss of E-cadherin expression on the surface of HCC cells is mainly found in poorly differentiated neoplasms (Shimoyama and Hirohashi 1991). Part of HCC express neural cadherin/N-cadherin, whereby overexpression of this adhesion molecular is a negative prognosticator (Seo et al. 2008). Epithelial cell adhesion molecule (EpCAM) is expressed by part of HCCs and is regarded as a stem cell marker in these neoplasms. EpCAM was preferentially expressed in HCC with a nodular growth pattern and high tumor grade (Bae et al. 2012). HCCs with progenitor cell features express the adhesion molecule, NCAM (Tsuchiya et al. 2011). A cell surface glycoprotein called MOC31 is consistently positive in cholangiocarcinomas and metastatic adenocarcinomas, but is negative in HCC (Proca et al. 2000).

An adhesion molecule that plays a significant role in HCC is CD44. The CD44 (cluster differentiation 44) isoform group is a conserved family of several transmembrane glycoproteins serving as cell surface adhesion molecules. CD44 mainly acts as a receptor for hyaluronan, but can also bind other glycosamino-glycans, glycoproteins, and proteins with lower affinity, including chondroitin sulfate, fibronectin, serglycin, and osteopontin. CD44 as an adhesion molecule is widely expressed in lymphoid cells, other leukocytes, and epithelial cells, and is an important component of lymphocyte homing. The cytoplasmic domain of CD44s interacts with several components of the cytoskeleton via ankyrin and proteins of the ezrin-moesin-radixin family. Upon binding of hyaluronan, CD44 activates the Rho GTPase signaling pathway. Interaction of CD44 isoform with cytoskeletal proteins is required for cell locomotion and plays a critical role for cell migration, specifically in cancer cell systems. Cells expressing CD44v(3,8–10) are capable to form membrane spikes or invadopodia required for locomotion, and CD44v(3,8–10) is closely associated with the actomyosin contractile system and with the active form of metalloproteinase-9. The activity of two metalloproteinases, MMP-2 and MMP-9, was stimulated by the interaction of the variant CD44, CD44st, with hyaluronan, associated with an invasive phenotype (Fang et al. 2011). Expression of CD44s is a well-known prognostic factor in various cancers, based on its functions as a tumor growth factor and adhesion

molecule affecting tumor cell invasion and spread. CD44 is not expression by normal hepatocytes (Mathew et al. 1996), but is expressed in HCCs in a membranous staining pattern (Washington et al. 1997;). CD44 expression in HCCs depends of differentiation and is an important progniticator. In a tissue array study of 260 HCC samples employing a primary mouse CD44s monoclonal antibody, expression of CD44s correlated with poor differentiation of HCC (high grade in Edmondson-Steiner grading) and shorter disease-free survival time (Ryu et al. 2011). A correlation with higher tumor grade was found in other studies (Beckebaum et al. 2008). In contrast, use of an antibody that does not distinguish between standard CD44 and splice variants did not show a correlation between CD44 expression and HCC grade (Washington et al. 1997), and reactivity for CD44 was not correlated with the proliferation index of HCC cells (Mathew et al. 1996). Immunoreactivity of CD44 in HCC is significantly correlated with vascular invasion (Mathew et al. 1996) and extrahepatic metastasis (Ogawa et al. 2004). CD44s expression in HCC is associated with higher cancer stage and the presence of lymph nodes metastases (Beckebaum et al. 2008). Apart from CD44 effects mediated by the modulation of tumor cell adhesion, the altered biologic behavior of HCC cells expressing CD44 and its variants may also be caused by a different cellular composition of CD44-expressing HCCs. Cancer stem cells/progenitor cells are highly enriched in CD133+/CD44+ populations of HCC (Zhu et al. 2010; Chan et al. 2014), suggesting the emergence of distinct cell lineages in these tumors.

Clathrin heavy chain positivity is a marker for HCC that already works in the diagnosis of small HCC (Di Tommaso et al. 2011). Golgi protein 73 (GP73) is expressed in HCC (Yao et al. 2013a) and appears in serum, whereby there is evidence that serum GP73 has a either a comparable or lesser accuracy to AFP for the diagnosis of HCC (Ozkan et al. 2011; Zhou et al. 2012). In contrast to cholangiocarcinomas, HCC cells are not reactive for epithelial membrane antigen/EMA, positive cases representing mixed hepato-cholangiocarcinomas (Sacho et al. 1991).

Oncogenes and Tumor Suppressor Genes

A majority of HCC revealed nuclear reactivity for p53 protein related to p53/TP53 gene mutations (Fig. 9; Cohen and DeRose 1994; Zhao et al. 1994; Kang et al. 1998).

The TP53 gene encodes a tumor suppressor protein, p53, composed of several domains, including transcriptional activation, DNA-binding, and oligomerization domains. P53 protein is a cellular stress response protein that regulates the expression of several genes affecting cell proliferation, apoptosis, DNA repair, and cell senescence. In a recent whole-genome sequencing analysis, TP53 was the most frequently mutated tumor suppressor in HCC (35.2 %; Kan et al. 2013). Mainly in East Asia and southern Africa, p53 protein expression is linked to a mutational hot spot at codon 249 of the p53 gene (Murakami et al. 1991; Debuire et al. 1993). However, p53 protein overexpression is frequent in European HCC largely independent of the codon 249 hotspot mutation (Volkmann et al. 1994). The TP53

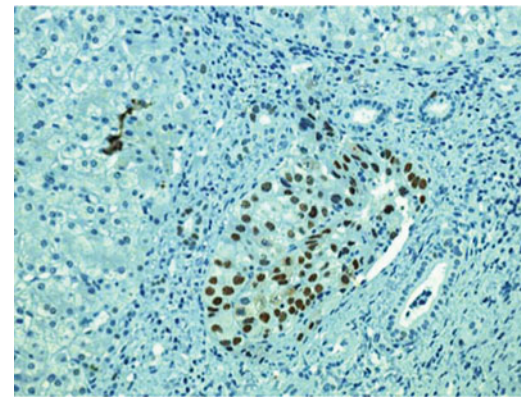

Fig. 9 This hepatocellular carcinoma, which has invaded a venous branch in a portal tract, shows strong nuclear reactivity for p53 protein. The lesion is surrounded by several small interlobular bile ducts (p53 immunostain)

gene mutational hot spots R249S and V157F were significantly associated with worse prognosis (Villanueva and Hoshida 2011). The patterns of p53 mutations have been shown to vary among tumors within the same liver (Tullo and Sbisa 2002), suggesting the emergence of several clones with a different genomic composition. Immunohistochemically, p53 protein reactivity presents as a strong nuclear positivity that may be patchy or diffuse. Nuclear staining restriction depends on the antibody used and was mainly found with the antibody CM-1, whereas other antibodies may also result in variable degrees of cytoplasmic staining (Zhao et al. 1994). There was no relationship between p53 immunostaining and type or grade of HCC (Zhao et al. 1994). However, one study showed a correlation between p53 reactivity and significantly higher Ki67 scores (D'Errico et al. 1994).

HCCs can express a tumor suppressor protein related to p53, p73 (Herath et al. 2000). The p73 gene is located at chromosome 1p36.3. Similar to p53, p73 is involved in the regulation of apoptosis. HCC which express p73 protein belong to a aggressive, high-risk group (Tannapfel et al. 1999).

Components of the Wnt/Beta-Catenin Signaling Pathway

Whole-genome sequencing demonstrated that beta-catenin, a key component of the Wnt signaling pathway, is the most frequently mutated oncogene (15.9 %; Kan et al. 2013). There is a tight correlation between beta-catenin gene mutations and the expression of Wnt target genes in HCC. In one investigation, 36 % of HCC displayed beta-catenin immunostaining, and this immunophenotype was associated with certain signification features, including a homogeneous microtrabeculo-acinar pattern, low-grade cellular atypia, and cholestasis, the latter visualized in the form of numerous bile plugs in acinar or canaliculus-like lumina (Audard et al. 2007). Abnormal beta-catenin reactivity in the cytoplasm and/or nuclei of HCC cells was also found at higher rates, e.g., 72.9 % (Fig. 10; Li et al. 2014).

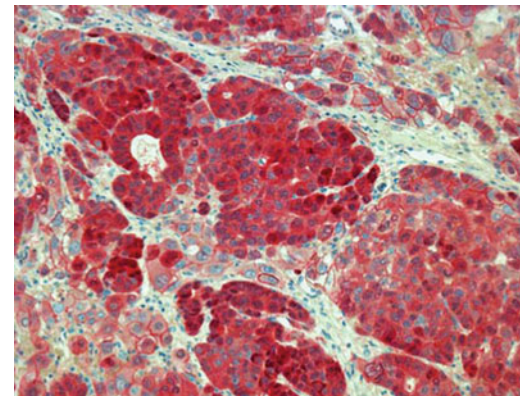

Fig. 10 Hepatocellular carcinoma with mixed cytoplasmic, membranous, and nuclear reactivity for beta-catenin (beta-catenin immunostain)

Similar to hepatoblastoma, overexpressed beta-catenin is correlated with cytoplasmic overexpression of cyclin D in HCC, and is associated with increased proliferative activity of tumor cells (Ueta et al. 2002). HCC that harbor exon-3 mutations of the beta-catenin/CTNNB1 gene showed a distinct phenotype with frequent macro-and microvascular invasion, a larger tumor size, a less common association with cirrhosis, and an aggressive behavior, as beta-catenin plays a significant role in the metastatic cascade (Cieply et al. 2009; Lai et al. 2011). In comparison with normal liver, HCC show much less reactivity for Wnt-5a (Li et al. 2014).

Extracellular Matrix of HCC

HCC possess, depending on the amount of stroma formation, a complex extracellular matrix which shares many proteins and glycoproteins with the normal hepatic matrix. Typical components of this matrix include interstitial collagens and mucopolysaccharides, basement membrane proteins (laminin, type IV collagen, nidogen, fibronectin), tenascin, protein receptors such as laminin receptors, and proteases and growth factors that are stored in

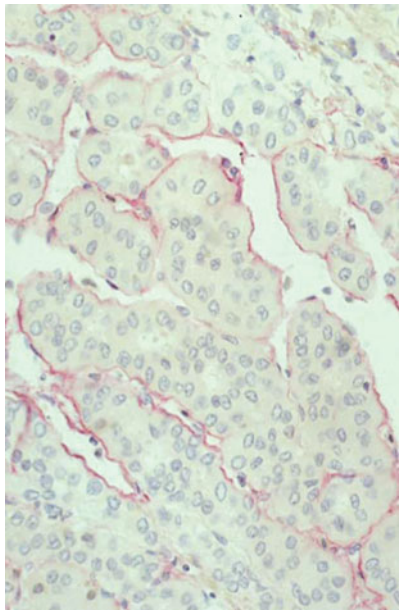

Fig. 11 This trabecular hepatocellular carcinoma shows a thin rim of peritrabecular extracellular matrix, situated between tumor cell plates and vascular channels. This matrix reveals reactivity for laminin (*red* reaction product; laminin immunostain)

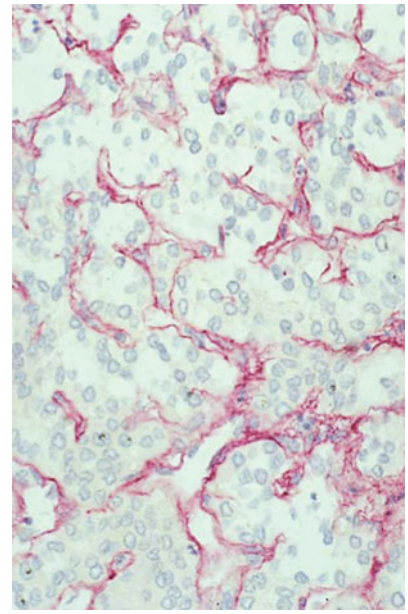

Fig. 12 As a marker for tumor extracellular matrix there is reactivity for tenascin in the peritrabecular space of this hepatocellular carcinoma (*red* reaction product; tenascin immunostain)

the matrix. Part of these proteins are present both within cancer cells and in the extracellular space, e.g., fibronectin (Okushin et al. 1987; Figs. 11 and 12).

The composition of the extracellular matrix affects the biologic behavior of HCC cells (Grigioni et al. 1991). Type IV collagen is predominantly present along sinusoid-like vascular channels in well-differentiated HCC, whereas laminin and type IV collagen in poorly differentiated HCC is mainly restricted to large intratumoral vessels (Grigioni et al. 1987). Most HCC show expression of tenascin, this expression being stronger than that of accompanying cirrhosis (Zhao et al. 1996) and the basement membrane protein nidogen (Cheng et al. 2012). Proteins of basement membrane substance, including type IV collagen and laminin, are differentially expressed in various types of HCC. As the extracellular matrix is less well developed in poorly differentiated HCC, such neoplasms showed a reduced expression of type IV collagen (Zhao et al. 1996). Agrin, a basement component, is a multifunctional heparan sulfate proteoglycan, is present in minor amounts in hepatic blood vessel walls and around bile ducts, but is upregulated in cirrhosis and HCC (Tatrai et al. 2009; Somoracz et al. 2010), the source probably being myofibroblasts (Tatrai et al. 2006). The stroma of HCC can contain heparan sulfate proteoglycans, e.g., syndecan-3 and perlecan, proteoglycans that may be involved in angiogenesis (Roskams et al. 1998). HCC can express various types of matrix metalloproteinases and their inhibitors. Tissue inhibitor of metalloproteinases (TIMP) is detectable in myofibroblasts, smooth muscle cells and endothelial cells of blood vessels, and bile ducts cells of normal livers, and is strongly expressed in the capsule of HCC (Fukuda et al. 1991). HCC also express factors involved in the production of an extracellular matrix, including several types of fibrokines and their regulators.

CD34 Expression in Vascular Endothelial Cells: An Important Diagnostic Feature

In normal liver tissue, CD34 immunostaining is restricted to portal tracts and few sinusoids in the periportal zone 1 of the lobule; whereas in HCC a diffuse and strong endothelial cell reactivity is present (Figs. 13, 14, 15, 16, and 17; Tanigawa et al. 1997).

CD34 immunostaining is in fact a highly sensitive method for the diagnosis of HCC, as it clearly outlines the abnormal growth pattern of

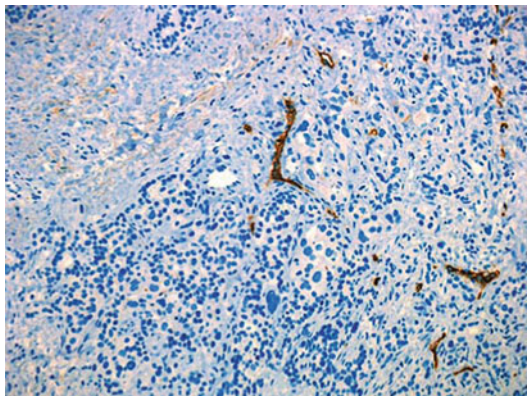

Fig. 13 CD34-reactive small feeding vessels at the periphery of hepatocellular carcinoma (CD34 immunostain)

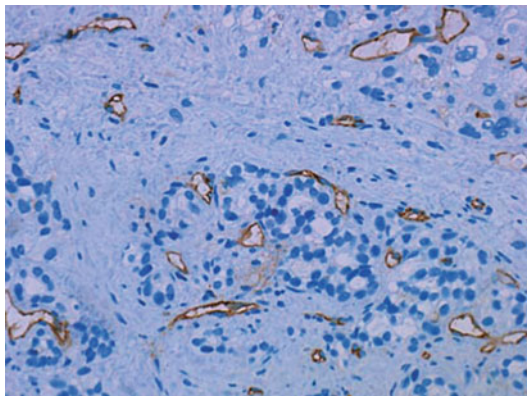

Fig. 14 Angiogenesis in hepatocellular carcinoma results in an intricate relationship between small tumor vessels (*brown*) and clusters of tumor cells (CD34 immunostain)

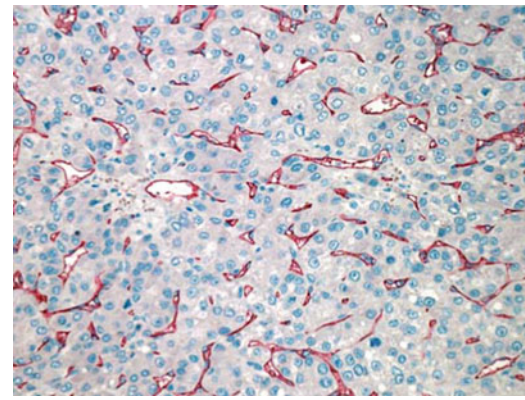

Fig. 15 The vascular channels of this trabecular hepatocellular carcinoma are lined by diffusely CD34-positive endothelial cells (CD34 immunostain)

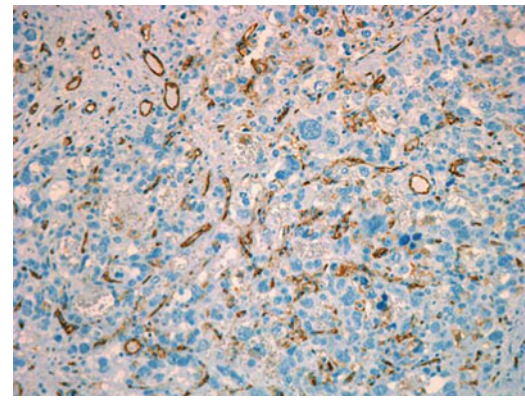

Fig. 16 At the invasion front of this hepatocellular carcinoma (upper third of figure), vigorous angiogenesis has taken place (CD34 immunostain)

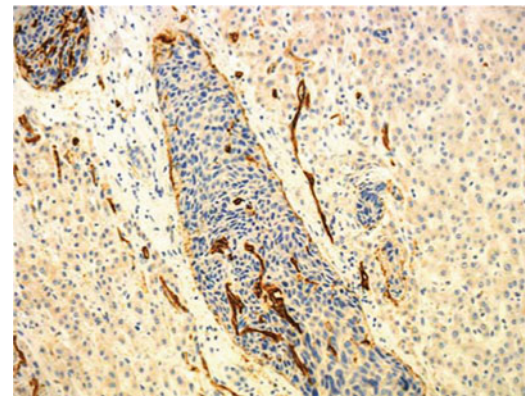

Fig. 17 An intravascular plug of hepatocellular carcinoma ("tumor thrombus") is secondarily vascularized by CD34-positive vascular sprouts (CD34 immunostain)

HCC, mainly well or moderately differentiated forms (Gottschalk et al. 1998; Wee and Nilsson 2003; Varma and Cohen 2004; Coston et al. 2008; Tatrai et al. 2009; Yao et al. 2013a). However, diffuse CD34 immunostaining is not specific for HCC, as it also occurs in part of liver cell adenomas and focal nodular hyperplasia (de Boer et al. 2000). These authors proposed that the reticulin stain may be superior to CD34 immunostaining in the diagnosis of HCC. There is evidence that CD34-positive endothelial cells may play a significant role in hepatocarcinogenesis. These cells may, at least in part, originate from circulating progenitor cells capable to transform into a distinct population of endothelial cells (Ohmori et al. 2001).

Markers Related to HCC Angiogenesis

As described in more detail in a separate chapter, angiogenesis is a prominent feature of HCC and exerts a strong influence on tumor biology (Semela and Dufour 2004; Fernandez et al. 2009). Angiogenesis in HCC is derived from endothelial cells of feeding arteries and sinusoid-like vascular channels, but liver-specific pericytes also play a role, mainly as mediators of sinusoidal remodeling (Lee et al. 2007). Several factors involved in angiogenesis are expressed, or upregulated, in HCC. Vascular endothelial growth factor/VEGF is expressed in HCC cells, but also in hepatocytes and vascular endothelial cells, but VEGF expression in endothelial cells is numerous times more common in HCC than in the surrounding liver, suggesting that VEGF plays an important role in tumor angiogenesis (An et al. 2000). CD105 (endoglin) is strongly expressed in tumor vessels and is related to prognosis (Duff et al. 2003; Yang et al. 2006). Endoglin is a co-receptor for several TGF-beta family cytokines, is expressed in dividing endothelial cells alongside ALK1 and ACVRL1, and is required for BMP9 (bone morphogenetic protein 9)/pSMAD1 signaling in endothelial cells. Endothelial cells of HCC, and mainly those of microvessels, are reactive for the chemokine receptor, CXCR7 (Monnier et al. 2012).

Other Markers

Part of HCC cells revealed reactivity for thrombospondin in the cytoplasm, but were also present in accompanying fibroblasts and endothelial cells (Hayashi et al. 1997). Reactivity for serine peptidase inhibitor, Kazal type 1 (SPINK1), was found in more than 90 % of HCC, but was not detectable in normal or cirrhotic liver tissues and in dysplastic nodules (Marshall et al. 2013). Early HCC were found to be reactive for CD147 (EMMPRIN) (Mamori et al. 2007). Few cases of HCC were immunoreactive for inhibin (McCluggage et al. 1997; Vrettou et al. 2005), inhibin as such not being a marker of the hepatocyte lineage or of most HCC, and positive results usually being caused by endogenous biotin (Iezzoni et al. 1999). Part of HCC are reactive for the transcription factor SALL4, which is a well-known marker for yolk sac tumor. In contrast to yolk sac tumor, which displays as diffuse finely granular nuclear staining pattern, HCC show a distinct punctuate/clumped nuclear pattern of SALL4 staining (Gonzalez-Roibon et al. 2013). Part of HCC express osteopontin, a secreted phosphoprotein implicated in cancer progression and metastasis (Pan et al. 2003; Hua et al. 2011), and osteonectin/SPARC, which is mainly expressed in stromal fibroblasts of HCC showing a high grade (Le Bail et al. 1999). Importin-alpha1 is produced by HCC cells and is a factor associated with progression of disease (Yoshitake et al. 2011). Aldo-ketoreductase family 1 member B10 (AKR1B10) reactivity seems to be promising diagnostic marker for HCC (Schmitz et al. 2011). Subsets of HCC are reactive for multidrug resistance-conferring transporters. Multidrug resistance-associated protein 1 (MRP1) expression was high in HCC with poor differentiation, large tumor size, and microvascular invasion and may reflect tumors with progenitor cell features and an aggressive biology (Vander Borght et al. 2008). Another immunohistochemical marker associated with poor tumor differentiation is p21 (Schoniger-Hekele et al. 2005). The PTEN phosphatase was expressed in 64–5 % of HCC, but immunoreactivity was lower and weaker than that in

surrounding non-neoplastic liver tissues (Wu et al. 2007). Prothymosin alpha, normally positive in the nuclei of bile duct cells but not in quiescent hepatocytes, is intensely expressed in regenerating hepatocytes and HCC cells, confirming that this protein is related to the regulation of liver cell proliferation (Fraga et al. 1993). Expression of the insulin-like growth factor-I receptor may participate in hepatocarcinogenesis (Yan et al. 2013). HCC, but also regenerating hepatocytes, overexpress hepatic prothymosin alpha, which may be a marker for this neoplasm. Reactivity is exclusively present in nuclei (Fraga et al. 1993; Wu et al. 1997).

Immunohistochemical Panels Serving for Diagnosis of HCC

The specificity of lineage marker expression can be augmented by combining the most efficient markers, namely arginase-1, Hep Par1, heat shock protein 70, glutamine synthetase, and glypican-3 (Sakamoto et al. 2008; Shin et al. 2011; Timek et al. 2012; Tremosini et al. 2012; Lagana et al. 2013), and eventually other markers. Histologic diagnosis of well-differentiated HCC can be difficult, especially in biopsies, as tumor cells may only slightly deviate in their morphology from normal hepatocytes or benign hepatocellular tumors. Apart from a careful analysis of cell morphology, reticulin patterns, and vascular architecture, panels of immunohistochemical stains are helpful in critical situations. A panel including glypican-3, heat shock protein 70, and glutamine synthetase have proven to be of use in the diagnosis of HCC, including small and well-differentiated HCC (Di Tommaso et al. 2009), early HCC (Tremosini et al. 2012), and to distinguish low-grade HCC from hepatocellular adenoma (Lagana et al. 2013). For the distinction of small HCC from dysplastic nodules, a combination panel of aminoacylase-1, glypican-3, and sequestosome-1 has been proposed (Jin et al. 2013). For separating HCC from intrahepatic cholangiocarcinoma, a combination of glypican-3 and CK19 was proposed as a first-line marker, with an accuracy rate of 73.5 %, and adding claudin 4 and MOC31 increased this rate to 88.5 % (Ryu et al. 2012), MOC31 mainly serving to distinguish HCC from cholangiocarcinoma and metastatic adenocarcinoma (Porcell et al. 2000).

References

Abdul-Al HM, Wang G, Makhlouf HR, Goodman ZD (2010) Fibrolamellar hepatocellular carcinoma: an immunohistochemical comparison with conventional hepatocellular carcinoma. Int J Surg Pathol 18:313–318

Ahmad W, Shabbiri K, Iljaz B, Asad S, Sarwar MT, Gull S, Kausar H, Fouzia K, Shahid I, Hassan S (2011) Claudin-1 required for HCV virus entry has high potential for phosphorylation and O-glycosylation. Virol J 8:229

Ahuja A, Gupta N, Kalra N, Srinivasan R, Chawla Y, Rajwanshi A (2008) Role of CD10 immunohistochemistry in differentiating hepatocellular carcinoma from metastatic carcinoma of the liver. Cytopathology 19:229–235

Aishima S, Nishihara Y, Kuroda Y, Taguchi K, Iguchi T, Taketomi A, Maehara Y, Tsuneyoshi M (2007) Histologic characteristics and prognostic significance in small hepatocellular carcinoma with biliary differentiation: subdivision and comparison with ordinary hepatocellular carcinoma. Am J Surg Pathol 31:783–791

Al-Muhannadi N, Ansari N, Brahmi U, Satir AA (2011) Differential diagnosis of malignant epithelial tumours in the liver: an immunohistochemical study on liver biopsy material. Ann Hepatol 10:508–515

An FQ, Matsuda M, Fujii H, Matsumoto Y (2000) Expression of vascular endothelial growth factor in surgical specimens of hepatocellular carcinoma. J Cancer Res Clin Oncol 126:153–160

Audard V, Grimber G, Elie C, Radenen B, Audebourg A, Letourneur F, Soubrane O et al (2007) Cholestasis is a marker for hepatocellular carcinomas displaying β-catenin mutations. J Pathol 212:345–352

Bae JS, Noh SJ, Jang KY, Park HS, Chung MJ, Park CK, Moon WS (2012) Expression and role of epithelial cell adhesion molecule in dysplastic nodule and hepatocellular carcinoma. Int J Oncol 41:2150–2158

Beckebaum S, Chen X, Sotiropoulos GC, Radtke A, Daoudaki M, baba HA, Wohlschlaeger J (2008) Role of osteopontin and CD44s expression for patients with hepatocellular carcinoma undergoing liver transplantation or resection. Transplant Proc 40:3182–3184

Bioulac-Sage P, Laumonier H, Rullier A, Cubel G, Laurent C, Zucman-Rossi J, Balabaud C (2009) Overexpression of glutamine synthetase in focal nodular hyperplasia: a novel easy diagnostic tool in surgical pathology. Liver Int 29:459–465

Blenkinsopp WK, Haffenden GP (1977) Alpha-1-antitrypsin bodies in the liver. J Clin Pathol 30:132–137

Borscheri N, Roessner A, Röcken C (2001) Canalicular immunostaining of neprilysin (CD10) as a diagnostic marker for hepatocellular carcinomas. Am J Surg Pathol 25:1297–1303

Brokalaki EI, Weber F, Sotiropulos GC, Daoudaki M, Cicinnati VR, Beckebaum S (2012) Claudin-7 expression in hepatocellular carcinoma. Transplant Proc 44:2737–2740

Brumm C, Schulze C, Charels K, Morohoshi T, Klöppel G (1989) The significance of alpha-fetoprotein and other tumour markers in differential immunocytochemistry of primary liver tumours. Histopathology 14:503–513

Busachi CA, Ferrari S, Ballardini PL, Landi P, Bazzocchi F, Santini D, Martinelli G et al (1986) Tissue antigen distribution in hepatocellular carcinoma. Tumori 72:1–5

Butler SL, Dong H, Cardona D, Jia M, Zheng R, Zhu H, Crawford JM, Liu C (2008) The antigen for Hep Par 1 is the hepatocytic urea cycle enzyme, carbamoyl phosphate synthetase 1. Lab Invest 88:78–88

Chan AWH, Tong JHM, Chan SL, Lai PBS, To KF (2014) Expression of stemness markers (CD133 and EpCAM) in prognostication of hepatocellular carcinoma. Histopathology 64:935–950

Chen IP, Ariizumi S, Nakano M, Yamamoto M (2014) Positive glypican-3 expression in early hepatocellular carcinoma predicts recurrence after hepatectomy. J Gastroenterol 49:117–125

Cheng ZX, Huang XH, Wang Q, Chen JS, Zhang LJ, Chen XL (2012) Clinical significance of decreased nidogen-2 expression in the tumor tissue and serum of patients with hepatocellular carcinoma. J Surg Oncol 105:71–80

Cheung ST, Leung KL, Ip YC, Chen X, Fong DY, Ng IQ, Fan ST, So S (2005) Claudin-10 expression level is associated with recurrence of primary hepatocellular carcinoma. Clin Cancer Res 11:551–556

Choi YL, Park SH, Jang JJ, Park CK (2001) Expression of the G1-S modulators in hepatitis B virus-related hepatocellular carcinoma and dysplastic nodule: association of cyclin D1 and p53 proteins with the progression of hepatocellular carcinoma. J Korean Med Sci 16:424–432

Chu PG, Ishizawa S, Wu E, Weiss LM (2002) Hepatocyte antigen as a marker of hepatocellular carcinoma: an immunohistochemical comparison to carcinoembryonic antigen, CD10, and alpha-fetoprotein. Am J Surg Pathol 26:978–988

Chu PG, Jiang Z, Weiss LM (2003) Hepatocyte antigen as a marker of intestinal metaplasia. Am J Surg Pathol 27:952–959

Cieply B, Zeng G, Proverbs-Singh T, Geller DA, Monga SP (2009) Unique phenotype of hepatocellular cancers with exon-3 mutations in beta-catenin gene. Hepatology 49:821–831

Cohen C, DeRose PB (1994) Immunohistochemical p53 in hepatocellular carcinoma and liver cell dysplasia. Mod Pathol 7:536–539

Cohen C, Berson SD, Budgeon LR (1982) Alpha-1-antitrypsin deficiency in Southern African hepatocellular carcinoma patients. An immunoperoxidase and histochemical study. Cancer 49:2537–2540

Cohen C, Berson SD, Shulman G, Budgeon LR (1984) Immunohisto-chemical ferritin in hepatocellular carcinoma. Cancer 53:1931–1935

Coston WM, Loera S, Lau SK, Ishizawa S, Jiang Z, Wu CL, Yen Y, Weiss LM, Chu PG (2008) Distinction of hepatocellular carcinoma from benign hepatic mimickers using glypican-3 and CD34 immunohistochemistry. Am J Surg Pathol 32:433–444

D'Errico A, Grigioni WF, Fiorentino M, Baccarini P, Grazi GL, Mancini AM (1994) Overexpression of p53 protein and Ki67 proliferative index in hepatocellular carcinoma: an immunohstochemical study on 109 Italian patients. Pathol Int 44:682–687

D'Errico A, Baccarini P, Fiorentino M, Ceccarelli C, Bonazzi C, Ponzetto A, Scoazec JY et al (1996) Histogenesis of primary liver carcinomas: strengths and weaknesses of cytokeratine profile and albumin mRNA detection. Hum Pathol 27:599–604

Dal Bello B, Rosa L, Campanini N, Tinelli C, Torello Viera F, D'Ambrosio G, Rossi S, Silini EM (2010) Glutamine synthetase immunostaining correlates with pathologic features of hepatocellular carcinoma and better survival after radiofrequency thermal ablation. Clin Cancer Res 16:2157–2166

David G, Bernfield M (1998) The emerging roles of cell surface heparan sulfate proteoglycans. Matrix Biol 17:461–463

De Boer CJ, van Krieken JH, Janssen-van Rhijn CM, Litvinov SV (1999) Expression of Ep-CAM in normal, regenerating, metaplastic, and neoplastic liver. J Pathol 188:201–206

de Boer WB, Segal A, Frost FA, Sterrett GF (2000) Can CD34 discriminate between benign and malignant hepatocytic lesions in fine-needle aspirates and thin core biopsies? Cancer 90:273–278

De Cat B, David G (2001) Developmental roles of the glypicans. Semin Cell Dev Biol 12:117–125

Debuire B, Paterlini P, Pontisso P, Basso G, May E (1993) Analysis of the p53 gene in European hepatocellular carcinomas and hepatoblastomas. Oncogene 8:2303–2306

Di Bisceglie AM, Disheiko GM, Paterson AC, Alexander J, Shouval D, Lee CS, Beasley RP et al (1986) Detection of alpha-foetoprotein messenger RNA in human hepatocellular carcinoma and hepatoblastoma tissue. Br J Cancer 54:779–785

Di Tommaso L, Destro A, Seok JY, Balladore E, Terracciano L, Sangiovanni A, Iavarone M et al (2009) The application of markers (HSP70, GPC3 and GS) in liver biopsies is useful for detection of hepatocellular carcinoma. J Hepatol 50:746–754

Di Tommaso L, Destro A, Fabbris V, Spagnuolo G, Laura Fracanzani A, Fargion S, Maggioni M et al (2011) Diagnostic accuracy of clathrin heavy chain staining in a marker panel for the diagnosis of small hepatocellular carcinoma. Hepatology 53:1549–1557

Ding SJ, Li Y, Tan YX, Jiang MR, Tian B, Liu YK, Shao XX, Ye SL, Wu JR, Zeng R et al (2004) From proteomic analysis to clinical significance: overexpression of cytokeratin 19 correlates with hepatocellular carcinoma metastasis. Mol Cell Proteomics 3:73–81

Dragovic T, Sekosan M, Becker RP, Erdös EG (1997) Detection of neutral endopeptidase 24.11 (neprilysin) in human hepatocellular carcinomas by immunocytochemistry. Anticancer Res 17:3222–3238

Duff SE, Li C, Garland JM, Kumar S (2003) CD105 is important for angiogenesis: evidence and potential applications. FASEB J 17:984–992

Enan ET, El-Hawary AK, El-Tantawy DA, Abu-Hashim MM, Helal NM (2013) Diagnostic role of glypican 3 and CD34 for differentiating hepatocellular carcinoma from nonmalignant hepatocellular lesions. Ann Diagn Pathol 17:490–493

Espinoza CG, Pillarisetti SG, Azar HA (1984) Immunohistochemsitry of hepatocellular carcinoma associated with cirrhosis. Ann Clin Lab Sci 14:467–473

Fan Z, van de Rijn M, Montgomery K, Rouse RV (2003) Hep par 1 antibody stain for the differential diagnosis of hepatocellular carcinoma: 676 tumors tested using tissue microarrays and conventional tissue sections. Mod Pathol 16:137–144

Fang XJ, Jiang H, Zaho XP, Jiang WM (2011) The role of a new CD44st in increasing the invasion capability of the human breast cancer cell line MCF-7. BMC Cancer 11:290

Feng M, Ho M (2014) Glypican-3 antibodies: a new therapeutic target for liver cancer. FEBS Lett 588:377–382

Fernandez M, Semela D, Bruix J, Colle I, Pinzani M, Bosch J (2009) Angiogenesis in liver disease. J Hepatol 50:604–620

Fernandez-Izquierdo A, llombart-Bosch A (1987) Immunohistochemical characterization of 130 cases of primary hepatic carcinomas. Pathol Res Pract 182:783–791

Filmus J, Capurro M (2004) Glypican-3 and alphafetoprotein as diagnostic tests for hepatocellular carcinoma. Mol Diagn 8:207–212

Filmus J, Capurro M (2013) Glypican-3: a marker and a therapeutic target in hepatocellular carcinoma. FEBS J 280:2471–2476

Filmus J, Selleck SB (2001) Glypicans: proteoglycans with a surprise. J Clin Invest 108:497–501

Fraga M, Garcia-Caballero T, Dominguez F, Pérez-Becerra E, Beiras A, Forteza J (1993) Immunohistochemical location of prothymosin alpha in regenerating human hepatocytes and hepatocellular carcinomas. Virchows Arch A Pathol Anat Histopathol 423:449–452

Fransson LA (2003) Glypicans Int J Biochem Cell Biol 35:125–129

Fu SJ, Qi CY, Xiao WK, Li SQ, Peng BG, Liang LJ (2013) Glypican-3 is a potential prognostic biomarker for hepatocellular carcinoma after cumative de section. Surgery 154:536–544 (Pubmed PMID 23601901)

Fujioka M, Nakashima Y, Nakashima O, Kojiro M (2001) Immunohistologic study on the expressions of alpha-fetoprotein and protein induced by vitamin K absence or antagonist II in surgically resected small hepatocellular carcinoma. Hepatology 34:1128–1134

Fujiwara M, Kwok S, Yano H, Pai RK (2012) Arginase-1 is a more sensitive marker of hepatic differentiation than HepPar-1 and glypican-3 in fine-needle aspiration biopsies. Cancer Cytopathol 120:230–237

Fukuda Y, Imoto M, Koyama Y, Miyazawa Y, Nakano I, Hattori M, Urano F, Kodama S et al (1991) Immunohistochemical study on tissue inhibitors of metalloproteinases in normal and pathological human livers. Gastroenterol Jpn 26:37–41

Gonzalez-Roibon N, Katz B, Chaux A, Sharma R, Munari E, Faraj SF, Illei PB, Torbenson M et al (2013) Immunohistochemcial expression of SALL4 in hepatocellular carcinoma, a potential pitfall in the differential diagnosis of yolk sac tumors. Hum Pathol 44:1293–1299

Gottschalk-Sabag S, Ron N, Glick T (1998) Use of CD34 and factor VIII to diagnose hepatocellular carcinoma on fine needle aspirates. Acta Cytol 42:691–696

Govaere O, Komuta M, Berkers J, Spee B, Janssen C, de Luca F, Katoonizadeh A et al (2014) Keratin 19: a key role player in the invasion of human hepatocellular carcinomas. Gut 63:674–685

Greenhill C (2013) Hepatocellular carcinoma: how does keratin 19 influence HCC? Nat Rev Gastroenterol Hepatol 10:565

Grigioni WF, D'Errico A, Mancini AM, Biagini G, Gozzetti G, Mazziotti A, Garbisa S (1987) Hepatocellular carcinoma: expression of basement membrane glycoproteins. An immunohistochemical approach. J Pathol 152:325–332

Grigioni WF, D'Errico A, Bacci F, Gaudio M, Mazziotti A, Gozzetti G, Mancini AM (1989) Primary liver neoplasms: evaluation of proliferative index using MoAb Ki67. J Pathol 158:23–29

Grigioni WF, Garbisa S, D'Errico A, Baccarini P, Stetler-Stevenson WG, Liotta LA et al (1991) Evaluation of hepatocellular carcinoma aggressiveness by a panel of extracellular matrix antigens. Am J Pathol 138:647–654

Guido M, Roskams T, Pontisso P, Fassan M, Thung SN, Giacomelli L, Sergio A, Farinati F et al (2008) Squamous cell carcinoma antigen in human liver carcinogenesis. J Clin Pathol 61:445–447

Hayashi et al. (1997) http://www.ncbi.nlm.nih.gov/pubmed/9049200

Hendrix MJ, Seftor EA, Chu YW, Trevor KT, Seftor RE (1996) Role of intermediate filaments in migration, invasion and metastasis. Cancer Metastasis Rev 15:507–525

Herath NI, Kew MC, Whitehall VL, Walsh MD, Jass JR, Khanna KK, Young J, Powell LW et al (2000) p73 is upregulated in a subset of hepatocellular carcinomas. Hepatology 31:601–605

Ho M (2011) Advances in liver cancer antibody therapies: a focus on glypican-3 and mesothelin. BioDrugs 25:275–284

Holczbauer A, Gyönggyösi B, Lotz G, Szijarto A, Kupcsulik P, Schaff Z, Kiss A (2013) Distinct claudin expression profiles of hepatocellular carcinoma and metastatic colorectal and pancreatic carcinomas. J Histochem Cytochem 61:294–305

Hua Z, Chen J, Sun B, Zhao G, Zhang Y, Fong Y, Jia Z, Yao L (2011) Specific expression of osteopontin and S100A6 in hepatocellular carcinoma. Surgery 149:783–791

Hurlimann J, Gardiol D (1991) Immunohistochemistry in the differential diagnosis of liver carcinomas. Am J Surg Pathol 15:280–288

Ichikawa T, Yamamoto T, Uenishi T, Tanaka H, Takemura S, Ogawa M, Tanaka S et al (2006) Clinicopathological implications of immunohistochemically demonstrated mucin core protein expression in hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 13:245–251

Iezzoni JC, Mills SE, Pelkey TJ, Stoler MH (1999) Inhibin is not an immunohistochemical marker for hepatocellular carcinoma. An example of the potential pitfall in diagnostic immunohistochemistry caused by endogenous biotin. Am J Clin Pathol 111:229–234

Imoto M, Nishimura D, Fukuda Y, Sugiyama K, Kumada T, Nakano S (1985) Immunohistochemical detection of alpha-fetoprotein, carcinoembryonic antigen, and ferritin in formalin-paraffin sections from hepatocellular carcinoma. Am J Gastroenterol 80:902–906

Izumi N (2012) Prediction and prevention of intrahepatic recurrence of hepatocellular carcinoma. Hepatol Res 42:226–232

Jacobsen LC, Theilgaard-Mönch K, Christensen EI, Borregaard N (2007) Arginase 1 is expressed in myelocytes/metamyelocytes and localized in gelatinase granules of human neutrophils. Blood 109:3084–3087

Jin GZ, Dong H, Yu WL, Li Y, Lu XY, Yu H, Xian ZH, Dong W, Liu YK, Cong WM et al (2013) A novel panel of biomarkers in distinction of small well-differentiated HCC from dysplastic nodules and outcome values. BMC Cancer 13:161

Johnson DE, Herndier BG, Medeiros LJ, Warnke RA, Rouse RV (1988) The diagnostic utility of the keratin profiles of hepatocellular carcinoma and cholangiocarcinoma. Am J Surg Pathol 12:187–197

Kamohara Y, Haraguchi N, Mimori K, Tanaka F, Inoue H, Mori M, Kanematsu T (2008) The search for cancer stem cells in hepatocellular carcinoma. Surgery 144:119–124

Kan Z, Zheng H, Liu X, Barber TD, Gong Z, Gao H, Hao K, Willard MD, Xu J, Hauptschein R et al (2013) Whole-genome sequencing identifies recurrent mutations in hepatocellular carcinoma. Genome Res 23:1422–1433

Kandil DH, Cooper K (2009) Glypican-3: a novel diagnostic marker for hepatocellular carcinoma and more. Adv Anat Pathol 16:125–129

Kandil D, Leiman G, Allegretta M, Trotman W, Pantanowitz L, Goulart R, Evans M (2007) Glypican-3 immunohistochemistry in liver fine-needle aspirates: a novel stain to assist in the differentiation of benign and malignant liver lesions. Cancer 111:316–322

Kang YK, Kim CJ, Kim WH, Kim HO, Kang GH, Kim YI (1998) p53 mutation and overexpression in hepatocellular carcinoma and dysplastic nodules in the liver. Virchows Arch 432:27–32

Karabork A, Kaygusuz G, Ekinci C (2010) The best immunohistochemical panel for differentiating hepatocellular carcinoma from metastatic adenocarcinoma. Pathol Res Pract 206:572–577

Kim H, Choi GH, Na DC, Ahn EY, Kim GI, Lee JE, Cho JY, Yoo JE, Choi JS et al (2011) Human hepatocellular carcinomas with "stemness"-related marker expression: keratin 19 expression and a poor prognosis. Hepatology 54:1707–1717

Kim GJ, Kim H, Park YN (2013) Increased expression of Yes-associated protein 1 in hepatocellular carcinoma with stemness and combined hepatocellular-cholangiocarcinoma. PLoS ONE 8:e75449

Kinoyama S, Yamada G, Nagashima H (1986) Ultrastructural observations of alpha-fetoprotein producing cells in human hepatocellular carcinoma using immunoperoxidase methods – comparison with fetal liver. Gastroenterol Jpn 21:152–161

Kitamura Y, Shiramata A, Sakuraba K, Goto T, Mizukami H, Saito M, Ishibashi K, Kigawa G et al (2011) Aberrant methylation of the vimentin gene in hepatocellular carcinoma. Anticancer Res 31:1289–1291

Koda T, Yamazaki S, Tamura I, Nakaba H, Takao T, Katayama S, Kurimura O (1993) Abnormal prothrombin: evaluation as a tumour marker and localization in tissues of patients with hepatocellular carcinoma. J Gastroenterol Hepatol 8:212–216

Kojiro M, Kawano Y, Isomura T, Nakashima T (1981) Distribution of albumin-and/or alpha-fetoprotein-positive cells in hepatocellular carcinoma. Lab Invest 44:221–226

Kozyraki R, Scoazec JY, Flejou JF, D'Errico A, Bedossa P, Terris B, Fiorentino M et al (1996) Expression of cadherins and alpha-catenin in primary epithelial tumors of the liver. Gastroenterology 110:1137–1149

Krings G, Ramachandran R, Jain D, Wu TT, Yeh MM, Torbenson M, Kakar S (2013) Immunohistochemical pitfalls and the importance of glypican 3 and arginase in the diagnosis of scirrhous hepatocellular carcinoma. Mod Pathol 26:782–791

Kuramitsu et al. (2006) http://www.ncbi.nlm.nih.gov/pubmed/16609938

Lagana SM, Salomao M, Bao F, Moreira RK, Lefkowitch JH, Remotti HE (2013) Utility of an immunohistochemical panel consisting of glypican-3, heat-shock protein-70, and glutamine synthetase in the distinction of low-grade hepatocellular carcinoma from hepatocellular adenoma. Appl Immunohistochem Mol Morphol 21:170–176

Lai TY, Su CC, Kuo WW, Yeh YL, Kuo WH, Tsai FJ, Tsai CH, Weng YJ, Huang CY et al (2011) β-catenin plays a

key role in metastasis of human hepatocellular carcinoma. Oncol Rep 26:415–422
Lamps LW, Folpe AL (2003) The diagnostic value of hepatocyte paraffin antibody 1 in differentiating hepatocellular neoplasms from nonhepatic tumors: a review. Adv Anat Pathol 10:39–43
Lau SK, Prakash S, Geller SA, Alsabeth R (2002) Comparative immunohistochemical profile of hepatocellular carcinoma, cholangiocarcinoma, and metastatic adenocarcinoma. Hum Pathol 33:1175–1181
Le Bail B, Faouzi S, Boussarie L, Guirouilh J, Blanc JF, Carles J, Bioulac-Sage P, Balabaud C et al (1999) Osteonectin/SPARC is overexpressed in human hepatocellular carcinoma. J Pathol 189:46–52
Lee NP (2012) The blood-biliary barrier, tight junctions and human liver diseases. Adv Exp Med Biol 763:171–185
Lee NP, Luk JM (2010) Hepatic tight junctions: from viral entry to cancer metastasis. World J Gastroenterol 16:289–295
Lee JS, Semela D, Iredale J, Shah VH (2007) Sinusoidal remodeling and angiogenesis: a new function for the liver-specific pericyte? Hepatology 45:817–825
Lee YL, Ahn BC, Lee Y, Lee SW, Cho JY, Lee J (2011) Targeting of hepatocellular carcinoma with glypican-3-targeting peptide ligand. J Pept Sci 17:763–769
Lee CW, Kuo WL, Yu MC, Chen TC, Tsai CN, Lee WC, Chen MF (2013) The expression of cytokeratin 19 in lymph nodes was a poor prognostic factor for hepatocellular carcinoma after hepatic resection. World J Surg Oncol 11:136
Leong AS, Sormunen RT, Tsui WM, Liew CT (1998) Hep Par 1 and selected antibodies in the immunohistological distinction of hepatocellular carcinoma from cholangiocarcinoma, combined tumours and metastatic carcinoma. Histopathology 33:318–324
Li B, Liu H, Shang HW, Li P, Li N, Ding HG (2013) Diagnostic value of glypican-3 in alpha fetoprotein negative hepatocellular carcinoma patients. Afr Health Sci 13:703–709
Li P, Cao Y, Li Y, Zhou L, Liu X, Geng M (2014) Expression of Wnt-5a and β-catenin in primary hepatocellular carcinoma. Int J Clin Exp Pathol 7:3190–3195
Liu H, Li P, Zhai Y, Qu CF, Zhang LJ, Tan YF, Li N, Ding HG (2010) Diagnostic value of glypican-3 in serum and liver for primary hepatocellular carcinoma. World J Gastroenterol 16:4410–4415
Liu XF, Hu ZD, Liu XC, Cao Y, Ding CM, Hu CJ (2013) Diagnostic accuracy of serum glypican-3 for hepatocellular carcinoma: a systematic review and meta-analysis. Clin Biochem 47:196–200
Lo RC, Ng IO (2011) Hepatocellular tumors: immunohistochemical analyses for classification and prognostication. Chin J Cancer Res 23:245–253
Lodi C, Szabo E, Holczbauer A, Batmunkh E, Szijarto A, Kupcsulik P, Kovalszky I et al (2006) Claudin-4 differentiates biliary tract cancers from hepatocellular carcinomas. Mod Pathol 19:460–469
Long J, Lang ZW, Wang HG, Wang TL, Wang BE, Liu SQ (2010) Glutamine synthetase as an early marker for hepatocellular carcinoma based on proteomic analysis of resected small hepatocellular carcinomas. Hepato-Biliary Pancreat Dis Int 9:296–305
Lu XY, Xi T, Lau WY, Dong H, Zhu Z, Shen F, Wu MC, Cong WM (2011) Hepatocellular carcinoma expressing cholangiocyte phenotype is a novel subtype with highly aggressive behavior. Ann Surg Oncol 18:2210–2217
Mamori S, Nagatsuma K, Matsuura T, Ohkawa K, Hano H, Fukunaga M, Matsushima M et al (2007) Useful detection of CD147 (EMMPRIN) for pathological diagnosis of early hepatocellular carcinoma in needle biopsy samples. World J Gastroenterol 13:2913–2917
Man XB, Tang L, Zhang BH, Li SJ, Qiu XH, Wu MC, Wang HY (2005) Upregulation of glypican-3 expression in hepatocellular carcinoma but downregulation in cholangiocarcinoma indicates its differential diagnostic value in primary liver cancers. Liver Int 25:962–966
Marrero JA, Lok ASF (2004) Newer markers for hepatocellular carcinoma. Gastroenterology 127:S113–S119
Marshall A, Lukk M, Kutter C, Davies S, Alexander G, Odom DT (2013) Global gene expression profiling reveals SPINK1 as a potential hepatocellular carcinoma marker. PLoS ONE 8:e59459
Masuda T, Miyoshi E (2011) Cancer biomarkers for hepatocellular carcinomas: from traditional markers to recent topics. Clin Chem Lab Med 49:959–966
Mathew J, Hines JE, Obafunwa JO, Burr AW, Toole K, Burt AD (1996) CD44 is expressed in hepatocellular carcinomas showing vascular invasion. J Pathol 179:74–79
Matsuno T, Goto I (1992) Glutaminase and glutamine synthetase activities in human cirrhotic liver and hepatocellular carcinoma. Cancer Res 52:1192–1194
Maurel M, Jalvy S, Ladeiro Y, Combe C, Vachet L, Sagliocco F, Bioulac-Sage P, Pitard V et al (2013) A functional screening identifies five microRNAs controlling glypican-3: role of miR-1271 down-regulation in hepatocellular carcinoma. Hepatology 57:195–204
McCluggage WG, Maxwell P, Patterson A, Sloan JM (1997) Immunohisto-chemical staining of hepatocellular carcinoma with monoclonal antibody against inhibin. Histopathology 30:518–522
McKnight et al. (2012) http://www.ncbi.nlm.nih.gov/pubmed/22298472
Minguez B, Lachenmayer A (2011) Diagnostic and prognostic molecular markers in hepatocellular carcinoma. Dis Markers 31:181–190
Mondada D, Bosman FT, Fontolliet C, Seelentag WK (2006) Elevated hepatocyte paraffin 1 and neprilysin expression in hepatocellular carcinoma are correlated with longer survival. Virchows Arch 448:35–45
Monnier J, Boissan M, L'helgoualc'h A, Lacombe ML, Turlin B, Zucman-Rossi J, Théret N et al (2012) CXCR7 is upregulated in human and murine hepatocellular carcinoma and is specifically expressed by endothelial cells. Eur J Cancer 48:138–148

Morford LA, Davis C, Jin L, Dobierzewska A, Peterson ML, Spear BT (2007) The oncofetal gene glypican 3 is regulated in the postnatal liver by zinc fingers and homeoboxes 2 and in the regenerating liver by alpha-fetoprotein regulator 2. Hepatology 46:1541–1547

Morrison C, Marsh W, Frankel WL (2002) A comparison of CD10 tp pCEA, MOC-31, and hepatocyte for the distinction of malignant tumors of the liver. Mod Pathol 15:1279–1287

Mun KS, Cheah PL, Baharudin NB, Looi LM (2006) Proliferating cell nuclear antigen (PCNA) activity in hepatocellular carcinoma, benign peri-neoplastic and normal liver. Malays J Pathol 28:73–77

Murakami Y, Hayashi K, Hirohashi S, Sekiya T (1991) Aberrations of the tumor suppressor p53 and retinoblastoma genes in human hepatocellular carcinomas. Cancer Res 51:5520–5525

Nakatsura T, Yoshitake Y, Senju S, Monji M, Komori H, Motomura Y, Hosaka S, Beppu T et al (2003) Glypican-3, overexpressed specifically in human hepatocellular carcinoma, is a novel tumor marker. Biochem Biophys Res Commun 306:16–25

Nakopoulou L, Theodoropoulos G, Kotsis L, Papacharalampous N (1982) Demonstration of alpha 1-antitrypsin in paraffin sections of hepatoma and cirrhosis. Virchows Arch A Pathol Anat Histol 397:163–170

Nemolato S, Fanni D, Naccarato AG, Ravarino A, Bevilacqua G, Faa G (2008) Lymphoepithelioma-like hepatocellular carcinoma: a case report and a review of the literature. World J Gastroenterol 14:4694–4696

Ng IO, Na J, Lai EC, Fan ST, Ng M (1995) Ki-67 antigen expression in hepatocellular carcinoma using monoclonal antibody MIB1. A comparison with proliferating cell nuclear antigen. Am J Clin Pathol 104:313–318

Ng A, Wong M, Viviano B, Erlich JM, Alba G, Pflederer C, Jay PY, Saunders S (2009) Loss of glypican-3 function causes growth factor-dependent defects in cardiac and coronary vascular development. Dev Biol 335:208–215

Nishioka M, Ibata T, Okita K, Harada T, Fujita T (1972) Localization of alpha-fetoprotein in hepatoma tissue by immunofluorescence. Cancer Res 32:162–166

Ogawa M, Yamamoto T, Kubo S, Uenishi T, Tanaka H, Shuto T, Tanaka S, Hirohashi K (2004) Clinicopathologic analysis of risk factors for distant metastasis of hepatocellular carcinoma. Hepatol Res 29:228–234

Ohmori S, Shiraki K, Sugimoto K, Sakai T, Fujikawa K, Wagayama H, Takase K, Nakano T (2001) High expression of CD34-positive sinusoidal endothelial cells is a risk factor for hepatocellular carcinoma in patients with HCV-associated chronic liver diseases. Hum Pathol 32:1363–1370

Ojanguren I, Ariza A, Llatjos M, Castella E, Mate JL, Navas-Palacios JJ (1993) Proliferating cell nuclear antigen expression in normal, regenerative, and neoplastic liver: a fine-needle aspiration cytology and biopsy study. Hum Pathol 24:905–908

Okada K, Nakayama I, Kobayashi M (1987) An immune-electron microscopic study on intra and extracellular localization of alpha-fetoprotein in human hepatocellular carcinoma. Acta Pathol Jpn 37:915–928

Okamura D, Ohtsuka M, Kimura F, Shimizu H, Yoshidome H, Kato A, Miyazaki M (2008) Ezrin expression is associated with hepatocellular carcinoma possibly derived from progenitor cells and early recurrence after surgical resection. Mod Pathol 21:847–855

Okushin H, Yamada G, Nagashima H (1987) Immunohistochemical study of fibronectin, lysozyme, and alpha-fetoprotein (AFP) in human hepatocellular carcinoma. Gastroenterol Jpn 22:44–54

Orban E, Szabo E, Lotz G, Kupcsulik P, Paska C, Schaff Z, Kiss A (2008) Different expression of occludin and ZO-1 in primary and metastatic liver tumors. Pathol Oncol Res 14:299–306

Osada T, Sakamoto M, Nagawa H, Yamamoto J, Matsuno Y, Iwamatsu A, Muto T et al (1999) Acquisition of glutamine synthetase expression in human hepatocarcinogenesis: relation to disease recurrence and possible regulation b < ubiquitin-dependent proteolysis. Cancer 85:819–831

Osada T, Nagashima I, Tsuno NH, Kitayama J, Nagawa H (2000) Prognostic significance of glutamine synthetase expression in unifocal advanced hepatocellular carcinoma. J Hepatol 33:247–253

Ozkan H, Erdal H, Tutkak H, Karaeren Z, Yakut M, Yüksel O, Köklü S (2011) Diagnostic and prognostic validity of Golgi protein 73 in hepatocellular carcinoma. Digestion 83:83–88

Palmer PE, Wolfe HJ (1976) Alpha-antitrypsin depiction in primary hepatic carcinomas. Arch Pathol Lab Med 100:232–236

Palmer PE, Christopherson WM, Wolfe HJ (1977) Alpha1-antitrypsin, protein marker in oral contraceptive –associated hepatic tumors. Am J Clin Pathol 68:736–739

Palmer PE, Ucci AA, Wolfe HJ (1980) Expression of protein markers in malignant hepatoma: evidence for genetic and epigenetic mechanisms. Cancer 45:1424–1431

Pan HW, Ou YH, Peng SY, Liu SH, Lai PL, Lee PH, Sheu JC, Chen CL, Hsu HC (2003) Overexpression of osteopontin is associated with intrahepatic metastasis, early recurrence, and poorer prognosis of surgically resected hepatocellular carcinoma. Cancer 98:119–127

Park JO, Stephen Z, Sun C, Veiseh O, Kievit FM, Fang C, Leung M, Mok H, Zhang M (2011) Glypican-3 targeting of liver cancer cells using multifunctional nanoparticles. Mol Imaging 10:69–77

Pitman MB, Triratanachat S, Young RH, Oliva E (2004) Hepatocyte paraffin 1 antibody does not distinguish primary ovarian tumors with hepatoid differentiation from metastatic hepatocellular carcinoma. Int J Gynecol Pathol 23:58–64

Pontisso P, Calabrese F, Benvegnu L, Lise M, Belluco C, Ruvoletto MG, Marino M et al (2004) Overexpression of squamous cell carcinoma antigen

variants in hepatocellular carcinoma. Br J Cancer 90:833–837
Porcell AI, De Young BR, Proca DM, Frankel WL (2000) Immunohisto-chemical analysis of hepatocellular and adenocarcinoma in the liver: MOC31 compares favorably with other putative markers. Mod Pathol 13:773–778
Proca DM, Niemann TH, Porcell AI, DeYoung BR (2000) MOC31 immunoreactivity in primary and metastatic carcinoma of the liver. Report of findings and review of other utilized markers. Appl Immunohistochem Mol Morphol 8:120–125
Purtilo DT, Yunis EJ (1971) Alpha-fetoprotein: its immunofluorecent localization in human fetal liver and hepatoma. Lab Invest 25:291–294
Qi XH, Wu D, Cui HX, Ma N, Su J, Wang YT, Jiang YH (2014) Silencing of the glypican-3 gene affects the biological behavior of human hepatocellular carcinoma cells. Mol Med Rep 10:3177–3184
Radwan NA, Ahmed NS (2012) The diagnostic value of arginase-1 immunostaining in differentiating hepatocellular carcinoma from metastatic carcinoma and cholangiocarcinoma as compared to HepPar-1. Diagn Pathol 7:149
Reintoft I, Hägerstrand I (1979) Demonstration of alpha 1-antitrypsin in hepatomas. Arch Pathol Lab Med 103:495–498
Roncalli M, Borzio M, de Biagi G, Servida E, Cantaboni A, Sironi M, Taccagni GL (1985) Liver cell dysplasia and hepatocellular carcinoma: a histological and immunohistochemical study. Histopathology 9:209–221
Roncalli et al. (2011) http://www.ncbi.nlm.nih.gov/pubmed/21459342
Roskams T, De Vos R, David G, Van Damme B, Desmet V (1998) Heparan sulphate proteoglycan expression in human primary liver tumors. J Pathol 185:290–297
Ryu et al. (2011) http://www.ncbi.nlm.nih.gov/pubmed/2184602
Ryu HS, Lee K, Shin E, Kim SH, Jing J, Jung HY, Lee H, Jang JJ (2012) Comparative analysis of immunohistochemical markers for differential diagnosis of hepatocellular carcinoma and cholangiocarcinoma. Tumori 98:478–484
Saad RS, Luckasevic TM, Noga CM, Johnson DR, Silverman JF, Liu YL (2004) Diagnostic value of HepPar1, pCEA, CD10, and CD34 expression in separating hepatocellular carcinoma from metastatic carcinoma in fine-needle aspiration cytology. Diagn Cytopathol 30:1–6
Sacho M, Setsu K, Hayashi K (1991) Histochemical and immunohisto-chemical analyses of primary carcinoma of the liver. Acta Med Okayama 45:423–432
Sakaguchi T, Suzuki S, Higashi H, Inaba K, Nakamura S, Baba S, Kato T, Konno H (2008) Expression of tight junction protein claudin-5 in tumor vessels and sinusoidal endothelium in patients with hepatocellular carcinoma. J Surg Res 147:123–131
Sakamoto M, Mori T, Masugi Y, Effendi K, Rie I, Du W (2008) Candidate molecular markers for histological diagnosis of early hepatocellular carcinoma. Intervirology 51(suppl 1):42–45
Sakurai K, Sohda T, Ueda S, Tanaka T, Hirano G, Yokoyama K, Morihara D, Aanan A et al (2014) Immunohistochemical demonstration of transferrin receptor 1 and 2 in human hepatocellular carcinoma tissue. Hepato-Gastroenterology 61:426–430
Sawada Y, Sakai M, Yoshikawa T, Ouji K, Nakatsura T (2012) A glypican-3-derived peptide vaccine against hepatocellular carcinoma. Oncoimmunology 1:1448–1450
Sawada Y, Yoshikawa T, Fujii S, Mitsunaga S, Nobuoka D, Mizuno S, Takahashi M et al (2013) Remarkable tumor lysis in a hepatocellular carcinoma patient immediately following glypican-3-derived peptide vaccination: an autopsy case. Hum Vaccin Immunother 9(6): 1228–1233
Schmilovitz-Weiss H, Tobar A, Halpern M, Levy I, Shabtai E, Ben-Ari Z (2011) Tissue expression of squamous cellular carcinoma antigen and Ki67 in hepatocellular carcinoma – correlation with prognosis: a historical prospective study. Diagn Pathol 6:121
Schmitz KJ, Sotiropoulos GC, Baba HA, Schmid KW, Müller D, Paul A, Auer T, Gamerith G et al (2011) AKR1B10 expression is associated with less aggressive hepatocellular carcinoma: a clinicopathological study of 168 cases. Liver Int 31:810–816
Schoniger-Hekele M, Hanel S, Wrba F, Muller C (2005) Hepatocellular carcinoma – survival and clinical characteristics in relation to various histologic molecular markers in Western patients. Liver Int 25:62–69
Semela D, Dufour JF (2004) Angiogenesis and hepatocellular carcinoma. J Hepatol 41:864–880
Seo DD, Lee HC, Kim HJ, Min HJ, Kim KM, Lim YS, Chung YH, Lee YS, Suh DJ, Yu E, Chun SY (2008) Neural cadherin overexpression is a predictive is a predictive marker for early postoperative recurrence in hepatocellular carcinoma patients. J Gastroenterol Hepatol 23:1112–1118
Shafizadeh N, Kakar S (2011) Diagnosis of well-differentiated hepatocellular lesions: role of immunohistochemistry and other ancillary techniques. Adv Anat Pathol 18:438–445
Shafizadeh N, Ferrell LD, Kakar S (2008) Utility and limitations of glypican-3 expression for the diagnosis of hepatocellular carcinoma at both ends of the differentiation spectrum. Mod Pathol 21:1011–1018
Shibuya M, Kondo F, Sano K, Takada T, Asano T (2011) Immuno-histochemical study of hepatocyte, cholangiocyte and stem cell markers of hepatocellular carcinoma. J Hepato-Biliary Pancreat Sci 18:537–543
Shimoyama Y, Hirohashi S (1991) Cadherin intercellular adhesion molecule in hepatocellular carcinomas: loss of E-cadherin expression in an undifferentiated carcinoma. Cancer Lett 57:131–135
Shin E, Ryu HS, Kim SH, Jung H, Jang JJ, Lee K (2011) The clinicopathological significance of heat shock protein 70 and glutamine synthetase expression in hepatocellular carcinoma. J Hepato-Biliary Pancreat Surg 18:544–550

Siddiqui MT, Saboorian MH, Gokaslan ST, Ashfaq R (2002) Diagnostic utility of the HepPar1 antibody to differentiate hepatocellular carcinoma from metastatic carcinoma in fine-needle aspiration samples. Cancer 96:49–52

Somoracz A, Tatrai P, Horvath G, Kiss A, Kupcsulik P, Kovalszky I, Schaff Z (2010) Agrin immunohistochemistry facilitates the determination of primary versus metastatic origin of liver carcinomas. Hum Pathol 41:1310–1319

Sun CK, Chua MS, He J, So SK (2011) Suppression of glypican 3 inhibits growth of hepatocellular carcinoma cells through up-regulation of TGF-β2. Neoplasia 13:735–747

Suzuki M, Sugimoto K, Tanaka J, Tameda M, Inagaki Y, Kusagawa S, Nojiri K, Beppu T et al (2010) Up-regulation of glypican-3 in human hepatocellular carcinoma. Anticancer Res 30:5055–5061

Swift JG, Mukherjee TM, Rowland R (1983) Intercellular junctions in hepatocellular carcinoma. J Submicrosc Cytol 15:799–810

Takai H, Ashihara M, Ishiguro T, Terashima H, Watanabe T, Kato A, Suzuki M (2009) Involvement of glypican-3 in the recruitment of M2-polarized tumor-associated macrophages in hepatocellular carcinoma. Cancer Biol Ther 8:2329–2338

Tanigawa N, Lu C, Mitsui T, Miura S (1997) Quantitation of sinusoid-like vessels in hepatocellular carcinoma: its clinical and prognostic significance. Hepatology 26:1216–1223

Tannapfel A, Wasner M, Krause K, Geissler F, Katalinic A, Hauss J, Mössner J, Engeland K et al (1999) Expression of p73 and its relation to histopathology and prognosis in hepatocellular carcinoma. J Natl Cancer Inst 91:1154–1158

Tatrai P, Dudas J, Batmunkh E, Mathé M, Zalatnai A, Schaff Z, Ramadori G, Kovalszky I (2006) Agrin, a novel basement membrane component in human and rat liver, accumulates in cirrhosis and hepatocellular carcinoma. Lab Invest 86:1149–1160

Tatrai P, Somoracz A, Batmunkh E, Schirmacher P, Kiss A, Schaff Z, Nagy P, Kovalszky I (2009) Agrin and CD34 immunohistochemistry for the discrimination of benign versus malignant hepatocellular lesions. Am J Surg Pathol 33:874–885

Thung SN, Gerber MA, Samo E, Popper H (1979) Distribution of five antigens in hepatocellular carcinoma. Lab Invest 41:101–105

Timek DT, Shi J, Liu H, Lin F (2012) Arginase-1, hepPar-1, and glypican-3 are the most effective panel of markers in distinguishing hepatocellular carcinoma from metastatic tumor on fine-needle aspiration specimens. Am J Clin Pathol 138:203–210

Tremosini S, Forner A, Boix L, Vilana R, Bianchi L, Reig M, Rimola J, Rodriguez-Lope C et al (2012) Prospective validation of an immunohistochemical panel (glypican 3, heat shock protein 70 and glutamine synthase) in liver biopsies for diagnosis of very early hepatocellular carcinoma. Gut 10:1481–1487

Tsuchiya A, Kamimura H, Tamura Y, Takamura M, Yamagiwa S, Suda T, Nomoto M, Aoyagi Y (2011) Hepatocellular carcinoma with progenitor cell features distinguishable by the hepatic stem/progenitor cell marker NCAM. Cancer Lett 309:95–103

Tullo A, Sbisa E (2002) Molecular characterization of p53 mutations in primary and secondary liver tumors: diagnostic and therapeutic perspectives. Mol Biotechnol 21:265–278

Tumova S, Woods A, Couchman JR (2000) Heparan sulfate proteoglycans on the cell surface: versatile coordinators of cellular functions. Int J Biochem Cell Biol 32:269–288

Turner AJ, Isaac RE, Coates D (2001) The neprilysin (NEP) family of zinc metalloendopeptidases: genomics and function. Bioessays 23:261–269

Uenishi T, Kubo S, Yamamoto T, Shuto T, Ogawa M, Tanaka H, Tanaka S, Kaneda K et al (2003) Cytokeratin 19 expression in hepatocellular carcinoma predicts early postoperative recurrence. Cancer Sci 94:851–857

Ueta T, Ikeguchi M, Hirooka Y, Kaibara N, Terada T (2002) Beta-catenin and cyclin D1 expression in human hepatocellular carcinoma. Oncol Rep 9:1197–1203

Van Eyken P, Sciot R, Paterson A, Callea F, Kew MC, Desmet VJ (1988) Cytokeratin expression in hepatocellular carcinoma: an immunohistochemical study. Hum Pathol 19:562–568

Van Malenstein H, Komuta M, Verslype C, Vandecaveye V, Van Calster B, Topal B et al (2012) Histology obtained by needle biopsy gives additional information on the prognosis of hepatocellular carcinoma. Hepatol Res 42:990–998

Vander Borght S, Komuta M, Libbrecht L, Katoonizadeh A, Aerts R, Dymarkowski S, Verslype C, Nevens F, Roskams T (2008) Expression of multidrug resistance-associated protein 1 in hepatocellular carcinoma is associated with a more aggressive tumour phenotype and may reflect a progenitor cell origin. Liver Int 28:1370–1380

Varma V, Cohen C (2004) Immunohistochemical and molecular markers in the diagnosis of hepatocellular carcinoma. Adv Anat Pathol 11:239–249

Vasuri F, Golfieri R, Fiorentino M, Capizzi E, Renzulli M, Pinna AD, Grigioni WF et al (2011) OATP 1B1/1B3 expression in hepatocellular carcinomas treated with orthotopic liver transplantation. Virchows Arch 459:141–146

Villanueva A, Hoshida Y (2011) Depicting the role of TP53 in hepatocellular carcinoma progression. J Hepatol 55:724–725

Volkmann M, Hofmann WJ, Muller M, Rath U, Otto G, Zentgraf H, Galle PR (1994) p53 overexpression is frequent in European hepatocellular carcinomas and largely independent oft he codon 249 hot spot mutation. Oncogene 9:195–204

Vrettou E, Hytiroglou P, Sikas N, Soultoyannis I, Goodman ZD (2005) Hepatic adenocarcinoma expressing inhibin in a young patient on oral contraceptives. Virchows Arch 446:560–565

Wang L, Vuolo M, Suhrland MJ, Schlesinger K (2006) HepPar1, MOC-31, pCEA, mCEA and CD10 for distinguishing hepatocellular carcinoma vs. metastatic adenocarcinoma in liver fine needle aspirates. Acta Cytol 50:257–262

Wang X, Zhou Y, Ying X, Guo L, Zhao Y, Fang Y (2007) Interaction between heat shock protein 72 and alpha-fetoprotein in human hepatocellular carcinomas. Clin Chim Acta 379:158–162

Wang ZS, Wu LQ, Yi X, Geng C, Li YJ, Yao RY, Hu WY, Han B (2012a) CK19 can be used to predict the early recurrence and prognosis of HBV-related hepatocellular carcinoma patients with low AFP serum concentration after R0 radical hepatectomy (in Chinese). Zhonghua Zhong Liu Za Zhi 34:753–758

Wang YL, Zhu ZJ, Teng DH, Yao Z, Gao W, Shen ZY (2012b) Glypican-3 expression and its relationship with recurrence of HCC after liver transplantation. World J Gastroenterol 18:2408–2414

Ward SC, Waxman S (2011) Fibrolamellar carcinoma: a review with focus on genetics and comparison to other malignant primary liver tumors. Semin Liver Dis 31:61–70

Ward SC, Huang J, Tickoo SK, Thung SN, Ladanyi M, Klimstra DS (2010) Fibrolamellar carcinoma of the liver exhibits immunohistochemical evidence of both hepatocyte and bile duct differentiation. Mod Pathol 23:1180–1190

Washington K, Telen MJ, Gottfried MR (1997) Expression of cell adhesion molecule CD44 in primary tumors of the liver: an immunohistochemical study. Liver 17:17–23

Wee A (2006) Diagnostic utility of immunohistochemistry in hepatocellular carcinoma, its variants and their mimics. Appl Immunohistochem Mol Morphol 14:266–272

Wee A, Nilsson B (1997) pCEA canalicular immunostaining in fine needle aspiration biopsy diagnosis of hepatocellular carcinoma. Acta Cytol 41:1147–1155

Wee A, Nilsson B (2003) Highly well differentiated hepatocellular carcinoma and benign hepatocellular lesions. Can they be distinguished on fine needle aspiration biopsy? Acta Cytol 47:16–26

Winter MJ, Nagelkerken B, Mertens AE, Rees-Bakker HA, Briaire-de Bruijn IH, Litvinov SV (2003) Expression of EpCAM shifts the state of cadherin-mediated adhesions from strong to weak. Exp Cell Res 285:50–58

Witjes CD, Ten Kate FJ, Verhoef C, de Man RA, Ijzermans JN (2013) Immunohistochemical characteristics of hepatocellular carcinoma in non-cirrhotic livers. J Clin Pathol 66:687–691

Wu CG, Habib NA, Mitry RR, Reitsma PH, van Deventer SJ, Chamuleau RA (1997) Overexpression of hepatic prothymosin alpha, a novel marker for human hepatocellular carcinoma. Br J Cancer 76:1199–1204

Wu SK, Wang BJ, Yang Y, Feng XH, Zhao XP, Yang DL (2007) Expression of PTEN, PPM1A and P-Smad2 in hepatocellular carcinomas and adjacent liver tissues. Wordl J Gastroenterol 13:4554–4559

Xiao SY, Wang HL, Hart J, Fleming D, Beard MR (2001) cDNA arrays and immunohistochemistry identification of CD10/CALLA expression in hepatocellular carcinoma. Am J Pathol 159:1415–1421

Xu C, Yan Z, Zhou L, Wang Y (2013) A comparison of glypican-3 with alpha-fetoprotein as a serum marker for hepatocellular carcinoma: a meta-analysis. J Cancer Res Clin Oncol 139:1417–1424

Yamada M, Shiroeda H, Sato K, Hayashi R, Nomura T, Tsutsumi M, Arisawa T (2011) Accelerated progression of hepatocellular carcinoma with cytokeratin 19 expression during treatment with lamivudine for hepatitis B virus-related cirrhosis. Scand J Gastroenterol 46:249–251

Yamashita T, Forgues M, Wang W, Kim JW, Ye Q, Jia H, Budhu A, Zanetti KA, Chen Y et al (2008) EpCAM and alpha-fetoprotein expression defines novel prognostic subtypes of hepatocellular carcinoma. Cancer Res 68:1451–1461

Yan BC, Gong C, Song J, Krausz T, Tretiakova M, Hyjek E, Al-Ahmadie H, Alves V et al (2010) Arginase-1: a new immunohistochemical marker of hepatocytes and hepatocellular neoplasms. Am J Surg Pathol 34:1147–1154

Yan B, Wei JJ, Qian YM, Zhao XL, Zhang WW, Xu AM, Zhang SH (2011) Expression and clinicopathologic significance of glypican 3 in hepatocellular carcinoma. Ann Diagn Pathol 15:162–169

Yan XD, Wang L, Zhang HJ, Yan MJ, Gu X, Shi Y, Chen J, Dong ZZ, Yao DF (2013) Overexpression of insulin-like growth-I receptor as a pertinent biomarker for hepatocytes malignant transformation. World J Gastroenterol 19:6084–6092

Yang LY, Lu WQ, Huang GW, Wang W (2006) Correlation between CD105 expression and postoperative recurrence and metastasis of hepatocellular carcinoma. BMC Cancer 6:110

Yang XR, Xu Y, Shi GM, Fan J, Zhou J, Ji Y, Sun HC, Qiu SJ, Yu B, Gao Q et al (2008) Cytokeratin 10 and cytokeratin 19: predictive markers for poor prognosis in hepatocellular carcinoma patients after curative resection. Clin Cancer Res 14:3850–3859

Yang XR, Xu Y, Yu B, Zhou J, Qiu SJ, Shi GM, Zhang BH, Wu WZ, Shi YH, Wu B et al (2010) High expression levels of putative hepatic stem/progenitor cell biomarkers related to tumour angiogenesis and poor prognosis of hepatocellular carcinoma. Gut 59:953–962

Yao DF, Huang ZW, Chen SZ, Huang JF, Lu JX, Xiao MB, Meng XY (1998) Diagnosis of hepatocellular carcinoma by quantitative detection of hepatoma-specific bands of serum gamma-glutamyltransferase. Am J Clin Pathol 110:743–749

Yao D, Jiang D, Huang Z, Lu J, Tao Q, Yu Z, Meng X (2000) Abnormal expression of hepatoma specific gamma-glutamyl transferase and alteration of gamma-glutalmyl transferase gene methylation status in patients with hepatocellular carcinoma. Cancer 88:761–769

Yao DF, Dong ZZ, Yao DB, Wu XH, Wu W, Qiu LW, Wang HM, Meng XY (2004) Abnormal expression of hepatoma-derived gamma-glutamyltransferase subtyping and its early alteration for carcinogenesis of hepatocytes. Hepato-Biliary Pancreat Dis Int 3:564–570

Yao S, Zhang J, Chen H, Sheng Y, Zhang X, Liu Z, Zhang C (2013a) Diagnostic value of immunohistochemical staining of GP73, GPC3, DCP, CD34, CD31, and reticulin staining in hepatocellular carcinoma. J Histochem Cytochem 61:639–648

Yao M, Yao DF, Bian YZ, Wu W, Yan XD, Yu DD, Qiu LW, Yang JL, Zhang HJ et al (2013b) Values of circulating GPC-3 mRNA and alpha-fetoprotein in detecting patients with hepatocellular carcinoma. Hepato-Biliary Pancreat Dis Int 12:171–179

Yokoyama Y, Kuramitsu Y, Takashima M, Iizuka N, Toda T, Terai S, Sakaida I, Oka M et al (2004) Proteomic profiling of proteins decreased in hepatocellular carcinoma from patients infected with hepatitis C virus. Proteomics 4:2111–2116

Yoon CH, Kim MJ, Park MJ, Park IC, Hwang SG, An S, Choi YH, Yoon G, Lee SJ (2010) Claudin-1 acts through c-Abl-protein kinase Cdelta (PKCdelta) signaling and has a causal role in the acquisition of invasive capacity in human liver cells. J Biol Chem 285:226–233

Yorita K, Takahashi N, Takai H, Kato A, Suzuki M, Ishiguro T, Ohtomo T, Nagaike K et al (2011) Prognostic significance of circumferential cell surface immunoreactivity of glypican-3 in hepatocellular carcinoma. Liver Int 31:120–131

Yoshitake K, Tanaka S, Mogushi K, Aihara A, Murakata A, Matsumura S, Mitsunori Y et al (2011) Importin-α1 as a novel prognostic target for hepatocellular carcinoma. Ann Surg Oncol 18:2093–2103

Yuan RH, Jeng YM, Hu RH, Lai PL, Lee PH, Cheng CC, Hsu HC (2011) Role of p53 and β-catenin mutations in conjunction with CK19 expression on early tumor recurrence and prognosis of hepatocellular carcinoma. J Gastrointest Surg 15:321–329

Zhao M, Zhang NX, Laissue JA, Zimmermann A (1994) Immunohistochemical analysis of p53 protein overexpression in liver cell dysplasia and in hepatocellular carcinoma. Virchows Arch 424:613–621

Zhao M, Laissue JA, Zimmermann A (1996) Tenascin and type IV collagen expression in liver cell dysplasia and in hepatocellular carcinoma. Histol Histopathol 11:323–333

Zhao M and Zimmermann A 1998. http://www.ncbi.nlm.nih.gov/pubmed/9690121

Zhou YM, Yang JM, Li B, Yin ZF, Xu F, Wang B, Xu W, Kan T (2010) Risk factors for early recurrence of small hepatocellular carcinoma after curative resection. Hepato-Biliary Pancreat Dis Int 9:33–37

Zhou Y, Yin X, Ying J, Zhang B (2012) Golgi protein 73 versus alpha-fetoprotein as a biomarker for hepatocellular carcinoma: a diagnostic meta-analysis. BMC Cancer 12:17

Zhu ZW, Friess H, Wang L, Abou-Shady M, Zimmermann A, Lander AD, Korc M et al (2001) Enhanced glypican-3 expression differentiates the majority of hepatocellular carcinomas from benign hepatic disorders. Gut 48:558–564

Zhu Z, Hao X, Yan M, Yao M, Ge C, Gu J, Li J (2010) Cancer stem/progenitor cells are highly enriched in CD133+CD44+ populations of hepatocellular carcinoma. Int J Cancer 126:2067–2078

Zhu AX, Gold PJ, El-Khoueiry AB, Abrams TA, Morikawa H, Ohnishi N, Ohtomo T et al (2013) First-in-man phase I study of GC33, a novel recombinant humanized antibody against glypican-3, in patients with advanced hepatocellular carcinoma. Clin Cancer Res 19:920–928

Zhuang PY, Zhang JB, Zhu XD, Zhang W, Wu WZ, Tan YS, Hou J, Tang ZY, Qin LX et al (2008) Two pathologic types of hepatocellular carcinoma with lymph node metastasis with distinct prognosis on the basis of CK19 expression in tumor. Cancer 112:2740–2748

Zimmermann RL, Burke MA, Young NA, Solomides CC, Bibbo M (2001) Diagnostic value of hepatocyte paraffin 1 antibody to discriminate hepatocellular carcinoma from metastatic carcinoma in fine-needle aspiration biopsies of the liver. Cancer 93:288–291

Invasion Patterns and Metastatic Patterns of Hepatocellular Carcinoma

4

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_4

Abstract

Hepatocellular carcinoma (HCC) is a highly invasive malignancy that frequently invades small and large blood vessels, the liver substance, and bile ducts. In contrast to cholangiocarcinoma, perineural and intraneural invasion is a less common invasion mode of HCC. Invasion of the portal vein, with or without associated venous thrombosis, is a typical feature of HCC and plays a central role in intrahepatic tumor spread. Hepatic microvascular invasion is more frequently observed in HCCs with a lower degree of differentiation and confers an aggressive tumor biology. HCCs with extranodular growth and contiguous multinodular growth patterns are prone to microvascular invasion. HCCs give rise to intrahepatic and remote metastases with high frequency. Risk factors for metastasis comprise macro- and microvascular invasion, large tumor size, multifocality, and poor histologic differentiation. Intrahepatic metastases, which may occur in more than 80 % of large tumors, appear as macro- or micrometastases. Extrahepatic metastases are predominantly found in the lung, bone, lymph nodes, and brain, followed by the gastrointestinal tract and other sites.

Invasion Patterns of Hepatocellular Carcinoma

Phenotypes of Invasion

HCCs are highly invasive neoplasms that have a marked tendency to invade small and large hepatic blood vessels, perivascular compartments (interstitial invasion), and bile ducts. As outlined in the analyses of small HCC, interstitial invasion can microscopically be classified into three patterns, i.e., a crossing type, in which HCC cell invades across fibrous septa of tumor nodules; a longitudinal type, in which HCC cells grow longitudinally within fibrous septa; and an irregular type, in which portal areas are irregularly invaded by cancer cells (Kondo et al. 1994). Intrahepatic neural invasion has been noted in HCC (Ueda et al. 1991), but this feature is probably less common in HCC than cholangiocarcinomas.

Blood Vessel Invasion

HCC has a strong tendency to invade large and small hepatic blood vessels (macrovascular and microvascular invasion; Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12).

Invasion-induced thrombosis of portal vein branches can result in organization and cavernous transformation. On the other hand, portal vein obstruction may be followed by perivenous collateral networks forming cavernous vasculatures (Terada et al. 1989). Terminal portal vein invasion, a crucial finding of early HCC, can be assessed by the use of Victoria blue staining (Kobayashi et al. 2012a). Microvascular invasion

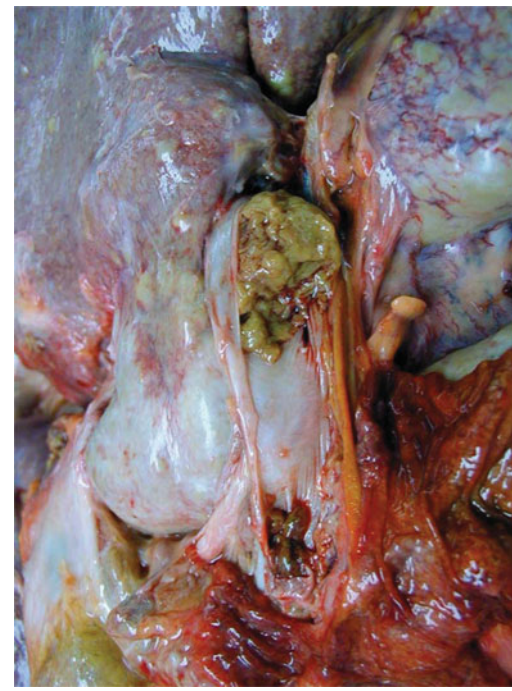

Fig. 1 Hepatocellular carcinoma with invasion of the extrahepatic portal vein. The vein is longitudinally opened and contains friable, greenish tumor masses in the absence of a thrombus (necropsy specimen)

is a common feature mainly in less well-differentiated HCC and is a parameter that confers aggressive tumor biology (Rodriguez-Peralvarez et al. 2013). Independent predictors of microvascular invasion were tumor size exceeding 4 cm or 5 cm and a high tumor grade (Kim et al. 2008; Esnaola et al. 2002). High-risk macroscopic growth patterns, i.e., single nodular type with extranodular growth and contiguous multinodular type, are strong predictors of microvascular invasion (Nagano et al. 2008). Patients with Edmondson-Steiner grade 1 and a tumor diameter of less than 5 cm had no microvascular invasion, while those with grade 2 or higher had higher incidences of microvascular invasion, even in small tumors (Kim et al. 2008). Apart from tumor size, high serum AFP and high levels of des-gamma-carboxyprothrombin in serum are significant factors in identifying microvascular invasion (Eguchi et al. 2010).

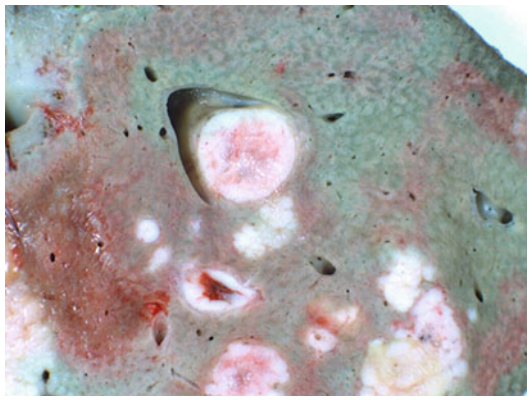

Fig. 2 A dilated intrahepatic portal vein branch shows an eccentrically placed HCC nodule that invaded the vein, forming a bulging mass. The tumor nodules in the vicinity may have resulted from intravenous cancer spread

Lymph Vessel Invasion

In the light of locoregional lymph node metastases, HCC will often invade intrahepatic lymph vessels, although it is difficult to identify invaded intrahepatic thin-walled vessels without immunohistochemistry. Lymphovascular invasion is more easily detectable in extrahepatic structures, e.g., the hepatoduodenal ligament, where also lymphangitis carcinomatosa is found. Lymphangitis carcinomatosa was first described by the French physician, Gabriel Andral, in 1824 (cited in Doyle 1989) and later studied in detail by Virchow. It is not an inflammatory change, as the term would suggest, but the presence of cancer cells in lymph vessels, sometimes associated with thrombus-like masses. Cancer cells, including HCC cells, can proliferate within lymph vessels and can produce nodule-like lesions that cause saccular lymph vessel dilatation. As with other malignancies, the mechanisms of lymphatic invasion and spread are complex and in part depend on tumor-induced lymphangiogenesis (review: Achen and Stacker 2008).

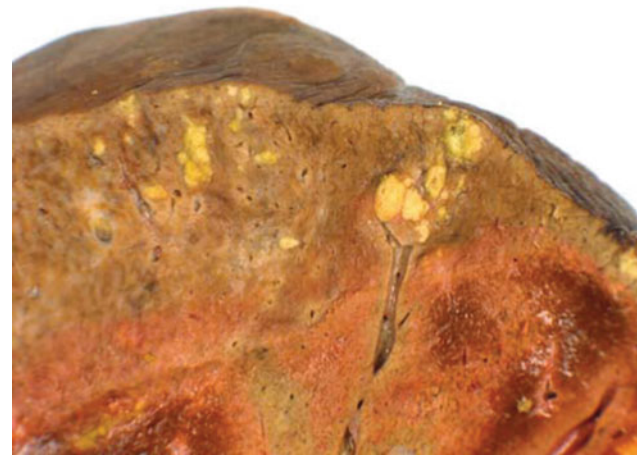

Fig. 3 Intrahepatic portal vein invasion by HCC can result in peripheral intrahepatic spread, causing numerous metastatic tumor nodules with a distribution reflecting the vascular tree

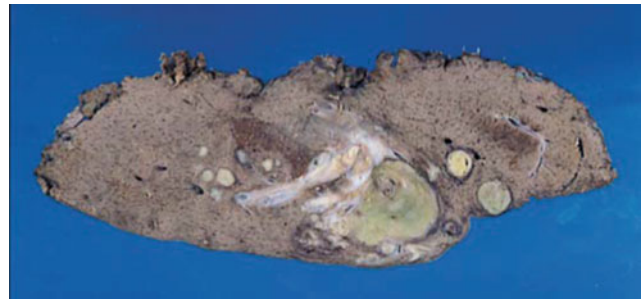

Fig. 4 A large hepatocellular carcinoma (greenish tumor nodule) invaded an adjacent large portal vein branch, followed by intravenous tumor spread with several intravenous tumor casts

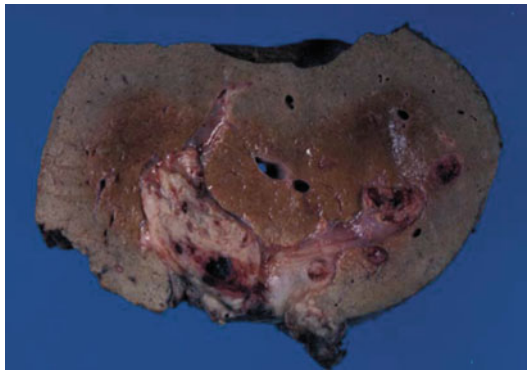

Fig. 5 Massive HCC invasion of hepatic veins. Note that the intravenous tumor displays hemorrhage and necrosis

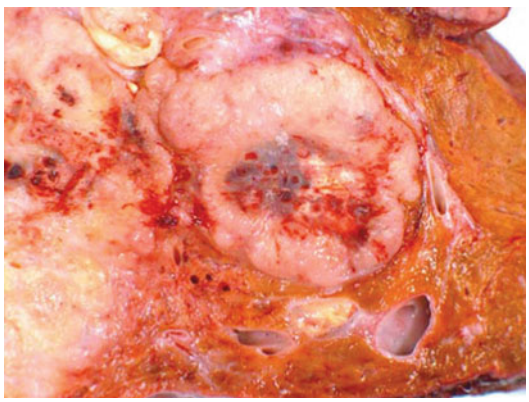

Fig. 6 Intrahepatic portal vein invasion by hepatocellular carcinoma (*center* of figure). The large tumor has completely obturated the dilated vein, but a probe could still be inserted between tumor and venous wall

Vasculogenic Mimicry

HCC cells with a metastatic phenotype can produce in vitro the chord-like structures that represent vasculogenic mimicry (VM). VM is

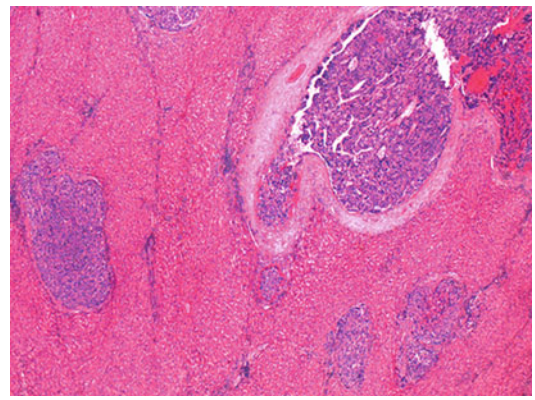

Fig. 7 Intravascular hepatocellular carcinoma ("tumor thrombus" of HCC) in a portal vein branch is accompanied by several smaller intravascular tumor foci, suggesting intravascular spread for the larger tumor focus (hematoxylin and eosin stain)

morphologically characterized by vessel-like channels lined by tumor cells. It is thought that VM plays an important role in invasion and spread within tumor stroma (Kirschmann et al. 2012). The establishment of VM depends on the activity of several factors in HCCs, including Twist1 (Ma et al. 2011; Sun et al. 2011), Slug (Sun et al. 2013b), ROCK signaling (Zhang et al., 2014a), Notch1 (Zhu et al. 2014), and autophagy mechanisms (Ding et al. 2014). The process of VM in HCC is critically regulated by osteopontin, probably through activation of matrix metalloproteinase 2 and urokinase-type plasminogen activator (Liu et al. 2011).

Interstitial Invasion Patterns

HCCs invade hepatic parenchyma, perivascular spaces, bile ducts, and periductal sheaths by

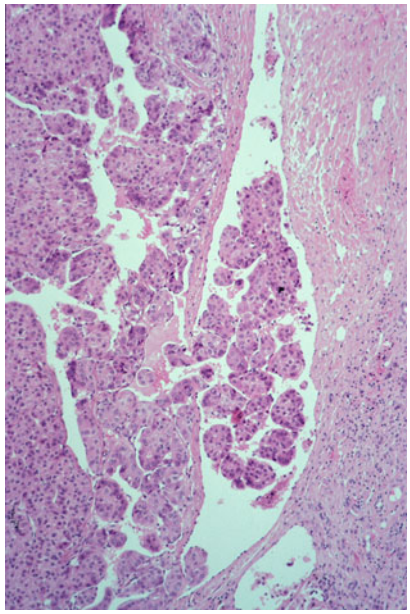

Fig. 8 In this hepatocellular carcinoma, tumor tissue invasion of an intrahepatic portal vein branch caused a break or gap in the venous wall (*middle* of figure; hematoxylin and eosin stain)

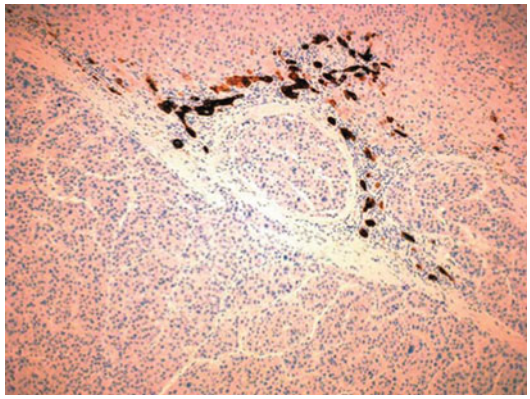

Fig. 9 This hepatocellular carcinoma underwent invasion of a small intrahepatic portal venous branch (*middle* of figure). This invasion is associated with a perifocal ductular reaction (brown profiles; cytokeratin 19 immunostain)

invasion mechanisms discussed in a later chapter. Infiltration of normal tissue via histolytic mechanisms allows the tumor to transgress tissue barriers and to reach peritumoral tissue compartments, including resection margins (Figs. 13 and 14).

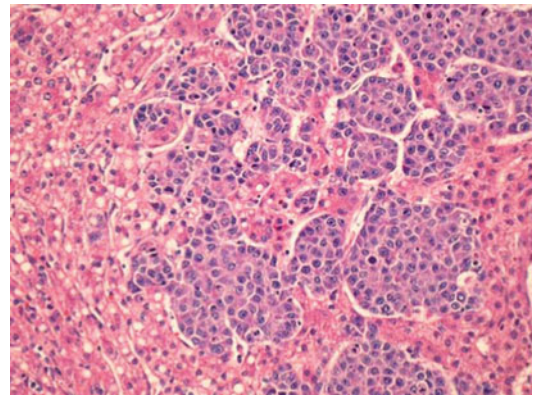

Fig. 10 Hepatocellular carcinoma, intrasinusoidal spread. Tumor cells grow within the dilated sinusoids, sometimes causing atrophy of hepatocyte plates (hematoxylin and eosin stain)

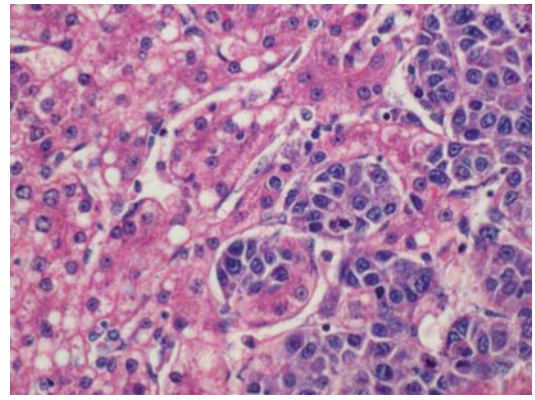

Fig. 11 Hepatocellular carcinoma, intrasinusoidal invasion. Neoplastic cells can invade hepatocyte plates, facilitating direct contact between tumor cells and liver cells (*below center* of figure). Heterologous cell interactions of this type play a role in tumor growth, invasion, and progression (hematoxylin and eosin stain)

Epithelial-Mesenchymal Transition (EMT) in Hepatocellular Carcinoma

Epithelial-mesenchymal transition (EMT) plays a central pathogenic role in the generation of a tumor microenvironment that favors an invasive phenotype. In addition, HCC cells and other tumor cells undergoing EMT become cells with a certain plasticity required for spread and homing at remote places. HCC EMT affects biology of disease, in that tumors showing EMT exhibit a

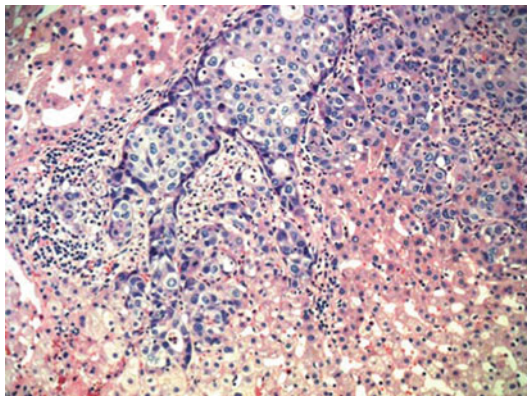

Fig. 12 Intrasinusoidal invasion of HCC cells is associated in this case with tumor cell presence in inlet veins and portal venous branches (hematoxylin and eosin stain)

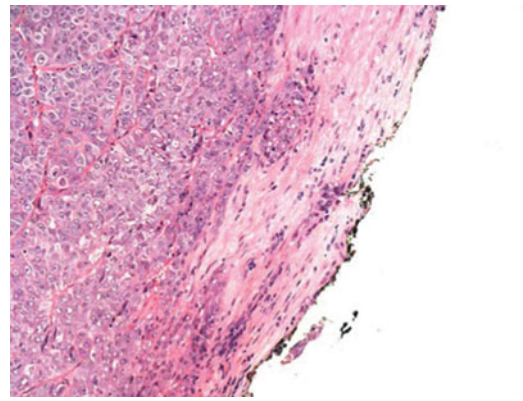

Fig. 14 Hepatocellular carcinoma, inked resection margin (*black* particles). Note that invading neoplastic cells have reached the inked surface at one place (hematoxylin and eosin stain)

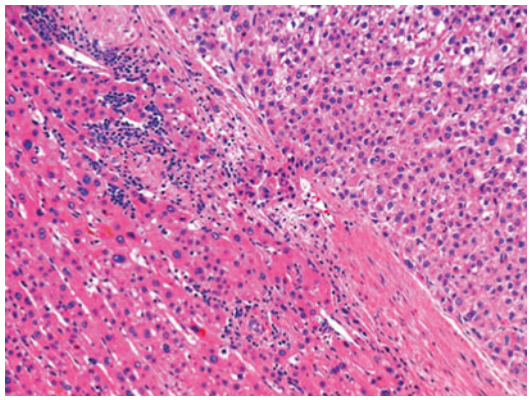

Fig. 13 A well-differentiated hepatocellular carcinoma (*right half* of figure) has perforated its fibrous pseudocapsule to invade adjacent liver tissue (*center*; hematoxylin and eosin stain)

more aggressive course (Yamada et al. 2014). Similarly, abnormal expression of EMT-related proteins such as S100A4, vimentin, and E-cadherin is correlated with prognosis in HCC (Zhai et al. 2014). Reduced E-cadherin expression indicates poor prognosis for patients with HCC (Chen et al. 2014).

EMT in HCCs is induced and controlled by numerous factors. EMT is promoted by the transcription factors ZEB1 and ZEB2, the expression of which is suppressed by p53 protein via upregulation of microRNA-200, which in turn represses ZEB1/ZEB2 expression (Kim et al. 2011). Periostin, an extracellular matrix protein involved in the regulation of EMT, is expressed in the stroma and epithelia of a subset of HCC and indicates aggressive biology of disease (Riener et al. 2010). Astrocyte elevated gene-1 (AEG-1) is a biomarker of EMT in HCC and seems to be involved in tumor progression (Zheng et al. 2014). HCC invasion depending on EMT is promoted by RANKL which induces NF-kappaB-mediated EMT (Song et al. 2014). In HCC cells, protocadherin 9 inhibits EMT and cell migration through activation of the GSK-3beta pathway situated within Wnt-beta-catenin signaling system (Zhu et al. 2014). A factor involved in the regulation of cell proliferation and differentiation, mammalian sterile-20-like kinase 4/MST4, promotes HCC EMT and metastasis through activation of the p-ERK pathway (Lin et al. 2014). EMT in HCCs is regulated by several microRNA species (review: Yang et al. 2014). The microRNA-200 family plays an important role in the regulation of EMT (Mongroo and Rustgi 2010). Downregulation of microRNA-200a induces EMT in hepatic stem cells through targeting the beta-catenin signaling pathway (Liu et al. 2013a). MicroRNA-141 suppresses HCC progression by targeting the EMT factor ZEB2 (Wu et al. 2014). Vasohibin 2, a factor involved in EMT and angiogenesis in HCCs, is upregulated by microRNA-200. Vasohibin 2 promotes EMT through the ZEB1/ZEB2 signaling pathway (Xue et al. 2014).

MicroRNA-122 triggers EMT in HCC, but suppresses cell motility and invasion by targeting RhoA (Wang et al. 2014). MicroRNA-26b inhibits EMT in HCC by targeting the 3′UTR of USP9X, which in turn affects EMT via Smad4 and the TGF-beta signaling pathway (Shen et al. 2014).

Metastatic Patterns of Hepatocellular Carcinoma

Introduction

Hepatocellular carcinoma is a malignancy with a high capacity for metastatic spread, critically linked to its frequent invasion (intravasation) of small and large hepatic blood vessels (Fig. 15).

Apart from intrahepatic metastases, which are the key feature of recurrent disease, HCCs can metastasize to remote organs, albeit with distinct metastatic patterns (reviews: Zhou 2002; Tang et al. 2004).

Factors Influencing HCC Metastasis

Risk factors for HCC metastasis mainly comprise vascular invasion, larger tumor size, multifocality, and poor histologic differentiation (Si et al. 2003).

Fig. 15 Intrahepatic metastasis of hepatocellular carcinoma. Most of the metastatic nodules are situated close to the primary tumor in the left lobe, while fewer nodules are found on the contralateral side

Early microvascular invasion followed by tumor cells distribution in the circulation is regarded as the most important step for metastatic spread and plays a central role in hepatic recurrence (Imamura et al. 2003). Vascular invasion by HCC cells is not only an inherent features of motile and histolytic cancer cells but is also regulated by distinct genes that affect metastatic spread, including metastatic tumor antigen 1 (MTA1) which directly promotes vascular invasion (Moon et al. 2004; Ryu et al. 2008), and the actions of microRNAs involved in metastasis regulation, e.g., microRNA-135a (Liu et al. 2012). The presence of circulating tumor cells (CTC) has been confirmed in several studies, and these cells are associated with metastasis and prognosis in HCC patients (Guo et al. 2007; Yang et al. 2008; Chiappini 2012; Zhang et al. 2012a).

Subsets of CTC express epithelial cell adhesion molecule (EpCAM), intercellular adhesion molecule 1 (ICAM-1), and/or SALL4 and therefore have features of HCC progenitor cells (Liu et al. 2013c; Sun et al. 2013a). EpCAM-positive CTC as a biomarker of systemic disease are significantly associated with survival (Schulze et al. 2013). Epithelial-mesenchymal transition (EMT), which plays a significant role in metastatic spread of malignancies, is involved in promoting the blood-borne dissemination of primary HCC cells (Li et al. 2013). CTC in HCC consist of several subgroups with varying epithelial, mesenchymal, liver-specific, and mixed features, whereby the representation of these subgroups affects distinct clinical patterns (Nel et al. 2013). Epigenetic upregulation of HGF and c-Met in CTC drives metastatic spread in HCC patients (Ogunwobi et al. 2013). CTC can be detected in early phases of spread by analyzing their molecular signatures, e.g., through analysis of the MAGE-3 and MAGE-4 genes (Hussein et al. 2012). The spread of the "HCC disease" in blood circulation is also assessable via analysis of surrogate markers of circulation entry by the tumor, e.g., endoglin/CD105 (Yagmur et al. 2007). Interestingly, there is also evidence that endothelial cell progenitor is present in the circulation of HCC patients, and the presence of such cells is associated with poor survival,

suggesting a role in tumor spread (Shao et al. 2011). How is the fate of CTC regulated? It is likely that only part of CRC remain viable, are capable to home to distinct vascular beds, perform egress into tissue, and can resume proliferation and growth to metastatic nodules. Subsets of CTC are subject to host defense mechanisms and undergo cell death. Resistance to anoikis is an important mechanism for metastatic spread. It has been shown that formation of cell aggregates by HCC cells mediates anoikis resistance (Zhang et al. 2008b). An important role in the elimination of spreading cancer cells is held by CD56-positive natural killer cells (NK cells). HCC patients showed a significant reduction of NK cells both in blood and tumors, and both peripheral and tumoral NK cells exhibited poorer capacity to produce IFN-gamma and kill target cells (Cai et al. 2008). Apart from NK cells, cytotoxic CD8 T cells are important mediators of anticancer cell activity. CD8 T-cell impairment occurs in HCC and is associated with poor survival. The pathway of impairment involves increased regulatory CD4 (+) T cells which counteract the effector function of CD8 T-cell and thus promote disease progression (Fu et al. 2007).

In addition to invasion of blood vessels, infiltration into and spread within lymphatic channels and lymph vessels play a significant role in HCC spread. This metastatic pathway is often associated with intralymphatic growth of cancer cells, i.e., carcinomatous lymphangiosis. This condition is sometimes massive in the pulmonary lymph vessel bed (Molina and Valente 2003) and may cause pulmonary dysfunction. Epithelial-mesenchymal transition (EMT) is a mechanism that plays a crucial role in the initiation and completion of a metastatic cascade. In HCC, Twist overexpression correlates with metastasis through the induction of EMT associated with downregulation of E-cadherin and hence cell adhesion (Lee et al. 2006).

Intrahepatic Metastases

HCC frequently undergoes intrahepatic intravascular dissemination that results in intrahepatic metastasis. The incidence of intrahepatic metastases in advanced HCC may exceed 80 % (Sugino et al. 2008). Intrahepatic HCC metastases appear as macrometastases or micrometastases. In small HCC with a diameter less than 3 cm, the presence of intrahepatic micrometastases is associated with distinct gross patterns. No micrometastases or portal vein invasion were found in the vaguely nodular type of small HCC. Tumors of the single nodular type with extranodular growth and of the confluent multinodular type showed a higher frequency of intrahepatic micrometastasis than the single nodular type (Nakashima et al. 2003). In solitary resected HCC with an appropriate resection margin, micrometastases were found at a distance of 0.05–6.1 cm from the main tumor, with a decreasing frequency gradient from areas close to the tumor to more remote from the tumor (Shi et al. 2004). Intrahepatic spread of HCC is based on both invasion of small liver blood vessels and invasion of large vessels, in particular branches of the portal vein. In an autopsy study, it was found that the metastatic process was initiated by vascular involvement whereby nests of neoplastic cells are surrounded by sinusoidal-like vessels and extend into portal and hepatic veins. This is associated with the formation of endothelium-coated tumor cell clusters that enter circulation to form emboli in liver and distant organs (Sugino et al. 2008). Apart from the widespread intrahepatic distribution of metastatic cells, there are situations where micrometastases develop in the tissue directly surrounding primary tumors. These microsatellites are detectable at various distances from their source. In one study, they were found with a range of 0.05–6.10 cm (Shi et al. 2004). The phenomenon of distances exceeding 1 cm is of great importance for the assessment of resection margins and requires the search for microsatellites in the setting of radical judgments. How can intrahepatic metastases of HCC be distinguished from multicentric HCC? The two situations are often difficult to separate (Yasui et al. 1997).

The morphology of intrahepatic metastases of HCC can differ from that of the primary tumor. At least part of the metastatic lesions exhibit a

less differentiated phenotype, but in other situations, primary and metastatic tumors may look almost the same. In one investigation, the part of the metastatic nodules showed well-differentiated, normotrabecular patterns, sometimes with a central core of less differentiated HCC, resulting in nodule-in-nodule lesion (Kondo and Wada 1991).

Portal Vein Invasion

Portal vein invasion with or without associated thrombosis is a frequent complication of HCC and was found in up to 37.8 % of patients (Olubuyide 1991). A literature survey of 1,497 patients with HCC revealed portal vein involvement in 35 % of patients (Lee and Geer 1987). Even in the presence of thrombosis, patients with portal vein involvement may remain asymptomatic, but part of them manifest signs of hepatic inflow failure, associated with ischemic hepatopathy, mainly in situations of general hypotension, and some patients will experience portal hypertension.

Extrahepatic HCC Metastases: General Aspects

Depending on the level of differentiation, HCC is a tumor which extensively metastasizes to various organs and structures. Extrahepatic metastatic disease in HCC is a condition associated with poor prognosis (Okusaka et al. 1997; Natsuizaka et al. 2005; Uka et al. 2007; Yang et al. 2007a). In an autopsy study, extrahepatic metastases were identified in 68 % of cases (Terada and Maruo 2013). Particularly frequent metastatic sites include the liver, lungs (at least 50 % of cases), bone (up to 40 %), and lymph nodes, followed by the gastrointestinal tract, adrenal glands, peritoneal surface, skin, brain, and muscle (Berman 1958. 1959; Anthony 1973; Linder et al. 1974; Nakashima et al. 1983; Lee and Geer 1987; Yuki et al. 1990; Katyal et al. 2000). In a mixed clinical and autopsy study of 137 patients with primary HCC, involvement of regional lymph nodes and other intra-abdominal organs was noted in 10.2 %, while distant metastases were recorded in 30.8 %, with the lung, bone, and brain being the most common metastatic sites (El-Domeiri et al. 1971). Among 1,573 HCC patients, the incidence rate of extrahepatic metastases, as detected during the lifetime after medical treatment of HCC, was approximately 13 % at 5 years (Kanda et al. 2008). In a study of 403 consecutive US patients with HCC, the most common extrahepatic metastatic site was the lung (55 %), followed by abdominal lymph nodes (41 %) and bone (28 %; Katyal et al. 2000). In an autopsy study of 490 HCC cases observed in a low-endemicity area (Sweden), metastases especially involved the lymph nodes (42 %), lungs (18 %), and skeleton (17 %), and metastases were associated with multinodular growth of the primary tumor, involvement of both liver lobes, low grade of differentiation, and vascular invasion (Kaczynski et al. 1995). There is a clear relationship between tumor size, tumor stage, and invasive features of the primary tumor and the prevalence of extrahepatic metastasis. In an autopsy study of 240 consecutive cases of HCC, the incidence of extrahepatic tumor spread was significantly higher for tumors measuring more than 5 cm in diameter (Yuki et al. 1990). Among 148 patients with extrahepatic metastases, 86 % had either intrahepatic stage IVA tumor (76 %) or an intrahepatic stage II tumor (11 %; Katyal et al. 2000). In a study of 65 patients with extrahepatic HCC metastases, 73.8 % of the patients with extrahepatic metastases had tumors with intrahepatic TNM stages T3 or T4, while only 28.5 % of patients without extrahepatic metastases had T3 or T4 stage disease. Macrovessel invasion was also more frequent in the group having extrahepatic metastasis (Natsuizaka et al. 2005). It is important to keep in mind that, albeit seldom, also very small or so-called minute HCCs can give rise to extrahepatic metastases (Kim et al. 1998). In most cases, extrahepatic HCC metastasis develops through intravascular spread, a mechanism that is also operational in intrahepatic metastases. In rare cases, metastasis-like spread occurs following invasion of organs and tissues adjacent to the liver, e.g., right-sided pedunculated HCC

caused by adrenal metastasis extending into the liver (Okuda et al. 1998), or through abnormal connections between the liver and neighboring organs, e.g., adrenohepatic fusion (Okano et al. 2004).

Invasion of Large Hepatic Veins and Associated Outflow Structures: Pathways for Pulmonary Spread

HCC has an important propensity to invade large veins. Invasion into major hepatic veins and the inferior vena cava occurs, but is less common than involvement of the portal vein (Culpepper and von Haam 1934; Close and Uri 1989; Okuda 1997). Although HCC can induce impressive intravascular tumor plugs, patients can survive such tumor manifestations for longer time periods. Following caval invasion, HCC may grow to the right atrium and produce intra-atrial growth (Gregory 1939; Kojiro et al. 1984; Barbero et al. 2012) and can even cross the tricuspid valve (Ohwada et al. 2008). Through such pathways, HCC can form pulmonary artery tumor thrombi and embolize to large- and medium-sized pulmonary artery branches (Blanloeil et al. 1983; Main et al. 1984; Willett et al. 1984; Harada et al. 1988; Putterman et al. 1994; Wilson et al. 2001; Gutiérrez-Macias et al. 2002; Papp et al. 2005; Jäkel et al. 2006). These complications can cause pulmonary hypertension (Brisbane et al. 1980), pulmonary infarction (Shinzato et al. 1990), and fatal pulmonary embolism (Chan et al. 2000; Kwok et al. 2003; Schmidt-Mutter et al. 2003; Wu et al. 2013).

Locoregional Lymph Node Metastasis

In comparison with intra- and extrahepatic cholangiocarcinomas, there are less numerous studies having analyzed the metastatic status of locoregional lymph nodes in patients with HCC (Tanaka et al. 1985; Lee and Geer 1987; Arakai et al. 1988; Olubuyide 1991; Toyoda et al. 1996; Efremidis et al. 1999; Uenishi et al. 2000; Ercolani et al. 2004; Sotiropoulos et al. 2007; Uchino et al. 2011; Ueda et al. 2012; Utsumi et al. 2012; Awazu et al. 2013). It is suggested that HCC cells obtain access to lymph nodes either via invasion of intrahepatic lymphatics (Nomura and Ohnishi 1991), or through secondary pathways involving invasion of the hepatoduodenal ligament. Incidences of abdominal lymph node metastases in HCC vary considerably among the analyses from different geographical areas, factors for this phenomenon including differences in stage and biology of tumors, therapy modalities, and the genetic background of patients. Lymph node metastases are more frequent in large primary tumors and those with poor differentiation (Uenishi et al. 2000; Lee et al. 2011a). Furthermore, nodal metastasis is more common in massive and multinodular nonencapsulated HC types than in encapsulated HCC (Abe et al. 2002). The clinicopathologic features of lymph node metastases have been investigated in 660 consecutive autopsy cases in Japan. Lymph node metastases were noted in 25.5 % and was more often found in massive than in nodular tumor types and, interestingly, most frequent in patients with pedunculated HCC. No locoregional lymph node metastases were detected in patients with tumor less than 3 cm, i.e., early or small HCC (Watanabe et al. 1994). In a literature review of 1,497 patients with HCC, portal lymph node metastases were registered in 27 % (Lee and Geer 1987). A US investigation on 403 patients found abdominal lymph node metastases in 41 % of patients. In this study, periceliac and portohepatic lymph nodes were the most commonly involved, and peripancreatic, aortocaval, and retrocaval were the least common (Katyal et al. 2000). Distant lymph node metastases were detected in 12 % of patients. There are investigations with markedly lower figure for nodal metastasis incidence. Among 968 patients from China with operable HCC, only 5.1 % showed lymph node metastasis (Sun et al. 2007). There is a relationship between the frequency of lymph node metastases and the growth patterns of primary tumors, being lowest in single nodular tumors and highest in diffuse and contiguous multinodular types (Yuki et al. 1990). Intra-abdominal nodal metastases can be

visualized intraoperatively by means of indocyanine green fluorescent imaging (Satou et al. 2013). Typically, HCC metastasizes to supradiaphragmatic lymph nodes, including mediastinal nodes (Tanaka et al. 2005), Virchow-Troisier's node (Schwarz et al. 1982), cervical lymph nodes (Kobayashi et al. 2012b; Terada and Maruo 2013), and supraclavicular nodes (Lau et al. 2000). Mediastinal, pretracheal, and cardiophrenic lymph node metastases were most frequent (Katyal et al. 2000). Extrahepatic extrathoracic model involvement is less frequent and chiefly occurs in patients with large, advanced, and poorly differentiated tumors. Rare nodal metastatic sites include mesenteric, axillary, pharyngeal, internal mammary, perirectal, retrocrural, iliac, and paraspinal lymph nodes, but in principle almost any nodal station can be involved (multiple systemic lymph node metastases; Ciriza et al. 1996; Toyoda et al. 1996; Alison et al. 2000). In rare situations, extraabdominal nodal metastasis occurs also in the presence of small primary tumors (Toyoda et al. 1996; Uehara et al. 2003).

Lymph node metastases negatively affect outcome. Hilar lymph node metastases had a negative prognostic value for both tumor recurrence and survival (Sotiropoulos et al. 2007). Among 523 HCC patients, those with nodal metastases had tumor recurrence in 82.05 %, versus 57.64 % in those without nodal metastasis (Xiaohong et al. 2010). Spontaneous rupture of metastatic peripancreatic lymph nodes can cause massive peritoneal bleeding (Terada et al. 2003), and spontaneous rupture of a metastatic mediastinal lymph node can cause hemothorax (Oh et al. 2013) or cardiac tamponade (Seki et al. 2001). The risk factors for locoregional lymph node metastases in HCC have not yet fully worked out. Expression of CK19 and matrix metalloproteinase 2 predicts lymph node metastasis in HCC (Xiang et al. 2011). Immunopositivity of CK19 and OV-6 in HCC with lymph node metastasis was higher than in those without, and the CK19(+) group had a shorter median survival, expression of CK 19 being an independent prognostic factor for overall survival in HCC with lymph node metastasis (Zhuang et al. 2008). The Axl receptor and its ligand growth arrest-specific 6/Gas6 are components of a signaling system involved in the pathogenesis of several malignancies. In HCC patients, differential expression of Axl was correlated with lymph node metastasis (He et al. 2010). Increased expression of vascular endothelial growth factor C, which is involved in lymphangiogenesis, is correlated with lymph node metastasis and poor prognosis in HCC (Xiang et al. 2009). There is also evidence that there is a characteristic gene expression signature for nodal metastasis, as observed in genome-wide analysis for metastasis-associated genes (Lee et al. 2009).

Gallbladder: A Neighboring Site for Invasion and Metastatic Spread

HCC, mainly right-sided tumors, can invade or metastasize into this organ (Murakami et al. 2008; Ryu et al. 2009; Kanzaki et al. 2011; Terada and Maruo 2013). Invading tumors macroscopically form a nodule that originates in the liver substance close to the gallbladder fossa and which extends into the gallbladder wall, with effacement of the wall structures. Invading HCC can result in polypoid intraluminal gallbladder masses mimicking primary gallbladder cancer (Ueno et al. 2001). In rare cases, the entire gallbladder may be integrated within a large and partially necrotic tumor mass. Metastatic HCC foci either present as discrete mural nodules or as large tumor masses not in continuity with the liver substance.

Pulmonary Metastasis

Among extrahepatic metastasis of HCC, the lung is the most commonly affected organ, with frequencies in Western countries in the range of 18.1–62 % (Tsai et al. 1984; Katyal et al. 2000; Zhang et al. 2008a; Terada and Maruo 2013). Radiologically, multiple nodulation and pleural effusion are the main findings, but miliary lesions and signs of carcinomatous lymphangiosis are also found (Tsai et al. 1984). In a Japanese investigation of 98 autopsy cases of HCC, extrahepatic

hematogenous metastasis was found in 64 %, and the lung was the most frequently involved (62 %). There was close relationship between hepatic vascular tumor invasion, in particular the rate of portal vein invasion, and pulmonary metastasis. Furthermore, the rate of pulmonary metastasis was lower in patients with well-differentiated tumors, HCC with an expanding growth pattern, and tumors with a diameter of less than 10 cm (Sawabe et al. 1987). Pulmonary spread of HCC may present as extensive lymphangiosis carcinomatosa, clinically causing shortness of breath and exertion dyspnea (Molina and Valente 2003). Involvement of the pleura is a well-known phenomenon that can cause hemothorax (Takagi et al. 1996).

Hepatocellular tissue histologically resembling well-differentiated HCC can be found within the pulmonary artery tree following traumatic liver tissue embolism (Johnston 1959; Voitk and Munkittrick 1986; Tozzini et al. 2004).

Bone and Skeletal Metastasis

HCC can metastasize to the skeleton which is the second most common extrahepatic organ site after the lungs. Incidences for bone metastasis of HCC ranged from 3 % to 20 % (Kaufmann 1922; Moon 1929; Bolker et al. 1937; Hedrick 1937; Okazaki et al. 1985; Fukutomi et al. 2001; Seong et al. 2005; Kim et al. 2007; Longo et al. 2014; Santini et al. 2014). Moon (1929) cites old reports describing this distinct clinicopathologic situation, e.g., reports by Schmidt (1897), Blumberg (1912), and Catsaras (1921). In a study of 211 deceased HCC patients with evidence of bone metastasis, the median time to the onset of bone metastasis was 13 months; 64.9 % of patients had multiple bone metastases, and the spine was the most common site (59.7 %). 82.4 % of the metastatic lesions were osteolytic (Santini et al. 2014). Other common sites for HCC metastases are the pelvis and the rib cage. In very rare cases, painful bone metastasis is the first manifestation of HCC (Ayan et al. 2013). Bone metastasis can be the initial presentation of HCC (Ruiz-Morales et al. 2014). In rare cases, disseminated carcinomatosis of bone marrow can develop (Honda et al. 2015).

Typically, the neoplastic cell masses fill the marrow spaces, associated with effacing of hematopoiesis, rarefaction of trabeculae of cancellated bone, and erosion of the outer shell of compact bone (osteolytic metastasis; Moon 1929). HCC tissue may break through the bony shell subsequent to massive bone lysis, forming a metastatic, invasive plaque between bone and periosteum. This may be followed by bleeding and marked inflammatory changes. Frequently, osteolytic metastases are followed by the formation of expansile soft tissue masses, which can result in an oncologic emergency (Kim et al. 2007; He et al. 2009; Seo et al. 2011). Small extensions of HCC tissue may follow the tracts of bone veins perforating the periosteum. The tumor tissue can contain bile, an important element for diagnosis, but it is sometimes difficult to distinguish an HCC metastasis from other granular cell tumors, immunohistochemistry being mandatory. Rarely, bone metastasis of HCC may present as massive osteoplastic metastases (Ohno et al. 1986). The pathogenic pathways involved in bone metastasis of HCC are not yet clarified. Osteolytic metastases are mediated by parathyroid hormone-related protein (PTHrP), interleukins 8 and 11, and vascular endothelial growth factor (VEGF), while osteoplastic metastases are induced by tumor-secreted endothelin-1, bone morphogenetic proteins, platelet-derived growth factor, connective tissue growth factor (CTGF), stanniocalcin, and adrenomedullin (Zhang et al. 2014b). Elevated serum levels of VEGF indicate advanced disease in HCC patients (Schoenleber et al. 2009). Immunoreactivity for VEGF was detectable in both primary HCC and its bone metastases (Iguchi et al. 2002), suggesting that secretion of VEGF by the tumor can induce bone resorption in situ.

Adrenal Gland

The adrenal gland was estimated to be the second most common site of extrahepatic hematogenous metastasis of HCC, although this mode of metastasis is less commonly diagnosed in a clinical

setting (Li et al. 1990; Ohwada et al. 1998; Yamamoto et al. 2002; Zeng et al. 2005; Yamakado et al. 2009; Chua and Morris 2012; Tariq et al. 2012; Zhang et al. 2012b; Ma et al. 2013).

In a series of 174 HCC patients undergoing hepatectomy, adrenal metastasis was found in 2.3 % (Popescu et al. 2007). Adrenal metastasis can cause severe retroperitoneal hemorrhage (Yang et al. 2007b), may be the first manifestation of HCC (Tsalis et al. 2005), and is sometimes diagnosed after long delay, e.g., 8.5 years after liver resection (Kuromatsu et al. 1993). In the part of patients, both adrenals are synchronously involved (Mundada et al. 2003), a situation that can cause adrenal insufficiency (Takamura et al. 1999). A subset of adrenal HCC metastasis seems to develop via adrenohepatic fusion which provides a bridge for the spread of HCC cells (Okano et al. 2004). Periadrenal HCC metastasis supplied by the hepatic artery has been described (Iwamoto et al. 1997). Also this situation is probably caused by preexisting adrenohepatic fusion. Adrenal HCC metastasis may be confounded with a primary adrenal neoplasm, including adrenocortical adenoma and adrenocortical carcinoma (Ohwada et al. 1998; Yasaka et al. 2013). The clinical and radiological presentation of adrenal metastases of HCC has been specified in numerous reports (Sai et al. 1982; Nakamura et al. 1989; Takayasu et al. 1989; Kitagawa et al 1996).

Peritoneal Metastases

Peritoneal metastasis (implant metastases, peritoneal seeding, intraperitoneal drop metastases) of HCC in a focal or diffuse seeding pattern is well known, although uncommon complication of this malignancy which occurs both synchronously and metachronously (Castro Fernandez et al. 1985; Kim et al. 1994; Kosaka et al. 1999; Yunoki et al. 1999; Kurachi et al. 2002; Uenishi et al. 2002; Yeh et al. 2002; Yoshida et al. 2002; Takahashi et al. 2004; Miyake et al. 2007; Otsuka et al. 2007; Matsukuma and Sato 2011). Peritoneal metastasis may appear as a solitary implant, but multiple nodules are more common (Kim et al. 1996). A special form of peritoneal seeding is omental seeding (Blandino et al. 1997). Among 749 patients with HCC recurrence after hepatic resection, 3.4 % developed isolated peritoneal implantation (Yeh et al. 2002). In an autopsy study, peritoneal seeding was detected in 9.4 % of cases, whereby the majority of patients exhibited a local peritoneal spread, most often involving the diaphragm followed by the omentum and the visceral serosa. Peritoneal spread was significantly associated with HCC rupture, direct diaphragmatic invasion, and locoregional lymph node metastasis (Matsukuma and Sato 2011). The correlation with lymph node metastasis may suggest a role of lymphatic spread in the pathogenesis of peritoneal seeding. Rupture of HCC is considered to be a special and independent risk factor for peritoneal seeding (Sonoda et al. 1989; Lin et al. 2006; Hung et al. 2008; Kwak et al. 2012). A severe complication of peritoneal HCC metastasis is tumor rupture (Yeh et al. 2002; Ishikawa et al. 2005), which may cause massive hematoperitoneum. Peritoneal metastasis can also occur following therapeutic interventions, e.g., after microwave coagulation therapy (Sato et al. 1999). Peritoneal seeding can occur after tumor biopsy or resection of ruptured HCC (Ryu et al. 2004), and after percutaneous ethanol injection therapy (Kurl et al. 1997; Miki et al. 2000). Generally, peritoneal metastasis follows a progressive course, but rare instances of apparently spontaneous regression have been reported (Terasaki et al. 2000). When other risk factors, such as age, sex, Child-Pugh score, and intrahepatic tumor stage, were matched, peritoneal metastasis failed to independently affect overall survival (Lin et al. 2009; Kwak et al. 2012).

Histologically, early implantations appear as tiny accumulations of cancer cells in the submesothelial tissue, sometimes associated with intravascular tumor deposits (carcinomatous hemangiosis and lymphangiosis). This finding suggests a spread to subserosal tissue compartments via small vessel and lymph vessel spread. In case seeding in fact develops in this way, the term implant would be a misnomer. Already early metastases are associated with a stromal reaction. The overlying mesothelium is still preserved in

early and very small lesions, whereas in later phases it reacts in the form of papillary microprojections or shows erosions, followed by a perifocal fibrinous peritonitis. Similar findings have been obtained in animal models (van de Molengraft et al. 1989).

Gastrointestinal Tract Metastasis

Involvement of the gastrointestinal tract from HCC uncommonly occurs, being observed in 0.5–6 % of cases (Anthony 1973; Nakashima et al. 1983; Chen et al. 1990). The most common site of involvement is the stomach, followed by duodenum and colon, usually via direct invasion, hematogenous metastasis, or through peritoneal seeding (Park et al. 2002). In one study, the most common clinical presentation was frank gastrointestinal bleeding, becoming evident in all cases. The median time between diagnosis of primary HCC and metastases was 4.5 months, and the sites of involvement were stomach, duodenum, and jejunum (Chen et al. 1990).

Several reports document metastasis of HCC to the esophagus, often with formation of large polypoid and even pedunculated lesions and often associated with tumor bleeding (Kume et al. 2000; Sohara et al. 2000; Cho et al. 2003; Tsubouchi et al. 2005; Yan et al. 2007; Fukatsu et al. 2012). Polypoid esophageal metastasis seems to progress from submucosal tumor masses (Choi et al. 2008). As tumor thrombi can be found in esophageal varices in HCC patients with cirrhosis (Arakawa et al. 1986), at least part of esophageal metastases may develop from such intravascular deposits. Gastric metastases of HCC tend to bleed (Maruyama et al. 1999) and are proposed to develop via a retrograde hematogenous pathway, spread eventually being promoted by a frequent tumor-associated portal vein thrombosis (Lin et al. 2000; Hu et al. 2010). On the other hand, due to its infrahepatic position, the stomach may also be directly invaded by HCC (Kimura et al. 2008). The duodenum, which is rather frequently affected by HCC in comparison with other parts of the GI tract, is either involved by hematogenous spread (eventually via a retrograde pathway in case of splanchnic vein/portal vein thrombosis), or through direct invasion (Yamada et al. 1998). Direct invasion mostly occurred from HCC located to the right liver lobe (Liang et al. 2012). The majority of duodenal HCC metastasis and invasion are complicated by duodenal bleeding (Humbert et al. 1987; Hung et al. 1998; Yamada et al. 1998). Small bowel metastases of HCC is a well-known complication often causing occult or frank hemorrhage (Narita et al. 1993; Yang et al. 1987; Kunizaki et al. 2012) or intussusception (Kim et al. 2006). HCC, by extending beyond the organ's limit, can directly invade the transverse colon or the right hepatic flexure, leading to sometimes large tumor masses that frequently tend to bleed (Chen et al. 1997; Hirashita et al. 2008). Apart from direct colonic invasion, true hematogenous HCC metastases to the colon have been observed (Fukui et al. 1993; Lin et al. 2000; Kaibori et al. 2007; Nozaki et al. 2008; Yoo et al. 2010). Similar to other GI tract sites of HCC metastasis, colonic metastases often cause hemorrhage, sometimes massive and life-threatening (Cosenza et al. 1999; Hwang et al. 2008).

Splenic Metastases

HCC metastasizes to the spleen in part of patients, and sometimes this is the only identifiable intra-abdominal metastasis. A splenic metastasis may be diagnosed in a patient with an otherwise asymptomatic HCC (Jain et al. 1997). However, splenic metastasis is sometimes synchronously associated with other metastases of HCC in abdominal or extraabdominal organs, small intestine, lungs, or adrenals (Yamamoto et al. 1986; Katoh et al. 1994; Hanada et al. 2004; Hayashi et al. 2006; Nakamura et al. 2006; Iwaki et al. 2008). Splenic metastases of HCC can cause spontaneous splenic rupture

(Horie et al. 1982) or associated with metachronous rupture of the splenic metastasis and the hepatic primary tumor (Sumiya et al. 2007) and may produce very large tumor masses (Fujimoto et al. 1990).

Overall, hematogenous metastasis of HCC to spleen is rare, with a reported incidence of 0.7–0.8 % in HCC patients.

Selected References Senenko and Glutbarg 1966; Fujimoto et al. 1990, 1992; Imada et al. 1991; Nakamuta et al. 1992; Filik et al. 2003; Yan et al. 2009; Duggal et al. 2010; Yu et al. 2011; Liu et al. 2013b.

Oropharyngeal Region

HCC is known to metastasize to the gingiva and oral mucosa, sometimes with formation of multiple metastatic nodules (Lund et al. 1970; Marker and Clausen 1991; Llanes et al. 1996; Maiorano et al. 2000; Shen et al. 2009; Terada 2011), and gingival metastasis may be the first manifestation of this malignancy (Terada 2011). However, oral cavity metastasis of HCC is less common than the three most frequent cancers metastasizing to this compartment, namely, lung carcinoma, breast carcinoma, and renal cell carcinoma. Clinically, gingival HCC metastases may present as hyperemic nodules morphologically resembling pyogenic granuloma (Ramon Ramirez et al. 2003).

Salivary Glands

Metastatic involvement of the parotid gland is uncommon, but nevertheless comprises up to 8 % of all parotid gland malignancies (Markowski et al. 2005; Nuyens et al. 2006), including very few instances of metastasis of HCC (Vitale et al. 2009; Yu et al. 2013). HCC metastatic to the parotid gland was diagnosed by the use of fine-needle aspiration biopsy (Dargent et al. 1998; Romanas et al. 2004). Due to the typical granularity of cytoplasm, metastatic HCC of the parotid gland was misinterpreted as salivary gland acinic cell carcinoma in a needle core biopsy, corrected after Hep Par1 immunostaining (Moore et al. 2010).

Renal Metastasis

HCC is well known to metastasize to the kidneys, although HCC metastatic to the kidneys is a rather rare event. In most cases reported so far, the primary liver tumor and renal metastasis were synchronous (Hsu et al. 1994; Fukushima et al. 1996; Mezawa et al. 2001; Sanz Mayayo et al. 2003; D'Antonio et al. 2010). In case of metastatic clear cell HCC, distinction from renal cell carcinoma of the clear cell (hypernephroid) type may be difficult, and metastatic HCC may mimic renal oncocytoma, but metastatic HCC lacks the typical nesting pattern of oncocytoma (D'Antonio et al. 2010). Renal metastasis of HCC may undergo spontaneous rupture (Mezawa et al. 2001), resembling the common hemorrhagic feature of renal cell carcinoma.

Gonadal Metastasis

The first case of ovarian metastasis of HCC was published in 1983 (Oortman and Elliott 1983). Since, several studies documented HCC metastases to the ovaries (Young et al. 1992; Khunamompong et al. 1999; de Groot et al. 2000; Kim et al. 2004; Kim 2005; McCluggage and Wilkinson 2005; Lee et al. 2011b). In a review of eleven cases published until 2011, the mean age at diagnosis was 45.6 years, and 3/11 patients showed bilateral ovarian metastases (Lee et al. 2011). The metastases can form large cystic masses, associated with a progressive elevation of serum AFP levels (Lee et al. 2011), or sometimes present as a large solitary mass (de Groot et al. 2000). As peritoneal seeding is usually absent, hematogenous spread has been

considered (Lee et al. 2011). HCC metastatic to the liver has to be distinguished from primary hepatoid carcinoma of the ovary (Lazaro et al. 2007; Pandey and Truica 2011). The ovary is a typical site for hepatoid carcinoma, and this neoplasm and HCC are difficult to distinguish, as both lesions share a common histology, and both are positive for AFP and Hep Par1. Hepatoid yolk sac tumor of the ovary may also be confounded with HCC metastasis. In cases of doubt, the presence of bile in or between tumor cells is a strong argument for HCC. In contrast to the ovary, HCC metastasis to the testis is an exceptional finding (Wang and Yang 2006).

Other and Rare Metastatic Sites

HCC metastases have been reported for the skin, orbit, heart, nasal cavity, external auditory canal, breast, and skeletal muscle (Nappi et al. 1992; Kim et al. 2000a; Royer et al. 2008; Terada and Sugiura 2010). Cutaneous metastasis may be the first and precocious manifestation of HCC (Royer et al. 2008).

Tumor Cell Seeding Following Percutaneous Approaches

Tumor seeding of HCC (implantation metastases following iatrogenic displacement of malignant cells, needle tract seeding, needle tract implantation) along the needle tract after percutaneous diagnostic core biopsies and fine-needle aspiration biopsies is a well-known complication that has been reported numerous times. Needle tract seeding is a severe or even catastrophic complication, in particular in patients that are transplantation candidates.

Selected References Sakurai et al. 1983; Smith 1991; Huang et al. 1996; Chapoutot et al. 1999; Kim et al. 2000b; Pelloni and Gertsch 2000; Takamori et al. 2000; Durand et al. 2001; Llovet et al. 2001; Chhieng 2004; Kosugi et al. 2004; Chang et al. 2005, 2008; Liu et al. 2007; Pavan et al. 2007; Perkins 2007; Rowe et al. 2007; Tung et al. 2007; Qua et al. 2008; Cabibbo and Craxi 2009; Silva et al. 2008; Robertson and Baxter 2011.

Needle tract seeding has an estimated frequency ranging from 0.6 % to 5.1 % of cases. However, in many reports, the incidence was lower than 3 %. In a literature review, it turned out that the incidence is 2.7 % overall or 0.9 % per year (Silva et al. 2008). In a large series of sonographically guided percutaneous biopsy of HCC, the overall frequency of needle tract implantation was 0.76 % (Chang et al. 2005). Implants following needle biopsy develop with sometimes considerable delay, with a reported range of 1 month to up to 72 months (Pelloni and Gertsch 2000; Liu et al. 2007). The implants usually appear as one or few, seldom numerous, round- to oval-shaped or lobular-enhancing nodules with a well-circumscribed margin along the needle tract on CT images, ranging from cutis or subcutis to intercostal and abdominal muscles to the subserosal space (review: Chang et al. 2008). There is evidence that biopsy using a coaxial cutting needle technique markedly reduces the risk of seeding, as the use of a needle introducer that remains in position during multiple passes protects normal tissue along the tract (Maturen et al. 2006).

Needle tract seeding also occurs in percutaneous ethanol injection, but is a rare complication in this procedure (Cedrone et al. 1992; Goletti et al. 1992; Yano et al. 2001; Arrivé et al. 2002; Kosugi et al. 2004; Almeida et al. 2008). Percutaneous radiofrequency ablation (PRFA) is a well-established alternative to percutaneous ethanol injection for single nonsurgical HCC. This procedure can be followed, similar to other percutaneous techniques, by HCC seeding (Llovet et al. 2001; Shirato et al. 2002; Espinoza et al. 2005; Jaskolka et al. 2005). Among 32 PRFA patients followed up in one study, 12.5 % showed biopsy-proven needle tract seeding detected between 4 and 18 months. Neoplastic seeding was related to subcapsular tumor location, poor differentiation, and baseline AFP levels (Llovet et al. 2001). In a review of

200 patients, 4 % were identified with needle tract seeding, based on imaging findings or surgical reintervention (Jaskolka et al. 2005).

Metastasis of HCC into Other Tumors and Metastasis of Other Tumors into HCC

In rare situations, and similar to other malignancies, HCC metastasizes into other neoplasms, e.g., medullary carcinoma of the thyroid (Sung et al. 2011). Exceptionally, extrahepatic cancers metastasized to primary HCC, e.g., esophageal carcinoma (Doihara et al. 1989), colorectal cancer (Maruyama et al. 1990), and Hodgkin's lymphoma (Utsunomiya et al. 2009).

Growth of Hepatocellular Carcinoma in the Regenerating Liver

The question as to whether growth and recurrence of HCC following resection is influenced by the regenerative status of the hepatocyte population is an important issue, as it may be anticipated that signaling pathways regulating hepatocyte regenerating might also favor the growth of surviving tumor cells. In a rat model of HCC, whereby hepatoma cells were implanted into livers following various degrees of partial hepatectomy, liver regeneration significantly facilitated the growth of microscopic HCC. The largest liver resections were also associated with HCC spread to the lungs (Shi et al. 2011).

References

Abe T, Furuse J, Yoshino M, Kinoshita T, Konishi M, Inoue K, Hasebe T (2002) Clinical characteristics of hepatocellular carcinoma with an extensive lymph node metastasis at diagnosis. Am J Clin Oncol 25:318–323

Achen MG, Stacker SA (2008) Molecular control of lymphatic metastasis. Ann N Y Acad Sci 1131:225–234

Alison MR, Leiman G, Kew MC (2000) Metastasis in an axillary lymph node in hepatocellular carcinoma: a case report. World J Gastroenterol 6:770–772

Almeida J, Mesquita M, Ferraz J, Yamanaka A, Escanhoela C, Boin IF, Pereira G et al (2008) Hepatocellular carcinoma developing at the puncture site after percutaneous ethanol injection. J Clin Ultrasound 36:105–107

Anthony PP (1973) Primary carcinoma of the liver: a study of 282 cases in Ugandan Africans. J Pathol 110:37–48

Arakai T, Hihara T, Karikomi M, Kachi K, Uchiyama G (1988) Hepatocellular carcinoma: metastatic abdominal lymph nodes identified by computed tomography. Gastrointest Radiol 13:247–252

Arakawa M, Kage M, Matsumoto S, Akagi Y, Noda T, Fukuda K, Nakashima T, Okuda K (1986) Frequency and significance of tumor thrombi in esophageal varices in hepatocellular carcinoma associated with cirrhosis. Hepatology 6:419–422

Arrivé L, Vurgait A, Monnier-Cholley L, Lewin M, Balladur P, Poupon R, Tubiana JM (2002) Long-term follow-up after neoplastic seeding complicating percutaneous ethanol injection for treatment of hepatocellular carcinoma. Eur Radiol 12:74–76

Awazu M, Fukumoto T, Takebe A, Ajiki T, Matsumoto I, Kido M, Tanaka M, Kuramitsu K, Ku Y (2013) Lymphadenectomy combined with locoregional treatment for multiple advanced hepatocellular carcinoma with lymph node metastases. Kobe J Med Sci 59: E17–E27

Ayan AK, Seven B, Orsal E, Demirci E (2013) Evaluation of bone metastasis as the first presentation of hepatocellular carcinoma using 18-fluorodeoxyglucose positron emission tomography-computed tomography. Indian J Nucl Med 28:171–172

Barbero C, Salizzoni S, Centofanti P, Molino F, Campisi P, Giorgi M, Rinadli M (2012) Right sided heart mass reveals hepatocellular carcinoma. Heart Lung Circ 21:817–818

Berman C (1958) Primary carcinoma of the liver. Adv Cancer Res 5:56–96

Berman C (1959) Primary carcinoma of the liver. Bull N Y Acad Med 35:275–292

Blandino A, Certo A, Versace P, Lamberto S, Crino M, Federle F, Pandolfo I (1997) Omental seeding of hepatocarcinoma: report of a case (in Italian). Radiol Med 93:468–470

Blanloeil Y, Paineau J, Vissett J, Dixneuf B (1983) Intraoperative pulmonary tumor embolism after hepatectomy for liver carcinoma. Can Anaesth Soc J 30:69–71

Bolker H, Jacobi M, Koven MT (1937) Primary carcinoma of the liver with bone metastasis. Ann Intern Med 10:1212–1221

Brisbane JU, Howell DA, Bonkowsky HL (1980) Pulmonary hypertension as a presentation of hepatocarcinoma. Report of a case and brief review of the literature. Am J Med 68:466–469

Cabibbo G, Craxi A (2009) Needle track seeding following percutaneous procedures for hepatocellular carcinoma. World J Hepatol 31:62–66

Cai L, Zhang Z, Zhou L, Wang H, Fu J, Zhang S, Shi M, Zhang H, Yang Y, Yang Y et al (2008) Functional impairment in circulating and intrahepatic NK cells and relative mechanism in hepatocellular carcinoma patients. Clin Immunol 129:428–437

Castro Fernandez M, Herrera Justiniano JM, Sayago Mota M, Aguilar Reine J (1985) Peritoneal metastasis of hepatocarcinoma. Report of 11 cases with laparoscopic diagnosis (in Spanish). Rev Esp Enferm Apar Dig 68:497–501

Cedrone A, Rapaccini GL, Pompili M, Grattagliano A, Aliotta A, Trombino C (1992) Neoplastic seeding complicating percutaneous ethanol injection for treatment of hepatocellular carcinoma. Radiology 183:787–788

Chan GS, Ng WK, Ng IO, Dickens P (2000) Sudden death from massive pulmonary tumor embolism due to hepatocellular carcinoma. Forensic Sci Int 108:215–221

Chang S, Kim SH, Lim HK, Lee WJ, Choi D, Lim JH (2005) Needle tract implantation after sonographically guided percutaneous biopsy of hepatocellular carcinoma: evaluation of doubling time, frequency, and features on CT. AJR Am J Roentgenol 185:400–405

Chang S, Kim SH, Lim HK, Kim SH, Lee WJ, Choi D, Lim YS, Rhim H (2008) Needle tract implantation after percutaneous interventional procedures in hepatocellular carcinomas: lessons learned from a 10-year experience. Korean J Radiol 9:268–274

Chapoutot C, Perney P, Fabre D, Taourel P, Bruel JM, Larrey D, Domergue J, Ciurana AJ et al (1999) Needle-tract seeding after ultrasound-guided puncture of hepatocellular carcinoma. A study of 150 patients (in French). Gastroenterol Clin Biol 23:552–556

Chen LT, Chen CY, Jan CM, Wang WM, Lan TS, Hsieh MY, Liu GC (1990) Gastrointestinal tract involvement in hepatocellular carcinoma: clinical, radiological and endoscopic studies. Endoscopy 22:118–123

Chen CY, Lu CL, Pan CC, Chiang JH, Chang FY, Lee SD (1997) Lower gastrointestinal bleeding from a hepatocellular carcinoma invading the colon. J Clin Gastroenterol 25:373–375

Chen J, Zhao J, Ma R, Lin H, Liang X, Cai X (2014) Prognostic significance of e-cadherin expression in hepatocellular carcinoma: a meta-analysis. PLoS One 9, e103952

Chhieng DC (2004) Fine needle aspiration biopsy of liver – an update. World J Surg Oncol 2:5

Chiappini F (2012) Circulating tumor cells measurements in hepatocellular carcinoma. Int J Hepatol 2012:684802

Cho A, Ryu M, Yoshinaga Y, Ishikawa Y, Miyazawa Y, Okazumi S, Ochiai T (2003) Hepatocellular carcinoma with unusual metastasis to the esophagus. Hepatogastroenterology 50:1143–1145

Choi CS, Kim HC, Kim TH, Seo GS, Kim KH, Cho EY, Seo SO, Oh HJ, Choi SC (2008) Does the endoscopic finding of esophageal metastatic hepatocellular carcinoma progress from submucosal mass to polypoid shape? Gastrointest Endosc 68:155–159

Chua TC, Morris DL (2012) Exploring the role of resection of extrahepatic metastases from hepatocellular carcinoma. Surg Oncol 21:95–101

Ciriza C, Rivero MA, de la Serna JP, Fernandez MJ, Romero MJ, Diaz-Rubio M (1996) Hepatocellular carcinoma with metastasis to the pharyngeal lymph nodes. J Clin Gastroenterol 23:243–245

Close P, Uri AK (1989) Hepatocellular carcinoma with tumor thrombus in inferior vena cava. Med Pediatr Oncol 17:232–235

Cosenza CA, Sher LS, Poletti BJ, Tschirhart D, Noguchi H, Hoffman AL, Lopez RR et al (1999) Metastasis of hepatocellular carcinoma to the right colon manifested by gastrointestinal bleeding. Am Surg 65:218–221

Culpepper AL, von Haam E (1934) Primary carcinoma of the liver with extensive metastasis to the right heart, and tumor-thrombosis of the inferior vena cava. Cancer Res 21:355–362

D'Antonio A, Caleo A, Caleo O, Addesso M, Boscaino A (2010) Hepatocellular carcinoma metastatic to the kidney mimicking renal oncocytoma. Hepatobiliary Pancreat Dis Int 9:550–552

Dargent JL, Deplace J, Schneider E, Morales J, Kentos A, Willemart S, Roufosse C et al (1998) Hepatocellular carcinoma metastatic to the parotid gland: initial diagnosis by fine needle aspiration biopsy. Acta Cytol 42:824–826

de Groot ME, Dukel L, Chadha-Ajwani S, Metselaar HJ, Tilanus HW, Huikeshoven FJ (2000) Massive solitary metastasis of hepatocellular carcinoma in the ovary two years after liver transplantation. Eur J Obstet Gynecol Reprod Biol 90:109–111

Ding YP, Yang XD, Wu Y, Xing CG (2014) Autophagy promotes the survival and development of tumors by participating in the formation of vasculogenic mimicry. Oncol Rep 31:2321–2327

Doihara H, Takiyama W, Moriwaki S, Mandai K, Nakanishi Y, Takashima S (1989) An autopsied case of esophageal cancer metastasizing to primary hepatocellular carcinoma (in Japanese). Gan No Rinsho 35:516–522

Doyle L (1989) Gabriel Andral (1797–1876) and the first reports of lymphangitis carcinomatosa. J R Soc Med 82:491–493

Duggal R, Garg M, Kalra N, Srinivasan R, Chawla Y (2010) Spleen metastasis from hepatocellular carcinoma: report of a case with diagnosis by fine needle aspiration cytology. Acta Cytol 54(5 Suppl):783–786

Durand F, Regimbeau JM, Belghiti J, Sauvanet A, Vilgrain V, Terris B, Moutardier V et al (2001) Assessment of the benefits and risks of percutaneous biopsy before surgical resection of hepatocellular carcinoma. J Hepatol 35:254–258

Efremidis SC, Vougiouklis N, Zafiriadou E, Sofianou F, Sbarounis C, Fardellas Y, Patsiaura K et al (1999) Pathways of lymph node involvement in upper abdominal

malignancies: evaluation with high-resolution CT. Eur Radiol 9:868–874
Eguchi S, Takatsuki M, Hidaka M, Soyama A, Tomonaga T, Muraoka I, Kanematsu T (2010) Predictor of histological microvascular invasion of hepatocellular carcinoma: a lesson from 229 consecutive cases of curative liver resection. World J Surg 34:1034–1038
El-Domeiri AA, Huvos AG, Goldsmith HS, Foote FW (1971) Primary malignant tumors of the liver. Cancer 27:7–11
Ercolani G, Grazi GL, Ravaioli M, Grigioni WF, Cescon M, Gardini A, Del Gaudio M et al (2004) The role of lymphadenectomy for liver tumors: further considerations on the appropriateness of treatment strategy. Ann Surg 239:202–209
Esnaola NF, Lauwers GY, Mirza NQ, Nagorney DM, Doherty D, Ikai I, Yamaoka Y et al (2002) Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. J Gastrointest Surg 6:224–232
Espinoza S, Briggs P, Duret JS, Lapeyre M, de Bère T (2005) Radiofrequency ablation of needle tract seeding in hepatocellular carcinoma. J Vasc Interv Radiol 16:743–746
Filik L, Biyikoglu I, Akdogan M, Oguz D, Köklü S, Köksal AS (2003) Two cases with hepatocellular carcinoma and spleen metastasis. Turk J Gastroenterol 14:138–140
Fu J, Xu D, Liu Z, Shi M, Zhao P, Fu B, Zhang Z, Yang H, Zhang H, Zhou C, Yao J et al (2007) Increased regulatory T cells correlate with CD8 T-cell impairment and poor survival in hepatocellular carcinoma patients. Gastroenterology 132:2328–2339
Fujimoto H, Murakami K, Ozawa K, Iino M, Kimura M, Fukunaga T, Shinozaki M (1990) Huge splenic metastasis from hepatocellular carcinoma; a case report (in Japanese). Rinsho Hoshasen 35:1439–1442
Fujimoto H, Murakami K, Nosaka K, Arimizu N (1992) Splenic metastasis of hepatocellular carcinoma. Accumulation of Tc-99m HDP. Clin Nucl Med 17:99–100
Fukatsu H, Miura S, Kishida H, Takagi S, Morishita H, Uchino K, Fujisawa M (2012) Gastrointestinal: esophageal metastasis from hepatocellular carcinoma. J Gastroenterol Hepatol 27:1536
Fukui H, Kashiwagi T, Shirai Y, Matsuda Y, Kawata S, Nishimura T, Kozuka T (1993) Metastasis of hepatocellular carcinoma to the colon demonstrated by Tc-99m PMT scintigraphy. Clin Nucl Med 18:512–515
Fukushima M, Isoyama E, Sakaridani N, Sanematsu H, Kadowaki H, Hirakawa S et al (1996) Renal metastasis originating from liver cancer. Nippon Hinyokika Gakkai Zasshi 87:710–713
Fukutomi M, Yokota M, Chuman H, Harada H, Zaitsu Y, Funakosh et al (2001) Increased incidence of bone metastasis in hepatocellular carcinoma. Eur J Gastroenterol Hepatol 13:1083–1088
Goletti O, De Negri F, Pucciarelli M, Sidoti F, Bertolucci A, Chiarugi M, Seccia M (1992) Subcutaneous seeding after percutaneous ethanol injection of liver metastasis. Radiology 183:785–786
Gregory R (1939) Primary carcinoma of the liver tumor thrombosis of the inferior vena cava and right auricle. Arch Intern Med (Chic) 64:566–578
Guo J, Yao F, Lou Y, Xu C, Xiao B, Zhou W, Chen J, Hu Y, Liu Z (2007) Detecting carcinoma cells in peripheral blood of patients with hepatocellular carcinoma by immunomagnetic beads and rt-PCR. J Clin Gastroenterol 41:783–788
Gutiérrez-Macias A, Barandiaran KE, Ercoreca FJ, De Zarate MM (2002) Acute cor pulmonale due to microscopic tumour embolism as the first manifestation of hepatocellular carcinoma. Eur J Gastroenterol Hepatol 14:775–777
Hanada K, Saito A, Nozawa H, Haruyama K, Hayashi N, Yamada M, Katagiri S, Katsuragawa H et al (2004) Histopathologically-diagnosed splenic metastasis in a hepatocellular carcinoma case with adrenal metastasis. Intern Med 43:484–489
Harada M, Ueno T, Hirai K, Wada T, Abe M, Abe H, Tanikawa K, Nakashima O (1988) A case report of hepatocellular carcinoma with tumor thrombus in the pulmonary artery demonstrated by MRI (in Japanese). Rinsho Hoshasen 33:907–910
Hayashi H, Tanaka S, Shuto T, Tanaka H, Ichikawa T, Yamamoto T, Takemura S, Hirohashi K (2006) Splenic metastasis of hepatocellular carcinoma. Osaka City Med J 52:79–82
He J, Zeng ZC, Tang ZY, Fan J, Zhou J, Zeng MS, Wang JH, Sun J, Chen B, Yang P et al (2009) Clinical features and prognostic factors in patients with bone metastases from hepatocellular carcinoma receiving external beam radiotherapy. Cancer 115:2710–2720
He L, Zhang J, Jiang L, Jin C, Zhao Y, Yang G, Jia L (2010) Differential expression of Axl in hepatocellular carcinoma and correlation with tumor lymphatic metastasis. Mol Carcinog 49:882–891
Hedrick DW (1937) Primary carcinoma of the liver with metastasis to bone. J Bone Joint Surg Am 19:817–820
Hirashita T, Ohta M, Iwaki K, Kai S, Shibata K, Sasaki A, Nakashima K, Kitano S (2008) Direct invasion to the colon by hepatocellular carcinoma: report of two cases. World J Gastroenterol 14:4583–4585
Honday et al. (2015) http://www.ncbi.nlm.nih.gov/pubmed/25041322
Horie Y, Suou T, Hirayama C, Nagasako R (1982) Spontaneous rupture of the spleen secondary to metastatic hepatocellular carcinoma: a report of a case and review of the literature. Am J Gastroenterol 77:882–884
Hsu YB, Lee PH, Sheu JC, Chen DS, Hsu HC (1994) Hepatocellular carcinoma with metastasis to the kidney: report of a case. J Formos Med Assoc 93:71–74
Hu ML, Tai WC, Chuah SK, Chiu YC, Wu KL, Chou YP, Kuo CM, Hu TH, Chiu KW (2010) Gastric metastasis of hepatocellular carcinoma via a possible existing retrograde hematogenous pathway. J Gastroenterol Hepatol 25:408–412
Huang GT, Sheu JC, Yang PM, Lee HS, Wang TH, Chen DS (1996) Ultrasound-guided cutting biopsy for the

diagnosis of hepatocellular carcinoma – a study based on 420 patients. J Hepatol 25:334–338
Humbert P, Sarmiento J, Boix J, Planas R, Quintero E, Franquet T, Villagrasa M (1987) Hepatocellular carcinoma presenting with bleeding due to duodenal perforation by the tumor. Endoscopy 19:37–38
Hung HC, Huang YS, Lin CC, Chao Y, Chi KH, Yen SH, Chang FY (1998) Radiotherapy in the treatment of duodenal bleeding due to hepatocellular carcinoma invasion. J Gastroenterol Hepatol 13:1143–1145
Hung MC, Wu HS, Lee YT, Hsu CH, Chou DA, Huang MH (2008) Intraperitoneal metastasis of hepatocellular carcinoma after spontaneous rupture: a case report. World J Gastroenterol 14:3927–3931
Hussein YM, Ghareib AF, Mohamed RH, Radwan MI, Elsawy WH (2012) MAGE-3 and MAGE-4 genes as possible markers for early detection of metastases in hepatitis C virus Egyptian patients complicated by hepatocellular carcinoma. Med Oncol 29:994–999
Hwang YY, Chan P, Law IC, Khin AT, Yau T (2008) Massive rectal bleeding in a patient with a history of hepatocellular carcinoma. Gut 57:1412
Iguchi H, Yokota M, Fukutomi M, Uchimura K, Yonemasu H, Hachitanda Y, Nakao Y et al (2002) A possible role of VEGF in osteolytic bone metastasis of hepatocellular carcinoma. J Exp Clin Cancer Res 21:309–313
Imada H, Nakata H, Horie A (1991) Radiological diagnosis of splenic metastasis and its prevalence at autopsy (in Japanese). Nippon Igaku Hoshasen Gakkai Zasshi 51:498–503
Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y et al (2003) Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 38:200–207
Ishikawa T, Yamasaki T, Isobe Y, Sakaida I, Kurokawa F, Okita K, Kimura T (2005) Rupture of peritoneal metastatic tumor that developed due to needle-tract implantation of hepatocellular carcinoma. J Gastroenterol 40:547–548
Iwaki K, Ohta M, Ishio T, Kai S, Iwashita Y, Shibata K, Himeno K, Seike M, Fujioka T et al (2008) Metastasis of hepatocellular carcinoma to spleen and small intestine. J Hepatobiliary Pancreat Surg 15:213–219
Iwamoto S, Okuda K, Takeda N, Sonoda K, Sanefuji H (1997) Case report: right-sided periadrenal metastasis supplied by the hepatic artery. Clue to the genesis of pedunculated hepatocellular carcinoma. J Gastroenterol Hepatol 12:392–397
Jain AK, Kumar N, Misra A, Puri SK, Malhotra V (1997) Asymptomatic hepatocellular carcinoma with splenic metastasis – a case report. Trop Gastroenterol 18:72–73
Jäkel J, Ramaswamy A, Köhler U, Barth PJ (2006) Massive pulmonary tumor microembolism from a hepatocellular carcinoma. Pathol Res Pract 202:395–399
Jaskolka JD, Asch MR, Kachura JR, Ho CS, Ossip M, Wong F, Sherman M, Grant DR et al (2005) Needle tract seeding after radiofrequency ablation of hepatic tumors. J Vasc Interv Radiol 16:485–491
Johnston EH (1959) Liver embolism to the lung as a complication of trauma. US Armed Forces Med J 10:1143–1151
Kaczynski J, Hansson G, Wallerstedt S (1995) Metastases in cases with hepatocellular carcinoma in relation to clinicopathologic features of the tumor. An autopsy study from a low endemic area. Acta Oncol 34:43–48
Kaibori M, Morita M, Tagami S, Uchida Y, Tanaka H, Yoshioka K, Takahashi Y, Sakaida N et al (2007) Cutaneous and colonic metastases after resection of hepatocellular carcinoma. Dig Dis Sci 52:1114–1117
Kanda M, Tateishi R, Yoshida H, Sato T, Masuzaki R, Ohki T, Imamura J, Goto T, Yoshida H et al (2008) Extrahepatic metastasis of hepatocellular carcinoma incidence and risk factors. Liver Int 28:1256–1263
Kanzaki R, Yamada T, Gotoh K, Takahashi H, Murata M, Tomita Y, Yano M, Ohigashi H et al (2011) Surgical resection for hepatocellular carcinoma with metastasis to the gallbladder: report of a case. Surg Today 41:285–291
Katoh M, Takeuchi K, Murashima N, Nakajima M, Yamaguchi H, Endo Y, Hara M (1994) Hepatocellular carcinoma with splenic metastasis developing after 16 years of chemotherapy for chronic myelogenous leukemia: a case report. Jpn J Clin Oncol 24:111–115
Katyal S, Oliver JH, Peterson MS, Ferris JV, Carr BS, Baron RL (2000) Extrahepatic metastases of hepatocellular carcinoma. Radiology 216:698–703
Kaufmann E (1922) Lehrbuch der speziellen pathologischen Anatomie, vol 1, 7th edn. Walter de Gruyter, Berlin, p 755
Khunamompong S, Siriaunkgul S, Chunduan A (1999) Metastatic hepatocellular carcinoma of the ovary. Int J Gynecol Obstet 64:189–191
Kim MJ (2005) A case of metastatic hepatocellular carcinoma of the ovary: an immunohistochemical study and literature review. Korean J Pathol 39:287–290
Kim PN, Kim IY, Lee KS (1994) Intraperitoneal seeding from hepatoma. Abdom Imaging 19:309–312
Kim TK, Han JK, Chung JW, Choi BI, Park JH, Han MC (1996) Intraperitoneal drop metastases from hepatocellular carcinoma: CT and angiographic findings. J Comput Assist Tomogr 20:638–642
Kim SR et al. (1998) http://www.ncbi.nlm.nih.gov/pubmed/9794186
Kim IT, Na SC, Jung BY (2000a) Hepatocellular carcinoma metastatic to the orbit. Korean J Ophthalmol 14:97–102
Kim SH, Lim HK, Lee WJ, Cho JM, Jang HJ (2000b) Needle-tract implantation in hepatocellular carcinoma: frequency and CT findings after biopsy with a 19.5-gauge automated biopsy gun. Abdom Imaging 25:246–250
Kim TH, Cheung DY, Chung WB, Son DK, Jo DH, Chung JS, Kim HK, Kim JK et al (2004) A case of metastatic hepatocellular carcinoma of the ovary (in Korean). Korean J Gastroenterol 43:215–218

Kim HS, Shin JW, Kim GY, Kim YM, Cha HJ, Jeong YK, Jeong ID, Bang SJ et al (2006) Metastasis of hepatocellular carcinoma to the small bowel manifested by intussusception. World J Gastroenterol 12:1969–1971

Kim S, Chun M, Wang H, Cho S, Oh YT, Kang SH, Yang J (2007) Bone metastasis from primary hepatocellular carcinoma: characteristics of soft tissue formation. Cancer Res 39:104–108

Kim BK, Han KH, Park YN, Park MS, Kim KS, Choi JS, Moon BS, Chon CY, Moon YM et al (2008) Prediction of microvascular invasion before curative resection of hepatocellular carcinoma. J Surg Oncol 97:246–252, 57, 121–126

Kim T, Veronese A, Pichiorri F, Lee TJ, Jeon YJ, Volinia S, Pineau P, Palatini J, Suh SS et al (2011) p53 regulates epithelial-mesenchymal transition through microRNAs targeting ZEB1 and ZEB2. J Exp Med 208:875–883

Kimura K, Miura H, Saito S, Suzaki A, Kondo K, Hamada T, Kitamura S, Yamada H (2008) Hepatocellular carcinoma with direct invasion to the stomach causing gastrointestinal hemorrhage. Intern Med 47:671–674

Kirschmann DA, Seftor EA, Hardy KM, Seftor RE, Hendrix MJ (2012) Molecular pathways: vasculogenic mimicry in tumor cells: diagnostic and therapeutic implications. Clin Cancer Res 18:2726–2732

Kitagawa Y, Tajika T, Kameoka N, Kanda Y, Watanabe T, Miura A, Teramoto T, Masai O et al (1996) Adrenal metastasis from hepatocellular carcinoma – report of a case. Hepatogastroenterology 11:1383–1386

Kobayashi S, Kim SR, Imoto S, Ando K, Hirakawa M, Saito J, Fukuda K, Otono Y et al (2012a) Histopathological diagnosis of early HCC through biopsy: efficacy of Victoria blue and cytokeratin 7 staining. Dig Dis 30:574–579

Kobayashi K, Himoto T, Tani J, Miyoshi H, Yoneyama H, Deguchi A, Kurokohchi K et al (2012b) A rare case of hepatocellular carcinoma accompanied by metastasis of a cervical lymph node. Intern Med 51:381–385

Kojiro M, Nakahara H, Sugihara S, Murakami T, Nakashima T, Kawasaki H (1984) Hepatocellular carcinoma with intra-atrial tumor growth. A clinicopathologic study of 18 autopsy cases. Arch Pathol Lab Med 108:989–992

Kondo Y, Wada K (1991) Intrahepatic metastasis of hepatocellular carcinoma a histopathologic study. Hum Pathol 22:125–130

Kondo F, Kondo Y, Nagato Y, Tomizawa M, Wada K (1994) Interstitial tumour cell invasion in small hepatocellular carcinoma. Evaluation in microscopic and low magnification views. J Gastroenterol Hepatol 9:604–612

Kosaka A, Hayakawa H, Kusagawa M, Takahashi H, Okamura K, Mizumoto R, Katsuta K (1999) Successful surgical treatment for implanted intraperitoneal metastases of ruptured small hepatocellular carcinoma report of case. Surg Today 29:453–457

Kosugi C, Furuse J, Ishii H, Maru Y, Yoshino M, Kinoshita T, Konishi M, Nakagohri T et al (2004) Needle tract implantation of hepatocellular carcinoma and pancreatic carcinoma after ultrasound-guided percutaneous puncture: clinical and pathologic characteristics and the treatment of needle tract implantation. World J Surg 28:29–32

Kume K, Murata I, Yoshikawa I, Kanagawa K, Otsuki M (2000) Polypoid metastatic hepatocellular of the esophagus occurring after endoscopic variceal band ligation. Endoscopy 32:419–421

Kunizaki M, Hidaka S, Isomoto H, Takeshita H, Nanashima A, Sawai T, Yasutake T et al (2012) Diagnosis of small-bowel metastasis of hepatocellular carcinoma by double-balloon enteroscopy. Int J Surg Case Rep 3:263–265

Kurachi K, Suzuki S, Yokoi Y, Okumura T, Inaba K, Igarashi T, Takehara Y, Konno H et al (2002) A 5-year survivor after resection of peritoneal metastases from pedunculated-type hepatocellular carcinoma. J Gastroenterol 37:571–574

Kurl S, Farin P, Rytkonen H, Soimakallio S (1997) Intraperitoneal seeding from hepatocellular carcinoma following percutaneous ethanol ablation therapy. Abdom Imaging 22:261–263

Kuromatsu R, Hirai K, Maijima Y, Fujimoto T, Shimauchi Y, Tsukiyama Y, Aoki E, Saitsu H et al (1993) A patient with hepatocellular carcinoma who underwent resection of the primary lesion 10 years ago and resection of a giant adrenal metastasis 8 and a half years later. Gatsroenterol Jpn 28:312–316

Kwak MS, Lee JH, Yoon JH, Yu SJ, Cho EJ, Jang ES, Kim YJ, Lee HS (2012) Risk factors, clinical features, and prognosis of the hepatocellular carcinoma with peritoneal metastasis. Dig Dis Sci 57:813–819

Kwok PC, Lam TW, Lam CL, Lai AK, Lo HY, Chan SC (2003) Rare pulmonary complications after transarterial chemoembolization for hepatocellular carcinoma: two case reports. Hong Kong Med J 9:457–460

Lau KK, Wong KW, Ho WC, Lai TS, Lee KC, Leung TW (2000) Hepatocellular carcinoma presenting with right supraclavicular lymph node metastasis and superior mediastinal syndrome. Liver 20:184–185

Lazaro J, Rubio D, Repolles M, Capote L (2007) Hepatoid carcinoma of the ovary and management. Acta Obstet Gynecol Scand 86:498–499

Lee YT, Geer DA (1987) Primary liver cancer pattern of metastasis. J Surg Oncol 36:26–31

Lee TK, Poon RT, Yuen AP, Ling MT, Kwok WK, Wang XH, Wong YC, Guan XY et al (2006) Twist overexpression correlates with hepatocellular carcinoma metastasis through induction of epithelial-mesenchymal transition. Clin Cancer Res 12:5369–5376

Lee CF, Ling ZQ, Zhao T, Fang SH, Chang WC, Lee SC, Lee KR (2009) Genomic-wide analysis of lymphatic metastasis-associated genes in human hepatocellular carcinoma. World J Gastroenterol 15:356–365

Lee CW, Chan KM, Lee CF, Yu MC, Lee WC, Wu TJ, Chen MF (2011a) Hepatic resection for hepatocellular

carcinoma with lymph node metastasis: clinicopathological analysis and survival outcome. Asian J Surg 34:53–62

Lee JM, Park KM, Lee SY, Choi J, Hwang DW, Lee YJ (2011b) Metastasis of hepatocellular carcinoma to the ovary: a case report and review of the literature. Gut Liver 5:543–547

Li CD, Kakizoe T, Tobisu K, Tanaka Y, Mizutani T, Makuuchi M, Ohkura H, Teshima S (1990) Solitary adrenal metastasis from hepatocellular carcinoma a case report of simultaneous successful resections. Jpn J Clin Oncol 20:420–425

Li YM et al. (2013) http://www.ncbi.nlm.nih.gov/pubmed/24091674

Liang JD, Chen CH, Hsu SJ, Sheu JC, Yang PM, Lee HS, Lee CZ, Huang GT (2012) Hepatocellular carcinoma with duodenal invasion and metastasis. J Gastroenterol Hepatol 27:677–683

Lin CP, Cheng JS, Lai KH, Lo GH, Hsu PI, Chan HH, Hsu JH, Wang YY, Pan HB et al (2000) Gastrointestinal metastasis in hepatocellular carcinoma: radiological and endoscopic studies of 11 cases. J Gastroenterol Hepatol 15:536–541

Lin CC, Chen CH, Tsang YM, Jan IS, Sheu JC (2006) Diffuse intraperitoneal metastasis after spontaneous rupture of hepatocellular carcinoma. J Formos Med Assoc 105:577–582

Lin CC, Liang HP, Lee HS, Huang GT, Yang PM, Ho MC, Lee PH, Tsang YM et al (2009) Clinical manifestations and survival of hepatocellular carcinoma patients with peritoneal metastasis. J Gastroenterol Hepatol 24:815–820

Lin ZH, Wang L, Zhang JB, Liu Y, Li XQ, Guo L, Zhang B, Zhu WW, Ye QH (2014) MST4 promotes hepatocellular carcinoma epithelial-mesenchymal transition and metastasis via activation of the p-ERK pathway. Int J Oncol 45:629–640

Linder GT, Crook JN, Cohn I (1974) Primary liver carcinoma. Cancer 33:1614–1629

Liu YW, Chen CL, Chen YS, Wang CC, Wang SH, Lin CC (2007) Needle tract implantation of hepatocellular carcinoma after fine needle biopsy. Dig Dis Sci 52:228–231

Liu W, Xu G, Ma J, Jia W, Li J, Chen K, Wang W, Hao C, Wang Y, Wang X (2011) Osteopontin as a key mediator for vasculogenic mimicry in hepatocellular carcinoma. Tohoku J Exp Med 224:29–39

Liu S, Guo W, Shi J, Li N, Yu X, Xue J, Fu X, Chu K, Lu C, Zhao J, Xie D, Wu M et al (2012) MicroRNA-135a contributes to the development of portal vein tumor thrombus by promoting metastasis in hepatocellular carcinoma. J Hepatol 56:389–396

Liu J, Ruan B, You N, Huang Q, Liu W, Dang Z, Xu W, Zhou T, Ji R, Cao Y, Li X et al (2013a) Downregulation of miR-200a induces EMT phenotypes and CSC-like signatures through targeting the β-catenin pathway in hepatic oval cells. PLoS One 8, e79409

Liu Q, Song Y, Zhou N, Xu X, Wang Z (2013b) Radiofrequency ablation of splenic tumors: a case series. J Gastrointest Liver Dis 22:105–108

Liu S, Li N, Xiao X, Cheng K, Hu J, Wang J, Zhang D, Cheng S, Liu S (2013c) Expression of intercellular adhesion molecule 1 by hepatocellular carcinoma stem cells and circulating tumor cells. Gastroenterology 144:1031–1041

Llanes F, Sanz-Ortega J, Suarez B, Sanz-Esponera J (1996) Hepatocellular carcinoma diagnosed following metastasis to the oral cavity report of 2 cases. J Periodontol 67:717–719

Llovet JM, Bru C, Bruix J (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19:329–338

Llovet JM, Vilana R, Bru C, Bianchi L, Salmeron JM, Boix L, Ganau S, Pagès M et al (2001) Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. Hepatology 33:1124–1129

Longo V, Brunetti O, D'Oronzo S, Ostuni C, Gatti P, Silvestris F (2014) Bone metastases in hepatocellular carcinoma: an emerging issue. Cancer Metastasis Rev 33:333–342

Lund BA, Soule EH, Moertel CG (1970) Hepatocellular carcinoma with metastases to gingival mucosa report of a case. J Oral Surg 28:604–607

Ma JL, Han SX, Zhu Q, Zhang D, Wang L, Lv Y (2011) Role of Twist in vasculogenic mimicry formation in hypoxic hepatocellular carcinoma cells in vitro. Biochem Biophys Res Commun 408:686–691

Ma X, Li H, Zhang X, Huang Q, Wang B, Shi T, Hu D, Ai Q, Liu S, Gao J, Yang Y et al (2013) Modified anatomical retroperitoneoscopic adrenalectomy for adrenal metastatic tumor: technique and survival analysis. Surg Endosc 27:992–999

Main BJ, Brown TC, Jones PG (1984) Intraoperative pulmonary tumour embolism during hepatectomy. Can Anaesth Soc J 31:117

Maiorano E, Piattelli A, Favia G (2000) Hepatocellular carcinoma metastatic to the oral mucosa: report of a case with multiple gingival localizations. J Periodontal 71:641–645

Marker P, Clausen PP (1991) Metastasis to the mouth and jaw from hepatocellular carcinoma: a case report. Int J Oral Maxillofac Surg 20:371–374

Markowski J, Gierek T, Zielinska-Pajak E, Witkowska M, Wodolazski A, Pajak J et al (2005) Distant metastases to the parotid gland – review of the literature and report of own two cases. Otolaryngol Pol 59:547–552

Maruyama C, Tamaoka Y, Matsuno H, Konishi F (1990) A case of Bormann type 4 colon cancer with a metastasis into hepatoma (in Japanese). Gan No Rinsho 36:1047–1052

Maruyama A, Murabayashi K, Hayashi M, Nakano H, Isaji S, Uehara S, Kusuda T et al (1999) Hepatocellular carcinoma complicated by gastrointestinal hemorrhage caused by direct tumor invasion of stomach. J Hepatobiliary Pancreat Surg 6:90–93

Matsukuma S, Sato K (2011) Peritoneal seeding of hepatocellular carcinoma: clinicopathological characteristics of 17 autopsy cases. Pathol Int 61:356–362

Maturen KE, Nghiem HV, Marrero JA, Hussain HK, Higgins EG, Fox GA, Francis IR (2006) Lack of tumor seeding of hepatocellular carcinoma after percutaneous needle biopsy using coaxial cutting needle technique. AJR Am J Roentgenol 187:1184–1187

McCluggage WG, Wilkinson N (2005) Metastatic neoplasms involving the ovary: a review with an emphasis on morphological and immunohistochemical features. Histopathology 47:231–247

Mezawa S, Homma H, Doi T, Takada K, Kukitsu T, Kinebuchi M et al (2001) Spontaneous rupture of renal metastasis of hepatocellular carcinoma: management by emergency transcatheter arterial embolization. Cardiovasc Intervent Radiol 24:143–144

Miki K, Makuuchi M, Takayama T, Matsukura A, Minagawa M, Kubota K, Hirata M (2000) Peritoneal seeding of hepatocellular carcinoma after ethanol injection therapy. Hepatogastroenterology 47:1428–1430

Miyake Y, Iwasaki Y, Shiraha H, Sakaguchi K, Shiratori Y (2007) Peritoneal dissemination of hepatocellular carcinoma treated with a combination therapy of interferon-alpha-2b and oral tegafur/uracil. Intern Med 46:565–569

Molina DK, Valente PT (2003) Lymphangitic spread of hepatocellular carcinoma. Arch Pathol Lab Med 127: E11–E13

Mongroo PS, Rustgi AK (2010) The role of the miR-200 family in epithelial-mesenchymal transition. Cancer Biol Ther 10:219–222

Moon VH (1929) Primary carcinoma of liver with metastasis to bone. Arch Pathol 8:938–943

Moon WS, Chang K, Tarnawski AS (2004) Overexpression of metastatic tumor antigen 1 in hepatocellular carcinoma: relationship to vascular invasion and estrogen receptor-alpha. Hum Pathol 35:424–429

Moore FR, Bergman S, Geisinger KR (2010) Metastatic hepatocellular carcinoma mimicking acinic cell carcinoma of the parotid gland: a case report. Acta Cytol 54:889–892

Mundada OP, Aron M, Sivaramakrishna B, Gupta NP (2003) Bilateral adrenal metastases from a primary hepatocellular carcinoma. Int Urol Nephrol 35:303–305

Murakami M, Nagano H, Kobayashi S, Marubashi S, Noda T, Tomimaru T, Takeda Y et al (2008) A case of hepatocellular carcinoma with gall bladder metastasis (in Japanese). Gan To Kagaku Ryoho 35:2089–2091

Nagano Y, Shimada H, Takeda K, Ueda M, Matsuo K, Tanaka K, Endo I, Kunisaki C et al (2008) Predictive factors of microvascular invasion in patients with hepatocellular carcinoma larger than 5 cm. World J Surg 32:2218–2222

Nakamura K, Sato Y, Nakata H (1989) Computed tomography of adrenal metastases in hepatocellular carcinoma. Report of four cases. Acta Radiol 30(5):550–552

Nakamura M, Nagano H, Wada H, Noda T, Ota H, Damdinsuren B, Marubashi S, Miyamoto A et al (2006) A case of hepatocellular carcinoma with multiple lung, spleen, and remnant liver metastasis successfully treated by combination chemotherapy with the novel oral DPD-inhibiting chemotherapeutic drug S-1 and interferon-alpha. J Gastroenterol 41:1120–1125

Nakamuta K, Oda H, Omagari K, Itsuno M, Murata I, Makiyama K, Hara K, Takshima F et al (1992) A autopsied case of primary hepatocellular carcinoma with expansive metastasis to the spleen (in Japanese). Nihon Shokakibyo Gakkai Zasshi 89:2808–2812

Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K, Ikari T (1983) Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. Cancer 51:863–877

Nakashima Y, Nakashima O, Tanaka M, Okuda K, Nakashima M, Kojiro M (2003) Portal vein invasion and intrahepatic micrometastasis in small hepatocellular carcinoma by gross type. Hepatol Res 26:142–147

Nappi O, Ferrara G, Ianniello G, Wick MR (1992) Metastatic hepatocellular carcinoma of the breast, simulating gynecomastia: diagnosis by fine-needle aspiration biopsy. Diagn Cytopathol 8:588–592

Narita T, Nakazawa H, Hizawa Y, Ishidoay T, Kudo H (1993) Hepatocellular carcinoma with unusual metastasis to the small intestine. Acta Pathol Jpn 43:779–782

Natsuizaka M, Omura T, Akaike T, Kuwata Y, Yamazaki K, Sato T, Karino Y, Toyota J et al (2005) Clinical features of hepatocellular carcinoma with extrahepatic metastases. J Gastroenterol Hepatol 20:1781–1787

Nel I, Baba HA, Ertle J, Weber F, Sitek B, Eisenacher M, Meyer HE, Schlaak JK et al (2013) Individual profiling of circulating tumor cell composition and therapeutic outcome in patients with hepatocellular carcinoma. Transl Oncol 6:420–428

Nomura F, Ohnishi K (1991) Intrahepatic lymphatics opacified during hepatic arteriography in a patient with hepatocellular carcinoma. Am J Gastroenterol 86:235–237

Nozaki Y, Kobayashi N, Shimamura T, Akiyama T, Inamori M, Iida H, Endo H, Fujita K et al (2008) Colonic metastasis from hepatocellular carcinoma: manifested by gastrointestinal bleeding. Dig Dis Sci 53:3265–3266

Nuyens M, Schüpbach J, Stauffer E, Zbären P (2006) Metastatic disease to the parotid gland. Otolaryngol Head Neck Surg 135:844–848

Ogunwobi OO, Puszyk W, Dong HJ, Liu C (2013) Epigenetic upregulation of HGF and c-Met drives metastasis in hepatocellular carcinoma. PLoS One 8, e63765

Oh SY, Seo KW, Jegal Y, Ahn JJ, Min YJ, Park CR, Hwang JC (2013) Hemothorax caused by spontaneous rupture of a metastatic mediastinal lymph node in hepatocellular carcinoma: a case report. Korean J Intern Med 28:622–625

Ohno K, Gotoh M, Yamawaki S, Ubayama Y, Isu K, Miyakawa A, Yamashiro K, Kajiwara M (1986) Massive osteoplastic bone metastasis of hepatocellular carcinoma – a case report (in Japanese). Gan No Rinsho 32:796–804

Ohwada S, Fukusato T, Kawashima Y, Kobayashi I, Ohya T, Nakamura S, Iino Y, Morishita Y (1998) Metastasis and invasion of hepatocellular carcinoma mimicking a right adrenal tumor. Hepatogastroenterology 22:1104–1110

Ohwada S, Takahashi T, Tsutsumi H, Kawate S, Ohki S, Hamada K (2008) Hepatocellular carcinoma with a tumour thrombus extending to the tricuspid valve: report of a successful en bloc resection. Hepatogastroenterology 55:903–906

Okano K, Usuki H, Maeta H (2004) Adrenal metastasis from hepatocellular carcinoma through an adrenohepatic fusion. J Clin Gastroenterol 38:912

Okazaki N, Yoshino M, Yoshida T, Hirohashi S, Kishi K, Shimosato Y (1985) Bone metastasis in hepatocellular carcinoma. Cancer 55:1991–1994

Okuda K (1997) Hepatocellular carcinoma: clinicopathological aspects. J Gastroenterol Hepatol 12:S314–S318

Okuda K, Arakawa M, Kubo Y, Sakata K, Kage M, Iwamoto S, Takeda S, Sonoda K et al (1998) Right-sided pedunculated hepatocellular carcinoma: a form of adrenal metastasis. Hepatology 27:81–85

Okusaka T, Okada S, Ishii H, Nose H, Nagahama H, Nakasuka H, Ikeda K, Yoshimori M (1997) Prognosis of hepatocellular carcinoma patients with extrahepatic metastases. Hepatogastroenterology 44:251–257

Olubuyide IO (1991) Pattern of metastasis of primary liver cancer at autopsy: an African series. Trop Gastroenterol 12:67–72

Oortman EH, Elliott JP (1983) Hepatocellular carcinoma metastatic to the ovary: a case report. Am J Obstet Gynecol 146:715–717

Otsuka T, Hagiwara S, Tojima H, Yoshida H, Takahashi T, Nagasaka T, Tomiola S et al (2007) Hepatocellular carcinoma with peritoneal dissemination which was regressed during vitamin K2 and vitamin E administration. Intern Med 46:711–715

Pandey M, Truica C (2011) Hepatoid carcinoma of the ovary. J Clin Oncol 29:e446–e448

Papp E, Keszthelyi Z, Kalmar NK, Papp L, Weninger C, Tornoczky T, Kalman E, Toth K et al (2005) Pulmonary embolization as primary manifestation of hepatocellular carcinoma with intracardiac penetration: a case report. World J Gastroenterol 11:2357–2359

Park MS, Kim KW, Yu JS, Kim MJ, Yoon SW, Chung KW, Lee JT, Yoo HS (2002) Radiologic findings of gastrointestinal tract involvement in hepatocellular carcinoma. J Comput Assist Tomogr 26:95–101

Pavan C, Parisi A, Girelli D (2007) Recurrent needle-tract metastases of hepatocellular carcinoma following fine-needle aspiration. Intern Med J 37:134–136

Pelloni A, Gertsch P (2000) Risks and consequences of tumor seeding after percutaneous fine needle biopsy four diagnosis of hepatocellular carcinoma (in French). Schweiz Med Wochenschr 130:871–877

Perkins JD (2007) Seeding risk following percutaneous approach to hepatocellular carcinoma. Liver Transpl 13:1603

Popescu I, Alexnadrescu S, Ciurea S, Brasoveanu V, Hrehoret D, Gangone E, Boros M et al (2007) Adrenalectomy for metastases from hepatocellular carcinoma – a single center experience. Langenbecks Arch Surg 392:381–384

Putterman D, Safadi R, Ilan Y, Rivkind AI, Ben-Chetrit E (1994) Pulmonary embolism as the presenting feature of hepatocellular carcinoma. Presse Med 23:474–476

Qua CS, Wong CH, Goh KL (2008) Tumour seeding following percutaneous needle biopsy of hepatocellular carcinoma. Singapore Med J 49:e8–e11

Ramon Ramirez J, Seoane J, Montero J, Esparza Gomez GC, Cerero R (2003) Isolated gingival metastasis from hepatocellular carcinoma mimicking a pyogenic granuloma. J Clin Periodontol 30:926–929

Riener MO, Fritzsche FR, Soll C, Pestalozzi BC, Probst-Hensch N, Clavien PA, Jochum W et al (2010) Expression of the extracellular matrix protein periostin in liver tumours and bile duct carcinomas. Histopathology 56:600–606

Robertson EG, Baxter G (2011) Tumour seeding following percutaneous biopsy: the real story! Clin Radiol 66:1007–1014

Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK (2013) A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol 20:325–339

Romanas MM, Cherian R, McGregor DH, Wu Y, May CL, Baranda JC (2004) Hepatocellular carcinoma diagnosed by fine-needle aspiration of the parotid gland. Diagn Cytopathol 30:401–405

Rowe LR, Mulvihill SJ, Emerson L, Gopez EV (2007) Subcutaneous tumor seeding following needle core biopsy of hepatocellular carcinoma. Diagn Cytopathol 35:717–721

Royer et al. (2008) http://www.ncbi.nlm.nih.gov/pubmed/18212552

Ruiz-Morales JM, Dorantes-Heredia R, Chable-Montero F, Vazquez-Manjarrez S, Méndez-Sanchez N et al (2014) Bone metastases as the initial presentation of hepatocellular carcinoma. Two case reports and a literature review. Ann Hepatol 13:838–842

Ryu JK, Lee SB, Kim KH, Yoh KT (2004) Surgical treatment in a patient with multiple implanted intraperitoneal metastases after resection of ruptured large hepatocellular carcinoma. Hepatogastroenterology 51:239–242

Ryu SH, Chung YH, Lee H, Kim JA, Shin HD, Min HJ, Seo DD, Jang MK, Yu E et al (2008) Metastatic tumor antigen 1 is closely associated with frequent postoperative recurrence and poor survival in patients with hepatocellular carcinoma. Hepatology 47:929–936

Ryu HS, Hwang ET, Choi CS, Kim TH, Kim HC, Yun KJ, Park DE (2009) A case of hepatocellular carcinoma invading the gallbladder misdiagnosed as a primary gallbladder carcinoma (in Korean). Korean J Hepatol 15:80–84

Sai S, Nakamura H, Kawamoto S, Morimoto K, Tanaka T, Hori S, Yoshioka H, Kuroda C (1982) Adrenal

metastasis of hepatocellular carcinoma (in Japanese). Ronsho Hoshasen 8:843–846
Sakurai M, Okamura J, Seki K, Kuroda C (1983) Needle tract implantation of hepatocellular carcinoma after percutaneous liver biopsy. Am J Surg Pathol 7:191–195
Santini D, Pantano F, Riccardi F, Di Costanzo GG, Addeo R, Guida FM, Ceruso MS et al (2014) Natural history of malignant bone disease in hepatocellular carcinoma: final results of a multicenter bone metastasis survey. PLoS One 9, e105268
Sanz Mayayo E, Mayayo Dehesa T, Gomez Garcia I, Saenz Medina J, Rodriguez-Patron Rodriguez R et al (2003) Renal metastasis of hepatocellular carcinoma. Actas Urol Esp 27:387–390
Sato M, Tokui K, Watanabe Y, Lee T, Kohtani T, Nezu K, Kawachi K, Kito K, Sugita A et al (1999) Generalized intraperitoneal seeding of hepatocellular carcinoma after microwave coagulation therapy: a case report. Hepatogastroenterology 46:2561–2564
Satou S, Ishizawa T, Masuda K, Kaneko J, Aoki T, Sakamoto Y, Hasegawa K, Sugawara Y et al (2013) Indocyanine green fluorescent imaging for detecting extrahepatic metastasis of hepatocellular carcinoma. J Gastroenterol 48:1136–1143
Sawabe M, Nakamura T, Kanno J, Kasuga T (1987) Analysis of morphological factors of hepatocellular carcinoma in 98 autopsy cases with respect to pulmonary metastasis. Acta Pathol Jpn 37:1389–1404
Schmidt-Mutter C, Breining T, Gangi A, Canela E, Jourdan I, Mutter D, Dupeyron JP (2003) Fatal bile pulmonary embolism after radiofrequency treatment of a hepatocellular carcinoma. Surg Endosc 17:2028–2031
Schoenleber SJ, Kurtz DM, Talwalkar JA, Roberts LR, Gores GJ (2009) Prognostic role of vascular endothelial growth factor in hepatocellular carcinoma: systemic review and meta-analysis. Br J Cancer 100:1385–1392
Schulze K, Gasch C, Staufer K, Nashan B, Lohse AW, Pantel K, Roethdorf S, Wege H (2013) Presence of EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. Int J Cancer 133:2165–2171
Schwarz KO, Schwartz IS, Marchevsky A (1982) Virchow-Troisier's lymph node as the presenting sign of hepatocellular carcinoma. Mt Sinai J Med 49:59–62
Seki S, Kitada T, Sakaguchi H, Nakatani K, Kamino T, Nakamura K, Yamada R (2001) Cardiac tamponade caused by spontaneous rupture of mediastinal lymph node metastasis of hepatocellular carcinoma. J Gastroenterol Hepatol 16:702–704
Senenko AN, Glutbarg BE (1966) Malignant hepatoma with splenic metastasis (in Russian). Vrach Delo 10:132–133
Seo HJ, Choi YJ, Kim HJ, Jeong YH, Cho A, Lee JH, Yun M, Choi HJ, Lee JD et al (2011) Evaluation of bone metastasis from hepatocellular carcinoma using (18)F-FDG PET/CT and (99m)Tc-HDP bone scintigraphy: characteristics of soft tissue formation. Nucl Med Mol Imaging 45:203–211
Seong J, Koom WS, Park HC (2005) Radiotherapy for painful bone metastasis from hepatocellular carcinoma. Liver Int 25:261–265
Shabo I, Svanvik J (2011) Expression of macrophage antigens by tumor cells. Adv Exp Med Biol 714:141–150
Shao YY, Lin ZZ, Chen TJ, Hsu C, Shen YC, Hsu CH, Cheng AL (2011) High circulating endothelial progenitor levels associated with poor survival of advanced hepatocellular carcinoma patients receiving sorafenib combined with metronomic chemotherapy. Oncology 81:98–103
Shen ML, Kang J, Wen YL, Ying WM, Hua CG, Tang XF (2009) Metastatic tumors to the oral and maxillofacial region. A retrospective study of 19 cases in West China and review of the Chinese and English literature. J Oral Maxillofac Surg 67:718–737
Shen G, Lin Y, Yang X, Zhang J, Xu Z, Jia H (2014) MicroRNA-26b inhibits epithelial-mesenchymal transition in hepatocellular carcinoma by targeting USP9X. BMC Cancer 14:393
Shi M, Zhang CQ, Zhang YQ, Liang XM, Li JQ (2004) Micrometastases of solitary hepatocellular and appropriate resection margin. World J Surg 28:376–381
Shi JH, Huitfeldt HS, Suo ZH, Line PD (2011) Growth of hepatocellular carcinoma in the regenerating liver. Liver Transpl 17:866–874
Shinzato J, Yamashita Y, Takahashi M, Miura K (1990) A case of pulmonary infarction secondary to emboli hepatoma (in Japanese). Rinsho Horshasen 35:971–974
Shirato K, Morimoto M, Tomita N, Kokawa A, Sugimori K, Saito T, Tanaka K (2002) Hepatocellular carcinoma: a case of extrahepatic seeding after percutaneous radiofrequency ablation using an expandable needle electrode. Hepatogastroenterology 49:897–899
Si MS, Amersi F, Golish SR, Ortiz JA, Zaky J, Finklestein D, Busuttil RW, Imagawa DK (2003) Prevalence of metastases in hepatocellular carcinoma: risk factors and impact on survival. Am Surg 69:879–885. metabolism and the pathophysiology of iron overload disorders. Clin Biochem Rev 27:5–16
Silva MA, Hegab B, Hyde C, Guo B, Buckels JAC, Mirza DF (2008) Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut 57:1592–1596
Smith EH (1991) Complications of percutaneous abdominal fine-needle biopsy. Rev Radiol 178:253–258
Sohara N, Takagi H, Yamada T, Ichikawa T, Abe T, Itoh H, Mori M (2000) Esophageal metastasis of hepatocellular carcinoma. Gastrointest Endosc 51:739–741
Song FN, Duan M, Liu LZ, Wang ZC, Shi JY, Yang LX, Zhou J, Fan J, Gao Q et al (2014) RANKL promotes migration and invasion of hepatocellular carcinoma cells via NF-kB-mediated epithelial-mesenchymal transition. PLoS One 9, e108507
Sonoda T, Kanematsu T, Takenaka K, Sugimachi K (1989) Ruptured hepatocellular carcinoma evokes risk of implanted metastases. J Surg Oncol 41:183–186

Sotiropoulos GC, Malago M, Molmenti EP, Lösch C, Lang H, Frilling A, Broelsch CE, Neuhäuser M (2007) Hilar lymph nodes sampling at the time of liver transplantation for hepatocellular carcinoma: to do or not to do ? Meta-analysis to determine the impact of hilar lymph nodes metastases on tumor recurrence and survival in patients with hepatocellular carcinoma undergoing liver transplantation. Transpl Int 20:141–146

Sugino T, Yamaguchi T, Hoshi N, Kusakabe T, Ogura G, Goodison S, Suzuki T (2008) Sinusoidal tumor angiogenesis is a key component in hepatocellular carcinoma metastasis. Clin Exp Metastasis 25:835–841

Sumiya H, Takayama H, Arai H, Mori K, Iizuka H, Sagawa T, Onozato Y, Ishihara H et al (2007) A survival case of hepatocellular carcinoma with splenic metastasis metachronous rupture at the liver primary and splenic metastasis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 104:1639–1644

Sun HC, Zhuang PY, Qin LX, Ye QH, Wang L, Ren N, Zhang JB, Qian YB, Lu L et al (2007) Incidence and prognostic values of lymph node metastasis in operable hepatocellular carcinoma and evaluation of routine complete lymphadenectomy. J Surg Oncol 96:37–45

Sun T, Sun BC, Zhao XL, Zhao N, Dong XY, Che N, Yao Z, Ma YM, Gu Q, Zong WK et al (2011) Promotion of tumor cell metastasis and vasculogenic mimicry by way of transcription coactivation by Bcl-2 and Twist1: a study of hepatocellular carcinoma. Hepatology 54:1690–1706

Sun YF, Xu Y, Yang XR, Guo W, Zhang X, Qiu SJ, Shi RY, Hu B, Zhou J, Fan J (2013a) Circulating stem-like epithelial cell adhesion molecule-positive tumor cells indicated poor prognosis of hepatocellular carcinoma after curative resection. Hepatology 57:1458–1468

Sun D, Sun B, Liu T, Zhao X, Che N, Gu Q, Dong X, Yao Z, Li R, Li J, Chi J, Sun R (2013b) Slug promoted vasculogenic mimicry in hepatocellular carcinoma. J Cell Mol Med 17:1038–1047

Sung TY, Lee SR, Lee JH, Lee YM, Lee AL, Hwang DW, Yoon JH, Gong G, Ong SJ, Park KM (2011) Hepatocellular carcinoma eats medullary thyroid carcinoma, a case of tumor-in-tumor metastasis. Endocr J 58:801–805

Takagi H, Shimoda R, Uehara M, Takayama H, Yamada T, Ojima T, Abe T, Mori M et al (1996) Hepatocellular carcinoma with pleural metastasis complicated by hemothorax. Am J Gastroenterol 91:1865–1866

Takahashi H, Konishi M, Nakagohri T, Inoue K, Takahashi S, Tanizawa Y, Monden M et al (2004) Aggressive multimodal treatment for peritoneal dissemination and needle tract implantation of hepatocellular carcinoma: a case report. Jpn J Clin Oncol 34:551–555

Takamori R, Wong LL, Dang C, Wong L (2000) Needle-tract implantation from hepatocellular cancer: is needle biopsy of the liver always necessary. Liver Transpl 6:67–72

Takamura T, Nagai Y, Yamashita H, Nohara E, Ando H, Kagaya M, Urabe T, Kaneko S et al (1999) Adrenal insufficiency due to metastatic hepatocellular carcinoma. Endocr J 46:591–596

Takayasu K, Muramatsu Y, Moriyama N, Yamazaki S, Kishi K (1989) Surgical treatment of adrenal metastasis following hepatectomy for hepatocellular carcinoma. Jpn J Clin Oncol 19:62–66

Tanaka T, Nakamura H, Choi S, Morimoto K, Kawamoto S, Hori S, Tokunaga K, Yoshioka H et al (1985) CT diagnosis of abdominal lymph node metastases in hepatocellular carcinoma. Eur J Radiol 5:175–177

Tanaka O, Kanematsu M, Kondo H, Goshima S, Nishibori H, Kato H, Kiryu RT, Tokoyam R et al (2005) Solitary mediastinal lymph node metastasis of hepatocellular carcinoma: MR imaging findings. Magn Reson Imaging 23:11–114

Tang ZY, Ye SL, Liu YK, Qin LX, Sun HC, Ye QH, Wang L, Zhou J, Qiu SJ, Li Y et al (2004) A decade's studies on metastasis of hepatocellular carcinoma. J Cancer Res Clin Oncol 130:187–196

Tariq U, Poder L, Carlson D, Courtier J, Joe BN, Coakley FV (2012) Multimodality imaging of fat-containing adrenal metastasis from hepatocellular carcinoma. Clin Nucl Med 37:e157–e159

Terada T (2011) Hepatocellular carcinoma metastatic to the gingiva as a first manifestation of hepatocellular carcinoma. J Maxillofac Oral Surg 10:271–274

Terada T, Maruo H (2013) Unusual extrahepatic metastatic sites from hepatocellular carcinoma. Int J Clin Exp Pathol 6:816–820

Terada T, Sugiura M (2010) Metastatic hepatocellular carcinoma of skin diagnosed with hepatocyte paraffin 1 and a-fetoprotein immunostainings. Int J Surg Pathol 18:433–436

Terada T, Hoso M, Nakanuma Y (1989) Development of cavernous vasculatures in livers with hepatocellular carcinoma. An autopsy study. Liver 9:172–178

Terada T, Takeuchi T, Hirano R, Nagata S, Kubota H, Honda S (2003) Spontaneous rupture of peripancreatic lymph node with hepatocellular carcinoma metastasis: report of an autopsy case with massive peritoneal bleeding. Hepatol Res 26:73–76

Terasaki T, Hanazaki K, Shiohara E, Matsunaga Y, Koide N, Amano J (2000) Complete disappearance of recurrent hepatocellular carcinoma with peritoneal dissemination and splenic metastasis: a unique clinical course after surgery. J Gastroenterol Hepatol 15:327–330

Toyoda H, Fukuda Y, Koyama Y, Nishimura D, Hoshino H, Katada N, Kato K, Hayakawa T (1996) Case report: multiple systemic lymph node metastases from a small hepatocellular carcinoma. J Gastroenterol Hepatol 11:959–962

Tozzini S, Anichini C, Gori F, Bartolini G (2004) Pulmonary embolism by liver tissue. Am J Forensic Med Pathol 25:87

Tsai GL, Liu JD, Siauw CP, Chen PH (1984) Thoracic roentgenologic manifestations in primary carcinoma of the liver. Chest 86:430–434

Tsalis K, Zacharakis E, Sapidis N, Lambrou I, Zacharakis E, Betsis D (2005) Adrenal metastasis as first presentation of hepatocellular carcinoma. World J Surg Oncol 3:50

Tsubouchi E, Hirasaki S, Kataoka J, Hidaka S, Kajiwara T, Yamauchi Y, Masumoto T et al (2005) Unusual metastasis of hepatocellular carcinoma to the esophagus. Intern Med 44:444–447

Tung WC, Huang YJ, Leung SW, Kuo FY, Tung HD, Wang JH, Hung CH, Lee CM et al (2007) Incidence of needle tract seeding and responses of soft tissue metastasis by hepatocellular carcinoma postradiotherapy. Liver Int 27:192–200

Uchino K, Tateishi R, Shiina S, Kanda M, Masuzaki R, Kondo Y, Goto T, Omata M et al (2011) Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. Cancer 117:4475–4483

Ueda K, Nakanuma Y, Terada T, Naito T, Matsui O (1991) Well-differentiated hepatocellular carcinoma showing intrahepatic neural invasion autopsied case. Jpn J Clin Oncol 21:143–146

Ueda J, Yoshida H, Mamada Y, Tainai N, Mineta S, Yoshioka M, Kawano Y, Shimizu T et al (2012) Surgical resection of a solitary para-aortic lymph node metastasis from hepatocellular carcinoma. World J Gastroenterol 18:3027–3031

Uehara K, Hasegawa H, Ogiso S, Sakamoto E, Ohira S, Igami T, Mori T (2003) Skip lymph node metastases from a small hepatocellular carcinoma with difficulty in preoperative diagnosis. J Gastroenterol Hepatol 18:345–349

Uenishi T, Hirohashi K, Shuto T, Kubo S, Tanaka H, Sakata C, Ikebe T, Kinoshita H (2000) The clinical significance of lymph node metastasis in patients undergoing surgery for hepatocellular carcinoma. Surg Today 30:892–895

Uenishi T, Kubo S, Hirohashi K, Hamba H, Tanaka H, Shuto T, Yamamoto T, Kinoshita H (2002) Successful surgical control for hepatocellular carcinoma disseminated to the peritoneum: a case report. Hepatogastroenterology 49:532–534

Ueno N, Kanamaru T, Kawaguchi K, Tanaka K, Inoue K, Idei Y, Yamamoto M (2001) A hepatocellular carcinoma with lymph node metastasis and invasion into the gallbladder preoperative difficulty ruling out a gallbladder carcinoma. Oncol Rep 8:331–335

Uka K, Aikata H, Takaki S, Shirakawa H, Jeong SC, Yamashina K, Hiramatsu A, Kodama H et al (2007) Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. World J Gastroenterol 13:414–420

Utsumi M, Matsuda H, Sadamori H, Shinoura S, Umeda Y, Yoshida R, Satoh D, Hashimoto M et al (2012) Resection of metachronous lymph node metastases from hepatocellular carcinoma after hepatectomy: report of four cases. Acta Med Okayama 66:177–182

Utsunomiya T, Okamoto M, Tsujita E, Yamamoto M, Tsutsui S, Fujihara M, Ishida T (2009) Hepatocellular carcinoma infiltrated with non-Hodgkin's lymphoma: report of a case. Surg Today 39:1010–1012

van de Molengraft F, Jap P, Poels L, Croes H, Vooijis P (1989) Tumor cell settling and early invasion of the peritoneum. Clin Exp Metastasis 7:187–199

Vitale AR, Compilato D, Coletti G, Calvisi G, Ciuffitelli V, Barbera D, Craxi A, Campisi G et al (2009) Metastatic hepatocellular carcinoma of the parotid region without lung metastasis: a case report. Int J Oral Maxillofac Surg 38:696–698

Voitk AJ, Munkittrick RC (1986) A fatal pulmonary embolus composed of gross liver tissue. Can J Surg 29:218–219

Wang CH, Yang S (2006) Testicular metastasis from hepatocellular carcinoma. Int J Urol 13:1033–1034

Wang SC, Lin XL, Li J, Zhang TT, Wang HY, Shi JW, Yang S, Zhao WT, Xie RY et al (2014) MicroRNA-122 triggers mesenchymal-epithelial transition and suppresses hepatocellular carcinoma cell motility and invasion by targeting RhoA. PLoS One 9, e101330

Watanabe J, Nakashima O, Kojiro M (1994) Clinicopathologic study on lymph node metastasis of hepatocellular carcinoma: a retrospective study of 660 consecutive autopsy cases. Jpn J Clin Oncol 24:37–41

Willett IR, Sutherland RC, O'Rourke MF, Dudley FJ (1984) Pulmonary hypertension complicating hepatocellular carcinoma. Gastroenteriology 87:1180–1184

Wills EJ (1968) Fine structure and surface adenosinetriphosphatase activity of a human hepatoma. Cancer 22:1046–1052

Wilson K, Guardino J, Shapira O (2001) Pulmonary tumor embolism as a presenting feature of cavoatrial hepatocellular carcinoma. Chest 119:657–658

Wu CH, Wong YC, Wu MY, Nan YY, Lin WL (2013) Education and imaging: hepatobiliary and pancreatic: fatal tumor embolism caused by hepatocellular carcinoma. J Gastroenterol Hepatol 28:380

Wu SM, Ai HW, Zhang DY, Han XQ, Pan Q, Luo FL, Zhang XL (2014) miR-141 targets ZEB2 to suppress HCC progression. Tumour Biol 35:9993–9997

Xiang Z, Zeng Z, Fan J, Sun H, Wu W, Tan Y (2009) Increased expression of vascular endothelial growth factor-C and nuclear CXCR4 in hepatocellular carcinoma is correlated with lymph node metastasis and poor outcome. Cancer J 15:519–525

Xiang ZL, Zeng ZC, Tang ZY, Fan J, Sun HC, Tan YS (2011) Expression of cytokeratin 19 and matrix metalloproteinase 2 predicts lymph node metastasis in hepatocellular carcinoma. Mol Biol Rep 38:3531–3539

Xiaohong et al. (2010) http://www.ncbi.nlm.nih.gov/pubmed/20174806

Xue X, Zhang Y, Zhi Q, Tu M, Xu Y, Sun J, Wei J, Lu Z, Miao Y, Gao W (2014) MiR200-upregulated Vasohibin 2 promotes the malignant transformation of tumors by inducing epithelial-mesenchymal transition in hepatocellular carcinoma. Cell Commun Signal 12:62

Yagmur E, Rizk M, Stanzel S, Hellerbrand C, Lammert F, Trautwein C, Wasmuth HE et al (2007) Elevation of endoglin (CD105) concentrations in serum of patients

with liver cirrhosis and carcinoma. Eur J Gastroenterol Hepatol 19:755–761

Yamada et al. (1998) http://www.ncbi.nlm.nih.gov/pubmed/9559232

Yamada S, Okumura N, Wei L, Fuchs BC, Fujii T, Sugimoto H, Nomoto S, Takeda S et al (2014) Epithelial to mesenchymal transition is associated with shorter disease-free survival in hepatocellular carcinoma. Ann Surg Oncol 21:3882–3890

Yamakado K, Anai H, Takaki H, Sakaguchi H, Tanaka T, Kichikawa K, Takeda K (2009) Adrenal metastasis from hepatocellular carcinoma: radiofrequency ablation combined with adrenal arterial chemoembolization in six patients. AJR Am J Roentgenol 192: W300–W305

Yamamoto R, Yamamoto S, Fukushima K, Ohmoto K, Hino K, Kojoh K, Ohumi Y, Ideguchi S et al (1986) Splenic metastasis of hepatocellular carcinoma (in Japanese). Gan No Rinsho 32:1486–1490

Yamamoto T, Takeuchi K, Nagashima N, Honjo H, Sakurai N, Okuda C, Kuyama Y (2002) Fatal adrenal metastasis from hepatocellular carcinoma. J Clin Gastroenterol 35:103–104

Yan SL, Hung YH, Yang TH (2007) Metastatic hepatocellular carcinoma of the esophagus: an unusual cause of upper gastrointestinal bleeding. Endoscopy 39(Suppl 1):E257–E258

Yan ML, Wang YD, Lai ZD, Tian YF, Chen HB, Qiu FN, Zhou SQ (2009) Pedunculated hepatocellular carcinoma and splenic metastasis. World J Gastroenterol 15:5239–5241

Yang PM, Sheu JC, Yang TH, Chen DS, Yu JY, Lee CS, Hsu HC, Sung JL (1987) Metastasis of hepatocellular carcinoma to the proximal jejunum manifested by occult gastrointestinal bleeding. Am J Gastroenterol 82:165–167

Yang Y, Nagano H, Ota H, Morimoto O, Nakamura M, Wada H, Noda T, Damdinsuren B et al (2007a) Patterns and clinicopathologic features of extrahepatic recurrence of hepatocellular carcinoma after curative resection. Surgery 141:196–202

Yang PW, Wang WY, Yang CH, Cou CC, Yen DH, Cou J (2007b) Treatment of massive retroperitoneal hemorrhage from adrenal metastasis of hepatoma. J Chin Med Assoc 70:126–131

Yang ZF, Ngai P, Ho DW, Yu WC, Ng MN, Lau CK, Li ML, Tam KH, Lam CT et al (2008) Identification of local and circulating cancer stem cells in human liver cancer. Hepatology 47:919–928

Yang L, Shen X, Li J, Yang J, Le Y, Gong Z (2014) MicroRNAs affect tumor metastasis through regulating epithelial-mesenchymal transition. Yi Chuan 36:637–645

Yano S, Nakamura K, Yamane K, Kakinuma T, Asahina A, Tamaki K (2001) Subcutaneous metastasis following percutaneous ethanol injection therapy for hepatocellular carcinoma. Acta Derm Venereol 81:213–214

Yasaka K, Gonoi W, Akai H, Katsura M, Akahane M, Kiryu S, Ohtomo K (2013) Differentiation of adrenal tumors in patients with hepatocellular carcinoma: adrenal adenoma versus metastasis. Eur J Radiol 82:1213–1218

Yasui M, Harada A, Nonami T, Takeuchi Y, Taniguchi K, Nakao A, Takagi H (1997) Potentially multicentric hepatocellular carcinoma: clinicopathologic characteristics and postoperative prognosis. World J Surg 21:860–864

Yeh CN, Chen MF, Jeng LB (2002) Resection of peritoneal implantation from hepatocellular carcinoma. Ann Surg Oncol 9:863–868

Yoo DJ, Chung YH, Lee YS, Kim SE, Jin YJ, Lee YM, Kim MJ (2010) Sigmoid colon metastasis from hepatocellular carcinoma. Korean J Hepatol 16:397–400

Yoshida H, Onda M, Tajiri T, Akimaru K, Takasaki H, Mamada Y, Taniai N, Nakamura Y et al (2002) Successful surgical treatment of peritoneal dissemination of hepatocellular carcinoma. Hepatogastroenterology 49:1663–1665

Young RH, Gersell DJ, Clement PB, Scully RE (1992) Hepatocellular carcinoma metastatic to the ovary: a report of three cases discovered during life with discussion of the differential diagnosis of hepatoid tumors of the ovary. Hum Pathol 23:574–580

Yu J, Liang P, Yu X, Wang Y, Gao Y (2011) Ultrasound-guided percutaneous microwave ablation of splenic metastasis: report of four cases and literature review. Int J Hyperthermia 27:517–522

Yu YD, Kim DS, Jung SW, Lee JH, Chae YS, Suh SO (2013) Metastatic hepatocellular carcinoma to the parotid gland: case report and review of the literature. Int J Surg Case Rep 4:76–80

Yuki K, Hirohashi S, Sakamoto M, Kanai T, Shimosato Y (1990) Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. Cancer 66:2174–2179

Yunoki Y, Takeuchi H, Makino Y, Murakami I, Yasui Y, Tanakaya K, Kawaguchi K, Konaga E (1999) Intraperitoneal seeding of ruptured hepatocellular carcinoma: case report. Abdom Imaging 24:398–400

Zeng ZC, Tang ZY, Fan J, Zhou J, Qin LX, Ye SL, Sun HC, Wang BL, Zhang JY et al (2005) Radiation therapy for adrenal gland metastases from hepatocellular carcinoma. Jpn J Clin Oncol 35:61–67

Zhai X, Zhu H, Wang W, Zhang S, Zhang Y, Mao G (2014) Abnormal expression of EMT-related proteins, S100A4, vimentin an E-cadherin, is correlated with clinicopathological features and prognosis in HCC. Med Oncol 31:970

Zhang SH, Zeng ZC, Tang ZY, Sun J, Cheng JM, Liu R, Wang P, Zhang BH (2008a) Prognostic analysis of pulmonary metastases from hepatocellular carcinoma. Hepatol Int 2:237–243

Zhang Z, Han L, Cao L, Liang X, Liu Y, Liu H, Du J, Qu Z, Zhu C, Liu S, Li H, Sun W (2008b) Aggregation formation mediated anoikis resistance of BEL7402 hepatoma cells. Folia Histochem Cytobiol 46:331–336

Zhang Y, Li J, Cao L, Xu W, Yin Z (2012a) Circulating tumor cells in hepatocellular carcinoma: detection

techniques, clinical implications, and future perspectives. Semin Oncol 39:449–460

Zhang HY, Wu QJ, Xie CH, Zhang G (2012b) Long-term survival of patients with hepatocellular carcinoma with pulmonary and adrenal metastasis: a case report. Exp Ther Med 3:699–702

Zhang JG, Li XY, Wang YZ, Zhang QD, Gu SY, Wu X, Zhu GH, Li Q, Liu GL (2014a) ROCK is involved in vasculogenic mimicry formation in hepatocellular carcinoma cell line. PLoS One 9, e107661

Zhang ZH, Wu YG, Qin CK, Rong ZH, Su ZX, Xian GZ (2014b) Stanniocalcin 2 expression predicts poor prognosis of hepatocellular carcinoma. Oncol Lett 8:2160–2164

Zheng J, Li C, Wu X, Yang Y, Hao M, Sheng S, Sun Y, Zhang H, Long J, Hu C (2014) Astrocyte elevated gene-1 is a novel biomarker of epithelial-mesenchymal transition and progression of hepatocellular carcinoma in two China regions. Tumour Bio 35:2265–2269

Zhou XD (2002) Recurrence and metastasis of hepatocellular carcinoma: progress and prospects. Hepatobiliary Pancreat Dis Int 1:35–41

Zhu MS, Xu LB, Zeng H, Shi XD, Wu WR, Liu C (2014) Association of Notch1 with vasculogenic mimicry in human hepatocellular carcinoma cell lines. Int J Exp Pathol 7:5782–5791

Zhuang PY, Zhang JB, Zhu XD, Zhang W, Wu WZ, Tan YS, Hou J, Tang ZY, Qin LX et al (2008) Two pathologic types of hepatocellular carcinoma with lymph node metastasis with distinct prognosis on the basis of CK19 expression in tumor. Cancer 112:2740–2748

Secondary Alterations of Hepatocellular Carcinoma

5

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_5

Abstract

Hepatocellular carcinoma (HCC) can undergo spontaneous or induced secondary tissue changes. HCCs, and particularly large tumors and those of poor differentiation, are prone to necrosis. This can be followed by dystrophic calcifications, which sometimes result in macroscopically and radiologically visible deposits. Tumor calcifications are also found following hepatic dearterialization. In some HCCs, calcifications present are peripheral sickle- and ring-shaped calcifications mimicking parasitic hydatid disease. Rarely, stromal calcifications are observed. Other secondary changes include spontaneous tumor regression and immune reactions of the host directed against the tumor. Induced secondary alterations of HCC are well known after microwave coagulation therapy or radiofrequency ablation. The lesions are characterized by coagulative necrosis with shadow cells and faded nuclei, a rim of palisading histiocytic/epithelioid cells, a foreign body-type giant cell reaction, and sometimes destruction of adjacent bile ducts.

Secondary Tissue Changes of Hepatocellular Carcinoma

Necrosis

Hepatocellular carcinomas (HCCs) can undergo extensive necrosis, mainly of their inner (core) parts which predominantly suffer from ischemia and hypoxia (Figs. 1, 2, 3, 4, and 5).

Hemorrhage

Necrosis of cancers, including HCC, can involve several types of tumor blood vessels, followed by tumor hemorrhage and eventually tumor rupture. In HCC, also the marked angioinvasive phenotype can favor vascular injury and hemorrhage (Figs. 6, 7, and 8).

Apoptosis

Apart from various types of necrosis, HCCs can undergo apoptosis as a secondary alteration, further discussed in a separate chapter (Fig. 9).

Calcifications

Part of HCCs show calcifications, which are therefore not always an indicator of fibrolamellar carcinoma (Scatarige et al. 1983; Chin et al. 1986; Teefey et al. 1987; Friedman 1988; Stevens et al. 1994; Bezerra et al. 2003; Kawada et al. 2008). This alteration has been found in up to 15.3 % of HCC (Scatarige et al. 1983). Calcifications may present as circumscribed small collections of basophilic corpuscles, usually within necrotic areas of the tumor, or may sometimes appear as larger deposits that become macroscopically detectable as yellowish or whitish speckles. At imaging, HCC calcifications are usually located eccentrically within a complex heterogeneous mass (Stoupis et al. 1998). Calcifications prevail in larger lesions, but have also been noted in small or even minute HCC (Muramatsu et al. 1985). Tumor calcifications were also seen following hepatic dearterialization (Bengmark 1989). In few tumors, calcifications are present as sickle-shaped alterations underneath the tumor capsule, appearing as so-called ring calcification or rim calcification on CT images, mimicking hydatid disease (Mitchell et al. 1994; Fukuya et al. 1999; Kawada et al. 2008). Ring calcifications also occur in encapsulated small HCC where they have been suggested to result from a circulatory disturbance caused by a high internal pressure exerted by the fibrous capsule (Murakami et al. 2013). Apart from calcifications involving the tumor substance as such, there are rare instances with calcification in the tumor stroma. Small stromal calcifications were seen in two carcinomas out of 60 primary HCCs (Patton and Horn 1964). In one case, viable tumor cells were detectable between the calcified stromal components (Moenandar 1974). Linear portal vein calcification was observed in a patient with HCC

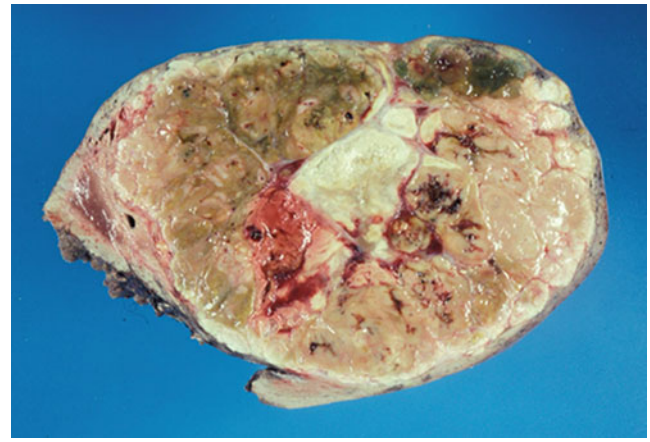

Fig. 1 Large hepatocellular carcinoma with an expanding growth pattern. This tumor has undergone partial necrosis, seen as a central white, rather well-delineated and shrunken focus. A second smaller area shows hemorrhagic necrosis, and small bleedings are also found in part of tumor nodules (*dark red speckles*)

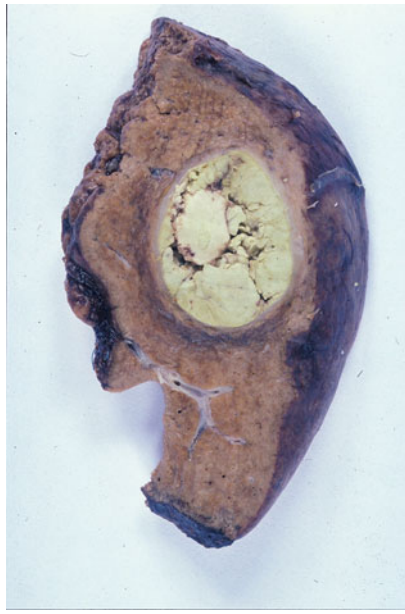

Fig. 2 In case of extensive necrosis of hepatocellular carcinoma, the tumor tissue becomes highly fragile. Typically, formalin-fixed tissue exhibits fissures and cracks upon sectioning

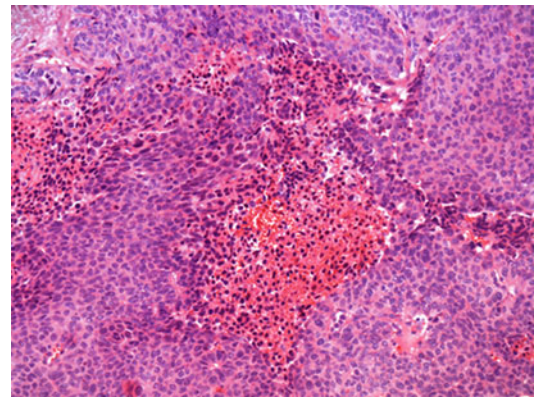

Fig. 3 Focal necrosis of poorly differentiated hepatocellular carcinoma (*center* and to the *top left*). Within eosinophilic decayed tissue areas, pycnotic nuclei and nuclear debris are found. In necrotic foci, dystrophic calcification can develop (hematoxylin and eosin stain)

associated with liver cirrhosis and portal hypertension (Del Val et al. 1991). Calcified primary HCC has to be distinguished from hepatic metastases undergoing calcification (Takahashi et al. 1971; Bernadino 1979) and from rare instances of calcification of cholangiocarcinoma (Hall et al. 1970). In very rare cases, calcification of HCC is associated with metaplastic ossification (ossified HCC; Maeda et al. 1986).

Pathology of HCC Following Nonsurgical Treatments

Several types of nonsurgical therapies of HCC can result in distinct morphologic patterns of tumor damage (Figs. 10, 11, and 12).

Histopathologic changes after microwave coagulation therapy or radiofrequency ablation of HCC are characterized by a tumor coagulative necrosis

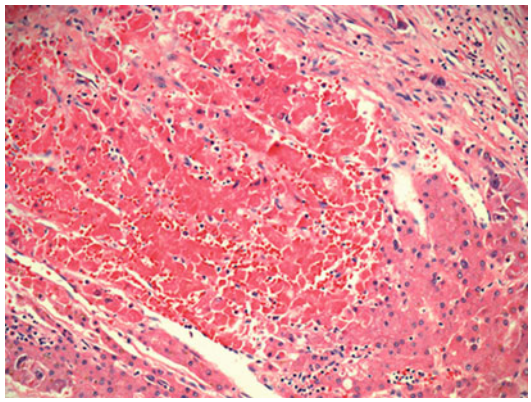

Fig. 4 In this trabecular hepatocellular carcinoma (G1/G2), an abrupt transition into almost complete necrosis is seen. The necrotic tumor tissue area exhibits shadow cells and shadow trabecules. This type of lesion is usually caused by hypoxia/ischemia (hematoxylin and eosin stain)

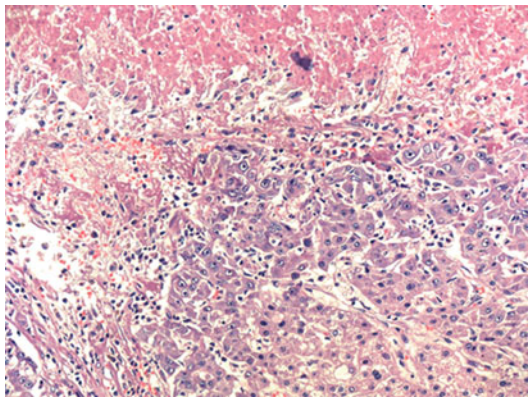

Fig. 5 Cancer regrowth following necrosis of hepatocellular carcinoma can be associated with increased cellular and nuclear atypia (*center of figure*; hematoxylin and eosin stain)

with eosinophilic shadow cells and faded nuclei and a rim of palisading, histiocytic, giant cell, inflammatory reaction associated with fibrotic bands (Yamashiki et al. 2003; Kim et al. 2004). Rarely, massive hepatic infarction can develop (Poggi et al. 2004; Chuang et al. 2005; Chiu et al. 2009). Foreign bodies may develop that can mimic disseminated tumor recurrence (Takahashi et al. 2008). The often marked necrosis after thermal ablation may cause destruction of bile duct walls followed by hemobilia (Enne et al. 2004) or hemocholecyst (Shin et al. 2011).

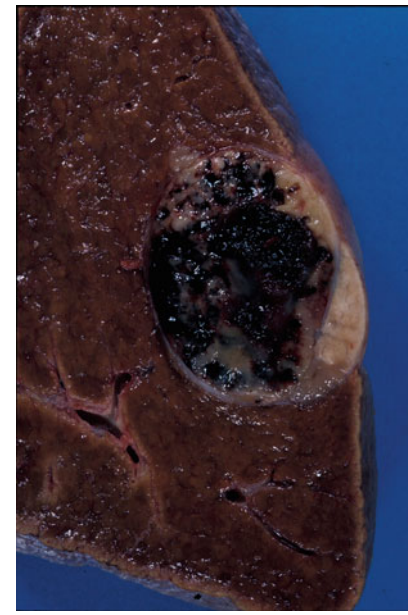

Fig. 6 Subcapsular nodular hepatocellular carcinoma with extensive fresh hemorrhage. Even in lesions with a pseudocapsule, as in the present case, massive hemorrhage can result in tumor rupture followed by hematoperitoneum

Following transcatheter arterial embolization (TAE), small HCC showed complete necrosis in up to 80.2 % of cases, but was much less frequent in large neoplasms, with viable tumor cells remaining in central parts in large tumors. Necrosis in large HCC after TAE is usually patchy, forming several necrosis units. Subsequent to TAE, most tumor capsules were affected by tumor necrosis and the following reparation process, resulting in a thick secondary capsule (Higuchi et al. 1994). Several patterns of changes take place following transarterial chemoembolization (TACE). Polyvinyl alcohol particles can reach and occlude distal arterioles and capillaries, but rarely leak into non-tumorous hepatic sinusoids (Lee et al. 2012). Part of the tumors undergo complete necrosis associated with a nonspecific inflammatory reaction at the periphery of the necrotic tumor mass. In part of tumors with remaining viable neoplasia, a change of differentiation was observed, with formation of cholangiolar, glandular, or spindle cell areas suggestive of a mixed hepatocholangiocellular phenotype and occurrence of cells with progenitor cell features, including CD133 positivity. CD133

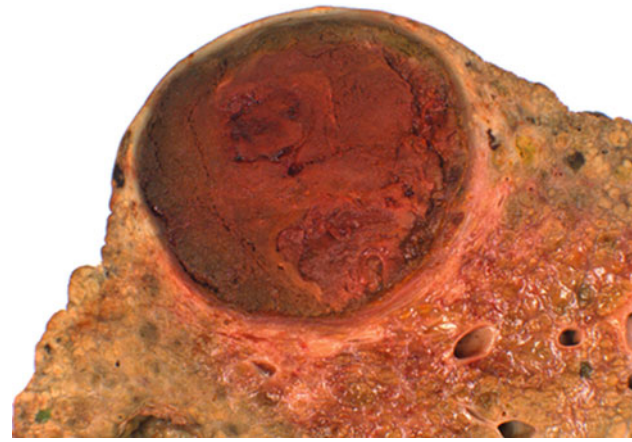

Fig. 7 This nodular hepatocellular carcinoma underwent complete hemorrhagic infarction. Tumor tissue is replaced by a clot of fresh blood surrounded by a pseudocapsule. Adjacent liver tissue shows cirrhosis

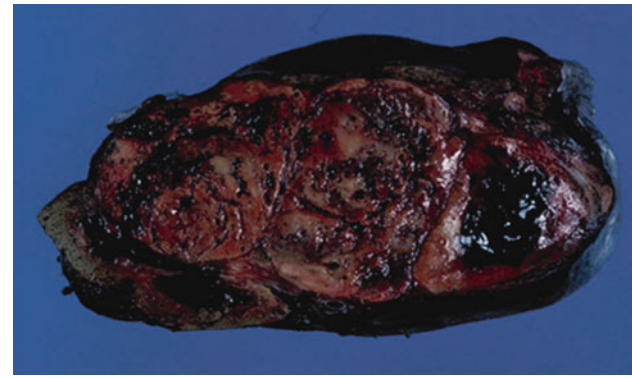

Fig. 8 Highly aggressive and poorly differentiated hepatocellular carcinoma with a massive growth pattern can show extensive hemorrhage, resulting in intratumoral hematoma, as seen in the right part of the figure. Such areas are prone to rupture

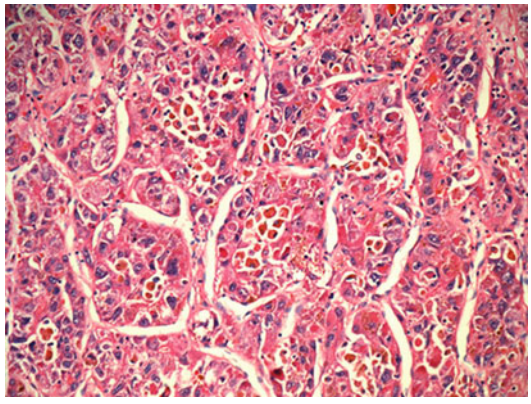

Fig. 9 Trabecular hepatocellular carcinoma with prominent apoptosis of neoplastic cells. Inner parts of trabecules show numerous, strongly eosinophilic and dense apoptotic bodies (hematoxylin and eosin stain)

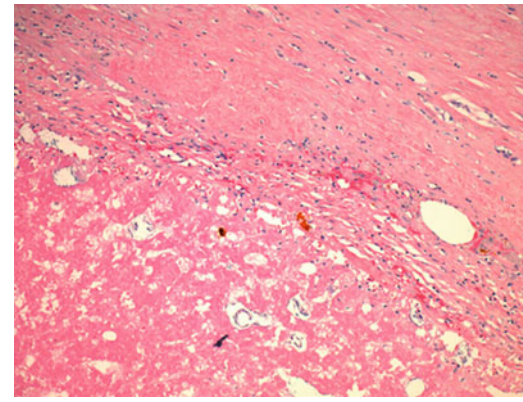

Fig. 10 Apparently total tumor necrosis following chemoembolization of hepatocellular carcinoma. Only eosinophilic shadow structures remain, with basophilic dots representing dystrophic microcalcifications (hematoxylin and eosin stain)

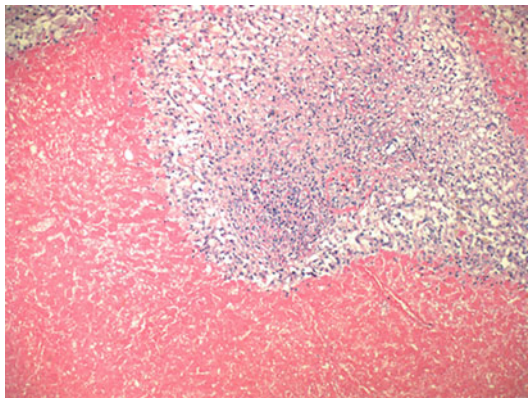

Fig. 11 Necrosis of hepatocellular carcinoma following chemoembolization. In this case, necrotic tissue is organized by a large tuft of vascularized granulation tissue (*upper part of figure*; hematoxylin and eosin stain)

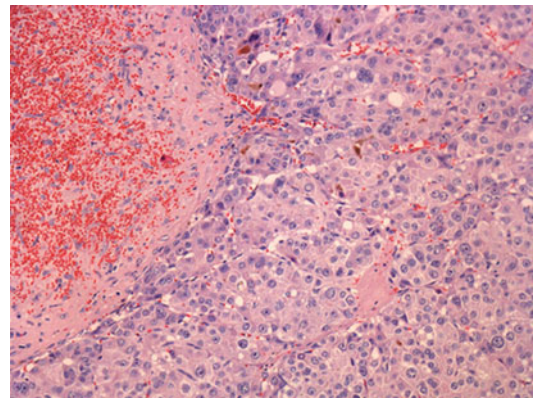

Fig. 13 Hepatocellular carcinoma with a spherical defect caused by needle biopsy (*left of figure*). Biopsy caused hemorrhage and necrosis which are now repaired by granulation tissue (hematoxylin and eosin stain)

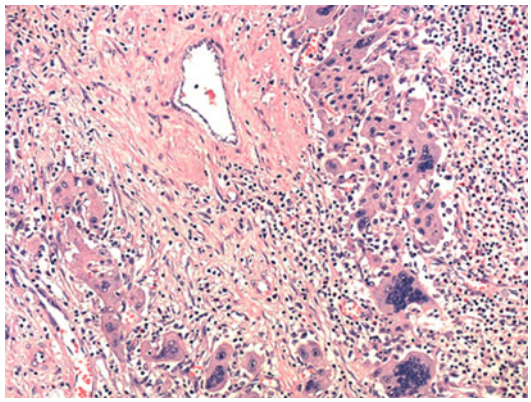

Fig. 12 Injected material in chemoembolization can, following leakage into tissue, elicit a vigorous foreign body reaction with multinucleated giant cells. In the present case, foreign material may have leaked from the blood vessel to the top that shows thinning of its wall at one place (hematoxylin and eosin stain)

reactive cells frequently coexpressed CK19, EpCAM, or NCAM. Patients with CD133-positive post-TACE HCC showed a higher recurrence rate (Zen et al. 2011). Arterial chemoembolization can cause fatal pulmonary oil embolism (Kwok et al. 2003; Czauderna et al. 2005). Tumor and/or hepatic infarction also occurs after pure ethanol injection (Chiu et al. 2009; Da Ines et al. 2010). A spectrum of changes in HCC is induced by therapy with the multikinase inhibitor, sorafenib, acting on several tyrosine protein kinases (VEGFR and PDGFR) and Raf kinases (Moeini et al. 2012; Chow et al. 2013; Di Marco et al. 2013; Dufour et al. 2013; Yang et al. 2014). The main alterations are necrosis, tumor cell apoptosis, cell junctional anomalies, reduced cell proliferation, and reduced angiogenesis. Distinct changes are also induced by transarterial radioembolization (TARE) with yttrium 90-impregnated microspheres (Dhingra et al. 2014).

As mentioned above, diverse nonsurgical treatments of HCC can induce epithelioid cell reaction and the formation of granulomas. However, a rare subset of HCC may contain granulomas induced by immune reactions (Tomimatsu et al. 1982). Apart from a foreign body reaction induced by necrotic tumors following diverse treatment modalities, granulomas in HCC were also induced by lipiodolized SMANCS, a polymer-conjugated derivative of neocarzinostatin (Ichikawa et al. 2002). Epithelioid cells induced within HCC by therapeutic measures or immune reactions of the host may appear in fine-needle aspirates and cause false-negative diagnostic results (Mourra and Flejou 2001).

A special situation of secondary change of HCC is tumor damage due to needle biopsy (Fig. 13).

Pathologic Changes in the Peritumoral Liver Substance

Liver tissue surrounding HCC nodules displays complex alterations, including formation of a distinct perinodular stroma consisting of an expanded fibrous matrix and a ductular reaction. Cytokeratin 19 expression in this perinodular stroma varies according to the underlying liver disease, being complex around cirrhotic nodules, attenuated around dysplastic nodules, and absent around HCC (Bioulac-Sage and Balabaud 2011). It was proposed that these patterns represent marked cellular alterations in cellular identity as an underlying mechanism that parallels progressive stages of intranodular hepatocarcinogenesis (Lennerz et al. 2011). In the absence of liver cirrhosis, a belt-like liver tissue zone surrounding HCC shows abnormal expression patterns of CD10 and CD105/endoglin expression. Compared with the background tissue, peritumoral liver parenchyma revealed significantly decreased CD10 staining, irrespective of HCC or metastatic carcinoma, and exhibited belt-like CD105 expression in 66.7 % of cases of metastatic carcinoma and in 88.6 % of those with HCC (Nakamura 2009).

Spontaneous Regression of Hepatocellular Carcinoma

Introduction

Spontaneous regression of malignant neoplasms (also termed spontaneous remission, spontaneous healing, or vanishing tumor; review: Everson and Cole 1968) is an intriguing phenomenon characterized by the apparently spontaneous and unexpected disappearance of a malignant lesion expected to behave in a progressive or aggressive manner. Spontaneous disappearance of tumors was already described in 1938 (Chamberlain 1938). In their seminal publication on numerous examples of spontaneous regression, Everson and Cole (1968) defined spontaneous regression of a tumor as the partial or complete disappearance of a malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on neoplastic disease. In principle, this is a definition that had previously been proposed (Stewart 1952), but the second part of the definition may have to be revised in the light of the development of therapies since 1968. The incidence of spontaneous tumor regression is difficult to judge; it has previously been estimated to occur in about 1 in 100,000 cancers (Everson and Cole 1968), but it may either be less common or more common (review: Challis and Stam 1990).

The first case of complete regression of malignant melanoma was reported in 1899 (Bennett 1899; cited in Papac 1998). Two years later, William Osler reported on *The Medical Aspects of Carcinoma of the Breast, with a Note on the Spontaneous Disappearance of Secondary Growths* (Osler 1901). A first series of cases was published in 1918 (Rohdenburg 1918). The author listed 302 cases, of which however only 70 cases with temporary or permanent regression were analyzed in detail. Interestingly, this series revealed that most cases with regression occurred following incomplete tumor removal or an acute febrile illness, suggesting a role of a systemic inflammatory response (see below). In a review of cases identified in the world literature from 1900 to 1960, and under exclusion of squamous cell carcinoma of the skin, leukemia, and Hodgkin's disease, the four most common examples of regression were renal cell carcinoma, neuroblastoma, malignant melanoma, and choriocarcinoma (Everson and Cole 1968).

Spontaneous regression of HCC is defined as vanishing of primary HCC in the absence of a specific therapy. It is a rare and fascinating phenomenon that delivers informations that may be employed for the development of more potent treatment modalities (Randolph et al. 2008). From published reports, the actual incidence of spontaneous regression of HCC can hardly be estimated, but the phenomenon may be more common that formerly anticipated. In most reports, the tumors were standard (ordinary) HCCs, but spontaneous regression was also observed in variants, e.g., clear-cell hepatocellular carcinoma (Stoelben et al. 1998; Jeon et al. 2005).

The rate of spontaneous objective partial regression among patients with HCC was estimated as 0.406 % (Oquiñena et al. 2009). Histologic proof of HCC prior to tumor regression is available for only part of the reported cases, the remaining tumors being diagnosed as HCC based on serum AFP elevation and imaging findings. It cannot, therefore, be excluded that a subset of the cases showing regression may not have been ordinary HCCs or other malignant hepatocellular tumors. In part of the tumors with regression, the neoplasm histologically revealed complete necrosis of the coagulative type (Lebon et al. 1950). Regression can also occur in HCC metastases or as an abscopal effect after therapy of metastases (Okuma et al. 2011).

Selected References Gottfried et al. 1982; Lam et al. 1982; Sato et al. 1985; Suzuki et al. 1989; Ayres et al. 1990; reviews of the literature: Postow et al. 2012; Yokoyama et al. 2012; Kermiche-Rahali et al. 2013; Okano et al. 2013; Sasaki et al. 2013; Saito et al. 2014.

Regression of Solitary HCCs Versus Multicentric HCC

Most reports on spontaneous regression of HCC refer to regression of solitary tumors with or without associated remote metastases. Several reports describe regression of rather small HCCs, i.e., with a diameter of 6 cm or less, but regression of large tumors has also been reported (Morimoto et al. 2002; Alqutub et al. 2011; Maejima et al. 2011). Typically, regression of HCC is accompanied by a reduction or normalization of serum AFP levels (Del Poggio et al. 2009; Alqutub et al. 2011). Regression of HCC has been found to coincide with shrinkage of the liver with a rise of SGOT to sometimes relatively high levels (Lam et al. 1982). Whether this phenomenon is related to a compromised portal circulation is not known, although regressing HCC has been found in association with portal vein thrombosis (Iiai et al. 2003). So far, there are no factors allowing to predict spontaneous regression. In particular, there seems to be no relationship between the type of underlying chronic liver disease and spontaneous regression of HCC. On ultrasonography and CT images, a significant reduction in tumor size is typical (Del Poggio et al. 2009; Yokoyama et al. 2012), either with a remaining small nodule with denser structure of cyst formation or with complete radiological vanishing of the tumor. In case of remnant tumor, the term spontaneous partial regression has been used (Meza-Junco et al. 2007). In residual nodules, an enhancing rim may persist over long time periods (Del Poggio et al. 2009). Apart from spontaneous regression of solitary HCCs, there are rare instances of regression involving several HCC nodules, i.e., multicentric HCC (Blondon et al. 2004). In one patient with alcohol-related liver cirrhosis and multiple HCC nodules, spontaneous regression of all tumor masses but one occurred, associated with normalization of serum AFP (Blondon et al. 2004). The finding of one HCC nodule not undergoing regression is of particular interest and may suggest immune-mediated mechanisms, with one nodule eventually not expressing the relevant antigens and thus being spared.

Recurrence After Regression

Is spontaneous regression of HCC a durable phenomenon? In several cases, follow-up exceeding 24 months has documented that regression may be followed by long-term remissions (Lin et al. 2004; Ohtani et al. 2005). However, after apparently complete regression, HCCs can recur, associated with the emergence of gross tumor nodules and rising serum AFP values (Magalotti et al. 1998; Lee et al. 2000). Recurrence may be characterized by rapid growth (Nakajima et al. 2004).

Regression of Metastasizing Hepatocellular Carcinoma

There are rare reported situations where spontaneous or therapy-induced regression of HCC was associated with regression of remote metastases. This phenomenon has also been observed with

several other tumor types (Everson and Cole 1968). HCC cases published so far include lung metastases (Toyoda et al. 1999; Ikeda et al. 2001; Kojima et al. 2006; Harimoto et al. 2012), skull metastases (Nam et al. 2005), other skeletal metastases (Sato et al. 1985), and splenic and peritoneal metastases (Terasaki et al. 2000). Complete regression of pulmonary HCC metastases has been seen following hepatectomy for HCC. In this patient, lung metastases developed after hepatectomy, with rising AFP levels, and the metastases regressed after 5 months in the absence of any therapy (Harimoto et al. 2012). Regression of multiple lung metastases of HCC has been observed following regression of the primary tumor after transcatheter arterial embolization (Heianna et al. 2007). It has been proposed that anti-metastasis immune reactions initiated by regression of the primary tumor and liberation of tumor antigens may play a role for metastasis regression (Heianna et al. 2007). In one reported patient, lung metastases remained regressed even though the hepatic primary continued to grow (Ikeda et al. 2001).

Abscopal Regression

Exceptionally, spontaneous regression of primary HCC occurs through an abscopal effect. The abscopal effect, coined by Mole (Mole 1953), denotes the impact that therapeutic irradiation of a tissue has on remote nonirradiated tissues. For example, irradiation of a tissue has been followed by regression of tumors located in a remote nonirradiated compartment. It has been proposed that this effect is mediated by a radiation-induced increase in circulating cytokine levels, such as TNF-alpha or IL-18 (Ohba et al. 1998; Nakanishi et al. 2008). However, there is increasing evidence that local radiotherapy elicits an immune response, mediated by T lymphocytes, which may then attack neoplastic cell populations in a remote site (review: Kroemer and Zitvogel 2012). For HCC, one report described a patient with an HCC that regressed after radiotherapy for thoracic vertebral bone metastasis. Serum levels of TNF-alpha increased after radiotherapy (Ohba et al. 1998).

Pathology of Spontaneous Regression of Hepatocellular Carcinoma

Macroscopically, complete regression may leave an atrophic region in the liver, with or without a central fibrous area. The regressed tumor may, however, also be visible as a demarcated necrotic mass with a rim of granulation tissue. Regression of HCCs may result in the formation of cysts filled with a clear or sanguinolent fluid (Nakajima et al. 2004). Histologically, complete necrosis of the tumor is present in part of the cases.

Selected references: Andreola et al. 1987; Ozeki et al. 1996; Stoelben et al. 1998; Izuishi et al. 2000; Lee et al. 2002; Li et al. 2003; Ohta et al. 2005; Ohtani et al. 2005; Arakawa et al. 2008; Maejima et al. 2011.

In regressed HCCs showing apparently complete necrosis, histology reveals a "dirty" necrotic background with shadow cells and few scattered, naked and irregular, damaged nuclei (Lee et al. 2002; Li et al. 2003). The necrotic tumor may be encircled by a dense inflammatory reaction, with infiltrates of granulocytes, lymphocytes, and macrophages (Arakawa et al. 2008). In part of the cases, this perinodular inflammation is followed by a rim of fibrosis, sometimes with formation of a fibrous pseudocapsule (Yokoyama et al. 2012). Postregression liver biopsy from the site of the previous tumor showed uninflamed liver tissue without dysplasia (Lam et al. 1982). The area of the liver previously occupied by HCC may be replaced by regenerating non-dysplastic liver parenchyma (Lam et al. 1982).

Differential Diagnosis of Tumor Regression

Spontaneously regressing HCC may be confounded with other liver cell tumors that may undergo regression, e.g., liver cell adenoma and focal nodular hyperplasia (FNH) (Siegel and Hartmann 1987).

Pathogenesis of Regression

Numerous pathogenic mechanisms for HCC regression have been proposed, including tumor hypoxia following thrombosis of feeding arteries, intratumoral bleeding, antitumoral immune reactions, blood transfusion, alcohol withdrawal, infection, hemorrhagic shock, tumor inhibition by growth factor and/or cytokines, induction of differentiation, angiogenesis inhibition, deranged telomere and telomerase metabolism, induction of massive apoptosis, and the use of herbal medicine (reviews: Cole 1976, 1981; Firminger 1976; Thomas 1976; Singh and McKinney 1979; Stoll 1992; Kaiser 1994; Papac 1998; Kaiser et al. 2000; Bodey 2002; Nelson and Ganss 2006). In a review of 75 cases described in the English literature, the most common mechanisms claimed to have caused regression were tumor hypoxia (28.0 %) and a systemic inflammatory response (33.3 %). In 38.7 %, no possible cause was mentioned (Huz et al. 2012).

Total necrosis owing to massive tumor hypoxia has been reported (Andreola et al. 1987; Lee et al. 2002; Ohta et al. 2005). This hypoxia may be caused by spontaneous occlusion of the tumor's feeding artery (Imaoka et al. 1994; Lee et al. 2002), thrombotic occlusion of intratumoral arteries (Yokoyama et al. 2012), artery stenosis due to subintimal injury (e.g., incurred by hepatic angiography; Takayasu et al. 1986), sustained systemic hypotension (Huz et al. 2012), and a steeling phenomenon caused by peritumoral arterioportal shunt deviating blood from the tumor (Misawa et al. 1999). Spontaneous remission of HCC has, e.g., been observed after massive gastrointestinal hemorrhage (Tocci et al. 1990; Bastawrous et al. 2012) and following portal vein thrombosis (Kermiche-Rahali et al. 2013). Intratumoral bleeding can cause hemorrhagic necrosis followed by regression of the tumor (Nakajima et al. 2004).

There is evidence that systemic inflammatory responses may cause or at least induce mechanisms finally resulting in complete regression of HCCs. Such responses included trauma, endotoxin shock, cholangitis, and systemic cytokine storms (e.g., with elevated levels of interleukin-18; Abiru et al. 2002). There is indirect evidence that antitumor immune reactions of the host induce HCC regression. In one patient, recurrent HCC after segmentectomy was first treated with transarterial embolization (TAE), followed by tumor growth and spontaneous regression 1 year later (Nakai et al. 2001). It may be theorized that TAE-induced tumor damage had facilitated contact of tumor antigens with the host's immune system, followed by a strong immune response directed against the recurrent tumor. As regressing HCC may be associated with dense lymphocytic infiltrates (a so-called lymphoid stroma; Park et al. 2009) or dense lymphocytic and plasmacellular infiltrates (resembling the phenotype of medullary breast cancer; Zimmermann et al. 2002), immune responses directed against tumor-associated antigens have been proposed to play a role in spontaneous regression of HCC (Park et al. 2009).

Immune Reactions and Inflammatory Changes in Hepatocellular Carcinoma

Introduction

The tumor microenvironment of HCC is characterized by the presence of immunologic effector cells that perform an immune response of the host directed against the tumor (Figs. 14 and 15).

The immunologic functions of tumor microenvironments of the liver are influenced or even determined by the unique immunologic features of this organ, forming some sort of tertiary lymphoid structure (Crispe 2009; Goc et al. 2013). The immune effector cells and associated cells involved in anti-liver cancer responses comprise several well-defined categories, namely, tumor-infiltrating lymphocytes (TILs), regulatory T cells (TREGs), monocytes and tumor-associated macrophages (TAMs), natural killer cells, dendritic cells, myeloid-derived suppressor cells, granulocytes, and mast cells (Bianchi et al. 2011; Chan et al. 2011; Zhao et al. 2012b; Lindau et al. 2013).

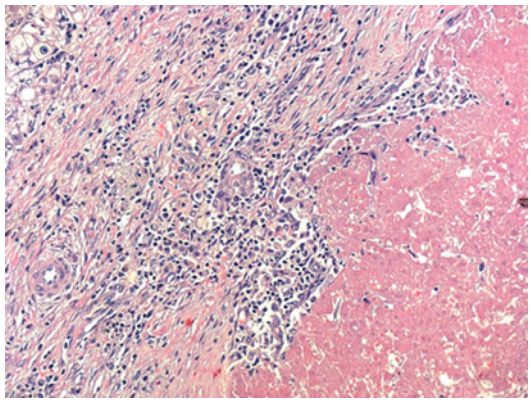

Fig. 14 Necrotic hepatocellular carcinoma is associated with an immune reaction characterized by lymphocytes and other immunologic effector cells. Part of these cells are in direct contact with necrotic tumor tissue (hematoxylin and eosin stain)

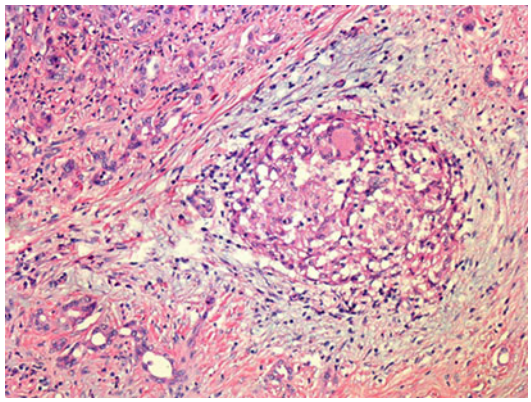

Fig. 15 In and around hepatocellular carcinomas, activated tumor-associated macrophages (TAMs) can transform into epithelioid cells and generate epithelioid cell granulomas, sometimes with Langhans-type giant cells (hematoxylin and eosin stain) (Reviews: O'Beirne and Harrison 2004; Berasain et al. 2009; Keibel et al. 2009; Korangy et al. 2010; Zamarron and Chen 2011; Guo et al. 2012; Leonardi et al. 2012; Nakagawa and Maeda 2012; Qin 2012; Senovilla et al. 2012; Aravalli 2013; Candido and Hagemann 2013; Fridman et al. 2013; Greten et al. 2013)

Lymphoid Cells: TILs and TREGs

Tumor-infiltrating lymphocytes (TILs) are a well-known phenomenon in HCC, albeit the density of TILs in HCCs is usually rather low (Shirabe et al. 2010). The density of TILs may increase as a function of tumor progression (Flecken et al. 2012). TIL accumulation is an early event in HCCs that determines long-term survival (Chew et al. 2012), whereby CD8(+) T cells located in the tumor stroma play a central role (An et al. 2014). Similar to dendritic cells, TILs are attracted to liver cancer through the action of locally released chemokines (Ben-Baruch 2012), but their recruitment is also influenced by interactions with other immune cells, in particular monocytoid cells (Kuang et al. 2010). Higher numbers of TILs are, however, relatively rare in HCCs and cholangiocarcinomas, but the presence of mixtures of CD3(+), CD4(+), and CD8(+) cells can affect prognosis (Shirabe et al. 2010). The calculated density of immune cells in tumor tissue was higher in the HCC group for which the prognosis was favorable, suggesting that lymphocyte density in HCC is a prognostic marker (Kawata et al. 1992). In few HCCs, the density of lymphoid cell or plasmacytoid infiltrates is excessively high, resulting in carcinoma with lymphoid stroma (Emile et al. 2000; Szekely 2001) or carcinomas resembling medullary carcinoma of the breast (Zimmermann et al. 2002).

A distinct and important category of lymphoid cells found in liver tumors are regulatory T cells (TREGs). TREGs were formerly known as suppressor T cells and constitute a subpopulation of T lymphocytes that modulate various immune responses, cause immune suppression of T cell-mediated responses, are involved in the inhibition of autoimmune reactions, play a role in cancer control, and maintain tolerance to self-antigens (Yu and Fu 2006; Wang and Wang 2007; Kosmaczewska et al. 2008; Wang 2008; Shirabe et al. 2010). In general, TREGs abrogate immune reactions of other immunologic effector cells (the so-called self-check mechanism). Based on the expression of several markers, TREGs come in several subpopulations, but the most important category has the phenotype, CD4(+), CD25(+), and Foxp3. The expression of Foxp3 is not specific for TREGs, as also recently activated non-TREG T lymphocytes express this transcription factor. TREGs make part of populations of immunologic effector cells in HCCs and are increased in part of the tumors (Yang et al. 2006;

Flecken et al. 2014). In one study, TREGs comprised 8.7 % of TILs (Unitt et al. 2005). TREGs infiltrating human HCCs promote, through their immunosuppressive function, immune evasion of these neoplasms (Pedroza-Gonzalez et al. 2013). Gamma/delta T cells infiltrating HCCs are functionally impaired by TREGs in an interleukin-10- and TGF-beta-dependent manner (Yi et al. 2013). TREG-induced immunosuppression also requires activation of Toll-like receptor 4/TLR4 signaling pathways (Yang et al. 2012). The presence of TREGs in HCCs is related to more aggressive biology, a highly invasive phenotype, and poor outcome (Gao et al. 2007; Zhou et al. 2009). Infiltration by Foxp3(+) TREGs in HCCs correlated with CD8(+) T cell impairment and was associated with portal vein tumor thrombosis and poor prognosis (Shen et al. 2011; Huang et al. 2012; Wang et al. 2012), whereby high Foxp3 expression levels were the most prominent predictors of poor outcome (Lin et al. 2013). Interestingly, TREG subsets with a different functional status are heterogeneously distributed in tumors and peritumoral tissues. In HCCs, intratumoral TREGs displayed higher frequencies and more suppressive phenotypic functions than those in the peritumoral compartment (Wu et al. 2013b).

Apart from T cells, B lymphocytes are also active in immune responses directed against HCCs. Specifically, infiltrating CD20(+) B lymphocytes are preferentially accumulated at the invasive front of the tumors (margin-infiltrating CD20(+) B cells). High densities of these cells were positively correlated with small tumor size, absence of vascular invasion, and increased density of CD8(+) T cells. Furthermore, high levels of margin-infiltrating B cells at the tumor invasion margin and penetrating the tumor capsule were associated with improved overall and recurrence-free survival (Shi et al. 2013).

Tumor-Associated Macrophages

Tumor-associated macrophages (TAMs) form an important group of immune effector cells that express a variety of tumor-promoting factors and factors that promote stroma formation, angiogenesis, and lymphangiogenesis.

Selected references: Van Loveren and Den Otter 1974; Biswas et al. 2008; Nardin and Abastado 2008; Yuan et al. 2008; Coffelt et al. 2009; Mantovani et al. 2009; Siveen and Kuutan 2009; Thelen et al. 2009; Sica 2010; Lawrence 2011; Fukuda et al. 2012; Wu and Zheng 2012; Biswas et al. 2013; Capece et al. 2013; Galdiero et al. 2013a; Long and Beatty 2013; Mano et al. 2013; Richards et al. 2013; You et al. 2013; Chazaud 2014.

TAMs form an important cell population in the inflammatory microenvironment of HCCs (Capece et al. 2013) and are mainly located to the tumor stroma where they undergo complex interactions with invading cancer cells, stromal myofibroblasts, endothelial cells, and other infiltrate cells, predominantly diverse classes of immunologic effector cells. TAMs are derived from circulating monocytes which in turn are produced in the bone marrow. TAMs promote cancer stem cell-like properties in HCCs through TGF-beta1-induced EMT (Fan et al. 2014).

TAMs, including those in liver cancers, form several functionally different subpopulations. TAMs basically present as fully polarized M1 cells and M2 or alternatively activated cells, with M1 and M2 cells forming the extremes of a continuum of functional TAM states (Sica and Mantovani 2012; Mantovani and Locati 2013). Classically activated M1 macrophages are also termed inflammatory macrophages, while alternatively activated M2 cells are termed regenerative macrophages (Zhou et al. 2014). Macrophages that infiltrate cancer tissues and become TAMs are usually driven by T cell-derived cytokines to acquired and alternative polarized of M2 phenotype (Mantovani et al. 2002). In most cancers, TAMs show properties of an alternative polarization phenotype (M2 TAMs) characterized by the expression of various chemokines, cytokines, and proteases that promote immunosuppression, tumor cell proliferation, and spreading of cancer cells (review: Través et al. 2012). TAMs affect EMT by downregulating the expression of E-cadherin

in HCC cells via an NF-kappaB/Slug pathway (Wang et al. 2014). The cells can also secrete angiogenic factors, e.g., vascular endothelial growth factor (VEGF), interleukin-8, matrix metalloproteinases (MMPs), and prostanoids, and through these products modulate the tumor microenvironment, pre-metastatic niche, and angiogenesis (Ono 2008). M2-polarized TAMs are preferentially present in glypican-3-positive HCCs (Takai et al. 2009). Inflammatory macrophages in liver are fibroblast-specific protein 1 positive and form a subpopulation that shows increased expression of COX2, osteopontin, inflammatory cytokines, and chemokines but reduced expression of MMP-3 and TIMP-3 compared with Kupffer cells and other macrophages (Österreicher et al. 2011). TAMs produce interleukin 6 and signal through STAT3 to promote expansion of HCC stem cells (Wan et al. 2014). c-Myc is expressed in TAMs and regulates their phenotype and function (Pello and Andrés 2013). The chemotactic cytokine CX3CR1 receptor contributes to TAM survival in cancers (Zheng et al. 2013). PD-L1-expressing monocytes/TAMs suppress tumor-specific T cell responses and hence promote tumor growth and progression (Kuang et al. 2009). As other macrophages, TAMs are derived from a bone marrow-derived monocyte lineage. Apart from mature TAMs, tumors including HCCs contain distinct types of monocytes that affect tumor behavior. Specifically, HCCs contain monocytes that express TIE2 (tyrosine kinase with Ig and endothelial growth factor (EGF) homology domain 2) (DePalma et al. 2013). These TIE2-expressing monocytes or TEMs are a marker for HCCs and modify growth and invasion of these neoplasms (Dapas et al. 2014). In particular, TEMs, through expression of the angiopoietin receptor TIE2, convey pro-angiogenic signals in HCCs (Germano and Daniele 2014).

HCC cells can trigger a transient activation of monocytes in stroma, whereby these cells acquire surface expression of PD-L1/B7-H1 molecules. This response is strengthened by the autocrine production of TNF-alpha and interleukin-10 released from activated monocytes, and the two factors themselves induce expression of PD-L1, thus forming an autocrine loop. Homing of TAMs to HCCs is mediated by upregulation of B7-H1, which mediates HCC immune escape (Chen et al. 2012). NF-kappaB has a central role in the recruitment and function of TAMs (Biswas and Lewis 2010; Mancino and Lawrence 2010; He and Karin 2011). In the cross talk between HCC cells and TAMs, NF-kappaB, STAT-3, and HIF-1 signaling pathways play a significant role (Capece et al. 2013; Mano et al. 2013). Expression of B7-H1 in HCC cells is associated with TAM infiltration of the tumors, whereby TAMs themselves induce B7-H1 expression in HCCs (Chen et al. 2012). In HCCs and peritumoral tissues, CD163(+) TAMs are more common than CD68(+) TAMs, but the density of CD68 (+) TAMs in peritumoral tissue was associated with better prognosis, but not of CD163(+) TAMs in peritumoral tissues (Kong et al. 2013). In HCCs, TAMs have complex functions that include antigen presentation, cytotoxicity directed against HCC cells, promotion of apoptosis, remodeling of cancer tissue and stroma, removal of dead cells and debris, and mediation of immune reactions. By these mechanisms, TAMs exert a marked influence on HCC progression (reviews: Shirabe et al. 2012). Proangiogenic TIE2(+)/CD31(+) TAMs are the predominant TAMs in metastatic lymph nodes (Kim et al. 2013b).

Granulomas and Sarcoid Reaction

In rare situations, TAMs in HCC are activated to become epithelioid cells and form granulomas (Cunningham et al. 1982; Tomimatsu et al. 1982). Granulomas have also been found in dysplastic nodules (Phelan and Nolan 2008). Similar to other visceral carcinomas, HCCs are sometimes associated with a marked granulomatous reaction in locoregional lymph nodes, a condition termed sarcoid reaction and caused by a strong cell-mediated immune reaction with transformation of activated macrophages into epithelioid cells (Adachi et al. 1993; Fong et al. 2012).

Natural Killer Cells and Pit Cells

Apart from B and T lymphocytes and macrophages, natural killer (NK) cells are involved in immune surveillance of liver tumors (Gao et al. 2008, 2009; Gao and Bertola 2011; Stojanovic and Cerwenka 2011; Desbois et al. 2012; Narni-Mancinelli et al. 2012; Bassiri et al. 2013; Cariani and Missale 2013; Tian et al. 2013; Vanherberghen et al. 2013). NK cells are abundant in the liver and serve as a central innate immune response component against a wide array of auto- and foreign antigens. It is estimated that NK cells, including pit cells, constitute 30–50 % of all hepatic lymphoid cells. Apart from regulation of immune responses, hepatic NK cells are also involved in reactions to acute or chronic liver damage, regeneration, and fibrotic processes (review: Cariani and Missale 2013). Homing of NK cells, including the liver, is subset specific, as visceral organs are preferentially populated by CD56(bright) CD16(neg/dull) noncytotoxic NK cells (Carrega and Ferlazzo 2012), whereby the cells are regulated by distinct microRNAs (Leong et al. 2012). There is evidence that tumor-associated NK cells become downregulated during tumor progression (Stojanovic et al. 2013). Tumor invasion and metastasis are regulated by an ubiquitin E3 ligase that plays an important role in the cytolytic activity of NK cells, NK lytic-associated molecule (NKLAM) (Hoover et al. 2012). Increased numbers of NK cells in HCCs and activated by monocytes can predict improved survival (Wu et al. 2013a). The anergy of NK cells is induced by cancer-expanded myeloid dendritic cells through membrane-bound TGF-beta1 (Li et al. 2009). Myeloid-derived suppressor cells (MDSCs) inhibit NK cells in HCC patients through the NKp30 receptor (Hoechst et al. 2009). A distinct population of hepatic large granular lymphocytes are the pit cells, a cell population that is critically involved in hepatic immune responses. In the course of liver regeneration, pit cells undergo a burst of proliferation followed by differentiation (Xu et al. 2011). In liver tumors there is an increase of large granular NK cells expressing the 12o kDa LAK-1 molecule (Stefanini et al. 1989).

Dendritic Cells

Dendritic cells (DCs) accumulate in the normal and inflamed liver (Lau and Thomson 2003; Ilkovitch and Lopez 2009). In comparison with liver cirrhosis, HCCs contain less DCs, in particular less CD83(+) DCs (Chen et al. 2000). In the course of hepatocarcinogenesis, DCs appear relatively late (Kapanadze et al. 2013). DCs in the nonneoplastic liver and in HCC consist of several categories, i.e., conventional DCs with intact antigen-presenting activity, functionally defective DCs with impaired motility and low ability to process and present antigens, and regulatory DCs with a high capacity to suppress T cell proliferation, induce the differentiation of regulatory T cells, or support immune tolerance (Umansky and Sevke 2013; Shurin et al. 2013). DCs serving as antigen-presenting cells accumulate in HCC tissues in variable numbers, and their presence affects local immune responses and tumor biology. HCC cells can inhibit the differentiation and maturation of DCs together with stimulating the production of TREGs (Li et al. 2007). A strong infiltration of DCs in HCCs is closely related to prognosis after surgical resection (Ido et al. 1994; Yin et al. 2003; Cai et al. 2006). DCs can be recruited to liver cancers and their microenvironments by the action of chemokines, cytokines, and chemotactic factors. The recruitment of dendritic cells is accomplished by the chemoattractant function of chemerin. Decreased chemerin expression in HCCs is associated with reduced DC accumulation and poor prognosis (Lin et al. 2011). HCC with low chemerin expression levels showed a more aggressive course and poorer survival (Lin et al. 2011), suggesting a role of the chemerin dendritic cell regulation loop. The function of tumor-associated dendritic cells is modulated by factors derived from HCC cells. Tumor-derived AFP impairs the differentiation and T cell stimulatory activity of dendritic cells (Pardee et al. 2014).

Myeloid-Derived Suppressor Cells (MDSCs)

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of early or immature myeloid cells of different stages of differentiation that are potent inhibitors of diverse immune reactions, mainly adaptive immune responses mediated by CD4(+) and CD8(+) T cells and cytotoxic effects of NK cells.

Reviews: Pan et al. 2008; Ostrand-Rosenberg and Sinha 2009; Lechner et al. 2010; Natarajan and Thomson 2010; Greten et al. 2011; Hu et al. 2011; Younos et al. 2011; Cohen et al. 2012; Ostrand-Rosenberg et al. 2012b; Chandra and Gravekamp 2013; Nagaraj et al. 2013; Zhong et al. 2013; Jackaman and Nelson 2014.

In the context of the present chapter, it is important that MDSCs suppress antitumor immune responses, hence contribute to tumor immune evasion (circumvention of tumor immunosurveillance), but these cells also promote cancer cell invasion, angiogenesis, and metastatic spread (Haile et al. 2012; Monu and Frey 2012; Qu et al. 2012). MDSCs are marrow-derived elements that originate from distinct stem/progenitor cell populations and which occur in two main lineages, i.e., granulocytic (or granulocyte/neutrophil-like) MDSCs, accounting for 80–90 % of all MDSCs, and monocytic (or monocyte-like) MDSCs, accounting for 10–20 %. Granulocytic MDSCs or neutrophil/G-MDSCs share many features with neutrophils, with which they have a complex relationship (review: Brandau et al. 2013). The immunophenotype of MDSCs, which can also be assessed in normal and tumor tissues, presents several subcategories of MDSCs. A common immunophenotype is CD33(+) CD11b(+) CD15(+)CD14(−)MHC class II(−), but a subset of MDSCs is CD(+)HLA-DR(−/low). Intracellular markers comprise arginase and iNOS2. For an Internet poster depicting important aspects of MDSCs, see www.nature.com/nci/poster/mdscs. Both G-MDSCs and M-MDSCs are able to polarize from a classically activated phenotype (M1) to an alternatively activated one (M2), similar to TAMs (Yang et al. 2013). From their precursors, MDSCs can be recruited and expanded by various factors, including the HGF/c-met signaling pathway and STAT-3 (Yen et al. 2013). MDSCs mainly consists of cells derived from neutrophilic and monocytic lineages (Duffy et al. 2013; Schmid and Varner 2012). However, MDSCs can also be induced from NK cells in tumor microenvironments (Park et al. 2013). Accumulation of MDSCs in tissues involves TNF signaling (Zhao et al. 2012c), uPA and uPA receptor-dependent pathways (Ilkovitch et al. 2012), and the action of SIRT1 (Liu et al. 2014). The accumulation of MDSCs is stimulated by the proinflammatory S100 proteins, S100A8 and S100A9 (Sinha et al. 2008). The development of functional MDSCs is promoted by microRNAs-155 and microRNAs-21 (Li et al. 2014). In tumor tissues, immature MDSCs are modulated in their differentiation and function through a complex interaction with the tumor microenvironment (Gabrilovich et al. 2012; Ostrand-Rosenberg et al. 2012b). The survival of MDSCs is controlled by apoptosis via caspase family proteins and the Fas/FasL pathway (Ostrand-Rosenberg et al. 2012a). MDSCs express Fas receptor and undergo apoptosis in response to T cell-expressed Fas ligand/FasL (Sinha et al. 2011). On the other hand, deregulation of Bcl-xL and Bax in MDSCs contributes to their apoptosis resistance (Hu et al. 2013).

MDSCs exert their immunosuppressive functions through several pathways. The express cytoplasmic arginase and nitric oxide synthase 2/NOS2, which together block the translation of the T cell CD3 zeta chain, in part through nitrotyrosine, thus inhibit T cell proliferation and promote T cell apoptosis. MDSCs also stimulate the production of immunosuppressive TREGs and secrete immunosuppressive cytokines. Circulating MDSCs correlate with immunosuppression and inflammation in patients with cancer (Ohki et al. 2012). The immunosuppressive function in cancer, which is important for the failure of immunosurveillance, is based on MDSC effects exerted on several immune cell systems, including

the activation of TREGs (Hoechst et al. 2008; Kalathil et al. 2013) and the downregulation of NK cells and dendritic cells (Haile et al. 2012; Monu and Frey 2012; Solito et al. 2012). In cancers, MDSCs also promote epithelial-mesenchymal transition (EMT) and tumor cell invasion and dissemination (Toh et al. 2011). Similar to TAMs, MDSCs in part mediate their effects on other cells through exosomal pathways (Burke et al. 2014).

CD14(+) MDSCs are an important immunomodulatory cell subpopulation in the liver and in hepatic tumors (Ren et al. 2012). The mechanisms of MDSC recruitment to the liver are not yet fully understood. As the name implies, the majority of these effector cells originate from the bone marrow. MDSCs can be induced from circulating monocytoid cells/monocytes by activated hepatic stellate cells (HSCs) (Chou et al. 2011; Hoechst et al. 2013). This process operates in a CD44-dependent manner. MDSCs accumulate in the liver in the setting of chronic viral infection, particularly chronic HCV infection (Velazquez et al. 2012). In the liver, upregulated MDSCs impair dendritic cell function and promote hepatocarcinogenesis (Hu et al. 2011).

Patients with HCCs display the common subset of MDSCs, but they also show the population of MDSCs characterized by CD14(+)HLA-DR(−/low) and increased in the blood. These MDSCs promote immunosuppression through the induction of CD4(+)CD25(+)Foxp3(+) TREGs (Hoechst et al. 2008). In one investigation, almost one third of hepatic CD11(+) myeloid DCs were CD14(+) MDSC (Kelly et al. 2014). Increased numbers of CD14(+) MDSCs in HCCs are correlated with tumor progression (Arihara et al. 2013). The most important mechanism for the promotion of tumor progression is probably related to the immunosuppressive function of MDSCs, abolishing antitumor immune reactions and favoring tumor immunoevasion. MDSCs inhibit NK cells in patients with HCC (Hoechst et al. 2009), but this effect is not found with all subsets of MDSCs, as, e.g., RAE-1-positive mononuclear MDSCs activate NK cells (Nausch et al. 2008). The activity of MDSCs in HCCs is associated with a downregulation of anticancer dendritic cell function (Hu et al. 2011). Tumor-infiltrating monocytic MDSCs mediate CCR5-dependent recruitment of TREGs (Schlecker et al. 2012), a further immunosuppressive mechanism. In mice, upregulated MDSCs promoted HCC development through impairment of dendritic cell function (Hu et al. 2011).

The development and function of myeloid cells in HCC and other cancers is also regulated by stromal cells. Myofibroblasts are involved in the upregulation of S100A8 and S100A9 and the differentiation of myeloid cells (Kim et al. 2012). A novel subset of MDSCs are so-called fibrocytes, a term that was previously preoccupied by the mature offspring of fibroblasts. Fibrocytes according to the new definition are hematopoietic stem cell-derived MDSCs that bear the phenotypic and functional hallmarks of fibrocytes and are implicated in chronic inflammation and fibrosis. Fibrocytes from cancer patients suppressed anti-CD3-mediated T cell proliferation (Zhang et al. 2013).

Granulocytes

Neutrophils interact with the substratum of the extracellular matrix of tumors in a complex way which affects various aspects of tumor cell behavior, in particular invasion (Dumitru et al. 2013). Neutrophil granulocytes, apart from the role as acute cellular reactants to cell and tissue injury and bacterial infection, can interact with several cell populations and secrete numerous cytokines and signaling molecules (review: Galdiero et al. 2013b). Neutrophils from patients with HCC differ from other neutrophils in that they can produce CCL2, the amount of CCL2 produced being a function of the tumor load. The survival rate of HCCs having high-level CCL2 production by neutrophils was significantly lower than that for other patients (Tsuda et al. 2012). Although eosinophil granulocytes can be found in the stroma of both HCCs and cholangiocarcinomas, relatively few informations are available regarding their function, in contrast to other neoplasms. There is evidence that eosinophils can exert antitumor cytotoxic activity

directed against HCCs. Experimental expression of eotaxin in HCC cells affected the growth of these cells, and eosinophils producing TNF-alpha could kill tumor cells (Kataoka et al. 2004).

Mast Cells

HCCs and cholangiocarcinomas can contain mast cells in their stroma, but the density of this cell type is usually low (Cervello et al. 2005). In HCCs, mast cell density did not correlate with age or sex of patients, tumor stage, or grade (Grizzi et al. 2003). Mast cells can mobilize myeloid-derived suppressor cells and TREGs in the tumor microenvironment via the IL-17 pathway (Yang et al. 2010). Mast cells and Foxp3(+) TREGs often accumulate in the peritumoral tissue or peripheral stromal components, and the combined presence of these two cell types predicts prognosis (Ju et al. 2009). Infiltrating mast cells in HCCs can promote tumor angiogenesis (Peng et al. 2005) and may be involved in capillarization of sinusoidal vascular channels (Grizzi et al. 2003). In human HCC cell lines, histamine and spontaneously released mast cell granules affect cell growth, in that histamine downregulated the expression of beta-catenin, associated with caspase-3 activation (Lampiasi et al. 2007).

Hepatic Stellate Cells

An important hepatic cell population that is involved in immune mechanisms in the liver are the hepatic stellate cells (HSCs), cells that are activated by overexpression of c-myc in hepatocytes (Nevzorova et al. 2013) and probably also HCC cells. HSCs have immunosuppressive properties, enhance the expression of cytokines, and promote proliferation and migration of cancer cells. HSCs accomplish these functions, which are thought to affect HCC behavior, through the induction of T cell hyporesponsiveness, accelerated activated T cell apoptosis, increase in the number of Treg cells, and inhibition of T cell-mediated cytotoxicity. They may therefore induce T cell anergy and by this facilitate the immunologic escape of HCC cells (Zhao et al. 2012a). Intratumoral HSCs influence the progression of HCC, and their presence in greater numbers was an independent factor for overall and recurrence-free survival in HCC patients (Sun et al. 2013).

Communication of Immune and Inflammatory Cells in Liver Tumors Through Exosomes and Related Vehicles

As discussed in more detail in the chapter of liver metastases, exosomes as distinct extracellular vesicles released from normal and tumor cells play an important role in intercellular communication. Exosomes and related vehicles carry a cargo that contains signal substances, growth factors, microRNA and other short RNAs, and DNA.

Reviews: Royo and Falcon-Perez 2012; Vickers and Remaley 2012; Bai et al. 2013; Crescitelli et al. 2013; Kim et al. 2013a; Rayner and Hennessy 2013; Wendler et al. 2013; Voloshin et al. 2014.

Exosome-mediated exchange of informations is increasingly recognized as a critical mechanism in tumor cell fating and in tumor-associated immune and inflammatory reactions, including those found in HCCs and cholangiocarcinomas. Exosomal cargo delivery may play a role in the overall function of the immunological synapse (Delon and Germain 2000). A particularly important role is played by microvesicle-/exosome-transported microRNAs (Boon and Vickers 2013). Myeloid-derived suppressor cells produce exosomes carrying signal substances (Burke et al. 2014), and microRNAs make part of the cargo of T cell exosomes (Mittelbrunn et al. 2011) and can be transferred from TAMs to HCC cells (Aucher et al. 2013). MicroRNA transfer from human macrophages to HCC cells inhibits proliferation of these cells (Aucher et al. 2013). Apart from a modulation of immune responses, exosomal microRNA derived from macrophages can also stimulate invasive features of cancer cells (Yang et al. 2011). It may be assumed that the physiological capability of

macrophages to locomote and invade tissues can be adopted by cancer cells via exosomal information transfer. Furthermore, promotion of growth of HCC cells can be acquired by exosomal microRNA exchange (Kogure et al. 2011). Immune cell-derived microparticles/exosomes can facilitate HCC metastasis by transferring integrin alpha(M)beta2 to tumor cells (Ma et al. 2013). Macrophages not only transmit exosomal signals to tumor cells but also communicate among each other through this pathway, a mechanism involved in the regulation of macrophage differentiation (Ismail et al. 2013). Hepatic exosomes are also involved in the transmission of HCV to induce productive infection (Cosset and Dreux 2014). Exosomes originating from normal liver cells can, through the transport of signal substances, affect other hepatic ells. E.g., microparticles from liver cells can activate hedgehog signaling in hepatic endothelial cells (Witek et al. 2009). Exosomal information transfer can also occur from extrahepatic sources to the liver. Exosomes from intestinal mucosal cells can carry prostaglandin E2 and suppress the activation of liver NK cells (Deng et al. 2013).

A distinct mode of vesicle-mediated transfer is found in neutrophils, also those acting in tumor microenvironments. Neutrophils can produce tubulovesicular extensions termed cytonemes ("cell threads," membrane tethers) anchored to the substrate of extracellular matrix via an L-selectin-dependent, beta1- and beta2-independent mechanism. This attachment has an important role in neutrophil function, specifically adhesion, secretory processes, and phagocytosis (Galkina et al. 2005, 2013). In principle, cytonemes are specialized filopodia which in turn are cellular protrusions implicated in numerous types of mechanosensory processes. Cytonemes are critically involved in the handling and dispersion of diverse morphogens (review: Kornberg 2014) and mediate important steps in cell-to-cell signaling (Gradilla and Guerrero 2013). It may be anticipated that crucial interactions between leukocytes present in the stromal niche and tumor cells depend on the function of cytonemes acting as signal-transporting nanotubes and related structures.

References

Abiru et al. (2002) http://www.ncbi.nlm.nih.gov/pubmed/11922591

Adachi S, Ueda H, Ishikawa T, Ozaki A (1993) A case report of sarcoid reactions with hepatocellular carcinoma and two early gastric carcinomas (in Japanese). Nihon Geka Gakkai Zasshi 94:534–537

Alqutub A, Peck D, Marotta P (2011) Spontaneous regression of a large hepatocellular carcinoma: case report. GMS Ger Med Sci 9. Doc07

An JL, Ji Q, An JJ, Masuda S, Tsuneyama K (2014) Clinicopathological analysis of CD8-positive lymphocytes in the tumor parenchyma and stroma of hepatocellular carcinoma. Oncol Lett 8:2284–2290

Andreola S, Audisio RA, Mazzaferro V, Doci R, Milella M (1987) Spontaneous massive necrosis of a hepatocellular carcinoma. Tumori 73:203–207

Arakawa Y, Mori H, Ikegami T, Hanaoka J, Kanamoto M, Kanemura H, Morine Y, Imura S et al (2008) Hepatocellular carcinoma with spontaneous regression: report of a rare case. Hepatogastroenterology 55:1770–1772

Aravalli RN (2013) Role of innate immunity in the development of hepatocellular carcinoma. World J Gastroenterol 19:7500–7514

Arihara F, Mizukoshi E, Kitahara M, Takata Y, Arai K, Yamashita T, Nakamoto Y, Kaneko S (2013) Increase in CD14+HLA-DR-/low myeloid-derived suppressor cells in hepatocellular carcinoma patients and its impact on prognosis. Cancer Immunol Immunother 62:1421–1430

Aucher A, Rudnicka D, Davis DM (2013) MicroRNAs transfer from human macrophages to hepatocarcinoma cells and inhibit proliferation. J Immunol 191:6250–6260

Ayres RC, Robertson DA, Dewbury KC, Millward-Sadler GH, Smith CL (1990) Spontaneous regression of hepatocellular carcinoma. Gut 31:722–724

Bai J, Xie X, Lei Y, An G, He L, Chen R (2013) Consideration of dual characters of exosomes in the tumour immune response. Cell Biol Int. doi:10.1002/cbin.10208

Bassiri H, Das R, Nichols KE (2013) Invariant NKT cells. Killers and conspirators against cancer. Oncoimmunol 12:e27440

Bastawrous S, Kogut MJ, Bhargava P (2012) Spontaneous regression of hepatocellular carcinoma in a cirrhotic patient: possible vascular hypothesis. Singapore Med J 53:e218–e221

Ben-Baruch A (2012) The tumor-promoting flow of cells into, within and out of the tumor site: regulation by the inflammatory axis of TNFα and chemokines. Cancer Microenviron 5:151–164

Bengmark S (1989) Tumour calcification after hepatic dearterialization. Br J Surg 76:317–318

Bennett WH (1899) Some peculiarities in the behavior of certain malignant and innocent growths. Lancet 1:3–7

Berasain C, Castillo J, Perugorria MJ, Latasa MU, Prieto J, Avila MA (2009) Inflammation and liver cancer: new molecular links. Ann N Y Acad Sci 1155:206–221

Bernadino ME (1979) Computed tomography of calcified liver metastases. J Comput Assist Tomogr 3:32–35

Bezerra A, D'Ippolito G, Martelli P, Pinto G, Galvao M, Szeijnfeld J (2003) Calcificaçoes hepaticas: frequência a significado. Radiol Bras 36:199–205

Bianchi G, Borgonovo G, Pistoia V, Raffaghello L (2011) Immunosuppressive cells and tumour microenvironment: focus on mesenchymal stem cells and myeloid derived suppressor cells. Histol Histopathol 26:941–951

Bioulac-Sage P, Balabaud C (2011) Perinodular CK19 loss in hepatocarcinogenesis. Clin Res Hepatol Gastroenterol 35:783–785

Biswas SK, Lewis CE (2010) Nf-kB as a central regulator of macrophage function in tumors. J Leukoc Biol 88:877–884

Biswas S, Sica A, Lewis CE (2008) Plasticity of macrophage function during tumor progression: regulation by distinct molecular mechanisms. J Immunol 180:2011–2017

Biswas SK, Allavena P, Mantovani A (2013) Tumor-associated macrophages: functional diversity, clinical significance, and open questions. Semin Immunopathol 35:585–600

Blondon H, Fritsch L, Cherqui D (2004) Two cases of spontaneous regression of multicentric hepatocellular carcinoma after intraperitoneal rupture: possible role of immune mechanisms. Eur J Gastroenterol Hepatol 16:1355–1359

Bodey B (2002) Spontaneous regression of neoplasms: new possibilities for immunotherapy. Expert Opin Biol Ther 2:459–476

Boon RA, Vickers KC (2013) Intercellular transport of microRNAs. Arterioscler Thromb Vasc Biol 33:186–192

Brandau S, Moses K, Lang S (2013) The kinship of neutrophils and granulocytic myeloid-derived suppressor cells in cancer: cousins, siblings or twins? Semin Cancer Biol 23:171–182

Burke M, Choksawangkarn W, Edwards NJ, Ostrand-Rosenberg S, Fenselau C (2014) Exosomes from myeloid derived suppressor cells carry biologically active proteins. J Proteome Res 13:836–843

Cai XY, Gao Q, Qiu SJ, Ye SL, Wu ZQ, Fan J, Tang ZY (2006) Dendritic cell infiltration and prognosis of human hepatocellular carcinoma. J Cancer Res Clin Oncol 132:293–301

Candido J, Hagemann T (2013) Cancer-related inflammation. J Clin Immunol 33(suppl 1):S79–S84

Capece D, Fischietti M, Verzella D, Gaggiano A, Cicciarelli G, Tessitore A, Zazzeroni F, Alesse E (2013) The inflammatory microenvironment in hepatocellular carcinoma: a pivotal role for tumor-associated macrophages. Biomed Res Int 13:187204

Cariani E, Missale G (2013) KIR/HLA immunogenetic background influences the evolution of hepatocellular carcinoma. Oncoimmunol 12:e26622

Carrega P, Ferlazzo G (2012) Natural killer cell distribution and trafficking in human tissues. Front Immunol 3:347

Cervello M, Foderaa D, Florena AM, Sorsi M, Tripodo C, D'Alessandro N, Montalto G (2005) Correlation between expression of cyclooxygenase-2 and the presence of inflammatory cells in human primary hepatocellular carcinoma: possible role in tumor promotion and angiogenesis. World J Gastroenterol 11:4638–4643

Challis GB, Stam HJ (1990) The spontaneous regression of cancer. A review of cases from 1990 to 1987. Acta Oncol 29:545–550

Chamberlain D (1938) Spontaneous disappearance of carcinoma. Br Med J 1:508–526

Chan T, Wiltrout RH, Weiss JM (2011) Immunotherapeutic modulation of the suppressive liver and tumor microenvironments. Int Immunopharmacol 11:879–889

Chandra D, Gravekamp C (2013) Myeloid-derived suppressor cells: cellular missiles to target tumors. Oncoimmunology 2:e26967

Chazaud B (2014) Macrophages: supportive cells for tissue repair and regeneration. Immunobiology 219:172–178

Chen S, Akbar SM, Tanimoto K, Ninomiya T, Iuchi H, Michitaka K, Horiike N, Onji M (2000) Absence of CD38-positive mature and activated dendritic cells at cancer nodules from patients with hepatocellular carcinoma: relevance to hepatocarcinogenesis. Cancer Lett 148:49–57

Chen J, Li G, Meng H, Fan Y, Song Y, Wang S, Zhu F, Guo C, Zhang L, Shi Y (2012) Upregulation of B7-H1 expression is associated with macrophage infiltration in hepatocellular carcinomas. Cancer Immunol Immunother 61:101–108

Chew V, Chen J, Lee D, Loh E, Lee J, Lim KH, Weber A, Slankamenac K, Poon RT et al (2012) Chemokine-driven lymphocyte infiltration: an early intratumoral event determining long-term survival in resectable hepatocellular carcinoma. Gut 61:427–438

Chin NW, Chapman I, Coopersmith H, Jimenez FA (1986) Parenchymal calcification in hepatocellular carcinoma. N Y State J Med 86:596–598

Chiu YC, Chuang CH, Tsai HM, Chen CY (2009) Massive hepatic infarction after pure ethanol injection and radiofrequency ablation therapy for hepatocellular carcinoma: a case report. Kaohsiung J Med Sci 25:156–159

Chou HS, Hsieh CC, Yang HR, Wang L, Arakawa Y, Brown K, Wu Q, Lin F, Peters M et al (2011) Hepatic stellate cells regulate immune response by way of induction of myeloid suppressor cells in mice. Hepatology 53:1007–1019

Chow AK, Ng L, Lam CS, Wong SK, Wan TM, Cheng NS, Yau TC, Poon RT et al (2013) The enhanced metastatic potential of hepatocellular carcinoma (HCC) cells with Sorafenib resistance. PLoS One 8:e78675

Chuang CH, Chen CY, Tsai HM (2005) Hepatic infarction and hepatic artery pseudoaneurysm with peritoneal

bleeding after radiofrequency ablation for hepatoma. Clin Gastroenterol Hepatol 3:A23
Coffelt SB, Hughes R, Lewis CE (2009) Tumor-associated macrophages: effectors of angiogenesis and tumor progression. Biochim Biophys Acta 11:11–18
Cohen PA, Ko JS, Storkus WJ, Spencer CD, Bradley JM, Gorman JE, McCurry DB et al (2012) Myeloid-derived suppressor cell adhere to physiologic STAT3-vs STAT5-dependent hematopoietic programming, establishing diverse tumor-mediated mechanisms of immunologic escape. Immunol Invest 41:680–710
Cole WH (1976) Spontaneous regression of cancer and the importance of finding its cause. Natl Cancer Inst Monogr 44:5–9
Cole WH (1981) Efforts to explain spontaneous regression of cancer. J Surg Oncol 17:201–209
Cosset and Dreux (2014) http://www.ncbi.nlm.nih.gov/pubmed/24512825
Crescitelli R, Lässer C, Szabo TG, Kittel A, Eldh M, Dianzani I, Buzas EI, Lötvall J (2013) Distinct RNA profiles in subpopulations of extracellular vesicles: apoptotic bodies, microvesicles and exosomes. J Extracell Vesic 2:20677
Crispe IN (2009) The liver as a lymphoid organ. Annu Rev Immunol 27:147–163
Cunningham D, Mills PR, Quigley EM, Patrick RS, Watkinson G, MacKenzie JF, Russell RI (1982) Hepatic granulomas: experience over a 10-year period in the west of Scotland. Q J Med 51:162–170
Czauderna P, Zbrzezniak G, Narozanski W, Sznurkowska K, Skoczylas-Stoba B, Stoba C (2005) Pulmonary embolism: a fatal complication of arterial chemoembolization for advanced hepatocellular carcinoma. J Pediatr Surg 40:1647–1650
Da Ines D, Buc E, Petitcolin V, Flamein R, Lannareix V, Achim A, Garcier JM (2010) Massive hepatic necrosis with gastric, splenic, and pancreatic infarctions after ethanol ablation for hepatocellular carcinoma. J Vasc Interv Radiol 21:1301–1305
Dapas B, Grassi M, Grassi G (2014) Can TIE-2 expressing monocytes represent a novel marker for hepatocellular carcinoma? Hepatobiliary Surg Nutr 3:175–178
Del Poggio P, Mattiello M, Gilardoni L, Jamoletti C, Colombo S, Zabbialini G (2009) The mysterious case of spontaneous disappearance of hepatocellular carcinoma. Dig Liver Dis 41:e21–e25
Del Val A, Nos P, Marti-Bonmati L, Talens A, Benages R, Berenguer J (1991) Calcification of the portal vein associated with hepatocarcinoma (in Spanish). Rev Esp Enferm Dig 80:130–132
Delon J, Germain RN (2000) Information transfer at the immunological synapse. Curr Biol 10: R923–R933
Deng ZB, Zhuang X, Ju S, Xiang X, Mu J, Liu Y, Jiang H, Zhang L, Mobley J, McClain C et al (2013) Exosome-like nanoparticles from intestinal mucosal cells carry prostaglandin E2 and suppress activation of liver NKT cells. J Immunol 190:3579–3589
DePalma M, Coukos G, Semela D (2013) TIE2-expressing monocytes: a novel cellular biomarker for hepatocellular carcinoma ? Hepatology 57:1294–1296
Desbois M, Rusakiewicz S, Locher C, Zitvogel L, Chaput N (2012) Natural killer cells in non-hematopoietic malignancies. Front Immunol 3:395
Dhingra S, Schwartz M, Kim E, Mabel Ko H, Ward SC, Fiel MI, Thung SN (2014) Histological changes in nontumoral liver secondary to radioembolization of hepatocellular carcinoma with Yttrium 90-impregnated microspheres: report of two cases. Semin Liver Dis 34:465–468
Di Marco V, De Vita F, Koskinas J, Semela D, Toniutto P, Verslype C (2013) Sorafenib: from literature to clinical practice. Ann Oncol 24(suppl 2):ii30–ii37
Duffy A, Zhao F, Haile L, Gamrekelashvili J, Fioravanti S, Ma C, Kapanadze T, Compton K et al (2013) Comparative analysis of monocytic and granulocytic myeloid-derived suppressor cell subsets in patients with gastrointestinal malignancies. Cancer Immunol Immunother 62:299–307
Dufour JF, Bargellini I, De Maria N, De Simone P, Goulis I, Marinho RT (2013) Intermediate hepatocellular carcinoma: current treatments and future perspectives. Ann Oncol 24(suppl 2):ii24–ii29
Dumitru CA, Lang S, Brandau S (2013) Modulation of neutrophil granulocytes in the tumor microenvironment: mechanisms and consequences for tumor progression. Semin Cancer Biol 23:141–148
Emile JF, Adam R, Sebagh M, Marchadier E, Falissard B, Dussaix E, Bismuth H, Reynes M (2000) Hepatocellular carcinoma with lymphoid stroma: a tumour with good prognosis after liver transplantation. Histopathology 37:523–529
Enne M, Pacheco-Moreira LF, Cerqueira A, Balbi E, Pereira JL, Martinho JM (2004) Fatal hemobilia after radiofrequency thermal ablation for hepatocellular carcinoma. Surgery 135:460–461
Everson T, Cole W (1968) Spontaneous regression of cancer. J.B. Saunder, Philadelphia
Fan QM, Jing YY, Yu GF, Kou XR, Ye F, Gao L, Li R, Zhao QD, Yang Y, Lu ZH et al (2014) Tumor-associated macrophages promote cancer stem cell-like properties via transforming growth factor-beta1-induced epithelial-mesenchymal transition in hepatocellular carcinoma. Cancer Lett 352:160–168
Firminger HI (1976) A pathologist looks at spontaneous regression of cancer. Natl Cancer Inst Monogr 44:15–18
Flecken et al. (2012) http://www.ncbi.nlm.nih.gov/pubmed/21479622
Flecken T, Schmidt N, Hild S, Gostick E, Drognitz O, Zeiser R, Schemmer P, Bruns H et al (2014) Immunodominance and functional alterations of tumor-associated antigen-specific CD8+ T-cell responses in hepatocellular carcinoma. Hepatology 59:1415–1426
Fong ZV, Wong J, Maley WR, Sandorfi N, Winter JM, Koniaris LG, Sauter PK, Yeo CJ et al (2012) Sarcoid-

reaction mimicking metastatic malignant hepatopancreatobiliary tumors. Report of two cases and review of the literature. J Gastrointest Surg 16:1245–1250

Fridman WH, Dieu-Nosjean MC, Pagès F, Cremer I, Damotte D, Sautès-Fridman C et al (2013) The immune microenvironment of human tumors: general significance and clinical impact. Cancer Microenviron 6:117–122

Friedman AC (1988) Calcification in hepatocellular carcinoma. AJR Am J Roentgenol 151:838–839

Fukuda K, Kobayashi A, Watabe K (2012) The role of tumor-associated macrophage in tumor progression. Front Biosci (Sch Ed) 4:787–798

Fukuya T, Yabuuchi H, Seo Y, Fukuda T, Koga M (1999) Hepatocellular carcinoma with ring calcification: report of two cases. Radiat Med 17:379–382

Gabrilovich DI, Ostrand-Rosenberg S, Bronte V (2012) Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 12:253–268

Galdiero MR, Garlanda C, Jaillon S, Maroe G, Mantovani A (2013a) Tumor associated macrophages and neutrophils in tumor progression. J Cell Physiol 228:1404–1412

Galdiero MR, Bonavita E, Barajon I, Garlanda C, Mantovani A, Jaillon S (2013b) Tumor associated macrophages and neutrophils in cancer. Immunobiology 218:1402–1410

Galkina SI, Molotkovsky JG, Ullrich V, Sud'ina GF (2005) Scanning electron microscopy study of neutrophil membrane tubulovesicular extensions (cytonemes) and their role in anchoring, aggregation and phagocytosis. The effect of nitric oxide. Exp Cell Res 304:620–629

Galkina SI, Fedorova NV, Stadnichuk VI, Sud'ina GF (2013) Membrane tubulovesicular extensions (cytonemes): secretory and adhesive cellular organelles. Cell Adh Migr 7:174–186

Gao B, Bertola A (2011) Natural killer cells take two tolls to destruct bile ducts. Hepatology 53:1076–1079

Gao Q, Qiu SJ, Fan J, Zhou J, Wang XY, Xiao YS, Xu Y, Li YW, Tang ZY (2007) Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol 25:2598–2693

Gao B, Jeong WI, Tian Z (2008) Liver: an organ with predominant innate immunity. Hepatology 47:729–736

Gao B, Radaeva S, Park O (2009) Liver natural killer and natural killer T cells: immunobiology and emerging roles in liver diseases. J Leukoc Biol 86:513–528

Germano D, Daniele B (2014) TIE2-expressing monocytes as a diagnostic marker for hepatocellular carcinoma correlates with angiogenesis. Hepatobiliary Surg Nutr 3:166–167

Goc J, Fridman WH, Sautès-Fridman C, Dieu-Nosjean MC (2013) Characteristics of tertiary lymphoid structures in primary cancers. Oncoimmunol 12:e26836

Gottfried EB, Steller R, Paronetto F, Lieber CS (1982) Spontaneous regression of hepatocellular carcinoma. Gastroenterology 82:770–774

Gradilla AC, Guerrero I (2013) Cytoneme-mediated cell-to-cell signaling during development. Cell Tissue Res 352:59–66

Greten TF, Manns MP, Korangy F (2011) Myeloid derived suppressor cells in human diseases. Int Immunopharmacol 11:802–807

Greten TF, Duffy AG, Korangy F (2013) Hepatocellular carcinoma from an immunological perspective. Clin Cancer Res 19:6678–6685

Grizzi F, Franceschini B, Chiriva-Internati M, Liu Y, Hermonat PL, Dioguardi N (2003) Mast cells and human hepatocellular carcinoma. World J Gastroenterol 9:1469–1473

Guo CL, Yang HC, Yang XH, Cheng W, Dong TX, Zhu WJ, Xu Z, Zhao L (2012) Associations between infiltrating lymphocyte subsets and hepatocellular carcinoma. Asian Pac J Cancer Prev 13:5909–5913

Haile LA, Greten TF, Korangy F (2012) Immune suppression: the hallmark of myeloid derived suppressor cells. Immunol Invest 41:581–594

Hall PM, Winkelman EI, Hawk WA, Hermann RE (1970) Calcification in the liver, an unusual feature of ductal cell hepatic carcinoma. Report of a case. Cleve Clin Q 37:93–105

Harimoto N, Shirabe K, Kajiyama K, Gion T, Takenaka M, Nagaie T, Maehara Y (2012) Spontaneous regression of multiple pulmonary recurrences of hepatocellular carcinoma after hepatectomy: report of a case. Surg Today 42:475–478

He G, Karin M (2011) NK-kB and STAT3 – key players in liver inflammation and cancer. Cell Res 21:159–168

Heianna J, Miyauchi T, Suzuki T, Ishida H, Hashimoto M, Watarai J (2007) Spontaneous regression of multiple lung metastases following regression of hepatocellular carcinoma after transcatheter arterial embolization. A case report. Hepatogastroenterology 54:1560–1562

Higuchi T, Kikuchi M, Okazaki M (1994) Hepatocellular carcinoma after transcatheter hepatic arterial embolization. A histopathologic study of 84 resected cases. Cancer 73:2259–2267

Hoechst B, Ormandy LA, Ballmaier M, Lehner F, Krüger C, Manns MP, Greten TF et al (2008) A new population of myeloid-derived suppressor cells in hepatocellular carcinoma patients induces CD4(+) CD25(+)Foxp3(+) T cells. Gastroenterology 135:234–243

Hoechst B, Voigtlaender T, Ormandy L, Gamrekalashvili J, Zhao F, Wedemeyer H et al (2009) Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. Hepatology 50:799–807

Hoechst B, Schildberg FA, Sauerborn P, Gäbel YA, Gevensleben H, Goltz D, Heukamp LC et al (2013) Activated human hepatic stellate cells induce myeloid derived suppressor cells from peripheral blood monocytes in a CD44-dependent fashion. J Hepatol 59:528–535

Hoover RG, Gullickson G, Kornbluth J (2012) Natural killer lytic-associated molecule plays a role in

controlling tumor dissemination and metastasis. Front Immunol 3:393
Hu CE, Gan J, Zhang RD, Cheng YR, Huang GJ (2011) Up-regulated myeloid-derived suppressor cell contributes to hepatocellular carcinoma development by impairing dendritic cell function. Scand J Gastroenterol 46:156–164
Hu X, Bardhan K, Paschall AV, Yang D, Waller JL, Park MA, Nayak-Kapoor A, Samuel TA (2013) Deregulation of apoptotic factors Bcl-xL and Bax confers apoptotic resistance to myeloid-derived suppressor cells and contributes to their persistence in cancer. J Biol Chem 288:19103–19115
Huang Y, Wang FM, Wang T, Wang YJ, Zhu ZY, Gao YT, Du Z (2012) Tumor-infiltrating FoxP3+ Tregs and CD8 + T cells affect the prognosis of hepatocellular carcinoma patients. Digestion 86:329–337
Huz JI, Melis M, Sarpel U (2012) Spontaneous regression of hepatocellular carcinoma is most often associated with tumour hypoxia or a systemic inflammatory response. HPB (Oxford) 14:500–505
Ichikawa T, Takagi H, Yamada T, Abe T, Ito H, Kojiro M, Mori M (2002) Granulomas in hepatocellular carcinoma induced by lipiodolized SMANCS, a polymer-conjugated derivative of neocarzinostatin. Histopathology 40:579–580
Ido E, Furihata M, Ohtsuki Y, Iwata J, Sonobe H (1994) S-100 protein-positive dendritic cells detected in hepatocellular-carcinoma in relation to tumor progression and prognosis. Int J Oncol 5:231–236
Iiai T, Sato Y, Nabatame N, Yamamoto S, Makino S, Hatakeyama K (2003) Spontaneous complete regression of hepatocellular carcinoma with portal vein tumor thrombus. Hepatogastroenterology 50:1628–1630
Ikeda M, Okada S, Ueno H, Okusaka T, Kuriyama H (2001) Spontaneous regression of hepatocellular carcinoma with multiple lung metastases: a case report. Jpn J Clin Oncol 31:454–458
Ilkovitch D, Lopez DM (2009) The liver is a site for tumor-induced myeloid-derived suppressor cell accumulation and immunosuppression. Cancer Res 69:5514–5521
Ilkovitch D, Carrio R, Lopez DM (2012) uPA and uPA-receptor are involved in cancer-associated myeloid-derived suppressor cell accumulation. Anticancer Res 32:4263–4270
Imaoka S, Sasaki Y, Masutani S, Ishikawa O, Furukawa H, Kabuto T, Kameyama M et al (1994) Necrosis of hepatocellular carcinoma caused by spontaneously arising arterial thrombus. Hepatogastroenterology 41:359–362
Ismail et al. (2013) http://www.ncbi.nlm.nih.gov/pubmed/23144169
Izuishi K, Ryu M, Hasebe T, Kinoshita T, Konishi M, Inoue K (2000) Spontaneous total necrosis of hepatocellular carcinoma: report of a case. Hepatogastroenterology 47:1122–1124
Jackaman C, Nelson DJ (2014) Are macrophages, myeloid derived suppressor cells and neutrophils mediators of local suppression in healthy and cancerous tissues in aging hosts ? Exp Gerontol 54:53–57
Jeon SW, Lee MK, Lee YD, Seo HE, Cho CM, Tak WY, Kweon YO (2005) Clear cell hepatocellular carcinoma with spontaneous regression of primary and metastatic lesions. Korean J Intern Med 20:268–273
Ju MJ, Qiu SJ, Gao Q, Fan J, Cai MY, Li YW, Tang ZY (2009) Combination of peritumoral mast cells and T-regulatory cells predicts prognosis of hepatocellular carcinoma. Cancer Sci 100:1267–1274
Kaiser HE (1994) Biological viewpoint of neoplastic regression. In Vivo 8:155–165
Kaiser HE, Bodey B, Siegel SE, Gröger AM (2000) Spontaneous neoplastic regression: the significance of apoptosis. In Vivo 14:773–788
Kalathil S, Lugade AA, Miller A, Iyer R, Thanavala Y (2013) Higher frequencies of GARP(+) CTLA-4(+) Foxp3(+) T regulatory cells and myeloid-derived suppressor cells I hepatocellular carcinoma patients are associated with impaired T-cell functionality. Cancer Res 73:2435–2444
Kapanadze T, Gamrekelashvili J, Ma C, Chan C, Zhao F, Hewitt S, Zender L, Kapoor V et al (2013) Regulation of accumulation and function of myeloid derived suppressor cells in different murine models of hepatocellular carcinoma. J Hepatol 59:1007–1013
Kataoka S, Knishi Y, Nishio Y, Fujikawa-Adachi K, Tominaga A (2004) Antitumor activity of eosinophils activated by IL-5 and eotaxin against hepatocellular carcinoma. DNA Cell Biol 23:549–560
Kawada N, Murata M, Nakayama T, Yukawa M, Okajima K, Ohta Y, Kudo M, Inoue M (2008) Unusual hepatocellular carcinoma with macroscopic biliary tumor thrombus accompanied by rim calcification and no arterial-phase enhancement. Acta Med Kinki Univ 33:59–63
Kawata A, Une Y, Hosokawa M, Uchino J, Kobayashi H (1992) Tumor-infiltrating lymphocytes and prognosis of hepatocellular carcinoma. Jpn J Clin Oncol 22:256–263
Keibel A, Singh V, Sharma MC (2009) Inflammation, microenvironment, and the immune system in cancer progression. Curr Pharm Des 15:1949–1955
Kelly A, Fahey R, Fletcher JM, Keogh C, Carroll AG, Siddachari R, Geoghegan J et al (2014) CD141+ myeloid dendritic cells are enriched in healthy human liver. J Hepatol 60:135–142
Kermiche-Rahali S, Di Fiore A, Drieux F, Di Fiore F, François A, Scotté M (2013) Complete pathological regression of hepatocellular carcinoma with portal thrombosis treated with sorafenib. World J Surg Oncol 11:171
Kim SH, Lim HK, Choi D, Lee WJ, Kim SH, Kim MJ, Lee SJ, Lim JH (2004) Changes in bile ducts after radiofrequency ablation of hepatocellular carcinoma: frequency and clinical significance. AJR Am J Roentgenol 183:1611–1617
Kim JH, Oh SH, Kim EJ, Park SJ, Hong SP, Cheon JH, Kim TI, Kim WH (2012) The role of myofibroblasts in upregulation of S100A8 and S100A9 and the differentiation of myeloid cells in the colorectal cancer

microenvironment. Biochem Biophys Res Commun 423:60–66
Kim DK, Kang B, Kim OY, Choi DS, Lee J, Kim SR, Go G, Yoon YJ, Kim JH, Jang SC (2013a) EVpedia: an integrated data base of high-throughput data for systemic analyses of extracellular vesicles. J Extracell Vesicles 2. doi:10.3402/jev.v2i0.20384
Kim OH, Kang GH, Noh H, Cha JY, Lee HJ, Yoon JH, Mamura M, Nam JS, Lee DH et al (2013b) Proangiogenic TIE2(+)/CD31(+) macrophages are the predominant population of tumor-associated macrophages infiltrating metastatic lymph nodes. Mol Cells 36:432–438
Kogure T, Lin WL, Yan IK, Braconi C, Patel T (2011) Intercellular nanovesicle-mediated microRNA transfer: a mechanism of environmental modulation of hepatocellular cancer cell growth. Hepatology 54:1237–1248
Kojima H, Tanigawa N, Kariya S, Komemushi A, Shomura Y, Sawada S, Arai E, Yokota Y (2006) A case of spontaneous regression of hepatocellular carcinoma with multiple lung metastases. Radiat Med 24:139–142
Kong LQ, Zhu XD, Xu HX, Zhang JB, Lu L, Wang WQ, Zhang QB, Wu WZ, Wang L et al (2013) The clinical significance of the CD163+ and CD68+ macrophages in patients with hepatocellular carcinoma. PLoS One 8: e59771
Korangy F, Höchst B, Manns MP, Greten TF (2010) Immune responses in hepatocellular carcinoma. Dig Dis 28:150154
Kornberg TB (2014) Cytonemes and the dispersion of morphogens. Wiley Interdiscip Rev Dev Biol 3:445–463
Kosmaczewska A, Ciszak L, Potoczek S, Frydecka I (2008) The significance of Treg cells in defective tumor immunity. Arch Immunol Ther Exp (Warsz) 56:181–191
Kroemer G, Zitvogel L (2012) Abscopal but desirable: the contribution of immune responses to the efficacy of radiotherapy. Oncoimmunology 1:407–408
Kuang DM, Zhao Q, Peng C, Xu J, Zhang JP, Wu C, Zheng L (2009) Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. J Exp Med 206:1327–1337
Kuang et al. (2010) http://www.ncbi.nlm.nih.gov/pubmed/20581151
Kwok PC, Lam TW, Lam CL, Lai AK, Lo HY, Chan SC (2003) Rare pulmonary complications after transarterial chemoembolization for hepatocellular carcinoma: two case reports. Hong Kong Med J 9:457–460
Lam KC, Ho JC, Yeung RT (1982) Spontaneous regression of hepatocellular carcinoma: a case study. Cancer 50:332–336
Lampiasi N, Azzolina A, Montalto G, Cervello M (2007) Histamine and spontaneously released mast cell granules affect the cell growth of human hepatocellular carcinoma cells. Exp Mol Med 39:284–294
Lau AH, Thomson AW (2003) Dendritic cells and immune regulation in the liver. Gut 52:307–314
Lawrence T (2011) Macrophages and NF-kB in cancer. Curr Top Microbiol Immunol 349:171–184
Lebon J, Claude R, Eisenbeth R, Gross A, Gauthier R (1950) Primary epithelioma of the liver with massive necrosis (in French). Alger Medicale 54:391–393
Lechner MG, Liebertz DJ, Epstein AL (2010) Characterization of cytokine-induced myeloid-derived suppressor cells from normal human peripheral blood mononuclear cells. J Immunol 185:2273–2284
Lee HS, Lee JS, Woo GW, Yoon JH, Kim CY (2000) Recurrent hepatocellular carcinoma after spontaneous regression. J Gastroenterol 35:552–556
Lee SC, Chung HW, Chung JB, Park YN, Ahn SH, Park SW, Chun CY, Moon YM et al (2002) Total necrosis of hepatocellular carcinoma due to spontaneous occlusion of feeding artery. Yonei Med J 43:123–127
Lee MY, Chuang VP, Wei CJ, Cheng TY, Cherng MT (2012) Histopathologic correlation of hepatocellular carcinoma after transcatheter arterial chemoembolization with polyvinyl alcohol particle of various sizes. Eur J Radiol 81:1976–1979
Lennerz JK, Chapman WC, Brunt EM (2011) Keratin 19 epithelial patterns in cirrhotic stroma parallel hepatocarcinogenesis. Am J Pathol 179:1015–1029
Leonardi GC, Candido S, Cervello M, Nicolosi D, Raiti F, Travali S, Spandidos DA et al (2012) The tumor microenvironment in hepatocellular carcinoma. Int J Oncol 40:1733–1747
Leong JW, Sullivan RP, Fehninger TA (2012) Natural killer cell regulation by MicroRNAs in health and disease. J Biomed Biotechnol 188:632329
Li AJ, Wu MC, Cong WM, Shen F, Yi B (2003) Spontaneous complete necrosis of hepatocellular carcinoma: a case report. Hepatobiliary Pancreat Dis Int 2:152–154
Li L, Li SP, Min J, Zheng L (2007) Hepatoma cells inhibit the differentiation and maturation of dendritic cells and increase the production of regulatory T cells. Immunol Lett 114:38–45
Li H, Han Y, Guo Q, Zhang M, Cao X (2009) Cancer-expanded myeloid-derived suppressor cells induced anergy of NK cells through membrane-bound TGF-beta 1. J Immunol 182:240–249
Li L, Zhang J, Diao W, Wang D, Wei Y, Zhang CY, Zen K (2014) MicroRNA-155 and MicroRNA-21 promote the expansion of functional myeloid-derived suppressor cells. J Immunol 192:1034–1043
Lin TJ, Liao LY, Lin CL, Shih LS, Chang TA, Tu HY, Chen RC, Wang CS (2004) Spontaneous regression of hepatocellular carcinoma: a case report of literature review. Hepatogastroenterology 51:579–582
Lin W, Chen YL, Jiang L, Chen JK (2011) Reduced expression of chemerin is associated with a poor prognosis and a lowed infiltration of both dendritic cells and natural killer cells in human hepatocellular carcinoma. Clin Lab 57:879–885
Lin SZ, Chen KJ, Xu ZY, Chen H, Zhou L, Xie HY, Zheng SS (2013) Prediction of recurrence and survival in

hepatocellular carcinoma based on two Cox models mainly determined by FoxP3+ regulatory T cells. Cancer Prev Res (Phila) 6:594–602
Lindau D, Gielen P, Kroesen M, Wesseling P, Adema GJ (2013) The immunosuppressive tumor network: myeloid-derived suppressor cells, regulatory T cells and natural killer T cells. Immunology 138:105–115
Liu G, Bi Y, Shen B, Yang H, Zhang Y, Wang X, Liu H, Lu Y, Liao J, Chen X, Chu Y (2014) SIRT1 limits the function and fate of myeloid-derived suppressor cells in tumors by orchestrating HIF-1α-dependent glycolysis. Cancer Res 74:727–737
Long KB, Beatty GL (2013) Harnessing the antitumor potential of macrophages for cancer immunotherapy. Oncoimmunology 12:e26860
Loveren V, Den Otter W (1974) Macrophages in solid tumors. I. Immunologically specific effector cells. J Natl Cancer Int 53:1057–1060
Ma J, Cai W, Zhang Y, Huang C, Zhang H, Liu J, Tang K, Xu P, Katirai F, Zhang J et al (2013) Innate immune cell-derived microparticles facilitate hepatocarcinoma metastasis by transferring integrin α(M)β2 to tumor cells. J Immunol 191:3453–3461
Maeda M, Kanayama M, Uchida T, Hasumura Y, Takeuchi J (1986) A case of hepatocellular carcinoma associated with ossification. A case report. Cancer 57:134–137
Maejima R, Nakayama H, Horii T, Tosa M, Dairaku N, Shiina M, Dairaku N, Oriuchi T et al (2011) A case of spontaneous complete necrosis of hepatocellular carcinoma sized 10 cm in diameter demonstrated by the resected specimen 8 (in Japanese). Nihon Shokakibyo Gakkai Zasshi 108:1902–1909
Magalotti D, Gueli C, Zoli M (1998) Transient spontaneous regression of hepatocellular carcinoma. Hepatogastroenterology 45:2369–2371
Mancino A, Lawrence T (2010) Nuclear factor-kappaB and tumor-associated macrophages. Clin Cancer Res 16:784–789
Mano Y, Aishima S, Fujita N, Tanaka Y, Kubo Y, Motomura T, Taketomi A, Shirabe K et al (2013) Tumor-associated macrophage promotes tumor progression via STAT3 signaling in hepatocellular carcinoma. Pathobiology 80:146–154
Mantovani A, Locati M (2013) Tumor-associated macrophages as a paradigm of macrophage plasticity, diversity, and polarization: lesions and open questions. Arterioscler Thromb Vasc Biol 33:1478–1483
Mantovani A, Sozzani S, Locati M, Allavena P, Sica A (2002) Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol 23:549–555
Mantovani A, Sica A, Allavena P, Garlanda C, Locati M (2009) Tumor-associated macrophages and the related myeloid-derived suppressor cells as a paradigm of the diversity of macrophage activation. Hum Immunol 70:325–330
Meza-Junco J, Montano-Loza AJ, Martinez-Benitez B, Cabrera-Aleksandrova T (2007) Spontaneous partial regression of hepatocellular carcinoma in a cirrhotic patient. Ann Hepatol 6:66–69
Misawa K, Hata Y, Manabe K, Matuoka S, Saito M, Takada J, Sano F (1999) Spontaneous regression of hepatocellular carcinoma. J Gastroenterol 34:410–414
Mitchell AW, Higgins JN, Tate J, Dick R (1994) Rim calcification in primary liver cell carcinoma mimicking hydatid disease. Gut 35:567–568
Mittelbrunn M, Gutiérrez-Vazquez C, Villarroya-Beltri C, Gonzalez S, Sanchez-Cabo F et al. (2011) Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells. Nat Commun 282. doi: 10.1038/ncomms1285
Moeini A, Cornella H, Villanueva A (2012) Emerging signaling pathways in hepatocellular carcinoma. Liver Cancer 1:83–93
Moenandar IM (1974) Extensive calcification in the stroma of a primary hepatic carcinoma. J Pathol 114:53–54
Mole RH (1953) Whole body irradiation: radiobiology or medicine? Br J Radiol 26:234–241
Monu NR, Frey AB (2012) Myeloid-derived suppressor cells and anti-tumor T cells: a complex relationship. Immunol Invest 41:595–613
Morimoto Y, Tanaka Y, Itoh T, Yamamoto S, Mizuno H, Fushimi H (2002) Spontaneous necrosis of hepatocellular carcinoma: a case report. Dig Surg 19:413–418
Mourra and Flejou (2001) http://www.ncbi.nlm.nih.gov/pubmed/1139820
Murakami T, Morioka D, Takakura H, Miura Y, Togo S (2013) Small hepatocellular carcinoma with ring calcification: a case report and literature review. World J Gastroenterol 19:129–132
Muramatsu Y, Moriyama N, Takayasu K, Yamada T, Hasegawa H, Kishi K (1985) A case of minute hepatocellular carcinoma with calcification (in Japanese). Rinsho Hoshasen 30:129–132
Nagaraj S, Youn JI, Gabrilovich DI (2013) Reciprocal relationship between myeloid-derived suppressor cells and T cells. J Immunol 191:17–23
Nakagawa H, Maeda S (2012) Inflammation-and stress-related signaling pathways in hepatocarcinogenesis. World J Gastroenterol 18:4071–4081
Nakai T, Shimomura T, Hirokawa F (2001) Spontaneous regression of recurrent hepatocellular carcinoma after TAE: possible mechanisms of immune mediation. Int J Clin Oncol 6:149–152
Nakajima T, Morigichi M, Watanabe T, Noda M, Fuji N, Minami M, Itoh Y, Okanoue T (2004) Recurrence of hepatocellular carcinoma with rapid growth after spontaneous regression. World J Gastroenterol 10:3385–3387
Nakamura T (2009) Changes in expression of bile canalicular CD10 and sinusoidal CD105 (endoglin) in peritumoral hepatic tissue. Tumori 95:495–500
Nakanishi M, Chuma M, Hige S, Asaka M (2008) Abscopal effect on hepatocellular carcinoma. Am J Gastroenterol 103:1320–1321
Nam SW, Han JY, Kim JI, Park SH, Cho SH, Han NI, Yang JM, Kim JK, Choi SW et al (2005) Spontaneous

regression of a large hepatocellular carcinoma with skull metastasis. J Gastroenterol Hepatol 20:488–492
Nardin A, Abastado JP (2008) Macrophages and cancer. Front Biosci 13:3494–3505
Narni-Mancinelli E, Ugolini S, Vivier E (2012) Tuning the threshold of natural killer cell responses. Curr Opin Immunol 25:53–58
Natarajan S, Thomson AW (2010) Tolerogenic dendritic cells and myeloid-derived suppressor cells: potential for regulation and therapy of liver auto-and alloimmunity. Immunobiology 215:698–703
Nausch N, Galani IE, Schlecker E, Cerwenka A (2008) Mononuclear myeloid-derived "suppressor" cells express RAE-1 and activate natural killer cells. Blood 112:4080–4089
Nelson D, Ganss R (2006) Tumor growth or regression: powered by inflammation. J Leukoc Biol 80:685–690
Nevzorova YA, Hu W, Cubero FJ, Haas U, Freimuth J, Tacke F, Trautwein C, Liedtke C (2013) Overexpression of c-myc in hepatocytes promotes activation of hepatic stellate cells and facilitates the onset of liver fibrosis. Biochim Biophys Acta 6:1765–1775
O'Beirne JP, Harrison PM (2004) The role of the immune system in the control of hepatocellular carcinoma. Eur J Gastroenterol Hepatol 16:1257–1260
Ohba K, Omagari K, Nakamura T, Ikuno N, Saeki S, Matsuo I, Kinoshita H, Masuda J et al (1998) Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. Gut 43:575–577
Ohki S, Shibata M, Gonda K, Machida T, Shimuda T, Nakamura I, Ohtake T, Koyama Y et al (2012) Circulating myeloid-derived suppressor cells are increased and correlate to immune suppression, inflammation and hypoproteinemia in patients with cancer. Oncol Rep 28:453–458
Ohta H, Sakamoto Y, Ojima H, Yamada Y, Hibi T, Takahashi Y, Sano T, Shimada K et al (2005) Spontaneous regression of hepatocellular carcinoma with complete necrosis: case report. Abdom Imaging 30:734–737
Ohtani H, Yamazaki O, Matsuyama M, Horii K, Shimizu S, Oka H, Nebiki H, Kioka K et al (2005) Spontaneous regression of hepatocellular carcinoma: report of a case. Surg Today 35:1081–1086
Okano A, Ohana M, Kusumi F, Nabeshima M (2013) Spontaneous regression of hepatocellular carcinoma due to disruption of the feeding artery. Case Rep Oncol 6:180–185
Okuma et al. (2011) http://www.ncbi.nlm.nih.gov/pubmed/2148591
Ono M (2008) Molecular links between tumor angiogenesis and inflammation: inflammatory stimuli of macrophages and cancer cells as targets for therapeutic strategy. Cancer Sci 99:1501–1506
Oquiñena S, Guillen-Grima F, Inarrairaegui M, Zozaya JM, Sangro B (2009) Spontaneous regression of hepatocellular carcinoma: a systematic review. Eur J Gastroenterol Hepatol 21:254–257
Osler W (1901) The medical aspects of carcinoma of the breast, with a note on the spontaneous disappearance of secondary growths. Am Med 25:63–66
Österreicher CH, Penz-Österreicher M, Grivennikov, Ostrand-Rosenberg S, Sinha P (2009) Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol 182:4499–4506
Österreicher et al. (2011) http://www.ncbi.nlm.nih.gov/pubmed/21173249
Ostrand-Rosenberg S, Sinha P, Chronoguz O, Ecker C (2012a) Regulating the suppressors: apoptosis and inflammation govern the survival of tumor-induced myeloid-derived suppressor cells (MDSC). Cancer Immunol Immunother 61:1319–1325
Ostrand-Rosenberg S, Sinha P, Beury DW, Clements VK (2012b) Cross-talk between myeloid-derived suppressor cells (MDSC), macrophages, and dendritic cells enhances tumor-induced immune suppression. Semin Cancer Biol 22:275–281
Ozeki Y, Matsubara N, Tateyama K, Kokubo M, Shimoji H, Katayama M (1996) Spontaneous complete necrosis of hepatocellular carcinoma. Am J Gastroenterol 91:391–392
Pan PY, Wang GX, Yin B, Ozao J, Ku T, Divino CM, Chen SH (2008) Reversion of immune tolerance in advanced malignancy: modulation of myeloid-derived suppressor cell development by blockade of stem-cell factor function. Blood 111:219–228
Papac RJ (1998) Spontaneous regression of cancer: possible mechanisms. In Vivo 12:571–578
Pardee AD, Shi J, Butterfield LH (2014) Tumor-derived α-fetoprotein impair the differentiation and T cell stimulatory activity of human dendritic cells. J Immunol 193:5723–5732
Park HS, Jang KY, Kim YK, Cho BH, Moon WS (2009) Hepatocellular carcinoma with massive lymphoid infiltration: a regressing phenomenon ? Pathol Res Pract 205:648–652
Park YJ, Song B, Kim YS, Kim EK, Lee JM, Lee GE, Kim JO, Kim YJ, Chang WS et al (2013) Tumor microenvironment conversion of natural killer cells into myeloid-derived suppressor cells. Cancer Res 73:5669–5681
Patton RB, Horn RC (1964) Primary liver carcinoma. Autopsy study of 60 cases. Cancer 17:757–768
Pedroza-Gonzalez A, Verhoef C, Ijzermans JN, Peppelenbosch MP, Kewkkeboom J et al (2013) Activated tumor-infiltrating CD4+ regulatory T cells restrain antitumor immunity in patients with primary or metastatic liver cancer. Hepatology 57:183–194
Pello OM, Andrés V (2013) Role of c-MYC in tumor-associated macrophages and cancer progression. Oncoimmunology 2:e22984
Peng SH, Deng H, Yang JF, Xie PP, Li C, Li H, Feng DY (2005) Significance and relationship between infiltrating inflammatory cell and tumor angiogenesis in hepatocellular carcinoma tissues. World J Gastroenterol 11:6521–6524

Phelan S, Nolan N (2008) Granulomas in dysplastic nodules – an unusual morphologic finding. Histopathology 53:114–115

Poggi G, Teragni C, Gazzaruso C, Bernado G (2004) Massive hepatic infarction complicating ultrasound-guided percutaneous radiofrequency thermal ablation. Liver Int 24:704–705

Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, Mu Z, Rasalan T et al (2012) Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 366:925–931

Qin LX (2012) Inflammatory immune responses in tumor microenvironment and metastasis of hepatocellular carcinoma. Cancer Microenviron 5:203–209

Qu P, Boelte KC, Lin PC (2012) Negative regulation of myeloid-derived suppressor cells in cancer. Immunol Invest 41:562–580

Randolph AC, Tharalson EM, Gilani N (2008) Spontaneous regression of hepatocellular carcinoma is possible and might have implications for future therapies. Eur J Gastroenterol Hepatol 20:804–809

Rayner KJ, Hennessy EJ (2013) Extracellular communication via microRNA: lipid particles have a new message. J Lipid Res 54:1174–1181

Ren D, Bi Q, Li L, Gao Y, Liang Y, Li Y, Liu J, Peng L, Xiao J (2012) Myeloid-derived suppressor cells accumulate in the liver site after sepsis to induce immunosuppression. Cell Immunol 279:12–20

Richards DM, Hettinger J, Feurer M (2013) Monocytes and macrophages in cancer: development and functions. Cancer Microenviron 6:179–191

Rohdenburg GL (1918) Fluctuations in the growth of malignant tumors in man, with especial reference to spontaneous regression. J Cancer Res 3:192–221

Royo F, Falcon-Perez JM (2012) Liver extracellular vesicles in health and disease. J Extracell Vesic 1:18825

Saito T, Naito M, Matsumura Y, Kita H, Kanno T, Nakada Y, Hamano M, Chiba M et al (2014) Spontaneous regression of a large hepatocellular carcinoma with multiple lung metastases. Gut Liver 8:569–574

Sasaki T, Fukumori D, Yamamoto K, Yamamoto F, Igimi H, Yamashita Y (2013) Management considerations for purported spontaneous regression of hepatocellular carcinoma: a case report. Case Rep Gastroenterol 7:147–152

Sato Y, Fujiwara K, Nakagawa S, Kanishima S, Ohta Y, Oka Y, Hayashi S, Oka H (1985) A case of spontaneous regression of hepatocellular carcinoma with bone metastasis. Cancer 56:667–671

Scatarige JC, Fishman EK, Saksouk FA, Siegelman SS (1983) Computed tomography of calcified liver masses. J Comput Assist Tomogr 7:83–89

Schlecker E, Stojanovic A, Eisen C, Quack C, Falk CS, Umnasky V, Cerwenka A (2012) Tumor-infiltrating monocytic myeloid-derived suppressor cells mediate CCR5-dependent recruitment of regulatory T cells favoring tumor growth. J Immunol 189:5602–5611

Schmid MC, Varner JA (2012) Myeloid cells in tumor inflammation. Vasc Cell 4:14

Senovilla L, Vacchelli E, Galon J, Adjemian S, Eggermont A, Fridman WH, Suatès-Fridman C et al (2012) Trial watch: prognostic and predictive value of the immune infiltrate in cancer. Oncoimmunology 1:1323–1343

Shen SL, Liang LJ, Peng BG, He Q, Kuang M, Lai JM (2011) Foxp3+ regulatory T cells and the formation of portal vein tumour thrombus in patients with hepatocellular carcinoma. Can J Surg 54:89–94

Shi JY, Gao Q, Wang ZC, Zhou J, Wang XY, Min ZH, Shi YH, Shi GM, Ding ZB et al (2013) Margin-infiltrating CD20(+) B cells display an atypical memory phenotype and correlate with favorable prognosis in hepatocellular carcinoma. Clin Cancer Res 19:5994–6005

Shin KY, Heo J, Kim JY, Lee SJ, Jang SY, Park SY, Jung MK, Cho CM, Tak WY et al (2011) A case of hemocholecyst associated with hemobilia following radiofrequency ablation therapy for hepatocellular carcinoma. Korean J Hepatol 17:148–151

Shirabe K, Motomura T, Muto J, Toshima T, Matono R, Mano Y, Takeishi K, Ijichi H et al (2010) Tumor-infiltrating lymphocytes and hepatocellular carcinoma: pathology and clinical management. Int J Clin Oncol 15:552–558

Shirabe K, Mano Y, Muto J, Matono R, Motomura T, Toshima T, Takeishi T, Uchiyama H et al (2012) Role of tumor-associated macrophages in the progression of hepatocellular carcinoma. Surg Today 42:1–7

Shurin GV, Ma Y, Shurin MR (2013) Immunosuppressive mechanisms of regulatory dendritic cells in cancer. Cancer Microenviron 6:159–167

Sica A (2010) Role of tumour-associated macrophages in cancer-related inflammation. Exp Oncol 32:153–158

Sica A, Mantovani A (2012) Macrophage plasticity and polarization: in vivo veritas. J Clin Invest 122:787–795

Siegel EG, Hartmann H (1987) Spontaneous regression of a large liver tumor with markedly elevated serum enzyme levels (in German). Z Gastroenterol 25:764–768

Singh BB, McKinney RV (1979) Tumor regression by differentiation of malignant cells to benign states. J Med Assoc Ga 68:1078–1079

Sinha P, Okoro C, Foell D, Freeze HH, Ostrand-Rosenberg S, Srikrishna G (2008) Proinflammatory S100 proteins regulate the accumulation of myeloid-derived suppressor cells. J Immunol 181:4666–4675

Sinha P, Chornoguz O, Clements VK, Artemenko KA, Zubarev RA, Ostrand-Rosenberg S (2011) Myeloid-derived suppressor cells express the death receptor Fas and apoptose in response to T cell-expressed FasL. Blood 117:5381–5390

Siveen KS, Kuutan G (2009) Role of macrophages in tumour progression. Immunol Lett 123:97–102

Solito S, Pinton L, Damuzzo V, Mandruzzato S (2012) Highlights on molecular mechanisms of MDSC-mediated immune suppression: paving the way for new working hypotheses. Immunol Invest 41:722–737

Stefanini GF, Mazzetti M, Zamorano MA, Capelli S, Castelli E, Degli Esposti P, Moretta L et al (1989)

Circulating LAK-1 cells and autologous mixed lymphocytes reaction in patients with hepatocellular carcinoma. Am J Gastroenterol 84:396–399
Stevens WR, Johnson CD, Stephens DH, Batts KP (1994) CT findings in hepatocellular carcinoma: correlation of tumor characteristics with causative factors, tumor size, and histologic tumor grade. Radiology 191:531–537
Stewart FW (1952) Experiences in spontaneous regression of neoplastic disease in man. Texas Rep Biol Med 10:239–253
Stoelben E, Koch M, Hanke S, Lossnitzer A, Gaertner HJ, Schentke KU, Bunk A et al (1998) Spontaneous regression of hepatocellular carcinoma confirmed by surgical specimen: report of two cases and review of the literature. Langenbecks Arch Surg 383:447–452
Stojanovic A, Cerwenka A (2011) Natural killer cells and solid tumors. J Innate Immun 3:355–364
Stojanovic A, Correia MP, Cerwenka A (2013) Shaping of NK cell responses by the tumor microenvironment. Cancer Microenviron 6:135–146
Stoll BA (1992) Spontaneous regression of cancer: new insights. Biotherapy 4:23–30
Stoupis C, Taylor HM, Paley MR, Buetow PC, Marre S, Baer HU, Vock P, Ros PR (1998) The rocky liver: radiologic-pathologic correlation of calcified hepatic masses. Radiographics 18:675–685
Sun B, Zhang X, Cheng X, Zhang Y, Chen L, Shi L, Liu Z, Qian H, Wu M, Yin Z (2013) Intratumoral hepatic stellate cells as a poor prognostic marker and a new treatment target for hepatocellular carcinoma. PLoS One 8:e80212
Suzuki M, Okazaki N, Yoshino M, Yoshida T (1989) Spontaneous regression of a hepatocellular carcinoma – a case report. Hepatogastroenterology 36:160–163
Szekely E (2001) Hepatocellular carcinoma with lymphoid stroma: 'lymphoepithelioma-like carcinoma' ? Histopathology 39:540
Takahashi T, Yamada S, Fukami A, Kin M (1971) Case of calcified hepatic metastasis of rectal cancer (in Japanese). Gan No Ronsho 17:711–715
Takahashi S, Chung H, Kitai S, Inoue T, Minami Y, Ueshima K, Kudo M (2008) Foreign body granuloma mimicking disseminated tumor recurrence after radiofrequency ablation for hepatocellular carcinoma. Liver Int 28:414–415
Takai H, Ashihara M, Ishiguro T, Terashima H, Watanabe T, Kato A, Suzuki M (2009) Involvement of glypican-3 in the recruitment of M2-polarized tumor-associated macrophages in hepatocellular carcinoma. Cancer Biol Ther 8:2329–2338
Takayasu K, Muramatsu Y, Shima Y, Moriyama N, Yamada T, Yoshida T, Makuuchi M et al (1986) Necrosis of hepatocellular carcinoma as a result of subintimal injury incurred by hepatic angiography: report of two cases. Am J Gastroenterol 81:979–983
Teefey SA, Stephens DH, Weiland LH (1987) Calcifications in hepatocellular carcinoma: not always an indication of fibrolamellar histology. AJR Am J Roentgenol 149:1173–1174
Terasaki T, Hanazaki K, Shiohara E, Matsunaga Y, Koide N, Amano J (2000) Complete disappearance of recurrent hepatocellular carcinoma with peritoneal dissemination and splenic metastasis: a unique clinical course after surgery. J Gastroenterol Hepatol 15:327–330
Thelen A, Jonas S, Benckert C, Weichert W, Schott E, Bötcher C, Dietz E, Wiedenmann B et al (2009) Tumor-associated lymphangiogenesis correlates with prognosis after resection of human hepatocellular carcinoma. Ann Surg Oncol 16:1222–1230
Thomas L (1976) Possible mechanisms in regression. Natl Cancer Inst Monogr 44:137–139
Tian Z, Chen Y, Gao B (2013) Natural killer cells in liver disease. Hepatology 57:1654–1662
Tocci G, Conte A, Guareascio P, Visco G (1990) Spontaneous remission of hepatocellular carcinoma after massive gastrointestinal haemorrhage. BMJ 300:641–642
Toh B, Wang X, Keeble J, Sim WJ, Khoo K, Wong WC, Kato M, Prevost-Blondel A et al (2011) Mesenchymal transition and dissemination of cancer cells is driven by myeloid-derived suppressor cells infiltrating the primary tumor. PLoS Biol 9:e1001162
Tomimatsu H, Kojiro M, Nakashima T (1982) Epithelioid granulomas associated with hepatocellular carcinoma. Arch Pathol Lab Med 106:538–539
Toyoda H, Sugimura S, Fukuda K, Mabuchi T (1999) Hepatocellular carcinoma with spontaneous regression of multiple lung metastases. Pathol Int 49:893–897
Través PG, Luque A, Hortelano S (2012) Macrophages, inflammation, and tumor suppressors: ARF, a new player in the game. Mediators Inflamm 18:568783
Tsuda Y, Fukui H, Asai A, Fukunishi S, Miyaji K, Fujiwara S, Teramura K, Fukuda A et al (2012) An immunosuppressive subtype of neutrophils identified in patients with hepatocellular carcinoma. J Clin Biochem Nutr 51:204–212
Umansky V, Sevke A (2013) Tumor microenvironment and myeloid-derived suppressor cells. Cancer Microenviron 6:169–177
Unitt E, Rushbrook SM, Marshall A, Davies S, Gibbs P, Morris LS, Coleman N, Alexander GJ (2005) Compromised lymphocytes infiltrate hepatocellular carcinoma: the role of T-regulatory cells. Hepatology 41:722–730
Vanherberghen B, Olofsson PE, Forslunf E, Sternberg-Simon M, Khorshidi MA, Pacouret S et al (2013) Classification of human natural killer cells based on migration behavior and cytotoxic response. Blood 121:1326–1334
Velazquez VM, Hon H, Ibegbu C, Knechtle SJ, Kirk AD, Grakoui A (2012) Hepatic enrichment and activation of myeloid dendritic cells during chronic hepatitis C virus infection. Hepatology 56:2071–2081
Vickers KC, Remaley AT (2012) Lipid-based carriers of microRNAs and intercellular communication. Curr Opin Lipidol 23:91–97
Voloshin T, Fremder E, Shaked Y (2014) Small but mighty: microparticles as mediators of tumor progression. Cancer Microenviron 7:11–21

Wan S, Zhao E, Kryczek I, Vatan L, Sadovskaya A, Ludema G, Simeone DM, Zou W et al (2014) Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. Gastroenterology 147:1393–1404

Wang RF (2008) CD8+ regulatory T cells, their suppressive mechanisms, and regulation in cancer. Hum Immunol 69:811–814

Wang HY, Wang RF (2007) Regulatory T cells and cancer. Curr Opin Immunol 19:217–223

Wang F, Jing X, Li G, Wang T, Yang B, Zhu Z, Gao Y, Zhang Q, Yang Y, Wang Y et al (2012) Foxp3+ regulatory T cells are associated with the natural history of chronic hepatitis B and poor prognosis of hepatocellular carcinoma. Liver Int 32:644–655

Wang X, Wang H, Li G, Song Y, Wang S, Zhu F, Guo C, Zhang L, Shi Y (2014) Activated macrophages downregulate expression of E-cadherin in hepatocellular carcinoma cells via NF-kB/Slug pathway. Tumour Biol 35:8893–8901

Wendler F, Bota-Rabassedas N, Franch-Marro X (2013) Cancer becomes wasteful: emerging roles of exosomes in cell-fate determination. J Extracell Vesic 2:22390

Witek RP, Yang L, Liu R, Jung Y, Omenetti A, Syn WK, Choi SS, Cheong Y, Fearing CM et al (2009) Liver cell-derived microparticles activate hedgehog signaling and alter gene expression in hepatic endothelial cells. Gastroenterology 136:320–330

Wu Y, Zheng L (2012) Dynamic education of macrophages in different areas of human tumors. Cancer Microenviron 5:195–201

Wu Y, Kuang DM, Pan WD, Wan YL, Lao XM, Wang D, Li XF, Zheng L (2013a) Monocyte/macrophage-elicited natural killer cell dysfunction in hepatocellular carcinoma is mediated by CD48/2B4 interactions. Hepatology 57:1107–1116

Wu H, Chen P, Liao R, Li YW, Yi Y, Wang JX, Cai XY, He HW, Jin JJ, Cheng YF et al (2013b) Intratumoral regulatory T cells with higher prevalence and more suppressive activity in hepatocellular carcinoma patients. J Gastroenterol Hepatol 28:1555–1564

Xu et al. (2011) http://www.ncbi.nlm.nih.gov/pubmed/21523657

Yamashiki N, Kato T, Bejaranao PA, Berho M, Montalvo B, Shebert RT, Goodman ZD et al (2003) Histopathological changes after microwave coagulation therapy for patients with hepatocellular carcinoma: review of 15 explanted livers. Am J Gastroenterol 98:2052–2059

Yang XH, Yamagiwa S, Ichida T, Matsuda Y, Sugahara S, Watanabe H, Sato Y, Abo T et al (2006) Increase of CD4+ CD25+ regulatory T-cells in the liver of patients with hepatocellular carcinoma. J Hepatol 45:254–262

Yang Z, Zhang B, Li D, Lv M, Huang C, Shen GX, Huang B (2010) Mast cells mobilize myeloid-derived suppressor cells and Trag cells in tumor microenvironment via IL-17 pathway in murine hepatocarcinoma model. PLoS One 5:e8922

Yang M, Chen J, Su F, Yu B, Su F, Lin L, Liu Y, Huang JD, Song E (2011) Microvesicles secreted by macrophages shuttle invasion-potentiation microRNAs into breast cancer cells. Mol Cancer 10:117

Yang J, Zhang JX, Wang H, Wang GL, Hu QG, Zheng QC (2012) Hepatocellular carcinoma and macrophage interaction induced tumor immunosuppression via Treg requires TLR4 signaling. World J Gastroenterol 18:2938–2947

Yang WC, Ma G, Chen SH, Pan PY (2013) Polarization and reprogramming of myeloid-derived suppressor cells. J Mol Cell Biol 5:207–209

Yang Y, Qin SK, Wu Q, Wang ZS, Zheng RS, Tong XH, Liu H, Tao L, He XD (2014) Connexin-dependent gap junction enhancement is involved in the synergistic effect of sorafenib and all-trans retinoic acid on HCC growth inhibition. Oncol Rep 31:540–550

Yen BL, Yen ML, Hsu PJ, Liu KJ, Wang CJ, Bai CH, Sytwu HK (2013) Multipotent human mesenchymal stromal cells mediate expansion of myeloid-derived suppressor cells via hepatocyte growth factor/c-Met and STAT3. Stem Cell Rep 1:139–151

Yi Y, He HW, Wang JX, Cai XY, Li YW, Zhou J, Cheng YF, Jin JJ, Fan J, Qiu SJ (2013) The functional impairment of HCC-infiltrating γδ T cells, partially mediated by regulatory T cells in a TGFβ- and IL-10-dependent manner. J Hepatol 58:977–983

Yin XY, Lu MD, Lai YR, Liang LJ, Huang JF (2003) Prognostic significances of tumor-infiltrating S-100 positive dendritic cells and lymphocytes in patients with hepatocellular carcinoma. Hepatogastroenterology 50:1281–1284

Yokoyama T, Yoshida H, Hirakata A, Makino H, Maruyama H, Suzuki S, Matsutani T et al (2012) Spontaneous complete necrosis of advanced hepatocellular carcinoma. J Nippon Med Sch 79:213–217

You Q, Holt M, Yin H, Li G, Hu CJ, Ju C (2013) Role of hepatic resident and infiltrating macrophages in liver repair after acute injury. Biochem Pharmacol 86:836–843

Younos I, Donkor M, Hoke T, Dafferner A, Samson H, Westphal S, Talmadge J (2011) Tumor-and organ-dependent infiltration by myeloid-derived suppressor cells. Int Immunopharmacol 11:816–826

Yu P, Fu YX (2006) Tumor-infiltrating T lymphocytes: friends or foes ? Lab Invest 86:231–245

Yuan A, Chen JJ, Yang PC (2008) Pathophysiology of tumor-associated macrophages. Adv Clin Chem 45:199–223

Zamarron BF, Chen W (2011) Dual roles of immune cells and their factors in cancer development and progression. Int J Biol Sci 7:651–658

Zen et al. (2011) http://www.ncbi.nlm.nih.gov/pubmed/21491587

Zhang H, Maric I, DiPrima MJ, Khan J, Orentas RJ, Kaplan RN, Mackall CL (2013) Fibrocytes represent a novel MDCS subset circulating in patients with metastatic cancer. Blood 122:1105–1113

Zhao W, Su W, Kuang P, Zhang L, Liu J, Yin Z, Wang X (2012a) The role of hepatic stellate cells in the regulation of T-cell function and the promotion of hepatocellular carcinoma. Int J Oncol 41:457–464

Zhao F, Korangy F, Greten TF (2012b) Cellular immune suppressor mechanisms in patients with hepatocellular carcinoma. Dig Dis 30:477–482

Zhao X, Rong L, Zhao X, Li X, Liu X, Deng J, Wu H, Xu X, Erben U, Wu P, Syrbe U et al (2012c) TNF signaling drives myeloid-derived suppressor cell accumulation. J Clin Invest 122:4094–4104

Zheng J, Yang M, Shao J, Miao Y, Han J, Du J (2013) Chemokine receptor CX3CR1 contributes macrophage survival in tumor metastasis. Mol Cancer 12:141

Zhong H, Gutkin DW, Han B, Keskinov AA, Shurin MR, Shurin GV (2013) Origin and pharmacological modulation of tumor-associated regulatory dendritic cells. Int J Cancer. doi:10.1002/ijc.28590

Zhou J, Ding T, Pan W, Zhu LY, Zheng L (2009) Increased intratumoral regulatory T cells are related to intratumoral macrophages and poor prognosis in hepatocellular carcinoma patients. Int J Cancer 125:1640–1648

Zhou D, Huang C, Lin Z, Zhan S, Kong L, Fang C, Li J (2014) Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. Cell Signal 26:192–197

Zimmermann A, Kappeler A, Friess H, Büchler MW (2002) Hepatocellular carcinoma with an unusual medullary-like histology and signs of regression ("medullary-like hepatocellular carcinoma"). Dig Liver Dis 34:748–753

Hepatocellular Carcinoma: Prognostic Factors

6

Contents

Abstract

Hepatocellular carcinoma (HCC) as a highly invasive and aggressive neoplasm displays a high rate of recurrence following surgery or ablation procedures. Numerous factors affect recurrence and prognosis. Among these, tumor stage is the most important prognosticator. Small and early HCCs have a better outcome than larger tumors. In addition to tumor size, the number of tumors (multiplicity) affects tumor biology. The status of the resection margin exerts a strong influence on prognosis. Future methods to evaluate the resection margin with respect to minimal residual cancer include molecular and nanosystem approaches. Other parameters of prognostic significance comprise distinct growth patterns in the liver, satellite lesions, large vessel invasion, presence of a pseudocapsule, tumor grade, microscopic invasion patterns, tumor angiogenesis, and a growing number of molecular features. The identification of distinct molecular signatures defining high-risk groups will become an important prognostic instrument in the future.

Introduction

In about 70 % of patients with HCC treated with surgery or ablation procedures, disease recurs within 5 years. Numerous factors affecting recurrence and prognosis have been identified and

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_6

discussed in surveys (reviews: Qin and Tang 2002a; Llovet et al. 2003; Mann et al. 2007).

Stage

Stage still is the most important prognosticator in patients with HCC (Hanazaki et al. 2001; Qin and Tang 2002b). This issue is further discussed in a separate chapter. Generally, tumor size exerts a variable influence on outcome in HCC. Large or very large HCC, i.e., those with a diameter of 10 cm or more, commonly showed recurrence following resection, but in some analyses overall survival was not different from patients with resected smaller lesions (Shah et al. 2007). Apart from tumor size, the number of tumors affects biology of disease (Germani et al. 2011). Apart from the general effects of stage, there are distinct T stage-related variants of HCC that differ from other cancers in regard to outcome. Generally, small and early HCCs have a better prognosis than larger HCC (Jwo et al. 1992; Hu et al. 2003). Solitary large HCC (SL-HCC) is a specific subtype of HCC which was associated with good outcome after hepatic resection (Yang et al. 2009), but the concept of SL-HCC has yet to be validated (Zhou et al. 2011).

Resection Margin

A negative resection margin was a favorable prognostic marker, and a positive margin a negative prognosticator, in part of investigations (Yoshida et al. 1989; Lai et al. 1990; Yamanaka et al. 1990; Matsutani et al. 1994; Chau et al. 1997; Young et al. 2007), while a clear resection margin $<$10 mm was a negative prognostic factor (Tralhao et al. 2007), and some analyses failed to show a significance of a clear resection margin in non-small HCC (Masutani et al. 1994). In HCC, the optimal liver resection margin is still a matter of controversy. It has been proposed that a resection margin of 2 cm is associated with a decreased recurrence rate and improved survival outcomes (Salloum and Castaing 2008). For large HCC, the presence of microsatellites and multiple nodules was associated with increased risk of positive resection margins. As such small lesions may often occur in a peritumoral rim of several mm width (Lai et al. 1993; Shi et al. 2002), resection with a margin of less than 5 mm was not regarded advisable (Lai et al. 1991; Zhou et al. 2007). In series of 288 HCC patients, the width of the resection margin did not affect postoperative recurrence rates. A positive margin was associated with a higher incidence of recurrence, but in most patients this was related to microsatellites and venous invasion (Poon et al. 2000). In a systematic review and meta-analysis of several randomized controlled trials and non-randomized trials, it turned out that there was no significant difference between the group with a margin $<$1 cm and the group with a margin $=>$ 2 cm in recurrence rate, one-year survival, 3-year survival, and 5-year survival (Tang et al. 2012). A clear resection margin is difficult or impossible to achieve in the presence of microsatellites and/or histologic venous permeation close to the primary tumor (Lai et al. 1993).

For a most optimal assessment of resection margins, novel mapping systems will be available to clearly identify margins and their orientation with respect to the resected liver, e.g., resection map systems (Lamata et al. 2010), image guidance systems (Kingham et al. 2012), and computer-assisted virtual liver resection planning (Mise et al. 2013). A special challenge is the detection of small clusters of residual tumor cells in the tissue of the resection margin (minimal residual cancer, MRC). Apart from histologic assessment of resection margins, including intraoperative frozen section, novel and in particular molecular and nanosystem approaches are developed to increase diagnostic sensitivity and to be employed in a theranostic setting (Braakhuis et al. 2010; Casciaro 2011). The aim of novel techniques, which make part of the concept of a theranostic and potentially personalized oncology (Omidi 2011; Kalia 2013; Yang et al. 2013), is to improve spatial resolution of cancer spread through molecular imaging of residual cancer cells or components thereof in resection margins (Alberti 2012). They include detection of tumor-associated proteins by tissue microarray

techniques (Li et al. 2011); methylation-based molecular margin analysis with microarrays (Zhang et al. 2006), e.g., with the CDKN2A methylation status as target (Yang et al. 2005); detection of promoter methylation of p16(INK4A), cytoglobin, E-cadherin, and transmembrane protein with EGF-like and two follistatin-like domains 2 (TMEFF2) (Shaw et al. 2013); tumor margin detection using quantitative near-infrared fluorescence (NIRF) molecular imaging targeting epithelial cell adhesion molecule (EpCAM) (NIRF-labeled anti-EpCAM antibody detection; Zhu et al. 2013); assessment of tissue by the use of molecular fluorescence imaging employing activatable cell-penetrating peptides as probes that may also be linked to nanoparticles (Nguyen et al. 2010; Olson et al. 2010); ultrasound-mediated transmembrane injection of labels contained in liposomal nanobubbles/bubble liposomes (Suzuki et al. 2013) or polymersomes (Thevenot et al. 2013); analysis through photothermal imaging of immune-targeted gold nanoparticles (Jakobsohn et al. 2012) or other nanocarriers; reconstruction of the spatial distribution of tumor cells using mass spectrometry (Gholami et al. 2011); assessment of tumor-associated genes in margins through quantitative RT-PCR analysis (de Carvalho et al. 2012); and detection of cancer-associated gene expression (e.g., TP53) via ligated DNA amplification (Poeta et al. 2009).

Other Morphologic Parameters

Important macroscopic morphologic parameters that are associated with more aggressive tumor biology include tumor size >2 cm, presence of satellite lesion, and large vessel invasion (Hanazki et al. 2001; Yeh et al. 2002; Hu et al. 2003; Kim et al. 2010). Tumor size in HCC predicts vascular invasion and histologic grade (Pawlik et al. 2005). Among three macroscopically nodular types of HCC, the single nodular type with extranodular growth (SNEG type) showed higher rates of portal vein invasion, intrahepatic metastasis, and poor differentiation (Shimada et al. 2001). Size is a dismal prognostic factor only in part, but not all HCC. A subset of solitary large HCC, a novel subtype with high-level differentiation, shows favorable prognosis (Zhou et al. 2011). Tumors with a thick capsule (marked encapsulation) had a better prognosis than those without (Franco et al. 1990; Ng et al. 1995), and encapsulation was found to be an independent prognosticator for longer disease-free survival (Lai et al. 1990). A favorable effect of the presence of a tumor capsule is not restricted to HCC but has also been found in other tumors, e.g., liver metastasis of colorectal cancer (Lunevicius et al. 2001). Also the macroscopic growth patterns have an impact on outcome. Among three nodular types of HCC, the single nodular with extranodular growth (SNEG) group revealed the worst survival, whereas there was no difference in outcome between single nodular and confluent multinodular groups (Shimada et al. 2001). In another study, the rate of microscopic invasion significantly increased from single nodular type to single nodular type with extranodular growth to contiguous multinodular type (Hui et al. 2000). Associated liver cirrhosis has an impact on outcome. Postoperative recurrence is frequent in cirrhotic patients (Takada et al. 2003). HCC without cirrhosis led to better overall and disease-free survival compared to cirrhotic HCC after curative liver resection (Nagasue et al. 2001; Grazi et al. 2003), but outcome in the non-cirrhotic group depends on preoperative hepatic function, margin status, and tumor multiplicity (Chen et al. 2003). Hypovascular HCC was biologically less aggressive, but evolved into a more aggressive malignancy in the course of further growth an increase of vascularity (Takayasu et al. 2013).

Different ground-glass hepatocyte patterns harbor specific HBV pre-S deletion mutants and are preneoplastic lesions in chronic HBV infection. The presence of a clustered ground-glass hepatocyte pattern in non-tumorous liver tissue was significantly associated with decreased local recurrence-free survival (Tsai et al. 2011). The presence of distinct phenotypes of small vessels in HCC has an impact on the tumor's biology of disease. HCCs display two main microvessel types, capillary-like and sinusoid-like vascular

channels. Patients with capillary-like vessel predominant HCC had a better disease-free and overall survival than those with sinusoid-like predominant tumors (Chen et al. 2011).

Tumor Grade and Differentiation Parameters

Tumor differentiation reflected as grade is an important prognostic factor in HCC and a crucial parameter for prognostication after therapy. In patients with advanced and sometimes mixed histologic grade, the worst histologic grade was found to determine prognosis after resection (Wu et al. 1996; Yamanaka et al. 2000; Zhou et al. 2011; Han et al. 2013). It was found that any proportion of poorly differentiated components is associated with poor prognosis in HCC patients after hepatectomy (Sasaki et al. 2014). Tumor grade can be combined with other parameters in order to obtain a combined prognosticator. For example, nuclear grade 1 with or without microvascular invasion and nuclear grade 2 without microvascular invasion formed a fair prognosis group, whereas nuclear grade 2 with microvascular invasion and nuclear grade 3 with or without microvascular invasion formed a poor prognosis group (Lauwers et al. 2002). Normal hepatocytes and HCC cells reveal cytoplasmic expression of the differentiation marker, DEC1 (human differentiated embryo chrondrocyte 1). HCC cells also show nuclear expression of DEC1, whereby high levels are found in well-differentiated HCC, whereas poorly differentiated HCCs fail to accumulate DEC1 in their nuclei (Shi et al. 2011). HCC with a progenitor cell phenotype, characterized by expression of cytokeratin 7 and/or 19, exhibited a higher rate of recurrence and a worse prognosis (Wu et al. 1996; Durnez et al. 2006; Lee et al. 2012). Arginase-1 as an enzyme that is typical for the hepatocyte lineage is an indicator of hepatocyte differentiation. HCC patients with higher arginase-1 expression showed less aggressive tumor features associated with higher cell differentiation, less vascular invasion, and lower TNM stage (Mao et al. 2013). Reduced levels of MUC15 in HCC are associated with shorter survival times of patients and reduced time to disease recurrence (Wang et al. 2013).

Parameters Related to Proliferation, Apoptosis, and Autophagy

The proliferation rate of HCC is generally elevated in comparison with normal and cirrhotic liver tissue and is roughly correlated with the differentiation grade. The Ki-67 labeling index of HCC with a diploid DNA pattern was significantly lower than that in aneuploid HCC, and HCC with an index exceeding 10 % showed a lower disease-free and overall survival (King et al. 1998). Microtubule-associated protein 1 light chain 3A (LC3A), a protein involved in autophagy, is differentially expressed in human malignancies. LC3A is highly expressed in HCC, and high expression in a “stone-like” pattern was correlated with poor differentiation, vascular invasion, and unfavorable prognosis (Xi et al. 2013). Abnormal spindle-like microcephaly-associated protein (ASPM) involved in the regulation of cell proliferation is overexpressed in subsets of HCC, associated with enhanced invasive and metastatic potential (Lin et al. 2008). Expression levels of TRAIL (the proapoptotic TNF-related apoptosis-inducing ligand) are downregulated in HCC in comparison with normal liver tissue (Piras-Straub et al. 2015), and expression of TRAIL receptors has prognostic relevance for HCCs (Kriegl et al. 2010). The biology of HCCs is also modulated by distinct expression patterns of apoptosis-inducing caspases. Cytosolic and nuclear caspase-8 have opposite impact on HCC biology and progression (Koschny et al. 2013).

Parameters Related to Tumor Invasion and Angiogenesis

Tumor invasion as a prerequisite for metastatic spread is a negative prognosticator in all cancers. The survival of HCC patients with macroscopic portal vein invasion and tumor thrombosis is poor (Zhou et al. 2006). Microscopic invasion of portal

venous branches is associated with poor differentiation of HCC, higher serum AFP levels, larger tumor size, and intrahepatic metastasis (Fujita et al. 2011). There is now evidence that microvascular invasion, including microscopic venous invasion, in patients with HCC is one of the most important risk factors affecting recurrence and survival (Tsai et al. 2000; McHugh et al. 2010; Hayashi et al. 2011; Lim et al. 2011; Rodriguez-Peralvarez et al. 2013). The presence of this feature is associated with greater tumor size, poor histologic grade, and intrahepatic micrometastasis (Ramos et al. 2006; Sumie et al. 2008; Eguchi et al. 2010; Gouw et al. 2011) and with an AFP level of more than 100 (McHugh et al. 2010).

Several factors and markers characterizing an invasive phenotype are altered in HCC, including several adhesion molecules (E-cadherin, N-cadherin, catenins, ICAM-1, and CD44 and its variants) (Endo and Terada 2000), tissue proteases, and angiogenesis regulators (review: Qin and Tang 2004). Adhesion-associated molecules ("adhesins") are altered in their cellular expression in early phases of the invasion cascade, and altered expression patterns reflect the mode of tumor cell invasion. Downregulation of E-cadherin in HCC is correlated with an invasive and metastatic phenotype (Endo et al. 2000; Guo et al. 2008), and E-cadherin expression is reduced in single nodular-type HCC with extranodular growth and in the contiguous multinodular type associated with increased invasion and high risk of recurrence (Inayoshi et al. 2003). Investigations on the expression patterns of N-cadherin in HCC provided controversial results. Reduced N-cadherin expression was associated with poorer tumor differentiation, increased cell migration, vascular invasion, and a metastatic phenotype in one study (Zhan et al. 2012), and also discontinuous N-cadherin immunostaining was associated with high risk of recurrence (Cho et al. 2008), while overexpression of neural cadherin (N-cadherin) was a predictive marker for early postoperative recurrence in HCC in another analysis (Seo et al. 2008). In HBV-related carcinogenesis, reduced or absent expression of E-cadherin as an important mechanism of cell contact loss is accomplished by epigenetic repression through histone deacetylation of CDH1 and downregulation of microRNA-373 (Arzumanyan et al. 2012). Also molecules associated with adhesion molecules are involved in this process and affect biology of disease. Serglycin, a proteoglycan, is overexpressed in HCC, and this overexpression is correlated with absence of E-cadherin and a poor prognosis (He et al. 2013), an aggressive invasive phenotype probably being linked to reduced cell-to-cell adhesion of tumor cells and their subsequent individualization. Interestingly, also absent expression of E-cadherin in noncancerous liver was associated with recurrence of HCC after curative resection (Minata et al. 2013a). Enhanced tissue remodeling mediated by matrix metalloproteinases affects the invasion process in a positive way. Tumor recurrence was associated with upregulation of matrix metalloproteinase-2 (MMP-2) in HCC (Théret et al. 2001). An association of E-cadherin and matrix metalloproteinase expression is correlation with HCC progression (Gao et al. 2006).

Tumor invasion requires tumor cell motility and locomotion linked to distinct functions of the actin-containing cytoskeleton. Control of fibrous actin formation involves several proteins, including formin-like 2, a member of the diaphanous-related formin family. Transfection of formin-like 2 into cells suppresses cell motility. Downregulation of formin-like 2 predicted poor prognosis in HCC (Liang et al. 2011), possibly via a mechanism favoring cell motility and migration. Filamin A is highly expressed in HCC cells and may be related to a metastatic phenotype (Ai et al. 2011). Expression of fascin (an actin-bundling protein) and cortactin was associated with poor prognosis in HCC (Iguchi et al. 2009; Huang et al. 2012). A factor stabilizing adherens junctions, MAGI1, suppresses invasion and metastasis. Downregulation of this factor in HCC is associated with aggressive disease and poor prognosis (Zhang et al. 2012). A factor involved in invasion is discoidin domain 1 receptor, showing a higher expression in HCC with recurrent disease (Jian et al. 2012). Overexpression of invasion-associated proteases

plays a role in recurrence and tumor spread. For example, poor prognosis of HCC was associated with overexpression of matrix metalloproteinase-12 (MMP-12) (Ng et al. 2011). On the other hand, TIMP-3 expression is associated with malignant behavior of HCCs (Gu et al. 2014). SERPINB3, a member of the family of serine protease inhibitors, is overexpressed in HCCs with an aggressive course and early recurrence (Pontisso 2014). A higher rate of vascular invasion and poor survival of HCC was correlated with the expression of the metastasis-associated colon cancer 1 (MACC1) gene (Qiu et al. 2011). An invasive phenotype of HCC was also associated with expression of the p53 gene (Hsu et al. 1993).

Pathways leading to an invasive and spreading phenotype in cancer are closely linked with tumor angiogenesis. Tumor angiogenesis is a major and critical event for HCC progression, recurrence, and metastasis. As angiogenesis is based on endothelial cell proliferation and the construction of a new microvessel networks, molecules serving as endothelial cell markers have been studied in HCC angiogenesis in detail, such as CD34 and CD105. The determination of tumor microvessel count appears to be useful prognostic marker for predicting HCC recurrence and patient survival (Nanashima et al. 2004). It is, therefore, to be expected that factors determining angiogenesis affect tumor progression. Strong expression of vascular endothelial growth factor (VEGF) was significantly associated with prognosis (Guo et al. 2006) and with metastatic recurrence following curative resection of HCC (Minata et al. 2013b). Expression of angiopoietin-2 in HCC correlated both with significantly shorter progression-free survival and overall survival (Miyahara et al. 2013). Similarly, expression of the proangiogenic factor endoglin (CD105), a co-receptor for several TGF-beta family cytokines, is correlated with increased postoperative recurrence and metastasis in patients with HCC (Yang et al. 2006). CD105 (endoglin) is overexpressed in microvessels emerging in the peritumoral nonneoplastic tissue as an angiogenic response, and this expression pattern is correlated with tumor recurrence and poorer prognosis (Ho et al. 2005; Yao et al. 2007; Wang et al. 2010). Part of the CD105-reactive endothelia of peritumoral liver are located in the sinusoid-like vessels (Yu et al. 2007). CD105 locally produced in the peritumoral angiogenic belt promotes the migration of HCC-derived endothelial cells (Benetti et al. 2008), suggesting a complex endotheliopoietic system involving the tumor and its peritumoral vascular network. Expression of claudin-10, closely related to angiogenesis, in HCC was correlated with poor prognosis (Huang et al. 2011). The hypoxic angiogenic zone surrounding HCC is a niche of endothelial progenitor cells and is an area overexpressing hypoxia-inducible factor-1 alpha, vascular endothelial growth factor A, and endostatin (Yu et al. 2010). Tumor-derived endothelial cells possess an increased angiogenic capability and are more resistant to angiogenesis inhibitor (Xiong et al. 2009). Expression of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) in HCC is closely related with angiogenesis and poorer relapse-free survival after curative resection (Zhu et al. 2011).

Parameters Related to Epithelial-Mesenchymal Transition (EMT)

Acquiring a mesenchymal phenotype by HCC epithelial cells is a critical feature of epithelial-mesenchymal transition (EMT), a phenomenon that has multiple important impacts on tumor cell behavior, including HCC cells (Marijon et al. 2011). Several mechanisms are involved in the transition of a primarily epithelial tumor cell to a mesenchymal cell, characterized by becoming vimentin positive. CD44, a major adhesion molecule in the extracellular matrix, promotes the neo-expression of vimentin in HCC cells and a downregulation of E-cadherin expression. This pathway is associated with a spindled morphology of cancer cells, an increased invasiveness, and a more aggressive course (Mima et al. 2012). Smad-interacting protein 1 (SIP1, ZEB2) is critically involved in EMT as a repressor of E-cadherin and is overexpressed in several cancers (Oztas

et al. 2010). Claudins are tight junction-associated proteins that affect important cell functions in HCC, including the regulation of epithelial-mesenchymal transition. In HCC, claudin-10 levels were higher than in normal tissue, and expression was correlated with microscopic venous invasion and shorter overall survival (Huang et al. 2011). ZEB1, a member of the ZFH protein family (zinc finger E-box binding homeobox), plays an important role in epithelial-mesenchymal transition in carcinogenesis. Overexpression of ZEB1 in HCC was correlated with advanced stage, intrahepatic metastasis, vascular invasion, and frequent early recurrence (Zhou et al. 2012). Snail, which plays an important role in EMT, is capable to suppress E-cadherin expression in HCC and characterizes poorly differentiated tumors (Woo et al. 2011). Krüppel-like factor 8 promotes EMT, besides effects on proliferation and apoptosis. Upregulation of this factor in HCC promotes tumor invasion and indicates poor prognosis (Li et al. 2010).

Effects of Host Defense Against Tumor

There is strong evidence that the density of tumor-infiltrating immune cells is a predictor of intrahepatic recurrence and survival in patients with HCC. Lymphocyte infiltration of HCC is an early event that is driven by chemokines (CXCL10, CCL5, CCL2) and that determines long-term survival (Chew et al. 2012). In one analysis, the density of CD45RO(+) memory T cells was lower in HCC in comparison with the surrounding liver, while the CD57(+) senescent T cell density was higher in the tumor. The infiltrating memory/senescent T cell ratio predicted extrahepatic metastasis of HCC (Gao et al. 2012).

Ploidy and Chromosomal Aberrations

HCCs, but also the cirrhotic livers in which they develop and precursor lesions, display alterations of ploidy. In patients with liver cirrhosis who developed HCC within 3 years, the DNA ploidy was widely spread from diploid to hyperpolyploid, with a small peak of triploid cells and differences of ploidy among the two nuclei of binucleated cells (Koike et al. 1982, 1985). Initially, HCCs are either diploid or aneuploid neoplasms or contain a mixture of diploid and aneuploidy, e.g., hypotetraploid cells (Saeter et al. 1988). Single HCCs are homogeneous with respect to ploidy in the majority of cases (Ng et al. 1994), while complex tumors may contain mixed ploidy patterns. However, intratumoral heterogeneity as to ploidy was not found in all analyses. Some tumors show several aneuploidy peaks (multiple aneuploidy; Iwao et al. 1993). HCC metastases may show similar or different ploidy pattern (Kuo et al. 1987; Ding et al. 1992), while second (metachronous) HCC lesions developing in the liver can show a ploidy pattern different from that of the first tumor (Ishizu 1989; Nagasue et al. 1992). In some metastases, a DNA ploidy reduction was noted (Yoshida et al. 1992). In the course of progressive genomic instability, the ploidy patterns within a given tumor become more and more heterogeneous. This might be the reason why DNA ploidy patterns were not a useful indicator for the prognosis of HCC (McEntee et al. 1992), although ploidy patterns were well correlated with the Edmondson-Steiner grade (Hamazaki et al. 1993) and with tumor size, vascular invasion, and the presence of intrahepatic metastases (Fujimoto et al. 1991). In a study of small HCCs with a diameter of less than 3 cm, 73.3 % were diploid, while 84.6 % of large HCC were aneuploid (Cong and Wu 1990).

HCCs with multiple allelic losses were less often associated with hepatitis viral infection, were more frequently poorly differentiated, had higher serum AFP levels, and were of higher stage. Patients with more than one loss of heterozygosity (LOH) exhibited poorer 3-year disease-free survival than those with one LOH or none, suggesting that cumulative LOH is a useful prognosticator (Tamura et al. 1997) and that comprehensive allelotyping and comparative genomic hybridization are an important approach for

prognostication (Nagai et al. 1997; Piao et al. 1998; Wong et al. 1999; Lau and Guan 2005; Moinzadeh et al. 2005; Homayounfar et al. 2009; Longerich et al. 2012). In addition, distinct chromosome losses were identified with a more aggressive course. Allelic losses on 8p are common in HCC and confer aggressive biology (Chan et al. 2002). Allelic loss on 13q may play an important role in contributing to a more aggressive feature of HCC (Wong et al. 2002).

Molecular Parameters

An increasing number of molecular features are currently defined to play a significant role in HCC biology, molecular classifications, outcome of disease, and prognostication (Table 1).

Selected References Sheu 1997; Qin and Tang 2002a; Qin and Tang 2004; Thorgeirsson et al. 2006; Boyault et al. 2007; Mann et al. 2007; Pang and Poon 2007; Tommasi et al. 2007; Roessler et al. 2010; Chang et al. 2011; Gehrau et al. 2011; Hoshida 2011; Murakata et al. 2011; Van Malenstein et al. 2011; Villanueva et al. 2011; Walther and Jain 2011; Zhang et al. 2011; Singhal et al. 2012; Nault et al. 2013.

HCCs display distinct molecular signatures, e.g., TP53 pathway (Hoshida 2011; van Malenstein et al. 2011). The tumors also show differential expressions of gene products involved in metastatic cascades, including the prometastatic metastasis-associated protein 1 (Moon et al. 2007) and the metastasis suppressor gene, KAI1, which is reduced in metastatic HCC (Guo et al. 1998). However, not only molecular signatures expressed in HCC play a significant role in tumor progression. Gene expression patterns in non-tumoral liver tissue surrounding the primary tumor affect outcome, analysis of these tissue providing insights into the pathobiology of HCC recurrence. The biology of HCCs is markedly regulated by epigenetic mechanisms (promoter DNA methylation) and the differential expression of microRNAs (review: Anwar and Lehmann 2014).

Table 1 Molecular features of hepatocellular carcinoma negatively affecting prognosis

	Effect(s)
Oncogene/suppressor gene expression patterns	
Low p57 expression	Aggressive phenotype
FAT10 oncogene expression (6q21.3)	Tumor progression
HTPAP transcription variant-1 downregulation (8p)	Metastasis, poor survival
SOX9 overexpression	Tumor progression
N-myc downstream-regulated gene 1 expression	Metastatic phenotype
Growth/cell cycle regulation factors	
DNA topoisomerase II alpha overexpression	Aggressive phenotype
Akt overexpression	Metastatic spread
SMAD3L expression	Shorter RFS
Notch1 expression	Shorter DFS
RECK gene polymorphism	Distant metastasis
Cytoskeletal/motility factors	
Talin overexpression	Poor prognosis
Wnt signaling pathway	
BCL9 expression	Aggressive phenotype
Invasion- and metastasis-associated factors	
Matrix metalloproteinases	Invasion
Serine protease inhibitors/SERPINS	Invasion
Expression of colon cancer 1/MACC1	Tumor progression
Epithelial-mesenchymal transition	
p300 expression	Shortened OS
Transcription factors	
FOXJ1 expression	Poor prognosis
FOXM1 expression	Aggressive phenotype
BRP/POZ-domain gene	Poor prognosis
Proinflammatory factors	
CXCL5 expression (neutrophil recruitment)	Tumor progression
CXCR6 upregulation (inflammatory ME)	Metastasis promotion
CXCR7 expression	Distant metastases
S100 calcium-binding protein expression	Proinvasive effects
Osteopontin overexpression	Poor prognosis
Hypoxia and hypoxia-inducible factors	
HIF-1alpha expression	Tumor recurrence
Senescence factors	
Downregulation of fibulin-3	Poor prognosis
Nuclear traffic factors	
Importin-alpha 1	Metastatic phenotype
MicroRNAs	
MiR-18b expression	Malignancy grade
MiR-130b expression	Poor prognosis
MiR-224 upregulation	Tumor progression
MiR-372 expression	Tumor progression
Drug resistance factors	
Expression of asparagine synthetase	Poor prognosis

DFS disease-free survival, *RFS* recurrence-free survival, *OS* overall survival, *ME* microenvironment

References

Ai et al. (2011) Pub Med PMID 21471709

Alberti C (2012) From molecular imaging in preclinical/clinical oncology to theranostic applications in targeted tumor therapy. Eur Rev Med Pharmacol Sci 16:1925–1933

Anwar SL, Lehmann U (2014) DNA methylation, microRNAs, and their crosstalk as potential biomarkers in hepatocellular carcinoma. World J Gastroenterol 20:7894–7913

Arzumanyan A, Friedman T, Kotei E, Ng IO, Lian Z, Feitelson MA (2012) Epigenetic repression of E-cadherin expression by hepatitis B virus x antigen in liver cancer. Oncogene 31:563–572

Benetti A, Berenzi A, Gambarotti M, Garrafa E, Gelati M, Dessy E, Portolani N, Piardi T et al (2008) Transforming growth factor-beta1 and CD105 promote the migration of hepatocellular carcinoma-derived endothelium. Cancer Res 68:8626–8634

Boyault S, Rickman DS, de Reyniès A, Balabaud C, Rebouissou S, Jeannot E, Hérault A et al (2007) Transcriptome classification of HCC is related to gene alterations and to new therapeutic targets. Hepatology 45:42–52

Braakhuis BJ, Bloemena E, Leemans CR, Brakenhoff RH (2010) Molecular analysis of surgical margins in head and neck cancer: more than a marginal issue. Oral Oncol 46:485–491

Casciaro S (2011) Theranostic applications: non-ionizing cellular and molecular imaging through innovative nanosystems for early diagnosis and therapy. World J Radiol 3:249–255

Chan KL, Lee JM, Guan XY, Fan ST, Ng IO (2002) High-density allelotyping of chromosome 8p in hepatocellular carcinoma and clinicopathologic correlation. Cancer 94:3179–3185

Chang SH, Suh KS, Yi NJ, Lee KH, Kim BY, Jang JJ (2011) Predicting the prognosis of hepatocellular carcinoma using gene expression. J Surg Res 171:524–531

Chau GY, Lui WY, Tsay SH, King KL, Loong CC, Chiu JH, Wu CW, P'eng FK (1997) Prognostic significance of surgical margin in hepatocellular carcinoma resection: an analysis of 165 Childs' A patients. J Surg Oncol 66:122–126

Chen MF, Tsai HP, Jeng LB, Lee WC, Yeh CN, Yu MC, Hung CM (2003) Prognostic factors after resection for hepatocellular carcinoma in noncirrhotic livers: univariate and multivariate analysis. World J Surg 27:443–447

Chen ZY, Wei W, Guo ZX, Lin JR, Shi M, Guo RP (2011) Morphologic classification of microvessels in hepatocellular carcinoma is associated with the progression after resection. J Gastroenterol Hepatol 26:866–874

Chew V, Chen J, Lee D, Loh E, Lee J, Lim KH, Weber A, Slankamenac K, Poon RT, Yang H, Ooi LL, Toh HC et al (2012) Chemokine-driven lymphocyte infiltration: an early intratumoral event determining long-term survival in resectable hepatocellular carcinoma. Gut 61:427–438

Cho SB, Lee KH, Lee JH, Park SY, Lee WS, Park CH, Kim HS, Choi SK, Rew JS (2008) Expression of E- and N-cadherin and clinicopathology in hepatocellular carcinoma. Pathol Int 58:635–642

Cong WM, Wu MC (1990) The biopathologic characteristics of DNA content of hepatocellular carcinomas. Cancer 66:498–501

De Carvalho AC, Kowalski LP, Campos AH, Soares FA, Carvalho AL, Vettore AL (2012) Clinical significance of molecular alterations in histologically negative surgical margins of head and neck cancer patients. Oral Oncol 48:240–248

Ding SF, Jalleh RP, Wood CB, Bowles L, Delhanty JD, Dooley J, Habib NA (1992) Different DNA changes in primary and recurrent hepatocellular carcinoma. Gut 33:1433–1435

Durnez A, Verslype C, Nevens F, Fevery J, Aerts R, Pirenne J, Lesaffre E, Libbrecht L et al (2006) The clinicopathological and prognostic relevance of cytokeratin 7 and 19 expression in hepatocellular carcinoma. A possible progenitor cell origin. Histopathology 49:138–151

Eguchi S, Takatsuki M, Hidaka M, Soyama A, Tomonaga T, Muraoka I, Kanematsu T (2010) Predictor of histological microvascular invasion of hepatocellular carcinoma: a lesson from 229 consecutive cases of curative liver resection. World J Surg 34:1034–1038

Endo K, Terada K (2000) Protein expression of Cd44 (standard and variant isoforms) in hepatocellular carcinoma: relationships with tumor grade, clinicopathologic parameters, p53 expression, and patient survival. J Hepatol 32:78–84

Endo K, Ueda T, Ueyama J, Ohta T, Terada T (2000) Immunoreactive E-cadherin, alpha-catenin, beta-catenin, and gamma-catenin proteins in hepatocellular carcinoma: relationships with tumor grade, clinicopathologic parameters, and patients' survival. Hum Pathol 31:558–565

Franco et al. (1990) Pub Med PMID 2153601

Fujimoto J, Okamoto E, Yamanaka N, Toyosaka A, Mitsunobu M (1991) Flow cytometric DNA analysis of hepatocellular carcinoma. Cancer 67:939–944

Fujita N, Aishima S, Iguchi T, Mano Y, Taketomi A, Shirabe K, Honda H, Tsuneyoshi M et al (2011) Histologic classification of microscopic portal venous invasion to predict prognosis in hepatocellular carcinoma. Hum Pathol 42:1531–1538

Gao ZH, Tretiakova MS, Liu WH, Gong C, Farris PD, Hart J (2006) Association of E-cadherin, matrix metalloproteinases, and tissue inhibitors of metalloproteinases with the progression and metastasis of hepatocellular carcinoma. Mod Pathol 19:533–540

Gao Q, Zhou J, Wang XY, Qiu SJ, Song K, Huang XW, Sun J, Shi YH, Li BZ, Xiao YS (2012) Infiltrating memory/senescent T cell ratio predicts extrahepatic metastasis of hepatocellular carcinoma. Ann Surg Oncol 19:455–466

Gehrau R, Mas V, Archer KJ, Maluf D (2011) Molecular classification and clonal differentiation of hepatocellular carcinoma: the step forward for patient selection for liver transplantation. Expert Rev Gastroenterol Hepatol 5:539–552

Germani G, Gurusamy K, Garcovich M, Toso C, Fede G, Hemming A, Suh KS, Weber A et al (2011) Which matters most: number of tumors, size of the largest tumor, or total tumor volume ? Liver Transpl 17 (suppl2):S58–S66

Gholami B, Agar NY, Jolesz FA, Haddad WM, Tannenbaum AR (2011) A compressive sensing approach for glioma margin delineation using mass spectrometry. Conf Proc IEEE Eng Med Biol Soc 2011:5682–5685

Gouw AS, Balabaud C, Kusano H, Todo S, Ichida T, Kojiro M (2011) Markers for microvascular invasion in hepatocellular carcinoma: where do we stand? Liver Transpl 17(suppl 2):S72–S80

Grazi GL, Cescon M, Ravaioli M, Ercolani G, Gardini A, Del Gaudio M, Vetrone G et al (2003) Liver resection for hepatocellular carcinoma in cirrhotics and noncirrhotics. Evaluation of clinicopathologic features and comparison of risk factors for long-term survival and tumour recurrence in a single centre. Aliment Pharmacol Ther 17(suppl 2):119–129

Gu X, Fu M, Ding Y, Ni H, Zhang W, Zhu Y, Tang X, Xiong L, Li J, Qiu L, Xu J, Zhu J (2014) TIMP-3 expression associates with malignant behaviors and predicts favorable survival in HCC. PLoS ONE 9, e106161

Guo XZ, Friess H, Di Mola FF, Heinicke JM, Abou-Shady-M, Graber HU, Baar HU et al (1998) KAI1, a new metastasis suppressor gene, is reduced in metastatic hepatocellular carcinoma. Hepatology 28:1481–1488

Guo RP, Zhong C, Shi M, Zhang CQ, Wei W, Zhang YQ, Li JQ (2006) Clinical value of apoptosis and angiogenesis factors in estimating the prognosis of hepatocellular carcinoma. J Cancer Res Clin Clin Oncol 132:547–555

Guo C, Liu QG, Yang W, Zhang ZL, Yao YM (2008) Relation among p130Cas, E-cadherin and beta-catenin expression, clinicopathologic significance and prognosis human hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 7:490–496

Hamazaki K, Kato T, Yunoki Y, Mori M, Gochi A, Mimura H, Orita K (1993) An analysis of DNA ploidy pattern of hepatocellular carcinoma. Acta Med Okayama 47:413–416

Han DH, Choi GH, Kim KS, Choi JS, Park YN, Kim SU, Park JY, Ahn SH, Han KH (2013) The prognostic significance of the worst grade in hepatocellular carcinoma with heterogeneous histologic grades of differentiation. J Gastroenterol Hepatol 28:1384–1390

Hanazaki K, Kajikawa S, Koide N, Adachi W, Amano J (2001) Prognostic factors after hepatic resection for hepatocellular carcinoma with hepatitis C virus infection: univariate and multivariate analysis. Am J Gastroenterol 96:1243–1250

Hayashi M, Shimizu T, Hirokawa F, Inoue Y, Komeda K, Asakuma M, Miyamoto Y et al (2011) Clinicopathological risk factors for recurrence within one year after initial hepatectomy for hepatocellular carcinoma. Am Surg 77:572–578

He L, Zhou X, Qu C, Tang Y, Zhang Q, Hong J (2013) Serglycin (SRGN) overexpression predicts poor prognosis in hepatocellular carcinoma patients. Med Oncol 30:707

Ho JW, Poon RT, Sun CK, Xue WC, Fan ST (2005) Clinicopathological and prognostic implications of endoglin (CD105) expression in hepatocellular carcinoma and its adjacent non-tumorous liver. World J Gastroenterol 11:176–181

Homayounfar K, Gunawan B, Cameron S, Haller F, Baumhoer D, Uecker S, Sander B et al (2009) Pattern of chromosomal aberrations in primary liver cancers identified by comparative genomic hybridization. Hum Pathol 40:834–842

Hoshida Y (2011) Molecular signatures and prognosis of hepatocellular carcinoma. Minerva Gastroenterol Dietol 57:311–322

Hsu HC, Tseng HJ, Lai PL, Lee PH, Peng SY (1993) Expression of p53 gene in 184 unifocal hepatocellular carcinomas: association with tumor growth and invasiveness. Cancer Res 53:4691–4694

Hu RH, Lee PH, Chang YC, Yu SC, Ho MC, Wu YM (2003) Prognostic factors for hepatocellular carcinoma $<$ or $=$ 3 cm in diameter. Hepatogastroenterology 50:2043–2048

Huang GW, Ding X, Chen S, Zeng L (2011) Expression of claudin 10 protein in hepatocellular carcinoma: impact on survival. J Cancer Res Clin Oncol 137:1213–1218

Huang X, Ji J, Xue H, Zhang F, Han X, Cai Y, Zhang J, Ji G (2012) Fascin and cortactin expression is correlated with poor prognosis in hepatocellular carcinoma. Eur J Gastroenterol Hepatol 24:633–639

Hui AM, Takayama T, Sano K, Kubota K, Akahane M, Ohtomo K, Makuuchi M (2000) Predictive value of gross classification of hepatocellular carcinoma on recurrence and survival after hepatectomy. J Hepatol 33:975–979

Iguchi T, Aishima S, Umeda K, Sanefuji K, Fujita N, Sugimachi K, Gion T, Taketomi A et al (2009) Fascin expression in progression and prognosis of hepatocellular carcinoma. J Surg Oncol 100:575–579

Inayoshi J, Ichida T, Sugitani S, Tsuboi Y, Genda T, Honma N, Asakura H (2003) Gross appearance of hepatocellular carcinoma reflects E-cadherin expression and risk of early recurrence after surgical treatment. J Gastroenterol Hepatol 18:673–677

Ishizu H (1989) Flow cytometric analysis of the nuclear DNA content of hepatocellular carcinoma. Jpn J Surg 19:662–673

Iwao Y, Kim YI, Kaketani K, Nakashima K, Okada K, Kobayashi M (1993) Stemline heterogeneity of nuclear DNA in hepatocellular carcinoma. Hepatogastroenterology 40:491–495

Jakobsohn K, Motiei M, Sinvani M, Popovtzer R (2012) Towards real-time detection of tumor margins using photothermal imaging of immune-targeted gold nanoparticles. Int J Nanomedicine 7:4707–4713

Jian ZX, Sun J, Chen W, Jin HS, Zheng JH, Wu YL (2012) Involvement of discoidin domain 1 receptor in recurrence of hepatocellular carcinoma by genome-wide analysis. Med Oncol 29:3077–3082

Jwo SC, Chiu JH, Chau GY, Loong CC, Lui WY (1992) Risk factors linked to tumor recurrence of human hepatocellular carcinoma after hepatic resection. Hepatology 16:1367–1371

Kalia M (2013) Personalized oncology: recent advances and future challenges. Metabolism 62(suppl 1): S11–S14

Kim SJ, Lee KK, Kim DG (2010) Tumor size predicts the biological behavior and influence of operative modalities in hepatocellular carcinoma. Hepatogastroenterology

King KL, Hwang JJ, Chau GY, Tsay SH, Chi CW, Lee TG, Wu LH, Wu CW, Lui WY (1998) Ki-67 expression as a prognostic marker in patients with hepatocellular carcinoma. J Gastroenterol Hepatol 13:273–279

Kingham TP, Scherer MA, Neese BW, Clements LW, Stefansic JD, Jarnagin WR (2012) Image-guided liver surgery: intraoperative projection of computed tomography images utilizing tracked ultrasound. HPB (Oxford) 14:594–603

Koike Y, Suzuki Y, Nagata A, Furuta S, Nagata T (1982) Studies on DNA content of hepatocytes in cirrhosis and hepatoma by means of microspectrophotometry and autoradiography. Histochemistry 73:549–562

Koike Y, Kamijyo K, Suzuki Y, Kiyosawa K, Nagata A, Furuta S, Nagata T (1985) DNA content of hepatocytes in various stages of liver cirrhosis. Liver 5:156–161

Koschny R, Brost S, Hinz U, Sykora J, Batke EM, Singer S, Breuhahn K, Stremmel W et al (2013) Cytosolic and nuclear caspase-8 have opposite impact on survival after liver resection for hepatocellular carcinoma. BMC Cancer 13:532

Kriegl L, Jung A, Engel J, Jackstadt R, Gerbes AL, Gallmeier E, Reiche JA, Hermeking H et al (2010) Expression, cellular distribution, and prognostic relevance of TRAIL receptors in hepatocellular carcinoma. Clin Cancer Res 16:5529–5538

Kuo SH, Sheu JC, Chen DS, Sung JL, Lin CC, Hsu HC (1987) DNA clonal heterogeneity of hepatocellular carcinoma demonstrated by Feulgen-DNA analysis. Liver 7:359–363

Lai EC, Ng IO, Ng MM, Lok AS, Tam PC, Fan ST, Choi TK, Wong J (1990) Long-term results of resection for large hepatocellular carcinoma: a multivariate analysis of clinicopathologic features. Hepatology 11:815–818

Lai EC, Ng IO, You KT, Choi TK, Fan ST, Mok FP, Wong J (1991) Hepatectomy for large hepatocellular carcinoma: the optimal resection margin. World J Surg 15:141–145

Lai EC, You KT, Ng IO, Shek TW (1993) The pathological basis of resection margin for hepatocellular carcinoma. World J Surg 17:786–790

Lamata P, Lamata F, Sojar V, Makowski P, Massoptier L, Casciaro S, Ali W, Stüdeli T et al (2010) Use of the Resection Map system as guidance during hepatectomy. Surg Endosc 24:2327–2337

Lau SH, Guan XY (2005) Cytogenetic and molecular genetic alterations in hepatocellular carcinoma. Acta Pharmacol Sin 26:659–665

Lauwers GY, Terris B, Balis UJ, Batts KP, Regimbeau JM, Chang Y, Graeme-Cook F et al (2002) Prognostic histologic indicators of curatively resected hepatocellular carcinomas: a multi-institutional analysis of 425 patients with definition of a histologic prognostic index. Am J Surg Pathol 26:25–34

Lee JI, Lee JW, Kim JM, Kim JK, Chung HJ, Kim YS (2012) Prognosis of hepatocellular carcinoma expressing cytokeratin 19: comparison with other liver cancers. Word J Gastroenterol 18:4751–4757

Li JC, Yang XR, Sun HX, Xu Y, Zhou J, Qiu SJ, Ke AW, Cui YH, Wang ZJ, Wang WM et al (2010) Up-regulation of Krüppel-like factor 8 promotes tumor invasion and indicates poor prognosis for hepatocellular carcinoma. Gastroenterology 139:2146–2157

Li N, Wang J, Shen S, Bu X, Tian X, Huang P (2011) Expression of p53, Ki-67 and c-Myc proteins is predictive of the surgical molecular margin in colorectal carcinoma. Pathol Oncol Res 17:479–487

Liang L, Guan J, Zeng Y, Wang J, Li X, Zhang X, Ding Y (2011) Down-regulation of formin-like 2 predicts poor diagnosis in hepatocellular carcinoma. Hum Pathol 42:1603–1612

Lim KC, Chow PK, Allen JC, Chia GS, Lim M, Cheow PC, Chung AY, Ooi LL et al (2011) Microvascular invasion is a better predictor of tumor recurrence and overall survival following surgical resection for hepatocellular carcinoma compared to the Milan criteria. Ann Surg 254:108–113

Lin SY, Pan HW, Liu SH, Jeng YM, Hu FC, Peng SY, Lai PL, Hsu HC (2008) ASPM is a novel marker for vascular invasion, early recurrence, and poor prognosis of hepatocellular carcinoma. Clin Cancer Res 14:4814–4820

Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. Lancet 362:1907–1917

Longerich T, Mueller MM, Breuhahn K, Schirmacher P, Benner A, Heiss C (2012) Oncogenic tree modeling of human hepatocarcinogenesis. Int J Cancer 130:575–583

Lunevicius R, Nakanishi H, Ito S, Kozaki K, Kato T, Tatematsu M, Yasui K (2001) Clinicopathological significance of fibrotic capsule formation around liver metastasis from colorectal cancer. J Cancer Res Clin Oncol 127:193–199

Mann CD, Neal CP, Garcea G, Manson MM, Dennison AR, Berry DP (2007) Prognostic molecular markers in hepatocellular carcinoma: a systematic review. Eur J Cancer 43:979–992

Mao H, Gao W, Lu G, Fang F, Teng L (2013) Clinicopathological and prognostic implications of arginase

expression in hepatocellular carcinoma. Clin Lab 59:37–43

Marijon H, Dokmak S, Paradis V, Zappa M, Bieche I, Bouattour M, Raymond E, Faivre S (2011) Epithelial-to-mesenchymal transition and acquired resistance to sunitinib in a patient with hepatocellular carcinoma. J Herpatol 54:1073–1078

Matsutani S, Sasaki Y, Imaoka S, Iwamoto S, Ohashi I, Kameyama M, Kabuto T, Ishikawa O et al (1994) The prognostic significance of surgical margin in liver resection of patients with hepatocellular carcinoma. Arch Surg 129:1025–1030

McEntee GP, Batts KA, Katzmann JA, Ilstrup M, Nagorney DM (1992) Relationship of nuclear DNA content to clinical and pathologic findings in patients with primary hepatic malignancy. Surgery 111:376–379

McHugh PP, Gilbert J, Vera S, Koch A, Ranjan D, Gedaly R (2010) Alpha-fetoprotein and tumour size are associated with microvascular invasion in explanted livers of patients undergoing transplantation with hepatocellular carcinoma. HPB (Oxford) 12:56–61

Mima K, Okabe H, Ishimoto T, Hayashi H, Nakagawa S, Kuroki H, Watanabe M, Beppu T et al (2012) CD44s regulates the TGF-β-mediated mesenchymal phenotype and is associated with poor prognosis in patients with hepatocellular carcinoma. Cancer Res 72:3414–3423

Minata M, Kudo M, Harada KH, Ikai I, Nishida N (2013a) Expression of E-cadherin and vascular endothelial growth factor in noncancerous liver is associated with recurrence of hepatocellular carcinoma after curative resection. Oncology 84(suppl 1):88–92

Minata M, Harada KH, Kudo M, Ikai I, Nishida N (2013b) The prognostic value of vascular endothelial growth factor in hepatocellular carcinoma for predicting metastasis after curative resection. Oncology 84(suppl 1):75–81

Mise Y, Tani K, Aoki T, Sakamoto Y, Hasegawa K, Sugawara Y, Kokudo N (2013) Virtual liver resection: computer-assisted operation planning using a three-dimensional liver representation. J Hepatobiliary Pancreat Sci 20:157–164

Miyahara K, Nouso K, Morimoto Y, Takeuchi Y, Hagihara H, Kuwaki K, Onishi H, Ikeda F et al (2013) Pro-angiogenic cytokines for prediction of outcomes in patients with advanced hepatocellular carcinoma. Br. J. Cancer . . ..

Moinzadeh P, Breuhahn K, Stützer H, Schirmacher P (2005) Chromosome alterations in human hepatocellular carcinomas correlate with aetiology and histological grade – results of an explorative CGH meta-analysis. Br J Cancer 92:935–941

Moon HE, Cheon H, Lee MS (2007) Metastasis-associated protein 1 inhibits p53-induced apoptosis. Oncol Rep 18:1311–1314

Murakata A, Tanaka S, Mogushi K, Yasen M, Noguchi N, Irie T, Kudo A, Nakamura N et al (2011) Gene expression signature of the gross morphology in hepatocellular carcinoma. Ann Surg 253:94–100

Nagai H, Pineau P, Tiollais P, Buendia MA, Dejean A (1997) Comprehensive allelotyping of human hepatocellular carcinoma. Oncogene 14:2927–2933

Nagasue N, Kohno H, Chang YC, Yamanoi A, Kimoto T, Takemoto Y, Nakamura T (1992) DNA ploidy pattern in synchronous and metachronous hepatocellular carcinomas. J Hepatol 16:208–214

Nagasue N, Ono T, Yamanoi A, Kohno H, El-Assal ON, Taniura H, Uchida M (2001) Prognostic factors and survival after hepatic resection for hepatocellular carcinoma without cirrhosis. Br J Surg 88:515–522

Nanashima A, Yano H, Yamaguchi H, Tanaka K, Shibasaki S, Sumida Y, Sawai T, Shindou H et al (2004) Immunohistochemical analysis of tumor biological features in hepatocellular carcinoma: relationship to clinicopathological factors and prognosis after hepatic resection. J Gastroenterol 39:148–154

Nault JC, De Reyniès A, Villanueva A, Calderaro J, Rebouissou S, Couchy G, Decaens T et al (2013) A hepatocellular carcinoma 5-gene score associated with survival of patients after liver resection. Gastroenterology 145:176–187

Ng IO, Lai EC, Ho JC, Cheung LK, Ng MM, So MK (1994) Flow cytometric analysis of DNA ploidy in hepatocellular carcinoma. Am J Clin Pathol 102:80–86

Ng IO, Lai EC, Fan ST, Ng MM, So MK (1995) Prognostic significance of pathologic features of hepatocellular carcinoma. A multivariate analysis of 278 patients. Cancer 76:2443–2448

Ng KT, Qi X, Kong KL, Cheung BY, Lo CM, Poon RT, Fan ST, Man K (2011) Overexpression of matrix metalloproteinase-12 (MMP-12) correlates with poor prognosis of hepatocellular carcinoma. Eur J Cancer 47:2299–2305

Nguyen QT, Olson ES, Aguilera TA, Jiang T, Scadeng M, Ellies LG, Tsien RY (2010) Surgery with molecular fluorescence imaging using activatable cell-penetrating peptides decreases residual cancer and improves survival. Proc Natl Acad Sci U S A 107:4317–4322

Olson ES, Jiang T, Aguilera TA, Nguyen QT, Ellies LG, Scadeng M, Tsien RY (2010) Activatable cell penetrating peptides linked to nanoparticles as dual probes for vivo fluorescence and MR imaging proteases. Proc Natl Acad Sci U S A 107:4311–4316

Omidi Y (2011) Smart multifunctional theranostics: simultaneous diagnosis and therapy of cancer. Bioimpacts 1:145–147

Oztas E, Avci ME, Ozcan A, Sayan AE, Tulchinsky E, Yagci T (2010) Novel monoclonal antibodies detect Smad-interacting protein 1 (SIP1) in the cytoplasm of human cells from multiple tumor tissue arrays. Exp Mol Pathol 89:182–189

Pang RW, Poon RT (2007) From molecular biology to targeted therapies for hepatocellular carcinoma: the future is now. Oncology 72(suppl 1):30–44

Pawlik TM, Delman KA, Vauthey JN, Nagorney DM, Ng IO, Ikai I, Yamaoka Y, Belghiti J et al (2005) Tumor size predicts vascular invasion and histologic grade:

implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl 11:1086–1092
Piao Z, Park C, Park JH, Kim H (1998) Allelotype analysis of hepatocellular carcinoma. Int J Cancer 75:29–33
Piras-Straub K, Khairzada K, Trippler M, Baba HA, Kaiser GM, Paul A, Canbay A et al (2015) TRAIL expression levels in human hepatocellular carcinoma have implications for tumor growth, recurrence and survival. Int J Cancer 136:E154–E160
Poeta ML, Manola J, Goldenberg D, Forastiere A, Califano JA, Ridge JA, Goodwin J et al (2009) The Ligamp TP53 assay for detection of minimal residual disease in head and neck squamous cell carcinomas surgical margins. Clin Cancer Res 15:7658–7665
Pontisso P (2014) Role of SERPINB3 in hepatocellular carcinoma. Ann Hepatol 13:722–727
Poon RT, Fan ST, Ng IO, Wong J (2000) Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. Ann Surg 231:544–551
Qin LX, Tang ZY (2002a) The prognostic molecular markers in hepatocellular carcinoma. World J Gastroenterol 8:385–392
Qin LX, Tang ZY (2002b) The prognostic significance of clinical and pathological features in hepatocellular carcinoma. World J Gastroenterol 8:193–199
Qin LX, Tang ZY (2004) Recent progress in predictive biomarkers for metastatic recurrence of human hepatocellular carcinoma: a review of the literature. J Cancer Res Clin Oncol 130:497–513
Qiu J, Huang P, Liu Q, Hong J, Li B, Lu C, Wang L, Wang J, Yuan Y (2011) Identification of MACC1 as a novel prognostic marker in hepatocellular carcinoma. J Transl Med 9:166
Ramos E, Llado L, Serrano T, Figueras A, Lastra R, Torras J, Figueras J, Rafecas A et al (2006) Utility of cell-cycle modulators to predict vascular invasion and recurrence after surgical treatment of hepatocellular carcinoma. Transplantation 82:753–758
Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK (2013) A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol 20:325–339
Roessler S, Jia HL, Budhu A, Forgues M, Ye QH, Lee JS, Thorgeirsson SS, Sun Z et al (2010) A unique metastasis gene signature enables prediction of tumor relapse in early-stage hepatocellular carcinoma patients. Cancer Res 70:10202–10212
Saeter G, Lee CZ, Schwarze PE, Ous S, Chen DS, Sung JL, Seglen PO (1988) Changes in ploidy distributions in human liver carcinogenesis. J Natl Cancer Inst 80:1480–1485
Salloum C, Castaing D (2008) Surgical margin status in hepatectomy for liver tumors (in French). Bull Cancer 95:1183–1191
Sasaki et al. (2014) Pub Med PMID 23798352
Seo DD, Lee HC, Kim HJ, Min HJ, Kim KM, Lim YS, Chung YH, Lee YS, Suh DJ et al (2008) Neural cadherin overexpression is a predictive marker for early postoperative recurrence in hepatocellular carcinoma patients. J Gastroenterol Hepatol 23:1112–1118
Shah SA, Wei AC, Cleary SP, Yang I, McGilvray ID, Gallinger S, Grant DR, Greig PD (2007) Prognosis and results after resection of very large (> or = 10 cm) hepatocellular carcinoma. J Gastrointest Surg 11:589–595
Shaw RJ, Hobkirk AJ, Nikolaidis G, Woolgar JA, Triantafyllou A, Brown JS, Liloglou T et al (2013) Molecular staging of surgical margins in oral squamous cell carcinoma using promoter methylation of p16 (INK4A), cytoglobin, E-cadherin, and TMEFF2. Ann Surg Oncol 20:2796–2802
Sheu JC (1997) Molecular mechanism of hepatocarcinogenesis. J Gastroenterol Hepatol 12:S309–S313
Shi M, Zhang C, Feng K, Zhang Y, Chen M, Guo R, Lin X, Li J (2002) Micrometastasis distribution in liver tissue surrounding hepatocellular carcinoma (in Chinese). Zhonghua Zhong Liu Za Zhi 24:257–260
Shi XH, Zheng Y, Sun Q, Cui J, Liu QH, Qü F, Wang YS (2011) DEC1 nuclear expression: a marker of differentiation grade in hepatocellular carcinoma. World J Gastroenterol 17:2037–2043
Shimada M, Rikimaru T, Hamatsu T, Yamashita Y, Terashi T, Taguchi K, Tanaka S et al (2001) The role of macroscopic classification in nodular-type hepatocellular carcinoma. Am J Surg 182:177–182
Singhal A, Jayaraman D, Dhanasekaran DN, Kohli V (2012) Molecular and serum markers in hepatocellular carcinoma: predictive tools for prognosis and recurrence. Crit Rev Oncol Hematol 82:116–140
Sumie S, Kuromatsu R, Okuda K, Ando E, Takata A, Fukushima N, Watanabe Y, Kojiro M et al (2008) Microvascular invasion in patients with hepatocellular carcinoma and its predictable clinicopathological factors. Ann Surg Oncol 15:1375–1382
Suzuki R, Oda Y, Omata D, Sawaguchi Y, Negishi Y, Maruyama K (2013) Novel diagnostics and therapeutics with ultrasound technologies and nanotechnologies. Yakugaku Zasshi 133:1263–1268
Takada Y, Otsuka M, Todoroki T, Fukao K (2003) Accompanying liver cirrhosis as a risk factor for recurrence after resection of solitary hepatocellular carcinoma. Hepatogastroenterology 50:1991–1995
Takayasu K, Arii S, Sakamoto M, Matsuyama Y, Kudo M, Ichida T, Nakashima O, Matsui O et al (2013) Clinical implication of hypovascular hepatocellular carcinoma studied in 4474 patients with solitary tumour equal or less than 3 cm. Liver Int 33:762–770
Tamura S, Nakamori S, Kuroki T, Sasaki Y, Furukawa H, Ishikawa O, Imaoka S, Nakamura Y (1997) Association of cumulative losses with tumor aggressiveness in hepatocellular carcinoma. J Hepatol 27:669–676
Tang YH, Wen TF, Chen X (2012) Resection margin in hepatectomy for hepatocellular carcinoma: a systematic review. Hepatogastroenterology 59:1393–1397
Théret N, Musso O, Turlin B, Lotrian D, Bioulac-Sage P, Campion JP, Boudjéma K, Clément B (2001) Increased extracellular matrix remodeling is associated with

tumor progression in human hepatocellular carcinomas. Hepatology 34:82–88

Thevenot J, de Oliveira H, Sandre O, Pourtau L, Andrés E, Miraux S, Thiaudière E et al (2013) Multifunctional polymersomes for cancer theranostics. J Control Release 172:e44–e45

Thorgeirsson SS, Lee JS, Grisham JW (2006) Molecular prognostication of liver cancer: end of the beginning. J Hepatol 44:798–805

Tommasi S, Pinto R, Pilato B, Paradiso A (2007) Molecular pathways and related target therapies in liver carcinoma. Curr Pharm Des 13:3279–3287

Tralhao JG, Kayal S, Dagher I, Sanhueza M, Vons C, Franco D (2007) Resection of hepatocellular carcinoma: the effect of surgical margin and blood transfusion on long-term survival. Analysis of 209 consecutive patients. Hepatogastroenterology 54:1200–1206

Tsai TJ, Chau GY, Lui WY, Tsay SH, King KL, Loong CC, Hsia CY, Wu CW (2000) Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. Surgery 127:603–608

Tsai HW, Lin YJ, Lin PW, Wu HC, Hsu KH, Yen CJ, Chan SH, Huang W, Su IJ (2011) A clustered ground-glass hepatocyte pattern represents a new prognostic marker for the recurrence of hepatocellular carcinoma after surgery. Cancer 117:2951–2960

Van Malenstein H, van Pelt J, Verslype C (2011) Molecular classification of hepatocellular carcinoma anno 2011. Eur J Cancer 47:1789–1797

Villanueva A, Hoshida Y, Battiston C, Tovar V, Sia D, Alsinet C, Cornella H, Liberzon A et al (2011) Combining clinical, pathology, and gene expression data to predict recurrence of hepatocellular carcinoma. Gastroenterology 140:1501–1512

Walther Z, Jain D (2011) Molecular pathology of hepatic neoplasms: classification and clinical significance. Pathol Res Int 2011:403929

Wang JY, Xu XY, Jia JH, Wu CH, Ge RW (2010) Expressions of SE-1, CD31 and CD105 in the vascular endothelial cells and serum of rat with hepatocellular carcinoma. Chin Med J (Engl) 123:730–733

Wang RY, Chen L, Chen HY, Hu L, Li L, Sun HY, Jiang F, Zhao J, Liu GM, Tang J et al. (2013). MUC15 inhibits dimerization of EGFR and PI3K-AKT signaling and is associated with aggressive hepatocellular carcinomas in patients. Gastroenterology . . .

Wong N, Lai P, Lee SW, Fan S, Pang E, Liew CT, Sheng Z, Lau JW, Johnson PJ (1999) Assessment of genetic changes in hepatocellular carcinoma by comparative genomic hybridization analysis: relationship to disease stage, tumor size, and cirrhosis. Am J Pathol 154:37–43

Wong CM, Lee JM, Lau TC, Fan ST, Ng IO (2002) Clinicopathological significance of loss of heterozygosity on chromosome 13q in hepatocellular carcinoma. Clin Cancer Res 8:2266–2272

Woo HY, Min AL, Choi JY, Bae SH, Yoon SK, Jung CK (2011) Clinicopathologic significance of the expression of Snail in hepatocellular carcinoma. Korean J Hepatol 17:12–18

Wu PC, Fang JW, Lau VK, Lai CL, Lo CK, Lau JY (1996) Classification of hepatocellular carcinoma according to hepatocellular and biliary differentiation markers. Clinical and biological implications. Am J Pathol 149:1167–1175

Xi SY, Lu JB, Chen JW, Cao Y, Luo RZ, Wu QL, Cai MY (2013) The "stone-like" pattern of LC3A expression and its clinicopathologic significance in hepatocellular carcinoma. Biochem Biophys Res Commun 431:760–766

Xiong YQ, Sun HC, Zhang W, Zhu XD, Zhuang PY, Zhang JB, Wang L, Wu WZ et al (2009) Human hepatocellular carcinoma tumor-derived endothelial cells manifest increased angiogenesis capability and drug resistance compared with normal endothelial cells. Clin Cancer Res 15:4838–4846

Yamanaka N, Okamoto E, Toyosaka A, Mitunobu M, Fujihara S, Kato T, Fujimoto J et al (1990) Prognostic factors after hepatectomy for hepatocellular carcinomas. A univariate and multivariate analysis. Cancer 65:1104–1110

Yamanaka J, Yamanaka N, Nakasho K, Tanaka T, Ando T, Yasui C, Kuroda N, Takata M et al (2000) Clinicopathologic analysis of stage II-III hepatocellular carcinoma showing early massive recurrence after liver resection. J Gastroenterol Hepatol 15:1192–1198

Yang B, Gao YT, Du Z, Zhao L, Song WQ (2005) Methylation-based molecular margin analysis in hepatocellular carcinoma. Biochem Biophys Res Commun 338:1353–1358

Yang LY, Lu WQ, Huang GW, Wang W (2006) Correlation between CD105 expression and postoperative recurrence and metastasis of hepatocellular carcinoma. BMC Cancer 6:110

Yang LY, Fang F, Ou DP, Wu W, Zeng ZJ, Wu F (2009) Solitary large hepatocellular carcinoma: a specific subtype of hepatocellular carcinoma with good outcome after hepatic resection. Ann Surg 249:118–123

Yang DJ, Tsai FY, Inoue T, Liao MH, Kong FL, Song S (2013) Molecular imaging-guided theranostics and personalized medicine. Biomed Res Int 2013:859453

Yao Y, Pan Y, Chen J, Sun X, Qiu Y, Ding Y (2007) Endoglin (CD105) expression in angiogenesis of primary hepatocellular carcinomas: analysis using tissue microarrays and comparisons with CD34 and VEGF. Ann Clin Lab Sci 37:39–48

Yeh CN, Chen MF, Lee WC, Jeng LB (2002) Prognostic factors of hepatic resection for hepatocellular carcinoma with cirrhosis: univariate and multivariate analysis. J Surg Oncol 81:195–202

Yoshida Y, Kanematsu T, Matsumata T, Takenaka K, Sugimachi K (1989) Surgical margin and recurrence after resection of hepatocellular carcinoma in patients with cirrhosis. Further evaluation of limited hepatic resection. Ann Surg 209:297–301

Yoshida Y, Kanematsu T, Korenaga D, Sonoda T, Sugimachi K (1992) DNA ploidy of primary hepatocellular carcinoma and pulmonary metastases. Clin Exp Metastasis 10:337–344

Young AL, Malik HZ, Abu-Hilal M, Guthrie JA, Wyatt J, Prasad KR, Toogood GJ, Lodge JP (2007) Large hepatocellular carcinoma: time to stop preoperative biopsy. J Am Coll Surg 205:453–462

Yu D, Zhuang L, Sun X, Chen J, Yao Y, Meng K, Ding Y (2007) Particular distribution and expression pattern of endoglin (CD105) in the liver of patients with hepatocellular carcinoma. BMC Cancer 7:122

Yu DC, Chen J, Ding YT (2010) Hypoxic and highly angiogenic non-tumor tissues surrounding hepatocellular carcinoma: the 'niche' of endothelial progenitor cells. Int J Mol Sci 11:2901–2909

Zhan DQ, Wei S, Liu C, Liang BY, Ji GB, Chen XP, Xiong M, Huang ZY (2012) Reduced N-cadherin expression is associated with metastatic potential and poor surgical outcomes of hepatocellular carcinoma. J Gastroenterol Hepatol 27:173–180

Zhang D, Bai Y, Ge Q, Qiao Y, Wang Y, Chen Z, Lu Z (2006) Microarray-based molecular margin methylation pattern analysis in colorectal carcinoma. Anal Biochem 355:117–124

Zhang Y, Wang S, Li D, Zhang J, Gu D, Zhu Y, He F (2011) A systems biology-based classifier for hepatocellular carcinoma diagnosis. PLoS ONE 6, e22426

Zhang G, Liu T, Wang Z (2012) Downregulation of MAGI1 associates with poor prognosis of hepatocellular carcinoma. J Invest Surg 25:93–99

Zhou J, Tang ZY, Wu ZQ, Zhou XD, Ma ZC, Tan CJ, Shi YH, Yu Y, Qiu SJ, Fan J (2006) Factors influencing survival in hepatocellular carcinoma patients with macroscopic portal vein thrombosis after surgery, with special reference to time dependency: a single-center experience of 381 cases. Hepatogastroenterology 53:275–280

Zhou XP, Quan ZW, Cong WM, Yang N, Zhang HB, Zhang SH, Yang GS (2007) Micrometastasis in surrounding liver and the minimal length of resection margin of primary liver cancer. World J Gastroenterol 13:4498–4503

Zhou L, Rui JA, Wang SB, Chen SG, Qu Q (2011) Prognostic factors of solitary large hepatocellular carcinoma: the importance of differentiation grade. Eur J Surg Oncol 37:521–525

Zhou YM, Cao L, Li B, Zhang RX, Sui CJ, Yin ZF, Yang JM (2012) Clinicopathological significance of ZEB1 protein in patients with hepatocellular carcinoma. Ann Surg Oncol 19:1700–1706

Zhu J, Yang Y, Ma C, Zhang G, Wang K, Hu S (2011) CEACAM1 cytoplastic expression is closely related to tumor angiogenesis and poorer relapse-free survival after curative resection of hepatocellular carcinoma. World J Surg 35:2259–2265

Zhu B, Wu G, Robinson H, Wilganowski N, Hall MA, Ghosh SC, Pinkston KL, Azhdarinia A et al (2013) Tumor margin detection using quantitative NIRF molecular imaging targeting EpCAM validated by far red gene reporter iRFP. Mol Imag Biol 15:560–568

Precursor Lesions of Hepatocellular Carcinoma

7

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_7

Abstract

In cirrhotic livers, several types of precursor lesions of hepatocellular carcinoma (HCC) have been identified. These lesions include both hepatocellular changes characterized by distinct atypias (small cell change and large cell change, previously termed small liver cell dysplasia and large liver cell dysplasia) and circumscribed dysplastic lesions that are either invisible on gross examination (dysplastic focus) or visible with the naked eye (dysplastic nodules). A dysplastic focus consists of a group of hepatocytes having dysplastic features, incidentally detected in histologic specimens and usually showing a diameter of less than 1 mm. Dysplastic hepatocytes in a dysplastic focus mostly show small cell change. Dysplastic nodules are single or multiple nodules ranging in diameter from few mm to 15 mm or even more. They are divided into two variants, low-grade dysplastic nodule and high-grade dysplastic nodules, depending on the degree of atypia. Dysplastic nodules have to be distinguished from large regenerative nodules (macroregenerative nodules).

Introduction

It was recognized since long that cirrhotic livers can contain hepatocellular nodules that differ from usual cirrhotic nodules both in their size and the cellular features. Based on these characteristics and parallels with nodules detected in murine models of hepatocarcinogenesis, such nodules were considered to be precancerous lesions (reviews: Okuda 1992; Kojiro 2000). These macroscopically visible nodules were variably termed "liver cell atypia," "hyperplastic nodule," "macroregenerative nodule" (MRN; Furuya et al. 1988; Hytiroglou et al. 1995), "adenomatous" or "adenomatoid" hyperplasia (Edmondson 1976; Sakamoto et al. 1991), "hepatocellular pseudotumor" (Nagasue et al. 1984), "dysplastic nodules" (Wada et al. 1988), and "atypical liver nodes" (Berman and Moore 1996). It was early recognized that the distinction between these oversized atypical nodules and early hepatocellular carcinoma (HCC) may be difficult (Higginson and Steiner 1961). Based on the presence or absence of cytologic and/or architectural atypias, MRN were classified into two types, i.e., nodules without atypia or type I MRN ("ordinary adenomatous hyperplasia") and nodules with atypia or type II MRN ("atypical adenomatous hyperplasia"; Furuya et al. 1988; Nakanuma et al. 1990, 1993). In part of type II MN, alterations suggestive for the diagnosis of early HCC may be found; for these lesions with an uncertain malignancy, the term "borderline nodule" had been proposed (Ferrell et al. 1993). Precancerous nodules may consist of two components, with a nodule of different cellular composition being surrounded by an MRN nodule with or without atypia ("nodule-in-nodule" patterns). Recently, precancerous lesions of the liver have been redefined, the diagnostic features standardized, and a consensus nomenclature worked out (Ferrell et al. 1993; International Working Party 1995). This had led to the replacement of the former type I MRN by the term, large regenerative nodules (LRN), and type II MRN by the term, dysplastic nodule, as discussed in more detail in the following paragraph (Anthony et al. 1973; Schwartz 1998).

Modern Concepts of Precursor Lesions: Definitions and Classification

In general pathology, dysplasia is defined as a condition that either refers to alteration of single cells, group of cells, or entire multicellular tissues. In the latter case, which is best known from dysplasia of cervical squamous epithelium, a distinct tissue compartment is replaced by immature and atypical cells associated with a decrease of normally differentiating cells. In contrast to metaplasia, atypia or even anaplastic changes must be present in dysplasia, which denotes not only a change in differentiation as in metaplasia but a disorder of growth and differentiation that represents a premalignant alteration. In contrast to dysplastic tissues (e.g., an epithelial lining of a mucosa), dysplasia is less well defined for single cells or groups

Table 1 Classification of precursor lesions of hepatocellular carcinoma (International Working Group 1995)

Cellular alterations
Small cell change (small liver cell change (SLCC))
Large cell change (large liver cell change (LLCC))
Focal and nodular lesions
Dysplastic focus (DF)
Dysplastic nodule (DN)
Low-grade dysplastic nodule (LGDN)
High-grade dysplastic nodule (HGDN)

of cells, such as found in the liver. This is due to the fact that, contrary to an epithelial lining, architectural features (including the effacement of a typical cellular gradient from bottom to top) are not evident, emphasis therefore being placed on cellular and nuclear atypia, as already specified in a classical publication on liver cell dysplasia (Anthony et al. 1973).

As compiled in Table 1, precursor lesions of the liver include both hepatocellular changes characterized by distinct atypias (small cell change, large cell change, and iron-free foci) and hepatocellular dysplastic lesions that are either invisible on gross examination (dysplastic focus; DF) or visible with the naked eye (dysplastic nodule; DN) (Crawford 1990; International Working Party 1995; Tannapfel and Wittekind 2001; Roncalli et al. 2007, 2008). The features of these lesions have recently been reviewed in the 2010 WHO Classification of Tumours of the Digestive System (Theise et al. 2010).

Small Cell Change

Small cell change (small liver cell change; SLCC) was originally described as small cell dysplasia or small liver cell dysplasia (Watanabe et al. 1983; Dumortier and Scoazec 2001). SLCC is defined as an alteration of hepatocytes characterized by decreased cell size/volume, increased nuclear-cytoplasmic ratio, mild hyperchromasia and nuclear atypia, cytoplasmic basophilia or amphophilia, and nuclear crowding (Fig. 1; see below). SLCC, which can exist as small groups of cells, foci, or components of DN, morphologically

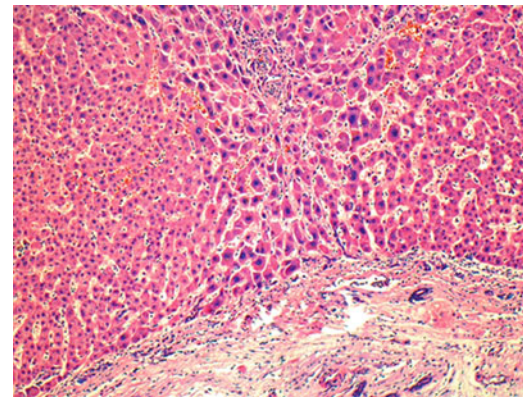

Fig. 1 A small area in a cirrhotic liver is occupied by abnormal hepatocytes with amphophilic cytoplasm and atypical nuclei (small cell change/small cell dysplasia; hematoxylin and eosin stain)

resembles early HCC and shares with HCC chromosomal and genomic alterations. The latter issue is discussed in more detail in the paragraph of pathogenic pathways.

Large Cell Change

Large cell change (large liver cell change, LLCC) was previously termed large cell dysplasia or large liver cell dysplasia (Anthony et al. 1973). In a histologic investigation of HCC associated with liver cirrhosis in Uganda, Anthony and coworkers (1973) defined LLCC as cells with cell body enlargement, nuclear pleomorphism, and multinucleation, occurring in cell groups or occupying entire cirrhotic nodules. Hepatocytes with LLCC display enlargement of both the cell body and the nucleus, with a preserved nuclear-cytoplasmic ratio. Nuclei show a moderate to marked hyperchromasia and sometimes multinucleation (Figs. 2, 3, and 4; see below histopathology).

There is evidence that LLCC exists in two forms regarding pathogenesis and biologic significance, i.e., a reactive form mainly occurring in cholestatic liver disease, and probably representing cellular senescence associated with polyploidization (Lee et al. 1997), and a form that is probably a true dysplastic, preneoplastic cell change and typically occurring in the setting of HBV infection (see below). Currently, there is consensus that LLCC

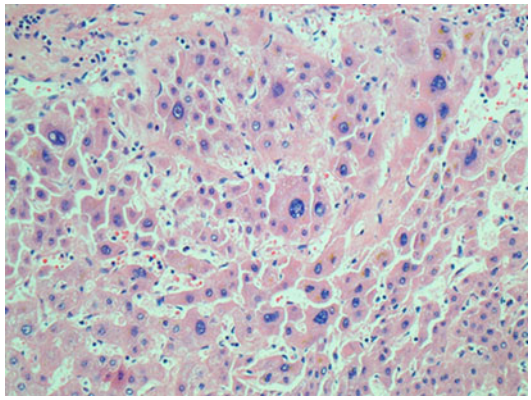

Fig. 2 In contrast to normal-sized hepatocytes in the lower part of the figure, the markedly enlarged cells show highly atypical nuclei and an irregular arrangement (large cell change/large cell dysplasia; hematoxylin and eosin stain)

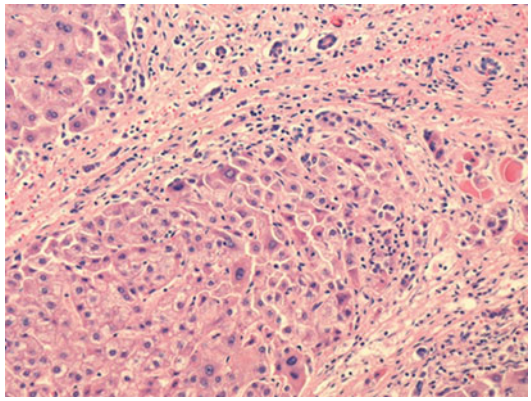

Fig. 3 This cirrhotic nodule exhibits a mixture of small and large dysplastic cells (small and large cell change combined; hematoxylin and eosin stain)

reflect acute to chronic cell injury that may predispose to a carcinogenic pathway.

Dysplastic Focus

The term dysplastic focus (DF) was proposed in the setting of a consensus meeting on nodular hepatic lesions (International Working Party 1995). DF is defined as a group or groups of hepatocytes having dysplastic features, incidentally found in histologic specimens and not macroscopically visible, in contrast to DN (Figs. 5 and 6). In the original definition,

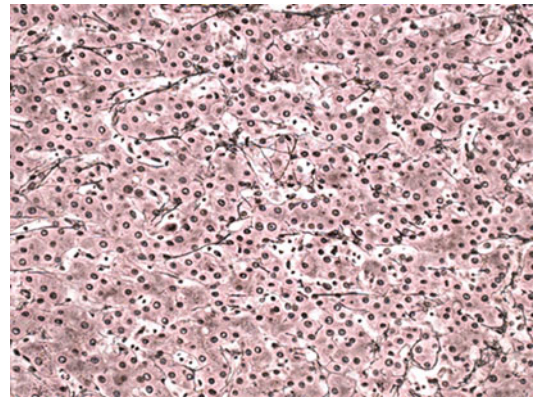

Fig. 4 Hepatocyte dysplasia (small and large cell change) leads to some cellular unrest in reticulin stains, but the general trabecular morphology is preserved (Gomori silver stain)

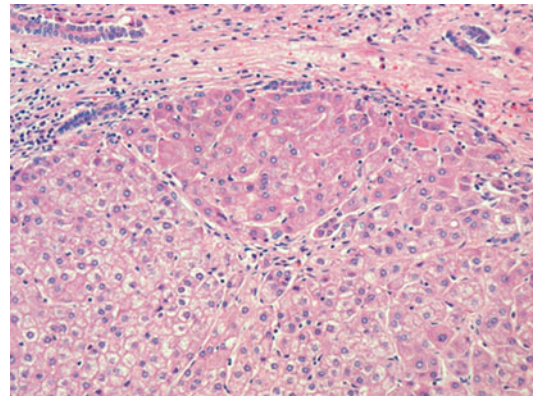

Fig. 5 Dysplastic focus. The nest of cells situated in the periphery of a cirrhotic nodules shows a cell morphology clearly different from that of adjacent hepatocytes (hematoxylin and eosin stain)

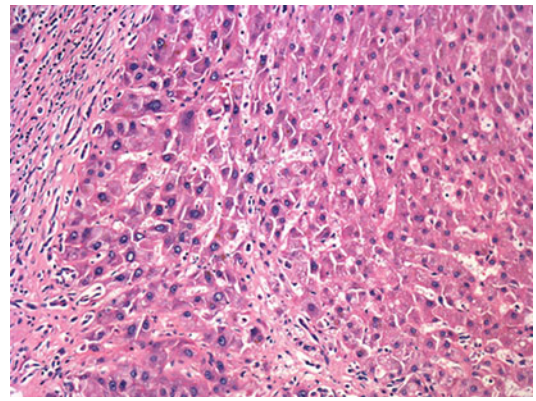

Fig. 6 This dysplastic focus shows a higher degree of cellular and nuclear atypia (hematoxylin and eosin stain)

DF is a lesion with a diameter lesser than 1 mm. This is an arbitrary size definition, which is related to the fact that DF occurs in a single liver lobule or within a cirrhotic nodule (Theise et al. 2010). As described below, DF usually consists of hepatocytes with SLCC, and DF with iron exclusion typically occurs in livers with hemochromatosis.

Dysplastic Nodule

Dysplastic nodules (DN; International Working Party 1995) are nodular lesions that have previously been termed adenomatous hyperplasia. In contrast to DF, DN are macroscopically visible, as single or multiple nodules with a diameter usually ranging from few mm to 15 mm or more, most DN however being smaller than 15 mm in diameter. DN differ from cirrhotic nodules in texture, color, and bulging activity. They are divided into two variants, low-grade DN (LGDN) and high-grade DN (HGDN), depending on the degree of atypia (Figs. 7, 8, 9, 10, 11, 12, and 13; International Working Party 1995). The histologic features are outlined in more detail below. There are certain differences or discrepancies between Eastern and Western interpretations of dysplastic nodules, in that Eastern specialist often identify "borderline nodules" as early HCC, while Western pathologists tend to term these lesions more commonly HGDN. It is expected that distinct molecular

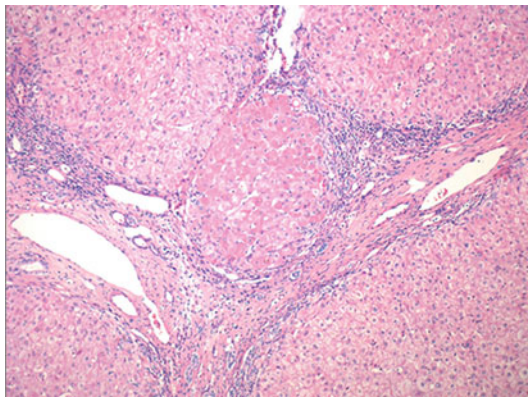

Fig. 7 The nodule in the center exhibits minor morphologic deviation in comparison with other cirrhotic nodules, mainly characterized by oxyphilic cells ("oxyphilic nodule"; hematoxylin and eosin stain)

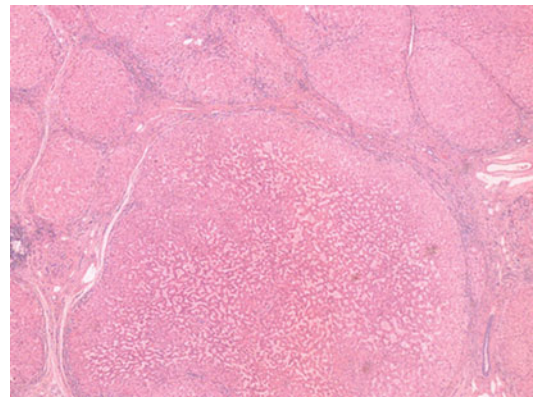

Fig. 8 Dysplastic nodule with slight cellular atypia but abnormal cell arrangement (low-grade dysplastic nodule; hematoxylin and eosin stain)

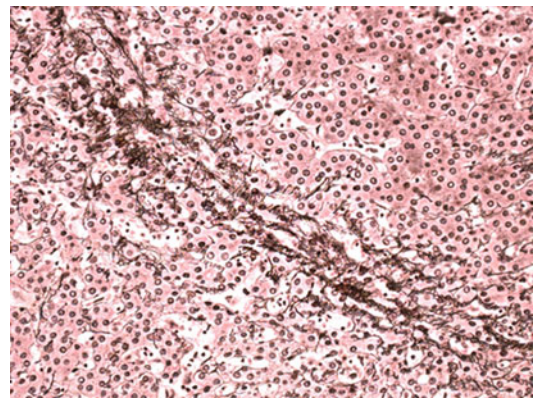

Fig. 9 The abnormal cell plate structure of dysplastic nodules is better visualized in reticulin preparations (Gomori silver stain)

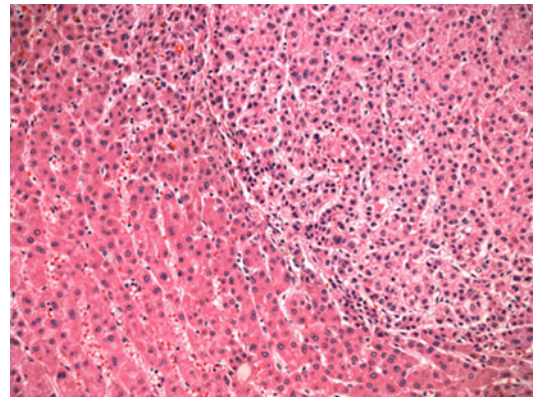

Fig. 10 The right half of the figure displays hepatocyte nodule with atypia and already abnormal cell plates (high-grade dysplastic nodule; hematoxylin and eosin stain)

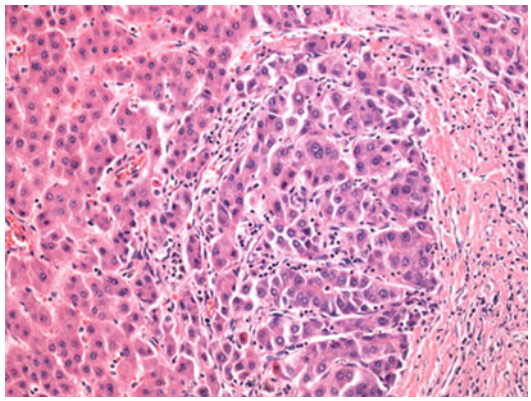

Fig. 11 The middle of the figure reveals a cluster of abnormal, basophilic hepatocytes, representing a small dysplastic nodule of high grade (hematoxylin and eosin stain)

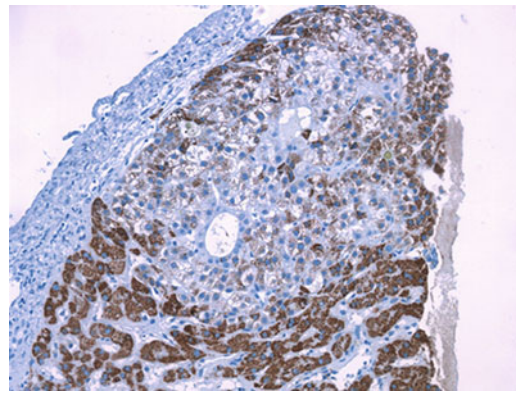

Fig. 13 The lower level of cell differentiation in a dysplastic nodule is shown here as reduced staining for a mitochondrial antigen, in comparison with mitochondria-rich normal hepatocytes (mitochondrial antigen immunostain)

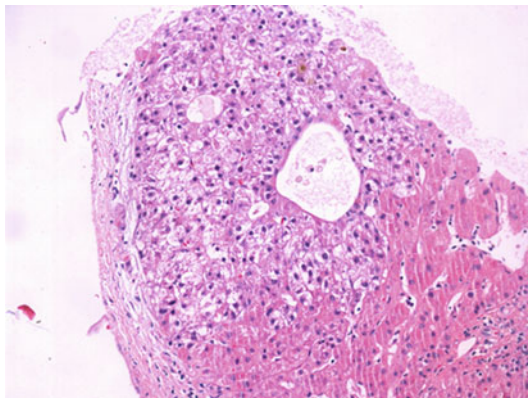

Fig. 12 Dysplastic nodules can contain clear cells and acinar structures (hematoxylin and eosin stain)

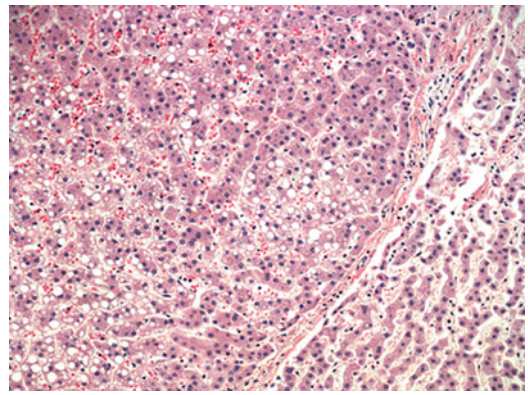

Fig. 14 Macroregenerative nodule. The nodule is well delineated and composed of normal-looking hepatocytes forming slender plates. There is focal fatty change. Note the perifocal parenchymal atrophy (hematoxylin and eosin stain)

signatures will help to better stratify these lesions as to their malignancy status (review: Roncalli et al. 2008).

Large Regenerative Nodules

In the consensus working formulation proposed in 1995 (International Working Party), the term large regenerative nodule (LRN) has replaced the former macroregenerative nodule type I or macronodule. LRN are larger than cirrhotic nodules occurring in micronodular cirrhosis and have a diameter of at least 5 mm (Fig. 14).

LRN mostly occur close to large portal tracts and are composed of hepatocytes without nuclear atypia. In contrast to DN, LRN are not considered to be precursor lesions of hepatic malignancy, as at the molecular level they do not differ from hyperplastic cells found in cirrhotic nodules, although they may, in the setting of their growth status, be different from normal hepatocytes in non-cirrhotic livers (Roncalli et al. 1999; Tiniakos and Brunt 1999; Borzio et al. 2003). The finding of monoclonality in LRN, assessed by use of X

chromosome inactivation-based techniques, is no longer considered to be an argument for a precursor of malignancy status, as this technique also identifies monoclonal cell patches or fields that normally occur during hepatic ontogenesis and may grow to mm size in the course of liver regeneration.

Iron-Free Hepatocyte Foci and Siderotic Foci and Nodules (Siderotic Dysplastic Nodules)

Livers with iron overload, and in particular livers of patients with hereditary hemochromatosis, can contain hepatocyte foci that do not accumulate stainable iron and are capable to exclude iron overload. Such foci are called iron-free foci and are considered to have a growth advantage due to reduced iron toxicity (similar to HCC) and to be precursor lesions for HCC which is a common complication of hepatic iron overload (Hirota et al. 1982; Terada and Nakanuma 1989; Deugnier et al. 1993). Iron-free nodules can also show persistent glycogen stores (Williams 1976), what is of interest with respect to glycogen-storing foci mainly known from animal experimentation (see below).

In contrast to iron-free foci, cirrhotic livers in the absence of generalized iron overload can contain hepatocyte nodules with marked iron overload/hemosiderosis, e.g., also in the setting of chronic viral hepatitis (Murakami et al. 1989; Mitchell et al. 1991; Lefkowitch et al. 1998; Krinsky et al. 2001; Zhang and Krinsky 2004; Cappellesso et al. 2013). Macroscopic nodules with marked iron accumulation are termed iron-rich nodules, siderotic regenerative nodules, or siderotic nodules. Iron-rich foci or nodules can be detected by means of CT and MR, showing nodules of high density or with heterogeneous regions of high density (Murakami et al. 1992), specifically with susceptibility-weighted MR imaging (Chen et al. 2012). MR imaging was used to distinguish between regenerative and dysplastic siderotic nodules (Krinsky et al. 2000). Iron-rich foci that are only found microscopically also occur but are less common alterations (Lefkowitch et al. 1998; Krinsky et al. 2001). Siderotic nodules come in two forms, i.e., those without atypia (regenerative siderotic nodules) and those with various degrees of atypia, termed high-grade siderotic DN and being precursors of HCC. Even low-grade siderotic nodules should be considered premalignant lesions as, similar to DN, they display marked architectural abnormalities, including a high rate of unpaired arteries (Krinsky et al. 2002). Within siderotic nodules, HCC can develop under the sign of a nodule-in-nodule lesion (Mitchell et al. 1991), and the occurrence of HCC may be associated causally with iron deposition in regenerative nodules in patients with cirrhosis (Ito et al. 1999). The reasons why subsets of HGDN are capable to accumulate large amounts of iron are currently unknown.

Glycogen-Storing Foci

In the setting of rodent models of hepatocarcinogenesis, early lesions are characterized by the emergence of clusters or foci of hepatocytes differing from normal parenchymal cells (foci of altered hepatocytes; FAH). Altered hepatocytes appear in several variants, namely, clear glycogen storage cells with a dislocation and relative reduction of granular endoplasmic reticulum, acidophilic glycogen storage cells with hypertrophy of the granular endoplasmic reticulum, fat-storing cells, and basophilic cells poor in glycogen and rich in ribosomes (Bannasch 1976). In these animal experiments, FAH have the features of precursor lesions in a hepatocarcinogenic pathway. Hepatocytes of these early lesions display distinct metabolic alterations, i.e., (a) focal excessive glycogen storage (termed glycogenosis) in hepatocytes giving rise to malignant neoplasms poor in glycogen and (b) an accumulation of mitochondria in hepatocytes, leading to an oncocytic cell lineage (Bannasch et al. 1984, 1997a, b). Clear and acidophilic glycogenotic cells precede the development of neoplastic nodules by weeks and months in mice (Bannasch 1976).

In the human liver, the occurrence and significance of FAH and glycogenic foci are less well studied. Glycogen-storing foci (GSF) and oncocytic foci have sometimes been observed in

human liver, mainly in chronic liver disease with or without associated HCC (Lefkowitch et al. 1980; Su et al. 1997; Libbrecht et al. 2000). However, other types or variants of FAH, as found in rodent models, have not reproducibly been detected in human livers. GSF in human livers are predominantly found in cirrhosis associated with HCC. The potential preneoplastic role of GSF in humans is not clarified. Part of GSF showed clusters of cells with SLCC, but whether there is really a sequence from GSF via liver cell dysplasia to HCC, as proposed, is still an open question (Su et al. 1997). It has also to be emphasized that liver cell dysplasia in cirrhosis, including the preneoplastic SLCC, is a rather common finding, while GSF are much rarer events (Libbrecht et al. 2001).

Hyperplastic Foci and Abnormal Regenerative Alterations

Japanese investigators reported on the occurrence of hyperplastic cell populations often containing small cells, termed hyperplastic focus (HPF; Shuto et al. 1999; Kato et al. 2001). Comparisons of the morphologic features of HPF and other small cell lesions suggest that HPF may be the same lesion as a small cell dysplastic focus, at least for a good part of cases. HPF are markedly proliferative lesions and were found to be an indicator of tumor recurrence following hepatic resection for small HCC (Shuto et al. 1999) and might, therefore, rather be precursor lesions instead of reactive, regenerative lesions. From a terminological point of view, HPF would therefore not be a suitable term, as hyperplasia implies a benign, reactive change.

In the Japanese literature, a distinct form of abnormal regeneration has been described under the term "irregular regeneration" (Shibata et al. 1998). Irregular regeneration is characterized by anisocytosis of hepatocytes (variations in cell size), pleomorphism of hepatocytes, bulging of parenchyma, and distinct homogeneous populations of liver cells separated from each other by a sharp border or outline. This pattern results in what was termed a "maplike distribution." Irregular regeneration was graded and severe forms regarded as a risk factor for the evolution of HCC. To date, the relationship between irregular regeneration and other forms of potential precursor lesions has not yet been clarified.

Epidemiology

The incidence of dysplastic changes and of dysplastic nodules in several types of liver cirrhosis varies considerably among reported case series, not the least caused by different definitions of precursor lesions in older studies in comparison with analyses performed after the consensus agreements and the novel definition of dysplasia, dysplastic foci, and dysplastic nodules (Karhunen and Penttilä 1987; Lefkowitch and Apfelbaum 1987). In a classical investigation (Anthony et al. 1973), liver cell dysplasia was found in only 2 of 200 patients with normal livers (1 %), in 3 of 43 (6.9 %) of patients with normal livers harboring HCC, 35 of 175 (20.3 %) of patients with cirrhosis, and in 80 of 124 (64.5 %) of patients with cirrhosis and HCC, suggesting an increase of dysplastic alterations in livers involved in a carcinogenic pathway. Liver cell dysplasia was identified in 60 % of 558 cases of cirrhosis with and without HCC in necropsies of Chinese individuals in Hong Kong from 1963 to 1978 (Ho et al. 1981). In liver tissues of 223 autopsy cases of cirrhosis and HCC, liver cell dysplasia was found in 94 or 42.2 % of cases, 37 from cases with cirrhosis only, and 53 from cases of cirrhosis with HCC. Cases with dysplasia disclosed significantly less frequently positivity for HBsAg (Akagi et al. 1984). In a study of 86 lesions of "macroregenerative" nodules, defined as nodular lesions exceeding 10 mm in diameter, the incidence of dysplastic changes (67.3 %) was significantly higher than that in cases without MRN (40.9 %), and the average size of MRN was greater in macronodular cirrhosis than in micronodular cirrhosis and greater in cirrhosis associated with HCC than in livers

without HCC (Furuya et al. 1988). Terada and coworkers found adenomatous hyperplasia in 21.5 % of 209 cirrhotic livers, and atypical adenomatous hyperplasia (type 2 lesions) were seen in 5.7 %. Among 38 cases of atypical adenomatous hyperplasia, 19 cases contained overt malignant hepatocellular foci (Terada et al. 1993b). In an autopsy series of 150 cases with cirrhosis, nodules of "adenomatous hyperplasia" were detected in 60 cases (40 %), and most patients belonged to the age group 30–60 years (Vaiphei et al. 1999). Rarely, nodular precursor lesions were diagnosed in old individuals, e.g., 82 years old (Gindhart et al. 1979).

Liver cell dysplasia and DN can develop in hepatic conditions known to be complicated by HCC. In regions with a high prevalence of HBV infection, the presence of dysplastic liver lesions is an important predictor of HBV-related HCC (Paterson et al. 1989). Large liver cell dysplasia, as it was previously termed, was detected in up to 82 % of adult alpha-1-antitrypsin deficiency (AAT) livers (69 % including infantile patients), and immunoreactive alpha-1-antitrypsin was detected in "dysplastic" cells (Cohen and Derose 1994a), but according to newer findings, large cell change in AAT livers may be related to cholestatic change (see below). In patients with early-stage ZZ AAT (stage 1 liver disease), increased CK-7-positive hepatic progenitor cell proliferation was seen compared to normal liver (Brunt et al. 2010), an alteration that may play a role in development of dysplastic lesions. Liver cell dysplasia is a typical feature of chronic liver disease developing in hereditary tyrosinemia type I, an inborn metabolism with a high rate of HCC development in chronic liver disease. Hepatic regenerating nodules, nests, or clusters of liver cell dysplasia and DN are found in tyrosinemia type I (Day et al. 1987; Dehner et al. 1989; Manowski et al. 1990; Mieles et al. 1990; Zerbini et al. 1992; Esquivel et al. 1994). In patients showing mutation reversion, reverted liver nodules interestingly revealed normal hepatocyte appearance and no dysplasia (Demers et al. 2003). By use of flow cytometry, DNA aneuploidy was detected in 10 % of cirrhotic nodules in this metabolic disorder (Zerbini et al. 1992). It was proposed that intermediates of tyrosine metabolism (maleylacetoacetate and fumarylacetoacetate) induce greatly increased chromosome breaks in tyrosinemia, causing chromosomal instability (Gilbert-Barness et al. 1990).

Clinical and Imaging Features

Dysplastic nodular lesions are in most patients asymptomatic, involved patients showing signs and symptoms of underlying liver cirrhosis. Patients with DN in the absence of frank HCC foci do not show elevated serum AFP levels (Kondo et al. 1990), with very few exceptions where secretion of AFP by dysplastic liver cells was found (Ng et al. 1999). Due to advanced imaging techniques, small nodular precursor lesions are now more easily and reliably detectable (Fukunaga et al. 2007). Ultrasonographically, the echogenicity of DN is variable, being either high or low. Contrast-enhanced Doppler ultrasonography is useful to distinguish precursor nodules from HCC, as the two lesion types markedly differ in their vascularity and hence intralesional arterial blood flow (Borzio et al. 1997; Fracanzani et al. 2001; Giorgio et al. 2011). Similar variability is seen on CT and MR images, but overall, common imaging findings of DN include low echogenicity, low attenuation, and high, low, or homogeneous intensity on T1- and T2-weighted MR images (Matsui et al. 1989; Kondo et al. 1990; Nomura et al. 1993; Choi et al. 1999; Tanaka et al. 2000; Takayasu et al. 2002; Kim et al. 2003; Krinsky 2004; Lim et al. 2004; O'Malley et al. 2005; Xu et al. 2005; Forner et al. 2008; Hanna et al. 2008; Park et al. 2009; Okamoto et al. 2010; Chou et al. 2011; Ouedraogo et al. 2011; Sersté et al. 2012; Iavarone et al. 2013; Quaia et al. 2013). In some studies, DN were not regularly detectable by use of ultrasonography (Libbrecht et al. 2002). In lesions with iron overload, MR imaging did not allow the distinction of regenerative and dysplastic nodules (Krinsky et al. 2000). The progression from dysplastic

changes to HCC is characterized by typical vascular changes (Efremidis and Hytiroglou 2002).

Pathology

Macroscopy

As specified above, only dysplastic nodules (DN) can be diagnosed macroscopically and appear as single or multiple lesions (Vaiphei et al. 1999; Roncalli et al. 2011). DN are usually small nodules which exhibit a diameter of few mm to 2 cm, but most DN have a diameter of less than 1.5 cm: Large and very large nodular lesions are also observed, reaching a diameter of up to 10 cm ("giant macroregenerative nodule"; Gurkan et al. 2001; Chen et al. 2002). In an autopsy study (150 cases of liver cirrhosis), nodular precursor lesions (termed adenomatous hyperplasia) measured 6 mm to 5 cm in diameter (Vaiphei et al. 1999). HGDN or so-called borderline nodules can be multiple and may have a relationship with a multicentric origin of HCC (Terada and Nakanuma 1995a). On cut surfaces, DN may have a color slightly different from that of non-DN cirrhosis nodules in the vicinity, but DN may sometimes be yellow owing to fatty change, are tan to orange stained, or appear as whitish lesions. In case the lesions are greenish due to bile accumulation, suspicion of early HCC should be raised. Bulging of the cut surface in the non-fixed state of the specimen can be recognized macroscopically and is a rather characteristic feature of larger DN with high-grade dysplasia, high proliferative activity, and compression of the adjacent liver substance. There is a tendency for size of nodules to increase in order from LGDN to HGDN to HCC; in one study, all nodules exceeding a diameter of 1.5 cm were HCC (Sakamoto et al. 1991).

Histopathology

As outlined above, hepatic precursor lesions appear in several types and variants, and diagnostic criteria to identify these lesions have been worked out (Table 2).

Small Cell Change (Small Liver Cell Change (SLCC))

SLCC is characterized by hepatocytes with decreased cell volume, markedly increased nuclear-cytoplasmic ratio, and a basophilic or amphophilic cytoplasm (Watanabe et al. 1983; Vaiphei et al. 1999; Su and Bannasch 2003). The decrease of cytoplasmic mass causes nuclei to be closer together than in normal liver cell plates, resulting in so-called nuclear crowding. Cells with SLCC exhibit a higher proliferative activity than cells in surrounding cirrhotic nodules, harbor genomic changes, and are considered to be preneoplastic cell populations. The distinct features of dysplastic cells, particularly the shapes and symmetry of nuclei, can be assessed by use of morphometry (Chen et al. 1984; Giannini et al. 1987; Pollice et al. 1988; Motohashi et al. 1992; Berman and Moore 1993). There was a relationship between the karyometric features of small cells and the features of poorly differentiated HCC (Zhao et al. 1994). Immunohistochemically, more than half of SLCC cell population consisted of small cells with the same immunohistochemical phenotype as putative hepatic progenitor cells, in contrast to LLCC cells (Libbrecht et al. 2000). The proliferative activity of SLCC as assessed by PCNA labeling was similar to that of grade 1 and grade 2 HCC (Adachi et al. 1993). In addition to SLCC elements belonging to a dysplastic cell compartment, hyperplastic small cells also occur in cirrhotic liver (Tezuka and Sawai 1983), giving rising to differential diagnostic problems. Dysplastic liver cells can reliably be identified by use of morphometric analysis (Vertemati et al. 2010).

Large Cell Change (Large Liver Cell Change (LLCC))

Large liver cell change (LLCC) was formerly termed large liver cell dysplasia. Cells with LLCC are oversized hepatocytes with enlarged nuclei, and these large cells are situated within liver cell plates with a normal architecture. In

Table 2 Histologic criteria for nodular precursor lesions of hepatocellular carcinoma (HCC) in comparison with early HCC

	LGDN	HGDN	Early HCC
Architectural features			
Liver cell plates of normal thickness	+[a]	±	–
Liver cell plates with a width of 3 cells	–	±	+
Effacement of reticulin network	–	±	+
Sinusoidal nuclear alignment	–	+	+
Intranodal portal tracts	+	±	–
Unpaired arteries	–	±	+
Growth patterns			
Clonal growth (in part maplike)	±	+	+
Nuclear atypia			
Hyperchromasia	±	+	+
Irregular nuclear shape	–	+	+
Proliferation of dysplastic cells			
Cells with SLCC	[a]+	++–+++	
Cells with LLCC	±	±	
Differentiation patterns			
Cell crowding	–	+	+
Microacinar structures	–	±	±
Fatty change	–	±	±
Mallory-Denk bodies	–	±	±
Iron-free cell populations	–	±	±
Invasive growth			
Stromal invasion	–	–	+
Microvascular invasion	–	–	±

LGDN low-grade dysplastic nodule, *HGDN* high-grade dysplastic nodule
[a]Legend: + or – means present or absent, respectively. In the rubric proliferation for SLCC, + means low and ++–+++ means moderate to marked, and for LLCC, 1/– means low or absent

contrast to SLCC, the cytoplasm is usually eosinophilic. Nuclei show atypia and are either hyperchromatic or hypochromatic, what had led to the separation of LLCC into two subtypes (Zhao et al. 1994), but whether this reflects two phenotypes of LLCC or two extremes of LLCC nuclear morphology has to be further clarified. Hepatocytes with large cell change revealed either an unchanged nuclear-cytoplasmic ratio (Vaiphei et al. 1999) or an increased morphometric nuclear-cytoplasmic and nucleolar-cytoplasmic ratio (Roncalli et al. 1988). LLCC, which is still a controversial alteration, refers to lesions that are often encountered in various types of chronic liver disease (Park and Roncalli 2006). There is evidence that LLCC is often a reactive change, often occurring in cholestatic liver disease and related to cellular senescence, and not a cellular alteration within a carcinogenic pathway (Henmi et al. 1985; Kovacs and Elek 1987; Lee et al. 1997). In particular, immunohistochemical studies showed that foci of LLCC did not show a correlation with putative progenitor cells (Libbrecht et al. 2000). The criteria for diagnosing LLCC in fine-needle biopsies have been worked out, and in such biopsies, the incidence of LLCC amounts to as much as 15–20 % of cases of liver cirrhosis (Guettier et al. 2001). The morphometric features of large cells more closely resemble those of regenerating hepatocytes, indicating their hyperplastic character rather than a precancerous phenotype (Matturri and Bauer 1988).

There is a complex relationship between normal hepatocytes, regenerating hepatocytes, and LLCC, depending on the underlying type of liver disease. In HBV-related cirrhosis, the p21,

p27, and p16 cell cycle checkpoint markers were activated in normal-looking cirrhotic hepatocytes but diminished gradually from LLCC, small liver cell change, to HCC, with a progressive increase in p53 expression. Conversely, cholestatic LLCC retained expression of cell cycle checkpoint markers. As HBV-related LLCC had a higher yield of p53 cells, it was suggested that LLCC as such is a heterogeneous condition but that cholestatic LLCC represents a reactive change, while HBV-related LLCC may represent dysplastic elements (Natarajan et al. 1997; Koo et al. 2005; Kim et al. 2009).

Dysplastic Foci (DF)

Dysplastic foci (DF) are macroscopically not identifiable and are usually incidental findings at microscopic examination of cirrhotic liver tissue (International Working Party 1995). DF histology consist of small groups of abnormal hepatocytes, whereby the lesion is per definition smaller than 1 mm in diameter. DF commonly consist of an expansion of proliferating hepatocytes with small cell change, but large cells also occur (Hytiroglou 2004). In hemochromatosis livers, DF often appear as iron-free foci. SLCC is considered to be a more advanced precursor lesion than LLCC (Park 2011), but the premalignant significance of DF has not yet systematically been studied, due to small size and the ill-defined status of these lesions. It is to be expected that modern techniques of cell isolation in situ, e.g., laser capture, will render it possible to analyze genomic changes of isolated DF cells.

Dysplastic Nodules

Dysplastic nodules (DN) are defined as nodular lesions, in which groups of dysplastic hepatocytes (SLCC and/or LLCC) have developed in a cirrhotic nodule or occupy an entire nodule (Anthony et al. 1973; Ferrell et al. 1993; International Working Party 1995). DN mostly occur in cirrhotic livers as solitary or multiple lesions, usually not exceeding a diameter of 15 mm. Generally, DN predominantly composed of SLCC cells in a background of ordinary cirrhotic nodules present as hypercellular lesions with increased cytoplasmic basophilia, nuclear and nucleolar enlargement, nuclear crowding, occasional microacini, and proliferating cells located to septa (Wada et al. 1988). Nuclear crowding is related to a change in the nuclear-cytoplasmic ratios, which are clearly greater in malignant liver cells than regenerative cells, specifically in the frequent small cells (Gallagher 1978; Chang et al. 2010), while the nuclear-cytoplasmic ratio was unchanged in most large cells (Watanabe et al. 1983). DN may show a maplike clonal growth pattern (review: Roncalli 2004). DN having a large proportion of LLCC cells show cellular enlargement, nuclear polymorphisms with hyperchromasia or hypochromasia, and multinucleation, and enlargement of both nuclei and the cytoplasmic body can be two- to threefold in non-small cell dysplastic lesions (Anthony et al. 1973). Large liver cell nodules contained more micronuclei and more often showed nuclear anomalies termed “broken eggs” (de Almeida et al. 2004). In contrast to HCC, liver cell plates are not thickened, and reticulin pattern is usually preserved in LGDN (Nakanuma et al. 1998), while HGDN may show liver cell plates reaching a width of three cell layers, sometimes associated with sinusoidal nuclear alignment characterized by continuous hepatocyte nuclear alignment toward sinusoid-like vascular channels.

According to the propositions of an International Working Party (1995), DN are divided into two variants according to the degree of atypia, i.e., low-grade DN (LGDN) and high-grade DN (HGDN). Both variants show evidence of a clonal expansion of abnormal hepatocytes, but LGDN shows minor nuclear anomalies in comparison with HGDN. In HGDN, focal or diffuse SLCC is particularly common, and while intranodular portal tracts are more common in LGDN, they are rare in HGDN, which however may contain unpaired arteries as a sign of abnormal arterialization. In contrast to LGDN, which show a plate architecture identical to that of normal liver, HGDN can show thickened liver cell plates (up to three cells), associated with formation of

microacini and expansile subnodules (foci; Theise et al. 2010). In HGDN lesions having subnodules, the degree of atypia may vary from one subnodule to the other, suggesting clonal diversification. Part of such subnodules were found to be early HCC (HCC arising in DN; Theise et al. 2010). In part of HGDN, Mallory-Denk body clustering was detected, all such foci being well-circumscribed lesions (Terada et al. 1989b). Small liver nodules can either exclude iron and appear as iron-free lesions or they may also store stainable iron. Iron exclusion is regarded as a typical feature of HGDN and is shared by HCC, which typically show resistance to iron (hemosiderin) accumulation (Hirota et al. 1982). HGDN may show unusual changes. One variant is characterized by marked fatty change, lesions previously termed, and fatty macroregenerative nodules (Terada et al. 1989a). These lesions develop in non-steatotic liver cirrhosis as well-demarcated nodules and show foci of clustering Mallory-Denk bodies, numerous hyaline globules, atypical and hyperchromatic nuclei, abnormal blood vessels, iron exclusion, few intranodular portal tracts, and association with HCC. It was proposed that the presence of Mallory-Denk bodies and hyaline globules are suggestive of neoplasia (Terada et al. 1989b), as these cytoplasmic features characterize HCC (Nakanuma et al. 1981; Nakanuma and Ohta 1986). Whereas HGDN can easily be distinguished from LGDN, the latter is difficult to distinguish from regenerative nodules, due to the minor degree of nuclear anomalies. Molecular signatures will in the future help to separate low-grade dysplastic lesion from mere hyperplasia.

HGDN differ from ordinary cirrhotic nodules with respect to vascular architecture. Both a pathologic arterialization and features of capillarization (capillaries with basement membranes instead of sinusoidal channels) are present in at least part of DN. Whereas as the parenchyma of normal liver, cirrhotic nodules, and large regenerative nodules reveal no or only very few arterial elements, arterial vessels are found in DN and so-called borderline lesions of the former nomenclature (Terada and Nakanuma 1995b). The number of both capillary units and unpaired arteries was significantly increased in HGDN and frank HCC over LGDN and cirrhotic nodules, suggesting that certain angiogenic features segregate HGDN from other nodular lesions (Roncalli et al. 1999). In a morphometric analysis, arteries were slightly more numerous and portal vein branches were slightly less frequent in DN, mainly in HGDN (or type 2 adenomatous hyperplasia nodules) compared with surrounding liver substance, while HCC revealed a number and cumulative luminal area of arteries that was much greater than that of surrounding liver (Ueda et al. 1992). HCC developing in the interior of DN seem to possess a vascular tree different from that of the surrounding DN. Following transarterial embolization, the HCC part can undergo selective necrosis, while the DN was spared (Ueda et al. 1991). In rare instances, adenomatous hyperplasia had a pattern of demarcated nodules with scat-like central fibrosis and a large number of arteries, resembling focal nodular hyperplasia (Terada et al. 1993b).

DN can show abnormalities of the extracellular matrix (ECM) but are usually poor in connective tissue. Areas with SLCC displayed a reduced expression of the ECM proteins, tenascin, and type IV collagen (Zhao et al. 1996). Part of DN exhibit a marked increase in connective tissue fibers and may even show a scirrhous change. Two types of scirrhous change in DN were identified, i.e., a pericellular type related to cholestatic change and Mallory-Denk body formation and a stellate type associated with extensive portal fibrosis. Scirrhous change was not a specific feature of HGDN (An et al. 2003). DN also differ from cirrhotic nodules in their content of non-hepatocytic cells. DN contain fewer hepatic stellate cells (HSC) than ordinary cirrhotic nodules, and HSC are more frequent in peripheral parts than in central parts of DN but still less frequent than in cirrhotic nodules (Park et al. 1997). These findings suggest that DN display a profound alteration of the perisinusoidal space, the dwelling place of HSC, possibly related to monoclonal growth of these lesions. On the other hand, HSC may exert an influence on hepatocarcinogenic pathways, including the morphogenesis of dysplasia. In platelet-derived

growth factor C (PDGF-C) transgenic mice, receptors for PDGF-C were localized on HSC, which upon activation produced growth factors and cytokines, including stromal cell-derived hepatocyte growth factors involved in paracrine induction of liver cell dysplasia (Wright et al. 2013).

Immunohistochemistry

In regard to cytokeratin expression, dysplastic cells and cells of DN do not differ from normal hepatocytes. In contrast to HCC, dysplastic lesions were negative for glypican-3 (Wang et al. 2010), and DN are not reactive for AFP (Tsuji et al. 1999). DN may contain few cytokeratin19-positive cells, both in the form of small intraparenchymal cell clusters being similar to ductules and of peripheral bile ductules, while HCC did not show such cells (Terada et al. 1995). Epithelial membrane antigen/EMA staining was found in a minority of nodular precursor lesions (Tsuji et al. 1999). The proliferative features of dysplastic lesions vary among several studies having addressed this issue. Macroregenerative nodules without atypia did not differ from surrounding cirrhotic liver with respect to PCNA labeling, whereas an increased PCNA labeling was found in nodule-in-nodule lesions, whether atypical or overly malignant (Theise et al. 1996). Hepatocytes with small cell change displayed an increased PCNA proliferation index (Zhao et al. 1994) and an increased Ki-67 proliferation index in comparison with cirrhotic nodules without small cell change (Koskinas et al. 2005). Similarly, DN reveal an increased PCNA index in comparison with regenerative nodules (Terada and Nakanuma 1992; Yamashita 1996; Tiniakos and Brunt 1999), and PCNA staining increased from low-grade to high-grade lesions (Le Bail et al. 1995). There was a gradual increase of Ki-67-reactive nuclei from cirrhosis to HGDN and HCC (Dutta et al. 1998; Yeh et al. 2007). Immunoreactivity for the mitogen, transforming growth factor-alpha, is marked in cirrhotic nodules but is weakly or not expressed in HGDN and HCC (Yeh et al. 2007). p53 protein is rarely expressed in dysplastic liver cells, in contrast to HCC (Cohen and DeRose 1994b), but expression of p53 protein in dysplastic cells was found to be associated with increased apoptosis as assessed with in situ DNA end labeling/ISEL (Zhao and Zimmermann 1997). The hepatocyte growth factor receptor, c-Met, is expressed in about half of HCC, but in dysplastic lesions it was only detectable in small cell change (Zhao and Zimmermann 1998).

There is and was an active search for proteins that immunohistochemically discriminate DN from hepatocytes in normal and cirrhotic liver. While normal hepatocytes show a marked membranous staining for E-cadherin, such a reactivity was not found in SLCC (Zhao and Zimmermann 1998). Reactivity for alpha-methylacyl-coenzyme A racemase (AMACR; P504S) was moderate or marked in HCC and dysplastic lesions but was low in normal hepatocytes (Guzman et al. 2006; Helal Tel et al. 2012). Established HCC express protein-induced vitamin K absence or antagonist II (PIVKA-II), while this protein was not detectable in nodular precursor lesions (Miskad et al. 2001). Immunoreactivity for ubiquitin, which is strong in advanced HCC (also in HCC foci forming the inner part of nodule-in-nodule lesions), was weaker in early HCC and weak in dysplastic nodular lesions, suggesting that ubiquitin staining increases in a stepwise manner from DN to advanced HCC (Osada et al. 1997). Similarly, immunoreactivity for leukocyte cell-derived chemotoxin 2 (LECT2), a protein also synthesized by hepatocytes, revealed a stepwise decrease from hepatocytes to DN to well-differentiated HCC and was negative in advanced HCC (Uchida et al. 1999). The immunohistochemical expression of the organic anion-transporting polypeptide 8 (OATP8) significantly decreased during multistep hepatocarcinogenesis, decreasing from LGDN to HGDN to HCC, which may explain the decrease in enhancement ratio on gadoxetic acid-enhanced MR imaging (Kitao et al. 2011).

Immunohistochemical studies also revealed an abnormal phenotype of endothelial cells and vascular channels present in DN. Expression of the endothelial cell markers, CD31, CD34, and BNH9, was detected in 29.8 % of dysplastic lesions and 47 % of HCC, but not in normal

liver tissue, and the three markers were more often found in areas of small cell than of large cell change (Frachon et al. 2001). CD34 expression was more than 30 % in both DN and HCC (Nascimento et al. 2009). Agrin, which is selectively deposed in HCC microvessels versus sinusoidal walls, shows an expression gradually increasing agrin-negative benign lesions to DN of low and high grade (Tatrai et al. 2009). Sinusoid-like endothelial cells exhibited increased caveolin expression in DN relative to adjacent cirrhotic liver, while HCC vessels did not or only to a minor degree (Yerian et al. 2004).

Differential Diagnosis

HGDN may be difficult to distinguish from established HCC (Hytiroglou and Theise 1998), and in fact there is a considerable morphological overlap between HGDN and small HCC, also in cytology specimens (Berman and McNeill 1988). In particular, a distinction between HGDN and early HCC is sometimes difficult, especially when only imaging techniques are employed (Libbrecht et al. 2005). A decisive feature allowing the distinction of HCC from HGDN is presence of tumor cell invasion into portal tracts included in the interior of the tumor nodule, called "stromal invasion." The detection of "stromal invasion" is particularly helpful in case of well-differentiated HCC with vaguely nodular contours (review: Kojiro 2004). Architectural features of thickened cell plates, formation of trabeculae, and loss of the normal reticulin pattern are typical for HCC and are not, or less often, seen in DN (Crawford 1990; Ferrell et al. 1992). Part of HGDN exhibit fatty change, but this feature is also encountered in up to 40 % of small early HCC, i.e., those with a diameter of about 1.5 cm or less, and is therefore not helpful as a discriminator. Fatty change usually vanished as HCC grows to larger size. Advanced HCC may be surrounded by small hepatic nodules, sometimes numerous, that are usually malignant lesions and not DN (Ezaki et al. 1996). Apart from HGDN mainly containing small cells, other small cell lesions have been described, including so-called hyperplastic foci which are associated with recurrence following hepatic resection for small HCC (Shuto et al. 1999).

Biology of Disease

In early reports, foci of cellular atypia or, as they are called now, dysplastic lesions had not been considered to be premalignant or malignant lesions from the beginning, arguments raised against a premalignant state including a difference in histology of atypical nodules vs. HCC (Steiner and Davies 1957) or that such foci can persist in liver cirrhosis for years without development of HCC (Scheuer 1968). The first report demonstrating the emergence of malignancy in adenomatous hyperplasia nodules appeared in 1986 (Arakawa et al. 1986). Development of carcinoma in nodular precursor lesions was reported 2 years later (Furuya et al. 1988; Tsuda et al. 1988). As DN, and specifically HGDN, contain transformed cells with monoclonal growth and accumulation of cancerogenic gene alterations (Facciorusso et al. 2012), they are prone to progress to HCC, reflecting a premalignant change and a dysplasia-carcinoma sequence.

Selected References Elias 1960; Anthony et al. 1973, Anthony 1976, 1979; Anthony et al. 1973; Sakurai 1978; Cohen et al. 1979; Cohen and Berson 1986; Nakanuma et al. 1990, 1993; Takayama et al. 1990; Eguchi et al. 1992; Theise et al. 1992; Terada et al. 1993a, b; Kaji et al. 1994; Borzio et al. 1995; Hytiroglou et al. 1995; Theise 1995; Earls et al. 1996; Riegler 1996; Le Bail et al. 1997; Su et al. 1997; Sakamoto and Hirohashi 1998; Shibata et al. 1998; Kim et al. 2000, 2007; Ishikawa et al. 2002; Suzuki et al. 2002; Taguchi et al. 2002; Borzio et al. 2003; Su and Bannasch 2003; Libbrecht et al. 2005; Shah et al. 2006; Hytiroglou et al. 2007; Sommayura et al. 2007).

A strong argument for the premalignant nature of DN is the observation of HCC, sometimes multiple, developing in the interior of such a dysplastic nodule (Itoh et al. 1991; Theise et al. 1993;

Midorikawa et al. 2002) or HCC coexistent with DN (Kurita et al. 1993). In one investigation, 68.4 % of cases with adenomatous hyperplasia evolved toward HCC after 8–31 months (mean 14.2 months; Lencioni et al. 1994). In another early study, foci of overt HCC were found in 11/53 nodules of atypical adenomatous hyperplasia, suggesting that this alteration (now called HGDN) may be a hepatocellular neoplasm, a borderline lesion, or a peculiar form of low-grade HCC, in which overt HCC is likely to develop (Nakanuma et al. 1990). In a prospective study of macronodules with a mean follow-up of 33 months, 31 % of nodules transformed into HCC. The incidence of HCC per 100 person-years of follow-up was 11.3 %, with a malignant transformation rate of 3.5 %, 15.5 %, 31 %, and 48.5 % at 1,2, 3, and 5 years, respectively. HGDN and extranodular large cell change were independent predictors of malignant transformation (Borzio et al. 2003). A morphologically defined progression from DN to HCC was also found in fine-needle aspiration cytology studies of dysplastic lesions (Lin et al. 2008). It was estimated that 30–40 % of HGDN will progress to HCC at 24 months (Di Tommaso et al. 2013), while another investigation documented a yield of 53 % HCC in HGDN vs. 18 % in LGDN (Kaji et al. 2004). However, not all DN will develop into HCC, due to only partially known reasons, and other studies found a lesser progression to HCC. DN may remain as stable lesions or may even regress or disappear (Kondo et al. 1990). In one study of DN less than 20 mm in diameter, 15/33 nodules (45.5 %) disappeared, 14 nodules (42.4 %) remained unchanged, and only 4 nodules (12.1 %) progressed to HCC. The latter four nodules were all hyperechoic on US and were composed of clear cells with fatty change or small cells with increased nuclear density (Seki et al. 2000). Apart from intrinsic features such as the mode of progressive genomic instability, vascular factors seem to play a role in the switching of DN to HCC. Small hepatocyte nodules with arterial hypovascularity and a preserved portal supply had a low risk of transformation (Fukunaga et al. 2007). DN can give rise to both HCC and cholangiocarcinoma (Kwon et al. 2002), suggesting the involvement of bipotential progenitor cells.

Irrespective of all these observations, the exact role played in hepatocarcinogenesis by liver cell dysplasia and DN as such is not yet fully clarified (Henmi et al. 1985). In particular, it is not yet exactly known which features of dysplastic lesions will with the highest probability lead to malignancy. SLCC, less common than LLCC, is accepted to be a precancerous condition (Thung et al. 1995; Szczepanski 1997). In 1 study of 72 consecutive patients with HCV-associated cirrhosis, SLCC was an independent risk factor for HCC (Makino et al. 2000). There is evidence that a DN with an increased ratio of nuclear density, small cell change, clear cell change, and fatty change should be recognized to be a high risk for the development of HCC (Terasaki et al. 1998). A high prevalence of distinct histologic changes, including SLCC, cytoplasmic basophilia, small microacinar structures, peripheral distribution of nuclei, nuclear irregularities, and thickened liver cell plates, was found in cirrhotic nodules located close to HCC (Ojanguren et al. 1997). A high proliferation rate in dysplastic lesions also seems to be a predictor of later malignancy (Borzio et al. 1998). In contrast, the significance of LLCC has been interpreted in variable ways, based on controversial findings. The difficulty in interpreting the cancerogenic significance of LLCC is linked to the fact that large cells occur as reactive alterations, preferentially in cholestatic liver disease. Several studies did not confirm a premalignant phenotype of LLCC (Thung et al. 1995). But there is evidence that large cells are related to dysplasia and hepatocarcinogenesis under certain circumstances (Ganne-Carrié et al. 1996). It may also be assumed that we deal with two or more types or phenotypes of large cell change, part of them being reactive, others preneoplastic, with the same or at least a very similar morphology. Molecular studies are expected to clarify this situation further. Similar to HGDN, extranodular large cell change was an independent predictor of malignant transformation (Borzio et al. 2003). LLCC observed in the setting of chronic HBV infection was one of the

risk factors for HCC (Koo et al. 2008), and cirrhosis and LLCD were independent risk factors for HCC development in viral-induced chronic liver disease (Libbrecht et al. 2001).

Pathogenic Pathways

There is evidence that HGDN contain transformed cell population with clonal features. Early studies demonstrated a higher prevalence of aneuploidy in DN or atypical adenomatous hyperplasia, suggesting transformation (Hoso and Nakanuma 1991; Thomas et al. 1992; Orsatti et al. 1993; Rubin et al. 1994; Eissa et al. 1997). Clonal analysis of DN by methylation pattern of the X-chromosome-linked human androgen receptor gene revealed monoclonality in part of the lesions (Paradis et al. 1998; Okuda et al. 2001). In a study of 26 macronodules, monoclonality detected by this method was found in 54 % of the nodules and in 45 % of LGDN and 60 % of HGDN (Paradis et al. 1998). Clonality of DN was also demonstrated by use of DNA fingerprinting (Aihara et al. 1996). An immortalizing marker suggesting transformation, activity of telomerase, is absent in cirrhotic nodules but was found in up to 86 % of DN. However, also some large regenerative nodules expressed telomerase, suggesting that telomerase activity is not an absolute indicator of malignant transformation in these cell systems (Hytiroglou et al. 1998).

What are the mechanisms involved in the transformation of DN cells? There is evidence that DN exhibit distinct gene and genome alterations giving rise to abnormal growth and survival. Dysplastic liver lesions may show multiple chromosomal abnormalities (Terris et al. 1997; Raidl et al. 2004) and harbor certain patterns of loss of heterozygosity (LOH). LOH of chromosome 1 has been proposed to be an initial event in human hepatocarcinogenesis and is also manifest in dysplastic nodules, mainly involving the 1p36–p34 region, and specifically at loci D1S2843 (1p36.12) and D1S513 (1p34.3) (Sun et al. 2001; van Dekken et al. 2005). LOH of microsatellites showed a stepwise increase from HGDN to well-differentiated minute HCC to large HCC (Dong et al. 2011). LOH of chromosome 8p21.3.p22 (containing platelet-derived growth factor receptor beta-like tumor suppressor gene/PRLTS and deletion in liver cancer-1 tumor suppressor gene) was detected in 40.9 % of DN and LOH of chromosome 11p13 (containing the HBV integration site and the WT1 tumor suppressor gene) in 15.8 % of DN (Kahng et al. 2003). Comparative genomic hybridization revealed several chromosomal abnormalities in liver cell dysplasia as an indicator of the premalignant status of these lesions (Marchio et al. 2001; Tornillo et al. 2002; van Dekken et al. 2003). In HBsAg-transgenic mice, loss of promyelocytic leukemia protein (PML) promoted chromosome breaks in liver cells and accelerated to induction of dysplasia (Chung and Wu 2013). Epigenetic mechanisms seem to be involved in the pathogenesis of dysplastic lesions. DNA methyltransferases (Dmt) are responsible for epigenetic DNA methylation. Nuclear expression of Dmt3 was not detectable in LGDN but was present in HGDN, similar to HCC (Choi et al. 2003). A recently identified target of methylation is RASSF1A, acting in concert with NORE1A in the proapoptotic pathways of RAS signaling and increasingly methylated from normal liver to cancerous lesions (Di Gioia et al. 2006).

The gene alterations involved in the pathogenesis of DN and genomic differences between DN and early HCC are only partially known. It is expected that DN as precursors of malignancy reveal progressive genomic instability affecting several genes. Telomere shortening, chromosomal instability, and inactivation of the cell cycle checkpoint protein p21 (WAF1/CIP1) function occur both in LGDN and HGDN (Lee et al. 2009). Shortening of telomeres and reactivation of telomerase occur in DN during early stages of hepatocarcinogenesis and with a clear increase of the phenomena from LGDN to HGDN (Komine et al. 2000; Oh et al. 2003). There are differences in gene expression between normal liver, dysplastic lesions, and HCC (Nam et al. 2005). In one investigation, 12 genes were significantly and differentially expressed in early HCC compared with DN, namely, TERT, glypican-3, gankyrin, surviving, TOP2A, LYVE1, E-cadherin, IGFBP3, PDGFRRA,

TGFA, cyclin D1, and hepatocyte growth factor (Llovet et al. 2006), and gene expression profiling revealed 24 genes distinguishing dysplasia from cirrhosis (Wurmbach et al. 2007). In cDNA microarrays, numerous genes were consistently deregulated in livers with dysplastic changes, including caveolin-1, semaphorin E, and FMS-like tyrosine kinase 3 ligand, genes that have a putative role in carcinogenic pathways of the liver (Anders et al. 2003). Part of the gene alteration found in dysplastic lesions affect cell proliferation and differentiation. Dysplastic liver cells, and particular nodular lesions, show an increased proliferative activity. Cell proliferation assessed by counting nucleolar organizer region-associated proteins (Ag-NOR) demonstrated a stepwise increment from LGDN and HGDN to nodule-in-nodule lesions and early HCC (Aoki et al. 1994). G1-S cell cycle modulators such as cyclin D1 and p53 are expressed in HCC but were not detected in DN, suggesting that cyclin D1 overexpression and aberrant p53 expression might have a less important role in DN-HCC progression (Choi et al. 2001), and no mutations in the p53 gene were detected in DN (Kang et al. 1998). Abnormalities of the Wnt/beta-catenin signaling pathway are typically found in HCC, but DN did not show nuclear positivity for beta-catenin and no beta-catenin gene mutations (Prange et al. 2003). DN often display abnormalities of the transforming growth factor-beta (TGF-beta) signaling pathways. The expression of TGF-beta1 is progressively decreased in the sequence from dysplastic cells to early and advanced HCC (Paik et al. 2003). Immunoreactivity for Smad7, an inhibitory Smad of the TGF-beta pathway, is present in the majority of advanced HCC but absent in DN and early HCC, suggesting that Smad7 makes part of a resistance mechanism in increased TGF-beta1 in late stages of hepatocarcinogenesis (Park et al. 2004).

The biogenesis and morphogenesis of dysplastic lesions and the involved mechanisms have been investigated in animal models of hepatocarcinogenesis. LLCC, which is often observed in HBV infection, can be reproduced in HBV x transgenic mice. In these animals, LLCC may, in contrast to humans, more frequently be involved in carcinogenesis (Koo et al. 2005). In double transgenic mice expressing the HBx genes, ATX and IRS-1, an increased frequency of dysplastic lesions and HCC was observed, associated with increased insulin growth factor 1, Wnt1, and Wnt3 mRNA levels (Longato et al. 2009). In a c-Myc transgenic mouse model with microdissection of hepatic lesions, c-Myc induction was associated with transcriptional upregulation of candidate genes and the development of liver cell dysplasia (Hunecke et al. 2012).

References

Adachi E, Hashimoto H, Tsuneyoshi M (1993) Proliferating cell nuclear antigen in hepatocellular carcinoma and small cell liver dysplasia. Cancer 72:2902–2909

Aihara T, Noguchi S, Sasaki Y, Nakano H, Monden M, Imaoka S (1996) Clonal analysis of precancerous lesion of hepatocellular carcinoma. Gastroenterology 111:455–461

Akagi G, Furuya K, Kanamura A, Chihara T, Otsuka H (1984) Liver cell dysplasia and hepatitis B surface antigen in liver cirrhosis and hepatocellular carcinoma. Cancer 54:315–318

An HJ, Illei P, Diflo T, John D, Morgan G, Teperman L, Theise N (2003) Scirrhous changes in dysplastic nodules do not indicate high-grade status. J Gastroenterol Hepatol 18:660–665

Anders RA, Yerian LM, Treatiakova M, Davison JM, Quigg RJ, Domer PH, Hoberg J et al (2003) cDNA microarray analysis of macroregenerative and dysplastic nodules in end-stage hepatitis C virus-induced cirrhosis. Am J Pathol 162:991–1000

Anthony PP (1976) Precursor lesions for liver cancer in humans. Cancer Res 36:2579–2583

Anthony PP (1979) Precancerous changes in the human liver. J Toxicol Environ Health 5:301–313

Anthony PP, Vogel CL, Barker LF (1973) Liver cell dysplasia: a premalignant condition. J Clin Pathol 26:217–223

Aoki K, Sakamoto M, Hirohashi S (1994) Nucleolar organizer regions in small nodular lesions representing early stages of human hepatocarcinogenesis. Cancer 73:289–293

Arakawa M, Kage M, Sugihara S, Nakashima T, Suenaga M, Okuda K (1986) Emergence of malignant lesions within an adenomatous hyperplastic nodule in a cirrhotic liver. Observation in five cases. Gastroenterology 91:198–208

Bannasch P (1976) Cytology and cytogenesis of neoplastic (hyperplastic) hepatic nodules. Cancer Res 36:2555–2562

Bannasch P, Hakcer HJ, Klimek F, Mayer D (1984) Hepatocellular glycogenosis and related pattern of

enzymatic changes during hepatocarcinogenesis. Adv Enzym Regul 22:97–121
Bannasch P, Klimek F, Mayer D (1997a) Early bioenergetic changes in hepatocarcinogenesis: preneoplastic phenotypes mimic responses to insulin and thyroid hormone. J Bioenerg Biomembr 29:303–313
Bannasch P, Jahn U, Hacker H, Su Q, Hoffmann W, Pichlmayr R, Otto G (1997b) Focal hepatic glycogenosis. Int J Oncol 10:261–268
Berman JJ, McNeill RE (1988) Cirrhosis with atypia. A potential pitfall in the interpretation of liver aspirates. Acta Cytol 32:11–14
Berman JJ, Moore GW (1993) Liver dysplasia and the interpretation of image and flow cytometric data of hepatocytes. Am J Clin Pathol 100:706–707
Berman JJ, Moore GW (1996) Dysplasia in atypical liver nodes. Hum Pathol 27:211–213
Borzio M, Bruno S, Roncalli M, Mels GC, Ramella G, Borzio F, Leandro G, Servida E et al (1995) Liver cell dysplasia is a major risk factor for hepatocellular carcinoma in cirrhosis: a prospective study. Gastroenterology 108:812–817
Borzio M, Borzio F, Croce A, Sala M, Salmi A, Leandro G, Bruno S, Roncalli M (1997) Ultrasonography-detected macroregenerative nodules in cirrhosis: a prospective study. Gastroenterology 112:1617–1623
Borzio M, Trerè D, Borzio F, Ferrari AR, Bruno S, Roncalli M, Colloredo G, Leandro G et al (1998) Hepatocyte proliferation rate is a powerful parameter for predicting hepatocellular carcinoma development in liver cirrhosis. Mol Pathol 51:96–101
Borzio M, Fargion S, Borzio F, Fracanzani AL, Croce AM, Stroffolini T, Oldani S, Cotichini R et al (2003) Impact of large regenerative, low grade and high grade dysplastic nodules in hepatocellular carcinoma development. J Hepatol 39:208–214
Brunt EM, Blomenkamp K, Ahmed M, Ali F, Marcus N, Teckman J (2010) Hepatic progenitor cell proliferation and liver injury in a-1-antitrypsin deficiency. J Pediatr Gastroenterol Nutr 51:626–630
Cappellesso R, Bombonato M, Fabbro M, Zanus G, Fassina A (2013) Cytopathological findings in a siderotic liver nodule. Cytopathology 24:61–62
Chang O, Yano Y, Masuzawa A, Fukushima N, Teramura K, Hayashi Y (2010) The cytological characteristics of small cell change of dysplasia in small hepatic nodules. Oncol Rep 23:1229–1232
Chen ML, Gerber MA, Thung SN, Thornton JC, Chung WK (1984) Morphometric study of hepatocytes containing hepatitis B surface antigen. Am J Pathol 114:217–221
Chen LK, Chang FC, Lai CR, Luo JC, Tsai ST, Hwang SJ (2002) Huge adenomatous hyperplasia of the liver. J Clin Gastroenterol 34:272–274
Chen W, DelProposto Z, Wu D, Wang J, Jiang Q, Xuan S, Ye Y, Zhang Z, Hu J (2012) Improved siderotic nodule detection in cirrhosis with susceptibility-weighted magnetic resonance imaging: a prospective study. PLoS One 7:e36454
Choi BI, Han JK, Hong SH, Kim TK, Song CS, Kim KW, Kim MJ, Han MC (1999) Dysplastic nodules of the liver: imaging findings. Abdom Imaging 24:250–257
Choi YL, Park SH, Jang JJ, Park CK (2001) Expression of the G1-S modulators in hepatitis B virus-related hepatocellular carcinoma and dysplastic nodule: association of cyclin D1 and p53 proteins with the progression of hepatocellular carcinoma. J Korean Med Sci 16:424–432
Choi MS, Shim YH, Hwa JY, Lee SK, Ro JY, Kim JS, Yu E (2003) Expression of DNA methyltransferases in multistep hepatocarcinogenesis. Hum Pathol 34:11–17
Chou CT, Chen RC, Chen WT, Lii JM (2011) Characterization of hyperintense nodules on T1-weighted liver magnetic resonance imaging: comparison of Ferucarbotran-enhanced MRI with accumulation-phase FS-T1WI and gadolinium-enhanced MRI. J Chin Med Assoc 74:62–68
Chung YL, Wu ML (2013) Promyelocytic leukaemia protein links DNA damage response and repair to hepatitis virus-related hepatocarcinogenesis. J Pathol 230:377–387
Cohen C, Berson SD (1986) Liver cell dysplasia in normal, cirrhotic, and hepatocellular carcinoma patients. Cancer 57:1535–1538
Cohen C, Derose PB (1994a) Liver cell dysplasia in alpha-1-antitrypsin deficiency. Mod Pathol 7:31–36
Cohen C, DeRose PB (1994b) Immunohistochemical p53 in hepatocellular carcinoma and liver cell dysplasia. Mod Pathol 7:536–539
Cohen C, Berson SD, Geddes EW (1979) Liver cell dysplasia: association with hepatocellular carcinoma, cirrhosis and hepatitis B antigen carrier status. Cancer 44:1671–1676
Crawford JM (1990) Pathologic assessment of liver cell dysplasia and benign liver tumors: differentiation from malignant tumors. Semin Diagn Pathol 7:115–128
Day DL, Letourneau JG, Allan BT, Sharp HL, Ascher N, Dehner LP, Thompson WM (1987) Hepatic regenerating nodules in hereditary tyrosinemia. AJR Am J Roentgenol 149:391–393
De Almeida TM, Leitao RC, Andrade JD, Beçak W, Carrilho FJ, Sonohara S (2004) Detection of micronuclei formation and nuclear anomalies in regenerative nodules of human cirrhotic livers and relationship to hepatocellular carcinoma. Cancer Genet Cytogenet 150:16–21
Dehner LP, Snoyer DC, Sharp HL, Ascher N, Nakhleh R, Day DL (1989) Hereditary tyrosinemia type I (chronic form): pathologic findings in the liver. Hum Pathol 20:149–158
Demers SI, Russo P, Lettre F, Tanguay RM (2003) Frequent mutation reversion inversely correlates with clinical severity in a genetic liver disease, hereditary tyrosinemia. Hum Pathol 34:1313–1320
Deugnier YM, Charalambous P, Le Quilleuc D, Turlin B, Searle J, Brissot P, Powell LW et al (1993) Preneoplastic significance of hepatic iron-free foci in genetic hemochromatosis: a study of 185 patients. Hepatology 18:1363–1369

Di Gioia S, Binachi P, Destro A, Grizzi F, Malesci A, Laghi L, Levrero M, Morabito A et al (2006) Quantitative evaluation of RASSF1A methylation in the non-lesional, regenerative and neoplastic liver. BMC Cancer 6:89

Di Tommaso L, Sangiovanni A, Borzio M, Park YN, Farinati F, Roncalli M (2013) Advanced precancerous lesions in the liver. Best Pract Res Clin Gastroenterol 27:269–284

Dong H, Cong WM, Xian ZH, Zhu ZZ (2011) using loss of heterozygosity of microsatellites to distinguish high-grade dysplastic nodule from early minute hepatocellular carcinoma. Exp Mol Pathol 91:578–583

Dumortier J, Scoazec JY (2001) Liver cell dysplasia: a crosstalk between the clinician and the pathologist (in French). Ann Pathol 21:117–120

Dutta U, Kench J, Byth K, Khan MH, Lin R, Liddle C, Farrell GC (1998) Hepatocellular proliferation and development of hepatocellular carcinoma: a case-control study in chronic hepatitis C. Hum Pathol 29:1279–1284

Earls JP, Theise ND, Weinreb JC, DeCorato DR, Krinsky GA, Rofsky NM, Mizrachi H et al (1996) Dysplastic nodules and hepatocellular carcinoma: thin-section MR imaging of explanted cirrhotic livers with pathologic correlation. Radiology 201:207–214

Edmondson HA (1976) Benign epithelial tumors and tumorlike lesions of the liver. In: Okuda K, Peters RL (eds) Hepatocellular carcinoma. Wiley, New York, pp 309–330

Efremidis SC, Hytiroglou P (2002) The multistep process of hepatocarcinogenesis in cirrhosis with imaging correlation. Eur Radiol 12:753–764

Eguchi A, Nakashima O, Okudaira S, Sugihara S, Kojiro M (1992) Adenomatous hyperplasia in the vicinity of small hepatocellular carcinoma. Hepatology 15:843–848

Eissa S, Wahed M, Ismail A, Amer K, Khalifa A, Elnaggar A (1997) DNA ploidy in hepatic cirrhosis, dysplasia and carcinoma. Oncol Rep 4:443–445

Elias H (1960) Multicentric carcinogenesis in the human liver. Acta Hepatosplenol 7:65–66

Esquivel CO, Gutierrez C, Cox KL, Garcia-Kennedy R, Berquist W, Concepcion W (1994) Hepatocellular carcinoma and liver cell dysplasia in children with chronic liver disease. J Pediatr Surg 29:1465–1469

Ezaki T, Koyanagi N, Yamagata M, Kajiyama K, Maeda T, Sugimachi K (1996) Small hepatic nodules surrounding hepatocellular carcinoma. Hepatogastroenterology 43:1182–1184

Facciorusso A, Nacchiero MC, Rosania R, Laonigro G, Giorgio F, Del Prete V, Panella C et al (2012) Minerva Gastroenterol Dietol 58:35–48

Ferrell LD, Wright T, Lake J, Roberts J, Ascher N (1992) Incidence and diagnostic features of macroregenerative nodules vs. small hepatocellular carcinoma in cirrhotic livers. Hepatology 16:1372–1381

Ferrell LD, Crawford JM, Dhillon AP, Scheuer PJ, Nakanuma Y (1993) Proposal for standardized criteria for the diagnosis of benign, borderline, and malignant hepatocellular lesions arising in chronic advanced liver disease. Am J Surg Pathol 17:1113–1123

Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, Boix L, Sala M, Varela M et al (2008) Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 47:97–104

Fracanzani AL, Burdick L, Borzio M, Roncalli M, Bonelli N, Borzio F, Maraschi A, Fiorelli G et al (2001) Contrast-enhanced Doppler ultrasonography in the diagnosis of hepatocellular carcinoma and premalignant lesions in patients with cirrhosis. Hepatology 34:1109–1112

Frachon S, Gouysse G, Dumortier J, Couvelard A, Nejjari M, Mion F, Berger F, Paliard P et al (2001) Endothelial cell marker expression in dysplastic lesions of the liver: an immunohistochemical study. J Hepatol 34:850–857

Fukunaga T, Kudo M, Tochio H, Okabe Y, Orino A (2007) Natural course of small nodular lesions with intranodular preserved portal supply in cirrhotic liver. Oncology 72(suppl 1):24–29

Furuya K, Nakamura M, Yamamoto Y, Togei K, Otsuka H (1988) Macroregenerative nodule of the liver. A clinicopathologic study of 345 autopsy cases of chronic liver disease. Cancer 61:99–105

Gallagher JC (1978) Quantitative nuclear-cytoplasmic ratios in human hepatomas. Arch Pathol Lab Med 102:189–192

Ganne-Carrié N, Chastang C, Chaepl F, Munz C, Pateron D, Sibony M, Dény P, Trinchet JC et al (1996) Predictive score for the development of hepatocellular carcinoma and additional value of liver large cell dysplasia in Western patients with cirrhosis. Hepatology 23:1112–1118

Giannini A, Zampi G, Bartoloni F, Omer S (1987) Morphological precursors of hepatocellular carcinoma: a morphometrical analysis. Hepatogastroenterology 34:95–97

Gilbert-Barness E, Barness LA, Meisner LF (1990) Chromosomal instability in hereditary tyrosinemia type I. Pediatr Pathol 10:243–252

Gindhart TD, Cimis RJ, Mosenthal WT, Longnecker DS (1979) Adenomatous hyperplasia of the liver. Arch Pathol Lab Med 103:34–37

Giorgio A, Calisti G, di Sarno A, Farella N, de Stefano G, Scognamiglio U, Giorgio V (2011) Characterization of dysplastic nodules, early hepatocellular carcinoma and progressed hepatocellular carcinoma in cirrhosis with contrast-enhanced ultrasound. Anticaner Res 31:3977–3982

Guettier C, Ganne-Carrié N, Ziol M, Arotcarena R, Christidis C, Beaugrand M (2001) Looking for large-cell dysplasia in liver needle biopsies how and why? (in French). Ann Pathol 21:137–144

Gurkan A, Sherlock MF, Chui AK, Thomson R, Verran D, Sheil AG, Painter D (2001) A giant multiacinar

macroregenerative nodule in an explanted liver. Transplantation 72:538–539
Guzman G, Wu SJ, Kajdacsy-Balla A, Cotler SJ (2006) Alpha-methylacyl-CoA racemase (AMACR/P504S) can distinguish hepatocellular carcinoma and dysplastic hepatocytes from benign nondysplastic hepatocytes. Appl Immunohistochem Mol Morphol 14:411–416
Hanna RF, Aguirre DA, Kased N, Emery SC, Peterson MR, Sirlin CB (2008) Cirrhosis-associated hepatocellular nodules: correlation of histopathologic and MR imaging features. Radiographics 28:747–769
Helal Tel A, Radwan NA, Abdel Kader Z, Helmy NA, Hammad SY (2012) Role of alpha methylacyl-coenzyme A racemase in differentiating hepatocellular carcinoma from dysplastic and nondysplastic liver cell lesions. Ann Diagn Pathol 16:330–334
Henmi A, Uchida T, Shikata T (1985) Karyometric analysis of liver cell dysplasia and hepatocellular carcinoma. Evidence against precancerous nature of liver cell dysplasia. Cancer 55:2594–2599
Higginson J, Steiner PE (1961) Definition and classification of malignant epithelial neoplasms of the liver. Acta Unio Int Contra Cancrum 17:593–603
Hirota N, Hamazaki M, Williams GM (1982) Resistance to iron accumulation and presence of hepatitis B surface antigen in preneoplastic and neoplastic lesions in human hemochromatosis livers. Hepatogastroenterology 29:49–51
Ho JC, Wu PC, Mak TK (1981) Liver cell dysplasia in association with hepatocellular carcinoma, cirrhosis and hepatitis B surface antigen in Hong Kong. Int J Cancer 28:571–574
Hoso M, Nakanuma Y (1991) Cytophotometric DNA analysis of adenomatous hyperplasia in cirrhotic livers. Virchows Arch A Pathol Anat Histopathol 418:401–404
Hunecke D, Spanel R, Länger F, Nam SW, Borlak J (2012) MYC-regulated genes involved in liver cell dysplasia identified in a transgenic model of liver cancer. J Pathol 228:520–533
Hytiroglou P (2004) Morphological changes of early human hepatocarcinogenesis. Semin Liver Dis 24:65–75
Hytiroglou P, Theise ND (1998) Differential diagnosis of hepatocellular nodular lesions. Semin Diagn Pathol 15:285–299
Hytiroglou P, Theise ND, Schwartz M, Mor E, Miller C, Thung SN (1995) Macroregenerative nodules in a series of adult cirrhotic liver explants: issues of classification and nomenclature. Hepatology 21:703–708
Hytiroglou P, Kotoula V, Thung SN, Tsokos M, Fiel MI, Papadimitriou CS (1998) Telomerase activity in precancerous hepatic nodules. Cancer 82:1831–1838
Hytiroglou P, Park YN, Krinsky G, Theise ND (2007) Hepatic precancerous lesions and small hepatocellular carcinoma. Gastroenterol Clin North Am 36:867–887
Iavarone M, Manini MA, Sangiovanni A, Fraquelli M, Forzenigo LV, Di Tommaso L et al (2013) Contrast-enhanced computed tomography and ultrasound-guided liver biopsy to diagnose dysplastic liver nodules in cirrhosis. Dig Liver Dis 45:43–49
International Working Party (1995) Terminology of nodular hepatocellular lesions. Hepatology 22:983–993
Ishikawa M, Sasaki K, Chikaishi H, Miyauchi T, Fukuda Y, Miyake H, Yogita S, Tashiro S (2002) A case of adenomatous hyperplasia of the liver with chronic hepatitis C that transformed into hepatocellular carcinoma. Hepatol Res 24:316
Ito K, Mitchell DG, Gabata T, Hann HW, Kim PN, Fujita T, Awaya H, Honjo K, Matsunaga N (1999) Hepatocellular carcinoma: association with increased iron deposition in the cirrhotic liver at MR imaging. Radiology 212:235–240
Itoh A, Taniguchi H, Sawai K, Takahashi T, Kawamoto K, Deguchi T, Kagawa K (1991) A case report of hepatocellular carcinoma within adenomatous hyperplasia: is adenomatous hyperplasia a precancerous lesion or not? Gastroenterol Jpn 26:536–542
Kahng YS, Lee YS, Kim BK, Park WS, Lee JY, Kang CS (2003) Loss of heterozygosity of chromosome 8p and 11p in the dysplastic nodule and hepatocellular carcinoma. J Gastroenterol Hepatol 18:430–436
Kaji K, Terada T, Nakanuma Y (1994) Frequent occurrence of hepatocellular carcinoma in cirrhotic livers after surgical resection of atypical adenomatous hyperplasia (borderline hepatocellular lesion): a follow-up study. Am J Gastroenterol 89:903–908
Kaji I, Kasugai H, Takenaka A, Ishikawa H, Inoue A, Iishi H, Ishiguro S, Tatsuta M (2004) Outcome of 51 nonmalignant nodules in the liver: usefulness of aspiration cytology for diagnosis of dysplastic nodules. J Exp Clin Cancer Res 23:425–431
Kang YK, Kim CJ, Kim WH, Kim HO, Kang GH, Kim YI (1998) p53 mutation and overexpression in hepatocellular carcinoma and dysplastic nodules in the liver. Virchows Arch 432:27–32
Karhunen PJ, Penttilä A (1987) Preneoplastic lesions of human liver. Hepatogastroenterology 34:10–15
Kato K, Ozaki D, Zheng K, Kondo F, Urashima T, Asano T, Ochiai T, Suzuki Y, Ebara M et al (2001) Characterization of hyperplastic foci observed in surgical specimens of hepatocellular carcinoma. Pathol Int 51:20–25
Kim SR, Hayashi Y, Kudo M, Matsuoka T, Imoto S, Song KB, Maekawa Y (2000) J Hepatol 33:857–858
Kim MJ, Lim JH, Lee SJ, Kim SH, Lee WJ, Lim HK, Park JM, Park CK (2003) Correlation between the echogenicity of dysplastic nodules and their histopathologically determined fat content. J Ultrasound Med 22:327–334
Kim SR, Ikawa H, Ando K, Mita K, Fuki S, Sakamoto M, Kanbara Y, Matsuoka T, Kudo M et al (2007) Multistep hepatocarcinogenesis from a dysplastic nodule to well-differentiated hepatocellular carcinoma in a patient with alcohol-related liver cirrhosis. World J Gastroenterol 13:1271–1274

Kim H, Oh BK, Roncalli M, Park C, Yoon SM, Yoo JE, Park YN (2009) Large liver cell change in hepatitis B virus-related liver cirrhosis. Hepatology 50:752–762

Kitao A, Matsui O, Yoneda N, Kozaka K, Shinmura R, Koda W, Kobayashi S, Gabata T et al (2011) The uptake transporter OATP8 expression decreases during multistep hepatocarcinogenesis: correlation with gadoxetic acid enhanced MR imaging. Eur Radiol 21:2056–2066

Kojiro M (2000) Premalignant lesions of hepatocellular carcinoma: pathologic viewpoint. J Hepatobiliary Pancreat Surg 7:535–541

Kojiro M (2004) Focus on dysplastic nodules and early hepatocellular carcinoma: an eastern point of view. Liver Transpl 10(suppl 1):S3–S8

Komine F, Shimojima M, Moriyama M, Amaki S, uchida T, Arakawa Y (2000) Telomerase activity of needle-biopsied liver samples: its usefulness for diagnosis and judgment of efficacy of treatment of small hepatocellular carcinoma. J Hepatol 32:235–241

Kondo F, Ebara M, Sugiura N, Wada K, Kita K, Hirooka N, Nagato Y, Kondo Y, Ohto M et al (1990) Histological features and clinical course of large regenerative nodules: evaluation of their precancerous potentiality. Hepatology 12:592–598

Koo JS, Seong JK, Park C, Yu DY, Oh BK, Oh SH, Park YH (2005) Large liver cell dysplasia in hepatitis B virus x transgenic mouse liver and human chronic hepatitis B virus-infected liver. Intervirology 48:16–22

Koo JS, Kim H, Park BK, Ahn SH, Han KH, Chon CY, Park C, Park YN (2008) Predictive value of liver cell dysplasia for development of hepatocellular carcinoma in patients with chronic hepatitis B. J Clin Gastroenterol 42:738–743

Koskinas J, Petraki K, Kavantzas N, Rapti I, Kountouras D, Hadziyannis S (2005) Hepatic expression of the proliferative marker Ki-67 and p53 protein in HBV or HCV cirrhosis in relation to dysplastic liver cell changes and hepatocellular carcinoma. J Viral Hepat 12:635–641

Kovacs L, Elek G (1987) Large cell dysplasia of hepatocytes, is it a premalignant condition? Acta Morphol Hung 35:47–57

Krinsky G (2004) Imaging of dysplastic nodules and small hepatocellular carcinomas: experience with explanted livers. Intervirology 47:191–198

Krinsky GA, Lee VS, Nguyen MT, Rofsky NM, Theise ND, Morgan GR, Teperman LW et al (2000) Siderotic nodules at MR imaging: regenerative or dysplastic ? J Comput Assist Tomogr 24:773–776

Krinsky GA, Lee VS, Nguyen MT, Rofsky NM, Theise ND, Morgan GR, Teperman LW, Weinreb JC (2001) Siderotic nodules in the cirrhotic liver at MR imaging with explant correlation: no increased frequency of dysplastic nodules and hepatocellular carcinoma. Radiology 218:47–53

Krinsky GA, Zivin SB, Thomer KM, Lee VS, Theise ND, Weinreb JC (2002) Low-grade siderotic dysplastic nodules: determination of premalignant lesions on the basis of vasculature phenotype. Acad Radiol 9:336–341

Kurita K, Yoshida A, Tanabe G, Shirao K, Hamanoue M, Aikou T, Shimazu H (1993) Hepatocellular carcinoma coexistent with adenomatous hyperplasia: report of a case. Surg Today 23:528–531

Kwon Y, Lee SK, Kim JS, Ro JY, Yu E (2002) Synchronous hepatocellular carcinoma and cholangiocarcinoma arising in two different dysplastic nodules. Mod Pathol 15:1096–1101

Le Bail B, Belleannée G, Bernard PH, Saric J, Balabaud C, Bioulac-Sage P (1995) Adenomatous hyperplasia in cirrhotic livers: histological evaluation, cellular density, and proliferative activity of 35 macronodular lesions in the cirrhotic explants of 10 adult French patients. Hum Pathol 26:897–906

Le Bail B, Bernard PH, Carles J, Balabaud C, Bioulac-Sage P (1997) Prevalence of liver cell dysplasia and association with HCC in a series of 100 cirrhotic liver explants. J Hepatol 27:835–842

Lee RG, Tsamandas AC, Demetris AJ (1997) Large cell change (liver cell dysplasia) and hepatocellular carcinoma in cirrhosis: matched case-control study, pathological analysis, and pathogenetic hypothesis. Hepatology 26:1415–1422

Lee YH, Oh BK, Yoo JE, Yoon SM, Choi J, Kim KS, Park YN (2009) Chromosomal instability, telomere shortening, and inactivation of p21 (WAF1/CIP1) in dysplastic nodules of hepatitis B virus-associated multistep hepatocarcinogenesis. Mod Pathol 22:1121–1131

Lefkowitch JH, Apfelbaum TF (1987) Liver cell dysplasia and hepatocellular carcinoma in non-A, non-B hepatitis. Arch Pathol Lab Med 111:170–173

Lefkowitch JH, Arborgh BA, Scheuer PJ (1980) Oxyphilic granular hepatocytes. Mitochondrion-rich cells in hepatic disease. Am J Clin Pathol 74:432–441

Lefkowitch JH, Yee HT, Sweeting J, Green PH, Magun AM (1998) Iron-rich foci in chronic viral hepatitis. Hum Pathol 29:116–118

Lencioni R, Caramella D, Bartolozzi C, Di Coscio G (1994) Long-term follow-up study of adenomatous hyperplasia in liver cirrhosis. Ital J Gastroenterol 26:163–168

Libbrecht L, Desmet V, Van Damme B, Roskams T (2000) The immunohistochemical phenotype of dysplastic foci in human liver: correlation with putative progenitor cells. J Hepatol 33:76–84

Libbrecht L, Craninx M, Nevens F, Desmet V, Roskams T (2001) Predictive value of liver cell dysplasia for development of hepatocellular carcinoma in patients with non-cirrhotic and cirrhotic chronic viral hepatitis. Histopathology 39:66–73

Libbrecht L, Bielen D, Verslype C, Vanbeckevoort D, Pirenne J, Nevens F, Desmet V et al (2002) Focal lesions in cirrhotic explant livers: pathological evaluation and accuracy of pretransplantation imaging examinations. Liver Transpl 8:749–761

Libbrecht L, Desmet V, Roskams T (2005) Preneoplastic lesions in human hepatocarcinogenesis. Liver Int 25:16–27

Lim JH, Kim MJ, Park CK, Kang SS, Lee WJ, Lim HK (2004) Dysplastic nodules in liver cirrhosis: detection

with triple phase helical dynamic CT. Br J Radiol 77:911–916
Lin CC, Lin CJ, Hsu CW, Chen YC, Chen WT, Lin SM (2008) Fine-needle aspiration cytology to distinguish dysplasia from hepatocellular carcinoma with different grades. J Gastroenterol Hepatol 23:e146–e152
Llovet JP, Chen Y, Wurmbach E, Roayaie S, Fiel I, Schwartz M, Thung SN, Khitrov G et al (2006) A molecular signature to discriminate dysplastic nodules from early hepatocellular carcinoma in HCV cirrhosis. Gastroenterology 131:1758–1767
Longato L, de la Monte S, Kuzushita N, Horimoto M, Rogers AB, Slagle BL, Wands JR (2009) Overexpression of insulin receptor substrate-1 and hepatitis Bx genes causes premalignant alterations in the liver. Hepatology 49:1935–1943
Makino Y, Shiraki K, Sugimoto K, Ito T, Yamanaka T, Fujikawa K, Takase K, Nakano T (2000) Histological features of cirrhosis with hepatitis C virus for prediction of hepatocellular carcinoma development; prospective study. Anticancer Res 20:3709–3715
Manowski Z, Silver MM, Roberts EA, Superina RA, Phillips MJ (1990) Liver cell dysplasia and early liver transplantation in hereditary tyrosinemia. Mod Pathol 3:694–701
Marchio A, Terris B, Meddeb M, Pineau P, Duverger A, Tiollais P, Bernheim A, Dejean A (2001) Chromosomal abnormalities in liver cell dysplasia detected by comparative genomic hybridization. Mod Pathol 54:270–274
Matsui O, Kadoya M, Kameyama T, Yoshikawa J, Arai K, Gabata T, Takashima T et al (1989) Adenomatous hyperplastic nodules in the cirrhotic liver: differentiation from hepatocellular carcinoma with MR imaging. Radiology 173:123–126
Matturri L, Bauer D (1988) Morphometric characteristics of hepatocellular dysplasia. Anal Quant Cytol Histol 10:339–342
Midorikawa Y, Ishikawa T, Kubota K, Mori M, Takayama T, Makuuchi M (2002) Development of well-differentiated hepatocellular carcinoma in large adenomatous hyperplasia after long-term follow-up: a case report. Hepatogastroenterology 49:1098–1101
Mieles LA, Esquivel CO, Van Thiel DH, Koneru B, Makowka L, Tzakis AG, Starzl TE (1990) Liver transplantation for tyrosinemia. A review of 10 cases from the University of Pittsburgh. Dig Dis Sci 35:153–157
Miskad UA, Yano Y, Nakaji M, Kishi S, Itoh H, Kim SR, Ku Y, Kuroda Y, Hayashi Y (2001) Histological study of PIVKA-II expression in hepatocellular carcinoma and adenomatous hyperplasia. Pathol Int 51:916–922
Mitchell DG, Rubin R, Siegelman ES, Burk DL, Rifkin MD (1991) Hepatocellular carcinoma within siderotic regenerative nodules: appearance as a nodule within a nodule on MR images. Radiology 178:101–103
Motohashi I, Okudaira M, Takai T, Kaneko S, Ikeda N (1992) Morphological differences between hepatocellular carcinoma and hepatocellular carcinomalike lesions. Hepatology 16:118–126
Murakami T, Marukawa T, Kuroda C, Harada K, Fujita N, Tokunaga K, Wakasa K et al (1989) Siderotic regenerating nodules in liver cirrhosis – evaluation by gradient echo (FLASH) imaging 1.5T (in Japanese). Nippon Igaku Hoshasen Gakkai Zasshi 49:1427–1429
Murakami T, Nakamura H, Hori S, Nakanishi K, Mitani T, Tsuda K, Kozuka T, Wakasa K et al (1992) CT and MRI of siderotic regenerating nodules in hepatic cirrhosis. J Comput Assist Tomogr 16:578–582
Nagasue N, Akamizu H, Yukaya H, Yuuki I (1984) Hepatocellular pseudotumor in the cirrhotic liver: report of three cases. Cancer 54:2487–2494
Nakanuma Y, Ohta G (1986) Expression of Mallory bodies in hepatocellular carcinoma in man and its significance. Cancer 57:81–86
Nakanuma Y, Sugiura H, Ohta G (1981) Cytoplasmic expressions seen in hepatocellular carcinoma. Acta hepatol Jpn 22:226–273
Nakanuma Y, Terada T, Terasaki S, Ueda K, Nonomura A, Kawahara E, Matsui O (1990) 'Atypical adenomatous hyperplasia' in liver cirrhosis: low-grade hepatocellular carcinoma or borderline lesion ? Histopathology 17:27–35
Nakanuma Y, Terada T, Ueda K, Terasaki S, Nonomura A, Matsui O (1993) Adenomatous hyperplasia of the liver as a precancerous lesion. Liver 13:1–9
Nakanuma Y, Hirata K, Terasaki S, Ueda K, Matsui O (1998) Analytical histopathological diagnosis of small hepatocellular nodules in chronic disease. Histol Histopathol 13:1077–1087
Nam SW, Park JY, Ramasamy A, Shevade S, Islam A, Long PM, Park CK, Park PE et al (2005) Molecular changes from dysplastic nodule to hepatocellular carcinoma through gene expression profiling. Hepatology 42:809–818
Nascimento C, Caroli-Bottino A, Paschoal J, Pannain VL (2009) Vascular immunohistochemical markers: contributions to hepatocellular nodule diagnosis in explanted livers. Transplant Proc 41:4211–4213
Natarajan S, Theise ND, Thung SN, Antonio L, Paronetto F, Hytiroglou P (1997) Large-cell change of hepatocytes in cirrhosis may represent a reaction to prolonged cholestasis. Am J Surg Pathol 21:312–318
Ng FH, Chow KC, Cheng CS, Kng C, Ng WF, Wong BC (1999) High alpha-fetoprotein level in HCV-related nodular liver cell dysplasia. Am J Gastroenterol 94:2296–2297
Nomura Y, Matsuda Y, Yabuuchi I, Nishioka M, Tarui S (1993) Hepato-cellular carcinoma in adenomatous hyperplasia: detection with contrast-enhanced US with carbon dioxide microbubbles. Radiology 187:353–356
O'Malley ME, Takayama Y, Sherman M (2005) Outcome of small (10–20 mm) arterial phase-enhancing nodules seen on triphasic liver CT in patients with cirrhosis or chronic liver disease. Am J Gastroenterol 100:1523–1528
Oh BK, Jo Chae K, Park C, Kim K, Jung Lee W, Han KH, Nyun Park Y (2003) Telomere shortening and telomerase reactivation in dysplastic nodules of human hepatocarcinogenesis. J Hepatol 39:786–792

Ojanguren I, Castella E, Ariza A, Santos J, Planas R, Bruguera M (1997) Liver cell atypias: a comparative study in cirrhosis with and without hepatocellular carcinoma. Histopathology 30:106–112

Okamoto E, Sato S, Sanchez-Siles AA, Ishine J, Miyake T, Amano Y, Kinoshita Y (2010) Evaluation of virtual CT sonography for enhanced detection of small hepatic nodules: a prospective pilot study. AJR Am J Roentgenol 194:1272–1278

Okuda K (1992) Hepatocellular carcinoma: recent progress. Hepatology 15:948–963

Okuda T, Wakasa K, Kudo S, Hamada T, Fujita M, Enomoto T, Haba T, Hirohashi K et al (2001) Clonal analysis of hepatocellular carcinoma and dysplastic nodule by methylation pattern of X-chromosome-linked human androgen receptor gene. Cancer Lett 164:91–96

Orsatti G, Theise ND, Thung SN, Paronetto F (1993) DNA image cytometric analysis of macroregenerative nodules (adenomatous hyperplasia) of the liver: evidence in support of their preneoplastic nature. Hepatology 17:621–627

Osada T, Sakamoto M, Nishibori H, Iwaya K, Matsuno Y, Muto T, Hirohashi S (1997) Increased ubiquitin immunoreactivity in hepatocellular carcinomas and precancerous lesiosn of the liver. J Hepatol 26:1266–1273

Ouedraogo NA, Danjoux-de-Volontat M, Auriol J, Peron JM, Rousseau H, Otal P (2011) Dysplastic hepatic nodules: radiological abnormalities and histopathological correlations. Eur J Radiol 79:232–236

Paik SY, Park YN, Kim H, Park C (2003) Expression of transforming growth factor-beta1 and transforming growth factor-beta receptors in hepatocellular carcinoma and dysplastic nodules. Mod Pathol 16:86–96

Paradis V, Laurendeau I, Vidaud M, Bedossa P (1998) Clonal analysis of macronodules in cirrhosis. Hepatology 28:953–958

Park YN (2011) Update on precursor and early lesions of hepatocellular carcinomas. Arch Pathol Lab Med 135:704–715

Park YN, Roncalli M (2006) Large liver cell dysplasia: a controversial entity. J Hepatol 45:734–743

Park YN, Yang CP, Cubukcu O, Thung SN, Theise ND (1997) Hepatic stellate cell activation in dysplastic nodules: evidence for an alternate hypothesis concerning human hepatocarcinogenesis. Liver 17:271–274

Park YN, Chae KJ, Oh BK, Choi J, Choi KS, Park C (2004) Expression of Smad7 in hepatocellular carcinoma and dysplastic nodules: resistance mechanism to transforming growth factor-beta. Hepatogastroenterology 51:396–400

Park HS, Lee JM, Kim SH, Chang S, Kim SJ, Han JK, Choi BI (2009) Differentiation of well-differentiated hepatocellular carcinomas from other hepatocellular nodules in cirrhotic liver: value of SPIO-enhanced MR imaging at 3.0 Tesla. J Magn Reson Imaging 29:328–335

Paterson AC, Kew MC, Duskeiko GM, Isaacson C (1989) Liver cell dysplasia accompanying hepatocellular carcinoma in southern Africa. Differences between urban and rural populations. J Hepatol 8:241–248

Pollice L, Ricco R, Russo S, Maiorano E, Pagniello G, Delfino-Pesce V (1988) Hepatocellular dysplasia: immunohistochemical and morphometrical evaluation. Appl Pathol 6:73–81

Prange W, Breuhahn K, Fischer F, Zilkens C, Pietsch T, Petmecky K, Eilers R, Dienes HP et al (2003) Beta-catenin accumulation in the progression of human hepatocarcinogenesis correlates with loss of E-cadherin and accumulation of p53, but not with expression of conventional WNT-1 target genes. J Pathol 201:250–259

Quaia E, De Paoli L, Pizzolato R, Angileri R, Pantano E, Degrassi F, Ukmar M, Cova MA (2013) Predictors of dysplastic nodule diagnosis in patients with liver cirrhosis on unenhanced and gadobenate dimeglumine-enhanced MRI with dynamic and hepatobiliary phase. AJR Am J Roentgenol 200:553–562

Raidl M, Pirker C, Schulte-Hermann R, Aubele M, Kandioler-Eckersberger D, Wrba F et al (2004) Multiple chromosomal abnormalities in human liver (pre) neoplasia. J Hepatol 40:660–668

Riegler JL (1996) Preneoplastic conditions of the liver. Semin Gastrointest Dis 7:74–87

Roncalli M (2004) Hepatocellular nodules in cirrhosis: focus on diagnostic criteria on liver biopsy. A western experience. Liver Transpl 10(suppl 1):S9–S15

Roncalli M, Borzio M, Tombesi MV, Ferrari A, Servida E (1988) A morphometric study of liver cell dysplasia. Hum Pathol 19:471–474

Roncalli M, Roz E, Coggi G, Di Rocco MG, Bossi P, Minola E, Gambacorta M, Borzio M (1999) The vascular profile of regenerative and dysplastic nodules of the cirrhotic liver: implications for diagnosis and classification. Hepatology 30:1174–1178

Roncalli M, Borzio M, Di Tommaso L (2007) Hepatocellular dysplastic nodules. Hepatol Res 37(suppl 2): S125–S134

Roncalli M, Borzio M, Di Tommaso L (2008) Hepatocellular dysplastic nodules. Ann Ital Chir 79:81–89

Roncalli M, Terracciano L, Di Tommaso L, David E, Colombo M, Gruppo Intaliano Patologi Apparato Digerente (GIPAD), Societa Italiana di Anatomia Patologica e Citopatologia Diagnostica/International Academy of Pathology, Italian division (SIPAEC/IAP) (2011) Liver precancerous lesions and hepatocellular carcinoma: the histology report. Dig Liver Dis 43(suppl 4):S361–S372

Rubin EM, DeRose PB, Cohen C (1994) Comparative image cytometric DNA ploidy of liver cell dysplasia and hepatocellular carcinoma. Mod Pathol 7:677–680

Sakamoto M, Hirohashi S (1998) Natural history and prognosis of adenomatous hyperplasia and early hepatocellular carcinoma: multi-institutional analysis of 53 nodules followed up for more than 6 months and 141 patients with single early hepatocellular carcinoma treated by surgical resection or percutaneous ethanol injection. Jpn J Clin Oncol 28:604–608

Sakamoto M, Hirohashi S, Shimosato Y (1991) Early stages of multistep hepatocarcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma. Hum Pathol 22:172–178

Sakurai M (1978) Liver cell dysplasia and hepatitis B surface and core antigens in cirrhosis and hepatocellular carcinoma of autopsy cases. Acta Pathol Jpn 28:705–719

Scheuer PJ (1968) Liver biopsy interpretation. Baillere, Tindall and Cassell, London

Schwartz MR (1998) Liver cell dysplasia and other atypical lesions: new insights and applications. Adv Anat Pathol 5:99–105

Seki S, Sakaguchi H, Kitada T, Tamori A, Takeda T, Kawada N, Habu D, Nakatani K et al (2000) Outcomes of dysplastic nodules in human cirrhotic liver: a clinicopathological study. Clin Cancer Res 6:3469–3473

Sersté T, Barrau V, Ozenne V, Vuillerme MP, Bedossa P, Farges O, Valla DC, Vilgrain V et al (2012) Accuracy and disagreement of computed tomography and magnetic resonance imaging for the diagnosis of small hepatocellular carcinoma and dysplastic nodules: role of biopsy. Hepatology 55:800–806

Shah TU, Semelka RC, Pamuklar E, Firat Z, Gerber RD, Shrestha R, Russo MW (2006) The risk of hepatocellular carcinoma in cirrhotic patients with small liver nodules on MRI. Am J Gastroenterol 101:533–540

Shibata M, Morizane T, Uchida T, Yamagami T, Onozuka Y, Nakano M, Mitamura K et al (1998) Irregular regeneration of hepatocytes and risk of hepatocellular carcinoma in chronic hepatitis and cirrhosis with hepatitis-C-virus infection. Lancet 351:1773–1777

Shuto T, Hirohashi K, Wakasa K, Ikebe T, Kinoshita H (1999) Hyperplastic foci as a prognostic factor after resection of hepatocellular carcinoma. Hepatogastroenterology 46:2439–2441

Sommayura P, Boonsakan P, Sobhonslidsuk A, Sriphojanart S, Euanorasetr C, Bunyaratvej S (2007) Dysplastic nodules and small primary carcinoma of the liver: a study detecting the early morphological changes during hepatocarcino-genesis. J Med Assoc Thai 90:352–362

Steiner PE, Davies JNP (1957) Cirrhosis and primary liver carcinoma in Uganda Africans. Br J Cancer 11:523–534

Su Q, Bannasch P (2003) Relevance of hepatic preneoplasia for human hepatocarcinogenesis. Toxicol Pathol 31:126–133

Su Q, Benner A, Hofmann WJ, Otto G, Pichlmayr R, Bannasch P (1997) Human hepatic preneoplasia: phenotypes and proliferation kinetics of foci and nodules of altered hepatocytes and their relationship to liver cell dysplasia. Virchows Arch 431:391–406

Sun M, Eshleman JR, Ferrell LD, Jacobs G, Sudilovsky EC, Tuthill R, Hussein MR et al (2001) An early lesion in hepatic carcinogenesis: loss of heterozygosity in human cirrhotic livers and dysplastic nodules at the 1p36–p34 region. Hepatology 33:1415–1424

Suzuki M, Maeyama S, Nishikawa K, Okuse N, Hashizume K, Mamada Y, Kobayashi Y et al (2002) Outcomes of small nodular lesions in heavy drinkers. Alcohol Clin Exp Res 26(8 suppl):55S–62S

Szczepanski W (1997) Liver cell dysplasia in liver cirrhosis and hepatocellular carcinoma. Pol J Pathol 48:147–157

Taguchi K, Asayama Y, Aishima S, Nishi H, Sugimachi K, Matsuura S, Terashi T, Yamanaka T et al (2002) Morphologic approach to hepatocellular carcinoma development in man: de novo or so-called 'dysplastic nodule-carcinoma' sequence? Oncol Rep 9:737–743

Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Okazaki N, Takaysu K, Kosuge T et al (1990) Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. Lancet 336:1150–1153

Takayasu K, Muramatsu Y, Wakao F, Mizuguchi Y, Iwata R, Maeda T, Moriyama N et al (2002) Hepatic nodules with early enhancement during computed tomography portography: report of six cases. J Gastroenterol Hepatol 17:779–784

Tanaka Y, Sasaki Y, Katayama K, Hiramatsu N, Ito A, Murata H, Enomoto N, Oshita M et al (2000) Probability of hepatocellular carcinoma of small hepatocellular nodules undetectable by computed tomography during arterial portography. Hepatology 31:890–898

Tannapfel A, Wittekind C (2001) Preneoplasia of the liver. Definition – differential diagnosis – clinical consequences (in German). Pathologe 22:399–406

Tatrai P, Somoracz A, Batmunkh E, Schirmacher P, Kiss A, Schaff Z, Nagy P, Kovalszky I (2009) Agrin and CD34 immunohistochemistry for the discrimination of benign versus malignant hepatocellular lesions. Am J Surg Pathol 33:874–885

Terada T, Nakanuma Y (1989) Iron-negative foci in siderotic macroregenerative nodules in human cirrhotic liver. A marker of incipient neoplastic lesions. Arch Pathol Lab Med 113:916–920

Terada T, Nakanuma Y (1992) Cell proliferative activity in adenomatous hyperplasia of the liver and small hepatocellular carcinoma. An immunohistochemical study demonstrating proliferating cell nuclear antigen. Cancer 70:591–598

Terada T, Nakanuma Y (1995a) Multiple occurrence of borderline hepatocellular nodules in human cirrhotic livers: possible multicentric origin of hepatocellular carcinoma. Virchows Arch 427:379–383

Terada T, Nakanuma Y (1995b) Arterial elements and perisinusoidal cells in borderline hepatocellular nodules and small hepatocellular carcinomas. Histopathology 27:333–339

Terada T, Nakanuma Y, Hoso M, Saito K, Sasaki M, Nonomura A (1989a) Fatty macroregenerative nodule in non-steatotic liver cirrhosis. A morphologic study. Virchows Arch A Pathol Anat 415:131–136

Terada T, Hoso M, Nakanuma Y (1989b) Mallory body clustering in adenomatous hyperplasia in human

cirrhotic livers: report of four cases. Hum Pathol 20:868–890

Terada T, Terasaki S, Nakanuma Y (1993a) A clinicopathologic study of adenomatous hyperplasia of the liver in 209 consecutive cirrhotic livers examined by autopsy. Cancer 72:1551–1556

Terada T, Ueda K, Nakanuma Y (1993b) Histopathological and morphometric analysis of atypical adenomatous hyperplasia of human cirrhotic livers. Virchows Arch A Pathol Anat Histopathol 422:381–388

Terada T, Kitani S, Ueda K, Nakanuma Y, Kitagawa K, Masuda S (1993c) Adenomatous hyperplasia of the liver resembling focal nodular hyperplasia in patients with chronic liver disease. Virchows Arch A Pathol Anat Histopathol 422:247–252

Terada T, Hoso M, Nakanuma Y (1995) Distribution of cytokeratin 19-positive biliary cells in cirrhotic nodules, hepatic borderline nodules (atypical adenomatous hyperplasia), and small hepatocellular carcinomas. Mod Pathol 8:371–379

Terasaki S, Kaneko S, Kobayashi K, Nonomura A, Nakanuma Y (1998) Histological features predicting malignant transformation of nonmalignant hepatocellular nodules: a prospective study. Gastroenterology 115:1216–1222

Terris B, Ingster O, Rubbia L, Dubois S, Belghiti J, Feldmann G, Degott C, Henin D (1997) Interphase cytogenetic analysis reveals numerical chromosome aberrations in large liver cell dysplasia. J Hepatol 27:313–319

Tezuka F, Sawai T (1983) Hyperplasia of small hepatic cells in the precancerous condition of cirrhotic livers. Tohoku J Exp Med 139:171–177

Theise ND (1995) Macroregenerative (dysplastic) nodules and hepatocarcinogenesis: theoretical and clinical considerations. Semin Liver Dis 15:360–371

Theise ND, Schwartz M, Miller C, Thung SN (1992) Macroregenerative nodules and hepatocellular carcinoma in forty-four sequential adult liver explants with cirrhosis. Hepatology 16:949–955

Theise ND, Lapook JD, Thung SN (1993) A macroregenerative nodule containing multiple foci of hepatocellular carcinoma in a noncirrhotic liver. Hepatology 17:993–996

Theise ND, Marcelin K, Goldfischer M, Hytiroglou P, Ferrell L, Thung SN (1996) Low proliferative activity in macroregenerative nodules: evidence for an alternate hypothesis concerning human hepatocarcinogenesis. Liver 16:134–139

Theise ND, Curado MP, Franceschi S, Hytiroglou P, Kudo M, Park YN, Sakamoto M et al (2010) Hepatocellular carcinoma. In: Bosman F et al (eds) WHO classification of tumours of the digestive system. IARC, Lyon, pp 212–214

Thomas RM, Berman JJ, Yetter RA, Moore GW, Hutchins GM (1992) Liver cell dysplasia: a DNA aneuploidy lesion with distinct morphologic features. Hum Pathol 23:496–503

Thung SN, Hytiroglou P, Fiel I, Theise N (1995) Preneoplastic lesions on chronic hepatitis C. Princess Takamatsu Symp 25:171–178

Tiniakos DG, Brunt EM (1999) Proliferating cell nuclear antigen and Ki-67 labeling in hepatocellular nodules: a comparative study. Liver 19:58–68

Tornillo L, Carafa V, Sauter G, Moch H, Minola E, Gambacorta M, Vecchione R, Bianchi L et al (2002) Chromosomal alterations in hepatocellular nodules by comparative genomic hybridization: high-grade dysplastic nodules represent early stages of hepatocellular carcinoma. Lab Invest 82:547–553

Tsuda H, Hirohashi S, Shimosato Y (1988) Clonal origin of atypical adenomatous hyperplasia of the liver and clonal identity with hepatocellular carcinoma. Gastroenterology 95:1664–1666

Tsuji M, Kashihara T, Terada N, Mori H (1999) An immunohistochemical study of hepatic atypical adenomatous hyperplasia, hepatocellular carcinoma, and cholangiocarcinoma with alpha-fetoprotein, carcinoembryonic antigen, CA19-9, epithelial membrane antigen, and cytokeratins 18 and 19. Pathol Int 49:310–307

Uchida T, Nagai H, Gotoh K, Kanagawa H, Kouyama H, Kawanishi T, Mima S, Yamagoe S et al (1999) Expression pattern of a newly recognized protein, LECT2, in hepatocellular carcinoma and its premalignant lesion. Pathol Int 49:147–151

Ueda K, Saito K, Terada T, Nakanuma Y (1991) Selective necrosis of encapsulated malignant lesion within atypical adenomatous hyperplasia of the liver following transarterial embolization. A report of two autopsy cases. J Clin Gastroenterol 13:709–714

Ueda K, Terada T, Nakanuma Y, Matsui O (1992) Vascular supply in adenomatous hyperplasia of the liver and hepatocellular carcinoma: a morphometric study. Hum Pathol 23:619–626

Vaiphei K, Ghosh UK, Vasishta RK (1999) Incidence of adenomatous hyperplasia in postmortem cirrhotic livers and study of cellular proliferative indices by light microscopy. Indian J Gastroenterol 18:7–10

van Dekken H, Wink J, Alers JC, de Man RA, Ijzermans JN, Zondervan PE (2003) Genetic evaluation of the dysplasia-carcinoma sequence in chronic viral liver disease: a detailed analysis of two cases and a review of the literature. Acta Histochem 105:29–41

van Dekken H, Verhoef C, Wink J, van Marion R, Vissers KJ, Hop WC, de Man RA et al (2005) Cell biological evaluation of liver cell carcinoma, dysplasia and adenoma by tissue micro-array analysis. Acta Histochem 107:161–171

Vertemati M, Quaglia A, Minola E, Moscheni C, Cossa M, Goffredi M, Vizzotto L (2010) Morphometric analysis of dysplastic nodules in hepatitis C virus-related liver cirrhosis: comparison with cirrhotic and large regenerative nodules. Anal Quant Cytol Histol 32:106–113

Wada K, Kondo F, Kondo Y (1988) Large regenerative nodules and dysplastic nodules in cirrhotic livers: a histopathologic study. Hepatology 8:1684–1688

Wang FH, Yip YC, Zhang M, Vong HT, Chan KI, Wai KC, Wen JM (2010) Diagnostic utility of glypican-3 for hepatocellular carcinoma on liver needle biopsy. J Clin Pathol 63:599–603

Watanabe S, Okita K, Harada T, Kodama T, Numa Y, Takemoto T, Takahashi T (1983) Morphologic studies of the liver cell dysplasia. Cancer 51:2197–2205

Williams GM (1976) Functional markers and growth behavior of preneoplastic hepatocytes. Cancer Res 36:2540–2543

Wright JH, Johnson MM, Shimizu-Albergine M, Bauer RL, Hayes BJ, Suraisitchat J et al (2013) Paracrine activation of hepatic stellate cells in platelet-derived growth factor C transgenic mice: evidence for stromal induction of hepatocellular carcinoma. Int J Cancer 134:778–788

Wurmbach E, Chen YB, Khitrov G, Zhang W, Roayaie S, Schwartz M, Fiel I, Thung S et al (2007) Genome-wide molecular profiles of HCV-induced dysplasia and hepatocellular carcinoma. Hepatology 45:938–947

Xu H, Kong X, Xiong Y, Zhang X (2005) MR features of regenerative nodules and dysplastic nodules in the cirrhotic liver. J Huazhong Univ Sci Technolog Med Sci 25:601–603

Yamashita A (1996) Comparison of the proliferative capacity of adenomatous hyperplasia and well differentiated hepatocellular carcinoma. J Gastroenterol 31:373–378

Yeh MM, Larson AM, Campbell JS, Fausto N, Rulyak SJ, Swanson PE (2007) The expression of transforming growth factor-alpha in cirrhosis, dysplastic nodules, and hepatocellular carcinoma: an immunohistochemical study of 70 cases. Am J Surg Pathol 31:681–689

Yerian LM, Anders RA, Tretiakova M, Hart J (2004) Caveolin and thrombospondin expression during hepatocellular carcinogenesis. Am J Surg Pathol 28:357–364

Zerbini C, Weinberg DS, Hollister KA, Perez-Atayde AR (1992) DANN ploidy abnormalities in the liver of children with hereditary tyrosinemia type I. Correlation with histopathologic features. Am J Pathol 140:1111–1119

Zhang J, Krinsky GA (2004) Iron-containing nodules of cirrhosis. NMR Biomed 17:459–464

Zhao M, Zimmermann A (1997) Apoptosis in human hepatocellular carcinoma and in liver cell dysplasia is correlated with p53 protein immunoreactivity. J Clin Pathol 50:394–400

Zhao M, Zimmermann A (1998) Liver cell dysplasia: reactivities for c-met protein, Rb protein, E-cadherin and transforming growth factor-beta 1 in comparison with hepatocellular carcinoma. Histol Histopathol 13:657–670

Zhao M, Zhang NX, Du ZY, Laissue JA, Zimmermann A (1994) Three types of liver cell dysplasia (LCD) in small cirrhotic nodules are distinguishable by karyometry and PCNA labeling, and their features resemble distinct grades of hepatocellular carcinoma. Histol Histopathol 9:73–83

Zhao M, Laissue JA, Zimmermann A (1996) Tenascin and type IV collagen expression in liver cell dysplasia and in hepatocellular carcinoma. Histol Histopathol 11:323–333

Early or Small Hepatocellular Carcinoma 8

ICD-O code 8170/3

Contents

Abstract

At the time point of diagnosis, subsets of hepatocellular carcinoma (HCC) show a small size. Part of these lesions are early cancers, but there are also small HCCs with a distinct histologic pattern. Lesions with a diameter of 3.5 cm or less were formerly termed minute HCC. Today, early HCC is frequently identified as a nodular HCC measuring 2 cm or less in diameter, the limit of 2 cm having been settled in an international consensus conference. These small neoplasms come in two basic growth patterns, one characterized by vaguely nodular, well-differentiated tumors (small HCC with indistinct margins or vaguely nodular small HCC) and the other by distinctly nodular tumor with the histology of ordinary HCC. Early and small HCCs are usually asymptomatic, but are associated with liver cirrhosis in most patients. At least part of early HCCs show a histological presentation that differs in several respects from that of larger ordinary HCCs, suggesting that some of these small tumors are not simply early stages of a classical HCC progression pathway, but rather represent a distinct variant of HCC.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_8

Introduction

There is a group of hepatocellular carcinomas (HCCs) characterized by small size at the time point of diagnosis. Formerly, such small lesions were mostly detected in resection specimens or in the setting of autopsies, but based on the higher efficiency of modern imaging techniques, small HCC are now commonly diagnosed in a clinical diagnostic setting. Small HCCs have also been termed microcarcinoma of the liver (Köhn 1956). HCCs of small size have previously been described as small HCC, mainly in the Japanese literature. As an international consensus regarding the biological nature of these lesions and their distinction from high-grade dysplastic nodules has been achieved (International Consensus Group for Hepatocellular Neoplasia 2009), recent classifications, including that of the WHO (Theise et al. 2010), now employ the term early HCC (E-HCC) to denote these neoplasms.

Originally, the term "small HCC" defined the neoplasm's size (diameter) and did not necessarily refer to an early stage of hepatocarcinogenesis. The concept of "small HCC" is complicated by several difficulties in regard to further definition and the integration of aspects of tumor biology. Concerning the maximum tumor diameter, the lesions have been defined in various ways, authors accepting tumors as "small HCC" with nodule diameters ranging from 2 cm or less (Yama-shita et al. 2012) to 5 cm. Lesions with a diameter of 3.5 cm or less were formerly also called "minute HCC." Today, E-HCC is usually defined as a poorly defined nodular hepatocellular neoplasm measuring 2 cm or less in diameter ("small HCC with indistinct margins," "vaguely nodular small HCC"; Theise et al. 2010), the limit of 2 cm in diameter having been settled in an international consensus publication (International Working Party 1995).

What are the arguments that "small HCC" are in fact E-HCC vs. "progressed-type" lesions? There is clear evidence that at least part of small tumors measuring 2 cm or less are E-HCC at the time point of diagnosis and may progress to advanced HCC afterward, becoming large lesions in the course of the disease (Grigioni et al. 1991; reviews: Hytiroglou 2004; Roncalli et al. 2010). But there is evidence that at least a fraction of tumors being small at diagnosis will remain small lesions, i.e., will exhibit slow growth or no documentable growth, and will behave in a more favorable manner. However, the fact that these neoplasms have reached a size rendering them visible at imaging or at macroscopic examination means that significant growth has taken place, probably for a long time period, and for still unknown reasons, further growth will not, or only slowly, take place following diagnosis.

Epidemiology

Numerous reports document the existence of small HCCs, in both cirrhotic and non-cirrhotic livers. Together with dysplastic nodules, well-differentiated E-HCCs are often detected in noncancerous liver tissue resected along with HCCs and in explanted cirrhotic livers (Kojiro and Roskams 2005). Part of these small cancers are incidental lesions. In explanted cirrhotic livers of 30 patients, E-HCC was incidentally found in 63.3 % of the livers, varying from microscopic focuses to 2 cm diameter lesions (Caroli-Bottino et al. 2005). In a study of 325 Chinese HCC patients with hepatitis and S-HCC, male gender and young age were typical for smaller tumor mass phenotypes (Carr et al. 2011).

Selected References Okuda et al. 1975; Mahmood and Schatzki 1976; Nakashima et al. 1977; Zhaoyou et al. 1979; Yu et al. 1980; Yamasaki et al. 1981; Chen et al. 1982; Shinagawa et al. 1982; Watanabe et al. 1986; Grigioni et al. 1989; Tang et al. 1989; Sasaki et al. 1996; Kojiro 1998; Fong et al. 1999; Utsunomiya et al. 2000; Toyoda et al. 2001; Sherman 2005; Carr et al. 2011; Kim et al. 2011 and Park 2011.

Clinical and Imaging Features

E-HCCs are usually asymptomatic lesions, but as they are associated with liver cirrhosis in the majority of, or all, patients (Gandolfi et al. 1987;

Zhou et al. 1991), signs and symptoms are dominated by the chronic cirrhotic liver disease. For subcentimeter hypervascular lesions, the clinical impact of individual lesions is limited owing to the longer time interval for tumor growth to reach a critical size, but diagnosis of early HCC shows to be aimed for lesions in the range of 1–2 cm (Yu et al. 2009). E-HCC can cause symptomatic disease in specific situations, e.g., in case the lesion is situated close to the hilum, causing obstructive jaundice (Ise et al. 2004). Serial measurement of serum AFP levels appears to be a very helpful method for detection of HCC at the early stage (Kanematsu et al. 1983; Chen et al. 1984; Dusheiko et al. 1986; Pancoska et al. 2011). In E-HCC with a diameter of 3 cm or less, serum levels of AFP-IgM complexes were higher than in patients with a tumor diameter exceeding 3 cm, suggesting the determination of this complex is of potential benefit for the diagnosis of E-HCC (Jiang et al. 2011).

Ultrasonographic findings in E-HCC have been described, characteristics of sonograms being posterior echoes (posterior acoustic enhancement) of the tumor, mosaic pattern of internal echoes, peripheral hypoechoic halo, and lateral shadows (Makuuchi et al. 1983; Shinagawa et al. 1984; Watanabe et al. 1984; Kanematsu et al. 1985; Itai et al. 1987; Livraghi et al. 1987; Higashi et al. 1988; Choi et al. 1989; Nagasue et al. 1989; Tanaka et al. 1989; Tang et al. 1993; Kanematsu et al. 1999; Jang et al. 2009), but the distinction between very small HCCs and other nodular lesions developing in cirrhotic livers is difficult. In particular, the sonographic features listed above become rare in nodules with a diameter inferior to 2 cm diameter (Makuuchi et al. 1983). However, real-time linear scan US has a detection rate exceeding 90 % even in very small lesions (Watanabe et al. 1986). The typical enhancement patterns of fast-in and fast-out (FIFO) or fast-in and slow-out (FISO) of E-HCC improve the diagnostic ability of ultrasound in cirrhotic livers (Chen et al. 2006). Contrast-enhanced ultrasound (CEUS) has been found to be a potent method to identify E-HCC (Wang et al. 2006; Kim et al. 2011). Assessment of the malignant potential of hypervascular E-HCC is possible by B-mode ultrasonography (Moribata et al. 2011). E-HCC are also identifiable by use of CT and MR (Hosoki et al. 1982; Takashima et al. 1982; Inamoto et al. 1983; Watanabe et al. 1984; Tsunetomi et al. 1989; Hirai et al. 1991; Inoue et al. 1993; Bhattacharjya et al. 2004; Golfieri et al. 2009; Yu et al. 2009; Sanuki-Fujimoto et al. 2010; Sherman 2010; Bartolozzi et al. 2011; Lv et al. 2011), but both portal and delayed phases of dynamic MR imaging had a limited diagnostic values for diagnosis of small hypervascular E-HCC (Yu et al. 2008). Diffusion-weighted sequences did also not improve the diagnostic accuracy (Di Martino et al. 2013). The ring sign detected on MR images is a feature typical for encapsulated E-HCC (Ebara et al. 1986). High-intensity patterns on MR images were associated with tumor steatosis, clear cell formation, and/or copper accumulation (Ebara et al. 1991). Lesions smaller than 20 mm in diameter can reliably be detected by use of 2 mm-pitch reconstruction CT (Teratani et al. 2004), and gadoxetic acid-enhanced MRI has proved to be an efficient method to detect E-HCC in chronic liver disease (Hwang et al. 2012; Kim et al. 2012). Single-photon emission computed tomography (SPECT) was inferior to the initial US screening examination in detecting E-HCC less than 2 cm in size, but its sensitivity was identical to that of the initial screening US study for detecting HCC of 2–5 cm diameter (Kudo et al. 1986).

A large fraction of small nodular lesions representing early or small HCC are hypervascular lesions. Arterial hypervascularity is one of the most sensitive findings in the diagnosis of HCC during dynamic CT or MR imaging, although the specificity is rather limited owing to hypervascular benign lesions occurring in cirrhotic livers. In large HCCs, washout in the venous phase is a highly specific feature in the diagnosis of hypervascular HCC, but the sensitivity of washout is more difficult to assess in small tumors (Jeong et al. 2002; Yu et al. 2008). Imaging enhanced by superparamagnetic iron oxide (SPIO) exhibits a sensitivity for nodular lesions with reduced amounts (or reduced function) of intralesional macrophages/Kupffer cells. HCCs typically harbor reduced numbers of

macrophages, in contrast to benign nodular hepatic lesions (Tang et al. 1999; Ward et al. 2000; Choi et al. 2001; Lim et al. 2001; Pauleit et al. 2002). In many small hypervascular HCCs up to 2 cm in diameter, SPIO-enhanced MR allowed reliable early diagnosis in the absence of washout on dynamic gadolinium-enhanced imaging (Yu et al. 2009). By use of gadoxetic acid-enhanced MR, S-HCC can be distinguished from arterial-enhancing pseudolesions (Sun et al. 2010). On the other hand, it is not yet known how many small arterial phase-enhancing nodules are in fact established S-HCCs. In a follow-up study of patients having such lesions, with a mean of six CT studies for each patient with a mean follow-up of 25 months, 44 % of the lesions were stable, 28 % decreased in size, and 28 % increased in size. These findings suggested that most small (10–20 mm diameter) arterial phase-enhancing nodular lesions seen on triphasic liver CT are not HCCs (O'Malley et al. 2005). Hypervascular lesions are reliably identified by use of conventional hepatic angiography (Ikeda et al. 1994), CT angiography (Ohnishi et al. 2010), and angiography combined with superselective infusion arteriography. In lesions smaller than 2 cm, a so-called tumor stain in the capillary phase was the only abnormality found in most, but not all, cases, unstained areas histologically representing fatty change, necrosis, or fibrosis (Sumida et al. 1986). What is the evidence that small hypervascular enhancing lesions are mostly small or early HCCs? Among 169 enhancing lesions on the arterial phase images of dynamic CT in 67 patients with liver cirrhosis, only 17 % were HCC at the final diagnosis, and these lesions were often early enhancing, centrally placed, and non-wedge-shaped. The low positive predictive value of such lesions requires serial follow-up for examining lesion growth or additional MR techniques (Hwang et al. 2008). It has been shown that rapid central washout after early enhancement of lesions and coronal enhancement surrounding the lesions are highly predictive of small hypervascular HCCs if present at multiarterial phase contrast-enhanced dynamic MR (Ito et al. 2004). How to properly interpret small hypovascular nodular lesions occurring in the setting of cirrhosis? Hypovascular tumors shown to be HCCs demonstrated as hypoattenuating nodules on late-phase CT were often not seen on late-phase MR imaging (Hayashida et al. 2008). Serial imaging of small arterially enhancing liver lesions has shown that lesions that increase in size, convert to hypointense or subsequent T1-weighted images, convert to hyperintense lesions in T2-weighted images, or develop rim enhancement on follow-up MR images are suspicious for S-HCCs (Korpraphong et al. 2009). The hypervascular status of E-HCC can be identified reliably by use of infusion hepatic angiography, which is a method considered to be superior to selective celiac angiography, which is not always able to detect foci with a diameter of less than 2 cm in diameter, owing to vascular proliferation which cannot be distinctly found by conventional angiography (Takashima and Matsui 1980).

Pathology

Macroscopy

Small HCCs measuring 2 cm or less in diameter macroscopically appear as one of several phenotypes (Table 1). They can be vaguely nodular, well-differentiated tumors (the typical "early HCC") and distinctly nodular tumors, with the histologic features of "classic" or "ordinary" HCC (Efremidis et al. 2007). However, transition forms between these two types exist, although some of the E-HCC may remain stable and thus

Table 1 Macroscopic phenotypes and classification of small/early hepatocellular carcinomas

Basic growth patterns
Vaguely nodular, well-differentiated tumors (classical early HCC)
Distinctly nodular tumors with histology of "ordinary" HCC
Kanai classification (Kanai et al. 1987)
Type 1: single nodular type
Type 2: single nodular type with extranodular growth
Type 3: contiguous multinodular type
Type 4: poorly demarcated nodular type

not being true early cancers, but rather a distinct biologic variant of HCC (Figs. 1, 2, and 3).

Kanai and coworkers classified E-HCC as type 1 or single nodular type, being expanding, roughly spherical, and often encapsulated; type2 or single nodular type with extranodular growth, with replacing growth often found in the area of extranodular growth; type 3 tumors or contiguous multinodular type, consisting of small nodules growing in contiguity, often with replacing growth at the periphery; and type 4 or poorly demarcated

Fig. 1 In this liver with incomplete cirrhosis, a slightly bulging nodular lesion representing early hepatocellular carcinoma is observed

Fig. 2 Small hepatocellular carcinoma on a background of complete liver cirrhosis. The tumor bulges from the cut surface. Its slightly greenish discoloration is caused by bile accumulation

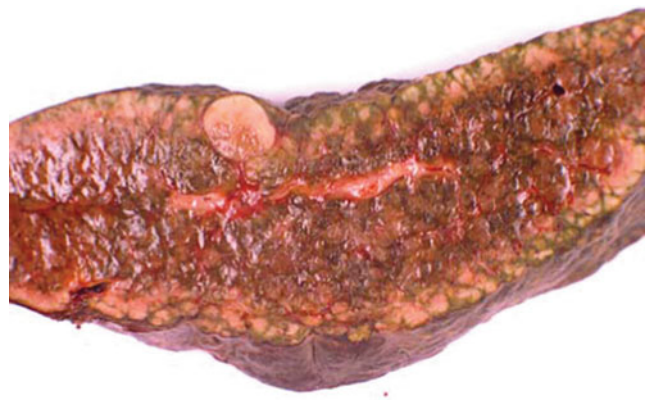

Fig. 3 Fresh, non-fixed resection specimen of early hepatocellular carcinoma in a cirrhotic liver

nodular type, showing infiltrative growth at its border (Kanai et al. 1987).

Notwithstanding pattern of growth, E-HCCs are defined as lesions with a diameter of 2 cm or less, part of neoplasms in a probably early phase of disease that have a diameter exceeding 2 cm. In an SEER study including 788 patients with early HCC, median tumor diameter was 3.2 cm, and 20 % of patients had neoplasms measuring 2 cm in diameter or less. Seventy-four percent were solitary nodules, and 82 % had no visible vascular invasion (Nathan et al. 2009). Part of the lesions are encapsulated (Okuda et al. 1977). In one study, 86.4 % of small HCCs were encapsulated, capsule formation being significantly higher in tumors found in cirrhotic livers (96.9 %; Hsu et al. 1985). Macroscopically, sign of gross invasion may be encountered, including invasion of bile ducts with tumor thrombus formation (Liu et al. 2010) or formation of an intrabiliary pedunculated polyp (Terada et al. 1989).

Histopathology

The histopathology of small or early HCC has been described in numerous reports (Table 2; Kondo et al. 1983; Nakashima et al. 1983; Ohno et al. 1990; Choi et al. 1993; Kojiro 2005; International Consensus Group 2009; Roskams and Kojiro 2010; Theise et al. 2010; Roncalli et al. 2011; Wee 2011).

E-HCCs show a histological presentation that differs in several respects from that of "ordinary" HCC (Figs. 4 and 5).

The majority of E-HCC consist predominantly of a G1 phenotype of HCC, with small- to medium-sized hepatocyte-like cells that may merge imperceptibly with the adjacent hepatic parenchyma (Theise et al. 2010), this feature being the reason for the vague-nodularity patterns of some E-HCC. Small and ill-defined lesions were described to have groups of basophilic

Table 2 Histopathologic features of early/small hepatocellular carcinoma

Population of well-differentiated small- to medium-sized hepatocyte-like cells
Merging of tumor cells with adjacent liver parenchyma
Increased nucleus-to-cytoplasm ratio with increased cell density and nuclear crowding
Thin trabecules (normotrabecular pattern rather than macrotrabecular pattern)
Acinar/pseudoglandular structures with or without bile accumulation
Fatty change (usually macrovesicular)
Clear cells with or without Mallory-Denk bodies
Foci of poorly differentiated cells in part of cases (sometimes in nodule-in-nodule lesions)
Copper storage (only in part of cases)
Presence of intratumoral portal tracts

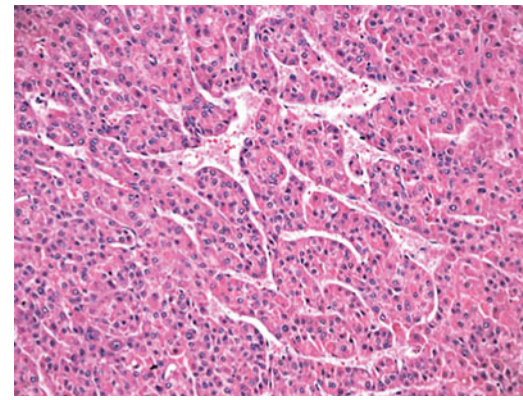

Fig. 4 Histologically, early hepatocellular carcinoma clearly differs from hyperplastic nodular lesions by the abnormal morphology of cell plates, trabecule width exceeding three cells (hematoxylin and eosin stain)

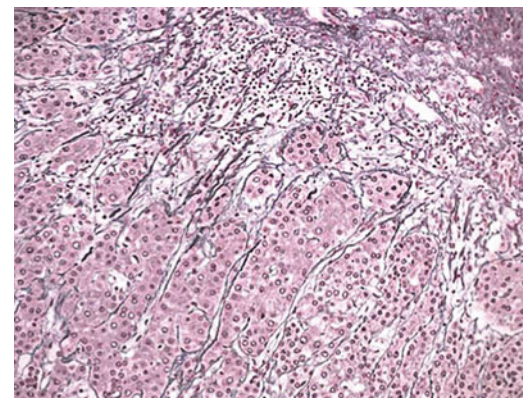

Fig. 5 As in larger hepatocellular carcinomas, early and small HCCs exhibit an abnormal reticulin pattern, reticulin fibers surrounding large tumor cell plates (Gomori silver stain)

cords showing acinar formations, bile congestion, and increased stromal elements with effacement of the sinusoidal network (Kondo et al. 1983). In a study of 21 autopsy cases, 19 tumors showed a trabecular morphology, only 1 was pseudoglandular/acinar, and one was of clear cell type. In at least part of E-HCC, the trabecular pattern is characterized by cell plates of almost normal thickness (the normotrabecular pattern; Kondo et al. 1987; Nakashima et al. 1995), a feature that may be misleading and cause misinterpretation as dysplastic nodule or even adenoma. However, even areas with a normotrabecular pattern typically show nuclear crowding, not observed in benign lesions. Fatty change is often observed in E-HCC and is mostly of the macrovesicular type. Fatty change was found in 40 % of high-grade dysplastic nodules and 75 % of well-differentiated E-HCC but was absent in low-grade dysplastic nodules and large regenerative nodules (Miyaaki et al. 2005). A part of E-HCC contains clear cells with or without Mallory-Denk bodies, in some cases almost all cells being involved (Nakanuma and Ohta 1984). In contrast to dysplastic nodules, E-HCCs usually lack deposits of stainable iron (Miyaaki et al. 2005), but few lesions exhibited excessive copper storage caused by lysosomal accumulation of copper metallothionein (Haratake et al. 1986; Kitagawa et al. 1991). Some E-HCCs show calcifications (Muramatsu et al. 1985). E-HCCs sometimes show intratumoral portal tracts, a feature usually not found in larger HCC. Unpaired arteries also occur in at least part of E-HCC but are less common than in other small HCC of the progressed lesion type. It has to be emphasized that all these histologic features are not specific for E-HCC, but may also be observed in tumors exceeding a diameter of 2 cm. Parts of E-HCC are located within, or are found adjacent to, dysplastic nodules, sometimes as so-called nodule-in-nodule lesions, suggesting a stepwise progression within hepatocarcinogenesis (Rim et al. 1993; Than et al. 1995; Kojiro 2010). This issue is further discussed in a separate chapter. It was found that the microvascular phenotype of E-HCC differs from that of larger lesions. In particular, a capillary-like pattern was more common in E-HCC than a sinusoid-like pattern (capillarization of nodules; Haratake et al. 1992; Chen et al. 2011). In a minority of cases, desmoplasia is prominent in E-HCC, and such lesions are therefore considered to be early scirrhous HCC (Fukii et al. 2007). E-HCCs are in part hypervascular lesions with a distinct vascular pattern that is also detectable by use of imaging. Capillary-like blood vessels are more common in E-HCC and were significantly associated with higher microvessel density (Chen et al. 2011).

Histopathologic Distinction of E-HCC from Other Forms of Small HCC

As already mentioned above, not all small HCCs defined as lesions with a diameter of 2 cm or less are bona fide E-HCC. A part of small HCC resembles in their macroscopic presentation classical or "ordinary HCC" in that they display a distinctly nodular phenotype rather than the vaguely nodular phenotype encountered in E-HCC. These distinctly nodular small lesions present, as a rule, a histology that corresponds to that seen in larger HCC, including macrotrabecular components admixed with acinar structures, variably differentiated cell populations, a well-developed sinusoid-like vascular system, and presence of paired arteries, suggesting that such neoplasms are biologically progressed lesions with a greater propensity for portal vein invasion and intrahepatic metastasis (Theise et al. 2010).

Invasive Features

Invasive features of E-HCC are sometimes difficult to assess, as many tumors are encapsulated. In a study of 28 E-HCC, 17 were encapsulated, and capsular invasion was found in 14 of the 17 encapsulated neoplasms, and vascular invasion was detected in 12 of 28 lesions. This observation illustrates that, even in the presence of a tumor capsule, E-HCC is an invasive lesion, but distant metastasis was seen in only 1 out of these 28 cases (Wakasa et al. 1985). Interstitial invasion in E-HCC was microscopically classified into three

patterns: (1) crossing type, in which HCC was invading across fibrous septa of tumor nodules; (2) longitudinal type, in which neoplastic cells grow longitudinally within fibrous septa; and (3) irregular type, in which the portal tract area was irregularly invaded by HCC. In G1 tumors, type 2 was the most common mode of invasion (Kondo et al. 1994).

Satellite Nodules

An interesting phenomenon in E-HCC that may be related to local spread is the presence of minute satellite nodules. In one investigation on solitary HCC with a diameter of 2 cm or less, 13 % of solitary E-HCCs showed preoperatively undetectable minute satellite nodules measuring 1.5–4.0 mm in diameter. Well-differentiated E-HCC had 1 or 2 min satellite nodules 6 cm or more away from the main lesion, and moderately to poorly differentiated E-HCC had 4 or more minute satellite nodules within 1 cm from the main tumor (Maeda et al. 2000a).

Pretreatment Biopsy Histology as an Element of Diagnosis

Preoperative histology may not be available for E-HCCs larger than 2 cm in diameter arising in cirrhotic livers, because at the EASL Monothematic Conference on HCC (Bruix et al. 2001), it was recommended that lesions larger than 2 cm did not require biopsy if the lesions were shown to be hypervascular on two dynamic radiological studies in the setting of a cirrhotic liver. Conversely, in a non-cirrhotic liver, where the pretest probability of HCC is much lower, biopsy is recommended. At the 2000 EASL Meeting, biopsy was recommended for smaller nodular lesions (diameter $\leq$2 cm) and follow-up for even smaller lesions (Bruix et al. 2001; Bruix and Sherman 2005). However, analysis of 72 liver nodules in 59 patients with liver cirrhosis showed that the noninvasive EASL criteria for diagnosis of HCC are satisfied in only 61 % of small nodules in cirrhosis, suggesting that biopsy is often required, specifically in the setting of small hypovascular lesions (Bolondi et al. 2005).

Grading of Early HCC

In principle, the same grading strategies as employed for large/advanced HCC apply to E-HCC. Many E-ECC are well-differentiated lesions (Edmondson-Steiner grades 1 and 2) and will therefore not produce grading difficulties. However, there are E-HCCs having multiple grades within a single lesion (Kenmochi et al. 1987; Sugihara et al. 1992; Maeda et al. 2000b). Among eight well-differentiated E-HCC, two tumors already contained less-differentiated components (Maeda et al. 2000b). There is evidence that diversification of grades and associated neoplastic cell lineages is a function of tumor progression. In one study, it was observed that, when HCC reach approximately 2 cm in diameter, one-third of them displayed various combinations or more than two cancerous tissues of different histologic grades. In such neoplasms, a core of less-differentiated HCC was almost always surrounded by well-differentiated cancer tissue. This rim of well-differentiated HCC vanished as a function of progression and will be replaced by moderately to poorly differentiated HCC tissue (dedifferentiation of E-HCC as a function of growth to larger lesions; Kojiro et al. 1996). As poorly differentiated components are expected to affect outcome, it was of interest to test whether poor differentiation and hence high-grade lesions may be predicted preoperatively. In a univariate analysis, serum hepatitis B surface antigen positivity, HCV antibody negativity, AFP level, des-gamma-carboxy prothrombin level, and a high contrast-to-noise ratio in T2-weighted MR images were significantly associated with the poorly differentiated type of small-sized HCC (Imai et al. 2009).

Immunohistochemistry

It has been proposed that reactivity for HSP70, CAP2, glypican-3, and glutamine synthetase could serve as molecular markers for early HCC

(review: Sakamoto 2009). Glypican-3 is a potent marker for E-HCC, specifically in combination with CD34 immunostaining (Wang et al. 2012), or in a panel with heat shock protein 70 and glutamine synthetase (Tremosini et al. 2012). In a comparative study of low-grade dysplastic nodules, high-grade dysplastic nodules, FNH-like nodules, and HCCs with a diameter $\leq$3 cm, it turned out that glypican-3 expression, on both immunohistochemistry and RT-PCR, was much higher in E-HCCs than in cirrhosis and other types of focal liver lesions, suggesting that the transition from premalignant nodular lesions to E-HCC is associated with a sharp increase of glypican-3 expression (Libbrecht et al. 2006). Expression of glypican-3 is not only of diagnostic relevance, but it also affects biology of disease: elevation of glypican-3 acted as an adverse indicator for HBV-related small HCC patients after curative resection (Yu et al. 2012). At least a part of E-HCC has cells reactive for glutamine synthetase (Long et al. 2010). In approaches using a panel of immunostains, addition of clathrin heavy chain immunostaining markedly increased the diagnostic accuracy for small HCC/E-HCC, and there was important gain in sensitivity (Di Tommaso et al. 2011). Part of neoplastic cells in E-HCC exhibit nuclear reactivity for p53 protein (Maeda et al. 2000b). Fatty change in cells of E-HCC is associated with immunoreactivity for insulin-like growth factor II, suggesting that this factor is involved in steatogenesis in small HCC (Sohda et al. 1997). E-HCCs generally have a low proliferative activity as estimated with PCNA or Ki-67 staining (Yamagata et al. 1999; An et al. 2001), but it is higher than in dysplastic or regenerative nodules.

Most E-HCCs show a capillarization of small vascular channels, with reactivity of vessel walls for collagen type IV (Dhillon et al. 1992) and laminin (Kin et al. 1994; Yamamoto et al. 1996). E-HCCs can be distinguished from dysplastic nodules by podocalyxin-like protein 1, which in HCCs stains tumor-associated microvasculature endothelial cells, while the protein is not or only focally expressed in vessels of dysplastic nodules (Heukamp et al. 2006). Part of the vascular network of E-HCC is reactive for CD34, whereby hypervascular regions preferentially found on poorly differentiated parts of the tumors are more often CD34 reactive, particularly in nodule-in-nodule lesions, suggesting that capillarization goes in hand with tumor dedifferentiation (Maeda et al. 1995). Podocalyxin-like protein 1 (PCLP1; thrombomucin/MEP21) is a CD34-related sialomucin which is expressed on hematopoietic stem cells (Doyonnas et al. 2005) and is, as an overexpressed protein, an independent factor of poor prognosis in colorectal cancer (Larsson et al. 2011).

Differential Diagnosis

The most difficult differential diagnosis is high-grade dysplastic nodules, which can achieve a size comparable to that of S-HCCs. The diagnostic approach may be complex in situations where E-HCC is situated inside a dysplastic nodule (Ohno et al. 1990; nodule-in-nodule lesion) or adjacent to dysplastic lesions (reviews: Kojiro 2000, 2010). The presence of tumor cell invasion into the intratumoral portal tracts (stromal invasion) is a helpful clue for distinguishing the two lesions (Kojiro 2004; Kojiro and Roskams 2005), and this invasive phenotype has been accepted as a decisive feature in distinguishing high-grade dysplastic nodules from E-HCC in an International Consensus Meeting (review: Kojiro 2010). Foci of E-HCC located in dysplastic nodules revealed a higher proliferative activity (PCNA immunostaining) than dysplastic hepatocytes or hepatocytes of regenerative hyperplasia (Terada and Nakanuma 1992; Seki et al. 1993).

Biology of Disease

General Features

In case that small HCCs are interpreted as E-HCC, it may be expected that such lesions undergo further growth to become non-small-HCC, but they may also remain silent in regard to growth for certain time periods. In fact, there are reports showing that E-HCC remained without

appreciable change in size for many years (Yoshida et al. 1982). Whether such a phenomenon reflects in inherent feature of certain E-HCC, i.e., being characterized by a limited final size, or whether it depends on growth control by the tumor's environment in the liver or antitumor defense of the host is not clear. In case the tumor continues growing, one may extrapolate proliferation features found in larger HCC lesions.

Risk Factors for Recurrence and Spread

Irrespective of their small size, E-HCCs are potentially invasive lesions that infiltrate adjacent liver parenchyma, invade blood vessels, and can even cause subcutaneous seeding following biopsy (Yamada et al. 1993). Furthermore, well-differentiated E-HCC can give rise to extrahepatic metastasis (Kim et al. 1998), sometimes with massive spread in the peritoneum (Kim et al. 2007). However, in a prospective study of 70 patients who had a diagnosis of a single (solitary) HCC 2 cm or less in diameter (stage T1) and curative hepatectomy, follow-up demonstrated that E-HCCs had, in comparison with advanced HCC, a lower rate microscopical regional spread, a longer time to recurrence, and a significantly better overall survival and recurrence-free survival (Takayama et al. 1998).

What are the risk factors that are associated with poorer outcome in certain subsets of G1 E-HCC? Several investigations demonstrated that tumor size and this tumor stage significantly affect biology of disease in E-HCC. Small lesion size in HCC is associated with a lower likelihood of macroscopic vascular invasion (Nakashima et al. 2003), but small HCCs with invasion of the inferior vena cava and the right atrium have been reported (Noguchi et al. 1994). Tumor diameter correlated significantly with poorer overall survival in patients with stage I E-HCC, but a positive survival effect for small lesions was not found in stage II tumors (Ko et al. 2011). Even though E-HCCs are those with, per definition, a diameter of 2 cm or less, a 3 cm cutoff seemed to best determine the biological behavior and clinical prognosis of patients undergoing partial hepatectomy for small HCC (Lu et al. 2011). In a Cox regression analysis study on E-HCC defined as nodules with a diameter of 5 cm or less, tumor size was an independent prognostic factor, a tumor diameter of 3 cm being the cut point that could dichotomize patients into different 5-year disease-free survival and cancer-specific survival risk groups (Chen et al. 2011). In a SEER study of 788 patients with early HCC, tumor size exceeding 2 cm, multifocality, and vascular invasion were independent predictors of poor survival (Nathan et al. 2009).

Similar to its larger HCC counterparts, macrovascular and microvascular invasion are negative prognosticators in E-HCC. Even 2 cm-sized HCC can be associated with microvascular invasion (Nakano et al. 1990; Yamashita et al. 2012). In an analysis of 43 patients with E-HCC, 28.9 % showed microinvasion, associated with poorer outcome, and three independent predictors of microinvasion were identified, i.e., invasive gross HCC type, poor histologic grade, and serum des-gamma-carboxy prothrombin > 100 mAU/ml (Yamashita et al. 2012). Presence of vascular invasion as such, even in tumors less than 2 cm in diameter, is associated with poorer prognosis (Kikuchi et al. 2009). In 80 patients with E-HCCs up to 2 cm diameter who had undergone hepatic resection, the overall survival rates at 3, 5, and 10 years were 83 %, 69 %, and 36 %, respectively. In this patient group, microscopic portal vein invasion, hepatic vein invasion, and intrahepatic metastasis were positive in 15 %, 4 %, and 10 % of the patients, respectively.

Typical E-HCC consists of well-differentiated neoplastic cells (G1), but there are subsets containing high-grade components, rendering grading an important prognosticator. E-HCCs with a diameter of ≤ 3 cm may contain poorly differentiated components, and such tumors more often show microvascular invasion and a worse prognosis. Poorly differentiated E-HCCs may be identified by a high contrast-to-noise ratio (CNR) in T2-weighted MR imaging (Imai et al. 2009). High-grade lesions may be associated with a higher proliferative activity, which itself affects outcome. Doubling times for HCC

obtained through ultrasonography and CT were 119 ± 96 days, the doubling time being shorter in HCC in patients with HBV surface antigen positivity (Yoshino 1983). In another investigation on small untreated HCC (however with a diameter of less than or equal to 5 cm), doubling time ranged from 27.2 days to 605.6 days (median 171.6 days), suggesting that great variability of growth modes exists among small HCC (Barbara et al. 1992). Tumor volume doubling times tended to correlate with mitotic index and were one of the determining factors of survival length (Okazaki et al. 1989). A high proliferative activity as estimated with PCNA immunostaining was closely related to recurrence and reduced survival rate (Kitamoto et al. 1993; Adachi et al. 1995).

Are there other risk factors apart from stage, growth and differentiation, and vascular invasion? Child-Pugh classification and portal vein invasion were independent prognostic factors for survival rate, and tumor differentiation was an independent prognostic factor for disease-free survival rate, suggesting that E-HCC already have the biologic characteristics of more advanced HCCs (Fukuda et al. 2005). A part of E-HCC shows extracapsular invasion in the form of tumor projection seen on CT and MR images (Imaeda et al. 1994). These invasion features may be the causative factor of tumor satellites. Invasion and penetration of the tumor capsule affect prognosis. In contrast to large HCC, invasion through the capsule in small HCC correlated well with recurrence (Hsu et al. 1985). Also, the type of tumor vascularization affects prognosis. E-HCCs more often show capillary-like microvessels, and the presence of such a vascularization type is associated with better prognosis (Chen et al. 2011). Among the two major microvessel types found in HCCs, i.e., capillary-like and sinusoid-like, the capillary-like phenotype was more common in E-HCC, was significantly associated with higher microvessel density, and was significantly correlated with better disease-free survival and overall survival (Chen et al. 2011).

In univariate and multivariate analyses of small HCC, significant risk factors for early recurrence were a tumor diameter greater than 2.2 cm (i.e., greater than the diameter defining E-HCC), intracapsular invasion, a tumor location deep in the liver, macroscopic and microscopic tumor invasion into the portal vein, and intrahepatic metastasis (Shirabe et al. 1991). Risk factor for early recurrence included a serum AFP level $>$ 100 ng/ml., lack of tumor capsule formation, microscopic vascular invasion, high Edmondson-Steiner grade, and cytokeratin-19 expression (Zhou et al. 2010). Another investigation showed that poor Child-Pugh score, tumor diameter exceeding 2 cm, portal vein tumor thrombus, and multiple lesions including satellite lesions were adverse factors affecting postoperative survival (Wu et al. 2005). Fibrosis and AST to platelet ratio (APRI) predict postoperative prognosis for solitary HBV-related E-HCC, minimal fibrosis diagnosed by APRI being associated with a lower incidence of recurrence and better survival (Hung et al. 2010). There are also molecular features of E-HCC that confer a more aggressive course. An elevated expression of osteopontin and glypican-3 acted as adverse indicators for HBV-related E-HCC (Yu et al. 2012).

How do these risk factors translate into outcome following treatment of E-HCC?

A meta-analysis revealed that anatomic liver resection can extend the 3-year disease-free survival rate of patients with E-HCC (Jing-Dong et al. 2011). In a study of 788 patients, the median tumor size was 3.2 cm, and 20 % of the patients had tumors $\leq$2 cm. Following surgery, overall median and 5-year survival were 45 % and 39 %, respectively. After adjusting for demographic factors and histologic grade, tumor size $>$2 cm, multifocality, and vascular invasion remained independent predictors of poor survival (Nathan et al. 2009). Solitary E-HCCs tend to be considered as less aggressive cancers, leading to nonsurgical treatment modalities. In patients with E-HCC $<$2 cm in diameter and solitary lesion, percutaneous ethanol injection treatment led to a local recurrence rate at 3 years of 10 % (Ebara et al. 2005). In patients with cirrhosis, radiofrequency ablation of E-HCC led to higher 2-year disease-free survival in comparison with ethanol injection (Seror et al. 2006). Also, percutaneous image-guided radiofrequency ablation has been shown to be an effective first-line treatment for cirrhotic patients with early-stage

HCC (Lencioni et al. 2005), and experience with percutaneous ethanol injection has accumulated (Vilana et al. 1992; Koda et al. 2000; Pompili et al. 2001; Huang et al. 2005; Kammula 2006; Liao et al. 2006).

Although surgical resection, radiofrequency ablation, or particle radiotherapy of early/small HCC are associated with favorable outcome, the exact biology of disease of E-HCC is still not fully known. Even after treatment, E-HCC may show a special recurrent pattern in the form of bile duct tumor thrombus formation (Liu et al. 2011). As most patients with E-HCC suffer from liver cirrhosis, treatment failure and death are often related to hepatic insufficiency irrespective of the treatment modality (Ohnishi et al. 1987). A more favorable biology disease in E-HCC is thought to be related to an early developmental status of these neoplasms, although one does not yet known how many of initially small lesions will, and during which time interval, progress to large lesions.

Selected references: Okuda et al. 1985; Ebara et al. 1986; Chen et al. 1994; Takayama et al. 1998; Llovet et al. 2000; Inoue et al. 2004; Suh 2005; Ferrari et al. 2006; Leoni et al. 2006; Okita 2006; Colombo 2008; Hosaka et al. 2009; Dahiya et al. 2010; Zhang and Chen 2010; Ikeda et al. 2011; Jing-Dong et al. 2011; Kim et al. 2011; and Komatsu et al. 2011.

Molecular Features and Pathogenic Pathways

S-HCC occurs in a wide array of chronic liver diseases/cirrhosis, including HCV infection and metabolic disorders such as Wilson disease (Kumagi et al. 2005). There is strong evidence for a dysplastic nodule-early HCC sequence (Park 2005). In fact, the evolution of dysplastic nodules to early HCC and fully established nodular HCC with distinct margins within several months to a few years is well established (reviews: Hytiroglou 2004; Kojiro 2005). E-HCC is considered a key step in the development of HCC, and molecular signatures found in such lesions may represent a baseline for molecular alterations occurring later in disease (reviews: Uchida 1995; Effendi and Sakamoto 2010; Suriawinata and Thung 2010; Tan et al. 2012). E-HCCs differ from advanced HCCs by the presence of distinctive pattern of gene expression as assessed via gene expression profiling (Mas et al. 2006). A part of small HCC/E-HCC is aneuploid in DNA analyses (Zeppa et al. 1993). There was a stepwise increasing fractional allelic loss of heterozygosity of microsatellites from high-grade dysplastic nodules to E-HHCs and large HCCs, suggesting that determination of microsatellite LOH is a helpful measure to distinguish dysplastic nodules from E-HCC (Dong et al. 2011). A distinct molecular signature distinguishes dysplastic nodules from E-HCC. In one investigation of HCC arising in HCV-associated liver cirrhosis, twelve genes were significantly and differentially expressed in early HCCs compared with dysplastic nodules; these genes included TERT, glyican-3 (GPC3), gankyrin, survivin, TOP2A, LYVE1, E cadherin, insulin-like growth factor binding protein 3 (IGFBP3), platelet-derived growth factor receptor A (PDGFRA), TGFA, cyclin D1, and hepatocyte growth factor (HGF). A group of three genes (GPC3, LYVE1, survivin) had a discriminative accuracy of 94 % (Llovet et al. 2006). Well-differentiated small hepatocellular tumors, which may represent the precursors of E-HCC, were shown to express the c-Yes oncogene in the nuclei, suggesting that this oncogene is a marker of early-stage HCC (Nonomura et al. 2007). Although E-HCC can metastasize, their more favorable biology is probably related to a lesser propensity for spread and metastasis, and this feature is associated with overexpression of a metastasis-suppressor gene, nm23-H1 (Boix et al. 1994).

References

Adachi E, Maeda T, Matsumata T, Shirabe K, Kinukawa N, Sugimachi K, Tsuneyoshi M (1995) Risk factors for intrahepatic recurrence in human small hepatocellular carcinoma. Gastroenterology 108:768–775

An FQ, Matsuda M, Fujii H, Tang RF, Amemiya H, Dai YM, Matsumoto Y (2001) Tumor heterogeneity in small hepatocellular carcinoma: analysis of tumor cell

proliferation, expression and mutation of p53 and beta-catenin. Int J Cancer 93:468–474

Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, Siringo S, Rigamonti A, Barbara C et al (1992) Natural history of small untreated hepatocellular carcinoma in cirrhosis: a multivariate analysis of prognostic factors of tumor growth rate and patient survival. Hepatology 16:132–137

Bartolozzi C, Battaglia V, Bozzi E (2011) Hepatocellular nodules in liver cirrhosis: contrast-enhanced MR. Abdom Imaging 36:290–299

Bhattacharjya S, Bhattacharjya T, Quaglia A, Dhillon AP, Burroughs AK, Patch DW et al (2004) Liver transplantation in cirrhotic patients with small hepatocellular carcinoma: an analysis of pre-operative imaging, explant histology and prognostic histologic indicators. Dig Surg 21:152–159

Boix L, Bruix J, Campo E, Sole M, Castells A, Fuster J, Rivera F, Cardesa A, Rodes J (1994) nm23-H1 expression and disease recurrence after surgical resection of small hepatocellular carcinoma. Gastroenterology 107:486–491

Bolondi L, Gaiani S, Celli N, Golfieri R, Grigioni WF, Leoni S, Venturi AM, Piscaglia F (2005) Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology 42:27–34

Bruix J, Sherman M (2005) Diagnosis of small HCC. Gastroenterology 129:134

Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E et al (2001) Clinical management of hepatocellular carcinoma: conclusions of the Barceloma-2000 EASL conference. J Hepatol 35:421–430

Caroli-Bottino A, Nascimento CM, Basto S, Ribeiro J, Silveira V, Carvalho AM, Castro PN et al (2005) Hepatocellular carcinoma: incidental finding in cirrhotic explanted livers. Transplant Proc 37:2791–2792

Carr BI, Lu SN, Pancoska P (2011) Small hepatocellular carcinoma in Chinese patients. Hepatogastroenterology 58:1334–1342

Chen DS, Sheu JC, Sung JL, Lai MY, Lee CS, Su CT, Tsang YM, How SW, Wang TH et al (1982) Small hepatocellular carcinoma – a clinicopathological study in thirteen patients. Gastroenterology 63:1109–1119

Chen DS, Sung JL, Sheu JC, Lai MY, How SW, Hsu HC, Lee CS, Wei TC (1984) Serum a-fetoprotein in the early stage of human hepatocellular carcinoma. Gastroenterology 86:1404–1409

Chen CL, Huang SM, Chien CH, Chang TT, Yu CY, Lee JC (1994) Successful resection of a minute icteric hepatocellular carcinoma – case report. Hepatogastroenterology 41:503–505

Chen MH, Dai Y, Yan K, Fan ZH, Yin SS, Yang W, Wu W, Wang YB, Li JY (2006) The role of contrast-enhanced ultrasound on the diagnosis of small hepatocellular carcinoma (</=3 cm) in patients with cirrhosis. Hepatol Res 35:281–288

Chen ZY, Wei W, Guo ZX, Lin JR, Shi M, Guo RP (2011a) Morphologic classification of microvessels in hepatocellular carcinoma is associated with the prognosis after resection. J Gastroenterol Hepatol 26:866–874

Chen YL, Ko CJ, Chien SY, Chen LS, Chen ML, Chi CW, Lai HW (2011b) Tumor size as a prognostic factor in resected small hepatocellular carcinoma: a controversy revisited. J Gastroenterol Hepatol 26:851–857

Choi BI, Kim CW, Han MC, Kim CY, Lee HS, Kim ST, Kim YI (1989) Sonographic characteristics of small hepatocellular carcinoma. Gastrointest Radiol 14:255–261

Choi BI, Takayasu K, Han MC (1993) Small hepatocellular carcinomas and associated nodular lesions of the liver: pathology, pathogenesis, and imaging findings. AJR Am J Roentgenol 160:1177–1187

Choi D, Kim S, Lim J, Lee W, Jang H, Lee S, Lim H (2001) Preoperative detection of hepatocellular carcinoma: ferumoxides-enhanced mr imaging versus combined helical CT during arterial portography and CT hepatic arteriography. AJR Am J Roentgenol 176:475–482

Colombo M (2008) Natural history of hepatocellular carcinoma. Ann Ital Chir 79:91–97

Dahiya D, Wu TJ, Lee CF, Chan KM, Lee WC, Chen MF (2010) Minor versus major hepatic resection for small hepatocellular carcinoma (HCC) in cirrhotic patients: a 20-year experience. Surgery 147:676–685

Dhillon AP, Colombari R, Savage K, Scheuer PJ (1992) An immunohistochemical study of the blood vessels within primary hepatocellular tumours. Liver 12:311–318

Di Martino M, Di Miscio R, De Filippis G, Lombardo CV, Saba L, Geiger D, Catalano C (2013) Detection of small (<= 2 cm) HCC in cirrhotic patients: added value of diffusion MR-imaging. Abdom Imaging 38:1254–1262

Di Tommaso L, Destro A, Fabbris V, Spagnuolo G, Laura Fracanzani A, Fargion S et al (2011) Diagnostic accuracy of clathrin heavy chain staining in a marker panel for the diagnosis of small hepatocellular carcinoma. Hepatology 53:1549–1557

Dong H, Cong WM, Xian ZH, Zhu ZZ (2011) Using loss of heterozygosity of microsatellites to distinguish high-grade dysplastic nodule from early minute hepatocellular carcinoma. Exp Mol Pathol 91:578–583

Doyonnas R, Nielsen JS, Chelliah S, Drew E, Hara T, Miyajima A, McNagny KM (2005) Podocalyxin is a CD34-related marker of murine hematopoietic stem cells and embryonic erythroid cells. Blood 105:4170–4178

Dusheiko GM, Conradie JC, Bowyer SM, Simjee A, Epstein B, Levien LJ, Beale P, Kew MC (1986) Small and asymptomatic hepatocellular carcinoma detected by alpha-fetoprotein screening in black hepatitis B carriers. A report of 2 cases. S Afr Med J 69:129–132

Ebara M, Ohto M, Watanabe Y, Kimura K, Saisho H, Tsuchiya Y, Okuda K, Arimizu N et al (1986a) Diagnosis of small hepatocellular carcinoma: correlation of MR imaging and tumor histologic studies. Radiology 159:371–377

Ebara M, Ohto M, Shinagawa T, Sugiura N, Kimura K, Matsutani S, Morita M, Saisho H et al (1986b) Natural history of minute hepatocellular carcinoma smaller than three centimeters complicating cirrhosis. A study in 22 patients. Gastroenterology 90:289–298

Ebara M, Watanabe S, Kita K, Yoshikawa M, Sugiura N, Ohto M, Kondo F, Kondo Y (1991) MR imaging of small hepatocellular carcinoma: effect of intratumoral copper content on signal intensity. Radiology 180:617–621

Ebara M, Okabe S, Kita K, Sugiura N, Fukuda H, Yoshikawa M, Kondo F, Saisho H (2005) Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. J Hepatol 43:458–464

Effendi K, Sakamoto M (2010) Molecular pathology in early hepatocarcino-genesis. Oncology 78:157–160

Efremidis SC, Hytiroglou P, Matsui O (2007) Enhancement patterns and signal-intensity characteristics of small hepatocellular carcinoma in cirrhosis: pathologic basis and diagnostic challenges. Eur Radiol 17:2969–2982

Ferrari FS, Stella A, Pasquinucci P, Vigni F, Civeli L, Pieraccini M, Magnolfi F (2006) Treatment of small hepatocellular carcinoma: a comparison of techniques and long-term results. Eur J Gastroenterol Hepatol 18:659–672

Fong Y, Sun RL, Jarnagin W, Blumgart LH (1999) An analysis of 412 cases of hepatocellular carcinoma at Western center. Ann Surg 229:790–799

Fukii T, Zen Y, Nakanuma Y (2007) Minute scirrhous hepatocellular carcinomas undergoing different carcinogenetic processes. Pathol Int 57:443–448

Fukuda S, Itamoto T, Nakahara H, Kohashi T, Ohdan H, Hino H, Ochi M, Tashiro H, Asahara T (2005) Clinicopathologic features and prognostic factors of resected solitary small-sized hepatocellular carcinoma. Hepatogastroenterology 52:1163–1167

Gandolfi L, Solmi L, Bertoni F, Muratori R, Stasi G (1987) Small hepatocellular carcinoma: an Italian experience. Hepatogastroenterology 34:100–102

Golfieri R, Marini E, Bazzocchi A, Fusco F, Trevisani F, Sama C, Mazzella G, Cavuto S et al (2009) Small (<or= 3 cm) hepatocellular carcinoma in cirrhosis: the role of double contrast agents in MR imaging vs. multidetector-row CT. Radiol Med 114:1239–1266

Grigioni WF, D'Errico A, Bacci F, Carella R, Macini AM (1989) Small liver masses in cirrhotic patients. A pathological clue for the morphogenesis of human hepatocellular carcinoma. Acta Pathol Jpn 39:520–527

Grigioni WF, D'Errico A, Fortunato C, Cassisa A, Carella R, Mancini AM (1991) The morphogenesis of human hepatocellular carcinoma. Ital J Gastroenterol 23:594–596

Haratake J, Horie A, Nakashima A, Takeda S, Mori A (1986) Minute hepatoma with excessive copper accumulation. Report of two cases with resection. Arch Pathol Lab Med 110:192–194

Haratake J, Hisaoka M, Yamamoto O, Horie A (1992) An ultrastructural comparison of sinusoids in hepatocellular carcinoma, adenomatous hyperplasia, and fetal liver. Arch Pathol Lab Med 116:67–70

Hayashida M, Ito K, Fujita T, Shimizu A, Sasaki K, Tanabe M, Matsunaga N (2008) Small hepatocellular carcinomas in cirrhosis: differences in contrast enhancement effects between helical CT and MR imaging during multiphasic dynamic imaging. Magn Reson Imaging 26:65–71

Heukamp LC, Fischer HP, Schirmacher P, Chen X, Breuhahn K, Nicolay C, Buttner R et al (2006) Podocalyxin-like protein 1 expression in primary hepatic tumours and tumour-like lesions. Histopathology 49:242–247

Higashi T, Tobe K, Asano K, Ikeda H, Ohsawa T, Iwasaki Y, Nouso K, Shinji N, Morimoto Y et al (1988) Ultrasonographic characteristics of small hepatocellular carcinoma. Acta Med Okayama 42:151–157

Hirai K, Aoki Y, Majima Y, Abe H, Nakashima O, Kojiro M, Tanikawa K (1991) Magnetic resonance imaging of small hepatocellular carcinoma. Am J Gastroenterol 86:205–209

Hosaka T, Ikeda K, Kobayashi M, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, Akuta N et al (2009) Predictive factors of advanced recurrence after curative resection of small hepatocellular carcinoma. Liver Int 29:736–742

Hosoki T, Chtani M, Mori S (1982) Dynamic computed tomography of hepatocellular carcinoma. AJR Am J Roentgenol 139:1099–1106

Hsu HC, Sheu JC, Lin YH, Chen DS, Lee CS, Hwang LY, Beasley RP (1985) Prognostic histologic features of resected small hepatocellular carcinoma (HCC) in Taiwan. A comparison with resected large HCC. Cancer 56:672–680

Huang GT, Lee PH, Tsang YM, Lai MY, Yang PM, Hu RH, Chen PJ, Kao JH et al (2005) Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: a prospective study. Ann Surg 242:36–42

Hung HH, Su CW, Lai CR, Chau GY, Chan CC, Huang YH, Huo TI, Lee PC et al (2010) Fibrosis and AST to platelet ratio index predict post-operative prognosis for solitary small hepatitis B-related hepatocellular carcinoma. Hepatol Int 4:691–699

Hwang SH, Yu JS, Kim KW, Kim JH, Chung JJ (2008) Small hypervascular enhancing lesions on arterial phase images of multiphase dynamic computed tomography in cirrhotic liver: fate and implications. J Comput Assist Tomogr 32:39–45

Hwang J, Kim SH, Lee MW, Lee JY (2012) Small (<- 2 cm) hepatocellular carcinoma in patients with chronic liver disease: comparison of gadoxetic acid-enhanced 3.0 T MRI and multiphasic 64-multirow detector CT. Br J Radiol 85:e314–e322

Hytiroglou P (2004) Morphological changes of early human hepatocarcinogenesis. Semin Liver Dis 24:65–75

Ikeda K, Saitoh S, Koida I, Tsubota A, Arase Y, Chayama K, Kumada H (1994) Imaging diagnosis of small hepatocellular carcinoma. Hepatology 20:82–87

Ikeda K, Kobayashi M, Kawamura Y, Imai N, Seko Y, Hirakawa M, Hosaka T, Sezaki H et al (2011) Stage progression of small hepatocellular carcinoma after radical therapy: comparison of radiofrequency ablation and surgery using the Markov model. Liver Int 31:692–699

Imaeda T, Kanematsu M, Mochizuki R, Goto H, Saji S, Shimokawa K (1994) Extracapsular invasion of small hepatocellular carcinoma: MR and CT findings. J Comput Assist Tomogr 18:755–760

Imai K, Beppu T, Nakayama Y, Ishiko T, Horino K, Komori H, Masuda T, Hayashi H et al (2009) Preoperative prediction of poorly differentiated components in small-sized hepatocellular carcinoma for safe local ablation therapy. J Surg Oncol 100:121–126

Inamoto K, Tanaka S, Yamazaki H, Okamoto E (1983) Computed tomography in the detection of small hepatocellular carcinomas. Gastrointest Radiol 8:321–326

Inoue E, Kuroda C, Fujita M, Narumi Y, Kadota T, Kuriyama K, Ishiguro S, Kasugai H et al (1993) MR features of various histological grades of small hepatocellular carcinoma. J Comput Assist Tomogr 17:75–79

Inoue K, Takayama T, Higaki T, Watanabe Y, Makuuchi M (2004) Clinical significance of early hepatocellular carcinoma. Liver Transpl 10(2 suppl 1):S16–S19

International Consensus Group for Hepatocellular Neoplasia (2009) Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology 49:658–664

International Working Party (1995) Terminology of nodular hepatocellular lesions. International Working Party. Hepatology 22:983–993

Ise N, Andoh H, Sato T, Yasui O, Kurokawa T, Kotanagi H (2004) Three cases of small hepatocellular carcinoma presenting as obstructive jaundice. HPB (Oxford) 6:21–24

Itai Y, Ohtomo K, Ohnishi S, Atomi Y, Itoh T, Fukuhisa K, Iinuma T (1987) Ultrasonography of small hepatic tumors. Radiat Med 5:14–19

Ito K, Fujita T, Shimizu A, Koike S, sasaki K, Matsunaga N, Hibino S, Yuhara M (2004) Multiarterial phase dynamic MRI of small early enhancing hepatic lesions in cirrhosis or chronic hepatitis: differentiating between hypervascular hepatocellular carcinomas and pseudolesions. AJR Am J Roentgenol 183:699–705

Jang HJ, Kim TK, Wilson SR (2009) Small nodules (1–2 cm) in liver cirrhosis: characterization with contrast-enhanced ultrasound. Eur J Radiol 72:418–424

Jeong YY, Mitchell DG, Kamishima T (2002) Small (<20mm) enhancing hepatic nodules seen on arterial phase MR imaging of the cirrhotic liver. Clinical implications. AJR Am J Roentgenol 178:1327–1334

Jiang J, Wu C, Shen Y, Xu B, Zheng X, Li X, Xu N (2011) Clinical application of determining serum AFP-IgM complexes for diagnosis of small hepatocellular carcinoma. Anticancer Res 31:687–691

Jing-Dong L, Yun-Hong T, Kanduri HK, Quan-Lin L, De-Xing L, Qiang L (2011) Prognosis in patients with small hepatocellular carcinoma. A meta-analysis. Hepatogastroenterology 58:110–111

Kammula US (2006) Predicting outcomes after percutaneous ethanol injection for small hepatocellular cancer. Cancer J 12:175–177

Kanai T, Hirohashi S, Upton MP, Noguchi M, Kishi M, Makuuchi M, Yamasaki S, Hasegawa H et al (1987) pathology of small hepatocellular carcinoma. A proposal for a new gross classification. Cancer 60:810–819

Kanematsu T, Takenaka K, Matsumata T, Furuta T, Sugimachi K, Inokuchi K (1983) Small liver cancer. Jpn J Surg 13:32–36

Kanematsu T, Sonoda T, Takenaka K, Matsumata T, Sugimachi K, Inokuchi K (1985) The value of ultrasound in the diagnosis and treatment of small hepatocellular carcinoma. Br J Surg 72:23–25

Kanematsu M, Hoshi H, Yamada T, Murakami T, Kim T, Kato M, Yokoyama R, Nakamura H (1999) Small hepatic nodules in cirrhosis: ultrasonographic, CT, and MR imaging findings. Abdom Imaging 24:47–55

Kenmochi K, Sugihara S, Kojiro M (1987) Relationship of histologic grade of hepatocellular carcinoma (HCC) to tumor size, and demonstration of tumor cells of multiple different grades in single small HCC. Liver 7:18–26

Kikuchi LO, Paranagua-Vezozzo DC, Chagas AL, Mello ES, Alves VA, Farias AQ et al (2009) Nodules less than 20 mm and vascular invasion are predictors of survival in small hepatocellular carcinoma. J Clin Gastroenterol 43:191–195

Kim SR, Hayashi Y, Matsuoka T, Park SY, Shintani S, Sasaki K, Asano J, Kim JH et al (1998) A case of well-differentiated minute hepatocellular carcinoma with extrahepatic metastasis. J Gastroenterol Hepatol 13:892–896

Kim SR, Ikawa H, Ando K, Mita K, Fuki S, Imoto S, Shimizu K, Kanbara Y, Sugimoto K et al (2007) Small hepatocellular carcinoma presenting with massive metastasis in the peritoneum, mimicking sarcomatous tumor. Hepatol Res 37:885–889

Kim TK, Lee KH, Khalili K, Jang HJ (2011) Hepatocellular nodules in liver cirrhosis: contrast-enhanced ultrasound. Abdom Imaging 36:244–263

Kim MJ, Lee M, Choi JY, Park YN (2012) Imaging features of small hepatocellular carcinomas with microvascular invasion on gadoxetic acid-enhanced MR imaging. Eur J Radiol 81:2507–2512

Kin M, Torimura T, Ueno T, Inuzuka S, Tanikawa K (1994) Sinusoidal capillarization in small hepatocellular carcinoma. Pathol Int 44:771–778

Kitagawa K, Matsui O, Kadoya M, Takashima T, Kawamori Y, Yamahana T, Kidani H et al (1991) Hepatocellular carcinomas with excessive copper accumulation: CT and MR findings. Radiology 180:623–628

Kitamoto M, Nakanishi T, Kira S, Kawaguchi M, Nakashio R, Suemori S, Kajiyama G et al (1993) The assessment of proliferating cell nuclear antigen immunohistochemical staining in small hepatocellular carcinoma and its relationship to histologic characteristics and prognosis. Cancer 72:1859–1865

Ko CJ, Chien SY, Chou CT, Chen LS, Chen ML, Chen YL (2011) Factors affecting prognosis of small hepatocellular carcinoma in Taiwanese patients following hepatic resection. Can J Gastroenterol 25:485–491

Koda M, Murawaki Y, Mitsuda A, Ohyama K, Horie Y, Suou T, Kawasaki H, Ikawa S (2000) Predictive factors for intrahepatic recurrence after percutaneous ethanol injection therapy for small hepatocellular carcinoma. Cancer 88:529–537

Köhn K (1956) Über das Vorkommen von Mikrocarcinomen in cirrhotischen Lebern. Z Krebsforsch 61:350–363

Kojiro M (1998) Pathology of early hepatocellular carcinoma: progression from early to advanced. Hepatogastroenterology 45(suppl 3):1203–1205

Kojiro M (2000) Premalignant lesions of hepatocellular carcinoma: pathologic viewpoint. J Hepatobiliary Pancreat Surg 7:535–541

Kojiro M (2004) Focus on dysplastic nodules and early hepatocellular carcinoma: an Eastern point of view. Liver Transpl 10(suppl 1):S3–S8

Kojiro M (2005) Histopathology of liver cancers. Best Pract Res Clin Gastroenterol 19:39–62

Kojiro M (2010) Pathological diagnosis at early stage: reaching international consensus. Oncology 78(suppl 1):31–35

Kojiro M, Roskams T (2005) Early hepatocellular carcinoma and dysplastic nodules. Semin Liver Dis 25:133–142

Kojiro M, Yano H, Nakashima O (1996) Pathology of early hepatocellular carcinoma: progression from early to advanced. Semin Surg Oncol 12:197–203

Komatsu S, Murakami M, Fukumoto T, Hori Y, Hishikawa Y, Ku Y (2011) Risk factors for survival and local recurrence after particle radiotherapy for single small hepatocellular carcinoma. Br J Surg 98:558–564

Kondo Y, Niwa Y, Akikusa B, Takazawa H, Okubayashi A (1983) A histopathologic study of early hepatocellular carcinoma. Cancer 52:687–692

Kondo F, Hirooka N, Wada K, Kondo Y (1987) Morphological clues for the diagnosis of small hepatocellular carcinoma. Virchows Arch A Pathol Anat Histopathol 411:15–21

Kondo F, Kondo Y, Nagato Y, Tomizawa M, ada K (1994) Interstitial tumour cell invasion in small hepatocellular carcinoma. Evaluation in microscopic and low magnification views. J Gastroenterol Hepatol 9:604–612

Korpraphong P, Leyendecker JR, Hildebolt CF, Narra V, Bae KT, Brown JJ (2009) Serial MR imaging of small arterially-enhancing liver lesions in patients with chronic liver disease. J Med Assoc Thai 92:548–555

Kudo M, Hirasa M, Takakuwa H, Ibuki Y, Fujimi K, Miyamura M, Tomita S, Komori H et al (1986) Small hepatocellular carcinomas in chronic liver disease: detection with SPECT. Radiology 159:697–703

Kumagi T, Horiike N, Abe M, Kurose K, Iuchi H, Matsumoto T, Joko K, Akbar SF et al (2005) Small hepatocellular carcinoma associated with Wilson's disease. Intern Med 44:439–443

Larsson A, Johansson ME, Wangefjord S, Gaber A, Nodin B, Kucharzewska P, Welinder C et al (2011) Overexpression of podocalyxin-like protein is an independent factor of poor prognosis in colorectal cancer. Br J Cancer 105:666–672

Lencioni R, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, Bartolozzi C (2005) Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 234:961–967

Leoni S, Piscaglia F, Righini R, Bolondi L (2006) Management of small hepatocellular carcinoma. Acta Gastroenterol Belg 69:230–235

Liao CS, Yang KC, Yen AM, Chen LS, Chen TH (2006) Remission, relapse, and metastasis/death of small hepatocellular carcinoma treated with percutaneous ethanol injection. Cancer J 12:194–200

Libbrecht L, Severi T, Cassiman D, Borght SV, Pirenne J, Nevens F, Verslype C et al (2006) Glypican-3 expression distinguishes small hepatocellular carcinomas from cirrhosis, dysplastic nodules, and focal nodular hyperplasia-like nodules. Am J Surg Pathol 30:1405–1411

Lim JH, Choi D, Cho SK, Kim SH, Lee WJ, Lim HK, Park CK, Paik SW, Kim YI (2001) Conspicuity of hepatocellular nodular lesions in cirrhotic livers at ferumoxides-enhanced MR imaging: importance of Kupffer cell number. Radiology 220:669–676

Liu QY, Huang SQ, Chen JY, Li HG, Gao M, Liu C, Liang BL (2010) Small hepatocellular carcinoma with bile duct tumor thrombi: CT and MRI findings. Abdom Imaging 35:537–542

Liu QY, Lai DM, Liu C, Zhang L, Zhang WD, Li HG, Gao M (2011) A special recurrent pattern in small hepatocellular carcinoma after treatment: bile duct tumor thrombus formation. World J Gastroenterol 17:4817–4824

Livraghi T, Sangalli G, Giordano F, Ravetto C, Solbiati L, Fornari F, Cavanna L, Matricardi L et al (1987) 240 hepatocellular carcinomas: ultrasound features, tumor size, cytologic and histologic patterns, serum alpha-fetoprotein and HBs Ag. Tumori 73:507–512

Llovet JM, Bruix J, Gores GJ (2000) Surgical resection versus transplantation for early hepatocellular carcinoma: clues for the best strategy. Hepatology 31:1019–1021

Llovet JM, Chen Y, Wurmbach E, Roayaie S, Fiel MI, Schwartz M, Thung SN et al (2006) A molecular signature to discriminate dysplastic nodules from early hepatocellular carcinoma in HCV cirrhosis. Gastroenterology 131:1758–1767

Long J, Lang ZW, Wang HG, Wang TL, Wang BE, Liu SQ (2010) Glutamine synthetase as an early marker for hepatocellular carcinoma based on proteomic analysis of resected small hepatocellular carcinomas. Hepatobiliary Pancreat Dis Int 9:296–305

Lu XY, Xi T, Lau WY, Dong H, Xian ZH, Yu H, Zhu Z, Shen F, Wu C, Cong WM (2011) Pathobiological

features of small hepatocellular carcinoma: correlation between tumor size and biological behavior. J Cancer Res Clin Oncol 137:567–575

Lv P, Lin XZ, Li J, Li W, Chen K (2011) Differentiation of small hepatic hemangioma from small hepatocellular carcinoma: recently introduced spectral CT method. Radiology 259:720–729

Maeda T, Adachi E, Kajiyama K, Takenaka K, Honda H, Sugimachi K, Tsuneyoshi M (1995) CD34 expression in endothelial cells of small hepatocellular carcinoma: its correlation with tumour progression and angiographic findings. J Gastroenterol Hepatol 10:650–654

Maeda T, Takenaka K, Taguchi K, Kajiyama K, Shirabe K, Shimada M, Honda H, Sugimachi K (2000a) Small hepatocellular carcinoma with minute satellite nodules. Hepatogastroenterology 47:1063–1066

Maeda T, Takenaka K, Taguchi K, Kajiyama K, Shirabe K, Shimada M, Tsuneyoshi M et al (2000b) Clinicopathological characteristics of surgically resected minute hepatocellular carcinomas. Hepatogastroenterology 47:498–503

Mahmood K, Schatzki PF (1976) Solitary small hepatocellular carcinoma. Am J Dig Dis 21:496–502

Makuuchi M, Hasegawa H, Yamazaki S, Bandai Y, Watanabe G, Ito T (1983) Ultrasonic characteristics of the small hepatocellular carcinoma. Ultrasound Med Biol (suppl.2): 489–491

Mas VR, Maluf DG, Archer KJ, Yanek K, Williams B, Fisher RA (2006) Differentially expressed genes between early and advanced hepatocellular carcinoma (HCC) as a potential tool for selecting liver transplant recipients. Mol Med 12:97–104

Miyaaki H, Fujimoto M, Kurogi M, Nakashima O, Eguchi K, Kojiro M (2005) Pathomorphological study on small nodular lesions in hepatitis C virus-related cirrhosis. Oncol Rep 14:1469–1474

Moribata K, Tamai H, Shingaki N, Mori Y, Enomoto S, Shiraki T, Deguchi H, Ueda K et al (2011) Assessment of malignant potential of small hypervascular hepatocellular carcinoma using B-mode ultrasonography. Hepatol Res 41:233–239

Muramatsu Y, Moriyama N, Takayasu K, Yamada T, Hasegawa H, Kishi K (1985) A case of minute hepatocellular carcinoma with calcification (in Japanese). Ronsho Hoshasen 30:129–132

Nagasue N, Kohno H, Chang YC, Galizia G, Hayashi T, Yukaya H, Nakamura T (1989) Intraoperative ultrasonography in resection of small hepatocellular carcinoma associated with cirrhosis. Am J Surg 158:40–42

Nakano M, Saito A, Takasaki K, Obata H, Kobayashi S (1990) A histopathologic study of early hepatocellular carcinoma: portal tract invasion and progression to advanced hepatocellular carcinoma. Acta Hepatol Jpn 31:754–762

Nakanuma Y, Ohta G (1984) Small hepatocellular carcinoma containing many Mallory bodies. Liver 4:128–133

Nakashima T, Sakamoto K, Okuda K (1977) A minute hepatocellular carcinoma found in a liver with Clonorchis sinensis infection: report of two cases. Cancer 39:1306–1311

Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K, Ikari T (1983) Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. Cancer 51:863–877

Nakashima O, Sugihara S, Kage M, Kojiro M (1995) Pathomorphologic characteristics of small hepatocellular carcinoma: a special reference to small hepatocellular carcinoma with indistinct margins. Hepatology 22:101–105

Nakashima Y, Nakashima O, Tanaka M, Okuda K, Nakashima M, Kojiro M (2003) Portal vein invasion and intrahepatic micrometastases in small hepatocellular carcinoma by gross type. Hepatol Res 26:142–147

Nathan H, Schulick RD, Choti MA, Pawlik TM (2009) Predictors of survival after resection of early hepatocellular carcinoma. Ann Surg 249:799–805

Noguchi H, Hirai K, Itano S, Ijuin H, Kajiwara M, Sakata K, Ono N, Hidaka R, Aritaka T et al (1994) Small hepatocellular carcinoma with intravascular tumor growth into the right atrium. J Gastroenterol 29:41–46

Nonomura T, Masaki T, Morishita A, Jian G, Uchida N, Himoto T, Izuishi K, Iwama H et al (2007) Identification of c-Yes expression in the nuclei of hepatocellular carcinoma cells: involvement in the early stages of hepatocarcinogenesis. Int J Oncol 30:105–111

O'Malley ME, Takayama Y, Sherman M (2005) Outcome of small (10–20 mm) arterial phase-enhancing nodules seen on triphasic liver CT in patients with cirrhosis or chronic liver disease. Am J Gastroenterol 100:1523–1528

Ohnishi K, Tanabe Y, Ryu M, Isono K, Yamamoto Y, Usui S, Hiyama Y, Goto N, Iwama S et al (1987) Prognosis of hepatocellular carcinoma smaller than 5 cm in relation to treatment: study of 100 patients. Hepatology 7:1285–1290

Ohnishi H, Sakaguchi K, Nouso K, Kobayashi Y, Nakamura S, Tanaka H, Miyake Y et al (2010) Outcome of small liver nodules detected by computed tomographic angiography in patients with hepatocellular carcinoma. Hepatol Int 4:562–568

Ohno Y, Shiga J, Machinami R (1990) A histopathological analysis of five cases of adenomatous hyperplasia containing minute hepatocellular carcinoma. Acta Pathol Jpn 40:267–278

Okazaki N, Yoshino M, Yoshida T, Suzuki M, Moriyama N, Takayasu K, Makuuchi M et al (1989) Evaluation of the prognosis for small hepatocellular carcinoma based on tumor volume doubling time. A preliminary report. Cancer 63:2207–2210

Okita K (2006) Clinical aspects of hepatocellular carcinoma in Japan. Intern Med 45:229–233

Okuda K, Kotoda K, Obata H, Hayashi N, Hisamitsu T (1975) Clinical observations during a relatively early stage of hepatocellular carcinoma, with special reference to serum alpha-fetoprotein levels. Gastroenterology 69:226–234

Okuda K, Nakashima T, Obata H, Kubo Y (1977) Clinicopathological studies of minute hepatocellular carcinoma. Analysis of 20 cases, including 4 with hepatic resection. Gastroenterology 73:109–115

Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K (1985) Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 56:918–928

Pancoska P, De Giorgio M, Fagiulo S, Carr BI (2011) Small HCCs identified by screening. Dig Dis Sci 56:3078–3085

Park YN (2005) Pathology of hepatocellular carcinoma: recent update (in Korean). Korean J Gastroenterol 45:227–233

Park YN (2011) Update on precursor and early lesions of hepatocellular carcinomas. Arch Pathol Lab Med 135:704–715

Pauleit D, Textor J, Bachmann R, Conrad R, Flacke S, Layer G, Kreft B, Schild H (2002) Hepatocellular carcinoma: detection with gadolinium-and ferumoxides-enhanced MR imaging of the liver. Radiology 222:73–80

Pompili M, Rapaccini GL, Covino M, Pignataro G, Caturelli E, Siena DA, Villani MR et al (2001) Prognostic factors for survival in patients with compensated cirrhosis and small hepatocellular carcinoma after percutaneous ethanol injection therapy. Cancer 92:126–135

Rim KS, Sakamoto M, Watanabe H, Matsuno Y, Nakanishi Y, Mukai K, Hirohashi S (1993) Pathology and DNA cytophotometry of small hepatocellular carcinoma with a nodule-in-nodule appearance- evidence for stepwise progression of hepatocellular carcinoma. Jpn J Clin Oncol 23:26–33

Roncalli M, Park YN, Di Tommaso L (2010) Histopathological classification of hepatocellular carcinoma. Dig Liver Dis 42(suppl 3):S228–S234

Roncalli M, Terracciano L, Di Tommaso L, David E, Colombo M, Gruppo Italiano Patologi Apparato Digerente (GIPAD) et al (2011) Liver precancerous lesions and hepatocellular carcinoma: the histology report. Dig Liver Dis 43(suppl 4):S361–S372

Roskams T, Kojiro M (2010) Pathology of early hepatocellular carcinoma: conventional and molecular diagnosis. Semin Liver Dis 30:17–25

Sakamoto M (2009) Early HCC: diagnosis and molecular markers. J Gastroenterol 44(suppl 19):108–111

Sanuki-Fujimoto N, Takeda A, Ohashi T, Kunieda E, Iwabuchi S, Takatsuka K, Koike N et al (2010) CT evaluation of focal liver reactions following stereotactic body radiotherapy for small hepatocellular carcinoma with cirrhosis: relationship between imaging appearance and baseline liver function. Br J Radiol 83:1063–1071

Sasaki Y, Imaoka S, Ishiguro S, nakano H, Kasugai H, Fujita M, Inoue E, Ishikawa O et al (1996) Clinical features of small hepatocellular carcinomas as assessed by histologic grades. Surgery 119:252–260

Seki S, Sakaguchi H, Kawakita N, Yanai A, Tamori A, Yabusako T, Nishiguchi S, Kuroki T et al (1993) Detection of the preneoplastic lesions of small hepatocellular carcinoma in cirrhotic livers. J Gastroenterol Hepatol 8:582–589

Seror O, N'kontchou G, Tin Tin Htar M, Durand-Zaleski I, Trinchet JC, Sellier N, Beaugrand M (2006) Ethanol versus radiofrequency ablation for treatment of small hepatocellular carcinoma in patients with cirrhosis. Gastroenterol Clin Biol 30:1265–1273

Sherman M (2005) Diagnosis of small hepatocellular carcinoma. Hepatology 42:14–16

Sherman M (2010) Optimum imaging for small suspected hepatocellular carcinoma. Gut 59:570–571

Shinagawa T, Ohto M, Kimura K, Tsunetomi S, Morita M, Saisho H, Tsuchiya Y, Okuda K et al (1982) Clinical features of small hepatocellular carcinoma (in Japanese). Nihon Shokakibyo Gakkai Zasshi 79:2277–2284

Shinagawa T, Ohto M, Kimura K, Tsunetomi S, Morita M, Saisho H, Tsuchiya Y, Saotome N et al (1984) Diagnosis and clinical features of small hepatocellular carcinoma with emphasis on the utility of real-time ultrasonography. A study 0f 51 patients. Gastroenterology 86:495–502

Shirabe K, Kanematsu T, Matsumata T, Adachi E, Akazawa K, Sugimachi K (1991) Factors linked to early recurrence of small hepatocellular carcinoma after hepatectomy: univariate and multivariate analyses. Hepatology 14:802–805

Sohda T, Kamimura S, Iwata K, Shijo H, Okumura M (1997) Immunohistochemical evidence of insulin-like growth factor II in human small hepatocellular carcinoma with hepatitis C virus infection: relationship to fatty change in carcinoma cells. J Gastroenterol Hepatol 12:224–228

Sugihara S, Nakashima O, Kojiro M, Majima Y, Tanaka M, Tanikawa K (1992) The morphologic transition in hepatocellular carcinoma. A comparison of the individual histologic features disclosed by ultrasound-guided fine-needle biopsy with those of autopsy. Cancer 70:1488–1492

Suh KS (2005) Systematic hepatectomy for small hepatocellular carcinoma in Korea. J Hepatobiliary Pancreat Surg 12:365–370

Sumida M, Ohto M, Ebara M, Kimura K, Okuda K, Hirooka N (1986) Accuracy of angiography in the diagnosis of small hepatocellular carcinoma. AJR Am J Roentgenol 147:531–536

Sun HY, Lee JM, Shin CI, Lee DH, Moon SK, Kim KW, Han JK, Choi BI (2010) Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular carcinomas (< or = 2 cm in diameter) from arterial enhancing pseudolesions: special emphasis on hepatobiliary phase imaging. Invest Radiol 45:96–103

Suriawinata A, Thung SN (2010) Molecular signature of early hepatocellular carcinoma. Oncology 78(suppl1):36–39

Takashima T, Matsui O (1980) Infusion hepatic angiography in the detection of small hepatocellular carcinomas. Radiology 136:321–325

Takashima T, Matsui O, Suzuki M, Ida M (1982) Diagnosis and screening of small hepatocellular carcinoma. Comparison of radionuclide imaging, ultrasound, computed tomography, hepatic angiography, and alpha 1-fetoprotein assay. Radiology 145:635–638

Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K, Kosuge T et al (1998) Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology 28:1241–1246

Tan Y, Yin P, Tang L, Xing W, Huang Q, Cao D, Zhao X, Wang W, Lu X, Xu Z, Wang H et al (2012) Metabolomics study of stepwise hepatocarcinogenesis from the model rats to patients: potential biomarkers effective for small hepatocellular carcinoma diagnosis. Mol Cell Proteomics 11:M111.010694

Tanaka S, Kitamura T, Nakanishi K, Okuda S, Kojima J, Fujimoto I (1989) Recent advances in ultrasonographic diagnosis of hepatocellular carcinoma. Cancer 63:1313–1317

Tang ZY, Yu YQ, Zhou XD, Ma ZC, Yang R, Lu JZ, Lin ZY, Yang BH (1989) Surgery of small hepatocellular carcinoma. Analysis of 144 cases. Cancer 64:536–541

Tang ZY, Yu YQ, Zhou XD, Yang BH, Ma ZC, Lin ZY (1993) Subclinical hepatocellular carcinoma: an analysis of 391 patients. J Surg Oncol Suppl 3:55–58

Tang Y, Yamashita Y, Arakawa A, Namimoto T, Mitsuzaki K, Abe Y, Katahira K, Takahashi M (1999) Detection of hepatocellular carcinoma arising in cirrhotic livers: comparison of gadolinium-and ferumoxides-enhanced MR imaging. AJR Am J Roentgenol 172:1547–1554

Terada T, Nakanuma Y (1992) Cell proliferative activity in adenomatous hyperplasia of the liver and small hepatocellular carcinoma. An immunohistochemical study demonstrating proliferating cell nuclear antigen. Cancer 70:591–598

Terada T, Nakanuma Y, Kawai K (1989) Small hepatocellular carcinoma presenting as intrabiliary pedunculated polyp and obstructive jaundice. J Clin Gastroenterol 11:578–583

Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Koike Y, Hamamura K, Akamatsu M et al (2004) A novel display of reconstruction computed tomography for the detection of small hepatocellular carcinoma. Liver Int 24:619–624

Than KW, Okayasu I, Akashi T (1995) Histopathological and immunohistochemical analysis of adenomatous hyperplasia and hepatocellular carcinoma: cellularity, thickness of cell cord, and Ki-67 proliferative activity. Bull Tokyo Med Dent Univ 42:67–81

Theise ND, Curado MP, Franceschi S, Hytiroglou P, Kudo M, Park YN, Sakamoto M et al (2010) Hepatocellular carcinoma. WHO Classification of tumours of the digestive system. IARC, Lyon, pp 214–215

Toyoda H, Kumada T, Nakano S, Takeda I, Sugiyama K, Kiriyama S, Sone Y, Hisanaga Y (2001) Characteristics and course of small hepatocellular carcinomas in patients with hepatitis C virus types 1 and 2. J Med Virol 63:120–127

Tremosini S, Forner A, Boix L, Vilana R, Bianchi L, Reig M, Rimola J, Rodriguez-Lope C et al (2012) Prospective validation of an immunohistochemical panel (glypican 3, heat shock protein 70 and glutamine synthetase) in liver biopsies for diagnosis of very early hepatocellular carcinoma. Gut 61:1481–1487

Tsunetomi S, Ohto M, Iino Y, Shinagawa T, Kimura K, Morita M, Saisho H, Tsuchiya Y et al (1989) Diagnosis of small hepatocellular carcinoma by computed tomography: correlation of CT findings and histopathology. J Gastroenterol Hepatol 4:395–404

Uchida T (1995) Small hepatocellular carcinoma: its relationship to multistep hepatocarcinogenesis. Pathol Int 45:175–184

Utsunomiya T, Shimada M, Taguchi KI, Hasegawa H, Yamashita Y, Hamatsu T, Aishima SI et al (2000) Clinicopathologic features and postoperative prognosis of multicentric small hepatocellular carcinoma. J Am Coll Surg 190:331–335

Vilana R, Bruix J, Bru C, Ayuso C, Sole M, Rodes J (1992) Tumor size determines the efficacy of percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Hepatology 16:353–357

Wakasa K, Sakurai M, Okamura J, Kuroda C (1985) Pathological study of small hepatocellular carcinoma: frequency of their invasion. Virchows Arch A Pathol Anat Histopathol 407:259–270

Wang JH, Lu SN, Hung CH, Chen TY, Chen CH, Changchien CS, Lee CM (2006) Small hepatic nodules ($<$ or $=$ 2 cm) in cirrhosis patients: characterization with contrast-enhanced ultrasonography. Liver Int 26:928–934

Wang F, Jing X, Wang T, Li G, Zhang Q, Huang Y, Li J, Wang Y, Gao Y, Han T et al (2012) Differential diagnostic value of GPC3-CD34 combined staining in small liver nodules with diameter less than 3 cm. Am J Clin Pathol 137:937–945

Ward J, Guthrie JA, Scott DJ, Atchley J, Wilson D, Davies MH, Wyatt JI, Robinson PJ (2000) Hepatocellular carcinoma in the cirrhotic liver: double-contrast MR imaging for diagnosis. Radiology 216:154–162

Watanabe A, Sakata T, Shiota T, Nagashima H (1984) Hepatocellular carcinoma of small size. Am J Med Sci 288:151–157

Watanabe A, Yamamoto H, Ito T, Nagashima H (1986) Diagnosis, treatment and prognosis of small hepatocellular carcinoma. Hepatogastroenterology 33:52–55

Wee A (2011) Fine-needle aspiration biopsy of hepatocellular carcinoma and related hepatocellular nodular lesions in cirrhosis: controversies, challenges, and expectations. Pathol Res Int 2011:587936

Wu FS, Zhao WH, Liang TB, Ma ZM, Teng LS, Wang M, Zheng SS (2005) Survival factors after resection of small hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 4:379–384

Yamada N, Shinzawa H, Ukai K, Wakabayashi H, Togashi H, Takahashi T, Seo N et al (1993) Subcutaneous seeding of small hepatocellular carcinoma after fine needle aspiration biopsy. J Gastroenterol Hepatol 8:195–198

Yamagata M, Masaki T, Okudaira T, Imai Y, Shiina S, Shiratori Y, Omata M (1999) Small hyperechoic nodules in chronic liver diseases include hepatocellular carcinomas with low cyclin D1 and Ki-67 expression. Hepatology 29:1722–1729

Yamamoto T, Ikebe T, Mikami S, Shuto T, Hirohashi K, Kinoshita H, Sakurai M (1996) Immunohistochemistry and angiography in adenomatous hyperplasia and small hepatocellular carcinomas. Pathol Int 46:364–371

Yamasaki S, Hasegawa H, Makuuchi M (1981) Clinicopathological observation of the minute liver cancer and the new methods of hepatectomy – analysis of 27 resected cases. Acta Hepatol Jpn 22:1714–1724

Yamashita Y, Tsuijita E, Takeishi K, Fujiwara M, Kira S, Mori M, Aishima S, Taketomi A et al (2012) Predictors for microinvasion of small hepatocellular carcinoma <= 2 cm. Ann Surg Oncol 19:2027–2034

Yoshida T, Okazaki N, Yoshino M, Kitaoka H, Hirohashi S, Shimozato Y (1982) Minute hepatocellular carcinoma without appreciable change in size for seven years: a case report. Cancer 19:1491–1495

Yoshino M (1983) Growth kinetics of hepatocellular carcinoma. Jpn J Clin Oncol 13:45–52

Yu YQ, Tang ZY, Zhou XD (1980) Experience in resection of small hepatocellular carcinoma. Chin Med J (Engl) 93:491–494

Yu JS, Lee JH, Chung JJ, Kim JH, Kim KW (2008) Small hypervascular hepatocellular carcinomas: limited value of portal and delayed phases of dynamic magnetic resonance imaging. Acta Radiol 49:735–743

Yu JS, Chung JJ, Kim JH, Kim KW (2009) Small hypervascular hepatocellular carcinomas; value of "washout' on gadolinium-enhanced dynamic MR imaging compared to superparamagnetic iron oxide-enhanced imaging. Eur Radiol 19:2614–2622

Yu MC, Lee YS, Lin SE, Wu HY, Chen TC, Lee WC, Chen MF, Tsai CN (2012) Recurrence and poor prognosis following resection of small hepatitis B-related hepatocellular carcinoma lesions are associated with aberrant tumor expression profiles of glypican 3 and osteopontin. Ann Surg Oncol 19(suppl 3):S455–S463

Zeppa P, Vetrani A, Palombini L, Chiacchio R, Zabatta A, De Sio I, Castellano L, Calandra M et al (1993) Evolution of DNA content in small and well-differentiated hepatocarcinoma. Anal Quant Cytol Histol 15:12–22

Zhang YJ, Chen MS (2010) Role of radiofrequency ablation in the treatment of small hepatocellular carcinoma. World J Hepatol 2:146–150

Zhaoyou T, Yegin Y, Zhiying L, Xinda Z, Binghui Y, Yunzhen C, Jizhen L, Chenlong T (1979) Small hepatocellular carcinoma: clinical analysis of 30 cases. Chin Med J (Engl) 92:455–462

Zhou XD, Tang ZY, Yu YQ, Ma ZC, Yang BH, Lu JZ, Lin ZY, Wang J (1991) Solitary minute hepatocellular carcinoma. A study of 14 patients. Cancer 67:2855–2858

Zhou YM, Yang JM, Li B, Yin ZF, Xu F, Wang B, Xu W, Kan T (2010) Risk factors for early recurrence of small hepatocellular carcinoma after curative resection. Hepatobiliary Pancreat Dis Int 9:33–37

Clear Cell Hepatocellular Carcinoma and Related Tumors

9

Contents

Abstract

Clear cell hepatocellular carcinoma (HCC) belongs to a growing spectrum of epithelial clear cell cancers of the alimentary tract. Morphologically, this neoplasm is characterized by a trabecular or solid growth of large cells with a clear cytoplasm. Due to varying diagnostic criteria, the epidemiology of clear cell HCC is complex, frequencies reported in the literature ranging from 0.4 % to 37 %. In case a clear cell component of at least 50 % is accepted, clear cell HCC accounts for 2.2–6.7 % of all HCCs. In contrast to ordinary HCC, females are more often involved, and antecedent liver cirrhosis is a common feature. Clear cell HCC usually presents as a large solitary tumor that shows a pseudocapsule more frequently than other HCCs. Histologically, the differential diagnosis between clear cell HCC and hepatic metastasis of other clear cell tumors may be difficult. Immunohistochemistry is an important diagnostic tool, most clear cell HCCs being positive for the hepatocyte/HCC markers, Hep Par 1 and arginase-1. Clear cell HCC appears to follow a more favorable course than ordinary HCC.+

Introduction

Hepatocellular carcinoma with clear cells (primary clear cell carcinoma of the liver, PCCCL; Liu et al. 2008) has been described in the early

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_9

literature under several and in part misleading names, including hypernephroid tumors and hepatic hypernephroma (Swenson 1917; Williams 1924; Ramsay 1929). Hepatic adrenal rest tumor appeared as a synonym of clear cell HCC in some reports, but this neoplasm seems to be a distinct entity and is dealt with in a separate chapter. Clear cell HCCs as they appear in hematoxylin- and eosin-stained sections have first been reported in 1937 (Bonne 1937). This phenotype later appears in several works (Berman 1951, 1958; Edmondson 1958), until a first series of 13 cases was systematically analyzed (Buchanan and Huvos 1974).

Clear cell HCCs make part of an increasing spectrum of epithelial clear cell tumors of the alimentary tract (Nappi et al. 1997; Ritter et al. 1997), which mainly comprise gastric clear cell carcinomas (pylorocardiac gland cell carcinoma; tubulopapillary clear cell gastric carcinoma, TCCGC), clear cell carcinomas of the bowel, pancreatic epithelial malignancies composed of clear cells, clear cell carcinomas of the hepatobiliary tract, and clear cell well-differentiated neuroendocrine carcinomas (review: Ritter et al. 1997).

Large Clear Cell Hepatocellular Carcinomas

Epidemiology

The epidemiology of clear cell HCC is complex, because the diagnostic criteria employed vary considerably from one study to the other. Thus, the frequency of large clear cell HCC varies in the literature between 0.4 % and 37 % in the largest published series (Lai et al. 1979; Kashala et al. 1990). Some authors have diagnosed this HCC variant when the tumor contained more than 30 % clear cells (Buchanan and Huvos 1974), whereas others considered less than 30 % of clear cells within a given tumor as sufficient for diagnosis (Lai et al. 1979). It seems that tumors entirely composed of clear cells are very rare (Buchanan and Huvos 1974; Pecorella et al. 1994). In case one accepts that the proportion of clear cells must at least be 50 %, clear cell HCC accounts for only 2.2–6.7 % of all HCCs. The diagnosis also depends on what is accepted to be a clear cell (see below). Therefore, clear cell HCC still awaits a reproducible diagnostic definition.

In one series, less than 10 % of HCC showed a clear cell component, but these cases revealed a slightly older mean age of the patients and a male/female ratio of 1.6:1, which is lower than the worldwide ratio of 6.7:1 for ordinary HCC (Buchanan and Huvos 1974). Among 118 cirrhotic patients with HCC, 10 patients (8.5 %) were reported to have clear cell HCC (Emile et al. 2001). In a recent series of 43 patients, the mean age at presentation was 53.6 years, and the male/female ratio was 2.9:1. 30.2 % of the tumors were in the left, 60.5 % were in the right liver lobe, and 9.3 % were bilateral (Liu et al. 2008). In a series from East Asia, 12.5 % of the cases studied were diffuse clear cell HCC (Lai et al. 1979). Among 223 sub-Saharan African HCC cases (from the then Zaire), the clear cell variant accounted for less than 1 % (Kashala et al. 1990). In an autopsy study of 287 HCCs in Hong Kong, there was a significantly higher incidence of bilobar involvement in clear cell HCC (Ho et al. 1981). In one instance, clear cell HCC was detected as a metastasis (Sister Mary Joseph's nodule) in the presence of an occult hepatic primary tumor (Shah et al. 2005).

In a clinicopathologic study of clear cell HCC, such lesions were more often associated with female gender, and antecedent cirrhosis was commoner than that seen with other carcinomas of the liver (90 % vs. 59 %) (Yang et al. 1996). However, the tumor has also been observed in non-cirrhotic livers (Mansinho et al. 1993; Adamek et al. 1998; Takahashi et al. 2008; Clayton et al. 2012). In a clinicopathologic study of 43 patients with clear cell HCC treated with hepatectomy (Liu et al. 2008), there was a positive rate of hepatitis C virus infection and capsule formation in the clear cell HCC group, higher than in common

HCC. On the other hand, the vascular invasion rate was notably lower in the clear cell HCC group. There are very few associations of clear cell HCC with other liver tumors. The lesion has been found to arise 25 years after successful treatment of hepatoblastoma (Basile et al. 2010).

Clinical and Imaging Features

The most common clinical presentation of clear cell HCC is similar to that of ordinary HCC. The clear cell variant is most often associated with liver cirrhosis. Similar to ordinary HCC, clear cell carcinoma can undergo tumor rupture, a complication observed in up to 15 % of cases (Liu et al. 2011). Several and extremely rare metabolic and hormonal disorders complicating clear cell HCC have been reported, albeit only in older publications. Hypoglycemia is a known paraneoplastic complication of HCC. In few cases of clear cell HCC, the tumors were clinically associated with hypoglycemia and hypercholesterolemia (Sasaki et al. 1981; Antoniello et al. 1986). A similar observation referred to a clear cell HCC in a patient who also showed erythrocytosis in addition to hypercholesterolemia and hypoglycemia, the latter having caused sudden death (Ross and Kurian 1985).

At imaging, clear cell HCC was more prone to form a pseudocapsule (Liu et al. 2011; Wang et al. 2014). On pre-contrast CT images, clear cell HCC showed slight hyperattenuation with a hypoattenuation halo, while at hepatic arterial phase, the mass showed early enhancement. Typical HCC enhancement patterns were found in 72.2 % of clear cell HCC in one series (Liu et al. 2011). At the equilibrium phase, the mass presented hypoattenuation with a rim enhancement. On MR images, the tumors were slightly hypointense on T1-weighted images (Liu et al. 2011). On T1-weighted sequences, the tumors are usually well circumscribed, sometimes with a high-intensity part inside, and the tumor may appear as a high-intensity lesion on T2-weighted images (Takahashi et al. 2008).

Pathology

Macroscopy

Grossly, clear cell HCCs usually present as solitary and sometimes large tumors. In the series of Liu and coworkers (2008), 74.4 % of 43 tumors were solitary/single lesions, and their diameter ranged from 2.1 to 22.3 cm (median, 6 cm), and only 37.2 % had a diameter of 5 cm or less than 5 cm. In this study, capsule formation was a prominent feature, observed in 88.4 % of the tumors. In a study of 20 cases, clear cell HCCs were also more prone to form pseudocapsules in comparison with ordinary HCCs (75 % vs. 49.6 %; Liu et al. 2011). The macroscopic growth pattern is not yet sufficiently clarified. In the study of Buchanan and Huvos (1974; $N = 13$), extensive replacement of hepatic parenchyma by invasive carcinoma was the most consistent finding. However, on section tumors tended to closely resemble conventional HCC. The color is described as gray to pale tan, yellow coloration being exceptional (Buchanan and Huvos 1974).

Histopathology

Microscopically, the clear cell phenotype is the hallmark, although the proportion of these cells varies from one tumor to the other. Lai and coworkers suggested that the diagnosis of this neoplasm can be made even when the proportion of clear cells is less than 30 % (Lai et al. 1979), whereas Buchanan and Huvos (1974) proposed that a proportion of more than 30 % is required. Today, there is agreement that diagnosis requires that the proportion of clear cells must be 50 % or more (Kida et al. 2012). Among 175 surgical specimens of HCC, 79 (45.1 %) showed varying amounts of clear cells (Wang and Liu 1986). According to the proportion and distribution of these cells, the authors divided clear cell HCC into three types: (a) scattered type (20.3 %), (b) localized type (54.4 %), and (c) diffuse type (25.3 %). Clear cells were detectable in HCCs of variable differentiation grades, i.e., not restricted to either

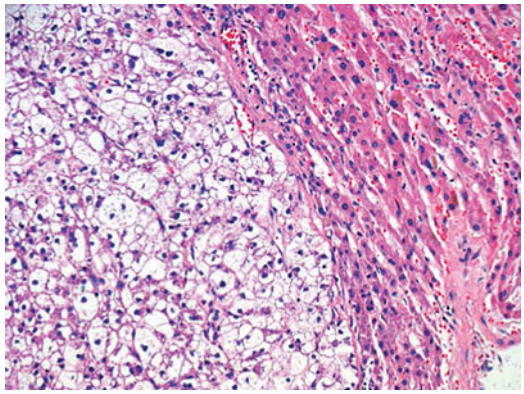

Fig. 1 Hepatocellular carcinoma, clear cell type. Tumor cells are larger than normal hepatocytes and display a water-clear and sometimes slightly spongy cytoplasm and rather small nuclei. The present tumor shows an expanding growth pattern and is associated with perifocal parenchymal atrophy (hematoxylin and eosin stain)

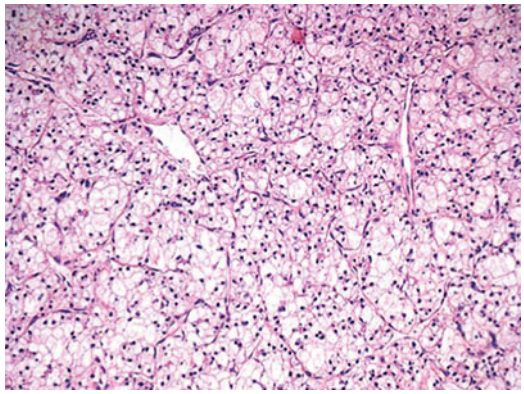

Fig. 2 Hepatocellular carcinoma, clear cell type. Most of these neoplasms exhibit as trabecular or solid growth pattern (hematoxylin and eosin stain)

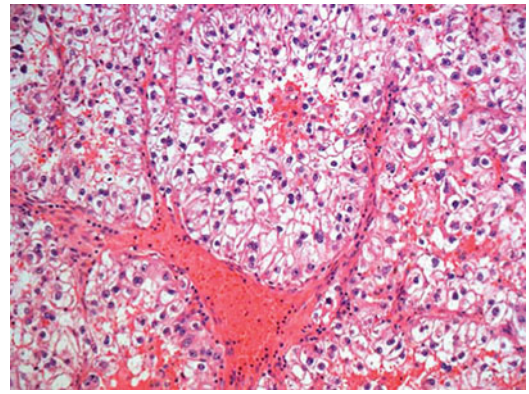

Fig. 3 Clear cell hepatocellular carcinoma. At higher magnification, the trabecular growth pattern is readily observed (hematoxylin and eosin stain)

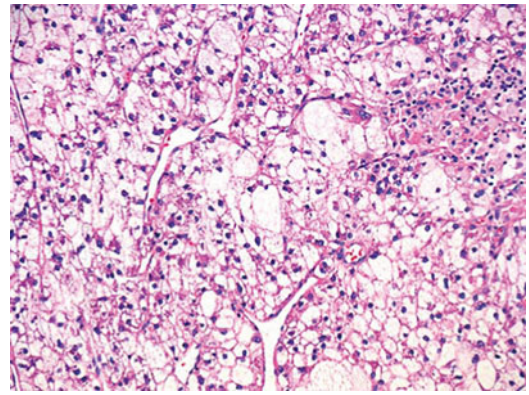

Fig. 4 In clear cell hepatocellular carcinoma, part of neoplastic cells may undergo marked ballooning followed by cell death and karyopyknosis (*center of figure*; hematoxylin and eosin stain)

well, moderately, or poorly differentiated tumors, although in one series of 18 cases, no grade 4 lesion was found in the set of clear cell HCCs (Lao et al. 2006). The clear cells are arranged, similar to ordinary HCC, in trabecular, acinar, or compact patterns (Figs. 1, 2, 3, 4, and 5).

The morphology of individual clear cells varies from apparently empty cytoplasm ("water-clear cells") to vacuolated cells and to foamy cells with a microvesicular pattern. These clear cells may be intermingled with cells that have an eosinophilic to granular cytoplasm. The cells are usually polygonal and may show a fine, granular condensation of cytoplasm, particularly adjacent to the cell membrane (Lao et al. 2006). Nuclei are often centrally placed, but larger lipid droplets may dislocate the nucleus to the cell's periphery. In tumors with variable contributions of clear cells, these cells are often scattered intimately among conventional tumor hepatocytes. The cellular features of clear cell HCC are also detectable in cytological diagnosis of this tumor (Yazdi 1985; Donat et al. 1991; Gupta et al. 1994; Singh et al. 1997; Kilinç et al. 2003). In tumors where the clear cell phenotype is chiefly caused by glycogen accumulation, the cells strongly stain with PAS (Wang and Liu

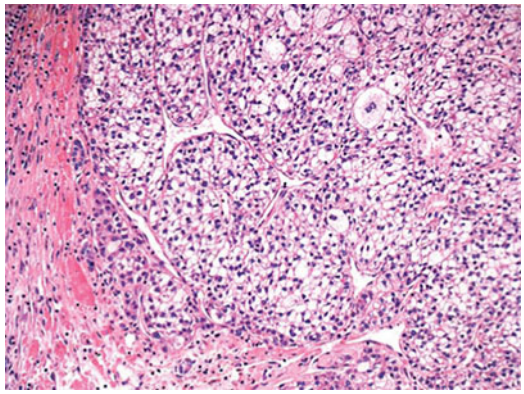

Fig. 5 Notwithstanding their differentiation, clear cell hepatocellular carcinomas show an invasive behavior, with infiltration of adjacent tissues (*left lower corner*; hematoxylin and eosin stain)

1986), the staining being mostly abolished after digestion. Apart from glycogen, lipids are reported to contribute to the clear cytoplasmic phenotype (Lao et al. 2006.

Ultrastructure

Some cases of clear cell HCC have been studied by the use of electron microscopy (Isomura and Nakashima 1980; Audisio et al. 1987; Wang and Liu 1986; Lapis 1988; Kwon et al. 1996; Clayton et al. 2012). In the largest series (seven patients; Audisio et al. 1987), the clear cell phenotype was ultrastructurally found to be caused by accumulation of excess glycogen and lipid droplets, a phenomenon also observed in another study and compared to what is found in precursor lesions of HCC (Wu et al. 1983; see above). In part of the cases, the cytoplasm of the HCC cells had fewer organelles, leading to void appearance, the rough endoplasmic reticulum was rarefied, and mitochondria were swollen. Mitochondria frequently aggregated on one side of the nucleus or near the cell membrane (Wang and Liu 1986). In an investigation of diverse types of clear cell carcinomas, it was found that, in addition to glycogen and/or lipid storage, cell swelling with dilated endoplasmic cisternae, formation of intracellular vacuoles, intracytoplasmic lumens, and organelle paucity are involved in the generation of a clear cell phenotype (Kwon et al. 1996).

Immunohistochemistry

In published cases and series, clear cell HCC lacked expression of cytokeratin 7 (with very few exceptions), of cytokeratin 19, and of epithelial membrane antigen (EMA) (Adamek et al. 1998; Leroy et al. 1998; Murakata et al. 2000; Clayton et al. 2012). In a study of ten cases, no tumor showed immunoreactivity for AFP (Murakata et al. 2000). Distinguishing primary clear cell HCC from hepatic metastases of other clear cell carcinomas may be very difficult and sometimes impossible without additional examinations. Immunohistochemical reactivity for a hepatocyte marker (hepatocyte paraffin 1/Hep Par 1) may be helpful in such situations (Murakata et al. 2000; Shah et al. 2005). Hep Par 1 alone was reported to be 82 % sensitive and 90 % specific in detecting HCC (Wennerberg et al. 1993; Minervini et al. 1997). Clear cell HCC is also reactive for the lineage marker, arginase-1 (Sang et al. 2013). In more than half of the cases of clear cell HCC, canalicular membrane immunostaining was found by the use of a polyclonal CEA (pCEA) antibody (Murakata et al. 2000).

Stromal reactions in clear cell HCC occur to variable degrees, similar to other HCCs, but not much is known about extracellular matrix proteins in these tumors. Fibronectin seems to show abnormal expression in HCC (Torbenson et al. 2002). When testing the expression pattern of fibronectin in HCCs by the use of immunohistochemistry, a marked increase of fibronectin was seen in fibrolamellar HCC, clear cell HCC, and encapsulated HCC (Jagirdar et al. 1985).

Cytogenetic and Molecular Features

In regard to cytogenetic and molecular features, the data for clear cell HCCs are still sparse. In one investigation, 11 cases of clear cell HCC were evaluated for DNA ploidy by means of image

analysis of Feulgen-stained tissue sections. 45.4 % of the tumors analyzed were diploid, and 54.5 % were non-diploid (four aneuploid, one tetraploid, and one multiploid). The non-diploid tumors displayed a moderate to severe degree of pleomorphism and a high mitotic rate (Orsatti et al. 1994). The authors suggested that the divergent data in the literature relating to biology of disease and outcome may be caused by aggressive features of a subset of these lesions.

Biology of Disease

The biology of disease of clear cell HCC is incompletely known so far, but it emerges that the biology of disease is more favorable in patients with clear cell HCC than in those with ordinary HCC (Li et al. 2011, 2013). Some early reports already suggested that the tumor seldom metastasizes and therefore has a rather favorable prognosis (Wu et al. 1983; Pecorella et al. 1994), but metastases known for ordinary HCC, such as bone metastases, are known to occur (Liu et al. 2004), sometimes with an occult hepatic primary tumor (Shah et al. 2005). In a systematic study of prognostic indicators in HCC, it was found that there was a better survival for the patients with clear cell HCC and that the survival figures are directly correlated with the proportion of clear cells within the tumor (Lai et al. 1979). Clear cell HCC may show spontaneous regression of metastases (McDermott and Khettry 1994) or synchronous regression of primary tumor and metastases (Jeon et al. 2005), associated with long-term survival, but spontaneous tumor regression is also known for other types of HCC (Lin et al. 2004). In a study of 64 patients, the median survival in the group having curative surgery was 38 months, while the group with curative resection plus postoperative chemotherapy with calcium folinate and tegafur had a median survival of 41 months. Capsule formation, preoperative liver function, hepatitis C virus infection, large vessel invasion, and multiple tumor recurrences were related to disease-free survival (Ji et al. 2010). Li and coworkers (2011) reported on a total of 214 clear cell HCCs treated by curative resection, and intrahepatic recurrences were classified into early ($\leq$1 year) and late (>1 year) recurrences. It was found that the 1-, 3-, and 5-year overall survival for patients with this tumor were significantly better than those of ordinary HCC patients. A similar result was reported in an alter investigation showing that clear cell HCCs have a favorable grade and longer survival times (Li et al. 2014). In a multivariate analysis, serum ALT and vascular invasion were independent risk factors for early intrahepatic recurrence, while age was the only significant risk factor for late intrahepatic recurrence (Li et al. 2011). In a recent clinicopathologic study of 43 cases, the Kaplan-Meier method showed that the 1-, 3-, and 5-year survival rates were significantly higher in the clear cell HCC group than in common HCC, and the better prognosis of clear cell HCCs was related to capsule formation, vascular invasion, liver cirrhosis, and clear cell ratio, higher clear cell ratios being a prognosticator for better outcome (Liu et al. 2008). In an investigation of 20 clear cell HCCs, no signs of lymph node metastasis were found (Liu et al. 2011). Other studies could not confirm a better outcome of patients with this lesion. An aggressive course of clear cell HCC with rapidly progressive disease has been reported (Audisio et al. 1987; Pecorella et al. 1994). A study of a larger series of patients with clear cell HCC ($N = 215$) documented a worse postoperative 5-year survival for this tumor type, i.e., 33 % vs. 46 % for conventional HCC (Yang et al. 1996). However, there was no difference in the overall long-term prognosis of clear cell HCC when compared with non-clear cell HCC. A similar biology of the two groups was also found in other studies (Kishi et al. 1983; Emile et al. 2001; Lao et al. 2006; Ye et al. 2010).

Small Hepatocellular Carcinomas with Clear Cell Change

In a series of 20 cases of clear cell HCC, small HCCs (diameter 3 cm or less) were found in 25 % (Liu et al. 2011). In a study of 44 small HCCs

defined as lesions with a diameter equal to or smaller than 5 cm, tumor recurrence did not correlate with the presence of clear cells (Hsu et al. 1985).

Clear Cell Formation in Precursor Lesions of Hepatocellular Carcinoma

In rat models of chemical hepatocarcinogenesis, at least four types of altered hepatocytes were recognized in foci of altered hepatocytes (FAH) and neoplastic liver nodules, i.e., clear glycogen storage cells, acidophilic glycogen storage cells, fat-storing cells, and basophilic cells (Bannasch 1976, 1996). A focal excessive storage of glycogen (focal glycogenosis) is a typical step of the sequence of events leading to liver cell neoplasia (Bannasch et al. 1997, 2003) and illustrates that massive glycogen accumulation is a cause of a clear cell phenotype also in HCC precursors. Clear cell foci have also been identified in human livers, lesions resembling those found in rats (Ribback et al. 2013). Electron microscopically, such lesions are characterized by massive glycogen storage, largely due to the reduced activity of the glycogenolytic enzyme, glucose-6-phosphatase. Hepatocytes in human clear cell foci overexpressed the insulin receptor and glucose transporter proteins. The cells exhibited upregulation of AKT/mTOR and Ras/MAPK pathways as well as enzymes of glycolysis, de novo lipogenesis, beta-oxidation, and cholesterol synthesis (Ribback et al. 2013).

Clear Cell Hepatocellular Carcinomas with Marked Stromal Reactions

In some instances, the clear cell variant of HCC is associated with a marked desmoplastic reaction (Buchanan and Huvos 1974). A clear cell HCC with an abundant myxoid stroma was observed in a 55-year-old man who had died of liver cancer (Fukuda et al. 1992). Autopsy revealed a large hepatic tumor located in the right lobe (10 ×10 × 8 cm) and metastatic nodules with a prominent myxoid appearance in multiple organs. Histologically, each tumor manifestation consisted of uniform small tumor cells with clear cytoplasm attributed to abundant accumulation of glycogen, and a rich myxoid stroma was also present. In addition to tumor cells, fibroblastoid cells and stellate cells were found within the myxoid substance. Some of these cells possessed a vacuolated cytoplasm showing similar histochemical findings to the tumor cells. Tumor cells within the myxoid stroma were immunoreactive for fibrinogen, ferritin, and prealbumin.

Clear Cell Variant of Fibrolamellar Hepatocellular Carcinoma

Fibrolamellar hepatocellular carcinoma (FL-HCC) is usually characterized by large and polygonal neoplastic cells that exhibit an eosinophilic and granular, sometimes even oncocytic-looking cytoplasm. Very uncommonly, the cells in FL-HCC have shown a clear cell phenotype (Cheuk and Chan 2001). The tumor described by these authors was incidentally detected in the non-cirrhotic liver of a 59-year-old female patient. The tumor measured up to 5 cm and was a predominantly circumscribed, bosselated, and firm mass situated in the subcapsular area of the right liver lobe. It was light tan and interspersed with concentric whitish streaks on the cut surface. Microscopically, the neoplasm consisted of the typical fibrolamellar structures and small islands of polygonal cells with either the classical FL-HCC phenotype or an abundant, clear, and finely reticular cytoplasm (about 50 % of the cells) highlighted by trichrome stain and immunostaining with an antimitochondrial antibody. The peculiar concentric streaks observed at gross examination were due to coalesced zones of fibrosis, with the collagen fibers being oriented radially. Ultrastructurally, the cytoplasm of the clear cells was packed with empty membrane-bound vesicles that occasionally contained short cristae. These features suggested that the clear cell phenotype resulted from ballooning and rarefactive changes of mitochondria. Clear cell FL-HCC has later been confirmed, also by aspiration cytology (Kaplan and Hoda 2007).

Differential Diagnosis of Clear Cell HCC

Clear cell HCC has to be distinguished from other primary liver tumors characterized by the presence of clear cells, including intrahepatic clear cell cholangiocarcinoma and other clear cell bile duct cancers (Vardaman and Albores-Saavedra 1995; Haas et al. 2007), clear cell papillary carcinoma of the liver (a variant of peripheral cholangiocarcinoma; Tihan et al. 1998), atypical bile duct adenoma, clear cell type (Albores-Saavedra et al. 2001), and variants of angiomyolipoma and other PEComas, including clear cell "sugar" tumors of the liver (Alexandrakis and Kling 1998; Dalle et al. 2000; Chen et al. 2009; Figs. 6 and 7).

A second group of important differential diagnosis comprises metastases of extrahepatic tumors having a clear cell component, such as renal cell carcinomas and clear cell neuroendocrine tumors. These tumors can be distinguished by their different nuclear and cytoplasmic features, by immunohistochemistry and by in situ hybridization, e.g., for albumin messenger RNA (Oliveira et al. 2000). Clear cell HCC may erroneously be interpreted as hepatic metastases of renal cell carcinoma (Hou et al. 2010). Clear cell gallbladder carcinoma was reported to invade the liver substance (Vaillo et al. 2004) and may thus mimic primary hepatic clear cell HCC. Primary peritoneal clear cell carcinoma is a rare entity (Hama et al. 2004) that may involve the liver surface.

Pathogenesis of Clear Cells in HCC

A clear cell change (cytoplasmic clearing; Cheuk and Chan 2001) develops in many different tumor types and is caused by cellular edema with or without organelle damage (ballooning), accumulation of cytoplasmic vesicles, glycogen storage, storage of lipids/glycolipids and/or glycoproteins, organelle (mainly mitochondrial) swelling, or tissue-processing artifacts (Kwon et al. 1996). In clear cell HCC, it has been suggested to be an epigenetic phenomenon, because no genomic changes were found to distinguish it from ordinary HCC (Laurent et al. 2006).

The observation that clear cell formation in clear cell HCCs and other clear cell carcinomas is associated with cellular swelling, vacuole formation, dilated cisternae, and paucity of organelles – features also encountered in hepatocyte ballooning – favors the hypothesis that a disorder of cellular water transport might be involved. The classical role of aquaporins, which are expressed in numerous tissues, including the hepatobiliary tract (review Portincasa et al. 2008), is facilitating transmembrane fluid transport and, for some

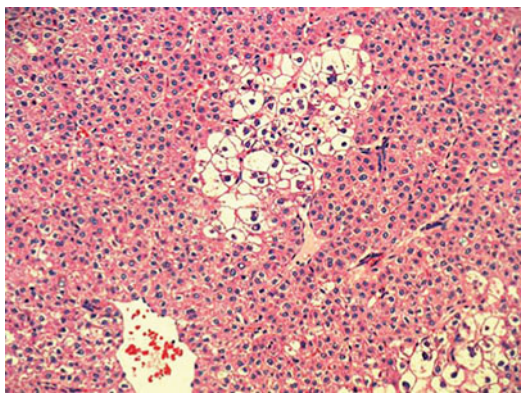

Fig. 6 Ordinary hepatocellular carcinoma rarely contains small foci of clear tumor cells. It is not yet known whether these are precursor lesions of clear cell HCC (hematoxylin and eosin stain)

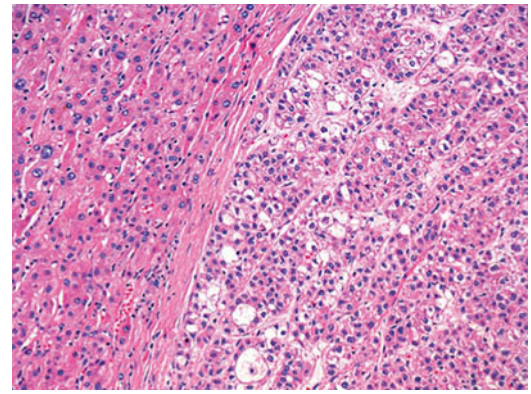

Fig. 7 This trabecular hepatocellular carcinoma contains few enlarged cells with clear cytoplasm and condensed nuclei. These cells represent tumor cell ballooning as a regressive phenomenon and must not be confounded with clear cell type HCC (hematoxylin and eosin stain)

aquaporins, the transport of small solutes such as glycerol. Thirteen aquaporins are known in mammals (aquaporins AQP0–AQP12), and they are subdivided in orthodox aquaporins (AQP0–AQP2, AQP4, and AQP5) and in aquaglyceroporins (the types 3, 7, 9, and 10) which enable the transport of glycerol as well as water. AQP6, AQP8, AQP11, and AQP12 are hardly classified within the above two main groups. AQP6 has permanent intracellular localization and has very low water permeability and shows conductance to inorganic ions upon acidic pH. AQP8 can act as a gate for ammonia and hydrogen peroxide in addition to water. Aquaporins 7 and 9 are glycerol channels in adipocytes and hepatocytes, aquaporin 9 being expressed at the basolateral membrane of the hepatocyte (review: Maeda et al. 2008). AQP9 knockout mice display defective glycerol metabolism (Rojek et al. 2007).

Potentially important for clear cell formation not related to glycogen storage is the fact that aquaporins are also involved in swelling of cells under stress (Verkman 2005).

Some aquaporins affect apoptotic pathways which are associated with organelle swelling. AQP8 and AQP9 have been identified in the inner mitochondrial membrane of various tissues, including the liver, where they mediate water transport associated with organelle and cell volume changes and participate in osmotic swelling induced by apoptotic stimuli (review: Lee and Thövenod 2006). Aquaporins facilitate cell migration, possibly related to facilitated water transport in lamellipodia (reviews: Verkman 2005; Papadopoulos et al. 2008). Aquaporins are involved in several pathologic mechanisms operational in cancer cells and tissues (Verkman et al. 2008), including the facilitation of tumor angiogenesis, endothelial cell migration, tumor cell extravasation, and metastatic spread. AQP0, AQP1, AQP3, AQP8, AQP9, and AQP11 are expressed in liver tissue, and AQP1 and AQP4 are expressed in intrahepatic bile ducts (review Portincasa et al. 2008). In hepatocytes, knockdown of hepatocyte AQP8 induces defective canalicular water transport (Larocca et al. 2009), suggesting that this aquaporin has a central role in hepatocytic water handling. On the other hand, obstructive extrahepatic cholestasis in the rat downregulates AQP9 at the basolateral hepatocyte domain, suggesting that AQP9 channels contribute to bile flow regulation (Calamita et al. 2008). Expression of aquaporin 1, a water channel protein expressed in many epithelial lineages and in endothelium, has been found to be expressed more frequently in clear cell renal cell carcinomas than in other renal cell carcinoma phenotypes and to be a prognostic indicator in clear cell renal cell carcinoma (Huang et al. 2009). It has been suggested that AQP1 is involved in the pathogenesis of certain hepatobiliary disorders, including neoplasias. In an immunohistochemical study, AQP1 staining was detected in 93 % of cholangiocarcinomas compared with 0 % in hepatocellular carcinomas and 30 % in colorectal carcinoma metastases, suggesting that expression of AQP1 is a marker for a differentiated cholangiocellular lineage (Mazal et al. 2005). AQP1 is downregulated in a subset of intrahepatic cholangiocarcinoma, and the downregulation is related to tumor progression and mucin (mucus core protein 5 AC) expression (Aishima et al. 2007). AQP8 and AQP9 expression is significantly decreased in HCC vs. normal liver, leading to increased resistance to apoptosis (Jablonski et al. 2007).

Glycogenotic Hepatocellular Carcinoma with Glycogen-Ground-Glass Hepatocytes

Introduction

Glycogenotic hepatocellular carcinoma with glycogen-ground-glass hepatocytes (GLY-HCC) is a novel phenotype of highly differentiated HCC cytologically and histologically characterized by the presence of glycogen-rich tumor cells with a ground-glass cytoplasm (Callea et al. 2012; Fig. 8).

Glycogenotic ground-glass hepatocytes are also observed in distinct populations of focal precancerous hepatocellular lesions, particularly in preneoplastic focal hepatic glycogenosis/FHG (recent review: Bannasch 2012).

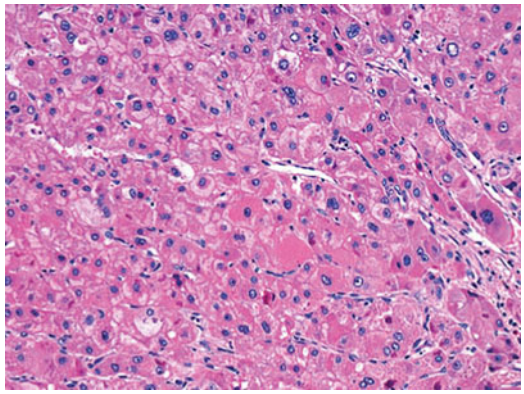

Fig. 8 Hepatocellular carcinoma with glycogen-ground-glass hepatocytes, visualized as large cells with a granular eosinophilic cytoplasm (hematoxylin and eosin stain)

Pathology

GLY-HCC are well-differentiated trabecular HCC with numerous large, glycogen-rich neoplastic cells with a ground-glass cytoplasm, these cells in part admixed with clear cells without a ground-glass cytoplasm (Callea et al. 2012) and eventually "standard" HCC cells. By microchemical analysis, complete deficiency of glucose-6-phosphatase activity was observed in the tumor cells (Callea et al. 2012).

Differential Diagnosis

The clear cell component has to be distinguished from the entity, clear cell HCC. Glycogen storage in HCC can be caused by enzymatic defects of glycogen metabolism (Christiansen et al. 1968).

References

Adamek HE, Spiethoff A, Kaufmann V, Jakobs R, Riemann JF (1998) Primary clear cell carcinoma of noncirrhotic liver: immunohistochemical discrimination of hepatocellular and cholangiocellular origin. Dig Dis Sci 43:33–38

Aishima S, Kuroda Y, Nishihara Y, Taguchi K, Iguchi T, Taketomi A, Maehara Y, Tsuneyoshi M (2007) Down-regulation of aquaporin-1 in intrahepatic cholangiocarcinoma is related to tumor progression and mucin expression. Hum Pathol 38:1819–1825

Albores-Saavedra J, Hoang MP, Murakata LA, Sinkre P, Yaziji H (2001) Atypical bile duct adenoma, clear cell type: a previously undescribed tumor of the liver. Am J Surg Pathol 25:956–960

Alexandrakis E, Kling O (1998) Clear cell tumor of the liver – morphological spectrum and pathogenesis. Verh Dtsch Ges Path 82:460–468

Antoniello S, Auletta M, Cigolari S, Vecchione R, Cacciatore L (1986) Hepatocarcinoma associated with hypoglycemia and LDL hypercholesterolemia (in Italian). Minerva Dietol Gastroenterol 32:79–85

Audisio RA, Bombelli L, Lombardi L, Andreola S (1987) A clinicopathologic study of clear-cell hepatocellular carcinoma. Tumori 73:389–395

Bannasch P (1976) Cytology and cytogenesis of neoplastic (hyperplastic) hepatic nodules. Cancer Res 36:2555–2562

Bannasch P (1996) Pathogenesis of hepatocellular carcinoma: sequential cellular, molecular, and metabolic changes. Prog Liver Dis 14:161–197

Bannasch P (2012) Glycogenotic hepatocellular carcinoma with glycogen-ground-glass hepatocytes: a heuristically highly relevant phenotype. World J Gastroenterol 18:6701–6708

Bannasch P, Klimek F, Mayer D (1997) Early bioenergetic changes in hepatocarcinogenesis: preneoplastic phenotypes mimic responses to insulin and thyroid hormone. J Bioenerg Biomembr 29:303–313

Bannasch P, Haertel T, Su Q (2003) Significance of hepatic preneoplasia in risk identification and early detection of neoplasia. Toxicol Pathol 31:134–139

Basile J, Caldwell S, Nolan N, Hammerle C (2010) Clear cell hepatocellular carcinoma arising 25 years after the successful treatment of an infantile hepatoblastoma. Ann Hepatol 9:465–467

Berman C (1951) Primary carcinoma of the liver: a study in incidence, clinical manifestations, pathology, and etiology. H.K. Lewis and Co., London, pp 61–62

Berman C (1958) Primary carcinoma of the liver: a pathological study of 43 cases treated at New York City Memorial Center of Cancer and Allied Diseases, and a comparison with Bantu cases in Southern Africa. Unpublished data, cited in Buchanan and Huvos, 1974

Bonne C (1937) Cancer and human races. Am J Cancer 30:435–454

Buchanan TF, Huvos AG (1974) Clear-cell carcinoma of the liver. A clinicopathologic study of 13 patients. Am J Clin Pathol 61:529–539

Calamita G, Ferri D, Gena P, Carreras FI, Liquori GE, Portincasa P, Marinelli RA, Svelto M (2008) Altered expression and distribution of aquaporin-9 in the liver of rat with obstructive extrahepatic cholestasis. Am J Physiol Gastrointest Liver Physiol 295:G682–G690

Callea F, Giovannoni I, Stefanelli M, Villanacci V, Lorini G, Francalanci P (2012) Glycogenotic hepatocellular carcinoma with glycogen-ground-glass hepatocytes: histological, histochemical and microbiochemical characterization of the novel variant. Histopathology 60:1010–1012

Chen P, Yuan T, Liu H (2009) Hepatic angiomyolipoma mimicking hepatic clear cell carcinoma. J Int Med Res 37:257–263

Cheuk W, Chan JK (2001) Clear cell variant of fibrolamellar carcinoma of the liver. Arch Pathol Lab Med 125:1235–1238

Christiansen RO, Page LA, Greenberg RE (1968) Glycogen storage in a hepatoma: dephosphophosphorylase kinase defect. Pediatrics 42:694–696

Clayton EF, Furth EE, Ziober A, Xu T, Yao Y, Hwang PG, Bing Z (2012) A case of primary clear cell hepatocellular carcinoma in a non-cirrhotic liver: an immunohistochemical and ultrastructural study. Rare Tumors 4: e29

Dalle I, Sciot R, De Vos R, Aerts R, Van Damme B, Desmet V, Roskams T (2000) Malignant angiomyolipoma of the liver: a hitherto unreported variant. Histopathology 36:443–450

Donat EE, Anderson V, Tao LC (1991) Cytodiagnosis of clear cell hepatocellular carcinoma. A case report. Acta Cytol 35:671–675

Edmondson HA (1958) Tumors of the liver and intrahepatic bile ducts. Armed Forces Institute of Pathology, Washington, DC

Emile JF, Lemoine A, Azoulay D, Debuire B, Bismuth H, Reynès M (2001) Histological, genomic and clinical heterogeneity of clear cell hepatocellular carcinoma. Histopathology 38:225–231

Fukuda T, Ohnishi Y, Miyazaki Y, Ohnuki K, Tachikawa S (1992) Clear cell hepatocellular carcinoma with abundant myxoid stroma. Acta Pathol Jpn 42:897–903

Gupta RK, Al Ansari AG, Fauck R (1994) Aspiration cytodiagnosis of clear cell hepatocellular carcinoma in an elderly woman. A case report. Acta Cytol 38:467–469

Haas S, Gütgemann I, Wolff M, Fischer HP (2007) Intrahepatic clear cell cholangiocarcinoma: immunohistochemical aspects in a very rare type of cholangiocarcinoma. Am J Surg Pathol 31:902–906

Hama Y, Iwasaki Y, Sakata I, Kusano S (2004) Primary peritoneal clear cell carcinoma. J Comput Assist Tomogr 28:617–619

Ho J, Wu PC, Kung TM (1981) An autopsy study of hepatocellular carcinoma in Hong Kong. Pathology 13:409–416

Hou TC, Wu CC, Yang CR, Wang J (2010) Synchronous renal cell carcinoma and clear cell hepatocellular carcinoma mimicking metastatic disease. Pathol Res Pract 206:342–345

Hsu HC, Sheu JC, Lin YH, Chen DS, Lee CS, Hwang LY, Beasley RP (1985) Prognostic histologic features of resected small hepatocellular carcinoma (HCC) in Taiwan. A comparison with resected large HCC. Cancer 56:672–680

Huang Y, Murakami T, Sano F, Kondo K, Nakaigawa N, Kishida T, Kubota Y, Nagashima Y, Yao M (2009) Expression of aquaporin 1 in primary renal tumors: a prognostic indicator for clear-cell renal cell carcinoma. Eur Urol 56:690–698

Isomura T, Nakashima T (1980) Ultrastructure of human hepatocellular carcinoma. Acta Pathol Jpn 30:713–726

Jablonski EM, Mattocks MA, Sokolov E, Koniaris LG, Hughes FM, Fausto N, Pierce RH, McKillop IH (2007) Decreased aquaporin expression leads to increased resistance to apoptosis in hepatocellular carcinoma. Cancer Lett 250:36–46

Jagirdar J, Ishak KG, Colombo M, Brambilla C, Paronetto F (1985) Fibronectin patterns in hepatocellular carcinoma and its clinical significance. Cancer 56:1643–1648

Jeon SW, Lee MK, Lee YD, Seo HE, Cho CM, Tak WY, Kweon YO (2005) Clear cell hepatocellular carcinoma with spontaneous regression of primary and metastatic lesions. Korean J Intern Med 20:268–273

Ji SP, Li Q, Dong H (2010) Therapy and prognostic features of primary clear cell carcinoma of the liver. World J Gastroenterol 16:764–769

Kaplan JS, Hoda RS (2007) Clear cell variant of fibrolamellar carcinoma: diagnosis of recurrence by fine-needle aspiration. Diagn Cytopathol 35:459–462

Kashala LO, Conne B, Kalengayi MM, Kapanci Y, Frei PC, Lambert PH (1990) Histopathologic features of hepatocellular carcinoma in Zaire. Cancer 65:130–134

Kida K, Oida T, Mimatsu K, Kano H, Kawasaki A, Fukino N, Kuboi Y (2012) Hand-assisted laparoscopic hepatectomy for primary clear cell hepatocellular carcinoma of the liver. Case Rep Gastroenterol 6:328–332

Kilinç N, Yalçin K, Degertekin H, Ozaydin M (2003) Clear cell carcinoma of the liver: a case report. Turk J Gastroenterol 14:211–214

Kishi K, Shikata T, Hirohashi S, Hasegawa H, Yamazaki S, Makuuchi M (1983) Hepatocellular carcinoma. A clinical and pathologic analysis of 57 hepatectomy cases. Cancer 51:542–548

Kwon TJ, Ro JY, Mackay B (1996) Clear-cell carcinoma: an ultrastructural study of 57 tumors from various sites. Ultrastruct Pathol 20:519–527

Lai CI, Wu PC, Lam KC, Todd D (1979) Histologic prognostic indicators in hepatocellular carcinoma. Cancer 44:1677–1683

Lao XM, Zhang YQ, Jin X, Lin XJ, Guo RP, Li GH, Li JQ (2006) Primary clear cell carcinoma of liver – clinicopathologic features and surgical results of 18 cases. Hepatogastroenterology 53:128–132

Lapis K (1988) Ultrastructural aspects of the human primary liver cancer. Appl Pathol 6:117–127

Larocca MC, Soria LR, Espelt MV, Lehmann GL, Marinelli RA (2009) Knockdown of hepatocyte aquaporin-8 by RNA interference induces defective bile canalicular water transport. Am J Physiol Gastrointest Liver Physiol 296:G93–G100

Laurent C, Quaglia A, Foroni L, Bioulac-Sage P, Balabaud C, Dhillon AP (2006) Genomic alteration is not associated with fatty and clear cell change in hepatocellular carcinomas and its precursor nodular lesions in cirrhotic liver. Hepatol Res 36:40–47

Lee WK, Thévenod F (2006) A role for mitochondrial aquaporins in cellular life-and-death decisions? Am J Physiol Cell Physiol 291:C195–C202

Leroy X, Moukassa D, Gosselin B (1998) Clear cell hepatocellular carcinoma: significance of CK 19 (in French). Ann Pathol 18:512–513

Li T, Fan J, Qin LX, Zhou J, Sun HC, Qiu SJ, Ye QH, Wang L, Tang ZY (2011) Risk factors, prognosis, and management of early and late intrahepatic recurrence after resection of primary clear cell carcinoma of the liver. Ann Surg Oncol 18:1955–1963

Li ZY, Bi XY, Zhao JJ, Zhao H, Zhou JG, Huang Z, Cai JQ, Zheng XC (2013) Clinicopathological and prognostic analysis of primary clear cell carcinoma of the liver (in Chinese). Zhonghua Zhong Liu Za Zhi 35:140–143

Li Z, Bi X, Yang L, Zhao J, Zhao H, Huang Z, Cai J, Zhenge X (2014) A clinicopathological and prognostic study of rare pathological subtype cases of hepatocellular carcinoma (in Chinese). Zhonghua Wai Ke Za Zhi 52:329–332

Lin TJ, Liao LY, Lin CL, Shih LS, Chang TA, Tu HY, Chen RC, Wang CS (2004) Spontaneous regression of hepatocellular carcinoma: a case report and literature review. Hepatogastroenterology 51:579–582

Liu JH, Tsai HL, Hsu SM, Hu DH, Chen SS (2004) Clear cell and non-clear cell hepatocellular carcinoma: a case report and literature review. Kaohsiung J Med Sci 20:78–82

Liu Z, Ma W, Li H, Li Q (2008) Clinicopathological and prognostic features of primary clear cell carcinoma of the liver. Hepatol Res 38:291–299

Liu QY, Li HG, Gao M, Lin XF, Li Y, Chen JY (2011) Primary clear cell carcinoma of the liver. CT and MRI findings. World J Gastroenterol 17:946–952

Maeda N, Funahashi T, Shimomura I (2008) Metabolic impact of adipose and hepatic glycerol channels aquaporin 7 and aquaporin 9. Nat Clin Pract Endocrinol Metab 4:627–634

Mansinho H, Ferreira M, Fernandes A, Chaves P, Assis e Santos (1993) Clear cell hepatocellular carcinoma (in Portuguese). Acta Med Port 6:397–400

Mazal PR, Susani M, Wrba F, Haitel A (2005) Diagnostic significance of aquaporin-1 in liver tumors. Hum Pathol 36:1226–1231

McDermott WV, Khettry U (1994) Clear cell carcinoma of the liver with spontaneous regression of metastases. J Surg Oncol 57:206–209

Minervini MI, Demetris AJ, Lee RG, Carr BI, Madriaga J, Nelesnik MA (1997) Utilization of hepatocyte-specific antibody in the immunocytochemical evaluation of liver tumors. Mod Pathol 10:686–692

Murakata LA, Ishak KG, Nzeako UC (2000) Clear cell carcinoma of the liver: a comparative immunohistochemical study with renal clear cell carcinoma. Mod Pathol 13:874–881

Nappi O, Mills SE, Swandon PE, Wick MR (1997) Clear cell tumors of unknown nature and origin: a systematic approach to diagnosis. Semin Diagn Pathol 14:164–174

Oliveira AM, Erickson LA, Burgart LJ, Lloyd RV (2000) Differentiation of primary and metastatic clear cell tumors in the liver by in situ hybridization for albumin messenger RNA. Am J Surg Pathol 24:177–182

Orsatti G, Arnold MM, Paronetto F (1994) DNA image cytometric analysis of primary clear cell carcinoma of the liver. Arch Pathol Lab Med 118:1226–1229

Papadopoulos MC, Saadoun S, Verkman AS (2008) Aquaporins and cell migration. Pflugers Arch 456:693–700

Pecorella I, Ciardi A, Aiello E, Piras MR, Farci C, Di Tondo U (1994) Clear cell hepatocellular carcinoma treated with liver transplantation. Pathologica 86:307–310

Portincasa P, Palasciano G, Svelto M, Calamita G (2008) Aquaporins in the hepatobiliary tract. Which, where and what they do in health and disease. Eur J Clin Invest 38:1–10

Ramsay TL (1929) Primary hypernephroma of the liver (Grawitz tumor). Ann Surg 90:41–46

Ribback S, Calvisi DF, Cigliano A, Sailer V, Peters M, Rausch J, Heidecke CD, Birth M et al (2013) Molecular and metabolic changes in human liver clear cell foci resemble the alterations occurring in rat hepatocarcinogenesis. J Hepatol 58:1147–1156

Ritter JH, Mills SE, Gaffey MJ, Nappi O, Wick MR (1997) Clear cell tumors of the alimentary tract and abdominal cavity. Semin Diagn Pathol 14:213–219

Rojek AM, Skowronski MT, Füchtbauer EM, Füchtbauer AC, Fenton RA, Agre P, Frokiaer J, Nielsen S (2007) Defective glycerol metabolism in aquaporin 9 (AQP9) knockout mice. Proc Natl Acad Sci U S A 104:3609–3614

Ross JS, Kurian S (1985) Clear cell hepatocellular carcinoma: sudden death from severe hypoglycemia. Am J Gastroenterol 80:188–194

Sang W, Gulinar A, Wang CH, Sheng WQ, Maiweilidan Y, Zhang W (2013) Role of arginase-1 expression in distinguishing hepatocellular carcinoma from non-hepatocellular tumors (in Chinese). Zhonghua Bing Li Xue Za Zhi 42:538–542

Sasaki K, Okuda S, Takahashi M, Sasaki M (1981) Hepatic clear cell carcinoma associated with hypoglycemia and hypercholesterolemia. Cancer 47:820–822

Shah S, Gupta S, Shet T, Maheswari A, Wuntkal R, Mohandas KM (2005) Metastatic clear cell variant of hepatocellular carcinoma with an occult hepatic primary. Hepatobiliary Pancreat Dis Int 4:306–307

Singh HK, Silverman JF, Geisinger KR (1997) Fine-needle aspiration cytomorphology of clear-cell hepatocellular carcinoma. Diagn Cytopatol 17:306–310

Swenson CG (1917) Hypernephroma of the liver. Surg Gynecol Obstet 25:570–571

Takahashi A, Saito H, Kanno Y, Abe K, Yokokawa J, Irisawa A, Kenjo A, Saito T et al (2008) Case of clear-cell hepatocellular carcinoma that developed in the normal liver of a middle-aged woman. World J Gastroenterol 14:129–131

Tihan T, Blumgart L, Klimstra DS (1998) Clear cell papillary carcinoma of the liver: an unusual variant of peripheral cholangiocarcinoma. Hum Pathol 29:196–200

Torbenson M, Wang J, Choti M, Ashfaq R, Maitra A, Wilentz RE, Boitnott J (2002) Hepatocellular

carcinomas show abnormal expression of fibronectin protein. Mod Pathol 15:826–830
Vaillo A, Rodriguez-Recio FJ, Gutierrez-Martin A, Ballestin C, Ruiz-Liso JM (2004) Fine needle aspiration cytology of clear cell carcinoma of the gallbladder with hepatic infiltration: a case report. Acta Cytol 48:560–564
Vardaman C, Albores-Saavedra J (1995) Clear cell carcinomas of the gallbladder and extrahepatic bile ducts. Am J Surg Pathol 19:91–99
Verkman AS (2005) More than just water channels: unexpected cellular roles of aquaporins. J Cell Sci 118:3225–3232
Verkman AS, Hara-Chikuma M, Papadopoulos MC (2008) Aquaporins – new players in cancer biology. J Mol Med 86:523–529
Wang WL, Liu J (1986) Ultrastructure of primary clear cell carcinoma of the liver (in Chinese). Zhonghua Zhong Liu Za Zhi 8:438–440
Wang H, Tan B, Zhao B, Gong G, Xu Z (2014) CT findings of primary clear cell carcinoma of liver: with analysis of 19 cases and review of the literature. Abdom Imaging 39:736–743
Wennerberg AE, Nalesnik MA, Coleman WB (1993) Hepatocyte paraffin 1: a monoclonal antibody that reacts with hepatocytes and can be used for the differential diagnosis of hepatic tumors. Am J Pathol 143:1050–1054
Williams JL (1924) A primary hypernephroma of the liver. Trans Chic Pathol Soc 12:90–92
Wu PC, Lai CL, Lam KC, Lok AS, Lin HJ (1983) Clear cell carcinoma of liver. An ultrastructural study. Cancer 52:504–507
Yang SH, Watanabe J, Nakashima O, Kojiro M (1996) Clinicopathologic study on clear cell hepatocellular carcinoma. Pathol Int 46:503–509
Yazdi HM (1985) Cytopathology of clear-cell hepatocellular carcinoma in ascitic fluid. Acta Cytol 29:911–913
Ye XP, Li LQ, Peng T, Xiao KY, Su ZX, Shang LM, Su M, Xu BH (2010) Diagnosis and treatment of primary clear cell carcinoma of the liver (in Chinese). Zhonghua Zhong Liu Za Zhi 32:64–66

Steatotic and Steatohepatitic Hepatocellular Carcinomas and Related Neoplasms

10

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_10

Abstract

A heterogeneous group of hepatocellular carcinoma (HCC) is characterized by the cellular accumulation of neutral fat (triglycerides), visualized as small, medium-sized, or large cytoplasmic vacuoles. HCCs with significant neutral fat accumulation in the absence of inflammatory changes are termed steatotic HCC. A significant fatty change that is grossly visible and detectable by imaging is a rare finding and is probably found in less than 2 % of all HCCs. Fatty change is more common in small tumors and seems to decrease with an increase of tumor diameter. In a subset of fatty HCCs, inflammatory alterations are observed, with a mixed leukocyte infiltration and sign of cell damage. These lesions are called steatohepatitic HCC. Tumors with this distinct morphology can occur without associated liver disease apart from cirrhosis, but they also develop in the setting of nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and alcoholic steatohepatitis, conditions known to be risk factors for HCC.

Steatotic Hepatocellular Carcinoma

Introduction

Tumors of the liver containing visible neutral fat accumulation are a heterogeneous group of lesions of both mesenchymal and epithelial lineages (Valls et al. 2006). Similar to normal hepatocytes, hepatocellular carcinomas and their nodular precursor lesions may accumulate visible fat, in the absence of inflammatory changes (fatty hepatocellular carcinoma; steatotic hepatocellular carcinoma; hepatocellular carcinoma with fatty metamorphosis; lipid-rich HCC; Peters 1976; Itai et al. 1987; Yoshikawa et al. 1988; Ueda et al. 1989; Tsai et al. 2006).

Epidemiology

Histologically, HCCs may show varying degrees of fatty change, but detection of gross steatosis on CT is not a frequent feature. In one series, only 1.6 % of the patients (10/600) showed areas of low attenuation consistent with fatty infiltration (Yoshikawa et al. 1988). Microscopically, the incidence of fat accumulation in HCC is much higher. In fine-needle aspirates, lipid vacuoles in HCC cells were found in 14–70 % of the cases (Wee et al. 1991; Das 1999). Fatty change is more frequent in small HCCs and particularly in well-differentiated HCCs (Kutami et al. 2000; Miyaaki et al. 2005; Kim et al. 2007). Generally, the frequency of fatty change in HCC seems to decrease with the increase of tumor diameter (Kutami et al. 2000).

Clinical and Imaging Features

Steatotic HCC/lipid-rich HCC without inflammatory changes can occur in the setting of nonalcoholic steatohepatitis (NASH), e.g., in patients with diabetes mellitus (Orikasa et al. 2001). Steatosis is detectable in well-differentiated HCCs by the use of ultrasonography, tumors with fatty change being frequently hyperechoic on US (Monzawa et al. 1999). Macroscopic fat within HCCs is well demonstrated on CT scans (Itai et al. 1987; Yoshikawa et al. 1988). Fatty change in HCC characteristically causes a low-attenuation area on CT, less than −10 H, and a highly echogenic area on sonography (Yoshikawa et al. 1988). Steatotic HCCs appear hyperintense on T1-weighted images and demonstrate signal intensity drop on chemical shift images (Basaran et al. 2005; Prasad et al. 2005). Some study results suggest that fatty change is the principal cause of hyperintensity on T1-weighted images of some HCCs and that this finding can help in establishing the diagnosis (Martin et al. 1996; Bartolozzi et al. 2001). At imaging, fat in the ablation zone following radiofrequency ablation can persist and does not necessarily indicate treatment failure (Pupulim et al. 2009).

Fatty Change as a Feature of Nodular Precursor Lesions of Liver Cancer

Steatosis, commonly of the macrovesicular type, has been observed in several types of

hepatocytic nodular lesions occurring in the context of liver cirrhosis. Fatty change has been seen in regenerative nodules (Morii et al. 2013) and in macroregenerative nodules (fatty macroregenerative nodules) in non-steatotic liver cirrhosis and suggested to be, at least in part, precursor lesions of a neoplastic process (Terada et al. 1989). Fatty change also develops in dysplastic nodules (Nakanuma et al. 1998) and has been identified as one of several risk factors for the evolution of hepatocellular nodules to HCC (Terasaki et al. 1998). In a study of nodular lesions in HCV-related liver cirrhosis found in 128 resections, fatty change was not seen in large regenerative nodules and low-grade dysplastic nodules, while it was found in 40 % of high-grade dysplastic nodules (Miyaaki et al. 2005). It seems that marked fat accumulation in small nodular hepatic lesions is an indicator of potential malignancy and that "yellow nodules" on the surface of the liver, detected by laparoscopy, may serve in early diagnosis of a neoplastic liver process (Kameda and Shinji 1992).

Fatty Change in Early or Small Hepatocellular Carcinomas

Fatty change is well documented for small or minute, well-differentiated hepatocellular carcinomas, and at ultrasonography, many of these small nodular lesions are hyperechoic, this feature being caused by the fatty change (Tanaka et al. 1983; Yoshikawa et al. 1988; Kanno et al. 1989; Yoshimatsu et al. 1989; Takayasu et al. 1995; Kim et al. 2005). In lesions less than 1.5 cm size, steatosis is usually diffuse, whereas larger well-differentiated tumors usually show patchy fat accumulation (Yoshikawa et al. 1988; Kim et al. 2005; Prasad et al. 2005). In the study of Yoshikawa and coworkers ($N = 10$; 1988), fatty change was diffuse in tumors less than 3.5 cm diameter and focal in tumors larger than 3.5 cm. In a systematic study of 39 histopathologically proven early HCCs with a mean diameter of 1.7 cm, low-density lesions in CT showed mild to moderate fatty change, and isodense lesions showed no or minimal fatty change (Takayasu et al. 1995). Fatty change can be seen in up to 40 % of small HCCs or well-differentiated HCCs in the early stage (Kojiro 2004). In detailed study of 260 HCC nodules 3 cm or less than 3 cm in diameter, fatty change (frequently of the diffuse type) was found in 19.6 %, and the frequency was highest (36.4 %) in the nodules whose diameter was 1.1–1.5 cm. With an increase of tumor diameter, moderately differentiated HCC with less or without fatty change progressively appeared, and focal fatty change in tumors was found more frequently. In HCCs 1.5 cm or less in diameter, the number of intratumoral arteries was significantly smaller in HCCs with fatty change, without any difference in intratumoral portal tracts (Kutami et al. 2000). In an ultrasonography study of 55 hyperechoic and 107 hypoechoic liver nodules less than 20 mm in diameter in patients with chronic liver disease, 76 % of hyperechoic nodules were histologically diagnosed as HCC, and 82 % of hyperechoic HCCs contained fatty change and/or clear cell change (Yamagata et al. 1999). In small HCCs with fatty change that develop in HCV-infected livers, insulin-like growth factor II/IGF-II was found in 80 %, suggesting pathogenic role of IGF-II for tumor steatosis (Sohda et al. 1997). HCV-associated HCC may also share mechanisms that operate in the pathogenesis of HCV-induced hepatic steatosis (review: Zimmermann 2006).

Fatty Change in Larger Hepatocellular Carcinoma

In contrast to small HCCs, where a diffuse steatosis is often noted, larger HCCs more commonly show localized fatty areas (Itai et al. 1987), and the presence of these "patchy" steatotic areas associated with areas of hemorrhage and/or necrosis may contribute to the characteristic mosaic pattern of HCC (Valls et al. 2006; Figs. 1, 2, and 3).

A steatotic phenotype of HCC has been found to persist in metastases, e.g., in peritoneal metastatic spread (Tsai et al. 2006). Marked steatosis of HCC occurs in both solitary and multiple lesions and in a variety of growth patterns of HCC.

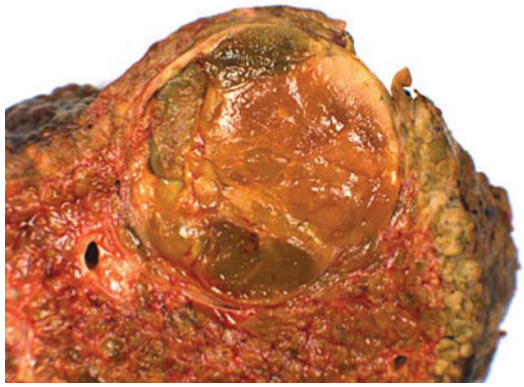

Fig. 1 Hepatocellular carcinoma with fatty/steatohepatitic change. The cut surface of this non-fixed resection specimen is heterogeneous and shows yellowish nodular areas that represent fat accumulation and fresh hemorrhage

Fig. 3 Multinodular steatotic/steatohepatitic hepatocellular carcinoma. Lipid accumulation has led to diffuse yellow discoloration of the neoplasm. The dark areas are hemorrhages altered by formalin fixation

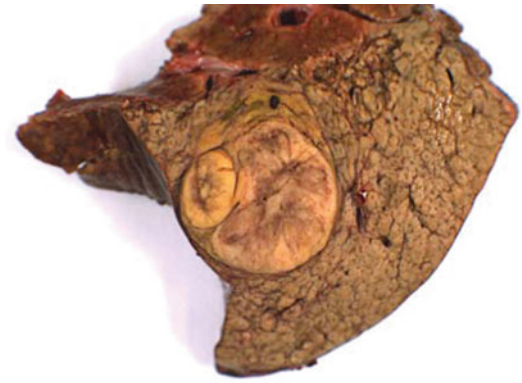

Fig. 2 In this nodular hepatocellular carcinoma in a cirrhotic liver, fatty change is marked, resulting in a yellow nodule that might be confused with metastasis of more common lipid-rich malignancies

However, we more frequently observed significant steatosis (and mainly the macrovesicular variant) in large tumors with an expanding growth pattern. On the cut surface, steatosis may be manifested in the form of a diffuse yellow color of the tissue or in the form of circumscribed yellow-stained sectors or yellow nodules. That is, in some HCC steatosis is a heterogeneous phenomenon that, in case of composite lesions, may only involve a subset of the tumor nodules. In situations where the steatotic HCC also stores bile (cholestatic features of the tumor), the lesion shows a distinct saffron-like or "pistachio" color almost exclusively encountered in such neoplasms. A fatty aspect was also found in metastases of steatotic HCC, e.g., in the pancreas (Nishiofuku et al. 2013).

As already outlined above, visible neutral fat in HCC may have several distribution patterns. In small HCCs, a *diffuse steatosis pattern* prevails, with all or almost all of the tumor tissue being occupied by cells with lipid droplets/vacuoles. In larger tumors, a *focal or patchy steatosis pattern* is more often and seems to roughly increase in frequency as a function of the tumor size. In large steatotic HCCs with intratumoral cholestasis, we noted the phenomenon that at least macrovesicular steatosis is more common in peripheral parts of the tumor (*peripheral steatosis pattern*). Tumor cell steatosis, similar to normal hepatocytes, microscopically ranges from small lipid droplets to classical macrovesicular steatosis, with cells mainly occupied by a large vacuole displacing the nucleus to the cell's periphery (Mathew and Affandi 1989; Mitchell and Sturgis 2009; Figs. 4, 5, 6, 7, and 8).

Both in small HCCs and in larger tumors, steatosis may be associated with clear cell change in the same area, a combination however more often noted in small tumors and well-differentiated HCCs. A second cell alteration seen in tumor steatosis is tumor cell ballooning, with or without formation of Mallory-Denk

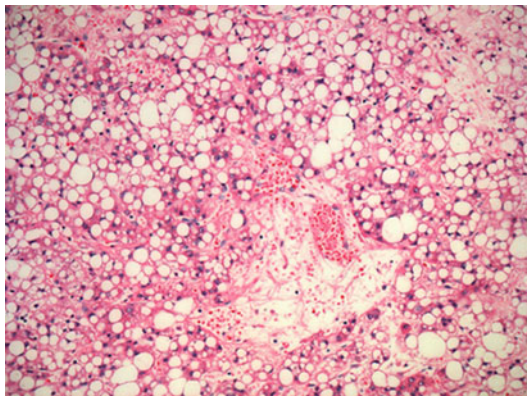

Fig. 4 Steatotic hepatocellular carcinoma (fatty HCC). Most of the tumor cells contain small to large droplets of neutral fat, similar to those observed in macrovesicular hepatic steatosis (hematoxylin and eosin stain)

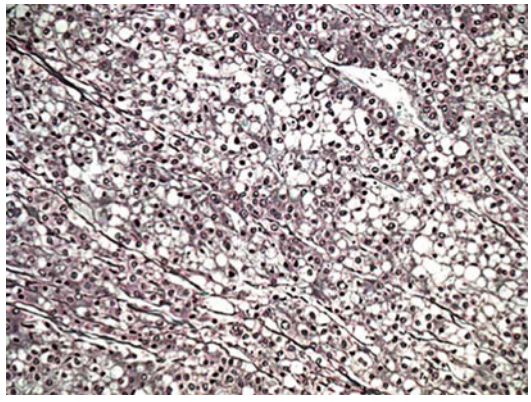

Fig. 5 As fat accumulation in steatotic HCC can efface typical structures of the tumor, the morphology thus resembling hepatic steatosis, a reticulin stain showing abnormally enlarged cell plates is of great diagnostic help (Gomori silver stain)

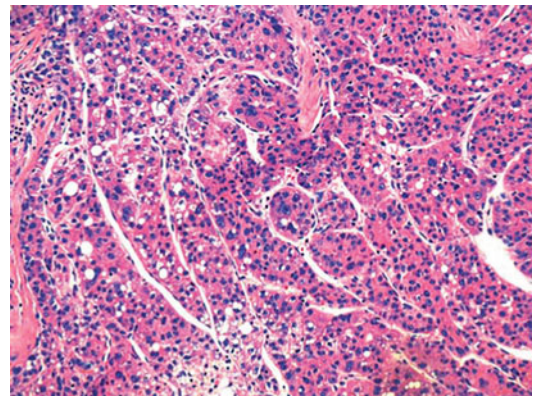

Fig. 6 In this trabecular hepatocellular carcinoma, fatty change is focal and not a prominent feature (hematoxylin and eosin stain)

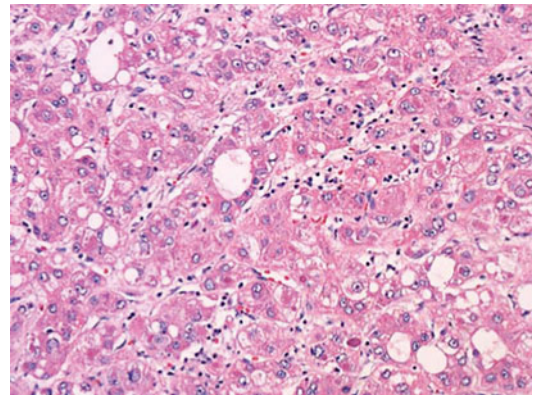

Fig. 7 This hepatocellular carcinoma illustrates that macrovesicular fatty change can also involve neoplastic cells of acinar structures. Few Mallory-Denk bodies are seen (hematoxylin and eosin stain)

bodies. Owing to the enlargement of cells by accumulated neutral fat, the structure of the intervening tumor vascular channels may be effaced, a phenomenon well recognized for massive liver steatosis. In marked tumor steatosis, oil droplets and/or lipogranuloma formation may develop. Accumulation of visible fat in hepatocyte nuclei seems to be restricted to the liver (review: Wegelin 1928). In normal hepatocytes and in HCC cells, nuclear fat is visualized in the form of larger or smaller sudanophilic and osmiophilic fat droplets or their vacuoles within nuclei. The droplets frequently show a clear halo, or they are delimited by a thin basophilic rim, already described by Wegelin in 1928. In the normal liver, Wegelin noted nuclear fat in 14 % of 160 organs examined in detail (Wegelin 1928). Stainable fat is sometimes present in HCC cells as nuclear lipid inclusions. Nuclear fat droplets in hepatocytes have first been described in 1909 (Brandts 1909). This author noted sudanophilic nuclear inclusions of hepatocytes mainly in non-steatotic livers and in those with atrophy and lipofuscinosis. Interestingly, Brandts also mentioned pigment grains within these inclusions, an observation suggesting that the inclusions result from cytoplasmic

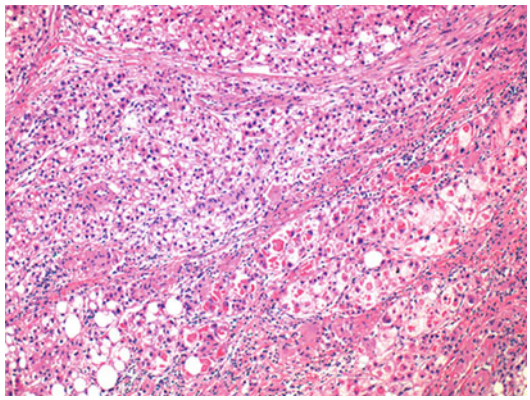

Fig. 8 Mixed hepatocellular carcinoma with focal fatty change and formation of Mallory-Denk bodies (hematoxylin and eosin stain)

invaginations containing fat and lipofuscin. Apart from fat visible at light microscopic examination, small fat droplets have been identified in HCCs by use of electron microscopy (Livni et al. 1977).

Steatohepatitic Hepatocellular Carcinoma (Hepatocellular Carcinoma with Steatohepatitic Features)

Introduction

HCC complicating NAFLD (nonalcoholic fatty liver disease), NASH (nonalcoholic steatohepatitis), or ASH (alcoholic steatohepatitis) is well recognized (Petta and Craxi 2010; Baffy et al. 2012; Rozman 2014; Wong et al. 2014), but many of these tumors developing in these metabolic disorders are histologically ordinary HCCs (Zen et al. 2001; Shimada et al. 2002; Chagas et al. 2009; Kawada et al. 2009). However, in a subset of HCC that are associated with NAFLD or NASH, a so-called steatohepatitic morphology is observed (steatohepatitic HCC, SH-HCC; steatohepatitis in HCC).

Selected References Zimmermann 2002; Salomao et al. 2010, 2012; Jain et al. 2013; Ahuja et al. 2014; Gupta et al. 2014; Shibahara et al. 2014.

In a series of HCCs, SH-HCC represented 13.5 % of cases, all but one case occurred in patients with underlying steatohepatitis, and SH-HCC was diagnosed in 35.7 % of patients with either NASH or ALD/ASH (Salomao et al. 2012). In another series of 101 cases of HCC with various etiologies in explanted livers from adults, the steatohepatitic variant was identified in 18.8 % of cases (Jain et al. 2013). SH-HCC was described to occur in the setting of hepatitis C-related cirrhosis with associated NAFLD/NASH and was detected in 35.5 % of these cases. Patients with SH-HCC were characterized by a higher frequency of diabetes mellitus and hypertension and showed higher serum levels of cholesterol and triglycerides than patients with ordinary HCC (Shibahara et al. 2014). Generally, SH-HCC seems to be a form of HCC strongly associated with metabolic syndrome (Jain et al. 2013).

Pathology

The histologic presentation of SH-HCC closely mimics that of NASH and florid alcoholic liver disease. SH-HCC are characterized by large droplet steatosis, ballooning (frequently associated with Mallory-Denk bodies), and inflammatory infiltrates and fibrosis. The leukocytic infiltrate is dominated by lymphocytes, plasma cells, and neutrophils, and neutrophil granulocytes were often seen aggregated around ballooned tumor cells (Fig. 9).

Inflammatory infiltrates occur in three main patterns. In the first pattern, tumors focally show an infiltrate composed of neutrophil granulocytes, chiefly in tumor areas with ballooned cells and Mallory-Denk body formation. The second pattern is characterized by the focal accumulation of macrophages, sometimes with formation of epithelioid cells (or even granulomas) and lipid-laden foamy cells (lipophages). The third pattern shows a focal infiltrate rich in lymphocytes and plasma cells. It is likely that these infiltration patterns reflect distinct phases of an inflammatory/immune reaction directed against the altered tumor cell population. In areas of florid ballooning, fibrosis is predominantly of the pericellular type, while a

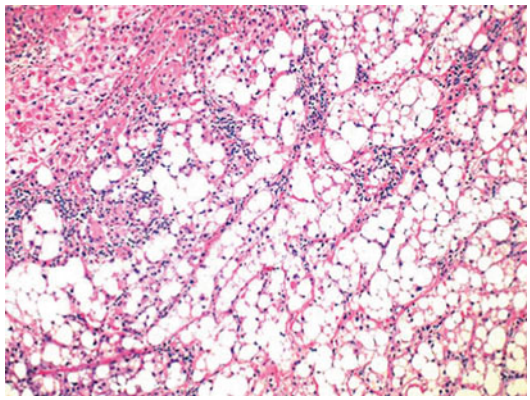

Fig. 9 Steatohepatitic hepatocellular carcinoma. There is marked macrovesicular fatty change, effacing the baseline growth pattern of the tumor. The neoplasm exhibits focal infiltration of inflammatory cells, mainly lymphocytes, and there is focal tumor cell apoptosis (hematoxylin and eosin stain)

bundled type of fibrosis is haphazardly distributed through the tumors (Salomao et al. 2010). In NASH, also large well-differentiated HCC with extensive fatty change can develop (Ishikawa et al. 2013).

Based on Japanese patients, a histologic diagnosis of SH-HCC was made if the tumor fulfilled four of the following five criteria: steatosis >5 % of tumor cells, cell ballooning or Mallory-Denk body formation, interstitial fibrosis, and inflammatory infiltrates (Shibahara et al. 2014).

Lipid-Rich Clear Cell Hepatocellular Carcinoma

Apart from steatotic hepatocellular carcinomas (HCC), which show an accumulation of triglyceride droplets in the cytoplasm of tumor cells (see the respective chapter), there are rare instances of clear cell and lipid-rich HCC which store a more complex mixture of lipids. These neoplasms have been termed lipid-rich clear cell HCC (Orikasa et al. 2001). The first case had been described in a 67-year-old female patient with diabetes mellitus and nonalcoholic steatohepatitis (Orikasa et al. 2001). The patient described by Orikasa and coworkers (2001) showed a hyperechoic liver lesion of 2.5 cm diameter. Biopsy of the nodules revealed HCC of the clear cell type associated with early cirrhosis of the peritumoral liver. The lesion was excised. Macroscopically, the resection specimen showed a nonencapsulated tumor with a maximum diameter of 2.6 cm, with a grayish-yellow cut surface. There was a clear boundary between the tumor and the adjacent liver substance. Histologically, the neoplasm consisted of cell nests, the tumor cells having a clear cytoplasm containing lipid droplets or varying size. The nuclei were rather small and round and lacked pleomorphism. Irregular cytoplasmic, low-molecular-weight cytokeratin-positive inclusions resembling Mallory-Denk bodies were detected. The tumor lacked the sinusoidal-like vascular patterns often seen in HCCs. Electron microscopically, the tumor cells contained numerous lipid droplets, abundant glycogen, and swollen mitochondria. Canalicular profiles with well-developed junctional complexes were in evidence, supporting the hepatocyte lineage of the neoplastic cells. The main differential diagnosis is steatotic HCC, which may sometimes show small lipid droplets in the cytoplasm but lacks clear cell features (Mitchell and Sturgis 2009).

Hepatocellular Carcinoma with Foamy Histiocyte-Like Appearance

Introduction

There exists a group of neoplasms with cells having a finely vacuolated cytoplasm resembling the morphology of foamy macrophages (foamy cells). These neoplasms seem to be capable of storing lipids in the cytoplasm in the form of small or very small lipid droplets (lipid bodies; lipid organelles), visualized in paraffin sections as a sponge-like texture of the cytoplasm. Such neoplasms are derived from several tissues and organs and include secretory breast carcinoma, foamy gland prostatic adenocarcinoma, pancreatic ductal carcinoma with foamy gland pattern, foamy variant of pancreatic intraepithelial neoplasia, certain endocrine neoplasms, sebaceous carcinomas, foamy cell balloon melanoma, foamy cell mesothelioma, foamy cell angiosarcoma, foamy cell

ependymoma, and malignant gliomas with lipidized/foamy tumor cells. Extremely rare forms of hepatocellular carcinoma can also develop a foamy cell phenotype.

Hepatocellular Carcinoma with Foamy Histiocyte-Like Appearance

This variant of hepatocellular carcinoma (HCC) was detected in a 63-year-old man with chronic hepatitis C who developed a tumor in liver segment 7. The hepatic resection specimen showed a tumor measuring up to 4.5 cm in diameter, with a yellow-white cut surface and a white central bulging area. Histology revealed a moderately differentiated HCC of the trabecular subtype. Numerous cells exhibited a foamy phenotype reminiscent of foamy macrophages/histiocytes, but immunohistochemically these cells were CD68-negative and represented cells of a hepatocyte lineage (Noro et al. 2010).

Secondary Fatty Change in Treated Hepatocellular Carcinoma

Several modes of nonsurgical treatment of HCC cause complex patterns of secondary changes, which are outlined in a separate chapter. Fatty change of residual HCC cells was noted following combined radiotherapy and hyperthermia (Seong et al. 1991).

Differential Diagnosis of Fatty Tumors in the Liver

Differential diagnosis of fatty HCC includes other liver masses that accumulate triglycerides, mainly benign fatty hepatocyte nodules, focal fatty change, and angiomyolipoma. Angiomyolipoma of the liver has distinct imaging features but may be confounded with steatotic HCC, mainly in situations of rather low fat content (Chung et al. 2002). On the other hand, hepatic angiomyolipoma may occur in conjunction with hepatocellular carcinoma in the same liver (Chang et al. 2001). Focal fatty change, less common than focal fatty sparing of the liver (Gabata et al. 2001), is typically situated subcapsular in location, has geographic margins, and causes no mass effect, and normal non-distorted vessels are seen inside. However, when focal fatty change has a nodular configuration, it may be difficult to exclude a fatty tumor (Valls et al. 2006). Multifocal hepatic steatosis (multifocal nodular fatty infiltration) has been reported to mimic malignancy in ultrasonography and CT imaging of the liver (Kröncke et al. 2000; Kemper et al. 2002).

Pathogenic Pathways

The pathogenesis of fatty change in HCC is not well understood, but several mechanisms have been suggested, such as metabolic disorders, hypoxia due to insufficient vascular supply, and the effects of hepatitis C virus.

Steatosis in HCC: Genomic and Metabolic Alterations

In a study of 22 nodular liver lesions (9 HCCs, 5 dysplastic nodules, and 8 large regenerative nodules), fatty and clear cell change was not associated with a distinct patterns of the genomic damage fraction/GDF (Laurent et al. 2006). Steatosis in HCC is in part regulated by growth factors. Immunohistochemically, expression of insulin-like growth factor II is more prominent in cells of steatotic HCCs than in ordinary HCCs (Sohda et al. 1997). In HCC, signaling and enzymatic pathways favoring a positive lipid balance are frequent events (Khan et al. 2010; Patterson et al. 2011). For example, HCC shows a coordinate activation of lipogenic enzymes (Yahagi et al. 2005).

An important role in pathogenic pathways leading to HCC steatosis is played by hypoxia and changes in blood circulation. In small HCCs with nodules smaller than 1.5 cm, the number of intratumoral arteries was significantly reduced when fatty change was present, suggesting that fatty change in HCCs is not only related to size but

also to insufficient development of tumor vessels (Kutami et al. 2000). On the other hand, fatty hepatic tissue impairs the liver's microcirculation and promotes ischemic injury (Selzner et al. 2000; Ijaz et al. 2003; Farrell et al. 2008). Free fatty acids delivered from steatotic liver cells sensitize hepatocytes to bile acid-induced apoptosis (Pusl et al. 2008), palmitic acid being more proapoptotic than oleate (Gomez-Lechon et al. 2007). There is a causal relationship between fatty change in normal or malignant hepatocytes and hepatitis C virus infection. Tumor cell lines derived from HCCs of HCV-positive patients progressively accumulated fat droplets in the cytoplasm, and fatty change in these cells seemed to be associated with less proliferative activity than was seen in small HCC cells without fatty change (Seki et al. 2002).

Steatosis and HCV Infection

Hepatitis C virus (HCV) infection is significantly involved in altered lipid metabolism of normal, regenerating, and neoplastic hepatocytes. HCV infection of the liver is frequently associated with fatty change of hepatocytes (reviews: Ramalho 2003; Adinolfi et al. 2005; Sheikh et al. 2008). This HCV-induced hepatic steatosis is associated with insulin resistance, the metabolic syndrome, and a fibrosis pathway in the liver (Cua et al. 2008). There is evidence that fatty change also develops in early liver cancer in patients with HCV infection (Sohda et al. 1997). The direct pathogenic role of HCV in liver steatosis is demonstrated by the association with HCV genotype 3 infection, the correlation between severity of steatosis and HCV replication levels, and the association between response to HCV infection treatment and disappearance of steatosis. It has been shown that the HCV core protein is capable to induce fat accumulation in hepatocytes, likely via interactions with lipid droplets and interference with very-low-density lipoprotein assembly (review: Negro 2006). It seems that PPARalpha activation is essential for HCV core protein-induced steatosis (Tanaka et al. 2008), whereas the PPARgamma/RXRalpha complex is involved, together with the Ku antigen, in the modulation of apolipoprotein C-IV by HCV core protein (Kim et al. 2008). In transgenic mice, the HCV core protein induces hepatic steatosis (Moriya et al. 1997). It has been shown that the HCV core protein is associated with the surface of lipid droplets and the endoplasmic reticulum membranes closely surrounding these droplets (review: Roingeard and Hourioux 2008). It was found that the core protein of both HCV genotypes 1b and 3a binds tightly to the surface of lipid droplets, but cells transfected with genotype 3a contain more neutral lipids in lipid droplets, and more large lipid droplets, than cells transfected with genotype 1b sequences (Piodi et al. 2008). In HCV genotype 3, two polymorphisms in the HCV core gene at positions 182 and 186 correlated with the presence and absence of hepatic steatosis, suggesting that core polymorphism has an important impact on liver cell lipid turnover (Jhaveri et al. 2008).

Induction of Inflammation in Liver and Liver Tumor Steatosis

The inflammatory reaction found in part of steatotic HCCs resembles steatohepatitis. This is of interest insofar as steatohepatitis, and in particular also NASH, is linked with abnormal intercellular matrix production, abnormal hepatocyte regeneration, and hepatic remodeling, eventually resulting in cirrhosis (reviews: Mehta et al. 2002; Choi and Diehl 2005; Farrell and Larter 2006; Gentile and Pagliassotti 2008). Several pathogenic factors are currently discussed to involve specifically the action of fatty acids and their oxidation products, viz., lipotoxicity (reviews: Gentile and Pagliassotti 2008; Greenfield et al. 2008; Malhi and Gores 2008). It has been shown that also oxidized phosphatidylcholine, in part localized to lipid droplets, is associated with the inflammatory activity of NASH (in particular, the number of recruited neutrophils in the liver tissue) and has an impact on the progression of fatty liver disease in humans (Ikura et al. 2006). The reasons as to why an inflammatory cellular infiltrate is established within the

tumor in some cases of steatotic HCC are not well understood, but mechanisms operational in fatty liver disease/NASH may be shared. Excess lipid accumulation in hepatocytes induces sustained hepatic generation of proinflammatory cytokines (review: Lalor et al. 2007), particularly when the hepatic innate immune system becomes Th-1 polarized (review: Choi and Diehl 2005). For example, patients with NASH have elevated serum levels of proinflammatory cytokines, such as interleukin-8 (IL-8; Bahcecioglu et al. 2005), and it has been found that palmitic acid, a component of neutral fat, induces production of IL-8 from steatotic hepatocytes (Joshi-Barve et al. 2007). Similarly, serum TNF-alpha levels are elevated in patients with NASH (Bahcecioglu et al. 2005), and this may be linked to the elevated intercellular adhesion molecule-1 (ICAM-1) levels in NASH (Ito et al. 2007), because TNF-alpha induces a strong expression of ICAM-1 on hepatocytes and/or sinusoidal endothelial cells. Triglycerides also potentiate the inflammatory response in Kupffer cells (Budick-Harmelin et al. 2008). Mallory-Denk bodies (MDBs), which may occur in conjunction with steatosis and tumor cell ballooning in HCCs and contain cytokeratins 8 and 18 (review: Zatloukal et al. 2007), may contribute to inflammatory responses in these neoplasms, similar to steatotic nonneoplastic liver parenchyma. In HCC, the priming events for MDB formation are not known, but MDB production continues in a subset of tumors for longer time periods. In a murine model of MDB reinduction, it has been found that persistent posttranslational chaperone modifications, coupled with protein cross-linking and altered chaperone expression and function, seem to contribute to a so-called toxic memory (Strand et al. 2008). The pathogenic role of one major component of MDBs, cytokeratins 8 and 18, is evident by the observation that CK8/18 germ line heterozygous mutations predispose to end-stage liver disease of multiple etiologies and to liver disease progression in patients with HCV infection (review: Ku et al. 2007). Hepatocytes damaged by fat accumulation and fatty acid oxidation derivatives release cytoskeletal components. For example, cytokeratin 18 fragments are increased in serum of children and adults with nonalcoholic fatty liver disease and are a biomarker for this disorder (Diab et al. 2008; Vos et al. 2008). Release of native or modified cytokeratins from the hepatocyte cytoskeleton may induce a local inflammatory response. There is also evidence that apoptosis-associated activation of caspase-3 activity causes cytokeratin 18 cleavage, resulting in the M-30 aggresome (Amidi et al. 2007), and that this cleavage is associated with milder hepatic inflammation and fibrosis (Valva et al. 2008). On the other hand, inflammatory stress exacerbates lipid accumulation in liver cells and fatty livers of apolipoprotein E knockout mice (Ma et al. 2008). Both alcoholic and nonalcoholic fatty liver disease are associated with increased rates of liver cell apoptosis (review: Feldstein and Gores 2005).

Mallory-Denk Bodies (MDBs) in Hepatocellular Carcinoma and MDB-Rich Hepatocellular Carcinoma

Introduction

Part of hepatocellular carcinomas (HCC) contain Mallory-Denk bodies (MDBs). There is increasing evidence that MDB formation in HCC cells is a heritable phenotype and is related to hepatocarcinogenic pathways. Hyaline intracytoplasmic bodies have been described by the American pathologist Frank Burr Mallory (1862–1941) in 1911 (Mallory 1911) and were later termed Mallory bodies (MB). Helmut Denk and coworkers described the first animal model of MB formation in 1975, feeding mice with griseofulvin (Denk et al. 1975). Based on the impact of these observations, it was proposed to rename MB as Mallory-Denk bodies (MDB; Zaloukal et al. 2007).

As MDBs are associated with liver cell injury (see below), these hyaline inclusions are relatively often seen in various forms of HCC, as HCC cells undergo complex patterns of cell and cytoskeletal damage. The identification of MDB, specifically small or incipient hyaline inclusion bodies, depends in their frequency and hence on sampling and on the methods used to detect them (special

stains; immunohistochemistry). However, there are subsets of HCC that are characterized by large numbers of MDBs that are easily recognized in routine histologic preparations (MDB-rich HCC). There is evidence that MDB formation is a heritable phenotype of certain subsets of HCC (Nakanuma and Ohta 1986).

Epidemiology and Clinical Features

In an autopsy study of 200 consecutive cases, 49 HCC showed MDB. In comparison with the 151 cases without MDB, the MDB group consisted of patients who were older, showed a higher association rate of liver cirrhosis, and had a lesser liver weight. Furthermore, a nodular growth pattern was more prevalent in the MDB group, while the other group had more cases with massive and diffuse growth patterns (Hoso and Nakanuma 1990).

Histopathology

MDB-rich HCC may be otherwise ordinary HCC, but there is also evidence that numerous MDBs occur in small encapsulated HCC (Kondo et al. 1986; Cameron et al. 1993) and in steatotic or lipid-rich HCC that develop in patients with steatohepatitis (Orikasa et al. 2001; Maeda et al. 2008; Figs. 10, 11, 12, and 13). Similar to hepatocytes in alcoholic liver disease of NASH, MDBs in HCC are irregularly shaped and strongly eosinophilic hyaline cytoplasmic inclusions (Norkin and Campagna-Pinto 1968) that have a characteristic ultrastructure (Roschlau and Kemmer 1967) and are composed of intermediate filaments and associated proteins (Virtanen et al. 1979).

MDBs are stainable by the use of the chromotrope aniline blue method (Roque 1953). MDBs are also visualized by the use of phloxine methylene blue staining after Zenker's acetic acid fixation, phosphotungstic acid-hematoxylin/PTAH staining after fixation in 95 % ethanol, and Laqueur's acid fuchsin. In HCC, the ultrastructural features of MDB are the same or similar as in nonneoplastic hepatocytes (Enat et al. 1973; Scotto et al. 1974; Ichida 1983) and closely resemble MDB found in alcoholic liver disease (Keeley et al. 1972). MDBs are more often encountered in well-differentiated HCC (Oda et al. 1972; Cadrin et al. 1990; Nakanuma et al. 1990) and in solitary HCC smaller than 1 cm in diameter (Nakanuma and Ohta 1984; Nakanuma et al. 1986). Based on autopsy cases, three patterns of MDB formation in HCC were recognized, i.e., clustering, diffuse, and sparse types (Nakanuma and Ohta 1986). The clustering type, characterized by formation of groups of MDB-containing carcinoma cells within the

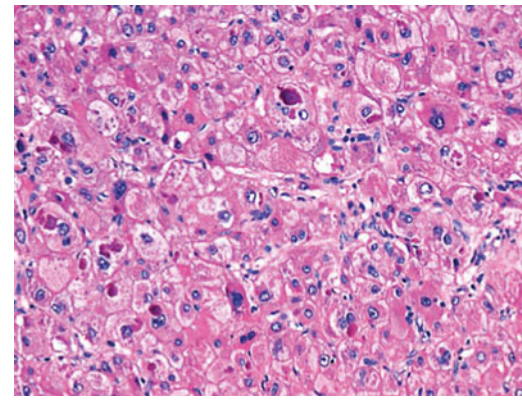

Fig. 10 Hepatocellular carcinoma with several Mallory-Denk bodies, characterized as strongly eosinophilic and dense, irregularly shaped intracytoplasmic inclusions (hematoxylin and eosin stain)

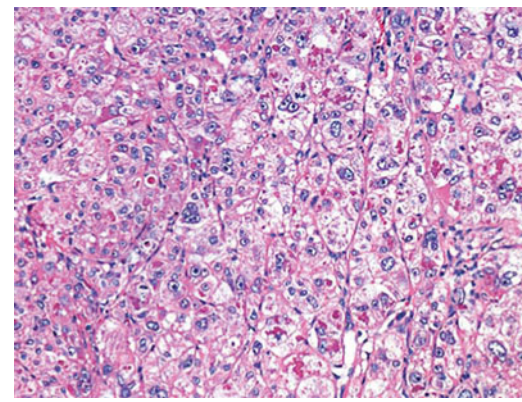

Fig. 11 This tumor displays numerous Mallory-Denk bodies (Mallory body-rich HCC; hematoxylin and eosin stain)

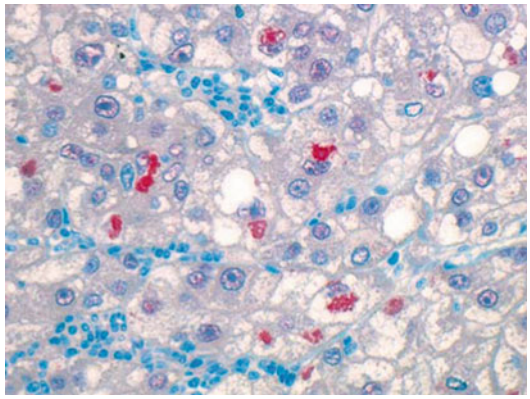

Fig. 12 Mallory-Denk bodies in hepatocellular carcinoma are readily detectable as ubiquitin-positive inclusions (*red bodies*). Mallory-Denk bodies can be associated with cell ballooning (*right lower corner*; ubiquitin immunostain)

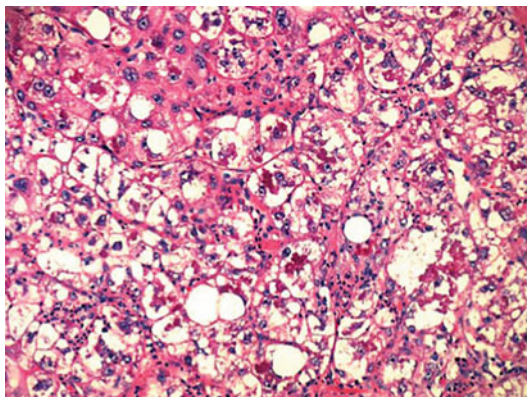

Fig. 13 Mallory-Denk body-rich hepatocellular carcinoma with marked tumor cell ballooning (hematoxylin and eosin stain)

tumor, was the most common and was detected in 21/28 autopsy cases. MDBs were also found in unusual types of HCC, e.g., black HCC with Dubin-Johnson-like pigment storage (Roth et al. 1982).

Both in normal hepatocytes and in HCC cells, MDBs are often associated with a strikingly clear cytoplasm associated with cell body enlargement, a change called ballooning. Ballooning of a hepatocyte containing MDB is already depicted in the original figure of intracellular hyaline published by Mallory in 1911. The clear change of cytoplasm characterizing ballooning is in part due to a shift of stained cytoskeletal components and organelles attached to them into MDB, MDB acting like an "attractor" causing collapse of the organelle network. On the other hand, ballooning is an indicator of a complex pattern of cell injury, with stress-induced changes of the endoplasmic reticulum (SEM), sometimes with fat droplet-associated dilation of the SER cisterns (Caldwell et al. 2010). There is an intricate relationship between cell death, ballooning, and MDB (Machado and Cortez-Pinto 2011).

Immunohistochemistry

Immunohistochemically, MDBs are typically reactive for cytokeratins 8 and 18 and less so for cytokeratins 19, 7, and 20 (Pei et al. 2004). MDBs are usually positive for ubiquitin (Ohta et al. 1988). In griseofulvin-fed mice with MDB, intermediate filaments surrounding mature MDB are decorated with ubiquitin, illustrating the intricate association of cytokeratins and ubiquitin in MDB (Ohta et al. 1988). It was found that MDBs in nonneoplastic liver disease and HCC closely share a common immunophenotype, suggesting a common pathogenic mechanism (Peters et al. 1982).

Intracellular Hyaline Bodies in Hepatocellular Carcinoma

Intracellular hyaline bodies (IHBs) are cytoplasmic inclusions that have hitherto only been observed in HCC cells and in hepatocytes altered by copper toxicosis. In one study, IHBs were found in 8.6 % of HCC cases, whereas both IHB and MDB were detected in 7.5 %. IHB and MDB may simultaneously occur in the same HCC cell. In addition, hybrid inclusions with a position intermediate between IHB and MDB regarding light microscopic morphology, ultrastructure, and composition occur. Both IHB and MDB contain the stress-inducible adaptor protein, p62, but in contrast to MDB, IHBs lack keratins, suggesting that alterations of the keratin cytoskeleton are required to transform IHB into MDB (Stumptner et al. 1999; Denk et al. 2006).

Sequelae and Effects of MDB in Hepatocellular Carcinoma

MDB formation in HCC is accompanied by a constant change in DNA content of HCC cells, in that MDB-containing cells are more often hyperploid or aneuploid (Hoso and Nakanuma 1989). Both in nonneoplastic liver and HCC, MDB can elicit a vigorous granulocyte reaction (Bautista 2002), sometimes with granulocytes forming a cluster or corona surrounding damaged cells containing MDB ("granulocyte satellites"). MDBs release substances that exert a positive chemotactic reaction of granulocytes (Peters et al. 1983). In MDB-rich HCC, inflammatory reactions mediated by neutrophils and, to a lesser degree, lymphocytes and macrophages can elicit a pattern resembling acute steatohepatitis ("steatohepatitis-like HCC"). It is assumed that a strong chemotactic/chemokinetic activity of MDB constituents for neutrophils is responsible for this phenomenon. On the other hand, HCC can induce neutrophil attraction in the absence of MDB. HCC can overexpress and release CXCL5 (epithelial neutrophil-activating peptide 78), a member of a proangiogenic subgroup of the CXC-type chemokine family that mediates neutrophil infiltration (Zhou et al. 2012). Similarly, expression of the chemokine receptor, CXCR6, by HCC is also associated with neutrophil accumulation in the tumor (Gao et al. 2012). MDBs evoke both cellular and humoral immune reactions (Gluud et al. 1981, review: Leevy and Elbeshbeshy 2005). The sometimes strong granulocyte and immune responses can, in both HCC and inflammatory liver disease, elicit tumor cell and hepatocyte apoptosis associated with nuclear DNA fragmentation (Takahashi et al. 2000). There is evidence that degranulation of granulocytes in contact with MDB-containing cells can lead to apoptosis (Jaeschke 2002). But neutrophils can also promote motility of cancer cells through a hyaluronan-mediate TLR4/PI3K activation loop (Wu et al. 2011). Neutrophils accumulating in HCC interact with HCC cells and promote their invasive properties via a paracrine regulation mediated by neutrophil-derived hepatocyte growth factor (Imai et al. 2005). The inflammatory response associated with peritumoral neutrophils fosters angiogenesis in HCC and induces tumor progression (Kuang et al. 2011). The presence of intratumoral neutrophils was a poor prognostic factor for HCC after resection (Li et al. 2011).

Significance of Mallory-Denk Bodies in Precursor Lesions and Hepatocellular Carcinomas

There is evidence that the presence of MDB in hepatocytes is a sign of preneoplasia. In autopsy studies comparing livers with HCC and cirrhotic livers without HCC, the frequency of MDB in nonneoplastic hepatocytes was 40 % in the HCC group with cirrhosis. In HCC-bearing livers with precirrhotic changes, 25 % showed NDB formation by nonneoplastic hepatocytes. HCCs were significantly more frequent in cirrhotic livers with MDB than in those cirrhotic livers without MDB, suggesting that MDB formation in hepatocytes might represent a preneoplastic change (Nakanuma and Ohta 1985). MDB can emerge in nodular hepatocyte lesions that are considered to play a role in hepatocarcinogenesis. MDBs have been found in adenomatous hyperplasia of the liver containing a small HCC in its center (Sakurai et al. 1989). Fatty macroregenerative nodules developing in non-steatotic liver cirrhosis can contain clustered MDB, suggesting that these nodular lesions are preneoplastic alterations (Terada et al. 1989). MDBs have also been demonstrated in large cell dysplasia developing in focal nodular hyperplasia of the liver (Agaimy et al. 2003).

Experimentally, MDB can develop in hepatoma cells induced by dimethylnitrosamine (Borenfreund et al. 1981) and the carcinogenic drug DDC (Nan et al. 2006; Oliva et al. 2008; French et al. 2011b), and MDBs are thus regarded as a marker for a hepatic carcinogenic pathway. Experimentally, hepatocarcinogenic agents induced MDBs in clusters of hepatocytes in mice. In these clusters, fatty acid synthase, ubiquitin B, GPC-3, and AFP mRNA levels significantly increased, suggesting that markers

characterizing HCC are upregulated in hepatocytes forming MDB (Nan et al. 2006). Pathogenetically, the oncogene FAT10 is involved in the pathway leading to MDB formation in chemically transformed hepatocytes, as FAT10 knockout mice fail to develop MDB upon DDC-induced carcinogenesis (French et al. 2012). FAT10 is localized at chromosome 6q21.3, a region frequently amplified in HCC, and is a gene product involved in the regulation of proliferation, apoptosis, and epithelial-mesenchymal transition.

Pathogenesis of Mallory-Denk Bodies in Hepatocellular Carcinomas

MDB as Aggresomes

MDBs are complex cytoplasmic structures and aggresomes composed of several proteins, part of which are components of the cytoskeleton (Denk et al. 1975; Okamura 1976; Osborn and Weber 1989; Jensen and Gluud 1994; Stumptner et al. 2000, 2001; Riley et al. 2002; Strnad et al. 2008, 2012; Omary et al. 2009). These hyaline cytoplasmic inclusions are composed of modified cytokeratins, ubiquitin, heat shock proteins, and protein p62. By the use of immunofluorescence, it was shown that cytokeratins are a key component of MDB (Denk et al. 1979), altered cytokeratins forming unique fimbriated rods of filaments within MDB (Franke et al. 1979). It is currently thought that MDBs serve to clear the hepatocyte from cytoskeletal components altered by oxidative and other stressors (Stumptner et al. 2002), e.g., also in steatosis and steatohepatitis (Nishida et al. 2013). The close relationship between MDB and constituents of the hepatocyte cytoskeleton is also illustrated by the finding that microtubules are required for MDB morphogenesis (Riley et al. 2003). MDBs are related to cytokeratin aggresomes that can be induced by several stressors, but differ from aggresomes both morphologically and in their composition (Riley et al. 2002; Bardag-Gorce et al. 2004). Among the diverse classes of cytokeratins, cytokeratins 8 and 18 are major constituents of MDB (Nakamichi et al. 2002; Fickert et al. 2003). These two keratins are the characteristic cytoskeletal cytokeratins of normal hepatocytes (review: Omary et al. 2002). In mice hepatocytes, overexpression of cytokeratin 8 promotes MDB formation (Nakamichi et al. 2005), and expression of cytokeratins 8 and 18 in MDB can be induced in the setting of CCl4-induced liver damage (Jeong et al. 2005). Cytokeratin aggresomes chiefly result from hyperphosphorylation of cytokeratin 8 by p38 kinase (Nan et al. 2006), cytokeratin 8 phosphorylation regulating its transamidation via cross-linking by transglutaminase-2 (Kwan et al. 2012). In the course of its alteration taking place in aggregates becoming MDB, CK8 undergoes conformational changes from predominantly alpha-helical to cross beta-sheet, while CK18 and p62 do not show such a change (Mahajan et al. 2011). MDB and other aggresomes contain p62, a scaffolding protein that binds polyubiquitin (Zatloukal et al. 2002). p62 plays a role in protein degradation by the proteasome. The significance of p62 in MDB formation is underlined by the observation that overexpression of p62 in drug-primed cultured hepatocytes enhanced MDB formation, and that overexpression of p62 in normal mouse hepatocytes induced MDB-like aggresomes (Nan et al. 2004). As aggresomes, MDBs contain heat shock proteins of the 70b and 90b categories, proteins thought to play an important role in MDB biogenesis (Riley et al. 2003).

Role of the Ubiquitin-Proteasome Pathway

Inhibition of proteasomal degradation of ubiquitinated cytokeratins plays an important role in MDB formation (Bardag-Gorce et al. 2001, 2002; McPhaul et al. 2002). Ethanol induces MDB via inhibition of proteasomal degradation of ubiquitinated cytokeratins (Bardag-Gorce et al. 2006). Inhibition of proteasome function by bortezomib causes intracellular aggregation of serpins and the formation of MDB (Hernandez-Espinosa et al. 2008). Sequestosome1/p62, a

stress-inducible scaffolding and adaptor protein that binds to ubiquitin and polyubiquitinated proteins and is involved in the degradation of proteins by the proteasome, is involved in MDB formation (Nan et al. 2004; Stumptner et al. 2007). Binding of p62 to abnormal cytoskeletal cytokeratins may allow hepatocytes to dispose potentially harmful proteins (Stumptner et al. 2002). Inhibition of the proteasomal pathway causes cytokeratin aggresome formation, these aggresomes however being different from complete MDB (Bardag-Gorce et al. 2004).

Genomic Regulation of MDB Formation

The alterations of cytokeratins 8 and 18 required for MDB formation are genetically regulated (Haybaeck et al. 2012). Gene expression levels required for MDB formation are regulated by the NF-kappaB-p105 signaling pathway through ERK (Nan et al. 2005).

Immune Mechanisms in MDB Formation and the Role of Inflammatory Pathways

Mechanisms mediating inflammatory reactions participate in MDB formation. Toll-like receptors (TLR), in particular TLR2/4 and the downstream signaling components, MyD88 and TRAF-6, are upregulated in the MDB DDC-fed mice model (Bardag-Gorce et al. 2010. In livers with steatohepatitis and in HCC, the immunoproteasome plays a role in MDB formation. In a case of HCC forming NDB in tumor cells, co-localization of FAT10 and ubiquitin with LMP2, LMP7, and MECL-1 within the MDB was found, associated with a shift of the 26S proteasome to the immunoproteasome (French et al. 2010, 2011a). Cytokines such as TNF-alpha and interferon induce the expression of the LMP2, LMP7, and MECL-1 subunits of the immunoproteasome and of a protein overexpressed in HCC, in UbD, and in HCC, an induction mechanism promoting the formation of MDB in HCC (Oliva et al. 2010).

Hepatocyte-Extracellular Matrix Interactions

The formation of MDB in hepatocytes also depends on interactions between hepatocytes and proteins of the extracellular matrix. Laminin-integrin signaling, which activates ERK, triggers MDB formation (Wu et al. 2005).

Fate of MDB in Hepatocellular Carcinoma

It is currently not clear as to how many HCC cells harboring MDB will survive or will enter an apoptotic pathway. In particular, it has not been clarified whether HCC cells containing MDB are capable to divide and to pass the hyaline bodies to daughter cells. It is surmised that cells developing MDB exhibit a severe stress response and damage that might prevent further cell division. In the DDC mouse model of MDB formation, autophagy was shown to be a mechanism for the elimination of cytokeratin 8-containing MDB (Harada 2010).

References

Adinolfi LE, Durante-Mangoni E, Zampino R, Ruggiero G (2005) Review article: hepatitis C virus-associated steatosis – pathogenic mechanisms and clinical implications. Aliment Pharmacol Ther 22(supll. 2):52–55

Agaimy A, Kaiser A, Wuensch PH (2003) Severe cytological atypia (large cell change) in focal nodular hyperplasia with numerous Mallory bodies. A benign (adaptive) change ? Pathol Res Pract 199:509–511

Ahuja A, Rastogi A, Bihari C, Patidar Y, Pamecha V, Sarin SK (2014) Steatohepatitic variant hepatocellular carcinoma: a case report of new histologic variant. Trop Gastroenterol 35:49–51

Amidi F, French BA, Chung D, Halsted CH, Medici V, French SW (2007) M-30 and 4HNE are sequestered in different aggresomes in the same hepatocyte. Exp Mol Pathol 83:296–300

Baffy G, Brunt EM, Caldwell SH (2012) Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. J Hepatol 56:1384–1391

Bahcecioglu IH, Yalniz M, Ataseven H, Ilhan N, Ozercan IH, Seckin D, Sahin K (2005) Levels of serum hyaluronic acid, TNF-alpha and IL-8 in patients with nonalcoholic steatohepatitis. Hepato-Gastroenterology 52:1549–1553

Bardag-Gorce F, French BA, Lue YH, Nguyen V, Wan YJ, French SW (2001) Mallory bodies formed in proteasome-depleted hepatocytes: an immunohistochemical study. Exp Mol Pathol 70:7–18

Bardag-Gorce F, van Leeuwen FW, Nguyen V, French BA, Li J, Riley N, McPhaul LW et al (2002) The role of ubiquitin-proteasome pathway in the formation of mallory bodies. Exp Mol Pathol 73:75–83

Bardag-Gorce F, Riley NE, Nan L, Montgomery RO, Li J, French BA, Lue YH, French SW (2004) The proteasome inhibitor, PS-341, causes cytokeratin aggresome formation. Exp Mol Pathol 76:9–16

Bardag-Gorce F, French BA, Nan L, Song H, Nguyen SK, Yong H, Dede J, French SW (2006) CYP2E1 induced by ethanol causes oxidative stress, proteasome inhibition and cytokeratin aggresome (Mallory body-like) formation. Exp Mol Pathol 81:191–201

Bardag-Gorce F, Oliva J, Lin A, Li J, French BA, French SW (2010) SAMe prevents the up regulation of toll-like receptor signaling in Mallory-Denk body forming hepatocytes. Exp Mol Pathol 88:376–379

Bartolozzi C, Cioni D, Donati F, Lencioni R (2001) Focal liver lesions: MR imaging-pathologic correlation. Eur Radiol 11:1374–1388

Basaran C, Karcaaltincaba M, Akata D, Karabulut N, Akinci D, Ozmen M, Akhan O (2005) Fat-containing lesions of the liver: cross-sectional imaging findings with emphasis on MRI. AJR Am J Roentgenol 184:1103–1110

Bautista AP (2002) Neutrophilic infiltration in alcoholic hepatitis. Alcohol 27:17–21

Borenfreund E, deHarven E, Garra L (1981) Mallory body-like abnormalities in carcinomas induced by cultured transformed rat liver cells. Hepatology 1:408–415

Brandts J (1909) Ueber Einschlüsse im Kern der Leberzelle und ihre Beziehungen zur Pigmentbildung a) beim Hund, b) beim Menschen (On nuclear inclusions of liver cells and their relationship to pigment formation a) in the dog, b) in humans). Zieglers Beitr. 45

Budick-Harmelin N, Dudas J, Demuth J, Madar Z, Ramadori G, Tirosh O (2008) Triglycerides potentiate the inflammatory response in rat Kupffer cells. Antioxid Redox Signal 10:2009–2022

Cadrin M, Kawahara H, Ohta M, Katsuma Y, Marceau N, French SW (1990) Mallory bodies in hepatomas and hyperplastic nodules: in vitro and in vivo studies. Prog Clin Biol Res 331:231–248

Caldwell S, Ikura Y, Dias D, Isomoto K, Yabu A, Moskaluk C, Pramoonjago P, Simmons W et al (2010) Hepatocellular ballooning in NASH. J Hepatol 53:719–723

Cameron RG, Greig PD, Farber E, Wilson S, Sherman M, Levy GA, Phillips MJ (1993) Small encapsulated hepatocellular carcinoma of the liver. Provisional analysis of pathogenetic mechanisms. Cancer 72:2550–2559

Chagas AL, Kikuchi LO, Oliveira CP, Vezozzo DC, Mello ES, Oliveira AC, Cella LC et al (2009) Does hepatocellular carcinoma in non-alcoholic steatohepatitis exist in cirrhotic and non-cirrhotic patients? Braz J Med Biol Res 42:958–962

Chang YC, Tsai HM, Chow NH (2001) Hepatic angiomyolipoma with concomitant hepatocellular carcinomas. Hepato-Gastroenterology 48:253–255

Choi S, Diehl AM (2005) Role of inflammation in nonalcoholic steatohepatitis. Curr Opin Gastroenterol 21:702–707

Chung AY, Ng SB, Thng CH, Chow PK, Ooi LP (2002) Hepatic angiomyolipoma mimicking hepatocellular carcinoma. Asian J Surg 25:251–254

Cua IH, Hui JM, Kench JG, George J (2008) Genotype-specific interactions of insulin resistance, steatosis, and fibrosis in chronic hepatitis C. Hepatology 48:723–731

Das DK (1999) Cytodiagnosis of hepatocellular carcinoma in fine-needle aspirates of the liver: Its differentiation from reactive hepatocytes and metastatic adenocarcinoma. Diagn Cytopathol 21:370–377

Denk H, Geschnait F, Wolff K (1975) Hepatocellular hyalin (Mallory bodies) in long term griseofulvin-treated mice: a new experimental model for the study of hyalin formation. Lab Invest 32:773–776

Denk H, Franke WW, Eckerstorfer R, Schmid E, Kerjaschki D (1979) Formation and involution of Mallory bodies ("alcoholic hyalin") in murine and human liver revealed by immunofluorescence microscopy with antibodies to prekeratin. Proc Natl Acad Sci U S A 76:4112–4116

Denk H, Stumptner C, Fuchsbichler A, Müller T, Farr G, Müller W, Terracciano L, Zatloukal K (2006) Are the Mallory bodies and intracellular hyaline bodies in neoplastic and non-neoplastic hepatocytes related? J Pathol 208:653–661

Diab DL, Yerian L, Schauer P, Kashyap SR, Lopez R, Hazen SL, Feldstein AE (2008) Cytokeratin 18 fragment levels as a noninvasive biomarker for nonalcoholic steatohepatitis in bariatric surgery patients. Clin Gastroenterol Hepatol 6:1249–1254

Enat R, Buschmann RJ, Chomet B (1973) Ultrastructure of cytoplasmic hyaline inclusions in a case of human hepatocarcinoma. Gastroenterology 65:802–810

Farrell GC, Larter CZ (2006) Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 43 (suppl 1):S99–S112

Farrell GC, Teoh NC, McCuskey RS (2008) Hepatic microcirculation in fatty liver disease. Anat Rec (Hoboken) 291:684–692

Feldstein AE, Gores GJ (2005) Apoptosis in alcoholic and nonalcoholic steatohepatitis. Front Biosci 10:3093–3099

Fickert P, Trauner M, Fuchsbichler A, Stumptner C, Zatloukal K, Denk H (2003) Mallory body formation in primary biliary cirrhosis is associated with increased amounts and abnormal phosphorylation and ubiquitination of cytokeratins. J Hepatol 38:387–394

Franke WW, Fenk H, Schmid E, Osborn M, Weber K (1979) Ultrastructural, biochemical, and immunologic characterization of Mallory bodies in livers of griseofulvin-treated mice. Fimbriated rods of filaments

containing prekeratin-like polypeptides. Lab Invest 40:207–220
French SW, Bardag-Gorce F, Li J, French BA, Oliva J (2010) Mallory-Denk body pathogenesis revisited. World J Hepatol 2:295–301
French BA, Oliva J, Bardag-Gorce F, French SW (2011a) The immunoproteasome in steatohepatitis: its role in Mallory-Denk body formation. Exp Mol Pathol 90:252–256
French SW, Bardag-Gorce F, French BA, Li J, Oliva J (2011b) The role of innate immunity in the pathogenesis of preneoplasia in drug-induced chronic hepatitis based on a mouse model. Exp Mol Pathol 91:653–659
French SW, French BA, Oliva J, Li J, Bardag-Gorce F, Tillman B, Canaan A (2012) FAT10 knock out mice livers fail to develop Mallory-Denk bodies in the DDC mouse model. Exp Mol Pathol 93:309–314
Gabata T, Kodoya M, Matsui O, Ueda K, Kawamori Y, Terayama N, Sanada J, Kobayashi S (2001) Peritumoral spared area in fatty liver: correlation between opposed-phase gradient-echo MR imaging and CT arteriography. Abdom Imaging 26:384–389
Gao Q, Zhao YJ, Wang XY, Qiu SJ, Shi YH, Sun J, Yi Y, Shi JY, Shi GM, Ding ZB et al (2012) CXCR6 upregulation contributes to a proinflammatory tumor microenvironment that drives metastasis and poor patient outcomes in hepatocellular carcinoma. Cancer Res 72:3546–3556
Gentile CL, Pagliassotti MJ (2008) The role of fatty acids in the development and progression of nonalcoholic fatty liver disease. J Nutr Biochem 19:567–576
Gluud C, Hardt F, Aldershvile J, Christoffersen P, Lyon H, Nielsen J (1981) Isolation of Mallory bodies and an attempt to demonstrate cell mediated immunity to Mallory body isolate in patients with alcoholic liver disease. J Clin Pathol 34:1010–1016
Gomez-Lechon MJ, Donato MT, Martinez-Romero A, Jimenez N, Castell JV, O'Connor JE (2007) A human hepatocellular in vitro model to investigate steatosis. Chem Biol Interact 165:106–116
Greenfield V, Cheung O, Sanyal AJ (2008) Recent advances in nonalcoholic fatty liver disease. Curr Opin Gastroenterol 24:320–327
Gupta N, Rastogi A, Bihari C (2014) Steatohepatitic hepatocellular carcinoma – a case report with literature review. Indian J Surg Oncol 5:161–163
Harada M (2010) Autophagy is involved in the elimination of intracellular inclusions, Mallory-Denk bodies, in hepatocytes. Med Mol Morphol 43:13–18
Haybaeck J, Stumptner C, Thueringer A, Kolbe T, Magin TM, Hesse M, Fickert P et al (2012) genetic background effects of keratin 8 and 18 in a DCC-induced hepatotoxicity and Mallory-Denk body formation mouse model. Lab Invest 92:857–867
Hernandez-Espinosa D, Miñano A, Martinez C, Ordoñez A, Pérez-ceballos E, de Arriba F et al (2008) Inhibition of proteasome by bortezomib causes intracellular aggregation of hepatic serpins and increases the latent circulating form of antithrombin. Lab Invest 88:306–317
Hoso M, Kananuma Y (1990) Clinicopathological characteristics of hepatocellular carcinoma bearing Mallory bodies: an autopsy study. Liver 10:264–268
Hoso M, Nakanuma Y (1989) Cytophotometric DNA analysis of hepatocellular carcinoma with Mallory bodies. Virchows Arch A Pathol Anat Histopathol 416:51–55
Ichida T (1983) Ultrastructural study of intracytoplasmic deposits in human hepatocellular carcinoma. Gastroenterol Jpn 18:560–576
Ijaz S, Yang W, Winslet MC, Seifalian AM (2003) Impairment of hepatic microcirculation in fatty liver. Microcirculation 10:447–456
Ikura Y, Ohsawa M, Suekane T, Fukushima H, Itabe H, Jomura H, Nishiguchi S, Inoue T et al (2006) Localization of oxidized phosphatidylcholine in nonalcoholic fatty liver disease: impact on disease progression. Hepatology 43:506–514
Imai Y, Kubota Y, Yamamoto S, Tsuji K, Shimatani M, Shibatani N, Takamido S, Matsushita M et al (2005) Neutrophils enhance invasion activity of human cholangiocellular carcinoma and hepatocellular carcinoma cells: an in vitro study. J Gastroenterol Hepatol 20:287–293
Ishikawa D, Shimada M, Utsunomiya T, Morine Y, Imura S, Ikemoto T, Mori H, Arakawa Y et al (2013) Atypically large well-differentiated hepatocellular carcinoma with extensive fatty metamorphosis: report of a case. J Med Invest 60:267–271
Itai Y, Ohtomo K, Kokubo T, Makita K, Okada Y, Machida T, Yashiro N (1987) CT and MR imaging of fatty tumors of the liver. J Comput Assist Tomogr 11:253–257
Ito S, Yukawa T, Uetake S, Yamauchi M (2007) Serum intercellular adhesion molecule-1 in patients with nonalcoholic steatohepatitis: comparison with alcoholic hepatitis. Alcohol Clin Exp Res 31(suppl1): S83–S87
Jaeschke H (2002) Neutrophil-mediated tissue injury in alcoholic hepatitis. Alcohol 27:23–27
Jain D, Nayak NC, Kumaran V, Saigal S (2013) Steatohepatitic hepatocellular carcinoma, a morphologic indicator of associated metabolic risk factors: a study from India. Arch Pathol Lab Med 137:961–966
Jensen K, Gluud C (1994) The Mallory body: morphological, clinical and experimental studies (Part1 of a literature survey). Hepatology 20:1061–1077
Jeong WI, Jeong DH, Do SH, Yang HJ, Hong IH, Chang SJ, Yuan DW, Kwak DM et al (2005) Expression of cytokeratins 8 and 18 on Mallory body and oval cell in rats during hepatic fibrosis. In Vivo 19:769–775
Jhaveri R, McHutchinson J, Patel K, Qiang G, Diehl AM (2008) Specific polymorphisms in hepatitis C virus genotype 3 core protein associated with intracellular lipid accumulation. J Infect Dis 197:283–291
Joshi-Barve S, Barve SS, Amancherla K, Gobejishvili L, Hill D, Cave M, Hote P, McClain CJ (2007) Palmitic acid induces production of proinflammatory cytokine interleukin-8 from hepatocytes. Hepatology 46:823–830

Kameda Y, Shinji Y (1992) Early detection of hepatocellular carcinoma by laparoscopy: yellow nodules as diagnostic indicators. Gastrointest Endosc 38:554–559

Kanno T, Kurioka N, Kim S, Tamori A, Kim K, Oka H et al (1989) Implications of hyperechoic lesions in small hepatocellular carcinoma. Gastroenterol Jpn 24:528–534

Kawada N, Imanaka K, Kawaguchi T, Tamai C, Ishihara R, Matsunaga T, Gotoh K et al (2009) Hepatocellular carcinoma arising from non-cirrhotic non-alcoholic steatohepatitis. J Gastroenterol 44:1190–1194

Keeley AF, Iseri OA, Gottlieb LS (1972) Ultrastructure of hyaline cytoplasmic inclusions in a human hepatoma: relationship to Mallory's alcoholic hyaline. Gastroenterology 62:280–293

Kemper J, Jung G, Poll LW, Jonkmanns C, Lüthen R, Moedder U (2002) CT and MRI findings of multifocal hepatic steatosis mimicking malignancy. Abdom Imaging 27:708–710

Khan M, Jahan S, Khaliq S, Iljaz B, Ahmad W, Samreen B, Hassan S (2010) Interaction of the hepatitis C virus (HCV) core with cellular genes in the development of HCV-induced steatosis. Arch Virol 155:1735–1753

Kim SR, Kim KI, Maekawa Y, Imoto S, Ninomiya T, Mita K, Ando K, Fukuda K, Fuki S, Kudo M et al (2005) Well-differentiated HCC manifesting hyperattenuation on CT during arterial portography. Hepato-Gastroenterology 52:1559–1562

Kim SR, Imoto S, Ikawa H, Ando K, Mita K, Fuki S, Sakamoto M, Kanbara Y, Matsuoka T, Kudo M, Hayashi Y (2007) Well-to moderately-differentiated HCC manifesting hyperattenuation on both CT during arteriography and arterial portography. World J Gastroenterol 13:5775–5778

Kim E, Li K, Lieu C, Tong S, Kawai S, Fukutomi T, Zhou Y, Wands J, Li J (2008) Expression of apolipoprotein C-IV is regulated by Ku antigen/peroxisome proliferator-activated receptor gamma complex and correlates with liver steatosis. J Hepatol 49:787–798

Kojiro M (2004) Focus on dysplastic nodules and early hepatocellular carcinoma: an Eastern point of view. Liver Transpl 10(suppl 1):S3–S8

Kondo Y, Kondo F, Wada K, Okabayashi A (1986) Pathologic features of small hepatocellular carcinoma. Acta Pathol Jpn 36:1149–1161

Kröncke TJ, Taupitz M, Kivelitz D, Scheer I, Daberkow U, Rudolph B, Hamm B (2000) Multifocal nodular fatty infiltration of the liver mimicking metastatic disease on CT: imaging findings and diagnosis using MR imaging. Eur Radiol 10:1095–1100

Ku NO, Strnad P, Zhong BH, Tao GZ, Omary MB (2007) Keratins let liver live: mutations predispose to liver disease and crosslinking generates Mallory-Denk bodies. Hepatology 46:1639–1649

Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L (2011) Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol 54:948–955

Kutami R, Nakashima Y, Nakashima O, Shiota K, Kojiro M (2000) Pathomorphologic study on the mechanism of fatty change in small hepatocellular carcinoma of humans. J Hepatol 33:282–289

Kwan R, Hanada S, Harada M, Strnad P, Li DH, Omary MB (2012) Keratin 8 phosphorylation regulates its transamidation and hepatocyte Mallory-Denk body formation. FASEB J 26:2318–2326

Lalor PF, Faint J, Aarbodem Y, Hubscher SG, Adams DH (2007) The role of cytokines and chemokines in the development of steatohepatitis. Semin Liver Dis 27:173–193

Laurent C, Quaglia A, Foroni L, Bioulac-Sage P, Balabaud C, Dhillon AP (2006) Genomic alteration is not associated with fatty and clear cell change in hepatocellular carcinomas and its precursor nodular lesions in cirrhotic liver. Hepatol Res 36:40–47

Leevy CB, Elbeshbeshy HA (2005) Immunology of alcoholic liver disease. Clin Liver Dis 9:55–66

Li YW, Qiu SJ, Fan J, Zhou J, Gao Q, Xiao YS, Xu YF (2011) Intratumoral neutrophils: a poor prognostic factor for hepatocellular carcinoma following resection. J Hepatol 54:497–505

Livni N, Behar A, Brautbar N (1977) Ultrastructure of hepatocellular carcinoma in a cirrhotic liver. Isr J Med Sci 13:590–599

Ma KL, Ruan XZ, Powis SH, Chen Y, Moorhead JF, Varghese Z (2008) Inflammatory stress exacerbates lipid accumulation in hepatic cells and fatty livers of apolipoprotein E knockout mice. Hepatology 48:770–781

Machado MV, Cortez-Pinto H (2011) Cell death and nonalcoholic steatohepatitis: where is ballooning relevant? Expert Rev. Gastroenterol Hepatol 5:213–222

Maeda T, Hashimoto K, Kihara Y, Ikegani T, Ishida T, Aimitsu S, Fujiwara M (2008) Surgically resected hepatocellular carcinomas in patients with non-alcoholic steatohepatitis. Hepato-Gastroenterology 55:1404–1406

Mahajan V, Klingstedt T, Simon R, Nilsson KP, Thueringer A, Kashofer K, Haybaeck J et al (2011) Cross b-sheet conformation of keratin 8 is a specific feature of Mallory-Denk bodies compared with other hepatocyte inclusions. Gastroenterology 141:1080–1090

Malhi H, Gores GJ (2008) Molecular mechanisms of lipotoxicity in nonalcoholic fatty liver disease. Semin Liver Dis 28:360–369

Mallory FB (1911) Cirrhosis of the liver: five different lesions from which it may arise. Bull Johns Hopkins Hosp 22:6975

Martin J, Sentis M, Puig J, Rué M, Falco J, Donoso L, Zidan A (1996) Comparison of in-phase and opposed –phase GRE and conventional SE MR pulse sequence in T1-weighted imaging of liver lesions. J Comput Assist Tomogr 20:890–897

Mathew T, Affandi MZ (1989) Fine needle aspiration biopsy of a hepatic mass. An example of a near error. Acta Cytol 33:861–864

McPhaul LW, Wang J, Hol EM, Sonnemans MA, Riley N, Nguyen V, Yuan QX, Lue YH et al (2002) Molecular misreading of the ubiquitin B gene and hepatic Mallory body formation. Gastroenterology 122:1878–1885

Mehta K, Van Thiel DH, Shah N, Mobarhan S (2002) Nonalcoholic fatty liver disease: pathogenesis and the role of antioxidants. Nutr Rev 60:289–293

Mitchell CM, Sturgis CD (2009) Lipid-rich hepatocellular carcinoma in fine-needle aspiration biopsy. Diagn Cytopathol 37:36–37

Miyaaki H, Fujimoto M, Kurogi M, Nakashima O, Eguchi K, Kojiro M (2005) Pathomorphological study on small nodular lesions in hepatitis C virus-related cirrhosis. Oncol Rep 14:1469–1474

Monzawa S, Omata K, Shimazu N, Yagawa A, Hosoda K, Araki T (1999) Well-differentiated hepatocellular carcinoma: findings of US, CT, and MR imaging. Abdom Imaging 24:392–397

Morii K, Nakamura S, Yamamoto T, Okushin H (2013) Steatotic regenerative nodules mimicking hepatocellular carcinoma. Liver Int. . . ..

Moriya K, Yotsuyanagi H, Shintani Y, Fujie H, Ishibashi K, Matsuura Y, Miyamura T, Koike K (1997) Hepatitis C virus core protein induces hepatic steatosis in transgenic mice. J Gen Virol 78:1527–1531

Nakamichi I, Hatakeyama S, Nakayama KI (2002) Formation of Mallory body-like inclusions and cell death induced by deregulated expression of keratin 18. Mol Biol Cell 13:3441–3451

Nakamichi I, Toivola DM, Strnad P, Michie SA, Oshima RG, Baribault H, Omary MB (2005) Keratin 8 overexpression promotes mouse Mallory body formation. J Cell Biol 171:931–937

Nakanuma Y, Ohta G (1984) Small hepatocellular carcinoma containing many Mallory bodies. Liver 4:128–133

Nakanuma Y, Ohta G (1985) Is Mallory body formation a preneoplastic change ? A study of 181 cases of liver bearing hepatocellular carcinoma and 82 cases of cirrhosis. Cancer 55:2400–2404

Nakanuma Y, Ohta G (1986) Expression of Mallory bodies in hepatocellular carcinoma in man and its significance. Cancer 57:81–86

Nakanuma Y, Ohta G, Sugiura H, Watanabe K, Doishita K (1986) Incidental solitary hepatocellular carcinomas smaller than 1 cm in size found at autopsy: a morphologic study. Hepatology 6:631–635

Nakanuma Y, Terada T, Doishita K, Miwa A (1990) Hepatocellular carcinoma in primary biliary cirrhosis: an autopsy study. Hepatology 11:1010–1016

Nakanuma Y, Hirata K, Terasaki S, Ueda K, Matsui O (1998) Analytical histopathological diagnosis of small hepatocellular nodules in chronic liver disease. Histol Histopathol 13:1077–1087

Nan L, Wu Y, Bardag-Gorce F, Li J, French BA, Fu AN, Francis T, Vu J, French SW (2004) p62 is involved in the mechanism of Mallory body formation. Exp Mol Pathol 77:168–175

Nan L, Bardag-Gorce F, Li J, French BA, Wilson LT, French SW (2005) The p105/50 NF-kappaB pathway is essential for Mallory body formation. Exp Mol Pathol 78:198–206

Nan L, Bardag-Gorce F, Wu Y, Li J, French BA, French SW (2006a) Mallory body forming cells express the preneoplastic hepatocyte phenotype. Exp Mol Pathol 80:109–118

Nan L, Dedes J, French BA, Bardag-Gorce F, Li J, Wu Y, French SW (2006b) Mallory body (cytokeratin aggresomes) formation is prevented in vitro by p38 inhibitor. Exp Mol Pathol 80:228–240

Negro F (2006) Mechanisms and significance of liver steatosis in hepatitis C virus infection. World J Gastroenterol 12:6756–6765

Nishida T, Tsuneyama K, Fujimoto M, Nomoto K, Hayashi S, Miwa S, Nakajima T, Nakanishi Y et al (2013) Spontaneous onset of nonalcoholic steatohepatitis and hepatocellular carcinoma in a mouse model of metabolic syndrome. Lab Invest 93:230–241

Nishiofuku H, Marugami N, Tanaka T, Anai H, Maeda S, Masada T, Takano M, Mitoro A, Kichikawa K (2013) Isolated fat-containing pancreatic metastasis from hepatocellular carcinoma. Jpn J Radiol 31:408–411

Norkin SA, Campagna-Pinto D (1968) Cytoplasmic hyaline inclusions in hepatoma. Histochemical study. Arch Pathol 86:25–32

Noro T, Gotohda N, Kojima M, Konishi M, Nakaghori T, Takahashi S, Hasebe T, Kinoshita T (2010) Hepatocellular carcinoma with foamy histiocyte-like appearance: a deceptively clear cell carcinoma appearing variant. Case Rep Gastroenterol 4:286–292

Oda M, Furuta S, Omori A, Hanaoka S, Nagata A (1972) Case of primary hepatic cancer accompanied with numerous Mallory bodies (in Japanese). Naika 29:582–586

Ohta M, Marceau N, Perry G, Manetto V, Gambetti P, Autilio-Gambetti L, Metuzals J et al (1988) Ubiquitin is present on the cytokeratin intermediate filaments and Mallory bodies of hepatocytes. Lab Invest 59:848–856

Okamura K (1976) A study of Mallory bodies. Isolation, ultrastructure and preliminary biochemical characterization of Mallory bodies from livers of alcoholic cirrhosis and malignant hepatoma. Acta Pathol Jpn 26:649–670

Oliva J, Bardag-Gorce F, French BA, Li J, McPhaul L, Amidi F, Dedes J, Habibi A et al (2008) Fat10 is an epigenetic marker for liver preneoplasia in a drug-primed mouse model of tumorigenesis. Exp Mol Pathol 84:102–112

Oliva J, Bardag-Gorce F, Lin A, French BA, French SW (2010) The role of cytokines in UbD promoter regulation and Mallory-Denk body-like aggresomes. Exp Mol Pathol 89:1–8

Omary MB, Ku NO, Toivola DM (2002) Keratins: guardians of the liver. Hepatology 35:251–257

Omary MB, Ku NO, Strnad P, Hanada S (2009) Toward unraveling the complexity of simple epithelial keratins in human disease. J Clin Invest 119:1794–1805

Orikasa H, Ohyama R, Tsuka N, Eyden BP, Yamazaki K (2001) Lipid-rich clear-cell hepatocellular carcinoma

arising in non-alcoholic steatohepatitis in a patient with diabetes mellitus. J Submiscrosc Cytol Pathol 33:195–200

Osborn M, Weber K (1989) Keratins, transglutaminase, and Mallory bodies – the really insoluble stuff. Lab Invest 61:585–587

Patterson AD, Maurhaofer O, Beyoglu D, Lanz C, Krausz KW, Pabst T, Gonzalez FJ et al (2011) Aberrant lipid metabolism in hepatocellular carcinoma revealed by plasma metabolomics and lipid profiling. Cancer Res 71:6590–6600

Pei RJ, Danbara N, Tsujita-Kyutoku M, Yuri T, Tsubura A (2004) Immunohistochemical profiles of Mallory body by a panel of anti-cytokeratin antibodies. Med Electron Microsc 37:114–118

Peters RL (1976) Pathology of hepatocellular carcinoma. In: Okuda K, Peters RL (eds) Hepatocellular carcinoma. Wiley, New York

Peters M, Tinberg HM, Govindarajan S (1982) Immunocytochemical identity of hepatocellular hyaline in alcoholic and non-alcoholic liver diseases. Liver 2:361–368

Peters M, Liebman HA, Tong MJ, Tinberg HM (1983) Alcoholic hepatitis: granulocytic chemotactic factor from Mallory body-stimulated human peripheral blood mononuclear cells. Clin Immunol Immunopathol 28:418–430

Petta S, Craxi A (2010) Hepatocellular carcinoma and non-alcoholic fatty liver disease: from a clinical to a molecular association. Curr Pharm Des 16:741–752

Piodi A, Chouteau P, Lerat H, Hézode C, Pawlotsky JM (2008) Morphological changes in intracellular lipid droplets induced by different hepatitis C virus genotype core sequences and relationship with steatosis. Hepatology 48:16–27

Prasad SR, Wang H, Rosas H, Menias CO, Narra VR, Middleton WD, Heiken JP (2005) Fat-containing lesions of the liver: radiologic-pathologic correlation. Radiographics 25:321–331

Pupulim LF, Hakimé A, Barrau V, Abdel-Rehim M, Zappa M, Vilgrain V (2009) Fatty hepatocellular carcinoma: radiofrequency ablation – imaging findings. Radiology 250:940–948

Pusl T, Wild N, Vennegeerts T, Wimmer R, Göke B, Brand S, Rust C (2008) Free fatty acids sensitize hepatocytes to bile acid-induced apoptosis. Biochem Biophys Res Commun 371:441–445

Ramalho F (2003) Hepatitis C virus infection and liver steatosis. Antiviral Res 60:125–127

Riley NE, Li J, Worrall S, Rothnagel JA, Swagell C, van Leeuwen FW, French SW (2002) The Mallory body as an aggresome: in vitro studies. Exp Mol Pathol 72:17–23

Riley NE, Bardag-Gorce F, Montgomery RO, Li J, Lungo W, Lu YH, French SW (2003a) Microtubules are required for cytokeratin aggresome (Mallory body) formation in hepatocytes: an in vitro study. Exp Mol Pathol 74:173–179

Riley NE, Li J, McPhaul LW, Bardag-Gorce F, Lue YH, French SW (2003b) Heat shock proteins are present in Mallory bodies (cytokeratin aggresomes) in human liver biopsy specimens. Exp Mol Pathol 74:168–172

Roingeard P, Hourioux C (2008) Hepatitis C virus core protein, lipid droplets and steatosis. J Viral Hepat 15:157–164

Roque AL (1953) Chromotrope aniline blue method of staining Mallory bodies of Laennec's cirrhosis. Lab Invest 2:15–21

Roschlau G, Kemmer C (1967) On the histochemical and submicroscopic structure of hyaline liver cell inclusions (in German). Gegenbaurs Morphol Jahrb 111:208–215

Roth JA, Berman E, Befeler D, Johnson FB (1982) A black hepatocellular carcinoma with Dubin-Johnson-like pigment and Mallory bodies: a histochemical and ultrastructural study. Am J Surg Pathol 6:375–382

Rozman D (2014) From nonalcoholic fatty liver disease to hepatocellular carcinoma: a systems understanding. Dig Dis Sci

Sakurai M, Wakasa K, Monden M, Yamada T, Kuroda C, Marukawa T, Okamura J (1989) Hepatocellular carcinoma in adenomatous hyperplasia of the liver. Cancer Chemother Pharmacol 23(suppl):S110–S113

Salomao M, Yu WM, Brown RS, Ermond JC, Lefkowitch JH (2010) Steatohepatitic hepatocellular carcinoma (SH-HCC): a distinctive histological variant of HCC in hepatitis C virus-related cirrhosis with associated NAFLD/NASH. Am J Surg Pathol 34:1630–1636

Salomao M, Remotti H, Vaughan R, Sigele AB, Lefkowitch JH, Moreira RK (2012) The steatohepatitic variant of hepatocellular carcinoma and its association with underlying steatohepatitis. Hum Pathol 43:737–746

Scotto J, Homberg JC, Stralin H, Caroli J (1974) Ultrastructural study of cytoplasmic inclusions in cases of viral hepatitis and hepatomas. Pathol Eur 9:211–216

Seki S, Kitada T, Kawada N, Kadoya H, Sakaguchi H, Nakatani K, Satake K (2002) Fatty change in human hepatocellular carcinoma cell lines derived from patients with antibodies to hepatitis C virus. Hepato-Gastroenterology 49:340–344

Selzner M, Rüdiger HA, Sindram D, Madden J, Clavien PA (2000) Mechanisms of ischemic injury are different in the steatotic and normal rat liver. Hepatology 32:1280–1288

Seong JS, Han EK, Han KH, Noh SH, Park CI, Loh JJK, Choi HJ (1991) Histological studies of surgically resected hepatocellular carcinoma following combined radiotherapy and hyperthermia. Yonsei Med J 32:147–156

Sheikh MY, Choi J, Qadri I, Friedman JE, Sanyal AJ (2008) Hepatitis C virus infection: molecular pathways to metabolic syndrome. Hepatology 47:2127–2133

Shibahara J, Ando S, Sakamoto Y, Kokudo N, Fukayama M (2014) Hepatocellular carcinoma with steatohepatitic features: a clinicopathological study of Japanese patients. Histopathology 64:951–962

Shimada M, Hashimoto E, Taniai M, Hasegawa K, Okuda H, Hayashi N, Takasaki K et al (2002)

Hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. J Hepatol 37:154–160

Sohda T, Kamimura S, Iwata K, Shijo H, Okumura M (1997) Immunohistochemical evidence of insulin-like growth factor II in human small hepatocellular carcinoma with hepatitis C virus infection: relationship to fatty change in carcinoma cells. J Gastroenterol Hepatol 12:224–228

Strand P, Tao GZ, So P, Lau K, Schilling J, Wei Y, Liao J, Omary MB (2008) "Toxic memory" via chaperone modification is a potential mechanisms for rapid Mallory-Denk body reinduction. Hepatology 48:931–942

Strnad P, Zatloukal K, Stumptner C, Kulaksiz H, Denk H (2008) Mallory-Denk-bodies: lessons from keratin-containing hepatic inclusion bodies. Biochim Biophys Acta 1782:764–774

Strnad P, Paschke S, Jang KH, Ku NO (2012) Keratins: markers and modulators of liver disease. Curr Opin Gastroenterol 28:209–216

Stumptner C, Heid H, Fuchsbichler A, Hauser H, Mischinger HJ, Zatloukal K, Denk H (1999) Analysis of intracytoplasmic hyaline bodies in a hepatocellular carcinoma. Demonstration of p62 as major constituent. Am J Pathol 154:1701–1710

Stumptner C, Omary MB, Fickert P, Denk H, Zatloukal K (2000) Hepatocyte cytokeratins are hyperphosphorylated at multiple sites in human alcoholic hepatitis and in a Mallory body mouse model. Am J Pathol 156:77–90

Stumptner C, Fuchsbichler A, Lehner M, Zatloukal K, Denk H (2001) Sequence of events in the assembly of Mallory body components in mouse liver: clues to the pathogenesis and significance of Mallory body formation. J Hepatol 34:665–675

Stumptner C, Fuchsbichler A, Heid H, Zatloukal K, Denk H (2002) Mallory body – a disease-associated type of sequestosome. Hepatology 35:1053–1062

Stumptner C, Fuchsbichler A, Zatloukal K, Denk H (2007) In vitro production of Mallory bodies and intracellular hyaline bodies: the central role of sequestosome 1/p62. Hepatology 46:851–860

Takahashi T, So-Wan T, Kamimura T, Asakura H (2000) Infiltrating polymorphonuclear leukocytes and apoptotic bodies derived from hepatocytes but not from ballooning hepatocytes containing Mallory bodies show nuclear DNA fragmentation in alcoholic hepatitis. Alcohol Clin Exp Res 24(suppl):68S-–73S

Takayasu K, Furukawa H, Wakao F, Muramatsu Y, Abe H, Terauchi T, Winter TC, Sakamoto M, Hirohashi S (1995) CT diagnosis of early hepatocellular carcinoma: sensitivity, findings, and CT-pathologic correlation. AJR Am J Roentgenol 164:885–890

Tanaka S, Kitamura T, Imaoka S, Sasaki Y, Taniguchi H, Ishiguro S (1983) Hepatocellular carcinoma: sonographic and histologic correlation. AJR Am J Roentgenol 140:701–707

Tanaka N, Moriya K, Kiyosawa K, Koike K, Gonzalez FJ, Aoyama T (2008) PPARalpha activation is essential for HCV protein-induced hepatic steatosis and hepatocellular carcinoma in mice. J Clin Invest 118:683–694

Terada T, Nakanuma Y, Hoso M, Saito K, Sasaki M, Nonomura A (1989) Fatty macroregenerative nodule in non-steatotic liver cirrhosis. A morphologic study. Virchows Arch A Pathol Anat Histopathol 415:131–136

Terasaki S, Kaneko S, Kobayashi K, Nonomura A, Nakanuma Y (1998) Histological features predicting malignant transformation of nonmalignant hepatocellular nodules: a prospective study. Gastroenterology 115:1216–1222

Tsai CC, Huang SC, Lin H, Ou YC, Ko SF, Liu YS (2006) Steatotic hepatocellular carcinomatosis mimicking malignant ovarian teratoma. Ultrasound Obstet Gynecol 27:586–587

Ueda E, Hirota S, Fujii M, Tanaka K, Shimizu M, Kono M, Hase M, Sako M (1989) Three cases of hepatocellular carcinoma with remarkable fatty metamorphosis (in Japanese). Rinsho Hoshasen 34:921–924

Valls C, Iannacconne R, Alba E, Murakami T, Hori M, Passariello R, Vilgrain V (2006) Fat in the liver: diagnosis and characterization. Eur Radiol 16:2292–2308

Valva P, De Matteo E, Galoppo M, Pedreira A, Giacove G, Lezama C, Marco I, Galoppo MC, Preciado MV (2008) Apoptosis markers in liver biopsy of nonalcoholic steatohepatitis in pediatric patients. Hum Pathol 39:1816–1822

Virtanen I, Lehto VP, Kurki P, Miettinen A, Linder E, Stenman S (1979) Intermediate filaments in hyaline material in alcoholic liver disease (Mallory bodies) and in cultures hepatoma cells. Virchows Arch B Cell Pathol 29:363–367

Vos MB, Barve S, Joshi-Barve S, Carew JD, Whitington PF, McClain CJ (2008) Cytokeratin 18, a marker of cell death, is increased in children with suspected nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr 47:481–485

Wee A, Nilsson B, Chan WC, Yap I (1991) Fine needle aspiration biopsy of hepatocellular carcinoma. Some unusual features. Acta Cytol 35:661–670

Wegelin C (1928) Ueber das Vorkommen von Fett in Leberzellkernen (On the presence of fat in hepatocyte nuclei). Verhandl Deutsch Pathol Ges 23:519–522

Wong RJ, Cheung R, Ahmed A (2014) Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 59:2188–2195

Wu Y, Nan L, Bardag-Gorce F, Li J, French BA, Wilson LT, Dedes J, French SW (2005) The role of laminin-integrin signaling in triggering MB formation. An in vivo and in vitro study. Exp Mol Pathol 79:1–8

Wu Y, Zhao Q, Peng C, Sun L, Li XF, Kuang DM (2011) Neutrophils promote motility of cancer cells via a hyaluronan-mediated TLR4/PI3K activation loop. J Pathol 225:438–447

Yahagi N, Shimano H, Hasegawa K, Ohashi K, Matsuzaka T, Najima Y, Sekiya M et al (2005) Co-ordinate activation of lipogenic enzymes in hepatocellular carcinoma. Eur J Cancer 41:1316–1322

Yamagata M, Masaki T, Okudaira T, Imai Y, Shiina S, Shiratori Y, Omata M (1999) Small hyperechoic nodules in chronic liver diseases include hepatocellular carcinomas with low cyclin D1 and Ki-67 expression. Hepatology 29:1722–1729

Yoshikawa J, Matsui O, Takashima T, Ida M, Takanaka T, Kawamura I, Kakuda K, Miyata S (1988) Fatty metamorphosis in hepatocellular carcinoma: radiologic features in 10 cases. AJR Am J Roentgenol 151:717–720

Yoshimatsu S, Inoue Y, Ibukuro K, Suzuki S (1989) Hypovascular hepatocellular carcinoma undetected at angiography and CT with iodized oil. Radiology 171:343–347

Zatloukal K, Stumptner C, Fuchsbichler A, Heid H, Schnoelzer M, Kenner R, Kleinert R et al (2002) p62 is a common component of cytoplasmic inclusions in protein aggregation diseases. Am J Pathol 160:255–263

Zatloukal K, French SW, Stumptner C, Strnad P, Harada M, Toivola DM, Cadrin M et al (2007) From Mallory to Mallory-Denk bodies: what, how and why ? Exp Cell Res 313:2033–2049

Zen Y, Katayanagi K, Tsuneyama K, Harada K, Araki I, Nakanuma Y (2001) Hepatocellular carcinoma arising in non-alcoholic steatohepatitis. Pathol Int 51:127–131

Zhou SL, Dai Z, Zhou ZJ, Wang XY, Yang GH, Wang Z, Huang XW, Fan J, Zhou J (2012) Overexpression of CXCL5 mediates neutrophil infiltration and indicates poor prognosis for hepatocellular carcinoma. Hepatology 56:2242–2254

Zimmermann A (2002) Hepatocellular carcinoma: the pathway from progenitor cells to novel entities. Ann Diagn Paediatr Pathol 6:21–28

Zimmermann A (2006) Malignant epithelial liver tumors in children, adolescents and adults: molecular pathways of cancerogenesis, growth. and spread. In: Lee F (ed) Liver cancer: new research. Nova, New York, pp 1–41

Hepatocellular Carcinomas with Increased Stromal Reactions

11

Contents

Abstract

A rare group of hepatocellular carcinoma (HCC) is characterized by the presence of an abundant desmoplastic stroma, similar to that observed in cholangiocarcinoma. Scirrhous HCC is an uncommon and heterogeneous variant that resembles fibrolamellar HCC and often shows a contiguous multinodular growth pattern. Histologically, scirrhous HCC shows a diffuse pattern of fibrosis with radiating structures. For diagnosis, at least 50 % of the tumor must consist of a scirrhous fibrotic component, but reproducible diagnostic criteria have not yet been worked out.

In sclerosing HCC, tumor cells are embedded in an abundant and sclerosing stroma that does not show a laminated pattern. Part of sclerosing HCCs are associated with paraneoplastic hypercalcemia caused by ectopic production of parathyroid hormone-like peptide or prostaglandin E. Biologically, stroma-rich HCCs seem to behave as ordinary HCCs.

Scirrhous Hepatocellular Carcinoma

Introduction

Scirrhous hepatocellular carcinoma (SHCC) is an uncommon variant of HCC characterized by diffuse fibrosis or diffuse desmoplasia of the tumor. SHCC must not be confounded with tumors called

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_11

"sclerosing hepatocellular carcinoma," a complex group of liver malignancies that develop in the non-cirrhotic liver and are characterized by unique metabolic disorders, in particular hypercalcemia (see the respective chapter). In contrast to SHCC, which is accepted as distinct variant of HCC, "sclerosing HCC" has been deleted from the WHO classification.

Epidemiology

SHCC is a rare lesion. In one study, 3.7 % of HCCs were SHCC, with a male-female ratio of 4:1 (Okamura et al. 2005). In a series of 546 consecutive resected HCCs without preoperative anticancer therapies, 25 SHCC were identified (4.6 %; Kurogi et al. 2006). In the latter study, 72 % of the tumors were located in the right liver lobe. 68 % of the 25 patients had a single tumor, and 32 % showed multiple tumors. In another analysis of 20 cases of SHCC, 15 tumors were solitary lesions and five patients had multiple tumors (Matsuura et al. 2005).

Clinical and Imaging Features

The clinical features of SHCC have previously been reported to not significantly differ from those of ordinary HCCs with regard to age, gender, positive rates of hepatitis viruses, serum AFP levels, Child-Pugh classification, and stage of tumor node metastases (Iha 1994; Matsuura et al. 2005; Kurogi et al. 2006). However, a more recent investigation showed that the SHCC group exhibited less HBV infection, low serum AFP level, less delayed washout during CT, and low usefulness of clinical diagnostic criteria compared with usual HCC. In addition, more portal vein invasion and less liver cirrhosis were noted in the SCC group than in the ordinary HCC group (Lee et al. 2012). In one study of 25 cases, the overall survival rate was significantly higher than the control HCCs (Kurogi et al. 2006), while another investigation of 21 patients with SHCC did not observe statistically significant differences in the 5-year cumulative survival and recurrence rates between SHCC and ordinary HCC (Kim et al. 2009a). Similarly, a recent study of 37 patients with SHCC showed survival rates similar between SHCC and the ordinary HCC control group (Lee et al. 2012).

On ultrasonography, SHCC patterns are mostly hypoechoic, and contrast-enhanced CT and MRI show mostly lesions with a heterogeneous density (Sanada et al. 2007; Kim et al. 2009a). Most SHCCs are radiologically characterized by confluent multinodularity, a location close to the liver capsule, stellate fibrosis, and lack of encapsulation. Furthermore, hypervascularity and an indentation of the liver surface on dynamic CT images seem to be characteristics of SHCC. In a group of 21 SHCCs, common CT features were an ill-defined tumor margin (76 %), peripheral rim-like enhancement on arterial and portal phases (62 %), presence of an area of prolonged and delayed enhancement on equilibrium phase (95 %), and hepatic surface retraction (59 %), whereas the presence of a washout area was uncommon in comparison with ordinary HCC (Kim et al. 2009a; Yachida et al. 2009). Part of small SHCCs may display atypical findings on imaging, with heterogeneous hypervascular nodules in the early-phase CT and a low-density lesion in the late phase (Kim et al. 2009b). Due to its diffuse stromal reaction, SHCC is often misdiagnosed as cholangiocarcinoma, mixed HCC-cholangiocarcinoma, or metastatic carcinoma on diagnostic images (Kurogi et al. 2006). Also on gadoxetic acid-enhanced MRI imaging, SHCCs are similar to intrahepatic cholangiocarcinomas, but the proportion of hyperenhancement of 20 % or more on the arterial phase is a helpful finding in distinguishing SHCC from intrahepatic cholangiocarcinoma (Park et al. 2013). In one study, the majority of SHCCs (88 %) were located close to the liver capsule (Kurogi et al. 2006). Small SHCCs may show a central scar detectable on MR images (Goshima et al. 2002).

Pathology

Macroscopy

At macroscopic examination, SHCCs may resemble mass-forming intrahepatic cholangiocarcinoma or metastatic carcinoma (Suguki

et al. 2009). Some of the tumors have a resemblance to fibrolamellar carcinoma. The tumors are whitish in color, solid and lobulated, and well demarcated and show an expansive growth pattern and are firm, owing to the marked desmoplasia. Matsuura and coworkers (2005) distinguished a more common contiguous multinodular type, in which tumors are formed by a cluster of small contiguous nodules, and a less common single nodular type. In one study of 15 cases, the tumor diameter ranged from 1.8 to 10 cm (Okamura et al. 2005). Most of the tumors (more than 80 %) are situated in the subcapsular area of the liver and may even protrude outside the liver. Among 25 cases, SHCC was located in the right lobe in 72 % (Kurogi et al. 2006). The tumors may show stellate fibrosis (seen in 84 %; Kurogi et al. 2006), are not encapsulated in most cases, and usually do not show grossly detectable hemorrhage or necrosis. In 21 SHCCs studied, tumor capsule formation was found in 29 %, and only 10 % of the cases showed tumor necrosis or hemorrhage, while portal or hepatic vein involvement was significantly more common than in normal HCC (Kim et al. 2009a). In another study, no case of encapsulation was reported (Kurogi et al. 2006); these differences may, apart from different populations with different genetic background studied, also depend on histologic criteria employed. The adjacent liver may show signs of chronic hepatitis, but liver cirrhosis seems to be less commonly associated with SHCC. In a study of 25 cases, liver cirrhosis was present in 28 % (Kurogi et al. 2006).

Histopathology

SHCC shows a diffuse pattern of fibrosis, the fibrotic areas forming radiating structures or being localized along the sinusoid-like vascular channels, as already described above. The histologic diagnostic criteria of SHCC are not yet settled in a satisfactory way. Kurogi et al. (2006) had defined SHCC as malignancy with diffuse fibrotic changes in almost the entire area of the largest cross-section of the tumor and a mean fibrotic area of 39 % compared with only 4.6 % in ordinary HCC. It may, for the moment being, be accepted that the diagnosis of SHCC requires that scirrhous areas exceed 50 % of the tumor area. Based on the pattern of fibrosis, the tumors were divided into radiating and sinusoidal types. The radiating structures are characterized by fibrous scars within the tumor, with thick dense fibrous bands radiating out from the scars to the surrounding tumor tissue. Conversely, the sinusoidal type is characterized by fibrous bands occupying the sinusoidal /perisinusoidal spaces, often with lymphocytic infiltrates. The radiating type of SHCC seems to be associated with larger tumors (Okamura et al. 2005). The stroma of SHCCs is usually not laminated, in contrast to fibrolamellar hepatocellular carcinoma. An important lymphocytic infiltration of the stroma is sometimes found in SHCC (Kurogi et al. 2006) but, as already stated, prevails in the so-called sinusoidal type of SHCC (Okamura et al. 2005). Scirrhous change of HCC can already be found in small tumor lesion (minute SHCC; Fujii et al. 2007; Sanada et al. 2007). In one published case of minute SHCC, the scirrhous well-differentiated HCC was situated in the center of a nodule that showed high-grade dysplasia at the periphery (Fujii et al. 2007). The neoplastic cells embedded in the fibrous stroma are mostly hepatocyte-like cells, as found in ordinary HCC.

In contrast to fibrolamellar hepatocellular carcinoma, an important differential diagnosis, the tumor cells are not different from those of "standard" HCC, which is an important diagnostic feature. The cells are usually moderately to well-differentiated and arranged in the form of cell plates/trabecules. Apart from hepatocyte-like cells, SHCC contains other epithelial cell types, such as cells that show clear cell change (84 % of cases in one study; Kurogi et al. 2006) and contain hyaline bodies. SHCC also shows small neoplastic cells at the periphery of tumor cell nests, which may represent progenitor cells. SHCC has been classified into three types, based on the presence or absence of these cells and their respective immunohistochemical profiles. Type I SHCCs have small cells that are reactive for CK7, ATP cassette transporter G2 (a marker of the side population phenotype), NCAM, and epithelial cell adhesion molecule and display, in addition, reactivity for CK19, NCAM, and epithelial cell

adhesion molecule. Type II tumors have small cells lacking the additional immunohistochemical features, and type III tumors lack small cells (Fujii et al. 2008).

Immunohistochemistry

SHCCs are significantly more often positive for CK7 than ordinary HCC (Matsuura et al. 2005). They share this feature with fibrolamellar carcinoma, where CK7 reactivity is a typical phenotype. The epithelial cells of SHCCs are variably reactive for the hepatocyte marker, Hep (Okamura et al. 2005), but Hep Par 1 reactivity is significantly less common in SHCC than in usual HCC (Matsuura et al. 2005). In one study of 14 cases, 43 % of tumors were Hep Par 1 negative (Suguki et al. 2009). The combination of Hep Par 1 negativity and desmoplasia in SHCC may cause misinterpretation of these neoplasms as adenocarcinomas. However, SHCCs are reactive for glypican-3 and arginase in the majority of cases, this phenomenon thus being an important diagnostic element (Krings et al. 2013). SHCCs express epithelial-mesenchymal (EMT)-related genes (Seok et al. 2012).

The stroma reveals a high density of alpha-SMA-positive myofibroblasts (Okamura et al. 2005; Kurogi et al. 2006; Fujii et al. 2008). Myofibroblasts are sparse in ordinary HCCs (Terada et al. 1996). In the extracellular matrix of the tumors, reactivity for collagen types I and III was detected, but there was no expression of laminin-5 in the stroma of SHCC, in contrast to intrahepatic cholangiocarcinoma (Okamura et al. 2005). Expression of metalloproteinase-7/MMP-7 was higher in SHCC than in ordinary HCC, while expression of tenascin-C was low in SHCC (Okamura et al. 2005).

Differential Diagnosis

Part of SHCCs exhibit a stellate type of fibrosis. A central fibrous scar is sometimes present in part of small scirrhous HCCs and may resemble scar-like structures found in cholangiocarcinomas (Goshima et al. 2002). Dysplastic nodules can develop scirrhous changes (An et al. 2003) and may histologically be confounded with a small and well-differentiated SHCC. Also ordinary HCC can undergo prominent stromal change at certain parts of the tumor and can thus resemble SHCC. HCCs can develop diffuse fibrosis following chemotherapy or chemoembolization.

Sclerosing Hepatocellular Carcinoma

Introduction

Sclerosing hepatocellular carcinoma (SHCC) is an uncommon variant of HCC characterized by tumor cells embedded in a dense fibrous (desmoplastic) stroma. SHCC differs from ordinary HCC by showing a well-developed stroma, lack of any pseudocapsular delineation, and a diffuse growth pattern.

Epidemiology

SHCC seems to have been first described in 1977 (Beaugrand et al. 1977), followed by relatively few reports. The lesion is rare: among a total of 1,390 HCCs observed between 1989 and 2005, six tumors were SHCC (0.43 %; Kim et al. 2006). In a study on 30 patients, there were 14 male and 16 female, with a mean age at presentation of 62.6 years (Omata et al. 1981). Among seven Taiwanese patients with SHCC, age at diagnosis ranged from 26 to 71 years (mean, 42.3 years).

Selected References Omata et al. 1981; Yamashita et al. 1992, 1993; Yoshida et al. 1992; Park and Park 1994; Kakita et al. 1995; Albar et al. 1996; Martinez et al. 1997; Medina Perez et al. 1997; Koyama et al. 1999; Llovet and Miguel 1999; Hong et al. 2001; Yeh et al. 2005; Kim et al. 2006, 2007; Mahoney et al. 2006; Kobayashi et al. 2008a.

Clinical and Imaging Features

The clinical presentation of SHCC does not differ from that of ordinary HCC. In a study of seven patients from Taiwan, abdominal fullness was the most common symptom (Yeh et al. 2005). Part of

SHCCs are associated with a distinct paraneoplastic syndrome, i.e., tumoral hypercalcemia. Paraneoplastic hypercalcemia is caused by secretion of variant forms of parathyroid hormone-like peptide (PTHrP) (Skrabanek et al. 1980; Suva et al. 1987) and is known to occur in any variant of HCC (Belaiche et al. 1975; Halabe et al. 1976; Roche et al. 1979; Polterauer et al. 1980; Oldenburg et al. 1982; Attali et al. 1984; Gentric et al. 1984; Ikeda et al. 1988; Suzuki et al. 1988; Otsuka et al. 1989; Yen et al. 1993; Tamura et al. 1994; Leone et al. 1999; Béchade et al. 2000; Ghobrial et al. 2002). Hypercalcemic HCC may induce hypercalcemia by production of prostaglandin E instead of PTHrP (Ikeda et al. 1988). Patients with SHCCs may or may not show paraneoplastic hypercalcemia (Omata et al. 1981; Martinez et al. 1997; Yamashita et al. 1992; Koyama et al. 1999; Kim et al. 2006; Mahoney et al. 2006). In an early report (Omata et al. 1981), the prevalence of paraneoplastic hypercalcemia in SHCC was 68.8 %. Hypercalcemia caused by SHCC may be a life-threatening disorder (Mahoney et al. 2006). Patients with HCC-associated hypercalcemia show elevated levels of PTHrP in serum (Yen et al. 1993; Koyama et al. 1999). Reduction of the tumor mass at least transiently abolished hypercalcemia, e.g., by transcatheter arterial chemoembolization (Roche et al. 1979; Attali et al. 1984; Suzuki et al. 1988).

On CT images, the tumors are manifest as hypoattenuating masses with peripheral rim enhancement at the hepatic arterial phase, followed by centripetal enhancement progressively during the portal venous and equilibrium phases (Yoshida et al. 1992; Kim et al. 2007). Although the tumors ar2e usually well defined, a pseudocapsule is not seen on CT images (Yamashita et al. 1993). SHCCs are hypervascular lesions that exhibit a corona on CT during hepatic arteriography, this corona representing drainage from the tumor vascular channels to sinusoids of the adjacent liver (Kobayashi et al. 2008a). On MR imaging, the tumors are hypointense on T1-weighted images and hyperintense on T2-weighted images. Characteristic for SHCC on dynamic MR images is a remarkable contrast enhancement, which continues to the delayed phase (Yamashita et al. 1993).

Pathology

Macroscopy

SHCC may either show a nodular growth pattern with formation of a well-delineated mass or show a diffuse growth pattern. The latter tumors are, owing to the lack of a pseudocapsule, ill-defined. The cut surface reveals a whitish and sometimes fasciculated tumor with a firm to hard consistency. Some lesions may show yellowish speckles or stripes, due to pigment accumulation in the sclerosed stroma and/or calcifications. The size of the tumors at diagnosis varies greatly; in one study, the tumor diameter ranged from 2.7 to 11 cm (mean: 7.2 cm; Kim et al. 2007). Scattered satellite nodules may be noted (Albar et al. 1996).

Histopathology

The tumor cell population is arranged in a trabecular or pseudoacinar pattern, although the former seems to be more common. In case of glandular structures, bile accumulation can be noted in the canaliculi or lumina. Typically, the tumor cells are embedded in a copious desmoplastic stroma with usually low cellularity and with thick collagen fiber bundles (Fig. 1).

In contrast to fibrolamellar carcinoma, the sclerosed stroma is not laminated, but rather reveals a “disordered” or fascicular arrangement of the matrix fibers.

Electron Microscopy

Cells of SHCC exhibit a microvillous surface structure, and the cytoplasm contains secretory granules with a diameter of 100 nm (Kitazawa et al. 1999).

Immunohistochemistry

Immunohistochemically, SHCCs present the same general marker patterns as ordinary HCCs. Cells of a subset of SHCCs have been shown to be immunoreactive for PTHrP (Albar et al. 1996; Kitazawa et al. 1999).

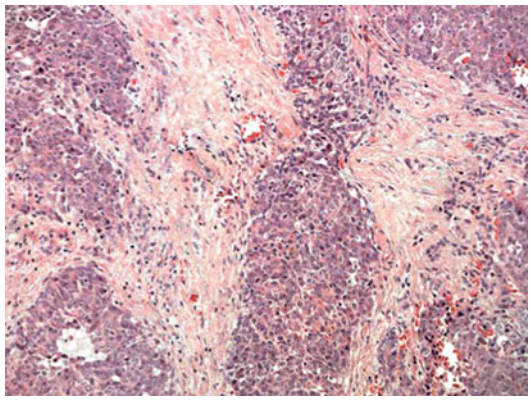

Fig. 1 Sclerosing hepatocellular carcinoma. The trabecular epithelial components are embedded in an abundant fibrosclerotic stroma (hematoxylin and eosin stain)

Molecular Studies

In one case of SHCC, PTHrP transcripts were demonstrated by in situ hybridization using a PCR-derived single-stranded DNA probe (Kitazawa et al. 1999).

Biology of Disease

In a study of six cases with hepatic resection, the prognosis was not worse than that of ordinary HCC (Yeh et al. 2005; Kim et al. 2006), although SHCC may undergo a rapid course (Medina Perez et al. 1997).

Differential Diagnosis

The main differential diagnosis at imaging comprises fibrolamellar carcinoma and desmoplastic intrahepatic cholangiocarcinomas. Fibrolamellar carcinomas are mostly diagnosed in younger individuals, while SHCCs occur in middle-aged to older persons, male predominant (Haratake and Horie 1989). Sclerosing hemangioma may mimic HCC with stroma formation (Lee et al. 2005).

Pathogenesis of Hypercalcemia in Sclerosing Hepatocellular Carcinoma

In the nonneoplastic liver, cells of reactive biliary ductules that express neuroendocrine markers also express PTHrP (Roskams et al. 1993a). The peptide is also detectable and rapidly inducible in human liver cell cultures that have a bile duct phenotype (Roskams et al. 1995). Apart from SHCCs, cholangiocarcinomas are associated with hypercalcemia (Kihara et al. 1973; Zelissen and van Hattum 1986; Trikudanathan and Dasanu 2010) and often express PTHrP (Roskams et al. 1993b; Yamada et al. 2000; Sohda et al. 2006), and PTHrP secretion has been found in primary squamous cell carcinoma of the liver (Asanuma et al. 2002; Saito et al. 2002) and primary adenosquamous carcinoma of the liver (Hayashi et al. 2001) associated with hypercalcemia. Also pancreatic tumors can present with this hypercalcemic syndrome, including adenosquamous carcinoma (Kobayashi et al. 2008b).

Diffuse Cirrhosis-Like Hepatocellular Carcinoma

Introduction

Most hepatocellular carcinomas (HCC) grow in the form of solitary or multiple nodules that are localized to one of few sites within the liver. In contrast, one recently reported rare variant of HCC produces small nodules distributed diffusely throughout the liver, in a cirrhosis-like manner. This unique pattern has been termed diffuse cirrhosis-like HCC/CL-HCC (Jakate et al. 2010). HCC with this growth pattern remains undetected as carcinoma clinically and radiographically and will unexpectedly be discovered in explanted livers in the setting of liver transplantation. In the study of ten patients reported by Jakate et al. (2010), nine were males, and all ten had liver cirrhosis of varying etiology, in the absence of pre-transplant suspicion of HCC. Only three patients had mild elevation of serum AFP, not exceeding 252 ng/mL.

Pathology

Macroscopically, CL-HCC is characterized by the presence of innumerable (sometimes more than 1,000) small HCC nodules measuring 0.2–0.6 cm in diameter scattered among cirrhotic

nodules. Histologically, the nodules showed well or moderately differentiated HCC, often with a pseudoglandular pattern, perinodular sclerotic rims, Mallory-Denk bodies (MDBs), cholestasis, and small vessel invasion. Immunohistochemically, the HCC revealed reactivity for ubiquitin (MDBs) and cytoplasmic and membranous CD10, but not AFP.

References

Albar JP, De Miguel F, Esbrit P, Miranda R, Fernandez-Flores A, Sarasa JL (1996) Immunohistochemical detection of parathyroid hormone-related protein in a rare variant of hepatic neoplasm (sclerosing hepatic carcinoma). Hum Pathol 27:728–731

An HJ, Illei P, Diflo T, John D, Morgan G, Teperman L, Theise N (2003) Scirrhous changes in dysplastic nodules do not indicate high-grade status. J Gastroenterol Hepatol 18:660–665

Asanuma N, Hagiwara K, Matsumoto I, Matsuda M, Nakamura F, Kouhara H, Miyamoto M et al (2002) PTHrP-producing tumor: squamous cell carcinoma of the liver accompanied by humoral hypercalcemia of malignancy, increased IL-6 and leukocytosis. Intern Med 41:371–376

Attali P, Houssin D, Roche A, Buffet C, Bismuth H, Etienne JP (1984) Hepatic arterial embolization for malignant hypercalcemia in hepatocellular carcinoma. Dig Dis Sci 29:466–469

Beaugrand M, de Saint Maur PP, Levy VG (1977) Diffuse sclerosing hepatoma. A liver cancer with difficult diagnosis (in French). Med Chir Dig 6:151–153

Béchade D, Algayres JP, Texier F, Bili H, Mennecier D, Hélie C (2000) Malignant humoral hypercalcemia complicating hepatocellular carcinoma and rectal adenocarcinoma (in French). Press Med 29:2096

Belaiche J, Vesin P, Kalifat R, Milhaud G, Cattan D (1975) Hypercalcemia in patients with primary carcinoma of the liver without bone metastases (in French). Arch Fr Mal App Dig 64:21–29

Fujii T, Zen Y, Nakanuma Y (2007) Minute scirrhous hepatocellular carcinomas undergoing different carcinogenetic processes. Pathol Int 57:443–448

Fujii T, Zen Y, Harada K, Niwa H, Masuda S, Kaizaki Y, Watanabe K, Kawashima A et al (2008) Participation of cancer stem/progenitor cells in tumorigenesis of scirrhous hepatocellular carcinoma – human and cell culture study. Hum Pathol 39:1185–1196

Gentric A, Pennec Y, Jouquan J, Youinou P, Mottier D, Baccino E, Le Menn G (1984) Hepatoma manifesting monoclonal gammapathy and hypercalcemia (in French). Ann Gastroenterol Hepatol (Paris) 20:211–212

Ghobrial MW, George J, Mannam S, Henien SR (2002) Severe hypercalcemia as an initial presenting manifestation of hepatocellular carcinoma. Can J Gastroenterol 16:607–609

Goshima S, Kanematsu M, Yamada T, Kondo H, Matsuo M, Osada S, Nakashima O et al (2002) Small scirrhous hepatocellular carcinoma with central scar: MR imaging findings. J Magn Reson Imaging 16:741–745

Halabe A, Cohen L, Pitlik S, Avidor J, Rosenfeld J (1976) Hypercalcemia associated with a primary tumor of the liver (in Hebrew). Harefuah 91:283–285

Haratake J, Horie A (1989) A histopathologic comparative study of European cases of fibrolamellar carcinoma and Japanese cases of sclerosing hepatocellular carcinoma (in Japanese). Gan No Rinsho 35:793–798

Hayashi T, Mizuki A, Yamaguchi T, Hasegawa T, Kunihiro T, Tsukada N, Matsuoka K et al (2001) Primary adenosquamous carcinoma of the liver which produces granulocyte-colony-stimulating factor and parathyroid hormone related protein: association with leukocytosis and hypercalcemia. Intern Med 40:631–634

Hong T, Lee R, Chiang J, Chang C (2001) Centrally-located sclerosing hepatocellular carcinoma: a case report with imaging findings before and after transcatheter arterial chemoembolization. Chin J Radiol 26:147–152

Iha H (1994) Clinicopathological study on scirrhous hepatocellular carcinoma. A study of 12 resected cases. Acta Hepatol Jpn 28:855–863

Ikeda T, Tozuka S, Hasumura Y, Takeuchi J (1988) Prostaglandin-E-producing hepatocellular carcinoma with hypercalcemia. Cancer 61:1813–1814

Jakate S, Yabes A, Giusto D, Naini B, Lassman C, Yeh MM, Ferrell LD (2010) Diffuse cirrhosis-like hepatocellular carcinoma: a clinically and radiographically undetected variant mimicking cirrhosis. Am J Surg Pathol 34:935–941

Kakita A, Iino Z, Takahashi T (1995) Sclerosing hepatic carcinoma (in Japanese). Ryoikibetsu Shokogun Sjirizu 7:467–469

Kihara I, Suzuki T, Takamiya H, Hirono S (1973) Cholangiocarcinoma with hypercalcemia – a case report studied by electron-microscope and radioimmunoassay. Acta Pathol Jpn 23:791–804

Kim SH, Lee SG, Hwang S, Lee YJ, Park KM, Kim KH, Ahn CS, Moon DB, Ha TY et al (2006) Surgical treatment of sclerosing hepatocellular carcinoma (in Korean). Korean J Hepatol 12:412–419

Kim SH, Lee WJ, Lim HK, Park CK (2007) Sclerosing hepatic carcinoma: Helical CT features. Abdom Imaging 32:725–729

Kim SR, Imoto S, Nakajima T, Ando K, Mita K, Fukuda K, Nishikawa R, Koma Y, Matsuoka T et al (2009a) Scirrhous hepatocellular carcinoma displaying atypical findings on imaging studies. World J Gastroenterol 15:2296–2299

Kim SH, Lim HK, Lee WJ, Choi D, Park CK (2009b) Scirrhous hepatocellular carcinoma: comparison with usual hepatocellular carcinoma based on CT

–pathologic features and long-term results after curative resection. Eur J Radiol 69:123–130
Kitazawa R, Kitazawa S, Yoon S, Kasuga M, Maeda S (1999) In situ demonstration of parathyroid hormone-related protein mRNA in sclerosing hepatic carcinoma. Virchows Arch 435:137–142
Kobayashi S, Matsui O, Gabata T, Sanada J, Koda W, Minami T, Kobayashi T (2008a) Hemodynamics of small sclerosing hepatocellular carcinoma without fibrous capsule: evaluation with single-level dynamic CT during hepatic arteriography. Abdom Imaging 33:425–427
Kobayashi N, Higurashi T, Iida H, Mawatari H, Endo H, Nozaki Y, Tomimoto A, Yoneda K et al (2008b) Adenosquamous carcinoma of the pancreas associated with humoral hypercalcemia of malignancy (HHM). J Hepatobiliary Pancreat Surg 15:531–535
Koyama Y, Ishijima H, Ishibashi A, Katsuya T, Ishizaka H, Aoki J, Endo K (1999) Intact PTH-producing hepatocellular carcinoma treated by transcatheter arterial embolization. Abdom Imaging 24:144–146
Krings G, Ramachandran R, Jain D, Wu TT, Yek MM, Torbenson M, Kakar S (2013) Immunohistochemical pitfalls and the importance of glypican 3 and arginase in the diagnosis of scirrhous hepatocellular carcinoma. Mod Pathol 26:782–791
Kurogi M, Nakashima O, Miyaaki H, Fujimoto M, Kojiro M (2006) Clinicopathological study of scirrhous hepatocellular carcinoma. J Gastroenterol Hepatol 21:1470–1477
Lee VT, Magnaye M, Tan HW, Thng CH, Ooi LL (2005) Sclerosing haemangioma mimicking hepatocellular carcinoma. Singapore Med J 46:140–143
Lee JH, Choi MS, Gwak GY, Lee JH, Koh KC, Paik SW, Yoo BC, Choi D, Park CK (2012) Clinicopathologic characteristics and long-term prognosis of scirrhous hepatocellular carcinoma. Dig Dis Sci 57:1698–1707
Leone N, Debernardi-Venon W, Marzano A, Massari M, Rizzetto M (1999) Hypercalcaemia secondary to hepatocellular carcinoma. Ital J Gastroenterol Hepatol 31:604–606
Llovet JM, Miguel R (1999) Sclerosing hepatic carcinoma in non-cirrhotic liver resembling metastatic adenocarcinoma. J Hepatol 30:131
Mahoney EJ, Monchik JM, Donatini G, De Lellis R (2006) Life-threatening hypercalcemia from a hepatocellular carcinoma secreting intact parathyroid hormone: localization by sestamibi single photon emission computed tomographic imaging. Endocr Pract 12:302–306
Martinez R, Sebastian JJ, Garcia S, Fuentes J, Navarro M, Alvarez R, Artigas JM, Herrero A (1997) Sclerosing hepatocarcinoma not associated with hypercalcemia (in Spanish). Rev Esp Enferm Dig 89:718–720
Matsuura S, Aishima S, Taguchi K, Asayama Y, Terashi T, Honda H, Tsuneyoshi M (2005) 'Scirrhous' type hepatocellular carcinomas: a special reference to expression of cytokeratin 7 and hepatocyte paraffin 1. Histopathology 47:382–390
Medina PM, Caballero GJ, Espino MA, Gonzalez MC (1997) Sclerosing hepatocellular carcinoma with rapid course (in Spanish). Rev Esp Enferm Dig 89:651–652
Okamura N, Yoshida M, Shibuya A, Sugiura H, Okayasu I, Ohbu M (2005) Cellular and stromal characteristics in the scirrhous hepatocellular carcinoma: comparison with hepatocellular carcinomas and intrahepatic cholangiocarcinomas. Pathol Int 55:724–731
Oldenburg WA, van Heerden JA, Sizemore GW, Abboud CF, Sheedy PF (1982) Hypercalcemia and primary hepatic tumors. Arch Surg 117:1363–1366
Omata M, Peters RL, Tatter D (1981) Sclerosing hepatic carcinoma: relationship to hypercalcemia. Liver 1:33–49
Otsuka N, Fukunaga M, Morita K, Shimato S, Morita R, Ohumi T, Yamamoto S, Hirano Y (1989) Accumulation of 99mTc-phosphorous compounds in primary hepatic tumors associated with hypercalcemia (in Japanese). Rinsho Hoshasen 34:293–295
Park C, Park YN (1994) Immunohistochemical profile of sclerosing hepatic carcinoma. Kor J Pathol 28:636–642
Park MJ, Kim YK, Park HJ, Hwang J, Lee WJ (2013) Scirrhous hepatocellular carcinoma on gadoxetic acid-enhanced magnetic resonance imaging and diffusion-weighted imaging: emphasis on the differentiation of intrahepatic cholangiocarcinoma. J Comput Assist Tomogr 37:872–881
Polterauer P, Kovarik J, Ulrich W (1980) Hypercalcemia in liver tumors (in German). Wien Klin Wochenschr 92:689–693
Roche A, Franco D, Dhumeaux D, Bismuth H, Doyon D (1979) Emergency hepatic arterial embolization for secondary hypercalcemia in hepatocellular carcinoma. Radiology 133:315–316
Roskams T, Campos RV, Drucker DJ, Desmet VJ (1993a) Reactive human bile ductules express parathyroid hormone-related peptide. Histopathology 23:11–19
Roskams T, Willems M, Campos RV, Drucker DJ, Yap SH, Desmet VJ (1993b) Parathyroid hormone-related peptide expression in primary and metastatic liver tumours. Histopathology 23:519–525
Roskams T, Moshage H, Depla E, Willems M, Desmet V, Yap P (1995) Parathyroid hormone-related peptide is expressed and rapidly inducible in human liver cell cultures that have a bile duct phenotype. J Hepatol 23:160–165
Saito T, Harada K, Tsuneyama K, Hirano M, Amaya S, Sasaki M, Kaneko S, Kobayashi K, Nakanuma Y (2002) Primary squamous cell carcinoma of the liver producing parathyroid hormone-related protein. J Gastroenterol 37:138–142
Sanada Y, Yoshida K, Itoh H (2007) Comparison of CT enhancement patterns and histologic features in hepatocellular carcinoma up to 2 cm: assessment of malignant potential with claudin-10 immunohistochemistry. Oncol Rep 17:1177–1182
Seok JY, Na DC, Woo HG, Roncalli M, Kwon SM, Yoo JE, Ahn EY, Kim GI, Choi JS et al (2012) A fibrous stromal

component in hepatocellular carcinoma reveals a cholangiocarcinoma-like gene expression trait and epithelial-mesenchymal transition. Hepatology 55:1776–1786

Skrabanek P, McPartlin J, Powell D (1980) Tumor hypercalcemia and "ectopic hyperparathyroidism". Medicine (Baltimore) 59:262–282

Sohda T, Shiga H, Nakane H, Watanabe H, Takeshita M, Sakisaka S (2006) Cholangiocellular carcinoma that produced both granulocyte-colony-stimulating factor and parathyroid hormone-related protein. Int J Clin Oncol 11:246–249

Suguki T, Yamamoto M, Taka K, Nakano M (2009) Specific characteristics of scirrhous hepatocellular carcinoma. Hepatogastroenterology 56:1086–1089

Suva LJ, Winslow GA, Wettenhall RE, Hammonds RG, Moseley JM, Diefenbach-Jagger H et al (1987) A parathyroid hormone-related protein implicated in malignant hypercalcemia: cloning and expression. Science 237:893–896

Suzuki K, Kono N, Ono A, Osuga Y, Kiyokawa H, Mineo I, Matsuda Y, Miyoshi S, Kawata S et al (1988) Transcatheter arterial chemo-embolization for humoral hypercalcemia of hepatocellular carcinoma. Gastroenterol Jpn 23:29–36

Tamura K, Kubota K, Take H, Kurabayashi H, Shirakura T (1994) Parathyroid hormone-related peptide as a possible cause of hypercalcemia in a hepatocellular carcinoma patient. Am J Gastroenterol 89:644–645

Terada T, Makimoto K, Terayama N, Suzuki Y, Nakanuma Y (1996) Alpha-smooth muscle actin-positive stromal cells in cholangiocarcinomas, hepatocellular carcinomas and metastatic liver carcinomas. J Hepatol 24:706–712

Trikudanathan G, Dasanu CA (2010) Cholangiocarcinoma and paraneoplastic hypercalcemia: a lethal combination revisited. South Med J 103:716–718

Yachida S, Wakabayashi H, Suzuki Y (2009) Scirrhous hepatocellular carcinoma: unique computed tomography findings. Clin Gastroenterol Hepatol 7:A28

Yamada S, Sanefuji H, Morimoto H, Harada Y, Mine S, Morimoto I, Eto S (2000) Parathyroid hormone-related peptide producing cholangiocellular carcinoma with a marked psammoma formation. J Gastroenterol Hepatol 15:1442–1446

Yamashita F, Iwao T, Torimura T, Tanaka M, Hirai K, Abe M, Toyonaga A, Sugihara S et al (1992) Sclerosing hepatocellular carcinoma with hypercalcemia – a case report. Kurume Med J 39:113–116

Yamashita Y, Fan ZM, Yamamoto H, Matsukawa T, Arakawa A, Miyazaki T, Harada M, Takahashi M (1993) Sclerosing hepatocellular carcinoma: radiologic findings. Abdom Imaging 18:347–351

Yeh CN, Hung CF, Lee KF, Chen MF (2005) Sclerosing hepatocellular carcinoma: clinicopathologic features in seven patients from Taiwan and review of the literature. Hepatogastroenterology 64:1201–1205

Yen TC, Hwang SJ, Wang CC, Lee SD, Yeh SH (1993) Hypercalcemia and parathyroid hormone-related protein in hepatocellular carcinoma. Liver 13:311–315

Yoshida J, Takayama T, Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Hasegawa H et al (1992) Computed tomography of sclerosing hepatocellular carcinoma. Comput Med Imaging Graph 16:125–130

Zelissen PM, van Hattum J (1986) A young woman with a liver tumor and hypercalcemia (in Dutch). Ned Tijdschr Geneeskd 130:1705–1707

Inflammatory Hepatic Carcinomas 12

Contents

Abstract

Rare variants of hepatocellular carcinoma (HCC) show dense infiltrates of several classes of mononuclear leukocytes, mainly lymphocytes and macrophages or histiocytes (inflammatory HCCs). As a sign of an antitumor immune reaction, most ordinary HCCs exhibit lymphocyte and macrophage infiltrates of low density, but this feature does not qualify for a diagnosis of inflammatory HCC. Uncommon HCCs display a massive lymphoid cell infiltration, mostly T cells (HCC with lymphoid stroma). A very rare variant of HCC shows dense plasmacytic infiltrates, associated with tumor cell apoptosis and tumor regression (medullary-like HCC). There are also uncommon HCCs rich in macrophages or histiocytes with or without epithelioid cell reaction. A last group of inflammatory HCCs are lymphoepithelial liver tumors (lymphoepithelial carcinomas) which also occur in the biliary tract and several extrahepatic locations. Part of the latter neoplasms is associated with Epstein-Barr virus infection.

Introduction

Hepatocellular carcinomas (HCCs) almost constantly show a usually loose infiltration by leukocytes, mainly lymphocytes and tumor-associated macrophages (TAM) as signs of an inflammatory/immune response directed against the tumor.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_12

Table 1 Types of inflammatory hepatic carcinomas

HCCs with low-density leukocyte infiltration
HCCs with lymphoid stroma
HCCs with dense plasmacellular infiltration (including medullary-type HCC)
Macrophage-rich HCCs with or without epithelioid reaction/granulomas
HCC with massive histiocyte infiltration
HCCs with steatohepatitis-like features
Hepatic lymphoepithelial carcinomas

This cellular infiltration is commonly more dense at the tumor border, i.e., in the peripheral contact area between tumor and host, while central parts of the tumors mostly display few round cells infiltrating either the epithelial components or the tumor stroma. In contrast to this "standard" situation, a subset of hepatic carcinomas, including certain HCCs, display a prominent cellular infiltration. These tumors may tentatively be grouped into six categories (Table 1). Similar to carcinomas in other organs, hepatic carcinomas with significant cellular infiltrates might have a more favorable prognosis (Choi and Choi 2008), but the biology of disease is not yet clarified for these rare tumors.

Hepatocellular Carcinomas with Low-Density Leukocyte Infiltration

HCCs are often associated with a low-density infiltration of lymphocytes, macrophages, and plasma cells (Shirabe et al. 1995; Wada et al. 1998). Lymphocyte infiltration of HCC tissue chiefly involves T lymphocytes of both helper and cytotoxic categories and is, at least in part of the cases, associated with an upregulated antitumor response and a more favorable biology of disease (Shirabe et al. 1995, 2010; O'Beirne and Harrison 2004; Zhao et al. 2012). Infiltrates of lymphocytes are often detected in the fibrous/stromal tissue and close to sinusoidal vessels located to the interface between tumor and peritumoral normal liver (Fig. 1).

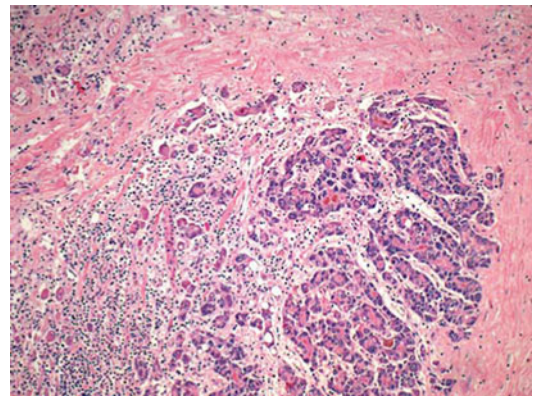

Fig. 1 Hepatocellular carcinoma with lymphocytic infiltration and fibrosis of stroma (hematoxylin and eosin stain)

These infiltrates constitute a mixture of T-cells, B-cells, and natural killer cells, but T-cells usually predominate. The T-cells mostly infiltrate areas in the tumor where endothelial cells strongly express HLA-DR antigen (Shirabe et al. 1995). 70–90 % of tumor-associated lymphocytes were of the antigen-experienced phenotype, and CD4+ CD25+ lymphocytes were more frequent within the tumor proper than in surrounding normal liver, while CD8+ cells predominate at the tumor-host contact site (Chen et al. 2007a). Sixty to seventy percent of the CD4+ or CD8+ lymphocytes in HCCs express the activation markers CD69 and HLA-DR (Chen et al. 2007a). In some HCCs, the peripheral infiltrate forms a band-like zone of lymphocytes with or without associated lymph follicles and sometimes germinal centers. Within the tumor, CD4+ and CD8+ T-cells are scattered among stromal cells, infiltrate the epithelial tumor trabecules or acini, and/or are clustered around tumor blood vessels. Small lymphocytes can be found in direct contact with tumor cells, sometimes with signs of emperipolesis. In most HCCs, the density of intratumoral lymphocytes is lower than that in the peritumoral liver substance and was found in one study to be in average 9.5 cells/HPF versus 17.8 cells/HPF in the noncancerous liver tissue (Ikeguchi et al. 2004). The density of peritumoral lymphocytes is

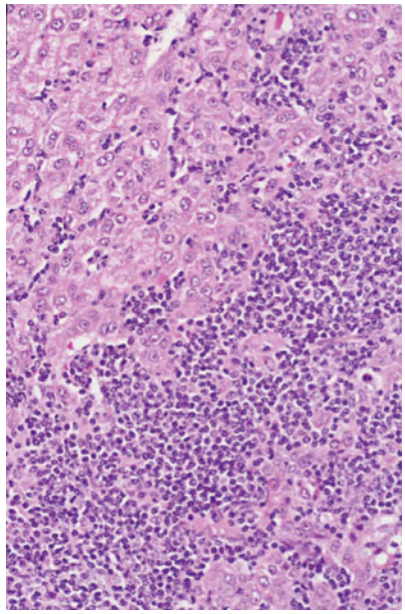

Fig. 2 This hepatocellular carcinoma exhibits a dense lymphocytic and plasmacellular infiltration. Such neoplasms are termed hepatocellular carcinoma with lymphoid stroma (hematoxylin and eosin stain)

modified by the type of underlying liver disease, e.g., being higher in patients with hepatitis C, whereas the density of intratumoral lymphocytes has been found to decrease with increasing tumor stage (Ikeguchi et al. 2004). In addition to lymphocytes, HCCs contain variable amounts of monocytoid cells and macrophages (tumor-associated macrophages, TAMs), discussed in more detail below. Most HCCs contain only small numbers of plasma cells in the stroma. Among tumor infiltrate cells, myeloid and plasmacytoid dendritic cells are also found in HCCs in variable numbers and play an important role in host defense directed against neoplastic cells (Ido et al. 1994; Yin et al. 2002, 2003; Lau and Thomson 2003; Cai et al. 2005, 2006; Kelly et al. 2014). Dendritic cells can engage in close contacts or even fusion with tumor cells, eventually forming "dendritomas" within tumors. However, in part of cases, CD38-positive mature and activated dendritic cells are reduced or lacking in HCC tissue (Chen et al. 2000), and HCC cells can inhibit the differentiation of dendritic cells (Li et al. 2007).

Hepatocellular Carcinoma with Massive Lymphoid Infiltration (Hepatocellular Carcinoma with Lymphoid Stroma)

There are rare instances where hepatic carcinomas are associated with massive lymphoid infiltration, but not representing typical LELC (Emile et al. 2000; Choi and Choi 2008; Park et al. 2009; Fig. 2). In one report, a 57-year-old male patient showed a regressing HCC consisting of a tumor 2.7 cm in size which was composed of two nodules. One nodule was replaced by a massive lymphoid infiltration with insignificant amounts of hepatocyte antigen (OCH1E5)-positive vital tumor cells, while the other nodules demonstrated a small portion of well- to moderately differentiated trabecular HCC, again with marked lymphocytic infiltration. The infiltrate chiefly consisted of CD3+ T lymphocytes, among which CD4+ cells predominated EBV was not detectable by EBER ISH (Park et al. 2009). The predominance of CD4+ cells in the lymphocytic infiltrate is in clear contrast to LELC, where CD8+ cells prevail.

Hepatocellular Carcinoma with Dense Plasmacellular Infiltration and Medullary-Like Hepatocellular Carcinoma

In a classical terminological approach, medullary carcinoma is defined as a carcinoma in which the epithelial component markedly exceeds the stromal component, resulting in a tumor that macroscopically assumes the features and, specifically, the consistency of fresh bone marrow (hence the term, medullary, "marrowish"). In distinct organs, and specifically the breast, other morphologic characters are employed to define medullary carcinoma,

such as a poorly differentiated type of cancer cells, a cohesive growth pattern, and a dense lymphocytic and plasmacytic infiltration of the tumor (Pedersen et al. 1994; Jacquemier et al. 2005; Malyuchik and Kiyamoya 2008; Foschini and Eusebi 2009). Neoplasms histologically resembling infiltrate-rich medullary carcinoma are termed carcinoma with medullary-like features. Medullary carcinomas are very rare in visceral organs. Gastric and colonic medullary carcinomas have been reported (Adachi et al. 1992; Chetty 2012).

In the breast, medullary carcinoma is a member of the so-called basal group which has been classified as tumors with a favorable prognosis in several studies, notwithstanding its high-grade morphology (Rakha et al. 2009; Cao et al. 2013), mainly in patients with so-called typical medullary carcinoma (Nurlaila et al. 2013), but there are also investigations that found no difference in outcome in comparison with invasive ductal carcinoma (Park et al. 2013). The downregulation of genes involved in cellular proliferation, an effective host immune response, enhanced tumor cell apoptosis, and elevated levels of metastasis-inhibiting and low levels of metastasis-promoting factors were suggested to account for the better prognosis (Yakirevich et al. 1999; Bertucci et al. 2006; Weigelt et al. 2008).

In the liver, medullary-like carcinoma has been described (Zimmermann et al. 2002). The liver resection specimen of a 56-year-old male patient with liver cirrhosis contained a 3.5 cm conglomerate of rather sharply delineated, brown-red or tan nodules, focally in close association with intrahepatic veins and with extensive macroangioinvasion. Histologically, the neoplasm consisted of large amphophilic or slightly basophilic cells with a solid and partly syncytial/cohesive, stroma-less (medullary) growth pattern. The tumor tissue was densely infiltrated with lymphocytes and plasma cells. Focally, the neoplasm showed marked tumor cell apoptosis and tumor shrinkage, remnant CK8-positive tumor cell nests situated within the dense round cell infiltrate (Figs. 3, 4, and 5). Immunohistochemically, the tumor cells were reactive for CK8, focally for CK19, and AFP. The proliferation fraction (Ki-67) exceeded 80 %. In contrast to medullary

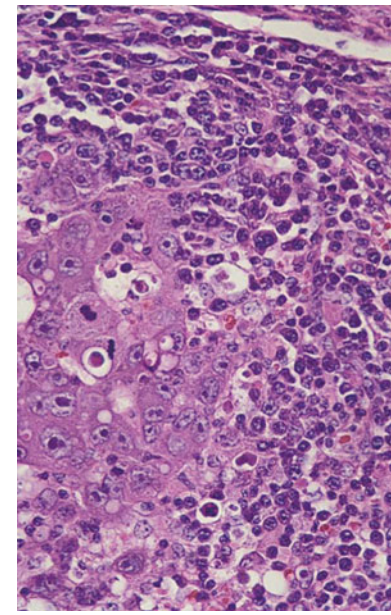

Fig. 3 Hepatocellular carcinoma with dense plasmacytic infiltration and marked tumor cell apoptosis (medullary HCC; hematoxylin and eosin stain)

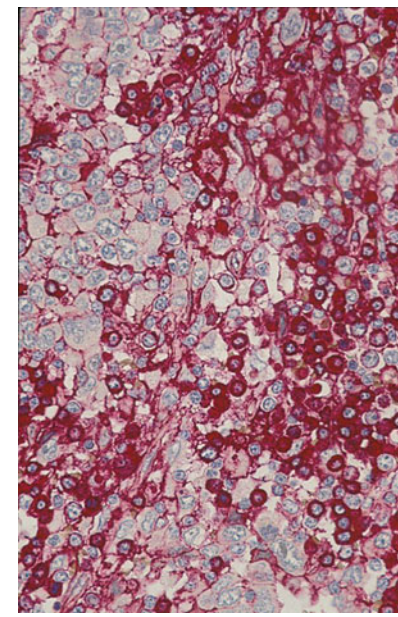

Fig. 4 Plasma cell-rich (medullary) hepatocellular carcinoma. Numerous CD138-positive plasma cells infiltrate this neoplasm (CD138/syndecan-1 immunostain)

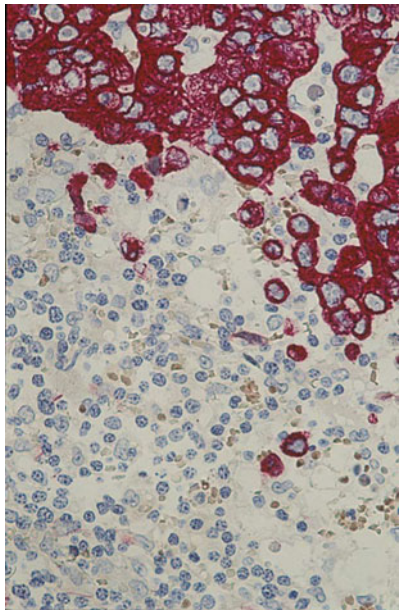

Fig. 5 Dense plasmacytic infiltrates in medullary hepatocellular carcinoma are associated with signs of tumor regression, visualized as loss and atrophy of tumor cells (CAM5.2 immunostain)

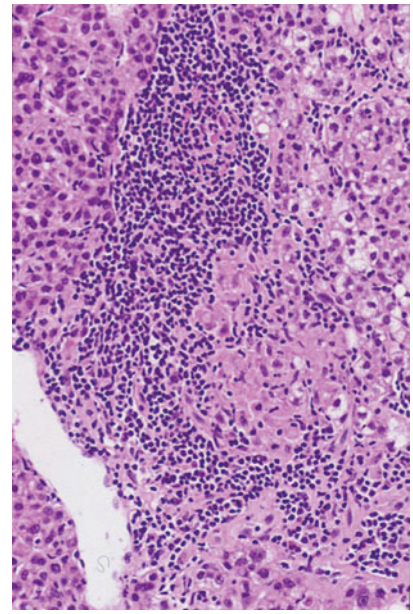

Fig. 6 Part of hepatocellular carcinomas with dense immune cell infiltrates also contain increased numbers of macrophages, sometimes with formation of epithelioid cell granulomas (hematoxylin and eosin stain)

carcinoma of the breast, where a significant proportion shows p53 positivity (Jacquemier et al. 2005), medullary-like HCC failed to show p53 protein reactivity. The plasma cells were strongly CD138 positive, while the lymphocytes were predominantly CD20- and CD79a-reactive B-cells. The tumor contained numerous S100 protein-positive cells with stellate or veiled morphology, probably antigen-presenting cells. Fas was detectable in a subset of lymphoid infiltrate cells, but not in tumor cells. Conversely, part of tumor cells expressed Fas-ligand. This rare type of HCC has subsequently been confirmed (Quist et al. 2014).

Macrophage-Rich Hepatocellular Carcinoma With or Without Epithelioid Cell Reaction

Tumor-associated macrophages (TAMs) play a significant role in tumor biology and are discussed in more detail in another chapter (Shirabe et al. 2012; Mano et al. 2013; Newell et al. 2013). TAMs also occur in most HCCs, but there are examples where this infiltrate cell is present in large numbers (Capece et al. 2013). CD68+ and CD63+ macrophages are present both within HCCs and in the peritumoral liver tissues, but CD163+ seem to predominate (Kong et al. 2013). Cellular immune reactions can be associated with marked macrophage activation resulting in epithelioid macrophages (epithelioid cells), granulomas, and macrophage fusion with formation of multinucleated giant cells (Fig. 6).

In native HCCs, epithelioid cell granulomas occur, as a so-called sarcoid-like reaction, albeit rarely and in small numbers (Neville et al. 1975; Tomimatsu et al. 1982; Mourra and Fléjou 2001). In the case reported by Tomimatsu and coworkers (1982), autopsy showed that the entire left liver lobe of a 55-year-old man was almost completely replaced by a massive poorly differentiated hepatocellular carcinoma. Histologically, granulomas having Langhans-type giant cells and varying numbers of lymphocytes were noted predominantly within the tumor and a few also within tumor thrombi of portal vein branches, but not in the noncancerous liver. However, other

observations documented the presence of granulomas also in livers harboring HCCs. Granulomas have also been found in hepatic dysplastic nodules and shown to contain multinucleated giant cells, in the absence of granuloma formation in associated HCC nodules (Phelan and Nolan 2008). Epithelioid cells and granulomas can be induced in HCCs in the course of therapeutic procedures. For example, granulomas can be induced by lipiodolized SMANCS, a polymer-conjugated derivate of neocarzinostatin (Ichikawa et al. 2002). Histologically, an epithelioid cell reaction in HCCs is seen in the form of small clusters of medium-sized to large and sometimes ovoid or spindle-shaped macrophages/histiocytes which are usually located close to carcinoma cell formations with or without signs of cell damage. Epithelioid cell granulomas in HCCs are often small and always noncaseating, with only a sparse peripherally lymphocyte cuff and often without detectable giant cells; however, few giant cells may be missed in thin tissue sections. Immunohistochemically, both epithelioid cells and granulomas are reactive for CD68.

Hepatocellular Neoplasm with Massive Histiocyte Infiltration

This rare variant of HCC was described based on the observation of a 73-year-old Japanese man presenting with a liver malignancy in the absence of hepatic viral infection. Histologically, the nodule consisted of hepatocyte-like tumor cells and abundant histiocytes with abundant foamy cytoplasm that filled up a sinusoid-like space, associated with central loose fibrosis. Most of the tumor revealed features of adenoma, but a focal HCC-like lesion was also present (Kai et al. 2010).

Hepatocellular Carcinomas with Steatohepatitis-Like Features (Steatohepatitic Hepatocellular Carcinoma)

This variant, further discussed in the chapter of lipid-rich HCCs, is characterized by neutral fat accumulation in tumor cells, tumor cell ballooning with or without formation of Mallory-Denk bodies, and an inflammatory infiltrate consisting of neutrophils, lymphocytes, and macrophages. In several respects, the histologic presentation of these HCCs reflects the morphology of acute nonalcoholic steatohepatitis (NASH), and it is assumed that similar pathogenic mechanisms are involved (reviews: Duvnjak et al. 2007; Perlemutter et al. 2007).

Lymphoepithelial Liver Tumors

Introduction

Lymphoepithelial liver tumors comprise a spectrum of lesions that share the general features of lymphoepithelioma-like carcinoma (LELC; synonym, lymphoid stroma-rich carcinoma). LELC is an undifferentiated carcinoma with a marked and predominantly lymphocytic infiltration, histologically mimicking nasopharyngeal carcinoma (NPC), and being associated with Epstein-Barr virus (EBV) in variable proportions. NPC differs significantly from other cancers of the head and neck anatomic compartments in its occurrence, causes, clinical course, and treatment responses. NPC is vastly more common in certain regions of East Asia, the Middle East, and Africa than elsewhere. In part of the reports referring to NPC and LELC, the term "lymphoepithelial-like" carcinoma has been employed, the designation "-like" denoted the uncertainty as to whether undifferentiated carcinomas with dense lymphocytic infiltration form a homogeneous group or rather a group of unrelated lesions with a similar morphology. Lymphoepithelioma, as it was originally termed, was primarily described in the 1920s by Regaud and Schmincke in the head and neck region of Asian patients. Alexander Schmincke (1877–1953), one of the persons appearing in the eponym, was a German doctor who became a pathologist at the Würzburg University in 1907. In 1921, he accepted to succeed Heinrich Albrecht as a professor in Graz, Austria, moving to the same tenure at Tübingen in 1922 and in 1928 to Heidelberg. He described the neoplasm in question in 1921, under the title, *Lymphoepithelial*

Growths (Schmincke 1921). Claude Regaud (1870–1941) was a French radiologist. He was agrégé for anatomy and pathology from 1901 to 1913 in Lyon and from 1913 onwards professor at the Pasteur Institute and director of the Radiophysiological Laboratory at the Radium Institute at the University of Paris. Apart from the most important localization in the head and neck regions, LELC is now known to develop in a broad array of organs and tissues including the breast, middle ear, oral cavity, major and minor salivary glands, specifically the parotid gland, lacrimal gland, larynx, trachea, lung, thyroid gland, thymus, esophagus, stomach, hepatobiliary tract (see below), pancreas, colon, rectum, renal pelvis, ureter, urinary bladder, ovary, uterine cervix, prostate, and skin. Many of these tumors, but specifically those originating from the nasopharynx, salivary glands, thymus, lung, and stomach show a close linkage with Epstein-Barr virus (EBV) infection (Iezzoni et al. 1995), discussed in more detail below.

Lymphoepithelioma-Like Carcinoma of the Liver

ICD-O 8082/3

LELC of the liver substance proper has been reported under several names, including hepatoma with marked lymphocyte infiltration (Isoda et al. 1982), hepatocellular carcinoma with lymphoid stroma (Emile et al. 2000; Szekely 2001a; Choi and Choi 2008), hepatocellular carcinoma with massive lymphoid infiltration (Park et al. 2009), and lymphoepithelioma-like hepatocellular carcinoma (Chen et al. 2007b; Nemolato et al. 2008; Shinoda et al. 2013; Patel et al. 2014). Lymphoepithelioma-like carcinoma was a term chosen to denote what was interpreted to be hepatocellular carcinoma with lymphoid stroma (Szekely 2001a; Chen et al. 2007b). In fact, the tumors may contain components histologically resembling HCC (Emile et al. 2000), and two reports described LELC with a HepPar1-positive component suggesting the involvement of a hepatocellular cell lineage (Chen et al. 2007b; Nemolato et al. 2008). However, other hepatic LELC lack features of bona fide hepatocellular carcinoma and are epithelial tumors of unknown cellular origin. All in all, relatively few cases of hepatic LELC have been described (Isoda et al. 1982; Wada et al. 1998; Emile et al. 2000; Szekely 2001a; Si et al. 2004; Chen et al. 2007b; Nemolato et al. 2008). Hepatic LELC was not associated with viral marker (HBV, HCV) positivity (Nemolato et al. 2008). LELC of the liver interpreted as HCC has been observed in extrahepatic location, e.g., the suprarenal space (Sturm et al. 2004). The clinical presentation does not differ from that observed in other primary epithelial liver tumors. Hepatic LELC occurs as solitary and single or multiple tumors. The majority of cases was found in cirrhotic livers, but LELC also occurs in the absence of cirrhosis (Nemolato et al. 2008). It is noteworthy that serum AFP is usually normal, in contrast to HCC (Emile et al. 2000). MRI imaging has demonstrated low signal intensity in the T1-weighted images and a moderate signal intensity in the T2-weighted images (Choi and Choi 2008). In dynamic MRI image, enhancement in the late arterial phase and washout in the portal venous phase was found (Choi and Choi 2008). The biology of hepatic LELC is not yet clarified, due to the low number of cases collected so far. In one recent study of eight patients, 37.5 % showed local recurrence (Patel et al. 2014).

LELC of the liver may be associated with Epstein-Barr virus (Si et al. 2004). EBV viral transcripts were detected by in situ hybridization (Si et al. 2004), by enumeration of chromosome 11 copy number (Si et al. 2004), and by polymerase chain reaction (PCR) for EBNA2 (Si et al. 2004) and for LMP1, the LMP1 gene being wild-type in one study. Some hepatic LELC failed to show EBV expression (Emile et al. 2000; Chen et al. 2007b; Choi and Choi 2008; Nemolato et al. 2008). It may be added here that the role of EBV in the pathogenesis of ordinary HCC is controversial, studies finding either no evidence (Akhter et al. 2003; zur Hausen et al. 2003) or detecting positive EBV PCR signals, e.g., in a subset of Chinese patients (Li et al. 2004) or Japanese patients (Sugawara et al. 2000). The pathogenic role of EBV in LELC is outlined in more detail below.

Pathology of Hepatic LELC

The tumors are usually well-circumscribed nodules that bulge from the cut surface and show a white-yellowish color, sometimes with necroses and small hemorrhages (Min et al. 2007). The histopathologic phenotype of the tumor cells in hepatic LELC comes in two main patterns. One pattern is characterized by poorly differentiated cells arranged in nests or solid structures, similar to the morphology of nasopharyngeal carcinoma (Fig. 7).

A cohesive pattern may be observed, but this is usually effaced by the dense lymphocytic infiltration. These cells are most often of intermediate size, at least smaller than normal hepatocytes, with an amphophilic to slightly basophilic and ill-defined cytoplasm and vesicular nuclei with a rather prominent nucleolus. Mitotic figures are regularly seen and may be abundant. The overall presentation is that of a solid growing, poorly differentiated (grade 3) carcinoma which fails to reflect a clear-cut cellular origin. At the interface between the carcinoma and the cellular infiltrate, a zone resembling piecemeal necrosis is often recognized (Choi and Choi 2008), but in fact, this phenomenon does not represent necrosis but rather apoptosis induced by the lymphocytes. Within the solid tumor parts, numerous apoptotic bodies may be seen, and sometimes the vital tumor tissue is markedly regressed owing to apoptotic cell loss. Apart from apoptosis, coagulation-type necrosis of tumor tissue is also found. The second and rarer pattern is that of standard hepatocellular carcinoma of the trabecular and usually moderately to well-differentiated type, either as a sole lesion or combined with the poorly differentiated component (Chen et al. 2007b). In both patterns, the stromal component, which is usually sparse, is not easily seen because it is occupied by a dense cellular infiltrate which is dominated by lymphocytes, but plasma cells and macrophages are also noted in variable numbers (the so-called lymphoid stroma). Lymph follicles, sometimes with germinal centers, are often found (Choi and Choi 2008). Typically, the caps of the germinal centers are randomly oriented. The lymphocytes invade the solid carcinoma tissue and are sometimes in close contact with viable-looking carcinoma cells or with apoptotic bodies. Emperipolesis is observed, and lymphocytes are visualized within vessel lumina, probably reflecting a homing mechanism.

The tumor cells have been shown to be reactive for cytokeratins, including pankeratin (AE1/AE3) and cytokeratins 8 and 18 and sometimes CK19, but a case not staining for cytokeratins 7, 19, and 20 has been reported (Nemolato et al. 2008; Fig. 8).

In the HCC-like pattern, the cells sometimes stain for HepPar1 (Chen et al. 2007b; Nemolato

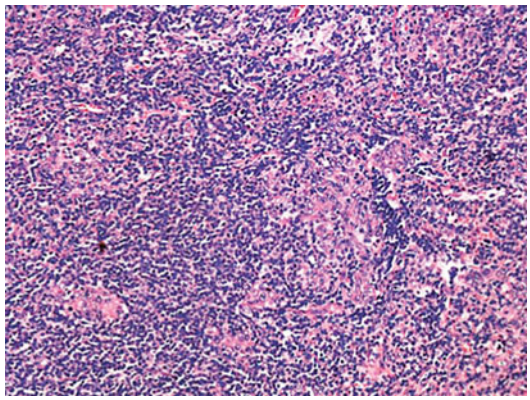

Fig. 7 Lymphoepithelial carcinoma of the liver. The histologic picture is dominated by a lymphocytic infiltrate with interspersed neoplastic epithelial cell nests (hematoxylin and eosin stain)

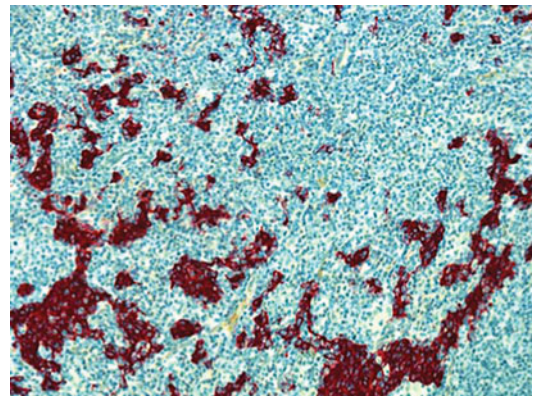

Fig. 8 The epithelial tumor cell nests in lymphoepithelial carcinoma as visualized by cytokeratin expression. Note that part of tumor cells are damaged and atrophic (CAM 5.2 immunostain)

et al. 2008) and for glypican-3 (Nemolato et al. 2008). In the poorly differentiated pattern, the proliferation fraction is very high and may exceed 80 %, as visualized in the Ki-67 immunostain. The lymphocyte population is dominated by T-cells with either a CD8+-dominated immunophenotype (Nemolato et al. 2008) or uniform distribution of CD4(+) and CD8(+) cells (Patel et al. 2014). There is a variable admixture of CD4+ T lymphocytes, CD20+ and CD79a + B lymphocytes, CD38+ polytypic plasma cells, and CD68+ macrophages. The lymph follicles and germinal centers are of B-cell lineage and exhibit the immunophenotype known from other localizations.

EBV Expression in LELC

Similar to other organs, part of hepatic LELC expresses Epstein-Barr virus components (Fig. 9).

In hepatic LELC-expressing Epstein-Barr virus (EBV), tumor cells are reactive for LMP1 and show nuclear signals for EBER in in situ hybridization (Weiss et al. 1989; Korabecna et al. 2003). EBV expression in LELC has been associated with p53 overexpression in the nuclei of EBV-infected tumor cells (Gulley et al. 1998) and with overexpression of Bcl-2 and the proliferation marker, PCNA (Niemhom et al. 2000).

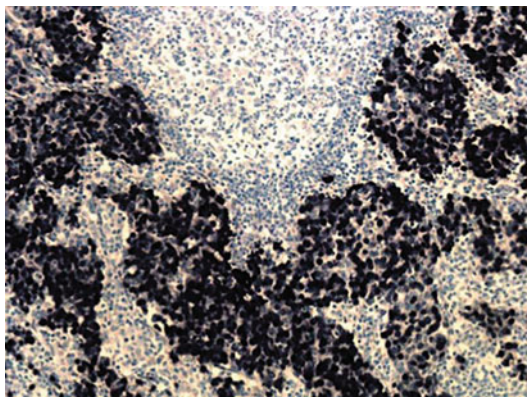

Fig. 9 Part of lymphoepithelial carcinomas of the hepatobiliary tract express Epstein-Barr virus (EBV) antigens. This figure shows strong nuclear reactivity of neoplastic cells for EBER (*black* nuclei). A germinal center is present in the upper part of the figure (in situ hybridization for EBV early RNA/EBER)

Lymphoepithelioma-Like Carcinoma of the Biliary Tract

ICD-O 8082/3

Apart from LELC of the liver substance proper, several reports have documented the occurrence of LELC in either the extrahepatic or intrahepatic bile ducts, however, with clear predominance in the intrahepatic bile duct system.

Selected References Hsu et al. 1996; Vortmeyer et al. 1998; Kim et al. 1999; Pratschke et al. 1999; Ortiz et al. 2000; Chen et al. 2001; Jeng et al. 2001; Szekely 2001b; Huang et al. 2004; Min et al. 2007; Adachi et al. 2008; Henderson-Jackson et al. 2010; Hur et al. 2011; Ishida et al. 2011; Lee 2011; Mao et al. 2011; Xiao et al. 2012.

The majority of individuals developing this cancer were older than 40 years of age, and almost half were more than 60. Females and males are equally affected. Interestingly, the right and left liver lobes were almost equally involved. Very few cases have been identified in the common bile duct (Ishida et al. 2011). Biliary tract LELC is usually not associated with liver cirrhosis, and the serum AFP levels are normal. Most biliary LELC reported so far were associated with EBV infection (Hsu et al. 1996; Vortmeyer et al. 1998; Ortiz et al. 2000; Chen et al. 2001; Jeng et al. 2001; Huang et al. 2004; Min et al.2007; Henderson-Jackson et al. 2010; Xiao et al. 2012; Chan et al. 2014), also tumors in the extrahepatic duct system (Ishida et al. 2011). Several patients, in part older than 60 years at diagnosis, were reported to be EBV negative (Kim et al. 1999; Szekely 2001b; Adachi et al. 2008; Hur et al. 2011; Lee 2011).

The prognosis of biliary tract LELC seems to be better than that of ordinary cholangiocarcinoma (Chan et al. 2014). Based on five cases, one patient died of disease after 4 years, while four patients were alive and free of disease after a period ranging from 2 months to 7 years (Jeng et al. 2001). In a compilation of 11 patients with available follow-up, only 2/11 died of disease and 1/11 died of surgical complications

(Huang et al. 2004). In a review of 13 patients, 4 patients had lymph node metastases, only 1 patient had remote metastases (lung and spleen), and 3 died of disease. With a follow-up ranging from 2 months to 7 years, eight patients were alive without disease (Henderson-Jackson et al. 2010). This better outcome is reflected by a similar biology of LELC located in the stomach (Shibata et al. 1991; Nakamura et al. 1994; Matsunou et al. 1996) and in the lung (Chen et al. 1998).

There are relatively few informations regarding the gross features of these neoplasms. In a patient with LELC of the extrahepatic bile duct, laparotomy revealed a whitish, firm tumor, originating from the common bile duct and reaching to the right hepatic duct (Pratschke et al. 1999). In the literature, the diameter of these lesions ranged from 3.0 to 12 cm. Intrahepatic biliary tract LELC have been described as well-defined, non-encapsulated tumors with a firm or rubbery consistency, and a white to yellowish cut surface and a more or less clear spatial relationship to larger intrahepatic bile ducts (Kim et al. 1999; Chen et al. 2001; Huang et al. 2004; Min et al. 2007; Lee 2011). In one case, serial macroscopic sections revealed that the tumor was located on the route of the hepatic duct and connected to it (Adachi et al. 2008). Large tumors may be associated with hepatic satellite nodules (Hsu et al. 1996). Association with liver cirrhosis has been reported (Kim et al. 1999; Lee 2011) but is uncommon. Lymph node metastases were described in two reports (Vortmeyer et al. 1998; Chen et al. 2001).

Biliary tract LELC has been described to be either composed of the undifferentiated component alone (morphologically corresponding to the undifferentiated subtype of nasopharyngeal carcinoma/NPC) or two components. Undifferentiated carcinoma is the variant in which tumor cells form ill-defined syncytia-like formations infiltrated by small lymphocytes, with irregular large nuclei with vesicular or open chromatin and prominent nucleoli, again similar to NPC. Within the sometimes very dense lymphocytic infiltrate, lymph follicles with or without germinal centers may develop (Vortmeyer et al. 1998; Huang et al. 2004). In the transition region between tumor cells' nests and lymphocyte infiltrates, piecemeal necrosis-like changes may be seen. In mixed forms, undifferentiated carcinoma is combined with moderately differentiated adenocarcinoma forming ductular structures (Henderson-Jackson et al. 2010), sometimes accompanied by a marked desmoplastic reaction, similar to ordinary cholangiocarcinoma (Hsu et al. 1996; Vortmeyer et al. 1998; Ortiz et al. 2000; Chen et al. 2001; Huang et al. 2004), but an association of LELC with intraductal cholangiocarcinoma has also been found. This component had a papillary structure of non-mucinous carcinoma cells, and transitions between the two components were noted (Adachi et al. 2008). The cellular infiltrate of biliary tract LELC may contain large and immunoblast-like forms and, rarely, multinuclear atypical cells somewhat resembling cells in Hodgkin's disease, but with negative results for CD30 reactivity (Pratschke et al. 1999; Szekely 2001b).

Immunohistochemistry

The cells of biliary tract LELC are reactive for pancytokeratin, CK7, CK8, CK22, EMA, and polyclonal CEA, but negative for CD20. CEA was negative in one case (Vortmeyer et al. 1998). Infiltrating lymphocytes form a mixture of phenotypes, but usually with predominance of CD3-reactive cells (Ortiz et al. 2000; Chen et al. 2001; Huang et al. 2004; Henderson-Jackson et al. 2010). Abundant nuclear reactivity for p53 protein has been observed (Ortiz et al. 2000).

EBV Expression in Biliary Tract LELC

Detection of EBV-encoded RNA (EBER1) by in situ hybridization results in nuclear staining, either patchy or diffuse (Ortiz et al. 2000; Huang et al. 2004). Based on PCR, one tumor extract showed EBV nuclear antigen 2 (type II EBNA2) of 400 bp and latent membrane protein (LMP) of 285 bp, due to a 30-bp internal deletion (Huang et al. 2004). PCR analysis for EBV nuclear antigen 2 was consistent with EBV strain type A (Vortmeyer et al. 1998). In the case of Hsu and coworkers, abundant EBV EBER1 was shown in both the LELC and adenocarcinoma component

of the tumor. Southern blot analysis and PCR showed a monoclonal episomal form of EBV, with a genotype characteristic for Chinese EBV strain type 1 (Hsu et al. 1996). In one report, the LMP1 gene was found to be wild type by PCR (Vortmeyer et al. 1998). Negative results for LMP1 immunostaining are reported in the literature (Ortiz et al. 2000). In contrast to these tumors, no EBV-encoded nuclear RNA and LMP1 were detected in 215 cases of intrahepatic cholangiocarcinoma from Japan (Ozaki et al. 2000).

EBV Expression in Hepatocellular Carcinoma

EBV is detectable in a subset of HCCs from hepatitis C-positive patients. This finding has led to the assumption that EBV could play a role in the development of HCV-related HCC (Sugawara et al. 2000).

References

Adachi Y, Mori M, Maehara Y, Sugimachi K (1992) Poorly differentiated medullary carcinoma of the stomach. Cancer 70:1462–1466

Adachi S, Morimoto O, Kobayashi T (2008) Lymphoepithelioma-like cholangiocarcinoma not associated with EBV. Pathol Int 58:69–74

Akhter S, Liu H, Prabhu R, DeLucca C, Bastian F, Garry RF, Schwartz M, Thung SN, Dash S (2003) Epstein-Barr virus and human hepatocellular carcinoma. Cancer Lett 192:49–57

Bertucci F, Finetti P, Cervera N, Charafe-Jauffret E, Mamessier E, Adelaide J et al (2006) Gene expression profiling shows medullary breast cancer is a subgroup of basal breast cancers. Cancer Res 66:4636–4644

Cai XY, Qiu SJ, Wu ZQ, Ye SL, Fan J, Zhou J, Tang ZY (2005) Relationship between dendritic cells and memory T lymphocytes in tumor site and prognosis of hepatocellular carcinoma (in Chinese). Zhonghua Yi Xue Za Zhi 85:671–675

Cai XY, Gao Q, Qiu SJ, YeWu ZQ, Fan J, Tang ZY (2006) Dendritic cell infiltration and prognosis of human hepatocellular carcinoma. J Cancer Res Clin Oncol 132:293–301

Cao AY, He M, Huang L, Shao ZM, Di GH (2013) Clinicopathologic characteristics at diagnosis and the survival of patients with medullary breast carcinoma in China: a comparison with infiltrating ductal carcinoma-not otherwise specified. World J Surg Oncol 11:91

Capece D, Fischietti M, Verzella D, Gaggiano A, Cicciarelli G, Tesitore A, Zazzeroni F et al (2013) The inflammatory microenvironment in hepatocellular carcinoma: a pivotal role for tumor-associated macrophages. Biomed Res Int 2013:187204

Chan AWH, Tong JHM, Sung MYM, Lai PBS, To K-F (2014) Epstein-Barr virus-associated lymphoepithelioma-like cholangiocarcinoma: a rare variant of intrahepatic cholangiocarcinoma with favourable outcome. Histopathology 65:674–683

Chen FF, Yan JJ, Lai WW, Jin YT, Su IJ (1998) Epstein-Barr virus-associated nonsmall cell lung carcinoma: undifferentiated "lymphoepithelioma-like" carcinoma as a distinct entity with better prognosis. Cancer 82:2334–2342

Chen S, Akbar SM, Tanimoto K, Ninomiya T, Iuchi H, Michitaka K, Horiike N, Onji M (2000) Absence of CD83-positive mature and activated dendritic cells at cancer nodules from patients with hepatocellular carcinoma: relevance to hepatocarcinogenesis. Cancer Lett 148:49–57

Chen TC, Ng KF, Kuo T (2001) Intrahepatic cholangiocarcinoma with lymphoepithelioma-like component. Mod Pathol 14:527–532

Chen CH, Lee HS, Huang GT, Yang PM, Yu WY, Cheng KC, Lee PH, Jeng YM et al (2007a) Phenotypic analysis of tumor-infiltrating lymphocytes in hepatocellular carcinoma. Hepatogastroenterology 54:1529–1533

Chen CJ, Jeng LB, Huang SF (2007b) Lymphoepithelioma-like hepatocellular carcinoma. Chang Gung Med J 30:172–177

Chetty R (2012) Gastrointestinal cancers accompanied by a dense lymphoid component: an overview with special reference to gastric and colonic medullary and lymphoepithelioma-like carcinomas. J Clin Pathol 65:1062–1065

Choi HJ, Choi JH (2008) Hepatocellular carcinoma with lymphoid stroma: report of two cases (in Korean). Korean J Hepatol 14:394–398

Duvnjak M, Lerotic I, Barsic N, Tomasic V, Virovic Jukic L, Velagic V (2007) Pathogenesis and management issues for non-alcoholic fatty liver disease. World J Gastroenterol 13:4539–4550

Emile JF, Adam R, Sebagh M, Marchadier E, Falissard B, Dussaix E et al (2000) Hepatocellular carcinoma with lymphoid stroma: a tumour with good prognosis after liver transplantation. Histopathology 37:523–529

Foschini MP, Eusebi V (2009) Rare (new) entities of the breast and medullary carcinoma. Pathology 41:48–56

Gulley ML, Burton MP, Allred DC, Nicholls JM, Amin MB, Ro JY, Schneider BG (1998) Epstein-Barr virus infection is associated with p53 accumulation in nasopharyngeal carcinoma. Hum Pathol 29:252–259

Henderson-Jackson E, Nasir NA, Hakam A, Nasir A, Coppola D (2010) Primary mixed lymphoepithelioma-like carcinoma and intra-hepatic cholangiocarcinoma: a case report and review of literature. Int J Clin Exp Pathol 3:736–741

Hsu HC, Chen CC, Huang GT, Lee PH (1996) Clonal Epstein-Barr virus associated cholangiocarcinoma with lymphoepithelioma-like component. Hum Pathol 27:848–850

Huang Y, Tsung JS, Lin CW, Cheng TY (2004) Intrahepatic cholangiocarcinoma with lymphoepithelioma-like carcinoma component. Ann Clin Lab Sci 34:476–480

Hur YH, Kim HH, Koh YS, Seoung JS, Cho CK (2011) Lymphoepithelioma-like cholangiocarcinoma not associated with Epstein-Barr virus. ANZ J Surg 81:652–653

Ichikawa T, Takagi H, Yamada T, Abe T, Ito H, Kojiro M, Mori M (2002) Granulomas in hepatocellular carcinoma induced by lipiodolized SMANCS, a polymer-conjugated derivative of neocarzinostatin. Histopathology 40:579–580

Ido E, Furihata M, Ohtsuki Y, Iwata J, Sonobe H (1994) S-100 protein-positive dendritic cells detected in hepatocellular-carcinoma in relation to tumor progression and prognosis. Int J Oncol 5:231–236

Iezzoni JC, Gaffey MJ, Weiss LM (1995) The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol 103:308–315

Ikeguchi M, Oi K, Hirooka Y, Kaibara N (2004) CD8+ lymphocyte infiltration and apoptosis in hepatocellular carcinoma. Eur J Surg Oncol 30:53–57

Ishida M, Mori T, Shiomi H, Naka S, Tujikawa T, Andoh A, Saito Y, Kurumi Y, Kojima F et al (2011) Non-Epstein-Barr virus associated lymphoepithelioma-like carcinoma of the inferior common bile duct. World J Gastrointest Oncol 3:111–115

Isoda Y, Sato Y, Otsuka Y, Ono K, Furutani S, Tsuji N, Moriyama S, Sonobe H (1982) Surgery of hepatoma with marked lymphocyte infiltration (in Japanese). Gan No Rinsho 28:259–262

Jacquemier J, Padovani L, Rabayrol L, Lkhani SR, Penault-Llorca F, Denoux Y, Fiche M et al (2005) Typical medullary breast carcinomas have a basal/myoepithelial phenotype. J Pathol 207:260–268

Jeng YM, Chen CL, Hsu HC (2001) Lymphoepithelioma-like cholangiocarcinoma: an Epstein-Barr virus-associated tumor. Am J Surg Pathol 25:516–520

Kai K, Miyoshi A, Tokunaga O, Kitahara K, Takahashi T, Miyake S, Egashira Y, Irie H et al (2010) A hepatocellular neoplasm accompanied with massive histiocyte infiltration. Clin J Gastroenterol 3:40–44

Kelly A, Fahey R, Fletcher JM, Keogh C, Carroll AG, Siddachari R, Geoghegan J et al (2014) CD141+ myeloid dendritic cells are enriched in healthy human liver. J Hepatol 60:135–142

Kim YB, Park YN, Han JY, Hong KC, Hwang TS (1999) Biliary lymphoepithelioma-like carcinoma not associated with Epstein-Barr virus. Arch Pathol Lab Med 123:441–443

Kong LQ, Zhu XD, Xu HX, Zhang JB, Lu L, Wang WQ, Zhang QB, Wu WZ, Wang L et al (2013) The clinical significance of the CD163+ and CD68+ macrophages in patients with hepatocellular carcinoma. PLoS One 8: e59771

Korabecna M, Ludvikova M, Skalova A (2003) Molecular diagnosis of Epstein-Barr virus in paraffin-embedded tissues of tumors with abundant lymphoid infiltration. Neoplasma 50:8–12

Lau AH, Thomson AW (2003) Dendritic cells and immune regulation in the liver. Gut 52:307–314

Lee W (2011) Intrahepatic lymphoepithelioma-like cholangiocarcinoma not associated with Epstein-Barr virus: a case report. Case Rep Oncol 4:68–73

Li W, Wu BA, Zeng YM, Chen GC, Li XX, Chen JT, Guo YW, Li MH, Zeng Y (2004) Epstein-Barr virus in hepatocellular carcinogenesis. World J Gastroenterol 10:3409–3413

Li L, Li SP, Min J, Zheng L (2007) Hepatoma cells inhibit the differentiation and maturation of dendritic cells and increase the production of regulatory T cells. Immunol Lett 114:38–45

Malyuchik SS, Kiyamoya RG (2008) Medullary breast carcinoma. Exp Oncol 30:96–101

Mano Y, Aishima S, Fujita N, Tanaka Y, Kubo Y, Motomura T, Taketomi A, Shirabe K et al (2013) Tumor-associated macrophage promotes tumor progression via STAT3 signaling in hepatocellular carcinoma. Pathobiology 80:146–154

Mao WB, Gong W, Huang Y, Xu SJ, Zhu YL, Zhao ZW (2011) Hepatic lymphoepithelioma-like cholangiocarcinoma: report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 40:493–494

Matsunou H, Konishi F, Hori H, Ikeda T, Sasaki K, Hirose Y, Yamamichi N (1996) Characteristics of Epstein-Barr virus-associated gastric carcinoma with lymphoid stroma in Japan. Cancer 77:1998–2004

Min HS, Shin E, Jang JJ (2007) Carcinoma with predominant lymphoid stroma in hepatobiliary system – report of 2 cases (in Korean). Korean J Hepatol 13:222–227

Mourra N, Fléjou JF (2001) Fine-needle aspiration of hepatocellular carcinoma: false-negative result due to epithelioid cells. Diagn Cytopathol 24:396–398

Nakamura S, Ueki T, Yao T, Ueyama T, Tsuneyoshi M (1994) Epstein-Barr virus in gastric carcinoma with lymphoid stroma. Special reference to its detection by the polymerase chain reaction and in situ hybridization in 99 tumors, including a morphologic analysis. Cancer 73:2239–2249

Nemolato S, Fanni D, Naccarato AG, Ravarino A, Bevilacqua G, Faa G (2008) Lymphoepithelioma-like hepatocellular carcinoma: a case report and a review of the literature. World J Gastroenterol 14:4694–4696

Neville E, Piyasena KHG, James DG (1975) Granulomas of the liver. Postgrad Med J 51:361–365

Newell P, Cottam B, Savage T, Hammill C, Wolf R, Bifulco C, Xiao HD, Crocenzi T et al (2013) Circulating and intratumoral macrophages in patients with hepatocellular carcinoma: correlation with therapeutic approach. Am J Surg 205:534–540

Niemhom S, Kitazawa S, Murao S, Kunachak S, Maeda S (2000) Co-expression of p53 and bcl-2 may correlate to the presence of Epstein-Barr virus genome and the

expression of proliferating cell nuclear antigen in nasopharyngeal carcinoma. Cancer Lett 160:199–208
Nurlaila I, Telisinghe PU, Ramasamy R (2013) CD8+ lymphocytes and apoptosis in typical and atypical medullary carcinomas of the breast. Immunol Lett 156:123–126
O'Beirne JP, Harrison PM (2004) The role of the immune system in the control of hepatocellular carcinoma. Eur J Gastroenterol Hepatol 16:1257–1260
Ortiz MR, Garijo G, Adrados M, Lopez-Bonet E, Acero D, Bernado L (2000) Epstein-Barr virus-associated cholangiocarcinoma with lymphoepithelioma-like component. Int J Surg Pathol 8:347–351
Ozaki S, Harada K, Watanabe K, Furubo S, Tsui WM, Nakanuma Y (2000) Absence of Epstein-Barr virus (EBV) in intrahepatic cholangiocarcinoma conformed by lack of EBV-coded nuclear RNA and latent membrane protein-1. Histopathology 36:50–53
Park HS, Jang KY, Kim YK, Cho BH, Moon WS (2009) Hepatocellular carcinoma with massive lymphoid infiltration: a regressing phenomenon? Pathol Res Pract 205:648–652
Park I, Kim J, Kim M, Bae SY, Lee SK, Kil WH, Lee JE, Nam SJ (2013) Comparison of the characteristics of medullary breast carcinoma and invasive ductal carcinoma. J Breast Cancer 16:417–425
Patel KR, Liu TC, Vaccharajani N, Chapman WC, Brunt EM (2014) Characterization of inflammatory (lymphoepithelioma-like) hepatocellular carcinoma: a study of 8 cases. Arch Pathol Lab Med 138:1193–1202
Pedersen L, Holck S, Schiodt T, Zedeler K, Mouridsen HT (1994) Medullary carcinoma of the breast, prognostic importance of characteristic histopathological features evaluated in a multivariate Cox analysis. Eur J Cancer 30A:1792–1797
Perlemutter G, Bigorgne A, Cassard-Doulcier AM, Naveau S (2007) Nonalcoholic fatty liver disease: from pathogenesis to patient care. Nat Clin Pract Endocrinol Metab 3:458–469
Phelan S, Nolan N (2008) Granulomas in dysplastic nodules – an unusual morphological finding. Histopathology 53:114–115
Pratschke J, Jonas S, Tillius SG, Neuhaus P (1999) Lymphoepitheliales carcinom des extrahepatischen gallengangs. Chirurg 70:605–607
Quist E, Talmon G, Hartman C, Wisecarver J (2014) Medullary-like hepatocellular carcinoma: an unusual histologic variant. Am J Clin Pathol 142:670–674
Rakha EA, Aleskandarany M, El-Sayed ME, Blamey RW, Elston CW, Ellis IO, Lee AH (2009) The prognostic significance of inflammation and medullary histological type in invasive carcinoma of the breast. Eur J Cancer 45:1780–1787
Shibata D, Tokunaga M, Uemura Y, Aato E, Tanaka S, Weiss LM (1991) Association of Epstein-Barr virus with undifferentiated gastric carcinomas with intense lymphoid infiltration. Lymphoepithelioma-like carcinoma. Am J Pathol 139:469–474
Shinoda M, Kadota Y, Tsujikawa H, Masugi Y, Itano O, Ueno A, Mihara K, Hibi T et al (2013) Lymphoepithelioma-like hepatocellular carcinoma: a case report and a review of the literature. World J Surg Oncol 11:97
Shirabe K, Matsumata T, Maeda T, Sadanaga N, Kuwano H, Sugimachi K (1995) A long-term surviving patient with hepatocellular carcinoma including lymphocytes infiltration – a clinicopathologic study. Hepatogastroenterology 42:996–1001
Shirabe K, Motomura T, Muto J, Toshima T, Matono R, Mano Y, Takeishi K, Ijichi H et al (2010) Tumor-infiltration lymphocytes and hepatocellular carcinoma: pathology and clinical management. Int J Clin Oncol 2010(15):552–558
Shirabe K, Mano Y, Muto J, Matono R, Motomura T, Toshima T, Takeishi K, Uchiyama H et al (2012) Role of tumor-associated macrophages in the progression of hepatocellular carcinoma. Surg Today 42:1–7
Si MW, Thorson JA, Lauwers GY, DalCin P, Furman J (2004) Hepatocellular lymphoepithelioma-like carcinoma associated with Epstein Barr virus: a hitherto unrecognized entity. Diagn Mol Pathol 13:183–189
Sturm N, Chaffanjon P, Salameire D, Zarski JP, Letoublon C, Sengel C, Brambilla E (2004) A case report of extrahepatic hepatocellular carcinoma with lymphocytic infiltration (in French). Ann Pathol 24:183–186
Sugawara Y, Makuuchi M, Takada K (2000) Detection of Epstein-Barr virus DNA in hepatocellular carcinoma tissues from hepatitis C-positive patients. Scand J Gastroenterol 35:981–984
Szekely E (2001a) Hepatocellular carcinoma with lymphoid stroma: 'lymphoepithelioma-like carcinoma'? Histopathology 39:540
Szekely E (2001b) Lymphoepithelioma-like cholangiocarcinoma (LELC) not associated with Epstein-Barr virus. Am J Surg Pathol 25:1464–1466
Tomimatsu H, Kojiro M, Nakashima T (1982) Epithelioid granulomas associated with hepatocellular carcinoma. Arch Pathol Lab Med 106:538–539
Vortmeyer AO, Kingma DW, Fenton RG, Curti BD, Jaffe ES, Duray PH (1998) Hepatobiliary lymphoepithelioma-like carcinoma associated with Epstein-Barr virus. Am J Clin Pathol 109:90–95
Wada Y, Nakashima O, Kutami R, Yamamoto O, Kojiro M (1998) Clinicopathologic study on hepatocellular carcinoma with lymphocytic infiltration. Hepatology 27:407–414
Weigelt B, Horlings HM, Kreike B, Hayes MM, Hauptmann M, Wessels LF, de Jong D et al (2008) Refinement of breast cancer classification by molecular characterization of histological special types. J Pathol 216:141–150
Weiss LM, Movahed LA, Butler AE, Swanson SA, Frierson HF, Cooper PH, Colby TV, Mills SE (1989) Analysis of lymphoepithelioma and lymphoepithelioma-like carcinomas for Epstein-Barr

viral genomes by in situ hybridization. Am J Surg Pathol 13:625–631

Xiao P, Shi H, Zhang H, Meng F, Peng J, Ke Z, Wang K, Liu Y, Han A (2012) Epstein-Barr virus-associated intrahepatic cholangiocarcinoma bearing an intense lymphoplasmacytic infiltration. J Clin Pathol 65:570–573

Yakirevich E, Izhak OB, Rennert G, Kovacs ZG, Resnick MB (1999) Cytotoxic phenotype of tumor infiltrating lymphocytes in medullary carcinoma of the breast. Mod Pathol 12:1050–1056

Yin X, Lu M, Liang L, Lai Y, Huang J, Li Z (2002) Infiltration of dendritic cells and lymphocytes in hepatocellular carcinoma tissue (in Chinese). Zhonghua Wai Ke Za Zhi 40:336–343

Yin XY, Lu MD, Lai YR, Liang LJ, Huang JF (2003) Prognostic significances of tumor-infiltrating S-100 positive dendritic cells and lymphocytes in patients with hepatocellular carcinoma. Hepatogastroenterology 50:1281–1284

Zhao F, Korangy F, Greten TF (2012) Cellular immune suppressor mechanisms in patients with hepatocellular carcinoma. Dig Dis 30:477–482

Zimmermann A, Kappeler A, Friess H, Büchler MW (2002) Hepatocellular carcinoma with an unusual medullary-like histology and signs of regression ("medullary-like hepatocellular carcinoma"). Dig Liver Dis 34:748–753

Zur Hausen A, van Beek J, Bloemena E, ten Kate FJ, Meijer CJ, van den Brule AJ (2003) No role for Epstein-Barr virus in Dutch hepatocellular carcinoma: a study at the DNA, RNA and protein levels. J Gen Virol 84:1863–1869

Variants of Hepatocellular Carcinoma 13

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_13

Abstract

Few hepatocellular carcinomas (HCC) show a morphologic pattern that deviates from the histology of ordinary HCC or established variants thereof, treated in detail in other chapters. Rare tumors show peliotic change with a presence of blood-filled spaces lacking an endothelial lining (peliotic HCC). One variant of HCC is characterized by multinuclear tumor cells resembling syncytial cells in giant cell hepatitis (syncytial giant cell HCC). This unusual neoplasm occurs both in the pediatric age group and in adults. Cells with a smooth chromophobic cytoplasm and clusters of cells with anaplastic changes are diagnostic features of the rare chromophobe HCC. HCCs with strongly eosinophilic and granular cells form the oxyphilic and oncocytic variants of HCC, the latter having increased number of mitochondria, similar to oncocytic tumors in other organs. Very rare HCCs are pigmented due to the accumulation of a Dubin-Johnson-like pigment. Other very rare variants of HCC include pleomorphic giant cell-rich HCC, spindle cell HCC, and ossifying HCC.

Peliotic Hepatocellular Carcinoma

Introduction

Peliosis of the liver is a lesion histologically characterized by the presence of few to multiple blood-filled cavities that lack a complete endothelial lining (see the respective chapter). Numerous causes or associations have been noted for hepatic peliosis. Rarely, peliotic change can also develop within liver tumors, in particular hepatocellular carcinoma.

Hepatocellular Carcinoma with Peliotic Change

Relatively few cases of hepatocellular carcinoma (HCC) with peliotic change (peliotic HCC; pelioid-type HCC) have been described in the literature (Balazs 1991; Moldvay et al. 1991; Chedid et al. 1999; Grazioli et al. 2000; Ji et al. 2001; Kawasaki et al. 2003; Kim et al. 2007a; Watanabe et al. 2008; Hoshimoto et al. 2009; Fujimoto et al. 2010; Ikeda et al. 2011). The exact prevalence of peliotic change in HCC is not yet known, but the alteration may be more common than generally anticipated. In a series of 294 consecutively resected HCC, peliotic change in tumor was observed in 39.5 % (Fujimoto et al. 2010). HCC with peliotic change has been observed under circumstances that also promote peliosis in nonneoplastic liver, e.g., long-term androgenic steroid therapy (Balazs 1991; Moldvay et al. 1991) and intake of oral contraceptives (Ikeda et al. 2011).

Clinical and Imaging Features

From the relatively few reports available, it surfaced that the overall clinical presentation of peliotic HCC is not different from that of other HCC. However, peliotic change in HCC has been suggested to be associated with a better prognosis (Chedid et al. 1999). Abdominal ultrasonography usually reveals hyperechoic lesions with mosaic patterns, and contrast-enhanced harmonic ultrasonography shows hemangioma-like findings, i.e., the peripheral globular enhancing pattern (Kawasaki et al. 2003). Dynamic CT and MR imaging showed early irregular enhancement of the peripheral part of the lesion, with this effect persisting into late phase, spreading into central parts of the tumor (Kim et al. 2007; Hoshimoto et al. 2009). Hepatic angiography showed the “cotton-wool” sign that usually characterizes hemangioma (Hoshimoto et al. 2009). Peliotic HCC may closely mimic hepatic hemangioma on angiography and contrast-enhanced harmonic ultrasonography (Kawasaki et al. 2003). Also in the course of technetium-99 m red blood cell scintigraphy, peliotic HCC may present as a lesion closely mimicking hepatic hemangioma (Ji et al. 2001), because both lesions are characterized by the entrapment of erythrocytes in dilated vessels or blood-filled spaces.

Pathology

At gross examination, peliotic HCC shows focal dark-red areas on cut surfaces, looking like focal hemorrhage (Ji et al. 2001) or presenting as a hemorrhagic honeycomb-like pattern (Fujimoto et al. 2010). In part of the tumors, the grossly visible peliotic change can occupy more than half of the cut surface. Apart from focal peliotic change, there are examples of extensive tumor peliosis, macroscopically showing a diffusely red discoloration and a spongy appearance of the tumor (Hoshimoto et al. 2009). In extensive peliotic change, the tumor grossly resembles giant cavernous hemangioma with hemorrhage (Kim et al. 2007). In contrast to tumor hemorrhage, tumor peliosis is not associated with grossly detectable necrosis. Peliotic HCCs were found to be encapsulated more frequently than in HCC without peliotic change (Kim et al. 2007; up to 93 %, Fujimoto et al. 2010). In one investigation, the mean tumor diameter of HCC with peliotic change was significantly larger than that of control HCC, and large tumor more often showed peliosis (Fujimoto et al. 2010).

Peliotic HCCs display, usually in a focal distribution and more often in central parts other tumor, variably sized spaces containing blood in the absence of a complete endothelial lining (Figs. 1 and 2).

Within large blood-filled spaces, trabecules of HCC seem to be isolated and sometimes fragmented, and there are areas where only cancer cell clusters remain. In marginal parts of the peliotic lesions, spaces with an incomplete endothelial lining may be found, suggesting a transition between the peliotic spaces and the surrounding tumor blood vessels. Peliotic zones in HCC s may, in fact, be surrounded by areas with telangiectasia. In one case, a dense eosinophil infiltration associated with the tumor was found (Watanabe et al. 2008).

Hepatocellular Carcinoma Associated with Peliosis Hepatis

Peliosis hepatis can be synchronously associated with hepatocellular carcinoma (Tocornal and Rosenberg 1981; Russmann et al. 2001).

Differential Diagnosis

On CT images, focal peliosis hepatis may itself mimic hepatocellular carcinoma (Han and Kim 2006; Atila et al. 2007; Kim et al. 2007) or metastatic liver disease (Tateishi et al. 1998; Wannesson et al. 2009). Other hepatic tumors sometimes showing peliosis include liver cell adenoma and angiomyolipoma (Akatsu et al. 2004).

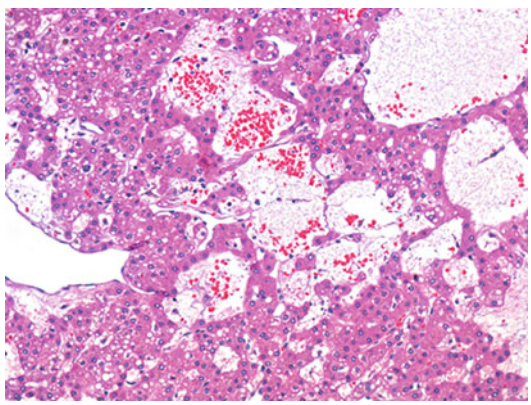

Fig. 1 Peliotic hepatocellular carcinoma. This tumor contains several large blood-filled spaces (hematoxylin and eosin stain)

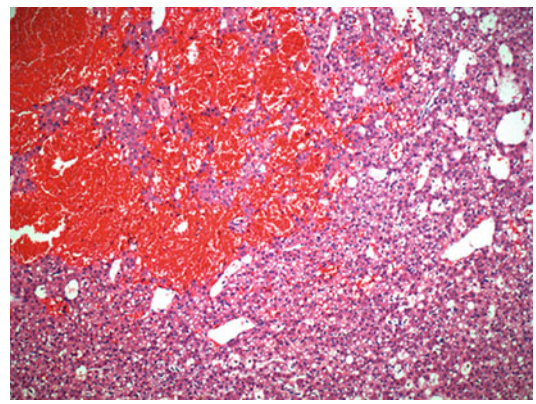

Fig. 2 In this peliotic hepatocellular carcinoma, blood-filled spaces lack an endothelial lining and are associated with tumor cell atrophy (hematoxylin and eosin stain)

Syncytial Giant Cell Hepatocellular Carcinoma

Introduction

Hepatocytes are capable of transforming into multinucleated cells, the syncytial giant cells. In nonneoplastic conditions, this phenomenon is well known to occur in several types of neonatal hepatitis, mainly in those associated with cholestasis (giant cell hepatitis; syncytial giant cell hepatitis) and also in adults (postnatal giant cell hepatitis). Syncytial giant cell formation is known in several types and locations of carcinoma, e.g., clear cell renal cell carcinoma (Lloreta et al. 2002). Hepatocellular tumors with syncytial giant cells are rare lesions that occur both in adult and pediatric patients. The giant cells occurring in these neoplasms are epithelial in nature, in contrast to the mesenchymal features of osteoclast-like multinucleated giant cells occurring in a distinct group of hepatobiliary tumors.

Syncytial Giant Cells in Adult-Type Hepatocellular Carcinoma

A first case of hepatocellular carcinoma with syncytial giant cells was published by Nazari in 1905. The figure published in this work shows a well-differentiated HCC of the trabecular type. At some places, huge multinucleated tumor cells are interspersed between the outer surface of the trabecules and the endothelial lining of intervening sinusoid-like vascular channels. The syncytial giant cells deeply bulge into these vascular spaces and are sometimes covered by a thin endothelial cell layer (Nazari 1905). A second case of multinucleated hepatocellular carcinoma was described in 1925 (Rowen and Mallory 1925). Histology of a malignant tumor in a 57-year-old male displayed hepatocellular carcinoma with a mixed trabecular and acinar growth pattern and bile production. The neoplasm contained numerous and in part very large, multinucleated hepatoid cells. The large cells, with a cytoplasm resembling that of hepatocytes, contained dozens of vesicular nuclei with prominent nucleoli, these nuclei being predominantly arranged at the cell periphery but also forming clusters in central parts of the cells. Some of these cells contained inspissated bile, and few cells had engulfed damaged cells of unknown character (emperipolesis). At least part of pleomorphic giant cell-rich hepatocellular carcinomas can also contain syncytial giant cells, in addition to pleomorphic giant cells with bizarre and lobulated nuclei (Vijay et al. 2011; Lampri et al. 2014).

Pediatric Syncytial Giant Cell Hepatocellular Carcinoma

A marked contribution of large syncytial giant cells was found in an hepatocellular carcinoma of an infant who presented with features of Cushing's syndrome due to bilateral adrenal hyperplasia (Atra et al. 2007). This patient was a 9-month-old girl with bilateral nodular hyperplasia of the adrenal glands and a cystic lesion in the left ovary that in addition showed a 5 cm-sized mass in the right liver lobe. Biopsy of the mass revealed hepatocellular carcinoma consisting of medium-sized hepatocyte-like cells forming both a trabecular and acinar pattern, with bile formation in the acini. The tumor contained numerous multinuclear giant cells of the syncytial type, similar to those seen in infantile giant cell hepatitis (Figs. 3 and 4).

The giant cells displayed the same nuclear atypias as the other HCC cells and were therefore not reactive elements. The adjacent liver did not show any giant cell change. The tumor giant cells were immunoreactive for the hepatocyte marker Hep Par 1 and cytokeratin 8. A mitochondrial immunostain showed that the tumor cells had less mitochondria than normal hepatocytes, except the giant cells, where mitochondria were numerous. Very few tumor cell nuclei were p53 protein positive. Beta-catenin was consistently expressed in both ordinary HCC cells and tumor giant cells, with a predominantly membranous staining pattern. The proliferation fraction of the HCC (Ki-67) was lower than 5 %, and no labeling was found in the nuclei of giant cells.

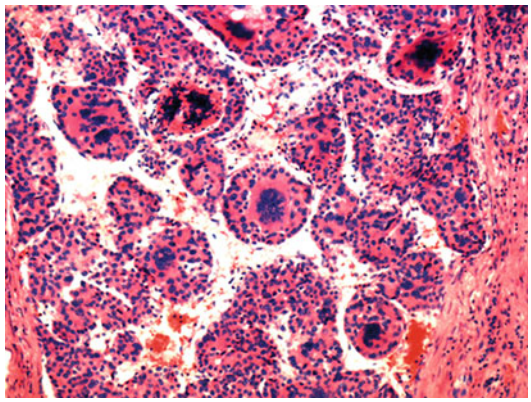

Fig. 3 Syncytial giant cell hepatocellular carcinoma. This trabecular tumor shows multinucleated giant cells situated in the interior of tumor cell plates (hematoxylin and eosin stain)

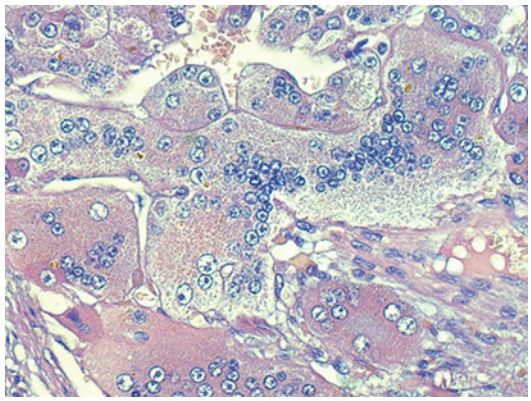

Fig. 4 Giant cells in syncytial giant cell hepatocellular carcinoma can become very large cells with numerous nuclei, the latter sometimes arranged in bands (hematoxylin and eosin stain).

Differential Diagnosis

The most important differential diagnosis of giant cell-rich hepatic carcinomas is hepatobiliary tumors with osteoclast-like giant cells. There are few other hepatic tumors that rarely develop a giant cell component, e.g., epithelioid angiomyolipoma (Alatassi and Sahoo 2009). Many ordinary HCCs display tumor cells with several nuclei, mainly in grade 3 lesions, but these cells are not syncytial-type giant cells.

Pathogenetic Pathways

Under normal conditions, several cell types are capable to change into multinucleated cells, mainly via the mechanism of cell fusion. Well-known examples are osteoclasts (derived from mononuclear preosteoclasts), syncytiotrophoblast, myotubes, and macrophages. Cell fusion has also been found to occur in infantile giant cell hepatitis (Koukoulis et al. 1999) and in adult autoimmune hepatitis with giant cell formation (Hayashi et al. 2011). Cell fusion is a unique phenomenon that is induced and regulated by numerous factors. In osteoclasts, several molecules have been reported to be fusion related, including CD44, CD47, ADAM12, MCP-1, IL-4, IL-13, and CD9. Macrophages can fuse among each other, but may also fuse with somatic cells and tumor cells, forming hybrid fusion products. CD44 expression is highly induced in macrophages at the onset of cell fusion. The intracellular domain of CD44 (CD44ICD) is cleaved in macrophages undergoing fusion, whereby CD44ICD promotes cell fusion via activation of NF-kappaB (Cui et al. 2006). A compound critical for both osteoclastogenesis and the generation of multinucleated macrophages (Langhans giant cells and foreign-body giant cells) is the seven-transmembrane-region receptor dendritic cell-specific transmembrane protein, DC-STAMP (Yagi et al. 2006). Much information has accumulated in studies of respiratory syncytial virus (RSV)-induced giant cell formation. RSV is an important human pathogen that causes severe respiratory infections in infants, the elderly, and immunocompromised hosts. RSV infection induces the activation of RhoA, a small GTPase, in cells, and inhibition of RhoA abolishes syncytium formation, indicating an important role of RhoA signaling in giant cell formation (Gower et al. 2005). Formation of multinucleated cells by liver cell neoplasms may represent a survival strategy. In HCC cells exposed to etoposide-induced DNA damage, resistance to toxicity and survival promoted by Akt/PTEN signaling is associated with multinucleation (Mukherjee et al. 2013).

The numerous nuclei in syncytial giant cells, also in those found in rare HCCs, have an

abnormal position in the cell body and distribution. The nucleus in eukaryotic cells has, on the one hand, a well-defined position in relation to the cytoskeleton, organelles, and cell surface but, on the other hand, can move within the cytoplasm. Positioning and movements of nuclei are controlled by a distinct protein interactome. The integral outer nuclear membrane (ONM) proteins implicated in these processes thus far all contain a conserved Klarsicht/ANC-1/Syne homology (KASH) domain at their C-terminus that associates with Sad1p/UNC-84 (SUN)-domain proteins of the inner nuclear membrane within the periplasmic space of the nuclear envelope (review: Wilhelmsen et al. 2006). ANC-1 consists of two actin-binding calponin domain and a nuclear envelope targeting KASH domain. ANC-1 functions to physically tether the actin cytoskeleton to the outer nuclear membrane, thus linked the nucleus to the cytoskeleton (Starr and Han 2002, 2005). UNC-84 is a SUN protein that is required for both nuclear migration and anchorage. UNC-84 recruits a second UNC protein, UNC-83, and ANC-1 to the nuclear envelope (McGee et al. 2006). In skeletal muscle cells, Syne proteins anchor nuclei at the neuromuscular junction (Grady et al. 2005), and SUN1 and SUN2 play critical but partially redundant roles in anchoring the nuclei.

Chromophobe Hepatocellular Carcinoma

Introduction

In an analysis of 219 Western HCC, a novel subtype of this tumor category was identified, characterized by a generally chromophobe appearance of neoplastic cells and abrupt focal anaplasia. This subtype was identified in 6 % of all HCC analyzed, with almost equal distribution of sexes and an average age of 61 years at presentation. 6/13 cases occurred in cirrhotic livers, with an enrichment of chronic hepatitis B. In contrast to ordinary HCC, where 8 % of cases were associated with the alternative lengthening of telomere (ALT) phenotype (a telomerase-independent mechanism of telomere maintenance), ALT positivity was found in 92 % of chromophobe HCC (Wood et al. 2013).

Pathology

Chromophobe HCC is composed of cells with a smooth chromophobic cytoplasm and of small clusters of tumor cells with marked nuclear atypia that are abruptly separated from the bland chromophobe background, a phenomenon termed abrupt focal anaplasia (Wood et al. 2013).

Oncocytic and Oxyphilic Hepatocellular Carcinoma

Introduction

In contrast to fibrolamellar hepatocellular carcinoma/FL-HCC, which is a well-established hepatic tumor entity characterized by large oxyphilic cells and oncocytes, other primary oxyphilic or oncocytic hepatocellular neoplasms are exceedingly rare (Figs. 5 and 6).

More common are bile duct neoplasms with oncocytic features, treated in a separate chapter.

Oncocytic lesions are characterized by epithelial cells showing an abundance (“proliferation”)

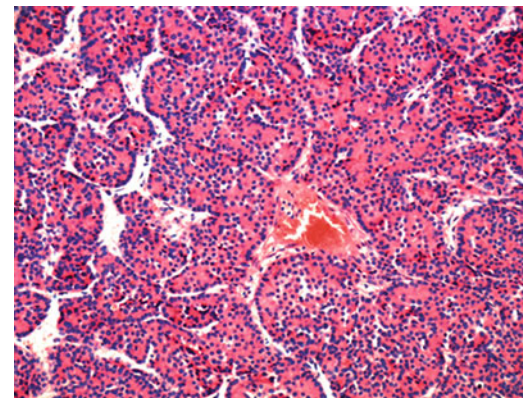

Fig. 5 Rare trabecular hepatocellular carcinomas show predominance of tumor cells with a strongly eosinophilic cytoplasm (oxyphilic hepatocellular carcinoma; hematoxylin and eosin stain)

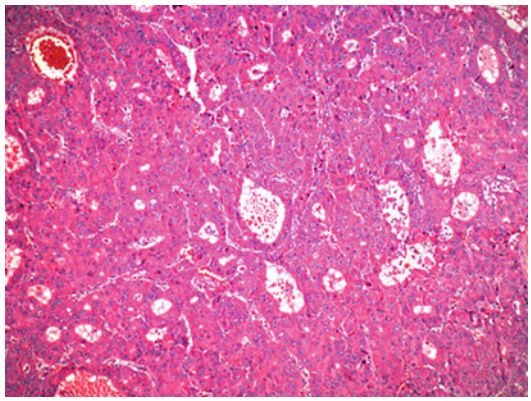

Fig. 6 The cells of this oxyphilic mixed trabecular and acinar hepatocellular carcinoma are enlarged and reminiscent of mitochondria-rich cells/oncocytes (hematoxylin and eosin stain)

of mitochondria (mitochondriosis), the oncocytes. Oncocytes can arise in numerous tissues and organs, both in nonneoplastic and neoplastic cells (reviews: Tallini 1998; Guaraldi et al. 2011). The presence of oncocytes in the liver has been documented for various hepatic conditions in several reports (Sternlieb 1979; Gerber and Thung 1981; Altmann 1990; Tanikawa et al. 2007). Liver cells rich in mitochondria have also been termed oxyphilic granular hepatocytes (Lefkowitch et al. 1980). The use of the term, oxyphilic, for cells that are in fact oncocytes may cause some misunderstandings. True epithelial oxyphilic cells possess their strongly eosinophilic features due to a marked increase of smooth endoplasmic reticulum rather than an increase in mitochondria. Oncocytic hepatocytes reveal mitochondrial DNA dysfunction characterized by significant deficiencies of mtDNA and mtDNA-encoded respiratory chain enzymes (Müller-Höcker 1998; Tanji et al. 2003).

Pathology of Oncocytic Hepatocellular Carcinoma

Only very few bona fide oncocytic tumors primary to the liver have been reported (Baithun and Pollock 1983; El Hag et al. 1994; Fukunaga et al. 1996; Papotti et al. 1999). The tumor described by Baithun and Pollock (1983) was found in the non-cirrhotic liver of a 51-year-old female. Macroscopy showed a well-circumscribed tumor measuring up to 20 cm in diameter, with a central fibrous scar. Histologically, the tumor cells were polygonal-shaped oncocytes embedded in a fibrous stroma. The histology does not seem to correspond to FL-HCC. The case reported by El-Hag et al. (1994) was an 18 cm-sized tumor located to the right liver lobe, in the absence of cirrhosis. Macroscopically, in another reported case, a large tumor occupying almost the entire left lobe was detected in a 67-year-old man with liver cirrhosis. Histopathologically, the tumor consisted of exclusively large, granular eosinophilic cells with moderate nuclear atypia and occasional mitotic figures. The growth pattern was mixed trabecular and pseudoglandular, without lamellar fibrosis. The tumor cells contained numerous, PAS-negative globular hyaline bodies. Ultrastructurally, the cells were rich in mitochondria with electron-dense, ovoid or polyhedral inclusions (Fukunaga et al. 1996). Sometimes, HCC with oncocytic features is identified in its metastases, e.g., in the kidneys, where such a tumor can mimic renal oncocytoma (D'Antonio et al. 2010).

Precursor Lesions with Oxyphilic or Oncocytic Features

Foci of altered hepatocytes (FAH) regarded as very early lesions in the hepatic carcinogenic pathway sometimes show cells with oncocytic features (Su et al. 1997).

Differential Diagnosis

Differential diagnosis mainly includes fibrolamellar hepatocellular carcinoma, oncocytic biliary neoplasms (Tabibian et al. 2008), metastatic oncocytic tumors including oncocytic adrenocortical carcinoma (Argyriou et al. 2008), metastasizing oncocytic endocrine tumors of the pancreas (Volante et al. 2006), and rare forms of

angiomyolipoma of the liver with oxyphilic cell change. Several reports document metastases of renal oncocytoma to the liver (Timbal and Rodier 1984; Aslam et al. 2009), and hepatic metastases of the oncocytic thyroidal Hürthle cell carcinoma have been described (Salvatori et al. 2004). Also the uncommon bile duct adenoma with oncocytic features may cause diagnostic difficulties in biopsies (Arena et al. 2006).

Pigmented Hepatocellular Carcinoma

Introduction

Most instances where a pigment is found in epithelial tumors of the liver are caused by Dubin-Johnson syndrome (DJS; OMIM 237500). This autosomal recessive disorder was independently described twice in the same year, 1954 (Dubin and Johnson 1954; Sprinz and Nelson 1954). The term, black liver disease, was coined in 1958 (Smiley et al. 1958). DJS is a rare benign hereditary (autosomal recessive) disorder of bilirubin metabolism, characterized by conjugated hyperbilirubinemia, a darkly pigmented liver, and the presence of an abnormal pigment in hepatocytes. The disorder is mapped to chromosome 10q24 and is caused by absent activity of a critical conjugate export pump of the hepatocyte, the MRP2 glycoprotein (see below). Several animal models of DJS are known, including mutant Corriedale sheep, and TR- and EHBR mutant rats.

Black Livers and Benign Black Liver Tumors: Dubin-Johnson Syndrome and Related Pigments

Livers of patients with DJS are characterized by the accumulation of a coarse, dark-brown pigment in the vicinity of the canalicular pole of hepatocytes (Arias and Blumberg 1979). The pigment is much darker than ordinary lipofuscin and lacks the golden color of hemosiderin. The pigment stains with the Fontana-Masson stain and has, therefore, been compared with melanin ("melanin-like") but is clearly different from melanin (Swartz et al. 1987).

Histochemically and immunohistochemically, the DJS pigment is very close to the pigment in pseudomelanosis coli (Park et al. 1990). Ultrastructurally, accumulation of membrane-bound, electron-dense lysosomal granules within the cytoplasm of hepatocytes is observed. These bodies are mostly located in the vicinity of the canalicular pole, as is to be expected from light microscopic findings. The same pigment is found in Kupffer cells which phagocytose it after hepatocyte decay (Muscatello et al. 1967; Baba and Ruppert 1972; Ueno et al. 1998; Sobaniec-Lotowska and Lebensztejn 2006). It has been reported that postoperative regeneration of the DJS liver is not different from that of normal livers according to portography and hepatic scintigraphy finings (Nakamura et al. 1984).

Exceptionally, black livers develop in the absence of DJS. In a patient with a black liver, massive accumulation of coarse brown granules was detected in the absence of Schmorl stain positivity of hepatocyte pigment and absent MRP2 mutation. The MRP2 protein was immunolocalized to the canalicular membrane in this liver (Kobayashi et al. 2004). Pigmented liver cell adenoma with extensive deposition of a DJS-like pigment in the pericanalicular cytoplasm of adenoma cells has been observed in patients without DJS (Bernard et al. 2000; Hasan et al. 2000; Ferko et al. 2003; Hechtman et al. 2011; Masuda et al. 2011; Koea and Kua 2012; Vij et al. 2012). In the male patient described by Bernard and coworkers (2000), numerous black tumors of different sizes were seen at laparoscopy, histologically representing liver cell adenomas. The expression of the canalicular multispecific organic anion transporter was decreased in the tumors but normal in the adjacent liver, thus ruling out DJS. In the 28-year-old female patient reported by Ferko et al. (2003), pigmentation of hepatocellular adenoma was interpreted to be caused by long-term use of phenobarbital. In one case, hepatocellular carcinoma developed within a pigmented telangiectatic adenoma with nuclear beta-catenin expression (Hechtman et al. 2011).

Pigmented Hepatocellular Carcinoma

Roth and coworkers (1982) described a unique, largely black hepatocellular carcinoma discovered in a patient without evidence of DJS, i.e., a situation similar to that of black liver cell adenomas. In this 62-year-old male with a mass in the right liver lobe, hepatic arteriogram showed a moderately vascular, 120-cm single intrahepatic tumor. An extended right hepatic lobectomy was performed. The resection specimen revealed a well-circumscribed, bulging tumor with a maximum diameter of 13 cm in a non-cirrhotic liver of normal color. On cut surfaces, about 85 % of the tumor was charcoal gray and the rest tan-brown. An incomplete fibrous capsule was present and fine fibrous strands subdivided the tumor into nodular regions. Foci of necrosis and old hemorrhage were present. Histology disclosed a well-differentiated HCC with a microtrabecular and solid growth pattern. The tumor cells were eosinophilic, with occasional multinucleated forms. Intracytoplasmic, coarse and dark-brown pigment granules were present in the tumor cells and in few sinusoidal cells (probably macrophages). Ultrastructurally, the pigment granules were membrane-bound particles containing clumps of electron-dense material similar to the granules seen in DJS.

Pigmented Hepatocellular Carcinoma, Not Otherwise Specified

Ultrastructural studies have shown that HCCs may contain the endogenous pigment, lipofuscin, in the cytoplasm (Ichida 1983). Ye and coworkers described an HCC characterized by the accumulation of a not otherwise specified pigment, occurring in a 42-year-old woman with a history of 25-year oral contraceptive use (Ye et al. 1999).

Nonpigmented Hepatocellular Carcinoma in Dubin-Johnson Syndrome

Several reports document the development of hepatocellular carcinoma in DJS, so far exclusively from Japan (Okamura et al. 1980; Sakamoto et al. 1987; Sano et al. 1988; Mori et al. 1991; Adachi et al. 1992; Kajikawa et al. 1993; Yakushiji et al. 1995; Ueno et al. 1998; Shikada et al. 2004). Adachi and coworkers (1992) reported that during an observation decade in Japan, 57 patients with DJS had associated cholelithiasis (14 %), chronic hepatitis (10 %), or HCC (3 %). Where documented, the macroscopic color of the tumors is described as pale or yellow, i.e., not like the adjacent darkly pigmented liver (Ueno et al. 1998). Apart from HCC, DJS is rarely associated with multiple hepatic cavernous hemangiomas (Li et al. 2013).

Hepatocellular Carcinoma with Mucin Production

Introduction

Combined hepatocellular and cholangiocellular carcinomas are defined as primary hepatic malignancies that show both hepatocellular and cholangiocellular components in an intricate mixture and usually a stromal reaction accompanying the cholangiocarcinoma components. Much less common are primary liver carcinomas with a dual phenotype, i.e., having a cell lineage expressing both hepatocyte and cholangiocyte features in the same cells, and not representing primary liver of intermediate phenotype. Such a situation, termed hepatocellular carcinoma (HCC) with mucin production has been first described in 2009, based on a 53-year-old Korean man with liver cirrhosis showing on CT a 10 × 9.8 cm heterogeneously enhancing mass in the right liver lobe (Lee et al. 2009). Based on the distinct histopathology of this tumor (see below), the authors classified the lesion as liver tumor of dual differentiation, different from combined HCC/CC.

Pathology

The resection specimen described by Lee et al. (2009) displayed a poorly circumscribed, firm, white to pink nodular tumor. Histopathology

revealed HCC with solid and trabecular components and extensive geographical necrosis. One part of the tumor consisted of hepatoid cells as found in ordinary HCC, while another part was composed of thick trabecules or irregularly shaped tumor island filled with compact or loose mucin-producing glands. These glands consisted of columnar cells with eosinophilic cytoplasm and apical microvilli, and there was intervening desmoplastic stroma. Some of the glandular cells contained PAS-positive mucin bodies, creating signet-ring cells. Immunohistochemically, tumors cells of both trabecular and glandular components were CK19-positive. In some glandular portions, positivity for CK7, EMA, and CEA was noted.

Pleomorphic Giant Cell-Rich Hepatocellular Carcinoma

Introduction

The pleomorphic giant cell-rich variant of hepatocellular carcinoma (PG-HCC) was first described in 1973 (Anthony 1973). Very few cases have been reported since (Chetty et al. 1990; Korkolis et al. 2009; Hu et al. 2010). The tumor is histologically characterized by a pleomorphic phenotype of the neoplastic cells and the presence of numerous highly atypical multinucleated giant cells of the non-osteoclast-like type. Multinucleated giant cells are a features of many HCCs and are a hallmark of Edmondson-Steiner grade 3 lesions, but here they usually occur in smaller numbers and in a focal distribution pattern and are less pleomorphic, while in PG-HCC, the giant cells are numerous, diffusely distributed, and highly pleomorphic.

Pathology

In one case, the tumor was described as an irregularly infiltrative, multifocal, grayish white tumor with necrosis and hemorrhage. The neoplasm had developed in a cirrhotic liver (Vijay et al. 2011). The neoplastic cells are large and pleomorphic and show an abundant eosinophilic cytoplasm. These cells contain one to few highly atypical nuclei with abnormal mitotic figures. These cells are arranged in nests or tiny nodules rather than plates/trabecules, and also solid growth patterns may occur. Numerous tumor giant cells are present, characterized by multiple pleomorphic and in part bizarre nuclei with prominent nucleoli. The cytoplasm of these giant cells may contain cell debris and remnants of phagocytosed neutrophils (Vijay et al. 2011).

Immunohistochemistry

The neoplastic cells are immunoreactive for cytokeratins, vimentin, and alpha-fetoprotein. In contrast to hepatic giant cell tumor with osteoclast-like giant cells, the multinucleated cells are not reactive for CD68 (Vijay et al. 2011).

Differential Diagnosis

The most important differential diagnosis consists of other HCCs showing giant cells, in particular grade 3 tumors which are known to have multinucleated giant cells. Pleomorphic giant cell carcinoma occurs in the pancreas and can metastasize to the liver. The latter tumor can be distinguished from primary PG-HCC by the different morphology of the hepatoid cells in the latter and by immunoreactivity for hepatocyte markers and AFP. Osteoclast-like giant cell tumor of the liver has a clearly different phenotype, the multinucleated cells lacking pleomorphism, with highly regular nuclei, and the cells being CD68-positive.

Spindle Cell Hepatocellular Carcinoma

Introduction

Carcinomas with formation of spindle cells are rare lesions in the hepatobiliary tract and are more often found to belong to the cholangiocarcinoma group and in the gallbladder, whereas most hepatocellular carcinomas with spindle cells

have been classified as carcinosarcomas. Spindle cell carcinomas (also termed metaplastic carcinomas, biphasic carcinomas, or biphasic sarcomatoid carcinomas; Nappi et al. 1994) are well recognized in the aerodigestive tract, in particular involving the oral cavity, the larynx, the thyroid gland, the lungs, and the esophagus. Generally, it seems that spindle cell formation is more common in squamous carcinomas than in adenocarcinomas. In spindle cell carcinomas *sensu strictiori* (metaplastic carcinomas), vimentin reactivity is a consistent feature, but reactivity for several cytokeratins and for epithelial membrane antigen (EMA) is more variable, probably depending on cell differentiation (Adem et al. 2002). It is evident that such developments may require that one redefines what, e.g., a carcinosarcoma is, this term still based on morphologic findings and numerous interpretations dating from the pre-immunohistochemistry era.

Spindle cell carcinomas of the liver have been reported sporadically or in relatively small series, using several terms to designate these uncommon lesions (review: Maeda et al. 1996). Craig et al. (1989) designated sarcomatoid hepatocellular carcinoma as spindle cell HCC. Others employed the term, spindle *variant* of HCC (Ishak et al. 1994). Kojiro and coworkers (1989) classified the sarcomatous appearance of some HCCs into two types: those consisting mainly of spindle-shaped cells ("spindle cell type") and those consisting of tumor cells that lacked mutual contact ("free cell type"). Based on these earlier discussions, Maeda and coworkers, in their study of 15 cases, designated HCCs with a spindle-cell-type *sensu strictiori* (Kojiro et al. 1989) as spindle cell hepatocellular carcinoma (SpHCC). Although carcinosarcomas of the liver are treated in a separate chapter, liver carcinomas with a predominantly spindled mesenchymal component are here discussed separately, under the use of Maeda's terminological proposition, SpHCC.

Clinical and Imaging Features

The clinical und imaging presentations of SpHCC do not differ from those of other HCCs. The biology of disease has not been clarified; specifically, it is clearly known whether SpHCCs behave similar or in a different way in comparison with ordinary HCCs, although few informations suggest that SpHCCs may behave in a more favorable manner (Chedid et al. 1999).

Histopathology

Relatively few examples of HCCs entirely composed of spindle cells (SpHCC *sensu strictiori* or Kojiro's spindle-cell-type HCC; Kojiro et al. 1989) have been reported (Andreola et al. 1987; Chan and Leung 1988; Kojiro et al. 1989; Ishijima et al. 1995; Maeda et al. 1996; Han et al. 1998; Chedid et al. 1999; Maruyama et al. 2002). In most other situations (the second group of spindle cell HCCs), the tumors exhibit foci where the hepatocyte-like tumor cells exhibit transitions to populations of fusiform or spindle cells, or foci of spindle cells are admixed with trabecular and/or pseudoglandular structures (Nam et al. 2006; Yoshida et al. 2013). This complex situation, which may reflect varying effects of EMT, is illustrated by the largest published clinicopathologic and immunohistochemical analysis which described the features of 15 cases (Maeda et al. 1996). The patients showed a mean age at presentation of 58.7 years, and all except one were males. Tumor sizes ranged from 2.1 to 14.0 cm (mean, 6.2 cm), and all tumors except one were located to the right liver lobe. Most tumors were grossly whitish, hard masses demonstrating foci of necrosis and hemorrhages. Two tumors were of the pedunculated growth pattern. Histologically, a gradual transition between the spindle cell component and ordinary HCC was present in some cases. In other cases, however, the spindle cell component and the ordinary HCC component were present separately, or the tumor cells demonstrated features of both spindle cells and ordinary HCC cells. In this series, the spindle cell component represented more than 10 % of the viable tumor in all cases. The tumor cells in the spindle cell component were positive for vimentin in 62 % of the tumors, and almost two thirds of the

tumors showed spindle cells which were also cytokeratin (CAM 5.2)-positive (Maeda et al. 1996).

An unusual and in part spindle cell liver neoplasm was reported by Schmid and coworkers (1979). The patient, a 36-year-old female, had a large mass in her right liver lobe. The surgical specimen contained a spherical tumor, 8.5 × 7.0 cm; a portion of this tumor reached the dome of the liver. This mass, macroscopically well-circumscribed, was mainly composed of a whitish-gray and moderately form tissue with small cystic areas. The surrounding liver was compressed by the tumor. Histologically, the tumor tissue was well demarcated, without sinusoidal infiltration. The lesion consisted of an association of elongated spindle cells, a diffuse and focal infiltration of inflammatory cells (mainly lymphocytes and plasma cells), and large cells, which were extremely pleomorphic, often multinucleated, and some of which were elongated with a ribbon-shaped appearance like skeletal muscle fibers. At the periphery, inflammatory cells were also conspicuous. Ultrastructurally, the neoplastic cells exhibited the features of hepatoid epithelial cells. A similar malignant hepatic spindle cell tumor containing large and multinucleated tumor giant cells was reported Grigsby and coworkers (Grigsby et al. 1987). In this young female patient with a long history of oral contraceptive intake, a liver cell adenoma had developed within this spindle cell carcinoma. The hepatectomy specimen showed a dominant mass of 8.2 cm maximum diameter, surrounded by several smaller satellite lesions. Within this dominant spindle cell tumor part was an oval, 0.9-cm-diameter, well-encapsulated nodule, which was the liver cell adenoma (Grigsby et al. 1987).

This second group has been designated by a variety of terms, including carcinosarcoma or hepatocellular carcinoma with sarcomatous change or sarcomatous appearance (Kakizoe et al. 1987; Tsuji et al. 2001; Koda et al. 2003). Two tumors designated by the latter terms were of interest insofar as immunohistochemistry showed the spindle cells to be positive for both vimentin and keratin (Ellis et al. 1988; Tsuji et al. 2001; Koda et al. 2003), but in one instance, this was also the population later found in metastatic lesions (Koda et al. 2003). In one case, electron microscopic examination showed desmosomes and Mallory-Denk bodies in the spindle cells, taken as an argument for the diagnosis of HCC (Andreola et al. 1987). Neoplasms with features of carcinosarcoma are discussed in more detail in a separate paragraph.

Differential Diagnosis

The histologic differential diagnosis includes several other tumors in the liver that contain a spindle cell population, i.e., carcinosarcomas (review: She and Szakacs 2005), primary or secondary mesenchymal tumors of the liver, inflammatory pseudotumors, and unusual situations such as primary hepatic lymphoma with spindle cell components (Hayashi et al. 2006).

Pathogenesis

It is currently thought that such tumors are monoclonal neoplasms originating from a putative stem cell giving rise to both a frankly epithelial and a spindle cell lineage. The field of carcinomas with spindle cells has generally become more complex based on the possibility of defining cell lineages involved in a much more reliable way, owing to immunohistochemistry and other modern methods. Two concepts have basically altered our understanding of such neoplasms: first, the finding that spindle cells may either show a mesenchymal lineage or may clearly express epithelial markers and addition to mesenchymal markers and, second, the phenomena related to mesenchymal-epithelial transition (MET; epithelial-mesenchymal transition, EMT; Doble and Woodgett 2007; Guarino et al. 2007; Zavadil et al. 2008). MET/EMT has been proposed as a histogenetic mechanism for the development of sarcomatoid carcinomas. The phenomenon has been studied in some detail for squamous cell carcinomas with a spindle cell lineage (Iwata et al. 2009), and markers for detecting several cell lineages in sarcomatoid carcinomas showing

features of MET/EMT have been analyzed (Cates et al. 2008). In these and other tumors, several factors regulate the switch between morphologically epithelial and spindle cells, including the catenin-cadherin signaling pathway; the transcription factors Snail-1, Slug, E47, twist, and single-minded-2/SIM2; notch signaling pathway; hedgehog signaling; stromal cell-derived factor-1alpha/CXCR4; and the Aurora-A kinase (Usami et al. 2008; Wan et al. 2008; Zidar et al. 2008). These factors form an intricate signaling network within EMT pathways. Snail and slug transcription factors promote EMT via beta-catenin-T-cell-factor-4-dependent expression of TGF-beta3 (Medici et al. 2008). Slug-induced EMT alters the expression profile of receptor tyrosine kinases, including discoid domain receptor 2 (Maeyama et al. 2008).

Ossifying Hepatocellular Carcinoma

Introduction

Ossification of liver tumors is a well-known phenomenon in mixed epithelial and mesenchymal hepatoblastomas and certain rare mixed malignant tumors occurring in adult patients. Exceptionally, ossification develops in hepatocellular carcinoma (Leger et al. 1980; Maeda et al. 1986).

Pathology

In one patient, ossification was present in the stroma of a hepatocellular carcinoma that had arisen in a patient with sarcoidosis (Leger et al. 1980). The patient described by Maeda and coworkers (1986) was a 54-year-old man suffering from liver cirrhosis. CT of the liver revealed localized fine conglomerated calcifications in the right liver lobe and arteriography suggested hepatocellular carcinoma. Autopsy showed an encapsulated tumor, 4.5 cm in diameter, with variegated hemorrhagic and necrotic areas. Histology showed partially necrotic hepatocellular carcinoma predominantly of the trabecular type, with focal acinar differentiation and bile production. In a localized area within the tumor, there were bony trabecules. These were surrounded by relatively small immature malignant cells associated with osteoid. Ossification is a feature of part of mixed epithelial and mesenchymal hepatoblastomas of the adult (Altmann 1992), an intriguing group of neoplasms further discussed elsewhere.

Pathogenesis

The pathogenic pathways leading to ossification in liver tumors are not elucidated. Calcification of neoplastic tissue, found in rare hepatocellular carcinomas (Friedman 1988) or hepatic mixed malignant tumors (Ludwig et al. 1975), may induce secondary bone tissue formation, as, e.g., observed in certain forms of ectopic ossification. In hepatocellular carcinomas showing significant calcification, this alteration is sometimes present in the tumor stroma (Moenandar 1974). Ossification occurring in primary epithelial liver tumors has to be distinguished from that in the rare primary osteosarcomas of the liver (Kitayama et al. 1995).

Solitary Large Hepatocellular Carcinoma

Introduction

Large hepatocellular carcinoma (HCC) is often considered to represent advanced disease and to frequently consist of unresectable neoplasms. Recently, a unique type of HCC has been identified, characterized by solitary large tumors with a good outcome after hepatic resection (solitary large HCC, SL-HCC; Yang et al. 2009). In comparison with nodular HCC, SL-HCC showed a better outcome. Disease-free survival of SL-HCC was similar to that of small HCC, whereas poorer overall survival was observed in SL-HCC patients than in patients with small HCC, accompanied by more frequent vascular invasion, more advanced TNM stage, and potentially higher Edmondson-Steiner grade (Zhou et al. 2011).

Pathology

SL-HCCs are solitary bulky tumor masses that usually show an expanding growth pattern. These large neoplasms can show extensive central necrosis. Otherwise, the gross and histologic features do not differ from HCC of smaller size.

References

Adachi Y, Nanno T, Yamamoto T (1992) Constitutional jaundice (in Japanese). Nippon Rinsho 50:677–685

Adem C, Reynolds C, Adlakha H, Roche PC, Nascimento AG (2002) Wide spectrum screening keratin as a marker of metaplastic spindle cell carcinoma of the breast: an immunohistochemical study of 24 patients. Histopathology 40:556–562

Akatsu T, Sakamoto M, Shimazu M, Kitajima M (2004) Pedunculated angiomyolipoma of the liver with a predominant pelioid pattern. Virchows Arch 444:467–469

Alatassi H, Sahoo S (2009) Epithelioid angiomyolipoma of the liver with striking giant cell component: fine-needle aspiration biopsy findings of a rare neoplasm. Diagn Cytopathol 37:192–194

Altmann HW (1990) Oncocytic hepatocytes (in German). Pathologe 11:137–142

Altmann HW (1992) Epithelial and mixed hepatoblastoma in the adult. Histological observations and general considerations. Pathol Res Pract 188:16–26

Andreola S, Audisio RA, Lombardi L (1987) A light microscopic and ultrastructural study of spindle-shaped hepatocellular carcinoma. Tumori 73:195–201

Anthony PP (1973) Primary carcinoma of the liver. A study of 282 cases in Ugandan Africans. J Pathol 110:37–48

Arena V, Arena E, Stigliano E, Capelli A (2006) Bile duct adenoma with oncocytic features. Histopathology 49:318–320

Argyriou P, Zisis C, Alevizopoulos N, Kefaloyannis EM, Gennatas C, Petraki CD (2008) Adrenocortical oncocytic carcinoma with recurrent metastases: a case report and review of the literature. World J Surg Oncol 6:134

Arias IM, Blumberg W (1979) The pigment in Dubin-Johnson syndrome. Gastroenterology 77:820–821

Aslam MI, Spencer L, Garcea G, Pollard C, Metcalfe MS, Harrison RF, Dennison AR (2009) A case of liver metastasis from an oncocytoma with a focal area of chromophobe renal cell carcinoma: a wolf in sheep's clothing. Int J Surg Pathol 17:158–162

Atila K, Coker A, Ucar D, Kakademir S, Sagol O, Atsarcioglu H, Astarcioglu I (2007) A rare clinical entity misdiagnosed as a tumor: peliosis hepatis. Ulus Travma Acil Cerrahi Derg 13:149–153

Atra A, Al-Asiri R, Wali S, Al-Husseini H, Al-Bassas A, Zimmermann A (2007) Hepatocellular carcinoma, syncytial giant cell: a novel variant in children: a case report. Ann Diagn Pathol 11:61–63

Baba N, Ruppert RD (1972) The Dubin-Johnson syndrome: electron microscopic observation of hepatic pigment – a case study. Am J Clin Pathol 57:306–310

Baithun SI, Pollock DJ (1983) Oncocytic hepatocellular tumour. Histopathology 7:107–112

Balazs M (1991) Primary hepatocellular tumours during long-term androgenic steroid therapy. A light and electron microscopic study of 11 cases with emphasis on microvasculature of the tumours. Acta Morphol Hung 39:201–216

Bernard PH, Blanc JF, Paulusma C, Le Bail B, Carles J, Balabaud C, Bioulac-Sage P (2000) Multiple black hepatocellular adenomas in a male patient. Eur J Gastroenterol Hepatol 12:1253–1257

Cates JM, Dupont WD, Barnes JW, Edmunds HS, Fasig JH, Olson SJ, Black CC (2008) Markers of epithelial-mesenchymal transition and epithelial differentiation in sarcomatoid carcinoma: utility in the differential diagnosis with sarcoma. Appl Immunohistochem Mol Morphol 16:251–262

Chan KW, Leung CC (1988) An unusual hepatocellular carcinoma: an ultrastructural and immunohistochemical study. Pathology 20:299–302

Chedid A, Ryan LM, Dayal Y, Wolf BC, Falkson G (1999) Morphology and other prognostic factors of hepatocellular carcinoma. Arch Pathol Lab Med 123:524–528

Chetty R, Learmonth GM, Taylor DE (1990) Giant cell hepatocellular carcinoma. Cytopathology 1:233–237

Craig JR, Peters RL, Edmondson HA (1989) Tumors of the liver and intrahepatic bile ducts, Atlas of Tumor Pathology, Fascicle 26, Series 2. Armed Forces Institute of Pathology, Washington, DC, pp 179–180

Cui W, Ke JZ, Zhang Q, Ke HZ, Chalouni C, Vignery A (2006) The intracellular domain of CD44 promotes the fusion of macrophages. Blood 107:796–805

D'Antonio A, Caleo A, Caleo O, Addesso M, Boscaino A (2010) Hepatocellular carcinoma metastatic to the kidney mimicking renal oncocytoma. Hepatobiliary Pancreat Dis Int 9:550–552

Doble BW, Woodgett JR (2007) Role of glycogen synthase kinase-3 in cell fate and epithelial-mesenchymal transitions. Cells Tissues Organs 185:73–84

Dubin IN, Johnson FB (1954) Chronic idiopathic jaundice with unidentified pigment in liver cells; new clinicopathologic entity with report of 12 cases. Medicine 33:155–197

El Hag IA, Ekberg H, Tranberg KG, Lundstedt C, Johansson S, Sassner P, Hägerstrand I (1994) Oncocytic liver tumours and arterial dilatation. Case report. Eur J Surg 160:55–59

Ellis IO, Bell J, Ronan JE, Elston CW, Blamey RW (1988) Immunocytochemical investigation of intermediate filament proteins and epithelial membrane antigen in spindle cell tumours of the breast. J Pathol 154:157–165

Ferko A, Bedrna J, Nozicka J (2003) Pigmented hepatocellular adenoma of the liver caused by long-term use of phenobarbital (in Czech). Rozhi Chir 82:192–195

Friedman AC (1988) Calcification in hepatocellular carcinomas. AJR Am J Roentgenol 151:838–839

Fujimoto M, Nakashima O, Komuta M, Miyaaki T, Kojiro M, Yano H (2010) Clinicopathological study of hepatocellular carcinoma with peliotic change. Oncol Lett 1:17–21

Fukunaga N, Fujioka A, Tanaka K, Toyama R (1996) Oncocytic hepatocellular carcinoma with numerous globular hyaline bodies. Pathol Int 46:286–291

Gerber MA, Thung SN (1981) Hepatic oncocytes. Incidence, staining characteristics, and ultrastructural features. Am J Clin Pathol 75:498–503

Gower TL, Pastey MK, Peeples ME, Collins PL, McCurdy LH, Hart TK, Guth A et al (2005) RhoA signaling is required for respiratory syncytial virus-induced syncytium formation and filamentous virion morphology. J Virol 79:5326–5336

Grady RM, Starr DA, Ackerman GL, Sanes JR, Han M (2005) Syne proteins anchor muscle nuclei at the neuromuscular junction. Proc Natl Acad Sci U S A 102:4359–4364

Grazioli L, Morana G, Caudana R, Benetti A, Portolani N, Talamini G, Colombari R et al (2000) Hepatocellular carcinoma: correlation between gadobenate dimeglumine-enhanced MRI and pathologic findings. Invest Radiol 35:25–34

Grigsby P, Meyer JS, Sicard GA, Huggins MB, Lamar DJ, DeSchryver-Kecskemeti K (1987) Hepatic adenoma within a spindle cell carcinoma in a woman with a long history of oral contraceptives. J Surg Oncol 35:173–179

Guaraldi F, Zang G, Dachiw AP, Caturegli P (2011) Oncocytic mania: a review of oncocytic lesions throughout the body. J Endocrinol Invest 34:383–394

Guarino M, Rubino B, Ballabio G (2007) The role of epithelial-mesenchymal transition in cancer pathology. Pathology 39:305–318

Han JK, Kim SH (2006) Focal peliosis hepatic mimicking hepatocellular carcinoma (in Korean). Korean J Hepatol 12:460–463

Han JH, Park YN, Jung WH, Chi HS, Park C (1998) A case with sarcomatoid hepatocellular carcinoma. Yonsei Med J 39:390–394

Hasan N, Coutts M, Portmann B (2000) Pigmented liver cell adenoma in two male patients. Am J Surg Pathol 24:1429–1432

Hayashi H, Ohtani H, Ueda T, Yamaguchi J, Izawa K, Hayashida T, Higami Y, Shimokawa I (2006) Primary hepatic lymphoma with spindle cell components: a case report. Virchows Arch 449:591–596

Hayashi H, Narita R, Hiura M, Abe S, Tabaru A, Tanimoto A, Sasaguri Y, Harada M (2011) A case of adult autoimmune hepatitis with histological features of giant cell hepatitis. Intern Med 50:315–319

Hechtman JF, Ragoufi M, Fiel MI, Taouli B, Facciuto M, Schiano TD, Blouin AG, Thung SN (2011) hepatocellular carcinoma arising in a pigmented telangiectatic adenoma with nuclear b-catenin and glutamine synthetase positivity: case report and review of the literature. Am J Surg Pathol 35:927–932

Hoshimoto S, Morise Z, Suzuki K, Tanahashi Y, Ikeda M, Kagawa T, Mizoguchi Y et al (2009) Hepatocellular carcinoma with extensive peliotic change. J Hepatobiliary Pancreat Surg 16:566–570

Hu S, Mrak RE, Goldblatt PJ (2010) tripartite components of a hepatocellular carcinoma with distinct immunohistochemical and metastatic features. Conn Med 74:79–83

Ichida T (1983) Ultrastructural study of intracytoplasmic deposits in human hepatocellular carcinoma. Gastroenterol Jpn 18:560–576

Ikeda N, Oka K, Yonekawa N, Takaku H, Suzuki T, Saitoh T, Nagakura S, Nakano M (2011) Pelioid-type well-differentiated hepatocellular carcinoma in a patient with a history of taking oral contraceptives: report of a case. Surg Today 41:1270–1274

Ishak KG, Anthony PP, Sobin LH (1994) Histological typing of tumours of the liver, 2nd edn. World Health Organization, Geneva

Ishijima M, Tanaka M, Lee K, Kokubun Y, Asaoka A, Ito K, Tsubaki K, Ariga H, Arakawa Y, Negishi N et al (1995) A case of hepatocellular carcinoma presumably transforming to malignant spindle cell tumor (in Japanese). Nippon Shokakibyo Gakkai Zasshi 92:1886–1890

Iwata H, Aoyama Y, Kamiya H, Ichiki Y, Kitajima Y (2009) Spindle cell squamous cell carcinoma showing epithelial-mesenchymal transition. J Eur Acad Dermatol Venereol 23:214–215

Ji EK, Ryu JS, Kang GH, Moon DH, Auh YH, Lee HK (2001) Pelioid-type hepatocellular carcinoma masquerading as a hepatic hemangioma on technetium-99m red blood cell scintigraphy. Clin Nucl Med 26:33–35

Kajikawa S, Horigome N, Hanasaki K, Shiohara E, Kin Y, Iida F, Tanaka E, Kiyosawa K, Furuta S (1993) Two cases of Dubin-Johnson syndrome associated with chronic hepatitis, type C and hepatocellular carcinoma (in Japanese). Acta Hepatol Jpn 34:161–165

Kakizoe S, Kojiro M, Nakashima T (1987) Hepatocellular carcinoma with sarcomatous change. Clinicopathologic and immunohistochemical studies of 14 autopsy cases. Cancer 59:310–316

Kawasaki T, Kudo M, Inui K, Ogawa C, Chung H, Minami Y (2003) Hepatocellular carcinoma mimicking cavernous hemangioma on angiography and contrast enhanced harmonic ultrasonography. A case report. Hepatol Res 25:202–212

Kim YK, Jang KY, Cho BH, Ko SW, Moon WS (2007a) Three-phase dynamic CT of pelioid hepatocellular carcinoma. AJR Am J Roentgenol 189:W160–W162

Kim SH, Lee JM, Kim WH, Han JK, Lee JY, Choi BI (2007b) Focal peliosis hepatis as a mimicker of hepatic tumors: radiological-pathological correlation. J Comput Assist Tomogr 31:79–85

Kitayama Y, Sugimura H, Arai T, Nagamatsu K, Kino I (1995) Primary osteosarcoma arising from cirrhotic liver. Pathol Int 45:320–325

Kobayashi Y, Ishihara T, Wada M, Kajihara S, Araki J, Mifuji R, Itani T, Kuroda M, Urawa F et al (2004)

Dubin-Johnson-like black liver with normal bilirubin level. J Gastroenterol 39:892–895
Koda M, Maeda Y, Matsunaga Y, Mimura K, Murawaki Y, Horie Y (2003) Hepatocellular carcinoma with sarcomatous change arising after radiofrequency ablation for well-differentiated hepatocellular carcinoma. Hepatol Res 27:163–167
Koea JB, Kua H (2012) Pigmented liver cell adenoma: rare but benign. ANZ J Surg 82:86–87
Kojiro M, Sugihara S, Kakizoe S, Nakashioma O, Kiyomatsu K (1989) Hepatocellular carcinoma with sarcomatous change; a special reference to the relationship with anticancer therapy. Cancer Chemother Pharmacol 23:4–8
Korkolis DP, Aggeli C, Plataniotis GD, Gontikakis E, Zerbinis H, Papantoniou N, Xinopoulos D et al (2009) Successful en bloc resection of primary hepatocellular carcinoma directly invading the stomach and pancreas. World J Gastroenterol 15:1134–1137
Koukoulis G, Mieli-Vergani G, Portmann B (1999) Infantile liver giant cells: immunohistochemical study of their proliferative state and possible mechanisms of formation. Pediatr Dev Pathol 2:353–359
Lampri ES, Ioachim E, Harissis H, Balasi E, Mitselou A, Malamou-Mitsi V (2014) Pleomorphic hepatocellular carcinoma following consumption of hypericum perforatum in alcoholic cirrhosis. World J Gastroenterol 20:2113–2116
Lee KH, Kim YB, Cho SB, Lee MC, Park CS, Lee JH (2009) Hepatocellular carcinoma with characteristic mucin production: a case report. Cases J 2:6789
Lefkowitch JH, Arborgh BA, Scheuer PJ (1980) Oxyphilic granular hepatocytes. Mitochondrion-rich liver cells in hepatic disease. Am J Clin Pathol 74:432–441
Leger L, Lemaigre G, Prémont M, Salmon R, Klioua Z, Battesti JP (1980) Portal hypertension in sarcoidosis. Three cases including one with liver fibrosis and malignant hepatoma with osseous stroma (in French). Nouv Presse Med 9:1021–1024
Li P, Wang Y, Zhang J, Geng M, Li Z (2013) Dubin-Johnson syndrome with multiple liver cavernous hemangiomas: report of a familial case. Int J Clin Exp Pathol 6:2636–2639
Lloreta J, Bielsa O, Munné A, Dominguez D, Keysers U, Gelabert A, Serrano S (2002) Renal cell carcinoma with syncytial giant cell component. Virchows Arch 440:330–333
Ludwig J, Grier W, Hoffman HN II, McGill DB (1975) Calcified mixed malignant tumor of the liver. Arch Pathol 99:162–166
Maeda M, Kanayama M, Uchida T, Hasumura Y, Takeuchi J (1986) A case of hepatocellular carcinoma associated with ossification. Cancer 57:134–137
Maeda T, Adachi E, Kajiyama K, Takenaka K, Sugimachi K, Tsuneyoshi M (1996) Spindle cell hepatocellular carcinoma. A clinicopathologic and immunohistochemical analysis of 15 cases. Cancer 77:51–57
Maeyama M, Koga H, Selvendiran K, Yanagimoto C, Hanada S, Taniguchi E, Kawaguchi T et al (2008) Switching in discoid domain receptor expression in SLUG, induced epithelial-mesenchymal transition. Cancer 113:2823–2831
Maruyama T, Nozue M, Aoyagi H, Sakamoto T, Fukue M, Matsui S, Kodaira Y, Monma E et al (2002) A case of spindle cell type hepatocellular carcinoma responding to hepatic intraarterial infusion chemotherapy (in Japanese). Gan To Kagaku Ryoho 29:137–141
Masuda T, Beppu T, Ikeda K, Ishiko T, Chikamoto A, Hayashi H, Okabe H, Otao R et al (2011) Pigmented hepatocellular adenoma: report of a case. Surg Today 41:881–883
McGee MD, Rillo R, Anderson AS, Starr DA (2006) UNC-83 is a KASH protein required for nuclear migration and is recruited to the outer nuclear membrane by a physical interaction with the SUN protein UNC-84. Mol Biol Cell 17:1790–1801
Medici D, Hay ED, Olsen BR (2008) Snail and slug promote epithelial-mesenchymal transition through beta-catenin-T-cell factor-4-dependent expression of transforming growth factor-beta3. Mol Biol Cell 19:4875–4887
Moenandar IM (1974) Extensive calcification in the stroma of a primary hepatic carcinoma. J Pathol 114:54
Moldvay J, Schaff Z, Lapis K (1991) Hepatocellular carcinoma in Fanconi's anemia treated with androgen and corticosteroid. Zentralbl Pathol 137:167–170
Mori I, Imamura K, Kitamura T, Irie J, Shigematsu K (1991) A case of Dubin-Johnson syndrome complicated by hepatocellular carcinoma (in Japanese). Rinsho Kenkyu 68:153–156
Mukherjee A, Misra S, Howlett NG, Karmakar P (2013) Multinucleation regulated by the Akt/PTEN signaling pathway is a survival strategy for HepG2 cells. Mutat Res 755:135–140
Müller-Höcker J (1998) Defects of the respiratory chain in hepatic oncocytes. Virchows Arch 432:349–356
Muscatello U, Mussini I, Agnolucci MT (1967) The Dubin-Johnson syndrome: an electron microscopic study of the liver cell. Acta Hepatosplenol 14:162–170
Nakamura S, Morioka S, Baba S, Maeda M, Muro H (1984) Massive hepatic resection for metastatic cancer associated with Dubin-Johnson syndrome (in Japanese). Nippon Geka Gakkai Zasshi (J Jpn Surg Soc) 84:135–140
Nam HS, Kim HK, Ma SU, Yu BH, Jung KM, Gong KT, Lee YJ, Park TI, Hu BW et al (2006) A case of sarcomatoid hepatocellular carcinoma in a young female without risk factor (in Korean). Korean J Gastroenterol 47:458–462
Nappi O, Glasner SD, Swanson PE, Wick MR (1994) Biphasic and monophasic sarcomatoid carcinomas of the lung. A reappraisal of 'carcinosarcomas' and 'spindle-cell carcinomas'. Am J Clin Pathol 102:331–340
Nazari A (1905) Contributo allo studio delle neoformazioni epiteliali associate a cirrosi del fegato (Contribution to the study of epithelial neoplasms associated with liver cirrhosis). Il Policlinico vol XII: 35

Okamura J, Monden M, Horikawa S, Sikujara O, Kosaki G, Seki K, Kuroda C, Sakurai M (1980) Hepatocellular carcinoma in a case of Dubin-Johnson syndrome treated successfully with right extended lobectomy. Jpn J Surg 10:343–347

Papotti M, Cassoni P, Taraglio S, Bussolati G (1999) Oncocytic and oncocytoid tumors of the exocrine pancreas, liver, and gastrointestinal tract. Semin Diagn Pathol 16:126–134

Park C, Cho NH, Jeong HJ (1990) Melanosis coli – histochemical and immunohistochemical comparison of the pigments of melanosis coli and Dubin-Johnson syndrome. Yonsei Med J 31:27–32

Roth JA, Berman E, Befeler D, Johnson FB (1982) A black hepatocellular carcinoma with Dubin-Johnson-like pigment and Mallory bodies: a histochemical and ultrastructural study. Am J Surg Pathol 6:375–382

Rowen HS, Mallory FB (1925) A multinucleated liver cell carcinoma. Am J Pathol 1:677–680

Russmann S, Zimmermann A, Krähenbühl S, Kern B, Reichen J (2001) Veno-occlusive disease, nodular regenerative hyperplasia and hepatocellular carcinoma after azathioprine treatment in a patient with ulcerative colitis. Eur J Gastroenterol Hepatol 13:287–290

Sakamoto A, Mori I, Kawai K, Tsuchiyama H (1987) Dubin-Johnson syndrome associated with hepatocellular carcinoma – report of an autopsy case (in Japanese). Gan No Rinsho 33:1361–1367

Salvatori M, Perotti G, Rufini V, Maussier ML, Summaria V, Fadda G, Troncone L (2004) Solitary liver metastasis from Hürthle cell thyroid cancer: a case report and review of the literature. J Endocrinol Invest 27:52–56

Sano S, Nakagawa T, Horie S, Hasegawa I, Makise H, Oikawa T, Iwanaga R, Nakanishi Y et al (1988) A resected case of primary liver cancer with liver cirrhosis accompanied with Dubin-Johnson syndrome (in Japanese). Sapporo Byoin Ishi 48:27–31

Schmid C, Lombardi L, Giordano F, Delgrossi S (1979) Unusual morphologic features of a primary liver neoplasm. Tumori 65:649–655

She R, Szakacs J (2005) Carcinosarcoma of the liver: a case report and review of the literature. Arch Pathol Lab Med 129:790–793

Shikada Y, Matsumata T, Suehiro T, Sugimachi K (2004) Hepatocellular carcinoma in a case of Dubin-Johnson syndrome treated successfully with a central bilateral segmentectomy. Hepatogastroenterology 51:833–836

Sobaniec-Lotowska ME, Lebensztejn DM (2006) Ultrastructure of Kupffer cells and hepatocytes in the Dubin-Johnson syndrome: a case report. World J Gastroenterol 12:987–989

Sprinz H, Nelson RS (1954) Persistent nonhemolytic hyperbilirubinemia associated with lipochrome-like pigment in liver cells: report of 4 cases. Ann Intern Med 41:952–962

Starr DA, Han M (2002) Role of ANC-1 in tethering nuclei to the actin cytoskeleton. Science 298:406–409

Starr DA, Han M (2005) A genetic approach to study the role of nuclear envelope components in nuclear positioning. Novartis Found Symp 264:208–219

Sternlieb I (1979) Electron microscopy of mitochondria and peroxisomes of human hepatocytes. Prog Liver Dis 6:81–104

Su et al. (1997) Pub Med PMID 9428927

Swartz HM, Chen K, Roth JA (1987) Further evidence that the pigment in the Dubin-Johnson syndrome is not melanin. Pigment Cell Res 1:69–75

Tabibian JH, Lassman CR, Margolis DJ, Landaverde C, Busuttil RW, Durazo FA (2008) Intraductal oncocytic papillary neoplasm of the liver: case and review of a rare variant. Ann Hepatol 7:168–173

Tallini G (1998) Oncocytic tumors. Virchows Arch 433:5–12

Tanikawa K, Kage M, Komuta M, Nakashima O, Yano H, Yatsuhashi H, Kojiro M (2007) Pathological analysis of oxyphilic granular hepatocytes and hepatocellular mitochondria in chronic hepatitis C. Hepatol Res 37:425–432

Tanji K, Bhagat G, Vu TH, Monzon L, Bonilla E, Lefkowitch JH (2003) Mitochondrial DNA dysfunction in oncocytic hepatocytes. Liver Int 23:397–403

Tateishi T, Machi J, Morioka WK (1998) Focal peliosis hepatis resembling metastatic liver tumor. J Ultrasound Med 17:581–584

Timbal Y, Rodier J (1984) Apropos of a case of renal oncocytoma with hepatic localization (in French). Ann Urol (Paris) 18:415–417

Tocornal J, Rosenberg H (1981) Peliosis hepatis, oral contraceptives and hepatic carcinoma: a case treated surgically (in Spanish). Rev Med Chil 109:236–238

Tsuji Y, Okada K, Fukuoka M, Watanabe Y, Ataka K, Minami R, Hanioka K, Tachibana S et al (2001) Hepatocellular carcinoma with a sarcomatous appearance: report of a case. Surg Today 31:735–739

Ueno S, Tanabe G, Hanazono K, Ogawa H, Yoshidome S, Aikou T, Yoshida A (1998) Postoperative management following massive hepatectomy in a patient with Dubin-Johnson syndrome: report of a case. Surg Today 28:1274–1278

Usami Y, Satake S, Nakayama F, Matsumoto M, Ohnuma K, Komori T, Semba S, Ito A, Yokozaki H (2008) Snail-associated epithelial-mesenchymal transition promotes oesophageal squamous cell carcinoma motility and progression. J Pathol 215:330–339

Vij M, Patra S, Rela M (2012) Pigmented hepatocellular adenoma with complete CD34 immunostaining pattern: a diagnostic dilemma. Indian J Pathol Microbiol 55:528–530

Vijay MK, Das P, Prabhu SB, Mouli P, Acharya SK, Mathur SR (2011) Pleomorphic giant cell-rich hepatocellular carcinoma presented as right atrial mass. Indian J Pathol Microbiol 54:632–634

Volante M, La Rosa S, Castellano I, Finzi G, Capella C, Bussolati G (2006) Clinico-pathological features of a series of 11 oncocytic endocrine tumours of the pancreas. Virchows Arch 448:545–551

Wan XB, Long ZJ, Yan M, Xu J, Xia LP, Liu L, Zhao Y, Huang XF, Wang XR, Zhu XF et al (2008) Inhibition of Aurora-A suppresses epithelial-mesenchymal transition and invasion by downregulating MAPK in nasopharyngeal carcinoma cells. Carcinogenesis 29:1930–1937

Wannesson L, Chigrinova E, Raditchkova M, Mazzucchelli L, Ghielmini M (2009) Peliosis hepatis in cancer patients mimicking infection and metastases. Onkologie 32:54–56

Watanabe T, Aikawa K, Kanefuji T, Yamazaki K, Hirono H, Hasegawa K, Soga K, Shibasaki K et al (2008) Pelioid-type hepatocellular carcinoma with numerous eosinophilic infiltrations in a patient with primary biliary cirrhosis. Hepatol Res 38:421–427

Wilhelmsen K, Ketema M, Truong H, Sonnenberg A (2006) KASH-domain proteins in nuclear migration, anchorage and other processes. J Cell Sci 119:5021–5029

Wood LD, Heaphy CM, Daniel HD, Naini BV, Lassman CR, Arroyo MR, Kamel IR (2013) Chromophobe hepatocellular carcinoma with abrupt anaplasia: a proposal for a new subtype of hepatocellular carcinoma with unique morphological and molecular features. Mod Pathol 26:1586–1593

Yagi M, Miyamoto T, Toyama Y, Suda T (2006) Role of DC-STAMP in cellular fusion of osteoclasts and macrophage giant cells. J Bone Miner Metab 24:355–358

Yakushiji H, Miyazaki K, Kitahara K, Isen A, Tsutsumi N, Hisatsugu T, Sakai T, Sasatomi E, Tokunaga K (1995) A case of double cancer, hepatocellular carcinoma and primary male breast cancer associated with Dubin-Johnson syndrome (in Japanese). Kann Tan Sui 30:729–733

Yang LY, Fang F, Ou DP, Wu W, Zeng ZJ, Wu F (2009) Solitary large hepatocellular carcinoma: a specific subtype of hepatocellular carcinoma with good outcome after hepatic resection. Ann Surg 249:118–123

Ye MQ, Suriawinata A, Ben Haim M, Parsons R, Schwartz ME (1999) A 42-year-old woman with liver masses and long-term use of oral contraceptives. Semin Liver Dis 19:339–344

Yoshida N, Midorikawa Y, Kajiwara T, Nakayama H, Sugitani M, Takayama T (2013) Hepatocellular carcinoma with sarcomatoid change without anticancer therapies. Case Rep Gastroenterol 7:169–174

Zarbo RJ, Crissman JD, Venkat H, Weiss MA (1986) Spindle-cell carcinoma of the upper aerodigestive tract mucosa. An immunohistologic and ultrastructural study of 18 biphasic tumors and comparison with seven monophasic spindle-cell tumors. Am J Surg Pathol 10:741–753

Zavadil J, Haley J, Kalluri R, Muthuswamy SK, Thompson E (2008) Epithelial-mesenchymal transition. Cancer Res 68:9574–9577

Zhou L, Rui JA, Wang SB, Chen SG, Qu Q (2011) Prognostic factors of solitary large hepatocellular carcinoma: the importance of differentiation grade. Eur J Surg Oncol 37:521–525

Zidar N, Gale N, Kojc N, Volavsek M, Cardesa A, Alos L, Höfler H, Blechschmidt K, Becker KF (2008) Cadherin-catenin complex and transcription factor snail-1 in spindle cell carcinoma of the head and neck. Virchows Arch 453:267–274

Hepatocellular Carcinoma with Progenitor Cell Features

14

Contents

Abstract

Subsets of hepatocellular carcinoma (HCC) can harbor hepatic progenitor cells or stem-like cells (HCCs with progenitor cell features). Stem/progenitor cells were also identified in combined hepatocellular-cholangiocarcinoma. Stem/progenitor cells detectable in HCCs share a marker profile with normal hepatic stem cells, but tumor cells may be deficient in part of the markers. For most progenitor cell features in HCC, the biologic significance is not yet clarified. However, there is strong evidence that expression of cytokeratin 19 as a stemness feature is associated with a high-risk biology of these neoplasms. The incidence of marked cytokeratin 19 expression in HCC cells is only partially known, but may amount to 10 %. Cytokeratin 19 expression in HCC may occur in combination with other stem cell-associated markers and is associated with expression of proteins involved in epithelial-to-mesenchymal transition. Cytokeratin 19 expression in HCCs predicts higher serum alpha-fetoprotein levels, tumor angiogenesis, accelerated tumor progression, early recurrence, and poorer survival.

Introduction

There is increasing evidence that certain subsets of hepatocellular carcinomas (HCCs) harbor cell populations with features of hepatic progenitor

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_14

cells or stem-like cells (Mikhail and He 2011; Tong et al. 2011; Ji and Wang 2012; Behnke et al. 2013; Sainz and Heeschen 2013; Hashimoto et al. 2014; Yamashita and Kaneko 2014; Ye et al. 2014). Stem/progenitor cells are also detectable in combined hepatocellular-cholangiocarcinomas (Ikeda et al. 2013; Sasaki et al. 2014), a phenomenon that influenced modern classifications of liver cancer (review: Lo and Ng 2013). As described in more detail in the chapter referring to hepatic stem cells, progenitor cells present in certain HCCs express a typical pattern in markers, among which CD133, CD90, epithelial cell adhesion molecule(EpCAM), and cytokeratin 19 are the most intensively studied (Jia et al. 2013; Ma 2013; Table 1).

The significance of progenitor cell features of HCCs is not fully clarified. In particular, it is not yet fully established whether the presence of progenitor cells in HCCs is critically related to an origin of these neoplasms from hepatic stem or stem-like cells (tumor-initiating cells (TICs)) or whether progenitor cells form a secondary population of cells with different functions (Lee et al. 2014). It has been proposed that liver progenitor cells present in various subtypes of HCCs are master regulators of HCC initiation, tumor spread, and progression, but this issue needs further in-depth studies (Wu et al. 1996; Oishi et al. 2014; review: Lo and Ng 2013). Markers found in stem or progenitor cells often appear as embryonic markers in cells of cancers undergoing dedifferentiation. The presence of progenitor cells in HCCs is, in fact, not necessarily a constitutive feature, but might represent a phenomenon that is subject to modifications in the course of tumor progression. For example, inflammatory cytokines, signal molecules produced by various cells in the tumor microenvironment, can promote the retrodifferentiation of tumor-derived hepatocyte-like cells to progenitor cells (Dubois-Pot-Schneider et al. 2014). The expansion of CD44 (+) HCC cells, i.e., cells with progenitor features, is promoted by interleukin-6 produced by tumor-associated macrophages (TAMs) located within HCCs via a signal transducer and activator of transcription 3 (STAT3)-dependent mechanism (Wan et al. 2014). TAMs can also promote stem cell-like properties in HCC through transforming growth factor-beta1-induced epithelial-to-mesenchymal transition (Fan et al. 2014). However, the presence of certain progenitor cell markers in HCCs affects the biology of disease, in that HCCs with progenitor cell features may show a high-risk biology and aggressive clinical behavior.

Table 1 Stem/progenitor cells markers detectable in HCCs with progenitor cell features

Epithelial cell adhesion molecule (EpCAM)
CD133
CD90/Thy-1
Cytokeratin 19
Cytokeratin 7
Nanog
OV6
c-Kit/CD117
CD44
CD34
Sox2
Nestin
ICAM1
NCAM
SALL4
Ezrin
OCT4
Delta-like 1
Granulin-epithelin precursor (GEP)
TLF4
ZFX
ABCG2
CITED1

Stemness Markers Expressed in HCCs and Their Significance

Epithelial Cell Adhesion Molecule (EpCAM)

EpCAM (CD326) is a cell surface protein that is present on a subset of normal epithelial and overexpressed in numerous cancers, being a marker of progenitor cells and tumor-initiating cells (review : Imrich et al. 2012). Part of HCCs expresses EpCAM, and this adhesion molecule is

also expressed in precursor lesions of HCC, including dysplastic nodules (Bae et al. 2012a). EpCAM expression was more frequently detected in HBV-associated liver cancers (Kimura et al. 2014). Expression of EpCAM in HCCs defines a distinct progenitor cell signature in these cancers, partially associated with the presence of other stemness markers, such as C-Kit and cytokeratin 19, and an activated Wnt/beta-catenin pathway. Conversely, EpCAM(−) HCCs represent a proliferation of cells that resemble mature hepatocytes. EpCAM(+) and EpCAM(−) HCCs could further be subclassified based on the level of AFP production (Yamashita et al. 2008, 2009). The switch between HCC cells with these progenitor cell features and cells with a mature hepatocyte-like phenotype is in part regulated by microRNAs, especially microRNA-122. HCCs with an EpCAM(+)AFP(+) signature contain self-renewing cell populations that can elicit highly invasive cancers in immunocompromised mice (Yamashita et al. 2009; Terris et al. 2010). Similar to HCCs expressing CK19, tumors with high levels of EpCAM showed a more aggressive course that HCCs without expression of this marker. Specifically, HCCs with marked immunoreactivity for EpCAM were associated with early recurrence and poor overall survival and recurrence-free survival (Guo et al. 2014; Xu et al. 2014), suggesting a potential role of EpCAM-targeted therapy (Ogawa et al. 2014). In one investigation, high levels of EpCAM expression were associated with elevated peritumoral ductular reactions, suggesting upregulation of progenitor cell activation (Xu et al. 2014).

CD133

CD133 is a marker for progenitor cells in several cancers, including HCC. The prevalence of CD133 expression in HCCs varies considerably among tumor collections studied so far (Piao et al. 2012). In HCCs occurring in an area endemic for HBV infection, 15.6 % of tumors were CD133(+), and CD133 expression was negatively correlated with the presence of HBsAg (Yeh et al. 2009). Generally, CD133 expression seems to be more common in HBV-associated HCCs than in HCV-associated tumors (Yilmaz et al. 2014). As with EpCAM expression, the presence of CD133(+) cells in HCCs predicted poor disease-free survival independently of p53 expression (Yeh et al. 2009; Guo et al. 2014; Yilmaz et al. 2014), and CD133(+) stem cells promote repeated recurrence of HCC after liver transplantation (Toshima et al. 2013).

CD90

Part of HCCs shows cell populations that express CD90/Thy-1 (Sukowati et al. 2013). CD90(+) and EpCAM(+) cells reside distinctively, whereby CD90(+) cells have features of vascular endothelial cells and enhance the motility of EpCAM(+) epithelial cancer cells (Yamashita et al. 2013). CD90(+) HCCs showed a more prominent stromal reaction with increased alpha-smooth muscle actin reactivity (Sukowati et al. 2013). HCCs with CD90(+) progenitor cell subsets showed a higher rate of early recurrence and a progression phenotype (Guo et al. 2014).

Other Stem/Progenitor Cells Markers

Expression of the pluripotency transcription factor, Nanog, in HCC is associated with poor differentiation and worse clinical outcome. Only a minority of cells in HCC are Nanog(+), and these cells show enhanced ability of self-renewal, clonogenicity, and tumor initiation, typical features of stem cells (Shan et al. 2012). Subsets of HCC cells express OV6, a marker of hepatic progenitor cells. The presence of OV6-positive cells is associated with tumor-initiating cells, augmented invasion, and metastasis potential (Yang et al. 2012). CD44, a protein associated with vimentin expression in HCC cells, may confer stemness features to HCCs via its known role as a promoter of epithelial-to-mesenchymal transition(EMT) (Mima et al. 2012). A progenitor cell marker present in certain liver cancers is nestin. Nestin-positive hepatic cells are considered to be the source of liver cancer cells in response to

lineage-specific mutations that target Wnt and Notch signaling, whereby expression of nestin is restricted by p53 in an Sp1/3 transcription factor-dependent manner. The loss of wild-type p53 expression, a common feature in diverse liver cancers, would therefore augment nestin expression and drive a progenitor cell pathway (Tschaharganeh et al. 2014). HCC cells with progenitor features can express intercellular adhesion molecule 1 (ICAM1) in humans and mice. ICAM1 is also present in circulating tumor cells (Liu et al. 2013). Another adhesion molecule that characterizes HCCs with progenitor cell features is neural cell adhesion molecule (NCAM). In one investigation, NCAM was detectable in 8.3 % of resected HCCs, and high NCAM levels in tumors were associated with an intrahepatic metastasis phenotype (Tsuchiya et al. 2011a). A subset of HCCs revealed expression of the oncofetal gene SALL4 (Sal-like protein 4), a zinc finger transcription factor that is present in fetal hepatocytes but is silenced in the adult liver. The presence of SALL4 in part of HCCs therefore represents an abnormal reexpression phenomenon that indicates progenitor cells and confers an aggressive behavior (Oikawa et al. 2013; Yong et al. 2013). In vitro, overexpression of SALL4 in cultured HCC cells resulted in increased proliferation, correlating with an increased expression of cytokeratin 19 and EpCAM (Oikawa et al. 2013). In progenitor-like cells of recurrent HCCs, expression of ezrin was found (Okamura et al. 2008). Expression of the transcription factor OCT4 (octamer binding transcription 4) in HCC cells is associated with low differentiation and tumor recurrence and is a stem cell lineage marker (Dong et al. 2012). Fetal liver cells have the surface antigen, Delta-like 1 (Dlk-1), which is then lost in mature adult hepatocytes. Dlk-1 is also expressed in several cancers, including HCC, and is a marker of HCC progenitor cells (Yanai et al. 2010; Nishina 2012; Xu et al. 2012). The hepatic oncofetal protein, granulin-epithelin precursor (GEP), which is expressed in fetal hepatocytes, but not in mature hepatocytes, is a protein that is co-expressed with proteins labeling stem cells, including EpCAM, CD133, Nanog, and Dlk-1. Expression of GEP defines a subset of hepatic cancer stem cells (Cheung et al. 2011). HCC cells with progenitor cell features can express Toll-like receptor 4 (TLR4), which acts as a receptor for lipopolysaccharides. The presence of TLR4 was associated with increased invasiveness and migration capability of HCC cells (Liu et al. 2015). TLR4 expression renders CD133(+) tumor-initiating cells tumorigenic, whereby TLR4/Nanog activation causes p53 protein degradation through phosphorylation of the protecting protein NUMB and its dissociation from p53 by the oncoprotein TBC1D15 (Machida et al. 2015). Zinc finger protein X-linked (ZFX), a member of the ZFY family, is a widely expressed stem cell marker that is also present in subsets of HCC cells, where it promotes self-renewal, colony formation ability, and proliferation (Lai et al. 2014). ATP-binding cassette subfamily G member 2 (ABCG2) is expressed in cancer stem cells of a minor subgroup of HCC and is associated with an aggressive phenotype (Zhang et al. 2013). A marker of hepatic progenitor cells that are involved in the development of embryonal liver cancers such as hepatoblastomas is the CBP/P-300 interacting transactivator 1 (CITED1) (Murphy et al. 2012).

Expression of Cytokeratin 19 in HCC as a Stemness Feature Associated with High-Risk Biology

Introduction

Expression of cytokeratin 19 (CK19) is a feature typical for many adenocarcinomas, in particular also cholangiocarcinomas, while it was formerly held that CK19 is not a feature characterizing hepatocellular carcinomas (HCC). Several types of cytokeratins are present in HCCs (Wee 2006) and in part relate to prognosis and metastatic potential. This specifically holds true for the expression of CK19 by hepatocellular malignancies. It has been proposed that HCC expressing a cholangiocyte phenotype is a novel subtype of HCC with highly aggressive behavior (see below). Such tumors have been termed, "dual-phenotype HCC/DPHHCC" (Lu et al. 2011).

However, expression of CK19 in HCCs not only represents the acquisition of a biliary phenotype but is also related to stemness acquisition.

CK19 Expression in HCCs Is a Stemness-Related Marker

It has been found that a subset of HCCs is characterized with the expression of stemness-related markers, including CK19 (Fujii et al. 2008; Kamohara et al. 2008; Bae et al. 2012b). Durnez and coworkers found a CK19(+)/CK7(−) phenotype in 6 % of HCCs, while a CK19(+)/CK7(+) was identified in 10 %. The distinct features of these HCC subsets suggested a progenitor cell origin (Durnez et al. 2006). In one investigation of these neoplasms, CK19 was most frequently expressed in combination with at least one other stemness-related marker, such as CD133, EpCAM, and c-kit. HCC expressing CK19 in part also expressed Yes-associated protein 1 (YAP1), a potential oncogene known to promote stem cell proliferation (Kim et al. 2013a). Expression of CK19 was also significantly associated with expression of proteins characterizing epithelial-to-mesenchymal transition (EMT), including vimentin, S100A4, uPAR, and ezrin (Kim et al. 2011). There is a significant inverse correlation between the expression of the organic anion transporter peptides (OATP) 1B1 and 1B3 and of CK7 and CK19, in that all HCCs expressing OATP 1B1/1B3 were CK7/CK19 negative (Vasuri et al. 2011).

CK19 Expression in HCC as a Feature Predicting High Risk

CK19 expression in HCCs predicts higher serum AFP levels, tumor angiogenesis, accelerated progression, early postoperative recurrence, and poorer survival (Uenishi et al. 2003; Yang et al. 2010; Kim et al. 2011; Yamada et al. 2011; Lee et al. 2012; van Malenstein et al. 2012; Wang et al. 2012; Greenhill 2013; reviews: Izumi 2012; Kim and Park 2014). CK19 expression in this neoplasm is a significant predictor for overall survival. In a study on 50 HCC patients, CK10 alone or in combination with CK19 expression was associated with a 7-year overall survival of 30.0 %, which was significantly lower than that of CK10−/CK19− patients (56.1 %; Yang et al. 2008). Among 155 HCCs, tumors with CK19 expression accounted for 10.1 %, and patients with this type of neoplasm have a significantly lower overall survival and recurrence-free survival (Lu et al. 2011). 35.7 % of 210 surgically resected HCCs were CK19 positive, and this feature predicted early tumor recurrence and poor prognosis (Yuan et al. 2011). CK19-expressing HCCs with stemness-related marker expression demonstrated more frequent large vessel invasion, increased tumor size, microvessel invasion, poor tumor encapsulation, and poor survival (Kim et al. 2011). In a cohort of surgical specimens, keratin 19 expression revealed the strongest correlation with increased tumor size, decreased tumor differentiation, metastasis, and microvascular invasion (Govaere et al. 2014). Hypovascular HCCs exhibited a significantly higher CK19 expression rate and earlier recurrence rate within 6 months compared to the patients with hypervascular HCCs (Chung et al. 2012). Expression of CK19 in HCC is related to high tumor recurrence after curative radio-frequency ablation (Tsuchiya et al. 2011b). The adverse effect of CK19 on prognosis, with early tumor recurrence, has also been found in small HCC after curative resection (Zhou et al. 2010), and particularly small HCCs (diameter less than 3 cm) additionally expressing mucin as an indicator for biliary differentiation form a high-risk group (Aishima et al. 2007). CK19 positivity in HCCs is an independent risk factor for developing lymph node metastasis (Ding et al. 2004; Zhuang et al. 2008). The expression of CK19 in HCCs is correlated with expression of matrix metalloproteinase 2, and also this co-expression predicts lymph node metastasis (Xiang et al. 2011). CK19 expression in HCCs is also correlated with a higher proliferating cell nuclear antigen (PCNA)-labeling index and lower differentiation (Wu et al. 1996; Zhuang et al. 2008) and expression of matrix metalloproteinase 9 (Zhuang et al. 2008). CK19-positive HCCs demonstrated longer telomeres than CK19-negative HCCs, and

telomere lengthening was associated with poor differentiation and reduced survival (Oh et al. 2008). CK19 expression in regional lymph nodes of livers harboring HCC was associated with lymph node metastasis and very poor outcome (Lee et al. 2013).

Part of HCCs expressing CK19 and showing aggressive behavior co-expresses other stemness-related markers, such as CD133, nestin, CD44, and ATP-binding cassette subfamily G member 2 (ABCG2) (Yang et al. 2010). One stemness-related marker, epithelial cell adhesion molecule (EpCAM), is highly expressed in premalignant hepatic tissues and in a subset of HCCs (De Boer et al. 1999). EpCAM-positive HCCs display a distinct molecular signature with features of hepatic progenitor cells including the presence CK19, c-kit, and activated Wnt/beta-catenin signaling (Yamashita et al. 2008). CK19 mRNA and protein expression correlate with the expression of multidrug resistance-associated protein 1 (MRP1) in HCCs. MRP1, together with MRP3 and BCRP, co-localizes with CK19 in the tumor, and this expression pattern suggests a progenitor cell origin of these aggressive tumors (Vander Borght et al. 2008). The aggressive phenotype of EpCAM-positive HCCs may be related to the observation that expression of EpCAM shifts the state of cadherin-mediated adhesions from strong to weak (Winter et al. 2003).

The reason why expression of CK19 is associated with higher aggressivity of HCCs is not yet known. From other tumor models, there is evidence that CK19 and other intermediate filaments play an important role in tumor cell migration, invasion, and metastasis (Hendrix et al. 1996). Keratin 19-positive HCC highly expressed invasion-related/metastasis-related markers and showed expression of members of the microRNA-200 family. Furthermore, primary human keratin 19-positive HCC showed increased invasiveness in vitro (Govaere et al. 2014). HCC expressing "stemness"-related proteins were characterized by increased telomere length, augmented expression hTERT and shelterin complex proteins, associated with increased chromosome instability, alterations favoring an aggressive tumor phenotype (Kim et al. 2013b).

CK19 Expression in HCCs as a Marker of Biliary Differentiation

A biliary differentiation characterized by the presence of ductal/ductular or glandular profiles and the immunohistochemical reactivity for CK7 and CK19 are typical features of mixed hepatocellular and cholangiocarcinomas. However, it is more difficult to judge whether the expression of CK19 in HCCs lacking morphological features of cholangiocellular differentiation is a marker for a biliary phenotype or rather a stemness-related marker. In one study, part of HCCs expressing CK19 also expressed the mucin core protein-1 (MUC-1) supported the presence of a bona fide biliary phenotype (Lu et al. 2011). Biliary differentiation characterized by positivity for CK19 and mucin expression does occur even in small HCCs and mucin-producing HCC cells and confer a higher risk for aggressive behavior (Aishima et al. 2007). One group of HCCs was classified as tumors with an intermediate (hepatocyte-cholangiocyte) phenotype (Kim et al. 2004) and is discussed in a separate chapter.

CK19 Expression in HCC Precursor Lesions

In a rat model of progenitor cell-derived HCC, microdissected samples of focal lesions, adenomas, and early and advanced HCCs showed that about 50 % of persistent nodules and all HCCs expressed CK19, whereas only 14 % of remodeling nodules were CK19 positive. CK19-expressing lesions displayed a distinct gene expression signature with a predominance of the AP-1/JUN network expression (Andersen et al. 2010).

Pathogenesis of CK19 Expression

The mechanism of the development of CK19 positivity in HCC remains to be studied in more detail. The form of CK19 synthesized and stored in HCC cells may be different from that of other cell systems, because CK19 produced by HCC

cell lines is in part secreted as a fragment, CYFRA 21-1 (Wu et al. 2002). CK19 fragments are also produced and secreted into serum by human HCCs (Nagai et al. 2001). It was demonstrated that the activation of the EGF-EGFR-signaling pathway is associated with the acquisition of CK19-positive HCC phenotype, possibly mediated by EGF-induced phosphorylation of c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (Yoneda et al. 2011). In HCC cells grown in culture, expression of CK19 was in any case associated with the expression of laminin, and laser scanning confocal microscopy demonstrated the concomitant presence of the two molecules in most of the positive cells. In two CK19-negative HCC cell lines, addition of laminin to the culture medium resulted in an induction of CK19 in a dose-dependent manner, suggesting that laminin is an inducer of CK19 upregulation in HCC cells in vitro (Su et al. 2003).

Stemness in HCC cells may be induced by viral factors. In cell culture and murine tumor xenograft models, HCV replicon-expressing hepatoma cells display a high-level expression of the stemness markers, DCAMKL-1 (doublecortin and CaM kinase-like-1) and CK19, suggesting that chronic HCV infection predisposes cells toward a path of acquiring cancer stem cell-like traits (Ali et al. 2011). A higher proportion of CK19 expression was detected in HCCs after preoperative transcatheter arterial chemoembolization (TACE) (Nishihara et al. 2008). Mixed phenotype HCC with expression of CD133, EpCAM, NCAM, and CK19 is more frequent after TACE and liver transplantation (Zen et al. 2011).

Pathogenesis of Progenitor Cell Features in HCCs

The stem cell marker EpCAM is activated by the Wnt/beta-catenin signaling pathway in HCC, whereby the beta-catenin activation target TCF-4 binds to the EpCAM promoter (Yamashita et al. 2007). Stemness of EpCAM(+) HCCs is regulated by the transcription factor SALL4, which also affects the expression of CD44 in these neoplasms (Zeng et al. 2014). In EpCAM-enriched HCC progenitor cells, epigenetic modification of microRNA-429 targets the retinoblastoma binding protein 4/OCT4 axis and contributes to self-renewal of the cells involved (Li et al. 2015). The mechanisms regulating the expression of CD133, a surface glycoprotein, in progenitor cells have in part been elucidated. CD133 expression in CD133(+)HCC cells is inhibited by the transcription factor Ikaros through direct binding to the CD133 P1 promoter, resulting in repression of stemness features in HCCs. Ikaros itself is upregulated by ETS1 regulated by the MAPK pathway (Zhang et al. 2014). Human CD133-positive liver cancer stem cells are inhibited by microRNA-150 via negative regulation of the transcription factor c-Myb (Zhang et al. 2012). Expression patterns of OCT4, Nanog, and EpCAM in HCC cells are modulated by c-MYC, which enhances stem cell marker expression at low expression levels, whereas high c-MYC blunts the stem cell response and induces a pro-apoptotic program (Akita et al. 2014).

Molecular markers of HCC stemness are closely linked with elements of the Wnt/beta-catenin signaling pathway. Beta-catenin activation characterizes a progenitor cell phenotype and is, in experimental models, a strong promoter of hepatocarcinogenesis (Mokkapati et al. 2014). Wnt/beta-catenin signaling in HCC transcriptionally activates microRNA-181 expression (Ji et al. 2011).

The presence of progenitor/stem cell features is linked with tumor cell epithelial-to-mesenchymal transition (EMT). There is strong evidence that cancer cells with EMT traits share numerous features with cancer stem cells. In HCC cells, the transcriptional coactivator with PDZ-binding motif (TAZ), one of the nuclear effectors of Hippo-related signaling pathways, promotes the expression of stem cell markers (OCT4, Nanog, and SOX2) through induction of EMT (Xiao et al. 2014). HCC cells with aberrant cell surface vimentin expression and absent CD133 expression display an EMT phenotype and have stem-like features (Mitra et al. 2014). Cellular features of HCCs, including stemness and EMT promotion, are markedly influenced by various species

of microRNAs (Meng et al. 2012; Chai and Ma 2013; Qi et al. 2013; Anwar and Lehmann 2014). The proportion of stem cells in HCC is augmented by microRNA-200 via upregulation of vasohibin 2 which induces EMT (Xue et al. 2014). EMT is also modulated by microRNAs acting on the Wnt/beta-catenin pathway. Beta-catenin signaling, which is required for EMT, is suppressed by microRNA-612 in HCC cells (Tang et al. 2014).

References

Aishima S, Nishihara Y, Kuroda Y, Taguchi K, Iguchi T, Taketomi A, Maehara Y, Tsuneyoshi M (2007) Histologic characteristics and prognostic significance in small hepatocellular carcinoma with biliary differentiation: subdivision and comparison with ordinary hepatocellular carcinoma. Am J Surg Pathol 31:783–791

Akita H, Marquardt JU, Dukin ME, Kitade M, Seo D, Conner EA, Andersen JB, Factor VM, Thorgeirsson SS (2014) MYC activates stem-like cell potential in hepatocarcinoma by a p53-dependent mechanism. Cancer Res 74:5903–5913

Ali N, Allam H, May R, Sureban SM, Bronze MS, Bader T, Umar S, Anant S, Houchen CW (2011) Hepatitis C virus-induced cancer stem cell-like signatures in cell culture and murine tumor xenografts. J Virol 85:12292–12303

Andersen JB, Loi R, Perra A, Factor VM, Ledda-Columbano GM, Columbano A, Thorgeirsson SS (2010) Progenitor-derived hepatocellular carcinoma model in the rat. Hepatology 51:1401–1409

Anwar SL, Lehmann U (2014) DNA methylation, microRNAs, and their crosstalk as potential biomarkers in hepatocellular carcinoma. World J Gastroenterol 20:7894–7913

Bae JS, Noh SJ, Jang KY, Park HS, Chung MJ, Park CK, Moon WS (2012a) Expression and role of epithelial cell adhesion molecule in dysplastic nodule and hepatocellular carcinoma. Int J Oncol 41:2150–2158

Bae JS, Choi HN, Noh SJ, Park BH, Jang KY, Park CK, Moon WS (2012b) Expression of K19 and K7 in dysplastic nodules and hepatocellular carcinoma. Oncol Lett 4:213–220

Behnke MK, Reimers M, Fisher RA (2013) Stem cell and hepatocyte proliferation in hepatitis C cirrhosis and hepatocellular carcinoma: transplant implications. Ann Hepatol 13:45–53

Chai S, Ma S (2013) Clinical implications of microRNAs in liver cancer stem cells. Chin J Cancer 32:419–426

Cheung PF, Cheng CK, Wong NC, Ho JC, Yip CW, Lui VC, Cheung AN, Fan ST, Cheung ST (2011) Granulin-epithelin precursor is an oncofetal protein defining hepatic cancer stem cells. PLoS One 6:e28246

Chung GE, Lee JH, Yoon JH, Myung SJ, Lee K, Jang JJ, Lee JM, Kim SH, Suh KS et al (2012) Prognostic implications of tumor vascularity and its relationship to cytokeratin 19 expression in patients with hepatocellular carcinoma. Abdom Imaging 37:439–446

De Boer CJ, van Krieken JH, Janssen-van Rhijn CM, Litvinov SV (1999) Expression of Ep-CAM in normal, regenerating, metaplastic, and neoplastic liver. J Pathol 188:201–206

Ding SJ, Li Y, Tan YX, Jiang MR, Tian B, Liu YK, Shao XX, Ye SL, Wu JR, Zeng R et al (2004) From proteomic analysis to clinical significance: overexpression of cytokeratin 19 correlates with hepatocellular carcinoma metastasis. Mol Cell Proteomics 3:73–81

Dong Z, Zeng Q, Luo H, Zou J, Cao C, Liang J, Wu D, Liu L (2012) Increased expression of OCT4 is associated with low differentiation and tumor recurrence in human hepatocellular carcinoma. Pathol Res Pract 208:527–533

Dubois-Pot-Schneider H, Fekir K, Coulouarn C, Glaise D, Aninat C, Jamouen K, Le Guével R, Kubo T, Ishida S et al (2014) Inflammatory cytokines promote the retrodifferentiation of tumor-derived hepatocyte –like cells to progenitor cells. Hepatology 60:2077–2090

Durnez A, Verslype C, Nevens F, Fevery J, Aerts R, Pirenne J, Esaffre E, Libbrecht L, Desmet V, Roskams T (2006) The clinical and prognostic relevance of cytokeratin 7 and 19 expression in hepatocellular carcinoma. A possible progenitor cell origin. Histopathology 49:138–151

Fan QM, Jing YY, Yu GF, Kou XR, Ye F, Gao L, Li R, Zhao QD, Yang Y, Lu ZH, Wei LX (2014) Tumor-associated macrophages promote cancer stem cell-like properties via transforming growth-beta1-induced epithelial-mesenchymal transition in hepatocellular carcinoma. Cancer Lett 352:160–168

Fujii T, Zen Y, Harada K, Niwa H, Masuda S, Kaizaki Y, Watanabe K, Kawashima A, Nakanuma Y (2008) Participation of liver cancer stem/progenitor cells in tumorigenesis of scirrhous hepatocellular carcinoma – human and cell culture study. Hum Pathol 39:1185–1196

Govaere O, Komuta M, Berkers J, Spee B, Janssen C, de Luca F, Katoonizadeh A et al (2014) Keratin 19: a key role player in the invasion of human hepatocellular carcinomas. Gut 63:674–685

Greenhill C (2013) Hepatocellular carcinoma: how does keratin 19 influence HCC? Nat Rev Gastroenterol Hepatol 10:565

Guo Z, Li LQ, Jiang JH, Ou C, Zeng LX, Xiang BD (2014) Cancer stem cell markers correlate with early recurrence and survival in hepatocellular carcinoma. World J Gastroenterol 20:2098–2106

Hashimoto N, Tsunedomi R, Yoshimura K, Watanabe Y, Hazama S, Oka M (2014) Cancer stem-like sphere cells induced from de-differentiated hepatocellular carcinoma-derived cell lines possess the resistance to anti-cancer drugs. BMC Cancer 14:722

Hendrix MJ, Seftor EA, Chu YW, Trevor KT, Seftor RE (1996) Role of intermediate filaments in migration,

invasion and metastasis. Cancer Metastasis Rev 15:507–525
Ikeda H, Harada K, Sato Y, Sasaki M, Yoneda N, Kitamura S, Sudo Y, Ooi A, Nakanuma Y (2013) Clinicopathologic significance of combined hepatocellular-cholangiocarcinoma with stem cell subtype components with reference to the expression of putative stem cell markers. Am J Clin Pathol 140:329–340
Imrich S, Hachmeister M, Gires O (2012) EpCAM and its potential role in tumor-initiating cells. Cell Adh Migr 6:30–38
Izumi N (2012) Prediction and prevention of intrahepatic recurrence of hepatocellular carcinoma. Hepatol Res 42:226–232
Ji J, Yamashita T, Wang XW (2011) Wnt/beta-catenin signaling activates microRNA-181 expression in hepatocellular carcinoma. Cell Biosci 1:4
Jia SQ, Ren JJ, Dong PD, Meng XK (2013) Probing the hepatic progenitor cell in human hepatocellular carcinoma. Gastroenterol Res Pract 2013:145253
Ji J, Wang XW (2012) Clinical implications of cancer stem cell biology in hepatocellular carcinoma. Semin Oncol 39:461–472
Kamohara Y, Haraguchi N, Mimori K, Tanaka F, Inoue H, Mori M, Kanematsu T (2008) The search for cancer stem cells in hepatocellular carcinoma. Surgery 144:119–124
Kim H, Park YM (2014) Hepatocellular carcinomas expressing 'stemness'-related markers: clinicopathological characteristics. Dig Dis 32:778–785
Kim H, Park C, Han KH, Choi J, Kim YB, Kim JK, Park YN (2004) Primary liver carcinoma of intermediate (hepatocyte-cholangiocyte) phenotype. J Hepatol 40:298–304
Kim H, Choi GH, Na DC, Ahn EY, Kim GI, Lee JE, Cho JY, Yoo JE, Choi JS et al (2011) Human hepatocellular carcinomas with "stemness"-related marker expression: keratin 19 expression and poor prognosis. Hepatology 54:1707–1717
Kim GJ, Kim H, Park YN (2013a) Increased expression of Yes-associated protein 1 in hepatocellular carcinoma with stemness and combined hepatocellular-cholangiocarcinoma. PLoS One 8:e75449
Kim H, Yoo JE, Cho JY, Oh BK, Yoon YS, Han HS, Lee HS, Jang JJ, Jeong SH et al (2013b) Telomere length, TERT and shelterin complex proteins in hepatocellular carcinomas expressing "stemness"-related markers. J Hepatol 59:746–752
Kimura O, Kondo Y, Kogure T, Kakazu E, Ninomiya M, Iwata T, Morosawa T, Shimosegawa T (2014) Expression of EpCAM increases in the hepatitis B related and the treatment-resistant hepatocellular carcinoma. Biomed Res Int 2014:172913
Lai KP, Chen J, He M, Ching AK, Lau C, Lai PB, To KF, Wong N (2014) Overexpression of ZFX confers self-renewal and chemoresistance properties in hepatocellular carcinoma. Int J Cancer 135:1790–1799
Lee JI, Lee JW, Kim JM, Kim JK, Chung HJ, Kim YS (2012) Prognosis of hepatocellular carcinoma expressing cytokeratin 19: comparison with other liver cancers. World J Gastroenterol 18:4751–4757
Lee CW, Kuo WL, Yu MC, Chen TC, Tsai CN, Lee WC, Chen MF (2013) The expression of cytokeratin 19 in lymph nodes was a poor prognostic factor for hepatocellular carcinoma after hepatic resection. World J Surg Oncol 11:136
Lee M, Marusawa H, Chiba T (2014) Characteristics of hepatocellular carcinomas with stem/progenitor cell phenotypes. Gastroenterology 146:579–581
Li L, Tang J, Zhang B, Yang W, LiuGao M, Wang R, Tan Y, Fan J, Chang Y, Fu J, Jiang F, Chen C et al (2015) Epigenetic modification of MiR-429 promotes liver tumour-initiating cell properties by targeting Rb binding protein 4. Gut 64:156–167
Liu S, Li N, Yu X, Xiao X, Cheng K, Hu J, Wang J, Zhang D, Cheng S, Liu S (2013) Expression of intercellular adhesion molecule 1 by hepatocellular carcinoma stem cells and circulating tumor cells. Gastroenterology 144:1031–1041
Liu W, Jing Y, Yu G, Han Z, Yu D, Fan Q, Ye F, Li R, Gao L, Zhao Q, Wu M, Wei L (2015) Toll like receptor 4 facilitates invasion and migration as a cancer stem cell marker in hepatocellular carcinoma. Cancer Lett. 358:136–143
Lo RC, Ng IO (2013) Hepatic progenitor cells: their role and functional significance in the new classification of primary liver cancers. Liver Cancer 2:84–92
Lu XY, Xi T, Lau WY, Dong H, Zhu Z, Shen F, Wu MC, Cong WM (2011) Hepatocellular carcinoma expressing cholangiocyte phenotype is a novel subtype with highly aggressive behavior. Ann Surg Oncol 18:2210–2217
Ma S (2013) Biology and clinical implications of CD133 (+) liver cancer stem cells. Exp Cell Res 319:126–132
Machida K, Feldman DE, Tsukamoto H (2015) TLR4-dependent tumor-initiating stem cell-like cells (TICs) in alcohol-associated hepatocellular carcinogenesis. Adv Exp Med Biol 815:131–144
Meng F, Glaser SS, Francis H, DeMorrow S, Han Y, Passarini JD, Stokes A, Cleary JP, Liu X, Venter J et al (2012) Functional analysis of microRNAs in human hepatocellular cancer stem cells. J Cell Mol Med 16:160–173
Mikhail S, He AR (2011) Liver cancer stem cells. Int J Hepatol 2011:486954
Mima K, Okabe H, Ishimoto T, Hayashi H, Nakagawa S, Kuroki H, Watanabe M, Beppu T, Tamada M et al (2012) CD44s regulates the TGF-β-mediated mesenchymal phenotype and is associated with poor prognosis in patients with hepatocellular carcinoma. Cancer Res 72:3414–3423
Mitra A, Satelli A, Xia X, Cultrera J, Mishra L, Li S (2014) Cell-surface vimentin: a mislocalized protein for isolating csVimentin+ CD133- novel stem-like hepatocellular carcinoma cells expressing EMT markers. Int J Cancer. doi:10.1002/ijc.29382
Mokkapati S, Niopek K, Huang L, Cunniff KJ, Ruteshouse EC, de Caestecker M, Finegold MJ, Huff V (2014) β-catenin activation in a novel liver progenitor cell

type is sufficient to cause hepatocellular carcinoma and hepatoblastoma. Cancer Res 74:4515–4525

Murphy AJ, de Caestecker C, Pierce J, Boyle SC, Ayers GD, Zhao Z, Libes JM, Correa H, Walter T et al (2012) CITED1 expression in liver development and hepatoblastoma. Neoplasia 14:1153–1163

Nagai T, Murota M, Nishioka M, Fujita J, Ohtsuki Y, Dohmoto K, Hojo S, Dobashi N, Takahara J (2001) Elevation of cytokeratin 19 fragment in patients with hepatoma: its clinical significance. Eur J Gastroenterol Hepatol 13:157–161

Nishihara Y, Aishima S, Kuroda Y, Iguchi T, Taguchi K, Asayama Y, Taketomi A, Kinukawa N et al (2008) Biliary phenotype of hepatocellular carcinoma after preoperative transcatheter arterial chemoembolization. J Gastroenterol Hepatol 23:1860–1868

Nishina H (2012) hDlk-1: a cell surface marker common to normal hepatic stem/progenitor cells and carcinomas. J Biochem 152:121–123

Ogawa K, Tanaka S, Matsumura S, Murakata A, Ban D, Ochiai T, Irie T, Kudo A, Nakamura N, Tanabe M, Arii S (2014) EpCAM-targeted therapy for human hepatocellular carcinoma. Ann Surg Oncol 21:1314–1322

Oh BK, Kim H, Park YN, Yoo JE, Choi J, Kim KS, Lee JJ, Park C (2008) High telomerase activity and long telomeres in advanced hepatocellular carcinomas with poor prognosis. Lab Invest 88:144–152

Oikawa T, Kamiya A, Zeniya M, Chikada H, Hyuck AD, Yamazaki Y, Wauthier E, Tajiri H, Miller LD, Wang XW et al (2013) Sal-like protein 4 (SALL4), a stem cell biomarker in liver cancers. Hepatology 57:1469–1483

Oishi N, Yamashita T, Kaneko S (2014) Molecular biology of liver cancer stem cells. Liver Cancer 3:71–84

Okamura D, Ohtsuka M, Kimura F, Shimizu H, Yoshidome H, Kato A, Miyazaki M (2008) Ezrin expression is associated with hepatocellular carcinoma possibly derived from progenitor cells and early recurrence after surgical resection. Mod Pathol 21:847–855

Piao LS, Hur W, Kim TK, Hong SW, Kim SW, Choi JE, Sung PS, Song MJ, Lee BC, Hwang D, Yoon SK (2012) CD133+ liver cancer stem cells modulate radioresistance in human hepatocellular carcinoma. Cancer Lett 315:129–137

Qi W, Liang W, Jiang H, Miuyee Waye M (2013) The function of miRNA in hepatic cancer stem cell. Biomed Res Int 2013:358902

Sainz B, Heeschen C (2013) Standing out from the crowd: cancer stem cells in hepatocellular carcinoma. Cancer Cell 23:431–433

Sasaki M, Sato H, Kakuda Y, Sato Y, Choi JH, Nakanuma Y (2014) Clinicopathological significance of 'subtypes with stem-cell feature' in combined hepatocellular-cholangiocarcinoma. Liver Int. doi:10.1111/liv.12563

Shan J, Shen J, Liu L, Xia F, Xu C, Duan G, Xu Y, Ma Q, Yang Z, Zhang Q, Ma L, Liu J, Xu S, Yan X et al (2012) Nanog regulates self-renewal of cancer stem cells through the insulin-like growth factor pathway in human hepatocellular carcinoma. Hepatology 56:1004–1014

Su Q, Fu Y, Liu YF, Zhang W, Liu J, Wang CM (2003) Laminin induces the expression of cytokeratin 19 in hepatocellular carcinoma cells growing in culture. World J Gastroenterol 9:921–929

Sukowati CH, Anfuso B, Torre G, Francalanci P, Crocè LS, Tiribelli C (2013) The expression of CD90/Thy-1 in hepatocellular carcinoma: an in vivo and in vitro study. PLoS One 8:e76830

Tang J, Tao ZH, Wen D, Wan JL, Liu DL, Zhang S, Cui JF, Sun HC, Wang L, Zhou J, Fan J, Wu WZ (2014) MiR-612 suppresses the stemness of liver cancer via Wnt/β-catenin signaling. Biochem Biophys Res Commun 447:210–215

Terris B, Cavard C, Perret C (2010) EpCAM, a new marker for cancer stem cells in hepatocellular carcinoma. J Hepatol 52:280–281

Tong CM, Ma S, Guan XY (2011) Biology of hepatic cancer stem cells. J Gastroenterol Hepatol 26:1229–1237

Toshima T, Yoshizumi T, Uchiyama H, Ikegami T, Soejima Y, Ikeda T, Kawanaka H, Yamashita Y, Morita M et al (2013) Effect of Cd133-positive stem cells in repeated recurrence of hepatocellular carcinoma after liver transplantation: a case report. Fukuoka Igaku Zasshi 104:383–388

Tschaharganeh DF, Xue W, Calvisi DF, Evert M, Michurina TV, Dow LE, Banito A, Katz SF, Kastenhuber ER et al (2014) p53-dependent Nestin regulation links tumor suppression to cellular plasticity in liver cancer. Cell 158:579–592

Tsuchiya A, Kamimura H, Tamura Y, Takamura M, Yamagiwa S, Suda T, Nomoto M, Aoyagi Y (2011a) Hepatocellular carcinoma with progenitor cell features distinguishable by the hepatic stem/progenitor cell marker NCAM. Cancer Lett 309:95–103

Tsuchiya K, Komuta M, Yasui Y, Tamaki N, Hosokawa T, Ueda K, Kuzuya T, Itakura J et al (2011b) Expression of keratin 19 is related to high recurrence of hepatocellular carcinoma after radiofrequency ablation. Oncology 80:278–288

Uenishi T, Kubo S, Yamamoto T, Shuto T, Ogawa M, Tanaka H, Tanaka S, Kaneda K et al (2003) Cytokeratin 19 expression in hepatocellular carcinoma predicts early postoperative recurrence. Cancer Sci 94:851–857

Van Malenstein H, Komuta M, Verslype C, Vandecaveye V, Van Calster B, Topal B et al (2012) Histology obtained by needle biopsy gives additional information on the prognosis of hepatocellular carcinoma. Hepatol Res 42:990–998

Vander Borght S, Komuta M, Libbrecht L, Katoonizadeh A, Aerts R, Dymarkowski S et al (2008) Expression of multidrug resistance-associated protein 1 in hepatocellular carcinoma is associated with a more aggressive tumour phenotype and may reflect a progenitor cell origin. Liver Int 28:1370–1380

Vasuri F, Golfieri R, Fiorentino M, Capizzi E, Renzulli M, Pinna AD, Grigioni WF et al (2011) OATP 1B1/1B3 expression in hepatocellular carcinomas treated with orthotopic liver transplantation. Virchows Arch 459:141–146

Wan S, Zhao E, Kryczek I, Vatan L, Sadovskaya A, Ludema G, Simeone DM, Zou W, Welling TH (2014) Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. Gastroenterology 147:1393–1404

Wang ZS, Wu LQ, Yi X, Geng C, Li YJ, Yao RY, Hu WY, Han B (2012) CK19 can be used to predict the early recurrence and prognosis of HBV-related hepatocellular carcinoma patients with low AFP serum concentration after R0 radical hepatectomy (in Chinese). Zhonghua Zhong Liu Za Zhi 34:753–758

Wee A (2006) Diagnostic utility of immunohistochemistry in hepatocellular carcinoma, its variants and their mimics. Appl Immunohistochem Mol Morphol 14:266–272

Winter MJ, Nagelkerken B, Mertens AE, Rees-Bakker HA, Briaire-de Bruijn IH, Litvinov SV (2003) Expression of EpCAM shifts the state of cadherin-mediated adhesions from strong to weak. Exp Cell Res 285:50–58

Wu PC, Fang JW, Lau VK, Lai CL, Lo CK, Lau JY (1996) Classification of hepatocellular carcinoma according to hepatocellular and biliary differentiation markers. Clinical and biological implications. Am J Pathol 149:1167–1175

Wu F, Nishioka M, Fujita J, Murota M, Ohtsuki Y, Ishida T, Kuriyama S (2002) Expression of cytokeratin 19 in human hepatocellular carcinoma cell lines. Int J Oncol 20:31–37

Xiang ZL, Zeng ZC, Tang ZY, Fan J, Sun HC, Tan YS (2011) Expression of cytokeratin 19 and matrix metalloproteinase 2 predicts lymph node metastasis in hepatocellular carcinoma. Mol Biol Rep 38:3531–3539

Xiao H, Jiang N, Zhou B, Liu Q, Du C (2014) TAZ regulates cell proliferation and epithelial-mesenchymal transition of human hepatocellular carcinoma. Cancer Sci. doi:10.1111/cas.12587

Xu X, Liu RF, Zhang X, Huang LY, Chen F, Fei QL, Han ZG (2012) DLK1 as a potential target against cancer stem/progenitor cells of hepatocellular carcinoma. Mol Cancer Ther 11:629–638

Xu M, Qian G, Xie F, Shi C, Yan L, Yu L, Zheng T, Wei L, Yang J (2014) Expression of epithelial cell adhesion molecule associated with elevated ductular reactions in hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 38:699–705

Xue X, Zhang Y, Zhi Q, Tu M, Xu Y, Sun J, Wei J, Lu Z, Miao Y, Gao W (2014) MiR200-upregulated vasohibin 2 promotes the malignant transformation of tumors by inducing epithelial-mesenchymal transition in hepatocellular carcinoma. Cell Commun Signal 12:62

Yamada M, Shiroeda H, Sato K, Hayashi R, Nomura T, Tsutsumi M, Arisawa T (2011) Accelerated progression of hepatocellular carcinoma with cytokeratin 19 expression during treatment with lamivudine for hepatitis B virus-related cirrhosis. Scand J Gastroenterol 46:249–251

Yamashita T, Kaneko S (2014) Orchestration of hepatocellular carcinoma development by diverse liver cancer stem cells. J Gastroenterol 49:1105–1110

Yamashita T, Budhu A, Forges M, Wang XW (2007) Activation of hepatic stem cell marker EpCAM by Wnt-beta-catenin signaling in hepatocellular carcinoma. Cancer Res 67:10831–10839

Yamashita T, Forgues M, Wang W, Kim JW, Ye Q, Jia H, Budhu A, Zanetti KA, Chen Y et al (2008) EpCAM and alpha-fetoprotein expression defines novel prognostic subtypes of hepatocellular carcinoma. Cancer Res 68:1451–1461

Yamashita T, Ji J, Budhu A, Forgues M, Yang W, Wang HY, Jia H, Ye Q, Qin LX, Wauthier E, Reid LM et al (2009) EpCAM-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/progenitor cell features. Gastroenterology 136:1012–1024

Yamashita T, Honda M, Nakamoto Y, Baba M, Nio K, Hara Y, Zeng SS, Hayashi T, Kondo M, Takatori H et al (2013) Discrete nature of EpCAM+ and CD90+ cancer stem cells in human hepatocellular carcinoma. Hepatology 57:144–1497

Yanai H, Nakamura K, Hijoka S, Komei A, Ikari T, Ishikawa Y, Shinozaki E, Mizunuma N et al (2010) Dlk-1, a cell surface antigen on foetal hepatic stem/progenitor cells, is expressed on hepatocellular, colon, pancreas and breast carcinomas at a high frequency. J Biochem 148:85–92

Yang XR, Xu Y, Shi GM, Fan J, Zhou J, Ji Y, Sun HC, Qiu SJ, Yu B, Gao Q et al (2008) Cytokeratin 10 and cytokeratin 19: predictive markers for poor prognosis in hepatocellular carcinoma patients after curative resection. Clin Cancer Res 14:3850–3859

Yang XR, Xu Y, Yu B, Zhou J, Qiu SJ, Shi GM, Zhang BH, Wu WZ, Shi YH, Wu B et al (2010) High expression levels of putative hepatic stem/progenitor cell biomarkers related to tumour angiogenesis and poor prognosis of hepatocellular carcinoma. Gut 59:953–962

Yang W, Wang C, Lin Y, Liu Q, Yu LX, Tang L, Yan HX, Fu J, Chen Y, Zhang HL, Tang L, Zheng LY et al (2012) OV6+ tumor-initiating cells contribute to tumor progression and invasion in human hepatocellular carcinoma. J Hepatol 57:613–620

Ye F, Jing YY, Guo SW, Yu GF, Fan QM, Qu FF, Gao L, Yang Y, Wu D, Meng Y, Yu FH, Wei LX (2014) Proliferative ductular reactions correlate with hepatic progenitor cell and predict recurrence in HCC patients after curative resection. Cell Biosci 4:50

Yeh CT, Kuo CJ, Lai MW, Chen TC, Lin CY, Yeh TS, Lee WC (2009) CD133-positive hepatocellular carcinoma in an area endemic for hepatitis B virus infection. BMC Cancer 9:324

Yilmaz G, Akyol G, Cakir A, Ilhan M (2014) Investigation of diagnostic utility and expression profiles of stem cell markers (CD133 and CD90) in hepatocellular carcinoma, small cell dysplasia, and cirrhosis. Pathol Res Pract 210:419–425

Yoneda N, Sato Y, Kitao A, Ikeda H, Sawada-Kitamura S, Miyakoshi M, Harada K et al (2011) Epidermal growth factor induces cytokeratin 19 expression accompanied by increased growth abilities in human hepatocellular carcinoma. Lab Invest 91:262–272

Yong KJ, Gao C, Lim JS, Yan B, Yang H, Dimitrov T, Kawasaki A, Ong CW, Wong KF, Lee S, Ravikumar S et al (2013) Oncofetal gene SALL4 in aggressive hepatocellular carcinoma. NEngl J Med 368:2266–2276

Yuan RH, Jeng YM, Hu RH, Lai PL, Lee PH, Cheng CC, Hsu HC (2011) Role of p53 and b-catenin mutations in conjunction with CK19 expression on early tumor recurrence and prognosis of hepatocellular carcinoma. J Gastrointest Surg 15:321–329

Zen C, Zen Y, Mitry RR, Corbeil D, Karbanova J, O'Grady J, Karani J, Kane P, Heaton N et al (2011) Mixed phenotype hepatocellular carcinoma after transarterial chemoembolization and liver transplantation. Liver Transpl 17:943–954

Zeng SS, Yamashita T, Kondo M, Nio K, Hayashi T, Hara Y, Nomura Y, Yoshida M, Hayashi T, Oishi N et al (2014) The transcription factor SALL4 regulates stemness of EpCAM-positive hepatocellular carcinoma. J Hepatol 60:127–134

Zhang J, Luo N, Luo Y, Peng Z, Zhang T, Li S (2012) microRNA-150 inhibits human CD133-positive liver cancer stem cells through negative regulation of the transcription factor c-Myb. Int J Oncol 40:747–756

Zhang G, Wang Z, Luo W, Jiao H, Wu J, Jiang C (2013) Expression of potential cancer stem cell marker ABCG2 is associated with malignant behaviors of hepatocellular carcinoma. Gastroenterol Res Pract 2013:782581

Zhang L, Li H, Ge C, Li M, Zhao FY, Hou HL, Zhu MX, Tian H, Zhang LX, Chen TY, Jiang GP, Xie HY et al (2014) Inhibitory effects of transcription factor Ikaros on the expression of liver cancer stem cell marker CD133 in hepatocellular carcinoma. Oncotarget 5:10621–10635

Zhou YM, Yang JM, Li B, Yin ZF, Xu F, Wang B, Xu W, Kan T (2010) Risk factors for early recurrence of small hepatocellular carcinoma after curative resection. Hepatobiliary Pancreat Dis Int 9:33–37

Zhuang PY, Zhang JB, Zhu XD, Zhang W, Wu WZ, Tan YS, Hou J, Tang ZY et al (2008) Two pathologic types of hepatocellular carcinoma with lymph node metastasis with distinct prognosis on the basis of CK19 expression in tumor. Cancer 112:2740–2748

Ectopic Hepatocellular Carcinoma 15

Contents

Abstract

Ectopic hepatocellular carcinoma (ectopic HCC) is defined as an HCC that arises from intrahepatic or extrahepatic bile ducts, the gallbladder, from liver parenchyma situated in an extrahepatic organ or tissue, or from extrahepatic hepatogenic progenitor cells. In advanced ectopic HCC, the source of the tumor may be difficult to assess, as ectopic liver tissue may have been completely destroyed by the tumor. Ectopic HCC is a very rare neoplasm, as its most common source, ectopic or heterotopic liver, has an estimated incidence of only 0.24–0.47 %. There is a propensity of ectopic liver to give rise to HCC. Ectopic HCC may be suspected in patients with markedly elevated serum alpha-fetoprotein levels in the absence of an orthotopic liver tumor. Ectopic HCC that develops in large bile ducts can show several growth patterns, one of the patterns characterized by endoluminal polypoid growths that cause biliary obstruction. Ectopic HCCs situated outside the liver can be attached to the organ by a vascular stalk. Uncommon tumors occur in visceral abdominal organs, in the peritoneal surface, in the retroperitoneal space, and within the thoracic cavities.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_15

Introduction

Ectopic hepatocellular carcinoma is defined as HCC arising from intrahepatic or extrahepatic bile ducts, from hepatic parenchyma that is located in an extrahepatic organ or tissue, although preexisting ectopic liver tissue cannot always be identified, or from extrahepatic hepatogenic cells/progenitor cells (Sasaki and Konishi 1995; Arakawa et al. 1999; Le Bail et al. 1999; Caygill and Gatenby 2004). Liver tissue as a source of HCC may be completely destroyed and replaced by cancer, or HCC may have originated from a tiny hepatic ectopia or from hepatogenic cells (progenitor cells) displaced into an extrahepatic, aberrant site. Based on potential pathogenic mechanisms involved, several basic types of liver ectopia have been proposed, i.e., (1) an accessory liver lobe attached to the liver by a vascularized stalk, (2) small accessory liver lobe equivalents ("liverlets") attached to the liver, (3) ectopic liver tissue that is situated outside the orthotopic liver without any connection with it, and (4) microscopic ectopic liver cell foci (Collan et al. 1978). An early displacement of small collections of hepatic progenitor cells to extrahepatic niches is supported by the observation of ectopic HCC relatively remote to the liver, e.g., in the spleen, the pancreas, the jejunum, the abdominal cavity, the diaphragm, or the chest wall.

Epidemiology

The reported incidence of ectopic or heterotopic liver (liver ectopia and liver heterotopia) is only 0.24–0.47 % (Eiserth 1940; Watanabe et al. 1989), and ectopic HCC is even rarer, but there seems to be propensity of ectopic liver to give rise to HCC (Le Bail et al. 1999; Arakawa et al. 1999; Caygill and Gatenby 2004). Out of approximately 100 cases of ectopic liver reported, HCC was detected in 28 of them (Arakawa et al. 1999; Asselah et al. 2001; Kim et al. 2003; Leone et al. 2004). Most cases of reported ectopic HCCs involved Asian patients, and only few Caucasian cases were published (Leone et al. 2004; Toonen and Smilde 2010). The presence of ectopic HCC may be suspected in patients having a markedly elevated serum AFP or other HCC markers in the absence of imaging evidence of a primary liver tumor or other tumors known to secrete AFP. Patients with ectopic HCC do not show the usual risk factors for orthotopic HCC, such as HBV infection and liver cirrhosis (Arakawa et al. 1999; Kubota et al. 2007). In very rare cases, ectopic HCC was associated with other condition, such as pachydermia (Dettmer et al. 2011).

Ectopic Hepatocellular Carcinoma Arising in Bile Ducts

Clinical and Imaging Features

The diagnosis of ectopic HCC in bile ducts requires that no trace of HCC can be detected in the liver, as manifestations of primary hepatic HCC in the biliary tract is well known (icteric-type HCC). Larger lesions cause stenosis of the common duct and obstructive jaundice and hence may mimic icteric-type HCC (Cho et al. 1996; Buckmaster et al. 1994; Kondo et al. 2003; Peng et al. 2004; Tsushimi et al. 2005; Makino et al. 2006; Yigit et al. 2007; Schmelzle et al. 2009). Cholangiography reveals a round defect in the bile duct (Tsushimi et al. 2005) or a circumscribed swelling of the duct wall (Schmelzle et al. 2009).

Pathology

Several types of gross presentation can be distinguished (Table 1). Intramural mass-forming tumors present as fusiform eccentric or concentric lesions that lead to circumscribed stricture or stenosis (Park et al. 1991; Hasegawa et al. 2002). Exophytic spherical tumors can grow as nodular masses or as polypoid masses covered by a capsule and connected with the underlying bile duct mucosa by a vascular stalk (Tsushimi et al. 2005;

Table 1 Gross growth patterns of ectopic HCC of bile ducts

Extrahepatic ectopic HCC of bile ducts
Type 1
Intramural mass-forming fusiform type
Type 2
Intraductal nodular type
Type 3
Intraductal pedunculated polypoid type
Type 4
Intraductal embolus-like type
Intrahepatic ectopic HCC of bile ducts
Type 5
Intrahepatic intramural nodular small type
Type 6
Intrahepatic intraductal polypoid type

Yigit et al. 2007). Embolus-type HCC of the biliary tract in the absence of primary hepatic HCC is an intriguing lesion that may in part derive from ectopic tissue, but failure of diagnosing an intrahepatic tumor has to be taken into account. Intrahepatic intrabiliary ectopic HCCs are small tumors in close association with a lobar or segmental bile duct (Yasui et al. 2004). They may show a pedunculated polypoid growth pattern (Terada et al. 1989).

Metastasis of intrahepatic HCC to bile ducts may grossly mimic these growth patterns. For example, metastatic manifestation of HCC in the hepatic duct was reported to grow as a polypoid mass with a stalk (Narita et al. 2002). Intrahepatic HCCs may chiefly grow in connection with bile ducts close to the liver hilum (Thomsen et al. 1998).

Histologically, ectopic liver tissues may show lobular-like architecture with central veins, in particular when the lesion is macroscopically visible. Microscopic ectopias may, in contrast, only consist of small collections of hepatocytes embedded in a connective tissue, without liver-specific angioarchitecture. A biliary drainage may or may not be present. The ectopic liver tissue can undergo secondary alterations, such as cholestasis, steatosis, inflammatory changes, and fibrosis or even cirrhosis.

Ectopic Hepatocellular Carcinoma in the Gallbladder

As ectopic liver is relatively frequent in the gallbladder, this organ is a common site of ectopic HCC (Tamura et al. 1985; Sarda 2005). Ectopic HCC of the gallbladder presents as nodular or polypoid, intraluminal mass, often in the body and/or fundus. The neoplasm may be confounded with primary gallbladder carcinoma, but an elevated serum AFP concentration should raise suspicion of ectopic HCC.

Ectopic Hepatocellular Carcinoma in Connection with the Main Liver, but Physically Separated from the Main Liver Substance

These are HCCs that form nodules that are separated from the liver, but are connected with the liver through a meso-like structure or by a pouch-like extension of the liver capsule. These tumors arise from liver anlages that have separated from the main organ in the course of the formation of the liver bud or from hepatogenic cell nests having been isolated from the remaining cell populations in the septum transversum. This type of ectopic HCC may be situated close to the inferior vena cava (Fukuda et al. 2009), in the triangular ligament (Kuo et al. 2008; Kanzaki et al. 2010).

Ectopic Hepatocellular Carcinoma in Visceral Abdominal Organs

Ectopic HCCs were found in the abdominal cavity (Matsunaga et al. 2003), on the peritoneum (Liu et al. 2007), the left subphrenic space (Seo et al. 2008), the hepatoumbilical ligament (Zonca et al. 2013), underneath the diaphragm (Takayasu et al. 1994; Kim et al. 2003; Nishikawa et al. 2011), at the lesser curvature of the stomach (Kuo et al. 2008), in the perigastric space (Nakamura et al. 2013), the jejunum (Shigemori et al. 2006), the pancreas (Hayashi et al. 2000;

Cardona et al. 2007; Kubota et al. 2007), and the spleen (Matsuyama et al. 2011).

Multiple Ectopic Hepatocellular Carcinomas in the Abdominal Cavity

In rare cases, multiple brown nodules were found on the peritoneal surface and in the mesentery, sometimes associated with hemorrhagic ascites (Kawahara et al. 1988; Miyake et al. 2012).

Ectopic HCC in the Retroperitoneal Space

Few cases of retroperitoneal ectopic HCC were reported (Horiuchi et al. 1969), sometimes with formation of large masses suspicious of germ cell tumor metastases (Toonen and Smilde 2010). Ectopic HCC has very rarely been observed in the renal hilum, masquerading an adrenal tumor (Singh et al. 2010).

Thoracic Ectopic Hepatocellular Carcinoma

Ectopic HCC was observed on the superior surface of the diaphragm (Moriwaki et al. 1987; Huang et al. 2007; Oldani and Garavoglia 2013), in the chest wall (Kawabata et al. 1996; Asselah et al. 2001; Nenekidis et al. 2011), and has also been diagnosed within the thoracic cavity, including the mediastinum (Rozen et al. 2011).

Differential Diagnosis

The most important differential diagnosis is metastatic HCC, but can be excluded in the absence of an orthotopic primary tumor. Hepatoid carcinoma originating in organs and tissues known to be a site of ectopic liver may resemble ectopic HCC, e.g., hepatoid carcinoma of the pancreas (Marchegiani et al. 2013).

Biology of Disease

In a minority of cases, ectopic HCC later produces recurrence in the main liver (Kawabata et al. 1996; Arakawa et al. 1999; Kim et al. 2003; Leone et al. 2004; Shigemori et al. 2006; Kuo et al. 2008). These situations were usually interpreted as metastases of the ectopic HCC, but a second metachronous primary tumor cannot be excluded with certainty.

Ectopic Liver: Anatomic Sites and Morphology

As ectopic HCC may originate from ectopic liver tissue, sites and morphology of ectopic liver tissue are of interest in this setting. Ectopic and accessory liver tissue has been described already in the old literature on abnormalities of liver development (Jacquemet 1896; Hanser 1930). Liver ectopia outside the bile ducts and the gallbladder is mostly an isolated phenomenon, but it can also occur in conjunction with other congenital abnormalities, including biliary atresia, caudate lobe agenesis, omphalocele, ductal plate malformations, and laparoschisis, Parts of liver tissue nodules sometimes identified as ectopic liver are connected to the orthotopic organ through a vascularized pedicle and are, therefore, not true ectopias but may rather be related to accessory and abortive liver lobes (hepar succenturiatum; Algin et al. 2008; Wang et al. 2012). In comparison with true liver ectopia, accessory liver lobes have been described numerous times (Levi et al. 1969; Pujari and Deodhare 1976; Go et al. 1978; Kuroiwa et al. 1984; Tomooka et al. 1988; Fogh et al. 1989; Massaro et al. 2007; Stattaus et al. 2008; Faraj et al. 2010; Wang et al. 2010; Kostov and Kobakov 2011). Accessory livers may have their own mesentery and, depending on their location, can drain into the biliary system or have no drainage system. Liver tissue connected with the main organ via a vascularized stalk may rarely have an unusual position, e.g., being situated within the suprahepatic part of the inferior vena cava, as a

floating intraluminal polypoid mass (Morris et al. 2012). An accessory liver lobe can be found in exomphalos/omphalocele (Tan and Tan 1971; Pereira et al. 2005). The gallbladder may be embedded in the right-sided inferior accessory lobe (Festen et al. 1988). Accessory liver lobes with a vessel-containing pedicle may undergo torsion, followed by infarction, both in children and adults (Olinde and Boggs 1958; Watson and Lee 1964; Peter and Strohm 1980; Betge 1995; Sanguesa et al. 1995; Koumanidou et al. 1998; Koplewitz et al. 1999; Bedda et al. 2003; Ladurner et al. 2005; Hundal et al. 2006; Pérez-Martinez et al. 2006; Negru et al. 2007; Carrabetta et al. 2009; Umehara et al. 2009; Jambhekar et al. 2010). Other secondary changes of such lobes comprise a rupture due to blunt trauma (Garba and Ameh 2002) and hemorrhage (Vykouril 1989). Accessory liver lobes can protrude through congenital abdominal wall defects (Johnstone 1965) or disturb the closure of the umbilical ring (Ito et al. 1999).

In contrast to accessory liver lobes, true liver ectopia is not connected to the main liver through a vascularized pedicle, but is completely separated from the orthotopic organ. Numerous sites of true ectopic livers have been identified (Table 2).

Table 2 Anatomic sites of ectopic liver

Perihepatic compartment
Gallbladder
Hepatic ligaments
Gastrohepatic ligament
Diaphragm
Abdominal organs and tissues
Spleen
Pancreas
Gastric wall
Jejunum
Greater omentum
Umbilical region
Abdominal wall
Umbilical cord
Omphalocele
Retroperitoneal space
Adrenal gland
Renal hilus
Retroperitoneal adipose tissue
Gonads
Testis (hepatogonadal fusion)
Thoracic organs and tissues
Chest wall
Supradiaphragmatic pleural space
Pericardium
Right atrium
Lung

Most true ectopias are clinically silent. In a minority of cases, the lesions become symptomatic, mostly due to hemorrhage and necrosis, compression of adjacent organs (e.g., stenosis of the gastric outlet), and intraperitoneal or intrathoracic bleeding. The natural course of true liver ectopias is unpredictable. Some of the lesions may disappear postnatally due to atrophy or remodeling processes.

The most important abdominal organ harboring ectopic liver is the gallbladder (Ribbert 1914; Walzel and Gold 1925; Bassis and Izenstark 1956; Angquist et al. 1975; Torchio and Maconi 1978; Natori et al. 1986; Fellbaum et al. 1987; Tejada and Danielson 1989; Watanabe et al. 1989; Castro Viera et al. 1990; Svane and Knudtzon 1991; Hamdani and Baron 1994; Acar et al. 2002; Griniatsos et al. 2002; Sakarya et al. 2002; Lundy et al. 2005; Kyeong et al. 2008; Triantafyllidis et al. 2009; Nagar et al. 2011; Karaman et al. 2012). Macroscopically, ectopic livers of the gallbladder most often present reddish-brown polypoid or bean-shaped nodules that are covered by intact serosa and are connected with the gallbladder wall via a vascularized pedicle. The size of these liverlets usually ranges from few millimeters to 1 or 2 cm, but larger lesions are occasionally seen. The ectopic livers are most often situated at the fundus and corpus of the gallbladder, but some of the lesions were also found in the gallbladder neck. Ectopic liver of the gallbladder wall can mimic a tumor mass (Hamdani and Baron 1994) and may undergo secondary changes, including hemorrhagic necrosis (Nagar et al. 2011), sometimes caused by torsion (Elsayes et al. 2005), cholangitis (Castro Viera et al. 1990), cholestasis (Svane and

Knudtzon 1991), and cirrhosis (Brühl 1926; Lieberman 1966; Angquist et al. 1975; Pesce et al. 1984). In comparison with other ectopic livers, liver ectopia of the gallbladder does seem to less commonly be complicated by HCC. The reason for this phenomenon is still unknown.

Other, much less common localizations include the bile duct system (see above); hepatic ligaments; abdominal cavity (Kawahara et al. 1988); omphalocele (Fock 1963); umbilical region (Nora and Carr 1946); diaphragm (Takayasu et al. 1994; Huang et al. 2007); greater omentum (Orth 1887; Brühl 1926; Elsayes et al. 2005); stomach wall (el Haddad et al. 1985); gastrohepatic ligament (Catani et al. 2011); pancreas (Kubota et al. 2007; Catani et al. 2011); spleen and splenic capsule (Schnyder 1926; Heid and Von Haam 1948; Ball et al. 1971; Matsuyama et al. 2010); parasplenic space (Diez et al. 2009); jejunum (Newland et al. 1989; Shigemori et al. 2006); intrathoracic structures (Rodriguez-Perez 1955; Sehdeva and Logan 1971; Babu and van der Avoirt 2001; Han and Soylu 2009; Kutner et al. 2010; Huang et al. 2011), including the pericardium (Kinnunen et al. 1997), right atrium (Brustmann 2002), and lung parenchyma (Iber and Rintala 1999; Tancredi et al. 2010); retroperitoneum (Pesce et al. 1984; Watanabe et al. 1989); adrenal glands (Honoré 1985; Buck and Koss 1988; Zlatkovic et al. 1998; Catani et al. 2011); testis (hepatogonadal fusion; Ferro et al. 1996); and umbilical cord (Preminger et al. 2001). A supradiaphragmatic liver is commonly disconnected to the main body of the liver (Hudson and Brown 1962; Lasser and Wilson 1975) and may be associated with other malformations, e.g., congenital cardiac anomalies (Shapiro and Metlay 1991) or congenital diaphragmatic hernia (Shah et al. 1987). Thoracic hepatic tissue may be a rare congenital alteration (Luoma and Raboei 2003; Kamath et al. 2010), but it can also develop in the setting of diaphragmatic hernias, either iatrogenic or subsequent to injury (Yoshino et al. 2006). Posttraumatic extension of the liver into the thoracic cavity may cause esophageal obstruction (Jimenez and Hayward 1971). Multiple intrapulmonary liver foci had been observed after orthotopic heart transplantation (Mehta et al. 2010).

The detailed anatomy of ectopic livers is sometimes difficult to analyze, because such liver structures (or "liverlets") are often not fed by a branch of the hepatic artery, do not show a portal venous circulation, and may not be connected to the biliary tract. In contrast to the often polypoid or pedunculated liver ectopias of the gallbladder, ectopic liver in other organs is usually manifest as a macroscopic or microscopic nodule of liver parenchyma surrounded by a capsule-like condensation of connective tissue. Histologically, liver ectopias of the gallbladder, but also those of other organs, consist of a hepatocytic parenchyma that either exhibits a lobular texture with central veins or does not show a lobular architecture, but contains normal-looking hepatocytes. The latter may, however, undergo secondary changes, the most common being cholestasis in cases without biliary drainage. Interestingly, not all ectopias lacking a biliary drainage accumulate the bile. This unexpected phenomenon may be linked to failure of ectopic hepatocytes to clear bilirubin from circulation due to a membrane defect. Most liver ectopias are fed by an autonomous artery that is embryological typical for tissues forming a niche for ectopia. Apart from bile accumulation, other secondary alterations of ectopic liver tissue include steatosis, chronic active inflammation (chronic active hepatitis), granulomatous hepatitis, iron overload, fibrosis, cirrhosis, metastatic disease, hepatocarcinogenesis, and development of non-HCC tumors. For example, ectopic intrathoracic liver contained infantile hemangioendothelioma (Shah et al. 1987) or cystic mesenchymal hamartoma (Antoniou et al. 2012). In very rare cases, alterations resembling congenital hepatic fibrosis were found in ectopic liver, in the absence of corresponding changes in the orthotopic liver (Zlatkovic et al. 1998).

Morphogenetic Pathways

Whereas the pathogenesis of accessory liver lobes can be regarded as a consequence of a segregation or sequestration of liver primordium from the

main liver, resulting in some sort of aberrant lobe connected to the hepatic vascular system and biliary tract, pathogenic pathways leading to true liver ectopias are more difficult to understand. The orthotopic liver develops through a series of reciprocal tissue interactions between the primed or fated embryonic endoderm and nearby mesoderm. Endodermal cells fated to become liver primordium are located in the ventral foregut endoderm, from where the hepatic diverticulum emerges, a pocket of thickened endodermal epithelium adjacent to the developing heart. Endodermal cells primed for a hepatocyte lineage develop into hepatoblasts which delaminate from the endoderm to invade the septum transversum mesenchyme and to form the liver bud. The liver bud is something like a pacemaker that determines, on the one hand, the construction of the later hepatocyte parenchyma and the ductal plate and, on the other hand, the generation of a highly liver-specific vascular system and a system of distinct mesenchymal cells, the hepatic stellate cells and their differentiated offspring. This sequence of events is orchestrated by a strictly controlled system of transcription factors and growth factors, in part expressed in the mesenchymal cells of the septum transversum which form a decisive platform for the stepwise progression of hepatogenesis (Le Douarin 1975; Zaret 2002, 2008; Lemaigre and Zaret 2004; Tremblay and Zaret 2005; Freedman et al. 2007; Lemaigre 2009; Wandzioch and Zaret 2009; Si-Tayeb et al. 2010; Boulter et al. 2013; Shin and Monga 2013; Yin et al. 2013). For ectopic liver tissue localized to organs in the vicinity of the liver, such as the pancreas, spleen, and adrenals, aberrant migration of hepatocyte progenitors having left the liver bud might be considered, but the generation of liver tissue would require the induction of a specific hepatogenic mesenchyme, as in the orthotopic liver. As most intra-abdominal ectopic livers are situated in the upper part of the abdomen, components of the embryonal septum transversum might be available for liver induction at these ectopic places. On the other hand, specification of cell lineages is a potentially bidirectional process, as tissue programming can be reversed (Zaret 2008). For liver ectopias in the thoracic cavity, other mechanisms have to be considered, because these sites are proximal to the hepatogenic endoderm and superior to the septum transversum. Ectopic priming of cells for a hepatocyte lineage proximal to the ventral foregut might play a role. On the other hand, conversion of pluripotent stem cells into endodermal cells or hepatoblasts (Sekine et al. 2012; Xu and Zaret 2012), or even a conversion of mesenchymal cells into hepatocytes, might be taken into account, as there is recent evidence that human adipose stem cells can directly differentiate into functional hepatocytes. Also aberrant, ectopic expression of transcription factors that have a programming role for liver induction, such as Sox9 (Kawaguchi 2013), might be involved.

Pathogenesis of Ectopic Hepatocellular Carcinoma

In the absence of usual HCC risk factors, the pathogenic pathways involved in ectopic HCC are not fully understood. It has been suggested that continuous cell damage with hyperregeneration, chronic cholestasis with bile acid toxicity, and impaired vascularization might play a role. Persistent regeneration of hepatocytes may be induced by cirrhosis developing in ectopic liver tissue, e.g., secondary biliary cirrhosis in the absence of biliary drainage (Pesce et al. 1984).

References

Acar T, Taçyildiz R, Karakayali S (2002) Ectopic liver tissue attached to the gallbladder. Acta Chir Belg 102:210–211

Algin C, Yaylak F, Olgun EG, Caglikulkci M (2008) Laparoscopic removal of an incidental ectopic liver: short report of a case. Case Rep Gastroenterol 2:134–137

Angquist KA, Boquist L, Domellöf L (1975) Ectopic liver lobules with portal cirrhosis. Acta Chir Scand 141:238–241

Antoniou D, Soutis M, Karentzou O (2012) Cystic mesenchymal hamartoma arising in intrathoracic heterotopic liver: a case report. J Pediatr Surg 47:e49–e51

Arakawa M, Kimura Y, Sakata K, Kubo Y, Fukushima T, Okuda K (1999) Propensity of ectopic liver to hepatocarcinogenesis: case reports and a review of the literature. Hepatology 29:57–61

Asselah T, Condat B, Cazals-Hatem D, Hassani Z, Bernuau J, Groussard O, Mussot S et al (2001) Ectopic hepatocellular carcinoma arising in the left chest wall: a long term follow-up. Eur J Gastroenterol Hepatol 13:873–875

Babu R, Van der Avoirt A (2001) Ectopic intrathoracic liver. Pediatr Surg Int 17:461–462

Ball JJ, Kanzaki T, Lum CH, Jim RT, Wong WL (1971) Aberrant liver tissue as accessory spleen on spleen scan following splenectomy. Hawaii Med J 30:393–395

Bassis ML, Izenstark JL (1956) Ectopic liver; its occurrence in the gall bladder. AMA Arch Surg 73:204–206

Bedda S, Bataille N, Montariol T, Zareski E (2003) Accessory liver lobe torsion mimicking a pancreatic tumor. Ann Chir 128:53–54

Betge L (1995) The torsion of an accessory liver lobe as the rare cause of acute abdomen. Dtsch Med Wochenschr 120:1318–1320

Boulter L, Lu WY, Forbes SJ (2013) Differentiation of progenitors in the liver: a matter of local choice. J Clin Invest 123:1867–1873

Brühl R (1926) Über eine Nebenleber mit zirrhotischen Veränderungen. Zbl Path 37:245

Brustmann H (2002) Heterotopic liver in the right cardiac auricle. Ann Diagn Pathol 6:248–249

Buck FS, Koss MN (1988) heterotopic liver in an adrenal gland. Pediatr Pathol 8:535–540

Buckmaster MJ, Schwartz RW, Carnahan GE, Strodel WE (1994) Hepatocellular carcinoma embolus to the common hepatic duct with no detectable primary hepatic tumor. Am J Surg 60:669–702

Cardona D, Grobmyer S, Crawford JM, Liu C (2007) Hepatocellular carcinoma from ectopic liver tissue in the pancreas. Virchows Arch 450:225–229

Carrabetta S, Piombo A, Podesta R, Aurati L (2009) Torsion and infarction of accessory liver lobe in young man. Surgery 145:448–449

Castro Viera GA, Sanuy ME, Camara HA, Cordoba OC (1990) Accessory liver gallbladder. Apropos of a case report (in Spanish). Rev Esp Enferm Dig 77:295–296

Catani M, De Milito R, Romagnoli F, Mingazzini P, Silvestri V, Usai V, Romeo V, Modini C (2011) Ectopic liver nodules: a rare finding during cholecystectomy. G Chir 32:255–258

Caygill C, Gatenby P (2004) Ectopic liver and hepatocarcinogenesis. Eur J Gastroenterol Hepatol 16:727–729

Cho HG, Chung JP, Lee KS, Chon CY, Kang JK, Park IS, Kim KW, Chi HS, Kim H (1996) Extrahepatic bile duct hepatocellular carcinoma without primary hepatic parenchymal lesions – a case report. Korean J Intern Med 11:169–174

Collan Y, hakkiluoto A, Hästbacka J (1978) Ectopic liver. Ann Chir Gynecol 67:27–29

Dettmer M, Itin P, Miny P, Gandhi M, Cathomas G, Willi N (2011) Giant ectopic liver, hepatocellular carcinoma and pachydermia – a rare genetic syndrome? Diagn Pathol 6:75

Diez MJ, Canela T, Villas A, Gil M (2009) Contribution of (99m) TC-mebrofenin scintigraphy to the diagnosis of ectopic liver. A case report (in Spanish). Rev Esp Med Nucl 28:125–127

Eiserth P (1940) Beiträge zur Kenntnis der Nebenlebern. Virchows Arch A Pathol Anat Histopathol 307:307–313

El Haddad MJ, Currie AB, Honeyman M (1985) Pyloric obstruction by ectopic liver tissue. Br J Surg 72:917

Elsayes HB, Elzein MA, Razik AM, Olude IO (2005) Torsion of an ectopic liver in a young child. J Pediatr Surg 40:E55–E58

Faraj W, Dar F, Marangoni G, Alvarez FE, Howlader M, Mukherji D, Heaton N, Rela M (2010) Liver transplantation for syndromic biliary atresia with a pedunculated accessory hepatic lobe. Pediatr Transplant 14:E1–E3

Fellbaum C, Beham A, Schmid C (1987) Isolated accessory liver (hepar succenturiatum) at the neck of the gallbladder. Case report with review of the literature (in German). Wien Klin Wochenschr 99:825–827

Ferro F, Lais A, Boldrini R, De Peppo F, Federici G, Bosman C (1996) Hepatogonadal fusion. J Pediatr Surg 31:435–436

Festen C, Severijnen RS, vd Staak FH (1988) Gallbladder embedded in an accessory liver lobe in umbilical cord hernia. J Pedaitr Surg 23:978–979

Fock G (1963) Ectopic liver in omphalocele. Acta Paediatr 52:288–292

Fogh J, Tromholt N, Jorgensen F (1989) Persistent impairment of liver function caused by a pendulated accessory liver lobe. Eur J Nucl Med 15:326–327

Freedman DA, Kashima Y, Zaret KS (2007) Endothelial cell promotion of early liver and pancreas development. Novartis Found Symp 283:207–216

Fukuda S, Yano K, Ohata K, Nonaka K, Tateyama M, Taura N, Komori A, Abiru S et al (2009) A case of ectopic hepatocellular carcinoma (in Japanese). Nihon Shokakibyo Gakkai Zasshi 106:1770–1777

Garba ES, Ameh EA (2002) Isolated rupture of an accessory liver from blunt abdominal trauma in childhood. Pediatr Surg Int 18:62–63

Go RT, Van Kirk OC, Schapiro RL, Christie JH (1978) Accessory left hepatic lobe –diagnostic contributions by various imaging techniques. J Comput Tomogr 2:155–158

Griniatsos J, Riaz AA, Isla AM (2002) Two cases of ectopic liver attached to the gallbladder wall. HPB (Oxford) 4:191–194

Hamdani SD, Baron RL (1994) Ectopic liver simulating a mass in the gallbladder wall: imaging findings. AJR Am J Roentgenol 162:647–648

Han S, Soylu L (2009) Accessory liver lobe in the left thoracic cavity. Ann Thorac Surg 87:1933–1934

Hanser R (1930) Missbildungen der Leber. In: Henke F, Lubarsch O (eds) Handbuch der speziellen pathologischen Anatomie und Histologie. Julius Springer, Berlin, pp 1–70

Hasegawa K, Kubota K, Mori M, Midorikawa Y, Takayama T, Makuuchi M (2002) Hepatocellular carcinoma originating from intramural cells in bile duct. Hepatogastroenterology 49:1688–1691

Hayashi T, Tsukioka T, Fukunaga J, Ishikawa T, Hishinuma S, Ozawa I, Ogata Y, Imura J et al (2000) A case of ectopic hepatocellular carcinoma which was suspected to be non-functioning pancreatic tail tumor. Acta Hepatol Jpn 40:53–58

Heid GJ, Von Haam E (1948) Hepatic heterotopy in the splenic capsule. Arch Pathol (Chic) 46:377–379

Honoré LH (1985) Intra-adrenal hepatic heterotopia. J Urol 133:652–654

Horiuchi S, Kitamura T, Okuda S, Tateishi R, Wada A, Omori K (1969) A case of hepatoma residing in the retroperitoneum separate from the liver. Acta Hepatol Jpn 10:259–262

Huang TW, Chan DC, Lee HS, Yao NS, Lee SC, Cheng YL (2007) Ectopic hepatocellular carcinoma of the diaphragm. Dig Dis Sci 52:1118–1120

Huang HJ, Yao LQ, Qu LJ, Yu YH, Zheng ZY (2011) A giant ectopic liver in right mediastinum: a case report (in Chinese). Zhonghua Gan Zang Bing Za Zhi 19:384–385

Hudson TR, Brown HN (1962) Ectopic (supradiaphragmatic) liver. J Thorac Cardiovasc Surg 43:552–555

Hundal RS, Ali J, Korsten MA, Khan AM (2006) Torsion and infarction of an accessory liver lobe. Z Gastroenterol 44:1223–1226

Iber T, Rintala R (1999) Intrapulmonary ectopic liver. J Pediatr Surg 34:1425–1426

Ito F, Ando H, Watanabe Y, Seo T, Murahashi O, Harada T, Kaneko K, Ishiguro Y (1999) An accessory lobe of the liver disturbing closure of the umbilical ring. Pediatr Surg Int 15:394–396

Jacquemet M (1896) Considérations sur les anomalies du foie et des voies biliaires (considerations on anomalies of the liver and the biliary tract). Thesis, Lyon

Jambhekar K, Pandey T, Kaushik C, Shah HR (2010) Intermittent torsion of accessory hepatic lobe: an unusual cause of recurrent right upper quadrant pain. Indian J Radiol Imaging 20:135–137

Jimenez AR, Hayward RH (1971) A cause of esophageal obstruction. Ann Thorac Surg 12:300–304

Johnstone G (1965) Accessory lobe of liver presenting through a congenital deficiency of anterior abdominal wall. Arch Dis Child 40:541–544

Kamath GS, Borkar S, Chauhan A, Chidanand B, Kashyap N, Warrier R (2010) A rare case of congenital diaphragmatic hernia with ectopic liver and absent pericardium. Ann Thorac Surg 89:e36–e37

Kanzaki R, Yamada T, Gotoh K, Takahashi H, Ohigashi H, Ishikawa O (2010) Ectopic hepatocellular carcinoma arising in the left triangular ligament of the liver. Case Rep Gastroenterol 4:138–143

Karaman K, Teke Z, Ercan M, Keklik TT, Bostanci EB, Akoglu M (2012) Ectopic liver (choristoma) attached to the gallbladder wall. ANZ J Surg 82:948

Kawabata K, Adachi Y, Ito T et al (1996) Occurrence of hepatocellular carcinoma 3 years after resection of a left chest wall tumor which was suspected as ectopic hepatocellular carcinoma (in Japanese). Kan Tan Sui 32:93–98

Kawaguchi Y (2013) Sox9 and programming of liver and pancreatic progenitors. J Clin Invest 123:1881–1886

Kawahara E, Kitamura T, Ueda H, Ogino T, Mai M, Ooi A, Nakanishi I (1988) Hepatocellular carcinoma arising in the abdominal cavity. An autopsy case of ectopic liver origin. Acta Pathol Jpn 38:1575–1581

Kim KA, Park CM, Kim CH, Choi SY, Park SW, Hong SJ, Seol HY, Cha IH (2003) Hepatocellular carcinoma in an ectopic liver: CT findings. Eur Radiol 13:L45–L47

Kinnunen P, Kulmala P, Kaarteenaho-Wiik R, Vuopala K (1997) Ectopic liver in the human pericardium. Histopathology 30:277–279

Kondo M, Dono K, Sakon M, Nagano H, Hayashi T, Umeshita K et al (2003) Two cases of hepatocellular carcinoma with bile duct invasion, but without a detectable tumor in the liver (in Japanese). Jpn J Gastroenterol Surg 36:482–487

Koplewitz BZ, Manson DE, Ein SH (1999) Posttraumatic torsion of accessory lobe of the liver and the gallbladder. Pediatr Radiol 29:799–802

Kostov DV, Kobakov GL (2011) Accessory hepatic lobe. Surg Radiol Anat 33:819–822

Koumanidou C, Nasi E, Koutrouveli E, Theophanopoulou M, Hilari S, Kakavakis K et al (1998) Torsion of an accessory hepatic lobe in a child: ultrasound, computed tomographic, and magnetic resonance imaging findings. Pediatr Surg Int 13:526–527

Kubota K, Kira J, Rokkaku K, Iwasaki Y, Sawada T, Imura J, Fujimori T (2007) Ectopic hepatocellular carcinoma arising from pancreas: a case report and review of the literature. World J Gastroenterol 13:4270–4273

Kuo YH, Wang JH, Hu TH, Lee CM (2008) Primary hepatocellular carcinoma in ectopic liver and later metastasis to mother liver: a case report and review of the literature. J Intern Med Taiwan 19:422–427

Kuroiwa T, Hirata H, Iwashita A, Yasumori K, Mogami H, Teraoka H (1984) Accessory hepatic lobe simulating a left hemodiaphragmatic tumor: a case report. Nippon Igaku Hoshasen Gakkai Zasshi 44:1033–1037

Kutner MA, Bromberg A, Korst RJ, Lee BE (2010) An unusual case of dysphagia from intrathoracic liver. Ann Thorac Surg 90:e54–e55

Kyeong HE, Park Y, Park S (2008) Ectopic liver associated with the gallbladder – a brief case report. Korean J Pathol 42:128–130

Ladurner R, Brandacher G, Mark W, Iannetti C, Lottersberger C, Steurer W, Königsrainer A et al (2005) Complete hepatic ischemia due to torsion of a large accessory liver lobe. First case to require transplantation. Transpl Int 18:467–469

Lasser A, Wilson GL (1975) Ectopic liver tissue mass in the thoracic cavity. Cancer 36:1823–1826

Le Bail B, Carles J, Saric J, Balabaud C, Bioulac-Sage P (1999) Ectopic liver and hepatocarcinogenesis. Hepatology 30:585–586

Le Douarin NM (1975) An experimental analysis of liver development. Med Biol 53:427–455

Lemaigre FP (2009) mechanisms of liver development: concepts for understanding liver disorders and design of novel therapies. Gastroenterology 137:62–79

Lemaigre F, Zaret KS (2004) Liver development update: new embryo models, cell lineage control, and morphogenesis. Curr Opin Genet Dev 14:582–590

Leone N, De Paolis P, Carrera M, Carucci P, Musso A, David E, Brunello F, Fronda G, Rizzetto M (2004) Ectopic liver and hepatocarcinogenesis: report of three cases with four years' follow-up. Eur J Gastroenterol Hepatol 16:731–735

Levi MM, Creque LC, Cinque S (1969) Accessory lobe of liver presenting symptoms of pelvic tumor. N Y State J Med 69:1334–1336

Lieberman MK (1966) Cirrhosis in ectopic liver tissue. Arch Pathol 82:443–446

Liu KL, Ho MC, Chen PJ (2007) Ectopic liver with hepatocellular carcinoma in the peritoneum. AJR Am J Roentgenol 188:W206–W207

Lundy J, Johnson E, Edwards K, Rivera D (2005) Laparoscopic management of gallbladder-associated ectopic liver. JSLS 9:485–487

Luoma R, Raboei E (2003) Supradiaphragmatic accessory liver: a rare cause of respiratory distress in a neonate. J Pediatr Surg 38:1413–1414

Makino T, Nakamori S, Kashiwaszaki M, Masuda N, Ikenaga M, Hirao M, Fujitani K, Mishima H et al (2006) An icteric type hepatocellular carcinoma with no detectable tumor in the liver: report of a case. Surg Today 36:633–637

Marchegiani G, Gareer H, Parisi A, Capelli P, Bassi C, Salvia R (2013) Pancreatic hepatoid carcinoma: a review of the literature. Dig Surg 30:425–433

Massaro M, Valencia MP, Guzman M, Mejia J (2007) Accessory hepatic lobe mimicking an intraabdominal tumor. J Comput Assist Tomogr 31:572–573

Matsunaga S, Mitsumoto Y, Seiji S, Kunihiko K, Mugitani T, Akira N, Tanaka T (2003) A case of ectopic hepatocellular carcinoma (in Japanese). Kan Tan Sui 47:907–913

Matsuyama M, Sugiura S, Kakita A, Sato Y, Kuroda M (2010) Hepatocellular carcinoma arising from ectopic liver tissue in the spleen producing insulin-like growth factor II. Pathol Res Pract 207:124–126

Mehta RI, Lai CK, Kee S, Fishbein MC (2010) Intrapulmonary ectopic liver after orthotopic heart transplantation. Arch Pathol Lab Med 134:1060–1062

Miyake T, Hoshino S, Yoshida Y, Aisu N, Tanimura S, Hisano S, Kuno N, Sohda T et al (2012) Multiple ectopic hepatocellular carcinomas arising in the abdominal cavity. Case Rep Gastroenterol 6:629–634

Moriwaki Y, Higashino K, Taktea K, Hada T, Tamura S, Yamaguchi K (1987) Immunohistochemical and affinity electrophoretic studies of alpha-fetoprotein of a patient with hepatocellular carcinoma in the intrathoracic space. Am J Gastroenterol 82:1207–1211

Morris MW, Helling TS, Creswell LL, Jordan B, Mitchell ME (2012) Ectopic liver masquerading as a floating intracaval mass. J Vasc Surg 55:1759–1761

Nagar S, Koffron A, Raofi V (2011) A case of hemorrhagic necrosis of ectopic liver tissue within the gallbladder wall. HPB Surg 2011:389381

Nakamura N, Irie T, Tanaka S, Arii S (2013) A case ectopic hepatocellular carcinoma with peritoneal dissemination. Nihon Shokakibyo Gakkai Zasshi 110:1968–1975

Narita R, Oto T, Mimura Y, Ono M, Abe S, Tabaru A, Yoshikawa I, Tanimoto A, Otsuki M (2002) Biliary obstruction caused by intrabiliary transplantation from hepatocellular carcinoma. J Gastroenterol 37:55–58

Natori T, Hawkin S, Aizawa M, Asai T, Kameda Y, Ikuyohashi K (1986) Intra-cholecystic ectopic liver. Acta Pathol Jpn 36:1213–1216

Negru D, Tudorache C, Marinescu M, Grigora M, Crumpei F, Georgescu S (2007) Torsion and infarction of an accessory liver lobe (in Romanian). Rev Med Chir Soc Med Nat Iasi 111:442–445

Nenekidis I, Anagnostakou V, Paralikas I, Kokkori A, Dedeilias P, Zisis C (2011) Ectopic hepatocellular carcinomas developed in the chest wall and skull. Asian Cardiovasc Thorac Ann 19:360–362

Newland JR, Markin RS, Wilson RB, Jones JW (1989) Heterotopic liver in the jejunum. Report of a case and a review. J Clin Gastroenterol 11:461–463

Nishikawa K, Watanabe K, Hisamatsu Y, Shirao K (2011) Ectopic hepatocellular carcinoma of the left sub-diaphragm with metastasis. Intern Med 50:1505–1506

Nora E, Carr CE (1946) Umbilical accessory liver. Am J Obstet Gynecol 52:330–335

Oldani A, Garavoglia M (2013) Hepatocellular cancer arising from ectopic liver tissue on diaphragm in association with desmoid mesenteric tumor. J Liver 2:4

Olinde HD, Boggs HW (1958) Infarction of an accessory lobe of the liver. AMA Arch Surg 77:650–651

Orth J (1887) Lehrbuch der speciellen pathologischen Anatomie. Hirschwald, Berlin

Park CM, Cha IH, Chung KB, Suh WH, Lee CH, Choi SY, Chae YS (1991) Hepatocellular carcinoma in extrahepatic bile ducts. Acta Radiol 32:34–36

Peng SY, Wang JW, Liu YB, Cai XJ, Deng DL, Xu B et al (2004) Surgical intervention for obstructive jaundice due to biliary tumor thrombus in hepatocellular carcinoma. World J Surg 28:43–46

Pereira RM, Simoes e Silva AC, Leite VH, Lanna JC, Guimaraes JT (2005) Successful management of concomitant omphalocele, accessory hepatic lobe, and biliary atresia in a 44-day-old boy. J Pediatr Surg 40: e21–e24

Pérez-Martinez A, Conde-Cortés J, Martinez-Bermejo MA, Bento-Bravo L (2006) Torsion of a pedunculated accessory hepatic lobe: differential diagnosis of projectile vomiting in a neonate. J Perinat Med 34:248–249

Pesce C, Colacino R, Tobia F (1984) Heterotopic liver tissue with micronodular cirrhosis. A case report. Ann Pathol 4:389–390

Peter H, Strohm WD (1980) Contortion of an accessory lobe of the liver causing acute abdominal distress (in German). Leber Magen Darm 10:203–206

Preminger A, Udassin R, Pappo O, Arad I (2001) Ectopic liver tissue within the umbilical cord. J Pediatr Surg 36:1085–1086

Pujari BD, Deodhare SG (1976) Symptomatic accessory lobe of liver with a review of the literature. Postgrad Med J 52:234–236

Ribbert H (1914) Geschwulstlehre. Cohen, Bonn

Rodriguez-Perez D (1955) Accessory intrapleural ectopic liver lobe. Bol Asoc Med PR 47:353–356

Rozen E, Stephens G, Asarian A, Xiao P (2011) Ectopic hepatic tissue presented as a posterior mediastinal mass. Int Sch Res Netw (ISRN) Gastroenterol 2011: ID 120690

Sakarya A, Erhan Y, Aydede H, Kara E, Ilkgül O, Ciftdogan C (2002) Ectopic liver (choristoma) associated with the gallbladder encountered during laparoscopic cholecystectomy: a case report. Surg Endosc 16:1106

Sanguesa C, Esteban MJ, Gomez J, Cotina H (1995) Liver accessory lobe torsion in the infant. Pedaitr Radiol 25:153–154

Sarda A (2005) Isolated primary extrahepatic hepatocellular carcinoma. Indian J Surg 67:335–336

Sasaki K, Konishi F (1995) Ectopic liver and ectopic hepatocellular carcinoma (in Japanese). Ryoikibetsu Shokogun Shirizu 7:282–284

Schmelzle M, Matthaei H, Lehwald N, Raffel A, Tustas RY, Pomjanski N, Reinecke P et al (2009) Extrahepatic intraductal ectopic hepatocellular carcinoma: bile duct filling defect. Hepatobiliary Pancreat Dis Int 8:650–652

Schnyder P (1926) Lebergewebe in der Milz einer Frühgeburt. Zbl Path 37:49

Sehdeva JS, Logan WD (1971) Heterotopic (supradiaphragmatic) liver. Ann Thorac Surg 11:468–471

Sekine K, Takebe T, Suzuki Y, Kamiya A, Nakauchi H, Taniguchi H (2012) Highly efficient generation of definitive endoderm lineage from human induced pluripotent stem cells. Transplant Proc 44:1127–1129

Seo UH, Lee HJ, Ryu WS, Kwak JM, Shin BK, Kim WB, Lee SI, Park SS, Choi JW et al (2008) Laparoscopic resection of a hepatocellular carcinoma arising from an ectopic liver. Surg Laparosc Endosc Percutan Tech 18:508–510

Shah KD, Beck AR, Jhaveri MK, Keohane M, Weinberg B, Gerber MA (1987) Infantile hemangioendothelioma of heterotopic intrathoracic liver associated with diaphragmatic hernia. Hum Pathol 18:754–756

Shapiro JL, Metlay LA (1991) Heterotopic supradiaphragmatic liver formation in association with congenital cardiac anomalies. Arch Pathol Lab Med 115:238–240

Shigemori M, Kondo M, Azechi H, Inoue F, Tamura J, Kobayashi H, Saiga T (2006) A case of ectopic hepatocellular carcinoma in the jejunum. J Gastroenterol 41:913–918

Shin D, Monga SP (2013) Cellular and molecular basis of liver development. Compr Physiol 3:799–815

Singh V, Sinha RJ, Sankhwar SN, Kumar S, Mehrotra B, Puri M, Sengottayan VK (2010) Primary hepatocellular carcinoma in ectopic liver masquerading as left adrenal carcinoma: a rare occurrence. Rare Tumors 2:e35

Si-Tayeb K, Lemaigre FP, Duncan SA (2010) Organogenesis and development of the liver. Dev Cell 18:175–189

Stattaus J, Kühl H, Forsting M (2008) Diagnosis of an accessory liver lobe established by magnetic resonance imaging-guided core biopsy. Z Gastroenterol 46:351–354

Svane S, Knudtzon J (1991) Ectopic liver in the gallbladder and cholestasis (in Norwegian). Tiddkr Nor Laegforen 111:2643–2644

Takayasu K, Itabashi M, Moriyama N (1994) Case report: ectopic hepatocellular carcinoma arising from the left diaphragm. Clin Radiol 49:579–581

Tamura S, Yanaginuma N, Fujiwara K et al (1985) A case of ectopic liver cancer – hepatocellular carcinoma that developed in the gallbladder. Jpn J Gastroenterol 82:2448

Tan KL, Tan AY (1971) Accessory lobe of the liver in an exomphalos with biliary cirrhosis. J Singpore Paediatr Soc 13:97–100

Tancredi A, Cuttitta A, de Martino DG, Scaramuzzi R (2010) Ectopic hepatic tissue misdiagnosed as a tumor of lung. Updates Surg 62:121–123

Tejada E, Danielson C (1989) Ectopic or heterotopic liver (choristoma) associated with the gallbladder. Arch Pathol Lab Med 113:950–952

Terada T, Nakanuma Y, Kawai K (1989) Small hepatocellular carcinoma presenting as intrabiliary pedunculated polyp and obstructive jaundice. J Clin Gastroenterol 11:578–583

Thomsen GH, Kruse A, Petersen A (1998) Hepatocellular carcinoma presenting as a tumour of the hilar and extrahepatic bile ducts. Eur J Gastroenterol Hepatol 10:803–804

Tomooka Y, Torisu M, Fujimura T, Sakaguchi N, Taira A (1988) Symptomatic accessory lobe of the liver associated with hyperthyroidism. J Pediatr Surg 23:1055–1056

Toonen F, Smilde T (2010) A retroperitoneal mass with elevated alpha-1-fetoprotein: not always a testicular carcinoma. Neth J Med 68:33–34

Torchio B, Maconi G (1978) Nodule of ectopic hepatic parenchyma in the wall of the gallbladder (in Italian). Minerva Chir 33:39–44

Tremblay KD, Zaret KS (2005) Distinct populations of endoderm cells converge to generate the embryonic liver bud and ventral foregut tissues. Dev Biol 280:87–99

Triantafyllidis I, Papapavlou L, Nikoloudis N, Economou A, Andreadis E, Chrissidou M et al (2009) Ectopic liver tissue attached to the gallbladder wall: a case report. Cases J 2:6786

Tsushimi T, Enoki T, Harada E, Orita M, Noshima S, Masuda M, Hamano K (2005) Ectopic hepatocellular carcinoma arising in the bile duct. J Hepatobiliary Pancreat Surg 12:266–268

Umehara M, Sugai M, Kudo D, hakamada K, Sasaki M, Munakata H (2009) Torsion of an accessory lobe of the liver in a child: report of a case. Surg Today 39:80–82

Vykouril L (1989) An uncommon cause of acute abdomen – hemorrhage into an accessory hepatic lobe. Rozhl Chir 68:253–257

Walzel P, Gold E (1925) Zur Anatomie der sog. Nebenleber (Hepar succenturiatum). Arch Klin Chir 135:1388

Wandzioch E, Zaret KS (2009) Dynamic signaling network for the specification of embryonic pancreas and liver progenitors. Science 324:1707–1710

Wang Y, Junlin L, Zhang WG, Chen JH, He Y, Chen JM (2010) Accessory lobe of right liver mimicking a pulmonary tumor in an adult male. Ann Thorac Surg 89: e9–e10

Wang C, Cheng L, Zhang Z, Xie T, Ding H, Deng Q, Yuan Z (2012) Accessory lobes of the liver: a report of 3 cases and review of the literature. Intract Rare Dis Res 1:86–91

Watanabe M, Matsura T, Takatori Y, Ueki K, Kobatake T, Hidaka M, Hirakawa H, Fukumoto S, Shimada Y (1989) Five cases of ectopic liver and a case of accessory lobe of the liver. Endoscopy 21:39–42

Watson JR, Lee RE (1964) Accessory lobe of the liver with infarction. Arch Surg 88:490–493

Xu CR, Zaret KS (2012) Chromatin "pre-pattern" and epigenetic modulation in the cell fate choice of liver over pancreas in the endoderm. Nucleus 3:150–154

Yasui O, Sato T, Andoh H, Kurokawa T, Watanabe D, Sageshima M, Nanjo H (2004) A resected case of a small hepatocellular carcinoma developing within the bile duct. J Hepatobiliary Pancreat Surg 11:193–196

Yigit T, Yigitler C, Demiriz M, Arslan I, Tufan T (2007) Hepatocellular carcinoma in the common bile duct "Hepatocellular Carcinoma". Liver Int 27:288–290

Yin C, Evason KJ, Asahina K, Stainier DYR (2013) Hepatic stellate cells in liver development, regeneration, and cancer. J Clin Invest 123:1902–1910

Yoshino I, Yamaguchi T, Kameyama T, Takuro K, Osoegawa A, Yohena T, Koga M et al (2006) Extension of liver tissue into the thorax following a right extrapleural pneumonectomy for malignant pleural mesothelioma. Ann Thorac Cardiovasc Surg 12:355–357

Zaret KS (2002) Regulatory phases of early liver development: paradigms of organogenesis. Nat Rev Genet 3:499–512

Zaret KS (2008) Genetic programming of liver and pancreas progenitors: lessons for stem-cell differentiation. Nat Rev Genet 9:329–340

Zlatkovic M, Duricic S, Plamenac P (1998) Congenital hepatic fibrosis of heterotopic hepatic tissue. Pathol Res Pract 194:523–526

Zonca P, Martinek L, Ihnat P, Fleege J (2013) Ectopic liver: different manifestations, one solution. World J Gastroenterol 19:6485–6489

Pediatric Hepatocellular Carcinoma

16

ICD-O code 8170/3

Contents

Abstract

Pediatric hepatocellular carcinoma (P-HCC) is a malignancy that resembles in many respects adult-type HCC. P-HCC is a highly invasive and aggressive neoplasm with a tendency for early metastatic spread. The tumor frequently develops in the setting of hepatitis B virus infection but also occurs in association with congenital hepatobiliary tract disorders and inborn errors of metabolism. Epidemiologically, P-HCC is rarer than hepatoblastoma. Only about 0.5 % of all pediatric malignancies are P-HCC. The tumor mainly occurs in an age group that is older than that of hepatoblastomas but also develops in infants and small children. The histological presentation of P-HCC appears to be the same as that in adult-type HCC, but future molecular studies will show whether P-HCC and adult-type HCC are in fact the same or different diseases.

Introduction

As in adult patients, hepatocellular of children (P-HCC) is a malignant neoplasm characterized by a proliferation of hepatocyte-like cells. P-HCC is a highly invasive and aggressive neoplasm with a tendency to produce early metastatic disease. Mainly in endemic areas, there is an important etiologic role played by HBV infection. In part of patients, P-HCC develops in the setting of

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_16

congenital disorders and inborn errors of metabolism.

Epidemiology

Overall, P-HCC is an epithelial malignancy that is rarer than hepatoblastoma (Reynolds 2001; Zaman et al. 2011; McAteer et al. 2013; Tanaka et al. 2013; Zhang et al. 2013). It is estimated that about 05 % of all pediatric malignancies are P-HCC, with an incidence of 0.5–1.0 cases per million (Czauderna et al. 2002; Emre and Mckenna 2004; Allan et al. 2014). This has been uncovered in several studies. Among 42 malignant hepatic tumors in children collected from the West Midlands Regional Children's Tumour Registry, UK, 27 were hepatoblastomas and only 3 were HCC, HCC being even rarer in this collection than rhabdomyosarcoma (Mann et al. 1990). However, the incidence of P-HCC is higher in areas with a high and very high endemicity of HBV infection, such as sub-Saharan Africa. Most P-HCCs occur in children that are older than the typical hepatoblastoma age group, i.e., older than 5 years (Chan et al. 2002). Typically, P-HCC manifests between 10 and 14 years, with a median age at diagnosis of 12 years in one study (Bellani and Massimo 1993). There are, however, marked differences in age distribution in different countries, in part due to the frequency and mode of HBV infection (Lee and Ko 1998). In a study of 73 P-HCC and 54 hepatoblastomas, mean age at presentation was 10.6 years for P-HCC versus 2.5 years for hepatoblastomas (Chen et al. 2005). However, P-HCC is also diagnosed in infants and even neonates (Sawyer 1950; Benson 1958; Koch and Bradford 1959; Dalal and Buhariwala 1966; Kumar and Singh 1966; Rao et al. 1967). In cases associated with HBV infection, P-HCC is more often diagnosed in males, whereas P-HCC is associated with congenital disorders and inborn errors of metabolism; the female-to-male occurrence ratio is equal. P-HCC is known to develop in congenital abnormalities and inborn errors of metabolism, part of which are known to result in chronic liver disease and even liver cirrhosis. Most P-HCCs, however, develop as seemingly de novo neoplasms and are apparently not related to preexisting liver disease, in contrast to HCC in adults (Czauderna 2002).

Single cases or small series of HCC have been reported in the last century. In early publications, where sometimes terms such "hepatoma" have been employed, it is in part difficult to judge, specifically in the absence of histology figures, whether we deal with bona fide HCC or with hepatoblastoma. As discussed in more detail in the respective chapter, these two entities were formerly regarded as one, hepatoblastoma being defined at a later time point. In fact, it was Willlis (1960, 1962) who demonstrated that primary malignant epithelial neoplasms of the pediatric liver are to be divided into two groups, hepatoblastoma and HCC. Before these publications, this distinction was not performed, but got acceptance in studies dating from the last fourth of the last century.

Selected References Griffith 1918; Kilfoy and Terry 1929; Hamburger 1938; Steiner 1938; Drummond and Tollman 1939; Packard and Stevenson 1944; Rosenblatt and May 1946; Beynon 1948; Brolen 1950; Sawyer 1950; O'Sullivan 1951; Stone 1952; Bigelow and Wright 1953; Packard and Palmer 1955; Roth and Duncan 1955; Edmondson 1956; McDougal and Gatzimos 1957; Knox et al. 1958; Koch and Bradford 1959; Silen et al. 1959; Shorter et al. 1960; Abdine and Mokhtar 1961; McWilliam 1961; Alcalde et al. 1962; Hünderwadel 1962; King 1963; Chandler and Walters 1964; Kandoth and Modi 1964; Bradham et al. 1965; Nixon 1965; Dalal and Buhariwara 1966; Fish and McCary 1966; Kumar and Singh 1966; Misugi et al. 1967; Rao et al. 1967; Fraumeni et al. 1968; Kasai and Watanabe 1970; Schiodt 1970; Exelby et al. 1971; Keeling 1971; Pollice 1973; Clatworthy et al. 1974; Ishak 1976; Watanabe 1977; Ettinger and Freeman 1979;

Lack et al.1983; Weinberg and Finegold 1983; Bellani and Massimino 1993; Douglass 1997; Chen et al. 1998.

Clinical and Imaging Features

As in adult patients, there are no characteristic signs and symptoms. Frequent findings include tender or non-tender hepatomegaly, dull abdominal pain or discomfort, weakness, anorexia and weight loss, gastric upsets, and diarrhea or constipation (Czauderna 2002). The duration of symptoms is often short, less than 1 month (Ishak and Glunz 1967). Jaundice and ascites are uncommon. In a minority of patients, the tumor disease is manifest as acute abdomen due to tumor rupture and intra-abdominal hemorrhage. In patients with P-HCC, hepatomegaly is probably the most common finding at the time point of diagnosis. In patients with underlying metabolic diseases, the clinical history may often be dominated by the sequelae of these disorders, sometimes hiding the presentations of HCC. Approximately 60–80 % of patients show significantly elevated serum AFP concentrations. Part of patients present at the time of diagnosis with metastatic disease, with locoregional lymph node metastases and distant metastases, most frequently to lungs and bones. In P-HCC with underlying liver cirrhosis, preexisting liver disease may dominate the clinical presentation, e.g., upper gastrointestinal bleeding due to esophageal varices (Jennuvat and Vithayyasai 2011).

By the use of ultrasonography, CT, and MR, P-HCC presents with an imaging pattern that is, in principle, similar to that of the adult counterparts (Margulis et al. 1956; Kaude et al. 1980; Isdale et al. 1982; Miller and Greenspan 1985; de Campo and de Campo 1988; Foulner and Cremin 1991; Das et al. 2009). Modern ultrasound techniques can provide valuable information on tumor extent and resectability (de Campo and de Campo 1988). In a subset of P-HCC, calcified foci are detectable, similar to other primary liver tumors (Kattan et al. 1959).

Is Pediatric HCC Different from Adult-Type HCC, or Is It the Same Disease?

As many types of malignant neoplasms developing in the pediatric age group reveal a biology that is different from that of the adult counterpart, it has been questioned whether P-HCC is a tumor that is different from adult-type HCC. So far, no difference in the macroscopy and histopathologic features have been detected, most P-HCC showing a histology characterized by a trabecular or acinar phenotype of HCC (Ishak and Glunz 1967; Schiodt 1970). Some HCC subtypes regularly found in adults are uncommon in children, such as clear cell HCC and sclerosing HCC, whereas fibrolamellar HCC is more often found in young individuals and older children. Also the aggressive biology typical for adult HCC is reflected in P-HCC, still with a poor overall outcome, and in some studies even worse than in adults (Chen et al. 1998; Czauderna 2002). In a recent investigation, a distinct immunohistochemical pattern distinguished P-HCC from adult-type tumors. All cases of P-HCC were diffusely positive for epithelial cell adhesion molecule (EpCAM), and EpCAM was also positive in fibrolamellar carcinoma and hepatoblastomas, while adult-type HCC EpCAM was only focally expressed in 15 % of cases (Zen et al. 2014). Future cytogenetic and molecular studies may identify novel signatures that serve to distinguish P-HCC from adult HCC. For example, cyclinD1 expression was significantly lower in P-HCC than in adult HCC, and LOH frequency on 13q was relatively higher in P-HCC than adult HCC (Kim et al. 2000).

Pathology

Macroscopy

The macroscopic presentation of P-HCC is the same as or similar to that in adult HCC, with three major growth patterns, i.e., expanding, invasive, or pedunculated tumors, and either with

solitary or multiple masses. In one study, multiple nodules of P-HCC were observed in half of patients (Ishak and Glunz 1967).

Histopathology

The histopathologic presentation of P-HCC corresponds to that of adult HCC in most cases (Ishak and Glunz 1967; Ito and Johnson 1969; Weinberg and Finegold 1983; Geramizadeh et al. 2010; Figs. 1, 2, and 3).

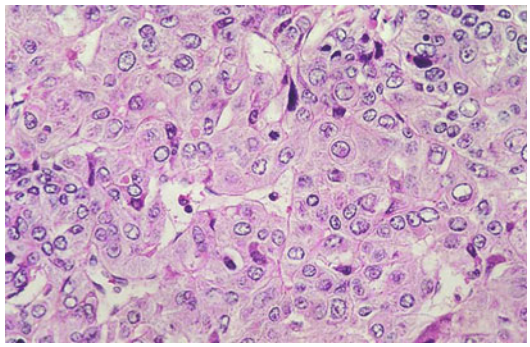

Fig. 1 Well-differentiated pediatric hepatocellular carcinoma (G1). Trabeculae of large hepatocyte-like cells are separated by sinusoidal vascular channels (hematoxylin and eosin stain)

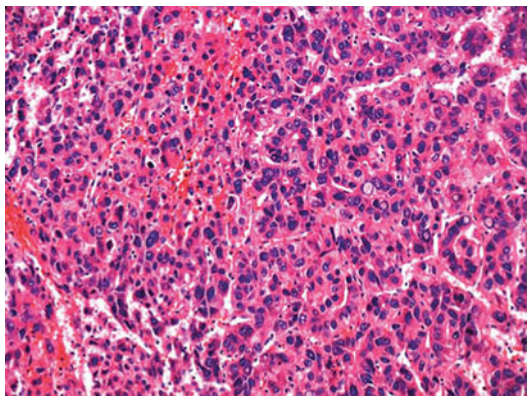

Fig. 2 Pediatric hepatocellular carcinoma, grade 3. Trabeculae are in evidence, but tumor cell nuclei are enlarged, with an increased nucleus-to-cytoplasm ratio (hematoxylin and eosin stain)

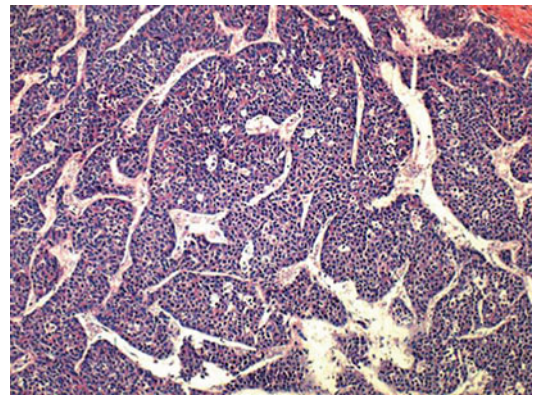

Fig. 3 Pediatric hepatocellular carcinoma, grade 4. This hypercellular "blue" tumor exhibits a solid to trabecular growth pattern, but the sinusoidal vascular pattern is replaced by a vascularized stroma (hematoxylin and eosin stain)

Most tumors show a trabecular pattern, with up to 20 layers of cells in each cell plate. These trabeculae are separated from each other by sinusoid-like vascular channels lined by endothelial cells. Again similar to adult HCC, pleomorphic and multinucleated giant tumor cells occur. Mixed HCC-cholangiocarcinoma may occur, but is very uncommon lesion (Ishak and Glunz 1967). Vascular invasion is usually a prominent feature. Focal calcification can occur (Kattan et al. 1959), probably following necrosis (dystrophic calcification). There is evidence that P-HCC developing in tyrosinemia differs in its histology from HCCs occurring in other etiologic contexts. P-HCC in patients with tyrosinemia 1 exhibit clear cell changes, a solid architecture, and only mild nuclear atypias (Zen et al. 2014).

Immunohistochemistry

Similar to adult-type HCC, P-HCC cells are immunoreactive for hepatocyte markers, glypican-3, cytokeratins 8 and 18, and AFP, the latter only in part of the neoplasms (O'Brien et al. 1989).

Differential Diagnosis

The most important differential diagnoses of P-HCC are certain variants of hepatoblastoma (mainly the macrotrabecular subtype) and transitional liver cell tumor.

Staging

For P-HHC, the PreText staging system mainly developed for hepatoblastomas is now employed in most clinical investigations (see ▶ Chap. 19, "Hepatoblastoma and the Hepatoblastoma Family of Tumors").

Biology of Disease

Already in early reports, it is stated that P-HCC is an aggressive neoplasm with a consistently unfavorable outcome, especially among children older than 4 years and in girls (Exelby et al. 1975; Haas et al. 1989), and this has been confirmed in recent investigations (Pham et al. 2007; McAteer et al. 2013; Zhang et al. 2013), in strong contrast to hepatoblastoma, where modern treatment strategies have brought about a favorable outcome in a large proportion of patients (Czauderna et al. 2002). However, recent treatment strategies start to bring about a change to the better, however, in strong dependence to the stage at the beginning of therapy (Perilongo et al. 1987). Patients with initially resectable HCC have a better prognosis, with an event-free survival for patients with stage I disease being as high as 88 % (Katzenstein et al. 2002). In contrast, outcome was uniformly poor for children with advanced-stage disease, unfortunately still a frequent situation, and due to this stage effect, overall survival for most reported series is still poor, being less than 30 %. Among 40 children with P-HCC, metastases were identified in 31 % and extrahepatic tumor extension, vascular invasion, or both in 39 %, illustrating the advanced disease at diagnosis (Czauderna et al. 2002). In this analysis, partial response to therapy was observed in 18 (49 %) of 37 patients, in only 36 % was complete tumor resection achieved, and overall survival at 5 years was 28 %. There is evidence that liver transplantation in selected patients is a good therapeutic modality for children with HCC (Esquivel et al. 1994; Arikan et al. 2006; Beaunoyer et al. 2007).

Etiology and the Role of Preexisting Liver Disease

Similar to adult-type HCC, numerous etiologic factors or risk factors for P-HCC have been identified (Table 1). Chronic HBV infection plays a significant role as an etiologic factor for P-HCC, mainly in east-southeast Asia and Africa

Table 1 Conditions associated with increased risk of pediatric HCC

Hepatitis B virus infection
Hepatitis C virus infection
Other forms of hepatitis
Infantile giant-cell hepatitis
Congenital abnormalities of the bile duct system
Biliary atresia
Choledochal cyst
Cholestatic disorders
Progressive familial intrahepatic cholestasis (PFIC)
Alagille syndrome
Aagenaes syndrome
Familial adenomatous polyposis
Inborn errors of metabolism
Tyrosinemia
Alpha-1-antitrypsin deficiency
Citrin deficiency (AGC2)
Transaldolase deficiency
Neonatal iron storage disease
Glycogenoses
Niemann-Pick disease
Wilson's disease
Fanconi anemia
Acute intermittent porphyria
Deoxyguanosine kinase deficiency
Mitochondriopathies (MPV17 deficiency)
Other congenital disorders
Neurofibromatosis

(De Potter et al. 1987; Leuscher et al. 1988; Chang et al. 1991; Cheah et al. 1990, 1991; Giacchino et al. 1991; Pontisso et al. 1992; Moore et al. 1997a; Hadley et al. 2004; Ni et al. 2004; Chen et al. 2005). In fact, HBV infection is the main cause of P-HCC in regions hyperendemic for HBV infection (review: Chang 1998). A study from Taiwan has demonstrated that P-HCC developed exclusively in HBV surface antigen carriers and that low positivity rates of serum HBeAg and liver hepatitis B core antigen coupled with a high frequency of liver cirrhosis indicate that an early HBeAg seroconversion to anti-HBe may play an important role in the rapid development of P-HCC (Hsu et al. 1987). A hotspot mutation in the pre-S2 region of HBV may represent a risk factor and prognosticator for P-HCC (Abe et al. 2009). In a Taiwanese series of P-HCC related to HBV infection, pre-S deletion was an independent risk factor for P-HCC and was found in nearly half of the children with HCC, suggesting a causal link between pre-S2 deletion and hepatic carcinogenesis (Huang et al. 2010). HCC can also develop following hepatitis virus infection in pregnancy (Shapiro 1960) or in the perinatal period. In Taiwan, transmission of HBV from the mothers during the perinatal period or early infancy was the most important mode of HBV transmission in P-HCC children (Chang et al. 1989). In an investigation analyzing the development of HCC among 426 prospectively followed Taiwanese children with chronic HBV infection, two boys developed HCC during 6250 person-years, with an incidence of 32 per 100,000 persons (Wen et al. 2004). The significance of HBV infection is underlined by studies showing that the incidence of P-HCC decreases in children following large-scale hepatitis B vaccination (Lee et al. 2003; Hsiao et al. 2009; Tajiiri et al. 2011).

In addition to virus-induced hepatitis, other forms of pediatric hepatitis are associated with HCC, including neonatal hepatitis (Moore et al. 1997b) and giant-cell hepatitis of infancy (Roth and Duncan 1955; Fajers et al. 1960). An increasing group of hepatic inflammatory disorders occurring in the pediatric age group is nonalcoholic fatty liver disease (NAFL)/nonalcoholic steatohepatitis (NASH; Berardis and Sokal 2014). Similar to adult patients, pediatric NAFL/NASH can elicit chronic fibrosing liver disease and cirrhosis (Bozic et al. 2013; Giorgio et al. 2013), whereby oxidative stress is an important component of the pathophysiology of this process, in part counteracted by paraoxonase 1 and catalase (Desai et al. 2014). One might anticipate that in the setting of a worldwide increase of pediatric NAFL/NASH, P-HCC developing in this liver disease will occur. P-HCC has been observed following long-standing total parenteral nutrition (Zen et al. 2014), a condition that can induce NAFL/NASH-like changes in the liver.

Congenital abnormalities of the bile duct system and chronic cholestatic disorders are known to be risk factors for P-HCC, such as biliary atresia (Okuyama 1965; Deoras and Dicus 1968; Iida et al. 2009; Hadzic et al. 2011; Romano et al. 2011), Alagille syndrome (Kaufman et al. 1987; Rabinovitz et al. 1989; Békassy et al. 1992; Bhadri et al. 2005), choledochal cyst (Romano et al. 2011), progressive familial intrahepatic cholestasis/PFIC (Dahms 1979; Ugarte and Gonzalez-Crussi 1981), and Aagenaes syndrome (Ladekarl et al. 2013). In Alagille syndrome, nodular hepatocyte hyperplasia can occur (Tajima et al. 2001), and such nodular can develop in association with P-HCC (Wetli et al. 2010). In chronic progressive familial intrahepatic cholestasis caused by mutations of the bile salt pumps, ATP8B1, encoding FIC1 (PFIC1), and ABCB11, encoding bile salt export pump/BESP (PFIC2), P-HCC is a known complication, around 15 % of patients developing HCC or cholangiocarcinoma (Knisely et al. 2006; Vilarinho et al. 2014). P-HCC is more prevent in the PFIC2 variant (Davit-Spraul et al. 2010).

Several other inborn errors of metabolism are known to be associated with P-HCC, including hereditary tyrosinemia type 1 (Weinberg et al. 1976; Fisch et al. 1978; Russo and O'Regan 1990; Tazawa et al. 1990; Arikan et al. 2006; Castilloux et al. 2007; Romano et al. 2011; review: Erez et al. 2011), glycogenoses (Franco et al. 2005; Romano et al. 2011; Mikuriya et al. 2012), alpha-1-antitrypsin deficiency (Hadzic et al. 2006; Topic et al. 2012),

transaldolase deficiency (Leduc et al. 2014), Niemann-Pick disease (Pennington et al. 1996; Birch et al. 2003), Fanconi anemia (Abbondanzo et al. 1986; Masserot-Lureau et al. 2012), and Wilson's disease (Savas et al. 2006). Tyrosinemia type 1 is an important model to study the effects of an inborn error of metabolism on carcinogenic pathways. Patients with hereditary tyrosinemia type 1 show early nodular regenerative reactions in the liver (Day et al. 1987), liver cell dysplasia (Manowski et al. 1990), and DNA damage caused by the accumulation of abnormal metabolites (Gilbert-Barness et al. 1990) and have impaired DNA repair and genomic stability (van Dyk and Pretorius 2012). Transaldolase deficiency is caused by a defect in the enzyme TALDO1. Children with this deficiency show abnormal metabolites of the pentose phosphate pathway (ribitol, D-arabitol, erythritol, sedoheptitol, sedoheptulose-7P) and liver cirrhosis (Verhoeven et al. 2001; Perl 2007; Qian et al. 2008; Wamelink et al. 2008; Tylki-Szymanska et al. 2009; Leduc et al. 2014) and can develop early-onset HCC (Leduc et al. 2014). Similar to hepatoblastomas, there is some evidence that the Wnt signaling pathway is involved in etiology and pathogenesis of P-HCC. For example, HCC in children has been found to be associated with familial adenomatous polyposis (Gruner et al. 1998).

Although HCC in children is less frequently associated with liver cirrhosis as in adults, chronic fibrosing liver disease and cirrhosis are known predisposing conditions for P-HCC (Kratkova and Masek 1956; Jones 1960; Bhatia et al. 2014). In chronic fibrosing liver disease of adult patients, a distinct spectrum of precursor lesions has been defined (see the respective chapter), in particular liver cell dysplasia, and it was expected that a dysplasia-HCC pathway might also be present in the pediatric age group. In children with liver cirrhosis due to various reasons, liver cell dysplasia was detected in the liver explants in almost half of the cases (Esquivel et al. 1994).

Pathogenetically, less molecular findings are known for P-HCC in comparison with adult-type HCC. In contrast to most adult HCCs, P-HCC have shown somatic mutations in the kinase domain of the c-Met/hepatocyte growth factor receptor gene (Park et al. 1999). p53 was overexpressed in a majority of P-HCC, but this a abnormal p53 expression does not seem to be caused by mutations in the p53 gene (Kennedy et al. 1994).

References

Abbondanzo SL, Manz HJ, Klappenbach RS, Gootenberg JE (1986) Hepatocellular carcinoma in an 11-year-old girl with Fanconi's anemia. Report of a case and review of the literature. Am J Pediatr Hematol Oncol 8:334–337

Abdine FH, Mokhtar NA (1961) Primary tumors of the liver in infancy and childhood. Arch Pathol 72:216–221

Abe K, Thung SN, Wu HC, Tran TT, Le Hoang P, Truong KD, Inui A, Jang JJ, Su IJ (2009) Pere-S2 deletion mutants of hepatitis B virus could have an important role in hepatocarcinogenesis in Asian children. Cancer Sci 100:2249–2254

Alcalde VM, Traisman HS, Baffes T (1962) Primary carcinoma of the liver in infancy and childhood. Am J Dis Child 104:245–251

Allan BJ, Wang B, Davis JS, Parikh PP, Perez EA, Neville HL, Sola JE (2014) A review of 218 pediatric cases of hepatocellular carcinoma. J Pediatr Surg 49:166–171

Arikan C, Kilic M, Nart D, Ozgenc F, Ozkan T, Tokat Y, Yagci RV, Aydogdu S (2006) Hepatocellular carcinoma in children and effect of living-donor liver transplantation on outcome. Pediatr Transplant 10:42–47

Beaunoyer M, Vanatta JM, Ogihara M, Strichartz D, Dahl G, Berquist WE, Castillo RO et al (2007) Outcomes of transplantation in children with primary hepatic malignancy. Pediatr Transplant 11:655–660

Békassy AN, Garwicz S, Wiebe T, Hägerstrand I, Jensen OA (1992) Hepatocellular carcinoma associated with arteriohepatic dysplasia in a 4-year-old girl. Med Pediatr Oncol 20:78–83

Bellani FF, Massimino M (1993) Liver tumors in childhood: epidemiology and clinics. J Surg Oncol Suppl 3:119–121

Benson RP (1958) Primary carcinoma of the liver in infancy: with a case report of a coloured infant. S Afr Med J 32:845–849

Berardis S, Sokal E (2014) Pediatric non-alcoholic fatty liver disease: an increasing public health issue. Eur J Pediatr 173:131–139

Beynon AE (1948) Primary carcinoma of liver in boy aged 15. Lancet 2:528

Bhadri VA, Stormon MO, Arbuckle S, Lam AH, Gaskin KJ, Shun A (2005) Hepatocellular carcinoma in children with Alagille syndrome. J Pediatr Gastroenterol Nutr 41:676–678

Bhatia V, Seth S, Kapoor A, Sibal A (2014) Incidentally detected hepatocellular carcinoma in cirrhotic children. Indian J Pediatr 81:816

Bigelow NH, Wright AW (1953) Primary carcinoma of the liver in infancy and childhood. Cancer 6:170

Birch NC, Radio S, Horslen S (2003) Metastatic hepatocellular carcinoma in a patient with Niemann-Pick disease, type C. J Pediatr Gastroenterol Nutr 37:624–626

Bozic MA, Subbarao G, Molleston JP (2013) Pediatric nonalcoholic fatty liver disease. Nutr Clin Pract 28:448–458

Bradham RR, Paul JR, Thrower WB, Mciver FA (1965) Malignant hepatoma in a child: survival following right hepatectomy, right pneumonectomy, and resection of diaphragmatic and parietal recurrence. Surgery 57:767–773

Brolen S (1950) Primary cancer of the liver in a boy aged two years. Acta Paediatr 39:441–445

Castilloux J, Laberge AM, Martin SR, Lallier M, Marchand V (2007) "Silent" tyrosinemia presenting as hepatocellular carcinoma in a 10-year-old girl. J Pediatr Gastroenterol Nutr 44:375–377

Chan KL, Fan ST, Tam PK, Chiang AK, Chan GC, Ha SY (2002) Paediatric hepatoblastoma and hepatocellular carcinoma: retrospective study. Hong Kong Med J 8:13–17

Chandler EM, Walters WD (1964) Solitary liver tumors in childhood: report of two cases. Ann Surg 160:986–993

Chang MH (1998) Hepatocellular carcinoma in children. Zhonghua Minguo Xiao Er Ke Yi Xue Hui Za Zhi 39:366–370

Chang MH, Chen DS, Hsu HC, Hsu HY, Lee CY (1989) Maternal transmission of hepatitis B virus in childhood hepatocellular carcinoma. Cancer 64:2377–2380

Chang MH, Chen PJ, Chen JY, Lai MY, Hsu HC, Lian DC, Liu YG, Chen DS (1991) Hepatitis B virus integration in hepatitis B virus-related hepatocellular carcinoma in childhood. Hepatology 13:316–320

Cheah PL, Looi LM, Lin HP, Yap SF (1990) Childhood primary hepatocellular carcinoma and hepatitis B virus infection. Cancer 65:174–176

Cheah PL, Looi LM, Lin HP, Yap SF (1991) A case of childhood hepatitis B virus infection related primary hepatocellular carcinoma with short malignant transformation time. Pathology 23:66–68

Chen JC, Chen CC, Chen WJ, Lai HS, Hung WT, Lee PH (1998) Hepatocellular carcinoma in children: clinical review and comparison with adult cases. J Pediatr Surg 33:1350–1354

Chen JC, Chang ML, Lin JN, Lai HS, Chen CC, Chen WJ, Hung WT (2005) Comparison of childhood hepatic malignancies in a hepatitis B hyperendemic area. World J Gastroenterol 11:5289–5294

Clatworthy HW, Schiller M, Grosfeld JL (1974) Primary liver tumors in infancy and childhood. 41 cases variously treated. Arch Surg 109:143–147

Czauderna P (2002) Adult type vs. childhood hepatocellular carcinoma – are they the same or different lesions ? Biology, natural history, prognosis, and treatment. Med Pediatr Oncol 39:519–523

Czauderna P, Mackinlay G, Perilongo G, Brown J, Shafford E, Aronson D, Pritchard J et al (2002) Hepatocellular carcinoma in children: results of the first prospective study of the International Society of Pediatric Oncology group. J Clin Oncol 20:2798–2804

Dahms BB (1979) Hepatoma in familial cholestatic cirrhosis of childhood: its occurrence in twin brothers. Arch Pathol Lab Med 103:30–33

Dalal SJ, Buhariwala RJ (1966) Carcinoma of the liver in infancy: report of a case. Indian Pediatr 3:26–28

Das CJ, Dhingra S, Gupta AK, Iyer V, Agarwala S (2009) Imaging of paediatric liver tumours with pathological correlation. Clin Radiol 64:1015–1025

Davit-Spraul A, Fabre M, Brancherau S, Baussan C, Gonzales E, Stieger B, Bernard O et al (2010) ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. Hepatology 51:1645–1655

Day DL, Letourneau JG, Allan BT, Sharp HL, Ascher N, Dehner LP, Thompson WM (1987) Hepatic regenerating nodules in hereditary tyrosinemia. AJR Am J Roentgenol 149:391–393

de Campo M, de Campo JF (1988) Ultrasound of primary hepatic tumours in childhood. Pediatr Radiol 19:19–24

De Potter CR, Robberecht E, Laureys G, Cuvelier CA (1987) Hepatitis B related childhood hepatocellular carcinoma. Childhood hepatic malignancies. Cancer 60:414–418

Deoras MP, Dicus W (1968) Hepatocarcinoma associated with biliary cirrhosis. A case due to congenital bile duct atresia. Arch Pathol 86:338–341

Desai S, Baker SS, Liu W, Moya DA, Browne RW, Mastrandrea L, Baker RD, Zhu L (2014) Paraoxonase 1 and oxidative stress in paediatric non-alcoholic steatohepatitis. Liver Int 34:110–117

Douglass EC (1997) Hepatic malignancies in childhood and adolescents (hepatoblastoma, hepatocellular carcinoma, and embryonal sarcoma). Cancer Treat Res 92:201–212

Drummond DH, Tollman JP (1939) Primary carcinoma of the liver in a child – case report. Am J Clin Pathol 9:361–366

Edmondson HA (1956) Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. J Dis Child 91:168–186

Emre S, McKenna GJ (2004) Liver tumors in children. Pediatr Transplant 8:632–638

Erez A, Shchelochkov OA, Plon SE, Scaglia F, Lee B (2011) Insights into the pathogenesis and treatment of cancer from inborn errors of metabolism. Am J Hum Genet 88:402–421

Esquivel CO, Gutiérrez C, Cox KL, Garcia-Kennedy R, Berquist W, Concepcion W (1994) Hepatocellular carcinoma and liver cell dysplasia in children with chronic liver disease. J Pediatr Surg 29:1465–1469

Ettinger LJ, Freeman AI (1979) Hepatoma in a child with neurofibromatosis. Am J Dis Child 133:528–531
Exelby PR, E-Domeri A, Huvos AG, Beattie EJ (1971) Primary malignant tumors of the liver in children. J Pediatr Surg 6:272–276
Exelby PR, Filler RM, Grosfeld JL (1975) Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of pediatrics Surgical Section Survey – 1974. J Pediatr Surg 10:329–337
Fajers CM, Falkmer S, Frisell E, Pehrson M (1960) Primary carcinoma of the liver and giant-cell hepatitis in infancy. Acta Paediatr 49:96–110
Fisch RO, McCabe ER, Doeden D, Koep LJ, Kohlhoff JG, Silverman A, Starzl TE (1978) Homotransplantation of the liver in a patient with hepatoma and hereditary tyrosinemia. J Pediatr 93:592–596
Fish JC, McCary RG (1966) Primary cancer of the liver in childhood. Arch Surg 93:355–359
Foulner D, Cremin B (1991) Childhood hepatocellular carcinoma and hepatoblastoma: integrated sonography and dynamic CT. Australas Radiol 35:346–349
Franco LM, Krishnamurty V, Bali D, Weinstein DA, Arn P, Clary B, Boney A, Sullivan J et al (2005) Hepatocellular carcinoma in glycogen storage disease type Ia: a case series. J Inherit Metab Dis 28:153–162
Fraumeni JF, Miller RW, Hill JA (1968) Primary carcinoma of the liver in childhood: an epidemiologic study. J Natl Cancer Inst 40:1087–1099
Geramizadeh B, Bahador A, Foroutan HR, Banani A, Nikeghbalian S, Malek-Hosseini SA (2010) Pathology of pediatric liver tumors, a single center experience from south of Iran. Indian J Pathol Microbiol 53:422–426
Giacchino R, Navone C, Facco F, Giambartolomei G, Pontisso P, Calles F (1991) HBV-DNA-related hepatocellular carcinoma occurring in childhood. Report of three cases. Dig Dis Sci 36:1143–1146
Gilbert-Barness E, Barness LA, Meisner LF (1990) Chromosomal instability in hereditary tyrosinemia type I. Pediatr Pathol 10:243–252
Giorgio V, Prono F, Graziano F, Nobili V (2013) Pediatric non-alcoholic fatty liver disease: old and new concepts on development, progression, metabolic insight and potential treatment targets. BMC Pediatr 13:40
Griffith JPC (1918) Primary carcinoma of the liver in infancy and childhood. Am J Med Sci 155:79–85
Gruner BA, DeNapoli TS, Andrews W, Tomlinson G, Bowman L, Weitman SD (1998) Hepatocellular carcinoma in children associated with Gardner syndrome of familial adenomatous polyposis. J Pediatr Hematol Oncol 20:274–278
Haas JE, Muczynski KA, Krailo M, Ablin A, Land V, Vietti TJ, Hammond GD (1989) Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. Cancer 64:1082–1095
Hadley GP, Govender D, Landers G (2004) Primary tumors of the liver in children: an African perspective. Pediatr Surg Int 20:314–318
Hadzic N, Quaglia A, Mieli-Vergani G (2006) Hepatocellular carcinoma in a 12-year-old child with PiZZ alpha-antitrypsin deficiency. Hepatology 43:194
Hadzic N, Quaglia A, Portmann B, Paramalingam S, Heaton ND, Rela M, Mieli-Vergani G et al (2011) Hepatocellular carcinoma in biliary atresia: King's College Hospital experience. J Pediatr 159:617–622
Hamburger HJ (1938) A calcified primary liver-cell carcinoma in a 5 years old child. Indian J Pediatr 5:98–101
Hsiao CC, Chuang JH, Tiao MM, Sheen JM, Shieh CS (2009) Patterns of hepatoblastoma and hepatocellular carcinoma in children after universal hepatitis B vaccination in Taiwan: a report from a single institution in southern Taiwan. J Pediatr Hematol Oncol 31:91–96
Hsu HC, Wu MZ, Chang MH, Su IJ, Chen DS (1987) Childhood hepatocellular carcinoma develops exclusively in hepatitis B surface antigen carriers in three decades in Taiwan. Report of 51 cases strongly associated with rapid development of liver cirrhosis. J Hepatol 5:260–267
Huang HP, Hsu HY, Chen CL, Ni YH, Wang HY, Tsuei DJ, Chiang CL, Tsai YC et al (2010) Pre-S2 deletions of hepatitis B virus and hepatocellular carcinoma in children. Pediatr Res 67:90–94
Hünerwadel U (1962) Lebertumoren im Kindesalter. Ann Paed 198:44–63
Iida T, Zendajas IR, Kayler LK, Magliocca JK, Kim RD, Hemming AW, Gonzalez-Peralta RP et al (2009) Hepatocellular carcinoma in a 10-month-old biliary atresia child. Pediatr Transplant 13:1048–1049
Isdale JM, Beck WP, Chappell JS (1982) The radiological investigation of hepatocellular carcinoma in children. S Afr Med J 62:688–690
Ishak KG (1976) Primary hepatic tumors in childhood. Prog Liver Dis 5:636–667
Ishak KG, Glunz PR (1967) Hepatoblastoma and hepatocarcinoma in infancy and childhood. Report of 47 cases. Cancer 20:396–422
Ito J, Johnson WW (1969) Hepatoblastoma and hepatoma in infancy and childhood. Light and electron microscopic studies. Arch Pathol 87:259–266
Jennuvat S, Vithayasai N (2011) Hepatocellular carcinoma in children presents with massive upper gastrointestinal bleeding: a case report. J Med Assoc Thai 94(Suppl 3): S222–S225
Jones E (1960) Primary carcinoma of the liver with associated cirrhosis in infants and children. Report of a case. Arch Pathol 70:5–12
Kandoth WK, Modi PJ (1964) Primary carcinoma of the liver in childhood; report of a case with a brief review of the literature. J Postgrad Med 10:31–36
Kasai M, Watanabe I (1970) Histologic classification of liver-cell carcinoma in infancy and childhood and its clinical evaluation. A study of 70 cases collected in Japan. Cancer 25:551–563
Kattan K, Langer L, Sufrun H (1959) Calcified foci in primary hepatic carcinoma in infancy. A case report-an x-ray and pathological study. Israel Med J 18:296–298

Katzenstein HM, Krailo MD, Malogolowkin MH, Ortega JA, Liu-Mares W, Douglass EC et al (2002) Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. J Clin Oncol 20:2789–2797

Kaude JV, Felman AH, Hawkins IF (1980) Ultrasonography in primary hepatic tumors in early childhood. Pediatr Radiol 9:77–83

Kaufman SS, Wood RP, Shaw BW, Markin RS, Gridelli B, Vanderhoof JA (1987) Hepatocarcinoma in a child with the Alagille syndrome. Am J Dis Child 141:698–700

Keeling JW (1971) Liver tumours in infancy and childhood. J Pathol 103:69–85

Kennedy SM, Macgeogh C, Jaffe R, Spurr NK (1994) Overexpression of the oncoprotein p53 in primary hepatic tumors of childhood does not correlate with gene mutations. Hum Pathol 25:438–442

Kilfoy EJ, Terry MC (1929) Primary carcinoma of the liver in childhood. Surg Gynecol Obstet 48:751–756

Kim H, Lee MJ, Kim MR, Chung IP, Kim YM, Lee JY, Jang JJ (2000) Expression of cyclin D1, cyclin E., cdk4 and loss of heterozygosity of 8p, 13q, 17p in hepatocellular carcinoma: comparison study of childhood and adult hepatocellular carcinoma. Liver 20:173–178

King CY (1963) Liver-cell carcinoma in the extremely young. Santo Tomas J Med (Manila) 18:51–59

Knisely AS, Strautnieks SS, Meier Y, Stieger B, Byrne JA, Portmann BC, Bull LN et al (2006) Hepatocellular carcinoma in ten children under five years of age with bile salt export pump deficiency. Hepatology 44:478–486

Knox WG, Zintel H, Begg CF (1958) Partial hepatectomy for primary carcinoma of the liver in childhood. Cancer 11:1044–1048

Koch K, Bradford J (1959) Primary carcinoma of the liver in infancy. AMA J Dis Child 98:86–89

Kratkova E, Masek R (1956) Multinodular liver carcinoma in cirrhosis following infectious hepatitis in a 8 years old boy (in Czech). Cesk Onkol 3:128–136

Kumar R, Singh S (1966) Primary carcinoma of the liver in infancy. Report of a case with review of the literature. Indian J Pediatr 33:107–110

Lack EE, Neave C, Vawter GF (1983) Hepatocellular carcinoma. Review of 32 cases in childhood and adolescence. Cancer 52:1510–1515

Ladekarl M, Villadsen GE, Rudbeck AR, Aaagenaes O, Nielsen JE, Hamilton-Dutoit S et al (2013) Advanced hepatocellular carcinoma in adolescence associated with congenital cholestasis: a case description. Case Rep Oncol 6:98–103

Leduc CA, Crouch EE, Wilson A, Lefkowitch J, Wamelink MM, Jakobs C, Salomons GS et al (2014) Novel association of early onset hepatocellular carcinoma with transaldolase deficiency. JIMD Rep 12:121–127

Lee CL, Ko YC (1998) Survival and distribution pattern of childhood liver cancer in Taiwan. Eur J Cancer 34:2064–2067

Lee CL, Hsieh KS, Ko YC (2003) Trends in the incidence of hepatocellular carcinoma in boys and girls in Taiwan after large-scale hepatitis B vaccination. Cancer Epidemiol Biomarkers Prev 12:57–59

Leuscher I, Harms D, Schmidt D (1988) The association of hepatocellular carcinoma in childhood with hepatitis B virus infection. Cancer 62:2363–2369

Mann JR, Kasthuri N, Raafat F, Pincott JR, Parkes SE, Muir KR, Ingram LC, Cameron AH (1990) Malignant hepatic tumours in children: incidence, clinical features and aetiology. Paediatr Perinat Epidemiol 4:276–289

Manowski Z, Silver MM, Roberts EA, Superina RA, Phillips MJ (1990) Liver cell dysplasia and early liver transplantation in hereditary tyrosinemia. Mod Pathol 3:694–701

Margulis AR, Nice CM, Rigler LG (1956) The Roentgen findings in primary hepatoma in infants and children. Radiology 66:809

Masserot-Lureau C, Adoui N, Degos F, de Bazelaire C, Soulier J, Chevret S, Socié G et al (2012) Incidence of liver abnormalities in Fanconi anemia patients. Am J Hematol 87:547–549

McAteer JP, Goldin AB, Healey PJ, Gow KW (2013) Hepatocellular carcinoma in children: epidemiology and the impact of regional lymphadenectomy on surgical outcomes. J Pediatr Surg 48:2194–2201

McDougal RA, Gatzimos CD (1957) Primary carcinoma of the liver in infants and children. Cancer 10:678–686

McWilliam PKA (1961) Malignant hepatoma in a boy aged 7 years with postoperative survival for over 3 years. Br J Surg 49:14–16

Mikuriya Y, Oshita A, Tashiro H, Amano H, Kobayashi T, Arihiro K, Ohdan H (2012) Hepatocellular carcinoma and focal nodular hyperplasia of the liver in a glycogen storage disease patient. World J Hepatol 4:191–195

Miller JH, Greenspan BS (1985) Integrated imaging of hepatic tumors in childhood. Part I: malignant lesions (primary and metastatic). Radiology 154:83–90

Misugi K, Okajima H, Misugi N, Newton WA (1967) Classification of primary malignant tumors of liver in infancy and childhood. Cancer 20:1760–1771

Moore L, Bourne AJ, Moore DJ, Preston H, Byard RW (1997a) Hepatocellular carcinoma following neonatal hepatitis. Pediatr Pathol Lab Med 17:601–610

Moore SW, Hesseling PB, Wessels G, Schneider JW (1997b) Hepatocellular carcinoma in children. Pediatr Surg Int 12:266–270

Ni YH, Chang MH, Wang KJ, Hsu HY, Chen HL, Kao JH, Yeh SH, Jeng YM et al (2004) Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma. Gastroenterology 127:1733–1738

Nixon HH (1965) Hepatic tumours in childhood and their treatment by major hepatic resection. Arch Dis Child 40:169–172

O'Brien WJ, Finlay JL, Gilbert-Barness EF (1989) Patterns of antigen expression in hepatoblastoma and hepatocellular carcinoma in childhood. Pediatr Hematol Oncol 6:361–365

O'Sullivan WD (1951) Hepatoma in five year old child treated with excision. Am J Surg 82:295
Okuyama K (1965) Primary liver cell carcinoma associated with biliary cirrhosis due to congenital bile duct atresia. J Pediatr 67:89–93
Packard GB, Palmer HD (1955) Primary neoplasms of the liver in infants and children. Ann Surg 142:214–227
Packard GB, Stevenson AW (1944) Hepatoma in infancy and childhood. Surgery 15:292
Park WS, Dong SM, Kim SY, Na EY, Shin MS, Pi JH, Kim BJ, Bae JH, Hong YK et al (1999) Somatic mutations in the kinase domain of the Met/hepatocyte growth factor receptor gene in childhood hepatocellular carcinomas. Cancer Res 59:307–310
Pennington DJ, Sivit CJ, Chandra RS (1996) Hepatocellular carcinoma in a child with Niemann-Pick disease: imaging findings. Pediatr Radiol 26:220–221
Perilongo G, Carli M, Guglielmi M, De Bernardi B, Bellani FF, Paolucci G, Pianca C et al (1987) Therapeutic approach to primary malignant epithelial tumors of the liver in childhood: results of the Italian retrospective study and literature survey. Pediatr Hematol Oncol 4:179–188
Perl A (2007) The pathogenesis of transaldolase deficiency. IUBMB Life 59:365–373
Pham TH, Iqbal CW, Grams JM, Zarrouq AE, Wall JC, Ishitani MB, Nagorney DM et al (2007) Outcomes of primary liver cancer in children: an appraisal of experience. J Pediatr Surg 42:834–839
Pollice L (1973) Primary hepatic tumors in infancy and childhood. Am J Clin Pathol 60:512–521
Pontisso P, Morsica G, Ruvoletto MG, Barzon M, Perilongo G, Basso G, Cecchetto G et al (1992) Latent hepatitis B virus infection in childhood hepatocellular carcinoma. Analysis by polymerase chain reaction. Cancer 69:2731–2735
Qian Y, Banerjee S, Grossman CE, Amidon W, Nagy G, Barcza M, Niland B, Karp DR (2008) Transaldolase deficiency influences the pentose phosphate pathway, mitochondrial homeostasis and apoptosis signal processing. Biochem J 415:123–134
Rabinowitz M, Imperial JC, Schade RR, Van Thiel DH (1989) Hepatocellular carcinoma in Alagille's syndrome: a family study. J Pediatr Gastroenterol Nutr 8:26–30
Rao BN, Kapur BM, Shah DK (1967) Primary carcinoma of the liver in infancy. Report of a case. Indian J Pediatr 34:437–439
Reynolds M (2001) Pediatric liver tumors. Cancer Treat Res 109:299–312
Romano F, Stroppa P, Bravi M, Casotti V, Lucianetti A, Guizzetti M, Sonzogni A, Colledan M et al (2011) Favorable outcome of primary liver transplantation in children with cirrhosis and hepatocellular carcinoma. Pediatr Transplant 15:573–579
Rosenblatt MS, May JA (1946) Primary carcinoma of the liver in infants and children. Northwest Med 45:96
Roth D, Duncan PA (1955) Primary carcinoma of the liver after giant-cell hepatitis of infancy; report of a case. Cancer 8:986–991
Russo P, O'Regan S (1990) Visceral pathology of hereditary tyrosinemia type I. Am J Hum Genet 47:317–324
Savas N, Canan O, Ozcay F, Bilezikci B, Karakayali H, Yilmaz U, Haberal M (2006) Hepatocellular carcinoma in Wilson's disease: a rare association of childhood. Pediatr Transplant 10:639–643
Sawyer DC (1950) Primary hepatoma in infancy. J Pediatr 36:508
Schiodt T (1970) Hepatoblastoma and hepatocarcinoma in infancy and childhood. Report of the pathology of eight cases from the University Hospital, Copenhagen. Acta Pathol Microbiol Scand 21(Suppl):181–192
Shapiro VS (1960) Primary cancer of the liver in children of mothers having sustained infectious hepatitis in pregnancy. Sov Med 22:42–47
Shorter RG, Baggenstoss AH, Logan GB, Hallenbeck GA (1960) Primary carcinoma of the liver in infancy and childhood. Report of 11 cases and review of the literature. Pediatrics 25:191–203
Silen W, Mawdsley D, Jensen P, Gardner RE (1959) Hepatic lobectomy in the treatment of tumors of the liver in children. Ann Surg 150:1065–1070
Steiner MM (1938) Primary carcinoma of the liver in childhood. Report of two cases, with a critical review of the literature. Am J Dis Child 55:807–824
Stone NC (1952) Primary carcinoma of the liver in a boy aged 20 months. J Pediatr 41:578–581
Tajima T, Honda H, Yanaga K, Kuriowa T, Yoshimitsu K, Irie H, Kuwabara Y, Taguchi K et al (2001) Hepatic nodular hyperplasia in a boy with Alagille syndrome: CT and MR appearances. Pediatr Radiol 31:584–588
Tajiri H, Tanaka H, Brooks S, Takano T (2011) Reduction of hepatocellular carcinoma in childhood after introduction of selective vaccination against hepatitis B virus for infants born to HBV carrier mothers. Cancer Causes Control 22:523–527
Tanaka Y, Inoue T, Horie H (2013) International pediatric liver cancer pathological classification: current trend. Int J Clin Oncol 18:946–954
Tazawa Y, Kikuchi M, Kurobane I, Watanabe A, Nakai H, Narisawa K, Tada K (1990) An acute form of tyrosinemia type I with multiple intrahepatic mass lesions. J Pediatr Gastroenterol Nutr 10:536–539
Topic A, Ljujic M, Radojkovic D (2012) Alpha-1-antitrypsin in pathogenesis of hepatocellular carcinoma. Hepatol Monit 12:e7042
Tylki-Szymanska A, Stradomska TJ, Wamelink MM, Solomons GS, Taybert J, Pawlowska J et al (2009) Transaldolase deficiency in two new patients with a relative mild phenotype. Mol Genet Metab 97:15–17
Ugarte N, Gonzalez-Crussi F (1981) Hepatoma in siblings with progressive familial cholestatic cirrhosis of childhood. Am J Clin Pathol 76:172–177
Van Dyk E, Pretorius PJ (2012) Impaired DNA repair and genomic stability in hereditary tyrosinemia type 1. Gene 495:56–61
Verhoeven NM, Huck JH, Roos B, Struys EA, Salomons GS, Douwes AC, van der Knaap MS et al (2001)

Transaldolase deficiency: liver cirrhosis associated with a new inborn error in the pentose phosphate pathway. Am J Hum Genet 68:1086–1092

Vilarinho S, Erson-Omay EZ, Harmanci AS, Morotti R, Carrion-Grant G, Baranoski J, Knisely AS, Ekong U et al (2014) Paediatric hepatocellular carcinoma due to somatic CTNNB1 and NFE2L2 mutations in the setting of inherited bi-allelic ABCB11 mutations. J Hepatol 61:1178–1183

Wamelink MM, Struys EA, Salomons GS, Fowler D, Jakobs C, Clayton PT (2008) Transaldolase deficiency in a two-year-old boy with cirrhosis. Mol Genet Metab 94:255–258

Watanabe I (1977) Histopathologic features of liver cell carcinoma in infancy and childhood and their relations to surgical prognosis (in Japanese). Jpn J Clin Oncol 23:691–697

Weinberg AG, Finegold MJ (1983) Primary hepatic tumors of childhood. Hum Pathol 14:512–537

Weinberg AG, Mize CE, Worthen HG (1976) The occurrence of hepatoma in the chronic form of hereditary tyrosinemia. J Pediatr 88:434–438

Wen WH, Chang MH, Hsu HY, Ni YH, Chen HL (2004) The development of hepatocellular carcinoma among prospectively followed children with chronic hepatitis B virus infection. J Pediatr 144:397–399

Wetli SC, Gralla ES, Schibli S, Stranzinger E (2010) Hepatocellular carcinoma and regenerating nodule in a 3-year-old child with Alagille syndrome. Pediatr Radiol 40:1696–1698

Willis RA (1960) Pathology of tumours, 3rd edn. Butterworths, London, pp 432–439, 936–941

Willis RA (1962) The pathology of tumours in children, 1st edn. Oliver and Boyd, London, pp 57–61, 182–184

Zaman S, Hanif G, Hussain M, Basit Z, Khan S, Rathore Z, Naeem A, Nasir M (2011) Hepatic tumors in childhood: an experience at the Childrens Hospital and Institute of Child Health, Lahore. J Pak Med Assoc 61:1079–1082

Zen Y, Vara R, Portmann B, Hadzic N (2014) Childhood hepatocellular carcinoma: a clinicopathologic study of 12 cases with special reference to EpCAM. Histopathology 64:671–682

Zhang XF, Liu XM, Wei T, Liu C, Li MX, Long ZD, Lv Y (2013) Clinical characteristics and outcome of hepatocellular carcinoma in children and adolescents. Pediatr Surg Int 29:763–770

Hepatoid Carcinomas (Adenocarcinomas with Hepatoid Features)

17

Contents

Abstract

Hepatoid carcinoma (adenocarcinoma with hepatoid features) is a highly aggressive carcinoma occurring in various organs, morphologically characterized by the presence of HCC-like cells that frequently express alpha-fetoprotein, but with a cytokeratin pattern that differs from that of classical HCC, in that tumor cells are often positive for cytokeratins 7 and 20. Similar to HCC, gastrointestinal hepatoid carcinomas can express the hepatocyte marker Hep Par 1. These neoplasms are associated with rapid progression and a poor outcome. Most hepatoid carcinomas found in the liver are metastases of gastric hepatoid carcinomas, the stomach being a frequent primary site. Primary hepatoid carcinomas also occur in bile ducts, the gallbladder, and the ampullary region, but these are uncommon locations. The histogenesis of this neoplasm has not yet been elucidated.

Introduction

Some carcinomas occurring in several organs, but in particular the gastrointestinal tract, can show signs of hepatocellular differentiation, either focally or almost exclusively. These lesions, which are termed hepatoid (adeno)carcinomas or extraheptic tumors with hepatoid features (EHTHF), may be associated with elevated serum AFP levels and an aggressive course

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_17

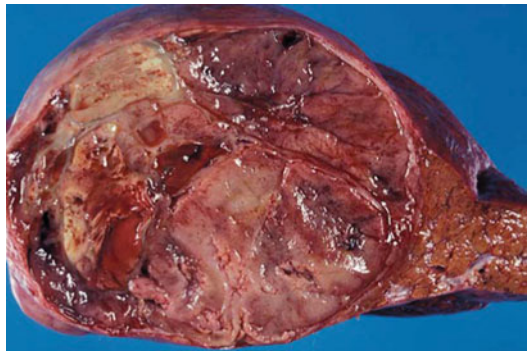

Fig. 1 Hepatoid carcinoma of the liver. These are rapidly growing, aggressive neoplasms developing in non-cirrhotic livers

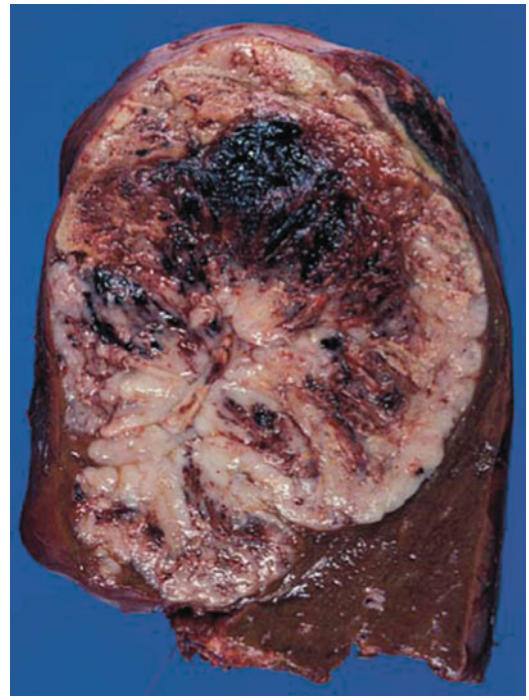

Fig. 2 The macroscopic morphology of hepatoid carcinomas of the liver resembles that of carcinoma metastases. Necrosis and hemorrhages are common features

(reviews: Kishimoto et al. 2000; Su et al. 2013). Typical primary sites of these carcinomas include the stomach (the most common site), esophagus, pancreas, gallbladder, colon, lung, ovary, urinary bladder, renal pelvis, uterus, fallopian tube, and adrenal gland. Hepatoid carcinomas usually have a distinct and unique immunophenotype, characterized by reactivity for cytokeratins 7, 8, 18, 19, and 20, alpha-fetoprotein (AFP), and pCEA (Terracciano et al. 2003). Immunoreactivity for AFP is variable, ranging from absence of staining to marked and diffuse staining of cancer cells, illustrating that not all carcinomas with a hepatoid morphology are producing AFP (Nagai et al. 1993). Many hepatoid carcinomas of the gastrointestinal tract show, similar to hepatocellular carcinomas, reactivity for hepatocyte paraffin 1 (Hep Par 1) antibody, underscoring the fact that Hep Par 1 expression is not unique to primary hepatocellular neoplasms (Maitra et al. 2001). At least part of hepatoid carcinomas are positive for glypican-3, a cell surface heparin sulfate proteoglycan expressed specifically in the fetal liver and in malignant neoplasms of the hepatocyte lineage (Hishinuma et al. 2006). Generally, hepatoid carcinomas are highly aggressive tumors (Figs. 1 and 2).

For example, it has been demonstrated that AFP-producing gastric carcinoma and hepatoid adenocarcinomas of the stomach had a more aggressive biology than that of common gastric cancer and that the prognosis of hepatoid tumors was poorer than that of AFP-producing gastric carcinoma (Liu et al. 2012).

Histologically, hepatoid carcinomas consist of large or medium-sized polygonal cells that are arranged in trabecular fashion or solid nests separated by narrow fibrous stroma bands and sinusoid-like channels (Fig. 3).

Rarely, hepatoid carcinomas showed, apart from the predominant adenocarcinoma, other components, e.g., endocrine carcinoma (Suzuki et al. 2012). It is often difficult to distinguish EHTHF from metastatic hepatocellular carcinoma (HCC) using any kinds of ancillary studies, with the exception of clinical-radiological identification of a hepatic tumor (Kwon et al. 2006).

Some of the extrahepatic carcinomas with morphological resemblance to hepatocellular carcinoma are AFP-negative, but may show positive signals for albumin mRNA in ISH preparations (Supriatna et al. 2005). On the other hand, it has to be emphasized that the mere presence of immunohistochemical markers known to be expressed

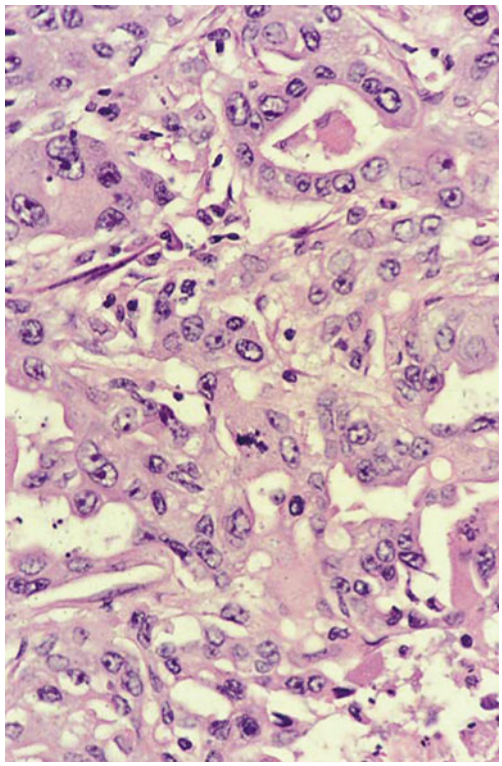

Fig. 3 Hepatoid carcinoma in the liver. The neoplasm consists of cells similar to those in hepatocellular carcinoma, but tubular structures are also encountered, and the tumors are often pleomorphic, with highly atypical nuclei and abnormal mitotic figures (hematoxylin and eosin stain)

in hepatoid cell lineages does not mean that we deal with EHTHF. It has, e.g., been shown that hepatoid carcinoma of the gastrointestinal tract (Maitra et al. 2001) and diverse types of cervical carcinomas (including ordinary adenocarcinoma, adenocarcinoma in situ, and squamous cell carcinomas) can be reactive for Hep Par 1 (Thamboo and Wee 2004) and that Hep Par 1 does not distinguish between EHTHF of the ovary from metastatic HCC (Pitman et al. 2004). AFP-producing adenocarcinoma without morphological hepatoid features may also be positive for glypican 3 (Hishinuma et al. 2006; Oishi et al. 2009). SALL4, a stem cell marker and a marker for fetal gut differentiation, is expressed in the majority of gastric EHTHF, but not in HCCs (Ushiku et al. 2010). On a molecular level, it has been found that foci of hepatoid differentiation in EHTHF show restricted expression of hepatocyte nuclear factor 4 alpha (Kishimoto et al. 2008). Expression of the PLUNC (palate, lung, and nasal epithelium carcinoma-associated protein) gene is a marker for EHTHF (Sentani et al. 2008). PLUNC, also termed lung-specific X protein (LUNX), is a major secreted protein product of the upper respiratory tract, of a still unknown function.

Hepatoid Carcinomas of the Extrahepatic Biliary Tract

Primary EHTHF of the extrahepatic ducts are very rare lesions. In one case, a 67-year-old female suffering from obstructive jaundice had a stenosing mass at the common hepatic duct, mimicking a Klatskin tumor, histologically representing hepatoid carcinoma. The tumor was associated with elevated serum AFP levels (Abdullah et al. 2010). A hepatoid tumor located to the common duct showed all immunohistochemical features characteristic for EHTHF, i.e., positivity for Hep Par 1, CK8, and CK18 (Wang et al. 2013).

Hepatoid Carcinoma of the Gallbladder

EHTHF is known to occur in the gallbladder (Watanabe et al. 1993; Vardaman and Albores-Saavedra 1995; Nishiwaki et al. 1997; St Laurent et al. 1999; Nakashima et al. 2000; Maitra et al. 2001; Sakamoto et al. 2004, 2005; Gakiopoulou et al. 2007; Koswara et al. 2007: van den Bos et al. 2007; Kao et al. 2009; Ellouze et al. 2011). The tumors may be associated with elevated serum AFP levels (van den Bos et al. 2007). In principle, the neoplasms show the same histologic features as those in other locations. Macroscopically, the tumors however often differ from ordinary gallbladder carcinoma by their more nodular and sometimes polypoid growth pattern. In one case of Sakamoto et al. (2005), a 74-year-old female with a long history of cholecystolithiasis exhibited a nodular and elevated gallbladder tumor of 5 cm diameter,

consisting of AFP-positive and Hep Par 1-positive hepatoid cells. Part of the tumors showed cholangiocarcinoma-like components, which also immunostained for AFP (Koswara et al. 2007). In a case reported in 1995, the AFP-producing tumor belonged to the group of clear cell carcinomas of the gallbladder (Vardaman and Albores-Saavedra 1995). Gallbladder carcinomas associated with elevated serum AFP levels are not always hepatoid lesions, but may instead represent other histologies, e.g., standard adenocarcinoma (Brown and Roberts 1992) or undifferentiated carcinoma (Ng and Ng 1995).

Hepatoid Carcinoma of the Ampullary Region

Few cases of primary hepatoid carcinoma of the ampullary/periampullary region have been described (Gardiner et al. 1992; Weng et al. 2009; Palas et al. 2013). The tumor described by Gardiner and co-workers (1992) was located to the papilla of Vater and consisted of a poorly differentiated adenocarcinoma with clear cells containing occasional hyaline droplets and exhibiting bile secretion. Immunohistochemically, AFP, alpha-1-antitrypsin, and CEA were detectable.

Liver Metastasis of Hepatoid Carcinomas

Hepatoid carcinoma of the stomach, the most common localization for this tumor, relatively often metastasizes to the liver, but also other primary intra-abdominal localizations give rise to hepatic metastatic disease (Yoshida et al. 2005; Jo et al. 2012). EHTHF with liver metastasis may mimic HCC (Pan et al. 2011; Jo et al. 2012; Moon et al. 2012), but EHTHF metastases are more commonly positive for CK19 and CK20 and are more often negative for Hep Par 1 than HCCs (Terracciano et al. 2003).

Differential Diagnosis

The main differential diagnoses include metastatic hepatocellular carcinoma and germ cell tumors with marked hepatoid differentiation. HCCs are known to show unusual metastasizing patterns and can, e.g., metastasize to the gallbladder, causing a lesion pattern that may not be distinguishable from primary hepatoid carcinoma (Terasaki et al. 1990). Apart from AFP, embryonal carcinoma has been found to secrete des-gamma-carboxy prothrombin (Hasegawa et al. 2005).

Pathogenic Pathways

Novel observations on the lineage relationships between pancreatic cells and hepatocytes, and their respective precursors, may shed a light on pathogenic mechanisms involved. Of course the liver and the pancreas ontogenically derive from a similar fated endodermal area, but this will not suffice for the understanding of carcinogenic pathways. A key molecule involved in the prenatal development of the stomach and liver is the transcription factor, GATA4. In AFP-producing gastric carcinoma cells, GATA4 expression is silenced via epigenetic histone deacetylation (Yamamura and Kishimoto 2012). Gastric carcinoma producing AFP was shown to share the main histologic features with combined hepatocellular and cholangiocarcinoma, but revealed a different histogenesis with respect to SALL4 expression. Specifically, the germ cell marker SALL4 was expressed in 95 % of AFP-producing gastric carcinomas, including those with a hepatoid component, but was not detectable in combined hepatocellular and cholangiocarcinoma (Ikeda et al. 2012).

References

Abdullah A, Jenkins-Mosure K, Lewis T, Patel Y, Strobel S, Pepe L (2010) Primary hepatoid carcinoma of the biliary tree: a radiologic mimicker of Klatskin-type tumor. Cancer Imaging 10:198–201

Brown JA, Roberts CS (1992) Elevated serum alpha-fetoprotein levels in primary gallbladder carcinoma without hepatic involvement. Cancer 70:1838–1840

Ellouze S, Slim C, Ahmad G, Naourez G, Ali A, Héla M, Mariem K, Mohamed BA et al (2011) Hepatoid adenocarcinoma of the gallbladder. World J Surg Oncol 9:103

Gakiopoulou H, Givalos N, Liapis G, Agrogiannis G, Patsouris E, Delladetsima I (2007) Hepatoid adenocarcinoma of the gallbladder. Dig Dis Sci 52:3358–3362

Gardiner GW, Lajoie G, Keith R (1992) Hepatoid adenocarcinoma of the papilla of Vater. Histopathology 20:541–544

Hasegawa Y, Tomita K, Hashimoto K, Shigeoka Y, Watanabe M, Yamasaki A, Shimizu E (2005) Des-gamma-carboxy prothrombin (PIVKA-II)-producing mediastinal embryonal carcinoma with features of hepatoid differentiation. Anticancer Res 25:4569–4571

Hishinuma M, Ohashi KI, Yamauchi N, Kashima T, Uozaki H, Ota S, Kodama T, Aburatani H, Fukayama M (2006) Hepatocellular oncofetal protein, glypican 3 is a sensitive marker for alpha-fetoprotein-producing gastric carcinoma. Histopathology 49:479–486

Ikeda H, Sato Y, Yoneda N, Harada K, Sasaki M, Kitamura S, Sudo Y, Ooi A, Nakanuma Y (2012) a-Fetoprotein-producing gastric carcinoma and combined hepatocellular and cholangiocarcinoma show similar morphology but different histogenesis with respect to SALL4 expression. Hum Pathol 43:1955–1963

Jo JM, Kim JW, Heo SH, Shin SS, Jeong YY, Hur YH (2012) Hepatic metastases from hepatoid adenocarcinoma of stomach mimicking hepatocellular carcinoma. Clin Mol Hepatol 18:420–423

Kao CY, Chang CR, Chiang H, Chen HT, Shih-Ming M, Cheng CY (2009) Well-differentiated gall bladder hepatoid carcinoma producing alpha-fetoprotein: a case report. J Med Case Rep 3:7303

Kishimoto et al (2000) pub Med PMID 11810459

Kishimoto T, Yano T, Hiroshima K, Inayama Y, Kawachi K, Nakatani Y (2008) A case of a-fetoprotein-producing pulmonary carcinoma with restricted expression of hepatocyte nuclear factor-4a in hepatoid foci: a case report with studies of previous cases. Hum Pathol 39:1115–1120

Koswara T, Marwoto W, Siregar NC, Gumay S, Azis H, Abdullah M, Himawan S (2007) Hepatoid carcinoma of the gallbladder. Acta Med Indones 39:179–182

Kwon JE, Kim SH, Cho NH (2006) No ancillary finding is valid to distinguish a primary ovarian hepatoid carcinoma from metastatic hepatocellular carcinoma. Int J Gynecol Cancer 16:1691–1694

Liu X, Sheng W, Wang Y (2012) An analysis of clinicopathological features and prognosis by comparing hepatoid adenocarcinoma of the stomach with AFP-producing gastric cancer. J Surg Oncol 106:299–303

Maitra A, Murakata LA, Albores-Saavedra J (2001) Immunoreactivity for hepatocyte paraffin 1 antibody in hepatoid adenocarcinomas of the gastrointestinal tract. Am J Clin Pathol 115:689–694

Moon JY, Kim GH, Cheong JH, Lee BE, Ryu DY, Song GA (2012) A case of hepatic metastases of gastric hepatoid adenocarcinoma mistaken for primary hepatocellular carcinoma (in Korean). Korean J Gastroenterol 60:262–266

Nagai E, Ueyama T, Yao T, Tsuneyoshi M (1993) Hepatoid adenocarcinoma of the stomach. A clinicopathologic and immunohistochemical analysis. Cancer 72:1827–1835

Nakashima et al (2000) pub Med PMID 10982619

Ng WK, Ng WF (1995) Elevated serum a-fetoprotein in a patient with undifferentiated carcinoma of the gall bladder. J Clin Pathol 48:1061–1063

Nishiwaki M, Kimura M, Gega M, Ohi Y, Nishioka A, Ashida H, Yamamura T, Utsunomiya J, Nishigami T (1997) A case of adenocarcinoma of the gallbladder with lymph node metastasis showing hepatoid adenocarcinoma and producing alfa-fetoprotein (in Japanese). Nippon Shokakibyo Gakkai Zasshi 94:874–878

Oishi C, Baba T, Kubota Y, Shimotsuma Y, Kitamura K, Honma T, Ikegami A, Inokuchi M et al (2009) Two cases of gastric cancer expressing glypican 3, but producing AFP with different lectin affinity (in Japanese). Nippon Shokakibyo Gakkai Zasshi 106:805–812

Palas J, Ramalho M, Matos AP, Herédia V (2013) Case 194: periampullary hepatoid adenocarcinoma with duodenal invasion. Radiology 267:959–963

Pan JH, Dong MJ, Ouyang XB (2011) A hepatoid adenocarcinoma of the stomach with liver metastasis mimicking hepatocellular carcinoma detected by F-18 FDG PET/CT imaging. Clin Nucl Med 36:1137–1139

Pitman MB, Triratanachat S, Young RH, Oliva E (2004) Hepatocyte paraffin 1 antibody does not distinguish primary ovarian tumors with hepatoid differentiation from metastatic hepatocellular carcinoma. Int J Gynecol Pathol 23:58–64

Sakamoto K, Monobe Y, Kouno M, Moriya T, Sasano H (2004) Hepatoid adenocarcinoma of the gallbladder: case report and review of the literature. Pathol Int 54:52–56

Sakamoto K, Kimura N, Tokumura H, Ogasawara T, Moriya T, Sasano H (2005) Hepatoid adenocarcinoma of the gallbladder. Histopathology 47:649–651

Sentani K, Oue N, Sakamoto N, Arihiro K, Aoyagi K, Sasaki H, Yasui W (2008) Gene expression profiling with microarray and SAGE identifies PLUNC as a marker for hepatoid adenocarcinoma of the stomach. Mod Pathol 21:464–475

St Laurent M, Esterl RM, Halff GA, Speeg KV (1999) Gallbladder carcinoma producing alpha-fetoprotein. J Clin Gastroenterol 28:55–58

Su JS, Chen YT, Wang RC, Wu CY, Lee SW, Lee TY (2013) Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: a literature review. World J Gastroenterol 19:321–327

Supriatna Y, Kishimoto T, Uno T, Nagai Y, Ishikura H (2005) Evidence for hepatocellular differentiation in alpha-fetoprotein-negative gastric adenocarcinoma with hepatoid morphology: a study with in situ hybridisation for albumin mRNA. Pathology 37:211–215

Suzuki A, Koide N, Kitazawa M, Mochizuka A, Ota H, Miyagawa S (2012) Gastric composite tumor of alpha fetoprotein-producing carcinoma/hepatoid adenocarcinoma and endocrine carcinoma with reference to cellular phenotypes. Pathol Res Int 2012:201375

Terasaki S, Nakanuma Y, Terada T, Unoura M (1990) Metastasis of hepatocellular carcinoma to the gall bladder presenting massive intraluminal growth: report of an autopsy case. J Clin Gastroenterol 12:714

Terracciano LM, Glatz K, Mhawech P, Vasei M, Lehmann FS, Vecchione R, Tornillo L (2003) Hepatoid adenocarcinoma with liver metastasis mimicking hepatocellular carcinoma: an immunohistochemical and molecular study of eight cases. Am J Surg Pathol 27:1302–1312

Thamboo TP, Wee A (2004) Hep Par 1 expression in carcinoma of the cervix: implications for diagnosis and prognosis. J Clin Pathol 57:48–53

Ushiku T, Shinozaki A, Shibahara J, Iwasaki Y, Tateishi Y, Funata N, Fukayama M (2010) SALL4 represents fetal gut differentiation of gastric cancer, and is diagnostically useful in distinguishing hepatoid gastric carcinoma from hepatocellular carcinoma. Am J Surg Pathol 34:533–540

Van den Bos IC, Hussain SM, Dwarkasing RS, Stoop H, Zondervan PE, Krestin GP, de Man RA (2007) Hepatoid adenocarcinoma of the gallbladder: a mimicker of hepatocellular carcinoma. Br J Radiol 80: e317–e320

Vardaman C, Albores-Saavedra J (1995) Clear cell carcinoma of the gallbladder and extrahepatic bile ducts. Am J Surg Pathol 19:91–99

Wang Y, Liu YY, Han GP (2013) Hepatoid adenocarcinoma of the extrahepatic duct. World J Gastroenterol 19:3524–3527

Watanabe M, Hori Y, Nojima T et al (1993) Alpha-fetoprotein producing carcinoma of the gallbladder. Dig Dis Sci 38:561–564

Weng JM, Wu WQ, Liu QY (2009) Hepatoid adenocarcinoma of duodenal papilla: report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 38:494

Yamamura N, Kishimoto T (2012) Epigenetic regulation of GATA4 expression by histone modification in AFP-producing gastric adenocarcinoma. Exp Mol Pathol 93:35–39

Yoshida H, Mamada Y, Taniai N, Mizuguchi Y, Nakamura Y, Nomura T, Yoshioka M et al (2005) Ruptured metastatic liver tumor from an alpha-fetoprotein-producing gastric cancer. J Nippon Med Sch 72:236–241

Fibrolamellar Hepatocellular Carcinoma

18

Contents

Abstract

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a distinct variant of hepatocellular carcinoma (HCC) that differs from classical HCC at histological, cytological, immunohistochemical, and molecular levels. FL-HCC is typically a tumor of adolescents and young adults, but may also occur in older individuals. In contrast to most HCCs, FL-HCC is not associated with liver cirrhosis. The neoplasm is histologically characterized by strands of large, eosinophilic hepatocyte-like cells embedded in a collagenous stroma forming striking lamellae. Clear cell and glandular variants are known. Clinically, the tumor often presents as a large solitary mass in the absence of elevated serum alpha-fetoprotein levels. FL-HCC may be associated with several metabolic paraneoplastic syndromes that include disorders of vitamin B12-binding protein, sex steroid metabolism, ammonia handling, neurotensin synthesis, and gonadotropin production. In contrast to previous views, there is now evidence that the biological behavior of FL-HCC is not different from that of classical HCC. The neoplasm shows a distinct genomic landscape characterized by a recurrent DNAJB1-PRKACA chimeric transcript arising from a deletion on chromosome 19, but the tumor also showed other molecular abnormalities.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_18

Introduction

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a distinct malignant liver cell tumor that differs from classical HCC at histological, cytological, immunohistochemical, and molecular levels. It mainly occurs in adolescents and young adults and is histologically characterized by strands of large, eosinophilic hepatocyte-like cells embedded in a fibrous stroma forming collagen-rich lamellae. FL-HCC was first described in 1956 (Edmondson 1956) and subsequently confirmed by Craig et al. (1980) and Berman et al. (1980). The typical clinicopathologic and molecular features of this tumor entity have been reviewed (Soreide et al. 1986; Vecchio 1988; Saab and Yao 1996; McLarney et al. 1999; El-Serag and Davila 2004; Torbenson 2007; Liu et al. 2009; Lim et al. 2014; Darcy et al. 2015a). After the first description, it took a rather long time period until the tumor entity was defined and accepted. Several alternative terms had been employed to denote this lesion, including hepatocellular carcinoma with laminar fibrosis, hepatocellular carcinoma with polygonal cell type and fibrous stroma, oncocytic hepatocellular carcinoma, and eosinophilic hepatocellular carcinoma with lamellar fibrosis.

Epidemiology

FL-HCC accounts for 1–9 % of HCCs overall, this impressive frequency range being caused by markedly variable prevalences in different geographic niches and differences in diagnostic criteria used (Craig et al. 1980; McLarney et al. 1999). Among 46,392 cases of HCC registered in the SEER program between 2000 and 2010, 191, tumors were FL-HCC, with an incidence of clearly less than 0.1 per 100,000 people (Eggert et al. 2013). In contrast to conventional HCC, FL-HCC is not associated with cirrhosis of the liver and other typical risk factors, although a relation to genetic syndromes has been suggested in part of the cases, e.g., Gardner syndrome (Gruner et al. 1998) and Fanconi anemia (LeBrun et al. 1991). FL-HCC is typically a tumor of adolescents and young adults, but rarely also occurs in older individuals. FL-HCC is rare in infants and small children (Cruz et al. 2008), but FL-HCC in older children has more often been encountered (Dellaportas et al. 2011). There is usually no gender predominance, but a predominance of the female gender has also been reported (Chagas et al. 2015). The tumor has been diagnosed during pregnancy (Kroll et al. 1991; Louie-Johnsun et al. 2003). In reviewing studies there is an age range of 5–69 years (mean in Western patients : 23 years), and most patients present in their second and third decades (McLarney et al. 1999). In contrast, conventional HCC is less common than FL-HCC in individuals younger than 40 years (Hernandez-Castillo et al. 2005).

The incidence of FL-HCC is relatively high in Western countries, but is rare in Oriental countries. Analysis of Japanese cases revealed an age range of 15–45 years, with a mean of 21.9 years, findings similar to those in Western countries (Kohno et al. 1988; Haratake et al. 1990; Tanaka et al. 1994; Hoshino et al. 1996; Nojiri et al. 2000; Magata et al. 2001; Yoshimi et al. 2002; Yoshinaga et al. 2002; Kanai et al. 2004; Morise et al. 2005). FL-HCC is apparently not uncommon in sub-Saharan Africa (Moore et al. 2004; Bhaijee et al. 2009) and Latin America (Arista-Nasr et al. 2002).

Clinical Features

FL-HCC characteristically manifests as a large hepatic mass in the absence of liver cirrhosis, elevated serum AFP values, or known risk factors for HCC. In most cases, FL-HCC presents with vague and nonspecific clinical signs and symptoms, often with abdominal discomfort or pain, malaise, and weight loss (Craig et al. 1980; Saab and Yao 1996; Hemming et al. 1997; reviews: Torbenson 2007; Chun and Zimmitti 2013). Due to its mass effect, FL-HCC can cause recurrent obstructive jaundice (Albaugh et al. 1984; Soyer et al. 1991a). It can, similar to ordinary HCC, invade large bile ducts and cause obstructive

Table 1 Metabolic disorders in fibrolamellar hepatocellular carcinoma

Increased serum vitamin B12-binding capacity
Increased neurotensin synthesis with increased serum levels
Paraneoplastic gynecomastia caused by increased aromatase P450 activity
Paraneoplastic production of beta-HCG
Paraneoplastic hyperammonemia with encephalopathy

jaundice, sometimes with subsequent migration of tumor fragments to the common bile duct and distal biliary obstruction (intrabiliary tumor thrombus; Eckstein et al. 1988; Kunz et al. 2002; De Gaetano et al. 2013; Arora 2015). FL-HCC reveals invasion of large liver veins less commonly than conventional HCC, but Budd-Chiari syndrome has been observed as the first manifestation of FL-HCC (Lamberts et al. 1992; Asrani and LaRusso 2012). Caval compression syndrome has been reported as a complication of FL-HCC (Kanai et al. 2004). Additional and usually less common or rare disorders sometimes associated with FL-HCC include severe anemia (Tanaka et al. 1994), nonbacterial thrombotic endocarditis (Vaideeswar et al. 1993), tumor-induced ascites in the case of peritoneal spread (Gupta et al. 1999), a clinical syndrome mimicking hepatic pyogenic abscess (Debray et al. 1994), and cold agglutinin disease (Al-Matham et al. 2011). FL-HCC has been observed in association with ulcerative colitis with primary sclerosing cholangitis (Snook et al. 1989).

FL-HCC patients can show complex patterns of metabolic disorders (Table 1).

The tumor shows abnormalities in the metabolism of vitamin B12 (cobalamin). An increase of serum levels of vitamin B12-binding capacity in patients with FL-HCC has first been reported in 1982 (Paradinas et al. 1982) and confirmed in later analyses (Sheppard et al. 1983; Wheeler et al. 1986; Lildballe et al. 2011). Increasing vitamin B12-binding capacity has been found in postoperative recurrence of FL-HCC (Kanai et al. 2004). However, elevation of vitamin B12 and B12-related proteins seems to be a common feature in HCCs and not only in FL-HCC (Simonsen et al. 2014). Transcriptional profiling of FL-HCC revealed an endocrine signature, in that 4 of the 16 genes most significantly overexpressed in pure FL-HCC were neuroendocrine genes, i.e., prohormone convertase 1/PCSK1, neurotensin, delta/notch-like EGF repeat containing, and calcitonin (Malouf et al. 2014). Serum neurotensin levels (especially levels of the C-terminal part) may be elevated in patients with FL-HCC, caused by secretion of this peptide by the tumor (Collier et al. 1984; Read et al. 1991). Neurotensin was originally isolated from bovine hypothalamus and is an important gastrointestinal regulatory peptide that affects pancreatic secretion, gut motility, gut mucosal growth, and the translocation of fatty acids from the intestinal lumen. The neurotensin gene is expressed in fetal human liver (but not adult liver) and in FL-HCCs (Ehrenfried et al. 1994). In the tumor itself, the neurotensin (6–13) peptide was detectable (Read et al. 1991).

FL-HCC can be associated with gynecomastia (McCloskey et al. 1988; Hany et al. 1997; Agarwal et al. 1998; Sher et al. 1998), mainly in cases of large tumor mass/metastasis. Gynecomastia may be the presenting sign of FL-HCC (McCloskey et al. 1988). Gynecomastia in this tumor is caused by increased aromatase P450 activity in the neoplasm (hyperaromatase syndrome; Hany et al. 1997; Agarwal et al. 1998; Muramori et al. 2011), which gives rise to markedly elevated serum levels of estrone and estradiol-17 beta, suppressing FSH and LH, respectively, and consequently testosterone (Agarwal et al. 1998). Northern analysis indicated the presence of P450 aromatase transcripts in total RNA from FL-HCC but not in the adjacent liver (Agarwal et al. 1998). FL-HCC can rarely produce beta-HCG and by this cause vaginal bleeding (Dahan and Kastell 2002). In part of patients, FL-HCC is associated with a recurrent non-hepatic/non-cirrhotic form of hyperammonemia (paraneoplastic hyperammonemia) complicated by encephalopathy. This complication may mimic a disorder of urea synthesis, e.g., ornithine transcarbamylase deficiency (Sulaiman and Geberhiwot 2014).

Imaging Features

Abdominal imaging shows a well-circumscribed, lobulated, heterogeneous mass that may resemble focal nodular hyperplasia (FNH). CT images document that FL-HCCs are predominantly solitary, well-delineated, and hypervascular lesions which are predominantly hypoattenuating compared with the liver (Bedi et al. 1988; Soyer et al. 1991b; Ichikawa et al. 2000; Marrannes et al. 2005; Selaru et al. 2007; Yen and Chang 2009; Terzis et al. 2010). Almost all tumors were heterogeneous on non-enhanced CT images. In portal venous phase and relative to enhanced liver, FL-HCCs appeared isoattenuating in 48 %, hyperattenuating in 16 %, and hypoattenuating in 36 % (Ichikawa et al. 1999). A central scar resembling the stellate scar seen in FNH is present in CT images in about a third to about 70 % of the cases (the "scar sign"; Kane et al. 1987; Soyer et al. 1991b; Ichikawa et al. 1999). In one study, 82 % of the scars showed a stellate morphology on CT images (Ichikawa et al. 1999). However, central or eccentric scars are also found in conventional HCC, cholangiocarcinoma, and some hepatic metastases (review: Kim et al. 2009). Among 31 cases, CT revealed well-defined margins in 77 % and ill-defined margins in seven cases (Ichikawa et al. 1999). PET-CT scans are a valuable modality in the diagnosis of FL-HCC (Liu et al. 2011). Tumor calcifications in FL-HCC have been reported in 15–68 % of cases at CT and occur in a wide variety of patterns (Soyer et al. 1991b; Stoupis et al. 1998; Ichikawa et al. 1999). Calcifications are more frequent in FL-HCC than in FNH (Caseiro-Alves et al. 1996).

Classification

FL-HCC has been divided into two separate entities, i.e., pure FL-HCC and mixed FL-HCC, differing in clinical presentation and course (Malouf et al. 2012). Pure FL-HCC typically occurs in patients younger than 30 years of age and is often complicated by lymph node metastasis at the time of diagnosis and more frequently shows extrahepatic recurrence. So far, combined or mixed FL-HCC has been regarded as rare lesion. However, in a more recent investigation of 54 patients, the mixed form was found in 25 % of the patients. In contrast to pure FL-HCC, the mixed variant appeared to resemble HCC, occurring in patients aged >40 years, often involving the liver as primary site of disease recurrence, and imparting an increased risk of death (Malouf et al. 2012). Pure FL-HCCs have a distinct transcriptomic signature characterized by strong expression of neuroendocrine genes, including prohormone convertase 1, neurotensin, delta/notch-like EGF repeat containing, and calcitonin, suggesting a complex cellular lineage (Malouf et al. 2014).

Pathology

Macroscopy

The tumors tend to be more common in the left liver lobe (about two thirds of cases; Craig et al. 1980), but relatively often involve both lobes (Ichikawa et al. 1999). In one study, 55 % of the cases had involvement of three or more hepatic segments, and 32 % had involvement of two segments (Ichikawa et al. 1999). Multifocality, gross vascular invasion, and cirrhosis are typically absent, but the tumor often demonstrates aggressive local invasion and nodal and distant metastases (Wong et al. 1982; Friedman et al. 1985; Francis et al. 1986; Gibson et al. 1986; Brandt et al. 1988; Ruffin 1990; Ichikawa et al. 1999; McLarney et al. 1999; Smith et al. 2008). Macroscopically, the tumors are well-delineated masses with a polycyclic border and an expansive growth pattern. A tumor capsule (usually incomplete) is seen in approximately half of the neoplasms. In a study of 31 cases, tumor diameter ranged from 3 to 27 cm, with an average of 13 cm (Ichikawa et al. 1999). In 80–90 % of the

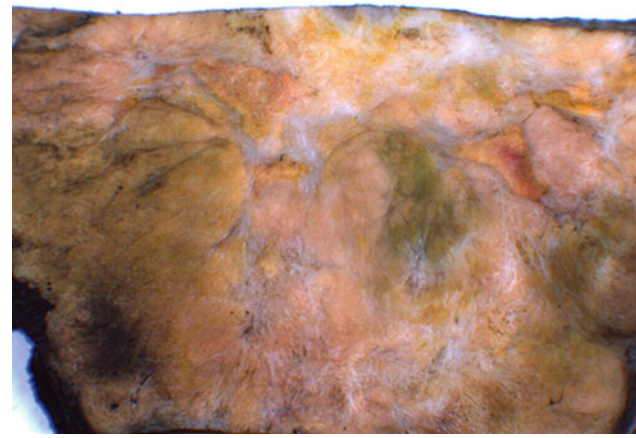

Fig. 1 Fibrolamellar hepatocellular carcinoma. On cut surfaces, the neoplasm exhibits a lobulated texture, lobules, or nodules separated from each other by fibrous septa

cases, a solitary tumor is present. In the remaining cases, there is a mass with small peripheral satellite lesions (10–15 %), a bilobed mass (5 %), or rarely a diffusely/multifocal mass (less than 1 %). Up to 20 % of the tumors show some degree of pedunculation. On cut surfaces, the neoplasms are yellow to tan and often show a nodular or radiated structure caused by radiating fibrous band that originates from central fibrous scar-like areas (Figs. 1 and 2).

In case of marked bile accumulation, a greenish discoloration of the tumor is seen. The neoplasms are encapsulated in about half of the cases, the pseudocapsule being mostly incomplete. A central scar-like structure resembling that seen in focal nodular hyperplasia was detected in about three quarters of cases (Ichikawa et al. 1999). Small necroses and/or hemorrhages may be noted, but are grossly visible in only about 10 %. Rare examples of tumors have revealed massive necrosis and/or hemorrhage, resulting in a multicystic morphology mimicking a primarily cystic liver tumor, but primary multicystic variants of FL-HCC also occur (Pombo et al. 1993). The adjacent liver does not show cirrhosis.

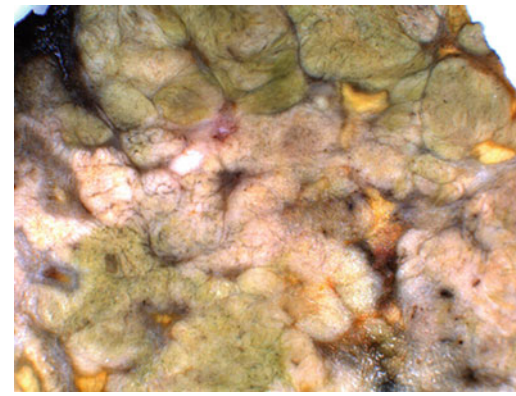

Fig. 2 Nodular structures in fibrolamellar hepatocellular carcinoma can form intertwining ribbons, resulting in a gyriform pattern

Histopathology

The typical cell of FL-HCC is a large polygonal cells having an abundant, deeply eosinophilic, faintly granular cytoplasm and well-defined cell borders . These oxyphilic cells are, however, cytologically different from oncocytes (Altmann 1990). The nuclei are large, round to ovoid and vesicular, and usually single, and they show a peripheral condensation of chromatin and a prominent, centrally placed amphophilic nucleolus. The typical morphologies of the cells and nuclei, together with lamellar fibrosis, are the three main criteria for diagnosis (Figs. 3, 4, 5, 6, and 7).

A part of the nuclei display intranuclear cytoplasmic pseudoinclusions (cytoplasmic invaginations). Large invaginations cause so-called empty nuclei. Mitotic figures are much less common

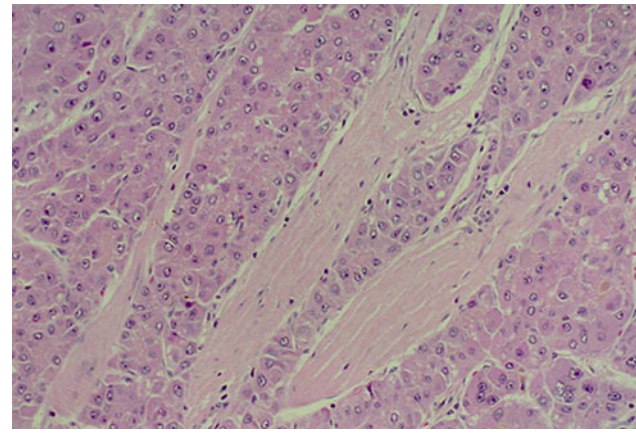

Fig. 3 Fibrolamellar hepatocellular carcinoma. Solid strands and ribbons of large eosinophilic tumor cells are separated by fibrous hypocellular tracks, the fibrolamellae (hematoxylin and eosin stain)

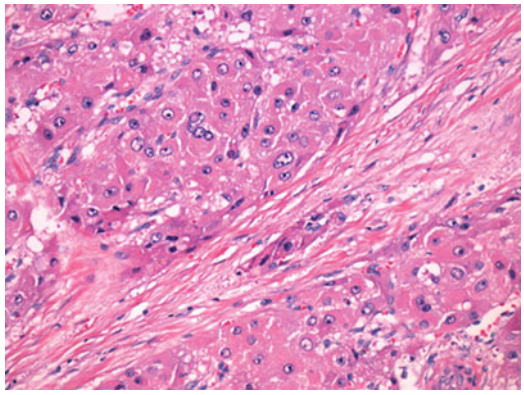

Fig. 4 Fibrolamellar hepatocellular carcinoma. The epithelial tumor cells are in direct contact with collagenous bands, without a visible interposed cellular stroma (hematoxylin and eosin stain)

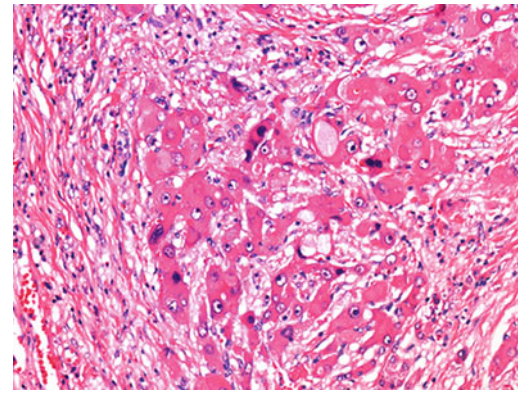

Fig. 5 Fibrolamellar hepatocellular carcinoma. Focally, stroma of slightly higher cellularity can occur, sometimes associated with dissociation of tumor cells (hematoxylin and eosin stain)

than in ordinary HCC (Farhi et al. 1983) and may have previously suggested that the tumor is of low malignancy, what is not the case. Less than 10 % of the cells exhibit PAS-positive globular cytoplasmic inclusions (2–7 μm in diameter; Farhi et al. 1982). About half of the tumor cells contain large ovoid cytoplasmic inclusions that are much less eosinophilic or are amphiphilic, the so-called pale bodies (Fig. 8) .

Pale bodies sometimes show a central hyaline core. Cholestasis is often seen. The tumor cells commonly show canaliculus-like lumina present between adjacent cells containing bile. Tumor cholestasis is, like in ordinary HCC, associated with deposition of copper (copper-binding protein in many cases (Lefkowitch et al. 1983). Small calcifications are sometimes seen, mostly in the central scar and within the fibrous bands. In a minority of FL-HCC, a mild macrovesicular steatosis may be found.

The solid components of medium- to large-sized polygonal cells are irregularly subdivided by connective tissue bands rich in collagen (the "fibrolamellae" that have given the tumor's name). The amount of collagen in the bands varies markedly, ranging from sclerosed bands to bands with a loose texture of tissue rich in glycosaminoglycans and higher spindle cell

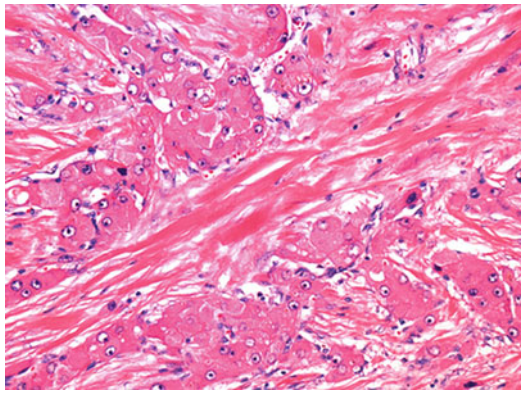

Fig. 6 Fibrolamellar hepatocellular carcinoma. In the fibrous lamellae, collagen-rich connective tissue may undergo hyaline change (hyaline sclerosis of stroma, center of figure; hematoxylin and eosin stain)

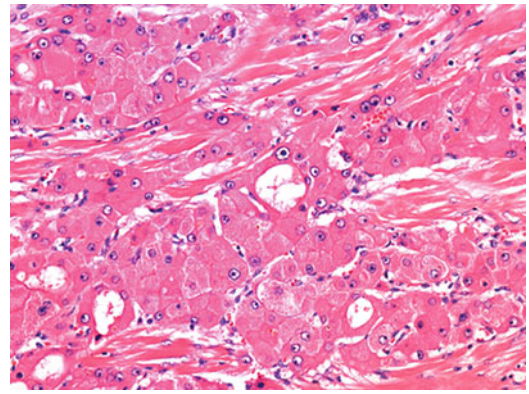

Fig. 7 Fibrolamellar hepatocellular carcinoma. The typical tumor cell is large, with abundant oxyphilic and granular cytoplasm. Nuclei are spherical to ovoid, with a hyperchromatic periphery and less dense center, and with prominent nucleoli. Pseudotubular lumina can be present (hematoxylin and eosin stain)

cellularity. However, it has been shown that the connective tissue content in FL-HCC is overall greater than in other liver tumors (Sarosi et al. 1991). The bands stain red in the van Gieson stain and bright blue with the trichrome stain. In the silver stain, the stroma shows a fine, dense, and complex network of reticulin fibers. The fibrolamellae often end in frayed edges. The fibrous matrix is predominantly composed of collagens I, III, and V, tenascin, and (less abundantly) basement membrane proteins such as laminin. In situ hybridization studies have shown that the fibroblastoid cells embedded in the matrix express collagen III-mRNA (Nerlich et al. 1992). FL-HCC cells may develop apparently intracellular lumina or spaces containing erythrocytes (Fig. 9).

Rare variants of FL-HCC, or certain regions in these tumors, may display a markedly solid component (Kojima et al. 2004). Based on the distinct cellular features and the distinct epithelial-stromal composition of FL-HCC, this neoplasm has been diagnosed by cytological methods (Suen et al. 1985; Perez-Guillermo et al. 1999; Jain et al. 2002; Kunz et al. 2002; Sarode et al. 2002; Mansouri et al. 2006; Gulati and Saran 2009). FL-HCC is an angioinvasive neoplasm that tends to invade large veins. Vascular invasion is present in about 40 % of the tumors (Farhi et al. 1983; Kakar et al. 2005). It was reported that FL-HCC arose in a background of focal nodular hyperplasia (Imkie et al. 2005). In a patient with generalized AA amyloidosis, amyloid was also deposited in the stroma of an FL-HCC (Llortea et al. 1994).

Ultrastructure

The neoplastic cells are rich in organelles and contain nuclei with often prominent cytoplasmic invaginations, the latter corresponding to the clear nuclear pseudoinclusions seen in light microscopy. The cytoplasm frequently contains numerous and densely packed, swollen mitochondria which are uniform in size and shape and often contain dense inclusions, resulting in a picture resembling oncocytes (Andreola et al. 1986). The endoplasmic reticulum is prominent, sometimes with dilated profiles. Dense cytoplasmic inclusions have been noted (Farhi et al. 1982; Andreola et al. 1986; Hasegawa 1996). Fully developed Mallory-Denk bodies are absent, but filamentous material resembling that found in these bodies has been detected (Caballero et al. 1985). Between two adjacent cells, lumina with microvilli can be found, representing abortive biliary canaliculi (Sato et al. 1997). The pale

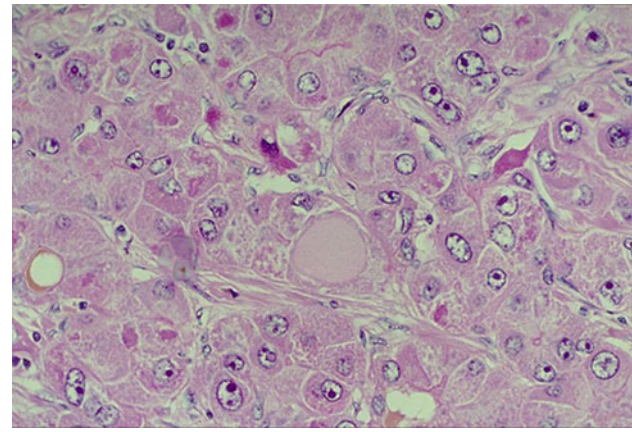

Fig. 8 Fibrolamellar hepatocellular carcinoma. Part of neoplastic cells contain large pale cytoplasmic inclusions (pale bodies, center of figure, hematoxylin and eosin stain)

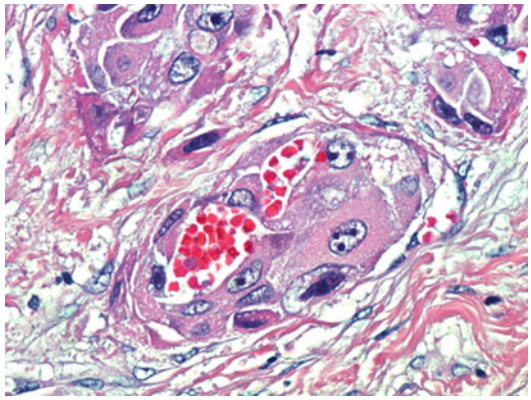

Fig. 9 Fibrolamellar hepatocellular carcinoma. Neoplastic cells can develop apparently intracellular lumina or spaces that contain erythrocytes (hematoxylin and eosin stain)

bodies seen at light microscopy ultrastructurally represent intracellular lumina lined with numerous microvilli. The central hyaline cores seen in part of the pale bodies are depositions of fine granular material (An et al. 1983). In part of the tumors, ultrastructural signs of neuroendocrine differentiation have been found (Payne et al. 1986; Garcia de Davila et al. 1987; Lloreta et al. 1994). The tumor cells are separated by broad, homogeneous bands of dense collagen with characteristic periodicity. The bands of collagen are lined by spindle cells with the features of fibroblasts or myofibroblasts, and these cells are interposed between collagen and tumor cells (Farhi et al. 1982).

Immunohistochemistry of the Epithelial Component

The immunophenotype of epithelial cells in FL-HCC has been analyzed in detail (Caballero et al. 1985; Teitelbaum et al. 1985; Berman et al. 1988). The cells of FL-HCC are positive for HepPar [hepatocyte paraffin 1] (Wennerberg et al. 1993; Klein et al. 2005; Ward et al. 2010; Patonai et al. 2013), suggesting that a hepatocyte-like differentiated cell is involved. Similar to conventional HCC, FL-HCC expresses the heparan sulfate proteoglycan, glypican-3, the positivity rate ranging from 17 % (Abdul-Al et al. 2010) to 59 % (Ward et al. 2010) and 64 % of cases (Shafizadeh et al. 2008). The tumor cells display canalicular membrane expression of pCEA (Ward et al. 2010). Interestingly, FL-HCC cells show a circumferential staining for pCEA, suggesting a loss of the normal apical-basolateral polarization of hepatocytes (own observations). The tumor cells may be positive for copper and copper-binding protein (Lefkowitch et al. 1983). The cells of FL-HCC typically and strongly express cytokeratin-7 in the cytoplasm (Van Eyken et al. 1990). Positivity for cytokeratin-7 has been confirmed in later studies (Gornicka et al. 2005; Klein et al. 2005; Abdul-Al et al. 2010; Fig. 10).

In one study, all cases of FL-HCC were positive for epithelial membrane antigen (EMA), and 36 % of FL-HCCs showed staining for cytokeratin-19, B72.3, and EpCAM (Ward

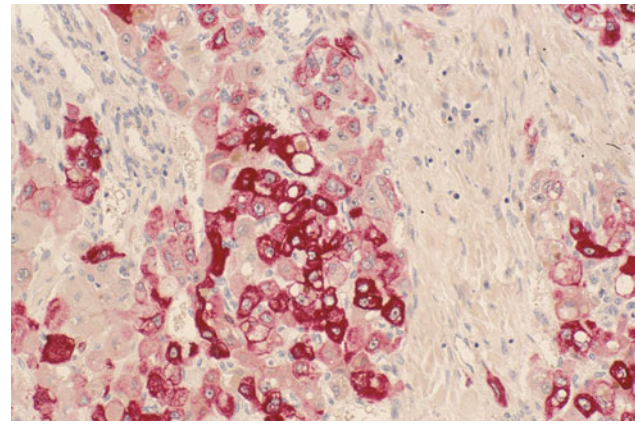

Fig. 10 Fibrolamellar hepatocellular carcinoma. Cells typically express cytokeratin-7 (CK7 immunostain)

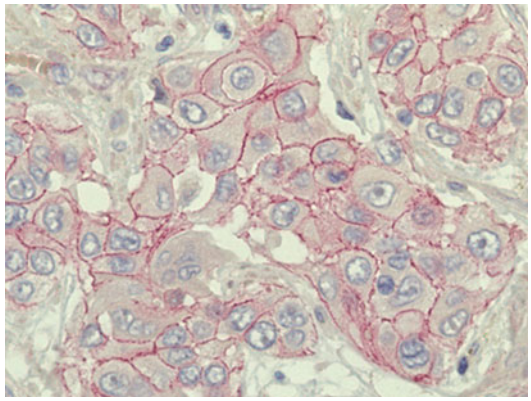

Fig. 11 Fibrolamellar hepatocellular carcinoma. The tumor cells show membranous reactivity for beta-catenin (beta-catenin immunostain)

et al. 2010). It has, however, been shown that FL-HCC is less often positive for CK19 than ordinary HCC (Abdul-Al et al. 2010). In ordinary HCC, expression of CK19 and EpCAM is associated with worse prognosis and the potential involvement of a bipotential progenitor cell (see the respective chapter). Cells of FL-HCC usually show a beta-catenin staining pattern similar to that of hepatocytes (Fig. 11).

Interestingly, the cells of FL-HCC are positive for CD68, a marker of lysosomal/endosomal membranes and typically positive in macrophages. The CD68 immunostaining, which involves almost all cases of FL-HCC, presents a distinctive granular, dot-like, or stippled pattern of the cytoplasm and had a sensitivity of 96 % and a specificity of 80 % (Ross et al. 2010). A part of FL-HCCs are immunoreactive for CD99 (Vasdev and Nayak 2003). Cells of FL-HCC produce several proteins that are also typical products of normal hepatocytes, including ferritin (Caballero et al. 1985) and alpha-1 antitrypsin, the latter sometimes accumulated in cytoplasmic globular inclusions or around such inclusions. FL-HCCs more often than ordinary HCCs express claudin-2 and claudin-5 (Patonai et al. 2011). FL-HCCs demonstrate hepatocyte growth factor receptor (c-met) levels similar to normal (Schoedel et al. 2003). In contrast to common HCC, FL-HCC has not been shown to express survivin (Kannangai et al. 2005). Similar to HCC, FL-HCC can express the CCK-B/gastrin receptor Caplin et al. 1999).

Immunohistochemistry of the Matrix Component

Immunohistochemically, the abundant extracellular matrix of FL-HCCs has been shown to contain large amounts of tenascin (Scoazec et al. 1996) and fibronectin (Jagirdar et al. 1985), whereas basement membrane proteins such as laminin seem to be less expressed. As FL-HCC cells more often express TGF-beta than HCC, it was suggested that fibrosclerosis and matrix protein production may be regulated by this fibrokine (Nerlich et al. 1992; Orsatti et al. 1997). The

tumor cells express a set of surface proteins that are important for cell-matrix interactions. The large epithelial cells are positive for alpha-1 integrin, E-cadherin, and the hepatocyte N-related cadherin, but lack beta-4 integrin (Scoazec et al. 1996). The tumor cells display a strong expression of CD44 (Washington et al. 1997), a widely distributed integral membrane protein and cell adhesion protein that has been implicated in cell-matrix contact, invasion, and metastatic spread. Most FL-HCCs revealed increased expression of active matrix metalloproteinase-2, in contrast to ordinary HCC (Schoedel et al. 2003). The sinusoid-like vascular channels of FL-HCC have diffusely CD34-positive endothelia (Abdul-Al et al. 2010).

Growth Features of FL-HCC

FL-HCCs typically grow with broad pushing borders. Invasion of adjacent parenchyma may be seen histologically, and portal tracts may be entrapped in the growing tumor front. FL-HCC has a very low mitotic activity, mitotic figures being normally structured in most cases. In a study of seven cases, the mitotic index was very low, i.e., 0–1 mitotic figure/10 high-power fields. The percentage of Ki-67 nuclear staining ranged from 1.0 to 29.7 %. There was no reactivity for S-phase kinase-associated protein (Skp) 2; all cases showed moderate to strong nuclear p16INK4 positivity (Dhingra et al. 2010).

Clear Cell Variant of Fibrolamellar Hepatocellular Carcinoma

A clear cell variant of FL-HCC has been described (Cheuk and Chan 2001). A 59-year-old female known to be a hepatitis B virus carrier was found to have a liver mass on routine checkup, visualized at CT as a solitary mass in the right liver lobe. Serum AFP was not elevated. The lesion was resected via right hepatectomy, and the patient was without of recurrence 13 months later. Grossly, the tumor was circumscribed, bosselated and formed a tumor measuring up to 50 mm in diameter. Histologically, the tumor consisted of oxyphilic cells and clear cells of about 50 % each, embedded in stroma consisting of strands of hyalinized collagen. Transitional forms between the two main cell types were seen. Pale bodies were found in part of the cells. Both the oxyphilic cells and the clear cells showed diffuse immunostaining for HepPar1, whereas antimitochondrial antibody stained the oxyphilic cells but weakened the clear cells. This variant has also been diagnosed by fine needle aspiration cytology (Kaplan and Hoda 2007.)

Glandular Variant of Fibrolamellar Hepatocellular Carcinoma

This probably rare and somewhat intriguing variant of FL-HCC is characterized by components of acinar or pseudoglandular structures, sometimes with mucin production (Goodman et al. 1985; Tanaka et al. 2005). The cells lining the gland-like spaces are structurally similar to other FL-HCC cells, but are usually smaller. Mucin is detectable within the neoplastic cells but also in the lumina of acinar profiles, and the mucinous substance is positive for mucicarmine and alkaline alcian blue (Goodman et al. 1985). The cells lining the pseudoglandular spaces immunohistochemically share features with cholangiocellular elements, i.e., positivity for biliary-type cytokeratins. This phenotype was also found in lymph node metastases of the tumor, a phenomenon which may exclude a collision tumor (Tanaka et al. 2005). This is the reason why such neoplasms were also termed, combined fibrolamellar carcinoma and cholangiocarcinoma, with biphenotypic antigen expression (Tanaka et al. 2005). This cholangiocyte-like differentiation is not associated with other histologic features of true cholangiocarcinoma; the biologic behavior of such combined tumors seems to be more in keeping with pure FL-HCC.

Combined Patterns

Combined tumors, albeit very rare, are of some theoretical interest because they may shed light on the cell of origin of FL-HCC. Exceptionally,

FL-HCC occurred in combination with conventional HCC (Hasegawa 1996; Okano et al. 1998; Seitz et al. 2002), the FL-HCC component being cytokeratin-7 positive, in contrast to the HCC component (Seitz et al. 2002; Zermani et al. 2005). In the tumor described by Hasegawa (1996), a common HCC element with trabecular structure existed at the periphery of the FL-HCC. In contrast, the tumor described by Seitz et al. (2002) showed HCC at the center of a large FL-HCC. In few cases, FL-HCC transformed into common HCC in recurrent lesions of the residual liver and in a remote metastasis (Yamamoto et al. 1999; Chang et al. 2003). FL-HCC has also been found to be associated synchronously with common HCC located in another part of the liver (Okada et al. 1993).

FL-HCC has been observed 5 years after hepatocellular adenoma in a 14-year-old girl (Terracciano et al. 2004). Nodular hyperplasia associated with or surrounding FL-HCC has been observed (Saul et al. 1987; Saxena et al. 1994). In a 14-year-old girl, a 9 cm subcapsular nodule was present in the right lobe of the liver, with a distinct zonation: ca central grayish white area of FL-HCC and peripheral fleshy, tan-colored rim of nodular hyperplastic liver parenchyma resembling FNH. It was suggested that the hyperplasia was a reaction to an abnormal arterialization of the tissue, the arteries originating from the central FL-HCC (Saxena et al. 1994). It has been assumed that FL-HCC may be the malignant counterpart of FNH (Vecchio et al. 1984), but there is no convincing evidence for this.

Biology of Disease

FL-HCC reveals a metastasizing pattern different from ordinary HCC. FL-HCC tends to metastasize within the abdominal cavity. This may lead to intriguing and misleading patterns, such as metastasis to the pancreatic head (Thirabanjasak et al. 2009) or the skeletal muscle (Kutluk et al. 2001). FL-HCC can metastasize to the ovaries (Benito et al. 2012) and has been shown to produce ovarian Krukenberg tumor as first tumor manifestation (Montero et al. 2007; Bilbao et al. 2008). FL-HCC is also a primary liver tumor that typically metastasizes to locoregional lymph nodes (Stipa et al. 2006; Tsilividis et al. 2010; Gras et al. 2012, Fig. 12), lymph node positivity representing a negative prognosticator and considered to be an indication for lymph node dissection (Yamamoto et al. 1995; Hiramatsu et al. 1999; Jaeck 2003).

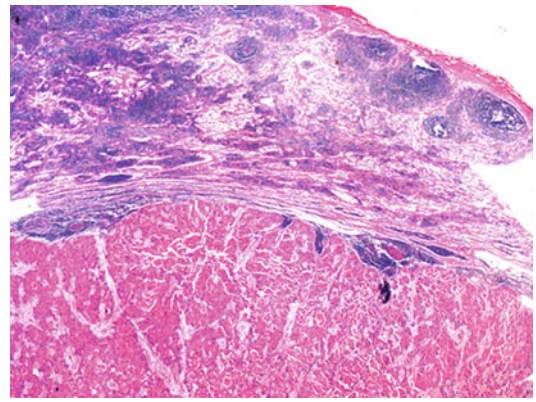

Fig. 12 Lymph node metastasis of fibrolamellar hepatocellular carcinoma. The typical tumor morphology, with strongly eosinophilic cells and fibrous bands, is recapitulated in metastatic disease (hematoxylin and eosin stain)

As ordinary HCC, FL-HCC can invade large vessels, including the inferior vena cava, and spread to the heart cavities and pulmonary arteries (Asrani and LaRusso 2012; Knudson et al. 2012).

Several studies have advocated that FL-HCC is less aggressive than conventional HCC (Berman et al. 1980; Craig et al. 1980; Lack et al. 1983; Wetzel et al. 1983; Nagorney et al. 1985; Hodgson 1987; Kaczynski et al. 1996; Pinna et al. 1997; Okuda 2002; El-Serag and Davila 2004; Meriggi and Forni 2007), and even in textbooks it is or was mentioned that FL-HCC is associated with a favorable prognosis (Everson and Trotter 2003; Sherlock and Dooley 2003; Ferrell 2004). There are single reports of long-term survival after surgery alone (Ishikawa et al. 2007), but in contrast to older suggestions, there is now evidence that the biology of FL-HCC in comparison with ordinary HCC is a complex issue, the presence or absence of differences in part being affected by artifacts of methodology (Njei 2014). For example, in patients with FL-HCC, the better outcome

in some patients is due to the absence of cirrhosis in these patients, and the presentation at a non-advanced stage, rather than its distinct clinicopathologic features (Stevens et al. 1995; Zografos et al. 1997). There is also evidence that tumor stage was in fact the most significant factor for prognosis in patients treated with resection and transplantation (Ringe et al. 1992; El-Gazzaz et al. 2000). The biology of FL-HCC shows, nevertheless, striking differences in comparison with conventional HCC, mainly what regards metastatic patterns and causes of death (Epstein et al. 1999). A study of the Pediatric Oncology Group (Pediatric Intergroup Hepatoma Protocol), analyzing 46 patients, showed that children with FL-HCC did not have a favorable prognosis and do not respond any differently to current therapeutic regimens than patients with common HCC (Katzenstein et al. 2003). In a study of 20 resected cases, the 5-year survival was 45 %, the overall mortality was 60 %, and mortality of FL-HCC was higher with metastatic disease at presentation. Age, gender, and tumor size did not correlate with survival (Kakar et al. 2005). In another retrospective investigation, however, age was a prognosticator, in that patients diagnosed before 23 of age had a worse outcome than those diagnosed after age 23 (Moreno-Luna et al. 2005). In a study on 41 patients, median tumor size in 28 patients treated with resection was 9 cm, 50 % of the patients had lymph node metastases, and nodal metastases were the only negative prognostic factor. Seventeen of these patients (61 %) underwent a second resection for recurrent disease. The 5-year survival of resected patients was 76 %, but 5-year recurrence-free survival was only 18 %, illustrating that this tumor has a characteristic tendency for recurrence (Stipa et al. 2006). In a series of ten patients, FL-HCC was treated with resection followed by close surveillance and aggressive management of relapse. Relapse occurred in all ten cases at a median of 2.2 years. With a combination of re-resection, systemic chemotherapy, and radiotherapy, the overall median survival was 9.3 years (Maniaci et al. 2009). FL-HCC is different from common HCC in its recurrence pattern after liver transplantation. Late recurrence (>1000 days) is typical for FL-HCC, and the tumors tend to be associated predominantly with extrahepatic or combined extra- and intrahepatic recurrence, while well-differentiated HCCs tended to recur within the liver (Schlitt et al. 1999). In the recent SIOPEL/Childhood Liver Tumour Strategy Group study on 24 patients with FL-HCC, long-term overall survival in FL-HCC and ordinary HCC was similar (Weeda et al. 2013). In contrast, the results of a nationwide survey using SEER data show that surgically treated patients with FL-HCC had better long-term outcomes than those with conventional HCC (Mayo et al. 2014). In the setting of a systematic review and meta-analysis of 368 FL-HCC patients, it turned out that overall there was a significant increase in 5-year survival for FL-HCC versus conventional HCC, but this difference was not detectable in the subgroup of non-cirrhotic patients (Njei et al. 2014).

Differential Diagnosis

There are conventional HCCs having a central scar and a scalloped tumor margin resembling FNH and FL-HCC. In one study, such tumors predominantly occurred in non-cirrhotic livers of patients in their 60s and were associated with a good surgical outcome (Yamamoto et al. 2006). There are other primary liver carcinomas with a marked stromal component, which may cause diagnostic problems (Malouf et al. 2009). Histologically, sclerosing hepatocellular carcinoma may mimic FL-HCC, but these tumors have smaller epithelial cells, the stroma is more cellular and not band-like, and the tumors occur in middle-aged persons, show a male predominance, and are associated with the typical HCC risk factors (Haratake and Horie 1989).

Pathogenesis

Cell Lineage(s) Involved

The cell lineage of FL-HCC is still not well known, despite the fact that the tumor cells resemble hepatocytes with oxyphilic features and that

the cells share with hepatocytes immunoreactivity for a hepatocyte marker, HepPar. Other findings that support a hepatocyte-like lineage in FL-HCC is the positivity for glypican-3, a canalicular staining pattern with polyclonal CEA/pCEA (see above), and the positivity for albumin mRNA by in situ hybridization (Ward et al. 2010). In contrast to normal hepatocytes, FL-HCC cells are usually positive for cytokeratin-7 and sometimes for cytokeratin-19 and for epithelial membrane antigen (EMA), normally expressed in cholangiocytes of the normal liver. These results have been interpreted to suggest that FL-HCCs show a dual differentiation, i.e., both hepatocellular and cholangiocellular (Ward et al. 2010). There is also immunohistochemical evidence for a stem cell-associated phenotype of FL-HCC. The tumor cells were positive for the stem cell markers CD133 and CD44, revealed reduced cell cycle progression, and displayed evidence of reduced differentiation (Zenali et al. 2010).

Cytogenetic Findings

FL-HCC generally reveals less ploidy and chromosomal aberrations than ordinary HCC and hence a greater genomic homogeneity (Lapis et al. 1990; Orsatti et al. 1994; Sirivatanauksorn et al. 2001; Ward and Waxman 2011). Specifically, 8p- and 17q+, which are typical for HCC, hardly occur in FL-HCC (Terraciano and Tornillo 2003). Also allele loss seems to be much less common that in conventional HCC (Ding et al. 1993). FL-HCCs with chromosomal alterations seem to behave more aggressively than tumors without cytogenetic abnormalities (Kakar et al. 2009). By the use of comparative genomic hybridization, chromosomal imbalances were identified in 6 out of 11 (55 %) of cases, and the mean number of aberrations per case was 3.9 for all cases and 7.2 in abnormal cases. The most common abnormalities were found in chromosomes 1, 7, 8 and 18, with gains in 1q and 8q and loss of 18q being the most common alterations (Kakar et al. 2009; review: Ward and Waxman 2011). As outlined in the next paragraph, 7p has a gene (AGR2) that is overexpressed in FL-HCC and affects cancer cell spread. Some of the tumors show complex chromosomal patterns, such as a nearly triploid karyotype (Hany et al. 1997). Genomic hybridization (CGH) studies demonstrated striking differences in recurrent cytogenetic aberrations between FL-HCC and common HCC (Wilkins et al. 2000). Loss of heterozygosity (LOH) on 6q at the mannose 6-phosphate/insulin-like growth factor II receptor locus has found in 33 % of FL-HCCs, in comparison with 69 % in common HCCs, suggesting that this gene may act as a tumor suppressor in HCC and FL-HCC (DeSouza et al. 1995). Previously (and in apparent contrast to conventional HCC), epigenetic instability manifesting as methylation of tumor suppressor promoters had been reported to be rare in FL-HCC (Vivekanandan and Torbenson 2008). In a later study, it was shown that FL-HCCs display frequent and distinct gene-specific hypermethylation in the absence of significant global hypomethylation. Frequent aberrant hypermethylation was found for the cyclin D2 and the RASSF1A genes as well as for the microRNA genes mir-9-1 and mir-9-2 (Tränkenschuh et al. 2010). The genomic features of FL-HCC loose homogeneity as a function of the tumor's spread, and recurrent metastatic tumors have complex karyotypes (Lowichik et al. 1996).

Molecular Findings

FL-HCC displays a distinct genomic landscape (Darcy et al. 2015b) and shows a unique genomic profile uncovering three robust molecular classes, i.e., a proliferation class, an inflammation class, and an unannotated class (Cornella et al. 2015). Recently, a recurrent DNAJB1-PRKACA chimeric transcript, arising as a result of a ~400 kb deletion on chromosome 19, was detected in FL-HCC. The chimeric RNA was predicted to code for a homolog of the molecular chaperone DNAJ, fused in frame with PRKACA, the catalytic domain of protein kinase A. The chimeric protein is expressed in tumor tissue and retains kinase activity (Honeyman et al. 2014; Xu et al. 2015).

FL-HCCs display various other molecular abnormalities. FL-HCC overexpresses epidermal growth factor receptor (EGFR), similar to conventional HCC (Buckley et al. 2008), probably due to polysomy 7 rather than gene amplification. Immunohistochemically, EGFR was strongly overexpressed on the cell membranes of more than 90 % of tumors tested (Buckley et al. 2006). FL-HCC exhibits overexpression of genes in the RAS, MAPK, PIK3, and xenobiotic degradation pathways (Kannangai et al. 2007) and reveals mTORC1 activation and FGFR1 overexpression (Riehle et al. 2015). FL-HCC cells express anterior gradient 2 (AGR2; Vivekanandan et al. 2009), a protein that is critical for normal embryonic development. AGR2 is located on chromosome 7p21.3 (Petek et al. 2000) and encodes the human homolog of a secreted protein identified in *Xenopus* (cement gland-specific gene), where it determines the formation of anterior structures during the generation of ectoderm. In the adult mammalian organism, AGR2 is mainly expressed in cells of the gastrointestinal tract. In the small intestine of mice, expression is found predominantly in Paneth, neuroendocrine, and goblet cells (Komiya et al. 1999; Wang et al. 2008). It has been shown that AGR2 encodes a protein disulfide isomerase (enzymes that aid protein folding and assembly), which is essential for the production of the intestinal mucin MUC2 (Park et al. 2009). A critical interacting protein of AGR2 is the ATP-binding protein, reptin (Maslon et al. 2010). AGR2 is expressed in several cancers, including pancreatic cancer, breast cancer, and lung cancer, where it affects cancer cell survival (via the p53 pathway), cancer cell motility, and cancer spread. Specifically, AGR2 promotes metastatic spread and its expression is associated with poor survival. This metastasis-promoting activity of AGR2 is repressed by ErbB3-binding protein 1 (Zhang et al. 2010). In FL-HCC, overexpression of AGR2 is associated with several polymorphisms, but no mutations (Vivekanandan et al. 2009). In contrast to ordinary HCC, where missense mutations and interstitial deletions of the beta-catenin gene and nuclear accumulation of beta-catenin are common, beta-catenin gene alterations were not yet detected in FL-HCCs (Terris et al. 1999), so that the Wnt-beta-catenin signaling pathway does not seem to be involved in the carcinogenesis of this tumor.

FL-HCC reveals alterations of mitochondrial structure and function. It is well known that ordinary HCCs show mitochondrial DNA mutations. In one molecular study, approximately 50 % of ordinary HCCs had lower levels of total mitochondrial DNA than paired nonneoplastic tissue, associated with deletions of the mitochondrial DNA control region. Despite their apparently increased numbers of mitochondria, primary FL-HCCs had lower levels of total mitochondrial DNA, while metastatic FL-HCCs had greatly increased mitochondrial DNA levels. Complete sequencing of the entire mitochondrial genome in FL-HCC identified several somatic mutations, but no consistent pattern of mutations was found (Vivekanandan et al. 2010).

HBV Infection

Ordinary HCC has an etiologic association with HBV in numerous cases. It was therefore of interest to test whether FL-HCC is also related to HBV infection, although this tumor is not associated with liver cirrhosis. The finding of integrated HBV DNA in certain instances of FL-HCC tissue may be consistent with an oncogenic role of HBV in at least a subset of the tumors (Davison et al. 1990; Dadke et al. 2002). This question has to be addressed in more detail with larger numbers of tumors.

References

Abdul-Al HM, Wang G, Makhlouf HR, Goodman ZD (2010) Fibrolamellar hepatocellular carcinoma: an immunohistochemical comparison with conventional hepatocellular carcinoma. Int J Surg Pathol 18:313–318

Agarwal VR, Takayama K, Van Wyk JJ, Sasano H, Simpson ER, Bulun SE (1998) Molecular basis of severe gynecomastia associated with aromatase expression in a fibrolamellar hepatocellular carcinoma. J Clin Endocrinol Metab 83:1797–1800

Albaugh JS, Keeffe EB, Krippaehne WW (1984) Recurrent obstructive jaundice caused by fibrolamellar hepatocellular carcinoma. Dig Dis Sci 29:762–767

Al-Matham K, Alabed I, Zaidi SZ, Qushmaq KA (2011) Cold agglutinin disease in fibrolamellar hepatocellular carcinoma: a rare association with a rare cancer variant. Ann Saudi Med 31:197–200

Altmann HW (1990) Some histological remarks on the fibrolamellar carcinoma of the liver. Pathol Res Pract 186:63–69

An T, Ghatak N, Kastner R, Kay S, Lee HM (1983) Hyaline globules and intracellular lumina in a hepatocellular carcinoma. Am J Clin Pathol 79:392–396

Andreola S, Audisio RA, Lombardi L (1986) A light microscopic and ultrastructural study of two cases of fibrolamellar hepatocellular carcinoma. Tumori 72:609–616

Arista-Nasr J, Gutierrez-Villalobos L, Nuncio J, Maldonado H, Bornstein-Quevedo L (2002) Fibrolamellar hepatocellular carcinoma in Mexican patients. Pathol Oncol Res 8:133–137

Arora R (2015) Fibrolamellar hepatocellular carcinoma presenting as obstructive jaundice: uncommon presentation of a rare entity. Pol J Radiol 80:168–171

Asrani SK, LaRusso NF (2012) Fibrolamellar hepatocellular carcinoma presenting with Budd-Chiari syndrome, right atrial thrombus, and pulmonary emboli. Hepatology 55:977–978

Bedi DG, Kumar R, Morettin LB, Gourley K (1988) Fibrolamellar carcinoma of the liver: CT, ultrasound and angiography. Case report. Eur J Radiol 8:109–112

Benito V, Segura J, Martinez MS, Arencibia O, Lubrano A (2012) Fibrolamellar hepatocellular carcinoma metastatic to the ovary. J Obstet Gynaecol 32:200–202

Berman MM, Libbey NP, Foster JH (1980) Hepatocellular carcinoma: polygonal cell type with fibrous stroma – an atypical variant with a favorable prognosis. Cancer 46:1448–1455

Berman MA, Burnham JA, Sheahan DG (1988) Fibrolamellar carcinoma of the liver: an immunohistochemical study of nineteen cases and a review of the literature. Hum Pathol 19:784–794

Bhajee F, Locketz ML, Krige JE (2009) Fibrolamellar hepatocellular carcinoma at a tertiary centre in South Africa: a case series. S Afr J Surg 47:108–111

Bilbao I, Vilallonga R, Allende E, Montero A, Quiroga S, Viladomiu L, Charco R, Margarit C (2008) Krukenberg's tumor as the first clinical manifestation of fibrolamellar hepatocarcinoma (in Spanish). Gastroenterol Hepatol 31:341–346

Brandt D, Johnson CD, Stephens DH, Weiland LH (1988) Imaging of fibrolamellar carcinoma. Am J Roentgenol 151:295–298

Buckley AF, Burgart LJ, Kakar S (2006) Epidermal growth factor receptor expression and gene copy number in fibrolamellar hepatocellular carcinoma. Hum Pathol 37:410–414

Buckley AF, Burgart LJ, Sahai V, Kakar S (2008) Epidermal growth factor receptor expression and gene copy number in conventional hepatocellular carcinoma. Am J Clin Pathol 129:245–251

Caballero T, Aneiros J, Lopez-Caballero J, Gomez-Morales M, Nogales F (1985) Fibrolamellar hepatocellular carcinoma. An immunohistochemical and ultrastructural study. Histopathology 9:445–456

Caplin M, Khan K, Savage K, Rode J, Varro A, Michaeli D, Grimes S, Brett B, Pounder R, Dhillon A (1999) Expression and processing of gastrin in hepatocellular carcinoma, fibrolamellar carcinoma and cholangiocarcinoma. J Hepatol 30:519–526

Caseiro-Alves F, Zins M, Mahfouz AE, Rahmouni A, Vilgrain V, menu Y, Mathieu D (1996) Calcification in focal nodular hyperplasia: a new problem for differentiation from fibrolamellar hepatocellular carcinoma. Radiology 198:889–892

Chagas AL, Kikuchi L, Herman P, Alencar RS, Tani CM, Diniz MA, Pugliese V, Rocha MS, D'Albuquerque LA et al (2015) Clinical and pathological evaluation of fibrolamellar hepatocellular carcinoma: a single center study of 21 cases. Clinics (Sao Paulo) 70:207–213

Chang YC, Dai YC, Chow NH (2003) Fibrolamellar hepatocellular carcinoma with a recurrence of classic hepatocellular carcinoma: a case report and review of Oriental cases. Hepatogastroenterology 50:1637–1640

Cheuk W, Chan JK (2001) Clear cell variant of fibrolamellar carcinoma of the liver. Arch Pathol Lab Med 125:1235–1238

Chun YS, Zimmitti G (2013) Fibrolamellar variant of hepatocellular carcinoma. Recent Results Cancer Res 190:101–110

Collier NA, Weinbren K, Bloom SR, Lee YC, Hodgson HJ, Blumgart LH (1984) Neurotensin secretion by fibrolamellar carcinoma of the liver. Lancet 1:538–540

Cornella H, Alsinet C, Sayols S, Zhang Z, Hao K, Cabellos L, Hoshida Y, Villanueva A, Thung S, Ward SC, Rodriguez-Carunchio L et al (2015) Unique genomic profile of fibrolamellar hepatocellular carcinoma. Gastroenterology 148:806–818

Craig JR, Peters RL, Edmondson HA, Omata M (1980) Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinicpathologic features. Cancer 46:372–379

Cruz O, Laguna A, Vancells M, Krauel L, Medina M, Mora J (2008) Fibrolamellar hepatocellular carcinoma in an infant and literature review. J Pediatr Hematol Oncol 30:968–971

Dadke D, Jaganath P, Krishnamurthy S, Chiplunkar S (2002) The detection of HBV antigens and HBx-transcripts in an Indian fibrolamellar carcinoma patient: a case study. Liver 22:87–91

Dahan MH, Kastell P (2002) Fibrolamellar hepatic carcinoma with a presentation similar to that of septic pregnancy. A case report. J Reprod Med 47:47–49

Darcy DG, Malek MM, Kobos R, Klimstra DS, DeMatteo R, La Quaglia MP (2015a) Prognostic factors in fibrolamellar carcinoma in young people. J Pediatr Surg 50:153–156

Darcy DG, Ciaroni-Clarke R, Murphy JM, Honeyman JN, Bhanot U, laQuaglia MP, Simon SM (2015b) The genomic landscape of fibrolamellar hepatocellular carcinoma: whole genome sequencing of then patients. Oncotarget 6:755–770

Davison FD, Fagan EA, Portmann B, Williams R (1990) HBV-DNA sequences in tumor and nontumor tissue in a patient with the fibrolamellar variant of hepatocellular carcinoma. Hepatology 12:676–679

De Gaetano AM, Nure E, Grossi U, Frongillo F, Russo R, Vecchio FM, Lirosi MC et al (2013) Fibrolamellar hepatocellular carcinoma with biliary tumor thrombus: an unreported association. Jpn J Radiol 31:706–712

De Souza AT, Hankins GR, Washington MK, Fine RL, Orton TC, Jirtle RL (1995) Frequent loss of heterozygosity on 6q at the mannose 6-phosphate/insulin-like growth factor II receptor locus in human hepatocellular tumors. Oncogene 10:1725–1729

Debray D, Pariente D, Fabre M, Foucaud P, Valayer J, Bernard O (1994) Fibrolamellar hepatocellular carcinoma: report of a case mimicking a liver abscess. J Pediatr Gastroenterol Nutr 19:468–472

Dellaportas D, Lykoudis P, Tsagkas A, Voros D, Kondi-Pafiti A (2011) A large fibrolamellar hepatocellular carcinoma in a 17-year-old male body builder. J BUON 16:780

Dhingra S, Li W, Tan D, Zenali M, Zhang H, Brown RE (2010) Cell cycle biology of fibrolamellar hepatocellular carcinoma. Int J Clin Exp Pathol 3:792–797

Ding SF, Delhanty JD, Bowles L, Dooley JS, Wood CB, Habib NA (1993) Infrequent chromosome allele loss in fibrolamellar carcinoma. Br J Cancer 67:244–246

Eckstein RP, Bambach CP, Stiel D, Roche J, Goodman BN (1988) Fibrolamellar carcinoma as a cause of bile duct obstruction. Pathology 20:326–331

Edmondson HA (1956) Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. Arch Dis Child 91:168–186

Eggert T, McGlynn KA, Duffy A, Manns MP, Greten TF, Altekruse SF (2013) Fibrolamellar hepatocellular carcinoma in the US, 2000–2010: a detailed report on frequency, treatment and outcome based on the surveillance, epidemiology, and end results database. U Eur Gastroenterol J 1:351–357

Ehrenfried JA, Zhou Z, Thompson JC, Evers BM (1994) Expression of the neurotensin gene in fetal human liver and fibrolamellar carcinoma. Ann Surg 220:484–489

El-Gazzaz G, Wong W, El-Hadary MK, Gunson BK, Mirza DF, Mayer AD, Buckels JA, McMaster P (2000) Outcome of liver resection and transplantation for fibrolamellar hepatocellular carcinoma. Transpl Int 13 (Suppl 1):S406–S409

El-Seraq HB, Davila JA (2004) Is fibrolamellar carcinoma different from hepatocellular carcinoma? A US population-based study. Hepatology 39:798–803

Epstein BE, Pajak TF, Haulk TL, Herpst JM, Oder SE, Abrams RA (1999) Metastatic nonresectable fibrolamellar hepatoma: prognostic features and natural history. Am J Clin Oncol 22:22–28

Everson GT, Trotter JF (2003) Transplantation of the liver. In: Schiff ER, Sorrell MF, Maddrey WC (eds) Diseases of the liver, vol 2, 9th edn. Lippincott, Williams and Wilkins, Philadelphia, pp 1585–1614

Farhi DC, Shikes RH, Silverberg SG (1982) Ultrastructure of fibrolamellar oncocytic hepatoma. Cancer 50:702–709

Farhi et al (1983) PubMed PMID 6311397

Ferrell LD (2004) Benign and malignant tumors of the liver. In: Odze RD, Goldblum JR, Crawford JM (eds) Surgical pathology of the GI tract, liver, biliary tract and pancreas. Souanders, Philadelphia, p 1012

Francis IR, Agha FP, Thompson NW, Keren DF (1986) Fibrolamellar hepatocarcinoma: clinical, radiologic, and pathologic features. Gastrointest Radiol 11:67–72

Friedman AC, Lichtenstein JE, Goodman Z, Fishman EK, Siegelman SS, Dachman AH (1985) Fibrolamellar hepatocellular carcinoma. Radiology 157:583–587

Garcia de Davila MT, Gonzalez-Crussi F, Mangkornkanok M (1987) Fibrolamellar carcinoma of the liver in a child: ultrastructural and immunohistologic aspects. Pediatr Pathol 7:319–331

Gibson AA, Soreide O, Hemingway AP, Carr DH, Blumgart LH, Allison DJ (1986) The radiology of fibrolamellar carcinoma. Clin Radiol 37:355–358

Goodman et al (1985) PubMed PMD 2578078

Gornicka B, Ziarkiewicz-Wroblewska B, Wroblewsi T, Wilczynski GM, Koperski L, Krawczyk M, Wasiutynski A (2005) Carcinoma, a fibrolamellar variant – immunohistochemical analysis of 4 cases. Hepatogastroenterology 52:519–523

Gras P, Truant S, Boige V, Ladrat L, Rougier P, Pruvot FR, Hebbar M (2012) Prolonged complete response after GEMOX chemotherapy in a patient with advanced fibrolamellar hepatocellular carcinoma. Case Rep Oncol 5:169–172

Gruner BA, DeNapoli TS, Andrews W, Tomlinson G, Bowman L, Weitman SD (1998) Hepatocellular carcinoma in children associated with Gardner syndrome or familial adenomatous polyposis. J Pediatr Hematol Oncol 20:274–278

Gulati G, Saran RK (2009) Fine needle aspiration cytology of fibrolamellar hepatocellular carcinoma: recognizing the oncocytic hepatocyte. Indian J Pathol Microbiol 52:288–289

Gupta P, Dhar S, Strickland NH (1999) Fibrolamellar carcinoma :an unusual clinico-radiological presentation. Eur J Radiol 32:119–123

Hany MA, Betts DR, Schmugge M, Schönle E, Niggli FK, Zachmann M, Plüss HJ (1997) A childhood fibrolamellar hepatocellular carcinoma with increased aromatase activity and a near triploid karyotype. Med Pediatr Oncol 28:136–138

Haratake J, Horie A (1989) A histopathologic comparative study of European cases of fibrolamellar carcinoma and

Japanese cases of sclerosing hepatocellular carcinoma (in Japanese). Gan No Ronsho 35:793–798
Haratake J, Horie A, Lee SD, Huh MH (1990) Fibrolamellar carcinoma of the liver in a middle-aged Korean man. J UOEH 12:349–354
Hasegawa A (1996) Fibrolamellar hepatocellular carcinoma: a report of a resected case with an electron microscopic and flow cytometric analysis. Pathol Int 46:84–90
Hemming AW, Langer B, Sheiner P, Greig PD, Taylor BR (1997) Aggressive surgical management of fibrolamellar hepatocellular carcinoma. J Gastrointest Surg 1:342–346
Hernandez-Castillo E, Mondragon-Sanchez R, Garduno-Lopez AL, Gomez-Gomez E, Ruiz-Molina JM et al (2005) Hepatocellular carcinoma in the youth. A comparative analysis with hepatocellular carcinoma in adulthood. Hepatogastroenterology 52:903–907
Hiramatsu K, Okamoto K, Uesaka K, Muakiyama H, Seno T (1999) Surgical management for lymph node recurrence of resected fibrolamellar hepatocellular carcinoma: a case report. Hepatogastroenterology 46:1160–1163
Hodgson HJ (1987) Fibrolamellar cancer of the liver. J Hepatol 5:241–247
Honeyman JN, Simon EP, Robine N, Chiaroni-Clarke R, Darcy DG, Lim II, Gleason CE et al (2014) Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. Science 343:1010–1014
Hoshino H, Katada N, Nishimura D, Imada J, Morita K, Yoshida N, Sano H, Okamoto K, Kato K (1996) Case report: fibrolamellar hepatocellular carcinoma in a Japanese woman: a case report and review of Japanese cases. J Gastroenterol Hepatol 11:551–555
Ichikawa T, Federle MP, Grazioli L, Madariaga J, Nalesnik M, Marsh W (1999) Fibrolamellar hepatocellular carcinoma: imaging and pathologic findings in 31 recent cases. Radiology 213:352–361
Ichikawa T, Federle MP, Grazioli L, Marsh W (2000) Fibrolamellar hepatocellular carcinoma: pre-and posttherapy evaluation with CT and MR imaging. Radiology 217:145–151
Imkie M, Myers SA, Li Y, Fan F, Bennett TL, Forster J, Tawfik O (2005) Fibrolamellar hepatocellular carcinoma arising in a background of focal nodular hyperplasia: a report of 2 cases. J Reprod Med 50:633–637
Ishikawa T, Kamimura H, Tsuchiya A, Watanabe K, Seki K, Ohta H, Yoshida T, Musya N et al (2007) A resected case of fibrolamellar hepatocellular carcinoma with chronic hepatitis(type B) (in Japanese). Nippon Shokakibyo Gakkai Zasshi 104:1076–1081
Jaeck D (2003) The significance of hepatic pedicle lymph nodes metastases in surgical management of colorectal liver metastases and of other liver malignancies. Ann Surg Oncol 10:1007–1011
Jagirdar J, Ishak KG, Colombo M, Brambilla C, Paronetto F (1985) Fibronectin patterns in hepatocellular carcinoma and its clinical significance. Cancer 56:1643–1648
Jain M, Niveditha SR, Bharadwaj M, Pathania OP (2002) Cytological features of fibrolamellar variant of hepatocellular carcinoma with review of literature. Cytopathology 13:179–182
Kaczynski J, Gustavsson B, Hansson G, Wallerstedt S (1996) Fibrolamellar hepatic carcinoma in an area with a low incidence of primary liver cancer: a retrospective study. Eur J Surg 162:367–371
Kakar S, Burgart LJ, Batts KP, Garcia J, Jain D, Ferrell LD (2005) Clinicopathologic features and survival in fibrolamellar carcinoma: comparison with conventional hepatocellular carcinoma with and without cirrhosis. Mod Pathol 18:1417–1423
Kakar S, Chen X, Ho C, Burgart LJ, Sahai V, Dachrut S, Yabes A, Jain D, Ferrell LD (2009) Chromosomal changes in fibrolamellar hepatocellular carcinoma detected by array comparative genomic hybridization. Mod Pathol 22:134–141
Kanai T, Takabayashi T, Kawano Y, Kuramochi S, Miyazawa N (2004) A case of postoperative recurrence of fibrolamellar hepatocellular carcinoma with increased vitamin B12 binding capacity in a young Japanese female. Jpn J Clin Oncol 34:346–351
Kane RA, Curatolo P, Khettry U (1987) "Scar sign" on computed tomography and sonography in fibrolamellar hepatocellular carcinoma. J Comput Tomogr 11:27–30
Kannangai R, Wang J, Liu QZ, Sahin F, Torbenson M (2005) Survivin overexpression in hepatocellular carcinoma is associated with p53 dysregulation. Int J Gastrointest Cancer 35:53–60
Kannangai R, Vivekanandan P, Martinez-Murillo F, Chori M, Torbenson M (2007) Fibrolamellar carcinomas show overexpression of genes in the RAS, MAPK, PIK3, and xenobiotic degradation pathways. Hum Pathol 38:639–644
Kaplan JS, Hoda RS (2007) Clear cell variant of fibrolamellar hepatocellular carcinoma: diagnosis of recurrence by fine-needle aspiration. Diagn Cytopathol 35:459–462
Katzenstein HM, Krailo MD, Malogolowkin MH, Ortega JA, Qu W, Douglass EC, Feusner JH et al (2003) Fibrolamellar hepatocellular carcinoma in children and adolescents. Cancer 97:2006–2012
Kim T, Hori M, Onishi H (2009) Liver masses with central or eccentric scar. Semin Ultrasound CT MR 30:418–425
Klein WM, Molmenti EP, Colombani PM, Grover DS, Schwarz KB, Boitnott J, Torbenson MS (2005) Primary liver carcinoma arising in people younger than 30 years. Am J Clin Pathol 124:512–518
Knudson JD, Goldberg JF, Ayres NA (2012) Fibrolamellar hepatocellular carcinoma with cardiac spread causing severe inferior vena cava obstruction in a 9-year-old child. Pediatr Cardiol 33:872–873
Kohno H, Nagasue N, Taniura H, Nakamura T, Nagaoka S (1988) Fibrolamellar carcinoma of the liver – a case report from Japan and a review of the literature. HPB Surg 1:77–80
Kojima M, Kunimura T, Inagaki T, Hayashi R, Morohoshi T, Shiokawa A, Ohta Y, Ohike N (2004) A

fibrolamellar carcinoma of the liver with a marked solid component. J Gastroenterol 39:905–907
Komiya T, Tanigawa Y, Hirohashi S (1999) Cloning of the gene gob-4, which is expressed in intestinal goblet cells in mice. Biochim Biophys Acta 1444:434–438
Kroll D, Mazor M, Zirkin H, Schulman H, Glezerman M (1991) Fibrolamellar carcinoma of the liver in pregnancy: a case report. J Reprod Med 36:823–827
Kunz G, Chung J, Ali SZ (2002) Hepatocellular carcinoma-fibrolamellar variant: cytopathology of an unusual case. Diagn Cytopathol 26:257–261
Kutluk MT, Yalçin B, Büyükpamukçu N, Kale G, Büyèkpamukçu M (2001) Fibrolamellar hepatocellular carcinoma with skeletal metastases. Pediatr Hematol Oncol 18:273–278
Lack EE, Neave C, Vawter GF (1983) Hepatocellular carcinoma. Review of 32 cases in childhood and adolescence. Cancer 52:1510–1515
Lamberts R, Nitsche R, de Vivie RE, Peitsch W, Schauer A, Schuster R, Tebbe U, Kreuzer H, Creutzfeldt W (1992) Budd-Chiari syndrome as the primary manifestation of a fibrolamellar carcinoma. Digestion 53:200–209
Lapis K, Schaff Z, Kopper L, Karacsonyi S, Ormos J (1990) Das fibrolamelläre Leberkarzinom. Zbl Allg Pathol Anat 136:135–149
LeBrun DP, Silver MM, Freedman MH, Phillips MJ (1991) Fibrolamellar carcinoma of the liver in a patient with Fanconi anemia. Hum Pathol 22:396–398
Lefkowitch JH, Muschel R, Price JB, Marboe C, Braunhut S (1983) Copper and copper-binding protein in fibrolamellar liver cell carcinoma. Cancer 51:97–100
Lildballe DL, Nguyen KQ, Poulsen SS, Nielsen HO, Nexo E (2011) Haptocorrin as marker of disease progression in fibrolamellar hepatocellular carcinoma. Eur J Surg Oncol 37:72–79
Lim II, Farber BA, LaQuaglia MP (2014) Advances I fibrolamellar hepatocellular carcinoma: a review. Eur J Pediatr Surg 24:461–466
Liu S, Chan KW, Wang B, Qiao L (2009) Fibrolamellar hepatocellular carcinoma. Am J Gastroenterol 104:2617–2624
Liu S, Wah CK, Tong J, Wang Y, Wang B, Qiao L (2011) PET-CT scan is a valuable modality in the diagnosis of fibrolamellar hepatocellular carcinoma: a case report and a summary of recent literature. QJM 104:477–483
Lloreta J, Vadell C, Fabregat X, Serrano S (1994) Fibrolamellar hepatic tumor with neurosecretory features and systemic deposition of AA amyloid. Ultrastruct Pathol 18:287–292
Louie-Johnsun M, Hewitt P, Perera D, Morris D (2003) Fibrolamellar hepatocellular carcinoma in pregnancy. HPB (Oxford) 5:191–193
Lowichik A, Schneider NR, Tonk V, Ansari MQ, Timmons CF (1996) Report of a complex karyotype in recurrent metastatic fibrolamellar hepatocellular carcinoma and a review of hepatocellular carcinoma cytogenetics. Cancer Genet Cytogenet 88:170–174
Magata S, Kitahara K, Watanabe K, Miyazaki K (2001) Fibrolamellar hepatocellular carcinoma – a case report (in Japanese). Acta Hepatol Jpn (Kanzo) 42:414–419
Malouf G, Falissard B, Azoulay D, Callea F, Ferrell LF, Goodman ZD, Hayashi Y, Hayashi HC et al (2009) Is histologic diagnosis of primary liver carcinomas with fibrous stroma reproducible among experts ? J Clin Pathol 62:519–524
Malouf GG, Brugières L, Le Deley MC, Faivre S, Fabre M, Paradis V, Aerts I, Le Tourneau C et al (2012) Pure and mixed fibrolamellar hepatocellular carcinomas differ in natural history and prognosis after complete surgical resection. Cancer 118:4981–4990
Malouf GG, Job S, Paradis V, Fabre M, Brugières L, Saintigny P, Vescovo L, Belghiti J et al (2014) Transcriptional profiling of pure fibrolamellar hepatocellular carcinoma reveals an endocrine signature. Hepatology 59:2228–2237
Maniaci V, Davidson BR, Rolles K, Dhillon AP, Hackshaw A, Regent RH, Meyer T (2009) Fibrolamellar hepatocellular carcinoma – prolonged survival with multimodality therapy. Eur J Surg Oncol 35:617–621
Mansouri D, Van Nhieu JT, Couanet D, Terrier-Lacombe MJ, Brugières L, Cherqui D, Suciu V, Vielh P (2006) Fibrolamellar hepatocellular carcinoma: a case report with cytological features in a sixteen-year-old girl. Diagn Cytopathol 34:568–571
Marrannes J, Gryspeerdt S, Hapseslagh M, van Holsbeeck B, Baekelandt M, Lefere P (2005) Fibrolamellar hepatocellular carcinoma in a 65-year-old woman: CT features. JBR-BTR 88:237–240
Maslon MM, Hrstka R, Vojtesek B, Hupp TR (2010) A divergent substrate-binding loop within the pro-oncogenic protein anterior gradient-2 forms a docking site for reptin. J Mol Biol 404:418–438
Mayo SC, Mavros MN, Nathan H, Cosgrove D, Herman JM, Kamel I, Anders RA et al (2014) Treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma: a national perspective. J Am Coll Surg 218:196–205
McCloskey JJ, Germain-Lee EL, Perman JA, Plotnick LP, Janoski AH (1988) Gynecomastia as a presenting sign of fibrolamellar carcinoma of the liver. Pediatrics 82:379–382
McLarney JK, Rucker PT, Bender GN, Goodman ZD, Kashitani N, Ros PR (1999) Fibrolamellar carcinoma of the liver: radiologic-pathologic correlation. Radiographics 19:453–471
Meriggi F, Forni E (2007) Surgical therapy of hepatic fibrolamellar carcinoma (in Italian). Ann Ital Chir 78:53–58
Montero A, Allende H, Tallada N, Ramon y Cajal S, Margarit C, Viladomiu L (2007) Fine needle aspiration cytology of massive bilateral ovarian metastasis of fibrolamellar hepatocellular carcinoma. Acta Cytol 51:682–683
Moore SW, Millar AJ, Hadley GP, Ionescu G, Kruger M, Poole J, Stones D, Wainwright L et al (2004)

Hepatocellular carcinoma and liver tumors in South African children: a case for increased prevalence. Cancer 101:642–649

Moreno-Luna LE, Arrieta O, Garcia-Leiva J, Martinez B, Torre A, Uribe M, Leon-Rodriguez E (2005) Clinical and pathologic factors associated with survival in young adult patients with fibrolamellar hepatocarcinoma. BMC Cancer 5:142

Morise Z, Sugioka A, Mizoguchi Y, Fujita J, Hoshimoto S, Kato T, Hasumi A (2005) Fibrolamellar carcinoma of the liver in a Japanese hepatitis B virus carrier. J Gastroenterol Hepatol 20:1136–1138

Muramori K, Taguchi S, Taguchi T, Kohashi K, Furuya K, Tokuda K, Ishii E (2011) High aromatase activity and overexpression of epidermal growth factor receptor in fibrolamellar hepatocellular carcinoma in a child. J Pediatr Hematol Oncol 33:e195–e197

Nagorney DM, Adson MA, Weiland LH, Knight CD, Smalley SR, Zinsmeister AR (1985) Fibrolamellar hepatoma. Am J Surg 149:113–119

Nerlich AG, Majewski S, Hunzelmann N, Brenner RE, Wiebecke B, Müller PK, Kreig T, Remberger K (1992) Excessive collagen formation in fibrolamellar carcinoma of the liver: a morphological and biochemical study. Mod Pathol 5:580–585

Njei B (2014) Fibrolamellar hepatocellular carcinoma versus conventional hepatocellular carcinoma: better 5-year survival or artifactual result of research methodology ? Gut 63:1374–1375

Njei B, Konjeti VR, Ditah I (2014) Prognosis of patients with fibrolamellar hepatocellular carcinoma versus conventional hepatocellular carcinoma: a systematic review and meta-analysis. Gastrointest Cancer Research 7:49–54

Nojiri T, Mitsumori N, Yoshida T, Shinohara T, Asakura J, Doi N et al (2000) A case of fibrolamellar hepatocellular carcinoma (in Japanese). Jpn J Gastroenterol Surg 33:1905–1909

Okada K, Kim YI, Nakashima K, Tada I, Yoshida T, Kobayashi M, Yokoyama S (1993) Fibrolamellar hepatocellular carcinoma coexistent with a hepatocellular carcinoma of common type: report of a case. Surg Today 23:626–631

Okano A, Hajiro K, Takakuwa H, Kobashi Y (1998) Fibrolamellar carcinoma of the liver with a mixture of ordinary hepatocellular carcinoma: a case report. Am J Gastroenterol 93:1144–1145

Okuda K (2002) Natural history of hepatocellular carcinoma including fibrolamellar and hepato-cholangiocarcinoma variants. J Gastroenterol Hepatol 17:401–405

Orsatti G, Greenberg PD, Rolfes DB, Ishak KG, Paronetto F (1994) DNA ploidy of fibrolamellar hepatocellular carcinoma by image analysis. Hum Pathol 25:936–939

Orsatti G, Hytiroglou P, Thung SN, Ishak KG, Paronetto F (1997) Lamellar fibrosis in the fibrolamellar variant of hepatocellular carcinoma: a role for transforming growth factor beta. Liver 17:152–156

Paradinas FJ, Melia WM, Wilkinson ML, Portmann B, Johnson PJ, Murray-Lyon IM, Williams R (1982) High serum vitamin B12 binding capacity as a marker of the fibrolamellar variant of hepatocellular carcinoma. Br Med J (Clin Res Ed) 285:840–842

Park SW, Zhen G, Verhaeghe C, Nakagami Y, Nguyenvu LT, Barczak AJ, Killeen N, Erle DJ (2009) The protein disulfide isomerase AGR2 is essential for production of intestinal mucus. Proc Natl Acad Sci U S A 106:6950–6955

Patonai A, Erdélyi-Belle B, Korompay A, Somoracz A, Straub BK, Schirmacher P et al (2011) Claudins and tricellulin in fibrolamellar hepatocellular carcinoma. Virchows Arch 458:679–688

Patonai A, Erdélyi-Belle B, Korompay A, Somoracz A, Törzsök P, Kovalszky I, Barbai T et al (2013) Molecular characteristics of fibrolamellar hepatocellular carcinoma. Pathol Oncol Res 19:63–70

Payne CM, Nagle RB, Paplanus SH, Graham AR (1986) Fibrolamellar carcinoma of liver: a primary malignant oncocytic carcinoid? Ultrastruct Pathol 10:539–552

Perez-Guillermo M, Masgrau NA, Garcia-Solano J, Sola-Perez J, de Agustin P (1999) Cytologic aspect of fibrolamellar hepatocellular carcinoma in fine-needle aspirates. Diagn Cytopathol 21:180–187

Petek E, Windpassinger C, Egger H, Kroisel PM, Wagner K (2000) Localization of the human anterior gradient-2 gene (AGR2) to chromosome band 7p21.3 by radiation hybrid mapping and fluorescence in situ hybridization. Cytogenet Cell Genet 89:141–142

Pinna AD, Iwatsuki S, Lee RG, Todo S, Madariaga JR, Marsh JW, Casavilla A et al (1997) Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantation. Hepatology 26:877–883

Pombo F, Rodriguez E, Arnal-Monreal F (1993) Multicystic fibrolamellar carcinoma. CT appearance. Clin Imaging 17:67–69

Read D, Shulkes A, Fernley R, Simpson R (1991) Characterization of neurotensin (6–13) from an hepatic fibrolamellar carcinoma. Peptides 12:887–892

Riehle KJ, Yeh MM, Yu JJ, Kenerson HL, Harris WP, Park JO, Yeung RS (2015) mTORC1 and FGFR1 signaling in fibrolamellar hepatocellular carcinoma. Mod Pathol 28:103–110

Ringe B, Wittekind C, Weimann A, Tusch G, Pichlmayr R (1992) Results of hepatic resection and transplantation for fibrolamellar carcinoma. Surg Gynecol Obstet 175:299–305

Ross HM, Daniel HD, Vivekanandan P, Kannangal R, Yeh MM, Wu TT, Makhlouf HR, Torbenson M (2010) Fibrolamellar carcinomas are positive for CD68. Mod Pathol 24:390–395

Ruffin MT (1990) Fibrolamellar hepatoma. Am J Gastroenterol 85:577–581

Saab S, Yao F (1996) Fibrolamellar hepatocellular carcinoma. Case reports and a review of the literature. Dig Dis Sci 41:1981–1985

Sarode VR, Castellani R, Post A (2002) Fine-needle aspiration cytology and differential diagnoses of fibrolamellar hepatocellular carcinoma metastatic to the mediastinum: case report. Diagn Cytopathol 26:95–98

Sarosi I, Kiss A, Schaff Z, Lapis K (1991) Connective tissue content of fibrolamellar carcinoma and other human liver tumors. Acta Morphol Hung 39:321–331

Sato S, Masuda T, Oikawa H, Satodate R, Suzuki K, Sato S, Suzuki A, Monma N (1997) Bile canaliculi-like lumina in fibrolamellar carcinoma of the liver: a light- and electron-microscopic study and three-dimensional examination of serial sections. Pathol Int 47:763–768

Saul SH, Titelbaum DS, Gansler TS, Varello M, Burke DR, Atkinson BF, Rosato EF (1987) The fibrolamellar variant of hepatocellular carcinoma. Its association with focal nodular hyperplasia. Cancer 60:3049–3055

Saxena R, Humphreys S, Williams R, Portmann B (1994) Nodular hyperplasia surrounding fibrolamellar carcinoma: a zone of arterialized liver parenchyma. Histopathology 25:275–278

Schlitt HJ, Neipp W, Weimann A, Oldhafer KJ, Schmoll E, Boeker K, Nashan B, Kubicka S et al (1999) Recurrence patterns of hepatocellular and fibrolamellar carcinoma after liver transplantation. J Clin Oncol 17:324–331

Schoedel KE, Tyner VZ, Kim TH, Michalopoulos GK, Mars WM (2003) HGF, MET, and matrix-related proteases in hepatocellular carcinoma, fibrolamellar variant, cirrhotic, and normal liver. Mod Pathol 16:14–21

Scoazec JY, Flejou JF, D'Errico A, Fiorentino M, Zamparelli A, Bringuier AF, Fedlmann G et al (1996) Fibrolamellar carcinoma of the liver: composition of the extracellular matrix and expression of cell-matrix and cell-cell adhesion molecules. Hepatology 24:1128–1136

Seitz G, Zimmermann A, Friess H, Büchler MW (2002) Adult-type hepatocellular carcinoma in the center of a fibrolamellar hepatocellular carcinoma. Hum Pathol 33:765–769

Selaru FM, Cross R, Drachenberg C, Cross R (2007) Electronic clinical challenges and images in GI. Fibrolamellar carcinoma. Gastroenterology 133: e1–e3

Shafizadeh N, Ferrell LD, Kakar S (2008) Utility and limitations of glypican-3 expression for the diagnosis of hepatocellular carcinoma at both ends of the differentiation spectrum. Mod Pathol 21:1011–1018

Sheppard KJ, Bradbury DA, Davies JM, Ryrie DR (1983) High serum vitamin B12 binding capacity as a marker of the fibrolamellar variant of hepatocellular carcinoma. Br Med J (Clin Res Ed) 286:57

Sher ES, Migeon CJ, Berkovitz GD (1998) Evaluation of boys with marked breast development at puberty. Clin Pediatr (Phila) 37:367–371

Sherlock S, Dooley J (eds) (2003) Malignant liver tumors. In: Diseases of the liver and biliary systems, 11th edn. Blackwell, Malden, pp 537–562

Simonsen K, Rode A, Nicoll A, Villadsen G, Espelund U, Lim L, Angus P, Arachchi N et al (2014) Vitamin B12 and its binding proteins in hepatocellular carcinoma and chronic liver diseases. Scand J Gastroenterol 49:1096–1102

Sirivatanauksorn Y, Sirivatanauksorn V, Lemoine NR, Willimason RC, Davidson BR (2001) Genomic homogeneity in fibrolamellar carcinomas. Gut 49:82–86

Smith MT, Blatt ER, Jedlicka P, Strain JD, Fenton LZ (2008) Best cases from the AFIP: fibrolamellar hepatocellular carcinoma. Radiographics 28:609–613

Snook JA, Kelly P, Chapman RW, Jewell DP (1989) Fibrolamellar hepatocellular carcinoma complicating ulcerative colitis with primary sclerosing cholangitis. Gut 30:243–245

Soreide O, Czerniak A, Bradpiece H, Bloom S, Blumgart L (1986) Characteristics of fibrolamellar hepatocellular carcinoma: a study of nine cases and a review of the literature. Am J Surg 151:518–523

Soyer P, Roche A, Levesque M (1991a) Fibrolamellar hepatocellular carcinoma presenting with obstructive jaundice. A report of two cases. Eur J Radiol 13:196–198

Soyer P, Roche A, Levesque M, Legmann P (1991b) CT of fibrolamellar hepatocellular carcinoma. J Comput Assist Tomogr 15:533–538

Stevens WR, Johnson CD, Stephens DH, Nagorney DM (1995) Fibrolamellar hepatocellular carcinoma: stage at presentation and results of aggressive surgical management. AJR Am J Roentgenol 164:1153–1158

Stipa F, Yoon SS, Liau KH, Fong Y, Jarnagin WR, D'Angelica M, Abou-Alfa G, Blumgart LH, DeMatteo RP (2006) Outcome of patients with fibrolamellar hepatocellular carcinoma. Cancer 106:1331–1338

Stoupis C, Taylor HM, Paley MR, Buetow PC, Marre S, Baer HU, Vock P, Ros PR (1998) The rocky liver: radiologic-pathologic correlation of calcified hepatic masses. Radiographics 18:675–685

Suen KC, Magee JF, Halparin LS, Chan NH, Greene CA (1985) Fine needle aspiration cytology of fibrolamellar hepatocellular carcinoma. Acta Cytol 29:867–872

Sulaiman RA, Geberhiwot T (2014) Fibrolamellar hepatocellular carcinoma mimicking ornithine transcarbamylase deficiency. JIMD Rep 16:47–50

Tanaka J, Baba N, Arii S, Fujita K, Tamura J, Kawakami Y, Tsuji S, Imamura M et al (1994) Typical fibrolamellar hepatocellular carcinoma in Japanese patients: report of two cases. Surg Today 24:459–463

Tanaka K, Honna T, Kitano Y, Kuroda T, Tanaka K, Morikawa N, Matsuda H, Kawashima N et al (2005) Combined fibrolamellar carcinoma and cholangiocarcinoma exhibiting biphenotypic antigen expression: a case report. J Clin Pathol 58:884–887

Teitelbaum DH, Tuttel S, Carey LC, Clausen KP (1985) Fibrolamellar carcinoma of the liver. Review of three cases and the presentation of a characteristic set of tumor markers defining this tumor. Ann Surg 202:36–41

Terracciano L, Tornillo L (2003) Cytogenetic alterations in liver cell tumors as detected by comparative genomic hybridization. Pathologica 95:71–82

Terracciano LM, Tornillo L, Avoledo P, Von Schweinitz D, Kühne T, Bruder E (2004) Fibrolamellar hepatocellular

carcinoma occurring 5 years after hepatocellular adenoma in a 14-year-old girl: case report with comparative genomic hybridization analysis. Arch Pathol Lab Med 128:222–226

Terris B, Pineau P, Bregeaud L, Valla D, Belghiti J, Tiollais P, Degott C, Dejean A (1999) Close correlation between beta-catenin gene alterations and nuclear accumulation of the protein in human hepatocellular carcinomas. Oncogene 18:6583–6588

Terzis I, Haritanti A, Economou I (2010) Fibrolamellar hepatocellular carcinoma: a case report with distinct radiological features. J Gastrointest Cancer 41:2–5

Thirabanjasak D, Sosothikul D, Mahayosnond A, Thorner PS (2009) Fibrolamellar carcinoma presenting as a pancreatic mass: case report and review of the literature. J Pediatr Hematol Oncol 31:370–372

Torbenson M (2007) Review of the clinicopathologic features of fibrolamellar carcinoma. Adv Anat Pathol 14:217–223

Tränkenschuh W, Puls F, Christgen M, Albat C, Heim A, Poczkaj J, Fleming P, Kreipe H, Lehmann U (2010) Frequent and distinct aberrations of DNA methylation patterns in fibrolamellar carcinoma of the liver. PLoS One 5:e13688

Tsilividis B, Huet E, Lubrano J, Lacaze L, Lestrat JP, François A, Riachi G, Scotté M (2010) Late supradiaphragmatic lymph node recurrence following resection of a fibrolamellar hepatocarcinoma: an unusual case. Surg Radiol Anat 32:123–127

Vaideeswar P, Pandit MJ, Deshpande JR, Sivaraman A, Vora IM (1993) Fibrolamellar carcinoma of the liver – an unusual presentation. J Postgrad Med 39:159–161

Van Eyken P, Sciot R, Brock P, Casteels-Van DM, Ramaekers FC, Desmet VJ (1990) Abundant expression of cytokeratin-7 in fibrolamellar carcinoma of the liver. Histopathology 17:101–107

Vasdev N, Nayak NC (2003) CD99 expression in hepatocellular carcinoma: an immunohistochemical study in the fibrolamellar and common variant of the tumour. Indian J Pathol Microbiol 46:625–629

Vecchio FM (1988) Fibrolamellar carcinoma of the liver: a distinct entity within the hepatocellular tumors. A review. Appl Pathol 6:139–148

Vecchio FM, Fabiano A, Ghirlanda G, Manna R, Massi G (1984) Fibrolamellar carcinoma of the liver: the malignant counterpart of focal nodular hyperplasia with oncocytic change. Am J Clin Pathol 81:521–526

Vivekanandan P, Torbenson M (2008) Epigenetic instability is rare in fibrolamellar carcinomas but common in viral-associated hepatocellular carcinomas. Mod Pathol 21:670–675

Vivekanandan P, Micchelli ST, Torbenson M (2009) Anterior gradient-2 is overexpressed by fibrolamellar carcinomas. Hum Pathol 40:293–299

Vivekanandan P, Daniel H, Yeh MM, Torbenson M (2010) Mitochondrial mutations in hepatocellular carcinomas and fibrolamellar carcinomas. Mod Pathol 23:790–798

Wang Z, Hao Y, Lowe AW (2008) The adenocarcinoma-associated antigen, AGR2, promotes tumor growth, cell migration, and cellular transformation. Cancer Res 68:492–497

Ward SC, Waxman S (2011) Fibrolamellar carcinoma: a review with focus on genetics and comparison to other malignant primary liver tumors. Semin Liver Dis 31:61–70

Ward SC, Huang J, Tickoo SK, Thung SN, Ladanyi M, Klimstra DS (2010) Fibrolamellar carcinoma of the liver exhibits immunohistochemical evidence of both hepatocyte and bile duct differentiation. Mod Pathol 23:1180–1190

Washington K, Telen MJ, Gottfried MR (1997) Expression of cell adhesion molecule CD44 in primary tumors of the liver: an immunohistochemical study. Liver 17:17–23

Weeda VB, Murawski M, McCabe AJ, Maibach R, Brugières L, Roebuck D, Fabre M et al (2013) Fibrolamellar variant of hepatocellular carcinoma does not have a better survival than conventional hepatocellular carcinoma – results and treatment recommendations from the Childhood Liver Tumour Strategy Group (SIOPEL) experience. Eur J Cancer 49:2698–2704

Wennerberg AE, Nalesnik MA, Coleman WB (1993) Hepatocyte paraffin 1: a monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumors. Am J Pathol 143:1050–1054

Wetzel WJ, Costin JL, Petrino RL (1983) Fibrolamellar carcinoma: distinctive clinical and morphologic variant of hepatoma. South Med J 76:796–798

Wheeler K, Pritchard J, Luck W, Rossiter M (1986) Transcobalamin I as a "marker" for fibrolamellar hepatoma. Med Pediatr Oncol 14:227–229

Wilkens L, Bredt M, Flemming P, Kubicka S, Klempnauer J, Kreipe H (2000) Cytogenetic aberrations in primary and recurrent fibrolamellar hepatocellular carcinoma detected by comparative genomic hybridization. Am J Clin Pathol 114:867–874

Wong LK, Link DP, Frey CF, Ruebner RH, Tesluk H, Pimstone NR (1982) Fibrolamellar hepatocellular carcinoma: radiology, management, and pathology. AJR Am J Roentgenol 139:172–175

Xu L, Hazard FK, Zmoos AF, Jahchan N, Chaib H, Garfin PM, Rangaswami A, Snyder MP (2015) Genomic analysis of fibrolamellar hepatocellular carcinoma. Hum Mol Genet 24:50–63

Yamamoto H, Watanabe K, Takayama W, Yamada S, Fujita Y, Honda I, Watanabe S et al (1995) Surgical management for lymph node recurrence of resected fibrolamellar carcinoma of the liver: a case report. Jpn J Clin Oncol 25:282–285

Yamamoto H, Watanabe K, Nagata M, Yano Y, Akai T, Honda I, Watanabe S, Soda H, Matsuzaki O (1999) Transformation of fibrolamellar carcinoma to common hepatocellular carcinoma in the recurrent lesions of the rectum and the residual liver: a case report. Jpn J Clin Oncol 29:445–447

Yamamoto M, Ariizumi S, Yoshitoshi K, Saito A, Nakano M, Takasaki K (2006) Hepatocellular carcinoma with a central scar and a scalloped tumor margin resembling focal nodular hyperplasia in macroscopic appearance. J Surg Oncol 94:587–591

Yen JB, Chang KW (2009) Fibrolamellar hepatocellular carcinoma – report of a case. Chang Gung Med J 32:336–339

Yoshimi F, Asato Y, Amemiya R, Itabashi M, Nakamura K (2002) Fibrolamellar hepatocellular carcinoma in a Japanese man: report of a case. Surg Today 32:174–179

Yoshinaga Y, Okazumi S, Takayama W, Makino H, Iwasaki K, Kondou S et al (2002) A resected case of fibrolamellar hepatocellular carcinoma in a 15 year old woman (in Japanese). Shoukaki Gazou 4:97–103

Zenali MJ, Tan D, Li W, Dhingra S, Brwon RE (2010) Stemness characteristics of fibrolamellar hepatocellular carcinoma: immunohistochemical analysis with comparisons to conventional hepatocellular carcinoma. Ann Clin Lab Sci 40:126–134

Zermani R, Charfi L, Kourda N, Farah F, Rammeh S, Trabesli O, Zaouch A, Ben Jilani S (2005) A particular hepatocellular carcinoma combining the ordinary and the fibrolamellar variant (in French). Tunis Med 83:419–421

Zhang Y, Ali TZ, Zhou H, D'Souza DR, Lu Y, Jaffe J, Liu Z, Passaniti A, Hamburger AW (2010) ErbB3 binding protein 1 represses metastasis-promoting gene anterior gradient protein 2 in prostate cancer. Cancer Res 70:240–248

Zografos GN, Palmer S, Papastratis G, Habib NA (1997) Aggressive surgical management of fibrolamellar hepatocellular carcinoma in puberty. Eur J Surg Oncol 23:570–572

Hepatoblastoma and the Hepatoblastoma Family of Tumors

19

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_19

Abstract

Hepatoblastoma (HB) is a rare malignant blastomatous liver tumor characterized by various combination of epithelial and mesenchymal cell lineages that recapitulate early phases of liver ontogenesis. HB is typically a pediatric liver neoplasm; most cases are diagnosed before the age of 5 years. Very rarely, HB develops in older children and adults. HB accounts for less than 5 % of pediatric malignancies. The tumor occurs more commonly in low birth weight children and is associated with several molecular and cytogenetic abnormalities, mutations in the Wnt/beta-catenin signaling pathway being frequent. Morphologically, HBs are divided into epithelial and mixed epithelial-mesenchymal types. Epithelial tumors are broken down into fetal, embryonal, macrotrabecular, and small cell undifferentiated subtypes, while mixed epithelial-mesenchymal HBs are grouped into those without or with teratoid features. A subset of small cell undifferentiated HB exhibits rhabdoid features associated with loss of INI1 expression, similar to malignant rhabdoid tumors. Although HBs are aggressive lesions with high recurrence rate and metastatic disease, modern therapies now produce excellent results. In order to improve treatment, molecular profiles are developed to refine risk stratification.

ICD-O Codes

Epithelial Variants	8970/3
Mixed Epithelial-Mesenchymal Variants	8970/3

Introduction

According to the 2010 WHO classification, hepatoblastoma is defined as a primary malignant blastomatous tumor of the liver characterized by various combinations of several epithelial and mesenchymal cell lineages. The epithelial lineages recapitulate early hepatic ontogenesis and include immature cells, embryonal and fetal hepatoblasts, and more mature hepatocyte-like cells (Zimmermann and Saxena 2010).

Epidemiology

Hepatoblastoma represents the most frequent epithelial liver tumor in infancy and childhood, comprising 50–60 % of all hepatic neoplasms in this age group and encompassing around 1 % of all pediatric malignancies (MacNab et al. 1952; Clatworthy et al. 1961, 1974; Hartley et al. 1990; Ross and Gurney 1998; Linely and Ross 2008; Spector and Birch 2012; Allan et al. 2013). Hepatoblastoma is a tumor of infants and small children . Most hepatoblastomas occur in children between 6 months and 3 years of age, around 90 % being diagnosed before the age of 5 years, but age at diagnosis ranges from prenatal stages to adulthood (Steiner 1938; Yamazaki et al. 2004; Admasse and Kebede 2007; Zheng et al. 2009). Only about 5 % of new hepatoblastoma cases are detected in children more than 4 years of age, and about 10 % of hepatoblastomas are diagnosed in the neonatal period (Florentin et al. 1956; Alagille 1961; Sallem et al. 2005; Cornert et al. 2007). Some hepatoblastomas are manifest at birth already, termed congenital hepatoblastoma (Stiller and Holzhausen 1983; Ammann et al. 1999; Worth et al. 1999; Shih et al. 2000a; Catanzarite et al. 2008). Few tumors are diagnosed prenatally (Shih et al. 2000b; Aviram et al. 2005; Ergin et al. 2008). Hepatoblastoma arising in the fetal period is one of the lesions inducing fetal nonimmune hydrops (Kazzi et al. 1989). In Western countries, the annual incidence rates range from 1 per 100,000 to 1 per 1,000,000 children under 15 years of age (Mann et al. 1990; Hughes and Michels 1992).

An increased incidence of hepatoblastoma has been observed between 1971 and 1983 at a Children's Tumor Registry in Manchester, United Kingdom, with an increase from 0.4 to 1.0 per million (Mann et al. 1990). Data on 849 children diagnosed with malignant hepatic tumors before the age of 15 years during 1978–1997 in Europe were extracted from the ACCIS (Automated Childhood Cancer Information System) database. Age-standardized incidence during 1988–1997 was 1.2 per million for hepatoblastoma and 0.2 per million for hepatocellular carcinoma.

Over 90 % of hepatoblastomas occurred before age 5 years (Stiller et al. 2006). In Germany, an annual incidence rate of 1 per 1,000,000 children under 15 years of age and of 6 per 1,000,000 children under 1 year of age was observed (Kaatsch 2002). In an epidemiological review based on the Surveillance, Epidemiology, and End Results (SEER) database, 918 primary hepatic malignancy deaths were reported for the United States among persons less than 20 years of age during the time period between 1979 and 1996. Between 1973 and 1997, 271 primary hepatic malignancy cases were reported to SEER among persons less than 20 years of age, of which 184 (67 %) and 83 (31 %) were hepatoblastoma and hepatocellular carcinoma, respectively (Darbari et al. 2003). A US trend in childhood cancer incidence analysis covering the time period 1992–2004 revealed an annual percent change of 4.3 % for hepatoblastoma (Linabery and Ross 2008). The main reason of an increase in hepatoblastoma incidence is thought to be the improved outcome of premature children, low and very low birth weight being a risk factor for hepatoblastoma (see below). For so far unknown reasons, hepatoblastoma occurs in males significantly more often than it does in females (Weinberg and Finegold 1983; Buckley et al. 1989).

Clinical Features

General Features

The pertinent clinical features have been reviewed in numerous publications. Main clinical signs and symptoms of hepatoblastoma in small children comprise abdominal distension with or without firmness, hepatomegaly, abdominal swelling, a palpable and/or rapidly growing abdominal mass, anorexia, weight loss, vomiting (sometimes projectile), and irritability or lethargy. Jaundice is found in a minority of patients (5 % or less).

Selected References Noeggerath 1854; Philipp 1908; MacRae 1935; Drummond and Tollman 1939; Debré et al. 1954; Edmondson 1956; Kempf and Korn 1956; Bohmig 1961; Watanabe and Kobayashi 1961; Willis 1962; Sinniah et al. 1974; Exelby et al. 1975; Ishak 1976; Dehner 1978; Lack et al. 1982; Schmidt et al. 1985; Hata 1990; Williams and Ferrell 1993; Stocker 1994, 2001; Reynolds 2001; Perilongo et al. 2002; Schnater et al. 2003; Roebuck and Perilongo 2006; Isaacs 2007; Meyers 2007; Wang et al. 2007; Finegold et al. 2008; Litten and Tomlinson 2008; Moore et al. 2008; Nakamura 1910; Perilongo et al. 2012; von Schweinitz 2012.

In up to 90 % of patients, a marked elevation of serum alpha-fetoprotein (AFP) concentration is found (Alpert and Seeler 1970). Monitoring of serum AFP levels is used as an outcome predictor (Van Tornout et al. 1997). AFP has an important role in ontogenesis and is associated with several tumors, including hepatocellular carcinoma, hepatoblastoma, certain germ cell tumors, hepatoid carcinomas, and less often with other neoplasms (Abelev 1971). Caution must be taken in monitoring serum AFP levels in young infants since an "adult" level of AFP (<25 ng/mL) is not reached until about 6 months of age. Serum AFP levels roughly parallel the course of disease and drop following resection of the tumor (Ikeda et al. 1981) or chemotherapy (Pritchard et al. 1982; Kubota et al. 2004). Serial monitoring of serum AFP levels during treatment may identify favorable and poor responders to therapy (Koh et al. 2011). However, serum AFP is not increased in all patients with AFP. There are sporadic reports of AFP-negative hepatoblastoma (Goedeke et al. 2011). Low serum AFP has been observed in a very low birth weight infant (717 g) having a hepatoblastoma of the well-differentiated fetal-type AFP in serum amounting to 322 ng (mL (Tsuchida et al. 1999). A later study showed the analysis of 21 patients with low serum AFP (<100 ng/mL) at diagnosis, accrued onto SIOPEL trials. Eight patients had extrahepatic extension and eight had a multifocal tumor. 11 out of 15 available histologies were epithelial HB, including nine with a small cell undifferentiated subtype. Only nine patients achieved a

partial response and 16 died. The 2-year survival rate was 24 %. These findings demonstrate that hepatoblastomas with a low serum AFP concentration at diagnosis form a high-risk group with extensive disease at diagnosis and poor outcome (De Ioris et al. 2008). High-risk histologies including small cell undifferentiated hepatoblastoma and neoplasms with rhabdoid features are overrepresented in this group.

Hematological Abnormalities

Marked thrombocytosis (exceeding 50 × 10(4)/μL) is often found in hepatoblastoma and can be a diagnostic clue (Nickerson et al. 1980; Shafford and Pritchard 1993; Yamaguchi et al. 1996). There is evidence that thrombocytosis in hepatoblastoma results from the production of thrombopoietin within the tumor tissues (Nickerson et al. 1980; Komura et al. 1998). However, it was also shown that in a patient with hepatoblastoma-associated thrombocytosis, serum thrombopoietin levels were not high at diagnosis, whereas high levels were found after chemotherapy, and thrombopoietin was detected by use of PCR in both normal liver and tumor, with no measurable difference between them (Yamaguchi et al. 1996). A second mechanism of thrombocytosis in hepatoblastoma may be related to the production of interleukin-6 by the tumors. Hepatoblastomas produce IL-1beta and thus induced secretion of IL-6 by stromal cells (von Schweinitz et al. 1993). Stromal cells derived from liver, including myofibroblasts in culture, are capable to produce IL-6 (Tiggelman et al. 1995). Also in other malignancies associated with paraneoplastic thrombocytosis, IL-6 production has been shown to be involved, e.g., ovarian cancer and renal cell carcinoma (van Rossum et al. 2009; Stone et al. 2012).

Hormonal Abnormalities

A minority of hepatoblastomas have been shown to be associated with precocious puberty due to production of gonadotropins. Following the first report in 1931 (Behrendt 1931), more than 30 cases of precocious puberty associated with hepatoblastoma have been reported, and all patients were male. In at least a fraction of these cases, human chorionic gonadotropin secretion by the tumor has been observed to be the cause of precocious puberty (Hung et al. 1963; Root et al. 1968; Braunstein et al. 1972; McArthur et al. 1973; Nakagawara et al. 1985). In part of cases, both hCG and AFP were synchronously elevated in serum (Nakagawara et al. 1985; Eren et al. 2009). In a study of four patients (all male), histology was mixed fetal and embryonal in all cases (Nakagawara et al. 1985). A predominantly embryonal morphology was documented in another report (Heimann et al. 1987). Immunohistochemically, hCG was shown to be produced by both well-differentiated cells (Morinaga et al. 1983) and multinucleated tumor giant cells (Nakagawara et al. 1982; Watanabe et al. 1987). In one report, the hCG-positive giant cells were regarded as suspicious to be derivatives of choriocarcinoma (Watanabe et al. 1987). Precocious puberty associated with hepatoblastoma is not always caused by production of hCG. In one case, this endocrine disorder was caused by testosterone-producing hepatoblastoma (Galifer et al. 1985). In addition to gonadotropins and sex steroids, rare hepatoblastomas can produce other hormones, e.g., the ectopic ACTH syndrome (Rabl et al. 1988; Grunewald et al. 2010), or production of renin, sometimes associated with severe hypertension (Moritake et al. 2000; Tavasoli et al. 2013).

Complications

Hepatoblastomas may undergo spontaneous or traumatic rupture (Nissel 1928; Nitta et al. 2012; Saettini et al. 2013): Tumor rupture sometimes occurs during delivery in case of large lesions (Lai and Burjonrappa 2012). Hepatoblastoma may initially present as hemoperitoneum, owing to tumor rupture (Giacomoni et al. 1986), also in the rare adult hepatoblastoma (Baroni et al. 1984). Hepatoblastoma can be associated with sudden unexpected death in infancy (Pryce et al. 2010).

Imaging Features

The imaging features of hepatoblastomas that have been reviewed are not treated in this chapter (Dachman et al. 1987; Helmberger et al. 1999; Sato et al. 2000; Roebuck and Perilongo 2006; Lu and Greer 2007; McCarville and Roebuck 2012; Meyers et al. 2012).

Classification of Hepatoblastomas

Hepatoblastomas and related neoplasms exhibit a distinct variety of histopathological patterns. This phenomenon has led to a variety of classifications, which are still in a phase of reappraisal and further development. One early observation was that hepatoblastomas can consist of both epithelial and mesenchymal components, leading to a separation of wholly epithelial versus mixed epithelial and mesenchymal hepatoblastomas (MEMHB) (Ishak and Glunz 1967; Nikaidoh et al. 1970; Schiodt 1970; Gonzalez-Crussi and Manz 1972; Gonzalez-Crussi et al. 1982; Iwafuchi et al. 1981; Lack et al. 1982; Weinberg and Finegold 1986; Conran et al. 1992). About 60 % of hepatoblastomas are entirely epithelial at diagnosis, while the remaining cases are mostly MEMH, and a small minority consists of unusual subtypes, such as teratoid hepatoblastoma . Issues of histological classification of hepatoblastomas have been reviewed in detail (Rowland 2002). The classification of SIOPEL (Childhood Liver Tumour Study Group) trials is shown in Table 1.

Table 1 Histopathologic classification of hepatoblastomas as used in SIOPEL (Zimmermann 2003; Zimmermann and Lopez-Terrada 2011)

Wholly epithelial hepatoblastoma
Purely fetal
Mixed fetal embryonal/embryonal
Macrotrabecular
Small cell undifferentiated
Mixed epithelial and mesenchymal
Without teratoid features
With teratoid features
Hepatoblastoma, not otherwise specified (NOS)

Table 2 Hepatoblastoma family of tumors (Zimmermann 2005, modified)

Wholly epithelial hepatoblastomas
Fetal subtype (including "purely fetal HB")
Embryonal and mixed embryonal/fetal subtype
Macrotrabecular HB subtype 2 (MT-2)
Undifferentiated subtype (diffuse or focal)
Small cell undifferentiated HB (SCUD)
Intermediate cell undifferentiated HB (ICUD)
Large cell undifferentiated HB (LCUD)
Liver cell tumors with a mature-looking hepatocellular phenotype
Macrotrabecular HB subtype 1 (MT-1)
Transitional liver cell tumor (TLCT)
Stromal-epithelial and stromal tumors
Mixed epithelial and mesenchymal hepatoblastoma (MEMHB)
Stromal-epithelial tumors, including nested stromal-epithelial tumor
Pediatric hepatic stromal tumors (PHST)
Hepatoblastoma-like tumors with a bimodal differentiation
Cholangioblastic hepatoblastoma
So-called ductal plate tumors
Hepatoblastoma family tumors with organoid features
Hamartoma-like hepatoblastomas
Multilineage tumors
Teratoid hepatoblastoma
Primitive multilineage tumors with stem cell-like features

The histologic types and subtypes listed in this table are described in detail in a subsequent paragraph. The recognition of other and novel tumor phenotypes, together with the refinement of immunohistochemical and molecular methods, has led to the proposition of extended classifications. In particular, a *hepatoblastoma family of tumors* has been proposed in the sense of a working formulation (Zimmermann 2005), compiled in Table 2.

A novel classification was worked out in the setting of an International Pathology Symposium in March 2011, by 22 expert pathologists of COG, SIOPEL, GPOH, and JPLT as well as by pediatric oncologists and surgeons specialized in this field arriving at a consensus classification (the Los Angeles Classification; Lopez-Terrada et al. 2014; Table 3). The 2011 Conference was the first collaborative step to develop a classification leading to a

Table 3 Los Angeles hepatoblastoma classification (Lopez-Terrada et al. 2014; modified)

Epithelial hepatoblastomas
Fetal HB
Well differentiated: uniform (10–20 μm in diameter), round nuclei, cords with minimal mitotic activity (<2 mitotic figures per 10/400× microscopic fields); extramedullary hematopoiesis present
"Crowded" or mitotically active: more than 2 mitotic figures per 10/400× microscopic fields; conspicuous nucleoli, usually less glycogen
"Pleomorphic, or poorly differentiated": moderate anisonucleosis, high nucleus/cytoplasmic ratio, prominent nucleoli
"Anaplastic": marked nuclear enlargement and pleomorphism, nuclear hyperchromasia, abnormal mitotic figures
Embryonal HB
Tumor cells 10–15 μm in diameter, high nucleus/cytoplasmic ratio, angulated nuclei, primitive tubular structures, extramedullary hematopoiesis usually absent
Macrotrabecular
Epithelial HB (fetal or embryonal) growing in trabeculae of more than five cells thick (between the sinusoids)
Small cell undifferentiated
Tumor cells 5–10 μm in diameter, no distinct architectural pattern, minimal pale amphophilic cytoplasm, round to oval nuclei with fine chromatin structure and inconspicuous nucleoli, mitotic figures present; part of tumors lack nuclear INI1 expression
Cholangioblastic HB
Bile duct-like profiles are present, usually at the periphery of epithelial HB islands; this pattern may predominate
Mixed epithelial-mesenchymal hepatoblastomas
HB with stromal derivatives
Presence of spindle cells ("blastema"), osteoid, skeletal muscle, cartilage
Teratoid HB
Mixed HB plus primitive endodermal components, neural derivatives, melanocytes, glandular elements

common treatment stratification system incorporating tumor histopathology.

General Pathology Features

Introduction

As shown in the section on classification, pathology of hepatoblastoma family tumors has become complex after this malignancy had been separated from "hepatomas" in the old literature. Apart from the identification of types and subtypes based on in-depth analyses of case groups and later large series of tumors, in part by use of refined immunohistochemical methods, the definition of distinct histopathologic categories has been led by the attempt to identify risk stratifications in a therapeutic setting (reviews: Lopez-Terrada and Finegold 2007; Zimmermann and Saxena 2010, 2011; Lopez-Terrada and Zimmermann 2012).

Macroscopy

Hepatoblastoma is located more often to the right lobe of the liver (about 60 %), with only 15 % being located in the left lobe and 25–30 % of the tumors extending into both lobes (Exelby et al. 1975; Keeling 1971; Ke et al. 2005). In a study of 32 patients, the tumor was confined to the right liver lobe in 16 cases and to the left lobe in 3 cases, while in 13 cases tumor nodules were scattered throughout the liver (Keeling 1971). Hepatoblastomas can also present as large or giant masses involving the liver hilum (Dong et al. 2009). The tumors are usually large at diagnosis, often with a diameter of 10–12 cm. Among 35 cases, the size of hepatoblastoma ranged from 6 to 17 cm in greatest dimension (Ishak and Glunz 1967). Generally, hepatoblastomas reveal a lobulated or nodular cut surface, and part of the tumors bulge or project from the liver surface (Figs. 1 and 2).

The consistency is firm, soft, or soft and friable, about a third each (Ishak and Glunz 1967). Expanding lesions cause compression atrophy of the adjacent liver substance, sometimes with formation of a pseudocapsule, but true capsules have also been noted (Ishak and Glunz 1967). Epithelial hepatoblastomas tend to show a homogeneous cut surface, while mixed hepatoblastomas are more often variegated, epithelial components being present as tan or gray-to-yellow nodules and mesenchymal components as firm or fibrous gray zones, sometimes speckled with whitish material representing osteoid. In a minority of cases of well-differentiated hepatoblastoma, bile accumulation can cause greenish or even bile-stained nodules. Large venous vessels, sometimes

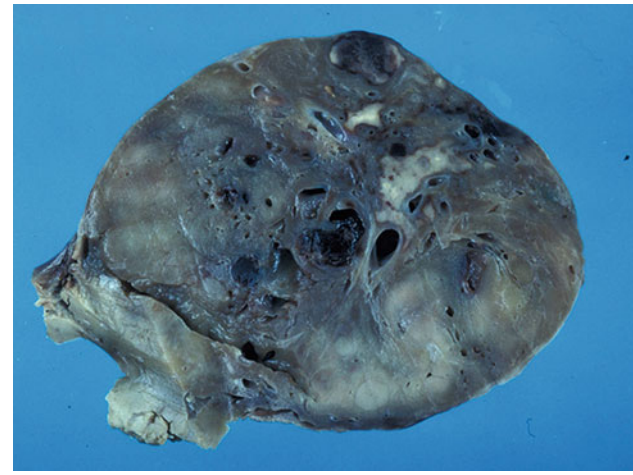

Fig. 1 Hepatoblastoma. Macroscopically, the large tumor shows an expanding growth pattern. Central parts exhibit extensive hemorrhage and whitish necroses (fixed specimen)

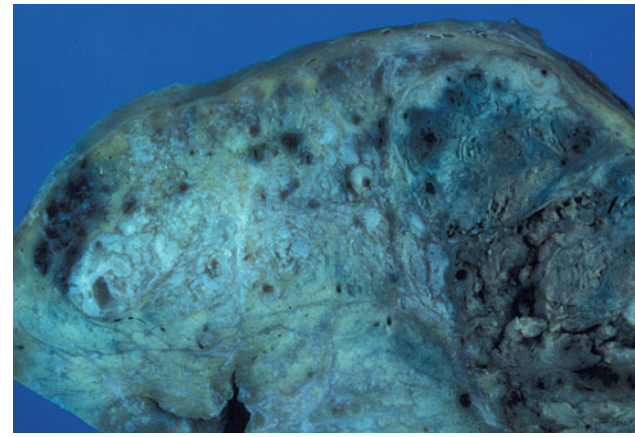

Fig. 2 Hepatoblastoma. The cut surface exhibits a complex mixture of partially necrotic nodular structures (fixed specimen)

thrombosed, may be present around the tumor, causing prominent vessels also at the capsular surface. A protocol for the examination of hepatoblastoma specimens has been developed (Finegold et al. 2007).

Histopathology: Distribution of Histologic Types and Subtypes

Among 105 hepatoblastomas classified on the basis of both their epithelial and mesenchymal components, 28 % were fetal, 17 % embryonal, 31 % mixed without teratoid features, 9 % mixed with teratoid features, 3 % macrotrabecular, 3 % SCUD, and 9 % hepatoblastoma not otherwise specified (NOS). When the tumors were classified on the basis of their epithelial component alone, the following distribution was found: 29 % of the tumors were fetal, 55 % embryonal, 3 % macrotrabecular, and 3 % small cell undifferentiated (Conran et al. 1992).

Hepatoblastoma, Wholly Epithelial Type: Fetal Hepatoblastomas (Fetal Subtype)

The morphology of fetal hepatoblastoma has been described in detail by Ishak and Glunz (1967). Fetal-type cells resemble, as their name indicates, cells of the prenatal fetal liver. They are polyhedral, uniform, and smaller than mature hepatocytes, with well-defined outlines. Two main cell types are recognized, i.e., a cell type with a granular and eosinophilic cytoplasm and a slightly

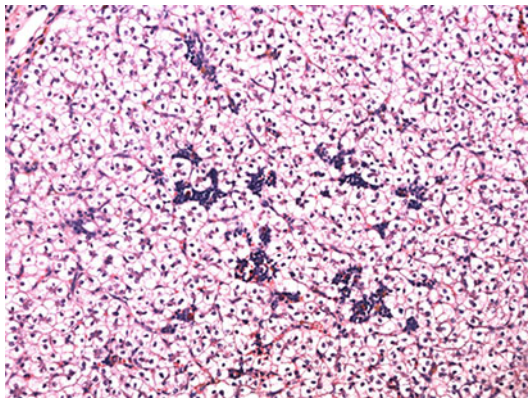

Fig. 3 Hepatoblastoma, fetal subtype. Tumor cells are medium sized, show a clear cytoplasm, and form slender cell plates. Several hematopoietic foci are present (hematoxylin and eosin stain)

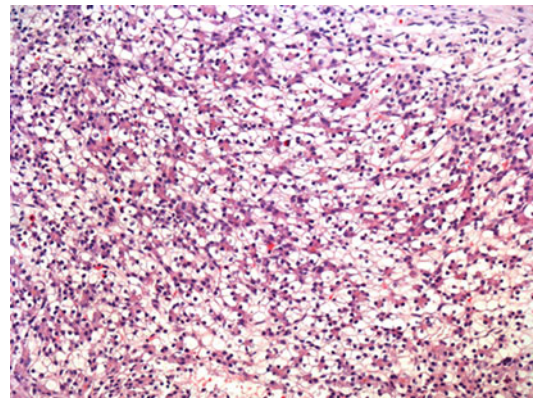

Fig. 4 Hepatoblastoma, fetal subtype. In addition to clear cells, neoplastic cells with a darker cytoplasm are noted (hematoxylin and eosin stain)

larger cell type with a clear and/or vacuolated cytoplasm. In frozen sections, it is shown that the clear cells contain oil red 0-positive fat droplets, and these cells also contain glycogen, with the glycogen particles being peripherally dispersed (Ishak and Glunz 1967). These two cell types often form clusters, causing the typical "dark and clear cell pattern" of fetal-type hepatoblastoma. Nuclei are usually centrally placed round or oval, with a fine chromatin structure and one nucleolus. The cells are mostly arranged in plates two cells thick, sometimes with bile canaliculi. These plates are lined by thin-walled channels resembling an immature sinusoidal network and are supported by a poorly developed reticulin web. Fetal-type cells are not always smaller than normal, nonneoplastic hepatocytes (Figs. 3, 4, 5, 6, 7, 8, 9, and 10).

Already in 1992, it was noted that, in a number of cases, the fetal-type cells appeared to be similar in size to the adjacent nonneoplastic hepatocytes rather than being smaller (Conran et al. 1992). Intervening thin-walled sinusoid-like vascular channels are lined by endothelial cells that show diffuse CD34 immunoreactivity. Fetal hepatoblastomas are often divided into irregular lobules with intervening collagenous septa containing the tumor vessels. The adventitia of these sometimes large and thick-walled vessels blends into the connective tissue of the septa. The septa may not represent tumor stroma, as

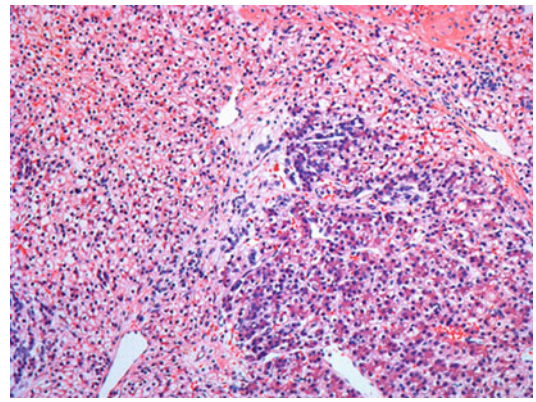

Fig. 5 Hepatoblastoma, fetal subtype. The left half of the figure shows a clear cell pattern, whereas an area with a higher cellularity is seen to the right (hematoxylin and eosin stain)

they often contain crowded preexistent bile ductules, suggesting the entrapment of portal tracts into these structures. The septa may thus be formed by the connective tissue pillars of the vascular tree feeding the tumor. The tumors may show a fibrous pseudocapsule, containing collagen and reticulin, and often this pseudocapsule may completely envelope the mass. Fetal hepatoblastomas typically contain foci of extramedullary hepatopoiesis, mainly of the erythroid lineage (Emura et al. 1985). In a systematic ultrastructural study of this phenomenon, it turned that hematopoiesis developed almost only in well-differentiated, fetal-type hepatoblastoma and that

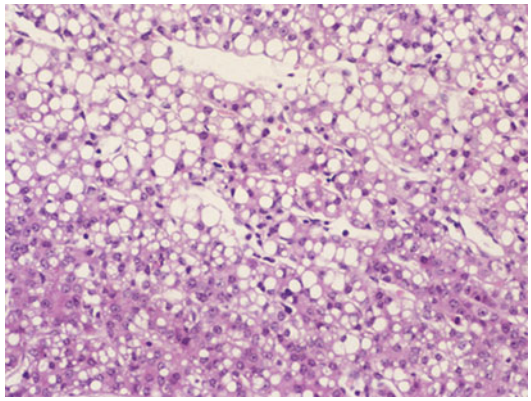

Fig. 6 Hepatoblastoma, fetal subtype, with marked, partly macrovesicular fatty change of neoplastic cells (hematoxylin and eosin stain)

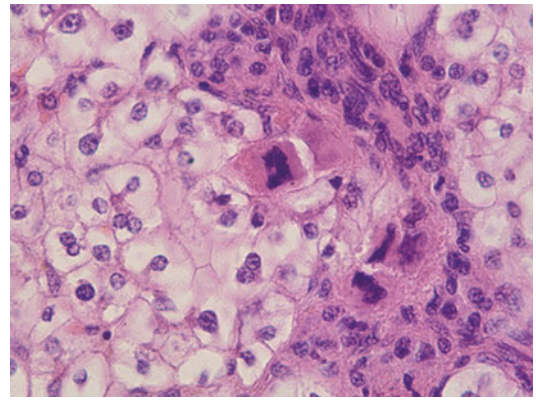

Fig. 8 Hepatoblastoma, fetal subtype. Extramedullary hepatopoiesis can also contain megakaryocytes in hepatoblastoma. There is a slight associated stromal reaction (hematoxylin and eosin stain)

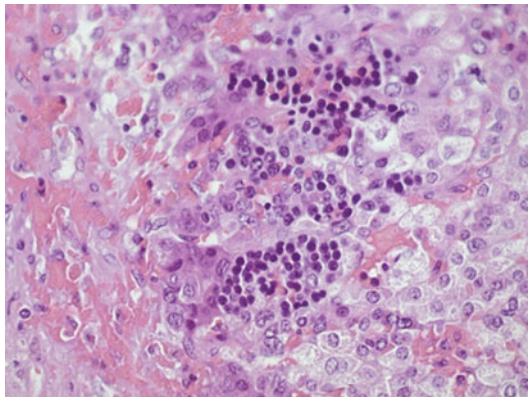

Fig. 7 Hepatoblastoma, fetal subtype. Hematopoietic cell nests (extramedullary hematopoiesis) are dominated by nucleated cells of the erythroid lineage (hematoxylin and eosin stain)

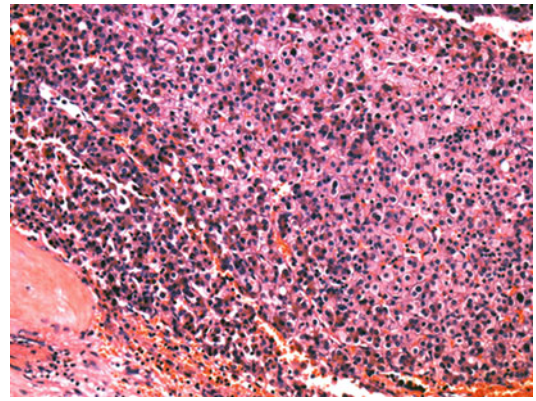

Fig. 9 Hepatoblastoma, fetal subtype. This tumor displays areas with higher proliferative activity and increased nuclear size, resulting in a "crowded pattern" (hematoxylin and eosin stain)

large immature erythroblasts were found among the tumor cells, whereas mature forms tended to gather in the subendothelial spaces or within the sinusoidal lumina. Desmosome-like attachment was often found between immature erythroblasts and tumor cells. Such hematopoietic nests were never found in lymph nodes, spleens, and nonneoplastic liver tissues obtained by surgery or autopsy of the patients (Emura et al. 1985).

Detailed analyses of fetal-type HB elucidated that this pattern can be broken down into three or four phenotypes with different biology of disease. The most common form of fetal HB is called *well-differentiated fetal HB* (*WDF*), *or pure fetal HB with low mitotic activity*. WDF is composed of the typical fetal cells having a diameter of 20–30 μm, arranged in cords one to two cells thick, either in sheets or slightly more cellular trabeculae. Nuclei of WDF have a finely stippled chromatin and inconspicuous nucleoli. Purely fetal HB has a very low mitotic activity, i.e., less than 2 mitotic figures per 10/400× microscopic fields. Based on PCNA immunohistochemistry, fetal hepatoblastomas exhibit a proliferation fraction that is clearly lower than that of embryonal-type cells (10.82 % vs. 59.85 %; Chopra et al. 2010).

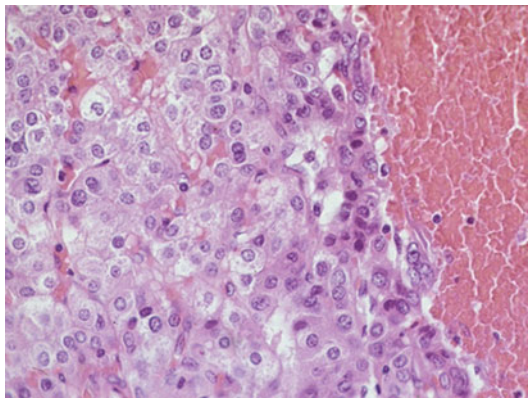

Fig. 10 Hepatoblastoma, fetal subtype. Tumor cells with increased nucleus-to-cytoplasm ratio and replicative activity at higher magnification (hematoxylin and eosin stain)

WDF is the variant that most commonly has hematopoietic foci. Tumors that have an exclusively WDF phenotype reveal a better outcome (Kasai and Watanabe 1970; Haas et al. 1989). All stage I WDF HB patients with tumors showing low or very low mitotic activity enrolled in COG protocols have been cured by surgery alone (Malogolowkin et al. 2011). However, the exact diagnosis of WDF requires the careful examination of pre-chemotherapy resection specimens and is, due to sampling problems, not feasible with small tumor biopsies or with post-chemotherapy specimens. A biopsy, which typically represents less than 3/100,000 of the entire tumor, will only rarely be representative for the lesion. In particular, post-chemotherapy resection specimens exhibit major regressive changes, and the mitotic activity of residual tumor cells cannot reliably be assessed (review: Lopez-Terrada et al. 2013).

A further variant of fetal-type HB is characterized by an elevated mitotic activity and is termed *mitotically active fetal HB or crowded fetal HB*. Already Conran et al. (1992) noted that there were isolated tumors with an elevated mitotic activity. This pattern has to be separated from "standard" WDF, because it has been shown to require chemotherapy. These neoplasms show more than two mitotic figures per 10 high-power fields at 400× magnification. Mitotically active fetal HBs show more cells with an amphophilic cytoplasm and an increased nucleus/cytoplasm ratio, resulting in a "hypernuclear" or "crowded" aspect. Mitotically active parts are often intermingled with typical WDF but may also represent a predominant pattern, and the crowded areas can be adjacent to embryonal-type HB parts, or even small cell undifferentiated parts. Within mitotically active fetal HB, the less mitotically active cells show a finely granular positivity for glypican-3. In regard to the biological impact of mitotically active component, it is currently unknown as to whether the amount of mitotically active parts, or their mere presence, is a decisive feature.

A third variant of fetal HB is characterized by increased nuclear atypia. This is called *pleomorphic* or *poorly differentiated fetal HB* and is more often encountered in post-chemotherapy specimens and in metastases following chemotherapy (review: Lopez-Terrada et al. 2013). The neoplastic cells still retain their typical fetal-type shape and fetal cytoplasmic features (more often with eosinophilic cytoplasm), but nuclei display an irregular shape, coarse chromatin, and large nucleoli. Some of the cells are difficult to distinguish from embryonal-type cells; therefore, the term "HB with a pleomorphic epithelial pattern" has been proposed (Lopez-Terrada et al. 2013). The tumors often show marked mitotic activity, but signs of anaplasia such as large cell size (three to four times the size of adjoining cells) are absent. As the pleomorphic pattern occurs in post-chemotherapy specimens, it is not yet clarified whether chemotherapy as such contributes, and to what extent, to nuclear pleomorphism.

Extramedullary hemopoiesis is a feature that is typical for the fetal subtype of hepatoblastoma (Stein 1952). It has also been reported in embryonal hepatoblastomas (Conran et al. 1992; Stein 1952), but seems to be rarer in this subtype. In the case reported by Stein (Stein 1952), multiple hematopoietic foci were found in metastases of hepatoblastoma, showing both fetal and embryonal morphologies. The embryonal liver is a source of stem cells and becomes the main site of hemopoiesis by 15 gestational weeks in humans and remains so until birth. The immature liver contains a specific stroma which supports homing, proliferation, and differentiation of hemopoietic progenitor cells. The mesenchymal elements

forming this stroma express both mesenchymal markers (vimentin, osteopontin, alpha-SMA, CD29, thrombospondin-1, calponin, Stro-1 antigens, and myocyte enhancer factor 2C) and epithelial markers (cytokeratins 7, 8, and 18, AFP, albumin, E-cadherin, and hepatocyte nuclear factor 3 alpha), suggesting epithelial-to-mesenchymal transition (Chagraoui et al. 2003; Zhang et al. 2005). These cells also express some hemopoiesis-related genes and have the ability to retain hemopoietic stem cells in an undifferentiated state in vitro during cytokine-stimulated proliferation (Zhang et al. 2005). The hemopoietic stem cells are resident in the bone marrow and are there associated with a distinct population of stromal cells which regulate proliferation and differentiation of hemopoietic precursors. In bone marrow, theses stem cells are largely quiescent and undergo only limited self-renewal. In contrast, stem cells located to the embryonal and fetal liver are more frequently cycling, owing to a specific interaction with hepatic stromal cells. These hemopoiesis-supporting fetal liver stromal cells induced a greater than tenfold enhanced proliferative capacity versus bone marrow stromal cells and revealed a higher expression of regulators of the Wnt signaling pathway (Martin and Bhatia 2005). Hemopoiesis in the embryonal and fetal liver seems to also be regulated by two components of basement membranes, nidogen-1 and nidogen-2, which are produced by hepatocytes, stellate cell precursors, endothelial cells, and hemopoietic cells themselves (Tomte et al. 2006). In hepatoblastomas, extramedullary hematopoiesis seems to be induced by fetal and embryonal tumor cells in cooperation with stromal cells by locally secreted cytokines (Von Schweinitz et al. 1995).

Hepatoblastoma, Wholly Epithelial Type: Embryonal and Mixed Embryonal/Fetal Subtype

Embryonal components are a common feature in HB. They are usually combined with a fetal-type pattern, but purely embryonal tumors also occur, albeit as rare lesions. The embryonal histology

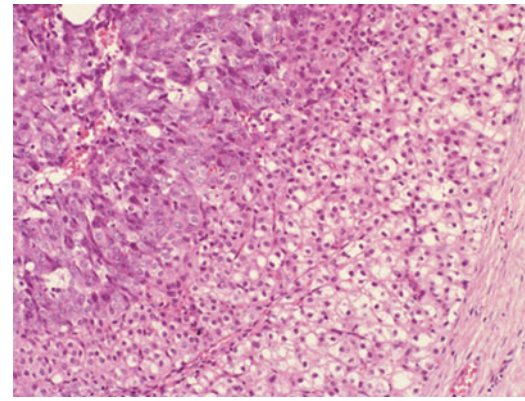

Fig. 11 Hepatoblastoma, fetal subtype. *(Right half)* with transition into larger, embryonal-type cells. *(Left half)* hematoxylin and eosin stain

resembles the morphology of the human liver at 6–8 weeks of gestation. The embryonal hepatoblasts reveal a scant and dark-looking, slightly granular cytoplasm usually lacking glycogen or lipid droplets. The nuclei are enlarged in comparison with fetal-type cells and contain a coarse chromatin and more conspicuous nucleoli. Embryonal cells are commonly arranged as solid nests or glandular/acinar structures, here and there with formation of pseudorosettes and/or papillary structures. In comparison with well-differentiated fetal HB, the mitotic activity is increased, a feature also demonstrable by use of PCNA immunohistochemistry (Rugge et al. 1998). Foci of extramedullary hematopoiesis are rarely present (Figs. 11, 12, 13, 14, and 15).

Hepatoblastoma, Wholly Epithelial Type: Macrotrabecular Subtype

Macrotrabecular HB (MT-HB) is defined as a distinct growth pattern of HB, characterized by the formation of trabeculae or plates which are 10–20 or more cells thick. Pictures of hepatoblastomas with a macrotrabecular growth patterns were published already in older articles (Neimann et al. 1963), and the tumors were defined in more detail by Gonzalez-Crussi et al. (1982), who documented the

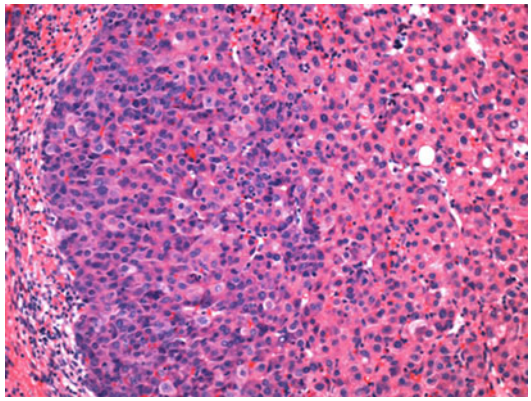

Fig. 12 Hepatoblastoma, mixed fetal and embryonal subtype, with immature embryonal cells to the left (hematoxylin and eosin stain)

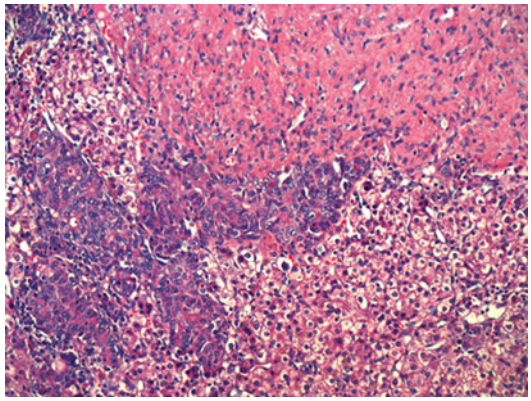

Fig. 13 Mixed fetal and embryonal hepatoblastoma with abortive acinar structures (hematoxylin and eosin stain)

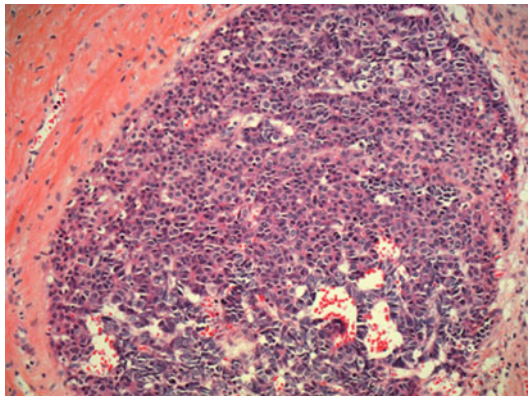

Fig. 14 Hepatoblastoma, embryonal subtype. Acinar structures are present in the *bottom* part (hematoxylin and eosin stain)

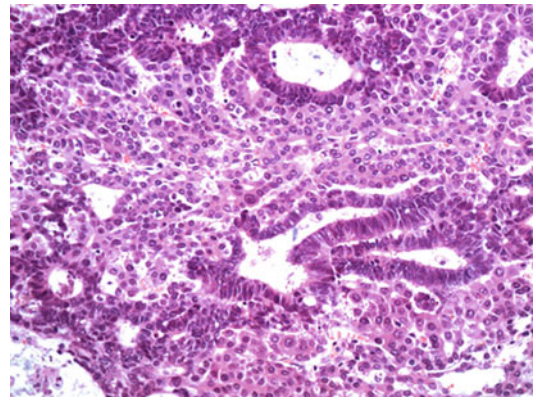

Fig. 15 Hepatoblastoma, mixed fetal and embryonal subtype. Atypical tubular structures with columnar cells are formed, similar to those found in teratoid hepatoblastoma (hematoxylin and eosin stain)

characteristic growth pattern with thick plates or trabeculae. Recent reevaluations of the morphology of MT-HB proposed to reduce the required plate thickness from 10 to 20 cells to 5 or more cells (Lopez-Terrada et al. 2014). Pure MT-HB is a rare variant, accounting for about 3 % of all HB, but MT components within other HB forms have been found in almost 20 % of tumors. Today, the term MT-HB should only be applied to neoplasms in which this pattern is a predominant feature. The macrotrabecular growth pattern in HB involves several types of neoplastic cells. Already Conran and coworkers (1992) specified that macrotrabecular hepatoblastoma contains either fetal- or embryonal-type cells or a third larger cell type with cytoplasm that is more abundant than in normal hepatocytes or fetal-type cells, or a combination of all three cell types. Most commonly, the thick plates are composed of a population of mixed fetal and embryonal cells. Less commonly, the plates consist of larger cells that resemble hepatocytes or cells of differentiated hepatocellular carcinoma. In tumors showing fetal and embryonal cells, these elements exhibit the same morphologic and proliferative features as those found in the respective tumors (see above). The variant with hepatocyte-like cells contains large cells with a granular and eosinophilic

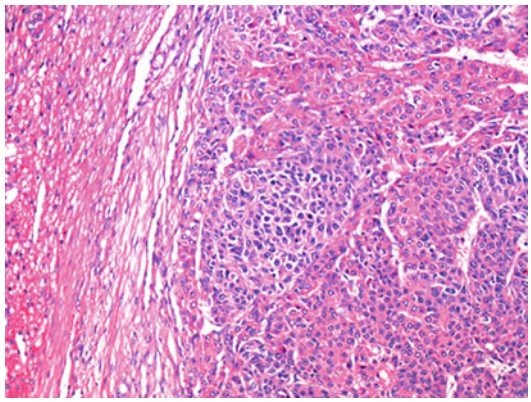

Fig. 16 Hepatoblastoma with a focal macrotrabecular pattern (hematoxylin and eosin stain)

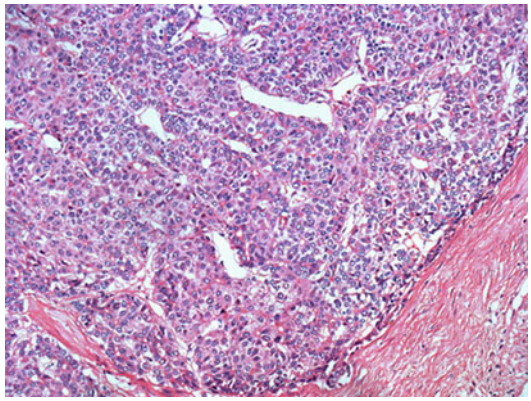

Fig. 17 Hepatoblastoma, macrotrabecular subtype. The large tumor cell plates consist of fetal- and embryonal-type cells (hematoxylin and eosin stain)

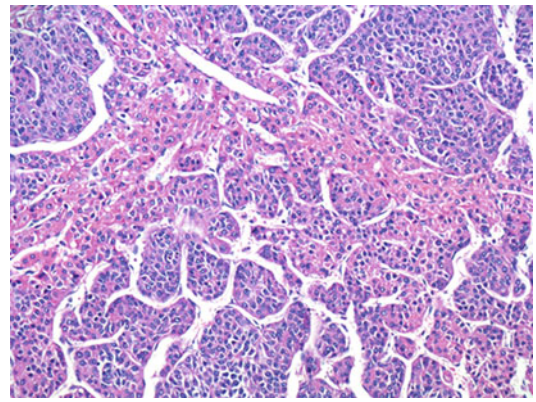

Fig. 18 Hepatoblastoma with macrotrabecular features (MT-1). The tumor cells forming large plates resemble those of hepatocellular carcinoma (hematoxylin and eosin stain)

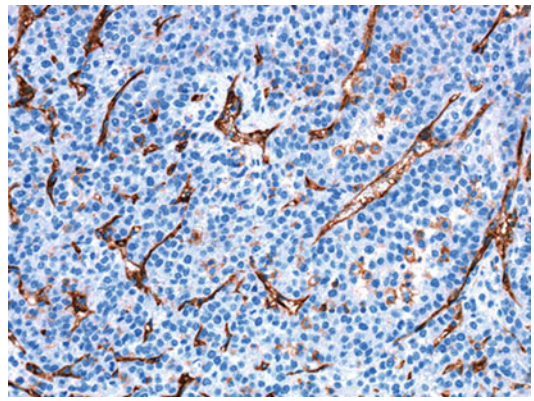

Fig. 19 Hepatoblastoma, macrotrabecular subtype. Immunostaining of intervening vascular channels for CD34 clearly uncovers the large cell plates (CD34 immunostain)

cytoplasm and vesicular nuclei with prominent nucleoli. Based on these two patterns, it was proposed to divide MT-HB into two variants, i. e., MT-1, characterized by HCC-like cells and expected to be a high-risk lesion, and MT-2, containing fetal and embryonal cells and expected to have standard risk (Zimmermann 2005). Histologically, MT-1 may be difficult to distinguish from HCC occurring in older children. The biology of disease of MT-HB is not yet known in detail. None of the three resected MT hepatoblastomas reported by Conran et al. (1992) survived (Figs. 16, 17, 18, and 19).

Hepatoblastoma, Wholly Epithelial Type: Small Cell Undifferentiated Subtype (SCUD)

Small cell undifferentiated hepatoblastoma (SCUD) is a very rare subtype of epithelial hepatoblastoma, with an estimated prevalence of 2–5 % of all hepatoblastomas. SCUD-HB can either occur as a very rare pure lesion (2 % or less of all HB) or make part of other types and subtypes of HB. In case SCUD components occur as focally expressed features in a tumor with an

otherwise different composition, the SCUD feature should be indicated in descriptive terms (HB, with focal SCUD component). In contrast to other subtypes of HB, patients with SCUD-HB reveal low or normal serum levels of AFP. Morphologically, SCUD makes part of the complex group of small blue cell tumors (Gonzalez-Crussi 1991; Sattler et al. 2000). This distinct subtype of hepatoblastoma was first described in 1970 using the term anaplastic hepatoblastoma (Kasai and Watanabe 1970) and was subsequently named undifferentiated small cell hepatoblastoma, in order to avoid confusion in regard to the term "anaplastic" which is used to designate a prognostically important cytological feature in nephroblastoma (Gonzalez-Crussi 1991). SCUD-HB is a high-risk lesion with an aggressive biology and poor outcome (Lack et al. 1982; Dehner and Manirel 1988). In a 1989 study that reported ten SCUD-HB cases, the estimated 24-month patient survival probability was 0 % (Haas et al. 1989). In patients with completely resected hepatoblastomas, the presence of a SCUD component may be a factor for unfavorable outcome, as 10 of 16 patients with this feature developed a disease recurrence (Haas et al. 2001). In a study of completely resected HB, a 38 % recurrence rate in tumors with a SCUD component was found (Ortega et al. 2000).

Macroscopically, SCUD hepatoblastomas tend to present as gray-to-white nodules with marked necrosis and hemorrhage, suggesting a tumor of high-grade malignancy. Invasion of large hepatic veins is a typical feature (Sattler et al. 2000).

Histologically, SCUD-HB is characterized by non-cohesive sheets of small round to ovoid cells resembling the cell of neuroblastoma or other small blue cell tumors. Typically, the cells are a little bit larger than lymphocytes, with a diameter of 7–8 μm. The cytoplasm is scant and amphophilic to basophilic, and nuclei show either a dense or a finely stippled chromatin, with usually small nucleoli (Figs. 20, 21, 22, 23, 24, 25, and 26).

Occasionally, SCUD-HBs contain spindled or stellate cells, usually in a mucoid matrix. The tumor cells, which show a highly invasive phenotype, are arranged as solid sheets, clusters, or nests

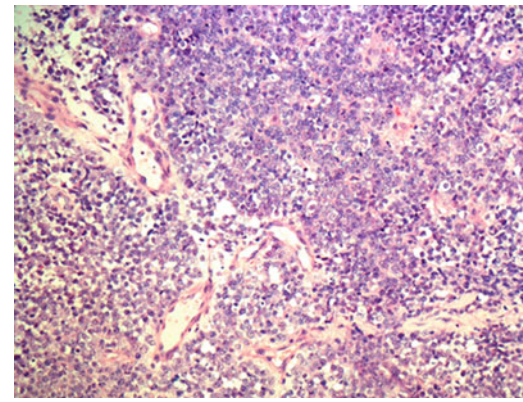

Fig. 20 Hepatoblastoma, small cell undifferentiated subtype. This "blue cellular tumor" consists of a solid growth of immature round cells with poorly developed cytoplasm (hematoxylin and eosin stain)

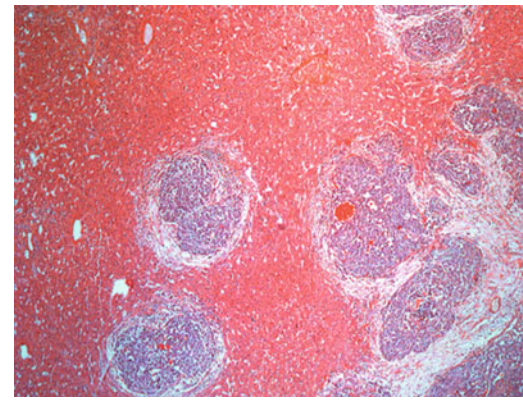

Fig. 21 Hepatoblastoma, small cell undifferentiated subtype. In this partly necrotic neoplasm, nests of immature tumor cells have survived around blood vessels (hematoxylin and eosin stain)

with an organoid pattern and show a variable mitotic rate, numerous apoptotic bodies, and often extensive necrosis. Sinusoid-like vascular channels are present, but they are usually less well developed than those in fetal or embryonal HBs. Based on histology and cytologic features alone, the diagnosis of SCD hepatoblastoma may be difficult, in particular difficult to distinguish from other anaplastic cellular tumors. Conran et al. (1992) stated that areas of other recognizable hepatoblastoma patterns must be present before a diagnosis of the small cell variant is made. Immunohistochemically, SCUD-HB cells are

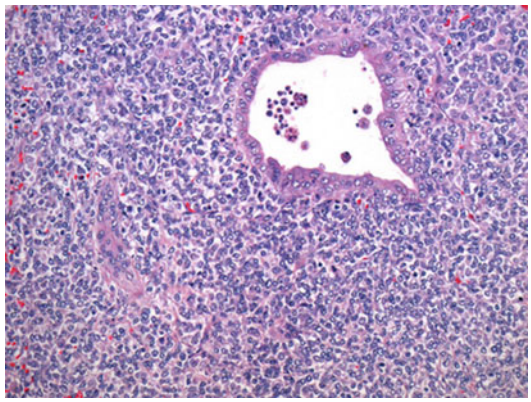

Fig. 22 Hepatoblastoma, small cell undifferentiated subtype. Damaged bile ducts are embedded in this hypercellular, highly invasive cancer (hematoxylin and eosin stain)

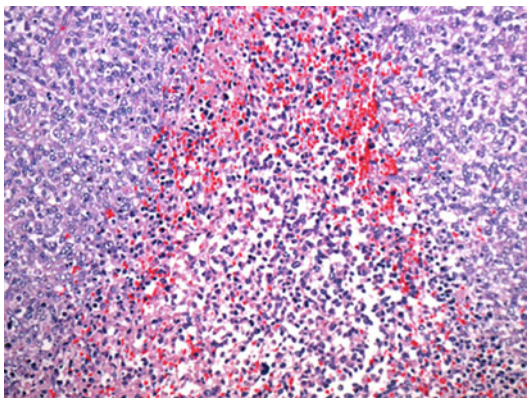

Fig. 23 Hepatoblastoma, small cell undifferentiated subtype, with focal necrosis, apoptosis, and numerous nuclear fragments (karyorrhexis; hematoxylin and eosin stain)

reactive for both cytokeratins (CK 8 and CK18) and vimentin, but not for AFP. Part of SCUD-HB cells are reactive for CD99, a phenotype that has been proposed as PNET-like small cell HB (Zimmermann 2005). Cytogenetically, SCUD-HBs are tumors with signs of genomic/chromosomal instability and various karyotypic abnormalities. In one patient, chromosomal analysis of cultured tumor cells revealed a translocation of most of the long arm of chromosome 22 to the distal long arm of chromosome 10 (Hansen et al. 1992).

SCUD-HB can occur in the form of several varieties, apart from the standard small cell

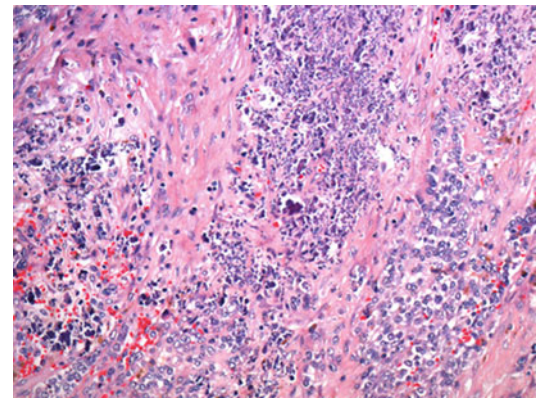

Fig. 24 Hepatoblastoma, small cell undifferentiated subtype, with postnecrotic, dystrophic calcifications (hematoxylin and eosin stain)

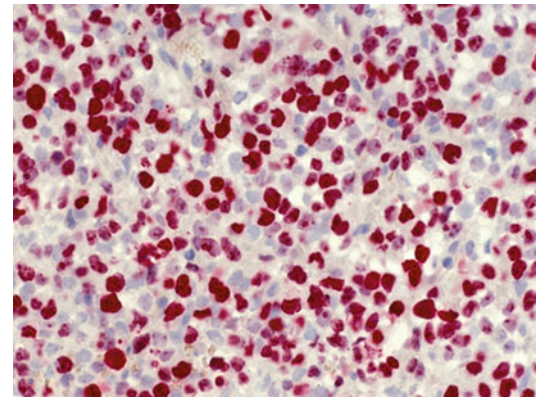

Fig. 25 Small cell undifferentiated hepatoblastomas have a very high proliferative activity (MIB1 immunostain)

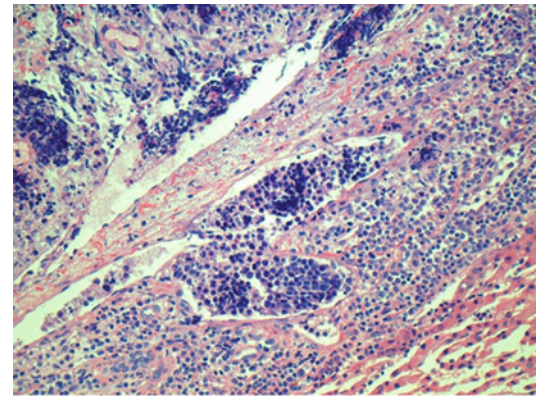

Fig. 26 Hepatoblastoma, small cell undifferentiated subtype, with marked vascular invasion (hematoxylin and eosin stain)

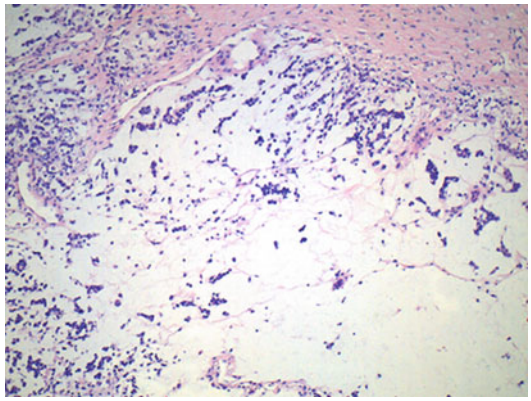

Fig. 27 Hepatoblastoma, mucoid/myxoid variant of small cell undifferentiated HB. Clusters of small neoplastic cells are embedded in a myxoid hypocellular matrix (hematoxylin and eosin stain)

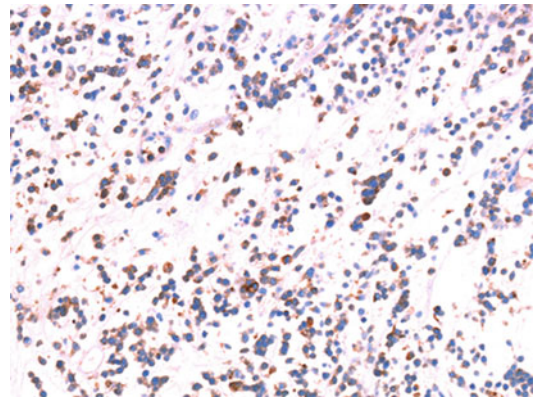

Fig. 29 Mucoid/myxoid variant of small cell undifferentiated HB. The scant cytoplasm of tumor cells shows expression of cytokeratins 8 and 18 (CAM5.2 immunostain)

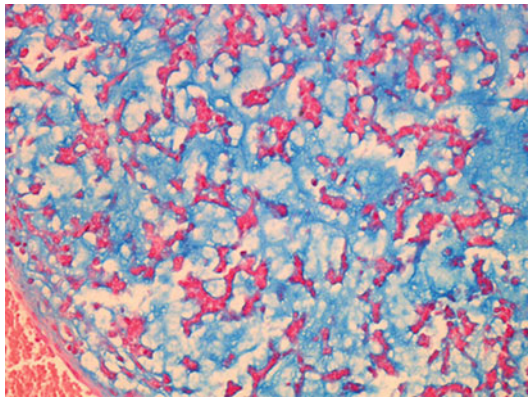

Fig. 28 Mucoid/myxoid variant of small cell undifferentiated HV. The myxoid matrix is rich in alcian blue-positive glycosaminoglycans (alkaline alcian blue stain)

morphology. One of the variants is *mucoid SCUD-HB*. Joshi and coworkers (Joshi et al. 1984) described a hepatoblastoma having, at gross examination, a soft to firm consistency; a cut surface that had a mucoid, glistening, grayish-white "cellular" appearance; and few small irregular cyst-like structures, 4–6 mm in diameters, containing mucoid material. The cells of the SCUD type were embedded in abundant amounts of ground substance rich in alcianophilic and PAS-negative acid mucopolysaccharides. Microcysts containing the same material were also in evidence (Figs. 27, 28, and 29).

Similar features were described in the metastasis of a SCUD hepatoblastoma, where SCUD cells were found in poorly cellular, highly myxoid stroma (Gonzalez-Crussi 1991). Some of the features of this variant of SCUD hepatoblastoma resemble yolk sac tumor. As the term SCUD implies, this subtype of HB is characterized by small cells. However, there are rare examples of undifferentiated HBs that are not, or not exclusively, composed of small cells. Within the SIOPEL pathology reviews, tumors with undifferentiated cells having an intermediate or large size were identified. In a working formulation, such neoplasms were denoted as *intermediate cell undifferentiated HB* (ICUD-HB) and *large cell undifferentiated HB* (LCUD-HB), respectively (Zimmermann 2005; Fig. 30). Large cell variants are known to occur in other blastomatous tumors, including medulloblastoma (Polydorides et al. 2008) and neuroblastoma (Tornoczky et al. 2004; Abramowsky et al. 2009).

Small Cell Undifferentiated Hepatoblastoma with Rhabdoid Features

Recently it has been shown that a subset of SCUD-HBs may present features characteristic of malignant rhabdoid tumors, in particular

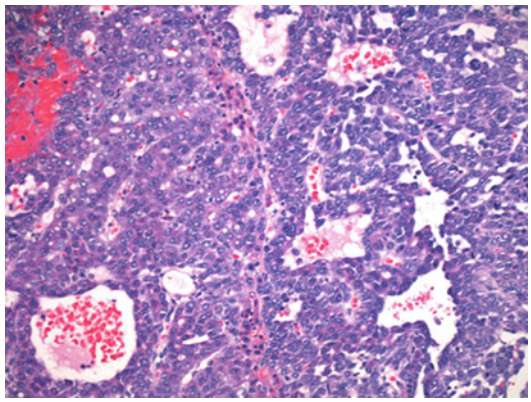

Fig. 30 Poorly/undifferentiated hepatoblastoma that consists of medium-sized cells ("intermediate cell undifferentiated hepatoblastoma"; ICUD; hematoxylin and eosin stain)

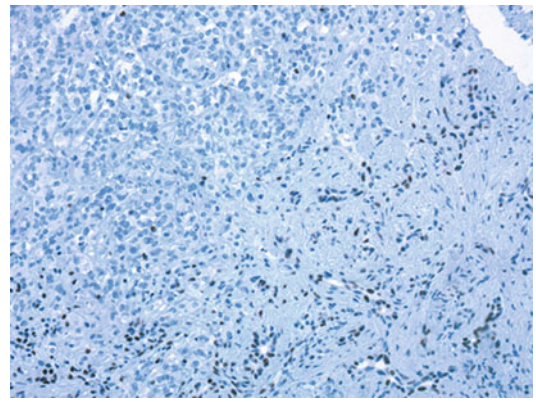

Fig. 32 Hepatoblastoma, small cell undifferentiated subtype with rhabdoid features. In contrast to nuclei of normal bile duct cells, vascular cells, and connective tissue cells, tumor cell nuclei are INI1-negative (INI1 immunostain)

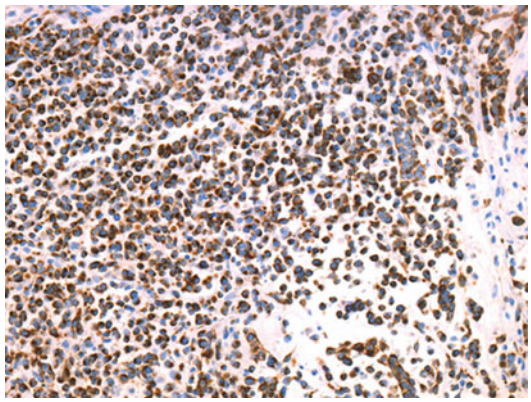

Fig. 31 Hepatoblastoma, small cell undifferentiated subtype with rhabdoid features. Similar to malignant rhabdoid tumors, these neoplasms show a *dot*-like cytoplasmic reactivity for vimentin (vimentin immunostain)

absence of nuclear INI1 expression (Wagner et al. 2007; Russo and Biegel 2009; Trobaugh-Lotrario et al. 2009). Lack of INI1/SMARCB1 expression by use of the BAF-47 antibody is typical for malignant rhabdoid tumors (RT) and has also been found in hepatic RT (Machado et al. 2010). These neoplasms seem to behave like malignant rhabdoid tumors rather than HB, and it will be important to distinguish INI1-negative SCUD-HB from INI1-positive SCUD-HB in order to stratify the lesions with respect to future treatment modalities. In addition, INI1-negative tumors should be submitted to molecular analyses for the detection of SMARCB1 mutations (Figs. 31 and 32).

Mixed Epithelial and Mesenchymal Hepatoblastoma (MEM-HB)

MEM-HB is a rather common variant of HB that may involve mechanisms of epithelial-mesenchymal transition. The tumors are mostly characterized by the presence of variable stromal components, such as fibroblastoid and osteoid tissue and other heterologous elements, intermingled with various lineages of epithelial cells (Figs. 33, 34, 35 and 36).

These features have an estimated prevalence of 20–50 % (Ishak and Glunz 1967). However, as in other types and subtypes of HB, such figures have to be interpreted with caution, mainly for pretreatment biopsies, as the incidences may be underestimated due to sampling errors. Furthermore, there is evidence that chemotherapy may favor the survival – and hence the prevalence – of mesenchymal components and particularly osteoid (Saxena et al. 1993; Heifetz et al. 1997). In addition to osteoid, HB-MEM may contain hyaline cartilage, usually immature looking, but cartilage is much more uncommon than osteoid.

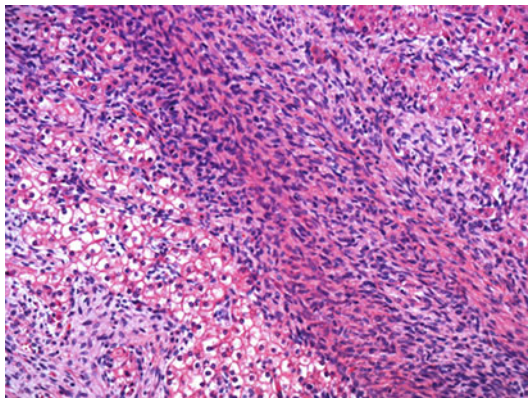

Fig. 33 Hepatoblastoma, mixed epithelial and mesenchymal type. Fetal-type cells are observed in the *left bottom* corner, while the *right half* is mainly occupied by densely packed tumor spindle cells (hematoxylin and eosin stain)

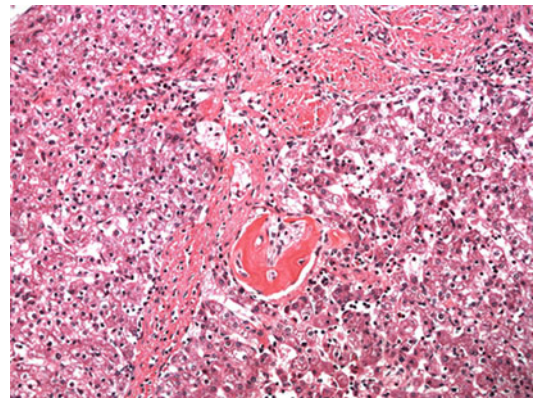

Fig. 35 Hepatoblastoma, mixed epithelial and mesenchymal type with formation of osteoid tissue (hematoxylin and eosin stain)

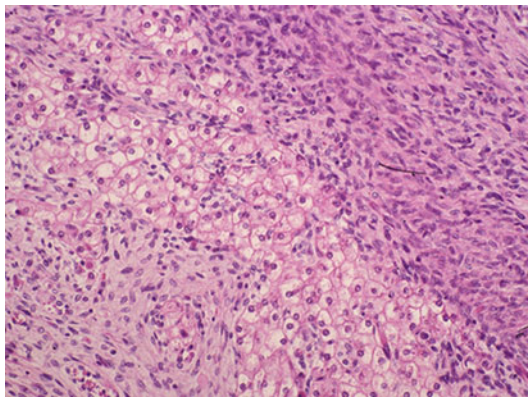

Fig. 34 In mixed epithelial and mesenchymal hepatoblastoma, some spindle cells (to the *right*) are eosinophilic and reveal a myoid phenotype (hematoxylin and eosin stain)

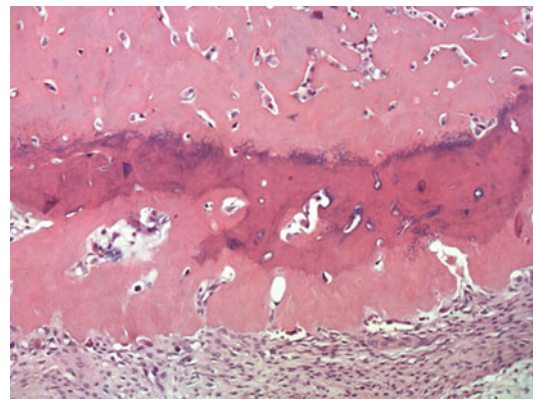

Fig. 36 Mixed epithelial and mesenchymal hepatoblastoma. In part of these neoplasms, osteoid formation is a dominant feature (hematoxylin and eosin stain)

Foci of hyaline tumor cartilage have probably been described for the first time by Grünberg in 1904 in a 2-year-old child, then a few times in the 10 years to come (Philipp 1908; Hippel 1910; Yamagiwa 1911; Idzumi 1912/1913), and later in 1928 in a mixed hepatoblastoma observed in a newborn female infant (Nissel 1928). In a 9-month-old male patient described by Philipp (1908), histology showed a mixed hepatoblastoma with foci of hyaline cartilage, but also epithelial structures composed of tall columnar cells, suspicious of teratoid hepatoblastoma. This feature has since been reported only a few times (Roth 1938; Pang 1961; Conran et al. 1992), reviewed by Pang (1961). In part of the cases, both cartilage and osteoid were present (Yamagiwa 1911; Idzumi 1912/1913; Nissel 1928; Leffers 1940/1941; Hünerwadel 1962; Fig. 37).

Striated muscle cells are observed in a minority of HB-MEM (Fig. 38). This feature has been documented in the older literature, first in a 6-year-old girl (Sheehan 1930), in 2.25-year-old boy (Williams (1953), and in 14-year-old boy (Pack and Miller 1956), illustrating that this phenomenon occurs in a wide age range. One case of mixed tumor occurring in 4-year-old girl and containing tumor cells with a typically striated

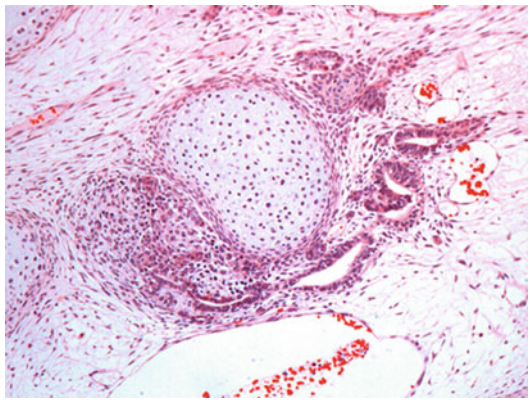

Fig. 37 Mixed epithelial and mesenchymal hepatoblastoma with formation of hyaline cartilage (*center*). This is a very uncommon feature of mixed hepatoblastomas (hematoxylin and eosin stain)

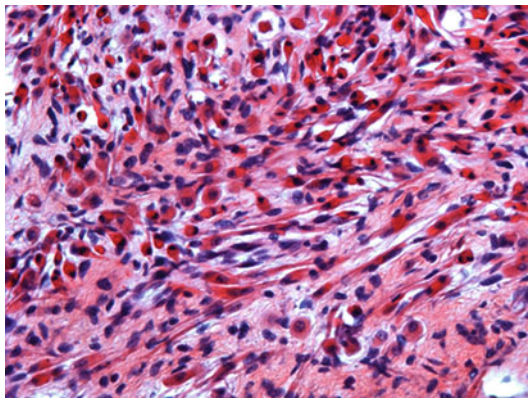

Fig. 38 Hepatoblastoma, mixed epithelial and mesenchymal type with immature cells of the striated muscle cell lineage (hematoxylin and eosin stain)

cytoplasm is intriguing insofar as the neoplasm also contained components indistinguishable from fibrosarcoma, a finding that is not known to occur in typical HB-MEM (Watanabe et al. 1975). Ultrastructurally, the osteoid foci showed fibroblast-like cells associated with collagen fiber formation (Silverman et al. 1975).

The first case of tumors now called mixed epithelial and mesenchymal hepatoblastoma (HB-MEM) was recorded in 1898, albeit erroneously described as a teratoma of the liver (Misick 1898). The right lobe of the liver of a boy who died at age 5 and a half weeks showed a large neoplasm containing large amounts of bony tissue requiring decalcification for histology. The tumor further consisted of embryonic liver cells, cysts, squamous epithelial pearls, immature mesenchyme, osteoblasts, and foci of hematopoiesis. This report is the first to document bone formation in a mixed hepatoblastoma, followed by a report in 1911 (Nakamura 1911). Mixed tumors in infancy and childhood, containing both epithelial cell lineages and immature mesenchyme with bony or cartilaginous differentiation, have subsequently been described and reviewed (Hippel 1910; Yamagiwa 1911; Idzumi 1912/1913; Nissel 1928; McRae 1935; Roth 1938; Webster 1938; Leffers 1940/1941; Milman and Grayzel 1951; Bigelow and Wright 1953; Allison and Willis 1956; Kattan et al. 1959; Wohlgemuth 1960). Nissel (1928) reviewed the German literature in 1928 and found 12 cases. Sheehan (1930) collected nine cases in 1930, two of which had not been listed in Nissel's series. Webster (1938) regarded the tumor he described as a hepatic analog of Wilms tumor. The case reported of Milman and Grayzel (1951) is often listed in the literature as an example of a mixed hepatoblastoma, but a careful study of their description fails to prove this. The patient described by Doris Milman and David Grayzel in 1951 was a 6-year-old boy admitted to the Jewish Hospital of Brooklyn. This child's illness had interestingly first been noted at the age of 20 months when it was observed that he was losing weight and that his abdomen was unusually large, and at the age of 26 months, he was found to have an enlarged liver. His abdomen continued to enlarge out of proportion to his skeletal growth, and he was later thought to have von Gierke's disease. Subsequent detailed investigations revealed a firm mass occupying the entire right side of the abdomen. Laparotomy showed a large globular tumor of 20 cm diameter arising from the under surface of the right liver lobe. Histology of a resection specimen displayed a lobulated tumor encapsulated by dense collagenous fibrous tissue. The description of the epithelial tumor cells indicates mixed fetal and embryonal hepatoblastoma associated with myxoid connective tissue, but no bona fide heterologous elements. Bigelow and Wright (1953)

reported a huge hepatic tumor from a 10-month-old female infant, showing hepatoid cells, squamous epithelial foci, and osteoid, but they classified this tumor in the category of carcinoma of the liver. The tumor type which we now term HB-MEM was again described in detail in 1956 (Allison and Willis 1956), by the use of the term ossifying embryonic mixed tumor. The epithelial component varied greatly in its differentiation, ranging from scattered groups of barely recognizable epithelial cells to well-formed masses of cuboidal cells arranged in trabeculae, without formation of lobules, and sometimes showing accumulation of fat. The less differentiated parts showed numerous mitoses and probably represent embryonal-type cells, while the better differentiated cells with fat were likely fetal-type cells. The mesenchymal component was characterized by abundant osteoid, without chondroid areas. Bone marrow was not observed by these authors and has in fact never been reported to occur in osseous tissue in hepatoblastoma. Kattan and coworkers (1959) reported on a primary hepatic carcinoma in infancy with calcified foci, probably representing tumor osteoid of a mixed hepatoblastoma. The case described by Roth (1938) is of special interest insofar as this female infant of 11 months also presented a unilateral overgrowth of the left side of the body and may thus have been the first report on hepatoblastoma associated with hemihypertrophy.

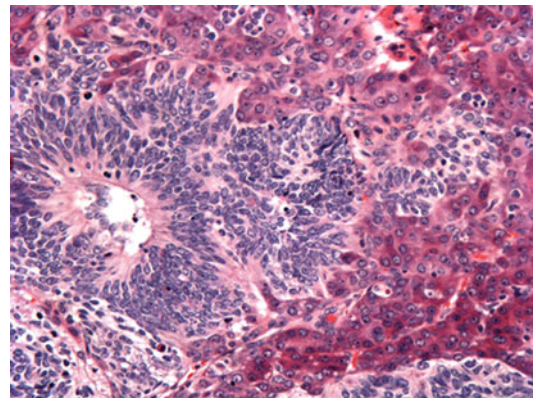

Fig. 39 Hepatoblastoma, mixed epithelial and mesenchymal type with teratoid features. Apart from hepatoid tumor cells (to the *top* and *right*), this neoplasm exhibits pseudostratified tubules reminiscent of early neural tube or ependymal structures (hematoxylin and eosin stain)

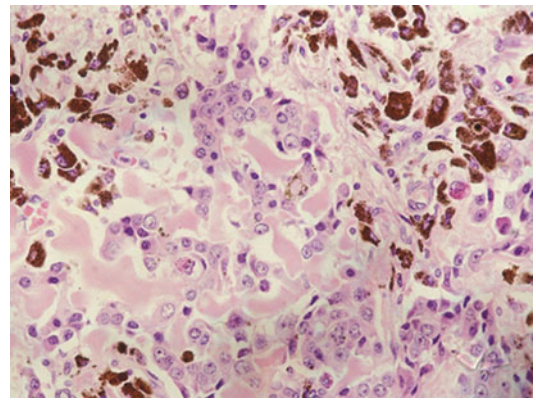

Fig. 40 Hepatoblastoma, mixed epithelial and mesenchymal type with teratoid features. This tumor contains numerous cells producing melanin (melanotic hepatoblastoma). In the center, epithelial tumor cells, osteoblast-like cells, and osteoid are seen (hematoxylin and eosin stain)

Teratoid Hepatoblastomas

In the group of hepatoblastomas currently classified as the mixed epithelial and mesenchymal type, a small subset is characterized by the presence of multiple lineages of differentiation, including neuroectodermal, rhabdomyoblastic, and endodermal cell lineages (Stranz 1913; Figs. 39, 40, and 41).

These lesions are termed teratoid hepatoblastomas (Misugi and Reiner 1965; Shabanov et al. 1981; Manivel et al.,1986; Lackner et al. 1990; Stocker 1994; Kim et al. 2001; Zhang et al. 2007; Buccoliero et al. 2008; Rabah 2012). Teratoid hepatoblastoma also occurs in adult patients (Zhang et al. 2007). Teratoid hepatoblastoma must not be confounded with a teratoma, which is a germ cell tumor.

One of the first descriptions (Wuester and Knauer 1961) referred to an 18-month-old male infant with a history of an enlarging tumor mass in the right upper abdomen of 10 weeks' duration. A roentgenogram showed a dense homogeneous opacity obscuring most of the abdomen. The mass was removed by a right lobectomy.

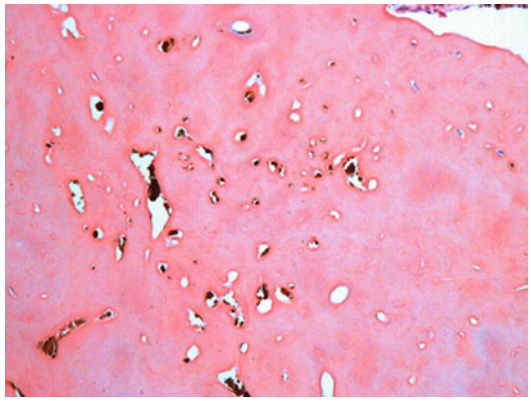

Fig. 41 Hepatoblastoma, mixed epithelial and mesenchymal type with teratoid features. The cavities of tumor osteoid harbor melanin-containing cells (hematoxylin and eosin stain)

Histologically, the tumor was composed of undifferentiated epithelial cells and of a mesenchyme with many embryonal rhabdomyoblasts with cross striation. Arthur P. Stout, who consulted this case, placed the tumor in the malignant teratoma class, but then preferred the term carcinosarcoma. The final histologic diagnosis was embryonal rhabdomyosarcohepatoma. A case originally diagnosed as malignant true teratoma of the liver (Misugi and Reiner 1965) has, based on the descriptions and figures in this paper, to be reclassified as teratoid hepatoblastoma. It is important to emphasize that these intriguing neoplasms should not be confounded with true teratomas, which are germ cell tumors. Part of teratoid hepatoblastomas contain cells producing melanin and typical melanin granules/melanosomes (Manivel et al. 1986; Kim et al. 2001). The tumors may contain melanin both in epithelial cells and mesenchymal cells, including those located within osteoid. Melanotic hepatoblastoma may contain large numbers of melanophages (macrophages/Kupffer cells containing phagocytosed melanin granules), ultrastructurally with melanosomes in the cytoplasm (Ruck and Kaiserling 1993). Melanotic components occur in other blastomatous tumors, including medulloblastoma (Polydorides et al. 2008). Teratoid tumors can contain rhabdomyoblastic elements (Shabanov et al. 1981), which may in some tumors even dominate the histologic pattern, similar to what is seen in some pediatric renal neoplasms. Teratoid hepatoblastomas sometimes show squamous differentiation (Rabah 2012), otherwise often seen following chemotherapy. Thyroid tumors may contain mucinous epithelia of bronchial or intestinal type, sometimes with formation of complex patterns involving mucin-producing and non-mucinous cells and formation of glandular structures. Similar to the GIT, CDX2 is a good marker for mucinous differentiation in teratoid hepatoblastomas (Fan and Lin 2013). The pathogenesis of teratoid hepatoblastomas is unknown. A stem cell origin has been suggested (Kim et al. 2001), but a formal proof of this hypothesis is lacking.

Unusual Variants of Hepatoblastoma

Unusual variants of HB are characterized by the presence of a highly diverse pattern of cell differentiation. These neoplasms have been termed "multilineage tumors" because they show cells apparently developing along several lines of differentiation, ranging from immature cells to more mature-looking, fetal, and/or embryonal cells and covering a broad array of ontogenetic pathways (Zimmermann 2011; Figs. 42 and 43).

Exceptionally, HB presents as a tumor with a fine papillary pattern (papillary HB; Zimmermann 2011; Fig. 44).

A rare subset of hepatoblastoma is characterized by a hypervascularized phenotype and the formation of multiple nodules, mimicking infantile hepatic hemangioendothelioma (hypervascular hepatoblastoma; Ingram et al. 2000; Lu and Greer 2007). These lesions demonstrate a delayed centripetal contrast medium fill in in MRI, a change that is more typical of hemangioendothelioma (Lu and Greer 2007).

Immature Stem-Like Cell Clusters in Hepatoblastomas

Clusters of "light cells" and of "primitive cells" occurring in HB have been published already in 1982 (Gonzalez-Crussi et al. 1982; Figs. 8 and 9

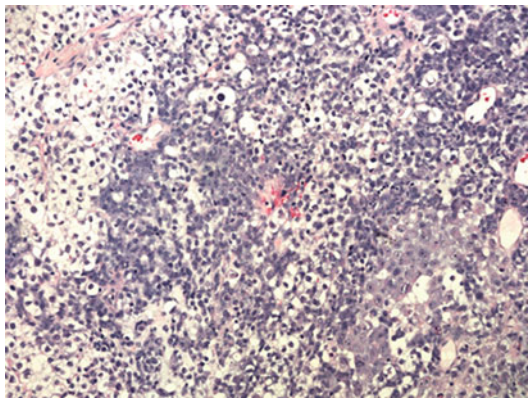

Fig. 42 Hepatoblastoma composed of several different epithelial lineages. Fetal-type cells are seen in the *left upper corner*. The center is dominated by small undifferentiated tumor cells, while large undifferentiated cells (large cell undifferentiated HB) are present in the *lower right corner* ("multilineage tumor"; hematoxylin and eosin stain)

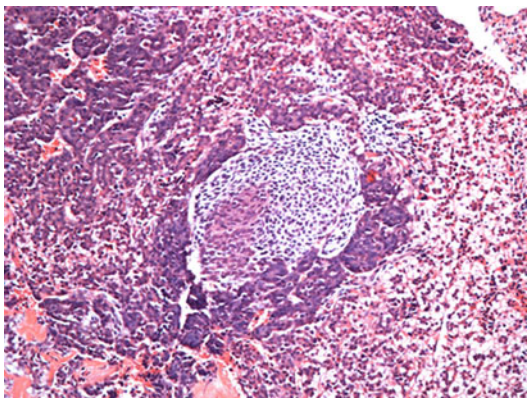

Fig. 43 Hepatoblastoma with a highly complex, "organoid" morphology, in part reflecting several phases of liver ontogenesis. The center shows a mesenchymal bud with an epithelial core (hematoxylin and eosin stain)

of this publication). We identified, both in fetal and mixed fetal-embryonal HB, nests of small and in part pale or clear cells with a roughly spherical shape (Zimmermann 2005; Zimmermann and Saxena 2010). These cells are clearly different from fetal and embryonal cells and have a poor development of cytoplasmic organelles, as estimated from a very weak immunostaining for a mitochondrial marker. Only few of these cells

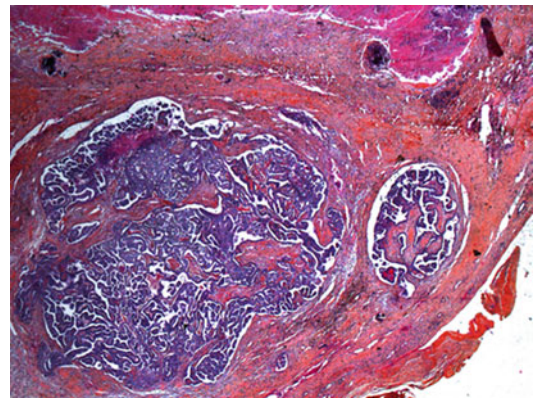

Fig. 44 Hepatoblastoma, papillary pattern. These very rare neoplasms reveal finely branching papillary structures resembling those of papillary thyroid carcinoma (hematoxylin and eosin stain)

show a Ki-67-reactive proliferative activity, whereas a thin rim of fetal or embryonal cells surrounding the nests exhibits a marked proliferative activity. In contrast to better differentiated adjoining cells, the cells in the nests display marked nuclear reactivity for beta-catenin. This distinct set of features might indicate that these are focal accumulations of tumor progenitor cells (Figs. 45, 46, 47, and 48).

Cytology Findings in Hepatoblastomas (Fine Needle Aspiration Cytology)

Hepatoblastoma can reliably be diagnosed by fine needle aspiration cytology (Cangiarella et al. 1994; Sola Perez et al. 1994; Us-Krasovec et al. 1996; Weir and Ali 2002; Iyer et al. 2005; Parikh et al. 2005; Philipose et al. 2006). It has been demonstrated that preparations of fine needle aspiration allow the distinction between poorly differentiated HB (including SCUD and embryonal subtypes) and differentiated HB (comprising fetal and macrotrabecular subtypes), while the separation of SCUD from embryonal HB is more complex and can be difficult to carry out (Sola Perez et al. 1994).

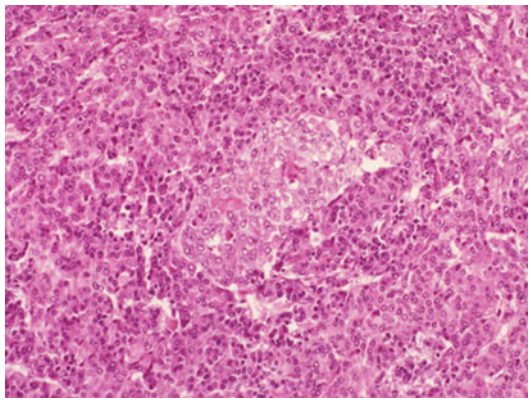

Fig. 45 Immature, progenitor cell-like cluster in hepatoblastoma. The cytoplasm of the cells is pale, and nuclear size is increased in comparison with fetal-type tumor cells (hematoxylin and eosin stain)

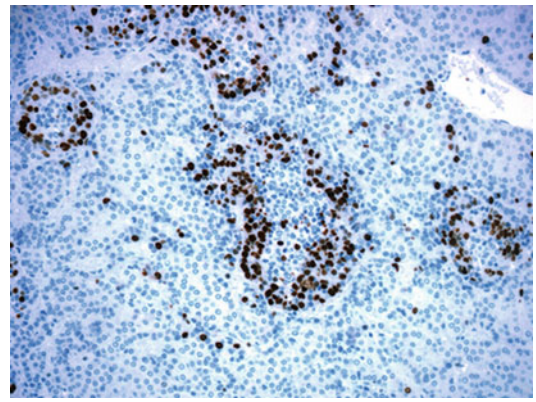

Fig. 47 Immature cell clusters in hepatoblastoma. The cells within the clusters reveal a low proliferative activity, whereas a tumor cell sheath encircling the clusters exhibits a very high proliferative activity (MIB1 immunostain)

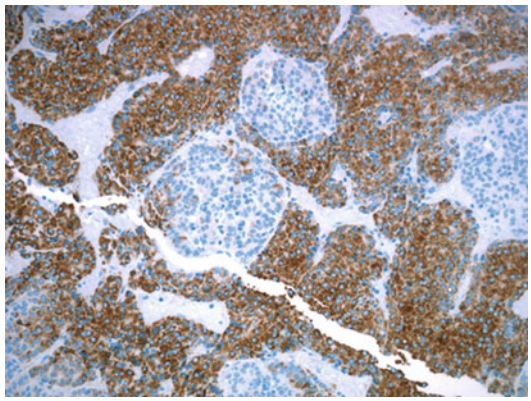

Fig. 46 Immature cell clusters in hepatoblastoma. In contrast to fetal-type cells, cluster cells are poor in mitochondria, reflecting their lower level of differentiation (mitochondrial antigen immunostain)

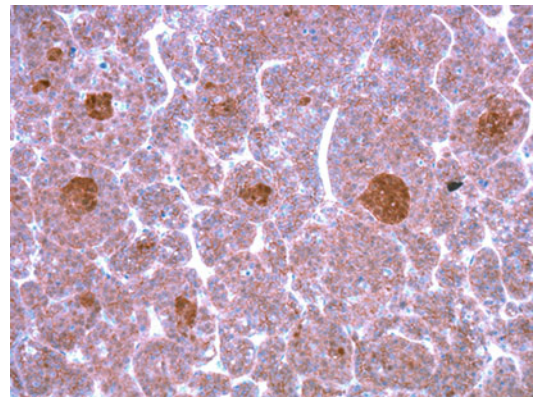

Fig. 48 Beta-catenin expression in immature cell clusters. The cells of the fetal hepatoblastoma background display membranous positivity, whereas cells in the spherical immature clusters show nuclear and cytoplasmic beta-catenin reactivity (beta-catenin immunostain)

Ultrastructural Features of Hepatoblastomas

Relatively few studies have investigated the electron microscopic features of hepatoblastomas (Ito and Johnson 1969; Silverman et al. 1975; Horie et al. 1979; Rosa and Grases 1980; Shabanov 1981, 1983; Stiller and Holzhausen 1983; Albenoza et al. 1987; Ruck and Kaiserling 1993; Veeramachaneni et al. 2003). Fetal cells display a rather well-developed cytoplasm containing numerous organelles, glycogen particles, and sometimes lipid droplets. In contrast to fetal cells, embryonal cells show a decreased number of cytoplasmic organelles, a poorly developed Golgi apparatus, and few or no visible glycogen particles (Ito and Johnson 1969; Stiller and Holzhausen 1983). Formation of biliary capillaries/canaliculi by tumor cells, with microvilli and typical junctional areas, has been described (Stiller and Holzhausen 1983; Ruck and Kaiserling 1993). Electron microscopically, the SCUD cells show a

cytoplasm with striking paucity of organelles (predominance of mitochondria; occasional RER profiles), absence of surface microvilli or canalicular domains, few lipid droplets and glycogen granules, sparse bundles of intermediate filaments, and primitive or few desmosomal cell junctions (Joshi et al. 1984; Gonzalez-Crussi 1991; Hansen et al. 1992; Ruck et al. 1996).

Immunohistochemistry of Hepatoblastomas

Cytokeratins

Immunohistochemically, the tumor cells variably express cytokeratins (mainly CK 8 and CK 18), vimentin, and sometimes CK 19 and CD34 (Fischer et al. 1987; O'Brien et al. 1989; Van Eyken et al. 1990; Pontisso et al. 1993; Sattler et al. 2000; Fig. 49).

In regard to expression of CK8, fetal-type cells with a granular cytoplasm are more strongly stained than pale/clear cells, and embryonal-type cells usually show a more variable and paranuclear staining. In contrast, CK18 reveals a more homogeneous and consistently marked staining for both fetal-type and embryonal-type cells (Van Eyken et al. 1990). A strong immunoreactivity for CK19 was found in embryonal-type cells (Van Eycken et al. 1990) and cholangioblastic hepatoblastomas (Zimmermann 2002). Embryonal cells situated in the center of macrotrabeculae in MTB hepatoblastomas can show CK19 reactivity (Van Eycken et al. 1990). In osteoid found in mixed epithelial and mesenchymal hepatoblastoma, epithelioid- or osteoblast-like cells in part express cytokeratins CK7, CK8, and CK19 (Van Eycken et al. 1990), suggesting mesenchymal-epithelial transition. CK 19 expression may occur in embryonal cells, but not or weakly in fetal-type cells (Cajaiba et al. 2006).

Hepatocyte Export Proteins

In a study of 19 cases, most of the differentiated hepatoblastomas were immunoreactive for cytokeratin and AFP and some for alpha-1-antitrypsin and ferritin (Abenoza et al. 1987; Cangiarella et al. 1994; Ramsay et al. 2008). Alpha-fetoprotein/AFP is detectable in epithelial cells of hepatoblastomas in a highly variable frequency, depending on tumor subtype and antibodies used (Norgaard-Pedersen et al. 1974; Abenoza et al. 1987; Fig. 50).

In an analysis of 12 needle core biopsies, AFP was positive in about half of the cases (Ramsay et al. 2008).

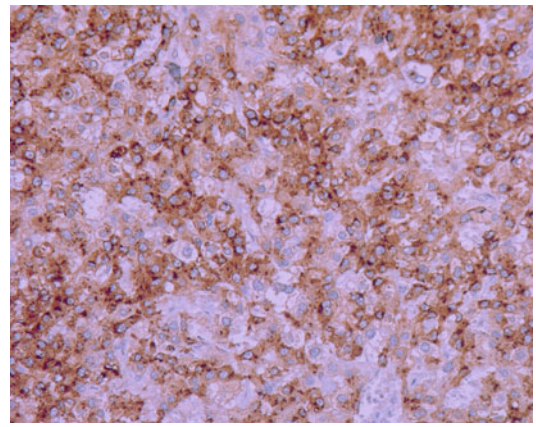

Fig. 49 Cytokeratin expression in epithelial hepatoblastoma (CAM5.2 immunostain)

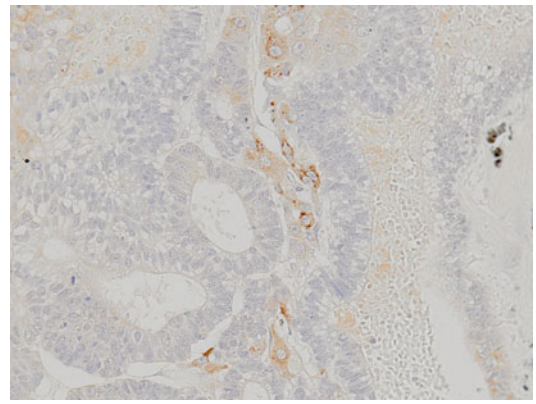

Fig. 50 Alpha-fetoprotein (*AFP*) reactivity in hepatoid cells of an epithelial hepatoblastoma (*center*; AFP immunostain)

Hep Par1

The differentiated epithelial cells of all hepatoblastomas seem to be positive for the marker, hepatocyte paraffin 1/Hep Par 1, with a granular intracytoplasmic pattern being less intense in embryonal cells than in fetal cells, probably reflecting the state of cell differentiation along the hepatocyte lineage (Fasano et al. 1998).

Glypican 3

An important marker for epithelial hepatoblastomas is glypican 3 (Toretsky et al. 2001; Chan et al. 2013), the product of one of the most overexpressed genes in hepatoblastoma by microarray analysis (Fig. 51).

In a study of 65 cases, cytoplasmic immunoreactivity for glypican 3 was found in all samples, with greater than 90 % of cases showing strong and diffuse positivity (Zynger et al. 2008). Expression of glypican 3 in hepatoblastoma cells depends on the activation of the Yes-associated protein, Yap, the effector of the Hippo kinase pathway (Li et al. 2012).

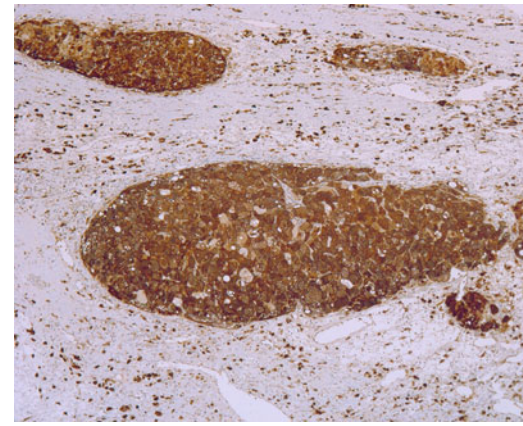

Fig. 51 Strong glypican-3 reactivity in epithelial hepatoblastoma (glypican-3 immunostain)

Beta-Catenin

HB cells often express beta-catenin in various patterns, depending on cell differentiation. Fetal-type cells display a membranous immunostaining, whereas less differentiated cells more often show a cytoplasmic and/or nuclear beta-catenin staining (Fig. 52).

A key target of beta-catenin is hepatic glutamine synthase/GS. GS can immunohistochemically be detected in neoplastic epithelial cells of the majority of hepatoblastomas (Fig. 53).

In hepatoblastomas carrying beta-catenin gene mutations, GS was only detected in tumor areas with epithelial differentiation, and particularly high expression of GS was found in hepatoblastoma cells directly neighboring a mesenchymal tumor area (Schmidt et al. 2011).

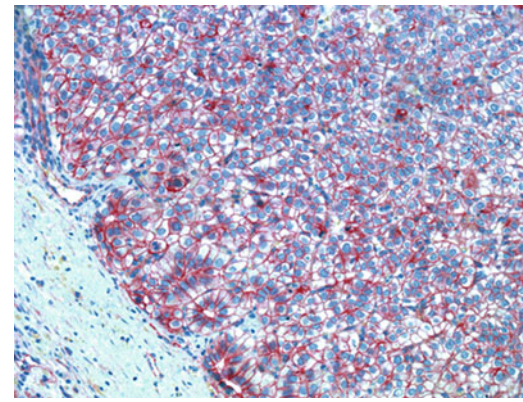

Fig. 52 Hepatoblastoma, fetal subtype. The tumor cells show marked beta-catenin reactivity with a membranous staining pattern (beta-catenin immunostain)

Markers of Progenitor Cells and Immature Cell Lineages

As hepatic progenitor cells are possible candidates as an origin of hepatoblastoma, HB cells were analyzed for the expression of stem cell markers. Significant fractions of hepatoblastomas express octamer-binding transcription factor 3/4 (Oct-3/4), epithelial cell adhesion molecule (EpCAM), and delta-like 1 homolog (DLK1) (Yun et al. 2013). Hepatoblastomas show an aberrant expression of the stem cell markers, CD44, CD90, and CD133 (Bahnassy et al. 2014). Cells of the embryonal subtype of HB are reactive for SALL4,

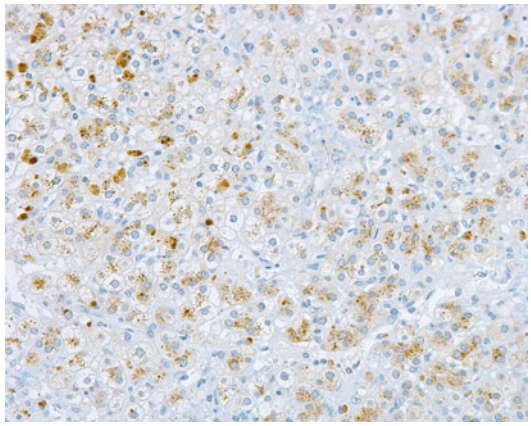

Fig. 53 Hepatoblastoma, fetal subtype. Part of neoplastic cells express glutamine synthetase in the cytoplasm (glutamine synthetase immunostain)

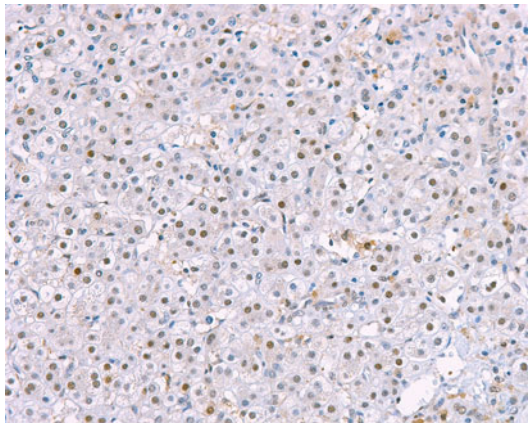

Fig. 54 Most hepatoblastomas show nuclear reactivity for INI1 (INI1 immunostain)

a marker of stem-like cells and germ cell tumors (Gnemmi et al. 2013). Apart from HB with rhabdoid features (see above), most HBs express INI1 in the nuclei (Fig. 54).

Other Markers

Cells of SCUD hepatoblastoma are positive for vimentin and may also show cytokeratin staining, as shown above (Abenoza et al. 1987). The canalicular domains found in fetal cells are reactive for polyclonal anti-carcinoembryonic (CEA) antigen (Fasano et al. 1998). Unusual antigens expressed in part of hepatoblastomas include CD99/MIC-2 and NCAM/CD56 (Ramsay etal. 2008) and common acute lymphoblastic leukemia antigen/CALLA (Von Schweinitz et al. 1996). Expression of CD99 is found in a subset of small cell undifferentiated hepatoblastomas (see above; Zimmermann 2005). Expression of claudins, members of a distinct family of transmembrane proteins, may be used to identify certain cell lineages in hepatoblastomas. Claudin1 and claudin2 are markedly expressed in fetal-type cells, but not in embryonal cells of hepatoblastomas, and the expression of these two claudins is inversely correlated with cell proliferation (Halasz et al. 2006). A further tight junction-associated protein, tricellulin, is also expressed in subsets of hepatoblastoma (Schlachter et al. 2014). Both fetal and embryonal tumor cells stained irregularly positive for intercellular adhesion molecule-1/ICAM-1 (Von Schweinitz et al. 1996). Primary hepatoblastomas express survivin, and survivin reactivity increased following chemotherapy, suggesting that this apoptosis inhibitor is involved in HB cell survival (Uehara et al. 2013).

Several novel markers expressed in HB cells have been reported. Delta-like protein, a transmembrane EGF-like homeotic protein encoded by the DLK1 gene, is expressed in a wide variety of embryonic tissues in the human organism and is a reliable marker for oval cells in the rat liver. Delta-like protein was found to be a sensitive marker for all types of hepatoblastoma (Dezsö et al. 2008). Dickkopf 3, a protein expressed in very early phases of hepatogenesis, is expressed in hepatoblastomas (Pei et al. 2009).

Hepatoblastomas express proteins of extracellular matrix, including laminin, fibronectin, and collagen types III, IV, and V (Ruck and Kaiserling 1992). In a subset of hepatoblastomas, immunohistochemical signs of neuroendocrine differentiation have been found, including reactivity for chromogranin A and/or neuron-specific enolase in fetal- and embryonal-type cells and in cells located within tumor osteoid. A fraction of embryonal cells also expressed serotonin or somatostatin (Ruck et al. 1990). Chromogranin A and

serotonin reactivity was also detected in a melanotic hepatoblastoma (Ruck and Kaiserling 1993).

Chemotherapy-Induced Alterations in Hepatoblastomas

Chemotherapy induces a wide array of secondary changes in HB and adjacent liver tissue (Figs. 55, 56, 57, 58, 59, 60, 61, 62 and 63).

Few studies have analyzed chemotherapy-induced alterations in hepatoblastomas (Forouhar et al. 1984; Saxena et al. 1993; Wang et al. 2010; Gupta et al. 2012). In contrast to other neoplasms, such as osteosarcomas and ES/PNETS (Raymond et al. 1987; review: Lowichik et al. 2000), a standardized prognostic factor grading system of chemotherapy effects has not yet been worked out for hepatoblastomas. In a study on 17 patients treated with preoperative chemotherapy compared with 11 patients not subjected to chemotherapy during the same 11-year period (Saxena et al. 1993), there was no correlation between the extant of necrosis and the number of chemotherapy courses. There also seemed to be no evidence of preferential ablation of a particular morphologic type of tumor. Interestingly, osteoid in case of mixed epithelial and mesenchymal hepatoblastomas was present in 36 % of untreated tumors, occupying less than 5 % of the surface area, while osteoid was present in 82 % of the cases treated with preoperative chemotherapy. It was suggested that an increase of osteoid and of the extent of mature mesenchymal tissues was induced by chemotherapy (Heifetz et al. 1997). It is, however, difficult to judge whether this reflects a true increase of osteoid (caused by a differential effect of therapy on osteoprogenitor cells) or whether this only reflects an apparent predominance of chemoresistant osteoid tissue owing to the shrinkage of other chemosensitive tumor components. In epithelial

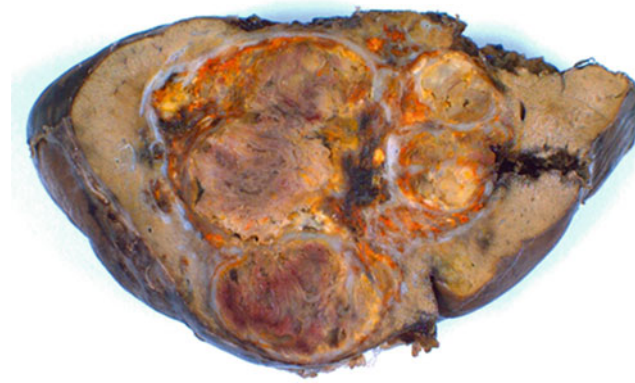

Fig. 55 Hepatoblastoma post-chemotherapy. The tumor presents as a conglomerate of necrotic nodules separated from adjacent liver by a fibrous, whitish pseudocapsule (fixed resection specimen)

Fig. 56 Hepatoblastoma after chemotherapy. There is an area of tumor shrinkage with scar tissue. The *yellowish* speckles seen on the *top* of the figure are foci of osteoid (fixed resection specimen)

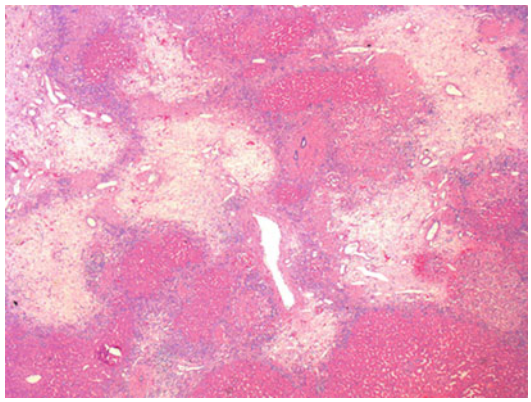

Fig. 57 Hepatoblastoma post-chemotherapy. Regressed tumor appears as pale shrunken areas intermingled with preserved hepatic parenchyma and portal tracts (hematoxylin and eosin stain)

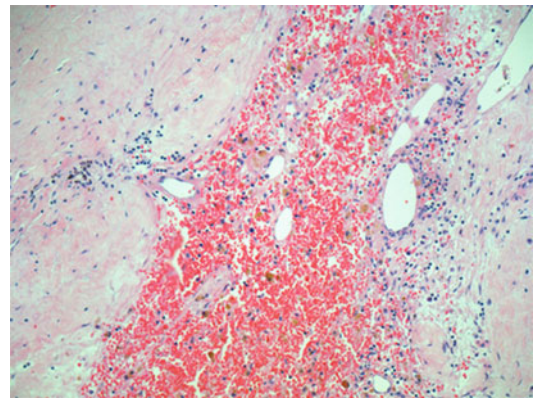

Fig. 59 Hepatoblastoma following chemotherapy. Necrotic tumor tissue may later be replaced by hypocellular connective tissue nodules (extreme *left* and *right*; hematoxylin and eosin stain)

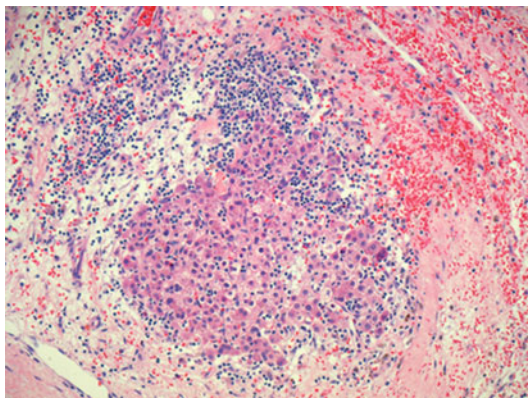

Fig. 58 Hepatoblastoma post-chemotherapy. A partly preserved focus of epithelial neoplastic tissue shows a lymphocytic infiltrate that probably represents an immune reaction (hematoxylin and eosin stain)

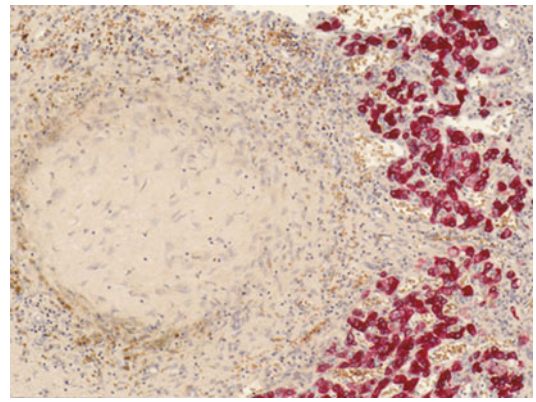

Fig. 60 Hepatoblastoma post-chemotherapy. In contrast to strong cytokeratin staining of intact normal hepatocytes (*right part*), the connective tissue sphere as a sclerosed tumor remnant is devoid of epithelial cells (CAM5.2 immunostain)

hepatoblastomas treated with chemotherapy, neoplastic epithelial cells may survive, however, with marked alterations (Table 4). The changes comprise fatty change of fetal-type cells, switch of fetal-type cells to a morphology resembling hepatocytes (so-called maturing hepatoblastoma), marked cellular and nuclear atypias mimicking high-grade cancer, and atrophy of tumor cells. A 15-year retrospective study of hepatoblastomas in 22 children who received neoadjuvant chemotherapy according to the COG protocol showed that, in addition to necrosis and fibroinflammatory changes, two thirds had areas of cytoarchitectural differentiation ("maturation") mimicking non-neoplastic liver, and a quarter revealed alterations mimicking hepatocellular carcinoma (Wang et al. 2010). In another study of 20 post-chemotherapy cases, tumor "maturation" and HCC-like changes of atypical epithelial components were also found as typical features, and the authors also observed peliotic-like foci and "glomeruloid clusters" (Gupta et al. 2012).

Surviving epithelial tumor components, mostly of the fetal type, are often difficult to be distinguished from normal hepatic parenchyma

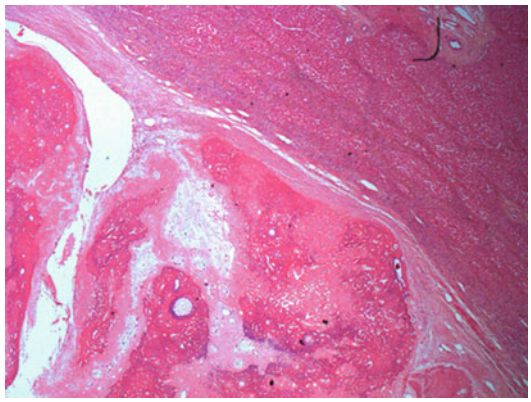

Fig. 61 Hepatoblastoma following chemotherapy. In treated mixed epithelial-mesenchymal hepatoblastomas with osteoid formation, remnant tumor may only consist of osteoid, which tends to resist chemotherapy (hematoxylin and eosin stain)

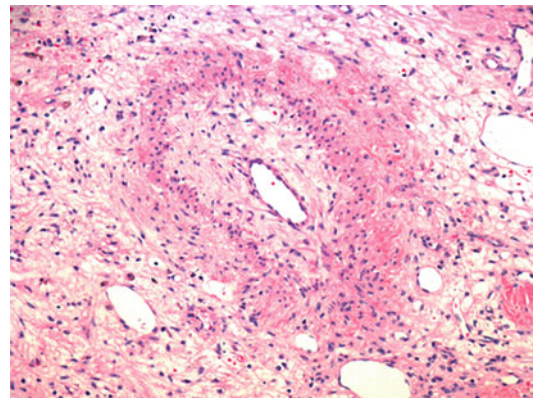

Fig. 63 Vascular changes in hepatoblastoma treated with chemotherapy. The tumor vessel in the center shows marked thickening of its intima and a damaged media (hematoxylin and eosin stain)

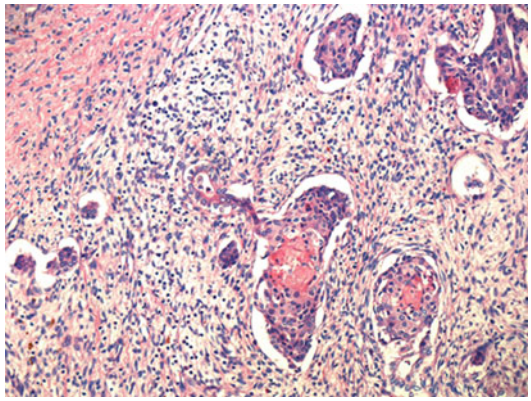

Fig. 62 Hepatoblastoma post-chemotherapy. In treated HB, nests and pearls of squamous epithelium are a common finding, sometimes associated with a foreign body reaction (hematoxylin and eosin stain)

entrapped within the regressing tumor, sometimes in the form of small nests or nodules of damaged hepatocytes. Immunohistochemical detection of nuclear beta-catenin reactivity in the cells of question may be helpful, as positivity favors the presence of tumor remnants (Wang et al. 2010). In one observation, a mature intestinal epithelium has been noted after chemotherapy using doxorubicin and cisplatin (Forouhar et al. 1984), but this might have been a teratoid hepatoblastoma before therapy already. Between the nodular scar-like lesions, collapsed tissue with blood-filled spaces resembling peliosis (Wang et al. 2010), inflammatory changes, accumulation of lipid-laden macrophages, hemosiderosis, and calcifications are found. Mesenchymal components have a tendency to persist more frequently than epithelial tumor cells (Fourouhar et al. 1984). They appear as hypocellular nodules or spheres ("regression spheres") that my contain central blood vessels and/or accumulations of hemosiderin and iron-positive macrophages. In post-chemotherapy resection specimens of hepatoblastoma, small foci of keratinizing squamous epithelium, forming "pearls," are often encountered. It has been proposed that this change is only seen in treated hepatoblastomas, but it also occurs in native tumors, albeit very rarely (McRae 1935; Leffers 1940/1941).

Changes of the Adjacent Normal Liver

Three foci of focal nodular hyperplasia (FNH) were found in the parenchyma surrounding a small cell undifferentiated hepatoblastoma of a 4-year-old boy with a history of stage IV neuroblastoma (Gutweiler et al. 2008). It is known that FNH can develop subsequent to treatment of other solid tumors in the pediatric age group (Icher-De Bouyn et al. 2003). On the other hand, FNH has been observed in association with other liver cell

Table 4 Morphologic alteration of hepatoblastomas following chemotherapy

Alterations of epithelial tumor cells
Necrosis
Fatty change
Swelling or ballooning
Cholestasis
Differentiation to a hepatocyte-like phenotype ("maturation")
Atrophy
Keratinizing squamous epithelium
Alterations of mesenchymal components
Nodular scar-like structures ("regression spheres")
Increase of tumor-associated osteoid in mixed hepatoblastomas
Fibrosis/scarring
Accumulation of lipid-laden macrophages
Hemosiderosis
Vascular sclerosis and obliteration
Other alterations
Inflammatory changes (lymphocytes, plasma cells)
Calcifications
Peliosis-like changes
Ductular proliferations

tumors, specifically hepatocellular carcinoma (Zhang et al. 2004; Langrehr et al. 2006). A perifocal hyperplasic reaction of hepatocytes may also be caused by tumor-induced alterations of local blood circulation. Portal vein invasion by diverse hepatic malignancies causes a derangement of portal venous blood flow, sometimes followed by peritumoral hyperplasia of hepatocytes (Arnason et al. 2013).

Differential Diagnosis

HB with hepatoid cells, i.e., non-fetal and non-embryonal cells, may be confounded with hepatocellular carcinoma, and undifferentiated small cell HB may mimic other small blue cell tumors. There are unusual situations where a malignant tumor different from hepatoblastoma can produce osteoid within the abdominal cavity, e.g., abdominal Ewing small cell sarcoma with the EWS/FLI1 fusion (Oshima et al. 2004).

References

Abelev GI (1971) Alpha-fetoprotein in ontogenesis and its association with malignant tumors. Adv Cancer Res 14:295–358

Abenoza P, Manivel JC, Wick MR, Hagen K, Dehner LP (1987) Hepatoblastoma: an immunohistochemical and ultrastructural study. Hum Pathol 18:1025–1035

Abramowsky CR, Katzenstein HM, Alvarado CS, Shehata BM (2009) Anaplastic large cell neuroblastoma. Pediatr Dev Pathol 12:1–5

Admasse D, Kebede T (2007) A case of hepatoblastoma; uncommon hepatic neoplasm occurring at unusual age. Ethiop Med J 45:313–317

Alagille D (1961) Tumours du foie et hépatectomie réglée chez le nourrisson. Cah Collège Med Hôpitaux Paris 2:495–500

Allan BJ, Parikh PP, Diaz S, Perez EA, Neville HL, Sola JE (2013) Predictors of survival and incidence of hepatoblastoma in the paediatric population. HPB (Oxford) 15:741–746

Allison RM, Willis RA (1956) An ossifying embryonic mixed tumor of an infant's liver. J Path Bact 72:155

Alpert ME, Seeler RA (1970) Alpha fetoprotein in embryonal hepatoblastoma. J Pediatr 77:1058–1060

Ammann RA, Plaschkes J, Leibundgut K (1999) Congenital hepatoblastoma: a distinct entity? Med Pediatr Oncol 32:466–468

Arnason T, Fleming KE, Wanless IR (2013) Peritumoral hyperplasia of the liver: a response to portal vein invasion by hypervascular neoplasms. Histopathology 62:458–464

Aviram R, Cohen IJ, Kornreich L, Braslavski D, Meizner I (2005) Prenatal imaging of fetal hepatoblastoma. J Matern Fetal Neonatal Med 17:157–159

Bahnassy AA, Fawzy M, El-Wakil M, Zekri AR, Abdel-Sayed A, Sheta M (2014) Aberrant expression of cancer stem cell markers (CD44, CD90, and CD133) contributes to disease progression and reduced survival in hepatoblastoma patients: 4-year survival data. Transl Res. doi:10.1016/j.trsl.2014.07.009

Baroni C, Tognoli S, Spadon S, Astuni M, Lora PA, Lazzarini G, Fantoni PA (1984) Hemoperitoneum caused by spontaneous rupture of a hepatoblastoma in an adult, with arrest of hemorrhage by preoperative cryoapplication (in Italian). Minerva Chir 39:1015–1018

Behrendt H (1931) Primäres Leberkarzinom bei einem 2 ½ jährigen Kind (primary liver carcinoma in a 2 ½-year-old child). Kinderärztl Praxis 10:463–464

Bigelow NH, Wright AW (1953) Primary carcinoma of the liver in infancy and childhood. Cancer 6:170

Bohmig HJ (1961) Das embryonale Hepatom. Zbl Allg Pathol 102:26–38

Braunstein GD, Bridson WE, Glass A, Hull EW, McIntire KR (1972) In vivo and in vitro production of human chorionic gonadotropin and alpha-fetoprotein by a virilizing hepatoblastoma. J Clin Endocrinol 35:857–862

Buccoliero AM, Castiglione F, Maio V, Moncini D, Sardi I, Taddei A, Martin A, Messineo A, Taddei GL (2008) Teratoid hepatoblastoma. Fetal Pediatr Pathol 27:274–281

Buckley JD, Sather H, Ruccione K et al (1989) A case-control study of risk factors for hepatoblastoma: a report from the Children's Cancer Study Group. Cancer 64:1169–1176

Cajaiba MM, Neves JI, Facco Casarotti FF, de Camargo B, ChapChap P, Treiger SS et al (2006) Hepatoblastomas and liver development: a study of cytokeratin immunoexpression in twenty-nine hepatoblastomas. Pediatr Dev Pathol 9:196–202

Cangiarella J, Greco MA, Waisman J (1994) Hepatoblastoma. Report of a case with cytologic, histologic and ultrastructural findings. Acta Cytol 38:455–458

Catanzarite V, Hilfiker M, Daneshmand S, Willert J (2008) Prenatal diagnosis of fetal hepatoblastoma : case report and review of the literature. J Ultrasound Med 27:1095–1098

Chan ES, Pawel BR, Corao DA, Venneti S, Russo P, Santi M, Sullivan LM (2013) Immunohistochemical expression of glypican-3 in pediatric tumors: an analysis of 414 cases. Pediatr Dev Pathol 16:272–277

Chargraoui J, Lepage-Noll A, Anjo A, Uzan G, Charbord P (2003) Fetal liver stroma consists of cells in epithelial-to-mesenchymal transition. Blood 101:2973–2982

Chopra A, Iyer VK, Agarwala S, Mathur SR, Apron M, Gupta SD, Verma K (2010) Apoptotic protein expression, glycogen content, DNA ploidy and cell proliferation in hepatoblastoma subtyping and their role in prognostication. Pediatr Surg Int 26:1173–1178

Clatworthy HW, Boles ET, Kottmeier PK (1961) Liver tumors in infancy and childhood. Ann Surg 154:475–484

Clatworthy HW, Schiller M, Grosfeld JL (1974) Primary liver tumors of infancy and childhood. 41 cases variously treated. Arch Surg 109:143–147

Conran RM, Hitchcock CL, Waclawiw MA, Stocker JT, Ishak KG (1992) Hepatoblastoma: the prognostic significance of histologic type. Pediatr Pathol 12:167–183

Cornert S, Vitrinel A, Akin Y, Mutlu GY, Tokuc G, Bakir B (2007) Abdominal mass in a neonate: hepatoblastoma. Indian J Pediatr 74:956–958

Dachman AH, Pakter RL, Ros PR, Fishman EK, Goodman ZD, Lichtenstein JE (1987) Hepatoblastoma: radiologic-pathologic correlation in 50 cases. Radiology 164:15–19

Darbari A, Sabin KM, Shpairo CN, Schwarz KB (2003) Epidemiology of primary hepatic malignancies in U.S. children. Hepatology 38:560–566

De Ioris M, Brugières L, Zimmermann A, Keeling J, Broch P, Maibach R, Pritchard J et al (2008) Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: the SIOPEL group experience. Eur J Cancer 44:545–550

Debré R, Mozziconacci P, Habib R (1954) L'Hépatoblastoma (tumeur maligne du foie à cellules embryonnaires) (in French). Arch Pédiat 11:1013–1034

Dehner LP (1978) Hepatic tumors in the pediatric age group: a distinctive clinicopathologic spectrum. Perspect Pediatr Pathol 4:227–239

Dehner LP, Manivel JC (1988) Hepatoblastoma: an analysis of the relationship between morphologic subtypes and prognosis. Am J Pediatr Hematol Oncol 10:301–307

Dezsö K, Halasz J, Bisgaard HC, Paku S, Tutanyi E, Schaff Z, Nagy P (2008) Delta-like protein (DLK) is a novel immunohistochemical marker for human hepatoblastoma. Virchows Arch 452:443–448

Dong Q, Jiang B, Lu Y, Zhang H, Jiang Z, Lu H, Yang C, Zhao J, Hao X (2009) Surgical management of giant liver tumor involving the hepatic hilum of children. World J Surg 33:1520–1525

Drummond DH, Tollman JP (1939) Primary carcinoma of the liver in a child. Case report. Am J Clin Pathol 9:361–366

Edmondson HA (1956) Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. Am J Dis Child 91:168–186

Emura I, Ohnishi Y, Yamashita Y, Iwafuchi M (1985) Immunohistochemical and ultrastructural study on erythropoiesis in hepatoblastoma. Acta Pathol Jpn 35:79–86

Eren E, Demirkaya M, Cakir ED, Sevinir B, Saglam H, Tarim O (2009) A rare cause of precocious puberty: hepatoblastoma. J Clin Res Pediatr Endocrinol 1:281–283

Ergin H, Yildirim B, Dagdeviren E, Yagci B, Ozen F, Sen N, Duzcan E (2008) A prenatally detected case of congenital hepatoblastoma. Pathol Oncol Res 14:97–100

Exelby PR, Filler RM, Grosfeld JL (1975) Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey – 1974. J Pediatr Surg 10:329–337

Fan R, Lin J (2013) CDX2 highlights mucinous epithelium in hepatoblastoma with teratoid components. Fetal Pediatr Pathol 32:316–317

Fasano M, Theise ND, Nalesnik M, Goswami S, Garcia de Davila MT, Finegold MJ, Greco MA (1998) Immunohistochemical evaluation of hepatoblastomas with use of the hepatocyte-specific marker, hepatocyte paraffin 1, and the polyclonal anti-carcinoembryonic antigen. Mod Pathol 11:934–938

Finegold MJ, Lopez-Terrada DH, Bowen J, Washington MK, Qualman SJ (2007) Protocol for the examination of specimens from pediatric patients with hepatoblastoma. Arch Pathol Lab Med 131:520–529

Finegold MJ, Egler RA, Goss JA, Guillerman RP, Karpen SJ, Krishnamurthy R, O'Mahony CA (2008) Liver tumors : pediatric population. Liver Transplant 14:1545–1556

Fischer HP, Altmannsberger M, Weber K, Osborn M (1987) Keratin polypeptides in malignant epithelial

liver tumors. Differential histogenetic aspects. Am J Pathol 127:530–537
Florentin P, Rauber G, Macinot C (1956) Hépatoblastome chez un nouveau-né. Ann Anat Pathol 1:507–513
Forouhar FA, Quinn JJ, Cooke R, Foster JH (1984) The effect of chemotherapy on hepatoblastoma. Arch Pathol Lab Med 108:311–314
Galifer RB, Sultan C, Margueritte G, Barneon G (1985) Testosterone-producing hepatoblastoma in a 3-year-old boy with precocious puberty. J Pediatr Surg 20:713–714
Giacomoni MA, Volpi ML, Cerizzi A, Heinen M (1986) Hemoperitoneum: the initial symptom of hepatoblastoma in a child operated on with success (in Italian). Minerva Pediatr 38:949–951
Gnemmi V, Leteurtre E, Sudour-Bonnange H, Devisme L, Guettier C, Buob D, Leroy X (2013) SALL4 is a marker of the embryonal subtype of hepatoblastoma. Histopathology 63:425–428
Goedeke J, Haeberle B, Schmid I, von Schweinitz D (2011) AFP negative cystic liver lesion in a child should let one think of hepatoblastoma. J Pediatr Hematol Oncol 33:e245–e247
Gonzalez-Crussi F (1991) Undifferentiated small cell (anaplastic) hepatoblastoma. Pediatr Pathol 11:155–161
Gonzalez-Crussi F, Manz HJ (1972) Structure of hepatoblastoma of pure epithelial origin. Cancer 29:1272–1280
Gonzalez-Crussi F, Upton MP, Maurer HS (1982) Hepatoblastoma. Attempt at characterization of histologic subtypes. Am J Surg Pathol 6:599–612
Grunewald TG, von Lüttichau I, Welsch U, Dörr HG, Höpner F, Kovacs K, Burdach S et al (2010) First report of ectopic ACTH syndrome and PTHrP-induced hypercalcemia due to a hepatoblastoma in a child. Eur J Endocrinol 162:813–818
Gupta K, Rane S, Das A, Marwaha RK, Menon P, Rao KL (2012) Relationship of b-catenin and postchemotherapy histopathologic changes with overall survival in patients with hepatoblastoma. J Pediatr Hematol Oncol 34:e320–e328
Gutweiler JR, Yu DC, Kim HB, Kozakewich HP, Marcus KJ, Shamberger RC, Weldon CB (2008) Hepatoblastoma presenting with focal nodular hyperplasia after treatment of neuroblastoma. J Pediatr Surg 43:2297–2300
Haas JE, Muczynski KA, Krailo M, Ablin A, Land V, Vietti TJ, Hammond GD (1989) Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. Cancer 64:1082–1095
Haas JE, Feusner JH, Finegold MJ (2001) Small cell undifferentiated histology in hepatoblastoma may be unfavorable. Cancer 92:3130–3134
Halasz J, Holczbauer A, Paska C, Kovacs M, Benvo G, Vverebély T, Schaff Z, Kiss A (2006) Claudin-1 and claudin-2 differentiate fetal and embryonal components in human hepatoblastoma. Hum Pathol 37:555–561
Hansen K, Bagtas J, Mark HF, Homans A, Singer DB (1992) Undifferentiated small cell hepatoblastoma with a unique chromosomal translocation: a case report. Pediatr Pathol 12:457–462
Hartley AL, Birch JM, Kelsey AM, Morris Jones PH, Harris M, Blair V (1990) Epidemiological and familial aspects of hepatoblastoma. Med Pediatr Oncol 18:103–109
Hata Y (1990) The clinical feature and prognosis of hepatoblastoma: follow up studies done on pediatric tumors enrolled in the Japanese pediatric tumor registry between 1971 and 1980. Part 1. Jpn J Surg 20:498–502
Heifetz SA, French M, Correa M, Grosfeld JL (1997) Hepatoblastoma: the Indiana experience with preoperative chemotherapy for inoperable tumors: clinicopathological considerations. Pediatr Pathol Lab Med 17:857–874
Heimann A, White PF, Riely CA, Ritchey AK, Flye MW, Barwick KW (1987) Hepatoblastoma presenting as isosexual precocity. The clinical importance of histologic and serologic parameters. J Clin Gastroenterol 9:105–110
Helmberger TK, Ros PR, Mergo PJ, Tomczak R, Reiser MF (1999) Pediatric liver neoplasms: a radiologic-pathologic correlation. Eur Radiol 9:1339–1347
Hippel B (1910) Zur Kenntnis der Mischgeschwülste der Leber. Virchows Arch Pathol Anat 201:326
Horie A, Kotto Y, Hayashi I (1979) Ultrastructural comparison of hepatoblastoma and hepatocellular carcinoma. Cancer 44:2184–2193
Hünerwadel U (1962) Lebertumoren im Kindesalter (Neoplasms of the liver in childhood). Ann Paediatr 198:44–63
Hughes and Michels (1992) http://www.ncbi.nlm.nih.gov/pubmed/1329510
Hung W, Blizzard RM, Migeon CJ, Camacho AM, Nyhan WL (1963) Precocious puberty in a boy with hepatoma and circulating gonadotropin. J Pediatr 63:895–903
Icher-De BC, Leclerc J, Raimondo G et al (2003) Hepatic focal nodular hyperplasia in children previously treated for a solid tumor : incidence, risk factors and outcome. Cancer 97:3107–3113
Idzumi G (1912/1913) Ueber einen Fall von primärem Lebercarzinom im Säuglingsalter. Arch Klin Chir 100:1181–1187
Ikeda K, Kimura N, Suita S, Hayashida Y, Nakagawara A, Kawaoi A (1981) Pre and postoperative changes of alpha-fetoprotein and human chorionic gonadotropin in hepatoma of children. Z Kinderchir 34:42–55
Ingram JD, Yerushalmi B, Connell J, Karrer FM, Tyson RW, Sokol RJ (2000) Hepatoblastoma in a neonate: a hypervascular presentation mimicking hemangioendothelioma. Pediatr Radiol 30:794–797
Isaacs H (2007) Fetal and neonatal hepatic tumors. J Pediatr Surg 42:1797–1803
Ishak KG (1976) Primary hepatic tumors in childhood. Prog Liver Dis 5:636–667
Ishak KG, Glunz PR (1967) Hepatoblastoma and hepatocarcinoma in infancy and childhood. Report of 47 cases. Cancer 20:396–422

Ito J, Johnson WW (1969) Hepatoblastoma and hepatoma in infancy and childhood. Light and electron microscopic studies. Arch Pathol 87:259

Iwafuchi M, Muto T, Ohsawa Y, Yamashita Y, Matsuda Y, Yoshida K (1981) Hepatoma in children – a clinical analysis on 15 cases. Jpn J Surg 11:454–459

Iyer VK, Kaila K, Agarwala S, Verma K (2005) Fine needle aspiration cytology of hepatoblastoma. Recognition of subtypes on cytomorphology. Acta Cytol 49:355–364

Joshi VV, Kaur P, Ryan B, Saad S, Walters TR (1984) Mucoid anaplastic hepatoblastoma. A case report. Cancer 54:2035–2039

Kaatsch P (2002) Annual report 2002 (1980–2001) of the German Childhood Cancer Registry, Mainz. www.kinderkrebsregister.de

Kasai M, Watanabe I (1970) Histologic classification of liver-cell carcinoma in infancy and childhood and its clinical evaluation. A study of 70 cases collected in Japan. Cancer 25:551

Kattan K, Langer L, Sufrun H (1959) Calcified foci in primary hepatic carcinoma in infancy. Israel Med J 18:296–298

Kazzi NJ, Chang CH, Roberts EC, Shankaran S (1989) Fetal hepatoblastoma presenting as nonimmune hydrops. Am J Perinatol 6:278–280

Ke et al. (2005) http://www.ncbi.nlm.nih.gov/pubmed/16273660

Keeling JW (1971) Liver tumours in infancy and childhood. J Pathol 103:69–85

Kempf J, Korn R (1956) Le cancer primitif du foie chez l'enfant. Ann Anat Path 1:514–547

Kim L, Park YN, Kim SE, Noh TW, Park C (2001) Teratoid hepatoblastoma: multidirectional differentiation of stem cell of the liver. Yonsei Med J 42:431–435

Koh KN, Park M, Kim BE, Bae KW, Kim KM, Im HJ, Seo JJ (2011) Prognostic implications of serum alpha-fetoprotein response during treatment of hepatoblastoma. Pediatr Blood Cancer 57:554–560

Komura E, Matsumura T, Kato T, Tahara T, Tsunoda Y, Swada T (1998) Thrombopoietin in patients with hepatoblastoma. Stem Cells 16:329–333

Kubota M, Yagi M, Kanada S, Yamazaki S, Tanaka S, Asami K, Ogawa A, Watanabe A et al (2004) Effect of postoperative chemotherapy on the serum alpha-fetoprotein level in hepatoblastoma. J Pediatr Surg 39:1775–1778

Lack EE, Neave C, Vawter GF (1982) Hepatoblastoma. A clinical and pathologic study of 54 cases. Am J Surg Pathol 6:693–705

Lackner H, Urban C, Sauer H, Lammer J, Pakisch B, Kaulfersch W, Gamillscheg A et al (1990) Primary and secondary inoperable teratoid hepatoblastoma – multidisciplinary management (in German). Pädiatr Pädolo 25:299–312

Lai M, Burjonrappa S (2012) Perinatal hemorrhage complicating neonatal hepatoblastoma: case report. J Pediatr Surg 47:e29–e32

Langrehr JM, Pfitzmann R, Hermann M et al (2006) Hepatocellular carcinoma in association with hepatic focal nodular hyperplasia. Acta Radiol 47:340–344

Leffers I (1940/1941) Über eine seltene, maligne Mischgeschwulst der Leber bei einem 16 Monate alten Knaben. Beitr Path Anat Allg Path 105:203–218

Li et al. (2012) http://www.ncbi.nlm.nih.gov/pubmed/22098159

Linabery and Ross (2008) http://www.ncbi.nlm.nih.gov/pubmed/18074355

Linely AM, Ross JA (2008) Trends in childhood cancer incidence in the U.S. (1992–2004). Cancer 112:416–432

Litten JB, Tomlinson GE (2008) Liver tumors in children. Oncologist 13:812–820

Lopez-Terrada D, Finegold MJ (2007) Tumors of the liver. In: Suchy FJ, Sokol RJ, Balistreri WF (eds) Liver disease in children, 3rd edn. Cambridge University Press, Cambridge, pp 943–974

Lopez-Terrada D, Zimmermann A (2012) Current issues and controversies in the classification of pediatric hepatocellular tumors. Pediatr Blood Cancer 59:780–784

Lopez-Terrada D, Alaggio R, De Davila MT, Czauderna P, Hiyama E, Katzenstein H et al (2014) Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium. Mod Pathol 27:472–491

Lowichik A, Zhou H, Pysher TJ, Smith L, Lemons R, Coffin CM (2000) Therapy associated changes in childhood tumors. Adv Anat Pathol 7:341–359

Lu M, Greer ML (2007) Hypervascular multifocal hepatoblastoma: dynamic gadolinium-enhanced MRI findings indistinguishable from infantile hemangioendothelioma. Pediatr Radiol 37:587–591

Machado et al. (2010) http://www.ncbi.nlm.nih.gov/pubmed/19770707

MacNab GH, Moncrieff SA, Bodian M (1952) Primary malignant hepatic tumors in childhood. In: British Empire Cancer Campaign 30th annual report 1952, pp 168–174

MacRae FW (1935) Unusual tumor (malignant adenoma) of liver in a baby. Am J Surg 28:575

Malogolowkin MH, Katzenstein HM, Meyers RL, Krailo MD, Rowland JM, Haas J, Finegold MJ (2011) Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: a report from the Children's Oncology Group. J Clin Oncol 29:3301–3306

Manivel C, Wick MR, Abenoza P, Dehner LP (1986) Teratoid hepatoblastoma: the nosologic dilemma of solid embryonic neoplasms of childhood. Cancer 57:2166–2174

Mann JR, Kasthuri N, Raafat F, Pincott JR, Parkes SE, Muir KR, Ingram LC, Cameron AH (1990) Malignant hepatic tumours in children: incidence, clinical features and aetiology. Paediatr Perinat Epidemiol 4:276–289

Martin MA, Bhatia M (2005) Analysis of the human fetal liver hematopoietic microenvironment. Stem Cells Dev 14:493–504

McArthur JW, Toll GD, Russfield AB, Reiss AM, Quinby WC, Baker WH (1973) Sexual precocity attributable to ectopic gonadotropin secretion by hepatoblastoma. Am J Med 54:390–403

McCarville MB, Roebuck DJ (2012) Diagnosis and staging of hepatoblastoma: imaging aspects. Pediatr Blood Cancer 59:793–799

McRae FW (1935) Unusual tumor (malignant adenoma) of liver in a baby. Am J Surg 28:575–581

Meyers RL (2007) Tumors of the liver in children. Surg Oncol 16:195–203

Meyers AB, Towbin AJ, Geller JI, Podberesky DJ (2012) Hepatoblastoma imaging with gadoxetate disodium-enhanced MRI-typical, atypical, pre-and post-treatment evaluation. Pediatr Radiol 42:859–866

Milman DH, Grayzel DM (1951) Mixed tumor of the liver; report of case with review of literature. Am J Dis Child 81:408–420

Misick OS (1898) A case of teratoma hepatis. J Pathol Bacteriol 5:128–136

Misugi K, Reiner CB (1965) A malignant true teratoma of liver in childhood. Arch Path 80:409–412

Misugi K, Okajima H, Misugi N, Newton WA (1967) Classification of primary malignant tumors of liver in infancy and childhood. Cancer 20:1760

Moore SW, Davidson A, Hadley GP, Kruger M, Poole J, Stones D, Wainwright L, Wessels G (2008) Malignant liver tumors in South African children: a national audit. World J Surg 32:1389–1395

Morinaga S, Yamaguchi M, Watanabe I, Kasai M, Ojima M, Sasano N (1983) An immunohistochemical study of hepatoblastoma producing human chorionic gonadotropin. Cancer 51:1647–1652

Moritake H, Taketomi A, Kamimura S, Ikuno Y, Seo Y, Fukuda T, Iguchi H, Okamura J (2000) Renin-producing hepatoblastoma. J Pediatr Hematol Oncol 22:78–80

Nakagawara A, Ikeda K, Hayashida Y, Tsuneyoshi M, Enjoji M, Kawaoi A (1982) Immunocytochemical identification of human chorionic gonadotropin- and alpha-fetoprotein-producing cells of hepatoblastoma associated with precocious puberty. Virchows Arch (Pathol Anat) 398:45–51

Nakagawara A, Ikeda K, Tsuneyoshi M, Daimaru Y, Enjoji M, Watanabe I, Iwafuchi M, Sawada T (1985) Hepatoblastoma producing both alpha-fetoprotein and human chorionic gonadotropin. Clinicopathologic analysis of four cases and a review of the literature. Cancer 56:1636–1642

Nakamura H (1910) Ueber einen Fall von primärem Leberkarzinom beim Säugling. GANN Ergebn Krebsf Jpn 5:210

Neimann N, Rauber G, Manciaux M, Prevot J, Duprez A (1963) Les tumeurs malignes du foie chez l'enfant. Rev Int Hepatol 13:81–129

Nickerson HJ, Silberman TL, McDonald TP (1980) Hepatoblastoma, thrombocytosis, and increased thrombopoietin. Cancer 45:315–317

Nikaidoh H, Boggs J, Swenson O (1970) Liver tumors in infants and children. Clinical and pathological analysis of 22 cases. Arch Surg 101:245–257

Nissel W (1928) Die Mischgeschwülste der Leber mit besonderer Berücksichtigung eines Falles von geplatzter Mischgeschwulst der Leber bei einem Neugeborenen. Virchows Arch Pathol Anat 279:446

Nitta A, Hisamatsu S, Fukuda H, Kurosawa H, Arisaka O (2012) Cardiopulmonary arrest on arrival in an infant due to ruptured hepatoblastoma. J Pediatr 160:351

Noeggerath E (1854) Geburtshindernis in Folge eines Lebercarcinoms beim Neugeborenen. Deut Klein 6:496

Norgaard-Pedersen B, Dabelsteen E, Edeling CJ (1974) Localisation of human alpha-foetoprotein synthesis in hepatoblastoma cells by immunofluorescence and immunoperoxidase methods. Acta Pathol Microbiol Scand A 82:169–174

O'Brien WJ, Finlay JL, Gilbert-Barness EF (1989) Patterns of antigen expression in hepatoblastoma and hepatocellular carcinoma in childhood. Pediatr Hematol Oncol 6:361–365

Ortega et al. (2000) http://www.ncbi.nlm.nih.gov/pubmed/10894865

Oshima Y, Kawaguchi S, Nagoya S, Wada T, Kokai Y, Ikeda T, Nogami S, Oya T et al (2004) Abdominal small round cell tumor with osteoid and EWS/FLI1. Hum Pathol 35:773–775

Pack GT, Miller TR (1956) Total right hepatic lobectomy for rhabdomyo-sarcoma. AMA Arch Surg 73:1060–1062

Pang SC (1961) Bony and cartilaginous hepatoblastoma. J Pathol Bacteriol 82:273–280

Parikh B, Jojo A, Shah B, Bansal R, Trivedi P, Shah MJ (2005) Fine needle aspiration cytology of hepatoblastoma: a study of 20 cases. Indian J Pathol Microbiol 48:331–336

Pei Y, Kano J, Ijima T, Morishita Y, Inodome Y, Noguchi M (2009) Overexpression of Dickkopf 3 in hepatoblastomas and hepatocellular carcinomas. Virchows Arch 454:639–646

Perilongo G, Plaschkes J, Zimmermann A (2002) Hepatic tumours. In: Shouhami RL et al (eds) Oxford textbook of oncology, 2nd edn. Oxford University Press, Oxford

Perilongo G, Malogolowkin M, Feusner J (2012) Hepatoblastoma clinical research: lessons learned and future challenges. Pediatr Blood Cancer 59:818–821

Philipose TR, Naik R, Rai S (2006) Cytologic diagnosis of small cell anaplastic hepatoblastoma: a case report. Acta Cytol 50:205–207

Philipp PW (1907) Ueber Krebsbildungen im Kindesalter. Ztschr Krebsforsch 5:361

Philipp PW (1908) Zwei interessante Fälle von bösartigen Neubildungen bei kleinen Kindern. Jahrb Kinderheilkunde Physische Erzieh 68:353–365

Polydorides AD, Perry A, Edgar MA (2008) Large cell medulloblastoma with myogenic and melanotic differentiation: a case report with molecular analysis. J Neuro Oncol 88:193–197

Pontisso P, Barzon M, Basso G, Cecchetto G, Perilongo G, Alberti A (1993) Cytokeratins patterns in childhood primary liver tumors. Int J Clin Lab Res 23:225–227

Pritchard J, da Cunha A, Combleet MA, Carter CJ (1982) Alpha feta (alpha FP) monitoring of response to Adriamycin in hepatoblastoma. J Pediatr Surg 17:429–430

Pryce J, Kiho L, Scheimberg I (2010) Sudden unexpected death in infancy associated with an epithelial-type hepatoblastoma in a 6-month-old infant. Pediatr Dev Pathol 13:338–340

Rabah R (2012) Teratoid hepatoblastoma with abundant neuroendocrine and squamous differentiation with extensive parenchymal metastasis. Arch Pathol Lab Med 136:911–914

Rabl W, Müller OA, Welsch U, Kruse K, Dörr H, Homoki J (1988) Ectopic ACTH syndrome, and 'tumor hypercalcemia' due to a hepatoblastoma (abstract). Pediatr Res 23:137

Ramsay AD, Bates AW, Williams S, Sebire NJ (2008) Variable antigen expression in hepatoblastomas. Appl Immunohistochem Mol Morphol 16:140–147

Raymond AK, Chawla SP, Carrasco CH, Ayala AG, Fanning CV, Grice B, Armen T et al (1987) Osteosarcoma chemotherapy effects: a prognostic factor. Semin Diagn Pathol 4:212–236

Reynolds M (2001) Current status of liver tumors in children. Semin Pediatr Surg 10:140–145

Roebuck DJ, Perilongo G (2006) Hepatoblastoma: an oncological review. Pediatr Radiol 36:183–186

Root AW, Bongiovanni AM, Eberlein WR (1968) A testicular-interstitial-cell-stimulating gonadotropin in a child with hepatoblastoma and sexual precocity. J Clin Endocrinol 28:1317–1322

Rosa F, Grases PJ (1980) Ultrastructural studies in a case of hepato-blastoma. Hum Pathol 11:70–72

Ross JA, Gurney JG (1998) Hepatoblastoma incidence in the United States from 1973 to 1992. Med Pediatr Oncol 30:141–142

Roth F (1938) Zur Kenntnis und Auffassung der Lebermischgeschwülste und des halbseitigen Riesenwuchses. Frankfurt Z Pathol 52:163–196

Rowland JM (2002) Hepatoblastoma: assessment of criteria for histologic classification. Med Pediatr Oncol 39:478–483

Ruck P, Kaiserling E (1992) Extracellular matrix in hepatoblastoma: an immunohistochemical investigation. Histopathology 21:115–126

Ruck P, Kaiserling E (1993) Melanin-containing hepatoblastoma with endocrine differentiation. An immunohistochemical and ultrastructural study. Cancer 72:361–368

Ruck P, Harms D, Kaiserling E (1990) Neuroendocrine differentiation in hepatoblastoma. An immunohistochemical investigation. Am J Surg Pathol 14:847–855

Ruck P, Xiao JC, Kaiserling E (1996) Small epithelial cells and the histogenesis of hepatoblastoma. Electron microscopic, immunoelectron microscopic, and immunohistochemical findings. Am J Pathol 148:321–329

Rugge M, Sonego F, Pollice L, Perilongo G, Guido M, Basso G, Ninfo V, Pennelli N, Gambini C, Guglielmi M et al (1998) Hepatoblastoma: DNA nuclear content, proliferative indices, and pathology. Liver 18:128–133

Russo P, Biegel JA (2009) SMARCB1/INI1 alterations and hepatoblastoma: another extrarenal rhabdoid tumor revealed ? Pediatr Blood Cancer 52:312–313

Saettini F, Conter V, Da Dalt L, Perilongo G, Hasegawa D, Giraldi E, Cavalleri L, Foglia C et al (2013) Ruptured hepatoblastoma: a case report and literature review. J Solids Tumor 3:46–50

Sallem et al. (2005) http://www.ncbi.nlm.nih.gov/pubmed/16283600

Sato M, Ishida H, Konno K, Naganuma H, Hamashima Y, Komatsuda T, Ishida J, Watanabe S (2000) Liver tumors in children and young patients: sonographic and color Doppler findings. Abdom Imaging 25:596–601

Sattler B, Gunawan B, Lorf T, Müller D, Ringe B, Füzesi I (2000) Undifferentiated small cell hepatoblastoma (in German). Pathologe 21:456–459

Saxena R, Leake JL, Shafford EA, Davenport M, Mowat AP, Pritchard J, Mieli-Vergani G et al (1993) Chemotherapy effects on hepatoblastoma. A histological study. Am J Surg Pathol 17:1266–1271

Schiodt T (1970) Hepatoblastoma and hepatocarcinoma in infancy and childhood: report on the pathology of eight cases from the University Hospital Copenhagen. Acta Pathol Microbiol Scand 212:181–192

Schlachter K, Gyugos M, Halasz J, Lendvai G, Baghy K, Garami M, Gyöngyösi B, Schaff Z et al (2014) High tricellulin expression is associated with better survival in human hepatoblastoma. Histopathology 65:631–641

Schmidt D, Harms D, Lang W (1985) Primary malignant hepatic tumours in childhood. Virchows Arch (Patrol Anat) 407:387–405

Schmidt A, Braeuning A, Ruck P, Seitz G, Armeanu-Ebinger S, Fuchs J, Warmann SW et al (2011) Differential expression of glutamine synthetase and cytochrome P450 isoforms in human hepatoblastoma. Toxicology 281:7–14

Schnater JM, Kohler SE, Lamers WH, von Schweinitz D, Aronson DC (2003) Where do we stand with hepatoblastoma ? A review. Cancer 98:668–678

Shabanov MA (1981) Histological and ultrastructural characteristics of primary malignant liver tumors in children (in Russian). Arkh Patol 43:45–51

Shabanov MA (1983) Ultrastructure of osteoid islets in mixed-type hepatoblastoma (in Russian). Arkh Patol 45:81–88

Shabanov MA, Pokrovskaia NN, Iasonov AV (1981) Congenital hepatoblastoma with a rhabdomyoblastic component (in Russian). Arkh Patol 43:73–77

Shafford EA, Pritchard J (1993) Extreme thrombocytosis as a diagnostic clue to hepatoblastoma. Arch Dis Child 69:171

Sheehan HL (1930) Embryonic tumour of liver containing striated muscle. J Pathol Bacteriol 33:251–258
Shih JC, Tsao PN, Huang SF, Yen BL, Lin JH, Lee CN, Hsieh FJ (2000a) Congenital hepatoblastoma. Ultrasound Obstet Gynecol 16:103
Shih JC, Tsao PN, Huang SF, Yen BL, Lin JH, Lee CN, Hsieh FJ (2000b) Antenatal diagnosis of congenital hepatoblastoma. Ultrasound Obstet Gynecol 16:94–97
Silverman JF, Fu YS, McWilliams NB, Kay S (1975) An ultrastructural study of mixed hepatoblastoma with osteoid elements. Cancer 36:1436–1443
Sinniah et al. (1974) http://www.ncbi.nlm.nih.gov/pubmed/4369060
Sola PJ, Perez-Guillermo M, Bas Bernal AB, Mercader JM (1994) Hepatoblastoma. An attempt to apply histologic classification to aspirates obtained by fine needle aspiration cytology. Acta Cytol 38:175–182
Spector LG, Birch J (2012) The epidemiology of hepatoblastoma. Pediatr Blood Cancer 59:776–779
Stein F (1952) Blutbildung in einem primären leberkrebs und in seinen Metastasen beim Säugling. Virchows Arch 322:145–158
Steiner MM (1938) Primary carcinoma of the liver in childhood. Report of two cases with a critical review of the literature. Am J Dis Child 55:807
Stiller D, Holzhausen HJ (1983) Congenital hepatoblastoma of mixed type. Light and electron microscopy studies (in German). Zbl Allg Pathol 128:317–326
Stiller et al. (2006) http://www.ncbi.nlm.nih.gov/pubmed/16919775
Stocker JT (1994) Hepatoblastoma. Semin Diagn Pathol 11:136–143
Stocker JT (2001) Hepatic tumors in children. Clin Liver Dis 5:259–281
Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, Rupairmoole R et al (2012) Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med 366:610–618
Stranz H (1913) Ueber Mischgeschwülste der Leber. Thesis, Breslau
Tavasoli A, Mehrazma M, Hooman N, Afshar KL (2013) Severe hypertension and encephalopathy due to renin-producing hepatoblastoma. Iran J Cancer Prev 6:227–230
Tiggelman AM, Boers W, Linthorst C, Brand HS, Sala M, Chamuleau RA (1995) Interleukin-6 production by human liver (myo)fibroblasts in culture. Evidence for a regulatory role of LPS, IL-1 beta and TNF alpha. J Hepatol 23:295–306
Tomte LT, Annatshah Y, Schluter NK, Miosge N, Herken R, Quondamatteo F (2006) Hematopoietic cells are a source of nidogen-1 and nidogen-2 during mouse liver development. J Histochem Cytochem 54:593–604
Toretsky JA, Zitomersky NL, Eskenazi AE, Voigt RW, Strauch ED, Sun CC, Huber R et al (2001) Glypican-3 expression in Wilms tumor and hepatoblastoma. J Pediatr Hematol Oncol 23:496–499
Tornoczky T, Kalman E, Kajtar PG, Nyari T, Pearson AD, Tweddle DA, Board J, Shimada H (2004) Large cell neuroblastoma: a distinct phenotype of neuroblastoma with aggressive clinical behavior. Cancer 100:390–397
Trobaugh-Lotrario AD, Tomlinson GE, Finegold MJ, Gore L, Feusner JH (2009) Small cell undifferentiated variant of hepatoblastoma: adverse clinical and molecular features similar to rhabdoid tumors. Pediatr Blood Cancer 52:328–334
Tsuchida Y, Ikeda H, Suzuki N, Takahashi A, Kuroiwa M, Sakai M, Shimizu H, Shitara T et al (1999) A case of well-differentiated, fetal-type hepatoblastoma with very low serum alpha-fetoprotein. J Pediatr Surg 34:1762–1764
Uehara S, Oue T, Kawatsu M, Nara K, Fukuzawa M (2013) Increased expression of surviving in hepatoblastoma after chemotherapy. Eur J Pediatr Surg 23:400–404
Us-Krasovec M, Pohar-Marinsek Z, Golouh R, Jereb B, Ferlan-Marolt V, Cerar A (1996) Hepatoblastoma in fine needle aspirates. Acta Cytol 40:450–456
Van Eyken P, Sciot R, Callea F, Ramaekers F, Schaart G, Desmet VJ (1990) A cytokeratin-immunohistochemical study of hepatoblastoma. Hum Pathol 21:302–308
Van Rossum AP, Vlasveld LT, Vlasveld IN, Jansen PM, Dik WA, Hooijkaas H, Castel A (2009) Granulocytosis and thrombocytosis in renal cell carcinoma: a pro-inflammatory cytokine response originating in the tumor. Neth J Med 67:191–194
Van Tonrout JM, Buckley JD, Quin JJ, Feusner JH, Krailo MD, King DR, Hammond GD, Ortega JA (1997) Timing and magnitude of decline in alpha-fetoprotein levels in treated children with unresectable or metastatic hepatoblastoma are predictors of outcome: a report from the Children's Cancer Group. J Clin Oncol 15:1190–1197
Veeramachaneni R, Herrera GA, Turbat-Herrera EA (2003) Hepatoblastoma in a 15-month-old male: cytomorphology, electron microscopy, and differential diagnosis. Ultrastruct Pathol 27:369–373
Von Schweinitz D (2012) Hepatoblastoma: recent developments in research and treatment. Semin Pediatr Surg 21:21–30
Von Schweinitz D, Hadam MR, Welte K, Mildenberger H, Pietsch T (1993) Production of interleukin-1 beta and interleukin-6 in hepatoblastoma. Int J Cancer 53:728–734
Von Schweinitz D, Schmidt D, Fuchs J, Welte K, Pietsch T (1995) Extramedullary hematopoiesis and intratumoral production of cytokines in childhood hepatoblastoma. Pediatr Res 38:555–563
Von Schweinitz et al. (1996) http://www.ncbi.nlm.nih.gov/pubmed/8972759
Wagner LM, Garrett JK, Ballard ET, Hill DA, Perry A, Biegel JA, Collins MH (2007) Malignant rhabdoid tumor mimicking hepatoblastoma: a case report and literature review. Pediatr Dev Pathol 10:409–415
Wang JD, Chang TK, Chen HC, Jan SL, Huang FL, Chi CS, Lin CC (2007) Pediatric liver tumors: initial

presentation, image finding and outcome. Pediatr Int 49:491–496
Wang LL, Filippi RZ, Zurakowski D, Archibald T, Vargas SO, Voss SD, Shamberger RC et al (2010) Effects of neoadjuvant chemotherapy on hepatoblastoma: a morphologic and immunohistochemical study. Am J Surg Pathol 34:287–299
Watanabe H, Kobayashi T (1961) Embryonal hepatoma in Japan : pathological study on 19 cases of hepatic carcinoma in infancy and childhood. Keio J Med 10:181–193
Watanabe I, Kasai M, Watanuki T, Amano S (1975) Malignant mixed tumor of the liver: report of a case and a review of the literature. Acta Hepatogastroenterol (Stugg) 22:158–164
Watanabe I, Yamaguchi M, Kasai M (1987) Histologic characteristics of gonadotropin-producing hepatoblastoma: a survey of seven cases from Japan. J Pediatr Surg 22:406–411
Webster R (1938) Malignant (teratoid) hepatoma in infancy. Med J Aust 2:381–383
Weinberg AG, Finegold MJ (1983) Primary hepatic tumors of childhood. Hum Pathol 14:512–537
Weinberg AG, Finegold MJ (1986) Primary hepatic tumors in childhood. In: Finegold M (ed) Pathology of neoplasia inc children and adolescents, vol 18, Major problems in Pathology. W.B. Saunders Company, Philadelphia
Weir EG, Ali SZ (2002) Hepatoblastoma: cytomorphologic characteristics in serous cavity fluids. Cancer 96:267–274
Williams AW (1953) Liver tumour of mixed type. Br J Surg 41:13–15
Williams RA, Ferrell LD (1993) Pediatric liver tumors. Pathology (Phila) 2:23–42
Willis RA (1962) The pathology of the tumours in children. Oliver & Boyd, Edinburgh/London, p 57
Wohlgemuth B (1960) Maligne Mischtumoren der kindlichen Leber. Zf Kinderheilkd 84:39–50
Worth et al. (1999) http://www.ncbi.nlm.nih.gov/pubmed/10573588
Wuester WO, Knauer WH (1961) Complete right hepatic lobectomy for rare teratoid liver cancer in infancy. Cancer 14:361–368
Yamagiwa K (1911) Zur Kenntnis des primären parenchymatösen Leberkarzinoms. Virchows Arch Pathol Anat 206:437–467
Yamaguchi H, Ishii E, Hayashida Y, Hirata Y, Sakai R, Miyazaki S (1996) Mechanism of thrombocytosis in hepatoblastoma: a case report. Pediatr Hematol Oncol 13:539–544
Yamazaki M, Ryu M, Okazumi S, Kondo F, Cho A, Okada T, Takayama W, Kawashima T et al (2004) Hepatoblastoma in an adult. A case report and clinical review of literatures. Hepatol Res 30:182–188
Yun WJ, Shin E, Lee K, Jung HY, Kim SH, Park YN, Yu E, Jang JJ (2013) Clinicopathologic implication of hepatic progenitor cell marker expression in hepatoblastoma. Pathol Res Pract 209:568–573
Zhang SH, Cong WM, Wu MC (2004) Focal nodular hyperplasia with concomitant hepatocellular carcinoma: a case report and clonal analysis. J Clin Pathol 57:556–559
Zhang H, Miao Z, He Z, Yang Y, Wang Y, Feng M (2005) The existence of epithelial-to-mesenchymal cells with the ability to support hematopoiesis in human fetal liver. Cell Biol Int 29:213–219
Zhang et al. (2007) http://www.ncbi.nlm.nih.gov/pubmed/17676493
Zheng MH, Zhang L, Gu DN, Shi HQ, Zeng QQ, Chen YP (2009) Hepatoblastoma in adult: review of the literature. J Clin Med Res 1:13–16
Zimmermann A (2002) Hepatoblastoma with cholangioblastic features ('cholangioblastic hepatoblastoma') and other liver tumors with bimodal differentiation in young patients. Med Pediatr Oncol 39:487–491
Zimmermann A (2003) Pathways to blastomas. Ann Diagn Paediatr Pathol 7:9–19
Zimmermann A (2005) The emerging family of hepatoblastoma tumours: from ontogenesis to oncogenesis. Eur J Cancer 41:1503–1514
Zimmermann A and Saxena R (2010) Hepatoblastoma. In: WHO classification of Tumors of the Digestive system. Bosman FT et al, eds. IARC, Lyan, pp 228–235
Zimmermann A (2011) Liver tumors of childhood. In: Saxena R (ed) Practical hepatic pathology. A diagnostic approach. Elsevier Saunders, Philadelphia, pp 521–546
Zimmermann A, Lopez-Terrada D (2011) Pathology of pediatric tumors. In: Zimmermann A, Perilongo G, Malogolowkin M, Von Schweinitz D (eds) Pediatric liver tumors. Springer Publisher, Berlin, pp 83–112
Zimmermann A, Saxena R (2010) Hepatoblastoma. In: Bosman FT et al (eds) WHO classification of tumours of the digestive system, vol 4. IARC, Lyon, pp 228–235
Zynger DL, Gupta A, Luan C, Chou PM, Yang GY, Yang XJ (2008) Expression of glypican 3 in hepatoblastoma: an immunohistochemical study of 65 cases. Hum Pathol 39:224–230

Variants of the Hepatoblastoma Tumor Family

20

Contents

Abstract

A small subset of neoplasms of the hepatoblastoma tumor family is characterized by a morphology that resembles hepatocellular carcinoma (HCC) or holds a position intermediate between classical hepatoblastomas (HB) and HCC. Such tumors currently include anaplastic HB variants, HB with HCC-like features, and so-called transitional liver cell tumors.

Rare variants of HB exhibit ductule-like structures and are termed cholangioblastic hepatoblastomas. A related tumor that consists of immature hepatocyte nests surrounded by cholangiocyte structures resembling the embryonal ductal plate makes part of so-called ductal plate tumors.

HB and similar mixed tumors occur in adult patients. However, it is not yet certain whether all tumors described as "adult HB" are in fact true HB. Molecular studies will probably clarify this question.

Hepatoblastomas with "HCC-Like Features" and "Transitional Cell Tumors"

There is a complex group of rare hepatoblastoma-like tumors that contain, apart from HB cells (mostly of the fetal type), cells that are HCC-like or seem to hold a position intermediate between HB and HCC. HB with such pleomorphic features

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_20

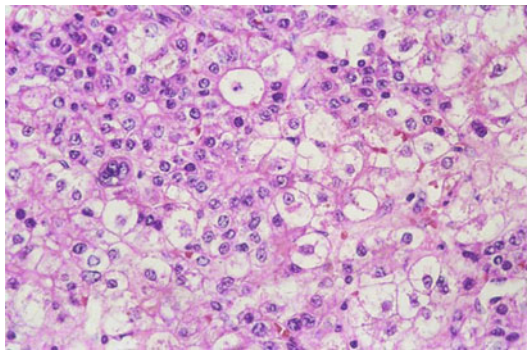

Fig. 1 HCC-like hepatoblastoma. Apart from clear cells resembling fetal-type cells, there are cells resembling hepatocellular carcinoma cells and polymorphous cells (hematoxylin and eosin stain)

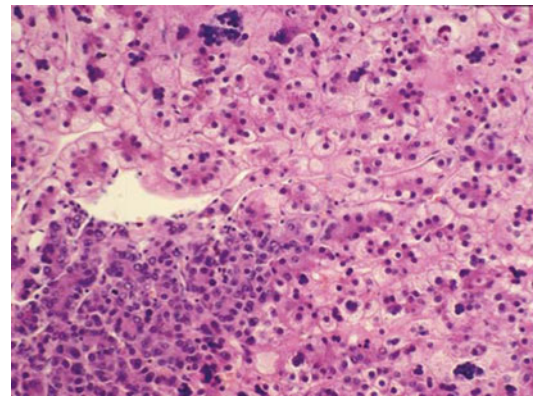

Fig. 2 HCC-like hepatoblastoma. Fetal-type cells (*right* and *upper* part of figure) are associated with less differentiated and highly atypical cells (*left lower corner*; hematoxylin and eosin stain)

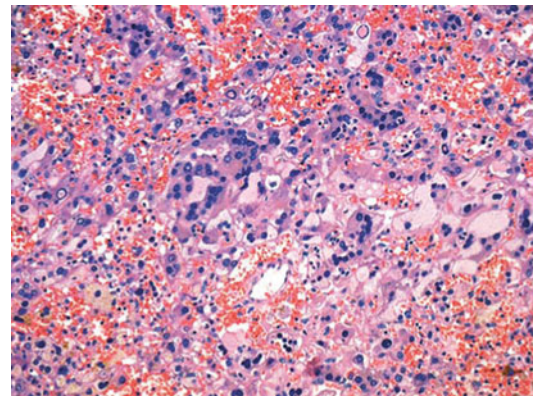

Fig. 3 HCC-like hepatoblastoma. This tumor exhibits pleomorphic cells and multinucleated giant cells (hematoxylin and eosin stain)

have been termed "HCC-like tumors" or "anaplastic tumors," but these terms seem to be obsolete, anaplasia having a different definition. Aggressive HB with HCC features or a HCC-like progeny exhibit a distinct genomic landscape characterized by CTNNB1 mutations, NFE2L2-KEAP1 pathway activation, loss of genomic stability, and TERT promoter mutations (Eichenmüller et al. 2014). Part of the tumors with HCC-like features has been observed in older children and adolescents. These lesions with a complex histology are characterized by an aggressive biology, very high serum AFP levels, and abnormal beta-catenin expression patterns and were termed "transitional liver cell tumors/TLCT" as a working formulation (Prokurat et al. 2002). This entire tumor group requires further definition and standardization (Figs. 1, 2, 3, 4, 5, and 6).

Bimodal Pediatric Liver Tumors: Cholangioblastic Hepatoblastoma (Hepatoblastoma with Cholangioblastic Features) and So-Called Ductal Plate Tumors

Cholangioblastic Hepatoblastoma

In a minority of hepatoblastoma family tumors, differentiation of neoplastic cells appears to develop along two lineages, i.e., hepatoblasts/hepatocytes and cholangiocytes, suggesting the involvement of an early bipotential progenitor cell not yet committed to either hepatocytes of cholangiocytes. In a case of mixed epithelial and mesenchymal hepatoblastoma, irregular gland-like spaces around which the cells assumed a columnar form, giving the appearance of immature bile ducts, were found in conjunction with fetal-type and embryonal cells (Allison and Willis 1956). This was probably the first description of the histologic features of cholangioblastic hepatoblastoma, a tumor characterized by the presence of immature, CK19-positive bile duct-like profiles in close association with hepatoblast islands either of the fetal or embryonal type (Zimmermann 2002, 2005; Figs. 7, 8, 9, and 10).

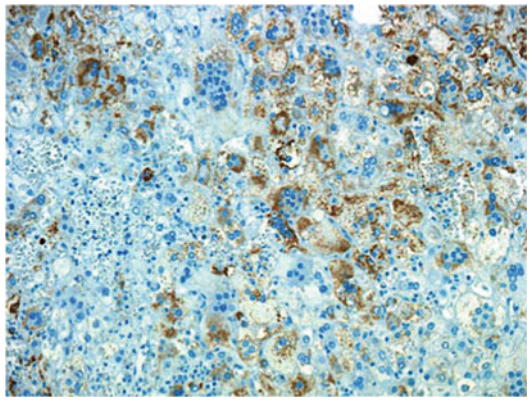

Fig. 4 HCC-like hepatoblastoma. The neoplasm shows focal reactivity for alpha-fetoprotein (AFP) in an irregular pattern (AFP immunostain)

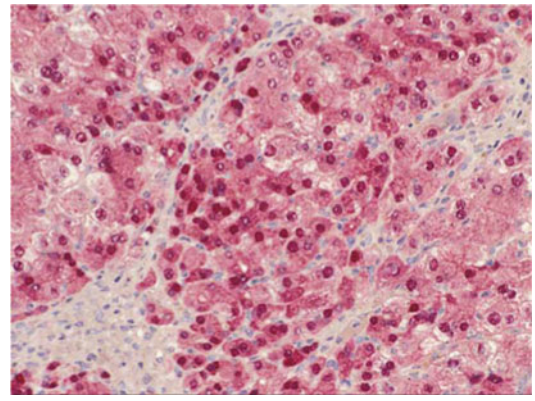

Fig. 6 HCC-like hepatoblastoma. Neoplastic cells display cytoplasmic and nuclear reactivity for beta-catenin (beta-catenin immunostain)

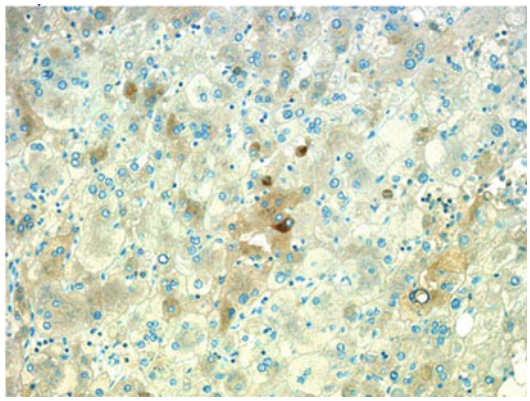

Fig. 5 HCC-like hepatoblastoma. Few tumor cells are reactive for glypican 3 (glypican 3 immunostain)

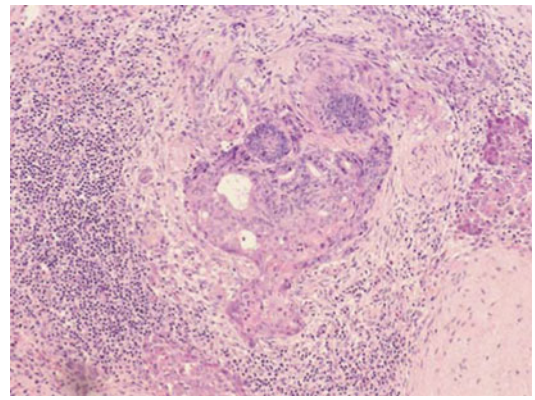

Fig. 7 Cholangioblastic hepatoblastoma. A central area of hepatoblastoma tissue shows focal formation of immature cholangiocellular acinar or tubular structures (hematoxylin and eosin stain)

Diagnosis of cholangioblastic hepatoblastoma requires the absence of ductular proliferations in the vicinity of the tumor. Stages of aberrant intrahepatic bile duct development in a mixed hepatoblastoma were reported (Libbrecht et al. 2003). An abundant cholangioblastic component was detected in a teratoid hepatoblastoma (Zhou et al. 2013).

Ductal Plate Tumors

Ductal plate tumors of the hepatobiliary tract are neoplasms that express structures resembling the embryonal ductal plate, a transient structure that acts as a pacemaker for the morphogenesis of intrahepatic bile ducts (Zimmermann 2002). Such a bimodal neoplasm of the liver was first observed in a young adult and was characterized by multiple small immature cell islands expressing hepatocyte lineage markers (so-called liverlets), consisting of small hepatoid cells arranged as a solid growth, surrounded by a CK19-positive double layer of cholangiocytes forming a rim in direct contact with the central hepatoid cell cluster. This double layer closely resembled the embryonal ductal plate (Gornicka et al. 2001; Figs. 11 and 12). Intrahepatic cholangiocarcinoma can also present with a

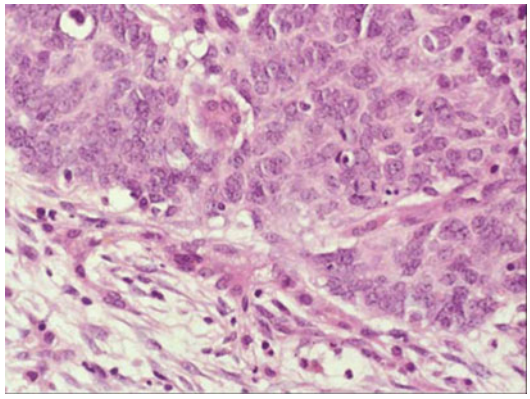

Fig. 8 Cholangioblastic hepatoblastoma. Embryonal-type cholangioblastoma is associated with few cholangiocellular nests forming abortive ductular structures (hematoxylin and eosin stain)

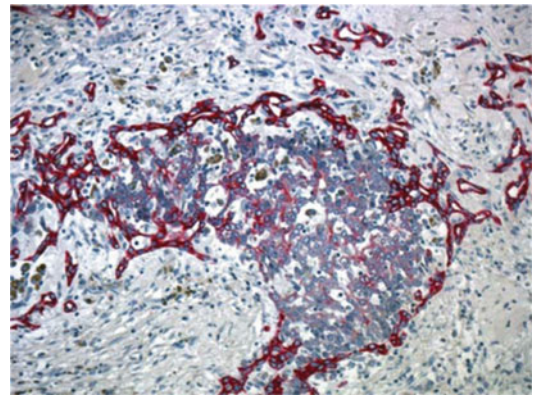

Fig. 10 Cholangioblastic hepatoblastoma. Within the tumor nodule and surrounding, there are numerous cytokeratin 19-positive elements (CK 19 immunostain)

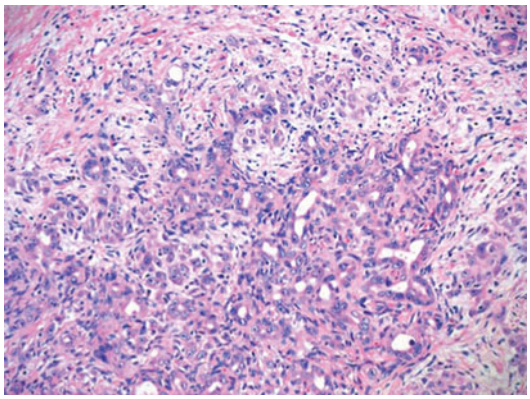

Fig. 9 Cholangioblastic hepatoblastoma. This neoplasm has produced numerous intertwining ductule-like profiles (hematoxylin and eosin stain)

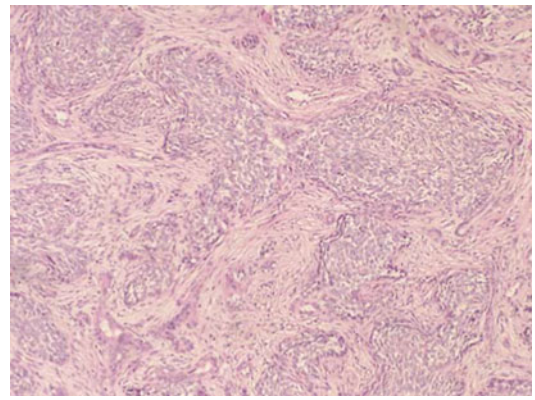

Fig. 11 Ductal plate tumor. Small nests or nodules of hepatoid cells ("liverlets") are surrounded by flattened biliary structures resembling the ductal plate (hematoxylin and eosin stain)

prominent ductal plate malformation pattern (Choe and Kim 2014).

Hepatoblastoma and Related or Similar Mixed Tumors in Adult Patients

True hepatoblastoma of the adult patient is an uncommon tumor, however, with a histology that is similar to or indistinguishable from hepatoblastoma occurring in infancy and childhood. It is not certain, whether all tumors described as "adult HB" are in fact true HB; this question is further discussed in a separate chapter.

On the other hand, the literature documents several examples of primary hepatic mixed neoplasms in adults that may more or less resemble components that we find in mixed hepatoblastomas of childhood. More than 40 cases of tumors have been reported that were either identified as hepatoblastomas of the adult or as mixed tumors that may share some features with hepatoblastoma.

Selected references: (Barnett et al. 1958; Bartok 1958a, b; Alexander 1961; Ojima et al. 1964; Kerr 1966; Blanding 1968; Carter 1969; Goldman and Friedman 1969; Ogata

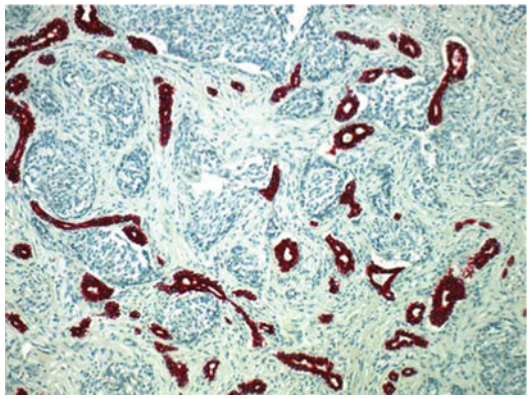

Fig. 12 Ductal plate tumor. In this cytokeratin 19 preparation, immature "liverlets" are in close contact with a double-layered biliary profile resembling the embryonal ductal plate (CK19 immunostain)

et al. 1973; Meyer et al. 1974; Ludwig et al. 1975; Baird and McGovern 1976; Jameson and Chatkadakis 1978; Yoshida et al. 1979; Honan and Haqqani 1980; Popper 1980; Barbaryka and von Bouguoy 1981; Baroni et al. 1984; Kishimoto et al. 1984; Kawarada et al. 1985; Bhatnagar et al. 1987; Misra et al. 1988; Green and Silva 1989; Hartleb et al. 1989; Seabrook et al. 1989; Sugino et al. 1989; Oda et al. 1990; Altmann 1992; Mondragon et al. 1994; Harada et al. 1995; Inoue et al. 1995; Kacker et al. 1995; Bortolasi et al. 1996; Kuniyasu et al. 1996; Ahn et al. 1997; Inagaki et al. 2001; Kasper et al. 2005; Ke et al. 2005; Beppu et al. 2006; Remes-Troche et al. 2006; Krzewinski et al. 2007; Mukhopadhyay et al. 2007; Zhang et al. 2007; Fiaschetti et al. 2010; Nakamura et al. 2010; Wang and Liu 2012; Cienfuegos et al. 2013).

Hepatoblastoma and related tumors in the adult may occur even in old age (more than 80 years; Oda et al. 1990; Ahn et al. 1997). In a literature review of 21 cases, the age range covered 19–84 years, and 14 patients were more than 40 years old at diagnosis. In this series, there were 13 males and 8 females (Ahn et al. 1997). Hepatoblastomas in adults can cause marked elevation of serum AFP (Sugino et al. 1989) and are known to sometimes grow to impressive size. In the series of 21 cases of Ahn and coworkers (1997), 8 tumors weighed 3,000 or more grams, one mass having a weight of 8,500 g. Histologies and subtypes, as far as specified in the published reports, are the same as those encountered in childhood hepatoblastoma, although the mixed epithelial and mesenchymal type seems to prevail. In the 21 case reports by Ahn et al. (1997), 19 were of the mixed type and only 2 were wholly epithelial. Also teratoid hepatoblastoma has been noted in the adult age group (Zhang et al. 2007). Very rarely, neuroendocrine differentiation was observed in HB of adolescent or adult age (Fragulidis et al. 2013; Zhang et al. 2013).

Hepatoblastoma of the adult may present with sign of acute cholangitis, with cholestatic jaundice and intermittent low-grade fever caused by involved of the bile ducts (Kacker et al. 1995). The pathogenesis of adult hepatoblastoma is unknown, and it is also not clear whether, irrespective of the histology, adult hepatoblastomas are the same or other tumors as those in childhood. In one patient, the tumor was associated with oral contraceptive administration (Meyer et al. 1974). In a hypertriploid stemline derived from a hepatoblastoma of an adult patient, multiple numerical and structural chromosomal aberrations, including +2 and +20, were found (Parada et al. 1997).

A mixed hepatic tumor in an adult and listed as hepatoblastoma in several articles on adult hepatoblastoma was published in 1951 (Milman and Grayzel 1951). But it is likely that Barnett et al. (1958) described the first case of bona fide adult hepatoblastoma, a 35-year-old male patient who was admitted owing to severe epigastric pain and a weight loss of 35 lb during the preceding 3 months. The patient underwent exploratory laparotomy and died after a few weeks. At necropsy, a foul-smelling necrotic neoplasm of the liver occupied the upper abdomen and extended to the pelvis. The liver including the yellow-white, soft, and gelatinous tumor weighed 8,500 g. The tumor displayed a central cavity caused by necrosis and obstructed the portal vein and the inferior vena cava and surrounded the gallbladder and the extrahepatic biliary ducts. Histology revealed the pattern of mixed epithelial and mesenchymal hepatoblastoma, the epithelial cell population representing a mixed fetal and embryonal

subtype. The mesenchymal component contained several elongated cells with distinct cross striation. A further case was published twice in the same year by Bartok. In the old reports, terms other than hepatoblastoma have been employed, e.g., malignant mixed tumor, embryonic mixed tumor, and rhabdomyosarcohepatoma. The study of these reports leaves some doubt as to whether these lesions were in fact what we now define as hepatoblastomas or whether they rather belong to the category of mixed hepatic tumors sensu strictiori, discussed in a separate chapter. In fact, some features of mixed tumors in adults that have been discussed as being related to hepatoblastomas contain cell types that do not usually occur in pediatric hepatoblastomas, such as areas of adenocarcinoma (Carter 1969), hepatocellular carcinoma (Kerr 1966; Carter 1969; Goldman and Friedman 1969; Ludwig et al. 1975), chondrosarcoma (Carter 1969; Ludwig et al. 1975), and osteosarcoma (Carter 1969; Goldman and Friedman 1969). Therefore, the issue whether part of mixed tumors belong to the hepatoblastoma family of tumors remains controversial.

Combined Hepatoblastoma and Hepatocellular Carcinoma

Combined hepatoblastoma and hepatocellular carcinoma occurring as a synchronous lesion is very rare (de Potter et al. 1987; Cho et al. 2004; Ishimura et al. 2007; Mourad et al. 2007; Masuda et al. 2009; Canberk et al. 2013). In one patient, a sarcomatoid hepatocellular carcinoma showed foci of embryonal-type and small undifferentiated cells reminiscent of hepatoblastoma (Cho et al. 2004). Local relapse with hepatocellular carcinoma after treatment of hepatoblastoma has been observed (Gauthier et al. 1986). Late relapse of hepatocellular carcinoma in a child suffering from combined hepatoblastoma and hepatocellular carcinoma has been reported (Postovsky et al. 2001). In one patient, a combined hepatoblastoma and hepatocarcinoma developed 10 years after sibling donor bone marrow transplantation for severe aplastic anemia (Ishimura et al. 2007). Clear cell hepatocellular carcinoma arose in a patient 25 years after successful treatment of infantile hepatoblastoma (Basile et al. 2010). In a 54-year-old man with HCV-associated liver cirrhosis, a 3-cm-sized hepatic tumor was found to a mixed epithelial and mesenchymal hepatoblastoma with osteoid formation. Two years after the first operation, multicentric hepatocellular carcinoma developed (Masuda et al. 2009). On the other hand, HCC has been shown to relapse as hepatoblastoma, e.g., mixed hepatoblastoma after liver transplantation. This case was an adult patient transplanted for alcoholic liver cirrhosis complicated by multifocal hepatocellular carcinoma. One of the lesions (2 cm diameter) was histologically classified as mixed, trabecular and glandular, and moderately differentiated HCC, while the two other lesions (less than 1 cm diameter) were trabecular well-differentiated HCC. Three months after liver transplantation, a tumor recurred, associated with increased serum AFP (5,500 ng/ml), and a mixed hepatoblastoma had invaded the whole transplanted liver. Histology of the liver, which weighed 4,667 g, revealed a heterogeneous neoplasm. Some nodules contained an HCC-like growth associated with hepatoblastoma-like epithelial components and with tumor areas containing osteoid (Dumortier et al. 1999).

Stromal-Predominant Liver Tumors in the Pediatric Age Group

There are rare instances of pediatric liver tumors of the HB family that are characterized by large areas of stromal tissue, mostly fibroblasoid or immature mesenchymal/blastemal, lacking any epithelial components or only showing small nests of ill-defined epithelial cells. Such lesions may provisionally be termed “pediatric hepatic stromal tumors/PHST” as long as they are not further defined in regard to the cell lineages involved. These neoplasms may represent the hepatic counterpart of renal metanephric stromal tumors. Stromal-predominant tumors form well-circumscribed firm masses with an expanding growth pattern and perifocal liver atrophy.

Histologically, these neoplasms are characterized by a mesenchymal neoplastic tissue that consists of spindle and stellate cells embedded in a variably developed extracellular matrix. The spindle cells resemble fibroblasts or myofibroblasts but sometimes exhibit an immature phenotype. The spindled cells form fascicles or whorls. Myxoid areas may be present. Rarely, small clusters of non-hepatocyte epithelial cells are found, suggesting mesenchymal to epithelial transition.

Hepatoblastoma Associated with Other Hepatic Tumors and Tumor-like Lesions

Hepatoblastoma has been observed in combination with yolk sac tumor (Cross and Variend 1992). The authors described 6-month-old boy presenting with a large abdominal mass, caused by a liver tumor arising in the right liver lobe. At autopsy, the right lobe contained many confluent nodular and cystic masses. Histology revealed two components, the first being mixed epithelial and mesenchymal hepatoblastoma, with a fetal-embryonal epithelial lineage and osteoid formation, while the second component was yolk sac tumor with glandular structures, rounded papillary structures with central capillaries covered by cuboidal cells, and Schiller-Duval bodies. Both components were immunoreactive for AFP. Interestingly, yolk sac tumor of the liver has also been found together with hepatocellular carcinoma in an adult patient (Morinaga et al. 1996). Few observations revealed the combination of hepatoblastoma with true teratoma (Conrad et al. 1993; Moll et al. 2009). The patient described by Conrad et al. (1993) was a 17-month-old boy with a hepatic mass that was suggested to be teratoma based on imaging studies, but serum AFP was markedly elevated. The resected tumor comprised adjoining benign cystic teratoma and epithelial hepatoblastoma. In the case of Moll and coworkers (2009), a 3-year-old boy, the hepatic tumor resection specimen showed a tumor of up to 16 cm diameter that showed multiple cysts with a diameter of up to 1.5 cm. Histology showed tumor areas of very variable differentiation patterns intermixed with each other, i.e., not like in a collision tumor. Part of the tumor consisted of a fetal and embryonal hepatoblastoma, whereas other parts revealed neuroblastoma-like components, spindle cells with cross striation, cystic epithelial structures, and osteoid. Based on the published figures and the histologic description, this case rather represents a teratoid hepatoblastoma than a combination of hepatoblastoma and teratoma.

References

Ahn HJ, Kwon KW, Choi YJ, Kim HJ, Hong SP, Oh D, Chung JS (1997) Mixed hepatoblastoma in an adult – a case report and literature review. J Korean Med Sci 12:369–373

Alexander M (1961) A mixed tumor of the liver in an adult. J Pathol 82:217–219

Allison RM, Willis RA (1956) An ossifying embryonic mixed tumor of an infant's liver. J Pathol Bacteriol 72:155

Altmann HW (1992) Epithelial and mixed hepatoblastomas in the adult. Histological observations and general considerations. Pathol Res Pract 188:16–26

Baird PV, McGovern VJ (1976) Embryonal hepatoblastoma with malignant epithelial and mesenchymal tissue component occurring in an adult. Pathology 8:170–171

Barbaryka I, von Bouguoy F (1981) Hepatoblastoma in the adult (in German). Leber Magen Darm 11:283–287

Barnett WH, Erickson EE, Halpert B (1958) Embryonic tumor of the liver in an adult. Cancer 11:306–309

Baroni C, Tognoli S, Spadon S, Astuni M, Lora PA, Lazzarini G, Fantoni PA (1984) Hemoperitoneum caused by spontaneous rupture of a hepatoblastoma in an adult, with arrest of hemorrhage by peroperative cryoapplication (in Italian). Minerva Chir 39:1015–1018

Bartok I (1958a) Hepatoblastoma causing metastasis in adult (in Hungarian). Orv Hetil 99:212–214

Bartok I (1958b) Metastasizing hepatoblastoma in an adult. Zentralbl Allg Pathol 98:55–60

Basile J, Caldwell S, Nolan N, Hammerle C (2010) Clear cell hepatocellular carciunoima arising 25 years after the successful treatment of an infantile hepatoblastoma. Ann Hepatol 9:465–467

Beppu T, Karashima R, Sugiyama S et al (2006) A successfully resected case of adult hepatoblastoma with hepatitis C (in Japanese). Jpn J Gastroenterol Surg 39:72–77

Bhatnagar A, Pathania OP, Champakam NS (1987) Hepatoblastoma in an adult female (letter). Indian J Gastroenterol 6:125–126

Blanding J (1968) Mixed malignant tumors of the liver of adults. Case report and review of some features. Arch Pathol Lab Med 86:108–110

Bortolasi L, Marchiori L, Dal Dosso I, Colombari R, Nicoli N (1996) Hepatoblastoma in adult age: a report of two cases. Hepatogastroenterology 43:1073–1078

Canberk S, Uludokumaci A, Sonmez C, Cakalir C, Gulsen F, Ozbay G (2013) Mixed hepatocellular carcinoma and hepatoblastoma: cytohistopathologic findings and differential diagnosis. Acta Cytol 57:91–95

Carter R (1969) Hepatoblastoma in the adult. Cancer 23:191–197

Cho MS, Lee SN, Sung SH, Han WS (2004) Sarcomatoid hepatocellular carcinoma with hepatoblastoma-like features in an adult. Pathol Int 54:446–450

Choe JY, Kim H (2014) Intrahepatic cholangiocarcinoma with predominant ductal plate malformation pattern. Clin Mol Hepatol 20:214–217

Cienfuegos JA, Labiano T, Pedano N, Zozaya GN, Marti-Cruchaga P, Panizo A, Rotellar F (2013) Adult hepatoblastoma. Rev Esp Enferm Dig 105:229–231

Conrad RJ, Gribbin D, Walker NI, Ong TH (1993) Combined cystic teratoma and hepatoblastoma of the liver. Probable divergent differentiation of an uncommitted hepatic precursor cells. Cancer 72:2910–2913

Cross SS, Variend S (1992) Combined hepatoblastoma and yolk sac tumor of the liver. Cancer 69:1323–1326

De Potter CR, Robberecht E, Laureys G, Cuvelier CA (1987) Hepatitis B related childhood hepatocellular carcinoma. Childhood hepatic malignancies. Cancer 60:414–418

Dumortier J, Bizollon T, Chevallier M, Ducerf C, Baulieux J, Scoazec JY, Trepo C (1999) Recurrence of hepatocellular carcinoma as a mixed hepatoblastoma after liver transplantation. Gut 45:622–625

Eichenmüller et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/25135868

Fiaschetti et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/21113306

Fragulidis GP, Chondrogiannis K, Vezakis A, Melemeni A, Kondi-Pafiti A, Primetis E, Polydorou A, Voros DC (2013) Neuroendocrine differentiation in embryonal type hepatoblastoma. Hepatol Res 43:320–326

Gauthier F, Valayer J, Thai BL, Sinico M, Kalifa C (1986) Hepatoblastoma and hepatocarcinoma in children: analysis of a series of 29 cases. J Pediatr Surg 21:424–429

Goldman R, Friedman N (1969) Rhabdomyosarcohepatoma in an adult and embryonal hepatoma in a child. Am J Clin Pathol 51:137–143

Gornicka B, Ziarkiewicz-Wroblewska B, Michalowicz B, Pawlak J, Wroblewski T, Krawczyk M, Wasiutynski A et al (2001) Immature hepatic tumor of bimodal differentiation in a young adult patient: a novel lesion expressing beta-catenin and mimicking a distinct phase of hepatogenesis. J Hepatol 34:955–961

Green LK, Silva EG (1989) Hepatoblastoma in an adult with metastases to the ovaries. Am J Clin Pathol 92:110–115

Harada T, Matsuo K, Kodama S, Higashihara H, Nakayama Y, Ikeda S (1995) Adult hepatoblastoma: case report and review of the literature. Aust N Z J Surg 65:686–688

Hartleb M, Koturbaz D, Paprotna M (1989) Hepatoblastoma in a boy aged 18. Quoted by Green and Silva, 1989

Honan RP, Haqqani MT (1980) Mixed hepato-blastoma in the adult: case report and review of the literature. J Clin Pathol 33:1050–1063

Inagaki M, Yagi T, Urushihara N, Shima Y, Sadamori H, Takakura N, Tanaka N, Oda M (2001) Successfully resected hepatoblastoma in a young adult with chronic hepatitis B: report of a case. Eur J Gastroenterol Hepatol 13:981–984

Inoue S, Nagao T, Ishida Y, Wada C, Beck Y, Uchida H, Okudaira M (1995) Successful resection of a large hepatoblastoma in a young adult: report of a case. Surg Today 25:974–977

Ishimura M, Ohga S, Nagatoshi Y, Okamura J, Tajiri T, Kohashi K, Oda Y, Takada H, Hara T (2007) Malignant hepatic tumor occurring 10 yrs after a histocompatible sibling donor bone marrow transplantation for severe aplastic anemia. Pediatr Transplant 11:945–949

Jameson CP, Chatkadakis CB (1978) Hepatoblastoma in a middle aged South African woman. SA Med J 53:143–144

Kacker LK, Khan EM, Gupta R, Kapoor VK, Pandey R, Gupta RK, Saraswat VA (1995) Hepatoblastoma in an adult with biliary obstruction and associated with portal venous thrombosis. HPB Surg 9:47–49

Kasper HU, Longerich T, Stippel DL, Kern MA, Drebber U, Schirmacher P (2005) Mixed hepatoblastoma in an adult. Arch Pathol Lab Med 129:234–237

Kawarada Y, Uehara S, Noda M, Yatani R, Mizumoto R (1985) Nonhepatocytic malignant mixed tumor primary in the liver. Cancer 55:1790–1798

Ke HY, Chen JH, Jen YM, Yu JC, Hsieh CB, Chen CJ, Liu YC, Chen TW, Chan DC (2005) Ruptured hepatoblastoma with massive internal bleeding in an adult. World J Gastroenterol 11:6235–6237

Kerr JFR (1966) Hepatic embryonic mixed tumor in an adult. J Pathol Bacteriol 92:238–240

Kishimoto Y, Hijiya S, Nagasaki R (1984) Malignant mixed tumor of the liver in adults. Am J Gastroenterol 79:229–235

Krzewinski W, Marcisz C, Slowik T, Antosz Z (2007) Hepatoblastoma in an adult (in Polish). Wiad Lek 60:479–482

Kuniyasu H, Yasui W, Shimaoto F et al (1996) Hepatoblastoma in an adult associated with c-met proto-oncogene imbalance. Pathol Int 46:1005–1010

Libbrecht L, Desmet V, Roskams T (2003) Stages of normal and aberrant intrahepatic bile duct development in a mixed hepatoblastoma. Histopathology 42:618–620

Ludwig J, Grier MW, Hoffman HN, McGill DB (1975) Calcified mixed malignant tumor of the liver. Arch Pathol Lab Med 99:162–166

Masuda T, Beppu T, Horino K, Komori H, Hayshi H, Okabe H, Ootao R, Horlad H et al (2009) Occurrence of hepatocellular carcinoma after hepatoblastoma resection in an adult with hepatitis C virus. Hepatol Res 39:525–530

Meyer P, Livolsi V, Cornog J (1974) Hepatoblastoma associated with oral contraceptive. Lancet 2:1387

Milman DH, Grayzel DM (1951) Mixed tumor of the liver; report of case with review of literature. Am J Dis Child 81:408–420

Misra et al. 1988. http://www.ncbi.nlm.nih.gov/pubmed/2846507

Moll A, Krenauer A, Bierbach U, Till H, Hirsch W, Leuschner I, Schmitz N, Wittekind C, Aigner T (2009) Mixed hepatoblastoma and teratoma of the liver in a 3-year-old child: a unique combination and clinical challenge. Diagn Pathol 4:37

Mondragon SR, Bernal MR, Sada NLA et al (1994) Hepatoblastomas epiteliales en el adulto. Rev Gastroenterol Mex 59:231–235

Morinaga S, Nishiya H, Inafuku T (1996) Yolk sac tumor of the liver combined with hepatocellular carcinoma. Arch Pathol Lab Med 120:687–690

Mourad W, Khalaf H, Tulbah A, Al Omari M, Al mana H, Neimatallah M (2007) Clinicopathologic features of hepatic neoplasma in explanted livers : a single institution experience. Ann Saudi Med 27:437–441

Mukhopadhyay P, Kundu SS, Banerjee A, Mukherjee A (2007) Adult hepatoblastoma in a female Down's. J Assoc Physicians India 55:242–243

Nakamura S, Sho M, Kanehiro H, Tanaka T, Kichikawa K, Nakajima Y (2010) Adult hepatoblastoma successfully treated with multimodal treatment. Langenbecks Arch Surg 395:1165–1168

Oda H, Honda K, Hara M, Arase Y, Ikeda K, Kumada H (1990) Hepatoblastoma in an 82 year old man. An autopsy case report. Acta Pathol Jpn 40:212–218

Ogata H, Kanzaki K, Hayakawa H et al (1973) A case of primary hepatic malignancy mixed tumor. Acta Hepatol Jpn 14:561–566

Ojima MA, Sugiyama T, Takeda T (1964) Six cases of rare malignant tumors of the liver. Acta Pathol Jpn 14:95–102

Parada LA, Bardi G, Hallén M, Hägerstrand I, Tranberg KG, Mitelman F, Johansson B (1997) Cytogenetic abnormalities and clonal evolution in an adult hepatoblastoma. Am J Surg Pathol 21:1381–1386

Popper H (1980) Bidermal hepatoblastoma in an adult. Zentralbl Allg Pathol 124:403–409

Postovsky S, Elhasid R, Otte GB, Ben Itzhak O, Gaitini D, Ben Arush MW (2001) Late recurrence of combined hepatocellular carcinoma and hepatoblastoma in a child: case report and review of the literature. Eur J Pediatr Surg 11:61–65

Prokurat A, Kluge P, Kosciesza A, Perek D, Kappeler A, Zimmermann A (2002) Transitional liver cell tumor (TLCT) in older children and adolescents: a novel group of aggressive hepatic tumors expressing beta-catenin. Med Pediatr Oncol 39:510–518

Remes-Troche JM, Montano-Loza A, Meza-Junco J, Garcia-Leiva J, Torre-Delgadillo A (2006) Hepatoblastoma in adult age. A case report and literature review. Ann Hepatol 5:179–181

Seabrook GR, Collin JR, Britton BJ (1989) Hepatoblastoma: successful resection in an adult. Br J Clin Pract 43:345–346

Sugino K, Dohi K, Matsuyama T, Asahara T, Yamamoto M (1989) A case of hepatoblastoma occurring in an adult. Jpn J Surg 19:489–493

Wang YX, Liu H (2012) Adult hepatoblastoma: systemic review of the English literature. Dig Surg 29:323–330

Yoshida T, Okozaki M, Yoshino N, Shimamura Y, Miyazawa N, Miyamoto K, Kishi K (1979) A case of hepatoblastoma in adult. Jpn J Clin Oncol 9:163–168

Zhang SH, Xu AM, Lin WH, Zhang XY (2007) Mixed hepatoblastoma with teratoid features in an adult. Pathology 39:453–456

Zhang Q, Ming J, Zhang S, Guo D, Qiu X (2013) A rare case of adult hepatoblastoma with neuroendocrine differentiation misdiagnosed as neuroendocrine tumor. Int J Clin Exp Pathol 6:308–313

Zhou S, Ranganathan S, Venkatramani R, Gomulia E, Wang L (2013) Teratoid hepatoblastoma with abundant cholangioblastic component in a child with full trisomy 13: a rare case report. Pediatr Dev Pathol 16:438–441

Zimmermann A (2002) Hepatoblastoma with cholangioblastic features ('cholangioblastic hepatoblastoma') and other liver tumors with bimodal differentiation in young patients. Med Pediatr Oncol 39:487–491

Zimmermann A (2005) The emerging family of hepatoblastoma tumours: from ontogenesis to oncogenesis. Eur J Cancer 41:1503–1514

Hepatoblastomas: Biology of Disease and Prognostic Factors

21

Contents

Abstract

Biology of disease and prognosis in hepatoblastoma (HB) strongly depend on the initial stage of disease. At primary diagnosis, 40–60 % of HB either present as large or very large tumors, or involve both liver lobes, rendering the tumors unresectable. Therefore, downstaging of tumors by chemotherapy is a crucial approach. Tumor staging in HB has been standardized in great detail. Similar to hepatocellular carcinoma, HB has a strong tendency to invade the vascular system (macrovessel and microvessel invasion). Apart from stage, which is the most powerful prognosticator in HB, other prognostic factors include serum alpha-fetoprotein (AFP) levels, tumor histology, and molecular features. HB patients with low serum AFP concentrations form a high-risk group. Among various histologic types and subtypes, the fetal pattern is a favorable histology, whereas the small cell undifferentiated phenotype with or without rhabdoid features confers a high-risk biology. An increasing number of molecular abnormalities will be used in the future as risk stratificators.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_21

Initial Tumor Extension, Invasion, Spread, and Metastasis

At primary diagnosis, 40–60 % of hepatoblastomas either present as large or very large tumors, or involve both liver lobes, causing the tumors unresectable. Preoperative chemotherapy results in downstaging in more than 80 % of patients, rendering the tumors resectable. Hepatoblastoma has a strong tendency to invade the vascular system, including portal and hepatic veins, the inferior vena cava, and smaller intrahepatic venous branches (macrovessel invasion and microvessel invasion; Wang et al. 2002). A main localization for distant metastases is the lung. Approximately 10–20 % of patients have lung metastases when first diagnosed. Lung metastases were already described in 1951 based on a postmortem examination of a 6-year-old boy with mixed hepatoblastoma (Milman and Grayzel 1951). Metastatic disease can also involve bronchopulmonary lymph nodes, and tumor can invade the pulmonary veins, tumor thrombi in pulmonary veins sometimes extending into the left atrium (Milman and Grayzel 1951). Hepatoblastoma metastases also involve the bony skeleton, brain, ovaries, and eye. Fetal or congenital hepatoblastoma may rarely cause extensive placental involvement, with diffuse tumor emboli in chorionic villus vessels (Robinson and Bolande 1985; Doss et al. 1998).

Biology of Disease and Modern Treatment

Previously, the prognosis of hepatoblastoma was very poor. Bodian (cited as a personal communication in Borman et al. 1961) had not had a survivor in all 13 cases in his experience. In a report of 1954, one patient lived 3 years after exploratory laparotomy (Debré et al. 1954), and another patient was reported to survive 10 years following excision (Tweedy 1956; personal communication to Borman et al. 1961). The first long-term survival of hepatoblastoma after hepatic lobectomy was reported in 1961. The patient was a 7-month-old girl having a globular tumor occupying nearly the whole of the left liver lobe. Based on the pathology description and the figure, the lesion probably represented mixed fetal and embryonal hepatoblastoma with numerous mitotic figures (Borman et al. 1961). Already in 1975 it had been reported that radiation and chemotherapy had a favorable effect in hepatoblastoma in which the tumor changed from inoperable to operable in three patients (Exelby et al. 1975). The 5-year survival of European patients with hepatoblastoma increased between 1978–1982 and 1993–1997 from 28 % to 66 % (Stiller et al. 2006) and has since further increased in an impressive manner. Based on modern surgical approaches, chemotherapies, and liver transplantation, numerous series of treatment results have been published.

Selected References Mahour et al. 1983; Giacomantonio et al. 1984; Koneru et al. 1991; Gururangan et al. 1992; Reynolds et al. 1992; Douglass et al. 1993; Reynolds 1995; Von Schweinitz et al. 1995; Ehrlich et al. 1997; Seo et al. 1998; Ortega et al. 2000; Pritchard et al. 2000; Reyes et al. 2000; Jung et al. 2001; Fuchs et al. 2002; Katzenstein et al. 2002; Sasaki et al. 2002; Schnater et al. 2002; Cillo et al. 2003; Matsunaga et al. 2003; Davies et al. 2004; Dicken et al. 2004; Otte et al. 2004, 2005; Perilongo et al. 2004, 2009; Czauderna et al. 2005; Mejia et al. 2005; Otte et al. 2005; Austin et al. 2006; Ang et al. 2007; Meyers 2007; Browne et al. 2008; Faraj et al. 2008; Baertschiger et al. 2010; Otte 2010; Zsiros et al. 2010, 2012, 2013; Malogolowkin et al. 2011, 2012; Semeraro et al. 2013; review: Horton et al. 2009.

Prognostic Factors

Stage

So far, tumor stage has been shown to be the most powerful prognosticator for the biology of hepatoblastomas. Features of hepatoblastoma predicting unresectability include multifocal tumors, high PRETEXT stage, involvement of large major liver blood vessels, and serum AFP

levels <100 ng/ml (Von Schweinitz et al. 1994; Fuchs et al. 2002; D'Antiga et al. 2007). The negative prognostic impact of hepatoblastomas presenting as tumor nodules throughout the liver has already been notes studied prior to systematic trials (Keeling 1971). It has in recent years been shown that hepatoblastoma staging has a central place as a predictor of outcome (Meyers 2007). The PRETEXT staging system, which has a moderate accuracy with a tendency to overstage patients, showed superior predictive value for survival and offers the opportunity to monitor the effects of preoperative therapy. In a study of 154 hepatoblastoma patients, 5-year overall survival and event-free survival were univariately associated with the PRETEXT stage and the presence of metastases. Additionally, tumor focality and enlargement of hilar lymph nodes at diagnosis were univariately associated with event-free survival (Brown et al. 2000). Following neoadjuvant chemotherapy, the extent of tumor necrosis independently predicted survival in patients with hepatoblastoma (Venkatramani et al. 2012). Congenital hepatoblastoma with its very early initiation and progression of disease does not appear to confer a worse prognosis (Trobaugh-Lotrario et al. 2013).

Serum Alpha-Fetoprotein/AFP

Hepatoblastoma patients with low serum alpha-fetoprotein (AFP) levels form a high-risk group (De Ioris et al. 2008). In a recent analysis of SIOPEL results covering 1995–2006 (541 patients with hepatoblastoma), reduced event-free survival correlated significantly with AFP <100 ng/ml, AFP => 1.2 × 10(6) ng/ml, metastatic disease, PRETEXT stage IV, multifocality, age >5 years, and borderline with small cell undifferentiated histology (Maibach et al. 2012).

Tumor Histology

Is tumor histology a risk stratificator? So far, the fetal phenotype was identified as a favorable histology (Haas et al. 1989; Conran et al. 1992), when compared with all other histologic pattern (Haas et al. 1989), and a small cell undifferentiated phenotype confers a high-risk biology (Dehner and Manivel 1988). Much less is known about the significance of other histomorphologies. In their analysis of the relationship between morphologic subtypes and prognosis, Dehner and Manivel (1988) had too few observations on MT-HB to be certain whether it is prognostically unfavorable or not. There is evidence that the proliferative activity of hepatoblastomas affects outcome. Fetal-type hepatoblastomas with a very low proliferative activity present the most favorable phenotype, while rapidly proliferating small cell undifferentiated hepatoblastoma is a highly aggressive tumor. Mitotic activity was associated with poor prognosis (Haas et al. 1989). Proliferative activity is assessable by the mitotic rate, the PCNA labeling index, the Ki-67/MIB-1 labeling index, and the expression of nucleolar organizing regions. The PCNA labeling index was found to be significantly higher in the embryonal than in the fetal phenotype (Rugge et al. 1998). The significant difference between fetal and embryonal cell proliferative activity assessed by immunohistochemistry was confirmed in a later study (Tsai et al. 2009). The Ki-67/MIB-1 labeling index varied from 0 % to 39.5 % in one study, with a mean value of 13.5 %. There was no significant correlation between this labeling index and age and sex, but with stage, in that the indices were lower in patients with stage I and stage II in comparison with higher stages (Ara et al. 1997). Overexpression of cyclin D1 and a high Ki-67 proliferation index was prognostically significant (Purcell et al. 2012).

Molecular Features

An increasing number of molecular abnormalities may be used in the future as prognosticators for hepatoblastoma. Expression of carcinoembryonic antigen-related cell adhesion molecule 1 has been found to be an adverse prognostic factor in hepatocellular carcinoma (Cruz et al. 2005), and loss of this molecule's expression predicts metachronous pulmonary metastasis and poor survival in

patients with hepatoblastoma (Tsukada et al. 2009). A high expression of the tight junction-associated protein, tricellulin, is associated with better survival in HB (Schlachter et al. 2014). Expression of a factor involved in epigenetic promoter hypermethylation, RAS association domain family protein 1/RASSF1A, indicates poor prognosis in hepatoblastoma (Honda et al. 2013). Prognosis of HBs can be estimated by use of distinct microRNA (miR) expression patterns. Specifically, high miR-21, low miR-222, and low miR-224 levels were associated with increased overall survival (Gyugos et al. 2014).

References

Ang JP, Heath JA, Donath S et al (2007) Treatment outcomes for hepatoblastoma: an institution's experience over two decades. Pediatr Surg Int 23:103–109

Ara T, Fukuzawa M, Oue T, Komoto Y, Kusafuka T, Imura K, Okada A (1997) Immunohistochemical assessment of the MIB-1 labeling index in human hepatoblastoma and its prognostic relevance. J Pediatr Surg 32:1690–1694

Austin MT, Leys CM, Feurer ID, Lovvom HN, O'Neill JA, Pinson CW, Pietsch JB (2006) Liver transplantation for childhood hepatic malignancy: a review of the United Network for Organ Sharing (UNOS) database. J Pediatr Surg 41:182–186

Baertschiger RM, Ozsahin H, Rougemont AL, Anooshiravani M, Rubbia-Brandt L et al (2010) Cure of multifocal hepatoblastoma: is liver transplantation always necessary? J Pediatr Surg 45:1030–1036

Borman JB, Harbott AJ, Morris D (1961) Hepatic lobectomy in infancy for hepatoblastoma. Br J Surg 49:11–13

Brown J, Perilongo G, Shafford E, Keeling J, Pritchard J, Brock P, Dicks-Mireaux C et al (2000) Pretreatment prognostic factors for children with hepatoblastoma – results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. Eur J Cancer 36:1418–1425

Browne M, Sher D, Grant D, Deluca E, Alonso E, Whitington PF, Superina RA (2008) Survival after liver transplantation for hepatoblastoma: a 2-center experience. J Pediatr Surg 43:1973–1981

Cillo et al. (2003) http://www.ncbi.nlm.nih.gov/pubmed/14697956

Conran RM, Hitchcock CL, Waclawiw MA, Stocker JT, Ishak KG (1992) Hepatoblastoma: the prognostic significance of histologic type. Pediatr Pathol 12:167–183

Cruz PV, Wakai T, Shirai Y, Yokoyama N, Hatakeyama K (2005) Loss of carcinoembryonic antigen-related cell adhesion molecule 1 expression is an adverse prognostic factor in hepatocellular carcinoma. Cancer 104:354–360

Czauderna P, Otte JB, Aronson DC, Gauthier F, Mackinley G, Roebuck D, Plaschkes J et al (2005) Guidelines for surgical treatment of hepatoblastoma in the modern age – recommendations form the Childhood Liver Tumour Strategy Group of the International Society for Paediatric Oncology (SIOPEL). Eur J Cancer 41:1031–1036

D'Antiga L, Vallortigara F, Cillo U, Talenti E, Rugge M, Zancan L, Dall'Igna P, De Salvo GL, Perilongo G (2007) Features predicting unresectability in hepatoblastoma. Cancer 110:1050–1058

Davies JQ, de la Hall PM, Kaschula RO, Sinclair-Smith CC, Hartley P, Rode H, Millar AJ (2004) Hepatoblastoma – evolution of management and outcome and significance of histology of the resected tumor. A 31-year experience with 40 cases. J Pediatr Surg 39:1321–1327

De Ioris M, Brugières L, Zimmermann A, Keeling J, Broch P, Maibach R, Pritchard J et al (2008) Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: the SIOPEL group experience. Eur J Cancer 44:545–550

Debré R, Mozziconacci P, Habib R (1954) L'Hépatoblastoma (tumeur maligne du foie à cellules embryonnaires) (in French). Arch Fr Pédiat 11:1013–1034

Dehner LP, Manivel JC (1988) Hepatoblastoma: an analysis of the relationship between morphologic subtypes and prognosis. Am J Pediatr Hematol Oncol 10:301–307

Dicken BJ, Bigam DL, Lees GM (2004) Association between surgical margins and long-term outcome in advanced hepatoblastoma. J Pediatr Surg 39:721–725

Doss BJ, Vicari J, Jacques SM, Qureshi F (1998) Placental involvement in congenital hepatoblastoma. Pediatr Dev Pathol 1:538–542

Douglass EC, Finegold M, Reynolds M et al (1993) Cisplatin, vincristine and fluorouracil therapy for hepatoblastoma: a Pediatric Oncology Group Study. J Clin Oncol 11:96–99

Ehrlich PF, Greenberg ML, Filler RM (1997) Improved long-term survival with preoperative chemotherapy for hepatoblastoma. J Pediatr Surg 32:999–1003

Exelby PR, Filler RM, Grosfeld JL (1975) Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey – 1974. J Pediatr Surg 10:329–337

Faraj W, Dar F, Marangoni G, Bartlett A, Mlenedez HV, Hadzic D, Dhawan A, Mieli-Vergani G et al (2008) Liver transplantation for hepatoblastoma. Liver Transpl 14:1614–1619

Fuchs J, Rydzynski J, Von Schweinitz D, Bode U, Hecker H, Weinel P, Burger D, Harms D et al (2002) Pretreatment prognostic factors and treatment results in children with hepatoblastoma a report from the German

Cooperative pediatric Liver Tumor Study HB 94. Cancer 95:172–182
Giacomantonio M, Ein SH, Mancer K, Stephens CA (1984) Thirty years of experience with pediatric primary malignant liver tumors. J Pediatr Surg 19:523–526
Gururangan S, O'Meara A, MacMahon C, Guiney EJ, O'Donnell B, Fitzgerald RJ, Breatnach F (1992) Primary hepatic tumours in children: a 26-year review. J Surg 50:30–36
Gyugos M, Lendvai G, Kenessey I, Schlachter K, Halasz J, Nagy P, Garami M, Jakab Z et al (2014) MicroRNA expression might predict prognosis of epithelial hepatoblastoma. Virchows Arch 464:419–427
Haas JE, Muczynski KA, Krailo M, Ablin A, Land V, Vietti TJ, Hammond GD (1989) Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. Cancer 64:1082–1095
Honda et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23989600
Horton JD, Lee S, Brown SR, Bader J, Meier DE (2009) Survival trends in children with hepatoblastoma. Pediatr Surg Int 25:407–412
Jung SE, Kim KH, Kim MY, Kim DY, Lee SC, Park KW, Kim WK (2001) Clinical characteristics and prognosis of patients with hepatoblastoma. World J Surg 25:126–130
Katzenstein HM, London WB, Douglass EC, Reynolds M, Plaschkes J, Finegold MJ, Bowman LC (2002) Treatment of unresectable and metastatic hepatoblastoma: a pediatric oncology group phase II study. J Clin Oncol 20:3438–3444
Keeling JW (1971) Liver tumours in infancy and childhood. J Path 103:69–85
Koneru B, Flye MW, Busuttil RW, Shaw BW, Lorber MI, Emond JC, Kalayoglu M et al (1991) Liver transplantation for hepatoblastoma. The American experience. Ann Surg 213:118–121
Mahour GH, Wogu GU, Siegel SE, Isaacs H (1983) Improved survival in infants and children with primary malignant liver tumors. Am J Surg 146:236–240
Maibach R, Roebuck D, Brugieres L, Capra M, Brock P, Dall'Igna P, Otte JB, De Camargo B et al (2012) Prognostic stratification for children with hepatoblastoma: the SIOPEL experience. Eur J Cancer 48:1543–1549
Malogolowkin MH, Katzenstein HM, Meyers RL, Krailo MD, Rowland JM, Haas J, Finegold MJ (2011) Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: a report from the Children's Oncology Group. J Clin Oncol 29:3301–3306
Malogolowkin MH, Katzenstein HM, Krailo M, Meyers RL (2012) Treatment of hepatoblastoma: the North American cooperative group experience. Front Biosci (Elite Ed) 4:1717–1723
Matsunaga T, Sasaki F, Ohira M, Hashizume K, Hayashi K, Hayashi A, Hayashi Y et al (2003) Analysis of treatment outcome for children with recurrent or metastatic hepatoblastoma. Pediatr Surg Int 19:142–146
Mejia A, Langnas AN, Shaw BW, Torres C, Sudan DL (2005) Living and deceased donor liver transplantation for unresectable hepatoblastoma at a single center. Clin Transpl 19:721–725
Meyers RL (2007) Tumors of the liver in children. Surg Oncol 16:195–203
Milman DH, Grayzel DM (1951) Mixed tumor of the liver; report of case with review of literature. Am J Dis Child 81:408–420
Ortega JA, Douglass EC, Feusner JH, Reynolds M, Quinn JJ, Finegold MJ, Haas JE et al (2000) Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: a report from the Children's Cancer Group and the pediatric Oncology Group. J Clin Oncol 18:2665–2675
Otte JB (2010) Progress in the surgical treatment of malignant liver tumors in children. Cancer Treat Rev 36:360–371
Otte JB, Pritchard J, Aronson DC, Brown J, Czauderna P, Maibach R, Perilongo G, Shafford E, Plaschkes J, International Society of Pediatric Oncology (SIOP) (2004) Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. Pediatr Blood Cancer 42:74–83
Otte JB, de Ville de Goyet J, Reding R (2005) Liver transplantation for hepatoblastoma: indications and contraindications in the modern era. Pediatr Transplant 9:557–565
Perilongo G, Shafford E, Maibach R, Aronson D, Brugières L, Brock P, Childs M, Czauderna P et al (2004) Risk-adapted treatment for childhood hepatoblastoma, final report of the second study of the International Society of Paediatric Oncology – SIOPEL-2. Eur J Cancer 40:411–421
Perilongo G, Maibach R, Shafford E, Brugières L, Brock P, Morland B, de Camargo B et al (2009) Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med 361:1662–1670
Pritchard J, Brown J, Shafford E et al (2000) Cisplatin, doxorubicin and delayed surgery for childhood hepatoblastoma: a successful approach. Results of the first prospective study of the International Society for Pediatric Oncology. J Clin Oncol 15:3819–3828
Purcell R, Childs M, Maibach R, Miles C, Turner C, Zimmermann A, Czauderna P, Sullivan M (2012) Potential biomarkers for hepatoblastoma: results from the SIOPEL-3 study. Eur J Cancer 48:1853–1859
Reyes JD, Carr B, Dvorchik I, Kocoshis S, Jaffe R, Gerber D, Mazariegos GV, Bueno J, Selby R (2000) Liver transplantation and chemotherapy for hepatoblastoma and hepatocellular cancer in childhood and adolescence. J Pediatr 136:795–804
Reynolds M (1995) Conversion of unresectable to resectable hepatoblastoma and long-term follow-up study. World J Surg 19:814–816

Reynolds M, Douglass EC, Finegold M, Cantor A, Glicksman A (1992) Chemotherapy can convert unresectable hepatoblastoma. J Pediatr Surg 27:1080–1083

Robinson HB, Bolande RP (1985) Case 3. Fetal hepatoblastoma with placental metastases. Pediatr Pathol 4:163–167

Rugge M, Sonego F, Pollice L, Perilongo G, Guido M, Basso G, Ninfo V, Pennelli N, Gambini C, Guglielmi M et al (1998) Hepatoblastoma: DNA nuclear content, proliferative indices, and pathology. Liver 18:128–133

Sasaki F, Matsunaga T, Iwafuchi M, Hayashi Y, Ohkawa H, Ohira M, Okamatsu T et al (2002) Outcome of hepatoblastoma treated with the JPLT-1 (Japanese Study Group for Pediatric Liver Tumor) Protocol-1: a report from the Japanese Study Group for Pediatric Liver Tumor. J Pediatr Surg 37:851–856

Schlachter K, Gyugos M, Halasz J, Lendvai G, Baghy K, Garami M, Gyöngyösi B, Schaff Z et al (2014) High tricellulin expression is associated with better survival in human hepatoblastoma. Histopathology 65:631–641

Schnater JM, Aronson DC, Plaschkes J, Perilongo G, Brown J, Otte JB, Brugieres L et al (2002) Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. Cancer 94:1111–1120

Semeraro M, Branchereau S, Maibach R, Zsiros J, Casanova M, Brock P, Domerg C et al (2013) Relapses in hepatoblastoma patients: clinical characteristics and outcome – experience of the International Childhood Liver Tumour Strategy Group (SIOPEL). Eur J Cancer 49:915–922

Seo T, Ando H, Watanabe Y, Harada T, Ito F, Kaneko K, Horibe K, Sugito T, Ito T (1998) Treatment of hepatoblastoma: less extensive hepatectomy after effective preoperative chemotherapy with cisplatin and adriamycin. Surgery 123:407–414

Stiller CA, Pritchard J, Steliarova-Foucher E (2006) Liver cancer in European children: incidence and survival, 1978–1997. Report from the Automated Childhood Cancer Information System project. Eur J Cancer 42:2115–2123

Trobaugh-Lotrario AD, Chaiyachati BH, Meyers RL, Häberle B, Tomlinson GE, Katzenstein HM et al (2013) Outcomes for patients with congenital hepatoblastoma. Pediatr Blood Cancer 60:1817–1825

Tsai HW, Tsai HH, Kuo FY, Chang KC (2009) Computerized analysis of morphology and proliferative activity differentiated hepatoblastoma from paediatric hepatocellular carcinoma. Histopathology 54:328–336

Tsukada M, Wakai T, Matsuda Y, Korita PV, Shirai Y, Ajioka Y, Hatakeyama K, Kubota M (2009) Loss of carcinoembryonic antigen-related cell adhesion molecule 1 expression predicts metachronous pulmonary metastasis and poor survival in patients with hepatoblastoma. J Pediatr Surg 44:1522–1528

Venkatramani R, Wang L, Malvar J, Dias D, Sposto R, Malogolowkin MH, Mascarenhas L (2012) Tumor necrosis predicts survival following neo-adjuvant chemotherapy for hepatoblastoma. Pediatr Blood Cancer 59:493–498

Von Schweinitz D, Wischmeyer P, leuschner I et al (1994) Clinicopathological criteria with prognostic relevance in hepatoblastoma. Eur J Cancer 30A:1052–1058

Von Schweinitz D, Hecker H, Harms D et al (1995) Complete resection before development of drug resistance is essential for survival from advanced hepatoblastoma. A report from the German Cooperative Pediatric Liver tumour Study HB-89. J Pediatr Surg 30:845–852

Wang JN, Chen JS, Chuang HY, Yang YJ, Chang KC, Wu JM (2002) Invasion of the cardiovascular system in childhood malignant hepatic tumors. J Pediatr Hematol Oncol 24:436–439

Zsiros J, Maibach R, Shafford E, Brugières L, Brock P, Czauderna P, Roebuck D, Childs M et al (2010) Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol 28:2584–2590

Zsiros J, Brugières L, Brock P, Roebuck D, Maibach R, Childs M, Morland B, Casanova M et al (2012) Efficacy of irinotecan single drug treatment in children with refractory or recurrent hepatoblastoma – a phase II trial of the childhood liver tumour strategy group (SIOPEL). Eur J Cancer 48:3456–3464

Zsiros J, Brugieres L, Brock P, Roebuck D, Maibach R, Zimmermann A, Childs M et al (2013) Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): a prospective, single-arm, feasibility study. Lancet Oncol 14:834–842

Hepatoblastoma Family of Tumors: Risk Factors and Pathogenic Pathways

22

Contents

Abstract

Hepatoblastoma (HB) is associated with several distinct risk factors, etiologies, and pathogenic pathways. A wide array of mainly congenital conditions is associated with HB, and part of these disorders are now classified as HB risk factors, including low and very low birth weight and Beckwith-Wiedemann syndrome. Low birth weight, and in particular a birth weight lower than 1,500 g, confers a disproportionate risk of HB. The pathogenesis of HB in low and very low birth weight is not yet known. HB shows recurrent patterns of chromosomal aberrations which are involved in carcinogenesis. Among molecular abnormalities involved in HB, deregulation of the Wnt/beta-catenin signaling pathway plays a central role. Somatic mutations in the beta-catenin gene are critically involved in the pathogenesis of sporadic HB. Other components of this important pathway may be altered in HB, including Axins and the adenomatous polyposis coli/APC protein. There is increasing evidence that deregulation of microRNAs and epigenetic mechanisms are effectors in HB pathogenesis.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_22

Risk Factors and Associations of Hepatoblastomas

A wide array of mainly congenital conditions can be associated with hepatoblastoma (Table 1), and some of these are regarded as risk factors for this malignancy. Part of the conditions involve genes directly involved in cancerogenic pathways, while others increase the risk of neoplastic transformation through indirect pathways, such as increased regeneration of target cells or induction of cell injury, or DNA damage. An important risk factor for hepatoblastoma is low birth weight, discussed in a separate paragraph following the Table.

Table 1 Risk factors and associations for hepatoblastoma (review: Buckley et al. 1989)

Low and very low birth weight	See below
Beckwith-Wiedemann syndrome	See below
Anomalies of Wnt/beta-catenin pathway	See below
Adenomatous polyposis coli	See below
Neurofibromatosis I	Uçar et al. (2005)
Aicardi syndrome	Tanaka et al. (1985) and Kamien and Gabbett (2009)
Glomerulocystic disease	Bhaskar et al. (1990), Greer et al. (1998), and Abdul-Rahman et al. (2009)
Polycystic renal disease	Kummerfeld et al. (2010)
Hypoplastic kidneys	Chan et al. (2014)
Genitourological abnormalities	Venkatramani et al. (2014)
PFIC	Richter et al. (2005)
Biliary atresia	Tatekawa et al. (2001)
Simpson-Golabi-Behmel syndrome	Buonuomo et al. (2005), Mateos et al. (2013), and Kosaki et al. (2014)
Fragile X syndrome	Wirojanan et al. (2008)
Glycogenosis type 1	Ito et al. (1987)
Multiple OXPHOS deficiency	Cosson et al. (2008)
Tyrosinemia type 1	Nobili et al. (2010)
Noonan syndrome	Yoshida et al. (2008)
Goldenhar syndrome	Corona-Rivera et al. (2006)
Sotos syndrome	Kato et al. (2009)
Fanconi anemia (FANCD1 mutation)	Kopic et al. (2011)
Ataxia telangiectasia	Cecinati et al. (2012)
Cardio-facio-cutaneous syndrome	Al-Rahawan et al. (2007)
Dandy-Walker malformation	Kisato et al. (2002)
Type 2 Abernathy malformation	Loomba et al. (2012)
Congenital absence of portal vein	Kawano et al. (2007) and Mistinova et al. (2010)
Prune belly syndrome	Becknell et al. (2011)
Trisomy 18	Mamlok et al. (1989), Bove et al. (1996), Kitanovski et al. (2009), and Tan et al. (2014)
Fetal alcohol syndrome	Khan et al. (1979)
Familial factors (familial HB)	See below

Hepatoblastoma and Low Birth Weight

Low birth weight (LBW; 1,500–2,500 g) and in particular very low birth weight (VLBW; <1,500 g) is associated with a disproportionate risk of hepatoblastoma. LBW infants amount to approximately 7 % of live births and VLBW infants to about 2 % in Europe and USA. Hepatoblastoma in infants of very low birth weight has increased in several countries.

Selected References Ikeda et al. 1997, 1998; Ross 1997; Feusner et al. 1998; Ribons and Slovis 1998; Tanimura et al. 1998; Maruyama et al. 1999, 2000; Tsuchida et al. 1999; Feusner and Plaschkes 2002; Jaing et al. 2002; Kisato et al. 2002; Oue et al. 2003; Kapfer et al. 2004; Latini et al. 2004; Reynolds et al. 2004; Spector et al. 2004, 2008, 2009; Ansell et al. 2005; McLaughlin et al. 2006; Slovis and Roebuck 2006; Pu et al. 2009; Heck et al. 2013; Turcotte et al. 2014.

In an investigation based on data of the Japan Children's Cancer Registry (543 children with hepatoblastomas), the relative risks of hepatoblastoma among children with birth weights of <1,000, 1,000–1,499, 1,500–1,999,

and 2,000–2,499 g were 15.64, 2.53, 2.71, and 1.21, respectively (Tanimura et al. 1998). In a UK national population-based case-control study, 3 of 24 children with hepatoblastoma weighed <1,500 g at birth, 2 of whom weighed <1,000 g (Ansell et al. 2005). Based on 58 hepatoblastoma cases diagnosed between 1985 and 2001 (New York State Cancer Registry), it was found that a birth weight less than 1,000 g was associated with a strongly increased risk of hepatoblastoma, with a relative risk of 56.9 (McLaughlin et al. 2006). In the largest case-control study, the odds ratio of hepatoblastoma in VLBW infants was 51 times higher than in those with normal birth weight (Reynolds et al. 2004). Overall, 20–40 % of hepatoblastoma patients were premature at birth, and it is estimated that at least 8 % were VLBW infants (review: Slovis and Roebuck 2006). In general, the increasing incidence of hepatoblastoma in children less than 4 years of age over the last 25 years corresponds roughly to the increased survival rate of infants with LWB and VLBW (Spector et al. 2004; Slovis and Roebuck 2006). In a case-control study comparing 12 hepatoblastoma cases and 75 birth weight-matched controls, it turned out that the gestational age of the hepatoblastoma cases tended to be lower than that of the controls and that all hepatoblastoma patients received oxygen therapy which had a longer duration than that of controls (Maruyama et al. 2000). One study showed that hepatoblastomas occurring in children with very low birth weight tend to be unfavorable, with a significant correlation between the gestational age and tumor stage (Ikeda et al. 1998). The pathogenesis of hepatoblastoma development in very low birth weight is not known. Tumors other than hepatoblastoma are also more common in very low birth weight infants, such as retinoblastoma and gliomas other than astrocytomas and ependymomas (Spector et al. 2009). The presence of erythropoietin receptor in some of the hepatoblastomas has been suggested to play a role (Trobaugh-Lotrario et al. 2007).

Pathogenic Pathways of Hepatoblastomas and Related Tumors

Cytogenetic Features

Karyotyping of hepatoblastomas has shown recurrent patterns of chromosomal aberrations. The most common alterations consist in trisomies, which may occur in conjunction with other structural anomalies and/or double-minute chromosomes.

Selected References Mascarello et al. 1990; Bardi et al. 1991; Fletcher et al. 1991; Swarts et al. 1996; Nagata et al. 1999, 2005; Ma et al. 2000; Parada et al. 2000; Yeh et al. 2000; Stejskalova et al. 2009; Terada et al. 2009; reviews: Tomlinson 2012; Tomlinson and Kappler 2012.

The most important recurring events include chromosome trisomies, unbalanced translocations with a breakpoint on the proximal short arm of chromosome 1, and reciprocal chromosomal arm 4 (Tomlinson 2012). Trisomies mainly involve chromosomes 2, 8, and 10. Gains in chromosomes 1q, 2 (or 2q), 8, 17q, and 20 and losses in chromosomes 4q and 11q were frequently identified (Steenman et al. 1999), and high-grade amplifications were detected at 7q34, 14q11.2, and 11q22.2 (Suzuki et al. 2008). Gains on chromosomes 1q and 2 have been recognized as a hallmark DNA copy number change in hepatoblastoma, with 2q24 as a critical chromosomal band. The rearrangement of 1q is usually in pericentromeric heterochromatin (Surace et al. 2002). In one study of 10 cases, trisomy 20 was the most commonly detected abnormality, followed by trisomies 2 and 8 (Surace et al. 2002). Furthermore, gains of 8q and 20 are associated with poor outcome (Weber et al. 2000). Hepatoblastoma can develop in trisomy 18 (Bove et al. 1996) and even multiple hepatoblastomas have been detected in a patient with trisomy 18 (Teraguchi et al. 1997). Rare events are translocations. Four cases of

hepatoblastoma with a derivative chromosome 4 from an unbalanced translocation between the long arms of chromosomes 1 and 4 were reported (Schneider et al. 1997). Translocation t(22;22)(q11;q13) was detected in small cell undifferentiated hepatoblastoma (Gunawan et al. 2002). In a fetal-type hepatoblastoma, del(3)(q11.2q13.2) was detected (Sandoval et al. 2002). Partial maternal isodisomy 7q was found in a 30-month-old girl with myelodysplasia and hepatoblastoma (Neas et al. 2006). Hepatoblastoma was found in an infant with paternal disomy 14 (Horii et al. 2012). Comparative genomic hybridization analysis revealed a high frequency of X-chromosome gains (Terracciano et al. 2003). In part of the cases, gains or losses of chromosomal parts have been allocated to distinct genes altered in hepatoblastoma. Gains immediately telomeric to the deleted locus del14q12 are associated with overexpression of FOXG1, suggested to contribute to the maintenance of an undifferentiated state in hepatoblastomas (Adesina et al. 2007).

DNA Ploidy

In early investigations, no correlation was found between DNA ploidy and the histologic type, although aneuploidy was detected in a significant proportion of cases (Conran et al. 1992). Today we know that hepatoblastomas reveal an abnormal nuclear DNA content which differs among the various histologic subtypes. Fetal-type cells are, like normal hepatocytes, diploid, while embryonal-type cells and anaplastic cells are aneuploidy.

Selected References Hata et al. 1991; Orozco-Florian et al. 1991; Conran et al. 1992; Schmidt et al. 1993; Kröber et al. 1995; Rugge et al. 1998; Chopra et al. 2010.

An investigation on 29 hepatoblastomas revealed a diploid phenotype in 79.9 % and an aneuploidy phenotype in 20.7 %. Patients with diploidy of their tumors were younger than the aneuploidy group and had a better prognosis, while aneuploidy tumors tended to occur in higher stages and had a worse prognosis (Schmidt et al. 1993). In one study, 8 out of 23 hepatoblastomas were aneuploid, and DNA aneuploidy was strongly associated with embryonal histological areas. DNA aneuploidy tumors showed a trend toward a more aggressive clinical behavior (Zerbini et al. 1998). In another study on 34 cases of hepatoblastoma, there was a significant association between histologic type, DNA content, and the percentage of cells in the S phase of the cell division cycle. Also this study revealed that aneuploidy and the highest proportions of S phase cells were significantly associated with embryonal-type histology (Rugge et al. 1998).

Role of Stem Cells

In the light of an apparent recapitulation of hepatogenic pathways in hepatoblastomas, and the finding of multilineage differentiation in mixed tumors, specifically in teratoid hepatoblastomas, a role of tumor stem/progenitor cells has been proposed (Ruck et al. 1995, 1996, 1997; Fiegel et al. 2004; Ward et al. 2010). Immunohistochemical features of oval cells with a biliary epithelium-type cytokeratin profile have been found in some hepatoblastomas (Ruck et al. 1997). In fetal-type hepatoblastoma, only few such cells were seen, and a moderate amount in embryonal-type tumors, while almost all cells in SCUD hepatoblastoma were of this cell type (Ruck et al. 1996). Stemlike cells resembling oval cells have been detected in atypical ducts of human hepatoblastomas. Furthermore, staining for stem cell marker Thy1 identified positive periductal clusters of cells resembling ganglionic groups, also expressing N-CAM/CD56 (Fiegel et al. 2004). Indirect evidence for a role of progenitor cells in hepatoblastoma is the finding of an overexpression of the hepatic progenitor cell marker, high mobility group AT-hook 2, and architectural nuclear factor (Lee et al. 2013). On the other hand, there are also findings that do not support the view that stem cells are involved in hepatoblastoma tumorigenesis. Small cells

occurring in hepatoblastoma lack an oval cell phenotype (Badve et al. 2003).

Familial Hepatoblastoma

Similar to hepatocellular carcinoma, there are rare reports on familial occurrence of hepatoblastoma (Fraumeni et al. 1969; Napoli and Campbell 1977; Surendran et al. 1989; Riikonen et al. 1990; de Chadarevian et al. 2002). In the first published report, two sisters of four sibs developed hepatoblastoma during infancy (Fraumeni et al. 1969).

Hepatoblastoma and Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS; OMIM 130650; originally termed EMG, standing for **e**xomphalos/omphalocele, **m**acroglossia, and **g**igantism/macrosomia; Beckwith 1963; Wiedemann 1964) is a genetically heterogeneous overgrowth disorder. It represents the most common overgrowth disease, with a reported incidence of 1 in 13,700 live births (reviews: Cohen 2005; Smith et al. 2007; Choufani et al. 2010). Similar to two other overgrowth syndromes, i.e., hemihypertrophy/hemihyperplasia and Sotos syndrome, BWS is associated with a distinct spectrum of tumors. The tumor frequency in BWS is 7.5 %, higher than in hemihypertrophy (5.9 %) and Sotos syndrome (2.2 %). The malignant neoplasm developing in BWS comprises Wilms' tumor and other renal blastomatous tumors, adrenocortical carcinoma, pancreatoblastoma, glioblastoma, neuroblastoma, sarcomas, and lymphomas. In addition, BWS is complicated by the development of hepatoblastoma (Hamada et al. 2003; The and Ong 2007). Several benign tumors also occur, such as adrenal adenoma, fibrous hamartomas, cardiac hamartoma, myxoma, ganglioneuroma, hemangiomas, and hamartomas of the bladder (DeBaun and Tucker 1998). Congenital or infantile hepatoblastomas have been observed in BWS (Molina et al. 1981; Haas et al. 1986; Little et al. 1988; Orozco-Florian et al. 1991; Wilfong et al. 1992; Martelli et al. 1993; Tsai et al. 1996; Worth et al. 1999; Fukuzawa et al. 2003; Hamada et al. 2003; Kobrinsky et al. 2005; Mussa et al. 2011). Serial serum AFP screening can identify early hepatoblastoma in BWS (Clericuzio et al. 2003). Hepatoblastomas have also been found in isolated hemihypertrophy /hemihyperplasia, a disorder which may represent one end of the clinical spectrum of BWS (Hoyme et al. 1998; Dempsey-Robertson et al. 2012).

Around 85 % of cases with BWS are sporadic, and the remaining have an autosomal-dominant inheritance with preferential maternal transmission. BWS is caused by alterations of genes imprinted at 11p15, while chromosomal anomalies of 11p15 occur only in 1–2 % of BWS patients (mainly sporadic or inherited translocation of inversion of 11p15). About 20 % of BWS cases have uniparental disomy of chromosome 11, and such cases seem to result from mitotic recombination occurring in early embryogenesis. Among 52 cases with this disorder, all cases demonstrated mosaic paternal isodisomy, and IGF2 and H19 were included in the segment of uniparental disomy in all cases (Cooper et al. 2007). Apart from BWS, other imprinting disorders comprise Prader-Willi syndrome, Angelman syndrome, transient neonatal diabetes mellitus, uniparental disomy (14) syndromes (MatUPD14, PatUPD14), pseudohypoparathyroidism 1b, maternal hypomethylation syndrome, and Silver-Russell syndrome (reviews: Temple 2007; Amor and Halliday 2008; Eggermann 2009). Loss of maternal alleles on chromosome arm 11p, a region of imprinting in BWS, was found in hepatoblastoma (Albrecht et al. 1994). Imprinting takes place in a parent-of-origin fashion, expression being dependent on the silencing (imprinting) of maternal or paternal genes. The 11p15 region contains two clusters of imprinted genes in BWS, and the imprinting centers in these two clustered domains have differentially methylated regions. The first gene cluster is telomeric at 11p15 and contains two important genes, insulin-like growth factor-II (IGF2) and H19. The H19 gene encodes a non-coding mRNA that is strongly expressed during embryogenesis and which is maternally

expressed, and the neighboring IGF2 gene is transcribed from the paternal allele. These two genes are coexpressed in endoderm- and mesoderm-derived tissues during ontogenesis (review: Gabory et al. 2006). H19 seems to be a transregulator in the fine-tuning of the imprinted gene network (Gabory et al. 2009). The second cluster is centromeric at 11p15 and contains several genes, three of them being important for the pathogenesis of BWS (KCNQ1, KCNQ1OT1, and CDKN1C). Alterations in these different gene clusters are the reason why BWS represents a spectrum of disorders (Cooper et al. 2005). In regard to tumor development, the type of neoplasms observed in BWS cases with telomeric defects are different from those with defects limited to the centromeric domain (Weksberg et al. 2001).

IGF2 is maternally silenced (imprinted) and therefore paternally expressed. Failure of differential silencing or imprinting results in biallelic expression of IGF2, seen in part of BWS patients and in tumors that develop in them (Li et al. 1995; Rainier et al. 1995; Yun et al. 1998; review: Cohen 2005). In contrast, H19 is paternally silenced and thus maternally expressed. Approximately a fifth of BWS patients reveal paternal uniparental disomy with two paternally derived copies of 11p15 and no maternal copies, probably caused by postzygotic somatic recombination, but most of these patients in fact show somatic mosaicism. It is suggested that this explains the patients with isolated hemihypertrophy/hemihyperplasia who develop a BWS spectrum of tumors (review: Cohen 2005). Loss of imprinting at IGF2, in association with H19 silencing, has been described in hepatoblastoma (Rainier et al. 1995) and in a subgroup of BWS patients who have an increased risk for Wilms tumor. In one family showing this constellation, paternal inheritance of a cis-duplication at 11p15.5 spanning the BWS IC1 region and including H19, IGF2, INS, and TH was found, implicating IGF2 in overgrowth and Wilms tumor tumorigenesis (Algar et al. 2007). In another child without BWS, who later developed hepatoblastoma, focal congenital hyperinsulinism resulting from a paternally inherited recessively acting mutation of ABCC8 and pancreatic paternal uniparental disomy for 11p15 was found (Calton et al. 2013). There is strong evidence for an association of the overgrowth syndrome, Beckwith-Wiedemann syndrome, and the development of neoplasia, including hepatoblastoma (review: Tan and Amor 2006). Loss of IGF2 imprinting correlates with hypermethylation of the H19 differentially methylated region in hepatoblastoma (Honda et al. 2008). The expression of the H19 gene was inactivated by maternal allelic loss or hypermethylation in seven out of eight "sporadic" hepatoblastomas, and loss of imprinting of the IGF2 gene was linked to inactivation of the H19 gene in part of the tumors (Fukuzawa et al. 1999). Hepatoblastomas show monoallelic expression of H19 (Ross et al. 2000). In hepatoblastomas associated with chromosome 11p15.5, uniparental isodisomy beta-catenin mutation and/or nuclear beta-catenin immunoreactivity in tumor cells was found, but no reactivity for beta-catenin was detected in the tissue with hepatomegaly which contained uniparental disomy cells, suggesting that Wnt signal activation occurs later in tumorigenesis in BWS (Fukuzawa et al. 2003). The 11p15.5 chromosomal region also contains TSSC5 (tumor-suppressing subchromosomal transferable fragment cDNA; also known as ORCTL2/IMPT1/BWR1A/SLC22A1L). This gene encodes an efflux transporter-like protein with ten transmembrane domains. The expression of TSSC5 is regulated through paternal imprinting, and mutations of TSSC5 have been found in certain tumors. TSSC5 is regulated via an ubiquitin ligase, RING105, that can function in concert with the ubiquitin-conjugating enzyme UbcH6 (Yamada and Gorbsky 2006).

What are the functions of IGF2? The IGF axis is disturbed in hepatoblastomas. IGF2 stimulates hepatoblastoma cell proliferation in vitro and is expressed in an autocrine manner in hepatoblastomas (Akmal et al. 1995). These cells express the IGFI receptor, and inhibition of this receptor with picropodophyllin abolishes the proliferative response of the cells (Tomizawa and Saisho 2006). IGF2 induces rapid beta-catenin relocation to the nucleus during epithelial-

mesenchymal transition (Morali et al. 2001). The expression of the genes of ILGF-binding protein/ILGF-binding protein-related proteins is altered in hepatoblastoma (von Horn et al. 2001, 2002). Reactivation of the known competitor of the IGF axis, insulin-like growth factor-binding protein 3/IGFBP3 decreases the aggressive properties of hepatoblastoma cells (Regel et al. 2012).

IGF2 and the IGF2 Regulator PLAG1

Aggressive biology and poor outcome in hepatoblastoma are associated with amplification of chromosome 8q. A critical region in this area, 8q11.2-q13, contains the gene of the oncogene PLAG1, which is highly expressed in part of hepatoblastomas (Zatkova et al. 2004). PLAG1 (pleomorphic adenoma gene-like 1) is the main translocation target in pleomorphic adenomas of the salivary glands. Together with two other members, the tumor suppressor candidate PLAG-like1 (also called ZAC1 or LOT1, lost on transformation 1) and PLAG2, PLAG1 forms a subfamily of zinc-finger proteins involved in cell proliferation, tissue-specific gene regulation, and embryonic development. This C(2)H(2) family is characterized by transcription activation through binding to the bipartite consensus sequence GRGGC(N)(6–8)GGG. The three members share high homology with each other, particularly in their zinc-finger amino-terminal region, and exert different DNA binding capacities (Hensen et al. 2002). The proteins however differ in regard to their functional properties. PLAG1 is a proto-oncogene located on chromosome 8q12; is rearranged in several tumors, but mainly in pleomorphic salivary gland adenomas, lipoblastomas, hepatoblastoma, and AML; and is a transcriptional activator of IGF2. The LOT1 gene, assigned to human chromosome 6q24-25, is maternally imprinted, is regulated by epigenetic mechanisms, and encodes a growth suppressor protein that is altered in several tumors (via LOH) and in transient neonatal diabetes mellitus/TNDM (reviews: Abdollahi 2007; Van Dyck et al. 2007). PLAG1 is developmentally regulated and its activity is suppressed by SUMOylation via the small ubiquitin-related modifier (SUMO) modification pathway (Van Dyck et al. 2004). PLAG1 SUMOylation causes PLAG1-induced IGF2 expression, and it transactivates transcription from the embryonic IGF2 promoter P3 in hepatoblastomas (Zatkova et al. 2004). SUMOylation and acetylation play opposite roles in the transactivation of both PLAG1 and PLAG2 (Zheng and Yang 2005). The protein Tip6o associates with PLAG2 through its zinc-finger domain, acetylates PLAG2, and thus acts as promoter-specific coactivator of PLAG2 (Ning et al. 2008). PLAG1 is regulated by miRNAs 181a, 181b, 107, 424, and 492, and these miRNAs are epigenetically silenced in chronic lymphatic leukemia (CLL), causing PLAG1 overexpression in CLL cells (Pallasch et al. 2009; Patz et al. 2010). miRNA 492 has been shown to be processed from the keratin 19 gene and is upregulated in metastatic hepatoblastoma, suggesting that this microRNA and its targets, in particular PLAG1, may play a role in metastatic spread of this tumor (von Frowein et al. 2011). Expression of the PLAG2 target gene IGF2 is markedly diminished by inactivation of PC2 via silencing through PC2 siRNA (Wezensyk et al. 2010). PC2 (positive cofactor 2), a component of the ARC/Mediator complex, cooperates with PLAG2 and Pu.1 to enhance the activity of the known PLAG2 target promoter, NCF2. The Mediator complex is a polyprotein structure that forms the bridge between transcriptional activators and RNA polymerase II and is required for the regulated transcription of nearly all RNA polymerase II-dependent genes. It mainly consists of proteins of the MED protein family, including the key component MED1 (PBP or TRAP220), which interacts with nuclear receptors such as estrogen receptor and PPARg and other transcriptional activators, and is required for the generation of hepatic steatosis (Bai et al. 2011). MED1 directly interacts with the protein arginine and glutamate-rich 1 (ARGLU1), an interaction that is crucial for the regulation of estrogen receptor-mediated gene transcription (Zhang et al. 2011). Also MED28 (magicin), an interactor of merlin and playing a role in neurofibromatosis, is a Mediator complex component. The Mediator complex

also associates directly with heterochromatin at telomeres and influences the exact boundary between active and inactive chromatin, whereby the Mediator components Med5 and Med7 play significant roles in the interaction with regions near subtelomeric X-elements and in the balance between Sir2 and Sas2 proteins. By this mechanism, Mediator influences telomeric silencing and cellular lifespan (Zhu et al. 2011). The PLAG2 target NCF2 (neutrophil cytosolic factor 2) is the 67 kDa cytosolic subunit of the multiprotein NADPH oxidase complex found in neutrophils. NCF2 is mutated in chronic granulomatous disease (Köker 2010).

Growth Regulation and Deregulation in HB: Significance of the Wnt/Beta-Catenin Signaling Pathway

The Wnt/beta-catenin signaling pathway plays an important role in the biology of hepatoblastomas and other liver cell tumors (reviews: Laurent-Puig and Zucman-Rossi 2006; Jin et al. 2008; Armengol et al. 2011). The Wnt/beta-catenin signaling complex is a multiprotein signaling pathway, degradation of cytosolic beta-catenin by the APC/AXIN1 destruction complex being the key regulated step of this pathway. The signaling pathways contain, in addition to beta-catenin, Axins and the APC protein and several other regulatory proteins, including Amer1 (see below), glycogen synthase kinase, and kindlin 2, a focal adhesion protein which forms a transcriptional complex with beta-catenin and TCF4 to enhance Wnt signaling. Kindlin 2 strengthens the occupancy of beta-catenin on the Wnt target gene AXIN2 (Yu et al. 2012). During normal liver morphogenesis, beta-catenin is expressed in a stage-specific manner, with a peak of expression during embryogenesis and a drop in the prenatal period (Micsenyi et al. 2004). However, a complex interplay between Wnt/beta-catenin signaling and maintenance of a regulated cell cycle still works in the adult liver (Gougelet and Colnot 2012). In the normal liver, beta-catenin expression is centrally involved in liver ontogenesis, development of hepatoblasts, hepatocyte proliferation, and regeneration. Beta-catenin deletion in hepatoblasts disrupts hepatic morphogenesis (Tan et al. 2008). Hepatoblast growth and differentiation require calpain-mediated cleavage of beta-catenin, and the presence of the beta-catenin N terminus correlates with the differentiation status of hepatoblasts (Lade et al. 2012). Stabilized beta-catenin enhances hepatocyte proliferation, suppresses TNF-alpha/ActD-induced apoptosis, and causes weak anchorage-independent cell growth (Shang et al. 2004). In a murine model, liver-specific loss of beta-catenin resulted in delayed hepatocyte proliferation after partial hepatectomy (Sekine et al. 2007).

Somatic mutations of beta-catenin play an important role in the pathogenesis of sporadic hepatoblastoma. Mutations of the beta-catenin CTNNB1 gene, prodemonantly in the degradation box, have been observed in HBs.

Selected References Bläker et al. 1999; Jeng et al. 2000; Park et al. 2001; Takayasu et al. 2001; Udatsu et al. 2001; Taniguchi et al. 2002; Cairo et al. 2008; Curia et al. 2008; Takigawa and Brown 2008; Lopez-Terrada et al. 2009; Cairo et al. 2012; Jia et al. 2014.

Hepatoblastomas often show a mutated degradation targeting box of the beta-catenin genes, albeit with variable reported frequencies (48 %, Koch et al. 1999; 67 %, Wei et al. 2000; 19 %, Curia et al. 2008; reviews: Buendia 2002; Ranganathan et al. 2005; Armengol et al. 2011). In a recent study of 32 hepatoblastoma patients, 87 % carried CTNNB1 mutations within the ubiquitination domain (Lopez-Terrada et al. 2009). Activation of beta-catenin in hepatoblastomas is, however, not exclusively due to mutations inhibiting its degradation but also to HGF/c-Met-induced beta-catenin activation (Purcell et al. 2011). There is a relationship between abnormalities of Wnt/beta-catenin signaling and the histologic subtype of hepatoblastomas carrying the alterations. Large deletion of the CTNNB1 gene was seen only in pure fetal cases, also characterized by overexpression of cyclin D1 and GLUL/glutamine synthase, while small cell undifferentiated

(SCUD) hepatoblastoma did not express GLUL (Lopez-Terrada et al. 2009). The relationship between beta-catenin gene mutations and beta-catenin protein accumulation varies markedly. Whereas in one study, the rate of beta-catenin gene mutation was 19 %, and beta-catenin protein accumulation was found in 67 % of cases (Curia et al. 2008). In cases with beta-catenin accumulation, the protein is typically localized to the nuclei (Yamaoka et al. 2006). The nuclear localization of beta-catenin is controlled by Rac1 activation, whereby the role of Rac1 depends on phosphorylation of beta-catenin at Ser191 and Ser605, which is mediated by JNK2 kinase (Wu et al. 2008). Among Wnt signal genes downstream of beta-catenin, E-cadherin was expressed in all hepatoblastomas, while cyclin D1 expression was significantly detected in tumors with an advanced stage of disease (Yamaoka et al. 2006). Similarly, deletions and mutations of the beta-catenin gene were associated with overexpression of cyclin D1 and fibronectin and with poorly differentiated histology in another investigation (Takayasu et al. 2001). Mutations of the beta-catenin gene are associated with overexpression of cyclin D1 and fibronectin and poorly differentiated histology (Takayasu et al. 2001). In hepatoblastomas and hepatocellular carcinomas with beta-catenin gene mutations, overexpression of regenerating islet-derived 1 alpha (REG1A) and 3 alpha (REG3A) genes was found. Hepatoblastomas show an overexpression of the Wnt antagonists Nkd-1 and beta-TrCP, supporting an activation of the Wnt signaling pathway in these neoplasms (Koch et al. 2005).

What is the evidence that alterations in the beta-catenin pathway affect growth of hepatoblastomas? Nuclear translocation of beta-catenin during mesenchymal stem cell differentiation into hepatocytes is associated with a tumoral phenotype (Herencia et al. 2012). By use of hepatoblastoma and HCC cell lines, it has been found that RNA interference against beta-catenin inhibits the proliferation of these tumor cells (Sangkhathat et al. 2006). One effect of a deranged Wnt/beta-catenin signaling might involve a pathway that promotes the emergence of maintenance of a progenitor cell phenotype in liver cell tumors. In HCC, nuclear beta-catenin accumulation induced an early liver progenitor phenotype and altered biology of disease in the sense of tumor recurrence promotion (Zulehner et al. 2010).

Factors Associated with Beta-Catenin in the Wnt Signaling Pathway

AXIN1, in cooperation with APC protein, is the chief destruction complex for the degradation of cytosolic beta-catenin (Stamos and Weis 2013). This destruction complex consists of APC, Axin, CK1a, and glycogen synthase kinase 3 beta, to foster phosphorylation of beta-catenin by earmarking it for Lys-48-linked polyubiquitination and proteasomal degradation. In this reaction, APC is conjugated with Lys-63-linked ubiquitin chains by the action of HectD1, an E3 ubiquitin ligase that modifies APC with Lys-63 polyubiquitin (Tran et al. 2013). This function of Axin is counteracted through relocalization of the Axin protein to the Wnt receptor complex. Beta-catenin is not only phosphorylated inside the AXIN1 complex but also ubiquitinylated and degraded via the proteasome, all within an intact AXIN1 complex that is not disassembled (Li et al. 2012a). AXIN1 and AXIN2 turnover is regulated by its poly-ADP-ribosylation catalyzed by tankyrase, requiring a direct interaction of AXIN1 with tankyrase. Poly-ADP-ribosylation of Axins destabilizes Axins and promotes signaling (Morrone et al. 2012). In order to maintain low steady-state levels of Axin proteins, a positive regulator of Wnt signaling, the RNF146 RING-type ubiquitin E3 ligase, destabilizes tankyrases 1 and 2 and, in a reciprocal manner, tankyrase activity reduces RNF146 protein levels (Callow et al. 2011). Based on the position of Axin proteins in the Wnt signal cascade, it can be expected that the deficient AXIN1 function causes a similar effect as loss-of-function mutations of the beta-catenin gene, from what has been observed in hepatoblastoma (Miao et al. 2003). Conditional disruption of AXIN1 leads to liver tumorigenesis in mice (Feng et al. 2012). AXIN2 (conductin) is a direct target gene of Wnt signaling in

hepatoblastomas. In part of hepatoblastomas, mutations in the AXIN2 have been observed, representing an alternative mechanism leading to activation of Wnt signaling in these neoplasms (Koch et al. 2004).

The *APC protein* holds a strategical position in the Wnt/beta-catenin signaling pathway, in that it forms a complex with Axin to promote the entrance of beta-catenin into a proteasomal degradation pathway. The regulatory protein, Amer1/WTX, binds to APC and acts as an inhibitor of Wnt signaling by inducing beta-catenin degradation, in that it stabilizes Axin and counteracts Wnt-induced degradation of Axin, which requires membrane localization of Amer1 (Tanneberger et al. 2011). An association between familial adenomatous polyposis coli (FAP) and hepatoblastoma is well established.

Selected References Kingston et al. 1982, 1983; Garber et al. 1988; Phillips et al. 1989; Bernstein et al. 1992; Hughes and Michels 1992; Kurahashi et al. 1995; Giardiello et al. 1996; Oda et al. 1996; Cetta et al. 1997, 2003; Thomas et al. 2003; Aretz et al. 2006; Sanders and Furman 2006; Lazzareschi et al. 2009; Evers et al., 2012; Krawczuk-Rybak et al. 2012; Gupta et al. 2013; review: Moore et al. 2012.

The association is thought to relate to APC alterations, a protein making part of the Wnt/beta-catenin signaling pathway. The adenomatous polyposis coli (APC) gene encodes a protein having multiple domains, through which APC can bind to various proteins, including components of the Wnt pathway (beta-catenin and Axin). The incidence of FAP in hepatoblastoma patients is about 100 times that in the general population, but the reported incidence of APC germline mutations in children with sporadic hepatoblastoma varies considerably. In FAP families, APC gene mutation (in the 5′ end of the gene) was identified in all seven FAP kindreds in which an at-risk member developed hepatoblastoma, with male predominance (Giardiello et al. 1996). In a series of 93 patients with hepatoblastoma, 8 (8.6 %) reported family histories suggestive of FAP (Hirschman et al. 2005). In sporadic hepatoblastomas occurring in non-FAP families, LOH at the APC and/or MCC loci was observed in 57 % informative cases, and two cases showed double mutations (Oda et al. 1996). De Chadarevian and coworkers (2002) reported a FAP family in which one boy developed hepatoblastoma and his brother multiple adenomas and a well-differentiated hepatocellular carcinoma, but no APC gene mutation was found in this family. Rather, FAP occurred as a result of chromosomal rearrangement (inversion 5q21 to 5q31.3 9), involving the APC gene locus inherited from their father and grandfather. Hepatoblastoma has been observed in siblings sharing a gene mutation for FAP inherited from their father (Thomas et al. 2003). In one hepatoblastoma with a germline APC mutation studied among 13 sporadic infantile hepatic tumors, southern blot analysis at the APC locus revealed that the neoplasm had lost the opposite allele and was isodisomic at this locus, and RNA analysis indicated that the tumor contained only the small APC transcript, from which exon 4 was entirely absent (Kurahashi et al. 1995). In a multidisciplinary clinical study on 20 pediatric patients younger than age 10 years with FAP, none had developed hepatoblastoma during the observation period (Attard et al. 2008). Based on blood samples from 29 children (18 boys) with sporadic hepatoblastoma, no APC mutations were found (Harvey et al. 2008). No APC mutations were detected in a series of 21 paraffin-embedded hepatoblastoma cases (Curia et al. 2008). No hepatoblastoma was detected among 242 members from 57 unrelated FAP families having Singapore familial adenomatous polyposis, suggesting that Singapore FAP patients have some features distinct from Caucasian FAP (Cao et al. 2006). The findings accumulated so far raised the question whether children at risk for FAP should be screened for hepatoblastoma and children with hepatoblastoma for APC gene mutations. Among 1,166 German FAP families, seven unrelated cases of hepatoblastoma were identified, and in patients with apparently sporadic hepatoblastoma, germline mutations in the APC gene were identified in 10 % (Aretz et al. 2006). The relationship between APC protein alterations

and a second key component of the Wnt signaling pathway is complex. It has, e.g., been shown that hepatoblastoma from a FAP patient has nuclear beta-catenin accumulation in the absence of an APC gene mutation (Inukai et al. 2004). Hepatoblastoma has also been observed in the setting of Gardner syndrome (Krush et al. 1988). The human *Dickkopf-1* gene encodes a secreted protein acting as a potential inhibitor of the Wnt signaling pathway. Eighty one percent of hepatoblastomas revealed expression of Dickkopf-1, but none of normal pediatric or fetal liver tissues. It was suggested that overexpression of Dickkopf-1 in hepatoblastomas might be related to uncontrolled Wnt signaling and a negative feedback mechanism (Wirths et al. 2003).

Other Factors Potentially Involved in Growth and Progression of HB

Hepatocyte growth factor (HGF) was expressed in fibroblastoid mesenchymal cells of the tumor, while the receptor c-met was expressed by epithelial tumor cells (Von Schweinitz et al. 1998), suggesting a paracrine growth mechanism. Transcription factors and transcription co-activator CBP/P-300-interacting transactivator 1 (CITED1), a transcriptional coactivator, are expressed in embryonal and regenerating hepatocytes, but are undetectable in normal adult liver. In one study, CITED1 was abnormally expressed in 87.8 % of hepatoblastoma specimens, with a predominant expression in mixed embryonal/fetal tumors and less so in fetal tumors (Murphy et al. 2012). Transcription factor GATA-4, which is expressed in early fetal liver and is essential for hepatic organogenesis, is abundantly expressed in hepatoblastomas, but not in adult-type HCC (Soini et al. 2012). The homeobox transcription factor, Prox1, is required for normal hepatic ontogenesis and morphogenesis. Prox1 is expressed in early embryonic hepatoblasts and is still expressed in adult hepatocytes, but is absent from cholangiocytes (Dudas et al. 2004). It is expected that abnormal expression of Prox1 plays a role in hepatoblastoma biology.

Cyclin D1 is encoded by the CCND1 gene and is a major regulator of the cell cycle transition from G1 to S. Hepatoblastomas may show a CCND1 polymorphism (G to A) at codon 242, the boundary of exon 4 and intron 4, affecting the splicing such that exon 5 is not expressed in the A allele. This polymorphism is correlated with the age of onset of hepatoblastoma, in that the A/A genotype is associated with an earlier age of onset compared with the G/A or G/G genotype (Pakakasama et al. 2004). The p57(KIP2) gene is located to 11p15.5, is predominantly expressed from the maternal allele, and encodes a cyclin-dependent kinase inhibitor. LOH at the KIP2 locus occurred in 25 % of hepatoblastomas, but no gene mutations were found. KIP2 was upregulated in the majority of cases, associated with upregulation of IGF2 mRNA expression. All hepatoblastomas showed monoallelic KIP2 expression. Overexpression of KIP2 in hepatoblastomas with maternal loss of 11p15.5 suggests a reactivation of the paternal allele in these cases (Hartmann et al. 2000). The p16INK4A protein is involved in the regulation of the cell cycle. 66.6 % of methylation-positive hepatoblastomas showed a complete lack of p16 immunoreactivity. It has therefore been suggested that hypermethylation of p16 is a major mechanism of the transcriptional repression of p16 in hepatoblastomas (Shim et al. 2003). In hepatoblastomas, the genes CDKN2A (encoding p16) and CDKN2B 8 encoding p15) are not transcribed, while CDKN2C (encoding p18) was clearly detectable in hepatoblastoma tissue (Iolascon et al. 1998). The transcription factor, FOXG1, is implicated in the repression of TGF-beta-induced expression of p21cip1 and is overexpressed in hepatoblastoma (Adesina et al. 2007). In many aggressive neoplasms, Ki27/Kip1 shows a reduced expression. In hepatoblastomas it was shown that well-differentiated fetal-type tumors without mitotic activity were strongly p27 positive; embryonal-type tumor revealed a variable p27 expression pattern (low activity in highly proliferative areas), and SCD hepatoblastoma was negative (Brotto and Finegold 2002). The PI3K/AKT pathway is activated as a downstream signaling

pathway of multiple tyrosine kinases. An increased signaling activity of this pathway and activating mutations of PIK3CA, encoding a PIK3 catalytic subunit, have been detected in several childhood cancers. It has been shown that PIK3 signaling plays an essential role in growth control of hepatoblastomas (Hartmann et al. 2009). Overexpression of autophagy-associated genes, BECN1 and ATG5, in hepatoblastoma cells is associated with an increase of PIEK signaling, essential for cell survival (Chang et al. 2011).

The hedgehog signaling pathway, which plays a central role in stem cell biology, embryogenesis, and maintenance of tissue homeostasis, is altered in hepatoblastomas. Three hedgehog members, i.e., sonic hedgehog, Indian hedgehog, and desert hedgehog, bind to Patch1 or Patch2 receptors to release the smoothened signal transducer from patched-dependent suppression. Smoothened then activated STK36 serine/threonine kinase to stabilize glioma-associated oncogene homolog 1 (GLI1) members and to phosphorylate SUFI for nuclear accumulation of GLI1 (review: Katoh and Katoh 2006). Expression of hedgehog components showed an increase in hepatoblastoma compared with normal liver tissue (Li et al. 2010). In part of hepatoblastomas, the hedgehog target genes GLI1 and Patched 1 (PTCH1) are overexpressed, and the gene encoding the hedgehog interacting protein (HHIP) is transcriptionally silenced by CpG island promoter hypermethylation. Block of the hedgehog pathway inhibited hepatoblastoma growth (Eichenmüller et al. 2009). Immunochemistry revealed a strong nuclear expression of the downstream effector of the Hippo kinase pathway, Yes-associated protein (Yap). Yap overexpression was associated with marked induction of the three Yap target genes, glypican 3, CTGF, and survivin (Li et al. 2012b). The oncogene PLK1 was found to be expressed at very high levels in part of HB in comparison with normal liver, and this high expression was associated with a poorer outcome (Yamada et al. 2004). Well-differentiated hepatoblastoma cells showing low proliferative activity markedly express transforming growth factor-alpha (TGF-alpha), while proliferating embryonal cells reexhibit a low-level expression of TGF-alpha (Kiss et al. 1998). Expression of TGF-alpha has also been observed in hepatocellular carcinoma (Hsia et al. 1992; Schaff et al. 1998).

Deregulation of Apoptosis in Hepatoblastomas

In hepatoblastomas, the death receptor Fas and its ligand are coexpressed, and the tumors express the Fas-resistance pathway component FAP-1, whereas Bcl-2 is not detectable (Lee et al. 1999). As hepatoblastomas may overexpress p53 protein (mostly in the absence of p53 gene mutations), this feature may play a role in apoptosis of this tumor. Hepatoblastoma cells that primarily express p53 in the cytoplasm translocate p53 to the nucleus under oxidative stress, independent of the effects of the cytoplasmic p53 retention protein, Parc. This nuclear p53 translocation is associated with increased apoptosis (Yamamoto et al. 2007). Nuclear expression of p53 is essential for several functions of this protein. Parc protein, a Parkin-like ubiquitin ligase, is a cytoplasmic anchor protein that directly interacts with p53 in the cytoplasm to form a complex. In the absence of stress, inactivation of Parc induces nuclear translocation of endogenous p53 and activation of p53-dependent apoptosis (Nikolaev et al. 2003). p53 is a tumor suppressor protein that exerts antiproliferative and apoptotic effects in response to various forms of stress, such as oxidative stress, DNA damage, and abnormal proliferative signals. P53 is tightly regulated through posttranslational modifications. Endogenous p53 protein in the cytoplasm is bound to the anchor protein Parc, a Parkin-like ubiquitin ligase (Nikolaev et al. 2003). Abnormalities in the expression of the p53 oncogene in hepatoblastomas are found in the literature with markedly variable results. In four reports using immunohistochemistry (antibodies BP53-12, AB-6, and CM1), nuclear p53 protein reactivity was found in 14 % (Choi et al. 1993), 33 % (Ruck et al. 1994), 67 % (Kennedy et al. 1994), and 45 % (Zhang et al. 1998) of hepatoblastomas. Among

ten cases of hepatoblastoma, one case revealed overexpression of p53 protein, but direct DNA sequencing failed to show a p53 gene mutation (Chen et al. 1995). Direct sequencing revealed no p53 gene mutation among seven hepatoblastomas (Debuire et al. 1993). In a PCR study on 38 hepatoblastomas, TP53 mutations were found in an anaplastic hepatoblastoma cell line, but no aberration in the TP53 gene (exons 5–9) was found in tumor samples (Ohnishi et al. 1996). In the study of Kennedy and coworkers (1994; 67 % immunohistochemical reactivity), no p53 gene mutation was observed. By use of PCR-single-strand conformation polymorphism (PCR-SSCP), no p53 gene mutation was found in 11 hepatoblastomas (Kusafuka et al. 1997). In contrast, a p53 gene mutation (codon 249) was detected in one patient without exposure to aflatoxin B1 (Kar et al. 1993), and mutations were found by direct sequencing (exons 5–8) in 9 out of 10 hepatoblastomas (Oda et al. 1995), and were detected in 24 % of sporadic hepatoblastomas in a more recent investigation (Curia et al. 2008).

Factors Affecting Invasion, Spread, Metastasis, and Angiogenesis

Hepatoblastomas express adhesion molecules affecting interactions between tumor cells and extracellular matrix. Embryonal and SCUD-HB cells expressed CALLA and the hyaluronate receptor, CD44 (HCAM), while both fetal and embryonal areas stained irregularly positive for ICAM-1, the latter not being detectable in SCUD cells (von Schweinitz et al. 1996). Inhibitors of chymotrypsin-like seine proteases are known as serpins (**ser**ine **p**rotease **in**hibitors). Well-known examples in human pathobiology are antithrombin and the antitrypsins. Serpins undergo complex gene mutations giving rise to the serpinopathies, characterized by the formation of ordered polymers that are often retained within the rough endoplasmic reticulum of the cell of synthesis, a prominent example being the Z variant of alpha-1-antitrypsin deficiency (Irvin et al. 2011). In a study of 42 children with hepatoblastoma, SERPINB3 was positive at the transcriptional level in 79 % of cases. Immunohistochemically, SERPINB3 was mainly found in the embryonic, blastemal, small cell undifferentiated components of hepatoblastomas, but it was not detectable in normal hepatocytes. There was a significant correlation between SERINB3 expression and upregulation of Myc and PRETEXT tumor extension (Turato et al. 2012). Expression of VEGF in all malignant pediatric liver tumors was higher than that in adult HCC, but VEGF expression was higher in pediatric HCC than in hepatoblastomas (Sun et al. 2005).

Genomic and Epigenetic Features

Hepatocellular carcinomas (HCC) and hepatoblastomas have different patterns of gene expression. For example, insulin-like growth factor-II (IGF2), fibronectin, DLK1, TGF-beta1, MALAT1, and MIG6 are overexpressed in hepatoblastoma versus HCC (Luo et al. 2006). IGF2 and H19 are affected by copy-neutral loss of heterozygosity (uniparental disomy, UPD) at chromosome 11p15, an alteration found in part of hepatoblastomas (Suzuki et al. 2008). By use of gene expression profiling, gene signatures have been identified that reveal deregulated growth features and molecular heterogeneity of hepatoblastomas, in part in a histologic subtype-specific manner (Luo et al. 2006; Adesina et al. 2009; Shin et al. 2011; review: Chen et al. 2009). In recent study analyzing several molecular pathways as a function of hepatoblastoma morphology and subtypes, HES1 expression and HES1/AXIN2 used to measure Notch versus Wnt activation ratio were particularly elevated in pure fetal cases and were lowest in small cell undifferentiated (SCUD) hepatoblastoma. Hepatocyte nuclear factor 4alpha was elevated only in embryonal components, while the bipotential oval cell marker DLK1, AXIN2, and EGFR were elevated in all subtypes, suggesting a distinct pattern of molecular microheterogeneity (Lopez-Terrada et al. 2009). A high expression of telomerase is an independent prognostic factor in hepatoblastoma. The prognosis of the patients with high hTERT

mRNA expression was significantly worse than that of others (Hiyama et al. 2004). This effect was, in particular, observed in patients with tumors lacking beta-catenin mutations (Ueda et al. 2011).

In hepatoblastomas, upregulation of miR-214, miR-199a, miR-150, and miR-125a and a downregulation of miR-148a were found (Magrelli et al. 2009). By use of methylation-specific PCR, testing of the methylation profile of hepatoblastomas revealed a high tumor-specific DNA hypermethylation in the promoter region of five genes, i.e., APC, CDH1, MT1G, RASSF1A, and SOCS1, whereby MT1G hypermethylation may be useful as a prognostic indicator for hepatoblastoma (Sakamoto et al. 2010). Aberrant promoter methylation and silencing of the RASSF1A gene have been found in a previous study (Harada et al. 2002). The JAK-binding and JAK-inhibiting protein, SOCS1 (JAB1, SSI-1), is reduced in about half of hepatoblastomas, this silencing being accomplished via hypermethylation (Nagai et al. 2003). Aberrant methylation of the 5′CpG islands of the p16 gene was detected in 50 % of hepatoblastoma cases and found to be a major mechanism of the transcriptional repression of p16 in these tumors (Shim et al. 2003).

References

Abdollahi A (2007) LOT1 (ZAC1/Plagl1) and its family members: mechanisms and functions. J Cell Physiol 210:16–25

Abdul-Rahman OA, Edghill EL, Kwan A, Enns GM, Hattersley AT (2009) Hypoplastic glomerulocystic kidney disease and hepatoblastoma: a potential association not caused by mutations in hepatocyte nuclear factor 1beta. J Pediatr Hematol Oncol 31:527–529

Adesina AM, Nuguyen Y, Guanaratne P, Pulliam J, Lopez-Terrada D, Margolin J, Finegold MJ (2007) FOXG1 is overexpressed in hepatoblastoma. Hum Pathol 38:400–409

Adesina AM, Lopez-Terrada D, Wong KK, Gunaratne P, Nguyen Y, Pulliam J, Margolin J et al (2009) Gene expression profiling reveals signatures characterizing histologic subtypes of hepatoblastoma and global deregulation in cell growth and survival pathways. Hum Pathol 40:843–853

Akmal SN, Yun K, MacLay J, Higami Y, Ikeda T (1995) Insulin-like growth factor 2 and insulin-like growth factor binding protein 2 expression in hepatoblastoma. Hum Pathol 26:846–851

Albrecht S, von Schweinitz D, Waha A, Kraus JA, von Deimling A, Pietsch T (1994) Loss of maternal alleles on chromosome arm 11p in hepatoblastoma. Cancer Res 54:5041–5044

Algar EM, St Heaps L, Darmanian A, Dagar V, Prawitt D, Peters GB, Collins F (2007) Paternally inherited sub-microscopic duplication at 11p15.5implications insulin-like growth factor II in overgrowth and Wilms' tumorigenesis. Cancer Res 67:2360–2365

Al-Rahawan et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17567882

Amor DJ, Halliday J (2008) A review of known imprinting syndromes and their association with assisted reproduction technologies. Hum Reprod 23:2826–2834

Ansell P, Mitchell CD, Roman E, Simpson J, Birch JM, Eden TO (2005) Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS. Eur J Cancer 41:741–748

Aretz S, Koch A, Uhlhaas S, Friedl W, Propping P, von Schweinitz D, Pietsch T (2006) Should children at risk for familial adenomatous polyposis be screened for hepatoblastoma and children with apparently sporadic hepatoblastoma be screened for APC germline mutations? Pediatr Blood Cancer 47:811–818

Armengol C, Cairo S, Fabre M, Buendia MA (2011) Wnt signaling and hepatocarcinogenesis: the hepatoblastoma model. Int J Biochem Cell Biol 43:265–270

Attard TM, Tajouri T, Peterson KD, Tinley S, Thorson AG, Lynch HT (2008) Familial adenomatous polyposis in children younger than age ten years: a multidisciplinary clinic experience. Dis Colon Rectum 51:207–212

Badve S, Logdberg L, Lal A, de Davila, Greco MA, Mitsudo S, Saxena R (2003) Small cells in hepatoblastoma lack "oval" cell phenotype. Mod Pathol 16:930–936

Bai et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21480322

Bardi G, Johansson B, Pandis N et al (1991) I(8q) as the primary structural chromosome abnormality in a hepatoblastoma (letter). Cancer Genet Cytogenet 51:281–283

Becknell B, Pais P, Onimoe G, Rangarajan H, Schaderer AL, McHugh K, Ranalli MA, Hains DS (2011) Hepatoblastoma and prune belly syndrome: a potential association. Pediatr Nephrol 26:1269–1273

Beckwith JB (1963) Extreme cytomegaly oft he adrenal fetal cortex, omphalocele, hyperplasia of kidneyes and pancreas, and Leydig-cell hyperplasia: another syndrome ? Abstract, Western Society for Pediatric Research, Nov 11, 1963, Los Angeles

Bernstein IT, Bülow S, Mauritzen K (1992) Hepatoblastoma in two cousins in a family with adenomatous polyposis. Report of two cases. Dis Colon Rectum 35:373–374

Bhaskar KV, Joshi K, Banerjee CK (1990) Hepatoblastoma with glomerulocystic disease – a mere coincidence or an association? Nephron 54:273–274

Bläker H, Hofmann WJ, Rieker RJ, Penzel R, Graf M, Otto HF (1999) Beta-catenin accumulation and mutation of the CTNNB1 gene in hepatoblastoma. Genes Chromosomes Cancer 25:3

Bove KE, Soukup S, Ballard ET, Ryckman F (1996) Hepatoblastoma in a child with trisomy 18: cytogenetics, liver anomalies, and literature review. Pediatr Pathol Lab Med 16:253–262

Brotto M, Fiengold MJ (2002) Distinct patterns of p27/KIP 1 gene expression in hepatoblastoma and prognostic implications with correlation before and after chemotherapy. Hum Pathol 33:198–205

Buckley JD, Sather H, Ruccione K et al (1989) A case-control study of risk factors for hepatoblastoma: a report from the Children's Cancer Study Group. Cancer 64:1169–1176

Buendia MA (2002) Genetic alterations in hepatoblastoma and hepatocellular carcinoma: common and distinctive aspects. Med Pediatr Oncol 39:530–535

Buonuomo PS, Ruggiero A, Vasta I, Attina G, Riccardi R, Zampino G (2005) Second case of hepatoblastoma in a young patient with Simpson-Golabi-Behmel syndrome. Pediatr Hematol Oncol 22:623–628

Cairo S, Armengol C, De Reyniès A, Wei Y, Thomas E, Renard CA, Goga A, Balakrishnan A et al (2008) Hepatic stem-like phenotype and interplay of Wnt/beta-catenin and Myc signaling in aggressive childhood liver cancer. Cancer Cell 14:471–484

Cairo S, Armengol C, Buendia MA (2012) Activation of Wnt and Myc signaling in hepatoblastoma. Front Biosci (Elite Ed) 4:480–486

Callow MG, Tran H, Phu L, Lau T, Lee J, Sandoval WN, Liu PS, Bheddah S, Tao J et al (2011) Ubiquitin ligase RNF146 regulates tankyrase and Axin to promote Wnt signaling. PLoS One 6:e22595

Calton EA, Karen TI, Mackay DJ, Lever M, Ellard S, Flanagan SE, Davies JH et al (2013) Hepatoblastoma in a child with a paternally-inherited ABCC8 mutation and mosaic paternal uniparental disomy 11p causing focal congenital hyperinsulinism. Eur J Med Genet 56:114–117

Cao X, Hong Y, Eu KW, Loi C, Cheah PY (2006) Singapore familial adenomatous polyposis (FAP) patients with classical adenomatous polyposis but undetectable APC mutations have accelerated cancer progression. Am J Gastroenterol 101:2810–2817

Cecinati V, Arcamone G, Mattia DD, Santoro N, Martire B (2012) hepatic non-Hodgkin lymphoma and hepatoblastoma complicating ataxia-teleangiectasia. Immunopharmacol Immunotoxicol 34:1–3

Cetta F, Montalto G, Petracci M (1997) Hepatoblastoma and APC gene mutation in familial adenomatous polyposis. Gut 41:417

Cetta F, Mazzarella L, Bon G, Zuckermann M, Casorelli A, Nounga H (2003) Genetic alterations in hepatoblastoma and hepatocellular carcinoma associated with familial adenomatous polyposis. Med Pediatr Oncol 41:496–497

Chan R, Mascarenhas L, Venkatramani R (2014) Hepatoblastoma and hypoplastic kidneys: a new association. Pediatr Blood Cancer 61:1476–1478

Chang Y, Chen L, Liu Y, Hu L, Li L, Tu Q, Wang R, Wu M, Yang J, Wang H (2011) Inhibition of autophagy may suppress the development of hepatoblastoma. FEBS J 278:4811–4823

Chen TC, Hsieh LL, Kuo TT (1995) Absence of p53 gene mutation and infrequent overexpression of p53 protein in hepatoblastoma. J Pathol 176:243–247

Chen F, Li S, Castranova V (2009) Signature genes for both hepatoblastoma and hepatocellular carcinoma. Eur J Gastroenterol Hepatol 21:1220–1222

Choi SW, Hytiroglou P, Geller SA, Kim SM, Chung KW, Park DH, Theise ND, Thung SN (1993) The expression of p53 antigen in primary malignant epithelial tumors of the liver: an immunohistochemical study. Liver 13:172–176

Chopra A, Iyer VK, Agarwala S, Mathur SR, Apron M, Gupta SD, Verma K (2010) Apoptotic protein expression, glycogen content, DNA ploidy and cell proliferation in hepatoblastoma subtying and their role in prognostication. Pediatr Surg Int 26:1173–1178

Choufani S, Shuman C, Weksberg R (2010) Beckwith-Wiedemann syndrome. Am J Med Genet C 154C:343–354

Clericuzio CL, Chen E, McNeil DE, O'Connor T, Zackai EH, Medne L, Tomlinson G et al (2003) Serum alpha-fetoprotein screening for hepatoblastoma in children with Beckwith-Wiedemann syndrome or isolated hemihyperplasia. J Pediatr 143:270–272

Cohen MM (2005) Beckwith-Wiedemann syndrome: historical, clinicopathological, and etiopathogenetic perspectives. Pediatr Dev Pathol 8:287–304

Conran RM, Hitchcock CL, Waclawiw MA, Stocker JT, Ishak KG (1992) Hepatoblastoma: the prognostic significance of histologic type. Pediatr Pathol 12:167–183

Cooper WN, Luharia A, Evans GA, Raza H, Haire AC, Grundy R, Bowdin SC, Riccio A et al (2005) Molecular subtypes and phenotypic expression of Beckwith-Wiedemann syndrome. Eur J Hum Genet 13:1025–1032

Cooper WN, Curley R, Macdonald F, Maher ER (2007) Mitotic recombination and uniparental disomy in Beckwith-Wiedemann syndrome. Genomics 89:613–617

Corona-Rivera JR, Sanchez-Zubieta F, Silva-Padilla N, Gonzalez-Ramella O, Lopez-Marure E et al (2006) Hepatoblastoma in a patient with Goldenhar syndrome born to a diabetic mother. Am J Med Genet A 140:2834–2837

Cosson MA, Touati G, Lacaille F, Valayannopoulos V, Guyot C, Guest G, Verkarre V et al (2008) Liver hepatoblastoma and multiple OXPHOS deficiency in the follow-up of a patient with methylmalonic aciduria. Mol Genet Metab 95:107–109

Curia MC, Zuckermann M, De Lellis L, Catalano T, Lattanzio R, Aceto G, Veschi S et al (2008) Sporadic childhood hepatoblastomas show activation of beta-catenin, mismatch repair defects and p53 mutations. Mod Pathol 21:7–14

De Chadarevian JP, Dunn S, Malatack JJ, Ganguly A, Blecker U, Punnett HH (2002) Chromosome rearrangement with no apparent gene mutation in familial adenomatous polyposis and hepatocellular neoplasia. Pediatr Dev Pathol 5:69–75

DeBaun MR, Tucker MA (1998) Risk of cancer during the first four years of life in children from the Beckwith-Wiedemann Syndrome Registry. J Pediatr 132:398–400

Debuire B, Paterlini P, Pontisso P, Basso G, May E (1993) Analysis of the p53 gene in European hepatocellular carcinomas and hepatoblastomas. Oncogene 8:2303–2306

Dempsey-Robertson M, Wilkes D, Stall A, Bush P (2012) Incidence of abdominal tumors in syndromic and idiopathic hemihypertrophy/isolated hemihyperplasia. J Pediatr Orthop 32:322–326

Dudas J, Papoutsi M, Hecht M, Elmaouhoub A, Saile B, Christ B, Tomarev SI, von Kaisneberg CS et al (2004) The homeobox transcription factor Prox1 is highly conserved in embryonic hepatoblasts and in adult and transformed hepatocytes, but is absent from bile duct epithelium. Anat Embryol (Berl) 208:359–366

Eggermann T (2009) Silver-Russell and Beckwith-Wiedemann syndromes: opposite (epi)mutations in 11p15 result in opposite clinical pictures. Horm Res 71(Suppl 2):30–35

Eichenmüller M, Gruner I, Hagl B, Häberle B, Müller-Höcker J, Von Schweinitz D, Kappler R (2009) Blocking the hedgehog pathway inhibits hepatoblastoma growth. Hepatology 49:482–490

Evers et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22692730

Feng GJ, Cotta W, Wei XQ, Poetz O, Evans R, Jardé T, Reed K, Meniel V, Williams GT et al (2012) Conditional disruption of Axin1 leads to development of liver tumors in mice. Gastroenterology 143:1650–1659

Feusner J, Plaschkes J (2002) Hepatoblastoma and low birth weight: a trend or chance observation? Med Pediatr Oncol 39:508–509

Feusner J, Buckley J, Robison L, Ross J, Van Tornout J (1998) Prematurity and hepatoblastoma: more than just an association. J Pediatr 133:585–586

Fiegel HC, Gluer S, Roth B et al (2004) Stem-like cells in human hepatoblastoma. J Histochem Cytochem 52:1495–1501

Fletcher JA, Kozakewich HP, Pavelka K et al (1991) Consistent cytogenetic aberrations in hepatoblastoma: a common pathway of genetic alterations in embryonal liver and skeletal muscle malignancies? Genes Chromosomes Cancer 3:37–43

Fraumeni J, Rosen P, Hull E, Barth RF, Shapiro SR, O'Connor JE (1969) Hepatoblastoma in infant sisters. Cancer 24:1086–1090

Fukuzawa R, Umezawa A, Ochi K, Urano F, Ikeda H, Hata J (1999) High frequency of inactivation of the imprinted H19 gene in "sporadic" hepatoblastoma. Int J Cancer 82:490–497

Fukuzawa R, Hata JI, Hayashi Y, Ikeda H, Reeve AE (2003) Beckwith-Wiedemann syndrome-associated hepatoblastoma: Wnt signal activation occurs later in tumorigenesis in patients with 11p15.5 uniparental disomy. Pediatr Dev Pathol 6:299–306

Gabory A, Ripoche MA, Yoshimizu T, Dandolo L (2006) The H19 gene: regulation and function of a non-coding RNA. Cytogenet Genome Res 113:188–193

Gabory A, Ripoche MA, Le Digarcher A, Watrin F, Ziyyat A, Forné T, Jammes H, Ainscough JF et al (2009) H19 acts as a trans regulator of the imprinted gene network controlling growth in mice. Development 136:3413–3421

Garber JE, Kingston JE, Krush AJ, Strong LC, Finegold MJ, Bertario L, Bülow S et al (1988) Hepatoblastoma and familial adenomatous polyposis. J Natl Cancer Inst 80:1626–1628

Giardiello FM, Petersen GM, Brensinger JD, Luce MC, Cayouette MC, Bacon J et al (1996) Hepatoblastoma and APC gene mutation in familial adenomatous polyposis. Gut 39:867–869

Gougelet A, Colnot S (2012) A complex interplay between Wnt/b-catenin signalling and the cell cycle in the adult liver. Int J Hepatol 2012:816125

Greer ML, Danin J, Lamont AC (1998) Glomerulocystic disease with hepatoblastoma in an neonate: a case report. Pediatr Radiol 28:703–705

Gunawan et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12010372

Gupta A, Sheridan RM, Towbin A, Geller JI, Tiao G, Bove KE (2013) Multifocal hepatic neoplasia in 3 children with APC gene mutation. Am J Surg Pathol 37:1058–1066

Haas OA, Zoubek A, Grümayer ER, Gadner H (1986) Constitutional interstitial deletion of 11p11 and pericentric inversion of chromosome 9 in a patient with Wiedemann-Beckwith syndrome and hepatoblastoma. Cancer Genet Cytogenet 23:95–104

Hamada Y, Takada K, Fukunaga S, Hioki K (2003) Hepatoblastoma associated with Beckwith-Wiedemann syndrome and hemihypertrophy. Pediatr Surg Int 19:112–114

Harada K, Toyooka S, Maitra A, Maruyama R, Toyooka KO, Timmons CF, Tomlinson GE et al (2002) Aberrant promoter methylation and silencing of the RASSF1A gene in pediatric tumors and cell lines. Oncogene 21:4345–4349

Hartmann W, Waha A, Koch A, Goodyer CG, Albrecht S, von Schweinitz D, Pietsch T (2000) P57(KIP2) is not mutated in hepatoblastoma but shows increased transcriptional activity in a comparative analysis of the three imprinted genes p57(KIP2), IGF2, and H19. Am J Pathol 157:1393–1403

Hartmann W, Küchler J, Koch A, Friedrichs N, Waha A, Endl E, Czerwitzki J, Metzger D et al (2009) Activation

of phosphatidylinositol-3′-kinase/AKT signaling is essential in hepatoblastoma survival. Clin Cancer Res 15:4538–4545

Harvey J, Clark S, Hyer W, Hadzic N, Tomlinson I, Hinds R (2008) Germline APC mutations are not commonly seen in children with sporadic hepatoblastoma. J Pediatr Gastroenterol Nutr 47:675–677

Hata Y, Ishizu H, Ohmori K, Hamada H, Sasaki F, Uchino J, Inoue K, Naitoh H, Fujita M et al (1991) Flow cytometric analysis of the nuclear DNA content of hepatoblastoma. Cancer 68:2566–2570

Heck JE, Meyers TJ, Lombardi C, Park AS, Cockburn M, Reynolds P, Ritz B (2013) Case-control study of birth characteristics and the risk of hepatoblastoma. Cancer Epidemiol 37:390–395

Hensen K, Van Valckenborgh IC, Kas K, Van de Ven WJ, Voz ML (2002) The tumorigenic diversity of the three PLAG family members is associated with different DNA binding capacities. Cancer Res 62:1510–1517

Herencia C, Martinez-Moreno JM, Herrera C, Corrales F, Santiago-Mora R, Espejo I et al (2012) Nuclear translocation of b-catenin during mesenchymal stem cells differentiation into hepatocytes is associated with a tumoral phenotype. PLoS One 7:e34656

Hirschman BA, Pollock BH, Tomlinson GE (2005) The spectrum of APC mutations in children with hepatoblastoma from familial adenomatous polyposis kindreds. J Pediatr 147:263–266

Hiyama F, Yamaoka H, Matsunaga T, Hayashi Y, Ando H, Suita S, Horie H, Kaneko M et al (2004) High expression of telomerase is an independent prognostic indicator of poor outcome in hepatoblastoma. Br J Cancer 91:972–979

Honda S, Arai Y, Haruta M, Sasaki F, Ohira M, Yamaoka H, Horie H, Nakagawara A et al (2008) Loss of imprinting of IGF2 correlates with hypermethylation of the H19 differentially methylated region in hepatoblastoma. Br J Cancer 99:1891–1899

Horii M, Horiguchi H, Momoeda M, Nakagawa M, Hirata M, Kusakawa I, Yamanaka M (2012) Hepatoblastoma in an infant with paternal uniparental disomy 14. Congenit Anomalies (Kyoto) 52:219–220

Hoyme HE, Seaver LH, Jones KL, Procopio F, Crooks W, Feingold M (1998) Isolated hemihyperplasia (hemihypertrophy): report of a prospective multicenter study of the incidence of neoplasia and review. Am J Med Genet 79:274–278

Hsia CC, Axiotis CA, Di Bisceglie AM (1992) Transforming growth factor-a in human hepatocellular carcinoma and coexpression with hepatitis B surface antigen in adjacent liver. Cancer 70:1049–1056

Hughes LJ, Michels VV (1992) Risk of hepatoblastoma in familial adenomatous polyposis. Am J Med Genet 43:1023–1025

Ikeda H, Matsuyama S, Tanimura M (1997) Association between hepatoblastoma and very low birth weight: a trend or a chance? J Pediatr 130:557–560

Ikeda H, Hachitanda Y, Tanimura M, Maruyama K, Koizumi T, Tsuchida Y (1998) Development of unfavorable hepatoblastoma in children of very low birth weight: results of a surgical and pathologic review. Cancer 82:1789–1796

Inukai T, Furuuchi K, Sugita K, Uno K, Ooi A, Sasaki F, Hamada J, Moriuchi T, Nakazawa S (2004) Nuclear accumulation of beta-catenin without an additional somatic mutation in coding region of the APC gene in hepatoblastoma from a familial adenomatous polyposis patient. Oncol Rep 11:121–126

Iolascon A, Giordani L, Moretti A, Basso G, Borriello A, Della Ragione F (1998) Analysis of CDKN2A, CDKN2B, CDKN2C, and cyclin Ds gene status in hepatoblastoma. Hepatology 27:989–995

Irvin JA, Ekeowa UI, Belorgey D, Hag I, Gooptu B, Miranda E, Pérez J, Roussel BD et al (2011) The serpinopathies studying serpin polymerization in vivo. Methods Enzymol 501:421–466

Ito E, Sato Y, Kawauchi K, Munakata H, Kamata Y, Yodono H, Yokoyama M (1987) Type 1a glycogen storage disease with hepatoblastoma in siblings. Cancer 59:1776–1780

Jaing TH, Hung IJ, Lin JN, Lien RI, Hsueh C, Lu CS (2002) Hepatoblastoma in a child of extremely low birth weight. Am J Perinatol 19:149–153

Jeng YM, Wu MZ, Mao TL, Chang MH, Hsu HC (2000) Somatic mutations of beta-catenin play a crucial role in the tumorigenesis of sporadic hepatoblastoma. Cancer Lett 152:45–51

Jia D, Dong R, Jing Y, Xu D, Wang Q, Chen L, Li Q, Huang Y, Zhang Y, Zhang Z et al (2014) Exome sequencing of hepatoblastoma reveals novel mutations and cancer genes in the Wnt pathway and ubiquitin ligase complex. Hepatology 60:1686–1696

Jin T, Fantus IG, Sun J (2008) Wnt and beyond Wnt: multiple mechanisms control the transcriptional property of b-catenin. Cell Signal 20:1697–1704

Kamien BA, Gabbett MT (2009) Aicardi syndrome associated with hepatoblastoma and pulmonary sequestration. Am J Med Genet A 149A:1850–1852

Kapfer SA, Petruzzi MJ, Caty MG (2004) Hepatoblastoma in low birth weight infants: an institutional review. Pediatr Surg Int 20:753–756

Kar et al. 1993. http://www.ncbi.nlm.nih.gov/pubmed/8395458

Kato M, Takita J, Takahashi K, Mimaki M, Chen Y, Koh K, Ida K, Oka A, Mizuguchi M et al (2009) Hepatoblastoma in a patient with Sotos syndrome. J Pediatr 155:937–939

Katoh Y, Katoh M (2006) Hedgehog signaling pathway and gastrointestinal stem cell signaling network (review). Int J Mol Med 18:1019–1023

Kawano S, Hasegawa S, Urushihara N, Okazaki T, Yoshida A, Kusafuka J, Mimaya J et al (2007) Hepatoblastoma with congenital absence of the portal vein – a case report. Eur J Pediatr Surg 17:292–294

Kennedy SM, Macgeogh C, Jaffe R, Spurr NK (1994) Overexpression of the oncoprotein p53 in primary hepatic tumors of childhood does not correlate with gene mutations. Hum Pathol 25:438–442

Khan A, Bader JL, Hoy GR, Sinks LF (1979) Hepatoblastoma in a child with fetal alcohol syndrome. Lancet 1:1403–1404

Kingston JE, Draper GJ, Mann JR (1982) Hepatoblastoma and polyposis coli. Lancet 1:457

Kingston JE, Herbert A, Draper GJ, Mann JR (1983) Association between hepatoblastoma and polyposis coli. Arch Dis Child 58:959–962

Kisato Y, Nishikubo T, Uchida Y, Kuwahara I, Minowa H, Kamitsuji H, Kanehiro H, Park YD, Sasaki F (2002) Hepatoblastoma in a low-birthweight infant with cleft palate, Dandy-Walker malformation and chronic lung disease. Pediatr Int 44:698–701

Kiss A, Szepesei A, Lotz G, Nagy P, Schaff Z (1998) Expression of transforming growth factor-alpha in hepatoblastoma. Cancer 83:690–697

Kitanovski L, Ovcak Z, Jazbec J (2009) Multifocal hepatoblastoma in a 6-month-old girl with trisomy 18: a case report. J Med Case Rep 3:8319

Kobrinsky NL, Sjolander DE, Goldenberg JA, Ortmeier TC (2005) Successful treatment of doxorubicin and cisplatin resistant hepatoblastoma in a child with Beckwith-Wiedemann syndrome with high dose acetaminophen and *N*-acetylcysteine rescue. Pediatr Blood Cancer 45:222–225

Koch A, Denkhaus D, Albrecht S, Leuschner I, von Schweinitz D, Pietsch T (1999) Childhood hepatoblastomas frequently carry a mutated degradation targeting box of the beta-catenin gene. Cancer Res 59:269–273

Koch A, Weber N, Waha A, Hartmann W, Denkhaus D, Behrens J, Birchmeier W, von Schweinitz D et al (2004) Mutations and elevated transcriptional activity of conductin (AXIN2) in hepatoblastomas. J Pathol 204:546–554

Koch A, Waha A, Hartmann W, Hrychyk A, Schüller U, Waha A, Wharton KA, Fuchs SY et al (2005) Elevated expression of What antagonists is a common event in hepatoblastomas. Clin Cancer Res 11:4295–4304

Köker MY (2010) Novel human pathological mutations. Gene symbol: NCF2. Disease: chronic granulomatous disease. Hum Genet 127:113

Kopic S, Eirich K, Schuster B, Hanenberg H, Varon-Mateeva R, Rittinger O, Schimpl G et al (2011) Hepatoblastoma in a 4-year-old girl with Fanconi anaemia. Acta Paediatr 100:780–783

Kosaki R, Takenouchi T, Takeda N, Kagami M, Nakabayashi K, Hata K, Kosaki K (2014) Somatic CTNNB1 mutation in hepatoblastoma from a patient with Simpson-Golabi-Behmel syndrome and germline GPC3 mutation. Am J Med Genet A 164A:993–997

Krawczuk-Rybak M, Jakubiuk-Tomaszuk A, Skiba E, Plawski A (2012) Hepatoblastoma as a result of APC gene mutation. J Pediatr Gastroenterol Nutr 55:334–336

Kröber S, Ruck P, Xiao JC, Kaiserling E (1995) Flow cytometric evaluation of nuclear DNA content in hepatoblastoma: further evidence for the inhomogeneity of the different subtypes. Pathol Int 45:501–505

Krush AJ, Traboulsi EI, Offerhaus JA, Maumenee IH, Yardley JH, Levin LS (1988) Hepatoblastoma, pigmented ocular fundus lesions and jaw lesions in Gardner syndrome. Am J Med Genet 29:323–332

Kummerfeld M, Klaunick G, Drückler E, Classen CF, Hauenstein C, Stuhldreier G (2010) Hepatoblastoma in association with bilateral polycystic kidneys. J Pediatr Surg 45:e23–e25

Kurahashi H, Takami K, Oue T, Kusafuka T, Okada A, Tawa A, Okada S, Nishisho I (1995) Biallelic inactivation of the APC gene in hepatoblastoma. Cancer Res 55:5007–5011

Kusafuka T, Fukuzawa M, Oue T, Komoto Y, Yoneda A, Okada A (1997) Mutation analysis of p53 gene in childhood malignant solid tumors. J Pediatr Surg 32:1175–1180

Lade A, Ranganathan S, Luo J, Monga SP (2012) Calpain induces N-terminal truncation of b-catenin in normal murine liver development: diagnostic implications in hepatoblastomas. J Biol Chem 287:22789–22798

Latini G, Gallo F, De Felice C (2004) Birth characteristics and hepatoblastoma risk in young children. Cancer 101:210

Laurent-Puig P, Zucman-Rossi J (2006) Genetics of hepatocellular tumors. Oncogene 25:3778–3786

Lazzareschi I, Barone G, Mastrangelo S, Furfaro IF, Rando G, Riccardi R (2009) Could APC gene screening be useful in children with hepatoblastoma ? Early onset of adenocarcinoma in a child with familial adenomatous polyposis and hepatoblastoma. Tumori 95:819–822

Lee SH, Shin MS, Lee JY, Park WS, Kim SY, Jang JJ, Dong SM, Na EY, Kim CS et al (1999) In vivo expression of soluble Fas and FAP-1: possible mechanisms of Fas resistance in human hepatoblastomas. J Pathol 188:207–212

Lee CT, Zhang L, Mounajjed T, Wu TT (2013) High mobility group AT-hook 2 is overexpressed in hepatoblastoma. Hum Pathol 44:802–810

Li X, Adam G, Cui H, Sandstedt B, Ohlsson R, Ekström TJ (1995) Expression, promoter usage and parental imprinting status of insulin-like growth factor II (IGF2) in human hepatoblastoma: uncoupling of IGF2 and H19 imprinting. Oncogene 11:221–229

Li YC, Deng YH, Guo ZH, Zhang MM, Zhu J, Pu CL, Xiang CP, Guo CB (2010) Prognostic value of hedgehog signal component expressions in hepatoblastoma patients. Eur J Med Res 15:468–474

Li H, Wolfe A, Septer S, Edwards G, Zhong X, Abdulkarim AB, Ranganathan S, Apte U (2012a) Deregulation of Hippo kinase signalling in human hepatic malignancies. Liver Int 32:38–47

Li VS, Ng SS, Boersema PJ, Low TY, Karthaus WR, Gerlach JP, Mohammed S et al (2012b) Wnt signaling through inhibition of b-catenin degradation n an intact Axin1 complex. Cell 149:1245–1256

Little MH, Thomson DB, Hayward NK, Smith PJ (1988) Loss of alleles on the short arm of chromosome 11 in a

hepatoblastoma from a child with Beckwith-Wiedemann syndrome. Hum Genet 79:186–189
Loomba RS, Telega GW, Gudausky TM (2012) Type 2 Abernethy malformation presenting as a portal vein-coronary sinus fistula. J Pediatr Surg 47:E25–E31
Lopez-Terrada D, Gunaratne PH, Adesina AM, Pulliam J, Hoang DM, Nguyen Y et al (2009) Histologic subtypes of hepatoblastoma are characterized by differential canonical Wnt and Notch pathway activation in DLK+ precursors. Hum Pathol 40:783–794
Luo JH, Ren B, Keryanov S, Tseng GC, Rao UN, Monga SP, Strom S, Demetris AJ et al (2006) Transcriptomic and genomic analysis of human hepatocellular carcinomas and hepatoblastomas. Hepatology 44:1012–1024
Ma SK, Cheung AN, Choy C, Chan GC, Ha SY, Ching LM, Wan TS, Chan LC (2000) Cytogenetic characterization of childhood hepatoblastoma. Cancer Genet Cytogenet 119:32–36
Magrelli A, Azzalin G, Salvatore M, Viganotti M, Tosto F, Colombo T, Devito R, Di Masi A et al (2009) Altered microRNA expression patterns in hepatoblastoma patients. Transl Oncol 2:157–163
Mamlok V, Nichols M, Lockhart L, Mamlok R (1989) Trisomy 18 and hepatoblastoma. Am J Med Genet 33:125–126
Martelli C, Blandamura S, Massaro S, Zulian M, Altavilla G, Piazza M (1993) A case study of Beckwith-Wiedemann syndrome associated with hepatoblastoma. Clin Exp Obstet Gynecol 20:82–87
Maruyama K, Ikeda H, Koizumi T, Tsuchida Y (1999) Prenatal and postnatal histories of very low birthweight infants who developed hepatoblastoma. Pediatr Int 41:82–89
Maruyama K, Ikeda H, Koizumi T, Tsuchida Y, Tanimura M, Nishida H, Takahashi N et al (2000) Case-control study of perinatal factors and hepatoblastoma in children with an extremely low birthweight. Pediatr Int 42:492–498
Mascarello JT, Jones MC, Kadora RP, Krous HF (1990) Hepatoblastoma characterized by trisomy 20 and double minutes. Cancer Genet Cytogenet 47:243–247
Mateos ME, Beyer K, Lopez-Laso E, Siles JL, Pérez-Navero JL, Peña MJ, Guzman J et al (2013) Simpson-Golabi-Behmel syndrome type 1 and hepatoblastoma in a patient with a novel exon 2–4 duplication of the GPC3 gene. Am J Med Genet A 161A:1091–1095
McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS (2006) Maternal and infant birth characteristics and hepatoblastoma. Am J Epidemiol 163:818–828
Miao J, Kusafuka T, Udatsu Y, Okada A (2003) Sequence variants of the Axin gene in hepatoblastoma. Hepatol Res 25:174–179
Micsenyi A, Tan X, Sneddon T, Luo JH, Michalopoulos GK, Monga SP (2004) Beta-catenin is temporally regulated during normal liver development. Gastroenterology 126:1134–1146
Mistinova J, Valacsai F, Varga I (2010) Congenital absence of the portal vein – case report and a review of the literature. Clin Anat 23:750–758
Molina J, Munoz M, de Migual C, Martinez-Peñuela JM, Villanueva A, Delgado A (1981) Wiedemann-beckwith syndrome with hepatoblastoma (in Spanish). An Esp Pediatr 15:365–370
Moore SW, Tshifularo N, Grobbelaar J (2012) Lessons from the hepatoblastoma-familial polyposis connection. S Afr Med J 102:888–889
Morali OG, Delmas V, Moore R, Jeanney C, Thiery JP, Larue L (2001) IGF-II induces rapid beta-catenin relocation to the nucleus during epithelium to mesenchyme transition. Oncogene 20:4942–4950
Morrone S, Cheng Z, Moon RT, Cong F, Xu W (2012) Crystal structure of a tankyrase-Axin complex and its implications for Axin and tankyrase substrate recruitment. Proc Natl Acad Sci U S A 109:1500–1505
Murphy AJ, de Caestecker C, Pierece J, Boyle SC, Ayers GD, Zhao Z, Libes JM et al (2012) CITED1 expression in liver development and hepatoblastoma. Neoplasia 14:1153–1163
Mussa A, Ferrero GB, Ceoloni B, Basso E, Chiesa N, De Crescenzo A, Pepe E, Silengo M et al (2011) Neonatal hepatoblastoma in a newborn with severe phenotype of Beckwith-Wiedemann syndrome. Eur J Pediatr 170:1407–1411
Nagai H, Naka T, Terada Y, Komazaki T, Yabe A, Jin E, Kawanami O, Kishimoto T et al (2003) Hypermethylation associated with inactivation of the SOCS-1 gene, a JAK/STAT inhibitor, in human hepatoblastomas. J Hum Genet 48:65–69
Nagata T, Mugishima H, Shichino H, Suzuki T, Chin M, Koshinaga S, Inoue M, Harada K (1999) Karyotype analyses of hepatoblastoma. Report of two cases and review of the literature suggesting chromosomal loci responsible for the pathogenesis of this disease. Cancer Genet Cytogenet 114:42–50
Nagata T, Nakamura M, Shichino H, Chin M, Sugito K, Ikeda T, Koshinaga T, Fukuzawa M et al (2005) Cytogenetic abnormalities in hepatoblastoma: report of two new cases and review of the literature suggesting imbalance of chromosomal regions on chromosomes 1, 4 and 12. Cancer Genet Cytogenet 156:8–13
Napoli VM, Campbell WG (1977) Hepatoblastoma in infant sister and brother. Cancer 39:2647–2650
Neas K, Peters G, Jackson J, Tembe M, Wu ZH, Brohede J, Hannan GN, Collins F (2006) Chromosome 7 aberrations in a young girl with myelodysplasia and hepatoblastoma: an unusual association. Clin Dysmorphol 15:1–8
Nikolaev AY, Li M, Puskas N, Qin J, Gu W (2003) Parc: a cytoplasmic anchor for p53. Cell 112:29–40
Ning J, Zheng G, Yang YC (2008) Tip60 modulates PLAG2-mediated transactivation by acetylation. J Cell Biochem 103:730–739
Nobili V, Jenker A, Francalanci P, Catellano A, Holme E, Callea F, Dionisi-Vici C (2010) Tyrosinemia type 1: metastatic hepatoblastoma with a favorable outcome. Pediatrics 126:e235–e238
Oda H, Nakatsuru Y, Imai Y, Sugimura H, Ishikawa T (1995) A mutational hot spot in the p53 gene is associated with hepatoblastoma. Int J Cancer 60:786–790

Oda H, Imai Y, Nakatsuru Y, Hata J, Ishikawa T (1996) Somatic mutations of the APC gene in sporadic hepatoblastomas. Cancer Res 56:3320–3323

Ohnishi H, Kawamura M, Hanada R, Kaneko Y, Tsunoda Y, Hongo T, Bessho F, Yokomori K, Hayashi Y (1996) Infrequent mutations of the TP53 gene and no amplification of the MDM2 gene in hepatoblastomas. Genes Chromosomes Cancer 15:187–190

Orozco-Florian R, McBride JA, Favara BE, Steele A, Brown SJ, Steele P (1991) Congenital hepatoblastoma and Beckwith-Wiedemann syndrome: a case study including DNA ploidy profiles of tumor and adrenal cytomegaly. Pediatr Pathol 11:131–142

Oue T, Kubota A, Okuyama H, Kawahara H, Nara K, Kawa K, Kitajima H (2003) Hepatoblastoma in children of extremely low birth weight: a report from a single perinatal center. J Pediatr Surg 38:134–137

Pakakasama S, Chen TT, Frawley W, Muller CY, Douglass EC, Lee R, Pollock BH, Tomlinson GE (2004) CCND1 polymorphism and age of onset of hepatoblastoma. Oncogene 23:4789–4792

Pallasch CP, Patz M, Park YJ, Hagist S, Eggle D, Claus R, Debey-Pascher S, Schulz A et al (2009) miRNA deregulation by epigenetic silencing disrupts suppression of the oncogene PLAG1 in chronic lymphocytic leukemia. Blood 114:3255–3264

Parada LA, Limon J, Illiszko M, Czauderna P, Gisselsson D, Höglund M, Kullendorff CM et al (2000) Cytogenetics of hepatoblastoma: further characterization of 1q rearrangements by fluorescence in situ hybridization: an international collaborative study. Med Pediatr Oncol 34:165–170

Park WS, Oh RR, Park JY, Kim PJ, Shin MS, Lee JH, Kim HS, Lee SH, Kim SY et al (2001) Nuclear localization of beta-catenin is an important prognostic factor in hepatoblastoma. J Pathol 193:483–490

Patz M, Pallasch CP, Wendtner CM (2010) Critical role of microRNAs in chronic lymphocytic leukemia: overexpression of the oncogene PLAG1 by deregulated miRNAs. Leuk Lymphoma 51:1379–1381

Phillips M, Dicks-Mireaux C, Kingston J, Malone M, Mitchell C, Pritchard J, Shafford E, Spitz L (1989) Hepatoblastoma and polyposis coli (familial adenomatous polyposis). Med Pediatr Oncol 17:441–447

Pu CL, Guo CB, Jin XQ, Deng C, Zhang MM, Li YC, Kang Q (2009) Retrospective analysis of maternal and infant birth features of hepatoblastoma (in Chinese). Zhonghua Gan Zang Bing Za Zhi 17:459–461

Purcell R, Childs M, Maibach R, Miles C, Turner C, Zimmermann A, Sullivan M (2011) HGF/c-Met related activation of b-catenin in hepatoblastoma. J Exp Clin Cancer Res 30:96

Rainier S, Dobry CJ, Feinberg AP (1995) Loss of imprinting in hepatoblastoma. Cancer Res 55:1836–1838

Ranganathan S, Tan X, Monga SPS (2005) b-Catenin and Met deregulation in childhood hepatoblastomas. Pediatr Dev Pathol 8:435–447

Regel I, Eichenmüller M, Joppien S, Liebl J, Häberle B, Müller-Höcker J, Vollmar A, Von Schweinitz D, Kappler R (2012) IGFBP3 impedes aggressive growth of pediatric liver cancer and is epigenetically silenced in vascular invasive and metastatic tumors. Mol Cancer 11:9

Reynolds P, Urayama KY, Von Behren J, Feusner J (2004) Birth characteristics and hepatoblastoma risk in young children. Cancer 100:1070–1076

Ribons LA, Slovis TL (1998) Hepatoblastoma and birth weight (letter). J Pediatr 132:750

Richter A, Grabhorn E, Schulz A, Schaefer HJ, Burdelski M, Ganschow R (2005) Hepatoblastoma in a child with progressive familial intrahepatic cholestasis. Pediatr Transplant 9:805–808

Riikonen P, Tuominen L, Seppa A, Perkkio M (1990) Simultaneous hepatoblastoma in identical male twins. Cancer 66:2429–2431

Ross JA (1997) Hepatoblastoma and birth weight: too little, too big, or just right ? J Pediatr 130:516–517

Ross JA, Radloff GA, Davies SM (2000) H19 and IGF-2 allele-specific expression in hepatoblastoma. Br J Cancer 82:753–756

Ruck P, Xiao J, Kaiserling E (1994) P53 protein expression in hepatoblastoma: an immunohistochemical investigation. Pediatr Pathol 14:79–85

Ruck P, Xiao JC, Kaiserling E (1995) The histogenesis of hepatoblastoma. Morphological and light-and electron-microscopic immunohistochemical findings (in German). Verh Dtsch Ges Pathol 79:120–125

Ruck P, Xiao JC, Kaiserling E (1996) Small epithelial cells and the histogenesis of hepatoblastoma. Electron microscopic, immunoelectron microscopic, and immunohistochemical findings. Am J Pathol 148:321–329

Ruck P, Xiao JC, Pietsch T, Von Schweinitz D, Kaiserling E (1997) Hepatic stem-like cells in hepatoblastoma: expression of cytokeratin 7, albumin and oval cell associated antigens detected by OV-1 and OV-6. Histopathology 31:324–329

Rugge M, Sonego F, Pollice L, Perilongo G, Guido M, Basso G, Ninfo V, Pennelli N et al (1998) Hepatoblastoma: DNA nuclear content, proliferative indices, and pathology. Liver 18:128–133

Sakamoto LH, De Camargo B, Cjaiba M, Soares FA, Vettore AL (2010) MT1G hypermethylation: a potential prognostic marker for hepatoblastoma. Pediatr Res 67:387–393

Sanders RP, Furman WL (2006) Familial adenomatous polyposis in two brothers with hepatoblastoma: implications for diagnosis and screening. Pediatr Blood Cancer 47:851–854

Sandoval C, Piper J, Mowery-Rushton PA, Jayabose S (2002) Fetal-type hepatoblastoma and del(3)(q11.2q13.2). Cancer Genet Cytogenet 134:162–164

Sangkhathat S, Kusafuka T, Miao J, Yoneda A, Nara K, Yamamoto S, Kaneda Y, Fukuzawa M (2006) In vitro RNA interference against beta-catenin inhibits the proliferation of pediatric hepatic tumors. Int J Oncol 28:715–722

Schaff ZS, Hsia CC, Sarosi I, Tabor E (1998) Overexpression of transforming growth factor-a in

hepatocellular carcinoma and focal nodular hyperplasia from European patients. Hum Pathol 25:644–651

Schmidt D, Wischmeyer P, Leuschner I, Sprenger E, Langenau E, Von Schweinitz D, Harms D (1993) DNA analysis in hepatoblastoma by flow and image cytometry. Cancer 72:2914–2919

Schneider NR, Cooley LD, Finegold MJ, Douglass EC, Tomlinson GE (1997) The first recurring chromosome translocation in hepatoblastoma: der(4)t. Genes Chromosomes Cancer 19:291–294

Sekine S, Gutierrez PJ, Lan BY, Feng S, Hebrok M (2007) Liver-specific loss of beta-catenin results in delayed hepatocyte proliferation after partial hepatectomy. Hepatology 45:361–368

Shang XZ, Zhu H, Lin K, Tu Z, Chen J, Nelson DR, Liu C (2004) Stabilized beta-catenin promotes hepatocytes proliferation and inhibits TNFalpha-induced apoptosis. Lab Invest 84:332–341

Shim YH, Park HJ, Choi MS, Kim JS, Kim H, Kim JJ, Jang JJ, Yu E (2003) Hypermethylation of the p16 gene and lack of p16 expression in hepatoblastoma. Mod Pathol 16:430–436

Shin E, Lee KB, Park SY, Kim SH, Ryu HS, Park YN, Yu E, Jang JJ (2011) Gene expression profiling of human hepatoblastoma using archived formalin-fixed and paraffin-embedded tissues. Virchows Arch 458:453–465

Slovis TL, Roebuck DJ (2006) Hepatoblastoma : why so many low-birth-weight infants ? Pediatr Radiol 36:173–174

Smith AC, Choufani S, Ferreira JC, Weksberg R (2007) Growth regulation, imprinted genes, and chromosome 11p15.5. Pediatr Res 61:43R–47R

Soini T, Haveri H, Elo JM, Kauppinen M, Kyrönlahti A, Salo MK, Lohi J, Andersson LC et al (2012) Transcription factor GATA-4 is abundantly expressed in childhood but not in adult liver tumors. J Pediatr Gastroenterol Nutr 54:101–108

Spector LG, Feusner JH, Ross JA (2004) Hepatoblastoma and low birth weight. Pediatr Blood Cancer 43:706

Spector LG, Johnson KJ, Soler JT, Puumala SE (2008) Perinatal risk factors for hepatoblastoma. Br J Cancer 98:1570–1573

Spector LG, Puumala SE, Carozza SE, Chow EJ, Fox EE, Horel S, Johnson KJ et al (2009) Cancer risk among children with very low birth weights. Pediatrics 124:96–104

Stamos JL, Weis WI (2013) The b-catenin destruction complex. Cold Spring Harb Perspect Biol 5:a007898

Steenman M, Tomlinson G, Westerveld A, Mannens M (1999) Comparative genomic hybridization analysis of hepatoblastomas: additional evidence for a genetic link with Wilms tumor and rhabdomyosarcoma. Cytogenet Cell Genet 86:157–161

Stejskalova E, Malis J, Snajdauf J, Pycha K, Urbankova H, Bajkova V, Stary J, Kodet R et al (2009) Cytogenetic and array comparative genomic hybridization analysis of a series of hepatoblastomas. Cancer Genet Cytogenet 194:82–87

Sun XY, Wu ZD, Liao XF, Yuan JY (2005) Tumor angiogenesis and its clinical significance in pediatric malignant liver tumor. World J Gastroenterol 11:741–743

Surace C, Leszl A, Perilongo G, Rocchi M, Basso G, Sainati L (2002) Fluorescent in situ hybridization (FISH) reveals frequent and recurrent numerical and structural abnormalities in hepatoblastoma with no informative karyotype. Med Pediatr Oncol 39:536–539

Surendran N, Radhakrishna K, Chellam VG (1989) Hepatoblastoma in siblings. J Paediatr Surg 24:1169–1171

Suzuki M, Kato M, Yuyan C, Takita J, Sanada M, Nannya Y, Yamamoto G, Takahashi A et al (2008) Whole-genome profiling of chromosomal aberrations in hepatoblastomas using high-density single-nucleotide polymorphism genotyping microarrays. Cancer Sci 99:564–570

Swarts S, Wisecarver J, Bridge JA (1996) Significance of extra copies of chromosome 20 and the long arm of chromosome 2 in hepatoblastoma. Cancer Genet Cytogenet 91:65–67

Takayasu H, Horie H, Hiyama E, Matsunaga T, Hayashi Y, Watanabe Y, Suita S, Kaneko M et al (2001) Frequent deletions and mutations of the b-catenin gene are associated with overexpression of cyclin D1 and fibronectin and poorly differentiated histology in childhood hepatoblastoma. Clin Cancer Res 7:901–908

Takigawa Y, Brown AM (2008) Wnt signaling in liver cancer. Curr Drug Targets 9:1013–1024

Tan TY, Amor DJ (2006) Tumour surveillance in Beckwith-Wiedemann syndrome and hemihyperplasia: a critical review of the evidence and suggested guidelines for local practice. J Paediatr Child Health 42:486–490

Tan X, Yuan Y, Zeng G, Apte U, Thompson MD, Cieply B, Stolz DB, Michalopoulos GK et al (2008) Beta-catenin deletion in hepatoblasts disrupts hepatic morphogenesis and survival during mouse development. Hepatology 47:1667–1679

Tan ZH, Lai A, Chen CK, Chang KT, Tan AM (2014) Association of trisomy 18 with hepatoblastoma and its implications. Eur J Pediatr 173:1595–1598

Tanaka T, Takakura H, Takashima S, Kodama T, Hasegawa H (1985) A rare case of Aicardi syndrome with severe brain malformation and hepatoblastoma. Brain Dev 7:507–512

Taniguchi K, Roberts LR, Aderca IN, Dong X, Qian C, Murphy LM, Nagorney DM et al (2002) Mutational spectrum of beta-catenin, AXIN1, and AXIN2 in hepatocellular carcinomas and hepatoblastomas. Oncogene 21:4863–4871

Tanimura M, Matsui I, Abe J, Ikeda H, Kobayashi N, Ohira M, Yokoyama M, Kaneko M (1998) Increased risk of hepatoblastoma among immature children with a lower birth weight. Cancer Res 58:3032–3035

Tanneberger K, Pfister AS, Kriz V, Bryja V, Schambony A, Behrens J (2011) Structural and functional characterization of the Wnt inhibitor APC membrane recruitment 1 (Amer 1). J Biol Chem 286:19204–19214

Tatekawa Y, Asonuma K, Uemoto S, Inomata Y, Tanaka K (2001) Liver transplantation for biliary atresia associated with malignant hepatic tumors. J Pediatr Surg 36:436–439

Teh SH, Ong GB (2007) Early presentation of right adrenal mass, hepatoblastoma and hepatic cavernous haemangioma in Beckwith-Wiedemann syndrome. Med J Malaysia 62:345–346

Temple IK (2007) Imprinting in human disease with special reference to transient neonatal diabetes and Beckwith-Wiedemann syndrome. Endocr Dev 12:113–123

Terada Y, Matsumoto S, Bando K, Tajiri T (2009) Comprehensive allelotyping of hepatoblastoma. Hepatogastroenterology 56:199–204

Teraguchi M, Nogi S, Ikemoto Y, Ogino H, Kohdera U, Sakaida N, Okamura A, Hamada Y, Kobayashi Y (1997) Multiple hepatoblastomas associated with trisomy 18 in a 3-year-old girl. Pediatr Hematol Oncol 14:463–467

Terracciano LM, Bernasconi B, Ruck P, Stallmach T, Briner J, Sauter G, Moch H, Vecchione R et al (2003) Comparative genomic hybridization analysis of hepatoblastoma reveals high frequency of X-chromosome gains and similarities between epithelial and stromal components. Hum Pathol 34:864–871

Thomas D, Pritchard J, Davidson R, McKiernan P, Grundy RG, de Ville de Goyet J (2003) Familial hepatoblastoma and APC gene mutations: renewed call for molecular research. Eur J Cancer 39:2200–2204

Tomizawa M, Saisho H (2006) Signaling pathway of insulin-like growth factor-II as a target of molecular therapy for hepatoblastoma. World J Gastroenterol 12:6531–6535

Tomlinson GE (2012) Cytogenetics of hepatoblastoma. Front Biosci (Elite Ed) 4:1287–1292

Tomlinson GE, Kappler R (2012) Genetics and epigenetics of hepatoblastoma. Pediatr Blood Cancer 59:785–792

Tran H, Bustos D, Yeh R, Rubinfeld B, Lam C, Shriver S, Zilberleyb I, Lee MW, Phu L et al (2013) HectD1 E 3 ligase modified adenomatous polyposis coli (APC) with polyubiquitin to promote the APC-Axin interaction. J Biol Chem 288:3753–3767

Trobaugh-Lotrario AD, Greffe B, Garza-Williams S, Haas JE, Odom LF (2007) Erythropoietin receptor presence in hepatoblastoma: a possible link to increased incidence of hepatoblastoma in very low birthweight infants. Pediatr Blood Cancer 49:365–366

Tsai SY, Jeng YM, Hwu WL, Ni YH, Chang MH, Wang TR (1996) Hepatoblastoma in an infant with Beckwith-Wiedemann syndrome. J Formos Med Assoc 95:180–183

Tsuchida et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10626849

Turato C, Buendia MA, Fabre M, Redon MJ, Branchereau S, Quarta S, Ruvoletto M et al (2012) Over-expression of SERPINB3 in hepatoblastoma: a possible insight into the genesis of this tumour ? Eur J Cancer 48:1219–1226

Turcotte LM, Georgieff MK, Ross JA, Feusner JH, Tomlinson GE, Malogolowkin MH et al (2014) Neonatal medical exposures and characteristics of low birth weight hepatoblastoma cases: a report from the Children's Oncology Group. Pediatr Blood Cancer 61:2018–2023

Uçar C, Caliskan U, Toy H, Günel E (2005) Hepatoblastoma in a child with neurofibromatosis type I. Pediatr Blood Cancer 49:357–359

Udatsu Y, Kusafuka T, Kuroda S, Miao J, Okada A (2001) High frequency of beta-catenin mutations in hepatoblastoma. Pediatr Surg Int 17:508–512

Ueda Y, Hiyama E, Kamimatsuse A, Kamei N, Ogura K, Sueda T (2011) Wnt signaling and telomerase activation of hepatoblastoma: correlation with chemosensitivity and surgical resectability. J Pediatr Surg 46:2221–2227

Van Dyck F, Delvaux EL, Van de Ven WJ, Chavez MV (2004) Repression of the transactivating capacity of the oncoprotein PLAG1 by SUMOylation. J Biol Chem 279:36121–36131

Van Dyck F, Declercq J, Braem CV, Van de Ven WJ (2007) PLAG1, the prototype of the PLAG gene family: versatility in tumour development (review). Int J Oncol 30:765–774

Venkatramani R, Spector LG, Georgieff M, Tomlinson GE, Krailo M, Malogolowkin M et al (2014) Congenital abnormalities and hepatoblastoma: a report from the Children's Oncology Group (COG) and the Utah Population Database (UPDB). Am J Med Genet A 164A:2250–2255

Von Frowein J, Pagel P, Kappler R, von Schweinitz D, Roscher A, Schmid I (2011) MicroRNA-492 is processed from the keratin 19 gene and up-regulated in metastatic hepatoblastoma. Hepatology 53:833–842

Von Horn H, Tally M, Hall K, Eriksson T, Ekstrom TJ, Gray SG (2001) Expression levels of insulin-like growth factor binding proteins and insulin receptor isoforms in hepatoblastomas. Cancer Lett 162:253–260

Von Horn H, Hwa V, Rosenfeld RG, Hall K, Teh BT, Tally M, Ekstrom TJ, Gray SG (2002) Altered expression of low affinity insulin-like growth factor binding protein related proteins in hepatoblastoma. Int J Mol Med 9:645–649

Von Schweinitz D, Leuschner I, Gluer S, Pietsch T (1996) Expression of cell adhesion molecules and common acute lymphoblastic leukaemia antigen in hepatoblastoma. Virchows Arch 429:235–241

Von Schweinitz D, Fuchs J, Gluer S, Pietsch T (1998) The occurrence of liver growth factor in hepatoblastoma. Eur J Pediatr Surg 8:133–136

Ward SC, Thung SN, Lim KH, Tran TT, Hong TKB, Hoang PL, Jang JJ, Park YN et al (2010) Hepatic progenitor cells in liver cancers from Asian children. Liver Int 30:102–111

Weber RG, Pietsch T, von Schweinitz D, Lichter P (2000) Characterization of genomic alterations in

hepatoblastomas. A role for gains on chromosomes 8q and 20 as predictors of poor outcome. Am J Pathol 157:571–578

Wei Y, Fabre M, Branchereau S, Gauthier F, Perilongo G, Buendia MA (2000) Activation of beta-catenin in epithelial and mesenchymal hepatoblastomas. Oncogene 19:498–504

Weksberg R, Nishikawa J, Caluseriu O, Fei Y, Loman C, Wei C, Steele L, Cameron J et al (2001) Tumor development in the Beckwith-Wiedemann syndrome is associated with a variety of constitutional molecular 11p15 alterations including imprinting defects of KCNQ1OT1. Hum Mol Genet 10:2989–3000

Wezensky SJ, Hanks TS, Wilkison MJ, Ammons MC, Siemsen DW, Gauss KA (2010) Modulation of PLAG2 transactivation by positive cofactor 2 (PC2), a component of the ARC/Mediator complex. Gene 452:22–34

Wiedemann HR (1964) Complexe malformatif familial avec hernie ombilicale et macroglossie, un syndrome nouveau. J Genet Hum 13:223–232

Wilfong AA, Parke JT, McCrary JA (1992) Opsoclonus-myoclonus with Beckwith-Wiedemann syndrome and hepatoblastoma. Pediatr Neurol 8:77–79

Wirojanan J, Kraff J, Hawkins DS, Laird C, Gane LW, Angkustsiri K, Tassone F, Hagerman RJ (2008) Two boys with fragile X syndrome and hepatic tumors. J Pediatr Hematol Oncol 30:239–241

Wirths O, Waha A, Weggen S, Schirmacher P, Kühne T, Goodyer CG, Albrecht S et al (2003) Overexpression of human Dickkopf-1, an antagonist of wingless/WNT signaling, in human hepatoblastomas and Wilms' tumors. Lab Invest 83:429–434

Worth LL, Slopis JM, Herzog CE (1999) Congenital hepatoblastoma and schizencephaly in an infant with Beckwith-Wiedemann syndrome. Med Pediatr Oncol 33:591–593

Wu X, Tu X, Joeng KS, Hilton MJ, Williams DA, Long F (2008) Rac1 activation controls nuclear localization of beta-catenin during canonical Wnt signaling. Cell 133:340–353

Yamada HY, Gorbsky GJ (2006) Tumor suppressor candidate TSSC5 is regulated by UbcH6 and a novel ubiquitin ligase RING105. Oncogene 25:1330–1339

Yamada S, Ohira M, Horie H, Ando K, Takayasu H, Suzuki Y, Sugano S, Hirata T et al (2004) Expression profiling and differential screening between hepatoblastomas and the corresponding normal livers: identification of high expression of the PLK1 onocgene as a poor-prognostic indicator of hepatoblastomas. Oncogene 23:5901–5911

Yamamoto H, Ozaki T, Nakanishi M, Kikuchi H, Yoshida K, Horie H, Kuwano H, Nakagawara A (2007) Oxidative stress induces p53-dependent apoptosis in hepatoblastoma cell through its nuclear translocation. Genes Cells 12:461–471

Yamaoka H, Ohtsu K, Sueda T, Yokoyama T, Hiyama E (2006) Diagnostic and prognostic impact of beta-catenin alterations in pediatric liver tumors. Oncol Rep 15:551–556

Yeh YA, Rao PH, Cigna CT, Middlesworth W, Lefkowitch JH, Murty VV (2000) Trisomy 1q, 2, and 20 in a case of hepatoblastoma : possible significance of 2q35-q37 and 1q12-q21 rearrangements. Cancer Genet Cytogenet 123:140–143

Yoshida R, Ogata T, Masawa N, Nagai T (2008) Hepatoblastoma in a Noonan syndrome patient with a PTPN11 mutation. Pediatr Blood Cancer 50:1274–1276

Yu Y, Wu J, Wang Y, Zhao T, Ma B, Liu Y, Fang W, Zhu WG, Zhang H (2012) Kindlin 2 forms a transcriptional complex with b-catenin and TCF4 to enhance Wnt signaling. EMBO Rep 13:750–758

Yun K, Jinno Y, Sohda T, Niikawa N, Ikeda T (1998) Promoter-specific insulin-like growth factor 2 gene imprinting in human fetal liver and hepatoblastoma. J Pathol 185:91–98

Zatkova A, Rouillard JM, Hartmann W, Lamb BJ, Kuick R, Eckart M, von Schweinitz D et al (2004) Amplification and overexpression of the IGF2 regulator PLAG1 in hepatoblastoma. Genes Chromosomes Cancer 39:126–137

Zerbini MC, Sredni ST, Grier H, Cristofani LM, Latorre MR, Hollister KA, Alves VA et al (1998) Primary malignant epithelial tumors of the liver in children: a study of DNA content and oncogene expression. Pediatr Dev Pathol 1:270–280

Zhang X, Li F, Cheng N (1998) Clinicopathological and immunohistochemical study of hepatoblastoma (in Chinese). Hua Xi Yi Ke Da Xue Xue Bao 29:298–301

Zhang D, Jiang P, Xu Q, Zhang X (2011) ARGLU1 interacts with MED1 and is required for estrogen receptor-mediated gene transcription and breast cancer cell growth. J Biol Chem 286:17746–17754

Zheng G, Yang YC (2005) Sumoylation and acetylation play opposite roles in the transactivation of PLAG1 and PLAG2. J Biol Chem 280:40773–40781

Zhu X, Liu B, Carlsten JO, Beye J, Nyström T, Myers LC, Gustafsson CM (2011) Mediator influences telomeric silencing and cellular lifespan. Mol Cell Biol 31:2413–2421

Zulehner G, Mikula M, Schneller D, van Zijl F, Huber H, Sieghart W, Grasl-Kraupp B et al (2010) Nuclear beta-catenin induces an early liver progenitor phenotype in hepatocellular carcinoma and prpmotes tumor recurrence. Am J Pathol 176:472–481

Nested Stromal-Epithelial Tumor of the Liver

23

Contents

Abstract

Nested stromal-epithelial tumor (NSET) is a rare and complex liver tumor characterized by multiple clustered nests of primitive-looking epithelial cells embedded in a spindle cell stroma, surrounded by a sheath of myofibroblastic cells, and associated with calcifications and ossification. The tumor occurs both in the pediatric age group and in adults and is not associated with preexisting liver disease. NSET may be associated with Cushing syndrome with production of ACTH due to ectopic synthesis of corticotropin-releasing hormone. NSET usually presents as a solitary liver neoplasm ranging in diameter from a few cm to 30 cm. A feature important for the elucidation of pathogenesis of NSET is the presence of nuclear beta-catenin expression in epithelial cells of the nests. This phenomenon is associated with mutations of the beta-catenin gene (exon 3) and expression of factors inducing epithelial-mesenchymal transition.

Introduction

Nested stromal-epithelial tumor (NSET; synonyms: ossifying stromal-epithelial tumor; ossifying malignant mixed epithelial and stromal tumor; desmoplastic nested spindle cell tumor of the liver; calcifying nested stromal-epithelial tumor/CNSET) is a rare non-hepatocytic, non-biliary tumor of the liver characterized by multiple,

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_23

clustered nests of primitive-looking epithelial cells embedded in a spindle cell stroma, surrounded by a sheath of myofibroblastic cells, and associated with calcifications and ossification. As at least part of the cells situated within the nests have features of immature hepatocytes, this neoplasm is treated in the setting of hepatocellular tumors.

Definition and Classification of the Entity

NSET was originally described as "ossifying stromal-epithelial tumor" of the liver in the 2001 third series AFIP fascicle (Ishak et al. 2001). A case published 1 year later under the term, "ossifying malignant mixed epithelial and stromal tumor of the liver" is on one of the three patients reported in 2001 (Heywood et al. 2002). However, the description of the tumor reported by these authors in several respects differs from what we nowadays understand to be NSET. The tumor was detected in a 28-year-old female patient without previous liver disease, except the presence of focal hepatic calcifications at age 4 which were noted on plain abdominal X-ray images acquired for unknown reasons. The calcification was attributed to a calcified hepatic hemangioma. The resected liver specimen contained a lobulated tumor with a maximum diameter of 14.5 cm. The histology part of the publication describes a malignant neoplasm consisting of a mixture of cytologically atypical spindle cells as a component of a myxoid stroma and epithelial areas with duct formation and mucin production, interpreted as infiltrating, desmoplastic adenocarcinoma. Extensive osteoid formation and scattered calcifications were present. There were numerous satellite lesions and portal and hepatic vein invasion. This description would not fit with NSET. However, the figures reproduced in the publication may be compatible with NSET. It remains unsettled whether this tumor is NSET or rather belongs into the category of so-called desmoplastic nested spindle cell tumor of the adult liver, treated in the following chapter.

In 2003, Hill et al. published a bona fide case of NSET with a histology similar to that described by Ishak and coworkers in 2000 (Hill et al. 2003). These authors observed tumors which they termed, "desmoplastic nested spindle cell tumor of the liver," in four previously healthy children. Since then, less than 30 more cases have been documented in the literature (Heerema-McKenney et al. 2005; Brodsky et al. 2008; Makhlouf et al. 2009; Meir et al. 2009; Rod et al. 2009; Grazi et al. 2010; Oviedo Ramirez et al. 2010; Hommann et al. 2011; More et al. 2011, Wang et al. 2011; Zimmermann and Lopez-Terrada 2011; Assmann et al. 2012; Geramidzadeh et al. 2012; Ghodke et al. 2012).

Epidemiology

Among the patients with NSET reported so far, age at presentation ranged from 2 years to more than 30 years, with a predominance of the female gender. NSET has rarely been observed in adult patients (Makhlouf et al. 2009; Grazi et al. 2010; Wang et al. 2011). NSET is not associated with preexisting liver disease. However, the neoplasm was observed in a patient having Beckwith-Wiedemann syndrome (Malowany et al. 2013).

Clinical Features

In the series of six patients reported by Heerema-McKenney et al. (2005), the patients were between 2 and 14 years of age at diagnosis, and all tumors presented as a solitary liver mass ranging from 4.0 to 30.0 cm in greatest diameter. In a subsequent series of nine patients, age at diagnosis ranged from 2 to 33 years, and four patients had a history of calcified liver nodules since childhood. The tumor size ranged from 5.5 to 20 cm (Makhlouf et al. 2009).

NSET may be associated with Cushing syndrome. Among six patients with NSET reported in 2005, two patients showed ectopic ACTH (adrenocorticotropic hormone) production associated with Cushing syndrome that abated after excision of the tumors. An association between NSET and

Cushing syndrome due to ectopic ACTH synthesis by the tumor was subsequently confirmed in other reports (Makhlouf et al. 2009; Rod et al. 2009; More et al. 2011; Geramidzadeh et al. 2012). Rod and coworkers (2009) described a 17-year-old female patient who had a large NSET with mild Cushingoid clinical features and intense biological hypercortisolism but moderate ACTH secretion. The epithelial component of the tumor co-expressed ACTH mildly, corticotropin-releasing hormone (CRH) strongly, and 11-beta-hydroxysteroid dehydrogenase at a level comparable with normal hepatocytes. The findings suggest that ectopic ACTH syndrome in these neoplasms may be caused by CRH production inducing ACTH synthesis. More et al. (2011) identified ectopic ACTH syndrome in one NSET patient among ten patients with this syndrome, seven other patients having well-differentiated neuroendocrine tumors (mostly bronchial carcinoid), one a poorly differentiated thymic carcinoma, and one an Ewing's sarcoma.

Pathology

Macroscopy

At gross examination, the tumors are medium-sized to sometimes large and circumscribed, lobular white to gray-white masses. The growth pattern is usually expanding, with signs of some perifocal atrophy of the liver substance. On cut surfaces, a granular aspect on a fibrous-looking background may be noted, owing to the presence of larger epithelioid nests. In the case of marked calcification and/or ossification, white speckles may be noted on the cut surface.

Histopathology

A characteristic feature of NSET is the presence of numerous small nests composed of epithelioid cells and spindle cells. At low magnification, these nests form discrete and well-demarcated foci scattered within a hypocellular and sometimes myxoid stroma, which itself exhibits a somewhat fuzzy border with respect to adjacent liver, but without clear-cut signs of invasive growth. These cellular nests are most often oval, but they may also show a more irregular shape, but even in these situations, maintaining smooth and rounded edges. The nests range in size from 0.1 to almost 1 cm. The largest nests were identified in tumors from adolescent females (Heerema-McKenney et al. 2005). The nests typically show a gradient of centrally placed epithelioid cells and more peripherally placed spindle cells. The epithelioid cells occur in the major variants, viz., eosinophilic cells (sometimes with hepatoid features), clear cells, and cells with a pale, ill-defined cytoplasm. The nuclei of the epithelioid cells are round to ovoid, with a finely stippled chromatin and small nucleoli. The transition to spindle cells is sometimes abrupt. Spindle cells are arranged in streams or parallelly oriented fascicles with a pale to slightly eosinophilic cytoplasm and larger oval nuclei with stippled chromatin, different from that of surrounding myofibroblasts. In few cases, psammoma bodies and/or osteoid foci are noted within the epithelioid nests (Figs. 1, 2, 3, 4, and 5).

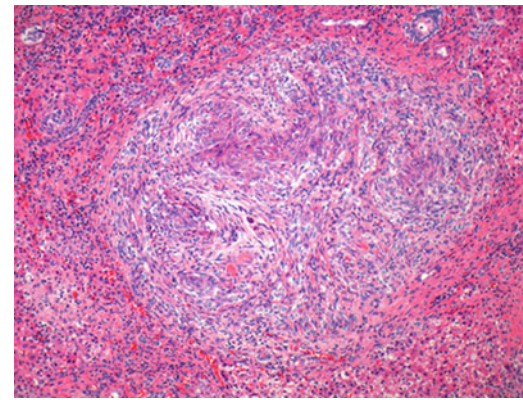

Fig. 1 NSET. A hypercellular tumor nodule consists of spindle cells arranged in haphazard manner (hematoxylin and eosin stain)

Large epithelioid nests may undergo cystic change, the cysts being lined by degenerating epithelioid cells. Such cysts may contain a lightly eosinophilic fluid (Heerema-McKenney et al. 2005). Mitotic activity in the nests is low (Hill et al. 2003). In the study of Heerema-McKenney et al. (2005), the majority of

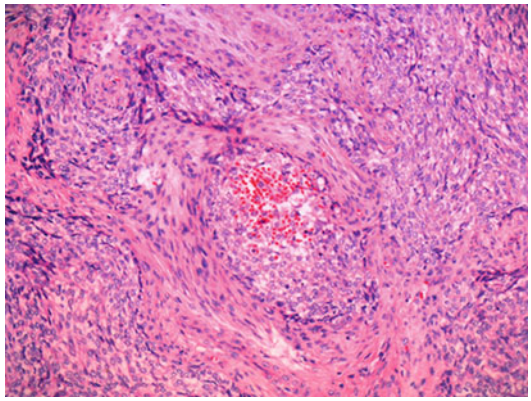

Fig. 2 NSET. The nodules show epithelial and spindle cells in interior parts and are surrounded by a sheath of eosinophilic, elongated spindle cells (hematoxylin and eosin stain)

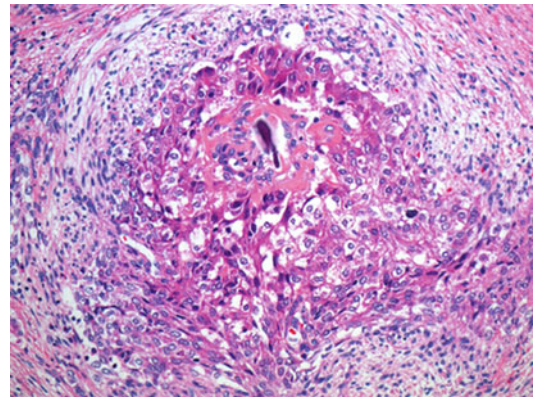

Fig. 4 NSET with osteoid formation in the center of a nodule (homogeneous eosinophilic structures). Note that a part of centrally located tumor cells have a hepatoid appearance (hematoxylin and eosin)

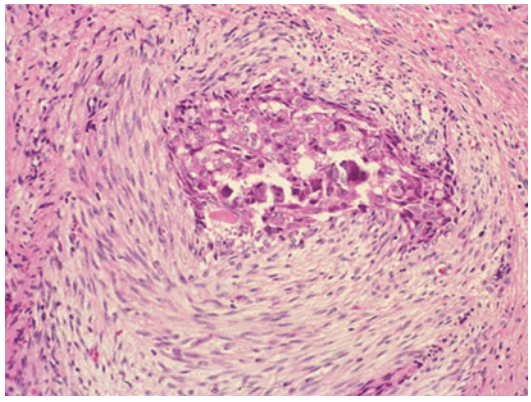

Fig. 3 NSET. The core of tumor nodules can contain calcifications (hematoxylin and eosin stain)

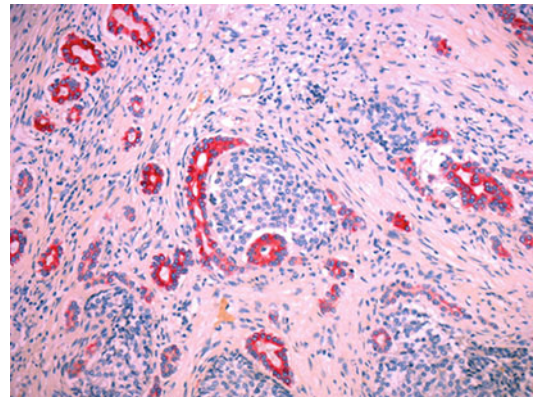

Fig. 5 NSET. The tumor nodules are associated with ductule-like cholangiocytic structures (cytokeratin 19 immunostain)

epithelioid nests had one or fewer mitotic figures per HPF, but there are cases having five or more mitotic figures per HPF. In some cases, confluence of nests was noted, with proliferative lesions entrapping stromal components and containing extensive necrosis with a foam cell reaction and some multinucleated giant cells (Heerema-McKenney et al. 2005). Tumors associated with ectopic ACTH syndrome were found to show a neuroendocrine-appearing trabecular architecture at the periphery of the tumors. In such areas, the surrounding stroma was attenuated (Heerema-McKenney et al. 2005). The nests are surrounded by a spindle cell sheath or collar of variable thickness, which is clearly demarcated from the stromal background of the tumor (Zimmermann and Lopez-Terrada 2011). The cells are morphologically typical myofibroblasts, with an amphophilic cytoplasm and elongated, tapered nuclei. The nuclei show a bland chromatin and tiny nucleoli. These cells are strongly reactive to alpha-SMA and are myofibroblasts. The myofibroblastic sheath can cause invaginations of the nests. Close to the nests and also outside the myofibroblastic sheath, one notes calcifications, sometimes of the psammomatous type, and osteoid with typical osteoblasts. In some nests, atrophy of the epithelioid and spindle cells seem to have occurred and only the calcifications

and the osteoid signal the former lesion. In some tumor, the osteoid tissue is maturing to lamellar bone and forms sickle-shaped structures surrounding the nests.

Ultrastructure

So far, only few information regarding the ultrastructure of NSET are available. In one case report, the nested tumor cells showed focally well-developed cell junctions, a basal lamina, and only few cytoplasmic organelles (Hill et al. 2003).

Immunohistochemistry

The cellular nests are variably immunoreactive for epithelial membrane antigen/EMA, pan-cytokeratin (AE1/AE3/LP34), S-100 protein, CD56, and CD57. Similar to spindle cells, epithelioid cells may be positive for WT-1 (amino terminus) (Hill et al. 2003; Heerema-McKenney et al. 2005; Makhlouf et al. 2009; Zimmermann and Lopez-Terrada 2011). Cell of the nests displays marked nuclear reactivity for beta-catenin, while other cells located in the tumor nodules are either negative or show membranous staining (Zimmermann 2005; Zimmermann and Lopez-Terrada 2011). The spindle cells of the cellular sheath surrounding the nests are markedly positive for alpha-SMA, representing myofibroblasts (Zimmermann and Lopez-Terrada 2011). The cells are negative for the hepatocyte marker, Hep Par 1 (Zimmermann and Lopez-Terrada 2011), negative for cytokeratins 7 and 20 (Makhlouf et al. 2009), and negative for AFP, polyclonal CEA, chromogranin A, synaptophysin, desmin, and inhibin (Heerema-McKenney et al. 2005). In cases with Cushing syndrome, the cells of the nests were immunoreactive for ACTH (Heerema-McKenney et al. 2005). The nuclei of spindle cells in the nests are strongly and diffusely positive for WT-1 (amino terminus). These cells are also reactive for vimentin, CD56, and neuron-specific enolase and focally for cytokeratin. The cells of the myofibroblastic collar are markedly positive for alpha-SMA and vimentin and focally positive for CD34 (Figs. 6, 7, 8, and 9).

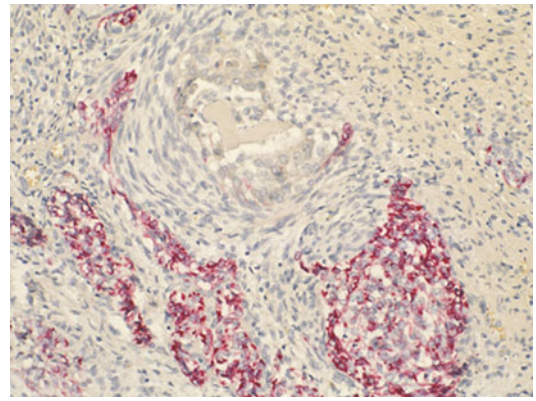

Fig. 6 NSET. Part of the epithelioid cells, but not the spindle cells of nodules, express cytokeratins 8/18 (CAM5.2 immunostain)

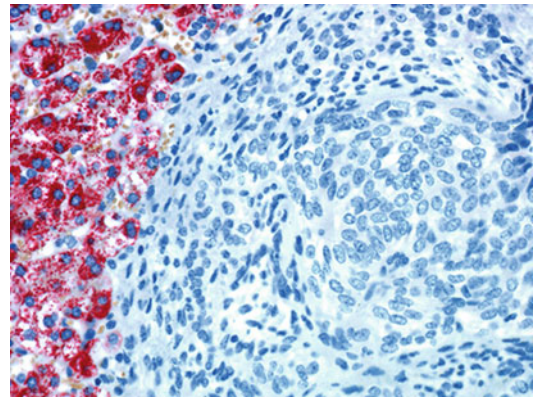

Fig. 7 NSET. In contrast to normal hepatocytes (to the *left*), nodule cells are not reactive for a hepatocyte marker (Hep Par 1 immunostain)

Differential Diagnosis

Hepatic tumors characterized by a mixture of spindled cells and epithelial/epithelioid cells as seen in NSET comprise other mixed tumors chiefly occurring in adults: synovial sarcoma of the liver, desmoplastic small round cell tumor (DSRCT), and epithelioid Schwann cell tumors. The histology of NSET, specifically its organoid structure, the distinctive nested arrangement of

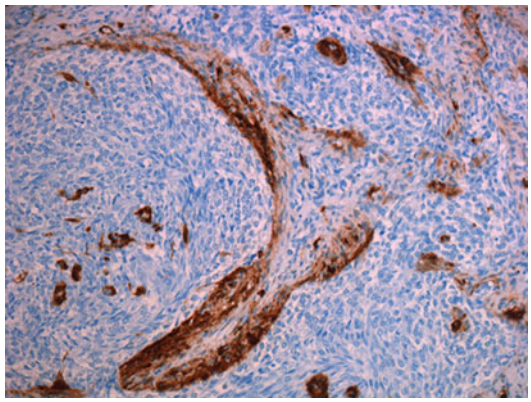

Fig. 8 NSET. The sheath of spindle cells surrounding the inner core of nodules is smooth muscle actin-positive and consists of myoid cells (alpha-SMA immunostain)

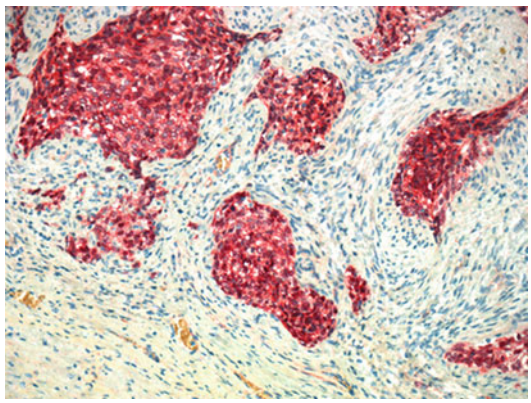

Fig. 9 NSET. Inner cells of tumor nodules are strongly reactive for beta-catenin, with both cytoplasmic and nuclear staining (beta-catenin immunostain)

the epithelioid cells, the myofibroblast sheath, and the osteoid formation together with psammomatous calcifications, is characteristic and will not be easily confounded with other bimorphic tumors.

Biology of Disease

NSETs often present as circumscribed tumors without evidence of local invasive growth or metastases at diagnosis. In an early study of four children with NSET, all patients were doing well after resection without recurrence after a follow-up ranging from 8 months to 7.5 years (Hill et al. 2003). However, a part of the NSET reveal a more aggressive course, with multifocal recurrence in the liver and extrahepatic metastasis (Heerema-McKinney et al. 2005; Brodsky et al. 2008; Makhlouf et al. 2009). Brodsky and coworkers reported a 17.5-year-old female with NSET causing Cushingoid features. After resection of the initial lesion, the tumor recurred in the form of multiple hepatic tumors 1 year later (Brodsky et al. 2008). In the series of nine patients reported by Makhlouf et al. (2009), two patients exhibited local recurrences successfully treated by radiofrequency ablation. In a 16-year-old girl with NSET, which was free of detectable metastases at diagnosis, liver transplantation was performed. At 28 months postoperatively, lung metastases were found and the patient died 37 months after transplantation from progressive pulmonary metastatic disease (Hommann et al 2011). So far, the biology of NSETs is best considered a low-grade malignancy (Makhlouf et al. 2009).

Pathogenesis

An interesting feature in the context of putative pathogenic pathways is the consistent finding of a marked nuclear immunoreactivity of nested cells for beta-catenin (Zimmermann 2005), a feature shared between NSET and many hepatoblastomas. It was later found that NSET can show mutations of the beta-catenin gene, characterized by large deletions in exon 3, resulting in an accumulation of beta-catenin in cytoplasm and nuclei of tumor cells (Assmann et al. 2012). In this investigation, the expression of the mesenchymal-epithelial transition factors Snail, Slug, Twist, c-met, vimentin, and beta-catenin was generally increased, whereas E-cadherin was decreased. It was suggested that NSET might be a variant of hepatoblastoma and showing impaired mesenchymal-epithelial transition (Assmann et al. 2012).

References

Assmann G, Kappler R, Zeindl-Eberehart E, Schmid I, Häberle B, Graeb C, Jung A et al (2012) b-catenin mutations in 2 nested stromal epithelial tumors of the liver – a neoplasia with defective mesenchymal-epithelial transition. Hum Pathol 43:1815–1827

Brodsky SV, Sandoval C, Sharma N, Yusuf Y, Facciuto ME, Humphrey M, Yeh YA et al (2008) Recurrent nested stromal epithelial tumor of the liver with extra-hepatic metastasis: case report and review of literature. Pediatr Dev Pathol 11:469–473

Geramidzadeh B, Foroutan H, Foroutan A, Bordbar M (2012) Nested stromal epithelial tumor of liver presenting with Cushing syndrome: a rare case report. Indian J Pathol Microbiol 55:253–255

Ghodke RK, Sathe PA, Kandalkar BM (2012) Calcifying nested stromal epithelial tumor of the liver – an unusual tumor of uncertain histogenesis. J Postgrad Med 58:160–162

Grazi GL, Vetrone G, d'Errico A, Caprara G, Ercolani G, Cescon M, Ravaioli M, Del Gaudio M et al (2010) Nested stromal-epithelial tumor (NSET) of the liver: a case report of an extremely rare tumor. Pathol Res Pract 206:282–286

Heerema-McKenney A, Leuschner I, Smith N, Sennesh J, Finegold MJ (2005) Nested stromal epithelial tumor of the liver. Six cases of a distinctive pediatric neoplasm with frequent calcifications and association with cushing syndrome. Am J Surg Pathol 29:10–20

Heywood et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/11920471

Hill DA, Swanson PE, Anderson K, Covinsky MH, Finn LS, Ruchelli ED, Nascimento AG et al (2003) Desmoplastic nested spindle cell tumor of liver: report of four cases of a proposed new entity. Am J Surg Pathol 29:1–9

Hommann M, Kaemmerer D, Daffner W, Prasad V, Baum RP, Petrovich A, Sauerbrey A et al (2011) Nested stromal epithelial tumor of the liver – liver transplantation and follow-up. J Gastrointest Cancer 42:292–295

Ishak KG, Goodman ZD, Stocker JT (2001) Miscellaneous malignant tumors (chapter 11). In: Rosai J, Sobin LH (eds) Tumors of the liver and intrahepatic bile ducts. Armed Forces Institute of Pathology, Washington, DC

Makhlouf HR, Abdul-Al HM, Wang G, Goodman ZD (2009) Calcifying nested stromal-epithelial tumors of the liver: a clinicopathologic, immunohistochemical, and molecular genetic study of 9 cases with a long-term follow-up. Am J Surg Pathol 33:976–983

Malowany JI, Merrit NH, Chan NG, Ngan BY (2013) Nested stromal epithelial tumor of the liver in Beckwith-Wiedemann syndrome. Pediatr Dev Pathol 16:312–317

Meir K, Maly A, Doviner V, Gross E, Weintraub M, Rabin L, Pappo O (2009) Nested (ossifying) stromal epithelial tumor of the liver: case report. Pediatr Dev Pathol 12:233–236

More J, Young J, Reznik Y, Raverot G, Borson-Chazot F, Rohmer V, Baudin E, Coutant R et al (2011) Ectopic ACTH syndrome in children and adolescents. J Clin Endocrinol Metab 96:1213–1222

Oviedo Ramirez MI, Bas Bernal A, Ortiz Ruiz E, Bermejo J, De Alava E, Hernandez T (2010) Desmoplastic nested spindle cell tumor of the liver in an adult. Ann Diagn Pathol 14:44–49

Rod A, Voicu M, Chiche L, Bazille C, Mittre H, Louiset E, Reznik Y (2009) Cushing's syndrome associated with a nested stromal epithelial tumor of the liver: hormonal, immunohistochemical, and molecular studies. Eur J Endocrinol 161:805–810

Wang Y, Zhou J, Huang WB, Rao Q, Ma HH, Zhou XJ (2011) Calcifying nested stroma-epithelial tumor of the liver: a case report and review of literature. Int J Surg Pathol 19:268–272

Zimmermann A (2005) The emerging family of hepatoblastoma tumours: from ontogenesis to oncogenesis. Eur J Cancer 41:1503–1514

Zimmermann A, Lopez-Terrada D (2011) Pathology of pediatric liver tumors. In: Zimmermann A, Perilongo G, Malogolowkin M, Von Schweinitz D (eds) Pediatric liver tumors, Pediatric oncology series. Springer, Berlin

Hepatocellular Adenoma

24

ICD-O code: 8170/0

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_24

Abstract

Hepatocellular adenoma (HCA) is defined as benign liver neoplasm composed of hepatocytes. HCA is a rare hepatic neoplasm, accounting for 0.6 % of all liver tumors. In occidental countries, it chiefly occurs in young females, with an estimated incidence of 3–4 cases per 100,000. The female preponderance is considered to be related to ingestion of sex steroids/oral contraceptives. The standard histology of HCA is characterized by mature-looking hepatocytes that form slender plates. The reticulin pattern is normal. The cells are rich in glycogen and may undergo steatosis. HCA can contain peliosis-like blood-filled spaces and has a tendency for hemorrhage. HCAs are circumscribed but lack a capsule. There are distinct variant patterns associated with molecular abnormalities. Modern classifications of HCA are based on specific molecular features and distinguish hepatocyte nuclear factor 1alpha mutated, beta-catenin mutated, beta-catenin activated, inflammatory, and combined/mixed forms. HCA can undergo malignant transformation.

Introduction

According to the WHO classification of tumors, hepatocellular adenoma (HCA) is defined as a benign liver neoplasm composed of hepatocytes.

Liver cell adenoma has been described in the nineteenth century already (Jungmann 1861; Griesinger 1864; Rindfleisch 1864; Mahomed 1877; Simmonds 1884), and only relatively few reports are known from the first part of the twentieth century (Shaw 1923; Wilens 1938). The issues of HCA morphology, classification, and biology have been reviewed several times in recent years, together with the elucidation of a novel classification based on distinct molecular features.

Selected References Bioulac-Sage et al. 2007a, b, c, 2008; Paradis 2010; Katabathina et al. 2011; Balabaud et al. 2013; Dhingra and Fiel 2014; Sempoux et al. 2014.

Epidemiology

Hepatocellular Adenoma in Adults

HCA is a rather rare lesion, estimated to account for 0.6 % of all liver tumors (Edmondson 1958). In occidental countries, HCAs now chiefly occur in young females, with an estimated incidence of 3–4 cases per 100,000. In Asia, the incidence is lower. In a review of 50,000 autopsies at the Los Angeles County Hospital from 1918 to 1954, only two HCA were detected. However, oral contraceptives and other sex steroid administrations have increased the frequency of these tumors (see below). The male-to-female incidence ratio is 1:17 (Foster and Berman 1977; Theruvath et al. 2011), this impressive asymmetry most probably being caused by the effect of endo- or exogenous aromatic steroids on HCA tumorigenesis (see below). It is estimated that around 80 % of HCAs occur in users of oral contraceptives, but in the course of low-estrogen preparation use, the incidence in women may decrease. In recent decades, there was a trend toward an increase in HCAs reported in men in several countries (Ronald et al. 2004; Chang et al. 2013). Also in Japan, the former strong preponderance of women was not found (Sasaki and Nakanuma 2012).

Pediatric Hepatocellular Adenoma

HCA can occur in neonates, children, and adolescents (Chandra et al. 1984). Also multiple HCAs (adenomatosis) can occur in the pediatric age group. The neoplasms often develop as sporadic lesions, but can also emerge in association with administration of steroids or diverse inborn conditions, including familial adenomatous polyposis, glycogenosis, disorders of cortisol metabolism, and microvillus inclusion disease.

Selected References Christopherson and Collier 1953; Pollice 1973; Corberand et al. 1975; Ishak 1976; Dehner 1978; Dehner et al. 1979; Ehren et al. 1983; Brunelle and Chaumont 1984; Chandra et al. 1984; Karhunen 1986; Lack and Ornvold 1986; Wheeler et al. 1986; Yandza and

Valayer 1986; Suh et al. 1987; Fremond et al. 1987; Brophy et al. 1989; Janes et al. 1993; Callea et al. 1993; Khoo et al. 1994; Resnick et al. 1995; Bala et al. 1997; Milillo et al. 1997; Applegate et al. 1999; Sato et al. 2000; Meyers and Scaife 2000; Marie-Cardine et al. 2001; Skarupa et al. 2004; Chung et al. 2006; Hussain et al. 2006; Franchi-Abella and Branchereau 2013; Vaithianathan et al. 2013.

Classification

Modern classifications of HCA are chiefly based on molecular approaches that have shown that HCA is a heterogeneous entity. The current classification of HCAs lists several categories, i.e., hepatocyte nuclear factor 1alpha-mutated HCA (H-HCA; 35 % of cases), beta-catenin-mutated HCA (b-HCA; 10 % or less), inflammatory HCA (IHCA; 55 %), beta-catenin-activated inflammatory HCA (b-IHCA; 10 % of IHCA), mixed/combined, and unclassifiable HCA (Table 1). An additional complex spectrum of lesions is telangiectatic HCA, most of these cases having previously been classified as telangiectatic focal nodular hyperplasia. These lesions are now, at least in part, listed together with inflammatory adenomas.

Selected References Bluteau et al. 2002; Chen et al. 2002; Takayasu et al. 2002; Zucman-Rossi et al. 2006; Bioulac-Sage et al. 2007c, 2009; Rebouissou et al. 2008; Shanbhogue et al. 2011; Sasaki and Nakanuma 2012; Fonseca et al. 2013; Liau et al. 2013; Nault and Zucman-Rossi 2013; Nault et al. 2013; Sempoux et al. 2013; Shafizadeh et al. 2014.

Table 1 Current classification of hepatocellular adenoma (HCA)

Type of HCA	Molecular alterations
HNF-1alpha-mutated HCA (H-HCA)	HNF-1alpha (TCF1 gene); CYP1B1
Beta-catenin-mutated HCA (b-HCA)	Beta-catenin (CTNNB1 gene)
Inflammatory HCA (IHCA)	IL6ST (65 %), STAT3 (6 %), GNAS (5 %)
Beta-catenin-activated IHCA (b-IHCA)	Beta-catenin
Combined/mixed HCA	
Unclassifiable HCAs	

HNF1A-Inactivated HCA (H-HCA)

Roughly 40–50 % of HCAs show mutations of hepatocyte nuclear factor-1alpha/HNF-1alpha/HNF1A encoded by the TCF1 gene (H-HCA; Bluteau et al. 2002; Bacq et al. 2003; Zucman-Rossi et al. 2006; Laumonier et al. 2008a; Holter et al. 2011; Sakellariou et al. 2011; Iwen et al. 2013; review: Bioulac-Sage et al. 2007c). HNF1A is a transcription factor involved in hepatocyte differentiation and glucose homeostasis. HNF1A mutations are known to cause maturity-onset diabetes of the young (MODY) type 3. H-HCA shows biallelic inactivating mutations of HNF1A, whereby in 85 % both mutations are of somatic origin, while in 15 % one mutation is germline and the other somatic. Somatic and germline mutations of HNF-1alpha were also detected in familial liver adenomatosis (Bacq et al. 2003). Patients having germline HNF1A mutation are generally younger and often have a family history of liver adenomatosis. In particular, families with autosomal-dominant MODY type 3 diabetes caused by HNF1A mutations are prone to develop liver tumors, including HCA and HCC (Reznik et al. 2004; Willson et al. 2013). However, the spectrum of HNF1A somatic mutations in HCA differs from that in patients with MODY type 3 (Jeannot et al. 2010). In a subset of patients with H-HCA, heterozygous germline mutations of CYP1B1, causing reduced activity cytochrome p450, were identified (Jeannot et al. 2007). In rare cases, H-HCA may coexist with IHCA (Castain et al. 2014), and there are rare "mixed" genotype adenomas with both mutations of HNF-1alpha and beta-catenin (Fonseca et al. 2013). Pathogenetically, there is evidence that loss of HNF1A leads to aberrant expression of several genes with a potential significance for tumorigenesis, including growth factor receptors, cell cycle regulators, and factors affecting angiogenesis

(Pelletier et al. 2010). The pathologic phenotype of H-HCA is usually adenoma with marked steatosis, lack of inflammatory changes, and absence of atypia. Typically, H-HCA lacks immunoreactivity for liver fatty acid-binding protein (LFABP). Transformation to malignancy is less common than in b-HCA.

b-HCA

Less than 10 % of HCA show mutations in the beta-catenin gene (the CTNNB1 gene) including exon 3 deletions (Zucman-Rossi et al. 2006; Bioulac-Sage et al. 2007a; Chu and Moon 2013). These mutations are associated with marked expression of two beta-catenin target genes, glutamine synthetase and G-protein-coupled receptor 49/GPR49. b-HCA more often occurs in males, is less frequently steatotic, and more commonly exhibits acinar structures and nuclear atypia. In most Western cases, b-HCA is strongly associated with malignant transformation and may thus represent a borderline lesion. Immunohistochemically, b-HCA is characterized by nuclear reactivity for beta-catenin and strong and diffuse immunostaining for glutamine synthase.

IHCA

The majority of HCAs lack mutations in HNF1A or beta-catenin genes. This is heterogeneous group of adenomas that probably contains several entities and also includes lesions that have previously been termed telangiectatic HCA (see below). The principal member of the group is inflammatory HCA (IHCA), a neoplasm that was formerly classified, at least in part, as telangiectatic HCA and as the telangiectatic variant of focal nodular hyperplasia/FNH. IHCA is more common in women and can be associated with a systemic inflammatory syndrome, anemia, and amyloidosis and is more often encountered in patients with high alcohol consumption and obesity (Paradis et al. 2007; review: Bioulac-Sage et al. 2007a). In one series, 50 % of involved women had taken oral contraceptives (Fonseca et al. 2013). Typical IHCA are characterized by the presence of an inflammatory infiltrate, variable angiectases, and overexpression of acute inflammatory response genes (Bioulac-Sage et al. 2007a). In up to 65 % of IHCAs, recurrent somatic mutations in the interleukin-6/IL-6 signal transducer (IL6ST) locus, encoding the IL-6 effector gp130, are present. These mutants are associated with constitutive and IL-6-independent activation of the JAK1(Janus kinase1)/STAT signaling pathway (Rebouissou et al. 2009; Sommer et al. 2012; Poussin et al. 2013). In a minority of cases of IHCA, activating mutations involve STAT3 involved in the activation of the JAK/STAT pathway (Pilati et al. 2011) and GNAS/G protein alpha subunit (Nault et al. 2012), but in almost 25 % of cases, no genetic abnormality has been identified so far (review: Nault and Zucman-Rossi 2013). In an IHCA found in a patient with Castleman's disease, the tumor transformed into HCC and showed mutations for both gp130 and beta-catenin. High IL-6 secretion by the lymphoproliferative disorder may have played a role (Chun et al. 2012). In patients with multiple IHCA, part of the nodules can in addition show beta-catenin activation (b-IHCA), suggesting that beta-catenin mutations might be a late event in the tumorigenic pathway (review: Bioulac-Sage et al. 2013). The features of IHCA are outlined in more detail in a following paragraph.

Around 10 % of IHCA exhibit abnormal beta-catenin activation and are termed beta-catenin-activated IHCA (b-IHCA).

Coexistent IHCA and H-HCA

Recently, coexistence of inflammatory HCA and HNF1alpha-inactivated HCA was described. This coexistence was found in eight female and one male patients, with variable numbers of nodules and sizes of largest and smallest HCAs. This observation suggests coexistence of different genotypes with multiple adenomas potentially caused by a "benign tumorigenic field effect" (Castain et al. 2014).

Clinical Features of Hepatocellular Adenoma

The clinical, pathologic, and radiologic features of HCA have been described in detail (Kerlin et al. 1983). Pain and abdominal dullness are frequent symptoms (Cho et al. 2008). In the overview of Yoshidome and coworkers, analyzing 32 cases (Yoshidome et al. 1999), 63 % of the patients were female, abdominal pain was the leading symptom in 59 %, and 41 % had evidence of tumor hemorrhage. In a study on eight female patients with multiple HCA/adenomatosis (Ribeiro et al. 1998), abdominal pain was the presenting symptom in 87.5 %, higher than in patients with solitary HCA (42.1 %). Obesity and features of metabolic syndrome were frequently observed in patients with HCA (-Bunchornavakul et al. 2011).

HCA can cause paraneoplastic syndromes, including prurigo (Loze et al. 2000) and erythrocytosis (Marie-Cardine et al. 2001; Vik et al. 2009).

Major complications of HCA consist of infarction, intratumoral hemorrhage, and spontaneous rupture, resulting in hemoperitoneum (Leborgne et al. 1990; Chiappa et al. 1999; Adusumilli et al. 2002; Kumar et al. 2004; Deneve et al. 2009; Santambrogio et al. 2009; van Aalten et al. 2012; Bieze et al. 2014). In part of the cases, spontaneous rupture occurred after prolonged use of oral contraceptives (Pollak 1979; Meissner 1998; Chiappa et al. 1999) or of methyltestosterone (Bird et al. 1979). HCAs are also prone to rupture subsequent to sometimes minor blunt abdominal trauma (Suarez-Penaranda et al. 2001). HCAs can undergo hemorrhage without rupture (Boulafendis et al. 1985; Fink et al. 1985; Mueller et al. 1995; Croes et al. 1998; Bagia et al. 2000; Closset et al. 2000; Heeringa and Sardi 2001; Gunsar et al. 2002; Minami et al. 2002; Cotta-Pereira et al. 2013). Tumor bleeding was present in 62.5 % in adenomatosis (mostly in lesions larger than 4 cm) and in 26.3 % of the patients with solitary HCA. In another study, intralesional hemorrhage was found in 75 % of cases (Ji et al. 2000). In one study, risk factors for bleeding of HCA included a diameter of 35 mm or more, visualization of lesional arteries, location in the left lateral liver, and exophytic growth (Bieze et al. 2014). Infarctions and hemorrhages are relatively frequent events in HCA (Grazioli et al. 2001). Therefore, HCA may clinically present as acute surgical emergencies, and therefore resection of HCA larger than 5 cm diameter has been advocated to reduce the risk of such complications (Terkivatan et al. 2001). There is evidence that intralesional hemorrhage is associated with the onset of menstruation in women taking oral contraceptives (Edmondson et al. 1976).

The pertinent imaging features of HCA have been documented in numerous reports.

Selected References Fléjou et al. 1985; Quinn et al. 1986; de Baets et al. 1993; Arrivé et al. 1994; Miyazaki et al. 1994; Paulson et al. 1994; Chung et al. 1995; Arsenault et al. 1996; Bartolozzi et al. 1997; Chiche et al. 2000; Ichikawa et al. 2000; Grazioli et al. 2000, 2001, 2013; Hung et al. 2001; Kebapci et al. 2001; Morel et al. 2002; Faria et al. 2004; Dietrich et al. 2005; Laumonier et al. 2008b, 2012; Ricci et al. 2008; Katabathina et al. 2011; Ronot et al. 2011; Ros and Goodman 2011; van Aalten et al. 2011a; Manichon et al. 2012; Yoneda et al. 2012; Abir et al. 2013; Thomeer et al. 2014.

General Pathology of Hepatocellular Adenoma

Macroscopy

HCAs, which can be solitary or multiple lesions, are classically soft and spheroid or globular, well-demarcated tumors sometimes deforming the involved part of the liver. Many HCAs have, at the time point of diagnosis, a diameter of 10–15 cm and a mass of about 500 g, but much smaller lesions with diameter of few mm also occur (microadenomas), mainly in case of multiple lesions and adenomatosis (see below). In adenomatosis, hundreds of small to tiny lesions may be found. Solitary HCA can grow to impressive size, with diameters of up to 30 cm and a

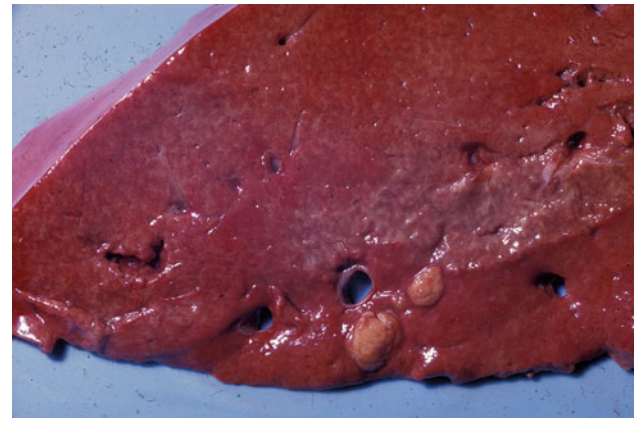

Fig. 1 Two small hepatocellular adenomas in a non-cirrhotic liver. In non-fixed specimens, the lesions appear as well-delineated *pale* to *yellow* and sometimes *tan* nodules

Fig. 2 In fixed resection specimens, hepatocellular adenomas present as *yellowish*, lobulated, and non-encapsulated tumor masses with an expanding growth pattern

weight of several kilograms ("giant liver cell adenoma"; Mueller et al. 1995; Nicastro et al. 1998). Giant HCA are associated with a particularly high incidence of rupture with intratumoral hemorrhage and may induce severe abdominal pain (Mueller et al. 1995; Reijnierse et al. 1997). HCA, in particular large tumors, can grow as exophytic or pedunculated masses (so-called hanging lesions; Ziegler and Glass 1966; Rafii 1971; Fléjou et al. 1985), and this phenomenon has also been detected in adenomatosis of the liver (Bader et al. 2001). HCA with beta-catenin activation may be larger than tumors of the other HCA types (Sasaki et al. 2011). On the cut surface, unchanged tumors exhibit a yellow to tan color; the tissue is soft or fleshy and may bulge from the surface. In part of the cases, marked accumulation of fat results in brightly yellow lesions (steatotic HCA). The tissue sometimes shows a nodular texture or a septate-like structure, but like in focal nodular hyperplasia, large blood vessels are often prominent within the tumor and on the surface (Figs. 1, 2, and 3).

Secondary Changes

HCA has a well-known tendency for intratumoral hemorrhage that may result in tumor rupture (Figs. 4, 5, 6, and 7). Necrosis and/or hemorrhage is frequently noted in tumors occurring subsequent to oral contraceptive therapy, and less often in other patients, fresh or old bleeding sometimes being an impressive change almost effacing the tumor tissue. In case of rupture, intratumoral hemorrhage is in direct continuation with the defect, which also contains fresh or coagulated blood, eventually resulting in a fistule-like alteration. HCA can undergo marked cystic change (Kobayashi et al. 1999), sometimes subsequent to necrosis and/or bleeding (Mays and Christopherson 1984). In rare cases, a giant multicystic tumor can develop (Katsuramaki et al. 2003). Calcifications and even bone formation with bone marrow have rarely been reported (Ranaldi et al. 1993). HCA are usually non-encapsulated tumors, although a thin pseudocapsule can occur, owing to the induction of matrix at the lesion's border (Craig et al. 1989).

Fig. 3 Large lipid-rich hepatocellular adenoma in a non-cirrhotic fatty liver

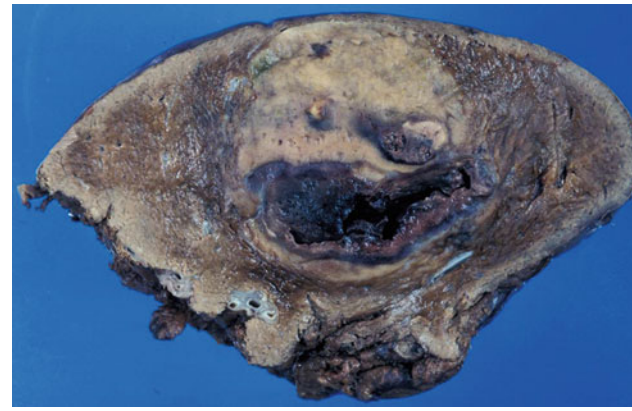

Fig. 4 Hepatocellular adenoma in a fixed resection specimen. More than a third of the tumor is occupied by rather fresh hemorrhage. The two *whitish* foci are necrotic tumor areas

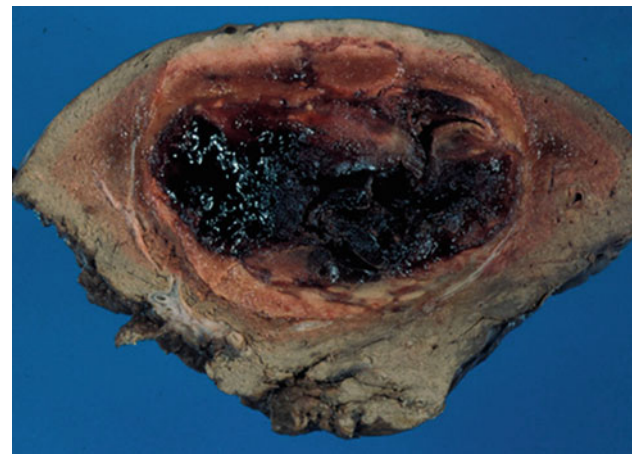

Fig. 5 Hepatocellular adenoma with massive hemorrhage ("tumor apoplexy"). Preserved tumor tissue is only present as a thin *yellow* rim at the periphery of the lesion

In rare cases, a thick capsule was found in large tumors (Ramakrishna et al. 1996). Remarkably, a fibrous capsule has been noted in all HCA occurring in five children (Wheeler et al. 1986), suggesting that there may be a difference in the response of the host organ between young and adult patients. Capsular features may be mimicked by the compression atrophy induced in adjacent liver substance. In case of (recurrent) bleeding at the periphery of the tumor, an inflammatory response followed by focal scarring can develop.

Fig. 6 Even small nodules of hepatocellular adenoma can develop hemorrhage, here in the form of tiny central speckles of bleeding

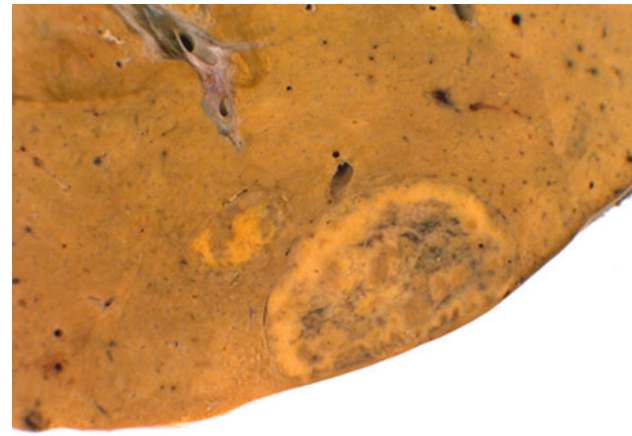

Fig. 7 Two peripherally located hepatocellular adenoma, one in a subcapsular position. Note the peripheral *yellow* tissue zone of the larger nodule, while numerous hemorrhages are present in the center

Histopathology

HCA consists of liver cell plates of normal or slightly increased width, and the hepatocytes are morphologically similar to normal parenchymal cells, albeit they are sometimes larger (Wegelin 1905; Fechner 1977; Ishak 1979; Bioulac-Sage et al. 2007b). The cells of HCA usually contain rather large amounts of glycogen. Deposition of neutral fat in tumor cells (steatosis) is rather common, and a part of HCAs exhibit marked fat accumulation (steatotic HCA), rendering the lesions macroscopically brightly yellow. A trabecular growth pattern mimicking normal liver cell plates predominates, but few tumors also display an acinar (or pseudoglandular) growth pattern. Nuclei are usually regular, nucleoli are not particularly prominent, and mitotic figures are mostly lacking (Figs. 8, 9, 10, 11, 12, 13, 14, and 15).

In a minority of HCA, nuclear atypias and increased mitoses are found. HCAs with acinar structures and nuclear atypia are difficult to distinguish from well-differentiated HCC by use of conventional diagnostic approaches. Uncommonly, the cells can display accumulation of hemosiderin, but not copper-associated protein, in contrast to fibrolamellar carcinoma, which is poor in glycogen and iron pigment, but usually shows copper-binding protein (Lefkowitch et al. 1983). In a minority of HCA, cells with steatosis also contain Mallory-Denk bodies, sometimes associated with steatohepatitis-like changes (Heffelfinger et al. 1987), a situation similar to alterations found in steatotic HCC. HCAs display a

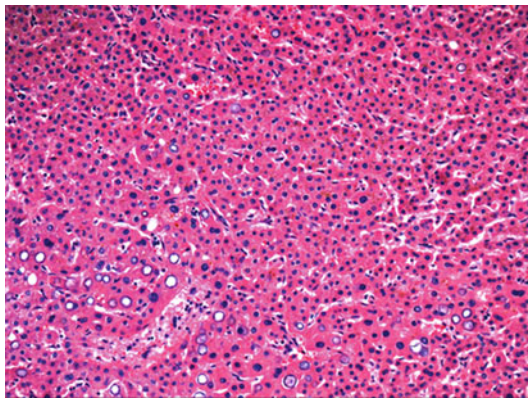

Fig. 8 Hepatocellular adenoma. Hepatocyte-like elements form slender cell plates that do not exceed a width of three cells. The microvascular system is sinusoidal. Part of neoplastic cells show nuclear vacuoles/invaginations (hematoxylin and eosin stain)

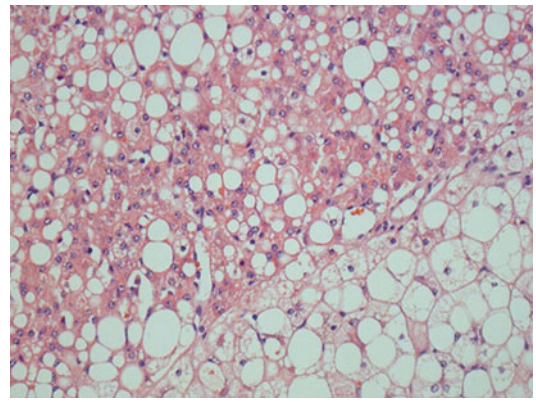

Fig. 10 Hepatocellular adenomas contain variable amounts of neutral fat/triglycerides, often in the form of macrovesicular steatosis. Tumor cells with a foamy cytoplasm may also develop (hematoxylin and eosin stain)

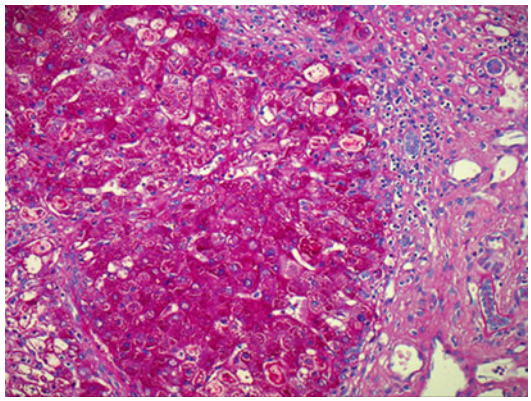

Fig. 9 In PAS stains, a high glycogen content of hepatocellular adenoma is in evidence (PAS stain)

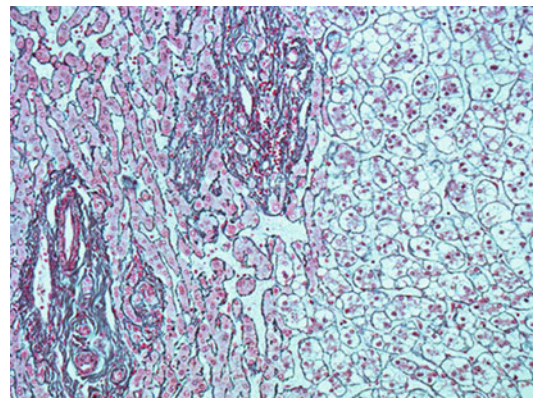

Fig. 11 In the reticulin stain, hepatocellular adenoma cell plates (*right half of figure*) are slender, but sometimes slightly thicker than normal hepatocyte plates seen in the *left half*. However, thin plates of normal hepatic tissue adjacent to tumor may in part be due to perifocal atrophy. Note that the sinusoidal channels of normal and tumor tissue are in continuation (*center*; Gomori silver stain)

reticulin pattern that is similar to that of normal liver, but clearly different from hepatocellular carcinoma (HCC), where the reticulin network is dramatically reduced. This difference manifests in fine-needle aspiration biopsies, where HCA cores are rigid, whereas HCC aspiration results in granular smears (Yang et al. 2004). However, reticulin loss can occur also in benign liver nodules in case of severe steatosis (Singhi et al. 2012).

HCA shows a characteristic vascular pattern. The parenchyma of the tumor is supplied by sometimes numerous thin-walled arteries that are not associated with portal tracts. The tumor discloses a sinusoidal vascular pattern conventionally similar to that in normal liver (Gouysse et al. 2004). The sinusoid-like channels may be dilated, and sometimes peliosis ensues. Immunohistochemically, the cells lining the channels are different from normal sinusoidal endothelium insofar as the cells in HCA are markedly reactive for CD34, similar to HCC, but in clear contrast to normal liver (Kong et al. 2000; Di

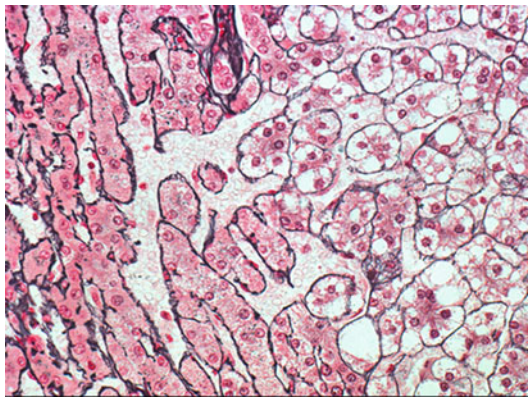

Fig. 12 At higher magnification, the distinct mode of vascular tumor feeding is characterized by a microvascular inlet structure that directs blood into the tumor periphery located to the right of the figure (Gomori silver stain)

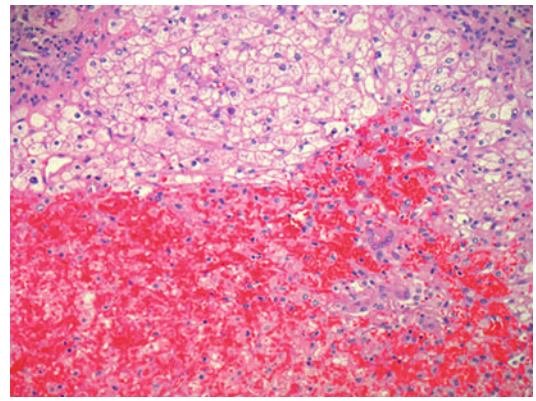

Fig. 14 Hepatocellular adenoma with fresh hemorrhage. Fragments of tumor within the hematoma are damaged and have lost the typical staining features (hematoxylin and eosin stain)

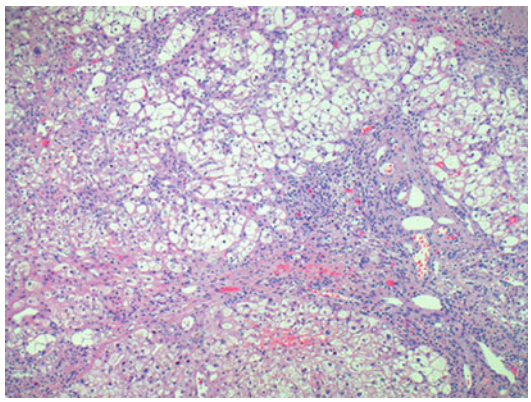

Fig. 13 Hepatocellular adenoma with inflammatory infiltrates, fibrosis, and focal clear cell change (hematoxylin and eosin stain)

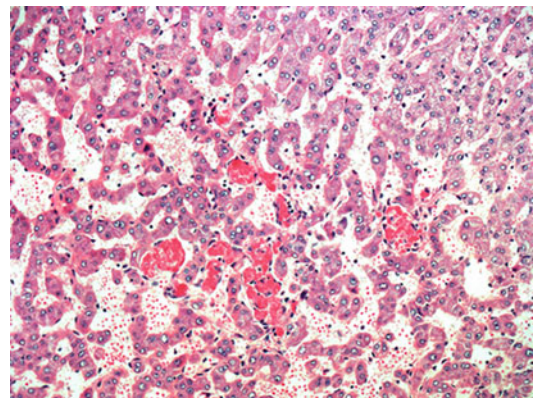

Fig. 15 Hepatocellular adenoma with ectatic sinusoids and fibrin-rich microthrombi with partial endothelialization (hematoxylin and eosin stain)

Carlo et al. 2002), suggesting an abnormal angiogenic response. In the acinus of the normal liver, CD34 expression is restricted to few sinusoidal endothelial cells in zone 1, i.e., close to the portal tracts, but CD34 is also expressed in endothelia of portal and hepatic veins (Theuerkauf et al. 2001). In some HCAs, these authors detected CD34 reactivity as reflecting a "lobular-like" vascular architecture, which is of interest insofar as HCA does not show a lobular internal pattern in routine sections. In addition, all HCAs had CD34-negative, CD105/endoglin-positive sinusoids which were oriented to draining veins, suggesting that these tumors have, in contrast to HCC, identifiable vascular inflow and outflow beds (Theuerkauf et al. 2001). The sinusoidal vascular channels of HCA contain Kupffer cells, in contrast to older views claiming that these tumors do not harbor such cells, although to variable amounts and with variable and sometimes reduced function (Goodman et al. 1987; Akatsu et al. 2004). Sometimes these hepatic macrophages are laden with PAS-positive material. In an immunohistochemical analysis of seven adenomas, lysozyme-reactive Kupffer cells were detected in each

lesion; three tumors had fewer Kupffer cells than the surrounding liver, three displayed about the same number, and one HCA showed more Kupffer cells (Goodman et al. 1987). In a retrospective review of 13 pathologically proven cases of HCA with technetium-99m sulfur colloid scintigrams, Kupffer cells were present in all 13 cases, and there were no histologic differences between tumors with colloid uptake and those without it (Lubbers et al. 1987). The presence of Kupffer cells indicates that the microenvironment for monocyte/macrophage homing into a vascular compartment in HCA is similar to that in the normal liver.

HCAs can undergo several common secondary changes. The most common alteration is hemorrhage, which may be focal and in some cases massive, almost effacing the tumor's tissue and rendering diagnosis difficult. In extreme situations, an HCA may present as a large hepatic hematoma, sometimes associated with rupture. Hemorrhage can be accompanied by edema, and in later phases, iron-loaded macrophages (siderophages) and granulation tissue followed by fibrosis (not real tumor stroma) can be found. Some HCAs show necrosis or even infarction, and part of these cases later show dystrophic calcification.

Less Common Histologic Features and Secondary Alterations

HCAs sometimes exhibit lipogranulomas, or intratumoral granulomas of unknown origin, and rarely numerous granulomas in both the tumor and the surrounding liver have been observed (Malatjalian and Graham 1982; Bieze et al. 2012). Granulomas have also been reported in liver adenomatosis, with granulomatous reactions in the tumors and/or the adjacent liver (Le Bail et al. 1992). The pathogenesis of epithelioid cell granulomas in HCA or in HCC, where they also may occur (Tomimatsu et al. 1982), is unknown. Other rare changes include the formation of intratumoral bone marrow tissue in tumors of children and adolescents (Wheeler et al. 1986; Anthony 1988), but also in adults (Ranaldi et al. 1993). The case of Ranaldi and coworkers involved a 65-year-old male patient with a large HCA showing hemorrhages, focal cystic change, and gross calcifications. Apart from the typical morphology of HCA, this tumor displayed multiple areas of trabecular bone, whose lumina were filled with adipose tissue and bone marrow, with a slight prevalence of erythroblasts. Extramedullary hematopoiesis is more frequently seen in other hepatic tumors, in particular hepatoblastomas. Interestingly, extramedullary hematopoiesis has also been noted in lesions classified as hepatic or hepatocellular adenoma of the placenta.

One very rare variant of HCA is characterized by the presence of adenoma cells embedded in an abundant matrix with myxoid features (myxoid HCA; Galassi et al. 1995). One report described a T1-hyperintense and T2-hypointense HCA with histologically proven iron overload of the tumor cells (siderotic liver cell adenoma; Cheng et al. 1995). Iron deposition occurs in other nodular hepatocyte lesions, including adenomatous hyperplasia and siderotic nodules in liver cirrhosis (Murakami et al. 1991).

Ultrastructure

HCAs exhibit alpha glycogen particles and lipid droplets in their cytoplasm. Typically, HCA cells have normal or reduced numbers of mitochondria (Garancis et al. 1969; Kay and Schatzki 1971; Sumner and Rosai 1981). Ultrastructurally, small blood vessels of HCAs have abnormal endothelial cells. These cells have an irregular thickness, most of them have few fenestrae. Instead of perivascular stellate cells, HCAs showed perivascular myofibroblast-like cells separated from endothelial cells by a basement membrane, corresponding to capillarization (Bioulac-Sage et al. 1986).

General Immunohistochemical Features

In this paragraph, general immunohistochemical features of HCAs are discussed, whereas specific immunophenotypical features of the novel HCA phenotypes are addressed in subsequent

paragraphs. Immunohistochemistry of HCAs is helpful to distinguish these lesions from FNH and HCC, also on needle biopsies (Ahmad et al. 2009; Bellamy et al. 2013; Bioulac-Sage et al. 2012a). HCA cells show cytokeratin 7 reactivity in patches, with gradual decrease in staining intensity as a function of hepatocyte differentiation (Iyer et al. 2008). But HCAs lack a cholangiocyte-related lineage and are therefore not, or only focally and weakly, reactive for cytokeratin 19 or NCAM (Iyer et al. 2008; Ahmad et al. 2009). In contrast to HCCs, HCA cells are not immunoreactive for glypican-3 (Wang et al. 2008; Lagana et al. 2013) or heat-shock protein-70/HSP-70 (Lagana et al. 2013), but are positive for HepPar-1 and arginase-1 (McKnight et al. 2012). Part of HCAs are reactive for glutamine synthetase (Lagana et al. 2013), but mostly those with beta-catenin mutation (see below). HCA cells show granular or globular cytoplasmic immunoreactivity for alpha-1-antitrypsin, but less frequently than HCC (Palmer et al. 1977). The cell surface adhesion molecule, cadherin, shows a more heterogeneous membranous expression in HCAs than in FNH or normal hepatocytes (Kozyraki et al. 1996). Expression of the adhesin, CD44, was detected in a minority of HCA (Washington et al. 1997). Carcinoembryonic antigen/CEA is usually not expressed in HCA (Koelma et al. 1986). In contrast to both, HCC and fibrolamellar carcinoma, HCAs show a significant level of immunoreaction to the basic (Ya) subunit of glutathione-S-transferase (Hayes et al. 1986). A part of HCAs express Golgi phosphoprotein 2/GOLPH2 (Riener et al. 2009). In contrast to HCCs, LCAs lack expression of matrix metalloproteinase-7 (Tretiakova et al. 2009). Lipid droplets in steatotic HCA stain for the lipid droplet-associated protein, perilipin, similar to lipid droplets in HCCs (Straub et al. 2010). In contrast to HCC, HCAs do not display p53 protein reactivity (Schaff et al. 1995) and are not reactive for the HCC marker, aldoketoreductase family 1B10/AKR1B10 (-Matkowskyi et al. 2014). With the exception of beta-catenin-activated HCA, adenoma cells show membranous beta-catenin expression, similar to normal hepatocytes (Fig. 16).

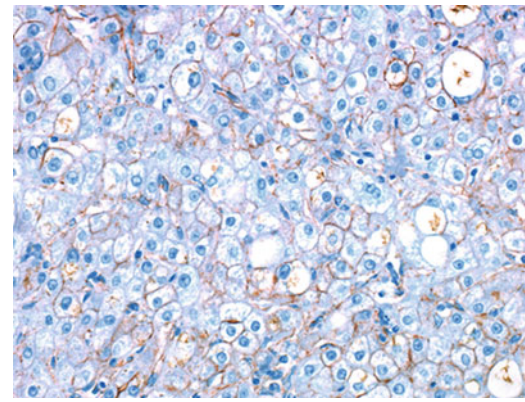

Fig. 16 Hepatocellular adenoma, beta-catenin expression. As with normal hepatocytes, beta-catenin reactivity is present as a membranous staining pattern (beta-catenin immunostain)

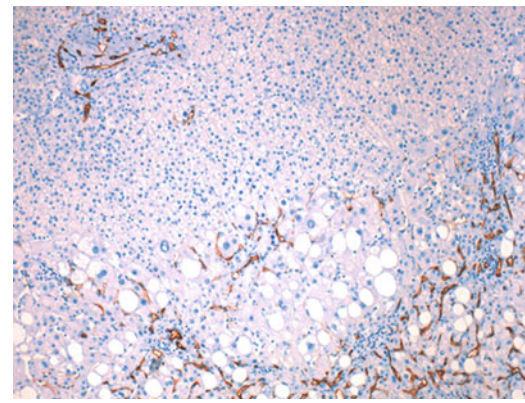

Fig. 17 Hepatocellular adenomas exhibit variable CD34 expression in their microvessels (CD34 immunostain)

HCAs can exhibit a diffuse endothelial staining for CD34 in microvessels (Ahmad et al. 2009; Fig. 17).

In contrast to neovessels in HCCs and high-grade dysplastic nodules, HCA vessels are not reactive for agrin (Tatrai et al. 2009). In comparison with normal hepatic tissue, HCAs showed an increase of angiopoietin-1 expression, possible associated with increased vascular remodeling to produce enlarged vessels and arterial sprouting (Gouw et al. 2010). Immunohistochemically, hepatic progenitor cells were identified in part of HCAs (Libbrecht et al. 2001).

Specific Pathology of HNF-1alpha-Mutated HCA (H-HCA)

H-HCA usually presents as a nodule with lobulated contours. A lobulated pattern is highly characteristic for this HCA variant, and this lobulated geometry is caused by coalescence of several adenomatous liver nodules. Nodule coalescence is supported by the occasional presence of normal or atrophic liver lobules trapped between HCA nodules. Small or tiny steatotic HCA nodules are characteristically found at some distance from the main lesion (Sempoux et al. 2014). Histologically, H-HCA present with a very homogeneous histologic aspect and often show the "classical" phenotype of adenoma, as described above, often with steatosis, but with no inflammatory changes, minor or absent sinusoidal congestion, and absence of nuclear atypia. Often, the steatotic nodule is sharply demarked from adjacent non-steatotic liver. Apart from steatotic hepatocytes, clear liver cells may also be present in variable numbers, but this feature is not a hallmark of H-HCA. H-HCAs more often show microadenomas, steatosis, and additional benign nodules (Bioulac-Sage et al. 2009). At low magnification, the tumors appear as nodular and clear lesions with a homogeneous histologic pattern. The growth pattern is trabecular, these rather thin plates composed of large hepatocytes steatosis, glycogen storage, and small dark nuclei. Tumor cell lipofuscinosis is often noted (Fonseca et al. 2013). Tumor bleeding is less frequently seen in this variant, but can be severe when it occurs (Bioulac-Sage et al. 2007a). The adjacent liver may show steatosis in a minority of cases.

An immunohistochemical and molecular analytic hallmark of H-HCA is the lacking expression of liver fatty acid-binding protein/LFABP, in contrast to normal adjacent liver showing marked expression. LFABP is a protein encoded by a gene that is positively regulated by HNF1A, whereby lack of LFABP is sometimes associated with more severe steatosis (Bioulac-Sage et al. 2007a; review: Bioulac-Sage et al. 2011). Steatosis in H-HCA may be related to lack of LFABP through deranged fatty acid trafficking. The tumor hepatocytes do not stain for SAA or CRP, and reactivity for glutamine synthetase/GS is lacking or is only seen at adenoma borders (Fonseca et al. 2013). GS reactivity may be present around veins or venules and in LFABP-expressing normal hepatocytes intermingled with adenoma cells at the adenoma-parenchyma transition.

Specific Pathology of Beta-Catenin-Activated HCA (b-HCA)

Beta-catenin-mutated HCAs (b-HCA) exhibit thicker liver cell plates, a more variable hepatocyte population, and more often show cytological/nuclear atypias with enlarged and irregular nuclei. The nodules may contain numerous vessels, a typical feature. The nuclear atypias may in part be related to cytogenetic alterations in b-HCA, including chromosome gains and losses. Significant steatosis is absent (Bioulac-Sage et al. 2007a, 2011; Chu and Moon 2013; Fonseca et al. 2013; Sempoux et al. 2014). In one patient, b-HCA had the features of pigmented adenoma with Dubin-Johnson-like pigment (Fonseca et al. 2013). The precise diagnosis of b-HCA is of particular importance, as this form of HCA is strongly associated with malignant transformation. Immunohistochemically, b-HCA is characterized by nuclear and cytoplasmic positivity for beta-catenin and patchy or marked and diffuse immunostaining for glutamine synthetase/GS (Bioulac-Sage et al. 2011, 2013). In a Korean study, glutamine synthetase (GS) staining was not always clearly diagnostic for beta-catenin-mutated HCA (Kim et al. 2013). Furthermore, diffuse GS overexpression was, in one patient, restricted to areas of peliosis in a beta-catenin-activated peliotic HCA (Berry et al. 2014).

Specific Pathology of Inflammatory HCA (IHCA)

The pathology of this group of HCAs is more complex, as this is a heterogeneous group of lesions that also contains telangiectatic HCA, a

mass previously interpreted as telangiectatic nodular hyperplasia. Many IHCAs are characterized by an adenoma showing inflammatory infiltrates and variable vascular anomalies, mainly dystrophic arteries, sinusoidal ectasias associated with congestion, peliosiform areas, and hemorrhage (Sempoux et al. 2014). Thick-walled arteries may be surrounded by inflammatory cells. Macroscopic and microscopic hemorrhage is more common in IHCA than in the other forms. Steatosis may occur in IHCA, mainly in patients with an elevated body mass index, and absent in tumors with high SAA (serum amyloid protein A) expression (Bioulac-Sage et al. 2007a; van Aalten et al. 2011). Steatotic cells may also be encountered in areas of sinusoidal ectasia (Sempoux et al. 2014). Very small nodules in a diameter range of few millimeters were observed in patients with multiple nodules, while in patients with a solitary IHCA, only rare nodules in the mm range were detectable (Bioulac-Sage et al. 2010). Livers harboring IHCAs show distinct alterations, both near the tumors and distant from them. Mild to moderate steatosis is found in a high frequency, as are sinusoidal dilatation, single arteries, and minute foci of CRP reactivity, the latter mainly in cases of multiple IHCA, indicating that these livers contain incipient IHCA foci (Han et al. 2012).

Immunohistochemically, infiltrate-containing structures containing CK7-positive ductular proliferations are found (Fonseca et al. 2013). The neoplastic hepatocytes often display reactivity for serum amyloid protein/SAA and C-reactive protein/CRP. CRP is more consistently expressed in tumor hepatocytes than SAA and is usually present as a diffuse and marked reactivity. SAA is expressed in tumor hepatocytes, but not in inflammatory cells. SAA overexpression in IHCA included all cases of tumors formerly classified as telangiectatic FNH (Lim et al. 2008), a strong argument that such lesions are in fact a variant of IHCA with telangiectatic features (Bioulac-Sage et al. 2007a). Expression of L-FABP is normal, and glutamine synthetase positivity is either absent or only seen at adenoma borders or around blood vessels, with few exceptions showing strong reactivity.

A minority of IHCAs are beta-catenin-activated tumors (b-IHCA). The nodules are characterized by sinusoidal dilatation, inflammatory infiltrates, and thick-walled dystrophic vessels. b-IHCAs show variable, either faint and heterogeneous, patchy, or strong and diffuse GS expression contrasting with the pericentral staining of normal liver parenchyma. In varying expression patterns, b-IHCA nuclei are reactive for beta-catenin, and cytoplasmic beta-catenin immunostaining may also be found (Sempoux et al. 2014).

Association of HCA with Other Synchronous Liver Alterations

In most instances, the liver harboring HCA does not show characteristic preexisting alterations, in particular no cirrhosis. In certain situations, the liver exhibits changes that are related to a disorder favoring HCA, e.g., glycogenosis. As inflammatory HCA is associated with obesity, mild to moderate hepatic steatosis was found in a high frequency in patients with this HCA type (Han et al. 2012).

HCA can simultaneously occur with focal nodular hyperplasia/FNH (Laurent et al. 2003; Dimitroulis et al. 2012). In a study from Bordeaux, HCA together with FNH was found in 5 out of 30 cases of multiple benign hepatocytic nodules. All five cases involved women on oral contraceptives. Possible causes of this association include local or systemic angiogenic anomalies induced by oral contraceptives, tumor-induced growth factors, or thrombosis and local arteriovenous shunting (Laurent et al. 2003). HCA can occur in a syndromic context, characterized by the synchronous occurrence of HCA, FNH, and hemangiomas of the liver (Di Carlo et al. 2003). A combination of HCA and FNH was also observed in association with spontaneous intrahepatic portosystemic shunt (Handra-Luca et al. 2006). HCA was observed in conjunction with nodular regenerative hyperplasia of the liver (Nguyen et al. 1986) and hepatic granulomas (Kazi et al. 2005).

Biology of Disease and Evolution

General Features

It is thought that HCAs grow rather slowly, an HCA of 10 cm diameter requiring an evolution time of 2–3 years. However, there are also information that HCA may progressively grow (Mariana et al. 1979), particularly in adenomatosis (Grazioli et al. 2000). A part of the HCAs are known to regress completely (at least radiologically), sometimes occurring in an apparently "spontaneous" fashion (Iijima et al. 2001). Regression may require as much as 8 years to be complete (Iijima et al. 2001). Conversely, rapid disappearance of even large HCA has been observed subsequent to contraceptive withdrawal (Kay 1977; Ramseur and Cooper 1978; Penkava and Rothenberg 1981; Steinbrecher et al. 1981; Bühler et al. 1982; Daldrup et al. 1995; Kawakatsu et al. 1997; Aseni et al. 2001), similar to steroid-induced FNH (Meunier et al. 1998), whereas in other situations, discontinuation of oral contraceptives resulted in no change of the tumor (Tajada et al. 2001). Regression of HCA following androgenic progestin therapy withdrawal was found (Svrcek et al. 2007), and regression was observed after discontinuation of danazol in patients with hereditary angioedema (Bork and Schneiders 2002).

Malignant Transformation of HCA

The first description of transition of HCA into HCC may be a thesis as of 1861 (Jungmann 1861). The malignant transformation of HCA to HCC (the adenoma-carcinoma sequence) is not a common phenomenon, but occurs more frequently in case of large and multiple tumors (Foster and Berman 1994; Nagorney 1996; Farges and Dokmak 2010) and is ten times more frequent in men than in women (Farges et al. 2011). A transformation process may start with focal cellular atypias in subsets of HCA (Fig. 18).

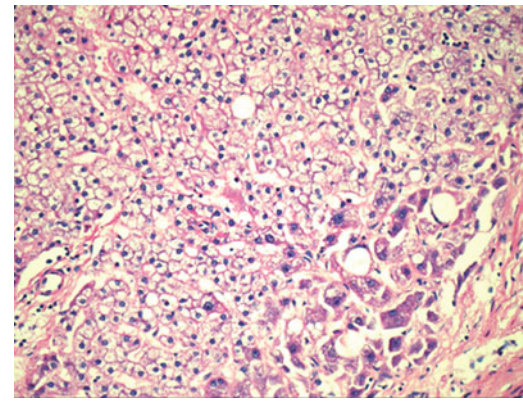

Fig. 18 Hepatocellular adenoma with focal cell and nuclear atypia (hematoxylin and eosin stain)

There is now evidence that certain molecular variants of HCA (see above), specifically, b-HCA, and obesity/overweight may represent a major risk of malignant transformation of HCA, possibly through the interleukin-6 pathway (Bioulac-Sage et al. 2012). In fact, presence of beta-catenin activation and absence of steatosis in HCAs seem to be indicators for increased malignancy risk (Van den Borght et al. 2007). In a genomic profiling study, integrative analysis of HCAs transformed to HCC showed beta-catenin mutation as an early alteration and TERT promoter mutations as a feature of the last step of an HCA-CC transition (Pilati et al. 2014). However, in H-HCA, where steatosis is rather common, transformation into HCC is not common (Zucman-Rossi et al. 2006). Also telangiectatic HCA can give rise to HCC (Gonzalez-Lara et al. 2013). Some of the observations described the development of HCC subsequent to the initial diagnosis of HCA (Grazioli et al. 2000). In a review of 39 HCAs, five patients subsequently developed HCC (Foster and Berman 1994). Among 58 patients who underwent surgery for HCA, 2 patients developed HCC 2 and 5 years after resection, respectively (Weimann et al. 1998). Dokmak and coworkers (2009) found eight cases of malignancy among 122 patients with HCA. Another report described HCC apparently having developed from HCA after 19 years (Janes et al. 1993). Based on a systematic literature search with a collection of

1,635 HCAs, the reported overall frequency of malignant transformation was 4.2 %. Only three cases of malignant alteration were found in a tumor smaller than 5 cm in diameter (Stoot et al. 2010). Recently, a potential derivation of non-cirrhotic hepatocellular carcinoma from HCA has been proposed (Liu et al. 2014). Well-differentiated HCCs in non-cirrhotic liver can contain areas that are similar to HCA. Among eleven cases of HCC arising in HCA in non-cirrhotic liver, atypical HCA-like areas were found in 64 %, and in more than half of these cases, the areas showed features of inflammatory HCA. It was suggested that HCA-like areas in such HCCs may represent an extremely well-differentiated variant of HCC (Kakar et al. 2014).

Selected References Davis et al. 1975; Boyd and Mark 1977; Gordon et al. 1986; Grigsby et al. 1987; Korula et al. 1991; Ferrell 1993; Herman et al. 1994; Perret et al. 1996; Scott et al. 1996; Ye et al. 1999; Closset et al. 2000; Choe and Yu 2002; Chuang et al. 2002; Ito et al. 2003; Burri et al. 2006; Micchelli et al. 2008; Dokmak et al. 2009; Baulieux et al. 2012; Seo et al. 2012; Kakar et al. 2014.

The pathogenic pathways involved in malignant transformation of HCA are incompletely known. In HCA developing in patients using oral contraceptives, liver cell dysplasia has been observed and suggested to be a premalignant change (Fink et al. 1985; Tao 1991; Closset et al. 2000; Hsu et al. 2003). The dysplastic changes appeared to arise after 9 years of oral contraceptive use (Tao 1991, 1992). As outlined above, B-HCA and b-IHCA are strongly associated with HCC transformation (reviews: Liau et al. 2013; Sempoux et al. 2013). A recent investigation showed recurrent somatic FRK mutations that induced constitutive kinase activity, STAT3 activation, and cell proliferation sensitive to Src inhibitors. In addition, uncommon recurrent mutations activating JAK1, gp130, and beta-catenin were detected. Integrative analysis of HCAs transformed to HCC exhibited beta-catenin mutations as an early change and TERT promoter mutations associated with the last step of the cancerogenic pathway (Pilati et al. 2014). A recent analysis demonstrated that HCCs that develop in non-cirrhotic livers have some clinical, morphological, or immunophenotypical associations currently described in HCAs (Liu et al. 2014).

Very rarely, HCA is followed by other hepatocellular tumors, e.g., fibrolamellar carcinoma (Terracciano et al. 2004). In a female patient with long history of oral contraceptive use, HCA was found within a large hepatic spindle cell carcinoma with positivity for keratins and alpha-1-antitrypsin (Grigsby et al. 1987).

Associations, Etiology, and Pathogenesis of Hepatocellular Adenoma

Sex Steroids

Apart from distinct mutations found in HCAs (see above), there are diverse factors, agents, and conditions that can trigger the initiation and progression of HCA, but in part of cases, the causes of HCA and LA are not yet fully clarified (Ribeiro et al. 1998; Yoshidome et al. 1999). Among probable nongenetic causes, sex steroids have aroused a major interest for long time periods. As both estrogen receptor-positive and estrogen receptor-negative tumors occurred in the same liver, it was concluded that estrogens may not play a decisive role in the pathogenesis of HCA/LA (Ribeiro et al. 1998; Torbenson et al. 2002). However, there is strong evidence that modified estrogens, in particular oral contraceptives, progestogens, and androgenic steroids, are involved in the pathogenesis of certain subsets of HCA.

Selected References for Estrogens Baum et al. 1973; Christopherson et al. 1975; Brander et al. 1976; Fechner 1977; Ishak 1979; Fléjou et al. 1985; Rabe et al. 1994; Perret et al. 1996; Tao 1992; Caballes and Caballes 1999; Crosnier et al. 2010.

The etiologic significance of steroids, and in particular sex steroids, for the development of HCA is underlined by the observation that HCA may

evolve or grow during, or at least being manifest in, pregnancy (gestational HCA; review: Cobey and Salem 2004). However, in the light of the slow growth of such lesions, it seems logical that large tumors detected during pregnancy were present before already (Monks et al. 1986; Rosel et al. 1990; Terkivatan et al. 2000). Interestingly, therapeutic abortion in a patient with a large HCA resulted in abrupt necrosis of the liver tumor, suggesting an effect of sudden estrogen deprivation (Stock et al. 1985). During pregnancy, the risk of rupture of HCA exists, associated with high maternal and fetal mortality (Bis and Waxman 1976; Rosel et al. 1990), requiring careful monitoring and, in case of large tumors (i.e., diameter 5 cm or more), eventual prophylactic resection (Terkivatan et al. 2000). Ninety-one of the cases reported in the older literature have been reviewed in 1976 (Bis and Waxman 1976), overall with a then-reported 59 % maternal and 62 % fetal mortality, in part due to delayed diagnosis and owing to associated disorders, such as preeclampsia. It has been suggested that high levels of sex steroids and an increased vascularity of the liver during pregnancy increase the risk of rupture.

Androgen administration, e.g., in patients with aplastic anemias and for the purpose of body building, is associated with the emergence of HCA.

Selected References Anthony 1975; Boyd and Mark 1977; Carrasco et al. 1984, 1985; McInerney et al. 1987; Leese et al. 1988; Pulpeiro et al. 1989; Gonzalez et al. 1994; Geders et al. 1995; Deodhar et al. 1996; Toso et al. 2003 Socas et al. 2005.

Few HCAs have been observed in patients receiving treatment with danazol, an attenuated androgen (Middleton et al. 1989; Watanabe and Kobayashi 1993), in one instance with formation of multiple HCAs (de Menis et al. 1999). In particular, HCA can develop subsequent to the treatment of hereditary angioedema with attenuated androgens such as danazol or stanozolol. Since 1999, four HCA patients having received long-term angioedema prophylaxis with danazol have been reported (Bork and Schneiders 2002).

Glycogenosis

HCA is now well known to occur in association with certain types of glycogen storage diseases (GSD; glycogenosis), most frequently in GSD type 1 (Mason and Andersen 1955; Nishio et al. 1981; Fink et al. 1985; Poe and Snover 1988; Fujiyama et al. 1990; Bianchi 1993; Labrune et al. 1997; Kelly and Poon 2001; Kudo 2001; Yoshikawa et al. 2001; Lee 2002; Rake et al. 2002; Lerut et al. 2003; Volmar et al. 2003; Di Rocco et al. 2008; Kishnani et al. 2009; Wang et al. 2011; Sakelliarou et al. 2012). In type I glycogenosis, HCA can occur in conjunction with HCC (Cassiman et al. 2010). HCA is much rarer in GSD type 3 (Labrune et al. 1997) and only exceptionally occurs in GSD type 4 (Alshak et al. 1994;). In GSD type 8, cirrhosis associated with a lesion tentatively interpreted to be adenomatous hyperplasia has been described (Shiomi et al. 1989). For GSD type 1, the first report of an associated HCA dates back to 1955 (Mason and Andersen 1955). Many of the cases observed in the following years have been reviewed (Bianchi 1993; Labrune et al. 1997; Lee 2002), and the radiologic features are known from several reports (Debaere et al. 1999). The range of prevalence in patients with GSD type 1 depends on the published series and amounts from 22 % to 75 %, indicating considerable selection bias; in fact, the true prevalence is still unknown. The retrospective European registry showed a 52 % prevalence of HCA in patients over 20 years of age (Moses 2002). The age at manifestation of HCA ranges from 3 to 54 years, even though more tumors are in evidence during or after puberty (Lee 2002) without gender preference (European GSD Registry; Rake et al. 2002). HCAs in GSD type 1 can be solitary tumors, but multiple lesions have also been reported (Howell et al. 1976; Coire et al. 1987; Endoh et al. 2001). Their biology seems to be similar to other HCA, i.e., they may bleed, recur after incomplete resection, or regress spontaneously (Iijima et al. 2001)

or upon dietary treatment (Parker et al. 1981). HCA developing in the setting of glycogenosis type I lacked HNF1A inactivation (Calderaro et al. 2013). Is HCA developing in GSD type 1 a precursor for HCC? Among the cases reported in the literature, at least ten have had associated HCC (Lee 2002), and in some situations, an evolution from HCA to HCC may have occurred (Limmer et al. 1988). The etiology and pathogenesis of HCA developing in GSD type 1 is unknown. HCAs do also occur in GSD type 3 and, rarely, in type 4, but these patients suffer from chronic fibrosing liver disease and eventually cirrhosis. It has been suggested that the hormonal imbalance of a high glucagon/insulin ratio characteristic of poorly controlled GSD patients may exert a permissive role in conjunction with specific growth factors in HCA formation, because strict diet can result in tumor regression (Bianchi 1993). However, patients with GSD types 6 and 9 have not been reported to develop liver tumors. Furthermore, the abnormal glycogen metabolism in liver tumor precursors occurring in rats does not mimic the situation of human HCA. It has also been proposed that the disordered fatty acid metabolism present in GSD may play a role in tumorigenesis, as, e.g., proposed for HCC (Ockner et al. 1993; Lee 2002), but further data are required to address this point in more detail. The clinical differential diagnosis of HCA evolving in glycogen storage disease includes focal nodular hyperplasia (FNH), which has been observed in these metabolic disorders (Suga et al. 2002), and HCC, which has been observed in GSD types 1, 3, 4, 6, and 9.

Abnormal Liver Circulation

Several reports documented an association between HCA and portosystemic shunt, a hepatic circulation disorder that may directly stimulate abnormal hepatocyte growth (Dhalluin-Venier et al. 2008; Pupulim et al. 2013). HCA was found in children with spontaneous intrahepatic portohepatic shunt (Kawakatsu et al. 1994). HCA also occurs in the setting of congenital absence of the portal vein, whereby the tumors showed HNF-1alpha inactivation (Tateishi et al. 2013). HCA and other nodular hepatocyte lesion occur in patients with idiopathic portal hypertension (Sugimoto et al. 2013).

Chromosomal and Molecular Genetic Alterations Other Than Those Discussed Above

Monoclonality of HCAs has been documented (Gong et al. 2006). So far, relatively few chromosomal and genetic changes have been detected in HCA, but they can in part distinguish HCA from HCC (Zucman-Rossi 2004; Chen et al. 2005). In contrast to HCC, no LOH or mutant sequences were observed for the p53 gene in HCA, and mutations of exon 3 of the beta-catenin gene were not found. In contrast to HCC, trisomies 1 and 8 are not found in HCA (Nasarek et al. 1995). HCA can molecularly be distinguished from well-differentiated hepatocellular carcinoma (HCC) by comparative genomic hybridization. In HCA, aberrations were detectable in a minority of cases, involving gains of chromosomes 7p, 17q, and 20, while most HCC had a complex array of chromosomal abnormalities involving numerous chromosomes (Wilkens et al. 2001). By use of microarray analysis, several genes were found downregulated in HCA in comparison with HCC (Yim et al. 2003).

References

Abir A, Cazejust J, Arrivé L, Menu Y (2013) MR features of inflammatory hepatic adenoma. Clin Res Hepatol Gastroenterol 37:109–110

Adusumilli PS, Lee B, Parekh K, Dolgopolov S (2002) Hemoperitoneum from spontaneous rupture of a liver cell adenoma in a male with hyperthyroidism. Am Surg 68:582–583

Ahmad SI, Hanaoka F, Kirk SH (2002) Molecular biology of Fanconi anaemia — an old problem, a new insight. Bioessays 24:439–448

Ahmad I, Iyer A, Marginean CE, Yeh MM, Ferrell L, Qin L, Bifulco CB, Jain D (2009) Diagnostic use of cytokeratins, CD34, and neuronal cell adhesion molecule staining in focal nodular hyperplasia and hepatic adenoma. Hum Pathol 40:726–734

Akatsu T, Ueda M, Shimazu M, Wakabayashi G, Aiura K, Tanabe M, Kawachi S, Tanimoto A et al (2004) Kupffer cell function of hepatocellular: pulse sequence effects in superparamagnetic iron oxide-enhanced magnetic resonance imaging. J Gastroenterol Hepatol 19:951–952

Alshak NS, Cocjin J, Podesta L, van de Velde R, Makowka L, Rosenthal P, Geller SA (1994) Hepatocellular adenoma in glycogen storage disease type IV. Arch Pathol Lab Med 118:88–91

Anthony PP (1975) Hepatoma associated with androgenic steroids. Lancet 1:685–686

Anthony PP (1988) Tumours and tumour-like lesions of the liver and biliary tract. In: Mac Sween RNM, Anthony PP, Scheuer PJ (eds) Pathology of the liver, 2nd edn. Churchill Livingstone, Edinburgh/London/Melbourne/New York, pp 574–645

Applegate KE, Ghei M, Perez-Atayde AR (1999) Prenatal detection of a solitary liver adenoma. Pediatr Radiol 29:92–94

Arrivé L, Fléjou JF, Vilgrain V, Belghiti J, Najmark D, Zins M, Menu Y, Tubiana JM et al (1994) Hepatic adenoma: MR findings in 51 pathologically proved lesions. Radiology 193:507–512

Arsenault TM, Johnson CD, Gorman B, Burgart LJ (1996) Hepatic adenomatosis. Mayo Clin Proc 71:478–480

Aseni P, Sansalone CV, Sammartino C, Benedetto FD, Carrafiello G, Giacomoni A, Osio C, Vertemati M, Forti D (2001) Rapid disappearance of hepatic adenoma after contraceptive withdrawal. J Clin Gastroenterol 33:234–236

Bacq Y, Jacquemin E, Balabaud C, Jeannot E, Scotto B, Branchereau S, Laurent C, Bourlier P et al (2003) Familial liver adenomatosis associated with hepatocyte nuclear factor 1a inactivation. Gastroenterology 125:1470

Bader TR, Braga L, Semelka RC (2001) Exophytic benign tumors of the liver: appearance on MRI. Magn Reson Imaging 19:623–628

Bagia S, Hewitt PM, Morris DL (2000) Anabolic steroid-induced hepatic adenomas with spontaneous haemorrhage in a bodybuilder. Aust N Z J Surg 70:686–687

Bala S, Wunsch PH, Ballhausen WG (1997) Childhood hepatocellular adenoma in familial adenomatous polyposis: mutations in adenomatous polyposis gene and p53. Gastroenterology 112:919–922

Balabaud C, Al-Rabih WR, Chen PJ, Evason K, Ferrell L, Hernandez-Prera JC, Huang SF et al (2013) Focal nodular hyperplasia and hepatocellular adenoma around the world viewed through the scope of the immunopathological classification. Int J Hepatol 2013:268625

Bartolozzi C, Lencioni R, Paolicchi A, Moretti M, Armillotta N, Pinto F (1997) Differentiation of hepatocellular adenoma and focal nodular hyperplasia of the liver: comparison of power Doppler imaging and conventional color Doppler sonography. Eur Radiol 7:1410–1415

Baulieux J, Manichon AF, Bancel B, D'Errico E, Raspado O, Ducerf C, Mabrut JY, Rode A (2012) Malignant transformation of multiple isolated hepatocellular adenomas. Therapeutic implications of immunohistochemical and radiological findings (in French). Bull Acad Natl Med 196:459–481

Baum JK, Bookstein JJ, Holz F, Klein EW (1973) Possible association between benign hepatomas and oral contraceptives. Lancet ii:926–929

Bellamy CO, Maxwell RS, Prost S, Azodo IA, Powell JJ, Manning JR (2013) The value of immunophenotyping hepatocellular adenomas: consecutive resections at one UK centre. Histopathology 62:431–445

Berry RS, Gullapalli RR, Wu J, Morris K, Hanson JA (2014) Diffuse glutamine synthetase overexpression restricted to areas of peliosis in b-catenin-activated hepatocellular adenoma: a potential pitfall in glutamine synthetase interpretation. Virchows Arch 465:241–245

Bianchi L (1993) Glycogen storage disease and hepatocellular tumors. Eur J Pediatr 152(Suppl1):S63–S70

Bieze M, Bioulac-Sage P, Verheij J, Balabaud C, Lauent C, van Gulik TM (2012) Hepatocellular adenomas associated with hepatic granulomas: experience in five cases. Case Rep Gastroenterol 6:677–683

Bieze M, Phoa SS, Verheij J, van Lienden KP, van Gulik TM (2014) Risk factors for bleeding in hepatocellular adenoma. Br J Surg 101:847–855

Bioulac-Sage P, Lamouliatte H, Saric J, Merlio JP, Balabaud C (1986) Ultrastructure of sinusoidal cells in a benign liver cell adenoma. Ultrastruct Pathol 10:49–54

Bioulac-Sage P, Rebouissou S, Thomas C, Blanc JF, Saric J, Sa Cunha A, Rullier A et al (2007a) Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. Hepatology 46:740–748

Bioulac-Sage P, Balabaud C, Bedossa P, Scoazec JY, Chiche L, Dhillon AP, Ferrell L et al (2007b) Pathologic diagnosis of liver cell adenoma and focal nodular hyperplasia: Bordeaux update. J Hepatol 46:521–527

Bioulac-Sage P, Blanc JF, Rebouisson S, Balabaud C, Zucman-Rossi J (2007c) Genotype phenotype classification of hepatocellular adenoma. World J Gastroenterol 13:2649–2654

Bioulac-Sage P, Laumonier H, Laurent C, Zucman-Rossi J, Balabaud C (2008) Hepatocellular adenoma: what is new in 2008. Hepatol Int 2:316–321

Bioulac-Sage P, Laumonier H, Couchy G, Le Bail B, Sa Cunha A, Rullier A, Laurent C et al (2009) Hepatocellular adenoma management and phenotype classification: the Bordeaux experience. Hepatology 50:481–489

Bioulac-Sage P, Balabaud C, Zucman-Rossi J (2010a) Focal nodular hyperplasia, hepatocellular adenomas: past, present, future. Gastroenterol Clin Biol 34:355–358

Bioulac-Sage P, Laumonier H, Cubel G, Rossi JZ, Balabaud C (2010b) Hepatic resection for inflammatory hepatocellular adenomas: pathological identification of micronodules expressing inflammatory proteins. Liver Int 30:149–154

Bioulac-Sage P, Cubel G, Balabaud C, Zucman-Rossi J (2011) Revisiting the pathology of resected benign hepatocellular nodules using new immunohistochemical markers. Semin Liver Dis 31:91–103

Bioulac-Sage P, Cubel G, Taouji S, Scoazec JY, Leteurtre E, Paradis V, Sturm N et al (2012a) Immunohistochemical markers on needle biopsies are helpful for the diagnosis of focal nodular hyperplasia and hepatocellular adenoma subtypes. Am J Surg Pathol 36:1691–1699

Bioulac-Sage P, Taouji S, Possenti L, Balabaud C (2012b) Hepatocellular adenoma subtypes: the impact of overweight and obesity. Liver Int 32:1217–1221

Bioulac-Sage P, Taouji S, Le Bail B, Possenti L, Balabaud C (2013a) Value and limits of routine histology alone or combined with glutamine synthetase immunostaining in the diagnosis of hepatocellular adenoma subtypes on surgical specimens. Int J Hepatol 2013:417323

Bioulac-Sage P, Sempoux C, Possenti L, Frulio N, Laumonier H, Laurent C, Chiche L et al (2013b) Pathological diagnosis of hepatocellular adenoma according to the clinical context. Int J Hepatol. doi:10.1155/2013/253261

Bird D, Vowles K, Anthony PP (1979) Spontaneous rupture of a liver cell adenoma after long term methyltestosterone: report of a case successfully treated by emergency right hepatic lobectomy. Br J Surg 66:212–213

Bis KA, Waxman G (1976) Rupture of the liver associated with pregnancy: a review of the literature and report of two cases. Obstet Gynecol Surv 31:763–773

Bluteau O, Jeannot E, Bioulac-Sage P, Marques JM, Blanc JF, Bui H, Beaudoin JC, Franco D et al (2002) Bi-allelic inactivation of TCF1 in hepatic adenomas. Nat Genet 32:312–315

Bork K, Schneiders V (2002) Danazol-induced hepatocellular adenoma in patients with hereditary angio-oedema. J Hepatol 36:707–709

Boulafendis D, Zafarnia ME, Samaan HA (1985) Liver cell adenoma presenting as acute abdomen. Int Surg 70:41–43

Boyd PR, Mark GJ (1977) Multiple hepatic adenomas and a hepatocellular carcinoma in a man on oral methyl testosterone for eleven years. Cancer 40:1765–1770

Brander WL, Vosnides G, Ogg CS, West IE (1976) Multiple hepatocellular tumors in a patient treated with oral contraceptives. Virchows Arch A Pathol Anat Histopathol 370:69–76

Brophy CM, Bock JF, West B, McKhann CF (1989) Liver cell adenoma: diagnosis and treatment of a rare neoplastic process. Am J Gastroenterol 84:429–432

Brunelle F, Chaumont P (1984) Hepatic tumors in children: ultrasonic differentiation of malignant from benign lesions. Radiology 150:695–699

Bühler H, Pirovino M, Akobiantz A, Altorfer J, Weitzerl M, Maranta E, Schmid M (1982) Regression of liver cell adenoma. A follow-up study of three consecutive patients after discontinuation of oral contraceptive use. Gastroenterology 82:775–782

Bunchornavakul C, Bahirwani R, Drazek D, Soulen MC, Siegelman ES, Furth EE et al (2011) Clinical features and natural history of hepatocellular adenomas: the impact of obesity. Aliment Pharmacol Ther 34:664–674

Burri E, Steuerwald M, Cathomas G, Mentha G, Majono P, Rubbia-Brandt L, Meier R (2006) Hepatocellular carcinoma in a liver-cell adenoma within a non-cirrhotic liver. Eur J Gastroenterol Hepatol 18:437–441

Caballes RL, Caballes RA (1999) Multiple hepatocellular adenomas in a patient with a history of oral contraception. Int J Gynecol Obstet 64:177–180

Calderaro J, Labrune P, Morcrette G, Rebouissou S, Franco D, Prévot S, Quaglia A et al (2013) Molecular characterization of hepatocellular adenomas developed in patients with glycogen storage disease type I. J Hepatol 58:350–357

Callea F, Bonetti M, Medicina D, Alberti D, Fabbretti G, Brisigotti M (1993) Hepatic tumor and tumor-like lesions in childhood. J Surg Oncol Suppl 3:170–172

Carrasco D, Barrachina M, Prieto M, Berenguer J (1984) Clomiphene citrate and liver-cell adenoma. N Engl J Med 310:1120–1121

Carrasco D, Prieto M, Pallardo L, Moll JL, Cruz JM, Munoz C, Berenguer J (1985) Multiple hepatic adenomas after long-term therapy with testosterone enanthate. Review of the literature. J Hepatol 1:573–578

Cassiman D, Libbrecht L, Verslype C, Meersseman W, Troisi R, Zucman-Rossi J, Van Vlierberghe H (2010) An adult male patient with multiple adenomas and a hepatocellular carcinoma: mild glycogen storage disease type Ia. J Hepatol 53:213–217

Castain C, Sempoux C, Brunt EM, Causse O, Heitzmann A, Hernandez-Prera JC et al (2014) Coexistence of inflammatory hepatocellular adenomas with HNF1a-inactivated adenomas: is there an association? Histopathology 64:890–895

Chandra et al (1984) http://www.ncbi.nlm.nih.gov/pubmed/6320760

Chang CY, Herandez-Prera JC, Roayaie S, Schwartz M, Thung SN (2013) Changing epidemiology of hepatocellular adenoma in the United States: review of the literature. Int J Hepatol. doi:10.1155/2013/604860

Chen YW, Jeng YM, Yeh SH, Chen PJ (2002) P53 gene and Wnt signaling in benign neoplasms: beta-catenin mutations in hepatic adenoma but not in focal nodular hyperplasia. Hepatology 36:927–935

Chen ZM, Crone KG, Watson MA, Pfeifer JD, Wang HL (2005) Identification of a unique gene expression signature that differentiates hepatocellular adenoma from well-differentiated hepatocellular carcinoma. Am J Surg Pathol 29:1600–1608

Cheng YF, Huang CC, Weng HH, Lee TY (1995) Magnetic resonance imaging of siderotic hepatic adenoma. J Formos Med Assoc 94:138–140

Chiappa A, Zbar A, Audisio R, Di Palo S, Bertani E, Staudacher C (1999) Ruptured hepatic adenoma in

liver adenomatosis: a case report of emergency surgical management. Hepatogastroenterology 46:1942–1943
Chiche et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/10636105
Cho SW, Marsh JW, Steel J, Holloway SE, Heckman JT, Ochoa ER, Geller DA, Gamblin TC (2008) Surgical management of hepatocellular adenoma: take it or leave it? Ann Surg Oncol 15:2795–2803
Choe MS, Yu ES (2002) Hepatocellular carcinoma arising in hepatocellular adenoma (in Korean). Taehan Kan Hakhoe Chi 8:107–109
Christopherson WM, Collier HS (1953) Primary benign liver-cell tumors in infancy and childhood. Cancer 6:853–861
Christopherson WM, Mays ET, Barrows GH (1975) Liver tumors in women on contraceptive steroids. Obstet Gynecol 46:221–223
Chu HH, Moon WS (2013) b-catenin activated hepatocellular adenoma. Clin Mol Hepatol 19:185–189
Chuang WY, Chen TC, Hsu HL, Lee WC, Jeng LB, Huang SF (2002) Liver cell adenoma with concomitant hepatocellular carcinoma: report of two cases. J Formos Med Assoc 101:798–802
Chun YS, Calderaro J, Zucman-Rossi J (2012) Synchronous hepatocellular carcinoma and Castleman's disease: the role of the interleukin-6-signaling pathway. Hepatology 56:392–393
Chung KY, Mayo-Smith WW, Saini S, Rahmouni A, Golli M, Mathieu D (1995) Hepatocellular adenoma: MR imaging features with pathology correlation. AJR Am J Roentgenol 165:303–308
Chung A, Leo K, Wong G, Chuah K, Ren J, Lee C (2006) Giant hepatocellular adenoma presenting with chronic iron deficiency anemia. Am J Gastroenterol 101:2160–2162
Closset J, Veys I, Peny MO, Braude P, Van Gansbeke D, Lambilliotton JP, Gelin M (2000) Retrospective analysis of 29 patients surgically treated for hepatocellular adenoma or focal nodular hyperplasia. Hepatogastroenterology 47:1382–1384
Cobey FC, Salem RR (2004) A review of liver masses in pregnancy and a proposed algorithm for their diagnosis and management. Am J Surg 187:181–191
Coire CI, Qizilbash AH, Castelli MF (1987) Hepatic adenomata in type Ia glycogen storage disease. Arch Pathol Lab Med 111:166–169
Corberand J, Pris J, Dutau G, Rumeau JL, Regnier C (1975) Association of Fanconi's disease and hepatic tumor in a patient undergoing long-term androgen treatment (in French). Arch Fr Pediatr 32:275–283
Cotta-Pereira RL, Valente LF, De Paula DG, Eiras-Araujo AL, Iglesias AC (2013) Rupture of a hepatic adenoma in a young woman after an abdominal trauma: a case report. World J Gastroenterol 19:4422–4426
Craig JR, Peters RL, Edmondson HA (1989) Tumors of the liver and intrahepatic bile ducts. In: Atlas of tumor pathology, 2nd series, fascicle 26. Armed Forces Institute of Pathology, Washington, DC
Croes EA, van Gulik TM, Bosma A, de Wit LT, Gouma DJ (1998) Treatment of 8 patients with an acute hemorrhage in a hepatocellular adenoma at the Academic Medical Center, Amsterdam (in Dutch). Ned Tijdschr Geneeskd 142:2463–2468
Crosnier H, Thibaud E, Duflos C, Polak M (2010) Norethisterone-induced hepatic adenomas can cause life-threatening bleeding in girls with inherited platelet disorders. Fertil Steril 94:2329.e1–2329.e3
Daldrup HE, Reimer P, Rummeny EJ, Fischer H, Bocker W, Peters PE (1995) The regression of a hepatocellular adenoma after the withdrawal of hormonal contraception (in German). Rofo Fortschr Geb Röntgenstr Neuen Bildgeb Verfahr 163:449–451
Davis M, Portmann B, Searle M, Wright R, Williams R (1975) Histological evidence of carcinoma in a hepatic tumor associated with oral contraceptives. Br Med J 4:496–498
De Baets MG, Hahn PF, Desmet VJ (1993) CT demonstration of steatotic liver cell adenoma. J Belge Radiol 76:314–315
de Menis E, Tramontin P, Conte N (1999) Danazol and multiple hepatic adenomas: peculiar clinical findings in an acromegalic patient. Horm Metab Res 31:476–477
Debaere C, Op de Beeck B, De Maeseneer M, Osteaux M (1999) Magnetic resonance imaging findings of hepatic adenomas in von Gierke (type I) glycogen storage disease: case report. Can Assoc Radiol J 50:161–164
Dehner LP (1978) Hepatic tumors in the pediatric age group: a distinctive clinicopathologic spectrum. Perspect Pediatr Pathol 4:217–268
Dehner LP, Parker ME, Franciosi RA, Drake RM (1979) Focal nodular hyperplasia and adenoma of the liver. A pediatric experience. Am J Pediatr Hematol Oncol 1:85–93
Deneve JL, Pawlik TM, Cunningham S, Clary B, Reddy S, Scoggins CR, Martin RC, D'Angelica M et al (2009) Liver cell adenoma: a multicentre analysis of risk factors for rupture and malignancy. Ann Surg Oncol 16:640–648
Deodhar KK, Desouza LJ, Jagannath P, Krishnamurthy S (1996) Spontaneously occurring liver cell adenoma in an adult male. Indian J Gastroenterol 15:28–29
Dhalluin-Venier V, Fabre M, Jacquemin E, Rangheard AS, Pelletier G, Buffet C (2008) Liver cell adenoma and portosystemic shunt. Gastroenterol Clin Biol 32:164–166
Dhingra S, Fiel I (2014) Update of the new classification of hepatic adenomas: clinical, molecular, and pathologic characteristics. Arch Pathol Lab Med 138:1090–1097
Di Carlo I, Fraggetta F, Lombardo R, Azzarello G, Vasquez E, Puelo S (2002) CD 34 expression in chronic and neoplastic liver diseases. Panminerva Med 44:365–367
Di Carlo I, Urrico GS, Ursino V, Russello D, Puleo S, Latteri F (2003) Simultaneous occurrence of adenoma, focal nodular hyperplasia, and hemangioma of the liver: are they derived from a common origin? J Gastroenterol Hepatol 18:357–358

Di Rocco M, Calevo MG, Taro' M, Melis D, Allegri AE, Parenti G (2008) Hepatocellular adenoma and metabolic balance in patients with type Ia glycogen storage disease. Mol Genet Metab 93:398–402

Dietrich CF, Schuessler G, Trojan J, Fellbaum C, Ignee A (2005) Differentiation of focal nodular hyperplasia and hepatocellular adenoma by contrast-enhanced ultrasound. Br J Radiol 78:704–707

Dimitroulis D, Lainas P, Charalampoudis P, Karatzas T, Delladetsima I, Sakellariou S et al (2012) Co-existence of hepatocellular adenoma and focal nodular hyperplasia in a young female. World J Hepatol 4:314–318

Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D, Bedossa P, Belghiti J (2009) A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. Gastroenterology 137:1698–1705

Edmondson HA (1958) Tumors of the liver and intrahepatic bile ducts. In: Hartmann WH, Sobin LH (eds) Atlas of tumor pathology, 1st edn, section VII, fascicle 25. Armed Forces Institute of Pathology, Washington, DC, p 18

Edmondson HA, Henderson B, Benton B (1976) Liver-cell adenomas associated with use of oral contraceptives. N Engl J Med 294:470–472

Ehren H, Mahour GH, Isaacs H (1983) Benign liver tumors in infancy and childhood. Report of 48 cases. Am J Surg 145:325–329

Endoh A, Inoue N, Katoh T, Nakamura T, Sugimura H, Ohzeki T (2001) A case of glycogen storage disease IA with multiple hepatic tumors managed by transcatheter arterial embolization and a acarbose diet. J Pediatr Gastroenterol Nutr 33:333–336

Farges O, Dokmak S (2010) Malignant transformation of liver adenoma: an analysis of the literature. Dig Surg 27:32–38

Farges O, Ferreira N, Dokmak S, Belghiti J, Bedossa P, Paradis V (2011) Changing trends in malignant transformation of hepatocellular adenoma. Gut 60:85–89

Faria SC, Iyer RB, Rashid A, Whitman GJ (2004) Hepatic adenoma. AJR Am J Roentgenol 182:1520

Fechner RE (1977) Benign hepatic lesions and orally administered contraceptives. Hum Pathol 8:255–268

Ferrell LD (1993) Hepatocellular carcinoma arising in a focus of multilobular adenoma. A case report. Am J Surg Pathol 17:525–529

Fink AS, Appelman HD, Thompson NW (1985) Hemorrhage into a hepatic adenoma and type Ia glycogen storage disease: a case report and review of the literature. Surgery 97:117–124

Fléjou JF, Barge J, Menu Y (1985) Liver adenomatosis: an entity distinct from liver adenoma? Gastroenterology 89:1132–1138

Fonseca S, Hoton D, Dardenne S, Annet L, Hubert C, Godecharles S, Jouret-Mourin A et al (2013) Histological and immunohistochemical revision of hepatocellular adenomas: a learning experience. Int J Hepatol. doi:10.1155/2013/398308

Foster JH, Berman MM (1977) The benign lesions: adenoma and focal nodular hyperplasia. In: Foster JH, Berman MM (eds) Solid liver tumors. W.B. Saunders, Philadelphia, pp 138–178

Foster JH, Berman MM (1994) The malignant transformation of liver cell adenomas. Arch Surg 129:712–717

Franchi-Abella S, Branchereau S (2013) Benign hepatocellular tumors in children: focal nodular hyperplasia and hepatocellular adenoma. Int J Hepatol 2013:215064

Fremond B, Jouan H, Sameh AH, Le Gall E, Bergeron C, Manac'h A, Gruel Y, Babut JM (1987) Tumors of the liver secondary to androgen therapy. Apropos of 2 cases in children (in French). Chir Pediatr 28:97–191

Fujiyama S, Sato K, Sakai M, Sato T, Tashiro S, Arakawa M (1990) A case of type Ia glycogen storage disease complicated by hepatic adenoma. Hepatogastroenterology 37:432–435

Galassi A, Pasquinelli G, Guerini A, Martinelli G, Venza E (1995) Benign myxoid hepatocellular tumor: a variant of liver cell adenoma. Liver 15:233–235

Garancis JC, Tang T, Panares R, Jurevics I (1969) Hepatic adenoma. Biochemical and electron microscopic study. Cancer 24:560–568

Geders JM, Haque S, Tesi RJ, Gerber MA, Lok AS (1995) A young man with a solitary hepatic mass. Hepatology 22:655–659

Gong L, Su Q, Zhang W, Li AN, Zhu SJ, Feng YM (2006) Liver cell adenoma: a case report with clonal analysis and literature review. World J Gastroenterol 12:2125–2129

Gonzalez A, Canga F, Cardenas F, Castellano G, Garcia H, Cuenca B, Sanchez F, Solis-Herruzo JA (1994) An unusual case of hepatic adenoma in a male. J Clin Gastroenterol 19:179–181

Gonzalez-Lara MF, Cordova-Ramon JC, Gamboa-Dominguez A, Cosme-Labarthe J et al (2013) Hepatocellular carcinoma arising in a telangiectatic hepatocellular adenoma. Ann Hepatol 12:626–628

Goodman ZD, Mikel UV, Lubbers PR, Ros PR, Langloss JM, Ishak KG (1987) Kupffer cells in hepatocellular adenomas. Am J Surg Pathol 11:191–196

Gordon SC, Reddy KR, Livingstone AS, Jeffers LJ, Schiff ER (1986) Resolution of a contraceptive steroid-induced hepatic adenoma with subsequent evolution into hepatocellular carcinoma. Ann Intern Med 105:547–549

Gouw AS, Zeng W, Buiskool M, Platteel I, van den Heuvel MC, Poppema S, de Jong KP et al (2010) Molecular characterization of the vascular features of focal nodular hyperplasia and hepatocellular adenoma: a role for angiopoietin-1. Hepatology 52:540–549

Gouysse G, Frachon S, Hervieu V, Fiorentino M, d'Errico A, Dumortier J, Boillot O et al (2004) Endothelial cell differentiation in hepatocellular adenomas: implications for histopathological diagnosis. J Hepatol 41:259–266

Grazioli L, Federle M, Ichikawa T, Balzano E, Nalesnik M, Madariaga J (2000) Liver adenomatosis: clinical,

histopathologic, and imaging findings in 15 patients. Radiology 216:395–402
Grazioli L, Federle MP, Brancatelli G, Ichikawa T, Olivetti L, Blachar A (2001) Hepatic adenomas: imaging and pathologic findings. Radiographics 21:877–892
Grazioli L, Olivetti L, Mazza G, Bondioni MP (2013) MR imaging of hepatocellular adenomas and differential diagnosis dilemma. Int J Hepatol 2013:374170
Griesinger K (1864) Das Adenoid der Leber Arch d Heilkde 5:380–384
Grigsby P, Meyer JS, Sicard GA, Huggins MB, Lamar DJ, DeSchryver-Kecskemeti K (1987) Hepatic adenoma within a spindle cell carcinoma in a woman with a long history of oral contraceptives. J Surg Oncol 35:173–179
Gunsar F, Aydin A, Tokat Y, Elmas N (2002) Idiopathic hepatocellular adenoma with intratumoral haemorrhage. Eur J Gastroenterol Hepatol 14:463–464
Han J, van den Heuvel MC, Kusano H, de Jong KP, Gouw AS (2012) How normal is the liver in which the inflammatory type hepatocellular adenoma develops? Int J Hepatol 2012:805621
Handra-Luca A, Paradis V, Vilgrain V, Dubois S, Durand F, Belghiti J, Valla D, Degott C (2006) Multiple mixed adenoma-focal nodular hyperplasia of the liver associated with spontaneous intrahepatic porto-systemic shunt: a new type of vascular malformation associated with the multiple focal nodular hyperplasia syndrome? Histopathology 48:309–311
Hayes PC, Portmann BC, Aldis PM, Williams R, Hayes JD (1986) Glutathione-S-transferase and carcinogenesis. Proceedings of a Workshop on Glutathione-S-transferases. Trinity College, Dublin
Heeringa B, Sardi A (2001) Bleeding hepatic adenoma: expectant treatment to limit the extent of liver resection. Am Surg 67:927–929
Heffelfinger S, Irani DR, Finegold MJ (1987) 'Alcoholic hepatitis ' in a hepatic adenoma. Hum Pathol 18:751–754
Herman P, Machado MA, Volpe P, Pugliese V, Vianna MR, Bacchell T, Machado MC, Pinotti HW (1994) Transformation of hepatic adenoma into hepatocellular carcinoma in patients with prolonged use of oral contraceptives (in Portuguese). Rev Hosp Clin Fac Med Sao Paulo 49:30–33
Holter S, Pollett A, Zogopoulos G, Kim H, Schwenter F, Sasi K, Gallinger S, Clendenning M et al (2011) Hepatic adenomas caused by somatic HNF1A mutations in children with biallelic mismatch repair gene mutations. Gastroenterology 140:735–736
Howell RR, Stevenson RE, Ben-Menachem Y, Phyliky RL, Berry DH (1976) Hepatic adenomata with type 1 glycogen storage disease. JAMA 236:1481–1484
Hsu CY, Chu CH, Lin SC, Yang FS, Yang TL, Chang KM (2003) Concomitant hepatocellular adenoma and adenomatous hyperplasia in a patient without cirrhosis. World J Gastroenterol 9:627–630
Hung CH, Changchien CS, Lu SN, Eng HL, Wang JH, Lee CM, Hsu CC, Tung HD (2001) Sonographic features of hepatic adenomas with pathologic correlation. Abdom Imaging 26:500–506
Hussain SM, van den Bos IC, Dwarkasing RS, Kuiper JW, den Hollander J (2006) Hepatocellular adenoma: findings at state-of-the-art magnetic resonance imaging, ultrasound, computed tomography and pathologic analysis. Eur Radiol 16:1873–1886
Ichikawa T, Federle MP, Grazioli L, Nalesnik M (2000) Hepatocellular adenoma: multiphasic CT and histopathologic findings in 25 patients. Radiology 214:861–868
Iijima H, Moriwaki Y, Yamamoto T, Takahashi S, Nishigami T, Hada T (2001) Spontaneous regression of hepatic adenoma in a patient with glycogen storage disease type I after hemodialysis: ultrasonographic and CT findings. Intern Med 40:891–895
Ishak KG (1976) Primary hepatic tumors in childhood. Prog Liver Dis 5:636–667
Ishak KG (1979) Hepatic neoplasms associated with contraceptive and anabolic steroids. Recent Results Cancer Res 66:73–128
Ito M, Sasaki M, Wen CY, Nakashima M, Ueki T, Ishibashi H, Yano M, Kage M, Kojiro M (2003) Liver cell adenoma with malignant transformation: a case report. World J Gastroenterol 9:2379–2381
Iwen KA, Klein J, Hubold C, Lehnert H, Weitzel JM (2013) Maturity-onset diabetes of the young and hepatic adenomatosis – characterisation of a new mutation. Exp Clin Endocrinol Diabetes 121:368–371
Iyer A, Robert ME, Bifulco CB, Salem RR, Jain D (2008) Different cytokeratin and neuronal cell adhesion molecule staining patterns in focal nodular hyperplasia and hepatic adenoma and their significance. Hum Pathol 39:1370–1377
Janes CH, McGill DB, Ludwig J, Krom RA (1993) Liver cell adenoma at the age of 3 years and transplantation 19 years later after development of carcinoma: a case report. Hepatology 17:583–585
Jeannot E, Poussin K, Chiche L, Bacq Y, Sturm N, Scoazec JY, Buffet C, Tran Van Nhieu J et al (2007) Association of CYP1B1 germ line mutations with hepatocyte nuclear factor 1a-mutated hepatocellular adenoma. Cancer Res 67:2611–2616
Jeannot E, Mellottee L, Bioulac-Sage P, Balabaud C, Scoazec JY, Tran Van Nhieu J et al (2010) Spectrum of HNF1A somatic mutations in hepatocellular adenoma differs from that in patients with MODY3 and suggests genotoxic damage. Diabetes 59:1836–1844
Ji Y, Zhu X, Sun H, Tan Y, Ma Z, Ye Q, Sujie A, Tang Z (2000) Hepatocellular adenoma and focal nodular hyperplasia: a series of 24 patients with clinicopathological and radiological correlation. Chin Med J (Engl) 113:852–857
Jungmann F (1861) Ein Fall von cirrhotischer Leber mit Adenombildung und Übergang desselben in Karzinom. Thesis, Berlin
Kakar S, Grenert JP, Paradis V, Pote N, Jakate S, Ferrell LD (2014) Hepatocellular carcinoma arising in adenoma:

similar immunohistochemical and cytogenetic features in adenoma and hepatocellular carcinoma portions of the tumor. Mod Pathol 27:1499–1509

Karhunen PJ (1986) Benign hepatic tumours and tumour like conditions in men. J Clin Pathol 39:183–188

Katabathina VS, Menias CO, Shanbhogue AK, Jagirdar J, Paspulati RM, Prasad SR (2011) Genetics and imaging of hepatocellular adenomas: 2011 update. Radiographics 31:1529–1543

Katsuramaki T, Nagayama M, Kimura Y, Meguro M, Furuhata T, Mukaiya M, Hirata K, Koito K et al (2003) Hepatocellular adenoma presenting as a giant multicystic tumor of the liver. J Gastroenterol 38:516–518

Kawakatsu M, Vilgrain V, Belghiti J, Fléjou JF, Nahum H (1994) Association of multiple liver cell adenomas with spontaneous intrahepatic portohepatic shunt. Abdom Imaging 19:438–440

Kawakatsu M, Vigrain V, Erlinger S, Nahum H (1997) Disappearance of liver cell adenoma: CT and MR imaging. Abdom Imaging 22:274–276

Kay S (1977) Nine year follow-up of a case of benign liver cell adenoma related to oral contraceptives. Cancer 40:1759–1760

Kay S, Schatzki PF (1971) Ultrastructure of a benign liver cell adenoma. Cancer 28:755–762

Kazi KC, Deshpande R, Soman R, Lala M, Shah S (2005) Liver cell adenoma with co-existing hepatic granulomas in an HIV-positive patient. Indian J Gastroenterol 24:274–275

Kebapci M, Kaya T, Aslan O, Bor O, Entok E (2001) Hepatic adenomatosis: gadolinium-enhanced dynamic MR findings. Abdom Imaging 26:264–268

Kelly PM, Poon FW (2001) Hepatic tumours in glycogen storage disease type 1 (von Gierke's disease). Clin Radiol 56:505–508

Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PF (1983) Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. Gastroenterology 84:994–1002

Khan SS, Fink M, King S (1992) Case report: liver adenomatosis presenting as multiple calcified masses. Clin Radiol 45:206–207

Khoo US, Nicholls JM, Lee JS, Saing H, Ng IO (1994) Cholestatic liver cell adenoma in a child with hirsutism and elevated serum levels of cortisol and ACTH. Histopathology 25:586–588

Kim H, Jang JJ, Kim DS, Yeom BW, Won NH (2013) Clinicopathological analysis of hepatocellular adenoma according to new Bordeaux classification: report of eight Korean cases. Korean J Pathol 47:411–417

Kishnani PS, Chuang TP, Bali D, Koeberl D, Austin S, Weinstein DA, Murphy E, Chen YT et al (2009) Chromosomal and genetic alterations in human hepatocellular adenomas associated with type Ia glycogen storage disease. Hum Mol Genet 18:4781–4790

Kobayashi M, Enzan H, Araki K, Kawai S, Kitagawa N (1999) Spontaneous hepatocellular adenoma with marked cystic change. Hepatogastroenterology 46:2955–2958

Koelma IA, Nap M, Huitema S, Krom RA, Houthoff HJ (1986) Hepatocellular carcinoma, adenoma, and focal nodular hyperplasia. Comparative histopathologic study with immunohistochemical parameters. Arch Pathol Lab Med 110:1035–1040

Kong CS, Appenzeller M, Ferrell LD (2000) Utility of CD34 reactivity in evaluating focal nodular hepatocellular lesions sampled by fine needle aspiration biopsy. Acta Cytol 44:218–222

Korula J, Yellin A, Kanel G, Campofiori G, Nichols P (1991) Hepatocellular carcinoma coexisting with hepatic adenoma. Incidental discovery after long-term oral contraceptive use. West J Med 155:416–418

Kozyraki R, Scoazec JY, Fléjou JF, D'Errico A, Bedossa P, Terris B, Fiorentino M et al (1996) Expression of cadherins and alpha-catenin in primary epithelial tumors of the liver. Gastroenterology 110:1137–1149

Kudo M (2001) Hepatocellular adenoma in type Ia glycogen storage disease. J Gastroenterol 36:65–66

Kumar AR, Wagner JE, Auerbach AD, Coad JE, Dietz CA, Schwarzenberg SJ, MacMillan ML (2004) Fatal hemorrhage from androgen-related hepatic adenoma after hematopoietic cell transplantation. J Pediatr Hematol Oncol 26:16–18

Labrune P, Trioche P, Duvaltier I, Chevalier P, Odievre M (1997) Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. J Pediatr Gastroenterol Nutr 24:276–279

Lack EE, Ornvold K (1986) Focal nodular hyperplasia and hepatic adenoma: a review of eight cases in the pediatric age group. J Surg Oncol 33:129–135

Lagana SM, Salomao M, Bao F, Moreira RK, Lefkowitch JH, Remotti HE (2013) Utility of an immunohistochemical panel consisting of glypican-3, heat-.shock protein-70, and glutamine synthetase in the distinction of low-grade hepatocellular carcinoma from hepatocellular adenoma. Appl Immunohistochem Mol Morphol 21:170–176

Laumonier H, Rullier A, Saric J, Balabaud C, Bioulac-Sage P (2008a) Unexpected discovery of 2 cases of hepatocyte nuclear factor 1alpha-mutated infracentimetric adenomatosis. World J Gastroenterol 14:4830–4833

Laumonier H, Biolac-Sage P, Laurent C, Zucman-Rossi J, Balabaud C, Trillaud H (2008b) Hepatocellular adenomas: magnetic resonance imaging features as a function of molecular pathological classification. Hepatology 48:808–816

Laumonier H, Cailliez H, Balabaud C, Possenti L, Zucman-Rossi J, Bioulac-Sage P et al (2012) Role of contrast-enhanced sonography in differentiation of subtypes of hepatocellular adenoma: correlation with MRI findings. AJR Am J Roentgenol 199:341–348

Laurent C, Trillaud H, Lepreux S, Balabaud C, Bioulac-Sage P (2003) Association of adenoma and focal

nodular hyperplasia: experience of a single French academic center. Comp Hepatol 2:6

Le Bail B, Jouhanole H, Deugnier Y, Salame G, Pellegrin JL, Saric J, Balabaud C, Bioulac-Sage P (1992) Liver adenomatosis with granulomas in two patients on long-term oral contraceptives. Am J Surg Pathol 16:982–987

Leborgne J, Lehur PA, Horeau JM, Dupas B, Bourcheix LM, Petiot JM, Cloarec D, Classe JM (1990) Therapeutic problems caused by rupture of large hepatic adenoma with central location. Apropos of 3 cases (in French). Chirurgie 116:454–460

Lee PJ (2002) Glycogen storage disease type I: pathophysiology of liver adenomas. Eur J Pediatr 161(Suppl 1): S46–S49

Leese T, Farges O, Bismuth H (1988) Liver cell adenomas. A 12-year surgical experience from a specialist hepatobiliary unit. Ann Surg 208:558–564

Lefkowitch JH, Muschel R, Price JB, Marboe C, Braunhut S (1983) Copper and copper-binding protein in fibrolamellar liver cell carcinoma. Cancer 51:97–100, Cancer Res. 11, 3654-3660

Lerut JP, Ciccarelli O, Sempoux C, Danse E, deFlandre J, Horsmans Y, Sokal E, Otte JB (2003) Glycogensosi type I diseases and evolutive adenomatosis: an indication for liver transplantation. Transpl Int 16:879–884

Liau SS, Qureshi MS, Praseedom R, Huguet E (2013) Molecular pathogenesis of hepatic adenomas and its implications for surgical management. J Gastrointest Surg 17:1869–1882

Libbrecht L, De Vos R, Cassiman D, Desmet V, Aerts R, Roskams T (2001) Hepatic progenitor cells in hepatocellular adenomas. Am J Surg Pathol 25:1388–1396

Lim KH, Ward SC, Roayaie S, Cohen E, Schwartz M, Fiel MI, Thung SN (2008) Multiple inflammatory and serum amyloid A positive telangiectatic hepatic adenomas with glycogenated nuclei arising in a background of nonalcoholic steatohepatitis. Semin Liver Dis 28:434–439

Limmer J, Fleig WE, Leupold D, Bittner R, Ditschneit H, Berger HG (1988) Hepatocellular carcinoma in type I glycogen storage disease. Hepatology 8:531–537

Liu TC, Vachharajani N, Chapman WC, Brunt EM (2014) Noncirrhotic hepatocellular carcinoma: derivation from hepatocellular adenoma? Clinicopathologic analysis. Mod Pathol 27:420–432

Loze I, Tessier MH, Jumbou O, Dreno B (2000) Hepatocellular adenomatosis presenting as prurigo. Br J Dermatol 142:384–386

Lubbers PR, Ros PR, Goodman ZD, Ishak KG (1987) Accumulation of technetium-99m sulphur colloid by hepatocellular adenoma: scintigraphic-pathologic correlation. AJR Am J Roentgenol 148:1105–1108

Mahomed FA (1877) On two cases of adenoma hepatis. Trans Pathol Soc Lond 28:147

Malatjalian DA, Graham CH (1982) Liver adenoma with granulomas. The appearance of granulomas in oral contraceptive-related hepatocellular adenoma and in the surrounding nontumorous liver. Arch Pathol Lab Med 106:244–246

Manichon AF, Bancel B, Durieux-Millon M, Ducerf C, Mabrut JY, Lepogam MA, Rode A (2012) hepatocellular adenoma: evaluation with contrast-enhanced ultrasound and MRI and correlation with pathologic and phenotypic classification in 26 lesions. HPB Surg 2012:418745

Mariana AF, Livingstone AS, Pereiras RV, van Zuiden PE, Schiff ER (1979) Progressive enlargement of an hepatic cell adenoma. Gastroenterology 77:1319–1325

Marie-Cardine A, Schneider P, Greene V, Metayer J, Bachy B, Vannier JP (2001) Erythrocytosis in a child with a hepatic adenoma. Med Pediatr Oncol 36:659–661

Mason HH, Andersen DH (1955) Glycogen disease of the liver (von Gierke's disease) with hepatomata: case report with metabolic studies. Pediatrics 16:785–799

Matkowskyi KA, Bai H, Liao J, Zhang W, Li H, Rao S, Omary R, Yang GY (2014) Aldoketoreductase family 1B10 (AKR1b10) as a biomarker to distinguish hepatocellular carcinoma from benign liver lesions. Hum Pathol 45:834–843

Mays ET, Christopherson W (1984) Hepatic tumors induced by sex steroids. Semin Liver Dis 4:147–157

McInerney PD, van Dessel MG, Berstock DA (1987) Spontaneous hemoperitoneum from rupture of a primary hepatic adenoma in an adult man. Gut 28:1170–1172

McKnight R, Nassar A, Cohen C, Siddiqui MT (2012) Arginase-1: a novel immunohistochemical marker of hepatocellular differentiation in fine needle aspiration cytology. Cancer Cytopathol 120:223–229

Meissner K (1998) Hemorrhage caused by ruptured liver cell adenoma following long-term oral contraceptives: a case report. Hepatogastroenterology 45:224–225

Meunier F, Boyer L, Abergel A, Perez N, Ravel A, Lhopital F, Viallet JF (1998) Regression of a focal nodular hyperplasia after stopping oral contraceptives (in French). J Radiol 79:341–343

Meyers RL, Scaife ER (2000) Benign liver and biliary tract masses in infants and toddlers. Semin Pediatr Surg 9:146–155

Micchelli ST, Vivekanandan P, Boitnott JK, Pawlik TM, Choti MA, Torbenson M (2008) Malignant transformation of hepatic adenomas. Mod Pathol 21:491–497

Middleton C, McCaughan GW, Painter DM, Stephen MS, Beale M, Fraser I (1989) Danazol and hepatic neoplasia: a case report. Aust NZ J Med 19:733–735

Milillo F, Romio P, Promenzio CM, Scala A, Pappacena G, Forciniti De Luca G (1997) Solitary hepatocellular adenoma in infancy. Pediatr Med Chir 19:125–126

Minami Y, Kudo M, Kawasaki T, Chung H, Matsui S, Kitano M, Suetomi Y, Onda H, Funai S et al (2002) Intrahepatic huge hematoma due to rupture of small hepatocellular adenoma: case report. Hepatol Res 23:145–151

Miyazaki T, Yamashita Y, Yamamoto H et al (1994) Dynamic MR imaging of hepatic adenomas with

pathologic correlation. Comput Med Imaging Graph 18:373–380
Monks PL, Fryar BG, Biggs WW (1986) Spontaneous rupture of an hepatic adenoma in pregnancy with survival of mother and fetus. Aust NZ J Obstet Gynaecol 26:155–157
Morel C, Vanwijck R, Broeckx J (2002) Hepatic adenomatosis: a fortuitous US finding. JBR-BTR 85:142–143
Moses (2002) http://www.ncbi.nlm.nih.gov/pubmed/12373565
Mueller J, Keeffe EB, Esquivel CO (1995) Liver transplantation for treatment of giant hepatocellular adenomas. Liver Transpl Surg 1:99–102
Murakami T, Nakamura H, Kuroda C, Hori S, Marukawa T, Kozuka T, Monden M, Wakasa K (1991) Siderotic nodules in hepatic cirrhosis disappearing after biliary haemorrhage: MR imaging. J Comput Assist Tomogr 15:1039–1041
Nagorney DM (1996) Are hepatic adenomas premalignant? HPB Surg 10:59–61
Nasarek A, Werner M, Nolte M, Klempnauer J, Georgii A (1995) Trisomy 1 and 8 occur frequently in hepatocellular carcinoma but not in liver cell adenoma and focal nodular hyperplasia. A fluorescence in situ hybridization study. Virchows Arch 427:373–378
Nault JC, Zucmann-Rossi J (2013) Molecular classification of hepatocellular adenomas. Int J Hepatol. doi:10.1155/2013/315947
Nault JC, Fabre M, Couchy G, Pilati C, Jennot E, Tran Van Nhieu J, Saint-Paul MC et al (2012) GNAS-activating mutations define a rare subgroup of inflammatory liver tumors characterized by STAT3 activation. J Hepatol 56:184–191
Nault JC, Bioulac-Sage P, Zucman-Rossi J (2013) Hepatocellular benign tumors – from molecular classification to personalized clinical care. Gastroenterology 144:888–902
Nguyen TD, Oakes D, Fogel MR, Williams R, Sherck JP, Kozar M (1986) Hepatocellular adenoma and nodular regenerative hyperplasia of the liver in a young man. J Clin Gastroenterol 8:478–482
Nicastro N, Finazzo M, Midiri M (1998) A case of giant hepatic adenoma: ultrasonography and computerized tomography findings (in Italian). Radiol Med (Torino) 96:405–407
Nishio S, Oka K, Tanaka K, Imagawa E, Omae T (1981) Type 1 glycogenosis with contracted kidneys and liver cell adenoma. Acta Pathol Jpn 31:873–881
Ockner RK, Kaikaus RM, Bass NM (1993) Fatty-acid metabolism and the pathogenesis of hepatocellular carcinoma: review and hypothesis. Hepatology 18:669–676
Palmer PE, Christopherson WM, Wolfe HJ (1977) Alpha1-antitrypsin, protein marker in oral contraceptive-associated hepatic tumors. Am J Clin Pathol 68:736–739
Paradis et al (2007) http://www.ncbi.nlm.nih.gov/pubmed/17596890
Paradis V (2010) Benign liver tumors: an update. Clin Liver Dis 14:719–729
Parker P, Burr I, Slonim A, Grishan FK, Greene H (1981) Regression of hepatic adenomas in type Ia glycogen storage disease with dietary therapy. Gastroenterology 81:534–536
Paulson EK, McClellan JS, Washington K, Spritzer CE, Meyers WC, Baker ME (1994) Hepatic adenoma: MR characteristics and correlation with pathologic findings. AJR Am J Roentgenol 163:113–116
Pelletier L, Rebouissou S, Paris A, Rathahao-Paris E, Perdu E, Bioulac-Sage P, Imbeaud S et al (2010) Loss of hepatocyte nuclear factor 1-alpha function in human hepatocellular adenomas leads to aberrant activation of signaling pathways involved in tumorigenesis. Hepatology 51:557–566
Penkava RR, Rothenberg J (1981) Spontaneous resolution of oral-contraceptive-associated liver tumor. J Comput Assist Tomogr 5:102–103
Perret AG, Mosnier JF, Porcheron J, Cuilleron M, Berthoux P, Boucheron S, Audigier JC (1996) Role of oral contraceptives in the growth of a multilobar adenoma associated with a hepatocellular carcinoma in a young woman. J Hepatol 25:976–979
Pilati C, Amessou M, Bihl MP, Balabaud C, Nhieu JT, Paradis V, Nault JC, Izard T et al (2011) Somatic mutations activating STAT3 in human inflammatory hepatocellular adenomas. J Exp Med 208:1359–1366
Pilati C, Letouzé E, Nault JC, Imbeaud S, Boulai A, Calderaro J, Poussin K, Franconi A et al (2014) Genomic profiling of hepatocellular adenomas reveals recurrent FRK-activating mutations and the mechanisms of malignant transformation. Cancer Cell 25:428–441
Poe R, Snover DC (1988) Adenomas in glycogen storage disease type 1. Two cases with unusual histologic features. Am J Surg Pathol 12:477–483
Pollack H (1979) Spontaneous rupture of a liver cell adenoma following many years' ingestion of an oral contraceptive (in German). MMW Munch Med Wochenschr 121:93–94
Pollice L (1973) Primary hepatic tumors in infancy and childhood. Am J Clin Pathol 60:512–521
Poussin K, Pilati C, Couchy G, Calderaro J, Bioulac-Sage P, Bacq Y, Paradis V, Leteurtre E et al (2013) Biochemical and functional analyses of gp130 mutants unveil JAK1 as a novel therapeutic target in human inflammatory hepatocellular adenoma. Oncoimmunology 2:e27090
Pulpeiro JR, Orduna M, Jimenez J, Gallego MS, Millan JM (1989) Primary hepatocellular adenoma in men. J Clin Ultrasound 17:269–274
Pupulim LF, Vuillerme MP, Paradis V, Valla D, Terraz S, Vilgrain V (2013) Congenital portosystemic shunts associated with liver tumours. Clin Radiol 68: e362–e369
Quinn SF, Hanks J, Shaffer H (1986) Sonographic diagnosis of a liver cell adenoma. South Med J 79:372–373
Rabe T, Feldmann K, Grunwald K, Runnebaum B (1994) Liver tumours in women on oral contraceptives. Lancet 344:1568–1569

Rafii MR (1971) A large pediculate liver cell adenoma (in German). Acta Hepatosplenol 18:128–135
Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GP (2002) Glycogen storage disease type I: diagnosis, management, clinical course and outcome. Results of the European Study of Glycogen Storage Disease Type I (ESGSD I). Eur J Pediatr 161(Suppl 1):S20–S34
Ramakrishna B, Sitaram V, Khanduri P (1996) Large encapsulated hepatocellular adenoma in a male. Liver 16:235–236
Ramseur WL, Cooper MR (1978) Asymptomatic liver cell adenomas. Another case of resolution after discontinuation of oral contraceptive use. JAMA 239:1647–1648
Ranaldi R, Rezai B, Brancorsini D, Bearzi I (1993) Hepatocellular adenoma with areas of bone marrow: report of a case. Am J Surg Pathol 17:952–953
Rebouissou S, Imbeaud S, Balabaud C, Boulanger V, Bertrand-Michel J, Terce F et al (2007) HNF1alpha inactivation promotes lipogenesis in human hepatocellular adenoma independently of SREBP-1 and ChREBP activation. J Biol Chem 82:14437–14446
Rebouissou S, Bioulac-Sage P, Zucman-Rossi J (2008) Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma. J Hepatol 48:163–170
Rebouissou S, Amessou M, Couchy G, Poussin K, Imbeaud S, Pilati C, Izard T, Balabaud C et al (2009) Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours. Nature 457:200–204
Reijnierse JE, Joosten HJ, de Koning RW (1997) Severe upper abdominal pain due to a large hepatocellular adenoma. Neth J Med 51:46–50
Resnick MB, Kozakewich HP, Perez-Atayde AR (1995) Hepatic adenoma in the pediatric age group. Clinicopathological observations and assessment of cell proliferative activity. Am J Surg Pathol 19:1181–1190
Reznik Y, Dao T, Coutant R, Chiche L, Jeannot E, Clauin S, Rousselot P, Fabre M et al (2004) Hepatocyte nuclear factor-1 alpha gene inactivation: cosegregation between liver adenomatosis and diabetes phenotypes in two maturity-onset diabetes of the young (MODY) 3 families. J Clin Endocrinol Metab 89:1476–1480
Ribeiro A, Burgart LJ, Nagorney DM, Gores GJ (1998) Management of liver adenomatosis: results with a conservative surgical approach. Liver Transplant Surg 4:388–398
Ricci P, Cantisani V, D'Onofrio M, Sahani D, Pagliara E, Calliada F, Mehmet E, Sanjeva K et al (2008) Behavior of hepatocellular adenoma on real-time low-mechanical index contrast-enhanced ultrasonography with a second-generation contrast agent. J Ultrasound Med 27:1719–1726
Riener MO, Stenner F, Liewen H, Soll C, Breitenstein S, Pestalozzi BC, Samaras P, Probst-Hensch N et al (2009) Golgi phosphoprotein 2 (GOLPH2) expression in liver tumors and its value as a serum marker in hepatocellular carcinomas. Hepatology 49:1602–1609
Rindfleisch GE (1864) Mikroskopische Studien über das Leberadenoid. Arch Heilkd 5:395
Ronald M, Woodfield J, McCall J, Koea J (2004) Hepatic adenomas in male patients. HPB (Oxford) 6:25–27
Ronot M, Bahrami S, Calderaro J, Valla DC, Bedossa P, Belghiti J, Vilgrain V, Paradis V (2011) Hepatocellular adenomas: accuracy of magnetic resonance imaging and liver biopsy in subtype classification. Hepatology 53:1182–1191
Ros PR, Goodman ZD (2011) Genetics and imaging of hepatocellular adenomas: 2011 update. Invited commentary. Radiographics 31:1543–1545
Rosel HD, Baier A, Mesewinkel F (1990) Exsanguination caused by liver cell adenoma and rupture of the hepatic capsule as cause of maternal death (in German). Zentralbl Gynakol 112:1363–1367
Sakellariou S, Morgan Y, Heaton N, Portmann B, Quaglia A, Tobal K (2011) New monoallelic (partial tandem duplication) mutation of HNF1a gene in steatotic hepatocellular adenoma. Eur J Gastroenterol Hepatol 23:623–627
Sakelliarou S, Al-Hussaini H, Scalori A, Samyn M, Heaton N, Portmann B, Tobal K, Quaglia A (2012) Hepatocellular adenoma in glycogen storage disorder type I: a clinicopathological and molecular study. Histopathology 60:E58–E65
Santambrogio R, Marconi AM, Ceretti AP, Costa M, Rossi G, Opocher E (2009) Liver transplantation for spontaneous intrapartum rupture of a hepatic adenoma. Obstet Gynecol 113:508–510
Sasaki M, Nakanuma Y (2012) Overview of hepatocellular adenoma in Japan. Int J Hepatol 2012:648131
Sasaki M, Yoneda N, Kitamura S, Sato Y, Nakanuma Y (2011) Characterization of hepatocellular adenoma based on the phenotypic classification: the Kanazawa experience. Hepatol Res 41:982–988
Sato M, Ishida H, Konno K, Naganuma H, Hamashima Y, Komatsuda T, Ishida J, Watanabe S (2000) Liver tumors in children and young patients: sonographic and color Doppler findings. Abdom Imaging 25:596–601
Schaff Z, Sarosi I, Hsia CC, Kiss A, Tabor E (1995) p53 in malignant and benign liver lesions. Eur J Cancer 31A:1847–1850
Scott FR, el-Refaie A, More L, Scheuer PJ, Dhillon AP (1996) Hepatocellular carcinoma arising in an adenoma: value of QBend 10 immunostaining in diagnosis of liver cell carcinoma. Histopathology 28:472–474
Sempoux C, Chang C, Gouw A, Chiche L, Zucman-Rossi J, Balabaud C, Bioulac-Sage P (2013) Benign hepatocellular nodules: what we have learned using the pathomolecular classification. Clin Res Hepatol Gastroenterol 37:322–327
Sempoux C, Balabaud C, Bioulac-Sage P (2014) Pictures of focal nodular hyperplasia and hepatocellular adenomas. World J Hepatol 6:580–595
Seo JM, Lee SJ, Kim SH, Park CK, Ha SY (2012) Hepatocellular carcinoma arising from hepatocellular adenoma in a hepatitis B virus-associated cirrhotic liver. Clin Radiol 67:329–333

Shafizadeh N, Gerrich G, Ferrell L, Kakar S (2014) Hepatocellular adenomas in a large community population, 2000 to 2010: reclassification per current World Health Organization classification and results of long-term follow-up. Hum Pathol 45:976–983

Shanbhogue A, Shah SN, Zaheer A, Prasad SR, Takahashi N, Vikram R (2011) Hepatocellular adenomas: current update on genetics, taxonomy, and management. J Comput Assist Tomogr 35:159–166

Shaw AFB (1923) Primary liver-cell adenoma (hepatoma). J Path Bact 26:475–484

Shiomi S, Saeki Y, Kim K, Nishiguchi S, Seki S, Kuroki T, Kobayashi K, Harihara S, Owada M (1989) A female case of type VIII glycogenosis who developed cirrhosis of the liver and hepatocellular tumor. Gastroenterol Jpn 24:711–714

Simmonds A (1884) Die knotige Hyperplasie und das Adenom der Leber. Dtsch Arch Klin Med 34:110

Singhi AD, Jain D, Kakar S, Wu TT, Ye MM, Torbenson M (2012) Reticulin loss in benign fatty liver: an important diagnostic pitfall when considering a diagnosis of hepatocellular carcinoma. Am J Surg Pathol 36:710

Skarupa DJ, Ellison EC, Vitellas KM, Frankel WL (2004) Hepatocellular adenomatosis is a rare entity that may mimic other hepatocellular lesions. Ann Diagn Pathol 8:43–49

Socas L, Zumbado M, Perez-Luzardo O, Ramos A, Perez C, Hernandez JR, Boada LD (2005) Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of the literature. Br J Sports Med 39:e27

Sommer J, Effenberger T, Volpi E, Watzig GH, Bernhardt M, Suthaus J, Garbers C et al (2012) Constitutively active mutant gp130 receptor protein from inflammatory hepatocellular adenoma is inhibited by an anti-gp130 antibody that specifically neutralizes interleukin 11 signaling. J Biol Chem 287:13743–13751

Steinbrecher UP, Lisbona R, Huang SN, Mishkin S (1981) Complete regression of hepatocellular adenoma after withdrawal of oral contraceptives. Dig Dis Sci 26:1045–1050

Stock RJ, Labudovich M, Ducatman B (1985) Asymptomatic first-trimester liver cell adenoma: diagnosis by fine-needle aspiration cytology with cytochemical and ultrastructural study. Obstet Gynecol 66:287–290

Stoot JH, Coelen RJ, De Jong MC, Dejong CH (2010) Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. HPB (Oxford) 12:509–522

Straub BK, Herpel E, Singer S, Zimbelmann R, Breuhahn K, Macher-Goeppinger S et al (2010) Lipid droplet-associated PAT-proteins show frequent and differential expression in neoplastic steatogenesis. Mod Pathol 23:480–492

Suarez-Penaranda JM, de la Calle MC, Rodriguez-Calvo MS, Munoz JI, Concheiro L (2001) Rupture of liver cell adenoma with fatal massive hemoperitoneum resulting from minor road accident. Am J Forensic Med Pathol 22:275–277

Suga K, Hara A, Ogasawara N, Matsunaga N, Kurokawa F, Okita K (2002) Scintigraphic findings of multiple focal nodular hyperplasias in type 1 glycogen storage disease. Clin Nucl Med 27:834–836

Sugimoto K, Kondo F, Furuichi Y, Oshiro H, Nagao T, Saito K, Yoshida H, Imai Y et al (2013) Focal nodular hyperplasia-like lesion of the liver with focal adenoma features associated with idiopathic portal hypertension. Hepatol Res. doi:10.1111/hepr.12273

Suh YL, Song HG, Chi JG (1987) Liver cell adenoma in a neonate – report of an autopsy case. J Korean Med Sci 2:189–194

Sumner HW, Rosai J (1981) Ackerman's surgical pathology, 6th edn. C.V. Mosby, St. Louis, pp 624–631, chapter 12

Svrcek M, Jeannot E, Arrivé L, Poupon R, Fromont G, Fléjou JF, Zucman-Rossi J et al (2007) Regressive liver adenomatosis following androgenic progestin therapy withdrawal: a case report with a 10-year follow-up and a molecular analysis. Eur J Endocrinol 156:617–621

Tajada M, Nerin J, Ruiz MM, Sanchez-Dehesa M, Fabre E (2001) Liver adenoma and focal nodular hyperplasia associated with oral contraceptives. Eur J Contracept Reprod Health Care 6:227–230

Takayasu H, Motoi T, Kanamori Y, Kitano Y, Nakanishi H, Tange T, Nakagawara A, Hashizume K (2002) Two case reports of childhood liver cell adenomas harbouring beta-catenin abnormalities. Hum Pathol 33:852–855

Tao LC (1991) Oral contraceptive-associated liver cell adenoma and hepatocellular carcinoma. Cytomorphology and mechanisms of malignant transformation. Cancer 68:341–347

Tao C (1992) Are oral contraceptive-associated liver cell adenomas premalignant? Acta Cytol 36:338–344

Tateishi Y, Furuya M, Kondo F, Torii I, Nojiri K, Tanaka Y, Umeda S, Okudela K, Inayama Y et al (2013) Hepatocyte nuclear factor-1 a inactivated hepatocellular adenomas in patient with congenital absence of the portal vein: a case report. Pathol Int 63:358–363

Tatrai P, Somoracz A, Batmunkh E, Schirmacher P, Kiss A, Schaff Z, Nagy P, Kovalszky I (2009) Agrin and CD34 immunohistochemistry for the discrimination of benign versus malignant hepatocellular lesions. Am J Surg Pathol 33:874–885

Terkivatan T, de Wilt JHW, de Man RA, Ijzermans JNM (2000) Management of hepatocellular adenoma during pregnancy. Liver 20:186–187

Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Zondervan PE, Tilanus HW, Ijzermans JN (2001) Indications and long-term outcome of treatment for benign hepatic tumors: a critical reappraisal. Arch Surg 136:1033–1038

Terracciano L, Tornillo L, Avoledo P, Von Schweinitz D, Kuhne T, Bruder E (2004) Fibrolamellar hepatocellular carcinoma occurring 5 years after hepatocellular

adenoma in a 14-year-old girl: a case report with comparative genomic hybridization analysis. Arch Pathol Lab Med 128:222–226

Theruvath TP, Izar B, McGillicuddy J, Stewar E, Reuben A, Chavin KD (2011) Hepatocellular adenoma in men: a rare cause for liver resection. Am Surg 77:373–376

Theuerkauf I, Zhou H, Fischer HP (2001) Immunohistochemical patterns of human liver sinusoids under different conditions of pathologic perfusion. Virchows Arch 438:498–504

Thomeer MG, Bröker ME, de Lussanet Q, Biermann K, Dwarkasing RS, de Man R et al (2014) Genotype-phenotype correlations in hepatocellular adenoma: an update of MRI findings. Diagn Interv Radiol 20:193–199

Tomimatsu H, Kojiro M, Nakashima T (1982) Epithelioid granulomas associated with hepatocellular carcinoma. Arch Pathol Lab Med 106:538–539

Torbenson M, Lee JH, Chori M, Gage W, Abraham SC, Montgomery E, Boitnott J, Wu TT (2002) hepatic adenomas: analysis of sex steroid receptor status and the Wnt signaling pathway. Mod Pathol 15:189–196

Toso C, Rubbia-Brandt L, Negro F, Morel P, Mentha G (2003) Hepatocellular adenoma and polycystic ovary syndrome. Liver Int 23:35–37

Tretiakova MS, Hart J, Shabani-Rad MT, Zhang J, Gao ZH (2009) Distinction of hepatocellular adenoma from hepatocellular carcinoma with and without cirrhosis using E-cadherin and matrix metalloproteinase immunohistochemistry. Mod Pathol 22:1113–1120

Vaithianathan R, Philipchandran, Selvambigai G, Jayaganesh P (2013) Spontaneous hepatocellular adenoma in paediatric age group – case report. J Clin Diagn Res 7:2962–2963

Van Aalten SM, Thomeer MG, Terkivatan T, Dwarkasing RS, Verheij J, de Man RA, Ijzermans JN (2011a) Hepatocellular adenomas: correlation of MR imaging findings with pathologic subtype classification. Radiology 261:172–181

Van Aalten SM, Verheij J, Terkivatan T, Dwarkasing RS, de Man RA, Ijzermans JN (2011b) Validation of a liver adenoma classification system in a tertiary referral centre: implications for clinical practice. J Hepatol 55:120–125

Van Aalten SM, de Man RA, Ijzermans JN, Terkivatan T (2012) Systematic review of haemorrhage and rupture of hepatocellular adenomas. Br J Surg 99:911–916

Van der Borght S, Libbrecht L, Katoonizadeh A, Aerts R, Nevens F, Verslype C, Roskams TA (2007) Nuclear beta-catenin staining and absence of steatosis are indicators of hepatocellular adenomas with an increased risk of malignancy. Histopathology 51:855–856

Vik A, Cui G, Isaksen V, Wik T, Hansen JB (2009) Erythropoietin production by a hepatic adenoma in a patient with severe erythrocytosis. Acta Haematol 121:52–55

Volmar KE, Burchette JL, Creager AJ (2003) Hepatic adenomatosis in glycogen storage disease type Ia: report of a case with unusual histology. Arch Pathol Lab Med 127:e402–e405

Wang HL, Anatelli F, Zhai QJ, Adley B, Chuang ST, Yang XJ (2008) Glypican-3 as a useful diagnostic marker that distinguishes hepatocellular carcinoma from benign hepatocellular mass lesions. Arch Pathol Lab Med 132:1723–1728

Wang DQ, Fiske LM, Carreras CT, Weinstein DA (2011) Natural history of hepatocellular adenoma formation in glycogen storage disease type I. J Pediatr 159:442–446

Washington K, Telen MJ, Gottfried MR (1997) Expression of cell adhesion molecule CD44 in primary tumors of the liver: an immunohistochemical study. Liver 17:17–23

Watanabe S, Kobayashi Y (1993) Exogenous hormones and human cancer. Jpn J Clin Oncol 23:1–13

Wegelin K (1905) Über das Adenokarzinom und Adenom der Leber. Thesis, Berne. Virchows Arch 179: 95–153

Weimann A, Fronhoff K, Gratz KF, Maschek H, Bartels M, Klempnauer J, Ringe B, Pichlmayr R (1998) Diagnostic and therapeutic strategies in hepatocellular adenoma (in German). Zentralbl Chir 123:140–144

Wheeler DA, Edmondson HA, Reynolds TB (1986) Spontaneous liver cell adenoma in children. Am J Clin Pathol 85:6–12

Wilens G (1938) Adenoma of the liver. Am J Dis Child 55:792–797

Wilkens L, Bredt M, Flemming P, Becker T, Klempnauer J, Kreipe HH (2001) Differentiation of liver cell adenomas from well-differentiated hepatocellular carcinomas by comparative genomic hybridization. J Pathol 193:476–482

Willson JS, Godwin TD, Wiggins GA, Guilford PJ, McCall JL (2013) Primary hepatocellular neoplasms in a MODY3 family with a novel HNF1A germline mutation. J Hepatol 59:904–907

Yandza T, Valayer J (1986) Benign tumors of the liver in children: analysis of a series of 20 cases. J Pediatr Surg 21:419–423

Yang GC, Yang GY, Tao LC (2004) Distinguishing well-differentiated hepatocellular carcinoma from benign liver by physical features of fine-needle aspirates. Mod Pathol 17:798–802

Ye MQ, Suriawinata A, Ben Haim M, Parsons P, Schwartz ME (1999) A 42-year-old woman with liver masses and long-term use of oral contraceptives. Semin Liver Dis 19:339–344

Yim SH, Ward JM, Dragan Y, Yamada A, Scacheri PC, Kimura S, Gonzalez FJ (2003) Microarray analysis using amplified mRNA from laser capture microdissection of microscopic hepatocellular precancerous lesions and frozen hepatocellular carcinomas reveals unique and consistent gene expression profiles. Toxicol Pathol 31:295–303

Yoneda N, Matsui O, Kitao A, Kozaka K, Gabata T, Sasaki M, Nakanuma Y, Murata K et al (2012) Beta-catenin-activated hepatocellular adenoma showing hyperintensity on hepatobiliary-phase gadoxetic-

enhanced magnetic resonance imaging and overexpression of OATP8. Jpn J Radiol 30:777–782

Yoshidome H, McMasters KM, Edwards MJ (1999) Management issues regarding hepatic adenomatosis. Am Surg 65:1070–1076

Yoshikawa M, Fukui K, Kuriyama S, Tsujimoto T, Nakatani Y, Toyokawa Y, Kurematsu Y, Awata J, Shiroi A, Fukui H, Tsutsumi M (2001) Hepatic adenomas treated with percutaneous ethanol injection in a patient with glycogen storage disease type Ia. J Gastroenterol 36:52–61

Ziegler PF, Glass W (1966) On a case of pediculated liver cell adenoma (in German). Zentralbl Chir 91:1961–1965

Zucman-Rossi J (2004) Genetic alterations in hepatocellular adenomas: recent findings and new challenges. J Hepatol 40:1036–1039

Zucman-Rossi J, Jeannot E, Nhieu JT, Scoazec JY, Guettier C, Rebouissou S, Bacq Y et al (2006) Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. Hepatology 43:515–524

Variants of Hepatocellular Adenoma 25

Contents

Abstract

Apart from its classical or typical form, hepatocellular adenoma (HCA) can present as one of several variants. HCA often occurs as solitary lesion, but some patients synchronously exhibit several or multiple tumors, a condition termed hepatocellular adenomatosis. Currently, adenomatosis is defined by the presence of more than ten adenomas in an otherwise normal parenchyma. Most of the former cases of telangiectatic focal nodular hyperplasia are now considered to be a variant of HCA (telangiectatic HCA) associated with systemic signs of inflammation. The majority of telangiectatic HCA exhibit inflammatory changes in the tumor. A further rare variant of HCA is pigmented HCA, solitary or multiple benign tumors having abundant Dubin-Johnson-like pigment granules in the cytoplasm.

Hepatocellular Adenomatosis

Hepatocellular adenoma (HCA) often manifests as solitary lesion. However, some patients exhibit several or multiple HCA. This distinctive clinicopathologic situation is termed liver adenomatosis (LA), thought to be an entity distinct from solitary HCA and first described under this term in 1985, based on a series of 13 cases and defined as a condition of ten or more HCA (Fléjou et al. 1985), and 1 year later by Okuda (1986). However, multiple or multicentric HCA have

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_25

been described already earlier, at least once under the term, hepatic adenomatosis. LA has been defined by the synchronous presence of more than three HCA in the same liver, the number of tumor nodules required for fulfilling the criteria however varies in the reports, ranging from just "more than three," "five or more" (Yoshidome et al. 1999), to "more than ten" (Fléjou et al. 1985; Shortell and Schwartz 1991; Chiche et al. 2000). Currently, LA is defined as the presence of more than ten adenomas in an otherwise normal parenchyma (Chiche et al. 2000). In one series, the diagnosis was made at a mean of 32 years (range, 13–75 years; Chiche et al. 2000). All cases reported between 1977 and 2008 have been reviewed (Yoshidome et al. 1999; Chiche et al. 2000; Veteläinen et al. 2008), amounting to 94 cases in 2008. In the review of Veteläinen and coworkers, 52 % of the female patients had a history of oral contraceptive use, and 18 % of patients had steatosis in the adjacent liver tissue. For further information, reference is made to numerous publications that have appeared on this issue (Marckwald 1896; Aleksic and Kosanovic 1956; Monges et al. 1963; Monaco et al. 1964; Mercadier et al. 1967; Caquet et al. 1976; Lui et al. 1980; Sinha and Prasad 1982; Chen and Bocian 1983). Since then, numerous cases have been reported, the age at presentation ranging from childhood to adolescents and adults.

Selected References Aleksic and Kosanovic 1956; Shortell and Schwartz 1991; Choi et al. 1991; Degos et al. 1994; Propst et al. 1995; Gokhale and Whitington 1996; Cristaldi et al. 1998; Grazioli et al. 2000; Rumi et al. 2000; Yunta et al. 2001; Balci et al. 2002; Musthafa et al. 2003; Barthelmes and Tait 2005; Lewin et al. 2006; Veteläinen et al. 2008; Bisceglia et al. 2009.

What is hepatocellular adenomatosis today? Recent investigations and modern classifications have shown that in all subtypes of HCA, and in all etiologic settings, the tumors can be solitary, multiple (<10 nodules), or multiple in the sense of adenomatosis (>10 nodules) (Frulio et al. 2014), suggesting that the term LA requires redefinition in the future.

Pathologically, the individual nodules occurring in adenomatosis are histologically of the type found in solitary HCA, with or without hemorrhage. The nodules may be associated with or surrounded by smaller nodules measuring 1–2 cm or less. These small nodules are either typical small HCAs or atypical nodules, the latter characterized by a polylobulated aspect with steatotic zones. Small atypical nodules may expand and join to form bigger nodules, followed by effacement of non-adenomatous components to end up with a typical HCA nodule (Lepreux et al. 2003b). The number of lesions detectable on imaging may be considerably less than that found in resection specimens (e.g., 10–50 per liver on imaging in a study on 15 patients, but many more in resections; Grazioli et al. 2000). Chiche and coworkers (2000) have divided LA into two forms with different presentations and evolution, i.e., a massive form and a multifocal form, the former being an aggressive form. The massive form, which predominates in the literature, can be unilobar, but more often, the entire liver is enlarged, associated with a hypervascularized nodular parenchyma. In contrast, the multifocal form is not associated with hepatomegaly, and only one or two nodules may eventually cause complications, this form therefore being less aggressive.

Telangiectatic FNH and Telangiectatic HCA: IHCA-Type Lesions

Previously, nodular liver lesions with a marked sinusoidal ectasia or even peliosis-like alterations were classified as telangiectatic focal nodular hyperplasia (TFNH) of the liver which was classified as a peculiar variant of FNH (Peterfy and Rosenthall 1990). The former TFNH was mainly regarded as a disorder of adult females (Gussick et al. 2005; Paradis 2007; Machida et al. 2008; Takayassu et al. 2009; Paradis 2010), with a mean age at diagnosis of 37 years (Paradis et al. 2004), but it also occurs in the pediatric or even perinatal age group, sometimes with spontaneous regression (Kim et al. 2003; Okamura et al. 2005;

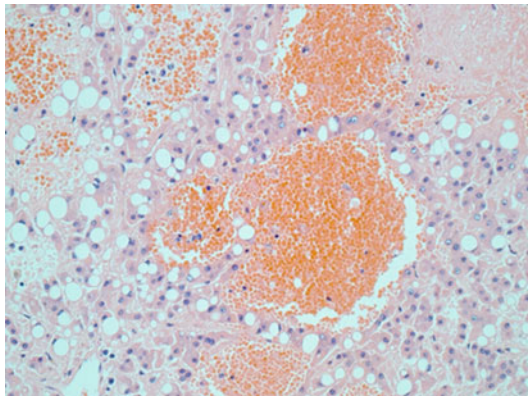

Fig. 1 Hepatocellular adenoma with peliosis-like and telangiectatic lesions (hematoxylin and eosin stain)

Hirakawa et al. 2009). Multiple foci were found in up to 62 % of patients (Attal et al. 2003; Fig. 1).

TFNH was described to show lack of central scar and radiating septa, medial muscular hypertrophy rather than intimal proliferation in target arteries, and direct drainage of abnormal blood vessels into adjacent sinusoids, while a direct sinusoidal drainage is not in evidence in typical FNH (Wanless et al. 1989; Nguyen et al. 1999; Attal et al. 2003).

Subsequently, telangiectatic nodular liver lesions were classified as a distinct variant of HCA, i.e., telangiectatic HCA (THCA). In fact, there are strong indications that the former TFNH is monoclonal and a true variant of HCA, specifically of the IHCA (inflammatory hepatocellular adenoma) type (adenoma with telangiectatic features; Paradis et al. 2004). In contrast with other types of HCA, THCA patients did not differ in the prevalence of oral contraceptive intake, but patients with THCA had longer periods of use than patients with other HCAs (Mounajied and Wu 2011). The histology is characterized by compact areas consisting of markedly vascularized portal tract-like structures, thickened arteries, and inflammatory infiltrated and ductular proliferations, these areas being surrounded by dilated sinusoids (Lepreux et al. 2003a). In one analysis, the mean diameter of nodules was 5 cm (range, 1–17 cm), and inflammatory changes were present in 91 %, steatosis in 53 %, vascular alterations in 59 %, and cellular atypias in 19 % (Paradis 2007). In a systematic study, no clinical difference was found between patients with TFNH and HCA. Hemorrhage, a typical feature of HCA, was found in 77 % of TFNH, which is unusual for "true" FNH. Patients with TFNH more often revealed multiple nodules, and there was evidence that TFNHs were monoclonal lesions (Bioulac-Sage et al. 2005). The telangiectatic lesions share with HCA a low mean value of the angiopoietin-1 and angiopoietin-2 mRNA ratio (2.1 in telangiectatic nodules, 2.6 in HCA, and 21.4 in FNH; Paradis et al. 2004). Telangiectatic HCA is associated with increased body mass index and systemic signs of inflammation (Paradis 2007). In rare situations, THCA presents as HCA variants also known for conventional HCA, e.g., pigmented HCA with nuclear beta-catenin reactivity and positivity for glutamine synthetase (Hechtman et al. 2011). Apart from associations known for other types of HCA, THCA was observed in primary sclerosing cholangitis (Maylee et al. 2012).

Notwithstanding the novel classification of telangiectatic nodular lesions, not all telangiectatic nodular lesions are HCA or IHCA, and a small subset of nodules may in fact still be FNHs or other hyperplastic nodular lesions with an abnormal vascularization pattern (Laumonier et al. 2010). THCA has histologically to be distinguished from nodular hyperplasic lesions with central telangiectatic fibrosis occurring in non-cirrhotic portal hypertension (Nakanuma et al. 1982).

Pigmented Liver Cell Adenoma

A mild lipofuscinosis occurs in some HCA, but other pigment depositions are exceptional. Few cases of pigmented HCA with deposition of Dubin-Johnson-like pigment have been reported (Bernard et al. 2000; Hasan et al. 2000; Ferko et al. 2003; Masuda et al. 2011; Koea and Kua 2012; Vij et al. 2012; Figs. 2 and 3). In one female patient, pigmented HCA was detected following long-term use of phenobarbital (Ferko et al. 2003). Multiple pigmented HCAs were observed in a male patient. The cut surfaces of these large and multinodular tumors had a few pale nodules of variable size standing out against

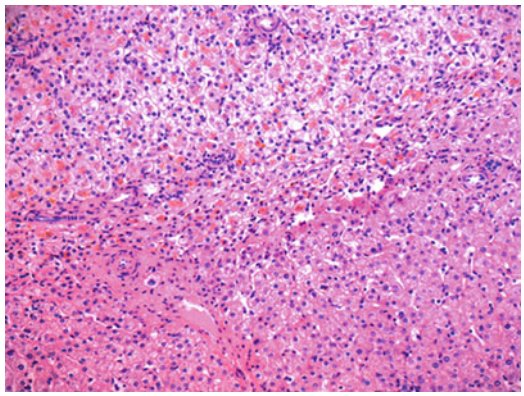

Fig. 2 Hepatocellular adenoma with accumulation of *yellow-brown,* Dubin-Johnson-like pigments (pigmented hepatocellular adenoma*, upper* half of figure; hematoxylin and eosin stain)

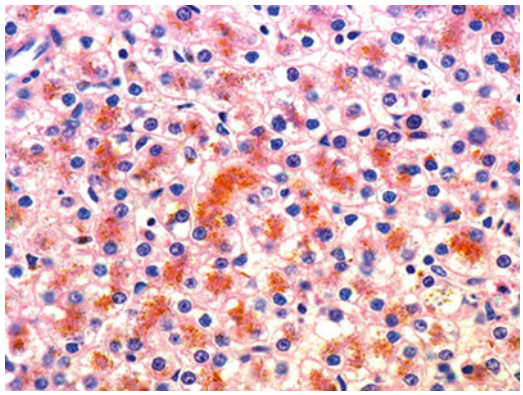

Fig. 3 Pigmented hepatocellular adenoma at higher magnification. Note the marked accumulation of Dubin-Johnson-like pigment granules in tumor cells, usually close to the canalicular pole of the cells (hematoxylin and eosin stain)

an overall strikingly dark gray or black color of the tumors. Histologically, most neoplastic cells are loaded with dark brown granules of Dubin-Johnson-like pigment, reactive in the Fontana-Masson stain and variably PAS-positive, whereas cells from the pale nodules were almost devoid of this pigment. Also ultrastructurally, the pigment granules strongly resemble those in Dubin-Johnson syndrome (Bernard et al. 2000). The accumulation of such a pigment in HCA in the absence of Dubin-Johnson syndrome is striking. In one case, the tumor showed a complete CD34-immunostaining pattern (Vij et al. 2012).

Dubin-Johnson syndrome is characterized by conjugated hyperbilirubinemia and by impaired secretion of anionic non-bile salt conjugates from hepatocytes into bile and is caused by the absence of multidrug-resistance protein 2 (MRP2; ABCC2), an ATP-dependent conjugate export pump at the canalicular membrane. Interestingly, a further case of "black" HCA (multiple tumors) showing a Dubin-Johnson-like pigment exhibited a decreased expression of cMOAT in the tumors in comparison with normal tissue, suggesting a partial defect of the MRP2 transporter in the neoplastic lesion (Bernard et al. 2000).

Ectopic Liver Cell Adenoma

Interestingly, a lesion morphologically similar to HCA occurs in the placenta (hepatic or hepatocellular adenoma of the placenta; Willis 1968; Chen et al. 1986; Fiutowski and Pawelski 1996; Vesoulis and Agamanolis 1998; Khalifa et al. 1998; Dargent et al. 2000). The case of Willis (1968) may rather represent hepatic heterotopia in the placenta. This is an extremely rare, solitary non-trophoblastic placental lesion of still disputed histogenesis. The tumor is incidentally found in woman between 20 and 30 years of age and is usually small, up to 1 cm. The histology is close to hepatic HCA, but fetal-type cells were reported to occur (Chen et al. 1986). It has been hypothesized that placental hepatocellular adenoma may take its origin from displaced yolk sac cells undergoing hepatocyte differentiation, a growing remnant of a fetus amorphous, a growing liver cell ectopia, or from a monodermal teratoma.

Hepatocellular Adenomatous Tumors of Doubtful Dignity

Atypical Hepatocellular Tumors Occurring in Fanconi Anemia

In some situations, HCA present with an unusual gross and/or microscopic presentation, being situated between bona fide HCA and highly differentiated HCC ("borderline lesions").

Interestingly, this has several times been documented and discussed for hepatocellular tumors developing in patients with Fanconi anemia (FA) and this may not only be related to not yet established dignity criteria in these partially older reports. Notwithstanding the fact that FA patients received corticosteroid and/or androgen therapy similar to other patients with different disorders, a disproportionally large number of liver tumor cases have been reported in FA (review: Schmidt et al. 1984). In part of these patients, a diagnosis of bona fide HCC can be confirmed by the histologic findings (Sarna et al. 1975; Cap et al. 1983; Abbondanzo et al. 1986; Moldvay et al. 1991). However, the data in the literature referring to hepatic tumors in FA do not always allow to clearly identify the type of liver lesions, because some masses were termed "hepatic tumors" (Farrell 1976; Shapiro et al. 1977; sometimes regressing subsequent to bone marrow transplantation with steroid weaning; Schmidt et al. 1984) and because some of the "hepatomas" reported may have had an unusual course (Sarna et al. 1975; Holder et al. 1975; Chandra et al. 1984). Is there a distinctive phenotype in hepatic neoplasms arising within the context of androgen therapy as such, or is the genotype of androgen- or corticosteroid-treated FA exerting a specific influence? In 1975, Anthony reviewed reports of 12 hepatocellular tumors associated with androgens, most of which had been originally reported as HCC (Anthony 1975). Employing strict histologic criteria, he accepted only two cases as having HCC, although other experienced pathologists have felt that some of the cases not accepted by Anthony were histologically malignant (Johnson 1975). Another group of experts had the opinion that of the cases reported since then, none would meet Anthony's criteria for malignancy, supported by the unusually benign course and even a tendency to regress after discontinuation of the therapy (Shapiro et al. 1977). Analysis of published reports raise doubts as to the appropriateness to call some of the lesions malignant: with the possible exception of the case described by Mokrohisky and coworkers (1977), death was not related to the presence of tumor, metastases not being observed, about half of the cases being incidentally detected at autopsy, and regression occurring in part of the tumors on discontinuation of androgen therapy (Johnson et al. 1972; Farrell 1976; Schmidt et al. 1984). In particular, the most appropriate terminology for the hepatocellular neoplasms associated with androgen therapy and/or arising in FA remains disputed. It has, therefore, been proposed to employ the term "hepatocellular neoplasm" for these unusual situations and to use HCA for clearly benign and HCC for clearly malignant lesions (Shapiro et al. 1977). Hence, it seems worthwhile to look at some of these published lesions in some more detail. The case of Holder and coworkers was described as a 4 cm tumor occurring in a non-cirrhotic liver, apparently "avascular" in a technetium scan; the lesion was described as "differentiated hepatoma," but a histologic description was not given (Holder et al. 1975). A tumor identified as "hepatoma" arising in a FA patient receiving androgen therapy was described as clinically and biologically "silent" (Meadows et al. 1974). In an 11-year-old boy with FA treated with androgens, corticosteroids, and transfusions, the liver showed peliosis and multiple tumors histologically representing well-differentiated hepatocellular carcinoma, a lesion being exceedingly rare in this age group (Moldvay et al. 1991). An informative case was described by Shapiro and coworkers (1977). This 13-year-old boy with FA treated with androgens and corticosteroids developed multiple liver nodules ranging in diameter from 0.5 to 4 cm, the larger nodules being hemorrhagic. The smaller nodules consisted of liver cell plates two cells thick, whereas the larger nodules were arranged in trabeculae and acini, the former not fulfilling the criteria of malignancy, while the latter were compatible with well-differentiated HCC. A striking feature was the marked cholestasis of the nodules. Among four patients with aplastic anemia (three with FA) having received oxymetholone (Chandra et al. 1984), all developed two to three unencapsulated, in part bulging nodules in their livers, the diameters ranging from 0.3 to 5 cm, histologically showing cells with enlarged nuclei, prominent nucleoli, scattered binucleate cells, and occasional

multinucleated cells, in the absence of mitotic activity or vascular invasion. Acinar formation was observed in two cases, and canalicular bile plugs were prominent in the nodules in all four. These changes were not detected in the non-androgen-related cases examined in parallel. Iron pigment was noted in the nodules, which is usually excluded from HCC. The authors concluded that these atypical lesions have an unknown malignant potential (Chandra et al. 1984). It therefore appears that in patients with androgen therapy, and in particular those with FA, a distinctive type of hepatocellular tumor may occur, whose biologic features require further investigation ("androgen hepatomas"; "Fanconi hepatomas").

Atypical Hepatocellular Adenoma-Like Neoplasms with Beta-Catenin Activation

A recently described tumor and termed atypical hepatocellular adenoma-like neoplasm with similarities to well-differentiated HCC is characterized by beta-catenin activation and cytogenetic features shared by well-differentiated HCC. In these neoplasms resembling HCA, beta-catenin mutations were more frequent (35 %), and transition into frank HCC was found in 1 out of 40 cases (Evason et al. 2013). It remains to be further studied whether such lesions are transitions between b-HCA and low-grade HCC.

References

Abbondanzo SL, Manz HJ, Klappenbach RS, Gootenberg JE (1986) Hepatocellular carcinoma in an 11-year-old girl with Fanconi's anemia. Report of a case and review of the literature. Am J Pediatr Hematol Oncol 8:334–337

Aleksic A, Kosanovic B (1956) Multiple hepatocellular adenoma of the liver. Acta Chir Iugosl 3:372–379

Anthony 1975. http://www.ncbi.nlm.nih.gov/pubmed/47110

Attal P, Vilgrain V, Brancatelli G, Paradis V, Terris B, Belghiti J, Taouli B, Menu Y (2003) Telangiectatic focal nodular hyperplasia: US, CT, and MR imaging findings with histopathologic correlation in 13 cases. Radiology 228:465–472

Balci NC, Sirvanci M, Duran C, Akinci A (2002) Hepatic adenomatosis: MRI demonstration with the use of superparamagnetic iron oxide. Clin Imaging 26:35–38

Barthelmes L, Tait IS (2005) Liver cell adenoma and liver cell adenomatosis. HPB (Oxford) 7:186–196

Bernard PH, Blanc JF, Paulusma C, Le Bail B, Carles J, Balabaud C, Bioulac-Sage P (2000) Multiple black hepatocellular adenomas in a male patient. Eur J Gastroenterol Hepatol 12:1253–1257

Bioulac-Sage P, Rebouissou S, Sa Cunha A, Jeannot E, Lepreux S, Blanc JF, Blanché H et al (2005) Clinical, morphologic, and molecular features defining so-called telangiectatic focal nodular hyperplasias of the liver. Gastroenterology 128:1211–1218

Bisceglia M, Gatta A, Tomezzoli A, Donataccio M (2009) Multiple spontaneous liver cell adenomas of different types (liver adenomatosis). Adv Anat Pathol 16:172–179

Cap J, Ondrus B, Danihel L (1983) Focal nodular hyperplasia of the liver and hepatocellular carcinoma of the liver in children with Fanconi's anemia after long-term treatment with androgens (in Slovak). Bratisl Lek Listy 79:73–81

Caquet R, Guillausseau PJ, Louvel A, d'Izam JJ, Laroche CI, Leger L (1976) Hepatic polyadenomatosis: a new case (in French). Nouv Presse Med 5:1474–1476

Chandra RS, Kapur SP, Kelleher J, Luban N, Patterson K (1984) Benign hepatocellular tumors in the young. A clinicopathologic spectrum. Arch Pathol Lab Med 108:168–171

Chen KTK, Bocian JJ (1983) Multiple hepatic adenomas. Arch Pathol Lab Med 107:274–275

Chen KT, Ma CK, Kassel SH (1986) Hepatocellular adenoma of the placenta. Am J Surg Pathol 10:436–440

Chiche L, Dao T, Salame E, Galais MP, Bouvard N, Schmutz G, Rousselot P, Bioulac-Sage P, Segol P, Gignoux M (2000) Liver adenomatosis: reappraisal, diagnosis, and surgical management: eight new cases and review of the literature. Ann Surg 231:74–81

Choi BI, Han JK, Kim SH, Han MC (1991) MR findings in liver adenomatosis. Gastrointest Radiol 16:234–236

Cristaldi M, Rovati M, Conte D, Elli M, Lesma A, Mezzabotta M, Vago L, Taschieri AM (1998) Primary liver adenomatosis. Report of two cases and literature review. Dig Surg 15:75–78

Dargent JL, Verdebout JM, Barlow P, Thomas D, Hoorens A, Goossens A (2000) Hepatocellular adenoma of the placenta: report of a case associated with maternal bicornuate uterus and fetal renal dysplasia. Histopathology 37:287–289

Degos F, Laraki R, Alsamad IA (1994) Multiple hepatic tumors in a female with idiopathic thrombopenic purpura (in French). Ann Intern Med 145:20–24

Evason KJ, Grenert JP, Ferrell LD, Kakar S (2013) Atypical hepatocellular adenoma-like neoplasms with b-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas. Hum Pathol 44:750–758

Farrell GC (1976) Fanconi's familial hypoplastic anaemia with some unusual features. Med J Aust 1:116–118
Ferko A, Bedrna J, Nozicka J (2003) Pigmented hepatocellular adenoma of the liver caused by long-term use of phenobarbital (in Czech). Rozhl Chir 82:192–195
Fiutowski M, Pawelski A (1996) Primary nontrophoblastic tumors of the placenta (in Polish). Ginekol Pol 67:515–519
Fléjou JF, Barge J, Menu Y (1985) Liver adenomatosis: an entity distinct from liver adenoma? Gastroenterology 89:1132–1138
Frulio N, Chiche L, Bioulac-Sage P, Balabaud C (2014) Hepatocellular adenomatosis: what should the term stand for! Clin Res Hepatol Gastroenterol 38:132–136
Gokhale R, Whitington PF (1996) Hepatic adenomatosis in an adolescent. J Pediatr Gastroenterol Nutr 23:482–486
Grazioli L, Federle MP, Ichikawa T, Balzano E, Nalesnik M, Madariaga J (2000) Liver adenomatosis: clinical, histopathologic, and imaging findings in 15 patients. Radiology 216:395–402
Gussick SD, Quebbeman EJ, Rilling WS (2005) Bland embolization of telangiectatic subtype of hepatic focal nodular hyperplasia. J Vasc Interv Radiol 16:1535–1538
Hasan N, Coutts M, Portmann B (2000) Pigmented liver cell adenoma in two male patients. Am J Surg Pathol 24:1429–1432
Hechtman JF, Raoufi M, Fiel MI, Taouli B, Facciuto M, Schiano TD, Blouin AG, Thung SN (2011) Hepatocellular carcinoma arising in a pigmented telangiectatic adenoma with nuclear b-catenin and glutamine synthetase positivity: case report and review of the literature. Am J Surg Pathol 35:927–932
Hirakawa H, Ueno S, Matuda H, Hinoki T, Kato Y (2009) Telangiectatic focal nodular hyperplasia of the liver in an infant with spontaneous regression: a case report. Tokai J Exp Clin Med 34:25–27
Holder LE, Gnarra DJ, Lampkin BC, Nishiyama H, Perkins P (1975) Hepatoma associated with anabolic steroid therapy. Am J Roentgenol Radium Ther Nucl Med 124:638–642
Johnson FL, Lerner KG, Siegel M, Feagler JR, Majerus PW, Hartmann JR (1972) Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. Lancet 2:1273–1276
Johnson 1975. http://www.ncbi.nlm.nih.gov/pubmed/190518
Khalifa MA, Gersell DJ, Hansen CH, Lage JM (1998) Hepatic (hepatocellular) adenoma of the placenta: a study of four cases. Int J Gynecol Pathol 17:241–244
Kim HS, Kim YA, Kim CJ, Suh YL, Jang JJ, Chi JG (2003) Telangiectatic focal nodular hyperplasia of the liver: a case detected at birth. J Korean Med Sci 18:746–750
Koea JB, Kua H (2012) Pigmented liver cell adenoma: rare but benign. ANZ J Surg 82:86–87
Laumonier H, Frulio N, Laurent C, Balabaud C, Zucman-Rossi J, Bioulac-Sage P (2010) Focal nodular hyperplasia with major sinusoidal dilatation: a misleading entity. BMJ Case Rep. doi:10.1136/bcr.09.2010.3311
Lepreux S, Laurent C, Le Bail B, Saric J, Balabaud C, Bioulac-Sage P (2003a) Multiple telangiectatic focal nodular hyperplasia: vascular abnormalities. Virchows Arch 442:226–230
Lepreux S, Laurent C, Blanc JF, Trillaud H, Le Bail B, Trouette H, Saric J, Zucman-Rossi J et al (2003b) The identification of small nodules in liver adenomatosis. J Hepatol 39:77–85
Lewin M, Handra-Luca A, Arrive L, Wendum D, Paradis V, Bridel E, Fléjou JF, Belghiti J et al (2006) Liver adenomatosis: classification of MR imaging features and comparison with pathologic findings. Radiology 241:433–440
Lui AFK, Hiratzka LF, Hirose FM (1980) Multiple adenomas of the liver. Cancer 45:1001–1004
Machida T, Hirayama M, Horita S, Hagiwara S, Ikari S, Kato T, Sasaki T, Kurose T et al (2008) Telangiectatic focal nodular hyperplasia accompanied with hemorrhage and necrosis during the course: report of a case (in Japanese). Nihon Shokakibyo Gakkai Zasshi 105:847–853
Marckwald E (1896) Das multiple Adenom der Leber. Virchows Arch 144:29
Masuda T, Beppu T, Ikeda K, Ishiko T, Chikamoto A, Hayashi H, Okabe H, Otao R et al (2011) Pigmented hepatocellular adenoma: report of a case. Surg Today 41:881–883
Maylee H, Harada K, Igarashi S, Tohda G, Yamamoto M, Ren XS, Osawa T, Hasegawa Y et al (2012) Case of telangiectatic/inflammatory hepatocellular adenoma arising in a patient with primary sclerosing cholangitis. Hepatol Res 42:611–618
Meadows AT, Naiman JL, Valdes-Dapena M (1974) Hepatoma associated with androgen therapy for aplastic anemia. J Pediatr 84:109–110
Mercadier M, Clot JP, Melliere D, Rambert P (1967) An unusual case of multinodular and multicentric hepatic adenomatosis (in French). Presse Med 75:1129–1130
Mokrohisky ST, Ambruso DR, Hathaway WE (1977) Fulminant hepatic neoplasia after androgen therapy. N Engl J Med 296:1411–1412
Moldvay J, Schaff Z, Lapis K (1991) Hepatocellular carcinoma in Fanconi's anemia treated with androgen and corticosteroid. Zentralbl Pathol 137:167–170
Monaco AP, Hallgrimsson J, McDermott WJ (1964) Multiple adenoma (hamartoma) of the liver treated by subtotal (90 %) resection: morphological and functional studies of regeneration. Ann Surg 159:513–519
Monges H, Payan H, Legre M, Vignoli R (1963) Considerations on a case of benign adenoma of the liver of the multinodular type (in French). Arch Mal Appar Dig 52:725–737
Mounajjed T, Wu TT (2011) Telangiectatic variant of hepatic adenoma: clinicopathologic features and correlation between liver needle biopsy and resection. Am J Surg Pathol 35:1356–1363
Musthafa CP, Chettupuzha AP, Syed AA, Ayshabi KA, Aravindan KP, Shobhana DR (2003) Liver adenomatosis. Indian J Gastroenterol 22:30–31

Nakanuma et al. 1982. http://www.ncbi.nlm.nih.gov/pubmed/7158342

Nguyen BN, Fléjou JF, Terris B, Bleghiti J, Degott C (1999) Focal nodular hyperplasia of the liver: a comprehensive pathologic study of 305 lesions and recognition of new histologic forms. Am J Surg Pathol 23:1441–1454

Okamura N, Nakadate H, Ishida K, Nakahara S, Isobe Y, Ohbu M, Okayasu I (2005) Telangiectatic focal nodular hyperplasia of the liver in the perinatal period: case report. Pediatr Dev Pathol 8:581–586

Okuda K (1986) Liver adenomatosis. Gastroenterology 90:1312–1313

Paradis V (2007) Telangiectatic adenoma: an entity associated with increased body mass index and inflammation. Hepatology 46:140–146

Paradis V (2010) Benign liver tumors: an update. Clin Liver Dis 14:719–729

Paradis V, Benzekri A, Dargère D, Bièche I, Laurendeau I, Vilgrain V, Belghiti J, Vidaud M et al (2004) Telangiectatic focal nodular hyperplasia: a variant of hepatocellular adenoma. Gastroenterology 126:1323–1329

Peterfy CG, Rosenthall L (1990) Large telangiectatic focal nodular hyperplasia presenting with normal radionuclide studies: case report. J Nucl Med 31:2037–2039

Propst A, Propst T, Waldenberger P, Vogel W, Judmaier G (1995) A case of hepatocellular adenomatosis with a follow-up of 11 years. Am J Gastroenterol 90:1345–1346

Rumi A, Somaglino C, Ronchi V, Pasqualin G (2000) A new case of hepatic adenomatosis. A critical review of the literature (in Italian). G Chir 21:37–43

Sarna G, Tomasulo P, Lotz MJ, Bubinak JF, Shulman NR (1975) Multiple neoplasms in two siblings with a variant form of Fanconi's anemia. Cancer 36:1029–1033

Schmidt E, Deeg HJ, Storb R (1984) Regression of androgen-related hepatic tumors in patients with Fanconi's anemia following marrow transplantation. Transplantation 37:452–455

Shapiro P, Ikeda RM, Ruebner BH, Connors MH, Halsted CC, Abildgaard CF (1977) Multiple hepatic tumors and peliosis hepatis in Fanconi's anemia treated with androgens. Am J Dis Child 131:1104–1106

Shortell CK, Schwartz SI (1991) Hepatic adenoma and focal nodular hyperplasia. Surg Gynecol Obstet 173:426–431

Sinha MR, Prasad SB (1982) Multiple adenomas of the liver. J Indian Med Assoc 79:16–18

Takayassu TC, Marchioni E, Eiras A, Cabral RF, Cabral FC, Btista RR, Zanetti G et al (2009) Telangiectatic adenoma – computed tomography and magnetic resonance findings: a case report and review of the literature. Cases J 2:24

Vesoulis Z, Agamanolis D (1998) Benign hepatocellular tumor of the placenta. Am J Surg Pathol 22:355–359

Veteläinen R, Erdogan D, de Graaf W, ten Kate F, Jansen PL, Gouma DJ, van Gulik TM (2008) Liver adenomatosis: re-evaluation of aetiology and management. Liver Int 28:499–508

Vij M, Patra S, Rela M (2012) Pigmented hepatocellular adenoma with complete CD34 immunostaining pattern: a diagnostic dilemma. Indian J Pathol Microbiol 55:528–530

Wanless IR, Albrecht S, Bilbao J, Frei JV, Heathcote EJ, Roberts EA, Chiasson D (1989) Multiple focal nodular hyperplasia of the liver associated with vascular malformations of various organs and neoplasia of the brain: a new syndrome. Mod Pathol 2:456–462

Willis RA (1968) Some unusual developmental heterotopias. Br Med J 3:267–272

Yoshidome H, McMasters KM, Edwards MJ (1999) Management issues regarding hepatic adenomatosis. Am Surg 65:1070–1076

Yunta PJ, Moya A, San-Juan F, Lopez-Andujar R, De Juan M, Orbis F, Mir J (2001) A new case of hepatic adenomatosis treated with orthotopic liver transplantation (in French). Ann Chir 126:672–674

Combined Hepatocellular-Cholangiocarcinoma

26

ICD-O code 8180/3

Contents

Abstract

Combined hepatocellular-cholangiocarcinoma (CHCC-C) is defined as a tumor that contains unequivocal, intimately mixed elements of both hepatocellular carcinoma and cholangiocarcinoma, resulting in a biphenotypic histologic picture. CHCC-C should not be confounded with collision tumors or rare hepatic mixed tumors. This is a rare liver malignancy of older individuals, probably accounting for less than 5 % of hepatic malignancies. The neoplasm develops in both non-cirrhotic and cirrhotic livers. Etiologic factors include hepatitis virus infections and alcoholic liver disease.

CHCC-C usually presents as a solitary tumor mass. Similar to hepatocellular carcinoma, the tumor tends to invade the portal vein system and bile ducts. Based on distinct histologic patterns, several types of CHCC-C are distinguished in the WHO classification, including a classical type and a type with stem cell features, the latter further subdivided into at least four subtypes. Rare variants of CHCC-C contain sarcomatoid components, or the HCC component is that of fibrolamellar hepatocellular carcinoma. CHCC-Cs are usually highly aggressive lesions with a high rate of metastatic spread.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_26

Introduction

The WHO tumor classification (Theise et al. 2010) defines combined hepatocellular-cholangiocarcinoma (CHCC-C) as a tumor containing unequivocal, intimately mixed elements of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). This biphenotypic tumor should be distinguished from separate HCC and CC arising in the same liver: Such tumors may be separated or intermixed ("collision tumor").

Combined hepatocellular and cholangiocellular carcinomas are an uncommon type of primary liver cancer with a distinct clinicopathologic presentation. Carcinomas of the liver having features of both hepatocyte and cholangiocyte lineages have formerly been reported under various names, including mixed tumors (L'Esperance 1915; Ewing 1940), primary duplex liver carcinoma (Koster and Kasman 1952), intermediate-type carcinoma (Bonne 1937), carcinoma of dual origin (Gustafsen 1937/1938), and cholangiohepatoma (Warvi 1944). In 1940, the term, combined type – adenocarcinoma and hepatoma – was first employed in a New England Journal of Medicine case presentation (Cabot 1940). More recent and now more commonly used names comprise combined hepatocellular-cholangiocarcinoma, combined hepatocellular/cholangiocellular carcinoma, combined hepatocholangiocarcinoma, and hepatocholangiocarcinoma. CHCC-C was first described in a comprehensive way in 1949 by Allen and Lisa, who also presented a first classification scheme for these neoplasms, and was recently reviewed (Lee et al. 2013; Singh et al. 2013; O'Connor et al. 2014).

Epidemiology

CHCC-C is a rare lesion; the reported frequency among adults with primary liver malignancies varies, however, widely, from a rate of 2.4 % (Goodman et al. 1985) to 5.3 (Ng et al. 1998) and even 14.2 % (Allen and Lisa 1949). Among 302 explant specimens of patients transplanted for HCC, 10 (3.3 %) showed CHCC-C (Sapisochin et al. 2011). Based on the SEER population-based registry (1973–2004), the frequency is lower and amounts to 0.87 % of primary liver tumors (Wachtel et al. 2008). The first example of CHCC-C may have been reported in 1903 (Wells 1903), followed by a report in 1915 (L'Esperance 1915), the latter author using the term mixed tumor. Relatively few cases have been reported until 1950 (Goldzieher 1928; Tramontano and Fittipaldi 1930; Koster and Kasman 1932; Rasario 1934, 1937; Bonne 1937; Gustafsen 1937/38; Cabot 1940; Ewing 1940; Neumann 1944; Warvi 1944; Allen and Lisa 1949). In few early reports on HCC, the data were very suggestive that bile duct cells participated in the malignant process (Prescott 1895; Moon 1929; Larson 1937; Neumann 1944; reviewed by Allen and Lisa 1949).

The mean patient age at diagnosis was 61 years in one study (range, 41–79 years; Jarnagin et al. 2002) and 55 years in a study on 43 patients (Park et al. 2011a). CHCC-C shows a variable male preponderance. The gender distribution varies considerably among several investigations. Among 27 cases, there were 88.9 % males and 11.1 % females (Zhan et al. 2012). In another study on 27 patients, 52 % were men and 48 % women (Jarnagin et al. 2002). The figures of the latter study are intermediate between HCC (67 % men and 33 % women) and CC (30 % men and 70 % women). In an analysis of 465 patients with CHCC-C compared with HCC and cholangiocarcinoma, this neoplasm was more common in patients who were white, male, and older than 65 years (Garancini et al. 2014). CHCC-C develops in cirrhotic or non-cirrhotic livers (Shiraishi et al. 1998; Zhan et al. 2012), cirrhosis having been found in 4 % (Jarnagin et al. 2002), 37 % (Zhan et al. 2012), 39 % (Taguchi et al. 1996), 54.2 %(Koh et al. 2005), and 77.8 % (Ng et al. 1998) of cases. These variable prevalences may be related to marked variations in the presence of factors causing liver cirrhosis, mainly epidemiological differences in the frequency of HBV and HCV infections. In certain regions, CHCC-C is associated with HBV infection (Chu et al. 2014). Interestingly, the study of Taguchi et al. (1996) has shown that cirrhosis was

more frequent in those tumors that had more features in common with HCC than in the cumulated group of CHCC-C (55 % vs. 39 %). In a study on 25 cases of CHCC-C, there was no statistical difference in etiologic risk factors between CHCC-C and HCC patients in regard to the presence of liver cirrhosis, chronic alcohol abuse, presence of hepatitis B surface antigen, and presence of hepatitis C virus/HCV antibody (Chantajitr et al. 2006). In a Japanese group of patients, the anti-HCV-positive rate was high in CHCC-C as in HCC (Tomimatsu et al. 1993). In a more recent investigation, risk factors for CHCC-C development included HBV infection, heavy alcohol consumption, a family history of liver cancer, and diabetes mellitus (Zhou et al. 2014). What can we learn from these observations? It emerges that, similar to HCC, there seem to be marked etiologic differences between patients of different countries with CHCC-C. For example, patients from Hong Kong had a high prevalence of cirrhosis and chronic hepatitis (Ng et al. 1998), while Japanese patients with CHCC-C often have chronic HCV infection (Tomimatsu et al. 1993). It has been suggested that, in Western populations, viral infection of the liver and cirrhosis may represent risk conditions for CHCC-C (Portolani et al. 2008).

Clinical and Imaging Features

CHCC-C in principle presents as other primary malignancies of the liver, but has shown some differences in comparison with cholangiocarcinoma: CHCC-C has a lower incidence of fever, chills, and jaundice, but a higher incidence of fatigue and weakness (Lee et al. 2002). Raised serum AFP levels (above 300 ng/ml) were present in 61.5 % of 21 patients (Ng et al. 1998). Elevation of serum AFP was found less commonly than in HCC (in one study, 46.2 % of CHCC-C patients had high AFP vs. 60.3 % in HCC; Tang et al. 2006), and the serum AFP levels in CHCC-C were found to be lower than those found in HCC (Chantajitr et al. 2006). High levels of serum AFP, CEA, and CA19-9 are regarded as a typical combination in CHCC-C (Nakamura et al. 1996). CHCC-C is more frequently associated with liver cirrhosis than intrahepatic cholangiocarcinoma (Lee et al. 2006). CHCC-C has been found in association with cholangitis (Yarze et al. 2005) or hepatolithiasis (Deniz et al. 2011). CHCC-C can be associated with paraneoplastic syndromes, including tumoral hypercalcemia (Pérez Roldan et al. 1995; Maarouf et al. 2008) and dermatomyositis (Horie et al. 1989). In patients with tumor-associated hypercalcemia, secretion of PTH-rP was detected (Maarouf et al. 2008; Matsumoto et al. 2014).

At sonography, the tumors are typically round or ovoid hypoechoic masses with a central hyperechoic area (target appearance) in most patients (Choi et al. 1994; Zhou et al. 2007). CT has shown irregular or relatively well-delineated hypodense or isodense masses with variable contrast enhancement (Aoki et al. 1993; Choi et al. 1994; Omagari et al. 1995; Hanazaki et al. 1998; Toh et al. 2004; Nishie et al. 2005; Sanada et al. 2005; Phongkitkarun et al. 2007; Shin et al. 2007; Hwang et al. 2012; Shetty et al. 2014). Hypervascular tumors are a common feature (Uenishi et al. 2000), supported by characteristic angiographic findings (Choi et al. 1994). Tumors with a large HCC component were well enhanced in the early CT phase and changed to low attenuation areas in the late phase. Conversely, in lesions grossly resembling CCC, the majority of the masses were enhanced only at the peripheral portions in the early phase and changed to low attenuation areas or had only central portions enhanced in the late phase (Fukukura et al. 1997). The distinct arrangement of the two main tumor components can result in imaging features resembling focal nodular hyperplasia (Willekens et al. 2009). It was demonstrated that the presence of a significant component of intermediate cells can cause misdiagnosis of CHCC-C on enhanced CT (Nishie et al. 2005). Rarely, the tumors have shown cyst formation at imaging (Utsunomiya et al. 2000). At axial MR, tumors are hypointense on T1-weighted scans and hyperintense in T2-weighted images (Hashimoto et al. 1994; Zhou et al. 2007; Fowler et al. 2013). In PET, CHCC-C showed high F18 deoxyglucose uptake (Shiomi et al. 1999).

Although there are consistent imaging findings in patients with CHCC-C, preoperative diagnosis remains difficult without tumor biopsy, even together with serum AFP and CA 19-9 results, because too many of the features are shared with both HCCs and CCs (Panjala et al. 2010). Among 15 patients with CHCC-C, only 2 patients were reliably diagnosed by enhanced CT prior to operation, the other 13 patients being diagnosed by histopathology and immunohistochemistry after operation (Zuo et al. 2007).

Pathology

Macroscopy

In most cases, CHCC-C presents a solitary tumor mass (de Campos et al. 2012), with rubbery, often ill-defined, whitish-yellow masses, while the HCC component may be visualized as tan or greenish nodules (Sonobe et al. 1987; Sugihara et al. 1987). Similar to HCC, CHCC-Cs tend to invade large veins, in particular the portal vein. Growth into the common bile duct has also been observed (Saito et al. 2001).

Histopathology

CHCC-C, Classical Type

The most common and typical form of CHCC-C (CHCC-C, classical type according to the WHO classification) displays areas of HCC and areas of cholangiocarcinoma, the latter most often of the intrahepatic type with variable desmoplasia (Sugihara et al. 1987; Bedossa 2007; Theise et al. 2010; review: Yeh 2010; Figs. 1 and 2). The HCC component in cases where it can easily be identified varies markedly in regard to composition and grade. Classical trabecular areas composed of moderately to well-differentiated large and eosinophilic cells as seen in ordinary HCC occur, but sometimes the HCC component is of the poorly differentiated small cell type, classification as HCC certainly requiring immunohistochemistry (Kim et al. 2004a). The cholangiocarcinoma component can present with

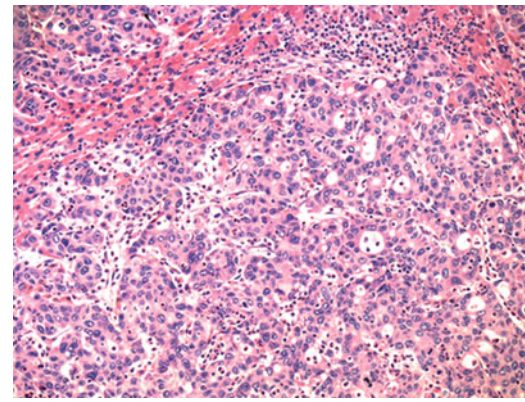

Fig. 1 Combined hepatocellular-cholangiocarcinoma. Apart from HCC-like cell plates, the neoplasm contains tubules and cribriform structures (hematoxylin and eosin stain)

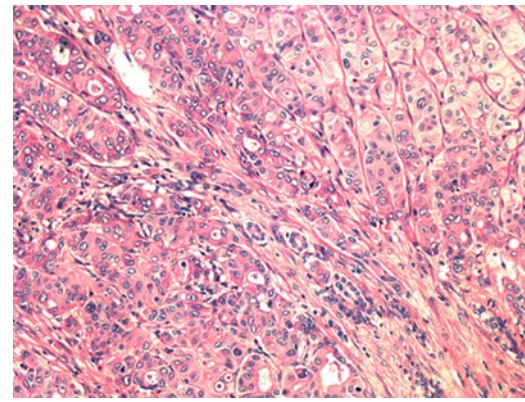

Fig. 2 In this combined hepatocellular-cholangiocarcinoma, the trabecular HCC component is readily discernible (*right upper* part). The *lower left* part of the figure shows tubular profiles (hematoxylin and eosin stain)

all the characteristic histologic features of intrahepatic CC and may show excessive mucin production (Wada et al. 1986; Morita et al. 2006) or undergo marked squamous cell differentiation/metaplasia (Tsuneyama et al. 2003). Sometimes, the mixed differentiation only reveals itself in metastases. For example, one tumor presented as HCC in the primary lesion, while intrahepatic metastases showed the typical features of CHCC-C (Morita et al. 2006).

CHCC-C often contains so-called transitional areas showing cells morphologically intermediate

between HCC and CC cells. Areas with an antler-like morphology were described, characterized by small or intermediate-sized cells being arranged in an antler-like anastomosing pattern (Tickoo et al. 2002; Park et al. 2011b). Areas of transition were found in at least 25 % of tumors in one analysis (Tickoo et al. 2002) and in all cases of another study, with strands/trabecules of small, uniform, and oval-shaped cells with scant cytoplasm and hyperchromatic nuclei, often embedded in a desmoplastic stroma (Zhang et al. 2008). The small cells found in transition areas look undifferentiated and share features with progenitor cells (Theise et al. 2003). In some tumors, the intermediate area is composed predominantly of spindle cells arranged in short fascicles (Park et al. 2011b).

Subtypes with Stem Cell Features

In a subset of CHCC-C, cells with progenitor cell features predominate. These CHCC-Cs with stem cell features include all three types of stem cell forms that have been described as components of CHCC-C (Theise et al. 2010; Akiba et al. 2013). The stemlike cells present in these malignancies are reactive for putative stem cell markers, including NCAM/CD56, CD133, EpCAM, CK19, and KIT, and in part express delta-like 1 homolog/DLK1 (Ikeda et al. 2013) and Yes-associated protein 1/YAP1 (Kim et al. 2013). There is evidence that CHCC-Cs with stem cell features and a stem cell component of more than 5 % have a poorer prognosis (Ikeda et al. 2013). At least four subtypes of CHCC-C with stem cell features have been described:

1. CHCC-C with stem cell features, typical subtype

   This subtype shows centrally placed clusters or nests of mature-looking hepatocytes (sometimes with clear cell change) with peripheral clusters of small cells with a high nucleus-to-cytoplasm ratio and hyperchromatic nuclei. These smaller cells are reactive for cytokeratins 7 and 19, NCAM1/CD56, KIT, and/or EpCAM, thus showing a progenitor cell phenotype. The progenitor-like cells may be embedded in a rich desmoplastic stroma. Typical subtype components were detectable in 16.1 % of CHCC-C (Sasaki et al. 2014).
2. CHCC-C with stem cell features, intermediate cell subtype

   This is a CHCC-C variant in which the predominant neoplastic cell population consists of cells with features intermediate between hepatocytes and cholangiocytes. This subtype is the most common one (Sasaki et al. 2014). Among 54 cases of CHCC-C from South Korea, 13 cases were of the intermediate type and demonstrated strands/trabecules of small, uniform, round-to-oval cells with scanty cytoplasm and hyperchromatic nuclei embedded within a thick desmoplastic stroma (so-called primary liver carcinoma of intermediate/hepatocyte-cholangiocyte phenotype; Kim et al. 2004a). The undifferentiated tumor cells are small and oval shaped with hyperchromatic nuclei and poor cytoplasm. Usually, these cells are embedded in an abundant desmoplastic stroma, where they form trabecules, solid nests, or strands. Well-developed glandular structures with mucin production are not present, but one may note few elongated and ill-defined gland-like profiles. Typically, the neoplastic cells co-express hepatocyte (Hep Par1 and AFP) and cholangiocyte (cytokeratin 19 and CEA) lineage markers, and KIT expression is common. The expression of CD133 and vimentin was found only in the intermediate cell subtype (Akiba et al. 2013). The cells, therefore, reflect an intermediate phenotype derived from a bipotential progenitor cell.
3. CHCC-C with stem cell features, cholangiocellular type

   This variant mainly consists of small cells with hyperchromatic oval nuclei, growing in the form of glandular structures and the "antler-like" pattern described above. Again, these primitive glandular cells are embedded in a desmoplastic stroma. The cells and their formations seem to mimic von Hering's canals or cholangioles. This is supported by their immunophenotype, characterized by positivity for cytokeratin 19, KIT, NCAM/Cd56, and

EpCAM. HCC-like and/or CC-like areas are often present at the periphery of the tumor nodules, where also a replacing pattern of growth is seen (Theise et al. 2010).

4. CHCC-C with stem cell features, ductal plate malformation type

   Intrahepatic cholangiocarcinoma with features of ductal plate malformation (DPM) has recently been described. A very rare variant of CHCC-C with stem cell features also shows DPM-like alterations. The index neoplasm was composed of well-differentiated HCC, well-differentiated cholangiocarcinoma, and intermediate tumor elements. Cholangiocarcinoma cells were present as tortuous, markedly irregular tubules with intraluminal cell projections, bridge formation, and intraluminal neoplastic biliary cells, features resembling ductal plate and DPM (Terada 2013).

Cytology

The presence of a dual cell population with features of malignancy in fine needle aspirates should raise the possibility of CHCC-C (Kilpatrick et al. 1993; Gibbons and de las Morenas 1997). However, the reliable diagnosis of CHCC-C on cytologic preparations alone is fraught with difficulty (Dusenbery 1997), particularly in the presence of so-called intermediate cells that have lost classic cytologic features of both HCC and CC (Wee and Nilsson 1999), so that additional methods, in particular immunocytochemistry, is strongly advocated.

Immunohistochemistry

The cells of the CC component are reactive for CK7 and CK19, as normal cholangiocytes (Goodman et al. 1985; Fisher et al. 1988; Hauben et al. 1996; Taguchi et al. 1996; Uenishi et al. 2002; Maeda et al. 2005), and for epithelial membrane antigen/EMA (Haratake and Hashimoto 1995; Tickoo et al. 2002). Positivities for CK7, CK19, and CK20 were 86.4 %, 90.9 %, and 18.2 %, respectively (Zhan et al. 2012). The hepatocyte-type population is reactive for cytokeratins 8 and 18 (Fisher et al. 1988) and for Hep Par1, but this marker is also expressed by a portion of the CC-type cells (Leong et al. 1998), in contrast to ordinary cholangiocarcinoma, where the tumor cells are usually not reactive for Hep Par1 (Kakar et al. 2003; Figs. 3, 4, and 5).

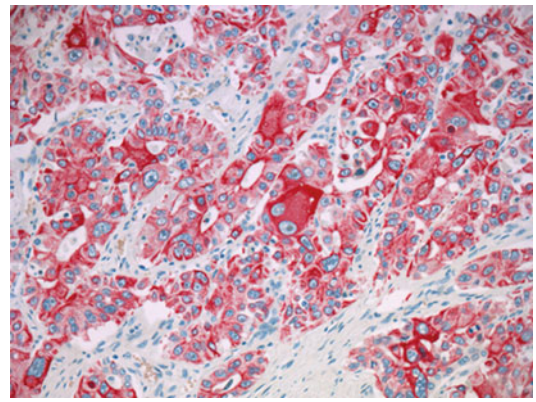

Fig. 3 Combined hepatocellular-cholangiocarcinomas exhibit heterogeneous immunostaining for cytokeratins 8 and 18, columnar cholangiocarcinoma cells often showing a more faint staining (CAM 5.2 immunostain)

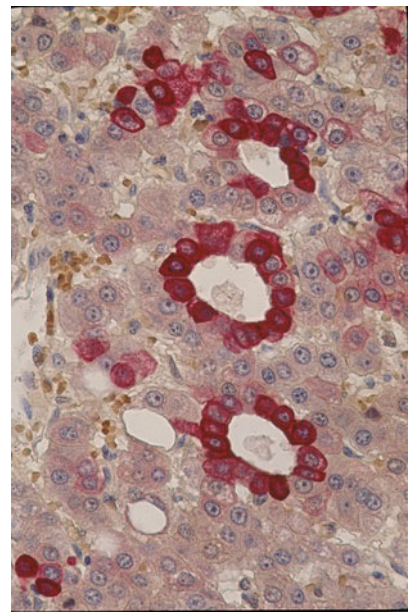

Fig. 4 Combined hepatocellular-cholangiocarcinoma with strong cytokeratin 19 expression of tubular, cholangiocellular structures (CK19 immunostain)

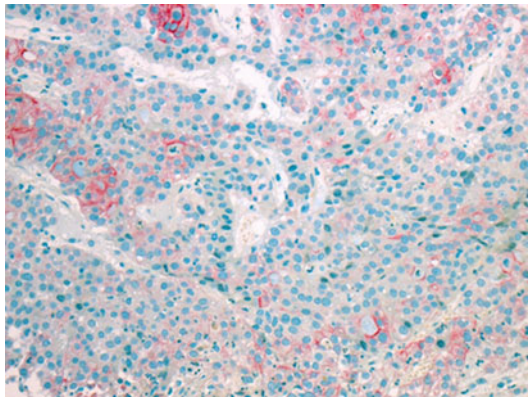

Fig. 5 In this combined hepatocellular-cholangiocarcinoma with predominance of HCC components, cytokeratin 19 is only focally expressed (CK19 immunostain)

The hepatoid cells in CHCC-C are reactive for glypican-3 (Shirakawa et al. 2009). It has been shown that cells that are morphologically intermediate between hepatocytes and cholangiocytes (cells of the transitional area) co-express CK19 and Hep Par1 (Tanaka et al. 2004). Simultaneous co-expression of Hep Par1 and CK7 or CK19 was demonstrated in 83.3 % of cases, and expression of c-kit was noted in 83.3 %, of which 70 % showed co-expression of OV-.6 (Zhang et al. 2008). Cells of the HCC component are reactive for AFP to variable degrees (Maeda et al. 2005). AFP reactivity was found in 55 % of tumors (Ng et al. 1998).

The CC components of CHCC-C rarely express the apomucins, MUC3 and MUC5AC, but they widely express MUC6 and MUC7, similar to certain subsets of cholangiocarcinomas (Sasaki et al. 1998). Immunoreactivity for E-cadherin and beta-catenin is present to variable degrees and may be used as prognosticator. E-cadherin and beta-catenin expressions are correlated with tumor differentiation and tumor progression in CHCC-C. Reduced expression of E-cadherin was significantly correlated with the tumor grade of HCC and CC components, intrahepatic metastases of HCC and CC components, and vascular invasion. There was a significant relationship between reduced expression of beta-catenin and the tumor grade of HCC components. The expression patterns of E-cadherin and beta-catenin of intrahepatic metastases were similar to those of the primary lesions in most cases (Asayama et al. 2002). CHCC-Cs express hepatocyte growth factor (HGF) and its receptor c-met. Immunoreactivity for HGF was significantly correlated with the differentiation degree of the CC components, being highest in well- and moderately differentiated and lowest in poorly differentiated components. No association was observed between expression of c-met or HGF and the presence of liver cirrhosis, vascular invasion, perineural invasion, lymphatic permeation, intrahepatic metastasis, or lymph node metastasis (Varnholt et al. 2002).

In Situ Hybridization (ISH)

ISH methods have been used as a diagnostic method in CHCC-C. Among 23 cases of CHCC-C, 96 % showed positive signals on ISH for albumin mRNA (Tickoo et al. 2002). Positivity for albumin mRNA and biliary markers confirms the biphenotypic differentiation in these tumors.

CHCC-C Combined with Other Tumors in the Liver

CHCC-C was found in combination with other liver tumors, e.g., hepatic angiosarcoma in a patient with thorotrastosis (Kojiro et al. 1982).

Classifications of CHCC-C

Macroscopically, the tumors have been classified according to variable criteria. Grossly, CHCC-C presents either as single nodular (SN) type or multinodular (MN) type (Sasaki et al. 2001). The nodular phase of CHCC-C can progress to a diffuse type of growth (Yoshida et al. 1985). Another group separated a more common HCC-predominant type from a CC-predominant type and from a separate-lesion type (Taguchi et al. 1996). Allen and Lisa (1949) proposed

Table 1 Allen-Lisa classification of CHCC-C (modified)

Type I
Separate tumors consisting of either hepatocyte-type cells or cholangiocyte-type cells
Comment:
Allen-Lisa Type I tumors seem to correspond to the collision tumors described by Goodman et al. (1985; see Table 2). This tumor type does no longer belong to CHCC-C *sensu strictiori* according to the WHO classification of tumors (Theise et al. 2010)
Type II
Contiguous tumors, each of different characters, that may mingle as they grow
Comment:
Allen-Lisa Type II tumors seem to correspond to the Type II tumors of Goodman et al. (1985; see Table 2)
Type III
Tumors that may display hepatocellular and cholangiocellular features intimately associated
Comment:
Allen-Lisa Type III tumors seem to correspond to a subset, but not all, of the tumors allocated to Type III of Goodman et al. (1985)

Table 2 Histopathological types of CHCC-C according to Goodman et al. (1985) (modified)

Type I
HCC and CC are clearly distinguished and are present as separate lesions at different sites within the same liver
Comment:
These are "collision tumors" or an apparently coincidental occurrence of HCC and CC within the same liver and may thus not represent bona fide CHCC-C. Therefore, they do not fulfill the WHO definition of classical CHCC-C
Type II
HCC and CC are contiguous, are present at adjacent sites, mingle with continued growth, and share transitional features
Comment:
These are "transitional tumors" showing a transition from HCC elements having a trabecular or solid pattern to components typical for CC having a tubular pattern and a fibrous stroma
Type III
HCC and CC are combined within the same tumor
Comment:
This is the intermediate type in which HCC elements and CC elements are almost indistinguishable, and the tumor cells are ovoid to round and show a solid growth and/or a cord-like pattern. The cells are considered to be intermediate in shape and structure between HCC and CC
In Goodman et al.'s original work (1985), part of these tumors contained a "fibrolamellar component" which resembles FLC, but which contains mucin-producing pseudoglands. It is this type which has led to considerable diagnostic and interpretational problems and hence to misunderstandings

three combinations of tumors of, as they called it, double nature, and this proposition entered in all future attempts at classifying CHCC-C. They distinguished (1) separate neoplastic masses comprised entirely of the liver cell type on the one hand and of the bile duct type on the other; (2) contiguous masses, each of different characters, which may mingle as they grow; and (3) individual masses that may display both features so intimately associated that they can be interpreted only as arising from the same site (Table 1). Later publications sometimes used Allen Types A, B, and C instead of Types I, II, and III.

Goodman et al. (1985) distinguished a collision type, apparently a coincidental occurrence of both HCC and CC in the same patient; a transitional type, with areas of intermediate differentiation and an identifiable transition between HCC and CC; and a fibrolamellar type which resembles the fibrolamellar variant of HCC but also contains mucin-producing pseudoglands (Table 2).

The separate (or separate-lesion) type seems to correspond to Goodman's collision type and is particularly rare (Hirohashi et al. 2002). It is defined by the synchronous presence of HCC and CC within the same liver as spatially separated lesions. To classify the separate-lesion type as CHCC-C is problematic because there is no evidence that the two tumors occurring in this situation have the same cellular origin. This is the reason why the WHO classification does not list this variant as a classical CHCC-C. In one series of lesions, Type I accounted for 17 %, Type II 66 %, and Type III 17 % (Taguchi et al. 1996).

An alternative classification was proposed by Wakasa et al. (2007). These authors distinguished: Type I, in which HCC and CC form nodules that can easily be distinguished from each other; Type II, in which both components are finely mixed, so that the two components are almost indistinguishable; and Type III, in which the tumors have

Table 3 Classification of CHCC-C according to the WHO tumor classification (2011)

CHCC-C, classical type
CHCC-C with stem cell features
Typical subtype
Intermediate cell subtype
Cholangiocellular subtype

lobular structures with HCC existing centrally and CC existing peripherally. The classification by the WHO is listed in Table 3.

Combined Hepatocellular and Cholangiocellular Carcinoma with Sarcomatoid Features

In a small subset of CHCC-Cs, sarcomatoid histologic features have been observed (Kimoto and Ugaki 1982; Nakajima et al. 1988; Nakasho et al. 1996, Papotti et al. 1997; Murata et al. 2001; Jeong et al. 2004; Kim et al. 2004b; Amano et al. 2005; Aishima et al. 2006; Boonsakan et al. 2007; Pua et al. 2009), similar to those known to occur in non-combined cholangiocarcinomas and hepatocarcinomas. These rare tumors have also been termed CHCC-C with sarcomatous transformation or with sarcomatous change. In one case, glandular areas of CHCC-C expressing mucins and AE1-reactive keratins showed transition toward a spindle cell sarcomatous growth in several areas of both the primary tumor and lymph node metastases. Based on S100 protein reactivity of the spindle cells, a Schwannoid cell differentiation was suggested (Papotti et al. 1997). Within the spindle cell areas, pleomorphic elements and osteogenesis have been observed (Nakajima et al. 1988), and the sarcomatous component can be dominated by vimentin-positive pleomorphic cells (Pua et al. 2009). The spindle cell component was immunoreactive for cytokeratins in one case (Jeong et al. 2004), suggesting mesenchymal-epithelial transition (MET) in these tumors. In one case, the tumor produced granulocyte colony-stimulating factor (Amano et al. 2005), a paraneoplastic phenomenon also known for HCC. Microsatellite loss of heterozygosity (LOH) at D8S555 was detected in both the carcinomatous and sarcomatous portions. 1-bp cytosine was deleted at codon 241 of exon 7 of the p53 gene in the combined portion, and p53 protein nuclear immunoreactivity was seen in sarcomatoid HCC and CC cells, suggesting that the combined tumor could be an offspring of the original HCC (Murata et al. 2001).

Combined Hepatocellular and Cholangiocellular Carcinoma

Cholangiocellular carcinoma is a very rare variant of intrahepatic biliary cancer and is thought to arise from cell systems of von Hering's canals or ductules, structures that contain a stem cell compartment. In a 71-year-old male, a tumor was observed that was a combination of HCC and a cholangiocellular carcinoma, the latter showing cells immunoreactive for CK7, CK20, and CAM5.2, but not for CK19 (Kanamoto et al. 2008). This very rare variant of CHCC-C should not be confounded with a subtype of CHCC-C with stem cell features as defined in the new WHO classification of tumors (Theise et al. 2010).

Combined Fibrolamellar Carcinoma and Cholangiocarcinoma

Fibrolamellar carcinoma (FLC) very rarely occurs in association with cholangiocarcinoma/CC (FL-CC; Goodman et al. 1985; Maeda et al. 1995; Ng et al. 1998; Tanaka et al. 2005a; Ward et al. 2010). Although Goodman et al. (1985) reported that 8/24 CHCC-C revealed features of FLC, it is questionable that all these tumors contained bona fide FLC, as this combination was found only very rarely thereafter. The involvement of a biliary-related cell lineage in these tumors is suggested based on the frequent immunoreactivity of FLC for the cholangiocyte marker cytokeratin CK7 (Van Eyken et al. 1990), but only very few FLCs show morphologic evidence of cholangiocytes. Histologically, FL-CC shows the large eosinophil cells typical for FLC, these cells being embedded in the characteristic

lamellar fibrous stroma (Tanaka et al. 2005a). Combined FLC and CC (FL-CC) was shown to express this phenotype also in its metastases (Tanaka et al. 2005a). In most reported cases, the presence of a cholangiocyte lineage was demonstrated by mucin-producing cells in FL-CC, with mucicarmine- and Alcian blue-positive mucin in the lumens (Ng et al. 1998; Tanaka et al. 2005a). As in ordinary FLC, the hepatoid cells of FL-CC show so-called pale bodies, which ultrastructurally consist of filamentous material packed densely into membrane-bound spherical structures (Tanaka et al. 2005a). Immunohistochemically, CEA was exclusively expressed in the cholangiocyte component of the primary hepatic tumor, while it was expressed in both CC and FLC cells in metastatic and recurrent tumors. Hep Par1 was also expressed in both components (Tanaka et al. 2005a).

Fibrolamellar Carcinoma with Mucin Production

This is a very rare tumor, characterized by a fibrolamellar carcinoma component that shows intracellular mucin, thought to represent an aberrant cholangiocellular differentiation in the sense of a variant CHCC-C (Rosa and Mohammadi 2014).

Differential Diagnosis

A differential diagnosis that may be difficult in the absence of appropriate immunohistochemistry is HCC with acinar/pseudoglandular structures (Kondo and Nakajima 1987). HCC and CCC can also develop from separate dysplastic nodules (Kwon et al. 2002) or may synchronously develop at different places within the liver (Li et al. 2012).

Biology of Disease

CHCC-C is a tumor that often exhibits a highly invasive phenotype with frequent venous permeation, direct invasion into adjacent liver substance and tumor satellite formation, and poor outcome (Ng et al. 1998; Hayashi et al. 2006; Kim et al. 2010; Park et al. 2011a; Ariizumi et al. 2012; Chi et al. 2012; Zhan et al. 2012; Lee et al. 2013; reviews: Zhou et al. 2007; Kassahun and Hauss 2008) and produces lymphonodal metastases and remote metastatic spread (Sonobe et al. 1987; Pérez Roldan et al. 1995). Similar to CC and HCC, CHCC-C is also known to cause gross portal vein invasion (Sonobe et al. 1987), but CHCC-C is more invasive to the portal vein than HCC (Yano et al. 2003). The characteristics of spread seem to be related to the gross growth patterns of the tumors. CHCC-C of the single nodular type shows a pattern of infiltration similar to HCC, while tumors of the multinodular type resembled intrahepatic cholangiocarcinoma (Sasaki et al. 2001). CHCC-C tends to locally recur, even following apparently complete resection. The most common site of recurrence was the remnant liver (Shin et al. 2007). The biology of CHCC-C disease is affected by several risk factors. Based on CT and MRI investigations, univariate log-rank analysis of imaging findings revealed that tumor necrosis, bile duct invasion, major vascular branch invasion, multiplicity, bilobar distribution, locoregional lymph node involvement, regional organ invasion, distant metastasis, and ascites had adverse influences on overall survival. Multivariate Cox proportional hazard analysis demonstrated that major vascular branch invasion, regional organ invasion, and nodal and distant metastases were independent prognostic factors that adversely affected overall survival rates (Lin et al. 2008).

Some authors had proposed that CHCC-C behaves like HCC, but in fact a biliary cell component is now thought to confer a poorer prognosis (Wu et al. 1996), and CHCC-C can undergo rapid progression (Saboo et al. 2011; Garancini et al. 2014; Kim et al. 2014) In a study on 25 patients, the overall median survival of CHCC-C patients was 38 weeks while that of HCC patients was 54 weeks (Chantajitr et al. 2006). In 29 Korean patients with CHCC-C who underwent liver resection or liver transplantation, disease-free survival rates at 6 months, 1 year, and 3 years were 51.1 %, 38.3 %, and

25.6 %, respectively. Univariate analysis revealed that the TNM stage was significantly associated with disease-free survival and that CA19-9 above 37 U/ml was predictive of low overall survival (Kim et al. 2009). Early TNM stage (I and II) compared with advanced stage (III and IV) correlated with higher overall survival on univariate analyses (Bhagat et al. 2006). Patients with localized tumors who were selected for cancer-directed surgery (CDS) were strongly associated with improved survival (Wang et al. 2010). On the other hand, a comparative analysis of stage I tumors showed that CHCC-C had shorter time to recurrence than HCC and CC and shorter overall survival than HCC (Lee et al. 2011). Among 21 patients with CHCC-C having undergone resection and compared with resected HCC and CC, the 5-year survival was lowest in patients with CHCC-C (24 %), but was not significantly different from that in patients with CC (33 %) or HCC (37 %) (Jarnagin et al. 2002). In a study on 43 patients, 32 underwent resection with curative intent. After resection, 27 patients (84.4 %) had tumor recurrence during the follow-up period of 18 months, and the median time to recurrence was 13 months. Overall median survival period was 34 months (Park et al. 2011a). The outcome following surgical treatment may be influenced by the histologic composition of the tumors, specifically by the proportion of hepatocellular versus cholangiocellular components. In one study, the mean survival period was significantly longer in the HCC-dominant group than in the CC-dominant group (Shin et al. 2007). Among 50 patients with CHCC-C treated with transcatheter arterial chemoembolization (TACE), 70 % were classified as responders. The median patient survival period was 12.3 months. Tumor size, tumor vascularity, Child-Pugh class, and portal vein invasion were independent factors associated with patient survival (Kim et al. 2010).

Genetic and Molecular Features

Genetically, the highest frequency of LOH in CHCC-C was seen on 4q and 17p, followed by 8p and 16q, but the patterns were distributed heterogeneously among the tumors studied (Fujii et al. 2000). Recurrent specific LOH was identified at 3p and 14q in more than 50 % of CC and CHCC-C, suggesting that CHCC-C is genetically closer to CC than HCC (Cazals-Hatem et al. 2004).

Pathogenic Pathways

Morphogenetic and pathogenic pathways involved in CHCC-C can be studied by use of in vitro models. CHCC-C cell lines were established and tested in the nude mouse model (Murakami et al. 1987). In human CHCC-C cell line, cells were shown to express functional characteristics of HCC, such as albumin synthesis, but cells growing on plastic dish were poorly differentiated and exhibited an overlap to CC cells. When grown within a Type I collagen gel matrix, cell morphology changed to a better differentiated HCC phenotype, while cells grown in the subcutis of nude mice revealed the phenotype of adenocarcinoma with mucin production (Yano et al. 1996). These findings suggest a marked plasticity of tumor cells constituting CHCC-C and imply the involvement of bipotential progenitor cells. In fact, it has been suggested that most CHCC-C arise from hepatic progenitor cells that retained their potential to differentiated into the hepatocyte and cholangiocyte lineages (Robrechts et al. 1998; Tanaka et al. 1998, 2005b; Kim et al. 2004a; Libbrecht 2006; Hunt and Varnholt 2008; Zhang et al. 2008). The precursor cell systems involved in the development of CHCC-C are, however, not known in detail. In one instance, a small CHCC-C was found to arise in a nodule of atypical adenomatous hyperplasia of the liver (Harada et al. 1993), suggesting a hepatocyte origin of these lesions. A hepatocyte origin of CHCC-C was also proposed based on the expression pattern of ABH and Lewis blood group antigens (Okada et al. 1987). Theise and coworkers (2003) identified undifferentiated cells with morphological and immunohistochemical features of hepatic progenitor cells in all cases of CHCC-C, and these findings were supported by a later study (Zhang et al. 2008). In a cohort of 80 patients with

CHCC-C, including 70 patients who underwent resection with curative intent, overall survival and disease-free survival were correlated with the proliferative activity of non-tumoral ductular reaction cells and the expression of progenitor cell markers. It turned out that proliferative ductular reaction related to hepatic progenitor cell activation was associated with recurrence of CHCC-C, in particular multifocal recurrence, suggesting a "field" effect of background progenitor activation (Cai et al. 2012). Mutational analyses of p53 and K-ras genes and allelotype studies of the Rb-1 produced evidence that both cellular components of CHCC-C (i.e., HCC cells and CC cells) might have arisen from the same cellular origin in some cases (Imai et al. 1996).

References

Aishima S, Kuroda Y, Asayama Y, Taguchi K, Nishihara Y, Taketomi A, Tsuneyoshi M (2006) Prognostic impact of cholangiocellular and sarcomatous components in combined hepatocellular and cholangiocarcinoma. Hum Pathol 37:283–291

Akiba J, Nakashima O, Hattori S, Tanikawa S, Takenaka M, Nakayama M, Kondo R, Nomura Y, Koura K et al (2013) Clinicopathologic analysis of combined hepatocellular-cholangiocarcinoma according to the latest WHO classification. Am J Surg Pathol 37:496–505

Allen RA, Lisa JR (1949) Combined liver cell and bile duct carcinoma. Am J Pathol 25:647–655

Amano H, Itamoto T, Emoto K, Hino H, Asahara T, Shimamoto F (2005) Granulocyte colony-stimulating factor-producing combined hepatocellular/ cholangiocellular carcinoma with sarcomatous change. J Gastroenterol 40:1158–1159

Aoki K, Takayasu K, Kawano T, Muramatsu Y, Moriyama N, Wakao F, Yamamoto J et al (1993) Combined hepatocellular carcinoma and cholangiocarcinoma: clinical features and computed tomographic findings. Hepatology 18:1090–1095

Ariizumi S, Kotera Y, Karagiri S, Nakano M, Yamamoto M (2012) Combined hepatocellular-cholangiocarcinoma had poor outcomes after hepatectomy regardless of Allen and Lisa class or the predominance of intrahepatic cholangiocarcinoma cells within the tumor. Ann Surg Oncol 19:1628–1636

Asayama Y, Taguchi KK, Aishima SS, Nishi H, Matsuda K, Tsuneyoshi M (2002) The mode of tumour progression in combined hepatocellular carcinoma and cholangiocarcinoma: an immunohistochemical analysis of E-cadherin, alpha-catenin and beta-catenin. Liver 22:43–50

Bedossa P (2007) Case 6: combined hepatocellular and cholangiocarcinoma (in French). Ann Pathol 27:112–114

Bhagat V, Javle M, Agrawal A, Gibbs JF, Kuvshinoff B, Nava E, Iyer R (2006) Combined hepatocholangiocarcinoma: case-series and review of literature. Int J Gastrointest Cancer 37:27–34

Bonne C (1937) Cancer and human races. Am J Cancer 30:435–454

Boonsakan P, Thangnapakorn O, Tapaneeyakorn J, Kositchaiwat S, Bunyaratvei S (2007) case report combined hepatocellular and cholangiocarcinoma with sarcomatous transformation. J Med Assoc Thai 90:574–580

Cabot J (1940) Case no. 26441. Primary cancer of the liver, combined type: adenocarcinoma and hepatoma. New Engl J Med 223:731–734

Cai X, Zhai J, Kalan DE, Zhang Y, Zhou L, Chen X, Qian G, Zhao Q, Li Y, Gao L et al (2012) background progenitor activation is associated with recurrence after hepatectomy of combined hepatocellular-cholangiocarcinoma. Hepatology 56:1804–1816

Cazals-Hatem D, Rebouissou S, Bioulac-Sage P, Bluteau O, Branché H, Franco D et al (2004) Clinical and molecular analysis of combined hepatocellular-cholangiocarcinomas. J Hepatol 41:292–298

Chantajitr S, Wilasrusmee C, Lertsitichai P, Phromsopha N (2006) Combined hepatocellular and cholangiocarcinoma: clinical features and prognostic study in a Thai population. J Hepatobiliary Pancreat Surg 13:537–542

Chi M, Mikhitarian K, Shi C, Goff LW (2012) Management of combined hepatocellular-cholangiocarcinoma: a case report and literature review. Gastrointest Cancer Res 5:199–202

Choi BI, Han JK, Kim YI, Kim HC, Park JH, Kim CW, Han MC (1994) Combined hepatocellular and cholangiocarcinoma of the liver: sonography, CT, angiography, and iodized-oil CT with pathologic correlation. Abdom Imaging 19:43–46

Chu KJ, Lu CD, Dong H, Fu XH, Zhang HW, Yao XP (2014) Hepatitis B virus-related combined hepatocellular-cholangiocarcinoma: clinicopathological and prognostic analysis of 390 cases. Eur J Gastroenterol Hepatol 26:192–199

De Campos RO, Semelka RC, Azevedo RM, Ramalho M, Heredia V, Armao DM, Woosley JT (2012) Combined hepatocellular carcinoma-cholangiocarcinoma: report of MR appearance in eleven patients. J Magn Reson Imaging 36:1139–1147

Deniz K, Torun E, Celikbilek M, Sözüer E (2011) Combined hepatocellular and cholangiocarcinoma associated with hepatolithiasis: report of a case. Surg Today 41:591–595

Dusenbery D (1997) Combined hepatocellular-cholangiocarcinoma. Cytologic findings in four cases. Acta Cytol 41:903–909

Ewing J (1940) Neoplastic diseases, 4th edn. W.B. Saunders Co., Philadelphia, p 740

Fisher HP, Doppel W, Osborn M, Altmannsberger M (1988) Evidence for a hepatocellular lineage in a combined hepatocellular-cholangiocarcinoma of transitional type. Virchows Arch B Cell Pathol Incl Mol Pathol 56:71–76

Fowler KJ, Sheybani A, Parker RA, Doherty S, Brunt M, Chapman WC, Menias CO (2013) Combined hepatocellular and cholangiocarcinoma (biphenotypic) tumors: imaging features and diagnostic accuracy of contrast-enhanced CT and MRI. AJR Am J Roentgenol 201:332–339

Fujii H, Zhu XG, Matsumoto T, Inagaki M, Tokusashi Y, Miyokawa N, Fukusato T et al (2000) Genetic classification of combined hepatocellular-cholangiocarcinoma. Hum Pathol 31:1011–1017

Fukukura Y, Taguchi J, Nakashima O, Wada Y, Kojiro M (1997) Combined hepatocellular and cholangiocarcinoma: correlation between CT findings and clinicopathologic features. J Comput Assist Tomogr 21:52–58

Garancini M, Goffredo P, Pagni F, Romano F, Roman S, Sosa JA, Giardini V (2014) Combined hepatocellular-cholangiocarcinoma: a population-level analysis of an uncommon primary liver tumor. Liver Transpl 20:952–959

Gibbons D, de las Morenas A (1997) Fine needle aspiration diagnosis of combined hepatocellular carcinoma and cholangiocarcinoma. A case report. Acta Cytol 41(suppl):1269–1272

Goldzieher MA (1928) Über multiple Carcinome, ein Beitrag zur Frage der Histogenese des Lebercarcinoms. Virchows Arch Pathol Anat 267:326–338

Goodman ZD, Ishak KG, Langloss JM, Sesterhenn IA, Rabin L (1985) Combined hepatocellular-cholangiocarcinoma. A histologic and immunohistochemical study. Cancer 55:124–135

Gustafsen E.G. (1937/38). An analysis of sixty-two cases of primary carcinoma of the liver based on 24'400 necropsies at Bellevue Hospital. Ann Int Med. 11:889–900

Hanazaki K, Fujimori Y, Kajikawa S, Nakata S, Shimozawa N, Adachi W, Amano J (1998) Mixed hepatocellular carcinoma and cholangiocarcinoma treated by extended left hepatic lobectomy with resection of the right hepatic vein and preservation of the inferior right hepatic vein after hepatic arterial infusion chemotherapy. Hepatogastroenterology 45:812–815

Harada K, Terada T, Nakanuma Y, Furukawa Y, Kurumaya H (1993) A case of small combined hepatocellular and cholangiocellular carcinoma arising in a nodule of atypical adenomatous hyperplasia of the liver. Am J Gastroenterol 88:1968–1969

Haratake J, Hashimoto H (1995) An immunohistochemical analysis of 13 cases with combined hepatocellular and cholangiocellular carcinoma. Liver 15:9–15

Hashimoto T, Nakamura H, Hori S, Tomoda K, Mitani T, Murakami T, Kozuka T, Monden M et al (1994) MR imaging of mixed hepatocellular and cholangiocellular carcinoma. Abdom Imaging 19:430–432

Hauben E, Struyf N, Michielsen P, van Marck E (1996) Cytokeratin profiles and mucin secretion in combined hepatocellular-cholangiocarcinoma. A case report. Pathol Res Pract 192:488–491

Hirohashi K, Uenishi T, Kubo S, Yamamoto T, Tanaka H, Shuto T, Kinoshita H (2002) The separate-lesion type combined hepatocellular carcinoma and cholangiocarcinoma. Hepatogastroenterology 49:806–809

Horie Y, Yamada M, Nakai K, Kawasaki H, Hirayama C, Matsui K, Kambe N, Shimao S (1989) Combined hepatocellular-cholangiocarcinoma associated with dermatomyositis. J Gastroenterol Hepatol 4:101–104

Hunt JP, Varnholt H (2008) Mixed hepatocellular-cholangiocarcinoma may derive from "hepatogones". Hepatobiliary Pancreat Dis Int 7:105

Hwang J, Kim YK, Park MJ, Lee MH, Kim SH, Lee WJ, Rhim HC (2012) Differentiating combined hepatocellular and cholangiocarcinoma from mass-forming intrahepatic cholangiocarcinoma using gadoxetic acid-enhanced MRI. J Magn Reson Imaging 36:881–889

Ikeda H, Harada K, Sato Y, Sasaki M, Yoneda N, Kitamura S, Sudo Y, Ooi A, Nakanuma Y (2013) Clinicopathologic significance of combined hepatocellular-cholangiocarcinoma with stem cell subtype components with reference to the expression of putative stem cell markers. Am J Clin Pathol 140:329–340

Imai Y, Oda H, Arai M, Shimizu S, Nakatsuru Y, Inoue T, Ishikawa T (1996) Mutational analysis of the p53 and K-ras genes and allelotype study of the Rb-1 gene for investigating the pathogenesis of combined hepatocellular-cholangiocellular carcinomas. Jpn J Cancer Res 87:1056–1062

Jarnagin WR, Weber S, Tickoo SK, Koea JB, Objekwe S, Fong Y, DelMatteo RP, Blumgart LH, Klimstra D (2002) Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors. Cancer 94:2040–2046

Jeong BJ, Hyun DH, Lee KW, Ryu ST, Lee JW, Lee JI, Jeong S, Lee DH, Kim PS, Kim HH, Kim YS, Kim JM (2004) A case of sarcomatoid combined hepatocellular-cholangiocarcinoma (in Korean). Korean J Gastroenterol 43:56–60

Kakar S, Muir T, Murphy LM, Lloyd RV, Burgart LJ (2003) Immunoreactivity of Hep Par 1 in hepatic and extrahepatic tumors and its correlation with albumin in situ hybridization in hepatocellular carcinoma. Am J Clin Pathol 119:361–366

Kanamoto M, Yoshizumi T, Ikegami T, Imura S, Morine Y, Ikemoto T, Sano N, Shimada M (2008) Cholangiolocellular carcinoma containing hepatocellular carcinoma and cholangiocellular carcinoma, extremely rare tumor of the liver: a case report. J Med Invest 55:161–165

Kassahun WT, Hauss J (2008) Management of combined hepatocellular and cholangiocarcinoma. Int J Clin Pract 62:1271–1278

Kilpatrick SE, Geisinger KR, Loggie BW, Hopkins MB (1993) Cytomorphology of combined hepatocellular-

cholangiocarcinoma in fine needle aspirates of the liver. A report of two cases. Acta Cytol 37:943–947
Kim H, Park C, Han KH, Choi J, Kim YB, Kim JK, Park YN (2004a) Primary liver carcinoma of intermediate (hepatocyte-cholangiocyte) phenotype. J Hepatol 40:298–304
Kim JH, Lee YG, Lee J, Jung CK, Kim HT, Kang H, Kho KH, Hong SP, Hwang SG et al (2004b) A case of combined hepatocellular-cholangiocarcinoma with sarcomatous transformation and second primary colon cancer (in Korean). Kor J Hepatol 10:142–147
Kim KH, Lee SG, Park EH, Hwang S, Ahn CS, Moon DB, Ha TY, Song GW, Jung DH et al (2009) Surgical treatments and prognoses of patients with combined hepatocellular carcinoma and cholangiocarcinoma. Ann Surg Oncol 16:623–629
Kim GM, Jeung HC, Kim D, Kim JH, Yoon SH, Jung ES, Shin SJ (2010a) A case of combined hepatocellular-cholangiocarcinoma with favorable response to systemic chemotherapy. Cancer Res Treat 42:235–238
Kim JH, Yoon HK, Ko GY, Gwon DI, Jang CS, Song HY, Shin JH, Sung KB (2010b) Nonresectable combined hepatocellular carcinoma and cholangiocarcinoma: analysis of the response and prognostic factors after transcatheter arterial chemoembolization. Radiology 255:270–277
Kim GJ, Kim H, Park YN (2013) Increased expression of Yes-associated protein 1 in hepatocellular carcinoma with stemness and combined hepatocellular-cholangiocarcinoma. PLoS One 8:e75449
Kim SH, Park YN, Lim JH, Choi GH, Choi JS, Kim KS (2014) Characteristics of combined hepatocellular-cholangiocarcinoma and comparison with intrahepatic cholangiocarcinoma. Eur J Surg Oncol 40:976–981
Kimoto T, Ugaki M (1982) Hepatocellular carcinoma combined with hepatic mesenchymal cell tumor and sarcoma. Acta Pathol Jpn 32:1131–1141
Koh KC, Lee H, Choi MS, Lee JH, Paik SW, Yoo BC, Rhee JC, Cho JW, Park CK, Kim HJ (2005) Clinicopathologic features and prognosis of combined hepatocellular cholangiocarcinoma. Am J Surg 189:120–125
Kojiro M, Kawano Y, Kawasaki H, Nakashima T, Ikezaki H (1982) Thorotrast-induced hepatic angiosarcoma, and combined hepatocellular and cholangiocarcinoma in a single patient. Cancer 49:2161–2164
Kondo Y, Nakajima T (1987) Pseudoglandular hepatocellular carcinoma. A morphogenetic study. Cancer 60:1032–1037
Koster H, Kasman LP (1932) Primary duplex liver carcinoma. Am J Surg 17:237–241
Kwon Y, Lee SK, Kim JS, Ro JY, Yu E (2002) Synchronous hepatocellular carcinoma and cholangiocarcinoma arising in two different dysplastic nodules. Mod Pathol 15:1096–1101
L'Esperance E (1915) Atypical hemorrhagic malignant hepatoma. J Med Res 32:225–249
Larson CP (1937) Multiple liver-cell carcinoma (primary type). Report of a case. Northwest Med 36:388–391
Lee CC, Wu CY, Chen JT, Chen GH (2002) Comparing combined hepatocellular-cholangiocarcinoma and cholangiocarcinoma: a clinicopathologic study. Hepatogastroenterology 49:1487–1490
Lee WS, Lee KW, Heo JS, Kim SJ, Choi SH, Kim YI, Joh JW (2006) Comparison of combined hepatocellular and cholangiocarcinoma with hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Surg Today 36:892–897
Lee JH, Chung GE, Yu SJ, Hwang SY, Kim JS, Kim HY, Yoon JH, Lee HS, Yi NJ et al (2011) Long-term prognosis of combined hepatocellular and cholangiocarcinoma after curative resection comparison with hepatocellular carcinoma and cholangiocarcinoma. J Clin Gastroenterol 45:69–75
Lee CH, Hsieh SY, Chang CJ, Lin YJ (2013) Comparison of clinical characteristics of combined hepatocellular-cholangiocarcinoma and other primary liver cancers. J Gastroenterol Hepatol 28:122–127
Leong AS, Sormunen RT, Tasui WM, Liew CT (1998) Hep Par 1 and selected antibodies in the immunohistological distinction of hepatocellular carcinoma from cholangiocarcinoma, combined tumours and metastatic carcinoma. Histopathology 33:318–324
Li X, Jiang W, Feng T, Wang Z (2012) Concurrent occurrence of primary hepatocellular and cholangiocellular carcinoma in the different part of the liver: a case report. Int J Clin Exp Med 5:355–357
Libbrecht L (2006) Hepatic progenitor cells in human liver tumor development. World J Gastroenterol 12:6261–6265
Lin G, Toh CH, Wu RC, Ko SF, Ng SH, Chou WC, Tseng JH (2008) Combined hepatocellular and cholangiocarcinoma: prognostic factors investigated by computed tomography/magnetic resonance imaging. Int J Clin Pract 62:1199–1205
Maarouf A, Adham M, Scoazec JY, Partensky C (2008) Mixed hepato/cholangiocarcinoma with paraneoplastic hypercalcemia. J Hepatobiliary Pancreat Surg 15:224–227
Maeda T, Adachi E, Kajiyama K, Sugimachi K, Tsuneyoshi M (1995) Combined hepatocellular and cholangiocarcinoma: proposed criteria according to cytokeratin expression and analysis of clinicopathologic features. Hum Pathol 26:956–964
Maeda A, Ebata T, Matsunaga K, Kanemoto H, Bando E, Yamaguchi S, Furukawa H, Uesaka K (2005) Primary liver cancer with bidirectional differentiation into hepatocytes and biliary epithelium. J Hepatobiliary Pancreat Surg 12:484–487
Matsumoto M, Wakiyama S, Shiba H, Gocho T, Misawa T, Ishida Y, Itsubo M, Suzuki M, Yanaga K (2014) Combined hepatocellular-cholangiocarcinoma producing parathyroid hormone-related protein: report of a case. Surg Today 44:1577–1583
Moon VH (1929) Primary carcinoma of liver with metastasis to bone. Arch Path 8:938–943
Morita D, Kagata Y, Ogata S, Tsuda H, Hatsuse K, Mochizuki H, Matsubara O (2006) Combined

hepatocellular carcinoma and cholangiocarcinoma with components of mucinous carcinoma arising in a cirrhotic liver. Pathol Int 56:222–226

Murakami T, Yano H, Maruiwa M, Sugihara S, Kojiro M (1987) Establishment and characterization of a human combined hepatocholangiocarcinoma cell line and its heterologous transplantation in nude mice. Hepatology 7:551–556

Murata M, Miyoshi Y, Iwao K, Wada H, Shibata K, Tateishi H, Shimano T, Ohasawa M et al (2001) Combined hepatocellular/cholangiocellular carcinoma with sarcomatoid features: genetic analysis for histogenesis. Hepatol Res 21:220–227

Nakajima T, Kubosawa H, Kondo Y, Konno A, Iwama S (1988) Combined hepatocellular-cholangiocarcinoma with variable sarcomatous transformation. Am J Clin Pathol 90:309–312

Nakamura S, Suzuki S, Sakaguchi T, Serizawa A, Konno H, Baba S, Baba S, Muro H (1996) Surgical treatment of patients with mixed hepatocellular carcinoma and cholangiocarcinoma. Cancer 78:1671–1676

Nakasho K, Yamanaka N, Okamoto E (1996) A case of combined or mixed hepatocellular and cholangiocarcinoma with sarcomatous components – immunohistochemical characteristics and histogenesis (in Japanese). Nihon Shokakibyo Gakkai Zasshi 93:206–211

Neumann MA (1944) Primary carcinoma of the liver with metastases to bone. Am J Pathol 20:895–909

Ng IO, Shek TW, Nicholls J, Ma LT (1998) Combined hepatocellular-cholangiocarcinoma: a clinicopathological study. J Gastroenterol Hepatol 13:34–40

Nishie A, Yoshimitsu K, Asayama Y, Irie H, Aibe H, Tajima T, Shinozaki K, Nakayama T et al (2005) Detection of combined hepatocellular and cholangiocarcinomas on enhanced CT: comparison with histologic findings. AJR Am J Roentgenol 184:1157–1162

O'Connor K, Walsh JC, Schaeffer DF (2014) Combined hepatocellular-cholangiocarcinoma (cHCC-CC): a distinct entity. Ann Hepatol 13:317–322

Okada Y, Jinno K, Moriwaki S, Morichika S, Torigoe S, Arima T, Nagashima H, Koprowski H (1987) Expression of ABH and Lewis blood group antigens in combined hepatocellular –cholangiocarcinoma. Possible evidence for the hepatocellular origin of combined hepatocellular-cholangiocarcinoma. Cancer 60:345–352

Omagari K, Makiyama K, Ikuno N (1995) Combined hepatocellular and cholangiocarcinoma (in Japanese). Ryoikibetsu Shokogun Shirizu 7:473–475

Panjala C, Senecal DL, Bridges MD, Kim GP, Nakleh RE, Nguyen JH, Harnois DM (2010) The diagnostic conundrum and liver transplantation outcome for combined hepatocellular-cholangiocarcinoma. Am J Transplant 10:1263–1267

Papotti M, Sambataro D, Marchesa P, Negro F (1997) A combined hepatocellular/cholangiocellular carcinoma with sarcomatoid features. Liver 17:47–52

Park H, Choi KH, Choi SB, Choi JW, Kim do Y, Ahn SH, Kim KS, Choi JS, Han KH, Chon CY, Park JY (2011a) Clinicopathological characteristics in combined hepatocellular-cholangiocarcinoma: a single center study in Korea. Yonsei Med J 52:753–760

Park HS, Bae JS, Jang KY, Lee JH, Yu HC, Jung JH, Cho BH, Chung MJ, Moon WS (2011b) Clinicopathologic study on combined hepatocellular carcinoma and cholangiocarcinoma: with emphasis on the intermediate cell morphology. J Korean Med Sci 26:1023–1030

Pérez-Roldan F, Carretero L, Aguirre A, Banares R, Casado M, Cos E, Clemente G (1995) Hepatocholangiocarcinoma with diffuse metastases and hypercalcemia (in Spanish). Rev Esp Enferm Dig 87:743–747

Phongkikarun S, Srisuwan T, Sornmayura P, Jatchavala J (2007) Combined hepatocellular and cholangiocarcinoma: CT findings with emphasis on multiphasic helical CT. J Med Assoc Thai 90:113–120

Portolani N, Baiocchi GL, Coniglio A, Piardi T, Grazioli L, Benetti A, Ferrari Bravo A, Giulini SM (2008) Intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma: a Western experience. Ann Surg Oncol 15:1880–1890

Prescott WH (1895) Seven cases of primary carcinoma of the liver. Med Surg Rep Boston City Hosp 6:245–267

Pua U, Low SC, Tan YM, Lim KH (2009) Combined hepatocellular and cholangiocarcinoma with sarcomatoid transformation: radiologic-pathologic correlation of a case. Hepatol Int 3:587–592

Rasario GM (1934) Adeno-carcinoma epatocellulare primitive del fegato. Riv di Clin Med 35:767–786

Rasario GM (1937) Ulteriore contributo allo studio clinico ed anatomo-patologico della cancro-cirrosi del fegato. Clin Med Ital 68:807–817

Robrechts C, De Vos R, Van den Heuvel M, Van Cutsem F, Van Damme B, Desmet V, Roskams T (1998) Primary liver tumour of intermediate (hepatocyte-bile duct cell) phenotype: a progenitor cell tumour? Liver 18:288–293

Rosa M, Mohammadi A (2014) Cytologic features of fibrolamellar carcinoma with mucin production: a rare variant of combined hepatocellular-cholangiocarcinoma. Diagn Cytopathol 42:431–435

Saboo SS, Krajewski KM, Jagannathan JP, O'Regan KN, Odze R, Ramaiya N, Wolpin BM (2011) Rapid progression of combined hepatocellular carcinoma and cholangiocarcinoma. Cancer Imaging 11:37–41

Saito M, Hige S, Takeda H, Tomaru U, Shibata M, Asaka M (2001) Combined hepatocellular carcinoma and cholangiocarcinoma growing into the common bile duct. J Gastroenterol 36:842–847

Sanada Y, Shiozaki S, Aoki H, Takakura N, Yoshida K, Yamaguchi Y (2005) A clinical study of 11 cases of combined hepatocellular-cholangiocarcinoma. Assessment of enhancement patterns on dynamics computed tomography before resection. Hepatol Res 32:185–195

Sapisochin G, Fidelman N, Roberts JP, Yao FY (2011) Mixed hepatocellular cholangiocarcinoma and

intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. Liver Transpl 17:934–942

Sasaki M, Nakanuma Y, Ho SB, Kim YS (1998) Cholangiocarcinomas arising in cirrhosis and combined hepatocellular-cholangiocellular carcinomas share apomucin profiles. Am J Clin Pathol 109:302–308

Sasaki A, Kawano K, Aramaki M, Ohno T, Tahara K, Takeuchi Y, Yoshida T, Kitano S (2001) Clinicopathologic study of mixed hepatocellular and cholangiocellular carcinoma: modes of spreading and choice of surgical treatment by reference to macroscopic type. J Surg Oncol 76:37–46

Sasaki M, Sato H, Kakuda Y, Sato Y, Choi JH, Nakanuma Y (2014) Clinicopathological significance of 'subtypes with stem-cell feature' in combined hepatocellular-cholangiocarcinoma. Liver Int. doi:10.1111/liv.12563

Shetty AS, Fowler KJ, Brunt EM, Agarwal S, Narra VR, Menias CO (2014) Combined hepatocellular-cholangiocarcinoma: what the radiologist needs to know about biphenotypic liver carcinoma. Abdom Imaging 39:310–322

Shin CI, Lee JM, Kim SH, Choi JY, Lee JY, Han JK, Jo SY, Choi BI (2007) Recurrence patterns of combined hepatocellular-cholangiocarcinoma on enhanced computed tomography. J Comput Assist Tomogr 31:109–115

Shiomi S, Sasaki N, Kawashima D, Jomura H, Fukuda T, Kuroki T, Koyama K, Kawabe J et al (1999) Combined hepatocellular carcinoma and cholangiocarcinoma with high F-18 fluorodeoxyglucose positron emission tomographic uptake. Clin Nucl Med 24:370–371

Shiraishi M, Takushi Y, Simoji H, Oshiro T, Shinzato S, Tanigawa N, Kusano T, Muto Y (1998) Combined hepatocellular and cholangiocellular carcinoma in a non-cirrhotic liver. J Gastroenterol 33:593–596

Shirakawa H, Kuronuma T, Nishimura Y, Hasebe T, Nakano M, Gotohda N, Takahashi S et al (2009) Glypican-3 is a useful diagnostic marker for a component of hepatocellular carcinoma in human liver cancer. Int J Oncol 34:649–656

Singh S, Chakraborty S, Bonthus N, Radio S, Hussain SM, Sasson A (2013) Combined hepatocellular cholangiocarcinoma: a case report and review of literature. Dig Dis Sci 58:2114–2123

Sonobe H, Hayashi K, Takahashi K, Ohtsuki Y, Matsumoto K, Ohnishi S, Jinno K (1987) Combined hepatocellular and cholangiocarcinoma arising in a cirrhotic liver. Report of an autopsy case. Acta Pathol Jpn 37:1945–1952

Sugihara S, Nakahara T, Maruiwa M, Kojiro M, Iwai I, Tanaka M, Hirai K, Majima Y et al (1987) An autopsy case with a combination of hepatocellular carcinoma and cholangiocellular carcinoma (in Japanese). Gan No Rinsho 33:205–210

Taguchi J, Nakashima O, Tanaka M, Hisaka T, Takazawa T, Kojiro M (1996) A clinicopathological study on combined hepatocellular and cholangiocarcinoma. J Gastroenterol Hepatol 11:758–764

Tanaka T, Imamura A, Hayashi S, Tsuruta K, Igari T, Koike M, Tanaka S (1998) Minute mixed hepatoma with two components: hepatocellular and cholangiocarcinoma which developed on liver cirrhosis with HCV. Hepatogastroenterology 45:220–223

Tanaka S, Hirohashi K, Uenishi T, Yamamoto T, Hamba H, Kubo S, Tanaka H, Shuto T et al (2004) A mixed hepatocellular carcinoma and cholangiocarcinoma: dual expression of biliary-type cytokeratin and hepatocyte specific marker. Hepatogastroenterology 51:839–841

Tanaka K, Honna T, Kitano Y, Kuroda T, Tanaka K, Morikawa N, Matsuda H, Kawashima N et al (2005a) Combined fibrolamellar carcinoma and cholangiocarcinoma exhibiting biphenotypic antigen expression: a case report. J Clin Pathol 58:884–887

Tanaka S, Yamamoto T, Tanaka H, Kodai S, Ogawa M, Ichikawa T, Hai S, Sakabe K et al (2005b) Potentiality of combined hepatocellular and intrahepatic cholangiocellular carcinoma originating from a hepatic precursor cell: immunohistochemical evidence. Hepatol Res 32:52–57

Tang D, Nagano H, Nakamura M, Wada H, Marubashi S, Miyamoto A, Takeda Y, Umeshita K et al (2006) Clinical and pathological features of Allen's type C classification of resected combined hepatocellular and cholangiocarcinoma: a comparative study with hepatocellular carcinoma and cholangiocellular carcinoma. Gastrointest Surg 10:987–998

Terada T (2013) Combined hepatocellular-cholangiocarcinoma with stem cell features, ductal plate malformation subtype: a case report and proposal of a new subtype. Int J Clin Exp Pathol 6:737–748

Theise ND, Yao JL, Harada K, Hytiroglou P, Portmann B, Thung SN, Tsui W, Ohta H, Nakanuma Y (2003) Hepatic 'stem cell' malignancies in adults: four cases. Histopathology 43:263–271

Theise ND, Nakashima O, Park YN, Nakanuma Y (2010) Combined hepatocellular-cholangiocarcinoma. WHO classification of tumours of the digestive system, 4th edn. IARC, Lyon, pp 225–227

Tickoo SK, Zee SY, Obiekwe S, Xiao H, Koea J, Robiou C, Blumgart LH, Jarnagin W et al (2002) Combined hepatocellular-cholangiocarcinoma. A histopathologic, immunohistochemical, and in situ hybridization study. Am J Surg Pathol 26:989–997

Toh CH, Cheung YC, Ng SH, Lin CY, Chan SC, Ng KK (2004) Combined hepatocellular-cholangiocarcinoma: a case report. Int J Clin Pract 58:1170–1173

Tomimatsu M, Ishiguro N, Taniai M, Okuda H, Saito A, Obata H, Yamamoto M, Takasaki K et al (1993) Hepatitis C virus antibody in patients with primary liver cancer (hepatocellular carcinoma, cholangiocarcinoma, and combined hepatocellular-cholangiocarcinoma) in Japan. Cancer 72:683–688

Tramontano V, Fittipaldi C (1930) Sui cosidetti tumori a cellule giganti. Tumori 16:501–518

Tsuneyama K, Kaizaki Y, Doden K, Kidani E, Harada K, Sasaki M, Nakanuma Y (2003) Combined

hepatocellular and cholangiocarcinoma with marked squamous cell carcinoma components arising in non-cirrhotic liver. Pathol Int 53:90–97

Uenishi T, Hirohashi K, Shuto T, Yamamoto T, Kubo S, Tanaka H, Ikebe T, Kinoshita H (2000) Surgery for mixed hepatocellular and cholangiocellular carcinoma. Hepatogastroenterology 47:832–834

Uenishi T, Hirohashi K, Shuto T, Tsukamoto T, Yamamoto T, Ogawa M, Kubo S, Tanaka H et al (2002) Primary liver cancer with dual expression of hepatocyte and bile duct epithelial markers. Hepatogastroenterology 49:1092–1094

Utsunomiya T, Saitsu H, Saku M, Takeshita M, Yoshida K, Kajiyama K, Sugimachi K (2000) A resected case of combined hepatocellular carcinoma and cholangiocarcinoma associated with cystic formation. Hepatogastroenterology 47:851–854

Van Eyken P, Sciot R, Brrock P, Casteels-Van Daele M, Ramaekers FCS, Desmet VJ (1990) Abundant expression of cytokeratin 7 in fibrolamellar carcinoma of the liver. Histopathology 17:101–107

Varnholt H, Asayama Y, Aishima S, Taguchi K, Sugimachi K, Tsuneyoshi M (2002) C-met and hepatocyte growth factor expression in combined hepatocellular and cholangiocarcinoma. Oncol Rep 9:35–41

Wachtel MS, Zhang Y, Xu T, Chiriva-Internati M, Frezza EE (2008) Combined hepatocellular cholangiocarcinomas; analysis of a large database. Clin Med Pathol 1:43–47

Wada K, Kondo F, Kubosawa H, Kondo Y (1986) Combined hepatocellular and mucinous carcinoma. Acta Pathol Jpn 36:285–291

Wakasa T, Wakasa K, Shutou T, Hai S, Kubo S, Hirohashi K, Umshita K, Monden M (2007) A histopathological study on combined hepatocellular and cholangiocarcinoma: cholangiocarcinoma component is originated from hepatocellular carcinoma. Hepatogastroenterology 54:508–513

Wang J, Wang F, Kessinger A (2010) Outcome of combined hepatocellular and cholangiocarcinoma of the liver. J Oncol 2010 pii:917356. doi:10.1155/2010/917356

Ward SC, Huang J, Tickoo SK, Thung SN, Ladanyi M, Klimstra DS (2010) Fibrolamellar carcinoma of the liver exhibits immunohistochemical evidence of both hepatocyte and bile duct differentiation. Mod Pathol 23:1180–1190

Warvi WN (1944) Primary neoplasms of the liver. Arch Pathol 37:367–382

Wee A, Nilsson B (1999) Combined hepatocellular-cholangiocarcinoma. Diagnostic challenge in hepatic fine needle aspiration biopsy. Acta Cytol 43:131–138

Wells HG (1903) Primary carcinoma of the liver. Am J Med Sci 126:403–417

Willekens I, Hoorens A, Geers C, Op de beeck B, Vandenbroucke F, de mey J (2009) Combined hepatocellular and cholangiocellular carcinoma presenting with radiological characteristics of focal nodular hyperplasia. World J Gastroenterol 15:3940–3943

Wu PC, Fang JW, Lau VK, Lai CL, Lo CK, Lau JY (1996) Classification of hepatocellular carcinoma according to hepatocellular and biliary differentiation markers. Clinical and biological implications. Am J Pathol 149:1167–1175

Yano H, Iemura A, Haramaki M, Momosaki S, Ogasawara S, Higaki K, Kojiro M (1996) A human combined hepatocellular and cholangiocarcinoma cell line (KMCH-2) that shows the features of hepatocellular carcinoma or cholangiocarcinoma under different growth conditions. J Hepatol 24:413–422

Yano Y, Yamamoto J, Kosuge T, Sakamoto Y, Yamasaki S, Shimada K, Ojima H et al (2003) Combined hepatocellular and cholangiocarcinoma: a clinicopathologic study of 26 resected cases. Jpn J Clin Oncol 33:283–287

Yarze JC, Herlihy KJ, Scalia SV (2005) Cholangiohepatoma presenting with recurrent cholangitis. Dig Dis Sci 50:552–553

Yeh MM (2010) Pathology of combined hepatocellular-cholangiocarcinoma. J Gastroenterol Hepatol 25:1485–1492

Yoshida T, Okazaki N, Yoshino M, Moriyama N, Hirohashi S (1985) A case of diffuse type of combined hepatocellular and cholangiocellular carcinoma initially presenting as a localized small nodule. Jpn J Cancer Res 76:1186–1192

Zhan Q, Shen BY, Deng XX, Zhu ZC, Chen H, Peng CH, Li HW (2012) Clinical and pathological analysis of 27 patients with combined hepatocellular-cholangiocarcinoma in an Asian center. J Hepatobiliary Pancreat Sci 19:361–369

Zhang F, Chen XP, Zhang W, Dong HH, Xiang S, Zhang WG, Zhang BX (2008) Combined hepatocellular cholangiocarcinoma originating from hepatic progenitor cells: immunohistochemical and double-fluorescence immunostaining evidence. Histopathology 52:224–232

Zhou YM, Yang JM, Wang B, Xu F, Tong Y, Li DQ (2007) Combined hepatocellular carcinoma and cholangiocarcinoma: a case report and review of the literature. Hepatobiliary Pancreat Dis Int 6:656–659

Zhou YM, Zhang XF, Wu LP, Sui CJ, Yang JM (2014) Risk factors for combined hepatocellular-cholangiocarcinoma: a hospital-based case-control study. World J Gastroenterol 20:12615–12620

Zuo HQ, Yan LN, Zeng Y, Yang JY, Luo HZ, Liu JW, Zhou LX (2007) Clinicopathological characteristics of 15 patients with combined hepatocellular carcinoma and cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 6:161–165

Part II

Tumors of the Cholangiocyte Lineage

Hilar/Perihilar Cholangiocarcinoma (Klatskin Tumor)

27

ICD-O code biliary-type adenocarcinoma 8140/3

Contents

Abstract

Carcinoma of the extrahepatic bile ducts is defined as an adenocarcinoma arising in proximal, middle third, and distal (lower third) parts of extrahepatic ducts. As anatomically a division of the duct system into thirds is artificial, novel classifications distinguish perihilar/hilar cholangiocarcinomas from those of the mid-region and the distal part of the common bile duct. For the definition of perihilar cancers, the separation point between intrahepatic and extrahepatic tumors is defined by the level of second-order bile ducts. Bile ducts located to the hepatic plate of the hilum correspond to extrahepatic bile ducts. The growth patterns and associated clinical sequelae vary as a function of anatomical location. Perihilar/hilar tumor forms concentrically stenosing lesions (Klatskin tumors). Tumors in the mid-region more commonly present as tubular lesion with thickening of the duct wall, whereas distal tumor more often shows an exophytic growth pattern. Histologically, the neoplasms are adenocarcinomas of the cholangiocyte lineage, usually associated with abundant stroma (desmoplasia). The cancers have a strong tendency for perineural and intraneural invasion, extension along bile ducts, and lymphatic spread.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_27

Introduction

In the 2010 WHO classification, carcinoma of the extrahepatic bile ducts is defined as malignant epithelial neoplasm usually with biliary, intestinal, foveolar, or squamous differentiation, arising in the extrahepatic bile ducts. Perihilar cholangiocarcinoma (PHC, hilar cholangiocarcinoma, Klatskin tumor, Altemeier-Klatskin tumor) is one of the three major forms of cancer of the extrahepatic bile ducts. Extrahepatic cholangiocarcinomas had previously been identified as a distinct entity. The concept of PHC had been refined and is now defined as a complex disease with several phenotypes. The meaning of the terms, hilar and perihilar, differs in several respects between surgeons and pathologists (see below; review: Castellano-Megias et al. 2013).

Selected references: Scudder and Richardson 1908; Poynton 1917; Renshaw 1922; Brocq and Maduro 1924; Wylegschanin 1927; Pliveric 1928; Shapiro and Lifvendahl 1931; David 1932; McLaughlin 1933; Lee and Totten 1934; Kirshbaum and Kozell 1941; Willis 1942; Hawk and Bishop 1946; Leiter 1947; Neibling et al. 1949; Sanford and Lowry 1949; Fleming 1953; Crocker 1955; Kuwayti et al. 1957; Sako et al. 1957; Alvarez 1958; Lippman et al. 1959; Thorbjarnarson 1959; Brown et al. 1961; Meyerowitz and Aird 1962; Okuyama et al. 1964; Tiesenga et al. 1964; Quattlebaum and Quattelbaum 1965; Whelton et al. 1969; Klippel and Shaw 1972; Altemeier and Culbertson 1973; Longmire et al. 1973; Ross et al. 1973; Ingis and Farmer 1975; Launois et al. 1979; Todoroki et al. 1980; Tompkins et al. 1981; Voyles et al. 1983; Blumgart et al. 1984; Beazley et al. 1984; Toyoda and Yoshida 1985; Burcharth 1988; Henson et al. 1992; Stain et al. 1992; Gazzaniga et al. 1993; Chow et al. 1994; Lillemoe 1994; Nakeeb et al. 1996; Madariaga et al. 1998; Kosuge et al. 1999; Launois et al. 1999, 2002; Chamberlain and Blumgart 2000; Cormier and Vauthey 2000; Jarnagin 2000; Jarnagin et al. 2001, 2003; Byrnes and Afdhal 2002; Knoefel et al. 2003; Clary et al. 2004; Costamagna et al. 2004; Tannapfel and Wittekind 2004; Zervos et al. 2005; Malhi and Gores 2006; Patel 2006; Slattery and Sahani 2006; Otto 2007; Tsalis et al. 2007; Yubin et al. 2008; Kuang and Wang 2010; Shin et al. 2010; Chatelain et al. 2012; Ito et al. 2012; Gandou et al. 2013; reviews: Chamberlain and Blumgart 2000; Nagino 2012; Somer et al. 2012; Castellano-Megias et al. 2013.

Schueppel is credited with being the first to describe carcinoma of the hepatic duct in 1878 (cited in David 1932), followed by observations in 1889 (Musser 1889) and 1908 (Scudder and Richardson 1908). A case of chronic jaundice and massive hepatomegaly due to cholangiocarcinoma commencing at the junction of the hepatic ducts was reported in 1905 (Parkes Weber and Michels 1905). A clinical communication referring to carcinoma at the junction (confluens ductuum) appeared in 1928 (Pliveric 1928). The distinct desmoplastic feature of the neoplasm has been described in 1957 under the term sclerosing carcinoma of bile ducts (Altemeier et al. 1957) and later by Klatskin (1965). However, descriptions of PHC are already found in the old literature. For example, professor Bernhard Naunyn from Königsberg (now Kaliningrad), who founded the Archiv für experimentelle Pathologie und Pharmakologie together with J. von Mikulicz-Radecki (later Naunyn-Schmiedeberg's Archives), reported in 1877 the autopsy findings of a female who had stenosing carcinoma at the confluence, extending into the left hepatic duct, what would now be called PHC type IIIb according to the modified Bismuth-Corlette classification (Howald 1890). A typically sclerosing cancer ("scirrhous neoplasm") situated in the confluence (Bismuth-Corlette type II) was reported in 1878 by Oscar von Schüppel (1878).

Definitions and Classification

Introduction

The definition of PHC or hilar cholangiocarcinoma is still subject to discussions (DeOliveira and Clavien 2012). Cholangiocarcinomas are currently classified into three broad groups: (1) intrahepatic, (2) perihilar, and

(3) distal carcinomas. Extrahepatic cholangiocarcinomas are or were divided into proximal (upper third), middle (middle third), and distal (lower third) subtypes (Tompkins et al. 1981). However, from anatomical and biological point of views, dividing the extrahepatic ducts into "thirds" is artificial and does not really reflect the oncologic situations of carcinomas in this region. Other systems divided extrahepatic cholangiocarcinomas into hilar/perihilar carcinoma, carcinomas of the lower mid-region (a rare group), and distal carcinomas (located to the terminal part of the common bile duct). As a subset of intrahepatic cholangiocarcinomas originate from large bile ducts and are therefore located close to the liver hilus, these neoplasms are also termed perihilar carcinomas. This term is however also employed for carcinomas of the extrahepatic ducts situated close to the hilus, including the confluens area, causing terminologic confusion.

What Is "Perihilar" vs. "Hilar" Cholangiocarcinoma?

The level between "mid-region" and "distal" is still not clearly defined, whereas the separation point between intrahepatic and extrahepatic cholangiocarcinomas is defined by the level of second-order bile ducts (De Oliveira and Clavien 2012). Bile ducts located to the hepatic plate system of the hilum correspond to extrahepatic bile ducts, with variable duct lengths for every segment (Masunari et al. 2008). Conventionally, the right and left hepatic ducts, their confluence, and their first to third branches are termed hilar and perihilar bile ducts, situated both intra- and extrahepatically. Large hilar/perihilar bile ducts situated proximal to the junction of second-order bile ducts are termed large intrahepatic bile ducts, as the visceral peritoneum is attached there. Conversely, the main hilar bifurcation involving right and left hepatic ducts is extrahepatic.

In tumor classifications based on surgical approaches, perihilar cholangiocarcinoma was defined as a cancer that requires resection of the hepatic duct bifurcation irrespective whether it has an intrahepatic component (Nakeeb et al. 1996; DeOliveira et al. 2007; DeOliveira and Clavien 2012). Certain authors identify perihilar carcinoma as a single entity that comprises all cancers involving the hepatic hilar area, irrespective of whether these lesions are extrahepatic or intrahepatic (extrahepatic hilar cholangiocarcinoma vs. intrahepatic hilar cholangiocarcinoma; Ebata et al. 2009). In the sixth edition of the "General Rules for Clinical and Pathological Studies on Cancer of the Biliary Tract", released in 2013, perihilar cholangiocarcinoma was proposed as an alternative to hilar cholangiocarcinoma, with perihilar cholangiocarcinoma defined as cholangiocarcinoma involving the perihilar bile ducts, despite the presence or absence of a significant liver mass component. This definition includes that both intrahepatic (hilus near) and extrahepatic perihilar tumors are grouped in the perihilar tumor category (review: Ebata et al. 2014). In recent studies, the classification of extrahepatic cholangiocarcinoma has been simplified and reduced to perihilar and distal cancers, the reasons being that carcinoma of the mid-region is very rare and their treatment is similar to that for Bismuth-Corlette type I PHC (review: Chung et al. 2008).

By tradition, the term PHC has been employed to denote all cholangiocarcinomas involving the hepatic confluence, but it had not been evaluated whether there is a biological difference between perihilar tumors with an intrahepatic versus an extrahepatic presentation. A recent study on 250 PHCs revealed that the two groups have comparable biological behavior, indicating that the concept of perihilar cholangiocarcinoma is valid (Ebata et al. 2009).

Pathology Classifications

Some authors divided PHC into several main growth patterns (Todoroki et al. 1980; Yamashita et al. 1992; Sakamoto et al. 1998; Table 1).

Both nodular and diffusely infiltrating subtypes are usually accompanied by a marked desmoplasia, resulting in ill-defined firm (sclerosed) lesions that represent the classical Klatskin tumor. Exophytic tumors have also been termed fungating lesions of burgeoning

Table 1 Classification of perihilar cholangiocarcinoma based on macroscopic pathology (growth patterns)

Diffusely infiltrative-sclerosing PHC
Nodular infiltrating PHC
Scirrhous constricting PHC
Nodular PHC
Papillary or polypoid (exophytic) PHC
Intraluminally growing PHC

tumors (Solovei et al. 1993) and are more often associated with loss of heterozygosity at chromosome 5q (Hidaka et al. 2001). These tumors have a friable, cauliflower-like aspect. The exophytic variant of PHC has been divided into two subgroups depending on the main location of the tumor, i.e., a nodular, often hypervascular subtype located mainly inside the liver, and a less common, usually hypovascular periductal subtype having a tendency to spread along the portal vein (Yamashita et al. 1992).

Epidemiology

PHC accounts for 40–70 % of all cholangiocarcinomas, however with some differences between eastern and western countries. Of 294 patients with cholangiocarcinoma from a center in the USA, 6 % had intrahepatic, 67 % had perihilar, and 27 % had distal tumors (Nakeeb et al. 1996). Overall, carcinoma of the major extrahepatic ducts is a rather uncommon disease (Gerhards 2000; Shahib and El-Serag 2004; Khan et al. 2005; Welzel et al. 2006; Blechacz and Gores 2008; Rocha et al. 2010). It was detected in 0.0135 % of all autopsies or 0.11 % of all carcinomas in one investigation (Stewart et al. 1940) and in 0.26 % of 12,000 autopsies of another study (Neibling et al. 1949). Two other studies reported autopsy incidence of 0.4 % (Kirshbaum and Kozell 1941) and 0.073 % (McLaughlin 1933). In a study of 65 patients with extrahepatic cholangiocarcinoma, the ratio of men to women was 1:1.71; the average age of men at diagnosis was 64.5 years and that of women was 70 years. In this study, 27.7 % of the tumors were located to the confluence (Sons and Borchard 1987). In the USA, PHC has an estimated annual incidence of about 1,300. PHC is a cancer disease of older patients, more often male than female, but tumors developing in patients with inflammatory bowel disease (e.g., ulcerative colitis; Ross and Braasch 1973) and those with primary sclerosing cholangitis are younger at diagnosis of PHC (Qualman et al. 1984). The estimated frequencies of PHC and other forms of cholangiocarcinomas depend on the criteria of definition used (Welzel et al. 2006; Khan et al. 2012). For example, under the third ICD-O edition, Klatskin tumors are cross-referenced to either IHBD or EHBD, which may lead to misclassifications and skewing of cholangiocarcinoma registration. There is evidence that risk factors for PHC include choledocholithiasis, hepatolithiasis, cholecystolithiasis, and smoking (Cai et al. 2011; Suarez-Munoz et al. 2013; Lee et al. 2014). Few observations documented PHC occurring together with bile duct microhamartomas/von Meyenburg complexes (Eguchi et al. 2004). PHC was associated with fibrosing masses of the hilar region caused by *Schistosoma japonicum* (Andoh et al. 2004). Similar to other extrahepatic bile duct cancers, PHC can occur metachronously (Kwon et al. 2014).

Clinical Features

The clinical presentation of PHC is often nonspecific. The most common clinical features are abdominal discomfort or pain, anorexia, weight loss, and pruritus due to cholestasis. Most patients are diagnosed after they have presented with progressive, non-painful, and particularly non-colicky jaundice. Jaundice may be preceded by pruritus. Jaundice is, however, initially not experienced in patients with incomplete biliary obstruction, e.g., only obstruction of the right or left hepatic duct. Patients with unilateral hepatic duct obstruction will develop lobar atrophy or atrophy/hypertrophy complex before they are symptomatic. Patients with the less common papillary polypoid tumors may show intermittent jaundice caused by the floating tumor exerting a ball-valve effect or detached tumor fragments.

Bacterial cholangitis is initially a rare finding. Carcinoma markers for PHC include CA19-9 and CEA in serum, with levels that are associated with tumor stage (Juntermanns et al. 2010). PHC is associated with liver cirrhosis in part of patients, what can modify the presentation of the tumor (Abdelwahab et al. 2014).

Pathology

Macroscopy

PHC shows a characteristic gross pathology presentation (Bosma 1990; Figs. 1, 2, 3, 4, 5, 6, 7, 8, and 9). The examination of resection specimens for tissue sampling and documentation of findings has been standardized (Henson et al. 2000; Washington et al. 2010). PHC presents in the form of three major gross phenotypes, i.e., sclerosing, nodular, and papillary (polypoid). pT1 tumors often show an exophytically growing component, sometimes with a polypoid configuration and a friable, finely papillary-granular surface, resembling villous adenoma. Polypoid PHC can grow to relatively large size and may then appear as fungating lesions. The lesions have also been termed, burgeoning form of cancer (Solovei et al. 1993). The most commonly encountered sclerosing tumors are usually grayish white and present as firm annular lesions extending along the involved duct for up to 4 cm while thickening

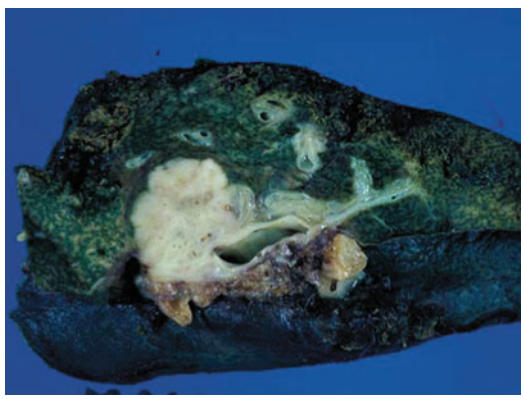

Fig. 1 Perihilar cholangiocarcinoma with extension into the liver substance

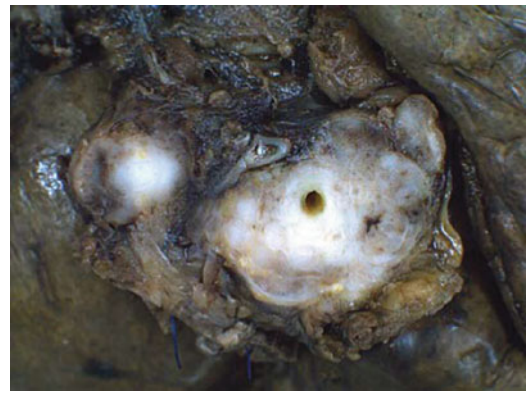

Fig. 2 Hilar cholangiocarcinoma with marked stenosis of the bile duct, which is cross-sectioned

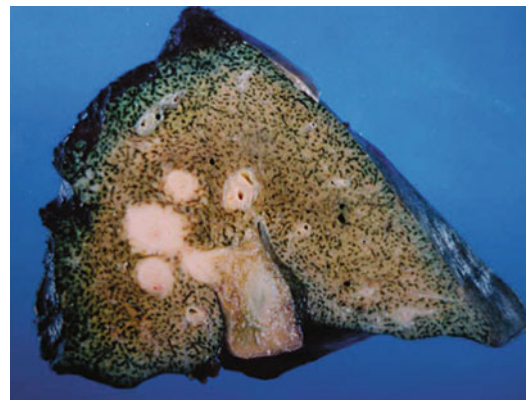

Fig. 3 Extension of perihilar cholangiocarcinoma along the intrahepatic ducts

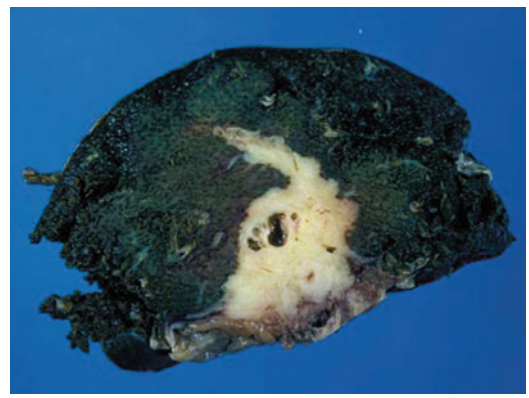

Fig. 4 Perihilar cholangiocarcinoma with prestenotic bile duct dilatation due to more distal duct obstruction. Note the marked cholestasis of the liver

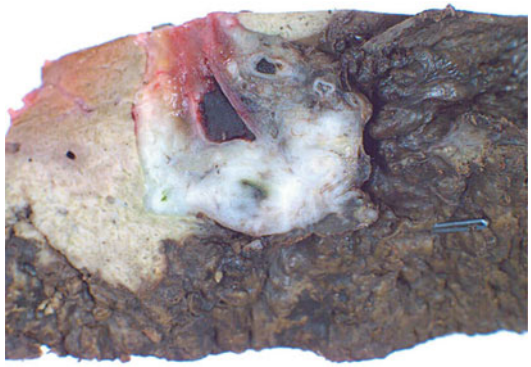

Fig. 5 Perihilar/hilar cholangiocarcinoma growing around the portal vein

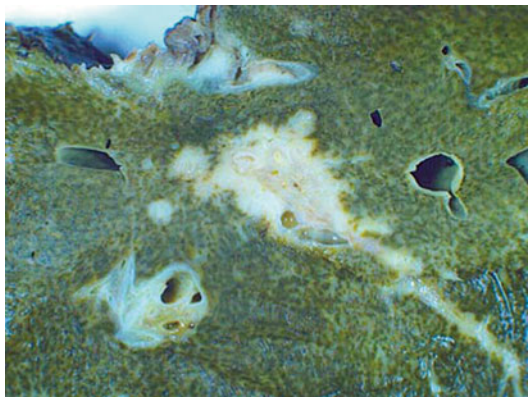

Fig. 6 Perihilar cholangiocarcinoma with intrahepatic periductal spread. Few satellite nodules are visible in the hepatic parenchyma

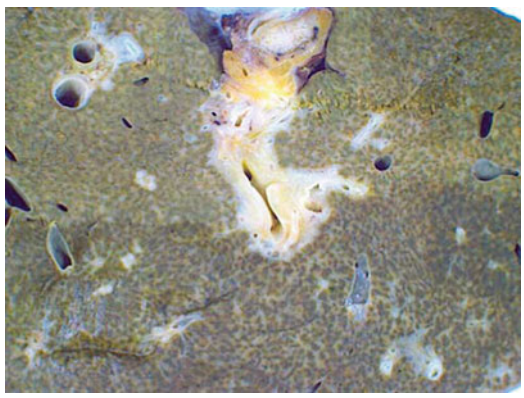

Fig. 7 Cholangiocarcinoma with intraductal growth, associated with periductal fibrosis

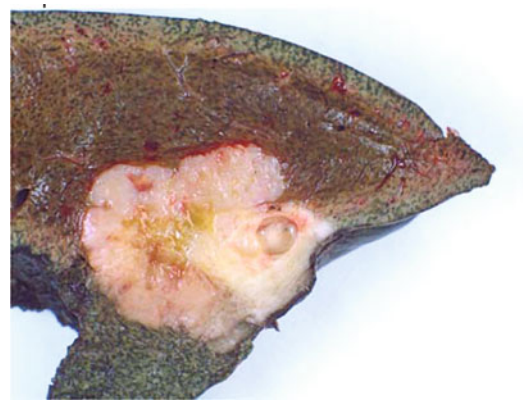

Fig. 8 Perihilar/hilar cholangiocarcinoma with polypoid intraductal growth

the duct wall up to 1 cm and showing extraductal extension in the form of a whitish fibrous tissue, sometimes with a stellate pattern (Weinbren and Mutum 1983; Beazley et al. 1984). Nodular tumors are characterized by a firm, irregular nodule often projecting into the duct. Typically, pT2 tumors are nodular lesions encasing the duct, leaving only a narrow or slit-like bile duct lumen on cross section. Sclerosing and nodular forms may occur as combined lesions (nodular-sclerosing PHC). In the course of invasion of perihilar structures, encasement of the portal vein or its branches and of bile ducts can develop (Hines and Pawlik 2010). This periductal and perivascular invasion, associated with marked desmoplasia, can result in a macroscopically impressive expansion of Glisson's triads, with formation of star-shaped whitish and firm structures. PHC may rarely undergo other secondary changes, including cystic change or calcification (Reuther and Horak 1997). Calcification of tumor is much less common than in intrahepatic peripheral cholangiocarcinoma, but may sometimes mimic a gallstone (Park et al. 2005).

Histopathology

The great majority of PHCs are adenocarcinomas with typical stroma formation (desmoplasia; Figs. 10, 11, 12, 13, 14, 15, and 16). The neoplastic cells are usually cuboidal to columnar, with a

Fig. 9 Secondary biliary cirrhosis due to stenosing hilar cholangiocarcinoma

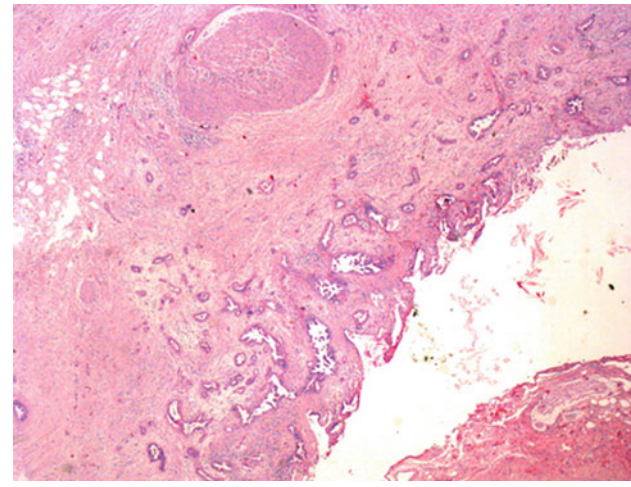

Fig. 10 Hilar cholangiocarcinoma. The adenocarcinoma has induced a marked transmural stromal reaction (desmoplasia, hematoxylin and eosin stain)

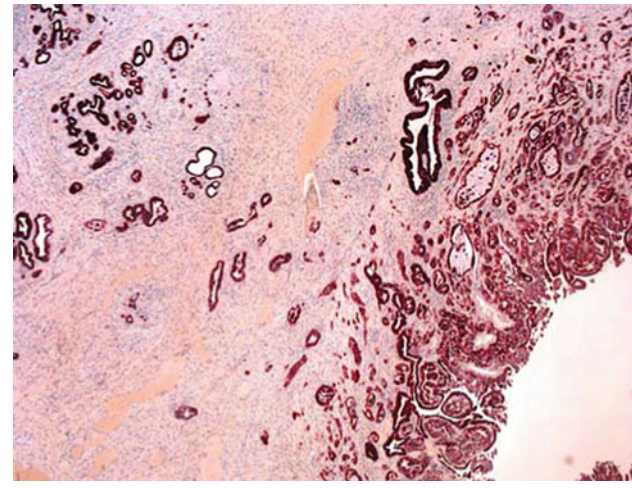

Fig. 11 Hilar cholangiocarcinoma, cytokeratin stain. Most of the tumor tissue involves the innermost layer of the ductal wall, but few cancer tubules have reached deeper parts as well. The *dark-brown* structures to the left are peribiliary glands (cytokeratin 7 immunostain)

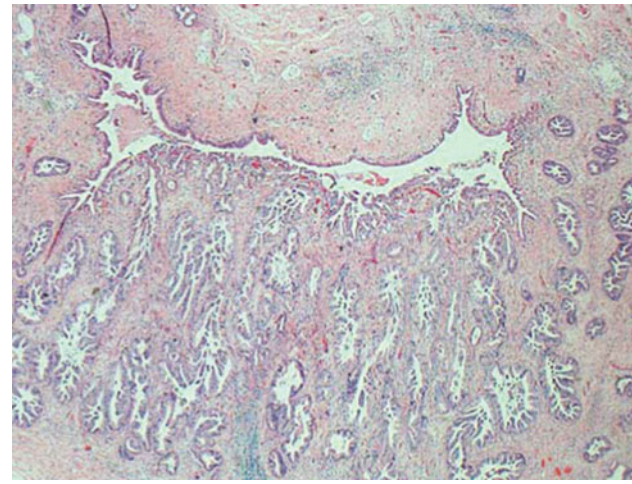

Fig. 12 Hilar cholangiocarcinoma with sectorial involvement of the bile duct. The tumor has caused severe duct stenosis, leaving a slit-like lumen (hematoxylin and eosin stain)

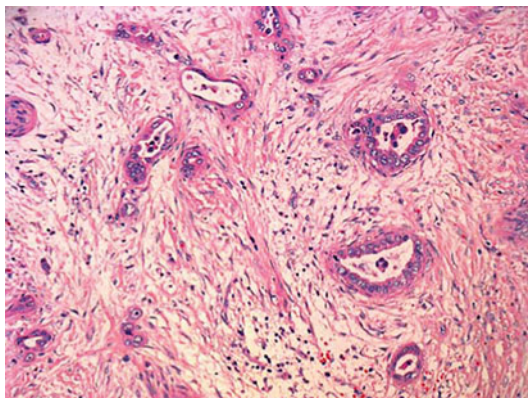

Fig. 13 Hilar cholangiocarcinoma with prominent desmoplasia. The stroma exhibits moderate cellularity and an abundant extracellular matrix (hematoxylin and eosin stain)

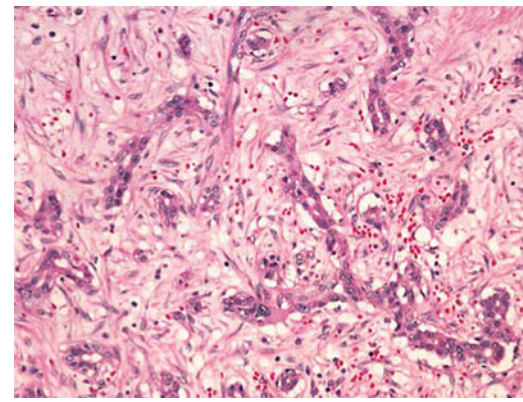

Fig. 14 The stroma of this perihilar cholangiocarcinoma shows high fibroblast cellularity. Stroma with numerous cancer-associated fibroblasts and other stromal cells is common in growing and invasive parts of carcinomas (hematoxylin and eosin stain)

pale and sometimes clear cytoplasm. These cells form complete or incomplete tubular profiles that may fuse to form cribroid structures. Due to desmoplasia, neoplastic tubules are often markedly separated from each other. The density of tubules is often higher close to the involved duct and decreases as a function of distance from the duct. This phenomenon is best recognized in immunostains, e.g., CK7, CK19, or CAM5.2. Nuclei are ovoid or less commonly elongated, often with a chromatin that is more coarse than that of normal cholangiocytes and cells of peribiliary glands. Nucleoli are seen, but they are not very prominent. Depending on the differentiation grade, mitotic figures are found, in grade 3 lesions with abnormal mitoses. The stroma is cellular in the region of the invasion front but is often hypocellular in central parts of the tumor. Stromal cells have the features of fibroblasts or myofibroblasts. The extracellular matrix of the stroma is partly amphophilic due to the deposition of glycosaminoglycans. The vascularity of the stroma is highly variable. Uncommon variants of extrahepatic cholangiocarcinomas show marked mucin production, sometimes with mucin ball formation (Kenjo et al. 2000).

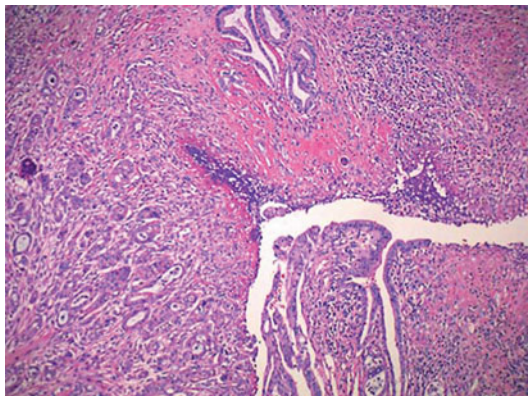

Fig. 15 Perihilar cholangiocarcinoma with severe duct ulceration reaching the level of perihilar glands (hematoxylin and eosin stain)

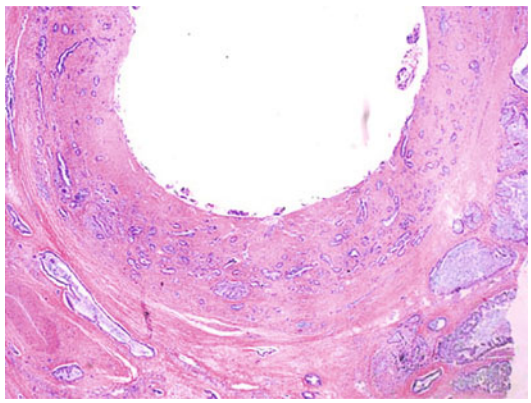

Fig. 16 Stented hilar cholangiocarcinoma, histology after removal of the stent. Note that the adenocarcinoma tubules reach the surface of the duct wall and that the stent has not induced gross tumor necrosis (hematoxylin and eosin stain)

For desmoplastic PHC, the general histopathologic features are very similar to stroma-rich variants of intrahepatic peripheral cholangiocarcinomas (Kuang and Wang 2010). There is also a striking resemblance to pancreatic duct adenocarcinomas, probably related to common embryogenetic pathways of the organ structures involved (Nakanuma and Sato 2014). Although rather slow-growing neoplasms, PHCs exhibit a highly invasive phenotype and infiltrate nerves, the perihilar tissues of the liver plate, the liver substance itself, and large liver vessels (both the portal vein and the hepatic artery). An important invasive feature is the tendency of PHC to invade and extend into second-order biliary radicles (see below).

Differentiation Patterns

The most common sclerosing, nodular, and mixed sclerosing-nodular carcinomas usually show a differentiation characterized by tubular and solid adenocarcinoma of the biliary type. The tumor cells are medium sized, cuboid, or columnar in shape, with a pale and sometimes mucinous cytoplasm, in the latter case with alcian blue-positive granules or droplets. The nuclei are usually larger than the nuclei of normal cholangiocytes, with a decontracted chromatin and small but well-recognizable nucleoli. The tubules and solid nests are embedded in a fibroblastoid-myofibroblastoid stroma of variable cellularity. Near the duct mucosal surface, the stroma is mixed with preexisting connective tissue of the duct wall, but the high cellularity and the homogeneous population of stromal cells are easily recognizable. Within the stroma, which participates in the growth and replacement of the duct wall, nonneoplastic small biliary glands can be found. In contrast to carcinoma cells, these glandular structures are composed of small cholangiocytes with small, regular, and dense nuclei. Papillary adenocarcinoma is a phenotype occurring in PHC, but it is less common than the classical nodular-sclerosing morphology (Weinbren and Mutum 1983; Yamaguchi et al. 1997; Albores-Saavedra et al. 2000; Hoang et al. 2002; Jarnagin et al. 2005). Invasive papillary carcinoma of the extrahepatic bile ducts amount to 4–5 % of carcinomas of this part of the biliary tract (Nomoto and Nakao 1996; Fatima et al. 2008). These variants are exophytically growing, soft tumors with a predominantly intraductal growth pattern, leading to expansion of the involved ductal segment. As in other exophytic carcinomas with a papillary pattern, invasive growth at the base is not a prominent feature and is, at least in some tumors, not easily detectable. The presence of a papillary component

is associated with more favorable outcome (Jarnagin et al. 2005). Less common variants of cellular differentiation, seen more often in intrahepatic cholangiocarcinomas and gallbladder carcinomas, comprise intestinal, foveolar, adenosquamous, or squamous lineages.

Histologic Variants of PHC

Apart from classical desmoplastic cholangiocarcinoma and papillary-exophytic variants, several other phenotypes occur, similar to the situation in intrahepatic cholangiocarcinoma (Table 2).

Few PHCs show the morphology of mucinous (colloid) carcinoma. In part of cases, this phenotype is the invasive part of papillary carcinomas (Albores-Saavedra et al. 2000). The mucin (colloid) accumulated in the duct wall or within stroma, sometimes with only few detectable carcinoma cells floating in the mucin lakes. These lakes can cause dissection of the duct wall and may induce a macrophage reaction with mucophages. Signet ring cell carcinoma is a very rare variant of extrahepatic bile duct carcinoma (Ogata et al. 2010). Very few PHCs show an intestinal differentiation with columnar cells that resemble those in colorectal carcinoma. An unusual variant of PHC exhibits a pancreatobiliary morphology. PHCs with a gastric foveolar differentiation are well-differentiated cancers composed of tubules with slender tall columnar cells with basally placed nuclei. Apart from foveolar-type tubules, irregular tubules with nuclear pseudostratification may occur (Albores-Saavedra et al. 1999). A very rare variant of PHC shows a pyloric gland-type morphology, with a very high differentiation level, glandular structures in a complex stellate pattern, pale to clear cells, and reactivity for MUC5AC and MUC6, but not MUC2. Notwithstanding their well-differentiated phenotype, these carcinomas are invasive and show perineural invasion (Albores-Saavedra et al. 2012). Similar to intrahepatic cholangiocarcinoma, few PHCs show a clear cell change, the neoplastic ells having a clear cytoplasm with PAS-positive granules. These cells are, in contrast to renal cell carcinoma, CK7 positive and are arranged in the form of solid nests, sheets, trabecules, or tubules (Vardaman and Albores-Saavedra 1995; Gu et al. 2010). Adenosquamous carcinoma is a well-recognized variant of hilar/perihilar carcinomas, characterized by complex mixtures of adenocarcinoma and squamous cells (CK5/6(+) p63(+)S100A2(+)) with or without keratinization. A poor outcome is paralleled with the proportion of squamous cell components (Lim et al. 2007; Hong et al. 2008). Squamous cell carcinoma of the perihilar area is very rare and less frequently found than adenosquamous carcinoma. Diagnosis requires complete lack of detectable glandular components. Perihilar squamous cell carcinoma is a highly aggressive neoplasm with poor outcome (Yamana et al. 2011). Among perihilar carcinomas with a squamous cell/keratinocyte component, mucoepidermoid carcinoma is the rarest lesion. One case was reported, with a tumor involving the common hepatic duct and extending into the proximal common bile duct (Koo et al. 1982).

Table 2 Histologic variants of perihilar cholangiocarcinoma

Mucinous (colloid) carcinoma
Signet ring cell carcinoma
Intestinal-type carcinoma
Pancreatobiliary-type carcinoma
Gastric foveolar-type carcinoma
Pyloric gland-type carcinoma
Clear cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
Mucoepidermoid carcinoma

Perineural and Intraneural Invasion

A characteristic feature of PHC is perineural and intraneural invasion (Figs. 17, 18, 19, 20, and 21). This mode of cancer spread has been described in 1905 (Ernst 1905) and has since been confirmed as a common invasion mode of this neoplasm

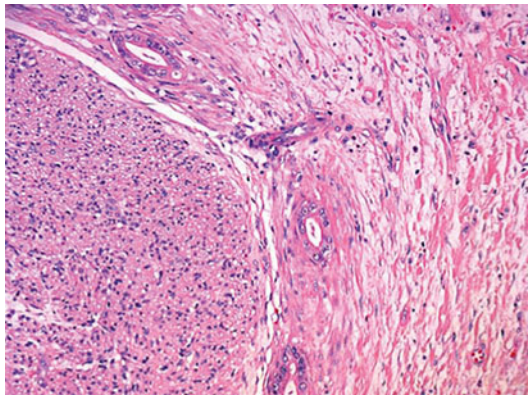

Fig. 17 Hilar cholangiocarcinoma. Invasion of the perineural sheath (hematoxylin and eosin stain)

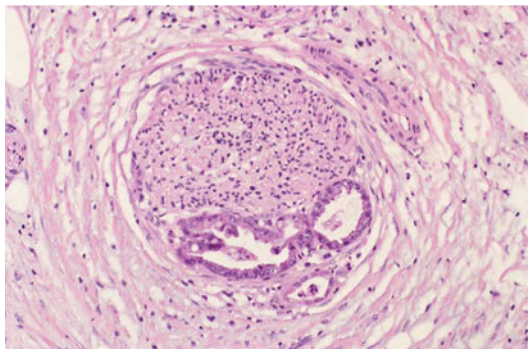

Fig. 18 Perihilar cholangiocarcinoma with perineural invasion. The carcinoma tubules are located at the entry site of the vasa nervorum (hematoxylin and eosin stain)

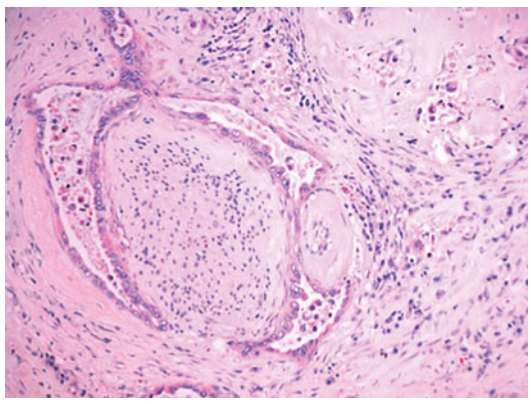

Fig. 19 Hilar cholangiocarcinoma, with circumferential perineural invasion. Involvement of the vascular "hilus" of the nerve is associated with fibrosclerosis of the vasa nervorum (hematoxylin and eosin stain)

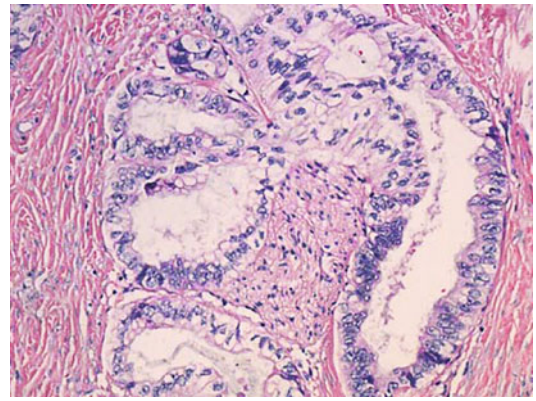

Fig. 20 Hilar/perihilar cholangiocarcinoma. Perineural invasion by a well-differentiated adenocarcinoma. The nerve is encircled by large tubules forming a cuff-like structure (hematoxylin and eosin stain)

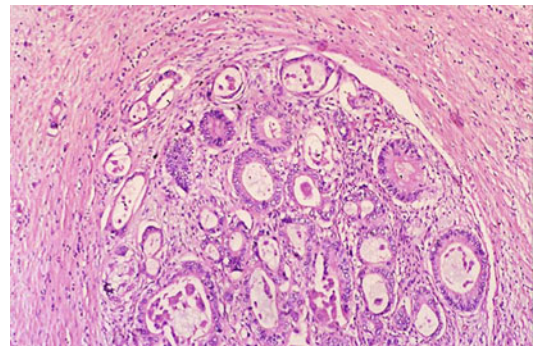

Fig. 21 Perihilar/hilar cholangiocarcinoma with intraneural and perineural invasion (hematoxylin and eosin stain)

(Davis et al. 1988). Perineural invasion is more common in PHC than in intrahepatic cholangiocarcinoma (Park et al. 2013). However, a relationship between site and incidence of perineural invasion in cholangiocarcinoma has not been found in another study (Bhuiya et al. 1992). Perineural invasion in PHC was detected in up to 75 % of cases (Yamaguchi et al. 1997). However, the incidence of perineural invasion varies among the different histologic types of cholangiocarcinoma. Perineural invasion was less frequently observed in papillary carcinomas (50 % positivity) than in well-differentiated (81.8 %), moderately differentiated (84.6 %), and poorly differentiated adenocarcinoma (100 %; Bhuiya

et al. 1992). Histologically, perineural invasion is visualized as carcinoma cells, either in rows or forming flat tubular or cribriform profiles, situated in a slit-like space between the neural fascicle and the peripheral border of the perineural sheath. These cell accumulations range in extension from small clusters to sickle-shaped infiltrates, to situations where the nerve is involved in its entire circumference. In some cases, perineural cancer cells surround – and possibly damage – the entry site of vasa nervorum.

Similar to ductal adenocarcinoma of the pancreas, molecules associated with nerve biology appear to be involved in cholangiocarcinoma perineural invasion, including nerve growth factor and its receptor, and neural cell adhesion molecule/NCAM (Shen et al. 2010). The pathogenesis of perineural invasion and factors promoting this invasion pattern have been studied in several carcinomas, particularly in pancreatic ductal carcinoma. Factors inducing, or associated with, perineural invasion include neurotransmitter substance P (Li et al. 2013), glial-derived neurotrophic factor (Liu et al. 2012), synuclein-gamma (Hibi et al. 2009), nerve growth factor and tyrosine kinase receptor A (Ma et al. 2008; Sakamoto et al. 2001), and activation of the STAT3 signaling pathway (Guo et al. 2013). The cellular source of these neurotrophic factors is not yet well known, but it was found that glial-derived neurotrophic factor is produced by endoneurial macrophages (Cavel et al. 2012).

Growth and Invasion Along the Bile Ducts

PHC tends to extend along structures of ducts and the hepatic plate to reach the liver substance. Extramucosal extent toward the hepatic side was detected in 77.8 % of cases and that toward the duodenal side in 44.4 %. The distance of extramucosal extent was longer on the hepatic side than on the duodenal side (Hayashi et al. 1994). Mucosal extension was predominantly found in nodular and exophytically growing tumors, while submucosal extension was predominant in infiltrating and nodular-infiltrating neoplasms. Submucosal extension usually consisted of direct or lymphatic invasion (Sakamoto et al. 1998).

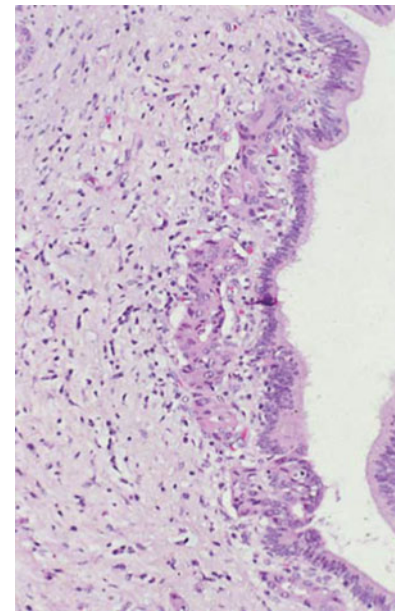

Fig. 22 Intramucosal (subepithelial) spread of cholangiocarcinoma in a bile duct (hematoxylin and eosin stain)

Part of PHC exhibits superficial mucosal spread (Sakamoto et al. 1998). This phenomenon, which is not the same as perineural spread, renders the estimation of tumor extension, and of resection radicality, difficult in some of the cases (Fig. 22).

Toyoda and Yoshida (1985) distinguished two types of PHC according to the type of infiltration. Type I included neoplasms, in which tumor cells were demonstrated in the mucosal or submucosal layer at a distance greater than 11 mm from the main tumor. Type II included neoplasms less than 11 mm distant. In regard to hepatic infiltration, vascular invasion, perineural invasion, and peritoneal invasion, type I was found to be more extended and aggressive. Among 117 cases of extrahepatic cholangiocarcinoma, 18 % were found to have extensive intramucosal spread, defined as spread $>$ or $=$ 20 mm from the main tumor (Nakanishi et al. 2008). In a study of 471 patients (351 perihilar and 120 distal cholangiocarcinomas), superficial spread, defined as noninvasive cancer extension of more than

20 mm, was detected in 14.6 %, with an average length of spread of 54 ± 19 mm. Interestingly, superficial spread was more often found in papillary and well-differentiated adenocarcinomas. Histologic indexes showing tumor aggressiveness, including lymphatic, venous, and perineural invasion, were lower in tumors with superficial spread, and staging levels were less advanced, suggesting this superficial spread is associated with less advanced and slower-growing tumors (Igami et al. 2009). There is evidence that PHC cells can spread via the peribiliary gland network, with formation of intraductal luminal spread and peribiliary invasion (Sato et al. 2013). In the liver, PHC cells have a tendency to spread between hepatocyte plates (Weinbren and Mutum 1983).

Ductal Recurrence of PHC

Following resection, PHC can recur at the level of the ductal stumps. Recurrence can start from remnant cancer cells in case of positive margins or can develop de novo from dysplastic cells that will evolve into carcinoma in situ and later invasive carcinoma. Theoretically, also carcinoma cells in perineural spaces may grow to the stump area and cause recurrence. At a molecular level, residual carcinoma in situ at ductal stumps was associated with nuclear expression of p53-binding protein 1/53BP1 which mediates the DNA damage response. This nuclear localization in neoplastic cells indicates 53BP1 inactivation and decreased apoptosis (Wakai et al. 2013).

Secondary Changes of PHC

Although desmoplastic stroma has a certain tendency to resist necrosis, extensive necrosis can occur in some PHC, specifically in those with rapid growth (Cha et al. 2013). PHC can undergo hemorrhage. Usually, bleeding presents as small focal extravasations, but massive bleeding can occur in few tumors. PHC may develop focal calcifications of the dystrophic type (Reuther and Horak 1997).

Locoregional Lymph Node Pathology

Cholangiocarcinoma of the extrahepatic ducts frequently metastasizes to locoregional lymph nodes (Ito et al. 2010). The frequency of nodal metastasis varies as a function of cancer localization. In one investigation, nodal metastases were present in 61 % of patients with distal bile duct carcinoma, 47 % with middle bile duct carcinoma, and 52 % with proximal bile duct carcinoma, and the number of involved nodes per node-positive patient was greater in patients with middle duct carcinoma than in those with proximal or distal cancers (Yoshida et al. 2003). In another study of 110 patients with PHC, 35.5 % had locoregional lymph node metastases, and 17.3 % had regional and para-aortic node metastases. The incidence of positive nodes was significantly higher in patients with pT3 disease than in those with stage pT2. Pericholedochal lymph nodes were the nodes most commonly involved (42.7 %), followed by periportal nodes (30.9 %), common hepatic nodes (27.3), and posterior pancreaticoduodenal nodes (14.5 %). In contrast, celiac and superior mesenteric nodes were rarely involved (Kitagawa et al. 2001). In a study of 320 patients with PHC, lymph node metastases were found in 45.6 % of patients (Aoba et al. 2013). Part of locoregional lymph nodes involved by carcinoma shows extracapsular involvement, in one study in up to 22 % of nodes (Noji et al. 2012). By use of immunohistochemistry, a higher proportion of nodal metastases are found in comparison with conventional histopathology. In a total of 954 lymph nodes from surgical specimens of 45 patients with histologically node-negative PHC, nodal micrometastases were detected immunohistochemically (CK8 and CK18) in 24.4 % of the 45 patients, being found in 13/954 (1.4 %) nodes examined. 84.6 % of micrometastases were found in the N2 regional node group rather than N1 (Tojima et al. 2003). As observed in other types of carcinoma, locoregional lymph nodes in PHC can show the development of epithelioid cell granulomas as a sign of a distinct type of cell-bound immune reactions, lesions sometimes mimicking sarcoidosis (Onitsuka et al. 2003). By measuring the size of

involved vs. noninvolved nodes, no cutoff point could be found for accurately predicting nodal involvement (Ruys et al. 2011).

Alterations of the Liver in Patients with PHC

Concomitant involvement of the right or left portal vein often causes hepatic lobar atrophy. Atrophy caused by ischemia has an important clinical implication for palling of surgery and considering biliary drainage in patients with unresectable cancer (review: Jarnagin and Winston 2005).

The biliary obstruction caused by stenosing PHC is followed by intrahepatic bile duct dilatation, cholangitis (sometimes purulent, with formation of multiple pyogenic abscesses), and biliary fibrosis. Cirrhotic remodeling is an exceptional finding, due to the short evolution phase available (Okuda et al. 1977), but secondary biliary cirrhosis or an atrophy/hypertrophy complex may develop in rare cases (Göke et al. 1989; Friesen et al. 2011). The liver tissue adjoining PHC usually shows various types of cellular infiltration or signs of inflammation. In case of infection, numerous neutrophils are observed in the region of the tumor and/or around dilated and inflamed bile ducts, sometimes with bile duct empyema or formation of multiple abscesses. The tissue directly surrounding the invasive carcinoma often shows a lymphocytic infiltrate, sometimes with formation of lymph follicles with or without germinal centers. Lymphocytes can also be found around nerves, both in nerves without cancer involvement and those with perineural or intraneural carcinoma invasion. Plasma cells occur along inflamed bile ducts, in particular in patients with signs of bacterial cholangitis. Infiltration of peritumoral but tumor-free parenchyma with IgG4-positive plasma cells has been observed in patients with PHC, suggesting that such plasma cells are of limited utility in distinguishing PHC from IgG4-associated sclerosing disease (Resheq et al. 2013).

Immunohistochemistry

Tumor cells of PHC typically express cholangiocyte lineage markers, i.e., cytokeratins 7 and 19, and epithelial membrane antigen/EMA. Immunohistochemically, MUC1 and S100 protein were significantly upregulated in PHC and mucin-producing intrahepatic cholangiocarcinomas in comparison with mixed intrahepatic cholangiocarcinomas and cholangiolocellular carcinoma (Mall et al. 2010; Komuta et al. 2012). The presence of MUC2, together with CDX2, expression in part of the tumors indicates that intestinal differentiation is present in certain subtypes of extrahepatic cholangiocarcinomas (Hong et al. 2005a). Many PHCs show nuclear expression of p53 (Fig. 23; Argani et al. 2001). Nearly all PHCs and extrahepatic cholangiocarcinomas are positive for S100 protein (Tsai et al. 2012). The proliferative activity of PHC cells can be assessed by means of PCNA and Ki-67 immunohistochemistry (Fig. 24). Extrahepatic cholangiocarcinomas showed significantly higher PCNA and Ki-67/MIB-1 indices than carcinoma in situ and nonneoplastic lesions (Lee 1996; Nishida et al. 1997). Normal cholangiocytes express E-cadherin and N-cadherin with a membranous staining pattern. However, cholangiocarcinomas differ in the patterns of cadherin expression from normal counterparts. While E-cadherin is

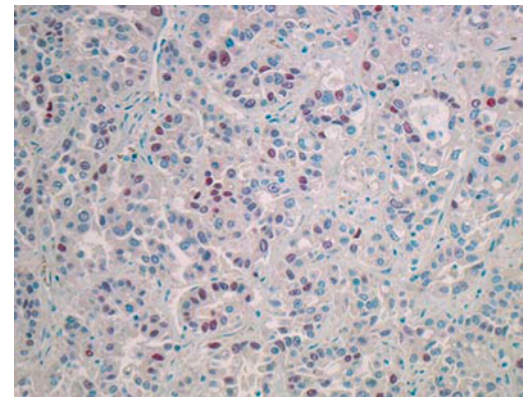

Fig. 23 Perihilar/hilar cholangiocarcinoma with nuclear expression of p53 protein (p53 immunostain)

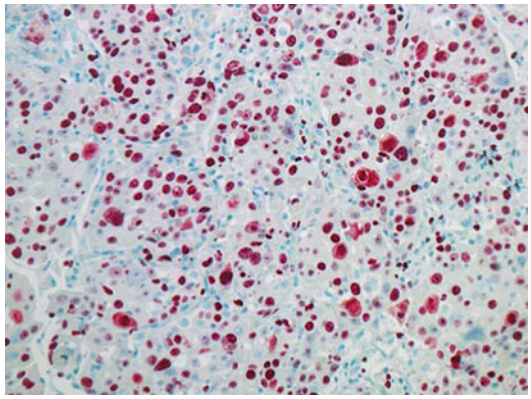

Fig. 24 Poorly differentiated cholangiocarcinoma. This tumor shows a high proliferation fraction (MIB-1 immunostain)

expressed in both intrahepatic cholangiocarcinomas and PHC, the expression of N-cadherin was significantly more frequent in peripheral than in hilar intrahepatic cholangiocarcinomas (Mosnier et al. 2009). P-cadherin and CD24 are expressed in cholangiocarcinomas with high frequency and are also expressed in precursor lesions (Riener et al. 2010). Invasive tumors abnormally express proteins that are components of intercellular junctions, including zonula occludens-1, occludin, and E-cadherin (Nemeth et al. 2009). A novel marker for carcinomas with a cholangiocyte linage is annexin A1/ANXA1 (Hongsrichan et al. 2013). Immunohistochemically, a subset of extrahepatic cholangiocarcinomas exhibit neuroendocrine differentiation, based on reactivities for synaptophysin and chromogranin A (Hong et al. 2005b).

Lymphangiosis Carcinomatosa of the Bile Ducts

Introduction

Lymphangiosis carcinomatosa is defined as the presence of clusters of carcinoma cells within the lumina of lymph vessels, sometimes with formation of tumor cell thrombi and dilatation of the vessels involved. In several tumor types, the presence of lymphangiosis carcinomatosa has been shown to be a negative prognosticator (Meyer et al. 2001) and should, therefore, be identified within a diagnostic and staging workup of a given tumor. However, the diagnosis required the reliable identification of lymph vessels, what may be difficult in H&E-stained preparations, as lymph vessels are difficult to distinguish from tissue slits or artifacts. This has changed with the introduction of lymphatic endothelial markers, in particular the D2-40 monoclonal antibody (Kahn and Marks 2002). This utility of this immunohistochemical approach has also been shown in human biliary tract cancers. It was, e.g., shown that perimuscular connective tissue of human gallbladder contained lymphatic vessels by D2-40 immunostaining (Nagahashi et al. 2007).

Clinical Features

The lymphatic vessels and lymph nodes in the gastrohepatic ligament are frequent sites of spread and metastasis from gastric carcinoma (Baker et al. 1987; Maruyama et al. 1989; Lyttkens et al. 1990). Lymphangiosis carcinomatosa of the bile duct caused by gastric carcinoma can produce obstructive jaundice (Lee et al. 1995; Gabata et al. 1998). In a retrospective cholangiographic study of 54 patients with advanced gastric carcinoma with obstructive jaundice, the causes of bile duct obstruction were lymph node metastases (93 %) in the hepatoduodenal ligament and direct invasion of the primary gastric tumor or recurrent tumor in 7 %. Fifteen percent were located at the level of the intrahepatic bile duct to the hilum, 46 % at the common hepatic duct, 32 % at the proximal half of the choledochus, and only 7 % at the distal choledochus. There was no evidence of lymphangiosis, but only part of the lesions (10/54) had been examined by exploratory laparotomy (Lee et al. 1995). Radiologically, lymphangiosis carcinomatosa causes concentric bile duct wall thickening (Gabata et al. 1998).

Lymph vessel involvement of the extrahepatic bile ducts is also detectable in patients with gallbladder carcinoma. Among 15 patients, submucosal lymph vessels of the extrahepatic bile duct, lined with D2-40-positive endothelial cells, were found to contain carcinoma cells in three patients (Chikamoto et al. 2009). As the lymphatic systems of the gallbladder are connected with the respective networks of the extrahepatic and intrahepatic bile ducts, and the liver, via the cystic duct network, gallbladder carcinoma can cause lymphangiosis carcinomatosa of the liver. However, this phenomenon is more often seen in cases where liver metastases have already developed (Itoh et al. 1988). Lymphangiosis carcinomatosa can cause progressive jaundice (Tada et al. 1996).

Pathology

Involvement of the biliary tract lymphatic system is detectable in diverse types and locations of lymphatics and can be associated with lymph node metastasis (Figs. 25, 26, 27, 28, and 29). Bile duct lymph vessels with or without lymphangiosis carcinomatosa are readily visualized through D2-40 immunostaining. Lymphangiosis carcinomatosa of the liver can cause a unique branching calcification (Matsumoto et al. 2004). The presence of lymphangiosis carcinomatosa in resection margins is a prognosticator, e.g., in non-small cell lung cancer (Passlick et al. 2001), but has not yet systematically been studied in biliary tract cancer.

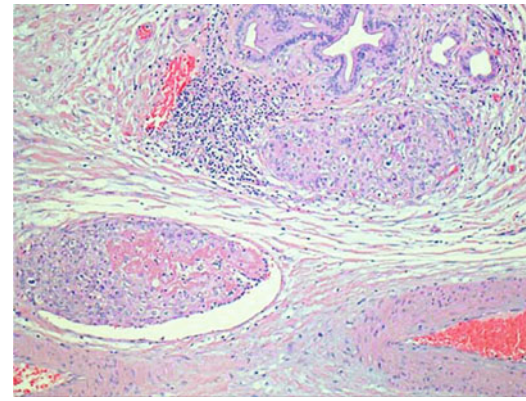

Fig. 26 Poorly differentiated cholangiocarcinoma, invasion of lymph vessels around peribiliary glands (*top*) and of a thin-walled dilated venule (*bottom*). The tumor cell plug in the venule contains thrombotic material (the so-called tumor thrombus, hematoxylin and eosin stain)

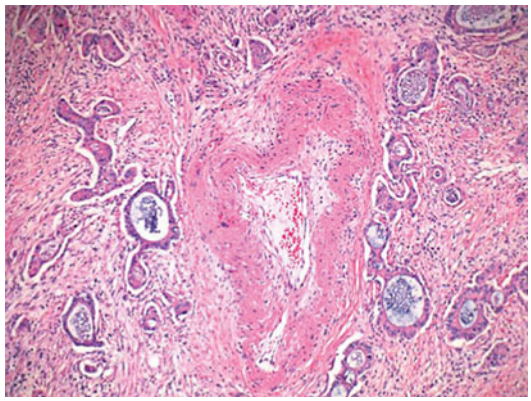

Fig. 25 Perihilar cholangiocarcinoma, invasion of perivascular lymphatic vessels. Due to lymphatic obstruction by the tumor cells, the blood vessel wall is damaged, with adventitional and intimal fibrosis (hematoxylin and eosin stain)

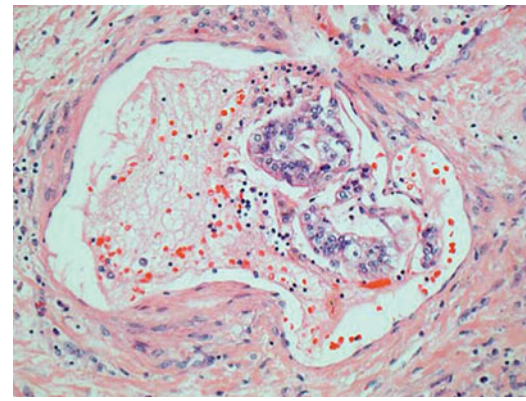

Fig. 27 Cholangio-carcinoma, invasion of a medium-sized, dilated lymph vessel (lymphangiosis carcinomatosa). The vessel lumen contains, in addition to tumor cells, a proteinaceous fluid with lymphocytes, i.e., lymph (hematoxylin and eosin stain)

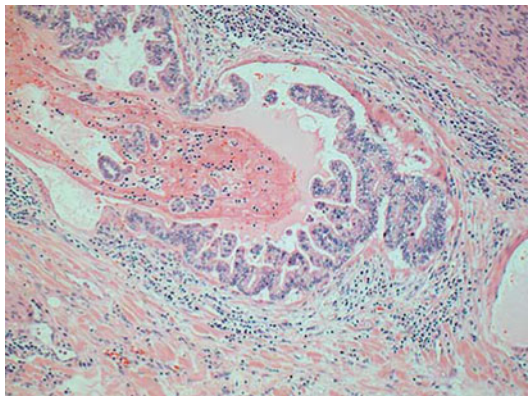

Fig. 28 Intralymphatic growth of cholangiocarcinoma, with formation of pseudopapillary structures (hematoxylin and eosin stain)

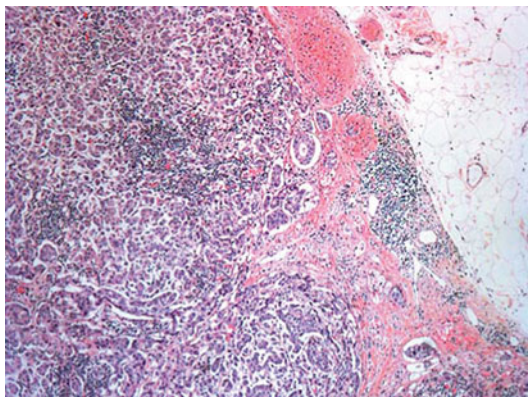

Fig. 29 Perihilar/hilar cholangiocarcinoma. Peripheral parts of a locoregional lymph node with metastasis (hematoxylin and eosin stain)

Determinants of Lymphatic Spread in Bile Duct Cancer

Determinants of lymphatic spread and lymph node metastasis include distinct modes of tumor cell motility, recognition of lymph vessel cells and lymph vessel-associated extracellular matrix components by cancer cells, differential adhesion of tumor cells (lymph vessel homing), lymphangiogenesis (see below), and changes in the adhesive properties of lymphatic endothelial cells in or near tumors. Invasion of local lymphatics and population of these vascular channels increases as a function of the depth of tumor infiltration into the duct wall (Takahashi 1996).

Neoplastic Lymphangiosis and Lymphangiogenesis

Both experimental tumor models and human clinicopathologic data indicate that growth of lymphatic vessels is induced by invasion of carcinoma cells (tumor-associated lymphangiogenesis, TALG; reviews: Achen and Stacker 2006, 2008). TALG mediates tumor cell dissemination and the formation of lymph node metastases in animal models of various neoplasms. Lymphangiogenic factors have been identified that promote formation of tumor lymphatics. They comprise VEGF-C and VEGF-D, which act via their cognate receptor tyrosine kinase VEGF receptor-3 (VEGFR-3) located to lymphatic endothelial cells (Von Marschall et al. 2005; Thelen et al. 2008a). Other growth factors inducing lymphangiogenesis are VEGF-A, platelet-derived growth factor-BB, and hepatocyte growth factor (review: Achen and Stacker 2008). In hilar cholangiocarcinoma, it was found that TALG correlates with lymph node metastases and prognosis (Thelen et al. 2008b,c; Thelen et al. 2010). In a study of 88 cases of intrahepatic cholangiocarcinoma, it was observed that poorly differentiated tumors showed a higher lymphatic vessel density in the tumor periphery and in the peritumoral area, and lymphatic invasion was significantly more prominent in the periphery than in the tumor center. Lymphatic invasion was correlated with VEGF-C expression, which was independent prognostic factor (Aishima et al. 2008). In extrahepatic bile duct carcinoma, the presence of carcinoma cells in lymph vessels significantly increased the hazard ratios of tumor recurrence and initial distant organ metastasis (Hasebe et al. 2005).

Differential Diagnosis

PHC has a broad differential diagnosis. It is estimated that about 5–15 % of specimens resected for presumed PHC prove not to be

Table 3 Differential diagnosis of perihilar carcinoma

Nonneoplastic conditions
Fibrosing inflammations of the hilar/perihilar region
Hepatolithiasis
Primary and secondary sclerosing cholangitis with dominant stricture
Various forms of chronic noninfectious or infectious cholangitis
Inflammatory pseudotumors
Amputation neuroma
IgG4-related sclerosing disease
Nodal sarcoidosis, tuberculosis, and other granulomatous disorders
Portal hypertensive biliopathy
Ischemic cholangiopathy
Retroperitoneal fibrosis
Sclerosing mesenteritis
Cysts and pseudocysts
Tissue ectopias/heterotopias
Cholelithiasis
Alveolar echinococcosis
Neoplastic conditions
Hilar/perihilar non-Hodgkin's lymphoma and Hodgkin's lymphoma
Various obstructing benign tumors of the bile ducts
Hepatic malignancies invading the hilar region
Intrabiliary (endoluminal) tumor thrombus (hepatocellular carcinoma and cholangiocarcinoma)
Bile duct metastasis
Perihilar myofibroblastic tumor

cholangiocarcinoma (Senthil Kumar and Marudanayagam 2012). A complex spectrum of neoplastic and nonneoplastic conditions can mimic PHC (Table 3).

For imaging diagnostic procedures, an important differential diagnosis of PHC is benign fibrosing disease at the hepatic confluence (Wetter et al. 1991; Verbeek et al. 1992; Medina-Franco et al. 2001; Koea et al. 2004; Corvera et al. 2005; Uhlmann et al. 2006; Dumitrascu et al. 2010; Juntermanns et al. 2011). Apart from fibrosing cholangiopathies, hepatolithiasis (Senda et al. 2011), follicular cholangitis (Lee et al. 2005; Fujita et al. 2010), autoimmune cholangiopathy (Shingina et al. 2011), primary sclerosing cholangitis (Kojima et al. 2004), tuberculosis (hepatic tuberculosis or tuberculosis of periductal lymph nodes; Arora et al. 2008; Hanafiah et al. 2013), amputation neuroma (Koike et al. 2000), IgG4-related sclerosing disease (Cheung and Lo 2008; Wakai et al. 2012), biliary inflammatory pseudotumor (Hammesfahr 1928; Worley et al. 2001; Gohy et al. 2007; Deng et al. 2010), heterotopic pancreatic tissue at the confluence (Heer et al. 2010), gastric mucosal heterotopia (Fukuda et al. 2013), biliary Erdheim-Chester disease (Gundling et al. 2007), and biliary sarcoidosis (Suzuki et al. 2011; Daniel Gonzalez et al. 2012) were found to mimic PHC. In a study of 171 patients with proximal biliary obstruction, 141 or 82.4 % had PHC. Alternative diagnoses other than PHC were encountered in 17.5 % of patients and included benign strictures (5.2 %) and other malignancies (12 %; Are et al. 2006). In rare instances, peripheral cholangiocarcinoma resulting in intrabiliary tumor thrombus resembled PHC (Lucidi et al. 2008). Non-carcinomatous tumors of the hilar region may mimic PHC, e.g., non-Hodgkin's lymphomas (André et al. 1996; Cristophides et al. 2009), neuroendocrine tumors (Chan et al. 2000), obstructing leiomyoma (Mandeville and Stawski 1991), neurilemmoma (Kamani et al. 2007), metastases (e.g., breast cancer; Coletta et al. 2014), or hilar inflammatory myofibroblastic tumor (Kim et al. 2011). Another lesion clinically and radiologically resembling PHC is mass-forming inflammatory periductal fibrosis of the hilar region (Hasegawa et al. 2000). In rare instances, obstructing bilateral stones in hepatic ducts or choledocholithiasis may mimic PHC (Läuffer et al. 1998; Dixit et al. 1999).

References

Abdelwahab M, El Nakeeb A, Salah T, Hamed H, Ali M, El Sorogny M, Shehta A et al (2014) Hilar cholangiocarcinoma in cirrhotic liver: a case-control study. Int J Surg 12:762–767

Achen MG, Stacker SA (2006) Tumor lymphangiogenesis and metastatic spread – new players begin to emerge. Int J Cancer 119:1755–1760

Achen MG, Stacker SA (2008) Molecular control of lymphatic metastasis. Ann NY Acad Sci 1131:225–234

Aishima S, Nishihara Y, Iguchi T, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2008) Lymphatic spread is

related to VEGF-C expression and D2-40 positive myofibroblasts in intrahepatic cholangiocarcinoma. Mod Pathol 21:256–264
Albores-Saavedra J, Delgado R, Henson DE (1999) Well-differentiated adenocarcinoma, gastric foveolar type, of the extrahepatic bile ducts: a previously unrecognized and distinctive morphologic variant of bile duct carcinoma. Ann Diagn Pathol 3:75–80
Albores-Saavedra J, Murakata L, Krueger JE, Henson DE (2000) Noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts. Cancer 89:508–515
Albores-Saavedra J, Chablé-Montero F, Méndez-Sanchez N, Mercado MA, Vilatoba-Chapa M, Henson DE (2012) Adenocarcinoma with pyloric gland phenotype of the extrahepatic bile ducts: a previously unrecognized and distinctive morphologic variant of extrahepatic bile duct carcinoma. Hum Pathol 43:2292–2298
Altemeier WA, Culbertson WR (1973) Sclerosing carcinoma of the hepatic bile ducts. Surg Clin North Am 53:1229–1243
Altemeier WA, Gall EA, Zinninger MM, Hoxworth PI (1957) Sclerosing carcinoma of the major intrahepatic bile ducts. Arch Surg 75:450–460
Alvarez AF (1958) Carcinoma of the main hepatic ducts, within the liver: a report of two cases, treated by intrahepatic cholangiojejunostomy. Ann Surg 148:773–782
Andoh H, Yasui O, Kurokawa T, Sato T (2004) Cholangiocarcinoma coincident with schistosomiasis japonica. J Gastroenterol 39:64–68
André SB, Farias AQ, Bittencourt PL, Guarita DR, Machado MC, Viana R, Laudanna AA (1996) Primary extranodal non-Hodgkin lymphoma of the extrahepatic bile duct mimicking Klatskin tumor. Rev Hosp Clin Fac Med Sao Paulo 51:192–194
Aoba T, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y, Nagino M (2013) Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. Ann Surg 257:718–725
Are C, Gonen M, D'Angelica M, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR (2006) Differential diagnosis of proximal biliary obstruction. Surgery 140:756–763
Argani P, Shaukat A, Kaushal M, Wilentz RE, Su GH, Sohn TA, Yeo CJ, Cameron JL et al (2001) Differing rates of loss of DPC4 expression and of p53 overexpression among carcinomas of the proximal and distal bile ducts. Cancer 91:1332–1341
Arora R, Sharma A, Bhowate P, Bansal VK, Guleria S, Dinda AK (2008) Hepatic tuberculosis mimicking Klatskin tumor: a diagnostic dilemma. Indian J Pathol Microbiol 51:383–385
Baker et al. 1987. http://www.ncbi.nlm.nih.gov/pubmed/3819124
Beazley RM, Hadjis N, Benjamin IS, Blumgart LH (1984) Clinicopathological aspects of high bile duct cancer. Experience with resection and bypass surgical treatments. Ann Surg 199:623–636
Bhuiya MR, Nimura Y, Kamiya J, Kondo S, Fukata S, Hayakawa N, Shionoya S (1992) Clinicopathologic studies on perineural invasion of bile duct carcinoma. Ann Surg 215:344–349
Blechacz B, Gores GJ (2008) Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment. Hepatology 48:308–321
Blumgart LH, Hadjis NS, Benjamin IS, Beazley R (1984) Surgical approaches to cholangiocarcinoma at confluence of hepatic ducts. Lancet 1:66–70
Bosma A (1990) Surgical pathology of cholangiocarcinoma of the liver hilus (Klatskin tumor). Semin Liver Dis 10:85–90
Brocq P, Maduro R (1924) Cancer du carrefour hepato-cholédoco-cystique (Cancer of the hepato-choledocho-cystic junction). Rev Chir 62:316–325
Brown DB, Strang R, Gordon J, Hendry EB (1961) Primary carcinoma of the extrahepatic bile-ducts. Br J Surg 49:22–28
Burcharth F (1988) Klatskin tumours. Acta Chir Scand Suppl 541:63–69
Byrnes V, Afdhal N (2002) Cholangiocarcinoma of the hepatic hilum (Klatskin tumor). Curr Treat Options Gastroenterol 5:87–94
Cai WK, Sima H, Chen BD, Yang GS (2011) Risk factors for hilar cholangiocarcinoma: a case-control study in China. World J Gastroenterol 17:249–253
Castellano-Megias VM, Ibarrola-de Andrés C, Colina-Ruizdelgado F (2013) Pathological aspects of so called "hilar cholangiocarcinoma". World J Gastrointest Oncol 5:159–170
Cavel O, Shomron O, Shabtay A, Vital J, Trejo-Leider L, Weizman N, Krelin Y, Fong Y et al (2012) Endoneurial macrophages induce perineural invasion of pancreatic cancer cells by secretion of GDNF and activation of RET tyrosine kinase receptor. Cancer Res 72:5733–5743
Cha IH, Kim JN, Oh MK, Ryu SH, Kim YS, Moon JS, Lee HK (2013) Total necrosis of rapid growing hilar cholangiocarcinoma. Gastrointest Endosc 77:956–957
Chamberlain RS, Blumgart LH (2000) Hilar cholangiocarcinoma: a review and commentary. Ann Surg Oncol 7:55–66
Chan C, Medina-Franco H, Bell W, Lazenby A, Vickers S (2000) Carcinoid tumor of the hepatic duct presenting as a Klatskin tumor in an adolescent and review of the world literature. Hepato-Gastroenterology 47:519–521
Chatelain D, Farges O, Fuks D, Trouillet N, Pruvot FR, Regimbeau JM (2012) Assessment of pathology reports on hilar cholangiocarcinoma: the results of a nationwide, multicenter survey performed by the AC-HC-2009 study group. J Hepatol 56:1121–1128
Cheung MT, Lo IL (2008) IgG4-related sclerosing lymphoplasmacytic pancreatitis and cholangitis mimicking carcinoma of pancreas and Klatskin tumour. ANZ J Surg 78:252–256

Chikamoto A, Tsuji T, Nakahara O, Sakamoto Y, Ikuta Y, Tanaka H, Takamori H, Hirota M et al (2009) Cancer cells spread through lymph vessels in the submucosal layer of the common bile duct in gallbladder carcinoma. J Hepato-Biliary Pancreat Surg 16:557–561

Chow WH, McLaughlin JK, Menck HR, Mack TM (1994) Risk factors for extrahepatic bile duct cancers: Los Angeles County, California (USA). Cancer Causes Control 5:267–272

Chung YE, Kim MJ, Park YN, Lee YN, Choi JY (2008) Staging of extrahepatic cholangiocarcinoma. Eur Radiol 18:2182–2195

Clary B, Jarnigan W, Pitt H, Gores G, Busuttil R, Pappas T (2004) Hilar cholangiocarcinoma. J Gastrointest Surg 8:298–302

Coletta M, Montalti R, Pistelli M, Vincenzi P, Mocchegiani F, Vivarelli M (2014) Metastatic breast cancer mimicking a hilar cholangiocarcinoma: case report and review of the literature. World J Surg Oncol 12:384

Cormier JN, Vauthey JN (2000) Biliary tract cancer. Curr Opin Gastroenterol 16:437–443

Corvera CU, Blumgart LH, Darvishian F, Klimstra DS, DeMatteo R, Fong Y, D'Angelica M, Jarnagin WR (2005) Clinical and pathologic features of proximal biliary strictures masquerading as hilar cholangiocarcinoma. J Am Coll Surg 201:862–869

Costamagna G, Tringali A, Petruzziello L, Spada C (2004) Hilar tumors. Can J Gastroenterol 18:451–454

Cristophides T, Samstein B, Emond J, Bhagat G (2009) Primary follicular lymphoma of the extrahepatic bile duct mimicking a hilar cholangiocarcinoma: case report and review of the literature. Hum Pathol 40:1808–1812

Crocker RA (1955) Hepatic duct carcinoma. J Tn State Med Assoc 48:60–64

Daniel Gonzalez H, Sahay SJ, Rahman SH (2012) Primary biliary sarcoidosis mimicking Klatskin tumor: case report and review of literature. Rev Esp Enferm Dig 104:284–286

David VC (1932) Carcinoma of the hepatic duct. Ann Surg 96:381–384

Davis RI, Sloan JM, Hood JM, Maxwell P (1988) Carcinoma of the extrahepatic biliary tract: a clinicopathological and immunohistochemical study. Histopathology 12:623–631

De Oliveira ML, Clavien PA (2012) A common language to describe perihilar cholangiocarcinoma. Br J Surg 99:885–886

Deng FT, Li YX, Ye L, Tong L, Yang XP, Chai XQ (2010) Hilar inflammatory pseudotumor mimicking hilar cholangiocarcinoma. Hepato-Biliary Pancreat Dis Int 9:219–221

DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, Choti MA, Yeo CJ et al (2007) Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 245:755–762

Dixit VK, Chaturvedi P, Pandey M, Agarwal AK, Shukla VK (1999) Hepatic duct stones masquerading as Klatskin tumour. J Assoc Physicians India 47:236–237

Dumitrascu T, Ionescu M, Ciurea S, Herlea V, Lupescu I, Popescu I (2010) Klatskin-mimicking lesions – a case series and literature review. Hepato-Gastroenterology 57:961–967

Ebata T, Kamiya J, Nishio H, Nagasaka T, Nimura Y, Nagino M (2009) The concept of perihilar cholangiocarcinoma is valid. Br J Surg 96:926–934

Ebata T, Yokoyama Y, Sugawara G, Igami T, Mizuno T, Fukaya M, Uehara K, Itatsu K et al (2014) Concept of perihilar cholangiocarcinoma in the General Rules for Clinical and Pathological Studies on Cancer of the Biliary Tract, 6th edition (in Japanese). Nihon Geka Gakkai Zasshi 115:201–205

Eguchi S, Tajima Y, Yanaga K, Okudaira S, Furui J, Hayashi T, Kanematsu T (2004) Hilar bile duct cancer associated with preoperatively undetectable von Meyenburg complex – report of a case. Hepato-Gastroenterology 51:1301–1303

Ernst P (1905) Über das Wachstum und die Verbreitung bösartiger Geschwülste, insbesondere des Krebses in den Lymphbahnen der Nerven (On the growth and spread of malignant neoplasms, in particular of cancer within lymphatic channels of nerves). Beitr Pathol Anat (suppl 7):29–51

Fatima S, Ahmad Z, Qureshi A, Minhas K, Pal I (2008) Minimally invasive papillary carcinoma of the extrahepatic bile ducts. J Coll Physicians Surg Pak 18:649–651

Fleming WB (1953) Carcinoma of the extrahepatic bile ducts. Aust N Z J Surg 23:148–155

Friesen BR, Gibson RN, Speer T, Vincent JM, Stella D, Collier NA (2011) Lobar and segmental liver atrophy associated with hilar cholangiocarcinoma and the impact of hilar biliary anatomical variants: a pictorial essay. Insights Imaging 2:525–531

Fujita T, Kojima M, Kato Y, Gotohda N, Takahashi S, Konishi M, Kinoshita T (2010) Clinical and histopathological study of "follicular cholangitis": sclerosing cholangitis with prominent lymphocytic infiltration masquerading as hilar cholangiocarcinoma. Hepatol Res 40:1239–1247

Fukuda S, Mukai S, Shimizu S, Kouchi M, Fujisaki S, Takahashi M, Sakimoto H, Eto T et al (2013) Heterotopic gastric mucosa in the hilar bile duct mimicking hilar cholangiocarcinoma: report of a case. Surg Today 43:91–95

Gabata T, Matsui O, Kadoya M, Yoshikawa J, Ueda K, Kawamori Y, Takashima T et al (1998) Obstructive jaundice caused by lymphangitis carcinomatosa of bile duct wall from gastric carcinoma. Abdom Imaging 23:177–179

Gandou C, Harada K, Sato Y, Igarashi S, Sasaki M, Ikeda H, Nakanuma Y (2013) Hilar cholangiocarcinoma and pancreatic ductal adenocarcinoma share similar histopathologies, immunophenotypes, and development-related molecules. Hum Pathol 44:811–821

Gazzaniga GM, Ciferri E, Bagarolo C, Filauro M, Bondanza G, Fazio S, Ermili F (1993) Primitive hepatic hilum neoplasm. J Surg Oncol Suppl 3:140–146

Gerhards MF (2000) Surgical strategies in the management of hilar cholangiocarcinoma. Thesis, Amsterdam

Gohy S, Hubert C, Deprez P, Van Beers BE, Annet L, Lhommel R, Sempoux C, Jean-François G (2007) Benign biliary inflammatory pseudotumor mimicking a Klatskin tumor. Hepato-Gastroenterology 54:1348–1352

Göke B, Ruschoff J, Schwerk WB (1989) Monolobar (unilateral), secondary biliary liver cirrhosis in Klatskin tumor (in German). Z Gastroenterol 27:99–102

Gu L, Jiang CH, Xu Q, Liu Q, Luo M, Wu ZY (2010) Primary clear cell carcinoma of hilar bile duct: a case report. J Dig Dis 11:63–65

Gundling F, Nerlich A, Heitland WU, Schepp W (2007) Biliary manifestation of Erdheim-Chester disease mimicking Klatskin's carcinoma. Am J Gastroenterol 102:452–454

Guo K, Ma Q, Li J, Wang Z, Shan T, Li W, Xu Q, Xie K (2013) Interaction of the sympathetic nerve with pancreatic cancer cells promotes perineural invasion through the activation of STAT3 signaling. Mol Cancer Ther 12:264–273

Hammesfahr C (1928) Choleddochusstriktur durch entzündlichen Reiztumor. Zentralbl Chir 55:3157

Hanafiah M, Alhabshi SM, Bag T, Low SF (2013) Probable hepatic tuberculosis masquerading as Klatskin tumour in an immunocompetent patient. BMJ Case Rep 2013, pii: bcr2013010262

Hasebe T, Konishi M, Iwasaki M, Endoh T, Nakagohri T, Takahashi S, Kinoshita T et al (2005) Histological characteristics of tumor cells and stromal cells in vessels and lymph nodes are important prognostic parameters of extrahepatic bile duct carcinoma: a prospective study. Hum Pathol 36:655–664

Hasegawa K, Kubota K, Komatsu Y, Mori M, Midorikawa Y, Takayama T, Makuuchi M (2000) Mass-forming inflammatory periductal fibrosis mimicking hilar bile duct carcinoma. Hepato-Gastroenterology 47:1230–1233

Hawk GW, Bishop GC (1946) Carcinoma of the hepatic duct s; a case report. Guthir Clin Bull 16:41–44

Hayashi S, Miyazaki M, Kondo Y, Nakajima N (1994) Invasive growth patterns of hepatic hilar ductal carcinoma. A histologic analysis of 18 surgical cases. Cancer 73:2922–2929

Heer C, Pförtner M, Hamberger U, Raute-Kreinsen U, Hanraths M, Bartsch DK (2010) Heterotopic pancreatic tissue in the bifurcation of the bile duct: rare diagnosis mimicking a Klatskin tumour (in German). Chirurgie 81:151–154

Henson DE, Albores-Saavedra J, Corle D (1992) Carcinoma of the extrahepatic bile ducts. Histologic types, stage of disease, and survival rates. Cancer 70:1498–1501

Henson DE, Albores-Saavedra J, Compron CC (2000) Protocol for the examination of specimens from patients with carcinomas of the extrahepatic bile ducts, exclusive of sarcomas and carcinoid tumors: a basis for checklists. Cancer Committee of the College of American Pathologists. Arch Pathol Lab Med 124:26–29

Hibi T, Mori T, Fukuma M, Yamazaki K, Hashiguchi A, Yamada T, Tanabe M, Aiura K et al (2009) Synuclein-gamma is closely involved in perineural invasion and distant metastasis in mouse models and is a novel prognostic factor in pancreatic cancer. Clin Cancer Res 15:2864–2871

Hidaka E, Yanagisawa A, Seki M, Setoguchi T, Kato Y (2001) Genetic alterations and growth pattern in biliary duct carcinomas: loss of heterozygosity at chromosome 5q bears a close relation with polypoid growth. Gut 48:656–659

Hines KF, Pawlik TM (2010) Portal vein encasement complicates resection of Klatskin's tumor. JAAPA 23:30–32

Hoang MP, Murakawa LA, Katabi N, Henson DE, Albores-Saavedra J (2002) Invasive papillary carcinomas of the extrahepatic bile ducts: a clinicopathologic and immunohistochemical study of 13 cases. Mod Pathol 15:1251–1258

Hong SM, Kang GH, Lee HY, Ro JY (2000) Smooth muscle distribution in the extrahepatic bile duct: histologic and immunohistochemical studies of 122 cases. Am J Surg Pathol 24:660–667

Hong SM, Cho H, Moskaluk CA, Frierson HF, Yu E, Ro JY (2005a) CDX2 and MUC2 protein expression in extrahepatic bile duct carcinoma. Am J Clin Pathol 124:361–370

Hong SM, Kim MJ, Pi DY, Jo D, Yu E, Ro JY (2005b) Neuroendocrine differentiation in extrahepatic bile duct carcinomas and its prognostic significance. Hum Pathol 36:732–740

Hong SM, Kim MJ, Jang KT, Yoon GS, Cho H, Frierson HF, Yu E (2008) Adenosquamous carcinoma of extrahepatic bile duct: clinicopathologic study of 12 cases. Int J Clin Exp Pathol 1:147–156

Hongsrichan N, Rucksaken R, Chamgramol Y, Pinlaor P, Techasen A, Yongvanit P et al (2013) Annexin A1: a new immunohistochemical marker of cholangiocarcinoma. World J Gastroenterol 19:2456–2465

Howald M (1890) Das primäre Carcinom des Ductus hepaticus und choledochus (The primary carcinoma of the hepatic and choledochal duct). Thesis, Bern, Switzerland

Igami T, Nagino M, Oda K, Nishio H, Ebata T, Yokoyama Y, Shimoyama Y (2009) Clinicopathologic study of cholangiocarcinoma with superficial spread. Ann Surg 249:296–302

Ingis DA, Farmer RG (1975) Adenocarcinoma of the bile ducts. Relationship of anatomic location to clinical features. Am J Dig Dis 20:253–261

Ito K, Ito H, Allen PJ, Gonen M, Klimstra D, D'Angelica MI, Fong Y, DeMatteo RP et al (2010) Adequate lymph node assessment for extrahepatic bile duct adenocarcinoma. Ann Surg 251:675–681

Ito Y, Kenmochi T, Irino T, Egawa T, Hayashi S, Nagashima A, Kitagawa Y (2012) Clinicopathological feature of extrahepatic cholangiocarcinoma without

jaundice: a single-center experience. Hepato-Gastroenterology 59:1744–1747
Itoh T, Kanaoka M, Obara A, Furuta M, Itoh H (1988) Lymphangiosis carcinomatosa of the liver. Acta Pathol Jpn 38:751–758
Jarnagin WR (2000) Cholangiocarcinoma of the extrahepatic bile ducts. Semin Surg Oncol 19:156–176
Jarnagin W, Winston C (2005) Hilar cholangiocarcinoma: diagnosis and staging. HPB (Oxford) 7:244–251
Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS et al (2001) Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 234:507–519
Jarnagin WR, Ruo L, Little SA, Klimstra D, D'Angelica M, DeMatteo RP, Wagman R et al (2003) Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 98:1689–1700
Jarnagin WR, Bowne W, Klimstra DS, Ben-Porat L, Roggin K, Cymes K, Fong Y, DeMatteo RP (2005) Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. Ann Surg 241:703–712
Juntermanns B, Radunz S, Heuer M, Hertel S, Reis H, Neuhaus JP, Vernadakis S et al (2010) Tumor markers as a diagnostic key for hilar cholangiocarcinoma. Eur J Med Res 15:357–361
Juntermanns B, Kaiser GM, Reis H, Saner FH, Radunz S, Vernadakis S, Heuer M et al (2011) Klatskin-mimicking lesions: still a diagnostical and therapeutical dilemma? Hepato-Gastroenterology 58:265–269
Kahn HJ, Marks A (2002) A new monoclonal antibody, D2-40, for detection of lymphatic invasion in primary tumors. Lab Invest 82:1255–1257
Kamani F, Dorudinia A, Goravanchi F, Rahimi F (2007) Extrahepatic bile duct neurilemmoma mimicking Klatskin tumor. Arch Iran Med 10:264–267
Kenjo A, Abe T, Saito T, Tsuchiya T, Yamada F, Kanzaki N, Gotoh M (2000) Mucin ball-producing extrahepatic bile duct carcinoma. Scand J Gastroenterol 35:1330–1334
Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD (2005) Cholangiocarcinoma. Lancet 366:1303–1314
Khan SA, Emadossadaty S, Ladep NG, Thomas HC, Elliott P, Taylor-Robinson SD, Toledano MB (2012) Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? J Hepatol 56:848–854
Kim BS, Joo SH, Kim GY, Joo KR (2011) Aggressive hilar inflammatory myofibroblastic tumor with hilar bile duct carcinoma in situ. J Korean Surg Soc 81(suppl 1):S59–S63, 47
Kirshbaum JD, Kozell DD (1941) Carcinoma of the gallbladder and extrahepatic ducts. A clinical and pathological study of 117 cases in 13,330 necropsies. Surg Gynecol Obstet 73:740–754
Kitagawa Y, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Nimura Y (2001) Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection. Ann Surg 233:385–392
Klatskin G (1965) Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features. Am J Med 38:241–256
Klippel AP, Shaw RB (1972) Carcinoma of the common bile duct. Report of a case of successful resection. Arch Surg 104:102–103
Knoefel WT, Prenzel KL, Peiper M, Hosch SB, Gundlach M, Eisenberger CF, Strate T et al (2003) Klatskin tumors and Klatskin mimicking lesions of the biliary tree. Eur J Surg Oncol 29:658–661
Koea J, Holden A, Chau K, McCall J (2004) Differential diagnosis of stenosing lesions at the hepatic hilus. World J Surg 28:466–470
Koike N, Todoroki T, Kawamoto T, Inagawa S, Yoshita S, Fukao K (2000) Amputation neuroma mimics common hepatic duct carcinoma. Hepato-Gastroenterology 47:639–643
Kojima T, Shimura T, Takahashi M, Haga N, Hashimoto S, Fukuda T, Kuwano H (2004) A localized primary sclerosing cholangitis preoperatively diagnosed as hilar cholangiocarcinoma; report of a case. Hepato-Gastroenterology 51:961–963
Komuta M, Govaere O, vandecaveye V, Akiba J, Van Steenbergen W, Verslype C et al (2012) Histological diversity in cholangiocellular carcinoma reflects the different cholangiocyte phenotypes. Hepatology 55:1876–1888
Koo J, Ho J, Wong J, Ong GB (1982) Mucoepidermoid carcinoma of the bile duct. Ann Surg 196:140–148
Kosuge T, Yamamoto J, Shimada K, Yamasaki S, Makuuchi M (1999) Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. Ann Surg 230:663–671
Kuang D, Wang GP (2010) Hilar cholangiocarcinoma: pathology and tumor biology. Front Med China 4:371–377
Kuwayti I, Baggenstoss AH, Stauffer MH, Priestley JT (1957) Carcinoma of the major intrahepatic and the extrahepatic bile ducts exclusive of the papilla of Vater. Surg Gynecol Obstet 104:357–366
Kwon HJ, Kim SG, Chun JM, Hwang YJ (2014) Classifying extrahepatic bile duct metachronous carcinoma by de novo neoplasia site. World J Gastroenterol 20:3050–3055
Läuffer JM, Baer HU, Schajor M, Halter F, Büchler MW (1998) Choledocholithiasis at the hepatic confluence mimicking a hilar cholangiocarcinoma. Hepato-Gastroenterology 45:2339–2343
Launois B, Campion JP, Brissot P, Gosselin M (1979) Carcinoma of the hepatic hilus. Surgical management and the case for resection. Ann Surg 190:151–157
Launois B, Terblanche J, Lakehal M, Catheline JM, Bardaxoglou E, Landen S, Campion JP et al (1999) Proximal bile duct cancer: high resectability rate and 5-year survival. Ann Surg 230:266–275

Launois B, Wemyss-Holden S, Maddern GJ (2002) Current and future trends in management and treatment of Klatskin tumour. Int J Clin Oncol 7:91–102

Lee CS (1996) Differences in cell proliferation and prognostic significance of proliferating cell nuclear antigen and Ki-67 antigen immunoreactivity in in situ and invasive carcinomas of the extrahepatic biliary tract. Cancer 78:1881–1887

Lee WE, Totten HP (1934) Primary carcinoma of the common bile duct. Ann Surg 99:930–938

Lee BH, Chin SYC, Kim SA et al (1995) Obstructive jaundice in gastric carcinoma: cause, site, and relationship to the primary lesion. Abdom Imaging 20:307–311

Lee JY, Lim JH, Lim HK (2005) Follicular cholangitis mimicking hilar cholangiocarcinoma. Abdom Imaging 30:744–747

Lee BS, Cha BH, Park EC, Roh J (2014) Risk factors for perihilar cholangiocarcinoma: a hospital-based case-control study. Liver Int. doi:10.1111/liv.12618

Leiter HE (1947) Carcinoma involving the common bile duct; report of four cases of successful resection. Surgery 22:627–647

Li X, Ma G, Ma Q, Li W, Liu J, Han L, Duan W, Xu Q, Liu H, Wang Z, Sun Q, Wang F et al (2013) Neurotransmitter substance P mediates pancreatic cancer perineural invasion via NK-1R in cancer cells. Mol Cancer Res 11:294–302

Lillemoe KD (1994) Current status of surgery for Klatskin tumors. Curr Opin Gen Surg 1994:161–167

Lim SH, Yang HW, Kim A, Cha SW, Jung SH, Go H, Lee WC (2007) Adenosquamous carcinoma of extrahepatic bile duct: a case report. Korean J Intern Med 22:206–210

Lippman HN, McDonald LC, Longmire WP (1959) Carcinoma of the extrahepatic bile ducts. Am Surg 25:819–826

Liu H, Li X, Xu Q, Lv S, Li J, Ma Q (2012) Role of glial cell line-derived neurotrophic factor in perineural invasion of pancreatic cancer. Biochem Biophys Acta 1826:112–120

Longmire WP, McArthur MS, Bastounis EA, Hiatt J (1973) Carcinoma of the extrahepatic biliary tract. Ann Surg 178:333–345

Lucidi V, Van Laethem JL, Sersté T, Gelin M, Donckier V (2008) Peripheral cholangiocarcinoma with endoluminal tumor thrombus in main bile duct mimicking a Klatskin tumor. J Gastrointest Surg 12:1149–1150

Lyttkens K, Forsberg L, Hederström E (1990) Ultrasound examination of lymph nodes in the hepatoduodenal ligament. Br J Radiol 63:26–30

Ma J, Jiang Y, Jiang Y, Sun Y, Zhao X (2008) Expression of nerve growth factor and tyrosine kinase receptor A and correlation with perineural invasion in pancreatic cancer. J Gastroenterol Hepatol 23:1852–1859

Madariaga JR, Iwatsuki S, Todo S, Lee RG, Irish W, Starzl TE (1998) Liver resection for hilar and peripheral cholangiocarcinomas: a study of 62 cases. Ann Surg 227:70–79

Malhi H, Gores GJ (2006) Review article: the modern diagnosis and therapy of cholangiocarcinoma. Aliment Pharmacol Ther 23:1287–1296

Mall AS, Tyler MG, Ho SB, Krige JE, Kahn D, Spearman W, Myer L, Govender D (2010) The expression of MUC mucin in cholangiocarcinoma. Pathol Res Pract 206:805–809

Mandeville GA, Stawski WS (1991) Obstructing leiomyoma of the common hepatic duct bifurcation simulating a Klatskin tumor. Am Surg 57:676–678

Maruyama K, Gunvén P, Okabayashi K et al (1989) Lymph nodes metastases of gastric cancer. Ann Surg 210:596–602

Masunari H, Shimada H, Endo I, Fujii Y, Tanaka K, Sekido H, Togo S (2008) Surgical anatomy of hepatic hilum with special reference of the plate system and extrahepatic duct. J Gastrointest Surg 12:1047–1053

Matsumoto S, Mori H, Ando Y, Miyake H (2004) Lymphangiosis carcinomatosa of the liver deriving from gastric carcinoma with a unique branching calcification. Eur Radiol 14:1519–1520

McLaughlin CW (1933) Tumors of the extrahepatic bile ducts, exclusive of the ampulla of Vater. Can Med Assoc J 28:255–265

Medina-Franco H, Listinsky C, Mel Wilcox C, Morgan D, Heslin MJ (2001) Concomitant sclerosing mesenteritis and bile duct fibrosis simulating Klatskin's tumor. J Gastrointest Surg 5:658–660

Meyer W, Awad-Allah A, Steinhäuser BB, Jurowich C, Kaiser A, Gebhardt C (2001) Prognostic importance of isolated peritumoral lymphangiosis carcinomatosa in lymph-node-negative colorectal carcinoma. Langenbecks Arch Surg 386:124–131

Meyerowitz BR, Aird I (1962) Carcinoma of the hepatic ducts within the liver. Br J Surg 50:78–83

Mosnier JF, Kandel C, Cazals-Hatem D, Bou-Hanna C, Gournay J, Jarry A, Laboisse CL (2009) N-cadherin serves as diagnostic biomarker in intrahepatic and perihilar cholangiocarcinomas. Mod Pathol 22:182–190

Musser JH (1889) Primary cancer of the gall-bladder and bile-ducts. Boston Med Surg J 212(525):553–581

Nagahashi M, Shirai Y, Wakai T, Sakata J, Ajioka Y, Hatakeyama K (2007) Perimuscular connective tissue contains more and larger lymphatic vessels than the shallower layers in human gallbladders. World J Gastroenterol 13:4480–4483

Nagino M (2012) Perihilar cholangiocarcinoma: a surgeon's viewpoint on current topics. J Gastroenterol 47:1165–1176

Nakanishi et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18425077

Nakanuma Y, Sato Y (2014) Hilar cholangiocarcinoma is pathologically similar to pancreatic duct adenocarcinoma: suggestions of similar background and development. J Hepato-Biliary Pancreat Sci 21:441–447

Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH et al (1996) Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 224:463–473

Neibling HA, Dockerty MB, Ward JM (1949) Carcinoma of the extrahepatic bile ducts. Surg Gynecol Obstet 89:429–438

Nemeth Z, Szasz AM, Somoracz A, Tatrai P, Nemeth J, Gyorffy H, Szijarto A, Kupcsulik P et al (2009) Zonula occludens-1, occluding, and E-cadherin protein expression in biliary tract cancers. Pathol Oncol Res 15:533–539

Nishida T, Nakao K, Hamaji M, Nakahara MA, Tsujimoto M (1997) Prognostic significance of proliferative cell nuclear antigen in carcinoma of the extrahepatic bile duct. World J Surg 21:634–639

Noji T, Miyamoto M, Kubota KC, Shinohara T, Ambo Y, Matsuno Y, Kashimura N, Hirano S (2012) Evaluation of extra capsular lymph node involvement in patients with extra-hepatic bile duct cancer. World J Surg Oncol 10:106

Nomoto S, Nakao A (1996) Papillary extrahepatic bile duct carcinoma, invasive papillary extrahepatic bile duct carcinoma (in Japanese). Ryoikibetsu Shokogun Shirizu 9:88–91

Ogata S, Kimura A, Hatsuse K, Yamamoto J, Shimazaki H, Nakanishi K, Kawai T (2010) Poorly differentiated adenocarcinoma with signet-ring cell carcinoma of the extrahepatic bile duct in a 42-year-old Japanese female: a case report. Acta Med Okayama 64:63–65

Okuda K, Kubo Y, Okazaki N, Arishima T, Hashimoto M (1977) Clinical aspects of intrahepatic bile duct carcinoma including hilar carcinoma: a study of 57 autopsy-proven cases. Cancer 39:232–246

Okuyama M, Motoki R, Hanzawa K, Hoshino S, Koseki M (1964) Management of jaundice caused by hepatic duct obstruction (in Japanese). Rinsho Geka 19:1314–1318

Onitsuka A, Katagiri Y, Kiyama S, Mimoto H, Nakamura T, Toda K, Shima H (2003) Hilar cholangiocarcinoma associated with sarcoid reaction in the regional lymph nodes. J Hepato-Biliary Pancreat Surg 10:316–320

Otto G (2007) Diagnostic and surgical approaches in hilar cholangiocarcinoma. Int J Colorectal Dis 22:101–108

Park HS, Han JK, Lee HS, Lee KH, Kim SH, Kim KW, Kim YJ, Kim HC, Choi BI (2005) Calcified Klatskin tumor mimicking intrahepatic stone: case report. Abdom Imaging 30:90–92

Park KW, Jung ES, Kim DG, Yoo YK, Hong TH, Lee IS, Koh YH, Kim JH, Lee MA (2013) ERCC1 can be a prognostic factor in hilar cholangiocarcinoma and extrahepatic bile duct cancer, but not in intrahepatic cholangiocarcinoma. Cancer Res Treat 45:63–69

Passlick B, Sitar I, Sienel W, Thetter O, Morresi-Hauf A (2001) Significance of lymphangiosis carcinomatosa at the bronchial resection margin in patients with non-small cell lung cancer. Ann Thorac Surg 72:1160–1164

Patel T (2006) Cholangiocarcinoma. Nat Clin Pract Gastroenterol Hepatol 3:33–42

Pliveric V (1928) Klinischer Beitrag zu den Karzinomen des Confluens ductuum (Clinical contribution to carcinomas of the ductal confluens). Zentralbl Chir 55:133–138

Poynton FJ (1917) Carcinoma of the common bile-duct without jaundice. Br Med J 1:483–489

Qualman SJ, Haupt HM, Bauer TW, Taxy JB (1984) Adenocarcinoma of the hepatic duct junction. A reappraisal of the histologic criteria of malignancy. Cancer 53:1545–1551

Quattlebaum JK, Quattelbaum JK (1965) Malignant obstruction of the major hepatic ducts. Ann Surg 161:876–889

Renshaw K (1922) Neoplasms of the extrahepatic bile ducts. Ann Surg 76:205–221

Resheq YJ, Quaas A, von Renteln D, Schramm C, Lohse AW, Lüth S (2013) Infiltration of peritumoral but tumour-free parenchyma with IgG4-positive plasma cells in hilar cholangiocarcinoma and pancreatic adenocarcinoma. Dig Liver Dis 45:859–865

Reuther G, Horak W (1997) Pathologic liver findings? Hilar cholangiocarcinoma (Klatskin tumor) with central calcinosis (in German). Radiologe 37:255–257

Riener MO, Vogetseder A, Pestalozzi BC, Clavien PA, Probst-Hensch N, Kristiansen G et al (2010) Cell adhesion molecules P-cadherin and CD24 are markers for carcinoma and dysplasia in the biliary tract. Hum Pathol 41:1558–1565

Rocha FG, Matsuo K, Blumgart LH, Jarnagin WR (2010) Hilar cholangiocarcinoma: the Memorial Sloan-Kettering Cancer Center experience. J Hepato-Biliary Pancreat Sci 17:490–496

Ross AP, Braasch JW (1973) Ulcerative colitis and carcinoma of the proximal bile ducts. Gut 14:94–97

Ross AP, Braasch JW, Warren KW (1973) Carcinoma of the proximal bile ducts. Surg Gynecol Obstet 136:923–928

Ruys AT, Kate FJ, Busch OR, Engelbrecht MR, Gouma DJ, van Gulik TM (2011) Metastatic lymph nodes in hilar cholangiocarcinoma: does size matter? HPB (Oxford) 13:881–886

Sakamoto et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9527064

Sakamoto Y, Kitajima Y, Edakuni G, Sasatomi E, Mori M, Kitahara K, Miyazaki K (2001) Expression of Trk tyrosine kinase receptor is a biologic marker for cell proliferation and perineural invasion of human pancreatic ductal adenocarcinoma. Oncol Rep 8:477–484

Sako K, Seitzinger GL, Garside E (1957) Carcinoma of the extrahepatic bile ducts; review of the literature and report of six cases. Surgery 41:416–437

Sanford GE, Lowry CC (1949) Carcinoma at the confluence of the hepatic bile ducts; a case report. South Surg 15:758–764

Sato H, Nakanuma Y, Kozaka K, Sato Y, Ikeda H (2013) Spread of hilar cholangiocarcinomas via peribiliary gland network: a hither-to-unrecognized route of periductal infiltration. Int J Clin Exp Pathol 6:318–322

Scudder CL, Richardson O (1908) IX. Primary carcinoma of the hepatic ducts: the report of a case with the autopsy. Ann Surg 47:728–729

Senda Y, Nishio H, Ebata T, Yokoyama Y, Igami T, Sugawara G, Nagino M (2011) Hepatolithiasis in the hepatic hilum mimicking hilar cholangiocarcinoma: report of a case. Surg Today 41:1243–1246

Senthil Kumar MP, Marudanayagam R (2012) Klatskin-like lesions. HPB Surg 2012, 107519

Shahib Y, El-Serag HB (2004) The epidemiology of cholangiocarcinoma. Semin Liver Dis 24:115–125

Shapiro PF, Lifvendahl RA (1931) Tumors of the extrahepatic bile-ducts. Ann Surg 94:61–79

Shen FZ, Zhang BY, Feng YJ, Jia ZX, An B, Liu CC, Deng XY, Kulkarni AD, Lu Y (2010) Current research in perineural invasion of cholangiocarcinoma. J Exp Clin Cancer Res 29:24

Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang Y, Wiangnon S, Sripa B et al (2010) Comparison of incidence of intrahepatic and extrahepatic cholangiocarcinoma – focus on East and South-Eastern Asia. Asian Pac J Cancer Prev 11:1159–1166

Shingina A, Owen D, Zwirewich C, Salh B (2011) Autoimmune cholangitis mimicking a Klatskin tumor: a case report. J Med Case Rep 5:484

Slattery JM, Sahani DV (2006) What is the current state-of-the-art imaging for detection and staging of cholangiocarcinoma? Oncologist 11:913–922

Solovei G, Alame A, Petit J, Favriel JM, Al Hareiss H, Glavier F, Cart P, Fauchart JP (1993) Burgeoning form of cancer of the superior biliary bifurcation. Nosological, diagnostic and therapeutic aspects. Apropos of a case (in French). Ann Radiol (Paris) 36:161–165

Somer L, Andrejic B, Milosevic P (2012) Origin and pathological characteristics of Klatskin tumor: a case report and literature review. Pol J Pathol 1:65–70

Sons HU, Borchard F (1987) Carcinoma of the extrahepatic bile ducts: a postmortem study of 65 cases and review of the literature. J Surg Oncol 34:6–12

Stain SC, Baer HU, Dennison AR, Blumgart LH (1992) Current management of hilar cholangiocarcinoma. Surg Gynecol Obstet 175:579–588

Stewart HL, Lieber MM, Morgan DR (1940) Carcinoma of the extrahepatic bile ducts. Arch Surg 41:622–713

Suarez-Munoz MA, Fernandez-Aguilar JL, Sanchez-Perez B, Perez-Daga JA, Garcia-Albiach B et al (2013) Risk factors and classifications of hilar cholangiocarcinoma. World J Gastrointest Oncol 5:132–138

Suzuki K, Morise Z, Furuta S, Tanahashi Y, Takeura C, Kagawa T, Ikeda M, Sugioka A (2011) Hepatic sarcoidosis mimicking hilar cholangiocarcinoma: case report and review of the literature. Case Rep Gastroenterol 5:152–158

Tada H, Morimoto M, Shima T, Hirana H, Nakagawa Y, Shimamoto K, Nagano N (1996) Progressive jaundice due to lymphangiosis carcinomatosa of the liver: CT appearance. J Comput Assist Tomogr 20:650–652

Takahashi M (1996) An investigation of the mode of local spreading of biliary tract carcinoma to microvascular and neural structure (in Japanese). Hokkaido Igaky Zasshi 71:449–462

Tannapfel A, Wittekind C (2004) Gallbladder and bile duct carcinoma. Biology and pathology (in German). Internist (Berl) 45:33–41

Thelen A, Scholz A, Benckert C, von Marschall Z, Schröder M, Wiedenmann B, Neuhaus P et al (2008a) VEGF-D promotes tumor growth and lymphatic spread in a mouse model of hepatocellular carcinoma. Int J Cancer 122:2471–2481

Thelen A, Scholz A, Benckert C, Schröder M, Weichert W, Wiedenmann B, Neuhaus P, Jonas S (2008b) Microvessel density correlates with lymph node metastases and prognosis in hilar cholangiocarcinoma. J Gastroenterol 43:959–966

Thelen A, Scholz A, Benckert C, Weichert W, Dietz E, Wiedenmann B, Neuhaus P et al (2008c) Tumor-associated lymphangiogenesis correlates with lymph node metastases and prognosis in hilar cholangiocarcinoma. Ann Surg Oncol 15:791–799

Thelen A, Scholz A, Weichert W, Wiedenmann B, Neuhaus P, Gessner R, Benckert C et al (2010) Tumor-associated angiogenesis and lymphangiogenesis correlate with progression of intrahepatic cholangiocarcinoma. Am J Gastroenterol 105:1123–1132

Thorbjarnarson B (1959) Carcinoma of the bile ducts. Cancer 12:708–713

Tiesenga MF, Neal RH, Hemwall GA (1964) Jaundice due to right hepatic duct obstruction. JAMA 187: 367–368

Todoroki T, Okamura T, Fukao K, Nishimura A, Otsu H, Sato H, Iwasaki Y (1980) Gross appearance of carcinoma of the main hepatic duct and its prognosis. Surg Gynecol Obstet 150:33–40

Tojima Y, Nagino M, Ebata T, Uesaka K, Kamiya J, Nimura Y (2003) Immunohistochemically demonstrated lymph node micrometastasis and prognosis in patients with otherwise node-negative hilar cholangiocarcinoma. Ann Surg 237:201–207

Tompkins RK, Thomas D, Wile A, Longmire WP (1981) Prognostic factors in bile duct carcinoma: analysis of 96 cases. Ann Surg 194:447–457

Toyoda T, Yoshida M (1985) Clinicopathological study of carcinoma of the bifurcation of hepatic duct. Gastroenterol Jpn 20:344–353

Tsai JH, Huang WC, Kuo KT, Yuan RH, Chen YL, Jeng YM (2012) S100P immunostaining identifies a subset of peripheral-type intrahepatic cholangiocarcinomas with morphological and molecular features similar to those of perihilar and extrahepatic cholangiocarcinomas. Histopathology 61:1106–1116

Tsalis K, Vasiliadis K, Kalpakidis V, Christoforidis E, Avgerinos A, Botsios D, Megalopoulos A et al (2007) A single-center experience in the management of Altemeier-Klatskin tumors. J Gastrointest Liver Dis 16:383–389

Uhlmann D, Wiedmann M, Schmidt F, Kluge R, Tannapfel A, Berr F, Hauss J, Witzigmann H (2006)

Management and outcome in patients with Klatskin-mimicking lesions of the biliary tree. J Gastrointest Surg 10:1144–1150

Vardaman C, Albores-Saavedra J (1995) Clear cell carcinomas of the gallbladder and extrahepatic bile ducts. Am J Surg Pathol 19:91–99

Verbeek PC, van Leeuwen DJ, de Wit LT, Reeders JW, Smits NJ, Bosma A, Huibregtse K et al (1992) Benign fibrosing disease at the hepatic confluence mimicking Klatskin tumors. Surgery 112:866–871

Von Marschall Z, Scholz A, Stacker SA, Achen MG, Jackson DG, Alves F, Schimer M et al (2005) Vascular endothelial growth factor-D induces lymphangiogenesis and lymphatic metastasis in models of ductal pancreatic cancer. Int J Oncol 27:669–679

Von Schüppel O (1878) Die Krankheiten der Gallenwege und der Pfortader. In: von Ziemssen HW (ed) Handbuch der Allgemeinen Pathologie und Therapie, vol VIII, p 71

Voyles CR, Bowley NJ, Allison DJ, Benjamin IS, Blumgart LH (1983) Carcinoma of the proximal extrahepatic biliary tree radiologic assessment and therapeutic alternatives. Ann Surg 197:188–194

Wakai T, Shirai Y, Sakata J, Maruyama T, Ohashi T, Korira PV, Ajioka Y, Hatakeyama K (2012) Clinicopathological features of benign biliary strictures masquerading as biliary malignancy. Am Surg 78:1388–1391

Wakai et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/11776457

Washington MK, Berlin J, Branton PA, Burgart LJ, Carter DK, Compron CC, Fitzgibbons PL et al (2010) Protocol for the examination of specimens from patients with carcinoma of the perihilar bile ducts. Arch Pathol Lab Med 134:e19–e24

Weber FP, Michels E (1905) A case of chronic jaundice and great enlargement of the liver due to primary carcinoma of the extrahepatic bile-ducts commencing at the junction of the hepatic ducts. Med Chir Trans 88:247–264

Weinbren HK, Mutum SS (1983) Pathological aspects of cholangiocarcinoma. J Pathol 139:217–238

Welzel TM, McGlynn KA, Hsing AW, O'Brien TR, Pfeiffer RM (2006) Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra-and extrahepatic cholangiocarcinoma in the United States. J Natl Cancer Inst 98:873–875

Wetter LA, Ring EJ, Pellegrini CA, Way LW (1991) Differential diagnosis of sclerosing cholangiocarcinomas of the common hepatic duct (Klatskin tumors). Am J Surg 161:57–62

Whelton MJ, Petrelli M, George P, Young WB, Sherlock S (1969) Carcinoma at the junction of the main hepatic ducts. Q J Med 38:211–230

Willis RA (1942) Some aspects of the pathology of carcinomata of the biliary tract. Med J Aust 2:340

Worley PJ, Roberts-Thomson IC, Dymock RB, Maddern GJ (2001) Benign inflammatory pseudotumour of the biliary tract masquerading as a Klatskin tumour. HPB (Oxford) 3:179–181

Wylegschanin MI (1927) Über primäre bösartige Neubildungen der Ductus hepatici. Frankf Ztschr Pathol 35:462–470

Yamaguchi K, Chijiiwa K, Saiki S, Shimizu S, Takashima M, Tanaka M (1997) Carcinoma of the extrahepatic bile duct: mode of spread and its prognostic implications. Hepato-Gastroenterology 44:1256–1261

Yamana I, Kawamoto S, Nagao S, Yoshida T, Yamashita Y (2011) Squamous cell carcinoma of the hilar bile duct. Case Rep Gastroenterol 5:463–470

Yamashita et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1321653

Yoshida T, Matsumoto T, Sasaki A, Morii Y, Shibata K, Ishio T, Kitano S (2003) Lymphatic spread duffers according to tumor location in extrahepatic bile duct cancer. Hepato-Gastroenterology 50:17–20

Yubin L, Chihua F, Zhixiang J, Jinrui O, Zixian L, Jianghua Z, Ye L, Haosheng J, Chaomin L (2008) Surgical management and prognostic factors of hilar cholangiocarcinoma: experience with 155 cases in China. Ann Surg Oncol 15:2113–2119

Zervos EE, Osborne D, Goldin SB, Villadolid DV, Hometz DP, Durkin A, Carey LC et al (2005) Stage does not predict survival after resection of hilar cholangiocarcinomas promoting an aggressive operative approach. Am J Surg 190:810–815

Extrahepatic Cholangiocarcinoma: Carcinoma of the Middle and Distal Common Bile Duct (Middle and Lower Bile Duct Carcinomas)

28

ICD-O code biliary-type adenocarcinoma 8140/3

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_28

Abstract

Cholangiocarcinomas of the distal bile duct system are conventionally defined as neoplasms located between the cystic duct entry and the end of the common bile duct in the ampullary region (infrahilar cancers). Cancers arising in a segment just distal to the cystic duct entry are sometimes classified as tumors of the duct mid-region, due to their rather distinct growth pattern (middle duct cancer), but middle and distal cancers are put together into one category by other authors. Japanese authors identified two infrahilar tumor groups and denote middle carcinomas by the abbreviation Bm and distal carcinomas by Bi. Distal-most forms of cholangiocarcinoma may be difficult to distinguish from periampullary carcinomas. Infrahilar variants of extrahepatic cholangiocarcinoma account for 20–30 % of all bile duct carcinomas, but incidence rates vary considerably among different regions of the world, due to varying prevalence of etiologic factors such as stone disease and liver fluke infestation. Macroscopically, infrahilar cholangiocarcinomas display nodular stenosing masses, masses with a tubular configuration, ulcerated tumors, diffusely growing tumors, and exophytic growths, the latter predominating in distal-most lesions.

Introduction

Cholangiocarcinomas of the distal common bile duct (CDBDs) are conventionally defined as carcinomas located between the cystic duct entry and the end of the common duct in the ampullary region (Lad and Kooby 2014). CDBDs form, in addition to perihilar carcinoma, the second important group of extrahepatic bile duct carcinomas. Clinically, the distal-most forms of CDBD are sometimes difficult to distinguish from ampullary or periampullary carcinomas (Dickson and Behrman 2014). These generally uncommon neoplasms have first been described in 1840 (Durand-Fardel 1840; carcinoma of common bile duct) and then in 1878 (Schueppel 1878; cited by Renshaw 1922) and were then described in detail in the first half of the twentieth century (Scudder and Richardson 1908; Cheney 1914; Renshaw 1922; Wahl 1924; Shapiro and Lifvendahl 1931; Lee and Totten 1934; Dick 1939; Stewart et al. 1940). In the nineteenth century, part of investigators, such as Rokitansky, thought that extrahepatic ducts with cancer were involved by secondary growths from nearby organs (Rokitansky 1849). A classification of extrahepatic cholangiocarcinomas according to anatomic location, i.e., proximal, middle, and distal, was first proposed by Longmire (1976). As the limits along the duct are not always easy to define, and as tumors tend to infiltrate into neighboring or adjacent duct parts, other classifications have been proposed. Tumors have been divided into intrahepatic, hilar, and distal carcinomas (Nakeeb et al. 1996).

Classifications: CDBD-M Versus CDBD-D

Jarnagin et al. (2001) proposed a two-category system of proximal and distal bile duct carcinoma, however with middle duct cancer defined as a separate category. Middle and distal cancers are put together into one category by other authors (Nakeeb et al. 1996; Razumilava and Gores 2013). In the nomenclature of the Japanese Society of Biliary Surgery, abbreviations used to denote the two infrahilar/perihilar categories are Bm for middle carcinomas and Bi for distal carcinomas. As mid-duct and distal carcinomas differ in their macroscopic presentation, growth patterns, and features of locoregional metastasis, they should be distinguished. In the present chapter, extrahepatic cholangiocarcinoma of the distal part of the large bile duct (i.e., distal to hilar/perihilar tumors) is divided into carcinoma of the mid-region (CDBD-M) and carcinoma of the distal or distal-most part of the duct (CDBD-D). However, the exact limit between these two lesions remains to be defined in more detail. Based on different patterns of spread, the anatomy of bile duct blood vessels and of the duct-associated lymph vessel and node systems might serve as separation guidelines.

Epidemiology

In large autopsy studies, the incidence of bile duct tumors varies from 0.01 % to 0.2 %, and overall, malignancies of the distal extrahepatic bile duct constitute about 20–30 % of all bile duct carcinomas (Jarnagin and Shoup 2004; Ustundag and Bayraktar 2008; Mosconi et al. 2009). The general incidence rates of cholangiocarcinoma vary considerably among different regions of the world, as a function of variable risk factors such as stone disease or liver flukes. It is important to recognize that intrahepatic and extrahepatic cholangiocarcinomas have different epidemiological features and risk factors. In addition, incidence rates are not stable over time. For example, the age-adjusted incidence rate of extrahepatic cholangiocarcinoma in the USA declined by 14 % between 1975–1979 and 1995–1999 (review: Shaib and El-Serag 2004).

Data regarding the incidence of CDBD and their proportion among all cholangiocarcinomas vary considerably among diverse studies, in part dependent on the definitions of anatomical limits (Khan et al. 2008). Rolleston (cited by Springer 1925), in a study of 100 collected cases, found that one third of all extrahepatic bile duct carcinomas had arisen in the lower terminal portion of the choledochus, but it cannot be extracted from this work whether ampullary carcinomas also made part of this group. Of all carcinomas occurring in the periampullary region, CDBD-D accounted for 14 % (Zerbi et al. 1998). Among 37 cases of extrahepatic cholangiocarcinoma from the USA, 43.2 % were located at the middle third of the common bile duct, 37.8 % in the upper third, and 18.9 % in the distal-most third (Chao and Greager 1991). One analysis found 25 % of cholangiocarcinomas located to the distal part of the bile duct (Bahra et al. 2006). Among 564 consecutive patients from the USA with bile duct cancer, 8 % had intrahepatic, 50 % had perihilar, and 42 % had distal tumors (DeOliveira et al. 2007). Among 40 patients reported by Johnson et al. (2001), 80 % were located at the bifurcation, 12.5 % in the middle duct, and 7.5 % in the distal part. In a study of 207 patients undergoing pancreaticoduodenectomy, a reclassification based on the independent reevaluation of the histology resulted in an incidence of CDBD of 28 % (Pominasowska et al. 2012). The prevalence of CDBD may be underestimated based on difficulties of histologically distinguishing CDBD from ampullary carcinoma and pancreatic carcinoma invading the distal bile duct (Pomianoska et al. 2012). In contrast to gallbladder cancer, CDBD mostly occurs in males and is most common between the ages of 50 and 70. Rarely, this carcinoma develops in young adults or even adolescents (Agrawal et al. 2012). In part of patients with CDBD, the tumor was associated with choledocholithiasis (Su et al. 1996), a finding which has been suggested to play an etiologic role (Nishimura et al. 2005). In endemic areas, CDBD may be associated with liver flukes, e.g., clonorchiasis (Kim 2003). CDBD was found in association with anomalies of the pancreaticobiliary junction area (Nakao et al. 1997; Takayashiki et al. 2002) and rare bile duct abnormalities, such as bile duct duplication (Kosar et al. 2010).

Clinical and Imaging Features

Ewing noted that "epithelial tumors of the large bile ducts present much the same etiologic gross anatomic and microscopic features as carcinoma of the gallbladder, but their location favors early mechanical obstruction of important channels which promptly declares itself in severe jaundice and rapidly fatal course of the disease" (Ewing 1928). The most common presenting complaints in patients with CDBD are jaundice, followed by abdominal discomfort and pain, nausea and vomiting, and weight loss (Neibling et al. 1949; Martin and Page 1951; Kuwayti et al. 1957; Sako et al. 1957; Lippman et al. 1959; White 1959; Brown et al. 1961; Permen and McCollum 1963; Thomas 1970; Chao and Greager 1991; Patel 2006). Similar to ampullary carcinomas, CDBD-D cause marked biliary obstruction. Obstructive jaundice was present in 96 % of patients in one series, but was the first sign only in 78 % (Zerbi et al. 1998). Rarely, CDBD can present as cholangitis (Lee et al. 2010); in few cases, biliary stenosis had induced biliary

cirrhosis (Stutman and Bozian 1960; Gulsrud et al. 1979). Complications of CDBD include hemorrhage, abscess formation, and choledochoduodenal fistula (Lin et al. 2009). The preoperative imaging diagnosis of CDBD is performed by ultrasound, intraductal IS, CT, MRI, and endoscopic retrograde pancreaticocholangiography (Dancygier et al. 1988; Schulte et al. 1990; Alper et al. 2011; Ito et al. 2012). On CT images, the majority of CDBD patients reveal prestenotic dilatation of the bile ducts (Thorsen et al. 1984).

Pathology

The pathologic presentation of CDBD resembles that of other cholangiocarcinomas, with some remarkable differences. The pathology workup of specimens has been standardized, with formulation of a detailed protocol for examination (Washington et al. 2010).

Macroscopy

The macroscopic presentation of CDBD is characterized by nodular stenosing masses, masses with a tubular conformation, ulcerated tumors, diffusely growing cancers, or exophytic growths forming a papillary texture or polypoid tumors (Fig. 1).

Already in 1934, Lee and Totten had distinguished three macroscopic forms, namely, villous growths, which may distend and fill the ducts, nodular masses which tend to encroach upon and constrict the duct, and a diffuse growth along the duct which converts it into a firm tube. The tumors have been divided into polypoid, nodular, scirrhous constricting, and diffusely infiltrating types (WHO Classification; Albores-Saavedra et al. 2010), but there are considerable differences in macroscopic patterns between mid-region and distal tumors, and there are overlaps between the diverse phenotypes. The consistency varies considerably and ranges from soft masses to firm neoplasms in case of marked desmoplastic reaction, similar to sclerosing perihilar carcinoma. Infiltration of the duct wall results in thickening and induration of the duct. Tumors of the mid-region (CDBD-M) tend to be either tubular neoplasms that sometimes produce a filiform stenosis of 1 cm to 2 or 3 cm length or diffusely growing carcinomas with ill-defined borders. CDBD-D situated in the distal-most part of the common bile duct show a similar morphology or more often exhibit an exophytic growth mode, with fungating or polypoid masses with a papillary texture. In principle, CDBD-D tumors macroscopically often resemble ampullary carcinomas. In each location along the extrahepatic duct, the carcinoma can invade adjacent tissues, as there is no formal anatomical barrier. The tumor may be accompanied by

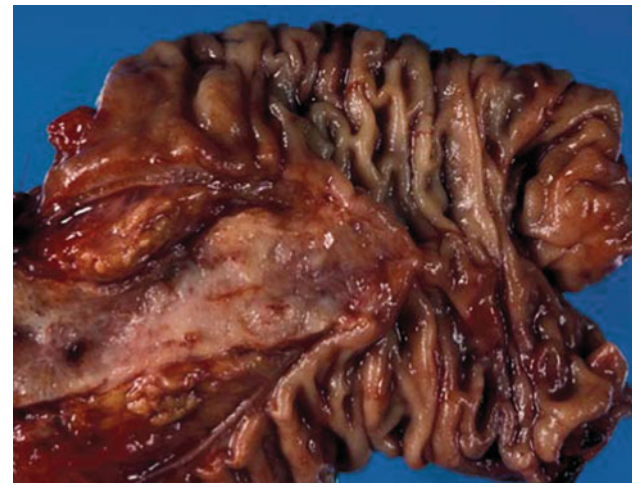

Fig. 1 Cholangiocarcinoma of the distal large bile duct. The duct mucosa is altered by granular and exophytically growing tumor tissue

enlarged and firm lymph nodes containing metastases. On cut surfaces of lymph nodes, small metastases are visualized as whitish nodules on the slightly tan-to-gray background of the lymph nodes, while large metastases may completely efface the lymph node architecture. Also, large perineural tumor deposits can be palpated or seen with the naked eye.

Histopathology

The histology of CDBD has already been described by Ziegler (1898), MacCallum (1919), Ewing (1919), Rolleston (1912), and Renshaw (1922). Based on the morphology of the carcinomatous epithelia, Rolleston (1912) proposed that most bile duct adenocarcinomas are derived from the biliary duct surface epithelium, which is in fact the leading cell lineage for adenocarcinoma NOS. Histologically, CDBD can present in various types and subtypes of adenocarcinoma and other carcinomas, as listed in the AJCC documents (Table 1).

A different classification of histologic types of CDBDs has been proposed in the protocol for the examination of specimens from patients with carcinoma of the distal extrahepatic bile ducts (Washington et al. 2010; Table 2).

Most CDBDs (at least 80 %) are adenocarcinomas, not otherwise specified/NOS, as defined in the 2010 fourth edition of the WHO Classification (Albores-Saavedra et al. 2010). Typical cholangiocarcinoma with a biliary cell lineage predominates in both CDBD-M and CDBD-D, and there is no difference in general differentiation between these two localizations. These adenocarcinomas often display a marked desmoplastic stromal reaction, thus resembling the sclerosing Klatskin tumors of the hilar/perihilar area. The epithelial cells of biliary-type adenocarcinomas are characterized by high columnar to cuboidal cells with a rather pale or even clear cytoplasm forming complete or incomplete tubular profiles embedded in a rich stroma (Laitio 1983; Davis et al. 1988). Cytoplasmic and/or luminal mucin is frequently present. This is the predominant pattern in well-differentiated carcinomas, whereas tumors with moderate or poor differentiation more often show solid parts or small nests or rows of cells in a desmoplastic stroma. In the latter situation, carcinoma cells tend to diffusely infiltrate the duct wall and the periductal connective tissue. The extensive and diffuse infiltration is impressively illustrated in immunohistochemical preparations, which may show many more dissipated tumor cells than anticipated in H&E-stained sections. A diffuse

Table 1 Cellular classification of extrahepatic bile duct cancer (according to AJCC; modified and extended by novel entities)

Carcinoma in situ
Adenocarcinoma, not otherwise specified
Papillary carcinoma, noninvasive
Papillary carcinoma, invasive
Adenocarcinoma, intestinal type
Adenocarcinoma, gastric foveolar type
Adenocarcinoma, pyloric gland type
Mucinous adenocarcinoma
Clear cell adenocarcinoma
Signet ring cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
Mucoepidermoid carcinoma
Lymphoepithelial carcinoma
Small cell (oat cell) carcinoma
Undifferentiated carcinoma (spindle and giant cell types, small cell types)
Carcinoma, NOS

Table 2 Histologic types of distal cholangiocarcinomas according to the CAP protocol (Washington et al. 2010)

Adenocarcinoma (not otherwise characterized)
Papillary adenocarcinoma
Mucinous adenocarcinoma
Clear cell adenocarcinoma
Signet ring cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
High-grade neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Small cell neuroendocrine carcinoma
Biliary cystadenocarcinoma
Others
Carcinoma, type cannot be determined

transmural growth pattern is typical for CDBD-M and results in the macroscopically tubular configuration of these mid-duct tumors, with short to long strictures. In contrast, desmoplastic CDBD-D more often tend to form nodular or mass lesions. A fraction of well-differentiated biliary-type adenocarcinomas may show focal intestinal differentiation and can contain goblet cells and neuroendocrine cells. Rarely, Paneth cells are noted.

As outlined below, adenocarcinoma can be accompanied by superficially spreading components or advanced dysplastic changes. These alterations may cause difficulties in the definition of clear margins, particularly in the setting of intraoperative frozen sections. Attempts to evaluate resection margins through frozen sections are also hampered in situations where a stent had placed prior to surgery. Stents can induce mucosal and tumor ulceration and necrosis of tumor tissue facing the stent, often associated with epithelial atypia caused by regeneration of cholangiocytes. These changes may be misinterpreted as dysplasia in frozen sections.

Histology of CDBD-M vs. CDBD-D

Overall, mid-region tumors form tubular invasive or nodular lesions, whereas distal carcinomas more often show an exophytic and papillary phenotype (Fig. 2). In an analysis of 96 extrahepatic cholangiocarcinomas, the histologic feature of lower third lesions was papillary in 26.7 %, 46.7 % of the tumors being well differentiated (Tompkins et al. 1981). However, if one lumps all extrahepatic bile duct carcinomas together, the papillary type is much rarer and does not exceed 5–6 % of all carcinomas, as this form very rarely occurs in the hilar/perihilar tumor group.

Perineural and Intraneural Invasion

Perineural invasion is a common feature of both CDBD-M and CDBD-D (Davis et al. 1988). Overall, perineural invasion was detected in 81.4 % of 75 resected bile duct cancers. In regard to tumor localization, incidences of perineural invasion were 80.7 %, 87.5 %, and 80 % for carcinomas of the hilar region, CDBD-M, and CDBD-D, respectively (Bhuiya et al. 1992). Perineural invasion is more frequently observed in nerves located in the deeper layers of involved bile ducts, but here a sampling effect may play a role, as larger nerves with easily detectable perineural invasion are more often found in the deep duct layer and in the duct's adventitia. In a first step, small deposits of carcinoma cells are found in the slit-like space of the perineurium, sometimes at entry sites of vasa nervorum. Later, as carcinoma undergoes further growth, sickle-shaped cancer deposits develop, which may sometimes encircle the entire nerve and cause

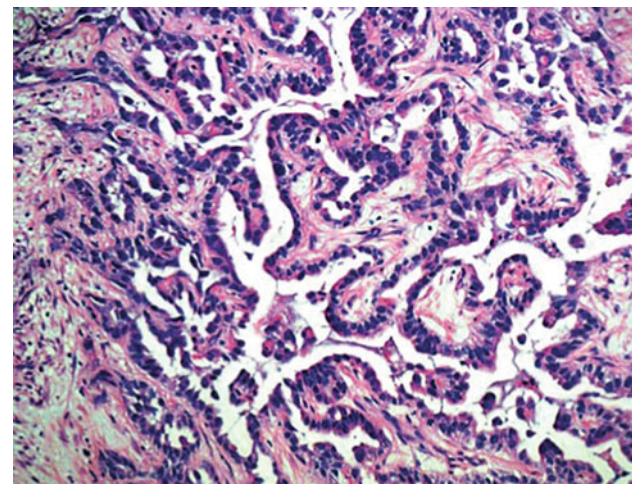

Fig. 2 Papillary cholangiocarcinoma of the distal extrahepatic bile duct. In distal parts of the extrahepatic biliary tract, papillary adenocarcinoma with an exophytic growth pattern is more common (hematoxylin and eosin stain)

neural atrophy. Tubular or cribriform structures may be found, with small necrotic foci and signs of tumor cell apoptosis. Apart from invasion of nerves in the immediate vicinity of tumor, also deep-seated neural plexus is involved. In one study, neural plexus invasion occurred in 20 % of patients, particularly involving the plexus in the hepatoduodenal ligament and around the pancreatic head (Kayahara et al. 1999). In order to estimate the extent of perineural invasion, a perineural invasion index (PNI) has been proposed, calculated as the ratio of the number of nerves invaded by tumor and total number of nerves with and without tumor invasion, determined in at least three places in each tumor (Bhuiya et al. 1992). PNI was graded as grade I (PNI = 0.00, no perineural invasion), grade II (PNI <0.70), and grade III (PNI => 0.70, severe perineural invasion). There seems to be a relationship between frequency and extent of perineural invasion and the histologic type. Perineural invasion was less often found in papillary adenocarcinoma than in other histologic types. The highest value (100 %) was found in poorly differentiated adenocarcinoma and in adenosquamous carcinoma (Bhuiya et al. 1992).

Grading

Grading of distal cholangiocarcinomas is performed as described in the chapter on hilar/perihilar carcinomas. In the CAP protocol for the workup for CDBD specimens (Washington et al. 2010), four histologic grades are distinguished (Table 3).

Table 3 Histologic grades for adenocarcinomas according to the CAP protocol (Washington et al. 2010)

GX: grade cannot be assessed
G1: well differentiated (greater than 95 % of tumor composed of glands)
G2: moderately differentiated (50–95 % of tumor composed of glands)
G3: poorly differentiated (less than 50 % of tumor composed of glands)
G4: undifferentiated

The grades are further defined as grade I being composed entirely of glands or having less than 5 % solid or cord-like growth patterns, grade II having more than 5 % but less than 50 % solid or cord-like growth patterns, and grade III having 50–100 % solid or cord-like growth patterns. About 75 % of all adenocarcinomas of the extrahepatic bile ducts are well to moderately differentiated. Among 96 cases of extrahepatic cholangiocarcinomas (including 49 % located to the upper third of the bile duct), 46 % were well differentiated, 25 % poorly differentiated, 20 % papillary, and 9 % sclerosing (Tompkins et al. 1981).

Immunohistochemistry

As other cholangiocarcinomas, CDBD tumor cells are reactive for the biliary cell lineage markers, CK7 and CK17, and for epithelial membrane antigen/EMA. Expression of carcinoembryonic antigen/CEA was found in most of the CDBD cells (Davis et al. 1988). Cholangiocarcinomas express IMP3 (Riener et al. 2009; Levy et al. 2010) and show nuclear and cytoplasmic reactivity for S100P (Levy et al. 2010).

Histologic Variants of Distal Cholangiocarcinoma

Adenocarcinoma, Intestinal Type

These carcinomas are characterized by tubular gland-like structures resembling those found in colorectal adenocarcinoma. A population of tall columnar cells predominates, and the pattern looks “basophilic” at low magnification. The epithelial cells are often arranged in a pseudostratified pattern, with nuclei in a basal position, but usually not in one single row, but rather arranged in several levels. Some of the nuclei move high up the epithelial lining, and nuclear debris and apoptotic bodies are found in the compartment of the tubuli. A less common variant of intestinal-type adenocarcinoma is characterized by a predominant population of

goblet cells, usually admixed with variable numbers of neuroendocrine cells. Intestinal-type adenocarcinoma of the distal bile duct can arise in zones of metaplastic biliary epithelium (Sano et al. 2003).

Adenocarcinoma, Gastric Foveolar Type

This variant is listed in the 2010 WHO classification of tumors of the digestive system. It is an unusual, well-differentiated adenocarcinoma composed of tall columnar cells with basally placed nuclei and abundant, mucin-containing cytoplasm. The tumors are composed of >95 % gastric foveolar-type epithelium, exhibit bland nuclei, and reveal a low mitotic index. The tumors can show perineural invasion and foci of less-differentiated adenocarcinoma (Albores-Saavedra et al. 1999). The cells are reactive for the MUC5AC mucin (Albores-Saavedara et al. 2010). The variant has been found in pure form in the extrahepatic bile duct system (Albores-Saavedra et al. 1999, 2000).

Adenocarcinoma, Pyloric Gland Type

Few cases of CDBD showing pyloric gland differentiation have been reported (Albores-Saavedra et al. 2012). The carcinomas revealed pyloric gland differentiation amounting to 80–1,000 %. Patients with this type of tumor were younger than those with adenocarcinoma NOS. Although the neoplasms were well differentiated, they displayed extensive perineural invasion. Histologically, the tumors showed small to medium-sized and cystically dilated glands arranged in a characteristic stellar pattern and embedded in desmoplastic stroma and composed of columnar cells with abundant mucin-containing cytoplasm. In part, MUC5AC and MUC6 were expressed in a pattern similar to that of pyloric gland adenomas of the gallbladder.

Mucinous Adenocarcinoma

Mucinous carcinomas (colloid carcinomas), characterized by extracellular accumulation of large amounts of mucin ("mucin lakes"), rarely occur in the extrahepatic bile duct and are less common in this site than, e.g., in the gallbladder. Among 170 cases of cholangiocarcinoma, 22 (12.9 %) were mucin-producing cholangiocarcinomas. Choledochoscopic findings included intraductal tumors in 40.9 % and infiltrative lesions with ductal stricture in 45.5 % (Chen et al. 1998). By convention, more than 50 % of the tumor contains extracellular mucin, which stains with PAS and alkaline alcian blue stains. One rare variant of mucinous bile duct carcinomas is characterized by marked neurotropism (neurotropic mucinous carcinoma). Macroscopically, the tumor is characterized by multiple transparent, mucinous nodules surrounding the main tumor and representing tumoral deposits following the ductal and periductal nerves. Histologically, peritumoral nerves are massively extended and spliced by large deposits of mucin with floating tumor cells.

Signet Ring Cell Carcinoma

Signet ring cell carcinoma, which as an entity is treated in a separate chapter, is a very rare primary tumor of the mid-duct and distal duct and is clearly rarer in this duct compartment than in the ampulla of Vater or the gallbladder. Signet ring cell carcinoma, as a poorly differentiated carcinoma, tends to grow in a disseminated pattern, diffusely infiltrating the duct wall, in association with variable desmoplasia and formation of a concentric duct stenosis. However, mass-forming lesions growing into the duct lumen are also known. As in gastric tumors, signet ring cells form small nests or files of round to void cells with a large mucin drop in the cytoplasm, displacing the sickle-shaped nucleus to the border of the cell. In contrast to other bile duct cancers, signet ring cell carcinoma tends to occur in a younger age group and is more often found in Asian countries. More cases situated in the CDBD-D (i.e., close to the ampulla) than in the CDBD-M

were described (Hiraki et al. 2007; Lee et al. 2010; Ogata et al. 2010; Matsumoto et al. 2011).

Papillary Carcinomas

Papillary adenocarcinoma of the extrahepatic bile ducts forms a distinct phenotype of cholangiocarcinoma that most commonly occurs in the distal half of the common bile duct and tends to show an exophytic/intraluminal growth pattern. Both invasive and apparently noninvasive variants are recognized. Frankly invasive papillary CDBD accounts for only 4–5 % of CDBD, and noninvasive and minimally invasive papillary carcinomas are even less common. Papillary carcinomas are often associated with adenomas or remnants of adenomas, which have been detected in up to 75 % of cases (Kozuka et al. 1984). Noninvasive and minimally invasive carcinomas are usually exophytically growing lesions with a polypoid shape. It has been shown that noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts, lesions different from biliary papillomatosis or intraductal papillary mucinous tumors, usually behave as in situ carcinomas and are associated with good to excellent prognosis, regardless of their cytological features or their immunohistochemical reactivity to p53 protein and proliferative activity assessed by MIB-1/Ki-67 (Albores-Saavedra et al. 2000; Fatima et al. 2008). Invasive papillary CDBD showed an equal gender distribution, and age at diagnosis ranged from 33 to 89 years (Hoang et al. 2002). Among 13 patients, five tumors were located in the distal portion, one in the mid portion, and six in the proximal portion of the common bile duct, and one tumor had arisen in the right hepatic duct (Hoang et al. 2002). In the invasive variant, infiltration of the bile duct wall, sometimes only the mucosal layer, is found, in polypoid tumor invasion commonly starting at the base of the tumor stalk (Nomoto and Nakao 1996). Depth of invasion is related to the growth pattern of tumors in that polypoid tumor rarely invades deeper than the fibromuscular layer, while flat or nodular carcinomas often infiltrate deeper than the fibromuscular layer (Kozuka et al. 1984). Of 174 invasive papillary carcinomas extracted from the SEER program, 71 tumors were confined to the ductal wall, and 61 had regional lymph node metastases. Even in the presence of locoregional lymph node metastases, invasive papillary carcinomas had a better outcome than adenocarcinoma NOS (Hoang et al. 2002).

Adenosquamous Cell Carcinoma and Squamous Cell Carcinoma

Relatively few cases of adenosquamous carcinoma of the extrahepatic bile ducts have been reported (Lantsberg et al. 1986; Hayashi et al. 1993; Hughes and Niemann 1996; Kimoto et al. 1996; Okabayashi et al. 2005; Lim et al. 2007; Kim et al. 2009; Aoki et al. 2012). Adenosquamous carcinomas of the bile duct are aggressive neoplasms, with a post-resection median survival in a Japanese cohort of 13 months (Okabayashi et al. 2005). This distinct tumor is discussed in more detail in a separate chapter. A very rare histologic variant of CDBD is squamous cell carcinoma (Burger et al. 1978; Gulsrud et al. 1979; La Greca et al. 2004; Sewkani et al. 2005). This type of biliary tract carcinoma has mostly been observed in the setting of hepatolithiasis, recurrent pyogenic cholangitis, and liver fluke disease. Squamous cell carcinoma of the common bile duct is much rarer than respective carcinomas in the gallbladder, intrahepatic bile ducts, or the ampulla of Vater. Squamous cell carcinoma found in the wall of the common bile duct is usually a metastasis from a primary tumor located elsewhere (Bass et al. 2010).

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma, histologically reflecting the phenotype of the respective salivary gland tumor, is a very exceptional bile duct tumor and has been observed in the distal-most (intrapancreatic) part of the common bile duct (Song et al. 2011; Moul et al. 2013). These

neoplasms are highly aggressive lesions that invade the underlying pancreas and peripancreatic tissue, sometimes with a pagetoid spread into the extrapancreatic common bile duct (Moul et al. 2013).

Lymphoepithelial Carcinoma

This type of carcinoma very rarely develops in the extrahepatic bile duct system and is treated in a separate chapter.

Poorly Differentiated Carcinoma, Undifferentiated Carcinoma, and Small Cell Carcinoma

Non-neuroendocrine high-grade undifferentiated carcinomas form cellular masses with poor desmoplasia (Nagai et al. 2002; Fujikawa et al. 2011). Typically, the tumors are composed of large cells with a high nuclear-to-cytoplasmic ratio, amphophilic cytoplasm, and nuclei with prominent nucleoli. Mitotic figures are frequent, as are apoptotic bodies and foci of necrosis. Part of undifferentiated carcinomas contain spindle cells and/or pleomorphic cells (Nagai et al. 2002). One variant of undifferentiated carcinoma of the distal duct is characterized by the presence of spindle cells and giant cells (undifferentiated spindle and giant cell carcinoma; Dowaki et al. 2003; Oikawa et al. 2007). Immunohistochemically, the neoplasms are reactive for AE1/AE3 and cytokeratins 8 and 18, but negative for chromogranin A, synaptophysin, and CD56 (Fujikawa et al. 2011). Due to their high cellularity and rapid growth, the tumors can form intraductal tumor thrombi (Fujikawa et al. 2011).

Carcinomas of the distal extrahepatic bile duct with a small cell morphology are almost always undifferentiated neuroendocrine carcinomas (Sabanathan et al. 1988; Van der Wal et al. 1990; Miyashita et al. 2001; Arakura et al. 2003; Kuraoka et al. 2003; Park et al. 2004; Kaiho et al. 2005; Viana Miguel et al. 2006; Hosonuma et al. 2008; Cho et al. 2009). In the protocol for the examination of specimens from patients with carcinoma of the distal extrahepatic bile ducts, the term small cell carcinoma has therefore been replaced by high-grade neuroendocrine carcinoma (Washington et al. 2010).

Mucosal Bile Duct Carcinoma with Superficial Spread

Distal adenocarcinoma may, similar to other cholangiocarcinomas, exhibit a mucosal localization with superficial spread/intraepithelial spread (IES) (Iwahashi et al. 1998; Sato et al. 2013), sometimes with extensive mucosal spread (Ogawa et al. 2010). IES has to be distinguished from BilIN-3 (Sato et al. 2013). Similar to carcinoma in situ/BilIN-3, IES lesions show flat or pseudopapillary pattern. The less frequent micropapillary pattern was found more often in BilIN-3 than in IES (Sato et al. 2013). In a study of 471 patients with cholangiocarcinoma (351 perihilar and 120 distal cancers), superficial spread was found in 14.6 %, and its length was 54 +/−19 mm. Superficial spread was detected more often in papillary and well-differentiated carcinomas, and lymphatic, venous, and perineural invasion were less frequent in carcinomas with superficial spread (Igami et al. 2009). It is difficult to judge whether this phenotype represents very early stage of cancer or whether some carcinomas have an inborn tendency to remain in a superficial layer of the duct for longer time periods. In one study, there was evidence that carcinomas with superficial spread might represent slower-growing and less advanced tumors with better survival (Igami et al. 2009).

Precursor Lesions of CDBD

Similar to intrahepatic cholangiocarcinoma, patients with CDBD may show various types of potential or established epithelial precursor lesions of the bile duct mucosa, either preceding invasive cancer or detectable synchronously with an already established carcinoma. This issue is further discussed in more detail in the ICC chapter. Low-grade or high-grade dysplasia was

observed in the distal bile duct, sometimes with a high frequency, in part associated with preexisting bile duct disease such as primary sclerosing cholangitis, stone disease, or liver fluke infestation (Davis et al. 1988; Haworth et al. 1989; lee et al. 1995). Primary sclerosing cholangitis is typically complicated by biliary dysplasia (Martins et al. 1994; Broomé et al. 1995; Fleming et al. 2001; Lewis et al. 2010). In an analysis covering 44 cases of extrahepatic cholangiocarcinomas, mild and in part multifocal dysplasia was detected in 91 % of cases and severe dysplasia in 45 % of cases (Laitio 1983). Adenocarcinoma in situ of the distal bile duct has been described (Yang et al. 2012). As outlined in the chapter on biliary precursor lesions, multistep carcinogenesis of cholangiocarcinoma is described by increasing grades of biliary intraepithelial neoplasia (BilIN), whereby BilIN-3 represents the stage of carcinoma in situ. BilIN-3 has to be distinguished from intraepithelial spread of carcinoma/IES, described in a later paragraph (Sato et al. 2013).

Biology of Disease

Outcome

Overall, the outcome of CDBD is better than that of ampullary carcinomas and carcinomas of the pancreatic head and similar to that of perihilar carcinoma, but worse than intrahepatic cholangiocarcinoma.

Selected references: Evander et al. 1980; Rodgers et al. 1981; Tompkins et al. 1981; Alexander et al. 1984; Anderson et al. 1985; Michelassi et al. 1989; Henson et al. 1992; Kayahara et al. 1992; Gozzetti and Principe 1995; Bortolasi et al. 2000; Heron et al. 2003; Albu et al. 2005; Bahra et al. 2008; Shimizu et al. 2008; Veillette and Castillo 2008; Lee et al. 2009; Ito et al. 2013.

In an investigation comparing 106 proximal and 98 distal resected extrahepatic cholangiocarcinomas, the estimated 5-year disease-specific survival (DSS) for all patients was 35 %, and tumor location (proximal vs. distal) was not associated with 5-year DSS (Allen et al. 2008). However, different results were found in other analyses, e.g., patients with distal bile duct cancer living longer than those with proximal cancers (Alden et al. 1995). The median survival for R0-resected patients with CDBD was 27 months, in comparison with 80 months for intrahepatic and 30 % for perihilar carcinomas (DeOliveira et al. 2007). In carcinomas of the distal-most part of the common bile duct, pancreaticoduodenectomy results in good 5-year survival rates (45 %; Shimizu et al. 2008).

Invasion and Spread

Perineural and neural plexus invasion is a common finding in CDBD (Bhuiya et al. 1992). Extrapancreatic neural plexuses were defined by the Japan Pancreas Society's Classification of Pancreatic Carcinoma (1966; Table 4).

Distant Metastases

Similar to other cholangiocarcinomas, CDBD produces distant metastases, sometimes late in the disease process and in a first round frequently to the liver and other visceral organs, including the stomach (Kim et al. 2009). Devic and Gallavardin (1901) already noted distant metastases in 20 % of patients. In an autopsy study on 65 patients, distant metastases were present in 75.4 % (Sons and Boerchard 1987). More patients with CDBD had liver metastases than patients with ampullary

Table 4 Classification of extrapancreatic neural plexuses (Japan Pancreas Society Classification of Pancreatic Carcinoma, 1996)

Celiac plexus (PL ce)
Superior mesenteric arterial plexus (PL sma)
Common hepatic arterial plexus (PL ch)
Plexus within the hepatoduodenal ligament (PL hdl)
Pancreatic head plexus I (PL ph I), which extends from the right celiac ganglion to the upper medial margin of the pancreas
Pancreatic head plexus II (PL ph II), which extends from the superior mesenteric artery to the medial margin of the uncinate process

adenocarcinoma (24 % vs. 10 %; Woo et al. 2007). Cholangiocarcinoma of the mid-common bile duct can produce umbilical metastasis, presenting as Sister Mary Joseph nodule (Agrawal et al. 2012). Extrahepatic cholangiocarcinomas can produce metastases to the ovary, sometimes with formation of Krukenberg tumors. Similar to other adenocarcinomas metastatic to the ovary, cholangiocarcinomas tend to undergo mucinous differentiation at the metastatic site and may even produce colloid carcinomas. In one study, mucinous epithelial differentiation was seen in 81 %, sometimes histologically resembling primary mucinous ovarian tumors (Young and Scully 1990; Young 2007; Khunamornpong et al. 2008).

Tumor Size

In inoperable distal tumors, tumor size was a significant variable associated with survival in univariate analysis (Kim et al. 2010). A threshold of 30 mm tumor diameter distinguished two survival profiles, tumors larger than 30 mm conferring about half the survival time in comparison with tumors smaller than 30 mm (Prat et al. 1998).

Perineural Invasion as a Risk Factor

Among 29 patients with CDBD-D, plexus invasion was detected in 27.6 %, mostly to the plexus pancreaticus capitalis (Kayahara et al. 1994). Overall, neural plexus invasion was more frequent in CDBD-D than in CDBD-M, and of eight patients with distal tumors, seven showed invasion of the superior pancreatic plexus (Kayahara et al. 1999). The presence of perineural invasion is a negative prognosticator (Murakami et al. 2007; Tan et al. 2013). Multivariate analysis indicated that perineural invasion was the only independent prognostic factor in one study (Shimizu et al. 2008).

Depth of Invasion

Among 147 patients with CDBD (49.7 % with T3 and 38.8 % with T4), most tumors had a depth invasion of 5 mm or more. Half of tumors had invaded to the duct 5–12 mm deep, and only 9.5 % had an invasion depth of less than 5 mm. It was found that depth of invasion was associated with worse outcome as tumor depth increased (Hong et al. 2009).

Pancreatic Invasion

Distal cholangiocarcinomas (CDBD-D) have a tendency to undergo invasive spread into the ampullary compartment and the pancreas. This mainly applies to those CDBD-D with a diffuse and/or sclerosing patterns and less so for papillary exophytic lesions. Pancreatic invasion was a significant prognostic factor in univariate analysis (Sakamoto et al. 2005). Among 20 patients with CDBD-D, ten showed pancreatic parenchymal invasion, and the frequency of lymph node metastasis in CDBD-D with pancreatic invasion was significantly greater than in CDBD-D without pancreatic invasion.

Vascular Invasion

Portal vein infiltration and lymph vessel invasion are strong predictors of outcome in patients with CDBD (Bahra et al. 2008).

Resection Margin

Univariate analyses revealed that a positive ductal and radial resection margin is a significant predictor of poor prognosis (Sakamoto et al. 2005; Murakami et al. 2007; Nomura et al. 2009; Lad and Kooby 2014). Multivariate analysis showed that negative resection margins are strong predictors for favorable prognosis (Bahra et al. 2008).

Lymph Node Metastasis

CDBDs (both CDBD-M and CDBD-D) have, similar to perihilar carcinomas, a tendency for locoregional lymph node metastasis (Kayahara

et al. 1993, 1999; Kiriyama et al. 2015). In a study of 42 patients, lymph node metastases were present in 60 % of patients, 42 % with pT2 tumors and 77 % with pT3 tumors. Also the total number of lymph node metastases was higher in pT3 lesions. All node-positive patients had involved nodes in the hepatoduodenal ligament or posterior pancreaticoduodenal region or both (Yoshida et al. 1999). In a previous study on 20 consecutive patients with carcinoma of the distal duct, lymph node metastases were detectable in 55 %, whereby posterior pancreaticoduodenal nodes were involved in 35 %, nodes around the hepatoduodenal ligament in 35 %, nodes around the common hepatic artery in 30 %, and para-aortic nodes in 25 %, in the latter mostly in the interaortocaval space (Yoshida et al. 1998a). In tumors with pancreatic invasion, metastases to nodes around the superior mesenteric artery (group 14) or around the aorta (group 16) were more frequent than in tumors without invasion of the pancreas (Yoshida et al. 1998b). In another study of 29 patients with CDBD-D, 68.9 % of patients had locoregional lymph node metastases and 37.9 % with involvement of the n3 group (Kayahara et al. 1994). In a systematic study of lymph flow in distal cholangiocarcinoma, lymph node numbers 12abp2 and 13a were important in lymphatic metastasis to superior mesenteric lymph node for distal bile duct cancer (Kayahara et al. 1993). A more recent study of 257 patients with extrahepatic bile duct adenocarcinoma found metastasis to regional lymph nodes in 34.6 %. The presence of nodal metastases was an independent prognostic factor of poor survival (Murakami et al. 2007; Ito et al. 2010). In a study comparing prognostic factors in patients with CDBD vs. ampullary carcinoma, only lymph node involvement was identified as a risk factor for recurrence of CDBD by multivariate analysis (Woo et al. 2007). Prognostically important lymph node factors were the number of involved nodes (Hong et al. 2005), common hepatic node metastasis, and para-aortic node metastasis (Nomura et al. 2009).

There is a difference in lymph node metastasis patterns between CDBD-M and CDBD-D lesions, however with variable findings in different investigations. Frequencies of nodal involvement were 57 % for CDBD-M and 71 % for CDBD-D. In a comparative study on 80 patients, the frequency of lymphnode spread of carcinomas in the proximal, middle, and distal parts of the large bile duct, excluding T1 tumors, was 48 %, 67 %, and 56 %, respectively. CDBD-D had a tendency to metastasize to nodes around the pancreatic head, while CDBD-M displayed a wide metastatic pattern, also including nodes around the mesenteric artery and the aorta (Kurosaki et al. 1996). The two topographic variants of CDBD also differ with respect to involvement of the resection margin, probably due to a difference in the growth pattern and differences in duct wall microcirculation. The tumor was present at the surgical margin in 50 % and 14 % of patients with mid-region carcinoma and distal carcinoma, respectively (Kayahara et al. 1999).

Histopathologic Type and Grade

The histologic grade is an important prognosticator affecting the prediction of overall survival (Kim et al. 2010). A papillary exophytic phenotype is associated with better outcome. In one study, papillary lesions were associated with a 50 % 22.3-month survival rate and a 31 % 5-year survival rate, as compared with a 50 % 9.8-month survival rate and an 8 % 5-year survival rate for well-differentiated non-papillary adenocarcinomas. The survival rates for poorly differentiated carcinomas were about the same as those of patients with well-differentiated tumors (Tompkins et al. 1981).

Other Prognostic Factors

A significant correlation was detected between a low proliferative activity as assessed through determination of the Ki-67/MIB-1 labeling index (less than 20 %) and survival (Rijken et al. 1998b). Low immunohistochemical expression of p53 (i.e., 0–30 %) is a favorable prognostic factor in patients with resectable CDBD (Rijken et al. 1999b), whereas overexpression of p53 in

CDBD was strongly associated with significantly reduced survival, independently of clinicopathologic prognostic factors (Cheng et al. 2007). p63 and p73 proteins were overexpressed in 26.3 % and 41.0 % of extrahepatic bile duct carcinomas. p63 expression was more frequent in tumors with vascular invasion and distal location, while p73 expression was more commonly found in carcinomas with deeper tumor invasion, and coexpression of both proteins was associated with a significantly worse overall survival (Hong et al. 2007). Epigenetic p16 hypermethylation may predict overall survival in curatively resected CDBD-M and CDBD-D (Park et al. 2013). Expression of the oncofetal protein insulin-like growth factor II mRNA-binding protein 3 (IMP3) was found in high-grade dysplasia of bile ducts, but not in low-grade dysplasia, and 58.3 % of bile duct carcinomas were strongly IMP3 positive. Cholangiocarcinoma IMP3 expression was associated with a higher proliferation rate and significantly reduced overall survival (Riener et al. 2009).

Differential Diagnosis

CDBD-M and CDBD-D can be mimicked by several neoplastic processes and reactive lesions that produce duct stenosis (Table 5).

Adenocarcinoma of the distal bile duct has to be distinguished from ampullary carcinoma and carcinoma of the pancreatic head infiltrating the distal-most part of the choledochus. Less common differential diagnoses include bile duct metastases of tumors outside the hepatobiliary tract and of hepatocellular carcinoma (Kim and Park 2012; Cha et al. 2013). Exophytically growing bile duct adenomas may radiologically be confounded with CDBD (Fletcher et al. 2004; Akaydin et al. 2009). Non-Hodgkin's lymphoma and Castleman's disease located to the duct wall have mimicked CDBD (Al-Salamah et al. 2005; Dote et al. 2009). Radiologically and histologically, adenomyoma may be confounded with well-differentiated cholangiocarcinoma (Läuffer et al. 1998; Ojima et al. 2000; Iwaki et al. 2008). Rare mesenchymal tumor of the common bile duct can simulate CDBD, including granular cell tumor, inflammatory myofibroblastic tumor, schwannoma, and leiomyoma (Jakobs et al. 2003; Goo et al. 2006; Martin Malagon et al. 2006; Tonsi et al. 2006). Neuroendocrine tumors primary to the common bile duct are rare lesions but can grow to relatively large size (Kim et al. 2006). Distal biliary stenosis due to bile duct stones can simulate CDBD (Plaza Santos et al. 2009). Heterotopic pancreas located to the bile duct wall can cause significant stenosis (Biswas et al. 2007). Tuberculosis of the common bile duct, pancreas, or periductal/peripancreatic lymph nodes can cause significant duct stenosis and obstructive jaundice (Chen et al. 1999; Colovic et al. 2008; Ray et al. 2012).

Table 5 Differential diagnosis of mid-duct and distal cholangiocarcinomas

Ampullary carcinoma
Carcinoma of the pancreatic head
Bile duct metastasis
Bile duct adenomas
Lymphomas of the bile duct
Adenomyoma of the bile duct
Mesenchymal tumors of the bile duct
Neuroendocrine tumors of the bile duct
Bile duct stones
Heterotopic pancreas
Tuberculosis of the common bile duct
Tuberculosis of the pancreas
Tuberculosis of periductal lymph nodes

Cytogenetic and Molecular Features

In CDBD, the most commonly lost chromosomal regions were, in decreasing order, 18q, 6q, 10p, 8p, 12q, 17p, 7q, 12p, and 22q. The most frequently gained regions were 8q, 20q, 12p, 17q, Xp, 2q, 6p, 7p, 11q, 13q, and 19q. These patterns resemble those found with pancreatic carcinoma (Rijken et al. 1999c). Flow cytometry and image cytometry investigations showed that 59 % of CDBDs were aneuploid (Rijken et al. 1999a). Among well-known oncogenes, K-ras codon 12 mutations are common in CDBD, but no prognostic values of these mutations could be

identified (Rijken et al. 1998a). In regard to molecular features, pertinent findings are summarized in the chapters on perihilar and intrahepatic cholangiocarcinomas.

References

Agrawal V, Garg PK, Mohanty D, Jaswal V (2012) Umbilical nodule in cholangiocarcinoma. Sister Mary Joseph Nodule. Saudi J Gastroenterol 18:345–346

Akayadin M, Ersoy YE, Erozgen F, Ferlengez E, Kaplan R, Celik A, Memmi N (2009) Tubulovillous adenoma in the common bile duct causing obstructive jaundice. Acta Gastroenterol Belg 72:450–454

Albores-Saavedra J, Delgado R, Henson DE (1999) Well-differentiated adenocarcinoma, gastric foveolar type, of the extrahepatic bile ducts: a previously unrecognized and distinctive morphologic variant of bile duct carcinoma. Ann Diagn Pathol 3:75–80

Albores-Saavedra J, Henson DE, Klimstra DS (eds) (2000a) Tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater. Armed Forces Institute of Pathology, Washington, DC

Albores-Saavedra J, Murakata L, Krueger JE, Henson DE (2000b) Noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts. Cancer 89:508–515

Albores-Saavedra J, Adsay NV, Crawford JM, Klimstra DS (2010) Carcinoma of the gallbladder and extrahepatic bile ducts. In: Bosman FT (ed) WHO classification of tumours of the digestive system. IARC, Lyon, pp 266–273

Albores-Saavedra J, Chablé-Montero F, Méndez-Sanchez N, Mercado MA, Vilatoba-Chapa M et al (2012) Adenocarcinoma with pyloric gland phenotype of the extrahepatic bile ducts: a previously unrecognized and distinctive morphologic variant of extrahepatic bile duct carcinoma. Hum Pathol 43:2292–2298

Albu S, Tantau M, Sparchez Z, Branda H, Suteu T, Badea R, Pascu O (2005) Diagnosis and treatment of extrahepatic cholangiocarcinoma: results in a series of 124 patients. Rom J Gastroenterol 14:33–36

Alden ME, Waterman FM, Topham AK, Barbot DJ, Shapiro MJ, Mohiuddin M (1995) Cholangiocarcinoma: clinical significance of tumor location along the extrahepatic bile duct. Radiology 197:511–516

Alexander F, Rossi RL, O'Bryan M, Khettry U, Braasch JW, Watkins E (1984) Biliary carcinoma. A review of 109 cases. Am J Surg 147:503–509

Allen PJ, Reiner AS, Gonen M, Klimstra DK, Blumgart LH, Brennan MF, D'Angelica M et al (2008) Extrahepatic cholangiocarcinoma: a comparison of patients with resected proximal and distal lesions. HPB (Oxford) 10:341–346

Alper E, Üstün Dao Y, Akca S, Arabul M, Buyrac Z, Baydar B (2011) The utility of radial endosonographic features in the diagnosis of cholangiocarcinoma arising from the distal common bile duct. Minerva Gastroenterol Dietol 57:434–435

Al-Salamah SM, Khan IA, Khalid K, Al-Shakweer WA (2005) Castleman disease presenting as obstructive jaundice. Saudi Med J 26:111–113

Anderson JB, Cooper MJ, Williamson RC (1985) Adenocarcinoma of the extrahepatic biliary tree. Ann R Coll Surg Engl 67:139–143

Aoki H, Kanazawa T, Fujiwara Y, Morihiro T, Takehara K, Seita M, Ohara T, Arata T, Nakagawa H, Tanakaya K et al (2012) A case of adenosquamous carcinoma of lower extrahepatic bile duct (in Japanese). Gan To Kagaku Ryoho 39:131–133

Arakura N, Hasebe O, Yokosawa S, Imai Y, Furuta S, Hosaka N (2003) A case of small cell carcinoma of the extrahepatic bile duct which could be diagnosed before operation (in Japanese). Nihon Shokakibyo Gakkai Zasshi 100:190–194

Bahra M, Langrehr JM, Neuhaus P (2006) Carcinoma of the distal bile duct (in German). Chirurg 77:335–340

Bahra M, Jacob D, Langrehr JM, Neumann UP, Neuhaus P (2008) Carcinoma of the distal and middle bile duct: surgical results, prognostic factors, and long-term follow-up. J Hepatobiliary Pancreat Surg 15:501–507

Bass G, O'Mahony CA, Smith R, Dennison MS, Goss JA (2010) Biliary epithelial metastasis of squamous carcinoma of the anus. Ir J Med Sci 179:605–606

Bhuiya MR, Nimura Y, Kamiya J, Kondo S, Fukata S, Hayakawa N, Shionoya S (1992) Clinicopathologic studies on perineural invasion of bile duct carcinoma. Ann Surg 215:344–349

Biswas A, Husain EA, Feakins RM, Abraham AT (2007) Heterotopic pancreas mimicking cholangiocarcinoma. Case report and literature review. JOP 8:28–34

Bortolasi L, Burgart LJ, Tsiotos CC, Luque-De Leon E, Sarr MG (2000) Adenocarcinoma of the distal bile duct. A clinicopathologic outcome analysis after curative resection. Dig Surg 17:36–41

Broomé U, Löfberg R, Veress B, Eriksson LS (1995) Primary sclerosing cholangitis and ulcerating colitis: evidence for increased neoplastic potential. Hepatology 22:1404–1408

Brown DB, Strang R, Gordon J, Hendry EB (1961) Primary carcinoma of the extrahepatic bile-ducts. Br J Surg 49:22–28

Burger RE, Meeker WR, Luckett PM (1978) Squamous cell carcinoma of the common bile duct. South Med J 71:216–219

Cha IH, Kim JN, Kim YS, Ryu SH, Moon JS, Lee HK (2013) Metastatic common bile duct cancer from pulmonary adenocarcinoma presenting as obstructive jaundice. Korean J Gastroenterol 61:50–53

Chao TC, Greager JA (1991) Carcinoma of the extrahepatic bile ducts. J Surg Oncol 46:145–150

Chen MF, Jan YY, Chen TC (1998) Clinical studies of mucin-producing cholangiocellular carcinoma: a study of 22 histopathology-proven cases. Ann Surg 227:63–69

Chen CH, Yang CC, Yeh YH, Yang JC, Chou DA (1999) Pancreatic tuberculosis with obstructive jaundice – a case report. Am J Gastroenterol 94:2534–2536

Cheney WF (1914) Diagnosis of cancer of the common duct. Arch Diagn 7:335–338

Cheng Q, Luo X, Zhang B, Jiang X, Yi B, Wu M (2007) Distal bile duct carcinoma: prognostic factors after curative surgery. A series of 112 cases. Ann Surg Oncol 14:1212–1219

Cho SB, Park SY, Joo YE (2009) Small cell carcinoma of extrahepatic bile duct presenting with hemobilia (in Korean). Korean J Gastroenterol 54:186–190

Colovic R, Grubor N, Jesic R, Micev M, Jovanovic T, Colovic N, Atkinson HD (2008) Tuberculous lymphadenitis as a cause of obstructive jaundice: a case report and literature review. World J Gastroenterol 14:3098–3100

Dancygier H, Rösch T, Lorenz R, Gössner W, Siewert JR, Classen M (1988) Preoperative staging of a distal common bile duct tumor by endoscopic ultrasound. Gastroenterology 95:219–222

Davis RI, Sloan JM, Hood JM, Maxwell P (1988) Carcinoma of the extrahepatic biliary tract: a clinicopathological and immunohistochemical study. Histopathology 12:623–631

DeOliveira ML, Cunningham SC, Cameron JL, Kamanagar F, Winter JM, Lillemoe KD et al (2007) Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 245:755–762

Devic G, Gallavardin L (1901) Etude sur le cancer primitif des canaux biliaires, cholédoque, hépatique et cystique. Rev Méd 21:557–575

Dick JC (1939) Carcinoma of the lower end of the bile duct. Br J Surg 26:756

Dickson PV, Behrman SW (2014) Distal cholangiocarcinoma. Surg Clin N Am 94:325–342

Dote H, Ohta K, Nishimura R, Teramoto N, Asagi A, Nadano S, Hamada M, Yoshida I, Kobatake T, Nozaki I et al (2009) Primary extranodal non-Hodgkin's lymphoma of the common bile duct manifesting as obstructive jaundice: report of a case. Surg Today 39:448–451

Dowaki S, Kijima H, Kashiwagi H, Tobita K, Ohtani Y, Sugio Y, Sekka T, Osamura RY et al (2003) Undifferentiated spindle and giant cell carcinoma of the common bile duct. Tokai J Exp Clin Med 28:127–130

Durand-Fardel M (1840) Recherches anat-path, sur la vésicule et les canaux biliaires. Arch gen de Med 8:167–171

Evander A, Fredlund P, Hoevels J, Ihse I, Bengmark S (1980) Evaluation of aggressive surgery for carcinoma of the extrahepatic bile ducts. Ann Surg 191:23–29

Ewing J (1919) Neoplastic diseases. Saunders, Philadelphia, p 1027

Ewing J (1928) Neoplastic diseases, 3rd edn. Saunders, Philadelphia, pp 698–701

Fatima S, Ahmad Z, Qureshi A, Minhas K, Pal I (2008) Minimally invasive papillary carcinoma of the extrahepatic bile ducts. J Coll Phys Surg Pak 18:649–651

Fleming KA, Boberg KM, Glaumann H, Bergquist A, Smith D, Clausen OP (2001) Biliary dysplasia as a marker of cholangiocarcinoma in primary sclerosing cholangitis. J Hepatol 34:360–365

Fletcher ND, Wise PE, Sharp KW (2004) Common bile duct papillary adenoma causing obstructive jaundice: case report and review of the literature. Am Surg 70:448–452

Fujikawa T, Tanaka A, Abe T, Yoshimoto H, Tokumitsu Y, Tada S, Matsumoto Y, Maekawa Y et al (2011) Undifferentiated carcinoma of the common bile duct with intraductal tumor thrombi: report of a case. Surg Today 41:579–584

Goo JC, Yi MY, Jeon WJ, Seo JC, Chae HB, Park SM, Youn SJ, Kim SH, Choi JW (2006) A case of leiomyoma in the common bile duct (in Korean). Korean J Gastroenterol 47:77–81

Gozzetti G, Principe A (1995) Primary carcinoma of the middle and distal third of the common bile duct, diagnosis, treatment and results (in Italian). Chir Ital 47:12–17

Gulsrud PO, Feinberg M, Koretz RL (1979) Rapid development of cirrhosis secondary to squamous cell carcinoma of the common bile duct. Dig Dis Sci 24:166–169

Haworth AC, Manley PN, Groll A, Pace R (1989) Bile duct carcinoma and biliary tract dysplasia in chronic ulcerative colitis. Arch Pathol Lab Med 113:434–436

Hayashi N, Yamaguchi Y, Ogawa M (1993) Concomitant adenosquamous carcinoma of the common bile duct and early adenocarcinoma of the gall-bladder. J Gastroenterol Hepatol 8:607–612

Henson DE, Albores-Saavedra J, Corle D (1992) Carcinoma of the extrahepatic bile ducts. Histologic types, stage of disease, and survival rates. Cancer 70:1498–1501

Heron DE, Stein DE, Eschelman DJ, Topham AK, Waterman FM, Rosato EL, Alden M et al (2003) Cholangiocarcinoma: the impact of tumor location and treatment strategy on outcome. Am J Clin Oncol 26:422–428

Hiraki M, Yakushiji H, Hashiguchi K, Harada S, Okada K, Goto Y, Ikeda H, Mori D et al (2007) Signet ring cell carcinoma of the lower bile duct with rapid growth: report of a case. Hepatogastroenterology 54:1922–1924

Hoang MP, Murakata LA, Katabi N, Henson DE, Albores-Saavedra J (2002) Invasive papillary carcinomas of the extrahepatic bile ducts: a clinicopathologic and immunohistochemical study of 13 cases. Mod Pathol 15:1251–1258

Hong SM, Cho H, Lee OJ, Ro JY (2005) The number of metastatic lymph nodes in extrahepatic bile duct carcinoma as a prognostic factor. Am J Surg Pathol 29:1177–1183

Hong SM, Cho H, Moskaluk CA, Yu E, Zaika AI (2007) p63 and p73 expression in extrahepatic bile duct carcinoma and their clinical significance. J Mol Histol 38:167–175

Hong SM, Pawlik TM, Cho H, Aggarwal B, Goggins M, Hruban RH, Anders RA (2009) Depth of tumor

invasion better predicts prognosis than the current American Joint Committee on cancer T classification for distal bile duct carcinoma. Surgery 146:250–257

Hosonuma K, Sato K, Honma M, Kashiwabara K, Takahashi H, Takagi H, Mori M (2008) Small-cell carcinoma of the extrahepatic bile duct: a case report and review of the literature. Hepatol Int 2:129–132

Hughes JH, Niemann TH (1996) Adenosquamous carcinoma of the bile duct: cytologic features of brush specimens from two cases. Diagn Cytopathol 15: 322–324

Igami T, Nagino M, Oda K, Nishio H, Ebata T, Yokoyama Y, Shimoyama Y (2009) Clinicopathologic study of cholangiocarcinoma with superficial spread. Ann Surg 249:296–302

Ito K, Ito H, Allen PJ, Gonen M, Klimstra D, D'Angelica MI, Fong Y, DeMatteo RP et al (2010) Adequate lymph node assessment for extrahepatic bile duct adenocarcinoma. Ann Surg 251:675–681

Ito Y, Kenmochi T, Egawa T, Hayashi S, Nagashima A, Kitagawa Y (2012) Diagnosis of distal cholangiocarcinoma after the removal of choledocholithiasis. Gastroenterol Res Pract 2012:396869

Ito Y, Kenmochi T, Egawa T, Hayashi S, Nagashima A, Kitagawa Y (2013) Clinicopathological features of early distal cholangiocarcinoma. Hepatogastroenterology 60:673–677

Iwahashi N, Hayakawa N, Yamamoto H, Maki A, Kawabata Y, Murayama A, Nimura Y et al (1998) Mucosal bile duct carcinoma with superficial spread. J Hepatobiliary Pancreat Surg 5:221–225

Iwaki K, Shibata K, Ohta M, Endo Y, Uchida H, Tominaga M, Okunaga R, Kai S, Kitano S (2008) Adenomyomatous hyperplasia of the common bile duct: report of a case. Surg Today 38:85–89

Jakobs R, Albert J, Schilling D, Nuesse T, Riemann JF (2003) Schwannoma of the common bile duct: a rare cause of obstructive jaundice. Endoscopy 35:695–697

Jarnagin WR, Shoup M (2004) Surgical management of cholangiocarcinoma. Semin Liver Dis 24:189–199

Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS, Youssef BA et al (2001) Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 234:507–517

Johnson SR, Kelly BS, Pennington LJ, Hanto DW (2001) A single experience with extrahepatic cholangiocarcinomas. Surgery 130:584–590

Kaiho T, Tanaka T, Tsuchiya S, Yanagisawa S, Takeuchi O, Miura M, Saigusa N, Hayasaka A et al (2005) A case of small cell carcinoma of the common bile duct. Hepatogastroenterology 52:363–367

Kayahara M, Nagakawa T, Ueno K, Ohta T, Kanno M, Nakano T, Mori K, Takeda T, Miyazaki I (1992) Surgical-management of carcinoma of the middle and distal bile-duct. Int J Oncol 1:319–323

Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I (1993) Lymphatic flow in carcinoma of the distal bile duct based on a clinicopathologic study. Cancer 72:2112–2117

Kayahara M, Nagakawa T, Tsukioka Y, Ohta T, Ueno K, Miyazaki I (1994) Neural invasion and nodal involvement in distal bile duct cancer. Hepatogastroenterology 41:190–194

Kayahara M, Nagakawa T, Ohta T, Kitagawa H, Tajima H, Miwa K (1999) Role of nodal involvement and the periductal soft-tissue margin in middle and distal bile duct cancer. Ann Surg 299:76–83

Khan SA, Toledano MB, Taylor-Robinson SD (2008) Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. HPB (Oxford) 10:77–82

Khunamornpong S, Lerwill MF, Siriaunkgul S, Suprasert P, Pojchamarnwiputh S, Chiangmai WN et al (2008) Carcinoma of extrahepatic bile ducts and gallbladder metastatic to the ovary: a report of 16 cases. Int J Gynecol Pathol 27:366–379

Kim YH (2003) Extrahepatic cholangiocarcinoma associated with clonorchiasis. CT evaluation. Abdom Imaging 28:68–71

Kim YC, Park MS (2012) Distal common bile duct metastasis from hepatocellular carcinoma. Hepatology 55:1638–1639

Kim DH, Song MH, Kim DH (2006) Malignant carcinoid tumor of the common bile duct: report of a case. Surg Today 36:485–489

Kim EM, Lee BS, Moon HS, Sung JK, Kim SH, Lee HY, Kang DY (2009a) Distal cholangiocarcinoma with gastric metastasis mimicking early gastric cancer. Gut Liver 3:222–225

Kim KW, Kim SH, Kim MA, Lee JM, Park HS, Kim JY, Lee JY, Han JK, Choi BI (2009b) Adenosquamous carcinoma of the extrahepatic bile duct: clinicopathologic and radiologic features. Abdom Imaging 34:217–224

Kim K, Chie EK, Jang JY, Kim SW, Oh DY, Im SA, Kim TY, Bang YJ, Ha SW (2010) Is duodenal invasion a relevant prognosticator in patients undergoing adjuvant chemoradiotherapy for distal common bile duct cancer? Int J Radiat Oncol Biol Phys 77:1186–1190

Kimoto E, Kuno N, Funakawa T (1996) Adenoacanthoma, adenosquamous carcinoma of the extrahepatic bile duct (in Japanese). Ryoikibetsu Shokogun Shirizu 9:47–49

Kiriyama M, Ebata T, Aoba T, Kaneoka Y, Arai T, Shimizu Y, Nagino M (2015) Prognostic impact of lymph node metastasis in distal cholangiocarcinoma. Br J Surg. doi:10.1002/bjs.9752

Kosar I, Ataseven H, Yönem O, Cakmak E, Özer O, Özer H, Topçu O (2010) A new variant of bile duct duplication with coexistence of distal cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 7:527–530

Kozuka S, Tsubone M, Hachisuka K (1984) Evolution of carcinoma in the extrahepatic bile ducts. Cancer 54:65–72

Kuraoka K, Taniyama K, Fujitaka T, Nakatsuka H, Nakayama H, Yasui W (2003) Small cell carcinoma of the extrahepatic bile duct: case report and immunohistochemical analysis. Pathol Int 53:887–891

Kurosaki I, Tsukada K, Hatakeyama K, Muto T (1996) The mode of lymphatic spread in carcinoma of the bile duct. Am J Surg 172:239–243

Kuwayti K, Baggenstoss AH, Staufer MH, Priestley JT (1957) Carcinoma of the major and the extrahepatic bile ducts exclusive of the papilla of Vater. Surg Gynecol Obstet 104:357–366

La Greca G, Conti P, Urrico GS, Catanuto G, Di Carlo I, Russello D, Latteri F (2004) Biliary squamous cell carcinoma. Chir Ital 56:289–295

Lad N, Kooby DA (2014) Distal cholangiocarcinoma. Surg Oncol Clin N Am 23:265–287

Laitio M (1983) Carcinoma of extrahepatic bile ducts. A histopathologic study. Pathol Res Pract 178:67–72

Lantsberg L, Khodadadi J, Goldstein J (1986) Adenosquamous carcinoma of the common bile duct: a case report. J Surg Oncol 33:140–142

Läuffer JM, Baer HU, Maurer CA, Fröhling S, Scheurer U, Zimmermann A, Büchler MW (1998) Adenomyoma of the distal common bile duct mimicking cholangiocarcinoma. Dig Dis Sci 43:1200–1204

Lee WE, Totten HP (1934) Primary carcinoma of the common bile-duct. Ann Surg 99:930–938

Lee JG, Leung JW, Baillie J, Layfield LJ, Cotton PB (1995) Benign, dysplastic, or malignant – making sense of endoscopic bile duct brush cytology: results in 149 consecutive patients. Am J Gastroenterol 90:722–726

Lee HG, Lee SH, Yoo DD, Paik KY, Heo JS, Choi SH, Choi DW (2009) Carcinoma of the middle bile duct: is bile duct segmental resection appropriate ? World J Gastroenterol 15:5966–5971

Lee EY, Kim C, Kim MJ, Park JY, Park SW, Song SY, Chung JB, Kim H, Bang S (2010a) Signet ring cell carcinoma of the extrahepatic bile duct. Gut Liver 4:402–406

Lee M, Banerjee S, Posner MC, Cartwright CA (2010b) Distal extrahepatic cholangiocarcinoma presenting as cholangitis. Dig Dis Sci 55:1852–1855

Levy M, Lin F, Xu H, Dhall D, Spaulding BO, Wang HL (2010) S100P, von Hippel-Lindau gene product, and IMP3 serve as a useful immunohistochemical panel in the diagnosis of adenocarcinoma on endoscopic bile duct biopsy. Hum Pathol 41:1210–1219

Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC (2010) Precancerous bile duct pathology in end-stage primary sclerosing cholangitis, with and without cholangiocarcinoma. Am J Surg Pathol 34:27–34

Lim SH, Yang HW, Kim A, Cha SW, Jung SH, Go H, Lee WC (2007) Adenosquamous carcinoma of extrahepatic bile duct: a case report. Korean J Intern Med 22:206–210

Lin CT, Hsu KF, Yu JC, Chu HC, Hsieh CB, Fu CY, Hong ZJ, Chan DC (2009) Choledochoduodenal fistula caused by cholangiocarcinoma of the distal common bile duct. Endoscopy 41(suppl 2):E319–E320

Lippman HN, McDonald LC, Longmire WP (1959) Carcinoma of the extrahepatic bile ducts. Am Surg 25:819–826

Longmire WP (1976) Tumors of the extrahepatic biliary radicals. Curr Probl Cancer 1:1–45

MacCallum WG (1919) Text-book on pathology. Saunders, Philadelphia, p 984

Martin Malagon A, Lopez-Tomassetti Fernandez E, Arteaga Gonzalez I, Carrilo Pallares A, Diaz Luis H (2006) Inflammatory myofibroblastic tumor of the distal bile duct associated with lymphoplasmacytic sclerosing pancreatitis. Case report and review of the literature. Pancreatology 6:145–154

Martin WF, Page GD (1951) Carcinoma of the extrahepatic bile duct; review of recent literature and a case report. South Med J 44:109–114

Martins EB, Fleming KA, Garrido MC, Hine KR, Chapman RW (1994) Superficial thrombophlebitis, dysplasia, and cholangiocarcinoma in primary sclerosing cholangitis. Gastroenterology 107:537–542

Matsumoto T, Inoue S, Masuo K, Okamoto Y, Fukushima M, Wada M, Shimeno N et al (2011) Signet ring cell carcinoma of the bile duct: a case report (in Japanese). Nihon Shokakibyo Gakkai Zasshi 108:2042–2049

Michelassi F, Erroi F, Dawson PJ, Pietrabissa A, Noda S, Handcock M, Block GE (1989) Experience with 647 consecutive tumors of the duodenum, ampulla, head of the pancreas, and distal common bile duct. Ann Surg 210:544–554

Miyashita T, Konishi K, Noto M (2001) A case of small cell carcinoma of the common bile duct (in Japanese). Nihon Shokakibyo Gakkai Zasshi 98:1195–1198

Mosconi S, Beretta GD, Labianca R, Zampino MG, Gatta G, Heinemann V (2009) Cholangiocarcinoma. Crit Rev Oncol Hematol 69:259–270

Moul AE, Bejarano PA, Casillas J, Levi JU, Garcia-Buitrago MT (2013) Mucoepidermoid carcinoma of the intrapancreatic common bile duct: immunohistochemical profile, prognosis, and review of the literature. Case Rep Pathol 2013:192458

Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T (2007a) Pancreatoduodenectomy for distal cholangiocarcinoma: prognostic impact of lymph node metastasis. Word J Surg 31:337–342

Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, Ohge H, Sueda T (2007b) Prognostic significance of lymph node metastasis and surgical margin status for distal cholangiocarcinoma. J Surg Oncol 95:207–212

Nagai E, Shinohara M, Yonemasu H, Kishikawa H, Tsuneyoshi M (2002) Undifferentiated carcinoma of the common bile duct: case report and review of the literature. J Hepatobiliary Pancreat Surg 9:627–631

Nakao A, Sakagami K, Uda M, Mitsuoka S (1997) Double cancers of the gallbladder and bile duct associated with anomalous choledochopancreatic duct junction. J Gastroenterol 32:110–113

Nakeeb A, Pitt HA, Shn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH, Lillemoe KD et al (1996) Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 224:463–473

Neibling HA, Dockerty MB, Waugh JM (1949) Carcinoma of the extrahepatic bile ducts. Surg Gynecol Obstet 89:429–438

Nishimura M, Naka S, Hanazawa K, Tani K, Fukami M, Okada S, Fjiyama Y (2005) Cholangiocarcinoma in the distal bile duct: a probable etiologic association with choledocholithiasis. Dig Dis Sci 50:2153–2158

Nomoto S, Nakao A (1996) Papillary extrahepatic bile duct carcinoma, invasive papillary extrahepatic bile duct carcinoma (in Japanese). Ryoikibetsu Shokogun Shirizu 9:88–91

Nomura T, Tsuchiya Y, Nashimoto A, Yabusaki H, Takii Y, Nakagawa S, Sato N, Kanbayashi C et al (2009) Prognostic factors for radical resection of middle and distal bile duct cancer. Hepatogastroenterology 56:294–298

Ogata S, Kimura A, Hatsuse K, Yamamoto J, Shimazaki H, Nakanishi K, Kawai T (2010) Poorly differentiated adenocarcinoma with signet-ring cell carcinoma of the extrahepatic bile duct in a 42-year-old Japanese female: a case report. Acta Med Okayama 64:63–65

Ogawa T, Horaguchi J, Noda Y, Kobayashi G, Ito K, Obana T, Takasawa O, Koshita S et al (2010) A case of distal bile duct cancer with extensive intraepithelial spread diagnosed preoperatively by peroral cholangioscopy combined with narrow band imaging. Nihon Shokakibyo Gakkai Zasshi 107:112–119

Oikawa H, Oka K, Nagakura S, Fukunaga M, Sando N, Kashimura J, Hakozaki H (2007) Spindle and giant cell type undifferentiated carcinoma arising in the common bile duct: a case report. Pathol Res Pract 203:179–184

Ojima H, Takenoshita S, Nagamachi Y (2000) Adenomyoma of the common bile duct: report of a case. Hepatogastroenterology 47:132–134

Okabayashi T, Kobayashi M, Nishimori I, Namikawa T, Okamoto K, Onishi S, Araki K (2005) Adenosquamous carcinoma of the extrahepatic biliary tract: clinicopathologic analysis of Japanese cases of this uncommon disease. J Gastroenterol 40:192–199

Park HW, Seo SH, Jang BK, Hwang JY, Park KS, Cho KB, Hwang JS, Ahn SH et al (2004) A case of primary small cell carcinoma in the common bile duct (in Korean). Korean J Gastroenterol 43:260–263

Park JS, Park YN, Lee KY, Kim JK, Yoon DS (2013) P16 hypermethylation predicts surgical outcome following curative resection of mid/distal bile duct cancer. Ann Surg Oncol . . ..

Patel T (2006) Cholangiocarcinoma. Nat Clin Pract 3:33–42

Permen LE, McCollum EB (1963) Primary carcinoma of the extrahepatic biliary ducts. Henry Ford Hosp Med Bul 11:167–183

Plaza Santos R, Burgos Garcia A, Gea Rodriguez F, Mora Sanz P, Rey Sanz R, Castro Carbajo P et al (2009) Distal biliary stenosis due to bile duct stones simulating cholangiocarcinoma (in Spanish). Gastroenterol Hepatol 32:666–667

Pomianowska E, Grzyb K, Westgaard A, Clausen OP, Gladhaug IP (2012) Reclassification of tumour origin in resected periampullary adenocarcinomas reveals underestimation of distal bile duct cancer. Eur J Surg Oncol 38:1043–1050

Prat F, Chapat O, Ducot B, Ponchon T, Fritsch J, Choury AD, Pelletier G, Buffet C (1998) Predictive factors for survival of patients with inoperable malignant distal biliary strictures: a practical management guideline. Gut 42:76–80

Ray S, Chatterjee S, Saha AK, Samanta S (2012) Obstructive jaundice due to tuberculosis of distal CBD and periampullary region mimickcholangiocarcinoma. Niger J Surg 18:17–18

Razumilava N, Gores GJ (2013) Classification, diagnosis, and management of cholangiocarcinoma. Clin Gastroenterol Hepatol 11:13–21

Renshaw K (1922) Malignant neoplasms of the extrahepatic biliary ducts. Ann Surg 76:205–221

Riener MO, Fritzsche FR, Clavien PA, Pestalozzi BC, Probst-Hensch N, Jochum W, Kristiansen G (2009) IMP3 expression in lesions of the biliary tract: a marker for high-grade dysplasia and an independent prognostic factor in bile duct carcinomas. Hum Pathol 40:1377–1383

Rijken AM, van Gulik TM, Polak MM, Sturm PD, Gouma DJ, Offerhaus GJ (1998a) Diagnostic and prognostic value of incidence of K-ras codon 12 mutations in resected distal bile duct carcinoma. J Surg Oncol 68:187–192

Rijken AM, Umezawa A, van Gulik TM, Bosma A, Polak MM, Offerhaus GJ, Obertop H, Gouma DJ (1998b) Prognostic value of cell proliferation (Ki-67 antigen) and nuclear DNA content in clinically resectable, distal bile duct carcinoma. Ann Surg Oncol 5:699–705

Rijken AM, Belien JA, van Gulik TM, Polak MM, Offerhaus GJ, Gouma DJ, Baak JP (1999a) DNA quantitation of distal bile duct carcinoma measured by image and flow cytometry. Anal Quant Cytol Histol 21:303–310

Rijken AM, Offerhaus GJ, Polak MM, Gouma DJ, van Gulik TM (1999b) p53 expression as a prognostic determinant in resected distal bile duct carcinoma. Eur J Surg Oncol 25:297–301

Rijken AM, Hu J, Perlman EJ, Morsberger LA, Long P, Kern SE, Hruban RH, Yeo CJ et al (1999c) Genomic alterations in distal bile duct carcinoma by comparative genomic hybridization and karyotype analysis. Genes Chromosom Cancer 26:185–191

Rodgers CM, Adams JT, Schwartz SI (1981) Carcinoma of the extrahepatic bile ducts. Surgery 90:596–601

Rokitansky C (1849) A manual of pathological anatomy, vol 2. Sydenham Society, London, p 147

Rolleston HD (1912) Diseases of the liver, gall-bladder and ducts. Macmillan, London, p 811

Sabanathan S, Hashimi H, Nicholson G, Edwards AS (1988) Primary oat cell carcinoma of the common bile duct. JR Coll Surg Edinb 33:285–286

Sakamoto Y, Kosuge T, Shimada K, Sano T, Ojima H, Yamamoto J, Yamasaki S, Takayama T (2005) Prognostic factors of surgical resection in middle and distal bile duct cancer: an analysis of 55 patients concerning

the significance of ductal and radial margins. Surgery 137:396–402
Sako K, Seitzinger GL, Garside E (1957) Carcinoma of the extrahepatic bile ducts; review of the literature and report of six cases. Surgery 41:416–437
Sano T, Kamiya J, Nagino M, Uesaka K, Oda K, Kanai M, Nimura Y (2003) Bile duct carcinoma arising in metaplastic biliary epithelium of the intestinal type: a case report. Hepatogastroenterology 50:1883–1885
Sato Y, Harada K, Sasaki M, Nakanuma Y (2013) Histological characteristics of biliary intraepithelial neoplasia-3 and intraepithelial spread of cholangiocarcinoma. Virchows Arch 462:421–427
Sherrill JG (1906) Cancer of the gall-bladder and ducts. Ann Surg 44:866–891
Schulte SJ, Baron RL, Teefey SA, Rohrmann CA, Freeny PC, Shuman WP, Foster MA (1990) CT of the extrahepatic bile ducts: wall thickness and contrast enhancement in normal and abnormal ducts. AJR Am J Roentgenol 154:79–85
Scudder CL, Richardson O (1908) IX. Primary carcinoma of the hepatic ducts: the report of a case with the autopsy. Ann Surg 47:728–729
Sewkani A, Kapoor S, Sharma S, Naik S, Juneja M, Jain A, Varshney S (2005) Squamous cell carcinoma of the distal common bile duct. JOP 6:162–165
Shaib Y, El-Serag HB (2004) The epidemiology of cholangiocarcinoma. Semin Liver Dis 24:115–125
Shapiro PF, Lifvendahl RA (1931) Tumors of the extrahepatic bile-ducts. Ann Surg 94:61–79
Shimizu Y, Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Miyazaki M (2008) The morbidity, mortality, and prognostic factors for ampullary carcinoma and distal cholangiocarcinoma. Hepatogastroenterology 55:699–703
Song BJ, Kwon JH, Kim JJ, Lee JW, Min SY, Lee KB, Jang JY, Ryu JK (2011) A case of primary mucoepidermoid carcinoma arising from the common bile duct (in Korean). Korean J Gastroenterol 57:319–322
Sons HU, Borchard F (1987) Carcinoma of the extrahepatic bile ducts: a postmortem study of 65 cases and review of the literature. J Surg Oncol 34:6–12
Springer E (1925) New growths involving the terminal bile and pancreatic ducts. Boston Med Surg J 192 (21):1035
Stewart HL, Lieber M, Morgan DR (1940) Carcinoma of the extrahepatic bile ducts. Arch Surg 41:662
Stutman LJ, Bozian RC (1960) Xanthomatous biliary cirrhosis secondary to carcinoma of the extrahepatic bile ducts. Ann Intern Med 52:229–234
Su WC, Chan KK, Lin XZ, Lin PW, Chow NH, Shin JS, Chen CY, Tsao CJ (1996) A clinical study of 130 patients with biliary tract cancers and periampullary tumors. Oncology 53:488–493
Takayashiki T, Miyasaki M, Kato A, Ito H, Nakagawa K, Ambiru S, Shimizu H, Furuya S et al (2002) Double cancer of gallbladder and bile duct associated with anomalous junction of the pancreaticobiliary ductal system. Hepatogastroenterology 49:109–112
Tan X, Xiao K, Liu W, Chang S, Zhang T, Tang H (2013) Prognostic factors of distal cholangiocarcinoma after curative surgery: a series of 84 cases. Hepatogastroenterology 60:1892–1895
Thomas D (1970) Carcinoma of the distal extrahepatic bile ducts: case report. Aust N Z J Surg 39:393–395
Thorsen MK, Quiroz F, Lawson TL, Smith DF, Foley WD, Stewart ET (1984) Primary biliary carcinoma: CT evaluation. Radiology 152:479–483
Tompkins RK, Thomas D, Wile A, Longmire WP (1981) Prognostic factors in bile duct carcinoma: analysis of 96 cases. Ann Surg 194:447–457
Tonsi A, Standish R, Desai C, Davidson BR (2006) Granular cell tumour of the bile duct mimicking distal cholangiocarcinoma: one case report and review of the literature. Minerva Chir 61:247–255
Ustundag Y, Bayraktar Y (2008) Cholangiocarcinoma: a compact review of the literature. World J Gastroenterol 14:6458–6466
van der Wal AC, Van Leeuwen DJ, Walford N (1990) Small cell neuroendocrine (oat cell) tumour of the common bile duct. Histopathology 16:398–400
Veillette G, Castillo CF (2008) Distal biliary malignancy. Surg Clin N Am 88:1429–1447
Viana Miguel MM, Garcia-Plata Polo E, Vidal Doce O, Aldea Martinez J, de la Plaza Galindo M et al (2006) Oat cell carcinoma of the common bile duct (in Spanish). Cir Esp 80:43–45
Wahl HR (1924) Carcinoma of the biliary tract. Med Clin N Am 7:1331–1356
Washington MK, Berlin J, Branton PA, Burgart LJ, Carter DK, Compton CC, Fitzgibbons PL et al (2010) Protocol for the examination of specimens from patients with carcinoma of the distal extrahepatic bile ducts. Arch Pathol Lab Med 134:e8–e13
White RJ (1959) Carcinoma of the larger bile ducts exclusive of the papilla of Vater; report of five personal cases. Ann Surg 149:762–772
Woo SM, Ryu JK, Lee SH, Yoo JW, Park JK, Kim YT, Jang JY, Kim SW, Kang GH et al (2007) Recurrence and prognostic factors of ampullary carcinoma after radical resection: comparison with distal extrahepatic cholangiocarcinoma. Ann Surg Oncol 14:3195–3210
Yang HJ, Kim JH, Chun JY, Kim SJ, Lee SH, Kim H, Hwang JH (2012) A case of adenocarcinoma in situ of the distal common bile duct diagnosed by percutaneous transhepatic cholangioscopy. Korean J Intern Med 27:211–215
Yoshida T, Aramaki M, Bandoh T, Kawano K, Sasaki A, Matsumoto T, Morii Y, Kitano S (1998a) Para-aortic lymph node metastasis in carcinoma of the distal bile duct. Hepatogastroenterology 45:2388–2391
Yoshida T, Aramaki M, Matsumoto T, Morii Y, Sasaki A, Kitano S (1998b) The pattern of lymphatic spread in carcinoma of the distal bile duct. Int Surg 83:124–127
Yoshida T, Shibata K, Yokoyama H, Morii Y, Matsumoto T, Sasaki A, Kitano S (1999) Patterns of lymph node metastasis in carcinoma of the distal bile duct. Hepatogastroenterology 46:1595–1598

Young RH (2007) From Krukenberg to today: the ever present problems posed by metastatic tumors in the ovary. Part II. Adv Anat Pathol 14:149–177

Young RH, Scully RE (1990) Ovarian metastases from carcinoma of the gallbladder and extrahepatic bile ducts simulating primary tumors of the ovary. A report of six cases. Int J Gynecol Pathol 9:60–72

Zerbi A, Balzano G, Leone BE, Angeli E, Veronesi P, Di Carlo V (1998) Clinical presentation, diagnosis and survival of resected distal bile duct cancer. Dig Surg 15:410–416

Ziegler E (1898) A text-book of special pathological anatomy. Macmillan, London, p 754, sections IX-XV

Intrahepatic Cholangiocarcinomas (ICCs)

29

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_29

Abstract

Intrahepatic cholangiocarcinoma (ICC) is a cholangiocellular malignancy arising in any portion of the intrahepatic biliary tract. ICC can develop from small bile ducts and then occupies a peripheral compartment of the liver, but it also occurs in perihilar intrahepatic ducts and has to be distinguished from perihilar/hilar carcinoma of extrahepatic ducts. Overall, ICC is a rare neoplasm that accounts for less than 2 % of all malignant solid tumors. In relation to bile ducts involved, ICC is classified as a bile duct type (conventional type), further subdivided into a small bile duct type (peripheral type) and a large bile duct type (perihilar type), and a bile ductular type (bile ductular carcinoma or cholangiolocellular carcinoma). Several systems of pathomorphological classification of ICC have been proposed. The most commonly used system of the Japanese Liver Cancer Study Group distinguished mass-forming ICC, periductal-infiltrating ICC, and intraductal growth ICC. In the setting of the novel category of intraductal papillary neoplasm of the bile duct (IPN-B), treated in a separate chapter, most cases of intraductal growth ICC can now be considered to be invasive forms of IPN-B.

ICD-O Codes:

Intrahepatic cholangiocarcinoma 8160/3

Intraductal papillary neoplasm with:

Low-or intermediate-grade intraepithelial neoplasia 8503/0

High-grade intraepithelial neoplasia 8503/2

An associated invasive carcinoma 8503/3

Biliary intraepithelial neoplasia grade 3 (BilIN-3) 8148/2

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a carcinoma with biliary epithelial differentiation that arises in any portion of the intrahepatic biliary tract (The Liver Cancer Study Group of Japan 1990; Chen 1999; Nakanuma et al. 2010). ICC can arise from cholangiocytes of segmental and areal bile ducts and their major branches to the smallest bile ducts and ductules, but different portions of the biliary system with their distinct cholangiocyte populations have an impact on the morphology of ICC. ICCs can originate from small bile ducts that are situated in the peripheral or mantle zone of the liver, but also from intrahepatic bile ducts that are close to the hilar area of the liver. ICCs originating from small intrahepatic ducts have been termed peripheral ICC, but this term should no longer be employed (Nakanuma et al. 2010). Perihilar ICC is defined as a tumor that arises from the large ducts that converge at the liver hilus. Such neoplasms may be difficult to distinguish from hilar cholangiocarcinoma or Klatskin tumor, which develops in the right or left hepatic duct or in the confluence region, particularly in situations of advanced stage. Careful anatomic preparation of resection specimens together with a consultation of CT and MR images is required to figure out which of the two tumor groups are involved.

Many ICCs harbor a population of mucin-producing cells and may originate from medium-sized to large ducts which normally have mucin-producing cylindrical cells. On the other extreme is cholangiolocellular carcinoma composed of non-mucin-producing and rather small cells, similar to those found in hepatic ductules. Between these two polar forms are various cancers that hold an intermediate position in regard to cell morphology and differentiation. The histologic phenotype of ICCs is also markedly influenced by the type of growth pattern of these carcinomas. Generally, mass-forming ICCs that grow within the liver substance predominantly show a tubular-to-solid morphology associated with desmoplasia, while ICCs growing within the lumina of bile ducts tend to produce papillary structures, a phenomenon also found in cancers of extrahepatic bile ducts. Finally, part of intrahepatic carcinomas exhibit a differentiation along a hepatocyte lineage, resulting in various types of combined cholangio-hepatocellular carcinomas.

Selected References (Carter and Smiley 1950; Goldenberg 1953; Thorbjarnarson 1959; Okuda et al. 1977; Schlinkert et al. 1992; Parkin et al. 1993; Colombari and Tsui 1995; Nakeeb et al. 1996; Thuluvath et al. 1997; Ahrendt et al. 2001; Ishak et al. 2001; Khan et al. 2005, 2008 Malhi and Gores 2006; Slattery and Sahani 2006; Gore and Shelhamer 2007; Blechacz and Gores 2008; Van Beers 2008; Yang and Yan 2008; Braconi and Patel 2010; Cardinale et al. 2010; de Martel et al. 2010; Gatto and Alvaro 2010; Blechacz et al. 2011; Vasilieva et al. 2012; Rizvi and Gores 2013).

Epidemiology

Cholangiocarcinoma as a whole is a rather uncommon malignancy that accounts for less than 2 % of all human malignant solid neoplasms, but is the second most frequent malignant intrahepatic primary liver tumor. It is estimated that about 5–15 % of primary liver cancers are ICCs (Craigh et al. 1989; Patel 2001; Okuda et al. 2002; Patel 2006; Cardinale et al. 2010), with certain geographical differences linked to the frequency of distinct risk factors, such as hepatolithiasis and liver flukes occurring in southeastern and eastern Asia. There are an estimated 2500 cases annually in the USA (a low-risk region), with 0.32–0.85 cases per 100,000 and a higher incidence in individuals of African descent. In comparison, 88 male cases per 100,000 were detected in one place in Thailand, a high-risk area due to a high frequency of liver fluke infestation. Several studies have shown that incidence and mortality of ICC are rising worldwide, whereas the incidence of extrahepatic cholangiocarcinoma (ECC) seems to decrease (Patel 2001; Khan et al. 2002, 2012; Shaib and El-Serag 2004; Shaib et al. 2005; Lazarides and Gores 2005; Singh and Patel 2006; Endo et al. 2008; Cardinale et al. 2010).

In the USA, the age-adjusted incidence rates of ICC increased by 165 % from 0.32 per 100,000 in 1975–1979 to 0.85 per 100,000 in 1995–1999 (Shaib and El-Serag 2004). This phenomenon may, at least in part, due to a potential role of chronic viral hepatitis, with or without liver cirrhosis, in the pathogenesis of ICC (Kobayashi et al. 2000; Khan et al. 2002; Hui et al. 2003; Shaib et al. 2005). In Europe, the mortality from ICC increased by around 9 % in both sexes from 1990 to 2008, reaching rates of 1.1/100,000 men and 0.75/100,000 women, the highest rates being in the UK, Germany, and France (Bertuccio et al. 2013). It was recently suggested that, in contrast to former views, cholangiocarcinoma is not uncommon in patients with hepatic cirrhosis (Lazarides and Gores 2005). When comparing 272 patients with ICC and 5829 patients with HCC, patients with ICC were more often elderly and had a lower proportion of asymptomatic tumors, less small tumors, or encapsulated tumors and a higher proportion of single tumors (Zhou et al. 2009). However, ICC also occurs in young patients, in part patients with preexisting congenital or acquired disorders of the biliary tract. Chinese ICC patients younger than 40 years had distinct features compared with older patients, including a low frequency of hepatolithiasis, a high positive rate of serum HBsAg and HBV-associated cirrhosis, a high frequency of elevated serum AFP, and often signs of hepatic inflammation (Zhou et al. 2010).

Clinical Features

At presentation, the most common symptoms and signs in patients with ICC comprise abdominal pain, malaise, weight loss, and hepatomegaly (Schlinkert et al. 1992; Kubo et al. 1995; Chu et al. 1997; Blechacz et al. 2011). In a series of 429 ICCs, upper abdominal discomfort or pain was recorded in 65 % of patients, but 12.1 % of patients were asymptomatic at diagnosis (Shen et al. 2009). Up to about 60 % of patients display elevated serum Ca 19-9, while CEA is detected in serum much less commonly. Some patients with ICC are seropositive for lectin-reactive alpha-fetoprotein/AFP. These patients showed a higher positivity rate for hepatitis viruses and more commonly chronic liver disease than those without

AFP positivity (Okuda et al. 2006). Most patients with ICC suffer from cholelithiasis, however, with varying prevalences in different geographical regions (Kaczynski et al. 1998). A complication of ICC is spontaneous tumor rupture, which may be followed by hemoperitoneum (Akatsu et al. 2005; Chong et al. 2006). In contrast to hepatocellular carcinoma, where spontaneous rupture is a rather common event, this complication is rarer in cholangiocarcinomas, probably due to a higher stroma content in cholangiocarcinoma increasing firmness and cohesion of tumor components. Rarely, ICC was associated with, or caused, Budd-Chiari syndrome (Kwon et al. 2007). Obstruction of local lymphatics in the course of carcinomatous lymphangiosis can result in lymph stasis and eventually chylous ascites (Yamamoto et al. 2004).

ICC can induce paraneoplastic syndromes. Few examples of ICC synthesizing granulocyte and granulocyte-macrophage colony-stimulating factor have been described (Kakinoki et al. 2000; Sasaki et al. 2003; Sohda et al. 2006; Takenaka et al. 2013). ICC producing granulocyte colony-stimulating factor can induce Sweet's syndrome (Shinojima et al. 2006). Another hormone that is sometimes secreted by cholangiocarcinomas is parathyroid hormone-related peptide, this production being associated with hypercalcemia (Audran et al. 1982; Davis et al. 1994; Yamada et al. 2000, 2009; Yen et al. 2004). ICC can produce more than one paraneoplastic factor at the same time, e.g., granulocyte colony-stimulating factor and parathyroid hormone-related peptide (Sohda et al. 2006). Paraneoplastic hypercalcemia induced by cholangiocarcinoma can be a lethal complication (Trikudanathan and Dasanu 2010). Very rarely, ICC was found to produce human chorionic gonadotropin/HCG (Izumi et al. 1986). Other paraneoplastic syndromes associated with cholangiocarcinoma include alopecia (Antoniou et al. 2012), disseminated porokeratosis (Torres et al. 2010), necrolytic migratory erythema (pseudoglucagonoma syndrome; Chiyomaru et al. 2010), paraneoplastic acrokeratosis of Bazex (Karabulut et al. 2006), and acanthosis nigricans (Ravnborg and Thomsen 1993).

Classifications of Intrahepatic Cholangiocarcinoma

Basic Classification: Perihilar Versus Peripheral Intrahepatic Cholangiocarcinomas

As outlined in more detail in the chapter on hilar/perihilar cholangiocarcinoma, classifications of cholangiocarcinomas are currently in a phase of redefinition, because past terminologies have led to some confusion. There is now strong evidence that both hilar carcinoma (Klatskin tumors) and ICC can involve bile ducts located in the "perihilar" region, rendering the distinction between ICCs situated close to the hilum and hilar carcinomas difficult in some cases. A current classification of ICC is based on the duct types involved. It basically distinguishes ICC derived from large (perihilar) and small (peripheral) bile ducts and tumors originating from bile ductules. Tumors developing from large perihilar ducts are termed large duct-type ICC or perihilar large duct type, and those originating from small peripheral ducts are called peripheral-type ICC or peripheral small duct type (Table 1; Nakanuma et al. 2008, 2010; Nakanuma 2012; Yeh et al. 2013; Aishima and Oda 2014).

Macroscopic Growth Patterns of Intrahepatic Cholangiocarcinoma

Several systems of pathomorphological classification of ICC have been proposed (Table 2; reviews: Yamaski 2003; Cardinale et al. 2013; Sanada et al. 2014). According to the classification approaches of the Liver Cancer Study Group of Japan, ICC was classified into three types based

Table 1 Basic classification of ICC in relation to bile ducts involved (Nakanuma et al. 2008, 2010; Aishima and Oda 2014)

Bile duct type (conventional type)
Small bile duct type (peripheral type)
Large bile duct type (perihilar type)
Bile ductular type (bile ductular carcinoma)

Table 2 Morphological classifications of intrahepatic cholangiocarcinoma

System of the LCSG of Japan
Mass-forming ICC (MF-ICC)
Periductal-infiltrating ICC (PI-ICC)
Intraductal growth ICC (IG-ICC)
Ohashi system (1994)
Mass-forming ICC
Periductal extension ICC
Spicula-forming ICC
Variant growth patterns
ICC with superficially spreading growth patterns
Minute nodular ICC
Vascularization patterns
Hypovascular (ordinary) ICC
Hypervascular ICC

on the macroscopic appearance of cut surfaces of tumors, i.e., mass-forming ICC/MF-ICC, periductal-infiltrating ICC/PI-ICC, and intraductal growth ICC/IG-ICC (Liver Cancer Study Group of Japan 1997; review: Yamasaki 2003). The morphology of these three phenotypes is presented in more detail in a later paragraph.

MF-ICC produces an apparent mass lesion in the liver and often shows remnant hepatic recurrence. Some MF-ICCs occasionally show invasion of the biliary tract with segmental bile duct stenosis or an intraluminal growth resembling icteric-type HCC (Sano et al. 1996). PI-ICC causes obstruction or stricture of intrahepatic bile ducts/with spread along Glisson's sheath but without formation of large mass. This form of ICC is usually detected by ultrasonography due to the development of peripheral biliary dilatations. IG-ICC exhibits papillary projections into ductal lumina (Yamamoto et al. 1993). This classification has been discussed and further worked out in several studies (Sano et al. 1999; Lim 2003; Yamasaki 2003). Ohashi and coworkers divided ICCs into three categories, mass-forming ICC, periductal extension ICC, and spicula-forming ICC (Ohashi et al. 1994). Based on distinct invasion patterns, Aishima and coworkers (2007) divided ICC according to their origin from different levels of the bile duct system. The hilar type of ICC (H-ICC) is derived from large bile ducts close to the liver hilus, while the peripheral type of ICC (P-HCC) originates from smaller intrahepatic ducts situated in the mantle zone of the liver. In one study, H-ICC and P-HCC differed markedly in their behavior and in the biology of disease, H-ICC representing a high-risk group. The frequency of perineural invasion, lymph node metastasis, and extrahepatic recurrence was higher in H-ICC than in P-ICC, and prognosis was poorer in H-ICC. H-ICC showed large duct involvement within the tumor, and in cases of large tumor size, intraductal spread was present in the tumor periphery (Aishima et al. 2007). Nakanuma and coworkers (2008, 2010) have proposed a novel pathological classification (see below) that incorporates the new status of IG-ICC as intraductal neoplasm-type lesions. In another analysis, clinicopathological features were almost similar between patients with peripheral versus hilar ICC (Murakami et al. 2012).

Based on the vascularization pattern found at imaging, ICCs were divided into hypovascular (ordinary) versus hypervascular tumors (Yoshida et al. 1999). On gadolinium-enhanced MR images, hypervascular ICC showed complete or near-complete arterial enhancement and washout on delayed phases (Kim et al. 2012). In particular, ICCs in liver cirrhosis are hypervascular in comparison with those in normal livers (Xu et al. 2012). This classification is relevant insofar as the prognosis of hypervascular cholangiocarcinoma (h-CCC) is reportedly better than that of ordinary hypovascular CCC (o-CCC). h-CCCs show a high angiogenic activity and a high expression of stem cells and probably represent an early stage of tumor development (Sato et al. 2013a).

Molecular Classifications

The advent of molecular signatures that characterize distinct phenotypes of cholangiocarcinomas leads to refined stratification of these neoplasms and to molecular classifications. By the use of gene expression profiles, high-density single-nucleotide polymorphism arrays, and mutational analyses, two main biological classes of ICC have been identified (Sia et al. 2013). One class, the

inflammation class (38 % of ICC), was characterized by activation of inflammatory signaling pathways, overexpression of cytokines, and STST3 activation. The second class, the proliferation class (62 % of ICC), was characterized by activation of oncogenic signaling pathways (RAS, MAPK, and MET), DNA amplifications at 11q13.2, deletions at 14q22.1, mutations in KRAS and BRAF, and gene expression signatures previously associated with poor outcomes for patients with hepatocellular carcinoma. The proliferation class was associated with worse outcome (Sia et al. 2013).

General Macroscopic Features

ICCs present with three major characteristic macroscopic patterns which separate these tumors from other hepatic malignancies (Table 2; Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10). These three forms (mass-forming, periductal-infiltrating, and intraductal growth ICCs) are discussed in more detail below. The striking differences between ICC and other primary liver tumors necessitate a specific approach when analyzing surgery and autopsy specimens. The examination of these tumors has been standardized in a protocol developed under the auspices of the College of American Pathologists (Washington et al. 2010). Specimen examinations to identify these features have been standardized (Washington et al. 2010).

ICC grows in one of several growth patterns that had led to macroscopic classifications of this tumor type by Japanese investigators. The Liver Cancer Study Group of Japan (1990) proposed a new classification based on the macroscopic appearance of ICC, i.e., the mass-forming (MF, mass-forming extraductal ICC) type, the periductal-infiltrating (PI) type, the intraductal growth (IG) type, and a mixed type having more than one of the three basic types, as already outlined above and discussed in more detail below. Macroscopically, the dominant mass-forming variant of ICC usually presents as a localized, more or less spherical tumor mass with a distinct border (Craigh et al. 1989), but more

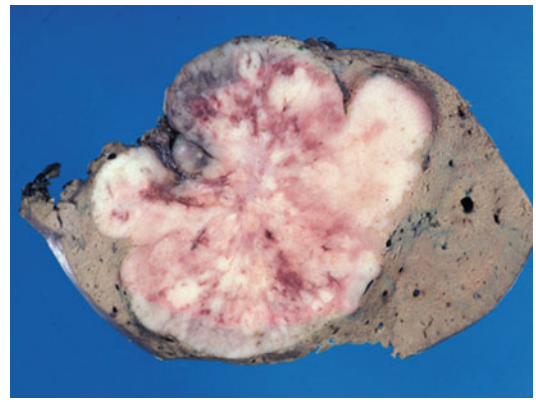

Fig. 1 Mass-forming intrahepatic cholangiocarcinoma (cut surface). The tumor reaches very close to the resection margin

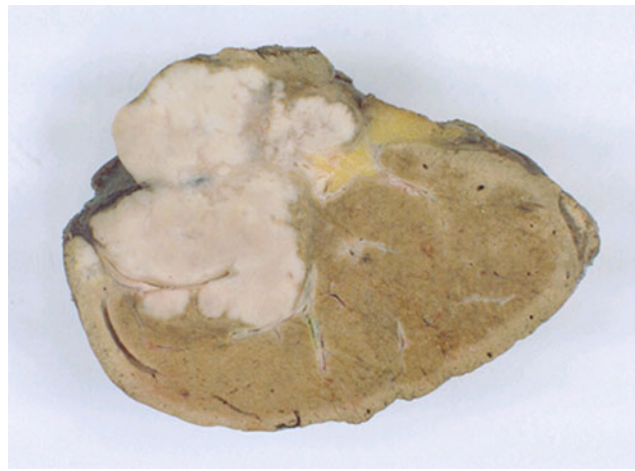

Fig. 2 Cut surface of a mass-forming intrahepatic cholangiocarcinoma with outgrowths and satellite lesions. The tumor starts to invade the adipose tissue at the base of the round hepatic ligament

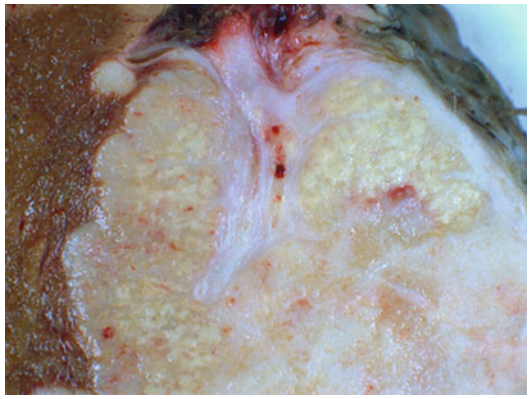

Fig. 3 Intrahepatic cholangiocarcinoma, periductal-infiltrating type

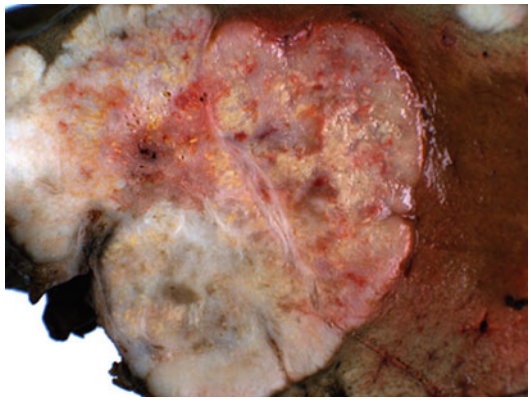

Fig. 4 Intrahepatic cholangiocarcinoma in a perihilar position. This tumor shows numerous necroses and hemorrhages

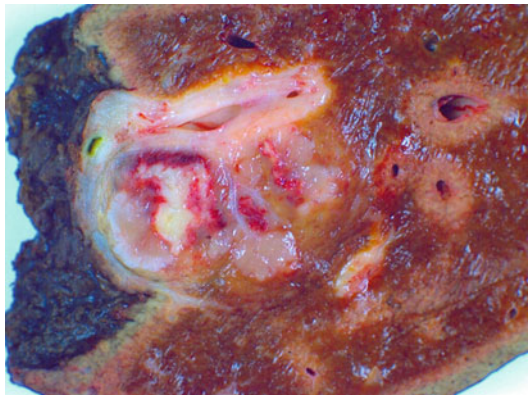

Fig. 5 Intrahepatic cholangiocarcinoma, intraductal type

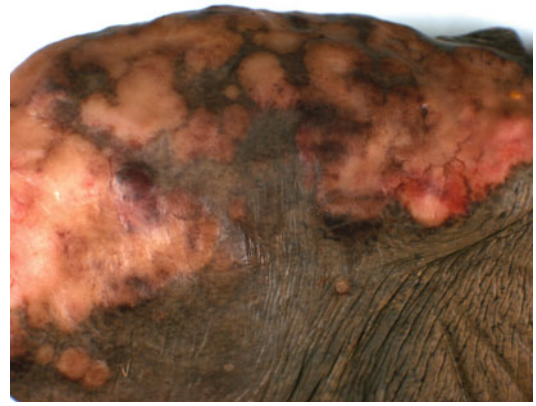

Fig. 6 Intrahepatic cholangiocarcinoma with multinodular subcapsular manifestations and tumor satellites

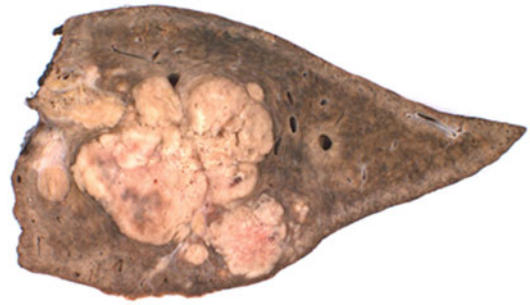

Fig. 7 Intrahepatic cholangiocarcinoma, indeterminate type

complex forms also occur, including clusters of nodules or a wedge-shaped form (Wachsberg et al. 1996). At a molecular level, the three patterns of conventional or bile duct-type ICCs are similar to hilar cholangiocarcinoma (Liau et al. 2014). The three main growth patterns of ICC have an impact on tumor biology and the efficacy of hepatic resection (Guglielmi et al. 2009; Yeh et al. 2012). ICC of the various subtypes can undergo secondary changes, including cyst formation (Kokubo et al. 1990) or even multicystic change (Fujii et al. 2005).

In addition to these three major forms, few other macroscopic growth patterns have been recognized. ICC can present as minute nodular lesions defined as lesions with a diameter less than 3 cm in the greatest dimension. In a series of 50 ICCs, six tumors with this morphology were

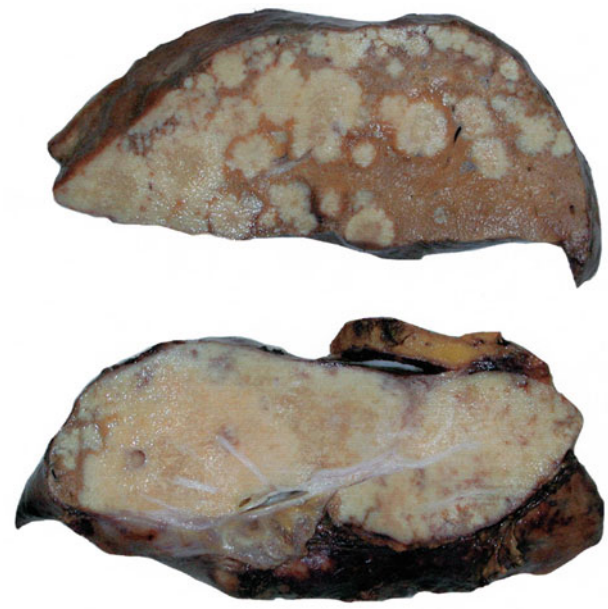

Fig. 8 Intrahepatic cholangiocarcinoma. The primary tumor (mass-forming type, *lower figure*) has led to numerous intrahepatic metastases (*upper figure*)

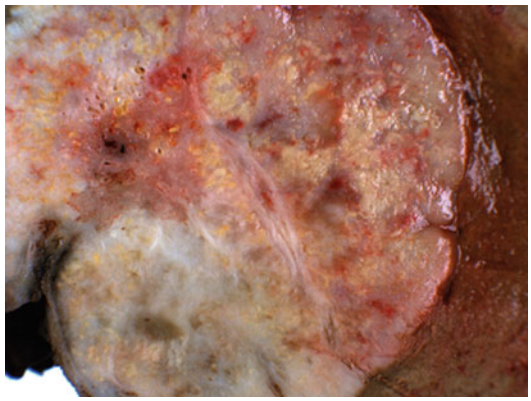

Fig. 9 Intrahepatic cholangiocarcinoma, mass-forming type, with numerous yellow necrotic foci and fresh hemorrhage

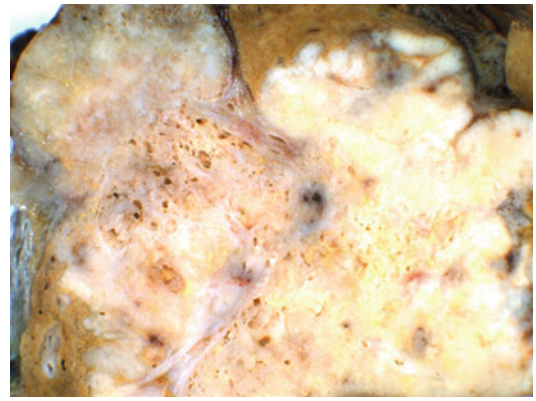

Fig. 10 Intrahepatic cholangiocarcinoma with extensive necrosis and formation of microcysts

detected, with a diameter ranging from 0.7 to 2.3 cm. The nodules were firm and had a gray to tan color and histologically showed desmoplasia. The average age of the patients was 57 years, with a male preponderance. Preoperatively, all these tumors except one were hypervascular on angiography or contrast-enhanced CT. Interestingly, these neoplasms are frequently associated with HCV infection and have a favorable biology of disease (Yamamoto et al. 1998). Very rarely, ICC can show a diffuse growth pattern, associated with extensive portal thrombi and acute hepatic failure (Uchida et al. 1998). Similar to hepatocellular carcinoma, ICC can present as an intrabile duct tumor, associated with obstructive jaundice and cholangitis. Macroscopically, a round tumor with a smooth surface was found to protrude into bile duct lumina, sometimes extending into the common bile duct (Sano et al. 1996; Yamamoto et al. 1997, 2009; Hai et al. 2005). It was shown that the intraductal growth (IG) type of ICC, and

also MF plus IG-ICC, had a better prognosis than other types of ICC (Yamamoto et al. 2009). The IG phenotype should not be confounded with intraductal growth ICC. In rare situations, invasion of the intrahepatic bile duct system is followed by detachment of tumor fragments, with free-floating tumor emboli causing intermittent obstructive jaundice (Capizzi et al. 1992).

Special Pathology of the Main ICC Types

Mass-Forming Intrahepatic Cholangiocarcinoma (MF-ICC)

MF tumors form the most frequently encountered type in a clinical setting and are grossly characterized as roughly spherical or potato-shaped masses with a distinct and sometimes slightly lobulated border. Irrespective of hilar invasion, MF lesions essentially show a macroscopically expansive growth pattern with formation of circumscribed masses without stellate extensions (Sano et al. 1999). MF-ICC can macroscopically closely mimic colorectal carcinoma metastasis, but look different from most hepatocellular carcinomas. Irrespective of their expanding growth pattern, MF-ICCs have marked tendency to invade adjacent structures. MF-ICC can grow along the surface of bile ducts and extend into the extrahepatic bile ducts (Regimbeau et al. 2003). Part of MF-ICCs show histologic bile duct invasion associated with segmental bile duct stenosis or an intraluminal growth resembling that of so-called icteric HCC (Kojiro et al. 1982; Sano et al. 1996). This invasion pattern was diagnosed in 26/41 patients with MF-ICC, and the presence of ductal invasion was correlated with an increased frequency of perineural invasion, lymphatic invasion, and a positive resection margin and lower survival rates, suggesting a more aggressive phenotype (Hirohashi et al. 2002a). Patients with this feature more often exhibited perineural invasion, lymphatic invasion, and a positive resection margin (Hirohashi et al. 2002a), suggesting a more aggressive phenotype among MF-ICC. There is a correlation between tumor size and spread, in that tumors with a diameter greater than 45 mm more often show invasion of portal and hepatic veins and more frequently exhibit invasion of lymphatics and perineural spaces (Sasaki et al. 2004). Some MF-ICCs develop intratumoral calcification (Kitade et al. 2005), but significant mineralizations are not a common feature of this tumor. Extraductal MF-ICCs were further subdivided into three categories. Type I lesions were those without biliary stricture; type II those with biliary stricture, but without jaundice; and type III those with biliary stricture with jaundice. Tumors without biliary stricture behaved more like hepatocellular carcinoma, while those with biliary stricture behaved more like hilar or extrahepatic cholangiocarcinomas (Yamanaka et al. 1995). Small ICCs of the MF subtype (diameter 3 cm or less) exhibit morphologic features different from larger lesions. In one series, small tumors did not show vascular or lymphatic invasion or perineural invasion, in resection specimens, and no patient had intrahepatic metastasis or lymph node metastasis (Kubo et al. 2004), suggesting that small and in particular peripheral MF lesions form a favorable risk group.

Periductal-Infiltrating (PI) Intrahepatic Cholangiocarcinoma (PI-ICC)

PI-ICC is a rare macroscopic type of cholangiocarcinoma with only a small mass or without any apparent mass that arises from the second order of intrahepatic bile ducts and shows a growth along dilated or narrowed bile ducts. Among 203 patients with ICC, only 7.9 % had PI-ICC (Uno et al. 2012). Radiologically, it manifests as an elongated, spiculated, or branching-like structure. Ultrasonographically, the tumors often present as a diffuse bile duct thickening with or without bile duct stenosis or obliteration, associated with dilatation of peripheral ducts, while CT and MR images display diffuse periductal thickening and increased enhancement associated with duct narrowing and prestenotic duct dilatations. This distinct growth pattern resembles that of many hilar/perihilar cholangiocarcinomas, with

the exception of a less prominent invasive phenotype. The PI type of ICC generally exhibits a diffuse invasion along the portal pedicle, but shows only minor or no invasion of the adjacent liver parenchyma (Sano et al. 1999; Uno et al. 2012). On resected specimens, a whitish ill-defined tumor is found that diffusely invades the tissues along the portal pedicles. A growth pattern mimicking PI-ICC results from intrahepatic periductal lymph vessel metastasis (lymphangiosis carcinomatosa) originating from extrahepatic cholangiocarcinoma (Tada et al. 1996). One variant of PI-ICC is a hilar type that usually causes obstructive jaundice. It presents as a diffuse low-density mass infiltrating the portal pedicle and causing unilateral or bilateral intrahepatic bile duct dilatation. These tumors can cause diffuse cancer invasion of the right or left hepatic artery and stenosis of the portal vein bifurcation (Sano et al. 1999). The prognosis of PI-ICC after surgery is better than that for MF-ICC without hilar invasion (Imai et al. 2010). In the study of Uno and coworkers (2012), the median survival was 7.7 years, with a 5-year survival rate of 62.1 %, and the overall outcome was better than that for MF plus PI-type ICC.

Intraductal Growth Intrahepatic Cholangiocarcinoma (IG-ICC): The Invasive Forms of Intraductal Papillary and Tubular Neoplasm of the Bile Duct (IPN-B and ITN-B)

The term intraductal growth ICC (IG-ICC; ICC of intraductal growth/IG type) was originally coined by the Liver Cancer Study Group of Japan and has been widely used until recently. IG-ICC encompasses a rare group of cancers that display intraductal exophytic growth, are associated with distinct precursor lesions, and can undergo a transition into invasive conventional ICC or mucinous carcinoma. There is a clear relationship between invasively growing intraductal cholangiocarcinomas and their non- or preinvasive partner lesion, intraductal papillary neoplasms of the bile duct (IPN-Bs), neoplasms discussed in a separate chapter. There is strong evidence that a majority of ICCs of intraductal growth (IG) type belong to neoplasms of an IPN-B lineage (Nakanuma et al. 2014).

Intraductal growth intrahepatic cholangiocarcinoma (formerly, intraductal variant of peripheral cholangiocarcinoma) is characterized by a cholangiocarcinoma that preferentially grows within intrahepatic bile ducts, often with a papillary or tubular growth pattern and variable invasion of adjacent liver tissue (Kim et al. 1989; Han and Lee 2004; Yeh et al. 2005; Nakanuma et al. 2008; Uno et al. 2012). In the original proposal of the Japanese classification of ICC, IG-ICC was designated as intraductal papillary ICC, a special type of ICC which developed a papillary projection into the duct lumen (Yamamoto et al. 1993). Intraductal variants of ICC had been reported previously (Kim et al. 1989). IG-ICC is also the invasive neoplasm that develops from intraductal papillary and tubular neoplasms of the bile duct (IPN-Bs and ITN-Bs). Among the three macroscopic subtypes of ICC, IG-ICC is the least common type, albeit with some differences between studies and countries. In a Japanese study of 64 patients with resected ICC, 28 were MF, 24 PI, and only 12 were IG-ICC (Sano et al. 1999). Among 98 Korean ICC cases, 42 were MF, 22 PI, 21 IG, and 13 mixed types (Suh et al. 2002). In a study of 16 patients, age at presentation ranged from 38 to 73 years (mean, 55.9 years), and 13 were men (Suh et al. 2000). The tumor occurs in the left and the right liver lobe with almost equal frequency. IG-ICC usually forms an ill-defined nodule, which is often smaller at presentation than those of other ICC subtypes. In an analysis of Suh and coworkers (2000), the average tumor diameter was 4.3 cm (range, 0.5–14 cm). Mucobilia is more frequent in this subtype than in MF and PI subtypes, as are anemia and elevated serum CEA levels (Yeh et al. 2005). IG-ICC is in most cases a neoplasm not associated with other neoplastic lesions, but has rarely been observed in conjunction with biliary papillomatosis (Güllüoglu et al. 2007). The tumors may cause, due to the intraductal exophytic growth, stenosis or obstruction of the involved intrahepatic duct. This is probably the

reason why a higher percentage of IG-ICC patients than non-IG-ICC patients presents physical signs at diagnosis and why these patients more often have signs of biliary tract infection, including bouts of fever, chills, and jaundice (Yeh et al. 2004). The imaging features of IG-ICC are characteristic (reviews: Suh et al. 2000). CT images show lobulated densities in the dilated bile ducts. In case of mucin secretion, dilatation of bile ducts is seen. Instead of a gross tumor mass, only cystic and tubular dilatation of the intrahepatic bile ducts may be noted (Lim et al. 2000). Cholangiography and ERCP reveal multiple filling defects in dilated intrahepatic bile ducts, sometimes mimicking gallstones.

In contrast to PI-ICC, which has a tendency to spread along Glisson's sheaths via lymphatic vessels (Sasaki et al. 1998b), ID-ICCs have a lower propensity for invasive growth, this probably being the main reason for the better outcome. ID-ICC less often produces lymph node metastases than any other ICCs (Suh et al. 2000; Isa et al. 2001). Among 16 patients with resected ID-ICC, not a single case showed lymph node metastases (Suh et al. 2000). Most studies demonstrate that, among ICCs, ID-ICC has the best prognosis (Suh et al. 2000; Tajima et al. 2004). In one study of five patients with resection, four were alive without recurrence, while one patient died 7 years and 7 months after surgery from a rapidly growing tumor in the liver remnant (Yamamoto et al. 1997). In a study of 98 ICCs, the 5-year cumulative survival rate was 23.3 % in the MF subtype, 0 % in the PI subtype, and 76.2 % in the ID subtype (Suh et al. 2002). In an analysis of the clinical features of 40 ID-ICCs (intraductal papillary type) having been treated by hepatectomy between 1977 and 2000, in comparison with 94 non-papillary-type ICC, both groups having similar age and sex distributions, the 5-year-survival rate was 24.7 % in the ID-ICC subtype versus 2.01 % in all other ICC types (Yeh et al. 2004). A papillary intraductal growth pattern was a positive prognosticator in a study of 373 peripheral ICCs (Jan et al. 2005). Even an intraductal papillary carcinoma component (IDPCC) in the tumor had a favorable effect on outcome, in that the presence of IDPCC, together with curative resection and the absence of perineural invasion, was a favorable independent prognostic factor in multivariate analysis (Tajima et al. 2004). Exophytic-papillary growth patterns generally seem to confer a favorable biology in cholangiocarcinomas. It has been shown, e.g., that a papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma (Jarnagin et al. 2005).

The macroscopic features of IG-ICC have been described in detail (Yamamoto et al. 1994). Including the involved bile ducts, IG-ICCs form rather small and circumscribed masses with a mean diameter of 4.3 cm in one study (Suh et al. 2000), but tumors exceeding 10 cm in diameter may exceptionally occur. In some cases, aneurysmal dilatation of involved bile ducts occurs (Jin et al. 2002). In case of large lesions, massively dilated intrahepatic bile ducts are filled with coarse or fine papillary and sometimes granular masses of whitish tumor tissue. After cutting through the tumor and the discharge of viscid fluid, the papillary fronds typically separate from each other, leaving a friable tissue with numerous slits between the exophytic tumor parts. In the rare IG-ICC with marked gross invasion, the presentation is more complex and sometimes no longer characterized by an exophytic, papillary growth pattern. In a detailed analysis of five cases, the tumors showed intrabile duct growth and superficial mucosal spread in two patients. In two other patients, an apparent mass lesion accompanied the intraluminal component, while in the remaining patient, a polypoid tumor infiltrated the portal tract system of the left lateral segment, where it had arisen (Yamamoto et al. 1997).

General Histologic Features

Most ICCs are histologically mucin-producing adenocarcinomas with variable degrees of differentiation (90 % of cases; Nakajima et al. 1988; Sinawat and Hemsrichart 1991; reviews: Nakanuma et al. 2003; Esposito and Schirmacher 2008; Zimmermann 2001). ICCs have a biliary origin, but the cellular sources have not yet fully been clarified, as apart from cholangiocytes and

progenitor cells, also hepatocytes may be the source of ICC (Guest et al. 2014). Depending on the level of differentiation, the cellular features of ICC cells resemble cells lining small, medium-sized, or large bile ducts. The cytoplasm is often pale or slightly eosinophilic, sometimes vacuolated. In solid parts, distended intra- or intercellular lumina (so-called second glands) are found, sometimes blending into cribriform structures (Nakajima and Kondo 1989). Even in well-differentiated tumors, irregular nuclear configurations are very common (Figs. 11, 12, 13, and 14).

As already outlined above, Nakanuma and coworkers proposed a pathological classification of ICC based on a novel concept (Nakanuma et al. 2008, 2010). The system distinguishes a bile duct or conventional type, further broken down into perihilar or large duct and a peripheral or small duct type, a bile ductular type, an intraductal neoplasm type, and rare variants.

The conventional or duct type is the most common phenotype. This type is further divided in the small duct type or peripheral type and the large duct type or perihilar type. Macroscopically, duct-type ICC displays compressive growth and no fibrous capsule. The small duct type presents as the MF-ICC type and histologically appears as a tubular or, less commonly, micropapillary adenocarcinoma with desmoplastic stroma and

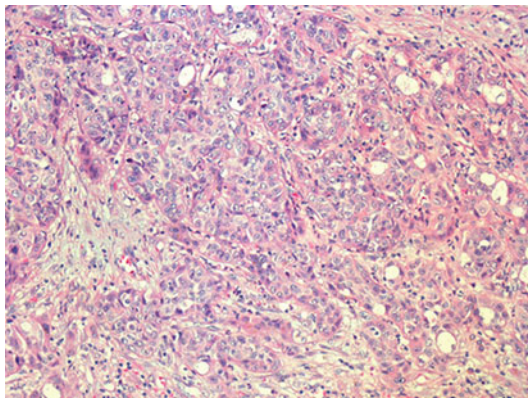

Fig. 11 Intrahepatic cholangiocarcinoma with poor desmoplasia (hematoxylin and eosin stain)

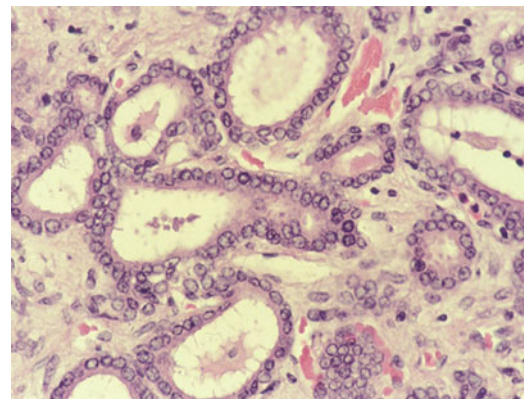

Fig. 13 Well-differentiated intrahepatic cholangiocarcinoma with formation of well-organized tubules and a homogeneous cell population (hematoxylin and eosin stain)

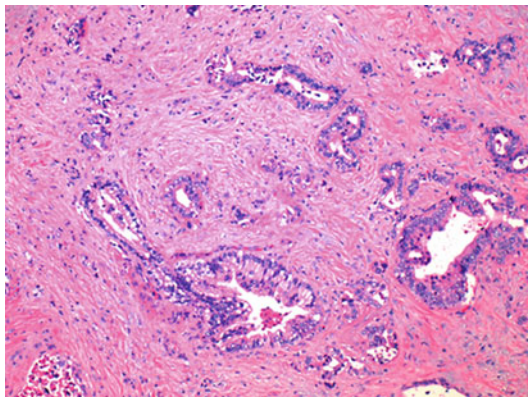

Fig. 12 Intrahepatic cholangiocarcinoma with marked stromal reaction (desmoplasia, hematoxylin and eosin stain)

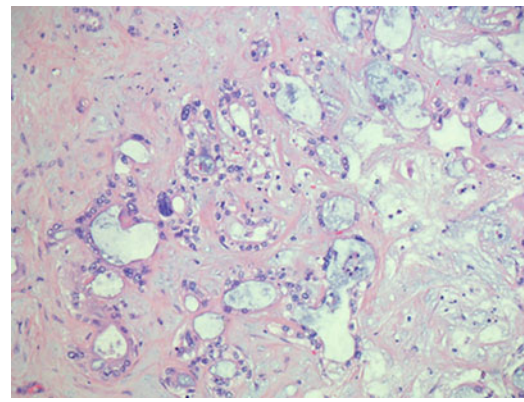

Fig. 14 Intrahepatic cholangiocarcinoma with mucin production and focal necrosis (hematoxylin and eosin stain)

inflammatory infiltrates and a compressive or replacing growth pattern. Most lesions are moderately differentiated and show central desmoplasia and/or necrosis. Immunohistochemically, the tumor cells, which are larger than normal cholangiocytes, are positive for cytokeratins 7, 8, 18, and 19, MUC1, MUC5AC, and MUC6, but not for NCAM (Nakanuma et al. 2008). The large duct or perihilar type presents macroscopically as PI-ICC or PI+MF-ICC types. The growth involves perihilar intrahepatic large bile ducts with formation of tubular, acinar, or micropapillary invasive tumor components and papillary or flat components growing within ducts. In addition, peribiliary glands can be involved (Nakanuma et al. 2010).

The bile ductular type usually presents as a MF-ICC with central scarring and a blurred margin blending into adjacent liver tissue. It consists of cells that are smaller than those in conventional ICC and mimicking those of ductules found in portal tracts. The tumor resembles collections of proliferated ductules (ductular proliferations), whereby small tubular profiles with slit-like lumina, acinar structures, or cord-like structures are present. Collagen bundles accompany the carcinoma cells. Bile ductular carcinoma exhibits a distinct replacing infiltrative growth of liver parenchyma. The invading tumor cells directly face parenchymal cells and appear to replace them. The cells are usually not alcian blue or PAS positive, except that some cells have discrete PAS-positive rim on their luminal face. Immunohistochemically, the tumor cells are reactive for cholangiocyte markers, NCAM, and often also vimentin. MUC1 is positive and MUC6 is focally present, but MUC2, MUC3, and MUC5AC are not detectable. The central desmoplasia histologically shows scar-like features and sometimes hyalinization. Within the fibrotic area, portal tract remnants may be found, together with trapped nodular or lobular parenchymal remnants (Nakanuma et al. 2008, 2010). A variant of ductular-type ICC mimics ductal plate malformations and presents as a carcinoma with an irregular configuration and branched, complex slit-like tubular spaces lined by cuboidal or columnar cells of high differentiation. A subset of ICCs show a combination of duct-type and ductule-type features (combined duct and ductular ICC), whereby the two components are present in amounts varying from one tumor to the other. These neoplasms exhibit ductular cholangiocarcinoma in the peripheral zone of the tumor and duct-type cholangiocarcinoma in central parts (Nakanuma et al. 2008).

The histology of IG-ICC is characterized by a papillary cholangiocarcinoma forming arborizing papillae that freely grow into the bile duct lumen, forming an exophytic mass. Thin papillary structures with a delicate vascular system are lined by a cuboid-to-columnar epithelium of the cholangiocellular type. The apical cytoplasm may contain PAS-positive and alkaline alcian blue-positive mucin. Depending on the grade, nuclei reveal variable degrees of atypia. One variant of IG-ICC is histologically characterized by mucosal spread, tubular and solid components with associated stroma growing within the mucosal lining of the intrahepatic bile duct (mucosal-spreading IG-ICC; Lim et al. 2000; Suh et al. 2000). In the vicinity of the neoplasm, variable degrees of epithelial dysplasia, immunoreactive for CA 19-9, can be observed in the bile duct mucosa (Ohta et al. 1991). A spatial association of dysplastic bile duct epithelium and IG-ICC is also found in ICC associated with hepatolithiasis, suggesting that biliary epithelium persistently exposed to biochemically altered bile may undergo a carcinogenic evolution (Ohta et al. 1991). The intraductal papillary neoplasm (IPN) type comprises the previous categories of biliary tract papilloma and papillomatosis and in part mimics intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, and includes three subtypes, i.e., intraductal papillary neoplasms of the bile duct (IPN-Bs), intraductal tubular neoplasms of the bile duct (ITN-Bs), and a superficial spreading type. Typically, both IPN-B and ITN-B are associated with, or preceded by, a spectrum of precursor lesions that are discussed in more detail in the following paragraph. Intraductal neoplasm-type lesions can undergo transition into invasive cancers that show a conventional (bile duct-type) morphology or a mucinous morphology and correspond to IG-ICC (Nakanuma et al. 2010).

Electron microscopic examinations showed that cells of well-differentiated cholangiocarcinomas contain relatively numerous ribosomes, but few organelles, while organelles become more frequent in tumors of lesser differentiation. Some of the cells display groups of fine fibrils. Neoplastic cell lining tubules exhibit surface microvilli. The cells are often surrounded by a thin basement membrane, which is incomplete or fragmented in poorly differentiated tumors. Subsets of cells may show tonofilaments indicating squamous cell differentiation (Alpert et al. 1974; Stitnimankarn et al. 1978; Sriurauranata et al. 1996).

Alternative Histologic Classifications

Histologically, ICCs were categorized into classical and nonclassical (Table 3; Sempoux et al. 2011).

Classical ICCs (54.8 %) were characterized by tubular, glandular, or nested patterns of growth and were significantly associated with a tumor size of more than 5 cm diameter and the absence of underlying liver disease. The main properties of nonclassical ICC (45.2 %) included trabecular architecture, features of extrahepatic carcinomas, and features of carcinomas considered to arise from hepatic progenitor cells, i.e., combined hepatocellular/cholangiocarcinomas and cholangiolocellular carcinomas (ductular type of ICC). Nonclassical tumors were also smaller and often developed in chronic underlying liver disease, in particular HCV infection and/or significant hepatic fibrosis (Sempoux et al. 2011).

Table 3 Classification of ordinary intrahepatic cholangiocarcinomas/ICCs (excluding special variants, see below; Sempoux et al. 2011)

Classical ICCs
Nonclassical ICCs
Tumors with a trabecular architecture
Tumors with features of extrahepatic carcinomas
Combined hepatocellular/cholangiocarcinomas
Cholangiolocellular carcinomas (ductular type of ICC)

Table 4 Differentiation groups of intrahepatic cholangiocarcinomas (ICCs)

Null-type ICC
Gastric foveolar-type ICC
Pyloric gland-type ICC
Gastric combined-type ICC

Based on mucin/MUC expression patterns, ICCs were classified into several differentiation groups (Table 4).

They include null type, gastric foveolar type, pyloric gland type, and gastric combined type, whereby half of the gastric foveolar and gastric combined types were located to the hilar region (Aishima et al. 2006). Part of these variants are associated with a distinct tumor biology. For example, the gastric foveolar type with a gastric mucin phenotype (predominance of MUC5AC) is associated with an aggressive tumor behavior (Aishima et al. 2006). ICCs tend to invade into and spread between hepatocyte plates, infiltrate adjacent portal tracts, grow along bile ducts, and invade perineural spaces (Weinbren and Mutum 1983; Shen et al. 2010). There are certain differences between ICC arising in cirrhotic livers and those that developed in normal livers. ICCs in non-biliary chronic advanced liver disease are more frequent of the bile ductular, while intraductal papillary neoplasms of the bile duct/IPN-Bs are more frequent in the patient group without chronic advanced liver disease (Nakanuma et al. 2011). ICCs arising in liver cirrhosis are hypervascular in comparison with those developing in normal livers (Xu et al. 2012). Secondary histologic changes in ICC comprise, apart from necrosis, apoptosis, and hemorrhage, focal calcification. In a case of ICC with paraneoplastic production of parathyroid hormone-related peptide, marked psammoma body formation was found in the tumor (Yamada et al. 2000).

Histological Variants

In rare instances (around 10 % of cases), ICC is histologically associated with components different from ordinary adenocarcinoma (Nakajima et al. 1988; Table 5). These variants are treated in separate paragraphs.

Table 5 Rare variants of intrahepatic cholangiocarcinoma

Mucinous ICC (mucin-producing ICC)
Signet ring cell ICC
Papillary ICC
Micropapillary ICC (*sensu strictiori*)
Cribriform ICC
Perihilar cholangiocarcinoma-like ICC (S100P+)
ICC with tumor infiltrative lymphocytes and autoimmune hepatitis-like features
ICC with lymphoepithelioma-like components
Clear cell ICC
Oncocytic ICC
ICC with squamous cell or adenosquamous components
ICC with thyroid-like structures
ICC with cyst formation
Microcystic ICC
ICC with a ductal plate malformation pattern
AFP-producing ICC
ICC with sarcomatous change

Markedly mucin-producing cholangiocarcinoma (mucinous and colloid adenocarcinomas) is a special variant that is associated with a more favorable course (Chou and Chan 1976; Sasaki et al. 1995; Chow et al. 1997; Chen et al. 1998), but can rarely be a composite tumor together with small cell carcinoma (Ikegami et al. 2013). Mucinous cholangiocarcinoma is defined as an adenocarcinoma with abundant deposition of extracellular mucin, amounting to more than 50 % of the tumor mass. Mucinous and signet ring cell tumors are treated in separate chapters. One variant of ICC originating in intrahepatic large bile ducts and associated with hepatolithiasis is intestinal-type ICC. This rare tumor exhibits a predominantly intraductal papillary growth pattern and is primarily composed of absorptive columnar cells, associated with widespread Paneth cell, goblet cell, and neuroendocrine cell metaplasia. The tumor shows only minor local invasion (Bae et al. 2002). One variant of ICC is characterized by cells resembling, or derived of, cholangiocytes of small ducts or ductules (cholangiolocellular ICC), while another variant shows an infiltrating replacement growth pattern and a striking resemblance to reactive proliferating ductules (bile ductular carcinoma; Kozaka et al. 2007). These neoplasms are listed in the Nakanuma classification as a distinct type (Nakanuma et al. 2010). ICC can present as a neoplasm with thick-walled cysts that resemble liver abscesses (Kokubo et al. 1990; Lee et al. 1995) or presents with a microcystic pattern, the latter also occurring in mucinous ICC (Mizukami et al. 1999). A distinct subset of peripheral ICCs that are associated with intrahepatic lithiasis resemble perihilar cholangiocarcinomas; are S100P positive, similar to perihilar and extrahepatic cholangiocarcinomas; and probably originate from larger intrahepatic ducts (Tsai et al. 2012). S100P nuclear expression in peripheral-type ICC significantly correlated with vascular invasion, lymphatic invasion, and lymph node metastasis (Aishima et al. 2011). A lymphoepithelioma-like component was reported, in part associated with expression of EBV-encoded RNA (Chen et al. 2001; Xiao et al. 2012). Other rare ICCs show dense tumor-infiltrative lymphocytes and may have autoimmune hepatitis-like features (Izumi et al. 2010). ICC predominantly consisting of adenocarcinoma can contain a component of squamous cell carcinoma or adenosquamous carcinoma (Nakajima et al. 1988; Nakajima and Kondo 1990). Uncommon variants of ICC revealed oncocytic change (Fujii et al. 2005), clear cell change (Toriyama et al. 2010), or a phenotype resembling a thyroid follicular neoplasm (Fornelli et al. 2010), these features discussed in separate paragraphs. A rare variant of well-differentiated ICC presented as a single nodule and histologically showed numerous vague, small carcinomatous areas with desmoplasia and epithelial formations resembling a ductal plate malformation (Nakanuma et al. 2012). Very rarely, ICC is associated with elevated serum AFP and marked AFP immunoreactivity of ICC cells (AFP-producing ICC; Vij and Wang 2008).

Grading, Growth, and Differentiation

Grading of ICCs is usually performed by the use of grading systems applied to other adenocarcinomas, although definitive criteria have not been established (Washington et al. 2010; Table 6).

The histologic grade of ICC has a strong impact on the biology of disease and outcome (see below). The growth patterns of ICCs vary as a function of differentiation, well-differentiated neoplasms showing few mitoses, while poorly differentiated ICCs can show a high proliferation fraction. The PCNA labeling index was lowest in MF-ICC and was higher in periductal growth ICCs (Ohashi et al. 1994). Synthesis of proteins as an important factor of cell differentiation is reflected by argyrophilic nucleolar organizer regions (AgNORs). AgNOR is loop DNA encoded for ribosomal RNA production on the nucleoli controlling protein synthesis. In ICC, differentiation is reflected by the number of AgNORs per nucleus (Hayashi et al. 1995).

Table 6 Grading of ICCs of the conventional adenocarcinoma type

Grade X	Grade cannot be assessed
Grade 1	Well differentiated (more than 95 % of tumor composed of glands and less than 5 % solid or cord-like components)
Grade 2	Moderately differentiated (50–95 % of tumor composed of glands and more than 5 % but less than 50 % solid or cord-like components)
Grade 3	Poorly differentiated (5–49 % of tumor composed of glands and 50–100 % solid or cord-like components)
Grade 4	Undifferentiated (less than 5 % of tumor composed of glands)

Stroma Formation (Desmoplastic Stroma, Desmoplasia)

Similar to extrahepatic cholangiocarcinomas, ICCs are often characterized by marked stroma formation (desmoplasia), whereby stromagenesis is usually more prominent in MF and PD than in ID-ICC. Some ICCs display a marked desmoplasia that mimics that of hilar cholangiocarcinomas (sclerosing ICC; Altemeier et al. 1957). The stroma is a cellular tissue rich in myofibroblasts (MFBs), cancer-associated fibroblasts (CAFs), and extracellular matrix proteins and proteoglycans and is the tissue in which tumor vessels are embedded. ICC cells grow within this stroma, and cancer cells engage in a close and complex interaction with stromal cells. Stromal MFBs are involved in the progression of ICC and promote cancer cell proliferation, migration, invasiveness, apoptosis resistance, and epithelial-mesenchymal transition/EMT, EMT playing a critical role in the metastatic pathway (review: Sirica 2011).

There are subsets of ICC that exhibit a markedly sclerosing stromal reaction (Figs. 15, 16, and 17).

According to the degree of stroma formation, ICCs have been divided into scirrhous-type ICC (SICC) and non-scirrhous-type ICC (NSICC). The two groups differed with respect to various morphologic and biologic parameters. In SICC tumors, lymphatic invasion, perineural invasion, and proliferative activity were higher than in NSICC, and patients with SICC revealed a poorer prognosis than those with NSICC (Kajiyama

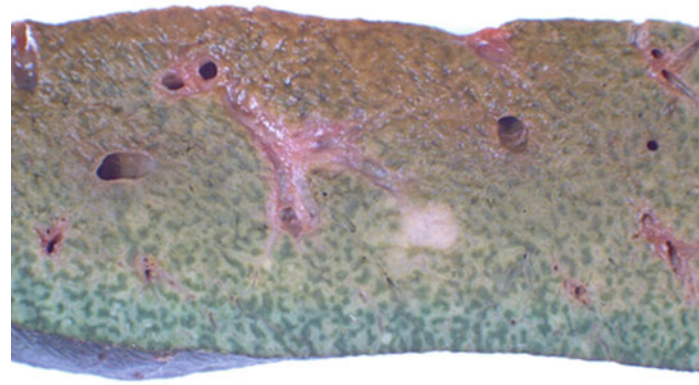

Fig. 15 Sclerosing intrahepatic cholangiocarcinoma. These tumors sometimes appear as small solitary lesions

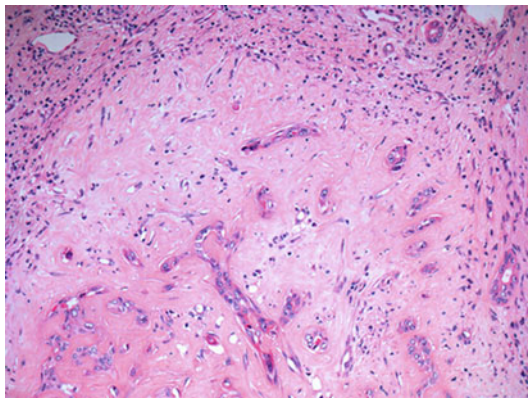

Fig. 16 Sclerosing intrahepatic cholangiocarcinoma. The tumor nodule is dominated by a sclerosed stroma with only few carcinoma tubules (hematoxylin and eosin stain)

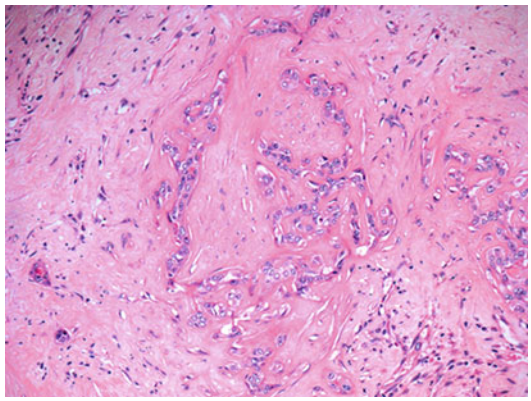

Fig. 17 Intrahepatic cholangiocarcinomas with marked fibrosclerosis and a poor contribution of small and monotonous carcinoma cells may mimic benign lesions such as adenofibroma (hematoxylin and eosin stain)

et al. 1999). Most ICCs show a fibromyxoid stroma rich in basement-membrane-type heparan sulfate proteoglycan (Sabit et al. 2001). The stroma of ICC was found to contain few S-100 protein-positive nerve fibers (Terada and Matsunaga 2001). Apart from fibroblastoid cells, alpha-SMA-positive MFBs are a predominant population, but their precursors, hepatic stellate cells, are also present in variable numbers, these cells being reactive for desmin, alpha-crystallin, and glial acidic fibrillary protein (Okabe et al. 2009). In stromal cell populations of ICC, alpha-SMA-reactive MFBs form two cell groups, i.e., peritumoral SMA-positive perisinusoidal cells and intratumoral SMA-positive stromal cells. There is evidence that SMA-positive peritumoral perisinusoidal cells are, in the course of tumor growth and invasion, incorporated into the stroma, where they then form the stromal MFBs. The number of both groups showed a positive correlation with the degree of tumor fibrosis (Terada et al. 1996a). The stroma of cholangiocarcinomas also harbors a population of CD10(+) fibroblasts, which are more involved in the progression of extrahepatic cholangiocarcinomas than that of ICC (Nishihara et al. 2009).

Stromal cells are biologically very active, engage in complex interactions with carcinoma cells, and are partners for mesenchymal cells derived from carcinoma cells in the setting of epithelial-to-mesenchymal transition (Sirica et al. 2011). Cholangiocarcinoma cells interact with stromal fibroblastoid cells via epithelial cell-derived neutrophil-activating peptide-78/CXCL5, a factor that causes accumulation of CD66(+) neutrophils in the tumor stroma (Okabe et al. 2012). Certain factors produced by stromal cells directly promote invasion. Periostin, produced by cholangiocarcinoma stromal cells, binds to carcinoma cells via integrin alpha5beta1, leading to activation of the invasion-promoting integrin/PI3K/AKT pathway (Utispan et al. 2012). In the stroma, hepatic stellate cells/HSCs or cells derived thereof interact with carcinoma cells. HSCs modify the behavior of carcinoma cells having contact with them or being exposed to their secreted products. On coculturing with HSC, ICC cells showed a marked increase in growth and invasive behavior (Okabe et al. 2009, 2011). Stromal-derived factor-1/SDF-1 produced by HSC induces cholangiocarcinoma cell migration via an interaction with CXCreceptor4 localized in carcinoma cells (Ohira et al. 2006; Gentilini et al. 2012). A direct interaction of cholangiocarcinoma cells with HSC promotes tube formation of human endothelial cells and accelerates the growth of the cancer cells (Okabe et al. 2011). A critical cell type of tumor stroma is the myofibroblast, a fibroblastoid cell that expresses alpha-smooth muscle actin and is

derived from the HSC lineage. In cholangiocarcinoma, stromal myofibroblasts promote proliferation of carcinoma cells through a pathway that drives epithelial cells into the S plus G2/M phases of the cell division cycle (Chuaysri et al. 2009). Fibroblastoid cells of cholangiocarcinomas produce periostin, which is a stromal factor that promotes an invasive phenotype (Utispan et al. 2010). Carcinoma-associated myofibroblasts also modulate ICC progression through their effects on apoptosis resistance and EMT, in part through aberrant hedgehog signaling between the two cells types involved (review: Sirica 2011).

Arterial vessels found within ICCs in part represent portal tracts that have been engulfed by the tumor. Aggressive invasion of tumors is manifest as decreased intratumoral arteries caused by portal tract destruction (Aishima et al. 2009). Extraductal mass-forming ICC can cause marked intrahepatic duct strictures/stenoses, whereby strictures confer a biology similar to that of perihilar or extrahepatic cholangiocarcinoma (Yamanaka et al. 1995).

Invasion and Spread

Intrahepatic Invasion and Spread

ICCs are highly invasive cancers that invade various hepatobiliary structures and tissues (Figs. 18, 19, 20, and 21). In regard to intrahepatic spreading, an analysis of 102 cases of ICC revealed expansion through sinusoidal spaces in 93 %, vascular invasion in 52 %, lymphatic involvement in 18 %, perineural invasion in 16 %, replacing growth in bile ducts in 12 %, and infiltration of portal connective tissue in 19 % (Nakajima et al. 1988).

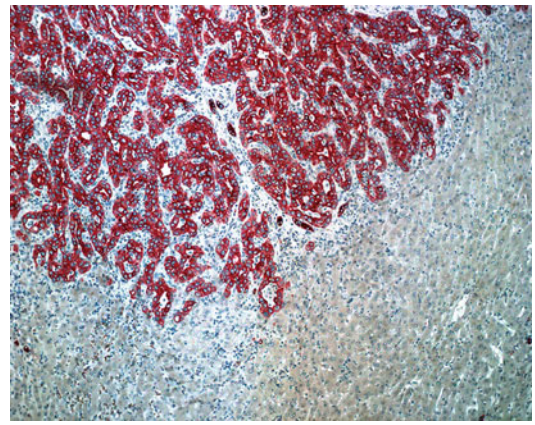

Fig. 19 Cytokeratin 7 expression in intrahepatic cholangiocarcinoma (CK 7 immunostain)

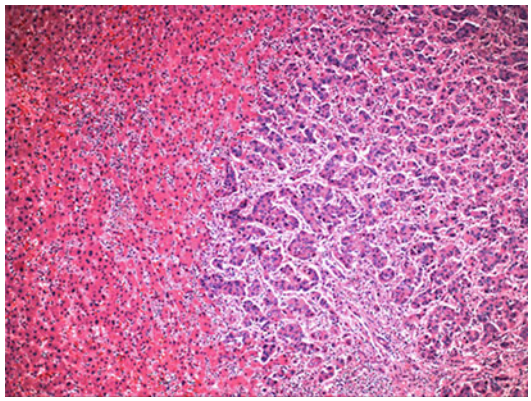

Fig. 18 Invasion front of a poorly differentiated intrahepatic cholangiocarcinoma (hematoxylin and eosin stain)

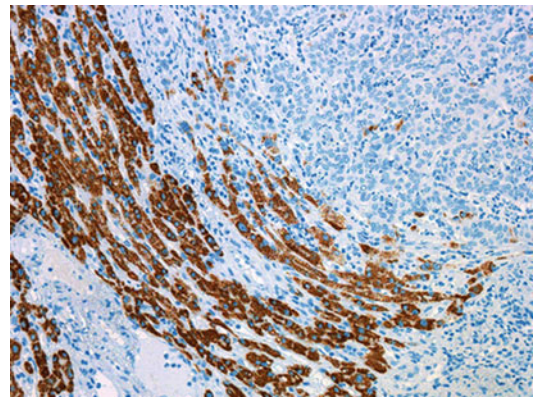

Fig. 20 Parenchymal invasion of intrahepatic cholangiocarcinoma associated with hepatocyte atrophy (HepPar-1 immunostain)

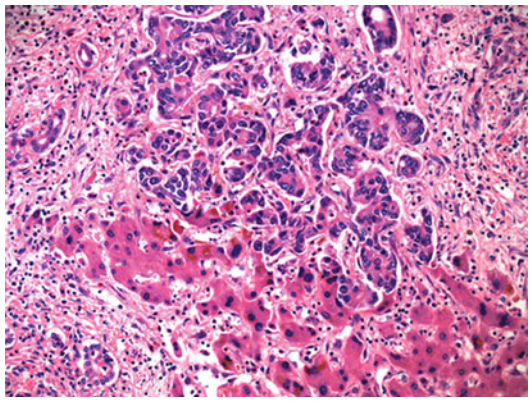

Fig. 21 Intrasinusoidal invasion of intrahepatic cholangiocarcinoma (hematoxylin and eosin stain)

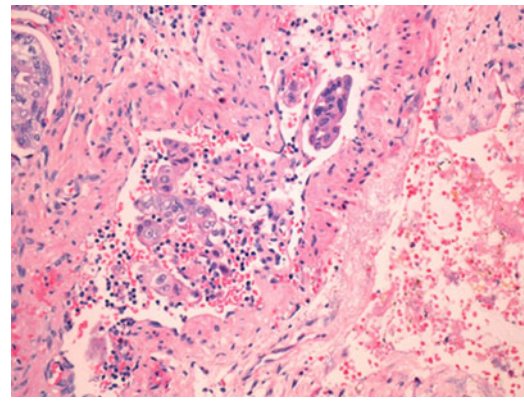

Fig. 22 Venous invasion of intrahepatic cholangiocarcinoma (hematoxylin and eosin stain)

Perineural Invasion

Perineural invasion is an important mode of spread for ICC, but is mainly observed in tumors located to areas where nerves are more common, i.e., close to the liver hilus. In a comparative investigation, the frequency of perineural invasion was higher in the hilar type of ICC than that in the peripheral type of ICC (Aishima et al. 2007). The recruitment of cholangiocarcinoma cells to the perineural compartment is accomplished by the actions of nerve growth factor and its receptors, neural cell adhesion molecule/NCAM, and matrix metalloproteinases (Shen et al. 2010).

Vascular Invasion

In contrast to hepatocellular carcinoma, gross invasion of the portal vein is less common, but portal tumor thrombi may be extensive and represent an unusual cause of hepatic failure or portal hypertension in patients with ICC (Terada et al. 1992; Soyer et al. 1998; Uchida et al. 1998; Kwon et al. 2000; Nakagohri et al. 2003; Uenishi et al. 2003). Obstructive portal vein invasion predominantly takes place when the portal vein branch is embedded within a large ICC mass. In addition to large intrahepatic veins, ICC also invades small venous vessels and venules (Fig. 22).

ICC may show a superficially spreading phenotype instead of an infiltrative growth pattern (Lim et al. 2000; Abe et al. 2005; Igami et al. 2009; Oshiro and Esaki 2011). ICC can be associated with extensive thrombosis of the inferior vena cava, causing Budd-Chiari syndrome (Law et al. 2005). The hepatic artery can also undergo direct invasion of ICC, followed by artery obstruction (Uenishi et al. 2003). A minority of ICC may show very unusual invasion patterns. In one case, well-differentiated mucin-producing ICC presented in the form of multiple irregularly shaped tumors in the liver. A mucinous fluid was found in the portal veins, the inner surface of which was lined with a single layer of tumor cells, reflecting an unusual mode of intravascular growth, while extravascular tissue invasion was hardly detectable (Minakawa et al. 2010).

Lymphatic Invasion and Lymph Node Metastasis

Similar to other forms of cholangiocarcinoma, ICC presents a high rate of lymphatic invasion and lymph node metastasis (Nozaki et al. 1998; Yamamoto et al. 1999; Okami et al. 2003; Nakagawa et al. 2005; Tamandl et al. 2009; Patel et al. 2011; review: Adachi and Eguchi 2014) (Fig. 23).

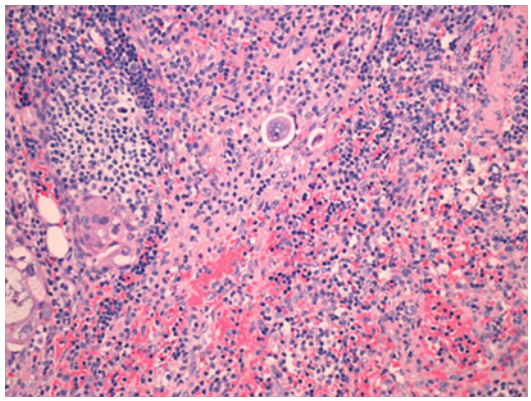

Fig. 23 Invasion of lymphatic vascular spaces by single cells of intrahepatic cholangiocarcinoma (hematoxylin and eosin stain)

Locoregional lymph node metastases were detected in up to 62 % of cases, with hilus-near cancers having slightly higher nodal metastasis rates than peripheral ones (Tsuji et al. 2001). Lymphatic spread in ICC is related to VEGF-C expression and D2-40-positive myofibroblasts, suggesting that a subset of myofibroblasts in stroma may contribute to lymphatic metastasis (Aishima et al. 2008) and is more often detectable in the tumor periphery and in peritumoral tissue than in the tumor center (Aishima et al. 2008). Lymph node dissection studies have shown that lymph node metastases in ICC were seldom limited to the locoregional nodes (Shimada et al. 2001). Involved nodes are located to the hepatoduodenal ligaments, along the hepatic and celiac arteries, around the abdominal aorta, on the posterior surface of the pancreatic head, along the left gastric artery, along the superior mesenteric artery, along the lesser curvature of the stomach, and around the cardia. The nodes of the hepatoduodenal ligament were the most common metastatic site, followed by nodes along the common hepatic artery, periaortic nodes, and nodes on the posterior surface of the pancreatic head (Tsuji et al. 2001). In another lymph node mapping analysis, nodal involvement was highest for nodes along the lesser gastric curvature (the left pathway), followed by nodes of the hepatoduodenal ligament (the right pathway; Okami et al. 2003). Lymph nodes in the hepatoduodenal ligament may be sentinel nodes for ICC lymphonodal metastases (Yamamoto et al. 1999; Chen et al. 2006). Metastases in nodes along the lesser gastric curvature and the left gastric artery were only observed in ICC that originated in the left liver lobe. The reported rate of perihepatic lymph node positivity for ICC was 27–62 % (Nozaki et al. 1998; Valverde et al. 1999; Yamamoto et al. 1999; Chen et al. 2006). In one study, metastatic nodes were divided into three groups, N1, N2, and N3, based on the classification proposed by the Liver Cancer Study Group of Japan. Among 23 patients with ICC, metastases were to N1 nodes in 10 patients, to N2 nodes in 9 patients, and to N3 nodes in 4 patients, and 19 patients had metastasis in nodes of the hepatoduodenal ligament, suggesting a sentinel node status (Yamamoto et al. 1999). However, the "true" incidence of perihepatic nodal metastases is not known, as micrometastases were not yet taken into account, but it was stated that the incidence of truly occult metastatic disease in perihepatic lymph nodes is low (Grobmyer et al. 2006). Rarely, ICC metastasizes to lymph nodes above the diaphragm, e.g., cervical lymph nodes (Hardeman et al. 2002; Imamura and Suzuki 2004).

Distant Metastasis

ICC has a complex metastasis pattern (Kim et al. 2003). Apart from intrahepatic metastases, metastatic spread involves the gastrointestinal tract (including the small intestine and colon; Izzo et al. 2010; Hayashi et al. 2011; Tokodai et al. 2012), pancreas (Labgaa et al. 2014), lung (Fukushima et al. 2011), skeleton including skull (Takahashi et al. 1994; Carlisle and Roberts 1999; Nishizawa et al. 2006; Kwon et al. 2007; Miyamoto et al. 2007; Fujimoto et al. 2013), soft tissue and muscle (Park et al. 2010), skin (Kondo et al. 2012), adrenal gland (Pandey et al. 2007), meninges (carcinomatous meningosis; Okamura et al. 2008), and brain (Mimatsu et al. 2011). Metastasis to the colon can cause intestinal obstruction (Tokodai et al. 2012). ICC may metastasize to the ovaries and mimic primary ovarian

cancer, but this is a rare metastatic pathway (Low et al. 2003; Khunamornpong et al. 2007; Corr et al. 2013). Ovarian ICC metastasis can result in Krukenberg tumor (Sharma et al. 1997).

Immune Reactions and Leukocyte Infiltration in Intrahepatic Cholangiocarcinoma

Lymphocytes that accumulate within and around ICC are of several types and reveal distinct distribution patterns. CD8(+) cytotoxic lymphocytes are most abundant at the invasion front of the tumor, whereas IL-17(+) and FOXP3(+) lymphocytes predominate in an intratumoral compartment (Gu et al. 2012). Similar to other carcinomas, ICCs harbor a distinct population of monocytes/macrophages, the tumor-associated macrophages/TAMs. TAMs located in the stroma play an important role in stromagenesis and in the regulation of tumor behavior. For example, TAMs are an important source of metalloproteinases and other proteinases, specifically MMP-9, in cholangiocarcinoma (Subimerb et al. 2010). In ICCs, the number of CD68(+) and CD163(+) macrophages is positively correlated with numbers of blood vessels and regulatory T cells. TAMs in ICC contribute to cancer progression via STAT3 activation (Hasita et al. 2010). Mast cells are detectable in the stromal tissue of ICC, and the density of these cells was higher in ICC than in hepatocellular carcinomas and higher than in portal tracts of normal liver (Terada and Matsunaga 2000). Mast cells may be involved in the generation of fibrosis in the stroma.

Immunohistochemistry

As neoplasms derived from cholangiocytes or progenitor cells that are primed to become bile duct cells, ICCs share at least part of the immunohistochemical reactivity patterns with normal biliary epithelial cells. Distinct immunohistochemical staining patterns will be helpful to improve stratification of these neoplasms (Iguchi et al. 2009).

Cytokeratins, Other Cholangiocyte Lineage Markers, and Markers of Cell Differentiation

Most ICCs reveal a characteristic marker profile, showing reactivity for CK7, CK8, CK17, CK18, CK19, and CD7 and lack of CDX2 (Maeda et al. 1996; Sasaki et al. 1999; Rullier et al. 2000; Shimonishi et al. 2000; reviews: Langer et al. 2006; Stroescu et al. 2006). Strong reactivity for CK7 in peritumoral ductular proliferations should not be confounded with cancer tubules (Fig. 24). In a comparative study, the most common cytokeratins positive in ICC were CK7, CK8, and CK19, and moderate and extensive expression of CK19 was found in almost all cases of well-differentiated ICC (Fig. 25), but expression decreased as a function of decreasing differentiation. CK20 is usually negative, but was occasionally detectable in poorly differentiated ICC, more frequent than in hilar cholangiocarcinoma (Shimonishi et al. 2000). Carcinoembryonic antigen/CEA is present in cells of invasive adenocarcinomas and in cells of carcinoma in situ, but is not detectable in hyperplastic lesions. In contrast, CA 19-9 is a typical marker of hyperplasia, reactivity being intermediate in dysplasia and low in invasive ICC (Terada and Nakanuma 1992). Practically all ICCs show marked membranous expression of epithelial membrane antigen/EMA, a marker which is

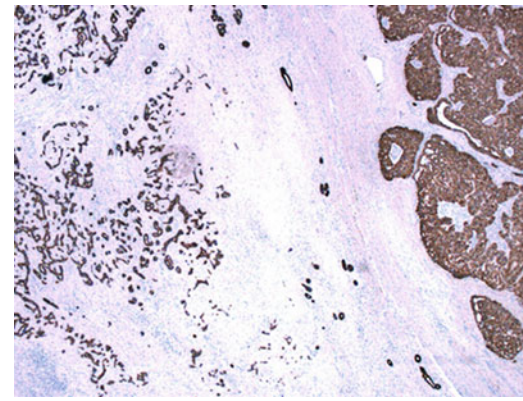

Fig. 24 Peritumoral ductular proliferations (*left half of figure*) in intrahepatic cholangiocarcinoma (cytokeratin 7 immunostain)

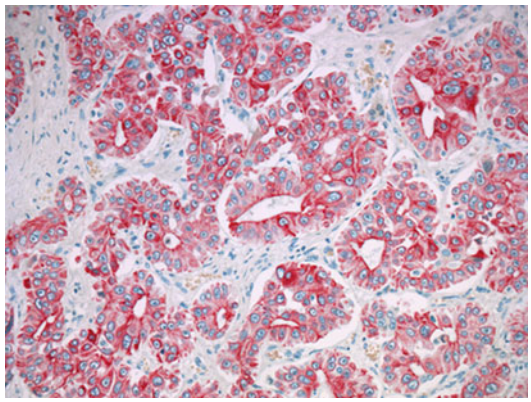

Fig. 25 Strong reactivity of intrahepatic cholangiocarcinoma cells for cytokeratin 19 (CK 19 immunostain)

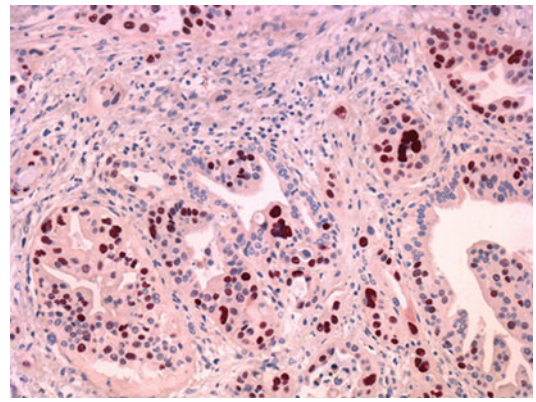

Fig. 26 Marked p53 protein reactivity of nuclei in intrahepatic cholangiocarcinoma (p53 immunostain)

important for distinction between ICC and pseudoglandular HCC (Bonetti et al. 1983). Two lineage markers of hepatocytes and hepatocellular carcinoma, HepPar-1 and arginase-1, were positive in a minority of cholangiocarcinomas (Leong et al. 1998; Radwan and Ahmed 2012). Most ICCs are reactive for fatty acid-binding protein 5 (Jeong et al. 2012). ICC cells do not, or only infrequently, express glypican-3 (Man et al. 2005), but may be positive for glutamine synthetase (Lagana et al. 2013). Human carcinoma antigen (HCA) is overexpressed in ICC and can be used a potential marker for ICC diagnosis (Zhou et al. 2011). The term HCA has been employed to collectively denote a group of mucin-type high molecular weight glycoproteins that are overexpressed in diverse epithelial cancers and are recognized by the monoclonal AE3 antibody (Thingstad et al. 1998; Palma et al. 2011). Peripheral ICCs express tubulin-betaIII more frequently than hilar carcinomas; this cytoskeletal protein serves as a helpful marker for ICC (Zen et al. 2014).

Stem Cell/Progenitor Cell Markers

Part of ICCs harbor population of tumor cells with progenitor cell or stem cell features. These cells may be reactive for NCAM and c-Kit (Xu et al. 2011), SALL4 (Oikawa et al. 2013), and/or CD44 and glioma-associated oncogene homologue 1/GLI1 (Nakanishi et al. 2013). CD133, a stem cell marker, shows distinct expression patterns in cholangiocarcinoma. CD133 reactivity is not restricted to stem cells, but also reflects the differentiation status of carcinoma cells. In cholangiocarcinoma, well-differentiated and moderately differentiated cancers were more often CD133 positive than poorly differentiated ones (Fan et al. 2011).

Oncogenes and Tumor Suppressors

A significant fraction of ICC shows nuclear immunoreactivity for p53 protein, positivity being detectable in up to 100 % of cases (Washington and Gottfried 1996; Batheja et al. 2000; Isa et al. 2002; Liu et al. 2006; Figs. 26 and 27). Positivity for p53 in ICC is, similar to other malignancies, associated with mutations in the TP53 gene in part of cases (Kiba et al. 1993; Liu et al. 2006), but epigenetic mechanisms that cause a stabilization of wild-type p53 also play a role (Furubo et al. 1999). There was no correlation between p53 reactivity and the gross appearance of ICC (Ohashi et al. 1995). Conversely, p53 reactivity is more frequent in well-differentiated ICC and less frequent in poorly differentiated ICC (Furubo et al. 1999). p73, a homologue of p53, was found in 41 % of cholangiocarcinomas, and p73 expression was not correlated with that of p53 (Tannapfel et al. 1999).

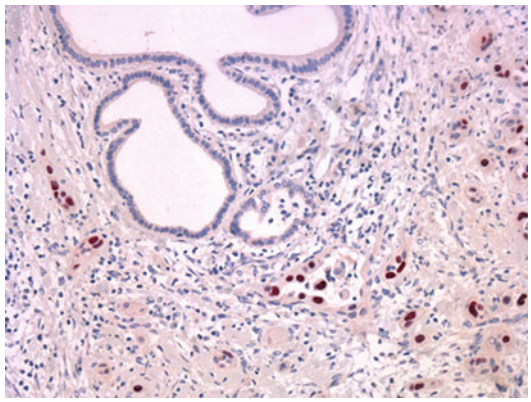

Fig. 27 p53 protein reactivity in intrahepatic cholangiocarcinoma cells within lymphatics surrounding peribiliary glands (p53 immunostain)

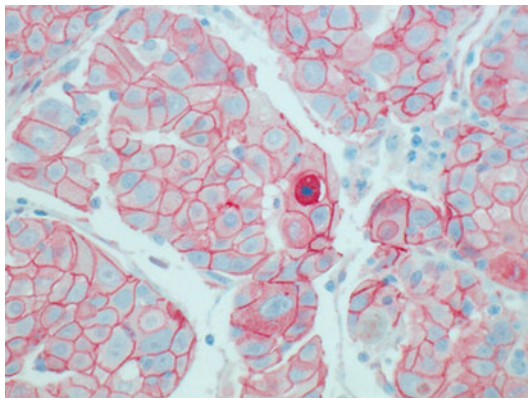

Fig. 28 Membranous expression of beta-catenin in intrahepatic cholangiocarcinoma. The *red* spherical structure with strong beta-catenin positivity is a tumor cell undergoing apoptosis (beta-catenin immunostain)

Ras p21 is expressed in part of ICC, but the expression is progressively lost with increasing dedifferentiation of tumor cells (Nonomura et al. 1987). The receptor for hepatocyte growth factor/HGF, MET, is not found in normal hepatic cells, but is present in conditions being a risk for cholangiocarcinogenesis, such as hepatolithiasis, where it is mainly seen in cells of hyperplastic septal and large bile ducts. MET overexpression was found in 58 % of ICC, being highest in well-differentiated tumors and lowest in poorly differentiated neoplasms (Terada et al. 1998). ICC cells show membranous expression of beta-catenin (Fig. 28).

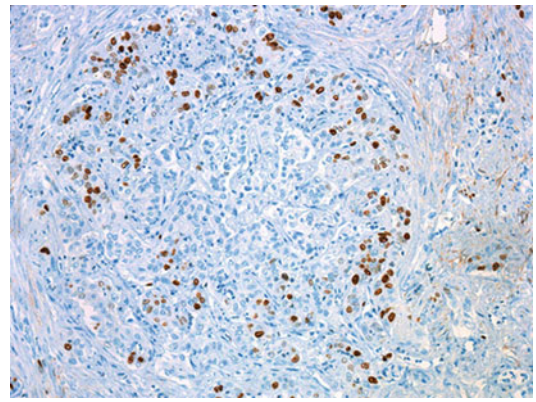

Fig. 29 High proliferative activity at the periphery of an intrahepatic cholangiocarcinoma nodule (MIB1 immunostain)

Proliferation and Apoptosis Markers

The proliferative activity of ICC cells can be assessed by PCNA and Ki-67 immunostaining (Minato and Nakanuma 1993; Settakorn et al. 2005; Fig. 29). The PCNA labeling index in poorly differentiated and moderately differentiated cholangiocarcinomas is higher than that of well-differentiated neoplasms (Minato and Nakanuma 1993). Estimation of the Ki-67 labeling may be used to classify ICC according to their growth features, as poorly differentiated tumors generally show higher Ki-67 indices (Wang et al. 2000), but the index has not been found to be a potent prognosticator (Kim et al. 1999). The Ki-67 index was correlated with overexpression of MDM2 protein, a protein which binds to and inactivates p53, and inhibits the p53-mediated transactivation processes (Horie et al. 2000).

Several factors operational in apoptosis are dysregulated in ICC. While normal cholangiocytes express Fas ligand/FasL, cholangiocarcinoma cells express both FasL and the Fas receptor and the FLICE inhibitor/I-FLICE, thus disabling Fas (Que et al. 1999). However, the percentage of Fas-expressing cells was significantly more often noted in extrahepatic tumors compared with ICC (Jhala et al. 2005). The reactivity for Bcl-2 in cholangiocarcinomas varies considerably from one investigation to another, ranging from non-detection (Okaro et al. 2001) or detection in occasional cases

(Terada and Nakanuma 1996) to reactivity in 100 % of cases (Skopelitou et al. 1996). Cytoplasmic positivity for Bcl-X(L) and Mcl-1 was found in 60–100 % of cholangiocarcinoma cells (Okaro et al. 2001). Part of cholangiocarcinoma cells express the receptor for tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/Apo2L) having the death domain, while another part of cholangiocarcinoma did not express the TRAIL decoy receptors lacking the death domain (Tanaka et al. 2000).

Mucin/MUC Status

Mucins expressed by various types of glandular epithelial cells are encoded by MUC genes, of which MUC1-4, 5AC, 5B, 6–8, 11–13, and 15–17 genes coding the backbone apomucin core protein have been found in humans. Several types of mucins are expressed in the intrahepatic bile duct systems and neoplasms derived thereof (Chou et al. 1976; Yamashita et al. 1993; Zen et al. 2006; reviews: Sasaki et al. 2007; Yeh et al. 2009; Yonezawa et al. 2010). Nondysplastic biliary epithelial cells in intrahepatic large bile ducts constantly express MUC3 apomucin, while expression of MUC3 and MUC5/6 apomucins was widespread in dysplastic biliary cells in hepatolithiasis (Sasaki et al. 1996). MUC1 was expressed in all three macroscopic subtypes of ICC, but MUC2 expression is rare and was expressed only in the ID-ICC subtype (Suh et al. 2002; Xu et al. 2009). Expression of MUC1 was detected immunohistochemically in 76 % of MF-ICC (Matsumura et al. 2002). In one study, MF-ICC showed significantly higher MUC1 expression rates than IP-HCC, while IP-ICC exhibited a more prominent MUC2 expression than MF-ICC (Higashi et al. 1999). Well-differentiated cholangiocarcinomas express MUC3 extensively in comparison with moderately or poorly differentiated tumors (Mall et al. 2010). Reactivity for MUC4, which is an intramembrane ligand for receptor kinase ErbB2 and involved in p27 regulation, was present in 37 % of MF-ICC and was a prognosticator (Shibahara et al. 2004). MUC5AC was found in 40 % and MUC6 in 21 % of ICC (Aishima et al. 2006). MUC6 apomucin was widely expressed in cholangiocarcinomas, irrespective of an association with liver cirrhosis, while MUC7 apomucin was frequently expressed in cholangiocarcinomas associated with cirrhosis (Sasaki et al. 1998a). Expression of MUC16 was found almost 50 % of MF-ICC (Higashi et al. 2012).

A group of proteins co-expressed with mucins are the trefoil factor family (TFF; TFF1, TFF2, and TFF3) peptides, which are mucin-associated molecules that are expressed in ICC and modify the behavior of cancer cells (Muenphom et al. 2006; Sasaki et al. 2007), acting via EGFR/MAPK activation (Kosriwong et al. 2011). TFF1 expression by intrahepatic cholangiocytes is increased in hepatolithiasis and is strongly upregulated in dysplastic bile duct epithelia and in noninvasive carcinoma, together with MUC5AC gastric-type mucin that colocalizes with TFF1. In contrast, TFF1 undergoes downregulation as soon as the carcinomas start an invasive growth pattern, probably accomplished by epigenetic methylation of the TFF1 promoter region (Sasaki et al. 2003).

Endocrine and Neuroendocrine Markers

Epithelial cells of bile ducts and cholangiocarcinomas, but not hepatocytes and hepatocellular carcinoma, express secretin receptors (Körner et al. 2006), secretin interacting with these receptors to induced bicarbonate-dependent, acid-independent bile flow.

Adhesion Molecules, Proteins of the Extracellular Matrix (ECM), and Proteins Involved in Invasion

ICC cells frequently exhibit N-cadherin at their surface membrane. Expression of N-cadherin together with CK7 resulted in a diagnostic

specificity of 98 % (Mosnier et al. 2009). Part of ICCs express the adhesion molecules, P-cadherin and CD24 (Su et al. 2006; Keeratichamroen et al. 2011), these expression patterns affecting the invasive phenotype. P-cadherin expression was found in up to 37 % of ICC and CD24 in 21 % of these neoplasms (Riener et al. 2010). About 50 % of ICCs express liver-intestine cadherin (LI-cadherin), a cadherin with seven cadherin repeats and a short cytoplasmic domain. Expression of LI-cadherin in ICC is associated with upregulation of placental growth factor (PIGF) and of metal-responsive transcription factor-1, via this mechanism promoting angiogenesis (Takamura et al. 2010). The alphaVbeta6 integrin is a highly specific immunohistochemical marker for cholangiocarcinoma (Patsenker et al. 2010), and expression of integrin alpha6 is associated with migratory and invasive phenotype in ICC (Ding et al. 2013). Laminin gamma 2 chain, an ECM protein critically involved in tumor cell migration and invasion, is expressed in ICC and is essentially localized in the stroma around cancer cells at the invasive front (Aishima et al. 2004). ICCs express the ECM proteins, laminin, tenascin, and collagen type IV in their stroma (Terada and Nakanuma 1994). Tenascin is typically expressed in actively invading parts of the tumor, specifically at the invasion front (Aishima et al. 2003). ICC cells express galectins, members of a family of beta-galactoside-binding lectins (Dechaphunkul et al. 2010). Galectin-3 is strongly expressed in the cytoplasm of well-differentiated ICC, but is reduced or absent in poorly differentiated ICC. In contrast, galectin-1 is predominantly expressed in ICC with high proliferative activity, is also expressed in tumor stroma, and may be involved in tumor progression (Shimonishi et al. 2001). Claudin-18, a tight junction protein, is aberrantly expressed in intraductal ICCs and intraductal neoplasms, expression associated with poor overall survival (Shinozaki et al. 2011). ICCs express matrix metalloproteinases (Terada et al. 1996b), and the majority of ICCs expressed maspin (Lok et al. 2014).

Other Markers

In larger bile ducts, S100P expression increases from reactive epithelial changes to low-grade BillN to high-grade BillN (Aishima et al. 2011), and S100P reactivity is generally useful as a diagnostic marker of cholangiocarcinomas (Levy et al. 2010) and the immunohistochemical expression of S100A2, involved in EMT. In one study, the relative expression level of S100P could determine cholangiocarcinoma at higher sensitivity than classical cytology (Hamada et al. 2011). S100P is also a potential prognostic marker in cholangiocarcinoma patients (Sato et al. 2013b). CD79a is a marker for hepatocellular carcinoma, but is not detectable in cholangiocarcinoma, thus representing a useful differential diagnostic marker (Li and Li 2013). In contrast to atypical cholangiocyte proliferations, invasive cholangiocarcinomas, including ICC, display loss of reactivity for SMAD4/DPC4 and share this feature with ductal pancreatic carcinomas (Tascilar et al. 2001; Chuang et al. 2004). Part of cholangiocarcinomas are reactive for salivary- and pancreatic-type amylase isoenzymes, reactivity being related to the differentiation grade, i.e., higher expression in well-differentiated tumors (Terada and Nakanuma 1993). Part of ICCs contain cytoplasmic hyaline inclusions that are p62(+) (Aishima et al. 2010).

Special Growth Patterns of Intrahepatic Cholangiocarcinoma

Peripheral ICC can present as a neoplasm with intraductal mucosa-spreading and mucin-producing morphology. Histologically, these neoplasms were characterized by a single layer of tall columnar cells with short intraluminal papillary projections lining the dilated bile ducts, the latter showing mucostasis. The process spreads diffusely and contiguously along intrahepatic bile ducts, with minimal invasion of the duct wall (Lim et al. 2000). It is suggested that such lesions form an overlap to the novel category of intraductal papillary mucinous neoplasms of the bile ducts, discussed in a separate chapter.

Intrahepatic Cholangiocarcinoma Synchronously Associated with Other Hepatobiliary Tumors

ICC can synchronously occur with hepatocellular carcinoma as spatially separated tumors (Kubo et al. 2004; Al Hamoudi et al. 2012). In one study, the incidence of double hepatic cancer was 0.25 % (Cao et al. 2013). Such patients may show evidence of hepatitis virus infection (Nagano et al. 2000; Jung et al. 2013), with HBV infection being found in up to 100 % of patients (Cao et al. 2013). Therefore, a common viral carcinogenic pathway involving hepatocyte and cholangiocyte lineage might be considered. In one Japanese patient, ICC was intricately admixed with fibrolamellar carcinoma (Tanaka et al. 2005). ICC was found in association with gallbladder papillary neoplasia and pancreaticobiliary malformation (Resende et al. 2012).

Differential Diagnosis

In rare instances, hepatic colorectal adenocarcinoma metastasis can undergo intrabile duct invasion and thus mimic cholangiocarcinoma (Kayashima et al. 2008). Other tumors or tumor-like lesions that may clinico-radiologically mimic ICC comprise inflammatory pseudotumors (Inaba et al. 2003; Ahn et al. 2012), ductocentric lymphomas, tuberculomas, and pyogenic liver abscesses. Histologically, inflammatory changes of intrahepatic bile may be associated with abnormal epithelial proliferations and cell atypia, not to be confounded with incipient cholangiocarcinoma (Fig. 30).

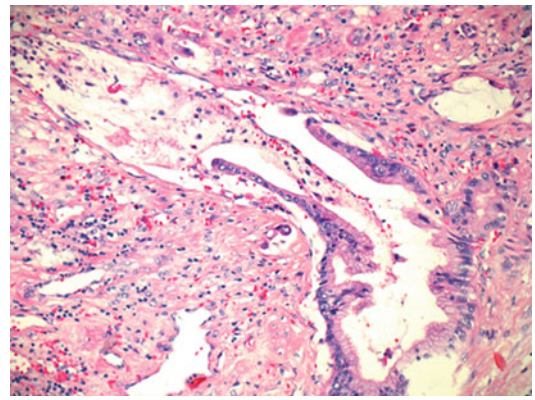

Fig. 30 Inflammatory changes of an eroded bile duct with cellular atypia and pseudopapillary structures (hematoxylin and eosin stain)

Biology of Disease

ICCs are aggressive malignancies of the liver that are still considered to be a fatal disease for many patients, because of a still low resectability (10–20 %) and frequent recurrences and spread following surgery. However, new treatment modalities have significantly improved outcome and survival in a selected subpopulation of patients (Berdah et al. 1996; Casavilla et al. 1997; El Rassi et al. 1999; Yamamoto et al. 2001; Hirohashi et al. 2002b; Morimoto et al. 2003; Fu et al. 2004; Endo et al. 2008; Yang and Yan 2008; Patel 2011; Yamamoto and Ariizumi 2011). In particular, unresected cholangiocarcinoma is a rapidly fatal process (Farley et al. 1995). The most obvious recurrence pattern following surgery was intrahepatic recurrence, in up to 60.9 % of patients (Miwa et al. 2006; Hyder et al. 2013). As other forms of cholangiocarcinoma, ICC tends to produce locoregional lymph node metastases, the presence of which is an important prognostic factor. In regard to outcome, there are certain differences between the main macroscopic subtypes of ICC, in that mass-forming (MF)-ICC with hilar invasion has a high load of local and hepatic recurrence, whereas the intraductal (ID) subtype and the periductal-infiltrating (PI) subtype without hilar invasion have a more favorable surgical outcome (Yedibela et al. 2009; Yamamoto and Ariizumi 2011). Even asymptomatic ICCs show perineural invasion and vascular or lymphatic involvement and are associated with poor prognosis. There are few reported instances of late recurrence of ICC (Kondo et al. 2012). In the course of pulmonary spread, pulmonary embolization followed by pulmonary hypertension may develop (Nakanishi et al. 2013).

References

Abe M, Kondo S, Hirano S, Ambo Y, Tanaka E, Saito K, Morikawa T, Okushiba S, Katoh H (2005) Superficially spreading cholangiocarcinoma. Int J Gastrointest Cancer 35:89–94

Adachi and Eguchi 2014. http://www.ncbi.nlm.nih.gov/pubmed/24027075

Ahn KS, Kang KJ, Kim YH, Lim TJ, Jung HR, Kang YN, Kwon JH (2012) Inflammatory pseudotumors mimicking intrahepatic cholangiocarcinoma of the liver; IgG4-positivity and its clinical significance. J Hepatobiliary Pancreat Sci 19:405–412

Ahrendt SA, Nakeeb A, Pitt HA (2001) Cholangiocarcinoma. Clin Liver Dis 5:191–218

Aishima et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15105812

Aishima S, Oda Y (2014) Pathogenesis and classification of intrahepatic cholangiocarcinoma: different characters of perihilar large duct type versus peripheral small duct type. J Hepatobiliary Pancreat Sci. doi:10.1002/jhpb.154

Aishima S, Taguchi K, Terashi T, Matsuura S, Shimada M, Tsuneyoshi M (2003) Tenascin expression at the invasive front is associated with poor prognosis in intrahepatic cholangiocarcinoma. Mod Pathol 16:1019–1027

Aishima S, Kuroda Y, Nishihara Y, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2006) Gastric mucin phenotype defines tumour progression and prognosis of intrahepatic cholangiocarcinoma: gastric foveolar type is associated with aggressive tumour behavior. Histopathology 49:35–44

Aishima S, Kuroda Y, Nishihara Y, Iguchi T, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2007) Proposal of progression model for intrahepatic cholangiocarcinoma: clinicopathologic differences between hilar type and perihilar type. Am J Surg Pathol 31:1059–1067

Aishima S, Nishihara Y, Iguchi T, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2008) Lymphatic spread is related to VEGF-C expression and D2-40-positive myofibroblasts in intrahepatic cholangiocarcinoma. Mod Pathol 21:256–264

Aishima S, Iguchi T, Nishihara Y, Fujita N, Taguuchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2009) Decreased intratumoral arteries reflect portal tract destruction and aggressive characteristics in intrahepatic cholangiocarcinoma. Histopathology 54:452–461

Aishima S, Fujita N, Mano Y, Iguchi T, Taketomi A, Maehara Y, Oda Y, Tsuneyoshi M (2010) p62+ hyaline inclusions in intrahepatic cholangiocarcinoma associated with viral hepatitis or alcoholic liver disease. Am J Clin Pathol 134:457–465

Aishima S, Fujita N, Mano Y, Kubo Y, Tanaka Y, Taketomi A, Shirabe K, Maehara Y et al (2011) Different roles of S100P overexpression in intrahepatic cholangiocarcinoma: carcinogenesis of perihilar type and aggressive behavior of peripheral type. Am J Surg Pathol 35:590–598

Akatsu M, Ueda M, Shimazu M, Kawachi S, Tanabe M, Aiura K, Wakabayashi G, Sakamoto M et al (2005) Spontaneous rupture of a mass-forming type peripheral cholangiocarcinoma. J Gastroenterol Hepatol 20:162–164

Al Hamoudi W, Khalaf H, Allam N, Al Sebayel M (2012) Coincidental occurrence of hepatocellular carcinoma and cholangiocarcinoma (collision tumors) after liver transplantation: a case report. Hepat Mon 12:e5871

Alpert LI, Zak FG, Werthamer S, Bochetto JF (1974) Cholangiocarcinoma: a clinicopathologic study of five cases with ultrastructural observations. Hum Pathol 5:709–728

Altemeier WA, Gall EA, Zinninger MM, Hoxworth PI (1957) Sclerosing carcinoma of the major intrahepatic bile ducts. AMA Arch Surg 75:45–460

Antoniou et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22717934

Audran M, Hingrat JY, Paineau J, Gaillard F, Cousin C, Grolleau JY, Hardy M, Visset J (1982) Paraneoplastic hypercalcemia disclosing cholangiocarcinoma. Remission after hepatectomy (in French). Gastroenterol Clin Biol 6:983–988

Bae JY, Park YN, Nakanuma Y, Lee WJ, Kim JY, Park C (2002) Intestinal type cholangiocarcinoma of intrahepatic large bile duct associated with hepatolithiasis – a new histologic subtype for further investigation. Hepatogastroenterology 49:628–630

Batheja N, Suriawinata A, Saxena R, Ionescu G, Schwartz M, Thung SN (2000) Expression of p53 and PCNA in cholangiocarcinoma and primary sclerosing cholangitis. Mod Pathol 13:1265–1268

Berdah SV, Delpero JR, Garcia S, Hardwigsen J, Le Treut YP (1996) A western surgical experience of peripheral cholangiocarcinoma. Br J Surg 83:1517–1521

Bertuccio P, Bosetti C, Levi F, Decarli A, Negri E, La Vecchia C (2013) A comparison of trends in mortality from primary liver cancer and intrahepatic cholangiocarcinoma in Europe. Ann Oncol 24:1667–1674

Blechacz B, Gores GJ (2008) Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment. Hepatology 48:308–321

Blechacz B, Komuta M, Roskams T, Gores GJ (2011) Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 8:512–522

Bonetti F, Chilosi M, Pisa R, Novelli P, Zamboni G, Menestrina F (1983) Epithelial membrane antigen expression in cholangiocarcinoma. An useful immunohistochemical tool for differential diagnosis with hepatocarcinoma. Virchows Arch A Pathol Anat Histopathol 401:307–313

Braconi C, Patel T (2010) Cholangiocarcinoma: new insights into disease pathogenesis and biology. Infect Dis Clin North Am 24:871–884

Cao J, Huang L, Liu C, Li J, Zhang X, Shen J, Shen J, Li J, Lu L, Xu F, Yan J, Wu M et al (2013) Double primary hepatic cancer (hepatocellular carcinoma and

intrahepatic cholangiocarcinoma) in a single patient: a clinicopathologic study of 35 resected cases. J Gastroenterol Hepatol 28:1025–1031
Capizzi PJ, Rosen CB, Nagorney DM (1992) Intermittent jaundice by tumor emboli from intrahepatic cholangiocarcinoma. Gastroenterology 103:1669–1673
Cardinale V, Semeraro R, Torrice A, Gatto M, Napoli C, Bragazzi MC, Gentile R, Alvaro D (2010) Intra-hepatic and extra-hepatic cholangiocarcinoma: new insight into epidemiology and risk factors. World J Gastrointest Oncol 2:407–416
Cardinale V, Bragazzi MC, Carpino G, Torrice A, Fraveto A, Gentile R, Pasqualino V et al (2013) Cholangiocarcinoma: increasing burden of classifications. Hepatobiliary Surg Nutr 2:272–280
Carlisle RT, Roberts CS (1999) Pathologic fracture of the humerus due to metastatic cholangiocarcinoma. South Med J 92:1216–1219
Carter RF, Smiley WA (1950) Primary carcinoma of intrahepatic bile ducts. J Kans Med Soc 51:281–282
Casavilla FA, Marsh JW, Iwatsuki S, Todo S, Lee RG, Madariaga JR, Pinna A, Dvorchik I et al (1997) Hepatic resection and transplantation for peripheral cholangiocarcinoma. J Am Coll Surg 185:429–436
Chen MF (1999) Peripheral cholangiocarcinoma (cholangiocellular carcinoma): clinical features, diagnosis and treatment. J Gastroenterol Hepatol 14:1144–1149
Chen MF, Jan YY, Chen TC (1998) Clinical studies of mucin-producing cholangiocellular carcinoma: a study of 22 histopathology-proven cases. Ann Surg 227:63–69
Chen TC, Ng KF, Kuo T (2001) Intrahepatic cholangiocarcinoma with lymphoepithelioma-like component. Mod Pathol 14:527–532
Chen Z, Yan JJ, Huang L, Wu MC, Yan YQ (2006) Lymph node metastasis of patients with intrahepatic cholangiocarcinoma (in Chinese). Zhonghua Wai Ke Za Zhi 44:454–457
Chiyomaru K, Takai T, Ohashi A, Nishigori C (2010) Necrolytic migratory erythema with cholangiocarcinoma: pseudoglucagonoma syndrome. Eur J Dermatol 20:238–239
Chong RW, Chung AY, Chew IW, Lee VK (2006) Ruptured peripheral cholangiocarcinoma with hemoperitoneum. Dig Dis Sci 51:874–876
Chou ST, Chan CW (1976) Mucin-producing cholangiocarcinoma: an autopsy study in Hong Kong. Pathology 8:321–328
Chou ST, Chan CW, Ng WL (1976) Mucin histochemistry of human cholangiocarcinoma. J Pathol 118:165–170
Chow LTC, Ahuja AT, Kwong KH, Fung KSC, Lai CK, Lau JWY (1997) Mucinous cholangiocarcinoma: an unusual complication of hepatolithiasis and recurrent pyogenic cholangitis. Histopathology 30:491–494
Chu KM, Lai ECS, Al-Hadeedi S, Arcilla CE, Lo CM, Liu CL, Fan ST (1997) Intrahepatic cholangiocarcinoma. World J Surg 21:301–306
Chuang SC, Lee KT, Tsai KB, Sheen PC, Nagai E, Mizumoto K, Tanaka M (2004) Immunohistochemical study of DPC4 and p53 proteins in gallbladder and bile duct cancers. World J Surg 28:995–1000
Chuaysri C, Thuwajit P, Paupairoj A, Chau-In S, Suthipongchai T, Thuwajit C (2009) Alpha-smooth muscle actin-positive fibroblasts promote biliary cell proliferation and correlate with poor survival in cholangiocarcinoma. Oncol Rep 21:957–969
Colombari R, Tsui WM (1995) Biliary tumors of the liver. Semin Liver Dis 15:402–413
Corr BR, Mantia-Smaldone G, Cantor J, Livolsi VA, Furth E, Chu CS (2013) Metastatic cholangiocarcinoma to the ovary: a case series. Int J Gynecol Pathol 32:562–565
Craigh JR, Peters RL, Edmondson HA (1989) Tumors of the liver and intrahepatic bile duct. In: Hartmann WH (ed) Atlas of tumor pathology, 2nd series, fascicle 26. Armed Forces Institute of Pathology, Washington, DC
Davis JM, Sadasivan R, Dwyer T, Van Veldhuizen P (1994) Case report: cholangiocarcinoma and hypercalcemia. Am J Med Sci 307:350–352
De Martel C, Plummer M, Franceschi S (2010) Cholangiocarcinoma: descriptive epidemiology and risk factors. Gastroenterol Clin Biol 34:173–180
Dechaphunkul A, Kanngurn S, Dechsukhum C, Tanutit P, Khow-Ean U, Sunpaweravong P (2010) The significance of galectin-3 immunohistochemistry, clinical characteristics and liver imaging in differentiating intrahepatic cholangiocarcinoma from adenocarcinoma liver metastasis. J Med Assoc Thai 93:523–528
Ding et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23306848
El Rassi ZE, Partensky C, Scoazec JY, Henry L, Lombard-Bohas C, Maddern G (1999) Peripheral cholangiocarcinoma: presentation, diagnosis, pathology and management. Eur J Surg Oncol 25:375–380
Endo et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18580211
Esposito I, Schirmacher P (2008) Pathological aspects of cholangiocarcinoma. HPB 10:83–86
Fan L, He F, Liu H, Zhu J, Liu Y, Yin Z, Wang L, Guo Y, Wang Z, Yan Q, Huang G (2011) CD133: a potential indicator for differentiation and prognosis of human cholangiocarcinoma. BMC Cancer 11:320
Farley DR, Weaver AL, Nagorney DM (1995) Natural history" of unresected cholangiocarcinoma: patient outcome after noncurative intervention. Mayo Clin Proc 70:425–429
Fornelli A, Bondi A, Jovine E, Eusebi V (2010) Intrahepatic cholangiocarcinoma resembling a thyroid follicular neoplasm. Virchows Arch 456:339–342
Fu XH, Tang ZH, Zong M, Yang GS, Yao XP, Wu MC (2004) Clinicopathologic features, diagnosis and surgical treatment of intrahepatic cholangiocarcinoma in 104 patients. Hepatobiliary Pancreat Dis Int 3:279–283
Fujii T, Harada K, Katayanagi K, Kurumaya H, Nakanuma Y (2005) Intrahepatic cholangiocarcinoma with

multicystic, mucinous appearance and oncocytic change. Pathol Int 55:206–209
Fujimoto K, Kuroda J, Makino K, Hasegawa Y, Kuratsu J (2013) Skull metastasis from intrahepatic cholangiocarcinoma: report of 3 cases and review of the literature. Neurol Med Chir (Tokyo) 53:717–721
Fukushima K, Kido M, Fukumoto T, Hori Y, Kusunoki N, Tsuchida S, Takahashi M, Tanaka M et al (2011) A case report of intrahepatic cholangiocarcinoma diagnosed as lung cancer with liver metastasis treated with radiofrequency ablation (in Japanese). Gan To Kagaku Ryoho 38:2030–2032
Furubo S, Harada K, Shimonishi T, Katayanagi K, Tsui W, Nakanuma Y (1999) Protein expression and genetic alterations of p53 and ras in intrahepatic cholangiocarcinoma. Histopathology 35:230–240
Gatto M, Alvaro D (2010) New insights on cholangiocarcinoma. World J Gastrointest Oncol 2:136–145
Gentilini A, Rombouts K, Galastri S, Caligiuri A, Mingarelli E, Mello T, Marra F, Mantero S et al (2012) Role of the stromal-derived factor-1 (SDF-1)-CXCR4 axis in the interaction between hepatic stellate cells and cholangiocarcinoma. J Hepatol 57:813–820
Goldenberg IS (1953) Carcinoma of the biliary tract. Conn State Med J 17:977–984
Gore RM, Shelhamer RP (2007) Biliary tract neoplasms: diagnosis and staging. Cancer Imaging 7(Spec. No. A): S15–S23
Grobmyer SR, Wang L, Gonen M, Fong Y, Klimstra D, D'Angelica M, DeMatteo RP et al (2006) Perihepatic lymph node assessment in patients undergoing partial hepatectomy for malignancy. Ann Surg 244:260–264
Gu FM, Gao Q, Shi GM, Zhang X, Wang J, Jiang JH, Wang XY, Shi YH, Ding ZB et al (2012) Intratumoral IL-17+ cells and neutrophils show strong prognostic significance in intrahepatic cholangiocarcinoma. Ann Surg Oncol 19:2506–2514
Guest et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24310400
Guglielmi A, Ruzzenente A, Campagnaro T, Pachera S, Valdegamberi A, Nicoli P, Capellani A et al (2009) Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. World J Surg 33:1247–1254
Güllüoglu MG, Ozden I, Poyanli A, Cevikbas U, Ariogul O (2007) Intraductal growth-type mucin-producing peripheral cholangiocarcinoma associated with biliary papillomatosis. Ann Diagn Pathol 11:34–38
Hai S, Kubo S, Uenishi T, Yamamoto T, Tanaka H, Shuto T, Takemura S, Hirohashi K (2005) Postoperative survival in intrahepatic cholangiocarcinoma showing intraductal growth. Hepatogastroenterology 52:374–377
Hamada S, Satoh K, Hirota M, Kanno A, Ishida K, Umino J, Ito H, Kikuta K, Kume K et al (2011) Calcium-binding protein S100P is a novel diagnostic marker of cholangiocarcinoma. Cancer Sci 102:150–156
Han JK, Lee JM (2004) Intrahepatic intraductal cholangiocarcinoma. Abdom Imaging 29:558–564
Hardeman et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12472031
Hasita H, Komohara Y, Okabe H, Maduda T, Ohnishi K, Lei XF, Beppu T, Baba H, Takeya M (2010) Significance of alternatively activated macrophages in patients with intrahepatic cholangiocarcinoma. Cancer Sci 101:1913–1919
Hayashi H, Maeda T, Adachi E, Shimada M, Matsumata T, Takenaka K (1995) Argyrophilic nucleolar organizer regions (AgNOR) of resected intrahepatic cholangiocellular carcinomas. Hepatogastroenterology 42:440–444
Hayashi H, Tani T, Tajima H, Shoji Y, Terai S, Onishi I, Takamura H, Kitagawa H et al (2011) Small intestinal metastasis from intrahepatic cholangiocarcinoma: report of a case. Surg Today 41:859–864
Higashi M, Yonezawa S, Ho JJ, Tanaka S, Irimura T, Kim YS, Sato E (1999) Expression of MUC1 and MUC2 mucin antigens in intrahepatic bile duct tumors: its relationship with a new morphological classification of cholangiocarcinoma. Hepatology 30:1347–1355
Higashi M, Yamada N, Yokoyama S, Kitamoto S, Tabata K, Koriyama C, Batra SK et al (2012) Pathobiological implications of MUC16/CA125 expression in intrahepatic cholangiocarcinoma – mass forming type. Pathobiology 79:101–106
Hirohashi K, Uenishi T, Kubo S, Yamamamoto T, Tanaka H, Shuto T, Yamasaki O, Horii K, Kinoshita H (2002a) Histologic bile duct invasion by a mass-forming intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 9:233–236
Hirohashi K, Uenishi T, Kubo S, Yamamoto T, Tanaka H, Shuto T, Kinoshita H (2002b) Macroscopic types of intrahepatic cholangiocarcinoma: clinicopathologic features and surgical outcomes. Hepatogastroenterology 49:326–329
Horie S, Endo K, Kawasaki H, Terada T (2000) Overexpression of MDM2 protein in intrahepatic cholangiocarcinoma: relationship with p53 overexpression, Ki-67 labeling, and clinicopathologic features. Virchows Arch 437:25–30
Hui CK, Yuen MF, Tso WK, Ng IO, Chan AO, Lai CL (2003) Cholangiocarcinoma in liver cirrhosis. J Gastroenterol Hepatol 18:337–341
Hyder O, Hatzaras I, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, Pulitano C et al (2013) Recurrence after operative management of intrahepatic cholangiocarcinoma. Surgery 153:811–818
Igami T, Nagino M, Oda K, Nishio H, Ebata T, Yokoyama Y, Shimoyama Y (2009) Clinicopathologic study of cholangiocarcinoma with superficial spread. Ann Surg 249:296–302
Iguchi T, Yamashita N, Aishima S, Kuroda Y, Terashi T, Sugimachi K, Taguchi K, Taketomi A et al (2009) A comprehensive analysis of immunohistochemical studies in intrahepatic cholangiocarcinoma using the survival tree model. Oncology 76:293–300

Ikegami T, Kayashima H, Sadanaga N, Morizono S, Nakashima A, Matsuura H, Shirabe K et al (2013) Composite small cell and mucinous carcinoma originating from the intrahepatic bile duct: report of a case. Surg Today 43:194–198

Imai K, Yamamoto M, Ariizumi S (2010) Surgery for periductal infiltrating type intrahepatic cholangiocarcinoma without hilar invasion provides a better outcome than for mass-forming type intrahepatic cholangiocarcinoma without hilar invasion. Hepatogastroenterology 57:1333–1336

Imamura S, Suzuki H (2004) Head and neck metastases from occult abdominal primary site: a case report and literature review. Acta Otolaryngol 124:107–112

Inaba K, Suzuki S, Yokoi Y, Ota S, Nakamura T, Konno H, Baba S, Takehara Y, Nakamura S (2003) Hepatic inflammatory pseudotumor mimicking intrahepatic cholangiocarcinoma: report of case. Surg Today 333:714–717

Isa et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12063950

Ishak KG, Goodman ZD, Stocker JT (2001) Intrahepatic cholangiocarcinoma and other malignant biliary tumors. In: Ishak KG, Goodman ZD, Stocker JT (eds) Fascicle 31. Atlas of tumor pathology: tumors of the liver and intrahepatic bile ducts. Armed Forces Institute of Pathology, Washington, DC, pp 245–270

Izumi R, Shima Y, Yabushita K, Watanabe T, Onoda H, Hirosawa H, Konishi K, Miyazaki I (1986) HCG-producing intrahepatic cholangiocarcinoma (in Japanese). Gan No Rinsho 32:1867–1871

Izumi S, Nakamura S, Mano S (2010) Large intrahepatic cholangiocarcinoma with tumor infiltrative lymphocytes and autoimmune hepatitis-like features. Case Rep Gastroenterol 4:46–51

Izzo F, Piccirillo M, Albino V, Botti G, Foggia M, Iodice R, Pagano F, Piccirillo G, Tornillo L et al (2010) Case report: appearance of an intestinal metastasis from intrahepatic cholangiocarcinoma occurring 5 years after resection of the primary tumor. Eur J Gastroenterol Hepatol 22:892–894

Jan YY, Yeh CN, Yeh TS, Chen TC (2005) Prognostic analysis of surgical treatment of peripheral cholangiocarcinoma: two decades of experience at Chang Gung Memorial Hospital. World J Gastroenterol 11:1779–1784

Jarnagin WR, Bowne W, Klimstra DS, Ben-Porat L, Roggin K, Cymes K, Fong Y et al (2005) Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. Ann Surg 241:703–712

Jeong CY, Hah YS, Cho BI, Lee SM, Joo YT, Jung EJ, Jeong SH, Lee YJ, Choi SK et al (2012) Fatty acid-binding protein 5 promotes cell proliferation and invasion in human intrahepatic cholangiocarcinoma. Oncol Rep 28:1283–1292

Jhala et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/15794670

Jin GY, Lee JM, Yu HC, Mun WS, Kim CS (2002) Intraductal papillary cholangiocarcinoma with aneurismal dilatation: a case of the mimicking abscess. Hepatogastroenterology 49:1523–1525

Jung KS, Chun KH, Choi GH, Jeon HM, Shin HS, Park YN, Park JY (2013) Synchronous development of intrahepatic cholangiocarcinoma and hepatocellular carcinoma in different sites of the liver with chronic B-viral hepatitis: two case reports. BMC Res Notes 6:250

Kaczynski J, Hansson G, Wallerstedt S (1998) Incidence, etiologic aspects and clinicopathologic features in intrahepatic cholangiocellular carcinoma – a study of 51 cases from a low-endemicity area. Acta Oncol 37:77–83

Kajiyama K, Maeda T, Takenaka K, Sugimachi K, Tsuneyoshi M (1999) The significance of stromal desmoplasia in intrahepatic cholangiocarcinoma: a special reference of 'scirrhous-type' and 'nonscirrhous-type' growth. Am J Surg Pathol 23:892–902

Kakinoki K, Takemori Y, Noda Y, Hoso M (2000) An autopsy case of intrahepatic cholangiocarcinoma producing granulocyte-colony stimulating factor (in Japanese). Nippon Shokakibyo Gakkai Zasshi 97:1165–1169

Karabulut AA, Sahin S, Sahin M, Eksioglu M, Ustün H (2006) Paraneoplastic acrokeratosis of Bazex (Bazex's syndrome): report of a female case associated with cholangiocarcinoma and review of the published work. J Dermatol 33:850–854

Kayashima H, Taketomi A, Yamashita Y, Kuroda Y, Kitagawa D, Harimoto N, Tsujita E et al (2008) Liver metastasis with intraductal invasion originating from rectal cancer: report of a case. Surg Today 38:765–768

Keeratichamroen S, Leelawat K, Thongtawee T, Narong S, Aegem U, Tujinda S, Praditphol et al (2011) Expression of CD24 in cholangiocarcinoma cells is associated with disease progression and reduced patient survival. Int J Oncol 39:873–881

Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC (2002) Changing international trends in mortality rates for liver, biliary and pancreatic tumours. J Hepatol 37:806–813

Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD (2005) Cholangiocarcinoma. Lancet 366:1303–1314

Khan SA, Toledano MB, Taylor-Robinson SD (2008) Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. HPB (Oxford) 10:77–82

Khan SA, Emadossadaty S, Ladep NG, Thomas HC, Elliott P, Taylor-Robinson SD et al (2012) Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? J Hepatol 56:848–854

Khunamornpong S, Siriaunkgul S, Suprasert P, Pojchamarnwiputh S, Chiangmai WN et al (2007) Intrahepatic cholangiocarcinoma metastatic to the ovary: a report of 16 cases of an underemphasized form of secondary tumor in the ovary that may mimic primary neoplasia. Am J Surg Pathol 31:1788–1799

Kiba T, Tsuda H, Pairojkul C, Inoue S, Sugimura T, Hirohashi S (1993) Mutations of the p53 tumor

suppressor gene and the ras gene family in intrahepatic cholangiocarcinomas in Japan and Thailand. Mol Carcinog 8:312–318
Kim YI, Yu ES, Kim ST (1989) Intraductal variant of peripheral cholangiocarcinoma of the liver in Clonorchis sinensis infection. Cancer 63:1562–1566
Kim et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10398901
Kim YJ, Yun M, Lee WJ, Kim KS, Lee JD (2003) Usefulness of 18F-FDG PET in intrahepatic cholangiocarcinoma. Eur J Nucl Mol Imaging 30:1467–1472
Kim SH, Lee CH, Kim BH, Kim WB, Yeom SK, Kim KA, Park CM (2012) Typical and atypical imaging findings of intrahepatic cholangiocarcinoma using gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging. J Comput Assist Tomogr 36:704–709
Kitade M, Yoshiji H, Yamao J, Fujimoto M, Kojima H, Mitoro A, Namisaki T, Toyohara M et al (2005) Intrahepatic cholangiocarcinoma associated with central calcification and arterio-portal shunt. Intern Med 44:825–828
Kobayashi et al. 2000. http://www.ncbi.nlm.nih.gov/pubmed/10861422
Kojiro M, Kawabata K, Kawano Y, Shirai F, Takemoto N, Nakashima T (1982) Hepatocellular carcinoma presenting as intrabile duct tumor growth: a clinicopathologic study of 24 cases. Cancer 49:2144–2147
Kokubo T, Itai Y, Nagao T (1990) Intrahepatic cholangiocarcinoma with cystic formation. Radiat Med 8:219–221
Kondo NI, Shirabe K, Mano Y, Taketomi A, Yoshizumi T, Ikegami T, Masuda T, Kayashima H et al (2012) Late recurrence after resection of mass-forming intrahepatic cholangiocarcinoma: report of a case. Surg Today 42:1210–1214
Körner M, Hayes GM, Rehmann R, Zimmermann A, Scholz A, Wiedenmann B, Miller LJ et al (2006) Secretin receptors in the human liver: expression in biliary tract and cholangiocarcinoma, but not in hepatocytes or hepatocellular carcinoma. J Hepatol 45:825–835
Kosriwong K, Menheniott TR, Giraud AS, Jearanaikon P, Sripa B, Limpaiboon T (2011) Trefoil factors: tumor progression markers and mitogens via EGFR/MAPK activation cholangiocarcinoma. World J Gastroenterol 17:1631–1641
Kozaka K, Sasaki M, Fujii T, Harada K, Zen Y, Sato Y, Sawada S, Minato H, Matsui O (2007) A subgroup of intrahepatic cholangiocarcinoma with an infiltrating replacement growth pattern and a resemblance to reactive proliferating bile ductules: 'bile ductular carcinoma'. Histopathology 51:390–400
Kubo S, Kinoshita H, Hirohashi K, Hamba H (1995) Hepatolithiasis associated with cholangiocarcinoma. World J Surg 19:637–641
Kubo S, Uenishi T, Yamamoto S, Hai S, Yamamoto T, Ogawa M, Takemura S, Shuto T et al (2004) Clinicopathologic characteristics of small intrahepatic cholangiocarcinomas of mass-forming type. Hepatol Res 29:223–227
Kwon BJ, Rhim H, Kom YS, Koh BH, Cho OK (2000) Peripheral cholangiocarcinoma with extensive tumor thrombi in the portal venous system: case report. Abdom Imaging 25:615–617
Kwon OS, Jun DW, Kim SH, Chung MY, Kim NI, Song MH, Lee HH, Kim SH et al (2007) Distant skeletal muscle metastasis from intrahepatic cholangiocarcinoma presenting as Budd-Chiari syndrome. World J Gastroenterol 13:3141–3143
Labgaa I, Carrasco-Avino G, Fiel MI, Schwartz ME (2014) Pancreatic recurrence of intrahepatic cholangiocarcinoma: case report and review of the literature. World J Gastrointest Surg 6:65–69
Lagana SM, Moreira RK, Remotti HE, Bao F (2013) Glutamine synthetase, heat shock protein-70, and glypican-3 in intrahepatic cholangiocarcinoma and tumors metastatic to liver. Appl Immunohistochem Mol Morphol 21:254–257
Langer F, von Wasiliewski R, Kreipe HH (2006) The importance of immunohistochemistry for the diagnosis of cholangiocarcinomas (in German). Pathologe 27:244–250
Law JK, Davis J, Buckley A, Salh B (2005) Intrahepatic cholangiocarcinoma presenting as the Budd-Chiari syndrome: a case report and literature review. Can J Gastroenterol 19:723–728
Lazarides KN, Gores GJ (2005) Cholangiocarcinoma. Gastroenterology 128:1655–1667
Lee SK, Choi BI, Cho JM, Han JK, Kim YI, Han MC (1995) Cystic peripheral cholangiocarcinoma: sonography and CT. Abdom Imaging 20:131–132
Leong AS, Sormunen RT, Tsui WM, Liew CT (1998) Hep Par 1 and selected antibodies in the immunohistochemical distinction of hepatocellular carcinoma from cholangiocarcinoma, combined tumours and metastatic carcinoma. Histopathology 33:318–324
Levy M, Lin F, Xu H, Dhall D, Spaulding BO, Wang HL (2010) S100P, von Hippel-Lindau gene product, and IMP3 serve as a useful immunohistochemical panel in the diagnosis of adenocarcinoma on endoscopic bile duct biopsy. Hum Pathol 41:1210–1219
Li H, Li C (2013) The CD79a (HM47/A9) antibody is effective in distinguishing between primary hepatocellular carcinoma and primary intrahepatic cholangiocarcinoma. Oncol Lett 5:1195–1198
Liau JY, Tsai JH, Yuan RH, Chang CN, Lee HJ, Jeng YM (2014) Morphological subclassification of intrahepatic cholangiocarcinoma: etiological, clinicopathological, and molecular features. Mod Pathol 27:1163–1173
Lim JH (2003) Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. AJR Am J Roentgenol 181:819–827
Lim JH, Kim YI, Park CK (2000) Intraductal mucosal-spreading mucin-producing peripheral cholangiocarcinoma of the liver. Abdom Imaging 25:89–92
Liu XF, Zhang H, Zhu SG, Zhou XT, Su HL, Xu Z, Li SJ (2006) Correlation of p53 gene mutation and

expression of P53 protein in cholangio-carcinoma. World J Gastroenterol 12:4706–4709
Liver Cancer Study Group of Japan (1990) Primary liver cancer in Japan: clinicopathologic features and results of surgical treatment. Ann Surg 211:277–287
Liver Cancer Study Group of Japan (1997) Clinical and surgical findings. In: Liver Cancer Study Group of Japan (ed) Classification of primary liver cancer. First English edition. Kanehara Shuppan, Toyko, pp 1–22
Lok T, Chen L, Lin F, Wang HL (2014) Immunohistochemical distinction between intrahepatic cholangiocarcinoma and pancreatic ductal adenocarcinoma. Hum Pathol 45:394–400
Low JJ, Chew SH, Chew SP, Han CC, Tay EH, Ho TH (2003) A rare case of ovarian carcinoma originating from primary intrahepatic cholangiocarcinoma. Case Rep Eur J Gynaecol Oncol 24:85–88
Maeda T, Kajiyama K, Adachi E, Takenaka K, Sugimachi K, Tsuneyoshi M (1996) The expression of cytokeratins 7, 19, and 20 in primary and metastatic carcinomas of the liver. Mod Pathol 9:901–909
Malhi H, Gores GJ (2006) Cholangiocarcinoma: modern advances in understanding a deadly old disease. J Hepatol 45:856–867
Mall AS, Tyler MG, Ho SB, Krige JE, Kahn D, Spearman W, Myer L, Govender D (2010) The expression of MUC mucin in cholangiocarcinoma. Pathol Res Pract 206:805–809
Man XB, Tang L, Zhang BH, Li SJ, Qiu XH, Wu MC, Wang HY (2005) Upregulation of gylpican-3 expression in hepatocellular carcinoma but downregulation in cholangiocarcinoma indicates its differential diagnosis value in primary liver cancers. Liver Int 25:962–966
Manikawa K, Oka K, Masuda A, Yonkawa N, Kashimura J, Nihei T (2010) Extensive endothelial replacement by tumor cells in the portal system: an autopsy case of intrahepatic cholangiocarcinoma. Pathol Int 60:591–594
Matsumura N, Yamamoto M, Aruga A, Takasagi K, Nakano M (2002) Correlation between expression of MUC1 core protein and outcome after surgery in mass-forming intrahepatic cholangiocarcinoma. Cancer 94:1770–1776
Mimatsu K, Oida T, Kawasaki A, Kano H, Fukino N, Kida K, Kuboi Y, Amano S (2011) Long-term survival after resection of mass-forming type intrahepatic cholangiocarcinoma directly infiltrating the transverse colon and sequential brain metastasis: report of a case. Surg Today 41:1410–1413
Minato H, Nakanuma Y (1993) Cell kinetic and morphological studies of human cholangiocellular carcinoma. Acta Pathol Jpn 43:111–120
Miwa S, Miyagawa S, Kobayashi A, Akahane Y, Nakata T, Mihara M, Kusama K, Soeda J, Ogawa S (2006) Predictive factors for intrahepatic cholangiocarcinoma recurrence in the liver following surgery. J Gastroenterol 41:893–900
Miyamoto J, Tatsuzawa K, Sasjima H, Mineura K (2007) Metastatic skull tumor from cholangiocarcinoma. Case Rep Neurol Med Chir (Tokyo) 47:132–135
Mizukami Y, Ohta H, Arisato S, Nakano Y, Murakami M, Orii Y, Saito H, Sakurai Y et al (1999) Case report: mucinous cholangiocarcinoma featuring a multicystic appearance and periportal collar in imaging. J Gastroenterol Hepatol 14:1223–1226
Morimoto Y, Tanaka Y, Ito T, Nakahara M, Nakaba H, Nishida T, Fujikawa M, Ito T et al (2003) Long-term survival and prognostic factors in the surgical treatment of intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 10:432–440
Mosnier JF, Kandel C, Cazals-Hatem D, Bou-Hanna C, Gounay J, Jarry A, Laboisse CL (2009) N-cadherin serves as diagnostic biomarker in intrahepatic and perihilar cholangiocarcinomas. Mod Pathol 22:182–190
Muenphom K, Limpaiboon T, Jearanaikoon P, Pairojkul C, Sripa B, Budhisawasdi V (2006) Amplification of chromosome 21q22.3 harboring trefoil factor family gene in liver fluke related cholangiocarcinoma is associated with poor prognosis. World J Gastroenterol 12:4143–4148
Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Sueda T (2012) Intrahepatic cholangiocarcinoma: clinicopathological differences between peripheral type and hilar type. J Gastrointest Surg 16:540–548
Nagano K, Fukuda Y, Nakano I, Katano Y, Toyoda H, Ebata M, Morita K, Yokozaki S et al (2000) A case of the development of two hepatocellular carcinomas and a cholangiocarcinoma with cirrhosis after elimination of serum hepatitis C virus RNA with interferon therapy. Hepatogastroenterology 47:1436–1438
Nakagawa T, Kamiyama T, Kurauchi N, Matsushita M, Nakanishi K, Kamachi H, Kudo T et al (2005) Number of lymph node metastases is a significant prognostic factor in intrahepatic cholangiocarcinoma. World J Surg 29:728–733
Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S, Tanizawa Y, Kobayashi A (2003) Mucin-producing intrahepatic cholangiocarcinoma with portal vein thrombosis. Hepatogastroenterology 50:2194–2195
Nakajima T, Kondo Y (1989) Well-differentiated cholangiocarcinoma: diagnostic significance of morphologic and immunohistochemical parameters. Am J Surg Pathol 13:569–573
Nakajima T, Kondo Y (1990) A clinicopathologic study of intrahepatic cholangiocarcinoma containing a component of squamous cell carcinoma. Cancer 65:1401–1404
Nakajima T, Kondo Y, Miyazaki M, Okui K (1988) A histopathologic study of 102 cases of intrahepatic cholangiocarcinoma: histologic classification and modes of spreading. Hum Pathol 19:1228–1234
Nakanishi D, Tanio Y, Tagawa H, Akiyama T, Takashima J, Motone M, Kawai T, Kondo T et al (2013) An autopsy

of a case of pulmonary hypertension secondary to pulmonary embolization of intrahepatic cholangiocarcinoma (in Japanese). Gan To Kagaku Ryoho 40:499–502

Nakanuma Y (2012) Classification of intrahepatic cholangiocarcinoma based on recent progress and new proposal. Nihon Shokakibyo Gakkai Zasshi 109:1865–1871

Nakanuma Y, Harada K, Ishikawa A, Zen Y, Sasaki M (2003) Anatomic and molecular pathology of intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 10:265–281

Nakanuma Y, Sasaki M, Ikeda H, Sato Y, Zen Y, Kosaka K, Harada K (2008) Pathology of peripheral intrahepatic cholangiocarcinoma with reference to tumorigenesis. Hepatol Res 38:325–334

Nakanuma Y, Sato Y, Harada K, Sasaki M, Xu J, Iheda H (2010) Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. World J Hepatol 2:419–427

Nakanuma Y, Xu J, Harada K, Sato Y, Saski M, Ikeda H, Kim J, Yu E (2011) Pathological spectrum of intrahepatic cholangiocarcinoma arising in non-biliary chronic advanced liver diseases. Pathol Int 61:298–305

Nakanuma Y, Sato Y, Ikeda H, Harada K, Kobayashi M, Sano K, Uehara T, Yamamoto M et al (2012) Intrahepatic cholangiocarcinoma with predominant "ductal plate malformation" pattern: a new subtype. Am J Surg Pathol 36:1629–1635

Nakanuma Y, Sato Y, Ojima H, Kanai Y, Aishima S, Yamamoto M, Ariizumi S, Furukawa T et al (2014) Clinicopathological characterization of so-called "cholangiocarcinoma with intraductal papillary growth" with respect to "intraductal papillary neoplasm of bile duct (IPNB)". Int J Clin Exp Pathol 7:3112–3122

Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH et al (1996) Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 224:463–473

Nishihara Y, Aishima S, Hayashi A, Iguchi T, Fujita N, Taketomi A, Honda H, Tsuneyoshi M (2009) CD10+ fibroblasts are more involved in the progression of hilar/extrahepatic cholangiocarcinoma than of peripheral intrahepatic cholangiocarcinoma. Histopathology 55:423–431

Nishizawa T, Higuchi H, Takaishi H, Iizuka H, Izumiya M, Yamagishi Y, Hisamatsu T et al (2006) A case of intrahepatic cholangiocarcinoma effectively treated by hepatic arterial infusion chemotherapy (in Japanese). Gan To Kagaku Ryoho 33:1657–1659

Nonomura A, Ohta G, Hayashi M, Izumi R, Watanabe K, Takayanagi N, Matsubara F (1987) Immunohistochemical localization of ras p21 and carcinoembryonic antigens (CEA) in cholangiocarcinoma. Liver 7:142–148

Nozaki Y, Yamamoto M, Ikai I, Yamamoto Y, Ozaki N, Fujii H, Nagahori K, Matsumoto Y et al (1998) Reconsideration of the lymph node metastasis pattern (N factor) from intrahepatic cholangiocarcinoma using the International Union Against Cancer TNM staging system for primary liver carcinoma. Cancer 83:1923–1929

Ohashi K, Nakajima Y, Tsutsumi M, Kanehiro H, Fukuoka T, Hisanaga M, Taki J, Nakae D et al (1994) Clinical characteristics and proliferating activity of intrahepatic cholangiocarcinoma. J Gastroenterol Hepatol 9:442–446

Ohashi et al. 1995. http://www.ncbi.nlm.nih.gov/pubmed/7557145

Ohira et al. 2006. http://www.ncbi.nlm.nih.gov/pubmed/16565491

Ohta T, Nagakawa T, Ueda N, Nakamura T, Akiyama T, Ueno K, Miyazaki I (1991) Mucosal dysplasia of the liver and the intraductal variant of peripheral cholangiocarcinoma in hepatolithiasis. Cancer 68:2217–2223

Oikawa et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23175232

Okabe H, Beppu T, Hayashi H, Horino K, Masuda T, Komori H, Ishikawa S, Watanabe M et al (2009) Hepatic stellate cells may relate to progression of intrahepatic cholangiocarcinoma. Ann Surg Oncol 16:2555–2564

Okabe H, Beppu T, Hayashi H, Ishiko T, Masuda T, Otao R, Horlad H, Jono H, Ueda M et al (2011) Hepatic stellate cells accelerate the malignant behavior of cholangiocarcinoma cells. Ann Surg Oncol 18:1175–1184

Okabe H, Beppu T, Ueda M, Hayashi H, Ishiko T, Masuda T, Otao R, Horlad H, Mima K et al (2012) Identification of CXCL5/ENA-78 as a factor involved in the interaction between cholangiocarcinoma cells and cancer-associated fibroblasts. Int J Cancer 131:2234–2241

Okami J, Dono K, Sakon M, Tsujie M, Hayashi N, Fujiwara Y, Nagano H, Umeshita K et al (2003) Patterns of regional lymph node involvement in intrahepatic cholangiocarcinoma of the left lobe. J Gastrointest Surg 7:850–856

Okamura Y, Harada A, Maeda A, Fujioka A, Horiba T, Ishigure K, Hirai A, Ito Y, Uesaka K (2008) Carcinomatous meningitis secondary to cholangiocarcinoma without other systemic metastasis. J Hepatobiliary Pancreat Surg 15:237–239

Okaro AC, Deery AR, Hutchins RR, Davidson BR (2001) The expression of antiapoptotic proteins Bcl-2, Bcl-X (L), and Mcl-1 in benign, dysplastic, and malignant biliary epithelium. J Clin Pathol 54:927–932

Okuda K, Kubo Y, Okazaki N, Arishima T, Hashimoto M (1977) Clinical aspects of intrahepatic bile duct carcinoma including hilar carcinoma: a study of 57 autopsy-proven cases. Cancer 39:232–246

Okuda K, Nakanuma Y, Miyazaki M (2002) Cholangiocarcinoma: recent progress. Part 1: epidemiology and etiology. J Gastroenterol Hepatol 17:1049–1055

Okuda H, Shiratori K, Yamamoto M, Takasaki K, Nakano M (2006) Clinicopathologic features of patients with intrahepatic cholangiocarcinoma who are seropositive

for a-fetoprotein-L3 and those with combined hepatocellular and cholangiocarcinoma. J Gastroenterol Hepatol 21:869–873

Oshiro T, Esaki M (2011) A case of intrahepatic cholangiocarcinoma with marked mucus production. Jpn J Clin Oncol 41:1388

Palma AS, Liu Y, Childs RA, Herbert C, Wang D, Chai W, Feizi T (2011) The human epithelial carcinoma antigen recognized by monoclonal antibody AE3 is expressed on a sulfoglycolipid in addition to neoplastic mucins. Biochem Biophys Res Commun 408:548–552

Pandey D, Lee KH, Wong SY, Tan KC (2007) Adrenal metastasis from intrahepatic cholangiocarcinoma. Liver Int 27:1016

Park SK, Kim YS, Kim SG, Jang JY, Moon JH, Lee MS, Kim BS, Koh ES, Park JM (2010) Detection of distant metastasis to skeletal muscle by 18F-FDG-PET in a case of intrahepatic cholangiocarcinoma. Korean J Hepatol 16:325–328

Parkin DM, Ohshima H, Srivatanakul P, Vatanasapt V (1993) Cholangiocarcinoma: epidemiology, mechanisms of carcinogenesis and prevention. Cancer Epidemiol Biomarkers Prev 2:537–544

Patel T (2001) Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 33:1353–1357

Patel T (2006) Cholangiocarcinoma. Nat Clin Pract Gastroenterol Hepatol 3:33–42

Patel T (2011) Cholangiocarcinoma – controversies and challenges. Nat Rev Gastroenterol Hepatol 8:189–200

Patel SH, Kooby DA, Staley CA, Sarmiento JM, Maithel SK (2011) The prognostic importance of lymphovascular invasion in cholangiocarcinoma above the cystic duct: a new selection criterion for adjuvant therapy? HPB (Oxford) 13:605–611

Patsenker E, Wilkens L, Banz V, Osterreicher CH, Weimann R, Eisele S, Keogh A et al (2010) The alphavbeta6 integrin is a highly specific immunohistochemical marker for cholangiocarcinoma. J Hepatol 52:362–369

Que et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10573518

Radwan NA, Ahmed NS (2012) The diagnostic value of arginase-1 immunostaining in differentiating hepatocellular carcinoma from metastatic carcinoma and cholangiocarcinoma as compared to HepPar-1. Diagn Pathol 7:149

Ravnborg L, Thomsen K (1993) Acanthosis nigricans and bile duct malignancy. Acta Derm Venereol 73:378–379

Regimbeau JM, Panis Y, Nemeth J, Pocard M, de Claviere G, Soyer P, Valleur P (2003) Mass-forming intrahepatic cholangiocarcinoma presenting tumor growth in extrahepatic bile duct and superficial spreading. Hepatogastroenterology 50:21–23

Resende V, Roda R, Pedrosa MS (2012) Gallbladder papillary neoplasia associated with intrahepatic carcinoma and pancreaticobiliary malformation. Gastroenterol Res 5:245–248

Riener MO, Vogetseder A, Pestalozzi BC, Clavien PA, Probst-hensch N, Kristiansen G, Jochum W (2010) Cell adhesion molecules P-cadherin and CD24 are markers for carcinoma and dysplasia in the biliary tract. Hum Pathol 41:1558–1565

Rizvi and Gores 2013. http://www.ncbi.nlm.nih.gov/pubmed/24140396

Rullier A, Le Bail B, Fawaz R, Blanc JF, Saric J, Bioulac-Sage P (2000) Cytokeratin 7 and 20 expression in cholangiocarcinomas varies along the biliary tract but still differs from that of colorectal carcinoma metastasis. Am J Surg Pathol 24:870–876

Sabit H, Tsuneyama K, Shimonishi T, Harada K, Cheng J, Ida H, Saku T, Saito K, Nakanuma Y (2001) Enhanced expression of basement-membrane-type heparan sulfate proteoglycan in tumor fibro-myxoid stroma of intrahepatic cholangiocarcinoma. Pathol Int 51:248–256

Sanada Y, Kawashita Y, Okada S, Azuma T, Matsuo S (2014) Review to better understand the macroscopic subtypes and histogenesis of intrahepatic cholangiocarcinoma. World J Gastrointest Pathophysiol 5:188–199

Sano T, Yamamoto J, Kosuge T, Inoue K, Shimada K, Takayama T, Yamazaki S, Sakamoto M et al (1996) Intrahepatic cholangiocarcinoma presenting intrabile duct tumor growth: report of a case. Hepatogastroenterology 43:667–670

Sano T, Kamiya J, Nagino M, Uesaka K, Kondo S, Kanai M, Hayakawa N, Nimura Y (1999) Macroscopic classification and preoperative diagnosis of intrahepatic cholangiocarcinoma in Japan. J Hepatobiliary Pancreat Surg 6:101–107

Sasaki M, Nakanuma Y, Shimizu K, Izumi R (1995) Pathological and immunohistochemical findings in a case of mucinous cholangiocarcinoma. Pathol Int 45:781–786

Sasaki M, Nakanuma Y, Kim YS (1996) Characterization of apomucin expression in intrahepatic cholangiocarcinomas and their precursor lesions: an immunohistochemical study. Hepatology 24:1074–1078

Sasaki M, Nakanuma Y, Ho SB, Kim YS (1998a) Cholangiocarcinomas arising in cirrhosis and combined hepatocellular-cholangiocellular carcinomas share apomucin profiles. Am J Clin Pathol 109:302–308

Sasaki A, Aramaki M, Kawano K, Morii Y, Nakashima K, Yoshida T, Kirano S (1998b) Intrahepatic peripheral cholangiocarcinoma: mode of spread and choice of surgical treatment. Br J Surg 85:1206–1209

Sasaki A, Kawano K, Aramaki M, Nakashima K, Yoshida T, Kitano S (1999) Immunohistochemical expression of cytokeratins in intrahepatic cholangiocarcinoma and metastatic adenocarcinoma of the liver. J Surg Oncol 70:103–108

Sasaki M, Tsuneyama K, Ishikawa A, Nakanuma Y (2003) Intrahepatic cholangiocarcinoma in cirrhosis presents granulocyte and granulocyte-macrophage colony-stimulating factor. Hum Pathol 34:1337–1344

Sasaki et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15011869

Sasaki M, Ikeda H, Nakanuma Y (2007) Expression profiles of MUC mucins and trefoil factor family (TFF) peptides in the intrahepatic biliary system: physiological distribution and pathological significance. Prog Histochem Cytochem 42:61–110

Sato Y, Ojima H, Onaya H, Mori T, Hiraoka N, Kishi Y, Nara S, Esaki M, Shimada K et al (2013a) Histopathological characteristics of hypervascular cholangiocellular carcinoma as an early stage of cholangiocellular carcinoma. Hepatol Res. doi:10.1111/hepr.12236

Sato Y, Harada K, Sasaki M, Nakanuma Y (2013b) Clinicopathological significance of S100 protein expression in cholangiocarcinoma. J Gastroenterol Hepatol 28:1422–1429

Schlinkert RT, Nagorney DM, Van Heerden JA, Adson MA (1992) Intrahepatic cholangiocarcinoma: clinical aspects, pathology and treatment. HPB Surg 5:95–101

Sempoux C, Jibara G, Ward SC, Fan C, Qin L, Roayaje S, Fiel MI, Schwartz M, Thung SN (2011) Intrahepatic cholangiocarcinoma: new insights in pathology. Semin Liver Dis 31:49–60

Settakorn J, Kaewpila N, Burns GF, Leong AS (2005) FAT, E-cadherin, beta catenin, HER 2/neu, Ki67 immunoexpression, and histological grade in intrahepatic cholangiocarcinoma. J Clin Pathol 58:1249–1254

Shaib Y, El-Serag HB (2004) The epidemiology of cholangiocarcinoma. Semin Liver Dis 24:115–125

Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA (2005) Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. Gastroenterology 128:620–626

Sharma P, Jaffe PE, Bhattacharyya A (1997) Metastatic cholangiocarcinoma presenting as ovarian cancer: a rare Krukenberg tumor. Am J Gastroenterol 92:531–533

Shen WF, Zhong W, Xu F, Kan T, Geng L, Xie F, Sui CJ, Yang JM (2009) Clinicopathological and prognostic analysis of 429 patients with intrahepatic cholangiocarcinoma. World J Gastroenterol 15:5976–5982

Shen FZ, Zhang BY, Feng YJ, Jia ZX, An B, Liu CC, Deng XY, Kulkarni AD, Lu Y (2010) Current research in perineural invasion of cholangiocarcinoma. J Exp Clin Cancer Res 29:24

Shibahara et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/14752841

Shimada M, Yamashita Y, Aishima S, Shirabe K, Takenaka K, Sugimachi K (2001) Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma. Br J Surg 88:1463–1466

Shimonishi T, Miyazaki K, Nakanuma Y (2000) Cytokeratin profile relates to histological subtypes and intrahepatic location of intrahepatic cholangiocarcinoma and primary sites of metastatic adenocarcinoma of liver. Histopathology 37:55–63

Shimonishi et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11274640

Shinojima Y, Toma Y, Terui T (2006) Sweet syndrome associated with intrahepatic cholangiocarcinoma producing granulocyte colony-stimulating factor. Br J Dermatol 155:1103–1104

Shinozaki A, Shibahara J, Noda N, Tanaka M, Aoki T, Kokudo N, Fukayama M (2011) Claudin-18 in biliary neoplasms. Its significance in the classification of intrahepatic cholangiocarcinoma. Virchows Arch 459:73–80

Sia D, Hoshida Y, Villanueva A, Roayaie S, Ferrer J, Tabak B, Peix J, Sole M, Tovar V et al (2013) Integrative molecular analysis of intrahepatic cholangiocarcinoma reveals 2 classes that have different outcomes. Gastroenterology 144:829–840

Sinawat P, Hemsrichart V (1991) A histopathologic study of 61 cases of peripheral intrahepatic cholangiocarcinoma. J Med Assoc Thai 74:448–453

Singh P, Patel T (2006) Advances in diagnosis, evaluation and management of cholangiocarcinoma. Curr Opin Gastroenterol 22:294–299

Sirica AE (2011) The role of cancer-associated myofibroblasts in intrahepatic cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 9:44–54

Sirica AE, Campbell DJ, Dumur CI (2011) Cancer-associated fibroblasts in intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol 27:276–284

Skopelitou A, Hadjiyannakis M, Alexopoulou V, Krikoni O, Kamina S, Agnantis N (1996) Topographical immunohistochemical expression of bcl-2 protein in human liver lesions. Anticancer Res 16:975–978

Slattery JM, Sahani DV (2006) What is the current state-of-the-art imaging for detection and staging of cholangiocarcinoma? Oncologist 11:913–922

Sohda T, Shiga H, Nakane H, Wtanabe H, Takeshita M, Sakisaka S (2006) Cholangiocellular carcinoma that produced both granulocyte-colony-stimulating factor and parathyroid hormone-related protein. Int J Clin Oncol 11:246–249

Soyer P, Pelage JP, Zidi SH, Boudiaf M, Rymer R (1998) Portal vein invasion by intrahepatic peripheral cholangiocarcinoma: a rare cause of portal hypertension. AJR Am J Roentgenol 171:1413–1414

Sriurauranata S, Tengchaisri T, Sirisinha S (1996) Ultrastructural characteristics of liver fluke associated human cholangiocarcinoma cell lines. Southeast Asian. J Trop Med Public Health 27:57–62

Stitnimankarn T, Thakerngpol K, Damrongsak C, Chinapak O, Sindhvananda K (1978) Ultrastructure of cholangiocarcinoma associated with opisthorchiasis. Southeast Asian J Trop Med Public Health 9:558–567

Stroescu C, Herlea V, Dragnea A, Popescu I (2006) The diagnostic value of cytokeratins and carcinoembryonic antigen immunostaining in differentiating hepatocellular carcinomas from intrahepatic cholangiocarcinomas. J Gastrointestin Liver Dis 15:9–14

Su et al. 2006. http://www.ncbi.nlm.nih.gov/pubmed/16125303

Subimerb C, Pinlaor S, Khuntikeo N, Leelayuwat C, Morris A, McGrath MS, Wongkham S (2010) Tissue

invasive macrophage density is correlated with prognosis in cholangiocarcinoma. Mol Med Rep 3:597–605
Suh KS, Roh HR, Koh YT, Lee KU, Park YH, Kim SW (2000) Clinicopathologic features of the intraductal growth type of peripheral cholangiocarcinoma. Hepatology 31:12–17
Suh KS, Chang SH, Lee HJ, Roh HR, Kim SH, Lee KU (2002) Clinical outcomes and apomucin expression of intrahepatic cholangiocarcinoma according the gross morphology. J Am Coll Surg 195:782–789
Tada et al. 1996. http://www.ncbi.nlm.nih.gov/pubmed/8708074
Tajima Y, Kuroki T, Fukuda K, Tsuneoka N, Furui J, Kanematsu T (2004) An intraductal papillary component is associated with prolonged survival after hepatic resection for intrahepatic cholangiocarcinoma. Br J Surg 91:99–104
Takahashi I, Nakamura Y, Suzuki Y, Mitsuhashi N, Niibe H, Osada J (1994) Case report: bone metastasis from cholangiocarcinoma showing unusual accumulation on bone scintigraphy and G67Ga scintigraphy. Br J Radiol 67:303–305
Takamura M, Yamagiwa S, Wakai T, Tamura Y, Kamimura H, Kato T, Tsuchiya A et al (2010) Loss of liver-intestine cadherin in human intrahepatic cholangiocarcinoma promotes angiogenesis by up-regulating metal-responsive transcription factor-1 and placental growth factor. Int J Oncol 36:245–254
Takenaka M, Akiba J, Kawaguchi T, Niizeki T, Arinaga-Hino T, Sata M, Nakashima O et al (2013) Intrahepatic cholangiocarcinoma with sarcomatous change producing granulocyte-colony stimulating factor. Pathol Int 63:233–235
Tamandl et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19591163
Tanaka S, Sugimachi K, Shirabe K, Shimada M, Wands JR (2000) Expression and antitumor effects of TRAIL in human cholangiocarcinoma. Hepatology 32:523–527
Tanaka K, Honna T, Kitano Y, Kuroda T, Tanaka K, Morikawa N, Matsuda H, Kawashima N et al (2005) Combined fibrolamellar carcinoma and cholangiocarcinoma exhibiting biphenotypic antigen expression: a case report. J Clin Pathol 58:884–887
Tannapfel A, Engeland K, Weinans L, Katalinic A, Hauss J, Mossner J, Wittekind C (1999) Expression of p73, a novel protein related to the p53 tumour suppressor p53, and apoptosis in cholangiocellular carcinoma of the liver. Br J Cancer 80:1069–1074
Tascilar M, Offerhaus GJ, Altink R, Argani P, Sohn TA, Yeo CJ, Cameron JL, Goggins M et al (2001) Immunohistochemical labeling for the Dpc4 gene product is a specific marker for adenocarcinoma in biopsy specimens of the pancreas and bile duct. Am J Clin Pathol 116:831–837
Terada T, Matsunaga Y (2000) Increased mast cells in hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Hepatol 33:961–966
Terada T, Matsunaga Y (2001) S-100-positive nerve fibers in hepatocellular carcinoma and intrahepatic cholangiocarcinoma: an immunohistochemical study. Pathol Int 51:89–93
Terada and Nakamura 1992. http://www.ncbi.nlm.nih.gov/pubmed/1348889
Terada T, Nakanuma Y (1993) An immunohistochemical survey of amylase isoenzymes in cholangiocarcinoma and hepatocellular carcinoma. Arch Pathol Lab Med 117:160–162
Terada T, Nakanuma Y (1994) Expression of tenascin, type IV collagen and laminin during human intrahepatic bile duct development and in intrahepatic cholangiocarcinoma. Histopathology 25:143–150
Terada T, Nakanuma Y (1996) Expression of apoptosis, proliferating cell nuclear antigen, and apoptosis-related antigens (bcl-2, c-myc, Fas, Lewis(y) and p53) in human cholangiocarcinomas and hepatocellular carcinomas. Pathol Int 46:764–770
Terada T, Kida T, Nakanuma Y, Noguchi T (1992) Extensive portal tumor thrombi with portal hypertension in an autopsy case of intrahepatic cholangiocarcinoma. Am J Gastroenterol 87:1513–1518
Terada T, Makimoto K, Terayama N, Suzuki Y, Nakanuma Y (1996a) Alpha-smooth muscle actin-positive stromal cells in cholangiocarcinomas, hepatocellular carcinomas and metastatic liver carcinomas. J Hepatol 24:706–712
Terada T, Okada Y, Nakanuma Y (1996b) Expression of immunoreactive matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases in human normal livers and primary liver tumors. Hepatology 23:1341–1344
Terada et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9490278
Thingstad T, Haavik S, Hansen K, Sletten K, Codington JF, Barsett H (1998) Human carcinoma-associated antigen (HCA), isolated from the endometrial carcinoma cell line KLE-1 and ascitic fluid of a patient with ovarian carcinoma: comparison with epiglycanin. Eur J Pharm Sci 6:121–129
Thorbjarnarson B (1959) Carcinoma of the bile ducts. Cancer 12:708–713
Thuluvath PJ, Rai R, Venbrux AC, Yeo CJ (1997) Cholangiocarcinoma: a review. Gastroenterologist 5:306–315
Tokodai K, Kawagishi N, Miyagi S, Takeda I, Sato K, Akamatsu Y, Sekiguchi S, Ishida K et al (2012) Intestinal obstruction caused by colonic metastasis from intrahepatic cholangiocarcinoma 6 years after removal of the primary tumor: report of a case. Surg Today 42:797–800
Toriyama E, Nanashima A, Hayashi H, Abe K, Kinoshita N, Yuge S, Nagayasu T, Uetani M et al (2010) A case of intrahepatic clear cell cholangiocarcinoma. World J Gastroenterol 16:2571–2576
Torres T, Velho GC, Selores M (2010) Disseminated superficial porokeratosis in a patient with cholangiocarcinoma: a paraneoplastic manifestation? An Bras Dermatol 85:229–231

Trikudanathan G, Dasanu CA (2010) Cholangiocarcinoma and paraneoplastic hypercalcemia: a lethal combination revisited. South Med J 103:716–718

Tsai JH, Huang WC, Kuo KT, Yuan RH, Chen YL, Jeng YM (2012) S100P immunostaining identifies a subset of peripheral-type intrahepatic cholangiocarcinomas with morphological and molecular features similar to those of perihilar and extrahepatic cholangiocarcinomas. Histopathology 61:1106–1116

Tsuji T, Hiraoka T, Kanemitsu K, Takamori H, Tanabe D, Tashiro S (2001) Lymphatic spreading pattern of intrahepatic cholangiocarcinoma. Surgery 129:401–407

Uchida M, Takahashi T, Sugiyama M, Takahashi K, Asakura H, Kamura T, Ajioka Y (1998) An autopsy case of the diffuse type of cholangiocellular carcinoma associated with extensive portal thrombi and acute hepatic failure (in Japanese). Nihon Shokakibyo Gakkai Zasshi 95:791–795

Uenishi T, Hirohashi K, Haba T, Wakasa K, Kubo S, Shuto T, Tanaka H, Yamamoto T, Tanaka S, Kinoshita H (2003) Portal thrombosis due to intrahepatic cholangiocarcinoma following successful treatment for hepatocellular carcinoma. Hepatogastroenterology 50:1140–1142

Uno M, Shimada K, Yamamoto Y, Nara S, Esaki M, Sakamoto Y, Kosuge T, Ojima H (2012) Periductal infiltrating type of intrahepatic cholangiocarcinoma: a rare macroscopic type without any apparent mass. Surg Today 42:1189–1194

Utispan K, Thuwajit P, Abiko Y, Charngkaew K, Paupairoj A, Chau-in S, Thuwajit C (2010) Gene expression profiling of cholangiocarcinoma-derived fibroblast reveals alterations related to tumor progression and indicates periostin as a poor prognostic marker. Mol Cancer 9:13

Utispan K, Sonongbua J, Thuwajit P, Chau-In S, Pairojkul C, Wongkham S, Thuwajit C (2012) Periostin activates integrin a5b1 through a PI3K/AKT-dependent pathway in invasion of cholangiocarcinoma. Int J Oncol 41:1110–1118

Valverde A, Bonhomme N, Farges O, Sauvanet A, Flejou JF, Belghiti J (1999) Resection of intrahepatic cholangiocarcinoma: a western experience. J Hepatobiliary Pancreat Surg 6:122–127

Van Beers BE (2008) Diagnosis of cholangiocarcinoma. HPB (Oxford) 10:87–93

Vasilieva LE, Papadhimitriou SI, Dourakis SP (2012) Modern diagnostic approaches to cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 11:349–359

Vij K, Wang HL (2008) Aberrant expression of a-fetoprotein in intrahepatic cholangiocarcinoma: an exceptional occurrence. Int J Surg Pathol 16:194–198

Wachsberg RH, Levine CD, Cho KC, Simmons MZ, Khan MY, Koneru B (1996) Wedge-shaped intrahepatic cholangiocarcinoma: MRI-pathologic correlation. Abdom Imaging 21:219–221

Wang X, Zhang J, Chen J (2000) Result of p53, ki-67 protein expression in cholangiocarcinoma with in situ hybridization and immunohistochemistry methods (in Chinese). Zhongguo Yi Xue Ke Xue Yuan Xue Bao 22:57–60

Washington K, Gottfried MR (1996) Expression of p53 in adenocarcinoma of the gallbladder and bile ducts. Liver 16:99–104

Washington MK, Berlin J, Branton PA, Burgart LJ, Carter DK, Compton CC, Frankel WL et al (2010) Protocol for the examination of specimens from patients with carcinoma of the intrahepatic bile ducts. Arch Pathol Lab Med 134:e14–e18

Weinbren K, Mutum SS (1983) Pathological aspects of cholangiocarcinoma. J Pathol 139:217–238

Xiao P, Shi H, Zhang H, Meng F, Peng J, Ke Z, Wang K, Liu Y, Han A (2012) Epstein-Barr virus-associated intrahepatic cholangiocarcinoma bearing an intense lymphoplasmacytic infiltration. J Clin Pathol 65:570–573

Xu HL, Inagaki Y, Seyama Y, Sugawara Y, Kokudo N, Nakata M, Wang FS, Tang W (2009) Expression of KL-6 mucin, a human MUC1 mucin, in intrahepatic cholangiocarcinoma and its potential involvement in tumor cell adhesion and invasion. Life Sci 85:395–400

Xu et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/22175889

Xu J, Igarashi S, Sasaki M, Matsubara T, Yoneda N, Kozaka K, Ikeda H, Kim J, Yu E et al (2012) Intrahepatic cholangiocarcinomas in cirrhosis are hypervascular in comparison with those in normal livers. Liver Int 32:1156–1164

Yamada S, Sanefuki H, Morimoto H, Harada Y, Mine S, Morimoto I, Eto S (2000) Parathyroid hormone-related peptide producing cholangiocellular carcinoma with a marked psammoma formation. J Gastroenterol Hepatol 15:1442–1446

Yamada M, Shiroeda H, Shiroeda S, Sato K, Arisawa T, Tsutsumi M (2009) Cholangiocarcinoma producing parathyroid hormone-related peptide treated with chemoradiation using gemcitabine and S-1. Intern Med 48:2097–2100

Yamamoto M, Ariizumi S (2011) Surgical outcomes of intrahepatic cholangiocarcinoma. Surg Today 41:896–902

Yamamoto J, Kosuge T, Shimada K, Takayama T, Yamasaki S, Ozaki H, Makuuchi M (1993) Intrahepatic cholangiocarcinoma: proposal of new macroscopic classification (in Japanese). Nippon Geka Gakkai Zasshi 94:1194–1200

Yamamoto M, Takasaki K, Ootsubo T, Yoshikawa T, Nakamura M, Hanyu F (1994) Gross appearance and corresponding clinicopathological features of cholangiocellular carcinoma. Nippon Shokaki Geka Gakkai Zasshi 27:52–55

Yamamoto J, Kosuge T, Takayama T, Shimada K, Yamasaki S, Sakamoto M, Hirohashi S et al (1997) Intrahepatic cholangiocarcinoma presenting intrabile duct extension: clinicopathologic study of five resected cases. Jpn J Clin Oncol 27:18–21

Yamamoto M, Takasaki K, Nakano M, Saito A (1998) Minute nodular intrahepatic cholangiocarcinoma. Cancer 82:2145–2149

Yamamoto M, Takasaki K, Yoshikawa T (1999) Lymph node metastasis in intrahepatic cholangiocarcinoma. Jpn J Clin Oncol 29:147–150

Yamamoto M, Takasaki N, Otsubo T, Katsuragawa H, Katagiri S (2001) Recurrence after surgical resection of intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 8:154–157

Yamamoto N, Shiraki K, Yamanaka Y, Sugimoto K, Murata K, Nakano T (2004) Images of interest. Hepatobiliary and pancreatic: cholangiocarcinoma with chylous ascites. J Gastroenterol Hepatol 19:1417

Yamamoto Y, Shimada K, Sakamoto Y, Esaki M, Nara S, Ban D, Kosuge T, Ojima H (2009) Clinicopathological characteristics of intrahepatic cholangiocarcinoma presenting intrahepatic bile duct growth. J Surg Oncol 99:161–165

Yamanaka N, Okamoto E, Ando T, Oriyama T, Fujimoto J, Furukawa K, Tanaka T et al (1995) Clinicopathologic spectrum of resected extraductal mass-forming intrahepatic cholangiocarcinoma. Cancer 76:2449–2456

Yamasaki 2003. http://www.ncbi.nlm.nih.gov/pubmed/1459814

Yamashita K, Yonezawa S, Tanaka S, Shirahama H, Sakoda K, Imai K, Xing PX, McKenzie IF et al (1993) Immunohistochemical study of mucin carbohydrates and core proteins in hepatolithiasis and cholangiocarcinoma. Int J Cancer 55:82–91

Yang J, Yan LN (2008) Current status of intrahepatic cholangiocarcinoma. World J Gastroenterol 14:6289–6297

Yedibela S, Demir R, Zhang W, Meyer T, Hohenberger W, Schönleben F (2009) Surgical treatment of mass-forming intrahepatic cholangiocarcinoma: an 11-year western single-center experience in 107 patients. Ann Surg Oncol 16:404–412

Yeh CN, Jan YY, Yeh TS, Hwang TL, Chen F (2004) Hepatic resection of the intraductal papillary type of peripheral cholangiocarcinoma. Ann Surg Oncol 11:606–611

Yeh TS, Tseng JH, Chen TC, Liu NJ, Chiu CT, Jan YY, Chen MF (2005) Characterization of intrahepatic cholangiocarcinoma of the intraductal growth-type and its precursor lesions. Hepatology 42:657–664

Yeh CN, Pang ST, Wu RC, Chen TW, Jan YY, Chen MF (2009) Prognostic value of MUC4 for mass-forming intrahepatic cholangiocarcinoma after hepatectomy. Oncol Rep 21:49–56

Yeh CN, Yeh TS, Chen TC, Jan YY, Chen MF (2013) Gross pathological classification of peripheral cholangiocarcinoma determines the efficacy of hepatectomy. J Gastroenterol 48:647–659

Yen Y, Chu PG, Feng W (2004) Paraneoplastic syndromes in cancer: case 3. Parathyroid hormone-related hypercalcemia in cholangiocarcinoma. J Clin Oncol 22:2244–2245

Yonezawa S, Higashi M, Yamada N, Yokoyama S, Goto M (2010) Significance of mucin expression in pancreatobiliary neoplasms. J Hepatobiliary Pancreat Sci 17:108–124

Yoshida Y, Imai Y, Murakami T, Nishikawa M, Kurokawa M, Yonezawa T, Tokunaga K et al (1999) Intrahepatic cholangiocarcinoma with marked hypervascularity. Abdom Imaging 24:66–68

Zen Y, Sasaki M, Fujii T, Chen TC, Chen MF, Yeh TS, Jan YY, Huang SF, Nimura Y et al (2006) Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct – an immunohistochemical study of 110 cases of hepatolithiasis. J Hepatol 44:350–358

Zen Y, Britton D, Mitra V, Pike I, Sarker D, Itoh T, Heaton N, Quaglia A (2014) Tubulin β-III: a novel immunohistochemical marker for intrahepatic peripheral cholangiocarcinoma. Histopathology. doi:10.1111/his.12497

Zhou et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19294418

Zhou HB, Wang H, Zhou DX, Wang H, Wang Q, Zou SS, Hu HP (2010) Etiological and clinicopathologic characteristics of intrahepatic cholangiocarcinoma in young patients. World J Gastroenterol 16:881–885

Zhou DX, Wang H, Zhou H, Li S, Qu HX, Kou X, Li J, Wang H, Hu HP (2011) Over-expression of human carcinoma-associated antigen in intrahepatic cholangiocellular carcinoma. Biochem Biophys Res Commun 405:325–332

Zimmermann A (2001) Tumors of the bile ducts – pathological aspects. Med Sci Monit 7(Suppl 1):91–100

Biology of Disease and Prognostic Factors of Cholangiocarcinomas

30

Contents

Abstract

Generally, cholangiocarcinomas are aggressive and invasive neoplasms with a high risk of local spread, tumor recurrence, and metastatic spread. To describe and predict the biology of disease, several prognostic factors have been identified for both intrahepatic and extrahepatic cholangiocarcinomas. In perihilar/hilar cholangiocarcinoma, preoperative stage is an important prognosticator for outcome. Negative histologic margins, concomitant partial hepatectomy, and well-differentiated histology are associated with improved outcome after resections. Perineural invasion is a strong predictor of an unfavorable course, and lymph node metastases constitute a major prognostic factor for survival after resection. Similar or the same prognostic factors have been identified for intrahepatic cholangiocarcinoma, but the gross growth pattern also plays a prognostic role in these neoplasms. Patterns with an infiltrative component, such as combined mass-forming and periductal-infiltrating types, confer increased risk for poorer survival. As in other tumors, molecular profiles and signatures are currently searched for in order to refine risk stratification.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_30

Hilar/Perihilar Cholangiocarcinoma

Prognostic Factors: General Features

Hilar/perihilar cholangiocarcinoma (PHC) is an aggressive neoplasm with a distinct pattern in invasion, spread, and metastasis. In most instances, the prognosis of this cancer is still poor. At present, surgical resection based on precise preoperative staging is the optimal treatment options. A prognostication of outcome depends on a complex pattern of prognosticators having variable power to predict biology of disease (Murakami et al. 2007; Singal et al. 2010; Cho et al. 2012; Kaiser et al. 2013). Negative histologic margins, concomitant partial hepatectomy, and well-differentiated tumor histology were associated with improved outcome after all resections; however, in patients with R0 resection, concomitant partial hepatectomy was the only independent predictor of long-term survival. In a retrospective series of 49 patients with resected PHC, univariate analysis identified eight significant factors affecting mortality, i.e., total bilirubin, curative resection, histologic type, perineural invasion, liver invasion, depth of cancer invasion, positive proximal resection margin, and positive surgical margin (Su et al. 1996). In patients who underwent an R0 resection, concomitant partial hepatectomy, well-dedifferentiated histology, and negative lymph nodes were independent predictors of long-term survival (Matsuo et al. 2012).

Stage

Preoperative stage is an important prognosticator for outcome. Patients with advanced Bismuth-Corlette stage showed a tendence for reduced mean survival time, but the differences were not significant (Weber et al. 2007). A tumor size over 3 cm predicted poor short-term outcome after resection of PHC (Regimbeau et al. 2015).

Biliary Resection Margin

Positive resection margins are negative predictors of outcome in PHC (Ribero et al. 2011). Based on final histopathologic examinations, resection margins have been classified as wide margin (bile duct and specimen margins negative), narrow margin (bile duct margin negative but specimen margins positive), and positive margin (bile duct and specimen margins positive; Endo et al. 2008a). In a novel classification system of resection margins, four categories were defined, i.e., "insufficient" (insufficient for diagnosis due to distortion of specimen), "negative for malignancy" (no atypia suggestive of neoplasia), "undetermined lesion" (specimen showing either cellular or structural atypia), and "positive for malignancy" (Konishi et al. 2009). Involvement of ductal resection margins is a significant and independent risk factor for recurrence and poor prognosis (Burke et al. 1998; Wakai et al. 2005; Ramacciato et al. 2006; Tamada et al. 2006; Sasaki et al. 2007; Higuchi et al. 2010; Lee et al. 2012a). The adverse effect of a positive margin seems to depend on the part of the duct wall involved. In a Japanese investigation, margins positive for malignancy in intramural lesions of the proximal margin displayed poor prognosis, whereas positive for malignancy or undetermined in the epithelial surface of the proximal margin showed no difference in outcome compared with negative for malignancy (Konishi et al. 2009). The unfavorable effect of positive margins in resected PHC is modified by additional postoperative radiotherapy (Stein et al. 2005).

Intraoperative frozen section examination of bile duct margins is often employed to guide surgical resection in patients with PHC, but this method has some technical and interpretational difficulties that one has to consider (Okazaki et al. 2002). A positive ductal margin found in the setting of intraoperative histologic examination of the proximal ductal margin was related to clinical outcome, a finding favoring additional duct resection (Konishi et al. 2010). However, a study of 303 cases showed that additional-resection of >5 mm in the proximal duct is difficult after maximal or near-maximal duct resection, and such an additional resection did not improve survival, even when a negative margin could be achieved by this measure (Shingu et al. 2010). The results of frozen section analysis differ from those obtained with final histopathology. This is due to

greater thickness and, in part, lesser quality of frozen sections (damage of tissue) and to differences in experience. A retrospective comparative analysis of 101 cases of PHC has demonstrated the frozen section analysis of the proximal bile duct margin was misleading in 9 % of patients (Endo et al. 2008a). In a small investigation, frozen section and permanent diagnoses of the ductal margin in gallbladder and bile duct carcinomas were inconsistent in up to 25 % of patients, due to overdiagnosis of frozen sections or new recognition of cancer in permanent histology (Yamaguchi et al. 2005). The presence of extensive intramucosal spread in involved ducts, defined as spread > or = 20 mm from the main tumor, was not an indicator of a poor prognosis (Nakanishi et al. 2008). There is evidence that remnant carcinoma in situ may later evolve into invasive carcinoma and determine recurrence of disease (Nakanishi et al. 2010).

Invasive Features and Tumor Depth

Noninvasive and minimally invasive carcinomas of the extrahepatic ducts are associated with better long-term prognosis, and this is specifically the case for tumor with a papillary phenotype (Fatima et al. 2008). In a series of 106 resected PHC, median survival was associated with the invasion depth of the tumor (>= 5 mm vs. <5 mm). On multivariate analysis, tumor depth remained predictive of disease-specific death (de Jong et al. 2011a).

Perineural Invasion and Vascular Invasion

Perineural invasion is a common path for invasion and spread of cholangiocarcinomas. It is highly correlated with an invasive phenotype and is a predictor of postoperative recurrence and an unfavorable biology of disease (Bhuiya et al. 1992; Su et al. 1996; Shen et al. 2010; Patel et al. 2011). In order to correlate perineural invasion with other parameters, a perineural invasion index (PNI) was proposed, defined as the quotient between the number of nerve fascicles invaded by tumor and total number of nerve fascicles with and without tumor invasion (Bhuiya et al. 1992). Carcinoma cells can spread along the perineural sheaths for long distances and reach the neural plexuses. Neural plexus invasion can be detected by the use of CT imaging (Fukuda et al. 1998). The presence of lymphovascular invasion was associated with reduced overall survival (Ishiyama et al. 1998; Patel et al. 2011).

Nodal Status

Lymph node metastases constitute a major prognostic factor for survival after resection of PHC (Kitagawa et al. 2001; Murakami et al. 2007; Oshiro et al. 2011; Guglielmi et al. 2013). Among 62 resected patients, the median survival was 41.9 months in patients with N0 stage compared with 22.7 months in patients with N+. The 5-year survival for patients above and below the lymph node ratio of 025 was 0 % and 22.5 %, respectively (Guglielmi et al. 2011). In the analysis of Kitagawa et al. (2001), 3-year and 5-year survival rates for patients with PHC were 55.4 % and 30.5 % for patients with N0, 31.8 % and 14.7 % for patients with regional node metastases, and 12.3 % and 12.3 % for patients with paraaortic node metastases. In a recent study of 320 patients with PHC, lymph node metastasis was an independent and powerful prognostic factor. The survival rates were not significantly different between patients with locoregional node metastasis alone and those with distant lymph node metastasis, but the survival for patients with multiple node metastasis was significantly worse than that for patients with single metastasis (Aoba et al. 2013). The presence of positive paraaortic lymph nodes has an additional adverse effect on prognosis (Murakami et al. 2011). In one study, the presence of immunohistochemically detected lymph node micrometastases in otherwise histologically node-negative PHC had no survival impact (Tojima et al. 2003), but in a second analysis, the presence of immunohistochemically detected nodal micrometastases had an impact on outcome (Taniguchi et al. 2006).

Locoregional lymph node metastasis of extrahepatic cholangiocarcinoma is also a risk factor for remote/distant metastasis, e.g., bone metastasis (Katayose et al. 2012).

Distant Metastases

Apart from locoregional lymph node metastases, PHC tends to produce intrahepatic and intra-abdominal metastases (Nagorney and McPherson 1988; Carriaga and Henson 1995; Maaouni et al. 2006; Schmeding et al. 2006), whereas extra-abdominal metastases are less prominent findings. The most common extrahepatic metastatic sites are the lymph nodes, peritoneum, and lungs, while other sites such as the skin are rare (Lee et al. 2009). Similar to gastric carcinoma, PHC can sometimes form ovarian metastases with the phenotype of Krukenberg tumor (Sharma et al. 1997; Maaoui et al. 2006). Implantation metastases can occur following resection of PHC, whereby preoperative ERCP with biliary drainage was associated with a higher frequency of such metastases (ten Hoopen-Neumann et al. 1999). Regional or hepatic metastases may be expected in 30–50 % of cases. In contrast, distant metastases are not common and appear late in the course of disease, most often located to the lesser omentum and other sites of the abdominal cavity. Lymph node metastases are one of the most important prognostic factors in PHC (Noji et al. 2012). The presence of liver metastases has a significant adverse effect on prognosis (Arvanitakis et al. 2006).

Vascularity

PHC exhibit a high degree of vascularity, and this phenomenon affects biology of disease. PHC with a high microvessel density had a significantly higher incidence of lymph node metastases and local recurrence, and high microvessel density was a significant overall survival disadvantage as well as disease-free survival disadvantage, suggesting that neovascularization may be critically involved in PHC progression (Thelen et al. 2008; Nanashima et al. 2009). In PHC, microvessel density is correlated with the expression of trophoblast cell surface antigen 2 (TROP2), a factor that is associated with tumor progression and poor prognosis in a variety of cancers, and was an independent prognostic factor in human PHC (Ning et al. 2013). The presence of blood vessel cancer emboli within stroma significantly increased hazard's ratio of tumor recurrence, initial distant organ metastasis, and death (Hasebe et al. 2005). Tumor-associated lymphangiogenesis correlates with lymph node metastases and prognosis in PHC (Thelen et al. 2008; Thelen et al. 2010). Also factors regulating angiogenesis and lymphangiogenesis are expected to affect biology of disease. There was a trend toward higher VEGF A expression in highly vascularized extrahepatic cholangiocarcinomas (Möbius et al. 2007). In another investigation, there was however no correlation between VEGF, angiopoietin-1, angiopoietin-2, and thrombospondin-1 expression and tumor size, invasive features, intrahepatic metastasis, and survival (Tang et al. 2006). Expression of hepatoma-derived growth factor in PHC is associated with increased VEGF expression and poorer survival (Liu et al. 2011).

Growth and Differentiation of Cancer Cells

An elevated level of proliferative activity affects biology of disease of PHC. Expression of the proliferative marker Ki-67 increased with the stage and invasive features of PHC (Zhao et al. 2014). The PCNA index is a significant prognosticator for PHC (Nishida et al. 1997). The chemokine receptor 4/CXCR4 promotes proliferation in PHC, is induced in these neoplasms, and augments neural invasion (Tan et al. 2014). Among factors affecting growth and apoptosis, p53 protein has a central role. Among 45 extrahepatic duct carcinomas, including PHC, the median survival of patients with p53-negative tumors was 25.7 months, whereas survival of those with p53-positive tumors was 5.2 months (Diamantis et al. 1995). Inhibition of apoptosis promotes

growth and favors an aggressive course. In extrahepatic cholangiocarcinoma, expression of the apoptosis inhibitor Bcl-2 is increased in comparison with dysplasia (Li et al. 2003). Autophagy may promote invasion of cholangiocarcinoma, and expression of the autophagy-associated protein Ambra1 correlated with lymph node metastasis and poor survival (Nitta et al. 2014).

The presence of a papillary carcinoma component is an important determinant of survival after resection of PHC, papillary carcinomas being associated with significantly longer disease-specific survival (Hoang et al. 2002; Jarnagin et al. 2005; Sano et al. 2008). This is probably due to the less frequent invasion of papillary/exophytic tumors beyond the fibromuscular layer (Kozuka et al. 1984). In a review of 13 patients with papillary carcinoma of the extrahepatic ducts, six were localized to the proximal part of the duct system (Hoang et al. 2002). Production of various mucin types affects risk and biology of disease. MUC1 and MUC5AC expression in cholangiocarcinomas is closely related to dedifferentiation, invasive growth, and poorer survival, while expression of MUC6 is a marker of well-differentiated carcinomas (Park et al. 2009). The expression of MUC4 in PHC is an independent factor for poor prognosis and predicts outcome (Tamada et al. 2006). Mesothelin, which is expressed in various carcinomas as a function of differentiation, is also present in PHC. Its high-level expression was associated with an aggressive tumor phenotype (Kawamata et al. 2012). Among factors that affect differentiation, the nonopioid sigma-1 receptor (Sig1R) is associated with poor differentiation in PHC (Xu et al. 2014a).

DNA Ploidy of Carcinoma Cells

DNA ploidy has been shown to affect progression of PHC and other extrahepatic cholangiocarcinomas (Nishida et al. 1997). Among 60 consecutive patients with PHC, 29 or 48 % had diploid neoplasms, and 31 or 51 % were found to have aneuploid tumors. Survival of patients with diploid tumors was significantly longer than those with aneuploid tumors (Iachino et al. 1998). A similar distribution of ploidy was observed in a second study ($N = 58$), with 48 % diploid and 52 % aneuploid neoplasms, again with a worse outcome for patients with aneuploid tumors (Sato et al. 1994).

Factors Affecting Invasion and Spread

As in other carcinomas, the invasive properties of PHC cells strongly depend on the differential expression of adhesion molecules and histolytic enzymes. Factors interfering with cell adhesion affect invasive properties of cancer cells. The E-cadherin repressor, snail, is expressed in part of PHC, and snail expression can predict poor survival of PHC regardless of pathologic features and cancer cell proliferation (Kong et al. 2012). E-cadherin expression in PHC is regulated by the E-cadherin repressor slug. Slug is overexpressed in PHC, resulting in E-cadherin downregulation and increased invasion (Zhang et al. 2010b). Expression of the adhesion molecule L1 in extrahepatic cholangiocarcinomas is significantly associated with perineural invasion and is an independent prognosticator for poor overall survival (Li et al. 2009). The E/N-cadherin switch mediates carcinoma progression of PHC through TGF-beta-induced epithelial-to-mesenchymal transition (EMT). During EMT, epithelial cadherin (E-cadherin) is downregulated while neural cadherin (N-cadherin) is upregulated, referred to as the so-called cadherin switch (Araki et al. 2011). Expression of E-cadherin is lower in cholangiocarcinoma cells than in benign bile duct lesions (Li et al. 2008). In its regulation of invasive features in cholangiocarcinoma, E-cadherin expression is correlated with expression of protein kinase C-iota, which is positively related to tumor cell differentiation and invasion (Li et al. 2008). Expression of CD24 predicts distant metastasis in extrahepatic cholangiocarcinoma (Kim et al. 2013).

Expression of matrix metalloproteinases (MMPs) affects invasive features of many cancers. PHC cells upregulate matrix metalloproteinases required for tissue invasion. MMP-2 plays an important role in PHC invasion and

metastasis, while tissue inhibitor of metalloproteinase-2 (TIMP-2) was shown to strongly inhibit cancer invasion (Xiao et al. 2004). MMP-2 expression is present in extrahepatic cholangiocarcinomas and gallbladder cancers, including PHC (Xiao et al. 2004), but was not found in Klatskin tumors in another study (Kirimlioglu et al. 2009). Expression of MMP-2 was found at higher levels in tumors with perineural invasion (Sakai 2004). By the use of zymography and PCR, activity of MMP-2 and its active form were detected in 80 % and 57 % of intrahepatic cholangiocarcinomas (Jo Chae et al. 2004). MMP-7 was an unfavorable postoperative prognostic factor of cholangiocarcinoma arising from large bile ducts (Miwa et al. 2002; Itatsu et al. 2008). In PHC, expression of MMP-9 indicates poor prognosis (Sun et al. 2014). The expression of MMP-9 was found to be elevated in PHC in comparison with normal tissues, while a protein inhibiting MMP expression, RECK, was downregulated (Li et al. 2005). Levels of MMP-9 expression in PHC appear to be partially related to the presence of tumor-associated macrophages secreting this protease (Subimerb et al. 2010).

The mechanisms leading to perineural and intraneural invasion are only partially clarified. Expression of nerve growth factor-beta is associated with nerve infiltration in human PHC (Xu et al. 2010a). Other factors involved in extrahepatic cholangiocarcinomas promoting invasion, metastasis, and tumor progression in general comprise expression of c-erbB-2 proto-oncogene (Zheng and Zhu 2007); the CCN family member WISP1v (Tanaka et al. 2003); the differentiation regulator LAPTM4B-35 (Zhou et al. 2008), CD24 (Agrawal et al. 2007), CD44 (Kunlabut et al. 2012), KIT (Hong et al. 2007), fascin (Won et al. 2009; Mao et al. 2013), S100 protein (Sato et al. 2013), and HER3 (Lee et al. 2012b); downregulation of p21 (Kim et al. 2009), and decreased expression of focal adhesion kinase (Hayashi et al. 2010) and of WW domain-containing oxidoreductase (WWOX) (Wang et al. 2009). Expression of relatively few factors was associated with a favorable prognosis, e.g., caveolin-I overexpression (Murakami et al. 2003) and expression of the transcription factor ets-1 (Ito et al. 2000).

Intrahepatic Cholangiocarcinoma

General Features

There are numerous attempts to stratify ICC according to various prognostic factors. As with other hepatobiliary cancers, established prognosticators such as TNM stage, histologic grade, and invasion features play a predominant prognostic role. There are also aims to enter such prognosticators into scoring systems. For example, the independent predictors of outcome, serum alkaline phosphatase, CA 19-9 levels, tumor boundary type, tumor size, and number of intrahepatic tumors were incorporated into the Fudan score, which may provide a relatively accurate prognostic predictor for ICC patients regardless of the resection status (Jiang et al. 2011).

Tumor Stage

Advanced stage at the time point of diagnosis or surgery is a strong predictor of outcome. Stage IVa tumors and those with intra- or perihepatic metastases had a poor prognosis (Jiang et al. 2011). Large tumor size (diameter > than 4.5 cm or 5 cm) was a significant predictor of outcome in MF-ICC in part of studies (Endo et al. 2008b; Shirabe et al. 2010; Schiffman et al. 2014). In one investigation, patients with resected MF-ICC having tumor with a diameter >45 mm more often developed recurrence in the remnant liver, lymph nodes, and lung than patients with tumors <45 mm diameter (Sasaki et al. 2004). However, tumor size provided no prognostic information in another investigation (de Jong et al. 2011). Other stage-associated parameters that are prognosticators in MF-ICC include serosal invasion, PV1 or PV2, LI1 or LI2, and hepatic venous invasion (Shirabe et al. 2010). In MF-ICC, serosal invasion was not always identified as a prognosticator. In one study, serosal invasion exhibited no survival impact after hepatic resection for MF-ICC

(Uenishi et al. 2005). In a more recent study, it turned out that the AJCC/UICC staging system failed to stratify Japanese patients with MF-ICC. In a new staging approach, tumor size, tumor number, and vascular invasion were independently associated with survival after curative resection of MF-ICC, whereas serosal and periductal invasion were not, this new staging system better stratifying survival after curative resection (Uenishi et al. 2014).

In patients with the MF-ICC, lymphatic invasion was found to be the most important invasion pathway, and lymph node metastases is a good predictor for prognosis (Nozaki et al. 1998; Yamamoto et al. 1998; Inoue et al. 2000; Suzuki et al. 2002; Nakagawa et al. 2005; Guglielmi et al. 2009; Shimada et al. 2007a, 2009; Tamandl et al. 2009; Shirabe et al. 2010; Clark et al. 2011; de Jong et al. 2011b; Patel et al. 2011; Horino et al. 2012; Adachi and Eguchi 2014). In one study, patients with MF-ICC having two or more lymph node metastases failed to survive beyond 2 years post-surgery, while those with no or a single lymph node metastasis displayed survival rates of 80 % and 33 % at 5 years, respectively (Suzuki et al. 2002). In one European study, the lymph node ratio (LNR) had a high prognostic value, whereas the location of positive nodes did not (Guglielmi et al. 2013). Traditionally, para-aortic lymph node metastasis has been defined as distant metastasis, but recently been classified as resectable disease (Nakayama et al. 2013).

Macroscopic ICC Subtype and Local Growth Patterns

As already mentioned above, the three main growth patterns of ICC (MF, PI, and IG) affect biology of disease and outcome. The 5-year survival rate after surgery was significantly lower in patients with MF plus PI tumors than in patients with MF or IG subtype tumors (Yamamoto et al. 1998). The difference in outcome may in part be related to the more complex, infiltrative pattern of MF plus PI, characterized by a large mass lesion associated with a tumor that invasively follows the periductal tracts for longer distances, resulting in an ill-defined neoplasm. In fact, MF plus PI tumors more frequently exhibit positive resection margins and perineural invasion (Hirohashi et al. 2002). The incidence of lymph nodes with metastases was significantly higher in the patient group with MF plus PI than in those with IG (Yamamoto et al. 1998). In contrast, "pure" MF-ICC was associated with a longer survival than MF plus PI and PI (Inoue et al. 2000; Guglielmi et al. 2009). The presence of satellite nodules, i.e., a presentation with multiple tumor nodules indicating a more aggressive phenotype, had a significant effect on patient survival (Jan et al 1996; Casavilla et al. 1997; Harrison et al. 1998; Roayaie et al. 1998; Isaji et al. 1999; Okabayashi et al. 2001). The number of tumors including satellites was not related to the presence of vascular invasion in one study (Okabayashi et al. 2001), but a later investigation found that multiple intrahepatic tumors were a significant determinant of adverse postoperative prognosis (Marubashi et al. 2014).

Resection Margin

The histologic status of the resection margin is a critical prognostic factor. Patients with positive ductal margins generally have a poor prognosis (Guglielmi et al. 2009; Luo et al. 2014; Murakami et al. 2014). An unfavorable effect of a positive resection margin was found in both peripheral and perihilar forms of ICC (Yeh et al. 2014). A negative resection margin had a favorable impact on survival of patients with MF-ICC (Chou et al. 1995; Jan et al. 1996; Harrison et al. 1998; Madariaga et al. 1998; Isaji et al. 1999; Kim et al. 1999; Inoue et al. 2000; Isa et al. 2001; Uenishi et al. 2001; Tamandl et al. 2008; Yeh et al. 2013; Sonbare 2014). In peripheral ICC, a positive resection margin was more frequently found in higher-stage tumors, those with hepatolithiasis, and those with periductal infiltrative or mixed periductal infiltrative and mass-forming ICC (Yeh et al. 2014).

Grading and Distinct Differentiation Patterns

The tumor grade affects biology of disease, and in some studies, tumor grade was an independent factor predicting survival (Shirabe et al. 2010; Murakami et al. 2014). Remote organ metastases are more often found in the less-differentiated ICC group that in the well-differentiated group. The distinct ICC differentiation pattern characterized by papillary growth (PCC; papillary cholangiocarcinoma) is associated with a more favorable outcome, whereby PCC survival decreases with progression of the invasive component (Onoe et al. 2014).

MUC1 expression in MF-ICC was an independent risk factor affecting outcome (Matsumura et al. 2002). The pro-metastatic effect of MUC1 may be related to the findings that MUC1 as a transmembrane mucin is often overexpressed in metastatic cancers, its extracellular domain serving as a ligand for stromal and endothelial cell receptors (Horm and Schroeder 2013). Furthermore, MUC1 drives c-Met-dependent cancer cell migration (Horm et al. 2012). Expression of MUC4 and/or MUC16 in MF-ICC was an independent factor of poor prognosis (Shibahara et al. 2004; Higashi et al. 2012). Certain keratin/cytokeratin expression patterns in ICC are associated with tumor biology. In MF-ICC, reduced expression of keratin 903 was correlated with a favorable prognosis and an HCC-like pattern (Aishima et al. 2002). The subset of ICC expressing keratin 20 was associated with male gender, hilar location, intraductal papillary type, intestinal phenotype, and MUC2 expression. Patients with these neoplasm had a poorer outcome, suggesting an aggressive phenotype for keratin 20-positive ICC (Choi et al. 2012). Histone deacetylase (HDAC) is critically involved in chromatin remodeling and gene expression and regulates cell differentiation. In ICC, increased HDAC expression is closely associated with hypoxia-inducible factor activation and correlates with a worse survival rate (Morine et al. 2012). ICC with progenitor/stem cell features generally exhibit a more aggressive tumor biology. CD133, a stem cell marker, was observed in up to 8 % of ICC, and its presence tended to be related to higher incidences of intrahepatic metastasis and was independently related to worse prognosis (Shimada et al. 2010).

Invasion Patterns and Factors Regulating Invasion

Macroscopic vascular invasion is significantly related to survival in patients with ICC (Okabayashi et al. 2001; Guglielmi et al. 2009). Taking MF and PI tumors together results in a group of ICC with a more unfavorable prognosis even after radical surgery, as these neoplasms were more often associated with bile duct invasion, portal vein invasion, lymph node metastasis, and positive resection margin (Shimada et al. 2007b). Lymphovascular invasion is associated with reduced overall survival in ICC (Fisher et al. 2012). Perineural invasion of ICC is an important negative prognosticator (Shirai et al. 2008; Chen et al. 2012; Fisher et al. 2012) and is strongly associated with KRAS mutations in ICC (Chen et al. 2012).

Certain proteins involved in adhesion and in the construction of the extracellular matrix (ECM) and hence in invasion are differentially expressed in various growth patterns of ICC. Reduced cell surface content of E-cadherin in cholangiocarcinoma facilitates invasion through cell individualization and is associated with reduced survival (Mao et al. 2013). Expression of CD24, a sialoglycoprotein involved in cell adhesion, in cholangiocarcinomas is associated with disease progression and reduced patient survival (Su et al 2006; Keeratichamroen et al. 2011). The laminin gamma 2 chain, a C protein that plays an important role in cell migration and invasion, was more frequently expressed in PI and ID types of ICC than the MF type, and its expression was correlated with an aggressive phenotype (Aishima et al. 2004). Expression of human carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), a molecule involved in adhesion and invasion properties of various malignancies, is higher in ICC cells than in adjacent nonneoplastic liver tissue. ICC with

CEACAM6 expressed displayed higher rate of lymphatic invasion and were correlated with poorer disease-free survival (Ieta et al. 2006). Reduced expression of syndecan-1, a cell surface transmembrane heparan sulfate proteoglycan involved in functional aspects of the ECM, is found in ICC cases with lymph node metastasis and aggressive course (Harada et al. 2003). Expression of connective tissue growth factor/CTGF is a prognostic marker for ICC (Gardini et al. 2005).

Factors that affect structure and function of the cytoskeleton and cell motility also exert an important influence on the invasive behavior of ICC cells. Expression of cytoskeleton-associated protein 4 in ICC is related to the frequency of lymphatic metastasis (Li et al. 2013). A protein involved in the stimulation of tumor cell migration and metastasis is phosphatase of regenerating liver-3 (PRL-3). In contrast to normal cholangiocytes, which do not display PRL-3 immunostaining, this factor is expressed in ICC and is correlated with invasion and metastasis (Xu et al. 2010b). PRL-3 induces EGFR activation and its downstream signaling cascades, directly interferes with integrin beta1 and regulates its phosphorylation, promotes cell migration via Arf-activity-dependent stimulation of integrin alpha5 recycling, induces angiogenesis by increasing extracellular signal-regulated kinase phosphorylation, provokes a tyrosine phosphoproteome involving proteins that play a role in the induction of EMT, and induces several miRNAs involved in the metastasis cascade, including miR-21, miR17, and miRNA-19a.

Several types of matrix metalloproteinases (MMPs) are expressed by ICC cells and play a crucial role in tissue destruction in the course of invasion. Expression and secretion of MMP-2 (Zhang et al. 2010a), MMP-7 (Miwa et al. 2002), and MMP-9 (Tian et al. 2014) by cholangiocarcinomas are markers for an aggressive phenotype. Serum MMP-7 levels are useful as a predictive marker for fluke-related cholangiocarcinoma (Prakobwong et al. 2012), and expression of MMP-7 by ICC cells is associated with poor prognosis in patients with resected ICC (Hirashita et al. 2012). Other peptidases/proteinases that favor an invasive phenotype and an aggressive course in ICC patients include neutral endopeptidase and dipeptidyl peptidase IV (Zhu et al. 2014). Maspin, a member of the serpin family and suppressor of tumor growth, is expressed in a subset of ICC and represents a prognostic factor. The associated expression of maspin and Bax delayed ICC progression via increase of apoptosis and decrease of invasion (Romani et al. 2006). There are other factors that favor an invasive phenotype of cholangiocarcinomas. Aberrant expression of GATA6, a zinc-finger transcription factor either acting as a tumor promoter or tumor suppressor, was correlated with marked tumor invasion, lymph node and liver metastasis, and poor prognosis in cholangiocarcinoma patients (Tian et al. 2013). A protein that participates in mediating G2 arrest of the cell cycle in several cancers is stratifin (14-3-3 s). Cytoplasmic stratifin expression was found in 52.6 % of MF-ICC after hepatectomy, and this expression was significantly associated with elevated CEA levels (Yeh et al. 2010). Stratifin may affect the invasive properties of cancer cells, because it exerts an important influence on the biology of cell-to-cell adhesive junctions. Stratifin limits plakophilin-3 exchange with the desmosomal plaque, resulting in decreased desmosomal adhesion and increased cell migration (Roberts et al. 2013).

Stromal Features, Epithelial-Mesenchymal Transition (EMT), and Vascularization

Invasion and spread of ICC are markedly influenced by cell systems of the tumor stroma, in particular myofibroblasts and their precursor cells, the hepatic stellate cells. Patients with high alpha-SMA expression in cells of their ICC exhibited worse outcomes (Okabe et al. 2009). Myofibroblasts in cholangiocarcinoma stroma promote progression of the tumor through activation of the EGFR, and cholangiocarcinoma cells produce TGF-beta1 which in turn induces expression of heparin-binding epidermal growth factor (HB-EGF) on myofibroblasts (Clapéron

et al. 2013). Several proteins upregulated in ICC stroma affect biology of disease, including osteopontin, TGF-beta2, and laminin. Osteopontin, which is expressed in ICC stroma cells, is an independent predictor of poor prognosis in ICC (Sulpice et al. 2013). Stromal cell populations also exhibit stem cell signatures, including an overexpression of epithelial cell adhesion molecule (EpCAM). EpCAM expression as an indicator of stromal progenitor cells affects ICC progression and is associated with reduced overall and disease-free survival (Sulpice et al. 2014).

Invasive features of cholangiocarcinomas are related to the effects of epithelial-mesenchymal transition (EMT). Expression of EMT-related markers is associated with an aggressive course and poor prognosis (Ryu et al. 2012). Loss of the epithelial marker E-cadherin and acquisition of the mesenchymal markers vimentin and N-cadherin in ICC was associated with aggressive tumor behavior, increased progression, and a poor outcome (Gu and Choi 2012; Yao et al. 2012; Gu and Choi 2014). In particular, aberrant expression of vimentin in ICC correlated with dedifferentiation and poor survival (Korita et al. 2010). EMT which favors progression of ICC is strongly stimulated in these tumors by the factor Snail1 (Huang et al. 2014). Downregulation of E-cadherin in the setting of EMT in ICC is mediated by the transcription repressor, Slug (SNAI2; Snail2), which is not expressed in normal liver cells, but is highly expressed in ICC, this upregulation being associated with a higher rate of lymph node metastasis and poor survival (Zhang et al. 2010b). In ICC, expression of fibroblast growth factor receptor 4 (FGFR4) induces EMT, promotes an invasive phenotype, and correlates with poor prognosis (Xu et al. 2014b).

Angiogenesis and vascularization strongly influence invasive spread and metastasis of cancers and hence are prognosticators. In ICC, a lower microvessel count was associated with larger tumor size, PI-ICC, and advanced stage. The 5-year survival rate in the higher microvessel count group was significantly greater than that in the lower microvessel count group (Nanashima et al. 2009).

Growth Features, Factors Regulating Tumor Cell Growth, and Apoptosis

In MF-ICC, a shorter preoperative tumor doubling time (less than 70 days) estimated by imaging was associated with worse overall survival (De Rose et al. 2013). A low nuclear expression of p27Kip1 protein was correlated with vascular invasion and significantly lower survival (Taguchi et al. 2001). Vitamin D3 exerts an antiproliferative effect on cholangiocarcinoma cells, and overexpression of vitamin D receptor in cholangiocarcinoma was associated with an overall more favorable prognosis (Seubwai et al. 2007). Expression of epithelial and endothelial tyrosine kinase (Etk; bone marrow X kinase), a kinase regulating cell proliferation and apoptosis, in ICC cells was a predictor of poor prognosis (Guo et al. 2008). Overexpression of EGFR is associated with the degree of malignancy and with poor prognosis (Zhou et al. 2013). Expression of insulin-like growth factor II mRNA-binding protein 3, an oncofetal mRNA-binding protein, plays an important role in the regulation of cell growth and is expressed in a subset of ICC. This expression is associated with an invasive phenotype and a poorer overall survival (Chen et al. 2013). Hepatocyte growth factor and its receptor, MET, form a regulatory unit that affects several biological features of cancer cells, including growth regulation. Expression of the glucose transporter, GLUT-1, in ICC is associated with aggressive biology and lymph node metastasis (Kubo et al. 2014). A hydrophobic protein, CD151, forms a functional complex with MET and affects growth, invasion, and metastasis. In ICC, overexpression of CD151 is correlated with an invasive and metastatic phenotype (Huang et al. 2010).

Expression of TRAIL by cholangiocarcinoma cells does not result in carcinoma cell death, but promotes their tumorigenicity and favor metastatic spread. This effect is counteracted by second mitochondria-derived activators of caspase/Smacs, which enhance proapoptotic death receptor signaling by causing cellular degradation of inhibitor of apoptosis (IAP) proteins (Fingas et al. 2010). Survivin, a member of the inhibitors-of-apoptosis protein family, is an independent

prognostic factor for poor survival in ICC, and its expression is modulated by the Yes-associated protein (Bai et al. 2012).

Other ICC Markers of Potential Prognostic Significance

Elevation of serum gamma-glutamyltransferase was a predictor of an aggressive tumor behavior in ICC patients (Yin et al. 2013). The AKT1 signaling pathway, which is important for the regulation of protein synthesis and cell survival, revealed differential expression in ICC. Overexpression of phosphorylated AKT1was associated with a better survival in ICC patients, independent of PTEN expression (Lee et al. 2012c).

References

Adachi T, Eguchi S (2014) Lymph node dissection for intrahepatic cholangiocarcinoma: a critical review of the literature to date. J Hepatobiliary Pancreat Sci 21:162–168

Agrawal S, Kuvshinoff BW, Khoury T, Yu J, Javle MM, LeVea C, Groth J, Coignet LJ et al (2007) CD24 expression is an independent prognostic marker in cholangiocarcinoma. J Gastrointest Surg 11:445–451

Aishima S, Asayama Y, Taguchi K, Sugimachi K, Shirabe K, Shimada M, Sugimachi K, Tsuneyoshi M (2002) The utility of keratin 903 as a new prognostic marker in mass-forming-type intrahepatic cholangiocarcinoma. Mod Pathol 15:1181–1190

Aishima S, Matsuura S, Terashi T, Taguchi K, Shimada M, Maehara Y, Tsuneyoshi M (2004) Aberrant expression of laminin gamma 2 chain and its prognostic significance in intrahepatic cholangiocarcinoma according to growth morphology. Mod Pathol 17:938–945

Aoba T, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y, Nagino M (2013) Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. Ann Surg 257:718–725

Araki K, Shimura T, Suzuki H, Tsutsumi S, Wada W, Yajima T, Kobayahi T, Kubo N et al (2011) E/N-cadherin switch mediates cancer progression via TGF-b-induced epithelial-to-mesenchymal transition in extrahepatic cholangiocarcinoma. Br J Cancer 105:1885–1893

Arvanitakis M, Van Laethem JL, Pouzere S, Le Moine O, Deviere J (2006) Predictive factors for survival in patients with inoperable Klatskin tumors. Hepatogastroenterology 53:21–27

Bai H, Gayyed MF, Lam-Himlin DM, Klein AP, Nayar SK, Yu Y, Khan M, Argani P et al (2012) Expression of Yes-associated protein modulates Survivin expression in primary liver malignancies. Hum Pathol 43:1376–1385

Bhuiya MR, Nimura Y, Kamiya J, Kondo S, Fukata S, Hayakawa N, Shionoya S (1992) Clinicopathologic studies on perineural invasion of bile duct carcinoma. Ann Surg 215:344–349

Burke EC, Jarnagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH (1998) Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg 228:385–394

Carriaga MT, Henson DE (1995) Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 75:171–190

Casavilla FA, Marsh JW, Iwatsuki S, Todo S, Lee RG, Madariaga JR, Pinna A, Dvorchik I et al (1997) Hepatic resection and transplantation for peripheral cholangiocarcinoma. J Am Coll Surg 185:429–436

Chen LP, Li C, Wang C, Wen TF, Yan LN, Li B (2012) Predictive factors of recurrence for patients with intrahepatic cholangiocarcinoma after hepatectomy. Hepatogastroenterology 59:1765–1768

Chen YL, Jeng YM, Hsu HC, Lai HS, Lee PH, Lai PL, Yuan RH (2013) Expression of insulin-like growth factor II mRNA-binding protein 3 predicts early recurrence and poor prognosis in intrahepatic cholangiocarcinoma. Int J Surg 11:85–91

Cho MS, Kim SH, Park SW, Lim JH, Choi GH, Park JS, Chung JB, Kim KS (2012) Surgical outcomes and predicting factors of curative resection in patients with hilar cholangiocarcinoma: 10-year single-institution experience. J Gastrointest Surg 16:1672–1679

Choi JE, Noh SJ, Lee JH, Bae JS, Chu HH, Park HS, Jang KY, Chung MJ, Kang MJ et al (2012) Expression of keratin 20 and its clinicopathological significance in intrahepatic cholangiocarcinoma. Oncol Lett 4:534–540

Chou FF, Sheen-Chen SM, Chen CL, Chen YS, Chen MC (1995) Prognostic factors of resectable intrahepatic cholangiocarcinoma. J Surg Oncol 59:40–44

Clapéron A, Mergey M, Aoudjehane L, Ho-Bouldoires TH, Wendum D, Prignon A, Merabtene F et al. (2013) Hepatic myofibroblasts promote the progression of human cholangiocarcinoma through activation of epidermal growth factor receptor. Hepatology. . ..

Clark CJ, Wood-Wentz CM, Reid-Lombardo KM, Kendrick ML, Huebner M, Que FG (2011) Lymphadenectomy in the staging and treatment of intrahepatic cholangiocarcinoma: a population-based study using the National Cancer Institute SEER database. HPB (Oxford) 13:612–620

de Jong MC, Hong SM, Augustine MM, Goggins MG, Wolfgang CL, Hirose K, Schulick RD et al (2011a)

Hilar cholangiocarcinoma: tumor depth as a predictor of outcome. Arch Surg 146:697–703

de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrecu S, Marques H, Pulitano C et al (2011b) Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol 29:3140–3145

De Rose AM, Cucchetti A, Clemente G, Ardito F, Giovannini I, Ercolani G, Giuliante F et al (2013) Prognostic significance of tumor doubling time in mass-forming type cholangiocarcinoma. J Gastrointest Surg 17:739–747

Diamantis I, Karamitopoulou E, Perentes E, Zimmermann A (1995) p53 protein immunoreactivity in extrahepatic bile duct and gallbladder cancer: correlation with tumor grade and survival. Hepatology 22:774–779

Endo I, House MG, Klimstra DS, Gönen M, D'Angelica M, Dematteo RP, Fong Y et al (2008a) Clinical significance of intraoperative bile duct margin assessment for hilar cholangiocarcinoma. Ann Surg Oncol 15:2104–2112

Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, D'Angelica M, DeMatteo RP et al (2008b) Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 248:84–96

Fatima S, Ahmad Z, Qureshi A, Minhas K, Pal I (2008) Minimally invasive papillary carcinoma of the extrahepatic bile ducts. J Coll Phys Surg Pak 18:649–651

Fingas CD, Blechacz BR, Smoot RL, Guicciardi ME, Mott J, Bronk SF, Werneburg NW et al (2010) A smac mimetic reduces TNF related apoptosis inducing ligand (TRAIL)-induced invasion and metastasis of cholangiocarcinoma cells. Hepatology 52:550–561

Fisher SB, Patel SH, Kooby DA, Weber S, Bloomston M, Cho C, Hatzaras I, Schmidt C et al (2012) Lymphovascular and perineural invasion as selection criteria for adjuvant therapy in intrahepatic cholangiocarcinoma: a multi-institution analysis. HPB (Oxford) 14:514–522

Fukuda T, Iwanaga S, Sakamoto I, Aso N, Nagaoki K, Hayashi K, Yamaguchi H, Okudaira S et al (1998) CT of neural plexus invasion in common bile duct carcinoma. J Comput Assist Tomogr 22:351–356

Gardini A, Corti B, Fiorentino M, Altimari A, Ercolani G, Grazi GL, Pinna AD, Grigioni WF et al (2005) Expression of connective tissue growth factor is a prognostic marker for patients with intrahepatic cholangiocarcinoma. Dig Liver Dis 37:269–274

Gu MJ, Choi JH (2012) Clinicopathological significance of E-cadherin, b-catenin and epidermal growth factor receptor expression in intrahepatic cholangiocarcinoma. Hepatogastroenterology 59:1241–1244

Gu MJ, Choi JH (2014) Epithelial-mesenchymal transition phenotypes are associated with patient survival in intrahepatic cholangiocarcinoma. J Clin Pathol 67:229–234

Guglielmi A, Ruzzenente A, Campagnaro T, Pachera S, Valdegamberi A, Nicoli P, Capellani A et al (2009) Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. World J Surg 33:1247–1254

Guglielmi A, Ruzzenente A, Campagnaro T, Pachera S, Conci S, Valdegamberi A, Sandri M et al (2011) Prognostic significance of lymph node ratio after resection of peri-hilar cholangiocarcinoma. HPB (Oxford) 13:240–245

Guglielmi A, Ruzzenente A, Campagnaro T, Valdegamberi A, Bagante F, Bertuzzo F et al (2013) Patterns and prognostic significance of lymph node dissection for surgical treatment of perihilar and intrahepatic cholangiocarcinoma. J Gastrointest Surg 17:1917–1928

Guo L, Guo Y, Yiao S (2008) Expression of Etk/Bmx tyrosine kinase in intrahepatic cholangiocarcinoma. J Surg Oncol 97:428–432

Harada K, Masuda S, Hirano M, Nakanuma Y (2003) Reduced expression of syndecan-1 correlates with histologic dedifferentiation, lymph node metastasis, and poor prognosis in intrahepatic cholangiocarcinoma. Hum Pathol 34:857–863

Harrison LE, Fong Y, Klimstra DS, Zee SY, Blumgart LH (1998) Surgical treatment of 32 patients with peripheral intrahepatic cholangiocarcinoma. Br J Surg 85:1068–1070

Hasebe T, Konishi M, Iwasaki M, Endoh T, Nakagohri T, Takahashi S, Kinoshita T et al (2005) Histological characteristics of tumor cells and stromal cells in vessels and lymph nodes are important prognostic parameters of extrahepatic bile duct carcinoma: a prospective study. Hum Pathol 36:655–664

Hayashi A, Aishima S, Inoue T, Nakata K, Morimatsu K, Nagai E, Oda Y, Tanaka M, Tsuneyoshi M (2010) Decreased expression of focal adhesion kinase is associated with a poor prognosis in extrahepatic bile duct carcinoma. Hum Pathol 41:859–866

Higuchi R, Ota T, Araida T, Kobayashi M, Furukawa T, Yamamoto M (2010) Prognostic relevance of ductal margins in operative resection of bile duct cancer. Surgery 148:7–14

Hirashita T, Iwashita Y, Ohta M, Komori Y, Eguchi H, Yada K, Kitano S (2012) Expression of matrix metalloproteinase-7 is an unfavorable prognostic factor in intrahepatic cholangiocarcinoma. J Gastrointest Surg 16:842–848

Hirohashi et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/11995443

Hoang MP, Murakata LA, Katabi N, Henson DE, Albores-Saavedra J (2002) Invasive papillary carcinomas of the extrahepatic bile ducts: a clinicopathologic and immunohistochemical study of 13 cases. Mod Pathol 15:1251–1258

Hong SM, Hwang I, Song DE, Choi J, Yu E (2007) Clinical and prognostic significances of nuclear and cytoplasmic KIT expressions in extrahepatic bile duct carcinomas. Mod Pathol 20:562–569

Horino K, Beppu T, Komori H, Masuda T, Hayashi H, Okabe H, Takamori H, Baba H (2012) Evaluation of

mass-forming intrahepatic cholangiocarcinoma with viral hepatitis. Hepatogastroenterology 59:1217–1219
Horm TM, Schroeder JA (2013) MUC1 and metastatic cancer: expression, function and therapeutic targeting. Cell Adh Migr 7:187–198
Horm TM, Bitler BG, Broka DM, Louderbough JM, Schroeder JA (2012) MUC1 drives c-Met-dependent migration and scattering. Mol Cancer Res 10:1544–1554
Huang XY, Ke AW, Shi GM, Ding ZB, Devbhandari RP, Gu FM, Li QL, Dai Z et al (2010) Overexpression of CD151 as an adverse marker for intrahepatic cholangiocarcinoma patients. Cancer 116:5440–5451
Huang XY, Zhang C, Cai JB, Shi GM, Ke AW, Dong ZR, Zhang PF, Fan J, Peng BG et al (2014) Comprehensive multiple molecular profile of epithelial mesenchymal transition in intrahepatic cholangiocarcinoma patients. PLoS ONE 9, e96860
Iachino C, Catsicojannis N, Dallera F (1998) Prognostic significance of tumor DNA content in carcinoma of the hepatic duct confluence. J Exp Clin Cancer Res 17:425–430
Ieta K, Tanaka F, Utsunomiya T, Kuwano H, Mori M (2006) CEACAM6 gene expression in intrahepatic cholangiocarcinoma. Br J Cancer 95:532–540
Inoue K, Makuuchi M, Takayama T, Torzilli G, Yamamoto J, Shimada K, Kosuge T et al (2000) Long-term survival and prognostic factors in the surgical treatment of mass-forming type cholangiocarcinoma. Surgery 127:498–505
Isa T, Kusano T, Shimoji H, Takeshima Y, Muto Y, Furukawa M (2001) Predictive factors for long-term survival in patients with intrahepatic cholangiocarcinoma. Am J Surg 181:507–511
Isaji S, Kawarada Y, Taoka H, Tabata M, Suzuki H, Yokoi H (1999) Clinicopathological features and outcome of hepatic resection for intrahepatic cholangiocarcinoma in Japan. J Hepatobiliary Pancreat Surg 6:108–116
Ishiyama S, Fuse A, Kuzu H, Igarashi Y, Urayama M, Suto K, Tsukamoto M (1998) Results of surgical treatments and prognostic factors for hepatic hilar bile duct cancer. J Hepatobiliary Pancreat Surg 5:429–436
Itatsu K, Zen Y, Yamaguchi J, Ohira S, Ihsikawa A, Ikeda H, Sato Y, Harada K, Sasaki M et al (2008) Expression of matrix metalloproteinase 7 is an unfavorable postoperative prognostic factor in cholangiocarcinoma of the perihilar, hilar, and extrahepatic bile ducts. Hum Pathol 39:710–719
Ito Y, Miyoshi E, Takeda T, Sakon M, Tsujimoto M, Yokosaki Y, Monden M, Matsuura N (2000) ets-1 expression in extrahepatic bile duct carcinoma and cholangiocellular carcinoma. Oncology 58:248–252
Jan YY, Jeng LB, Hwang TL, Wang CS, Chen MF, Chen TJ (1996) Factors influencing survival after hepatectomy for peripheral cholangiocarcinoma. Hepatogastroenterology 43:614–619
Jarnagin WR, Bowne W, Klimstra DS, ben-Porat L, Roggin K, Cymes K, Fong Y, DeMatteo RP et al (2005) Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. Ann Surg 241:703–712
Jiang BG, Ge RL, Sun LL, Zong M, Wei GT, Zhang YJ (2011a) Clinical parameters predicting survival duration after hepatectomy for intrahepatic cholangiocarcinoma. Can J Gastroenterol 25:603–608
Jiang W, Zeng ZC, Tang ZY, Fan J, Sun HC, Zhou J, Zeng MS, Zhang BH, Ji Y et al (2011b) A prognostic scoring system based on clinical features of intrahepatic cholangiocarcinoma: the Fudan score. Ann Oncol 22:1644–1652
Jo Chae K, Rha SY, Oh BK, Koo JS, Kim YJ, Choi J, Park C, Park YN (2004) Expression of matrix metalloproteinase-2 and -9 and tissue inhibitor of metalloproteinase-1 and -2 in intraductal and nonintraductal growth type of cholangiocarcinoma. Am J Gastroienterol 99:68–75
Kaiser GM, Paul A, Sgourakis G, Molmenti EP, Dechêne A, Trarbach T, Stuschke M et al (2013) Novel prognostic scoring system after surgery for Klatskin tumor. Am Surg 79:90–95
Katayose Y, Nakagawa K, Yamamoto K, Yoshida H, Hayashi H, Mizuma M, Ihtsuka H et al (2012) Lymph nodes metastasis is a risk factor for bone metastasis from extrahepatic cholangiocarcinoma. Hepatogastroenterology 59:1758–1760
Kawamata F, Kamachi H, Einama T, Homma S, Tahara M, Miyazaki M, Tanaka S, Kamiyama T et al (2012) Intracellular localization of mesothelin predicts patient prognosis of extrahepatic bile duct cancer. Int J Oncol 41:2109–2118
Keeratichamroen S, Leelawat K, Thongtawee T, Narong S, Aegem U, Tujinda S, Praditphol (2011) Expression of CD24 in cholangiocarcinoma cells is associated with disease progression and reduced patient survival. Int J Oncol 39:873–881
Kim HJ, Yun SS, Jung FH, Kwun WH, Choi JH (1999) Intrahepatic cholangiocarcinoma in Korea. J Hepatobiliary Pancreat Surg 6:142–148
Kim WB, Han HJ, Lee HJ, Park SS, Song TJ, Kim HK, Suh SO, Kim YC, Choi SY (2009) Expression and clinical significance of cell cycle regulatory proteins in gallbladder and extrahepatic bile duct cancer. Ann Surg Oncol 16:23–34
Kim K, Min HS, Chie EK, Jang JY, Kim SW, Han SW, Oh DY, Im SA, Kim TY, Bang YJ et al (2013) CD24 expression predicts distant metastasis in extrahepatic bile duct cancer. World J Gastroenterol 19:1438–1443
Kirimlioglu H, Türkmen I, Bassüllü N, Dirican A, Karadag N, Kirimlioglu V (2009) The expression of matrix metalloproteinases in intrahepatic cholangiocarcinoma, hilar (Klatskin tumor), middle and distal extrahepatic cholangiocarcinoma, gallbladder cancer and ampullary carcinoma: role of matrix metalloproteinases in tumor progression and prognosis. Turk J Gastroenterol 20:41–47
Kitagawa Y, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Nimura Y (2001) Lymph node metastasis from hilar cholangiocarcinoma: audit

of 110 patients who underwent regional and paraaortic node dissection. Ann Surg 233:385–392

Kong D, Liang J, Li R, Liu S, Wang J, Zhang K, Chen D (2012) Prognostic significance of snail expression in hilar cholangiocarcinoma. Braz J Med Biol Res 45:617–624

Konishi M, Ochiai A, Ojima H, Hasebe T, Mano M, Ohta T, Ito I, Sasaki K, Yasukawa S et al (2009) A new histological classification for intra-operative histological examination of the ductal resection margin in cholangiocarcinoma. Cancer Sci 100:255–260

Konishi M, Iwasaki M, Ochiai A, Hasebe T, Ojima H, Yanagisawa A (2010) Clinical impact of intraoperative histological examination of the ductal resection margin in extrahepatic cholangiocarcinoma. Br J Surg 97:1363–1368

Korita PV, Wakai T, Ajioka Y, Inoue M, Takamura M, Shirai Y, Hatakeyama K (2010) Aberrant expression of vimentin correlates with dedifferentiation and poor prognosis in patients with intrahepatic cholangiocarcinoma. Anticancer Res 30:2279–2285

Kozuka et al (1984) http://www.ncbi.nlm.nih.gov/pubmed/6327000

Kubo Y, Aishima S, Tanaka Y, Shindo K, Mizuuchi Y, Abe K, Shirabe K, Maehara Y, Honda H et al (2014) Different expression of glucose transporters in the progression of intrahepatic cholangiocarcinoma. Hum Pathol 45:1610–1617

Kunlabut K, Vaeteewoottacharn K, Wongkham C, Khuntikeo N, Waraasawapati S, Paitojkul C (2012) Aberrant expression of CD44 in bile duct cancer correlates with poor prognosis. Asian Pac J Cancer Prev 13 (suppl):95–99

Lee et al (2009) http://www.ncbi.nlm.nih.gov/pubmed/19094134

Lee JH, Hwang DW, Lee SY, Park KM, Lee YJ (2012a) The proximal margin of resected hilar cholangiocarcinoma: the effect of microscopic positive margin on long-term survival. Am Surg 78:471–477

Lee HJ, Chung JY, Hewitt SM, Yu E, Hong SM (2012b) HER3 overexpression is a prognostic indicator of extrahepatic cholangiocarcinoma. Virchows Arch 461:521–530

Lee D, Do IG, Choi K, Sung CO, Jang KT, Choi D, Heo JS, Choi SH, Kim J, Park JY et al (2012c) The expression of phospho-AKT1 and phospho-MTOR is associated with a favorable prognosis independent of PTEN expression in intrahepatic cholangiocarcinomas. Mod Pathol 25:131–139

Li SM, Yao SK, Yamamura N, Nakamura T (2003) Expression of Bcl-2 and Bax in extrahepatic biliary tract carcinoma and dysplasia. World J Gastroenterol 9:2579–2582

Li et al (2005) http://www.ncbi.nlm.nih.gov/pubmed/16463672

Li Q, Wang JM, Liu C, Xiao BL, Lu JX, Zou SQ (2008) Correlation of a aPKC-iota and E-cadherin expression with invasion and prognosis of cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 7:70–75

Li S, Jo YS, Lee JH, Min JK, Lee ES, Park T, Kim JM, Hong HJ (2009) L1 cell adhesion molecule is a novel independent poor prognostic factor of extrahepatic cholangiocarcinoma. Clin Cancer Res 15:7345–7351

Li MH, Dong LW, Li SX, Tang GS, Pan YF, Zhang J, Wang H, Zhou HB, Tan YX et al (2013) Expression of cytoskeleton-associated protein 4 is related to lymphatic metastasis and indicates prognosis of intrahepatic cholangiocarcinoma patients after surgery resection. Cancer Lett 337:248–253

Liu YF, Zhao R, Guo S, Wang XQ, Lian PL, Chen YG, Xu KS (2011) Expression and clinical significance of hepatoma-derived growth factor as a prognostic factor in human hilar cholangiocarcinoma. Ann Surg Oncol 18:872–879

Luo X, Yuan L, Wang Y, Ge R, Sun Y, Wei G (2014) Survival outcomes and prognostic factors of surgical therapy for all potentially resectable intrahepatic cholangiocarcinoma: a large single-center cohort study. J Gastrointest Surg 18:562–572

Maaouni S, Benaddi L, Kabbaj N, Errabih I, Alhamany Z, Benaissa A (2006) Krukenberg tumor: rare metastasis of hilar cholangiocarcinoma (in French). Presse Med 35:1181–1184

Madariaga JR, Iwatsuki S, Todo S, Lee RG, Irish W, Starzl TE (1998) Liver resection for hilar and peripheral cholangiocarcinoma: a study of 62 cases. Ann Surg 227:70–79

Mao X, Chen D, Wu J, Li J, Zhou H, Wu Y, Duan X (2013) Differential expression of fascin, E-cadherin and vimentin: proteins associated with survival of cholangiocarcinoma patients. Am J Med Sci 346:261–268

Marubashi S, Gotoh K, Takahashi H, Ohigashi H, Yano M, Ishikawa O, Sakon M (2014) Prediction of the postoperative prognosis of intrahepatic cholangiocarcinoma (ICC): importance of preoperatively-determined anatomic invasion level and number of tumors. Dig Dis Sci 59:201–213

Matsumura N, Yamamoto M, Aruga A, Takasagi K, Nakano M (2002) Correlation between expression of MUC1 core protein and outcome after surgery in mass-forming intrahepatic cholangiocarcinoma. Cancer 94:1770–1776

Matsuo K, Rocha FG, Ito K, D'Angelica MI, Allen PJ, Fong Y, DeMatteo RP, Gonen M et al (2012) The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. J Am Coll Surg 215:343–355

Miwa S, Miyagawa S, Soeda J, Kawasaki S (2002) Matrix metalloproteinase-7 expression and biologic aggressiveness of cholangiocellular carcinoma. Cancer 94:428–434

Möbius C, Demuth C, Aigner T, Wiedmann M, Wittekind C, Mössner J, Hauss J, Witzigmann H (2007) Evaluation of VEGF A expression and microvascular density as prognostic factors in extrahepatic cholangiocarcinoma. Eur J Surg Oncol 33:1025–1029

Morine Y, Shimada M, Iwahashi S, Utsunomiya T, Imura S, Ikemoto T, Mori H, Hanaoka J et al (2012) Role of histone deacetylase expression in intrahepatic cholangiocarcinoma. Surgery 151:412–419

Murakami S, Miyamoto M, Hida Y, Cho Y, Fukunaga A, Oshikiri T, Kato K, Kurokawa T et al (2003) Caveolin-I overexpression is a favorable prognostic factor for patients with extrahepatic bile duct carcinoma. Br J Cancer 88:1234–1238

Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, Ohge H, Sueda T (2007) Prognostic significance of lymph node metastasis and surgical margin status for distal cholangiocarcinoma. J Surg Oncol 95:207–212

Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Kondo N, Sakabe R et al (2011) Is para-aortic lymph node metastasis a contraindication for radical resection in biliary carcinoma? World J Surg 35:1085–1093

Murakami S, Ajiki T, Okazaki T, Ueno K, Kido M, Matsumoto I, Fukumoto T, Ku Y (2014) Factors affecting survival after resection of intrahepatic cholangiocarcinoma. Surg Today 44:1847–1854

Nagorney DM, McPherson GA (1988) Carcinoma of the gallbladder and extrahepatic bile ducts. Semin Oncol 15:106–115

Nakagawa T, Kamiyama T, Kurauchi N, Matsushita M, Nakanishi K, Kamachi H, Kudo T et al (2005) Number of lymph node metastases is a significant prognostic factor in intrahepatic cholangiocarcinoma. World J Surg 29:728–733

Nakanishi Y, Zen Y, Kawakami H, Kubota K, Itoh T, Hirano S, Tanaka E, Nakanuma Y et al (2008) Extrahepatic bile duct carcinoma with extensive intraepithelial spread: a clinicopathological study of 21 cases. Mod Pathol 21:807–816

Nakanishi Y, Kondo S, Zen Y, Yonemori A, Kubota K, Kawakami H, Tanaka E, Hirano S et al (2010) Impact of residual in situ carcinoma on postoperative survival in 125 patients with extrahepatic bile duct carcinoma. J Hepatobiliary Pancreat Sci 17:166–173

Nakayama T, Tsuchikawa T, Shichinohe T, Nakamura T, Ebihara Y, Hirano S (2013) Pathological confirmation of para-aortic lymph node status as a potential criterion for the selection of intrahepatic cholangiocarcinoma patients for radical resection with regional lymph node dissection. World J Surg. . . ..

Nanashima A, Shibata K, Nakayama T, Tobinaga S, Araki M, Kunizaki M, Takshita H et al (2009) Relationship between microvessel count and postoperative survival in patients with intrahepatic cholangiocarcinoma. Ann Surg Oncol 16:2123–2129

Ning S, Guo S, Xie J, Xu Y, Lu X, Chen Y (2013) TROP2 correlates with microvessel density and poor prognosis in hilar cholangiocarcinoma. J Gastrointest Surg 17:360–368

Nishida T, Nakao K, Hamaji M, Nakahara MA, Tsujimoto M (1997) Prognostic significance of proliferative cell nuclear antigen in carcinoma of the extrahepatic bile duct. World J Surg 21:634–639

Nitta T, Sato Y, Ren XS, Harada K, Sasaki M, Hirano S, Nakanuma Y (2014) Autophagy may promote carcinoma cell invasion and correlate with poor prognosis in cholangiocarcinoma. Int J Clin Exp Pathol 7:4913–4921

Noji T, Miyamoto M, Kubota KC, Shinohara T, Ambo Y, Matsuno Y, Kashimura N, Hirano S (2012) Evaluation of extra capsular lymph node involvement in patients with extra-hepatic bile duct cancer. World J Surg Oncol 10:106

Nozaki Y, Yamamoto M, Ikai I, Yamamoto Y, Ozaki N, Fujii H, Nagahori K, Matsumoto Y et al (1998) Reconsideration of the lymph node metastasis pattern (N factor) from intrahepatic cholangiocarcinoma using the International Union Against Cancer TNM staging system for primary liver carcinoma. Cancer 83:1923–1929

Okabayashi T, Yamamoto J, Kosuge T, Shimada K, Yamasaki S, Takayama T, Makuuchi M (2001) A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. Cancer 92:2374–2383

Okabe H, Beppu T, Hayashi H, Horino K, Masuda T, Komori H, Ishikawa S, Watanabe M et al (2009) Hepatic stellate cells may relate to progression of intrahepatic cholangiocarcinoma. Ann Surg Oncol 16:2555–2564

Okazaki Y, Horimi T, Kotaka M, Morita S, Takasaki M (2002) Study of the intrahepatic surgical margin of hilar bile duct carcinoma. Hepatogastroenterology 49:625–627

Onoe S, Shimoyama Y, Ebata T, Yokoyama Y, Igami T, Sugawara G, Nakamura S, Nagino M (2014) Prognostic delineation of papillary cholangiocarcinoma based on the invasive proportion: a single-institution study with 184 patients. Surgery 155:280–291

Oshiro Y, Sasaki R, Kobayashi A, Murata S, Fukunaga K, Kondo T, Oda T, Ohkochi N (2011) Prognostic relevance of the lymph node ratio in surgical patients with extrahepatic cholangiocarcinoma. Eur J Surg Oncol 37:60–64

Park SY, Roh SJ, Kim YN, Kim SZ, Park HS, Jang KY, Chung MJ, Kang MJ et al (2009) Expression of MUC1, MUC2, MUC5AC and MUC6 in cholangiocarcinoma: prognostic impact. Oncol Rep 22:649–657

Patel SH, Kooby DA, Staley CA, Sarmiento JM, Maithel SK (2011) The prognostic importance of lymphovascular invasion in cholangiocarcinoma above the cystic duct: a new selection criterion for adjuvant therapy ? HPB (Oxford) 13:605–611

Prakobwong et al (2012) http://www.ncbi.nlm.nih.gov/pubmed/219935919

Ramacciato G, Corigliano N, Mercantini P, Di Benedetto F, Masetti M, Ercolani G, Lauro A et al (2006) Prognostic factors after surgical resection for hilar cholangiocarcinoma (in French). Ann Chir 131:379–385

Regimbeau et al (2015) http://www.ncbi.nlm.nih.gov/pubmed/2492279

Ribero D, Amisano M, Lo Tesoriere R, Rosso S, Ferrero A, Capussotti L (2011) Additional resection of an intraoperative margin-positive proximal bile duct improves survival in patients with hilar cholangiocarcinoma. Ann Surg 254:776–781

Roayaie S, Guarrera JV, Ye MQ, Thung SN, Emre S, Fishbein TM, Guy SR, Sheiner PA et al (1998) Aggressive surgical treatment of intrahepatic cholangiocarcinoma: predictors of outcomes. J Am Coll Surg 187:365–372

Roberts BJ, Reddy R, Wahl JK (2013) Stratifin (14-3-3 s) limits plakophilin-3 exchange with the desmosomal plaque. PLoS ONE 8, e77012

Romani AA, Soliani P, Desenzani S, Borghetti AF, Crafa P (2006) The associated expression of Maspin and Bax proteins as a potential prognostic factor in intrahepatic cholangiocarcinoma. BMC Cancer 6:255

Ryu HS, Chung JH, Lee K, Shin E, Jing J, Choe G, Kim H, Xu X, Lee HE, Kim DG et al (2012) Overexpression of epithelial-mesenchymal transition-related markers according to cell dedifferentiation: clinical implications as an independent predictor of poor prognosis in cholangiocarcinoma. Hum Pathol 43:2360–2370

Sakai T (2004) Immunohistochemical expression and matrix metalloproteinases in bile duct cancer tissue. Kurume Med J 51:215–223

Sano T, Shimada K, Sakamoto Y, Ojima H, Esaki M, Kosuge T (2008) Prognosis of perihilar cholangiocarcinoma: hilar bile duct cancer versus intrahepatic cholangiocarcinoma involving the hepatic hilus. Ann Surg Oncol 15:590–599

Sasaki A, Kawano K, Aramaki M, Ohno T, Tahara K, Kitano S (2004) Correlation between tumor size and mode of spread in mass-forming intrahepatic cholangiocarcinoma. Hepatogastroenterology 51:224–228

Sasaki R, Takeda Y, Funato O, Nitta H, Kawamura H, Uesugi N, Sugai T, Wakabayashi G et al (2007) Significance of ductal margin status in patients undergoing surgical resection for extrahepatic cholangiocarcinoma. World J Surg 31:1788–1796

Sato Y, van Gulik TM, Bosma A, Lygidakis NJ, Koyama K, van der Heyde MN (1994) Prognostic significance of tumor DNA content in carcinoma of the hepatic duct confluence. Surgery 115:488–494

Sato Y, Harada K, Sasaki M, Nakanuma Y (2013) Clinicopathological significance of S100 protein expression in cholangiocarcinoma. J Gastroenterol Hepatol 28:1422–1429

Schiffman SC, Nowacki MR, Spencer L, McMasters KM, Scoggins CR, Martin RC (2014) Molecular factors associated with recurrence and survival following hepatectomy in patients with intrahepatic cholangiocarcinoma: a guide to adjuvant clinical trials. J Surg Oncol 109:98–103

Schmeding et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/16981275

Seubwai W, Wongkham C, Puapairoj A, Khuntikeo N, Wongkham S (2007) Overexpression of vitamin D receptor indicates a good prognosis for cholangiocarcinoma: implications for therapeutics. Cancer 109:2497–2505

Sharma et al (1997) http://www.ncbi.nlm.nih.gov/pubmed/9068492

Shen FZ, Zhang BY, Feng YJ, Jia ZX, An B, Liu CC, Deng XY, Kulkarni AD, Lu Y (2010) Current research in perineural invasion of cholangiocarcinoma. J Exp Clin Cancer Res 29:24

Shibahara H, Tamada S, Higashi M, Goto M, Batra SK, Hollingsworth MA, Imai K et al (2004) MUC4 is a novel prognosis factor of intrahepatic cholangiocarcinoma – mass forming type. Hepatology 39:220–229

Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Ojima H (2007a) Surgical outcomes of the mass-forming plus periductal infiltrating types of intrahepatic cholangiocarcinoma: a comparative study with the typical mass-forming type of intrahepatic cholangiocarcinoma. World J Surg 31:2016–2022

Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Ojima H (2007b) Clinical impact of the surgical margin status in hepatectomy for solitary mass-forming type intrahepatic cholangiocarcinoma without lymph node metastases. J Surg Oncol 96:160–165

Shimada K, Sano T, Nara S, Esaki M, Sakamoto Y, Kosuge T, Ojima H (2009) Therapeutic value of lymph node dissection during hepatectomy in patients with intrahepatic cholangiocellular carcinoma with negative lymph node involvement. Surgery 145:411–416

Shimada M, Sugimoto K, Iwahashi S, Utsunomiya T, Morine Y, Imura S, Ikemoto T (2010) Cd133 expression is a potential prognostic indicator in intrahepatic cholangiocarcinoma. J Gastroenterol 45:896–902

Shingu Y, Ebata T, Nishio H, Igami T, Shimoyama Y, Nagino M (2010) Clinical value of additional resection of a margin-positive proximal bile duct in hilar cholangiocarcinoma. Surgery 147:49–56

Shirabe K, Mano Y, Taketomi A, Soejima Y, Uchiyama H, Aishima S, Kayashima H et al (2010) Clinicopathological prognostic factors after hepatectomy for patients with mass-forming type intrahepatic cholangiocarcinoma: relevance of the lymphatic invasion index. Ann Surg Oncol 17:1816–1822

Shirai K, Ebata T, Oda K, Nishio H, Nagasaka T, Nimura Y, Nagino M (2008) Perineural invasion is a prognostic factor in intrahepatic cholangiocarcinoma. World J Surg 32:2395–2402

Singal AG, Rakoski MO, Salgia R, Pelletier S, Welling TH, Fontana RJ, Lok AS, Marrero JA (2010) The clinical presentation and prognostic factors for intrahepatic and extrahepatic cholangiocarcinoma in a tertiary care centre. Aliment Pharmacol Ther 31:625–633

Sonbare DJ (2014) Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma:

a multicenter study by the AFC-IHCC-2009 Study Group. Ann Surg 259, e36

Stein DE, Heron DE, Rosato EL, Anne PR, Topham AK (2005) Positive microscopic margins alter outcome in lymph node-negative cholangiocarcinoma when resection is combined with adjuvant radiotherapy. Am J Clin Oncol 28:21–23

Su CH, Tsay SH, Wu CC, Shyr YM, King KL, Lee CH, Lui WY, Liu TJ, P'eng FK (1996) Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. Ann Surg 223:384–394

Su MC, Hsu C, Kao HL, Jeng YM (2006) CD24 expression is a prognostic factor in intrahepatic cholangiocarcinoma. Cancer Lett 235:34–39

Subimerb C, Pinlaor S, Khuntikeo N, Leelayuwat C, Morris A, McGrath MS, Wongkham S (2010) Tissue invasive macrophage density is correlated with prognosis in cholangiocarcinoma. Mol Med Rep 3:597–605

Sulpice L, Rayar M, Desille M, Turlin B, Fautrel A, Boucher E, Llamas-Gutierrez F et al (2013) Molecular profiling of stroma identifies osteopontin as an independent predictor of poor prognosis in intrahepatic cholangiocarcinoma. Hepatology 58:1992–2000

Sulpice L, Rayar M, Turlin B, Boucher E, Bellaud P, Desille M, Meunier B, Clément B, Boudjema K, Coulouarn C (2014) Epithelial cell adhesion molecule is a prognosis marker for intrahepatic cholangiocarcinoma. J Surg Res. doi:10.1016/j.jss.2014.05.017

Sun Q, Zhao C, Xia L, He Z, Lu Z, Liu C, Jia M, Wang J, Niu J (2014) High expression of matrix metalloproteinase-9 indicates poor prognosis in human hilar cholangiocarcinoma. Int J Clin Exp Pathol 7:6157–6164

Suzuki S, Sakaguchi T, Yokoi Y, Okamoto K, Kurachi K, Tsuchiya Y, Okumura T, Konno H et al (2002) Clinicopathological prognostic factors and impact of surgical treatment of mass-forming intrahepatic cholangiocarcinoma. World J Surg 26:687–693

Taguchi K, Aishima S, Asayama Y, Kajiyama K, Kinukawa N, Shimada M, Sugimachi K et al (2001) The role of p27kip1 protein expression on the biological behavior of intrahepatic cholangiocarcinoma. Hepatology 33:1118–1123

Tamada S, Shibahara H, Higashi M, Goto M, Batra SK, Imai K, Yonezawa S (2006) MUC4 is a novel prognostic factor of extrahepatic bile duct carcinoma. Clin Cancer Res 12:4257–64., Oncol. Rep. 15, 525–32

Tamandl D, Herberger B, Gruenberger B, Puhalla H, Klinger M, Gruenberger T (2008) Influence of hepatic resection margin on recurrence and survival in intrahepatic cholangiocarcinoma. Ann Surg Oncol 15:2787–2794

Tamandl D, Kaczirek K, Gruenberger B, Koelblinger C, Maresch J, Jakesz, Gruenberger T (2009) Lymph node ratio after curative surgery for intrahepatic cholangiocarcinoma. Br J Surg 96:919–925

Tanaka S, Sugimachi K, Kameyama T, Maehara S, Shirabe M, Wands JR, Maehara Y (2003) Human WISP1v, a member of the CCN family, is associated with invasive cholangiocarcinoma. Hepatology 37:1122–1129

Tang D, Nagano H, Yamamoto H, Wada H, Nakamura M, Kondo M, Ota H, Yoshioka S et al (2006) Angiogenesis in cholangiocellular carcinoma: expression of vascular endothelial growth factor, angiopoietin-1/2, thrombospondin-1 and clinicopathological significance. Oncol Rep 15:525–532

Taniguchi K, Tabata M, Iida T, Hori T, Yagi S, Uemoto S (2006) Significance of lymph node micrometastasis in pN0 hilar bile duct carcinoma. Eur J Surg Oncol 32:208–212

ten Hoopen-Neumann H, Gerhards MF, van Gulik TM, Bosma A, Verbeek PC, Gouma DJ (1999) Occurrence of implantation metastases after resection of Klatskin tumors. Dig Surg 16:209–213

Thelen A, Scholz A, Benckert C, Schröder M, Weichert W, Wiedenmann B, Neuhaus P, Jonas S (2008) Microvessel density correlates with lymph node metastases and prognosis in hilar cholangiocarcinoma. J Gastroenterol 43:959–966

Thelen A, Scholz A, Weichert W, Wiedenmann B, Neuhaus P, Gessner R, Benckert C et al (2010) Tumor-associated angiogenesis and lymphangiogenesis correlate with progression of intrahepatic cholangiocarcinoma. Am J Gastroenterol 105:1123–1132

Tian F, Li D, Chen J, Liu W, Cai L, Li J, Jiang P, Liu Z, Zhao X, Guo F, Li X, Wang S (2013) Aberrant expression of GATA binding protein 6 correlates with poor prognosis and promotes metastasis in cholangiocarcinoma. Eur J Cancer . . ..

Tian X, Wang Q, Li Y, Hu J, Wu L, Ding Q, Zhang C (2014) The expression of S100A4 protein in human intrahepatic cholangiocarcinoma: Clinicopathologic significance and prognostic value. Pathol Oncol Res . . ..

Tojima Y, Nagino M, Ebata T, Uesaka K, Kamiya J, Nimura Y (2003) Immunohistochemically demonstrated lymph node micrometastasis and prognosis in patients with otherwise node-negative hilar cholangiocarcinoma. Ann Surg 237:201–207

Uenishi T, Hirohashi K, Kubo S, Yamamoto T, Yamazaki O, Kinoshita H (2001) Clinicopathological factors predicting outcome after resection of mass-forming intrahepatic cholangiocarcinoma. Br J Surg 88:969–974

Uenishi T, Yamazaki O, Yamamoto T, Hirohashi K, Tanaka H, Tanaka S, Hai S, Kubo S (2005) Serosal invasion in TNM staging of mass-forming intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 12:479–483

Uenishi T, Ariizumi S, Aoki T, Ebata T, Ohtsuka M, Tanaka E, Yoshida H, Imura S et al (2014) Proposal of a new staging system for mass-forming intrahepatic cholangiocarcinoma: a multicenter analysis by the

Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci 21:499–508

Wakai T, Shirai Y, Moroda T, Yokoyama N, Hatakeyama K (2005) Impact of ductal resection margin status on long-term survival in patients undergoing resection for extrahepatic cholangiocarcinoma. Cancer 103:1210–1216

Wang M, Gu J, Wang Y, Gong B (2009) Loss of WWOX expression in human extrahepatic cholangiocarcinoma. J Cancer Res Clin Oncol 135:39–44

Weber A, Landrock S, Schneider J, Stangl M, Neu B, Born P, Classen M, Rösch T et al (2007) Long-term outcome and prognostic factors of patients with hilar cholangiocarcinoma. World J Gastroenterol 13:1422–1426

Won KY, Kim GY, Lim SJ, Park YK, Kim YW (2009) Prognostic significance of fascin expression in extrahepatic bile duct carcinomas. Pathol Res Pract 205:742–748

Xiao M, Zhou NX, Huang ZQ, Lu YL, Chen LH, Wang DJ, Chang WL (2004) The ratio of MMP-2 to TIMP-2 in hilar cholangiocarcinoma: a semi-quantitative study. Hepatobiliary Pancreat Dis Int 3:599–602

Xu LB, Liu C, Gao GQ, Yu XH, Zhang R, Wang J (2010a) Nerve growth factor-beta expression is associated with lymph node metastasis and nerve infiltration in human hilar cholangiocarcinoma. World J Surg 34:1039–1045

Xu Y, Zhu M, Zhang S, Liu H, Qin C (2010b) Expression and prognostic value of PRL-3 in human intrahepatic cholangiocarcinoma. Pathol Oncol Res 16:169–175

Xu D, Yi W, Chen Y, Ma L, Wang J, Yu G (2014a) Overexpression of Sig1R is closely associated with tumor progression and poor outcome in patients with hilar cholangiocarcinoma. Med Oncol 31:261

Xu YF, Yang XQ, Lu XF, Guo S, Liu Y, Iqbal M, Ning SL, Yang H, Suo N, Chen YX (2014b) Fibroblast growth factor receptor 4 promotes progression and correlates to poor prognosis in cholangiocarcinoma. Biochem Biophys Res Commun 446:54–60

Yamaguchi K, Shirahane K, Nakamura M, Su D, Konomi H, Motoyama K, Sugitani A et al (2005) Frozen section and permanent diagnoses of the bile duct margin in gallbladder and bile duct cancer. HPB (Oxford) 7:135–138

Yamamoto M, Takasaki K, Yoshita T, Ueno K, Nakano M (1998) Does gross appearance indicate prognosis in intrahepatic cholangiocarcinoma ? J Surg Oncol 69:162–167

Yao et al (2012) http://www.ncbi.nlm.nih.gov/pubmed/23091390

Yeh CN, Pang ST, Jung SM, Chen TW, Jan YY, Chen MF (2010) Cytoplasmic overexpression with membrane accentuation of stratifin in intrahepatic mass-forming cholangiocarcinoma after hepatectomy: correlation with clinicopathologic features and patient survival. J Surg Oncol 102:608–614

Yeh CN, Yeh TS, Chen TC, Jan YY, Chen MF (2013) Gross pathological classification of peripheral cholangiocarcinoma determines the efficacy of hepatectomy. J Gastroenterol 48:647–659

Yeh CN, Hsieh FJ, Chiang KC, Chen JS, Yeh TS, Jan YY, Chen MF (2014) Clinical effect of a positive surgical margin after hepatectomy on survival of patients with intrahepatic cholangiocarcinoma. Drug Des Dev Ther 9:163–174

Yin X, Zheng SS, Zhang BH, Zhou Y, Chen XH, Ren ZG, Qiu SJ, Fan J (2013) Elevation of serum g-glutamyltransferase as a predictor of aggressive tumor behaviors and unfavorable prognosis in patients with intrahepatic cholangiocarcinoma: analysis of a large monocenter study. Eur J Gastroenterol Hepatol . . ..

Zhang C, Tu Z, Du S, Wang Y, Wang Q (2010a) Expression of matrix metalloproteinase 2 and extracellular matrix metalloproteinase inducer are unfavorable postoperative prognostic factors in intrahepatic cholangiocarcinoma. Pathol Oncol Res 16:47–53

Zhang KJ, Wang DS, Zhang SY, Jiao XL, Li CW, Wang XS, Yu QC, Cui HN (2010b) The E-cadherin repressor slug and progression of human extrahepatic hilar cholangiocarcinoma. J Exp Clin Cancer Res 29:88

Zhao W, Zhang B, Guo X, Zhang X, Hu J, Hu X, Lu Y (2014) Expression of Ki-67, Bax and p73 in patients with hilar cholangiocarcinoma. Cancer Biomark 14:197–202

Zheng J, Zhu YM (2007) Expression of c-erbB-2 protooncogene in extrahepatic cholangiocarcinoma and its clinical significance. Hepatobiliary Pancreat Dis Int 6:412–415

Zhou L, He XD, Cui QC, Zhou WX, Qu Q, Zhou RL, Rui JA, Yu JC (2008) Expression of LAPTM4B-35: a novel marker of progression, invasiveness and poor prognosis of extrahepatic cholangiocarcinoma. Cancer Lett 264:209–217

Zhou Q, Gong Y, Huang F, Lin Q, Zeng B, Li Z, Chen R (2013) Expression levels and significance of nuclear factor-kB and epidermal growth factor receptor in hepatolithiasis associated with intrahepatic cholangiocarcinoma. Dig Surg 30:309–316

Zhu J, Guo X, Qiu B, Li Z, Xia N, Yang Y, Liu P (2014) Prognostic significance of the combined expression of neutral endopeptidase and dipeptidyl peptidase IV in intrahepatic cholangiocarcinoma patients after surgery resection. Onco Targets Ther 7:297–304

Etiology and Pathogenic Pathways of Cholangiocarcinoma

31

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_31

Abstract

Pathways leading from normal cholangiocytes and their progenitors to cholangiocarcinoma are complex and involve a wide array of genes and their products. For carcinomas of extrahepatic ducts in Western countries, the most common predisposing condition is probably primary sclerosing cholangitis. Congenital biliary cystic disease, in particular choledochal cysts and Caroli's disease, also plays an important role. In Southeast Asia and Japan, hepatolithiasis and liver fluke infestation are important factors. An established precursor of extrahepatic cholangiocarcinoma is biliary intraepithelial neoplasia (BillN), suggesting a dysplasia-carcinoma sequence. Precursor lesions found in bile ducts are also involved in the pathogenesis of intrahepatic cholangiocarcinoma. For this type of cancer, intraductal papillary neoplasms that later become invasive lesions play a significant role. For both intrahepatic and extrahepatic cholangiocarcinomas, molecular mechanisms involved in cholangiocarcinogenesis are currently identified.

Hilar/Perihilar Cholangiocarcinoma

Introduction

Most PHCs are sporadic cancers and are thought to arise from the superficial epithelial of proximal extrahepatic bile ducts and bile ducts close to the confluence. In addition, there is evidence that part of these neoplasms may originate from peribiliary glands (Terada et al. 1992). The pathways leading from normal cholangiocytes – and eventually their progenitors – to cholangiocarcinoma are complex and involve a wide array of genes and their products (reviews: Okuda et al. 2002; Wise et al. 2008; Hassid et al. 2009). Probably the most common predisposing condition of PHC in Western countries is primary sclerosing cholangitis (PSC). Occult cholangiocarcinoma has been found in up to 40 % of autopsy specimens of patients with PSC and up to 36 % of explanted livers in PSC. A second predisposing condition is congenital biliary cystic disease, in particular choledochal cysts and Caroli's disease. In certain parts of Southeast Asia and in Japan, hepatolithiasis is a well-known risk factor for cholangiocarcinoma. Liver flukes mainly occurring in Southeast Asia (*Opisthorchis viverrini*, *Clonorchis sinensis*) are also an important etiologic factor for cholangiocarcinoma.

Dysplasia-Carcinoma Sequence in Hilar/Perihilar Cholangiocarcinoma

Biliary intraepithelial neoplasia (BillN) is an established precursor lesion of PHC and other extrahepatic cholangiocarcinomas (Sato et al. 2014). Advanced dysplastic changes and carcinoma in situ can develop in the extrahepatic biliary tract, suggesting a dysplasia-carcinoma sequence (Komenaka et al. 2003). It was proposed that flat-type biliary intraepithelial neoplasia (BillN) and papillary-type intraductal papillary neoplasm of the bile duct (IPN-B) are precursor lesions of invasive perihilar intrahepatic cholangiocarcinoma (Nakanuma et al. 2009). The authors proposed three carcinogenetic pathways, i.e., BillN progressing to tubular adenocarcinoma and IPN-B progressing to tubular adenocarcinoma and colloid carcinoma. Carcinogenesis through BillN was characterized by MUC2/CK20 with MUC1 expression. p53 expression was upregulated at the invasive stage of BillN, but was low in noninvasive BillN (Nakanuma et al. 2009). It was proposed that BillN and IPN-B (IPNB) may represent lesions analogous to pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms, respectively (review: Bickenbach et al. 2009). Parts of sysplastic lesions of the extrahepatic biliary tract are associated with long-standing inflammatory bile duct disease, in particular primary sclerosing cholangitis (Katabi and Albores-Saavedra 2003). Dysplastic epithelia in extrahepatic bile ducts exhibit an immunophenotype that differs from normal cholangiocytes. While normal epithelia and low-grade dysplasia are negative for S100A4 protein and mesothelin, high-grade

dysplasia and carcinoma express these two factors at high rates (Zhao et al. 2007).

Cytogenetic and Molecular Features

Cholangiocarcinoma cells, but mainly those of intrahepatic carcinomas, overexpress the polycomb group protein Bmi1, a stemness gene involved in the maintenance of stem cells, malignant transformation, and malignancy grade in diverse neoplasms, and probably acting by repression of cellular senescence (Sasaki et al. 2009).

Tumor Suppressor Genes and Oncogenes

Similar to other cholangiocarcinomas, PHC show various types of abnormal expression of oncogenes and tumor suppressor genes (reviews: Rashid 2002; Enjoji et al. 2004). At least part of PHC shows mutations of the p53 gene, in part not associated with nuclear immunoreactivity for p53 protein (Jonas et al. 1998; Sturm et al. 1998; Della Torre et al. 2000; Chuang et al. 2004; Khan et al. 2005). There is a difference in the type of p53 gene mutations (except 175) between PHC occurring in European patients and with p53 mutation found in East Asian intrahepatic cholangiocarcinomas. In one study of European PHC, all p53 mutations occurred in exon 5 (Tullo et al. 2000). The expression of P53-binding protein 1 (53BP1), an early DNA damage response protein rapidly recruited to sites of DNA double-strand breaks, is an indicator for endogenous strand breaks in genomic instability. In PHC it was found that expression of 53BP1 is associated with local recurrence at ductal stumps following resection (Wakai et al. 2011, 2013). Part of PHCs show mutations in the K-ras oncogene (Sturm et al. 1998). In bile duct carcinogenesis, mutations of p16Ink4/CDKN2 rather than p15Ink4B appear to be important (Yoshida et al. 1995; Ueki et al. 2004). However, alterations of the p16Ink4 pathway were not found by other investigators (Della Torre et al. 2000). Part of cholangiocarcinomas, in particular those located in the common bile duct, display mutations of the candidate tumor suppressor gene, DPC4/Smad4, known to be inactivated in about half of ductal adenocarcinomas of the pancreas (Hahn et al. 1998; Suto et al. 2002). A relationship between choledochal cholangiocarcinomas and pancreatic carcinomas is underlined by the observation that DPC4 mutations occur more frequently in cholangiocarcinomas of the distal part of the common bile duct (Argani et al. 2001). Whereas K-ras mutations seem to be uncommon in periampullary cancers and cancers of the gallbladder, such mutations have been found in cholangiocarcinomas (Lee et al. 1995). In one study, the incidence of K-ras mutations in extrahepatic cholangiocarcinomas was 9.6 %, compared to a rate of 32.7 % for p53 gene (Suto et al. 2000).

Markers of Biliary Tract Development

PHCs share the expression of some ontogenically expressed factors with ductal carcinomas of the pancreas. Anterior gradient protein-2 and S100P are frequently expressed in PHC and pancreatic ductal adenocarcinoma, while PDX1 and HES1 were often expressed in ductal cancers of the pancreas, but less in PCH. Furthermore, PHC and pancreatic cancers reveal a similar expression of mucin types as well as certain transcription factors.

Factors Regulating the Cell Division Cycle

The expression of p27 decreased progressively from proximal to distal in cancers of the biliary tract, and the expression patterns of p27 and cyclin in PHC were more similar to that of gallbladder cancers than to intrahepatic peripheral cholangiocarcinomas (Jarnagin et al. 2006). Overexpression of ErbB-2 seems to be a rare phenomenon in extrahepatic cholangiocarcinomas and was detected in only 5.1 % of cases, similar to epidermal growth factor receptor (8.1 %), and both were associated with gene amplification (Nakazawa et al. 2005).

Factors Affecting Epithelial-Mesenchymal Transition (EMT) and Stromagenesis

EMT is a critical mechanism affecting cancer invasion and spread. In cholangiocarcinoma cells, EMT is induced by TGF-beta1/Snail activation, and this EMT induction is in turn associated with aggressive growth (Sato et al. 2010).

Epigenetic Mechanisms

There is increasing evidence that epigenetic mechanisms play a role in the pathogenesis of cholangiocarcinoma, specifically in intrahepatic tumors (Kohya et al. 2006; Tischoff et al. 2006). A significant proportion of cholangiocarcinomas showed promoter hypermethylation of tumor suppressor and tumor-related genes (Tozawa et al. 2004). Frequencies of promoter methylation were 70 % for p16/INK4a, 49 % for *O*-(6)-methylguanine-DNA methyltransferase (MGMT), 46 % for hMLH1, 41 % for E-cadherin, and 32 % for DAPK genes. Cholangiocarcinomas with MGMT methylation expressed multigene methylation more frequently than tumors without MGMT methylation, and reduced MGMT expression may increase the malignant potential of cholangiocarcinomas (Koga et al. 2005). Epigenetic silencing of DAP-kinase appears to be a significant prognostic factor in cholangiocarcinoma (Tozawa et al. 2004).

Intrahepatic Cholangiocarcinoma

Introduction

A growing list of risk factors has been recognized to be involved in cholangiocarcinomas (review: Bragazzi et al. 2012). Generally, risk factors for ICC can be divided into two major groups. The first, more common group of ICC represents a consequence of recurrent infestations of the biliary tract by liver flukes mainly occurring in East and Southeast Asia. The second group of ICC is a much rarer cancer induced by a wide array of etiologic factors and occurring worldwide (reviews: de Martel et al. 2010; Shin et al. 2010). Literature reviews and meta-analyses uncovered that, specifically in Western countries, liver cirrhosis, chronic HBV and HCV infection, alcohol abuse, diabetes mellitus, and obesity are major risk factors for ICC (Palmer and Patel 2012).

Precursor Lesions of Intrahepatic Cholangiocarcinoma

Typical precursor lesions of cholangiocarcinomas originating in larger bile ducts are termed biliary intraepithelial neoplasm (BillN), a distinct group of dysplastic processes that evolve into carcinoma in situ (Figs. 1, 2, and 3). BillN is generally confined to large and septal-sized bile ducts (Sato et al. 2013, 2014; Aishima et al. 2014). Precursor lesions, in particular biliary epithelial dysplasia, form a distinct precancerous change in extrahepatic bile ducts, but also develop in large intrahepatic bile ducts of patients with several risk factors of ICC. As BillNs are typically premalignant changes that occur in large ducts, they play a role in ICC located to perihilar intrahepatic ducts, i.e., in large-duct ICC. In contrast, precursor lesions of peripheral ICC are not yet well established. In a minority of peripheral ICC, bile duct adenoma, bile duct adenoma-like lesions, biliary adenofibroma, biliary microhamartomas (von Meyenburg complexes), and atypical bile duct lesions involving small bile ducts may be related to the development of this cancer (review: Nakanuma et al. 2014).

The histologic criteria for lesions previously termed intraepithelial atypical/proliferative biliary epithelial lesions have worked out by the study of stone-containing intrahepatic bile ducts of hepatolithiasis (Zen et al. 2005a). In livers with established ICC, dysplastic lesions occur both near and remote from ICC lesions (Shimonishi et al. 2000b). Precursors of invasive, perihilar, or peripheral intrahepatic cholangiocarcinoma (ICC) include flat-type biliary intraepithelial neoplasia (BillN) and papillary-type intraductal papillary neoplasm of bile duct (IPN-B). These two pathways have specifically been identified in ICC

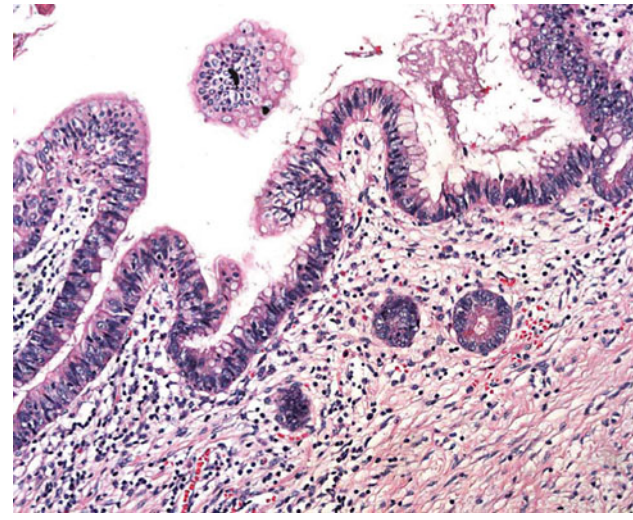

Fig. 1 BiIIN, low grade, in a bile duct (hematoxylin and eosin stain)

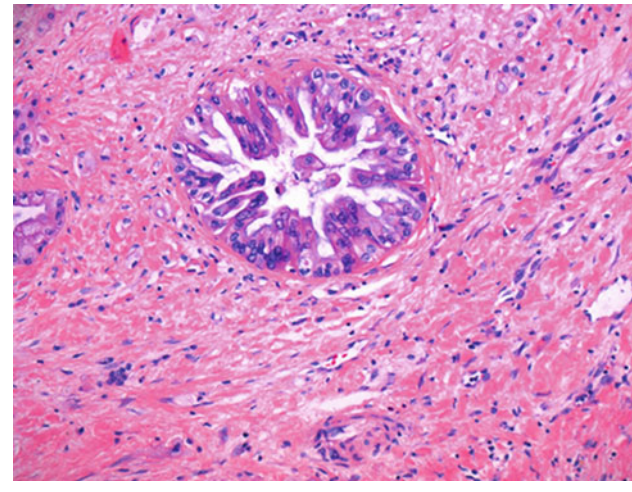

Fig. 2 BiIIN, moderate grade (hematoxylin and eosin stain)

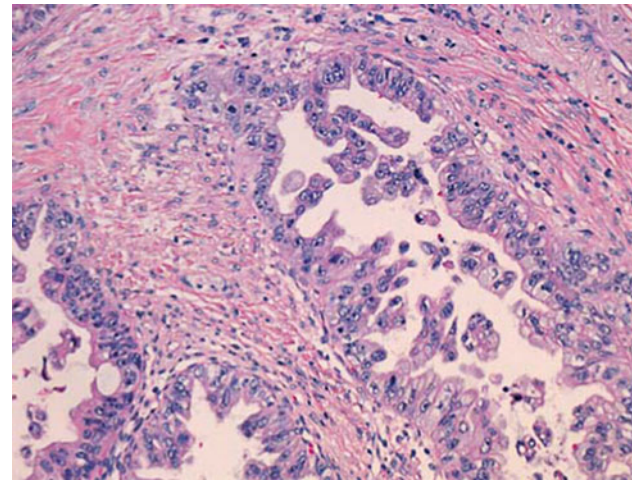

Fig. 3 BiIIN, high grade, in part with a papillary pattern (hematoxylin and eosin stain)

Table 1 Classification of flat-type biliary intraepithelial neoplasia (BillN; Zen et al. 2005b, 2007)

BilIN-1	Low-grade dysplasia of biliary epithelium, mild cellular-nuclear atypia suggestive of neoplasia
BillN-2	High-grade dysplasia of biliary epithelium, cellular-nuclear atypia evident but insufficient to represent overt malignancy
BillN-3	Carcinoma in situ, cellular-nuclear atypia representing overt malignancy

patients with hepatolithiasis, and a three-level grading system for BillN has been developed (Zen et al. 2005b, 2007; Table 1). For ICCs, three carcinogenic pathways have been proposed, viz., BillN progressing to tubular adenocarcinoma and IPN-B progressing to tubular adenocarcinoma or to colloid carcinoma.

In one analysis, carcinogenesis via BillN was characterized by MUC2-/CK7+/CK20- with increasing MUC1 expression, whereas IPN-B showed an intestinal phenotype with MUC2+/CK20+. Transition to invasive tubular adenocarcinoma was associated with increasing MUC1 expression and to that of colloid carcinomas with MUC1 loss (Zen et al. 2006). Other studies showed that progression from BillN involves an MUC1(+)MUC2(−)CK20(−)-associated pathway and upregulation of p53 in the switch to invasion (review: Nakanuma et al. 2009). In patients with hepatolithiasis, Sato and coworkers (2013) distinguished two forms of carcinoma in situ, i.e., (BillN-3), biliary intraepithelial neoplasia-3 and intraepithelial spread of carcinoma (IES). The two forms, which histologically mostly present as flat or pseudopapillary lesions, differ in their demarcation from the normal epithelial lining. BillN-3 is an atypia that gradually decreases toward the transition to the normal biliary epithelium, whereas in IES, the lesion displays an abrupt transition to normal epithelium. Both lesions were only found in livers with invasive ICC. BillN-3 and IES differ in their distribution within the intrahepatic bile ducts. Whereas BillN-3 was not present in septal and small ducts, IES was often found in such ducts (Sato et al. 2013).

The precursor lesions are associated with deranged expression of components of the Wnt signaling pathway. The membranous expression of beta-catenin decreased along with the progression of both BillN and IPN-B changes, and decreased E-cadherin expression was a marker for invasive ICC with BillN and IPN-B in comparison with noninvasive counterparts. BillNs 1–3 are not or only weakly associated with expression of the invasion markers MMP-7 amd MT1-MPP, while these two enzymes are expressed in invasive lesions (Itatsu et al. 2007). Expressions of p53, p21, and cyclin D1 were upregulated in both BillN and IPN-B, whereas Dpc4 was downregulated in these lesions. In bile ducts with BillN, expression of p21 is an early alteration, while expression of p53 is low in precursor lesions and undergoes a dramatic increase in invasive neoplastic lesions (Nakanishi et al. 2008).

Several types of chronic liver diseases have been analyzed for the expression patterns of BillN. Precursor lesions such as BillN are well-known for biliary cirrhosis (Aishima et al. 2011), specifically in patients with PSC, but can also develop in non-biliary cirrhosis, mainly alcohol- and HCV-induced cirrhosis (Torbenson et al. 2007; Rougemont et al. 2010). In cirrhosis, biliary neoplasia can show extensive intraductal spread (Aishima et al. 2008). In a series of explanted livers, those transplanted for alcoholic liver disease and alcoholic liver disease plus HCV cirrhosis had the highest prevalence of BillN, higher grades of BillN, and greater numbers of intrahepatic ducts with BillN as compared with HCV alone and non-cirrhotic livers, suggesting that alcohol and HCV infection may play a role in intrahepatic cholangiocarcinogenesis (Wu et al. 2009). In patients with end-stage PSC, livers with cholangiocarcinoma are more likely to have metaplastic duct changes, dysplasia/BillN of any grade, and high-grade dysplasia (Lewis et al. 2010). ICC has been observed in the setting of biliary papillomatosis (Cox et al. 2005).

Chronic Biliary Tract Inflammation and Bile Duct Cancer

ICC is found in association with cholangitis, cholelithiasis/hepatolithiasis, alcoholic liver disease, liver cirrhosis, chronic inflammatory bowel disease, and parasitoses (Ben-Menachem 2007;

Welzel et al. 2007; Khan et al. 2008; Zhou et al. 2008; Tyson and El-Serag 2011; Sibulesky et al. 2012). Established risk factors comprise primary sclerosing cholangitis, other inflammatory disorders of the biliary tree (including parasitoses), and choledochal cyst, but several other conditions are significantly associated with both ICC and ECC, such as biliary cirrhosis, cholelithiasis, alcoholic liver disease, nonalcoholic steatohepatitis with or without diabetes mellitus, hepatitis virus infection, nonspecific cirrhosis, smoking, and chronic pancreatitis (Shaib et al. 2005; Welzel et al. 2007). There is evidence that any process that results in increased epithelial cell turnover or hyperplasia of cholangiocytes can switch into a dysplasia-adenoma sequence increasing the risk of cholangiocarcinoma (Kurashina et al. 1988; Vianna et al. 1989; Pinho et al. 2012). Important effectors of inflammation-induced derangement of epithelial proliferation modes and subsequent carcinogenesis are certain cytokines. One of them is interleukin-6/IL-6 and its receptor. Most, if not all, inflammatory reactions taking place in bile ducts cause upregulation of IL-6 secretion, which in turn triggers several signal pathways, including PI3 kinase, JAK/STAT, and p38 MAP kinase, leading to increased cell proliferation and protection from apoptosis (review: Johnson et al. 2012). IL-6 also decreases cell senescence and increases telomerase activity in cholangiocarcinoma (Yamagiwa et al. 2006). The differential effects of IL-6 on diverse genes are in part mediated by the induction of epigenetic gene promoter methylation (Wehbe et al. 2006). In malignant human cholangiocytes, IL-6 epigenetically regulates microRNA-370, in the IL-6 overexpression reduced miR-370 expression, a gene target of which is the oncogene, mitogen-activated protein kinase kinase 8/MAP3K8 (Meng et al. 2008). On the other hand, the microRNA let-7a modulates the IL6-dependent STAT-3 survival signaling in cholangiocarcinoma cells (Meng et al. 2007).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a well-recognized risk factor for cholangiocarcinoma, and is regarded as the most common predisposing factor for cholangiocarcinoma in the West, and patients with PSC develop cholangiocarcinoma at younger age, i.e., 30–50 years, in comparison with the general population (MacCarty et al. 1985; Martins et al. 1994; Knechtle et al. 1995; Chalasani et al. 2000; Maggs and Chapman 2008; Fevery and Verslype 2010). The prevalence of cholangiocarcinoma in patients with PSC ranges from 7 % to 13 % (review: Lazarides and Gores 2006), but there are reports giving a figure of 40 % (Shaib and El-Serag 2004). The cumulative annual risk of cholangiocarcinoma in patients with PSC is 1.5 % per year after the development of jaundice. In patients who concomitantly suffer from inflammatory bowel disease, the 10-year and 20-year risks for cholangiocarcinoma are 14 % and 31 %, respectively. The patient group with the highest risk for cholangiocarcinoma is that with large-duct PSC in contrast to small-duct PSC. However, in case small-duct disease progresses to large-duct disease, the risk for cholangiocarcinoma seems to increase (Björnsson et al. 2008). Apart from effects exerted by chronic inflammation and the associated deregulation of cytokine and growth factor secretion, there is evidence that genetic factors are involved in PSC-related carcinogenesis (Forsbring et al. 2009). In PSC, the biliary tract is prone to the development of various precursor lesions of cholangiocarcinoma, as discussed above, in particular various grades of dysplasia (Fleming et al. 2001). In a series of 100 consecutive liver explants of patients with PSC, mucinous metaplasia, pyloric metaplasia, and pancreatic acinar metaplasia were detected in 77 %, 73 %, and 10 %, respectively, and these rates did not differ between cancerous and noncancerous livers. In contrast, livers with ICC were more likely to have intestinal metaplasia, dysplasia of any grade, and high-grade dysplasia (Lewis et al. 2010). Two distinct pathways of cholangiocarcinogenesis in PSC have been proposed. Cholangiocarcinoma and biliary intraepithelial neoplasia were classified into intestinal and non-intestinal classical types, the former being slightly more common. Intestinal-type lesions revealed histological features resembling

intestinal dysplasia or adenocarcinoma and often exhibited an intraductal papillary proliferation and mucinous nodules. Patients with intestinal-type cholangiocarcinoma had a more favorable cancer-specific prognosis than those with classical-type cholangiocarcinoma (Zen et al. 2011).

Liver Fluke Disease

As specified in more detail in a separate chapter, liver flukes are well-known to be an important risk factor for the development of ICC (liver fluke-associated ICC; Flavell 1981; Kurathong et al. 1985; Choi et al. 1988; Riganti et al. 1989; Shirai et al. 1992; Haswell-Elkins et al. 1994; Elkins et al. 1996; reviews; Schwartz 1986; Watanapa and Watanapa 2002; Hughes et al. 2006; Ong et al. 2012). Liver fluke disease is not only a major challenge in endemic regions of Southeast and East Asia but also for numerous immigrants of these countries now living in other countries. It has been estimated in the 1970s that up to 26 % of Asian immigrants had active liver fluke infestation (Schwartz 1986). Cholangiocarcinogenesis induced by liver fluke infestation is a multistage process involving a pathway leading from inflammation to altered gene expression patterns in involved tissues (Pairojkul et al. 1991). The gene expression patterns of ICC differ between tumors associated with *O. viverrini* and nonparasite-associated ICC (Jinawath et al. 2006). More details are found in the chapter on parasitic diseases of the biliary tract.

Hepatolithiasis

Hepatolithiasis has been found to be associated with cholangiocarcinoma, mainly in East Asian countries, while this association is unusual in Western countries (Nakanuma et al. 1985; Lesurtel et al. 2002; Tabrizian et al. 2012). The presence of hepatolithiasis and the associated inflammatory changes centered on involved bile ducts can hinder diagnosis of ICC (Chen et al. 2000). The biology of ICC associated with hepatolithiasis is complex and probably modulated by associated inflammatory changes of and immune responses taking place in the bile ducts. The pathogenesis of ICC developing in hepatolithiasis is complex and includes an interplay of factors related to inflammation and altered expression of cancer-related genes (review: Kuroki et al. 2005). Bile ducts containing calculi regularly show cholangiocyte hyperplasia, but also an increased proliferative activity in peribiliary glands (Lee and Sheen 1999), probably induced by chronic inflammation. In hepatolithiasis, hyperplastic change can be followed by metaplastic and dysplastic changes which are the precursor lesions of cholangiocarcinoma and display a distinct gene expression signature (Terada and Nakanuma 1992; Lee et al. 2006). Similar to the liver with PSC, hepatolithiasis is associated with various metaplastic changes, including pyloric gland metaplasia, intestinal metaplasia, goblet cell metaplasia, and Paneth cell metaplasia (Kurumaya et al. 1990). A stepwise increase of the number of interphase AgNORs in bile duct cells was observed in the order, normal, hyperplasia, dysplasia, carcinoma in situ, and invasive carcinoma (Terada et al. 1992). The dysplastic areas were in part found in the vicinity of invasive carcinomas and were CA 19-9 immunoreactive (Ohta et al. 1991). In hepatolithiasis, epithelial proliferations start to express c-Erb-2 protein, which is then also expressed in cholangiocarcinomas (Terada et al. 1998a). The development of epithelial dysplasia in the livers with hepatolithiasis is associated with changes in the expression of factors known to be involved in dysplasia, e.g., loss of expression of the DPC4/SMAD4 gene (Lee et al. 2006), a gene that is inactivated in part of ICC (Argani et al. 2001) and is also inactivated in more than half of ductal pancreatic carcinomas. The features of ICC occurring in hepatolithiasis have been treated in numerous studies and reports.

Selected References Chen et al. 1984; Nakayama and Koga 1984; Ohta et al. 1984, 1988; Koga et al. 1985; Nishihara et al. 1986;

Nakanuma et al. 1988; Terada et al. 1989; Chu et al. 1997; Sato et al. 1998; Lee and Liu 2001; Lee et al. 2002a; Kim et al. 2003; Shoda et al. 2003; Hwang et al. 2004; Kawakami et al. 2007; Liu et al. 2011; Suzuki et al. 2012.

Hepatitis Viruses

HBV and HCV play an etiological role for ICC (Nakanuma et al. 2003; Liu et al. 2003; Hai et al. 2005; Lee et al. 2008; Zhou et al. 2008, 2009, 2011, 2012, 2014a; El-Serag et al. 2009; Li et al. 2012a; Matsumoto et al. 2014). As the development of ICC is related to liver cirrhosis, this is one pathway through which hepatitis viruses can promote cholangiocarcinogenesis. There is increasing evidence that there is an increased risk for developing ICC in patients with cirrhosis (Terada et al. 1994a; Sorensen et al. 1998; Kuper et al. 2001). In Western countries, ICC may be more common in patients without liver cirrhosis (Nkontchou et al. 2013). However, there is also increasing evidence that both HBV and HCV might play a direct role in the induction of intra- and extrahepatic cholangiocarcinomas (Yamamoto et al. 2004; Gatselis et al. 2007; Lee et al. 2009a; Zhou et al. 2010, 2012; Peng et al. 2011). Mainly in Japan and East Asia, ICC was found to be associated with a high prevalence of HCV infection (Tomimatsu et al. 1993; Yamamoto et al. 1998; Kobayashi et al. 2000). A strong association between HCV infection and ICC was found for minute nodular ICCs (Yamamoto et al. 1998). Viral hepatitis (B or C) was associated with a cholangiocellular differentiation pattern and N-cadherin expression (Yu et al. 2011). A recent meta-analysis showed a statistically significant increased risk of ICC incidence with HBV and HCV infection. Nucleic acids of both viral types can be detected in HCC cells. In one investigation, 27 % of ICC cases from the US contained HBV and/or HCV nucleic acids, suggesting a pathogenic role for these viruses in some ICC (Perumal et al. 2006). Bile duct dysplasia, a precursor lesion for ICC, was observed in the setting of chronic hepatitis C (Torbenson et al. 2007). The direct effects of HCV-associated viral proteins on cholangiocytes and in the pathway to cholangiocarcinoma cells are only partially known, but in part involve effects of core protein on cell proliferation (Chen et al. 2005) and mechanisms related to epithelial-mesenchymal transition (EMT) (Balsano et al. 2011). HCV core protein plays important roles in the development of ICC and induces EMT (Li et al. 2010). microRNA-124 is downregulated in HCV-induced ICC via epigenetic regulation, and this decreased expression promotes cell migration and invasion via upregulation of MMP9 (Zeng et al. 2012).

There is evidence that ICCs that develop in the setting of hepatitis virus infections differ from other ICCs. In a Japanese investigation, the proportion of patients who underwent curative resection was higher in the HCV-positive than in the HCV-negative group, and tumors were significantly smaller in the HCV-positive group (Hai et al. 2005). ICCs developing in HBV-infected patients are more often of the MF subtype and are associated with lower lymphatic invasion, a higher prevalence of capsule formation, and better survival (Wu et al. 2013). HBV infection has a favorable effect on outcome in ICC (Zhang et al. 2010; Zhou et al. 2011). HBV infection or HBV vaccination prior to resection, together with adjuvant chemotherapy, was independently associated with improved survival in patients with ICC (Liu et al. 2013).

Congenital Malformation Syndromes of the Biliary Tract

Caroli's disease (CD) is a rare condition that belongs to the group of congenital ductal plate malformations and that is characterized by segmental cystic dilatations of intrahepatic bile ducts (reviews: Taylor and Palmer 1998; Parada et al. 1999; Sgro et al. 2004; Yonem and Bayraktar 2007). Dilated bile ducts in CD often undergo chronic inflammation complicated by stone disease and eventually subsequent dysplastic alterations of the epithelium. Apart from dysplastic epithelial changes, carcinoma in situ was

observed in CD (Joly et al. 1990), suggesting a dysplasia-carcinoma in situ-invasive carcinoma sequence. In a relatively few patients, CD is complicated by invasive cholangiocarcinoma.

Selected References Phinney et al. 1981; Ludwig et al. 1982; Dayton et al. 1983; Ginaldi 1987; Takei et al. 1991; Balsells et al. 1993; Falco et al. 1993; Abdalla et al. 1999; Totkas and Hohenberger 2000; Takatsuki et al. 2001; Vlachogiannakos et al. 2004; Kasper et al. 2006; Mabrut et al. 2013.

Cholangiocarcinoma as a complication of CD was also noted in monolobar disease (Abdalla et al. 1999). The source of cholangiocarcinoma in CD is probably linked to continuous hyperregeneration caused by inflammation-induced cholangiocyte injury, followed by dysplastic changes, CD thus being a potentially premalignant condition (Dayton et al. 1983). Both in CD and congenital hepatic fibrosis, matrix proteins of basement membranes are degraded around bile ducts, mainly laminin and type IV collagen, probably mediated by proteases secreted by cholangiocytes, a mechanism that might contribute to cystic bile duct dilatation. This phenomenon was also observed in cholangiocarcinomas developing in the setting of CD (Yasoshima et al. 2009), suggesting that an unstable basement could favor the transition from carcinoma in situ into invasive carcinoma. ICC was found to arise in congenital hepatic fibrosis, an autosomal recessive ductal plate malformation disorder caused by mutations of fibrocystin/polyductin (Yamato et al. 1998). Very rarely, ICC develops in the setting of biliary cirrhosis caused by congenital biliary atresia (Kulkarni and Beatty 1977). Cholangiocarcinomas can also develop in bile duct cysts, whereby type I and type IV cysts showed higher cancer incidences, even after cyst resection (Soreide and Soreide 2007). ICC can arise after excision of type IV A choledochal cyst after a long delay, e.g., 28 years (Kumamoto et al. 2014). ICC was also found in association with developmental liver cysts (Azizah and Paradinas 1980; Imamura et al. 1984) or with polycystic kidney and liver disease (Landais et al. 1984).

Preexisting Hepatic Tumors and Tumor-like Lesions

ICC rarely develops from bile duct adenomas. In one case, there was a gradual dedifferentiation from a central adenoma-like lesion to an infiltrative ICC (Börnfors 1984). ICC can arise in bile duct adenoma with focal areas of bile duct microhamartoma (Hasebe et al. 1995). ICC was found in association with multiple bile duct microhamartomas (von Meyenburg complexes), a pathogenic link between the two lesions being suggested by a continuity between microhamartoma cells and those of ICC (Dekker et al. 1989; Röcken et al. 2000; Wisniewski et al. 2002; Orii et al. 2003; Neto et al. 2007; Droy et al. 2009; Xu et al. 2009). Hyperplastic and dysplastic alterations of peribiliary gland may be a potential source for ICC. Papillary and atypical hyperplasia of peribiliary glands, observed in less than 1 % of livers, may precede ICC. In one study, carcinomatous transformation and atypical hyperplasia coexisted, however in only 1 out of 799 livers (Terada and Nakanuma 1990).

Thorotrastosis

As outlined in more detail in another chapter, thorotrast exposure was significantly associated with the development of various liver malignancies, including cholangiocarcinoma (thorotrast-associated cholangiocarcinoma, TACC; Rota et al. 1971; Johnson and Babb 1975; Herzog et al. 1976; Rubel and Ishak 1982; Gras Borrell et al. 1985; Imai et al. 1988; Ito et al. 1988; Sasaki et al. 1989; Lee et al. 1996; Liu et al. 2002; Sahani et al. 2003; Zhu et al. 2004; review: Lipshutz et al. 2002). Thorotrast-induced cholangiocarcinomas are much more frequently intrahepatic than hilar tumors. In a study of 44 TACC, 91.7 % of the tumors were located in the middle-peripheral portion of the liver, while 77.8 % of cholangiocarcinomas not related to thorotrast were located in the hilar portion (Ito et al. 1988). Similar to other thorotrast-associated hepatic malignancies, TACC may be diagnosed after a long delay, in one case observed 40 years after

thorotrast administration (Sakai et al. 1984). There is some evidence that thorotrast-induced liver cancers are inclined to grow rapidly and to early produce intrahepatic metastases (Imai et al. 1988). In few cases, two thorotrast-associated hepatic tumors occurred synchronously, e.g., ICC+HCC, ICC+angiosarcoma, or ICC + hemangioendothelioma (Winberg and Ranchod 1979; Sakai et al. 1984).

Other Hepatobiliary Inflammatory Disorders

There is evidence that nonalcoholic steatohepatitis (NASH) with or without associated diabetes mellitus might be associated with ICC. In a US study on 181 patients who underwent resection for ICC, 31 or 17.1 % had underlying NASH (Reddy et al. 2013). In a study on 57 consecutive Caucasian patients with ICC in the absence of bile duct disease or cirrhosis, macrovesicular steatosis, steatohepatitis, and hepatic iron overload were prominent features, in part associated with high alcohol consumption, elevated BMI, and/or diabetes mellitus (Nkontchou et al. 2013).

Cancer Predisposition Syndromes

ICC was found in association with Muir-Torre syndrome (Vernez et al. 2007), a rare autosomal dominant syndrome with sebaceous skin lesions, basaliomas, spinaliomas, and hereditary nonpolyposis colorectal cancer.

Other and Rare Risk Factors

Cholangiocarcinoma has been observed after childhood radiotherapy for nephroblastoma/Wilms' tumor (Cunningham 1990).

Pathogenic Pathways of Intrahepatic Cholangiocarcinoma

Pathogenic pathways involved in ICC are, also due to the various known etiologies, complex and in many ways different from those of extrahepatic cholangiocarcinomas (reviews: Nakanuma et al. 2003; Berthiaume and Wands 2004; Blechacz and Gores 2008; Khan et al. 2008; Wise et al. 2008; Fava 2010; Kumar et al. 2011; Nault and Zucman-Rossi 2011; Wadsworth et al. 2011; Fava and Lorenzini 2012; Leyva-Illades et al. 2012; Rizvi and Gores 2013; Sia et al. 2013).

Cellular Origin of ICC

It is usually held that ICC originates from cholangiocytes of intrahepatic bile ducts. However, novel findings have shed a different light onto this question, suggesting a more complex cellular origin (Cardinale et al. 2012; Carpino et al. 2012; Komuta et al. 2012). Also based on the observation that there is a relation between hepatitis virus infection, in particular HCV infection, and ICC, it has been suggested that the hepatocyte lineage might be involved in ICC carcinogenetic pathways. Biliary lineage cells giving rise to ICC may in fact derive from hepatocytes via a Notch-mediated cell conversion (Sekiya and Suzuki 2012). In subsets of ICC, cells with hepatobiliary progenitor cell features were identified. Part of ICC are reactive for stem cell factor and its receptor, c-Kit (Mansuroglu et al. 2009). The expression of hepatic progenitor cells markers, NCAM and c-Kit, was higher in ICC with chronic advanced liver disease (Xu et al. 2011a). Part of cholangiocarcinoma cells co-expressed stem cell factor and its receptor, c.Kit, but these proteins were also detectable in tumor-associated macrophages and in stromal myofibroblastic cells. In the tumor, upregulation of stem cell factor was stronger than that of c-Kit (Mansuroglu et al. 2009). There are subsets of cholangiocarcinomas expressing the stem cell marker, CD133. A strong expression of CD133 was associated with nodal metastasis, a positive resection margin, and increased invasion (Leelawat et al. 2011). SALL4, a stem cell biomarker in liver cancers, is strongly expressed in part of cholangiocarcinomas, this expression indicating a more aggressive phenotype (Oikawa et al. 2012). ICC contains cells that express

CD44 and glioma-associated oncogene homologue-1 (GLI1), and ICC with such stemlike cells had a poor prognosis (Nanashima et al. 2013).

Gene Mutations in Intrahepatic Cholangiocarcinoma: LOH, Oncogenes, Tumor Suppressor Genes, and Genes Involved in Invasion

The chromosomal and molecular pathology of cholangiocarcinomas has been investigated and resulted in the recognition of distinct molecular profiling patterns.

Selected References Cong et al. 2001; Momoi et al. 2001; Okuda et al. 2002; Kumar et al. 2011; Andersen et al. 2012; Andersen and Thorgeirsson 2012; Fava and Lorenzini 2012; Andersen and Thorgeirsson 2013; Subrungruanga et al. 2013; Voss et al. 2013; Patel 2014; Rizvi and Gores 2014.

Cholangiocarcinomas as a whole show a high frequency of loss of heterozygosity (LOH) involving several chromosomal loci. Particularly, allelic loss plays an important role in microsatellite alterations at chromosome 1p36, a locus that is thought to play a special role in fluke-associated ICC (Limpaiboon et al. 2006). Fifty percent of cases with MF + PI types were frequently detected by LOH at D8S258 compared to cases of the MF or ID growth type (Kawaki et al. 2000). Deregulated gene functions in ICC are in part related to distinct chromosomal abnormalities found in these neoplasms, in particular losses of heterozygosity (LOHs) involving chromosomal loci 3p13-p21, 4q, 5q35-qter, 6q, 8p22, 9q, 16q, 17p13, and 18q and gains of 5p, 7p, 13q, and 20q (Kang et al. 2000; Koo et al. 2001; Momoi et al. 2001). MF-ICC showed higher frequencies of LOH (Momoi et al. 2001). 17p13 involves p53. Genome-wide analyses of gene expression will lead to the identification of distinct gene expression signatures in cholangiocarcinoma (Obama et al. 2005a; Wang et al. 2006; Miller et al. 2009; Seol et al. 2011). In one investigation, 52 genes were identified that were commonly upregulated and 421 genes that were downregulated in ICC (Obama et al. 2005a).

K-RAS (KRAS) mutations are rather common in ICC and in experimental models of this tumor and are now considered to play a central pathogenic role and have been found in 22–48 % of these cancers (Tada et al. 1992; Ohashi et al. 1994, 1995; Boberg et al. 2000; Tannapfel et al. 2000; Isa et al. 2002; Xu et al. 2011b; O'Dell et al. 2012; reviews: Rashid 2002; Chen et al. 2012; Hsu et al. 2013). The prevalence of KRAS mutations depends on the underlying risk factor for ICC. KRAS mutations, in conjunction with TP53 mutations, are frequently observed in cholangiocarcinomas that develop in the setting of primary sclerosing cholangitis (Ahrendt et al. 2000; Boberg et al. 2000). In contrast, KRAS mutations are less common in ICC developing in thorotrastosis in comparison with non-thorotrast-associated ICC, while p53 mutations are more frequent (Kamikawa et al. 1999). Generally, genetic alterations in thorotrast-related ICC are more similar to those in other cholangiocarcinomas than those in hepatocellular carcinoma (Liu et al. 2004). In addition to ICC, KRAS mutations also occur in potential precursor lesions of invasive bile duct cancer, i.e., biliary intraepithelial neoplasia-2 (BilIN-2) and BilIN3 (Hsu et al. 2013). The presence of KRAS mutations is more often noted in the PI-ICC subtype (Ohashi et al. 1995) and is strongly associated with perineural invasion and represents an independent prognostic factor of ICC after hepatectomy (Chen et al. 2012). Overall, the presence of KRAS and GNAS mutations in ICC was associated with poor overall survival (Jang et al. 2014). The RAF/MEK/ERK (mitogen-activated protein kinase-MAPK) signal transduction pathway is an important mediator of cell proliferation and survival and is modified in several malignancies. The B-RAF (BRAF) gene, an isoform of human RAF, is activated by oncogenic Ras. Mutations in the BRAF gene have been identified in cholangiocarcinoma, but not in hepatocellular carcinoma (Tannapfel et al. 2003). In contrast to KRAS mutations, BRAF mutations are less frequent in cholangiocarcinomas (Xu et al. 2011a; Robertson

et al. 2013). BRAF V600E-specific mutations seem to be restricted to ICC, while no extrahepatic cholangiocarcinomas showed BRAF mutations (Goeppert et al. 2014). As already specified above, ICC regularly displays alterations of p53 protein expression, in part caused by mutations in the TP53 gene, in part by epigenetic mechanisms (Petmitr et al. 1998; Kang et al. 1999; reviews: Khan et al. 2005, 2006; O'Dell et al. 2012). P53 mutations causing p53 inactivation are common events in cholangiocarcinomas (Terada et al. 1994b; review: Khan et al. 2005). In one investigation, mutations in TP53 were detected in 37 % of ICC (Tannapfel et al. 2002).

The INK4a-ARF locus on chromosome 9p21 encodes two cell cycle-regulatory proteins, p16 (INK4a) and p14(ARF), acting through the Rb-CDK4 and p53 pathways. A minority of ICC revealed homozygous deletion of the INK4a-ARF locus, but specific mutations were not detected (Tannapfel et al. 2002). Runt-related transcription factor 3 (RUNX3) is a tumor suppressor gene on chromosome 1p36. The gene product, RUNX3 protein, is involved in TGFbeta-SMAD signaling. Downregulation of RUNX3 was found in liver fluke-associated ICC, caused by DNA copy number loss at 1p36.1 and promoter hypermethylation (Dachrut et al. 2009). Deleted in malignant brain tumor-1 (DMBT-1) is more frequently expressed in biliary epithelia in hepatolithiasis, but is markedly decreased in invasive ICC due to homozygous deletion of the DMBT-1 gene, a late event in ICC pathogenesis (Sasaki et al. 2003). The fragile histidine triad (FHIT) gene, a putative tumor suppressor gene on chromosome 3p14.2, is lost in part of ICC via LOH (Koch et al. 2003), but reduced expression of FHIT is also accomplished by promoter methylation (Foja et al. 2005). In some ICC, mutations in genes encoding factors required for invasion were identified. Mutations of exons 7, 8, and 9 of the E-cadherin gene were found, correlated with downregulated E-cadherin protein expression, reduced cell adhesiveness, and high histological grade (Endo et al. 2001). Isocitrate dehydrogenase 1 and 2 genes are mutated in a subset of ICC, and these mutations are more commonly encountered in ICC than in extrahepatic cholangiocarcinoma (Kipp et al. 2012; Wang et al. 2013). Sporadic ICCs display complex changes of the FGFR and EGFR pathways (Borad et al. 2014). ICCs show alterations of fibroblast growth factor receptor 2 (EGFR2), while amplifications of ERBB2 nd ROS1 are rare events (Graham et al. 2014). More than 40 % of ICCs contained somatic mutations of the protein tyrosine phosphatase, PTPN3, and activating mutations and high expression levels of PTPN3 were associated with tumor recurrence (Gao et al. 2014).

Deregulation of microRNA in Intrahepatic Cholangiocarcinoma

Differential expression patterns of microRNAs (miRNAs) play an important role of the expression of gene involved in cholangiocarcinogenesis (Stutes et al. 2007; Chen et al. 2009; Plieskatt et al. 2014). A cluster of more than 30 miRNAs is distinguished between ICC and normal hepatic tissues (Chen et al. 2009; Karakatsanis et al. 2013). One of the miRNAs that is consistently expressed in cholangiocarcinoma is miRNA-21, which regulated the expression of PTEN and PDCD4 (Liu et al. 2012). Inhibitors of miR-21 increased protein levels of programmed cell death 4 (PDCD4) and tissue inhibitor of metalloproteinases 3 (TIMP3) (Selaru et al. 2009). miRNA-370 is underexpressed in a large cohort of human cholangiocarcinomas, induced by silencing of the paternal allele through genomic imprinting and time-dependent silencing of the maternal allele of miRNA-370 by interleukin-6 (An et al. 2012). A further miRNA that is downregulated in cholangiocarcinoma is miRNA-494, regulating the G1/S checkpoint, an effect counteracting miRNA-494-induced growth retardation (Olaru et al. 2011). In cholangiocarcinomas, miRNA-26a promotes tumor cell growth by activating beta-catenin and thus the Wnt signaling pathway, glycogen synthase kinase-3beta being a direct target of miRNA-26a (Zhang et al. 2012). In ICC, miRNA-31 has RAS p21 GTPase activating protein 1 (RASA1) as its direct target. Downregulation of RASA1 by miRNA-31 promoted cell proliferation and inhibited apoptosis,

in part by upregulation of the activity of the RAS-MAPK signaling pathway (Hu et al. 2013; Sun et al. 2013). miR-124 is epigenetically regulated by HCV core protein and promotes migration and invasion of ICC cells by targeting SMAD3 and the downstream target genes, c-Myc and MMP9 (Zeng et al. 2012). Downregulation of miR-214 contributes to ICC spread and metastasis through targeting of Twist, a protein involved in EMT (Li et al. 2012b). The pre-miRNA-886/nc886, a novel type of noncoding RNA, inhibits activation of protein kinase R which has a pro-apoptotic activity though eukaryotic initiation factor 2alpha phosphorylation. This mechanism is important on host defense against viral infections. In cholangiocarcinoma cells, nc886 is downregulated, causing disinhibition/activation of protein kinase R and the pro-survival nuclear factor-kappaB pathway (Kunkeaw et al. 2013). miRNA-421 is an oncogenic miRNA/oncomir in cholangiocarcinomas. A decrease of miRNA-421 expression was correlated with induction of G0/G1 cell cycle arrest, while increased miRNA-421 expression downregulated farnesoid X receptor expression, a tumor suppressor for several cancers (Zhong et al. 2012). miRNA-204 was frequently downregulated in ICC, and the low-level expression of this miRNA was associated with lymph node metastasis. miRNA-204 inhibits EMT by targeting slug in ICC cells, and lack of miRNA-204 therefore favors an EMT-mediated invasive phenotype (Qiu et al. 2013). A further miRNA that affects EMT in ICC is miRNA-214. miRNA-214 levels are decreased in metastatic ICC, associated with increased Twist levels and promotion of pro-metastatic EMT (Li et al. 2012).

Growth Factors and Growth Inhibitors in Intrahepatic Cholangiocarcinoma

In cholangiocarcinomas, several factors regulating cell proliferation and differentiation exhibit altered expression patterns, including the p16INK4a-ARF pathway (Kang et al. 2002; Tannapfel et al. 2002; Karamitopoulou et al. 2008; Sasaki et al. 2008), p27(KIP1) pathway (Taguchi et al. 2001; Hashimoto et al. 2009), p38 kinase system (Dai et al. 2012), and cyclin kinase subunit-2 (Shen et al. 2013). The expression of cell cycle-regulatory proteins varies as a function of the tumors' localization within the biliary tract (Jarnagin et al. 2006). Overexpression and gene amplification of cyclin D1 are frequent in ICC and contribute to increased proliferation carcinogenesis (Ito et al. 2000a; Sugimachi et al. 2001a; Shen et al. 2013). Overexpression of cyclin D1 leads to the escape of ICC from the growth inhibitory effect of TGFbeta-1 (Zen et al. 2005a). ICC cells express receptors for insulin-like growth factor 1 and estrogens, which cooperate in the modulation of both cell proliferation and apoptosis (Alvaro et al. 2006). Loss of expression of DPC4 (deleted for pancreas cancer, locus 4)/SMAD4, a factor involved in several carcinogenic pathways and functioning as a tumor suppressor (Hann et al. 1996), is observed in both extrahepatic and intrahepatic bile duct cancers and is detectable in tumor cells by immunohistochemistry (Tascilar et al. 2001). In carcinomas of the common bile duct, loss of this factor was detected in 15% (Hahn et al. 1998), while loss of expression was found in 15–54.2 % of ICC (Argani et al. 2001; Kang et al. 2002; Chuang et al. 2004). In one analysis, loss of DPC4/SMAD4 was associated with frequent 18q allelic loss and with the pTNM stage (Kang et al. 2002), and another study demonstrated an association of DPC4/SMAD4 loss with dysplasia and ICC emerging in hepatolithiasis (Lee et al. 2006). Loss of DPC4 also characterizes a subset of tumors now classified as biliary intraductal papillary mucinous neoplasms (Sclabas et al. 2012). Loss of DPC4/SMAD4 in cholangiocarcinomas can act through several pathways, and it frequently affects the TGFbeta signaling pathway. DPC4/SMAD4 is required for TGFbeta-induced epithelial-to-mesenchymal transition in cancer cells (Deckers et al. 2006). Loss of DPC4/SMAD4 can operate through upregulation of the TGFbeta pathway known to promote carcinogenesis. In cholangiocarcinoma cell lines, TGFbeta-1 is produced, which stimulates TGFbeta-1 production and function in an autocrine manner and which accelerates the expression of interleukin-6, this interaction contributing to cell growth promotion (Shimizu et al. 2006). A TGF-beta-independent

tumor suppressor action of DPC4/SMAD4 involves its function to induce resistance to serum-deprivation-induced cell death through a PAK1-PUMA pathway (Lee et al. 2011). DPC4/SMAD4 downregulates an invasion-promoting matricellular protein, SPARC (Volmer et al. 2004), and loss of DPC4 will therefore promote the pro-invasive action of SPARC. DPC4 also mediates tumor suppression through suppression of angiogenesis, having a function as an angiogenic switch via the angiogenic mediators, vascular endothelial growth factor, and thrombospondin-1 as key target genes (Schwarte-Waldhoff et al. 2000). Based on these mechanisms, inactivation of SMAD4 is a prognostic factor in ICC (Yan et al. 2013). The DPC4 suppression mechanism in cancer itself involves somatic inactivating SMAD4 gene mutations, but also suppression via microRNA 421 (Hao et al. 2011). The growth factor receptors, EGFR, HGFR, and IGFR1, are expressed in cholangiocarcinoma cell lines (Xu et al. 2010) and in ICC (Yoshikawa et al. 2008; Zhou et al. 2013). The epidermal growth factor receptor (EGFR) was strongly expressed in 47 % of human cholangiocarcinomas (Jan et al. 2004). The c-erbB-2 proto-oncogene encoding a transmembrane protein highly homologous to the EGFR and an important factor in carcinogenesis, including cholangiocarcinoma (Roskoski 2004; Sirica 2008; Hynes and MacDonald 2009), is expressed in up to 70 % of cholangiocarcinomas, but was not correlated with proliferative activity or p53 protein expression (Terada et al. 1998b; Aishima et al. 2002a; Endo et al. 2002; Sirica et al. 2002; Zheng and Zhu 2007). In contrast, overexpression of c-erbB-2 in ECC varied markedly among several reports, being detectable in only 5.1 % in one analysis (Nakazawa et al. 2005) and 80 % in another (Zheng and Zhu 2007). RAD51AP1 (RAD51 associating protein-1), which interacts with RAD51, a molecule involved in DNA repair, is a proliferation-promoting factor that is upregulated in and induces growth in ICC (Obama et al. 2008). The Wilms' tumor 1-associated protein (WTAP), a nuclear protein that regulates cell proliferation and apoptosis, is upregulated in cholangiocarcinomas and regulates the motility of the cancer cells (Jo et al. 2013). Factors that initiate DNA synthesis are altered in ICC. PSF2 (partner of SLD five 2), a member of the GIBS multiprotein complex involved in initiation of DNA replication, is upregulated in ICC (Obama et al. 2005b). Loss of cilia (deciliation) in cholangiocytes is associated with an increased proliferation rate and induction of anchorage-independent growth, through a MAPK and hedgehog activation pathway. Deciliation in cholangiocarcinoma cells is induced by histone deacetylase 6 and promotes an increased growth phenotype (Gradilone et al. 2013). Progranulin, a growth factor overexpressed in several caners, is also upregulated in cholangiocarcinoma cells, driven by the action of IL-6 (Frampton et al. 2012). The polycomb protein Mbi1 is overexpressed in cholangiocarcinomas and promotes cell proliferation and represses cell senescence (Sasaki et al. 2009).

Defects and Abnormalities in the Cell Division Machinery

Dysregulation of mitosis is a common phenomenon in cancer. In ICC, several proteins operational in mitosis show a nuclear overexpression, including Aurora-A, Aurora-B, survivin, and p53 protein, and simultaneous overexpression of Aurora-A and Aurora-B was correlated with that of p53 (Shen et al. 2009). More than half of cholangiocarcinoma showed centrosome abnormalities mainly centrosome hyperamplification, which can result in multipolar division spindles, unbalanced chromosome segregation, and aneuploidy (Kuo et al. 2000).

Cell Death Mechanisms and Autophagic Pathways

As in other malignancies, deregulation of cell death and in particular apoptosis plays an important role in pathways leading to cholangiocarcinoma. Mutations in TP53, a common alteration in ECC and ICC, affect transcription of the pro-apoptotic Fas gene, causing a lack in cellular Fas expression and a blunted cell death response. The number and ratios of Fas-expressing cells are higher in ECC

than in ICC, and Fas expression decreased from dysplastic epithelium to cholangiocarcinoma, suggesting that reduced Fas expression is an early event in cholangiocarcinogenesis (Jhala et al. 2005). Whereas Fas expression counteracts cell growth and induces apoptosis in cultured cholangiocarcinoma cells (Pickens et al. 1999), Fas expression in cholangiocarcinomas decreases in cases with poor differentiation and high proliferative activity, and both expressions of Fas and Fas ligand thus reflect distinct biological features rather than the status of apoptosis in these tumors (Ito et al. 2000b). Human cholangiocarcinoma cells exhibit reciprocal co-expression of Fas and Fas ligand (Fas-L) (Que et al. 1999), regulated by NF-kappaB which inhibits Fas expression and increases FasL expression through binding to the promoters of the respective genes (Shimonishi et al. 2000a; Pan et al. 2007). Upregulation of Fas ligand in ICC is found in early-stage disease, while it is downregulated in progressed stages (Shimonishi et al. 2000a). Cholangiocarcinomas can express several factors counteracting apoptosis and promoting increased cell survival. Variable proportions of cholangiocarcinomas express Bcl-2 protein (Charlotte et al. 1994). Expression of this antiapoptotic protein is important, as Bcl-2 interacts with Bax to regulate apoptosis in biliary epithelial cells (Stähelin et al. 1999). Bcl-2 expression in cholangiocarcinomas is less common than that of p53 (Terada and Nakanuma 1996; Arora et al. 1999), When present, Bcl-2 expression is more frequent than in normal cholangiocytes (Harnois et al. 1997), and more frequently observed in well- or moderately differentiated cholangiocarcinomas (Ito et al. 2000c), but the tumors display a greater expression of Bcl-2 mRNA than that of the Bcl-2 protein (Fiorentino et al. 1999). Overexpression of IL-6 in cholangiocarcinoma cells enhances cell survival (Meng et al. 2006). Resistance to apoptosis in cholangiocarcinoma cells is accomplished through enhanced myeloid cell leukemia 1 (Mcl-1) expression induced by interleukin-6/IL-6-mediated signal transducers and activators of transcription 3 (STAT-3) phosphorylation. IL-6 contributes to Mcl-1 upregulation and TRAIL resistance through an Akt-signaling pathway (Kobayashi et al. 2005). Mcl-1 itself mediates resistance to the action of TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) by blocking the mitochondrial pathway of cell death (Taniai et al. 2004). Epigenetic silencing of cytokine signaling 3 (SOCS) is responsible for sustained IL-6/STAT-3 signaling in the tumor cells (Isomoto et al. 2007). Another mechanism to protect Fas-expressing cholangiocarcinoma cells from cell death involves cyclooxygenase-2 (COX-2), an enzyme that produces prostanoids and is expressed in cholangiocarcinomas. COX-2 counteracts Fas-mediated apoptosis through prostaglandin E2-induced expression of the TRAIL antagonist, Mcl-1 (Nzeako et al. 2002). Expression of Yes-associated protein in ICC modulates a member of the inhibitors-of-apoptosis family, survivin. Survivin expression is an independent prognostic factor for poor survival in ICC (Bai et al. 2012). Autophagy serves to recycle damaged organelles and long-lived proteins in normal cells and cancer cells. One of the key regulators of autophagy is Beclin-1. Interestingly, beclin-1 is expressed in a subset of ICC, a feature associated with a metastatic phenotype (Dong et al. 2011).

Regulation of Cell Differentiation

ICC cells containing increased amounts of IL-6 are usually well-differentiated neoplasms, while poorly differentiated cholangiocarcinomas exhibit a downregulation of IL-6, suggesting that IL-6 expression is inversely related to cell proliferation and positively related to differentiation (Sugiwara et al. 1998).

Epithelial-Mesenchymal Transition (EMT) in Intrahepatic Cholangiocarcinoma

EMT is an important process in which epithelial cells lose epithelial cell features and assume properties that characterize mesenchymal cells. EMT is a mechanism that is critically involved in carcinoma-stroma interactions and cancer invasion and spread. During progression, many carcinoma

cells acquire a gene expression signature that more and more resembles that of mesenchymal cells, observations that change our views regarding the properties of metastasizing carcinoma cells. EMT is activated by numerous gene products, including growth factors and cytokines. In ICC, tumor necrosis factor-alpha (TNF-alpha) stimulates the EMT regulator Snail (Techasen et al. 2012). EMT induced by TGFbeta/Snail activation increased invasive growth of cholangiocarcinoma cells (Sato et al. 2010), while EMTs induced by Notch1 expression affect the migration capability of cholangiocarcinoma cells (Zhou et al. 2013). Smad7, a factor involved in EMT, is markedly overexpressed in cholangiocarcinoma in comparison with normal liver, and this expression pattern was associated with perineural invasion and lymph node metastasis (Huang et al. 2012). Proteins selectively upregulated in the course of EMT also include vimentin, which characterized mesenchymal cells, fascin, and E-cadherin. In the setting of EMT mechanisms in cholangiocarcinoma, fascin and vimentin are overexpressed, while E-cadherin is downregulated. The expression of fascin and vimentin indicated dedifferentiation and an invasive phenotype (Iguchi et al. 2009; Mao et al. 2013). In the course of EMT in cholangiocarcinoma, downregulation of the ANXA8 gene product by the EGF-FOXO4 signaling axis is involved in cell scattering (cell individualization) and metastatic spread (Lee et al. 2009b). Angiotensin II enhances EMT through an interaction between activated stellate cells and the stromal cell-derived factor-1 (CXCR4) axis (Okamoto et al. 2012). EMT in ICC is also regulated by microRNAs. Inactivation of miR-200c resulted in induction of EMT, whereas inactivation of miR-200c led to a reduction of EMT including reduced cell migration and invasion of ICC cells (Oishi et al. 2012).

Mechanisms of Invasion

The initiation of an invasion cascade requires individualization of cancer cells through tight junction decay mechanisms and a novel world of cell-cell and cell-matrix interactions via differential expression of adhesion molecules. Part of ICC cells display aberrant expression of the tight junction protein, claudin-18, normally restricted to the stomach and lung, but claudin-18 expression in ICC is less common than in other biliary tract cancers and biliary intraepithelial neoplasias. Among ICCs, claudin-18-positive cases showed higher frequencies of the PI subtype, perineural invasion and lymphonodal metastasis (Shinozaki et al. 2011). Several adhesion molecules that affect early steps of invasion and spread are variously expressed in ICC. CD24, an adhesion molecule which controls morphogenetic processes, induces invasion of cholangiocarcinoma cells by upregulating CXCR4 and increasing the phosphorylation of ERK1/2 (Leelawat et al. 2013). E-cadherin, an important adhesion molecule in the biliary tract, is downregulated in ICCs, in part caused by altered expression of beta-catenin which has a role in E-cadherin cell surface expression (Sugimachi et al. 2001b). Integrins hold a central position in mediating adhesion and intercellular recognition pathways and are therefore involved in cancer cell invasion. The integrin alpha6 subunit, part of the integrin alpha6beta1 and alpha6beta4 complexes, is overexpressed in human ICC, associated with a migratory and invasive phenotype (Ding et al. 2013). A protein expressed by cholangiocarcinoma stromal cells, periostin, activates alpha5beta1 integrin through a PI3K/AKT-dependent signaling pathway (Utispan et al. 2012). A secreted adhesive glycoprotein is osteopontin, which is overexpressed or downregulated in ICC (Hass et al. 2008). Its downregulation in ICC causes reduced cell adhesion and invasive phenotype with perineural and lymphatic invasion (Terashi et al. 2004).

Relatively few informations are available regarding the most important factors that regulate cancer cell motility in ICC. Expression of the cell adhesion molecules P-cadherin and CD24 in cholangiocarcinomas is a mechanism that increased motility in these neoplasms (Riener et al. 2010). Basic fibroblast growth factor induced cholangiocarcinoma cell migration via activation of the MEK1/2 pathway (Narong and Leelawat 2011). Nuclear expression of the

calcium-binding protein, S100A4, a protein also involved in EMT and the metastasis cascade (Sherbet and Lakshmi 1998; Helfman et al. 2005), promotes motility and invasiveness of tumor cells in cholangiocarcinoma (Fabris et al. 2011). The regulation of ICC cell motility also involves an interaction between the receptor CXCR4, produced by ICC cells, and its ligand, stromal-derived factor-1, and TNFalpha released from stromal cells. In this interactome, TNFalpha enhances CXCR4 expression on cancer cells (Ohira et al. 2008). Extracellular matrix protein-1 (ECM1) is significantly overexpressed in part of cholangiocarcinomas and is a factor contributing to tumor cell migration and invasion (Xiong et al. 2012).

An invasive phenotype also depends on a tumor cell-stromal cell cross talk. TGFbeta1 secreted by tumor cells acts on stromal cells where it reduces the expression of stromal-derived factor 1 involved in invasion (Ohira et al. 2006). Bone morphogenetic protein (BMP) signaling plays a role in carcinoma cell spread and invasion. The activity of BMPs in the extracellular space of carcinomas is regulated by the Twisted gastrulation (TWSG1) protein, which is expressed in cholangiocarcinoma (Johnston et al. 2012). Migration and invasion of cholangiocarcinoma is promoted by expression of the small nuclear protein, nuclear protein-1 (NUPR1), a protein that is responsive to various stress stimuli (Kim et al. 2012). Expressions of ErbB family receptor tyrosine kinases (see above) are expressed in part of ICC and play a role not only in cell proliferation but also in cell migration and invasion (Spencer et al. 2000).

Invasion of carcinoma cells into adjacent normal tissues strongly depends on the expression of diverse types of enzymes that degrade proteins and glycosaminoglycans of the extracellular matrix (ECM) or are involved in fibrinolysis. The most prominent proteases in cholangiocarcinoma are matrix metalloproteinases (MMPs) MMP-2, MMP-7, and MMP-9, and their tissue inhibitors, IMP-1 and TIMP-2 (Terada et al. 1996; Jo Chae et al. 2004; Hirashita et al. 2012). The upregulation of MMP-9 in cholangiocarcinoma is induced by the cytokine, tumor necrosis factor-alpha (TNFalpha; Tanimura et al. 2005), a mechanism regulated by overexpression of fascin (Onodera et al. 2009). TNFalpha induces the activation of cyclooxygenase-2 (COX-2), the subsequent production of prostaglandin E2 (PGE2) upregulating MMP-9 expression through binding to the PGE2 receptor (Wu 2005; Itatsu et al. 2009). COX-2-derived PGE2 also promotes cholangiocarcinoma cell growth and invasion through EP1 receptor-mediated activation of EGFR and AKT (Han and Wu 2005). In ICC cells, expression of MMP-2 is induced by overexpression of a factor involved in spread and metastasis of cancer cells, calpain small subunit 1 (Capn4) (Zhang et al. 2013). Enhanced expression of MMPs in cholangiocarcinoma is also correlated with downregulation of reversion-inducing cysteine-rich protein with Kazal motifs (RECK), suggesting that RECK functions as a metastasis suppressor in cholangiocarcinoma (Namwat et al. 2011). In cholangiocarcinoma, MMP-9 is stabilized by lipocalin 2 (neutrophil gelatinase-associated lipocalin, NGAL), which forms a complex with MMP-9 (Nuntagowat et al. 2010). Expression of urokinase plasminogen activator (uPA) in cholangiocarcinomas is associated with lymphatic invasion and metastasis (Thummarati et al. 2012).

The Tumor Microenvironment

The neoplastic transformation of cholangiocytes and/or their progenitor cells/stem cells to cholangiocarcinoma strongly depends on the generation of a distinct microenvironment that provides the developing, expanding, and spreading tumor with stromal cells, immunomodulatory cells, blood vessels, and access to lymph vessels (review: Leyva-Illades et al. 2012). The invasive phenotype of malignancies, including ICC, depends on angiogenesis that prepares a terrain for further growth and spread of cancer cells and is required for stroma formation and EMT. Establishment of a tumor-type microvascular system through tumor-induced angiogenesis is an important prerequisite for invasion and spread of cancer cells. In progressing cholangiocarcinoma,

angiogenesis is induced by various types of growth factors, in particular vascular endothelial growth factors (VEGFs) and fibroblast growth factors (FGFs). The expression of VEGF in cholangiocarcinomas is itself subject to regulators, e.g., endothelin, which decreases tumor growth via inhibition of VEGF expression (Fava et al. 2009). Apart from VEGF, angiopoietin-2 acts as a proangiogenic factor in cholangiocarcinomas, while thrombospondin-1 may play an inhibitory role in CC angiogenesis (Tang et al. 2006). Enhanced expression of thrombospondin-1 in cholangiocarcinoma is associated with tumor hypovascularity (Kawahara et al. 1998). Apart from "classical" angiogenic factors such as VEGFs, a further proangiogenic pathway operational in ICC is the Slit2/roundabout1 (Robo1) signaling pathway, which however also affects tumor cell proliferation and migration in these malignancies (Mano et al. 2013). Robo1 is a transmembrane receptor of the immunoglobulin family, and Slit2 is one of its ligands (Wang et al. 2013). In cancer cells, Robo1 is cleaved by metalloproteinases and gamma-secretase and migrates to the nucleus. Slit molecules belong to the repellent factor protein family that functions as morphogenetic proteins in foregut separation, as repulsive factors in growing axons of the nervous system, but also affects activated migration of certain cancer cells. Robo1 and Robo4 modulate endothelial cell motility and migration and via this effect promote angiogenesis (Legg et al. 2008). In ICC, factors regulating angiogenesis are altered in their expression, and part of these expression patterns are correlated with prognosis, e.g., expression of thrombospondin-1 (Aishima et al. 2002b). Also lymphangiogenesis has a central place in invasive pathways and the spread of tumor cells. Vascular endothelial growth factor-C (VEGF-C) is a critical lymphangiogenetic factor. 41.7 % of ICC showed a strong expression of VEGF-C, associated with a more aggressive phenotype, lymph node metastasis, and poor prognosis (Park et al. 2006). Certain factors present in the tumor microenvironment exert an influence on stromal leukocytes which in turn affect invasion patterns. The CXC-type chemokine family member CXCL5 is overexpressed in ICC, promotes metastasis, and recruits neutrophils in the stroma. Neutrophils in turn contribute to tumor metastasis (Zhou et al. 2014b).

Epigenetic Mechanisms

Several genes considered to play a role in the pathogenesis of ICC are subject to epigenetic alterations through gene promoter methylation (Lee et al. 2002b; Yang et al. 2005; Tischoff et al. 2006; Stutes et al. 2007; Sandhu et al. 2008; Isomoto 2009). Epigenetic inactivation of the p16 (INK4A) gene is a frequent event in cholangiocarcinoma (Tannapfel et al. 2000). Epigenetic hypermethylation of the p16 (INK4A) promoter is induced by overexpression of the polycomb protein EZH2 in cholangiocarcinoma (Sasaki et al. 2008). Other genes subject to methylation in ICC comprise RASSF1A, p15INK4b, APC, E-cadherin, p14(ARF), p73 and DAPK (Yang et al. 2005), and integrinalpha4 (Uhm et al. 2010).

References

Abdalla EK, Forsmark CE, Lauwers GY, Vauthey JN (1999) Monolobar Caroli's disease in an adult. Case report. Hepatogastroenterology 50:2185–2187

Ahrendt SA, Rashid A, Chow JT, Eisenberger CF, Pitt HA, Sidransky D (2000) p53 overexpression and K-ras gene mutations in primary sclerosing cholangitis-associated biliary tract cancer. J Hepatobiliary Pancreat Surg 7:426–431

Aishima S, Taguchi K, Sugimachi K, Asayama Y, Nishi H, Shimada M, Sugimachi K et al (2002a) The role of thymidine phosphorylase and thrombospondin-1 in angiogenesis and progression of intrahepatic cholangiocarcinoma. Int J Surg Pathol 10:47–56

Aishima SI, Taguchi KI, Sugimachi K, Shimada M, Sugimachi K, Tsuneyoshi M (2002b) c-erbB-2 and c-Met expression relates to cholangiocarcinogenesis and progression of intrahepatic cholangiocarcinoma. Histopathology 40:269–278

Aishima S, Nishihara Y, Tsujita E, Taguchi K, Soejima Y, Taketomi A, Ikeda Y, Maehara Y et al (2008) Biliary neoplasia with extensive intraductal spread associated with liver cirrhosis: a hitherto unreported variant of biliary intraepithelial neoplasia. Hum Pathol 39:939–947

Aishima S, Iguchi T, Fujita N, Taketomi A, Maehara Y, Tsuneyoshi M, Oda Y (2011) Histological and immunohistological findings in biliary intraepithelial neoplasia arising from a background of chronic biliary disease compared with liver cirrhosis of non-biliary aetiology. Histopathology 59:867–875

Aishima S, Kubo Y, Tanaka Y, Oda Y (2014) Histological features of precancerous and early cancerous lesions of biliary tract carcinoma. J Hepatobiliary Pancreat Sci 21:448–452

Alvaro D, Barbaro B, Franchitto A, Onori P, Glaser SS, Alpini G, Francis H, Marucci L et al (2006) Estrogens and insulin-like growth factor 1 modulate neoplastic cell growth in human cholangiocarcinoma. Am J Pathol 169:877–888

An F, Yamanaka S, Allen S, Roberts LR, Gores GJ, Pawlik TM, Xie Q, Ishida M et al (2012) Silencing of miR-370 in human cholangiocarcinoma by allelic loss and interleukin-6 induced maternal to paternal epigenotype switch. PLoS One 7:e45606

Andersen JB, Thorgeirsson SS (2012) Genetic profiling of intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol 28:266–272

Andersen JB, Thorgeirsson SS (2013) Genomic decoding of intrahepatic cholangiocarcinoma reveals therapeutic opportunities. Gastroenterology 144:687–690

Andersen JB, Spee B, Blechacz BR, Avital I, Komuta M, Barbour A, Conner EA, Gillen MC (2012) Genomic and genetic characterization of cholangiocarcinoma identifies therapeutic targets for tyrosine kinase inhibitors. Gastroenterology 142:1021–1031

Argani P, Shaukat A, Kaushal M, Wilentz RE, Su GH, Sohn TA, Yeo CJ, Cameron JL et al (2001) Differing rates of loss of DPC4 expression and of p53 overexpression among carcinomas of the proximal and distal bile ducts. Cancer 91:1332–1341

Arora DS, Ransdale J, Lodge JP, Wyatt JI (1999) p53 but not bcl-2 is expressed by most cholangiocarcinomas: a study of 28 cases. Histopathology 34:497–501

Azizah N, Paradinas FJ (1980) Cholangiocarcinoma coexisting with developmental liver cysts: a distinct entity different from liver cystadenocarcinoma. Histopathology 4:391–400

Bai H, Gayyed MF, Lam-Himlin DM, Klein AP, Nayar SK, Yu Y, Khan M, Argani P et al (2012) Expression of Yes-associated protein modulates Survivin expression in primary liver malignancies. Hum Pathol 43:1376–1385

Balsano C, Conti B, Arciello M (2011) Regarding: epithelial-mesenchymal transition induced by hepatitis C virus core protein in cholangiocarcinoma. Ann Surg Oncol 18:896

Balsells J, Margarit C, Murio E, Lazaro JL, Charco R, Vidal MT, Bonnin J (1993) Adenocarcinoma in Caroli's disease treated by liver transplantation. HPB Surg 7:81–86

Ben-Menachem T (2007) Risk factors for cholangiocarcinoma. Eur J Gastroenterol Hepatol 19:615–617

Berthiaume EP, Wands J (2004) The molecular pathogenesis of cholangiocarcinoma. Semin Liver Dis 24:127–137

Bickenbach K, Galka E, Roggin KK (2009) Molecular mechanisms of cholangiocarcinogenesis: are biliary intraepithelial neoplasia and intraductal papillary neoplasms of the bile duct precursors to cholangiocarcinoma? Surg Oncol Clin N Am 18:215–224

Björnsson E, Olsson R, Bergquist A, Lindgren S, Braden B, Chapman RW, Boberg KM et al (2008) The natural history of small-duct primary sclerosing cholangitis. Gastroenterology 134:975–980

Blechacz B, Gores GJ (2008) Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment. Hepatology 48:308–321

Boberg KM, Schrumpf E, Bergquist A, Broomé U, Pares A, Remotti H, Schjölberg A et al (2000) Cholangiocarcinoma in primary sclerosing cholangitis: K-ras mutations and Tp53 dysfunction are implicated in the neoplastic development. J Hepatol 32:374–380

Borad MJ, Champion MD, Egan JB, Liang WS, Fonseca R, Bryce AH, McCullough AE et al (2014) Integrated genomic characterization reveals novel, therapeutically relevant drug targets in FGFR and EGFR pathways in sporadic intrahepatic cholangiocarcinoma. PLoS Genet 10, e1004135

Börnfors M (1984) The development of cholangiocarcinoma from multiple bile duct adenomas. Report of a case and review of the literature. Acta Pathol Microbiol Immunol Scand A 92:285–289

Bragazzi MC, Cardinale V, Carpino G, Venere R, Semeraro R, Gentile R, Gaudio E et al (2012) Cholangiocarcinoma: epidemiology and risk factors. Transl Gastrointest Cancer 1:21–32

Cardinale V, Carpino G, Reid L, Gaudio E, Alvaro D (2012) Multiple cells of origin in cholangiocarcinoma underlie biological, epidemiological and clinical heterogeneity. World J Gastrointest Oncol 4:94–102

Carpino G, Cardinale V, Reid L, Alvaro D, Gaudio E (2012) Cells of origin and cancer stem cells in cholangiocarcinoma. Transl Gastrointest Cancer 1:33–43

Chalasani N, Baluyut A, Ismail A, Zaman A, Sood G, Ghalib R, McCashland TM, Reddy KR et al (2000) Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case-control study. Hepatology 31:7–11

Charlotte F, L'Herminé A, Martin N, Geleyn Y, Nollet M, Gaulard P, Zafrani ES (1994) Immunohistochemical detection of bcl-2 protein in normal and pathological human liver. Am J Pathol 144:460–465

Chen PH, Lo HW, Wang CS, Tsai KR, Chen YC, Lin KY, Siauw CP, Hwang RR et al (1984) Cholangiocarcinoma in hepatolithiasis. J Clin Gastroenterol 6:539–547

Chen MF, Jan YY, Hwang TL, Jeng LB, Yeh TS (2000) Impact of concomitant hepatolithiasis on patients with peripheral cholangiocarcinoma. Dig Dis Sci 45:312–316

Chen RF, Li ZH, Zou SQ, Chen JS (2005) Effect of hepatitis C virus core protein on modulation of cellular proliferation and apoptosis in hilar cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 4:71–74

Chen L, Yan HX, Yang W, Hu L, Yu LX, Liu Q, Li L, Huang DD, Ding J, Shen F et al (2009) The role of microRNA expression pattern in human intrahepatic cholangiocarcinoma. J Hepatol 50:358–369

Chen TC, Jan YY, Yeh TS (2012) K-ras mutation is strongly associated with perineural invasion and represents an independent prognostic factor of intrahepatic cholangiocarcinoma after hepatectomy. Ann Surg Oncol 19(Suppl 3):S675–S681

Choi BI, Park JH, Kim YI, Yu ES, Kim SH, Kim WH, Kim CY, Han MC (1988) Peripheral cholangiocarcinoma and clonorchiasis: CT findings. Radiology 169:149–153

Chu KM, Lo CM, Liu CL, Fan ST (1997) Malignancy associated with hepatolithiasis. Hepatogastroenterology 44:352–357

Chuang SC, Lee KT, Tsai KB, Sheen PC, Nagai E, Mizumoto K, Tanaka M (2004) Immunohistochemical study of DPC4 and p53 proteins in gallbladder and bile duct cancers. World J Surg 28:995–1000

Cong WM, Bakker A, Swalsky PA, Raja S, Woods J, Thomas S, Demetris AJ, Finkelstein SD (2001) Multiple genetic alterations involved in the tumorigenesis of human cholangiocarcinoma: a molecular genetic and clinicopathological study. J Cancer Res Clin Oncol 127:187–192

Cox et al. (2005) Pub Med PMID 16341314

Cunningham (1990) Pub Med PMID 2170255

Dachrut S, Banthaisong S, Sripa M, Paeyao A, Ho C, Lee SA, Kosinksi C, Patil MA et al (2009) DNA copy-number loss on 1p36.1 harbouring RUNX3 with promoter hypermethylation and associated loss of RUNX3 expression in liver fluke-associated intrahepatic cholangiocarcinoma. Asian Pac J Cancer Prev 10:575–582

Dai R, Li J, Fu J, Chen Y, Wang R, Zhao X, Luo T, Zhu J, Ren Y, Cao J, Qian Y et al (2012) The tyrosine kinase c-Met contributes tot he pro-tumorigenic function of the p38 kinase in human bile duct cholangiocarcinoma cells. J Biol Chem 287:39812–39823

Dayton MT, Longmire WP, Tompkins RK (1983) Caroli's disease: a premalignant condition? Am J Surg 145:41–48

De Martel C, Plummer M, Franceschi S (2010) Cholangiocarcinoma: descriptive epidemiology and risk factors. Gastroenterol Clin Biol 34:173–180

Deckers M, van Dinther M, Buijs J, Que I, Löwik C, van der Pluijm G, ten Dijke P (2006) The tumor suppressor Smad4 is required for transforming growth factor beta-induced epithelial to mesenchymal transition and bone metastasis of breast cancer cells. Cancer Res 66:2202–2209

Dekker A, Ten Kate FJ, Terpstra OT (1989) Cholangiocarcinoma associated with multiple bile-duct hamartomas of the liver. Dig Dis Sci 34:952–958

della Torre G, Pasquini G, Pilotti S, Alasio L, Civelli E, Cozzi G, Milella M, Salvetti M et al (2000) TP53 mutations and mdm2 protein overexpression in cholangiocarcinomas. Diagn Mol Pathol 9:41–46

Ding YB, Deng B, Huang YS, Xiao WM, Wu J, Zhang YQ, Wang YZ, Wu DC, Lu GT et al (2013) A high level of integrin a6 expression in human intrahepatic cholangiocarcinoma cells is associated with a migratory and invasive phenotype. Dig Dis Sci 58:1627–1635

Dong LW, Hou YJ, Tan YX, Tang L, Pan YF, Wang M, Wang HY (2011) Prognostic significance of Beclin 1 in intrahepatic cholangiocellular carcinoma. Autophagy 7:1222–129

Droy L, Sagan C, Paineau J, Gournay J, Mosnier JF (2009) Cholangiocarcinomas developing on multiple bile duct hamartomas syndrome (in French). Ann Pathol 29:24–27

Elkins DB, Mairiang E, Sithithaworn P, Mairiang P, Chaiyakum J, Chamadol N, Loapaiboon V et al (1996) Cross-sectional patterns of hepatobiliary abnormalities and possible precursor conditions of cholangiocarcinoma associated with *Opisthorchis viverrini* infection in humans. Am J Trop Med Hyg 55:295–301

El-Serag HB, Engels EA, Landgren O, Chiao E, Henderson L, Amaratunge HC, Giordano TP (2009) Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: a population-based study of U.S. veterans. Hepatology 49:116–123

Endo K, Ashida K, Miyake N, Terada T (2001) E-cadherin gene mutations in human intrahepatic cholangiocarcinoma. J Pathol 193:310–317

Endo K, Yoon BI, Pairojkul C, Demetris AJ, Sirica AE (2002) ERBB-2 overexpression and cyclooxygenase-2 up-regulation in human cholangiocarcinoma and risk conditions. Hepatology 36:439–450

Enjoji M, Nakamuta M, Nawata H (2004) Oncogenes in tumors of gallbladder and biliary tract. Fukuoka Igaku Zasshi 95:31–35

Fabris L, Cadamuro M, Moserle L, Dziura J, Cong X, Sambado L, Nardo G, Sonzogni A et al (2011) Nuclear expression of S100A4 calcium-binding protein increases cholangiocarcinoma invasiveness and metastasization. Hepatology 54:890–899

Falco E, Nardini A, Celoria G, Briglia R, Stefani R, Gadducci G, Belloni E (1993) Caroli's disease associated with cholangiocarcinoma. A case of our own observation (in Italian). Minerva Chir 48:961–964

Fava G (2010) Molecular mechanisms of cholangiocarcinoma. World J Gastrointest Pathophysiol 1:12–22

Fava G, Lorenzini I (2012) Molecular pathogenesis of cholangiocarcinoma. Int J Hepatol 2012:630543

Fava G, Demorrow S, Gaudio E, Franchitto A, Onori P, Carpino G, Glaser S, Francis H et al (2009) Endothelin inhibits cholangiocarcinoma growth by a decrease in the vascular endothelial growth factor expression. Liver Int 29:1031–1042

Fevery J, Verslype C (2010) An update on cholangiocarcinoma associated with primary sclerosing cholangitis. Curr Opin Gastroenterol 26:236–245

Fiorentino M, D'Errico A, Altimari A, Barozzi C, Grigioni WF (1999) High levels of BCL-2 messenger RNA detected by in situ hybridization in human hepatocellular carcinoma and cholangiocellular carcinomas. Diagn Mol Pathol 8:189–194

Flavell DJ (1981) Liver-fluke infection as an aetiological factor in bile-duct carcinoma of man. Trans R Soc Trop Med Hyg 75:814–824

Fleming KA, Boberg KM, Glaumann H, Bergquist A, Smith D, Clausen OP (2001) Biliary dysplasia as a marker of cholangiocarcinoma in primary sclerosing cholangitis. J Hepatol 34:360–365

Foja S, Goldberg M, Schagdarsurengin U, Dammann R, Tannapfel A, Ballhausen WG (2005) Promoter methylation and loss of coding exons of the fragile histidine triad (FHIT) gene in intrahepatic cholangiocarcinomas. Liver Int 25:1202–1208

Forsbring M, Vik ES, Dalhus B, Karlsen TH, Bergquist A, Schrumpf E, Bjoras M, Boberg KM et al (2009) Catalytically impaired hMYH and NEIL1 mutant proteins identified in patients with primary sclerosing cholangitis and cholangiocarcinoma. Carcinogenesis 30:1147–1154

Frampton G, Invernizzi P, Bernuzzi F, Pae HY, Quinn M, Horvat D, Galindo C, Huang L et al (2012) Interleukin-6-driven progranulin expression increases cholangiocarcinoma growth by an Akt-dependent mechanism. Gut 61:268–277

Gao Q, Zhao YJ, Wang XY, Guo WJ, Gao S, Wei L, Shi JY, Shi GM, Wang ZC, Zhang YN et al (2014) Activating mutations in PTPN3 promote cholangiocarcinoma cell proliferation and migration and are associated with tumor recurrence in patients. Gastroenterology 146:1397–1407

Gatselis NK, Tepetes K, Loukopoulos A, Vasiou K, Zafiriou A, Gioti C, Dalekos GN (2007) Hepatitis B virus and intrahepatic cholangiocarcinoma. Cancer Invest 25:55–58

Ginaldi S (1987) Cholangiocarcinoma arising in a choledochal cyst: diagnostic value of computed tomography and ultrasonography. Gastrointest Radiol 12:212–214

Goeppert B, Frauenschuh L, Renner M, Roessler S, Stenzinger A, Klauschen F, Warth A et al (2014) BRAF V600E-specific immunohistochemistry reveals low mutation rates in biliary tract cancer and restriction to intrahepatic cholangiocarcinoma. Mod Pathol 27:1028–1034

Gradilone SA, Radtke BN, Bogert PS, Huang BQ, Gajdos GB, Larusso NF (2013) HDAC6 inhibition restores ciliary expression and decreases tumor growth. Cancer Res 73:2259–2270

Graham RP, Barr Fritcher EG, Pestova E, Schulz J, Sitailo LA, Vasmatzis G, Murphy SJ et al (2014) Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. Hum Pathol 45:1630–1638

Gras Borrell A, Sanchez E, Bertomeu F, Lopez A, Vera-Roman JM, Richart C (1985) Hepatic angiosarcoma and cholangiocarcinoma in a patient with thorotrast deposits (in Spanish). Med Clin (Barc) 84:363–365

Hahn SA, Bartsch D, Schroers A, Galehdari H, Becker M, Ramaswamy A, Schwarte-Waldhoff I et al (1998) Mutations oft he DPC4/Smad4 gene in biliary tract carcinoma. Cancer Res 58:1124–1126

Hai S, Kubo S, Yamamoto S, Uenishi T, Tanaka H, Shuto T, Takemura S, Yamazaki O et al (2005) Clinicopathologic characteristics of hepatitis C virus-associated intrahepatic cholangiocarcinoma. Dig Surg 22:432–439

Han C, Wu T (2005) Cyclooxygenase-2-derived prostaglandin E2 promotes human cholangiocarcinoma cell growth and invasion through EP1 receptor-mediated activation of the epidermal growth factor receptor and Akt. J Biol Chem 280:24053–24063

Hann SA, Schutte M, Hoque AT (1996) DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science 271:350–353

Hao J, Zhang S, Zhou Y, Liu C, Hu X, Shao C (2011) MicroRNA 421 suppresses DPC4/Smad4 in pancreatic cancer. Biochem Biophys Res Commun 406:552–557

Harnois DM, Que FG, Celli A, LaRusso NF, Gores GJ (1997) Bcl-2 is overexpressed and alters the threshold for apoptosis in a cholangiocarcinoma cell line. Hepatology 26:884–890

Hasebe T, Sakamoto M, Mukai K, Kawano N, Knonishi M, Ryu M, Fukamachi S, Hirohashi S (1995) Cholangiocarcinoma arising in bile duct adenoma with focal areas of bile duct hamartoma. Virchows Arch 426:209–213

Hashimoto N, Yachida S, Okano K, Wakabayashi H, Imaida K, Kurokohchi K, Masaki T et al (2009) Immunohistochemically detected expression of p27 (Kip1) and Skp2 predicts survival in patients with intrahepatic cholangiocarcinomas. Ann Surg Oncol 16:395–403

Hass HG, Nehls O, Jobst J, Frilling A, Vogel U, Kaiser S (2008) Identification of osteopontin as the most consistently over-expressed gene in intrahepatic cholangiocarcinoma: detection by oligonucleotide microarray and real-time PCR analysis. World J Gastroenterol 14:2501–2510

Hassid VJ, Orlando FA, Awad ZT, Tan D, Khoury T, Ahmed BH, Alrawi SJ (2009) Genetic and molecular abnormalities in cholangiocarcinogenesis. Anticancer Res 29:1151–1156

Haswell-Elkins MR, Mairiang E, Mairiang P, Chaiyakum J, Chamadol N, Loapaiboon V et al (1994) Cross-sectional study of Opisthorchis viverrini infection and cholangiocarcinoma in communities within a high-risk area in northeast Thailand. Int J Cancer 59:505–509

Helfman DM, Kim EJ, Lukanidin E, Grigorian M (2005) The metastasis associated protein S100A4: role in tumour progression and metastasis. Br J Cancer 92:1955–1958

Herzog BF, Barlow JF, Panning WP, Akim DP (1976) Thorotrast induced cholangiocarcinoma. SDJ Med 29:5–8

Hirashita T, Iwashita Y, Ohta M, Komori Y, Eguchi H, Yada K, Kitano S (2012) Expression of matrix metalloproteinase-7 is an unfavorable prognostic factor in intrahepatic cholangiocarcinoma. J Gastrointest Surg 16:842–848

Hsu M, Sasaki M, Igarashi S, Sato Y, Nakanuma Y (2013) KRAS and GNAS mutations and p53 overexpression in biliary intraepithelial neoplasia and intrahepatic cholangiocarcinomas. Cancer 119:1669–1674

Hu C, Huang F, Deng G, Nie W, Huang W, Zeng X (2013) miR-31 promotes oncogenesis in intrahepatic cholangiocarcinoma cells via the direct suppression of RASA1. Exp Ther Med 6:1265–1270

Huang Q, Liu L, Liu CH, Shao F, Xie F, Zhang CH, Hu SY (2012) Expression of Smad7 in cholangiocarcinoma: prognostic significance and implications for tumor metastasis. Asian Pac J Cancer Prev 13:5161–5165

Hughes NR, Pairojkul C, Royce SG, Clouston A, Bhathal PS (2006) Liver fluke-associated and sporadic cholangiocarcinoma: an immunohistochemical study of bile duct, peribiliary gland and tumour cell phenotypes. J Clin Pathol 59:1073–1078

Hwang JH, Yoon YB, Kim YT, Cheon JH, Jeong JB (2004) Risk factors for recurrent cholangitis after initial hepatolithiasis treatment. J Clin Gastroenterol 38:364–367

Hynes NE, MacDonald G (2009) ErbB receptors and signaling pathways in cancer. Curr Opin Cell Biol 21:177–184

Iguchi T, Aishima S, Taketomi A, Nishihara Y, Fujita N, Sanefuji N, Sugimachi K, Yamashita Y et al (2009) Fascin overexpression is involved in carcinogenesis and prognosis of human intrahepatic cholangiocarcinoma: immunohistochemical and molecular analysis. Hum Pathol 40:174–180

Imai H, Kiyosawa K, Nakamura M, Gibo Y, Sodeyama T, Furuta S (1988) A case of cholangiocarcinoma detected after follow-up for seven years for thorotrast deposition. Gastroenterol Jpn 23:570–575

Imamura et al. (1984) Pub Med PMID 6091444

Isa T, Tomita S, Nakachi A, Miyazato H, Shimoji H, Kusano T, Muto Y, Furukawa M (2002) Analysis of microsatellite instability, K-ras gene mutation and p53 protein overexpression in intrahepatic cholangiocarcinoma. Hepatogastroenterology 49:604–608

Isomoto H (2009) Epigenetic alterations associated with cholangiocarcinoma (review). Oncol Rep 22:227–232

Isomoto H, Mott JL, Kobayashi S, Werneburg NW, Bronk SF, Haan S, Gores GJ (2007) Sustained Il-6/STAT-3 signaling in cholangiocarcinoma cells due to SOCS-3 epigenetic silencing. Gastroenterology 132:384–396

Itatsu K, Zen Y, Ohira S, Ishikawa A, Sato Y, Harada K, Ikeda H, Saski M, Nimura Y et al (2007) Immunohistochemical analysis of the progression of flat and papillary preneoplastic lesions in intrahepatic cholangiocarcinogenesis in hepatolithiasis. Liver Int 27:1174–1184

Itatsu K, Sasaki M, Yamaguchi J, Ohira S, Ishikawa A, Ikeda H, Sato Y, Harada K et al (2009) Cyclooxygenase-2 is involved in the up-regulation of matrix metalloproteinase-9 in cholangiocarcinoma induced by tumor necrosis factor-alpha. Am J Pathol 174:829–841

Ito Y, Kojiro M, Nakashima T, Mori T (1988) Pathomorphologic characteristics of 102 cases of thorotrast-related hepatocellular carcinoma, cholangiocarcinoma, and hepatic angiosarcoma. Cancer 62:1153–1162

Ito Y, Takeda T, Sasaki Y, Sakon M, Yamada T, Ishiguro S, Imaoka S, Tsujimoto M et al (2000a) Expression of Fas and Fas ligand reflects the biological characteristics but not the status of apoptosis of intrahepatic cholangiocellular carcinoma. Int J Mol Med 6:581–586

Ito Y, Takeda T, Sakon M, Monden M, Tsujimoto M, Matsuura N (2000b) Expression and clinical significance of the G1-S modulation in carcinoma of the extrahepatic bile duct. Anticancer Res 20:337–344

Ito Y, Takeda T, Sasaki Y, Sakon M, Monden M, Yamada T, Ishiguro S, Imaoka S et al (2000c) Bcl-2 expression in cholangiocellular carcinoma is inversely correlated with biologically aggressive phenotypes. Oncology 59:63–67

Jan YY, Yeh TS, Yeh JN, Yang HR, Chen MF (2004) Expression of epidermal growth factor receptor, apomucins, matrix metalloproteinases, and p53 in rat and human cholangiocarcinoma: appraisal of an animal model of cholangiocarcinoma. Ann Surg 240:89–94

Jang S, Chun SM, Hong SM, Sung CO, Park H, Kang HJ, Kim KP, Lee YJ, Yu E (2014) High throughput molecular profiling reveals differential mutation patterns in intrahepatic cholangiocarcinomas arising in chronic advanced liver diseases. Mod Pathol 27:731–739

Jarnagin WR, Klimstra DS, Hezel M, Gonen M, Fong Y, Roggin K, Cymes K, DeMatteo RP et al (2006) Differential cell cycle-regulatory protein expression in biliary tract adenocarcinoma: correlation with anatomic site, pathologic variables, and clinical outcome. J Clin Oncol 24:1152–1160

Jhala NC, Vickers SM, Argani P, McDonald JM (2005) Regulators of apoptosis in cholangiocarcinoma. Arch Pathol Lab Med 129:481–486

Jinawath N, Chamgramol Y, Furukawa Y, Obama K, Tsunoda T, Sripa B, Pairojkul C et al (2006) Comparison of gene expression profiles between Opisthorchis viverrini and non-Opisthorchis viverrini associated human intrahepatic cholangiocarcinoma. Hepatology 44:1025–1038

Jo Chae K, Rha SY, Oh BK, Koo JS, Kim YJ, Choi J, Park C, Park YN (2004) Expression of matrix metalloproteinase-2 and -9 and tissue inhibitor of metalloproteinase-1 and -2 in intraductal and nonintraductal growth type of cholangiocarcinoma. Am J Gastroenterol 99:68–75

Jo HJ, Shim HE, Han ME, Kim HJ, Kim KS, Baek S, Choi KU, Hur GY, Oh SO (2013) WTAP regulates migration and invasion of cholangiocarcinoma cells. J Gastroenterol 48:1271–1282

Johnson PK, Babb RR (1975) Cholangiocarcinoma in a patient previously given thorotrast. Am J Dig Dis 20:384–390

Johnson C, Han Y, Hughart N, McCarra J, Alpini G, Meng F (2012) Interleukin-6 and its receptor, key players in hepatobiliary inflammation and cancer. Transl Gastrointest Cancer 1:58–70

Johnston J, Al-Bahrani R, Abuetabh Y, Chiu B, Forsman CL, Nagamori S, Leng R et al (2012) Twisted gastrulation expression in cholangiocellular and hepatocellular carcinoma. J Clin Pathol 65:945–948

Joly I, Choux R, Baroni JL, Payan MJ, Mazel C, Branger D, Ponte J, Sastre B, Sahel J (1990) Carcinoma in situ in localized Caroli's disease (in French). Gastroenterol Clin Biol 14:90–92

Jonas S, Springmeier G, Tauber R, Wiedenmann B, Lobeck H, Gessner R, Kreft B et al (1998) p53 mutagenesis in Klatskin tumors. Hum Pathol 29:955–960

Kamikawa T, Amenomori M, Itoh T, Momoi H, Hiai H, Machinami R, Ishikawa Y, Mori T et al (1999) Analysis of genetic changes in intrahepatic cholangiocarcinoma induced by thorotrast. Radiat Res 152(6 Suppl): S118–S124

Kang YK, Kim WH, Lee HW, Lee HK, Kim YI (1999) Mutation of p53 and K-ras, and loss of heterozygosity of APC in intrahepatic cholangiocarcinoma. Lab Invest 79:477–483

Kang YK, Kim YI, Kim WH (2000) Allelotype analysis of intrahepatic cholangiocarcinoma. Mod Pathol 13:627–631

Kang YK, Kim WH, Jang JJ (2002) Expression of G1-S modulators (p53, p16, p27, cyclin D1, Rb) and Smad4/Dpc4 in intrahepatic cholangiocarcinoma. Hum Pathol 33:877–883

Karakatsanis A, Papaconstantinou I, Gazouli M, Lyberopoulou A, Polymeneas G, Voros D (2013) Expression of microRNAs, miR-21, miR-31, miR-122, miR-145, miR-146a, miR-200c, miR-221, miR-222, and miR-223 in patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma and its prognostic significance. Mol Carcinog 52:297–303

Karamitopoulou E, Tornillo L, Zlobec I, Cioccari L, Carafa V, Borner M, Schaffner T et al (2008) Clinical significance of cell cycle- and apoptosis-related markers in biliary tract cancer: a tissue microarray-based approach revealing a distinctive immunophenotype for intrahepatic and extrahepatic cholangiocarcinomas. Am J Clin Pathol 130:780–786

Kasper HU, Stippel DL, Tox U, Drebber U, Dienes HP (2006) Primary cholangiocarcinoma in a case of Caroli's disease: case report and literature review (in German). Pathologe 27:300–304

Katabi N, Albores-Saavedra J (2003) The extrahepatic bile duct lesions in end-stage primary sclerosing cholangitis. Am J Surg Pathol 27:349–355

Kawahara N, Ono M, Taguchi K, Okamoto M, Shimada M, Takenaka K, Hayashi K et al (1998) Enhanced expression of thrombospondin-1 and hypovascularity in human cholangiocarcinoma. Hepatology 28:1512–1517

Kawakami H, Kuwatani M, Onodera M, Hirano S, Kondo S, Nakanishi Y, Itoh T, Asaka M (2007) Primary cholesterol hepatolithiasis associated with cholangiocellular carcinoma: a case report and literature review. Intern Med 46:1191–1196

Kawaki J, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Yoshidome H, Uzawa K, Tanzawa H et al (2000) Allelic loss in human intrahepatic cholangiocarcinoma: correlation between chromosome 8p22 and tumor progression. Int J Cancer 88:228–231

Khan SA, Thomas HC, Toledano MB, Cox IJ, Taylor-Robinson SD (2005) p53 mutations in human cholangiocarcinoma: a review. Liver Int 25:704–716

Khan SA, Taylor-Robinson SD, Carmichael PL, Habib N, Lemoine NR, Thomas HC (2006) Analysis of p53 mutations for a mutational signature in human intrahepatic cholangiocarcinoma. Int J Oncol 28:1269–1277

Khan SA, Toledano MB, Taylor-Robinson SD (2008) Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. HPB (Oxford) 10:77–82

Kim YT, Byun JS, Kim J, Jang YH, Lee WJ, Ryu JK, Kim SW, Yoon YB, Kim CY (2003) Factors predicting concurrent cholangiocarcinomas associated with hepatolithiasis. Hepatogastroenterology 50:8–12

Kim KS, Jin DI, Yoon S, Baek SY, Kim BS, Oh SO (2012) Expression and roles of NUPR1 in cholangiocarcinoma cells. Anat Cell Biol 45:17–25

Kipp BR, Voss JS, Kerr SE, Barr Fritcher EG, Graham RP, Zhang L, Highsmith WE et al (2012) Isocitrate dehydrogenase 1 and 2 mutations in cholangiocarcinoma. Hum Pathol 43:1552–1558

Knechtle SJ, D'Alessandro AM, Harms BA, Pirsch JD, Belzer FO, Kalayoglu M (1995) Relationships between sclerosing cholangitis, inflammatory bowel disease, and cancer in patients undergoing liver transplantation. Surgery 118:615–619

Kobayashi M, Ikeda K, Saitoh S, Suzuki F, Tsubota A, Suzuki Y, Arase Y, Murashima N et al (2000) Incidence of primary cholangiocellular carcinoma of the liver in Japanese patients with hepatitis C virus-related cirrhosis. Cancer 88:2471–2477

Kobayashi S, Werneburg NW, Bronk SF, Kaufmann SH, Gores GJ (2005) Interleukin-6 contributes to Mcl-1 up-regulation and TRAIL resistance via an Akt-signaling pathway in cholangiocarcinoma cells. Gastroenterology 128:2054–2065

Koch E, Fiedler W, Tannapfel A, Ballhausen WG (2003) Alteration of the fragile histidine triad gene in intrahepatic cholangiocarcinoma. Eur J Gastroenterol Hepatol 15:907–913

Koga A, Ichimiya H, Yamaguchi K, Miyazaki K, Nakayama F (1985) Hepatolithiasis associated with

cholangiocarcinoma. Possible etiologic significance. Cancer 55:2826–2829

Koga Y, Kirajima Y, Miyoshi A, Sato K, Kitahara K, Soejima H, Miyazaki K (2005) Tumor progression through epigenetic gene silencing of O(6)-methylguanine-DNA methyltransferase in human bilary tract cancers. Ann Surg Oncol 12:354–363

Kohya N, Koga Y, Kitajima Y, Miyazaki K (2006) Aberrant promoter hypermethylation in biliary tract carcinoma. J Hepatobiliary Pancreat Surg 13:296–305

Komenaka IK, Mir R, de Graft-Johnson JB, Wise L (2003) Severe high-grade dysplasia and in-situ carcinoma oft he common bile duct and pancreatic duct. Lancet Oncol 4:373–375

Komuta M, Govaere O, Vandecaveye V, Akiba J, Van Steenbergen W, Verslype C et al (2012) Histological diversity in cholangiocellular carcinoma reflects the different cholangiocyte phenotypes. Hepatology 55:1876–1888

Koo SH, Ihm CH, Kwon KC, Park JW, Kim JM, Kong G (2001) Genetic alterations in hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Cancer Genet Cytogenet 130:22–28

Kulkarni PB, Beatty E (1977) Cholangiocarcinoma associated with biliary cirrhosis due to congenital biliary atresia. Am J Dis Child 131:442–444

Kumamoto T, Tanaka K, Takeda K, Nojiri K, Mori R, Taniguchi K, Matsuyama R, Ueda M et al (2014) Intrahepatic cholangiocarcinoma arising 28 years after excision of a type IV-A congenital choledochal cyst: report of a case. Surg Today 44:354–358

Kumar M, Zhao X, Wang XW (2011) Molecular carcinogenesis of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: one step closer to personalized medicine? Cell Biosci 1:5

Kunkeaw N, Jeon SH, Lee K, Johnson BH, Tanasanvimon S, Javle M, Pairojkul C et al (2013) Cell death/proliferation roles for nc886, a non-coding RNA, in the protein kinase R pathway in cholangiocarcinoma. Oncogene 32:3722–3731

Kuo KK, Sato N, Mizumoto K, Maehara N, Yonemasu H, Ker CG, Sheen PC, Tanaka M (2000) Centrosome abnormalities in human carcinomas of the gallbladder and intrahepatic and extrahepatic bile ducts. Hepatology 31:59–64, Cancer 61:2469–2474

Kuper H, Ye W, Broomé A, Romelsjö A, Mucci LA, Ekbom A, Adami HO, Trichopoulos D et al (2001) The risk of liver and bile duct cancer in patients with chronic viral hepatitis, alcoholism, or cirrhosis. Hepatology 34:714–718

Kurashina M, Kozuka S, Nakasima N, Hirabayashi N, Ito M (1988) Relationship of intrahepatic bile duct hyperplasia to cholangiocellular carcinoma. Cancer 61:2469–2474

Kurathong S, Lerdverasirikul P, Wongpaitoon V, Pramoolsinsap C, Kanjanapitak A, Varavithya W et al (1985) Opisthorchis viverrini infection and cholangiocarcinoma. A prospective, case-controlled study. Gastroenterology 89:151–156

Kuroki T, Tajima Y, Kanematsu T (2005) Hepatolithiasis and intrahepatic cholangiocarcinoma: carcinogenesis based on molecular mechanisms. J Hepatobiliary Pancreat Surg 12:463–466

Kurumaya H, Terada T, Nakamura Y (1990) 'Metaplastic lesions' in intrahepatic bile ducts in hepatolithiais: a histochemical and immunohistochemical study. J Gastroenterol Hepatol 5:530–536

Landais P, Grünfeld JP, Droz D, Drüeke T, Albouze G, Gogusev J, Chauveau D, Moynot A (1984) Cholangiocellular carcinoma in polycystic kidney and liver disease. Arch Intern Med 144:2274–2276

Lazaridis KN, Gores GJ (2006) Primary sclerosing cholangitis and cholangiocarcinoma. Semin Liver Dis 26:42–51

Lee KT, Liu TS (2001) Altered mucin gene expression in stone-containing intrahepatic bile ducts and cholangiocarcinomas. Dig Dis Sci 46:2166–2172

Lee KT, Sheen PC (1999) Proliferating cell nuclear antigen expression in peribiliary glands of stone-containing intrahepatic bile ducts. Dig Dis Sci 44:2251–2256

Lee et al. (1995) Pub Med PMID 8541732

Lee FI, Tharakan J, Vasudev KS, Isaacs PE (1996) Malignant hepatic tumours associated with previous exposure to Thorotrast: four cases. Eur J Gastroenterol Hepatol 8:1121–1124

Lee CC, Wu CY, Chen GH (2002a) What is the impact of coexistence of hepatolithiasis on cholangiocarcinoma? J Gastroenterol Hepatol 17:1015–1020

Lee S, Kim WH, Jung HY, Yang MH, Kang GH (2002b) Aberrant CpG island methylation of multiple genes in intrahepatic cholangiocarcinoma. Am J Pathol 161:1015–1022

Lee KT, Chang WT, Wang SN, Chuang SC, Chai CY, Hu SW (2006) Expression of DPC4/Smad4 gene in stone-containing intrahepatic bile duct. J Surg Oncol 94:338–343

Lee TY, Lee SS, Jung SW, Jeon SH, Yun SC, Oh HC, Kwon S, Lee SK, Seo DW et al (2008) Hepatitis B virus infection and intrahepatic cholangiocarcinoma in Korea: a case-control study. Am J Gastroenterol 103:1716–1720

Lee CH, Chang CJ, Lin YJ, Yeh CN, Chen MF, Hsieh SY (2009a) Viral hepatitis-associated intrahepatic cholangiocarcinoma shares common disease processes with hepatocellular carcinoma. Br J Cancer 100:1765–1770

Lee MJ, Yu GR, Yoo HJ, Kim JH, Yoon BT, Choi YK, Kim DG (2009b) ANXA8 down-regulation by EGF-FOXO4 signaling is involved in cell scattering and tumor metastasis of cholangiocarcinoma. Gastroenterology 137:1138–1150

Lee SH, Jung YS, Chung JY, Oh AY, Lee SJ, Choi DH, Jang SM, Jang KS, Paik SS et al (2011) Novel tumor suppressive function of Smad4 in serum starvation-induced cell death through PAK1-OUMA pathway. Cell Death Dis 2:e235

Leelawat K, Thongtawee T, Narong S, Subwongcharoen S, Treepongkaruna SA (2011) Strong expression of

CD133 is associated with increased cholangiocarcinoma progression. World J Gastroenterol 17:1192–1198

Leelawat K, Keeratichamroen S, Leelawat S, Tohtong R (2013) CD24 induces the invasion of cholangiocarcinoma cells by upregulating CXCR4 and increasing the phosphorylation of ERk1/2. Oncol Lett 6:1439–1446

Legg JA, Herbert JM, Clissold P, Bicknell R (2008) Slits and roundabouts in cancer, tumour angiogenesis and endothelial cell migration. Angiogenesis 11:13–21

Lesurtel M, Regimbeau JM, Farges O, Colombat M, Sauvanet A, Belghiti J (2002) Intrahepatic cholangiocarcinoma and hepatolithiasis: an unusual association in Western countries. Eur J Gastroenterol Hepatol 14:1025–1027

Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC (2010) Precancerous bile duct pathology in end-stage sclerosing cholangitis, with and without cholangiocarcinoma. Am J Surg Pathol 34:27–34

Leyva-Illades D, McMillin M, Quinn M, Demorrow S (2012) Cholangiocarcinoma pathogenesis: role of the tumor microenvironment. Transl Gastrointest Cancer 1:71–80

Li T, Li D, Cheng L, Wu H, Gao Z, Liu Z, Jiang W, Gao YH, Tian F, Zhao L, Wang S (2010) Epithelial-mesenchymal transition induced by hepatitis C virus core protein in cholangiocarcinoma. Ann Surg Oncol 17:1937–1944

Li M, Li J, Li P, Li H, Su T, Zhu R, Gong J (2012a) Hepatitis B virus infection increases the risk of cholangiocarcinoma: a meta-analysis and systematic review. J Gastroenterol Hepatol 27: 1561–1568

Li B, Han Q, Zhu Y, Yu Y, Wang J, Jiang X (2012b) Down-regulation of miR-214 contributes to intrahepatic cholangiocarcinoma metastasis by targeting Twist. FEBS J 279:2393–2398

Limpaiboon T, Tapdara S, Jearanaikoon P, Sripa B, Budhisawasdi V (2006) Prognostic significance of microsatellite alterations at 1p36 in cholangiocarcinoma. World J Gastroenterol 12:4377–4382

Lipshutz GS, Brennan TV, Warren RS (2002) Thorotrast-induced liver neoplasia: a collective review. J Am Coll Surg 195:713–718

Liu D, Momoi H, Li L, Ishikawa Y, Fukumoto M (2002) Microsatellite instability in thorotrast-induced human intrahepatic cholangiocarcinoma. Int J Cancer 102:366–371

Liu XF, Zou SQ, Qiu FZ (2003) Pathogenesis of cholangiocarcinoma in the porta hepatis and infection of hepatitis virus. Hepatobiliary Pancreat Dis Int 2:285–289

Liu D, Wada I, Tateno H, Ogino D, Suzuki M, Li L, Lu W, Kojiro M, Fukayama M, Okabe H et al (2004) Allelotypic characteristics of thorotrast-induced intrahepatic cholangiocarcinoma: comparison to liver cancers not associated with thorotrast. Radiat Res 161:235–243

Liu ZY, Zhou YM, Shi LM, Yin ZF (2011) Risk factors of intrahepatic cholangiocarcinoma in patients with hepatolithiasis: a case-control study. Hepatobiliary Pancreat Dis Int 10:626–631

Liu CZ, Liu W, Zheng Y, Su JM, Li JJ, Yu L, He XD, Chen SS (2012) PTEN and PDCD4 are bona fide targets of microRNA-21 in human cholangiocarcinoma. Chin Med Sci J 27:65–72

Liu et al. (2013) Pub Med PMID 24139471

Ludwig J, Wiesner RH, LaRusso NF (1982) Focal dilatation of intrahepatic bile ducts (Caroli's disease), cholangiocarcinoma, and sclerosis of extrahepatic bile ducts: a case report. J Clin Gastroenterol 4:53–57

Mabrut JY, Kianmanesh R, Nuzzo G, Castaing D, Boudjema K, Létoublon C, Adham M et al (2013) Surgical management of congenital intrahepatic bile duct dilatation, Caroli's disease and syndrome; long-term results of the French Association of Surgery Multicenter Study. Ann Surg 258:713–721

MacCarty RL, LaRusso NF, May GR, Bender CE, Wiesner RH, King JE, Coffey RJ (1985) Cholangiocarcinoma complicating primary sclerosing cholangitis: cholangiographic appearances. Radiology 156:43–46

Maggs JR, Chapman RW (2008) An update on primary sclerosing cholangitis. Curr Opin Gastroenterol 24:377–383

Mano Y, Aishima S, Fukuhara T, Tanaka Y, Kubo Y, Motomura T, Toshima T, Iguchi T et al (2013) Decreased roundabout 1 expression promotes development of intrahepatic cholangiocarcinoma. Hum Pathol 44:2419–2426

Mansuroglu T, Ramadori P, Dudas J, Malik I, Hammerich K, Füzesi L, Ramadori G (2009) Expression of stem cell factor and its receptor c-Kit during the development of intrahepatic cholangiocarcinoma. Lab Invest 89:562–574

Mao X, Chen D, Wu J, Li J, Zhou H, Wu Y, Duan X (2013) Differential expression of fascin, E-cadherin and vimentin: proteins associated with survival of cholangiocarcinoma patients. Am J Med Sci 346:261–268

Martins EB, Fleming KA, Garrido MC, Hine KR, Chapman RW (1994) Superficial thrombophlebitis, dysplasia, and cholangiocarcinoma in primary sclerosing cholangitis. Gastroenterology 107:537–542

Matsumoto K, Onoyama T, Kawata S, Takeda Y, Harada K, Ikebuchi Y, Ueki M, Miura N et al (2014) Hepatitis B and C virus infection is a risk factor for the development of cholangiocarcinoma. Intern Med 53:651–654

Meng F, Yamagiwa Y, Ueno Y, Patel T (2006) Over-expression of interleukin-6 enhances cell survival and transformed cell growth in human malignant cholangiocytes. J Hepatol 44:1055–1065

Meng F, Henson R, Wehbe-Janek H, Smith H, Ueno Y, Patel T (2007) The MicroRNA let-7a modulates interleukin-6-dependent STAT-3 survival signaling in malignant human cholangiocytes. J Biol Chem 282:8256–8264

Meng F, Wehbe-Janek H, Henson R, Smith H, Patel T (2008) Epigenetic regulation of microRNA-370 by interleukin-6 in malignant human cholangiocytes. Oncogene 27:378–386

Miller G, Socci ND, Dhall D, D'Angelica M, De Matteo RP, Allen PJ, Singh B, Fong Y et al (2009) Genome wide analysis and clinical correlation of chromosomal and transcriptional mutations in cancers of the biliary tract. J Exp Clin Cancer Res 28:62

Momoi H, Okabe H, Kamikawa T (2001) Comprehensive allelotyping of human intrahepatic cholangiocarcinoma. Clin Cancer Res 7:2648–2655

Nakanishi Y, Zen Y, Kondo S, Itoh T, Itatsu K, Nakanuma Y (2008) Expression of cell cycle-related molecules in biliary premalignant lesions: biliary intraepithelial neoplasia and biliary intraductal papillary neoplasm. Hum Pathol 39:1153–1161

Nakanuma Y, Terada T, Tanaka Y, Ohta G (1985) Are hepatolithiasis and cholangiocarcinoma aetiologically related? A morphological study of 12 cases of hepatolithiasis associated with cholangiocarcinoma. Virchows Arch A Pathol Anat Histopathol 406:45–58

Nakanuma Y, Yamaguchi K, Ohta G, Terada T (1988) Pathologic features of hepatolithiasis in Japan. Hum Pathol 19:1181–1186

Nakanuma Y, Harada K, Ishikawa A, Zen Y, Sasaki M (2003) Anatomic and molecular pathology of intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 10:265–281

Nakanuma Y, Sasaki M, Sato Y, Ren X, Ikeda H, Harada K (2009) Multistep carcinogenesis of perihilar cholangiocarcinoma arising in the intrahepatic large bile ducts. World J Hepatol 1:35–42

Nakanuma Y, Tsutsui A, Ren XS, Harada K, Sato Y, Sasaki M (2014) What are the precursor and early lesions of peripheral intrahepatic cholangiocarcinoma? Int J Hepatol 2014, ID 805973

Nakayama F, Koga A (1984) Hepatolithiasis: present status. World J Surg 8:9–14

Nakazawa K, Dobashi Y, Suzuki S, Fujii H, Takeda Y, Ooi A (2005) Amplification and overexpression of c-erbB-2, epidermal growth factor receptor, and c-met in biliary tract cancers. J Pathol 206:356–365

Namwat N, Puetkasichonpasutha J, Loilome W, Yongvanit P, Techasen A, Puapairoj A et al (2011) Downregulation of reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) is associated with enhanced expression of matrix metalloproteinases and cholangiocarcinoma metastases. J Gastroenterol 46:664–675

Nanashima A, Hatachi G, Tsuchiya T, Matsumoto H, Arai J, Abo T, Murakami G, Tominaga T et al (2013) Clinical significances of cancer stem cells markers in patients with intrahepatic cholangiocarcinoma who underwent hepatectomy. Anticancer Res 33:2107–2114

Narong S, Leelawat K (2011) Basic fibroblast growth factor induces cholangiocarcinoma cell migration via activation of the MEK1/2 pathway. Oncol Lett 2:821–825

Nault JC, Zucman-Rossi J (2011) Genetics of hepatobiliary carcinogenesis. Semin Liver Dis 31:173–187

Neto AG, Dainiak C, Qio LH, Salem RR, Jain D (2007) Intraductal papillary cholangiocarcinoma associated with von Meyenburg complexes: a case report. Dig Dis Sci 52:2643–2645

Nishihara K, Koga A, Sumiyoshi K, Kayashima K, Koso E (1986) Intrahepatic calculi associated with cholangiocarcinoma. Jpn J Surg 16:367–370

Nkontchou G, Tran Van Nhieu J, Ziol M, Tengher I, Mahmoudi A, Roulot D, Bourcier V et al (2013) Peripheral intrahepatic cholangiocarcinoma occurring in patients without cirrhosis or chronic bile duct diseases: epidemiology and histopathology of distant nontumoral liver in 57 White patients. Eur J Gastroenterol Hepatol 25:94–98

Nuntagowat C, Leelawat K, Tohtong R (2010) NGAL knockdown by siRNA in human cholangiocarcinoma cells suppressed invasion by reducing NGAL/MMP-9 complex formation. Clin Exp Metastasis 27:295–305

Nzeako UC, Guicciardi ME, Yoon JH, Bronk SF, Gores GJ (2002) COX-2 inhibits Fas-mediated apoptosis in cholangiocarcinoma cells. Hepatology 35:552–559

O'Dell MR, Huang JL, Whitney-Miller CL, Deshpande V, Rothberg P, Grose V, Rossi RM et al (2012) Kras (G12D) and p53 mutation cause primary intrahepatic cholangiocarcinoma. Cancer Res 72:1557–1567

Obama K, Ura K, Li M, Katagiri T, Tsunoda T, Nomura A, Satoh S, Nakamura Y, Furukawa Y (2005a) Genome-wide analysis of gene expression in human intrahepatic cholangiocarcinoma. Hepatology 41:1339–1348

Obama K, Ura K, Satoh S, Nakamura Y, Furukawa Y (2005b) Up-regulation of PSF2, a member of the GINS multiprotein complex, in intrahepatic cholangiocarcinoma. Oncol Rep 14:701–706

Obama K, Satoh S, Hamamoto R, Sakai Y, Nakamura Y, Furukawa Y (2008) Enhanced expression of RAD51 associating protein-1 is involved in the growth of intrahepatic cholangiocarcinoma cells. Clin Cancer Res 14:1333–1339

Ohashi K, Tsutsumi M, Nakajima Y, Noguchi O, Okita S, Kitada H, Tsujiuchi T, Kabayashi E et al (1994) High rates of Ki-ras point mutation in both intra-and extrahepatic cholangiocarcinomas. Jpn J Clin Oncol 24:305–310

Ohashi K, Nakajima Y, Kanehiro H, Tsutsumi M, Taki J, Aomatsu Y, Yoshimura A et al (1995) Ki-ras mutations and p53 protein expressions in intrahepatic cholangiocarcinomas: relation to gross tumor morphology. Gastroenterology 109:1612–1617

Ohira S, Itatsu K, Sasaki M, Harada K, Sato Y, Zen Y, Ishikawa A, Oda K, Nagasaka T et al (2006) Local balance of transforming growth factor-beta1 secreted from cholangiocarcinoma cells and stromal-derived factor-1 secreted from stromal fibroblasts is a factor involved in invasion of cholangiocarcinoma. Pathol Int 56:381–389

Ohira S, Sasaki M, Harada K, Sato Y, Zen Y, Isse K, Kozaka K, Ishikawa A, Oda K et al (2008) Possible regulation of migration of intrahepatic cholangiocarcinoma cells by interaction of CXCR4 expressed in carcinoma cells with tumor necrosis factor-alpha and stromal-derived factor-1 released in stroma. Am J Pathol 168:1155–1168

Ohta G, Nakanuma Y, Terada T (1984) Pathology of hepatolithiasis: cholangitis and cholangiocarcinoma. Prog Clin Biol Res 152:91–113

Ohta T, Nagakawa T, Konishi I, Ueno K, Kanno M, Akiyama T, Kayahara M, Izumi R et al (1988) Clinical experience of intrahepatic cholangiocarcinoma associated with hepatolithiasis. Jpn J Surg 18:47–53

Ohta et al. (1991) Pub Med PMID 1655206

Oikawa T, Kamiya A, Zeniya M, Chikada H, Hyuck AD, Yamazaki Y, Wauthier E, Tajiri H et al (2013) Sal-like protein (SALL4), a stem cell biomarker in liver cancers. Hepatology 57:1469–1483. Pub Med PMID 23175232

Oishi N, Kumar MR, Roessler S, Ji J, Forgues M, Budhu A, Zhao X, Andersen JB et al (2012) Transcriptomic profiling reveals hepatic stem-like gene signatures and interplay of miR-200c and epithelial-mesenchymal transition in intrahepatic cholangiocarcinoma. Hepatology 56:1792–1803

Okamoto K, Tajima H, Nakanuma S, Sakai S, Makino I, Kinoshita J, Hayashi H, Nakamura K et al (2012) Angiotensin II enhances epithelial-to-mesenchymal transition through the interaction between activated hepatic stellate cells and the stromal cell-derived factor-1/CXCR4 axis in intrahepatic cholangiocarcinoma. Int J Oncol 41:573–582

Okuda K, Nakanuma Y, Miyazaki M (2002) Cholangiocarcinoma: recent progress. Part 2: molecular pathology and treatment. J Gastroenterol Hepatol 17:1056–1063

Olaru AV, Ghiaur G, Yamanaka S, Luvsanjav D, An F, Popescu I, Alexandrescu S, Allen S et al (2011) MicroRNA down-regulated in human cholangiocarcinoma control cell cycle through multiple targets involved in the G1/S checkpoint. Hepatology 54:2089–2098

Ong CK, Subimerb C, Pairojkul C, Wongkham S, Cutcutache I, Yu W, McPherson JR et al (2012) Exome sequencing of liver fluke-associated cholangiocarcinoma. Nat Genet 44:690–693

Onodera M, Zen Y, Harada K, Sato Y, Ikeda H, Itatsu K, Sato H, Ohta T, Asaka M, Nakanuma Y (2009) Fascin is involved in tumor necrosis factor-alpha-dependent production of MMP9 in cholangiocarcinoma. Lab Invest 89:1261–1274

Orii T, Ohkohchi N, Sasaki K, Satomi S, Watanabe M, Moriya T (2003) Cholangiocarcinoma arising from preexisting biliary hamartoma of liver – report of a case. Hepatogastroenterology 50:333–336

Pairojkul C, Shirai T, Hirohashi S, Thamavit W, Budhisawat W, Uttaravicien T, Itoh M et al (1991) Multistage carcinogenesis of liver-fluke-associated cholangiocarcinoma in Thailand. Princess Takamatsu Symp 22:77–86

Palmer WC, Patel T (2012) Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. J Hepatol 57:69–76

Pan G, Ahn EY, Chen Y, Feng G, Reddy V, Jhala NC, McDonald JM (2007) Reciprocal co-expression of Fas and Fas ligand in human cholangiocarcinoma. Int J Oncol 31:843–850

Parada LA, Hallèn M, Hägerstrand I, Tranberg KG, Johansson B (1999) Clonal chromosomal abnormalities in congenital bile duct dilation (Caroli's disease). Gut 45:780–782

Park BK, Paik YH, Park JY, Park KH, Bang S, Park SW, Chung JB, Park YN et al (2006) The clinicopathologic significance of the expression of vascular endothelial growth factor-C in intrahepatic cholangiocarcinoma. Am J Clin Oncol 29:138–142

Patel T (2014) New insights into the molecular pathogenesis of intrahepatic cholangiocarcinoma. J Gastroenterol 49:165–172

Peng NF, Li LQ, Qin X, Guo Y, Peng T, Xiao KY, Chen XG, Yang YF, Su ZX et al (2011) Evaluation of risk factors and clinicopathologic features for intrahepatic cholangiocarcinoma in Southern China: a possible role of hepatitis B virus. Ann Surg Oncol 18:1258–1266

Perumal V, Wang J, Thuluvath P, Choti M, Torbenson M (2006) Hepatitis C and hepatitis B nucleic acids are present in intrahepatic cholangiocarcinomas from the United States. Hum Pathol 37:1211–1216

Petmitr S, Pinlaor S, Thousungnoen A, Karalak A, Migasena P (1998) K-ras oncogene and p53 gene mutations in cholangiocarcinoma from Thai patients. Southeast Asian J Trop Med Public Health 29:71–75

Phinney PR, Austin GE, Kadell BM (1981) Cholangiocarcinoma arising in Caroli's disease. Arch Pathol Lab Med 105:194–197

Pickens A, Pan G, McDonald JM, Vickers SM (1999) Fas expression prevents cholangiocarcinoma tumor growth. J Gastrointest Surg 3:374–381

Pinho AC, Melo RB, Oliveira M, Almeida M, Lopes J, Graça L, Costa-Maia J (2012) Adenoma-carcinoma sequence in intrahepatic cholangiocarcinoma. Int J Surg Case Rep 3:131–133

Plieskatt JL, Rinaldi G, Feng Y, Peng J, Yonglitthipagon P, Easley S, Laha T, Pairojkul C et al (2014) Distinct miRNA signatures associate with subtypes of cholangiocarcinoma from infection with the tumourigenic liver fluke Opisthorchis viverrini. J Hepatol 61:850–858

Qiu YH, Wei YP, Shen NJ, Wang ZC, Kann T, Yu WL, Yi B, Zhang YJ (2013) miR-204 inhibits epithelial to mesenchymal transition by targeting slug in intrahepatic cholangiocarcinoma cells. Cell Physiol Biochem 32:1331–1341

Que FG, Phan VA, Phan VH, Celli A, Batts K, LaRusso NF, Gores GJ (1999) Cholangiocarcinomas express Fas ligand and disable the Fas receptor. Hepatology 30:1398–1404

Rashid A (2002) Cellular and molecular biology of biliary tract cancers. Surg Oncol Clin N Am 11:995–1009

Reddy SK, Hyder O, Marsh JW, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H et al (2013) Prevalence of nonalcoholic steatohepatitis among patients with resectable intrahepatic cholangiocarcinoma. J Gastrointest Surg 17:748–755

Riener MO, Vogetseder A, Pestalozzi BC, Clavien PA, Probst-Hensch N, Kristiansen G, Jochum W (2010) Cell adhesion molecules P-cadherin and CD24 are markers for carcinoma and dysplasia in the biliary tract. Hum Pathol 41:1558–1565

Riganti M, Pungpak S, Punpoowong B, Bunnag D, Harinasuta T (1989) Human pathology of Opisthorchis viverrini infection: a comparison of adults and children. Southeast Asian J Trop Med Public Health 20:95–100

Rizvi S, Gores GJ (2013) Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology 145:1215–1229

Rizvi S, Gores GJ (2014) Molecular pathogenesis of cholangiocarcinoma. Dig Dis 32:564–569

Robertson S, Hyder O, Dodson R, Nayar SK, Poling J, Beierl K, Eshleman JR, Lin MT et al (2013) The frequency of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. Hum Pathol 44:2768–2773

Röcken C, Pross M, Brucks U, Ridwelski K, Roessner A (2000) Cholangiocarcinoma occurring in a liver with multiple bile duct hamartomas (von Meyenburg complexes). Arch Pathol Lab Med 124:1704–1706

Roskoski R (2004) The ErbB/HER receptor protein-tyrosine kinases and cancer. Biochem Biophys Res Commun 319:1–11

Rota AN, Weindling HK, Goodman PG (1971) Cholangiocarcinoma associated with thorium dioxide (thorotrast): report of a case. Mich Med 70:911–915

Rougemont AL, Genevay M, MCKee TA, Gremaud M, Mentha G, Rubbia-Brandt L (2010) Extensive biliary intraepithelial neoplasia (BillN) and multifocal early intrahepatic cholangiocarcinoma in non-biliary cirrhosis. Virchows Arch 456:711–717

Rubel LR, Ishak KG (1982) Thorotrast-associated cholangiocarcinoma: an epidemiologic and clinicopathologic study. Cancer 50:1408–1415

Sahani D, Prasad SR, Tannabe KK, Hahn PF, Mueller PR, Saini S (2003) Thorotrast-induced cholangiocarcinoma: case report. Abdom Imaging 28:72–74

Sakai K, Shiina M, Ishihara N, Kato Y (1984) Thorotrast-induced multiple primary malignant tumors of the liver – cholangiocarcinoma and malignant hemangioendothelioma. Jpn J Clin Oncol 14:411–416

Sandhu DS, Shire AM, Roberts LR (2008) Epigenetic DNA hypermethylation in cholangiocarcinoma: potential roles in pathogenesis, diagnosis and identification of treatment targets. Liver Int 28:12–27

Sasaki F, Kido C, Sato Y, Tateno H (1989) Roentgenologic appearance of a thorotrast-induced small cholangiocarcinoma in a case of thorotrastosis. An autopsy case of massive gastrointestinal bleeding of esophageal varices. Nippon Igaku Hoshasen Gakkai Zasshi 49:568–573

Sasaki M, Huang SF, Chen MF, Jan YY, Yeh TS, Ishikawa A, Mollenhauer J, Poustka A et al (2003) Decrease of deleted in malignant brain tumour-1 (DMBT-1) expression is a crucial late event in intrahepatic cholangiocarcinoma. Histopathology 43:340–346

Sasaki M, Yamaguchi J, Itatsu K, Ikeda H, Nakanuma Y (2008) Over-expression of polycomb group protein EZH2 relates to decreased expression of p16 INK4a in cholangiocarcinogenesis in hepatolithiasis. J Pathol 215:175–183

Sasaki M, Yamaguchi J, Ikeda H, Itatsu K, Nakanuma Y (2009) Polycomb group protein Bmi1 is overexpressed and essential in anchorage-independent colony formation, cell proliferation and repression of cellular senescence in cholangiocarcinoma: tissue and culture studies. Hum Pathol 40:1723–1730

Sato M, Watanabe Y, Ueda S, Ohno J, Kashu Y, Nezu K, Kawachi K (1998) Intrahepatic cholangiocarcinoma associated with hepatolithiasis. Hepatogastroenterology 45:137–144

Sato Y, Harada K, Itatsu K, Ikeda H, Kakuda Y, Shimomura S, Shan RX, Yoneda N et al (2010) Epithelial-mesenchymal transition induced by transforming growth factor-{beta}1/Snail activation aggravates invasive growth of cholangiocarcinoma. Am J Pathol 177:141–152

Sato Y, Harada K, Sasaki M, Nakanuma Y (2013) Histological characteristics of biliary intraepithelial neoplasia-3 and intraepithelial spread of cholangiocarcinoma. Virchows Arch 462:421–427

Sato Y, Harada K, Sasaki M, Nakanuma Y (2014) Histological characterization of biliary intraepithelial neoplasia with respect to pancreatic intraepithelial neoplasia. Int J Hepatol 2014:678260

Schwarte-Waldhoff I, Volpert OV, Bouck NP, Sipos B, Hahn SA, Klein-Scory S, Lüttges J et al (2000) Smad4/DPC4-mediated tumor suppression through suppression of angiogenesis. Proc Natl Acad Sci U S A 97:9624–9629

Schwartz DA (1986) Cholangiocarcinoma associated with liver fluke infection: a preventable source of morbidity in Asian immigrants. Am J Gastroenterol 81:76–79

Sclabas GM, Barton JG, Smyrk TC, Barrett DA, Khan S, Kendrick ML, Reid-Lombardo KM et al (2012) Frequency of subtypes of biliary intraductal papillary mucinous neoplasm and their MUC1, MUC2, and DPC4 expression patterns differ from pancreatic intraductal papillary mucinous neoplasm. J Am Coll Surg 214:27–32

Sekiya S, Suzuki A (2012) Intrahepatic cholangiocarcinoma can arise from Notch-mediated conversion of hepatocytes. J Clin Invest 122:3914–3918

Selaru FM, Olaru AV, Kan T, David S, Cheng Y, Mori Y, Yang J, Paun B, Jin Z, Agarwal R et al (2009) MicroRNA-21 is overexpressed in human cholangiocarcinoma and regulates programmed cell death 4 and

tissue inhibitor of metalloproteinase 3. Hepatology 49:1595–1601
Seol MA, Chu IS, Lee MJ, Yu GR, Cui XD, Cho BH, Ahn EK, Leem SH, Kim IH et al (2011) Genome-wide expression patterns associated with oncogenesis and sarcomatous transdifferentiation of cholangiocarcinoma. BMC Cancer 11:78
Sgro M, Rossetti S, Barozzio T, Toi A, Langer J, Harris PC, Harvey E, Chitayat D (2004) Caroli's disease: prenatal diagnosis, postnatal outcome and genetic analysis. Ultrasound Obstet Gynecol 23:73–76
Shaib Y, El-Serag HB (2004) The epidemiology of cholangiocarcinoma. Semin Liver Dis 24:115–125
Shaib et al (2004) Pub Med PMID 15123362
Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA (2005) Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. Gastroenterology 128:620–626
Shen YC, Hu FC, Jeng YM, Chang YT, Lin ZZ, Chang MC, Hsu C, Cheng AL (2009) Nuclear overexpression of mitotic regulatory proteins in biliary tract cancer: correlation with clinicopathologic features and patient survival. Cancer Epidemiol Biomarkers Prev 18:417–423
Shen DY, Zhan YH, Wang QM, Rui G, Zhang ZM (2013) Oncogenic potential of cyclin kinase subunit-2 in cholangiocarcinoma. Liver Int 33:137–148
Sherbet GV, Lakshmi MS (1998) S100A4 (MTS1) calcium binding protein in cancer growth, invasion and metastasis. Anticancer Res 18:2415–2421
Shimizu T, Yokomuro S, Mizuguchi Y, Kawahigashi Y, Arima Y, Taniai N, Mamada Y et al (2006) Effect of transforming growth factor-beta1 on human intrahepatic cholangiocarcinoma cell growth. World J Gastroenterol 12:6316–6324
Shimonishi T, Isse K, Shibata F, Aburatani I, Tsuneyama K, Sabit H, Harada K, Miyazaki K et al (2000a) Up-regulation of fas ligand at early stages and down-regulation of Fas at progressed stages of intrahepatic cholangiocarcinoma reflect evasion from immune surveillance. Hepatology 32:761–769
Shimonishi T, Sasaki M, Nakanuma Y (2000b) Precancerous lesions of intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 7:542–550
Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang YY, Wiangnon S, Sripa B et al (2010) Epidemiology of cholangiocarcinoma: an update focusing on risk factors. Cancer Sci 101:579–585
Shinozaki A, Shibahara J, Noda N, Tanaka M, Aoki T, Kokudo N, Fukayama M (2011) Claudin-18 in biliary neoplasms. Its significance in the classification of intrahepatic cholangiocarcinoma. Virchows Arch 459:73–80
Shirai T, Pairojkul C, Ogawa K, Naito H, Thamavit W, Bhudhisawat W, Ito N (1992) Histomorphological characteristics of cholangiocellular carcinomas in northeast Thailand, where a region infection with the liver fluke, *Opisthorchis viverrini* is endemic. Acta Pathol Jpn 42:734–739
Shoda J, Tanaka N, Osuga T (2003) Hepatolithiasis – epidemiology and pathogenesis update. Front Biosci 8:e398–e409
Sia D, Tovar V, Moeini A, Llovet JM (2013) Intrahepatic cholangiocarcinoma: pathogenesis and rationale for molecular therapies. Oncogene 32:4861–4870
Sibulesky L, Nguyen J, Patel T (2012) Preneoplastic conditions underlying bile duct cancer. Langenbecks Arch Surg 397:861–867
Sirica AE (2008) Role of ErbB family receptor tyrosine kinases in intrahepatic cholangiocarcinoma. World J Gastroenterol 14:7033–7058
Sirica AE, Lai GH, Endo K, Zhang Z, Yoon BI (2002) Cyclooxygenase-2 and ERBB-2 in cholangiocarcinoma: potential therapeutic targets. Semin Liver Dis 22:303–313
Soreide K, Soreide JA (2007) Bile duct cyst as precursor to biliary tract cancer. Ann Surg Oncol 14:1200–1211
Sorensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, Trichopoulos D et al (1998) Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology 28:921–925
Spencer KS, Graus-Porta D, Leng J, Hynes NE, Klemke RL (2000) ErbB2 is necessary for induction of carcinoma cell invasion by ErbB family receptor tyrosine kinases. J Cell Biol 148:385–397
Stähelin BJ, Marti U, Zimmermann H, Reichen J (1999) The interaction of Bcl-2 and Bax regulates apoptosis in biliary epithelial cells of rats with obstructive jaundice. Virchows Arch 434:333–339
Sturm PD, Baas IO, Clement MJ, Nakeeb A, Johan G, Offerhaus A, Hruban RH, Pitt HA (1998) Alterations of the p53 tumor-suppressor gene and K-ras oncogene in perihilar cholangiocarcinomas from a high-incidence area. Int J Cancer 78:695–698
Stutes M, Tran S, DeMorrow S (2007) Genetic and epigenetic changes associated with cholangiocarcinoma: from DNA methylation to microRNAs. World J Gastroenterol 13:6465–6469
Subrungruanga I, Thawornkunob C, Chawalitchewinkoon-Petmitrc P, Pairojkul C, Wongkham S et al (2013) Gene expression profiling of intrahepatic cholangiocarcinoma. Asian Pac J Cancer Prev 14:557–563
Sugimachi K, Taguchi K, Aishima S, Tanaka S, Shimada M, Kajiyama K, Sugimachi K et al (2001a) Altered expression of beta-catenin without genetic mutation in intrahepatic cholangiocarcinoma. Mod Pathol 14:900–905
Sugimachi K, Aishima S, Taguchi K, Tanaka S, Shimada M, Kajiyama K, Sugimachi K et al (2001b) The role of overexpression and gene amplification of cyclin D1 in intrahepatic cholangiocarcinoma. J Hepatol 35:74–79
Sugiwara H, Yasoshima M, Katayanagi K, Kono N, Watanabe Y, Harada K, Nakanuma Y (1998) Relationship between interleukin-6 and proliferation and differentiation in cholangiocarcinoma. Histopathology 33:145–153

Sun D, Yu F, Ma Y, Zhao R, Chen X, Zhu J, Zhang CY, Chen J, Zhang J (2013) MicroRNA-31 activates the RAS pathway and functions as an oncogenic MicroRNA in human colorectal cancer by repressing RAS p21 GTPase activating 1 (RASA1). J Biol Chem 288:9508–9518

Suto T, Habano W, Sugai T, Uesugi N, Funato O, Kanno S, Saito K, Nakamura (2000) Aberrations of the K-ras, p53, and APC genes in extrahepatic bile duct cancer. J Surg Oncol 73:158–163

Suto et al. (2002) Pub Med PMID 12168833

Suzuki Y, Mori T, Abe N, Sugiyama M, Atomi Y (2012) Predictive factors for cholangiocarcinoma associated with hepatolithiasis determined on the basis of Japanese multicenter study. Hepatol Res 42:166–170

Tabrizian P, Jibara G, Shrager B, Schwartz ME, Roayaie S (2012) Hepatic resection for primary hepatolithiasis: single-center Western experience. J Am Coll Surg 215:622–626

Tada M, Omata M, Ohto M (1992) High incidence of ras gene mutation in intrahepatic cholangiocarcinoma. Cancer 69:1115–1118

Taguchi K, Aishima S, Asayama Y, Kajiyama K, Kinukawa N, Shimada M, Sugimachi K et al (2001) The role of p27kip1 protein expression on the biological behavior of intrahepatic cholangiocarcinoma. Hepatology 33:1118–1123

Takatsuki M, Uemoto S, Inomata Y, Egawa H, Kiuchi T, Hayashi M, Ueda M, Tanaka K (2001) Living-donor liver transplantation for Caroli's disease with intrahepatic adenocarcinoma. J Hepatobiliary Pancreat Surg 8:284–286

Takei M, Yoda H, Kamijo N, Kawakami H, Hirabayashi K, Aizawa T, Simakura K, Kiyosawa K et al (1991) A case of Caroli's disease with hepatolithiasis, choledocholithiasis, and cholangiocarcinoma. Gastroenterol Jpn 26:224–229

Tang D, Nagano H, Yamamoto H, Wada H, Nakamura M, Kondo M, Ota H, Yoshioka S et al (2006) Angiogenesis in cholangiocellular carcinoma: expression of vascular endothelial growth factor, angiopoietin-1/2, thrombospondin-1 and clinicopathological significance. Oncol Rep 15:525–532

Taniai M, Grambihler A, Higuchi H, Werneburg N, Bronk SF, Farrugia DJ, Kaufmann SH et al (2004) Mcl-1 mediates tumor necrosis factor-related apoptosis-inducing ligand resistance in human cholangiocarcinoma cells. Cancer Res 64:3517–3524

Tanimura Y, Kokuryo T, Tsunoda N, Yamazaki Y, Oda K, Nimura Y, Naing MN et al (2005) Tumor necrosis factor alpha promotes invasiveness of cholangiocarcinoma cells via its receptor, TNFR2. Cancer Lett 219:205–213

Tannapfel A, Benicke M, Katalinic A, Uhlmann D, Köckerling F, Hauss J, Wittekind C (2000) Frequency of p16(INK4A) alterations and K-ras mutations in intrahepatic cholangiocarcinoma of the liver. Gut 47:721–727

Tannapfel A, Sommerer F, Benicke M, Weinans L, Katalinic A, Geissler F, Uhlmann D et al (2002) Genetic and epigenetic alterations oft he INK4a-ARF pathway in cholangiocarcinoma. J Pathol 197:624–631

Tannapfel A, Sommerer F, Benicke M, Katalinic A, Uhlmann D, Witzigmann H, Hauss J et al (2003) Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut 52:706–712

Tascilar M, Offerhaus GJ, Altink R, Argani P, Sohn TA, Yeo CJ, Cameron JL, Goggins M et al (2001) Immunohistochemical labeling for the Dpc4 gene product is a specific marker for adenocarcinoma in biopsy specimens of the pancreas and bile duct. Am J Clin Pathol 116:831–837

Taylor AC, Palmer KR (1998) Caroli's disease. Eur J Gastroenterol Hepatol 10:105–108

Techasen A, Namwat N, Loilome W, Bungkanjana P, Khuntikeo N, Puapairoi A, Jearanaikoon P et al (2012) Tumor necrosis factor-a (TNF-a) stimulates the epithelial-mesenchymal transition regulator Snail in cholangiocarcinoma. Med Oncol 29:3083–3091

Terada T, Nakanuma Y (1990) Pathological observations of intrahepatic peribiliary glands in 1000 consecutive autopsy livers. II. A possible source of cholangiocarcinoma. Hepatology 12:92–97

Terada T, Nakanuma Y (1992) Cell kinetic analyses and expression of carcinoembryonic antigen, carbohydrate antigen 19-9 and DU-PAN-2 in hyperplastic, pre-neoplastic and neoplastic lesions of intrahepatic bile ducts in livers with hepatoliths. Virchows Arch A Pathol Anat Histopathol 420:327–335

Terada T, Nakanuma Y (1996) Expression of apoptosis, proliferating cell nuclear antigen, and apoptosis-related antigens (bcl-2, c-myc, Fas, Lewis(y) and p53) in human cholangiocarcinomas and hepatocellular carcinomas. Pathol Int 46:764–770

Terada T, Kurumaya H, Nakanuma Y (1989) Intrahepatic cholesterol stones associated with peripheral cholangiocellular carcinoma: an autopsy case. Am J Gastroenterol 84:1434–1436

Terada T, Sasaki M, Nakanuma Y, Takeda Y, Masunaga T (1992) Hilar cholangiocarcinoma (Klatskin tumor) arising from intrahepatic peribiliary glands. J Clin Gastroenterol 15:79–81

Terada T, Shimizu K, Izumi R, Nakanuma Y (1994a) Methods in pathology. p53 expression in formalin-fixed, paraffin-embedded archival specimens of intrahepatic cholangiocarcinoma: retrieval of p53 antigenicity by microwave oven heating of tissue sections. Mod Pathol 7:249–252

Terada T, Kida T, Nakanuma Y, Kurumaya H, Dishita K, Takayanagi N (1994b) Intrahepatic cholangiocarcinomas associated with nonbiliary cirrhosis. A clinicopathologic study. J Clin Gastroenterol 18:335–342

Terada T, Okada Y, Nakanuma Y (1996) Expression of immunoreactive matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases in human normal livers and primary liver tumors. Hepatology 23:1341–1344

Terada T, Nakanuma Y, Sirica AE (1998a) Immunohistochemical demonstration of MET overexpression in human intrahepatic cholangiocarcinoma and in hepatolithiasis. Hum Pathol 29:175–180

Terada T, Ashida K, Endo K, Horie S, Maeta H, Matsunaga Y, Takashima K, Ohta T et al (1998b) c-erbB-2 protein is expressed in hepatolithiasis and cholangiocarcinoma. Histopathology 33:325–331

Terashi T, Aishima S, Taguchi K, Asayama Y, Sugimachi K, Matsuura S, Shimada M et al (2004) Decreased expression of osteopontin is related to tumor aggressiveness and clinical outcome of intrahepatic cholangiocarcinoma. Liver Int 24:38–45

Thummarati P, Wijitburaphat S, Prasopthum A, Menakongka A, Sripa B, Tohtong R et al (2012) High level of urokinase plasminogen activator contributes to cholangiocarcinoma invasion and metastasis. World J Gastroenterol 18:244–250

Tischoff I, Wittekind C, Tannapfel A (2006) Role of epigenetic alterations in cholangiocarcinoma. J Hepatobiliary Pancreat Surg 13:274–279

Tomimatsu M, Ishiguro N, Taniai M, Okuda H, Saito A, Obata H, Yamamoto M, Tahasaki K et al (1993) Hepatitis C virus antibody in patients with primary liver cancer (hepatocellular carcinoma, cholangiocarcinoma, and combined hepatocellular-cholangiocarcinoma) in Japan. Cancer 72:683–688

Torbenson M, Yeh MM, Abraham SC (2007) Bile duct dysplasia in the setting of chronic hepatitis C and alcohol cirrhosis. Am J Surg Pathol 31:1410–1413

Totkas S, Hohenberger P (2000) Cholangiocellular carcinoma associated with segmental Caroli's disease. Eur J Surg Oncol 26:520–521

Tozawa T, Tamura G, Honda T, Nawata S, Kimura W, Makino N, Kawata S, Sugai T et al (2004) Promoter hypermethylation of DAP-kinase is associated with poor survival in primary biliary tract carcinoma patients. Cancer Sci 95:736–740

Tullo A, D'Erchia AM, Honda K, Kelly MD, Habib NA, Saccone C, Sbisa E (2000) New p53 mutations in hilar cholangiocarcinoma. Eur J Clin Invest 30:798–803

Tyson GL, El-Serag HB (2011) Risk factors for cholangiocarcinoma. Hepatology 54:173–184

Ueki T, Hsing AW, Gao YT, Wang BS, Shen MC, Chng J, Deng J, Fraumeni JF, Rashid A (2004) Alterations of p16 and prognosis in biliary tract cancers from a population-based study in China. Clin Cancer Res 10:1717–1725

Uhm KO, Lee JO, Lee YM, Lee ES, Kim HS, Park SH (2010) Aberrant DNA methylation of integrin alpha4: a potential novel role for metastasis of cholangiocarcinoma. J Cancer Res Clin Oncol 136:187–194

Utispan K, Sonongbua J, Thuwajit P, Chau-In S, Pairojkul C, Wongkham S, Thuwajit C (2012) Periostin activates integrin a5b1 through a PI3K/AKT-dependent pathway in invasion of cholangiocarcinoma. Int J Oncol 41:1110–1118

Vernez M, Hutter P, Monnerat C, Halkic N, Gugerli O, Bouzourene H (2007) A case of Muir-Torre syndrome associated with mucinous hepatic cholangiocarcinoma and a novel germline mutation oft he MSH2 gene. Fam Cancer 6:141–145

Vianna MR, Gayotto LC, Telma R, Santos M, Alves VA, Fukushima J, de Britto T (1989) Intrahepatic bile duct changes in human hepatosplenic schistosomiasis mansoni. Liver 9:100–109

Vlachogiannakos J, Potamianos T, Triantos C, Makri I, Imvrios G, Patsiaoura K, Avgerinos A (2004) Monolobar Caroli's disease complicated by cholangiocarcinoma in a 70-year-old man, previously asymptomatic. Gastrointest Endosc 60:297–300

Volmer MW, Radacz Y, Hahn SA, Klein-Scory S, Stühler K, Zapatka M, Schmiegel W et al (2004) Tumor suppressor Smad4 mediates downregulation oft he anti-adhesive invasion-promoting matricellular protein SPARC: landscaping activity of Smad4 is revealed by a "secretome" analysis. Proteomics 4:1324–1334

Voss JS, Holteggard LM, Kerr SE, Barr Fritcher EG, Roberst LR, Gores GJ, Zhang J, Highsmith WE et al (2013) Molecular profiling of cholangiocarcinoma shows potential for targeted therapy treatment decisions. Hum Pathol 44:1216–1222

Wadsworth CA, Dixon PH, Wong JH, Chapman MH, Mckay SC, Sharif A, Spalding DR et al (2011) Genetic factors in the pathogenesis of cholangiocarcinoma. Dig Dis 29:93–97

Wakai T, Shirai Y, Sakata J, Korita PV, Matsuda Y, Takamura M, Ohashi R, Nagahashi M et al (2011) Alteration of p53-binding protein 1 expression as a risk factor for local recurrence in patients undergoing resection for extrahepatic cholangiocarcinoma. Int J Oncol 38:1227–1236

Wakai T, Shirai Y, Sakata J, Korita PV, Ajioka Y, Harakeyama K (2013) Early DNA damage response in residual carcinoma in situ at ductal stumps and local recurrence in patients undergoing resection for extrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 20:362–369

Wang AG, Yoon SY, Oh JH, Jeon YJ, Kim M, Kim JM, Byun SS, Yang JO, Kim JH et al (2006) Identification of intrahepatic cholangiocarcinoma related genes by comparison with normal liver tissues using expressed sequence tags. Biochem Biophys Res Commun 345:1022–1032

Wang P, Dong Q, Zhang C, Kuan PF, Liu Y, Jeck WR, Andersen JB, Jiang W, Savich GL et al (2013) Mutations in isocitrate dehydrogenase 1 and 2 occur frequently in intrahepatic cholangiocarcinomas and share hypermethylation targets with glioblastomas. Oncogene 32:3091–3100

Wang Z, Hou Y, Guo X, van der Voet M, Boxem M, Dixon JE, Chisholm AD, Jin Y (2013) The BAX-type cullin-RING E3 ligase and Hsp90 guard the protein quality of the SAX-3/Robo receptor in developing neurons. Neuron 79:903–916

Watanapa P, Watanapa WB (2002) Liver fluke-associated cholangiocarcinoma. Br J Surg 89:962–970

Wehbe H, Henson R, Meng F, Mize-Berge J, Patel T (2006) Interleukin-6 contributes to growth in cholangiocarcinoma cells by aberrant promoter methylation and gene expression. Cancer Res 66:10517–10524

Welzel TM, Mellemkjaer L, Gloria G, Sakoda LC, Hsing AW, Ghormli LE, Olsen JH et al (2007) Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case-control study. Int J Cancer 120:638–641

Winberg CD, Ranchod M (1979) Thorotrast induced hepatic cholangiocarcinoma and angiosarcoma. Hum Pathol 10:108–112

Wise C, Pilanthananond M, Perry BF, Alpini G, McNeal M, Glaser SS (2008) Mechanisms f biliary carcinogenesis and growth. World J Gastroenterol 14:2986–2989

Wisniewski B, Tordjman G, Tran Van Nhieu J, Bettan L, Courillon-Mallet A (2002) Cholangiocarcinoma developing in von Meyenburg complexes in haemochromatosis (in French). Gastroenterol Clin Biol 26:922–924

Wu T (2005) Cyclooxygenase-2 and prostaglandin signaling in cholangiocarcinoma. Biochim Biophys Acta 1755:135–150

Wu TT, Levy M, Correa AM, Rosen CB, Abraham SC (2009) Biliary intraepithelial neoplasia in patients without chronic biliary disease: analysis of liver explants with alcoholic cirrhosis, hepatitis C infection, and noncirrhotic liver diseases. Cancer 115:4564–4575

Wu ZF, Yang N, Li DY, Zhang HB, Yang GS (2013) Characteristics of intrahepatic cholangiocarcinoma in patients with hepatitis B virus infection: clinicopathologic study of resected tumours. J Viral Hepat 20:306–310

Xiong GP, Zhang JX, Gu SP, Wu YB, Liu JF (2012) Overexpression of ECM1 contributes to migration and invasion in cholangiocarcinoma cell. Neoplasma 59:409–415

Xu AM, Xian ZH, Zhang SH, Chen XF (2009) Intrahepatic cholangiocarcinoma arising in multiple bile duct hamartomas: report of two cases and review of the literature. Eur J Gastroenterol Hepatol 21:580–584

Xu L, Hausmann M, Dietmeier W, Kellermeier S, Pesch T, Stieber-Gunckel M, Lippert E et al (2010) Expression of growth factor receptors and targeting of EGFR in cholangiocarcinoma cell lines. BMC Cancer 10:302

Xu RF, Sun JP, Zhang SR, Zhu GS, Li LB, Liao YL, Xie JM, Liao WJ (2011a) KRAS and PIK3CA but not BRAF genes are frequently mutated in Chinese cholangiocarcinoma patients. Biomed Pharmacother 65:22–26

Xu J, Sasaki M, Harada K, Sato Y, Ikeda H, Kim JH, Yu E, Nakanuma Y (2011b) Intrahepatic cholangiocarcinoma arising in chronic advanced liver disease and the cholangiocarcinomatous component of hepatocellular carcinoma share common phenotypes and cholangiocarcinogenesis. Histopathology 59:1090–1099

Yamagiwa Y, Meng F, Patel T (2006) Interleukin-6 decreases senescence nd increases telomerase activity in malignant human cholangiocytes. Life Sci 78:2494–2502

Yamamoto M, Takasaki N, Nakano M, Saito A (1998) Minute nodular intrahepatic cholangiocarcinoma. Cancer 82:2145–2149

Yamamoto S, Kubo S, Hai S, Uenishi T, Yamamoto T, Shuto T, Takemura S, Tanaka H et al (2004) Hepatitis C virus infection as a likely etiology of intrahepatic cholangiocarcinoma. Cancer Sci 95:592–595

Yamato T, Sasaki M, Hoso M, Sakai J, Ohta H, Watanabe Y, Nakanuma Y (1998) Intrahepatic cholangiocarcinoma arising in congenital hepatic fibrosis: report of an autopsy case. J Hepatol 28:717–722

Yan XQ, Zhang W, Zhang BX, Liang HF, Zhang WG, Chen XP (2013) Inactivation of Smad4 is a prognostic factor in intrahepatic cholangiocarcinoma. Chin Med J (Engl) 126:3039–3043

Yang B, House MG, Guo M, Herman JG, Clark DP (2005) Promoter methylation profiles of tumor suppressor genes in intrahepatic and extrahepatic cholangiocarcinoma. Mod Pathol 18:412–420

Yasoshima M, Sato Y, Furubo S, Kizawa K, Sanzen T, Ozaki S, Harada K, Nakanuma Y (2009) Matrix proteins of basement membrane of intrahepatic bile ducts are degraded in congenital hepatic fibrosis and Caroli's disease. J Pathol 217:442–451

Yonem O, Bayraktar Y (2007) Clinical characteristics of Caroli's disease. World J Gastroenterol 13:1930–1933

Yoshida S, Todoroki T, Ichikawa Y, Hanai S, Suzuki H, Hori M, Fukao K, Miwa M et al (1995) Mutations of p16Ink4/CDKN2 and p15Ink4B/MTS2 genes in biliary tract cancers. Cancer Res 55:2756–2760

Yoshikawa D, Ojima H, Iwasaki M, Hiraoka N, Kosuge T, Kasai S, Hirohashi S, Shibata T (2008) Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. Br J Cancer 98:418–425

Yu TH, Yuan RH, Chen YL, Yang WC, Hsu HC, Jeng YM (2011) Viral hepatitis is associated with intrahepatic cholangiocarcinoma with cholangiolar differentiation and N-cadherin expression. Mod Pathol 24:810–819

Zen Y, Harada K, Sasaki M, Chen TC, Chen MF, Yeh TS, Jan YY, Huang SF, Nimura Y et al (2005a) Intrahepatic cholangiocarcinoma escapes from growth inhibitory effect of transforming growth factor-beta1 by overexpression of cyclin D1. Lab Invest 85:572–581

Zen Y, Aishima S, Ajioka Y, Haratake J, Kage M, Kondo F, Nimura Y, Sakamoto M et al (2005b) Proposal of histological criteria for intraepithelial atypical/ proliferative biliary epithelial lesions of the bile duct in hepatolithiasis with respect to cholangiocarcinoma: preliminary report based on interobserver agreement. Pathol Int 55:180–188

Zen Y, Adsay NV, Bardadin K, Colombari R, Ferrell L, Haga H, Hong SM, Hytiroglou P et al (2007) Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnosis criteria. Mod Pathol 20:701–709

Zen et al. (2006) Pub Med PMID 16360234

Zen Y, Quaglia A, Heaton N, Rela M, Portmann B (2011) Two distinct pathways of carcinogenesis in primary sclerosing cholangitis. Histopathology 59:1100–1110

Zeng B, Li Z, Chen R, Guo N, Zhou J, Zhou Q, Lin Q, Cheng D, Liao Q, Zheng L, Gong Y (2012) Epigenetic regulation of miR-124 by hepatitis C virus core protein promotes migration and invasion of intrahepatic cholangiocarcinoma cells by targeting SMYD3. FEBS Lett 586:3271–3278

Zhang L, Cai JQ, Zhao JJ, Bi XY, Tan XG, Yan T, Li C, Zhao P (2010) Impact of hepatitis B virus infection on outcome following resection for intrahepatic cholangiocarcinoma. J Surg Oncol 101:233–238

Zhang J, Han C, Wu T (2012) Micro-RNA-26a promotes cholangiocarcinoma growth by activating b-catenin. Gastroenterology 143:246–256

Zhang C, Bai DS, Huang XY, Shi GM, Ke AW, Yang LX, Yang XR, Zhou J, Fan J (2013) Prognostic significance of capn4 overexpression in intrahepatic cholangiocarcinoma. PLoS One 8:e54619

Zhao H, Davydova L, Mandich D, Cartun RW, Ligato S (2007) S100A4 protein and mesothelin expression in dysplasia and carcinoma of the extrahepatic bile duct. Am J Clin Pathol 127:374–379

Zheng J, Zhu YM (2007) Expression of c-erbB-2 proto-oncogene in extrahepatic cholangiocarcinoma and its clinical significance. Hepatobiliary Pancreat Dis Int 6:412–415

Zhong XY, Yu JH, Zhang WG, Wang ZD, Dong Q, Tai S, Cui YF, Li H (2012) MicroRNA-421 functions as an oncogenic miRNA in biliary tract cancer through down-regulating farnesoid X receptor expression. Gene 493:44–51

Zhou YM, Yin ZF, Yang JM, Li B, Shao WY, Xu F, Wang YL, Li DQ (2008) Risk factors for intrahepatic cholangiocarcinoma: a case-control study in China. World J Gastroenterol 14:632–635

Zhou XD, Tang ZY, Fan J, Zhou J, Wu ZO, Qin LX, Ma ZC, Sun HC, Qiu SJ et al (2009) Intrahepatic cholangiocarcinoma: report of 272 patients compared with 5829 patients with hepatocellular carcinoma. J Cancer Res Clin Oncol 135:1073–1080

Zhou H, Wang H, Zhou D, Wang H, Wang Q, Zou S, Tu Q, Wu M, Hu H (2010) Hepatitis B virus-associated intrahepatic cholangiocarcinoma and hepatocellular carcinoma may hold common disease process for carcinogenesis. Eur J Cancer 46:1056–1061

Zhou HB, Wang H, Li YQ, Li SX, Wang H, Zhou DX, Tu QQ, Wang Q, Zou SS et al (2011) Hepatitis B virus infection: a favorable prognostic factor for intrahepatic cholangiocarcinoma after resection. World J Gastroenterol 17:1292–1303

Zhou Y, Zhao Y, Li B, Huang J, Wu L, Xu D, Yang J, He J (2012) Hepatitis viruses and risk of intrahepatic cholangiocarcinoma: evidence from a meta-analysis. BMC Cancer 12:289

Zhou Q, Wang Y, Peng B, Liang L, Li J (2013) The roles of Notch1 expression in the migration of intrahepatic cholangiocarcinoma. BMC Cancer 13:244

Zhou HB, Hu JY, Hu HP (2014a) Hepatitis B virus infection and intrahepatic cholangiocarcinoma. World J Gastroenterol 20:5721–5729

Zhou SL, Dai Z, Zhou ZJ, Chen Q, Wang Z, Xiao YS, Hu ZQ, Huang XY, Yang GH, Shi YH, Qiu SJ et al (2014b) CXCL5 contributes to tumor metastasis and recurrence of intrahepatic cholangiocarcinoma by recruiting infiltrative intratumoral neutrophils. Carcinogenesis 35:597–605

Zhu AX, Lauwers GY, Tanabe KK (2004) Cholangiocarcinoma in association with Thorotrast exposure. J Hepatobiliary Pancreat Surg 11:430–433

Pediatric and Adolescent Cholangiocarcinoma and Related Lesions

32

Contents

Abstract

Bile duct cancers similar to those of adult patients also develop in the pediatric age group, but pediatric cholangiocarcinoma is a very rare condition in infants and children. The neoplasms become slightly more common in adolescents. Pediatric cholangiocarcinoma is usually associated with congenital hepatobiliary disorders, including congenital biliary dilatation and choledochal cysts, congenital pancreaticobiliary maljunction, and congenital biliary atresia. Cholangiocarcinoma can also develop in individuals who suffered from primary sclerosing cholangitis in childhood and in adolescents following pediatric-onset inflammatory bowel disease.

Introduction

Pediatric cholangiocarcinoma (PA-CC) is one of the rarest primary cancers of the biliary tract in infants and children. The tumor becomes slightly more common in adolescents and young adults, significantly associated with primary sclerosing cholangitis in this age group (Klein et al. 2005; Björnsson and Angulo 2007). In children, both PA-CCs of the extra- and intrahepatic bile ducts have been described. Probably the first example of intrahepatic PA-CC was reported in 1922 (Dansie and Eng 1922). PA-CC either develops without obvious predisposition or identifiable cause or arises in the setting of congenital or acquired hepatobiliary disorders.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_32

Pediatric Cholangiocarcinoma Not Associated with Hepatobiliary Disorders

Less than five cases of this unusual tumor have been reported (Dansie and Eng 1922; Imai et al. 1995; Andiran et al. 1997), but pathology reviews in the setting of trials of pediatric liver tumors have identified several cases that have not been published (own observations). In one patient, CC was diagnosed 12 years after pediatric liver transplantation (Channabasappa et al. 2010).

Pediatric Cholangiocarcinoma Associated with Congenital Hepatobiliary Disorders

Congenital Biliary Dilatation and Choledochal Cysts

Congenital biliary dilatation (CBD) is probably the most frequent cause of cholangiocarcinoma developing in childhood and young adult age (Iwai et al. 1990; Kuriyama et al. 1997; Tanaka et al. 2006; Nakamura et al. 2008; Saikusa et al. 2009; Ono et al. 2010). In adults, CBD is highly associated with hepatobiliary malignancies (Dexter 1957; Young et al. 1992; Tsuchida et al. 2003; Ono et al. 2008), and CBD-associated chronic mucosal lesions appear to be a strong driving force for the development of CC in young individuals. In a review of 11 cases, seven were male and five female, with an age range at diagnosis of 11–19 years (Tanaka et al. 2006). PA-CC was also found in a 3-year-old Japanese boy with Todani type 1a congenital biliary dilatation. The histology revealed well-differentiated tubular adenocarcinoma with lymphovascular invasion (Saikusa et al. 2009). A second very young patient was an 11-year-old Japanese boy with Todani type IV-A congenital biliary dilatation. The tumor was situated in the dilated choledochal duct, and dilatation was associated with pancreaticobiliary maljunction. Nodal metastasis was found in one of the mesenteric lymph nodes, and vascular invasion was detected in the region of the primary tumor (Tanaka et al. 2006). A 14-year-old girl died of recurrent PA-CC of the common bile duct 2 years after the initial resection of a choledochal cyst (Ono et al. 2010). The pathogenesis of CBD-associated cholangiocarcinoma is not fully established, but it was shown that bile from choledochal cysts exerts a proliferative activity on human cholangiocarcinoma cells through a COX-2 and PGE(2) pathway (Wu et al. 2003).

Congenital Pancreaticobiliary Maljunction

Congenital pancreaticobiliary maljunction (CPBM) or anomalous pancreaticobiliary ductal union is a disorder causing pancreaticobiliary reflux. CPBM is associated with an increased risk of cholangiocarcinoma in adults and children (Kobayashi et al. 1999; Ono et al. 2011). It has been suggested that reflowing pancreatic juice admixed with bile can exert a pro-proliferative effect on biliary epithelia, e.g., documented in the gallbladder mucosa (Ono et al. 1999; Tanno et al. 1999). Cholangiocarcinoma may develop early in patients with CPBM, mainly in those with associated cystic bile duct dilatation, e.g., at 13 years (Ueda et al. 2000) or 15 years of age (Nakamura et al. 2008).

Congenital Biliary Atresia

An 11-year-old girl was diagnosed with PA-CC in association with secondary biliary cirrhosis due to congenital biliary atresia (Kulkarni and Beatty 1977). Among 157 patients with biliary atresia who had been followed-up after Kasai's operation, 13 developed liver tumors, including one cholangiocarcinoma (Yoon et al. 2014).

Congenital Metabolic Disorders

Intrahepatic PA-CC developed in two girls with progressive familial intrahepatic cholestasis

caused by mutations of the bile salt export pump ABCB11. It was proposed that bile composition shifts or bile acid damage of cells might be significant factors for biliary carcinogenesis in this disorder (Scheimann et al. 2007).

Pediatric Cholangiocarcinoma Associated with Acquired Hepatobiliary Disorders

Primary sclerosing cholangitis (PSC) is a well-known risk factor for the development of cholangiocarcinoma, and carcinogenesis proceeds along a dysplasia-carcinoma sequence in at least part of adult patients (Ahrendt et al. 1999). In a study from Utah, PA-CC was detected in follow-up in 6.9 % of children with primary sclerosing cholangitis (Deneau et al. 2013). Rarely, cholangiocarcinoma already arises in young individuals, e.g., at age 15–18 years (Deneau et al. 2011; Lai et al. 2012; Liu et al. 2014). Cholangiocarcinoma was also found in small duct sclerosing cholangitis (Lai et al. 2012). PA-CC in adolescents was also observed following pediatric-onset inflammatory bowel disease (Peneau et al. 2013).

Pathology

PA-CC histologically shows patterns that are known for adult-type cholangiocarcinomas (Figs. 1, 2, and 3), an observation that has however been reported only few times. Dansie and Eng (1922) described a 10-week-old male infant with a primary liver malignancy. At autopsy, the liver was mottled with purplish areas, and these areas varied from a mere spot to about 0.25 in. in diameter. Histologically, the tumor is rich in stroma, with an epithelial tumor cell population forming retiform strands which had infiltrated the parenchyma. Some of the strands showed an open center, and the cells resembled bile duct cells. An own observation revealed a classical desmoplastic cholangiocarcinoma with the typical hypocellular, desmoplastic/sclerosing stroma, and atypical glands composed of neoplastic, CK-9-positive cholangiocytes.

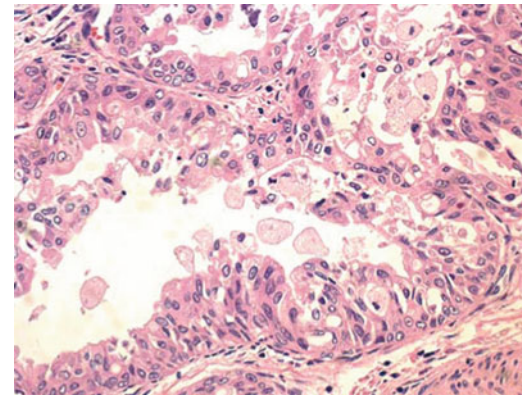

Fig. 1 Pediatric cholangiocarcinoma. Enlarged tubular structures are lined with atypical columnar cells with signs of tumor cell shedding (hematoxylin and eosin stain)

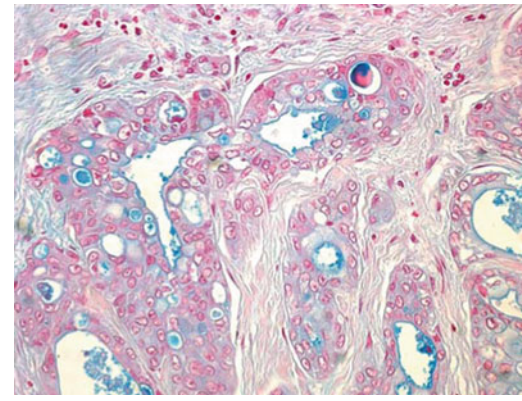

Fig. 2 Pediatric cholangiocarcinoma. This tumor exhibits marked mucin production, mostly with intracellular mucin accumulation (alkaline Alcian blue stain)

Alpha-Fetoprotein (AFP)-Producing Pediatric Cholangiocarcinoma

AFP-producing cholangiocarcinoma is a very rare variant of cholangiocarcinoma in adult patients, characterized by aberrant synthesis and secretion of AFP by biliary carcinoma cells. The tumors are usually of the desmoplastic variant. We observed

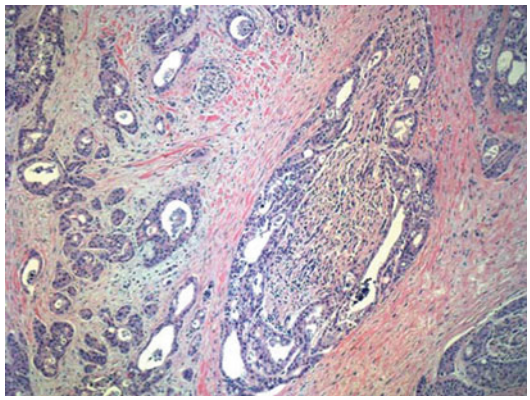

Fig. 3 Pediatric cholangiocarcinoma with perineural invasion (hematoxylin and eosin stain)

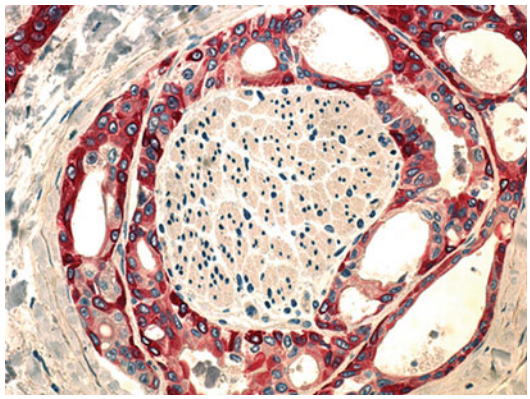

Fig. 4 Pediatric cholangiocarcinoma, alpha-fetoprotein (AFP)-expressing variant. AFP-reactive cancer cells have invaded a perineural space (AFP immunostain)

one small child with such an unusual tumor (Fig. 4).

Pediatric Biliary Papillomatosis

Biliary papillomatosis is a rare condition of the biliary tract in adults, known to transform into cholangiocarcinoma in part of the patients (see the respective chapter). Exceptionally, multiple biliary papillomatosis occurs in children (Bines et al. 1992). Papilloma of the ampulla of Vater was observed in an infant (Shabot et al. 1975).

References

Ahrendt SA, Pitt HA, Nakeeb A, Klein AS, Lillemoe KD, Kalloo AN, Cameron JL (1999) Diagnosis and management of cholangiocarcinoma in primary sclerosing cholangitis. J Gastrointest Surg 3:357–367

Andiran F, Tanyel FC, Kale G, Akhan O, Akçören Z, Hiçsönmez A (1997) Obstructive jaundice resulting from adenocarcinoma of the ampulla of Vater in an 11-year-old boy. J Pediatr Surg 32:636–637

Bines JE, Shamberger RC, Perez-Atayde A, Rosenberg SJ, Winter HS (1992) Multiple biliary papillomatosis in a child. J Pediatr Gastroenterol Nutr 14:309–313

Björnsson E, Angulo P (2007) Cholangiocarcinoma in young individuals with and without primary sclerosing cholangitis. Am J Gastroenterol 102:1677–1682

Channabasappa N, Johnson-Welch S, Mittal N (2010) De novo cholangiocarcinoma after liver transplantation in a pediatric patient. Pediatr Transplant 14:E110–E114

Dansie CB, Eng MRCS (1922) Primary malignant growth of the liver in infants. Lancet I:228–229

Deneau M, Adler DG, Schwartz JJ, Hutson W, Sorensen J, Book L, Lowichik A, Guthery S (2011) Cholangiocarcinoma in a 17-year-old boy with primary sclerosing cholangitis and inflammatory bowel disease. J Pediatr Gastroenterol Nutr 52:617–620

Deneau M, Jensen MK, Holmen J, Williams MS, Book LS, Guthery SL (2013) Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. Hepatology 58:1392–1400

Dexter D (1957) Choledochal cyst with carcinoma of the intrahepatic bile ducts and pancreatic ducts. Br J Cancer 11:18–25

Imai Y, Oda H, Nakatsuru Y, Ishikawa T (1995) A polymorphism at codon 160 of human O6-methylguanine-DNA methyltransferase gene in young patients with adult type cancers and functional assay. Carcinogenesis 16:2441–2445

Iwai N, Deguchi E, Yanagihara J (1990) Cancer arising in a choledochal cyst in a 12-year-old girl. J Pediatr Surg 25:1261–1263

Klein WM, Molmenti EP, Colombani PM, Grover DS, Schwarz KB, Boitnott J, Torbenson MS (2005) Primary liver carcinoma arising in people younger than 30 years. Am J Clin Pathol 124:512–518

Kobayashi S, Asano T, Yamasaki M, Kenmochi T, Nakagohri T, Ochiai T (1999) Risk of bile duct carcinogenesis after excision of extrahepatic bile ducts in pancreaticobiliary maljunction. Surgery 126:939–944

Kulkarni PB, Beatty E (1977) Cholangiocarcinoma associated with biliary cirrhosis due to congenital biliary atresia. Am J Dis Child 131:442–444

Kuriyama Y, Kawamura K, Enomoto H et al (1997) Biliary carcinoma associated with choledochal cyst in a 15-year-old girl. Jpn J Pediatr Surg 32:314–318

Lai J, Taouli B, Iyer KR, Arnon R, Thung SN, Magid MS, Kerkar N (2012) Cholangiocellular carcinoma in a

pediatric patient with small duct sclerosing cholangitis: a case report. Semin Liver Dis 32:360–366

Liu R, Cox K, Guthery SL, Book L, Witt B, Chadwick B, Adler DG (2014) Cholangiocarcinoma and high-grade dysplasia in young patients with primary sclerosing cholangitis. Dig Dis Sci 59:2320–2324

Nakamura H, Katayose Y, Rikiyama T, Onogawa T, Yamamoto K, Yoshida H, Hayashi H, Ohtsuka H, Hayashi Y et al (2008) Advanced bile duct carcinoma in a 15-year-old patient with pancreaticobiliary maljunction and congenital biliary cystic disease. J Hepatobiliary Pancreat Surg 15:554–559

Ono et al. 2008. Pub Med PMID 18558159

Ono S, Tokiwa K, Iwai N (1999) Cellular activity in the gallbladder of children with anomalous arrangement of the pancreaticobiliary duct. J Pediatr Surg 34:962–966

Ono S, Fumino S, Shimadera S, Iwai N (2010) Long-term outcomes after hepaticojejunostomy for choledochal cyst: a 10-to 27-year follow-up. J Pediatr Surg 45:376–378

Ono S, Fumino S, Iwai N (2011) Diagnosis and treatment of pancreaticobiliary maljunction in children. Surg Today 41:601–605

Peneau A, Savoye G, Turck D, Dauchet L, Fumery M, Salleron J, Lerebours E, Ligier K et al (2013) Mortality and cancer in pediatric-onset inflammatory bowel disease: a population-based study. Am J Gastroenterol 108:1647–1653

Saikusa N, Naito S, Iinuma Y, Ohtani T, Yokoyama N, Nitta K (2009) Invasive cholangiocarcinoma identified in congenital biliary dilatation in a 3-year-old boy. J Pediatr Surg 44:2202–2205

Scheimann AO, Strautnieks SS, Knisely AS, Byrne JA, Thompson RJ, Finegold MJ (2007) Mutations in bile salt export pump (ABCB11) in two children with progressive familial intrahepatic cholestasis and cholangiocarcinoma. J Pediatr 150:556–559

Shabot MM, Asch MJ, Moore TC, State D (1975) Benign obstructing papilloma of the ampulla of Vater in infancy. Surgery 78:560–563

Tanaka S, Kubota M, Yagi M, Okuyama N, Ohtaki M, Yamazaki S, Hirayama Y, Kurosaki I, Hatakeyama K (2006) An 11-year-old male patient demonstrating cholangiocarcinoma associated with congenital biliary dilatation. J Pediatr Surg 41:e15–e19

Tanno S, Obara T, Fujii T, Mizukami Y, Yanagawa N, Izawa T, Ura H, Kohgo Y (1999) Epithelial hyperplasia of the gallbladder in children with anomalous pancreaticobiliary ductal union. Hepatogastroenterology 46:3068–3073

Tsuchida A, Kasuya K, Endo M, Saito H, Inoue K, Nagae I, Aoki T, Koyanagi Y (2003) High risk of bile duct carcinogenesis after primary resection of a congenital biliary dilatation. Oncol Rep 10:1183–1187

Ueda J, Neduka H, Yamamoto S et al (2000) A case of pancreaticobiliary maljunction associated with congenital bile duct dilatation with early bile duct cancer in a 13-year-old girl (in Japanese). J Biliary Tract Pancreas 21:593–597

Wu GS, Zou SQ, Luo XW, Wu JH, Liu ZR (2003) Proliferative activity of bile from congenital choledochal cyst patients. World J Gastroenterol 9:184–187

Yoon HJ, Jeon TY, Yoo SY, Kim JH, Eo H, Lee SK, Kim JS (2014) Hepatic tumours in children with biliary atresia: single-centre experience in 13 cases and review of the literature. Clin Radiol 69:e113–e119

Young WT, Thomas GV, Blethyn AJ, Lawrie BW (1992) Choledochal cyst and congenital anomalies of the pancreatico-biliary junction: the clinical findings, radiology and outcome in nine cases. Br J Radiol 65:33–38

Intraductal Neoplasms of the Biliary Tract

33

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_33

Abstract

Intraductal papillary neoplasm of the bile duct (IPN-B) is a rare epithelial bile duct tumor characterized by a predominantly papillary growth pattern, a phase of intraluminal noninvasive growth, and a later high risk of transition into invasive cholangiocarcinoma. A recently proposed more general term is intraductal neoplasm of the bile duct (IN-B), because not all of these neoplasms are papillary lesions. IPN-B is now regarded as the biliary counterpart of intraductal mucinous papillary neoplasm of the pancreas. Histologically, the majority of IPN-Bs exhibit a papillary or tubulopapillary morphology, but a rarer variant is characterized by a tubular morphology. A mucinous phenotype, which is regularly found in pancreatic intraductal neoplasms, is not a constant finding in IPN-B. IPN-B lesions undergo dysplastic changes, divided into four groups, i.e., low-grade dysplasia, high-grade dysplasia, carcinoma in situ, and IPN-B associated with invasive carcinoma. In analogy to pancreatic lesions, IPN-B is subclassified into branch duct type, main duct type, and mixed type. Distinct epithelial changes developing in peribiliary glands are considered as precursor lesions of IPN-B.

ICD-O codes

IPN with low- or intermediate-grade intraepithelial neoplasia	8503/0
IPN with high-grade intraepithelial neoplasia	8503/2
IPN with associated invasive carcinoma	8503/3

Introduction

Intraductal neoplasm of the bile duct (IPN-B) is a group of neoplasms presenting with a complex spectrum ranging from preneoplastic lesions to noninvasive and invasive carcinomas, whereby the invasive phenotype of the papillary form of intraductal neoplasm in many or most cases appears to correspond to the previous intraductal growth intrahepatic cholangiocarcinoma (IG-ICC) (see the chapter of intrahepatic cholangiocarcinoma).

Intraductal neoplasm of the bile duct (IPN-B) is a rare epithelial bile duct tumor characterized by a predominantly papillary growth pattern, intraluminally growing in a first phase of evolution, but a high risk of transition into invasive carcinoma. IPN-B in part mimics intraductal mucinous papillary neoplasm (IPMN) of the pancreas and has previously been described under several terms (mucin-hypersecreting bile duct tumor or mucin-secreting bile duct adenoma, intraductal papillary neoplasm (IPN), intraductal papillary mucinous neoplasm of the bile duct (IPMN-B)). A distinct clinicopathologic pattern of intrahepatic mucin-producing cholangiocarcinomas, characterized by a cystic or ductectatic presentation, has been described by Okamoto and coworkers (Sakamoto et al. 1999). Intraductal neoplasms of the bile ducts are now accepted to be the biliary counterpart of the long-known pancreatic intraductal neoplasms (Klöppel and Kosmahl 2006). Both types of neoplasms share a predominantly exophytic macroscopic growth pattern with a tendency to fill the involved ducts, histologically a papillary or tubulopapillary growth pattern, and the development of dysplastic changes that can result in invasive carcinoma (Aishima et al. 2014). However, one rare variant is characterized by a tubular morphology rather than a papillary growth pattern (review: Nakanuma et al. 2010a).

Selected References Kim et al. 2000; Chen et al. 2001; Chung et al. 2001; Nakanuma et al. 2002, 2010a; Oshikiri et al. 2002; Shibahara et al. 2004; Yeh et al. 2004; Aoki et al. 2005; Zen et al. 2006a, 2011; Yamashita et al. 2007; Ji et al. 2008; Crippa and Falconi 2012; Lapsia 2012; Rocha et al. 2012; Xu et al. 2012; Yang et al. 2012; Klöppel et al. 2013; Minagawa et al. 2013; Wan et al. 2013; and Ohtsuka et al. 2014.

Definitions and Classifications

According to the recent WHO classification, these tumors are termed intraductal papillary neoplasms of the bile duct (IPN-B). The concept of IPN-B was first proposed by Chen et al. (2001) and Nakanuma et al. (2002). IPN-B includes the

previous categories of biliary papilloma and papillomatosis and other forms of intraductal neoplasms with a papillary or tubular phenotype and is characterized by dilated intrahepatic bile ducts containing a noninvasive papillary, villous, tubulopapillary, or tubular biliary neoplasm.

A recently proposed, more general term is intraductal neoplasm of the bile duct (IN-B). IN-B is usually found in the intrahepatic bile ducts, but similar lesions also occur in the hilar/perihilar and extrahepatic bile ducts. IN-B is further subdivided into the most common papillary form (intraductal papillary neoplasm of the bile duct, sensu stricto IPN-B), intraductal tubular neoplasm of the bile duct (ITN-B), and a rare form characterized by extensive spread along the luminal surface of intrahepatic bile ducts (superficial spreading type of IN-B; Nakanuma et al. 2010a). For reasons of comparison of literature data, the term IPN-B will be employed in this chapter throughout.

As the mucinous phenotype regularly found in pancreatic intraductal neoplasms (IPMN) is not a constant feature in the biliary tract counterpart, papillary biliary lesions are more often termed IPN with an added "B" for biliary tract or "L" for liver (IPN-B and IPN-L, respectively), whereby IPN-B is more commonly used now. As specified above, a term covering all variants of intraductal lesions has also been proposed, i.e., intraductal neoplasm of the bile duct (IN-B). IPN-B usually shows intraductal intraepithelial spread involving large to small bile ducts. The cell types of hepatobiliary tract IPN present with four main cell lineages, namely, a pancreatobiliary type, an intestinal type, an oncocytic type, and a gastric type (Shibahara et al. 2004; Nakanuma 2010). Furthermore, both types of intraductal neoplasms give rise to morphologically similar invasive carcinomas, i.e., ductal adenocarcinoma in the pancreas and intrahepatic cholangiocarcinoma of the intraductal growth type (ID-ICC) in the liver. The dysplastic changes developing in IPN have been divided into four groups, i.e., IPN with low-grade dysplasia (group 1), IPN with high-grade dysplasia (group 2), IPN lined with carcinoma in situ and no or only microinvasion (group 3), and IPN associated with distinct invasive carcinoma (group 4).

Table 1 Classification of intraductal neoplasms of intrahepatic bile ducts

Intraductal papillary neoplasm of the bile duct (IPN-B)
IPN-B with low- or intermediate-grade intraepithelial neoplasia
IPN-B with high-grade intraepithelial neoplasia
IPN-B associated with mucosa-confined carcinoma
IPN-B associated with invasive carcinoma (intraductal growth intrahepatic cholangiocarcinoma, ID-ICC)
Intraductal tubular neoplasm of the bile duct (ITN-B)
Intraductal neoplasm of the bile duct, superficial spreading type
Variant forms

In analogy to pancreatic lesions, IPN-Bs have been subclassified into branch duct type, main duct type, and mixed type (Lim et al. 2011a; Nakanishi et al. 2011; Fujita et al. 2013; Kato et al. 2013). In all reported cases, cystic or papillary lesions were present in peribiliary glands. Lim and coworkers (2011b) reported that certain types of cystic IPN-Bs that originate from peribiliary glands are considered to be a counterpart of the branch duct type of pancreatic IPMN. More recently, cystic and micropapillary epithelial changes of peribiliary glands have been studied in detail and proposed to represent a precursor lesion of IPN-B, including the branch duct type (Sato et al. 2014). The subclassification into duct types may have an impact on the biology of disease, as IPN of the branch duct type had no malignant component, had limited wall invasion, and were not associated with lymph node metastasis, while all patients with main duct and mixed duct types IPN-B had a malignant component (Kato et al. 2013).

A proposal of a classification is shown in Table 1.

Intraductal Papillary Neoplasm of the Bile Ducts: Relationship to Cholangiocarcinoma with Intraductal Growth

IPN-B as an emerging tumor category may be confounded by what is or was termed intraductal growth type of intrahepatic cholangiocarcinoma

(IG-ICC) or biliary tract carcinoma of papillary growth (BTC-PG). In fact, IPN-B with a marked invasive component may show a marked overlap with intraductal growth cholangiocarcinoma. It has been proposed that among the intraductal growth type of intrahepatic cholangiocarcinoma and papillary carcinoma of extrahepatic bile ducts, cases with a clearly intraductal component consisting of papillary fronds with fine vascular cores are exclusively included in IPN-B (Ohtsuka et al. 2014). There is evidence that the two lesion groups are related, in that IPN-B is a precursor lesion of invasive intraductal carcinomas. A recent clinicopathologic study has shown that in fact a majority of IG-ICC and BTC-PG could be regarded as an IPN-B lineage (Nakanuma et al. 2014a,b).

Epidemiology

Probably due to improved diagnostic techniques and increased awareness, the frequency of diagnosis for pancreatic IPN has increased during the last years (Klibansky et al. 2012; Zen et al. 2014). Whether this will turn out to also be the case for biliary tract IPN (IPN-B) remains to be demonstrated. Overall, IPN-B is mainly observed in Far Eastern areas, including Japan, Korea, and Taiwan, and regions with an elevated incidence of hepatolithiasis and liver fluke infestations, specifically clonorchiasis (Nakanuma et al. 1988; Wan et al. 2013). IPN-B is mainly diagnosed in individuals of 50–70 years of age, with a male-to-female ratio that varies somewhat from one area to another. While in Japan the two sexes are equally affected, patients from Korea and Western countries are twice as often males than females, whereas the inverse exists in Taiwan. IPN-B is more common than mucinous cystic neoplasms of the liver (MCN-L) of the hepatobiliary tract. In a retrospective Asian comparative pathology study, the ratio between IPN-B and MCN-L was 5.7:1 (Zen et al. 2014). The tumor has also been observed in the setting of *Clonorchis sinensis* infestation (Jang et al. 2008) and of primary sclerosing cholangitis (Hachiya et al. 2014). Other and rare associations, such as gallbladder agenesis (Kim et al. 2012b), are likely to be coincidental.

IN-B with or without associated invasive carcinoma can occur in conjunction with other neoplastic disease, mainly including synchronous intraductal papillary tumors of the pancreas (Joo et al. 2000; Ishida et al. 2002; Zalinski et al. 2007; Valente et al. 2012), metachronous intracystic papillary tumor of the gallbladder (Sato et al. 2013), mucinous cystic neoplasm of the liver (Budzynska et al. 2014), and rarely other neoplasms, such as hepatocellular carcinoma (Xu et al. 2011) and adenoneuroendocrine carcinoma (Onishi et al. 2013).

General Clinical and Imaging Features

As IPN causes significant bile duct disease due to luminal obstruction, many patients are symptomatic at presentation, but asymptomatic disease is also reported, and incidental detection in up to 20 % of patients is known (Hayashi et al. 2008; Paik et al. 2008). In few patients, IPN only manifests as dilatation of lobar or segmental bile ducts (Lim et al. 2008). Intraluminal tumor growth, excessive mucin discharge into the ducts, and tumor tissue sludge can cause biliary obstruction and cholestatic jaundice (Verma et al. 2009). The abundance of mucin secretion and hence the frequency of mucin-related sequelae depend on the histologic type of IPN, mucin hypersecretion being more common in patients with intestinal or gastric-type lesions than pancreatobiliary or oncocytic-type lesions (Kim et al. 2012a).

Radiologically, there may few to multiple tumors along the bile ducts which are dilated due to obstruction by tumor tissue, secreted mucin, and/or sludged tumor debris. Debris and mucin plugs may be confounded with bile duct stones (Lim et al. 2002, 2008; Carrafiello et al. 2008; Nanashima et al. 2008a; Lim and Jang 2010; Wan et al. 2013; Yoon et al. 2013; Bal et al. 2014). In one study, bile duct dilatation was found in 92 % of patients (Paik et al. 2008). Cystic lesions contain enhancing or non-enhancing solid parts (Martin et al. 2002),

and on CT images, the mass can present as hypodense lesions in comparison with the surrounding tissue during the basal phase and with a light peripheral enhanced rim in the arterial phase, increasing in the portal venous phase, while in late phase, the lesions displayed a punctate aspect due to the presence of intratumoral hypervascular spots (Carrafiello et al. 2008; Ogawa et al. 2012). On CT images, cystic variants of IPN-B can be distinguished from mucinous cystic tumors mainly by the presence of mural nodules and dilatation of the bile ducts distal to the cystic tumor (Lim et al. 2007). ERCP is useful in diagnosis and localization of IPN-B (Pavone et al. 1997; Somogyi et al. 2003). Carcinoma arising from IPN-B can produce a circumscribed mass appeared as an impacted stone on ERCP (Ustundag et al. 2006). Cholangiographically, several patterns of IPN-B mainly seen in East Asian patients have been described, based on the presence of hepatolithiasis and associated strictures, mucobilia, and localization of neoplasias (Yeh et al. 2006). Biliary IPN is detectable on fluorodeoxyglucose positron emission tomography (Inoue et al. 2009; Dong et al. 2012) and by direct cholangioscopy (Somogyi et al. 2003; Tsuyuguchi et al. 2010; Lim et al. 2011; Zou et al. 2011; D'souza et al. 2013).

Pathology of Intraductal Papillary Neoplasm of the Bile Ducts (IPN-Bs)

Introduction

IPN-B is the most common form of IN-B and is the first intraductal papillary lesion mimicking the pancreatic counterpart that has been described. Clinicopathologically, IPN-B is classified into several subtypes (Table 2).

The papillomatosis or papilloma type covers a majority of those lesions that have previously been classified as biliary papillomatosis and solitary bile duct papilloma. It appears, however, not yet settled whether all cases of "biliary papillomatosis" described in the older literature completely fit into the novel concept of IPN-B, as there are certain morphologic differences in part of the cases. This issue is therefore addressed in a later paragraph. The intraductal growing type of IPN-B is the "standard variant" and is described in more detail below. The mucin-producing type (M-IPN-B) is less common and often closely mimics its mucinous counterpart of the pancreas. Similar to the pancreas, the mucinous type of IPN-B can produce copious amounts of mucin that is secreted into the bile duct lumen and causes mucobilia and bile duct obstruction, bile duct dilatation, and eventually discharge of mucin through the orificium of the common bile duct. The cystic type is a distinct phenotype of biliary cystic tumor with a bile duct communication, in contrast to hepatobiliary mucinous cystic neoplasms that do not communicate with the biliary system.

Table 2 Clinicopathologic classification of intraductal papillary neoplasm of the bile ducts (IPN-Bs) (Nakanuma et al. 2010a)

Papillomatosis or papilloma type
Intraductal growing type
Mucin-producing type (mucin-producing IPN-B; M-IPN-B)
Cystic type

Macroscopy

Macroscopically, IPN-B is characterized by intraductal growths of soft, friable tissue with granular surface caused by the tips of multiple papillary structures (Figs. 1, 2, and 3). The presentation of the lesions was described as polypoid, cast-like intraductal growth, and cyst forming (Nanashima et al. 2008a; Kim et al. 2011). The lesions occur as solitary or multiple tumors of grayish, tan, or yellowish color. Markedly papillary growths are whitish, red, or tan, depending on the presence and amounts of hemorrhage and/or necrosis. These masses may fill the ducts and cause dilated ducts that are fusiform or cystic, in an unilocular or multilocular pattern. IPN-Bs develop in one or multiple intrahepatic ducts, in the hilar duct area, and/or in the extrahepatic bile

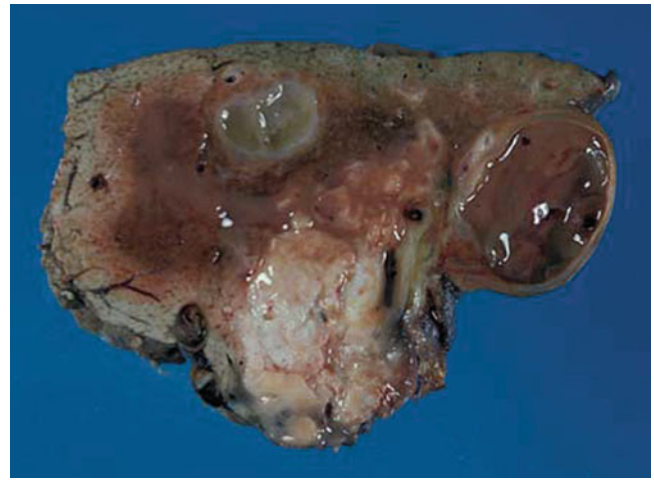

Fig. 1 IPN-B. The dilated bile duct is filled with an exophytically growing tumor. Dilated bile duct segment contain mucus

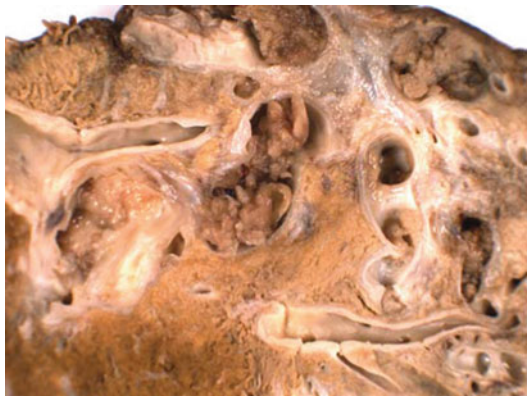

Fig. 2 IPN-B. Exophytic tumor masses in several dilated intrahepatic bile ducts

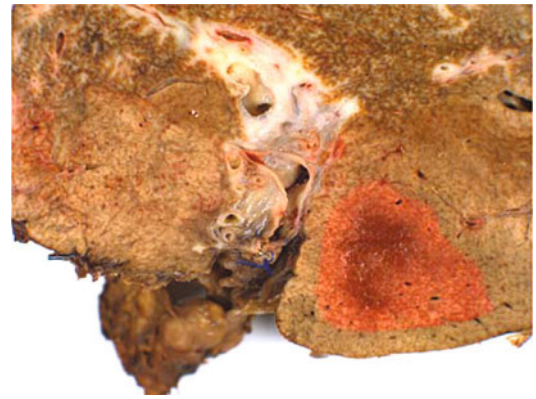

Fig. 3 Small intraductal papillary tumor of an intrahepatic bile duct (*upper third* of figure)

ducts. Tumors can occur in both intra- and extrahepatic ducts in a synchronous or metachronous manner. The slit-like spaces in the papillary growth mostly contain a bile-stained or clear watery fluid, but in about a third of the cases, mucin secretion by the tumors results in a viscid intraductal fluid or even in mucobilia (the mucin-producing type; M-IPN-B). M-IPN-B has to be distinguished from mucinous cystic neoplasms of the liver (Kubota et al. 2014). Part of IPN-Bs are characterized by marked cystic dilatation of the involved ducts, causing macrocystic lesions (cyst-forming IPN-B or cystic type; Lim et al. 2011b, Mano et al. 2011; Shimoda et al. 2013). The cysts are multilocular or unilocular and appear as aneurysm-like dilatations of the bile ducts which, when crowded, leave the impression of a multicystic hepatic tumor. Part of the patients showed diverticulum-like cystic tumors with or without communication, and cystic tumors laterally attached to bile ducts occur (Lim et al. 2011b). Very rarely, the cystic IPN-B manifests as an unilocular cyst with minor papillary components, mimicking a simple hepatic cyst or a hepatic hemorrhagic cyst (Kakisaka et al. 2013). Cyst-forming IPN-B typically occurs at the level of intrahepatic bile ducts but may also develop in the hilar region (Makino et al. 2010). Such lesions may be confounded with mucinous cystic neoplasms of the liver, but in contrast to the latter, cystic forms of IPN show bile duct communication (Zen et al. 2006b; Li et al. 2009).

Histopathology

Histologically, IPN-B is characterized by papillary growths that form in part large tumors with long papillae that are anchored to the mucosa by a vascular interface and which grow into the lumen. Most of the lesions consist of simple papillae that arborize but do have cellular bridges. However, a subset of neoplasms possess complex fused papillary structures that form cribriform lesions. This pattern is associated with a worse biology and was proposed to be called mucosa-confined cholangiocarcinoma (Jung et al. 2012). In IPN-B, two main histopathologic categories have been distinguished, i.e., a columnar type composed of pseudostratified columnar intestinal-type cells and elongated nuclei and a cuboidal type composed of pancreatobiliary and/or oncocytic elements (Shibahara et al. 2004). Further studies confirmed that the papillary structures and tubulopapillary profiles consist of one of four epithelial lineages or combinations thereof, i.e., a pancreatobiliary type, an intestinal type, an oncocytic type, and a gastric type (Table 3; Figs. 4, 5, 6, 7, 8, 9, and 10).

Intestinal and Pancreatobiliary Types

Intestinal and pancreatobiliary types were the most prevalent in all locations of IPN-B, while gastric-type cells prevailed in lesions located to the intrahepatic ducts (Choi et al. 2010; Kubota et al. 2014). In a study of 119 cases of IPN-B, 51 were of the pancreatobiliary type, 33 of the intestinal type, 23 of the oncocytic type, and only 12 of the gastric type (Kubota et al. 2014). Intestinal-type cells are usually columnar elements that cover papillary fibrovascular cores, with basally placed nuclei in low-grade dysplastic lesions and nuclear pseudostratification in high-grade dysplastic lesions. The cells may contain variable amounts of mucin, mainly in the apical part of the cells. IPN-Bs with significant mucin production are very similar to pancreatic IPN (Ohtsuka et al. 2011). Pancreatobiliary-type neoplastic cells are mostly cuboidal to columnar elements with a slightly basophilic, amphophilic, or, rarely, clear cytoplasm. Part of the cells may contain mucin vacuoles (PAS and Alcian Blue positive) or basal mucin deposits or retronuclear/subnuclear mucin vacuoles, but clearly less pronounced than in the gastric type. In some tumor

Table 3 Cell lineages involved in intraductal papillary neoplasm of the bile ducts (IPN-Bs)

Intestinal type
Pancreatobiliary type
Gastric type
Oncocytic type (intraductal oncocytic papillary neoplasm, IOPN)
Mixed types

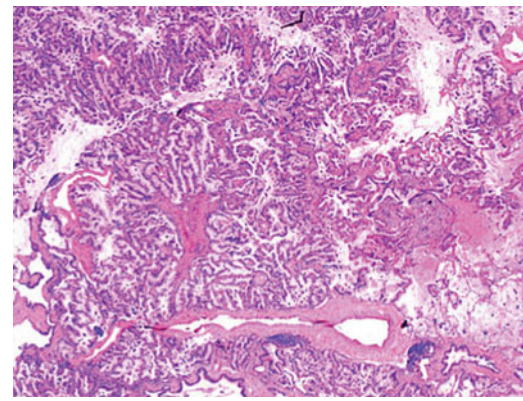

Fig. 4 IPN-B. A dilated bile duct displays masses of papillary tumor structures. Papillary growths start from connective tissue/stroma stalks (hematoxylin and eosin stain)

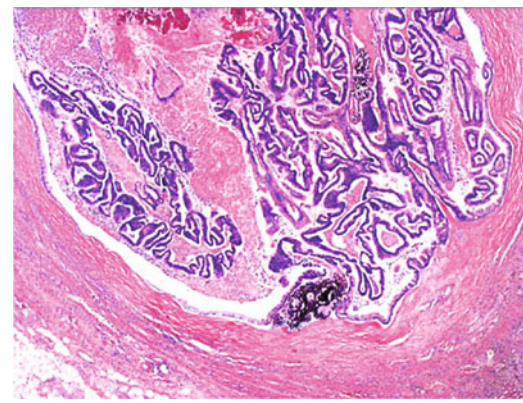

Fig. 5 IPN-B with focal necrosis and erosion of papillary structures. A small, probably dystrophic calcification is seen (below the middle; hematoxylin and eosin stain)

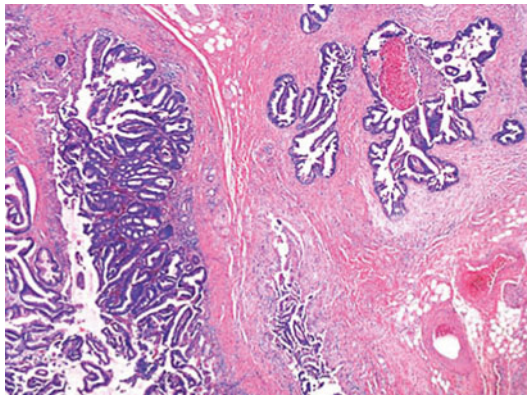

Fig. 6 IPN-B. The papillary growth to the top right corner is associated with induction of a cellular stroma. This may be an early sign of invasion (hematoxylin and eosin stain)

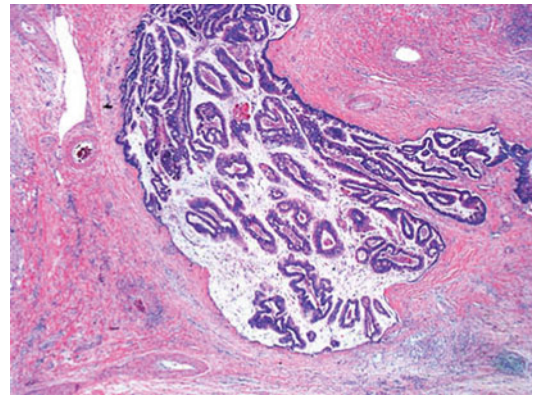

Fig. 8 IPN-B with marked production and discharge of mucus. Extracellular mucus is visible as a slightly basophilic matter filling the interpapillary spaces (hematoxylin and eosin stain)

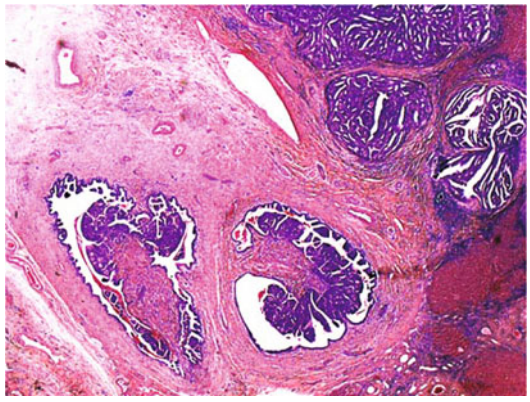

Fig. 7 IPN-B. Two tumor foci show a well-developed stalk (hematoxylin and eosin)

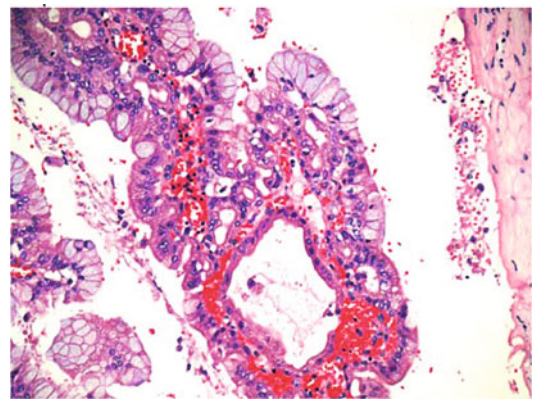

Fig. 9 IPN-B with abundant mucin production, in part with formation of goblet-like cells (hematoxylin and eosin stain)

cells, a large paranuclear eosinophilic structure representing a hypertrophic Golgi area is seen. Nuclei are basally placed in low-grade dysplasia, while in higher grades of dysplasia, they are irregularly arranged within the epithelial lining, also being positioned in the apical part of the epithelium. In the course of increasing dysplasia, nuclear morphology shifts from ovoid ort elongated nuclei with a coarse chromatin to more and more enlarged vesicular nuclei with prominent nucleoli. There seems to be a relationship between the presence of these two most important histologies and underlying bile duct disease. In Korean patients, a pancreatobiliary cellular phenotype was predominant in patients with *Clonorchis sinensis* infestation, while an intestinal phenotype was more often detected in patients without liver fluke disease (Jang et al. 2008).

Gastric Type

Pancreatic IPMN of gastric-type differentiation has been described, with a cell lineage characterized by mucin-rich columnar cells resembling those of gastric foveolae (Ban et al. 2006; Kim et al. 2012a). A similar cell type is observed in a minority of IPN-B, where a cell population

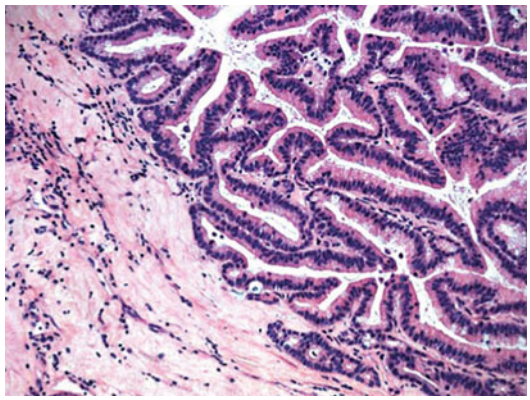

Fig. 10 Well-differentiated IPN-B. The finely branching papillae are lined with a columnar epithelium with basally placed nuclei (hematoxylin and eosin stain)

dysplastic columnar cells resembling pyloric glands was found (Tajiri et al. 2012). Apart from intracellular mucin accumulation, part of IPN-B secrete mucin, sometimes in large quantities. Mucin is more often and more strongly secreted by tumors with an intestinal or gastric phenotype than with a pancreatobiliary or oncocytic phenotype (Kim et al. 2012a). On the other hand, IPN-B with macroscopically visible mucin secretion showed striking similarities to INP of the pancreas (Ohtsuka et al. 2011).

Oncocytic Type (Intraductal Oncocytic Papillary Neoplasm (IOPN))

IPN-Bs with oncocytic cells form a rare subgroup, particularly those entirely composed of oncocytes (intraductal oncocytic papillary neoplasms (IOPN); Martin et al. 2002; Spector et al. 2004; Terada and Taniguchi 2004; Rouzbahman et al. 2007; Tabibian et al. 2008; Lee et al. 2009; Nakanishi et al. 2009; Tanaka et al. 2009; Cocieru et al. 2010; Liszka et al. 2010; Kato et al. 2012; Jurczyk et al. 2013; Watanabe et al. 2013). Apart from intrahepatic ducts, IOPN rarely also occurs in the extrahepatic ducts/common bile duct, in a part with a high-grade morphology (Rouzbahman et al. 2007; Terada 2012). The oncocytic variant of IPN-B often forms large hepatic cysts with papillary projections, cyst diameters reaching more than 20 cm in some patients (Martin et al. 2002; Tanaka et al. 2009; Watanabe et al. 2013). IOPN often forms lesions with finely arborizing papillary formations and/or cribriform structures composed of medium-sized to large granular and strongly eosinophilic cells containing numerous mitochondria. The cells stain with an antimitochondrial antibody (Tanaka et al. 2009) and show a mucin core profile similar to the counterparts in the pancreas, i.e., positivity for MUC3, MUC4, MUC5AC, MUC5B, and MUC6 (Rouzbahman et al. 2007). IOPN may be admixed with various types of non-oncocytic cells (Tanaka et al. 2009). The situation as regards origin of cell lineages is complex, as oncocytic populations can occur together with pancreatobiliary or gastric foveolar-type cell populations within the same lesion (Liszka et al. 2010), suggesting the involvement of a common cellular ancestor. IOPN frequently shows microscopically minimal invasion (Tanaka et al. 2009), but it can also transform into a frankly invasive carcinomatous neoplasm which has been termed intraductal oncocytic papillary carcinoma (Cocieru et al. 2010). Oncocytic biliary cystadenocarcinoma was considered to be a form of oncocytic IPN-B (Sudo et al. 2001). In one study, oncocytes of IPN-B produced gastric-type mucins (MUC5AC and MUC6) and showed immunoreactivity for claudin-18 and Hep Par 1 (Tanaka et al. 2009).

Immunohistochemistry

The epithelial cells of IPN are reactive for CK7 (Fig. 11; Matsubara et al. 2012) and, in case of the intestinal-type cell lineage, CK 20 (Kloek et al. 2011). The expression of mucin genes seems to play a significant role in IPN and carcinomas derived thereof, as in other types of intrahepatic cholangiocarcinomas and their precursor lesions (Sasaki et al. 1995, 1998). IPN of the intestinal type expressed MUC2 and CK20 ("intestinal metaplasia"; Sasaki et al. 1996; Shimonishi et al. 2002; Yaman et al. 2009; Nakanuma et al. 2010b), and progression to invasive carcinoma was accompanied by an increasing MUC1 expression (Zen et al. 2006c). Expression

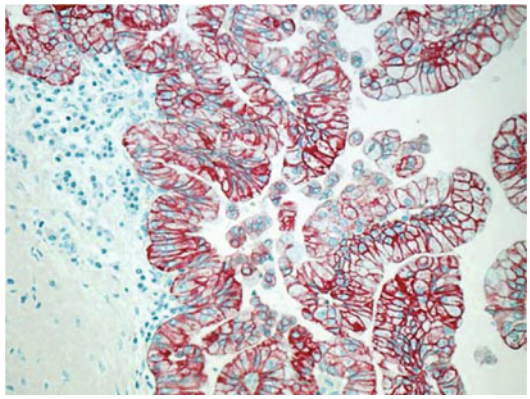

Fig. 11 Expression pattern of cytokeratin 7 in IPN-B (CK 7 immunostain)

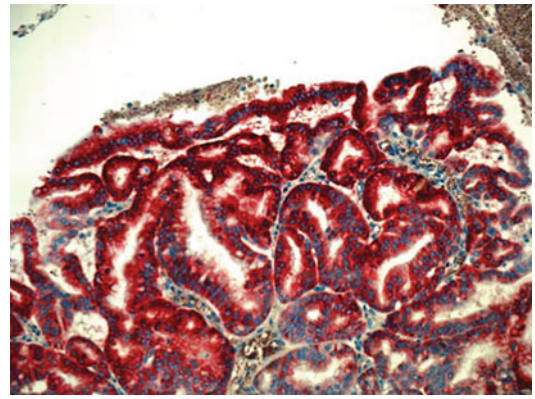

Fig. 12 IPN-B with expression of MUC5AC (MUC5AC immunostain)

of the gastrointestinal markers, CK20 und MUC2, is more frequently expressed in IPN than that in non-papillary biliary tract neoplasms, while the cholangiocyte marker, CK7, is decreased in IPN (Shimonishi et al. 2002). Specifically, IPN cells express MUC5AC widely and MUC2 focally, and this expression pattern is associated with aberrant expression of the homeodomain protein CDX2 (Ishikawa et al. 2004a; Yeh et al. 2005; Nakanuma et al. 2010b). CDX2 protein is, in the target cells of IPN, immunohistochemically either expressed in the nuclei or in the cytoplasm, in a mutually exclusive pattern (Ishikawa et al. 2004a). It has been suggested that aberrant expression of MUC5AC starts in cholangiocytes at an early stage of the carcinogenic pathway occurring in hepatolithiasis, which is found in low-grade INP, followed by expression of MUC2 along with the progression of IPN-L to mucinous ICC (Sasaki et al. 1995, 1996; Shimonishi et al. 2002), this assumption being supported by the observation of MUC2-positive neoplastic cells being situated within areas with MUC5AC expression, coexpression of both MUC2 and MUC5AC probably representing a feature typical for established mucinous ICC (Ishikawa et al. 2004a). The MUC2 phenotype of IPN is reflected by its pancreatic counterpart: whereas MUC2 is rarely expressed in pancreatic ductal carcinoma, it is highly expressed in IPM with mucinous carcinoma, and there seems to be a progression of MUC2 expression from IPM with simple hyperplasia and pyloric gland adenomas to those with associated dysplasia (Terris et al. 2002; Nakamura et al. 2002; Adsay et al. 2003).

In regard to MUC and cytokeratin (CK) expression, the patterns of the four histologic subtypes (pancreatobiliary, intestinal, gastric, and oncocytic) may be summarized as follows: MUC5AC is expressed by all four types (Fig. 12). Pancreatobiliary lineage is MUC1(+)/MUC2(−), intestinal is MUC1(−)/MUC2(+), gastric is MUC1(−)/MUC2(−), and oncocytic is MUC1(focal+)/MUC2(focal+). All four lesions are CK7(+) and CK20(+).

Nuclear expression of p53 protein is present in about a third of IPN but increases as a function of progression along the dysplasia-carcinoma pathway (Shimonishi et al. 2002) and is considered to play a significant role in carcinogenesis of IPN (Nakanishi et al. 2008). In low-grade IPN, p53 expression is less frequent and of low-level, while it reached a higher plateau in high-grade lesions, similar to invasive carcinoma (Nakanishi et al. 2008). IPN cells (in particular the pancreatobiliary-type cells) show membrane immunostaining for beta-catenin, which decreases in the course of progressive increase in the grade of dysplasia (Itatsu et al. 2007). Expression of SOX9, a transcription factor important for developmental pathways, in cells of IPN is low in comparison with normal cholangiocytes (Kuroki et al. 2013). Similar to IPN of the pancreas, the majority of IPN expresses claudin-18, while expression of this protein is less frequent in intrahepatic cholangiocarcinoma (Shinozaki et al. 2011).

Grading of IPN-B

Noninvasive IPN-B can show cellular and nuclear atypia, which are classified as low-grade, intermediate-grade, and high-grade dysplasia (Zen et al. 2006a, b; Nakanishi et al. 2008; Kubota et al. 2014; Figs. 13, 14, 15, 16, and 17). IPN-B can show a relative high proportion of lesions with advanced atypia and high grade. Among 119 Japanese cases of IPN-B, 53 cases were low or intermediate grade and 23 were high grade, while 43 lesions showed invasive growth (Kubota et al. 2014). There is evidence that IPN-B has a higher proportion of tumors with high grade than IPN of the pancreas (Zen et al. 2014).

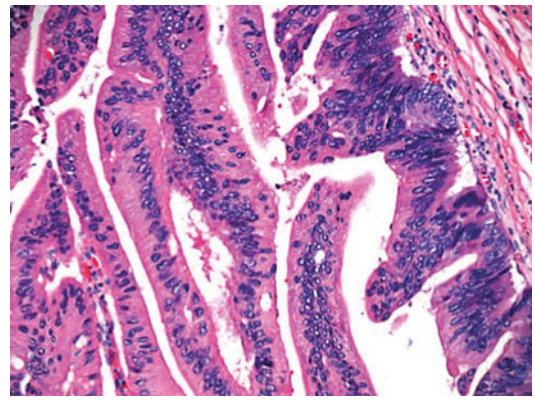

Fig. 14 IPN-B with moderate dysplasia (hematoxylin and eosin stain)

Transition of IPN-B into Invasive Carcinoma of the Bile Duct

In part of the cases, microinvasion or frank invasion of the bile duct wall is found (IPN-B with associated invasive carcinoma; Fig. 18). The transition of microinvasion into deeper invasion is associated with formation (induction) of a tumor stroma (desmoplasia), similar to that found in other intrahepatic cholangiocarcinoma. Adenocarcinoma arising from IPN-B is in most cases cholangiocarcinoma of the intraductal growth type (IG-ICC). Carcinoma arising in IPN-B consisting of pancreatobiliary-type cells is usually a "classical" cholangiocarcinoma, while

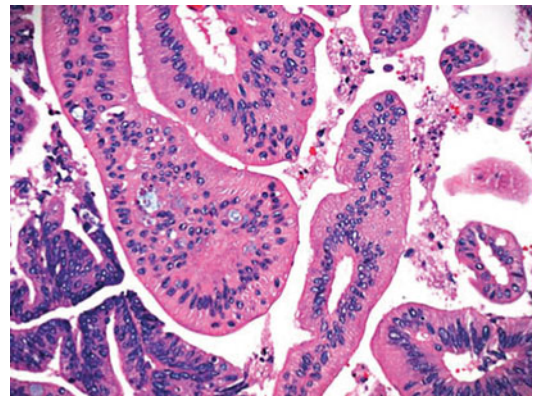

Fig. 15 IPN-B with focal oxyphilic cell change and low-grade to moderate dysplasia (hematoxylin and eosin stain)

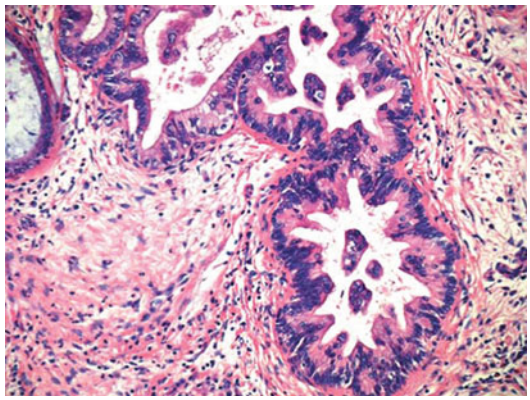

Fig. 13 IPN-B with low-grade dysplasia (hematoxylin and eosin stain)

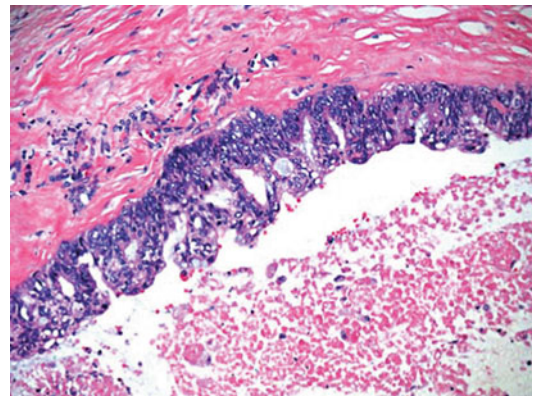

Fig. 16 IPN-B, high-grade dysplasia (hematoxylin and eosin stain)

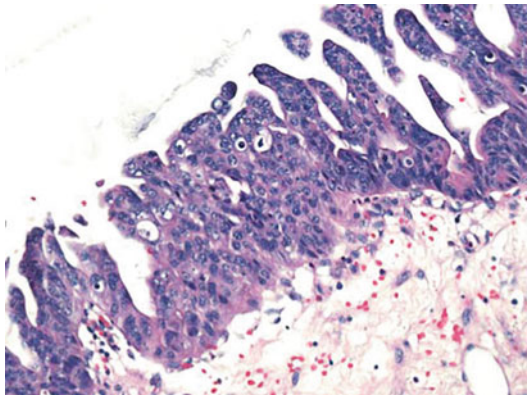

Fig. 17 IPN-B with high-grade dysplasia and carcinoma in situ (hematoxylin and eosin stain)

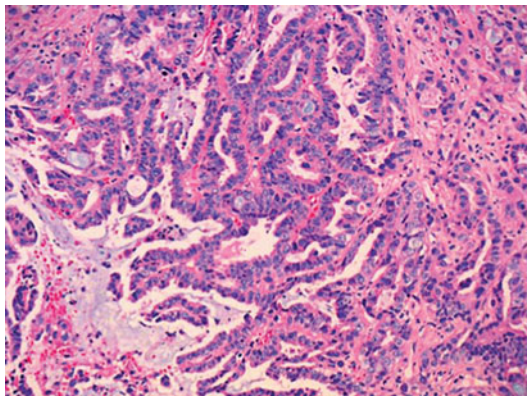

Fig. 18 High-grade IPN-B with transition into invasive adenocarcinoma (hematoxylin and eosin stain)

carcinomas arising in intestinal-type IPN-B often show a colloid adenocarcinoma phenotype (Kang et al. 2012), and carcinomas derived from gastric-type IPN-B are mucin-rich adenocarcinomas (Choi et al. 2010).

Intraductal Tubular Neoplasm of the Bile Ducts (ITN-B)

Most intraductal tumors of the biliary tract reveal a papillary growth pattern. Exceptionally, different growth patterns may develop, including intraductal tubular neoplasms that have been observed in the common bile duct but also develop in intrahepatic ducts. These tubular neoplasms may form several subgroups, as both the histomorphology and immunohistochemical phenotype differed among the cases reported so far. There are lesions that show an almost exclusively tubular phenotype (Sato et al. 2010), while others present a tubulopapillary morphology with high-grade dysplasia (intraductal tubulopapillary neoplasm, ITPN-B; Park et al. 2010). Intraductal tubulopapillary neoplasm of the bile duct was suggested to take its origin from peribiliary cysts (Zen et al. 2012). Mucin secretion is usually absent, but there are variants with marked mucin production. ITN-B displays the characteristic spectrum of precursor lesions, although within the same tumor.

Sato and coworkers (2010) reported a rare case of intraductal tubular neoplasm (ITN) arising in the distal common bile duct of an elderly woman. Macroscopically, the tumor presented as polypoid mass of up to 10 mm in diameter. Histologically, the neoplasm was composed of an admixture of tubular glands resembling pyloric gland adenoma with minimal atypia or low-grade tubular adenoma and glands resembling intestinal-type tubular adenoma or high-grade tubular adenoma. Papillary structures were absent. There were small foci of carcinoma in situ of intestinal type. The low-grade tubular component expressed MUC5AC and MUC6 and was negative for MUC2 and CD20, while the high-grade intestinal-type tubular adenoma and the carcinoma in situ lesions expressed MUC2 and CD20. Later, Katabi and coworkers (2012) reported ten cases of biliary intraductal neoplasms with a predominantly tubular architecture. Three male and seven female patients (38–78 years) had obstructive jaundice or abdominal pain. The neoplasms ranged in size from 0.6 to 8.0 cm. Eight lesions were intrahepatic, one lesion extrahepatic, and one in the common bile duct. Histologically, the neoplasms showed intraductal back-to-back tubular glands and solid sheets with minimal papillary components. The tumor cells were cuboidal to columnar with mild to moderate cytological atypia. Six cases showed intraductal necrosis. In seven cases, an extraductal invasive carcinoma was present. In contrast to the case reported by Sato et al. (2010), the tumors were

immunohistochemically negative for MUC2 and MUC5AC, but expressed MUC1 and MUC6. Four patients with invasive carcinoma experienced metastases, in three patients quite late.

Intraductal Neoplasm of the Bile Duct, Superficial Spreading Type

In principle, this is a variant of intrahepatic cholangiocarcinoma (ICC) which presents an extensive spread along the luminal (mucosal) surface of intrahepatic bile ducts, without or with only minor invasion of the duct walls or the adjacent liver substance. The involved bile duct mucosa is flat, without nodular lesions (Nakanuma et al. 2010a). In one patient, CT showed cystic and tubular dilatation of intrahepatic ducts without grossly visible tumor mass. Histologically, a neoplasm spread diffusely and contiguously along the intrahepatic ducts, with minimal duct invasion. The duct surface was lined by a single layer of columnar tumor cells with short intraluminal papillary projections (Lim et al. 2000).

Variants of IPN

Recently, a distinct category of IPN lesions has been identified, characterized by the presence of complex fused or cribriform papillae instead of simple papillae, and associated with worse prognosis. This group of neoplasms has been proposed to be termed mucosa-confined cholangiocarcinoma (Jung et al. 2012).

Biology of Disease

IPN-Bs are a group of neoplastic lesions that, similar to those in the pancreas, have a complex biology and are high-risk lesions for later invasive carcinoma. Intrahepatic tumors can extend distally and may then protrude into the large extrahepatic ducts (Uchiyama et al. 2007). The lesions can also extend superficially from the intrahepatic to the extrahepatic bile ducts, sometimes in the form of carcinoma in situ that continually extends along the mucosa, or replaced the normal mucosal surface epithelium (Nanashima et al. 2006). Rarely, IPN-B can produce fistulation, e.g., into the common bile duct (Barnardo et al. 2007). Even low-grade IPN-B lesions can, albeit rarely, lead to severe complications apart from transition into frank carcinoma. One patient with low-grade IPN developed, 6 years after surgical treatment of the primary tumor, pseudomyxoma peritonei, suggested to be caused by spillage of tumor cells in the course of the intervention (Jhuang and Hsieh 2012). A case of needle tract seeding of IPN-B after percutaneous biopsy has been reported (Takahashi et al. 2014).

Part of IPN-B can undergo transition into an invasive cancer, mainly resulting in intraductal growth cholangiocarcinoma/IG-ICC rather than mass-forming intrahepatic cholangiocarcinoma (Fukatsu et al. 2006; Nanashima et al. 2008b; Bickenbach et al. 2009; Takanami et al. 2011; Matsubara et al. 2012). This transition into cancer varies among diverse investigations, but overall 40–80 % of IPN-Bs contain a component of invasive carcinoma of various types (Yeh et al. 2005; Ohtsuka et al. 2011; Rocha et al. 2012; review: Wan et al. 2013). Apart from conventional adenocarcinoma, also colloid carcinoma and papillary cholangiocarcinoma can develop (Onoe et al. 2014). The frequency of invasive carcinoma in the pancreatobiliary type of IPN-B was significantly higher than those in intestinal and gastric types (Takasu et al. 2010; Kim et al. 2012a). In cases of IPN-B associated with invasive carcinoma, vascular invasion and lymph node metastases may be less common than in other forms of cholangiocarcinoma (Nanashima et al. 2008). There was no difference in regard to depth of invasion and lymph node metastasis between lesions located to intrahepatic ducts, hilar area, or large extrahepatic ducts (Choi et al. 2010). The prognosis of IPN-B in the absence of invasive carcinoma is better in comparison with conventional intrahepatic cholangiocarcinoma (Chen et al. 1998; Nakanuma et al. 2002; Kubota et al. 2014). In a series of 25 patients, the median survival time of resected patients was 59.8 %, and the 1-, 2-, and 4-year survival rates were 90.5 %,

84.0 %, and 84.0 %, respectively, and all patients with low-grade IPN remained alive (Paik et al. 2008). The poorer prognosis of IPN-B in comparison with the pancreatic counterpart is probably related to a higher proportion of IPN-B tumors with high grade and a more advanced stage of an associated invasive cancer (Zen et al. 2014).

The influence on outcome exerted by the diverse types of invasive carcinoma originating from IPN-B is not fully known, but there was a tendency for patients with invasive carcinomas derived from intestinal-type IPN-B to have a better prognosis than those whose invasive carcinomas were derived from IPN with a pancreatobiliary type (Takasu et al. 2010; Bronsert et al. 2013). In a recent study, gastric-type IPN-Bs were associated with a better 10-year survival rate than both pancreatobiliary- and intestinal-type lesions (Kubota et al. 2014). There is evidence that carcinomas that express the pan-epithelial membrane-associated mucin, MUC1, but do not express MUC2, display an aggressive behavior with poor outcome, while noninvasive IPN with MUC2, but not MUC1, expression shows a favorable course (Yonezawa et al. 2010; Sasaki et al. 2013). Interestingly, distinct differentiation and growth pattern of noninvasive IPN exert an influence on the biology of disease. IPN-B with complex fused or cribriform papillae showed a worse prognosis than IPN with simple papillae (Jung et al. 2012; see above). Multiplicity of IPN-B had a negative impact on prognosis (Kang et al. 2013).

IPN-Bs are proliferative lesions, and cell proliferation is also a prerequisite for those lesions that undergo invasion. Expression of molecules involved in cell cycle regulation is often upregulated in IPN-B. Cyclin D1 and c-Myc, target molecules of Wnt/beta-catenin signaling, are frequently upregulated in IPN-B (Itatsu et al. 2007). Whereas enzymes involved in invasion and spread, including matrix metalloproteinase-7 and membrane type 1-matrix metalloproteinase, are not or only very weakly expressed in noninvasive IPN-B, enzyme activity significantly increases in invasive lesions (Itatsu et al. 2007). IPN-Bs with a stepwise progression to invasive carcinoma involve common molecular pathways associated with alterations in K-Ras and TP53 regulation and loss of p16 (Schlitter et al. 2014).

Differential Diagnosis

IPN-B with an important cystic component may be difficult to distinguish from mucinous cystic neoplasms (Li et al. 2009). In contrast to mucinous cystic neoplasms (MCN) of the hepatobiliary tract, cystic variants of IPN do never show a subepithelial ovarian-like stroma, an important differential diagnostic element. In addition, IPN-Bs are in communication with the bile duct system, while MCN are not or only exceptionally so, and the female preponderance typical for MCN does not apply for IPN-B. Mucin-producing intraductal tumors can extend from the main pancreatic duct into the distal bile duct system. A mucin-filled bile duct was found as a complication of pancreatic IPN (Patel et al. 2005), and pancreatic IPN can in rare instances penetrate into the common bile duct (Goto et al. 2012). In rare cases, colorectal carcinoma metastases to the liver showed an intraductal papillary growth pattern mimicking IPN-N (Nanashima et al. 2011).

Biliary Papillomatosis: A Long-Known Condition Now Classified as Preinvasive Papillary Forms of Intraductal Neoplasm of the Bile Ducts

Introduction

Biliary papillomatosis (BP) was previously classified a rare neoplastic entity of the intra- and extrahepatic biliary tract, characterized by the development of multiple papillary cholangiocellular and frequently recurring lesions on a focal, multifocal, or diffuse distribution within bile ducts, associated with significant risk of malignant transformation. Most, if not all, cases of BP are now considered to represent the

preinvasive papillary variant of intraductal neoplasm of the bile ducts (IPN-Bs).

This unique lesion has first been reported in 1894 (Chappet 1894) and was described in more detail in 1959, based on a choledochal lesion (Caroli et al. 1959). Numerous observations were published in the following years (Boerner 1960; Eiss et al. 1960; James and Gardner 1974; Madden and Smith 1974; Padfield 1988; and Yeung et al. 2003). BP was regarded a disease of multicentricity due to generalized biliary tract field changes (Tireli and Uslu 1992; Holtkamp and Reis 1994; Nakanuma et al. 2002; Yeung et al. 2003; Braeye and Vanheste 2010). BP has a tendency to spread superficially along the bile duct mucosa, finally resulting in diffuse papillomatosis (Terada et al. 1991), but invasive growth and transformation into carcinoma are well-established complications of BP. BP occurs in the pediatric age group and is as rare as pediatric cholangiocarcinoma (Bines et al. 1992). Apart from extrahepatic ducts, BP also arises in the intrahepatic large bile ducts, and the neoplastic and nonneoplastic parts of the intrahepatic biliary tree exhibit segmental and saccular dilatation. The extrahepatic biliary tract is involved either in combination with intrahepatic BP or as a lesion restricted to the common bile duct (Sagar et al. 1993; Centorrino et al. 1998; Sotiropoulos et al. 2003). In a study of 33 patients, concomitant intrahepatic and extrahepatic disease was observed in 42 % (Yeung et al. 2003). BP may involve the cystic duct and extend into the gallbladder. BP may be restricted to the distal biliary tract (Sotiropoulos et al. 2003). BP can arise in congenital choledochal cysts (Ohta et al. 1993; Iwasaki et al. 2002; Negi et al. 2009; Sen et al. 2012) but may also form cystic cavities lined by papillary growths in the absence of a congenital cystic bile duct disorder (Aoki et al. 2005). There are rare observations of BP occurring in conjunction with other liver disorders, including recurrent pyogenic cholangitis (Cheng et al. 1999) and autoimmune hepatitis (Kageyama et al. 2003).

Originally, BP was classified as either a mucin-hypersecreting type (mucinous biliary papillomatosis (MBP); review: Padfield et al. 1988) or a non-mucin-producing type (NMBP), because both these disease types have similar macroscopic and microscopic findings but may have a different pathogenesis and outcome. In one study, NMBP was twice as frequent as MBP (Lee et al. 2004).

Pathology

Macroscopy

Resected tumors are described as grayish tan to yellow, friable, papillary, or granular masses that fill dilated bile duct portions. MBP and NMBP showed no gross differences, except for mucin in the ductal lumen in the case of MBP (Lee et al. 2004).

Histopathology

The histopathologic presentation of BP is the same as that described for IPN-B (see above). The lesions shows a villous, papillo-tubular, papillary, or papillo-villous growth pattern (James and Gardner 1974; Lee et al. 2004).

The villous pattern is characterized by sharp arrow head-like formations. Many of the lesions resemble low-grade tubulovillous or villous colorectal adenomas. The growths possess a usually thin fibrovascular stalk which often contains a mild degree of lymphocytic infiltration. In NMBP, the predominant epithelial cell type has either a biliary epithelial (cholangiocyte) phenotype or a pyloric gland-like phenotype. The biliary phenotype is characterized by a tall single to multilayered epithelium with a variable cytoplasmic staining, while the pyloric gland-like phenotype resembles pseudopyloric gland metaplasia of the gallbladder as seen in chronic cholecystitis, i.e., with a clear and abundant cytoplasm and flattened nuclei on the basal layer. Goblet cell metaplasia and colon-like metaplasia are often seen, and goblet cell metaplasia tends to predominate in MBP (Lee et al. 2004). Rarely, Paneth cell metaplasia may occur. The apical cell parts show a prominent zone of PAS-positive mucinous material, and almost all cells exhibit an Alcian Blue-positive

mucin rim in the luminal border and sometimes in the supranuclear cytoplasm.

Etiology, Pathogenic Pathways, and Molecular Features of Intraductal Neoplasms

The etiology of IPN-B has not yet been fully clarified. In Far Eastern countries, hepatolithiasis and clonorchiasis are major risk factors (review: Wan et al. 2013). In one study from Taiwan, nearly 87 % of patients with IPN-B suffered from hepatolithiasis (Yeh et al. 2005). Both hepatolithiasis and liver fluke infestation are associated with, or directly cause, chronic inflammation of the bile duct mucosa, followed by cholangiocyte proliferation and long-standing hyper regeneration. This phenomenon increases the risk of mutational events, selection of pro-growth mutations, generation of dysplastic changes, and finally neoplastic transformation (an inflammation-hyperplasia-dysplasia-neoplasia pathway). It is estimated that the time lag between active hepatolithiasis and the development of IPN-B is the region of 6–8 years, while in situ carcinoma requires 1–2 years to become an invasive lesion (summarized in Wan et al. 2013).

Distinct types of genomic and molecular alterations have been detected in intraductal papillary mucinous neoplasms of the pancreas, which are known for a longer time period than their hepatobiliary tract counterparts. Based on the similarity between these neoplasms and IPN-B with respect to histogenesis and morphology (Ohtsuka et al. 2011), it may be anticipated that biliary tract IPN expresses similar changes, all the more so as pancreatic and IPN-B can occur simultaneously (Ishida et al. 2002). Similar to its pancreatic counterpart, IPN-B lacks expression of the stem cell marker, CD133 (Ohtsubo et al. 2012). High-level microsatellite instability was present in 11.8 % of IPN-B, while low-level instability was present in 35.3 % in IPN-B, with a difference in the pattern of allelic shifts between the noninvasive and invasive components (Abraham et al. 2002).

Certain gene mutations known to play a role in hepatobiliary carcinogenic pathways were observed in IPN-B. In IPN-B associated with invasive carcinoma, the same K-ras mutations were present in both the intraductal and invasive components. Activating mutations in codon 12 of the K-ras gene were detectable in 29–32 % of IPN-B, whereas mutations in the beta-catenin gene were not found (Abraham et al. 2003; Tsai et al. 2013; Schlitter et al. 2014). However, there are also differences in the molecular signature between pancreatic and biliary IPN. For example, GNAS codon 201 mutations that are found in approximately two thirds of IPMNs of the pancreas are less common in IPN-B, but amount to up to 46.2 % of cases (Matthaei et al. 2012; Sasaki et al. 2013a; Tsai et al. 2013). GNAS, the gene of which is located on chromosome 20q, is the alpha subunit of a stimulatory G protein which activates a cyclic 3′-5′-cyclic AMP-mediated intracellular signaling cascade regulating cell proliferation. Overexpression of TP53 and loss of p16 were detected in low-grade IPN-B, whereas loss of SMAD4 was found in late phases of tumor development (Schlitter et al. 2014). In comparison with normal cholangiocytes, IPN-B showed decreased expression of the transcription factor, SOX9, which also plays a role in the development of pancreatic IPMNs (Kuroki et al. 2013).

Recently, IPN-Bs have been studied with respect to CDX2. IPN-Bs, mainly those occurring in the Far East, frequently express MUC2 and MUC5AC associated with aberrant expression of the homeodomain protein CDX2 (Ishikawa et al. 2004a). CDX2 is a caudal-related homeobox gene encoding an intestine-specific transcription factor, and expression is detectable in the nuclei of goblet cell-type intestinal epithelial cells (Yamamoto et al. 2003; Werling et al. 2003). Expression of this gene in cells examined in vitro affects intestinal cell differentiation and the transcription of intestine-specific genes (Qualtrough et al. 2002; Hinoi et al. 2002; Werling et al. 2003). This role as a differentiation switch is exemplified for gastric mucosa, where ectopic expression of CDX2 induces, or is associated with, intestinal metaplasia, while normal gastric mucosa does not express the gene (Silberg et al. 2002; Mutoh et al. 2002; Bai et al. 2002; Almeida et al. 2003). Furthermore, ectopic CDX2

expression characterizes the distinctive phenotype of intestinal-type cells developing in Barrett's esophagus (Eda et al. 2003). Based on transgenic mice, it has been suggested that expression of CDX2 is linked to the expression of MUC2 and alkaline phosphatase in the CDX2-expressing target cells (Silberg et al. 2002). This has been confirmed by the finding of a CDX2 interaction with the MUC2 promoter, thus activating MUC2 transcription (Yamamoto et al. 2003). Factors regulating the cell division cycle may be altered in the expression and activity in IPN-B. Inactivation of p16INK4a, mainly through promoter hypermethylation, is an early event in the transition from IPN-B to invasive carcinoma in patients with hepatolithiasis (Ishikawa et al. 2004b).

References

Abraham SC, Lee JH, Boitnott JK, Argani P, Furth EE, Wu TT (2002) Microsatellite instability in intraductal papillary neoplasms of the biliary tract. Mod Pathol 15:1309–1317

Abraham SC, Lee JH, Hruban RH, Argani P, Furth EE, Wu TT (2003) Molecular and immunohistochemical analysis of intraductal papillary neoplasms of the biliary tract. Hum Pathol 34:902–910

Adsay NV, Merati K, Nassar H, Shia J, Sarkar F, Pierson CR, Cheng JD, Visscher DW, Hruban RH, Klimstra DS (2003) Pathogenesis of colloid (pure mucinous) carcinoma of exocrine organs: coupling of gel-forming mucin (MUC2) production with altered cell polarity and abnormal cell-stroma interaction may be the key factor in the morphogenesis and indolent behavior of colloid carcinoma in the breast and pancreas. Am J Surg Pathol 27:571–578

Aishima S, Kuba Y, Tanaka Y, Oda Y (2014) Histological features of precancerous and early cancerous lesions of biliary tract carcinoma. J Hepato-Biliary-Pancreat Sci. doi:10.1002/jhbp.71

Almeida R, Silva E, Santos-Silva F, Silberg DG, Wang J, De Bolos C, David L (2003) Expression of intestine-specific transcription factors, CDX1 and CDX2, in intestinal metaplasia and gastric carcinomas. J Pathol 199:36–40

Aoki S, Okayama Y, Kitajima Y, Hayashi K, Imai H, Okamoto T, Akita S, Gotoh K, Ohara H et al (2005) Intrahepatic biliary papilloma morphologically similar to biliary cystadenoma. J Gastroenterol Hepatol 20:321–324

Bai YQ, Yamamoto H, Akiyama Y, Tanaka H, Takizawa T, Koike M, Kenji Yagi O, Saitoh K, Takeshita K, Iwai T, Yuasa Y (2002) Ectopic expression of homeodomain protein CDX2 in intestinal metaplasia and carcinomas of the stomach. Cancer Lett 176:47–55

Bal MM, Goel M, Ramadwar M, Deodhar K (2014) Intraductal papillary neoplasm of the bile duct: a rarity. Indian J Pathol Microbiol 57:144–145

Ban S, Naitoh Y, Ogawa F, Shimizu Y, Shimizu M, Yasumoto A, Koyama I (2006) Intraductal papillary mucinous neoplasm (IPMN) of the gastric-type with focal nodular growth of the arborizing papillae: a case of high-grade transformation of the gastric-type IPMN. Virchows Arch 449:112–116

Barnardo A, Fotiadis N, Meenan J, Wilskinson M, Wong T (2007) Endoscopic management of intraductal papillary mucinous tumors fistulating into the common bile duct. Gastrointest Endosc 66:1060–1062

Bickenbach K, Galka E, Roggin KK (2009) Molecular mechanisms of cholangiocarcinogenesis: are biliary intraepithelial neoplasia and intraductal papillary neoplasms of the bile duct precursors to cholangiocarcinoma? Surg Oncol Clin N Am 18:215–224

Bines JE, Shamberger RC, Perez-Atayde A, Rosenberg SJ, Winter HS (1992) Multiple biliary papillomatosis in a child. J Pediatr Gastroenterol Nutr 14, 309–313

Boerner P (1960) A papillomatosis of the intra-and extrahepatic biliary tract (in German). Z Krebsforschung 63:474–480

Braeye L, Vanheste R (2010) Biliary papillomatosis. Hepatology 52:1512–1514

Bronsert P, Kohler I, Werner M, Makowiec F, Kuesters S, Hoeppner J, Hopt UT, Keck T et al (2013) Intestinal-type of differentiation predicts favourable overall survival: confirmatory clinicopathological analysis of 198 periampullary adenocarcinomas of pancreatic, biliary, ampullary and duodenal origin. BMC Cancer 13:428

Budzynska A, Hartleb M, Nowakowska-Dulawa E, Krol R, Remiszewski P, Mazurkiewicz M (2014) Simultaneous liver mucinous cystic and intraductal papillary mucinous neoplasms of the bile duct. A case report. World J Gastroenterol 20:4102–4105

Caroli J, Soupault R, Champeau M, Eleve J, Hivet M (1959) Papillomas and papillomatosis of the common bile duct. Rev Med Chir Mal Foie 34:191

Carrafiello G, Bertolotti E, Sessa F, Cafaro T, Dionigi G, Genovese E, Dionigi R, Fugazzola C (2008) Intraductal papillary mucinous tumor of bile ducts radiologic and pathologic features: a case report. Cases J 1:319

Centorrino T, Panté S, Ciccolo A, Lepore V, Pagano G, Versaci A (1998) Clinical considerations and therapeutic options in papillomatosis of common bile duct. Clinical case (in Italian). G Chir 19:232–234

Chappet V (1894) Cancer epithelial primitif du canal cholédoque. Lyon Med 76:145

Chen MF, Jan YY, Chen TC (1998) Clinical studies of mucin-producing cholangiocellular carcinoma: a study of 22 histopathology-proven cases. Ann Surg 227:63–69

Chen T, Nakanuma Y, Zen Y, Chen M, Jan Y, Yeh T, Chiu C, Kuo T, Kamiya J, Oda K et al (2001)

Intraductal papillary neoplasm of the liver associated with hepatolithiasis. Hepatology 34:651–658
Cheng MS, AhChong AK, Mak KL, Yip AW (1999) Case report: two cases of biliary papillomatosis with unusual associations. J Gastroenterol Hepatol 14:464–467
Choi SC, Lee JK, Jung JH, Lee JS, Lee KH, Lee KT, Rhee JC, Jang KT, Choi SH et al (2010) The clinicopathological features of biliary intraductal papillary neoplasms according to the location of tumors. J Gastroenterol Hepatol 25:725–730
Chung JP, Lee SJ, Song SY, Chung JB, Lee SI, Kang JK (2001) Intraductal papillary mucinous tumor of the bile duct: why not? Endoscopy 33:191–192
Cocieru A, Kesha K, El-Fanek H, Saldinger PF (2010) Hepatic intraductal oncocytic papillary carcinoma. Am J Surg 199:e57–e58
Crippa S, Falconi M (2012) Intraductal papillary mucinous neoplasms of the biliary and pancreatic ducts – a shape shifting outlook into an increasingly recognized disease. Dig Liver Dis 44:183–184
D'Souza MA, Isaksson B, Löhr M, Enochsson L, Swahn F, Lundell L, Arnelo U (2013) The clinicopathological and management of intraductal papillary mucinous neoplasm of the bile duct (IPMN-B). Scand J Gastroenterol 48:473–479
Dong A, Dong H, Zhang L, Zuo C (2012) F-18 FDG uptake in borderline intraductal papillary neoplasms of the bile duct. Ann Nucl Med 26:594–598
Eda et al (2003) http://www.ncbi.nlm.nih.gov/pubmed/12560917
Eiss S, Dimaio D, Caedo JP (1960) Multiple papillomas of the entire biliary tract: case report. Ann Surg 152:320–324
Fujita M, Wakui N, Yamauchi Y, Takeda Y, Sato T, Ueki N, Otsuka T, Oba N, Nishinakagawa S et al (2013) A case of branch duct type intraductal papillary neoplasm of the bile duct treated by open surgery after 11 years of follow-up. Mol Clin Oncol 1:965–969
Fukatsu H, Kawamoto H, Kato H, Hirao K, Kurihara N, Nakanishi T, Mizuno O, Okamoto Y et al (2006) Intraductal papillary mucinous adenocarcinoma of the bile ducts. Gastrointest Endosc 64:438–439
Goto N, Yoshioka M, Hayashi M, Itani T, Mimura J, Hashimoto K (2012) Intraductal papillary-mucinous neoplasm of the pancreas penetrating to the stomach and the common bile duct. JOP 13:61–65
Hachiya H, Kita J, Shiraki T, Iso Y, Shimoda M, Kubota K (2014) Intraductal papillary neoplasm of the bile duct developing in a patient with primary sclerosing cholangitis: a case report. World J Gastroenterol 20:15925–15930
Hayashi J, Matsuoka S, Inami M, Oshiro S, Ishigami A, Fujikawa H, Miyagawa M, Mimatsu K et al (2008) A case of asymptomatic intraductal papillary neoplasm of the bile duct without hepatolithiasis. World J Gastroenterol 14:1625–1629
Hinoi T, Lucas PC, Kuick R, Hanash S, Cho KR, Fearon ER (2002) CDX2 regulates liver intestine-cadherin expression in normal and malignant colon epithelium and intestinal metaplasia. Gastroenterology 123:1565–1577
Holtkamp N, Reis HE (1994) Papillomatosis of the bile ducts: papilloma-carcinoma sequence. Am J Gastroenterol 89:2253–2255
Inoue H, Isaji S, Takei Y (2009) Intraductal papillary neoplasm of bile duct detected on fluorodeoxyglucose-positron emission tomography performed for cancer scanning. Clin Gastroenterol Hepatol 7:e71
Ishida M, Seki K, Honda K, Kimura T, Katayama K, Hirose K, Dojo M, Azuma T, Imamura Y et al (2002) Intraductal mucinous tumors occurring simultaneously in the liver and pancreas. J Gastroenterol 37:1073–1078
Ishikawa A, Sasaki M, Ohira S, Ohta T, Oda K, Nimura Y, Chen MF, Jan YY, Yek TS et al (2004a) Aberrant expression of CDX2 is closely related to the intestinal metaplasia and MUC2 expression in intraductal papillary neoplasm of the liver in hepatolithiasis. Lab Invest 84:629–638
Ishikawa A, Sasaki M, Sato Y, Ohira S, Chen MF, Huang SF, Oda K, Nimura Y, Nakanuma Y (2004b) Frequent p16ink4a inactivation is an early and frequent event of intraductal papillary neoplasm of the liver arising in hepatolithiasis. Hum Pathol 35:1505–1514
Itatsu K, Zen Y, Ohira S, Ishikawa A, Sato Y, Harada K, Ikeda H, Sasaki M, Nimura Y et al (2007) Immunohistochemical analysis of the progression of flat and papillary preneoplastic lesions in intrahepatic cholangiocarcinogenesis in hepatolithiasis. Liver Int 27:1174–1184
Iwasaki Y, Shimoda M, Furihata T, Rokkaku K, Sakuma A, Ichikawa K, Fujimori T, Kubota K (2002) Biliary papillomatosis arising in a congenital choledochal cyst: report of a case. Surg Today 32:1019–1022
James JM, Gardner WS (1974) Multiple biliary papillomatosis. Cancer 34:1316–1320
Jang KT, Hong SM, Lee KT, Lee JG, Choi SH, Heo JS, Choi DW, Choi D, Lim JH (2008) Intraductal papillary neoplasm of the bile duct associated with Clonorchis sinensis infection. Virchows Arch 453:589–598
Jhuang JY, Hsieh MS (2012) Pseudomyxoma peritonei (mucinous carcinoma peritonei) preceded by intraductal papillary neoplasm of the bile duct. Hum Pathol 43:1148–1152
Ji Y, Fan J, Zhou J, Wang BS, Liu HB, Wu ZW, Tan YS (2008) Intraductal papillary neoplasms of bile duct. A distinct entity like its counterpart in pancreas. Histol Histopathol 23:41–50
Joo YH, Kim MH, Lee SK, Seo DW, Yoo KS, Min YI, Chang JJ, Yu E (2000) A case of mucin-hypersecreting intrahepatic bile duct tumor associated with pancreatic intraductal papillary mucinous tumor. Gastrointest Endosc 52:409–412
Jung G, Park KM, Lee SS, Yu E, Hong SM, Kim J (2012) Long-term clinical outcome of the surgically resected intraductal papillary neoplasm of the bile duct. J Hepatol 57:787–793

Jurczyk MF, Zhu B, Villa C, Defrias D, Lin X (2013) Cytomorphology of intraductal oncocytic papillary neoplasm of the liver. Diagn Cytopathol. doi:10.1002/dc.23073

Kageyama F, Takehira Y, Yamada M, Murohisa G, Hirasawa K, Kataoka H, Iwaoka Y et al (2003) A case of intrahepatic biliary papillomatosis associated with autoimmune hepatitis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 100:1322–1327

Kakisaka T, Kamiyama T, Yokoo H, Naknishi K, Wakayama K, Tsuruga Y, Kamachi H et al (2013) An intraductal papillary neoplasm of the bile duct mimicking a hemorrhagic hepatic cyst: a case report. World J Surg Oncol 11:111

Kang GH, Moon HS, Lee ES, Kim SH, Sung JK, Lee B, Jeong HY (2012) A case of colloid carcinoma arising in association with intraductal papillary neoplasm of the liver. Korean J Gastroenterol 60:386–390

Kang MJ, Jang JY, Lee KB, Han IW, Kim SW (2013) Impact of macroscopic morphology, multifocality, and mucin secretion on survival outcome of intraductal papillary neoplasm of the bile duct. J Gastrointest Surg 17:931–938

Katabi N, Torres J, Klimstra DS (2012) Intraductal tubular neoplasms of the bile ducts. Am J Surg Pathol 36:1647–1655

Kato Y, Konishi M, Kinoshita T, Takahashi S, Gotohda N, Kinoshita T (2012) Intraductal oncocytic papillary neoplasm of the extrahepatic bile duct: report of a case. Surg Today 42:1240–1243

Kato H, Tabata M, Azumi Y, Osawa I, Kishiwada M, Hamada T, Mizuno S, Usui M et al (2013) Proposal for a morphological classification of intraductal papillary neoplasm of the bile duct (IPN-B). J Hepato-Biliary-Pancreat Sci 20:165–172

Kim HJ, Kim MH, Lee SK, Yoo KS, Park ET, Lim BC, Park HJ, Myung SJ, Seo DW et al (2000) Mucin-hypersecreting bile duct tumor characterized by a striking homology with an intraductal papillary mucinous tumor (IPMT) of the pancreas. Endoscopy 32:389–393

Kim H, Lim JH, Jang KT, Kim MJ, Lee J, Lee JY, Choi D, Lim HK, Choi DW, Lee JK et al (2011) Morphology of intraductal papillary neoplasm of the bile ducts: radiologic-pathologic correlation. Abdom Imaging 36:438–446

Kim KM, Lee JK, Shin JU, Lee KH, Lee KT, Sung JY, Jang KT, Heo JS, Choi SH et al (2012a) Clinicopathologic features of intraductal papillary neoplasm of the bile duct according to histologic subtype. Am J Gastroenterol 107:118–125

Kim BS, Joo SH, Lim SJ, Joo KR (2012b) Intrahepatic biliary intraductal papillary mucinous neoplasm with gallbladder agenesis: case report. Surg Laparosc Endosc Percutaneous Tech 22:e277–e280

Klibansky DA, Reid-Lombardo KM, Gordon SR, Gardner TB (2012) The clinical relevance of the increasing incidence of intraductal papillary mucinous neoplasm. Clin Gastroenterol Hepatol 10:555–558

Kloek JJ, van der Gaag NA, Erdogan D, Rauws EA, Busch OR, Gouma DJ, ten Kate FJ et al (2011) A comparative study of intraductal papillary neoplasia of the biliary tract and pancreas. Hum Pathol 42:824–832

Klöppel G, Kosmahl M (2006) Is the intraductal papillary mucinous neoplasia of the biliary tract a counterpart of pancreatic papillary mucinous neoplasm? J Hepatol 44:249–250

Klöppel G, Adsay V, Konukiewitz B, Kleeff J, Schlitter AM, Esposito I (2013) Precancerous lesions of the biliary tree. Best Pract Res Clin Gastroenterol 27:285–297

Kubota K, Nakanuma Y, Kondo F, Hachiya H, Miyazaki M, Nagino M, Yamamoto M et al (2014) Clinicopathological features and prognosis of mucin-producing bile duct tumor and mucinous cystic tumor of the liver: a multi-institutional study by the Japan Biliary Association. J Hepato-Biliary-Pancreat Sci 21:176–185

Kuroki T, Tanaka T, Kitasato A, Adachi T, Ono S, Hirabaru M, Takatsuki M, Eguchi S (2013) Decreased expression of SOX9 in intraductal papillary mucinous neoplasms of the bile duct. Hepatogastroenterology 60:1573–1576

Lapsia SK (2012) Intraductal papillary neoplasm of the bile ducts. AJR Am J Roentgenol 198:W627

Lee SS, Kim MH, Lee SK, Jang SJ, Song MH, Kim KP, Kim HJ, Seo DW, Song DE et al (2004) Clinicopathologic review of 58 patients with biliary papillomatosis. Cancer 100:783–793

Lee S, Kim YS, Lee WJ, Jang KT (2009) Intraductal oncocytic papillary neoplasm of the bile duct: ultrasonography and CT findings with pathological correlations. Clin Radiol 64:841–844

Li T, Ji Y, Zhi XT, Wang L, Yang XR, Shi GM, Zhang W, Tang ZY (2009) A comparison of hepatic mucinous cystic neoplasms with biliary intraductal papillary neoplasms. Clin Gastroenterol Hepatol 7:586–593

Lim JH, Jang KT (2010) Mucin-producing bile duct tumors: radiological-pathological correlation and diagnostic strategy. J Hepato-Biliary-Pancreat Sci 17:223–229

Lim JH, Kim YI, Park CK (2000) Intraductal mucosal-spreading mucin-producing peripheral cholangiocarcinoma of the liver. Abdom Imaging 25:89–92

Lim JH, Yi CA, Lim HK, Lee WJ, Lee SJ, Kim SH (2002) Radiological spectrum of intraductal papillary tumors of the bile ducts. Korean J Radiol 3:57–63

Lim JH, Jang KT, Rhim H, Kim YS, Lee KT, Choi SH (2007) Biliary cystic intraductal papillary mucinous tumor and cystadenoma/cystadenocarcinoma: differentiation by CT. Abdom Imaging 32:644–651

Lim JH, Jang KT, Choi D (2008) Biliary intraductal papillary-mucinous neoplasm manifesting only as dilatation of the hepatic lobar or segmental bile ducts: imaging features in six patients. AJR Am J Roentgenol 191:778–782

Lim LG, von Delius S, Meining A (2011a) Cholangioscopy and probe-based confocal laser

endomicroscopy in the diagnosis of an unusual liver cyst. Diagnosis: biliary intraductal papillary mucinous neoplasia. Gastroenterology 141:e5–e6

Lim JH, Zen Y, Jang KT, Kim YK, Nakanuma Y (2011b) Cyst-forming intraductal papillary neoplasm of the bile ducts: description of imaging and pathologic aspects. AJR Am J Roentgenol 197:1111–1120

Liszka L, Pajak J, Zielinska-Pajak E, Krzych L, Golka D, Mrowiec S, Lampe P (2010) Intraductal oncocytic papillary neoplasms of the pancreas and bile ducts: a description of five new cases and review based on a systematic survey of the literature. J Hepato-Biliary-Pancreat Sci 17:246–261

Madden JJ, Smith GW (1974) Multiple biliary papillomatosis. Cancer 34:1316–1320

Makino I, Yoshimitsu Y, Sakuma H, Nakai M, Ueda H (2010) A large cystic tumor with bile duct communication originating around the hepatic hilum. J Gastrointest Liver Dis 19:77–80

Mano Y, Aishima S, Fujita N, Taketomi A, Shirabe K, Maehara Y, Oda Y (2011) Cystic tumors of the liver: on the problems of diagnostic criteria. Pathol Res Pract 207:659–663

Martin RC, Klimstra DS, Schwartz L, Yilmaz A, Blumgart LH, Jarnagin W (2002) Hepatic intraductal oncocytic papillary carcinoma. Cancer 95:2180–2187

Matsubara T, Sato Y, Sasaki M, Harada K, Nomoto K, Tsuneyama K, Nakamura K et al (2012) Immunohistochemical characteristics and malignant progression of hepatic cystic neoplasms in comparison with pancreatic counterparts. Hum Pathol 43:2177–2186

Matthaei H, Wu J, Dal Molin M, Debeljak M, Lingohr P, Katabi N, Klimstra DS, Adsay NV et al (2012) GNAS codon 201 mutations are uncommon in intraductal papillary neoplasms of the bile duct. HPB (Oxford) 14:677–683

Minagawa N, Sato N, Mori Y, Tamura T, Higure A, Yamaguchi K (2013) A comparison between intraductal papillary neoplasms of the biliary tract (BT-IPMNs) and intraductal papillary mucinous neoplasms of the pancreas (P-IPMNs) reveals distinct clinical manifestations and outcomes. Eur J Surg Oncol 39:554–558

Mutoh H, Hakamata Y, Sato K, Eda A, Yanaka I, Honda S, Osawa H, Kaneko Y, Sugano K (2002) Conversion of gastric mucosa to intestinal metaplasia in Cdx2-expressing transgenic mice. Biochem Biophys Res Commun 294:470–479

Nakamura A, Horinouchi M, Goto M, Nagata K, Sakoda K, Takao S, Imai K, Kim YS, Sato E, Yonezawa S (2002) New classification of pancreatic intraductal papillary-mucinous tumour by mucin expression: its relationship with potential for malignancy. J Pathol 197:201–210

Nakanishi Y, Zen Y, Kondo S, Itoh T, Itatsu K, Nakanuma Y (2008) Expression of cell cycle-related molecules in biliary premalignant lesions: biliary intraepithelial neoplasia and biliary intraductal papillary neoplasm. Hum Pathol 39:1153–1161

Nakanishi Y, Zen Y, Hirano S, Tanaka E, Takahashi O, Yonemori A, Doumen H, Kawakami H et al (2009) Intraductal oncocytic papillary neoplasm of the bile duct: the first case of peribiliary gland origin. J Hepato-Biliary-Pancreat Sci 16:869–873

Nakanishi Y, Nakanuma Y, Ohara M, Iwao T, Kimura N, Ishidate T, Kijima H (2011) Intraductal papillary neoplasm arising from peribiliary glands connecting with the inferior branch of the bile duct of the anterior segment of the liver. Pathol Int 61:773–777

Nakanuma Y (2010) A novel approach to biliary tract pathology based on similarities to pancreatic counterparts: is the biliary tract an incomplete pancreas? Pathol Int 60:419–429

Nakanuma Y, Yamaguchi K, Ohta G, Terada T (1988) Pathologic features of hepatolithiasis in Japan. Hum Pathol 19:1181–1186

Nakanuma Y, Sasaki M, Ishikawa A, Tsui W, Chen TC, Huang SF (2002) Biliary papillary neoplasm of the liver. Histol Histopathol 17:851–861

Nakanuma Y, Curado MP, Franceschi S, Gores G, Paradis V, Sripa B, Tsui WMS et al (2010a) Intrahepatic cholangiocarcinoma. In: Bosman F et al (eds) WHO classification of tumours of the digestive system. IARC, Lyon, pp 223–224

Nakanuma Y, Zen Y, Harada K, Ikeda H, Sato Y, Uehara T, Sasaki M (2010b) Tumorigenesis and phenotypic characteristics of mucin-producing bile duct tumors: an immunohistochemical approach. J Hepato-Biliary-Pancreat Sci 17:211–222

Nakanuma Y, Harada K, Sasaki M, Sato Y (2014a) Proposal of a new disease concept "biliary diseases with pancreatic counterparts". Anatomical and pathological bases. Histol Histopathol 29:1–10

Nakanuma Y, Sato Y, Ojima H, Kanai Y, Aishima S, Yamamoto M, Ariizumi SI, Furukawa T et al (2014b) Clinicopathological characterization of so-called "cholangiocarcinoma with intraductal papillary growth" with respect to "intraductal papillary neoplasm of bile duct (IPNB)". Int J Clin Exp Pathol 7:3112–3122

Nanashima A, Sumida Y, Tamaru N, Nakanuma Y, Abo T, Tanaka K, Sawai T, Yasutake T et al (2006) Intraductal papillary neoplasm of the bile duct extending superficially from the intrahepatic to extrahepatic bile duct. J Gastroenterol 41:495–499

Nanashima A, Kinoshita N, Nakanuma Y, Zen Y, Sumida Y, Abo T, Hidaka S, Takeshita H et al (2008a) Clinicopathological features of "intraductal papillary neoplasm of the bile duct" and patient outcome after surgical resection. Hepatogastroenterology 55:1167–1173

Nanashima A, Sumida Y, Tomoshige K, Takeshita H, Shibata K, Sawai T, Yasutake T et al (2008b) A case of intraductal papillary neoplasm of the bile duct with stromal invasion. Case Rep Gastroenterol 2:314–320

Nanashima A, Tobinaga S, Araki M, Kunizaki M, Abe K, Hayashi H, Harada K, Nakanuma Y et al (2011) Intraductal papillary growth of liver metastasis

originating from colon carcinoma in the bile duct: report of a case. Surg Today 41:276–280
Negi SS, Gondal R, Chaudhary A (2009) Biliary papillomatosis with adenocarcinoma arising in choledochal cyst. Trop Gastroenterol 30:221–222
Ogawa H, Itoh S, Nagasaka T, Suzuki K, Ota T, Naganawa S (2012) CT findings of intraductal papillary neoplasm of the bile duct: assessment with multiphase contrast-enhanced examination using multi-detector CT. Clin Radiol 67:224–231
Ohta H, Yamaguchi Y, Yamakawa O, Watanabe H, Satomura Y, Matoo Y, Okai T et al (1993) Biliary papillomatosis with the point mutation of K-ras gene arising in congenital choledochal cyst. Gastroenterology 105:1209–1212
Ohtsubo I, Ajiki T, Hori Y, Murakami S, Shimizu K, Itoh T, Shimizu M, Fukumoto T et al (2012) Distinctive expression of CD133 between intraductal papillary neoplasms of the bile duct and bile duct adenocarcinomas. Hepatol Res 42:574–582
Ohtsuka M, Kimura F, Shimizu H, Yoshidome H, Kato A, Yoshitomi H, Furukawa K et al (2011) Similarities and differences between intraductal papillary tumors of the bile duct with and without macroscopically visible mucin secretion. Am J Surg Pathol 35:512–521
Ohtsuka M, Shimizu H, Kato A, Yoshitomi H, Furukawa K, Tsuyuguchi T, Sakai Y, Yokosuka O et al (2014) Intraductal papillary neoplasms of the bile duct. Int J Hepatol 2014:459091
Onishi I, Kitagawa H, Harada K, Maruzen S, Sakai S, Makino I, Hayashi H, Nakagawara H et al (2013) Intraductal papillary neoplasm of the bile duct accompanying biliary mixed adenoneuroendocrine carcinoma. World J Gastroenterol 19:3161–3164
Onoe S, Shimoyama Y, Ebata T, Yokoyama Y, Igami T, Sugawara G, Nakamura S et al (2014) Prognostic delineation of papillary cholangiocarcinoma based on the invasive proportion: a single-institution study with 184 patients. Surgery 155:280–291
Oshikiri T, Kashimura N, Katanuma A, Maguchi H, Shinohara T, Shimizu M, Kondo S et al (2002) Mucin-secreting bile duct adenoma – clinicopathological resemblance to intraductal papillary mucinous tumor of the pancreas. Dig Surg 19:324–327
Padfield CJ, Ansell ID, Furness PN (1988) Mucinous biliary papillomatosis: a tumour in need of wider recognition. Histopathology 13:687–694
Paik KY, Heo JS, Choi SH, Choi DW (2008) Intraductal papillary neoplasm of the bile ducts: the clinical features and surgical outcome of 25 cases. J Surg Oncol 97:508–512
Park HJ, Jang KT, Heo JS, Choi YL, Han J, Kim SH (2010) A potential case of intraductal tubulopapillary neoplasms of the bile duct. Pathol Int 60:630–635
Patel A, Lambiase L, Decarli A, Fazel A (2005) Management of the mucin filled bile duct. A complication of intraductal papillary mucinous tumor of the pancreas. JOP 6:255–259
Pavone E, Mehta SN, Hilzenrat N, Bret P, Lough J, Goresky CA, Barkun AN, Jabbari M (1997) Role of ERCP in the diagnosis of intraductal papillary mucinous neoplasms. Am J Gastroenterol 92:887–890
Qualtrough D, Hinoi T, Fearon E, Paraskeva C (2002) Expression of CDX2 in normal and neoplastic human colon tissue and during differentiation of an in vitro model system. Gut 51:184–190
Rocha FG, Lee H, Katabi N, DeMatteo RP, Fong Y, D'Angelica MI, Allen PJ, Klimstra DS et al (2012) Intraductal papillary neoplasm of the bile duct: a biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas ? Hepatology 56:1352–1360
Rouzbahman M, Serra S, Adsay NV, Bejarano PA, Nakanuma Y, Chetty R (2007) Oncocytic papillary neoplasms of the biliary tract: a clinicopathological, mucin core and Wnt pathway protein analysis of four cases. Pathology 39:413–418
Sagar PM, Omar M, Macrie J (1993) Extrahepatic biliary papillomatosis occurring after removal of a dysplastic gall bladder. HPB Surg 6:219–221
Sakamoto E, Hayakawa N, Kamiya J, Kondo S, Nagino M, Miyachi M, Uesaka K, Nimura Y et al (1997) Treatment strategy for mucin-producing intrahepatic cholangiocarcinoma: values of percutaneous transhepatic biliary drainage and cholangioscopy. World J Surg 23:1038–1043
Sakamoto et al (1999) http://www.ncbi.nlm.nih.gov/pubmed/10512944
Sasaki M, Nakanuma Y, Terada T, Kim YS (1995) Biliary epithelial expression of MUC1, MUC2, MUC3 and MUC5/6 apomucins during intrahepatic bile duct development and maturation. An immunohistochemical study. Am J Pathol 147:574–579
Sasaki M, Nakanuma Y, Kim Y (1996) Characterization of apomucin expression in intrahepatic cholangiocarcinomas and their precursor lesions: an immunohistochemical study. Hepatology 24:1074–1078
Sasaki M, Nakanuma Y, Kim Y (1998) Expression of apomucins in the intrahepatic biliary tree in hepatolithiasis differs from that in normal liver and extrahepatic biliary obstruction. Hepatology 27:46–53
Sasaki M, Matsubara T, Nitta T, Sato Y, Nakanuma Y (2013a) GNAS and KRAS mutations are common in intraductal papillary neoplasms of the bile duct. PLoS One 8:e81706
Sasaki M, Matsubara T, Yoneda N, Tsuneyama K, Sato Y, Nakanuma Y (2013b) Overexpression of enhancer of zeste homolog 2 and MUC1 may be related to malignant behaviour in intraductal papillary neoplasm of the bile duct. Histopathology 62:446–457
Sato Y, Osaka H, Harada K, Sasaki M, Nakanuma Y (2010) Intraductal tubular neoplasm of the common bile duct. Pathol Int 60:516–519
Sato H, Sato Y, Harada K, Sasaki M, Hirano K, Nakanuma Y (2013) Metachronous intracystic and intraductal papillary neoplasms of the biliary tree. World J Gastroenterol 19:6125–6126

Sato Y, Harada K, Sasaki M, Nakanuma Y (2014) Cystic and micropapillary epithelial changes of peribiliary glands might represent a precursor lesion of biliary epithelial neoplasms. Virchows Arch 464:157–163

Schlitter AM, Born D, Bettsteiner M, Specht K, Kim-Fuchs C, Riener MO, Jeliazkova P et al (2014) Intraductal papillary neoplasms of the bile duct: stepwise progression to carcinoma involves common molecular pathways. Mod Pathol 27:73–86

Sen I, Raju RS, Vyas FL, Eapen A, Sitaram V (2012) Benign biliary papillomatosis in a patient with a choledochal cyst presenting as haemobilia: a case report. Ann R Coll Surg Engl 94:e20–e21

Shibahara H, Tamada S, Goto M, Oda K, Nagino M, Nagasaka T, Batra SK, Hollingsworth MA et al (2004) Pathologic features of mucin-producing bile duct tumors: two histopathologic categories as counterparts of pancreatic intraductal papillary-mucinous neoplasms. Am J Surg Pathol 28:327–338

Shimoda T, Yoshida H, Hirakata A, Makino H, Yokoyama T, Maruyama H, Ueda J et al (2013) Surgical resection of cystic intraductal papillary adenocarcinoma of the bile duct: report of case. J Nippon Med Sch 80:234–239

Shimonishi T, Zen Y, Chen TC, Chen MF, Jan YY, Yeh TS, Nimura Y, Nakanuma Y (2002) Increasing expression of gastrointestinal phenotypes and p53 along with histologic progression of intraductal papillary neoplasia of the liver. Hum Pathol 33:503–511

Shinozaki A, Shibahara J, Noda N, Tanaka M, Aoki T, Kokudo N, Fukayama M (2011) Claudin-18 in biliary neoplasms. Its significance in the classification of intrahepatic cholangiocarcinoma. Virchows Arch 459:73–80

Silberg DG, Sullivan J, Kang E, Swain GP, Moffett J, Sund NJ, Sackett SD, Kaestner KH (2002) Cdx2 ectopic expression induces gastric intestinal metaplasia in transgenic mice. Gastroenterology 122:689–696

Somogyi L, Dimashkieh H, Weber FL, Buell J (2003) Biliary intraductal papillary mucinous tumor: diagnosis and localization by endoscopic retrograde cholangioscopy. Gastrointest Endosc 57:620–622

Sotiropoulos GC, Lang H, Nadalin S, Holtmann G, Dirsch O, Broelsch CE (2003) Papillomatosis confined to the distal biliary tract – a rare cause of obstructive jaundice: report of a case. Surg Today 33:781–784

Spector SA, Bejarano PA, Amortegui JD, Renfrow MR, Livingstone AS (2004) Intraductal oncocytic papillary neoplasm of the extrahepatic biliary tree: first report. Am Surg 70:55–58

Sudo Y, Harada K, Tsuneyama K, Katayanagi K, Zen Y, Nakanuma Y (2001) Oncocytic biliary cystadenocarcinoma is a form of intraductal oncocytic papillary neoplasm of the liver. Mod Pathol 14:1304–1309

Tabibian JH, Lassman CR, Margolis DJ, Landaverde C, Busuttil RW, Durazo FA (2008) Intraductal oncocytic papillary of the liver: case and review of a rare variant. Ann Hepatol 7:168–173

Tajiri T, Tate G, Matsumoto K, Hoshino H, Iwamura T, Kodaira Y, Takahashi K, Ohike N et al (2012) Diagnostic challenge: Intraductal neoplasms of the pancreatobiliary system. Pathol Res Pract 208:691–696

Takahashi N, Taniguchi T, Adachi M (2014) A case of needle tract seeding of an intraductal papillary neoplasm of the bile duct (IPNB) after percutaneous biopsy. Eur J Dermatol 24:128–130

Takanami K, Yamada T, Tsuda M, Takase K, Ishida K, Nakamura Y, Kanno A, Shimosegawa T et al (2011) Intraductal papillary mucinous neoplasm of the bile ducts: multimodality assessment with pathologic correlation. Abdom Imaging 36:447–456

Takasu N, Kimura W, Moriya T, Hirai I, Takeshita A, Kamio Y, Nomura T (2010) Intraductal papillary-mucinous neoplasms of the gastric and intestinal types may have less malignant potential than the pancreatobiliary type. Pancreas 39:604–610

Tanaka M, Fukushima N, Noda N, Shibahara J, Kokudo N, Fukayama M (2009) Intraductal oncocytic papillary neoplasm of the bile duct: clinicopathologic and immunohistochemical characteristics of 6 cases. Hum Pathol 40:1543–1552

Terada T (2012) Malignant intraductal oncocytic papillary neoplasm of the common bile duct. Int J Clin Exp Pathol 5:96–101

Terada T, Taniguchi M (2004) Intraductal oncocytic papillary neoplasm of the liver. Pathol Int 54:116–123

Terada T, Mitsui T, Nakanuma Y, Miura S, Toya D (1991) Intrahepatic biliary papillomatosis arising in nonobstructive intrahepatic biliary dilatations confined to the hepatic left lobe. Am J Gastroenterol 86:1523–1526

Terris B, Dubois S, Buisine MP, Sauvanet A, Rusziewski P, Aubert JP, Porchet N, Couvelard A, Degott C, Fléjou JF (2002) Mucin gene expression in intraductal papillary-mucinous pancreatic tumours and related lesions. J Pathol 197:632–637

Tireli M, Uslu A (1992) Multiple biliary papillomatosis. HPB Surg 6:125–127

Tsai JH, Yuan RH, Chen YL, Liau JY, Jeng YM (2013) GNAS is frequently mutated in a specific subgroup of intraductal papillary neoplasms of the bile duct. Am J Surg Pathol 37:1862–1870

Tsuyuguchi T, Sakai Y, Sugiyama H, Miyakawa K, Ishihara T, Ohtsuka M, Miyazaki M et al (2010) Endoscopic diagnosis of intraductal papillary mucinous neoplasm of the bile duct. J Hepato-Biliary-Pancreat Sci 17:230–235

Uchiyama S, Chijiiwa K, Hiyoshi M, Nagano M, Ohuchida J, Nagaike K, Kai M, Kondo K (2007) Mucin-producing bile duct tumor of the caudate lobe protruding into the common hepatic duct. J Gastrointest Endosc 11:1570–1572

Ustundag Y, Baron TH, Smyrk TC (2006) Bile duct cancer in the setting of intraductal papillary mucinous tumor appearing as an impacted bile duct stone on ERCP. Gastrointest Endosc 63:861–862

Valente R, Capurso G, Pierantognetti P, Iannicelli E, Piciucchi M, Romiti A, Mercantini P et al (2012) Simultaneous intraductal papillary neoplasms of the bile duct and pancreas treated with chemoradiotherapy. World J Gastrointest Oncol 4:22–25

Verma A, Batey A, Greenberg E, Uzoaru I (2009) An uncommon etiology of cholestatic jaundice: intraductal mucinous papillary tumor of the bile duct. South Med J 102:422–424

Wan XS, Xu YY, Qian JY, Yang XB, Wang AQ, He L, Zhao HT, Sang XT (2013) Intraductal papillary neoplasm of the bile duct. World J Gastroenterol 19:8595–8604

Watanabe A, Suzuki H, Kubo N, Araki K, Kobayashi T, Sasaki S, Wada W, Arai H et al (2013) An oncocytic variant of intraductal papillary neoplasm of the bile duct that formed a giant hepatic cyst. Rare Tumors 5: e30

Werling RW, Yaziji H, Bacchi CE, Gown AM (2003) CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. Am J Surg Pathol 27:303–310

Xu J, Sato Y, Harada K, Yoneda N, Ueda T, Kawashima A, Akishiooi, Nakanuma Y (2011) Intraductal papillary neoplasm of the bile duct in liver cirrhosis with hepatocellular carcinoma. World J Gastroenterol 17:1923–1926

Xu XW, Li RH, Zhou W, Wang J, Zhang RC, Chen K, Mou YP (2012) Laparoscopic resection of synchronous intraductal papillary mucinous neoplasms: a case report. World J Gastroenterol 18:6510–6514

Yamamoto H, Bai YQ, Yuasa Y (2003) Homeodomain protein CDX2 regulates goblet-specific MUC2 gene expression. Biochem Biophys Res Commun 300:813–818

Yaman B, Nart D, Yilmaz F, Coker A, Zeytunlu M, Kilic M (2009) Biliary intraductal papillary mucinous neoplasia: three case reports. Virchows Arch 454:589–594

Yamashita Y, Fukuzawa K, Taketomi A, Aishima S, Yoshizumi T, Uchiyama H, Tsujita E et al (2007) Mucin-hypersecreting bile duct neoplasm characterized by clinicopathological resemblance to intraductal papillary mucinous neoplasm (IPMN) of the pancreas. World J Surg Oncol 5:98

Yang J, Wang W, Yan L (2012) The clinicopathological features of intraductal papillary neoplasms of the bile duct in a Chinese population. Dig Liver Dis 44:251–256

Yeh CN, Jan YY, Yeh TS, Hwang TL, Chen MF (2004) Hepatic resection of the intraductal papillary type of peripheral cholangiocarcinoma. Ann Surg Oncol 11:606–611

Yeh TS, Tseng JH, Chen TC, Liu NJ, Chiu CT, Jan YY, Chen MF (2005) Characterization of intrahepatic cholangiocarcinoma of the intraductal growth-type and its precursor lesions. Hepatology 42:657–664

Yeh TS, Tseng JH, Chiu CT, Liu NJ, Chen TC, Jan YY, Chen MF (2006) Cholangiographic spectrum of intraductal papillary mucinous neoplasm of the bile ducts. Ann Surg 244:248–253

Yeung YP, AhChong K, Chung CK, Chun AY (2003) Biliary papillomatosis: report of seven cases and review of English literature. J Hepato-Biliary-Pancreat Sci 10:390–395

Yonezawa S, Higashi M, Yamada N, Yokoyama S, Goto M (2010) Significance of mucin expression in pancreatobiliary neoplasms. J Hepato-Biliary-Pancreat Sci 17:108–124

Yoon HJ, Kim YK, Jang KT, Lee KT, Lee JK, Choi DW, Lim JH (2013) Intraductal papillary neoplasm of the bile ducts: description of MRI and added value of diffusion-weighted MRI. Abdom Imaging 38:1082–1090

Zalinski S, Paradis V, Valla D, Belghiti J (2007) Intraductal papillary mucinous tumors of both biliary and pancreatic ducts. J Hepatol 46:978–979

Zen Y, Fujii T, Itatsu K, Nakamura K, Minato H, Kasashima S, Kurumaya H, Katayanagi K et al (2006a) Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas. Hepatology 44:1333–1343

Zen Y, Fujii T, Itatsu K, Nakamura K, Konishi F, Masuda S, Mitsui T, Asada Y, Miura S et al (2006b) Biliary cystic tumors with bile duct communication: a cystic variant of intraductal papillary neoplasm of the bile duct. Mod Pathol 19:1243–1254

Zen Y, Sasaki M, Fujii T, Chen TC, Chen MF, Yeh TS, Jan YY, Huang SF, Nimura Y et al (2006c) Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct – an immunohistochemical study of 110 cases of hepatolithiasis. J Hepatol 44:350–358

Zen Y, Pedica F, Patcha VR, Capelli P, Zamboni G, Casaril A, Quaglia A, Nakanuma Y et al (2011) Mucinous cystic neoplasms of the liver: a clinicopathological study and comparison with intraductal papillary neoplasms of the bile duct. Mod Pathol 24:1079–1089

Zen Y, Amarapurkar AD, Portmann BC (2012) Intraductal tubulopapillary neoplasm of the bile duct: potential origin from peribiliary cysts. Hum Pathol 43:440–445

Zen Y, Jang KT, Ahn S, Kim DH, Choi DW, Choi SH, Heo JS, Yeh MM (2014) Intraductal papillary neoplasms and mucinous cystic neoplasms of the hepatobiliary system: demographic differences between Asian and Western populations, and comparison with pancreatic counterparts. Histopathology 65:164–173

Zou XP, Zhang M, Li W, Wu YL (2011) Biliary intraductal papillary-mucinous neoplasm diagnosed by peroral direct cholangioscopy using a slim upper endoscope (with video). Surg Laparosc Endosc Percutaneous Tech 21:e263–e265

Cholangiocarcinomas Arising in Cystic Lesions of the Hepatobiliary Tract and in Pancreaticobiliary Maljunction

34

Contents

Abstract

There is a well-known association between cholangiocarcinomas and several types of cystic lesions of the hepatobiliary tract and pancreaticobiliary maljunction. Specifically, biliary tract cysts and inflammatory changes occurring in them result in significant risk for cholangiocarcinogenesis. These cysts include cystic dilatation of the common bile duct, diverticulum of the extrahepatic duct, choledochocele, multiple extrahepatic biliary cysts, and Caroli's disease. Among complications of choledochal cysts, malignant transformation is in fact the most concerning. Carcinomas develop either in the cyst wall itself or in undilated parts of intrahepatic or extrahepatic ducts. Histologically, cyst-associated cancers are mostly classical cholangiocarcinomas, but squamous cell carcinomas and other malignancies may also occur. A second group of biliary tract conditions that are associated with increased carcinoma risk are various forms of pancreaticobiliary maljunction.

Cancers Arising in Choledochal Cysts

Introduction

Choledochal cysts are uncommon congenital or acquired cystic dilatations of the extrahepatic or intrahepatic bile ducts. These distinct lesions were

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_34

Table 1 Todani classification of biliary tree cysts (modified)

Type	Morphologic features
I	Cystic dilatation of the common bile duct
	I A: saccular, involving the entire extrahepatic bile duct
	I B: saccular, involving a limited segment of the extrahepatic duct
	I C: fusiform, involving all or most of the extrahepatic duct
II	True diverticulum of the extrahepatic bile duct
III	Choledochocele (cystic change limited to the intraduodenal portion of the distal common bile duct)
IV	Multiple extrahepatic biliary cysts
	IV A: associated intrahepatic cysts
	IV B: extrahepatic cysts only
V	Caroli's disease

first described by Vater and Ezler in 1723. In 1852, Douglas described the clinical features of choledochal cyst based on a jaundiced female adolescent patient who showed a palpable abdominal mass (reviews: Yamaguchi 1980; Lipsett et al. 1994; Gigot et al. 1996; Soreide et al. 2004; Visser et al. 2004; Wiseman et al. 2005).

The cysts were first classified in 1959 (Alenso-Lej et al. 1959), based on the clinical and anatomic findings of 96 cases. The authors divided choledochal cysts into three types. This classification system was later refined by Todani and coworkers. The Todani classification of these lesions is based on five main types (Todani et al. 1977, 2003; Table 1).

Type I cysts are the most common (80–90 %) and are characterized by saccular or fusiform dilatation of the entire common bile duct and common hepatic duct or of parts/segments of each. As seen in the Table, the cyst morphology and the extent of involvement are used to subdivide type I cysts into three subtypes. Type II cysts present as mostly isolated protrusions projecting from the common duct wall. The diverticular morphology ranges from rather flat or sessile to pedunculated lesions showing a stalk. In Type IV A, the most common configuration is that of a large extrahepatic solitary cyst associated with multiple smaller cysts of the intrahepatic bile ducts. Type IV B show multiple dilatations involving exclusively the extrahepatic bile duct system. Type V, identical to Caroli's disease, shows dilatations of the intrahepatic biliary radicles that mostly involve both liver lobes. Unilobar/monolobar disease may also occur and usually involves the left liver lobe.

Epidemiology

Among complications of choledochal cysts, malignant transformation is the most concerning. This is an age-related phenomenon occurring in 10–14 % of adults with choledochal cysts. All studies have shown that cholangiocarcinoma and other carcinomas complicating choledochal cysts occur more often in adults than in children.

Selected References Ferraris et al. 1944; Irwin and Morison 1944; Armanino 1946; Wilson et al. 1956; Dexter 1957; Fischer 1958; McKenzie et al. 1958; George and Maingot 1962; Nakajima et al. 1963; Ashby 1964; Kelly and Schlueter 1964; Fukuuchi 1967; Hizawa et al. 1967; Macfarlane and Glenn 1967; Thistlethwaite and Horwitz 1967; Schiewe et al. 1968; Tanaka et al. 1968, 1969; Jones and Shreeve 1970; Lorenzo et al. 1971; Nasu et al. 1971; Weber et al. 1971; Gallagher et al. 1972; Spitz 1972; Uchimura et al. 1972; Yoshimura et al. 1972; Shimomura et al. 1974; Fukushima 1975; Iinuma 1975; Shinagawa et al. 1975; Aikawa et al. 1976; Fujiwara et al. 1976; Keminger et al. 1976; Komi et al. 1976; Tsurimi et al. 1976; Yamamura et al. 1976; Flanigan 1977; Todani et al. 1977; Tsuchiya et al. 1977; Kagawa et al. 1978; Chaudhuri et al. 1982; Bova et al. 1983; Voyles et al. 1983; Bourdin et al. 1984; Nagorney et al. 1984; Samshima et al. 1986; Yeoh et al. 1986; Baumann et al. 1987; Rossi et al. 1987; Valabrega et al. 1987; Binstock et al. 1988; Leong et al. 1988; Okayama

et al. 1991; Pisano et al. 1991; Holzinger et al. 1996; Han and Choi 1996; Stalder et al. 1996; Todani and Toki 1996; Ishibashi et al. 1997; Kale and Kuzu 1997; Lenriot et al. 1998; Yoshikane et al. 1998; Okamura et al. 2000; Patel et al. 2001; de Vries et al. 2002; Jan et al. 2002; Atkinson et al. 2003; Tseng et al. 2003; Tsuchida et al. 2003b; Zheng et al. 2004.

Carcinomas and other malignancies develop either in the cyst wall itself or in remnant tissues or undilated parts of the intrahepatic or extrahepatic bile duct system. The tumors are either detected at primary operations or secondary operations (review: Kagawa et al. 1978), but several cases were found at autopsy only, without previous operation (Armanino 1946; Dexter 1957; George and Maingot 1962; Jones and Shreeve 1970; Nasu et al. 1971; Gallagher et al. 1972).

Gallbladder carcinoma or cholangiocarcinoma was noted in 9.7 % of 42 patients (Lipsett et al. 1994). Among 42 patients with various types of choledochal cysts, cholangiocarcinoma was found in six patients, four of whom had previously undergone internal drainage procedures (de Vries et al. 2002). In a follow-up study of 72 adult patients who presented with choledochal cysts, the incidence of cholangiocarcinoma with non-cyst excision or non-operated congenital choledochal cysts was 10.8 % (Zheng et al. 2004). Intrahepatic cholangiocarcinoma can develop in patients subsequent to choledochal cyst resection, sometimes after a period exceeding 30 years (Fukuuchi 1967; Gallagher et al. 1972; Shields 1977; Chaudhuri et al. 1982; Yoshikawa et al. 1986; Scudamore et al. 1994; Kobayashi et al. 1999; Watanabe et al. 1999; Goto et al. 2001; Suzuki et al. 2004; Ono et al. 2008; Shimamura et al. 2009). In a review of nine cases of cholangiocarcinoma developing subsequent to resection of a choledochal cyst, the time period between cyst resection and diagnosis of carcinoma ranged from 2 to 34 years, in five cases exceeding 10 years and in four cases exceeding 20 years (Shimamura et al. 2009). Cholangiocarcinoma has been found in an adult patient aged 26 years after an infantile choledochal cyst resected at the age of 5 months (Ono et al. 2008).

Choledochal Cyst-Associated Adenocarcinoma

The types of cancer that have been reported in these lesions or the draining intrahepatic bile ducts mainly comprised classical cholangiocarcinoma and less commonly squamous cell carcinoma. In one of the first reports, from 1944, the tumor arising in a stone-containing choledochal cyst itself was squamous carcinoma (Irwin and Morison 1944). In a study reviewing 40 cases, adenocarcinoma was found in 31 cases, undifferentiated carcinoma in seven cases, and squamous cell carcinoma in two cases (Kagawa et al. 1978). Carcinoma can develop at the anastomotic site of hepaticojejunostomy (Yamamoto et al. 1996). It is known that late bile duct cancer is a complication of biliary-enteric anastomosis as such, i.e., not only after resection of choledochal cyst (Strong 1999). Among 204 patients with adult choledochal cyst disease in whom cysts were resected, de novo malignancy at the cyst remnant occurred in two patients (1 %; Cho et al. 2011). A part of congenital choledochal cysts are associated with pancreaticobiliary maljunction. In a study of 1433 Japanese patients with choledochal cysts, 151 patients had maljunction (Yamaguchi 1980). There is evidence that maljunction increases the risk of biliary tract carcinogenesis in choledochal cyst disease (Kobayashi et al. 1999; Song et al. 1999; Sugiyama et al. 1999; Matsumoto et al. 2003; Tashiro et al. 2003). Extrahepatic cholangiocarcinoma has been found in patients having choledochal cyst associated with pancreaticobiliary maljunction (Baumann et al. 1987; Sameshima et al. 1987; Okamura et al. 2000). Among 52 patients with choledochal cyst, pancreaticobiliary maljunction was associated with choledochal cyst in 64 % of the cases, but maljunction was only found in Todani types I

and IV. Carcinoma developed only in the maljunction group (32 %; Song et al. 1999).

Early Choledochal Cyst-Associated Carcinoma

Early carcinoma can sometimes be detected in choledochal cysts. In one case, a resected cyst showed a white plain area of thickness 3 and 8 mm in diameter, histologically characterized by well-differentiated tubular adenocarcinoma (Kraus et al. 2003). There are few published observations referring to precursor lesions of cholangiocarcinoma found in choledochal cysts. Adenomatous hyperplasia was detected in a simple excision specimen of cysts, followed by cholangiocarcinoma 2 years later (Coyle and Bradley 1992). Development of cholangiocarcinoma from an adenoma in choledochal cyst has also been described. In one patient, the resected cyst was lined with a shaggy papillary pink mucosa histologically representing a predominantly villous adenoma, at one place with a transition to cholangiocarcinoma (Franko et al. 2006). In rarer situations, early cancer or invasive adenocarcinoma has been observed in the dilated intrahepatic ducts associated with choledochal cysts (Tajiri et al. 1997; Kawamoto et al. 1998). It is currently thought that chronic inflammatory damage of epithelium and erosion/ulceration followed by persistent regeneration is the main pathogenic pathway for cancerogenesis in these cysts. Cholangiocarcinoma may also develop after surgical treatment of choledochal cysts (Tsuchida et al. 2003b), possibly caused by ascending cholangitis. In one patient with treated Todani type Ia congenital biliary dilatation, intrahepatic cholangiocarcinoma developed 10 years after Roux-en-Y hepaticoduodenostomy (Goto et al. 2001).

Choledochal Cyst-Associated Squamous Cell Carcinoma

Few cases of squamous cell carcinoma have been reported (Todani et al. 1977; Harris et al. 2002; Jan et al. 2002; Price et al. 2008). These carcinomas may develop from squamous metaplasia within cysts. Metaplasia can undergo dysplasia, thus initiating a dysplasia-carcinoma sequence.

Biliary Papillomatosis/Intraductal Papillary Neoplasms

Choledochal cyst can be complicated by the development of biliary papillomatosis followed by adenocarcinoma (Negi et al. 2009). A patient with congenital choledochal cyst associated with intrahepatic gallstones developed biliary papillomatosis with point mutation of the K-ras gene (Ohita et al. 1993).

Cyst-Associated Sarcomas

Very rarely, choledochal cysts are complicated by development of sarcomas, e.g., pleomorphic rhabdomyosarcoma (Tufail et al. 2006). On the other hand, embryonal rhabdomyosarcoma of the common bile duct may radiologically mimic choledochal cyst in childhood (Tireli et al. 2005).

Carcinoma Arising in Caroli's Disease

Caroli's disease is a congenital disorder of the hepatobiliary tract characterized by usually nonobstructive fusiform or saccular dilatations of larger intrahepatic bile ducts (review: Yonem and Bayraktar 2007). Probably owing to progressive damage and regeneration of epithelia, there is an increased risk of cholangiocarcinoma (Leroy et al. 1980; Balsells et al. 1993; Falco et al. 1993; Abdalla et al. 1999; Totkas and Hohenberger 2000; Wang 2002; Vlachogiannakos et al. 2004; Kasper et al. 2006). Cholangiocarcinoma was observed in a female patient with Caroli's disease accompanied by hepatolithiasis and choledochlithiasis (Takei et al. 1991). Carcinoma in situ of dilated bile duct segments was detected in Caroli's disease (Joly et al. 1990).

Carcinoma Arising in Ciliated Foregut Cyst

Ciliated foregut cyst is a rare congenital cystic lesion of the liver derived from the embryonic foregut. The term was coined in 1984 to describe an hepatic cyst sharing common histologic features with both esophageal and bronchial/bronchogenic cysts (Wheeler and Edmondosn 1984). The cysts are thought to originate from evagination of a foregut component into the liver anlage. This type of cyst is usually located in the left liver lobe, with a strong predilection for segment IV, but it has also been observed in the right liver lobe, the gallbladder, the pancreas, and the retroperitoneal space. The cyst is lined by a single layer of ciliated cuboidal to prismatic cells. A little more than 100 cases have been reported, with less than 20 cases diagnosed in children (review: Fujita et al. 2011). Carcinomas can develop in ciliated foregut cysts. Almost all cases were squamous cell carcinomas (Vick et al. 1999; de Lajarte-Thirouard et al. 2002; Furlanetto and De Tos 2002; Zhang et al. 2009). This type of carcinoma may develop on the basis of squamous metaplasia known to occur in foregut cysts of the liver. In most instances, metaplasia was found in cysts that also had squamous cell carcinoma (Vick et al. 1999; de Lajarte-Thirouard et al. 2002; Furlanetto and Dei Tos 2002). In one case without associated carcinoma, the cyst was lined mainly by a regular squamous epithelium without keratinization. The squamous epithelial cells expressed cytokeratin 5/6 and cytokeratin 19, while the superficial squamous cells expressed cytokeratin 7. Focally, a ciliated pseudostratified columnar epithelium with some goblet cells was found. This ciliated epithelium expressed cytokeratins 7 and 19 (Ben Mena et al. 2006).

Cancer Arising in Nonparasitic Simple Liver Cysts

Cholangiocarcinoma can develop in simple developmental liver cysts (Ackerholm et al. 1981). Typically, the involved cysts show hemorrhage and/or inflammatory changes and have been found to be filled with chocolate-colored fluid. Squamous cell carcinoma was also demonstrated in simple nonparasitic cysts (Richmond 1956; Greenwood and Orr 1972; Bloustein and Silverberg 1976; Bloustein 1977; Lynch et al. 1988; Nieweg et al. 1992; Pliskin et al. 1992; Banbury et al. 1994; Weimann et al. 1996; Monteagudo et al. 1998; Hsieh et al. 2005). Symptoms and signs described in this type of tumor include pain and loss of weight. Jaundice and a palpable mass in the epigastrium have sometimes been found. At least a part of the tumors described in the literature were large lesions within remnants of a cyst. The carcinoma often grows into the tissue encircling the cyst, making resection difficult. The tumor tends to metastasize to the locoregional lymph nodes, while remote metastases have less often been found. Large squamous cell carcinoma tends to undergo necrosis and form central cysts, but the presence of innocuous epithelium in the cystic parts of the mass excludes the possibility that the cyst had arisen from necrosis of a preexistent primary or metastatic solid tumor. Biliary carcinosarcoma was also found in a simple liver cyst (Terada et al. 1994).

Carcinoma in Autosomal Dominant Polycystic Disease

Intrahepatic cholangiocarcinoma rarely develops in autosomal dominant polycystic kidney disease (ADPKD) with liver involvement (Imamura et al. 1984; Kataoka et al. 1985; Carone et al. 1994; Sasaki et al. 2002; Matsuoka et al. 2005). In one autopsy case (Sasaki et al. 2002), a 69-year-old man with known ADPKD, the liver was mildly enlarged, and many cysts up to 3 cm in diameter were mainly distributed along the biliary tree at the liver hilus and to a lesser degree in the hepatic parenchyma. A yellowish-white firm tumor (6 cm) was present in the right hepatic hilus, extending into the right lobe of the liver and involving several of the cystic lesions. Histologically, the mass was

composed of a well to moderately differentiated, desmoplastic tubular adenocarcinoma with vascular, lymphatic, and perineural invasion. In addition, there was well-differentiated papillary adenocarcinoma spreading in the lumen of several cysts embedded in and adjacent to the main carcinoma.

Cystadenocarcinoma Originating from Hepatic Cysts

Cystadenocarcinoma without mesenchymal stroma can develop in association with benign hepatic cysts (Azizah and Paradinas 1980). In one case, this lesion was associated with progressive morphologic changes assessed by follow-up imaging during 10 years (Akiyoshi et al. 2003).

Cholangiocarcinoma in Disorders of the Pancreaticobiliary Ductal Union

Introduction

Anomalous pancreaticobiliary ductal union (APBDU; synonym: pancreaticobiliary maljunction) is a congenital anomaly more commonly encountered in Asian than Western countries and significantly more common in females. The common feature of this condition is a pancreaticobiliary ductal union located proximal to the sphincter of Oddi, an anomaly first reported in 1969 (Babbitt 1969). APBDU is, therefore, characterized by union of the pancreatic and bile ducts located outside the duodenal wall, forming a very long common channel (usually >15 mm; average length in one study, 24.7 mm, Tanaka et al. 1998). Normally, the two ducts open into the duodenum either separately or via a common channel. The length of the common channel in normal subjects ranges from 1 to 12 mm, with a mean of 4.5 mm (Misra et al. 1989; Misra and Dwivedi 1990). The mode of union has been classified into two groups. The biliary-pancreatic (B-P) type junction has a common bile duct joining the main pancreatic duct; the pancreaticobiliary (P-B) type junction is the reverse of this (Kimura et al. 1985). APBDU may also be classified into dilated and non-dilated types in regard to the morphology of the common bile duct, the dilated type being more frequent. In a study of 1627 patients with APBDU enrolled and analyzed by the Japanese Study Group on Pancreaticobiliary Maljunction, 1239 patients had the dilated type, and 388 had the non-dilated type. Individuals with latter type were significantly older than those of the former (47 years vs. 24 years, respectively). APBDU is associated with various pancreaticobiliary diseases, including pancreatitis and biliary cancer (Kato et al 1983; Kamisawa et al. 2002, 2003, 2006, 2009b, 2010b; Matsumoto et al. 2002; Kimura et al. 2005; Miyazaki et al. 2008; Funabiki et al. 2009; Kimura 2009). The occurrence rate of cancer in the biliary tract was 10.6 % in the dilated type and 37.9 % in the non-dilated type (Tashiro et al. 2003).

APBDU is associated with a narrow portion of the terminal choledochus, and this narrow distal segment represents the functional region of the sphincter of Oddi (Kune 1964, 1970). Hence, the presence of APBDU is determined by two parameters, the length of the common channel and the length of the narrow segment (review: Nomura et al. 2002). Among patients with APBDU, biliary dilatation (>10 mm) was more frequent in those with the narrow choledochal portion (Nomura et al. 2005). A distinct entity is dilatation of the intrahepatic bile duct system associated with anomalous junction of the cystic duct, in the absence of APBDU (Ohama and Ishikawa 2006). APBDU is likely to be caused by disturbance in the morphogenesis of the connections of the pancreatic and biliary duct system that occurs very early during gestation when the common bile duct joins with the ventral pancreatic duct system (Matsumoto et al. 2001). Familial occurrence of APBDU has been described (Miyazaki et al. 1989). The long common channel causes two-way fluid regurgitation, with bile flowing into the pancreatic duct and pancreatic juice flowing into the bile duct, because the sphincter now cannot functionally affect the channel (Kamisawa and Okamoto 2006; Kamisawa

et al. 2009a). There is a relation between pancreaticobiliary reflux and the length of the common channel. The minimum length of a common channel that could induce a markedly elevated amylase level in bile was determined as 5 mm. Based on this observation, high confluence of pancreaticobiliary ducts (HCPBD) was defined as cases with a common channel > or = 5 mm, in which the communication between the pancreatic and bile ducts was occluded with the sphincter contraction (Kamisawa et al. 2010a). In the majority of cases, APBDU is associated with a normal intrapancreatic duct morphology, but in a minority, there is dorsal pancreatic duct dominance. In this situation, most pancreatic juice in the upper dorsal pancreatic duct is drained into the duodenum through the minor duodenal papilla, and reflux of pancreatic juice to the biliary tract may be reduced, resulting in reduced damage (Kamisawa et al. 2005).

How frequent is APBDU? Among 680 individuals with clearly visualized pancreaticobiliary radiograms during ERCP, 8.7 % had APBDU (Wang et al. 1998). In a nationwide Korean cooperative prospective study of 10,243 patients undergoing ERCP, the frequency of APBDU and choledochal cyst was 4.1 % and 0.32 %, respectively (Kim et al. 2002). In a prospective study of 354 ERCP cases, a common channel was detected in 131 cases (37 %). Among these, 11 had APBDU and 13 a high confluence of pancreaticobiliary ducts (Kamisawa et al. 2007). A strong association of APBDU with congenital duct dilatation or choledochal cyst has been confirmed in several studies (Kimura et al. 1977; Ono et al. 1982; Todani et al. 1984; Okada et al. 1990), the incidence ranging from 64 % (Song et al. 1999) to 93.8 % (Wang et al. 1998). In one study, APBDU was found only in type I and type IV choledochal cysts according to Todani's classification (Song et al. 1999). In congenital dilatation of the common bile duct associated with APBDU, epithelial hyperplasia accompanied by round cell infiltration and increased thickness of the duct wall with fibrosis was observed histologically in the resected bile duct in all patients (Oguchi et al. 1988).

Cholangiocarcinoma of the Extrahepatic Bile Ducts in APBDU

Cholangiocarcinoma involving the extrahepatic bile duct in APBDU is less often reported than gallbladder carcinoma, and the incidence varies considerably in the different reports (Kato et al. 1983; Suda et al. 1983; Strijk et al. 1984; Ohta et al. 1990; Tsai 2001; Nakamura et al. 2008; Saji et al. 2010). In an autopsy study of 72 cases of biliary tract carcinoma APBDU was found in 8/34 cases of common bile duct carcinoma and in 4/24 gallbladder carcinomas (Suda et al. 1983). Cholangiocarcinoma in APBDU associated with congenital biliary dilatation can already develop in childhood (Tanaka et al. 2006; Saikusa et al. 2009). In one study, 9/27 (33.3 %) patients with APBDU had common bile duct cancer, but only 1/47 (2.1 %) had hilar carcinoma (Wang et al. 1998). In another study, a long common channel was an infrequent finding in patients with cholangiocarcinoma. The mean length of the common channel in patients with cholangiocarcinoma was 6.43 mm, which was comparable to the length of the common channel in normal subjects (Sharma 1994). In a nationwide survey in Japan, a close relationship was shown between biliary tract carcinogenesis and APBDU, according to the type of maljunction (dilated vs. non-dilated types) and age distribution. APBDU patients with cystic dilatation of the bile duct had a high risk of bile duct cancer, even in those who were young (aged less than 20 years), and the incidence of gallbladder cancer increased markedly in patients older than 40 years. In contrast, the incidence of gallbladder carcinoma gradually increased in APBDU patients having the undilated type (Hasumi et al. 2000; Miyazaki et al. 2008). In a study of 38 patients with APBDU, the incidence of malignancy was 17.8 % in the dilated type (two patients with cholangiocarcinoma and three with gallbladder carcinoma) and 90 % in the non-dilated type (all with gallbladder carcinoma) (Tanaka et al. 1998). The predominance of gallbladder carcinomas over cholangiocarcinomas in non-dilated APBDU was shown in a previous study (Tanaka et al. 1993). The importance of the bile dilation status was

confirmed in another study. Ninety-eight cases of APBDU were divided into five groups according to the maximum diameter of the extrahepatic bile duct. Gallbladder carcinoma developed in 55 % of patients whose maximum diameter of the extrahepatic duct was < or = 30 mm, but no gallbladder carcinoma occurred in patients with APBDU whose duct diameter was > or = 31 mm. Bile duct carcinoma occurred in 12 % of patients whose duct diameter was > or = 21 mm, but no bile duct carcinoma occurred in those with a duct diameter of < or = 20 mm (Kamisawa et al. 2006).

Carcinoma of the Gallbladder in APBDU

APBDU confers a significant risk for gallbladder cancer. There is a clear predominance of female patients (Kamisawa et al. 2008). Even a long common channel (≥8 mm) in the absence of APBDU is associated with a higher frequency of gallbladder carcinoma (review: Misra and Dwivedi 1990). Among 106 Japanese patients with biliary tract cancer (58 patients with gallbladder carcinoma and 48 patients with cholangiocarcinoma), 10 patients (9.4 %) had APBDU (Sandoh et al. 1997). In a Chinese cohort of patients, the frequency of APBDU was significantly higher in patients with gallbladder carcinoma (Hu et al. 2003). Among 14 patients with APBDU, five patients developed gallbladder carcinoma, associated with a more frequent development of gallbladder mucosal metaplasia (Jung et al. 2004).

Selected References Kato et al. 1983; Kimura et al. 1985; Nagata et al. 1985; Yamauchi et al. 1987; Miyazaki et al. 1989; Sautereau et al. 1989; Ohta et al. 1990; Mori et al. 1993, 1999; Tanaka et al. 1993; Sandoh et al. 1997; Chang et al. 1998; Tanno et al. 1998a; Yoshida et al. 1999; Hasumi et al. 2000; Jung et al. 2004; Adham et al. 2005; Minami et al. 2008; Oshiro et al. 2008; Lahmar et al. 2010.

APBDU may be associated with hyperplastic polyp of the gallbladder (Okada et al. 2009), with adenomyomatosis of the gallbladder (more often in the presence of the undilated type of APBDU; Chang et al. 1998; Tanno et al. 1998b), and with multiseptate gallbladder (Yamamoto et al. 2005).

Pathogenesis of Cancer in APBDU

APBDU is associated with hyperplastic, metaplastic, and dysplastic alterations in the extrahepatic biliary tract and the gallbladder (review: Tsuchida and Itoi 2010). Children with APBSU showed epithelial hyperplasia of the gallbladder mucosa in up to 60 % (Tanno et al. 1999). In adults, 63 % of patients with APBDU has gallbladder epithelial hyperplasia, and this hyperplasia was significantly more frequent in the undilated type of APBDU. 2/9 high-grade hyperplasias revealed codon 12 K-Ras mutations (Tanno et al. 1998a). APBDU is associated with papillary epithelial hyperplasia in both the extrahepatic bile ducts and the gallbladder, which is a precursor lesion for cancer (Seki et al. 2005). In a study of 45 children with APBDU (median age: 2.9 years), the most common histological finding was villus-type mucosal hyperplasia (57.1 %) (Ono et al. 2010). Diffuse papillary hyperplasia of the gallbladder mucosa in APBDU exhibits senescent features such as expression of p16 (INK4A) and low cell proliferative activity and is induced by lysolecithin, a lipid the level of which is elevated in gallbladder bile in APBDU (Yamaguchi et al. 2009). An effect of APBDU on carcinogenesis is shown in choledochal cysts, where carcinomas develop more frequently when the cysts are associated with APBDU (Song et al. 1999). Mutation of K-Ras (codon 12) seems to be involved in APBDU-associated biliary tract cancers (reviews: Matsubara et al. 1995; Matsumoto et al. 2003; Tsuchida et al. 2003a). In a series of 20 adult patients with APBDU, point mutations of K-Ras were detected in 80 % of the cancerous cases and 58 % of the hyperplastic and metaplastic lesions (Matsubara et al. 1996). Among 35 pediatric patients with APBDU, PCR analysis of cholangiocyte DNA revealed that K-Ras mutations were detected in five children, four of whom showed epithelial hyperplasia or metaplasia. In a 12-year-old girl,

adenocarcinoma had developed in a choledochal cyst, and here both K-Ras and DPC-4 (Smad-4) mutations were found, suggesting a multistep cancerogenic process with K-Ras mutations occurring as an early event (Shimotake et al. 2003). Mutations of K-Ras and p53 genes were also found in noncancerous biliary epithelia of adult patients with APBDU (Matsubara et al. 2002). Even in the presence of a relatively long common channel (high confluence) alone without fulfilled criteria of APBDU, overexpression of p53 and K-Ras was found in epithelial of the gallbladder (Kamisawa et al. 2004). In gallbladder mucosal cells of patients with APBDU, Bcl-2 expression and activation of telomerase are early events involved in carcinogenesis (Ichikawa et al. 2004).

There is evidence that the COX-2 pathway is involved in APBDU-induced carcinogenesis. Generally, COX-2 expression is strongly related to cancer progression or development by means of its anti-apoptotic effect, promotion of angiogenesis, and/or decrease of cell-to-cell adhesive activity. Bile from APBDU can significantly promote the proliferation of human cholangiocarcinoma cells. This response is associated with marked upregulation of COX-2 transcripts, and the proliferative reaction can be abolished by a COX-2 inhibitor (Wu et al. 2003). Immunohistochemically, overexpression of COX-2 in biliary tract tissues of patients with APBDU was found in 20 % of regenerative epithelium, 11.1 % of hyperplasia without atypia, 86.4 % of hyperplasia with mild atypia, and 75 % each of dysplasia and carcinoma. COX-2 expression was associated with expression of VEGF (Tsuchida et al. 2003c). In a second immunohistochemical study, COX-2 expression in noncancerous biliary tract tissue of patients with APBDU and biliary cancer was 20 % vs. 7.1 % in patients without APBDU (Watanabe et al. 2004).

The reflux phenomena associated with APBDU may cause bacterial colonization of the biliary tract. One microorganism considered to be a causative factor for biliary cancer is *Helicobacter bilis*. By the use of PCR analysis of bile juice and biliary tissue samples, it has been shown that *Helicobacter bilis* colonization of the biliary system is very common in patients with APBDU (Kosaka et al. 2010).

APBDU causes regurgitation of pancreatic juice into the biliary tract and into choledochal cysts. In choledochal cysts associated with APBDU, fatty acid calcium stones (Kaneko et al. 2008) and protein plugs develop. One component secreted by pancreatic acinar cells is lithostathine, which is an important component of protein plugs. Lithostathine is the major nonenzymatic protein of pancreatic secretions and has several synonyms, including pancreatic stone protein, protein-X, pancreatic thread protein, and P19, and is now termed Reg protein (review: De Reggi and Gharib 2001). The Reg I gene makes a part of the Reg protein gene family and encodes a 166-amino acid glycosylated protein with a 22-amino acid signal peptide (review: Okamoto 1999). The Reg I gene product has been identified as a regenerative/proliferative factor for pancreatic islet cells, but it is also active in other cell systems and in cancer cells and affects liver regeneration (Wang et al. 2009). It is upregulated in blood after trauma, and here it binds to and activates neutrophils (Keel et al. 2009).

In choledochal cysts associated with APBDU, protein plugs are an important or dominant cause of symptoms, and the plugs consist mostly of lithostathine. Activated trypsin from pancreatic juice is present together with lithostathine in bile of APBDU patients (Ochiai et al. 2004), and trypsin cleaves soluble lithostathine into insoluble forms that aggregate to form plugs (Kaneko et al. 2007). Lithostathine-containing protein plugs in choledochal cysts/APBDU are dissolved by acidic and basic solutions (Kaneko et al. 2009).

References

Abdalla EK, Forsmark CE, Lauwers GY, Vauthey JN (1999) Monolobar Caroli's disease and cholangiocarcinoma. HPB Surg 11:271–276

Ackerholm P, Benediktsdottir K, Lundell L, Thulin A (1981) Cholangiocarcinoma in a patient with biliary cysts. Acta Chir Scand 147:605–607

Adham M, Valette PJ, Partensky C (2005) Pancreaticobiliary maljunction without choledochal dilatation associated with gallbladder cancer: report of 2 European cases. Surgery 138:961

Aikawa S, Hayasaka A, Nozaki N et al (1976) Carcinoma arising in a choledochal cyst after choledochocystoduodenostomy. Jpn J Pediatr Surg 12:55

Akiyoshi T, Yamaguchi K, Chijiwa K, Tanaka M (2003) Cystadenocarcinoma of the liver without mesenchymal stroma: possible progression from a benign cystic lesion suspected by follow-up imaging. J Gastroenterol 38:588–592

Alonso-Lej F, Rever WB, Pessagno DJ (1959) Congenital choledochal cyst, with a report of 2, and an analysis of 94, cases. Int Abstr Surg 108:1–30

Armanino LP (1946) Idiopathic dilatation of the common bile duct with coexistent primary hepatic carcinoma. Ann Intern Med 24:714

Ashby BS (1964) Carcinoma in a choledochal cyst. Br J Surg 51:493

Atkinson H, Fischer C, de Jong C, Madhavan KK, Parks RW, Garden OJ (2003) Choledochal cysts in adults and their complications. HPB Surg 5:105–110

Azizah N, Paradinas FJ (1980) Cholangiocarcinoma coexisting with developmental liver cysts: a distinct entity different from liver cystadenocarcinoma. Histopathology 4:391–400

Babbitt DP (1969) Congenital choledochal cysts: new etiological concept based on anomalous relationships of the common bile duct and pancreatic bulb. Ann Radiol 12:231–240

Balsells J, Margarit C, Murio E et al (1993) Adenocarcinoma in Caroli's disease treated with liver transplantation. HPB Surg 7:81–86

Banbury J, Conlon KC, Ghossein R, Brennan MF (1994) Primary squamous cell carcinoma within a solitary nonparasitic hepatic cyst. J Surg Oncol 57:210–212

Baumann R, Uettwiller H, Duclos B, Jouin H, Kerschen A, Adloff M, Weill JP (1987) Congenital cystic dilatation of the common bile duct, anomaly of the biliopancreatic junction and cancer of the bile ducts (in French). Gastroenterol Clin Biol 11:849–855

Ben Mena N, Zalinski S, Svrcek M, Lewin M, Fléjou JF, Wendum D, Paye F (2006) Ciliated hepatic foregut cyst with extensive squamous metaplasia: report of a case. Virchows Arch 449:730–733

Binstock M, Sondak VK, Herd J, Reimnitz C, Lindsay K, Brinkman C, Roslyn JJ (1988) Adenocarcinoma in a choledochal cyst during pregnancy: a case report and guidelines for management. Surgery 103:588–592

Bloustein PA (1977) Association of carcinoma with congenital cystic condition of the liver and bile ducts. Am J Gastroenterol 67:40–46

Bloustein PA, Silverberg SG (1976) Squamous cell carcinoma originating in a hepatic cyst. Case report with a review of the hepatic cyst-carcinoma association. Cancer 38:2002–2005

Bourdin G, Olivier A, Rene E, Charleux H (1984) Biliary cancer developing on a congenital cystic dilatation of the common bile duct. Apropos of a case (in French). J Chir (Paris) 121:715–718

Bova JG, Dempsher CJ, Sepulveda G (1983) Cholangiocarcinoma associated with a type 2 choledochal cyst. Gastrointest Radiol 8:41–43

Carone F, Bacallao R, Kanwar Y (1994) Biology of polycystic kidney disease. Lab Invest 70:437–448

Chang LY, Wang HP, Wu MS, Huang HT, Wang HH, Lin CC, Lin JT (1998) Anomalous pancreaticobiliary ductal union – an etiologic association of gallbladder cancer and adenomyomatosis. Hepatogastroenterology 45:2016–2019

Chaudhuri PK, Chaudhuri B, Schuler JJ, Nyhus LM (1982) Carcinoma associated with congenital cystic dilatation of bile ducts. Arch Surg 117:1349–1351

Cho MJ, Hwang S, Lee YJ, Kim KH, Ahn CS, Moon DB, Lee SK, Kim MH, Lee SS et al (2011) Surgical experience of 204 cases of adult choledochal cyst disease over 14 years. World J Surg 35:1094–1102

Coyle KA, Bradley EL (1992) Cholangiocarcinoma developing after simple excision of a type II choledochal cyst. South Med J 85:540–544

De Lajarte-Thirouard AS, Rioux-Leclercq N, Boudjema K, Gandon Y, Ramée MP, Turlin B (2002) Squamous cell carcinoma arising in a hepatic foregut cyst. Pathol Res Pract 198:697–700

De Reggi M, Gharib B (2001) Protein-X, Pancreatic Stone-, Pancreatic thread-, reg-protein, P19, lithostathine, and now what? Characterization, structural analysis and putative function(s) of the major non-enzymatic protein of pancreatic secretions. Curr Protein Pept Sci 2:19–42

De Vries JS, de Vries S, Aroson DC, Bosman DK, Rauws EA, Bosma A, Heij HA et al (2002) Choledochal cysts: age of presentation, symptoms, and late complications related to Todani's classification. J Pediatr Surg 37:1568–1573

Dexter D (1957) Choledochal cyst with carcinoma of the intrahepatic bile ducts and pancreatic ducts. Br J Cancer 11:18

Falco E, Nardini A, Celoria G, Briglia R, Stefani R, Gadducci G, Belloni E (1993) Caroli's disease associated with cholangiocarcinoma. A case of our own observation (in Italian). Minerva Chir 48:961–964

Ferraris LV, Navarro A, Escargiel A (1944) Dilatacion congenital del hepaticoledoco y adenocarcinoma. Bol Soc Cir Cordoba 5:21

Fischer HG (1958) Primäres Karzinom in der Wand einer angeborenen zystischen Gallengangserweiterung. Zentralbl Chir 24:1234

Flanigan DP (1977) Biliary carcinoma associated with biliary cysts. Cancer 40:880–883

Franko J, Nussbaum ML, Morris JB (2006) Choledochal cyst cholangiocarcinoma arising from adenoma: case report and a review of the literature. Curr Surg 63:281–284

Fujita AW, Steelman CK, Abramowsky CR, Ricketts RR, Durham MM, Clifton MS, Pandya SR, Shehata B (2011) Ciliated hepatic foregut cyst: four case reports with a review of the literature. Pediatr Dev Pathol 14:418–421

Fujiwara Y, Ohizumi T, Kakizaki G, Ishidate T (1976) A case of congenital choledochal cyst associated with carcinoma. J Pediatr Surg 11:587–588

Fukushima M (1975) An autopsy case of a choledochal cyst associated with carcinoma (in Japanese). Rinsho Kenkyu 52:157

Fukuuchi T (1967) A case of choledochal carcinoma disclosed seven years after anastomosis operation for congenital choledochal dilatation. Geka Skinryo 9:1134

Funabiki T, Matsubara T, Miyakawa S, Ishihara S (2009) Pancreaticobiliary maljunction and carcinogenesis to biliary and pancreatic malignancy. Langenbecks Arch Surg 394:159–169

Furlanetto A, Del Tos AP (2002) Squamous cell carcinoma arising in a ciliated hepatic foregut cyst. Virchows Arch 441:296–298

Gallagher PJ, Millis RR, Mitchinson MJ (1972) Congenital dilatation of the intrahepatic bile ducts with cholangiocarcinoma. J Clin Pathol 25:804–808

George PA, Maingot R (1962) Choledochus cyst associated with carcinoma in the liver – report of a case. Br J Surg 50:339

Gigot J, Nagorney D, Farnell M, Moir C, Ilstrup D (1996) Bile duct cysts: a changing spectrum of disease. J Hepatobiliary Pancreat Surg 3:405–411

Goto N, Yasuda I, Uematsu T, Kanemura N, Takao S, Ando K, Kato T, Osada S, Takao H et al (2001) Intrahepatic cholangiocarcinoma arising 10 years after the excision of congenital extrahepatic biliary dilatation. J Gastroenterol 36:856–862

Greenwood N, Orr WM (1972) Primary squamous-cell carcinoma arising in a solitary non-parasitic cyst of the liver. J Pathol 107:145–148

Han JK, Choi BI (1996) Carcinoma in a choledochal cyst. Abdom Imaging 21:179–181

Harris M, Angus P, Davis ID (2002) Choledochal cyst and squamous cell carcinoma of the biliary tract. Int Med J 32:491–496

Hasumi A, Matsui H, Sugioka A, Uyama I, Komori Y, Fujita J, Aoki H (2000) Precancerous conditions of biliary tract cancer in patients with pancreaticobiliary maljunction: reappraisal of nationwide survey in Japan. J Hepatobiliary Pancreat Surg 7: 551–555

Hizawa K, Fukuda F, Akagi G et al (1967) Carcinoma associated with idiopathic choledochus cyst. Acta Pathol Jpn 17:101

Holzinger F, Baer HU, Schilling M, Stauffer EJ, Büchler MW (1996) Congenital bile duct cyst: a premalignant lesion of the biliary tract associated with adenocarcinoma – a case report. Z Gastroenterol 34:382–385

Hsieh CB, Chen CJ, Yu JC, Chang TM, Gao HW, Liu YC (2005) Primary squamous cell carcinoma of the liver arising from a complex liver cyst: report of a case. Surg Today 35:328–331

Hu B, Gong B, Zhou DY (2003) Association of anomalous pancreaticobiliary ductal junction with gallbladder carcinoma in Chinese patients: an ERCP study. Gastrointest Endosc 57:541–545

Ichikawa Y, Kamiyama M, Sekido H, Ishikawa T, Miura Y, Kamiya N, Morita T, Shimada H (2004) Telomerase activity and Bcl-2 expression in gallbladders of pancreaticobiliary maljunction patients: a preliminary study. J Hepatobiliary Pancreat Surg 11:34–39

Iinuma Y (1975) Two cases of choledochal cysts combined with carcinoma (in Japanese). Jpn J Gastroenterol 72:643

Imamura M, Miyashita T, Tani T, Naito A, Tobe T, Takahashi K (1984) Cholangiocellular carcinoma associated with multiple liver cysts. Am J Gastroenterol 79:790–795

Irwin ST, Morison JE (1944) Congenital cyst of the common bile duct containing stones and undergoing cancerous stones. Br J Surg 32:319

Ishibashi T, Kasahara K, Yasuda Y, Nagai H, Makino S, Kanazawa K (1997) Malignant change in the biliary tract after excision of choledochal cyst. Br J Surg 84:1687–1691

Jan YY, Chen HM, Chen MF (2002) Malignancy in choledochal cysts. Hepatogastroenterology 49:100–103

Joly I, Choux R, Baroni JL, Payan MJ, Mazel C, Branger D, Ponte J, Sastre B, Sahel J (1990) Carcinoma in situ in localized Caroli's disease (in French). Gastroenterol Clin Biol 14:90–92

Jones AW, Shreeve DR (1970) Congenital dilatation of intrahepatic biliary ducts with cholangiocarcinoma. Br Med J 2:277

Jung YS, Lee KJ, Kim H, Kim WH, Kim IG, Yoo BM, Kim JH, Kim MW (2004) Risk factor for extrahepatic bile duct cancer in patients with anomalous pancreaticobiliary ductal union. Hepatogastroenterology 51:946–949

Kagawa Y, Kashihara S, Kuramoto S, Maetani S (1978) Carcinoma arising in a congenitally dilated biliary tract: report of a case and review of the literature. Gastroenterology 74:1286–1294

Kale IT, Kuzu MA (1997) Porta choledochal fistula: an unusual complication of a cholangiocarcinoma arising from a type I choledochal cyst. Eur J Surg Oncol 23:188–189

Kamisawa T, Okamoto A (2006) Biliopancreatic and pancreaticobiliary refluxes in cases with and without pancreaticobiliary maljunction: diagnosis and clinical implications. Digestion 73:228–236

Kamisawa T, Amemiya K, Tu Y, Egawa N, Sakaki N, Tsuruta K, Okamoto A, Munakata A (2002) Clinical significance of a long common channel. Pancreatology 2:122–128

Kamisawa T, Matsukawa M, Amemiya K, Tu Y, Ehgawa N, Okamoto A, Aizawa S (2003) Pancreatitis associated with pancreaticobiliary maljunction. Hepatogastroenterology 50:1665–1668

Kamisawa T, Funata N, Hayashi Y, Egawa N, Nakajima H, Tsuruta K, Okamoto A, Yamaguchi T (2004) Pathologic changes in the non-carcinomatous epithelium of the gallbladder in patients with a relatively long common channel. Gastrointest Endosc 60:56–60

Kamisawa T, Egawa N, Nakajima H, Matsukawa M (2005) Dorsal pancreatic duct dominance in pancreaticobiliary maljunction. Pancreas 30:e60–e63

Kamisawa T, Tu Y, Kuwata G, Egawa N, Nakajima H, Tsuruta K, Okamoto A, Matsukawa M (2006) Biliary carcinoma risk in patients with pancreaticobiliary maljunction and the degree of extrahepatic bile duct dilatation. Hepatogastroenterology 53:816–818

Kamisawa T, Tu Y, Nakajima H, Egawa N, Tsuruta K, Okamoto A (2007) The presence of a common channel and associated pancreaticobiliary diseases: a prospective ERCP study. Dig Liver Dis 39:173–179

Kamisawa T, Munakata W, Tu Y, Egawa N, Tsuruta K, Okamoto A (2008) Sex-based differences in gallbladder cancer associated with pancreaticobiliary maljunction. Hepatogastroenterology 55:21–23

Kamisawa T, Kurata M, Honda G, Tsuruta K, Okamoto A (2009a) Biliopancreatic reflux – pathophysiology and clinical implications. J Hepatobiliary Pancreat Surg 16:19–24

Kamisawa T, Takuma K, Anjiki H, Egawa N, Kurata M, Honda G, Tsuruta K, Sasaki T (2009b) Pancreaticobiliary maljunction. Clin Gastroenterol Hepatol 7 (11 Suppl):S84–S88

Kamisawa T, Suyama M, Fujita N, Maguchi H, Hanada K, Ikeda S, Igarashi Y, Itoi T et al (2010a) Pancreaticobiliary reflux and the length of a common channel. J Hepatobiliary Pancreat Sci 17:865–870

Kamisawa T, Honda G, Kurata M, Tokura M, Tsuruta K (2010b) Pancreaticobiliary disorders associated with pancreaticobiliary maljunction. Dig Surg 27:100–104

Kaneko K, Ando H, Seo T, Ono Y, Tainaka T, Sumida W (2007) Proteomic analysis of protein plugs: causative agent of symptoms in patients with choledochal cyst. Dig Dis Sci 52:1979–1986

Kaneko K, Ono Y, Tainaka T, Sumida W, Ando H (2008) Fatty acid calcium stones in patients with pancreaticobiliary maljunction/choledochal cyst as another cause of obstructive symptoms besides protein plugs. J Pediatr Surg 43:564–567

Kaneko K, Ono Y, Tainaka T, Sumida W, Ando H (2009) Acidic and basic solutions dissolve protein plugs made of lithostathine complicating choledochal cyst/pancreaticobiliary maljunction. Dig Dis Sci 54:1475–1480

Kasper HU, Stippel DL, Töx U, Drebber U, Dienes HP (2006) Primary cholangiocarcinoma in a case of Caroli's disease: case report and literature review (in German). Pathologe 27:300–304

Kataoka K, Iwado T, Kobayashi T, Kurokawa T, Mimura H, Kobayashi S (1985) Carcinoma originating in a hepatic cyst of polycystic disease – a case report (in Japanese). Gan No Rinsho 31:199–205

Kato O, Hattori K, Suzuki T, Tachino F, Yuasa T (1983) Clinical significance of anomalous pancreaticobiliary union. Gastrointest Endosc 29:94–98

Kawamoto S, Hiraoka T, Maruta S, Watanabe E, Kanemitsu K, Tsuji T (1998) A case of early cancer in cystic intrahepatic duct associated with congenital choledochal cyst. Hepatogastroenterology 45:428–432

Keel M, Härter L, Reding T, Sun LK, Hersberger M, Seifert B, Bimmler D, Graf R (2009) Pancreatic stone protein is highly increased during posttraumatic sepsis and activates neutrophil granulocytes. Crit Care Med 37:1642–1648

Kelly TR, Schlueter TM (1964) Choledochal cyst with coexistent carcinoma of the pancreas. Am Surg 30:209

Keminger VK, Depisch D, Rauhs R (1976) Malignant degeneration of a congenital common bile duct cyst (in German). Zentralbl Chir 101:298–301

Kim HJ, Kim MH, Lee SK, Sao DW, Kim YT, Lee DK, Song SY, Roe IH, Kim JH et al (2002) Normal structure, variations, and anomalies of the pancreaticobiliary ducts of Koreans: a nationwide cooperative prospective study. Gastrointest Endosc 55:889–896

Kimura W (2009) Congenital dilatation of the common bile duct and pancreaticobiliary maljunction: clinical implications. Langenbecks Arch Surg 394:209–213

Kimura K, Ohto M, Ono T, Tsuchiya Y, Saisho H, Kawamura K, Yogi Y, Karasawa E, Okuda K (1977) Congenital cystic dilatation of the common bile duct: relationship to anomalous pancreaticobiliary ductal union. AJR Am J Roentgenol 128:571–577

Kimura K, Ohto M, Saisho H, Unozawa T, Tsuchiya Y, Morita M, Ebara M, Matsutani S, Okuda K (1985) Association of gallbladder carcinoma and anomalous pancreaticobiliary ductal union. Gastroenterology 89:1258–1265

Kimura Y, Nishikawa N, Okita K, Furuhata T, Mizuguchi T, Nobuoka T, Nishimori H, Zenbutsu H et al (2005) Biliary tract malignancy and chronic inflammation from the perspective of pancreaticobiliary maljunction. Oncology 69(Suppl 1):41–45

Kobayashi S, Asano T, Yamasaki M, Kenmochi T, Nakagohri T, Ochiai T (1999) Risk of bile duct carcinogenesis after excision of extrahepatic bile ducts in pancreaticobiliary maljunction. Surgery 6:939–944

Komi N, Utaka H, Ogasawara K et al (1976) Two cases of choledochal cysts associated with carcinoma. Geka Shinryo 18:1266

Kosaka T, Tajima Y, Kuroki T, Mishima T, Adachi T, Tsuneoka N, Fukuda K, Kanematsu T (2010) Helicobacter bilis colonization of the biliary system in patients with pancreaticobiliary maljunction. Br J Surg 97:544–549

Kraus I, Rubinic M, Uravic M, Kovac D, Brncic N, Kraus D, Vojnikovic B (2003) Early cancer in congenital choledochal cyst. Coll Antropol 27:677–683

Kune GA (1964) Surgical anatomy of common bile duct. Arch Surg 89:995–1004

Kune GA (1970) The influence of structure and function in the surgery of the biliary tract. Ann R Coll Surg Engl 47:78–91

Lahmar A, Abid SB, Arfa MN, Bayar R, Khalfallah MT, Mzabi-Regaya S (2010) Metachronous cancer of gallbladder and pancreas with pancreaticobiliary maljunction. World J Gastrointest Surg 2:143–146

Lenriot JP, Gigot JF, Segol P, Fagniez PL, Fingerhut A, Adloff M (1998) Bile duct cysts in adults: a multi-

institutional retrospective study. French Associations for Surgical Research. Ann Surg 228:159–166
Leong AF, Nambiar R, Tan LK (1988) Cholangiocarcinoma in a choledochal cyst – a case report and review of the literature. Ann Acad Med Singap 17:104–106
Leroy JP, Charles JF, Diveres B, Bellet M (1980) Cholangio-carcinoma arising in Caroli's disease (in French). Sem Hop 56:272–276
Lipsett PA, Pitt HA, Colombani PM, Boitnott JK, Cameron JL (1994) Choledochal cyst disease. A changing pattern of presentation. Ann Surg 220:644–652
Lorenzo GA, Seed RW, Beal JM (1971) Congenital dilatation of the biliary tract. Am J Surg 121:510
Lynch MJ, McLeod MK, Weatherbee L, Gilsdorf JR, Guice KS, Eckhauser FE (1988) Squamous cell cancer of the liver arising from a solitary benign nonüarasitic hepatic cyst. Am J Gastroenterol 83:426–431
Macfarlane JR, Glenn F (1967) Carcinoma in choledochal cyst. JAMA 202:1003–1006
Matsubara T, Tsuji T, Miyama A, Yamaguchi H, Funabiki T (1995) Mutagenicity of bile and pancreatic juice from patients with pancreatico-biliary maljunction. Hepatogastroenterology 42:113–116
Matsubara T, Sakurai Y, Sasayama Y, Hori H, Ochiai M, Funabiki T, Matsumoto K, Hirono I (1996) K-ras point mutations in cancerous and noncancerous biliary epithelium in patients with pancreaticobiliary maljunction. Cancer 77(Suppl 8):1752–1757
Matsubara T, Sakurai Y, Zhi LZ, Miura H, Ochiai M, Funabiki T (2002) K-ras and p53 gene mutations in noncancerous biliary lesions of patients with pancreaticobiliary maljunction. J Hepatobiliary Pancreat Surg 9:312–321
Matsumoto Y, Fujii H, Itakura J, Mogaki M, Matsuda M, Morozumi A, Fujino MA, Suda K (2001) Pancreaticobiliary maljunction: etiologic concepts based on radiologic aspects. Gastronintest Endosc 53:614–619
Matsumoto Y, Fujii H, Itakura J, Matsuda M, Nobukawa B, Suda K (2002) Recent advances in pancreaticobiliary maljunction. J Hepatobiliary Pancreat Surg 9:45–54
Matsumoto Y, Fujii H, Itakura J, Matsuda M, Yang Y, Nobukawa B, Suda K (2003) Pancreaticobiliary maljunction: pathophysiological and clinical aspects and the impact on biliary carcinogenesis. Langenbecks Arch Surg 388:122–131
Matsuoka M, Komuro T, Yamao M, Kitahara T, Abe H, Aizawa R, Miyakawa Y, Aizawa Y, Sakata A (2005) A case of cholangiocellular carcinoma associated with autosomal dominant polycystic kidney disease (in Japanese). Nippon Shokakibyo Gakkai Zasshi 102:1434–1438
McKenzie AD, Sandy JT, Anderson DO (1958) Choledochal cyst associated with carcinoma. Can J Surg 2:88
Minami Y, Hasuike Y, Takeda Y, Tsujinaka T (2008) Metachronous double cancer of the gallbladder and pancreas associated with pancreaticobiliary maljunction. J Hepatobiliary Pancreat Surg 15:330–333
Misra SP, Dwivedi M (1990) Pancreaticobiliary ductal union. Gut 31:1144–1149
Misra SP, Gulati P, Thorat VK, Vij JC, Anand BS (1989) Pancreaticobiliary ductal union in biliary diseases. Gastroenterology 96:907–912
Miyazaki K, Date K, Imamura S, Ogawa Y, Nakayama F (1989) Familial occurrence of anomalous pancreaticobiliary duct union associated with gallbladder neoplasms. Am J Gastroenterol 84:176–181
Miyazaki M, Takada T, Miyakawa S, Tsukada K, Nagino M, Kondo S, Furuse J, Saito H et al (2008) Risk factors for biliary tract and ampullary carcinomas and prophylactic surgery for these factors. J Hepatobiliary Pancreat Surg 15:15–24
Monteagudo M, Vidal G, Moreno M, Bella R, Diaz MJ, Colomer O, Santesmasses A (1998) Squamous cell carcinoma and infection in a solitary hepatic cyst. Eur J Gastroenterol Hepatol 10:1051–1053
Mori K, Nagakawa T, Ohta T, Nakano T, Kayahara M, Kanno M et al (1993) Association between gallbladder cancer and anomalous union of the pancreaticobiliary ductal system. Hepatogastroenterology 40:56–60
Mori K, Akimoto R, Kanno M, Kamata T, Hirono Y, Matsumura A (1999) Anomalous union of the pancreaticobiliary ductal system without dilatation of the common bile duct or tumor: case reports and literature review. Hepatogastroenterology 46:142–147
Nagata E, Sakai K, Kinoshita H, Kobayashi Y (1985) The relation between carcinoma of the gallbladder and an anomalous connection between the choledochus and the pancreatic duct. Ann Surg 202:182–190
Nagorney DM, McIlrath DC, Adson MA (1984) Choledochal cysts in adults: clinical management. Surgery 96:656–663
Nakajima F, Shimizu M, Yokogawa Y (1963) Carcinoma of the biliary tract associated with congenital disease (in Japanese). Kohtsu Igaku 16:593
Nakamura H, Katayose Y, Rikiyama T, Onogawa T, Yamamoto K, Yoshida H, Hayashi H et al (2008) Advanced bile duct carcinoma in a 15-year-old patient with pancreaticobiliary maljunction and congenital biliary cystic disease. J Hepatobiliary Pancreat Surg 15:554–559
Nasu S, Sakurai M, Nishikawa M et al (1971) A case of carcinoma arising in the congenital intrahepatic cyst (in Japanese). Nihon Rinsho 29:131
Negi SS, Gondal R, Chaudhary A (2009) Biliary papillomatosis with adenocarcinoma arising in choledochal cyst. Trop Gastroenterol 30:221–222
Nieweg O, Slooff MJ, Grond J (1992) A case of primary squamous cell carcinoma of the liver arising in a solitary cyst. HPB Surg 5:203–208
Nomura T, Shirai Y, Sandoh N, Nagakura S, Hatakeyama K (2002) Cholangiographic criteria for anomalous union of the pancreatic and biliary ducts. Gastrointest Endosc 55:204–208

Nomura T, Shirai Y, Wakai T, Yokoyama N, Sakata J, Hatakeyama K (2005) Narrow portion of the terminal choledochus is a cause of upstream biliary dilatation in patients with anomalous union of the pancreatic and biliary ducts. World J Gastroenterol 11:6503–6507

Ochiai K, Kaneko K, Kitagawa M, Ando H, Hayakawa T (2004) Activated pancreatic enzyme and pancreatic stone protein (PSP/reg) in bile of patients with pancreaticobiliary maljunction/choledochal cyst. Dig Dis Sci 49:1953–1956

Oguchi Y, Okada A, Nakamura T, Okumura K, Miyata M, Nakao K, Kawashima Y (1988) Histopathologic studies of congenital dilatation of the bile duct as related to an anomalous junction of the pancreaticobiliary ductal system: clinical and experimental studies. Surgery 103:168–173

Ohama K, Ishikawa N (2006) Dilatation of the intrahepatic bile duct associated with congenital anomalous junction of the cystic duct – a new disease entity. J Pediatr Surg 41:1996–1998

Ohita H, Yamaguchi Y, Yamakawa O, Watanabe H, Satomura Y, Motoo Y, Okai T et al (1993) Biliary papillomatosis with the point mutation of K-ras gene arising in congenital choledochal cyst. Gastroenterology 105:1209–1212

Ohta T, Nagakawa T, Ueno K, Maeda K, Ueda N, Kayahara M, Akiyama T, Kanno M et al (1990) Clinical experience of biliary tract carcinoma associated with anomalous union of the pancreaticobiliary ductal system. Jpn J Surg 20:36–43

Okada A, Nakamura T, Higaki J, Okumura K, Kamata S, Oguchi Y (1990) Congenital dilatation of the bile duct in 100 instances and its relationship with anomalous junction. Surg Gynecol Obstet 171:291–298

Okada T, Sasaki F, Honda S, Matsuno Y, Kubota K, Todo S (2009) Hyperplastic polyp of the gallbladder associated with pancreaticobiliary maljunction in a 9-year-old girl. Pediatr Surg Int 25:999–1002

Okamoto H (1999) The Reg gene family and Reg proteins: with special attention to the regeneration of pancreatic beta-cells. J Hepatobiliary Pancreat Surg 6:254–262

Okamura K, Hayakawa H, Kuze M, Takahashi H, Kosaka A, Mizumoto R, Katsuta K (2000) Triple carcinomas of the biliary tract associated with congenital choledochal dilatation and pancreaticobiliary maljunction. J Gastroenterol 35:465–471

Okayama N, Miyamoto T, Kurokawa T, Oono N, Tuji S, Yamada K, Hayakawa T, Mizuno H et al (1991) Congenital dilatation of the biliary tract accompanied with an early cholangiocarcinoma in the aged (in Japanese). Nippon Shokakibyo Gakkai Zasshi 88:105–110

Ono J, Sakoda K, Akita H (1982) Surgical aspect of cystic dilatation of the bile duct. An anomalous junction of the pancreaticobiliary tract in adults. Ann Surg 195:203–208

Ono S, Sakai K, Kimura O, Iwai N (2008) Development of bile duct cancer in a 26-year-old man after resection of infantile choledochal cyst. J Pediatr Surg 43:E17–E19

Ono et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/21042916

Oshiro H, Matsuo K, Mawatari H, Inayama Y, Yamanaka S, Nagahama K, Endo I, Shimada H et al (2008) Mucin-producing gallbladder adenocarcinoma with focal small cell and large cell neuroendocrine differentiation associated with pancreaticobiliary maljunction. Pathol Int 58:780–786

Patel YD, Sarwar ZU, Morehouse HT, Parithivel VS (2001) Radiological management of an inoperable cholangiocarcinoma arising from a choledochal cyst. Clin Radiol 56:503–505

Pisano G, Donlon JB, Platell C, Hall JC (1991) Cholangiocarcinoma in a type III choledochal cyst. Aust NZ J Surg 61:855–857

Pliskin A, Cualing H, Stenger RJ (1992) Primary squamous cell carcinoma originating in congenital cysts of the liver. Report of a case and review of the literature. Arch Pathol Lab Med 116:105–107

Price L, Kozarek R, Agoff N (2008) Squamous cell carcinoma arising within a choledochal cyst. Dig Dis Sci 53:2822–2825

Richmond HG (1956) Carcinoma arising in congenital cysts of the liver. J Pathol Bacteriol 72:681–683

Rossi RL, Silverman ML, Braasch JW, Munson JL, Remine SG (1987) Carcinomas arising in cystic conditions of the bile ducts. A clinical and pathologic study. Ann Surg 205:377–384

Saikusa N, Naito S, Iinuma Y, Ohtani T, Yokoyama N, Nitta K (2009) Invasive cholangiocarcinoma identified in congenital biliary dilatation in a 3-year-old boy. J Pediatr Surg 44:2202–2205

Saji N, Amano K, Sakai T, Kimata T, Murase M, Kato M (2010) Double bile duct and gallbladder cancer associated with pancreaticobiliary maljunction. Intern Med 49:521–522

Sameshima Y, Maeda J, Ashizawa K, Taguchi H, Kawai K, Tsuchiyama H (1986) Adenocarcinoma arising in congenital dilatation of the intrahepatic bile duct (in Japanese). Gan No Rinsho 32:1591–1598

Sameshima Y, Uchimura M, Muto Y, Maeda J, Tsuchiyama H (1987) Coexistent carcinoma in congenital dilatation of the bile duct and anomalous arrangement of the pancreatico-bile duct. Carcinogenesis of coexistent gall bladder carcinoma. Cancer 60:1883–1890

Sandoh N, Shirai Y, Hatakeyama K (1997) Incidence of anomalous union of the pancreaticobiliary ductal system in biliary cancer. Hepatogastroenterology 44:1580–1583

Sasaki M, Katayanagi K, Watanabe K, Takasawa K, Nakanuma Y (2002) Intrahepatic cholangiocarcinoma arising in autosomal dominant polycystic kidney disease. Virchows Arch 441:98–100

Sautereau D, Sava P, Dupuy JF, Cessot F, Cubertafond P, Claude R, Pillegand B (1989) Cancer of the extrahepatic biliary tracts and abnormality of the biliopancreatic junction (in French). Gastroenterol Clin Biol 13:298–301

Schiewe R, Braudisch E, Ehrhart G (1968) Angeborene intrahepatische Gallengangszyste mit Steinbildung und maligner Entartung. Bruns Beitr Klein Chir 216:264

Scudamore CH, Hemming AW, Teare JP, Fache JS, Erb SR, Watkinson AF (1994) Surgical management of choledochal cysts. Am J Surg 167:497–500

Seki M, Yanagisawa A, Ninomiya Y, Ohta H, Saiura A, Yamamoto J, Yamaguchi T, Aruga A et al (2005) Clinicopathology of pancreaticobiliary maljunction: relationship between alterations in background biliary epithelium and neoplastic development. J Hepatobiliary Pancreat Surg 12:254–262

Sharma SS (1994) Pancreaticobiliary ductal union in cholangiocarcinoma. Gastrointest Endosc 40:171–173

Shields HM (1977) Occurrence of an adenocarcinoma in the choledochoenteric anastomosis 14 years after pancreatoduodenectomy for benign disease. Gastroenterology 72:322–324

Shimamura K, Kurosaki I, Sato D, Takano K, Yokoyama N, Sato Y, Hatakeyama K, Nakadaira K, Yagi M (2009) Intrahepatic cholangiocarcinoma arising 34 years after excision of a type Iv-A congenital choledochal cyst: report of a case. Surg Today 39:247–251

Shimomura T, Ono N, Nakao T et al (1974) Carcinoma in a congenital choledochal cyst (in Japanese). Jpn J Clin Surg 35:112

Shimotake T, Aoi S, Tomiyama H, Iwai N (2003) DPC-4 (Smad-4) and K-ras gene mutations in biliary tract epithelium in children with anomalous pancreaticobiliary ductal union. J Pediatr Surg 38:694–697

Shinagawa G, Shimura H, Tamesue K et al (1975) Successful removal of carcinoma arising in a congenital choledochal cyst (in Japanese). Jpn J Gastroenterol 72:1215

Song HK, Kim MH, Myung SJ, Lee SK, Kim HJ, Yoo KS, Seo DW, Lee HJ, Lim BC, Min YI (1999) Choledochal cyst associated with the anomalous union of pancreaticobiliary duct (AUPBD) has a more grave clinical course than choledochal cyst alone. Korean J Intern Med 14:1–8

Soreide K, Korner H, Havnen J, Soreide JA (2004) Bile duct cysts in adults. Br J Surg 91:1538–1548

Spitz L (1972) The surgical treatment of choledochal cyst. S Afr J Surg 10:161

Stalder PA, Desbiolles AM, Neff U (1996) Choledochus carcinoma in choledochal cyst – a rarity. Presentation of the disease with a case report (in German). Swiss Surg 3:123–126

Strijk SP, Boetes C, Yap SH (1984) Anomalous pancreaticobiliary duct union associated with bile duct carcinoma. Gastrointest Radiol 9:49–51

Strong RW (1999) Late bile duct cancer complicating biliary-enteric anastomosis for benign disease. Am J Surg 177:472–474

Suda K, Miyano T, Konuma I, Matsumoto M (1983) An abnormal pancreatico-choledocho-ductal junction in cases of biliary tract carcinoma. Cancer 52:2086–2088

Sugiyama M, Atomi Y, Kuroda A (1999) Pancreatic disorders associated with anomalous pancreaticobiliary junction. Surgery 126:492–497

Suzuki S, Amano K, Harada N, Tanaka S, Hayashi T, Suzuki M et al (2004) A case of intrahepatic cholangiocarcinoma arising 26 years after excision of congenital biliary dilatation (in Japanese). Jpn J Gastroenterol Surg 37:416–421

Tajiri K, Takenawa H, Yamaoka K, Yamane M, Marumo F, Sato C (1997) Choledochal cyst with adenocarcinoma in the cystically dilated intrahepatic bile duct. Abdom Imaging 22:190–193

Takei M, Yoda H, Kamijo N, Kawakami H, Hirabayashi K, Aizawa T, Simakura K, Kiyosawa K, Furuta S (1991) A case of Caroli's disease with hepatolithiasis, choledocholithiasis, and cholangiocarcinoma. Gastroenterol Jpn 26:224–229

Tanaka S, Watanabe S, Kaji H (1968) Carcinogenesis from common duct dilated idiopathically (in Japanese). Rinsho Geka 23:99

Tanaka T, Kouchi T, Wakumoto H et al (1969) A case of multiple biliary cysts (in Japanese). Shindan Chiryo 44:709

Tanaka K, Nishimura A, Yamada K, Ishibe R, Ishizaki N, Yoshimine M, Hamada N, Taira A (1993) Cancer of the gallbladder associated with anomalous junction of the pancreaticobiliary duct system without bile duct dilatation. Br J Surg 80:622–624

Tanaka K, Ikoma A, Hamada N, Nishida S, Kadono J, Taira A (1998) Biliary tract cancer accompanied by anomalous junction of pancreaticobiliary ductal system in adults. Am J Surg 175:218–220

Tanaka S, Kubota M, Yagi M, Okuyama N, Ohtaki M, Yamazaki S, Hirayama Y, Kurosaki I, Hatakeyama K (2006) An 11-year-old male patient demonstrating cholangiocarcinoma associated with congenital biliary dilatation. J Pediatr Surg 41:e15–e19

Tanno S, Obara T, Fujii T, Mizukami Y, Shudo R, Nishino N, Ura H, Klein-Szanto AJ, Kohgo Y (1998a) Proliferative potential and K-ras mutation in epithelial hyperplasia of the gallbladder in patients with anomalous pancreaticobiliary ductal union. Cancer 83:267–275

Tanno S, Obara T, Maguchi H, Fujii T, Mizukami Y, Shudo R, Takahashi K, Nishino N et al (1998b) Association between anomalous pancreaticobiliary ductal union and adenomyomatosis of the gall-bladder. J Gastroenterol Hepatol 13:175–180

Tanno S, Obara T, Fujii T, Mizukami Y, Yanagawa N, Izawa T, Ura H, Kohgo Y (1999) Epithelial hyperplasia of the gallbladder in children with anomalous pancreaticobiliary ductal union. Hepatogastroenterology 46:3068–3073

Tashiro S, Imaizumi T, Ohkawa H, Okada A, Katoh T, Kawaharada Y, Shimada H et al (2003) Pancreaticobiliary maljunction: retrospective and nationwide survey in Japan. J Hepatobiliary Pancreat Surg 10:345–351

Terada T, Notsumata K, Nakanuma Y (1994) Biliary carcinosarcoma arising in nonparasitic simple cyst of the liver. Virchows Arch 424:331–335

Thistlethwaite JR, Horwitz A (1967) Choledochal cyst followed by carcinoma of the hepatic duct. South Med J 60:872–874

Tireli GA, Sander S, Dervisoglu S, Demirali O, Unal M (2005) Embryonal rhabdomyosarcoma of the common bile duct mimicking choledochal cyst. J Hepatobiliary Pancreat Surg 12:263–265

Todani T, Toki A (1996) Cancer arising in choledochal cyst and management (in Japanese). Nippon Geka Gakkai Zasshi 97:594–598

Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K (1977) Congenital bile duct cysts. Classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. Am J Surg 134:263–269

Todani T, Watanabe Y, Fujii T, Uemura S (1984) Anomalous arrangement of the pancreaticobiliary ductal system in patients with a choledochal cyst. Am J Surg 147:672–676

Todani T, Watanabe Y, Toki A, Morotomi Y (2003) Classification of congenital biliary cystic disease: special reference to type Ic and Iva cysts with primary ductal stricture. J Hepatobiliary Pancreat Surg 10:340–344

Totkas S, Hohenberger P (2000) Cholangiocellular carcinoma associated with segmental Caroli's disease. Eur J Surg Oncol 26:520–521

Tsai CJ (2001) Porcelain gallbladder and cholangiocarcinoma with anomalous pancreaticobiliary union. Dig Dis Sci 46:773–775

Tseng JH, Pan KT, Hung CF, Hsieh CH, Liu NJ, Tang JH (2003) Choledochal cyst with malignancy: magnetic resonance imaging and magnetic resonance cholangiopancreatographic features in two cases. Abdom Imaging 28:838–841

Tsuchida A, Itoi T (2010) Carcinogenesis and chemoprevention of biliary tract cancer in pancreaticobiliary maljunction. World J Gastrointest Oncol 2:130–135

Tsuchida A, Itoi T, Aoki T, Koyanagi Y (2003a) Carcinogenetic process in gallbladder mucosa with pancreaticobiliary maljunction (Review). Oncol Rep 10:1693–1699

Tsuchida A, Kasuya K, Endo M, Saito H, Inoue K, Nagae I, Aoki T, Koyanagi Y (2003b) High risk of bile duct carcinogenesis after primary resection of a congenital biliary dilatation. Oncol Rep 10:1183–1187

Tsuchida A, Nagakawa Y, Ksuya K, Itoi T, Endo M, Ozawa T, Aoki T, Koyanagi Y (2003c) Immunohistochemical analysis of cyclooxygenase-2 and vascular endothelial growth factor in pancreaticobiliary maljunction. Oncol Rep 10:339–343

Tsuchiya R, Harada N, Ito T, Furukawa M, Yoshihiro I (1977) Malignant tumors in choledochal cysts. Ann Surg 186:22–28

Tsurimi T, Harada H, Mandai M et al (1976) A case of choledochal cyst associated with carcinoma. Stomach Intestine 11:1183

Tufail M, Rizwan MM, Majid HJ (2006) Pleomorphic rhabdomyosarcoma within a choledochal cyst: a rare cause of obstructive jaundice. J Pak Med Assoc 56:379–381

Uchimura M, Tsuchiya R, Sho Y et al (1972) Evaluation of surgical treatment for congenital choledochal cyst. Shujutsu 26:577

Valabrega S, Barillari P, De Angelis R, Di Lorenzo N, Gozzo P, Ramacciato G, Indinnimeo M (1987) Carcinoma arising in previously partially excised congenital choledochal dilatation. Case report and review of literature. Ital J Surg Sci 17:257–259

Vick DJ, Goddman ZD, Ishak KG (1999) Squamous cell carcinoma arising in a ciliated hepatic foregut cyst. Arch Pathol Lab Med 123:1115–1117

Visser BC, Suh I, Way LW, Kang SM (2004) Congenital choledochal cysts in adults. Arch Surg 139:855–860

Vlachogiannakos J, Potamianos S, Triantos C, Makri I, Imvrios G, Patsiaoura K, Avgeronis A (2004) Monolobar Caroli's disease complicated by cholangiocarcinoma in a 70-year-old man, previously asymptomatic. Gastrointest Endosc 60:297–300

Voyles CR, Smadja C, Shands C, Blumgart L (1983) Carcinoma in choledochal cysts. Arch Surg 118:986–988

Wang HL (2002) Carcinomatous arteriopathy as an unusual feature of pulmonary spread of cholangiocarcinoma arising in Caroli disease. Arch Pathol Lab Med 126:717–720

Wang HP, Wu MS, Lin CC, Chang LY, Kao AW, Wang HH, Lin JT (1998) Pancreaticobiliary diseases associated with anomalous pancreaticobiliary ductal union. Gastrointest Endosc 48:184–189

Wang J, Koyota S, Zhou X, Ueno Y, Ma L, Kawagoe M, Koizumi Y, Okamoto H, Sugiyama T (2009) Expression and localization of regenerating gene I in a rat liver regeneration model. Biochem Biophys Res Commun 380:472–477

Watanabe Y, Toki A, Todani T (1999) Bile duct cancer developed after cyst excision for choledochal cyst. J Hepatobiliary Pancreat Surg 6:207–212

Watanabe O, Yoshimatsu K, Shiozawa S, Tsuchiya A, Oshibe N, Aiba M, Ogawa K (2004) Different expression of cyclooxygenase-2 in biliary epithelia of bile duct cancer with or without pancreaticobiliary maljunction. Anticancer Res 24:671–674

Weber BB, Soler FJ, Font RG, Nance FC (1971) Carcinoma arising in a choledochal cyst. Am J Dig Dis 16:1019–1025

Weimann A, Klempnauer J, Gebel M, Maschek H, Bartels M, Ringe B, Pichlmayr R (1996) Squamous cell carcinoma of the liver originating from a solitary non-parasitic cyst: case report and review of the literature. HPB Surg 10:45–49

Wheeler DA, Edmondson HA (1984) Ciliated hepatic foregut cyst. Am J Surg Pathol 8:467–470

Wilson FE, Morrissey GE, McConnel RW (1956) Bile duct cyst with malignant degeneration. J Iowa Med Soc 46:72

Wiseman K, Buczkowski AK, Chung SW, Francoeur J, Schaeffer D, Scudamore CH (2005) Epidemiology, presentation, diagnosis, and outcomes of choledochal cysts in adults in an urban environment. Am J Surg 189:527–531

Wu GS, Zou SQ, Liu ZR, Wang DY (2003) Bile from a patient with anomalous pancreaticobiliary ductal union promotes the proliferation of human cholangiocarcinoma cells viaCOX-2 pathway. World J Gastroenterol 9:1094–1097

Yamaguchi M (1980) Congenital choledochal cyst. Analysis of 1,433 patients in the Japanese literature. Am J Surg 140:653–657

Yamaguchi J, Sasaki M, Harada K, Zen Y, Sato Y, Ikeda H, Itatsu K, Yokoyama Y, Ando H et al (2009) Papillary hyperplasia of the gallbladder in pancreaticobiliary maljunction represents a senescence-related lesion induced by lysolecithin. Lab Invest 89: 1018–1031

Yamamoto J, Shimamura Y, Ohtani I, Ohtani H, Yano M, Fukuda K et al (1996) Bile duct carcinoma arising from the anastomotic site of hepaticojejunostomy after the excision of congenital biliary dilatation: a case report. Surgery 119:476–479

Yamamoto T, Matsumoto J, Hashiguchi S, Yamaguchi A, Sakoda K, Taki C (2005) Multiseptate gallbladder with anomalous pancreaticobiliary ductal union: a case report. World J Gastroenterol 11:6066–6068

Yamamura T, Matsumori H, Kameyama Y et al (1976) Congenital choledochal cyst (in Japanese). Geka Shinryo 18:416

Yamauchi S, Koga A, Matsumoto S, Tanaka M, Nakayama F (1987) Anomalous junction of pancreaticobiliary duct without congenital choledochal cyst: a possible risk factor for gallbladder cancer. Am J Gastroenterol 82:20–24

Yeoh NT, Somasundaram K, Alhady SF, Paramsothy M (1986) Choledochal cyst and cholangiocarcinoma. Med J Malaysia 41:365–369

Yonem O, Bayraktar Y (2007) Clinical characteristics of Caroli's disease. World J Gastroenterol 13:1930–1933

Yoshida T, Shibata K, Matsumoto T, Sasaki A, Hirose R, Kitano S (1999) Carcinoma of the gallbladder associated with anomalous junction of the pancreaticobiliary duct in adults. J Am Coll Surg 189:57–62

Yoshikane H, Hashimoto S, Hidano H, Sasakibara A, Ayakawa T, Mori S, Kojima Y (1998) Multiple early bile duct carcinoma associated with congenital choledochal cyst. J Gastroenterol 33:454–457

Yoshikawa K, Yoshida K, Shirai Y, Sato N, Kashima Y, Coutinho DSS et al (1986) A case of carcinoma arising in the intrahepatic terminal choledochus 12 years after primary excision of a giant choledochal cyst. Am J Gastroenterol 81:378–384

Yoshimura M, Muto T, Narai S et al (1972) Idiopathic choledochal cyst combined with carcinoma. Niigata Igaku Zasshi 86:137

Zhang X, Wang Z, Dong Y (2009) Squamous cell carcinoma arising in a ciliated hepatic foregut cyst: case report and literature review. Pathol Res Pract 205:498–501

Zheng LX, Jia HB, Wu DQ, Shang H, Zhong XY, Wang QS, Zhou WX, Sun ZH (2004) Experience of congenital choledochal cysts in adults: treatment, surgical procedures and clinical outcome in the Second Affiliated Hospital of Harbin Medical University. J Korean Med Sci 19:842–847

Bile Duct Carcinomas with Marked Extracellular or Intracellular Mucin Accumulation: Mucinous and Signet Ring Cell Carcinomas

35

Contents

Abstract

Uncommon variants of cholangiocarcinoma, both of intrahepatic and extrahepatic ducts, are characterized by marked production of mucin. Depending on secretion or storage of mucins, two major groups of mucin-rich carcinomas are distinguished, i.e., mucinous cholangiocarcinoma or signet ring cell carcinoma. Mucinous cholangiocarcinoma (colloid carcinoma) is a rare cancer that may develop as a complication of hepatolithiasis. A part of these neoplasms also occur in the setting of intraductal papillary neoplasms of bile ducts. Most mucinous cholangiocarcinomas are intrahepatic neoplasms, but very rare forms also occur in extrahepatic ducts and cystic duct. Due to massive extracellular mucin accumulation, mucinous cholangiocarcinomas can show rapid mass increase. In contrast to mucinous cancers, the rare signet ring cell carcinomas of bile duct do not secrete mucin, but store it within cells, resulting in intracellular mucin deposits with peripheral displacement of the nucleus. Signet ring cell carcinomas show a diffuse growth pattern and are highly invasive lesions.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_35

Mucinous Cholangiocarcinoma (Colloid Carcinoma of the Biliary Tract)

Introduction

Mucinous cholangiocarcinoma (mucinous carcinoma; colloid carcinoma) is a very rare primary liver malignancy (Chou and Chan 1976; Sugihara and Kojiro 1987; Nakajima et al. 1988; Motoo et al. 1993; Sakamoto et al. 1995; Sasaki et al. 1995; Chow et al. 1997; Mizukami et al. 1999; Kenjo et al. 2000; Nakagohri et al. 2003). The prevalence varies considerably in the literature, probably also depending on the histologic diagnostic criteria used. Among 102 consecutively studied cases of intrahepatic cholangiocarcinoma, there was only one case of mucinous cholangiocarcinoma (Nakajima et al. 1988). A study of 61 cases of intrahepatic cholangiocarcinoma from Thailand listed 13.66 % of mucinous cholangiocarcinoma (Sinawat and Hemsrichart 1991). Mucinous carcinoma may develop as a complication of hepatolithiasis (Chow et al. 1997). At least a part of these neoplasms seem to develop at the invasive parts of intraductal papillary neoplasms of the bile ducts (review: Nakanuma et al. 2010).

Clinical and Imaging Features

Most of the mucinous hepatic cholangiocarcinomas develop within the liver, but other primary sites also occur, including the extrahepatic bile duct (Sakamoto et al. 1995; Yamanaka 1996; Mizukami et al. 1999; Kenjo et al. 2000), the cystic duct (Oku et al. 2006), and the ampulla of Vater (Malik et al. 1992; Seidel et al. 2002; Wolfson 2002; Inagaki et al. 2007). Due to massive mucin production, mucinous cholangiocarcinomas may rapidly grow (Motoo et al. 1993). Intrahepatic mucinous cholangiocarcinoma may be associated with portal vein thrombosis (Nakagohri et al. 2003).

Ultrasonographically, mucinous cholangiocarcinomas are high-echoic tumors with less echogenic portions (Motoo et al. 1993). CT scans showed low-density lesions characterized by the features of large mucinous lakes throughout the tumor (Hayashi et al. 1996; Lee et al. 2001). MRI has shown low intensity on T1-weighted images and high intensity on T2-weighted images (Motoo et al. 1993). Some tumors are microcystic (Sonobe et al. 1995) or have a multicystic appearance and show a periportal collar in imaging (Mizukami et al. 1999). A part of the tumors may show calcifications at imaging (Hayashi et al. 1996; review: Nagakura et al. 1999).

Macroscopic Pathology

Grossly, the tumors are bulky and often circumscribed lesions with a sometimes expanding growth mode. Typically, colloid carcinomas exhibit a glassy or transparent aspect caused by the massive accumulation of mucin in the interstitial space. When cutting through a fresh, unfixed specimen, the copious mucin forms viscous threads between the knife and the cut surface. Large tumors may contain whitish to yellow foci of calcification in the center. The glassy aspect of the tumor is also in evidence in metastatic lesions.

Histopathology

Mucinous adenocarcinoma is histologically characterized by medium-sized to large tumor cells containing abundant mucin. A large part of this mucin is, in contrast to signet ring cells, secreted into the extracellular space, where it forms large masses of PAS-, mucicarmin-, and Alcian blue-positive mucin, producing an expanding mass (Figs. 1 and 2). The tumor cells float in these mucin lakes, which may show a lobulated architecture. The floating cells are either present as single cells and small cell groups or form incomplete or, less commonly, complete tubular profiles. In situations of massive extracellular mucin deposition, it may be difficult to detect viable cancer cells. Sparse neoplastic cells are detectable by use of cytokeratin immunohistochemistry. A part of the tumors show a multicystic appearance

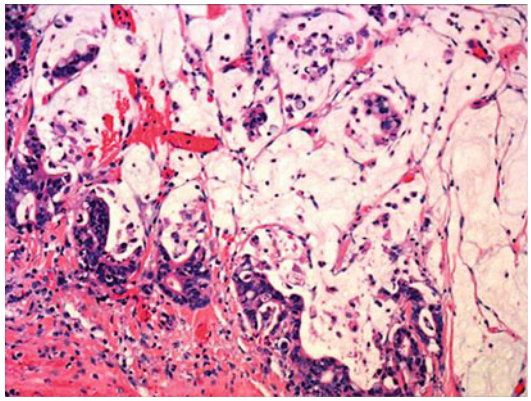

Fig. 1 Mucinous cholangiocarcinoma. Abundant extracellular mucin contains nests of carcinoma cells (hematoxylin and eosin stain)

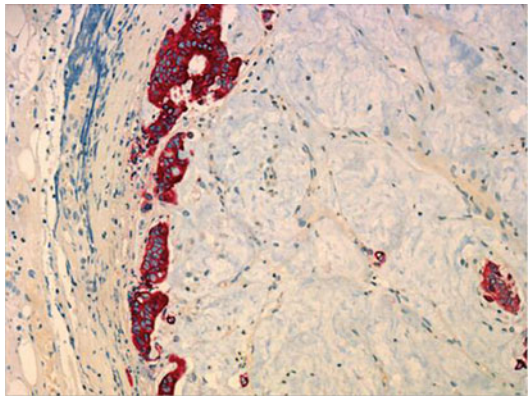

Fig. 2 Mucinous cholangiocarcinoma. Most of the tumor mass consists of extracellular mucin (cytokeratin 7 immunostain)

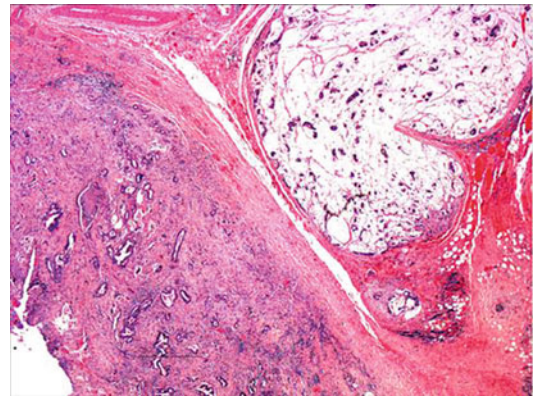

Fig. 3 Perihilar cholangiocarcinoma with mucinous component. The adenocarcinoma in the bile duct wall (*lower left corner*) reveals a classical cholangiocarcinoma morphology, while a mucinous component with abundant extracellular mucin has developed in a tumor part with intraneural invasion (*right upper corner*; hematoxylin and eosin stain)

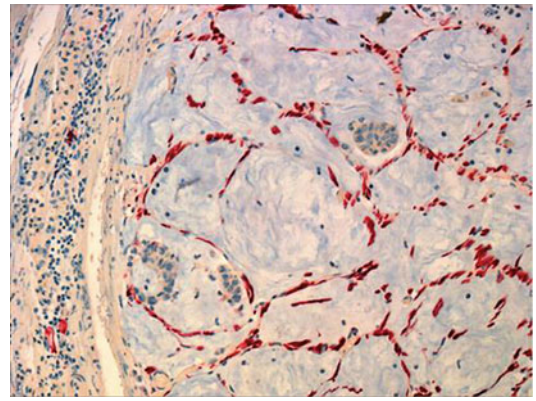

Fig. 4 Mucinous cholangiocarcinoma with intraneural invasion. Clusters of carcinoma cells are suspended in mucin masses. S100 protein-positive nerve elements (Schwann cells) are dissociated by the mucin lakes (S100 protein immunostain)

(Mizukami et al. 1999) or display microcystic features (Sonobe et al. 1995). Mucinous cholangiocarcinoma usually does not secrete mucin into the bile duct lumina (Motoo et al. 1993). A rare subset of mucinous cholangiocarcinoma tends to produce massive peri- and intraneural invasion with formation of colloid-like nodules along regional nerves (neurotropic mucinous carcinoma; Figs. 3 and 4). Mucinous cholangiocarcinoma can show mineral deposits (calcification /mineralization) visualized as basophilic structures, usually within the mucinous lakes. Among nine cases of focally calcified cholangiocarcinomas reported in the literature, six were of the mucinous type (Nagakura et al. 1999). Some of the neoplasms are mixed in regard to mucin storage, i.e., with formation of signet cells (Sasaki et al. 1995). In the vicinity of the tumor, extracellular mucin can induce several tissue reactions. The mucin can cause tissue dissection, with formation of clefts or mucin-filled pseudocysts. Mucin is in part pinocytosed by tumor-associated macrophages (mucophages), which sometimes form mucin granulomas. Activation of macrophages and lymphocytes by

abnormal mucin can result in the secretion of chemokines and fibrokines, ending up with a fibrotic reaction around mucin depositions.

Mucinous cholangiocarcinoma display a characteristic pattern of MUC gene expression. In particular, mature MUC1 mucin and core protein of MUC1 mucin are expressed (Sasaki et al. 1995). The tumors show variable positivity for carcinoembryonic antigen (CEA); Lewis Y, T, and Tn antigens; Lewis X antigen; sialyl-Lewis X antigen; sialyl-Tn antigen; and carbohydrate antigen 19-9 (Sasaki et al. 1995). Electron microscopy revealed mucin-containing vacuoles in the cytoplasm of carcinoma cells (Motoo et al. 1993).

Combined Tumors

Colloid carcinoma can develop from preexisting intraductal papillary mucinous neoplasm of the liver (Bu-Ghanim et al. 2004). Mucinous cholangiocarcinoma has been found in combination with hepatocellular carcinoma (Wada et al. 1986; Morita et al. 2006).

Associated Conditions

Mucin-producing intrahepatic cholangiocarcinoma was observed in conjunction with several disease states, including primary sclerosing cholangitis (Yokomuro et al. 2007), hepatolithiasis with pyogenic cholangitis (Chow et al. 1997), and clonorchiasis (Shim et al. 2004). This type of carcinoma was also found in a patient with Muir-Torre syndrome caused by MSH2 gene mutation (Vernez et al. 2007).

Differential Diagnosis

Metastases of mucinous colorectal cancers may mimic mucinous intrahepatic cholangiocarcinoma (Aoki et al. 1990; Tokai et al. 2006). Recurrence of mucinous neoplasms of the appendix has been observed at the porta hepatis (Sugarbaker and Bijelic 2008).

Biology of Disease

In other organs, mucinous carcinomas exhibit variable evolutions. In the colon they have been shown to progress more rapidly and are associated with a poorer prognosis than non-mucinous cancers (Nozoe et al. 2000; Goi et al. 2006), while gastric mucinous adenocarcinomas either revealed a worse overall survival rate (albeit correlated with more advanced stage at diagnosis) (Wu et al. 1998) or did not differ in outcome in comparison with non-mucinous gastric carcinomas (Yasuda et al. 2001; Hidaka et al. 2008). In contrast, mucinous carcinoma of the breast has a favorable outcome (Di Saverio et al. 2008). Biliary mucinous/colloid carcinomas metastasize to the locoregional lymph nodes (Gotoh et al. 1999) and, similar to gastric mucinous carcinomas, to the ovaries, causing Krukenberg tumors (Andrieu et al. 1972; Sharma et al. 1997; Khunamornpong et al. 2007, 2008; Young 2007). Generally, carcinomas of the gallbladder and the bile ducts often metastasize to the ovaries. In one of the main studies on Krukenberg tumors, 10 % of the tumors had originated from the gallbladder or, in one case, from a bile duct (Schlagenhaufer 1902).

Microcystic (Multicystic) Mucinous Cholangiocarcinoma

Introduction

Microcystic or multicystic mucinous cholangiocarcinoma is a distinct variant of peripheral mucinous cholangiocarcinoma characterized by marked mucin production and a striking microcystic appearance (Sonobe et al. 1995). Mucinous carcinoma with considerable mucin production is a rare variety of cholangiocarcinoma first described in 1987 (Sugihara and Kojiro 1987). This distinct phenotype has an incidence of 0.8 % in autopsied cholangiocarcinoma cases and shows a rapid progression with poor prognosis (Nakajima et al. 1988; Motoo et al. 1993; Sasaki et al. 1995).

Clinical and Imaging Features

Ultrasonography of the liver reveals multiple, small cystic lesions with varying echogenicity. These lesions are also in evidence in CT images and may be associated with a slight dilatation of the intrahepatic bile ducts (Mizukami et al. 1999).

Pathology

Resection specimens show multiple irregularly shaped cystic lesions which contain a gelatinous, viscous mucus, sometimes causing a honeycomb-like appearance. The cysts have a diameter of 0.2–0.4 cm (Sonobe et al. 1995). The internal surface of the microcysts is lined with one or more layers of neoplastic cells, sometimes with a papillary growth pattern. The carcinoma cells are seen to invade both the portal tracts and the liver parenchyma. Interestingly, the invasive carcinoma component tends to show tubular structures associated with a stromal reaction (Sonobe et al. 1995; Mizukami et al. 1999). The cysts contain copious mucus. Some of the cysts may rupture, causing variably sized mucus lakes with accumulation of detached and mostly non-vital cancer cells and macrophages (mucophages).

Intrahepatic Multicystic Mucinous Cholangiocarcinoma with Oncocytic Change

In this rare variant of intrahepatic cholangiocarcinoma, the carcinomatous epithelia may rarely undergo oncocytic change, cells being markedly immunoreactive for mitochondrial antigen, in the absence of an ovarian-like stroma (Fuji et al. 2005).

Signet Ring Cell Carcinoma of the Biliary Tract

ICD-O Code 8490/3

Introduction

Signet ring cell carcinoma (SRCC) is known to develop in several organs, but it occurs most frequently in the stomach, accounting for 15–30 % of all gastric cancers (Kim et al. 1994; Adachi et al. 2000), while the colon is less often involved (about 1 % of all colorectal cancers; Anthony et al. 1996; Nissan et al. 1999). SRCC occurring in the biliary tract including the ampullary region is a rare type of neoplasm, which represents a variant of adenocarcinoma characterized by the presence of greater than 50 % signet ring cells (Fig. 5).

Signet Ring Cell Carcinoma of the Extrahepatic Bile Ducts

SRCC has been observed in the lower common bile duct (Hiraki et al. 2007; Lee et al. 2010; Ogata et al. 2010; Matsumoto et al. 2011). The 55-year-old man described by Lee and coworkers (2010) presented with jaundice and pruritus, and CT and PET suggested the presence of a distal common bile duct cancer. A pylorus-preserving Whipple's operation was performed, with postoperative chemoradiotherapy because of positive proximal margins. The patient survived with no evidence of recurrence for 2 years. Ogata et al. (2010) described a 42-year-

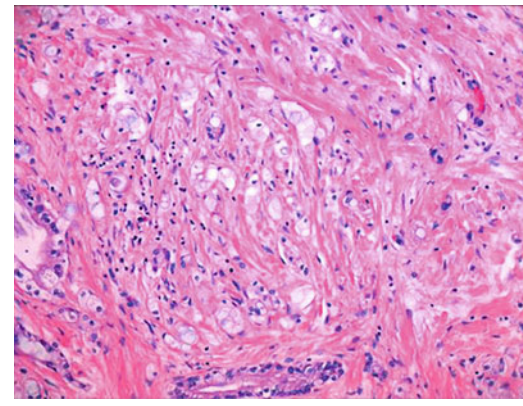

Fig. 5 Sigillocellular cholangiocarcinoma (hematoxylin and eosin stain)

old woman with obstructive jaundice and a stricture of the common bile duct in the absence of gallstones. Based on the diagnosis of malignancy, a pylorus-preserving pancreatoduodenectomy was performed. The resection specimen revealed a common bile duct with a thick whitish wall and a narrow lumen. Histology showed signet ring cell carcinoma, the tumor cells being CK7-positive and their nuclei p53 protein positive. In a 72-year-old male patient reported by Matsumoto and coworkers (2011), the tumor had taken its origin from the lower part of the common bile duct, showed intraluminal growth, and contained cystic components.

Signet Ring Cell Carcinoma of the Intrahepatic Bile Ducts

Very few data are found regarding intrahepatic cholangiocarcinomas with a signet ring cell component (Saito and Nakanuma 1995; Nakanuma et al. 2010).

Signet Ring Cell Carcinoma of the Ampullary Region

SRCC of the ampullary region is uncommon but somewhat more frequent than SRCC in the biliary tract proper. This neoplasm may sometimes be difficult to distinguish from SRCC located to the distal-most part of the common bile duct, due to the diffuse, ill-defined invasive growth pattern. The tumor mainly occurs in older subjects, but has also been observed in a young adult (Purohit et al. 2005). In a review of 14 reported cases, eight involved men and six women. The median age at diagnosis was 57 years (range: 32–83 years), i.e., similar to that of colorectal SRCC, but about 15 years older than patients with gastric SRCC (Akatsu et al. 2007). In a more recent case review of 30 reported patients, 16 were male and 9 female, with an age at presentation ranging from 32 to 83 years and with most tumors having a diameter smaller than 2 cm (Acharya et al. 2013). In a review of 14 cases, the median tumor diameter was 1.8 cm, with a range of 0.8–2.5 cm (Akatsu et al. 2007). The tumors usually present as nodular, firm, and ulcerated lesions. As the neoplasms are associated with marked stromal reactions and tend to show diffuse growth in deeper parts of the ampulla, SRCCs are markedly stenosing lesions that often cause obstructive jaundice and, sometimes, acute pancreatitis (Tas et al. 2011). In some patients, a diffuse infiltration encircling the ampullary duct and extending into the parenchyma of the adjacent pancreatic head was found (Acharya et al. 2013). Specifically, ampullary SRCC may extend into the wall of the distal common bile duct and cause its stenosis. Stenosis of the ampullary duct by SRCC may induce acute pancreatitis (Tas et al. 2011). Immunohistochemically, SRCCs of the ampullary region have been divided into pancreaticobiliary type (CK7+, CK20−, CDX2−, and MUC2−) and an intestinal type (CK7−, CD20+, CDX-2+, and MUC2+), the pancreatobiliary type having a more aggressive course associated with poorer outcome (Gheza et al. 2011). Expression of MUC2 and CDX-2 was previously found in ampullary cancers with signet ring cell components (Chu et al. 2005).

As in other locations, SRCC can result in widespread, disseminated carcinomatosis (Nabeshima et al. 2003), including metastases to CNS and meninges (Paplomata and Wilfong 2011). Ampullary SRCC was associated with ampullary adenocarcinoma in one patient (Maekawa et al. 2011). Although SRCC generally predicts a poor prognosis elsewhere in the gastrointestinal tract, the course of ampullary SRCC may sometimes be more favorable. Ampullary SRCC was found as tumor coexisting with ordinary adenocarcinoma of the ampulla (Maekawa et al. 2011). Periampullary SRCC can occur as a collision tumor together with high-grade neuroendocrine carcinoma (Kurana et al. 2011).

Selected References Sekuguchi and Mizumoto 1979; Gardner et al. 1990; Arnal Monreal et al. 1994; Casella et al. 1994; Hara et al. 2002; Tseng et al. 2002; Eriguchi et al. 2003; Nabeshima et al. 2003; Fang et al. 2004; Li et al. 2004; Ramia et al. 2004; Chu et al. 2005; Purohit et al. 2005; Valeri et al. 2005; Bloomston et al. 2006; Akatsu

et al. 2007; Gao et al. 2009; Ishibashi et al. 2009; Garcia et al. 2011; Tas et al. 2011; Terada 2012; Acharya et al. 2013; Talebi et al. 2014.

Signet Ring Cell Carcinoma of the Gallbladder

SRCC of the gallbladder is a rare but well-established entity (Nishida et al. 1997; Yamauchi et al. 2000; Krunic et al. 2007; Karabulut et al. 2008; Khoo and Nurul 2008; Czysczon and Alatassi 2010; Mondal 2010; Pavic et al. 2010) and will be further treated in the chapter of gallbladder tumors.

Pathology

As in the stomach, signet ring cell carcinomas of the bile duct system show a diffuse invasive growth pattern associated with marked desmoplasia, causing stenosis of the involved duct. The cells are usually medium sized and show a prominent, mucin droplet or glycoprotein body that displaces the flattened and sickle-shaped nucleus to the margin of the cell, resulting in a structure resembling a signet ring. Frequently, the mucin droplet dominates the cell mass, leaving only a thin rim of cytoplasm. In HE preparations, the mucin droplet is amphophilic or slightly basophilic, either homogeneous or with a finely spongy structure. Due to the compact nucleus and the sparse cytoplasm, signet ring cells may be missed, particularly when they are embedded in a stroma with a leukocytic infiltration rich in macrophages. Macrophages that have pinocytosed mucin (mucophages) can strikingly resemble signet ring cells, calling for mucin stains and immunohistochemistry to avoid misinterpretations.

Differential Diagnosis

Differential diagnostically, the distinction between ampullary and duodenal (periampullary) SRCC may be difficult, specifically in the presence of large tumors, where the center of the neoplastic process is not easily identifiable. In addition, duodenal SRCC was found in synchronous conjunction with intestinal-type ampullary carcinoma (Aurello et al. 2011). Sometimes one may observe benign signet ring cell aggregates in the gallbladder mucosa, visualized as loose, cytokeratin-positive cell aggregates overlying ulcerated mucosal surfaces, without signs of invasive growth (Michal et al. 1998).

Nonneoplastic Signet Ring Cells in the Hepatobiliary Tract

Nonneoplastic signet ring cells (NNSRCs) may cause considerable differential diagnostic problems, mainly in the assessment of resection margins in the setting of intraoperative frozen sections. Apart from the typical signet ring cell carcinomas best known from the stomach, signet ring cells have been in many tissues and cell systems (review: Wang et al. 2003). Typical situations include acute inflammations, such as acute erosive gastritis (Dimet et al. 2004), pseudomembranous colitis (Schiffman 1996; Damiani and Campidelli 2002; Abdulkader et al. 2003), and ischemic enteritis (Galli 2000; Biedrzycki et al. 2005). Macrophages can undergo a change that is hardly distinguishable from neoplastic signet ring cells. The best example is signet ring cell sinus histiocytosis of lymph nodes (mucicarminophilic histiocytosis), an alteration that may easily be confounded with cancer metastasis without performing immunohistochemistry (Gould et al. 1989; Frost et al. 1992; Guerrero-Medrano et al. 1997; Groisman et al. 1998; Pathi et al. 2009). This type of lymph node pathology is mimicked by mucicarminophilic histiocytosis caused by polyvinylpyrrolidone (Kuo and Hsueh 1984). A part of these situations share acute mucosal and epithelial damage associated with inflammatory reactions, probably causing dropout of damaged mucin-rich cells/goblet cells. In fact, NNSRCs in enteritis are found as dissociated cells within the lumina of damaged dilated crypts, and immunohistochemistry showed that the cells had a striking localization to the lower aspect of the altered

mucosa, in the absence of the cells within the mucosal connective tissue (Biedrzycki et al. 2005). That acute cell damage may cause a signet ring cell-like change supported by the observation that thermic damage can induce such a cytological change, e.g., signet ring cells found in prostatic tissue of transurethral prostatectomy specimens (Alguacil-Garcia 1986), and signet ring cell change of stromal fibroblasts after thermocauterization of the uterine cervix (McKenna and McCluggage 2008).

NNSRCs have been observed in the ulcerated gallbladder mucosa (Michal et al. 1998; Suri et al. 2001; Ragazzi et al. 2009). In these situations, there were focal collections of these cells both on the mucosal surface and within the lumina of glands. The cells were positive for Mayer's mucicarmine and were immunoreactive for keratin AE1/AE3. Typically, NNSRCs are, in contrast to their neoplastic counterpart, not embedded in a desmoplastic stroma. These cells, which were admixed with macrophages and other inflammatory cells, were interpreted to be damaged normal goblet cells (Ragazzi et al. 2009).

References

Abdulkader I, Cameselle-Teijeiro J, Forteza J (2003) Signet-ring cells associated with pseudomembranous colitis. Virchows Arch 442:412–414

Acharya MN, Panagiotopoulos N, Cohen P, Ahmad R, Jiao LR (2013) Poorly-differentiated signet-ring cell carcinoma of the ampulla of Vater: report of a rare malignancy. JOP 14:190–194

Adachi Y, Yasuda K, Inomata M, Sato K, Shiraishi N, Kitano S (2000) Pathology and prognosis of gastric carcinoma: well versus poorly differentiated type. Cancer 89:1418–1424

Akatsu T, Aiura K, Takahashi S, Kameyama K, Kitajima M, Kitagawa Y (2007) Signet-ring cell carcinoma of the ampulla of Vater: report of a case. Surg Today 37:1110–1114

Alguacil-Garcia A (1986) Artefactual changes mimicking signet ring cell carcinoma in transurethral prostatectomy specimens. Am J Surg Pathol 10:795–800

Andrieu J, Parache RM, fery M (1972) A further case of Krukenberg's tumor manifesting a vesiculo-choledochal cancer (in French). Chirurgie 98:219–223

Anthony T, George R, Rodriguez-Bigas M, Petrelli NJ (1996) Primary signet-ring cell carcinoma of the colon and rectum. Ann Surg Oncol 3:344–348

Aoki K, Takayasu K, Muramatsu Y, Moriyama N, Matsue H, Yamada T (1990) Liver metastases of mucinous colorectal carcinoma: clinic-radiological study of six cases (in Japanese). Nippon Acta Radiol 50:1513–1518

Arnal Monreal FM, Lorenzo Patino MJ, Sacristan F, Ghanime Saide G (1994) Carcinoma de células en anillo de sello de la ampolla de Vater. Rev Esp Enferm Dig 85:391–393

Aurello P, Petrucciani N, D'Angelo F, Nigri G, Picchetto A, Cicchini C, Maglio R, Ramacciato G (2011) Synchronous signet-ring carcinoma of the duodenum and ampullary intestinal-type carcinoma. Am Surg 77:E262–E264

Biedrzycki OJ, Aranout A, Coppen MJ, Shepherd NA (2005) Isolated intramucosal goblet cells in subacute ischaemic enteritis: mimicry of signet ring cell carcinoma. Histopathology 46:460–462

Bloomston M, Walker M, Frankel WL (2006) Radical resection in signet ring carcinoma of the ampulla of Vater: report of an 11-year survivor. Am Surg 72:193–195

Bu-Ghanim M, Suriawinata A, Killackey M, Schwartz ME, Jaffe D, Fiel MI (2004) Invasive colloid carcinoma arising from intraductal papillary neoplasm in a 50-year-old woman with primary sclerosing cholangitis. Semin Liver Dis 24:209–212

Casella R, Rittmann WW, Meier R, Wegmann W, Widmer MK, Hunger T (1994) Signet ring cell carcinoma of Vater's papilla: a very rare malignancy (in German). Helv Chir Acta 60:987–990

Chou ST, Chan CW (1976) Mucin-producing cholangiocarcinoma: an autopsy study in Hong Kong. Pathology 8:321–328

Chow LT, Ahuja AT, Kwong KH, Fung HS, Lai CK, Lau JW (1997) Mucinous cholangiocarcinoma: an unusual complication of hepatolithiasis and recurrent pyogenic cholangitis. Histopathology 30:491–494

Chu PG, Schwarz RE, Lau SK, Yen Y, Weiss LM (2005) Immunohistochemical staining in the diagnosis of pancreatobiliary and ampulla of Vater adenocarcinoma: application of CDX2, CK17, MUC1, and MUC2. Am J Surg Pathol 29:359–367

Czysczon IA, Alatassi H (2010) Signet ring cell carcinoma of the gallbladder in a 22-year-old man: a case report and review of the literature. Int J Surg Pathol 18:358–362

Damiani S, Campidelli C (2002) Pseudomembranous colitis with signet-ring cells. Histopathology 41:176–177

Di Saverio S, Gutierrez J, Avisar E (2008) A retrospective review with long term follow up of 11,400 cases of pure mucinous breast carcinoma. Breast Cancer Res Treat 111:541–547

Dimet S, Lazure T, Bedossa P (2004) Signet-ring cell change in acute erosive gastropathy. Am J Surg Pathol 28:1111–1112

Eriguchi N, Aoyagi S, Jimi A (2003) Signet-ring cell carcinoma of the ampulla of vater: report of a case. Surg Today 33:467–469

Fang CL, Chu JS, Hsieh MC, Wu MS (2004) Signet-ring cell carcinoma of the ampulla of Vater. J Formos Med Assoc 103:793–796

Frost AR, Shek YH, Lack EE (1992) "Signet ring" sinus histiocytosis mimicking metastatic adenocarcinoma: report of two cases with immunohistochemical and ultrastructural study. Mod Pathol 5:497–500

Fujii T, Harada K, Katayanagi K, Kurumaya H, Nakanuma Y (2005) Intrahepatic cholangiocarcinoma with multicystic, mucinous appearance and oncocytic change. Pathol Int 55:206–209

Galli C (2000) Signet ring cells in ischemic ileitis. Int J Surg Pathol 8:239

Gao JM, Tang SS, Fu W, Fan R (2009) Signet-ring cell carcinoma of ampulla of vater: contrast-enhanced ultrasound findings. World J Gastroenterol 15:888–891

Garcia AB, Arranz EM, Sanz RR, Serrano EM, Arranz MD, Sanz-Agero PG, Bellido EC (2011) Signet ring cell carcinoma of the ampulla of Vater (in Spanish). Gastroenterol Hepatol 34:141–146

Gardner HA, Matthews J, Ciano PS (1990) A signet-ring cell carcinoma of the ampulla of Vater. Arch Pathol Lab Med 114:1071–1072

Gheza F, Cervi E, Pulcini G, Villanacci V, Giulini SM, Schiavo-Lena M, Ferrari AB et al (2011) Signet ring cell carcinoma of the ampulla of Vater: demonstration of a pancreatobiliary origin. Pancreas 40:791–793

Goi et al. 2006. http://www.ncbi.nlm.nih.gov/pubmed/17256436

Gotoh et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10643307

Gould E, Perez J, Alobores-Saavedra J, Legaspi A (1989) Signet ring cell sinus histiocytosis. A previously unrecognized histologic condition mimicking metastatic adenocarcinoma in lymph nodes. Am J Clin Pathol 92:509–512

Groisman GM, Amar M, Weiner P, Zamir D (1998) Mucicarminophilic histiocytosis (benign signet-ring cells) and hyperplastic mesothelial cells: two mimics of metastatic carcinoma within a single lymph node. Arch Pathol Lab Med 122:282–284

Guerrero-Medrano J, Delgado R, Albores-Saavedra J (1997) Signet-ring sinus histiocytosis: a reactive disorder that mimics metastatic adenocarcinoma. Cancer 80:277–285

Hara T, Kawashima H, Ishigooka M, Kashiyama M, Takanashi S, Hosokawa Y (2002) Signet-ring-cell carcinoma of the ampulla of Vater: a case report. Hepatogastroenterology 49:561–563

Hayashi M, Matsui O, Ueda K, Kadova M, Yoshikawa J, Gabata T, Takashima T, Izumi R, Nakanuma Y (1996) Imaging findings of mucinous type of cholangiocellular carcinoma. J Comput Assist Tomogr 20:386–389

Hidaka S, Tanaka K, Takeshita H, Sumida Y, Fukuoka H, Abo T, Yano H, Nanashima A et al (2008) Clinicopathology and prognosis of mucinous gastric carcinoma. Hepatogastroenterology 55:791–794

Hiraki M, Yakushiji H, Hashiguchil K, Harada S, Okada K, Goto Y, Ikeda H, Mori D, Tokunaga O, Miyazaki K, Hiraki M, Yakushiji H, Hashiguchil K, Harada S, Okada K, Goto Y, Ikeda H, Mori D, Tokunaga O, Miyazaki K (2007) Signet ring cell carcinoma of the lower bile duct with rapid growth: report of a case. Hepatogastroenterology 54:1922–1924

Inagaki M, Obara M, Suzuki S, Ishizaki A, Takahashi K, Matsumoto K, Haneda M, Tokusashi Y et al (2007) Mucinous carcinoma of Vater's ampulla with a unique extension along the main pancreatic duct. J Hepatobiliary Pancreat Surg 14:518–521

Ishibashi Y, Ito Y, Omori K, Wakabayashi K (2009) Signet ring cell carcinoma of the ampulla of Vater. A case report. JOP 10:690–693

Karabulut Z, Yildirim Y, Abaci I, IIgici D, Özyilkan O (2008) Signet-ring cell carcinoma of the gallbladder: a case report. Adv Ther 25:520–523

Kenjo A, Abe T, Saito T, Tsuchiya T, Yamada F, Kanzaki N, Gotoh M (2000) Mucin ball-producing extrahepatic bile duct carcinoma. Scand J Gastroenterol 35:1330–1334

Khoo JJ, Nurul AM (2008) A clinicopathological study of nine cases of gallbladder carcinoma in 1122 cholecystectomies in Johor, Malaysia. Malays J Pathol 30:21–26

Khunamornpong S, Siriaunkgul S, Suprasert P, Pojchamarnwiputh S, Chiangmai W, Young RH (2007) Intrahepatic cholangiocarcinoma metastatic to the ovary: a report of 16 cases of an underemphasized form of secondary tumor in the ovary that may mimic primary neoplasia. Am J Surg Pathol 31:1788–1799

Khunamornpong S, Lerwill MF, Siriaunkgul S, Suprasert P, Pojchamarnwiputh S, Chiangmai WN, Young RH (2008) Carcinoma of extrahepatic bile ducts and gallbladder metastatic to the ovary: a report of 16 cases. Int J Gynecol Pathol 27:366–379

Kim JP, Kim SC, Yang HK (1994) Prognostic significance of signet ring cell carcinoma of the stomach. Surg Oncol 3:221–227

Krunic AL, Chen HM, Lopatka K (2007) Signet-ring cell carcinoma of the gallbladder with skin metastases. Australas J Dermatol 48:187–189

Kuo TT, Hsueh S (1984) Mucicarminophilic histiocytosis. A polyvinyl-pyrrolidone (PVP) storage disease simulating signet-ring cell carcinoma. Am J Surg Pathol 8:419–428

Kurana A, Sharma A, Gupta G, Gandhi JS (2011) Periampullary collision tumor – high grade neuroendocrine carcinoma and signet ring cell carcinoma: a case report and review of literature. Indian J Pathol Microbiol 54:161–163

Lee WJ, Lim HK, Jang KM, Kim SH, Lee SJ, Lim JH, Choo IW (2001) Radiologic spectrum of cholangiocarcinoma: emphasis on unusual manifestations and differential diagnosis. Radiographics 21(Spec no): S97–S116

Lee EY, Kim C, Kim MJ, Park JY, Park SW, Song SY, Chung JB, Kim H, Bang S (2010) Signet ring cell carcinoma of the extrahepatic bile duct. Gut Liver 4:402–406

Li L, Chen QH, Sullivan JD, Breuer FU (2004) Signet-ring cell carcinoma of the ampulla of Vater. Ann Clin Lab Sci 34:471–475

Maekawa H, Sakurada M, Orita H, Sato K (2011) Signet-ring cell carcinoma co-existing with adenocarcinoma of the ampulla of Vater. A case report. JOP 12:162–166

Malik AK, Bhaskar KV, Wig JD (1992) Periampullary carcinoma with special reference to their mucin characteristics – a pathologic study of 53 cases. Indian J Pathol Microbiol 35:81–87

Matsumoto T, Inoue S, Masuo K, Okamoto Y, Fukushima M, Wada M, Shimeno N et al (2011) Signet ring cell carcinoma of the bile duct: a case report (in Japanese). Nihon Shokakibyo Gakkai Zasshi 108:2042–2049

McKenna M, McCluggage WG (2008) Signet ring cells of stromal derivation in the uterine cervix secondary to cauterisation: report of a previously undescribed phenomenon. J Clin Pathol 61:648–651

Michal M, Chlumska A, Mukensnabl P (1998) Signet-ring cell aggregates simulating carcinoma in colon and gallbladder mucosa. Pathol Res Pract 194:197–200

Mizukami Y, Ohta H, Arisato S, Nakano Y, Murakami M, Orii Y, Saito H, Sakurai Y et al (1999) Case report: mucinous cholangiocarcinoma featuring a multicystic appearance and periportal collar in imaging. J Gastroenterol Hepatol 14:1223–1226

Mondal SK (2010) Signet ring cell carcinoma of gallbladder with celiac lymph node metastasis in a young man. J Cancer Res Ther 6:379–381

Morita D, Kagata Y, Ogata S, Tsuda H, Hatsuse K, Mochizuki H, Matsubara O (2006) Combined hepatocellular carcinoma and cholangiocarcinoma with components of mucinous carcinoma arising in a cirrhotic liver. Pathol Int 56:222–226

Motoo Y, Sawabu N, Minamoto T, Kawakami H, Ohta H, Okai T, Fujimoto T, Mai M et al (1993) Rapid growing mucinous cholangiocarcinoma. Intern Med 32:116–121

Nabeshima S, Kishihara Y, Nabeshima A, Yamaga S, Kinjo M, Kashiwagi S, Hayashi J (2003) Poorly differentiated adenocarcinoma with signet-ring cells of the Vater's ampulla, without jaundice but with disseminated carcinomatosis. Fukuoka Igaku Zasshi 94:235–240

Nagakura S, Shirai Y, Yamai K, Hatakeyama K (1999) Calcification in mucinous cholangiocellular carcinoma. Hepatogastroenterology 46:465–466

Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S, Tanizawa Y, Kobayashi A (2003) Mucin-producing intrahepatic cholangiocarcinoma with portal vein thrombosis. Hepatogastroenterology 50:2194–2195

Nakajima T, Kondo Y, Miyazaki M, Okui K (1988) A histopathologic study of 102 cases of intrahepatic cholangiocarcinoma: histologic classification and modes of spreading. Hum Pathol 19:1228–1234

Nakanuma Y, Sato Y, Harada K, Sasaki M, Xu J, Ikeda H (2010) Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. World J Hepatol 2:419–427

Nishida T, Iwasaki H, Johzaki H, Tanaka S, Watanabe R, Kikuchi M (1997) A human gall-bladder signet ring cell carcinoma cell line. Pathol Int 47:368–376

Nissan A, Guillem JG, Paty PB, Wong WD, Cohen AM (1999) Signet-ring cell carcinoma of the colon and rectum: a matched control study. Dis Colon Rectum 42:1176–1180

Nozoe T, Anai H, Nasu S, Sugimachi K (2000) Clinicopathological characteristics of mucinous carcinoma of the colon and rectum. J Surg Oncol 75:103–107

Ogata S, Kimura A, Hatsuse K, Yamamoto J, Shimazaki H, Nakanishi K, Kawai T (2010) Poorly differentiated adenocarcinoma with signet-ring cell carcinoma of the extrahepatic bile duct in a 42-year-old Japanese female: a case report. Acta Med Okayama 64:63–65

Oku T, Wada Y, Waga E, Misu K, Hazama K, Suzuki Y, Fujita M, Namamachi Y, Maeda M (2006) A case of mucin-producing cystic duct cancer protruding into the common bile duct (in Japanese). Nippon Shokakibyo Gakkai Zasshi 103:44–51

Paplomata E, Wilfong L (2011) Signet ring cell carcinoma of the ampulla of Vater with leptomeningeal metastases: a case report. J Clin Oncol 29:e627–e629

Pathi R, Lawrence WD, Barroeta JE (2009) Signet ring cell histiocytosis in axillary lymph nodes: a sheep in wolves' clothing? A potentially under-recognized pitfall in the diagnosis of metastatic breast cancer. Breat J 15:302–303

Pavic I, Marusic Z, Mijic A, Balicevic D, Kruslin B, Tomas D (2010) A case of signet-ring cell carcinoma of the gallbladder: immunohistochemistry and differential diagnosis. Acta Chir Croat 49:159–162

Purohit RC, Kant K, Bhargava N, Kothari N, Purohit V (2005) Signet ring cell carcinoma of ampulla of Vater in a young adult. Indian J Gastroenterol 24:222–223

Ragazzi M, Carbonara C, Rosai J (2009) Nonneoplastic signet-ring cells in the gallbladder and uterine cervix. A potential source of overdiagnosis. Hum Pathol 40:326–331

Ramia JM, Mansilla A, Villar J, Muffak K, Garrote D, Ferron JA (2004) Signet-ring-cell carcinoma of Vater's ampulla. JOP 5:495–497

Saito K, Nakanuma Y (1995) Signet ring cell carcinoma of the intrahepatic bile duct (in Japanese). Ryoikibetsu Shokogun Shirizu 7:395–397

Sakamoto H, Satoh M, Yabana T (1995) Mucinous cholangiocarcinoma, mucus producing carcinoma (in Japanese). Ryoikibetsu Shokogun Shirizu 7:414–416

Sasaki M, Nakanuma Y, Shimizu K, Izumi R (1995) Pathological and immunohistochemical findings in a case of mucinous cholangiocarcinoma. Pathol Int 45:781–786

Schiffman R (1996) Signet-ring cells associated with pseudomembranous colitis. Am J Surg Pathol 20:599–602

Schlagenhaufer F (1902) Ueber das metastatische Ovarialcarcinom nach Krebs des Magens, Darms und

anderer Bauchorgane (On the metastatic ovarian carcinoma subsequent to cancer of the stomach, the intestinal tract and other abdominal organs) (in German). Monatschr Geburtshilfe Gynäkol 15:484–528

Seidel G, Zahurak M, iacobuzio-Donahue C, Sohn TA, Adsay NV, Yeo CJ, Lillemoe KD et al (2002) Almost all infiltrating colloid carcinomas of the pancreas and the periampullary region arise from in situ papillary neoplasms: a study of 39 cases. Am J Surg Pathol 26:56–63

Sekuguchi T, Mizumoto R (1979) Clinicopathological study of papilla of Vater. Geka Chiryo 41:1–5

Sharma P, Jaffe PE, Bhattacharyya A (1997) Metastatic cholangiocarcinoma presenting as ovarian cancer: a rare Krukenberg tumor. Am J Gastroenterol 92:531–533

Shim HS, Lim BJ, Kim MJ, Lee WJ, Park C, Park YN (2004) Mucinous cholangiocarcinoma associated with Clonorchis sinensis infestation: a case report (in Korean). Korean J Hepatol 10:223–227

Sinawat P, Hemsrichart V (1991) A histopathologic study of 61 cases of peripheral intrahepatic cholangiocarcinoma. J Med Assoc Thai 74:448–453

Sonobe H, Enzan H, Ido E, Furihata M, Iwata J, Ohtsuki Y, Watanabe R (1995) Mucinous cholangiocarcinoma featuring a unique microcystic appearance. Pathol Int 45:292–296

Sugarbaker PH, Bijelic L (2008) The porta hepatis as a site of recurrence of mucinous appendiceal neoplasms treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. Tumori 94:694–700

Sugihara S, Kojiro M (1987) Pathology of cholangiocarcinoma. In: Okuda K, Ishak KG (eds) Neoplasms of the liver. Springer, Tokyo

Suri VS, Sakhuja P, Malhotra V, Gondal R, Sachdev AK, Negi SS (2001) Benign signet ring cell change with multilayering in the gallbladder mucosa – a case report. Pathol Res Pract 197:785–788

Talebi A, Mohammadizadeh F, Hani M, Bagheri M, Bagheri A (2014) Signet ring carcinoma of ampulla of Vater. Adv Biomed Res 3:30

Tas A, Özer E, Köklü S, Kocak E (2011) Signet ring cell carcinoma of the ampulla of Vater: a rare cause of acute pancreatitis. Scand J Gastroenterol 46:126–127

Terada T (2012) Primary signet-ring cell carcinoma of the ampulla of Vater: a case report with an immunohistochemical study. Appl Immunohistochem Mol Morphol 20:427–428

Tokai H, Kawashita Y, Eguchi S, Kamohara Y, Takatsuki M, Okudaira S, Tajima Y, Hayashi T, Kanematsu T (2006) A case of mucin producing liver metastases with intrabiliary extension. World J Gastroenterol 12:4918–4921

Tseng LJ, Jao YT, Mo LR (2002) Signet ring cell carcinoma of major papilla. Gastrointest Endosc 56:733

Valeri S, Caricato M, Ripetti V, Crucitti P, Ausania F, Garberini A, Giarratano G, Gullotta G, Coppola R (2005) Signet-ring cell carcinoma of the Vater's ampulla: report of a clinical case (in Italian). Suppl Tumori 4:S61

Vernez M, Hutter P, Monnerat C, Halkic N, Gugerli O, Bouzourene H (2007) A case of Muir-Torre syndrome associated with mucinous hepatic cholangiocarcinoma and a novel germline mutation of the MSH2 gene. Fam Cancer 6:141–145

Wada K, Kondo F, Kubosawa H, Kondo Y (1986) Combined hepatocellular and mucinous carcinoma. Acta Pathol Jpn 36:285–291

Wang K, Weinrach D, Lal A, Musunuri S, Ramirez J, Ozer O, Keh P, Rao MS (2003) Signet-ring cell change versus signet-ring cell carcinoma: a comparative analysis. Am J Surg Pathol 27:1429–1433

Wolfson WL (2002) Colloid carcinomas of the pancreas and periampullary region. Am J Surg Pathol 26:952

Wu CY, Yeh HZ, Shih RT, Chen GH (1998) A clinicopathologic study of mucinous gastric carcinoma including multivariate analysis. Cancer 83:1312–1318

Yamanaka T (1996) Mucin producing extrahepatic bile duct carcinoma (in Japanese). Ryoikibetsi Shokogun Shirizu 9:92–94

Yamauchi K, Ozeki Y, Sumi Y, Yamada T, Koyama H (2000) A case of signet ring cell carcinoma of the gallbladder with anomalous pancreaticobiliary ductal union (in Japanese). Nippon Shokakibyo Gakkai Zasshi 97:204–208

Yasuda K, Adachi Y, Shiraishi N, Yamaguchi K, Shiromizu A, Kitano S (2001) Pathology and prognosis of mucinous gastric carcinoma. J Surg Oncol 76:272–277

Yokomuro S, Arima Y, Mizuguchi Y, Shimizu T, Kawahigashi Y, Kannda T, Arai M, Uchida E et al (2007) Mucin-producing bile duct carcinoma arising from sclerosing cholangitis: a case report. J Nippon Med Sch 74:61–64

Young RH (2007) From Krukenberg to today: the ever present problems posed by metastatic tumors in the ovary. Part II. Adv Anat Pathol 14:149–177

Special Variants of Cholangiocarcinoma

36

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_36

Abstract

Apart from classical cholangiocarcinoma with a desmoplastic adenocarcinoma morphology, several variants of these neoplasms are recognized. A part of these tumors differ from cholangiocarcinoma by the cell lineages involved, including intestinal, gastric foveolar, pyloric gland types, and carcinomas with Paneth cell metaplasia. One rare variant of bile duct carcinoma derives from cells of small ducts or ductules (cholangiolocellular carcinoma). Uncommon cholangiocarcinomas exhibit distinct growth patterns or cell arrangements, such as cribriform carcinoma, micropapillary carcinoma, and cholangiocarcinoma with a thyroid follicular neoplasm-like pattern. An unusual variant of cholangiocarcinoma displays a ductal plate malformation pattern. Very rare forms of cholangiocarcinoma show production of alpha-fetoprotein (AFP), with intracellular accumulation of AFP. This neoplasm has also been observed in children.

Cholangiocarcinoma: Intestinal, Gastric Foveolar, and Pyloric Gland Types

Introduction

A subset of cholangiocarcinomas of the extrahepatic and intrahepatic biliary tract is characterized by a glandular cell lineage deviating from the cholangiocellular phenotype. The mechanisms causing this phenotypic diversity have not been clarified, but pathways of metaplasia/transdifferentiation, stem cell effects, and the role of distinct cell systems present in the bile ducts but not yet characterized have been discussed.

Intestinal-Type Cholangiocarcinoma

Intestinal-type adenocarcinoma is well defined for the gallbladder (Albores-Saavedra et al. 1986b) but is less well known in the biliary tract. It has been described as a new entity in 2002 (Bae et al. 2002). These authors reported an intestinal-type cholangiocarcinoma in a large intrahepatic bile duct, associated with hepatolithiasis. The striking resemblance to colorectal carcinoma may pose differential diagnostic problems, but the imaging features will help in the decision process. Intestinal cellular features may be focally expressed in intrahepatic cholangiocarcinoma (Nakanuma et al. 2003). Distal bile duct carcinoma with an intestinal phenotype has been suggested to have arisen in a hyperplastic mucosa showing metaplastic biliary epithelium of the intestinal type (Sano et al. 2003).

In the original description, the tumor showed mainly an intraductal papillary growth primarily composed of absorptive columnar cells, and Paneth cell metaplasia was widespread, and goblet cells and neuroendocrine cells were also observed (Bae et al. 2002). Otherwise the histology of this variant is characterized by tubular structures and papillary formations consisting of columnar cells of the intestinal/colonic type and by pseudostratification of the elongated atypical nuclei, with or without interspersed goblet cells or Paneth cells. On cytology aspirates, intestinal-type cholangiocarcinoma mimics colorectal adenocarcinoma, columnar cells having cigar-shaped nuclei with marked atypia, crowding, and pseudostratification, on a background with signs of necrosis (Chaudhary et al. 2005). The bile duct mucosa adjacent to the tumor may show intestinal metaplasia and dysplastic changes in these areas (Bae et al. 2002).

Intraductal papillary neoplasia of the liver (IPNL) often presents gastrointestinal metaplasia with aberrant expression of MUC2 and MUC5AC and oversecretion of mucin into the ductal lumen. Aberrant expression of CDX2, a homeodomain protein involved in the regulation of intestinal development and differentiation, is closely related to the overexpression of MU2 in IPNL associated with hepatolithiasis (Ishikawa et al. 2004).

Pyloric Gland-Type Cholangiocarcinoma

A pyloric gland component seems to a rather common change in intrahepatic cholangiocarcinomas. In one study, albeit defining the

tumors also through MUC typing, 11/100 intrahepatic cholangiocarcinomas were of the pyloric gland type (Aishima et al. 2006).

Gastric Foveolar-Type Cholangiocarcinoma

Gastric foveolar-type cholangiocarcinoma is a rare variant of well-differentiated adenocarcinoma that has been found in the extrahepatic bile ducts (Albores-Saavedra et al. 1999). The tumors were composed predominantly (>95 %) of gastric foveolar-type epithelium. The resemblance to gastric epithelium in this variant of cholangiocarcinoma has caused confusion with adenocarcinomas of the gallbladder (Albores-Saavedra et al. 1999). This variant of cholangiocarcinoma has subsequently been observed. Among 100 intrahepatic cholangiocarcinomas, a gastric foveolar type was found in 36 of the tumors, i.e., with a very high frequency, but the tumor subtyping was also based on the expression pattern MUC gene products. According to the expression frequency of MUCs (MUC2, MUC5AC, and MUC6), the tumors were classified into the following groups: null type, gastric foveolar type, pyloric gland type, and gastric combined type (Aishima et al. 2006). The tumors originally described in 1999 (Albores-Saavedra et al. 1999) were morphologically defined and were located in the extrahepatic bile ducts. Half of intrahepatic cholangiocarcinomas with a gastric foveolar phenotype were located in the hilar region of the liver. The gastric foveolar type was associated with a higher incidence of lymph node metastases and was more often associated with an aggressive course and worse survival (Aishima et al. 2006).

Histologically, the neoplastic glands are lined by a single layer of rather tall columnar cells rich in mucin. These reveal basal nuclei with minor structural anomalies, small nucleoli, and a low mitotic activity. Focally, a micropapillary or polypoid to lobular growth patterns may be noted (Albores-Saavedra et al. 1999). Foci of less differentiated adenocarcinoma and perineural invasion were reported for the first two cases. The neoplastic cells and extracellular mucin were PAS and Alcian Blue positive (Albores-Saavedra et al. 1999). Aspirate smears of this variant of cholangiocarcinoma show cuboidal-to-columnar epithelial cells with relatively bland nuclear features, low nuclear-cytoplasmic ratios, and an abundant, mucin-producing cytoplasm (PAS, mucicarmine, and alkaline Alcian Blue positive), this morphology resembling gastric foveolar-type epithelium (Chaudhary et al. 2005). Focal expression of a gastric foveolar-type neoplastic epithelium has been observed in intraductal papillary cholangiocarcinoma associated with von Meyenburg complexes (Neto et al. 2007). Similar to normal gastric foveolar epithelium, the tumor cells are reactive for cytokeratins 8 and 20 and for cathepsin D, as reported for normal foveolar cells (Albores-Saavedra et al. 1999).

Pyloric/Pseudopyloric Gland (Antral) Metaplasia of the Biliary Tract

Pyloric gland metaplasia (antral metaplasia) is well known to occur in the gallbladder, the pancreas, and the colon, in the organ usually in the context of inflammatory bowel disease. In the gallbladder, this type of metaplasia is sometimes extensive and complex (Laitio 1975, 1976) and may represent a component of metaplasia-dysplasia-carcinoma sequence (Azadeh and Parai 1980; Hirai 1980; Lewis et al. 2007). Gallbladder adenomas consisting of pyloric-type cells can develop pyloric gland-type adenoma, co-expressing gastric and biliary phenotypes (Nagata et al. 2007), and gallbladder adenocarcinomas can undergo a differentiation toward gastric foveolar cells (Kushima et al. 1996). Cells of pyloric gland metaplasia are reactive for lysozyme, class III mucin (Tsutsumi et al. 1984).

In contrast, less is still known regarding pyloric metaplasia in bile ducts. Gastric/pyloric metaplasia resembling the morphologic features of pyloric glands may be observed within and near pathologically altered large intrahepatic bile ducts, together with the expression of gastric epithelial-type mucins, i.e., MUC5AC and MUC6 (Sasaki et al. 1998; Hoang et al. 2001; Nakanuma

et al. 2003). Among 42 pancreaticoduodenectomy specimens (32 with neoplastic lesions and 10 with inflammatory changes of the extrahepatic bile ducts), 40 % of the neoplastic specimens and 70 % of the inflammatory specimens had metaplastic changes in the extrahepatic bile ducts, and pyloric gland metaplasia was the most common change (80 % of the metaplasias). Only 5 % of the metaplasias were of the intestinal type, 10 % were mixed pyloric and intestinal metaplasia, and 5 % had a component of squamous metaplasia. None of the normal bile ducts obtained from ten autopsies had metaplastic changes (Hoang et al. 2001). The predominance of pyloric gland metaplasia in the bile duct system was also documented in other studies (Tsuru 1984; Kurumaya et al. 1990). In an investigation of 22 cases of hepatolithiasis, intrahepatic bile ducts had pyloric gland metaplasia in all cases, and the rate of intestinal metaplasia was (23 %), i.e., much higher than in bile ducts having cholangiocarcinoma or inflammation not related to lithiasis (Kurumaya et al. 1990). The biologic behavior of cells in pyloric gland metaplasia, apart from being a potentially precancerous lesion, is only partly known. In the gallbladder, pyloric gland metaplasia is usually confined to the lamina propria of the mucosa, but the so-called florid variant extends to the muscular wall and serosa, mimicking cancer invasion (Albores-Saavedra et al. 1993). Intriguing are observations that florid pyloric gland metaplasia, albeit benign, may show perineural and intraneural invasion, e.g., in the gallbladder (Albores-Saavedra and Henson 1999).

Intestinal Metaplasia

In the gallbladder, intestinal metaplasia has been studied in detail (Järvi and Laurén 1967). The extent of metaplasia differs as a function of the presence of endocrine cells: in the absence of endocrine cells, intestinal metaplasia was restricted to isolated or small clusters of mature goblet cells. While gallbladders with endocrine cells showed, in addition, gland-like structures resembling colonic crypts and Paneth cells (Albores-Saavedra et al. 1986a), colonic-type epithelial metaplasia is found in hyperplastic and dysplastic biliary epithelia (Shimonishi et al. 2002), sometimes associated with goblet cell change and formation of Paneth cells in peribiliary glands. Goblet cells in intestinal metaplasia stain for antigen 17NM (Hughes et al. 2006), 17NM being an antigen expressed in the mucus vacuole of colonic goblet cells and detectable by a monoclonal antibody (Hughes et al. 1986).

For intestinal metaplasia in the biliary tract, less information is available (Järvi and Laurén 1967), but it is considered as a precancerous state (Iguchi et al. 1982). In a retrospective study, up to 20 % of cases of bile duct cancer and gallbladder cancer displayed intestinal metaplasia in the surrounding mucosa, with Paneth cells, enterochromaffin cells, and goblet cells (Kozuka et al. 1984). In a study comparing bile duct mucosa in autopsy cases and surgical specimens with and without cholangiocarcinoma, pyloric gland metaplasia was generally more often seen than intestinal metaplasia characterized by goblet cells, although bile ducts with cholangiocarcinoma revealed a higher yield of goblet cells than bile ducts with benign obstruction (Tsuru 1984). Among 22 cases with hepatolithiasis, intestinal metaplasia with goblet cells and Paneth cells amounted to 23 %, while all cases had pyloric gland metaplasia (Kurumaya et al. 1990).

Paneth Cell Carcinoma of the Biliary Tract

Paneth Cells in Neoplasia

Contribution of Paneth cells has been described in several tumor types and tumor localizations, including the duodenum, small intestine, colon, appendix, and stomach (Gibbs 1969; Miyajima and Takeguchi 1976; Shousa 1979; Heitz and Wegmann 1980; Lundqvist and Wilander 1983; London et al. 1988; Wada et al. 1992; Serio and Zampatti 2000). Paneth cells participate in the adenoma-carcinoma sequence in that precursor lesions in the colon may show Paneth cell

metaplasia (Wada 2009). A Paneth cell differentiation may take place in tubular adenomas of the colon (in minute adenomas in up to 32.5 % of cases; Wada et al. 1992) and in some benign neoplasms, e.g., adenomyoma of the ileum (Takahashi et al. 2006). The biliary tract is rarely involved, and Paneth cell tumors mainly develop in the ampulla of Vater. Widespread Paneth cell metaplasia was observed in an intrahepatic intestinal-type cholangiocarcinoma with intraluminal spread, associated with hepatolithiasis (Bae et al. 2002).

Paneth Cell Tumors of the Ampulla of Vater

Variable contributions of Paneth cells have been noted in few malignant tumors of the ampulla of Vater (Ferrell and Beckstead 1991; Kimura et al. 1994; Mora et al. 2004). The case reported by Mora et al. (2004) was that of 64-year-old man who presented with obstructive jaundice. Cholangiography revealed an ampullary stricture and biopsy showed adenocarcinoma. The resected specimen of the ampulla showed a yellow-tan mass within the mucosa measuring up to 2.3 cm. Histology displayed a moderately to poorly differentiated carcinoma. The neoplastic cells formed rudimentary, misshapen, gland-like structures, whereas other areas showed haphazardly arranged cells. Most of cells had a rich cytoplasm with coarse and brightly eosinophilic granules which immunohistochemically expressed lysozyme. Lysozyme was also detected in the tumor reported by Ferrell and Beckstead (1991). It is currently unknown whether neoplastic Paneth cells recapitulate the capability of normal Paneth cells to create a niche for (neoplastic) stem cells.

Paneth Cell Tumors of the Gallbladder

Intestinal-type adenocarcinoma of the gallbladder can contain few Paneth cells (Albores-Saavedra et al. 1986b), but extensive Paneth cell metaplasia has been observed in gallbladder adenocarcinoma only very rarely (Sakaki et al. 2000).

Paneth Cells Are Highly Specialized Intestinal Cells Involved in Innate Immunity

Paneth cells are specialized cells found at the bottom of crypts of the entire intestine and proximal colon, including the appendix. They contain specific granules which contain lysozyme, defensins, and IgA (Geller and Thung 1983). In the intestinal crypts, mature Paneth cells constitute the niche for Lgr5 stem cells. Genetic removal of Paneth cells in vivo results in the concomitant loss of Lgr5 stem cells, but this Paneth cell requirement can be substituted by a pulse of exogenous Wnt (Sato et al. 2011). The differentiation pathways of specific crypt cell derivatives are regulated by an intricate factor system, mainly involving notch/gamma-secretase inhibitors which block crypt cell proliferation and induce secretory cell differentiation. The atonal homolog 1 (Atoh1) transcription factor is required for all effects of the notch/gamma-secretase inhibitor (Kazanjian et al. 2010). The goblet cell lineage, characterized by the expression of goblet cell genes AGR2, MUC2, RETLNB, and SPINK4, is induced by the epithelial ETS transcription factor, SAM pointed domain ETS factor (SPDEF) (Noah et al. 2010). In the Paneth cell differentiation pathway, APC/beta-catenin/Tcf signaling plays a role (Joo et al. 2009), and Paneth cell maturation depends on E-cadherin which is required for the intestinal epithelial lining by providing mechanical integrity (Schneider et al. 2010).

Paneth cells have a central role in intestinal antimicrobial defense and innate mucosal immunity (Quellette 2010). Paneth cells produce alpha-defensin peptides (mainly the human alpha-defensins [HDs] HD-5 and HD-6) which modulate the complex composition of the intestinal microflora. Defensins are small cysteine-rich cationic proteins which exist in both invertebrates and vertebrates, are produced by leukocytes or Paneth cells, and are active against bacteria, fungi, and enveloped and non-enveloped viruses. Alpha-defensins (synonym: cryptdins) are a group of antimicrobial peptides encoded by the genes DEFA1 (neutrophil defensin 1), DEFA1B (defensin alpha 1),

DEFA3 (neutrophil defensin 3), DEFA4 (corticostatin, neutrophil defensin 4), DEFA5 (Paneth cell specific, defensin 5), and DEFA6 (Paneth cell specific, defensin 6). Beta-defensins are the most widely distributed defensins and are secreted by leukocytes and epithelial cells of many kinds. They comprise DEFB1 (beta-defensin 1), DEFB2 (beta-defensin 2), and DEFB103A (beta-defensin 103), DEFB107B (beta-defensin 107), DEFB110 (beta-defensin 110), and DEFB136 (beta-defensin 136). q-defensins are rare, have been identified in leukocytes of rhesus macaque and olive baboons, and are vestigial in humans and other primates (DEFT1P). It follows that two alpha-defensin species are produced by Paneth cells, i.e., defensins 5 and 6 (Defensin database, Singapore; Quellette 2005; Mastroianni and Quellette 2009). Ligation of Toll-like receptor 9 (TLR9), e.g., by the action of *Toxoplasma gondii*, leads to Paneth cell degranulation and release of defensins (Buzoni-Gatel 2010; Foureau et al. 2010). In Crohn's disease, alpha-defensins 5 and 6 are specifically reduced, and ileal extracts from Crohn's disease patients are comprised in clearing bacteria, and enteroadherent *Escherichia coli* colonize the mucosa ("Paneth's disease"). The mechanisms for defective antimicrobial Paneth cell function in Crohn's disease are complex and include an association with a NOD2 loss of function mutation, a disturbance of the Wnt pathway transcription factor TCF7L2 (TCF4), the autophagy factor ATG16L1, the endosomal stress protein XBP1, the Toll-like receptor TLR9, the calcium-mediated potassium channel KCNN4, as well as mutations or inactivation of HD5 (Wehkamp et al. 2007; Wehkamp and Stange 2010). Defensin-4 (cryptdin-4) has the most potent microbicidal activity and predominantly affects noncommensal bacteria (Masuda et al. 2011). Human defensin-5 is one of the major antimicrobial peptides secreted by Paneth cells in the human small intestine. As the other defensins, defensin-5 is produced and stored as a propeptide in Paneth cell granules, secreted in response to stimulation by cholinergic reagents or bacterial components. The activation process involves trypsin (Ishikawa et al. 2009). Human defensin-5 is expressed in Paneth-type gastric cancer cells (Inada et al. 2005).

Cholangiolocellular Carcinoma and Bile Ductular Carcinoma

Carcinomas of Small Bile Ducts

A small subset of cholangiocarcinomas have features of, or eventually arise from, bile ductules. These tumors are termed cholangiolocellular carcinoma or bile ductular carcinoma (Steiner and Higginson 1959; Mukerjee and Maheshwari 1964; Shiota et al. 2001; Sasaki et al. 2003; Kim et al. 2004). Two variants of these unusual tumors have been described.

Cholangiolocellular Carcinoma

Cholangiolocellular carcinoma (CLC) is a rare subtype of cholangiocarcinoma that has been described in 1959 (Steiner and Higginson 1959). CLC is characterized by a neoplastic proliferation of small cholangiocytes of a type normally found in ductules, the cholangioles. Since 1959, relatively few cases have been reported.

CLC accounts for about 1 % of all primary liver cancers. Steiner and Higginson described the tumor as being characterized by small epithelial profiles resembling cholangioles or the canals of Hering and ductular reaction-like anastomosing glands in abundant fibrous stroma.

Selected References Mukerjee and Maheshwari 1964; Sugihara et al. 1987; Yamamoto et al. 1996; Fukukura et al. 2000; Takeuchi et al. 2005; Okuda et al. 2005; Matsuda et al. 2006; Kanamoto et al. 2008; Joshita et al. 2009; Motosugi et al. 2009; Asayama et al. 2010; Sempoux et al. 2011; Iwahashi et al. 2013; Maeda et al. 2013.

The term cholangiolocellular carcinoma was first employed by Steiner at the Kampala Conference on liver cancer in 1956 (Steiner 1957).

In their publication of 1959, Steiner and Higginson noted that "in theory, a tumor should exist that corresponds to every type of normal cell in the body in which division can occur. On this basis one gap has persisted in carcinomas of the liver; no tumor has been described that corresponds to the epithelium of the cholangioles or canals of Hering (end of quotation)" (Steiner and Higginson 1959). In 1959, Steiner and Higginson described a series of 11 liver carcinomas that seemed to meet the criteria for designation as cholangiolocellular carcinoma. An analysis of the previous literature showed that this lesion is unusual. It did not occur in a series of 100 liver cancers reported from Los Angeles by Edmondson and Steiner (1954), and one case was found among a total of 40 in Chicago (Steiner 1957). In a total of 863 liver cancers in Trans-Saharan native Africans studied by Steiner in 1957, in nine different case collections, there were ten additional examples of this tumor (cited in Steiner and Higginson 1959). In their review of 1959, these authors refer to potential other previous cases in the literature, mainly based on published figures of liver cancers. For example, Fig. 5 in a 1911 book on liver cancer may show this tumor (Goldzieher and von Bökay 1911), and in Ninard's book on liver tumors, Fig. 175 illustrates a tumor that may represent cholangiolocellular carcinoma (Ninard 1950). In the case review of 1959, the overall frequency was, therefore, 11 cholangiolocellular carcinomas among 1030 primary liver cancers of all types or about 1 %. The sex ratio was four cases in women and seven in men, which is similar to that seen in cholangiocarcinoma. The range in age was from 22 to 64 years, with an average age of 49.5 years. In a more recent study, two cases were identified among 708 consecutively resected cases of primary liver cancer or 0.56 %, with an average patient age at presentation of 66 years, i.e., much higher than in Steiner and Higginson's study (Shiota et al. 2001).

CLC may represent a progenitor/stem cell-derived neoplasm. CLC seems to have "junctional potentialities" because part of CLC had HCC-like features (Steiner and Higginson 1959). This was the first observation suggesting that this neoplasm might be related to a stem cell process. CLC has been proposed to originate from cells of cholangioles or canals of Hering, structures that harbor progenitor cells (Roskams et al. 2004). More recent findings in fact suggest a derivation from hepatic progenitor cells, with immunoreactivity of CLC cells for keratins 7 and 19, prominin-1, OCT4, and c-Kit (Komuta et al. 2008). An immunohistochemical study revealed positivity of CLC cells for the stem cell markers CD133, EpCAM, and CD44 (Iwahashi et al. 2013). That the pathogenesis of CLC is strongly linked to stem/progenitor cells is supported by the findings that this neoplasm can contain hepatocellular carcinoma (HCC) and/or cholangiocarcinoma components, suggesting the involvement of a bipotential progenitor cell (Kanamoto et al. 2008). Out of 30 cases, 19 showed papillary and/or glandular formations with mucin production, representing areas of cholangiocarcinoma, and all cases exhibited HCC-like areas, mainly at tumor boundaries (Komuta et al. 2008).

Among 30 patients, a single tumor was observed in 25 (83.3 %), whereas multiple (2–8) tumors considered as intrahepatic metastases were found in five patients (16.7 %). Coexistence of HCC was detected in three patients. Maximum tumor diameter ranged from 0.8 to 11 cm (mean, 4.9 cm) (Komuta et al. 2008). CLC may be associated with seropositivity for AFP-L3 alone, with low AFP serum concentration (Okuda et al. 2005). The clinical behavior of CLC has not been clarified in detail, but may be similar to intrahepatic cholangiocarcinoma (Maeda et al. 2013). In the study of Komuta et al. (2008), tumors with a diameter greater than 4 cm showed a higher recurrence rate compared to smaller CLC cases. Rapidly progressing CLC has been reported (Takeuchi et al. 2005). On dynamic CT or MRI, the tumors presented hypervascular masses with delayed washout, the lesions showing peripheral enhancement with concentric delayed filling (Fukukura et al. 2000; Asayama et al. 2010). On arterial phase images, tumors appeared as masses exhibiting early and complete enhancement or predominantly peripheral enhancement. Retention of contrast media in the masses was detected

in half of the lesions (Motosugi et al. 2009). Persistent enhancement in the late phase by contrast-enhanced CT has been described (Joshita et al. 2009). It seems that early enhancement with persistent delayed enhancement is a characteristic feature of this rare tumor.

Macroscopic Pathology

Macroscopically, tumors were described as whitish in color, solid, lobulated, not encapsulated, and with irregular margins (Komuta et al. 2008). The liver with cholangiolocellular carcinoma usually shows numerous small nodules up to several cm in diameter in part of the liver or in the entire organ. The lesions develop mostly in a non-cirrhotic liver. The nodules may show some confluence, and one nodule may be larger and dominant. The nodules are firm and creamy in color. The average weight of the tumor-bearing livers was, in the review of 11 cases (Steiner an Higginson 1959), 2916 g, an average which is about 500 g less than that for hepatocellular carcinoma in African natives, but about 500 g more than that for a series of cholangiocarcinoma (Steiner, unpublished data; cited in Steiner and Higginson 1959). Metastases were present in seven of the ten patients upon whom an autopsy had been performed, and the primary metastatic sites were the portal lymph nodes and the lungs.

Histopathology

The tumor is chiefly (90 %) composed of small monotonous and/or antler-like anastomosing glands resembling abnormal ductular reactions and forming moniliform structures (Fig. 1). Typically, the neoplastic cells are arranged in cords that usually appear solid but may show miniature lumina or form small ductules resembling ductular profiles. In these areas, the tumor cells are cuboidal and clearly smaller than normal hepatocytes. Unlike the cells of ordinary cholangiocarcinoma, the cells of cholangiolocellular carcinoma are often slightly eosinophilic. They

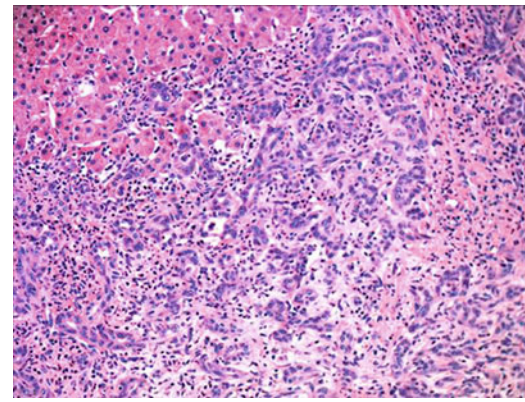

Fig. 1 Cholangiolocellular carcinoma (hematoxylin and eosin stain)

have a scanty cytoplasm and small round nuclei with distinct nucleoli, the nuclei being slightly atypical in comparison with cells of normal ductules. In addition, papillary and clear cell glandular formations resembling ordinary cholangiocarcinoma are seen. Where an apical domain facing a lumen is present, the apical membrane is positive in Mallory's phosphotungstic acid stain. Cholangiolocellular carcinoma, similar to ordinary cholangiocarcinoma, is a markedly desmoplastic lesion. Desmoplasia has been documented in studies (Goldzieher and von Bökay 1911; Steiner and Higginson 1959; Shiota et al. 2001). This stroma may appear pale owing to a high content in interstitial glycosaminoglycans and exhibits a variable cellularity. In grossly firm and larger tumor nodules, the central parts tend to be densely fibrous, with only scarce cancer cells. Necrosis may also be found in these central regions.

At the tumor border, solid or trabecular components mimicking HCC are found. In a series of six cases, two cases contained HCC-like areas in addition to the cholangiolocellular component (Shiota et al. 2001). In another study, all cases showed HCC-like areas, mainly at the tumor boundary (Komuta et al. 2008). Based on morphology, a putative transition of hepatocytes into cholangiolar cells in such tumors had already been proposed in 1911 (Goldzieher and von Bökay 1911). Here, the cells are mildly atypical and have an abundant eosinophilic cytoplasm. The HCC-like

cells seem to replace the normal adjacent liver cell plates, with only scanty stroma. These three patterns reveal transitional zones with each other (Komuta et al. 2008). The association of CLC with HCC in the same lesion (Sugihara et al. 1987) or with ordinary cholangiocarcinoma and a component representing HCC (Kanamoto et al. 2008) has been described. CLC has also been observed in combination with HCC located elsewhere in the liver (Matsuda et al. 2006). The main part of CLC usually shows an abundant stroma with edema, hyalinization, and focal lymphocytic infiltrations.

The tumor cells of the predominant, pure CLC component are strongly positive for CK7 and CK19 (Shiota et al. 2001). pCEA showed an intraluminal staining pattern in all cases, but CD10 and Hep Par 1 are negative in these areas. 86.7 % of the cases showed immunoreactivity for NCAM, and in the CLC area, the tumor cells displayed a diffuse apical MDR1 expression and basolateral MRP1, MRP3, and BCRP expression (Komuta et al. 2008). At the tumor boundary, most cases show HCC-like trabecular areas with canalicular expression of CD10/polyclonal CEA and submembranous CK7 expression, a pattern resembling that of intermediate hepatocytes. In these HCC-like areas, small cells with scanty cytoplasm show strong cytoplasmic CK7 and CK19 reactivity, cells representing HPC (Komuta et al. 2008). As already outlined above, a part of tumor cells express several stem cell markers (Iwahashi et al. 2013). In contrast to bile duct adenomas and ductular reactions, CLC cells are reactive for the polycomb group protein, EZH2 (Sasaki et al. 2014).

CLC has to be distinguished from bile duct adenoma and circumscribed forms of benign ductular proliferations (Sempoux et al. 2011).

Bile Ductular Variant of Peripheral Intrahepatic Cholangiocarcinoma

Bile ductular intrahepatic cholangiocarcinoma (BD-IHC; "bile ductular carcinoma") is an uncommon subgroup of peripheral intrahepatic cholangiocarcinoma with an infiltrating growth pattern and a resemblance to ductular proliferations (Kozaka et al. 2007). These neoplasms are similar to the cholangiolocellular carcinomas described above, but in contrast to those, they form a subgroup of *peripheral* cholangiocarcinomas.

In one study, all peripheral CCs with a ductular phenotype comprised whitish nodules with a blurred margin against the surrounding liver. The adjacent liver did not seem to be compressed (Kozaka et al. 2007). In one systematic study, 15/24 peripheral cholangiocarcinomas exhibited the features of BD-IHC, with structures resembling reactive proliferating ductules (RBD) at both the peripheral and central parts of the nodules in 8/24 (the RBD/RBD phenotype) and with RBD-like structures at the periphery and ordinary CC in the center in 7/24 (the RBD/OAC phenotype) (Kozaka et al. 2007). At the periphery, RBD/RBD-type carcinoma cells were directly apposed to the adjacent hepatocytes, and a distinct infiltrating replacement growth pattern was in evidence. The central areas of RBD type showed variable dense fibrosis (desmoplasia) and even scarring, and ghostlike outlines of portal tracts or a nodular fibrous framework were found. Within the latter, cord-like carcinoma cell with pericellular fibrosis was identifiable, reflecting the replacement of hepatocellular cords of preexisting hepatic lobules or regenerative nodules by carcinoma cells. No fibrous capsules were encountered. In contrast to normal and mature small bile ducts and bile ductules, but similar to proliferating ductules, 75 % of RBD/RBD and 71.4 % of RBD/OAC showed a positive immunohistochemical reaction of the cancer cells for NCAM. Cytokeratins 7, 8, 18, and 19 were variably expressed in carcinoma cells of all cases.

Bile duct hamartomas may mimic liver metastases of BD-IHC (Nagano et al. 2006).

Pathogenesis

The presence of CK7-/CK19-positive hepatic progenitor cells (HPCs) in the tumor, cells that are also positive for prominin-1 (CD133), c-kit receptor, octamer-4 transcription factor, and leukemia

inhibitory factor, suggests a progenitor cell origin of CLC (Komuta et al. 2008). This is supported by the expression of stem cell markers EpCAM, CD133, and CD44 in these tumors (Iwahashi et al. 2013). HPCs normally exist in the smallest and peripheral-most branches of the biliary tree, the ductules, and the canals of Hering (review: Roskams et al. 2004). HPCs represent bipotential liver-specific adult stem cells that are activated when fully differentiated hepatocytes or cholangiocytes are injured or lost. HPC activation is histologically characterized by the presence of increased numbers of HPC and intermediate hepatocytes in the portal tracts in the lobular zone 1 adjacent to portal tracts, associated with an increase of periductular extracellular matrix and fibroblastoid cells (the periductular sheath). Cells of CLC may have undergone a cholangiocyte lineage switch that requires activation of notch (review: Roskams et al. 2010).

Cribriform Carcinoma of the Biliary Tract

Cribriform carcinoma of the biliary tract is a distinct variant of cholangiocarcinoma. The histology reveals a striking resemblance to infiltrating cribriform carcinoma of the breast, which is a well-established entity (Venable et al. 1990; Fig. 2). These breast tumors showed a positivity for sex steroid receptors in 69 % of cases (Venable et al. 1990). In the gastrointestinal tract, cribriform carcinoma has also been described in the pancreas (Kimura et al. 2001) and the gallbladder (Albores-Saavedra et al. 2008).

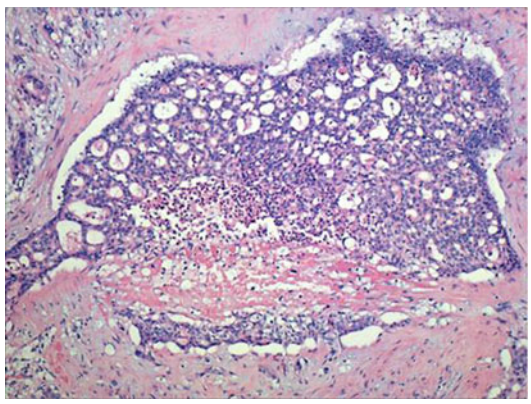

Fig. 2 Cribriform carcinoma of the bile duct (hematoxylin and eosin stain)

Micropapillary Cholangiocarcinoma (Bile Duct Adenocarcinoma with Micropapillary Components; Biliary Invasive Micropapillary Carcinoma, BD-IMPC)

Introduction

Invasive micropapillary carcinoma (IMPC) is a distinct variety of adenocarcinoma with an aggressive biology and a propensity to invade lymph vessels (lymphotropism) and to produce lymph node metastases (reviews: Nassar 2004; Yoshizawa et al. 2014). Histologically, the hallmark is a distinctive cleft formation around the neoplastic cell clusters which is presumably caused by the detachment of the epithelial cells from the stroma. It has been described in several organs, although the lesion is best known as a distinct, aggressive entity of breast cancer (Luna-Moré et al. 1994; Nassar et al. 2001; Zekioglu et al. 2004). The neoplasm has been observed in the major salivary glands (Nagao et al. 2004), lung (Amin et al. 2002), stomach (Kondo et al. 2008), biliary tract (see below), pancreas (Kitagawa et al. 2007), colon (Kuroda et al. 2007), and urinary bladder (Amin et al. 1994). In many of these tumors, the IMPC growth pattern was generally a focal component in otherwise typical invasive ductal carcinomas or other adenocarcinomas (Nassar et al. 2001).

Biliary Invasive Micropapillary Carcinoma (BD-IMPC)

Few examples of IMPC of the biliary tract have been reported (Kondo 2009; Yoshizawa et al. 2014). A tumor detected in the common bile duct was measuring 11 mm on cut surface and was histologically composed of conventional adenocarcinoma with severe neutrophil

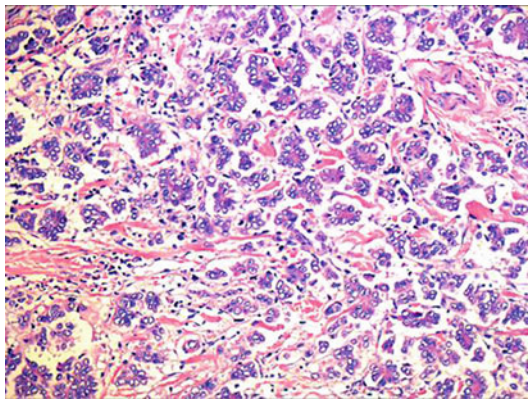

Fig. 3 Invasive micropapillary carcinoma of the bile duct. The small micropapillary structures are surrounded by a clear space (hematoxylin and eosin stain)

infiltration and a small focus (2 mm) of micropapillary carcinoma. The tumor showed marked lymphatic invasion. Resected regional lymph nodes revealed micrometastasis of a few cancer cells in a micropapillary pattern only in one lymph node (Kondo 2009). Yoshizawa and coworkers (2014) identified 13 tumors with an IMPC component among 93 consecutive cases of extrahepatic bile duct cancers. The presence of an IMPC component was significantly correlated with lymph node metastasis, lymphatic invasion, poor disease-free survival, and prognosis. IMPC also develops in the ampullary/periampullary region, with marked lymphotropism, and is associated with neutrophil infiltration, both within cancer epithelia and the stroma (Khayyata et al. 2005).

Histologically, the small-to-medium-sized cells form clusters or micropapillary structures that seem to float within clear spaces resembling lymphatic channels (Fig. 3). However, there is no immunoreactivity supporting the view that we deal with vascular channels (review: Nassar 2004). The clefts are an artifact and are not seen in frozen sections. The periphery of these clear spaces is formed by the contact border of the adjacent extracellular matrix of the stroma. The cell clusters consist of cells with an eosinophilic, finely granular-to-dense cytoplasm, contain nuclei with only moderate atypia, and display a variable mitotic activity. The tumor cells characteristically show a reverse polarity, termed an "inside-out" growth pattern. The clusters are devoid of fibrovascular cores and often show tubular profiles in their center. The stroma forms thin strands delineating the clear spaces, leading to a "spongy" appearance of the stroma. Immunohistochemically, the cells are characterized by MUC1 staining predominantly in the stroma-facing surface of the cell clusters in all cases (Nassar et al. 2004; Khayyata et al. 2005). E-cadherin expression was cytoplasmic rather than membranous, and the tumor stains for galectin-3 (Khayyata et al. 2005).

IMPC of the Gallbladder

In a study of 90 consecutive cases of gallbladder carcinoma, 20 cases had foci of IMPC, which ranged from 5 % to 10 % of the primary tumor tissue. Tumors with IMPC had marked lymphatic invasion, and for those 20 cases, 17 (85 %) also included lymph node metastasis, which was more frequent than in conventional carcinoma (32.8 %). This illustrates that lymphotropism is also a feature of gallbladder IMPC (Hara et al. 2010).

Differential Diagnosis

In light of the specific histology, only metastases may pose differential diagnostic problems. Bile duct wall metastasis from IMPC of the urinary bladder has been observed (Hong et al. 2002).

Pathogenesis

The highly characteristic feature of IMPC, i.e., the pericellular cleft formation, has not been clarified. It has, however, been suggested that the tumor cells may have undergone a reversal of their polarity or orientation ("inside-out growth") in regard to the adjacent matrix, based on the fact that EMA shows an inverse immunostaining and the glycoprotein MUC1 is largely limited to the basal surface of the cells and not, as usual, to the apical

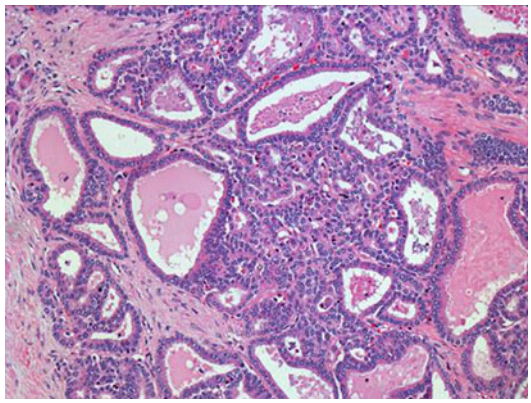

Fig. 4 Thyroid-like intrahepatic cholangiocarcinoma. This tumor shows numerous follicle-like structures mimicking follicular thyroid carcinoma (hematoxylin and eosin stain)

surface (Nassar et al. 2004). Cytoplasmic immunostaining for E-cadherin in IMPC (Khayyata et al. 2005) may also indicate loss or derangement of cell polarity.

Thyroid Follicular Neoplasm-Like Cholangiocarcinoma

In very rare instances, intrahepatic cholangiocarcinoma can present as a well-differentiated neoplasm with a prominent follicular architecture that resembles follicular carcinoma of the thyroid (Fig. 4). The follicular structures contain a colloid-like eosinophilic, homogeneous material with so-called resorption vacuoles, lined by uniform cuboidal cells. In contrast to follicular thyroid carcinomas, these tumor cells are negative for thyroglobulin and thyroid transcription factor-1 (Fornelli et al. 2010).

AFP-Producing Cholangiocarcinoma

Introduction

Alpha-fetoprotein (AFP) is a glycoprotein that is normally produced by fetal and regenerating hepatocytes, certain gastrointestinal cells, and yolk sac cells (Gitlin et al. 1972). Serum AFP is widely used as a tumor marker for diagnosis and follow-up of hepatocellular carcinoma, hepatoblastoma, and certain germ cell tumors. However, other tumors may rarely produce AFP at high serum levels, including hepatoid adenocarcinomas of the hepatobiliary tract (Abdullah et al. 2010), mixed hepatocellular and cholangiocellular carcinomas (Sasaki et al. 2001), renal cell carcinomas (Morimoto et al. 1988), collecting duct carcinoma of the kidney (Blandamura et al. 2005), certain gastric carcinomas (Adachi et al. 2003), distinct lung carcinomas (Saka et al. 1988; Yoshino et al. 1996), rare colorectal carcinomas (Nakajima et al. 1985; Hocking et al. 1995), acinar cell carcinomas of the pancreas (Itoh et al. 1992; Mueller et al. 2005), pancreatoblastoma (Iseki et al. 1986), and bile duct carcinomas.

AFP-Producing Cholangiocarcinoma

Elevated serum AFP has been detected in a minority of intrahepatic cholangiocarcinomas showing a histology typical for this tumor, i.e., without any evidence of a hepatocytic lineage. Elevation of serum AFP to levels higher than 20 ng/ml is found in approximately 20 % of intrahepatic cholangiocarcinoma patients (Liver Cancer Study Group of Japan 1990), but only very few patients with this type of tumor show an elevation of serum AFP to levels higher than 1000 ng/ml. The group with high levels mainly consists of typical intrahepatic cholangiocellular adenocarcinomas (Tanigawa et al. 1987; Nonomura et al. 1989; Omori et al. 2004; Ishikawa et al. 2007; Vij and Wang 2008; Zhou et al. 2008; Ishii et al. 2010). Among 131 patients who underwent surgical resection for pathologically confirmed intrahepatic cholangiocarcinoma, 32 showed serum AFP of more than 20 ng/ml, and among these AFP-positive cases, liver cirrhosis and positivity for HBsAg were more frequent than in the group with normal serum AFP (Zhou et al. 2008). A retrospective study of 429 intrahepatic cholangiocarcinomas diagnosed in China showed 90 patients with serum AFP >20 ng/ml (21.3 %; Shen et al. 2009). Production

of AFP was found to be more common in poorly differentiated cholangiocarcinomas (Nonomura et al. 1989). In AFP-producing cholangiocarcinomas, a part of the tumor cells are immunoreactive for AFP (Ishikawa et al. 2007).

Some intrahepatic cholangiocarcinomas are associated with elevated lectin-reactive AFP, but have low AFP levels (Okuda et al. 2005, 2006). In one 57-year-old female patient with Budd-Chiari syndrome, hepatocellular carcinoma was resected, and AFP returned to normal after surgery. However, *Lens culinaris* agglutinin-reactive AFP (AFP-L3) later increased, and ultrasonography showed a nodule 2 cm in diameter located in the left liver lobe, which was resected and exhibited the histology of tubular cholangiocellular adenocarcinoma with focal AFP immunostaining (Yamamoto et al. 2005). AFP production (up to 2265 ng/ml) has been observed in patients with a clear cell carcinoma arising from the extrahepatic bile duct (Kure et al. 2000; Miyazawa et al. 2006).

A subset of gallbladder carcinomas can produce AFP, mainly poorly differentiated variants (Haruta et al. 1987; Sugaya et al. 1989; Brown and Roberts. 1992; Ng and Ng 1995; Cocquyt et al. 1996; St. Laurent et al. 1999).

Pathogenesis

The pathogenesis of AFP production by cholangiocarcinomas has not been clarified. The fact that the tumor cells expressed CK14 and CD133 in one case suggested the contribution of a liver stem cell (Ishikawa et al. 2007). In one study, AFP enhancer/promoter-driven EGFP gene was transfected into human cholangiocarcinoma cell lines, and one of the lines expressed both AFP and EGFP. Clonal analyses revealed that one EGFP-positive cell generated both EGFP-positive and EGFP-negative cell fractions. However, one EGFP-negative cell never produced EGFP-positive cells. The AFP-producing cells were therefore suggested to be cancer stem cells (Ishii et al. 2010). Derepression of the AFP gene caused by genomic instability of the tumor may be an alternative hypothesis.

Cholangiocarcinoma with Ductal Plate Malformation Pattern

A small subset of intrahepatic cholangiocarcinomas is characterized by the presence of a "ductal plate malformation" pattern. In one case, the neoplasm was composed of numerous small carcinomatous areas with desmoplastic reaction, and neoplastic glandular structures exhibited a dilated lumen lined with a single layer of cuboidal to low columnar cells, resembling ductal plate malformation. The cells were reactive for cytokeratin 19, EMA, and epithelial cell adhesion molecule (Nakanuma et al. 2012; Choe and Kim 2014). A part of the features resemble those of ductal plate tumor, a neoplasm originally identified in a young adult (review: Zimmermann 2002).

Inflammatory Cholangiocarcinoma

A very rare variant of intrahepatic cholangiocarcinoma is characterized by high densities of tumor-infiltrating lymphocytes (TILs), similar to certain hepatocellular carcinomas. This alteration can be associated with autoimmune hepatitis-like features of the tumor-bearing liver (Izumi et al. 2010).

References

Abdullah A, Jenkins-Mosure K, Lewis T, Patel Y, Strobel S, Pepe L (2010) Primary hepatoid carcinoma of the biliary tree: a radiologic mimicker of Klatskin-type tumor. Cancer Imaging 10:198–201

Adachi Y, Tsuchihashi J, Shiraishi N, Yasuda K, Etoh T, Kitano S (2003) AFP-producing gastric carcinoma: multivariate analysis of prognostic factors in 270 patients. Oncology 65:95–101

Aishima S, Kuroda Y, Nishihara Y, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2006) Gastric mucin phenotype defines tumour progression and prognosis of intrahepatic cholangiocarcinoma: gastric foveolar type is associated with aggressive tumour behaviour. Histopathology 49:35–44

Albores-Saavedra J, Henson DE (1999) Pyloric gland metaplasia with perineural invasion of the gallbladder: a lesion that can be confused with adenocarcinoma. Cancer 86:2625–2631

Albores-Saavedra J, Nadji M, Henson DE, Ziegels-Weissman J, Mones JM (1986a) Intestinal metaplasia of the gallbladder: a morphologic and immunocytochemical study. Hum Pathol 17:614–620

Albores-Saavedra J, Nadji M, Henson DE (1986b) Intestinal-type adenocarcinoma of the gallbladder: a clinicopathologic study of seven cases. Am J Surg Pathol 10:19–25

Albores-Saavedra J, Vardaman C, Vuitch F (1993) Non-neoplastic polypoid lesions and adenomas of the gallbladder. Pathol Annu 28:145–177

Albores-Saavedra J, Delgado R, Henson DE (1999) Well-differentiated adenocarcinoma, gastric foveolar type, of the extrahepatic bile ducts: a previously unrecognized and distinctive morphologic variant of bile duct carcinoma. Ann Diagn Pathol 3:75–80

Albores-Saavedra J, Henson DE, Moran-Portela D, Lino-Silva S (2008) Cribriform carcinoma of the gallbladder: a clinicopathologic study of 7 cases. Am J Surg Pathol 32:1694–1698

Amin MB, Ro JY, el-Sharkawy T, Lee KM, Troncoso P, Silva EG, Ordonez NG, Ayala AG (1994) Micropapillary variant of transitional cell carcinoma of the urinary bladder. Histologic pattern resembling ovarian papillary serous carcinoma. Am J Surg Pathol 18:1224–1232

Amin MB, Tamboli P, Merchant SH, Ordonez NG, Ro J, Ayala AG, Ro JY (2002) Micropapillary component in lung adenocarcinoma: a distinctive histologic feature with possible prognostic significance. Am J Surg Pathol 26:358–364

Asayama Y, Tajima T, Okamoto D, Nishie A, Ishigami K, Ushijima Y, Kakihara D et al (2010) Imaging of cholangiolocellular carcinoma of the liver. Eur J Radiol 75:e120–e125

Azadeh B, Parai SK (1980) Argentaffin cells, intestinal metaplasia and antral metaplasia in carcinoma of the gall bladder. Histopathology 4:653–659

Bae JY, Park YN, Nakanuma Y, Lee WJ, Kim JY, Park C (2002) Intestinal type cholangiocarcinoma of intrahepatic large bile duct associated with hepatolithiasis – a new histologic subtype for further investigation. Hepatogastroenterology 49:628–630

Blandamura S, Vendraminelli R, Aversa S, Federigo M (2005) Collecting duct carcinoma of kidney producing alpha-fetoprotein. Eur J Surg Oncol 31:1039–1041

Brown JA, Roberts CS (1992) Elevated serum alpha-fetoprotein levels in primary gallbladder carcinoma without hepatic involvement. Cancer 70:1838–1840

Buzoni-Gatel D (2010) TLR9-dependent induction of intestinal alpha-defensin by Toxoplasma gondii. J Immunol 184:7022–7029

Chaudhary HB, Bhanot P, Logrono R (2005) Phenotype diversity of intrahepatic and extrahepatic cholangiocarcinoma on aspiration cytology and core needle biopsy: case series and review of the literature. Cancer 105:220–228

Choe JY, Kim H (2014) Intrahepatic cholangiocarcinoma with predominant ductal plate malformation pattern. Clin Mol Hepatol 20:214–217

Cocquyt V, Pipeleers-Marichal M, Delvaux G, Van Belle S (1996) Increasing serum levels of alpha-fetoprotein in a patient with relapsing gallbladder carcinoma. Am J Clin Oncol 19:465–468

Edmondson HA, Steiner PE (1954) Primary carcinoma of the liver, study of 100 cases among 48,900 necropsies. Cancer 7:462–503

Ferrell LD, Beckstead JH (1991) Paneth-like cells in an adenoma and adenocarcinoma of the ampulla of Vater. Arch Pathol Lab Med 115:956–958

Fornelli A, Bondi A, Jovine E, Eusebi V (2010) Intrahepatic cholangiocarcinoma resembling a thyroid follicular neoplasm. Virchows Arch 456:339–342

Foureau DM, Mielcarz DW, Menard LC, Schulthess J, Werts C, Vasseur V, Ryffel B, Kasper LH, Fornelli A, Bondi A, Jovine E, Eusebi V (2010) Intrahepatic cholangiocarcinoma resembling a thyroid follicular neoplasm. Virchows Arch 456:339–342

Fukukura Y, Hamanoue M, Fujiyoshi F, Sasaki M, Haruta K, Inoue H, Aiko T, Nakajo M (2000) Cholangiolocellular carcinoma of the liver: CT and MR findings. J Comput Assist Tomogr 24:809–812

Geller SA, Thung SN (1983) Morphologic unity of Paneth cells. Arch Pathol Lab Med 107:476–479

Gibbs NM (1969) Incidence and significance of argentaffin and Paneth cells in some tumors of the large intestine. J Clin Pathol 20:826–831

Gitlin D, Perricelli A, Gitlin GM (1972) Synthesis of a-fetoprotein by liver, yolk sac, and gastrointestinal tract of the human conceptus. Cancer Res 32:979–982

Goldzieher M, von Bökay Z (1911) Der primäre Leberkrebs. Virchows Arch Pathol Anat 203:75–131

Hara S, Kijima H, Okada K, Igarashi Y (2010) Invasive micropapillary variant of the gallbladder adenocarcinoma and its aggressive potential for lymph node metastasis. Biomed Res 31:89–95

Haruta J, Kanayama K, Tachino F, Hayakawa M, Kusakabe A, Oka Y, Ito S, Uno H et al (1987) A clinicopathological evaluation of AFP-positive gallbladder cancer – with special reference to two autopsy cases investigated by an immunological method (in Japanese). Gan No Rinsho 33:1839–1845

Heitz PU, Wegmann W (1980) Identification of neoplastic Paneth cells in an adenocarcinoma of the stomach using lysozyme as a marker, and electron microscopy. Virchows Arch A Pathol Anat Histol 386:107–116

Hirai S (1980) Clinicopathologic study on metaplasia in resected gallbladder: as a background of histogenesis of gallbladder cancer. Jpn J Gastroenterol Surg 13:35–44

Hoang MP, Murakata LA, Padilla-Rodriguez AL, Albores-Saavedra J (2001) Metaplastic lesions of the extrahepatic bile ducts: a morphologic and immunohistochemical study. Mod Pathol 14:1119–1125

Hocking GR, Shembrey M, Hay D, Ostör AG (1995) Alpha-fetoprotein-producing adenocarcinoma of the sigmoid colon with possible hepatoid differentiation. Pathology 27:277–279

Hong SP, Park SW, Lee SJ, Chung JP, Song SY, Chung JB, Kang JK, Cho NH (2002) Bile duct wall metastasis from micropapillary variant transitional cell carcinoma of the urinary bladder mimicking primary hilar cholangiocarcinoma. Gastrointest Endosc 56:756–760

Hughes NR, Walls RS, Newland RC, Payne JE (1986) Antigen expression in normal and neoplastic colonic mucosa: three tissue-specific antigens using monoclonal antibodies to isolated colonic glands. Cancer Res 46:2164–2171

Hughes NR, Pairojkul C, Royce SG, Clouston A, Bhathal PS (2006) Liver fluke-associated and sporadic cholangiocarcinoma: an immunohistochemical study of bile duct, peribiliary gland and tumour cell phenotypes. J Clin Pathol 59:1073–1078

Iguchi K, Tanaka T, Inaba S et al (1982) Histological study of biliary cancer: relationship between CEA and biliary cancer with intestinal metaplasia. J Jpn Pract Surg Soc 43:1090–1095

Inada KI, Mizoshita T, Tsukamoto T, Porter EM, Tatematsu M (2005) Paneth type gastric cancer cells exhibit expression of human defensing-5. Histopathology 47:330–331

Iseki M, Suzuki T, Koizumi Y, Hirose M, Laskin WB, Nakazawa S, Ohaki Y (1986) Alpha-fetoprotein-producing pancreatoblastoma. A case report. Cancer 57:1833–1835

Ishii T, Yasuchika K, Suemori H, Nakatsuji N, Ikai I, Uemoto S (2010) Alpha-fetoprotein producing cells act as cancer progenitor cells in human cholangiocarcinoma. Cancer Lett 294:25–34

Ishikawa A, Sasaki M, Ohira S, Ohta T, Oda K, Nimura Y, Chen MF, Jan YY, Yeh TS, Nakanuma Y (2004) Aberrant expression of CDX2 is closely related to the intestinal metaplasia and MUC2 expression in intraductal papillary neoplasm of the liver in hepatolithiasis. Lab Invest 84:629–638

Ishikawa K, Sasaki A, Haraguchi N, Yoshikawa Y, Mori M (2007) A case of an alpha-fetoprotein-producing intrahepatic cholangiocarcinoma suggests probable cancer stem cell origin. Oncologist 12:320–324

Ishikawa C, Tanabe H, Maemoto A, Ito T, Watari J, Kono T, Fujiya M, Ashida T, Kohgo Y (2009) Precursor processing of human defensing-5 is essential to the multiple functions in vitro and in vivo. J Innate Immun 2:66–76

Itoh T, Kishi K, Tojo M, Kitajima N, Kinoshita Y, Inatome T, Fukuzaki H, Nishiyama N et al (1992) Acinar cell carcinoma of the pancreas with elevated serum alpha-fetoprotein levels: a case report and review of 28 cases reported in Japan. Gastroenterol Jpn 27:785–791

Iwahashi S, Utsunomiya T, Shimada M, Saito Y, Morine Y, Imura S, Ikemoto T, Mori H, Hanaoka J, Bando Y (2013) High expression of cancer stem cell markers in cholangiolocellular carcinoma. Surg Today 43:654–660

Izumi S, Nakamura S, Mano S (2010) Large intrahepatic cholangiocarcinoma with tumor infiltrative lymphocytes and autoimmune hepatitis-like features. Case Rep Gastroenterol 4:46–51

Järvi O, Laurén P (1967) Intestinal metaplasia in the mucosa of the gallbladder and common bile duct. Ann Med Exp Fenn 45:213–223

Joo M, Shahsafaei A, Odze RD (2009) Paneth cell differentiation in colonic epithelial neoplasms: evidence for the role of the Apc/beta-catenin/Tcf pathway. Hum Pathol 40:872–880

Joshita S, Ichijo T, Suzuki F, Yokoyama T, Sugiyama Y, Fukushima M, Kamijo A, Komatsu M et al (2009) A case of well-differentiated cholangiolocellular carcinoma visualized with contrast-enhanced ultrasonography using Sonazoid. Hepatol Res 39:207–212

Kanamoto M, Yoshizumi T, Ikegami T, Imura S, Morine Y, Ikemoto T, Sano N, Shimada M (2008) Cholangiolocellular carcinoma containing hepatocellular carcinoma and cholangiocellular carcinoma, extremely rare tumor of the liver: a case report. J Med Invest 55:161–165

Kazanjian et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20621629

Khayyata S, Bastruk O, Adsay NV (2005) Invasive micropapillary carcinomas of the ampullopancreatobiliary region and their association with tumor-infiltrating neutrophils. Mod Pathol 18:1504–1511

Kim H, Park C, Han KH, Choi J, Kim YB, Kim JK, Park YN (2004) Primary liver carcinoma of intermediate (hepatocyte-cholangiocyte) phenotype. J Hepatol 40:298–304

Kimura et al. 1994. http://www.ncbi.nlm.nih.gov/pubmed/7511574

Kimura W, Futakawa N, Zhao B, Wada Y (2001) A case report of cribriform carcinoma of the pancreas with long time survival. Hepatogastroenterology 48:273–276

Kitagawa H, Nakamura M, Tani T, Tajima H, Nakagawara H, Ohnishi I, Takamura H et al (2007) A pure invasive micropapillary carcinoma of the pancreatic head: long disease-free survival after pancreatoduodenectomy and adjuvant chemotherapy with gemcitabine. Pancreas 35:190–192

Komuta M, Spee B, Van der Borght S, De Vos R, Verslype C, Aerts R, Yano H et al (2008) Clinicopathological study on cholangiolocellular carcinoma suggesting hepatic progenitor cell origin. Hepatology 47:1544–1556

Kondo T (2009) Bile duct adenocarcinoma with minor micropapillary component: a case report. Cases J 2:51

Kondo T, Kitazawa R, Kitazawa S (2008) Gastric remnant adenocarcinoma with micropapillary component. Dig Dis Sci 53:2287–2289

Kozaka K, Sasaki M, Fujii T, Harada K, Zen Y, Sato Y, Sawada S, Minato H et al (2007) A subgroup of intrahepatic cholangiocarcinoma with an infiltrating

replacement growth pattern and a resemblance to reactive proliferating bile ductules: 'bile ductular carcinoma'. Histopathology 51:390–400

Kozuka S, Kurashina M, Tsubone M, Hachisuka K, Yasui A (1984) Significance of intestinal metaplasia for the evolution of cancer in the biliary tract. Cancer 54:2277–2285

Kure M, Mizokami Y, Shiraishi T, Otsubo T, Kariya Y, Shirai K, Nakamura H, Takeyama H et al (2000) A case of clear cell carcinoma of the hepatic bile duct with production of alpha-fetoprotein (AFP) (in Japanese). Nippon Shokakibyo Gakkai Zasshi 97:936–940

Kuroda N, Oonishi K, Ohara M, Hirouchi T, Mizuno K, Hayashi Y, Lee GH (2007) Invasive micropapillary carcinoma of the colon: immunohistochemical study. Med Mol Morphol 40:226–230

Kurumaya H, Terada T, Nakanuma Y (1990) 'Metaplastic lesions' in intrahepatic bile ducts in hepatolithiasis: a histochemical and immunohistochemical study. J Gastroenterol Hepatol 5:530–536

Kushima R, Lohe B, Borchard F (1996) Differentiation towards gastric foveolar, mucopeptic and intestinal goblet cells in gallbladder adenocarcinomas. Histopathology 29:443–448

Laitio M (1975) Goblet cells, enterochromaffin cells, superficial gastric-type epithelium and antral-type glands in gallbladder. Beitr Pathol 156:343–358

Laitio M (1976) Intestinal, gastric body- and antral-type mucosal metaplasia in the gallbladder. Beitr Pathol 159:271–279

Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC (2007) Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. Am J Surg Pathol 31:907–913

Liver Cancer Study Group of Japan (1990) Clinicopathologic features and results of surgical treatment. Ann Surg 211:277–287

London NJM, Leese T, Bingham P, O'Reilly K, Self JB (1988) Paneth cell-rich adenocarcinoma of the duodenum. Br J Hosp Med 40:222–223

Luna-Moré S, Gonzalez B, Acedo C, Rodrigo I, Luna C (1994) Invasive micropapillary carcinoma of the breast. A new special type of invasive mammary carcinoma. Pathol Res Pract 190:668–674

Lundqvist M, Wilander E (1983) Exocrine and endocrine cell differentiation in small intestinal adenocarcinomas. Acta Pathol Microbiol Immunol Scand A 91:469–474

Maeda T, Hashimoto K, Ishida T, Yamashita Y, Saeki H, Kawanaka H, Uchiyama H, Ikeda T, Tsujitani S et al (2013) Repeat hepatectomy for intrahepatic recurrence of cholangiocellular carcinoma. Fukuoka Igaku Zasshi 104:564–568

Mastroianni JR, Quellette AJ (2009) Alpha-defensins in enteric innate immunity: functional Paneth cell alpha-defensins in mouse colonic lumen. J Biol Chem 284:27848–27856

Masuda K, Sakai N, Nakamura K, Yoshioka S, Ayabe T (2011) Bactericidal activity of mouse a-defensin cryptdin-4 predominantly affects noncommensal bacteria. J Innate Immun 3:315–326

Matsuda M, Hara M, Suzuki T, Kono H, Fujii H (2006) Synchronously resected double primary hepatic cancers – hepatocellular carcinoma and cholangiolocellular carcinoma. J Hepatobiliary Pancreat Surg 13:571–576

Miyajima H, Takeguchi T (1976) Paneth cell tumor: an additional case of duodenal adenoma with malignant change. Beitr Pathol 167:419–425

Miyazawa M, Torii T, Toshimitsu Y, Kamizasa N, Suzuki T, Shinozuka N et al (2006) Alpha-fetoprotein-producing clear cell carcinoma of the extrahepatic bile ducts. J Clin Gastroenterol 40:555–557

Mora JI, Barroeta JE, Bernstein DA, Lechago J (2004) Paneth cell carcinoma of the ampulla of Vater. Arch Pathol Lab Med 128:908–910

Morimoto H, Tanigawa N, Inoue H, Muraoka R, Hosokawa Y, Hattori T (1988) Alpha-fetoprotein-producing renal cell carcinoma. Cancer 61:84–88

Motosugi U, Ichikawa T, Nakajima H, Araki T, Matsuda M, Suzuki T, Fujii H, Nakazawa T, Yamaguchi H (2009) Cholangiolocellular carcinoma of the liver: imaging findings. J Comput Assist Tomogr 33:682–688

Mueller SB, Micke O, Herbst H, Schaefer U, Willich N (2005) Alpha-fetoprotein-positive carcinoma of the pancreas: a case report. Anticancer Res 25:1671–1674

Mukerjee S, Maheshwari HB (1964) Cholangiolocellular carcinoma of the liver. J Indian Med Assoc 43:240–241

Nagano Y, Matsuuo K, Gorai K, Sugimori K, Kunisaki C, Ike H, Tanaka K, Imada T, Shimada H (2006) Bile duct hamartomas (von Meyenburg complexes) mimicking liver metastases from bile duct cancer: MRC findings. World J Gastroenterol 12:1321–1323

Nagao T, Gaffey TA, Visscher DW, Kay PA, Minato H, Serizawa H, Lewis JE (2004) Invasive micropapillary salivary duct carcinoma: a distinct histologic variant with biologic significance. Am J Surg Pathol 28:319–326

Nagata S, Aijoka Y, Nishikura K, Watanabe G, Inoue T, Yamaguchi K, Watanabe H, Tanaka M, Tsuneyoshi M (2007) Co-expression of gastric and biliary phenotype in pyloric-gland type adenoma of the gallbladder: immunohistochemical analysis of mucin profile and CD10. Oncol Rep 17:721–729

Nakajima T, Okazaki N, Morinaga S, Tsumuraya M, Shimosato Y, Saiki S (1985) A case of alpha-fetoprotein-producing rectal carcinoma. Jpn J Clin Oncol 15:679–685

Nakanuma Y, Harada K, Ishikawa A, Zen Y, Sasaki M (2003) Anatomic and molecular pathology of intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 10:265–281

Nakanuma Y, Sato Y, Ikeda H, Harada K, Kobayashi M, Sano K, Uehara T, Yamamoto M et al (2012) Intrahepatic cholangiocarcinoma with predominant 'ductal plate malformation' pattern: a new subtype. Am J Surg Pathol 36:1629–1635

Nassar H (2004) Carcinomas with micropapillary morphology: clinical significance and current concepts. Adv Anat Pathol 11:297–303

Nassar H, Wallis T, Andea A, Dey J, Adsay V, Visscher D (2001) Clinicopathologic analysis of invasive micropapillary differentiation in breast carcinoma. Mod Pathol 14:836–841

Nassar H, Pansare V, Zhang H, Che M, Sakr W, Ali-Fehmi R, Grignon D, Sarkar F, Cheng J, Adsay V (2004) Pathogenesis of invasive micropapillary carcinoma: role of MUC1 glycoprotein. Mod Pathol 17:1045–1050

Neto AG, Dainiak C, Qin L, Salem RR, Jain D (2007) Intraductal papillary cholangiocarcinoma associated with von Meyenburg complexes: a case report. Dig Dis Sci 52:2643–2645

Ng WK, Ng WF (1995) Elevated serum alpha-fetoprotein in a patient with undifferentiated carcinoma of the gall bladder. J Clin Pathol 48:1061–1063

Ninard B (1950) Tumeurs du Foie. Texte, atlas. Le François éd, Paris

Noah TK, Kazanjian A, Whitsett J, Shroyer NF (2010) SAM pointed domain ETS factor (SPDEF) regulates terminal differentiation and maturation of intestinal goblet cells. Exp Cell Res 316:452–465

Nonomura A, Mizukami Y, Matsubara F, Izumi R, Nakanuma Y, Hayashi M, Watanabe K, Takayanagi N (1989) Human chorionic gonadotropin and alpha-fetoprotein in cholangiocarcinoma in relation to the expression of ras p21: an immunohistochemical study. Liver 9:205–215

Okuda H, Saito A, Shiratori K, Yamamoto M, Takasaki K, Nakano M (2005) Clinicopathologic features of patients with primary malignant hepatic tumors seropositive foe alpha-fetoprotein-L3 alone in comparison with other patients seropositive for alpha-fetoprotein-L3. J Gastroenterol Hepatol 20:759–764

Okuda H, Shiratori K, Yamamoto M, Takasaki K, Nakano M (2006) Clinicopathologic features of patients with intrahepatic cholangiocarcinoma who are seropositive for alpha-fetoprotein-L3 and those with combined hepatocellular and cholangiocarcinoma. J Gastroenterol Hepatol 21:869–873

Omori J, Niimi A, Furuichi Y, Takeuchi E, Ishikawa T, Yanagisawa A, Ogihara S, Tsuchiya M et al (2004) A case of AFP-producing cholangiocarcinoma with difficulty in differential diagnosis from hepatocellular carcinoma (in Japanese). Nippon Shokakibyo Gakkai Zasshi 101:1106–1111

Quellette AJ (2005) Paneth cell alpha-defensins: peptide mediators of innate immunity in the small intestine. Springer Semin Immunopathol 27:133–146

Quellette AJ (2010) Paneth cells and innate mucosal immunity. Curr Opin Gastroenterol 26:547–553

Roskams TA, Theise ND, Balabaud C, Bhagar G, Bhathal PS, Bioulac-Sage P et al (2004) Nomenclature of the finer branches of the biliary tree: canals, ductules, and ductular reactions in human livers. Hepatology 39:1739–1745

Roskams T, Katoonizadeh A, Komuta M (2010) Hepatic progenitor cells: an update. Clin Liver Dis 14:705–718

Saka H, Sakai S, Kondo N, Ito M, Shimokata K (1988) Successful resection of alpha-fetoprotein-producing lung cancer. Chest 94:879–880

Sakaki M, Hirokawa M, Sano T, Horiguchi H, Wakatsuki S, Ogata S (2000) Gallbladder adenocarcinoma with florid neuroendocrine cell nests and extensive Paneth cell metaplasia. Endocr Pathol 11:365–371

Sano T, Kamiya J, Nagino M, Uesaka K, Oda K, Kanai M, Nimura Y (2003) Bile duct carcinoma arising in metaplastic biliary epithelium of the intestinal type: a case report. Hepatogastroenterology 50:1883–1885

Sasaki M, Nakanuma Y, Kim YS (1998) Expression of apomucins in the intrahepatic biliary tree in hepatolithiasis differs from that in normal liver and extrahepatic biliary obstruction. Hepatology 27:54–61

Sasaki A, Kawano K, Aramaki M, Ohno T, Tahara K, Takeuchi Y, Yoshida T, Kitano S (2001) Clinicopathologic study of mixed hepatocellular and cholangiocellular carcinoma: modes of spreading and choice of surgical treatment by reference to macroscopic type. J Surg Oncol 76:37–46

Sasaki M, Tsuneyama K, Ishikawa A, Nakanuma Y (2003) Intrahepatic cholangiocarcinoma in cirrhosis presents granulocyte and granulocyte-macrophage colony-stimulating factor. Hum Pathol 34:1337–1344

Sasaki M, Matsubara T, Kakuda Y, Sato Y, Nakanuma Y (2014) Immunostaining for polycomb group protein EZH2 and senescent marker p16INK4a may useful to differentiate cholangiolocellular carcinoma from ductular reaction and bile duct adenoma. Am J Surg Pathol 38:364–369

Sato T, van Es JH, Snippert HJ, Stange DE, Vries RG, van den Born M, Barker N, Shroyer NF et al (2011) Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts. Nature 469:415–418

Schneider MR, Dahlhoff M, Horst D, Hirschi B, Trülzsch K, Müller-Höcker J, Vogelmann R et al (2010) A key role for E-cadherin in intestinal homeostasis and Paneth cell maturation. PLoS One 5: e14325

Sempoux C, Fan C, Singh P, Obeidat K, Roayaie S, Schwartz M, Fiel MI, Thung SN (2011) Cholangiolocellular carcinoma: an innocent-looking malignant liver tumor mimicking ductular reaction. Semin Liver Dis 31:104–110

Serio G, Zampatti C (2000) Predominant Paneth cell differentiation in a colonic adenocarcinoma. Histopathology 36:187–188

Shen WF, Zhong W, Xu F, Kan T, Geng L, Xie F, Sui CJ, Yang JM (2009) Clinicopathological and prognostic analysis of 429 patients with intrahepatic cholangiocarcinoma. World J Gastroenterol 15:5976–5982

Shimonishi T, Zen Y, Chen CT, Chen MF, Jan YY, Yeh TS, Nimura Y, Nakanuma Y (2002) Increasing expression of gastrointestinal phenotypes and p53 along with histologic progression of intraductal papillary neoplasia of the liver. Hum Pathol 33:503–511

Shiota K, Taguchi J, Nakashima O, Nakashima M, Kojiro M (2001) Clinicopathologic study of cholangiocellular carcinoma. Oncol Rep 8:263–268

Shousa S (1979) Paneth cell-rich papillary adenocarcinoma and a mucoid adenocarcinoma occurring synchronously in colon: a light and electron microscopic study. Histopathology 3:489–501

St. Laurent M, Esterl RM, Halff GA, Speeg KV (1999) Gallbladder carcinoma producing alpha-fetoprotein. J Clin Gastroenterol 28:155–158

Steiner PE (1957) Carcinoma of liver in United States. Acta Unio Int Contra Cancrum 13:628–645

Steiner PE, Higginson J (1959) Cholangiolocellular carcinoma of the liver. Cancer 12:753–759

Sugaya Y, Sugaya H, Kuronuma Y, Hisauchi T, Harada T (1989) A case of gallbladder carcinoma producing both alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA). Gastroenterol Jpn 24:325–331

Sugihara S, Nakahara T, Maruiwa M, Kojiro M, Iwai I, Tanaka M, Hirai K, Majima Y, Tanikawa K (1987) An autopsy case with a combination of hepatocellular carcinoma and cholangiolocellular carcinoma (in Japanese). Gan No Rinsho 33:205–210

Takahashi Y, Fukushima J, Fukusato T, Mori S (2006) Adenomyoma with goblet and Paneth cells in the ileum. Pathol Res Pract 202:549–553

Takeuchi S, Sugai N, Seki H, Miura A, Fujita J, Suzuki J, Fukazawa Y (2005) An autopsy case of rapid progressed cholangiolocellular carcinoma (in Japanese). Nippon Shokakibyo Gakkai Zasshi 102:718–722

Tanigawa T, Takagi S, Suga K, Morikawa Y, Hotta T, Haruyama H, Kusaba A, Akashi K et al (1987) A case of intrahepatic cholangiocarcinoma with marked high levels of CEA, AFP and CA19-9 (in Japanese). Nippon Naika Gakkai Zasshi 76:138–141

Tsuru T (1984) Clinicopathological study on metaplasia in the bile duct mucosa with special reference to bile duct carcinoma (in Japanese). Nippon Geka Gakkai Zasshi 85:482–491

Tsutsumi Y, Nagura H, Osamura Y, Watanabe K, Yanaihara N (1984) Histochemical studies of metaplastic lesions in the human gallbladder. Arch Pathol Lab Med 108:917–921

Venable JG, Schwartz AM, Silverberg SG (1990) Infiltrating cribriform carcinoma of the breast: a distinctive clinicopathologic entity. Hum Pathol 21:333–338

Vij K, Wang HL (2008) Aberrant expression of alpha-fetoprotein in intrahepatic cholangiocarcinoma: an exceptional occurrence. Int J Surg Pathol 16:194–198

Wada R (2009) Proposal of a new hypothesis on the development of colorectal epithelial neoplasia: nonspecific inflammation – colorectal Paneth cell metaplasia – colorectal epithelial neoplasia. Digestion 79(suppl 1):9–12

Wada R, Miwa H, Abe H, Santo RM, Kitamura S, Kuwabara N, Suda K, Kondo K, Yamada S et al (1992) Incidence of Paneth cells in minute tubular adenomas and adenocarcinomas of the large bowel. Acta Pathol Jpn 42:579–564

Wehkamp J, Stange EF (2010) Paneth's disease. J Crohns Colitis 4:523–531

Wehkamp J, Wang G, Kübler I, Nuding S, Gregorieff A, Schnabel A, Kays RJ, Fellermann K et al (2007) The paneth cell alpha-defensin deficiency of ileal Crohn's disease is linked to Wnt/Tcf-4. J Immunol 179:3109–3118

Yamamoto M, Takasaki K, Nakano M, Saito A (1996) Hepatic recurrence of cholangiolocellular carcinoma: report of a case. Hepatogastroenterology 43:1046–1050

Yamamoto M, Otsubo T, Arilzumi S, Nakano M, Takasaki K (2005) Intrahepatic cholangiocarcinoma detected by elevated levels of alpha-fetoprotein-L3 after hepatectomy for hepatocellular carcinoma in a patient with Budd-Chiari syndrome. Int Surg 90:81–84

Yoshino I, Hayashi I, Yano T, Takai E, Mizutani K, Ichinose Y (1996) Alpha-fetoprotein-producing adenocarcinoma of the lung. Lung Cancer 15:125–130

Yoshizawa T, Toyoki Y, Hirai H, Haga T, Toba T, Sakuraba S, Okano K, Wu Y, Seino H et al (2014) Invasive micropapillary carcinoma of the extrahepatic bile duct and its malignant potential. Oncol Rep 32:1355–1361

Zekioglu O, Erhan Y, Ciris M, Bayramoglu H, Ozdemir N (2004) Invasive micropapillary carcinoma of the breast: high incidence of lymph node metastasis with extranodal extension and its immunohistochemical profile compared with invasive ductal carcinoma. Histopathology 44:18–23

Zhou YM, Yang JM, Li B, Yin ZF, Xu F, Wang B, Liu P, Li ZM (2008) Clinicopathologic characteristics of intrahepatic cholangiocarcinoma in patients with positive serum a-fetoprotein. World J Gastroenterol 14:2251–2254

Zimmermann A (2002) Hepatoblastoma with cholangioblastic features ('cholangioblastic hepatoblastoma') and other liver tumors with bimodal differentiation in young patients. Med Pediatr Oncol 39:487–491

Clear Cell Carcinomas of the Bile Ducts 37

Contents

Abstract

Similar to clear cell hepatocellular carcinoma, rare variants of cholangiocarcinoma are characterized by clear cells that resemble cells of metastasizing renal cell carcinomas. Clear cell cholangiocarcinoma with a glandular or acinar pattern develops in extrahepatic bile ducts and in the gallbladder, but very rare forms have also been observed within the liver, whereby intrahepatic clear cell cholangiocarcinomas were usually small and peripheral lesions. These neoplasms exhibit a stromal reaction (desmoplasia) similar to that of classical cholangiocarcinomas. A very rare subset of clear cell cholangiocarcinoma shows a papillary component (clear cell papillary carcinoma of the liver).

Clear Cell Carcinoma of the Extrahepatic Bile Ducts

According to the histologic classifications for tumors of the gallbladder and biliary system from the World Health Organization, clear cell carcinomas of the biliary system are a special tumor type resembling metastatic renal cell carcinoma (Albores-Saavedra et al. 1991). Few single reports of this distinct lesions appeared in the literature (Paraf 1996; Gu et al. 2010). Vardaman and Albores-Saavedra reported the clinical and histologic characteristics of ten clear cell carcinomas of the gallbladder and extrahepatic bile ducts

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_37

detected in 7 of 550 patients with carcinoma of the gallbladder (1.3 %) and in 3 of 168 patients with carcinoma of extrahepatic bile ducts (1.8 %; Vardaman and Albores-Saavedra 1995).

Intrahepatic Clear Cell Cholangiocarcinoma

Several reports have document clear cell intrahepatic cholangiocarcinoma as a distinct entity (Nakajima et al. 1988; Logani and Adsay 1998; Haas et al. 2007; Fig. 1). In a large study, a clear cell component was identified in as many as 6 of 102 (5.9 %) intrahepatic cholangiocarcinomas (Nakajima et al. 1988). In one case, cholangiocarcinoma of the cystic duct exhibited clear cell change in lymph node metastases (Tajiri et al. 2006). The clear cell variant of peripheral intrahepatic cholangiocarcinoma has been reported very few times only (Adamek et al. 1998; Falta et al. 1999) and presents as rather small and nodular peripheral lesions. On one report, this unusual tumor was detected in a 50-year-old diabetic male who underwent open cholecystectomy for acute gangrenous cholecystitis. A mass measuring 1.5 cm was identified peripherally in the right lobe of the liver. Grossly, the lesion had a white appearance and a firm character. Histology showed a carcinoma consisting of clear cells growing in an acinar pattern and in form of nests embedded in a stromal matrix, with tumor cells seemingly emerging directly from bile ducts. The neoplastic cells were PAS-positive and this staining reaction was diastase resistant, indicating accumulation of mucin. Immunohistochemical staining showed reactivity for cytokeratins 7 and 8 and for epithelial membrane antigen (EMA), but not for CK20, and staining for CEA did not reveal the presence of a canalicular domain (Falta et al. 1999). The immunohistochemical differentiation from clear cell hepatocellular carcinoma has been specified (Adamek et al. 1998; Haas et al. 2007). The tumor cells have been shown to be positive for CK7, CK8, CK18, variably CK19, and CD56 (Haas et al. 2007). Electron microscopically, the neoplastic cells showed optical empty vacuoles, presumably representing lipid droplets. Only scanty glycogen granules were detected (Haas et al. 2007).

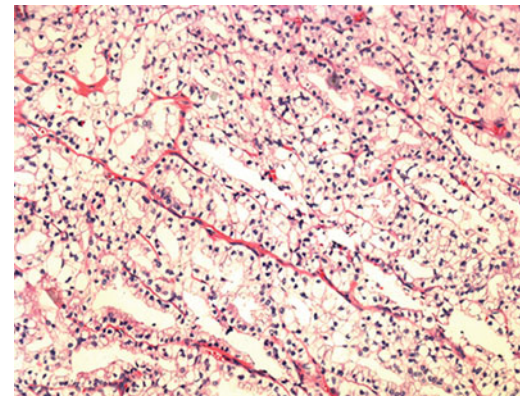

Fig. 1 Clear cell carcinoma of the bile duct (hematoxylin and eosin stain)

The immunostaining for CD56 is of both diagnostic and theoretical interest. In the liver, CD56 is associated with regeneration of damaged bile duct epithelium and is expressed in proliferated bile ductules and transiently during early developmental stages of the ductal plate. CD56 is expressed in bile duct adenomas, but only rarely in intrahepatic and extrahepatic cholangiocarcinomas (Gütgemann et al. 2006).

Clear Cell Papillary Carcinoma of the Liver (Clear Cell Papillary Cholangiocarcinoma)

A subset of clear cell cholangiocarcinomas show a papillary component. Only very few patients with this unique neoplasm have been reported in the literature.

One of these lesions was found in a 72-year-old patient with a liver mass not associated with elevated serum AFP (Tihan et al. 1998). Abdominal ultrasound revealed a 13 cm mass replacing the left lobe of the liver. Cut sections of the resection specimen disclosed a rubbery, tan-pink, solid 15 cm mass within the parenchyma, with lobulated borders that were sharply outlined. The center of the mass contained firm, yellow-gray, necrotic appearing components. On histologic

examination, the invasively growing neoplasm had a lobulated appearance with relatively cellular nests separated by stromal bands. There was a biphasic architecture, papillary and micropapillary areas (about 60 % of the lesion) projecting into small cystic spaces alternating with small glands and solid nests of cells. In the center, geographic necrosis was present. The cells had a clear cytoplasm and were cuboidal to columnar with ragged luminal borders. The cells forming glandular profiles and solid areas also had a clear cytoplasm. The mitotic rate was low. The cells stained focally positive with mucicarmine and showed diastase-sensitive PAS positivity. Immunohistochemically, the cells were reactive for cytokeratins 7, 8, and 19, but not for cytokeratin 20. EMA showed focal strong positivity. Ultrastructurally, the neoplastic cells were joined by scattered desmosomes and cell junctions. The cytoplasm contained numerous lipid droplets and clusters of beta-type glycogen particles. No bile canaliculi were noted. It was concluded that this tumor represents a distinct variant of peripheral cholangiocarcinoma (Tihan et al. 1998). A second example of this lesion had been observed in a 64-year-old female who underwent a partial hepatectomy for a liver mass measuring 12 cm in maximum diameter. Histologically, the tumor showed the pattern of clear cell cholangiocarcinoma, sometimes reminiscent of the histology of renal cell carcinoma, again with focal expression of a papillary phenotype (Logani and Adsay 1998). A similar case was reported more recently (Khera et al. 2014).

Alpha-Fetoprotein-Producing Clear Cell Carcinoma of Bile Ducts

This is a rare and unusual tumor, although some elevation of serum AFP may be observed in as much as 20 % of carcinomas of the intrahepatic bile ducts (Okuda and The Liver Cancer Study Group of Japan 1980). It has been reported as a clear cell cholangiocarcinoma located either to extrahepatic bile ducts (one case in the series of Vardaman and Albores-Saavedra 1995; Kure et al. 2000) or to the hilar/perihilar region (Miyazawa et al. 2006), associated with a significantly elevated serum AFP. In the patient reported by Miyazawa and coworkers, pathologic examination of a resected perihilar tumor (6 × 4 cm size) revealed a fragile composition with papillary-shaped structures growing into the duct lumen and forming frond-like growths, but glandular and solid profiles were also noted. The neoplastic cells were negative for the mucicarmine stain, but were immunoreactive for AFP (Miyazawa et al. 2006). AFP-positive carcinoma, albeit not of the clear cell type, has also been observed in the gallbladder (Haruta et al. 1987).

Differential Diagnosis

The differential diagnosis mainly includes clear cell tumors of a non-cholangiocytic lineage arising in the bile ducts or the gallbladder (with secondary involvement of bile ducts or liver). They mainly comprise clear cell carcinoma of the gallbladder (Bittinger et al. 1995; Paraf 1996; Piana et al. 2002; Vaillo et al. 2004), which also exists as a papillary variant (Sartelet et al. 2004), clear cell carcinoid tumors of the gallbladder and biliary tract (Sinkre et al. 2001; Konishi et al. 2003; Todoroki et al. 2007), which are in part associated with von Hippel-Lindau disease (Sinkre et al. 2001). Very small nodular clear cell cholangiocarcinomas may be confounded with clear cell type bile duct adenoma (Albores-Saavedra et al. 2001). Clear cell tumors metastatic to the liver mainly include renal cell carcinomas with a clear cell phenotype. The differentiation of primary vs. metastatic clear cell tumors in the liver is facilitated by cytokeratin immunohistochemistry and, for clear cell HCC, by in situ hybridization for albumin messenger RNA (Oliveira et al. 2000).

References

Adamek HE, Spiethoff A, Kaufmann V, Jakobs R, Riemann JF (1998) Primary clear cell carcinoma of noncirrhotic liver: immunohistochemical discrimination of hepatocellular and cholangiocellular origin. Dig Dis Sci 43:33–38

Albores-Saavedra J, Henson DE, Sobin LH (1991) Histological typing of tumours of the gallbladder and extrahepatic bile ducts. World Health Organization, Berlin

Albores-Saavedra J, Hoang MP, Murakata LA, Sinkre P, Yaziji H (2001) Atypical bile duct adenoma, clear cell type: a previously undescribed tumor of the liver. Am J Surg Pathol 25:956–960

Bittinger A, Altekruger I, Barth P (1995) Clear cell carcinoma of the gallbladder. A histological and immunohistochemical study. Pathol Res Pract 191:1259–1265

Falta EM, Rubin AD, Harris JA (1999) Peripheral clear cell cholangiocarcinoma: a rare histologic variant. Am Surg 65:592–595

Gu L, Jiang CH, Xu Q, Liu Q, Luo M, Wu ZY (2010) Primary clear cell carcinoma of hilar bile duct: a case report. J Dig Dis 11:63–65

Gütgemann I, Haas S, Berg JP et al (2006) CD56 expression aids in the differential diagnosis of cholangiocarcinomas and benign cholangiocellular lesions. Virchows Arch 448:407–411

Haas S, Gütgemann I, Wolff M, Fischer HP (2007) Intrahepatic clear cell cholangiocarcinoma: immunohistochemical aspects in a very rare type of cholangiocarcinoma. Am J Surg Pathol 31:902–906

Haruta J, Kanayama K, Tachino F, Hayakawa M, Kusakabe A, Kurokawa S, Oka Y, Ito S et al (1987) A clinicopathological evaluation of AFP-positive gallbladder cancer – with special reference to two autopsy cases investigated by an immunological method (in Japanese). Gan No Rinsho 33:1839–1845

Khera R, Uppin SG, Uppin MS, Sundaram C (2014) Clear cell papillary cholangiocarcinoma: a case report with review of literature. Indian J Pathol Microbiol 57:105–108

Konishi E, Nakashima Y, Smyrk TC, Masuda S (2003) Clear cell carcinoid tumor of the gallbladder. A case without von Hippel-Lindau disease. Arch Pathol Lab Med 127:745–747

Kure M, Mizokami Y, Shiraishi T, Otsubo T, Kariya Y, Shirai K, Nakamura H, Takeyama H et al (2000) A case of clear cell carcinoma of the hepatic bile duct with production of alpha-fetoprotein (AFP) (in Japanese). Nippon Shokakibyo Gakkai Zasshi 97:936–940

Logani S, Adsay V (1998) Clear cell cholangiocarcinoma of the liver is a morphologically distinctive entity. Hum Pathol 29:1548–1549

Miyazawa M, Torii T, Toshimitsu Y, Kamizasa N, Suzuki T, Shinozuka N, Ishizawa K, Koyama I (2006) Alpha-fetoprotein-producing clear cell carcinoma of the extrahepatic bile ducts. J Clin Gastroenterol 40:555–557

Nakajima T, Kondo Y, Miyazaki M, Okui K (1988) A histopathologic study of 102 cases of intrahepatic cholangiocarcinoma: histologic classification and modes of spreading. Hum Pathol 19:1228–1234

Okuda K, The Liver Cancer Study Group of Japan (1980) Primary liver cancers in Japan. Cancer 45:2663–2669

Oliveira AM, Erickson LA, Burgart LJ, Lloyd RV (2000) Differentiation of primary and metastatic clear cell tumors in the liver by in situ hybridization for albumin messenger RNA. Am J Surg Pathol 24:177–182

Paraf F (1996) Clear cell cancer of the gallbladder and extrahepatic bile ducts (in French). Gastroenterol Clin Biol 20:124–125

Piana S, Cavazza A, Corrado S, Putrino I, Gardini G (2002) Combined small cell carcinoma and clear cell carcinoma of the gallbladder: report of a case and review of the literature. Pathol Res Pract 198:821–824

Sartelet H, Simon H, Alowanou A, Yasser K, Pinteaux A (2004) Papillary tumor of the gallbladder: the clear cells carcinoma (in French). Ann Pathol 24:58–61

Sinkre PA, Murakata L, Rabin L, Hoang MP, Albores-Saavedra J (2001) Clear cell carcinoid tumor of the gallbladder: another distinctive manifestation of von Hippel-Lindau disease. Am J Surg Pathol 25:1334–1339

Tajiri K, Shimizu Y, Mihara H, Kawanishi Y, Orihara T, Takahashi H, Ishizawa S, Kawai S, Sugiyama T (2006) Cholangiocarcinoma at the cystic duct discovered by lymph node metastases with clear cell transformation. Intern Med 45:1045–1048

Tihan T, Blumgart L, Klimstra DS (1998) Clear cell papillary carcinoma of the liver: an unusual variant of peripheral cholangiocarcinoma. Hum Pathol 29:196–200

Todoroki T, Sano T, Yamada S, Hirahara N, Toda N, Tsukada K, Motojima R, Motojima T (2007) Clear cell carcinoid tumor of the distal common bile duct. World J Surg Oncol 5:6

Vaillo A, Rodriguez-Recio FJ, Gutierrez-Martin A, Ballstin C, Ruiz-Liso JM (2004) Fine needle aspiration cytology of clear cell carcinoma of the gallbladder with hepatic infiltration: a case report. Acta Cytol 48:560–564

Vardaman C, Albores-Saavedra J (1995) Clear cell carcinoma of gallbladder and extrahepatic bile ducts. Am J Surg Pathol 19:91–99

Bile Duct Tumors with Oncocytic Features

38

Contents

Abstract

Several bile duct tumors are characterized by the presence of oncocytes (bile duct tumors with oncocytic features). Oncocytes show an abundant, eosinophilic, and finely granular cytoplasm due to increased numbers of mitochondria. Similar to the exocrine pancreas, variants of intraductal papillary neoplasm of bile ducts (IPNB) are characterized by oncocytic neoplastic cells. Intraductal oncocytic papillary neoplasms of the bile ducts are rare neoplasms, but a focal or partial oncocytic change of IPNB may occur more frequently than anticipated. The cell lineage involved is not yet well elucidated, but oncocytic cells in these neoplasms can produce mucins. Few examples of intrahepatic cholangiocarcinoma with oncocytic change have been described. Rarely, biliary cystadenocarcinoma (malignant biliary mucinous cystic neoplasm) can show oncocytic features. An oncocytic variant of bile duct adenoma (peribiliary gland hamartoma) is known.

Introduction

Oncocytes were first described by Hamperl in 1931 as epithelial cells, which show abundant, eosinophilic, and finely granular cytoplasm by light microscopy due to an increased number of mitochondria. The cells are called oncocytes because of the "swollen" appearance they have

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_38

as a result of the striking accumulation of mitochondria. Oncocytic tumors represent a unique set of lesions with distinctive granular cytoplasmic eosinophilia of the neoplastic cells (reviews: Chang and Harawi 1992; Tallini 1998). Biliary tract tumors with oncocytic features are rare lesions. Part of these neoplasms have their phenotypic parallels in oncocytic intraductal tumors of the pancreas (Albores-Saavedra et al. 2005).

Intraductal Oncocytic Papillary Neoplasm of the Intrahepatic Bile Ducts

Intraductal oncocytic papillary neoplasms (IOPNs) were first described in the pancreas to differentiate a subset of pancreatic neoplasms from the intraductal papillary mucinous neoplasms (IPMNs) (Adsay et al. 1996) and were later identified among cases of intraductal papillary neoplasms of bile duct (IPNB). Three cases were reported in 2002, and all three presented with well-defined intrahepatic cystic masses ranging in size from 7.2 to 21.1 cm. The most prominent cells of the lining epithelium were columnar with oncocytic features showing abundant granular eosinophilic cytoplasm and a centrally placed nucleus (Martin et al. 2002). A further case was that of a 63-year-old male Japanese patient suffering from abdominal pain and jaundice. Imaging revealed a unilocular cystic neoplasm of 14 cm diameter in the left liver lobe. The tumor communicated with the left segmental intrahepatic bile duct, which contained mucus produced by the tumor. Histologically, the neoplasm consisted of papillary growth of atypical epithelial cells with oncocytic change. Atypical goblet cells were also present. Bile duct near the tumor exhibited dysplastic epithelial change. The tumor cell was immunoreactive for cytokeratins 7, 18, and 19 and for mitochondrial antigen (Terada and Taniguchi 2004). Other single cases have been reported (Spector et al. 2004; Ji et al. 2008; Lee et al. 2009; Cocieru et al. 2010; Liszka et al. 2010; Kakisaka et al. 2013; Watanabe et al. 2013). The prevalence of oncocytic features in intraductal papillary neoplasms may be higher than anticipated from case reports. Among 126 Japanese cases of IPNBs, 19 were oncocytic types (Nakanuma et al. 2014). In a collective of 119 mucin-producing intraductal papillary neoplasms of intrahepatic bile duct (M-IPNB), 23 were of the oncocytic type (Kubota et al. 2014). The biological significance of oncocytic features has not yet been sufficiently clarified. The lesion may be associated with a dysplastic and carcinogenic pathway. In one case, IOPN was associated with adenocarcinoma in situ apparently derived from IOPN (Watanabe et al. 2013). In an analysis of four cases of extrahepatic biliary tract IOPN, two of the lesions showed invasive growth, the invading cells having oncocytic features as well. None of the cases showed aberrant expression of Wnt signaling proteins (beta-catenin, E-cadherin, APC protein), although cyclin D1 was markedly overexpressed in all. Three of four cases showed the following mucin profile: MUC3, MUC4, MUC5A, MUC5B, and MUC6-positive (Rouzbahman et al. 2007). In a further series of six cases, four appeared grossly to be cystic neoplasms with papillary projections located in the liver and the other two were papillary neoplasms of the dilated hilar bile duct that ranged from 1.5 to 16 cm in size. The majority of the neoplastic cells had typical oncocytic features with marked positivity for mitochondrial antigen. Four neoplasms were mixed with minor components of non-oncocytic cells. The oncocytic cells as well as the non-oncocytic cells produced gastric-type mucin (MUC5AC and MUC6) and showed claudin-18 and Hep Par 1 positivity (Tanaka et al. 2009). The positivity for Hep Par 1, also known for IOPNs of the pancreas, was interpreted as a consequence of mitochondriosis, because Hep Par 1 binds predominantly to carbamoyl phosphate synthase 1, typically located in the mitochondria. What is the biological behavior of hepatobiliary IOPNs? Among 19 cases reviewed in 2009 (Tanaka et al. 2009), the mean age at diagnosis was 62 years, with a male to female ratio of 10:8. The mean diameter of the lesions was 5.9 cm, smaller than intraductal papillary neoplasms of

the bile ducts without oncocytic change (IPNB) (7.5 cm). Fifteen percent of the lesions were adenoma or borderline, 59 % noninvasive carcinoma, and 26 % invasive carcinoma. The mean overall survival was 20 months, shorter than that of IPNB (28 months). In contrast to IPNs, IOPNs lack K-Ras gene mutations (Liszka et al. 2010).

Intraductal Oncocytic Papillary Neoplasm of the Extrahepatic Bile Duct

IDPN with oncocytic features/IOPNs of the extrahepatic bile duct are very rare tumors. Among six cases of IDPN of the common bile duct, one tumor was composed of malignant oncocytes and was therefore regarded as intraductal oncocytic papillary carcinoma (Terada 2012).

Biliary tract IOPN has been described to derive from a peribiliary gland of a hepatic duct. In this situation, macroscopic examination of the surgically resected specimen revealed a reddish papillary tumor in the left hepatic duct just proximal to the bifurcation of the hepatic ducts. The biliary mucosa around the tumor was flat and focally reddish. The tumor itself displayed a polypoid appearance on the cut surface and originated from a cystic space in the bile duct wall. Histologically, the cystic space at the bottom of the tumor corresponded to a dilated peribiliary gland, covered by carcinoma in situ. There was a direct connection between the papillary oncocytic tumor and carcinoma in situ in the cystically altered peribiliary gland (Nakanishi et al. 2009).

Intrahepatic Cholangiocarcinoma with Oncocytic Change

Few examples of intrahepatic cholangiocarcinoma with oncocytic features of the neoplastic cells have been reported (Fujii et al. 2005; Güllüoglu et al. 2007). Focal oncocytic change has been noted in an intraductal growth-type mucin-producing peripheral cholangiocarcinoma associated with biliary papillomatosis (Güllüoglu et al. 2007).

Intrahepatic Cholangiocarcinoma with Multicystic Mucinous Appearance and Oncocytic Change

Extensive oncocytic change has been found in the multicystic and mucinous variant of intrahepatic cholangiocarcinoma, a distinct subtype of intrahepatic cholangiocarcinoma different from cystic carcinomas. The oncocytic variant of this tumor (Fujii et al. 2005) had macroscopically a spongy or honeycomb appearance. In this tumor, the numerous mucin-containing microcysts were lined by micropapillary adenocarcinoma cells with oncocytic features, reactive for mitochondrial antigen. This example illustrates that also oncocytic carcinomas may produce and secrete mucin.

Oncocytic Biliary Cystadenocarcinoma

Biliary cystadenocarcinoma with oncocytic change was first reported in 1992 (Wolf et al. 1992). This first patient was a 56-year-old male. The resected tumor was a well-demarcated cyst filled with numerous branching papillary fronds. The tumor cells had oncocytic features, and the mitochondriosis was proven by electron microscopy. Few further cases were described between 2001 and 2004. In the patient of Sudo et al. (2001), the tumor was observed in 71-year-old male who showed multicystic lesions in the left hepatic lobe. At autopsy, the tumor was found to be composed of adjoining multiple cystic lesions and a solid lesion with infiltration of the hepatic hilus. Histologically, the cysts were lined by a papillary epithelium with an oncocytic cytoplasm. The subepithelial matrix of the cysts did not reveal ovarian-like mesenchymal stroma. The solid component represents mucinous carcinoma with acidophilic and granular cells. It was suggested that this variant of cystadenocarcinoma is a form of intraductal oncocytic papillary neoplasm of the liver (Sudo et al. 2001). The neoplastic epithelia are immunoreactive for cytokeratin 7. Absence of mesenchymal stroma in oncocytic hepatobiliary cystadenocarcinoma was confirmed in later reports (Bardin et al. 2004).

Bile Duct Adenoma with Oncocytic Features

Oncocytic bile duct adenoma is a very uncommon variant of benign epithelial bile duct tumor (Arena et al. 2006). The lesion described by these authors was found incidentally at autopsy in a 57-year-old female patient. Macroscopically, the lesion was 3 mm in diameter, located to the right liver lobe. Histology revealed small to medium tubular structures with secondary cystic dilatation of some affected bile ducts. The epithelium of the tubules consisted of large granular eosinophilic cells with central small nuclei. No mitotic activity was noted. Immunohistochemically, the cells were positive for CEA, EMA, and cytokeratin 7, but negative for Hep Par 1.

Oncocytic Metaplasia of Biliary Epithelia

Oncocytic metaplasia of interlobular bile duct epithelia was observed in a patient with hepatic graft versus host reaction after bone marrow transplantation (Bligh et al. 1995).

References

Adsay NV, Adair CF, Heffess CS, Klimstra DS (1996) Intraductal oncocytic papillary neoplasms of the pancreas. Am J Surg Pathol 20:980–994

Albores-Saavedra J, Wu J, Crook T, Amirkhan RH, Jones L, Hruban RH (2005) Intestinal and oncocytic variants of pancreatic intraepithelial neoplasia. A morphological and immunohistochemical study. Ann Diagn Pathol 9:69–76

Arena V, Arena E, Stigliano E, Capelli A (2006) Bile duct adenoma with oncocytic features. Histopathology 49:318–320

Bardin RL, Trupiano JK, Howerton RM, Geisinger KR (2004) Oncocytic biliary cystadenocarcinoma: a case report and review of the literature. Arch Pathol Lab Med 128:e25–e28

Bligh J, Morton J, Durrant S, Walker N (1995) Oncocytic metaplasia of bile duct epithelium in hepatic GVHD. Bone Marrow Transplant 16:317–319

Chang A, Harawi SJ (1992) Oncocytes, oncocytosis, and oncocytic tumors. Pathol Annu 1:263–304

Cocieru A, Kesha K, El-Fanek H, Saldinger PF (2010) Hepatic intraductal oncocytic papillary carcinoma. Am J Surg 199:e57–e58

Fujii T, Harada K, Katayanagi K, Kurumaya H, Nakanuma Y (2005) Intrahepatic cholangiocarcinoma with multicystic, mucinous appearance and oncocytic change. Pathol Int 55:206–209

Güllüoglu MG, Ozden I, Poyanli A, Cevikbas U, Ariogul O (2007) Intraductal growth-type mucin-producing peripheral cholangiocarcinoma associated with biliary papillomatosis. Ann Diagn Pathol 11:34–38

Ji Y, Fan J, Zhou J, Wang BS, Liu HB, Wu ZW, Tan YS (2008) Intraductal papillary neoplasms of bile duct. A distinct entity like its counterpart in pancreas. Histol Histopathol 23:41–50

Kakisaka T, Kamiyama T, Yokoo H, Nakanishi K, Wakayama K, Tsuruga Y, Kamachi H, Mitsuhashi T, Taketomi A (2013) An intraductal papillary neoplasm of the bile duct mimicking a hemorrhagic hepatic cyst: a case report. World J Surg Oncol 11:111

Kubota K, Nakanuma Y, Kondo F, Hachiya H, Miyazaki M, Nagino M, Yamamoto M, Isayama H, Tabata M et al (2014) Clinicopathologic features and prognosis of mucin-producing bile duct tumor and mucinous cystic tumor of the liver: a multi-institutional study by the Japan Biliary Association. J Hepato-Biliary Pancreat Soc 21:176–185

Lee S, Kim YS, Lee WJ, Jang KT (2009) Intraductal oncocytic papillary neoplasm of the bile duct: ultrasonography and CT findings with pathological correlations. Clin Radiol 64:841–844

Liszka L, Pajak J, Zielinska-Pajak E, Krzych L, Golka D, Mrowiec S, Lampe P (2010) Intraductal oncocytic papillary neoplasm of the pancreas and bile ducts: a description of five new cases and review based on a systematic survey of the literature. J Hepato-Biliary Pancreat Sci 17:246–261

Martin RC, Klimstra DS, Schwartz L, Yilmaz A, Blumgart LH, Jarnagin W (2002) Hepatic intraductal oncocytic papillary carcinoma. Cancer 95:2180–2187

Nakanishi Y, Zen Y, Hirano S, Tanaka E, Takahashi O, Yonemori A, Doumen H, Kawakami H et al (2009) Intraductal oncocytic papillary neoplasm of the bile duct: the first case of peribiliary gland origin. J Hepato-Biliary Pancreat Surg 16:869–873

Nakanuma Y, Sato Y, Ojima H, Kanai Y, Aishima S, Yamamoto M, Ariizumi S, Furukawa T, Hayashi H et al (2014) Clinicopathological characterization of so – called "cholangiocarcinoma with intraductal papillary growth" with respect to "intraductal papillary neoplasm of bile duct (IPNB)". Int J Clin Exp Pathol 7:3112–3122

Rouzbahman M, Serra S, Adsay NV, Bejarano PA, Nakanuma Y, Chetty R (2007) Oncocytic papillary neoplasms of the biliary tract: a clinicopathological, mucin core and Wnt pathway protein analysis of four cases. Pathology 39:413–418

Spector SA, Bejarano PA, Amortequi JD, Renfroe MR, Livingstone AS (2004) Intraductal oncocytic papillary neoplasm of the extrahepatic biliary tree: first report. Am Surg 70:55–58

Sudo Y, Harada K, Tsuneyama K, Katayanagi K, Zen Y, Nakanuma Y (2001) Oncocytic biliary cystadenocarcinoma is a form of intraductal oncocytic papillary neoplasm of the liver. Mod Pathol 14:1304–1309

Tallini G (1998) Oncocytic tumours. Virchows Arch 433:5–12

Tanaka M, Fukushima N, Noda N, Shibahara J, Kokudo N, Fukayama M (2009) Intraductal oncocytic papillary neoplasm of the bile duct: clinicopathologic and immunohistochemical characteristics of 6 cases. Hum Pathol 40:1543–1552

Terada T (2012) Non-invasive intraductal papillary neoplasms of the common bile duct: a clinicopathologic study of six cases. Int J Clin Exp Pathol 5:690–697

Terada T, Taniguchi M (2004) Intraductal oncocytic papillary neoplasm of the liver. Pathol Int 54:116–123

Watanabe A, Suzuki H, Kubo N, Araki K, Kobayashi T, Sasaki S, Wada W, Arai H, Sakamoto K, Sakurai S et al (2013) An oncocytic variant of intraductal papillary neoplasm of the bile duct that formed a giant hepatic cyst. Rare Tumor 5:e30

Wolf H, Garcia J, Bossen E (1992) Oncocytic differentiation in intrahepatic biliary cystadenocarcinoma. Mod Pathol 5:665–668

Mucinous Cystic Neoplasms (MCN) and Related Cystic Neoplasms of the Hepatobiliary Tract

39

Contents

Abstract

Mucinous cystic neoplasms (MCNs) of the liver and biliary tract are cyst-forming epithelial neoplasms with cyst lines by a mucin-producing epithelium, frequently associated with a subepithelial cellular ovarian-like stroma. Noninvasive MCNs were previously termed mucinous hepatobiliary cystadenoma with mesenchymal stroma, whereas the invasive form was termed hepatobiliary cystadenocarcinoma. MCN are mostly located within the liver and present as solitary or multiloculated large cystic masses, but very rare microcystic variants have been reported. The neoplasms usually show an expanding growth pattern and can undergo secondary changes, including hemorrhage. Histologically, the cystic spaces are lined by a single layer of mucin-producing columnar cells, sometimes with papillary projections. The underlying stroma is hypercellular and forms a characteristic, ovarian-like tissue, with nuclear expression of estrogen receptors and/or progesterone receptors. The stromal cells are reactive for inhibin-alpha. Signs of malignant transformation are similar to those in other organs where a dysplasia-carcinoma sequence occurs, eventually resulting in invasive carcinoma.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_39

ICD-O codes

MCN with low- or intermediate-grade intraepithelial neoplasia	8470/0
MCN with high-grade intraepithelial neoplasia	8470/2
MCN with an associated invasive carcinoma	8470/3

Introduction

According to the definition of the WHO classification (Tsui et al. 2010), mucinous cystic neoplasms (MCNs) of the liver and biliary tract are cyst-forming epithelial neoplasms with cysts lined by a cuboidal to columnar, variably mucin-producing epithelium resembling cholangiocytes, often, but not always, associated with an underlying subepithelial cellular ovarian-like stroma. MCNs are typically intrahepatic tumors, but MCNs also occur in the extrahepatic bile ducts and the gallbladder. With few exceptions, MCNs do not communicate with the bile duct system, in contrast to intraductal papillary neoplasms of the bile ducts. MCNs predominantly occur in women, but variants without an ovarian-like stroma also develop in males. MCN are principally subdivided into noninvasive and invasive (carcinomatous) forms. In noninvasive forms, the neoplasms are categorized based on the highest degree of atypia into MCN with low-grade dysplasia, MCN with intermediate-grade dysplasia, and MCN with high-grade dysplasia. In invasive forms, the invasive part originating from the dysplastic cyst lining has a morphology that is very similar to cholangiocarcinoma.

Formerly, noninvasive MCNs have been termed mucinous hepatobiliary cystadenoma with mesenchymal stroma (CMS; hepatobiliary cystadenoma with ovarian-like stroma), and invasive MCNs were named hepatobiliary cystadenocarcinoma (Table 1). For practical reasons, the term, cystadenocarcinoma instead of MCN associated with invasive carcinoma, is maintained in the present chapter.

Table 1 Comparison of current (WHO 2010) and previous nomenclatures of cystic epithelial neoplasms of the hepatobiliary tract

Previous nomenclature	Current nomenclature
Hepatobiliary cystadenoma	Mucinous cystic neoplasm (MCN)
	Low-grade dysplasia
	Intermediate-grade dysplasia
	High-grade dysplasia
Hepatobiliary cystadenocarcinoma	MCN with associated invasive carcinoma

Mucinous Cystic Neoplasm of the Liver (Hepatobiliary Cystadenoma)

Introduction

Biliary cystadenoma, or now termed MCN, was first described in 1889 under the term cystadenoma of the bile duct (Siegmund 1889). The first report of resection for biliary cystadenoma was made by Keen in 1892 (Keen 1892), followed about 10 years later by a second report (Bishop 1901). In the following years, these lesions were reported under a wide spectrum of terms, including multilocular cystadenoma (Bevan 1919), cystic adenoma of bile ducts (Evans 1921), bile duct cystadenoma (Snedecor 1967), biliary cystadenoma (Short et al. 1971), cystadenoma of the liver (Martin et al. 1973), and cystic hamartoma of the bile duct (Ansari et al. 1976). The lesion was comprehensively described in 1958, coining the tumors cystadenoma with mesenchymal stroma/CMS (Edmondson 1958; Wheeler and Edmondson 1985). The definition of CMS has undergone some changes as a function of time and the description of more and more lesions. In their 1985 publication, Wheeler and Edmondson specify that "The original suggestion that the term "cystadenoma" be confined to multilocular cystic tumors lined by mucin secreting columnar epithelium overlying a dense cellular (mesenchymal)

stroma (Edmondson 1958) has proved to be inadequate as review of the literature reveals that a number of the reported cystadenoma cases lack at least the cellular (mesenchymal) stroma." Recently, hepatic, pancreatic, splenic, and mesenteric mucinous cystic neoplasms (MCNs) have been proposed to be lumped together as extraovarian MCNs (Shiono et al. 2006).

Epidemiology

CMS amounts to about 4.5 % of intrahepatic biliary cystic lesions (Geist 1954) and occurs predominantly in adults and among these in middle-aged women (more than 85 %; mean age of 50 years). Relatively few reports of noninvasive MCN document the occurrence of CMS in males (Kazama et al. 2005). However, invasive forms, i.e., MCN associated with invasive carcinoma (the former cystadenocarcinoma), seem to occur in females and males with equal frequency. MCN associated with invasive carcinoma is diagnosed in an older patient age group (mean: 59 years as compared with 45 years for noninvasive MCN). A part of published MCN with invasive features, specifically those involving the extrahepatic bile duct system and occurring in males, would now be classified as intraductal papillary neoplasms (IPNs) of the bile ducts with marked cystic changes (see the respective chapter). MCNs of the liver and bile ducts are usually lesions not associated with other hepatobiliary pathologies, but MCN can occur in association with mucinous cystic tumor of the pancreas (Brachet et al. 2007). MCN is very uncommon in the pediatric age group, observed in children of 8 months to 4 years of age.

Selected References Alexander 1925; Claggett and Hawkins 1946; Warren and Polk 1958; Beasley et al. 1986; Williams et al. 1990; Wood et al. 1998; Senyüz et al. 2004; Tran et al. 2013. In regard to MCN in adults, several reports have appeared, in part with literature reviews (Daivella 1950; Courtois-Suffit and Chaleux, 1960; Williams 1961; Corrin 1962; Mondini 1962; Koban 1964; Snedecor 1967; Kosaka et al. 1968; Monnin 1969; Short et al. 1971; Martin et al. 1973; Merchant 1973; Forde et al. 1974; Marsh et al. 1974; Ishak et al. 1977; Cahill et al. 1982; Kokal et al. 1983; Nagorney et al. 1984; Organ and Petrek 1984; Wheeler and Edmondson 1985; Marcial et al. 1986; Okamura et al. 1987; Akwari et al. 1990; Adam and Nonas 1995; Busoni et al. 1996; Gadzijev et al. 1996; Tsiftsis et al. 1997; Kim et al. 1998; Hwang et al. 2000; Dixon et al. 2001; Florman and Slakey 2001; Owono et al. 2001; Barabino et al. 2004; Park et al. 2004; Sima et al., 2004; Thomas et al. 2005; Vogt et al. 2005; Yamashita et al. 2005; Beuran et al. 2006; Carson et al. 2006; Manouras et al. 2006; Teoh et al. 2006; Zhou et al. 2007; Fukunaga et al. 2008; Yu et al. 2008a; Qu et al. 2009; Yi et al. 2009; Bogert et al. 2010; Erdogan et al. 2010; Yu et al. 2010; Gad et al. 2011; Hennessey and Traynor 2011; Cecka et al. 2011; Doepker et al. 2011; Kim et al. 2011; Meng et al. 2011; Romagnoli et al. 2011; Sang et al. 2011; Yoon et al. 2011; Ahanatha Pillai et al. 2012; Ratti et al. 2012; Sendt et al. 2012; Fei et al. 2013; Martel et al. 2013; Soares et al. 2014.

Clinical and Imaging Features

Most of the lesions develop within the liver (more than 80 %; intrahepatic cystadenoma). Among the intrahepatic cystadenomas, 50 % occupy the right lobe, 35 % occupy the left lobe, and 15 % are bilateral lesions. Extrahepatic MCNs located to the hepatic ducts or common bile duct have also been observed, amounting to less than 10 % of all cases (Rogers 1946; Burhans and Myers 1971; Ansari et al. 1976; Ishak et al. 1977; Udoff et al. 1979; Thomsen et al. 1984; Byrne et al. 1989; Coulter and Baxter 1989; Nagorney et al. 1984; Hodgson and Bayjoo 1991; Davies et al. 1995; Kimura et al. 1998; Park et al. 2004; Shima et al. 2004; Hedayat et al. 2005; Mohan et al. 2006; Trummer et al. 2006; Seidel

et al. 2007). Extrahepatic cystadenomas have the following duct distribution: right hepatic duct, 14.3 %; left hepatic duct, 28.6 %; common hepatic duct, 32.1 %, common bile duct, 21.4 %; and cystic duct, 3.6 % (Davies et al. 1995). Among 19 patients with extrahepatic cystadenoma, 18 were female (Davies et al. 1995). Extrahepatic MCN may grow in an exophytic manner, producing a pedunculated mass (Sankar et al. 2009). MCNs located to the extrahepatic bile ducts have been hypothesized to arise from ectopic embryonic tissue destined to form the adult gallbladder. Chronic biliary obstruction caused by MCN of the common bile duct caused secondary biliary cirrhosis (Thomsen et al. 1984).

In the majority of cases, MCN are asymptomatic or oligosymptomatic, sometimes presenting with nonspecific abdominal discomfort or dull pain, mostly in the right upper quadrant, thought to be due to a mass effect (in 55 % of 53 patients reviewed; Akwari et al. 1990; Ahanatha et al. 2012). Diffuse abdominal discomfort was noted in 16 %, and 59 % complained of an abdominal mass that was freely movable with respiration and confirmed by physical examination in the right upper quadrant or epigastrium (review: Akwari et al. 1990). Acute pain may arise in intracystic hemorrhage or cyst infection, the latter also causing fever and eventually septicemia. Intermittent or constant and in part obstructive jaundice may occur in up to 39 % of patients (Akwari et al. 1990; Gadzijev et al. 1995; Nunes et al. 2006; Gonzalez et al. 2009; Li Petri et al. 2010; Saravanan et al. 2010; Harmouch et al. 2011; Soochan et al. 2012), associated with extrahepatic lesions or tumor-induced cholangitis (Ansari et al. 1976; Beretta et al. 1986; Buetow et al. 1995; Davies et al. 1995; Taketomi et al. 1998; Preetha et al. 2004; Erdogan et al. 2006; Siriwardana and Pathirana 2009; Ray et al. 2010). In a series of 19 extrahepatic cystadenomas compiled by Davies et al. (1995), jaundice was noted in 17 patients. Jaundice may be more commonly expected in cystadenocarcinoma (Kanamori et al. 1985). In a review of 35 analyzable patients compiled from the literature, the mean duration of symptoms before final treatment was 2.2 years and varied from 5 days to 17 years (Akwari et al. 1990). The detection of a cystic hepatic lesion associated with elevated serum CA 19-9 is highly suggestive of MCN and of good diagnostic help (Thomas et al. 1992; Horsmans et al. 1996; Lee et al. 1996; Mantke et al. 2001; Li et al. 2013), the CA 19-9 levels decreasing to normal after complete surgical resection (Kim et al. 1998). The cyst fluid of cystadenomas also shows elevated concentrations of CA 19-9 (Horsmans et al. 1996; Lee et al. 1996), and CA 19-9 is produced by the tumor epithelia where it can be demonstrated immunohistochemically (Thomas et al. 1992).

MCR may undergo complications such as "spontaneous" rupture (Chang et al. 1995; Lempinen et al. 2005; Elfadili et al. 2010; Sun et al. 2010), intracystic bleeding (Naganuma et al. 2006), infection, intermittent obstruction of the inferior vena cava (Catto et al. 1999), pleural effusion (Yu et al. 2012), and malignant transformation (see below). In an MCN with intracystic hemorrhage, contrast-enhanced sonography (CEUS) showed microbubbles oozing from the cyst wall into the cystic cavity after intravenous contrast injection (Naganuma et al. 2006). Exceptionally, MCN may cause bile duct obstruction via ingrowth of tumor into the extrahepatic duct system, sometimes with a tumor embolus-like lesion (Van Steenbergen et al. 1984; Beretta et al. 1986; Sielezneff et al. 1992; Sutton et al. 2000; Siriwardana and Pathirana 2009; Yi et al. 2009; Abe et al. 2012). In one patient, the dilated extrahepatic bile duct was filled with fluidlike matter at imaging, shown to be part of a cystic tumor originating from the intrahepatic duct of segment 4 and protruding into the duct lumen (Yi et al. 2009).

Ultrasonography examinations show fluid-filled hypoechoic masses with echogenic septations (Forrest et al. 1980; Choi et al. 1989; Palacios et al. 1990; Xu et al. 2012). In abdominal X-ray images, displacement of the duodenum, stomach, or colon by a large hepatic mass has been found. In CT images, a well-demarcated hypoattenuating cystic mass is the characteristic finding, without evidence of enhancement within the lesion or wall structures. Septations were seen in almost all tumors studied, usually with no or

less nodularity than in cystadenocarcinoma (Choi et al. 1989; Korobkin et al. 1989; Palacios et al. 1990; Buetow et al. 1995; Seidel et al. 2007; Pojchamarnwiputh et al. 2008; Nakagawa et al. 2011; Facy et al. 2012; Qian et al. 2013). At MRI, T2-weighted images showed all lesions to be hyperintense, while T1-weighted images showed either hypointense or isointense lesions (Lewin et al. 2006). ERCP and percutaneous transhepatic cholangiography showed obstruction or compression of the biliary tree (review: Akwari et al. 1990).

Most MCNs are macrocystic and multilocular (the macrocystic variant).

The microcystic variants are less common. The diameter of the cysts does not exceed 1 cm, and CT scans with contrast show multiple small cysts delineated by enhanced thin walls. MRI shows a typical fluid-containing lesion with low signal on SE T1-weighted images and high signal on SE T2-weighted images. After intravenous administration of gadolinium-DTPA, SE T1-weighted images demonstrate enhancement of the cyst walls, giving the lesion of honeycomb pattern (Meyer et al. 1997). MCN may cause mucobilia, suggesting a communication between the cystic space of the tumor and the lumina of the biliary tract. A subset of MCNs deviate from these more common patterns. MCN may consist of a large principal mass associated with a smaller daughter cyst (Verbeeck and Hoebeke 1997). Unilocular extrahepatic MCN may grow to very large size (giant cystadenomas; Busoni et al. 1996; Hwang et al. 2000; Kazama et al. 2005) and mimic choledochal cyst at sonography and CT examination (Park et al. 2004) or may produce a phenotype resembling cystic lymphangioma (Hwang et al. 2000) or parasitic hydatid cyst (Kapoor et al. 1997; De Backer et al. 2000; Raza et al. 2009). In case of a solitary MCN with mucin secretion, the lesion may mimic a simple hepatic cyst at imaging (Stoupis et al. 1994; Matsumoto et al. 1997). Exceptionally, gallstone formation has been seen within cysts of MCN (Lei et al. 1994). A subset of biliary MCNs can protrude and grow into the bile duct system (Gadzijev et al. 1998). MCN has been observed in conjunction with unilateral mucinous cystadenoma of the ovary (Skopelitou and Hadjiyannakis 1996). Radiologically, MCN may be difficult to distinguish from simple hepatic cysts, requiring a combined diagnostic approach. Comparing with simple cysts, symptoms, left-lobe cyst, thick wall, septation, mural nodule, bile duct dilatation, and increase in serum alkaline phosphatase were significantly frequent in biliary cystic tumors.

Pathology

Macroscopy

Macroscopically, the lesions are either solitary or multiloculated, are globular in shape, and show a diameter ranging from few cm to 30 cm or even more (Figs. 1 and 2). The cysts are usually not communicating with the bile duct systems, with few exceptions (Marrone et al. 2011; Billington et al. 2012). Multiloculated lesions prevail in most studies (review: Akwari et al. 1990). In these patterns, a large cyst (the macrocystic variant) may contain numerous smaller cysts, mainly at the periphery or within septated trabecular structures. These smaller cysts commonly bulge outward (Ishak et al. 1977). Very rare variants of MCN exclusively consist of small cysts (microcystic variant; Meyer et al. 1997). The tumors show an expanding growth pattern and may bulge from the liver surface. On cutting, a watery to slightly viscous fluid of various color is

Fig. 1 Solitary mucinous cystic neoplasm (MCN) of the liver with incompletely segmented chambers. The cavities contain a mucinous, viscous fluid (fixed resection specimen)

Fig. 2 Multiloculated mucinous cystic neoplasm of the liver. Usually, the larger cavities are located to central parts of the tumor (fixed resected specimen)

seen, which may become coagulated after formalin fixation, leaving a cloudy gel-like substance, depending on protein concentration. The color of the cyst fluid depends on admixtures of blood or blood products, presence of granulocytes in infected cysts, and eventually bile, but most often the fluid looks either like water or is whitish turbid. In sediment of the fluid, cholesterol crystals were found (Ishak et al. 1977). In case of cyst hemorrhage, a thick dark red to brown-red mass, frankly coagulated red-blue blood may be seen. These blood masses may coalesce to balls or spheres with a rough, spiny surface. After removal of the fluid, a smooth and often glistening inner surface of the cyst is seen, with a network of fine vasculature and occasional trabeculations. The aspect may closely resemble or be grossly indistinguishable from simple nonparasitic cysts. The walls of the larger cysts vary in thickness from a few millimeters to 2 cm or more (Gourley et al. 1992). CMS may show mural nodules similar to those found in ovarian mucinous cystadenoma (Joseph et al. 1993).

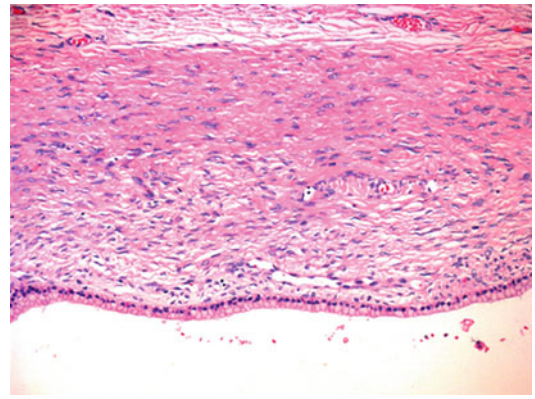

Fig. 3 Hepatobiliary mucinous cystic neoplasm. The cystic space is lined by a mucin-producing neoplastic epithelium. There is a subepithelial band of hypercellular ovarian-like mesenchymal stroma (hematoxylin and eosin stain). Adjacent liver may show perifocal pressure atrophy, ductular proliferations, and sometimes biliary microhamartomas in the portal tracts (Wheeler and Edmondson 1985; Tomiaka et al. 1986)

Histopathology

Histologically, the wall of MCN consists of three layers: an inner single epithelial lining of cuboidal to columnar cells, a moderately to densely cellular stroma composed of spindle cells (see below), and a dense layer of hypovascular collagenous connective tissue which may even undergo hyaline change. The cuboidal to columnar epithelial cells are similar to those seen in interlobular bile ducts, but the nuclei may be somewhat larger. The columnar cells may show basal nuclei and PAS- and Alcian Blue-positive mucin accumulated in the middle and apical parts of the cell, sometimes with signs of mucin secretion (Figs. 3, 4, 5, and 6). The morphology of the columnar epithelial cells has been described as being similar to that of the developing gallbladder (Subramony et al. 1993). The presence of detectable mucin varies considerably among the CMA, ranging from tumors resembling mucinous ovarian tumors to lesions where mucin is detectable in a minority of the cells only. In the latter situation, MCN may be confounded with simple hepatic cysts, particularly in cases where the subepithelial band is hypocellular or otherwise poorly developed. Mucin-rich cells are often more easily found in

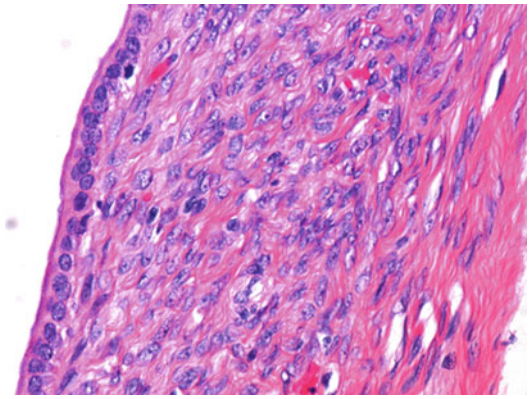

Fig. 4 Mucinous cystic neoplasm of the liver. The cells of ovarian-like mesenchymal stroma differ from conventional fibroblasts seen in the collagenous connective tissue at the right end of the figure (hematoxylin and eosin stain)

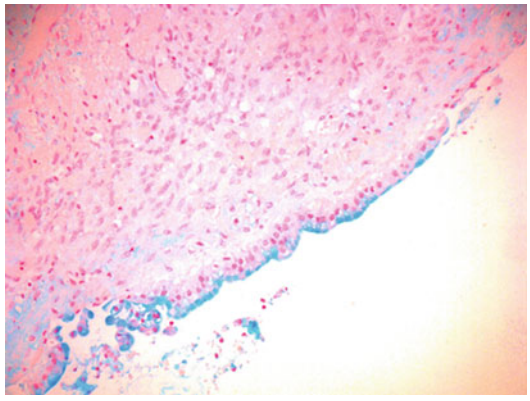

Fig. 5 Mucinous cystic neoplasm of the liver. Mucin production by epithelium lining the cystic spaces predominates in apical portions of the neoplastic cells (alkaline Alcian Blue stain)

small tumors, whereas large lesions display atrophy of the tumor epithelium with poor or lacking mucin storage. Copious sampling from different parts of the cyst walls should be performed, mainly from regions without scarring or calcifications. Some regions of cyst walls may show polypoid or papillary structures or papillary projections covered by mucin-containing cells. The bases ("crypts") of these papillary formations are seen in the form of tubular or ectatic glands (Gourley et al. 1992), sometimes difficult to distinguish from microinvasion in lesions with malignant transformation. The cells in these

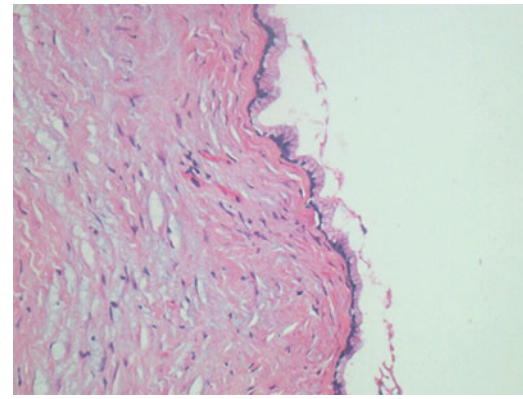

Fig. 6 Mucinous cystic neoplasm of the liver with absence of ovarian-like mesenchymal stroma (hematoxylin and eosin stain)

glandular structures contain immature forms like in primitive crypt-like glands, goblet cells, Paneth cell-like elements with eosinophilic supranuclear cytoplasmic granules, and endocrine cell-like cells (Gourley et al. 1992). Mainly in larger cysts, atrophy of the inner wall components may be associated with ulceration, followed by granulation tissue formation and accumulation of macrophages (in part pigmented, with PAS-positive lipofuscin) in the cyst wall (Ishak et al. 1977). The cyst walls may contain numerous cholesterol clefts with or without formation of cholesterol granulomas. In the microcystic variant, eosinophilic differentiation of the cyst epithelium has been noted, without underlying cellular stroma (Meyer et al. 1997). Whether this phenotype reflect mucinous or serous cystadenoma is difficult to judge from the pathology description.

A large percentage of MCNs show a characteristic zone of hypercellular stroma beneath the epithelia lining, termed mesenchymal stroma or ovarian-like stroma (synonym: ovarian-type stroma), because this stromal lamella closely resembles ovarian cortex stroma (Wheeler and Edmondson 1985). This stroma is not present in cystadenomas occurring in male patients. The stroma consists of densely packed small-to medium-sized spindle cells sometimes forming whorls and shows a characteristic vascular network. Scattered lymphocytes and monocytes/macrophages may be noted within the stroma.

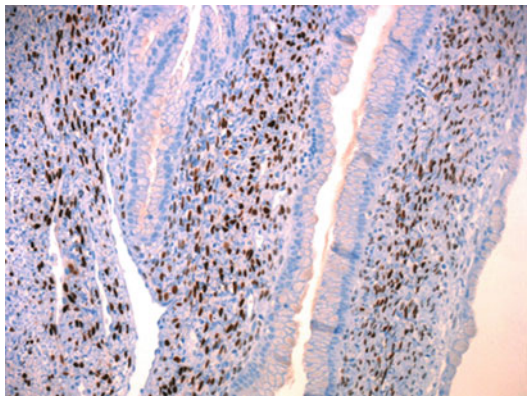

Fig. 7 Mucinous cystic neoplasm of the liver. Marked nuclear expression of estrogen receptor (*dark brown* reaction product; estrogen receptor immunostain)

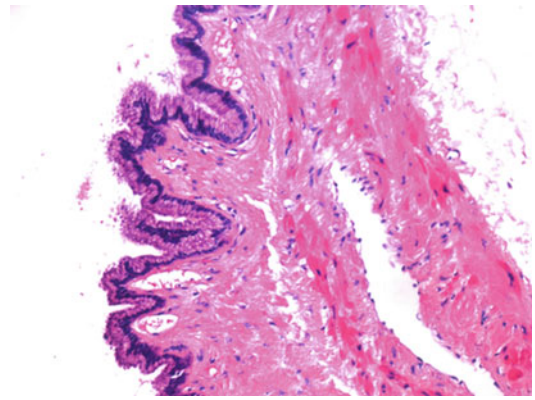

Fig. 8 Mucinous cystic neoplasm of the liver with low-grade dysplasia (hematoxylin and eosin)

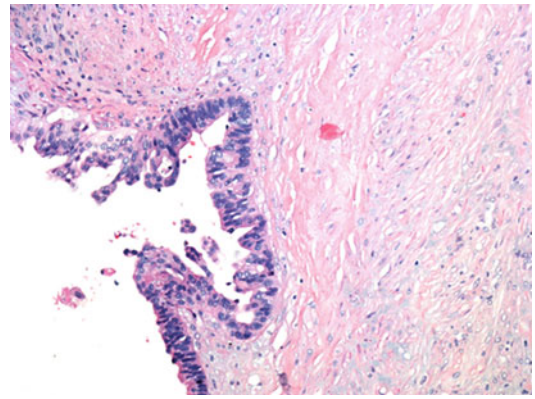

Fig. 9 Mucinous cystic neoplasm of the liver with moderate- to high-grade dysplasia (hematoxylin and eosin stain)

Usually, the stroma reaches very close to the epithelial lining, whereas the transition to the peripheral collagenous zone is less sharp. In pancreatic mucinous cystic tumors, stromal luteinization was detected in 32.4 % of the cases (Izumo et al. 2003), but this phenomenon is not seen in hepatic MCN. The stromal cells are reactive for vimentin and, in part, for alpha-smooth muscle actin (SMA; Abdul-al et al. 2007). Typically, the mesenchymal stroma shows nuclear expression of both estrogen and progesterone receptors (Fig. 7; Scott et al. 1995; Grayson et al. 1996; Weihing et al. 1997; Pedram-Canihac et al. 2000; Daniels et al. 2006; Abdul-Al et al. 2007). The immunohistochemical detection of these receptors in stromal cell nuclei perfectly works on formalin-fixed tissue (Scott et al. 1995). The stromal cells are also reactive for inhibin-alpha, also detectable in mucinous tumors of the pancreas (Riddeer et al. 1998; Izumo et al. 2003; Yeh et al 2004; Abdul-Al et al. 2007). A comparative study showed that the stroma of hepatic MCN had greater estrogen and progesterone receptor staining and more consistent inhibin-alpha staining than pancreatic mucinous tumors (Lam et al. 2008).

Signs of incipient malignant transformation are similar to those defined in great detail for lesions characterized by an adenoma-carcinoma sequence, chiefly in the colon. In cystadenomas, early changes are focal anaplasias consisting of glandular crowding, stratification of enlarged hyperchromatic nuclei, loss of cytoplasmic mucin, and up to 20 mitotic figures per 10 HPFs (Gourley et al. 1992). This alteration pattern may represent low-grade to moderate-grade dysplasia. High-grade dysplasia in MCN is characterized by "blue areas" at low magnification, seen both in flat epithelial lining and in papillary formations (Figs. 8, 9, 10, and 11). At high magnification, changes seen in adenocarcinoma in situ

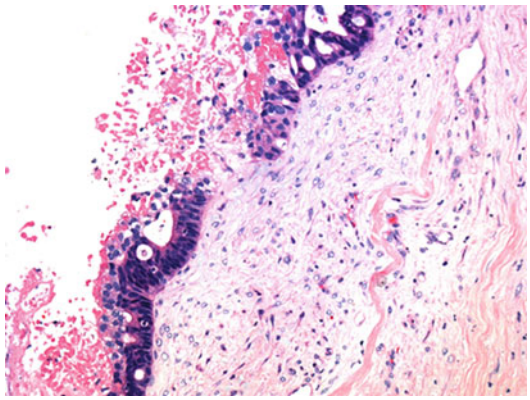

Fig. 10 Mucinous cystic neoplasm of the liver with high-grade dysplasia and focal erosion (hematoxylin and eosin stain)

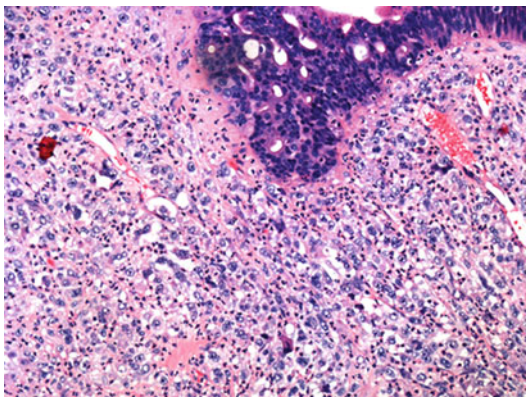

Fig. 11 Mucinous cystic neoplasm of the liver with high-grade dysplasia-carcinoma in situ and transition into poorly differentiated invasive carcinoma (hematoxylin and eosin stain)

are noted. In this situation, numerous samples and sections may be required to find or exclude focal microinvasion, usually with cribriform structures or at least fused glands and an incipient stromal reaction being loose in contrast to the compact ovarian-like stroma. In fact, microinvasive lesions with stromal reaction may form a characteristic gap in the preexisting band of mesenchymal stroma. Diagnosis of MCN may be obtained through fine needle aspiration and cytologic examination (Logrono et al. 2002).

Immunohistochemistry of Epithelial Components

The epithelia of mucinous MCN express cytokeratins 7 and 19, epithelial membrane antigen (EMA), CA 19-9, and sometimes carcinoembryonic antigen (Tomiaka et al. 1986; Gourley et al. 1992; Thomas et al. 1992; Maruyama et al. 2003). In cystadenocarcinomas, CA 19-9 may be expressed in a focal pattern (Horsmans et al. 1997). The epithelial lining has been found to express hepatocyte growth factor and its receptor, c-Met (Lam et al. 2008). Paneth cell-like cells, mainly found in glands, are reactive for lysozyme (Gourley et al. 1992). About 50 % of hepatobiliary MCN and cystadenocarcinomas contain neuroendocrine cells immunoreactive for chromogranin A and several hormones, including serotonin, gastrin, and somatostatin (Gourley et al. 1992). These cells tend to be located beneath and among the columnar epithelial cells. Based on the close spatial relationship between endocrine cells of cystic tumors and the endocrine cells found in peribiliary glands, it has been suggested that MCN may originate from these glands (Terada et al. 1997).

Variants of MCN

Neoplasms with an Oncocytic Lineage

A minority of MCN exhibit aberrant differentiation patterns of the epithelial lining. In 1992, an intrahepatic cystadenocarcinoma with oncocytic differentiation was reported. The neoplasm showed a prominent papillary growth pattern, and the tumor cells were characterized an abundant granular, intensively eosinophilic cytoplasm on light microscopy examination and large numbers of densely packed mitochondria by electron microscopy (Wolf et al. 1992). A second case, diagnosed in a 43-year-old woman, was reported in 2004 (Bardin et al. 2004). This tumor lacked an ovarian-like subepithelial stroma. It was proposed that these neoplasms should be classified as a form

of intraductal papillary neoplasm (IPN) with oncocytic differentiation (Sudo et al. 2001), similar to those occurring in the pancreas.

Neoplasms Without Ovarian-Like Stroma

As discussed above, the majority of MCNs exhibit a subepithelial cellular ovarian-like stroma. There are, however, neoplasms that lack such a stroma, mainly in MCNs occurring in male patients (Kishida et al. 2014).

Malignant Transformation of MCN (MCN with an Associated Invasive Carcinoma)

The spontaneous biologic behavior of hepatobiliary MCN is difficult to judge, because most lesions grow slowly, and only a fraction shows malignant behavior in early phases of evolution. However, traditional treatment of cysts such as aspiration, drainage, and marsupialization results in near universal recurrence and occasional malignant transformation, clearly showing that even benign-looking cystadenomas require a therapeutic approach that is different from simple hepatic nonparasitic cysts, preferably complete resection (Thomas et al. 2005; Delis et al. 2008; Limongelli et al. 2009). Among benign-looking CMS, up to 25 % recurred after primary surgery (Akwari et al. 1990). Transformation from MCN to cystadenocarcinoma has been described several times (Thompson and Wolff 1965; Woods 1981; Wheller and Edmondson 1985; O'Shea et al. 1987; Coulter and Baxter 1989; Lei and Howard 1992; Matsuoka et al. 1997; Del Poggio et al. 2000; Peyrègne et al. 2001) and may be a multistep process involving increasing degrees of dysplasia and carcinoma in situ. In the study of Wheeler and Edmondson (1985), malignant transformation was noted in 4 out of 17 patients. In a review of 53 patients, malignancy seemingly arose from MCN epithelium in seven cases (Akwari et al. 1990). Sarcomatous change of the mesenchymal stroma has been reported (Akwari et al. 1990).

Differential Diagnosis

In MCN located to bile ducts, the most important differential diagnosis is intraductal papillary neoplasm (IPN). Both neoplasms form mucin-containing cysts lined by a cuboidal to columnar epithelium. A diagnosis of IPN is favored by the presence of a communication to the bile duct system and the absence of an ovarian-like stroma. A further differential diagnosis is intrahepatic cholangiocarcinomas (ICCs) with cystic components. At least part of these neoplasms originate from preexisting IPN and, similarly to the latter, lack a subepithelial ovarian-like stroma with sex steroid receptor expression. MCNs are rarely mimicked by multicystic lesions of peribiliary glands, which have been suggested to be site or origin of MCN. Hepatobiliary MCN was found to develop in conjunction with multiple liver cysts (Hara et al. 2001), rendering the detection of the adenoma component difficult. Expanding intrahepatic cholangiocarcinoma may rarely show cyst formation and thus mimic MCN (Horie et al. 1987; Kokubo et al. 1990; Lee et al. 1995). Marked cystic change in adult mesenchymal hamartoma of the liver mimicked bile duct cystadenoma (Yamamoto et al. 1994). Hemorrhagic hepatic cysts sometimes mimic biliary MCN, because the coagulated blood at the cyst walls shows, at ultrasound, CT, and MRI, mural nodules on irregularly thickened walls, high-density straps inside the cyst, and flame-like prominences on the wall (Zhang et al. 2009). Intracystic hemorrhage of a simple liver cyst has also mimicked biliary cystadenocarcinoma (Kitajima et al. 2003). MCN may develop in the retroperitoneal space and mimic a primary retroperitoneal cystic process of different nature (Isse et al. 2004). MCN rarely presents under the clinical picture of hydatid disease (Geramizadeh et al. 2010; Kumar et al. 2011), and may mimic biliary smooth muscle neoplasms (Wong et al. 2001).

Hepatobiliary Mucinous Cystadenocarcinoma with or Without Mesenchymal Stroma (MCN Associated with Invasive Carcinoma)

Introduction

Hepatobiliary cystadenocarcinoma is a rare lesion which has first been described in 1943 (Willis 1943). For practical diagnostic reasons, three main types of cystadenocarcinoma may be distinguished, i.e., mucinous cystadenocarcinoma (developing from CMS in at least part of the cases), the much rarer serous hepatobiliary cystadenocarcinoma (see below), and a group of diverse hepatic tumors showing the macroscopic and histopathologic patterns of biliary cystadenocarcinoma, but revealing neither a mucinous nor a typically serous phenotype (hepatobiliary cystadenocarcinoma not otherwise specified, NOS). Expectedly, the latter group is mainly seen with tumors of low-grade differentiation.

The malignant variant of mucinous cystadenoma is a rare lesion and estimated to have an incidence of one per ten million individuals. Older patients, in their sixth decade of life, are more likely to present with malignant tumors. However, the true incidence of cystadenocarcinoma and of malignant transformation of preexisting cystadenoma is not known, in part caused by the lack of reproducible criteria for diagnosing malignancy, varying considerable in the published reports. Cystadenocarcinoma was found to be connected to the hepatic duct, characterized by a cystadenoma with a mural nodule showing in situ papillary adenocarcinoma (Sato et al. 2003). Biliary cystadenocarcinoma has been observed to arise in a congenital cyst (Devine and Ucci 1985), to be associated with hepatolithiasis (Tseng et al. 2004), and to develop in the setting of congenital fibropolycystic disease of the liver (Theise et al. 1993). Cystadenocarcinoma can invade adjacent tissues and organs, e.g., spread into extrahepatic bile ducts (Matsumoto et al. 2001), and lead to complications, such as invasion of the hepatic veins (Facy et al. 2012), inferior vena cava obstruction (Arkadopoulos et al. 2013), or perforation of bile ducts (Harima et al. 1984; Bacher et al. 1999), sometimes mimicking invasive hydatid disease (Bacher et al. 1999). Cystadenocarcinoma perforating into bile ducts can give rise to mucobilia and mucus-induced biliary obstruction (Chamberlain and Blumgart 2000). Similar to intrahepatic cholangiocarcinomas, cystadenocarcinoma can give rise to extrahepatic metastases, including the skeleton (Berijan et al. 1981).

Selected References Freeman 1957; Hodel 1966; More 1966; Yamasaki et al. 1976; Kanamori et al. 1985; Boillot et al. 1990; Courly et al. 1992; Boudeville et al. 1993; Theise et al. 1993; Devaney et al. 1994; Wee et al. 1993; Frameglia et al. 1996; Läuffer et al. 1998; Asahara et al. 1999; Filippi de la Palavesa et al. 1999; Kinoshita et al. 2001; Szubert et al. 2001; Williams et al. 2001; Kubota et al. 2003; Tseng et al. 2004; Vogt et al. 2005; Zhang et al. 2005; Koroglu et al. 2006; Lewin et al. 2006; Lee et al. 2009; Yamamoto et al. 2009; Yu et al. 2009; Genç et al. 2010; Gomez-Martin et al. 2010; Ohno et al. 2010; Ren et al. 2010; Yu et al. 2010; Kamyab et al. 2011; Pais-Costa et al. 2011; Facy et al. 2012; Wang et al. 2012; Okano et al. 2013; Soares et al. 2014.

Pathology

Grossly, the cystadenocarcinomas are usually multiloculated tumors, with a morphology mostly similar to that of noninvasive MCN (Ishak et al. 1977).

Histologically, papillary adenocarcinoma with finely arborizing micropapillary structures with fibrovascular axes prevails. The malignant epithelial lining is generally multilayered and shows high-grade dysplastic changes, with marked anisocytosis and anisonucleosis, loss of polarity and loss of most of the mucin, and microinvasive or frankly invasive growth. Vascular invasion may be observed (Ishak et al. 1977). The cells are columnar, polygonal, or round and commonly with a finely granular eosinophilic cytoplasm with

variable numbers of small vacuoles containing remnant mucin. Most tumor cells possess one nucleus, but occasional multinucleated cells are present (Ishak et al. 1977). Mitotic figures, a part of them with visible anomalies, are often seen. The locules lined by nonmalignant epithelium resemble those seen in cystadenomas (Ishak et al. 1977). In some cases, the diagnosis of carcinoma seems to have been based on abnormal growth patterns, e.g., the intracystic growth of markedly arborizing papillary formations (Kubota et al. 2003). Similar to MCN without invasive features, cystadenocarcinoma can show a subepithelial cellular stroma, but cases without ovarian-like stroma are also known (Ishibashi et al. 2007).

Mucinous Cystic Neoplasm and Cystadenocarcinoma of the Gallbladder

Cystadenoma of the gallbladder has occasionally been reported (Bishop 1901; Kordenat 1930; Sambaugh 1933), and also cystadenocarcinoma of the gallbladder is very rare (Ishak et al. 1977; Nakagawa et al. 1990; Spector et al. 2003; Terada et al. 2003; Rooney et al. 2005; Waldmann et al. 2006; Sistla et al. 2009). Cystadenocarcinoma of the gallbladder was observed in an 88-year-old man and presented as multilocular cystic tumor of the fundus, up to 3.5 cm in size, containing a seromucous fluid and associated with hemobilia, but not protruding into the gallbladder lumen. Histologically, the tumor consisted of mucin-rich columnar cells compatible with cystadenoma, but at some places, papillotubular structures and invasive growth were found, indicating malignant transformation (Terada et al. 2003). In one patient, a 50-year-old female patient, the tumor clinically presented with an abscess in the gallbladder fossa (Sistla et al. 2009).

Serous Hepatobiliary Cystadenoma and Cystadenocarcinoma

Very few cases of hepatobiliary serous cystic neoplasms (SCN; serous hepatobiliary cystadenoma and serous cystadenocarcinoma, non-mucinous cystic tumor) have been reported, sometimes without specification of the serous features (Fig. 12; Devaney et al. 1994; Anthony 1995; Suh et al. 1997; Akiyoshi et al. 2003; Ishibashi et al. 2007; Tani et al. 2008; Yu et al. 2009). In principle, these very unusual lesions resemble their counterpart in the pancreas. The neoplasms are probably almost always malignant lesions that occur on both sexes. At imaging, the cystic masses may exceed 20 cm in diameter (Yu et al. 2009) and are associated with elevated serum CA 19-9 and CA125 (Yu et al. 2009). In the lack of a clearly identifiable serous phenotype, the tumors are, on descriptive terms, cystadenocarcinomas without mesenchymal stroma. These tumors are usually not associated with a preexisting hepatobiliary cystadenoma with mesenchymal stroma and occur both in women and men. These lesions are thought to be more aggressive, but there are rare examples with normal CA 19-9 levels and a prolonged course (Horsmans et al. 1997). As in many of these tumors, it will be impossible to clearly identify the epithelial cell lineage involved (mainly in poorly differentiated neoplasms); we propose, as a working formulation, to denote the tumors as hepatobiliary cystadenocarcinoma, not otherwise specified (NOS). The pathogenesis of non-mucinous cystadenocarcinoma is unknown. In one patient,

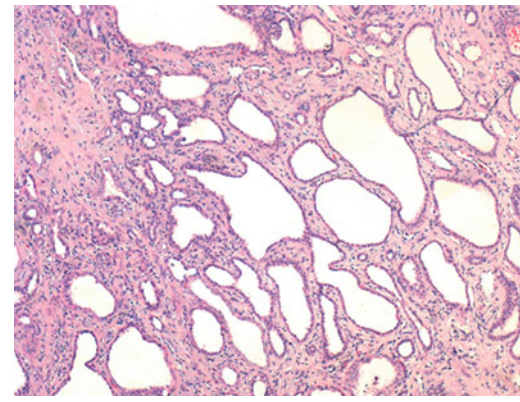

Fig. 12 Multilocular serous cystic neoplasm of the liver. The cystic spaces are lined with a flat, serous (non-mucinous) epithelium. This very rare tumor resembles its pancreatic counterpart, serous cystadenoma (hematoxylin and eosin stain)

progression from a benign cystic lesion to cystadenocarcinoma without mesenchymal stroma has been suggested (Akiyoshi et al. 2003).

Differential diagnostically, serous cystadenocarcinoma of the pancreas (malignant serous cystic neoplasm) is known to metastasize to the liver (Eriguchi et al. 1998; Strobel et al. 2003; Franko et al. 2008). But even benign-looking pancreatic serous cystadenoma (serous cystic neoplasm) may show an aggressive behavior and give rise to hepatic metastases (Wu et al. 1999), thus representing highly differentiated serous cystadenocarcinoma. Serous cystadenocarcinoma of the ovary (Lee et al. 2002) and of the retroperitoneal space (Kaku et al. 2004) can metastasize to the liver and may mimic primary serous neoplasms of the liver in a biopsy.

Hepatic Cystadenocarcinosarcoma

Primary hepatic cystadenocarcinosarcoma is a very unusual lesion that has been described in 2008, based on a case observed in 42-year-old woman presenting with a 4-month history of a mass in the upper abdomen (Yu et al. 2008b). It is a carcinosarcoma that is distinguished from its solid counterparts by the presence of a large, multilocular cystic mass with a large mural nodule, internal septa, and solid portions. On CT images, the enhancing tumor resembled hepatobiliary cystadenoma and cystadenocarcinoma.

Pathogenic Pathways

The similarities between pancreatic and hepatobiliary mucinous cystic tumors in regard to gender, morphology, stromal reactions, and sex steroid receptor expression suggested a common pathway for their development (Zamboni et al. 1999). Several hypotheses have been proposed to explain the pathogenesis of CMS and related lesions. The epithelia of cystadenomas resemble those of the developing gallbladder, also in regard to their ultrastructural features, and the fetal gallbladder also shows a subepithelial stromal band positive for alpha-smooth muscle actin (Subramony et al. 1993). Based on 11-year-long follow-up of a hepatic cystic lesion, it has been suggested that CMS may develop from a preexisting simple hepatic cyst (Fukunaga et al. 2008).

The origin and biologic features of ovarian-type stromal cells are still unknown. The development of a sex steroid-responsive Müllerian stroma outside the ovaries is known not only for mucinous tumors of the pancreas and the liver but was also observed in non-mucinous tumors such as cystic nephroma (multilocular renal cyst; Steele et al. 1994) and the normal or inflamed biliary tract (Alvaro et al. 2002, 2006). Involvement of a mesenchymal progenitor cell may be suggested owing to the emergence of other cell lineages in the this unique stroma, e.g., neoplastic osteoclast-like, CD68-positive giant cells (pancreatic giant cell tumor within mucinous cystadenocarcinoma; Bergman et al. 1995). Subsets of mesenchymal stem cells are estrogen-responsive, express estrogen receptor (Wang et al. 2006), and estrogen can exert an osteogenic effect in these cells (Hong et al. 2006). Whether the cell lineage forming the typical mesenchymal stroma of CMS have an origin similar to that of gonadal stromal cells is unknown. However, it is of interest to note that both gonadal stromal cells and stromal cells in hepatic and pancreatic mucinous tumors produce inhibin-alpha, a member of a pleiotropic effector family, inhibiting gonadotropin release (apart from gonadotropin-inhibitory hormone, GnIH; review: Tsutsui 2009) and being a tumor suppressor in mice (Ball et al. 2004).

References

Abdul-Al HM, Makhlouf HR, Goodman ZD (2007) Expression of estrogen and progesterone receptors and inhibin-alpha in hepatobiliary cystadenoma : an immunohistochemical study. Virchows Arch 450:691–697

Abe Y, Kasuya K, Itoi T, Kikuchi S, Ikeuchi N, Ishii K, Serizawa H, Shimazu M (2012) Hepatobiliary cystadenoma of the liver prolapsing into the extrahepatic bile duct (with video). Gastrointest Endosc 75:1099

Adam YG, Nonas CJ (1995) Hepatobiliary cystadenoma. South Med J 88:1140–1143

Ahanatha Pillai S, Velayutham V, Perumal S, Ulagendra Perumal S, Lakshmanan A et al (2012) Biliary cystadenomas: a case for complete resection. HPB Surg 2012:501705

Akiyoshi T, Yamaguchi K, Chijiiwa K, Tanaka M (2003) Cystadenocarcinoma of the liver without mesenchymal stroma: possible progression from a benign cystic lesion suspected by follow-up imagings. J Gastroenterol 38:588–592

Akwari OE, Tucker A, Seigler HF, Itani KM (1990) Hepatobiliary cystadenoma with mesenchymal stroma. Ann Surg 211:18–27

Alexander RC (1925) Solitary nonparasitic cysts of the liver. Edinb Med J 32:61–68

Alvaro D, Alpini G, Onori P, Franchitto A, Glaser SS, le Sage G, Folli F, Attili AF et al (2002) Alfa and beta estrogen receptors and the biliary tree. Mol Cell Endocrinol 193:105–108

Alvaro D, Mancino MG, Onori P, Franchitto A, Alpini G, Francis H, Glaser S, Gaudio E (2006) Estrogens and the pathophysiology of the biliary tree. World J Gastroenterol 12:3537–3545

Ansari A, Silvis S, Vennes J, Hay L (1976) Cystic hamartoma of the left hepatic duct. Cause of recurrent jaundice. JAMA 235:630–631

Anthony PP (1995) Tumors of the hepatobiliary system. In: Fletcher CDM (ed) Diagnostic histopathology of tumors. Chruchill Livingstone, New York, pp 275–317

Arkadopoulos N, Yiallourou AI, Palialexis C, Stamatakis E, Kairi-Vassilatou E, Smyrniotis V (2013) Inferior vena cava obstruction and collateral circulation as unusual manifestations of hepatobiliary cystadenocarcinoma. Hepatobiliary Pancreat Dis Int 12:329–331

Asahara T, Itamoto T, Katayama K, Nakahara H, Okamoto Y, Hino H, Ono E, Dohi K, Shimamoto F (1999) A case of biliary cystadenocarcinoma of the liver. Hiroshima J Med Sci 48:45–48

Bacher H, Cerwenka H, Werkgartner G, El-Shabrawi A, Höss G, Preidler K, Klimpfinger M et al (1999) primary biliary cystadenocarcinoma perforating the duodenum and left intrahepatic biliary tree – mimicking a hydatid cyst. Liver 19:39–41

Ball EM, Mellor SL, Risbridger GP (2004) Cancer progression: is inhibin alpha from Venus or Mars?. Cytokine Growth Facter Rev 15, 291–296

Barabino M, Leone S, Dapri G, Marsetti M, Ghislandi R, Opocher E (2004) Hepatobiliary cystadenoma: diagnostic uncertainty. HPB (Oxford) 6:52–54

Bardin RL, Trupiano JK, Howerton RM, Geisinger KR (2004) Oncocytic biliary cystadenocarcinoma: a case report and review of the literature. Arch Pathol Lab Med 128:e25–e28

Beasley SW, de Campo M, Chow CW, Auldist AW (1986) Biliary cystadenoma in a young child. Pediatr Surg Int 1:72–73

Beretta E, De Franchis R, Staudacher C et al (1986) Biliary cystadenoma: an uncommon cause of recurrent cholestatic jaundice. Am J Gastroenterol 81:138–140

Bergman S, Medeiros LJ, Radr T, Mangham DC, Lewandrowski KB (1995) Giant cell tumor of the pancreas arising in the ovarian-like stroma of a mucinous cystadenocarcinoma. Int J Pancreatol 18:71–75

Berijan RA, Nime F, Douglass HO, Nava H (1981) Biliary cystadenocarcinoma: report of a case presenting with osseous metastasis and a review of the literature. J Surg Oncol 18:305–316

Beuran M, Venter MD, Dumitru L (2006) Large mucinous biliary cystadenoma with "ovarian-like" stroma: a case report. World J Gastroenterol 12:3779–3781

Bevan AD (1919) Multilocular cystadenoma of the liver. Surg Clin N Am 3:887–892

Billington PD, Prescott RJ, Lapsia S (2012) Diagnosis of a biliary cystadenoma demonstrating communication with the biliary system by MRI using a hepatocyte-specific contrast agent. Br J Radiol 85:e35–e36

Bishop ES (1901) An undescribed innocent (?) growth of the gall-bladder. Lancet 2:72–73

Bogert JN, Taner T, Nagorney DM (2010) Education and imaging. Hepatobiliary and pancreatic: mucinous cystadenoma of the biliary tree. J Gastroenterol Hepatol 25:1332

Boillot O, Domergue J, Fabre JM, Guillon F, Lestra PM, Barneon G, Bruel JM, Baumel H (1990) Intrahepatic bile duct cystadenocarcinoma: case report and imaging diagnosis. J Surg Oncol 43:193–195

Boudeville JC, Chiche S, Grataloup C, Marty O, Hernigou A, Mainardi CM, Plainfossé MC (1993) Biliary cystadenocarcinoma: apropos of a case (in French). J Radiol 74:21–25

Brachet D, Mucci S, Desolneux G, Leboulanger G, Amie F, Pessaux P, Arnaud JP (2007) The simultaneous occurrence of mucinous cystadenomas in liver and pancreas. Eur J Gastroenterol Hepatol 19:801–804

Buetow PC, Buck JL, Pantongrag-Brown L, Ros PR, Devaney K, Goodman ZD, Cruess DF (1995) Biliary cystadenoma and cystadenocarcinoma: clinical-imaging-pathologic correlations with emphasis on the importance of ovarian stroma. Radiology 196:805–810

Burhans R, Myers R (1971) Benign neoplasms of the extrahepatic biliary ducts. Ann Surg 37:161–166

Busoni F, Neri E, Gibilisco G, Ricci E (1996) A giant unifocal biliary cystadenoma: a chance finding in a young asymptomatic athlete (in Italian). Radiol Med (Torino) 91:480–482

Byrne DJ, Walker MA, Pringle R, Ramesar K (1989) Extrahepatic biliary cystadenoma: report of a case and review of the literature. J R Coll Surg Edinb 34:223–224

Cahill CJ, Bailey ME, Smith MG (1982) Mucinous cystadenomas of the liver. Clin Oncol 8:171–177

Carson JG, Huerta S, Butler JA (2006) Hepatobiliary cystadenoma: a case report and a review of the literature. Curr Surg 63:285–289

Catto JWF, Madan M, Alexander DJ (1999) Hepatobiliary cystadenoma presenting with intermittent inferior vena caval obstruction. J Hepatobiliary Pancreat Surg 6:324–326

Cecka F, Ferko A, Subrt Z, Jon B (2011) Giant biliary cystadenoma: a case report. Acta Chir Belg 111:176–178

Chamberlain RS, Blumgart LH (2000) Mucobilia in association with a biliary cystadenocarcinoma of the caudate duct: a rare cause of malignant biliary obstruction. HPB Surg 11:345–351

Chang MS, Chen MC, Chou FF, Sheen-Chen SM, Chen WJ (1995) Spontaneous rupture of hepatobiliary cystadenoma: a case report. Changgeng Yi Xue Za Zhi 18:392–397

Choi BI, Lim JH, Han MC, Lee DH, Kim SH, Kim YI, Kim C (1989) Biliary cystadenoma and cystadenocarcinoma: CT and sonographic findings. Radiology 171:57–61

Claggett OT, Hawkins WJ (1946) Cystic disease of the liver. Ann Surg 123:111–118

Corrin B (1962) Cystadenoma of the liver. J Pathol Bacteriol 84:441–443

Coulter GN, Baxter JN (1989) Cystadenoma of the common bile duct with malignant transformation. Aust NZ J Surg 59:291–294

Courly WK, Kumar D, Bouton MS, Fish JC, Nealon W (1992) Cystadenoma and cystadenocarcinoma with mesenchymal stroma of the liver: immunohistochemical analysis. Arch Pathol Lab Med 116:1047–1050

Courtois-Suffit M, Charleux H (1960) Biliary cystadenomas and polycystic disease of the liver (in French). Sem Hop 36:3408–3414

Daniels JA, Coad JE, Payne WD, Kosari K, Sielaff TD (2006) Biliary cystadenomas: hormone receptor expression and clinical management. Dig Dis Sci 51:623–628

Davies W, Chow M, Nagorney D (1995) Extrahepatic biliary cystadenomas and cystadenocarcinoma. Report of seven cases and review of the literature. Ann Surg 222:619–625

De Backer AI, De Schepper AM, Michielsen PP, De Maeyer M, Bogers JJ, Vaneerdeweg W (2000) Hepatobiliary cystadenoma with mesenchymal stroma mimicking hydatid cyst. Report of a case. Acta Gastroenterol Belg 63:317–320

Del Poggio P, Jamoletti C, Forloni B, De Benedictis R, Mattiello M, Corti D, Pezzica E (2000) Malignant transformation of biliary cystadenoma: a difficult diagnosis. Dig Liver Dis 32:733–736

Delis SG, Touloumis Z, Bakoyannis A, Tassopoulos N, Paraskeva K, Athanassiou K et al (2008) Intrahepatic biliary cystadenoma: a need for radical resection. Eur J Gastroenterol Hepatol 20:10–14

Devaney K, Goodman ZD, Ishak KG (1994) Hepatobiliary cystadenoma and cystadenocarcinoma: a light microscopic and immunohistochemical study of 70 patients. Am J Surg Pathol 18:1078–1091

Devine P, Ucci AA (1985) Biliary cystadenocarcinoma arising in a congenital cyst. Hum Pathol 16:92–94

Divella D (1950) Voluminous unilocular cystadenoma of the liver (in Italian). Policlinico Chir 57:162–171

Dixon E, Sutherland F, Burak K, McKinnon G, May G (2001) Cystadenoma of the liver without mesenchymal stroma in a female following hormonal therapy for acne. HPB (Oxford) 3:183–186

Doepker M, Chang CK, Engel A (2011) Biliary cystadenoma: case series and review of the literature. Am Surg 77:505–506

Edmondson HA (1958) Tumors of the liver and the bile ducts: atlas of tumor pathology. Sect. VII, Fascicle 25. Armed Forces Institute of Pathology, Washington D.C

Elfadili H, Majbar A, Zouaidia F, Elamrani N, Sabbah F, Raiss M, Mahassini N, Hrora A et al (2010) Spontaneous rupture of a recurrent hepatic cystadenoma. World J Hepatol 2:322–324

Erdogan D, Busch OR, Rauws EA, van Delden OM, Gouma DJ, van-Gulik TM (2006) Obstructive jaundice due to hepatobiliary cystadenoma or cystadenocarcinoma. World J Gastroenterol 12:5735–5738

Erdogan D, Kloek J, Lamers WH, Offerhaus GJ, Busch OR, Gouma DJ, van Gulik TM (2010) Mucinous cystadenoma in liver: management and origin. Dig Surg 27:19–23

Eriguchi N, Aoyagi S, Nakayama T, Hara M, Miyazaki T, Kutami R, Jimi A (1998) Serous cystadenocarcinoma of the pancreas with liver metastases. J Hepatobiliary Pancreat Surg 5:467–470

Evans A (1921) cystie adenoma of the bile ducts, Br J surg 9:155–156

Facy O, Rode A, Mabrut JY (2012) Segment I intrahepatic biliary cystadenocarcinoma impinging on the hepatic vein. J Visc Surg 149:423–425

Fei Z, Zhou Y, Peng A, Wu B, Sun M, Wu S (2013) Asymptomatic hepatobiliary cystadenoma of the hepatic caudate lobe: a case report. J Biomed Res 27:336–338

Filippi de la Palavesa MM, Vasilescu C, Habersetzer F, Roy C (1999) Biliary cystadenocarcinoma: sonographic and cytologic findings. J Clin Ultrasound 27:210–212

Florman SS, Slakey DP (2001) Giant biliary cystadenoma: case report and literature review. Am Surg 67:727–732

Forde KA, Wolff M, Fuld SL, Price JB (1974) Hepatic lobectomy for biliary cystadenoma. Am Surg 40:647–650

Forrest ME, Cho KJ, Shields JJ, Wicks JD, Silver TM, McCormick TL (1980) Biliary cystadenoma: sonographic-angiographic-pathologic correlations. AJR Am J Roentgenol 135:723–727

Frameglia M, Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, Kanai M, Miyachi M (1996) Biliary cystadenocarcinoma resected by segment 3 and 4 hepatectomy. Hepatogastroenterology 43:1029–1034

Franko J, Cole K, Pezzi CM, Montone KT, Redmond J (2008) Serous cystadenocarcinoma of the pancreas with metachronous hepatic metastasis. Am J Clin Oncol 31:624–625

Freeman CW (1957) Cystadenocarcinoma of the liver; primary malignant cyst. Am J Clin Pathol 27:80–83

Fukunaga N, Ishikawa M, Ishikura H, Ichimori T, Kimura S, Sakata A, Sato K, Nagata J, Fujii Y (2008) Hepatobiliary cystadenoma exhibiting morphologic

changes from simple hepatic cyst shown by 11-year follow up images. World J Surg Oncol 6:129–135
Gad H, Bojal SA, Leung KF, Mostafa A, Meshikhes AW (2011) Image of the month. Mucinous cystadenoma of the liver. Arch Surg 146:363–364
Gadzijev E, Dragan S, Verica FM, Jana G (1995) Hepatobiliary cystadenoma protruding into the common bile duct, mimicking complicated hydatid cyst of the liver. Report of a case. Hepatogastroenterology 42:1008–1010
Gadzijev E, Ferlan-Marolt V, Grkman J (1996) Hepatobiliary cystadenomas and cystadenocarcinoma. Report of five cases. HPB Surg 9:83–92
Gadzijev EM, Pleskovic A, Stanisavljevic D, Ferlan-Marolt V, Trotovsek B (1998) Hepatobiliary cystadenoma can protrude and grow into the bile ducts. Hepatogastroenterology 45:1446–1451
Geist DC (1954) Solitary nonparasitic cyst of the liver. Arch Surg 140:906–910
Genç V, Cakmak A, Akbari M, Orozakunov E, Ersöz S (2010) Primary biliary cystadenocarcinoma mimicking a complicated hydatid cyst. Chirurgia (Bucur) 105:249–251
Geramizadeh B, Asadian M, Hourang MH (2010) Hepatobiliary cystadenoma mimicking liver hydatid cyst. Arch Iran Med 13:556–558
Gomez-Martin C, Rodriguez A, Malon D, Cortés-Funes H (2010) Biliary cystadenocarcinoma with mesenchymal stroma. Clin Transl Oncol 12:234–237
Gonzalez M, Majno P, Terraz S, Morel P, Rubbia-Brandt L, Mentha G (2009) Biliary cystadenoma revealed by obstructive jaundice. Dig Liver Dis 41:e11–e13
Gourley WK, Kumar D, Bouton MS, Fish JC, Nealon W (1992) Cystadenoma and cystadenocarcinoma with mesenchymal stroma of the liver. Immunohistochemical analysis. Arch Pathol Lab Med 116:1047–1050
Grayson W, Teare J, Myburgh JA, Paterson AC (1996) Immunohistochemical demonstration of progesterone receptor in hepatobiliary cystadenoma with mesenchymal stroma. Histopathology 29:461–463
Hara H, Morita S, Sako S, Dohi T, Iwamoto M, Inoue H, Tanigawa N (2001) Hepatobiliary cystadenoma combined with multiple liver cysts: report of a case. Surg Today 31:651–654
Harima Y, Shiraishi T, Tsubura A, Matsumoto Y, Tsukuda Y, Harima K, Murata T, Sawada S et al (1984) A case of perforated biliary cystadenocarcinoma (in Japanese). Gan No Rinsho 30:93–98
Harmouch T, Vullierme MP, Sauvanet A, Paradis V, Amarti A (2011) Hepatobiliary cystadenoma revealed by a jaundice: a case report. Case Rep Gastrointest Med 2011:895605
Hedayat A, Sotoudehmanesh R, Khatibian M, Mahmoodzadeh H, Sotoudeh M (2005) Choledochal cystadenoma. Endoscopy 37:498
Hennessy DB, Traynor O (2011) Extrahepatic biliary cystadenoma with mesenchymal stroma: a true biliary cystadenoma? A case report. J Gastrointest Liver Dis 20:209–211
Hodel C (1966) Primary cystadenocarcinoma of the liver (in German). Zentralbl Allg Pathol 109:62–66
Hodgson T, Bayjoo P (1991) Case report: extrahepatic biliary cystadenoma in association with adenomyomatosis of the gallbladder. Clin Radiol 43:210–212
Hong L, Colpan A, Peptan IA (2006) Modulations of 17-beta estradiol on osteogenic and adipogenic differentiations of human mesenchymal stem cells. Tissue Eng 12:2747–2753
Horie Y, Hirayama C, Katsube Y (1987) Bile duct carcinoma in a focal dilatation of the intrahepatic bile duct. Clin Radiol 38:209–211
Horsmans Y, Laka A, Gigot JF, Geubel AP (1996) Serum and cystic fluid CA 19-9 determinations as a diagnostic help in liver cysts of uncertain nature. Liver 16:255–257
Horsmans Y, Laka A, van Beers BE, Descamps C, Gigot JF, Geubel AP (1997) Hepatobiliary cystadenocarcinoma without ovarian stroma and normal CA 19-9 levels. Unusually prolonged evolution. Dig Dis Sci 42:1406–1408
Hwang IK, Namkung S, Yoo YS, Kim HK, Choi YH (2000) Huge biliary cystadenoma mimicking cholecystic lymphangioma in subhepatic space. J Comput Assist Tomogr 24:652–654
Ishak KG, Willis GW, Cumins SD, Bullock AA (1977) Biliary cystadenoma and cystadenocarcinoma: report of 14 cases and review of the literature. Cancer 39:322–338
Ishibashi Y, Ojima H, Hiraoka N, Sano T, Kosuge T, Kanai Y (2007) Invasive biliary cystic tumor without ovarian-like stroma. Pathol Int 57:794–798
Isse K, Harada K, Suzuki Y, Ishiguro K, Sasaki M, Kajiura S, Nakanuma Y (2004) Retroperitoneal mucinous cystadenoma: report of two cases and review of the literature. Pathol Int 54:132–138
Izumo A, Yamaguchi K, Eguchi T, Nishiyama K, Yamamoto H, Yonemasu H, Yao T, Tanaka M, Tsuneyoshi M (2003) Mucinous cystic tumor of the pancreas: immunohistochemical assessment of "ovarian-type stroma". Oncol Rep 10:515–525
Joseph L, Augustine J, Omana M (1993) Multilocular cystadenoma of the liver with mural nodules. Indian J Pathol Microbiol 36:308–310
Kaku M, Ohara N, Seima Y, Imanishi K, Tomura N, Kobayashi A, Yamasaki M, Hirata Y, Murao S (2004) A primary retroperitoneal serous cystadenocarcinoma with clinically aggressive behavior. Arch Gynecol Obstet 270:302–306
Kamyab A, Curtiss W, Mittal V, Jacobs M (2011) Primary intrahepatic biliary cystadenocarcinoma. Am Surg 77: e117–e118
Kanamori H, Kawahara H, Oh S, Mine T, Osawa H, Murakami T, Ogata E (1985) A case of biliary cystadenocarcinoma with recurrent jaundice: diagnostic evaluation of computed tomography. Cancer 55:2722–2724
Kapoor R, Calton N, Verghese M (1997) Cystadenoma with mesenchymal stroma mistaken for hepatic hydatid cyst. Indian J Gastroenterol 16:73–74

Kazama S, Hiramatsu T, Kuriyama S, Kuriki K, Kobayashi R, Takabayashi N, Furukawa K et al (2005) Giant intrahepatic biliary cystadenoma in a male: a case report, immunohistopathological analysis, and review of the literature. Dig Dis Sci 50:1384–1389

Keen WW (1892) On resection of the liver, especially for hepatic tumors. Boston Med Surg J 126:405–409

Kim K, Choi J, Park Y, Lee W, Kim B (1998) Biliary cystadenoma of the liver. J Hepatobiliary Pancreat Surg 5:348–352

Kim HH, Hur YH, Koh YS, Cho CK, Kim JW (2011) Intrahepatic biliary cystadenoma: is there really an almost exclusively female preponderance? World J Gastroenterol 17:3073–3074

Kimura H, Kagawa K, Deguchi T, Sumida Y, You K, Komaki T, Teramae N, Fukui S et al (1998) Extrahepatic biliary cystadenocarcinoma arising from the left hepatic duct. J Gastroenterol 33:895–898

Kinoshita H, Tanimura H, Ohnishi H, Kasano Y, Uchiyama K, Yamaue H (2001) Clinical features and imaging diagnosis of biliary cystadenocarcinoma of the liver. Hepatogastroenterology 48:250–252

Kishida N, Shinoda M, Masugi Y, Itano O, Fujii-Nishimura Y, Ueno A, Kitago M, Hibi T, Abe Y, Yagi H et al (2014) Cystic tumor of the liver without ovarian-like stroma or bile duct communication: two case reports and a review of the literature. World J Surg Oncol 12:229

Kitajima Y, Okayama Y, Hirai M, Hayashi K, Imai H, Okamoto T, Aoki S, Gotoh K, Ohara H et al (2003) Intracystic hemorrhage of a simple liver cyst mimicking a biliary cystadenocarcinoma. J Gastroenterol 38:190–193

Koban R (1964) 2 cases operated on for liver cystadenoma (in German). Wien Klin Wochenschr 76:376–378

Kokal KC, Abraham PP, Pimparkar BD, Desai AP, Bapat RD (1983) Biliary cystadenoma of the liver. (A case report). J Postgrad Med 29:53

Kokubo T, Itai Y, Nagao T (1990) Intrahepatic cholangiocarcinoma with cystic formation. Radiat Med 8:219–221

Kordenat RA (1930) Cystadenoma of the gallbladder: report of a case. Wis Med J 29:634–637

Korobkin M, Stephens DH, Lee JK, Stanley RJ, Fishman EK, Francis IR, Alpern MB, Rynties M (1989) Biliary cystadenoma and cystadenocarcinoma: CT and sonographic findings. AJR Am J Roentgenol 153:507–511

Koroglu M, Akhan O, Akpinar E, Oto A, Gumus B (2006) Biliary cystadenoma and cystadenocarcinoma: two rare cystic liver lesions. JBR-BTR 89:261–263

Kosaka H, Ota A, Kihara T, Sato O, Mihara Y (1968) 2 cases of cystoma of the common bile duct (in Japanese). Rinsho Hoshasen 13:648–655

Kubota E, Katsumi K, Iida M, Kishimoto A, Ban Y, Nakata K, Takahashi N, Kobayashi K et al (2003) Biliary cystadenocarcinoma followed up as benign cystadenoma for 10 years. J Gastroenterol 38:278–282

Kumar S, Gupta A, Gupta S, Noba AL, Agrawal N (2011) Giant intrahepatic biliary cystadenoma mimicking hepatic hydatid cyst. Trop Gastroenterol 32:72–74

Lam MM, Swanson PE, Upton MP, Yeh MM (2008) Ovarian-type stroma in hepatobiliary cystadenomas and pancreatic mucinous cystic neoplasms: an immunohistochemical study. Am J Clin Pathol 129:211–218

Läuffer JM, Baer HU, Maurer CA, Stoupis C, Zimmermann A, Büchler MW (1998) Biliary cystadenocarcinoma of the liver: the need for complete resection. Eur J Cancer 34:1845–1851

Lee SK, Choi BI, Cho JM, Han JK, Kim YI, Han MC (1995) Cystic peripheral cholangiocarcinoma: sonography and CT. Abdom Imaging 20:131–132

Lee JH, Chen DR, Pang SC, Lai YS (1996) Mucinous biliary cystadenoma with mesenchymal stroma: expressions of CA 19-9 and carcinoembryonic antigen in serum and cystic fluid. J Gastroenterol 31:732–736

Lee JH, Kim KS, Chung CW, Park YN, Kim BR (2002) Hepatic resection of metastatic tumor from serous cystadenocarcinoma of the ovary. J Korean Med Sci 17:415–418

Lee JH, Lee KG, Park HK, Lee KS (2009) Biliary cystadenoma and cystadenocarcinoma of the liver: 10 cases of a single center experience. Hepatogastroenterology 56:844–849

Lei S, Howard JM (1992) Biliary cystadenocarcinoma arising from benign cystadenoma. Arch Surg 127:1478

Lei S, Domenico DR, Howard JM (1994) Intrahepatic biliary cystadenoma with intracystic gallstone formation. HPB Surg 7:241–247

Lempinen M, Halme L, Numminen K, Arola J, Nordin A, Makisalo H (2005) Spontaneous rupture of a hepatic cystadenoma and cystadenocarcinoma: report of two cases. J Hepatobiliary Pancreat Surg 12:409–414

Lewin M, Moura N, Honigman I, Fléjou JF, Parc R, Arrive L, Tubiana JM (2006) Assessment of MRI and MRCP in diagnosis of biliary cystadenoma and cystadenocarcinoma. Eur Radiol 16:407–413

Li PS, Pagano D, Echeverri GJ, Cintorino D, Gruttadauria S, Traina M, Caruso S et al (2010) Different surgical approach to treat hepatobiliary cystadenomas presenting as an acute abdomen. Am Surg 76:E170–E172

Li X, Zhang JL, Wang YH, Song SW, Wang FS, Shi R, Liu YF (2013) Hepatobiliary cystadenoma and cystadenocarcinoma: a single center experience. Tumori 99:261–265

Limongelli P, Pai M, Damrah O, Lauretta A, Atijosan O, Habib N, Jiao LR (2009) Cystic tumors of the biliary tract: a complete excision is crucial. Int Surg 94:136–140

Logrono R, Rampy BA, Adegboyega PA (2002) Fine needle aspiration cytology of hepatobiliary cystadenoma with mesenchymal stroma. Cancer 96:37–42

Manouras A, Markogiannakis H, Lagoudianakis E, Katergiannakis V (2006) Biliary cystadenoma with mesenchymal stroma: report of a case and review of the literature. World J Gastroenterol 12:6062–6069

Mantke R, Ridwelski K, Rocken C, Pross M, Schulz HU, Lippert H (2001) Hepatobiliary cystadenoma (in German). Chirurg 72:277–280

Marcial HA, Hauser SC, Cibas ES, Braver J (1986) Intrahepatic biliary cystadenoma: clinical, radiological and pathological findings. Dig Dis Sci 31:884–888

Marrone G, Maggiore G, Carollo V, Sonzogni A, Luca A (2011) Biliary cystadenoma with bile duct communication depicted on liver-specific contrast agent-enhanced MRI in a child. Pediatr Radiol 41:121–124

Marsh JL, Dahms B, Longmire WP (1974) Cystadenoma and cystadenocarcinoma of the biliary system. Arch Surg 109:41–43

Martel G, Alsharif J, Aubin JM, Marginean C, Mimeault R, Fairfull-Smith RJ, Mohammad WM et al (2013) The management of hepatobiliary cystadenomas: lessons learned. HPB (Oxford) 15:617–622

Martin AG, Wendt WP, La Fond DJ, Rater CJ (1973) Cystadenoma of the liver; a rare tumor. Description of a case. Review of the literature. Wis Med J 72:220–227

Maruyama S, Hirayama C, Yamamoto S, Inoue M, Umeki K, Maeta Y, Konishi I, Suzuki K et al (2003) Hepatobiliary cystadenoma with mesenchymal stroma in a patient with chronic hepatitis C. J Gastroenterol 38:593–597

Matsumoto S, Miyake H, Mori H (1997) Case report: biliary cystadenoma with mucin-secretion mimicking a simple hepatic cyst. Clin Radiol 52:316–318

Matsumoto J, Kondo S, Okushiba S, Morikawa T, Sugiura H, Omi A, Hirano S, Ambo Y et al (2001) Biliary cystadenocarcinoma with superficial spread to the extrahepatic bile duct. Hepatogastroenterology 48:647–649

Matsuoka Y, Hayashi K, Yano M (1997) Case report: malignant transformation of biliary cystadenoma with mesenchymal stroma: documentation by CT. Clin Radiol 52:318–321

Meng XF, Li J, Zhang WZ, Chen YL, Shi XJ, Ji WB, Huang XQ, Wang J, Dong JH (2011) Intrahepatic biliary cystadenoma: experience with 10 consecutive cases at a single center (in Chinese). Nan Fang Yi KeDa Xue Xue Bao 31:1733–1736

Merchant FJ (1973) Multiloculated cystadenoma of the liver. IMJ Ill Med J 144:129–130

Meyer X, Henry L, Garcia P, Berger F, Saignol G, Chavaillon A, Valette PJ (1997) Micocystic variant of biliary mucinous cystadenoma: US, CT, and MR findings. J Comput Assist Tomogr 21:1015–1017

Mohan H, Bal A, Arya S, Jain P, Bawa AS (2006) Hepatobiliary cystadenoma with mesenchymal stroma – a case report. Indian J Pathol Microbiol 49:291–293

Mondini S (1962) Cystadenoma of the liver. Anatomoclinical description of a case (in Italian). Arch Ital Chir 88:600–610

Monnin CA (1969) Multilocular cystadenoma of the liver. J Fla Med Assoc 56:108–110

More JR (1966) Cystadenocarcinoma of the liver. J Clin Pathol 19:470–474

Naganuma H, Funaoka M, Fujimori S, Niwa M, Ishida H, Komatsuda T, Yamada M, Furukawa K (2006) Contrast-enhanced sonographic findings in a case of hepatobiliary cystadenoma with intracystic bleeding. J Clin Ultrasound 34:412–415

Nagorney DM, LeSage GD, Charboneau JW, McGough PF (1984) Cystadenoma of the proximal common hepatic duct: the use of abdominal ultrasonography and transhepatic cholangiography in diagnosis. Mayo Clin Proc 59:118–121

Nakagawa M, Matsumoto T, Suguro Y, Takanosu S (1990) A case of mucinous cystadenocarcinoma of the gallbladder. Nippon Geka Gakkai Zasshi 91:434–437

Nakagawa M, Matsuda M, Masaji H, Goro W (2011) Successful preoperative diagnosis of biliary cystadenoma with mesenchymal stroma and its characteristic imaging features: report of two cases. Turk J Gastroenterol 22:631–615

Nunes QM, Wight ND, Aithal GP, Dunn WK, Kaye PV, Lobo DN (2006) Concurrent mucinous cystadenoma of the liver and bile duct: a rare cause of jaundice. Gastrointest Endosc 63:870–872

O'Shea JS, Shah D, Cooperman AM (1987) Biliary cystadenocarcinoma of extrahepatic duct origin arising in previously benign cystadenoma. Am J Gastroenterol 82:1306–1310

Ohno A, Mori A, Doi R, Yonenaga Y, Asano N, Uemoto S (2010) Successful left hemihepatectomy and perioperative management of a patient with biliary cystadenocarcinoma, complicated by MELAS syndrome: report of a case. Surg Today 40:878–882

Okamura T, Murakami S, Nishioka Y, Hirayama R, Mishima Y, Awazu R (1987) Biliary cystadenoma of the extrahepatic bile ducts: report of a case and review of the literature. Jpn J Surg 17:281–288

Okano K, Oshima M, Yamamoto N, Yachida S, Suzuki Y (2013) Education and imaging. Hepatobiliary and pancreatic: intrahepatic biliary cystadenocarcinoma. J Gastroenterol Hepatol 28:753

Organ B, Petrek J (1984) Biliary cystadenoma. South Med J 77:262–265

Owono P, Scoazec JY, Valette PJ, Dumortier J, Gouysse G, Berger F, Boulez J, Partensky C (2001) Hepatobiliary cystic tumors. Clinical, radiological and histopathological study of 7 cases (in French). Gastroenterol Clin Biol 25:414–421

Pais-Costa SR, Martins SJ, Araujo SL, Lima OA, Paes MA, Guimaraes ML (2011) Successful surgical management of an extrahepatic biliary cystadenocarcinoma. Rare Tumors 3, e36

Palacios E, Shannon M, Solomon C et al (1990) Biliary cystadenoma: ultrasound, CT, and MRI. Gastrointest Radiol 15:313–316

Park JH, Lee DH, Kim HJ, Ko YT, Lim JW, Yang MH (2004) Unilocular extrahepatic biliary cystadenoma mimicking choledochal cyst: a case report. Korean J Radiol 5:287–290

Pedram-Canihac M, Le Bail B, Rivel J, Blanc J, Saric J, Bioulac-Sage P (2000) Hepatobiliary cystadenoma with mesenchymal stroma: a hormone dependent tumor. Report of five cases with immunohistochemical study of hormone receptors (in French). Ann Pathol 20:14–18

Peyrègne V, François Y, Isaac S, Grandclément E, Sadeghi-Looyeh B, Sayag-Beaujard A et al (2001) Liver cystadenocarcinoma originating in cystadenoma without mesenchymal stroma. Therapeutic strategy in case of atypical radiological criteria. A case report. Hepatogastroenterology 48:247–249

Pojchamarnwiputh S, Na Chiangmai W, Chotirosniramit A, Lertprasertsuke N (2008) Computed tomography of biliary cystadenoma and biliary cystadenocarcinoma. Singap Med J 49:392–396

Preetha M, Chung AYF, Lim-Tan SK, Lim DTH, Thug CH (2004) Intrahepatic biliary cystadenoma presenting with obstructive jaundice. Asian J Surg 27:243–245

Qian LJ, Zhu J, Zhuang ZG, Xia Q, Liu Q, Xu JR (2013) Spectrum of multilocular cystic hepatic lesions. CT and MR imaging findings with pathologic correlation. Radiographics 33:1419–1433

Qu ZW, He Q, Lang R, Pan F, Jin ZK, Sheng QS, Zhang D, Zhang XS, Chen DZ (2009) Giant hepatobiliary cystadenoma in a male with obvious convex papillate. World J Gastroenterol 15:1906–1909

Ratti F, Ferla F, Paganelli M, Cipriani F, Aldrighetti L, Ferla G (2012) Biliary cystadenoma: short- and long-term outcome after radical hepatic resection. Updates Surg 64:13–18

Ray S, Khamrui S, Mridha AR, Mukherjee B (2010) Extrahepatic biliary cystadenoma: an unusual cause of recurrent cholangitis. Am J Surg 199:e3–e4

Raza MH, Rab AZ, Khan S, Ahmad R (2009) Biliary cystadenoma mimicking hydatid cyst. Saudi J Gastroenterol 15:199–200

Ren XL, Yan RL, Yu XH, Zheng Y, Liu JE, Hou XB, Zuo SY, Fu XY, Chang H, Lu JH (2010) Biliary cystadenocarcinoma diagnosed with real-time contrast-enhanced ultrasonography: report of a case with diagnostic features. World J Gastroenterol 16:131–135

Ridder GJ, Maschek H, Flemming P, Nashan B, Klempnauer J (1998) Ovarian-like stroma in an invasive mucinous cystadenocarcinoma of the pancreas positive for inhibin. A hint concerning its possible histogenesis. Virchows Arch 432:451–454

Rogers KE (1946) A papillary cystadenoma of the common hepatic duct. Can Med Assoc J 55:597–599

Romagnoli R, Patrono D, Paraluppi G, David E, Tandoi F, Strignano P, Lupo F, Salizzoni M (2011) Liver transplantation for symptomatic centrohepatic biliary cystadenoma. Clin Res Hepatol Gastroenterol 35:408–413

Rooney TB, Schofer JM, Stanley MD, Banks SL (2005) Biliary cystadenocarcinoma of the gallbladder. AJR Am J Roentgenol 185:1571–1572

Sambaugh P (1933) Multilocular papillary cystadenoma of the gallbladder. Am J Surg 22:229–231

Sang X, Sun Y, Mao Y, Yang Z, Lu X, Yang H, Xu H, Zhong S, Huang J (2011) Hepatobiliary cystadenomas and cystadenocarcinomas: a report of 33 cases. Liver Int 31:1337–1344

Sankar S, Subramanian M, Joseph LD, Rajinikanth S, Nandigam V (2009) Pedunculated extra hepatic biliary cystadenoma mimicking as a stone. Indian J Gastroenterol 28:37

Saravanan MN, Singh B, Ravindranath K, Raghavendra RR (2010) Episodic jaundice due to an intrahepatic biliary cystadenoma with biliary stricture masquerading as hydatid cyst. Trop Gastroenterol 31:332–335

Sato M, Watanabe Y, Tokui K, Kohtani T, Nakata Y, Chen Y, Kawachi K (2003) Hepatobiliary cystadenocarcinoma connected to the hepatic duct: a case report and review of the literature. Hepatogastroenterology 50:1621–1624

Scott FR, More L, Dhillon AP (1995) Hepatobiliary cystadenoma with mesenchymal stroma: expression of oestrogen receptors in formalin-fixed tissue. Histopathology 26:555–558

Seidel R, Weinreich M, Pistorius G, Fries P, Schneider G (2007) Biliary cystadenoma of the left intrahepatic duct. Eur Radiol 17:1380–1383

Sendt W, Voigt R, Jandt K, Settmacher U, Altendorf-Hofmann AK (2012) Benign biliary cystadenoma – a rare differential diagnosis (in German). Zentralbl Chir 137:69–70

Senyüz OF, Numan F, Eroglu E, Sarimurat N, Bozkurt P, Cantasdemir M, Dervisoglu S (2004) Hepatobiliary mucinous cystadenoma in a child. J Pediatr Surg 39: E6–E8

Shima Y, Horimi T, Shibuya Y, Sakurama K, Nishie M, Morita S (2004) Resected cystadenoma of the common bile duct. J Hepatobiliary Pancreat Surg 11:438–440

Shiono S, Suda K, Nobukawa B, Arakawa A, Yamasaki S, Sasahara N, Hosokawa Y, Suzuki F (2006) Pancreatic, hepatic, splenic, and mesenteric mucinous cystic neoplasms (MCN) are lumped together as extra ovarian MCN. Pathol Int 56:71–77

Short WF, Ndwich A, Levry HA, Howard JM (1971) Biliary cystadenoma: report of a case and review of literature. Arch Surg 102:78–80

Siegmund A (1889) Ueber eine cystische Geschwulst der Leber (Gallengangs-cystadenom). Arch Pathol Anat Physiol 115:155–175

Sielezneff I, Ferrero A, Chapel F, Le Treut YP (1992) Cystadenoma of the extrahepatic bile ducts: a rare cause of cholestasis (in French). Gastroenterol Clin Biol 16:708–713

Siriwardana PN, Pathirana A (2009) Episodic biliary obstruction due to an intrahepatic biliary cystadenoma: a case report. J Med Case Rep 3:9032

Sistla SC, Sankar G, Basu D, Venkatesan B (2009) Biliary cystadenocarcinoma of the gall bladder: a case report. J Med Case Rep 3:75

Skopelitou A, Hadjiyannakis M (1996) Hepatobiliary cystadenoma with mesenchymal stroma (CMS) in association with unilateral mucinous cystadenoma of the ovary (MCO): case report and review of the literature. Eur J Gynaecol Oncol 17:234–240

Snedecor PA (1967) Bile duct cystadenoma of the liver. Am Surg 33:581–583

Soares KC, Amaoutakis DJ, Kamel I, Anders R, Adams RB, Bauer TW, Pawlik TM (2014) Cystic neoplasms of the liver: biliary cystadenoma and cystadenocarcinoma. J Am Coll Surg 218:119–128

Soochan D, Keough V, Wanless I, Molinari M (2012) Intra and extrahepatic cystadenoma of the biliary duct. Review of literature and radiological and pathological characteristics of a very rare case. BMJ Case Rep 2012: pii: bcr0120125497

Spector SA, Fernandez VE, Vernon SE, Dunkin B, Livingstone AS (2003) Gallbladder cystadenoma and common bile duct obstruction. Int J Gastrointest Cancer 34:151–155

Steele R, Daroca PJ, Hill S, Reed RJ, Thomas R (1994) Multilocular renal cyst (cystic nephroma) with mullerian-like stroma. Urology 43:549–553

Stoupis C, Ros PR, Dolson DJ (1994) Recurrent biliary cystadenoma: MR imaging appearance. J Magn Reson Imaging 4:99–101

Strobel O, Z'Graggen K, Schmitz-Winnenthal FH, Friess H, Kappeler A, Zimmermann A, Uhl W, Buchler MW (2003) Risk of malignancy in serous cystic neoplasms of the pancreas. Digestion 68:24–33

Subramony C, Herrera GA, Turbat-Herrera EA (1993) Hepatobiliary cystadenoma. A study of five cases with reference to histogenesis. Arch Pathol Lab Med 117:1036–1042

Sudo Y, Harada K, Tsuneyama K, Katayanagi K, Zen Y, Nakanuma Y (2001) Oncocytic biliary cystadenocarcinoma is a form of intraductal oncocytic papillary neoplasm of the liver. Mod Pathol 14:1304–1309

Suh JI, Kim JH, Lee DJ, Kim KY, Park CW, Kim TN, Chung MK (1997) A case of biliary cystadenocarcinoma. Korean J Intern Med 12:109–113

Sun Y, Lu X, Xu Y, Mao Y, Yang Z, Sang X, Zhong S, Huang J (2010) Spontaneous rupture of a giant hepatobiliary serous cystadenoma: report of a case and literature review. Hepatol Int 5:603–606

Sutton CD, White SA, Berry DP, Dennison AR (2000) Intrahepatic biliary cystadenoma causing luminal common bile duct obstruction. Dig Surg 17:297–299

Szubert A, Bialek P, Biejat Z, Uryszek M, Zajac L, Polanski JA (2001) Liver cystadenocarcinoma – case report. Med Sci Monit 7(suppl 1):292–293

Taketomi A, Tamada R, Takenaka K, Kawano R, Maeda T, Sugimachi K (1998) A case of biliary cystadenoma with obstructive jaundice. Oncol Rep 5:833–835

Tani A, Yoshida H, Mamada Y, Taniai N, Naito Z, Tajiri T (2008) Case of biliary cystadenocarcinoma with intracystic bleeding. J Nippon Med Sch 75:293–297

Teoh AY, Ng SS, Lee KF, Lai PB (2006) Biliary cystadenoma and other complicated cystic lesions of the liver: diagnostic and therapeutic challenges. World J Surg 30:1560–1566

Terada T, Kitamura Y, Ohta T, Nakanuma Y (1997) Endocrine cells in hepatobiliary cystadenomas and cystadenocarcinomas. Virchows Arch 430:37–40

Terada T, Takeuchi T, Taniguchi M (2003) Hepatobiliary cystadenocarcinoma with cystadenoma elements of the gall bladder in an old man. Pathol Int 53:790–795

Theise ND, Miller F, Worman HJ, Morris P, Schwartz M, Miller C, Thung SN (1993) Biliary cystadenocarcinoma arising in a liver with fibropolycystic disease. Arch Pathol Lab Med 117:163–165

Thomas JA, Scriven MW, Puntis MC, Jasani B, Williams GT (1992) Elevated serum CA 19-9 levels in hepatobiliary cystadenoma with mesenchymal stroma. Two case reports with immunohistochemical confirmation. Cancer 70:1841–1846

Thomas KT, Welch D, Trueblond A, Sulur P, Wise P, Gorden DL, Chari RS, Wright JK et al (2005) Effective treatment of biliary cystadenoma. Ann Surg 241:769–773

Thompson JE, Wolff M (1965) Intra-hepatic cystadenoma of bile duct origin, with malignant alteration. Report of a case, treated with total left hepatic lobectomy. Mil Med 130:218–224

Thomsen P, Vasehus Madsen P, Moesgaard F, Lykkegaard Nielsen MC (1984) Biliary cystadenoma of the common bile duct with secondary biliary cirrhosis. Report of a case. Acta Med Scand 216:327–330

Tomiaka T, Tsuchiya R, Harada N, Tsunoda T, Matsuo T (1986) Cystadenoma and cystadenocarcinoma of the liver: localization of carcinoembryonic antigen. Jpn J Surg 16:62–67

Tran S, Berman L, Wadhwani NR, Browne M (2013) Hepatobiliary cystadenoma: a rare pediatric tumor. Pediatr Surg Int 29:841–845

Trummer A, Oldhafer KJ, Flemming P, Hollerbach S (2006) Detection of recurrent extrahepatic hepatobiliary cystadenoma by EUS (with video). Gastrointest Endosc 64:658–660

Tseng CA, Pan YS, Chen CY, Liu CS, Wu DC, Wang WM, Jan CM (2004) Biliary cystadenocarcinoma associated with atrophy of the left hepatic lobe and hepatolithiasis mimicking intrahepatic cholangiocarcinoma: a case report. Kaohsiung J Med Sci 20:198–203

Tsiftsis D, Christodoulakis M, de Bree E, Sanidas E (1997) Primary intrahepatic biliary cystadenomatous tumors. J Surg Oncol 64:341–346

Tsui WMS, Adsay NV, Crawford JM, Hruban R, Klöppel G, Wee A (2010) Mucinous cystic neoplasms of the liver. In: Bosman FT (ed) WHO classification of tumours of the digestive system. IARC, Lyon, pp 236–238

Tsutsui K (2009) A new key neurohormone controlling reproduction, gonadotropin-inhibitory hormone

(GnIH): biosynthesis, mode of action and functional significance. Prog Neurobiol 88:76–88
Udoff EJ, Harrington DP, Kaufman SL, Cameron JL (1979) Cystadenoma of the common bile duct demonstrated by percutaneous transhepatic cholangiography. Am Surg 45:662–664
Van Steenbergen W, Pnette E, Marchal G, Vanneste A, Geboes K, van Rijkel JP, Fevery J et al (1984) Cystadenoma of the common bile duct demonstrated by endoscopic retrograde cholangiography: an uncommon cause of extrahepatic obstruction. Am J Gastroenterol 79:466–470
Verbeeck N, Hoebeke Y (1997) Hepatic cystic mass with a daughter cyst: a feature of mucinous cystadenoma. J Belg Radiol 80:113–115
Vogt DP, Henderson JM, Chmielewski E (2005) Cystadenoma and cystadenocarcinoma of the liver: a single center experience. J Am Coll Surg 200:727–733
Waldmann J, Zielke A, Moll R, Schweinsberg TS, Rothmund M, Langer P (2006) Cystadenocarcinoma of the gallbladder. J Hepatobiliary Pancreat Surg 13:594–599
Wang Q, Yu JH, Zhai HH, Zhao QT, Chen JW, Shu L, Li DQ, Liu DY, Dong C, Ding Y (2006) Temporal expression of estrogen receptor alpha in rat bone marrow mesenchymal stem cells. Biochem Biophys Res Commun 347:117–123
Wang C, Miao R, Liu H, Du X, Liu L, Lu X, Zhao H (2012) Intrahepatic biliary cystadenoma and cystadenocarcinoma: an experience of 30 cases. Dig Liver Dis 44:426–431
Warren KW, Polk RC (1958) benign cysts of the liver and biliary tract. Surg Clin N Am 38:707
Wee A, Nilsson B, Kang JY, Tan LK, Rauff A (1993) Biliary cystadenocarcinoma arising in a cystadenoma. Report of a case diagnosed by fine needle aspiration cytology. Acta Cytol 37:966–970
Weihing RR, Shintaku IP, Geller SA, Petrovic LM (1997) Hepatobiliary and pancreatic mucinous cystadenocarcinomas with mesenchymal stroma: analysis of estrogen receptors / progesterone receptors and expression of tumor-associated antigens. Mod Pathol 10:372–379
Wheeler DA, Edmondson HA (1985) Cystadenoma with mesenchymal stroma (CMS) in the liver and bile ducts. A clinicopathologic study of 17 cases, 4 with malignant change. Cancer 56:1434–1445
Williams B (1961) Cystadenoma of the liver. Proc R Soc Med 54:157–158
Williams JG, Newman BM, Sutphen JL, Madison J, Frierson H, McIlhenny J (1990) Hepatobiliary cystadenoma: a rare hepatic tumor in a child. J Pediatr Surg 25:1250–1252
Williams DM, Vitellas KM, Sheafor D (2001) Biliary cystadenocarcinoma: seven year follow-up and the role of MRI and MRCP. Magn Reson Imaging 19:1203–1208
Willis RA (1943) Carcinoma arising in congenital cysts of the liver. J Pathol Bacteriol 50:492–495
Wolf HK, Garcia JA, Bossen EH (1992) Oncocytic differentiation in intrahepatic biliary cystadenocarcinoma. Mod Pathol 5:665–668
Wong NA, Arnott ID, Pope I, Palmer KR, Garden OJ, Thomas JS, Piris J (2001) Hepatobiliary cystadenoma with mesenchymal stroma may mimic biliary smooth muscle neoplasms. Histopathology 39:434–436
Wood JA, McLeary MS, Thomas RD, Zuppan CW (1998) Biliary cystadenoma in a child: CT and MR appearances. Pediatr Radiol 28:922
Woods GL (1981) Biliary cystadenocarcinoma: case report of hepatic malignancy originating in benign cystadenoma. Cancer 47:2936–2940
Wu CM, Fishman EK, Hruban RK, Schlott WD, Cameron JL (1999) Serous cystic neoplasm involving the pancreas and liver: an unusual clinical entity. Abdom Imaging 24:75–77
Xu HX, Lu MD, Liu LN, Zhang YF, Guo LH, Liu C, Wang S (2012) Imaging features of intrahepatic biliary cystadenoma and cystadenocarcinoma on B-mode and contrast-enhanced ultrasound. Ultraschall Med 33: E241–E249
Yamamoto M, Hagihara H, Mogaki M, Iimuro Y, Fujii H, Ainota T, Akahane Y, Matsumoto Y (1994) Adult mesenchymal hamartoma of the liver mimicking bile duct cystadenoma. J Gastroenterol 29:518–524
Yamamoto T, Fukumoto N, Ichikawa T, Hai S, Ogawa M, Tanaka S, Uenishi T, Tsukamoto T et al (2009) Huge liver abscess radiologically mimicking cystadenocarcinoma. Osaka City Med J 55:53–59
Yamasaki I, Tagata K, Hamamoto Y, Goto S (1976) An autopsy case of mucinous cystadenocarcinoma of the liver. Yonago Acta Med 20:142–146
Yamashita K, Shinozaki K, Kunitake N, Matsumoto S, Matsuura H, Nakashima A (2005) Cystadenoma of the liver with ovarian-like stroma: case report. Abdom Imaging 30:741–743
Yeh MM, Tang LH, Wang S, Robert ME, Zheng W, Jain D (2004) Inhibin expression in ovarian-type stroma in mucinous cystic neoplasms of the pancreas. Appl Immunohistochem Mol Morphol 12:148–152
Yi B, Cheng QB, Jiang XQ, Liu C, Luo XJ, Dong H, Zhang BH, Wu MC (2009) A special growth manner of intrahepatic biliary cystadenoma. World J Gastroenterol 15:6134–6136
Yoon MH, Yoon JW, Han BH (2011) Mucinous cystadenoma of the liver with ovarian-like stroma: the need for complete resection. J Korean Surg Soc 81 (suppl 1):S51–S54
Yu FC, Chen JH, Yang KC, Wu CC, Chou YY (2008a) Hepatobiliary cystadenoma: a report of two cases. J Gastrointest Liver Dis 17:203–206
Yu RS, Chen Y, Jiang B, Wang LH, Xu XF (2008b) Primary hepatic sarcomas: CT findings. Eur Radiol 18:2196–2205
Yu Q, Chen T, Wan YL, Min J, Cheng Y, Guo H (2009) Intrahepatic biliary cystadenocarcinoma: clinical analysis of 4 cases. Hepatobiliary Pancreat Dis Int 8:71–74

Yu J, Wang Y, Yu X, Liang P (2010) Hepatobiliary mucinous cystadenoma and cystadenocarcinoma: report of six cases and review of the literature. Hepatogastroenterology 57:451–455

Yu YQ, Lou BH, Yan HC, Ma R, Xu JH, Bhugowar N, Jin Y, Peng SY, Li JT (2012) Intrahepatic biliary cystadenoma presenting with pleural effusion. Chin Med J (Engl) 125:1355–1357

Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, Talamini G, Sessa F, Capella C et al (1999) Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. Am J Surg Pathol 23:410–422

Zhang M, Yu J, Yan S, Zheng SS (2005) Cystadenocarcinoma of the liver: a case report. Hepatobiliary Pancreat Dis Int 4:464–467

Zhang YL, Yuan L, Shen F, Wang Y (2009) Hemorrhagic hepatic cysts mimicking biliary cystadenoma. World J Gastroenterol 15:4601–4603

Zhou JP, Dong M, Zhang Y, Kong FM, Guo KJ, Tian YL (2007) Giant mucinous biliary cystadenoma: a case report. Hepatobiliary Pancreat Dis Int 6:101–103

Benign Epithelial Tumors and Hamartomas of the Biliary Tract

40

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_40

Abstract

The extrahepatic and intrahepatic biliary tree develops several types of benign epithelial neoplasms and hamartomas. Rarely, papillary and tubulopapillary adenomas, sometimes with a villous configuration, occur in the extrahepatic ducts. These lesions can present as solitary neoplasms, but also develop in the form of numerous lesions involving large parts of the biliary. The latter condition was previously termed biliary papillomatosis. Its relation to multiple intraductal papillary neoplasms of the bile duct (IPN-B) has to be further clarified. Small benign epithelial nodules often located in peripheral parts of the liver were termed bile duct adenoma and are now classified as peribiliary gland hamartomas. The most common variant consists of cholangiocyte-like cells. Rare variants include clear cell, oncocytic and signet-ring cell hamartomas, and a variant with endocrine features. A variant with a marked stromal component is called biliary adenofibroma. A rather common hamartoma of the liver is biliary microhamartoma (von Meyenburg complex). The hamartomas consist of a microcystic network of biliary spaces that may contain bile. These lesions occur as solitary changes or as numerous lesions that can involve both liver lobes synchronously.

Papillary Adenoma and Tubulopapillary Adenoma (Villous and Tubulovillous Adenoma) of the Bile Ducts

ICD-O codes

ICD-O Papillary adenoma	8260/0
ICD-O Tubulopapillary adenoma	8263/0

Introduction

Historically, part of biliary tract adenomas with a papillary or tubulopapillary growth pattern have been referred to as villous adenomas. This term was chosen to denote lesions with a striking gross

morphology, characterized by a growth with an arborizing structure and having a velvety surface that somewhat resembles intestinal villi. In principle, villous adenomas may be regarded as excessive forms of papillary adenomas. As numerous examples of this potentially premalignant neoplasm have been reported under the name villous adenoma instead of papillary adenoma, the main features of this lesion are summarized in this paragraph. Localized or solitary papillary (villous) adenoma in contrast to diffuse biliary papillomatosis was described as a distinct entity by Caroli and coworkers in 1959, who also defined a third papillary lesion, adenoma of the ampulla (Caroli et al. 1959). In this report, Caroli et al. also described the mucin-hypersecreting variant of bile duct adenoma.

Epidemiology

Papillary adenomas can develop at any site in the gastrointestinal tract, but they are most often encountered in the colon and rectum, less commonly in the small intestine, and very rarely in the biliary tract. Marshall (1932) reported the 20-year experience at the Mayo Clinic with bile duct tumors. In over 20,000 operations on the biliary tract, 49 cases of carcinoma were found, but only four cases of benign tumors were encountered, none of which was papillary. The first case of villous/papillary bile duct adenoma was probably reported in 1946. The patient had a recurrent "papillary adenoma" of the common hepatic duct with progressive extension into the left hepatic duct producing cholangitis, liver abscesses, and eventual death (Rogers 1946). A report of 1950 summarized a collected series of 30 well-documented tumors of the extrahepatic biliary system, and the most common type was papillary, but nine-tenths of these were located to the ampulla (Chu 1950). In 1962, 16 cases of polypoid or papillary bile duct tumors were reviewed, and among these, 14 were solitary neoplasms of the distal common bile duct in the region of the ampulla (Cattell et al. 1962). Most papillary biliary adenomas develop in ampullary region, followed by the common bile duct and the hepatic ducts. The tumor rarely also occurs in the intrapancreatic distal bile duct, cystic duct, cystic duct remnants, and choledochoceles.

Selected references: *Common bile duct* (Mendel 1987; Saxe et al. 1988; Harshfield et al. 1990; Sturgis et al. 1992; Buckley and Salimi 1993; Hanafy and McDonald 1993; De Mas 1994; Amar et al. 1996; Blot et al. 1996; Kawakatsu et al. 1997; Inagaki et al. 1999; Skelly et al. 1999; Chang et al. 2001; Ariche et al. 2002; Aggarwal et al. 2003; Goh et al. 2003; Jao et al. 2003; Fletcher et al. 2004; Xu and Chen 2008; Munshi and Hassan 2010), *common hepatic duct* (Rogers 1946; Mendel 1987; Jennings et al. 1990; Chae et al. 1999; Colarian and Wescott 2001), *hepatic ducts* (O'Shea et al. 2002), *intrapancreatic distal bile duct* (Cattell et al. 1962; Mancheron et al. 1988; Gainant et al. 1995; Aparajita et al. 2008; Kim et al. 2008), *cystic duct* (Loh et al. 1994; Ho and Lee 2006), and *cystic duct remnant* (Kunisaki et al. 2005), *within a choledochocele* (Kawakami et al. 2007).

Clinical and Imaging Features

Whereas adenomas of the gallbladder often remain asymptomatic, papillary adenomas of the extrahepatic biliary tree usually present clinical signs and symptoms, albeit after a rather long evolution. As other benign bile duct tumors (Burhans and Myers 1971), these lesions are thought to remain "dormant" for long time periods (up to 14 years) and may first cause vague symptoms due to local pressure effects (Harshfield et al. 1990). Clinical findings reported for lesions in the common bile duct comprise jaundice without fever (biliary obstruction with obstructive jaundice, Mendel 1987; Saxe et al. 1988; Jennings et al. 1990; Buckley and Salimi 1993; Chae et al. 1999; Skelly et al. 1999; Fletcher et al. 2004; Akaydin et al. 2009; Sotona et al. 2010), right-upper-quadrant abdominal pain, nausea, vomiting, and sometimes weight loss. Tumors located to the common bile duct generally mimic the signs and symptoms of an ampullary obstructing tumor. Most distally

located lesions may cause acute pancreatitis (Mancheron et al. 1988). Adenoma of the major duodenal papilla can undergo intraductal extension into the lower common bile duct (Uchiyama et al. 2008).

Diverse imaging modalities, including ultrasonography, CT, MRI, MRCP, and ERCP, have been employed in identifying these tumors with variable and overall limited success. Ultrasonography reveals an echogenic exophytic lesion associated with prestenotic bile duct dilatation. Fairly well-defined expansive solid intraductal masses without posterior acoustic shadow are rather characteristic, but may also be seen in sludge, blood clots, non-shadowing stones, and other tumors (Xu and Chen 2008). ERCP reveals a filling defect with a polypoid configuration (Mancheron et al. 1988).

Pathology

Papillary adenomas can be divided into non-mucin-secreting adenoma and mucin-secreting adenoma. Macroscopically, non-secreting adenomas are more often large lesions that have a stalk and float within the duct lumen. Specifically, large villous adenomas of the ampulla of Vater may be pedunculated lesions (Katsinelos et al. 2004). Histologically, the main feature is a growth with collections of long papillary structures with a fibrovascular core and a lining of columnar with basally place elongated nuclei. Non-mucin-secreting villous adenomas can show variable degrees of dysplasia, similar to their colorectal counterparts. High-grade dysplasia may be encountered (O'Shea et al. 2002; Goh et al. 2003), rendering the distinction from adenocarcinoma in situ difficult. Part of the adenomas contain glandular or tubular structures in addition to papillary components and are termed tubulopapillary or tubulovillous adenomas. Part of villous adenomas of the extrahepatic bile ducts are mucin-(hyper) secreting lesions (Styne et al. 1986; Doberauer et al. 1997). These tumors were first described in 1959 (Caroli et al. 1959) and may in fact represent solitary variants of intraductal papillary mucinous tumor (IPMT) (Oshikiri et al. 2002). When located in the most distal part of the common bile duct, such lesions present with a dilated orifice of Vater's papilla with mucus exiting (the fishmouth sign) and a filling defect in the bile duct (Katsinelos et al. 2006).

Bile Duct Adenomas in Familial Adenomatous Polyposis

Solitary adenomas of the extrahepatic bile ducts have been observed in few patients with adenomatous polyposis of the colon (APC). The lesions were found in the distal common bile duct (Järvinen et al. 1983). In one patient, there was diffuse polyposis involving the hepatic and common ducts (Järvinen et al. 1983). APC can also be associated with cholangiocarcinoma of the extrahepatic ducts (Spigelman et al. 1991).

Biology of Disease

Villous adenomas may undergo an adenoma-carcinoma sequence, with stepwise increase of dysplastic changes (Heidecke et al. 2002) and transition into adenocarcinoma/cholangiocarcinoma (Mendel 1987; Ariche et al. 2002; Genc et al. 2007; Aparajita et al. 2008; Kim et al. 2008). Carcinoma in situ arising in a tubulovillous adenoma of the distal common bile duct was described (Kim et al. 2008). Transition into adenocarcinoma has also been observed in villous adenoma arising in a choledochal cyst (Lee et al. 2009).

Pyloric Gland Adenoma of the Bile Ducts

Introduction

Pyloric gland adenoma is a rarely described tumor of the gastric mucosa characterized by a nodular or polypoid growth of glands resembling pyloric glands. The lesion has, however, also been detected in the gallbladder, the main pancreatic duct, the esophagus, and the bile ducts (Kushima

et al. 1996; Bakotic et al. 1999; Vieth et al. 2003; Nakayama et al. 2005). This type of adenoma has been observed in heterotopic gastric mucosa located to the duodenum (Kushima et al. 1999) or the rectum (Vieth et al. 2005). The gastric neoplasm was first described in 1976 (Elster 1976) but misinterpreted as adenoma-like hyperplasia of mucoid glands. Lesions in the stomach have a predilection in the gastric corpus, and here they are often found in patients suffering from autoimmune gastritis, but it has been suggested that many of these lesions are underdiagnosed (Vieth et al. 2003). Pyloric gland adenomas of the stomach seem to be precancerous lesions, since 30 % reveal a transition to a gastric-type carcinoma (Schmitz and Stolte 1997; Vieth et al. 2003; Kushima et al. 2006). Pyloric gland adenomas have a distinct immunophenotype. Typically, they are strongly positive for mucin 6 (deep mucoid gastric glands), and the lesions express this mucin over the whole lesion up to the surface often only with a small layer of the columnar epithelium expressing apomucin 5AC (Vieth et al. 2006).

Histopathology

Among 90 patients with pyloric gland adenomas, three had bile duct adenomas of this type (Vieth et al. 2003). The morphology is characterized by closely packed pyloric-type glands. The glands are lined by cuboidal or columnar, mucus-secreting cells with basal, round nuclei lacking atypia. The cytoplasm is pale eosinophilic. Few of the glands may form ectatic foveolae.

Immunohistochemically, the cells of pyloric gland adenomas are positive for mucin 6, with paradoxical concanavalin A staining being specific for the mucin of pyloric gland cells, mucous neck cells, and Brunner gland cells. Lesions located to the gallbladder have been shown to be reactive for MUC5A (38 %), MUC6 (100 %), human gastric mucin (HGM, 50 %), M-GGMC-1 (pyloric gland-type mucin, 93 %), and, for the biliary marker, CD10 (34 %), suggesting that these adenomas show a differentiation toward pyloric glands, but accompanied by a biliary phenotype (Nagata et al. 2007).

Pathogenesis

In contrast to the gallbladder, where pyloric gland metaplasia is well recognized, less is known in regard to glandular epithelium metaplastic changes in the large bile ducts (Hoang et al. 2001). In the latter study of 42 pancreaticoduodenectomy specimens and ten autopsy cases serving for comparison, 20/42 total resected cases (48 %) had metaplastic duct changes, and pyloric gland metaplasia was the most common type (16/20, 80 %), whereas intestinal metaplasia was seen in 5 %. Conversely, none of the autopsy cases had ductal metaplasia (Hoang et al. 2001). In an investigation focusing at intrahepatic bile ducts in hepatolithiasis, pyloric/pseudo-pyloric metaplasia was found in all cases (Kurumaya et al. 1990). Pyloric gland metaplasia, which may rarely give rise to bile duct pyloric gland-type adenoma, has been observed in association with anomalous arrangement of the pancreaticobiliary ductal system (pancreaticobiliary maljunction; Noda et al. 2007). Patients with such an anomaly also exhibit an increased proliferative activity of large bile duct epithelia (Fujii et al. 1999).

Bile Duct Adenoma (Peribiliary Gland Hamartoma, Intrahepatic Bile Duct Adenoma) and Its Variants

ICD-O Code 8160/0

Introduction

Bile duct adenoma (BDA, synonyms: peribiliary gland hamartoma, intrahepatic cholangiocellular adenoma) is a benign neoplasm derived from cholangiocytes. Recently, it has been proposed to call these lesions peribiliary gland hamartoma, based on a possibly or probable origin of the lesions from cells of peribiliary glands (Bhathal et al. 1996; Hughes et al. 2010). In regard to their location, BDAs are classified as either *intrahepatic BDA* or *extrahepatic BDA*. This paragraph refers to the intrahepatic variant, while the extrahepatic variant is discussed in the chapter on tumors of the larger bile ducts.

Epidemiology

BDAs are rare hepatic tumors and are mostly incidental lesions. They are usually solitary tumors, but may occur as multiple tumors (bile duct adenomatosis; Levin et al. 1974). In a study of 16 patients, the lesions were multiple in two (Govindarajan and Peters 1984). Rarely, BDA is combined with other liver tumors, e.g., FNH, hemangioma and angiomyolipoma (Langner et al. 2001). Because of their rarity and apparently innocuous nature, reports of BDA are rather scarce. Among 50,000 autopsies, only four cases of BDA were reported (Edmondson 1958). Gold and coworkers have reported ten cases of BDA in a review of 45 cases of benign hepatic tumors (Gold et al. 1978). In a study on 11 BDAs, the female-male ratio was 7:4, and the mean age at presentation was 57 years ± 15 SD (Guzman et al. 1977). BDA behaves in a benign way; no recurrent lesions have been observed after their resection (Anderson et al. 1992).

Selected references: Wagner 1861; Ribbert 1904; Luddecke and Yoon 1958; Gold et al. 1978; Guzman et al. 1977; Cho et al. 1978; Edmondson 1958; Govindarajan and Peters 1984; Foucar 1985; Karhunen 1986; Ishak 1988; Allaire et al. 1988; Skelly et al. 1999; Ibrarullah and Sreenivasa 2003; Kim et al. 2010; Fernandez Fernandez et al. 2015; and Chen et al. 2014.

Clinical and Imaging Findings

Due to their small size and benign biology, BDAs are in most instances asymptomatic lesions and are detected incidentally. In CT, even the typically small masses show distinct delayed or prolonged enhancement (Tajima et al. 1999). Angiographically, BDAs present as circumscript hypervascular masses with early nodular enhancement (Tajima et al. 1999; Kim et al. 2010). The nodules are enhanced in the arterial phase and hypo-enhanced in the portal venous and late phases, findings that may suggest malignancy in some cases (Ignee et al. 2009), in particular hepatic metastatic disease (Takumi et al. 2013). In MRI, the lesion was described as a well-defined mass that appears hyperintense on T2-weighted images and hypointense on T1-weighted images (Semelka et al. 1999; Boraschi et al. 2007), but other cases appeared hypointense on both T1- and T2-weighted images (Maeda et al. 2006). Prolonged ring enhancement is a typical feature (Semelka et al. 1999).

Pathology

Macroscopy

BDAs are usually subcapsular lesions and are visualized in the form of spheroid, frequently flattened nodules of gray to white color. BDAs are well circumscribed and typically nonencapsulated. They range in size from 1 mm to more than 20 mm. In a study of 152 cases, the mean diameter was 5.8 mm (Allaire et al. 1988). Exceptionally, BDA can grow to very large size, in one case with a diameter of 9.2 cm (Koga et al. 2012). Very rarely, BDA has been observed deeper within the liver substance (Otani et al. 2006).

Histopathology

The nodules consist of usually densely packed and irregular, branching bile duct-like structures, the cells of which look normal or then show only minor nuclear anomalies (Figs. 1, 2, and 3). In addition to profiles with a lumen, there are also epithelial formations that look solid and have no lumen. In contrast to biliary microhamartoma, the duct-like profiles are not cystically dilated, do not form arborizing structures, and do not contain bile (Govindarajan and Peters 1984). The cells of the ductules or tubules are cuboidal and typical for the normal cells seen in the smallest bile ducts or ductules. However, the nuclei of BDA cells may be somewhat lighter than in normal duct and ductule cells. There are varying amounts of intervening stroma which can contain sparse lymphocytic infiltrates, the latter sometimes more pronounced at the margins of the lesions (Allaire

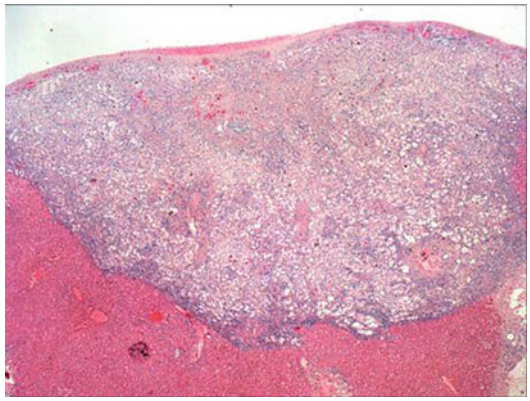

Fig. 1 Peribiliary gland hamartoma (bile duct adenoma). A subcapsular, well-delineated nodule consists of numerous small cholangiocyte tubules or ductules (hematoxylin and eosin stain)

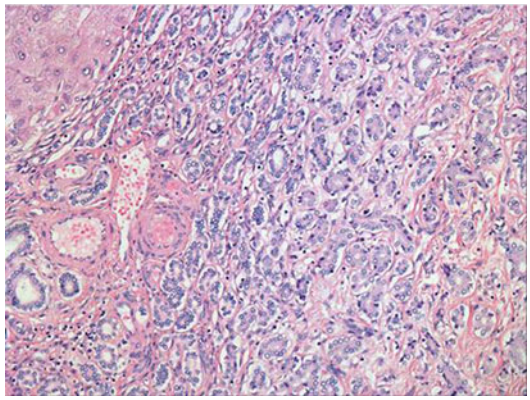

Fig. 2 Peribiliary gland hamartoma (bile duct adenoma). There is a dense collection of homogeneous cholangiocyte tubules without atypia. A portal tract with an interlobular bile duct is seen to the extreme left of the figure (hematoxylin and eosin stain)

et al. 1988). The interface to adjacent liver substance is smooth at low magnification, but shows a finely jagged border at higher magnification, caused by interdigitation of ducts and stroma with parenchyma. This spectrum of changes may render it difficult to distinguish BDA from well-differentiated cholangiocarcinoma, particularly in intraoperative frozen sections (Albores-Saavedra et al. 2001). BDA may undergo secondary changes, such as calcification (Maeda et al. 2006) and hyalinization.

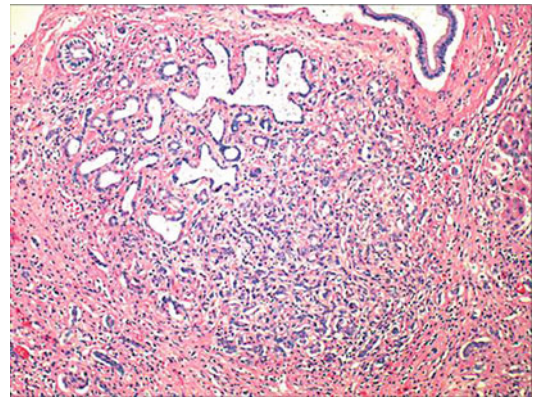

Fig. 3 Peribiliary gland hamartoma (bile duct adenoma) combined with biliary microhamartoma (hematoxylin and eosin stain)

Immunohistochemical Phenotype of BDA

The immunophenotype of BDA epithelial cells is similar to that of normal ductules and interlobular bile ducts (Allaire et al. 1988; Lai et al. 1989; Van Eyken et al. 1991). Expectedly, the cells are markedly reactive for cytokeratins 7 and 19, however, with some variation in staining from one tubular profile to the other (Fig. 4). Part of BDAs also express epithelial membrane antigen (EMA), with a luminal- and cytoplasmic-type staining pattern, whereby the luminal type resembles a ductular reaction and the cytoplasmic-type interlobular bile ducts (Aishima et al. 2014). BDAs have been found to express five foregut antigens, i.e., MUC6 (94 %), MUC5AC (90 %), TFF2 (80 %), D10 (67 %), and 1F6 (61 %); 40 % of BDAs expressed all of these five markers. The findings suggest that BDA displays the same phenotype as pyloric gland metaplasia and that the lesions might represent a localized biliary healing response equivalent to the function of a peribiliary gland or pyloric gland metaplasia in the foregut (Hughes et al. 2010). On the other hand, BDA and peribiliary glands both express two foregut antigens, i.e., D10 and 1F6, and are characterized by the secretion of acid mucin. Peribiliary gland cells invariably expressed D10, 1F6, MUC6, and TFF2, while expression of MUC5AC was only

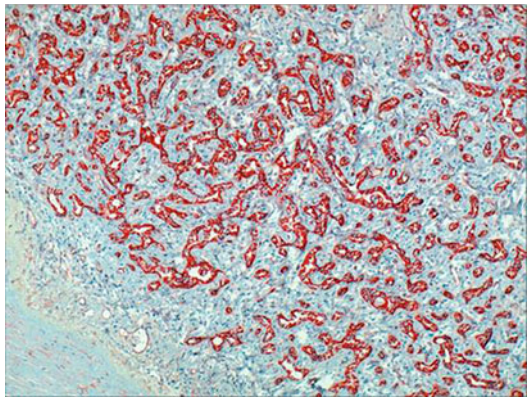

Fig. 4 Peribiliary gland hamartoma (bile duct adenoma) with strong and diffuse expression of cytokeratin 19 (CK 19 immunostain)

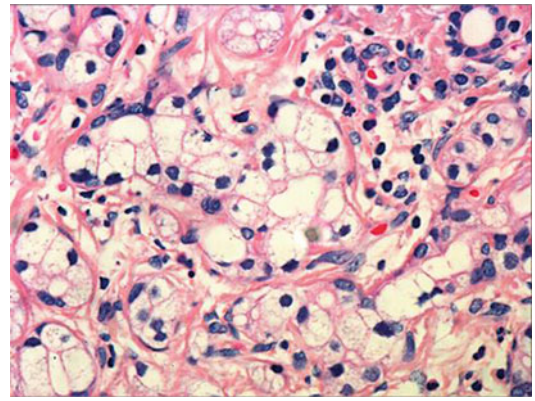

Fig. 5 Peribiliary gland hamartoma (bile duct adenoma), clear cell type. The large cells have a clear or slightly vacuolated cytoplasm. Many of the small nuclei are excentrically placed (hematoxylin and eosin stain)

found in inflamed, but not in normal, peribiliary glands. Most BDAs express MUC6, MUC5AC, and TFF2, while about two thirds of these lesions are reactive for D10 and 1F6, suggesting a relationship between BDA and peribiliary glands (Hughes et al. 2010). More than 80 % of BDAs expressed the senescence marker p16(INK4a), much more frequently than cholangiocarcinoma (Sasaki et al. 2014). The majority of BDAs were found to be reactive for CD56, whereas von Meyenburg complexes expressed CD56 only very focally in less than 5 % of lesional cells, and only very few cholangiocarcinomas were positive in part the carcinomas with a clear cell morphology (Gütgemann et al. 2006). BDAs have been found to have an exceedingly low proliferation activity as based on Ki-67 immunostaining (Tan et al. 2004). In contrast to the malignant counterpart, cholangiocarcinoma, BDA cells are not immunoreactive for the glucose transporter protein 1 (Glut-1; Zimmerman et al. 2002). In contrast to cholangiolocarcinoma, BDA is not reactive for the polycomb protein EZH2 (Sasaki et al. 2014).

BDA, Clear Cell Type

In 2001, three examples of an unusual variant of BDA were reported (Albores-Saavedra et al. 2001). All three tumors were incidental findings occurring in two males and one female (age range, 25–64 years). The lesions measured from 0.8 to 1.1 cm and represented atypical BDA histologically characterized by clear cells that closely resembled metastatic renal cell carcinoma (Figs. 5 and 6). The neoplasm was, therefore, termed atypical BDA, clear cell type (Albores-Saavedra et al. 2001). As described in the original report, this variant of BDA is immunoreactive for CK 7, epithelial membrane antigen (EMA), CEA, and p53 protein (Albores-Saavedra et al. 2001). CK19 reactivity is also observed (Fig. 6). This rare tumor has since been observed by other investigators (Wu et al. 2014).

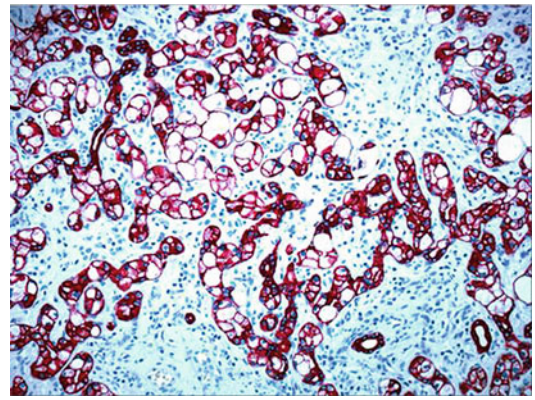

Fig. 6 Clear cell variant of peribiliary gland hamartoma (bile duct adenoma), cytokeratin 19 expression (CK19 immunostain)

BDA, Oncocytic Type

Rarely, the epithelial cells of BDA undergo oncocytic change (oncocytic BDA, BDA with oncocytic features; Figs. 7 and 8; Arena et al. 2006; Hastir et al. 2013; Johannesen et al. 2014). In one case, the tubular epithelium of the nodular lesion was composed of a homogeneous population of cells with abundant, granular, and eosinophilic cytoplasm. The nuclei were small to medium in size and centrally located, and nucleoli were not detectable. Occasional binucleated cells were noted. A lymphocytic infiltration was present in the stroma (Arena et al. 2006).

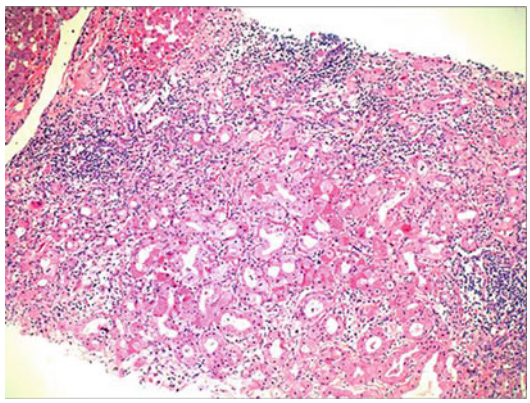

Fig. 7 Peribiliary gland hamartoma (bile duct adenoma), oncocytic variant (needle biopsy, hematoxylin and eosin stain)

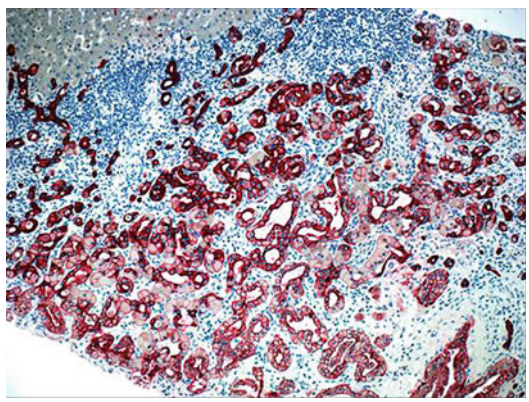

Fig. 8 Peribiliary gland hamartoma (bile duct adenoma) with focal oncocytic features. In this cytokeratin 19 stain, oncocytic elements show reduced and only membranous staining in comparison with non-oncocytic cells (CK 19 immunostain)

BDA, Signet-Ring Cell Type

This variant of BDA is characterized by the presence of PAS-positive diastase-resistant intracytoplasmic globules conferring a signet-ring appearance to the cells. In one case, similar globules were found in the biliary epithelium in the peritumoral portal tracts and in periportal hepatocytes. All these inclusions were strongly positive for alpha-1-antitrypsin, and the patient had the heterozygous M (Malton) genotype (Gambarotti et al. 2008).

BDA with an Endocrine Component

A subset of BDA contains, in addition to the typical small caliber ducts/ductules, periductular nests and clusters of endocrine cells (O'Hara et al. 1992). It was shown that these cell nests decorate with several endocrine markers, including NSE, chromogranin, synaptophysin, and Leu-7, and these (neuro-) endocrine proliferations morphologically resemble pulmonary tumorlets (O'Hara et al. 1992).

Bile Duct Adenoma: A Lesion Associated with Malignancy?

In one case, a BDA was found to have atypical ductular profiles, with cells showing hyperchromatic large nuclei. At the periphery of the lesion, the ductules revealed an invasive behavior. The findings were interpreted to be cholangiocarcinoma arising in BDA (Hasebe et al. 1995). One patient with biopsy-diagnosed BDA described in 1978 (Gold et al. 1978) was followed up. Fifteen years after the lesion was first documented, the female patient died of her tumor. At autopsy, the 8,600 g liver was extensively replaced by a bile duct neoplasm, and there were metastases in the lungs and in lymph nodes. In

most areas, the histologic appearance of the tumor at autopsy showed the same bland appearance demonstrated earlier in the disease course. This situation made it difficult to decide whether to classify this neoplasm as a very unusual cholangiocarcinoma or a BDA (as originally diagnosed) with malignant transformation (Foucar 1985). However, it was argued in a letter that this lesion might not have been bona fide BDA (Govindarajan 1985). Another patient with multiple BDAs was reported to have developed an asymptomatic cholangiocarcinoma, identified at autopsy 10 years after the diagnosis of the BDAs (Bornfors 1984).

Differential Diagnosis

Histologically, BDA of the common, "ordinary" type may be confounded with biliary microhamartoma (von Meyenburg complex) or small, peripheral well-differentiated intrahepatic cholangiocarcinoma.

Pathogenic Pathways

The etiology and pathogenesis of BDA are not clear. Different from liver cell adenoma, BDAs do not exhibit a relationship to oral contraceptive intake (Guzman et al. 1977). There is one case report describing the synchronous occurrence of BDA ("cholangioma") and cholangiocarcinoma several decades after thorotrast administration (Sachs and Encke 1991).

Bile Duct Adenofibroma

Introduction

Biliary adenofibroma (BAF) is a very rare benign neoplasm of bile duct origin with an indolent behavior (Tsui et al. 1993), histologically somewhat resembling biliary hamartoma. Since 1993, less than ten cases have been reported (Parada et al. 1997; Garduno-Lopez et al. 2001; Haberal et al. 2001; Akin and Coskun 2002; Varnholt et al. 2003; Gurrera et al. 2010). The variegated histologic presentation in regard to the amount of stroma present may render it difficult, and sometimes arbitrary, to distinguish BAF from bile duct adenoma with marked stromal reaction or from hepatobiliary cystadenoma with mesenchymal stroma. Cytogenetically, monosomy 22 has been detected in one case of biliary adenofibroma (Parada et al. 1997).

Pathology

In the index patient (Tsui et al. 1993), a wedge resection from the right liver lobe contained a circumscribed, nonencapsulated tumor that abutted on the hepatic capsule, causing a smooth protuberance. The spherical mass had a diameter of 7 cm and a spongy cut surface with multiple, closely apposed, thin-walled, round-to-oval cysts ranging from 1 to 5 mm. The cystic structures were assembled into lobular aggregates by slender septa. The remainder of the tumor consisted of a compact stromal mass. Histologically, tubules (in part branched), glandular profiles, and cysts were embedded in an abundant fibrous vascularized stroma and were lined by flattened to cuboidal cells of biliary type (Figs. 9 and 10). Microcysts can show polypoid projections into their locules or reveal an apocrine-like epithelial configuration. Few tubules contain debris or bile concretions. The poorly vascularized stroma was fibroblastic and highly collagenous, albeit with only focal sclerosis. A modest, patchy inflammatory cell infiltrate is present in the stroma, consisting predominantly of lymphocytes.

Immunohistochemically, the tubular profiles share a cytokeratin expression phenotype with that of interlobular or larger intrahepatic bile ducts, i.e., reactivity for CK7 and CK19 and EMA (Gurrera et al. 2010), suggesting that BAF is derived from this biliary duct system

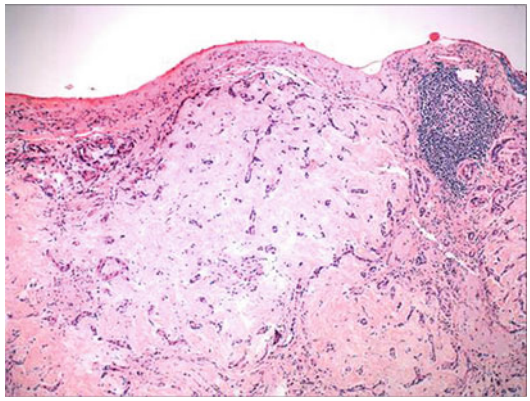

Fig. 9 Adenofibroma of the bile duct. The hypocellular subcapsular fibrous nodule contains only a few bile ductule-like profiles. Note that accompanying lymph follicle with a germinal center (hematoxylin and eosin stain)

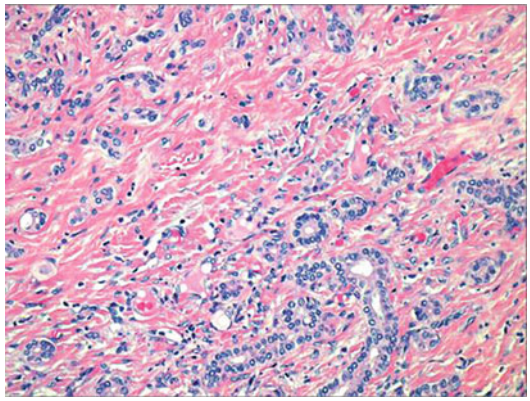

Fig. 10 Adenofibroma of the bile duct. Bile ductule-like profiles are embedded in a collagenous matrix (hematoxylin and eosin stain)

(Tsui et al. 1993; Varnholt et al. 2003). The stromal cells are strongly and diffusely positive for alpha-smooth muscle actin, suggesting their myofibroblastic nature (Gurrera et al. 2010).

Malignant Evolution of Biliary Adenofibroma

In rare instances, BAF may recur, and very few reports have described malignant transformation of such lesions (Haberal et al. 2001; Akin and Coskun 2002). In one case, diagnostically confirmed by biopsy, the lesion grew to a size of 20 cm, with central necrosis and hepatic and pulmonary metastases (Akin and Coskun 2002).

Variants of Biliary Adenofibroma

Apart from classical adenofibroma, lesions resembling this rare growth occur and may pose differential diagnostic difficulties. Kai and coworkers (2012) described a tumor of 7-cm diameter presenting as a multicystic mass. The cystic part of the tumor was composed of locules lined by biliary epithelium with variable atypia, papillary growth, and apocrine snouts. The solid part revealed a tubulocystic proliferation of tumor cells embedded in a dense and partly hyalinized stroma. The lesion was classified as a multicystic biliary tumor with adenofibroma features.

Multicystic Adenofibroma-Like Tumor of the Bile Duct

Introduction

This type of multicystic tumor was observed in an 40-year-old Japanese man, whereby abdominal CT revealed a well-circumscribed multicystic mass measuring approximately 7 × 6 cm (Kai et al. 2012).

Histologically, the tumor was composed of a cystic and a solid lesion. The multicystic part exhibited locules lined by cholangiocyte-like cells with various cytological atypia. The stroma was fibrous and the neoplastic cells showed marked apocrine snouts. Part of the tumor showed a papillary growth with more pronounced cytological atypia. The solid component displayed a tubulocystic proliferation of neoplastic cells, again with prominent apocrine snouts, embedded in dense and partially hyalinized fibrous stroma. This solid part resembled biliary adenofibroma (Kai et al. 2012).

Bile Duct Hamartoma (Biliary Microhamartoma)

Introduction

Bile duct hamartoma (BDH, synonyms: biliary hamartoma, biliary microhamartoma, von Meyenburg complex, biliary cholangiomatosis, minute bile duct adenomas, fibroadenomata, intracapsular aberrant bile ducts) is, according to WHO, defined as a benign lesions consisting of a collection of bile ducts set in a fibrous stroma which is frequently hyalinized. The term now used to designate this lesion has a spectrum of earlier synonyms, as exemplified in the title of the chapter. BDH and its relation to other benign hepatic biliary tumors have recently been reviewed (Tsui 1998). BDHs are clearly nonneoplastic nodules, and their pathogenesis, although not yet fully clarified, seems to be related to a disordered construction of the ductal plate. The recognition of this type of lesion goes back to von Meyenburg, who in 1918 described groups or clusters of small bile ducts in lover lobules separate from portal tracts and interpreted these as being vestigial intrahepatic bile ducts that had formed normally in the embryo, but failed to involute after birth to then undergo cystic dilatation (Von Meyenburg 1918). Hanns (with two n's) von Meyenburg (1887–1971) made his medical thesis in Zurich in 1912; worked under the surgeon, Ernst Ferdinand Sauerbruch; became full professor of pathology at Lausanne in 1921; and then followed a call to the pathology chair at Zurich in 1925 (Uehlinger 1972). The lesions having his eponym were described in an article on polycystic liver disease in 1918.

What is a hamartoma? The term, hamartoma, was introduced in 1904 (Albrecht 1904) to designate a tumor-like malformation. A hamartoma is basically a malformative lesion resembling a tumor and having many features of a tumor, without being neoplastic. It is a focal, often circumscribed overgrowth in improper proportions of tissues normally present in that part of the body. Eugen Albrecht (1872–1908), who created the entities hamartoma and choristoma, was a German pathologist appointed to succeed Weigert as director of the Senckenberg Institute of Pathology. He is the founder of the Frankfurter Zeitschrift für Pathologie (1907). Pulmonary tuberculosis caused his untimely death at the age of only 36 years (Ober 1978). In his 1904 article, Albrecht wrote: "One has to distinguish a novel class of tumors distinct from neoplasms. For these I wish to introduce two new terms:(1) Choristoma (from Greek: 'to separate'), i.e. tumor-like formations located in abnormal places but true parts of these organs : normal tissues abnormally placed; (2) Hamartoma (from Greek: 'to err'), i.e. tumor-like formations in which we can demonstrate abnormal mixture of normal components of the organ in which they occur either by amount, structure, degree of maturity or all three together. . .We can assume that the formation of these above growths took place by abnormal mixing or fundamental disturbance in the course of development" (Ober 1978). It is seen that this was a modern concept of abnormal tissue development, and bile duct hamartoma is in fact an excellent example for the original description as to what a hamartoma is.

Epidemiology

In a series of 1697 consecutive liver needle biopsies, a total of six patients or 0.35 % were confirmed by histology to have BDH (Lin et al. 2013). In autopsy investigation, the incidence of these lesions is somewhat higher. In a large series of autopsies, BDHs were found in 0.69 % (Chung 1979). In another study of 2,843 autopsies, 157 cases having BDH or cysts in the liver were identified. The prevalence of BDH increased with age, an increase found in both sexes, and similar trends were seen if solitary BDH or multiple BDHs were considered separately. BDHs were found in 5.6 % of adults and 0.9 % of children, and macroscopic hepatic cysts were detected in 16.9 % of livers that also had BDH; of livers with hepatic cysts, 73.5 % also had BDH, and among

adults with APKD, BDHs were observed in 97 % (Redston and Wanless 1996). Based on these observations, these authors allocated BDH to three types, namely, type I (BDH with APKD), type II (BDH with liver cysts and without APKD), and type III (BDH without APKD or liver cysts). Overall, the data support a pathogenetic association of BDH and cystic liver disease, but the authors also concluded that, as APKD could account for only 11 % of the patients with BDH, such lesions occurring in the absence of APKD are a manifestation of a different disease. In regard to the incidence in biopsies, 12/2,000 (0.6 %) needle biopsies showed a total of 15 BDHs (as two biopsies contained two and three BDH, respectively; Thommesen 1978).

Patterns of Presentation: Solitary vs. Multiple Lesions

BDH can present as a solitary mass (Shin 2011), sometimes mimicking a liver neoplasm. The presence of multiple BDH lesions (multiple biliary hamartomatosis), usually with a diameter of about 5–8 mm, is a rather frequent finding which has repeatedly been described, sometimes as an incidental finding, but lesions mimicking hepatic metastatic disease, small liver abscesses, or dilated intrahepatic ducts in other instances. In cases where numerous small lesions were observed, the term "diffuse miliary benign fibrocholangioma" had been used by Caroli and coworkers (1974).

Selected references: Chung 1970; Eisenberg et al. 1986; Arenson et al. 1988; Mauri et al. 1988; Martinoli et al. 1992; Slone et al. 1993; Sada and Ramakrishna 1994; Bravo and Laing 1994; Lev-Toaff et al. 1995; Gallego et al. 1995; Iha et al. 1996; Wei et al. 1997; Bastart et al. 1998; Wohlgemuth et al. 1998; Luo et al. 1998; Semelka et al. 1999; Duran-Vega et al. 2000; Chen et al. 2000; Alazmi et al. 2002; Orlandi et al. 2002; Bruegel et al. 2005; Panaro et al. 2004; Hettinger et al. 2005; Davidoff et al. 2006; Kai et al. 2008; and Beltran Romero et al. 2009.

Clinical and Imaging Features

Many, if not most, BDHs are incidental findings. The lesions are seen in hepatic imaging performed for other reasons and/or are seen during laparoscopy or upper abdominal surgery. In a minority of cases, diffuse abdominal pain and discomfort or signs reminiscent of cholangitis were observed (Sinakos et al. 2011). Larger lesions can cause nonspecific upper-quadrant discomfort, and multiple BDHs may induce portal hypertension (Yoshida et al. 2009).

BDHs have a rather characteristic presentation in US, CT, and MRI imaging (Eisenberg et al. 1986; Vogel et al. 1986; Cooke and Cooke 1987; Arenson et al. 1988; Evans et al. 1989; Tan et al. 1989; Niizawa et al. 1991; Martinoli et al. 1992; Slone et al. 1993; Brunner et al. 1994; Bravo and Laing 1994; Sada and Ramakrishna 1994; Gallego et al. 1995; Cheung et al. 1997; Wohlgemuth et al. 1998; Luo et al. 1998; Maher et al. 1999; Chen et al. 2000; Chen and Goldstein 2002; Mortelé et al. 2002; Mendez-Sanchez et al. 2003; Martins Machado et al. 2003; Neri et al. 2004; Zheng et al. 2005). It has, however, been emphasized that definitive diagnosis could only be obtained by the use of histologic examination (Principe et al. 1997). In US, scattered hypoechoic or hyperechoic lesions (with or without posterior acoustic reverberation) are noted. Lesions studied so far in more detail were hypoechoic in two reports (Eisenberg et al. 1986; Martinoli et al. 1992), hyperechoic in one report (Tan et al. 1989) and mixed hypo- and hyperechoic in a further report (Slone et al. 1993). Multiple lesions may be more readily detectable in US than solitary lesions (Vogel et al. 1986; Markhardt et al. 2006). Contrast-enhanced sonography has been found to detect very small BDHs, but the findings may be confounded with malignancy (Hohmann et al. 2009). CT reveals well-outlined hypodense areas or nodules that fail to take up contrast medium (Eisenberg et al. 1986; Cooke and Cooke 1987; Arenson et al. 1988; Tan et al. 1989; Salo et al. 1992; Ryu et al. 2010), with the exception of one case in which enhancement with IV

contrast material was reported (Martinoli et al. 1992). In a study of 18 patients who covered a broad spectrum of lesions, ranging from one or two BDHs to innumerable lesions, all cases were hypodense on contrast-enhanced CT scans and hypoechoic on sonograms (Lev-Toaff et al. 1995). Multicystic forms may occur (Ryu et al. 2010), with dilatation of the duct-like structures. The small lesions (typically <1.5 cm) usually have a high signal intensity on heavily T2-weighted images and coronal MR cholangiography, corresponding to low signal intensity on T1-weighted images (Bruegel et al. 2005; Tohmé-Noun et al. 2008; Dilli et al. 2012; Gong et al. 2012; Lung et al. 2013). Gadolinium enhancement may be useful for better resolution of the lesions (Semelka et al. 1999). Multiple lesions may mimic diffuse hepatic metastases (Guiu et al. 2009; Madhusudhan and Das 2009). The angiographic appearance of BDH was characterized by abnormal vascularity, consisting of grape-like clusters of small rings, which could be confused with other benign and malignant conditions demonstrable by angiography (McLoughlin and Phillips 1975). It has been suggested that lesions seen on CT images may represent either solitary lesions or aggregates of multiple BDHs, and there was no correlation between the presentation on imaging and the morphotype of the lesions (Lev-Toaff et al. 1995).

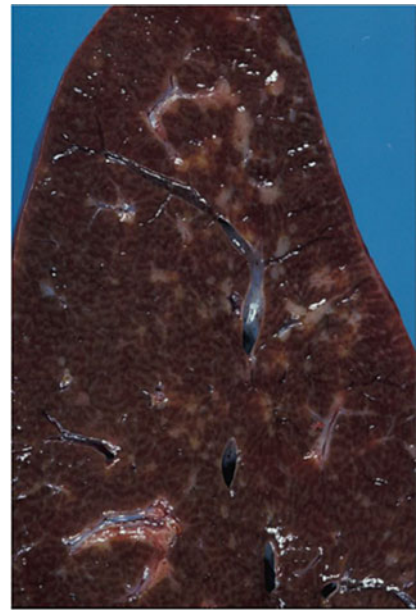

Fig. 11 This liver with signs of chronic congestion exhibits numerous whitish parenchymal lesions representing multiple biliary microhamartomas

Pathology

Macroscopy

BDHs are usually small or very small lesions, however, clearly detectable with the naked eye. They are small, rather well-defined spheroid nodules that are usually creamy white in unfixed specimens, sometimes with bulging after sectioning, and whitish-gray after fixation (Fig. 11). Lesions located to the subcapsular space may show a flat dimple or may exhibit umbilication, particularly in larger nodules. A gross resemblance to small metastases or granulomas is sometime striking, also during laparoscopy (Ioannidis et al. 2012), whereas microabscesses are distinguishable owing to their yellow rather than white color. Typically, BDFs do not leave fluid on the knife upon sectioning. In a study of 18 cases where both pathologic and radiologic informations were available, the lesions varied in size from ≤1 to 1.5 cm in diameter. In six patients, the lesions were less than 1 mm in diameter; in eight they were 1–5 mm; in two, 6–10 mm; and in two, 1–1.5 cm (Lev-Toaff et al. 1995). One report described nodules ranging in size from 0.7 to 3.0 cm (Martinoli et al. 1992). In larger peripheral BDH, the liver capsule may be retracted. Rarely, BDHs present as dark or even "black" nodules on a smooth liver surface, owing to the accumulation of thickened bile within the ductular lumina (Ohta and Ushio 1984). Rare variants of BDH show clusters of macroscopically visible cysts measuring up to 1.2 cm in diameter (macrocystic BDH; Kobayashi et al. 2005).

In regard to the distribution within the organ, many lesions seem to be located to the periphery or even the subcapsular compartment of the liver, visible at laparoscopy (Henning et al. 1982), but this may be biased by sampling and visibility from outside the organ. It has in fact been suggested

that the distribution of BDH is consistently uniform throughout the liver (Slone et al. 1993).

Histopathology

The main histologic features of BDH are characteristic and allow the morphologic diagnosis in needle biopsies (Figs. 12 and 13; Thommesen 1978; Bhusnurmath et al. 1980). They comprise an apparently frequent peripheral and, even more typically, subcapsular and less frequently deeper distribution (the latter particularly in cases of polycystic disease; see below), but this may not be true because deeper lesions may be missed owing to sampling reasons: a close relation to portal tracts in deep-seated lesions, nonencapsulated but relatively well-circumscribed boundaries, a complex network of dilated small duct-like profiles embedded in a sometimes fibrotic stroma that may be hyalinized, visible communications between the profiles and adjacent small bile ducts (Chung 1970), and variable amounts of mainly lymphocytic infiltrations in the matrix (mostly of low density). The lumina of the duct-like structures look ramified and are tubular or cleft shaped, with varying degrees of dilatation. The epithelium lining the duct-like profiles is cubic to low columnar, and there is, similar to normal bile ducts, only slight variation in the height of the epithelial cells within a single lesion, but the epithelium characteristically higher in small BDH than in larger lesions (Thommesen 1978). In most cases, a close spatial relationship to portal tracts is seen.

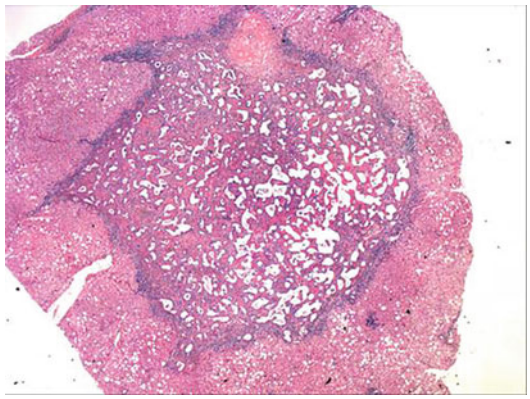

Fig. 12 Biliary microhamartoma (von Meyenburg complex). The well-delineated lesion consists of numerous microcystically dilated ductular profiles. Lymphocytic infiltration is present at the level of the lesion interface (hematoxylin and eosin stain)

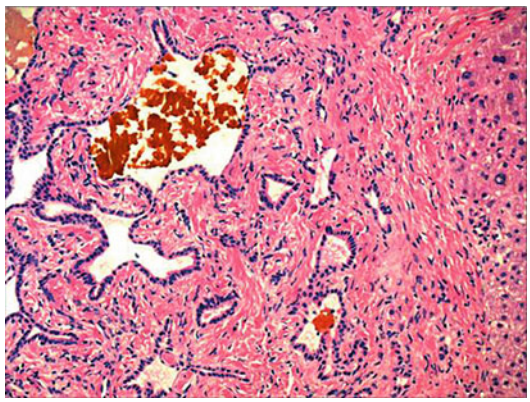

Fig. 13 Biliary microhamartoma (von Meyenburg complex). Irregular and communicating cystic spaces with a normal-looking cholangiocyte lining are embedded in a fibrous matrix. The spaces can contain bile (hematoxylin and eosin stain)

In a biopsy series, all BDHs were located interlobularly in close relation to portal tracts, and the connective tissue of the BDH always merged directly with the connective tissue of the adjacent portal tracts (Thommesen 1978). In serial sections, a communication between all the lumina in each BDH was in fact proven (Thommesen 1978; Ohta and Ushio 1984). The lumina of the cystically dilated ducts of BDH are either empty or contain an amorphous or thready material, or pale to dark, inspissated bile, and sometimes even bile plugs or bile-containing concrements (Thommesen 1978; Röcken et al. 2000). Rarely, intraluminal dystrophic calcifications were found, also visualized as punctiform calcified lesions on CT images (Gil-Bello et al. 2012). The partly hyalinized connective tissue contains only a few visible blood vessels without sclerosis of the walls. At the periphery of the lesions, biliary ductules may be found, sometimes interdigitating with adjacent hepatic parenchyma (Thommesen 1978). At least one report described the presence of nerves within the lesions (autopsy case; Honda et al. 1986). BDH can rarely occur together with a lesion representing to morphology of bile duct

adenoma (Hasebe et al. 1995). Based on the morphology of the biliary channels seen within BDH, the lesions have been attributed to class 1 (solid lesions with narrow bile channels), class 2 (intermediate, the most frequent one), and class 3 (predominantly cystic lesions with prominent dilated bile channels; Lev-Toaff et al. 1995). In one case, BDH was associated or complicated with microscopic polyangiitis (Sato et al. 2013).

The fact that BDH can contain bile supports the view that these lesions are in continuation with structures physiologically transporting bile. Already von Meyenburg found a communication between all the lumina of the single lesions, but did not examine connections to adjacent bile ducts (Von Meyenburg 1918). Later authors found areas of direct transition from liver cell plates to the epithelium of some BDH (Melnick 1955; Chung 1970). The spatial relationship between the ductular profiles of BDH and the resident intrahepatic bile ducts has been studied by the use of histological reconstruction (Ohta and Ushio 1984). These authors observed spicular branches from the BDH penetrated into the liver parenchyma to form what appeared to be canalicular junctions with liver cell plates, and the tubular branches of the hamartoma were in direct contact with ordinary small, terminal bile ducts of neighboring portal tracts. From this observation the authors suggested that BDH is an equivalent of a functioning bile duct (Ohta and Ushio,1984). The finding of such communications has been confirmed in a later microanatomical study of samples from polycystic disease (Grimm et al. 1990).

Immunohistochemistry

Immunohistochemically, the cells of the duct-like profiles are, expectedly, reactive for the biliary-type cytokeratins, CK7 and CK-19 (Pontisso et al. 1993). BDHs also express MUC1 apomucin, but less or not mature MUC1 mucin, suggesting an immature phenotype of the biliary epithelium involved (Sasaki and Nakanuma 1996). Only a minority of BDHs are immunoreactive for CD20 (10 %), and they are negative for mCEA, p63, and p53 protein (Hornick et al. 2005). In contrast to cholangiocarcinoma that reveals immunostaining for glucose transporter protein 1 (Glut-1) in 50 % of cases, no Glut-1 staining was found in BDH, similar to bile duct adenomas that also fail to be reactive (Zimmerman et al. 2002). In contrast to malignant epithelial tumors of the liver, including cholangiocarcinomas, BDH cells are not reactive for enhancer of zeste homologue 2/EZH2 (Hajosi-Kalcakosz et al. 2012).

Is BDH a Precancerous Lesion?

Several observations have documented an association of BDH with hepatic malignancy, specifically intrahepatic cholangiocarcinoma and perihilar cholangiocarcinoma with features that are not different from cholangiocarcinoma in general (Lindgren et al. 1961; Homer et al. 1968; Börnfors 1984; Honda et al. 1986; Dekker et al. 1989; Burns et al. 1990; Hasebe et al. 1995; Yaziji et al. 1997; Kim et al. 1999; Blanc et al. 2000; Jain et al. 2000; Röcken et al. 2000; Wisniewski et al. 2002; Orii et al. 2003; Eguchi et al. 2004; Song et al. 2008; Droy et al. 2009; Xu et al. 2009; Takahashi et al. 2010). This is of interest in the light of the generally increased incidence of biliary malignancies in developmental disorders of the bile duct system, including polycystic liver disease, Caroli's disease, choledochal cyst, abnormal biliopancreatic junction syndrome, and ductal plate malformations (Willis 1943; Daroca et al. 1975; Bloustein 1977; Flanigan 1977; Tsuchiya et al. 1977; Kagawa et al. 1978; Scott et al. 1980; Landais et al. 1984; Baumann et al. 1987; Yamato et al. 1998; Totkas and Hohenberger 2000). It seems that cholangiocarcinoma was more frequently observed in situations where multiple BDHs are present (Homer et al. 1968; Börnfors 1984; Honda et al. 1986; Dekker et al. 1989; Burns et al. 1990; Yaziji et al. 1997; Röcken et al. 2000). Furthermore, at least three observations document the association of cholangiocarcinoma or hepatocellular carcinoma and BDH in the setting of hemochromatosis (Yaziji et al. 1997; Blanc et al. 2000; Wisniewski et al. 2002).

Few reports described an association of BDHs with hepatocellular carcinoma (Heinke et al. 2008; Jain et al. 2010). It is currently unknown whether this is an incidental association or whether the association reflects a pathogenic link between the two lesions. A unique case of an adenocarcinoid, positive for chromogranin A and gastrin, arisen in an area of a large biliary hamartoma has been reported (Papadogiannakis et al. 1996). What are the arguments for an eventual hamartoma-carcinoma sequence? Histologically, a gradual transition from BDH to hyperplastic or adenomatous lesions, carcinoma in situ, and cholangiocarcinoma have been suggested as evidence for a "neoplastic transformation" of BDH (reviews of the literature: Röcken et al. 2000; Jain et al. 2000), suggesting a hamartoma-dysplasia-carcinoma sequence. In fact, dysplastic features of biliary epithelia in BDH associated with cholangiocarcinoma were reported by several publications (Homer et al. 1968; Burns et al. 1990; Hasebe et al. 1995; Yaziji et al. 1997). In an autopsy case, the stroma surrounding BDHs showed infiltrating carcinoma, characterized by nests of pleomorphic cells which often formed rudimentary ductal structures, and areas of transition between seemingly benign and clearly malignant epithelium were found occasionally (Honda et al. 1986).

Differential Diagnosis

The histologic differential diagnosis of BDH includes bile duct adenoma and adenofibroma. Moreover, BDH might be confounded with situations of ductular proliferation/reaction occurring in several disorders, including biliary obstruction and hepatic remodeling. Bile ductular hyperplasia may also occur as an isolated phenomenon in patients with persistently abnormal liver function tests (idiopathic isolated ductular hyperplasia; Sonzogni et al. 2004). Abnormal bile duct profiles developing in congenital liver fibrosis may mimic BDSH, but are easily identified owing to the characteristic concentric arrangement of ductal plate derivatives. Microcystic lesions histologically similar to BDH have been observed subsequent to hepatic ischemia (including liver infarcts) and ischemic bile duct damage ("ischemic cholangitis") caused by arteritis, in particular polyarteritis nodosa (Popovsky et al. 1979; Doppman et al. 1979; Amir et al. 1984; Chang et al. 2003) and, very rarely, temporal arteritis (Rousselet et al. 1989). That ischemic bile duct injury can induce cystic alterations of small bile ducts has also been documented by experimental small vessel hepatic artery occlusion in an animal model (Doppman et al. 1979). Multiple BDHs can mimic diffuse hepatic metastases (Nagano et al. 2006; Salles et al. 2007; Fuks et al. 2009; Singhal et al. 2010). Histologically, specifically in biopsies, BDH may be confounded with metastases of tubular adenocarcinomas, in particular ductal carcinoma of the pancreas. In cases of doubt, immunohistochemistry may help in the differential diagnosis. It has been found that p53 protein, TAG-72, mCEA, and mesothelin had the highest specificity for pancreatic adenocarcinoma, with mCEA having the highest sensitivity (92 %). No significant differences were observed in the degree of CK7, CK8/CK18, CK19, or pCEA expression between metastatic adenocarcinoma and BDH (Hornick et al. 2005). Rarely, BDH has mimicked other cystic hepatic tumors, e.g., biliary cystadenocarcinoma (Karahan et al. 2007).

Pathogenetic Considerations

Based on the morphologic presentation, there seems to be some analogy of BDH and remodeling of the primitive human biliary system (Desmet 1998; Sergi et al. 2000; Awasthi et al. 2004).

Association of BDH with Adult Polycystic Liver Disease

An association between adult polycystic disease and BDH has been noted since long (Melnick 1955; Naim et al. 1987) and has more recently studied in detail (Grimm et al. 1990; Redston and Wanless 1996; Lalosevic et al. 2005). In polycystic livers, the frequently multiple BDHs are

grossly visualized as small whitish nodules in the septal-like structures situated between the cysts, and histologically a close spatial relationship between the hamartomas and the cyst walls is seen. It seems that BDHs in polycystic liver disease (PLD) are related to the evolution of disease. The relationship between BDH and adult PLD was studied in a series of ten autopsy cases. BDHs were found in every case and were the most abundant in livers with cyst size of 1 cm or less and were rare in cases with the largest cysts, suggesting that BDHs prevail in early phases of PLD and that they might transform into cysts (Karhunen 1986). Another study also described that the density of BDH and the stage of PLD in ADPKD were strongly correlated and that 41.4 % of the hepatic cysts were connected to BDH (Ramos et al. 1990), suggesting that hepatic cysts in ADPKD might result from cystic change of BDH. In contrast, BDHs were not communicating with the biliary tract lumen in autopsy specimens of congenital biliary dilatation in ADPKD in another study (Terada and Nakanuma 1988). Peribiliary glands have been shown to be cystically dilated in ADPKD (Kida et al. 1992). Hepatic peribiliary cysts (also called hepatic hilar cysts) were first reported in 1984 (Nakanuma et al. 1984) and were speculated to derive from cystic dilatations of intrahepatic peribiliary glands (review of the literature: Terada et al. 2003).

Association of BDH with Caroli's Disease or Caroli's Syndrome

BDHs have been observed in conjunction with Caroli's syndrome (Aguilera et al. 2004), the so-called "complex" type with congenital hepatic fibrosis (Nakanuma et al. 1982; Davies et al. 1986; Sung et al. 1992). Portal tract-associated lesions similar to BDH have also been noted in an experimental model of this disorder, i.e., the polycystic kidney rat (PCK rat; Lager et al. 2001; Sanzen et al. 2001). In the PCK rat, biliary dysgenesis is associated with an activation of the MAPK/extracellular signal-regulated protein kinase 5 (ERK5) (MEK5/ERK5) cascade that seems to play a pivotal role in the maldevelopment of the bile duct cell lineages (Sato et al. 2005).

Association of BDH with Congenital Liver Fibrosis

BDH may develop in association with congenital liver fibrosis (CLF, synonym: biliary fibroangioadenomatosis), a ductal plate malformation caused by mutations of the fibrocystin gene (see below). CLF was first published in 1954 under the term fibrocystic disease of the liver (Grumbach et al. 1954). The association of CLF with renal dysplasia and renal cystic disease was already noted by these authors and confirmed 4 years later (Leger et al. 1958). The clinical features have been reviewed.

Other Associations

BDHs have been observed in ectopic livers (Watanabe et al. 1989).

Hamartomatous collections of small bile ducts were detected in congenital disorder of glycosylation Ib (CDG Ib; Damen et al. 2004). CDG Ib is caused by deficiency of phosphomannose isomerase (E.C. 5.3.1.8; de Koning et al. 1998; Schollen et al. 2000). Interestingly, patients with CDG Ib also exhibit a distinct type of hepatic fibrosis in addition to protein-losing enteropathy (Oren and Houwen 1999), characterized by mild portal tract fibrosis and an excess of bile duct structures in ductal plate configuration (de Koning et al. 2000), further supporting a link between ductal plate malformations and the pathogenesis of BDH.

Hamartomatous Lesions Probably Related to Biliary Hamartomas

Introduction

Apart from the common hamartomas, i.e., biliary microhamartoma and peribiliary hamartoma/bile duct adenoma, several other, rare hamartomatous lesions of the hepatobiliary tract have been described.

Intrahepatic Multicystic Biliary Hamartoma of the Liver

This is a very rare type of nodular hamartoma which has first been found around the falciform ligament close to the hepatic capsule in the form of protruding lesions. Histologically, these nodular lesions consisted of ductal structures, periductal glands, and fibrous connective tissue. Similar to myoid multicystic hamartoma, these small nodules also contained myoid spindle cells. Bile-like material was observed within some of the ductal profiles. Two cases were associated with a xanthogranulomatous inflammation (Zen et al. 2006). Few further cases have subsequently been reported (Kai et al. 2008; Ryu et al. 2010; Song et al. 2013). The lesions were situated near the liver surface, and imaging showed that the nodules are often intermingled with normal liver parenchyma within the peripheral portion of the lesions (Ryu et al. 2010). In one patient, a 55-year-old man, the liver showed a localized nodular lesion of 5-cm diameter, displaying a multicystic honeycomb appearance. Histologically, the nodule consisted of ductal structures, periductal glands, vascularized connective tissue, and a ductocentric xanthogranulomatous inflammation (Kai et al. 2008).

Myoid Hamartoma

Myoid hamartoma is a hepatic mesenchymal hamartoma containing numerous biliary ductules (Gornicka et al. 2004). The index case showed, in a liver resection specimen, an unencapsulated solid hilar tumor measuring up to 5 cm in diameter. Histologically, it predominantly consisted of eosinophilic spindled or fusiform cells with blunt-ended nuclei, the cells intermingled with cholangiocyte ductules. Immunohistochemically, most of the spindle cells were reactive for smooth muscle actin (alphaSMA), whereas only few cells were positive for CD34 and desmin. The proliferation fraction (Ki-67) was less than 5 %.

The cellular origin of myoid hamartoma of the liver is unknown. It has been shown that hepatic ductules are surrounded by a myoid cell layer (Badaruddin et al. 1976). More recent knowledge refers to myoid cells and myofibroblasts located to the portal tracts (mainly in a periductular sheath), representing the differentiated offspring of hepatic stellate cells situated in a compartment outside the perisinusoidal space, i.e., in an extralittoral compartment (Tang et al. 1994; Tuchweber et al. 1996; Zimmermann et al. 1999; Kinnman and Housset 2002; Ramadori and Saile 2004). These portal myofibroblasts seem to affect the development of intrahepatic bile ducts (Libbrecht et al. 2002). There is evidence to indicate that bile ducts may stimulate chemoattraction of stellate cells mediated by platelet-derived growth factor (PDGF; Kinnman et al. 2000). PDGF-BB apparently produced by cholangiocytes (Grappone et al. 1999; Kinnman et al. 2000). But peribiliary fibrogenic cells can also undergo a myofibroblastic conversion distinct from hepatic stellate cells and stimulated by PDGF (Kinnman et al. 2003). Whether the pathogenesis of myoid hamartoma is related to an abnormal interaction between proliferating small bile ducts and their associated myoid cells is unknown, but it has been observed that another hepatic hamartoma, mesenchymal hamartoma, contains a stromal component consisting of myofibroblasts (Cook et al. 2002).

Myoid Multicystic Hamartoma of the Liver

Rare hamartomatous lesions of the liver are characterized by conglomerates of cysts associated with other tissue components normally occurring in the liver. In one instance, such a lesion observed in an adolescent patient was huge, measuring up to 21 cm, and presented as a smooth multicystic tumor showing cysts up to 6 cm in diameter, but sometimes also with duct-like features. The cyst linings consisted of two types of epithelium, i.e., a mucinous component with cuboidal to columnar cells and an intestinal-type epithelium with goblet cells, Paneth cells and neuroendocrine cells. The cyst walls contained small bundles of smooth muscle as well as groups of small duct-like profiles resembling peribiliary glands, also associated

with smooth muscle (Azar et al. 2003). Part of this cystic lesions resembled congenital solitary nonparasitic cysts (CSNPC) of the liver.

Giant Biliary Hamartomas and Other Hepatobiliary Hamartomas with a Contribution of Bile Ducts

Rarely, liver hamartomas with a predominant bile duct component are unusually large. In one reported case, the lesion was associated with an adenocarcinoid and presented as a well-demarcated area measuring up to 7 cm, with increased consistency and gray-yellow cut surface with multiple cystic dilated spaces and a 1.5-cm tumor-like lesion in the periphery (Papadogiannakis et al. 1996). Histologically, the larger area showed an admixture of bile ducts (mostly cystically dilated) and vascular channels, while the tumor-like lesion consisted of an adenocarcinoid.

Cystic Hamartoma of Bile Ducts

These are hamartomatous lesions arising in large extrahepatic bile ducts at or near the porta hepatis (Dowdy et al. 1962; Toledo-Pereyra et al. 1973; Ansari et al. 1976). In one adult patient, the mass produced intermittent obstructive jaundice and was found to cause a smooth, oblong filling defect in the left hepatic bile duct. Laparotomy revealed a soft, cystic mass measuring 2 cm on the anteromedial wall of the duct. Microscopic examination of the resected specimen displayed cystic spaces lined by a flat or cuboid-to-columnar epithelium, the walls consisting of connective tissue, bundles of smooth muscle, and ductular profiles (Ansari et al. 1976).

Hepatic Nodular Hamartoma with Signs of Ductal Plate Malformation

Terada (2011) described a complex hamartomatous liver lesion observed in 83-year-old man. This patient was found to have a low-echoic and low-density hepatic tumor measuring 7.2 × 5.6 cm. Histologically, the complex mass consisted of liver cysts, ductal plate malformation lesions, peribiliary glands, hepatocytes, portal tracts, and mesenchymal tissue. The cysts were lined by a layer of cuboidal, biliary-type (CK7- and CK-19-positive) epithelia with multiple papillary protrusions. This lesion may represent a hamartomatous growth of several components of hepatic ontogenesis, associated with ductal plate malformation. In fact, ductal plate malformation can occur as a circumscribed lesion limited to restricted areas of the liver, e.g., described as monolobar ductal plate malformation (Terada and Moriki 2010).

Hamartomas of the Hepatic Pedicle

Cystic hamartomatous lesions associated with the hepatic pedicle have very rarely been observed (Bugnon et al. 1987; Alamowitch 1988). In one young adult patient, US and CT showed a partitioned, polylobulated fluid mass which appeared to be connected to the liver. The removed, polycystic mass (20 g, up to 5-cm diameter) was found to originate from the hepatic pedicle, close to the cystic duct. The cysts contained a clear fluid, and the compact wall disclosed several small cavities. Histologically the cyst walls were composed of a fibrovascular tissue with some smooth muscle bundles, adipose tissue, and nerves. The epithelial lining was not specified, but the wall contained glandular structures (Bugnon et al. 1987). In a second patient, a spherical cystic mass measuring 5 cm in diameter was found at US in the region of the pancreatic head, more precisely situated between the gallbladder and the inferior caval vein. At resection, this cyst was attached to the hepatic pedicle. Histologically, the incomplete lining consisted of a mucoid epithelium, and the wall of the cyst contained smooth muscle (Alamowitch 1988). Whether the interpretation of the author that this lesion represents a hamartoma is correct has to be left open, because an intestinal-type duplication may also be taken into account.

Complex Hamartomas with a Marked Ductular Component: Mixed Hamartomas and Solid Hamartoma of the Liver (Solid Hepatic Hamartoma)

Mixed hamartomas of the liver are rare lesions with a histology probably situated between biliary hamartomas and focal nodular hyperplasia (FNH). An impressive case, detected in a 3-month-old child, was described in 1978. A large midline mass, palpable inferior to the liver edge for about 8 cm, extended into the right-upper quadrant. Laparotomy revealed a large and pedunculated, solid pale red-brown nodular mass arising from the caudate lobe, but involving both liver lobes. The resection specimen showed a multinodular tumor with firm to rubbery consistency. The nodules, up to 1 cm in diameter, had white centers and were surrounded by thin septa, similar to the pattern seen in FNH. In contrast to typical FNH, the nodules were histologically subdivided into numerous small PSE, and most of the nodules have a portal tract in the center (not as in FNH), with radiating smaller branches that tended to subdivide the nodules. Abnormal blood vessels typical for FNH were in evidence (Rhodes et al. 1978). Is this type of mixed hamartoma just an early report of FNH? The main difference between this lesion and classical FNH is the unique organoid pattern of the hepatic lesion with pseudolobulation of the nodules, with a large bile duct-containing area occupying the centers, and a peripheral rim of hepatocytic nests or lobular fragments. This hamartoid pattern is not seen in typical FNH. In a small infant, a mixed hamartoma measured 7.5 cm and weighed 179 g. It consisted of loose fibrous stroma intermingled with spindle and polygonal cells and ductular structures (Toda et al. 1990). This pattern seems to mimic mesenchymal hamartoma, which is discussed in another chapter.

Under the term solid hamartoma, an unusual lesion observed in the left liver lobe of an infant was described. It presented as a well-defined, solid nodular lesion with irregularly shaped yellow islands of parenchyma and white-gray fibrous nodules, histologically composed of a mosaic of parenchyma, fibrous stroma, prominent ductular proliferations, and vascular proliferation, resulting in a fibroadenomatous pattern (Sonobe et al. 1988). Hamartomatous nodules with ductular proliferation somewhat resembling FNH have been seen in patients with developmental disorders of the biliary tract, including Alagille's syndrome (Nishikawa et al. 1987; Tuset et al. 1995) and biliary atresia (Ohtomo et al. 1991).

References

Aggarwal S, Kumar S, Kumar A, Bhasin R, Garg PK, Bandhu S (2003) Extra-hepatic bile duct adenoma in a patient with a choledochal cyst. J Gastroenterol Hepatol 18:351–352

Aguilera V, Rayon M, Perez-Aguilar F, Berenguer J (2004) Caroli's syndrome and imaging: report of a case. Rev Esp Enferm Dig (Madrid) 96:74–76

Akaydin M, Ersoy YE, Erozgen F, Ferlengez E, Kaplan R, Celik A, Memmi N (2009) Tubulovillous adenoma in the common bile duct causing obstructive jaundice. Acta Gastroenterol Belg 72:450–454

Akin O, Coskun M (2002) Biliary adenofibroma with malignant transformation and pulmonary metastases: CT findings. AJR Am J Roentgenol 179:280–281

Alamowitch C (1988) Hamartomas of the hepatic pedicle in the adult (in French). J Chir (Paris) 125:673–674

Alazmi WM, Rosen CM, De La Ossa MM, Willis I, Barkin JS (2002) Bile duct hamartomas. Gastrointest Endosc 56:565–566

Albores-Saavedra et al. (2001) PubMed PMID 11420469

Albrecht E (1904) Ueber Hamartome. Verh Dtsch Ges Pathol 7:153–157

Allaire et al. (1988) PubMed PMID 3046396

Amar A, Lenk C, Lombard F, Hillion G, Jouannelle A, Egarnes M, Valyi L, Marry JP, Edouard A (1996) Adenoma of the choledochus (in French). J Chir (Paris) 133:186–188

Amir R, Jacobs PH, Piepsz A (1984) Unusual cholescintigraphic findings in polyarteritis nodosa. Clin Nucl Med 9:585–587

Anderson et al. (1992) PubMed PMID 1602511

Ansari A, Silvis S, Vennes J, Hay L (1976) Cystic hamartoma of the left hepatic duct. Cause of recurrent jaundice. JAMA 235:630–631

Aparajita R, Gomez D, Verbeke CS, Menon KV (2008) Papillary adenoma of the distal common bile duct associated with a synchronous carcinoma of the periampullary duodenum. JOP 9:212–215

Arena et al. (2006) PubMed PMID 16918984

Arenson AM, Rosen IE, McKee JD, Hamilton PA (1988) Ultrasonography and CT of multiple bile duct hamartomas simulating dilated intrahepatic ducts. Can Assoc Radiol J 39:26–28

Ariche A, Shelef I, Hilzenrat N, Dreznik Z (2002) Villous adenoma of the common bile duct transforming into a cholangiocarcinoma. Isr Med Assoc J 4:1149–1150

Awasthi A, Das A, Srinivasan R, Joshi K (2004) Morphological and immunohistochemical analysis of ductal plate malformation: correlation with fetal liver. Histopathology 45:260–267

Azar GM, Kutin N, Kahn E (2003) Unusual hepatic tumor with features of mesenchymal hamartoma and congenital solitary nonparasitic cyst. Pediatr Dev Pathol 6:265–269

Badaruddin RH, Waldrop FS, Puchtler H (1976) Alterations of the myoid pericanalicular layer in liver. A light microscopical pilot study of human autopsy material. Arch Pathol Lab Med 100:616–619

Bakotic BW, Robinson MJ, Sturm PD, Hruban RH (1999) Pyloric gland adenoma of the main pancreatic duct. Am J Surg Pathol 23:227–231

Bastart F, Vila A, Padros J, Escape I, Bruguera M (1998) Multiple biliary hamartomatosis: a multidisciplinary diagnosis (in Spanish). Gastroenterol Hepatol 21:115

Baumann R, Uettwiller H, Duclos B, Jouin H, Kerschen A, Adloff M, Weill JP (1987) Congenital cystic dilatation of the common bile duct, anomaly of the biliopancreatic junction and cancer of the bile ducts (in French). Gastroenterol Clin Biol 11:849–855

Beltran Romero LM, Muñiz Grijalvo O, Catsell Monsalve FJ (2009) Multiple biliary hamartomatosis (in Spanish). Med Clin (Barc) 132:687

Bhathal et al. (1996) PubMed PMID 8669534

Bhusnurmath SR, Bhagwat AG, Koshy A (1980) Bile duct-hamartoma in needle biopsy of liver. Indian Pediatr 17:203

Blanc JF, Bernard PH, Carles J, Le Bail B, Balabaud C, Bioulac-Sage P (2000) Cholangiocarcinoma arising in von Meyenburg complex associated with hepatocellular carcinoma in genetic hemochromatosis. Eur J Gastroenterol Hepatol 12:233–237

Blot E, Heron F, Cardot F, Kerleau JM, Metayer J, Michot F, Bourreille J (1996) Villous adenoma of the common bile duct. J Clin Gastroenterol 22:77–79

Bloustein PA (1977) Association of carcinoma of congenital cystic conditions of the liver and bile ducts. Am J Gastroenterol 67:40–46

Boraschi P, Donati F, Volpi A, Pollina LE (2007) Solitary hilar biliary adenoma: MR imaging and MR cholangiography features with pathologic correlation. Dig Liver Dis 39:1031–1034

Börnfors M (1984) The development of cholangiocarcinoma from multiple bile-duct adenomas. Acta Pathol Microbiol Immunol Scand A 92:285–289

Bravo SM, Laing FC (1994) Multiple bile duct hamartomas: von Meyenburg complexes detected on sonography and CT scanning. J Ultrasound Med 13:649–651

Bruegel M, Rummeny EJ, Gaa J (2005) Image of the month. Multiple biliary hamartomas as an incidental finding in a patient with neuroendocrine carcinoma of the pancreas. Gastroenterology 128:259–523

Brunner P, Baudeau C, Mainguene C, Sedat J, Padovani B, Fitte H, Lasserre M, Bruneton JN, Mourou MY (1994) Magnetic resonance imaging of Von Meyenburg complexes: report of a pathologically documented case. Magn Reson Imaging 12:969–973

Buckley JG, Salimi Z (1993) Villous adenoma of the common bile duct. Abdom Imaging 18:245–246

Bugnon PY, Martinot JC, Servais B, Lecomte-Houcke M, Gautier-Benoit C (1987) Cystic hamartoma of the hepatic pedicle in the adult. A case and review of the literature (in French). Chirurgie 113:906–909

Burhans R, Myers RT (1971) Benign neoplasms of the extrahepatic biliary ducts. Am Surg 37:161–166

Burns CD, Kuhns JG, Wieman TJ (1990) Cholangiocarcinoma in association with multiple biliary microhamartomas. Arch Pathol Lab Med 11:1287–1289

Caroli J, Soupault R, Champeau J, Eteve J, Hivet M (1959) Papillomes et papillomatoses de la voie biliaire principale (Papillomas and papillomatoses of the principal biliary tract) (in French). Rev Medicochir Mal Foie 34:191–230

Caroli J, Hadchouel P, Huguet C (1974) Diffuse miliary benign fibrocholangioma. Biliary microhamartoma (in French). Med Chir Dig 3:367–369

Cattell et al 1962 PubMed PMID 13877392

Chae BW, Chung JP, Park YN, Yoon DS, Yu JS, Lee SJ, Lee KS, Chung JB et al (1999) Villous adenoma of the bile ducts: a case report and a review of the reported cases in Korea. Yonsei Med J 40:84–89

Chang YT, Wang HP, Sun CT, Chang MC, Chang YC, Wu MS, Lin JT (2001) Papillary adenoma of the bile duct. Gastrointest Endosc 53:777

Chang HK, Chung J, Lee DH, Kim KT, Jang HJ (2003) A limited polyarteritis nodosa of the liver and gallbladder accompanied with a solitary cystic dilatation of the intrahepatic bile duct. Clin Exp Rheumatol 21:525

Chen LL, Goldstein RB (2002) Case 2. Biliary hamartomas (von Meyenburg complex). J Ultrasound Med 21:589–606

Chen YC, Chien RN, Chen MF, Ng KF, Tseng JH (2000) Biliary hamartomas associated with biliary stones presenting as multiple microabscesses: case report. Chang Gung Med J 23:560–565

Chen L, Xu MY, Chen F (2014) Bile duct adenoma: a case report and literature review. World J Surg Oncol 12:125

Cheung YC, Tan CF, Wan YL, Lui KW, Tsai CC (1997) MRI of multiple biliary hamartomas. Br J Radiol 70:527–529

Cho C, Rullis I, Rogers LS (1978) Bile duct adenomas as liver nodules. Arch Surg 113:272–274

Chu PT (1950) Benign neoplasms of the extrahepatic biliary ducts. Arch Pathol 50:84–97

Chung EB (1970) Multiple bile-duct hamartomas. Cancer 26:287–296

Colarian JH, Wescott CJ (2001) Villous adenoma of the common hepatic duct. Gastrointest Endosc 54:226

Cook JR, Pfeifer JD, Dehner LP (2002) Mesenchymal hamartoma of the liver in the adult: association with distinct clinical features and histological changes. Hum Pathol 33:893–898

Cooke JC, Cooke DAP (1987) The appearances of multiple biliary hamartomas of the liver (von Meyenburg complexes) on computed tomography. Clin Radiol 38:101–102

Damen G, de Klerk H, Huijmans J, den Hollander J, Sinaasappel M (2004) Gastrointestinal and other clinical manifestations in 17 children with congenital disorders of glycosylation type Ia, Ib, and Ic. J Pediatr Gastroenterol Nutr 38:282–287

Daroca PJ, Tuthill R, Reed RJ (1975) Cholangiocarcinoma arising in congenital hepatic fibrosis. A case report. Arch Pathol 99:592–595

Davidoff S, Kim S, Friedman B (2006) Von Meyenburg complexes (bile duct hamartomas). Clin Gastroenterol Hepatol 4:XXXVI

Davies CH, Stringer DA, Whyte H, Daneman A, Mancer K (1986) Congenital hepatic fibrosis with saccular dilatation of intrahepatic bile ducts and infantile polycystic kidneys. Pediatr Radiol 16:302–305

De Koning TJ, Dorland L, van Diggelen OP, Boonman AM, de Jonbg GJ, van Noort WL et al (1998) A novel disease of *N*-glycosylation due to phosphomannose isomerase deficiency. Biochem Biophys Res Commun 245:38–42

De Koning TJ, Nikkels PG, Dorland L, Bekhof J, De Schrijver JE, van Hattum J, van Diggelen OP et al (2000) Congenital hepatic fibrosis in 3 siblings with phosphomannose isomerase deficiency. Virchows Arch 437:101–105

De Mas CR (1994) Adenoma of the common bile duct simulating a calculus (in German). Z Gastroenterol 32:113–116

Dekker A, Ten Kate FJW, Terpstra OT (1989) Cholangiocarcinoma associated with multiple bile duct hamartomas of the liver. Dig Dis Sci 34:952–958

Desmet VJ (1998) Ludwig symposium on biliary disorders – part I. Pathogenesis of ductal plate abnormalities. Mayo Clin Proc 73:80–89

Dilli A, Ayaz UY, Yüksel I, Damar C, Ayaz S, Hekimoglu B (2012) Computed tomography and magnetic resonance imaging findings in a case with biliary microhamartomas. Case Rep Med 2012:976078

Doberauer C, Henning B, Rupp KD (1997) Villous bile duct adenoma with mucinous bile (in German). Dtsch Med Wochenschr 122:1248–1252

Doppman JL, Dunnick NR, Girton M, Fauci AS, Popovsky MA (1979) Bile duct cysts secondary to liver infarcts: report of a case and experimental production by small vessel hepatic artery occlusion. Radiology 130:1–5

Dowdy GS, Olin WG, Shelton EL, Waldron GW (1962) Benign tumors of the extrahepatic bile ducts. Report of three cases and review of the literature. Arch Surg 85:503–513

Droy L, Sagan C, Paineau J, Gournay J, Mosnier JF (2009) Cholangiocarcinomas developing on multiple bile duct hamartomas syndrome (in French). Ann Pathol 29:24–27

Duran-Vega HC, Luna-Martinez J, Gonzalez-Guzman R, Azamar-Gracia F, Barra-Garcia R, Ruiz-Cruz A, Leon-Trueba H et al (2000) Hamartoma of the bile ducts. Report of a case and review of the literature (in Spanish). Rev Gastroenterol Mex 65:124–128

Edmondson HA (1958) Tumors of the liver. Atlas of tumor pathology. Armed Forces Institute of Pathology, section 7, pt. AFIP, Washington, DC, 25, pp 19–24

Eguchi S, Tajima Y, Yanaga K, Okudaira S, Furui J, Hayashi T, Kanematsu T (2004) Hilar bile duct cancer associated with preoperatively undetectable von meyenburg complex – report of a case. Hepatogastroenterology 51:1301–1303

Eisenberg D, Hurwitz L, Yu AC (1986) CT and sonography of multiple bile-duct hamartomas simulating malignant liver disease (case report). AJR Am J Roentgenol 147:279–280

Elster K (1976) Histologic classification of gastric polyps. In: Morson BC (ed) Pathology of the gastro-intestinal tract. Springer, Berlin, pp 78–92

Evans SE, Harris I, Williams CE (1989) Benign cholangioma of the liver. Clin Radiol 40:427–428

Fernandez Fernandez JM, Muriel Cueto P, Sanchez Sanchez AM, Dulanto Vargas M et al (2015) Bile duct adenoma (hamartoma of peribiliary glands): importance of an adequate diagnosis. Cir Esp. 93: e95–e96

Flanigan DP (1977) Biliary carcinoma associated with biliary cysts. Cancer 40:880–883

Fletcher ND, Wise PE, Sharp KW (2004) Common bile duct papillary adenoma causing obstructive jaundice: case report and review of the literature. Am Surg 70:448–452

Foucar E (1985) Bile duct adenoma. Arch Pathol Lab Med 109:590

Fujii H, Yang Y, Tang R, Kunitomo K, Itakura J, Mogaki M, Matsuda M, Suda K, Nobukawa B, Matsumoto Y (1999) Epithelial cell proliferation activity of the biliary ductal system with congenital biliary malformations. J Hepatobiliary Pancreat Surg 6:294–302

Fuks D, Le Mouel JP, Chatelain D, Sabbagh C, Demuynck F, Brevet M, Brehant O et al (2009) A pitfall in the diagnosis of unresectable liver metastases: multiple bile duct hamartomas (von Meyenburg complexes). Case Rep Gastroenterol 3:198–201

Gainant A, Antarieu S, Sautereau D, Pillegand B, Labrousse F, Cubertafond P (1995) Degenerative villous adenoma of the intrapancreatic choledochus (in French). Gastroenterol Clin Biol 19:850–851

Gallego JC, Suarez I, Soler R (1995) Multiple bile duct hamartomas: US, CT, and MR findings. A case report. Acta Radiol 36:273–275

Gambarotti M, Medicina D, Baronchelli C, Bercich L, Bonetti F, Facchetti F (2008) Alpha-1-antitrypsin-positive "signet-ring" bile duct adenoma in a patient with M(MALTON) mutation. Int J Surg Pathol 16:218–221

Garduno-Lopez AL, Mondragon-Sanchez R, Bernal-Maldonado R, Hinojosa-Becerril CA, Meneses-Garcia A (2001) A case of biliary adenofibroma of the liver causing elevated CA 19-9 levels. Clin Trans Oncol 4:271–273

Gil-Bello D, Ballesteros E, Sanfeliu E, Andreu FJ (2012) Calcification in biliary hamartomatosis. Br J Radiol 85: e99–e101

Goh J, Kelleher B, Clarke E, O'Keane JC, MacMathuna P (2003) Early neoplasia of the gallbladder and bile duct: an "unstable" biliary epithelium? Endoscopy 35:538–541

Gold JH, Guzman IJ, Rosai J (1978) Benign tumors of the liver: pathological examination of 45 cases. Am J Clin Pathol 70:6–17

Gong J, Kang W, Xu J (2012) MR imaging and MR cholangiopancreatography of multiple biliary hamartomas. Quant Imag Med Surg 2:133–134

Gornicka B, Ziarkiewicz-Wroblewska B, Wroblewski T, Koperski L, Pawlak J, Nyckowski P et al (2004) Myoid hamartoma of the liver – a novel variant of hamartoma developing in the hilar region and imitating a malignant liver tumor. Med Sci Monit 10:CS23–CS26

Govindarajan S (1985) Bile duct adenoma (in reply). Arch Pathol Lab Med 109:590–591

Govindarajan S, Peters RL (1984) The bile duct adenoma. A lesions distinct from Meyenburg complex. Arch Pathol Lab Med 108:922–924

Grappone C, Pinzani M, Parola M, Pellegrini G, Caliguri A, DeFranco R, Marra F, Herbst H et al (1999) Expression of platelet-derived growth factor in newly formed cholangiocytes during experimental biliary fibrosis in rats. J Hepatol 31:100–109

Grimm PC, Crocker JF, Malatjalian DA, Ogborn MR (1990) The microanatomy of the intrahepatic bile duct in polycystic disease: comparison of the cpk mouse and human. J Exp Pathol (Oxford) 71:119–131

Grumbach R, Bourillon J, Auvert JP (1954) Maladie fibrokystique du foie avec hypertension portale chez l'enfant. Sem Hôp Arch Anat Path 74:30

Guiu B, Guiu S, Loffroy R, Cercueil JP, Krausé D (2009) Multiple biliary hamartomas mimicking diffuse liver metastases. Dig Surg 26:209

Gurrera A, Alaggio R, Leone G, Aprile G, Magro G (2010) Biliary adenofibroma of the liver: report of a case and review of the literature. Pathol Res Int 2010:504584

Gütgemann I, Haas S, Berg JP, Zhou H, Büttner R, Fischer HP (2006) CD56 expression aids in the differential diagnosis of cholangiocarcinomas and benign cholangiocellular lesions. Virchows Arch 448:407–411

Guzman IJ, Gold JH, Rosai J, Schneider PD, Varco RL, Buchwald H (1977) Benign hepatocellular tumors. Surgery 82:495–503

Haberal AN, Bilezikçi B, Demirhan B, Karakayali H, Haberal H (2001) Malignant transformation of biliary adenofibroma: a case report. Turk K Gastroenterol 12:149–153

Hajosi-Kalcakosz S, Dezsö K, Bugyik E, Bödör C, Paku S, Pavai Z, Halasz J, Schlachter K et al (2012) Enhancer of zeste homologue 2 (EZH2) is a reliable immunohistochemical marker to differentiate malignant and benign hepatic tumors. Diagn Pathol 7:86

Hanafy M, McDonald P (1993) Villous adenoma of the common bile duct. J R Soc Med 86:603–604

Harshfield DL, Teplick SK, Stanton M, Tunuguntla K, Diner WC, Read RC (1990) Obstructing villous adenoma and papillary adenomatosis of the bile ducts. AJR Am J Roentgenol 154:1217–1218

Hasebe T, Sakamoto M, Mukai K, Kawano N, Konishi M, Ryu M, Fukamachi S, Hirohashi S (1995) Cholangiocarcinoma arising in bile duct adenoma with focal area of bile duct hamartoma. Virchows Arch 426:209–213

Hastir D, Verset L, Demetter P (2013) Intrahepatic bile duct adenoma with oncocytic features. Liver Int 33:273

Heinke T, Pellacani LB, Costa HO, Fuziy RA, Franco M (2008) Hepatocellular carcinoma in association with bile duct hamartomas: report of two cases and review of the literature. Ann Diagn Pathol 12:208–211

Henning H, Friedrich K, Luders CJ (1982) Laparoscopic aspect and clinical relevance of cholangiofibromas (in German). Z Gastroenterol 20:744–751

Hettinger M, Klotz M, Bolay L, Weber P (2005) Multiple bile duct hamartomas of the liver – a rare differential diagnosis to liver metastasis (in German). Ultraschall Med 26:150–153

Ho CM, Lee PH (2006) Image of the month. Papillary adenoma of the cystic duct. Arch Surg 141:315

Hoang MP, Murakata LA, Padilla-Rodriguez AL, Albores-Saavedra J (2001) Metaplastic lesions of the extrahepatic bile ducts: a morphologic and immunohistochemical study. Mod Pathol 14:1119–1125

Hohmann J, Loddenkemper C, Albrecht T (2009) Assessment of a biliary hamartoma with contrast-enhanced sonography using two different contrast agents. Ultraschall Med 30:185–188

Homer LW, White HJ, Read RC (1968) Neoplastic transformation of v. Meyenburg complexes of the liver. J Pathol Bacteriol 96:499–502

Honda N, Cobb C, Lechago J (1986) Bile duct carcinoma associated with multiple von Meyenburg complexes in the liver. Hum Pathol 17:1287–1290

Hornick JL, Lauwers GY, Odze RD (2005) Immunohistochemistry can help distinguish metastatic pancreatic adenocarcinomas from bile duct adenomas and hamartomas of the liver. Am J Surg Pathol 29:381–389

Hughes NR, Goodman ZD, Brathal PS (2010) An immunohistochemical profile of the so-called bile duct adenoma: clues to pathogenesis. Am J Surg Pathol 34:1312–1318

Ibrarullah M, Sreenivasa D (2003) Bile duct adenoma: management by subtotal excision. Trop Gastroenterol 24:93–94

Ignee A, Piscaglia F, Ott M, Salvatore V, Dietrich CF (2009) A benign tumour of the liver mimicking malignant liver disease – cholangiocellular adenoma. Scand J Gastroenterol 44:633–636

Iha H, Nakashima Y, Fukukura Y, Tanaka M, Wada Y, Takazawa T, Nakashima O, Kojiro M (1996) Biliary hamartomas simulating multiple hepatic metastasis on imaging findings. Kurume Med J 43:231–235

Inagaki M, Ishizaki A, Kino S, Onodera K, Matsumoto K, Yokoyama K, Makino I, Ojima H et al (1999) Papillary

adenoma of the distal common bile duct. J Gastroenterol 34:535–539
Ioannidis O, Iordanidis F, Paraskevas G, Ntoumpara M, Tsigkriki L, Chatzopoulos S et al (2012) Incidentally discovered white subcapsular liver nodules during laparoscopic surgery: biliary hamartoma and peribiliary gland hamartoma. Klin Onkol 25:468–470
Ishak KG (1988) Benign tumors and pseudotumors of the liver. Appl Pathol 6:82–104
Jain D, Sarode VR, Abdul-Karim FW, Homer R, Robert ME (2000) Evidence for the neoplastic transformation of Von-Meyenburg complexes. Am J Surg Pathol 24:1131–1139
Jain D, Nayak NC, Saigal S (2010) Hepatocellular carcinoma arising in association with von Meyenburg complexes: an incidental finding or precursor lesions ? A clinicopathologic study of 4 cases. Ann Diagn Pathol 14:317–320
Jao YT, Tseng LJ, Wu CJ, Young TM, Mo LR, Wang CH, Wey KC (2003) Villous adenoma of common bile duct. Gastrointest Endosc 57:561–562
Järvinen HJ, Nyberg M, Peltokallio P (1983) Biliary involvement in familial adenomatosis coli. Dis Colon Rectum 26:525–528
Jennings PE, Rode J, Coral A, Dowsett J, Lees WR (1990) Villous adenoma of the common hepatic duct: the role of ultrasound in management. Gut 31:558–560
Johannesen EJ, Wu Z, Holly JS (2014) Bile duct adenoma with oncocytic features. Case Rep Pathol 2014:282010
Kagawa Y, Kashihara S, Kuramoto S, Maetani S (1978) Carcinoma arising in a congenitally dilated biliary tract. Report of a case and review of the literature. Gastroenterology 74:1286–1294
Kai K, Takahashi T, Miyoshi A, Yasui T, Tokunaga O, Miyazaki K (2008) Intrahepatic multicystic biliary hamartoma: report of a case. Hepatol Res 38:629–634
Kai K, Yakabe T, Kohya N, Miyoshi A, Iwane S, Mizuta T, Miyazaki K, Tokunaga O (2012) A case of unclassified multicystic biliary tumor with biliary adenofibroma features. Pathol Int 62:506–510
Karahan OI, Kahriman G, Soyuer I, Ok E (2007) Hepatic von Meyenburg complex simulating biliary cystadenocarcinoma. Clin Imaging 31:50–53
Karhunen PJ (1986a) Benign hepatic tumors and tumor-like conditions. J Clin Pathol 39:183–188
Karhunen PJ (1986b) Adult polycystic liver disease and biliary microhamartomas (von Meyenburg's complexes). Acta Pathol Microbiol Immunol Scand A 94:397–400
Katsinelos P, Pilpilids I, Paroutoglou G, Tsolkas P, Kotakidou R, Panagiotopoulou K et al (2004) Endoscopic snare resection of an intrapapillary pedunculated villous adenoma presenting as acute recurrent pancreatitis. Surg Endosc 18:347
Katsinelos P, Basdanis G, Chatzimavroudis G, Karagiannoulou G, Katsinelos T, Paroutoglou G et al (2006) Pancreatitis complicating mucin-hypersecreting common bile duct adenoma. World J Gastroenterol 12:4927–4929
Kawakami H, Kuwatani M, Onodera M, Asaka M, Hirano S, Kondo S (2007) Villous adenoma arising in choledochocele. Gastrointest Endosc 66:1231–1232
Kawakatsu M, Vilgrain V, Zins M, Vullierme M, Belghiti J, Menu Y (1997) Radiologic features of papillary adenoma and papillomatosis of the biliary tract. Abdom Imaging 22:87–90
Kida et al. (1992) PubMed PMID 1639342
Kim YW, Park YK, Park JH, Lee J, Lee SM, Hong SW, Yang MH (1999) A case with intrahepatic double cancer: hepatocellular carcinoma and cholangiocarcinoma associated with multiple von Meyenburg complexes. Yonsei Med J 40:506–509
Kim BS, Joo SH, Joo KR (2008) Carcinoma in situ arising in a tubulovillous adenoma of the distal common bile duct: a case report. World J Gastroenterol 14:4705–4708
Kim YS, Rha SE, Oh SN, Jung SE, Shin YR, Choi BG, Byun JY, Jung ES, Kim DG (2010) Imaging findings of intrahepatic bile duct adenoma (peribiliary gland hamartoma): a case report and literature review. Korean J Radiol 11:560–565
Kinnman N, Housset C (2002) Peribiliary myofibroblasts in biliary type liver fibrosis. Front Biosci 7:d496–d503
Kinnman N, Hultcrantz R, Barbu V, Rey C, Wendum D, Poupon R, Housste C (2000) PDGF-mediated chemoattraction of hepatic stellate cells by bile duct segments in cholestatic liver injury. Lab Invest 80:697–707
Kinnman N, Francoz C, Barbu V, Wendum D, Rey C, Hultcrantz R, Poupon R, Housset C (2003) The myofibroblastic conversion of peribiliary fibrogenic cells distinct from hepatic stellate cells is stimulated by platelet-derived growth factor during liver fibrogenesis. Lab Invest 83:163–173
Kobayashi A, Takahashi S, Hasebe T, Konishi M, Nakagohri T, Gotohda N, Kinoshita T (2005) Solitary bile duct hamartoma of the liver. Scand J Gastroenterol 40:1378–1381
Koga F, Tanaka H, Takamatsu S, Baba S, Takihara H, Hasegawa A, Yanagihara E, Inoue T et al (2012) A case of very large intrahepatic bile duct adenoma followed for 7 years. World J Clin Oncol 3:63–66
Kunisaki SM, Hertl M, Bodner BE, Cosimi AB (2005) Mirizzi syndrome secondary to an adenoma of the cystic duct. J Hepatobiliary Pancreat Surg 12:159–162
Kurumaya H, Terada T, Nakanuma Y (1990) 'Metaplastic lesions' in intrahepatic bile ducts in hepatolithiasis: a histochemical and immunohistochemical study. J Gastroenterol Hepatol 5:530–536
Kushima R, Remmele W, Stolte M, Borchard F (1996) Pyloric gland type adenoma of the gallbladder with squamoid spindle cell metaplasia. Pathol Res Pract 192:963–969
Kushima R, Ruthlein HJ, Stolte M, Bamba M, Hattori T, Borchard F (1999) 'Pyloric gland-type adenoma' arising in heterotopic gastric mucosa of the duodenum, with dysplastic progression of the gastric type. Virchows Arch 435:452–457

Kushima R, Vieth M, Borchard F, Stolte M, Mukaisho K, Hattori T (2006) Gastric-type well-differentiated adenocarcinoma and pyloric gland adenoma of the stomach. Gastric Cancer 9:177–184

Lager DJ, Qian Q, Bengal RJ, Ishibashi M, Torres VE (2001) The pck rat: a new model that resembles human autosomal dominant polycystic kidney and liver disease. Kidney Int 59:126–136

Lai YS, Thung SN, Gerber MA, Chen ML, Schaffner F (1989) Expression of cytokeratin in normal and diseased livers and in primary hepatocellular carcinoma. Arch Pathol Lab Med 113:134–138

Lalosevic D, Milosebic P, Vuckovic N, Uzurov V, Andelkovic Z, Dolai M (2005) Von Meyenburg complex associated with adult polycystic liver disease (in Serbian). Med Pregl 58:191–195

Landais P, Grundfeld JP, Droz D, Drueke T, Albouze G, Gogusev J, Chaeveau D, Moynot A (1984) Cholangiocellular carcinoma in polycystic kidney and liver disease. Arch Intern Med 144:2274–2276

Langner C, Homayounfar K, Ruten B, Fass J, Rüschoff J (2001) Gleichzeitiges Auftreten von Angiomyolipom, fokaler nodulärer hyperplasia, cholangiozellulärem Adenom und Hämangion in der Leber. Pathologe 22:417–423

Lee TS, Kim HK, Ahn HM, Lee UJ, Choi YC, John BM, Park TI, Koo JH (2009) A case of early bile duct cancer arising from villous adenoma in choledochal cyst (in Korean). Korean J Gastroenterol 54:55–59

Leger L, Boquien Y, Kernéis JP et al (1958) Dysgénésies congénitales complexes des voies biliaires intrahépatiques au cours des cirrhosis juvenile averc hypertension portale. Presse Med 66:1147

Levin SE, Dail DH, Saik RP (1974) Letter: bile duct adenomatosis of the liver. Arch Surg 108:880

Lev-Toaff AS, Bach AM, Wechsler RJ, Hilpert PL, Gatalica Z, Rubin R (1995) The radiologic and pathologic spectrum of biliary hamartomas. AJR Am J Roentgenol 165:309–313

Libbrecht L, Cassiman D, Desmet V, Roskams T (2002) The correlation between portal myofibroblasts and development of intrahepatic bile ducts and arterial branches in human liver. Liver 22:252–258

Lin S, Weng Z, Xu J, Wang MF, Zhu YY, Jiang JJ (2013) A study of multiple biliary hamartomas based on 1697 liver biopsies. Eur J Gastroenterol Hepatol 25:948–952

Lindgren AGH, Hansson G, Nilsson LA (1961) Primary carcinoma arising in conjunction with biliary cholangiomatosis. Acta Path Microbiol Scand 52:343–348

Loh A, Kamar S, Dickson GH (1994) Solitary benign papilloma (papillary adenoma) of the cystic duct: a rare cause of biliary colic. Br J Clin Pract 48:167–168

Luddecke HF, Yoon IL (1958) Surgical importance of bile duct adenoma of liver. Am J Surg 96:118–121

Lung PF, Jaffer OS, Akbar N, Sidhu PS, Ryan SM (2013) Appearances of von Meyenburg complex on cross sectional imaging. J Clin Imag Sci 3:22

Luo TY, Itai Y, Eguchi N, Kurosaki Y, Onaya H, Ahmadi T, Niitsu M, Tsunoda HS (1998) Von Meyenburg complexes of the liver: imaging findings. J Comput Assist Tomogr 22:372–378

Madhusudhan KS, Das CJ (2009) von Meyenburg's complex in a patient with primary malignancy: role of MRI. Indian J Surg 71:98–100

Maeda E, Uozumi K, Kato N, Akahane M, Inoh S, Inoue Y, Beck Y, Goto A, Makuuchi M, Ohtomo K (2006) Magnetic resonance findings of bile duct adenoma with calcification. Radiat Med 24:459–462

Maher MM, Dervan P, Keogh B, Murray JG (1999) Bile duct hamartomas (von Meyenburg complexes): value of MR imaging at diagnosis. Abdom Imaging 24:171–173

Mancheron H, Dupas JL, Sevestre H, Delcenserie R, Capron JP (1988) Acute pancreatitis caused by papillary adenoma of the distal common bile duct. Treatment by endoscopic excision (in French). Gastroenterol Clin Biol 12:259–261

Markhardt BK, Rubens DJ, Huang J, Dogra VS (2006) Sonographic features of biliary hamartomas with histopathologic correlation. J Ultrasound Med 25:1631–1633

Marshall JM (1932) Tumors of the bile ducts. Surg Gynecol Obstet 54:6–12

Martinoli C, Cittadini G, Rollandi GA, Conzi R (1992) Case report: imaging of bile duct hamartomas. Clin Radiol 45:203–205

Martins Machado M, Ferreira Rosa AC, de Barros N, Martins Azeredo L, Mendes de Oliveira Cerri L et al (2003) Ultrasonography findings in patients with bile duct hamartomas (von Meyenburg complex): result of an active search of eight years (in Portuguese). Radiol Bras 36:153–156

Mauri MF, Lo RV, Fibbi ML, Valduga C, Mariscotti C (1988) Multiple biliary microhamartomas (von Meyenburg's complex). Description of 4 cases (in Italian). Pathologica 80:91–96

McLoughlin MJ, Phillips MJ (1975) Angiographic findings in multiple bile-duct hamartomas of the liver. Radiology 116:41–43

Melnick PJ (1955) Polycystic liver, analysis of seventy cases. Arch Pathol 59:162–172

Mendel R (1987) Highly differentiated adenocarcinoma in a villous adenoma of the common bile duct near the papilla. Dtsch Med Wschr 112:1906–1907

Mendez-Sanchez N, Pichardo-Bahena R, Uribe M (2003) Images in hepatology. Microhamartomas (Von Meyenburg complexes). Ann Hepatol 2:98

Mortelé B, Mortele K, Seynaeve P, Vandevelde D, Kunnen M, Ros PR (2002) Hepatic bile duct hamartomas (von Meyenburg complexes): MR and MR cholangiography findings. J Comput Assist Tomogr 26:438–443

Munshi AG, Hassan MA (2010) Common bile duct adenoma: case report and brief review of literature. Surg Laparosc Endosc Perkutan Tech 20: e193–e194

Nagano Y, Matsuo K, Gorai K, Sugimori K, Kunisaki C, Ike H, Tanaka K, Imada T, Shimada H (2006) Bile duct hamartomas (von Meyenburg complexes) mimicking liver metastases from bile duct cancer. World J Gastroenterol 12:1321–1323

Nagata S, Aijoka Y, Nishikura K, Watanabe G, Inoue T, Yamaguchi K, Watanabe H et al (2007) Co-expression of gastric and biliary phenotype in pyloric-gland type adenoma of the gallbladder: immunohistochemical analysis of mucin profile and CD10. Oncol Rep 17:721–729

Naim M, Tyahi N, Hameed F, Ahmad KN, Lakhtakhia HS, Ullah M (1987) Adult polycystic liver and the Meyenburg complexes biliary ectasia. Indian J Pathol Microbiol 30:151–155

Nakanuma Y, Terada T, Ohta G, Kurachi M, Matsubara F (1982) Caroli's disease in congenital hepatic fibrosis and infantile polycystic disease. Liver 2:346–354

Nakanuma et al. (1984) PubMed PMID 6093347

Nakayama Y, Inoue H, Hamada Y, Takeshita M, Iwasaki H, Maeshiro K, Iwanaga S et al (2005) Intraductal tubular adenoma of the pancreas, pyloric gland type: a clinicopathologic and immunohistochemical study of 6 cases. Am J Surg Pathol 29:607–616

Neri S, Mauceri B, Cilio D, Sciacca C, Di Prima P, Finazzo M (2004) Biliary hamartomas (von Meyenburg complex): magnetic resonance imaging in a case report. Int Med J 34:71–72

Niizawa M, Itoh M, Mukojima T, Ishida H, Masamune O (1991) Sonographic features of von Meyenburg's complexes. J Clin Ultrasound 19:288–293

Nishikawa A, Mori H, Takahashi M, Ojima A, Shimokawa K, Furuta T (1987) Alagille's syndrome. A case with a hamartomatous nodule of the liver. Acta Pathol Jpn 37:1319–1326

Noda Y, Fujita N, Kobayashi G, Ito K, Horaguchi J, Takasawa O, Obana T, Ishida K et al (2007) Histological study of gallbladder and bile duct epithelia in patients with anomalous arrangement of the pancreaticobiliary ductal system: comparison between those with and without a dilated common bile duct. J Gastroenterol 42:211–218

O'Shea M, Fletcher HS, Lara JF (2002) Villous adenoma of the extrahepatic biliary tract: a rare entity. Am Surg 68:889–891

Ober WB (1978) Selected items from the history of pathology: Eugen Albrecht, MD (1872–1908): hamartoma and choristoma. Am J Pathol 91:606

O'Hara BJ, McCue PA, Miettinen M (1992) Bile duct adenomas with endocrine component. Immunohistochemical study and comparison with conventional bile duct adenomas. Am J Surg Pathol 16:21–25

Ohta W, Ushio H (1984) Histological reconstruction of a Von Meyenburg complex on the liver surface. Endoscopy 16:71–74

Ohtomo K, Itai Y, Hasizume K, Kosaka N, Iio M (1991) CT and MR appearance of focal nodular hyperplasia of the liver in children with biliary atresia. Clin Radiol 43:88–90

Oren A, Houwen RH (1999) Phosphomannose isomerase deficiency as the cause of protein-losing enteropathy and congenital liver fibrosis. J Pediatr Gastroenterol Nutr 29:231–232

Orii T, Ohkohchi N, Sasaki K, Satomi S, Watanabe M, Moriya T (2003) Cholangiocarcinoma arising from preexisting biliary hamartoma of liver – report of a case. Hepatogastroenterology 50:333–336

Orlandi PE, Imbriani M, Mattioli R, Montanari N, Ziosi A (2002) Multiple biliary hamartomas (von Meyenburg complex). A case report. Radiol Med (Torino) 103:418–420

Oshikiri T, Kashimura N, Katanuma A, Maguchi H, Shinohara T, Shimizu M, Kondo S, Katoh H (2002) Mucin-secreting bile duct adenoma – clinicopathological resemblance to intraductal papillary mucinous tumor of the pancreas. Dig Surg 19:324–327

Otani K, Tohara K, Mihara K, Ueki T, Tanaka M, Sakaguchi S, Matsui T, Yao T, Haraoka S, Iwashita A (2006) A case of intrahepatic bile duct adenoma (in Japanese). Nippon Shokakibyo Gakkai Zasshi 103:37–43

Panaro F, Gauff G, Dong G, Testa G, Benedetti E (2004) Images of interest. hepatobiliary and pancreatic: multiple biliary hamartomas (von Meyenburg complex). J Gastroenterol Hepatol 19:463

Papadogiannakis N, Gad A, Sjöstedt S, Tour R, Thörne A, Seensalu R (1996) Adenocarcinoid of the liver arising within an area of hamartoma with predominant bile duct component. J Clin Gastroenterol 23:145–151

Parada LA, Bardi G, Hallen M, Hagerstrand I, Tranberg KG, Mitelman F, Johansson B (1997) Monosomy 22 in a case of biliary adenofibroma. Cancer Genet Cytogenet 93:183–184

Pontisso P, Barzon M, Basso G, Cecchetto G, Perilongo G, Alberti A (1993) Cytokeratin patterns in childhood primary liver tumors. Int J Clin Lab Res 23:225–227

Popovsky MA, Costa JC, Doppman JL (1979) Meyenburg complexes of the liver and bile cysts as a consequence of hepatic ischemia. Hum Pathol 10:425–432

Principe A, Lugaresi ML, Lords RC, D'Errico A, Polito E, Gallo MC, Bicchierri I, Cavallari A (1997) Bile duct hamartomas: diagnostic problems and treatment. Hepatogastroenterology 44:994–997

Ramadori G, Saile B (2004) Portal tract fibrogenesis in the liver. Lab Invest 84:153–159

Ramos et al. (1990) PubMed PMID 2302034

Redston MS, Wanless IR (1996) The hepatic von Meyenburg complex: prevalence and association with hepatic and renal cysts among 2843 autopsies [corrected]. Mod Pathol 9:233–237

Rhodes RH, Marchildon MB, Luebke DC, Edmondson HA, Mikity VG (1978) A mixed hamartoma of the liver: light an electron microscopy. Hum Parthol 9:211–221

Ribbert (1904) Geschwulstlehre. Cohen, Bonn, p 176

Röcken C, Pross M, Brucks U, Ridwelski K, Roessner A (2000) Cholangiocarcinoma occurring in a liver with multiple bile duct hamartomas (von Meyenburg complexes). Arch Pathol Lab Med 124:1704–1706

Rogers KE (1946) A papillary cystadenoma of the common hepatic duct. Can Med Assoc J 55:597–599

Rousselet MC, Kettani S, Rohmer V, Saint-Andre JP (1989) A case of temporal arteritis with intrahepatic arterial involvement. Pathol Res Pract 185:329–331

Ryu Y, Matsui O, Zen Y, Ueda K, Abo H, Nakanuma Y, Gabata T (2010) Multicystic biliary hamartoma: imaging findings in four cases. Abdom Imaging 35:543–547

Sachs M, Encke A (1991) Synchronous development of benign cholangiomas and a cholangiocarcinoma in the liver of a patient 43 years after thorotrast administration (in German). Langenbecks Arch Chir 376:176–181

Sada PN, Ramakrishna B (1994) Computed tomography of von Meyenburg complex simulating micro-abscesses. Australas Radiol 38:225–226

Salles VJ, Marotta A, Netto JM, Speranzini MB, Martins MR (2007) Bile duct hamartomas – the von Meyenburg complex. Hepatobiliary Pancreat Dis Int 6:108–109

Salo J, Bru C, Vilella A, Gines P, Gilabert R, Castells A, Bruguera M, Rodes J (1992) Bile-duct hamartomas presenting as multiple focal lesions on hepatic ultrasonography. Am J Gastroenterol 87:221–223

Sanzen T, Harada K, Yasoshima M, Kawamura Y, Ishibashi M, Nakanuma Y (2001) Polycystic kidney rat is a novel animal model of Caroli's disease associated with congenital hepatic fibrosis. Am J Pathol 158:1605–1612

Sasaki M, Nakanuma Y (1996) Abnormal expression of MUC1 apomucin and mature MUC1 mucin in biliary epithelial cells in various cystic liver diseases. Hepatology 24:539–543

Sasaki M, Matsubara T, Kakuda Y, Sato Y, Nakanuma Y (2014) Immunostaining for polycomb group protein EZH2 and senescent marker p16INK4a may be useful to differentiated cholangiolocellular carcinoma from ductular reaction and bile duct adenoma. Am J Surg Pathol 38:364–369

Sato Y, Harada K, Kizawa K, Sanzen T, Furubo S, Yasoshima M, Ozaki S, Ishibashi M, Nakanuma Y (2005) Activation of the MEK5/ERK5 cascade is responsible for biliary dysgenesis in a rat model of Carol's disease. Am J Pathol 166:49–60

Sato S, Watanabe H, Asano T, Saito R, Iwadate H, Kobayashi H, Ohira H (2013) Biliary hamartomas (von Meyenburg complex) complicated with microscopic polyangiitis. Mod Rheumatol 23:611–613

Saxe J, Lucas C, Ledgerwood AM, Sugawa C (1988) Villous adenoma of the common bile duct. Arch Surg 123:96–97

Schmitz JM, Stolte M (1997) Gastric polyps as precancerous lesions. Gastroenterol Clin N Am 1:29–46

Schollen E, Dorland L, de Koning TJ, van Diggelen OP, Huijmans JG, Marquardt T et al (2000) Genomic organization of the human phosphomannose isomerase (MPI) gene and mutation analysis in patients with congenital disorders of glycosylation type Ib (CDG-Ib). Hum Mutat 16:247–252

Scott J, Shousha S, Thomas HC, Sherlock S (1980) Bile duct carcinoma: a late complication of congenital hepatic fibrosis. Am J Gastroenterol 73:113–119

Semelka RC, Hussain SM, Marcos HB, Woosley JT (1999) Biliary hamartomas: solitary and multiple lesions shown on current MR techniques including gadolinium enhancement. J Magn Reson Imaging 10:196–201

Sergi C, Adam S, Kahl P, Otto HF (2000) The remodeling of the primitive human biliary system. Early Hum Dev 58:167–178

Shin YM (2011) Biliary hamartoma presented as a single mass. Korean J Hepatol 17:331–334

Sinakos E, Papalavrentios L, Chourmouzi D, Dimopoulou D, Drevelegas A, Akriviadis E (2011) The clinical presentation of Von Meyenburg complexes. Hippokratia 15:170–173

Singhal A, Kanagala R, Wright HI, Kohli V (2010) Multiple bile duct hamartomas mimicking diffuse hepatic metastasis: GI image. J Gastrointest Surg 14:1629–1631

Skelly RT, Lee J, Sloan JM, Diamond T (1999) Incidental bile duct adenomas in a patient with obstructive jaundice. Ulster Med J 68:114–115

Slone HW, Bennett WF, Bova JG (1993) MR findings of multiple biliary hamartomas. AJR Am J Roentgenol 161:581–583

Song JS, Lee YJ, Kim KW, Huh J, Jang SJ, Yu E (2008) Cholangiocarcinoma arising in von Meyenburg complexes: report of four cases. Pathol Int 58:503–512

Song JS, Noh SJ, Cho BH, Moon WS (2013) Multicystic biliary hamartoma of the liver. Korean J Pathol 47:275–278

Sonobe H, Ohtsuki Y, Enzan H, Kurashige T, Matsuura K, Kaneko A, Ogata T (1988) An unusual case of solid hamartoma in the liver. Acta Pathol Jpn 38:75–82

Sonzogni A, Colloredo G, Fabris L, Cadamuro M, Paris B, Roffi L, Pozzi M, Bovo G, Del Poggio P et al (2004) Isolated idiopathic bile ductular hyperplasia in patients with persistently abnormal liver function tests. J Hepatol 40:592–598

Sotona O, Cecka F, Neoral C, Ferko A, Rejchrt S, Podhola M, Subrt Z, Jon B (2010) Papillary adenoma of the extrahepatic biliary tract – a rare cause of obstructive jaundice. Acta Gastroenterol Belg 73:270–273

Spigelman AD, Farmer KCR, James M, Richman PI, Phillips RKS (1991) Tumours of the liver, bile ducts, pancreas and duodenum in a single patient with familial adenomatous polyposis. Br J Surg 78:979–980

Sturgis TM, Fromkes JJ, Marsh W (1992) Adenoma of the common bile duct: endoscopic diagnosis and resection. Gastrointest Endosc 38:504–506

Styne P, Warren GH, Kumpe DA, Halgrimson C, Kern F (1986) Obstructive cholangitis secondary to mucus secreted by a solitary papillary bile duct tumor. Gastroenterology 90:748–753

Sung JM, Huang JJ, Lin XZ, Ruaan MK, Lin CY, Chang TT, Shu HF, Chow NH (1992) Caroli's disease and congenital hepatic fibrosis associated with polycystic kidney disease. A case presenting with acute focal bacterial nephritis. Clin Nephrol 38:324–328

Tajima T, Honda H, Kuroiwa T, Yoshimitsu K, Irie H, Aibe H, Taguchi K, Shimada M, Masuda K (1999) Radiologic features of intrahepatic bile duct adenoma: a look at the surface of the liver. J Comput Assist Tomogr 23:690–695

Takahashi S, Takada K, Kawano Y, Miyanishi K, Ishiwatari H, Hayashi T, Sagawa T et al (2010) Cholangiocarcinoma with bile duct adenoma and hamartoma-like lesion in the bile duct (in Japanese). Nippon Shokakibyo Gakkaii Zasshi 107:461–469

Takumi K, Fukukura Y, Nagasato K, Nakajo M, Natsugoe S, Higashi M (2013) Intrahepatic bile duct adenoma mimicking hepatic metastasis: case report and review of the literature. Magn Reson Med Sci 12:141–145

Tan A, Shen JF, Hecht AH (1989) Sonogram of multiple bile duct hamartomas. J Clin Ultrasound 17:667–669

Tan G, Yilmaz A, De Young BR, Behling C, Lehman A, Frankel WL (2004) Immunohistochemical analysis of biliary tract lesions. Appl Immunohistochem Mol Morphol 12:193–197

Tang L, Tanaka Y, Marumo F, Sato C (1994) Phenotypic change in portal fibroblasts in biliary fibrosis. Liver 14:76–82

Terada et al. (2003) PubMed PMID 14516324

Terada T (2011) Hepatic nodular hamartoma containing liver cysts, ductal plate malformations and peribiliary glands. Hepatol Res 41:93–98

Terada T, Moriki T (2010) Monolobar ductal plate malformation disease of the liver. Pathol Int 60:407–412

Terada T, Nakanuma Y (1988) Congenital biliary dilatation in autosomal dominant adult polycystic disease of the liver and kidneys. Arch Pathol Lab Med 112:1113–1116

Thommesen N (1978) Biliary hamartomas (von Meyenburg complexes) in liver needle biopsies. Acta Pathol Microbiol Scand A 86:93–99

Toda T, Yamada M, Nakama B, Yamazato M, Hokama A, Muto Y (1990) Immunohistochemical and electron microscopic findings in a case of mixed hamartoma of the liver. Jpn J Surg 20:1010–1106

Tohmé-Noun C, Cazals D, Noun R, Menassa L, Valla D, Vilgrain V (2008) Multiple biliary hamartomas: magnetic resonance features with histopathologic correlation. Eur Radiol 18:493–499

Toledo-Pereyra LH, Goodale RL, Najarian JS, Ward P (1973) Hamartoma of the hepatic bile ducts. Minn Med 56:20–22

Totkas S, Hohenberger P (2000) Cholangiocellular carcinoma associated with segmental Caroli's disease. Eur J Surg Oncol 26:520–521

Tsuchiya R, Harada N, Ito T, Furukawa M, Yoshihiro I (1977) Malignant tumors in choledochal cysts. Ann Surg 186:22–28

Tsui WMS (1998) How many types of biliary hamartomas and adenomas are there? Adv Anat Pathol 5:16–20

Tsui WMS, Loo KT, Chow LTC, Tse CCH (1993) Biliary adenofibroma. A heretofore unrecognized benign biliary tumor of the liver. Am J Surg Pathol 17:186–192

Tuchweber B, Desmouliere A, Bochaton-Piallat ML, Rubbia-Brandt L, Gabbiani G (1996) Proliferation and phenotypic modulation of portal fibroblasts in the early stages of cholestatic fibrosis in the rat. Lab Invest 74:265–278

Tuset E, Ribera JM, Domenech E, Vaquero M, Oller B, Armengol M, Planas R, Navarro JT, Feliu E (1995) Pseudotumorous hyperplasia of the caudate lobe of the liver in a patient with Alagille syndrome (in Spanish). Med Clin (Barc) 104:420–422

Uchiyama S, Chijiwa K, Imamura N, Hiyoshi M, Ohuchida J, Nagano M, Nagaike K, Takahashi N, Akiyama Y (2008) Adenoma of the major duodenal papilla with intraductal extension into the lower common bile duct. J Gastrointest Surg 12:1146–1148

Uehlinger E (1972) In memoriam Hanns von Meyenburg (June 6, 1887–Nov. 6, 1971). Verh Dtsch Ges Pathol 56:697–701

Van Eyken P, Sciot R, Desmet VJ (1991) Immunocytochemistry of cytokeratins in primary human liver tumors. APMIS Suppl 23:77–85

Varnholt H, Vauthey JN, Cin PD, Marsh Rde W, Bhathal PS, Hughes NR, Lauwers GY (2003) Biliary adenofibroma: a rare neoplasm of bile duct origin with an indolent behavior. Am J Surg Pathol 27:693–698

Vieth M, Kushima R, Borchard F, Stolte M (2003) Pyloric gland adenoma: a clinico-pathological analysis of 90 cases. Virchows Arch 442:317–321

Vieth M, Kushima R, de Jonge JP, Borchard F, Oellig F, Stolte M (2005) Adenoma with gastric differentiation (so-called pyloric gland adenoma) in a heterotopic gastric mucosa in the rectum. Virchows Arch 446:542–545

Vieth M, Vogel C, Kushima R, Borchard F, Stolte M (2006) Pyloric gland adenoma – how to diagnose? Cesk Patol 42:4–7

Vogel HM, Friedrich K, Koch H (1986) Ultrasound in cholangiofibromas of the liver detected by laparoscopy. Endoscopy 18:185–187

Von Meyenburg H (1918) Ueber die Cystenleber. Beitr Path Anat 84:477–532

Wagner (1861) Drüsengeschwülste der Leber. Arch Heilk 2:473

Watanabe et al. (1989) PubMed PMID 2917536

Wei SC, Huang GT, Chen CH, Sheu JC, Tsang YM, Hsu HC, Chen DS (1997) Bile duct hamartomas: a report of two cases. J Clin Gastroenterol 25:608–611

Willis RA (1943) Carcinoma arising in congenital cysts of the liver. J Pathol Bacteriol 55:492

Wisniewski B, Tordjman G, Tran Van Nhieu J, Bettan L, Courillon-Mallet A (2002) Cholangiocarcinoma developing in von Meyenburg complexes in

haemochromatosis (in French). Gastroenterol Clin Biol 26:922–924

Wohlgemuth WA, Bottger J, Bohndorf K (1998) MRI, CT, US and ERCP in the evaluation of bile duct hamartomas (von Meyenburg complex): a case report. Eur Radiol 8:1623–1626

Wu WW, Gu M, Lu D (2014) Cytopathologic, histopathologic, and immunohistochemical features of intrahepatic clear cell bile duct adenoma: a case report and review of the literature. Case Rep Pathol 2014:874826

Xu HX, Chen LD (2008) Villous adenoma of extrahepatic bile duct: contrast-enhanced sonography findings. J Clin Ultrasound 36:39–41

Xu AM, Xian ZH, Zhang SH, Chen XF (2009) Intrahepatic cholangiocarcinoma arising in multiple bile duct hamartomas: report of two cases and review of the literature. Eur J Gastroenterol Hepatol 21:580–584

Yamato T, Sasaki M, Hoso M, Sakai J, Ohta H, Watanabe Y, Nakanuma Y (1998) Intrahepatic cholangiocarcinoma arising in congenital hepatic fibrosis: report of an autopsy case. J Hepatol 28:717–722

Yaziji N, Martin L, Hillon P, Favre JP, Henninger JF, Piard F (1997) Cholangiocarcinome dévelopé sur microhamartomes biliaires chez un malade atteint d'hémochromatose. Ann Pathol (Paris) 17:346–349

Yoshida S, Kurokohchi K, Ueno T, Yoshino M, Shimada M, Masaki T (2009) Hepatic von Meyenburg complex: a trigger of severe portal hypertension. Liver Int 29:614–615

Zen Y, Terahata S, Miyayama S, Mitsui T, Takehara A, Miura S, Nobata K, Kitao A et al (2006) Multicystic biliary hamartoma: a hitherto undescribed lesion. Hum Pathol 37:339–344

Zheng RQ, Zhang B, Kudo M, Onda H, Inoue T (2005) Imaging findings of biliary hamartomas. World J Gastroenterol 11:6354–6359

Zimmerman RL, Fogt F, Burke M, Murakata LA (2002) Assessment of Glut-1 expression in cholangiocarcinoma, benign biliary lesions and hepatocellular carcinoma. Oncol Rep 9:689–692

Zimmermann A, Zhao D, Reichen J (1999) Myofibroblasts in the cirrhotic rat liver reflect hepatic remodeling and correlate with fibrosis and sinusoidal capillarization. J Hepatol 30:646–652

Tumors and Tumor-like Lesions of Peribiliary Glands

41

Contents

Abstract

Peribiliary glands are tubular-alveolar glands with serous and mucinous acini embedded in a fibromuscular bed of ductal walls. These glands can develop several types of lesions that may mimic tumors. The glands may undergo hyperplastic changes, most commonly emerging in the setting of chronic bile duct inflammation, with or without associated bile duct cancer. Hyperplasia may be multifocal and less frequently diffuse, involving intrahepatic and extrahepatic glands. Marked hyperplasia of peribiliary glands, in part associated with dysplasia, is observed in patients with hepatolithiasis and those with liver fluke infestation. Peribiliary glands can give rise to rare cystic and papillary neoplasms and to invasive carcinomas. They play a role in hepatic cancer spread, due to their close spatial relationship with bile duct walls and sharing of a vascular plexus. The glands can also undergo tumor-like cystic changes.

Introduction

Peribiliary glands, bile duct-associated glandular structures important for biliary epithelial homeostasis and bile composition, were not studied in detail in the older hepatobiliary pathology literature but have now gained more attention, mainly by the work of Japanese authors (Nakanuma et al. 1994a, b). Peribiliary glands show a broad

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_41

spectrum of hyperplastic, dysplastic, hamartomatous, neoplastic, and cystic changes and participate in biliary tract carcinogenesis (review: Cardinale et al. 2014).

Normal Morphology and Function of Peribiliary Glands

Peribiliary glands (glands of the biliary tree) are tubular-alveolar glands with serous and mucinous acini. The small glands are deeply embedded in a fibromuscular bed of the duct walls. Peribiliary glands are divided into intramural mucous glands and extramural seromucous glands, and both types are continuous with the lining epithelium of bile ducts (Terada et al. 1987; Terada and Nakanuma 1988; Nakanuma et al. 1994a, 1997). Intramural glands consist of irregularly distributed simple tubular glands with much mucin, while extramural glands show seromucinous acini (sometimes admixed with pancreatic exocrine acini), excretory units, and a conducting system. Analysis of biliary casts and SEM investigations showed that treelike projections from large bile ducts at the bifurcation frequently anastomosed each other and represented extramural peribiliary glands, while pouch-like projections corresponded to intramural glands (Ishida et al. 1989). In intrahepatic bile ducts, peribiliary glands start at the level of septal bile ducts, while interlobular bile ducts lack these glands. Usually, peribiliary glands are more common and dense at the level of large area and segmental intrahepatic ducts. In the extrahepatic biliary tract, peribiliary glands are found along the entire duct system and are also present in the terminal common, pancreatobiliary segment. Generally, peribiliary glands predominate in areas of branching points, i.e., the perihilar region, periampullary area, and cystic duct entrance (Cardinale et al. 2011). Peribiliary glands also occur in transverse fissures and are, in this anatomical locations, the "aberrant biliary structures" of former investigations (El Gharbawy et al. 2011). The gallbladder has no peribiliary glands. Epithelial cells of peribiliary glands consistently express two foregut antigens termed D10 and 1F6 (Hughes et al. 2006, 2010). In normal livers, the pancreatic duodenal homeobox factor 1/PDX1 is frequently expressed in peribiliary glands, but HES1/hairy and enhancer of spli1, which is often expressed in bile duct lining epithelia, is only focally expressed in glands. The glands normally also express SOX9 and EpCAM (Igarashi et al. 2013). Extrahepatic and intrahepatic peribiliary glands express alpha-amylase isoenzymes, trypsin, and pancreatic lipase, immunoreactivity being located to the Golgi area (Terada and Nakanuma 1991, 1993a, b; Terada et al. 1993). Morphological and immunohistochemical investigations showed that intrahepatic peribiliary glands arise from periportal immature hepatocytes at the hepatic hilum, with a stable cytokeratin phenotype during development, and that differentiation of peribiliary glands into mucus-producing acini occurs 3 months after birth (Terada and Nakanuma 1993c).

Peribiliary glands of larger bile ducts are a niche of stem/progenitor cells that can contribute to biliary epithelial replacement and regeneration (Cardinale et al. 2011; Carpino et al. 2012; Sutton et al. 2012). Such progenitor cells have the phenotypic features of endodermal stem cells and express endodermal transcription factors in the nuclei, including SOX9, SOX17, FOXA2, PX1, HES1, NGN3, and PROX1, and show stem cell surface markers, such as EpCAM, NCAM, CD133, and CXCR4 (Cardinale et al. 2011). Cells with the phenotype of biliary stem/progenitor cells are located at the bottom of peribiliary glands near the fibromuscular layer. These progenitors form a heterogeneous population, variably expressing SOX9/17, PDX1, SOX17, EpCAM, NCAM, CXCR4, Lgr5, and OCT4, whereby the most proximal/primitive group was PDX1(+)/SOX17(+)/EpCAM(+/−) (Carpino et al. 2012). In injured extrahepatic bile duct specimen showing epithelial cell loss, large numbers of Ki-67(+) cells were observed in peribiliary glands, which also contained few c-Kit-positive cells, suggesting that peribiliary glands might contribute to biliary regeneration as a source of progenitor cells (Sutton et al. 2012). In the absence of peribiliary glands in the gallbladder, progenitor cells are situated in mucosal crypts in this organ (Carpino et al. 2014). It has been

proposed that these progenitor cell populations play a role in the pathogenesis of cholangiocarcinoma (review: Cardinale et al. 2014).

There is direct and indirect evidence that peribiliary glands play a role in regeneration and repair of bile duct epithelia and the pathogenesis of bile duct inflammation and fibrotic changes. Injury of peribiliary glands, in particular deep-seated glands, together with damage of vascular plexus was associated with the occurrence of biliary strictures after transplantation (op den Dries et al. 2014).

Hyperplastic Changes of Peribiliary Glands

Most cases of peribiliary gland hyperplasia were observed in the setting of chronic bile duct inflammation, with or without associated bile duct cancer. Hyperplasia may be multifocal and less frequently diffuse and involves intrahepatic and extrahepatic glands. It consistently develops in hepatolithiasis (Terada and Nakanuma 1988; Nakanuma et al. 1988) and more variably in other conditions, such as bile duct infection and infestation, and following submassive liver necrosis (Nakanuma et al. 1994b). Marked peribiliary gland hyperplasia, in part associated with dysplasia (see below), was often found in intrahepatic bile ducts of patients with hepatolithiasis (Lee and Sheen 1999). In livers without hepatolithiasis, hyperplastic changes are generally less frequent. In a systematic study of 1000 consecutive autopsy liver specimens, hyperplasia of intramural glands was observed rather evenly in normal livers and in livers with various hepatobiliary diseases. The prevalence of hyperplasia of extramural mucous acini was high in cirrhosis, submassive hepatic necrosis, cholangitis, systemic infection, and extrahepatic biliary obstruction (Terada and Nakanuma 1992). A marked hyperplasia of peribiliary glands was observed in patients with liver fluke-associated cholangiocarcinoma, the hyperplastic cells being D10-positive (Hughes et al. 2006). There is a weak correlation between gland-type involvement and underlying hepatobiliary disease. Hyperplasia of extramural glands is more common in cirrhosis, submassive hepatic necrosis, cholangitis, systemic infection/sepsis, and biliary obstruction, while hyperplasia of intramural glands prevails in intrahepatic cholangitis with or without associated hepatolithiasis. Dumas and coworkers (1998) described a rare case of diffuse, severe, macroscopically recognizable hyperplasia of peribiliary glands of intrahepatic and extrahepatic ducts. This condition was detected in a patient with massive hepatic necrosis, and the cause of hyperplasia could not be elucidated. Through increased production and secretion of seromucinous substance discharged in duct lumens, peribiliary gland hyperplasia can induce mucin-related biliary disease. Histologically, multifocal hyperplasia shows both an increased number of glands and signs of epithelial hyperplasia. Differential diagnostically, hyperplasia of peribiliary glands may histologically be confounded with well-differentiated cholangiocarcinoma.

Cystic and Papillary Neoplasms Derived from Peribiliary Glands

A rare variant of cystic and papillary tumor derives from peribiliary glands, thought to derive from stem/progenitor cells located in these glands (Nakanuma and Sato 2012). Similarly, intraductal papillary neoplasm may arise from peribiliary glands, these tumors being composed of papillary and glandular components, and the tumor cells being similar to gastric foveolar and pyloric gland epithelia (Nakanishi et al. 2011). There is one report referring to two patients with intraductal tubulopapillary neoplasm of intrahepatic bile ducts. These neoplasms were associated with multiple peribiliary cysts located to the hilar region. As these cysts were partly lined by carcinoma cells that were continuous with the papillotubular neoplasms, it was suggested that this form of intraductal neoplasm might originate from peribiliary gland cysts (Zen et al. 2012). Based on radiologic findings showing diverticulum-like cystic lesions, part of cyst-forming intraductal papillary neoplasms of bile ducts were suggested to arise from peribiliary

glands (Lim et al. 2011). Intraductal oncocytic papillary neoplasm originating from peribiliary glands was described (Nakanishi et al. 2009). In this case, the oncocytic tumor originated from a cystic space in the bile duct wall, histologically identified as a cystically dilated peribiliary gland. This space contained carcinoma in situ.

Invasive Carcinomas Originating from Peribiliary Glands

Invasive "classical" cholangiocarcinoma arising from peribiliary glands is probably a rare neoplasm. Hilar cholangiocarcinoma (Klatskin tumor) originating from peribiliary gland has been reported (Terada et al. 1992a). Usuda and coworkers (2009) described carcinoma of Vater's ampulla arising from peribiliary gland.

Peribiliary Glands as a Potential Source of Cholangiocarcinomas

It has been suggested that peribiliary glands may have a tumorigenic role or contribute to the development of biliary tract cancers in a complex manner. In patients with hepatolithiasis and associated chronic cholangitis, so-called chronic proliferative cholangitis and atypical glandular proliferations can occur, the latter associated with dysplastic changes. These proliferative changes are now known to involve, or originate from, peribiliary glands. In a systemic investigation of 799 autopsy livers, papillary hyperplasia of peribiliary glands as a form of atypical hyperplasia was found in 0.8 %, papillary hyperplasia and atypical hyperplasia coexisted in 0.5 % (Terada and Nakanuma 1990a). Both hyperplastic and dysplastic alterations of peribiliary glands exhibit elevated PCNA levels, but dysplastic cells had a higher PCNA labeling index than hyperplastic cells. Also cells in extramural glands displayed a higher proliferative activity than those in intramural glands, suggesting that high turnover in dysplastic cells and extramural glands may have a higher neoplastic potential (Lee and Sheen 1999). Peribiliary glands can harbor cystic and cystic-micropapillary changes that might represent tumor precursor lesions. In an autopsy study of 938 livers, cystic-micropapillary and cystic lesions were detected in 1 % and 4 % of cases, respectively (Sato et al. 2014). MUC5AC expression was more frequent in the cystic-micropapillary group than in cystic lesions. The mean Ki-67 labeling index was higher in the former than in the latter, and cystic-micropapillary lesions expressed cyclin D1 and S100P, reflecting a pattern similar to that of the branch-type intraductal papillary mucinous neoplasm of pancreas. In the rare cystic-micropapillary lesion group, atypia of micropapillary epithelia was usually mild, but was associated with invasive adenocarcinoma in one case. Overall, the findings suggested that cystic-papillary lesions have neoplastic lesions and a status of biliary cancer precursors. It has been proposed that mucin-producing cholangiocarcinoma might derive from biliary stem/progenitor cells located in peribiliary glands (Cardinale et al. 2012).

Peribiliary Glands: Their Role in Hepatic Cancer Spread

Due to their close spatial relationship with bile duct walls, sharing of a vascular plexus with that of ducts and a distinct periglandular matrix, peribiliary glands might play a role in spread of biliary tract cancers. Hilar well-differentiated cholangiocarcinoma can extensively involve the peribiliary gland networks, with or without association with in situ-like spread of carcinoma cells in bile duct lumen (Sato et al. 2013).

Peribiliary Gland Hamartoma (Bile Duct Adenoma)

The former bile duct adenoma is now most often designated as peribiliary gland hamartoma (Bhathal et al. 1996). Both so-called biliary adenomas and peribiliary glands are characterized by the expression of two foregut antigens, known as D10 and 1F6, and secretion of mucin. Both cell systems often express MUC6, MUC5AC being

expressed in "adenoma," but not normal (quiescent) peribiliary glands, which becomes MUC5AC(+) when inflamed (Hughes et al. 2010). As, however, most of the literature employed the term "adenoma," this lesion is treated in a separate paragraph in more detail.

Hepatobiliary Hamartomas Containing Elements of Peribiliary Glands

Zen and coworkers (2006) described three cases of unusual hamartomatous nodules of the liver, located close to the capsule of the left lobe and protruding from the liver. The nodules consisted of ductal structures, periductal glands, and vascularized fibrous connective tissue and were associated in part of cases with xanthogranulomatous inflammation. A hepatobiliary nodular hamartoma involving peribiliary gland elements was described by Terada (2011). An 83-year-old man showed a hepatic tumor measuring up to 7.2 cm suggesting intrahepatic cholangiocarcinoma. Histologically the mass consisted of liver cysts, ductal plate malformations (resembling the fetal ductal plate), peribiliary glands, hepatocytes, portal tracts, and mesenchymal tissue. The cysts were lined by a layer of cuboidal cells with multiple papillary protrusions.

Monolobar Ductal Plate Malformation Disease

Under this term, Terada and Moriki (2010) described an interesting combination of Caroli's disease, peribiliary cysts, peribiliary gland proliferation, ductal plate malformations, hepatolithiasis, and portal phlebosclerosis. This combination of alterations was found in a 73-year-old man with multiple segmental dilatations of left intrahepatic bile ducts. The left liver lobe was atrophic and partly fibrotic. In some respects, the changes resembled monolobar Caroli's disease with ductal plate malformation, but a striking feature was the involvement of peribiliary glands.

Intrahepatic Peribiliary Gland Cysts

Multiple hilar cysts of the liver derived from peribiliary glands occur and have first been described in 1984 by Nakanuma and coworkers, who detected them in the hilar peribiliary connective tissue in livers with portal hypertension and/or portal vein thrombosis (Nakanuma et al. 1984). Since their first description, numerous reports have documented peribiliary gland cysts/PBGC, although this entity is still not well known in clinical practice (Nakanuma 2001). The lesions were described under various terms, including multiple cysts at the hepatic hilum, hepatic cysts of periductal gland origin, mucinous hamartoma of the biliary system, peribiliary cysts, multiple hilar cysts, and Nakanuma disease. The cysts are usually multiple, mostly develop around large intrahepatic bile ducts, and range in diameter from few millimeters to more than 3 cm, albeit most cysts are smaller than 1 cm. Cysts also develop in peribiliary glands of extrahepatic ducts, but this seems to be a less common pathology.

Selected References Wanless et al. 1987; Chin et al. 1988; Terada and Nakanuma 1990; Baron et al. 1994; Itai et al. 1994; Nakanuma et al. 1994b; Terayama et al. 1995; Fujioka et al. 1997; Colina et al. 1998; Kudo 2001; Motoo et al. 2001; Nakanuma 2001; Okada et al. 2001; Seguchi et al. 2004; Miura et al. 2006; Kai et al. 2008; Nakayama 2010; Da Ines et al. 2011; Montoriol et al. 2012; Seo et al. 2012.

Intrahepatic PBGC are lesions with varying reported frequencies. In a systematic study of 1000 autopsy livers, a cystic change was noted in 20.2 %, often associated with necroinflammatory changes, portal hypertension, or obstruction (Terada and Nakamura 1990b). In contrast, they were detected in only 0.26 % of autopsied patients with chronic fibrosing liver disease or cirrhosis (cited in Fujioka et al. 1997). These cysts correspond to cystic dilatation of peribiliary glands and are arranged along intrahepatic bile ducts both in large portal tracts

and in the hilar area (Itai et al. 1994). PBGC most often occur in patients with fibrosing liver disease or liver cirrhosis, in particular alcoholic cirrhosis or alcoholic hepatitis (Nakayama 2010; Seo et al. 2012), but have also been found in association with severe liver disease, hepatolithiasis, portal vein thrombosis, adult-type polycystic disease (Kida et al. 1992), and liver malignancy. Many cases of PBGC are probably asymptomatic, but part of cases can exert external compression of bile ducts and, in case of bilateral intrahepatic duct involvement, eventually induce biliary obstruction (Wanless et al. 1987; Stevens et al. 1996; Seguchi et al. 2004; Yokomichi et al. 2006; Kai et al. 2008; Fujiwara et al. 2009; Pang et al. 2010). PBGC can be complicated by cholangitis and sepsis (Otani et al. 2006). Peribiliary gland cysts are visualized by ultrasound, showing hilar multicystic echo complexes around portal venous branches near the hilum (Terada et al. 1992b). Clinico-radiologically, PBGC can mimic Caroli's disease (Fusai et al. 2005). On contrast-enhanced CT images, PBGC are clusters of relatively small and usually multiple cystic lesions that are found along the larger portal veins up to the third- or fourth-order branch, while on cholangiographic contrast-enhanced CT scans, the cystic areas were located adjacent to or surrounding bile ducts (Itai et al. 1994; Hoshiba et al. 1996; Terayama et al. 1995; Tohma et al. 2009). On MR images, cysts appeared as tubular structures or of high intensity on T2-weighted images, sometimes mimicking dilated bile ducts or as clusters of cysts (Baron et al. 1994; Motoo et al. 2001; Montoriol et al. 2012). There is radiological evidence that both number and size of PBGC can increase with time (Ahmadi et al. 1997; Kudo 2001; Motoo et al. 2001).

Pathogenetically, several mechanisms have been suggested (Nakanuma 2004). It has been proposed that chronic inflammatory alterations may damage and destroy the peribiliary glandular conduits (Terada et al. 1990), resulting in stasis and prestenotic dilatation. In fact, peribiliary cysts have been observed in the setting of cholesterol hepatolithiasis associated with a foreign-body reaction (Terada et al. 2003) and in primary sclerosing cholangitis, where cystic lesions were considered to reflect peribiliary gland dilatation (Terasaki et al. 1997). Alcohol-related liver disease is associated with the development of PBGC, including alcoholic liver cirrhosis (Fujioka et al. 1997; Seo et al. 2012). In one study based on clinical and autopsy cases, the frequency of these cysts was correlated with the degree of alcohol-related hepatic fibrosis (Matsubara et al. 2014). PBGC have been observed in the setting of cholesterol hepatolithiasis (Terada et al. 2003), suggesting that biliary stone disease may be involved in PBGC pathogenesis. Hilar peribiliary cysts have been observed as a rare posttransplant biliary tract complication, often presenting as cystically dilated peribiliary glands with multilocular, sometimes multiple cavities ranging up to 2 cm in diameter (Colina et al. 1998). Cystic dilatation of peribiliary glands was frequently observed in the setting of adult polycystic liver disease and less frequently in patients with solitary nonparasitic liver cysts (Kida et al. 1992).

Macroscopically, PBGC appear as few to numerous small cysts within large portal tracts or the hilar area (Seguchi et al. 2004), ranging in diameter from 2 mm to more than 3 cm (Ahmadi et al. 1997; Colina et al. 1998) and containing a serous or, less commonly, mucinous fluid. This accumulation is linked to the capability of peribiliary glands to produce and secrete neutral and acid mucins into the gland lumen (Nakanuma et al. 1994a). The surface of the cysts is glistening and the cyst walls are semitranslucent and thin (Fujioka et al. 1997). On cut surfaces of autopsy liver or liver resection specimens, the cysts are typically arranged along large intrahepatic bile ducts close to the hilar region.

Histologically, the cysts are lined by a single layer of flattened or cuboidal epithelial cells without cellular or nuclear atypia, and cysts may be associated with atrophic remnants of peribiliary glands that still show acinar structures in part of cases (Fig. 1; Seguchi et al. 2004). In some patients, numerous dilated peribiliary glands may accompany macroscopically

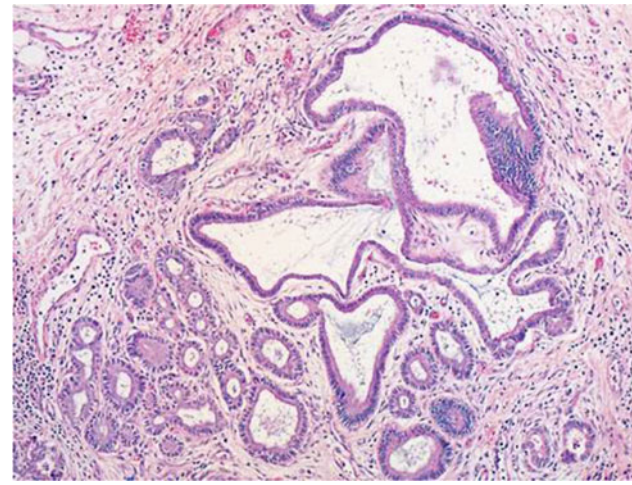

Fig. 1 Peribiliary gland cysts (hematoxylin and eosin stain)

recognizable cysts (Fujioka et al. 1997). Part of the lining cells have PAS-and/or Alcian blue-positive material in the apical portion of the cytoplasm. The mucinous material within cysts is partly stained with both PAS and Alcian blue, but the cysts did not contain bile (Fujioka et al. 1997). The cysts lack goblet cells and Paneth cells. The epithelial cyst cells are immunoreactive for cytokeratin 19 (Fujioka et al. 1997). The cyst walls consist of connective tissue, with absence of smooth muscle cells and elastic fibers. Some of the cysts are associated with inflammatory changes.

Peribiliary Gland Cysts of Extrahepatic Bile Ducts

In contrast to PBGC developing in intrahepatic ducts, peribiliary cysts arising in extrahepatic ducts are rare lesions. In some patients, a solitary large PBGC was detectable either in the hilar area, the hepatic ducts, or the common bile duct (Lee et al. 1999; Johnson et al. 2007; Ikenaga et al. 2009). PBGC of the common bile duct can cause obstruction and refractory obstructive jaundice (Johnson et al. 2007; Ikenaga et al. 2009; Takahashi et al. 2009). Intrahepatic PBGC can occur together with such cysts located to the cystic duct (Miyake et al. 2001).

References

Ahmadi T, Itai Y, Onaya H, Eguchi N, Ebihara R (1997) Hepatic peribiliary cysts: increases in size and number on computed tomography. Radiat Med 15:255–257

Baron RL, Campbell WL, Dodd GD (1994) Peribiliary cysts associated with severe liver disease: imaging-pathologic correlation. AJR Am J Roentgenol 162:631–636

Bhathal PS, Hughes NR, Goodman ZD (1996) The so-called bile duct adenoma is a peribiliary gland hamartoma. Am J Surg Pathol 20:858–864

Cardinale V, Wang Y, Carpino G, Cui CB, Gatto M, Rossi M, Berloco PB, Cantafora A et al (2011) Multipotent stem/progenitor cells in human biliary tree give rise to hepatocytes, cholangiocytes, and pancreatic islets. Hepatology 54:2159–2172

Cardinale V, Wang Y, Carpino G, Reid LM, Gaudio E, Alvaro D (2012) Mucin-producing cholangiocarcinoma might derive from biliary tree stem/progenitor cells located in peribiliary glands. Hepatology 55:2041–2042

Cardinale V, Bragazzi MC, Carpino G, Torrica A, Wang Y, McAdams Reid L, Gaudio E et al (2014) Cholangiocarcinomas: new insights from the discovery of stem cell niches in peribiliary glands of the biliary tree. Adv Hepatol. article ID 794953

Carpino G, Cardinale V, Onori P, Franchitto A, Berloco PB, Rossi M, Wang Y, Semeraro R et al (2012) Biliary tree stem/progenitor cells in glands of extrahepatic and intrahepatic bile ducts: an anatomical in situ study yielding evidence of maturational lineages. J Anat 220:186–199

Carpino G, Cardinale V, Gentile R, Onori P, Semeraro R, Franchitto A, Wang Y, Bosco D et al (2014) Evidence for multipotent endodermal stem/progenitor cell populations in human gallbladder. J Hepatol 60:1194–1202

Chin NW, Chapman I, Jimenez FA (1988) Mucinous hamartoma of the biliary duct system causing obstructive jaundice. Hum Pathol 19:1112–1114

Colina F, Castellano VM, Gonzalez-Pinto I, Garcia I, Novo O, Garcia-Hidalgo E, Garcia-Munoz H et al (1998) Hilar biliary cysts in hepatic transplantation. Report of three symptomatic cases and occurrence in resected liver grafts. Transpl Int 11:110–116

Da Ines D, Essamet W, Montoriol PF (2011) Peribiliary cysts. Hepatology 54:2271–2272

Dumas A, Thung SN, Lin CS (1998) Diffuse hyperplasia of the peribiliary glands. Arch Pathol Lab Med 122:87–89

El Gharbawy RM, Skandalakis LJ, Heffron TG, Skandalakis JE (2011) Aberrant bile ducts, 'remnant surface bile ducts', and peribiliary glands: descriptive anatomy, historical nomenclature, and surgical implications. Clin Anat 24:429–440

Fujioka Y, Kawamura N, Tanaka S, Fujita M, Suzuki H, Nagashima K (1997) Multiple hilar cysts of the liver in patients with alcoholic cirrhosis: report of three cases. J Gastroenterol Hepatol 12:137–143

Fujiwara H, Gobara H, Mimura H, Hiraki T, Iguchi T, Kanazawa S (2009) Sclerotherapy for peribiliary cysts accompanied by biliary stenosis. J Vasc Interv Radiol 20:1644–1645

Fusai G, Tucker O, Nik Sulaiman NM, Karani J, Rela M, Portmann B (2005) Peribiliary cysts can mimic Caroli's disease: a case report. Int J Surg Pathol 13:379–382

Hoshiba K, Matsui O, Kadoya M, Yoshikawa J, Gabata T, Terayama N, Takashima T (1996) Peribiliary cysts in cirrhotic liver: observation on computed tomography. Abdom Imaging 21:228–232

Hughes NR, Pairojkul C, Royce SG, Clouston A, Bhathal PS (2006) Liver fluke-associated and sporadic cholangiocarcinoma: an immunohistochemical study of bile duct, peribiliary gland and tumour cell phenotypes. J Clin Pathol 59:1073–1078

Hughes NR, Goodman ZD, Bhatal PS (2010) An immunohistochemical profile of the so-called bile duct adenoma: clues to pathogenesis. Am J Surg Pathol 34:312–1318

Igarashi S, Sato Y, Ren XS, Harada K, Sasaki M, Nakanuma Y (2013) Participation of peribiliary glands in biliary tract pathophysiologies. World J Hepatol 5:425–432

Ikenaga N, Chijiiwa K, Otani K, Ohuchida J, Uchiyama S (2009) A case of peribiliary cyst presenting with obstructive jaundice. J Gastrointest Surg 13:174–176

Ishida F, Terada T, Nakanuma Y (1989) Histologic and scanning electron microscopic observations of intrahepatic peribiliary glands in normal human livers. Lab Invest 60:260–265

Itai Y, Ebihara R, Tohno E, Tsunoda HS, Kurosaki Y, Saida Y, Doy M (1994) Hepatic peribiliary cysts: multiple tiny cysts within the larger portal tract, hepatic hilum, or both. Radiology 191:107–110

Johnson MA, Ravichandran P, Surendran R (2007) Solitary extra-hepatic hilar peribiliary cyst presenting with obstructive jaundice: a case report. Acta Chir Belg 107:716–719

Kai K, Eguchi Y, Kumagai T, Sugita Y, Tokunaga O (2008) An autopsy case of obstructive jaundice due to hepatic multiple peribiliary cysts accompanying hepatolithiasis. Hepatol Res 38:211–216

Kida T, Nakanuma Y, Terada T (1992) Cystic dilatation of peribiliary glands in livers with adult polycystic disease and livers with solitary nonparasitic cysts: an autopsy study. Hepatology 16:334–340

Kudo M (2001) Hepatic peribiliary cysts: clinically harmless disease with potential risk due to gradual increase in size and number. J Gastroenterol 36:286–288

Lee KT, Sheen PC (1999) Proliferating cell nuclear antigen expression in peribiliary glands of stone-containing intrahepatic bile ducts. Dig Dis Sci 44:2251–2256

Lee JM, Jung SE, Lee KY, Kim SN, Sun HS (1999) A large peribiliary cyst in the extrahepatic bile duct. AJR Am J Roentgenol 173:621–623

Lim JH, Zen Y, Jang KT, Kim YK, Nakanuma Y (2011) Cyst-forming intraductal papillary neoplasm of the bile ducts: description of imaging and pathologic aspects. AJR Am J Roentgenol 197:1111–1120

Matsubara T, Sato Y, Igarashi S, Matsui O, Gabata T, Nakanuma Y (2014) Alcohol-related injury to peribiliary glands is a cause of peribiliary cysts: based on analysis of clinical and autopsy cases. J Clin Gastroenterol 48:153–159

Miura F, Takada T, Amano H, Yoshida M, Isaka T, Toyota N, Wada K, Takagi K, Kato K (2006) A case of peribiliary cysts accompanying bile duct carcinoma. World J Gastroenterol 12:4596–4598

Miyake H, Yuasa N, Kamiya J, Nagino M, Uesaka K, Oda K, Sano T, Nimura Y (2001) Images in focus. Peribiliary cysts both in the cystic duct and in the intrahepatic biliary tract. Endoscopy 33:643

Montoriol PF, Poincloux L, Petitcolin V, Da Ines D (2012) Peribiliary cysts mistaken for a biliary dilatation in a cirrhosis patient. Clin Res Hepatol Gastroenterol 36: e93–e95

Motoo Y, Yamaguchi Y, Watanabe H, Okai T, Sawabu N (2001) Hepatic peribiliary cysts diagnosed by magnetic resonance cholangiography. J Gastroenterol 36:271–275

Nakanishi Y, Zen Y, Hirano S, Tanaka E, Takahashi O, Yonemori O, Doumen H, Kawakami H et al (2009) Intraductal oncocytic papillary neoplasm of the bile duct: the first case of peribiliary gland origin. J Hepatobiliary Pancreat Surg 16:869–873

Nakanishi Y, Naanuma Y, Ohara M, Iwao T, Kimura N, Ishidate T, Kijima H (2011) Intraductal papillary neoplasm arising from peribiliary glands connecting with the inferior branch of the bile duct of the anterior segment of the liver. Pathol Int 61:773–777

Nakanuma Y (2001) Peribiliary cysts: a hitherto poorly recognized disease. J Gastroenterol Hepatol 16:1081–1083

Nakanuma Y (2004) Peribiliary cysts have at least two different pathogeneses. J Gastroenterol 39:407–408

Nakanuma Y, Sato Y (2012) Cystic and papillary neoplasm involving peribiliary glands: a biliary counterpart of branch-type intraductal papillary mucinous neoplasm? Comment Hepatology 55:2040–2041

Nakanuma Y, Kurumaya H, Ohta G (1984) Multiple cysts in the hepatic hilum and their pathogenesis. A suggestion of periductal gland origin. Virchows Arch A Pathol Anat Histopathol 404:341–350

Nakanuma Y, Yamaguchi K, Ohta G, Terada T (1988) Pathologic features of hepatolithiasis in Japan. Hum Pathol 19:1181–1186

Nakanuma Y, Katayanagi K, Terada T, Saito K (1994a) Intrahepatic peribiliary glands of humans. I. Anatomy, development and presumed functions. J Gastroenterol Hepatol 9:75–79

Nakanuma Y, Sasaki M, Terada T, Harada K (1994b) Intrahepatic peribiliary glands of humans. II. Pathological spectrum. J Gastroenterol Hepatol 9:80–86

Nakanuma Y, Hoso M, Sanzen T, Sasaki M (1997) Microstructure and development of the normal and pathologic biliary tract in humans, including blood supply. Micros Res Tech 38:552–570

Nakayama S (2010) Development of multiple peribiliary cysts following acute alcoholic hepatitis. Indian J Gastroenterol 29:129

Okada S, Kojima Y, Morozumi A, Ainota T, Miyazaki Y, Akahane Y (2001) Multiple hepatic peribiliary cysts discovered incidentally at a medical examination. J Gastroenterol Hepatol 16:1167–1169

op den Dries S, Westerkamp AC, Karimian N, Gouw AS, Bruinsma BG, Markmann JF et al (2014) Injury to peribiliary glands and vascular plexus before liver transplantation predicts formation of non-anastomotic biliary strictures. J Hepatol 60:1172–1179

Otani K, Ueki T, Kawamoto K, Noma E, Shimizu A, Fujimura N, Sakaguchi S, Matsui T et al (2006) Clinical course of 4 cases of hepatic peribiliary cysts and a summary of the 38 clinical cases reported in Japan (in Japanese). Nihon Shokakibyo Gakkai Zasshi 103:961–968

Pang T, Kuo S, Hugh TJ, Davidson T, Eckstein RP, Bell C, Samra JS (2010) The role of peribiliary cysts in biliary obstruction. ANZ J Surg 80:699–702

Sato H, Nakanuma Y, Kozaka K, Sato Y, Ikeda H (2013) Spread of hilar cholangiocarcinomas via peribiliary gland network: a hither-to-unrecognized route of periductal infiltration. Int J Clin Exp Biol 6:318–322

Sato Y, Harada K, Sasaki M, Nakanuma Y (2014) Cystic and micropapillary epithelial changes of peribiliary glands might represent a precursor lesion of biliary epithelial neoplasms. Virchows Arch 464:157–163

Seguchi T, Akiyama Y, Itoh H, Tanaka H, Naganuma S, Nagaike K, Uchiyama S, Kataoka H (2004) Multiple hepatic peribiliary cysts with cirrhosis. J Gastroenterol 39:384–390

Seo JY, Oh TH, Jeon TJ, Seo DD, Shin WC, Choi WC (2012) A case of hepatic peribiliary cysts in a patient with alcoholic liver cirrhosis (in Korean). Korean J Gastroenterol 60:119–122

Stevens W, Harford W, Lee E (1996) Obstructive jaundice due to multiple hepatic peribiliary cysts. Am J Gastroenterol 91:155–157

Sutton ME, op den Dries S, Koster MH, Lisman T, Gouw AS, Porte RJ (2012) Regeneration of human extrahepatic biliary epithelium: the peribiliary glands as progenitor cell compartment. Liver Int 32:554–559

Takahashi H, Miwa S, Nomoto K, Hayashi S, Tsuneyama K, Takano Y (2009) Peribiliary cyst of common bile duct: possible cause of refractory jaundice. Pathol Int 59:692–693

Terada T (2011) Hepatic nodular hamartoma containing liver cysts, ductal plate malformations and peribiliary glands. Hepatol Res 41:93–98

Terada T, Moriki T (2010) Monolobar ductal plate malformation disease of the liver. Pathol Int 60:407–412

Terada T, Nakanuma Y (1988) Morphological examination of intrahepatic bile ducts in hepatolithiasis. Virchows Arch A Pathol Anat Histopathol 413:167–176

Terada T, Nakanuma Y (1990a) Pathological observations of intrahepatic peribiliary glands in 1,000 consecutive autopsy livers. II. A possible source of cholangiocarcinoma. Hepatology 12:92–97

Terada T, Nakanuma Y (1990b) Pathological observation of intrahepatic peribiliary glands in 1000 consecutive autopsy livers. III. Survey of necroinflammation and cystic dilatation. Hepatology 12:1229–1233

Terada T, Nakanuma Y (1991) Immunohistochemical demonstration of pancreatic alpha-amylase and trypsin in intrahepatic bile ducts and peribiliary glands. Hepatology 14:1129–1135

Terada T, Nakanuma Y (1992) Pathologic observations of intrahepatic peribiliary glands in 1,000 consecutive autopsy livers: IV. Hyperplasia of intramural and extramural glands. Hum Pathol 23:483–490

Terada T, Nakanuma Y (1993a) Pancreatic lipase is a useful phenotypic marker of intrahepatic large and septal bile ducts, peribiliary glands, and their malignant counterparts. Mod Pathol 6:419–426

Terada T, Nakanuma Y (1993b) Expression of alpha-amylase isoenzymes and trypsin by the proliferating epithelium of large intrahepatic bile ducts and intrahepatic peribiliary glands in hepatolithiasis. Histopathology 22:467–473

Terada T, Nakanuma Y (1993c) Development of human intrahepatic peribiliary glands. Histological, keratin immunohistochemical, and mucus histochemical analyses. Lab Invest 68:261–269

Terada T, Nakanuma Y, Ohta G (1987) Glandular elements around the intrahepatic bile ducts in man; their morphology and distribution in normal livers. Liver 7:1–8

Terada et al. (1990) Pub Med PMID 2182371

Terada T, Sasaki M, Nakanuma Y, Takeda Y, Masunaga T (1992a) Hilar cholangiocarcinoma (Klatskin tumor) arising from intrahepatic peribiliary glands. J Clin Gastroenterol 15:79–81

Terada T, Minato H, Nakanuma Y, Shinozaki K, Kobayashi S, Matsui O (1992b) Ultrasound visualization of hepatic peribiliary cysts: a comparison with morphology. Am J Gastroenterol 87:1499–1502

Terada T, Kida T, Nakanuma Y (1993) Extrahepatic peribiliary glands express alpha-amylase isozymes, trypsin and pancreatic lipase: an immunohistochemical analysis. Hepatology 18:803–808

Terada T, Matsushita H, Tashiro J, Sairenji T, Eriguchi M, Osada I (2003) Cholesterol hepatolithiasis with peribiliary cysts. Pathol Int 53:716–720

Terasaki S, Nakanuma Y, Unoura M, Kaneko S, Kobayashi K (1997) Involvement of peribiliary glands in primary sclerosing cholangitis: a histopathologic study. Intern Med 36:766–770

Terayama N, Matsui O, Hoshiba K, Kadoya M, Yoshikawa J, Gabata T, Takashima T et al (1995) Peribiliary cysts in liver cirrhosis: US, CT, and MR findings. J Comput Assist Tomogr 19:419–423

Tohma T, Miura F, Cho A, Okazumi S, Asano T (2009) Usefulness of computed tomography during cholangiography for the diagnosis of multiple hepatic peribiliary cysts: a report of three cases with chronic liver disease. J Hepatobiliary Pancreat Surg 16:372–375

Usuda A, Shiozawa S, Tsuchiya A, Kim DH, Usui T, Inose S, Aizawa M, Masuda T et al (2009) Carcinoma of the ampulla of Vater arising from the peribiliary gland. Hepatogastroenterology 56:1542–1544

Wanless IR, Zahradnik J, Heathcote EJ (1987) Hepatic cysts of periductal gland origin presenting as obstructive jaundice. Gastroenterology 93:894–898

Yokomichi H, Tsuji K, Hayashi Y, Kaneko M, Nakadoi K, Ishida Y, Kuwabara T, Tsumuna T et al (2006) A case of multiple hepatic peribiliary cysts which contributed to the obstructive jaundice and led to liver failure at the young man with von Recklinghausen's disease. Hepatol Res 35:222–227

Zen Y, Terahata S, Miyayama S, Mitsui T, Takehara A, Miura S, Nobata K, Kitao A et al (2006) Multicystic biliary hamartoma: a hitherto undescribed lesion. Hum Pathol 37:339–344

Zen Y, Amarapurkar AD, Portmann BC (2012) Intraductal tubulopapillary neoplasm of the bile duct: potential origin from peribiliary cysts. Hum Pathol 43:440–445

Part III

Hepatobiliary Tumors Derived from Other Epithelial Lineages

Carcinomas with a Squamous Cell Lineage

42

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_42

Abstract

Several types of bile duct cancer are characterized by a squamous cell lineage. Squamous cell carcinomas with keratinization can occur in both extrahepatic and intrahepatic bile ducts. These tumors may present as lesions entirely composed of cancerous keratinocytes or occur in conjunction with other cellular components, such as adenocarcinoma. Overall, these are rare neoplasms that account for less than 2 % of biliary malignancies. Most of squamous cell carcinomas originate from bile ducts, but the site of origin may be difficult to determine in intrahepatic tumors. There is evidence that squamous cell carcinoma can develop in the liver substance without detectable association with bile ducts. These neoplasms can also develop in various types of hepatic cysts, in particular choledochal cysts. Adenosquamous carcinoma is a rare malignancy containing both squamous and glandular elements. In the liver, it develops either as a variant of cholangiocarcinoma or as a neoplasm not proven to be related to bile ducts. A further and very uncommon hepatobiliary carcinoma that possesses a squamous cell lineage is mucoepidermoid carcinoma.

Squamous Cell Carcinoma of the Hepatobiliary Tract

ICD-O code 8070/3

Introduction

Squamous cell carcinoma of the biliary tract is rare, accounting for less than 2 % of biliary malignancies. This biliary neoplasm was first described in 1930 (Cabot 1930). Squamous cell carcinoma can develop in the intrahepatic or extrahepatic bile ducts. It may present as a tumor entirely composed of keratinocytes or may occur in conjunction with other cellular components, such as adenocarcinoma or neuroendocrine neoplasms. Clinically, the tumors show the growth pattern of mass lesions and therefore cause duct stenosis with all sequelae known from classical cholangiocarcinoma. As squamous cell carcinomas of the biliary tract are rapidly growing, highly invasive, and aggressive lesions, they are clinically characterized by large tumor size and high stage at diagnosis, aggressive modes of intrahepatic spreading, and frequent metastasis (Nakajima and Kondo 1990).

Squamous Cell Carcinoma of the Extrahepatic Bile Ducts

Extrahepatic duct squamous cell carcinomas develop in the hepatic duct (Hagemann 1964; Abbas et al. 2008) or common bile duct (Cabot 1930; Neibling et al. 1949; Sako et al. 1957; Shani et al. 1974; Andersson et al. 1977; Burger et al. 1978; Gulsrud et al. 1979; Nakajima et al. 1988; Funakawa et al. 1996; Gatof et al. 2004; La Greca et al. 2004; Sewkani et al. 2005; Sanada et al. 2010). Very few cases of squamous cell carcinoma of the hilar area are found in the literature (Aranha et al. 1980; Nakajima and Kondo 1990). There is only one report describing squamous cell carcinoma of the cystic duct. This tumor developed in a patient with occupational asbestos, and asbestos bodies were detected within the tumor (Szendroi et al. 1983).

Squamous Cell Carcinoma of the Intrahepatic Bile Ducts

Several reports have document pure or mixed squamous cell carcinoma apparently developing in intrahepatic bile ducts, although the site of origin may be difficult to determine (Aranha et al. 1980; Song et al. 1984; Nakajima and Kondo 1990; Roediger and Dymock 1991; Saito and Nakanuma 1995; Shinagawa et al. 1996; Tsuneyama et al. 2003; La Greca et al. 2004). For cases that are not clearly related to the intrahepatic bile duct system, the term squamous cell carcinoma of the liver is used. Most squamous cell tumors occurring in intrahepatic bile ducts are mixed lesions, consisting of squamous cell carcinoma with focal adenocarcinoma,

adenosquamous carcinoma, adenocarcinoma with focal squamous differentiation, and anaplastic carcinoma with either squamous, adenoid, or combined squamous-adenoid differentiation (Nakajima and Kondo 1990). In one reported case, squamous cell carcinoma was in close association with a cholangiocarcinoma and hepatocellular carcinoma (Tsuneyama et al. 2003). Squamous cell carcinoma of bile ducts was found in association with hepatolithiasis (Song et al. 1984).

As in other organs, the tumor is histologically characterized by a stratified epithelium consisting of keratinocytes in various phases of differentiation. Hepatobiliary squamous cell carcinomas may show marked keratinization (Nakajima and Kondo 1990; Tsuneyama et al. 2003).

Primary Squamous Carcinoma of the Liver

Introduction

Primary hepatic squamous cell carcinoma (SCC-L) is defined as a squamous cell carcinoma apparently arising in the liver substance without detectable association with the biliary tract or congenital or acquired cysts. In part of the reports relating to SCC-L, it is difficult to judge from which tissue structure the tumor had arisen, and an origin from intrahepatic ducts may be difficult to exclude. However, in few instances the hepatic origin of this rare tumor has been verified by autopsy. Younger females and the left liver lobe seem to be more frequently involved. There is an association of this tumor type with hepatolithiasis (Song et al. 1984), a disorder also complicated by cholangiocarcinoma (Chen et al. 1984).

Selected References (Imai 1934a,b; Geddes 1970; Song et al. 1984; Gresham and Rue 1985; Pawelczak et al. 1987; Mandai et al. 1989; Clements et al. 1990; Koyama et al. 1990; Banbury et al. 1994; Quijano Orvananos et al. 1994; Shinagawa et al. 1996; Doctor et al. 1998; Yoshida et al. 1998; Saito et al. 2002; Kaji et al. 2003; Klug et al. 2003; Bondini et al. 2005; Lee et al. 2006; Shchegolev et al. 2006; Yuki et al. 2006; Naik et al. 2009).

There is evidence that many of SCC-Ls might have arisen from hepatic epidermoid cysts (Lombardo et al. 1995; Caratozzolo et al. 2001); congenital cysts (Pliskin et al. 1992; Steffani et al. 2003; Hsieh et al. 2005), including the ciliated hepatic foregut cyst (Vick et al. 1999b; Furlanetto and Dei Tos 2002); or solitary nonparasitic cysts (Edmondson 1958; Greenwood and Orr 1972; Bloustein and Silverberg 1976; Bloustein 1977; Kasai et al. 1977; Beppu et al. 1978; Gresham and Rue 1985; Lynch et al. 1988; Nieweg et al. 1992; Banbury et al. 1994; Weimann et al. 1996; Chou et al. 1997; Charles and Gupta 2001; Yagi et al. 2004).

Clinical and Imaging Features

Clinically, these tumors may present as right upper abdominal fullness and/or pain, hepatomegaly, weight loss, and intermittent fever (Roediger and Dymock 1991; Caratozzolo et al. 2001). A literature review had shown that abdominal pain is the chief symptom of primary SCC-L (Yuki et al. 2006). SCC-L has been found in association with liver cirrhosis (Yuki et al. 2006). In some patients, the tumor was associated with hypercalcemia (Arase et al. 1988), and more recently, it surfaced that part of these tumors produce, as a paraneoplastic phenomenon and similar to squamous carcinomas located elsewhere (Welsh and Powers 1993; Jais et al. 1997; Crespo et al. 1999), parathyroid hormone-related peptide/protein (PTHrP) (Asanuma et al. 2002; Saito et al. 2002), this peptide being immunohistochemically detectable in the neoplastic cells (Saito et al. 2002). In one patient, PTHrP production was associated with increased serum levels of IL-6, thought to result from induced osteoblasts (Asanuma et al. 2002). Similar to adenosquamous carcinoma (see below), primary SCC-L has been shown to rarely produce granulocyte colony-stimulating factor (Koyama et al. 1990). The diagnosis may be suspected in bile cytology specimens from PTCD (Shinagawa et al. 1996). The prognosis of this type of hepatic cancer is extremely poor, no patient having survived longer

than 6 months after diagnosis, as far as can be judged from the literature (Bloustein and Silverberg 1976; Clements et al. 1990; Yagi et al. 2004; Lee et al. 2006). In case the squamous cell carcinoma arises in a hepatic cyst, an unusual color of the cyst fluid upon puncture (blood-stained or brown fluid), cyst infection, and rapid cyst recurrence subsequent to conservative treatment should raise suspicion of malignancy.

Pathology

Macroscopy

SCC-Ls are usually large or very large tumors with either an expanding or grossly invasive growth pattern, and even in case where the tumor took its origin from a preexistent hepatic cyst, most of the cystic space may be replaced or occupied by the cancer masses. In one case, a unilocular hepatic cyst was buried within a large tumor mass, but the carcinoma also exhibited an intracystically growing, exophytic component, forming an impressive intraluminal fungating mass (Pliskin et al. 1992).

Histopathology

Histologically, the phenotype found in other such tumors is observed, i.e., medium-sized to large keratinocytes forming strands in a variably developed stroma (Figs. 1, 2, 3, and 4). Marked keratinization of the neoplastic cells can develop (Chou et al. 1997), sometimes with decay of the keratinocyte masses and formation of a central cystic lesion. In such a situation, the tumor may be clinically confounded with a hepatic abscess (Doctor et al. 1998). On the other hand, part of the tumors lacked keratinization (Shchegolev et al. 2006).

Interestingly, tumors with a basaloid component have also been detected as primary hepatic lesions (basaloid-squamous carcinoma, BSC; Bastiaan de Boer 2000). The entity of BSC was first described in 1986 based on a group of ten unusual cancers involving the mucosa and underlying tissue of the

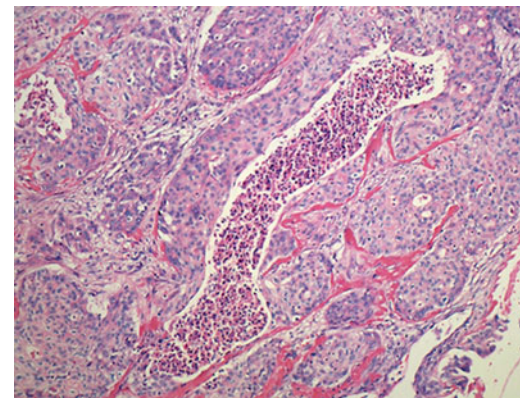

Fig. 2 Poorly differentiated squamous cell carcinoma of the hepatobiliary tract. Note the focal necrosis (*center* of figure; hematoxylin and eosin stain)

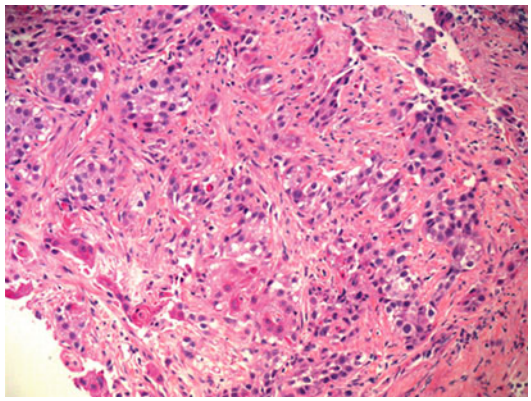

Fig. 1 Well-differentiated squamous cell carcinoma of the hepatobiliary tract with focal keratinization (hematoxylin and eosin stain)

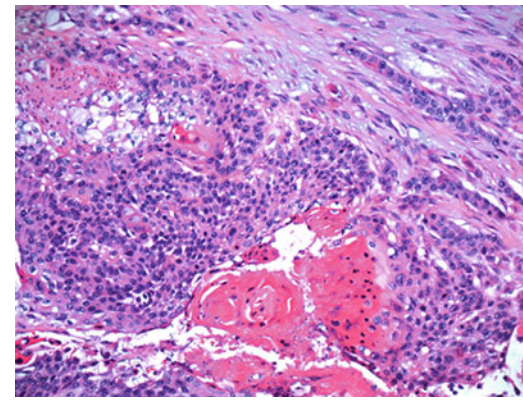

Fig. 3 Keratinizing hepatobiliary squamous cell carcinoma with a large area of parakeratosis (*below* of the *middle*; hematoxylin and eosin stain)

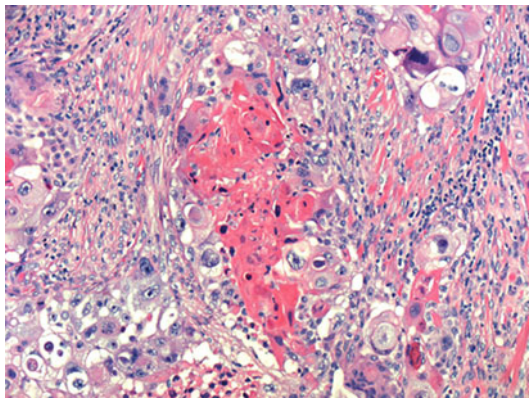

Fig. 4 Hepatobiliary squamous cell carcinoma with parakeratosis, dyskeratosis (single cell keratinization), tumor cell ballooning, and apoptosis (hematoxylin and eosin stain)

tongue, hypopharynx, and larynx and originally was termed basaloid-squamous carcinoma (Wain et al. 1986). BSC is a highly aggressive neoplasm, histologically characterized by an intimate association of a basaloid pattern with squamous cell carcinoma, the basaloid part consisting of small crowded cells with hyperchromatic nuclei, scant cytoplasm, small cystic spaces, foci of tumor necrosis, and prominent hyalinosis. The only case reported for the liver was in a 46-year-old female and presented as a huge, i.e., 27 cm-sized, centrally necrotic tumor in the right liver lobe (Bastiaan de Boer 2000).

Differential Diagnosis

Apart from squamous cell carcinoma arising from bile ducts, the principal differential diagnosis is metastasis of extrahepatic squamous cell carcinomas, which have numerous primary sites. However, esophageal SCC is a predominant primary lesion producing hepatic metastases (Maclean et al. 1962; Sumi et al. 2000; Nakajima et al. 2001; Ikeda et al. 2003; Pouessel et al. 2005; Pawlik et al. 2007; Morris et al. 2011; Sanal et al. 2011). Hepatic metastases of SCC can present as hepatic cysts (Morris et al. 2011). Squamous cell carcinoma arising in adjacent organs can directly invade the liver, e.g., squamous cell carcinoma of the esophagus (Akagi et al. 2011).

Pathogenesis

Squamous cell metaplasia with varying degrees of dysplasia has been reported in conjunction with squamous cell carcinoma of the bile duct (Song et al. 1984; Shinagawa et al. 1996; Abbas et al. 2008), but metaplasia was not detected in one study (Nakajima and Kondo 1990). Squamous metaplasia also occurs in the gallbladder (Hanada et al. 1986; Daud et al. 2007), where squamous cell carcinoma is a rather common entity, again suggesting that a metaplasia-dysplasia-carcinoma sequence may be involved. A progression from adenocarcinoma to squamous cell carcinoma has been observed in a cholangiocellular carcinoma nude mouse strain (Iemura et al. 1992).

Squamous Cell Carcinoma in Hepatic Cysts

Introduction

Several types of hepatic cysts with an epithelial lining can undergo metaplastic changes, including squamous metaplasia. This alteration may be the starting point of a dysplasia-carcinoma sequence, ending up with squamous cell carcinoma. Most observations of cystogenic squamous cell carcinoma relate to simple nonparasitic liver cysts, which are the most frequent hepatic cystic lesions.

Squamous Cell Carcinoma in Simple Nonparasitic Hepatic Cysts

Solitary nonparasitic (simple) hepatic cysts are relatively common developmental disorders of the biliary cell system, probably related to ductal plate malformations and related lesions (Flagg and Robinson 1967). Squamous cell carcinoma arising from a nonparasitic cyst is a rare entity with an unfavorable prognosis. It is assumed that this type of cancer develops in an epithelial cyst lining having undergone squamous metaplasia. However, squamous cell carcinoma of the liver has also been found to arise adjacent to a nonparasitic cyst (Iimuro et al. 2011). Squamous

cell carcinoma may develop in simple hepatic cysts after a long delay, in one patient after a 15-year follow-up (Yagi et al. 2004). In a review of ten cases, age range was 30–78 years, with a marked male predominance. Of the seven patients of whom follow-up was available, the survival ranged from 13 days to 16 months, six patients not surviving longer than 6 months (Weimann et al. 1996).

Selected References (Greenwood and Orr 1972; Bloustein and Silverberg 1976; Sanz Esponera et al. 1979; Gresham and Rue 1985; Lynch et al. 1988; Nieweg et al. 1992; Pliskin et al. 1992; Banbury et al. 1994; Weimann et al. 1996; Chou et al. 1997; Monteagudo et al. 1998; Steffani et al. 2003; Yagi et al. 2004; Hsieh et al. 2005; Iimuro et al. 2011).

Malignancy in a simple cyst may be suspected when the cyst fluid is hemorrhagic and the cyst recurs several times after conservative treatment. However, it is also known that repeated episodes of spontaneous intracystic hemorrhage may occur in the absence of malignancy (Chang et al. 2000). In one patient, the tumor was found in the context of cyst recurrence after six attempts of conservative treatment with sonography-guided drainage over a period of more than 1 year, leading to surgical cyst deroofing (Weimann et al. 1996).

Squamous Cell Carcinoma in Polycystic Liver Disease

Carcinomas developing in the cystic spaces of adult-type polycystic liver disease are very uncommon. The few cases reported so far included papillary adenocarcinoma (Rehulova and Dite 1981), cholangiocellular carcinoma (Inamura et al. 1984; Landais et al. 1984), and poorly differentiated adenocarcinoma (Kataoka et al. 1985).

Squamous Cell Carcinoma in Ciliated Foregut Cyst

Ciliated foregut cyst is a rare benign cystic lesion of the liver that arises from the embryonic foregut, like the bronchogenic cysts (Wheeler and Edmondson 1984). Most ciliated foregut cysts occur in the left liver lobe, particularly in segment IV (Jakowski et al. 2004; Sharma et al. 2008), but they also develop in the right liver lobe, the gallbladder, the pancreas, and the retroperitoneal space (Kaijya et al. 1997; Munshi et al. 1998; Chatelain et al. 2000). The mean age at diagnosis is 50 years, and there is a slight male predilection (Vick et al. 1999a). It is usually a solitary uniocular asymptomatic lesion, but it rarely causes portal hypertension by hepatic vein compression or jaundice by bile duct compression. Histologically, the cyst lining is a pseudostratified ciliated columnar epithelium.

There are relatively few reports on squamous cell carcinoma arising in ciliated hepatic foregut cysts (Vick et al. 1999b; Caratozzolo et al. 2001; De Lajarte-Thirouard et al. 2002; Furlanetto and Dei Tos 2002; Zhang et al. 2009). Ciliated foregut cysts rarely show squamous metaplasia, in contrast to bronchogenic cysts, but rare cysts may undergo extensive squamous epithelial metaplasia almost hiding the preexistent ciliated epithelium (Ben Mena et al. 2006). Squamous metaplasia may be the field change promoting malignant transformation. In fact, four cases of this type of cyst with squamous metaplasia were always associated with squamous cell carcinoma (Vick et al. 1999b; Caratozzolo et al. 2001; De Lajarte-Thirouard et al. 2002; Furlanetto and Dei Tos 2002). In the case of Caratozzolo and coworkers (2001), the zone of invasive squamous cell carcinoma was separated from the ciliated columnar epithelium by a zone of squamous metaplasia.

Squamous Cell Carcinoma in Hepatic Epidermoid Cyst

Development of dysplasia, carcinoma in situ, and squamous cell carcinoma is well established in epidermoid cysts occurring in several organs. Squamous cell carcinoma has been identified in epidermoid cysts of the liver (Lombardo et al. 1995; Ödemis et al. 2006). In the case reported by Ödemis and coworkers (2006), the cyst was situated in segment VIII and was lined

by a markedly keratinizing stratified squamous epithelium without endodermal or neuroectodermal components, blending into an invasively growing squamous cell carcinoma.

Squamous Cell Carcinoma in Cystic Hepatic Teratoma

There is a single case report describing the development of squamous cell carcinoma in a cystic teratoma of the liver (Imai 1934a, b).

Squamous Cell Carcinoma in Choledochal Cysts

Choledochal cysts are rare congenital or acquired cystic dilatations of the intrahepatic or extrahepatic bile ducts. The estimated incidence is around 1 in 100,000–150,000 persons (Lipsett et al. 1994). These cystic dilatations, when untreated, cause bile stasis, inflammation, and scarring, conditions that may lead to epithelial damage, dysplasia, and eventually cancer. Pathology of resected choledochal cysts has shown denudation, erosion or even ulceration of the cyst mucosa, acute and chronic inflammation, fibrosis (Swisher et al. 1994), and disruption of elastic fibers in the cyst wall (Jordan et al. 2004).

Malignant transformation in choledochal cysts is an age-related phenomenon that occurs in 10–14 % of adults with this disorder. Most commonly reported malignancies include adenocarcinomas of the cholangiocarcinoma type, but other carcinomas also develop in choledochal cysts (Voyles et al. 1983; Fieber and Nance 1997; Bismuth and Krissat 1999; Jan et al. 2002). Squamous cell carcinoma in choledochal cysts has been reported several times (Todani et al. 1977; Harris et al. 2002; Jan et al. 2002; Price et al. 2008). Primary adenosquamous carcinoma has also been reported in a congenital choledochal cyst (Terada 2009).

Squamous cell carcinoma may be manifest after a long time period. In one patient, the cancer was detected more than 30 years after cyst excision (Harris et al. 2002). In another patient, a poorly differentiated squamous cell carcinoma was found in the residual posterior wall of a cyst 22 years after cystojejunostomy and Roux-en-Y hepaticojejunostomy (Jan et al. 2002). In a third patient, the tumor was observed to arise from the posterior wall of a drained cyst 2 years after choledochocystoduodenostomy (Todani et al. 1977). Carcinoma may develop in the remaining intrapancreatic biliary tract years after the primary excision of a choledochal cyst (Fujisaki et al. 1999). Squamous cell carcinoma in these cystic dilatations is sometimes associated with multiple intracystic calculi (Price et al. 2008), which may play a pathogenic role for the generation of metaplastic and dysplastic changes. Pathogenetically, the tumor is possibly related to squamous cell metaplasia of the epithelial cyst lining. Squamous cell carcinoma has also been observed in conjunction with hepatolithiasis (Song et al. 1984).

Differential Diagnosis

Primary squamous cell carcinoma of the liver may undergo necrosis and thus present as a cyst or a liver abscess (Doctor et al. 1998). Squamous cell carcinoma has an unexplained tendency to develop cystic changes in its metastases, including those located to the liver (Marcy et al. 2004; Nair and Pai 2005; Morris et al. 2011). Liver metastases of squamous cell carcinoma, e.g., originating in the female genital tract, can mimic polycystic liver disease (Estermann et al. 1996; Alsolaiman et al. 2002).

Adenosquamous Carcinoma of the Hepatobiliary Tract

ICD-O code 8560/3

Introduction

Adenosquamous carcinoma (ASC; adenoacanthoma (AA)) is defined as a cancer containing both squamous and glandular elements

in the same lesion, with each component comprising at least 10 % of the entire tumor (WHO). ASCs occur in numerous organs and tissues; in the liver, they develop either as variants of cholangiocarcinomas (CCs) or as primary tumors not proven to be related to intrahepatic bile ducts, the latter probably representing a minority of the cases. ASC is one of the best-known cholangiocarcinoma variants, with numerous reports describing this distinct lesion.

Selected References (Urushizaki et al. 1973; Barr and Hancock 1975; Muto et al. 1982; Kubo et al. 1983; Moore et al. 1984; Lantsberg et al. 1996; Ohyanagi et al. 1986; Tomioka et al. 1987; Hu et al. 1988; Mandai et al. 1989; Nakajima and Kondo 1990; Suga et al. 1990; Hamaya et al. 1991; Horiuchi et al. 1991; Baba et al. 1992; Hayashi et al. 1993; Higuchi et al. 1993; Kitakado et al. 1993; Ahn et al. 1994; Hamamoto et al. 1994; Sasaki et al. 1994; Hayshi and Onitsuka 1995; Hughes and Niemann 1996; Kimoto et al. 1996; Ochiai et al. 1996; Yamamoto et al. 1996; Isa et al. 1997; Maeda et al. 1997; Nakazawa et al. 1997; Takahashi et al. 1997; Okamura et al. 2000; Yavuz et al. 2000; Kwon et al. 2001; Sato et al. 2001; Zhang et al. 2001; Ono et al. 2002; Suzuki et al. 2002; Ueno et al. 2002; Yeh et al. 2002, 2003; Tsuneyama et al. 2003; Nakai et al. 2004; Demir et al. 2005; Gu et al. 2005; Kobayashi et al. 2005; Okabayashi et al. 2005; Shin et al. 2006; Song et al. 2006; Lim et al. 2007; Yokota et al. 2007; Hong et al. 2008; Kim et al. 2009).

Classification: Hepatic Versus Biliary Tract Adenosquamous Carcinoma

Most ASCs develop in the intrahepatic or extrahepatic bile duct system (ASC-BD). ASC can develop along the entire biliary tract, including the gallbladder.

Selected References (Kusakina and Nigmatulina 1980; Muto et al. 1982; Stamatiadis et al. 1989; Kojima et al. 1994; Nishihara et al. 1994; Nishihara et al. 1995; Wagreich et al. 1998; Ercolani et al. 1999; Saito et al. 1999; Kondo et al. 2002; Oohashi et al. 2002; Akcali et al. 2005; Fujita et al. 2005b; Mingoli et al. 2005; Chan et al. 2007; Lada et al. 2007).

Primary ASC of the liver (ASC-L) sensu strictiori develops as a mass-forming lesion and seems, with respect to the growth pattern and probably origin, to occur in two variants, i.e., one related to intrahepatic CC and the other without a clear-cut relation to preexisting bile duct cancer. In several reports, it is claimed that the first observation was published in 1971 (Pianzola and Drut 1971), but these authors in fact described a hepatic mucoepidermoid carcinoma, and the ADC of the liver/bile duct was probably reported in 1973 under the term "adenoacanthoma" (Urushizaki et al. 1973).

Epidemiology

Overall, this type of carcinoma is rare, the incidence among cholangiocarcinomas being 2–3 %. The reported data markedly depend on definitions employed to denote a tumor as adenosquamous carcinoma. One study analyzed a set of 177 histologically defined cases of intrahepatic cholangiocarcinomas observed from 1975 to 1988 in Japan. Of these, 11 cases (1 surgical and 10 autopsy cases) showed a feature of squamous carcinoma (Nakajima and Kondo 1990). The authors had further broken down the cases with respect to the other histologic components present. Adenosquamous carcinoma was accepted in case the tumor contained equal amounts of squamous and glandular elements. Of the 11 cases of cholangiocarcinoma with squamous cell features, 3/11 were classified as bona fide adenosquamous carcinoma, 3/11 as squamous cell carcinoma with focal adenocarcinoma, 3/11 as adenocarcinoma with focal squamous cell carcinoma, 1/11 as anaplastic carcinoma with adenocarcinoma and squamous cell carcinoma, and 1/11 as anaplastic carcinoma with squamous cell carcinoma. 3/11 patients showed gallstones. In this series, there was no instance of a pure form of squamous cell carcinoma. In a study of 228 surgically treated cholangiocarcinoma patients,

12 (5.3 %) had adenosquamous carcinomas (Yeh et al. 2002). A male predominance is observed in the reported cases, as is a prominent relationship to hepatolithiasis.

Clinical and Imaging Presentation

Clinically, the tumor causes abdominal pain, and the majority of the masses are associated with obstructive jaundice (Kim et al. 2009). The tumor may clinically present as liver abscess (Kwon et al. 2001) and has been shown to produce biliary fistula (Ohyanagi et al. 1986) or extrahepatic growth with formation of a tumor-colon fistula (Shin et al. 2006). The tumor has been found to develop in association with congenital choledochal dilatation and pancreaticobiliary maljunction (Okamura et al. 2000; Terada 2009). In one patient, primary adenosquamous carcinoma of the liver was associated with an elevated level of serum squamous cell carcinoma-related antigen (Yamamoto et al. 1996).

Imaging features are shared with other carcinomas developing in the extrahepatic biliary tract (Yokota et al. 2007; Kim et al. 2009). In CT scans, the lesion was diagnosed as bile duct cancer of the periductal infiltrative type seen as a segmentally thickened ductal wall encircling the lumen, with delayed enhancement. Rarely, intraductal polypoid lesions occur. The highly invasive phenotype is manifest as periductal fat infiltration, seen as a fatty strand in the periductal soft tissue on CT scan. Hyperattenuation of the lesion on portal venous phase was commonly shown (Kim et al. 2009).

Pathology

Macroscopy

ASCs developing in bile ducts (ASC-BD) form large and invasive masses that cause duct obstruction. The neoplasms are usually nodular lesions with ill-defined margins. Similarly, most ASC-Ls are mass-forming and sometimes large lesions, and their diameter may exceed 15 cm. Rarely, the tumors grossly present as a focally cystic tumor (Barr and Hancock 1975). Growth is either expanding or macroscopically invasive, sometimes associated with peritumoral satellites or intrahepatic metastases. Owing to desmoplasia, the tumors exhibit a form consistency, but the center may be friable due to extensive necrosis. Rare variants of ASC-L present as multinodular or multicystic lesions with spongiform changes (Park et al. 2012). ASC-L can also mimic a liver abscess (Yeung et al. 2012).

Histopathology

In the majority of cases, a moderately to well-differentiated (G1 and G2) biliary-type adenocarcinoma prevails, commonly with easily recognizable gland-like structures and focally abundant mucin production as seen in alkaline Alcian blue preparations (Fig. 5). Papillary components may be found. Admixed with areas of adenocarcinoma and sometimes occurring as separate sheets of neoplastic cells are foci of squamous cell carcinoma, with varying differentiation of the neoplastic keratinocytes. These foci are characterized by cell groupings with a pavement-like appearance. Individual cell keratinization is common, and squamous pearl formation has been reported, albeit rarely.

In comparison with purely adenoid-/glandular-type intrahepatic cholangiocarcinoma, cholangiocarcinoma with a squamous cell component was

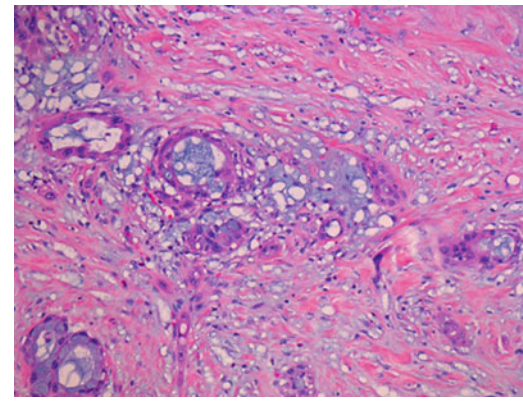

Fig. 5 Adenosquamous carcinoma of the biliary tract. There are only small squamous cell nests (hematoxylin and eosin stain)

found to show a higher incidence in sinusoidal invasion, vascular involvement, permeation in the portal tract connective tissue, perineural or intraneural invasion, and lymphatic involvement, but replacing growth along the bile duct epithelium was not detected in tumors with a squamous component, in contrast to other cholangiocarcinomas, where this was noted in 15.8 % (Nakajima and Kondo 1990). In general, a similar histologic pattern (i.e., the concurrent presence of glandular and squamous components) was observed at various metastatic sites (Nakajima and Kondo 1990). An acantholytic pattern may occur in the squamous component, a feature that has previously been described for adenosquamous carcinoma of the pancreas (Alwaheeb and Chetty 2005).

Immunohistochemistry

Immunohistochemically, the adenocarcinoma components are reactive for both cytokeratin 7 and 19. In admixed regions, cytokeratin 7 and 19 expression tends to be more marked in the central parts, where adenoid components with tubulo-glandular formations prevail. The squamous cell carcinoma components were positive for cytokeratin 7 in all cases but positive for cytokeratin 19 in only about two thirds of the cases. In contrast to squamous cell carcinomas, adenosquamous carcinomas in the liver were positive for CJ 903 only in about a third. Adenosquamous carcinomas frequently express cytokeratins 8 and 18 (Maeda et al. 1997). An interesting immunohistochemical pattern is seen when testing for the expression of high-molecular-weight cytokeratins. In admixed regions, cells with squamoid features located more to the periphery of the cancer cell formations tend to be more strongly stained, thus suggesting a transition between squamous cells of varying grades of differentiation and glandular components. CYFRA 21-1 is a tumor marker which is useful in evaluating carcinomas with a squamous cell component (Yen et al. 1998).

Combined Tumors

Adenosquamous carcinoma of the liver has been observed in combination with hepatocellular carcinoma (Zhang et al. 2001; Tsuneyama et al. 2003). Also synchronous hepatic ASC and hepatocellular carcinoma have been described (Shimizu et al. 2013). In a middle-aged female patient with recurrent fever and a clinical diagnosis of hepatic abscess, adenosquamous carcinoma was found to have arisen in biliary cystadenocarcinoma (Moore et al. 1984). Adenosquamous carcinoma has also been observed to arise in mucinous cystic tumor of the pancreas (Campman et al. 1997).

Differential Diagnosis

Apart from hepatic metastases of adenosquamous carcinoma (which tend to produce cystic liver masses; Mizuguchi et al. 1997; Hyodo et al. 1999), adenosquamous carcinoma of the gallbladder may invade the hilar structures and/or the liver. This type of carcinoma has been reported to arise in the gallbladder several times (Nishihara et al. 1994; Saito et al. 1999; Kondo et al. 2002; Akcali et al. 2005; Mingoli et al. 2005; Noske and Pahl 2006; Chan et al. 2007).

Biology of Disease

In regard to the biological behavior, adenosquamous carcinomas usually have a poorer prognosis than common adenocarcinomas in other organs, such as the stomach, pancreas, or gallbladder (Mori et al. 1986; Nishihara et al. 1994). In a set of eight patients (age range: 49–69 years), time to death after diagnosis ranged from 3 to 8 months (Maeda et al. 1997). In a study of 11 cases of intrahepatic cholangiocarcinomas with a squamous component identified among 117 intrahepatic cholangiocarcinomas (three of them adenosquamous carcinomas sensu strictiori), this tumor type was prone to develop in a rather advanced stage of the disease, as

indicated by short survival time, large tumor size, aggressive modes of intrahepatic spreading, and frequent metastasis. Intrahepatic metastases were seen in 100 % versus 67.1 % and lymph node metastases in 81.8 % versus 68.3 %, in tumors with a squamous component versus those who had not, respectively. Conversely, in an analysis of 12 patients with adenosquamous cholangiocarcinoma, there was no significant difference in overall survival between adenosquamous carcinoma and other cholangiocarcinomas (Yeh et al. 2002).

Pathogenesis of Hepatic Adenosquamous Carcinoma

The potential of cholangiocarcinoma to undergo differentiation along a squamous cell lineage is illustrated by cholangiocarcinoma cell lines propagated in vitro or in nude mice (Iemura et al. 1992; Momosaki et al. 1995). In cultured adenocarcinoma cells, transfection of human papillomavirus DNA can induce squamous metaplasia (Kinjo et al. 2003). Adenosquamous carcinomas are aggressive lesions and seem to undergo genomic instability, also suggested by desilencing of genes, e.g., with production of parathyroid-related peptide/protein (Hyodo et al. 1999; Inoue et al. 2004), sometimes with paraneoplastic hypercalcemia (Fujita et al. 2005a). Squamous cell carcinoma antigen (SSCA), previously termed TA-4, is encoded by two highly homologous genes, SCCA1 and SCCA2. An elevated level of SCCA has only once been documented in hepatic adenosquamous carcinoma (Yamamoto et al. 1996). In some squamous carcinomas, the ratio of increased expression of SCCA1 and SCCA2 was correlated with aggressive behavior and poor prognosis (Hsu et al. 2007).

Mucoepidermoid Carcinoma of the Hepatobiliary Tract

ICD-O code 8430/3

Introduction

Mucoepidermoid carcinoma (MEC; previous terminology: "mucoepidermoid tumor") is defined as a malignant neoplasm comprising mucus-secreting cells, epidermoid cells/keratinocytes, and intermediate cells in variable combinations; forming cysts and solid islands, MECs chiefly occur in major and minor salivary glands, oral cavity, larynx, thyroid, bronchopulmonary system, esophagus, skin, and breast. Less common localizations include several visceral organs, e.g., the pancreas and the hepatobiliary tract. MEC is the commonest malignant salivary gland neoplasm in adults, adolescents, and children. Patients with low-grade salivary gland MEC now show a favorable outcome, with more than 90 % of patients surviving for more than 5 years after diagnosis, while high-grade MEC is associated with poor prognosis (Friedrich et al. 2007).

Hepatobiliary Mucoepidermoid Carcinoma

The first report on hepatic MEC dates back to 1971 (Pianzola and Drut 1971). Since then, less than 25 other observations of this rare tumor have been published. An origin from the biliary tract (both intrahepatic and extrahepatic) has been suggested from both spatial relationships and ultrastructural features supporting a cholangiocyte-derived cell lineage (Di Palma et al. 1992), and the tumor has in fact been regarded to be a variant of cholangiocarcinoma (Kim et al. 1984). In few cases, an origin from bile ducts has explicitly been specified, e.g., the common bile duct (Koo et al. 1982; Shuangshoti and Shuangshoti 2000; Song et al. 2011; Moul et al. 2013). In one patient, the tumor involved the common hepatic duct, cystic duct, gallbladder, and proximal common bile duct (Koo et al. 1982). Shuangshoti and Shuangshoti found, in their review, 11 patients reported in the English literature, including their own case; among these, nine tumors were intrahepatic, two were extrahepatic and arose in the common bile ducts, three were in

the right lobe, and six were in the left liver lobe. There were six males and five females, 44–78 years old, with a mean age of 60 years. In a more recent review of 17 cases, the range for age at diagnosis was 35–81 years; ten patients were male and seven were female (Arakawa et al. 2008).

Selected References (Ho 1980; Koo et al. 1982; Katsuda et al. 1984; Kim et al. 1984, 1994; Lambrianides et al. 1986; Hayashi et al. 1987; Sasaki et al. 1991, 1995; Di Palma et al. 1992; Minami et al. 1992; Shuangshoti and Shuangshoti 2000; Kang et al. 2003; Choi et al. 2004; Arakawa et al. 2008; Song et al. 2011; Nishiyama et al. 2012; Moul et al. 2013).

It is not known whether there are distinct underlying hepatic or biliary alterations that predispose for MEC. Koo and coworkers (1982) suggested that hepatobiliary MEC may be related to *Clonorchis sinensis* infestation with or without associated chronic bacterial cholangitis, because three of five reported patients had clonorchiasis and two showed evidence of recurrent bacterial pyogenic cholangitis. In few patients, MEC was suggested to arise from preexisting congenital cysts (Katsuda et al. 1984; Hayashi et al. 1987; Choi et al. 2004). The first of these cases relates to an autopsy case of a 78-year-old male who showed a massive tumor of up to 11 cm in size in the left lobe of the liver associated with multiple sero-mucinous cysts. These cysts were lined with a single layer of cuboidal or columnar cells and were apparently not in communication with bile ducts. Part of these cyst-lining cells were in continuity with carcinoma cells (Katsuda et al. 1984). Hepatobiliary MEC has been observed in synchronous association with hepatocellular carcinoma (Minami et al. 1992; Kang et al. 2003). In one patient, hepatobiliary MEC was associated with thorotrastosis (Lambrianides et al. 1986).

Clinical Features

Among 17 reviewed patients, 8 patients presented with abdominal pain and only 2 with jaundice. Seven tumors were located to the right liver lobe and ten to the left liver lobe (Arakawa et al. 2008). The size of the tumors ranged from 1.5 to 18 cm in the greatest dimension (average: 8.4 cm). As other hepatic tumors with a squamous cell component, MEC can present as a cystic lesion or may mimic a liver abscess (Choi et al. 2004). Similar to SCC-L and ASC-L, MEC is an aggressive tumor with a very poor prognosis, invading the portal vein and frequently metastasizing to locoregional lymph nodes and to the lung; ten patients died within 11 months regardless of the treatments (Shuangshoti and Shuangshoti 2000). Of 14 patients compiled in a recent review, 9 patients died within 6 months of admission or surgery; 6 patients who had undergone surgery lived for at least 45 days, and 1 of them was alive 1 year after surgery; 6 patients received only conservative treatment, and 4 of these died between 2 weeks and 3 months, 1 being lost to follow-up (Kang et al. 2003). In the review of 17 patients compiled by Arakawa et al. (2008), locoregional lymph node metastases were found in 7 patients, while intrahepatic metastases were observed in only 2 patients. Fifteen patients died after a survival period ranging from 14 days to 3 years; one patient was alive after 1 year, and in one patient, no follow-up information was available (Arakawa et al. 2008).

Pathology

Macroscopically, MECs of the liver are medium-sized to large and firm tumors exhibiting an expanding growth pattern and forming polycyclic masses of gray to whitish color, sometimes with extended central necrosis (Arakawa et al. 2008), or formation of cystic spaces. In the distal common bile duct, the tumors cause stenosing lesions that may infiltrate the duct wall and extend into the ampullary and pancreatic region (Moul et al. 2013).

Histologically, this neoplasm is dominated by irregularly arranged, mucin-filled cysts and solid tumor nests composed of mucous, epidermoid (squamous; keratinocytic), and nondescript intermediate cells in variable combinations. The

association between squamous cell and mucin-producing cells is usually intimate. The mucin-containing components are PAS and alkaline Alcian Blue positive. Within the squamous parts, individual keratinization may occur. MEC of the hepatobiliary tract may contain oxyphilic cells (Katsuda et al. 1984), a feature which has been described in respective carcinomas arising from salivary glands (oncocytic mucoepidermoid carcinoma; Jahan-Parwar et al. 1999; Jing et al. 2012). There is marked desmoplasia, with production of sclerotic stroma. In particular at the tumor's periphery, an inflammatory reaction (probably an immune response) is encountered. In case mucin is extruded from the cells, a foreign body-type reaction to mucin is elicited, contributing to the deposition of extracellular matrix. Necrotic keratinized squamous cells can induce keratin granulomas, although keratin formation is usually sparse or even lacking. Although the tumors reveal expanding features at gross examination, microscopy usually shows irregular invasive borders, with infiltration of adjacent liver substance, including invasion of hepatic sinusoids. Angioinvasion and invasion of perineural spaces in Glisson's sheaths or at the porta hepatis may be observed.

The mucin-producing cells of hepatic MEC were immunoreactive for cytokeratin 7, but variably for CK 20, many cases being CK20 negative (Choi et al. 2004; Moul et al. 2013). Part of the cells were MUC1 positive, while luminal cells also expressed MUC5 (Moul et al. 2013). Epidermoid cell nuclei of the tumor have been shown to be p63 positive (Choi et al. 2004).

Differential Diagnosis

The differential diagnosis of primary MEC of the liver includes primary hepatic adenosquamous carcinoma and extrahepatic MEC metastatic to the liver (Chen et al. 1995; Gruttadauria et al. 2000; Sato et al. 2002; Herd et al. 2012). In MEC metastasizing to the liver, a cytokine-induced leukemoid reaction has been observed. Immunohistochemistry of the metastatic tumor revealed staining for IL-1 alpha and IL-6, and elevation of cytokine levels in the fluid of necrotic tumor included IL-1 alpha, IL-6, granulocyte-macrophage colony-stimulating factor, and granulocyte colony-stimulating factor by ELISA testing (Chen et al. 1995).

Pathogenesis

It has been suggested that MECs of the liver take their origin from bile duct cells, therefore being variants of intrahepatic CCC (Di Palma et al. 1992; Shuangshoti and Shuangshoti 2000). MEC has also been found to have arisen in a preexistent hepatic cyst (Hayashi et al. 1987). In one patient, hepatic MEC was associated with thorotrastosis, known to be complicated by the emergence of CC and HCC (Lambrianides et al. 1986). Rarely, MEC of the liver has been observed together with HCC (apparent double primaries) at two different places within the liver (Minami et al. 1992; Kang et al. 2003).

Subsets of MEC of the salivary glands, lung, thyroid, breast, and skin exhibit a characteristic translocation, t(11;19)(q21-22; p13), resulting in a chimeric gene linking WAMTP1/Mect1 /Torc1/CRTC1 to exons 2–5 of the Mastermind-like (MAML) gene (Tonon et al. 2003; reviews: Seethala et al. 2010; Chenevert et al. 2011). Specifically, this translocation fuses 42 residues from AMTP1/Mect1 (mucoepidermoid carcinoma translocated-1)/Torc1, a cyclic AMP (cAMP)-responsive element binding protein (CREB)-dependent transcriptional coactivator (CRTC1; CREB regulated transcription coactivator), with 982 residues from MAML2, a Notch receptor coactivator (see below), leading to altered Notch signaling as a pathogenic mechanism for tumorigenesis. Molecular classification of MEC in relation to this translocation has a clinical impact, in that the translocation negatively affects tumor cell growth (Komiya et al. 2006) and that fusion-positive patients had a significantly lower risk of local recurrence, metastases, or tumor-related death compared to fusion-negative patients (Behboudi et al. 2006; Okabe et al. 2006).

References

Abbas R, Willis J, Kinsella T, Siegel C, Sanabria J (2008) Primary squamous cell carcinoma of the main hepatic bile duct. Can J Surg 51:E85–E86

Ahn KC, Ahn HS, So BJ, Chae KM (1994) A case of adenosquamous of the liver. Kor J Surg 47:1034–1037

Akagi I, Miyashita M, Makino H, Nomura T, Okawa K, Hagiwara N, Ueda J, Yamada T et al (2011) Pyogenic liver abscess caused by direct invasion of esophageal squamous cell carcinoma to the liver: report of a case. Surg Today 41:1247–1251

Akcali Z, Ozyilkan O, Sakalli H, Bal N, Noyan T (2005) Gallbladder adenosquamous cell carcinoma: report of two cases. Acta Gastroenterol Belg 68:440–442

Alsolaiman MM, MacDermott RP, Bartholomew C (2002) Hepatic pseudocyst as the first presentation of squamous cell carcinoma of uterine cervix. Dig Dis Sci 47:2459–2462

Alwaheeb S, Chetty R (2005) Adenosquamous carcinoma of the pancreas with an acantholytic pattern together with osteoclast-like and pleomorphic giant cells. J Clin Pathol 58:987–990

Andersson A, Bergdahl L, van der Linden W (1977) Malignant tumors of the extrahepatic bile ducts. Surgery 81:198–202

Arakawa Y, Shimada M, Ikegami T, Kubo T, Imura S, Morine Y, Kanemura H, Mori H (2008) Mucoepidermoid carcinoma of the liver: report of a rare case and review of the literature. Hepatol Res 38:736–742

Aranha GV, Reyes CV, Greenlee HB, Field T, Brosnan J (1980) Squamous cell carcinoma of the proximal bile duct – a case report. J Surg Oncol 15:29–35

Arase Y, Endo Y, Hara M, Kumada H, Ikeda K, Yoshiba A (1988) Hepatic squamous cell carcinoma with hypercalcemia in liver cirrhosis. Acta Pathol Jpn 38:643–650

Asanuma N, Hagiwara K, Matsumoto I, Matsuda M, Nakamura F, Kouhara H, Miyamoto M, Miyashita Y, Noguchi S, Morimoto Y (2002) PTHrP-producing tumor: squamous cell carcinoma of the liver accompanied by humoral hypercalcemia of malignancy, increased IL-6 and leukocytosis. Intern Med 41:371–376

Baba H, Yasunaga C, Tsujitani S, Korenaga D, Maehara Y, Sugimachi K et al (1992) Liver adenosquamous carcinoma invading the esophago-gastric junction: a case report and review of the literature. Int J Oncol 1:787–790

Banbury J, Conlon KC, Ghossein R, Brennan MF (1994) Primary squamous cell carcinoma within a solitary nonparasitic hepatic cyst. J Surg Oncol 57:210–212

Barr RJ, Hancock DE (1975) Adenosquamous carcinoma of the liver. Gastroenterology 69:1326–1330

Bastiaan de Boer W (2000) Basaloid squamous carcinoma in the liver. Pathology 32:147–151

Behboudi A, Enlund F, Winnes M, Andren Y, Nordkvist A, Leivo I, Flaberg A, Szekely L et al (2006) Molecular classification of mucoepidermoid carcinomas – prognostic significance of the MECT1-MAML2 fusion oncogene. Genes Chromosomes Cancer 45:470–481

Ben Mena N, Zalinski S, Svrcek M, Lewin M, Fléjou JF, Wendum D, Paye F (2006) Ciliated hepatic foregut cyst with extensive squamous metaplasia: report of a case. Virchows Arch 449:730–733

Beppu M, Sakon M, Fujimoto K, Hikita K, Kurita K, Hirai T, Murai N, Taniguchi S, Kitai A, Shinji Y, Doi Y, Yoshimoto S, Ohta T, Matuo M (1978) Carcinoma arising in a solitary nonparasitic cyst of the liver (in Japanese). Nippon Shokakibyo Gakkai Zasshi 75:738–745

Bismuth H, Krissat J (1999) Choledochal cystic malignancies. Ann Oncol 10(Suppl 4):94–98

Bloustein PA (1977) Association of carcinoma with congenital cystic conditions of the liver and bile ducts. Am J Gastroenterol 67:40–46

Bloustein PA, Silverberg SG (1976) Squamous cell carcinoma originating in an hepatic cyst. case report with a review of the hepatic cyst-carcinoma association. Cancer 38:2002–2005

Bondini S, Leoni S, Bolondi L (2005) Squamous cell carcinoma of the liver: metastasis or primary neoplasm? J Clin Ultrasound 33:477–478

Burger RE, Meeker WR, Luckett PM (1978) Squamous cell carcinoma of the common bile duct. South Med J 71:216–219

Cabot RC (1930) Squamous-cell carcinoma of the common bile duct. Case records of the Massachusetts General Hospital. Case 16261. N Engl J Med 202:1260–1262

Campman SC, Fajardo MA, Rippon MB, Kraegel SA, Ruebner BH (1997) Adenosquamous carcinoma arising in a mucinous cystadenoma of the pancreas. J Surg Oncol 64:159–162

Caratozzolo E, Massani M, Recordare A, Ciardo L, Antoniutti M, Jelmoni A, Bassi N (2001) Squamous cell liver cancer arising from an epidermoid cyst. J Hepatobiliary Pancreat Surg 8:490–493

Chan KM, Yu MC, Lee WC, Jan YY, Chen MF (2007) Adenosquamous/squamous cell carcinoma of the gallbladder. J Surg Oncol 95:129–134

Chang SS, Chan CC, Wang SS, Chang FY, Lee SD (2000) Repeated episodes of spontaneous hemorrhage of hepatic cysts mimicking malignancy. Zhonghua Yi Xue Za Zhi (Taipei) 63:256–261

Charles AR, Gupta AK (2001) Giant congenital solitary cyst of the liver: report of a case. Surg Today 31:732–734

Chatelain D, Chailley-Heu B, Terris B, Molas G, Le Cae A, Vilgrain V, Belghiti J, Degott C et al (2000) The ciliated hepatic foregut cyst, an unusual bronchiolar foregut malformation: a histological, histochemical, and immunohistochemical study of 7 cases. Hum Pathol 31:241–246

Chen PH, Lo HW, Wang CS, Tsai KR, Chen YC, Lin KY, Siauw CP, Hwang RR, Liu MH, Ko HC et al (1984) Cholangiocarcinoma in hepatolithiasis. J Clin Gastroenterol 6:539–547

Chen YM, Whang-Peng J, Liu JM, Chao Y, Lai CR, Wang SY, Peng RP (1995) Leukemoid reaction resulting from multiple cytokine production in metastatic mucoepidermoid carcinoma with central necrosis. Jpn J Clin Oncol 25:168–172

Chenevert J, Barnes LE, Chiosea SI (2011) Mucoepidermoid carcinoma: a five-decade journey. Virchows Arch 458:133–140

Choi D, Kim H, Lee KS, Lee KG, Park CK (2004) Mucoepidermoid carcinoma of the liver diagnosed as a liver abscess: report of a case. Surg Today 34:968–972

Chou YY, Lee WJ, Su CT, Hsu HC (1997) Case report: primary cystic keratinizing squamous cell carcinoma of the liver in a patient with treated nasopharyngeal carcinoma. J Gastroenterol Hepatol 12:229–232

Clements D, Newman P, Etherington R, Lawrie BW, Rhodes J (1990) Squamous carcinoma in the liver. Gut 31:1333–1334

Crespo M, Sopena B, Orloff JJ, Cameselle Teijeiro JF, Dann P, Andrade MA, Freire M, de la Fuente J, Martinez-Vazquez C (1999) Immunohistochemical detection of parathyroid hormone-related protein in a cutaneous squamous cell carcinoma causing humoral hypercalcemia of malignancy. Arch Pathol Lab Med 123:725–730

Daud MS, Salomao FC, Salomao EC, Salomao BC (2007) Gastric heterotopia together with squamous metaplasia in the gallbladder. Acta Gastroenterol Latinoam 37:164–167

De Lajarte-Thirouard AS, Rioux-Leclercq N, Boudjema K, Gandon Y, Ramée MP, Turlin B (2002) Squamous cell carcinoma arising in a hepatic foregut cyst. Pathol Res Pract 198:697–700

Demir G, Yanmaz T, Celik AF, Ozbay G, Serdengecti S (2005) Primary adenosquamous carcinoma of the liver: case with the longest survival. J Clin Gastroenterol 39:924–925

Di Palma S, Andreola S, Audisio RA, Doci R, Lombardi L (1992) Primary mucoepidermoid carcinoma of the liver. A case report. Tumori 78:65–68

Doctor N, Dafnios N, Jones A, Davidson BR (1998) Primary squamous carcinoma of liver: presentation as liver abscess. Indian J Gastroenterol 17:28–29

Edmondson HA (1958) Tumors of the liver and intrahepatic bile ducts. Atlas of tumor pathology. Armed Forces Institute of Pathology, Washington, DC

Ercolani G, Nagino M, Sano T, Kamiya J, Kondo S, Kanai M, Nishio H, Nimura Y (1999) Advanced adenosquamous carcinoma of the gallbladder with bilio-biliary fistula: an uncommon case treated by hepatopancreatoduodenectomy. Hepatogastroenterology 46:1650–1654

Estermann F, Thiebault S, Turnani C, Djabri M, Wiedemann R, Sondag D (1996) Pseudocystic metastases of carcinoma of the uterine cervix mimicking polycystic liver disease (in French). Gastroenterol Clin Biol 20:1125–1128

Fieber SS, Nance FC (1997) Choledochal cyst and neoplasm: a comprehensive review of 106 cases and presentation of two original cases. Am Surg 63:982–987

Flagg RS, Robinson DW (1967) Solitary nonparasitic hepatic cysts. Report of the oldest known case and review of the literature. Arch Surg 95:964–973

Friedrich RE, Klapdor R, Bartel-Friedrich S (2007) Rapidly progressive and metastatic mucoepidermoid carcinoma: application of serological tumor markers. Anticancer Res 27:2099–2100

Fujisaki S, Akiyama T, Miyake H, Amano S, Tomita R, Fukuzawa M, Yamagami H et al (1999) A case of carcinoma associated with the remained intrapancreatic biliary tract 17 years after the primary excision of a choledochal cyst. Hepatogastroenterology 46:1655–1659

Fujita T, Fukuda K, Nishi H, Takao T, Ohmura Y, Mano M, Komatsubara S (2005a) Paraneoplastic hypercalcemia with adenosquamous carcinoma of the colon. Int J Clin Oncol 10:144–147

Fujita T, Fukuda K, Ohmura Y, Nishi H, Mano M, Komatsubara S, Doihara H, Shimizu N (2005b) Long-term survival of a patient with advanced adenosquamous carcinoma of the gallbladder after radical resection. J Hepatobiliary Pancreat Surg 12:147–150

Funakawa T, Fujishiro N, Kuno N, Kobayashi S, Kimoto E, Suzuki K (1996) Squamous cell carcinoma of the extrahepatic bile duct (in Japanese). Ryoikibetsu Shokogun Shirizu 9:61–63

Furlanetto A, Dei Tos AP (2002) Squamous cell carcinoma arising in a ciliated hepatic foregut cyst. Virchows Arch 441:296–298

Gatof D, Chen YK, Shah RJ (2004) Primary squamous cell carcinoma of the bile duct diagnosed by transpapillary cholangioscopy: case report and review. Gastrointest Endosc 60:300–304

Geddes EW (1970) Hepatomegaly due to primary squamous carcinoma. Proc Mine Med Off Assoc 49:189–191

Greenwood N, Orr WM (1972) Primary squamous-cell carcinoma arising in a solitary non-parasitic cyst of the liver. J Pathol 107:145–148

Gresham GA, Rue LW (1985) Squamous cell carcinoma of the liver. Hum Pathol 16:413–416

Gruttadauria S, Marino G, Catalano F, Sgroi AV, Heffron T, Basile F (2000) Secondary carcinoma of the liver from parotid gland tumor. Chir Ital 52:179–182

Gu MJ, Choi JH, Park WK, Chang JC, Kim HJ (2005) Primary adenosquamous carcinoma of the liver: a case report (in Korean). Korean J Hepatol 11:86–89

Gulsrud PO, Feinberg M, Koretz RL (1979) Rapid development of cirrhosis secondary to squamous cell carcinoma of the common bile duct. Dig Dis Sci 24:166–169

Hagemann W (1964) Primary squamous cell carcinoma of the hepatic duct (in German). Zentralbl Allg Pathol 105:531–534

Hamamoto Y, Koyama H, Takasu K, Tateishi S (1994) An autopsy case of adenosquamous cell carcinoma of the

extrahepatic bile duct with endobronchial mass obstructing the left main bronchus and masquerading as asthma (in Japanese). Nihon Kyobu Shikkan Gakkai Zasshi 32:161–167

Hamaya K, Nose S, Mimuta T, Sasaki K (1991) Solid adenosquamous carcinoma of the liver: a case report and review of the literature. Acta Pathol Jpn 41:834–840

Hanada M, Shimizu H, Takami M (1986) Squamous cell carcinoma of the gallbladder associated with squamous metaplasia and adenocarcinoma in situ of the mucosal columnar epithelium. Acta Pathol Jpn 36:1879–1886

Harris M, Angus P, Davis ID (2002) Choledochal cyst and squamous-cell carcinoma of the biliary tract. Intern Med J 32:491

Hayashi I, Tomoda H, Tanimoto M et al (1987) Mucoepidermoid carcinoma arising from a preexisting cyst of the liver. J Surg Oncol 36:122–125

Hayashi N, Yamaguchi Y, Ogawa M (1993) Concomitant adenosquamous carcinoma of the common bile duct and early adenocarcinoma of the gall-bladder. J Gastroenterol Hepatol 8:607–612

Hayshi M, Onitsuka A (1995) Adenosquamous carcinoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:405–407

Herd MK, Murugaraj V, Ghataura SS, Brennan PA, Anand R (2012) Low-grade mucoepidermoid carcinoma of the palate A previously unreported case of metastasis to the liver. J Oral Maxillofac Surg 70:2343–2346

Higuchi T, Harada T, Okazaki M, Kikuchi M (1993) Primary adenosquamous carcinoma of the liver. Aust NZ J Surg 63:319–323

Ho JCI (1980) Two cases of mucoepidermoid carcinoma of the liver in Chinese. Pathology 12:123–128

Hong SM, Kim MJ, Jang KT, Yoon GS, Cho H, Frierson HF, Yu E (2008) Adenosquamous carcinoma of extrahepatic bile duct: clinicopathologic study of 12 cases. Int J Clin Exp Pathol 1:147–156

Horiuchi T, Sakaguchi M, Oka S, Yamamoto S, Kamada Y, Tanaka S, Tabuse K (1991) A case report of adenosquamous carcinoma of the liver with hepatolithiasis (in Japanese with English abstract). Jpn J Gastroenterol Surg 24:880–884

Hsieh CB, Chen CJ, Yu JC, Chang TM, Gao HW, Liu YC (2005) Primary squamous cell carcinoma of the liver arising from a complex liver cyst: report of a case. Surg Today 35:328–331

Hsu KF, Huang SC, Shiau AL, Cheng YM, Shen MR, Chen YF, Lin CY, Lee BH, Chou CY (2007) Increased expression level of squamous cell carcinoma antigen 2 and 1 ratio is associated with poor prognosis in early-stage uterine cervical cancer. Int J Gynecol Cancer 17:174–181

Hu TJ, Chen MF, Jan YY, Chen TJ (1988) Adenosquamous cell carcinoma of the liver: report of two cases. Chang Keng I Hsueh Tsa Chih 11:152–159

Hughes JH, Niemann TH (1996) Adenosquamous carcinoma of the bile duct: cytologic features of brush specimens from two cases. Diagn Cytopathol 15:322–324

Hyodo N, Tashiro T, Hyodo T, Yamanaka T, Ota M, Yamada S (1999) A case of adenosquamous pancreatic cancer with high serum level of parathyroid related protein in which both primary and liver metastatic lesions showed remarkable cystic changes (in Japanese). Nippon Shokakibyo Gakkai Zasshi 96:181–188

Iemura A, Yano H, Mizoguchi A, Kojiro M (1992) A cholangiocellular carcinoma nude mouse strain showing histologic alteration from adenocarcinoma to squamous cell carcinoma. Cancer 70:415–422

Iimuro Y, Asano Y, Suzumura K, Yada A, Hirano T, Iijima H, Nishiguchi S, Hirota S et al (2011) Primary squamous cell carcinoma of the liver: an uncommon finding in contrast-enhanced ultrasonography imaging. Case Rep Gastroenterol 5:628–635

Ikeda Y, Niimi M, Kann S, Shatari T, Takami H, Kodaira S (2003) Conformal radiation therapy for liver metastasis of esophageal carcinoma. Hepatogastroenterology 50:532–534

Imai T (1934a) Ein Fall von zystischem Teratom der Leber, in welchem Plattenepithelkrebs entstand. Trans Soc Pathol Jpn 24:578–580

Imai T (1934b) A case of cystic teratoma of the liver, in which squamous cell cancer developed (in German). Trans Soc Pathol Jap 24:578–580

Inamura M, Miyashita T, Tani T, Naito A, Tobe T, Takahashi K (1984) Cholangiocellular carcinoma associated with multiple liver cysts. Am J Gastroenterol 79:790–795

Inoue T, Nagao S, Tajima H, Okudaira K, Hashiguchi K, Miyazaki J, Matsuzaki K, Tzuzaki Y et al (2004) Adenosquamous pancreatic cancer producing parathyroid hormone-related protein. J Gastroenterol 39:176–180

Isa T, Kusano T, Muto Y, Furukawa M, Kiyuna M, Toda T (1997) Clinicopathologic features of resected primary adenosquamous carcinomas of the liver. J Clin Gastroenterol 25:623–627

Jahan-Parwar B, Huberman RM, Donovan DT, Schwartz MR, Ostrowski ML (1999) Oncocytic mucoepidermoid carcinoma of the salivary glands. Am J Surg Pathol 23:523–529

Jais P, Bouizar Z, Binn M, Vissuzaine C, Hayem G, Mignon M, Lewin MJ (1997) Parathyroid hormone-related protein in an esophageal squamous cell carcinoma with tumor-induced hypercalcemia. Am J Gastroenterol 92:343–346

Jakowski JD, Lucas JG, Seth S, Frankel WL (2004) Ciliated hepatic foregut cyst: a rare but increasingly reported liver cyst. Ann Diagn Pathol 8:342–346

Jan YY, Chen HM, Chen MF (2002) Malignancy in choledochal cysts. Hepatogastroenterology 49:100–103

Jing H, Meng Q, Tai Y (2012) Oncocytic mucoepidermoid carcinoma with prominent tumour-associated lymphoid proliferation of the submandibular gland. Oral Oncol 48:e7–e8

Jordan et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15191877

Kaijya Y, Nakajo M, Ichinari N, Yamazumi K, Otuji T, Tanaka T (1997) Retroperitoneal foregut cyst. Abdom Imaging 22:111–113

Kaji R, Sasaki N, Tateishi I, Nagata E, Okabe Y, Yoshida T, Sata M, Ueno T (2003) A case report of primary hepatic squamous cell carcinoma that remarkably responded to low dose arterial injection of anti-cancer drugs. Kurume Med J 50:71–75

Kang H, Park YN, Kim SE, Sohn KR, Yoo NC, Park JY, Kim KS, Park C (2003) Double primary mucoepidermoid carcinoma and hepatocellular carcinoma of the liver – a case report. Hepatogastroenterology 50:238–241

Kasai Y, Sasaki E, Tamaki A, Koshino I, Kawanishi N (1977) Carcinoma arising in the cyst of the liver – report of three cases. Jpn J Surg 7:65–72

Kataoka K, Iwado T, Kobayashi T, Kurokawa T, Mimura H, Kobayashi S (1985) Carcinoma originating in a hepatic cyst of polycystic disease – a case report (in Japanese). Gan No Rinsho 31:199–205

Katsuda S, Nakanishi I, Kajikawa K et al (1984) Mucoepidermoid carcinoma of the liver. Acta Pathol Jpn 34:153–157

Kim YI, Kim WH, Kim ST (1984) Mucoepidermoid carcinoma: a variant of cholangiocarcinoma; report of a case. Seoul J Med 25:256–259

Kim JM, Won JH, Kim JH et al (1994) A case of mucoepidermoid carcinoma of the liver. Kor J Med 47:547–551

Kim KW, Kim SH, Kim MA, Lee JM, Park HS, Kim JY, Han JK, Choi BI (2009) Adenosquamous carcinoma of the extrahepatic bile duct: clinicopathologic and radiologic features. Abdom Imaging 34:217–224

Kimoto E, Kuno N, Funakawa T (1996) Adenoacanthoma, adenosquamous carcinoma of the extrahepatic bile duct (in Japanese). Ryoikibetsu Shokogun Shirizu 9:47–49

Kinjo T, Kamiyama K, Chinen K, Iwamasa T, Kurihara K, Hamada T (2003) Squamous metaplasia induced by transfection of human papillomavirus DNA into cultured adenocarcinoma cells. Mol Pathol 56:97–108

Kitakado Y, Simomatsuya T, Takahashi K, Horiuchi T, Masuda Y, Tanigawa N, Muraoka R, Hayashi N (1993) A case report of adenosquamous carcinoma of the liver (in Japanese with English abstract). Jpn J Gastroenterol Surg 26:2212–2216

Klug R, Sega W, Aufschnaiter M (2003) Squamous cell carcinoma of the liver. A rare diagnosis in the course of intrahepatic cholangiolithiasis (in German). Chirurg 74:69–72

Kobayashi M, Okabayashi T, Okamoto K, Namikawa T, Araki K (2005) A clinicopathologic study of primary adenosquamous carcinoma of the liver. J Clin Gastroenterol 39:544–548

Kojima H, Sakaguchi Y, Fukui H, Tsujii T, Tsuruzono T, Nishimura K, Saito M (1994) A case of synchronous early gastric cancer and gallbladder adenosquamous carcinoma (in Japanese). Nippon Shokakibyo Gakkai Zasshi 91:80–83

Komiya T, Park Y, Modi S, Coxon AB, Oh H, Kaye FJ (2006) Sustained expression of Mect1-Maml2 is essential for tumor cell growth in salivary gland cancers carrying the t(11,19) translocation. Oncogene 25:6128–6132

Kondo M, Dono K, Sakon M, Shimizu J, Nagano H, Nakamori S, Umeshita K, Wakasa K, Monden M (2002) Adenosquamous carcinoma of the gallbladder. Hepatogastroenterology 49:1230–1234

Koo J, Wong J, Ong GB (1982) Mucoepidermoid carcinoma of the bile duct. Ann Surg 196:140–148

Koyama R, Segawa H, Nagai T, Matsumoto S, Koyanagi T, Matsuura M, Ito K, Sakamaki S, Takago H, Niitsu Y (1990) A case of primary liver squamous cell carcinoma producing granulocyte colony stimulating factor (in Japanese). Nippon Naika Gakkai Zasshi 79:1732–1734

Kubo S, Sakai T, Nagata E, Ikawa S, Hirohashi K, Kinoshita H, Sakai K, Kobayashi Y (1983) Resection of adenosquamous carcinoma of the liver: a case report (in Japanese). Gastroenterol Surg 6:1775–1779

Kusakina GK, Nigmatulina AA (1980) Adenosquamous cancer of the gallbladder (in Russian). Arkh Patol 42:57–59

Kwon OS, Lee HS, Koh DW, Cho YJ, Park YH, Park DK, Oh YL, Seo JH, Chun HJ et al (2001) A case of primary adenosquamous carcinoma of the liver presenting with liver abscess. Korean J Intern Med 16:270–273

La Greca G, Conti P, Urrico GS, Catanuto G, Di Carlo I, Russello D, Latteri F (2004) Biliary squamous cell carcinoma. Chir Ital 56:289–295

Lada PE, Taborda B, Sanchez M, Tommasino J, Rosso FF, Gramatica L, Alecha Gil J, Echenique Elizondo M (2007) Adenosquamous and squamous carcinoma of the gallbladder (in Spanish). Cir Esp 81:202–206

Lambrianides SL, Askew AR, Lefevre I (1986) Case report: thorotrast-associated mucoepidermoid carcinoma of the liver. Br J Radiol 59:791–793

Landais P, Grünfeld JP, Droz D, Drüeke T, Albouze G, Gogusev J, Chauveau D, Moynot A (1984) Cholangiocellular carcinoma in polycystic kidney and liver disease. Arch Intern Med 144:2274–2276

Lantsberg L, Khodadadi J, Goldstein J (1996) Adenosquamous carcinoma of the common bile duct: a case report. J Surg Oncol 33:140–142

Lee HL, Liu YY, Yeh CN, Chiang KC, Chen TC, Jan YY (2006) Primary squamous cell carcinoma of the liver: a successful surgically treated case. World J Gastroenterol 12:5419–5421

Lim SH, Yang HW, Kim A, Cha SW, Jung SH, Go H, Lee WC (2007) Adenosquamous carcinoma of extrahepatic bile duct: a case report. Korean J Intern Med 22:206–210

Lipsett PA, Pitt HA, Colombani PM (1994) Choledochal cyst disease. Ann Surg 220:644

Lombardo FP, Hertford DE, Tan LK, Kazam E, Ramirez de Arellaro E (1995) Epidermoid cyst of the liver complicated by microscopic squamous cell carcinoma: CT,

ultrasound, and pathology. J Comput Assist Tomogr 19:131–134
Lynch MJ, McLeod MK, Weatherbee L, Gilsdorf JR, Guice KS, Eckhauser FE (1988) Squamous cell cancer of the liver arising from a solitary benign nonparasitic hepatic cyst. Am J Gastroenterol 83:426–431
Maclean MD, Murray FH, Bacon HE (1962) Hepatic metastasis of squamous cell carcinoma of the anal canal: review of literature and case report. Dis Colon Rectum 5:51–55
Maeda T, Takenaka K, Taguchi K, Kajiyama K, Shirabe K, Shimada M, Tsuneyoshi M, Sugimachi K (1997) Adenosquamous carcinoma of the liver: clinicopathologic characteristics and cytokeratin profile. Cancer 80:364–371
Mandai K, Moriwaki S, Doihara H, Nakanishi Y, Motoi M, Tanada M, Wada T, Jinno K, Morita M (1989) Adenosquamous carcinoma and squamous cell carcinoma of the liver: a resected case and three autopsied cases (in Japanese). Gan No Rinsho 35:1439–1447
Marcy PY, Magné N, Bailet C, Pivot X, Dassonville O, Poissonnet G, Demard F (2004) Liver metastases from head and neck squamous cell carcinomas: radiological and biological features. Onkologie 27:157–160
Minami R, Morita S, Inui A, Oimomi T, Kasuga M, Satonaka K, Maeda S (1992) A case of double cancer of hepatocellular carcinoma and mucoepidermoid carcinoma of the liver with cirrhosis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 98:1314–1318
Mingoli A, Brachini G, Petroni R, Antoniozzi A, Cavaliere F, Simonelli L, Chirletti P, Modini C (2005) Squamous and adenosquamous cell carcinomas of the gallbladder. J Exp Clin Cancer Res 24:143–150
Mizuguchi M, Nishi K, Tachibana H, Ohka T, Kurumaya H, Fujimara M, Matsuda T (1997) Adenosquamous cell carcinoma of the lung with multiple cystic metastases in the liver (in Japanese). Nihon Kyobu Shikkan Gakkai Zasshi 35:306–310
Momosaki et al. 1995. http://www.ncbi.nlm.nih.gov/pubmed/7742926
Monteagudo M, Vidal G, Moreno M, Bella R, Diaz MJ, Colomer O, Santesmasses A (1998) Squamous cell carcinoma and infection in a solitary hepatic cyst. Eur J Gastroenterol Hepatol 10:1051–1053
Moore S, Gold RP, Lebwohl O, Price JB, Lefkowitch JH (1984) Adenosquamous carcinoma of the liver arising in biliary cystadenocarcinoma: clinical, radiologic, and pathologic features with review of the literature. J Clin Gastroenterol 6:267–275
Mori M, Iwashita A, Enjoji M (1986) Adenosquamous carcinoma of the stomach: a clinicopathologic analysis of 28 cases. Cancer 57:333–339
Morris CJ, Selvaggi G, Tzakis A, Weisbaum G, Martin P, Schiff E (2011) Metastatic squamous cell carcinoma to the liver presenting as hepatic cysts. J Clin Gastroenterol 45:293–294
Moul AE, Bejarano PA, Casillas J, Levi JU, Garcia-Buitrago MT (2013) Mucoepidermoid carcinoma of the intrapancreatic common bile duct: immunohistochemical profile, prognosis, and review of the literature. Case Rep Pathol 2013:192458
Munshi IA, Parra-Davila E, Casillas VJ, Sleeman D, Levi JU (1998) Ciliated foregut cyst of the pancreas. HPB Surg 11:117–119
Muto Y, Uchimura M, Waki S, Hayashi T, Sameshina Y, Okamoto K (1982) Clinico pathologic study on adenosquamous carcinoma of the gallbladder and the bile duct (in Japanese). Jpn J Cancer Clin 28:440–444
Naik S, Waris W, Carmosino L, Mehrishi A, Safi MW (2009) Primary squamous cell carcinoma of the liver. J Gastrointest Liver Dis 18:487–489
Nair A, Pai DR (2005) Single cystic liver metastasis in residual carcinoma of the uterine cervix. Eur J Obstet Gynecol Reprod Biol 122:126–127
Nakai T, Ono K, Terayama K, Yamagami T, Nishimura T (2004) Case report: adenosquamous carcinoma of the liver successfully treated with repeated transcatheter arterial infusion chemotherapy (TACE) with degradable starch microspheres. Br J Radiol 77:516–518
Nakajima T, Kondo Y (1990) A clinicopathologic study of intrahepatic cholangiocarcinoma containing a component of squamous cell carcinoma. Cancer 65:1401–1404
Nakajima T, Kondo Y, Miyazaki M, Okui K (1988) A histopathologic study of 102 cases on intrahepatic cholangiocarcinoma: histologic classification and modes of spreading. Hum Pathol 19:1228–1234
Nakajima Y, Nagai K, Kawano T, Inoue H, Nara S, Kumagai Y, Iwai T (2001) Therapeutic strategy for postoperative liver metastasis from esophageal squamous cell carcinoma: clinical efficacy of and problem with hepatic arterial infusion chemotherapy. Hepatogastroenterology 48:1652–1655
Nakazawa T, Kanbayashi H, Nozawa A, Kobayashi I, Sugimoto F, Saito M, Sekiya T, Yukawa T, Igarashi T (1997) A case of adenosquamous carcinoma of the intrahepatic bile duct (in Japanese). Tan to Sui (Gallbladder and Pancreas) 18:939–943
Neibling H, Dockerty MB, Waugh JM (1949) Carcinoma of the extrahepatic bile ducts. Surg Gynecol Obstet 89:429–438
Nieweg O, Slooff MJ, Grond J (1992) A case of primary squamous cell carcinoma of the liver arising in a solitary cyst. HPB Surg 5:203–208
Nishihara K, Nagai E, Izumi Y, Yamaguchi K, Tsuneyoshi M (1994) Adenosquamous carcinoma of the gallbladder: a clinicopathological, immunohistochemical and flow cytometric study of twenty cases. Jpn J Cancer Res 85:389–399
Nishihara K, Takashima M, Furuta T, Haraguchi M, Tsuneyoshi M (1995) Adenosquamous carcinoma of the gall-bladder with gastric foveolar-type epithelium. Pathol Int 45:250–256
Nishiyama M, Mizukami Y, Kume M, Ogawa A, Jinno A, Kisaka Y, Tanaka Y, Murakami S et al (2012) Mucoepidermoid carcinoma of the intrahepatic bile duct with metastasis to the cranial skin (in Japanese). Nihon Shokakibyo Gakkai Zasshi 109:1953–1959

Noske A, Pahl S (2006) Combined adenosquamous and large-cell neuroendocrine carcinoma of the gallbladder. Virchows Arch 449:135–136

Ochiai T, Yamamoto J, Kosuge T, Shimada K, Takayama T, Yamasaki S, Osaki H, Nakanishi Y, Mukai K (1996) Adenosquamous carcinoma with different morphologic and histologic components arising from the intrahepatic bile duct: report of a case. Hepatogastroenterology 43:663–666

Ödemis B, Köksal AS, Yüksel O, Kacar S, Turhan N (2006) Squamous cell cancer of the liver arising from an epidermoid cyst: case report and review of the literature. Dig Dis Sci 51:1278–1284

Ohyanagi H, Kanamaru T, Onoyama H, Saito Y (1986) Incurable biliary fistula with adenosquamous carcinoma of the liver followed hepatic lateral segmentectomy (in Japanese). Gastroenterol Surg 9:104–106

Okabayashi T, Kobayashi M, Nishimori I, Namikawa T, Okamoto K, Onishi S, Araki K (2005) Adenosquamous carcinoma of the extrahepatic biliary tract: clinicopathological analysis of Japanese cases of this uncommon disease. J Gastroenterol 40:192–199

Okabe M, Miyabe S, Nagatsuka H, Terada A, Hanai N, Yokoi M, Shimozato K, Eimoto T et al (2006) MECT1-MAML2 fusion transcript defines a favorable subset of mucoepidermoid carcinomas. Clin Cancer Res 12:3902–3907

Okamura K, Hayakawa H, Kuze M, Takahashi H, Kosaka A, Mizumoto R, Katsuta K (2000) Triple carcinomas of the biliary tract associated with congenital choledochal dilatation and pancreaticobiliary maljunction. J Gastroenterol 35:465–471

Ono F, Nakamura R, Itoh K, Kondoh N, Noto N (2002) A resected case of primary adenosquamous carcinoma of the liver. Jpn J Gastroenterol Surg 35:1803–1807

Oohashi Y, Shirai Y, Wakai T, Nagakura S, Watanabe H, Hatakeyama K (2002) Adenosquamous carcinoma of the gallbladder warrants resection only if curative resection is feasible. Cancer 94:3000–3005

Park SY, Cha EJ, Moon WS (2012) Adenosquamous carcinoma of the liver. Clin Mol Hepatol 18:326–329

Pawelczak I, Pichurski R, Sandlak M, Konecki J (1987) Primary squamous cell carcinoma of the liver (in Polish). Wiad Lek 40:188–190

Pawlik TM, Gleisner AL, Bauer TW, Adams RB, Reddy SK, Clary BM, Martin RC, Scoggins CR et al (2007) Liver-directed surgery for metastatic squamous cell carcinoma to the liver: results of a multi-center analysis. Ann Surg Oncol 14:2807–2816

Pianzola LE, Drut R (1971) Mucoepidermoid carcinoma of the liver. Am J Clin Pathol 56:758–761

Pliskin A, Cualing H, Stenger RJ (1992) Primary squamous cell carcinoma originating in congenital cysts of the liver. Report of a case and review of the literature. Arch Pathol Lab Med 116:105–107

Pouessel D, Thezenas S, Culine S, Becht C, Senesse P, Ychou M (2005) Hepatic metastases from carcinomas of unknown primary site. Gastroenterol Clin Biol 29:1224–1232

Price L, Kozarek R, Agoff N (2008) Squamous cell carcinoma arising within a choledochal cyst. Dig Dis Sci 53:2822–2825

Quijano Orvananos F, Varela Gutierrez G, Sanchez Rodriguez C, Rodriguez Jerkov J, Butron L (1994) Squamous cell carcinoma of the liver (in Spanish). Rev Gastroenterol Mex 59:236–237

Rehulova E, Dite P (1981) Multiple carcinomas arising from congenital cysts of the liver and kidneys (in Czech). Cesk Patol 17:198–2003

Roediger WE, Dymock RB (1991) Primary squamous carcinoma of the liver: clinical and histopathological features. Aust NZ J Surg 61:720–722

Saito K, Nakanuma Y (1995) Squamous cell carcinoma of the intrahepatic bile duct (in Japanese). Ryoikibetsu Shokogun Shirizu 7:417–419

Saito A, Noguchi Y, Doi C, Mukai K, Fukuzawa K, Yoshikawa T, Amano T, Kondo J, Ito T, Izutsu H (1999) A case of primary adenosquamous/squamous cell carcinoma of gallbladder directly invaded duodenum. Hepatogastroenterology 46:204–207

Saito T, Harada K, Tsuneyama K, Hirano M, Amaya S, Sasaki M, Kaneko S, Kobayashi K, Nakanuma Y (2002) Primary squamous cell carcinoma of the liver producing parathyroid hormone-related protein. J Gastroenterol 37:138–142

Sako K, Seitzinger GL, Garside E (1957) Carcinoma of the extrahepatic bile ducts. Review of the literature and report of six cases. Surgery 41:416–437

Sanada Y, Osada S, Tokuyama Y, Tanaka Y, Takahashi T, Yamaguchi K, Yoshida K (2010) Critical role of c-Met and Ki67 in progress of biliary carcinoma. Am Surg 76:372–379

Sanal SM, Sivrikoz ON, Karapolat I, Karademir S (2011) Complete clinical response in squamous cell carcinoma of the rectum with liver metastases. J Clin Oncol 29: e806–e808

Sanz Esponera J, Castiella Muruzabai T, Lazaro Perez J (1979) Squamous cell carcinoma of the liver developed in a simple nonparasitic cyst. Pathology 165:158

Sasaki Y, Hinoda Y, Takayama Y, Nakagawa N, Imai K, Yabana T, Yachi A, Enomoto K (1991) A case of mucoepidermoid carcinoma of the intrahepatic bile duct (in Japanese). Nippon Shokakibyo Gakkai Zasshi 88:1110–1115

Sasaki H, Hayashi M, Miyahara S, Shimomura M, Takahazhi H, Kawarada Y (1994) Adenosquamous carcinoma of the liver: case report. J Hepatobiliary Pancreat Surg 2:179–183

Sasaki Y, Sakamoto H, Hinoda Y, Yabana T (1995) Mucoepidermoid carcinoma of the liver or the intrahepatic bile duct (in Japanese). Ryoikibetsu Shokogun Shirizu 7:426–428

Sato M, Yajima Y, Takahashi N, Aoki C, Miyazaki A, Eda Y, Ohira S, Naganuma H, Kato H, Sakai N (2001) A case of adenosquamous carcinoma of the liver containing squamous components demonstrating

a character of adenocarcinoma with immunohistochemical stains (in Japanese). Nippon Shokakibyo Gakkai Zasshi 98:964–969

Sato H, Kuroda M, Maruta M, Maeda K, Koide Y (2002) Mucoepidermoid carcinoma of the ascending colon: report of a case. Surg Today 32:1004–1007

Seethala RR, Dacic S, Cieply K, Kelly LM, Nikiforova MN (2010) A reappraisal of the MECT1/MAML2 translocation in salivary mucoepidermoid carcinomas. Am J Surg Pathol 34:1106–1121

Sewkani A, Kapoor S, Sharma S, Naik S, Juneja M, Jain A, Varshney S (2005) Squamous cell carcinoma of the distal common bile duct. JOP 6:162–165

Shani M, Hart J, Modan B (1974) Cancer of the biliary system: a study of 445 cases. Br J Surg 61:98–100

Sharma S, Dean AG, Corn A, Kohli V, Wright HI, Sebastian A, Jabbour N (2008) Ciliated hepatic foregut cyst: an increasingly diagnosed condition. Hepatobiliary Pancreat Dis Int 7:581–589

Shchegolev AI, Dubova EA, Paklina OV, Tin'kova IO (2006) Primary squamous-cell carcinoma of the liver (in Russian). Arkh Patol 68:28–30

Shimizu S, Oshita A, Tashiro H, Amano H, Kobayashi T, Tanaka M, Arihito K, Ohdan H (2013) Synchronous double cancers of primary hepatic adenosquamous carcinoma and hepatocellular carcinoma: report of a case. Surg Today 43:418–423

Shin JU, Jung JT, You SS, Kwon JG, Kim EY, Lee CH, Kim HG, Park JB (2006) A case of primary adenosquamous carcinoma of the liver with formation of colonic fistula (in Korean). Korean J Gastroenterol 48:360–364

Shinagawa T, Tadokoro M, Takagi M, Yasuda R, Adachi Y, Komoriyama H, Yamaguchi S (1996) Primary squamous cell carcinoma of the liver: a case report. Acta Cytol 40:339–345

Shuangshoti S, Shuangshoti S (2000) Primary mucoepidermoid carcinoma of the intrahepatic bile duct: a case report with review of literature. J Med Assoc Thai 83:197–203

Song E, Kew MC, Grieve T, Isaacson C, Myburgh JA (1984) Primary squamous cell carcinoma of the liver in association with hepatolithiasis. Cancer 53:542–546

Song HG, Yoo KS, Ju NR, Park JC, Jung JO, Shin WG, Moon JH, Kim JP, Park CH et al (2006) A case of adenosquamous carcinoma of the papilla of Vater (in Korean). Korean J Gastroenterol 48:132–136

Song BJ, Kwon JH, Kim JJ, Lee JW, Min SY, Lee KB, Jang JY, Ryu JK (2011) A case of primary mucoepidermoid carcinoma arising from the common bile duct (in Korean). Korean J Gastroenterol 57:319–322

Stamatiadis AN, Papadimitriou C, Zombolas BT, Vatasos AA, Manouras AJ (1989) Adenosquamous carcinoma of the gallbladder (in Italian). Minerva Chir 44:2085–2087

Steffani K, Erbersdobler A, Broering DC (2003) Primary squamous cell carcinoma of the liver. Surprising findings in dysontogenetic liver cysts (in German). Dtsch Med Wochenschr 128:1947–1950

Suga K, Furukawa M, Nakata T, Kusano T, Lin Y, Tashiro K, Tachibana K, Miyazaki K (1990) Two cases of adenosquamous carcinoma of the intrahepatic bile duct (in Japanese with English abstract). Jpn J Gastroenterol Surg 24:904–908

Sumi H, Ohtsu A, Boku N, Muto M, Nagashima F, Hosokawa K, Yoshida S, Satake M, Ishikura S et al (2000) A case of inoperable esophageal carcinoma with hepatic and nodal metastases which showed a long-term survival after chemoradiotherapy including nedaplatin. Jpn J Clin Oncol 30:406–409

Suzuki E, Hirai R, Ota T, Shimizu N (2002) Primary adenosquamous carcinoma of the liver: case report. J Hepatobiliary Pancreat Surg 9:769–773

Swisher SG, Cates JA, Hunt KK, Robert ME, Bennion RS, Thompson JE, Roslyn JJ, Reber HA (1994) Pancreatitis associated with adult choledochal cysts. Pancreas 9:633–637

Szendroi M, Nemeth L, Vajta G (1983) Asbestos bodies in a bile duct cancer after occupational exposure. Environ Res 30:270–280

Takahashi H, Hayakawa H, Tanaka M, Okamura K, Kosaka A, Mizumoto R, Katsuta K, Yatani R (1997) Primary adenosquamous carcinoma of liver resected by right trisegmentectomy: report of a case and review of the literature. J Gastroenterol 32:843–847

Terada T (2009) Adenosquamous carcinoma in a congenital choledochal cyst associated with pancreaticobiliary maljunction. Pathol Int 59:482–485

Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K (1977) Congenital bile duct cysts. Classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cysts. Am J Surg 134:263–269

Tomioka T, Tsunoda T, Harada N, Tsuchiya R, Kajiwara Y, Tokunaga S, Matsuo T, Ikeda T (1987) Adenosquamous carcinoma of the liver. Am J Gastroenterol 82:1203–1206

Tonon G, Modi S, Wu L, Kubo A, Coxon AB, Komiya T, O'Neil K, Stover K, El-Naggar A et al (2003) t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. Nat Genet 33:208–213

Tsuneyama K, Kaizaki Y, Doden K, Kidani E, Harada K, Sasaki M, Nakanuma Y (2003) Combined hepatocellular and cholangiocarcinoma with marked squamous cell carcinoma components arising in non-cirrhotic liver. Pathol Int 53:90–97

Ueno N, Sano T, Kanamaru T, Tanaka K, Nishihara T, Idei Y, Yamamoto M, Okuno T, Kawaguchi K (2002) Adenosquamous cell carcinoma arising from the papilla major. Oncol Rep 9:317–320

Urushizaki I, Kitago M, Natori H, Koyama Y, Gocho Y, Fukuda M, Ogawa K (1973) A rare case of adenoacanthoma originally developed from intrahepatic bile duct. Jpn J Cancer Clin 19:152–155

Vick DJ, Goddman ZD, Deavers MT, Cain J, Ishak KG (1999a) Ciliated hepatic foregut cyst: a study of six

cases and review of the literature. Am J Surg Pathol 23:671–677
Vick DJ, Goodman ZD, Ishak KG (1999b) Squamous cell carcinoma arising in a ciliated hepatic foregut cyst. Arch Pathol Lab Med 123:1115–1117
Voyles CR, Smadja C, Shands C, Blumgart L (1983) Carcinoma in choledochal cysts. Arch Surg 118:986–988
Wagreich JM, Shapiro RS, Glajchen N, Seijo L (1998) MRI findings in adenosquamous carcinoma of the gallbladder. Clin Imaging 22:130–133
Wain SL, Kier R, Vollmer RT, Bossen EH (1986) Basaloid-squamous carcinoma of the tongue, hypopharynx, and larynx: report of 10 cases. Hum Pathol 17:1158–1166
Weimann A, Klempnauer J, Gebel M, Maschek H, Bartels M, Ringe B, Pichlmayr R (1996) Squamous cell carcinoma of the liver originating from a solitary non-parasitic cyst. Case report and review of the literature. HPB Surg 10:45–49
Welsh DA, Powers JS (1993) Elevated parathyroid hormone-related protein and hypercalcemia in a patient with cutaneous squamous cell carcinoma complicating hidradenitis suppurativa. South Med J 86:1403–1404
Wheeler DA, Edmondson HA (1984) Ciliated hepatic foregut cyst. Am J Surg Pathol 8:467–470
Yagi H, Ueda M, Kawachi S, Tanabe M, Aiura K, Wakabayashi G, Shimazu M, Sakamoto M, Kirajima M (2004) Squamous cell carcinoma of the liver originating from non-parasitic cysts after a 16 year follow-up. Eur J Gastroenterol Hepatol 16:051–1056
Yamamoto K, Takenaka K, Kajiyama K, Maeda T, Shirabe K, Shimada M, Sugimachi K (1996) A primary adenosquamous carcinoma of the liver with an elevated level of serum squamous cell carcinoma related antigen. Hepatogastroenterology 43:658–662
Yavuz E, Kapran Y, Ozden I, Bulut T, Dizdaroglu F (2000) Pancreatobiliary adenosquamous carcinoma (report of two cases). Pathologica 92:323–326
Yeh CN, Jan YY, Chen MF (2002) Adenosquamous carcinoma of the liver: clinicopathologic features in 12 patients and review of the literature. Int Surg 87:125–129
Yeh CN, Jan YY, Chen MF (2003) Adenosquamous carcinoma of the liver: clinicopathologic study of 10 surgically treated cases. World J Surg 27:168–172
Yen TC, Lin WY, Kao CH, Cheng KY, Wang SJ (1998) A study of a new tumour marker, CYFRA 21-1, in squamous cell carcinoma of the head and neck, and comparison with squamous cell carcinoma antigen. Clin Otolaryngol Allied Sci 23:82–86
Yeung JT, Fan WC, Cheng RL (2012) Adenosquamous carcinoma presenting as liver abscess. Singapore Med J 53:e110–e113
Yokota H, Matoba M, Tonami H, Hasegawa T, Saito H, Kurose N (2007) Imaging findings in primary adenosquamous carcinoma of the liver: a case report. Clin Imaging 31:279–282
Yoshida T, Aoki H, Kurinaga A, Ikeda Y, Kitazoe K, Katoh M, Kishimoto N, Hoshijima Y, Kawai H (1998) An autopsy case of primary squamous cell carcinoma of the liver associated with hepatitis C virus antibody positive liver cirrhosis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 95:1141–1146
Yuki N, Hijikata Y, Kato M, Kawahara K, Wakasa K (2006) Squamous cell carcinoma as a rare entity of primary liver tumor with grave prognosis. Hepatol Res 36:322–327
Zhang Z, Nonaka H, Nagayama T, Hatori T, Ihara F, Zhang L, Akima M, Shiba T (2001) Double cancer consisting of adenosquamous and hepatocellular carcinomas of the liver. Pathol Int 51:961–964
Zhang X, Wang Z, Dong Y (2009) Squamous cell carcinoma arising in a ciliated hepatic foregut cyst: case report and literature review. Pathol Res Pract 205:498–501

Hepatobiliary Tumors with Acinar Cell and Adenoid Cystic Cell Lineages

43

Contents

Abstract

Acinar cell carcinoma, a well-known pancreatic neoplasm, very rarely occurs as a primary tumor in the hepatobiliary tract. In contrast to their pancreatic counterparts, hepatic acinar cell carcinomas are usually heterogeneous tumors that contain well-differentiated acinar cells, endocrine-like cells, and less differentiated elements. Acinar carcinomas of the liver can form large solitary masses with an expanding growth pattern. In at least part of cases, production of trypsin, amylase, or lipase can be detected. The tumors can also develop from heterotopic pancreatic tissues and can invade the distal bile duct system from a primary tumor located in the pancreas. Adenoid cystic carcinoma, a tumor well known from salivary glands, can very rarely develop as a primary lesion in the hepatobiliary tract.

Acinar Cell Carcinoma of the Hepatobiliary Tract

ICD-O Code 8550/3

Introduction

Acinar cell carcinoma, usually a pancreatic neoplasm, very rarely occurs as a primary tumor in the hepatobiliary tract. Acinar cell carcinoma of the pancreas is also a rare tumor that accounts for

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_43

only about 1–2 % of exocrine pancreas tumors in adults. Acinar cell tumors of the pancreas can present with three subtypes, i.e., classical acinar cell carcinoma, acinar cell cystadenocarcinoma, and mixed acinar-endocrine carcinoma. Endocrine components can also occur in hepatic acinar cell carcinomas.

Primary Acinar Cell Carcinoma of the Liver and Bile Ducts

Few cases of primary hepatic acinar cell carcinoma have been reported (Hervieu et al. 2008; Agaimy et al. 2011; Terris et al. 2011; Wildgruber et al. 2013; Fig. 1). In one patient, a 35-year-old woman, imaging studies showed a hypervascular mass, and serum alpha-fetoprotein (AFP) was elevated at 6000 IU/mL. Histologically, the neoplasm displayed a heterogeneous composition and consisted of well-differentiated acinar structures with granular, trypsin-positive cells and of endocrine-like cells in less differentiated areas. Immunoreactive AFP was present in about 30 % of cells, and some cells were positive for chromogranin A and synaptophysin (Hervieu et al. 2008). Agaimy and coworkers (2011) reported a primary hepatic acinar carcinoma that had arisen in non-cirrhotic livers of two males and two females with a mean age at presentation of 65 years (range, 49–72 years). The liver tumors were large, well-circumscribed masses with a mean diameter of 12 cm and lobulated or multinodular cut surface. Histologically, the neoplasms revealed a predominantly microacinar pattern, with occasional trabecular, solid, and microcystic parts, and variable cellular atypia and mitotic activity. Immunohistochemically, the cancer cells were reactive for CK18 and at least one acinar cell marker (trypsin, amylase, or lipase). Two neoplasms were focally reactive for synaptophysin and chromogranin A. During a mean follow-up of 22 months, no metastases occurred, but one patient developed local recurrence (Agaimy et al. 2011). In a patient described by Terris and coworkers (2011), the acinar cell carcinoma was located at the liver hilum.

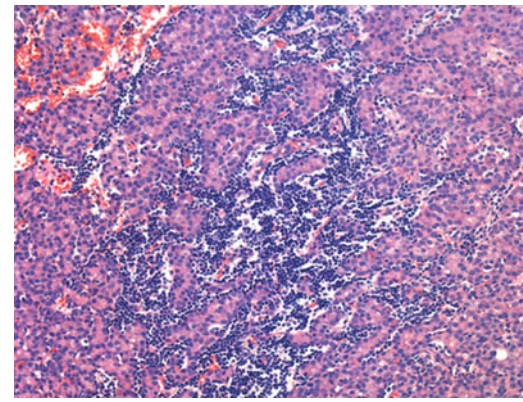

Fig. 1 Acinar cell carcinoma of the liver with focal lymphocytic infiltration (hematoxylin and eosin stain)

Acinar Cell Carcinoma Probably Derived from Heterotopic or Metaplastic Pancreatic Foci

There are few examples of intra-abdominal acinar cell carcinomas found in the absence of a primary pancreatic tumor, e.g., located in pancreatic lymph nodes or the colon. The neoplasms exhibited a predominantly acinar cell differentiation intermingled with a ductal component, with intracellular or extracellular mucin production by at least 25 % of tumor cells, and one case showed endocrine differentiation. An origin from heterotopic or metaplastic pancreatic foci was postulated (Terris et al. 2011). Also primary intrahepatic acinar cell carcinoma might take its origin from hepatic ectopic/heterotopic exocrine pancreatic tissue, which is known to occur in diverse sites of the liver and the biliary tract. In fact, adenocarcinoma arising from intrahepatic heterotopic pancreas was reported (Yan et al. 2012).

On the other hand, there is evidence from animal experiments and in vitro cell cultures that hepatocytes can transdifferentiate into pancreatic acinar cells and vice versa (Kanoh et al. 2011; Yi et al. 2012). In humans, pancreatic trypsinogen/trypsin and cathepsin can be expressed in cells of cholangiocarcinomas and hepatocellular carcinomas (Terada et al. 1995), while solid adenoma of the pancreas can present as an exclusively hepatocellular tumor (Cuilliere et al. 2002). Also pancreatic islet cells appear to have the potential to

transdifferentiate into albumin-producing neoplastic hepatocytes (Nozawa and Pour 2005), suggesting that two major derivatives of the ventral foregut endoderm, pancreas and liver, retain their capacity to switch into each other. Signaling signatures defining hepatic and pancreatic progenitor cell lineage divergence can be reprogrammed to convert adult hepatic cells into pancreatic cells (Rodriguez-Seguel et al. 2013). A further pathway potentially involved in the generation of acinar cell carcinomas in the hepatobiliary tract refers to the role of intrahepatic/intrabiliary plutipotential stem cells. The biliary tree is a rich reservoir of multipotent stem cells. In particular, peribiliary glands contain multipotent stem cells which self-replicate and can differentiate into hepatocytes, cholangiocytes, or pancreatic islet cells. Similar cells are found in the gallbladder (Cardinale et al. 2012). Embryonic stem cells are capable to differentiate into pancreatic cells (Lee and Chung 2011).

Secondary Involvement of the Bile Duct System by Acinar Cell Carcinoma of the Pancreas

Acinar cell carcinoma located in the pancreatic head can show an intraductal polypoid growth and extend into the intrapancreatic part of the common bile duct, with formation of intraluminal casts (Yamaguchi et al. 2006; Nagata et al. 2012). Hepatic metastasis of acinar cell carcinoma can invade intrahepatic bile ducts and form a bile duct tumor thrombus that may mimic a primary biliary manifestation (Kiitaka et al. 2012).

Differential Diagnosis

Acinar cell carcinoma of the liver has been distinguished from hepatic metastases of acinar cell carcinoma originating in the pancreas. Pancreatic acinar cell carcinoma is well known to produce solitary or multiple liver metastases (Tatli et al. 2005; Kim et al. 2011; Nishimizu et al. 2011; Bhosale et al. 2013). In a study of 30 patients, liver metastases were detected in 40 %, and the metastases typically were well circumscribed, hypoattenuating to the hepatic parenchyma on all the phases of contrast enhancement, and had a lobulated margin (Bhosale et al. 2013). The hepatic metastatic lesions may grow to giant size (Nishimizu et al. 2011). Also mixed acinar-neuroendocrine carcinoma of the pancreas metastasizes to the liver (Lee et al. 2013). Metastatic pancreatic acinar cell carcinoma may result in a confusing situation, as part of these tumors can produce alpha-fetoprotein (Nojima et al. 1992; Lin et al. 2007; Lin 2012).

Adenoid Cystic Carcinoma of the Hepatobiliary Tract

Introduction

Adenoid cystic carcinoma (ACC; cylindroma) is a malignant epithelial tumor showing a characteristic cribriform growth pattern. Tumors of the salivary glands are currently classified by the WHO not only according to morphological features but also in accordance to biologic behavior, prognosis, and treatment results. High-grade tumors with a more aggressive course comprise ACC, high-grade mucoepidermoid carcinoma, salivary duct carcinoma, squamous cell carcinoma, carcinoma ex-pleomorphic adenoma, adenocarcinoma NOS, and undifferentiated carcinoma. Salivary gland adenoid cystic carcinoma (SACC), which can metastasize to the liver, is a relatively frequent type of salivary gland malignancy characterized by relatively slow growth, multiple local recurrences, a distinct propensity for perineural invasion (Shimamoto et al. 2012), and a prolonged clinical course often with delayed development of distant metastases (SEER review of 3026 patients: Ellington et al. 2012). In most series, ACC accounts for 10–15 % of all parotid gland malignancies, and parotid SACC is reported to metastasize in 24 % of cases (Bradley 2001). The organs involved by metastasis of SACC in decreasing order of frequency are the lung, bone, brain, and liver (Spiro et al. 1974).

Primary Adenoid Cystic Carcinoma of the Hepatobiliary Tract

There is a single reported case of adenoid cystic carcinoma primary to the liver (Ziarkiewicz-Wroblewska et al. 2001). The hepatic tumor was detected incidentally during pregnancy in an asymptomatic 21-year-old female patient. No focal lesions in other organs were found in imaging examinations. A huge tumor of 30 cm diameter was found during surgery, encompassing almost the whole left and right lobes of the liver.

The tumor described by Ziarkiewicz-Wroblewska et al. (2001) showed all morphological features of salivary gland-type ACC (SACC). The epithelial cells are often arranged in a cribriform (sieve-like) pattern with neatly punched out spaces resembling a cookie cutter, but nests or cords representing solid components are also noted. The cells show a scanty and slightly eosinophilic cytoplasm and round to ovoid nuclei of regular shape. The cells surround circular areas or cyst-like spaces that are not true glandular lumina but are circular profiles or spherules/nodules in continuity with the ECM of stroma and consisting of basement membrane material. In a basal position, one notes small cells of the myoepithelial lineage. As shown in the single case of primary hepatic ACC, the tumor cells express glandular-type cytokeratins and share some phenotypes with biliary tract epithelia (Ziarkiewicz-Wroblewska et al. 2001).

Hepatic Metastasis of Adenoid Cystic Carcinoma

The main differential diagnosis is adenoid cystic carcinoma metastatic to the liver (Akhavan et al. 2013; Garg et al. 2014). In rare case, liver metastasis is the first clinical manifestation of adenoid cystic carcinoma (Spolverato et al. 2014). The likelihood of developing distant metastases of salivary gland tumors is associated with high-grade tumors, such as adenoid cystic carcinoma, salivary duct carcinoma, and high-grade mucoepidermoid carcinoma, local or neck recurrence, the presence of locoregional nodal metastasis, and tumors located in the submandibular gland, posterior tongue, and pharyngeal tumors. In contrast to the lung, SACC rarely metastasizes to the liver. In one series of cases, out of 46 patients with metastases of ACC, only one had liver metastasis, in conjunction with pulmonary and bone metastases (Sung et al. 2003). For hepatic metastases, the primary tumor is often located in the salivary glands (Garg et al. 2014), other primary locations comprising the lacrimal gland, external auditory canal, breast, Bartholin's gland, and other even more uncommon primary sites (Deshpande and Kelkar 2009; Shahabi et al. 2009; Balducci et al. 2011; Scuderi et al. 2011). Hepatic metastasis of ACC is generally seen as a part of disseminated tumor disease, isolated liver metastasis in ACC being very rare (Spiro 1997; Balducci et al. 2011). In few instances, hepatic metastasis of SACC was diagnosed by cytodiagnosis based on fine needle aspiration (Plafker and Nosher 1983; Thomas et al. 1991; Deshpande and Kelkar 2009). Liver metastasis can occur after a long delay, e.g., 10 years after resection of a salivary gland primary tumor (Qureshi et al. 2005), and may be the initial clinical manifestation of SACC (Deshpande and Kelkar 2009).

Pathogenesis

Part of ACC displays a chromosomal rearrangement characterized by a recurrent and specific t(6;9)(q22–23;p23–24) translocation causing MYB-NFIB chimeric fusion, with translocation of NFIB sequences to proximal or distal sites of the MYB gene (review: Bhaijee et al. 2011).

References

Agaimy A, Kaiser A, Becker K, Bräsen JH, Wünsch PH, Adsay NV, Klöppel G (2011) Pancreatic-type acinar cell carcinoma of the liver: a clinicopathologic study of four patients. Mod Pathol 24:1620–1626

Akhavan A, Binesh F, Navabii H (2013). Adenoid cystic carcinoma of hard palate with coincidental metastases to lung and liver. BMJ Case Rep pii: bcr0120125658. doi:10.1136/bcr-01-2012-5658. http://www.ncbi.nlm.nih.gov/pubmed/23446045

Balducci G, Sagnotta A, Muroni M, Cacchi C, D'Amato A (2011) An unusual case of exclusive liver metastases from adenoid cystic carcinoma of the submandibular gland: a role for surgery? Report of a case. Surg Today 41:596–599

Bhaijee F, Pepper DJ, Pitman KT, Bell D (2011) New developments in the molecular pathogenesis of head and neck tumors: a review of tumor-specific fusion oncogenes in mucoepidermoid carcinoma, adenoid cystic carcinoma, and NUT midline carcinoma. Ann Diagn Pathol 15:69–77

Bhosale P, Balachandran A, Wang H, Wei W, Hwang RF, Fleming JB, Varadhachary G et al (2013) CT imaging features of acinar cell carcinoma and its hepatic metastases. Abdom Imaging 38:1383–1390

Bradley PJ (2001) Distant metastases from salivary glands cancer. ORL J Otorhinolaryngol Relat Spec 63:233–242

Cardinale V, Wang Y, Carpino G, Mendel G, Alpini G, Gaudio E, Reid LM, Alvaro D (2012) The biliary tree – a reservoir of multipotent stem cells. Nat Rev Gastroenterol Hepatol 9:231–240

Cuilliere P, Lazure T, Bui M, Fabre M, Buffet C, Gayral F, Bedossa P (2002) Solid adenoma with exclusive hepatocellular differentiation: a new variant among pancreatic benign neoplasms? Virchows Arch 441:519–522

Deshpande AH, Kelkar AA (2009) Hepatic metastasis as an initial manifestation of salivary adenoid cystic carcinoma: cytologic diagnosis. Diagn Cytopathol 37:45–47

Ellington CL, Goodman M, Kono SA, Grist W, Wadsworth T, Chen AY, Owonikoko T, Ramalingam S et al (2012) Adenoid cystic carcinoma of the head and neck: incidence and survival trends based on 1973–2007 surveillance, epidemiology, and end results data. Cancer 118:4444–4451

Garg N, Tomar R, Goyal S, Singh UR (2014) Isolated liver metastases in an adenoid cystic carcinoma of the submandibular gland on fine needle aspiration cytology: an unusual presentation. Cytopathology 25:137–138

Hervieu V, Lombard-Bohas C, Dumortier J, Boillot O, Scoazec JY (2008) Primary acinar cell carcinoma of the liver. Virchows Arch 452:337–341

Kanoh Y, Tomotsune D, Shirasawa S, Yoshie S, Ichikawa H, Yokoyama T, Mae S, Ito J, Mizuguchi M et al (2011) In vitro transdifferentiation of HepG2 cells to pancreatic-like cells by CCl4, D-galactosamine, and ZnCl2. Pancreas 40:1245–1252

Kim YJ, Chung DJ, Byun JH, Kim YS (2011) Metastatic acinar cell carcinoma of the liver from a benign-appearing pancreatic lesion: a mimic of hepatocellular carcinoma. Br J Radiol 84:e151–e153

Kittaka H, Takahashi H, Ohigashi H, Gotoh K, Yamada T, Shingai T, Motoori M, Kishi K, Noura S et al (2012) Multimodal treatment of hepatic metastasis in the form of a bile duct tumor thrombus from pancreatic acinar cell carcinoma: a case report of successful resection after chemoradiation therapy. Case Rep Gastroenterol 6:518–522

Lee DH, Chung HM (2011) Differentiation into endoderm lineage: pancreatic differentiation from embryonic stem cells. Int J Stem Cells 4:35–42

Lee L, Bajor-Dattilo EB, Das K (2013) Metastatic mixed acinar-neuroendocrine carcinoma of the pancreas to the liver: a cytopathology case report with review of the literature. Diagn Cytopathol 41:164–170

Lin LF (2012) Endoscopic ultrasound image of alpha-fetoprotein-producing pancreatic acinar cell carcinoma. Dig Liver Dis 44:e3

Lin YC, Lee PH, Yao YT, Hsiao JK, Sheu JC, Chen CH (2007) Alpha-fetoprotein-producing pancreatic acinar cell carcinoma. J Formos Med Assoc 106:669–672

Nagata et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22487469

Nishimizu T, Minemura M, Kajiura S, Tokimitsu Y, Itaya Y, Yamawaki H, Tajiri K, Nakayama Y et al (2011) A case of pancreatic acinar cell carcinoma with a giant liver metastasis successfully treated with combination of gemcitabine and peroral S-1 (in Japanese). Gan To Kagaku Ryoho 38:309–312

Nojima T, Kojima T, Kato H, Sato K, Koito K, Nagashima K (1992) Alpha-fetoprotein-producing acinar cell carcinoma of the pancreas. Hum Pathol 23:828–830

Nozawa F, Pour PM (2005) Pancreatic hepatocellular tumor. Pancreatology 5:410–415

Plafker J, Nosher JL (1983) Fine needle aspiration of liver with metastatic adenoid cystic carcinoma. Acta Cytol 27:323–325

Qureshi SS, Nadkarni MS, Shrikhande SV, Desai S, Deodhar K, Ramadwar M, Shukla PJ (2005) Hepatic resection for metastasis from adenoid cystic carcinoma of parotid gland. Indian J Gastroenterol 24:29–30

Rodriguez-Seguel E, Mah N, Naumann H, Pongrac IM, Cerda-Esteban N, Fontaine JF, Wang Y et al (2013) Mutually exclusive signaling signatures define the hepatic and pancreatic progenitor cell lineage divergence. Genes Dev 27:1932–1946

Scuderi V, Ceriello A, Romano M, Migliaccio C, Marino MG, Calise F (2011) Recurrent adenoid cystic carcinoma in the liver: a repeated laparoscopic surgical approach. Updat Surg 63:301–306

Shahabi S, Nathan LM, Chanana C, Garett W, Zheng W, Rutherford TJ (2009) Liver metastasis in a case of adenoid cystic carcinoma of the Bartholin's gland: a rare presentation. Arch Gynecol Obstet 279:747–750

Shimamoto H, Chindasombatjaroen J, Kakimoto N, Kishino M, Murakami S, Furukawa S (2012) Perineural spread of adenoid cystic carcinoma in the oral and maxillofacial regions: evaluation with contrast-enhanced CT and MRI. Dentomaxillofac Radiol 41:143–151

Spiro RH (1997) Distant metastasis in adenoid cystic carcinoma of salivary origin. Am J Surg 174:495–498

Spiro RH, Huvos AG, Strong EW (1974) Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases. Am J Surg 128:512–520

Spolverato G, Fite J, Bishop J, Argani P, Pawlik TM (2014) Liver metastasis as the initial presentation of adenoid cystic carcinoma. Dig Dis Sci 59:2004–2006

Sung MW, Kim KH, Kim JW, Min YG, Seong WJ, Roh JL, Lee SJ, Kwon TK, Park SW (2003) Clinicopathologic predictors and impact of distant metastasis from adenoid cystic carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 129:1193–1197

Tatli S, Mortele KJ, Levy AD, Glickman JN, Ros PR, Banks PA, Silverman SG (2005) CT and MRI features of pure acinar cell carcinoma of the pancreas in adults. AJR Am J Roentgenol 184:511–519

Terada T, Ohta T, Minato H, Nakanuma Y (1995) Expression of pancreatic trypsinogen/trypsin and cathepsin B in human cholangiocarcinoma and hepatocellular carcinomas. Hum Pathol 26:746–752

Terris B, Genevay M, Rouquette A, Audebourg A, Mentha G, Dousset B, Rubbia-Brandt L (2011) Acinar cell carcinoma: a possible diagnosis in patients without intrapancreatic tumour. Dig Liver Dis 43:971–974

Thomas DJ, Kissin MW, Webb AJ (1991) Hepatic metastases in adenoid cystic carcinoma of the submandibular gland. Eur J Surg Oncol 17:541–542

Wildgruber M, Rummeny EJ, Gaa J (2013) Primary acinar cell carcinoma of the liver. Röfo 185:572–573

Yamaguchi R, Okabe Y, Jimi A, Shiota K, Kodama T, Naito Y, Yasunaga M, Kinoshita H, Kojiro M (2006) Pancreatic acinar cell carcinoma extending into the common bile and main pancreatic ducts. Pathol Int 56:633–637

Yan ML, Wang YD, Tian YF, Lin Y (2012) Adenocarcinoma arising from intrahepatic heterotopic pancreas: a case report and literature review. Word J Gastroenterol 18:2881–2884

Yi F, Liu GH, Belmonte JCI (2012) Rejuvenating liver and pancreas through cell transdifferentiation. Cell Res 22:616–619

Ziarkiewicz-Wroblewska B, Gornicka B, Bogdanska M, Otto W, Wroblewski T, Krawczyk M, Wasiutynski A (2001) Carcinoma adenoides cysticum as a primary neoplasm most probably derived from biliary ducts – case report. Med Sci Monit 7(suppl1):123–126

Rare Malignant and Semimalignant Epithelial Neoplasms of the Biliary Tract

44

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_44

Abstract

The hepatobiliary tract is the site of an intriguing group of malignancies occurring in several other organs, extrapulmonary small cell carcinoma. In contrast to its bronchopulmonary counterpart, extrapulmonary small cell carcinomas occur with similar rates in female and male patients. With the exception of the gallbladder, the biliary tract is very rarely involved. Small cell carcinomas of the hepatobiliary tract belong to several categories, i.e., neuroendocrine type, mixed type, non-neuroendocrine type, and not otherwise specified types. Small cell carcinomas are highly aggressive neoplasms. Diagnosis and classification require immunohistochemical and molecular methods. Poorly differentiated or undifferentiated carcinomas of the bile ducts also include spindle cell carcinoma and carcinomas with rhabdoid features. Unusual neoplasms primary to the bile ducts also comprise hepatoid carcinoma and solid pseudopapillary tumor, a neoplasm better known from the pancreas.

Small Cell Carcinomas of the Hepatobiliary Tract

Introduction

Extrapulmonary small cell carcinoma is a distinct category of high-grade malignancies distinct from bronchopulmonary small cell carcinoma. In the United States, the estimated incidence is between 0.1 % and 0.4 % of all cancers (Levenson et al. 1981; Richardson and Weiland 1982; Remick and Ruckdeschel 1992; Walenkamp et al. 2009). In a study from South East England, covering the years 1970–2004, the incidence of extrapulmonary SCC was much lower than for SCC of the lung, similar in males and females, with incidence rates of 0.45 per 100,000 in males and 0.37 in females (Wong et al. 2009). The pathology of extrapulmonary SCC has been reviewed (Frazier et al. 2007). Poorly differentiated or undifferentiated small cell carcinomas also arise in the gastrointestinal tract, including the hepatobiliary tract.

Epidemiology

In the entire gastrointestinal tract, 0.1–1 % of all malignancies are small cell carcinomas, with the esophagus being the most common primary site (Galanis et al. 1997; Fenoglio-Preiser 2001; Brenner et al. 2004a; Brenner et al. 2007; Lee et al. 2007). With the exception of the gallbladder, the biliary tract is very rarely involved by this malignancy. Among 544 reviewed gastrointestinal cases, 46 were located to the gallbladder (8.4 %), 6 in the ampulla (1.1 %), 3 in the common bile duct (0.5 %), and 7 in the liver (1.3 %) (Brenner et al. 2004b). In a study of 52 patients with extrapulmonary SCC, 33 (62.3 %) were detected in the esophagus, 5 in the cervix, 4 in the larynx, 3 in the pharynx, 2 in the upper sinus, 2 in the rectum and sublingual gland, 1 in the thyroid gland, 1 in the pleura, and 1 in the liver (Yuan et al. 2006).

Classification

Primary small cell carcinomas (PSCC) of the hepatobiliary tract can come in five basically different forms, i.e., (1) PSCC of the neuroendocrine type, (2) PSCC of mixed type, (3) PSCC of non-neuroendocrine type, (4) PSCC of hepatoid type, and (5) PSCC of unknown type (PSCC, not otherwise specified (NOS)) (Table 1). Part of PSCC described in the older literature are usually PSCC-NOS, owing to the lack of immunohistochemical examinations.

Table 1 Types of primary small cell carcinomas (PSCC) of the hepatobiliary tract

PSCC of the neuroendocrine type
PSCC of mixed type
PSCC of non-neuroendocrine type
PSCC of hepatoid type
PSCC, not otherwise specified

Small Cell Carcinoma of the Liver and Bile Ducts

Introduction

Small cell carcinoma can develop as a very rare primary or apparently primary malignancy within the liver substance, without proven connection to intrahepatic bile ducts. PSCC of the liver forms a heterogeneous group of lesions, as part of the cases in the old literature were reported without immunohistochemical and/or ultrastructural examinations and are therefore difficult to classify. Based on what we know today, most of the reported cases probably were undifferentiated neuroendocrine tumors. As bronchopulmonary small cell carcinoma can be small even in the metastasizing phase of disease, some small cell carcinomas purported to be liver tumors may in fact have been a metastasis of a missed lung primary.

Clinical and Imaging Features

Similar to other aggressive primary liver malignancies, PSCC present with hepatomegaly, upper abdominal discomfort or pain, fever, and jaundice in part of the patients (Sengoz et al. 2003; Yuan et al. 2006; Otten et al. 2013). Serum AFP is, in most patients, not elevated, with the exception of the very uncommon PSCC with AFP secretion (Walshauser et al. 2013). Imaging reveals solitary or multiple, sometimes lobulated masses, predominantly in the right liver lobe. On CT scans, invasion of the portal vein and the hepatic artery had been detected (Jo et al. 2013).

Hepatic PSCC of the Neuroendocrine Type

Extrapulmonary PSCC shares many features with bronchopulmonary small cell undifferentiated carcinoma (Remick et al. 1987; Vrouvas and Ash 1995). This includes the cytological and histological appearance, an aggressive behavior, and the frequent short-lasting response to either chemotherapy or radiotherapy. Very few PSCC of the neuroendocrine type have been reported.

Selected References Nakasuka et al. (1998), Kim et al. (2004, 2006a, b), Ryu et al. (2005), Choi et al. (2007), Balta et al. (2008), Iwasa et al. (2010), Kaman et al. (2010), and Jo et al. (2013).

In one patient, neuroendocrine PSCC was associated with adenoid cystic carcinoma of a salivary gland (Premkumar et al. 2013). In a review of the few published cases (Choi et al. 2007), most patients were elderly to old males, and tumor diameters ranged from 6.7 to 12 cm. It is assumed that these neoplasms arise from the neuroendocrine cell system of the liver. The neoplasms usually present as large and solitary, highly invasive and advanced-stage lesions at diagnosis, although multiple synchronous hepatic tumors have also been reported (Nakasuka et al. 1998). In part of the reported cases, immunohistochemistry clearly proved the neuroendocrine features of these neoplasms (Kim et al. 2004; Ryu et al. 2005; Choi et al. 2007).

Hepatic PSCC, Mixed Types

In some rare PSCC of the liver, a second carcinomatous component was found in addition to the small cell neuroendocrine lineage. In one patient, PSCC had arisen from combined hepatocellular and cholangiocarcinoma (Khaw et al. 2011). Very rare cases of hepatocellular carcinomas can contain a small cell tumor component with neuroendocrine features, the HCC component expressing hepatocyte markers and AFP, and the SCC component reactive for chromogranin A and synaptophysin (Yamaguchi et al. 2004; Garcia et al. 2006; Yang et al. 2009). Composite small cell and mucinous adenocarcinoma can also originate from intrahepatic bile ducts (see below; Ikegami et al. 2013).

Combined SCC and adenocarcinomas have been observed in the stomach (Jang et al. 2007) and the colon (Scherwitz et al. 2002) and found to have metastasized to the liver. Malignant neoplasms with such a mixed phenotypes involving at least two different cell lineages may originate from progenitor cells having two cell fating strategies.

PSCC, Non-neuroendocrine Type or with Unknown Neuroendocrine Features

In few examples of PSCC primary to the liver, the neuroendocrine status was negative or not known, although the cytologic and histopathologic features were those of bronchopulmonary small cell or oat cell carcinoma (Sengoz et al. 2003; Morikawa et al. 2008; Ochsenreither et al. 2009; Groeschl et al. 2013).

Small Cell Hepatoid Carcinoma of the Liver

This is a still ill-defined category of primary liver tumors characterized by a small cell neoplasm arising in non-cirrhotic livers, composed of broad nests of small epithelial cells with little supporting tissue. The tumor cells were immunohistochemically positive for low molecular weight keratins and alpha-fetoprotein and erratically for neuroendocrine markers. Such neoplasms were suggested to be a variant of hepatocellular carcinoma (Zanconati et al. 1996).

Small Cell Carcinoma of the Bile Ducts

Relatively few cases of small cell carcinoma primary to the common bile duct have been published. These neoplasms clinically present as other malignancies developing in this anatomical compartment, i.e., with abdominal pain and obstructive jaundice. Probably caused by massive necrosis, the tumor may cause hemobilia (Cho et al. 2009). On CT, an intraluminal mass is detectable (Park et al. 2004; Okamura et al. 2009), and MRI has shown a tumor mass surrounding the common bile duct wall, with ERCP showing a smooth narrowing of the bile duct (Arakura et al. 2008). In one case, the tumor was associated with clonorchiasis (Thomas et al. 2005). Identical p53 gene mutation has been identified in small cell carcinoma of the bile duct and malignant proliferating trichilemmal tumor in the same patient (Nakai et al. 2008). Histology and immunohistochemistry are the same as with small cell gallbladder carcinomas (Kuraoka et al. 2003). Mucinous adenocarcinoma of intrahepatic bile ducts can rarely be combined with small carcinoma, the tumors showing CK 19-positive and chromogranin A-positive cell populations (Ikegami et al. 2013). Small cell carcinoma of the bile ducts exhibits an aggressive biology (Jeon et al. 2006), the longest reported survival after multidisciplinary management being 23 months (Okamura et al. 2009).

Selected References Sabanathan et al. (1988), Motojima et al. (1990), Van der Wal et al. (1990), Miyashita et al. (2001), Arakura et al. (2003, 2008), Hazama et al. (2003), Kuraoka et al. (2003), Park et al. (2004), Kaiho et al. (2005), Thomas et al. (2005), Jeon et al. (2006), Viana Miguel et al. (2006), Nakai et al. (2008), Cho et al. (2009), Okamura et al. (2009), and Groeschl et al. (2013).

Differential Diagnosis

The main differential diagnosis of hepatobiliary PSCC is metastasis of bronchopulmonary small cell undifferentiated carcinoma (Vaideeswar et al. 2012; Sato et al. 2013), followed by metastasis of extrapulmonary SCCs (mainly the esophagus, the pancreas, and the lower digestive tube; Akiyama et al. 2011; Al-Jiffry and Al-Malki 2013), several types of other anaplastic neuroendocrine and PNET tumors (O'Byrne et al. 1994), and other small cell undifferentiated neoplasms (Khalbuss et al. 2005). Another small cell tumor

of poor differentiation metastasizing to the liver is Merkel cell carcinoma (Bottles et al. 1984; Gollub et al. 1996).

Undifferentiated Carcinomas of the Bile Ducts

There are bile duct carcinomas with a low to very low level of cell differentiation. This is a typical feature of lymphoepithelial carcinomas, treated in a separate chapter. In addition, a very small fraction of intrahepatic cholangiocarcinomas show an undifferentiated phenotype. These neoplasms consist of medium-sized to large cells showing a solid growth pattern in the absence of any glandular structures. In the light of these morphologic features, diagnosis of cholangiocarcinoma is difficult, apart from a close spatial relation to intrahepatic ducts. A derivation from cholangiocytes is suggested by the positivity for cytokeratin 7 and CAM5.2 (Fujikawa et al. 2011).

Spindle Cell-Type Carcinoma of Bile Ducts

Apart from carcinosarcomas with a spindle cell component, rare variants of cholangiocarcinoma partially or entirely consist of spindle cells, which are only attributable to an epithelial cell lineage after performing immunohistochemistry. These lesions are of theoretical interest insofar as they may represent examples of epithelial-mesenchymal transition.

Spindle cell carcinoma also develops in the region of the hepatic hilus and may then mimic classical Klatskin tumor. In one 59-year-old patient, the tumor had led to complete obliteration of the left hepatic duct and stenosis of the bile duct from the superior to the right hepatic duct. Histologically, the tumor was a mixture of tubular adenocarcinoma and spindle cell carcinoma, the spindle cells being immunoreactive for CAM5.2 and AE1/AE3 (Nakanishi et al. 2007). Generally, spindle cell carcinoma developing in other organs co-expresses epithelial and mesenchymal markers, positivity for epithelial markers being somewhat more often expressed than vimentin (Lewis et al. 2005).

The differential diagnosis of hepatobiliary spindle cell carcinoma mainly includes sarcomatous cholangiocarcinomas (Imazu et al. 1995; Matsuo et al. 1999) and other malignant sarcomatoid liver tumors (Eriguchi et al. 2001; Matsui et al. 2010), which may also contain spindle cell components. Very rarely, primary liver carcinomas entirely consist of spindle cells (Grigsby et al. 1987).

Primary Hepatoid Carcinoma of the Bile Ducts

Introduction

Hepatoid carcinomas have a distinct and unique immunophenotype, characterized by reactivity for cytokeratins 7, 8, 18, 19, and 20, alpha-fetoprotein (AFP), and p-CEA (Terracciano et al. 2003). The immunoreactivity for AFP is variable, ranging from the absence of staining to massive staining, illustrating that not all carcinomas with a hepatoid morphology are producing AFP (Nagai et al. 1993). Many hepatoid carcinomas of the gastrointestinal tract show, similar to hepatocellular carcinomas, reactivity for hepatocyte paraffin 1 (Hep Par 1) antibody, underscoring the fact that Hep Par 1 expression is not unique to primary hepatocellular neoplasms (Maitra et al. 2001). Hepatoid carcinomas are reactive for glypican-3, a cell surface heparin sulfate proteoglycan expressed specifically in the fetal liver and malignant neoplasms of the hepatocyte lineage (Hishinuma et al. 2006).

Histologically, hepatoid carcinomas consist of large polygonal cells that are arranged in trabecular fashion or solid nests separated by narrow fibrous stroma bands and sinusoid-like vascular channels. The differential diagnosis between manifestations of hepatocellular carcinoma and hepatoid carcinoma is often difficult, owing to the almost identical histology and part of the

immunohistochemical findings. Co-expression of antigens not found in a liver cell lineage may be helpful, e.g., in the stomach, where hepatoid carcinoma expresses the fetal gut differentiation stem cell marker, SALL4, lacking in HCCs and hepatoblastomas (Ushiku et al. 2010). Hepatoid adenocarcinoma of the stomach expresses the palate, lung, and nasal epithelium carcinoma-associated protein (PLUNC) gene, and PLUNC immunostaining differentiates hepatoid carcinomas from ordinary adenocarcinomas (Sentani et al. 2008).

Hepatoid Carcinoma of the Bile Ducts

Hepatoid carcinoma is an exceptional neoplasm of the biliary tract. Hepatoid carcinoma was observed in the common hepatic duct where it mimicked Klatskin tumor, causing bile duct stenosis and obstructive jaundice (Abdullah et al. 2010).

Hepatoid Carcinoma of the Gallbladder

Few cases of hepatoid carcinoma of the gallbladder have been reported (Nakashima et al. 2000; Maitra et al. 2001; Sakamoto et al. 2004, 2005; Gakiopoulou et al. 2007; Koswara et al. 2007; van den Bos et al. 2007; Kao et al. 2009). The tumors may be associated with elevated serum AFP (van den Bos et al. 2007). They show the same histologic features as those in other locations, but may show cholangiocarcinoma-like components, which also immunostain for AFP (Koswara et al. 2007).

Solid Pseudopapillary Tumor (Papillary Cystic Tumor) of the Liver/ Bile Duct

Introduction

Solid pseudopapillary tumor (SPPT; papillary cystic tumor; Frantz tumor) is a rare pancreatic tumor clinico-radiologically belonging to the cystic tumor group (Adams et al. 2008; Lee et al. 2008; Chakhachiro and Zaatari 2009). The neoplasm typically occurs in females and only rarely in males: an analysis of 1014 patients reported in the literature revealed only 137 (13.5 %) males (Lin and Stabile 2010). SPPT is usually an expandingly growing mass lesion, but a solid, infiltrating variety also exists (Matsunou et al. 1990). The biology of disease is that of benign or low-grade malignant behavior, metastases (mostly to the liver) being uncommon (Gonzalez-Campora et al 1995; Nagri et al. 2007). Males had a twofold higher incidence of metastases and a threefold higher death rate, and SPPT therefore has an atypically aggressive biology in males (Lin and Stabile 2010). The cell of origin is not known, but suspected to be a pancreatic stem cell.

Solid Pseudopapillary Tumor Primary to the Liver

A case of a primary tumor of the liver with pathologic features strikingly similar to pancreatic SPPT has been observed in a 41-year-old female patient (Kim et al. 1990). In this patient, two large, solid and cystic tumors with extensive hemorrhage and necrosis were detected in the right and left liver lobes, measuring 30 cm and 5.5 cm, respectively, in diameter. The pancreas was free of tumor.

Morphologic and Biologic Features of Solid Pseudopapillary Tumor

Histologically, SPPTs are characterized by loosely cohesive, relatively uniform polygonal cells with a slightly eosinophilic or pale cytoplasm, sometimes with vacuolization. The nuclei exhibit grooving and have a finely stippled chromatin. These cells surround delicate capillary-sized blood vessels. As an artifact, cell layers around vessels may separate from each other, hence resulting in a pseudopapillary pattern (Santini et al. 2006; Fig. 1).

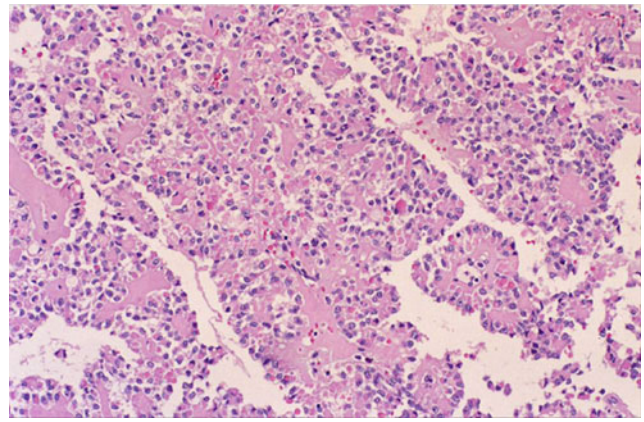

Fig. 1 Solid pseudopapillary tumor (papillary cystic tumor) of the liver (hematoxylin and eosin stain)

There are few very rare histologic variants of SPPT, including clear cell SPPT (Hav et al. 2009), pigmented SPPT (Daum et al. 2005), a spindle cell variant (El-Bahrawy et al. 2010), and ossifying SPPT (Kim et al. 2005). Immunohistochemically, the tumor is complex and polyphenotypic, positive marker including vimentin, CD10, CD56, alpha-1-antichymotrypsin, neuron-specific enolase, synaptophysin, estrogen receptor beta, and progesterone receptor (Pettinato et al. 1992; Morales et al. 2003; Santini et al. 2006; Serra and Chetty 2008). SPPT shows a peculiar claudin expression profile and the highly specific pattern of claudins 5 and 7 differentiates SPPT from other pancreatic tumors (Comper et al. 2009).

SPPTs of the pancreas almost always harbor mutations of the beta-catenin gene, with nuclear accumulation of beta-catenin being present in 95 % of the cases (Abraham et al. 2002; El-Bahrawy et al 2008; Kang et al 2009; reviews: Antonello et al. 2008; Serra and Chetty 2008). Nuclear expression of beta-catenin and loss of E-cadherin are important diagnostic features of SPPT (Kim et al. 2008; Burford et al. 2009). Nuclear relocalization of beta-catenin in SPPT is associated with loss of E-cadherin and decrease or loss of p120, a protein which regulates E-cadherin and is responsible for its degradation (Audard et al. 2008; Chetty et al. 2008). In the pathogenesis of SPPT, the Notch signaling pathway is also involved (Cavard et al. 2009).

Tumors with Rhabdoid Features of the Biliary Tract

Introduction

Malignant tumors containing variable amounts of rhabdoid cells commonly exhibit a more aggressive biology. Therefore, the identification of rhabdoid features is an important diagnostic element. The nomenclature of these lesions is not yet standardized. Several terms have been employed to denote the presence of rhabdoid cells in neoplasm, including rhabdoid features, rhabdoid phenotype, rhabdoid differentiation, rhabdoid transformation, rhabdoid areas, and rhabdoid as an adjective preceding the name of the tumor (such as rhabdoid adenocarcinoma). Carcinomas and adenocarcinomas with rhabdoid features occur in most organs and tissue derived from the foregut. They comprise the thyroid (including follicular carcinoma), the lung, the esophagus, the stomach, the pancreas (including neuroendocrine carcinoma), the small intestine, and the colon. In the liver, tumors with rhabdoid features chiefly comprise a distinct lesion mostly occurring in the pediatric age group, i.e., malignant extrarenal rhabdoid tumor.

Intrahepatic Cholangiocarcinoma with Rhabdoid Features

Intrahepatic CC with rhabdoid features (synonyms: intrahepatic CC with rhabdoid

transformation; rhabdoid cholangiocarcinoma) is a very rare malignant neoplasm of the intrahepatic biliary tree, characterized by a variable component of cells with a rhabdoid phenotype (Honda et al. 1996; Lim et al. 2004; Sugano et al. 2013). The patient reported by Honda and coworkers, a 61-year-old female, showed multiple liver masses at imaging. Histologically, these tumors exhibited both sarcomatous and ordinary tubular adenocarcinomas, the sarcomatous areas being occupied by rhabdoid cells expressing both vimentin and cytokeratin (Honda et al. 1996). In the case of Lim and coworkers (a 41-year-old female), a left hepatic lobectomy showed a huge mass (up to 17 cm) with extensive necrosis and an infiltrative border. The viable tumor, found only in the peripheral portion of the mass, was reddish yellow to tan and hemorrhagic. Histologically, the entire tumor was composed of loosely cohesive, round to polygonal cells with abundant eosinophilic, glassy cytoplasm. The vesicular nuclei were eccentrically placed. Close to the nuclei, the cytoplasmic body typical for rhabdoid cells was noted. Some of the cells had mucin-containing vacuoles. Immunohistochemically, the cells expressed both vimentin and epithelial markers (Lim et al. 2004). Differential diagnostically, peritoneal spread of adenocarcinomas with rhabdoid features should be distinguished from malignant peritoneal mesothelioma containing rhabdoid cells (Matsukuma et al. 1996).

Primary Rhabdoid Tumor of the Gallbladder

In a 46-year-old male patient, the gallbladder showed a slight thickening in the body wall, measuring 1 cm. The lesion was located on the peritoneal side, i.e., away from the liver bed. Sections from this area revealed collections of loosely arranged plump cells with the features of rhabdoid cells, which showed the typical eccentric, paranuclear positivity for vimentin (Suri et al. 2003). A second case of gallbladder carcinoma with a rhabdoid component, but associated with sarcomatoid features, was reported in a 61-year-old female patient. This tumor of 4.5 cm size was located in the neck portion of the gallbladder (Kim et al. 2003).

Pathogenesis

At least in part of rhabdoid tumors and tumors with rhabdoid features, genetic alterations of the INI1 gene are well established (see ▶ Chap. 78, "Malignant Rhabdoid Tumors and Tumors with Rhabdoid Features"). In mucinous carcinoma with rhabdoid features, INI1/SMARCB1 missense mutations (codon 116) have been identified (Cho et al. 2006).

References

Abdullah A, Jenkins-Mosure K, Lewis T, Patel Y, Strobel S, Pepe L (2010) Primary hepatoid carcinoma of the biliary tree: a radiologic mimicker of Klatskin-type tumor. Cancer Imaging 10:198–201

Abraham SC, Klinstra DS, Wilentz RE, Yeo CJ, Conlon K, Brennan M, Cameron JL et al (2002) Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol 160:1361–1369

Adams AL, Siegal GP, Jhala NC (2008) Solid pseudopapillary tumor of the pancreas: a review of salient clinical and pathologic features. Adv Anat Pathol 15:39–45

Akiyama S, Niitani T, Narasaka T, Ohto T, Gamoh M (2011) Poorly-differentiated neuroendocrine carcinoma of ascending colon with liver metastases successfully treated with carboplatin and etoposide (in Japanese). Gan To Kagaku Ryoho 38:1209–1212

Al-Jiffry BO, Al-Malki O (2013) Neuroendocrine small cell rectal cancer metastasizing to the liver: a unique treatment strategy, case report, and review of the literature. World J Surg Oncol 11:153

Antonello D, Gobbo S, Corbo V, Sipos B, Lemoine NR, Scarpa A (2008) Update on the molecular pathogenesis of pancreatic tumors other than common ductal adenocarcinoma. Pancreatology 9:25–33

Arakura N, Hasebe O, Yokosawa S, Imai Y, Furuta S, Hosaka N (2003) A case of small cell carcinoma of the extrahepatic bile duct which could be diagnosed before operation (in Japanese). Nippon Shokakibyo Gakkai Zasshi 100:190–194

Arakura N, Muraki T, Komatsu K, Ozaki Y, Hamano H, Tanaka E, Kawa S (2008) Small cell carcinoma of the extrahepatic bile duct diagnosed with EUS-FNA and effectively treated with chemoradiation. Intern Med 47:621–625

Audard V, Cavard C, Richa H, Infante M, Couvelard A, Sauvanet A, Terris B, Paye F, Fléjou JF (2008) Impaired E-cadherin expression and glutamine synthetase overexpression in solid pseudopapillary neoplasm of the pancreas. Pancreas 36:80–83

Balta Z, Sauerbruch T, Hirner A, Büttner R, Fischer HP (2008) Primary neuroendocrine carcinoma of the liver. From carcinoid tumor to small-cell hepatic carcinoma: case reports and review of the literature (in German). Pathologe 29:53–60

Bottles K, Lacey CG, Goldberg J, Lanner-Cusin K, Hom J, Miller TR (1984) Merkel cell carcinoma of the vulva. Obstet Gynecol 63(3 Suppl):61S–65S

Brenner B, Shah MA, Gonen M, Klimstra DS, Shia J, Kelsen DP (2004a) Small-cell carcinoma of the gastrointestinal tract: a retrospective study of 64 cases. Br J Cancer 90:1720–1726

Brenner B, Tang LH, Klimstra DS, Kelsen DP (2004b) Small-cell carcinomas of the gastrointestinal tract: a review. J Clin Oncol 22:2730–2739

Brenner B, Tang LH, Shia J, Klimstra DS, Kelsen DP (2007) Small cell carcinoma of the gastrointestinal tract: clinicopathological features and treatment approach. Semin Oncol 34:43–50

Burford H, Baloch Z, Liu X, Jhala D, Siegal GP, Jhala N (2009) E-cadherin/beta-catenin and CD10: a limited immunohistochemical panel to distinguish pancreatic endocrine neoplasm from solid pseudopapillary neoplasm of the pancreas on endoscopic ultrasound-guided fine-needle aspirates of the pancreas. Am J Clin Pathol 132:831–839

Cavard C, Audebourg A, Letourneur F, Audard V, Beuvon F, Cagnard N, Radenen B et al (2009) Gene expression profiling provides insights into the pathways involved in solid pseudopapillary neoplasm of the pancreas. J Pathol 218:201–209

Chakhachiro ZI, Zaatari G (2009) Solid-pseudopapillary neoplasm: a pancreatic enigma. Arch Pathol Lab Med 133:1986–1993

Chetty R, Jain D, Serra S (2008) p120 catenin reduction and cytoplasmic localization leads to dysregulation of E-cadherin in solid pseudopapillary tumors of the pancreas. Am J Clin Pathol 130:71–76

Cho YM, Choi J, Lee OJ, Lee HI, Han DJ, Ro JY (2006) SMARCB1/INI1 missense mutations in mucinous carcinoma with rhabdoid features. Pathol Int 56:702–706

Cho SB, Park SY, Joo YE (2009) Small cell carcinoma of extrahepatic bile duct presenting with hemobilia (in Korean). Korean J Gastroenterol 54:186–190

Choi SJ, Kim JM, Han JY, Ahn SI, Kim JS, Kim L, Park IS, Chu YC (2007) Extrapulmonary small cell carcinoma of the liver: clinicopathological and immunohistochemical findings. Yonsei Med J 48:1066–1071

Comper F, Antonello D, Beghelli S, Gobbo S, Montagna L, Pederzoli P, Chilosi M, Scarpa A (2009) Expression pattern of claudin 5 and 7 distinguishes solid-pseudopapillary form pancreatoblastoma, acinar cell and endocrine tumors of the pancreas. Am J Surg Pathol 33:768–774

Daum O, Sima R, Mukensnabl P, Vanecek T, Brouckova M, Benes Z, Michal M (2005) Pigmented solid-pseudopapillary neoplasm of the pancreas. Pathol Int 55:280–284

El-Bahrawy MA, Rowan A, Horncastle D, Tomlinson I, Theis BA, Russell RC, Stamp G (2008) E-cadherin/catenin complex status in solid pseudopapillary tumor of the pancreas. Am J Surg Pathol 32:1–7

El-Bahrawy MA, Khorsandy S, Williamson R, Stamp GW (2010) Spindle cell solid pseudopapillary tumor of the pancreas: a newly described variant. Pancreas 39:255–257

Eriguchi N, Aoyagi S, Hara M, Okuda K, Fukuda S, Tamae T, Kanazawa N (2001) Malignant sarcomatoid tumor of the liver: report of a case. Surg Today 31:170–173

Fenoglio-Preiser CM (2001) Gastrointestinal neuroendocrine/neuroectodermal tumors. Am J Clin Pathol 115 (suppl):S79–S93

Frazier SR, Kaplan PA, Loy TS (2007) The pathology of extrapulmonary small cell carcinoma. Semin Oncol 34:30–38

Fujikawa T, Tanaka A, Abe T, Yoshimoto H, Tokumitsu Y, Tada S, Matsumoto Y, Maekawa H, Aoyama K et al (2011) Undifferentiated carcinoma of the common bile duct with intraductal tumor thrombi: report of a case. Surg Today 41:579–584

Gakiopoulou H, Givalos N, Liapis G, Agrogiannis G, Patsouris E, Delladetsima I (2007) Hepatoid adenocarcinoma of the gallbladder. Dig Dis Sci 52:3358–3362

Galanis E, Frytak S, Lloyd RV (1997) Extrapulmonary small cell carcinoma. Cancer 79:1729–1736

Garcia MT, Bejanaro PA, Yssa M, Buitrago E, Livingstone A (2006) Tumor of the liver (hepatocellular and high grade neuroendocrine carcinoma): a case report and report of the literature. Virchows Arch 449:376–381

Gollub MJ, Gruen DR, Dershaw DD (1996) Merkel cell carcinoma: CT findings in 12 patients. AJR Am J Roentgenol 167:617–620

Gonzalez-Campora R, Rios Martin JJ, Villar Rodriguez JL, Otal S, Alaverri C, Hevia Vazquez A et al (1995) Papillary cystic neoplasm of the pancreas with liver metastasis coexisting with thyroid papillary carcinoma. Arch Pathol Lab Med 119:268–273

Grigsby P, Meyer JS, Sicard GA, Huggins MB, Lamar DJ, DeSchryver-Kecskemeti K (1987) Hepatic adenoma within a spindle cell carcinoma in a woman with a long history of oral contraceptives. J Surg Oncol 35:173–179

Groeschl RT, Christians KK, Turaga KK, Gamblin TC (2013) Management of primary hepatopancreatobiliary small cell carcinoma. J Surg Oncol 107:692–695

Hav M, Lem D, Chhut SV, Kong R, Pauwels P, Cuvelier C, Piet P (2009) Clear-cell variant of solid-pseudopapillary neoplasm of the pancreas: a case report and review of the literature. Malays J Pathol 31:137–141

Hazama K, Suzuki Y, Takahashi M, Takahashi Y, Yoshioka T, Takano S, Kondoh S, Katoh H (2003) Primary small cell carcinoma of the common bile duct, in which surgical treatment was performed after neoadjuvant chemotherapy: report of a case. Surg Today 33:870–872

Hishinuma M, Ohashi KI, Yamauchi N, Kashima T, Uozaki H, Ota S, Kodama T, Aburatani H, Fukayama M (2006) Hepatocellular oncofetal protein, glypican 3 is a sensitive marker for alpha-fetoprotein-producing gastric carcinoma. Histopathology 49:479–486

Honda M, Enjoji M, Sakai H, Yamamoto I, Tsuneyoshi M, Nawata H (1996) Case report: intrahepatic cholangiocarcinoma with rhabdoid transformation. J Gastroenterol Hepatol 11:771–774

Ikegami T, Kayashima H, Sadanaga N, Morizono S, Nakashima A, Matsuura H, Shirabe K et al (2013) Composite small cell and mucinous carcinoma originating from the intrahepatic bile duct: report of a case. Surg Today 43:194–198

Imazu H, Ochiai M, Funabiki T (1995) Intrahepatic sarcomatous cholangiocarcinoma. J Gastronterol 30:677–682

Iwasa S, Morizane C, Okusaka T, Uena H, Ikeda M, Kondo S, Tanaka T, Nakachi K et al (2010) Cisplatin and etoposide as first-line chemotherapy for poorly differentiated neuroendocrine carcinoma of the hepatobiliary tract and pancreas. Jpn J Clin Oncol 40:313–318

Jang JS, Yim HJ, Lee BJ, Kim SY, Kim DI, Lee HS, Lee SW, Choi JH (2007) A case of hepatic metastasis of small cell carcinoma from mixed small cell carcinoma and adenocarcinoma of the stomach (in Korean). Korean J Gastroenterol 50:193–198

Jeon WJ, Chae HB, Park SM, Youn SJ, Choi JW, Kim SH (2006) A case of primary small cell carcinoma arising from the common bile duct (in Korean). Korean J Gastroenterol 48:438–442

Jo JM, Cho YK, Hyun CL, Han KH, Rhee JY, Kwon JM, Kim WK, Han SH (2013) Small cell carcinoma of the liver and biliary tract without jaundice. World J Gastroenterol 19:8146–8150

Kaiho T, Tanaka T, Tsuchiya S, Yanagisawa S, Takeuchi O, Miura M, Saigusa N et al (2005) A case of small cell carcinoma of the common bile duct. Hepatogastroenterology 52:363–367

Kaman L, Iqbal J, Pall M, Bal A (2010) Primary small cell carcinoma of liver: a rare tumor. Gastroenterol Res 3:180–184

Kang CM, Kim HK, Kim H, Choi GH, Kim KS, Choi JS, Lee WJ (2009) Expression of Wnt target genes in solid pseudopapillary tumor of the pancreas: a pilot study. Pancreas 38:e53–e59

Kao CY, Chang CR, Chiang H, Chen HT, Shih-Ming M, Cheng CY (2009) Well.-differentiated gall bladder hepatoid carcinoma producing alpha-fetoprotein: a case report. J Med Case Reports 3:7303

Khalbuss WE, Grigorian S, Bui MM, Elhosseiny A (2005) Small-cell tumors of the liver: a cytological study of 91 cases and a review of the literature. Diagn Cytopathol 33:8–14

Khaw YL, Nolan N, Heaslip I, McCormick PA, Sheahan K (2011) Primary intrahepatic small-cell carcinoma arising from combined hepatocellular and cholangiocarcinomas. J Clin Oncol 29:e630–e633

Kim et al. 1990. http://www.ncbi.nlm.nih.gov/pubmed/2340471

Kim MJ, Yu E, Ro JY (2003) Sarcomatoid carcinoma of the gallbladder with a rhabdoid tumor component. Arch Pathol Lab Med 127:e406–e408

Kim YH, Kwon R, Jung GJ, Roh MH, Han SY, Kwon HC, Jeong JS, Shin TB, Oh JY, Lee KN (2004) Extrapulmonary small-cell carcinoma of the liver. J Hepatobiliary Pancreat Surg 11:333–337

Kim NR, Han J, Chung DH, Ha SY (2005) Solid and papillary epithelial neoplasm of the pancreas with ossification: a report of two cases. Histopathology 46:355–357

Kim KJ, Yim HJ, Kim MJ, Choung RS, Yeon JE, Lee HS, Byun KS, Lee SW et al (2006a) A case of primary small cell neuroendocrine carcinoma of the liver (in Korean). Korean J Gastroenterol 48:37–41

Kim KO, Lee HY, Chun SH, Shin SJ, Kim MK, Lee KH, Hyun MS, Bae SH, Ryoo HM (2006b) Clinical overview of extrapulmonary small cell carcinoma. J Korean Med Sci 21:833–837

Kim MJ, Jang SJ, Yu E (2008) Loss of E-cadherin and cytoplasmic-nuclear expression of beta-catenin are the most useful immunoprofiles in the diagnosis of solid-pseudopapillary neoplasm of the pancreas. Hum Pathol 39:251–258

Koswara T, Marwoto W, Siregar NC, Gumay S, Azis H, Abdullah M, Himawan S (2007) Hepatoid carcinoma of the gallbladder. Acta Med Indones 39:179–182

Kuraoka K, Taniyama K, Fujitaka T, Nakatsuka H, Nakayama H, Yasui W (2003) Small cell carcinoma of the extrahepatic bile duct: case report and immunohistochemical analysis. Pathol Int 53:887–891

Lee SS, Lee JL, Ryu MH, Chang HM, Kim TW, Kim WK, Lee JS, Jang SJ, Khang SK, Kang YK (2007) Extrapulmonary small cell carcinoma: single center experience with 61 patients. Acta Oncol 46:846–851

Lee SE, Jang JY, Hwang DW, Park KW, Kim SW (2008) Clinical features and outcome of solid pseudopapillary neoplasm: difference between adults and children. Arch Surg 143:1218–1221

Levenson RM, Ihde DC, Matthews MJ, Cohen MH, Gazdar AF, Bunn PA, Minna JD et al (1981) Small cell carcinoma presenting as an extrapulmonary neoplasm: sites of origin and response to chemotherapy. J Natl Cancer Inst 67:607–612

Lewis JS, Ritter JH, El-Mofty S (2005) Alternative epithelial markers in sarcomatoid carcinomas of the head and neck, lung, and bladder – p63, MOC-31, and TTF-1. Mod Pathol 18:1471–1481

Lim BJ, Kim KS, Lim JS, Kim MJ, Park C, Park YN (2004) Rhabdoid cholangiocarcinoma: a variant of

cholangiocarcinoma with aggressive behavior. Yonsei Med J 45:543–546

Lin MY, Stabile BE (2010) Solid pseudopapillary neoplasm of the pancreas: a rare and atypically aggressive disease among male patients. Am Surg 76:1075–1078

Maitra A, Murakata LA, Albores-Saavedra J (2001) Immunoreactivity for hepatocyte paraffin 1 antibody in hepatoid adenocarcinomas of the gastrointestinal tract. Am J Clin Pathol 115:689–694

Matsui T, Tsuji K, Ichiya T, Komaba F, Kang JH, Kodama Y, Sakurai Y, Kato S et al (2010) Sarcomatoid carcinoma of the liver: a case report and review of the literature (in Japanese). Nippon Shokakibyo Gakkai Zasshi 107:1175–1183

Matsukuma S, Aida S, Hata Y, Sugiura Y, Tamai S (1996) Localized malignant peritoneal mesothelioma containing rhabdoid cells. Pathol Int 46:389–391

Matsunou H, Konishi F, Yamamichi N, Takayanagi N, Mukai M (1990) Solid, infiltrating variety of papillary cystic neoplasm of the pancreas. Cancer 65:2747–2757

Matsuo S, Shinozaki T, Yamaguchi S, Takami Y, Obata S, Tsuda N, Kanematsu T (1999) Intrahepatic cholangiocarcinoma with extensive sarcomatous change: report of a case. Surg Today 29:560–563

Miyashita T, Konishi K, Noto M, Taniguchi K, Kaji M, Kimura H, Maeda K, Yabishita K, Miwa A (2001) A case of small cell carcinoma of the common bile duct (in Japanese). Nippon Shokakibyo Gakkai Zasshi 98:1195–1198

Morales A, Duarte-Rojo A, Angeles-Angeles A, Mery CM, Ruiz-Molina JM, Diaz-Sanchez V, Robles-Diaz G (2003) The beta form of the estrogen receptor is predominantly expressed in the papillary cystic neoplasm of the pancreas. Pancreas 26:258–263

Morikawa H, Nakayama Y, Maeda T, Nadatani Y, Kobayashi S, Iwai S, Enomoto M et al (2008) A case of primary small cell carcinoma of the liver that was treated with chemotherapy. Hepatol Int 2:500–504

Motojima K, Furui J, Terada M, Shiogama T, Kohara N, Tsunoda T, Tsuchiya R (1990) Small cell carcinoma of the pancreas and biliary tract. J Surg Oncol 45:164–168

Nagai E, Ueyama T, Yao T, Tsuneyoshi M (1993) Hepatoid adenocarcinoma of the stomach. A clinicopathologic and immunohistochemical analysis. Cancer 72:1827–1835

Nagri S, Abdu A, Anand S, Krishnajah M, Arya V (2007) Liver metastasis four years after Whipple's resection for solid-pseudopapillary tumor of the pancreas. JOP 8:223–227

Nakai N, Takenaka H, Hamada S, Kishimoto S (2008) Identical p53 gene mutation in malignant proliferating trichilemmal tumour of the scalp and small cell carcinoma of the common bile duct: the necessity for therapeutic caution ? Br J Dermatol 159:482–485

Nakanishi Y, Ito T, Kubota K, Takeda H, Yonemori A, Kawakami H, Zen Y, Kondo S (2007) Spindle cell type undifferentiated carcinoma of the common bile duct of the hepatic hilus: report of a case. Surg Today 37:708–712

Nakashima H, Nagafuchi K, Satoh H, Takeda K, Yamasaki T, Yonemasu H, Kishikawa H (2000) Hepatoid adenocarcinoma of the gallbladder. J Hepatobiliary Pancreat Surg 7:226–230

Nakasuka H, Okada S, Okusaka T, Ishii H, Ikeda M, Ito R, Kosakamoto H, Yoshimora M et al (1998) Undifferentiated carcinoma of the liver with neuroendocrine features: a case report. Jpn J Clin Oncol 28:401–404

O'Byrne KJ, Goggins MG, McDonald GS, Daly PA, Kelleher DP, Weir DG (1994) A metastatic neuroendocrine anaplastic small cell tumor in a patient with multiple endocrine neoplasia type 1 syndrome. Assessment of disease status and response to doxorubicin, cyclophosphamide, etoposide chemotherapy through scintigraphic imaging with 111In-pentetreotide. Cancer 74:2374–2378

Ochsenreither S, Marnitz-Schultze S, Schneider A, Koehler C, Daum S, Loddenkemper C et al (2009) Extrapulmonary small cell carcinoma (EPSCC): 10 years' multi-disciplinary experience at Charité. Anticancer Res 29:3411–3415

Okamura Y, Maeda A, Matsunaga K, Kanemoto H, Boku N, Furukawa H, Sasaki K, Uesaka K (2009) Small-cell carcinoma in the common bile duct treated with multidisciplinary management. J Hepatobiliary Pancreat Surg 16:575–578

Otten M, Sepehrkhouy S, van Everdingen K, Haas L (2013) Primary small cell carcinoma of the liver, a rare entity. BMJ Case Rep 2013:pii: bcr2013201990

Park HW, Seo SH, Jang BK, Hwang JY, Park KS, Cho KB, Hwang JS, Ahn SH et al (2004) A case of primary small cell carcinoma in the common bile duct (in Korean). Korean J Gastroenterol 43:260–263

Pettinato G, Manivel JC, Ravetto C, Terraciano LM, Gould EW, di Tuoro A, Jaszcz W et al (1992) Papillary cystic tumor of the pancreas. A clinicopathologic study of 20 cases with cytologic, immunohistochemical, ultrastructural, and flow cytometric observations, and a review of the literature. Am J Clin Pathol 98:478–488

Premkumar J, Karthnik S, Sathyakumar M, Martin Y (2013) Concurrent occurrence of adenoid cystic carcinoma of the salivary glands with small cell carcinoma of the liver: a rare case report. J Oral Maxillofac Pathol 17:288–291

Remick SC, Ruckdeschel JC (1992) Extrapulmonary and pulmonary small-cell carcinoma: tumor biology, therapy, and outcome. Med Pediatr Oncol 20:89–99

Remick SC, Hafez GR, Carbone PP (1987) Extrapulmonary small-cell carcinoma. A review of the literature with emphasis on therapy and outcome. Medicine (Baltimore) 66:457–471

Richardson RL, Weiland LH (1982) Undifferentiated small cell carcinomas in extrapulmonary sites. Semin Oncol 9:484–496

Ryu SH, Han SY, Suh SH, Koo YH, Cho JH, Han SH, Lee SW, Cho JH, Jeong JS (2005) A case of primary small

cell carcinoma of the liver (in Korean). Korean J Hepatol 11:289–292
Sabanathan S, Hashimi H, Nicholson G, Edwards AS (1988) Primary oat cell carcinoma of the common bile duct. JR Coll Surg Edinb 33:285–286
Sakamoto K, Monobe Y, Kouno M, Moriya T, Sasano H (2004) Hepatoid adenocarcinoma of the gallbladder: case report and review of the literature. Pathol Int 54:52–56
Sakamoto K, Kimura N, Tokumura H, Ogasawara T, Moriya T, Sasano H (2005) Hepatoid adenocarcinoma of the gallbladder. Histopathology 47:649–651
Santini D, Poli F, Lega S (2006) Solid-papillary tumors of the pancreas: histopathology. JOP 7:131–136
Sato K, Takeyama Y, Tanaka T, Fukui Y, Gonda H, Suzuki R (2013) Fulminant hepatic failure and hepatomegaly caused by diffuse liver metastases from small cell lung carcinoma: 2 autopsy cases. Respir Invest 51:98–102
Scherwitz P, Lindenfelser R, Krüger I (2002) Localization of primary small cell carcinoma with liver metastasis: a rare combination of colonic adenocarcinoma and undifferentiated small cell carcinoma (in German). Chirurg 73:859–861
Sengoz M, Abacioglu U, Salepci T, Eren F, Yumuk F, Turhal S (2003) Extrapulmonary small cell carcinoma: multimodality treatment results. Tumori 89:274–277
Sentani K, Oue N, Sakamoto N, Arihiro K, Aoyagi K, Sasaki H, Yasui W (2008) Gene expression profiling with microarray and SAGE identifies PLUNC as a marker for hepatoid adenocarcinoma of the stomach. Mod Pathol 21:464–475
Serra S, Chetty R (2008) Revision 2: an immunohistochemical approach and evaluation of solid pseudopapillary tumour of the pancreas. J Clin Pathol 61:1153–1159
Sugano I, Senda T, Hayashi S, Okaya T, Yamazaki K, Ishida Y (2013) A rhabdoid-mimicking intrahepatic cholangiocarcinoma. Pathol Int 63:422–424
Suri VS, Gondal R, Agarwal A, Malhotra V, Sakhuja P, Singhal S (2003) Primary rhabdoid tumor of the gallbladder: report of a case. Surg Today 33:464–466
Terracciano LM, Glatz K, Mhawech P, Vasei M, Lehmann FS, Vecchione R, Tornillo L (2003) Hepatoid adenocarcinoma with liver metastasis mimicking hepatocellular carcinoma: an immunohistochemical and molecular study of eight cases. Am J Surg Pathol 27:1302–1312
Thomas NE, Burroughs FH, Ali SZ (2005) Small-cell carcinoma of the extrahepatic bile duct and concurrent clonorchiasis. Diagn Cytopathol 32:92–93
Ushiku T, Shinozaki A, Shibahara J, Iwasaki Y, Tateishi Y, Funata N, Fukayama M (2010) SALL4 represents fetal gut differentiation of gastric cancer, and is diagnostically useful in distinguishing hepatoid gastric carcinoma from hepatocellular carcinoma. Am J Surg Pathol 34:533–540
Vaideeswar P, Munot S, Rojekar A, Deodhar K (2012) Hepatic diffuse intra-sinusoidal metastases of pulmonary small-cell carcinoma. J Postgrad Med 58:230–231
Van den Bos IC, Hussain SM, Dwarkasing RS, Stoop H, Zondservan PE, Krestin GP, de Man RA (2007) Hepatoid adenocarcinoma of the gallbladder: a mimicker of hepatocellular carcinoma. Br J Radiol 80:e317–e320
Van der Wal AC, Van Leeuwen DJ, Walford N (1990) Small cell neuroendocrine (oat cell) tumour of the common bile duct. Histopathology 16:398–400
Viana Miguel MM, Garcia-Plata Polo E, Vidal Doce O, Aldea Martinez J, de la Plaza Galindo M, Santamaria Garcia JL (2006) Oat cell carcinoma of the common bile duct (in Spanish). Cir Esp 80:43–45
Vrouvas J, Ash DV (1995) Extrapulmonary small cell cancer. Clin Oncol (R- Coll Oncol) 7:377–381
Walenkamp AM, Sonke GS, Sleijfer DT (2009) Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. Cancer Treat Rev 35:228–236
Walshauser MA, Ishii K, Murugappan K, Masoom S, Yong S, Bhoopalam N (2013) a-fetoprotein secreting extrapulmonary small-cell carcinoma of the liver. J Clin Oncol 31:e152–e154
Wong YNS, Jack RH, Mak V, Henrik M, Davies EA (2009) The epidemiology and survival of extrapulmonary small cell carcinoma in South East England, 1970–2004. BMC Cancer 9:209–215
Yamaguchi R, Nakashima O, Ogata T, Hanada K, Kumabe T, Kojiro M (2004) Hepatocellular carcinoma with an unusual neuroendocrine component. Pathol Int 54:861–865
Yang et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19686999
Yuan ZY, Guan ZZ, Zhou ZM, Xia Y, Huang WZ, Yang XL (2006) Extrapulmonary small cell carcinoma in 52 patients (in Chinese). Ai Zheng 25:1131–1133
Zanconati F, Falconieri G, Lamovec J, Zidar A (1996) Small cell carcinoma of the liver: a hitherto unreported variant of hepatocellular carcinoma. Histopathology 29:449–453

Epithelial Tumors of the Liver of Uncertain Lineage

45

Contents

Abstract

The hepatobiliary tract is the primary site of a small group of tumors that are, in regard to their origin, characterized by uncertain cell lineages. Adrenal rest tumor is an unusual lesion thought to take its origin from an adrenal rest, probably deriving from aberrant adrenal primordia or extraadrenal cells. This neoplasm is typically a gonadal tumor but very rarely also develops in the liver. The neoplasms are circumscribed lesion that typically develop close to the liver capsule and histologically resemble adrenocortical cells. A second group of hepatic tumors of uncertain pathogenesis are progenitor cell tumors, lesions that include undifferentiated liver tumor with stem cell-like features, and progenitor cell neoplasms with an intermediate cellular phenotype.

Adrenal Rest Tumor

Introduction

Adrenal rest tumor (ART) denotes a tumorous or multinodular lesion thought to take its origin from an adrenal rest, which probably derives from an aberrant adrenal primordium or from extraadrenal cells secondarily committed to become adrenocortical cells (Barwick et al. 2005). ART occurs at several sites, including the retroperitoneal space (including the perirenal region), testis, ovary, broad ligament, spinal nerves, and liver, but

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_45

excluding the limbs. ARTs are very well recognized to occur in the testis (testicular adrenal rest tumor; TART) of patients with congenital adrenal hyperplasia, caused by 21-hydroxylase deficiency in more than 90 % of the patients (Cakir et al. 2012; Delfino et al. 2012; Aycan et al. 2013). TART are usually bilateral lesions and are mostly localized to the rete testis rather than the testicular parenchyma. The aberrant adrenocortical cells within the testicular compartment are stimulated by pro-opiomelanocortin in periods of suboptimal hormonal control inducing hypertrophy and hyperplasia (Claahsen-van der Grinten et al. 2009).

Adrenal Rest Tumor of the Liver: An Intriguing Entity

Hepatic ART (HART; obsolete synonyms, primary "hypernephroma" of the liver; hypernephroid tumors of the liver; primary hypernephroid cancer of the liver) is a rare finding and is, similar to ART located elsewhere, thought to derive from misplaced adrenocortical cells within the capsule, or under the capsule, of the liver. Based on a resemblance of the tumor cells with those of renal cell carcinoma, the term "hypernephroma of the liver" has been employed in some of the early reports. The designations, "primary adrenal carcinoma of the liver" (Powell et al. 1908) or "primary liver tumor of probable adrenocortical origin," (Cirio 1922) have also been used. The identification and definition of the lesion require the presence of normally located extrahepatic and perirenal normal adrenal glands to exclude AHA or AHF (Craig et al. 1989), and the detection of steroid hormone synthesis/production is one essential component for the diagnosis.

Selected References Schmorl 1891; Kaufmann 1897; Pepere 1902; De Vecchi 1904; Donati 1905; Phillips and Spilsbury 1905; Powell et al. 1908; De Ahna 1912; Hirschler 1912; Swenson 1917; Cirio 1922; Williams 1924; Abell 1928; Anardi 1928; Horn 1929; Ramsey 1929; Patrassi 1932; Mason and Speese 1933; Bini 1934; Massa 1938; Kopac 1940; Inama 1948; Pendl and Scherlacher 1950; Wilkins and Ravitch 1952; Tallarigo 1954; Goffrini 1955; Vitagliano 1956; Ceccont 1958; Hyams et al. 1960; Zverev 1963; Schechter 1968; Hamperl 1970; Pollice 1973; Wallace et al. 1981; Contreras et al. 1985; Miyazaki and Shimizu 1995; Arai et al. 2000; Tajima et al. 2001; Baba et al. 2008; Shin 2010.

Is HART a bona fide neoplastic process? Hamperl (1970) started his detailed review article on hepatic ART with the question: "Do adrenal rest tumors of the liver really exist?" In particular for small subcapsular lesions, this question is difficult to answer, because a distinction between reactive growth of ectopic adrenocortical-like cells and neoplasia may not be possible by the use of morphologic analysis. Schmorl (1891) had described adrenal rests in the liver similar to those found in the kidney, and these observations were confirmed by Beer (1904) and Weller (1925), who found adrenal rests in 4 % and 0.34 %, respectively, of their cases (cited from Hamperl 1970). Conversely, large tumors are thought to be neoplastic and may even represent carcinomas; in fact, malignant transformation of ART has been reported (Craig et al. 1989; Goren et al. 1991), but more cases have to be collected in order to arrive at a more precise description of the lesions' biology.

Epidemiological, Clinical, and Imaging Features

Hepatic ART (HART) is a very uncommon neoplasm. Among 26 cases compiled by Hamperl (1970), age at diagnosis ranged from 14 months to 70 years. The male to female ratio was 15:11. HART has been observed in infants and children (Mason and Speese 1933; Zverev 1963). The clinical presentation of hepatic adrenal rest tumors is variegated.

One of the early reports described a boy aged 17 months who was admitted with the chief complaint of severe upper abdominal pain having developed suddenly and high fever. The abdomen was distended, and palpation revealed a hard,

irregular, tender mass in the left hypochondrium. At laparotomy, a vascular, orange-sized and encapsulated, firm tumor was discovered attached to the under surface of the right liver lobe (today we would call this a pediculated tumor). Histology showed a neoplasm containing cells resembling those of the inner zone of the adrenal zona glomerulosa. In addition, there were acinar-like areas lined by cuboidal cells or lacking any epithelial lining. The majority of these acini were filled with a hyaline, colloid-like material. Five years later, the child presented multiple bony metastases attributed to hypernephroid renal carcinoma (Mason and Speese 1933). This example highlights the difficulties in diagnosis. Was this HART later followed by hypernephroma or was the liver tumor an early metastatic manifestation of a then still small renal cell carcinoma? However, this patient later also developed signs of an androgen-producing tumor, with coarse face, precocious enlargement of the genitals and development of pubic hair, and a small sella, suggesting HART.

In fact, HART are either nonfunctional (Tajima et al. 2001) or functional and then may cause Cushing's syndrome amenable to successful therapy with ketoconazole, blocking tumoral steroidogenesis (Contreras et al. 1985). Most HART are nonfunctioning and benign. A combination of virilization and a mild degree of Cushing's syndrome has also been reported, associated with elevated androgen levels, loss of cortisol circadian rhythm, and marked increase in urinary 17-ketogenic and 17-ketosteroids; in this young female patient with a hepatic ART, both the adrenals and the ovaries were atrophic (Wallace et al. 1981). Virilism combined with Cushing's syndrome owing to HART has also been observed in a small child (Wilkins and Ravitch 1952).

Most of the tumors were localized in the right liver lobe and often on its under surface. The ultrasonography reveals a solid mass showing heterogeneous echogenicity. At imaging, hepatic ART have been described to have CT features of a hypodense mass containing components of both fat density and soft tissue density with early fill-in and early fill out (Shin 2010). The masses appear to be isointense on T1-weighted, hypointense on T2-weighted, and hyperintense on superparamagnetic iron oxide-enhanced MR imaging (Baba et al. 2008) and showing homogeneous hypervascularity in angiography (Tajima et al. 2001). HART appear to be nourished by branches of the hepatic artery (Pollice 1973; Wallace et al. 1981; Contreras et al. 1985; Arai et al. 2000).

Pathology

Macroscopy

At gross examination, HART are usually located close to the liver capsule and present as solid and well circumscribed or even encapsulated, yellowish or yellowish-brown to glossy masses with an expanding growth pattern. On the fresh cut surface, the tumors tend to bulge, with retraction of the adjacent liver substance. The surface looks geographic, sometimes with gyrifications or a puzzle-like arrangement of the tissue. HART are mostly rather small or minute lesions, 5–7 mm, but larger tumors have also been reported (Arai et al. 2000; Baba et al. 2008) and huge multinodular masses even resulting in hepatomegaly (Wallace et al. 1981). However, HART are mostly incidental findings if there are no signs of steroidogenic activity. Central hemorrhagic necrosis is observed in some case, and marked calcification has been noted (Pollice 1973; Craig et al. 1989).

Histopathology

Histologically, the cells of HART resemble adrenocortical cells that form a mass with a thin capsule, which is usually incomplete. Frequently, so-called pale cells or clear cells ("hypernephroid cells"), being PAS-negative, predominate, while eosinophilic, sometimes large and polygonal cells, are more frequent toward the center of the lesion (Arai et al. 2000). In frozen sections, most of the cells are sudanophilic owing to their high lipid content. The cells may contain birefringent lipid droplets of rather uniform size. The tumor

cells are arranged in the form of alveolar or fascicular structures (Arai et al. 2000; Baba et al. 2008), in some way mimicking the architecture of the adrenal cortex, with intervening thin-walled vascular channels and fibrous strands. Some of the vacuolated cells resemble those of the adrenocortical zona fasciculata. Nuclei are small or of intermediate size and ovoid, with tiny or lacking nucleoli and only minor atypia, and mitotic figures are usually not found. Small foci with increased cellular pleomorphism can occasionally be found, predominantly with pale or clear cells.

Immunohistochemistry

Immunohistochemically, the tumor cells did not stain for cytokeratin, epithelial membrane antigen, vimentin, S-100 protein, AFP, or chromogranin, but staining for adrenal 4-binding protein (Ad4BP) and six types of steroidogenic enzymes has been reported (Arai et al. 2000).

Electron Microscopy

Ultrastructurally, lipid droplets and mitochondria with tubulo-vesicular cristae have been identified, features regarded as typical for steroid-producing cells (Arai et al. 2000). HART consistently lack adrenomedullary tissue. There are usually no signs of invasive growth; rather the HART cells interdigitate with liver tissue at sites of incomplete encapsulation, sometimes with apparent infiltration of parenchymal sinusoids (Craig et al. 1989), and preexistent hepatocytes and/or bile duct profiles can be entrapped within HART tissue.

Differential Diagnosis

The most important differential diagnosis is other hepatic tumors with a clear cytoplasm. They include clear cell hepatocellular carcinoma, clear cell perivascular epithelioid tumors (PEComas; including clear cell epithelioid angiomyolipoma and so-called sugar tumors), and metastases of a diverse spectrum of extrahepatic primary tumors with a clear cell population. Adrenal rest tumor can rarely develop in the immediate vicinity of the liver, e.g., in the retroperitoneal space (Akishima-Fukasawa et al. 2011).

Etiology and Pathogenesis

The etiology and pathogenesis of ART and HART have not been elucidated. One hypothesis claims that HART originate from misplaced adrenocortical cells. Schmorl was the first to deport on misplaced adrenal tissue within the light liver lobe. He found this phenomenon four times among 510 necropsies (Schmorl 1891). Bothe (1926) reported on a 16 mm human embryo where he noted the juxtaposition of adrenal anlage cells with the primitive cell masses of the liver, kidney, and gonads. For extrahepatic ART, and in particular for gonadal ART, a relationship with congenital adrenal disorders is well established. Male patients with congenital adrenal hyperplasia caused by steroid enzyme defects (e.g., 11-hydroxylase deficiency) can develop testicular tumors with the features of ART, these lesions being more frequently manifest in adolescents and adults (Clark et al. 1990; Oberman et al. 1993; Stikkelbroeck et al. 2001; Proto et al. 2001). We are not aware of any case of HART being related to congenital adrenal disorders. In situations not related to congenital adrenal disease, a histogenic pathway originating from misplaced adrenal progenitor cells or metaplastic coelomic cells has been suggested (Adashi et al. 1980). A similar pathogenesis may be discussed for ART arising in the liver, i.e., priming of preexistent coelomogenic cells to enter an adrenocortical cell lineage. What is the evidence that ART cells in fact belong to such a lineage? Immunohistochemically, reactivity for the adrenal 4-binding protein (Ad4BP) and a number of enzymes involved in the synthesis of adrenocortical steroids have been detected (Arai et al. 2000; Baba et al. 2008). The presence of the 11-hydroxylase B1 in adrenal rest tumors is of special importance, because this enzyme is a marker for the adrenal zona fasciculata/reticularis (the enzyme form B2 is exclusively expressed in the zona glomerulosa). Similar to ART occurring

in other sites and specifically in the testis, it may be assumed that adrenal rest cells may fail to undergo regression and may be stimulated for growth and differentiation into tumor-like lesions.

Progenitor Cell Tumors of the Liver

Introduction

Both hepatocellular carcinoma and various types of cholangiocarcinoma can contain cell lineages with progenitor/stem cell-like features. This issue has been addressed in the respective chapters referring to these neoplasms. In addition, there are primary hepatic neoplasms that seem to predominantly consist of progenitor cells. Such tumors are denoted by the use of several not yet standardized names, including stem cell tumors of the liver, progenitor cell tumors, or tumors with progenitor cell-like features.

Undifferentiated Liver Tumors with Stem Cell-Like Features

It may be anticipated that distinct subsets of undifferentiated or poorly differentiated liver neoplasms showing features of "small cell blue tumors" contain variants composed of primitive progenitor cells primed or not primed for a known liver cell lineage. Chu and coworkers reported a hepatic tumor in an adult male that was composed of solidly packed small, round and uniform, undifferentiated cells with an immunophenotype c-kit+, EpCAM+, E-cadherin+, keratin 7, keratin 19, and AFP. C-kit mutations were not detected. It was concluded that this neoplasm consisted of a primitive lineage with stem cell features (Chu et al. 2014).

Progenitor Cell Tumors with an Intermediate Cellular Phenotype

In case stem/progenitor cells driving a hepatic neoplasm are primed to become bipotential cells, tumors with a phenotype intermediate between hepatocyte and cholangiocyte lineages might be expected. Such an interesting lesion was observed in a 57-year-old female. The aggressive neoplasm exhibited a trabecular growth pattern and was composed of uniform small cells that were immunoreactive for both hepatocytes (cytokeratins 8 and 18) and bile duct cells (cytokeratins 7 and 19). Also parathyroid hormone-related peptide, a cholangiocarcinoma marker, was expressed. It was suggested that this neoplasm with an intermediate phenotype represents an immature progenitor cell tumor (Robrechts et al. 1998). Tumors with such an intermediate phenotype, in part characterized by small round to oval cells with scanty cytoplasm and a desmoplastic stroma, were described in subsequent studies, and part of these lesions expressed c-kit (Theise et al. 2003; Kim et al. 2004). A further liver tumor showing bidirectional differentiation proposed to be related to bipotential progenitor cells was observed in a patient with citrin deficiency (Soeda et al. 2008).

Progenitor Cell Tumors of the Liver: Distinction from Hepatocellular Carcinomas and Cholangiocarcinomas with Stem Cell-Like Features

As outlined elsewhere, part of hepatocellular carcinomas (HCCs) and cholangiocarcinomas (CCs) contain neoplastic cells with features shared by normal hepatobiliary stem or progenitor cells (Lee et al. 2006, 2014; Komuta et al. 2008; Yamashita et al. 2009; Kim et al. 2011; Cheuk-lam Lo and Ng 2013; Iwahashi et al. 2013; Kim and Park 2014; Oishi et al. 2014; Xu et al. 2014). Also combined hepatocellular-cholangiocarcinoma displays subtypes with stem cell features (Sasaki et al. 2014). It is proposed that such neoplasms should not be termed progenitor cell tumors as long as the majority of the neoplastic cells are typical for either HCC or CC. In fact, progenitor-like cells can form a minor component in otherwise "classical" HCCs or CCs. It was found that about 8.3 % of resected HCCs expressed the stem cell marker neural cell adhesion molecule/NCAM (Tsuchiya et al. 2011). Stem-like cells contributing to HCC

or CC may represent a constitutive component of the neoplasms, or may be selected from another cell pool by the distinct microenvironment of the cancers. It has been demonstrated that inflammatory cytokines present in an inflammatory environment can promote the retrodifferentiation of tumor-derived hepatocyte-like cells to progenitor cells (Dubois-Pot-Schneider et al. 2014). Loss of p53 expression facilitates the dedifferentiation of mature hepatocytes into nestin-positive progenitor-like cells, a further mechanism for cellular plasticity in hepatic neoplasms (Tschaharganeh et al. 2014).

Epithelial Tumors Originating from Epithelial Inclusions in Locoregional Lymph Nodes of the Liver

Introduction

Lymph nodes sometimes contain benign epithelial glandular or cystic inclusions that may be misinterpreted as metastatic disease. The most common situations include breast epithelia in axillary lymph nodes (Zynger et al. 2009), thyroid follicles in cervical lymph nodes (folliculosis; Meyer and Steinberg 1969), genital epithelia in pelvic nodes (endosalpingiosis and endocervicosis;), and various glandular structures in pulmonary/mediastinal nodes (Lewis et al. 2011). Benign epithelial nodal inclusions may be remote from the orthotopic normal epithelium. For example, endosalpingiosis can occur in axillary lymph nodes (Carney et al. 2014).

Epithelial Inclusions in the Liver and Pancreas Associated and Abdominal Lymph Nodes

Epithelial inclusions can occur in lymph nodes at the liver hilus (Arcidiacono 1952). Hilar lymph node inclusions may give rise to malignancies, e. g., serous papillary adenocarcinoma (Terada 2012). Peripancreatic lymph nodes may contain squamous cell nests glandular cystic inclusions (Zheng et al. 2012) and very rarely cystic lymphoepithelial lesions (Sako et al. 1999). Simple benign glandular inclusions also occur in retroperitoneal lymph nodes (Horn and Bilek 1996), and abdominal lymph nodes may contain squamous cell nests together with mucin-containing cells (Arai et al. 1992). A non-Müllerian benign epithelial choristoma was incidentally detected in a celiac lymph node (Carr et al. 1987).

References

Abell I (1928) Primary hypernephroma of the liver. Ann Surg 87:829–836

Adashi EY, Rosenshein NB, Parmley TH, Woodruff JD (1980) Histogenesis of the broad ligament adrenal rest. Int J Gynaecol Obstet 18:102–104

Akishima-Fukasawa Y, Yoshihara A, Ishikawa Y, Watanabe N, Hiroi N, Akasaka Y et al (2011) Malignant adrenal rest tumor of the retroperitoneum producing adrenocortical steroids. Endocr Pathol 22:112–117

Anardi T (1928) Sui tumori ipernefroidi a sede renale ed epatica. Tumori 2:337–372

Arai T, Kino I, Nakamura S, Ogawa H (1992) Epidermal inclusions in abdominal lymph nodes. Report of two cases studied immunohistochemically. Acta Pathol Jpn 42:126–129

Arai K, Muro H, Suzuki M, Oba N, Ito K, Sasano H (2000) Adrenal rest tumor of the liver: a case report with immunohistochemical investigation of steroidogenesis. Pathol Int 50:244–248

Arcidiacono G (1952) Presence of epithelial inclusions in a lymph node of the liver hilus (in Italian). Arch Ital Anat Istol Patol 25:302–310

Aycan Z, Bas VN, Cetinkaya S, Yilmaz Agladioglu S, Tiryaki T (2013) Prevalence and long-term follow-up outcomes of testicular adrenal rest tumours in children and adolescent males with congenital adrenal hyperplasia. Clin Endocrinol (Oxf) 78:667–672

Baba Y, Beppu T, Imai K, Masuda T, Iyama K, Sasano H, Baba H (2008) A case of adrenal rest tumor of the liver: radiological imaging and immunohistochemical study of steroidogenic enzymes. Hepatol Res 38:1154–1158

Barwick TD, Malhotra A, Webb JA, Savage MO, Reznek RH (2005) Embryology of the adrenal glands and its relevance to diagnostic imaging. Clin Radiol 60:953–959

Beer E (1904) Über Nebennierenkeime in der Leber. Z Heilkde Abt Pathol Anat 25:380–388

Bini G (1934) Su di un caso di tumore ipernefroide nel fegato. Pathologica 26:183–187

Bothe AE (1926) Hypernephromata. Ann Surg 84:57–88
Cakir ED, Mutlu FS, Eren E, Pasa AO, Saglam H, Tarim O (2012) Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia. J Clin Pediatr Endocrinol 4:94–100
Carney E, Cimino-Mathews A, Argani C, Kronz J, Vang R, Argani P (2014) A subset of nondescript axillary lymph node inclusions have the immunophenotype of endosalpingosis. Am J Surg Pathol 38:1612–1617
Carr RF, Tang CK, Carrozza MJ, Rodriguez FC (1987) Unusual cystic epithelial choristoma in a celiac lymph node. Hum Pathol 18:866–869
Ceccont F (1958) Tumors of the liver of hypernephroid structure (in Italian). Arch Ital Chir 84:215–228
Cheuk-lam-Lo R, Ng I (2013) Hepatic progenitor cells: their role and functional significance in the new classification of primary liver cancers. Liver Cancer 2:84–92
Chu HH, Cho BH, Song JS, Kim KM, Moon WS (2014) C-KIT-positive undifferentiated tumor of the liver. A case report. Oncol Lett 8:1665–1669
Cirio L (1922) Sopra un tumore primitive del fegato di probabile origine cortico-surrenale. Pathologica 14:197–207
Claahsen-van der Grinten HL, Otten BJ, Stikkelbroeck MML, Sweep FCGJ, Hermus ARMM (2009) Testicular adrenal rest tumours in congenital adrenal hyperplasia. Best Pract Res Clin Endocrinol Metab 23:209–220
Clark RV, Albertson BD, Munabi A, Cassorla F, Aguilera G, Warren DW, Sherins RJ, Loriaux DL (1990) Steroidogenic enzyme activities, morphology, and receptor studies of a testicular adrenal rest in a patient with congenital adrenal hyperplasia. J Clin Endocrinol Metab 70:1408–1413
Contreras P, Altieri E, Liberman C et al (1985) Adrenal rest tumor of the liver causing Cushing's syndrome: treatment with ketoconazole preceding an apparent surgical cure. J Clin Endocrinol Metab 60:21–28
Craig JR, Peters RL, Edmondson HA (1989) Tumors of heterotopic tissues and uncertain origin. In: Hartmann WH, Sobin LH (eds) Atlas of tumor pathology. Tumors of the liver and intrahepatic bile ducts, vol 2. Armed Forces Institute of pathology, Washington, DC, pp 102–122, fasc. 26
De Ahna M (1912) Über einen Fall von Hypernephrom der Leber, geheilt durch Resektion. Charité Ann 36:390–393
De Vecchi B (1904) Über einen Fall von Hypernephrom der Leber. Virchows Arch 177:133–150
Delfino M, Elia J, Imbrogno N, Argese N, Mazzilli R, Toscano V, Mazzilli F (2012) Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. J Ultrasound Med 31:383–388
Donati M (1905) Ipernefroma maligno del fegato. Arch Sci Med 29:154–164
Dubois-Pot-Schneider H, Fekir K, Coulouarn C, Glaise D, Aninat C, Jarnouen K, Le Guével R et al (2014) Inflammatory cytokines promote the retrodifferentiation of tumor-derived hepatocyte-like cells to progenitor cells. Hepatology 60:2077–2090
Goffrini P (1955) Tumore ipernefroide in sede epatica. Studio anatomo-clinico. Arch Sci Med (Torino) 99:214–223
Goren et al. 1991. http://www.ncbi.nlm.nih.gov/pubmed/1877141
Hamperl H (1970) "Adrenal rest-tumors" (hypernephromas) of the liver. Z Krebsforsch 74:310–317
Hirschler M (1912) Ein Nebennierentumor in der Leber. Frankfurt Z Pathol 9:343–361
Horn K (1929) Ein primäres Karzinom der Leber von hypernephroidem Bau. Frankfurt Z Pathol 37:579–590
Horn LC, Bilek K (1996) Atypical (carcinoma-like) and simple glandular inclusions in retroperitoneal lymph nodes. Gen Diagn Pathol 141:319–325
Hyams VJ, Thomas DF, Sarkisian SS (1960) Adrenal rest tumor of the liver. Am J Surg 99:960–963
Inama K (1948) Ueber ein hypernephroides Karzinom der Leber. Krebsarzt 3:132–138
Iwahashi S, Utsunomiya T, Shimada M, Saito Y, Morine Y, Imura S, Ikemoto T, Mori H et al (2013) High expression of cancer stem cell markers in cholangiocellular carcinoma. Surg Today 43:654–660
Kaufmann E (1897) Geschwulst der rechten Nebenniere. Allgem Med Centralzeitg 234(19):112–114
Kim H, Park YN (2014) Hepatocellular carcinomas expressing 'stemness'-related markers: clinicopathological characteristics. Dig Dis 32:778–785
Kim H, Park C, Han KH, Choi J, Kim YB, Kim JK, Park YN (2004) Primary liver carcinoma of intermediate (hepatocyte-cholangiocyte) phenotype. J Hepatol 40:298–304
Kim H, Choi GH, Na DC, Ahn EY, Kim GI, Lee JE, Cho JY, Yoo JE, Choi JS et al (2011) Human hepatocellular carcinomas with 'stemness'-related marker expression: keratin 19 expression and a poor prognosis. Hepatology 54:1707–1717
Komuta M, Spee B, Vander Borght S, De Vos R, Verslype C, Aerts R, Yano H, Suzuki T et al (2008) Clinicopathological study on cholangiocellular carcinoma suggesting hepatic progenitor cell origin. Hepatology 47:1544–1556
Kopac Z (1940) Hypernephroma malignum capsulae hepatis. Zbl Pathol 74:305–309
Lee JS, Heo J, Libbrecht L, Chu IS, Kaposi-Novak P, Calvisi DF, Mikaelyan A, Roberts LR et al (2006) A novel prognostic subtype of human hepatocellular carcinoma derived from hepatic progenitor cells. Nat Med 12:410–416
Lee M, Marusawa H, Chiba T (2014) Characteristics of hepatocellular carcinoma with stem/progenitor cell phenotypes. Gastroenterology 146:579–581

Lewis AL, Truong LD, Cagle P, Zhai QJ (2011) Benign salivary gland tissue inclusion in a pulmonary hilar lymph node from a patient with invasive well-differentiated adenocarcinoma of the lung: a potential misinterpretation for the staging of carcinoma. Int J Surg Pathol 19:382–385

Mason JB, Speese J (1933) Tumor of liver of adrenal origin. Ann Surg 97:150–153

Massa G (1938) Sopra un caso di ipernefroma del fegato. Arch Ital Chir 52:904–909

Meyer JS, Steinberg LS (1969) Microscopically benign thyroid follicles in cervical lymph nodes. Serial section study of lymph node inclusions and entire thyroid gland in 5 cases. Cancer 24:302–311

Miyazaki I, Shimizu K (1995) Adrenal rest tumor of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:285–287

Oberman AS, Flatau E, Luboshitzky R (1993) Bilateral testicular adrenal rests in a patient with 11-hydroxylase deficient congenital adrenal hyperplasia. J Urol 149:350–352

Oishi N, Yamashita T, Kaneko S (2014) Molecular biology of liver cancer stem cells. Liver Cancer 3:71–84

Patrassi G (1932) Hypernephroides Adenom der Leber mit Einschlüssen von Knochen und Knochenmark. Zbl Pathol 55:241–247

Pendl O, Scherlacher A (1950) Über einen Fall von Hypernephrom der Leber. Österr Z Kinderheilk 4:270–279

Pepere A (1902) Tumeur primitive du foie originaire des germes aberrants de la capsule surrénale. Arch Med Exp 14:765–808

Philipps P, Spilsbury A (1905) Cancer du foie de nature surrénale. Presse Méd 405:XX

Pollice L (1973) Primary hepatic tumors in infancy and childhood. Am J Clin Pathol 60:512–521

Powell A, White C, Mair W (1908) A case of primary adrenal carcinoma of the liver. J Pathol Bacteriol 12:107–110

Proto G, Di Donna A, Grimaldi F, Mazzolini A, Purinan A, Bertolissi F (2001) Bilateral testicular adrenal rest tissue in congenital adrenal hyperplasia: US and MR features. J Endocrinol Invest 24:529–531

Ramsey TL (1929) Primary hypernephroma of the liver (Grawitz tumor). Ann Surg 90:41–46

Robrechts C, De Vos R, Van den Heuvel M, Van Cutsem E, Van Damme B, Desmet V, Roskams T (1998) Primary liver tumour of intermediate (hepatocyte-bile duct cell) phenotype: a progenitor cell tumour? Liver 18:288–293

Sako S, Isozaki H, Hara H, Tsutsumi A, Tanigawa N (1999) Cystic lymphoepithelial lesions of the pancreas and peripancreatic region: report of two cases. Surg Today 29:467–471

Sasaki M, Sato H, Kakuda Y, Sato Y, Choi JH, Nakanuma Y (2014) Clinicopathological significance of 'subtypes with stem-cell feature' in combined hepatocellular-cholangiocarcinoma. Liver Int. doi:10.1111/liv.12563

Schechter DC (1968) Aberrant adrenal tissue. Ann Surg 167:421–425

Schmorl G (1891) Zur Kenntnis der accessorischen Nebennieren. Beitr Pathol Anat 9:523–529

Shin YM (2010) Hepatic adrenal rest tumor mimicking hepatocellular carcinoma. Korean J Hepatol 16:338–341

Soeda J, Yazaki M, Nakata T, Miwa S, Ikeda S, Hosoda W, Iijima M, Kobayashi K, Saheki T et al (2008) Primary liver carcinoma exhibiting dual hepatocellular-biliary epithelial differentiations associated with citrin deficiency: a case report. J Clin Gastroenterol 42:855–860

Stikkelbroeck NM, Otten BJ, Pasic A, Jager GJ, Sweep CG, Noordam K, Hermus AR (2001) High prevalence of testicular adrenal rest tumors, impaired spermatogenesis, and Leydig cell failure in adolescent and adult males with congenital adrenal hyperplasia. J Clin Endocrinol Metab 86:5721–5728

Swenson CG (1917) Hypernephroma of the liver. Surg Gynecol Obstet 25:570–571

Tajima T, Funakoshi A, Ikeda Y, Hachitanda Y, Yamaguchi M, Yokota M, Yabuuchi H, Satoh T, Koga M (2001) Nonfunctioning adrenal rest tumor of the liver: radiologic appearance. J Comput Assist Tomogr 25:98–101

Tallarigo A (1954) Sui cosidetti tumori ipernefroidi del fegato. Rif Med 68:141–148

Terada T (2012) Serous papillary adenocarcinoma probably arising from epithelial inclusions of the hepatic hilar lymph node. Arch Gynecol Obstet 286:193–195

Theise ND, Yao JL, Harada K, Hytiroglou P, Portmann B, Thung SN, Tsui W, Ohta H et al (2003) Hepatic 'stem cell' malignancies in adults: four cases. Histopathology 43:263–271

Tschaharganeh DF, Xue W, Calvisi DF, Evert M, Michurina TV, Dow LE, Banito A, Katz SF et al (2014) p53-dependent Nestin regulation links tumor suppression to cellular plasticity in liver cancer. Cell 158:579–592

Tsuchiya A, Kamimura H, Tamura Y, Takamura M, Yamagiwa S, Suda T, Nomoto M, Aoyagi Y (2011) Hepatocellular carcinoma with progenitor cell features distinguishable by the hepatic stem/progenitor cell marker NCAM. Cancer Lett 309:95–103

Vitaglio G (1956) Case of hypernephroid tumor of the liver (in Italian). Tumori 42:469–475

Wallace EZ, Leonidas JR, Stanek AE, Avramides A (1981) Endocrine studies in a patient with functioning adrenal rest tumor of the liver. Am J Med 70:1122–1126

Weller CW (1925) Heterotopia of adrenal in liver and kidney. Am J Med 169:696–712

Wilkins L, Ravitch MM (1952) Adrenocortical tumor arising in the liver of a 3 year old boy, with signs of virilism and Cushing's syndrome: report of a case with cure after partial resection of right lobe of liver. Pediatrics 9:671–680

Williams JL (1924) A primary hypernephroma of the liver. Tr Chic Path Soc 12:90–92

Xu M, Qian G, Xie F, Shi C, Yan L, Yu L, Zheng T, Wei L, Yang J (2014) Expression of epithelial cell adhesion molecule associated with elevated ductular reactions in hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 38:699–705

Yamashita T, Ji L, Budhu A, Forgues M, Yang W, Wang HY, Jia H, Ye Q, Qin LX, Wauthier E et al (2009) EpCAM-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/progenitor cell features. Gastroenterology 136:1012–1024

Zheng Z, Molinari M, Sapp H, Jung SM, Wanless I, Huang WY (2012) Benign epithelial inclusions in peripancreatic lymph nodes: a report of two cases and review of the literature. Int J Surg Pathol 20:570–576

Zverev AF (1963) Primary hypernephroid cancer of the liver in an infant (in Russian). Vestn Khir Im I I Grek 90:122–123

Zynger DL, McCallum JC, Everton MJ, Yeldandi AV, Susnik B (2009) Paracortical axillary sentinel lymph node ectopic breast tissue. Pathol Res Pract 205:427–432

Part IV

Mixed Epithelial-Mesenchymal Tumors of the Hepatobiliary Tract (Tumors with Epithelial-Mesenchymal Transition)

Hepatobiliary Carcinosarcomas and Related Neoplasms

46

Contents

Abstract

In the hepatobiliary tract, several types of malignancies characterized by a complex mixture of epithelial and mesenchymal components can develop. Previously, most of these lesions were classified as either carcinosarcomas or mixed tumors, but novel findings suggest that these neoplasms in fact reflect aspects of epithelial-mesenchymal transition or mesenchymal-epithelial transition. Carcinosarcomas are usually adenocarcinomas admixed with heterologous components, which can include most known types of neoplastic mesenchymal tissues. Rarely, hepatocellular carcinoma occurs with sarcoma as a combined neoplasm. Carcinosarcomas are difficult to distinguish from an ill-defined group of tumors termed sarcomatoid carcinoma of the liver. These are most commonly hepatocellular carcinomas and cholangiocarcinomas that contain sarcoma-like spindle cell components.

Carcinosarcomas of the Liver

ICD-O Code 8980/3

Introduction

Carcinosarcomas are defined as malignant neoplasms in which epithelial and mesenchymal neoplastic cell lineages synchronously occur together

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_46

within the same tumor (Wick and Swanson 1993). For the liver, the WHO Classification defines carcinosarcomas as tumor containing both carcinomatous (either hepatocellular or cholangiocellular) and sarcomatous elements, including malignant mixed tumors in this category. Carcinosarcoma of the liver (CSL) has formerly been defined as hepatocellular carcinoma combined with differentiated sarcomatous elements (Ishak et al. 2001), i.e., excluding cholangiocarcinoma. An alternative term sometimes used is sarcomatoid carcinoma (Nishie et al. 2003), but such tumors are treated in another paragraph, because the lesions do not fit the requirements for a diagnosis of CSL.

Craig and coworkers had suggested that the term, carcinosarcoma of the liver, should be reserved for primary hepatic tumors with both hepatocellular carcinoma (HCC) and non-spindle cell sarcoma, such as osteosarcoma, chondrosarcaoma, angiosarcoma or malignant schwannoma (Craig et al. 1989). Also in the 2001 edition of the AFIP's tumor atlas, Ishak and coworkers emphasized that carcinosarcoma of the liver should be defined as hepatic tumors with both HCC and a non-spindle cell sarcomas such as osteosarcoma, chondrosarcoma, or rhabdomyosarcoma (Ishak et al. 2001). The reason for this restriction may be that a spindle cell component, or a transformation into spindle cells, is sometimes seen in HCC in the absence of other components that would result in a diagnosis of CSL. The restriction of carcinosarcoma to those containing HCC as the epithelial component is problematic, as there are rare instances of hepatic adenocarcinomas/cholangiocarcinomas associated with sarcomas (Nomura et al. 2000; Kwon et al. 2007; Zhao et al. 2010).

Epidemiology and Clinical Features

CSL are rare malignant neoplasms with a very poor prognosis. So far, little or nothing is known about the epidemiology, risk factors, the significance of preexisting liver disease, and pathogenic factors. The majority of cases have been reported from Japan, but it is difficult to judge whether this reflects a geographic prevalence or an effect of more frequent reporting. The risk factors for these neoplasms are not known, but have been suggested to be similar to those for HCC. In a review of 11 cases, the tumors were found in patients with an age range of 46–84 years; 5/11 report finding liver cirrhosis and one reports precirrhotic fibrosis (She and Szakacs 2005). Thus, chronic fibrosing hepatopathy associated with remodeling of the liver may play a pathogenic role in part of the cases. The biology of disease of CSL is highly aggressive, and all of the 11 patients reviewed in 2005 had shown a fatal outcome, the longest survival being 9 months after diagnosis (She and Szakacs 2005).

Less than 70 cases of these highly interesting lesions (excluding those termed, sarcomatoid carcinoma) have been reported so far.

Selected References (Epshtein 1957; Bialik 1964; Kerr 1966; Isoda et al. 1976; Bogdanskaia 1979; Jinnouchi et al. 1989; Iareshko et al. 1992; Leger-Ravet et al. 1996; Fayyazi et al. 1998; Nomura et al. 2000; Eriguchi et al. 2001; Ishak et al. 2001; Nishie et al. 2003; Freeman et al. 2004; Jelovsek et al. 2004; Morise et al. 2004; Wang et al. 2004; She and Szakacs 2005; Garcez-Silva et al. 2006; Huang et al. 2009; Park et al. 2009; Shu et al. 2010; Sun and Zhong 2010; Yamamoto et al. 2010; Aparicio et al. 2011).

Pathology

Based on the absence of a generally accepted definition, the tumors discussed in this paragraph are regarded as CSL, irrespective whether the epithelial component is of the HCC type or the adenocarcinoma type, although it has to be emphasized that one definition restricted the use of the term CSL, to those tumors having an HCC component (Craig et al. 1989).

Macroscopy

At gross examination, this variant of CSL either presents in the form of large, usually greyish-

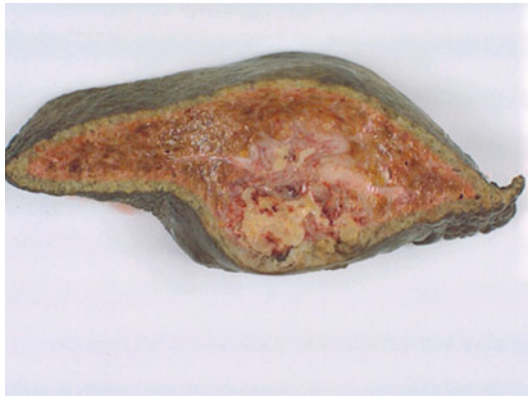

Fig. 1 Carcinosarcoma of the liver with large central necrosis

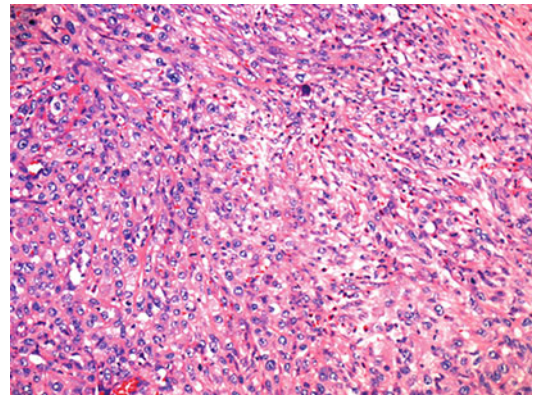

Fig. 2 Carcinosarcoma of the liver. This poorly differentiated neoplasm shows a complex mixture of immature epithelial cell nests and tumor spindle cells (hematoxylin and eosin stain)

white liver masses with hemorrhage and necrosis, or as multinodular lesions (Fig. 1). In case the heterologous component consists of osteoid matrix, the cut surface may be gritty. Satellite nodules may be in evidence (Morise et al. 2004). Some of the lesions have shown cystic changes (Wang et al. 2004), probably due to colliquation of necroses.

Histopathology of Epithelial Components

Adenoid structures have been observed in the epithelial part of the tumors, and have sometimes been designated, adenocarcinoma (Nomura et al. 2000; Freeman et al. 2004; Wang et al. 2004; Zhao et al. 2010; Yamamoto et al. 2014). Combined hepatocellular/cholangiocarcinoma and sarcoma has been described (Nakasho et al. 1996; Papotti et al. 1997). From the descriptions, it is sometimes difficult to judge what this epithelial component in fact represents (adenoid features of HCC vs. biliary-type adenocarcinoma). In few reports, the adenoid component was clearly interpreted as cholangiocarcinoma (Nomura et al. 2000; Kwon et al. 2007). In a fraction of the cases, the HCC component has been described as such (Saphir and Vass 1938; Jaffe 1924; Isoda et al. 1976; Uno et al. 1977; Dolorme 1978; Shin et al. 1981; Kimoto and Ugaki 1982; Kishimoto et al. 1984; Sonoda et al. 1984; Kubosawa et al. 1988; Jinnouchi et al. 1989; Craig et al. 1989; Ishiwata et al. 1990; Oda et al. 1994; Leger-Ravet et al. 1996; Akasofu et al. 1999; Tsuji et al. 2001; Figs. 2 and 3).

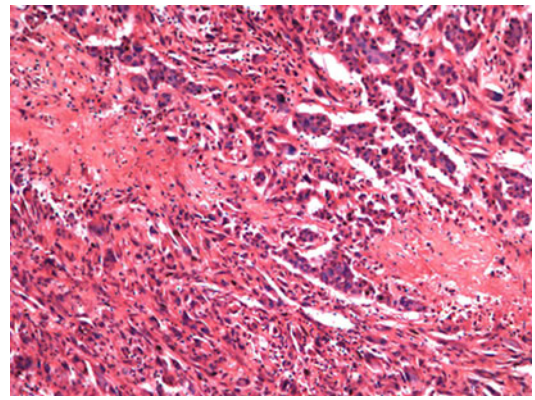

Fig. 3 Carcinosarcoma of the liver. The epithelial component with a solid growth pattern is found to the top and right of the figure, whereas a mesenchymal component is seen to the bottom and left lower corner (hematoxylin and eosin stain)

Immunohistochemistry has been performed in several of the tumors reported in the literature. Expectedly, the HCC components showed reactivities usual for this tumor, while the different sarcomatous components expressed the markers of the respective mesenchymal lineages

(Ooi et al. 1987; Oda et al. 1994; Nakasho et al. 1996; Ikebe et al. 1998; Nomura et al. 2000; Eriguchi et al. 2001; Tsuji et al. 2001; Freeman et al. 2004; Morise et al. 2004; Wang et al. 2004; Lin et al. 2013).

Histopathology of Mesenchymal Components

The heterologous components observed in reported cases are listed in the Table. It is of interest to note that most cases of HCC-type CSL with osteosarcoma components also have a coexisting spindle cell sarcomatous lesion, but these two components are separated in Table 1. Furthermore, tumors with a spindle cell component are only included as CSL if this component was looking like a sarcoma, excluding cases now identified as sarcomatoid HCC.

Spindle Cell Components

Part of CSL show a combination of HCC and bona fide spindle cell sarcoma, the latter sometimes identified as fibrosarcoma. In the case of Nakano et al. (1974), the HCC component was described as anaplastic. A CSL with a fibrosarcomatous component developing in a 35-year-old female patient was associated with oral contraceptive use (Ladaga et al. 1979). In this tumor, epithelial and spindle cells were in part intermingled, and fibrosarcoma showed entrapped small bile ducts. In a study of 14 autopsy cases, HCCs with sarcomatous change were characterized by negative or low serum AFP levels and a high incidence of extrahepatic metastases. Grossly, the tumors were of infiltrative, mixed expanding and infiltrative, and pedunculated types. Histologically, the sarcomatous component was prominent and consisted of vimentin-, but also cytokeratin-positive spindle cells and giant cells, whereas the epithelial component revealed an HCC phenotype (Kakizoe et al. 1987). There are, however, also neoplasms where the spindle cells fail to express cytokeratins, but strongly express vimentin (Figs. 4 and 5).

Table 1 Heterologous components in carcinosarcoma of the liver

Spindle cell sarcoma
Chondrosarcoma
Osteosarcoma
Rhabdomyosarcoma
Leiomyosarcoma
Angiosarcoma
Malignant mesenchymoma
Malignant fibrous histiocytoma
Several mesenchymal and other components

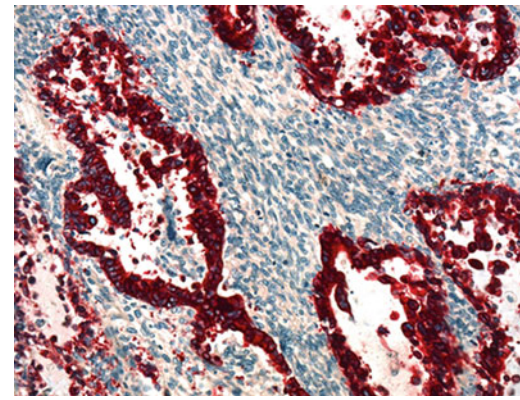

Fig. 4 Carcinosarcoma of the liver, cytokeratin expression pattern. The carcinoma component forming tubules is strongly positive, while intervening tumor spindle cells are not cytokeratin-reactive (CAM5.2 immunostain)

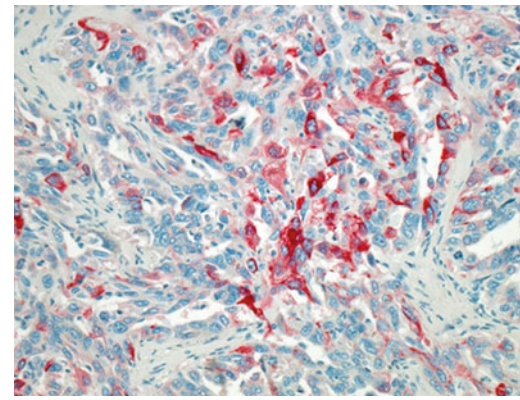

Fig. 5 Vimentin expression in hepatic carcinosarcoma. Vimentin-reactive mesenchymal tumor cells are intermingled with epithelial/carcinomatous cells (vimentin immunostain)

As cytokeratin positivity is seen in spindle cells of spindle cell-type HCCs, it is difficult to judge whether all the reported CSL with spindle cells were in fact true CSL. Overall it has to be emphasized that only rare tumors showing a fibrosarcomatous component with cytokeratin-negative spindle cells may qualify for CSL. Most authors exclude HCC with bland spindle cell components from true CSL, and classify these tumors as spindle cell HCC, discussed in a separate chapter.

Selected References (Nakano et al. 1974; Ladaga et al. 1979; Kimoto and Ugaki 1982; Miyazaki et al. 1983; Kakizoe et al. 1987; Kojiro et al. 1989; Haratake and Horie 1991; Nakasho et al. 1996; Komada et al. 1997; Papotti et al. 1997; Tsuji et al. 2001; Kim et al. 2004; Morise et al. 2004; Wang et al. 2004; Sumiyoshi et al. 2007; Park et al. 2009; Aparicio et al. 2011; Wang et al. 2012).

Chondroid Components

Chondroid or chondrosarcomatous tissue is known to occur in mixed hepatoblastomas of the pediatric age group, but it also occurs as the single histologic feature of primary hepatic sarcomas (primary chondrosarcoma of the liver; HCS) or as a component of CSL. True carcinosarcomas with chondroid/chondrosarcomatous components are now a well-recognized entity (Imholz and Noltenius 1977; Kishimoto et al. 1984; Ooi et al. 1987; Leger-Ravet et al. 1996; Fayyazi et al. 1998; Ikebe et al. 1998; Fu et al. 2000). For CSL showing a chondroid or chondrosarcomatous component, several terms have been employed to denote such lesions, including chondrosarcoma (Kishimoto et al. 1984; Sonoda et al. 1984), chondrosarcoma with hepatoma (Ojima et al. 1964), sarcomatoid HCC with chondroid variant (Fu et al. 2000), HCC with chondrosarcomatous variation (Ooi et al. 1987; Ikebe et al. 1998). This variant of CSL may grow to large or very large tumors which produce intrahepatic metastases. At gross examination, the presentation is similar to that of HCC. Histologically, the epithelial HCC component is intermingled with neoplastic mesenchymal tissue, disclosing spindle-shaped cells (sometimes in a storiform pattern) and foci of matrix-rich chondrosarcoma. The chondroid parts may be separated from the remaining tumor tissue by a thin fibrous band, but a complex interdigitation of the different lineages occurs as well, and transitional features of poorly differentiated HCC and sarcomatous tissue may be present, epithelial and mesenchymal cells being situated face to face (Ikebe et al. 1998).

The chondrosarcomatous component is sometimes only recognized within immature mesenchymal areas otherwise consisting of spindle cells (Sonoda et al. 1984; Ikebe et al. 1998). In the tumor described by Ikebe and others, the mesenchymal component was characterized by a diffuse proliferation of spindle-shaped, atypical cells that showed focal transition to a poorly differentiated HCC. These cells were partially arranged in a storiform pattern. Within these areas, clearly malignant cells were embedded in a hyaline chondroid matrix, this lesion fulfilling the morphologic criteria of chondrosarcoma (Ikebe et al. 1998). In another observation, the sarcomatous part of the tumor contained multinodular chondroid foci, with chondroid cells embedded in a hyaline chondroid matrix. Cellularity of this area was low, and there was no marked pleomorphism of the chondroid cells, but here was an apparent transition from the sarcomatoid component (pleomorphic spindle cells) to the chondroid component. Interestingly, the chondroid cells were not only immunoreactive for vimentin and S100 protein, but also for AFP, and the authors thus concluded that the chondroid component was a metaplastic growth of sarcomatoid HCC (Fu et al. 2000). In one patient, chondrosarcoma in CSL was associated with osteosarcoma (Leger-Ravet et al. 1996). Expectedly, the chondroid cells are reactive for vimentin, and a strong and selective immunostaining for S100 protein has been observed in cells embedded in the chondroid matrix (Ikebe et al. 1998). In cases where the chondroid component is associated with poorly differentiated spindle cells, the latter may express

cytokeratins and AFP, suggesting a spindle cell HCC component (Fayyazi et al. 1998). In addition to HCC, adenocarcinoma of the liver can also contain a chondrosarcomatous component (Volkov et al. 1979; Nomura et al. 2000). In this situation, carcinosarcoma is defined as a tumor with both adenocarcinoma and non-spindle cell sarcoma (so-called adenosarcoma).

Osseous Components

Primary malignant bony neoplasms (primary hepatic osteosarcoma) are exceedingly unusual lesions (Liony et al. 1990; Kitayama et al. 1995; Govender and Rughubar 1998; Boldt et al. 1999). Similarly, CLS combining HCC with osteoid and malignant bone formation have rarely been described (Kerr 1966; Ladaga et al. 1979; Blanding 1986; Maeda et al. 1986; Nakajima et al. 1988; Leger-Ravet et al. 1996; Ishak et al. 2001; Morise et al. 2004; Kwon et al. 2007; Goto et al. 2010; Yamamoto et al. 2010). The osteosarcomatous component may develop together with a chondrosarcomatous differentiation (Leger-Ravet et al. 1996; Kwon et al. 2007; Goto et al. 2010), or represent the only detectable heterologous component. The latter situation has been described for a CSL both with an HCC component (Kerr 1966; Yamamoto et al. 2010), or with a cholangiocellular epithelial lineage (Celikbilek et al. 2011).

In the first reported case of "osteosarcohepatoma" (Kerr 1966), a 56-year-old man with liver cirrhosis showed, at autopsy, a large and friable, hemorrhagic and extensively necrotic tumor mass arising from the right liver lobe. Histology showed ordinary HCC blending into an immature mesenchymal component containing multiple foci of osteoid tissue, in the absence of chondroid tissue. In the autopsy case reported by Nakajima and coworkers, the HCC component of this CSL was combined with cholangiocarcinoma (Nakajima et al. 1988). In part of these neoplasms, the exact identification of the nature of epithelia remains difficult without immunohistochemistry. A large hepatic tumor (8 cm diameter) reported by Kwon et al. (2007) mainly consisted of a sarcomatous component with a diffuse proliferation of spindle cells. In this area, chondrosarcomatous change was found, with a hyaline chondroid matrix and foci of osteoid. Clusters of epithelial cells, in part arranged as tubules, were found in the sarcoma, these cells being reactive for cytokeratins 7 and 19, and for EMA, but not for a hepatocyte marker, compatible with poorly differentiated cholangiocarcinoma.

Are the osteoid and osteoid-associated bone-forming cells found in bone-forming CSL malignant changes or a reactive alteration? In mixed epithelial and mesenchymal hepatoblastomas, where osteoid formation is frequently encountered (Allison and Willis 1956; Pang 1961), the osteoid is regarded as a manifestation of the neoplastic lineage per se, although the osteoblast-like cells embedded in the osteoid matrix are unusual elements, because they markedly express cytokeratins. Interestingly, cytokeratin reactivity of malignant neoplastic cells has also been detected in a variant of osteosarcoma of adults, osteosarcoma with epithelioid features (Hasegawa et al. 1993). In CSL, this question has not been addressed in similar detail. An earlier observation of such a CSL used the term, HCC associated with *ossification*, and not osteosarcoma (Maeda et al. 1986). In this autopsy report, the authors described trabecules of partially mineralized osteoid within the tumor, and this osteoid seemed to develop into well-formed bony trabecules. These structures were surrounded by relatively small malignant cells, and the morphologic features of some of the cells located inside the osteoid matrix suggested the production of malignant osteoid by malignant cells (Maeda et al. 1986). In the report of Nakajima et al. the respective figure illustrates that highly atypical cells surrounding osteoid scatter into this matrix, and resulting picture looks like osteosarcoma indeed (Nakajima et al. 1988). In cases where foci of osteoid are situated within an area of immature-looking spindle cell mesenchyme (Kwon et al. 2007), a role of mesenchymal tumor stem cells having the capability to be primed for osteoprogenitor cells may be anticipated.

Rhabdomyoid/ Rhabdomyosarcomatous Components

Hepatobiliary rhabdomyosarcoma is a well-known, although rare, entity in the pediatric age group. The exceptional cases of primary rhabdomyosarcoma in the adult liver, which do not have a connection with the biliary tract, are less well recognized, but several cases have been reported. They can occur as pure hepatic rhabdomyosarcomas (HRMS; Watanabe et al. 1983; Shibata et al. 1987; Scheiden et al. 1988; McArdle et al. 1989; Cote and Urmacher 1990; Hayakawa et al. 1990; Zornig et al. 1992; Burrig and Knauer 1994; Hiyama 1995; Tominaga et al. 1995; Meyer-Pannwitt et al. 1996; McRae and Lee 2005). Even less commonly, rhabdomyosarcoma makes part of carcinosarcoma of the liver.

A typical case of this unusual combination is the autopsy observation of Goldman and Friedman (1969). This lesion, termed "rhabdomyosarcohepatoma" by the authors, comprised two divergent patterns, one rhabdomyosarcoma of the embryonal type, the other hepatoma. The former consisted of sheets of rhabdomyoblasts which occasionally assumed an alveolar configuration. The cells were characterized by scant to moderately abundant brightly eosinophilic "myogenic" cytoplasm which often was elongated and tapered. Cross-striations were infrequent but unequivocal. The epithelial component was composed of nests, columns, and trabecules of cells typified by well-defined granular amphophilic cytoplasm, resembling the morphology of HCC. The two components at some places showed intimate intermingling.

Selected References Goldman and Friedman 1969; Mori et al. 1979; Hatanaka et al. 1983; Kawarada et al. 1985; Morimoto et al. 1986; Kubosawa et al. 1988; Hayakawa et al. 1990; Akasofu et al. 1999; Aito and Seki 2006; Lao et al. 2007; Lai et al. 2011; Wang et al. 2012.

CSL with rhabdomyosarcomatous components occurs in two main patterns. In the first pattern, rhabdomyosarcoma cells are intermingled with carcinoma cells or other neoplastic mesenchymal elements. In the tumor described by Kawarada et al. (1985), tumor cells with cross-striation were associated with poorly differentiated cartilage and osteoid tissues. The epithelial elements may be difficult to identify. A tumor showing rhabdomyoblastic features was classified to be CSL due to its marked reactivity for AFP (Mori et al. 1979). In the second pattern HCC and rhabdomyosarcoma are clearly separated within the tumor. In one of the other reported CSL cases, the lesion was therefore suggested to represent a collision tumor (Morimoto et al. 1986). In the case of Akasofu et al. (1999), autopsy of a 55-year-old man revealed a massive tumor measuring up to 19 cm in diameter occupied almost the entire right liver lobe. Several satellite nodules were present in both liver lobes. Most of the neoplasm consisted of small undifferentiated cells admixed with desmin-positive rhabdomyoblasts showing cross-striation. Within this large sarcomatous tumor, a 2 cm-sized nodule of HCC was detected. Also in the large CSL described by Aito and Seki (2006), a nodule of HCC was found within a desmin-and SMA-positive spindle cell sarcoma. The tumor produced granulocyte colony-stimulating factor. The epithelial and mesenchymal components may show different metastasizing features. The encapsulated liver tumor reported by Kubosawa and coworkers (1988) was an HCC situated within a rhabdomyosarcoma. Metastasis of the HCC component was only seen in the left adrenal gland, whereas intrahepatic metastatic foci as well as tumor thrombi occluding the portal vein branches were composed exclusively of rhabdomyosarcoma.

Histologically, rhabdomyosarcomatous CSL usually show a mixture of poorly differentiated or undifferentiated small and short spindle-shaped cells, and rhabdomyoblast-like cells with plum eosinophilic cytoplasm, the latter sometimes with cross-striation seen in either H&E-stained preparations or by use of the phosphotungstic acid stain (Kubosawa et al. 1988). Ultrastructrally, rhabdomyoblast-like cells occurring in these tumors exhibit thick myosin filaments assembled in parallel fashion, and a hexagonal arrangement of thick and thin (actin) filaments (Kubosawa et al. 1988). The neoplastic mesenchymal cells

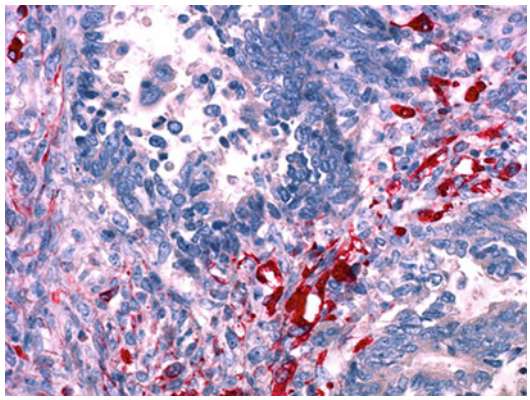

Fig. 6 This hepatic carcinosarcoma exhibits focal rhabdomyosarcomatous differentiation with desmin-reactive tumor cells (desmin immunostain)

may be embedded in a myxoid matrix. The neoplastic rhabdomyoblasts have been shown to be reactive for desmin (Fig. 6), myoglobin, and HHF 35 (on the cross-striations), and negative for hepatocyte-type cytokeratin (Akasofu et al. 1999). The poorly differentiated small cells may be positive for both, cytokeratins and desmin (Akasofu et al. 1999), suggesting that these cells may represent an immature and only partially primed neoplastic progenitor cell.

Angiosarcomatoid Components

Only very few reports describe the combination of HCC with a hepatic hemangioendothelial sarcoma/angiosarcoma (Imholz and Noltenius 1977; Dolorme 1978; Kimoto and Ugaki 1982). One observation found an association of angiosarcoma of the liver and HCC in a vinyl chloride worker (Dolorme 1978). This 51-year-old male patient had been in contact with vinyl chloride for 23 years and died with signs of liver failure. Autopsy revealed a liver of 3000 g weight, showing a tumor mass of 15 cm in the right lobe. One part of this tumor showed HCC of the trabecular type but of high grade, with numerous mitotic figures. A second component of the neoplasm consisted of typical angiosarcoma. The latter was also found in a lymph node metastasis of the process (Dolorme 1978). A similar combination has been observed in an experimental model of vinyl chloride carcinogenicity (Maltoni and Lefemine 1974). In a further adult patient without history of thorotrast exposure and a CT diagnosis of HCC, autopsy revealed a tumor of 15 cm size in the right lobe of a cirrhotic liver. The report notes marked adhesion of the right liver to the right adrenal gland and kidney, and a resemblance of the tumor to a Grawitz tumor. Histologically, this neoplasm showed two main morphologic patterns, i.e., liver parenchymal and mesenchymal/sarcomatous. The first component fulfilled the criteria of trabecular-type HCC combined with mixed cholangio–hepatocellular carcinoma. The second component presented as fibrosarcoma and angiosarcoma (hemangioendothelioma), the latter thought to have been derived from sinusoidal endothelial cells. The spindle cell part also contained multinucleated giant cells. Then metastases were exclusively sarcomatous (Kimoto and Ugaki 1982).

Other Mesenchymal Components

CSL can containing spindle cells components corresponding to the former malignant fibrous histiocytoma (Wang et al. 2012).

Combined Hepatocellular Carcinoma and Osteoclast-Like Giant Cell Tumor

A single case of this tumor was observed in a 74-year-old woman. The neoplasm consisted of ordinary HCC and a giant cell tumor composed of monocytoid cells and CD68-positive osteoclast-like giant cells. The boundary between the two components showed transitional features (Tanahashi et al. 2009).

Multilineage Carcinosarcoma

Composite hepatic malignancies showing more than the usual histologic components discussed above may be termed, multilineage carcinosarcomas. In the light of the highly diverse

differentiations found in such rare tumors, a pathogenetic role of pluripotent tumor stem cells may be considered. In a patient reported by She and Szakacs (2005), a highly complex liver neoplasm consisted of HCC, fibrolamellar carcinoma, neuroendocrine carcinoma, spindle cell sarcoma, leiomyosarcoma, rhabdomyosarcoma, and osteosarcoma.

Fibrolamellar Carcinoma with Heterologous Components

Only one published observation reports on the concurrence of fibrolamellar-type carcinoma with adenocarcinoma, a poorly differentiated spindle cell component, leiomyosarcoma, desmin-reactive rhabdomyosarcoma, and osteosarcoma (She and Szakacs 2005).

Combined (Composite) Hepatic Carcinomas and Sarcomas

In rare situations, hepatic carcinoma and sarcoma occur in the form of combined lesions, but not forming single tumors with both components present in the same lesion as in carcinosarcoma (coexistence of two different neoplasms in the same organ). Most patients with this type of neoplasms were elderly males with liver cirrhosis (Saltykow 1909; Jaffe 1924; Edmondson 1958; Ojima et al. 1964; Ishizu et al. 1974; Nagamine et al. 1978; Shin et al. 1981; Takaoka et al. 1983; Sonoda et al. 1984). Among ten cases compiled by Sonoda et al. (1984), the carcinoma was HCC in nine and cholangiocarcinoma in one, whereas the sarcomas were stated as spindle cell tumor or fibrosarcoma in eight, rhabdomyosarcoma in one, and chondrosarcoma in one patient.

Differential Diagnosis

Gastrointestinal extrahepatic carcinosarcomas can metastasize to the liver (Shen et al. 2010). There are instances where HCCs exhibit a massively developed and in part myxoid stroma that may suggest a sarcomatoid lesion. This alteration has been reported for clear cell HCC, where and abundant myxoid stroma was also found in metastatic nodules at necropsy (Fukuda et al. 1992). Rarely, HCC can show an osseous stroma (osseous stromal metaplasia; Leger et al. 1980), extensive stromal calcification (Moenandar 1974), parenchymal calcification (Itai et al. 1979; Kunstilger et al. 1980; Scatarige et al. 1983; Muramatsu et al. 1985; Chin et al. 1986; Teefey et al. 1987; Friedman 1988), which may also be in evidence subsequent to hepatic desarterialization (Bengmark 1989), or so-called ring/rim calcification (Mitchell et al. 1994; Fukuya et al. 1999).

Cytogenetic and Molecular Features

Relatively few informations regarding cytogenetic features are available. As the tumors seem have marked genomic instability, complex karyotypes have been identified, without a specific alteration (Schaefer et al. 2012).

Sarcomatoid Carcinoma of the Liver

Introduction

Sarcomatoid carcinoma of the liver (SCL) forms a group of neoplasms different from carcinosarcoma of the liver. SCL have not yet been sufficiently defined. This also shows up in a host of synonymous terms that have been employed to denote such tumors, including hepatic carcinomas with sarcomatoid features; spindle cell hepatocellular carcinoma. sarcomatous hepatocellular carcinoma; hepatocellular carcinoma with sarcomatous lesions; hepatocellular carcinoma with sarcomatous appearance; hepatocellular carcinoma with sarcomatous transformation; hepatocellular carcinoma with sarcomatous change; hepatocellular carcinoma with sarcomatous proliferation, and hepatic sarcomatoid tumor. As a working formulation, the term, SCL, denotes liver tumors, mostly hepatocellular carcinomas and more rarely cholangiocarcinomas or mixed

hepatocellular/cholangiocellular carcinomas, which show a characteristic morphologic transition between HCC cells and sarcomatoid cells.

Selected References (Isomura et al. 1979; Schmid et al. 1979; Miyazaki et al. 1983; Tsujimoto et al. 1984; Andreola et al. 1987; Kakizoe et al. 1987; Chan and Leung 1988; Ishii et al. 1988; Nakajima et al. 1988; Kojiro et al. 1989; Ishiwata et al. 1990; Haratake and Horie 1991; Matsuoka et al. 1992; Oda et al. 1994; Honda et al. 1996; Maeda et al. 1996; Komada et al. 1997; Mirejovsky and Mirejovsky 1997; Papotti et al. 1997; Han et al. 1998; Morishita et al. 1998; Yamanaka et al. 2000; Eriguchi et al. 2001; Tsuji et al. 2001; Nishie et al. 2003; Kishino et al. 2004; Sato et al. 2006; Matsui et al. 2010).

Epidemiology

The incidence and prevalence of SCL are not known for Western countries, but SCL has been detected in one study in 12.6 % of autopsied cases in Japan (Ishii et al. 1988), and in another study of 579 autopsy cases of HCC in 9.4 % (Kojiro et al. 1989). However, the incidence of HCC with spindle cell features or spindle cell components sometimes suggesting sarcoma may increasingly be reported, in part associated with the more frequent use of transarterial chemoembolization and local ablation therapy. It has been suggested that a spindle cell change may be induced by ischemic and/or necrotic lesions caused by such therapies (Morise et al. 2004). A sarcomatous appearance was found in 20 out of 335 autopsy cases of HCC (5.9 %) during the 12 years from 1969 to 1980, and in 35 out of 244 autopsy cases of HCC (14.3 %) during the 6 years before 1989, when effective anticancer therapies, such as one-shot injection of anticancer agents into the hepatic artery and transcatheter arterial embolization (TAE) have become popular. Among these various anticancer therapies, a sarcomatous component was most frequent (27.6 %) in cases with repeated TAE (Kojiro et al. 1989).

Clinical Features

SCL develop in older adult patients and exhibit an aggressive course and show poor prognosis, often with wide-spread metastatic disease (Tsujimoto et al. 1984; Kakizoe et al. 1987; Honda et al. 1996; Maeda et al. 1996; Eriguchi et al. 2001). In particular, lymphatic and peritoneal metastasis occurs almost twice as frequently as it does in HCC without sarcomatous components (Kojiro et al. 1989; Honda et al. 1996). Among six patients, lymphadenopathy was found in 100 % and intrahepatic metastasis in 83 % (Honda et al. 1996). SCL also have a greater tendency to invade the portal vein (Maeda et al. 1996). Among other prognostic parameters tested in 513 cases of HCC, a sarcomatous component was more frequent in a tumor group showing massive early recurrence after liver resection in comparison with a group showing later recurrence (63 % vs. 3 %, Yamanaka et al. 2000).

Pathology

Macroscopically, infiltrative, mixed expanding and infiltrative, and pedunculated growth patterns were found (Kakizoe et al. 1987), i.e., gross pattern similar to those known for ordinary HCC.

Histologically, the sarcomatoid component usually consists of malignant-looking round, stellate or spindle cells in close association with the HCC cells. A round cell sarcoma component may be prominent (Sato et al. 2006). Transitional forms between the morphologically epithelial cells and mesenchymal-looking cells have been described and are a histologic hallmark of these neoplasms (Miyazaki et al. 1983; Tsujimoto et al. 1984; Andreola et al. 1987; Nakajima et al. 1988). Some of the tumors contain pleomorphic cells or multinucleated giant cells. Extreme variations of SCL exclusively consist of spindle cells, however showing expression of epithelial markers (Eriguchi et al. 2001). Very rarely, the epithelial component of a sarcomatoid tumor is combined hepatocellular-cholangiocarcinoma (Jeong et al. 2004).

Immunohistochemically, the HCC component shows the usual features of epithelial cells forming this tumor (Oda et al. 1994). In contrast, the spindle cells have been shown to be reactive for vimentin, alpha-SMA, and sometimes desmin (Kakizoe et al. 1987; Chan and Leung 1988; Ishiwata et al. 1990; Oda et al. 1994; Maeda et al. 1996; Mirejovsky and Mirejovsky 1997; Han et al. 1998; Eriguchi et al. 2001; Tsuji et al. 2001). Some of these cells may also be keratin (CK 8)-positive (Ishiwata et al. 1990; Haratake and Horie 1991; Tsuji et al. 2001), but lack expression of AFP or alpha-1-antitrypsin (Haratake and Horie 1991), supporting their transitional status. Ultrastructurally, desmosomes were restricted to the epithelial component (Andreola et al. 1987), and one study suggested the an epithelial nature of the spindle cells (Chan and Leung 1988).

Unusual Combined Hepatocellular Carcinomas

There are few examples of hepatocellular carcinomas (HCC) that are, in contrast to mixed hepatocellular and cholangiocarcinoma, combined with other cellular components, resulting in complex phenotypes. The tumors include HCC and high-grade neuroendocrine carcinoma (Garcia et al. 2006), HCC and yolk sac tumor (Morinaga et al. 1996), HCC and malignant lymphoma (Shikuwa et al. 1996), HCC and hepatic sarcoma (Shin et al. 1981), and HCC mixed with fibrolamellar carcinoma (Okano et al. 1998; Seitz et al. 2002). In some of these tumors, a common oncogenic developmental pathway may be present (e.g., in the case of fibrolamellar carcinoma), whereas in others, the combination may have occurred by change.

References

Aito K, Seki K (2006) Carcinosarcoma of the liver producing granulocyte-colony stimulating factor. Pathol Int 56:413–419

Akasofu M, Kawahara E, Kaji K, Nakanishi I (1999) Sarcomatoid hepatocellular-carcinoma showing rhabdomyoblastic differentiation in the adult cirrhotic liver. Virchows Arch 434:511–515

Allison RM, Willis RA (1956) An ossifying embryonic mixed tumour of an infant's liver. J Pathol Bacteriol 72:155–159

Andreola S, Audisio RA, Lombardi L (1987) A light microscopic and ultrastructural study of spindle-shaped hepatocellular carcinoma. Tumori 73:195–201

Aparicio MA, Esteban C, Bengoechea O, Muñoz-Bellvis L (2011) Primary carcinosarcoma of the liver: an unusual case with clearly separated epithelial and mesenchymal components. Rev Esp Enferm Dig 103:336–338

Bengmark S (1989) Tumour calcification after hepatic dearterialization. Br J Surg 76:317–318

Bialik VV (1964) Carcinosarcoma of the liver (in Russian). Arkh Patol 26:76–78

Blanding JD (1986) Mixed malignant tumor of the liver in an adult. Case report and review of some features. Arch Pathol 86:108–110

Bogdanskaia NI (1979) Carcinosarcoma of the liver (in - Russian). Arkh Patol 41:40–42

Boldt C, Pabst U, Nitsche R, Burrig KF (1999) Primary osteosarcoma of the liver. Case report and literature review (in German). Pathologe 20:359–364

Burrig KF, Knauer S (1994) Rhabdomyosarcoma of the liver in adulthood. Case report and review of the literature (in German). Pathologe 15:54–57

Celikbilek M, Deniz K, Torun E, Artis T, Ozaslan E, Karahan OI, Patiroglu TE, Ozbakir O (2011) Primary hepatic carcinosarcoma. Hepatobiliary Pancreat Dis Int 10:101–103

Chan KW, Leung CC (1988) An unsual hepatocellular carcinoma: an ultrastructural and immunohistochemical study. Pathology 20:299–302

Chin NW, Chapman I, Coopersmith H, Jimenez FA (1986) Parenchymal calcification in hepatocellular carcinoma. N Y State J Med 86:596–598

Cote RJ, Urmacher C (1990) Rhabdomyosarcoma of the liver associated with long-term oral contraceptive use: possible role of estrogens in the genesis of embryologically distinct liver tumors. Am J Surg Pathol 14:784–790

Craig JR, Peters RL, Edmondson HA (1989) Tumors of the liver and intrahepatic bile ducts, vol 2, Atlas of tumor pathology. Armed Forces Institute of Pathology, Washington, DC, pp 179–180

Dolorme F (1978) Association of angiosarcoma of the liver and hepatoma in vinyl chloride worker. Ann Anat Pathol (Paris) 23:105–113

Edmondson HA (1958) Tumors of the liver and intrahepatic bile ducts. Atlas of Tumor Pathology, Armed Forces Institute of Pathology, Washington, DC

Epshtein IG (1957) Carcinosarcoma of the liver (in - Russian). Khirurgiia (Mosk) 33:141–144

Eriguchi N, Aoyagi S, Hara M, Okuda K, Fukuda S, Tamae T, Kanazawa N (2001a) Malignant sarcomatoid tumor of the liver: report of a case. Surg Today 31:170–173

Eriguchi N, Aoyagi S, Okuda K, Hara M, Fukuda S, Tamae T, Ohdo M, Kanazawa N et al (2001b) Unusual liver carcinomas with sarcomatous features: analysis of four cases. Surg Today 31:530–533

Fayyazi A, Nolte W, Oestmann JW, Sattler B, Ramadori G, Radzun HJ (1998) Carcinosarcoma of the liver. Histopathology 32:385–387

Freeman AJ, Bullpitt P, Keogh GW (2004) Primary hepatic carcinosarcoma. ANZ J Surg 74:1021–1023

Friedman AC (1988) Calcification in hepatocellular carcinomas. AJR Am J Roentgenol 151:838–839

Fu Y, Kobayashi S, Kushida Y, Saoo K, Haba R, Mori S, Miki H, Ohmori M (2000) Sarcomatoid hepatocellular carcinoma with chondroid variant: case report with immunohistochemical findings. Pathol Int 50:919–922

Fukuda T, Ohnishi Y, Niyazaki Y, Ohnuki K, Tachikawa S (1992) Clear cell hepatocellular carcinoma with abundant myxoid stroma. Acta Pathol Jpn 42:897–903

Fukuya T, Yabuuchi H, Seo Y, Fukuda T, Koga M (1999) Hepatocellular carcinoma with ring calcification: report of two cases. Radiat Med 17:379–382

Garcez-Silva MH, Gonzalez AM, Moura RA, Linhares MM, Lanzoni VP, Trivino T (2006) Carcinosarcoma of the liver: a case report. Transplant Proc 38:1918–1919

Garcia MT, Bejarano PA, Yssa M, Buitrago E, Livingstone A (2006) Tumor of the liver (hepatocellular and high grade neuroendocrine carcinoma). a case report and review of the literature. Virchows Arch 449: 376–381

Goldman RL, Friedman NB (1969) Rhabdomyosarcohepatoma in an adult and embryonal hepatoma in a child. Am J Clin Pathol 51:137–143

Goto H, Tanaka A, Kondo F, Takeshita K, Nagashima I, Hanawa N, Aiso M, Takamori Y et al (2010) Carcinosarcomaof the liver. Intern Med 49:2577–2582

Govender D, Rughubar KN (1998) Primary hepatic osteosarcoma: case report and literature review. Pathology 30:323–325

Han JH, Park YN, Jung WH, Chi HS, Park C (1998) A case with sarcomatoid hepatocellular carcinoma. Yonsei Med J 39:390–394

Haratake J, Horie A (1991) An immunohistochemical study of sarcomatoid liver carcinomas. Cancer 68:93–97

Hasegawa T, Shibata T, Hirose T, Seki K, Hizawa K (1993) Osteosarcoma with epithelioid features. An immunohistochemical study. Arch Pathol Lab Med 117:295–298

Hatanaka S, Sawada S, Midorikawa O (1983) Autopsy case of hepatoma associated with rhabdomyosarcoma of a probable hepatic origin (in Japanese). Nippon Rinsho 41:895–900

Hayakawa K, Shibata T, Yamashita K, Hamanaka D, Tanigawa N, Urata Y, Hosokawa Y et al (1990) Computed tomography and angiogram of primary hepatic rhabdomyosarcoma: report of two adult cases. Radiat Med 8:35–39

Hiyama Y (1995) Primary hepatic leiomyosarcoma and rhabdomyosarcoma (in Japanese). Ryoikibetsu Shokogun Shirizu 7:463–466

Honda H, Hayashi T, Yoshida K, Takenaka K, Kaneko K, Fukuya T, Tateshi Y, Ro T et al (1996) Hepatocellular carcinoma with sarcomatous change: characteristic findings of two-phased incremental CT. Abdom Imaging 21:37–40

Huang YJ, Wang HP, Wu YM (2009) Education and imaging. Hepatobiliary and pancreatic: huge hepatic carcinosarcoma. J Gastroenterol Hepatol 24:929

Iareshko VG, Popov PI, Matakov VV (1992) A case of carcinosarcoma of the liver (in Russian). Klin Khir 5:74–75

Ikebe T, Wakasa K, Sasaki M, Hamba H, Kaneko M, Yamamoto T, Mikami S, Shuto T et al (1998) Hepatocellular carcinoma with chondrosarcomatous variation: case report with immunohistochemical findings, and review of the literature. J Hepatobiliary Pancreat Surg 5:217–220

Imholz H, Noltenius H (1977) Malignant mixed tumor of the liver in an adult (in German). Zentralbl Allg Pathol 121:239–242

Ishak KG, Goodman ZD, Stocker IT (2001) Tumors of the liver and intrahepatic bile ducts, Atlas of tumor pathology, 3rd series, fascicle 31. Armed Forces Institute of Pathology, Washington, DC

Ishii M, Abe M, Hirai K, Majima Y, Sakai T, Miura T et al (1988) The clinical study of hepatocellular carcinoma with sarcoma-like feature (in Japanese with English abstract). Acta Hepatol Jpn 29:734–741

Ishiwata T, Yamada N, Yokoyama M, Asano G (1990) A hepatocellular carcinoma showing sarcomatous features and an extensive metastasis (in Japanese). Gan No Rinsho 36:2587–2593

Ishizu H, Handa F, Mitsutani N, Mukuda T, Koizumi T, Indo K, Sakurai M (1974) A case of primary hepatic carcinoma and hepatic sarcoma with cirrhosis of the liver. Liver 15:248–253

Isoda K, Nagahana H, Hamamoto Y (1976) An autopsy case of carcino-sarcoma of the liver. Bull Osaka Med Sch 22:7–17

Isomura T, Arakawa M, Wada T, Shimokawa Y (1979) Hepatocellular carcinoma with sarcoma-like transformation: a case report (in Japanese with English Abstract). Kanzou (Acta Hepatol Jpn) 20:70–75

Itai Y, Nishikawa J, Tasaka A (1979) Computed tomography in the evaluation of hepatocellular carcinoma. Radiology 131:165–170

Jaffe RH (1924) Sarcoma and carcinoma of the liver following cirrhosis. Arch Intern Med 33:330–342

Jelovsek JE, Winans C, Brainard J, Falcone T (2004) Endometriosis of the liver containing Mullerian adenosarcoma: case report. Am J Obstet Gynecol 191:1725–1727

Jeong BJ, Hyun DH, Lee KW, Ryu ST, Lee JW, Lee JI, Jeong S, Lee DH, Kim PS et al (2004) A case of sarcomatous combined hepatocellular-

cholangiocarcinoma (in Korean). Korean J Gastroenterol 43:56–60
Jinnouchi S, Hoshi H, Watanabe K, Maruyama R, Kouno T (1989) Hepatic carcinosarcoma demonstrated by Ga-67 scintigraphy. Ann Nucl Med 3:99–102
Kakizoe S, Kojiro M, Nakashima T (1987) Hepatocellular carcinoma with sarcomatous change. Clinicopathologic and immunohistochemical studies of 14 autopsy cases. Cancer 59:310–316
Kawarada Y, Uehara S, Noda M, Yatani R, Mizumoto R (1985) Nonhepatocytic malignant mixed tumor primary in the liver. Report of two cases. Cancer 55:1790–1798
Kerr JF (1966) Hepatic embryonic mixed in an adult. J Pathol Bacteriol 92:238–240
Kim JH, Lee YG, Lee J, Jung CK, Kim HT, Kang H, Kho KH, Hong SP, Hwang SG et al (2004) A case of combined hepatocellular-cholangiocarcinoma with sarcomatous transformation and second primary colon cancer (in Korean). Korean J Hepatol 10: 142–147
Kimoto T, Ugaki M (1982) Hepatocellular carcinoma combined with hepatic mesenchymal cell tumor and sarcoma. Acta Pathol Jpn 32:1131–1141
Kishimoto Y, Hijiya S, Nagasako R (1984) Malignant mixed tumor of the liver in adults. Am J Gastroenterol 79:229–235
Kishino T, Mori H, Nishikawa K, Ishiyama N, Yasui H, Sugiyama M, Atomi Y et al (2004) Hepatocellular carcinoma containing sarcomatous lesions in a normal liver, accompanied by secondary Budd-Chiari syndrome. J Clin Gastroenterol 38:296–297
Kitayama Y, Sugimura H, Arai T, Nagamatsu, Kino I (1995) Primary osteosarcoma arising from cirrhotic liver. Pathol Int 45:320–325
Kojiro M, Sugihara S, Kakizoe S, Nakashima O, Kiyomatsu K (1989) Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. Cancer Chemother Pharmacol 23(Suppl):S4–S8
Komada N, Yamagata M, Komura K, Hayashi K, Maruyama T, Kataoka H, Koono M, Tsubouchi H (1997) Hepatocellular carcinoma with sarcomatous change arising in primary biliary cirrhosis. J Gastroenterol 32:95–101
Kubosawa H, Ishige H, Kondo Y, Konno A, Yamamoto T, Nagao K (1988) Hepatocellular carcinoma with rhabdomyoblastic differentiation. Cancer 62:781–786
Kunstilger FK, Federie MP, Moss AA, Marks W (1980) Computed tomography of hepatocellular carcinoma. Am J Roentgenol 134:431–437
Kwon JH, Kang YN, Kang KJ (2007) Carcinosarcoma of the liver: a case report. Korean J Radiol 8:343–347
Ladaga L, Kay S, Melcher M, King JN (1979) Combined epithelial and sarcomatous elements in a liver cancer associated with oral contraceptive use. Am J Surg Pathol 3:185–190
Lai Q, Levi Sandri GB, Melandro F, Di Laudo M, Garofalo M, Guglielmo N, Grieco M et al (2011) An unusual case of hepatic carcinosarcoma. G Chir 32:372–373
Lao XM, Chen DY, Zhang YQ, Xiang J, Guo RP, Lin XJ, Li JQ (2007) Primary carcinosarcoma of the liver: cliinicopathologic features of 5 cases and a review of the literature. Am J Surg Pathol 31:817–826
Leger L, Lemaigre G, Premont M, Salmon R, Klioua Z, Battesti JP (1980) Portal hypertension in sarcoidosis. Three cases including one with liver fibrosis and malignant hepatoma with osseous stroma (in French). Nouv Presse Med 9:1021–1024
Leger-Ravet MB, Borgonovo G, Amato A, Lemaigre G, Franco D (1996) Carcinosarcoma of the liver with mesenchymal differentiation: a case report. Hepatogastroenterology 43:255–259
Lin YS, Wang TY, Lin JC, Wang HY, Chou KF, Shih SC, Chen MJ (2013) Hepatic carcinosarcoma: clinicopathologic features and a review of the literature. Ann Hepatol 12:495–500
Liony C, Lemarchand P, Manchon ND, Becret A, Bercoff E, Pellerin A, Tayot J, Bourreille J (1990) A case of primary osteosarcoma of the liver (in French). Gastroenterol Clin Biol 14:1003–1006
Maeda M, Kanayama M, Uchida T, Hasumura Y, Takeuchi J (1986) A case of hepatocellular carcinoma associated with ossification. A case report. Cancer 57:134–137
Maeda T, Adachi E, Kajiyama K, Takenaka K, Sugimachi K, Tsuneyoshi M (1996) Spindle cell hepatocellular carcinoma. Cancer 77:51–57
Maltoni C, Lefemine G (1974) Carcinogenicity bioassays of vinyl chloride. 1. Research plan and early results. Environ Res 7(3)
Matsui T, Tsuji K, Ichiya T, Komaba F, Kang JH, Kodama Y, Sukurai Y, Kato S, Aoki H et al (2010) Sarcomatoid carcinoma of the liver: a case report and review of the literature (in Japanese). Nihon Shokakibyo Gakkai Zasshi 107:1175–1183
Matsuoka N, Yamamoto T, Haratake J, Hashimoto H, Unoki H (1992) Sarcomatoid liver carcinoma diagnosed clinically as hemangioma (in Japanese). J UOEH 14:297–303
McArdle JP, Hawley I, Shevland J, Brain T (1989) Primary rhabdomyosarcoma of the adult liver. Am J Surg Pathol 13:961–965
McRae BL, Lee JR (2005) Pathologic quiz case: right upper quadrant abdominal mass in a young woman. Primary hepatorenal embryonal rhabdomyosarcoma with differentiation. Arch Pathol Lab Med 129: e51–e52
Meyer-Pannwitt U, Kummerfeldt K, Broelsch CE (1996) Primary pleomorphic rhabdomyosarcoma of the liver (in German). Langenbecks Arch Chir 381:75–81
Mirejovsky T, Mirejovsky P (1997) Sarcomatous hepatocellular carcinoma (in Czech). Cesk Patol 33:127–131
Mitchell AW, Higgins JN, Tate J, Dick R (1994) Rim calcification in primary liver cell carcinoma mimicking hydatid disease. Gut 35:567–568
Miyazaki M, Matsubara O, Kanno J, Kasuga T, Kamiyama R, Kato M, Goto S, Yokokawa M (1983)

Liver cell carcinoma with extensive proliferation of sarcoma-like neoplastic cells – an autopsy case (in Japanese). Gan No Rinsho 29:1344–1350

Moenandar IM (1974) Extensive calcification in the stroma of a primary hepatic carcinoma. J Pathol 114:53–54

Mori H, Matsubara N, Fujii M, Kawai T, Tanaka T, Takahashi M (1979) Alpha-fetoprotein producing rhabdomyosarcoma of the adult liver. Acta Pathol Jpn 29:485–491

Morimoto H, Takada Y, Akita T, Kato Y, Tanigawa N, Muraoka R, Urata Y (1986) A resected case of collision tumor of hepatocellular carcinoma and primary liver rhabdomyosarcoma (in Japanese). Nippon Geka Gakkai Zasshi 87:456–463

Morinaga S, Nishiya H, Inafuku T (1996) Yolk sac tumor of the liver combined with hepatocellular carcinoma. Arch Pathol Lab Med 120:687–690

Morise Z, Sugioka A, Mizoguchi Y, Fujita J, Kato T, Hasumi A (2004) Carcinosarcoma of the liver: a case report with interesting histologic and immunohistochemical features. J Gastroenterol Hepatol 19:948–950

Morishita Y, Etori F, Sawada K, Kachi H, Yamada T, Kawamori T, Tanaka T (1998) Sarcomatous hepatocellular carcinoma with malignant ascites. A report of two cases. Acta Cytol 42:759–764

Muramatsu Y, Moriyama N, Takayasu K, Yamada T, Hasegawa H, Kishi K (1985) A case of minute hepatocellular carcinoma with calcification (in Japanese). Rinsho Hoshasen 30:129–132

Nagamine Y, Sasaki K, Kaku K, Takahashi M (1978) Hepatic sarcoma associated with hepatoma. Acta Pathol Jpn 28:645–651

Nakajima T, Kubosawa H, Kondo Y, Konno A, Iwama S (1988) Combined hepatocellular-cholangiocarcinoma with variable sarcomatous transformation. Am J Clin Pathol 90:309–312

Nakano M, Nagao K, Die G, Sakai S, Kawano K, Kotouda K, Yoshida S, Morohashi Y, Okuda K (1974) An autopsy case of anaplastic liver cell carcinoma. Jpn J Clin Med 32:3626–3633

Nakasho K, Yamanaka N, Okamoto E (1996) A case of combined or mixed hepatocellular and cholangiocarcinoma with sarcomatous components – immunohistochemical characteristics and histogenesis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 93:206–211

Nishie W, Iitoyo M, Koshiyama T, Kusama T (2003) Sarcomatoid carcinoma of the liver with skin and pleural metastases. Br J Dermatol 148:1069–1071

Nomura K, Aizawa S, Ushigome S (2000) Carcinosarcoma of the liver. Arch Pathol Lab Med 124:888–890

Oda Y, Katsuda S, Nakanishi I (1994) An autopsy case of hepatic sarcomatoid tumor: immunohistochemical comparison with a sarcomatous component of hepatocellular carcinoma. Pathol Int 44:230–236

Ojima A, Sugiyama T, Takeda T, Hazama F, Nakakuki F, Uesugi Y, Miyazaki A, Suzuki Y, Fukushima M (1964) Six cases of rare malignant tumors of the liver. Acta Pathol Jpn 14:95–102

Okano A, Hajiro K, Takakuwa H, Kobashi Y (1998) Fibrolamellar carcinoma of the liver with a mixture of ordinary hepatocellular carcinoma: a case report. Am J Gastroenterol 93:1144–1145

Ooi A, Katsuda S, Nakanishi I, Nakamura N, Matsushita F, Tanaka N, Kobayashi K (1987) Hepatocellular carcinoma with chondrosarcomatous variation. A case report and review of the literature. Acta Pathol Jpn 37:1165–1173

Pang SC (1961) Bony and cartilaginous hepatoblastoma. J Pathol Bacteriol 82:273–280

Papotti M, Sambataro D, Marchesa P, Negro F (1997) A combined hepatocellular/cholangiocellular carcinoma with sarcomatoid features. Liver 17:47–52

Park SH, Lee KH, Kang KJ, do Shin H, Jung HW, Choi SH, Jang KT (2009) A case of carcinosarcoma in the liver (in Korean). Korean J Gastroenterol 53:198–201

Saltykow S (1909) Sarcoma and carcinoma of liver. Corr Bl Schweiz Aerzte 44:385–396

Saphir O, Vass A (1938) Carcinosarcoma. Am J Cancer 36:331–361

Sato K, Murai H, Ueda Y, Katsuda S (2006) Intrahepatic sarcomatoid cholangiocarcinoma of round cell variant: a case report and immunohistochemical studies. Virchows Arch 449:585–590

Scatarige JC, Fishmen EK, Saksouk FA, Siegelman SS (1983) Computed tomography of the calcified liver masses. J Comput Assist Tomogr 7:83–89

Schaefer IM, Schweyer S, Kuhlgatz J (2012) Chromosomal imbalances in primary hepatic carcinosarcoma. Hum Pathol 43:1328–1333

Scheiden R, Kiesler J, Breitfellner G (1988) Primary embryonal rhabdomyosarcoma of the liver simulating malignant liver mesenchymoma (in German). Pathologe 9:37–41

Schmid C, Lombardi L, Giordano F, Delgrossi S (1979) Unusual morphologic features of a primary liver neoplasm. Tumori 65:649–655

Seitz G, Zimmermann A, Friess H, Büchler MW (2002) Adult-type hepatocellular carcinoma in the center of a fibrolamellar hepatocellular carcinoma. Hum Pathol 33:765–769

She R, Szakacs J (2005) Carcinosarcoma of the liver: a case report and review of the literature. Arch Pathol Lab Med 129:790–793

Shen ZL, Wang S, Ye YJ, Wang YL, Sun KK, Yang XD, Jiang KW (2010) Carcinosarcoma of pancreas with liver metastasis combined with gastrointestinal stromal tumour of the stomach: is there a good prognosis with the complete resection? Eur J Cancer Care (Engl) 19:118–123

Shibata T, Hayakawa K, Yamashita K, Hamanaka D, Odori T, Ishii Y (1987) Two cases of primary rhabdomyosarcoma in adults (in Japanese). Rinsho Hoshasen 32:653–656

Shikuwa S, Ito M, Nakashima M, Hamasaki K, Naito S, Sekine I, Fujii H (1996) Autopsy case of colocalized tumors of hepatocellular carcinoma and malignant lymphoma. J Gastroenterol 31:129–132

Shin P, Ohmi S, Sakurai M (1981) Hepatocellular carcinoma combined with hepatic sarcoma. Acta Pathol Jpn 31:815–824

Shu RY, Ye M, Yu WY (2010) A case of primary liver carcinosarcoma: CT findings. Chin J Cancer 29:346–348

Sonoda T, Toyoshima S, Enjoji M, Kanematsu T, Inokuchi K (1984) Simultaneous occurrence of primary carcinoma and chondrosarcoma in the liver. A case report and a review of the literature. Acta Pathol Jpn 34:919–924

Sumiyoshi S, Kikuyama M, Matsubayashi Y, Kageyama F, Ide Y, Kobayashi Y, Nakamura H (2007) Carcinosarcoma of the liver with mesenchymal differentiation. World J Gastroenterol 13:809–812

Sun PP, Zhong DR (2010) Primary liver carcinosarcoma: report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 39:713–714

Takaoka Y, Mori T, Akeyama T, Yoshihara H, Taketani N, Inoue A, Minakawa T, Kotoh K (1983) Coexistence of hepatocellular carcinoma and rhabdomyosarcoma in the liver. Acta Hepatol Jpn 24:320–324

Tanahashi C, Nagae H, Nukaya T, Hasegawa M, Yatabe Y (2009) Combined hepatocellular carcinoma and osteoclast-like giant cell tumor of the liver: possible clue to histogenesis. Pathol Int 59:813–816

Teefey SA, Stephens DH, Weiland LH (1987) Calcification in hepatocellular carcinoma: not always an indication of fibrolamellar histology. AJR Am J Roentgenol 149:1173–1174

Tominaga J, Kawase S, Ochi T, Yoshida M, Izawa M (1995) A case of primary rhabdomyosarcoma of liver at autopsy – literature review of 7 cases reported in Japan (in Japanese). Nippon Shokakibyo Gakkai Zasshi 92:255–258

Tsuji Y, Okada K, Fukuoka M, Watanabe Y, Ataka K, Minami R, Hanioka K, Tachibana S et al (2001) Hepatocellular carcinoma with a sarcomatous appearance: report of a case. Surg Today 31:735–739

Tsujimoto M, Aozasa K, Nakajima Y, Kariya M (1984) Hepatocellular carcinoma with sarcomatous proliferation showing an unusual and wide-spread metastasis. Acta Pathol Jpn 34:839–845

Uno Y, Hattori T, Oka T (1977) Hepatoma with primary lesions in the liver and sarcomatous presentation in part. Jpn J Clin Med 35:1565–1567

Volkov VP, Lazdin OA, Sadikov ID (1979) Adenosarcoma of the liver in patient with liver cirrhosis (in Russian). Klin Med (Mosk) 57:105–107

Wang XW, Liang P, Li HY (2004) Primary hepatic carcinosarcoma: a case report. Chin Med J (Engl) 117:1586–1587

Wang QB, Cui BK, Weng JM, Wu QL, Qiu JL, Lin XJ (2012) Clinicopathological characteristics and outcome of primary sarcomatoid carcinoma and carcinosarcoma of the liver. J Gastrointest Surg 16:1715–1726

Watanabe A, Motoi M, Mizobuchi K, Hara I, Nishimura K, Nagashima H (1983) An adult case with rhabdomyosarcoma of the liver. Jpn J Med 22:240–244

Wick MR, Swanson PE (1993) Carcinosarcomas: current perspectives and an historical review of nosological concepts. Semin Diagn Pathol 10:118–127

Yamamoto Y, Ojima H, Shimada K, Onaya H, Hiraoka N, Mizuguchi Y, Kosuge T, Kanai Y (2010) Long-term recurrence-free survival in a patient with primary hepatic carcinosarcoma: case report with a literature review. Jpn J Clin Oncol 40:166–173

Yamamoto T, Kurashima Y, Ohata K, Hashiba R, Tanaka S, Uenishi T, Ohno K, Ikebe T et al (2014) Carcinosarcoma of the liver: report of a case. Surg Today 44:1161–1170

Yamanaka J, Yamanaka N, Nakasho K, Tanaka T, Ando T, Yasui C, Kuroda N, Takata M et al (2000) Clinicopathologic analysis of stage II–III hepatocellular carcinoma showing early massive recurrence after liver resection. J Gastroenterol Hepatol 15:1192–1198

Zhao Q, Su CQ, Dong H, Lu XY, Wu MC, Cong WM (2010) Hepatocellular carcinoma and hepatic adenocarcinosarcoma in a patient with hepatitis B virus-related cirrhosis. Semin Liver Dis 30:107–112

Zornig C, Kremer B, Henne-Bruns D, Weh HJ, Schröder S, Brölsch CE (1992) Primary sarcoma of the liver in the adult: report of five surgically treated patients. Hepatogastroenterology 39:319–321

Giant Cell Tumors of the Hepatobiliary Tract

47

Contents

Abstract

Few primary hepatobiliary tumors are characterized by multinucleated giant cells that are different from the giant cells observed in less-well-differentiated hepatocellular carcinomas and pleomorphic hepatic carcinomas. A distinct example is hepatocellular carcinoma (HCC) with osteoclast-like giant cells, a counterpart of a well-defined pancreatic tumor. These lesions usually present as large, solitary, and expanding neoplasms occurring in the sixth to seventh decades with nearly equal gender ratio. Histologically, HCC cells of variable differentiation are admixed with large cells that contain numerous and uniformly shaped nuclei, strikingly resembling osteoclasts and the giant cells of osteoclastoma of the bone. In contrast to HCC, the giant cells are positive for the macrophage markers, CD68. Osteoclast-like giant cell tumors behave in a more favorable manner than HCCs, with a predilection for local spread and slower metastasis formation. Tumors of this type rarely also develop in large bile ducts and gallbladder.

Hepatocellular Carcinoma with Osteoclast-Like Giant Cells

Introduction

Hepatocellular carcinoma with osteoclast-like giant cells (HCC-OGC; hepatic giant cell carcinoma) is a very rare entity characterized by the

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_47

presence of multinucleated giant cells of the osteoclast-like type in a background of liver cell carcinoma. A similar tumor occurs in the pancreas, being more common than its hepatic counterpart. The first description of HCC-OGC dates from 1980 (Munoz et al. 1980) and referred to an 87-year-old man with macronodular liver cirrhosis and a histology characterized by abundant osteoclast-like giant cells. The authors interpreted the neoplasm to be of reticuloendothelial (Kupffer cell) origin. Relatively few cases have since been reported (Kuwano et al. 1984; Andreola et al. 1985; Horie et al. 1987; Chetty et al. 1990; Hood et al. 1990; Rosai 1990; McCluggage and Toner 1993; Westra et al. 1998; Ikeda et al. 2003; Ahaouche et al. 2005; Rudloff et al. 2005; Bauditz et al. 2006; Schildhaus and Dombrowski 2006; Matsumoto et al. 2012; Zhang et al. 2012; Rastogi et al. 2013).

Clinical and Imaging Features

HCC-OGC usually present in the sixth to seventh decades, with a nearly equal gender ratio. The clinical presentation is nonspecific and has been reported as abdominal pain and a sometimes rapidly enlarging liver mass.

Macroscopic Pathology

The tumors are usually large, solitary, and expanding lesions. They form roundish masses with a pushing border and a grayish red to whitish cut surface (Fig. 1).

Histopathology

The neoplasm consists of two clearly different cell lineages. One component is characterized by hepatocellular carcinoma of various grades, usually growing in a trabecular pattern. These HCC components are admixed with striking non-epithelial multinuclear giant cells resembling osteoclasts (Fig. 2). The giant cells usually display 10–20 uniformly shaped and small nuclei and lack cellular or nuclear atypia, hence closely resembling osteoclastomas of the bone. The tumor cells may rarely contain prominent intracytoplasmic hyaline bodies (Rastogi et al. 2013). Some tumors contain small mononuclear cells with cytological atypias and an increased mitotic count (Bauditz et al. 2006). Instead of a clear-cut HCC component, epithelial cells corresponding to mucin-producing adenocarcinoma or cells undergoing squamous metaplasia have also been noted (Bauditz et al. 2006).

Electron microscopically, both mononuclear and multinucleated giant cells showed features of mesenchymal and epithelial cells (Hood et al. 1990).

The HCC-like epithelial cells are reactive for cytokeratins 8 and 18 (Fig. 3), whereas the osteoclast-like giant cells are immunoreactive for

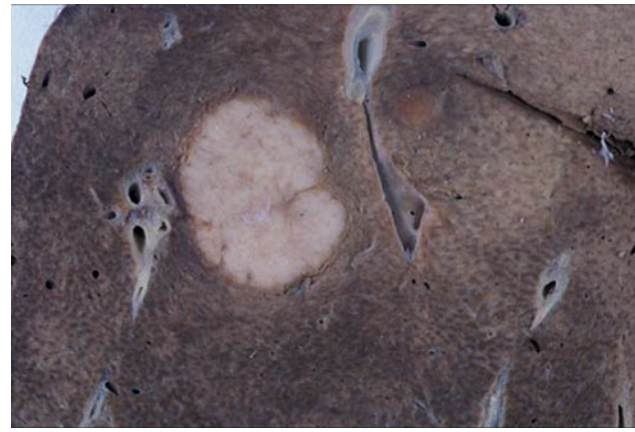

Fig. 1 Giant cell tumor of the liver. The neoplasm presents as a well-delineated mass with an expanding growth pattern

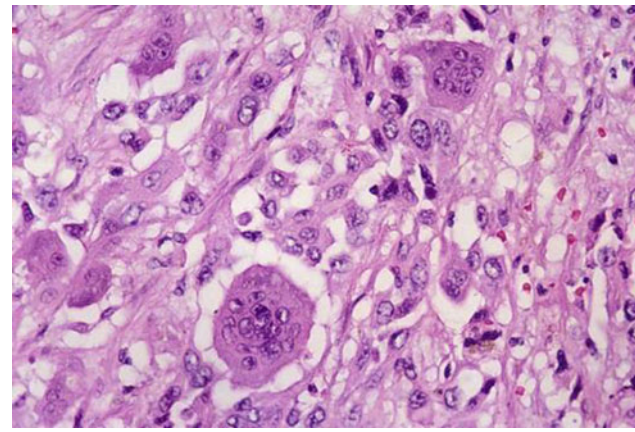

Fig. 2 Hepatic giant cell tumor with osteoclast-like giant cells (Hematoxylin and eosin stain)

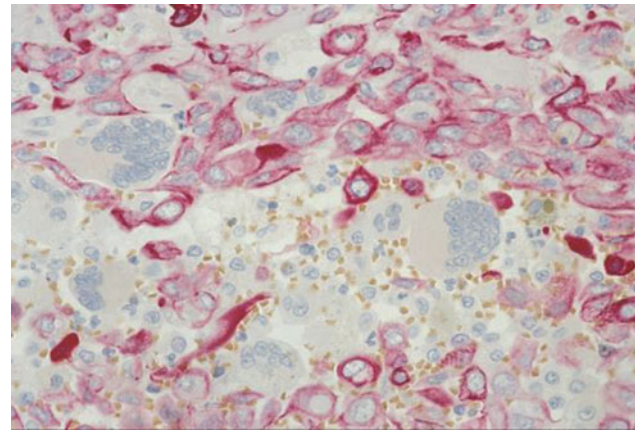

Fig. 3 Hepatic giant cell tumor. In contrast to the osteoclast-like giant cells, mononuclear neoplastic cells are cytokeratin-reactive (CAM5.2 immunostain)

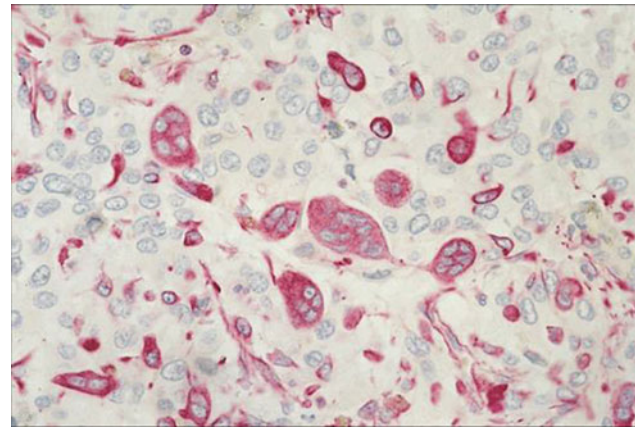

Fig. 4 Hepatic giant cell tumor. Multinucleated, osteoclast-like giant cells are CD68-reactive, nonneoplastic cells derived from fused macrophages (CD68 immunostain)

CD68 (Fig. 4), vimentin (Ikeda et al. 2003; Bauditz et al. 2006), CD163, CD51, CD54, and matrix metalloproteinase-9 (Ikeda et al. 2003). The giant cells are also positive for alpha-1 antitrypsin and anti-chymotrypsin (Hood et al. 1990). The hepatocellular lineage of the non-giant cells is also supported by the expression of albumin (Ikeda et al. 2003).

Differential Diagnosis

HCC-OGC has to be distinguished from other non-osteoclast-like giant or pleomorphic variants of HCC (Korkolis et al. 2009) and Edmondson-Steiner grade 3 HCCs which exhibit multinuclear tumor cells, albeit not of the osteoclast-like type. Pleomorphic and giant cells in HCCs express epithelial markers, and not CD68. This is also the case for the rare syncytial giant cell HCC occurring in the pediatric age group (Atra et al. 2007). Epithelioid angiomyolipoma of the liver can rarely manifest as a giant cell tumor (Alatassi and Sahoo 2009). Osteoclastomas originating from other organs and tissues may metastasize to the liver, e.g., those originating in the pancreas (Cho et al. 2005), although osteoclast giant cell tumors of the bone usually metastasize to the lung in case of metastatic spread, which occurs in a minority of cases (Cai et al. 2007; Gupta et al. 2008). However, these tumors do not contain epithelial components, but consist of osteoclast-like cells and a spindle-cell component. Osteoclast-rich giant cell tumor of the gastrointestinal tract resembling clear cell sarcoma of soft parts metastasized to the liver (Zambrano et al. 2003). Another giant cell tumor metastasizing to the liver is epithelioid hemangioendothelioma with osteoclast-like giant cells (Tsuji et al. 2002). Reactive giant cells derived from fused macrophages develop after spontaneous or induced tumor necrosis, e.g., after microwave coagulation therapy of HCC (Yamashiki et al. 2003). Histologically, it is important to clearly identify osteoclast-like giant cells with their distinct nuclear morphology and arrangement of the nuclei within the cell body, clearly different from other tumor giant cells. In cases of doubt, immunohistochemistry to detect or exclude an epithelial differentiation of neoplastic cells is mandatory.

Biology of Disease

Pure osteoclast-like giant cell tumors usually behave in a more favorable manner than HCCs, with a predilection for local spread and slower metastasis formation, mostly not to locoregional lymph nodes. However, and similar to its pancreatic counterpart, HCC-OGC may show an aggressive course with multiple metastases, e.g., to the bone and soft tissues (Rastogi et al. 2013). In one case, widespread intra-abdominal and pulmonary metastases developed within 3 months of hemihepatectomy (Rudloff et al. 2005). On the other hand, long-term survival has been achieved with a combination of surgical resection, radiofrequency ablation, and chemotherapy (Bauditz et al. 2006).

Molecular Features

K-ras mutations have been detected in these neoplasms, and in each analyzed case, the same K-ras mutation was present both in the epithelial component and in the mononuclear cells, but the authors suggested that the finding of K-ras mutations in the osteoclast-like giant cells may reflect their propensity to phagocytose tumor cells (Westra et al. 1998). In situ hybridization revealed the expression of receptor activator of nuclear factor-kappaB (RANK) in the giant cells and receptor activator of nuclear factor-kappaB ligand (RANKL) in the hepatoid tumor cells, suggesting an osteoclastogenesis by hepatocyte-derived cells (Ikeda et al. 2003).

Sarcomatoid Giant Cell Tumor with Osteoclast-Like Giant Cells

These rare liver tumors are characterized by the morphologic features of a giant cell tumor of the osteoclast-like type in the absence of features of HCC (Horie et al. 1987; Sasaki et al. 1997). In the case reported by Horie and coworkers, electron microscopy offered no definitive evidence whether the neoplasm arose from epithelial cells or non-epithelial cells. These neoplasms may originate from cells undergoing mesenchymal-epithelial transition, as part of the mononuclear cells have been shown to be reactive not only for mesenchymal markers but also for cytokeratins 7, 8, and 19 (Sasaki et al. 1997).

Combined Hepatic HCC-OGC

Tanahashi et al. (2009) reported a case of simultaneous hepatocellular carcinoma and osteoclast-like giant cell tumor in a single hepatic tumor. Histologically, this neoplasm consisted of two distinct components: mononuclear and multinuclear giant cells of the osteoclast type and a conventional hepatocellular carcinoma. The giant cells were reactive for vimentin and CD68, but negative for cytokeratins, whereas the HCC cells were reactive for cytokeratin-8 and AFP. The boundary between the two components showed transitional features.

Carcinomas with Osteoclast-Like Giant Cells of the Biliary Tract

Few examples of these rare neoplasms have been reported (Albores-Saavedra et al. 2006; Fan et al. 2010; Griglione et al. 2010). Three male patients (mean age, 55 years) described by Albores-Saavedra et al. (2006) presented with biliary obstruction. Two tumors were located to the common bile duct and one tumor to the cystic duct. Histologically, the tumors were similar to giant cell tumors of the bone, with a mixture of non-atypical mononuclear cells and multinucleated osteoclast-like giant cells. The former were CD163 positive, while the latter were positive for CD68 and HAM 56. Apart from neoplasms located to the extrahepatic biliary tract, intrahepatic sarcomatoid cholangiocarcinoma with osteoclast-like giant cells has also been observed (Fan et al. 2010).

Carcinomas with Osteoclast-Like Giant Cells of the Gallbladder

Giant cell carcinomas with osteoclast-like giant cells rarely develop in the gallbladder (Grosso and Gonzalez 1992; Ito et al. 1992; Akatsu et al. 2006; Albores-Saavedra et al. 2006). As in HCC-OGC, the osteoclast-like cells are of macrophage/histiocyte origin (Akatsu et al. 2006). The epithelial component is usually of the glandular adenocarcinoma type (Ito et al. 1992), but adenosquamous carcinoma has also been noted (Grosso and Gonzalez 1992; Akatsu et al. 2006). Long-term survival without recurrence was found (Akatsu et al. 2006).

References

Ahaouche M, Cazals-Hatem D, Sommacale D, Cadranel JF, Belghiti J, Degott C (2005) A malignant hepatic tumour with osteoclast-like giant cells. Histopathology 46:590–592

Akatsu T, Kameyana K, Kawachi S, Tanabe M, Aiura K, Wakabayashi G, Ueda M, Shimazu M et al (2006) Gallbladder carcinoma with osteoclast-like giant cells. J Gastroenterol 41:83–87

Alatassi H, Sahoo S (2009) Epithelioid angiomyolipoma of the liver with striking giant cell component: fine-needle aspiration biopsy findings of a rare neoplasm. Diagn Cytopathol 37:192–194

Albores-Saavedra J, Grider DJ, Wu J, Henson DE, Goodman ZD (2006) Giant cell tumor of the extrahepatic biliary tree: a clinicopathologic study of 4 cases and comparison with anaplastic spindle and giant cell carcinoma with osteoclast-like giant cells. Am J Surg Pathol 30:495–500

Andreola S, Lombardi L, Scurelli A, Bersiga A (1985) Osteoclastoma-like giant-cell tumor of the liver. Case report. Tumori 71:615–620

Atra A, Al-Asiri R, Wali S, Al-Husseini H, Al-Bassas A, Zimmermann A (2007) Hepatocellular carcinoma, syncytial giant cell: a novel variant in children: a case report. Ann Diagn Pathol 11:61–63

Bauditz J, Rudolph B, Wermke W (2006) Osteoclast-like giant cell tumors of the pancreas and liver. World J Gastroenterol 12:7878–7883

Cai G, Ramdall R, Garcia R, Levine P (2007) Pulmonary metastasis of giant cell tumor of the bone diagnosed by fine-needle aspiration biopsy. Diagn Cytopathol 35:358–362

Chetty R, Learmonth GM, Taylor DA (1990) Giant cell hepatocellular carcinoma. Cytopathology 1:233–237

Cho SH, Cheon JH, Lee SW, Park HS, Kim SH, Park SJ, Lee WJ, Hong EK, Park JW et al (2005) A case of osteoclast-like giant cell tumor of the pancreas (in Korean). Korean J Gastroenterol 45:441–445

Fan XS, Chen J, Wu HY, Qiu YD, Zhang WW, Kong WT (2010) Intrahepatic sarcomatoid cholangiocarcinoma with osteoclast-like giant cells: report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 39:640–641

Griglione NM, Klapproth JM, Keilin SA (2010) Giant cell tumor of the common bile duct. Clin Gastroenterol Hepatol 8:A30

Grosso LE, Gonzalez JG (1992) Stromal osteoclast-like giant cells in an adenosquamous carcinoma of the gallbladder. Hum Pathol 23:703–706

Gupta R, Seethalaksmi V, Jambhekar NA, Pradbudesai S, Merchant N, Puri A, Agarwal M (2008) Clinicopathologic profile of 470 giant cell tumors of bone from a cancer hospital in western India. Ann Diagn Pathol 12:239–248

Hood DL, Bauer TW, Leibel SA, McMahon JT (1990) Hepatic giant cell carcinoma. An ultrastructural and immunohistochemical study. Am J Clin Pathol 93:111–116

Horie Y, Hori T, Hirayama C, Hashimoto K, Yumoto T, Tanikawa K (1987) Osteoclast-like giant cell tumor of the liver. Acta Pathol Jpn 37:1327–1335

Ikeda T, Seki S, Maki M, Noguchi N, Kawamura T, Arii S, Igari T, Koike M, Hirokawa K (2003) Hepatocellular carcinoma with osteoclast-like giant cells. Possibility of osteoclastogenesis by hepatocyte-derived cells. Pathol Int 53:450–456

Ito M, Hsu CT, Naito S, Matsuo T, Onizuka S, Sekine I, Fujii H, Matsuoka Y (1992) Osteoclast-like giant cell tumour of the gallbladder. Virchows Arch A Pathol Anat Histopathol 420:359–366

Korkolis DP, Aggeli C, Plataniotis GD, Gontikakis E, Zerbinis H, Papantoniou N, Xinopoulos D et al (2009) Successful en bloc resection of primary hepatocellular carcinoma directly invading the stomach and pancreas. World J Gastroenterol 15:1134–1137

Kuwano H, Sonoda T, Hashimoto H, Enjoji M (1984) Hepatocellular carcinoma with osteoclast-like giant cells. Cancer 54:837–842

Matsumoto R, Yoshida K, Nakajima J, Atarashi T, Takeda T, Yanagisawa H, Kikuchi H, Kikuchi K (2012) Osteoclast-like giant cell tumor (OGCT) of the liver: report of a case (in Japanese). Nihon Shokakibyo Gakkai Zasshi 109:255–262

McCluggage WG, Toner PG (1993) Hepatocellular carcinoma with osteoclast-like giant cells. Histopathology 23:187–189

Munoz PA, Rao MS, Reddy JK (1980) Osteoclastoma-like giant cell tumor of the liver. Cancer 46:771–779

Rastogi A, Bihari C, Jain D, Gupta NL, Sarin SK (2013) Hepatocellular carcinoma presenting with multiple bone and soft tissue metastases and atypical cytomorphological features – a rare case report. Diagn Cytopathol 41:640–643

Rosai J (1990) Liver cell carcinoma with osteoclast-like giant cells: nonepitheliogenic giant cells in diverse malignancies. Hepatology 12:782–783

Rudloff U, Gao ZQ, Fields S, Gecelter GR (2005) Osteoclast-like giant cell tumor of the liver: a rare neoplasm with an aggressive clinical course. J Gastrointest Surg J Gastrointest Surg 9:207–214

Sasaki A, Yokoyama S, Nakayama I, Nakashima K, Kim YI, Kitano S (1997) Sarcomatoid hepatocellular carcinoma with osteoclast-like giant cells: case report and immunohistochemical observations. Pathol Int 47:318–324

Schildhaus HU, Dombrowski F (2006) Undifferentiated (sarcomatoid) carcinoma of the liver with osteoclast-like giant cells presenting as tumor thrombus in the inferior vena cava. Virchows Arch 448:659–660

Tanahashi C, Nagae H, Nukaya T, Hasegawa M, Yatabe Y (2009) Combined hepatocellular carcinoma and osteoclast-like giant cell tumor of the liver: possible clue to histogenesis. Pathol Int 59:813–816

Tsuji M, Ozaki T, Tsutsumi A (2002) Epithelioid hemangioendothelioma with osteoclast-like giant cells. Pathol Res Pract 198:501–505

Westra WH, Sturm P, Drillenburg P, Choti MA, Klimstra DS, Albores-Saavedra J, Montag A et al (1998) K-ras oncogene mutations in osteoclast-like giant cell tumors of the pancreas and liver: genetic evidence to support origin from the duct epithelium. Am J Surg Pathol 22:1247–1254

Yamashiki N, Kato T, Bejarano PA, Berho M, Montalvo B, Shebert RT, Goodman ZD, Seki T et al (2003) Histopathological changes after microwave coagulation therapy for patients with hepatocellular carcinoma: review of 15 explanted livers. Am J Gastroenterol 98:2052–2059

Zambrano E, Reyes-Mugica M, Franchi A, Rosai J (2003) An osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: reports of 6 cases of a GIST simulator. Int J Surg Pathol 11:75–81

Zhang J, Chen L, Li F, Xiao Y, Zhuang H (2012) Recurrent and metastatic osteoclast-like giant cell tumor of the liver revealed by FDG PET/CT. Clin Nucl Med 37:1016–1017

Mixed Tumors of the Liver and Related Neoplasms

48

Contents

Abstract

Malignant mixed tumors of the hepatobiliary tract form a not well-defined and heterogeneous group of malignancies that share complex mixed patterns of several neoplastic cell lineages. As more refined classification parameters become available, more and more of these neoplasms are now allocated to better defined entities. Malignant mixed tumors of liver and bile ducts traditionally include nonhepatocytic malignant mixed tumors of the adult (neoplasms that histologically differ from carcinosarcoma), Müllerian adenosarcoma, hepatocytic tumors with atypical mesenchymal reactions, and a group of ossifying and stromal tumors of the liver. A further group of mixed tumors consists of mixed epithelial and mesenchymal hepatoblastomas or hepatoblastoma-like tumors in adults.

Malignant Mixed Tumors of the Liver in Adults

Malignant mixed tumors of the liver form a not well-defined, heterogeneous group of primary hepatic malignancies. In the literature, these lesions are either described as nonhepatocytic malignant mixed tumors (the most characteristic group) or as tumors that contain hepatoid cells. The latter are, based on published descriptions, often very difficult to distinguish from

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_48

carcinosarcomas, and part of the neoplasms would now be classified as adult mixed hepatoblastomas.

Malignant mixed tumor of the liver (MMTL) in adults is rarely reported in the literature. A first review of cases described up to the first 4th of the 20th in the German literature century listed only 12 patients (Nissel 1928), and Sheehan in 1930 collected nine cases, two of which had not been included in Nissel's series (Sheehan 1930). The patients' age at presentation ranged from 20 to 80 years, with an equal gender distribution. In most cases, the clinical history has been one of progressive jaundice and hepatomegaly. The majority of lesions has been solitary and located to the right liver lobe. In contrast to children, MMTL rarely metastasized outside the liver in adult patients (Walter 1896; Bramwell 1897; Marx 1904; Dominici and Merle 1909; Nissel 1928; Milman and Grayzel 1951; Barnett et al. 1958; Alexander 1961; Ojima et al. 1964; Blanding 1968). The literature data present a highly variable spectrum of histologies, and a consistent picture cannot be extracted so far. In what follows, a brief survey of the pertinent morphologies is presented.

Walter (1896) reported on a multiple tumor of the cirrhotic liver of a man of 76 years in which tumor tissue strongly reminiscent of liver parenchyma was intimately mixed with a spindle cell sarcoma. The young adult patient reported by Bramwell in 1897 had a single encapsulated tumor in the right lobe, composed of spindle cells and adenomatous formations, and interpreted by the author to be an angiosarcoma (Bramwell 1897). Another patient (male, 56 years old) exhibited, again in a cirrhotic liver, a tumor in which epithelial and sarcomatous components were spatially separated, indicating a collision tumor (Dominici and Merle 1909). The male patient described by Saltykow (1914) had a single tumor nodule in a cirrhotic liver composed of epithelial tissue resembling liver parenchyma, alveolar structures, spindle cells, cartilage, osteoid, and bone, but the lack of adequate illustrations does not permit to exactly judge this situation. The 35-year-old male patient described by Barnett and coworkers in 1958 revealed, at autopsy, a huge necrotic neoplasm of the liver (organ weight: 8500 g) with extrahepatic growth. Grossly, the tumor was yellow-white, soft, and gelatinous. Microscopically, the lesion was composed of embryonic-looking tissue elements. The main components were elongated cells in stream-like pattern, rather small epithelial cells in nests embedded in a scanty stroma, cords of epithelial cells in an immature stroma, and striated myocytes (Barnett et al. 1958). The 68-year-old female patient described by Alexander (1961) showed, at necropsy, that the right lobe of the liver was enlarged and almost entirely replaced by a rounded mass of growth 15 cm in diameter. The center of the tumor was necrotic; the periphery consisted partly of soft white tissue and partly of firmer tissue which appeared to contain thin seams of cartilage. The remainder of the liver was normal. Histological examination revealed a mixed neoplasm consisting of variably sized, poorly differentiated epithelial cells forming strands and nests, interspersed with scattered pleomorphic cells and multinucleated giant cells. In addition, some epithelia formed acinar and tubular structures lined by cuboidal cells. The second component consisted of an immature-looking, loose cellular mesenchyme and islands of primitive cartilage. This constellation might suggest mixed hepatoblastoma of the adult, but some findings, based on the figures of the report and the tumor description, may not support such a diagnosis. Specifically, pleomorphic and multinuclear giant cells do not usually occur in hepatoblastoma without previous chemotherapy. In the patient described by Blanding (1968), autopsy revealed an enlarged liver (3000 g) grossly irregular due to multiple tumor nodules, predominantly in the right lobe. These nodules measured up to 8 cm in diameter and exhibited a variegated tan-to-yellow bulging cut surface with scattered areas of necrosis and hemorrhage. Histology showed the neoplasm to consist of adenoid epithelial structures supported by loose, edematous, and in part myxoid mesenchymal tissue with interspersed islands of squamous epithelial cells and small foci of poorly differentiated cartilage, chondroid, and osteoid tissues. The epithelial component was not blastomatous,

the tumor thus not representing adult-type mixed hepatoblastoma, although squamous islands are well recognized in hepatoblastoma. Very few further examples have been reported since these older reports (Shono et al. 2008).

Adenosarcoma of the Liver

Müllerian adenosarcoma is an uncommon biphasic, mixed mesodermal tumor (a variant of Müllerian mixed tumor) characterized by a benign-looking epithelial or glandular component and a low-grade sarcomatous mesenchymal/stromal component (Clement and Scully 1990; Gallardo and Prat 2009; D'Angelo and Prat 2011). This neoplasm mainly arises in endometrial tissue and hence can develop in ectopic foci of endometriosis. Immunohistochemically, the sarcomatous cells are reactive for estrogen and progesterone receptors (Amant et al. 2004a), supporting the origin from steroid-responsive cells of the genital tract, and for CD10 (Amant et al. 2004b).

Malignant neoplasms are known to develop in endometriosis. In a review of 205 cases, extragonal sites of endometriosis accounted for 20 % of the endometriosis-associated malignancies (Heaps et al. 1990). In a further analysis, adenosarcomas accounted for 12 % of the lesions (Clement and Scully 1990). However, adenosarcoma can develop in tissues other than endometrium (Clement and Scully 1978), including the ovary (Litta et al. 2004), the vagina (Toyoshima et al. 2004), the testis (Fleshman et al. 2005), the peritoneal surface (Kanngurn et al. 2005), and the pelvic area (Roman et al. 1993). In adenosarcoma, the mesenchymal component of the process can predominate and lead to a heterologous sarcoma with the sarcomatous part increasing and overgrowing with each recurrence of the tumor (Tackin et al. 2006). Stromal overgrowth associated with the formation of fetal-type cartilage has also been observed in primary peritoneal adenosarcoma (Kanngurn et al. 2005). The pluripotentiality of the neoplastic mesenchymal cells is illustrated by the rare finding of a rhabdomyosarcomatous lineage in the stromal component of adenosarcoma (Mikami et al. 2004).

The only well-recognized situation where true primary adenosarcoma has been observed in the liver is in the context of the rare hepatic endometriosis (N'Senda et al. 2000; Jelovsek et al. 2004). In one 54-year-old patient who had had a hysterectomy 6 years previously, CT demonstrated a huge heterogeneous hypodense mass with cystic changes in the liver. The hepatectomy specimen revealed adenosarcoma with a benign-looking epithelial component and a malignant mesenchymal component associated with hepatic endometriosis (N'Senda et al. 2000). In another postmenopausal patient, liver endometriosis was first treated with leuprolide. After treatment failure, the mass was resected and showed to contain focal areas of adenosarcoma (Jelovsek et al. 2004).

Hepatocytic Tumors with Marked and Atypical Mesenchymal Reactions

There are instances where HCCs exhibit a massively developed and myxoid stroma that may suggest a sarcomatoid reaction. This alteration has been reported for clear cell hepatocellular carcinoma, where the abundant myxoid stroma was also found in metastatic nodules at necropsy (Fukuda et al. 1992).

Nonhepatocytic Malignant Mixed Tumor (NHMMT) of the Liver

NHMMT is a term proposed to denote primary hepatic malignancies which consist of adenocarcinoma-like components associated with a spindle cell component (Kawarada et al. 1985). In a case reported by Kawarada et al. (1985), the large and pedunculated liver tumor consisted of epithelial and mesenchymal elements. The mesenchymal cells were spindle shaped and proliferated over the entire tumor, in which the variegated epithelial islands were scattered, sometimes forming structures with mucin secretion. There was squamous

differentiation of the epithelial component with keratinization. In another tumor, the neoplastic tissue contained benign-looking nonhepatocytic, in part tubular epithelia, and a mesenchymal component with foci of osteoid and numerous osteoclast-like giant cells (Shono et al. 2008).

Ossifying Malignant Mixed Epithelial and Stromal Tumor of the Liver

This lesion was found in an adult patient and was characterized by three distinct neoplastic phenotypes: malignant spindle cells, adenocarcinoma, and extensive osteoid formation. Following resection, the patient was alive 8 years postoperatively (Heywood et al. 2002).

Hepatoblastoma-Like Tumors in Adults

Adult-Type Hepatoblastoma

The probably first case of bona fide adult-type hepatoblastoma has been cited in 1951, referring to an old reference of Marx of 1904 (Milman and Gryzel 1951). Several cases have since been reported, but it is sometimes difficult to judge from these observations whether the tumors were true hepatoblastomas or rather other mixed hepatic tumors as described in the previous paragraph.

Selected References (Bartok 1958; Barnett et al. 1958; Alexander 1961; Ojima et al. 1964; Kerr 1966; Blanding 1968; Carter 1969; Goldman and Friedman 1969; Meyer et al. 1974; Ludwig et al. 1975; Baird and McGovern 1976; Jameson and Chatkadakis 1978; Yoshida et al. 1979; Honan and Haqqani 1980; Popper 1980; Barbaryka and von Bouquoy 1981; Genova and Rimi 1982; Kishimoto et al. 1984; Mildeova and Bednar 1984; Kawarada et al. 1985; Bhatnagar et al. 1987; Diaz-Faes et al. 1987; Misra and Mansharamani 1988; Green and Silva 1989; Seabrook et al. 1989; Sugino et al. 1989; Oda et al. 1990; Slugen et al. 1990; Altmann 1992; Mondragon Sanchez et al. 1994; Harada et al. 1995; Inoue et al. 1995; Kacker et al. 1995; Bortolasi et al. 1996; Kuniyasu et al. 1996; Ahn et al. 1997; Parada et al. 1997; Reddy et al. 1997; Diotallevi et al. 1999; Inagaki et al. 2001; Vicente et al. 2001; Yamazaki et al. 2004; Kasper et al. 2005; Ke et al. 2005; Shchegolev et al. 2005; Beppu et al. 2006; Remes-Troche et al. 2006; Krzewinski et al. 2007; Mukhopadhyay et al. 2007; Zhang et al. 2007, 2013; Zheng et al. 2009; Fiaschetti et al. 2010; Nakamura et al. 2010; Di Benedetto et al. 2011; Rougemeont et al. 2012; Wang and Liu 2012; Al-Jiffry 2013).

In a recent literature review of 40 patients, the median age at presentation was 41.5 years, with 21 males and 19 females. Liver cirrhosis was only confirmed in seven patients. Prognosis was worse than in the pediatric age group, with a median survival time for 27 patients with available follow-up of 4 months and a 1-year survival rate of 29.6 %. However, part of the reports date from a time period when modern chemotherapy and surgery schemes were not yet available (Wang and Liu 2012). Similar to pediatric cases, part of these tumors in adults were of the mixed epithelial and mesenchymal type (Barnett et al. 1958; Baird and McGovern 1976; Honan and Haqqani 1980; Popper 1980; Barbaryka and Bouquoy 1981; Diaz-Faes et al. 1987; Oda et al. 1990; Altmann 1992). The term, mixed hepatoblastoma, goes back to Willis (1960). However, the literature of mixed hepatoblastomas in adults is controversial and somewhat confusing, owing to the various terms that have been used in the older literature, including mixed malignant tumors, which have been discussed above, and embryonic mixed tumor, rhabdomyosarcohepatoma, and carcinosteochondrosarcoma. It has been suggested that some authors may have hesitated to employ the designation, "blastoma," for tumors occurring in the adult liver, although the histologic presentation is the same or at least very similar in children and adults (Honan and Haqqani 1980). The diagnosis of mixed hepatoblastoma of the adult patient requires that the epithelial component shows clear features of fetal and/or embryonal hepatoblastoma

and, based on published figures and descriptions, at least a fraction of the reported cases seem to fulfill this criterion. The heterologous components in adult-type mixed hepatoblastoma include fibrosarcomatoid (Carter 1969), chondrosarcomatoid (Carter 1969; Ludwig et al. 1975), osteoid/osteosarcomatoid (Ludwig et al. 1975; Honan and Haqqani 1980), and rhabdomyoblastic (Goldman and Friedman 1969) morphologies. Similar to tumors occurring in children, adult-type hepatoblastoma may show unusual epithelial differentiation, such as marked neuroendocrine differentiation (Zhang et al. 2013). Teratoid hepatoblastoma also occurs in adult patients (Zhang et al. 2007).

Adult-Type Hepatoblastoma Combined with Hepatocellular Carcinoma

There are several reported cases of adult-type hepatoblastoma or mixed liver tumors sharing features with hepatoblastoma containing foci of hepatocellular carcinoma (Kerr 1966; Carter 1969; Goldman and Friedman 1969; Ludwig et al. 1975; Yoshida et al. 1979; Serezhin and Paikova 1984; Harada et al. 1995; Ahn et al. 1997; Ishimura et al. 2007; Canberk et al. 2013). It may be surmised that a transformed hepatoid cell lineage can differentiate along several carcinogenic pathways, with one lineage failing to switch from a hepatoblast phenotype to a hepatocyte lineage. A relationship between hepatocellular carcinoma and hepatoblastoma has also been recognized in children. In one patient suffering from combined hepatoblastoma and hepatocellular carcinoma, late recurrence of disease after 5 years was characterized by the HCC component only (Postovsky et al. 2001).

Adult-Type Mixed Hepatic Tumors with Hepatoblastoma-Like Features

There is a small group of interesting primary hepatocellular tumors which contain hepatoblastoma-like components. A sarcomatoid hepatocellular carcinoma with hepatoblastoma-like features has been described in a 66-year-old male patient with chronic HCV infection (Cho et al. 2004). This mixed epithelial and mesenchymal tumor of the liver showed an epithelial component composed of poorly differentiated hepatocellular carcinoma and more primitive-looking components, which were embryonal and small cell undifferentiated components of hepatoblastoma-like areas. The small cell undifferentiated cells surrounded HCC and the embryonal component of hepatoblastoma-like areas and revealed a transition to areas of rhabdomyosarcoma. A small portion of chondrosarcoma was also noted.

Metachronous Hepatocellular Carcinoma Following Hepatoblastoma

Few reports described the emergence of various types of metachronous hepatocellular carcinoma following hepatoblastoma that had been treated in infancy and childhood (Masuda et al. 2009; Basile et al. 2010). In one patient, clear cell hepatocellular carcinoma arose 25 years after the successful treatment of infantile hepatoblastoma (Basile et al. 2010). We observed a similar case.

Metachronous Hepatoblastoma Following Hepatocellular Carcinoma

This is a very unusual situation described only once so far. An adult patient was transplanted for alcoholic liver cirrhosis complicated by multifocal hepatocellular carcinoma. Recurrence of the tumor was in the form of mixed hepatoblastoma invading the entire transplanted liver, suggesting a filiation between hepatocellular carcinoma and hepatoblastoma in adults (Dumortier et al. 1999).

Multilineage Tumors

Very rarely, primary epithelial liver tumors reveal a differentiating along several lineages, including epithelial, mesenchymal, and neuroectodermal

lineages. One such tumor consisted of mixed hepatoblastoma, hepatocellular carcinoma, cholangiocarcinoma, and neuroectodermal tumor/apudoma (Serezhin and Paikova 1984). The involvement of pluripotent stem/progenitor cells may be considered to play a pathogenic role.

References

Ahn HJ, Kwon KW, Choi YJ, Kim HJ, Hong SP, Oh D, Chung JS (1997) Mixed hepatoblastoma in an adult – a case report and literature review. J Korean Med Sci 12:369–373

Alexander M (1961) A mixed tumor of the liver in an adult. J Pathol 82:217–219

Al-Jiffry BO (2013) Adult hepatoblastoma: a case report and literature review. Int J Surg Case Rep 4:204–207

Altmann HW (1992) Epithelial and mixed hepatoblastoma in the adult. Histological observations and general considerations. Pathol Res Pract 188:16–26

Amant F, Schurmans K, Steenkiste E, Verbist L, Abeler VM, Tulunay G, De Jonge E et al (2004a) Immunohistochemical determination of estrogen and progesterone receptor positivity in uterine adenosarcoma. Gynecol Oncol 93:680–685

Amant F, Steenkiste E, Schurmans K, Verbist L, Abeler VM, Tulunay G, de Jonge E et al (2004b) Immunohistochemical expression of CD10 antigen in uterine adenosarcoma. Int J Gynecol Cancer 14:1118–1121

Baird PJ, McGovern VJ (1976) Test and teach number 7 diagnosis: embryonal hepatoblastoma with malignant epithelial and mesenchymal tissue components occurring in an adult. Pathology 8:170–171

Barbaryka I, Bouquoy F (1981) Hepatoblastoma in adults (in German). Leber Magen Darm 11:283–287

Barnett W, Erikson E, Halpert B (1958) Embryonic tumor of the liver in an adult. Cancer 11:306–309

Bartok I (1958) Hepatoblastoma causing metastasis in adult (in Hungarian). Orv Hetil 99:212–214

Basile J, Caldwell S, Nolan N, Hammerle C (2010) Clear cell hepatocellular carcinoma arising 25 years after the successful treatment of an infantile hepatoblastoma. Ann Hepatol 9:465–467

Beppu T, Karashima R, Sugiyama S et al (2006) A successfully resected case of adult hepatoblastoma with hepatitis C (in Japanese). Jpn J Gastroenterol Surg 39:72–77

Bhatnagar A, Pathania OP, Champakam NS (1987) Hepatoblastoma in an adult female. Indian J Gastroenterol 6:125–126

Blanding J (1968) Mixed malignant tumors of the liver of adults. Case report and review of some features. Arch Pathol Lab Med 86:108–110

Bortolasi L, Marchiori L, Dal Dosso I, Colombari R, Nicoli N (1996) Hepatoblastoma in adult age: a report of two cases. Hepatogastroenterology 43:1073–1078

Bramwell B (1897) A case of enormous primary sarcoma of the liver in which a large blood cyst simulating hepatic abscess was developed. Lancet 1:170–173

Canberk S, Uludokumaci A, Sonmez C, Cakalir C, Gulsen F, Ozbay G (2013) Mixed hepatocellular carcinoma and hepatoblastoma: cytohistopathologic findings and differential diagnosis. Acta Cytol 57:91–95

Carter R (1969) Hepatoblastoma in the adult. Cancer 23:191–197

Cho MS, Lee SN, Sung SH, Han WS (2004) Sarcomatoid hepatocellular carcinoma with hepatoblastoma-like features in an adult. Pathol Int 54:446–450

Clement PB, Scully RE (1978) Extrauterine mesodermal (müllerian) adenosarcoma: a clinicopathologic analysis of five cases. Am J Clin Pathol 69:276–283

Clement PB, Scully RE (1990) Müllerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. Hum Pathol 21:363–381

D'Angelo E, Prat J (2011) Pathology of mixed Müllerian tumours. Best Pract Res Clin Obstet Gynaecol 25:705–718

Di Benedetto F, Di Sandro S, D'Amico G, De Santis M, Gerunda GE (2011) Role of chemoembolization as a rescue treatment for recurrence of resected hepatoblastoma in adult patients. Surg Innov 18:136–140

Diaz-Faes M, Lamamie de Clairac E, Pozo F, Urdiales G, Valverde D, Sampedro A (1987) Mixed hepatoblastoma in an adult (in Spanish). Rev Esp Enferm Apar Dig 71:157–160

Diotallevi P, Cristofaro M, Broglia L, Carletta C (1999) Hepatoblastoma in an HCV-positive adult. Report of a case (in Italian). Radiol Med 97:319–321

Dominici H, Merle P (1909) Composition tumor of liver carcinoma and sarcoma following cirrhosis. Arch Med Exp Anat Pathol 21:136–153

Dumortier J, Bizollon T, Chevallier M, Ducerf C, Baulieux J, Scioazec JY, Trepo C (1999) Recurrence of hepatocellular carcinoma as a mixed hepatoblastoma after liver transplantation. Gut 45:622–625

Fiaschetti V, Fiori R, Gaspari E, Crusco S, Simonetti G (2010) Mixed hepatoblastoma in a young male adult: a case report and literature review. Case Rep Med 2010:919457

Fleshman RL, Wasman JK, Bodner DG, Young RH, MacLennan GT (2005) Mesodermal adenosarcoma of the testis. Am J Surg Pathol 29:420–423

Fukuda T, Ohnishi Y, Miyazaki Y, Ohnuki K, Tachikawa S (1992) Clear cell hepatocellular carcinoma with abundant myxoid stroma. Acta Pathol Jpn 42:897–903

Gallardo A, Prat J (2009) Müllerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma. Am J Surg Pathol 33:278–288

Genova G, Rimi C (1982) Hepatoblastoma in adults. Description of a case (in Italian). Pathologica 74:687–690

Goldman R, Friedman N (1969) Rhabdomyosarcohepatoma in an adult and embryonal hepatoma in a child. Am J Clin Pathol 51:137–143

Green LK, Silva EG (1989) Hepatoblastoma in an adult with metastasis to the ovaries. Am J Clin Pathol 92:110–115

Harada T, Matsuo K, Kodama S, Higashihara H, Yoshifuku N, Ikeda S (1995) Adult hepatoblastoma: case report and review of the literature. Aust N Z J Surg 65:686–688

Heaps JM, Nieberg RK, Berek JS (1990) Malignant neoplasms arising in endometriosis. Obstet Gynecol 75:1023–1028

Heywood G, Burgart LJ, Nagorney DM (2002) Ossifying malignant mixed epithelial and stromal tumor of the liver: a case report of a previously undescribed tumor. Cancer 94:1018–1022

Honan RP, Haqqani MT (1980) Mixed hepatoblastoma in the adult: case report and review of the literature. J Clin Pathol 33:1058–1063

Inagaki M, Yagi T, Urushihara N, Shima Y, Sadamori H, Takakura N, Tanaka N, Oda M (2001) Successfully resected hepatoblastoma in a young adult with chronic hepatitis B: report of a case. Eur J Gastroenterol Hepatol 13:981–984

Inoue S, Nagao T, Ishida Y, Wada C, Beck Y, Uchida H, Okudaira M (1995) Successful resection of a large hepatoblastoma in a young adult: report of a case. Surg Today 25:974–977

Ishimura M, Ohga S, Nagatoshi Y, Okamura J, Tajiri T, Kohashi K, Oda Y, Takada H et al (2007) Malignant hepatic tumor occurring 10 yrs after a histocompatible sibling donor bone marrow transplantation for severe aplastic anemia. Pediatr Transplant 11:945–949

Jameson CP, Chatkadakis CB (1978) Hepatoblastoma in a middle-aged white South African woman. A case report. S Afr Med J 53:143–144

Jelovsek JE, Winans C, Brainard J, Falcone T (2004) Endometriosis of the liver containing mullerian adenosarcoma: case report. Am J Obstet Gynecol 191:1725–1727

Kacker LK, Khan EM, Gupta R, Kapoor VK, Pandey R, Gupta RK, Saraswat VA (1995) Hepatoblastoma in an adult with biliary obstruction and associated portal venous thrombosis. HPB Surg 9:47–49

Kanngurn S, Somran J, Art-Ong C, Lamlertthon W, Porncharoenpong S (2005) Primary peritoneal adenosarcoma with stromal overgrowth and fetal type cartilage: a case report and literature review. J Med Assoc Thai 88:849–854

Kasper HU, Longerich T, Stippel DL, Kern MA, Drebber U, Schirmacher P (2005) Mixed hepatoblastoma in an adult. Arch Pathol Lab Med 129:234–237

Kawarada Y, Uehara S, Noda M, Yatani R, Mizumoto R (1985) Nonhepatocytic malignant mixed tumor primary in the liver. Cancer 55:1790–1798

Ke HY, Chen JH, Jen YM, Yu JC, Hsieh CB, Chen CJ, Liu YC, Chen TW, Chan DC (2005) Ruptured hepatoblastoma with massive internal bleeding in an adult. World J Gastroenterol 11:6235–6237

Kerr JF (1966) Hepatic embryonic mixed tumour in an adult. J Pathol Bacteriol 92:238–240

Kishimoto Y, Hijiya S, Nagasaki R (1984) Malignant mixed tumor of the liver in adults. Am J Gastroenterol 79:229–235

Krzewinski W, Marcisz C, Slowik T, Antosz Z (2007) Hepatoblastoma in an adult (in Polish). Wiad Lek 60:479–482

Kuniyasu H, Yasui W, Shimamoto F et al (1996) Hepatoblastoma in an adult associated with c-met proto-oncogene imbalance. Pathol Int 46:1005–1010

Litta P, Pozzan C, Sacco G, Merlin F, Saccardi C, Ambrosini A (2004) Adenosarcoma of the ovary. A case report. Eur J Gynaecol Oncol 25:507–508

Ludwig J, Grier M, Hoffman H, McGill D (1975) Calcified mixed malignant tumor of the liver. Arch Pathol Lab Med 99:162–166

Marx H (1904) Ueber einen eigenartigen primären Tumor der Leber. Nebst Bemerkungen zur Chorionepitheliomfrage. Beitr Pathol Anat Z Allg Pathol 36:585–605

Masuda T, Beppu T, Horino K, Komori H, Hayashi H, Okabe H, Ootao R, Horlad H et al (2009) Occurrence of hepatocellular carcinoma after hepatoblastoma resection in an adult with hepatitis C virus. Hepatol Res 39:525–530

Meyer P, Livolsi V, Cornog J (1974) Hepatoblastoma associated with oral contraceptive. Lancet 2:1387

Mikami M, Tanaka K, Onouchi M, Komiyama S, Ishikawa M, Hirose T (2004) A case of ovarian adenosarcoma with heterologous rhabdomyosarcoma component: a brief case report. Eur J Obstet Gynecol Reprod Biol 117:112–114

Mildeova E, Bednar B (1984) Resected hepatoblastoma in an adult woman (in Czech). Sb Lek 86:148–150

Milman D, Grayzel D (1951) Mixed tumor of the liver. Review of a case with review of the literature. Am J Dis Child 81:408–420

Misra SC, Mansharamani GG (1988) Hepatoblastoma of adulthood. Indian J Gastroenterol 7:58–59

Mondragon Sanchez R, Bernal Maldonado R, Sada Navarro LA, Hernandez AI, Hurtado Andrade H et al (1994) Epithelial hepatoblastomas in the adult (in Spanish). Rev Gastroenterol Mex 59:231–235

Mukhopadhyay P, Kundu SS, Banerjee A, Mukherjee A (2007) Adult hepatoblastoma in a female Down's. J Assoc Physicians India 55:242–243

N'Senda P, Wendum D, Balladur P, Dahan H, Tubiana JM, Arrive L (2000) Adenosarcoma arising in hepatic endometriosis. Eur Radiol 10:1287–1289

Nakamura S, Sho M, Kanehiro H, Tanaka T, Kichikawa K, Nakajima Y (2010) Adult hepatoblastoma successfully treated with multimodal treatment. Langenbecks Arch Surg 395:1165–1168

Nissel W (1928) Die Mischgeschwülste der Leber. Virchows Arch Pathol Anat 269:446–452

Oda H, Honda K, Hara M, Arase Y, Ikeda K, Kumada H (1990) Hepatoblastoma in an 82-year-old man. An autopsy case report. Acta Pathol Jpn 40:212–218

Ojima MA, Sugiyama T, Takeda T (1964) Six cases of rare malignant tumors of the liver. Acta Pathol Jpn 14:95–102

Parada LA, Bardi G, Hallen M, Hägerstrand I, Tranberg KG, Mitelman F, Johansson B (1997) Cytogenetic abnormalities and clonal evolution in an adult hepatoblastoma. Am J Surg Pathol 21:1381–1386

Popper H (1980) Bidermal hepatoblastoma in an adult (in German). Zbl Allg Pathol 124:403–409

Postovsky S, Elhasid R, Otte GB, Ben Itzhak O, Gaitini D, Ben Arush MW (2001) Late recurrence of combined hepatocellular carcinoma and hepatoblastoma in a child: case report and review of the literature. Eur J Pediatr Surg 11:61–65

Reddy KS, Karak PK, Sharma S, Rao RC, Vijayaraghavan M, Sahni P (1997) Epithelial hepatoblastoma in a middle aged woman. Trop Gastroenterol 18:163–164

Remes-Troche JM, Montano-Loza A, Meza-Junco J, Garcia-Leiva J, Torre-Delgadillo A (2006) Hepatoblastoma in adult age. A case report and literature review. Ann Hepatol 5:179–181

Roman LD, Mitchell MF, Tornos C, Glover A, Kavanagh JJ (1993) Dedifferentiated extrauterine adenosarcoma responsive to chemotherapy. Gynecol Oncol 49:389–394

Rougemont AL, McLin VA, Toso C, Wildhaber BE (2012) Adult hepatoblastoma: learning from children. J Hepatol 56:1392–1403

Saltykow S (1914) Über den Krebs der grossen Gallengänge und die primären bösartigen Geschwülste der Leber. Corresp Bl Schweiz Aerzte 44:462–468

Seabrook GR, Collin JR, Britton BJ (1989) Hepatoblastoma: successful resection in an adult. Br J Clin Pract 43:345–346

Serezhin BS, Paikova LV (1984) Malignant liver tumor of complex histogenesis: mixed hepatoblastoma, hepatocellular and cholangiocellular cancer and apudoma (in Russian). Arkh Patol 46:63–67

Shchegolev AI, Skuba ND, Paklina OV, Tin'kova IO, Vishnevskii VA (2005) Adult hepatoblastoma (in Russian). Arkh Patol 67:41–42

Sheehan HL (1930) Embryonic tumor of liver containing striated muscle. J Pathol Bacteriol 33:251

Shono Y, Tsuji T, Horiuchi T, Nakai T, Uchiyama K, Nakatani Y, Kinoshita H, Tabuse K, Yamaue H (2008) Nonhepatocytic malignant mixed tumor of the liver in adults: report of a long surviving case. Int Surg 93:55–58

Slugen I, Fiala P, Pauer M, Majercik M, Ondrias F, Cernak P (1990) Mixed hepatoblastoma in the adult: morphological and immunohistochemical findings. Bratisl Lek Listy 91:507–515

Sugino K, Dohl K, Matsuyama T, Asahara T, Yamamoto M (1989) A case of hepatoblastoma occurring in an adult. Jpn J Surg 19:489–493

Tackin S, Bozaci EA, Sonmezer M, Ekinci C, Ortac F (2006) Late recurrence of uterine Mullerian adenosarcoma as heterologous sarcoma: three recurrences in 8 months increasing in number and grade of sarcomatous components. Gynecol Oncol 101:179–182

Toyoshima M, Akahira J, Moriya T, Hayakawa S, Yaegashi N (2004) Primary vaginal adenosarcoma with sarcomatous overgrowth. Gynecol Oncol 95:759–761

Vicente D, Berrnabé R, Mazo J, Moreno Nogueira JA (2001) Hepato-blastoma in an adult (in Spanish). Med Clin (Barc) 116:758

Walter M (1896) Ueber das multiple Auftreten primärer, bösartiger Neoplasman. Arch Klin Chir 53:1–58

Wang YX, Liu H (2012) Adult hepatoblastoma: systemic review of the English literature. Dig Surg 29:323–330

Willis RA (1960) Pathology of tumours, 3rd edn. Butterworth, London, pp 934–938

Yamazaki M, Ryu M, Okazumi S, Kondo F, Cho A, Okada T, Takayama W, Kawashima T et al (2004) Hepatoblastoma in an adult. A case report and clinical review of literatures. Hepatol Res 30:182–188

Yoshida T, Okazaki N, Yoshino M et al (1979) A case of hepatoblastoma in adult. Jpn J Clin Oncol 9:163–168

Zhang SH, Xu AM, Lin WH, Zhang XY (2007) Mixed hepatoblastoma with teratoid features in an adult. Pathology 39:453–456

Zhang Q, Ming J, Zhang S, Guo D, Qiu X (2013) A rare case of adult hepatoblastoma with neuroendocrine differentiation misdiagnosed as neuroendocrine tumor. Int J Clin Exp Pathol 6:308–313

Zheng MH, Zhang L, Gu DN, Shi HQ, Zeng QQ, Chen YP (2009) Hepatoblastoma in adult: review of the literature. J Clin Med Res 1:13–16

Part V

Vascular Tumors of the Hepatobiliary Tract

Cavernous and Small Vessel Hemangiomas of the Hepatobiliary Tract

49

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_49

Abstract

Among primary vascular tumors of the liver, cavernous hemangiomas are the most common lesions. Autopsy data document an incidence of up to more than 7 %. There is a female preponderance. These tumors, which consist of dilated vascular channels with an endothelial lining and a fibrous intervascular tissue, occur as solitary or multiple lesions in livers that usually do not show preexistent disease, although the tumors can occur in conjunction with other hepatic changes, such as focal nodular hyperplasia. Macroscopically, cavernous hemangiomas are dark red to bluish, well-delineated tumors that may show a spongy aspect. Many hemangiomas are small lesions, but large tumor also occurs (giant hemangiomas). Large hemangiomas are sometimes synchronously accompanied by several or numerous small lesions. Cavernous hemangiomas show complex feeding vessels that are visualized by modern imaging techniques. The tumors may undergo secondary changes, including thrombosis, inflammation, necrosis, hemorrhage, calcifications, and fibrosis. Cavernous hepatic hemangiomas can undergo spontaneous regression. A second group of hepatic hemangiomas is characterized by dense collections of small vessels (small vessel hemangiomas and capillary hemangiomas).

Cavernous Hemangioma of the Liver

ICD-O code 9121/0

Introduction

Cavernous hemangioma of the liver (synonym: cavernoma) is a relatively common primary hepatic angiomatous tumor morphologically characterized by a circumscribed, tumor-forming growth of often dilated vascular channels (cavities, caverns) forming a spongy-like and blood-rich mass (reviews: Hamilton and Holmes 1950; O'Donoghue and Nicosia 1950; Ochsner and Halpert 1958; Olmsted and Stocker 1975; Starzl et al. 1980; Reading et al. 1988; Hobbs 1990; Hanazaki et al. 1999; Herman et al. 2005; Bioulac-Sage et al. 2008; Etemadi et al. 2011). Hepatic cavernomas were first described in German by Virchow in 1852 (review: Kuske 1938). In the English literature, hepatic hemangioma has first been reported by Frerichs (1861). The author did not consider this tumor be of clinical importance ("The pathologic and clinical significance of the cavernous tumor is very slight"). In 1942, already 66 cases in which an operation had been performed could be reviewed; among these 66 cases, 56 had been resected (Shumacker 1942).

Epidemiology

In regard to frequency, there are considerable differences between autopsy data and clinico-radiological informations. Autopsy series reported an incidence of 0.4–7.3 % (Ochsner and Halpert 1958; Ishak and Robin 1975). In larger series, mean or median age at presentation varies considerably, e.g., 35 years (Lise et al. 1992) and 49 years (Tait et al. 1992), respectively. In Shumacker's review of 66 cases (1942), the average age at diagnosis was 44 years. Most authors report a marked preponderance of female patients: in Shumacker's review 4.5:1 (1942), other reviews showing 5:1 (Henson et al. 1956), and 10:1 in symptomatic patients. Diameters of giant liver hemangiomas reported are 8.5 cm (median; Lise et al. 1992), 11 cm (median; Brouwers et al. 1997), 13.9 cm (mean; Hanazaki et al. 1999), and 19 cm (mean; Vishnevsky et al. 1991). Most of the tumors are sporadic, but familial hemangioma of the liver has been reported (Moser et al. 1998; Admiraal et al. 2004; Diez Redondo et al. 2004a). Apart from the influence of steroid hormones (see below), relatively few factors have been identified to induce cavernous hemangiomas. Systemic lupus erythematodes is associated with a fivefold increased odds of liver hemangiomas (Berzigotti et al. 2011).

Clinical Features

Clinically, small, but even giant, hepatic hemangiomas frequently exhibit a static nature and may remain symptomless ("asymptomatic" hemangioma; Tait et al. 1992). Lesions smaller than 4 cm rarely become manifest. Other tumors, mainly giant hemangiomas (larger than 4 cm), may produce symptoms ("symptomatic" hemangioma), including abdominal discomfort or pain, digestive difficulties, the sensation of an abdominal mass, or distention. In a Japanese review of symptomatic cases, 24 % of patients had abdominal pain, and 20 % had sense of fullness (Kato et al. 1975). In a series from the Mayo Clinic, 41 % of 49 patients with hemangiomas larger than 4 cm were symptomatic (Trastek et al. 1983). Large cavernous hemangiomas can cause complications, including portal hypertension (Takahashi et al. 1997), bile duct stenosis (Issahar-Zadeh et al. 1997; Cortes-Blanco and Martinez-Lazaro 2000), Budd-Chiari syndrome (Hanazaki et al. 2001; Kim et al. 2005), cavernous transformation of the portal vein (Tuncer et al. 2002), and hemobilia (Mikami et al. 1998), and a minority of these lesions present with alarming systemic symptoms and signs, including the Kasabach-Merritt phenomenon (see below), fever of unknown origin (FUO; Lee et al. 1994), polymyalgia rheumatica (Kadry et al. 2000), and a febrile inflammatory syndrome, sometimes with weight loss, pain, accelerated erythrocyte sedimentation rate, anemia, and thrombocytosis (Pateron et al. 1991; Taillandier et al. 1995; Pol et al. 1998; Poupardin et al. 2002). In particular, large lesions (giant hemangioma) have been found in association with fever and an inflammatory syndrome (Taillandier et al. 1995). The pathogenesis of this inflammatory syndrome is not clarified, as hemangiomas that have been histologically analyzed in this situation lacked inflammatory changes (Pol et al. 1998). Spontaneous rupture (Dessoff 1967; Scribano et al. 1996; Cappellani et al. 2000; Chan et al. 2010) or traumatic rupture can occur but is an uncommon event (review: Ribeiro et al. 2010). Large pedunculated hemangiomas may undergo torsion and cause an acute abdomen suggesting acute appendicitis (Ersoz et al. 2010). Very rarely, and similar to infantile hepatic hemangioendothelioma, adult hepatic cavernous hemangiomas may be associated with highly elevated serum AFP, thought to be caused by AFP secretion by the tumor (Han et al. 2010). Large hemangiomas can compress bile ducts and cause obstructive jaundice (Losanoff and Millis 2008). Polycythemia associated with elevated serum erythropoietin levels was found in a patient with hepatic hemangioma (Lanne et al. 2010). In one patient with giant hepatic hemangioma, elevated plasma TGF-beta1 levels were observed, thought to be involved in an altered immune status and decreasing after resection (Ito et al. 1997).

In large hepatic hemangiomas, particularly in giant hemangiomas with a large vascular surface, a distinct coagulopathy with thrombocytopenia, termed Kasabach-Merritt phenomenon (KMP; eponym: Kasabach-Merritt syndrome), can exceptionally occur (Kasabach and Merritt 1940; Vogel et al. 2002; Ontachi et al. 2005; Aslan et al. 2009; Concejero et al. 2009; Tani et al. 2010). It has to be emphasized that KMP is rarely associated with classical hemangioma but rather with kaposiform hemangioendothelioma and tufted hemangioma with evidence of lymphatic malformation (Enjolras and Mulliken 1997). Based on a review of 74 cases, a median age at presentation of 7 weeks was found (Shim 1986). The use of KMP should be restricted to cases caused by hemangioma and not refer to a chronic consumptive coagulopathy occurring throughout the life of patients with vascular malformations (Enjolras and Mulliken 1997). In KMP, profound and sometimes life-threatening thrombocytopenia is the primary hematologic manifestation and is followed by consumption of coagulation factors. Thrombosis occurring in the vascular spaces of a hemangioma is associated with an increase in the tumor's mass and with inflammatory changes. The pathogenic mechanisms involved in KMP have not yet been clarified. At least for non-visceral vascular tumors, it has been observed that KMP was seldom associated with classic hemangioma but rather in lesions exhibiting a lymphatic component, in particular kaposiform hemangioendothelioma and tufted

angioma (Enjolras and Mulliken 1997). However, relatively few reports document KMP in hepatic and usually giant hemangiomas with an apparently capillary or cavernous phenotype, occurring in adults (Margarit et al. 1986; About et al. 1994; Akiyoshi et al. 2000; Hochwald and Blumgart 2000; Billio et al. 2001) and sometimes requiring liver transplantation (Longeville et al. 1997). KMP can also occur in diffuse neonatal hemangiomatosis (see below) which involves the liver (Lopriore and Markhorst 1999). Hepatic giant cavernous hemangioma can be associated with microangiopathic hemolytic anemia/MAHA (Prematilleke 1972), hypofibrinogenemia (Behar et al. 1963), and consumption coagulopathy (Prematilleke 1972, Watanabe et al. 1978; Banton et al. 2005), which is arrested by resection of the tumor (Shimizu et al. 1990).

Imaging Features

Differentiation of hepatic hemangiomas from other tumors is possible by sonography, CT, and MR (Olmsted and Stocker 1975; McArdle 1978; Freeny et al. 1979; Itai et al. 1980; Gandolfi et al. 1983; Chin 1984; Tung et al. 1994; Soyer et al. 1997; Yamashita et al. 1997; Yu et al. 1998; Vilgrain et al. 2000; Brancatelli et al. 2001; Coumbaras et al. 2002; Danet et al. 2003; Mastropasqua et al. 2004; Caseira-Alves et al. 2007; Choi et al. 2009). The ultrasonographic presentation is that of a hyperechoic homogeneous mass for small lesions (less than 3 cm diameter), while larger tumors hyperechoic and heterogeneous. Typical for hemangiomas is a posterior enhancement of a hyperechoic mass. In gray-scale and color Doppler sonography, the tumors manifest as rather homogeneous or slightly heterogeneous, solid masses showing a similar or slightly lower echogenicity than the surrounding liver substance. The Doppler presentation depends on the vascularization mode and the presence of shunts, but feeding arteries and draining veins with high velocity and low pulsatility flow in comparison with intrahepatic vessels are noted. In some cavernous hemangiomas, atypical peripheral rim activity on hepatic blood pool imaging was noted (Özdemir and Friedman 2003). Such a typical presentation may, however, lack in fetal and infantile tumors (see below). On CT images, cavernous hemangioma reveals a low-density area in the parenchyma. After contrast medium, scans show early peripheral opacification followed by variable degrees of filling in of the central parts (Johnson et al. 1981). Well-defined, dense and continuously spreading enhancement on single level dynamic CT is a characteristic sign of hepatic cavernous hemangioma (Itai et al. 1989). Particularly in case of multiple hemangiomas, it may be difficult to distinguish such lesions from hepatic metastases. In a study comparing 91 patients with cavernous hemangioma and 47 patients with hepatic metastases, 76 % of hemangiomas had globular enhancement on CT images, compared to 10 % of metastases. 72 % of cavernous hemangiomas had enhancement isodense with the aorta, and 96 % of metastases were hypodense, and 76 % of hemangiomas had peripheral enhanced compared to 38 % of metastases (Leslie et al. 1995). MR can distinguish hemangioma from hepatic malignancies with a 90 % sensitivity, 92 % specificity, and an overall accuracy of 90 % (Stark et al. 1985). On MR images, an inverse relationship between the number of endothelial cells in histologic specimens and the mean T2 value of the tumor was found (Tung et al. 1994). In an analysis of 115 patients, it turned out that MR is the best method to reliably arrive at diagnosis. The diagnosis of hemangioma was established by ultrasonography in 57 % of patients, by CT scan in 73 %, and by MR in 84 % (Yoon et al. 2003).

In a comparative radiological study, Vilgrain et al. (2000) have proposed several categories of hepatic hemangiomas based on imaging presentation, including typical hemangiomas, large heterogeneous hemangiomas (giant hemangiomas if >4 cm), rapidly filling hemangiomas (16 % of all hemangiomas but seen in 42 % of hemangiomas smaller than 1 cm), hyalinized hemangioma (rare lesions that represent the end stage of tumor involution), cystic or multilocular hemangioma, hemangioma with fluid-fluid level, hemangioma with arterioportal shunt, and hemangioma with capsular retraction.

Relatively few mass lesions are confounded with hemangioma at imaging, including telangiectatic focal nodular hyperplasia (Sasaki et al. 2001). Hepatic angiosarcoma may mimic cavernous hemangioma of the liver on dynamic CT (Itai and Teraoka 1989). On the other hand, hepatic hemangioma may mimic primary liver cancer (Zheng et al. 2004), cholangiocarcinoma (Sood et al. 2009), or metastatic disease (Sood et al. 1996).

Pathology

Macroscopically, about 80 % of cavernous hemangiomas are solitary lesions, and 20 % are multiple. In a minority of patients numerous lesions form a diffuse growth pattern (Pierini and Zanniello 1964; Hercberg et al. 1982). The right liver lobe is more often involved; in a study of 50 cases, the right liver lobe was affected in 39, the left lobe in 5, and both lobes in 6 cases (Petri et al. 1993). There is a tendency for cavernous hemangiomas, in particular the smaller ones, to be situated underneath the liver capsule, macroscopically visualized as either flat, umbilicated, or fungating blue-red to almost black masses. Virchow (1863) wrote that the tumors prevail at the lower liver margin and close to the suspensory ligament. Most of the small lesions are spherical, the part touching the capsule being flattened. Cavernous hemangioma of the liver displays several gross and microscopic growth patterns (Table 1; Figs. 1, 2, 3, 4, 5, and 6).

Table 1 Growth patterns of cavernous hemangioma of the liver

Solitary mass-forming type (SMF)
SMF with peripheral satellite lesions
Multiple mass-forming type (MMF)
MMF with dominant mass and multiple small tumors
MMF without dominant mass
Giant cavernous hemangioma
Pedunculated type
Diffuse type

Solitary Versus Multiple Hepatic Hemangiomas

Besides tumors manifesting as a single mass within one lobe, liver hemangiomas with bilobar extension, tumors with satellite nodules (Valls

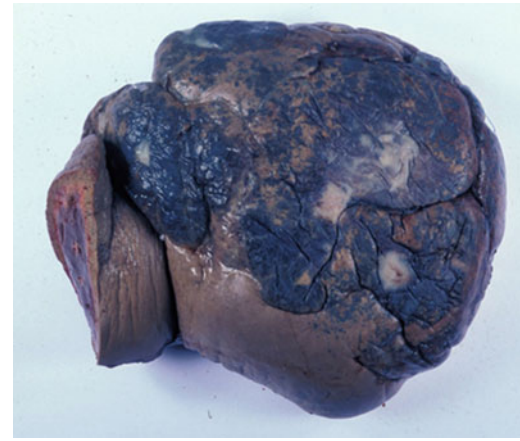

Fig. 1 Giant cavernous hemangioma of the liver. A large part of the liver lobe has been replaced by a well-delineated vascular tumor (fixed resection specimen)

Fig. 2 Pedunculated cavernous hemangioma of the liver (cut surface)

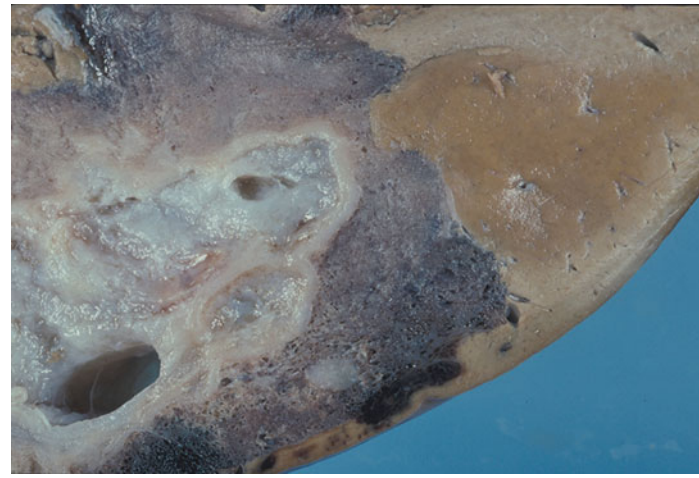

Fig. 3 Cavernous hemangioma of the liver. The tumor is well-delimitated from the adjacent liver tissue but has grown around a large Glisson's tract (fixed specimen, cut surface)

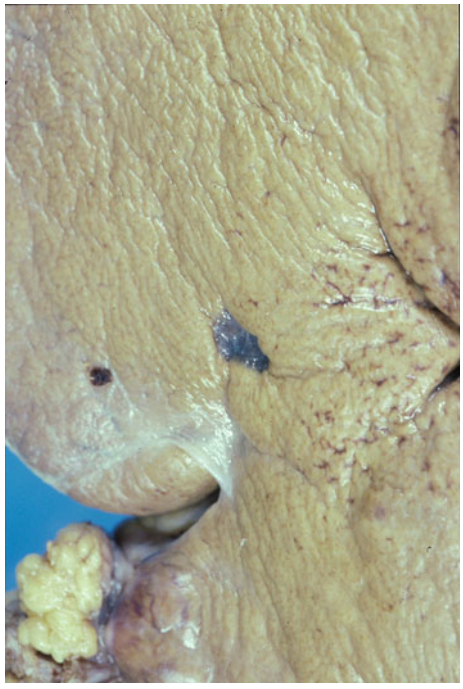

Fig. 4 Very small hepatic hemangioma, visible as a *tiny red* and sunken area

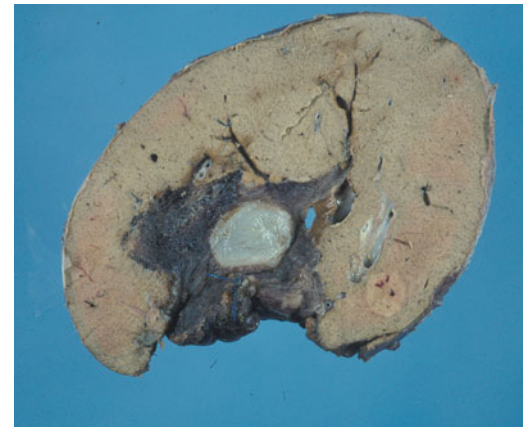

Fig. 5 Hepatic cavernous hemangioma with central regression. Note the *gray-white* focuses in a vascular spongy mass (fixed specimen, cut surface)

et al. 1996), or large tumors accompanied by smaller lesions elsewhere in the organ are known, sometimes producing what has been termed massive hepatic hemangiomatosis, a situation which may require liver transplantation (Keegan et al. 2001). Furthermore, large lesions may grow outside the organ's contour to form polypoid masses (pedunculated giant hemangioma; Bhatnagar et al. 1987; Parikh and Iyer 1990; Kumarakrishnan et al. 1997; Maekawa et al. 1997; Tsai et al. 1999; Liang et al. 2002; Kudara et al 2004; Masui et al. 2005; Moon et al. 2011). Similar to certain malignant tumors, hepatic hemangiomas may induce capsular retraction visualized in CT and MR (Yang et al. 2001; Lee et al. 2001; Blachar et al. 2009). Hemangiomas may rarely produce cystic spaces, sometimes with formation of giant cysts (Hanazaki et al. 2001) or the presentation as a multilocular cystic mass (Yonemoto et al. 1966; Hihara

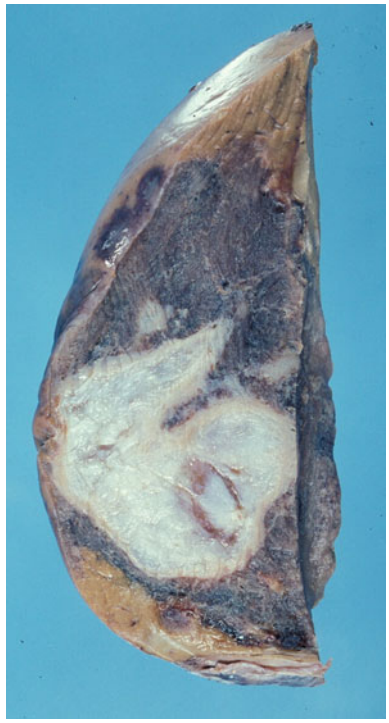

Fig. 6 Hepatic hemangioma with marked regressive changes in the center of the tumor (fixed specimen, cut surface)

et al. 1990; Hussain et al. 1992; Cha et al. 2008). In large tumors with cystic change, multicystic loculi were mainly found at the periphery of the tumor, the cysts being lined by a single layer of endothelial cells, while the center of the tumor was occupied by necrosis of serous fluid or thrombi (Cha et al. 2008). Therefore, peripheral cystic change may be a secondary alteration following marked regression of central tumor parts.

Giant Cavernous Hemangioma of the Liver

Giant cavernous hemangioma of the liver has been defined as a lesion exceeding 4 cm in diameter. In the literature, such large lesions have also been termed enormous angioma, massive hemangioma, or gigantic hemangioma of the liver.

Selected References M'Weeney 1912; Shumacker 1942; Wilson and Tyson 1952; Polikarpova 1955; Sewell and Weiss 1961; Ecker and Doane 1969; Adam et al. 1970; Ang and Tanoue 1972; Grinberg 1975; Wald et al. 1976; Spoor et al. 1977; Taitelbaum et al. 1982; Sharma et al. 1991; Taillandier et al. 1995; Diez Redondo et al. 2004b.

Old reports document, in fact, "enormous" lesions. Pfannenstiel, the inventor of the obstetric surgery technique still having his name (the Pfannenstiel laparotomy), in lectures held in 1897 and 1898 at the "medicinal section of the Silesian Society for patriotic culture," reported on the successful extirpation of a giant hepatic hemangioma that weighed, after flowoff of much of the blood, five pounds, estimated to have the mass doubled before surgery (Pfannenstiel 1898). In a study of 22 patients, 12 were females and 10 males, and the ages at diagnosis ranged from 4 months to 77 years, with an average age of 51 years. Eighteen of 22 patients were symptomatic (epigastric and right upper quadrant pain, abdominal discomfort, diffuse abdominal distention, diffuse peritoneal irritation as a result of rupture). Tumor diameters ranged from 6 to 45 cm (Adam et al. 1970; Koszka et al. 2010) As giant hemangiomas can show large vascular spaces, thrombosis followed by phleboliths can develop (Holtz et al. 1977).

Giant liver hemangiomas exhibit distinct growth pattern, which may have an impact on resectability, in particular with respect to the sometimes relative ease to remove even very large lesions. Liver resection has been shown to be indicated for giant liver hemangiomas with abdominal discomfort, especially for lesions greater than 20 cm in size (Jiang et al. 2011). Outcome is related to the operative approach used for resection (Lerner et al. 2004). In a retrospective study on the tumor borders of ten giant hemangiomas, Zimmermann and Baer (1996) identified four distinct interface patterns (Table 2): fibrous interface (pattern A), interdigitating interface (pattern B), compression interface (pattern C), and irregular/spongy interface (pattern D). In five tumors, a single interface pattern (pattern A)

was detected, whereas the remaining tumors showed a mixed interface type, but seven lesions were exclusively or partially separated from the liver substance by a fibrous, pseudocapsule-like interface (Zimmermann and Baer 1996). In another study of 19 hepatic cavernous hemangiomas, irregular interface instead of a well-defined fibrous pseudocapsule was found in 84 % (Kim et al. 2006a). A fibrous interface in giant hemangiomas may favor a rather easy resection or enucleation even in case of very large lesions (Baer et al. 1992).

Histopathology

The typical histology is that of a dense collection of blood-filled spaces representing abnormal, often markedly dilated vascular channels (vascular cavities; Figs. 7 and 8). In serial sections, these cavities are round, elliptical, or polygonal, and the caverns communicate with each other, with partial or complete loss of septa. The number of tandem chambers does not seem to exceed three chambers in sequence. There are, however, also communications in the shape of bifurcated vascular channels or tubes situated within the connective tissue, lacking a media and an elastic interna (Kuske 1938). These dilated "caverns" have given the lesion its name. The spaces are lined by a usually flat and monolayered endothelial lining with pale cytoplasm and elongated, dense and small nuclei. Between the spaces are thin fibrous septa containing the stromal cells of hemangioma and, in few cases, round cell infiltrated. The stromal cell population consists of fibroblastoid cells, myofibroblasts, and rare smooth muscle cells. A part of septa can contain small bile ducts, considered to be remnant structures trapped within the growing hemangioma (Kuske 1938). Although the vascular lumina of cavernous hemangiomas resemble thin-walled abnormal postcapillary venules, these channels seem to be derived from vessels of the arterial port. Scanning electron microscopic studies have shown that the vascular channels of hemangioma often form a labyrinth of caves 50–150 μm in diameter, the caves being separated by septa 20–40 μm in width. The inner endothelial surface of the cavities resembled that of the hepatic artery and clearly differed from that of portal vein or hepatic vein. Specifically, endothelial cells were spindle shaped and arranged in parallel, what is found in arterial vessels (Yamamoto et al. 1983). The vascular spaces usually contain fluid blood.

Table 2 Types of tumor boundaries in giant hepatic hemangioma (Zimmermann and Baer 1996)

Pattern A: Fibrous interface
Pattern B: Interdigitating interface
Pattern C: Compression interface
Pattern D: Irregular/spongy interface

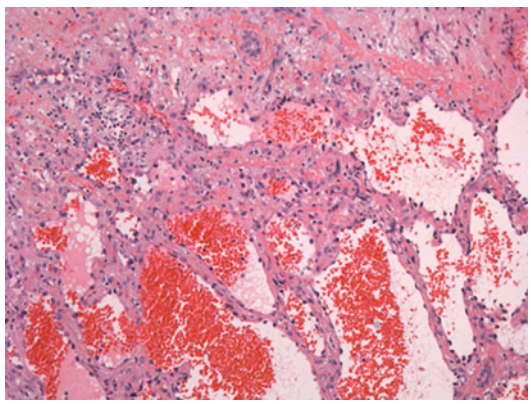

Fig. 7 Cavernous hemangioma of the liver. A spongy network of dilated vascular spaces with a flat endothelial lining characterized this tumor (hematoxylin and eosin stain)

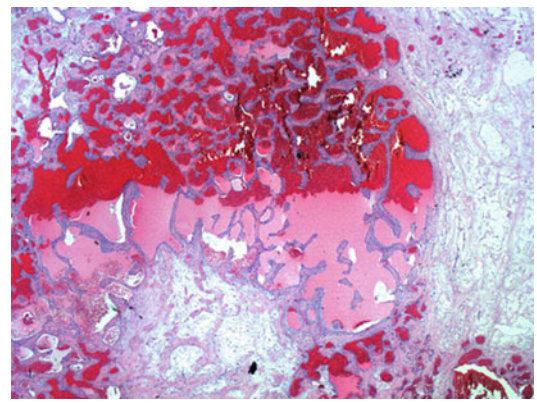

Fig. 8 Hepatic cavernous hemangioma with blood sedimentation after storage of a resection specimen (hematoxylin and eosin stain)

In resection specimens stored in fixative, blood sedimentation takes place in the vascular spaces, later seen as a sickle-shaped erythrocyte-rich structure in stained sections. In part of hemangiomas, mostly in large tumors, thrombosis can occur (see below), followed by organization by granulation tissue and fibrosis. Both the preserved hemangioma and thrombosed areas can be diagnosed by needle biopsy (Caturelli et al. 1986; Cronan et al. 1988; Tung and Cronan 1993), but this procedure bears risks and will not be required in most cases, owing to the advanced imaging techniques now available. The extracellular matrix of cavernous hemangiomas contains collagen and basement membrane proteins. Few elastic fibers have been observed (Kim et al. 2006a).

The boundary of hepatic hemangiomas is either smooth, with an interposed layer of fibrous tissue (sometimes a pseudocapsule) and compression and atrophy of adjacent liver substance, or irregular, with a "corona" of vascular channels interdigitating with liver parenchyma in a complex manner. In the latter situation, abnormal, malformed, and often dilated vascular channels are found outside the hemangioma proper. It is not clear whether these channels belong to the vascular system supporting the tumor and whether they represent vessels of a growing tumor.

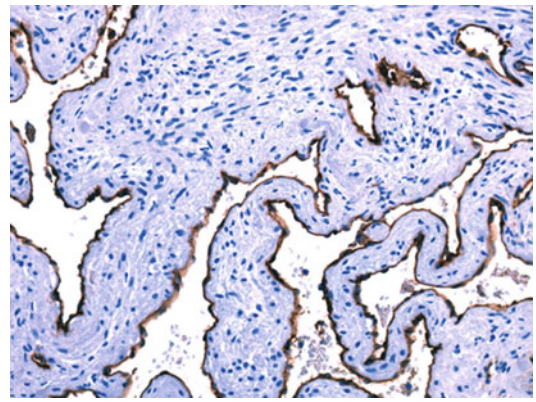

Fig. 9 Hepatic hemangioma, flat endothelial lining of the vascular spaces (CD34 immunostain)

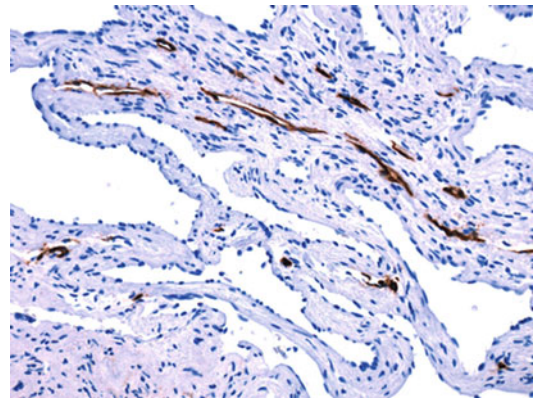

Fig. 10 The fibrous septa separating vascular spaces in hepatic hemangioma can contain lymph vessels (D2-40 immunostain)

Ultrastructure

Endothelial cells contained pinocytotic vesicles, scattered ribosomes, rough endoplasmic reticulum, and Golgi apparatus. A distinct basement membrane was present beneath the endothelial cells. In addition to endothelial cells, hemangiomas also contained stromal cells, forming a population of fibroblast-like cells, myofibroblasts, and smooth muscle cells (Kojimahara 1986).

Immunohistochemistry

The endothelial cells of cavernous hemangiomas are variably immunoreactive for CD31, CD34 (Fig. 9), and factor VII-associated antigen. Cavernous hemangiomas only exceptionally contained lesional cells immunoreactive for simple epithelial keratins (Miettinen and Fetsch 2000). Most of the lesions express decorin, in contrast to angiosarcomas and Kaposi's sarcoma (Salomäki et al. 2008). The endothelium of the hemangiomas does not express the hyaluronan receptor for endocytosis, suggesting that these tumors demonstrate vascular but not sinusoidal differentiation (Duff et al. 2002). Estrogen and progesterone receptors were not detected in these tumors (Kim et al. 2006). Prox1 expression is generally absent in cavernous hemangiomas, in contrast to venous hemangiomas and lymphangiomas (Miettinen and Wang 2012). Lymph vessels may be present in septa separating vascular channels (Fig. 10).

Hemangiomas Located Outside the Normal Hepatic Parenchyma

Giant cavernous hemangioma has been found to arise from the Glisson's capsule (Guibert and Candon 1957) and from accessory lobe of the liver (Avdei and Vas'kovsij 1975). Hemangioma-like lesions develop in portal biliopathy (cavernous transformation of the portal vein, portal vein cavernoma). This issue is further discussed in another chapter.

Vascular Supply of Cavernous Hemangiomas of the Liver

The first who systematically studied the vascular supply of hepatic cavernous hemangiomas was Virchow, who performed injections with staining substances of the entire liver and found that the tumor was connected both with the hepatic artery and the portal vein (reviewed in Virchow 1863; Fig. 11). Ribbert injected staining material directly into a cavernoma and found that vessels in the interstitial were stained, but the capillaries in the vicinity of the hemangioma, suggesting that hepatic cavernous hemangioma has a vascular system of its own, are not connected with the hepatic capillary network (Ribbert 1898). However, analyses of tumor borders reveal that the microvascular system of cavernous hemangiomas is in direct continuation with adjacent parenchymal microvessels (Fig. 12). In serial sections of a cavernous hepatic hemangioma, Kuske found one single artery directly entering a cavity, proving arteries as direct feeding vessels of hemangioma (Kuske 1938). In histological sections, medium-sized to large blood vessels are seen in the vicinity of hemangiomas. In larger tumors, these vessels may be found up to 2 cm beyond the confines of the hepatic tumor (so-called hemangioma-like vessels; Kim et al. 2006). The vascular supply of hemangiomas has been studied by serial selective hepatic arteriography (Li et al. 2003). This technique has uncovered that the tumors are supplied by one to numerous arterial branches. In the portal phase of portography, contrast medium failed to enter the tumors, and the intrahepatic portal venous branches were pushed aside by the tumor. In this study, no arterioportal fistula was detected within the tumor (Li et al. 2003). However, hepatic cavernous hemangioma with shunt formations is now a recently recognized entity. Arterioportal shunts have been described more commonly (Kim et al. 2001, 2006; Tanaka et al. 2002; Han and Kim 2004), but the less common combined arterioportal and portosystemic shunts are well documented (Hekimoglu and Ustundag 2010).

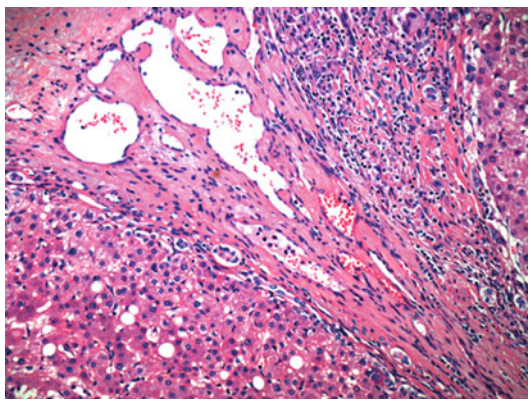

Fig. 11 Border of hepatic hemangioma with feeding vessels (hematoxylin and eosin stain)

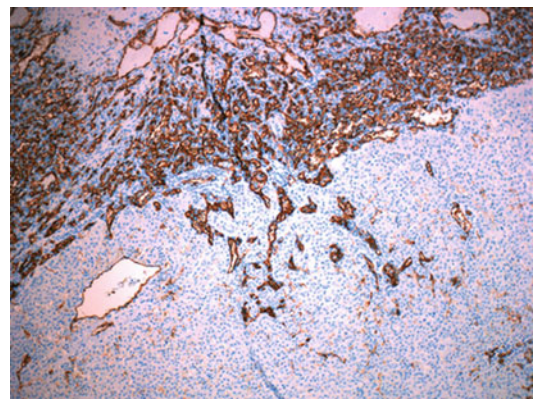

Fig. 12 Hepatic hemangioma. The vascular network of the tumor is focally in continuation with abnormal parenchymal blood vessels (CD34 immunostain)

Secondary Changes of Hepatic Cavernous Hemangioma

Thrombosis

Dilated vascular spaces in cavernous hemangiomas may undergo thrombosis due to blood stasis, mainly in large or giant hemangiomas (Figs. 13, 14, 15, and 16). With time, and similar to other thrombi, granulation tissue sprouts into the thrombotic material and organizes it and in the end leaving a scar tissue with collapse and obliteration of the involved cavity/cavern. In rare instances, thrombi in hemangiomas undergo colliquation and puriform change (abscess formation) or develop into phleboliths (angiomatous phleboliths). Thrombosis of cavities in cavernous hemangioma may be complicated by pulmonary embolism (Dennis 1980).

Infection and Inflammation

Bacteria circulating in peripheral blood can be trapped within the vascular spaces of hepatic hemangioma, particularly in thrombi, and cause infected hemangioma, sometimes with formation of a central large abscess (Figs. 17 and 18; Pinkernelle et al. 2007). However, abscesses in

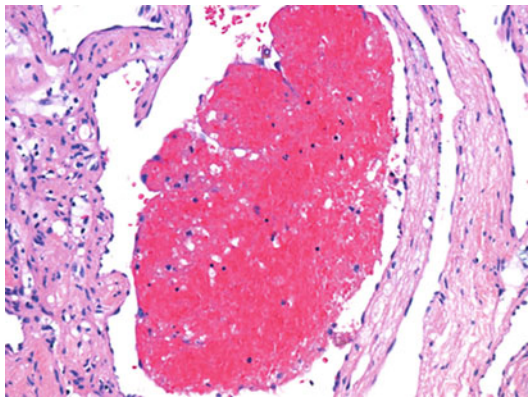

Fig. 13 Thrombosis of hepatic cavernous hemangioma (hematoxylin and eosin stain)

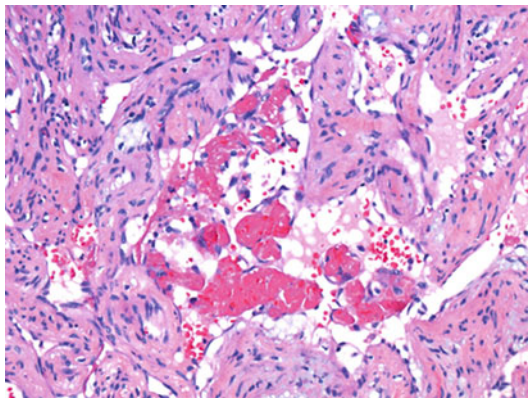

Fig. 14 Thrombosis of hepatic hemangioma. A part of the thrombi are already endothelialized (flat nucleated cells covering the thrombus surface, hematoxylin, and eosin stain)

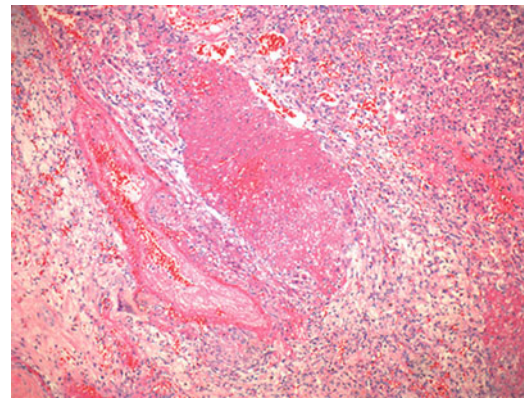

Fig. 15 Hepatic cavernous hemangioma with extensive thrombosis and organization of coagulated blood by granulation tissue (hematoxylin and eosin stain)

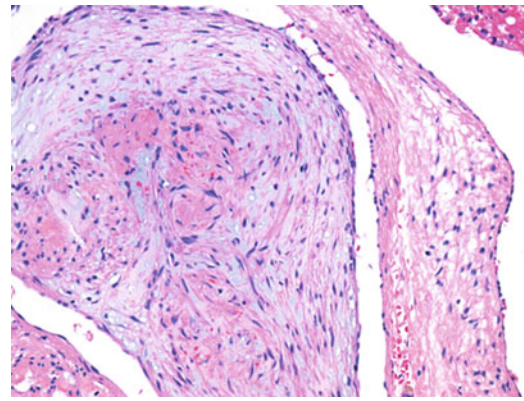

Fig. 16 Hepatic hemangioma. Organization of a thrombus resulting in the formation of an intravascular connective tissue polyp (hematoxylin and eosin stain)

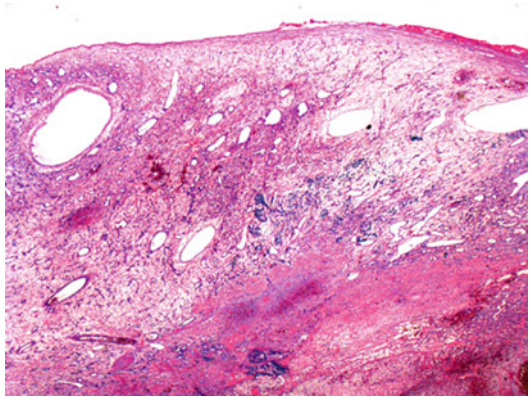

Fig. 17 Infection of hepatic hemangioma. The structure of this hemangioma is effaced by a leukocytic infiltrate, necrosis, and hemorrhage (hematoxylin and eosin stain)

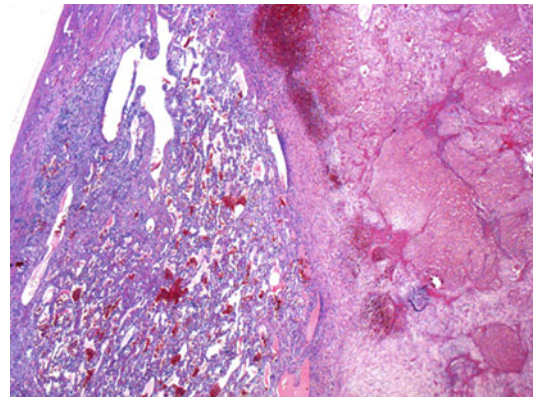

Fig. 19 Hepatic cavernous hemangioma with large hemorrhage (*right half* of figure; hematoxylin and eosin stain)

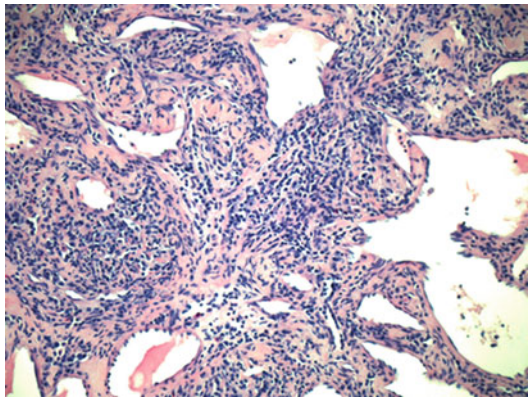

Fig. 18 Inflamed (inflammatory) hepatic hemangioma. The fibrous septa are densely infiltrated with leukocytes (mainly lymphocytes; hematoxylin and eosin stain)

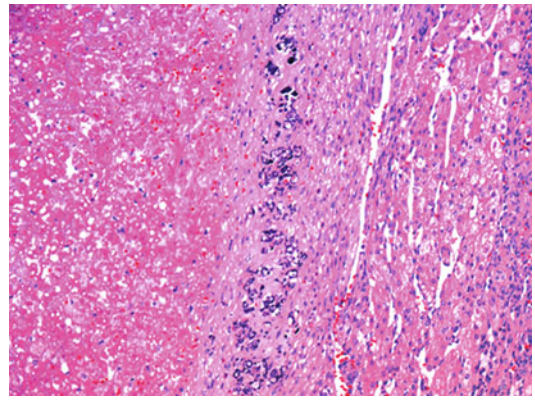

Fig. 20 Hepatic hemangioma with necrosis (*left*) and dystrophic calcifications (*middle*; hematoxylin and eosin stain)

cavernous hemangioma have also found in the absence of obvious bacterial infection (Berliner et al. 1983). As briefly outlined above, hepatic cavernous hemangiomas are sometimes associated with a clinical inflammatory syndrome, but these cases do not necessarily show inflammation of the hemangioma itself (Pol et al. 1998).

Intratumoral Hemorrhage

Intratumoral hemorrhage was seen in giant hepatic hemangioma (Fig. 19; Feldman and Regev 2007). The pathogenesis of hemorrhage in the absence of trauma is not known but may be related to thrombosis and thrombosis-associated damage of the vascular walls.

Calcification

Hepatic hemangiomas, particularly large (giant) lesions and those with thrombosis and necrosis, can undergo extensive calcification (Fig. 20), which is visualized on sonographic, CT, and MR images (Plachta 1962, 1965; Bhatt et al. 1970; Scatarige et al. 1983; Mitsudo et al. 1995; Stoupis et al. 1998; Toshikuni

et al. 2006). In giant hemangiomas, calcifications are large and coarse, usually found in central parts of the tumors where fibrosis has developed (Stoupis et al. 1998).

Marked Cellular Fibrosis in Organizing Lesions

Following thrombosis, fibromatosis-like lesions may develop within the cavernous spaces of hemangiomas (Morita et al. 1970).

Spontaneous Regression

A minority of cavernous hemangiomas undergo slow regression, possibly following thrombosis, organization, and fibrosis. The end result of this process has been termed hyalinized hemangioma (Vilgrain et al. 2000) and may resemble sclerosed hemangioma (Miyaki et al. 2011), which is however thought to be a different lesion and therefore treated in a separate chapter. Exceptionally, cavernous hemangiomas reveal spontaneous rapid regression (Chiu et al. 2005).

Deformation by Hepatic Remodeling

Subcapsular hemangioma can be distorted by liver cirrhosis (de caralt et al. 1999), due to the space-occupying effect of regenerative nodules and the marked rearrangement of hepatic vasculature in cirrhosis.

Atrophic and Hyperplastic Changes in the Adjacent Liver

Hepatic hemangiomas can induce both atrophy and hyperplastic changes in the surrounding liver parenchyma. Localized peritumoral nodular hepatocyte proliferations have been described. In one study, the angiomatous hepatic nodules had dark, congested centers surrounded by a pale yellow to tan periphery. The nodules were well circumscribed and partially encapsulated. The centers consisted of cavernous hemangiomas, while the peripheral nodular area consisted of hepatocyte nodules similar to those of focal nodular hyperplasia (Ndimbie et al. 1990). True FNH has been observed in association with hepatic hemangioma (Mathieu et al. 1989).

Peliosis Hepatis

In rare instances, hepatic hemangioma is synchronously associated with peliosis of the liver (Herrera et al. 1981). The pathogenesis is unclear, but an abnormal circulation in the vicinity of the tumor, with shunting channels and sinusoidal flow overload, may play a role.

Colonizing by Malignant Tumor Cells

Metastases of extrahepatic malignancies may localize to hepatic hemangiomas, which offer an extended vascular system potentially trapping circulating tumor cells. Colonization of hemangioma by metastasizing colorectal cancer cells has been reported (Faccini et al. 2005). Cavernous hemangioma of the liver can be infiltrated in the setting of leukemias, e.g., chronic lymphocytic leukemia (Fig. 21).

Combination with Other Liver Lesions

Cavernous hemangioma of the liver is sometimes associated with other synchronous liver lesions, e.g., hepatic tuberculosis (Astrukov and Baev 1990), focal nodular hyperplasia/FNH (Mathieu et al. 1989; Vilgrain et al. 2003), and combinations of liver adenoma and FNH (Di Carlo et al. 2003; Kondo 2003). Patients with FNH are more likely to have an associated hepatic hemangioma (Vilgrain et al. 2003). In two elderly men, multiple hepatic hemangiomas were synchronously associated with focal regenerative nodules (Ndimbie et al. 1990).

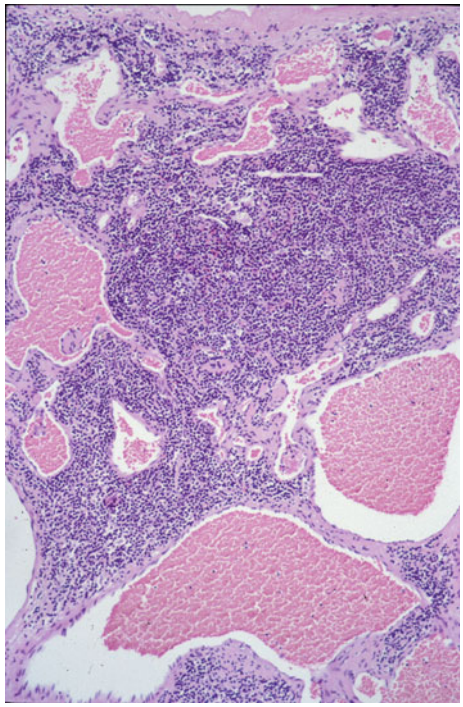

Fig. 21 Hepatic cavernous hemangioma with massive infiltration in chronic lymphocytic leukemia (hematoxylin and eosin stain)

Hemangiomas of the Bile Ducts

Hemangiomatous lesions of the large bile ducts are exceptional findings. Juvenile hepatic hilar hemangioma is a rare cause of extrahepatic biliary tract obstruction (Szavay et al. 2013). A case of angioleiomyoma of the common bile duct was reported (Pönkä et al. 1983). The differential diagnosis of true angiomatous tumors of bile ducts includes intramural collaterals ("varices") in portal vein thrombosis (Denys et al. 1998) and intramural portal cavernoma (Novellas et al. 2004).

Biology of Disease

Many hepatic cavernous hemangiomas seem to arrest their growth after they have reached a certain size (Gandolfi et al. 1991), but other will undergo a slow progressive growth, interrupted by phases of growth arrest (Conter and Longmire 1988; Nghiem et al. 1997). Ultrasonographically, no change over time has been found for many hepatic hemangiomas. Forty-seven patients with 68 hemangiomas were rescanned 1–6 years after the initial study. Eighty-two percent showed an identical appearance on follow-up study. Only 12 lesions (18 %) had an appreciably changed sonographic appearance: three lesions could no longer be found, seven were less obvious, one was larger, and one was smaller (Gibney et al. 1987). Similar results have been obtained in other investigations (Mungovan et al. 1994; Okano et al. 2001). In the study of Nghiem and coworkers (1997), four cavernous hepatic hemangiomas were shown to have doubled to tripled in diameter on follow-up imaging studies done between 34 months and 10.5 years after the initial diagnosis. The mechanisms driving this evolution are not well known. In a study of 180 hepatic hemangiomas, the diameter increased over time in 7.7 % of cases. The tumor volume doubling time of these lesions ranged from 17.3 to 178.1 months (Yeh et al. 2007). Liver hemangiomas may undergo rapid growth following interferon treatment for hepatitis C (Strzelczyk et al. 2004). The growth of hepatic cavernous hemangiomas seems to be influenced by endogenous or exogenous female sex steroids, although significant enlargement occurs only in a minority of cases (Morley et al. 1974; Conter and Longmire 1988; Glinkova et al. 2004; Ozakyol and Kebapci 2006; van Malenstein et al. 2011). Enlargement of hepatic cavernomas has been observed in pregnancy (Koskela 1965; Saegusa et al. 1995; Au and Liu 2005) and in puberty (Baker et al. 1985). On the other hand, a case-control study could not demonstrate an association of liver hemangiomas with menstrual, reproductive, and oral contraception use history (Gemer et al. 2004).

Malignant Transformation of Hepatic Cavernous Hemangioma

The question whether hepatic cavernous hemangioma may transform into malignancy has not been solved. Two reports described hepatic

cavernous hemangioma surrounded by angiosarcoma, suggesting eventual malignant transformation of the former (probably the same patient reported twice; Drouot et al. 1990; Tohme et al. 1991).

Cavernous Hemangiomas of the Liver in Fetuses and Infants

Large or giant liver hemangiomas can present during the fetal stage (Imai et al. 1995; Dreyfus et al. 1996; Gembruch et al. 2002), may show calcifications (Dreyfus et al. 1996), and may result in the Kasabach-Merritt phenomenon (Gembruch et al. 2002), but usually hepatic angiomas in this group are small, i.e., frequently in the range of 3 mm to about 1 cm (Sepulveda et al. 1993), and exhibit different imaging and Doppler features, showing strongly hyperechogenic patterns similar to regressing hemangiomas and only a low flow perfusion (Sepulveda et al. 1993). In newborns and infants, solitary or multiple liver hemangiomas are well known as well (Beal et al. 1974; Somppi et al. 1974; Malamou-Mitsi et al. 1996). They occur more frequently in girls and show clinical manifestations differing as a function of gross tumor morphology and age at presentation. Solitary and large infantile tumors are usually present at birth and may show the clinical triad of hepatomegaly, congestive heart failure, and anemia (triad in a larger series: 3/16 patients; Boon et al. 1996). Conversely, multiple tumors manifest at 1–16 weeks of age and may present with the same triad plus multiple cutaneous lesions (triad in 19/23 patients, Boon et al. 1996; Enjolras and Mulliken 1997). In the series of Boon et al. (1996), no patient showed the Kasabach-Merritt phenomenon (see below). Infantile hepatic hemangiomas have recently been classified into five types on the basis of angiographic findings, i.e., classic appearance with stagnation of contrast and without shunting (type 1), high-flow nodules without direct shunts (type 2), lesions with arteriovenous shunts (type 3), with portovenous shunts (type 4), and with both arteriovenous and portovenous shunts (type 5), indicating the heterogeneity of these tumors with respect to hemodynamic features (Kassarjian et al. 2002). In infants and children, hepatic hemangiomas have a tendency to regress, similar to cutaneous lesions (Berman and Lim 1978; Cohen and Myers 1986). Rupture is a very rare complication of hepatic hemangioma in the pediatric age group. It has been observed as an intrapartum complication (Krasuski et al. 2001).

Etiology and Pathogenesis

Endothelial Cells and Other Cells in Cavernous Hemangioma

Hemangiomas of the liver chiefly consist of endothelial cells, but they also contain mesenchymal cells and cells associated with the vascular channels. Whether the fibroblastoid cells interspersed between the endothelial channels are members of a neoplastic lineage or are nonneoplastic bystander cells is not yet known. Endothelial cells of hepatic cavernous hemangiomas are different in several respects from other endothelia. Morphologically, they are often spindle shaped, and their arrangement on the vascular surface resembles that of arteries, with formation of parallel streams. Endothelial cells derived from cavernous hemangioma showed overexpression of alphavbeta3 (Zhang et al. 2006) and of Derlin-1, a rhomboid pseudoprotease involved in retrotranslocation of misfolded proteins which inhibits ER expansion in endothelial cells (Hu et al. 2006; Greenblatt et al. 2011).

In other organs, hemangiomas have also been shown to be formed by cells expressing high levels of alphavbeta3 integrins and lacking acetylated LDL uptake (Aurrand-Lions et al. 2004). Cultured endothelial cells from human hepatic cavernous hemangiomas released more vascular endothelial growth factor A, produced significantly more pro-matrix metalloproteinase 2 and activated matrix metalloproteinase 2, and exhibited higher procoagulant and fibrinolytic activities compared with liver sinusoidal endothelial cells (Zhang et al. 2006).

Cytokines, Chemokines, and Growth Factors

Interleukin-17, which pays a role in angiogenesis, is significantly upregulated in the tissues of hepatic hemangiomas and was proposed to mediate hemangioma angiogenesis in a IL-6-STAT3-dependent manner (Wang et al. 2012).

Sclerosed Angioma and Sclerosed Cavernous Hemangioma of the Liver

Introduction

Sclerosed hemangioma of the liver (synonyms: hyalinized hemangioma, hemangioma with fibrosclerotic changes, thrombosed hemangioma) is a variant of mostly cavernous hemangioma of the liver characterized by a significant increase of cellular or hyalinized fibrous tissue obliterating the vascular channels. The first report of hepatic sclerosed hemangioma was documented in 1983, based on five patients with an unusual lesion in the liver which had a hyalinized fibrotic capsule with a completely necrotic core, i.e., a type of solitary necrotic nodule resulting from regression of hemangioma (Shepherd and Lee 1983). A similar case of post-hemangioma necrotic nodule was reported 2 years later (Berry 1985). An alternative term for sclerosed hemangioma, as used by Goldman (1987), is sclerosing hemangioma (Yamashita et al. 2000), formally describing two phases of an ongoing process of fibrous tissue development.

Most hepatic cavernous hemangiomas remain stable on follow-up imaging (Gibney et al. 1987; Gandolfi et al. 1991; Okano et al. 2001), with relatively few tumors showing enlargement over time (Mungovan et al. 1994; Nghiem et al. 1997), but there is a fraction of these tumors which may develop thrombosis (Dennis 1980; Berliner et al. 1983; Ros et al. 1987) and/or undergo inflammation followed by a fibroblastic reaction, i.e., sclerosed hemangioma (Goldman 1987). Sclerosis is, similar to situations in other organs and tissues, a late stage of fibrosis with predominance of extracellular matrix over fibroblastoid cells, and hyalinosis is an even later phase of this process, characterized by marked hypocellularity and hyaline change of the collagenous matrix. Based on the cellular and matrix composition, the lesions are classified as sclerosing hemangioma, sclerosed hemangioma, and hyalinized hemangioma.

Epidemiology

Sclerosed hemangioma of the liver is a rare lesion. Of 675 hemangiomas accessioned from 1970 to 1999, only 20 cases of sclerosed hemangiomas were identified from the files of the Armed Forces Institute of Pathology (AFIP) (Makhlouf and Ishak 2002). In a review of 11 cases, age at diagnosis ranged from 41 to 72 years; seven patients were female and one was male, and in two cases, the data were not available (Mori et al. 2008).

Clinical and Imaging Features

Most patients with sclerosed hepatic hemangiomas are asymptomatic, the lesions being detected in the course of abdominal imaging performed due to other reasons. The imaging appearance of sclerosed hemangioma is that of so-called atypical hemangioma of the liver. The features of these lesions have been presented in detail and reviewed (Vilgrain et al. 2000; Jang et al. 2003; Mori et al. 2008; Jin 2010). Typical alteration in atypical hepatic hemangioma includes the bright-dot sign, atypical low signal on T2-weighted MR images, a heterogeneous appearance with central scar, the presence of calcification, central cystic degeneration, and fluid-fluid levels. The lesions may be associated with arterial-portal shunt, capsular retraction, and surrounding nodular hyperplasia of parenchyma. Suggestive features of sclerosed hemangioma comprise geographic outline of hypodense masses, capsular retraction, decrease in size over time, and loss of previously seen regions of enhancement, presence of transient hepatic attenuation difference (THAD), rim enhancement, and nodular regions of intense enhancement as seen in ordinary hemangiomas (Shim et al. 1995; Vilgrain

et al. 2000; Yamashita et al. 2000; Aibe et al. 2001; Doyle et al. 2007; Mori et al. 2008). Rim enhancement has been described in part of the reports (Takayasu et al. 1986; Haratake et al. 1992; Yamashita et al. 2000). At imaging, the size of sclerosed hemangiomas varies considerably. In one study of ten cases, the diameter of the lesions ranged from 1.4 to 7.7 cm (mean, 3.7 cm) (Doyle et al. 2007). MR reveals a mass with low signal intensity in T1-weighted images and high signal intensity and focal low signal in T2-weighted images (Mori et al. 2008; Park et al. 2009). Sclerosed hepatic hemangioma may show a high apparent diffusion coefficient (ADC), presenting as a heterogeneously hyperintense mass in fat-suppressed T2-weighted images (Hida et al. 2010). Based on the imaging features, sclerosed hepatic hemangioma may be confounded with other tumors, particularly intrahepatic cholangiocarcinoma (Park et al. 2009), hepatocellular carcinoma (Mathieu et al. 1994; Cheng et al. 1995; Lee et al. 2005), and hepatic metastasis (Yamashita et al. 2000). The presence of a ring-like enhancement in enhanced CT in up to 60 % of the cases may be confusing, because this ring is a typical sign of adenocarcinomas in the liver, similar to the hypoechoic ring in some cavernous hemangiomas resembling malignant tumor (Choi et al. 2009).

Pathology

Macroscopy

Sclerosed hemangiomas are sharply delineated, firm masses with a whitish cut surface. In a study of 18 cavernous hepatic hemangiomas with fibrosclerotic changes, all sclerosed hemangiomas and the majority of sclerosing hemangiomas were solitary, sclerosing lesions were larger than sclerosed lesions (mean 6 $\pm$ 4.73 cm vs. 3 $\pm$ 2.2 cm diameter), and sclerosing tumors occurred much more frequently in the right lobe than sclerosed tumors (Makhlouf and Ishak 2002). The peripheral contour is often irregular, with spikes probably representing obliterated feeding vessels with perivascular fibrosis. The cut surface is usually homogeneous, but by use of a magnification glass, one may note a granular structure caused by scarred foci of granulation tissue adjacent to collapsed and obliterated tumor vessels. Brown-to-red areas correspond to old hemorrhage or regions of thrombosis with accumulation of iron pigment. Mainly in larger tumors, central necrosis with or without calcification and central cavities containing clear, turbid, or hemorrhagic fluid may occur. Gross and sometimes sickle-shaped calcifications of whitish or cream-white color may be seen in the fibrous capsule of the lesions. In the hyalinized end stage of the lesions, the tumors are hard, and the cut surface has a homogeneous, porcelain-like aspect, resisting the penetration even of a sharp-tipped probe.

Histopathology

Histologically, three major patterns of sclerosis can be distinguished (Table 3; Fig. 22).

Table 3 Histological patterns of sclerosed hepatic hemangioma

Pattern 1: Central regression with or without cyst, peripheral fibrosis
Pattern 2: Internal fibrosclerosis with or without thrombosed vessels
Pattern 3: Complete fibrosclerosis
Pattern 4: Hyalinosis

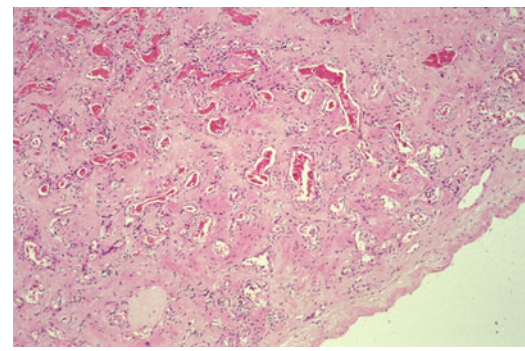

Fig. 22 Sclerosed hepatic hemangioma. Abnormal vascular channels are separated from each other by a fibrosclerosed connective tissue (hematoxylin and eosin stain)

Pattern 1 is characterized by fibrous tissue surrounding a core of regressed and eventually necrotic hemangioma, with or without a central cyst; pattern 2 shows internal fibrosclerosis in a geographic pattern, with or without thrombosed vessels and granulation tissue; pattern 3 is complete fibrosclerosis; and pattern 4 is hyalinosis. The peripheral rim of fibrous tissue in pattern 1 corresponds to a halo surrounding a central isoechoic mass in sonography (Takayasu et al. 1986). These patterns, together with the structure of the vascular channels, can be integrated into three major types of presentation, viz., sclerosing, sclerosed, and hyalinized hemangiomas.

Sclerosing cavernous hemangiomas are "active" lesions which are composed of thin-walled and often dilated vessels with a single layer of endothelial cells, probably representing a vascular growth phase with signs of proliferation. The fibrotic component varies from scanty (fibrillar) to abundant (sclerotic and eventually hyaline), with the patterns 2, 3, or 4. The vascular spaces may contain thrombi, with or without signs of organization by granulation tissue. Interestingly, the sclerosed matrix contains elastic fibers (mild to moderate) in most of the cases (Makhlouf and Ishak 2002). Close to 30 % of these lesions show mineralizations/calcifications, sometimes with formation of psammomatous bodies, and the majority of the tumors display hemorrhages and hemosiderin deposits.

Sclerosed cavernous hemangiomas are "silent" or "burnt-out" lesions which are characterized by abundant collagen and elastin deposition with the patterns 3 and 4, with extensive collapse, atrophy, and obliteration of the vascular bed and with hyalinization being complete in about 25 % of the cases (Makhlouf and Ishak 2002). Numerous thick-walled blood vessels are present in most of these lesions. The sclerotic tissue may contain mast cells, as seen in other hemangiomas (Hagiwara et al. 1999; Makhlouf and Ishak 2002; Tan et al. 2004; Sun et al. 2007). In a systematic study of 18 cases of sclerosing and sclerosed hepatic hemangiomas, the density of mast cells was higher in sclerosing lesions than in sclerosed lesions. The number of mast cells was significantly correlated with vascular proliferation and inversely related to the degree of fibrosis (Makhlouf and Ishak 2002). One variant of hepatic hemangioma with sclerosing changes is characterized by a peculiar type of pericapillary smooth muscle cell proliferation (Choi et al. 2008). This lesion is further discussed in a separate paragraph.

Immunohistochemistry

The basement membranes of the vascular channels are reactive for type IV collagen, beta chain of laminin, and perlecan, as in other hemangiomas (Tan et al. 2000). Type IV collagen and laminin were more uniformly positive in sclerosing ("active") hemangiomas than in sclerosed hemangiomas, and endothelial markers (FVIII-related antigen, CD 31 abd CD34) were more diffusely positive in sclerosing hemangiomas than in sclerosed hemangiomas, reflecting vascular proliferation and active matrix remodeling in sclerosing tumors, the latter representing lesions in an earlier phase of evolution.

Hyalinized Hemangioma of the Liver

Fibrosclerosis may end up with hyaline change of the tumor's connective tissue (Haratake et al. 1992, 1995; Cheng et al. 1995; Hosokawa et al. 2005). Such lesions have been termed hyalinized hemangioma of the liver. Hyalinized hemangioma of the liver may represent a highly hypocellular variant or end stage of sclerosed hepatic hemangioma. Haratake and coworkers (1992) specified the morphology of these lesions in detail. They diagnosed a hepatic tumor measuring 2.6 × 1.8 cm in a 64-year-old woman, located in segment 8. On CT images, the lesion was of low density and was circularly enhanced with contrast medium. A late post-contrast scan showed that this ring enhancement pattern remained unchanged. The resection specimen revealed a circumscribed and firm, evenly whitish tumor. Histologically, the tumor was composed of a dense collagenous tissue with marked hyalinization and scattered small blood vessels, sclerosed vessels being in evidence in the

tumor's center. Around these sclerotic vessels, numerous concentric elastic fibers were noted. This histologic pattern resembled somewhat to part of cases described as solitary necrotic nodules.

Differential Diagnosis

On CT images, sclerosed hepatic hemangiomas may be confounded with stroma-rich liver metastases of gastrointestinal tract adenocarcinomas (Yamada et al. 2012).

Pathogenesis

One mechanism that may operate in sclerosis of hepatic hemangiomas is thrombosis of vascular spaces followed by organization by a granulation tissue, which in turn will transform into connective tissue. The pathogenic role of secondary involutive changes is supported by the observation of a significant "spontaneous" regression of a cavernous hepatic hemangioma to a sclerosed hemangioma over 12 years (Miyaki et al. 2011).

Liver Hemangiomas with a Myoid Component

Leiomyomatous Hemangioma of the Liver

This is a very rare lesion which had first been described based on 74-year-old male patient who had died of cardiac arrest. Autopsy revealed a normal-sized liver with several white, solid tumors on the cut surface of both lobes. The nodules ranged in diameter from 0.3 to 0.6 cm and had a firm texture. Histologically, the tumors were well circumscribed and consisted of interlacing bundles of spindle-shaped cells with a smooth muscle cell phenotype. Some of the tumors appeared to arise from smooth muscle of veins, and the lesions were associated with cavernous hepatic hemangioma (Key and Rao 1986).

Sclerosing Liver Hemangioma with Pericapillary Smooth Muscle Proliferation

As discussed in the respective chapter, sclerosis of liver hemangiomas is a rare event (Makhlouf and Ishak 2002), and there are only a few reports on imaging findings of this lesion which may mimic metastasis or hepatocellular carcinoma.

Sclerosing hepatic hemangioma may develop a myoid component. In a 63-year-old man, CT and MRI revealed a 14 cm-sized ill-demarcated hypoattenuating mass arising from the right liver lobe, containing multifocal low-attenuation areas and multiple small calcifications. On dynamic CT, an enlarged and tortuous right hepatic artery, prominent intratumoral vessels, and multifocal patchy enhancement were seen during the arterial phase. The right lobectomy specimen showed an ill-demarcated, solid, and myxoid mass of 15.5 cm diameter with multiple blood-containing areas and a yellowish portion 0f 4.5 cm size. Histology showed sclerosing and hyalinized hemangioma, with the yellowish focus being a fully hyalinized area. Interestingly, the vascular channels showed a marked, SMA-positive perivascular smooth muscle proliferation, in the form of bundles and nodules of myocytes surrounding the hemangioma vessels (Choi et al. 2008).

Small Vessel Hepatic Hemangioma of the Capillary Type (Capillary Hemangioma of the Liver)

ICD-O code 9131/0

Capillary Hemangioma of the Liver in Adults

Capillary hepatic hemangioma and mixed capillary-cavernous hemangioma of the liver are very uncommon primary tumors of the liver in adults (Fig. 23; Ascari and Lusvarghi 1963; Astrukov and Baev 1990; Matsuo and Uchida 1990; Kojima et al. 2000; Noda et al. 2005;

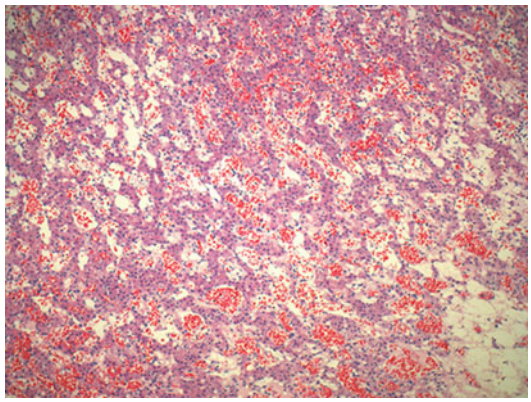

Fig. 23 Capillary hemangioma of the liver (hematoxylin and eosin stain)

Jhuang et al. 2011; Unal et al. 2011), and its entity has been discussed in the context of other hemangiomas (Scialpi et al. 2010).

In a 55-year-old male patient with a hepatic tumor, ultrasonography revealed a hypoechoic mass with a peripheral hypoechoic ring, the latter being characteristic of hepatocellular carcinoma. CT showed an enhancement pattern different from that of hepatocarcinoma or cavernous hemangioma. The resection specimen displayed a tumor measuring 22 × 20 mm, of reddish-brown color, with a clear boundary and solid components usually not encountered in cavernous hemangioma. Histology showed capillary hemangioma characterized by a proliferation of capillary-type blood vessels with a small diameter of 20 μm (Noda et al. 2005). In two other reported cases of hepatic capillary hemangioma in adults, the ultrasonographic patterns were either mosaic, hyperechoic (Kojima et al. 2000), or mixed (Matsuo and Uchida 1990). Capillary hepatic hemangioma was diagnosed in a 71-year-old female patient, in whom abdominal sonography revealed a 2 cm nodular lesion and fatty liver. CT showed a hypervascular tumor. It was decided to observe lesion which increased in size to 3 cm within 2 years. Resection showed a capillary hemangioma associated with steatohepatitis (Jhuang et al. 2011). The clinical presentation of hepatic capillary hemangiomas, which are sometimes compact and almost solid masses with almost slit-like or even collapsed vascular spaces ("compressed sponges"), may mimic that of hepatocellular carcinoma. In one patient, liver transplantation was performed for such a hemangioma, revealing atypical imaging features and resembling hepatocarcinoma (Unal et al. 2011).

Capillary Hemangioma of the Liver in Infancy and Childhood

In the pediatric age group, capillary hemangioma of the liver was reported to be a manifestation of diffuse neonatal hemangiomatosis (Satoh et al. 1994) or to accompany Kasabach-Merritt syndrome (Akiyoshi et al. 2000). In Rubinstein-Taybi syndrome, large areas of cutaneous capillary hemangioma may be associated with hepatic hemangioma (Sahiner et al. 2009). It has been shown that extracutaneous infantile hemangioma, including tumors in the liver, is GLUT1 positive (Drut and Drut 2004). In fact, GLUT1 endothelial reactivity distinguishes hepatic infantile hemangioma from congenital hepatic vascular malformation with associated capillary proliferation (Mo et al. 2004).

Differential Diagnosis

Hepatic hemangiomas, also those with a contribution of small vessels, may be difficult to distinguish from hepatocellular carcinoma at sonography and imaging. If initial US examinations of a cirrhotic liver depicts a hepatic hemangioma, confirmatory findings of imaging studies are necessary since 50 % of hemangiomas found in one study were hyperechogenic HCCs (Caturelli et al. 2001). Hepatic infantile hemangioma is GLUT1 positive and therefore distinguished from GLUT1-negative hepatic vascular malformation with capillary proliferation (HVMCP).

Lobular Capillary Hemangioma of the Hepatobiliary Tract

Introduction

Lobular capillary hemangioma (LCH; current synonym: pyogenic granuloma) is a common, usually solitary benign vascular tumor, mainly occurring in the skin or mucous membranes. This lesion group was first described by in 1897 under the French term "botryomycose" (botryomycosis; Poncet and Dor 1897), the word meaning "grape-like fungus." Later, numerous synonyms have been created, most of them no longer in use (telangiectatic granuloma, botryomycoma, botryomycosis, pyogenic granuloma, granuloma pediculatum, eruptive angioma, proliferating angioma). The original view was that the lesion now termed LCH was a reactive growth or rather overgrowth of granulation tissue in the context of disordered wound healing, i.e., an outgrowth of fibrovascular tissue through an epidermal or mucosal gap failing to be reepithelialized on time. Deletion (21)(q21.2q22.12) was the sole clonal cytogenetic abnormality found in LCH of the nasal cavity (Truss et al. 2006).

In the skin, superficial lesions are much more frequent than subcutaneous lesions (reviews: Patrice et al. 1991; Lin and Janniger 2004; Jafarzadeh et al. 2006; Fortna and Junkins-Hopkins 2007; Salum et al. 2008; Godfraind et al. 2013). LCHs of the skin are equally prevalent in male and female patients. The peak incidence of LCH of the skin was found in the second decade of life, and the most common cutaneous sites were the trunk, upper extremities, and head, and the mucosal lesions were common on the lips, gingiva, and tongue (Harris et al. 2000). LCH may enlarge gradually or can evolve rapidly over a few weeks. They are known to recur (recurrent pyogenic granulomas; Eng and Hong 1993). Now regarded as a neoplastic process, the etiology of LCH is unknown. Hormonal factors may play a role, as oral LCHs are known to occur more frequently during pregnancy (so-called granuloma gravidarum or pregnancy tumor; epulis gravidarum; Sills et al. 1996; Demir et al. 2004; Rader et al. 2008). However, LCH cells do not express estrogen or progesterone receptors (Nichols et al. 1992). LCH can present rarely in a disseminated form, usually associated with other disorders. These disseminated LCH may develop suddenly in adults (Gönül et al. 2005). Involvement of visceral organs is rare but has been observed in the esophagus (Van Eeden et al. 2004), the stomach (Kusakabe et al. 2005), the duodenum (Park et al. 2009), the small intestine (Yao et al. 1995; Van Eeden et al. 2004; Kuga et al. 2009; sometimes causing obstruction and intussusception; Stojsic et al. 2008), and the colon (Carmen Gonzalez-Vela et al. 2005). LCH may occur as an intravenous lesion (intravenous pyogenic granuloma; Ghekiere et al. 2005) or develop in arteriovenous malformations (Hung et al. 2004).

Macroscopically, LCHs arising from skin or mucous membranes are flat to polypoid vegetations of meat-red to dark bluish-red color, easily bruising owing to the fragility of the capillary vessels. The typical aspect has led to the term "proud flesh" (Caro luxurians in Latin; exuberant flesh), describing the view that tissue overgrowth had ensued. Histologically, the tumorous lesion shows a lobular structure and consists of proliferating capillary-type vessels associated with small feeding arteries, dilated vascular channels with or without perivascular hemorrhage, and a fibroblastic or myofibroblastic stroma rich in glycosaminoglycans, containing macrophages and sometimes numerous neutrophils, the latter mostly in case of infection of superficial lesions (Fig. 24). The tissue may home hematogenic progenitor cells leading to extramedullary hematopoiesis (Vega Harring et al. 2004). Immunohistochemically, endothelial cells of LCH are reactive for factor VIII-associated antigen, CD31, and CD34 but, in contrast to other hemangiomas, not for glucose transporter-1 (GLUT-1) protein (Stojsic et al. 2008; Browning et al. 2009).

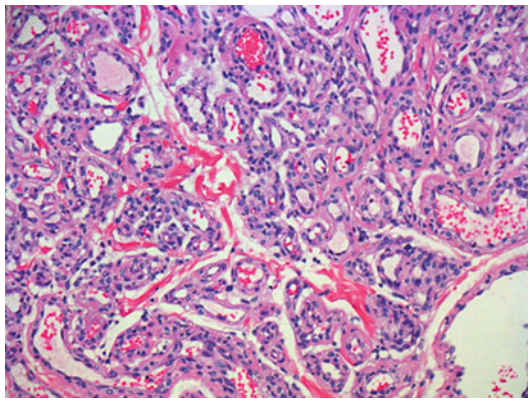

Fig. 24 Lobular hemangioma of the liver (hematoxylin and eosin stain)

Lobular Capillary Hemangioma of the Liver

Hepatic lobular hemangioma was described in 35-year-old female patient presenting with a large asymptomatic hepatic mass discovered during abdominal ultrasound for evaluation of gross hematuria (Abaalkhail et al. 2009). Sonography revealed a distinct 4.6 cm mass in the right liver lobe, with significant intralesional vascular flow on Doppler evaluation. On CT scans, the mass measured 5 cm in diameter, and MRI revealed a vascular lesion with a central scar. A later MRI showed unusual signal intensity in T2-weighted imaging and exhibited prominent vascularity within the lesion.

The resection specimen showed a well-circumscribed tan-brown tumor measuring 4 cm in diameter, having a 0.3 cm central scar on the cut surface. Histologically, the mass was composed of a lobular proliferation of vascular channels, lined by plump, CD31-, and CD34-positive endothelial cells without any atypia and without mitotic activity. In certain areas, the channels were compressed, imparting a solid appearance. Multiple thick-walled veins were present at the periphery and within the center of the mass. There was a focal extramedullary hematopoiesis.

Lobular Capillary Hemangioma of the Biliary Tract

A 69-year-old female patient with a history of cholecystectomy and side-to-side choledochoduodenostomy and recurrent attacks of cholangitis presented with right upper quadrant pain. Endoscopy of the distal common bile duct revealed a semipedunculated, smooth polypoid lesion 5 mm in diameter, hyperemic, and dark red. The lesion was removed by snare polypectomy and showed the histology of ulcerated pyogenic granuloma with a dense network of CD31-positive capillary vessels (Lee et al. 2007).

Anastomosing Hemangioma of the Liver

Introduction

Anastomosing hemangioma (ASH) is a rare variant of capillary hemangioma predominantly found in the genitourinary tract of adult patients, specifically the kidney, but other organs are also involved, including the adrenal gland, ovary, and gastrointestinal tract (Montgomery and Epstein 2009; Kryvenko et al. 2011; Ross et al. 2012; Lin et al. 2013; Wetherell et al. 2013; Zhao et al. 2013). ASH is characterized by a distinct anastomosing sinusoidal network of capillary-sized vessels, strikingly reminiscent of the splenic red pulp, sometimes mimicking angiosarcoma. Within the vascular channels, endothelial cells often exhibit hobnail morphology, but most of the cells look bland, with immunoreactivity for CD31 and CD34. Mitoses are absent or rare. A part of the tumor cells contain eosinophilic intracytoplasmic globules. Between the endothelial-lined channels, non-endothelial supporting cells are found. The growth pattern is typically lobulated, with intervening hypocellular and even hyaline areas. Extramedullary hematopoiesis was observed in part of the tumors (Kryvenko et al. 2011). Macroscopically, the lesions were described as well-demarcated,

spongy nodules of mahogany brown color (Kryvenko et al. 2011). ASH can present as an intravenous hemangioma with closely packed, fenestrated vascular channels. The course is benign, although some tumors can extend into adjacent connective or adipose tissue.

Anastomosing Hemangioma of the Liver

ASH is rarely observed in the gastrointestinal tract, including the liver (Lin et al. 2013). Similar to their genitourinary counterparts, the tumors were of gray-brown spongy appearance. Histologically, the lesions had a loosely lobular architecture and consisted of a pulp-like vascular tissue with the typically anastomosing pattern of capillary-sized sinusoidal blood vessels with intervening supporting cells. Endothelial cells, in part of the hobnail type, were positive for CD31 and CD34. Two thirds of the lesions revealed vascular thrombi. There were no recurrences or metastases.

References

Abaalkhail F, Castonguay M, Driman DK, Parfitt J, Marotta P (2009) Lobular capillary hemangioma of the liver. Hepatobiliary Pancreat Dis Int 8:323–325

About I, Capdeville J, Bernard P, Lazorthes F, Boneu B (1994) Unresectable giant hepatic hemangioma and Kasabach-Merritt syndrome (in French). Rev Med Interne 15:846–850

Adam YG, Huyos AG, Fortner JG (1970) Giant hemangiomas of the liver. Ann Surg 172:239–245

Admiraal GC, Van Schie A, Van Meyel JJ, Vasmel WL (2004) Giant liver hemangioma in three sisters. J Gastroenterol Hepatol 19:344–345

Aibe H, Hondo H, Kuroiwa T, Yoshimitsu K, Irie H, Tajima T, Shinozaki K, Asayama Y et al (2001) Sclerosed hemangioma of the liver. Abdom Imaging 26:496–499

Akiyoshi K, Mizote H, Tanaka Y, Nakagawa M (2000) Capillary hemangioma of the liver with Kasabach-Merritt syndrome in a neonate: report of a case. Surg Today 30:86–88

Ang M, Tanoue R (1972) Giant hemangioma of the liver. Hawaii Med J 31:266–268

Ascari E, Lusvraghi E (1963) Transitory lineal thrombosis caused by capillary hemangioma of the left lobe of the liver. Semeiological study and splenoportography (in Italian). Miverva Med 54:1352–1355

Aslan A, Meyer Zu Vilsendorf A, Kleine M, Bredt M, Bekats H (2009) Adult Kasabach-Merritt syndrome due to hepatic giant hemangioma. Case Rep Gastroenterol 3:306–312

Astrukov E, Baev S (1990) Combined capillary with cavernous hemangioma and tuberculosis of the liver (in - Bulgarian). Khirurgiia (Sofia) 43:84

Au WY, Liu CL (2005) Growth of giant hepatic hemangioma after triplet pregnancy. J Hepatol 42:781

Aurrand-Lions M, Johnson-Leger C, Pepper MS, Imhof BA (2004) Haemangiomas are formed by cells expressing high levels of avb3 integrin and lacking acetylated LDL uptake. J Pathol 203:700–709

Avdei LV, Vas'kovskii GD (1975) Cavernous hemangioma of the accessory lobe of the liver (in Russian). Khirurgiia (Mosk) (10):137–139

Baer HU, Dennison AR, Mouton W, Stain SC, Zimmermann A, Blumgart LH (1992) Enucleation of giant hemangiomas of the liver. Technical and pathologic aspects of a neglected procedure. Ann Surg 216:673–676

Baker ER, Manders E, Whitney CW (1985) Growth of cavernous hemangioma with puberty. Clin Pediatr (Phila) 24:596–598

Banton KL, D'Cunha J, Laudi N, Flynn C, Hammerschmidt D, Humar A, Sielaff T (2005) Postoperative severe microangiopathic haemolytic anemia associated with a giant hepatic cavernous hemangioma. J Gastrointest Surg 9:679–685

Beal W, Soin JS, Burdine JA (1974) Hepatic cavernous hemangioma presenting as an "avascular mass" in a newborn. J Nucl Med 15:902–903

Behar A, Moran E, Izak G (1963) Acquired hypofibrinogenemia associated with a giant cavernous hemangioma of the liver. Am J Clin Pathol 40:78–82

Berliner L, el Ferzli G, Gianvito L, Worth MH, Lowry J, Redmond P, Silich R (1983) Giant cavernous hemangioma of the liver complicated by abscess and thrombosis. Am J Gastroenterol 78:835–840

Berman B, Lim HW (1978) Concurrent cutaneous and hepatic hemangioma in infancy. Report of a case and review of the literature. J Dermatol Surg Oncol 4:869–873

Berry CL (1985) Solitary "necrotic nodule" of the liver: a probable pathogenesis. J Clin Pathol 38:1278–1280

Berzigotti A, Frigato M, Manfredini E, Pierpaoli L, Mulè R, Tiani C, Zappoli P, Magalotti D et al (2011) Liver hemangioma and vascular diseases in patients with systemic lupus erythematosus. Wordl J Gastroenterol 17:4503–4508

Bhatnagar A, Pathania OP, Champakam NS (1987) Giant pedunculated haemangioma of the liver. Indian J Gastroenterol 6:51–52

Bhatt J, Udawat JP, Sharma ML (1970) Calcified cavernous hemangioma of the liver. A case report. Int Surg 54:24–27

Billio A, Pescosta N, Rosanelli C, Zanon GF, Gamba PG, Savastano S, Coser P (2001) Treatment of Kasabach-Merritt syndrome by embolisation of a giant liver hemangioma. Am J Hematol 66:140–141

Bioulac-Sage P, Laumonier H, Laurent C, Blanc JF, Balabaud C (2008) Benign and malignant vascular tumors of the liver in adults. Semin Liver Dis 28:302–314

Blachar A, Federle MP, Sosna J (2009) Liver lesions with hepatic capsular retraction. Semin Ultrasound CT MR 30:426–435

Boon LM, Enjolaras O, Mulliken JB (1996) Congenital hemangioma: evidence of accelerated involution. J Pediatr 128:329–335

Brancatelli G, Federle MP, Blachar A, Grazioli L (2001) Hemangioma in the cirrhotic liver: diagnosis and natural history. Radiology 219:69–74

Brouwers MA, Peeters PM, de Jong KP, Haagsma EB, Klompmaker IJ, Bijleveld CM, Zwaveling JH, Slooff MJ (1997) Surgical treatment of giant haemangioma of the liver. Br J Surg 84:314–316

Browning JC, Eldin KW, Kozakewich HP, Mulliken JB, Bree AF (2009) Congenital disseminated pyogenic granuloma. Pediatr Dermatol 26:323–327

Cappellani A, Zanghi A, Di Vita M, Zanghi G, Tomarchio G, Petrillo G (2000) Spontaneous rupture of a giant hemangioma of the liver. Ann Ital Chir 71:379–383

Carmen Gonzalez-Vela M, Fernando Val-Bernal J, Francisca Garijo M, Garcia-Suarez C (2005) Pyogenic granuloma of the sigmoid colon. Ann Diagn Pathol 9:106–109

Caseiro-Alves F, Brito J, Araujo AE, Belo-Soares P, Rodrigues H, Cipriano A, Siusa D, Mathieu D (2007) Liver haemangioma: common and uncommon findings and how to improve the differential diagnosis. Eur Radiol 17:1544–1554

Caturelli E, Rapaccini GL, Sabelli C, De Simone F, Fabiano A, Romagna-Manoja E, Anti M, Fedeli G (1986) Ultrasound-guided fine-needle aspiration biopsy in the diagnosis of hepatic hemangioma. Liver 6:326–330

Caturelli E, Pompili M, Bartolucci F, Siena DA, Sperandeo M, Andriulli A, Bisceglia M (2001) Hemangioma-like lesions in chronic liver disease: diagnostic evaluation in patients. Radiology 220:337–342

Cha EY, Kim KW, Choi YJ, Song JS, Cho KJ, Lee MG (2008) Multicystic cavernous hemangioma of the liver: ultrasonography, CT, MR appearances and pathological correlation. Br J Radiol 81:e37–e39

Chan WH, Huang HJ, Chen HC, Lee PC, Chan CP, Chang HC, Chen YL (2010) Traumatic rupture of two giant hepatic hemangiomas – a case report. J Trauma 69:476

Cheng HC, Tsai SH, Chiang JH, Chang CY (1995) Hyalinized liver hemangioma mimicking malignant tumor at MR imaging. AJR Am J Roentgenol 165:1016–1017

Chin WS (1984) Computed tomography of hepatic cavernous hemangioma. Singap Med J 25:168–172

Chiu YF, Chen JH, Chen YF, Ho YJ, Tzeng IH (2005) Spontaneous rapid regression of a giant hemangioma mimicking a liver abscess. AJR Am J Roentgenol 185:815–816

Choi YJ, Kim KW, Cha EY, Song JS, Yu E, Lee MG (2008) Case report. Sclerosing liver haemangioma with pericapillary smooth muscle proliferation: atypical CT and MR findings with pathological correlation. Br J Radiol 81:e162–e165

Choi JC, Baek YH, Jeong JS, Lee SW, Han SY, Cho JH (2009) Discrete hypoechoic ring in hepatic cavernous hemangioma resembling a malignant tumor: correlation with histologic features. Gut Liver 3:226–230

Cohen RC, Myers VA (1986) Diagnosis and management of massive hepatic hemangiomas in childhood. J Pediatr Surg 21:6–9

Concejero AM, Chen CL, Chen TY, Eng HL, Kuo FY (2009) Giant cavernous hemangioma of the liver with coagulopathy: adult Kasabach-Merritt syndrome. Surgery 145:245–247

Conter RL, Longmire WP (1988) Recurrent hepatic hemangiomas. Possible association with estrogen therapy. Ann Surg 207:115–119

Cortes-Blanco A, Martinez-Lazaro R (2000) Bile duct stenosis seemingly caused by a giant pedunculated hemangioma with hypogastric growth. Clin Nucl Med 25:299–300

Coumbaras M, Wendum D, Monnier-Cholley L, Dahan H, Tubiana JM, Arrivé L (2002) CT and MR imaging features of pathologically proven atypical giant hemangiomas of the liver. AJR Am J Roentgenol 179:1457–1463

Cronan JJ, Esparza AR, Dorfman GS, Ridlen MS, Paolella LP (1988) Cavernous hemangioma of the liver: role of percutaneous biopsy. Radiology 166:135–138

Danet IM, Semelka RC, Braga L, Armao D, Woosley JT (2003) Giant hemangioma of the liver: MR imaging characteristics in 24 patients. Magn Res Imag 21:95–101

De Caralt TM, Ayuso JR, Ayuso C, Schorlemmer WC (1999) Distortion of subcapsular hepatic hemangioma by hepatic cirrhosis. Can Assoc Radiol J 50:137–138

Demir Y, Demir S, Aktepe F (2004) Cutaneous lobular capillary hemangioma induced by pregnancy. J Cutan Pathol 31:77–80

Dennis PM (1980) Fatal pulmonary embolism due to thrombosis of a hepatic cavernous haemangioma. Med Sci Law 20:287–288

Denys A, Hélénon O, Lafortune M, Corréas JM, Patriquin H, Moreau JF, Menu Y (1998) Thickening of the wall of the bile duct due to intramural collaterals in three patients with portal vein thrombosis. AJR Am J Roentgenol 171:455–456

Dessoff S (1967) Ruptured cavernous hemangioma of the liver: report of a case. Med Ann Dist Columbia 36:538–539

Di Carlo I, Urrico GS, Ursino V, Russello D, Puleo S, Latteri F (2003) Simultaneous occurrence of adenoma, focal nodular hyperplasia, and hemangioma of the liver: are they derived from a common origin? J Gastroenterol Hepatol 18:227–230

Diez Redondo P, Velicia Llames R, Caro-Paton A (2004) Familial hepatic hemangiomas (in Spanish). Gastroenterol Hepatol 27:314–316

Diez RP, Velicia LR, Caro-Paton A (2004) Giant cavernous hemangiomas of the liver (in Spanish). Rev Esp Enferm Dig 96:665

Doyle DJ, Khalili K, Guindi M, Atri M (2007) Imaging findings of sclerosed hemangioma. AJR Am J Roentgenol 189:67–72

Dreyfus M, Baldauf JJ, Dadoun K, Becmeur F, Berrut F, Ritter J (1996) Prenatal diagnosis of hepatic hemangioma. Fetal Diagn Ther 11:57–60

Drouot F, Piard F, Thome C, Arnould L, Jacquot JP, Bernard A, Michiels R (1990) A case of liver angiosarcoma arising in a pre-existing cavernous hemangioma (in French). Ann Pathol 10:336–340

Drut RM, Drut R (2004) Extracutaneous infantile haemangioma is also Glut1 positive. J Clin Pathol 57:1197–1200

Duff B, Weigel JA, Bourne P, Weigel PH, McGary CT (2002) Endothelium in hepatic cavernous hemangiomas does not express the hyaluronan receptor for endocytosis. Hum Pathol 33:265–269

Ecker JA, Doane WA (1969) Massive cavernous hemangioma of the liver. Case reports and review of the literature. Am J Gastroenterol 52:25–36

Eng AM, Hong HY (1993) Recurrent pyogenic granulomas: a form of lobular capillary hemangioma. Cutis 52:101–103

Enjolras O, Mulliken JB (1997) Vascular tumors and vascular malformations (new issues). Adv Dermatol 13:375–423

Ersoz F, Ozcan O, Toros AB, Culcu S, Bektas H, Sari S, Pasaoglu E, Arikan S (2010) Torsion of a giant pedunculated liver hemangioma mimicking acute appendicitis: a case report. World J Emerg Surg 18:5

Etemadi A, Golozar A, Ghassabian A, Zarei M, Hashemi Taheri AP, Dawsey SM, Malekzadeh R (2011) Cavernous hemangioma of the liver: factors affecting disease progression in general hepatology practice. Eur J Gastroenterol Hepatol 23:354–358

Facchini G, Fiore F, Caraglia M, D'Angelo R, Nasti G, Camponigro F, Formato R (2005) A liver angioma colonized by colon cancer cells in a patient with two primitive localizations by colon adenocarcinoma: biologic, diagnostic and therapeutic implications. Ann Oncol 16:1980–1981

Feldman PA, Regev A (2007) Atypical giant hepatic hemangiomas with intratumoral hemorrhage. Clin Gastroenterol Hepatol 5:A24

Fortna RR, Junkins-Hopkins JM (2007) A case of lobular capillary hemangioma (pyogenic granuloma), localized to the subcutaneous tissue, and a review of the literature. Am J Dermatopathol 29:408–411

Freeny PC, Vimont TR, Barnett DC (1979) Cavernous hemangiomas of the liver: ultrasonography, arteriography and computed tomography. Radiology 132:143–148

Frerichs FT (1861) Clinical treatise on disease of the liver, vol 2. New Sydenham Society, London

Gandolfi L, Solmi L, Bolondi L, Rossi A, Casanova P, Leo P (1983) The value of sonography in the diagnosis of hepatic haemangiomas. Eur J Radiol 3:222–226

Gandolfi L, Leo P, Solmi L, Vitelli E, Verros G, Colecchia A (1991) Natural history of hepatic haemangiomas: clinical and ultrasound study. Gut 32:677–680

Gembruch U, Baschat AA, Gloeckner-Hoffmann K, Gortner L, Germer U (2002) Prenatal diagnosis and management of fetuses with liver hemangiomata. Ultrasound Obstet Gynecol 19:454–460

Gemer O, Moscovici O, Dosoretz Ben-Horin CL, Linov L, Peled R, Segal S (2004) Oral contraceptives and liver hemangioma: a case-control study. Acta Obstet Gynecol Scand 83:1199

Ghekiere O, Galant C, Van de Berg B (2005) Intravenous pyogenic granuloma or intravenous lobular capillary hemangioma. Skelet Radiol 34:343–346

Gibney RG, Hendin AP, Cooperberg PL (1987) Sonographically detected hepatic hemangiomas: absence of change over time. AJR Am J Roentgenol 149:953–957

Glinkova V, Sehvah O, Boaz M, Levine A, Shirin H (2004) Hepatic hemangiomas: possible association with female sex hormones. Gut 53:1352–1355

Godfraind C, Calicchio ML, Kozakewich H (2013) Pyogenic granuloma, an impaired wound healing process, linked to vascular growth driven by FLT4 and the nitric oxide pathway. Mod Pathol 26:247–255

Goldman ZD (1987) Benign tumors of the liver. In: Okuda K, Ishak KG (eds) Neoplasms of the liver. Springer, Tokyo, pp 105–125

Gönül M, Gul U, Gunduz H, Artantas S, Demiriz M (2005) Disseminated lobular capillary hemangioma: two case reports. J Dermatol 32:996–999

Greenblatt EJ, Olzmann JA, Kopito RR (2011) Derlin-1 is a rhomboid pseudoprotease required for the dislocation of mutant a-1 antitrypsin from the endoplasmic reticulum. Nat Struct Mut Biol 18:1147–1152

Grinberg SB (1975) Gigantic cavernous hemangioma of the liver (in Russian). Vestn Khir Im II Grek 114:117

Guibert HL, Candon J (1957) Giant cavernous hemangioma of Glisson's capsule (in French). Presse Med 65:1720–1722

Hagiwara K, Khaskhely NM, Uezato H, Nonaka S (1999) Mast cell "densities" in vascular proliferations: a preliminary study of pyogenic granuloma, portwine stain, cavernous hemangioma, cherry angioma, Kaposi's sarcoma, and malignant hemangioendothelioma. J Dermatol 26:577–586

Hamilton FE, Holmes RH (1950) Cavernous hemangioma of the left lobe of the liver; report of a case. US Armed Forces Med J 1:443–446

Han JK, Kim SH (2004) Hepatic hemangioma with arterioportal shunts (in Korean). Korean J Hepatol 10:158–160

Han SL, Wu XL, Jia ZR, Wang PF (2010) Adult hepatic cavernous haemangioma with highly elevated alpha-fetoprotein. Hong Kong Med J 16:400–4002

Hanazaki K, Kajikawa S, Matsushita A, Monma T, Koide N, Nimura Y, Yazawa K, Watanabe H, Nishio A, Adachi W, Amano J (1999) Hepatic resection of giant cavernous hemangioma of the liver. J Clin Gastroenterol 29:257–260

Hanazaki K, Koide N, Kajikawa S, Ushiyama T, Watanabe T, Adachi V, Amano J (2001) Cavernous hemangioma of the liver with giant cyst formation: degeneration or apoptosis? J Gastroenterol Hepatol 16:352–355

Haratake J, Horie A, Nagafuchi Y (1992) Hyalinized hemangioma of the liver. Am J Gastroenterol 87:234–236

Haratake J, Arai K, Makino H (1995) Hemangioma and hyalinized hemangioma of the liver (in Japanese). Ryokibetsu Shokogun Shirizu 7:336–338

Harris MN, Desai R, Chuang TY, Hood AF, Mirowski GW (2000) Lobular capillary hemangiomas: an epidemiologic report, with emphasis on cutaneous lesions. J Am Acad Dermatol 42:1012–1016

Hekimoglu K, Ustundag Y (2010) Cavernous hemangioma with arterioportal and portosystemic shunts: precise diagnosis with dynamic multidetector computed tomography imaging. Abdom Imaging 35:328–331

Henson SW, Gray HK, Dockerty MB (1956) Benign tumors of the liver. Surg Gynecol Obstet 103:327–331

Hercberg S, Kammerer J, Zimmermann P, Fouet P (1982) Diffuse cavernous hemangioma of the liver. General review apropos of a case treated and followed for 7 years (in French). Med Chir Dig 11:49–52

Herman P, Costa ML, Machado MA, Pugliese V, D'Albuquerque LA, Machado MC, Gama-Rodrigues JJ, Saad WA (2005) Management of hepatic hemangiomas: a 14-year experience. J Gastrointest Surg 9:853–859

Herrera LO, Glassman CI, Teixido RA, Oglesby JT, Andrade EL, Rodrigue RB (1981) Peliosis hepatis associated with cavernous hemangioma and hepatocarcinoma. Am Surg 47:502–506

Hida T, Nishie A, Tajima T, Taketomi A, Aishima S, Honda H (2010) Sclerosed hemangioma of the liver: possible diagnostic value of diffusion-weighted magnetic resonance imaging. Jpn J Radiol 28:235–238

Hihara T, Araki T, Katou K, Odashima H, Ounishi H, Kachi K, Uchiyama G (1990) Cystic cavernous hemangioma of the liver. Gastrointest Radiol 15:112–114

Hobbs KE (1990) Hepatic hemangiomas. World J Surg 14:468–471

Hochwald SN, Blumgart LH (2000) Giant hepatic hemangioma with Kasabach-Merritt syndrome: is the appropriate treatment enucleation or liver transplantation ? HPB Surg 11:413–419

Holtz U, Fiedrich M, Sörensen R (1977) Giant multifocal cavernous hemangioma of the liver with phleboliths (in German). Radiologe 17:77–82

Hosokawa A, Maeda T, Tateishi U, Satake M, Iwata R, Ojima H, Arai Y (2005) Hepatic hemangioma presenting atypical radiologic findings: a case report. Radiat Med 23:371–375

Hu D, Ran YL, Zhong X, Hu H, Yu L, Lou JN, Sun LX, Yang ZH (2006) Overexpressed Derlin-1 inhibits ER expansion in the endothelial cells derived from human hepatic cavernous hemangioma. J Biochem Mol Biol 39:677–685

Hung CH, Kuo HW, Chiu YK, Huang PH (2004) Intravascular pyogenic granuloma arising in an acquired arteriovenous malformation: report of a case and review of the literature. Dermatol Surg 30:1050–1053

Hussain MZ, Ohtomo K, Hihara T, Uchiyama G, Ainoda T, Yamamoto M, Suda K (1992) Multilocular cystic hemangioma: CT and MR appearance. Radiat Med 10:206–209

Imai M, Amano K, Nishijima M (1995) A case of giant fetal hepatic hemangioma (in Japanese). Nippon Sanka Fujinka Gakkai Zasshi 47:1371–1374

Ishak KG, Sesterhenn IA, Goodman ZD, Rabin L, Stromeyer FW (1984) and Matsuzawa Y (1997) Increased circulating transforming growth factor beta1 in a patient with giant hepatic hemangioma : possible contribution to an impaired immune function. Hepatology 25:93–96

Issahar-Zadeh A, Monnier-Cholley L, Tiret E, Le Treut YP, Garcia S, Tubiana JM, Arrive L (1997) Giant hepatic hemangioma causing dilatation of the intrahepatic biliary ducts (in French). J Radiol 78:381–384

Itai Y, Teraoka T (1989) Angiosarcoma of the liver mimicking cavernous hemangioma on dynamic CT. J Comput Assist Tomogr 13:910–912

Itai Y, Furui S, Araki T, Yashiro N, Tasaka A (1980) Computed tomography of cavernous hemangioma of the liver. Radiology 137:149–155

Itai Y, Araki T, Ohtomo K, Kokubo T, Yoshida H, Minami M, Yashiro N (1989) Well-defined, dense and continuously spreading enhancement on single level dynamic CT of the liver: a characteristic sign of hepatic cavernous haemangioma. Röfo 151:697–701

Ito et al. 1997 PubMed PMID8985271

Jafarzadeh H, Sanatkhani M, Mohtasham N (2006) Oral pyogenic granuloma: a review. J Oral Sci 48:167–175

Jang HJ, Kim TK, Lim HK, Park SJ, Sim JS, Kim HY et al (2003) Hepatic hemangioma: atypical appearances on CT, MR imaging, and sonography. AJR Am J Roentgenol 180:135–141

Jhuang JY, Lin LW, Hsieh MS (2011) Adult capillary hemangioma of the liver: case report and literature review. Kaohsiung J Med Sci 27:344–347

Jiang H, Chen Z, Prasoon P, Wu H, Zeng Y (2011) Surgical management for giant liver hemangiomas greater than 20 cm in size. Gut Liver 5:228–233

Jin SY (2010) Sclerosed hemangioma of the liver. Korean J Hepatol 16:410–413

Johnson CM, Sheedy PF, Stanson AW, Stephens DH, Hattery RR, Adson MA (1981) Computed tomography and angiography of cavernous hemangiomas of the liver. Radiology 138:115–121

Kadry Z, Mentha G, Cereda JM (2000) Polymyalgia rheumatica as a manifestation of a large hepatic cavernous hemangioma. J Hepatol 32:358–360

Kasabach HH, Merritt KK (1940) Capillary hemangioma with extensive purpura, report of a case. Am J Dis Child 59:1063–1070

Kassarjian A, Dubois J, Burrows PE (2002) Angiographic classification of hepatic hemangiomas in infants. Radiology 222:693–698

Kato M, Sugawara I, Okada A, Kuwata K, Satani M (1975) Hemangioma of the liver. Diagnosis with combined use of laparoscopy and hepatic arteriography. Am J Surg 129:698–703

Keegan MT, Kamath GS, Vasdev GM, Findlay JY, Gores GJ, Steers JL, Plevak DJ (2001) Liver transplantation for massive hepatic angiomatosis causing restrictive lung disease. Br J Anaesth 86:431–434

Key RD, Rao RN (1986) Leiomyomatous hemangiomas of the liver mimicking primary leiomyomas. Arch Pathol Lab Med 110:658–659

Kim KW, Kim TK, Han JK, Kim AY, Lee HJ, Choi BI (2001) Hepatic hemangiomas with arterioportal shunt: findings at two-phase CT. Radiology 219:707–711

Kim DY, Pantelic MV, Yoshida A, Jerius J, Abouljoud MS (2005) Cavernous hemangioma presenting as Budd-Chiari syndrome. J Am Coll Surg 2000:470–471

Kim KW, Kim AY, Kim TK, Kim SY, Kim MJ, Park MS, Park SH, Lee KH, Kim JK et al (2006a) Hepatic hemangiomas with arterioportal shunt: sonographic appearances with CT and MRI correlation. AJR Am J Roentgenol 187:W406–W414

Kim GF, Thung SN, Tsui WM, Ferrell LD (2006b) Hepatic cavernous hemangioma: underrecognized associated histologic features. Liver Int 26:334–338

Kojima K, Tamano M, Oguma M, Matsumura A, Kuniyoshi T, Sugaya H et al (2000) Hepatic benign tumor with hepatocellular carcinoma like appearance on image diagnosis (in Japanese). Liver Cancer 6:70–74

Kojimara M (1986) Ultrastructural study of hemangiomas. 4. Cavernous hemangioma of the liver. Acta Pathol Jpn 36:1477–1485

Kondo F (2003) Is there a common cause of adenoma, focal nodular hyperplasia, and hemangioma of the liver? J Gastroenterol Hepatol 18:357–358

Koskela O (1965) Large cavernous haemangioma of the liver complicating pregnancy. Ann Chir Gynaecol Fenn 54:201–207

Koszka AJ, Ferreira FG, de Aquino CG, Ribeiro MA, Gallo AS, Apranzana EM, Szutan LA (2010) resection of a rapid-growing 40-cm giant liver hemangioma. World J Hepatol 2:292–294

Krasuski P, Poniecka A, Gal E, Wali A (2001) Intrapartum spontaneous rupture of liver hemangioma. J Matern Fetal Med 10:290–292

Kryvenko ON, Gupta NS, Meier FA, Lee MW, Epstein JI (2011) Anastomosing hemangioma of the genitourinary system: eight cases in the kidney and ovary with immunohistochemical and ultrastructural analysis. Am J Clin Pathol 136:450–457

Kudara N, Chiba T, Andoh T, Tsukahara M, Oana S, Terui T, Endoh M, Inomata M et al (2004) A case of hepatic hemangioma with pedunculated extrahepatic growth simulating submucosal tumor of the stomach (in Japanese). Nihon Shokakibyo Gakkai Zasshi 101:293–299

Kuga R, Furuya CK, Fylyk SN, Sakai P (2009) Solitary pyogenic granuloma of the small bowel as the cause of obscure gastrointestinal bleeding. Endoscopy 41(Suppl 2):E76–E77

Kumarakrishnan S, Gupta A, Srinivasan K, Gupta A (1997) Pedunculated giant hemangioma of liver. Indian J Gastroenterol 16:35–36

Kusakabe A, Kato H, Hayashi K et al (2005) Pyogenic granuloma of the stomach successfully treated by endoscopic resection after transarterial embolization of the feeding artery. J Gastroenterol 40:530–535

Kuske HJ (1938) Vergleichende Untersuchung über Bau und Pathogenese von Leber-und Hautkavernom. Frankf Ztschr Pathol 51:131–149

Lanne JS, Dumortier J, Hervieu V, Pilleul F, Scoazec JY, Adham M (2010) Polycythemia and elevated serum erythropoietin associated with a liver haemangioma. Gastroenterol Clin Biol 34:629–632

Lee CW, Chung YH, Lee GC, Kim JY, Lee JS (1994) A case of giant hemangioma of the liver presenting with fever of unknown origin. J Korean Med Sci 9:200–204

Lee SH, Park CM, Cheong IJ, Kwak MS, Cha SH, Choi SY, Kim CH (2001) Hepatic capsular retraction: unusual finding of cavernous hemangioma. J Comput Assist Tomogr 25:231–233

Lee VT, Magnaye M, Tan HW, Thng CH, Ooi LL (2005) Sclerosing haemangioma mimicking hepatocellular carcinoma. Singap Med J 46:140–143

Lee CK, Dong SH, Jung SH, Jang JY, Kim HJ, Kim BH, Chang YW, Chang R, Kim YW (2007) Pyogenic granuloma of the common bile duct in a patient with choledochoduodenostomy. Endoscopy 39(Suppl 1): E282–E283

Lerner SM, Hiatt JR, Salamandra J, Chen PW, Farmer DG, Ghobrial RM, Busuttil RW (2004) Giant cavernous liver hemangiomas: effect of operative approach on outcome. Arch Surg 139:818–821

Leslie DF, Johnson CD, Johnson CM, Ilstrup DM, Harmsen WS (1995) Distinction between cavernous hemangiomas of the liver and hepatic metastases on CT: value of contrast enhancement patterns. AJR Am J Roentgenol 164:625–629

Li GW, Chen QL, Jiang JT, Zhao ZR (2003) The origin of blood supply for cavernous hemangioma of the liver. Hepatobiliary Pancreat Dis Int 2:367–370

Liang RJ, Chen CH, Chang YC, Hu RH, Sheu JC (2002) Pedunculated hepatic hemangioma: report of two cases. J Formos Med Assoc 101:437–441

Lin RL, Janniger CK (2004) Pyogenic granuloma. Cutis 74:229–233

Lin J, Bigge J, Ulbright TM, Montgomery E (2013) Anastomosing hemangioma of the liver and gastrointestinal tract: an unusual variant histologically mimicking angiosarcoma. Am J Surg Pathol 37:1761–1765

Lise M, Feltrin G, Da Pian PP, Miotto D, Pilati PL, Rubaltelli L, Zane D (1992) Giant cavernous hemangiomas: diagnosis and surgical strategies. World J Surg 16:516–520

Longeville JH, de la Hall P, Dolan P, Holt AW, Lillie PE, Williams JA, Padbury RT (1997) Treatment of a giant hemangioma of the liver with Kasabach-Merritt syndrome by orthotopic liver transplant: a case report. HPB Surg 10:159–162

Lopriore and Markhorst 1999 PubMed PMID 10090556

Losanoff JE, Millis JM (2008) Liver hemangioma complicated by obstructive jaundice. Am J Surg 196:e3–e4

M'Weeney EJ (1912) Enormous angioma of liver. J Pathol Bacteriol 16:401

Maekawa S, Mizutani Y, Terachi T, Okada Y, Yoshida O (1997) A case of exophytic hepatic hemangioma mimicking adrenal tumor. Hinyokika Kiyo 43:123–126

Makhlouf HR, Ishak KG (2002) Sclerosed hemangioma and sclerosing cavernous hemangioma of the liver: a comparative clinicopathologic and immunohistochemical study with emphasis on the role of mast cells in their histogenesis. Liver 22:70–78

Malamou-Mitsi VD, Goussia A, Andronikou S, Stefanou D, Dallas P, Lapatsanis PD (1996) Giant hemangioma in infant. A case presentation and literature review. Arch Anat Cytol Pathol 44:199–201

Margarit C, Martinez-Brotons F, Macarulla E, Osorio A, Sarro M, Curto JA (1986) Giant hepatic cavernous hemangioma and Kasabach-Merritt syndrome (in Spanish). Rev Clin Esp 178:283–286

Mastropasqua M, Kanematsu M, Leonardou P, Braga L, Woosley JT, Semelka RC (2004) Cavernous hemangiomas in patients with chronic liver disease: MR imaging findings. Magn Reson Imaging 22:15–18

Masui T, Katayama M, Nakagawara M, Shimizu S, Kojima K (2005) Exophytic giant cavernous hemangioma of the liver with growing tendency. Radiat Med 23:121–124

Mathieu D, Zafrani ES, Anglade H, Dhumeaux D (1989) Association of focal nodular hyperplasia and hepatic hemangioma. Gastroenterology 97:154–157

Mathieu D, Rahmouni A, Vasile N, Jazaerli N, Duvoux C, Tran JV, Zafrani ES (1994) Sclerosed liver hemangioma mimicking malignant tumor at MR imaging: pathologic correlation. J Magn Reson Imaging 4:506–508

Matsuo N, Uchida H (1990) A case of hepatic capillary hemangioma with difficulty of definitive diagnosis from hepatocellular carcinoma (in Japanese). Nichidoku-ihou 35:66–67

McArdle CR (1978) Ultrasonic appearance of a hepatic hemangioma. J Clin Ultrasound 6:124

Miettinen M, Fetsch JF (2000) Distribution of keratins in normal endothelial cells and a spectrum of vascular tumors: implications in tumor diagnosis. Hum Pathol 31:1062–1067

Miettinen M, Wang ZF (2012) Prox1 transcription factor as a marker for vascular tumors – evaluation of 314 vascular endothelial and 1086 nonvascular tumors. Am J Surg Pathol 36:351–359

Mikami T, Hirata K, Oikawa I, Kimura M, Kimura H (1998) Hemobilia caused by a giant benign hemangioma of the liver: report of a case. Surg Today 28:948–952

Mitsudo K, Watanabe Y, Saga T, Dohke M, Sato N, Minami K, Shigeyasu M (1995) Nonenhanced hepatic cavernous hemangioma with multiple calcifications: CT and pathologic correlation. Abdom Imaging 20:459–461

Miyaki D, Aikata H, Waki K, Murakami E, Hashimoto Y, Nagaoki Y, Katamura Y, Kawaoka T et al (2011) Significant regression of a cavernous hepatic hemangioma to a sclerosed hemangioma over 12 years: a case study. Nihon Shokakibyo Gakkai Zasshi 108:954–961

Mo JQ, Dimashkieh HH, Bove KE (2004) GLUT1 endothelial reactivity distinguishes hepatic infantile hemangioma from congenital hepatic vascular malformation with associated capillary proliferation. Hum Pathol 35:200–209

Montgomery E, Epstein JI (2009) Anastomosing hemangioma of the genitourinary tract: a lesion mimicking angiosarcoma. Am J Surg Pathol 33:1364–1369

Moon HK, Kim HS, Heo GM, Shin WG, Kim KH, Jang MK, Lee JH, Kim HY, Kim DJ et al (2011) A case of pedunculated hepatic hemangioma mimicking submucosal tumor of the stomach. Korean J Hepatol 17:66–70

Mori H, Ikegami T, Imura S, Shimada M, Morine Y, Kanemura H, Arakawa Y, Kanamoto M et al (2008) Sclerosed hemangioma of the liver: report of a case and review of the literature. Hepatol Res 38:529–533

Morita M, Sakakiyama Y, Shiono H, Muraoka S (1970) An autopsy case of cavernous hemangioma with solitary fibromatous fibrosis within the cavernous space in the liver of an adult. Sapporo Igaku Zasshi 38:1–17

Morley JE, Myers JB, Sack FS, Kalk F, Epstein EE, Lannon J (1974) Enlargement of cavernous hemangioma associated with exogenous administration of estrogen. S Afr Med J 48:695–697

Moser C, Hany A, Spiegel R (1998) Familial giant hemangiomas of the liver. Study of a family and review of the literature (in German). Schweiz Rundsch Med Prax 87:461–468

Mungovan JA, Cronan JJ, Vacarro J (1994) Hepatic cavernous hemangiomas: lack of enlargement over time. Radiology 191:111–113

Ndimbie OK, Goodman ZD, Chase RL, Ma CK, Lee MW (1990) Hemangiomas with localized nodular proliferation of the liver. A suggestion on the pathogenesis of focal nodular hyperplasia. Am J Surg Pathol 14:142–150

Nghiem HV, Bogost GA, Ryan JA, Lund P, Freeny PC, Rice KM (1997) Cavernous hemangiomas of the liver: enlargement over time. AJR Am J Roentgenol 169:137–140

Nichols GE, Gaffey MJ, Mills SE, Weiss LM (1992) Lobular capillary hemangioma. An immunohistochemical study including steroid hormone receptor status. Am J Clin Pathol 97:770–775

Noda T, Sasaki Y, Yamada T, Eguchi H, Takachi K, Noura S, Miyashiro I, Murata K et al (2005) Adult capillary hemangioma of the liver: report of a case. Surg Today 35:796–799

Novellas S, Chevallier P, Peroux JL, Bruneton JN (2004) Rare localization of a portal cavernoma in the wall of the common bile duct. Clin Imaging 28:132–134

O'Donoghue JB, Nicosia AJ (1950) Cavernous hemangioma of the liver. Ill Med J 98:15–17

Ochsner JL, Halpert B (1958) Cavernous hemangioma of the liver. Surgery 43:577–582

Okano H, Shiraki K, Inoue H, Ito T, Yamanaka T, Deguchi M, Sugimoto K, Sakai T et al (2001) Natural course of cavernous hepatic hemangioma. Oncol Rep 8:411–414

Olmsted WW, Stocker JT (1975) Cavernous hemangioma of the liver. Radiology 117:59–62

Ontachi Y, Asakura H, Omote M, Yoshida T, Matsui O, Nakao S (2005) Kasabach-Merritt syndrome associated with giant liver hemangioma: the effect of combined therapy with danaparoid sodium and tranexamic acid. Haematologica 90(Suppl):ECR29

Ozakyol A, Kebapci M (2006) Enhanced growth of hepatic hemangiomatosis in two adults after postmenopausal estrogen replacement therapy. Tohoku J Exp Med 210:257–261

Özdemir S, Friedman A (2003) Hepatic cavernous hemangioma with atypical peripheral rim activity on hepatic blood pool imaging. Clin Nucl Med 28:834–835

Parikh VP, Iyer GN (1990) Pedunculated hepatic hemangioma: CT findings. AJR Am J Roentgenol 155:1137–1138

Park SM, Shin SM, Seo HE, Kim SH, Kim HS, Park JH, Kim JH, Sohn KR (2009a) A case of sclerosed hemangioma mimicking intrahepatic cholangiocarcinoma (in Korean). Korean J Gastroenterol 54:399–403

Park SY, Park CH, Lee WS, Kim HS, Choi SK, Rew JS (2009b) Pyogenic granuloma of the duodenum treated successfully by endoscopic mucosal resection. Gut Liver 3:48–51

Pateron D, Babany G, Belghiti J, Hadengue A, Menu Y, Flejou JF, Erlinger S, Benhamou JP (1991) Giant hemangioma of the liver with pain, fever, and abnormal liver tests. Dig Dis Sci 36:524–527

Patrice SJ, Wiss K, Mulliken JB (1991) Pyogenic granuloma (lobular capillary hemangioma): a clinicopathologic study of 178 cases. Pediatr Dermatol 8:267–276

Petri A, Karacsonyi S, Nagy KK (1993) Surgical treatment of cavernous haemangiomas of the liver. Langenbecks Arch Chir 378:322–324

Pfannenstiel HJ (1898) Erfolgreiche Exstirpation eines grossen cavernösen Leberangiomas. Allgem Med Central-Zeitung 67:177–179

Pierini A, Zaniello JM (1964) Diffuse cavernous hemangioma of the liver. Apropos of a case (in Spanish). Bol Trab Soc Cir B Aires 48:270–278

Pinkernelle J, Neumann U, Hänninen EL (2007) An unusual cause of epigastric pain: infected giant liver hemangioma. Acta Radiol 48:142–144

Plachta A (1962) Calcified cavernous hemangioma of the liver. Review of the literature and report of 13 cases. Radiology 79:783–788

Plachta A (1965) The triad syndrome inherent to calcified cavernous hemangioma of the liver. Angiology 16:594–599

Pol B, Disdier P, Le Treut YP, Campan P, Hardwigsen J, Weiller PJ (1998) Inflammatory process complicating giant hemangioma of the liver: report of three cases. Liver Trans Surg 4:204–207

Polikarpova MD (1955) Giant cavernous angioma of the liver. Khirurgiia (Mosk) 3:68

Poncet P, Dor A (1897) De la botryomycose humaine. Rev Chir (Paris) 18:996–997

Pönkä A, Laasonen L, Strengell-Usanov L (1983) Angioleiomyoma of the common bile duct. Acta Med Scand 213:407–410

Poupardin E, Regimbeau JM, Kianmanesh R, Colombat M, Farges O, Sauvanet A, Belghiti J (2002) Giant hemangioma of the liver revealed by an inflammatory syndrome (in French). Gastroenterol Clin Biol 26:93–95

Prematilleke MN (1972) Micro-angiopathic haemolytic anaemia associated with a giant haemangioma of the liver. Postgrad Med J 48:111–113

Rader et al. 2008 PubMed PMID 18294552

Reading NG, Forbes A, Nunnerly HB, Williams R (1988) Hepatic hemangioma: a critical review of diagnosis and management. Q J Med 67:431–445

Ribbert VA (1898) Über Bau, Wachsthum und Genese der Angiome, nebst Bemerkungen über Cystenbildung. Arch Pathol Anat 151:381

Ribeiro MAF, Papaiordanou F, Gonçalves JM, Chaib E (2010) Spontaneous rupture of hepatic hemangiomas: a review of the literature. World J Hepatol 2:428–433

Ros PR, Lubbers PR, Olmsted WW, Morillo G (1987) Hemangioma of the liver: heterogeneous appearance on T2-weighted images. AJR Am J Roentgenol 149:1167–1170

Ross M, Polcari A, Picken M, Sankary H, Milner J (2012) Anastomosing hemangioma arising from the adrenal gland. Urology 80:e27–e28

Saegusa T, Ito K, Oba N, Matsusda M, Kojima K, Tohyama K et al (1995) Enlargement of multiple cavernous hemangioma of the liver association with pregnancy. Intern Med 34:207–211

Sahiner UM, Senel S, Erkek N, Karacan C, Yoney A (2009) Rubinstein Taybi syndrome with hepatic hemangioma. Med Princ Pract 18:162–164

Salomäki HH, Sainio AO, Söderström M, Pakkanan S, Laine J, Järvelainen HT (2008) Differential expression of decorin by human malignant and benign vascular tumors. J Histochem Cytochem 56:639–646

Salum FG, Yurgel LS, Cherubini K, De Figueiredo MA, Medeiros IC, Nicola FS (2008) Pyogenic granuloma, peripheral giant cell granuloma and peripheral

ossifying fibroma: retrospective analysis of 138 cases. Minerva Stomatol 57:227–232
Sasaki et al. 2001 PubMed PMID 11729680
Satoh H, Kinukawa N, Kishimoto H, Ogawa Y, Shuro F (1994) An autopsy case of diffuse neonatal hemangiomatosis (in Japanese). Saitama Syouni Iryou Ceter Ishi 11:23–27
Scatarige JC, Fishman EK, Saksouk FA, Siegelman SS (1983) Computed tomography of calcified liver masses. J Comput Assist Tomogr 7:83–89
Scialpi M, Piscioli I, Pusiol T, Franceschetti I (2010) Does hepatic adult capillary hemangioma exist? Surg Today 40:92
Scribano E, Loria G, Ascenti G, Vallone A, Gaeta M (1996) Spontaneous hemoperitoneum from a giant multicystic hemangioma of the liver: a case report. Abdom Imaging 21:418–419
Sepulweda WH, Donetch G, Giuliano A (1993) Prenatal sonographic diagnosis of fetal hepatic hemangioma. Eur J Obstet Gynecol Reprod Biol 48:73–76
Sewell JH, Weiss K (1961) Spontaneous rupture of hemangioma of liver. Arch Surg 83:729–731
Sharma V, Chaudhuri MM, Chandra AK (1991) Giant cavernous hemangioma of liver. Indian J Gastroenterol 10:146–147
Shepherd NA, Lee G (1983) Solitary necrotic nodule of the liver simulating hepatic metastasis. J Clin Pathol 36:1181–1183
Shim WK (1986) Hemangiomas of infancy complicated by thrombocytopenia. Am J Surg 116:896–906
Shim KS, Suh JM, Yang YS, Kim JG, Kang SJ, Jeon JS, Kim BS (1995) Sclerosis of hepatic cavernous hemangioma: CT findings and pathologic correlation. J Korean Med Sci 10:294–297
Shimizu M, Miura J, Itoh H, Saitoh Y (1990) Hepatic giant cavernous hemangioma with microangiopathic hemolytic anemia and consumption coagulopathy. Am J Gastroenterol 85:1411–1413
Shumaker HB (1942) Hemangioma of the liver. Surgery 11:209–212
Somppi E, Niemi K, Ruuskanen O, Arajärvi P, Lauslahti K (1974) Cavernous hepatic hemangioma in the newborn infant: case report of a successful resection. J Pediatr Surg 9:239–241
Sood A, Sandhu P, Sood N, Kharay AS, Sandhu BS (1996) Giant cavernous hemangiomas of liver mimicking metastasis. J Assoc Physicians India 44:784–785
Sood D, Kumaran V, Buxi TB, Nundy S, Soin AS (2009) Liver hemangioma mimicking cholangiocarcinoma – a diagnostic dilemma. Trop Gastroenterol 30:44–46
Soyer P, Dufresne AC, Somveille E, Scherrer A (1997) Hepatic cavernous hemangioma: appearance on T2-weighted fast spin-echo MR imaging with and without fat suppression. AJR Am J Roentgenol 168:461–465
Spoor TC, Page CP, Rogers W (1977) Massive cavernous hemangioma of the liver. South Med J 70:490–492
Stark DD, Felder RC, Wittenberg J, Saini S, Butch RJ, White ME, Edelman RR et al (1985) Magnetic resonance imaging of cavernous hemangioma of the liver: tissue-specific characterization. AJR Am J Roentgenol 145:213–222
Starzl TE, Koep LJ, Weil R, Fennell RH, Iwatsuki S, Kano T, Johnson ML (1980) Excisional treatment of cavernous hemangioma of the liver. Ann Surg 192:25–27
Stojsic Z, Brasanac D, Kokai G, Vujovic D, Zivanovic D, Boricic I, Bacetic D (2008) Intestinal intussusception due to pyogenic granuloma. Turk J Pediatr 50:600–603
Stoupis C, Taylor HM, Paley MR, Buetwo PC, Marre S, Baer HU, Vock P, Ros PR (1998) The rocky liver: radiologic-pathologic correlation of calcified hepatic masses. Radiographics 18:675–685
Strzelczyk J, Bialkowska J, Loba J, Jablkowski M (2004) Rapid growth of liver hemangioma following interferon treatment for hepatitis C in a young woman. Hepatogastroenterology 51:1151–1153
Sun ZJ, Zhao YF, Zhao JH (2007) Mast cells in hemangioma: a double-edged sword. Med Hypotheses 68:805–807
Szavay P, Kurth R, Schaefer J, Kirschner H, Luithle T, Sturm E (2013) A rare cause for extrahepatic biliary tract obstruction: juvenile hepatic hilar hemangioma. Eur J Pediatr Surg 23:415–417
Taillandier J, Alemanni M, Veyssier P, Smadja C, Manigand G, Franco D (1995) Giant hemangioma of the liver disclosed by fever and an inflammatory syndrome. Apropos of 3 cases (in French). Ann Med Intern (Paris) 146:319–321
Tait N, Richardson AJ, Muguti G, Little JM (1992) Hepatic cavernous haemangioma: a 10 year review. Aust N Z J Surg 62:521–524
Taitelbaum G, Hinchey EJ, Herba MJ, Lough J (1982) Giant hemangioma of the liver. Can J Surg 25:652–654
Takahashi T, Katoh H, Dohke M, Okushiba S (1997) A giant hepatic hemangioma with secondary portal hypertension: a case report of successful surgical treatment. Hepatogastroenterology 44:1212–1214
Takayasu K, Moriyama N, Shima Y, Muramatsu Y, Yamada T, Makuuchi M, Yamasaki S, Hirohashi S (1986) Atypical radiographic findings in hepatic cavernous hemangiomas: correlation with histologic features. AJR Am J Roentgenol 146:1149–1153
Tan ST, Velickovic M, Ruger BM, Davis PF (2000) Cellular and extracellular markers of hemangioma. Plast Reconstr Surg 106:529–538
Tan ST, Wallis RA, He Y, Davis PF (2004) Mast cells and hemangioma. Plast Reconstr Surg 113:999–1011
Tanaka A, Morimoto T, Yamamori T, Moriyasu F, Yamaoka Y (2002) Atypical liver hemangioma with shunt: long-term follow-up. J Hepatobiliary Pancreat Surg 9:750–754
Tani A, Yoshida H, Mamada Y, Taniai N, Kawano Y, Uchida E (2010) Extrahepatic portal venous obstruction due to a giant hepatic hemangioma associated with Kasabach-Merritt syndrome. J Nihon Med Sch 77:269–272

Tashikuni N, Takagi S, Morii K, Fujisawa M (2006) Education and imaging. Hepatobiliary and pancreatic: calcified cavernous hemangiomas in the liver. J Gastroenterol Hepatol 21:1626

Tohme C, Drouot E, Piard F, Bernard A, Brachet A, Chauffert B, Viard H (1991) Cavernous hemangioma of the liver associated with angiosarcoma: malignant transformation? (in French). Gastroenterol Clin Biol 15:83–86

Trastek VF, van Heerden JA, Sheedy PF, Adson MA (1983) Cavernous hemangiomas of the liver: respect or observe? Am J Surg 145:49–53

Truss L, Dobin SM, Donner LR (2006) Deletion (21)(q21.2q22.12) as a sole clonal cytogenetic abnormality in a lobular capillary hemangioma of the nasal cavity. Cancer Genet Cytogenet 170:69–70

Tsai CC, Yen TC, Tzen KY (1999) Pedunculated giant liver hemangioma mimicking a hypervascular gastric tumor on Tc-99m RBC SPECT. Clin Nucl Med 24:132–133

Tuncer I, Arslan H, Harman M (2002) Two giant cavernous hemangioma caused by cavernous transformation of the portal vein in a pregnant woman. Turk J Gastroenterol 13:229–231

Tung GA, Cronan JJ (1993) Percutaneous needle biopsy of hepatic cavernous hemangioma. J Clin Gastroenterol 16:117–122

Tung GA, Vaccaro JP, Cronan J, Rogg JM (1994) Cavernous hemangioma of the liver: pathologic correlation with high-field MR imaging. AJR Am J Roentgenol 162:1113–1117

Unal E, Francis F, Aquino A, Xu R, Morgan G, Teperman L (2011) Liver transplant for mixed capillary-cavernous hemangioma masquerading as hepatocellular carcinoma in a patient with hepatocellular carcinoma. Exp Clin Transplant 9:344–348

Valls C, Rene M, Gil M, Sanchez A, Narvaez JA, Hidalgo F (1996) Giant cavernous hemangioma of the liver: atypical CT and MR findings. Eur Radiol 6:448–450

Van Eeden S, Offerhaus GJ, Morsink FH, van Rees BP, Busch OR, van Noesel CJ (2004) Pyogenic granuloma: an unrecognized cause of gastrointestinal bleeding. Virchows Arch 444:590–593

Van Malenstein H, Maleux G, Monbaliu D, Verslype C, Komuta M, Roskams T, Laleman W et al (2011) Giant liver hemangioma: the role of female sex hormones and treatment. Eur J Gastroenterol Hepatol 23:438–443

Vega Harring SM, Niyaz M, Okada S, Kudo M (2004) Extramedullary hematopoiesis in a pyogenic granuloma: a case report and review. J Cutan Pathol 3:555–557

Vilgrain V, Boulos L, Vullierme M-P, Denys A, t'Terris B, Menu Y (2000) Imaging of atypical hemangiomas of the liver with pathologic correlation. RadioGraphics 20:379–397

Vilgrain V, Uzan F, Brancatelli G, Federle MP, Zappa M, Menu Y (2003) Prevalence of hepatic hemangioma in patients with focal nodular hyperplasia: MR imaging analysis. Radiology 229:75–79

Virchow R (1863) Angiome. In: Die krankhaften Geschwülste, vol 3. August Hirschwald, Berlin

Vishnevsky VA, Mohan VS, Pomelov VS, Todua FI, Guseinov EK (1991) Surgical treatment of giant cavernous hemangioma of liver. HPB Surg 4:69–78

Vogel T, Lammers B, von Herbay A, Kunz BM, Donner AJ, Fürst G, Goretzki PE (2002) Kasabach-Merritt syndrome in giant hemangioma of the liver. A case report (in German). Chirurg 73:729–732

Wald SL, Moor BJ, Karrer FW, Lewis JK (1976) Giant cavernous hemangioma of the liver: case report and review of the literature. Nebr Med J 61:407–412

Wang Z, Yuan Y, Zhuang H, Jiang R, Hou J, Chen Q, Zhang F (2012) Hepatic hemangiomas: possible association with IL-17. J Clin Pathol 65:146–151

Watanabe M, Yuasa S, Taketa K, Konaga F, Okajima K (1978) A case of giant cavernous hemangioma of the liver complicated by intravascular coagulopathy. Acta Med Okayama 32:61–68

Wetherell DR, Skene A, Manya K, Manecksha RP, Chan Y, Bolton DM (2013) Anastomosing haemangioma of the kidney: a rare morphological variant of haemangioma characteristic of genitourinary tract location. Pathology 45:193–196

Wilson H, Tyson T (1952) Massive hemangiomas of the liver. Ann Surg 135:765–770

Yamada S, Shimada M, Utsunomiya T, Morine Y, Imura S, Ikemoto T, Mori H, Hanaoka J et al (2012) Hepatic sclerosed hemangioma which was misdiagnosed as metastasis of gastric cancer: report of a case. J Med Invest 59:270–274

Yamamoto K, Itoshima T, Ito T, Ukida M, Ogawa H, Kitadai M, Hattori S, Mizutani S et al (1983) Scanning electron microscopy of a liver cavernous hemangioma. Gastroenterol Jpn 18:15–20

Yamashita Y, Ogata I, Urata J, Takahashi M (1997) Cavernous hemangioma of the liver: pathologic correlation with dynamic CT findings. Radiology 203:121–125

Yamashita Y, Shimada M, Taguchi K, Gion T, Hasegawa H, Utsunomiya T, Hamatsu T et al (2000) Hepatic sclerosing hemangioma mimicking a metastatic liver tumor: report of a case. Surg Today 30:849–852

Yang DM, Yoon MH, Kim HS, Kim HS, Chung JW (2001) Capsular retraction in hepatic giant hemangioma: CT and MR features. Abdom Imaging 26:36–38

Yao T, Nagai E, Utsunomiya T, Tsuneyoshi M (1995) An intestinal counterpart of pyogenic granuloma of the skin. A newly proposed entity. Am J Surg Pathol 19:1054–1060

Yeh WC, Yang PM, Huang GT, Sheu JC, Chen DS (2007) Long-term follow-up of hepatic hemangiomas by ultrasonography: with emphasis on the growth rate of the tumor. Hepatogastroenterology 54:475–479

Yonemoto H, Hashizume Y, Kita S, Kochi T, Yoshimoto T (1966) Case of cystic hemangioma of the liver (in Japanese). Iryo 20:382–385

Yoon SS, Chamy CK, Fong Y, Jarnagin WR, Schwartz LH, Blumgart LH, DeMatteo RP (2003) Diagnosis, management, and outcomes of 115 patients with hepatic hemangioma. J Am Coll Surg 197:392–402

Yu JS, Kim MJ, Kim KW, Chang JC, Jo BJ, Kim TH, Lee JT, Yoo HS (1998) hepatic cavernous hemangioma: sonographic patterns and speed of contrast enhancement on multiphase dynamic MR imaging. AJR Am J Roentgenol 171:1021–1025

Zhang WJ, Ye LY, Wu LQ, Xin YL, Gu F, Niu JX, Yang ZH, Zhu GJ, Grau GE et al (2006) Morphologic, phenotypic and functional characteristics of endothelial cells derived from human hepatic cavernous hemangioma. J Vasc Res 43:522–532

Zhao M, Li C, Zheng J, Sun K (2013) Anastomosing hemangiomas of the kidney: a case report of a rare subtype of hemangioma mimicking angiosarcoma and review of the literature. Int J Clin Exp Pathol 6:757–765

Zheng RD, Yang Z, Rao RC, Xu CR (2004) Giant hepatic hemangioma mimicking primary liver cancer: report of one case (in Chinese). Di Yi Jun Yi Da Xue Xue Bao 24:342

Zimmermann A, Baer HU (1996) Fibrous tumor-liver interface in large hepatic neoplasms: its significance for tumor resection and enucleation. Liver Trans Surg 2:192–199

Variants of Hepatobiliary Angiomatous Tumors

50

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_50

Abstract

Apart from the common cavernous and small-vessel hemangiomas of the liver, there is a group of other but rare benign vascular tumors in the pediatric and adult liver. Multiple hepatic hemangiomas with a cavernous histology and different from infantile hepatic hemangioma/hemangioendothelioma exist in the pediatric age group and are termed congenital, neonatal, and infantile hemangiomatosis. These lesions can be accompanied with extrahepatic hemangiomas, e.g., those of the skin. One variant is characterized by a diffuse hemangiomatosis involving several organ systems. Diffuse hepatic hemangiomatosis also occurs in adult patients as a rare condition, whereby liver lobes are densely involved by vascular nodules of variable size. The disorder may be associated with splenic hemangiomatosis. Hepatic angiomatosis also develops in the setting of Osler's disease. An unusual form of hepatic vascular tumor is intravascular papillary endothelial hyperplasia, a reactive lesion usually occurring in the skin and subcutis of adult patients. Hepatic hemangiomas can rarely be associated with proliferation of smooth muscle cells (angioleiomyoma). A further, very rare hepatic vascular tumor is hemangioblastoma, which occurs as a sporadic lesion or develops in the setting of von Hippel-Lindau disease.

Congenital, Neonatal, and Infantile Hepatic Hemangiomatosis

Introduction

Apart from neonatal and infantile hepatic angiomatous tumors classified as hemangioendotheliomas (type 1 lesions), discussed in a special chapter, there are situations where cavernous vascular malformations (hemangiomas) of the skin are associated with similar lesions in the liver. This combination may be present at birth (congenital or neonatal hepatic hemangiomatosis), manifest postnatally, or later in infancy (infantile hemangiomatosis).

Congenital Hemangiomas Associated with Hepatic Vascular Tumors: Benign Neonatal Hemangiomatosis

A part of infantile hepatic hemangiomas develop in the context of congenital hemangiomas of the skin and other organs and in the setting of hemangiomatosis. A neonate with multiple hemangiomatosis can be categorized into two main clinical entities: (1) benign neonatal hemangiomatosis (BNH; Stern et al. 1981) and (2) diffuse or disseminated neonatal hemangiomatosis (DNH). Multiple cutaneous infantile hemangiomas (hemangiomatosis) are reported to arise in 10–25 % of infants with cutaneous hemangiomas (Achauer et al. 1997). Multiple hemangiomas of the skin in infants, in particular more than five lesions, are a marker of possible internal hemangiomatosis, with the liver being an important site (concurrent cutaneous and hepatic hemangiomas; Robinson and Hambleton 1977; Berman and Lim 1978; Metry et al. 2004). Among 47 patients with segmental hemangiomas of the skin, 79 % of the patients had their skin hemangiomas on the face, and 43 % showed liver hemangiomas, followed by the gastrointestinal tract (34 %) and the brain (34 %). Forty percent of the patients in this study fulfilled the criteria of PHACE syndrome (posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta, cardiac defects, and eye abnormalities) (Metry et al. 2001, 2004). Multiple congenital hemangiomas of the skin in a neonate have been found to be associated with hepatic angiosarcoma (Nord et al. 2006).

Diffuse Neonatal Hemangiomatosis

In some of the patients with congenital hemangiomas, the development of the lesions follows a diffuse pattern (diffuse congenital/neonatal hemangiomatosis). Diffuse/disseminated neonatal hemangiomatosis (DNH) is a rare neonatal condition in which cutaneous and visceral hemangiomas coexist. The disorder is also termed multiple miliary neonatal hemangiomatosis (review: Enjolras and Mulliken 1998). DNH

hemangiomas are either present at birth or develop during the first week of life and are twice as frequent in girls in comparison with boys (Holden and Alexander 1970; Golitz et al. 1986; Ho et al. 2000; Schulze et al. 2006; Wananukul et al. 2006; Gouedard et al. 2007; Al-Kaabi et al. 2009; Glick et al. 2012). The first sign of DNH is the appearance of cutaneous hemangiomas, which may become more numerous and extensive. In addition to multiple hemangiomas of the skin, other possibly involved organs include the liver and, less commonly, pleura, lungs, intestines, central nervous system, and eyes. Involvement is limited to the skin and liver in part of the patients. If left untreated, DNH is often fatal at an early age, carrying an estimated 60–95 % mortality, although novel treatments have improved prognosis.

DNH reveals liver angiomas with variable frequencies (Pavlenishvili and Nemsadze 1978; Young et al. 1981; Montgomery et al. 1990; Hurvitz et al. 2000; Gottschling et al. 2006). Hepatic hemangiomas arising in the setting of DNH may grow to large size (e.g., 4 cm diameter; Gottschling et al. 2006). Hepatic hemangiomas in DNH may be associated with cardiac insufficiency caused by blood shunting through the tumor's vascular channels (Hurvitz et al. 2000; Gottschling et al. 2006). DNH with or without liver involvement may be associated with placental chorioangioma (Witters et al. 2003; Bakaris et al. 2004).

Previously, the mean age at death was 11 weeks (Stratte et al. 1996). In a retrospective analysis of the literature, it turned out that the mortality rate was 77.4 % in untreated patients and 27 % in treated patients, important risk factors for adverse outcome being congestive heart failure, coagulopathy, and the involvement of five or more organs (Lopriore and Markhorst 1999). Complications of DNH include high-output cardiac failure, marked thrombocytopenia with hemorrhage, consumption coagulopathy, and hepatic failure. In adult long-term survivors of DNH, visceral hemangiomas in the absence of cutaneous hemangiomas have been observed (Ohnishi et al. 2002). In some of these adults, DNH is visualized on CT images as multiple calcifications in the liver, spleen bowel wall, and adrenals (Latifi and Siegel 1992), representing dystrophic calcification of regressed hemangiomatous lesions. Rarely, DNH develops in congenital overgrowth syndromes, e.g., Simpson-Golabi-Behmel syndrome (Poetke et al. 2002).

The previous concept of DNH may require revision, specifically in regard to the exact types of vascular tumors involved. A recent evidence-based review of case reports of DNH was based on the hypothesis that many cases reported as DNH did in fact not have infantile hemangiomas and also other forms of neonatal vascular diseases. Between the years 1950 and 2009, 73 cases were selected from the literature and categorized into three groups: infantile or probable (P) infantile hemangioma (IH/P-IH), multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT/P-MLT), and multifocal vascular lesions, not otherwise specified. Of these 73 cases, 43 had IH/P-IH, 17 had MLT/P-MLT, and 13 had multifocal vascular lesion NOS. Five percent of patients in the IH/P-IH group died, in contrast to a death rate of 65 % in the MNLT/P-MLT group (Glick et al. 2012).

Hepatic Hemangiomatosis of Infancy

There are published observations of infantile hemangioma, i.e., postneonatal hemangiomatosis characterized by the combination of cutaneous hemangiomas and visceral/hepatic hemangiomas, i.e., cavernomas and not hemangioendotheliomas (Robinson and Hambleton 1977; Rotman et al. 1980; Larcher et al. 1981; Vorse et al. 1983; Platokouki et al. 1998; Mendiratta et al. 2008). Hepatic hemangiomas may be combined with other visceral hemangiomas, in particular splenic lesions (Platokouki et al. 1998). Similar to the neonatal situations, large and/or multiple lesions can cause cardiac failure (Vorse et al. 1983).

Pathogenic Pathways

The concomitant development of angiomatous lesions in the skin and visceral organs is striking and suggests an abnormal multifocal angiogenic

mechanism leading to the emergence of multiple circumscribed angiomatous malformations. The cause of this angiogenic response is not known, and we also do not know why such characteristic multifocal patterns arise and why certain organs and not others are involved. As some of the lesions can later undergo involution, a complex derangement of vascular growth versus vascular remodeling and regression through apoptosis may be operational. The transient growth of angiomatous lesions, in part modulated by external factors, in some way mimics the emergence of a definitive vascular network but with a highly abnormal growth overshoot.

Diffuse Hepatic Hemangiomatosis of Adults

Introduction

Diffuse hepatic hemangiomatosis of adults is a very rare condition with so far not well-known etiology and natural history. The disorder is mostly known from infants and is much less common in adults. It is defined as the presence of numerous synchronous hemangiomas, mostly of the cavernous type, in one liver lobe, right and left lobe, or the entire liver, in the absence of extrahepatic hemangiomas. The difference between "numerous" hemangiomas (diffuse hemangiomatosis) and "multiple" hemangiomas has not been clearly worked out. For the diagnosis of diffuse hemangiomatosis, the distribution pattern of the lesions is crucial, i.e., involvement of large parts of the liver or the entire liver. The prevalence of diffuse hemangiomatosis of the liver is not well known. Among 26 patients with hepatic hemangiomas, six were diffuse lesions (Dickie et al. 2009). Sometimes, accompanying hemangiomatosis of the spleen is present (diffuse hepatosplenic hemangiomatosis; Tarazov et al. 1990; Langner et al. 2001). Most patients are women (Popa et al. 1984; Langsteger et al. 1990; Lehmann et al. 1999; Moon et al. 2000; Guzman-Valdivia Gomez et al. 2006; Kim et al. 2008).

Clinical and Imaging Features

The clinical presentation of hepatic hemangiomatosis is usually nonspecific and related to multiple mass effects and hepatomegaly. Some of the patients experience moderate to intense abdominal pain. Patients with diffuse liver hemangiomas sometimes produce significant tumor-associated shunts, followed by heart failure (Jayanthi et al. 2000). Diffuse hepatic hemangiomatosis with its enormous coagulative vascular surface with altered endothelial features can cause thrombocytopenia (Jayanthi et al. 2000). Extensive hemangiomatosis can cause sinusoidal compression/congestion, thereby causing a sinusoidal blockage and eventually portal hypertension with esophagogastric varices. The hemangiomas may behave in a stable way, with minor or absent change with time, but progressive forms extending from liver lobe to the other are known (Lehmann et al. 1999). Diffuse hepatic hemangiomatosis can be associated with secondary polycythemia (Popa et al. 1984). The cause of progressive growth is not established, but enhanced growth of hepatic hemangiomatosis was observed in two adults following postmenopausal estrogen replacement therapy (Ozakyol and Kebapci 2006). One patient with secondary polycythemia has been described (Popa et al. 1984).

Diffuse hepatic hemangiomatosis has characteristic imaging features on US, CT, and MR images (Crespo Uriguen et al. 1988; Feurle 1990; Langsteger et al. 1990; Frangides et al. 1995; Lehmann et al. 1999; Moon et al. 2000; Vilgrain et al. 2000; Mihalche and Dumitrache 2004; Guzman-Valdivia Gomez et al. 2006; Blondet et al. 2007). Ultrasonography shows small to large, hypoechoic masses with ill-defined margins to the adjacent liver substance, but confluent hyperechoic masses are also in evidence (Vilgrain et al. 2000). Contrast enhancement with a centripetal filling pattern of the entire tumors on the delayed phase of dynamic CT and inhomogeneous diffuse uptake of the entire tumor on delayed blood-pool images on

99mTc-labeled red blood cell scans are characteristic features (Kim et al. 2008). As the tumorous lesions have prominent flow, hepatic artery branches as the feeding vessels are dilated (Moon et al. 2000). On MR images, most tumors showed a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted images. Areas with macroscopic cystic change have foci of lower intensity than the remainder of tumor on T1-weighted images and higher intensity than the remainder of tumor on T2-weighted images (Moon et al. 2000).

Pathology

In most cases, the liver lobes are densely involved by hemangiomatous nodules of variable diameters (Fig. 1), resulting in distinct patterns summarized in Table 1. In part of patients, the entire liver is packed with typical, well-delineated angiomatous tumors, with thin and partly atrophic parenchymal bridges between the nodules (massive panhepatic hemangiomatosis, MPHH). In regard to the distribution of lesions, a diffuse pattern, in which numerous tumors are present as isolated, more or less evenly distributed hemangiomas, and nodular pattern consisting of multiple coalescent nodules measuring <5 mm in diameter have been distinguished (Jhaveri et al. 2011). Individual tumors may exceed 4 cm in diameter and therefore qualify for giant hemangiomas. In fact, hemangiomatosis can be associated with giant hepatic hemangiomas in a significant proportion of cases (Adam et al. 1970; Jhaveri et al. 2011). In a series of 22 patients with giant hepatic hemangioma, associated diffuse hemangiomatosis involving the right and left liver lobes was found in four patients (Adam et al. 1970). At laparoscopy, multiple to numerous medium-sized to large blue-black spongy masses are seen, sometimes bulging from the liver surface (Guzman-Valdivia Gomez et al. 2006). Pedunculated lesions also occur (Blondet et al. 2007). The number and size of hemangiomas may be such as to grossly mimic massive diffuse hepatic metastatic disease.

Most tumors show the typical histology of cavernous hemangiomas, with large, endothelium-lined channels prevailing in the core region of the tumors and smaller vascular channels at the periphery of the nodules, where also feeding vessels are found, and regressive changes in the center (fibrosis, thrombosis, granulation tissue). As in isolated giant liver hemangiomas, large tumors may show extended central fibrosclerosis or even hyalinosis and sometimes fresh or old infarctoid necrosis. The adjacent liver substance reveals perifocal parenchymal atrophy or fatty change of hepatocytes and may contain dilated veins or intermediate vessels, sometimes rather remote from the tumor nodules (Lehmann et al. 1999).

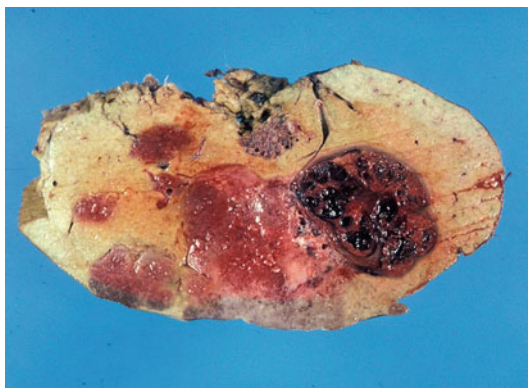

Fig. 1 Hepatic hemangiomatosis of the adult. The liver contains several well-delineated foci of hemangioma, in part with fresh thrombosis

Table 1 Proposed classification of macroscopic patterns of diffuse hepatic hemangiomatosis of adults

General patterns
Diffuse hepatic small-nodular hemangiomatosis
Diffuse hepatic hemangiomatosis associated with giant hemangiomas
Diffuse hepatic hemangiomatosis with pedunculated lesions
Massive panhepatic hemangiomatosis (MPHH)
Diffuse versus nodular patterns (Jhaveri et al. 2011)
Diffuse pattern (more or less even distribution of isolated tumors)
Nodular pattern (multiple coalescent small nodules)

Diffuse Hemangiomatosis of the Liver and Spleen (Diffuse Hepatosplenic Hemangiomatosis)

In part of the patients with diffuse hemangiomatosis, the liver and spleen are synchronously involved (Tarazov et al. 1990, 1991; Langner et al. 2001). This entity may be associated with progressive liver failure, thrombocytopenia, and coagulopathy (Langner et al. 2001).

Focal and Diffuse Hemangiomatosis Associated with Giant Hepatic Hemangioma

Circumscribed or focal, or even diffuse, hemangiomatosis with the development of multiple small nodules may be noted in association with large cavernous hepatic hemangiomas (so-called giant hemangiomas; Melis 1954; Jhaveri et al. 2011). Among 42 cases of giant hepatic hemangioma, associated hepatic hemangiomatosis was detected in 18 patients (44 %). Twelve patients had a diffuse pattern of hemangiomatosis (67 %), and six patients showed a nodular pattern consisting of multiple coalescent nodules measuring <5 mm (33 %). There was no association between the size of the giant hemangioma and extent of hemangiomatosis (Jhaveri et al. 2011). The pathogenesis of this alteration has not been clarified. Theoretically, small and satellite-like hemangiomas in the vicinity of a large lesion may emerge due to the abnormal blood circulation surrounding the large lesion, or may reflect a field effect, i.e., emergence of multiple angiomas within an abnormal vascular bed, with one and large predominant lesion.

Hepatic Hemangiomas in Systemic Adult Hemangiomatosis (Polysomatic Hemangiomatosis)

Systemic hemangiomatosis (diffuse hemangiomatosis, hemangiomatosis diffusa) is a very rare condition characterized by the occurrence of cavernous hemangiomas in multiple organ systems, including the skin, bone, central nervous system, and visceral organs. The process has either been interpreted to be neoplastic or to represent a hamartoma-like malformation, but the involvement of numerous tissue and organ types together with continuous growth in at least part of the patients favors a highly abnormal angiogenic and probably neoplastic process. The disease is sporadic, without evidence of a familial trait (Fischer and Roeckl 1961; Tsukagoshi et al. 1998; Erdogan et al. 2003). Visceral manifestations can involve several intra-abdominal organs, e.g., the spleen, liver, intestine, peritoneum, and lymph nodes, in one and the same patient (Maeda et al. 1981; Ribback et al. 2011). Some cases have revealed an aggressive course with poor prognosis, owing to continuous growth of the lesions (Böhm et al. 1980).

Liver involvement in the form of cavernous hemangiomas has been observed (Bargon and Yu 1968; Gordin et al. 1975; Maeda et al. 1981; Erdogan et al. 2003; Edlow et al. 2006). Liver involvement can be associated with angiomatous lesions of the intestine, spleen, and lymph nodes (Maeda et al. 1981). The angiomatous lesions developing in the liver may be extensive and cystic, resulting in a "honeycomb-like" liver (Tsukagoshi et al. 1998).

Hepatic Hemangiomas Combined with Skeletal Hemangiomatosis

Diffuse skeletal hemangiomatosis (disappearing bone disease) is a very uncommon disorder, which is characterized by osteolytic angiomatous lesions causing vanishing bone in part of the patients (syndrome of phantom bone or disappearing bone). An aggressive form of the disease that shows regional involvement and massive osteolysis, frequently involving the shoulder and hip areas, is called Gorham's disease. In the marrow cavities of involved bones, numerous thin-walled and partly dilated vascular channels are present, with signs of bone substance lysis in

the vicinity (Bezold 1951; Gorham et al. 1954; Ishida et al. 1994; Wallis et al. 1994, Clayer 2002).

The disorder is sometimes associated with visceral and in particular hepatic hemangiomas (Bargon and Yu 1968; Waldron and Zeller 1969; Kane and Newman 1973; van den Bosch et al. 1975; Rolain et al. 1978; Körster and Jansen 1981; Kiriyama et al. 2001). In an old female patient described by Kane and Newman (1973), marked hepatomegaly was found, tender to palpation. A large left lobe presented as an epigastric mass with a systolic bruit. A liver scan showed an enlarged pattern with increased uptake in the left lobe. Transfemoral visceral angiography demonstrated numerous diffuse capillary-sized hemangiomatous vessels accounting for hepatomegaly and bruit. There was rapid shunting to the hepatic veins and inferior vena cava and retrograde filling of the portal vein, coronary vein, and gastric and mesenteric collateral veins.

Hepatic Hemangioma in Cystic Angiomatosis of the Bone

Cystic angiomatosis of the bone (CAB, diffuse cystic angiomatosis of the bone; Gorham's vanishing bone disease; Gorham's massive osteolysis; Gorham-Stout syndrome; phantom bone disease; idiopathic massive osteolysis) is a rare, multicentric disease characterized by involvement of blood and lymph vessel systems, producing diffuse cystic lesions in the skeleton, predominantly affecting the trunk bones (review: Möller et al. 1999).

This intriguing disorder has been described in 1914 (Shennan 1914; "histologically nonmalignant angioma, with numerous metastases"), and the term CAB was coined in 1953 (Jacobs and Kimmelstiel 1953). In most cases, CAB will show a widespread distribution in the skeleton, but very rare localized forms have also be encountered, e.g., in the cranio-cervical region (Pavanello et al. 2007). Familial CAB has been observed in one family over four generations (Reid et al. 1989) and four siblings showing congenital generalized lipodystrophy accompanied by CAB (Brunzell et al. 1968). In its presentation, CAB is similar to diffuse angiomatosis of the bone, but the relationship between these two disorders has not yet been clarified. Histologically, CAB shows a contribution of lymph vessels, a feature usually lacking in diffuse angiomatosis of the bone. CAB causes osteolytic lesions with internal septation of the bone and a honeycomb appearance of the skeletal system (Jacobs and Kimmelstiel 1953; Ritchie and Zeier 1956; Boyle 1972; Shivaram et al. 2007; Pulido-Zamudia 2001; Malik et al. 2008).

CAB may be associated with chylothorax (Deveci et al. 2011) and with visceral hemangiomas, including hepatic hemangiomas and splenic angiomas/angiomatosis (Fernandez Jimenez et al. 2000; Vanhoenacker et al. 2003). In two patients found in the literature, only splenomegaly was noted (Shennan 1914). Lymphangioma of the spleen has been described in CAB (Boyle 1972), further supporting the involvement of the lymph vessel system and a systemic lymphangial disorder in CAB.

Hepatic Hemangiomas in Segmental Infantile Hemangioma and Reticular Infantile Hemangioma

Introduction

An uncommon form of cutaneous infantile hemangioma is characterized by a flat, blotchy lesion, which, in the past, has been called "port-wine stain-like". When occurring in the face, this variant is called "segmental" and is known to be an indicator for posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta, cardiac defects, and eye malformations (the PHACE association; Frieden et al. 1996; Haggstrom et al. 2010). Later, this variant of cutaneous hemangioma has been renamed, reticular infantile hemangioma, to denote this distinctive macular, network-like lesion (Mulliken et al. 2007).

Liver Involvement in Segmental Hemangioma

A total of 47 cases of solitary segmental hemangiomas of the skin in association with visceral hemangiomatosis has been reviewed. Among these cases, the liver was the most common internal organ involved by hemangiomas (43 % of the cases; Metry et al. 2004).

Liver Involvement in Reticular Hemangioma

In this hemangioma, liver manifestations may be present. In one male infant with reticular cutaneous hemangioma associated with arteriovenous shunting in the pelvis and lower extremity, the liver showed multiple nodular enhancing lesions on T2-weighted MRI, consistent with multiple hemangiomas (Mulliken et al. 2007).

Intravascular Papillary Endothelial Hyperplasia (IPEH) of the Liver

Introduction

Intravascular papillary endothelial hyperplasia (IPEH; synonyms: Masson's pseudoangiosarcoma; Masson lesion; Masson's tumor) was described by Masson in 1923 under the term, hémangioendothéliome végétant intravasculaire (vegetant intravascular hemangioendothelioma, Masson 1923; review: Steffen 2003). In 1932, the lesion was described again by use of a different terminology (thrombopoietic proliferating endovasculitis; Henschen 1932). IPEH is now regarded as a benign, nonneoplastic vascular lesion originating from an organizing vascular thrombus or, less frequently, from a hematoma, with unusual reactive proliferation of endothelial cells (Clearkin and Enzinger 1976; Hashimoto et al. 1983). Variants of PEH developing in an extravascular compartment and specifically in hematomas are termed extravascular papillary endothelial hyperplasia (EPEH; Pins et al. 1993; Sezgin et al. 2005).

The lesion typically occurs in adults, but pediatric cases have also been reported. IPEH has a propensity to occur in the skin and subcutis, but other locations are also well documented, including the breast and mammary subcutaneous tissue, oral cavity, hypopharynx and larynx, parotid gland, lung, intestinal tract, spleen, tendon sheaths, kidney, urinary bladder, renal vein, other large vessels and their aneurysms, adrenal, retroperitoneal space, bone, central nervous system, and liver (Hong et al. 2004; Kan et al. 2004). In the skin, IPEH may present as multiple recurrent dark to almost black papular lesions involving the entire body, resembling cutaneous metastases of malignant melanoma. IPEH is commonly a slow-growing lesion, but phases of rapid enlargement of the process may be caused by repeated bleeding into the lesion, and hemorrhage from IPEH may be massive (Jung et al. 2005; Rizza et al. 2009).

IPEH of the Hepatobiliary System

IPEH can involve the gastrointestinal tract (Meadows et al. 2010). Very rarely, IPEH has been detected in the liver (Hong et al. 2004; Kan et al. 2004). A 69-year-old female showed, on abdominal CT scan, a 10 × 7 cm-sized, lobulated heterogeneous contrast-enhancing soft tissue mass involving the entire left liver lobe (Hong et al. 2004). In the arterial phase of CT, the mass had a focal nodular enhancement around its peripheral portion, whereas in the delayed phase, there was a persistent low-density noncontrast-enhancing portion in the tumor center. Angiography exhibited some tumor-supplying arteries originating from the left hepatic artery. The mass seen during operation was limited to the left liver lobe, of 10 × 7 cm size, and was a nonhomogeneous multinodular mass including focal necrosis. No major vessel invasion was observed. Histology of the resection specimen showed IPEH. The 65-year-old male patient described by Kan and coworkers (Kan et al. 2004) had a cystic, focally calcified mass of several cm diameter located within a dilated left ventricular cavity. This mass appeared to float

between the ventricle and mitral valve area. Multiple hyperechoic hepatic nodules were also identified on an abdominal sonograph. Histology of the resected lesion showed IPEH, and similar alterations were found in liver biopsies. The liver nodules had the same papillary structures within the liver parenchyma but had spared the portal tracts.

Pathology

Based in the pattern of lesion development, IPEH is pathologically classified in three subtypes: a pure form, the most common, in which the lesion arises in dilated blood vessels; a mixed form in which IPEH arises in preexisting vascular alterations (hemangioma, aneurysm, arteriovenous malformation, and pyogenic granuloma), and an extravascular form, the latter called EPEH.

Histologically, two different papillary structures are observed: one defined as inflammatory papilla constantly associated with thrombotic material and the other defined as fibrous papilla in the absence of a visible thrombus (Eusebi et al. 1980). IPEH may mimic Kaposi's sarcoma (Reed et al. 1984; Torres and Rodriguez 1984). Immunohistochemically, the endothelial structures are reactive for CD34, and the spindle cells are positive for vimentin and, in part, smooth muscle actin (Soares et al. 2008). Reactivity of endothelial cells for factor VIII-associated antigen was only observed in advanced or "mature" lesions, similar to what happens in organizing thrombi (Albrecht and Kahn 1990).

Pathogenesis

There is clear evidence that IPEH arises from an exuberant organizing reaction within a thrombus (organizing thrombus theory; Del Rio et al. 1992). Similar lesions are sometimes found within hematomas, i.e., outside vascular spaces (EPEH; see above; Pins et al. 1993; Aulicino et al. 1995; Sezgin et al. 2005).

Hepatic Angioleiomyoma

Introduction

Angioleiomyoma (angiomyoma, vascular leiomyoma) is a benign soft tissue tumor that usually develops in the subcutaneous tissue of the lower extremities. These circumscribed nodules consist of intertwined thick-walled, abnormal vessel structures formed by proliferating smooth muscle cells and narrow or slit-like vascular channels (reviews: Hachisuga et al. 1984; Ramesh et al. 2004).

Clinical and Imaging Findings

Angioleiomyoma commonly presents as a painful mass in about 60 % of the cases. Tumors located in the extremities, and specifically in the hand, typical display swelling with physical activity of the involved part (Hachisuga et al. 1984; Ramesh et al. 2004). Pain of the nodule (tuberculum dolorosum) is thought to be caused by local ischemia due to contraction of the tumor vessels. In an analysis of 229 cases, the lesions were detected in high incidence in the fourth to sixth decade, with a clear predilection for females (Katenkamp et al. 1988).

Cytogenetic Findings

Relatively few data are available concerning karyotypic aberrations in angioleiomyomas, including t(X;10)(q22;q23.2) (Sonobe et al. 1996), del (6)(p21p23), del(21)(q21)[12] (Heim et al. 1986), t(X;11)(p11.4;p15) (Hennig et al. 1999)), and t(4;5)(p12;q33), der(13;15)(q10;q10) (Welborn et al. 2010), and del(6)(q13q23), add(8)(q24),del (19)(q10) (Welborn et al. 2010). Comparative genomic hybridization was employed to study relative DNA copy number changes in 33 angioleiomyomas. In about a third of the cases, DNA copy number changes involved one or two chromosomes with losses of chromosome 22 being the most common (Nishio et al. 2004).

Angioleiomyoma of the Hepatobiliary Tract

Angioleiomyoma of the liver has been described in 60-year-old woman with mild upper right quadrant pain for 1 month. Plain spiral CT scans showed a solitary, well-demarcated liver lesion of 4 cm diameter in liver segment VIII. CT with contrast revealed slight homogeneous enhancement (60 HU) of the tumor in relation to the surrounding normal liver substance. Tumor biopsy showed typical angioleiomyoma, with medium-sized blood vessels with thickened walls. The vessel wall cells were in concentric order with intervening radiant emission of spindle and epithelioid cells in intervascular bundles. The patient had an eventful course (Beissert et al. 2002). Angioleiomyoma has been observed in the gallbladder, sometimes causing hemobilia and acute colicky pain (Aschl et al. 1999; Segura-Sampedro et al. 2012).

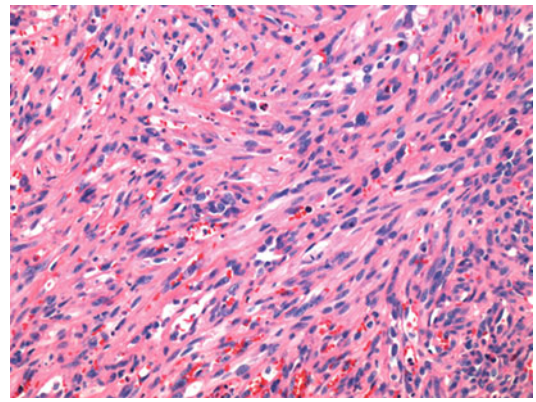

Fig. 2 Hepatic angioleiomyoma. Slit-like vascular spaces with intervening smooth muscle cells (hematoxylin and eosin stain)

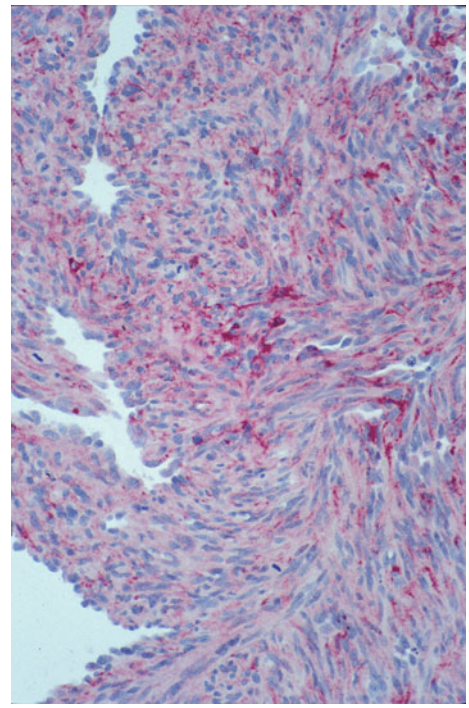

Fig. 3 Hepatic angioleiomyoma. Numerous neoplastic spindle cells are reactive for smooth muscle actin (alpha-SMA immunostain)

Pathology

Histologically, four variants have been described, i.e., solid/capillary forms (18 %), venous forms (38 %), mixed/combined forms (43 %), and cavernous forms (<1 %) (Hachisuga et al. 1984; Katenkamp et al. 1988; Figs. 2 and 3). Mixed and cavernous forms seem to be more frequent in male patients (Katenkamp et al. 1988). Most of the cells forming the nodule are strongly reactive for alpha smooth muscle actin. Immunohistochemically, the tumor itself does not contain CD34-positive stromal cells, but bundles of such cells are present at the tumor border and in the adventitial tissue of the surrounding normal vessels (Nakayama et al. 2002). Subcutaneous smooth muscle tumors stain for p16 (Longano et al. 2010).

Hemangioblastoma

ICD-O code 9161/1

Introduction

Hemangioblastoma (synonym, capillary hemangioblastoma) is a distinct benign vascular tumor of uncertain histogenesis characterized by

a network of vascular channels admixed with often lipid-laden macrophages (the stromal cells). Most hemangioblastoma develops in the central nervous system, particularly in the area of the cerebellum and less often in the lateral ventricle, corpus callosum, spinal cord, retina, optic nerve, pituitary gland, pineal gland, and meninges. Up to 2.5 % of all intracranial tumors are hemangioblastomas. Hemangioblastomas occur as sporadic lesions or arise in the setting of von Hippel-Lindau disease. A distinct pathway is involved in angioblastomas developing in von Hippel-Lindau (VHL) disease. In this disorder, angioblastomas typically emerge in the retina and the central nervous system, but they may also occur in other parts of the body. Organs and tissue involved with sporadic hemangioblastoma outside the CNS include the kidney, adrenal gland, and retroperitoneum. In the lung, a novel hemangioblastoma-like clear cell stromal tumor was found that may have a relation to the hemangioblastoma-associated stromal cells (Falconieri et al. 2013). Few hemangioblastomas have been shown to contain complex differentiation patterns, e.g., rhabdoid features (Yin et al. 2012). Hemangioblastomas occurring in the setting of VHL contain mast cells that seem to be tumor-derived (Merrill et al. 2013).

Primary Hepatic Angioblastoma

Hemangioblastoma can very rarely develop in the liver, even as multifocal hyperechogenic lesions (Rojiani et al. 1991; McGrath et al. 1992; Hayasaka et al. 1999). These hypervascular and arterialized masses have been reported to show the same histologic pattern as the respective CNS tumors, i.e., a complex mixture of vascular structures and stromal cells mainly representing lipid-laden foamy macrophage-like cells (Rojiani et al. 1991; Hayasaka et al. 1999). This morphologic presentation is clearly different from typical hepatic hemangioma, which may rarely occur in VHL (Zeitlin 1942). A part of the hepatic hemangioblastomas were developed in the setting of VHL (Hayasaka et al. 1999). In one patient with VHL, multiple hepatic and pulmonary hemangioblastomas were demonstrated (McGrath et al. 1992).

Other Hepatic Lesions Associated with von Hippel-Lindau Disease

Patients with VHL can develop ordinary hepatic hemangiomas (Yavas et al. 2013) and hepatic cysts (Lee et al. 2010) as a part of the VHL-associated multiple cyst syndrome.

Differential Diagnosis

The very rare hepatic hemangioblastomas may histologically be confounded with other hepatic angiomatous lesions having small vascular channels, such as capillary or lobular hemangiomas.

Pathogenic Pathways

Hemangioblastomas composed of a probably still immature endothelial lineage and stromal cells seem to represent a mimicker of an early mesodermal phase of angiogenesis. The potential involvement of an early mesodermal switch is supported by the reactivity of these tumors for the mesodermal transcription factor, brachyury/Bra (Barresi et al. 2012). The typical stromal cells of hemangioblastoma are thought to be committed stem cells, because they express both CD133 and Oct4, and are suggested to produce the distinct CD133-positive endothelium of these tumors (Welten et al. 2012). It has also been proposed that the tumors might derive from neoplastic transformation of neural stem cells in a specific niche (Ma et al. 2011) or from embryologic multipotent cells (Park et al. 2007). In the cerebella of patients with VHL, developmentally arrested structural elements (arrest of angioblastic lineage) were detected (Vortmeyer et al. 2003). These structures are composed of poorly differentiated cells expressing hypoxia-inducible factor (HIF)2alpha, but not HIF1alpha or brachyury. These elements were mainly found

in the molecular layer of the dorsum cerebelli, structures proposed to be developmentally arrested hemangioblast progenitor cells (Shively et al. 2011).

The cell systems involved in the pathogenesis of hemangioblastoma are subject to the complex metabolic alterations associated with von Hippel-Lindau disease (VHL), an autosomal-dominant disorder (OMIM 193300). Patients with VHL suffer from familial and sporadic hemangioblastomas, clear cell carcinoma of the kidney, pheochromocytoma, distinct neuroendocrine tumors, epididymal papillary cystadenomas, microcystic adenomas of the pancreas, endolymphatic sac tumors, cysts in several organs (mainly pancreas), and inherited forms of erythrocytosis (review: Maher et al. 2011). VHL is caused by germ line mutations of the VHL tumor suppressor gene and of the gene product, pVHL (review: Kortmeyer et al. 2013).

pVHL, which is localized to the cytoplasm of normal and neoplastic cells (Corless et al. 1997). has a central role in the regulation of oxygen sensing via the hypoxia-inducible factor (HIF) signaling cascade. HIFs are heterodimeric oxygen-sensing transcription factors that are crucially involved in the cellular adaptation to low oxygen environments. The extensive transcriptional program regulated by HIFs involves the induction of genes that control angiogenesis, cell proliferation and apoptosis, and mechanisms involved in metastasis. HIFs are heterodimers consisting of HIF-alpha and HIF-beta subunits. HIF-2alpha-dependent gene expression, such as ANGPLT4 and erythropoietin, are regulated by PARP-1/poly(ADP-ribose) polymerase-1 in the hypoxic response (Gonzalez-Flores et al. 2014). VHL acts as a master regulator of HIF activity by recognizing the substrate-recognition component of an E3 ubiquitin ligase complex that ubiquitinylates the hydroxylated catalytic alpha subunit of HIF for oxygen-dependent degradation (review: Haase 2009). Three cellular oxygen sensors mark the HIFs for pVHL-mediated degradations, i.e., the prolyl hydroxlyases PHD1, PHD2, and PHD3 (Pientka et al. 2012; Jaakkola and Rantanen 2013; Myllyharju and Koivunen 2013). The stability of HIF1alpha is increased by interaction of the transitionally controlled tumor protein/TCTP and degradation of pVHL. In hypoxic tumor tissues, VEGF expression is positively regulated by histone deacetylase 1/HDAC1 and negatively regulated by the pVHL via HIF1alpha (Reynoso-Roldan et al. 2012). HIF2alpha is regulated, in its action as a proangiogenic factor, by the orphan nuclear receptor TLX (Zeng et al. 2012). The role of HIFs as proliferation-stimulating factors depend on their role as an mTORC1 activator (Elorza et al. 2012).

pVHL binds to two subunits of the transcription elongation complex elongin, causing a decreased activity of this complex, suggesting that pVHL functions as a negative regulator of transcription elongation. There is evidence that regulated accumulation of HIF caused by failure of pVHL-mediated HIF degradation is an important factor in oncogenic pathways operating in VHL, e.g., in clear cell renal carcinoma. A second proposed oncogenic mechanism related to HIF involves E-cadherin, an adhesion molecule playing a significant role in cancerogenesis. pVHL promotes an E2-box-dependent E-cadherin transcription by HIF-mediated regulation of the transcription repressors SIP1 and snail (Evans et al. 2007). pVHL is also involved in the control of genomic stability. In response to DNA double-strand breaks, the suppressor of cytokine signaling 1 (SOCS1) promotes nuclear redistribution and K63 ubiquitinylation of pVHL. Loss of pVHL function in VHL compromises its K63 ubiquitinylation and attenuates the DNA-damage response, causing persistence of DNA double-strand breaks and promoting genomic instability and tumorigenesis (Metcalf et al. 2013). A further important role of pVHL, proposed to be involved in tumorigenesis, is related to cilial function. Primary cilium formation in renal cells requires the action of pVHL (Lutz and Burk 2006), and defective function of pVHL in VHL may thus promote renal and other cysts by failure of ciliogenesis (Rankin et al. 2006). This effect of pVHL on ciliogenesis depends of the phosphorylating factor, Nek1 (Patil et al. 2013). The high frequency of renal carcinomas in VHL may also be connected with a cilial connection of pVHL. It was found that human renal carcinomas have a lower frequency of cilia than the

neighboring parenchymal tissue (Basten et al. 2013). Mice with targeted inactivation of the VHL gene developed hepatic cavernous hemangiomas (Haase et al. 2001), while in another murine model, VHL and PTEN conditional deletions caused multiple cavernous liver lesions in a coordinated manner (Chen et al. 2010). The probability of developing familial or recurrent sporadic hemangioblastoma in patients with mutated VHL is higher in the presence of a vitronectin M381T polymorphism (Huang et al. 2009).

Liver Involvement in Splenic Littoral Cell Tumors

Introduction

Littoral cell vascular tumors of the spleen form a unique group of vascular neoplasms are derived from cells of the red pulp, with a variable biology of disease. Littoral cell angioma, the most common form within the group, was first described in 1991 (Falk et al. 1991). Since then, other variants have been defined. The neoplastic cell is regarded as the transformed offspring of splenic littoral cells or venous sinus-lining cells (Rosso et al. 1995, 1996; Johnson et al. 2007; Kranzfelder et al. 2012; Larsen et al. 2013). The tumors can be divided into splenic littoral cell angioma (SLCA), splenic littoral cell hemangioendothelioma (SLCH), and littoral cell angiosarcoma (SLCAS) (He et al. 2014).

SLCA is regarded as benign and usually occurs in adults without gender predilection. The solitary or multiple nodules can cause significant asymptomatic or symptomatic splenomegaly. Multiple nodules are found in 85 % of cases. SLCA can occur with concomitant visceral malignancies, such as colorectal cancer, pancreatic carcinoma, renal cell carcinoma, urologic cancer, ovarian cancer, and lung carcinomas, and was also observed in association with melanoma and lymphoma. SLCH shows a protracted course (Ben-Izhak et al. 2001) and can behave in a low-grade malignant manner. SLCAS exists as low- and high-grade malignancy lesions (Rosso and Paulli 2004). Histologically, littoral cell vascular tumors are composed of a network of ectatic blood-filled channels lined by plump, bland, or atypical cells that may form intraluminal papillary fronds and show erythrophagocytosis. There seems to be a transition from littoral cell angioma to low-grade malignant forms (Fernandez et al. 2006). Immunohistochemically, the littoral tumor cells are reactive for CD31, CD68, CD21, and CD163 but negative for CD34 . This unique cell therefore expresses both endothelial and macrophage/histiocyte markers (Fernandez et al. 2006; Larsen et al. 2013). Littoral cells or splenic venous sinus-lining cells highly express the formin homology domain protein 1, the red blood cell Duffy antigen receptor for chemokines, CD8 a/a, and SIRPa (CD172a).

Liver Involvement in Littoral Cell Hemangioendothelioma and Littoral Cell Angiosarcoma

Both SLCH and SLCAS can metastasize to the liver (Fernandez et al. 2006; Wang et al. 2013; He et al. 2014). In SLCH, two forms have been shown to metastasize to the liver, a more common typical hemangioendothelioma with nuclear atypia and necrosis, and an uncommon variant with bland, plump cells (Fernandez et al. 2006). Most cases of SLCAS metastasizing to the liver form metastatic nodular masses, but diffuse spread to the liver is also known. Specifically, low-grade SLCAS can spread to the liver with a diffusely infiltrating pattern (Larsen et al. 2013). SLCH and SLCAS metastasizing to the liver show the same histology and immunohistochemical phenotype as the primary splenic tumors.

Hepatic Hemangioendothelioma with Epithelioid Morphology and Eosinophilia

Introduction

Vascular tumors are characterized by an epithelioid phenotype of endothelial cells from a complex group of neoplasms with a broad spectrum of

biologic behavior, ranging from benign to potentially malignant and frankly malignant (the family of epithelioid vascular tumors; Tsang and Chan 1993). The most common epithelioid vascular tumor of the liver is epithelioid hemangioendothelioma (HEHE), but there are few lesions with an epithelioid phenotype that deviate from the features of HEHE. Hepatic hemangioendothelioma with epithelioid morphology and eosinophilia is a very rare example of such unusual vascular liver tumors.

Clinical Features

As described in the original report (Kimura et al. 2006), a 33-year-old man was found to have hepatosplenomegaly, an itchy eczematous rash scattered on the trunk and the extremities, marked peripheral blood eosinophilia, markedly elevated IgE serum levels, and an increased serum IL-5. A bone marrow biopsy showed a hypercellular hemopoietic tissue with increased eosinopoiesis but without signs of malignancy. No chromosomal anomalies were detected in marrow cells. Liver biopsy revealed an eosinophil infiltrated and a vascular proliferation characterized by well-formed blood vessels lined with plump endothelial cells (positive for CD31 and factor VIII-associated antigen but not for CD34) with eosinophilic cytoplasm and a large vesicular nucleus. Steroid therapy improved the skin lesions and hydroxyurea normalized eosinophilia, but 1 year after diagnosis, liver failure ensued causing death.

Pathology

Autopsy revealed massive hepatomegaly (4,160 g) and ill-defined multiple spongy lesions scattered throughout the liver. In addition, nodular gray to white areas, 2–6 cm in diameter, were observed in this organ.

Microscopically, the lesions were composed of vascular proliferations with epithelioid endothelial cells as already seen in the liver biopsy. A part of these endothelial cells had a vacuolated cytoplasm. Dilated vascular channels and solid areas with few vascular spaces were noted.

The histologic phenotype somewhat resembles other vascular proliferations with an inflammatory response, encompassing such entities as angiolymphoid hyperplasia with eosinophilia (ALHE), inflammatory angiomatous nodules, atypical pyogenic granuloma, histiocytoid hemangioma, and Kimura's disease.

References

Achauer BM, Chang CJ, Vander Kam VM (1997) Management of hemangioma of infancy: review of 245 patients. Plast Reconstr Surg 99:1301–1308

Adam YG, Huvos AG, Fortner JG (1970) Giant hemangiomas of the liver. Ann Surg 172:239–245

Albrecht S, Kahn HJ (1990) Immunohistochemistry of intravascular papillary endothelial hyperplasia. J Cutan Pathol 17:16–21

Al-Kaabi A, Yanofsky R, Bunge M, Hyman J, Rafay MF (2009) Diffuse hemangiomatosis with predominant central nervous system involvement. Pediatr Neurol 40:54–57

Aschl G, Wallner M, Tuppy H, Frohler W, Kramar R (1999) Angioleiomyoma of the gallbladder: a rare cause of hemobilia in a patient on dialysis (in German). Dtsch Med Wochenschr 124:13–16

Aulicino MR, Kaneko M, Uinger PD (1995) Excessive endothelial cell proliferation occurring in an organizing thyroid hematoma: report of a case and review of the literature. Endocr Pathol 6:153–158

Bakaris S, Karabiber H, Yuksel M, Parmaksiz G, Kiran H (2004) Case of large placental chorioangioma associated with diffuse neonatal hemangiomatosis. Pediatr Dev Pathol 7:258–261

Bargon G, Yu D (1968) Diffuse hemangiomatosis of the skeleton, liver, kidney and soft tissues (in German). Fortschr Geb Röntgenstr Nuklearmed 109:805–808

Barresi V, Vitarelli E, Branca G, Antonelli M, Giangaspero F, Barresi G (2012) Expression of brachyury in hemangioblastoma: potential use in differential diagnosis. Am J Surg Pathol 36:1052–1057

Basten SG, Willekers S, Vermaat JS, Slaats GG, Voest EE, van Diest PJ, Giles RH (2013) Reduced cilia frequencies in human renal cell carcinomas versus neighboring parenchymal tissue. Cilia 2:2

Beissert M, kenn W, Schultz G, Keberle M, Eck M, Hahn D (2002) Hepatic angiomyoma: CT and MRI findings. Abdom Imaging 27:40–42

Ben-Izhak O, Bejar J, Ben-Eliezer S, Vlodavsyl E (2001) Splenic littoral cell haemangioendothelioma: a new low-grade variant of malignant littoral cell tumour. Histopathology 39:469–475

Berman B, Lim H (1978) Concurrent cutaneous and hepatic hemangiomata in infancy: report of a case and a review of the literature. J Dermatol Surg Oncol 4:869–873

Bezold K (1951) A case of disseminated bone hemangiomatosis (in German). Fortschr Geb Röntgenstr 75:636–641

Blondet A, Ridereau-Zins C, Michalak S, Pessaux P, Aubertin A, Aubé C (2007) Multiple pedunculated liver hemangiomas presenting with volvulus (in French). J Radiol 88:891–894

Böhm N, Behrens R, Imm W, Nöldge G (1980) Generalized hemangiomatosis. A hamartoma-like malformation of the vascular system with poor prognosis (in German). Med Welt 31:1291–1294

Boyle WJ (1972) Cystic angiomatosis of bone. A report of three cases and review of the literature. J Bone Joint Surg 54:626–636

Brunzell JD, Shankle SW, Bethune JE (1968) Congenital generalized lipodystrophy accompanied by cystic angiomatosis. Ann Intern Med 69:501–516

Chen S, Sanford CA, Sun J, Choi V, Van Dyke T, Samulski RJ, Rathmell WK (2010) VHL and PTEN loss coordinate to promote mouse liver vascular lesions. Angiogenesis 13:59–69

Clayer M (2002) Skeletal angiomatosis in association with gastrointestinal angiodysplasia and paraproteinemia: a case report. J Orthop Surg (Hong Kong) 10:85–88

Clearkin KP, Enzinger FM (1976) Intravascular papillary endothelial hyperplasia. Arch Pathol Lab Med 100:441–444

Corless CL, Kibel AS, Iliopoulos O, Kaelin WG (1997) Immunostaining of the von Hippel-Lindau gene product in normal and neoplastic human tissues. Hum Pathol 28:459–464

Crespo Uriguen M, Martinez Torres D, Miyar Gonzalez A (1988) Diffuse giant cavernous hemangioma of the liver: apropos of 2 cases 8 (in Spanish). Rev Esp Enferm Apar Dig 73:289–292

Del Rio E, Aguilar A, Sanchez Yus E (1992) Intravascular papillary endothelial hyperplasia: a reorganizing thrombus. Int J Dermatol 31:713–714

Deveci M, Inan N, Corapcioglu F, Ekingen G (2011) Gorham-Stout syndrome with chylothorax in a six-year-old boy. Indian J Pediatr 78:737–739

Dickie B, Dasgupta R, Nair R, Alonso MH, Ryckman FC, Tiao GM, Adams DM, Aizikhan RG (2009) Spectrum of hepatic hemangiomas: management and outcome. J Pediatr Surg 44:125–133

Edlow BL, Burnett MG, Belasco J, Marcotte PJ, D'Angio G, Furth EE (2006) Recurring polysomatic hemangiomatosis: a new syndrome? J Pediatr Hematol Oncol 28:471–475

Elorza A, Soro-ARnaiz I, Melendez-Rodriguez F, Rodriguez-Vaello V, Marsboom G et al (2012) HIF2a acts as an mTORC1 activator through the amino acid carrier SLC7A5. Mol Cell 48:681–691

Enjolras O, Mulliken JB (1998) Vascular tumors and vascular malformations (new issues). Adv Dermatol 13:375–422

Erdogan B, Sen O, Aydin VM, Yildirim T, Birçan S, Altinors N (2003) Multi-organ cavernous hemangiomas: case report. Neurol Res 25:92–94

Eusebi V, Fanti PA, Fedeli F, Mancini AM (1980) Masson's intravascular vegetant hemangioendothelioma. Tumori 66:489–498

Evans AJ, Russell RC, Roche O, Burry TN, Fish JE, Chow VW, Kim WY, Saravanan A et al (2007) VHL promotes E2 box-dependent E-cadherin transcription by HIF-mediated regulation of SIP1 and snail. Mol Cell Biol 27:157–169

Falconieri G, Mirra M, Michal M, Suster S (2013) Hemangioblastoma-like clear cell stromal tumor of the lung. Adv Anat Pathol 20:130–135

Falk S, Stutte HJ, Frizzera G (1991) Littoral cell angioma. A novel splenic vascular lesion demonstrating histiocytic differentiation. Am J Surg Pathol 15:1023–1033

Fernandez Jimenez I, Alvarez Muñoz V, Pelaez Mata D, Diaz Blanco M, Galbe Sada M et al (2000) Cystic angiomatosis (in Spanish). Ann Esp Pediatr 52:389–391

Fernandez S, Cook GW, Arber DA (2006) Metastasizing splenic littoral cell hemangioendothelioma. Am J Surg Pathol 30:1036–1040

Feurle GE (1990) Arteriovenous shunting and cholestasis in hepatic hemangiomatosis associated with metoclopramide. Gastroenterology 99:258–262

Fischer C, Roeckl H (1961) A case of systemized hemangiomatosis (in German). Hautarzt 12:79–82

Frangides C, Kounis NG, Papadaki PJ, Goudevenos J, Zavras GM (1995) Diffuse hepatic haemangiomatosis in the elderly. Br J Clin Pract 49:215–216

Frieden IJ, Reese V, Cohen D (1996) PHACE syndrome. The association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects and eye abnormalities. Arch Dermatol 132:307–311

Glick ZR, Frieden IJ, Garzon MC, Mully TW, Drolet BA (2012) Diffuse neonatal hemangiomatosis: an evidence-based review of case reports in the literature. J Am Acad Dermatol 67:898–903

Golitz LE, Rudikoff J, O'Meara OP (1986) Diffuse neonatal hemangiomatosis. Pediatr Dermatol 3:145–152

Gonzalez-Flores A, Aguilar-Quesada R, Siles E, Pozo S, Rodriguez-Lara MI, Lopez-Jimenez L et al (2014) Interaction between PARP-1 and HIF-2a in the hypoxic response. Oncogene 33:891–898

Gordin et al. 1975 PubMed PMID 128276

Gorham LW, Wright AW, Shultz HH, Maxon FC (1954) Disappearing bone: a rare form of massive osteolysis. Report of two cases, one with autopsy finding. Am J Med 17:674–682

Gottschling S, Schneider G, Meyer S, Reinhard H, Dill-Mueller D, Graf N (2006) Two infants with life-threatening diffuse neonatal hemangiomatosis treated with cyclophosphamide. Pediatr Blood Cancer 46:239–242

Gouedard C, Dupé-Goetghebeur D, Gagneur A, Sannier K, Misery L (2007) Neonatal haemangiomatosis in

identical twins with twin-twin transfusion syndrome (in French). Ann Dermatol Venereol 134:863–866
Guzman-Valdivia Gomez G, Lazaro-Martinez VM, Aguilar-Cruz E, Kuri-Osorio J, Zaga-Minian I (2006) Case study of diffuse hemangiomatosis of the liver (in Spanish). Gac Med Mex 142:341–344
Haase VH (2009) The VHL tumor suppressor: master regulator of HIF. Curr Pharm Des 15:3895–3903
Haase VH, Glickman JN, Socolovsky M, Jaenisch R (2001) Vascular tumors in livers with targeted inactivation of the von Hippel-Lindau tumor suppressor. Proc Natl Acad Sci U S A 98:1583–1588
Hachisuga T, Hashimoto H, Enjoji M (1984) Angioleiomyoma. A clinicopathologic reappraisal of 562 cases. Cancer 54:126–130
Haggstrom AN, Garzon MC, Baselga E, Chamlin SL, Frieden IJ, Holland K, Maguiness S et al (2010) Risk for PHACE syndrome in infants with large facial hemangiomas. Pediatrics 126:e418–e426
Hashimoto H, Daimaru Y, Enjoji M (1983) Intravascular papillary endothelial hyperplasia: a clinicopathologic study of 91 cases. Am J Dermatopathol 5:539–546
Hayasaka K, Tanaka Y, Satoh T, Mutoh H (1999) Hepatic hemangioblastoma: an unusual presentation of von Hippel-Lindau disease. J Comput Assist Tomogr 23:565–566
He P, Yan XD, Wang JR, Guo RC, Zhang HB (2014) Splenic littoral cell hemangioendothelioma: report of a case with hepatic metastases and review of the literature. J Clin Ultrasound 42:308–312
Heim S, Mandahl N, Kristoffersson U, Mitelman F, Rööser B, Rydholm A, Willén H (1986) Structural chromosome aberrations in a case of angioleiomyoma. Cancer Genet Cytogenet 20:325–330
Hennig Y, Caselitz J, Stern C, Barnitzke S, Bullerdiek J (1999) Karyotype evolution in a case of uterine angioleiomyoma. Cancer Genet Cytogenet 108:79–80
Henschen P (1932) L'endovasculite proliférante thrombopoétique dans la lésion vasculaire locale. Ann Anat Pathol 9:113–121
Ho V, Krol A, Bhargava R, Osiovich H (2000) Diffuse neonatal haemangiomatosis. J Paediatr Child Health 36:286–289
Holden KR, Alexander F (1970) Diffuse neonatal hemangiomatosis. Pediatrics 46:411–421
Hong SG, Cho HM, Chin HM, Park IY, Yoo JY, Hwang SS, Kim JG, Park WB, Chun CS (2004) Intravascular papillary endothelial hyperplasia (Masson's hemangioma) of the liver: a new hepatic lesion. J Korean Med Sci 19:305–308
Huang JS, Lin CM, Cheng YC, Hung KL, Chien CC, Chen CK, Chang CJ, Chen CW et al (2009) A vitronectin M381T polymorphism increases risk of hemangioblastoma in patients with VHL gene defect. J Mol Med (Berl) 87:613–622
Hurvitz et al 2000 PubMed PMID 11132222
Ishida T, Dorfman HD, Steiner GC, Norman A (1994) Cystic angiomatosis of bone with sclerotic changes mimicking osteoblastic metastases. Skelet Radiol 23:247–252
Jaakkola PM, Rantanen K (2013) The regulation, localization, and functions of oxygen-sensing prolyl hydroxylase PHD3. Biol Chem 394:449–457
Jacobs JE, Kimmelstiel P (1953) Cystic angiomatosis of the skeletal system. J Bone Joint Surg Am 35 (A2):409–420
Jayanthi V, Shankar TR, Ravindran C, Sudalaimuthu S, Chandrasekar TS (2000) Diffuse hepatic hemangiomatosis: case report. Trop Gastroenterol 21:188–189
Jhaveri KS, Vlachou PA, Guindi M, Fischer S, Khalili K, Cleary SP, Ayyappan AP (2011) Association of hepatic hemangiomatosis with giant cavernous hemangioma in the adult population: prevalence, imaging appearance, and relevance. AJR Am J Roentgenol 196:809–815
Johnson C, Goyal M, Kim B, Wasdahl D, Nazinitsky K (2007) Littoral cell angioma. Clin Imaging 31:27–31
Jung TY, Jung S, Lee MC, Kim IY, Kang SS, Kim SH (2005) Papillary endothelial hyperplasia associated with repeated bleeding. Br J Neurosurg 19:428–431
Kan CD, Yae CT, Yang YJ (2004) Left ventricular haemangioma with papillary endothelial hyperplasia and liver involvement. Heart 90:e49
Kane RC, Newman AB (1973) Diffuse skeletal and hepatic hemangiomatosis. Calif Med 118:41–44
Katenkamp D, Kosmehl H, Langbein L (1988) Angiomyoma. A pathologo-anatomic analysis of 229 cases (in German). Zentralbl Allg Pathol 134:423–433
Kim EH, Park SY, Ihn YK, Hwang SS (2008) Diffuse hepatic hemangiomatosis without extrahepatic involvement in an adult patient. Korean J Radiol 9:559–562
Kimura T, Mukai M, Kaneko Y, Hirakata M, Okamoto S, Sakamoto M, Okada Y, Ikeda Y (2006) Unusual hemangioendothelioma of the liver with epithelioid morphology associated with marked eosinophilia: autopsy case. Pathol Int 56:694–701
Kiriyama K, Yabu M, Taniguti M, Katou T, Manabe N, Matusima N, Himeno S (2001) A case of giant hepatic hemangiomas which associated with skeletal hemangiomas (in Japanese). Nihon Shokakibyo Gakkai Zasshi 98:1362–1367
Körster R, Jansen H (1981) Diffuse skeletal hemangiomatosis with involvement of internal organs (in German). Röfo 134:69–74
Kortmeyer AO, Falke EA, Gläsker S, Li J, Oldfield EH (2013) Nervous system involvement in von Hippel-Lindau disease: pathology and mechanisms. Acta Neuropathol 125:333–350
Kranzfelder M, Bauer M, Richter T, Rudelius M, Huth M, Wagner P, Friess H, Stadler J (2012) Littoral cell angioma and angiosarcoma of the spleen: report of two cases in siblings and review of the literature. J Gastrointest Surg 16:863–867
Langner C, Thonhofer R, Hegenbarth K, Trauner M (2001) Diffuse hemangiomatosis of the liver and spleen in an adult (in German). Pathologe 22:424–428

Langsteger W, Lind P, Költringer P, Eber O (1990) An unusual case of hepatic hemangiomatosis: sonographic, CT, and 99m-Tc-RBC findings. AJR Am J Roentgenol 143:423

Larcher VF, Howard ER, Mowat AP (1981) Hepatic haemangiomata: diagnosis and management. Arch Dis Child 56:7–14

Larsen BT, Bishop MC, Hunter GC, Renner SW (2013) Low-grade, metastasizing splenic littoral cell angiosarcoma presenting with hepatic cirrhosis and splenic artery aneurysm. Int J Surg Pathol 21:618–626

Latifi HR, Siegel MJ (1992) Diffuse neonatal hemangiomatosis: CT findings in an adult. J Comput Assist Tomogr 16:971–973

Lee SH, Park BJ, Kim TS, Lim YJ (2010) Long-term follow-up clinical courses of cerebellar hemangioblastoma in von Hippel-Lindau disease: two case reports and a literature review. J Korean Neurosurg Soc 48:263–267

Lehmann FS, Beglinger C, Schnabel K, Terracciano L (1999) Progressive development of diffuse liver hemangiomatosis. J Hepatol 30:951–954

Longano AB, Beech PA, Nelva P (2010) P16 staining of subcutaneous smooth muscle tumours. Pathology 42:173–174

Lopriore E, Markhorst DG (1999) Diffuse neonatal haemangiomatosis: new views on diagnostic criteria and prognosis. Acta Paediatr 88:93–97

Lutz MS, Burk RD (2006) Primary cilium formation requires von Hippel-Lindau gene function in renal-derived cells. Cancer Res 66:6903–6907

Ma D, Zhang M, Chen L, Tang Q, Tang X, Mao Y, Zhou L (2011) Hemangioblastomas might derive from neoplastic transformation of neural stem cells/progenitors in the specific niche. Carcinogenesis 32:102–109

Maher ER, Neumann HP, Richard S (2011) Von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet 19:617–623

Malik R, Malik R, Tandon S, Tandon P (2008) Skeletal angiomatosis – rare cause of bone destruction: a case report with review of the literature. Indian J Pathol Microbiol 51:515–518

Masson P (1923) Hémangioendothéliome végétant intravasculaire. Bull Soc Anat Paris 93:517–523

McGrath FP, Gibney RG, Morris DC, Owen DA, Erb SR (1992) Case report: multiple hepatic and pulmonary haemangioblastomas – a new manifestation of von Hippel-Lindau disease. Clin Radiol 45:37–39

Maeda et al. 1981 PubMed PMID 7234417

Meadows MC, Sun X, Dardik M, Tarantino DR, Chamberlain RS (2010) Intraabdominal intravascular papillary endothelial hyperplasia (Masson's tumor): a rare and novel cause of gastrointestinal bleeding. Case Rep Gastroenterol 4:124–132

Melis M (1954) Hemangiomatosis of the liver with voluminous angiocavernoma; anatomicopathological study (in Italian). Arch Ital Anat Istol Patol 26:520–530

Mendiratta V, Anand R, Chander R, Harjai B, Gupta T (2008) Multiple neonatal haemangiomatosis with liver hemangiomas and anaemia. Australas J Dermatol 49:42–43

Merrill MJ, Edwards NA, Lonser RR (2013) Hemangioblastoma-associated mast cells in von Hippel-Lindau disease are tumor derived. Blood 121:859–860

Metcalf JL, Bradshaw PS, Komosa M, Greer SN, Stephen Meyn M, Ohh M (2013) K63-ubiquitylation of VHL by SOCs1 mediates DNS double-strand break repair. Oncogene 33:1055–1065

Metry DW, Dowd CF, Barkovich AJ, Frieden IJ (2001) The many faces of PHACE syndrome. J Pediatr 139:117–123

Metry DW, Hawrot A, Altman C, Frieden IJ (2004) Association of solitary, segmental hemangiomas of the skin with visceral hemangiomatosis. Arch Dermatol 140:591–596

Mihalche C, Dumitrache D (2004) Diffuse hepatic hemangiomatosis – case report (in Romanian). Rev Med Chir Soc Med Nat Iasi 108:366–368

Möller G, Priemel M, Amling M, Werner M, Kuhlmey AS, Delling G (1999) The Gorham-Stout syndrome (Gorham's massive osteolysis). J Bone Joint Surg 81:501–506

Montgomery SP, Guillot AP, Barth RA (1990) MRI of disseminated neonatal hemangiomatosis: case report. Pediatr Radiol 20:204–205

Moon WS, Yu HC, Lee JM, Kang MJ (2000) Diffuse hepatic hemangiomatosis in an adult. J Korean Med Sci 15:471–474

Mulliken et al. 2007 PubMed PMID 17845155

Myllyharju J, Koivunen P (2013) Hypoxia-inducible factor prolyl 4-hydroxylases: common and specific roles. Biol Chem 394:435–448

Nakayama H, Enzan H, Miyazaki E, Kuroda N, Toi M (2002) Lack of CD34 positive stromal cells within angiomyomas (vascular leiomyomas). J Clin Pathol 55:395–396

Nishio J, Iwasaki H, Ohjimi Y, Ishiguro M, Kobayashi K, Nabeshima K, Naito M, Kikuchi M (2004) Chromosomal imbalances in angioleiomyomas by comparative genomic hybridization. Int J Mol Med 13:13–16

Nord KM, Kandel J, Lefkowitch JH, Lobritto SJ, Morel KD, North PE, Garzon MC (2006) Multiple cutaneous infantile hemangiomas associated with hepatic angiosarcoma: case report and review of the literature. Pediatrics 118:e907–e913

Ohnishi S, Miyagishima T, Nakagawa M, Kamata T, Kishimoto A, Choi GH, Kudo M, Okabe M (2002) Diffuse neonatal hemangiomatosis without cutaneous lesions in an adult – a case report. Angiology 53:235–237

Ozakyol A, Kebapci M (2006) Enhanced growth of hepatic hemangiomatosis in two adults after postmenopausal estrogen replacement therapy. Tohoku J Exp Med 210:257–261

Park DM, Zhuang Z, Chen L, Szerlip N, Maric I, Li J, Sohn T, Kim SH, Lubensky IA et al (2007) Von Hippel-Lindau disease-associated hemangioblastomas are derived from embryologic multipotent cells. PLoS Med 4:e60

Patil M, Pabla N, Huang S, Dong Z (2013) Nek1 phosphorylates Von Hippel-Lindau tumor suppressor to promote its proteasomal degradation and ciliary destabilization. Cell Cycle 12:166–171

Pavanello M, Piatelli G, Ravegnani M, Consales A, Rossi A, Nozza P, Milanaccio C et al (2007) Cystic angiomatosis of the craniocervical junction associated with Chiari I malformation: case report and review of the literature. Childs Nerv Sys 23:697–700

Pavlenishvili IV, Nemsadze KP (1978) Disseminated hemangiomatosis of the liver in a newborn infant (in Russian). Vopr Okhr Materin Det 23:85–87

Pientka FK, Hu J, Schindler SG, Brix B, Thiel A, Jöhren O, Fandrey J, Berchner-Pfannschmidt U et al (2012) Oxygen sensing by the prolyl-4-hydroxylase PHD2 within the nuclear compartment and the influence of compartmentalisation on HIF-1 signalling. J Cell Sci 125:5168–5176

Pins MR, Rosenthal DI, Springfield DS, Rosenberg AE (1993) Florid extravascular papillary endothelial hyperplasia (Masson's pseudoangiosarcoma) presenting as a soft-tissue sarcoma. Arch Pathol Lab Med 117:259–263

Platokouki H, Aronis S, Mitsika A, Keramidas D, Harokopos E (1998) Diffuse splenic and visceral hemangiomas complicated by chronic consumption coagulopathy. Acta Paediatr Jpn 40:381–384

Poetke M, Jamil B, Muller U, Berlien HP (2002) Diffuse neonatal hemangiomatosis associated with Simpson-Golabi-Behmel syndrome: a case report. Eur J Pediatr Surg 12:59–62

Popa G, Ambarus V, Dolinescu C, Daniil C, Ungureanu E, Cosma M (1984) Diffuse hepatic hemangioma associated with secondary polycythaemia. Rev Med Chir Soc Med Nat Iasi 88:375–377

Pulido-Zamudio T, Orr W, Lertzman M (2001) Cystic angiomatosis of the bone appearing as intrathoracic lung masses. Can Respir J 8:187–190

Ramesh P, Annapureddy SR, Khan F, Sutaria PD (2004) Angioleiomyoma: a clinical, pathological and radiological review. Int J Clin Pract 58:587–591

Rankin EB, Tomaszewski JE, Haase VH (2006) Renal cyst development in mice with conditional inactivation of the von Hippel-Lindau tumor suppressor. Cancer Res 66:2576–2583

Reed CN, Cooper PH, Swerlick RA (1984) Intravascular papillary endothelial hyperplasia. Multiple lesions simulating Kaposi's sarcoma. J Am Acad Dermatol 10:110–113

Reid AB, Reid IL, Johnson G, Hamonic MM, Major P (1989) Familial diffuse cystic angiomatosis of bone. Clin Orthop Relat Res 238:211–218

Reynoso-Roldan A, Roldan M, Cancino-Diaz JC, Rodriguez-Martinez S, Cancino-Diaz ME (2012) Vascular endothelial growth factor production is induced by histone deacetylase 1 and suppressed by von Hippel-Lindau protein in HaCaT cells. Clin Invest Med 35: E340–E350

Ribback S, Thiele A, Rosenberg C, Friesecke S, Neumann V, Tannapfel A, Dombrowski F (2011) Nodular hemangiomatosis of pleura and peritoneum. Pathol Res Pract 207:718–721

Ritchie G, Zeier FG (1956) Hemangiomatosis of the skeleton and spleen. J Bone Joint Surg 38:115

Rizza V, Coletti G, Di Cocco P, Mazzotta C, Famulari A, Pisani F (2009) Serious renal hemorrhage in Masson tumor. Transplant Proc 41:1402–1404

Robinson D, Hambleton G (1977) Cutaneous and hepatic haemangiomata. Arch Dis Child 52:155–157

Rojiani AM, Owen DA, Berry K, Woodhurst B, Anderson FH, Scudamore CH, Erb S (1991) Hepatic hemangioblastoma. An unusual presentation in a patient with von Hippel-Lindau disease. Am J Surg Pathol 15:81–86

Rolain G, Olive D, Marchal C, Leveau P, Hoeffel JC, Bretagne MC (1978) A radiological study of a case multiple liver and bone angiomas in an infant (in French). J Radiol Electrol Med Nucl 59:109–111

Rosso R, Paulli M (2004) Littoral cell angiosarcoma: a truly malignant tumor. Am J Surg Pathol 28:1255

Rosso R, Paulli M, Gianelli U, Boveri E, Stella G, Magrini U (1995) Littoral cell angiosarcoma of the spleen. Case report with immunohistochemical and ultrastructural analysis. Am J Surg Pathol 19:1203–1208

Rosso R, Gianelli U, Chan JK (1996) Further evidence supporting the sinus lining cell nature of splenic littoral cell angiosarcoma. Am J Surg Pathol 20:1531

Rotman M, John M, Stowe S, Inamdar S (1980) Radiation treatment of pediatric hepatic hemangiomatosis and coexisting cardiac failure. N Engl J Med 302:852

Schulze SM, Moser RL, Bhattacharyya N (2006) A rare case of diffuse neonatal hemangiomatosis. Am Surg 72:359–362

Segura-Sampedro JJ, Alamo-Martinez JM, Cañete-Gomez J, Suarez-Artacho G, Gonzalez-Canton JR et al (2012) Gallbladder leiomyoma in absence of immune system disorders: an unusual diagnosis. Rev Esp Enferm Dig 104:382–384

Sezgin S, Kotiloglu E, Kaya H, Inanli S (2005) Extravascular papillary endothelial hyperplasia of the larynx: a case report and review of the literature. Ear Nose Throat J 84:52–53

Shennan T (1914) Histologically non-malignant angioma, with numerous metastases. J Pathol Bacteriol 19:139

Shivaram GM, Pai RK, Ireland KB, Stevens KJ (2007) Temporal progression of skeletal cystic angiomatosis. Skelet Radiol 36:1199–1204

Shively SB, Falke EA, Li J, Tran MG, Thompson ER, Maxwell PH, Roessler E, Oldfield EH et al (2011) developmentally arrested structures preceding cerebellar tumors in von Hippel-Lindau disease. Mod Pathol 24:1023–1030

Soares et al. 2008 PubMed PMID 18929993

Sonobe H, Ohtsuki Y, Mizobuchi H, Toda M, Shimizu K (1996) An angiomyoma with t(X;10)(q22; q23.2). Cancer Genet Cytogenet 90:54–56

Steffen C (2003) The man behind the eponym: C.L. Pierre Masson. Am J Dermatopathol 25:71–76

Stern JK, Wolf JE, Jarratt M (1981) Benign neonatal hemangiomatosis. J Am Acad Dermatol 4:442–445

Stratte et al. 1996 PubMed PMID 8655722
Tarazov PG, Polysalov VN, Ryzhkov VK (1990) Hemangiomatosis of the liver and spleen: successful treatment with embolization and splenectomy. AJR Am J Roentgenol 155:1235–1236
Tarazov PG, Polysalov VN, Ryzhkov VK (1991) Hemangiomatosis of liver and spleen in a female patient: interventional radiologic and surgical treatment (in Russian). Vestn Rentgenol Radiol (1):71–73
Torres VM, Rodriguez FJ (1984) Kaposi's sarcoma-like tumors due to intravascular papillary endothelial hyperplasia. Bol Assoc Med PR 76:223–226
Tsang WY, Chan JK (1993) The family of epithelioid vascular tumors. Histol Histopathol 8:187–212
Tsukagoshi H, Iwasaki Y, Toyoda M, Sato T, Takagi H, Mori M, Sasaki A, Kumakura H et al (1998) An autopsy case of systemic hemangiomatosis with honeycomb-like liver and focal splenic sarcomatous changes. Intern Med 37:847–852
van den Bosch J, Van Damme B, Baert A, Verwilghen RL (1975) Diffuse skeletal hemangiomatosis with visceral hemangiomas (in Dutch). Ned Tijdschr Geneeskd 119:1669–1674
Vanhoenacker FM, Schepper AM, Raeve H, Berneman Z (2003) Cystic angiomatosis with splenic involvement: unusual MRI findings. Eur Radiol 13(Suppl 4):L35–L39
Vilgrain V, Boulos L, Vullierme MP, Denys A, Terris B, Menu Y (2000) Imaging of atypical hemangiomas of the liver with pathologic correlation. RadioGraphics 20:379–397
Vorse HB, Smith EI, Luckstead EF, Fraser JJ (1983) Hepatic hemangiomatosis of infancy. Am J Dis Child 137:672–673
Vortmeyer AO, Frank S, Jeong SY, Yuan K, Ikejiri B, Lee YS, Bhowmick D, Lonser RR et al (2003) Developmental arrest of angioblastic lineage initiates tumorigenesis in von Hippel-Lindau disease. Cancer Res 63:7051–7055
Waldron RL, Zeller JA (1969) Diffuse skeletal hemangiomatosis with visceral involvement. J Can Assoc Radiol 20:119–123
Wallis LA, Asch T, Maisel BW (1964) Diffuse skeletal hemangiomatosis – report of two cases and review of literature. Am J Med 37:545–563
Wananukul S, Voramethkul W, Nuchprayoon I, Seksarn P (2006) Diffuse neonatal hemangiomatosis: report of 5 cases. J Med Assoc Thai 89:1297–1303
Wang L, Xiu D, Jiang B, Ma Z, Yuan C, Li L (2013) Simultaneous laparoscopic splenectomy and right hemihepatectomy for littoral cell angiosarcoma accompanied with liver metastases. World J Surg Oncol 11:215
Welborn J, Fenner S, Parks R (2010) Angioleiomyoma: a benign tumor with karyotype aberrations. Cancer Genet Cytogenet 199:147–148
Welten CM, Keats EC, Ang LC, Khan ZA (2012) Hemangioblastoma stromal cells show committed stem cell phenotype. Can J Neurol Sci 39:821–827
Witters I, Van Damme MT, Ramaekers P, Van Assche FA, Fryns JP (2003) Benign multiple diffuse neonatal hemangiomatosis after a pregnancy complicated by polyhydramnios and a placental chorioangioma. Eur J Obstet Gynecol Reprod Biol 106:83–85
Yavas GF, Okur N, Küsbeci T, Norman E, Inan U (2013) A case of von Hippel-Lindau disease with juxtapapillary retinal capillary hemangioma and nutcracker phenomenon. Int Ophthalmol 33:309–314
Yin WH, Li J, Chan JK (2012) Sporadic haemangioblastoma of the kidney with rhabdoid features and focal CD10 expression: report of a case and literature review. Diagn Pathol 7:39
Young RS, Zalneraitis EL, Bauman ML (1981) Disseminated neonatal hemangiomatosis: successful hepatic resection with subsequent development of hydrocephalus. J Pediatr Surg 16:752–753
Zeitlin H (1942) Hemangioblastomas of the meninges and their relation to Lindau's disease. J Neuropathol Exp Neurol 1:14–23
Zeng ZJ, Johansson E, Hayashi A, Chavali PL, Akrap N, Yoshida T, Kohno K, Izumi H et al (2012) TLX controls angiogenesis through interaction with the von Hippel-Lindau protein. Biol Open 1:527–535

Hepatic Epithelioid Hemangioendothelioma

51

Contents

Abstract

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular neoplasm which is the hepatic counterpart of lesions that develop in various tissues and organs. This tumor consists of a distinct vascular cell type that resembles epithelial cells, but not belonging to an epithelial cell lineage, hence the term epithelioid. HEHE occurs in all age groups, but is more common in individuals older than 40 years. Macroscopically, HEHE presents as solitary to multiple firm to rubbery nodules with infiltrative borders. Multiplicity was observed in more than 80 %. Histologically, the lesion consists of three cell types, i.e., epithelioid, dendritic, and intermediate cells. The common eosinophilic epithelioid cells form strands embedded in stroma. Formation of signet ring-like cells with intracytoplasmic lumina or vacuoles is a typical feature. Dendritic cells show a spindled or stellate morphology and intracytoplasmic lumina as well. Immunohistochemically, the cells are reactive for CD31, CD34, and vimentin and sometimes also cytokeratins. HEHE generally behaves as a low-grade malignant tumor with a slow progression phenotype, but may follow a more aggressive course in older subjects, with metastases and fatal outcome.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_51

ICD-O code 9133/1

Introduction

Epithelioid hemangioendothelioma (EHE) was first described as a distinct entity in 1982, based on 41 soft tissue lesions, as a vascular tumor with unpredictable biology (Weiss and Enzinger 1982), estimated to be of intermediate malignancy. EHE can occur as a solitary tumor in diverse organs or can rarely also present with multiorgan involvement (Weiss et al. 1986; Celikel et al. 2007). The primary liver manifestation of EHE, hepatic epithelioid hemangioendothelioma (HEHE), is an uncommon vascular tumor. This neoplasm consists of a distinct vascular cell type occurring in three morphotypes, and not an epithelial cell, hence the term epithelioid. Owing to the lack of any conclusive marker profiles, the diagnosis of HEHE is difficult and therefore requires histologic and immunohistochemical confirmation by use of a biopsy.

Selected References (Ishak et al. 1984; Kawabe et al. 1987; Noguchi et al. 1987; Ruebner and Eggleston 1987; Cobden et al. 1988; Darras et al. 1988; Kelleher et al. 1989; Bancel et al. 1993; Hidaka et al. 1995; Läuffer et al. 1996; Pokharna et al. 1997; Makhlouf et al. 1999; Uchimura et al. 2001; d'Annibale et al. 2002, with a literature update; Woddall et al. 2008; Lutgendorf et al. 2009).

Epidemiology

HEHE has been reported to occur predominantly in females in contrast to tumors arising in soft tissues (61 % vs. 39 %; Makhlouf et al. 1999), but this has not been confirmed for Japanese patients (Uchimura et al. 2001). The mean age at presentation varies between about 46 years and 60 years, depending on the series. In a collection of 137 patients, only relatively few patients are 20 or less than 20 years old at presentation (Makhlouf et al. 1999; Da Ines et al. 2010; Zhang et al. 2010). In a study of 12 pediatric patients, age at diagnosis ranged from fetal to 5 years, with nine females versus three males (Zhang et al. 2010). HEHE may very rarely be associated with malformations, e.g., congenital hemihypertrophy (Miller et al. 1999).

Clinical and Imaging Features

Apart from asymptomatic patients (42 % in a series of 137 patients; Makhlouf et al. 1999), HEHE may present with abdominal pain, jaundice, and ascites (Makhlouf et al. 1999; Ben-Haim et al. 1999). In rare circumstances, HEHE may be complicated by Budd-Chiari syndrome (Clements et al. 1986; Hayashi et al. 1999; Ozturk et al. 2009) or by hepatic vein invasion with a VOD-like presentation (Fukayama et al. 1984; Eckstein and Ravich 1986). On the other hand, invasion of outflow tract veins by HEHE can mimic Budd-Chiari syndrome (Walsh et al. 1998). The angioinvasive phenotype, characterized by spreads through medium-sized to large vein (Fukayama et al. 1984), can cause ischemia followed by hepatic necrosis and fever of unknown origin (De Man et al. 1994). Necrosis and hemorrhage can result in rupture of the tumor (Lau et al. 1989). Exceptionally, HEHE was found to cause Kasabach-Merritt syndrome (Imanishi et al. 2002; Frider et al. 2005). HEHE may occur in combination with EHE located elsewhere, e.g., the lung and mediastinum (Maamouri et al. 2008). In rare instances, HEHE was found in association with multiple focal nodular hyperplasia and cavernous hemangiomas of the liver (Bralet et al. 1999; Wanless 2000) or with nodular regenerative hyperplasia (Malamut et al. 2001).

HEHE generally behaves as a low-grade malignant tumor with a slow progression phenotype (Mosoia et al. 2008), but the neoplasm appears to be resistant to chemotherapy, and it may have an unfavorable outcome in older patients (Wang et al. 2012) and even follow a fatal course due to metastasizing (Ekfors et al. 1986; Bellmunt et al. 1989; Lee et al. 1989; Buccellato et al. 1990; Uchimura et al. 2001); Kayler et al. 2002; Aalaei and Jakate 2005; (Kassam and Mandel 2008; Komatsu et al. 2010;

Kim and Kim 2011), malignancy rarely also occurring in children (Taege et al. 1999). Part of patients with extensive liver disease are subjected to liver transplantation (Marino et al. 1988; Gelin et al. 1989; Kelleher et al. 1989; Van de Stadt et al. 1989; Bancel et al. 1993; Nudo et al. 2008; Tonglet et al. 2009), also in children (Guiteau et al. 2010; Otte and Zimmerman 2010). In a recent retrospective study on 11 patients, 7 patients had extrahepatic lesions, detected at preoperative imaging or discovered at exploration, two resections of apparently localized lesions were followed by rapid and aggressive recurrence, and of five patients undergoing liver transplantation, two died of tumor recurrence (Ben-Haim et al. 1999). In a minority of cases, extrahepatic metastases developed without intrahepatic recurrence after resection (Jeong et al. 2008). Few cases of HEHE present as a primarily malignant neoplasm (Sugahara et al. 1974; Dean et al. 1985; Dietze et al. 1989; review: Mehrabi et al. 2006).

Radiologically, about 20 % of the lesions exhibit focal calcifications, sometimes even resulting in subtotal liver calcification (Boruchowicz et al. 1993; den Bakker et al. 1998), and are nodular lesions at early stages, to then sometimes change into a diffuse growth pattern (Furui et al. 1989). Multiple nodules of HEHE may closely mimic metastatic hepatic disease (Kubota et al. 2012). On enhanced CT, the lesions showed peripheral enhancement only, whereas MRI exhibited low tumor signal on T1-weighted images and moderately high signal on T2-weighted images, and color Doppler ultrasound revealed a moderate vascularity at the periphery of nodules as well as central neovascularity (Darras et al. 1988; Radin et al. 1988; Terg et al. 1988; Miller et al. 1992; Van Beers et al. 1992; Pokharna et al. 1997; Shen et al. 1999; Kehagias et al. 2000; Nagase et al. 2000; Uchimura et al. 2001; Lyburn et al. 2003; Dighe et al. 2004; Mermuys et al. 2004; Matsushita et al. 2005; Askri et al. 2009; Ji et al. 2010; Lin and Ji 2010; Thin et al. 2010; Amin et al. 2011; Bruegel et al. 2011; Chen et al. 2011; Liu et al. 2011; Lupinacci et al. 2012; Mistry et al. 2012). On MRI images, the nodules may show multilayered target appearance with prominent peripheral rim with high signal intensity on T1-weighted images and very low signal intensity on T2-weighted images, corresponding to thrombosed or tumor-filled vascular channels (bright-dark sign; (Economopoulos et al. 2008). By use of MRI employing RES-specific contrast agent, a "bright-bright" sign is found (Paolantonio et al. 2009). PET revealed intense FDG uptake by these tumors (Nguyen 2004; Lin and Agoff 2007; Suga et al. 2009; Dong et al. 2013).

Pathology

Macroscopy

Macroscopically, HEHE was reported to usually present as pale and firm to rubbery lesions with infiltrative borders, single tumors having a mean diameter of 5.6 cm, and multiple lesions ranging from 0.2 to 14 cm (Fig. 1; (Makhlouf et al. 1999). In the latter series of 137 patients, multiplicity was detected in 82 % of cases, and such lesions may involve the entire liver. The cut surface is often heterogeneous, with red-brown flecks, abnormal vessels, and central fibrosis/scarring or infarction. Multiple and large tumors have also been observed in pediatric HEHE. In a study of 12 pediatric patients, the size of solitary lesions ranged from 5 to 13.8 cm, and solitary tumors presented as well-circumscribed, red-brown tumors with a

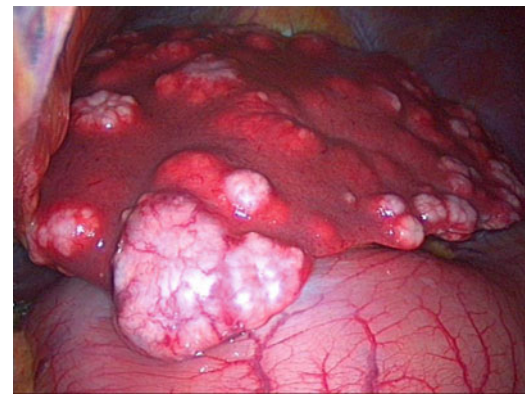

Fig. 1 Hepatic epithelioid hemangioendothelioma with exophytically growing, umbilicated nodules

smooth and glittering appearance and a capsule with abundant blood vessels (Zhang et al. 2010). Superficial/subcapsular tumors may show umbilication. In cases with multiple tumors, the liver capsule becomes highly irregular. In such cases, tumor size may be smaller, in the region of 1–2 cm, sometimes with coalescence of nodules.

Histopathology

Histologically, the neoplastic cell exhibits epithelioid, dendritic, or intermediate features, i.e., consists of three main cell types (Ishak et al. 1984; Dietze et al. 1989; Fedeli et al. 1991; Furuta et al. 1992; Jurczyk et al. 2014). The eosinophilic epithelioid cells occur in all cases and may show signet ring cell-like features representing intracytoplasmic lumina sometimes containing erythrocytes ("vacuoles"; Elias and Ryan 2003; Figs. 2, 3, 4, and 5). Dendritic cells reveal a spindle or stellate morphology with interdigitating processes; they can contain intracytoplasmic lumina as well and were observed to predominate in 16 % of HEHE (Makhlouf et al. 1999). The detection of mitotic figures varies markedly; in a large series, no mitoses were observed in 58 % (Makhlouf et al. 1999). The third cell type, the intermediate cell, is seen in nearly all cases. Typically, HEHE produces a stroma which may either be scanty or abundant, in the latter case with myxohyaline and sclerotic features which may be pronounced in the center of the tumor. The stroma may obliterate the hepatocyte plates, and in early lesions, the stromal reaction is particularly prominent in acinar zone 3 or the central parts of the lobules, i.e., preferring the outflow tract. HEHE exhibits a distinct growth pattern within the liver. The epithelioid cells invade the sinusoids, thereby resulting in hepatocyte plate atrophy, and veins (terminal, hepatic and portal veins), frequently producing polypoid or tufted intravenous structures (Makhlouf et al. 1999). There are variants of HEHE with a deviant histopathologic presentation, e.g., solid and vasoformative growth similar to hemangioendothelioma of bone, involvement of bone and the testis in addition to the liver, and marked peripheral eosinophilia (Kimura et al. 2006).

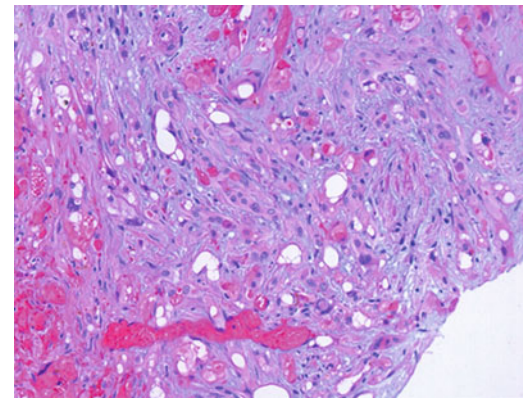

Fig. 2 Hepatic epithelioid hemangioendothelioma. Strands of tumor cells are embedded in a fibrous matrix and show large vacuoles (hematoxylin and eosin stain)

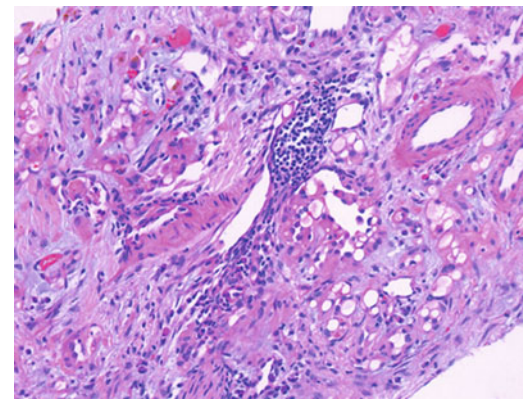

Fig. 3 Hepatic epithelioid hemangioendothelioma. Part of tumor cells with vacuoles project into vascular spaces (*right to the center* of figure; hematoxylin and eosin stain)

Immunohistochemistry

The origin of the neoplastic cell of HEHE is difficult to define, because the cells exhibit a complex marker profile (Makhlouf et al. 1999), with immunoreactivity for factor VIII-associated antigen (FVIII-AA; Ishak et al. 1984; Walsh et al. 1998; Hayashi et al. 1999; Miller et al. 1999; Uchimura et al. 2001), CD31 (Fig. 6; Makhlouf et al. 1999), CD34 (Walsh et al. 1998;

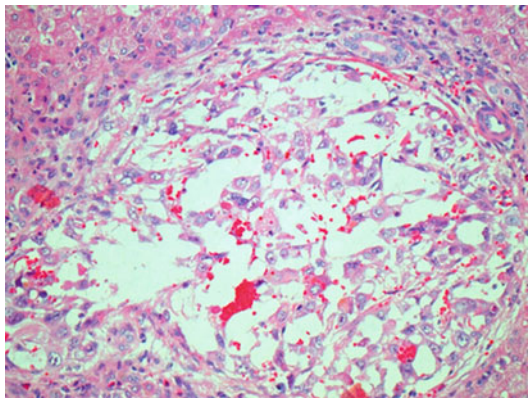

Fig. 4 Hepatic epithelioid hemangioendothelioma. Larger tumor focus with dissociation of cells, vacuole formations, and erythrophagocytosis (hematoxylin and eosin stain)

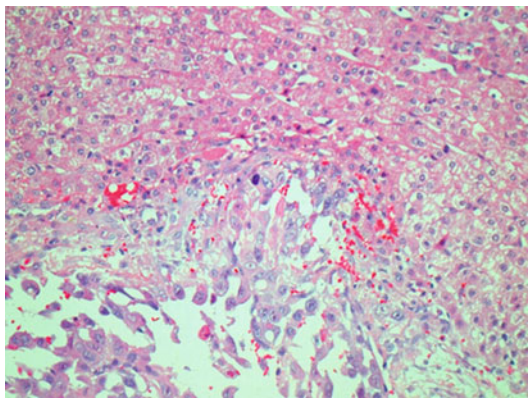

Fig. 5 Hepatic epithelioid hemangioendothelioma. In this tumor with pseudopapillary projections, the epithelioid aspect of tumor cells is clearly in evidence (hematoxylin and eosin stain)

Hayashi et al. 1999; Miller et al. 1999), vimentin (Hayashi et al. 1999), and UEA-1 (Hayashi et al. 1999). CD34 reactivity has been proposed to be more sensitive than FVIII-AA for recognition of disease (Demetris et al. 1997). In addition, cytokeratins have been observed in HEHE (Gray et al. 1990; in 14 %; Makhlouf et al. 1999) what has also been found in other EHEs (K7, K8, and K18, most frequently K18; Miettinen and Fetsch 2000). EHEs, including HEHE, show reactivity for claudin-5 (Miettinen et al. 2011), for

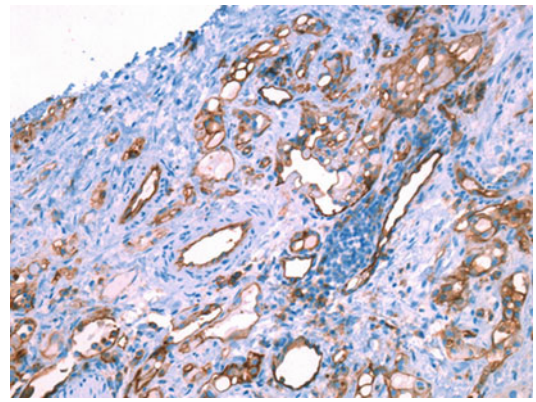

Fig. 6 Hepatic epithelioid hemangioendothelioma. The vacuolated tumor cells are reactive for CD31 (CD31 immunostain)

podoplanin (Fujii et al. 2008), and for CD10, the latter having a sensitivity of 78 % and a specificity of 70 % for EHE (Weinreb et al. 2009). HEHE regularly expresses VEGF, but only occasionally fms-related tyrosine kinase1/Flt-1 (Emamaullee et al. 2010).

Ultrastructure

Most of the tumor cells reveal features suggestive of an endothelial cell lineage, including presence of Weibel-Palade bodies and signs of vasoformative growth, characterized by formation of both intra-and extracellular vascular channels ("vacuoles"). Part of the cells share a phenotype with pericytes (Scoazec et al. 1989).

Cytogenetic and Molecular Features

EHE was found to have a recurrent WWTR1-CAMTA1 gene fusion, associated with t(1;3)(p36.3;q25), as consistent abnormality (Errani et al. 2011, 2012). CAMTA1 is a member of a calmodulin-binding transcription activator family of proteins, potentially involved in Ca2+ signaling-dependent cell cycle regulation. WWTR1 (synonym: TAZ) is a transcriptional co-activator with PDZ-binding motif, acting as a

downstream effector of the Hippo pathway controlling cell proliferation and apoptosis. Analysis of the WWTR1-CAMTA1 breakpoints revealed that multifocal EHEs are monoclonal lesions (Errani et al. 2012).

Pathogenesis

The observation of cytokeratin expression, albeit not found in all studies and also thought to be the result of antibody cross-reactivity (Makhlouf et al. 1999), is not a proof for an epithelial phenotype, because endothelia can express cytokeratins (Ramani et al. 1990; Miettinen and Fetsch 2000). Therefore, HEHEs seem to represent endothelium-derived tumors, but an alternative view has also been suggested, i.e., an origin from a "reticuloendothelial" cell differentiating along endothelial and dendritic cell pathways (Demetris et al. 1997). The endothelial phenotype of HEHE cells is further underlined by the ultrastructural observation of Weibel-Palade bodies in the tumor cells (Scoazec et al. 1989; Hayashi et al. 1999), but EM studies have, in addition, uncovered a cell type exhibiting the features resembling those of pericytes (Scoazec et al. 1989), suggesting that HEHE may differentiate along a complex mixture of cell lineages, mimicking successive steps of vascular morphogenesis.

So far, informations about the genetic background, biochemical properties, or the expression of angiogenic factors of/in EHE are very limited. In two EHE, cytogenetic studies have uncovered translocation t(1;3)(p36.3;q25) as a nonrandom aberration, but this has not been confirmed with other tumors so far (Mendlick et al. 2001). In a pulmonary EHE, expression of glucocorticoid receptor and 11-beta-hydroxysteroid dehydrogenase has been observed (Kumazawa et al. 2002). Immunohistochemically, VEGF and VEGF receptor flk-1 reactivity has been detected in a pediatric malignant HEHE, suggesting the regulation of tumor growth by this signaling pathway (Taege et al. 1999).

References

Aalaei S, Jakatre S (2005) Right upper quadrant pain and fever in a 41-year-old man. Epithelioid hemangioendothelioma of the liver with metastasis to porta hepatis lymph nodes and lung. Arch Pathol Lab Med 129: e134–e135

Amin S, Chung H, Jha R (2011) Hepatic epithelioid hemangioendothelioma: MR imaging findings. Abdom Imaging 36:407–414

Askri A, Mannai S, Landolsi S, Ben Farhat L, Said W, Dali N, Khalfallah MT, Hendaoui L (2009) Hepatic epithelioid hemangioendothelioma: review of 3 cases (in French). J Radiol 90:310–314

Bancel B, Patricot LM, Caillon P, Ducerf C, Pouyet M (1993) Hepatic epithelioid hemangioendothelioma. A case with liver transplantation. Review of the literature (in French). Ann Pathol 13:23–28

Bellmunt J, Allende E, Navarro M, Morales S, Sans M, Jolis L, Garcia AA, Rubio D (1989) Epithelioid hemangioendothelioma of the liver with myocardial metastases. Jpn J Clin Oncol 19:153–158

Ben-Haim M, Roayaie S, Ye MQ, Thung SN, Emre S, Fishbein TA, Sheiner PM, Miller CM, Schwartz ME (1999) Hepatic epithelioid hemangioendothelioma: resection or transplantation, which and when? Liver Transpl Surg 5:526–531

Boruchowicz A, Maunoury V, Foulet A, Stekelorom T, Gosselin B, Pruvot FR, Paris JC (1993) Hepatic calcifications revealing epithelioid hemangioendothelioma (in French). Gastroenterol Clin Biol 17:492–494

Bralet MP, Terris B, Vilgrain V, Brégeaud L, Molas G, Corbic M, Belghiti J, Fléjou JF et al (1999) Epithelioid hemangioendothelioma, multiple focal nodular hyperplasias, and cavernous hemangiomas of the liver. Arch Pathol Lab Med 123:846–849

Bruegel M, Muenzel D, Waldt S, Specht K, Rumeny EJ (2011) Hepatic epithelioid hemangioendothelioma: findings at CT and MRI including preliminary observations at diffusion-weighted echo-planar imaging. Abdom Imaging 36:415–424

Buccellato A, Cabibbo L, La Seta F, Milazzo G, Pisa R, Rinaldi F, SCiarrino E (1990) Malignant epithelioid hemangioendothelioma of the liver. Description of a case (in Italian). Radiol Med 79:634–636

Celikel C, Yumuk PF, Basaran G, Yildizeli B, Kodalli N, Ahiskali R (2007) Epithelioid hemangioendothelioma with multiple organ involvement. APMIS 115:881–888

Chen Y, Yu RS, Qiu LL, Jiang DY, Tan YB, Fu YB (2011) Contrast-enhanced multi-phase imaging features in hepatic epithelioid hemangioendothelioma. World J Gastroenterol 17:3544–3553

Clements D, Hubscher S, West R, Elias E, McMaster P (1986) Epithelioid hemangioendothelioma. J Hepatol 2:441–449

Cobden I, Johri S, Terry G, Robinson KB, Bennett MK, Lendrum R (1988) Hepatic epithelioid

hemangioendothelioma: difficult name, difficult diagnosis? Postgrad Med J 64:128–131

d'Annibale M, Piovanello P, Carlini P, Del Nonno F, Sciaretta F, Rossi M, Berloco P, Iapelli M, Lonardo MT, Perrone R, Donnorso R (2002) Epithelioid hemangioendothelioma of the liver: case report and review of the literature. Transplant Proc 34:1248–1251

Da Ines D, Petitcolin V, Joubert-Zakeyh J, Demeocq F, Garcier JM (2010) Epithelioid hemangioendothelioma of the liver with metastatic coeliac lymph nodes in an 11-year-old boy. Pediatr Radiol 40:1293–1296

Darras T, Moisse R, Colette JM (1988) Epithelioid hemangioendothelioma of the liver. J Belge Radiol 71:722–723

De Man RA, Bac DJ, van Blankenstein M, Zondervan PE (1994) Sterile necrosis of the liver due to primary epithelioid haemangio-endothelioma presenting as fever of undetermined origin. Neth J Med 45:25–29

Dean PJ, Haggitt RC, O'Hara CJ (1985) Malignant epithelioid hemangioendothelioma of the liver in young women: relationship to contraceptive use. Am J Surg Pathol 10:695–704

Demetris AJ, Minervini M, Raikow RB, Lee RG (1997) Hepatic epithelioid hemangioendothelioma: biological questions based on pattern of recurrence in an allograft and tumor immunophenotype. Am J Surg Pathol 21:263–270

den Bakker MA, den Bakker AJ, Beenen R, Mulder AH, Eulderink F (1998) Subtotal liver calcification due to epithelioid hemangioendothelioma. Pathol Res Pract 194:189–194

Dietze O, Davies SE, Williams R, Portmann B (1989) Malignant epithelioid hemangioendothelioma of the liver: a clinicopathological and histochemical study of 12 cases. Histopathology 15:225–237

Dighe MK, Parnell S, Yeh MM, Lalani T (2004) Hepatic epithelioid hemangioendothelioma: multiphase CT appearance and correlation with pathology. Crit Rev Comput Tomogr 45:343–354

Dong A, Dong H, Wang Y, Gong J, Lu J, Zuo C (2013) MRI and FDG PET/CT findings of hepatic epithelioid hemangioendothelioma. Clin Nucl Med 38:e66–e73

Eckstein RP, Ravich RBM (1986) Epithelioid hemangioendothelioma of the liver: report of two cases histologically mimicking veno-occlusive disease. Pathology 18:459–462

Economopoulos N, Kelekis NL, Argentos S, Tsompanlioti C, Patapis P, Nikolaou I, Gouliamos A (2008) Bright-dark ring sign in MR imaging of hepatic hemangioendothelioma. J Magn Reson Imaging 27:908–912

Ekfors TO, Joensuu K, Toivio I, Laurinen P, Pelttari L (1986) Fatal epithelioid hemangioendothelioma presenting in the lung and liver. Virchows Arch A Pathol Anat Histopathol 410:9–16

Elias KR, Ryan CK (2003) Epithelioid hemangioendothelioma and the elusive vacuole. Liver Transpl 9:310–312

Emamaullee JA, Edgar R, Toso C, Thiesen A, Bain V, Bigam D, Kneteman N, Shapiro AM (2010) Vascular endothelial growth factor expression in hepatic epithelioid hemangioendothelioma: implications for treatment and surgical management. Liver Transpl 16:191–197

Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, Healey JH, Antonescu CR (2011) A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. Genes Chromosomes Cancer 50:644–653

Errani C, Sung YS, Zhang L, Healey JH, Antonescu CR (2012) Monoclonality of multifocal epithelioid hemangioendothelioma of the liver by analysis of WWTR1-CAMTA1 breakpoints. Cancer Genet 205:12–17

Fedeli G, Certo M, Cannizzaro O, Forti G, Gimbo G, Abagnale R, Vecchio FM (1991) Epithelioid hemangioendothelioma of the liver: report of two cases. Ital J Gastroenterol 23:261–263

Frider B, Bruno A, Selser J, Vanesa R, Pascual P, Bistoletti R (2005) Kasabach-Merritt syndrome and adult hepatic epithelioid hemangioendothelioma an unusual association. J Hepatol 42:282–283

Fujii T, Zen Y, Sato Y, Sasaki M, Enomae M, Minato H, Masuda S, Uehara T, Katsuyama T et al (2008) Podoplanin is a useful diagnostic marker for epithelioid hemangioendothelioma of the liver. Mod Pathol 21:125–130

Fukayama M, Nihei Z, Takizawa T, Kawaguchi K, Harada H, Koike M (1984) Malignant epithelioid hemangioendothelioma of the liver, spreading through the hepatic veins. Virchows Arch A Pathol Anat Histopathol 404:275–287

Furui S, Itai Y, Ohtomo K, Yamauchi T, Takenaka E, Iio M, Ibukuro K, Shichijo Y, Inoue Y (1989) Hepatic epithelioid hemangioendothelioma: report of five cases. Radiology 171:63–68

Furuta K, Sodeyama T, Usuda S, Yoshizawa K, Kiyosawa K, Furuta S, Imai Y, Itoh N et al (1992) Epithelioid hemangioendothelioma of the liver diagnosed by liver biopsy under laparoscopy. Am J Gastroenterol 87:797–800

Gelin M, Van de Stadt J, Rickaert F, De Prez C, Levarlet M, Adler M, Lambillotte JP (1989) Epithelioid hemangioendothelioma of the liver following contact with vinyl chloride: recurrence after orthotopic liver transplantation. J Hepatol 8:99–106

Gray MH, Rosenberg AE, Dickersin GR, Bhan AK (1990) Cytokeratin expression in epithelioid vascular neoplasms. Hum Pathol 21:212–217

Guiteau JJ, Cotton RT, Karpen SJ, O'Mahony CA, Goss JA (2010) Pediatric liver transplantation for primary malignant liver tumors with a focus on hepatic epithelioid hemangioendothelioma: the UNOS experience. Pediatr Transplant 14:326–331

Hayashi Y, Inagaki K, Hirota S, Yoshikawa T, Ikawa H (1999) Epithelioid hemangioendothelioma with

marked liver deformity and secondary Budd-Chiari syndrome: pathological and radiological correlation. Pathol Int 49:547–552

Hidaka H, Nakamura K, Tsuneyoshi M (1995) Hepatic epithelioid hemangioendothelioma. Radiat Med 13:43–45

Imanishi H, Kawata M, Yanagihara M, Nakayama N, Sato T, Furukawa Y, Fukunaga N et al (2002) Epithelioid hemangioendothelioma of the liver associated with thrombocytopenia and coagulopathy. Hepatogastroenterology 49:1673–1675

Ishak KG, Sesterhenn IA, Goodman ZD, Rabin L, Stromeyer FW (1984) Epithelioid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. Hum Pathol 15:839–852

Jeong SW, Woo HY, You CR, Huh WH, Bae SH, Choi JY, Yoon SK, Jung CK et al (2008) A case of hepatic epithelioid hemangioendothelioma that caused extrahepatic metastases without intrahepatic recurrence after hepatic resection (in Korean). Korean J Hepatol 14:525–531

Ji ZF, Shen XZ, Zhang DY, Liu HY, Zhou Y, Guo MY, Dong L (2010) Hepatic epithelioid hemangioendothelioma: a report of six patients. J Dig Dis 11:254–258

Jurczyk M, Zhu B, Laskin W, Lin X (2014) Pitfalls in the diagnosis of hepatic epithelioid hemangioendothelioma by FNA and needle core biopsy. Diagn Cytopathol 42:516–520

Kassam A, Mandel K (2008) Metastatic hepatic epithelioid hemangioendothelioma in a teenage girl. J Pediatr Hematol Oncol 30:550–552

Kawabe T, Tagawa K, Unuma T, Takanashi R, Oka T (1987) Hepatic epithelioid hemangioendothelioma in a young female. Dig Dis Sci 32:1422–1427

Kayler LK, Merion RM, Arenas JD, Magee JC, Campbell DA, Rudich SM, Punch JD (2002) Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. Transplantation 74:128–130

Kehagias DT, Moulopoulos LA, Antoniou A, Psychogios V, Vourtsi A, Vlahos LJ (2000) Hepatic epithelioid hemangioendothelioma: MR imaging findings. Hepatogastroenterology 47: 1711–1713

Kelleher MB, Iwatsuki S, Sheahan DG (1989) Epithelioid haemangioendothelioma of liver. Clinicopathological correlation of 10 cases treated by orthotopic liver transplantation. Am J Surg Pathol 13:999–1008

Kim SJ, Kim YC (2011) Unusual extrahepatic metastasis to the soft tissue of the left cervical neck area from hepatic epithelioid hemangioendothelioma. Hepatology 54:1480–1481

Kimura T, Mukai M, Kaneko Y, Hirakata M, Okamoto S, Sakamoto M, Okada Y, Ikeda Y (2006) Unusual hemangioendothelioma of the liver with epithelioid morphology associated with marked eosinophilia: autopsy case. Pathol Int 56:694–701

Komatsu Y, Koizumi T, Yasuo M, Urushihata K, Yamamoto H, Hanaoka M, Kubo M (2010) Malignant hepatic epithelioid hemangioendothelioma with rapid progression and fatal outcome. Intern Med 49:1149–1153

Kubota S, Baba H, Kumamoto K, Hatano S, Amano K, Ohsawa T, Okada T, Kumagai Y et al (2012) A case of multiple hepatic epithelioid hemangioendothelioma mimicking metastatic hepatic tumor (in Japanese). Gan To Kagaku Ryoho 39:2012–2014

Kumazawa Y, Maeda K, Ito M, Yamakawa M, Hino T, Nakamura C, Uchimura F, Arai S (2002) Expression of glucocorticoid receptor and 11beta hydroxysteroid dehydrogenase in a case of pulmonary epithelioid haemangioendothelioma. Mol Pathol 55:61–64

Lau WY, Dewar GA, Li AK (1989) Spontaneous rupture of hepatic epithelioid haemangio-endothelioma. Aust N Z J Surg 59:972–974

Läuffer JM, Zimmermann A, Krähenbühl L, Triller J, Baer HU (1996) Epithelioid hemangioendothelioma of the liver. A rare hepatic tumor. Cancer 78:2318–2327

Lee KS, Rossleigh MA, Fernandes VB, Morris JG (1989) Scintigraphic features of malignant epithelioid hemangioendothelioma. Clin Nucl Med 14:501–503

Lin E, Agoff N (2007) Recurrent hepatic epithelioid hemangioendothelioma: detection by FDG PET/CT. Clin Nucl Med 32:949–951

Lin J, Ji Y (2010) CT and MRI diagnosis of hepatic epithelioid hemangioendothelioma. Hepatobiliary Pancreat Dis Int 9:154–158

Liu YI, Brown SS, Elihu A, Bonham CA, Concepcion W, Longacre TA, Kamaya A (2011) Hepatic epithelioid hemangioendothelioma. Dig Dis Sci 56:303–306

Lupinacci RM, Rocha S, Herman P (2012) Hepatic epithelioid hemangioendothelioma: an unusual lesion of the liver. Clin Gastroenterol Hepatol 10:e15–e16

Lutgendorf MA, Magann EF, Yousef M, Hill JB, Foster DT (2009) Hepatic epithelial hemangioendothelioma in pregnancy. Gynecol Obstet Invest 67:238–240

Lyburn ID, Torreggiani WC, Harris AC, Zwirewich CV, Buckley AR, Favis JE, Chung SW et al (2003) Hepatic epithelioid hemangioendothelioma: sonographic, CT, and MR imaging appearances. AJR Am J Roentgenol 180:1359–1364

Maamouri F, Ennaifer Jerbi E, Tounsi Guettiti H, Boussen H, Dellagi K (2008) Multicentric epithelioid hemangioendothelioma involving lung, mediastinum and liver (in French). Tunis Med 86:616–617

Makhlouf HR, Ishak KG, Goodman ZD (1999) Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. Cancer 85:562–582

Malamut G, Perlemuter G, Buffet C, Bedossa P, Joly JP, Colombat M, Kuoch V, Pelletier G (2001) Epithelioid hemangioendothelioma associated with nodular regenerative hyperplasia (in French). Gastroenterol Clin Biol 25:1105–1107

Marino IR, Todo S, Tzakis AG, Klintmalm G, Kelleher M, Iwatsuki S, Starzl TE, Edquivel CO (1988) Treatment

of hepatic epithelioid hemangioendothelioma with liver transplantation. Cancer 62:2079–2084

Matsushita M, Shimizu S, Nagasawa M, Katayama M, Masui T, Souda K, Kobayashi Y et al (2005) Epithelioid hemangioendothelioma of the liver: imaging diagnosis of a rare hepatic tumor. Dig Surg 22:416–418

Mendlick MR, Nelson M, Pickering D, Johansson SL, Seemayer TA, Nelson JR, Vergara G, Rosenthal H, Bridge JA (2001) Translocation t(1;3)(p36.3;q25) is a nonrandom aberration in epithelioid hemangioendothelioma. Am J Surg Pathol 25:684–687

Mermuys K, Vanhoenacker PK, Roskams T, D'haenens P, Van Hoe L (2004) Epithelioid hemangioendothelioma of the liver: radiologic-pathologic correlation. Abdom Imaging 29:221–223

Miettinen M, Fetsch JF (2000) Distribution of keratins in normal endothelial cells and a spectrum of vascular tumors: implications for tumor diagnosis. Hum Pathol 31:1062–1067

Miettinen M, Sarlomo-Rikala M, Wang ZF (2011) Claudin-5 as an immunohistochemical marker for angiosarcoma and hemangioendotheliomas. Am J Surg Pathol 35:1848–1856

Miller WJ, Dodd GD, Federle MP, Baron RL (1992) Epithelioid hemangioendothelioma of the liver: imaging findings with pathologic correlation. AJR Am J Roentgenol 159:53–57

Miller JH, Gillet PM, Hendry GMA, Wallace WHB (1999) Congenital hemihypertrophy and epithelioid haemangioendothelioma in a 10-year-old boy: a case report. Pediatr Radiol 29:613–616

Mistry AM, Gorden DL, Busler JF, Coogan AC, Kelly BS (2012) Diagnostic and therapeutic challenges in hepatic epithelioid hemangioendothelioma. J Gastrointest Cancer 43:521–525

Mosoia L, Mabrut JY, Adham M, Boillot O, Ducerf C, Partensky C, Baulieux J (2008) Hepatic epithelioid hemangioendothelioma: long-term results of surgical management. J Surg Oncol 98:432–437

Nagase M, Ryu M, Kinoshita T, Konishi M, Inoue K, Titku V, Nawano S (2000) Epithelioid hemangioendothelioma of the liver. J Hepatobiliary Pancreat Surg 7:443–447

Nguyen BD (2004) Epithelioid hemangioendothelioma of the liver with F-18 FDG PET imaging. Clin Nucl Med 29:828–830

Noguchi M, Upton MP, Hirohashi S, Shimosata Y, Takaysu K, Yamasaki S (1987) A case of epithelioid hemangioendothelioma of the liver. Jpn J Clin Oncol 17:275–284

Nudo CG, Yoshida EM, Bain VG, Marleau D, Wong P, Marotta PJ, Renner E, Watt KD et al (2008) Liver transplantation for hepatic epithelioid hemangioendothelioma: the Canadian multicentre experience. Can J Gastroenterol 22:821–824

Otte JB, Zimmerman A (2010) The role of liver transplantation for pediatric epithelioid hemangioendothelioma. Pediatr Transplant 14:295–297

Ozturk B, Coskun U, Yaman E, Cakir A, Akdemir UO, Yildiz R, Akyol G, Demirci U et al (2009) Adult hepatic epithelioid hemangioendothelioma presenting with Kasabach-Merritt syndrome: a case report. J Clin Pathol 62:1053–1055

Paolantonio P, Rengo M, Ferrari R, Vecchietti F, Vasselli F, Laghi A (2009) Hepatic epithelioid hemangioendothelioma (HEH) at MRI using reticuloendothelial system (RES)-specific contrast agent: the "bright-bright sign" rather than the "bright-dark sign". J Magn Reson Imaging 29:994–995

Pokharna RK, Garg PK, Gupta SD, Dutta U, Tandon RK (1997) Primary epithelioid haemangioendothelioma of the liver: case report and review of the literature. J Clin Pathol 50:1029–1031

Radin DR, Craig JR, Colletti PM, Ralls PW, Halls JM (1988) Hepatic epithelioid hemangioendothelioma. Radiology 1969:145–148

Ramani P, Bradley NJ, Fletcher CD (1990) QBEND/10, a new monoclonal antibody to endothelium: assessment of its diagnostic utility in paraffin sections. Histopathology 17:237–242

Ruebner BH, Eggleston JC (1987) What is new in epithelioid hemangioendothelioma of the liver? Pathol Res Pract 182:110–112

Scoazec J-Y, Degott C, Reynes M, Benhamou J-P, Feldmann G (1989) Epithelioid hemangioendothelioma of the liver: an ultrastructural study. Hum Pathol 20:673–681

Shen CH, Tsi MH, Chen TC, Liu NJ, Sheen IS (1999) Primary hepatic epithelioid hemangioendothelioma: case report. Changgang Yi Xue Za Zhi 22:486–491

Suga K, Kawakami Y, Hiyama A, Hori K (2009) F-18 FDG PET/CT monitoring of radiation therapeutic effect in hepatic epithelioid hemangioendothelioma. Clin Nucl Med 34:199–202

Sugahara K, Shirakura T, Kawano N, Kino I (1974) Primary malignant hemangioendothelioma of the liver. Report of a successful case or resection and review of the Japanese literature. Am J Gastroenterol 62:240–244

Taege C, Holzhausen H, Gunter G, Flemming P, Rodeck B, Rath FW (1999) Malignant epithelioid hemangioendothelioma of the liver- a very rare tumor in children (in German). Pathologe 20:345–350

Terg R, Bruguera M, Campo E, Hojman R, Levi D, Podesta A (1988) Epithelioid hemangioendothelioma of the liver: report of two cases. Liver 8:105–110

Thin LW, Wong DD, De Boer BW, Ferguson JM, Adams L, Macquillan G, Delriviere L et al (2010) Hepatic epithelioid hemangioendothelioma: challenges in diagnosis and management. Intern Med J 40:710–715

Tonglet M, Delfosse V, Detry O, De Roover A, Scagnol I, Delhougne B, Brixko C, Dresse D et al (2009) Clinical case of the month. Liver transplantation for hepatic epithelioid hemangioendothelioma (in French). Rev Med Liege 64:68–70

Uchimura K, Nakamuta M, Osoegawa M, Takeaki S, Nishi H, Iwamoto H, Enjoji M, Nawata H (2001)

Hepatic epithelioid hemangioendothelioma. J Clin Gastroenterol 32:431–434

Van Beers B, Roche A, Mathieu D, Menu Y, Delos M, Otte JB, Lalonde L, Pringot J (1992) Epithelioid hemangioendothelioma of the liver: MR and CT findings. J Comput Assist Tomogr 16:420–424

Van de Stadt J, Gelin M, Adler M, Lambillotte JP (1989) Epithelioid hemangioendothelioma and liver transplantation. Gastroenterology 96:275–276

Walsh MM, Hytiroglou P, Thung SN, Fiel MI, Siegel D, Emre S, Ishak KG (1998) Epithelioid hemangioendothelioma of the liver mimicking Budd-Chiari syndrome. Arch Pathol Lab Med 122:846–848

Wang LR, Zhou JM, Zhao YM, He HW, Chai ZT, Wang M, Ji Y, Chen Y, Liu C et al (2012) Clinical experience with primary hepatic epithelioid hemangioendothelioma: retrospective study of 33 patients. World J Surg 36:2677–2683

Wanless IR (2000) Epithelioid hemangioendothelioma, multiple focal nodular hyperplasia, and cavernous hemangiomas of the liver. Arch Pathol Lab Med 124:1105–1107

Weinreb I, Cunningham KS, Perez-Ordonez B, Hwang DM (2009) CD10 is expressed in most epithelioid hemangioendotheliomas: a potential diagnostic pitfall. Arch Pathol Lab Med 133:1965–1968

Weiss SW, Enzinger FM (1982) Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. Cancer 50:970–981

Weiss SW, Ishak KG, Dail DH, Sweet DE, Enzinger FM (1986) Epithelioid hemangioendothelioma and related lesions. Semin Diagn Pathol 3:259–287

Woodall CE, Scoggins CR, Lewis AM, McMasters KM, Martin RC (2008) Hepatic malignant epithelioid hemangioendothelioma: a case report and review of the literature. Am Surg 74:64–68

Zhang et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20233031

Infantile Hepatic Hemangioma/ Hemangioendothelioma

52

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_52

Abstract

Infantile hepatic hemangioma (IHE; previously termed infantile hepatic hemangioendothelioma) is a vascular liver tumor presenting as solitary or multiple lesions and diagnosed almost exclusively in infants and children before 6 months of age. Apart from focal involvement of the liver, a diffuse phenotype is also recognized. IHE usually manifests as hepatomegaly, but part of patients show cardiovascular failure due to intratumoral shunting, coagulopathy, jaundice, respiratory distress, and a distinct form of consumptive hypothyroidism. IHE can be associated with angiomatous lesions in other organs, including chorangioma of the placenta. Macroscopically, IHE manifests as solitary or multiple, well-circumscribed, and spherical vascular tumors. Histology is characterized by a network of densely arranged and thin vascular channels with an endothelial lining. Calcifications and other regressive changes can develop. Part of patients show a histology with variable cellular atypias, previously termed type 2 lesions. There is an overlap between such lesions and a distinct form of infantile hepatic angiosarcoma.

Introduction

Infantile hepatic hemangioma (IHE) (synonym: infantile hepatic hemangioendothelioma, IHHE) is a vascular liver tumor that presents with solitary or multiple lesions, presents almost exclusively in children before 6 months of age, and has a slight female preponderance. The term hemangioendothelioma was first coined in 1912, based on a tumor observed in a cirrhotic liver (Kothny 1912). Multiple hepatic hemangioendotheliomas were first reported in 1911 (Bondy 1911) and in 1913 (Veeder and Austin 1913). These authors described a 10-week-old female infant who died with increasing abdominal distention and progressive weakness (heart failure), and autopsy revealed multiple hepatic nodules consisting of vascular spaces with interposed fibrosed hepatic tissue. Foote (1919) reported a further case and reviewed the literature on congenital hemangioendothelioma of the liver. He proposed that these lesions be called hemangioendotheliosarcoma, because they originated from a rapid and seemingly unrestrained proliferation of hepatic vascular endothelia. The ten patients reviewed by Foote (1919) showed a fatal termination of disease before they were 6 months of age. Numerous cases have since been reported, using different terms to denote the lesions.

Selected References Goodale 1930; Kunstadter 1933; Taylor and Moore 1933; Howard 1936; Dodrick 1938; Schumann 1941; Blauel 1942; Andries and Kaump 1944; Schwartz 1945; Videback 1946; Berezin et al. 1948; Hendrick 1948; Sweed and Weinberg 1950; Caussade et al. 1954; Winters et al. 1954; Berman et al. 1955; Packard and Palmer 1955; Siderys et al. 1962; Arcardi and Nezelof 1963; Desbaillets 1963; Christaens et al. 1964; Schneegans et al. 1964; Bellini and Beltrame 1965; Cruveiller et al. 1965; Daudet 1965; Falcone et al. 1965; Robbins and Castle 1965; Stone and Nielsen 1965; Burman et al. 1967; De Lorimier et al. 1967; Graivier et al. 1967; Hurmuzache et al. 1968; Berdon and Baker 1969; Selke and Cornell 1969; Diaz et al. 1970; Touloukian 1970; Dehner and Ishak 1971; Tawes et al. 1971; McLean et al. 1972; Verger et al. 1972; Leonidas et al. 1973; Matolo and Johnson 1973; Chabalko and Fraumeni 1975; Pollice and Pagliarulo 1975; Stovis et al. 1975; Van Acker et al. 1975; Bohm and Jacobi 1976; Sloane et al. 1977; Stanley et al. 1977; Dehner 1978; Othersen and Watanatittan 1978; Pavlenishvili and Nemsadze 1978; Dachman et al. 1983; Weinberg and Finegold 1983; Dehner 1987; Selby et al. 1994.

Hemangioendothelioma Versus Hemangioma: Novel Issues of Definition and Classification of Hepatic Hemangiomas in Infants and Children

The terminology of IHE has gone through an entire spectrum of names, having resulted in some confusion, as in several reports the exact

nature of the vascular tumor can only be reconstructed with difficulty. Terms to denote the lesions comprise hemangioma, capillary hemangioma, cavernous hemangioma, cellular hemangioma, hemangiomatosis, arteriovenous malformation, and hemangioendothelioma. At least part of the tumors have, e.g., been called hemangiomatosis (Braun et al. 1975) or juvenile hemangioendothelioma of the liver (Blumenfeld et al. 1969). It has to be emphasized that the term hemangioendothelioma was not used for hepatic lesions in the same sense as for those located in other organs, e.g., the skin, where the term cellular hemangioma has been proposed to be preferable at a certain time (Gonzales-Crussi and Reyes-Mugica 1991). IHE shared biological and morphologic features with cutaneous infantile or juvenile hemangioma, and frequently cutaneous and hepatic lesions coexist in the same patient. Infantile hemangioma of the skin, which may be associated with hepatic hemangioendotheliomas, is the most common vascular tumor. It is an endothelial cellular proliferation, stimulated after birth (tenth day), and then usually undergoes a slow involution. Congenital hemangioma of the skin is a lesion different from infantile hemangioma, because it develops prenatally and is fully developed at birth. The outcome follows two pathways, i.e., non-involuting congenital hemangioma (NICH), which requires surgery, and rapidly involuting congenital hemangioma (RICH). As also infantile hepatic hemangiomas can undergo involution, it is tempting to assume that the cutaneous and visceral forms of infantile hemangiomas are closely linked entities. To date, the widely used term, IHHE, has therefore been replaced by the term, infantile hepatic hemangioma (IHE; Christison-Lagay et al. 2007), and this new nomenclature will be employed in the present chapter. Recently, other classification schemes have been proposed. IHE was classified as single focus, multiple foci, and diffuse phenotypes (Christison-Lagay et al. 2007; Dickie et al. 2009; Dong et al. 2009; Table 1). According to Christison-Lagay et al. (2007), focal lesions are well-defined, solitary, and spherical tumors that are hypointense relative to the liver on T1-weighted sequences and hyperintense on T2-weighted sequences. The lesions can show central necrosis and hemorrhage. Most focal lesions are asymptomatic and are rarely accompanied by cutaneous hemangiomas. Many focal tumors are detected antenatally on routine prenatal ultrasonography. The lesions variably demonstrate the presence of high-flow shunts, and some of the lesions are associated with minor anemia or thrombocytopenia. Multifocal lesions present as homogeneously enhancing spherical tumors by MRI, and flow voids present in or adjacent to the nodules may indicate the presence of arteriovenous shunts. Multifocal IHE is associated with cutaneous hemangiomas. Some of the lesions are asymptomatic, while others cause high-output heart failure and/or coagulopathy. The lesions may undergo the typical course of involution, as cutaneous hemangiomas. Diffuse lesions are those which exhibit extensive hepatic involvement and near-total replacement of parenchyma with innumerable centripetally enhancing lesions. Most of the infants with the diffuse form have severe clinical manifestations with massive hepatomegaly with compression effects, but the diffuse form is usually not associated with cardiac failure. The patients may develop hypothyroidism (see below). Based on patients studied in a hemangioma registry (cases entering the registry between 1995 and 2010; www.liverhemangioma.org), tumor was studied according to this three-level classification. Of 119 tumors, 33 were focal, 68 were multifocal, and 18 were diffuse lesions. The focal type had a balanced sex distribution, whereas multifocal and diffuse types were more common in women (66.2 % and 70.0 %, respectively) (Kulungowski et al. 2012).

Table 1 Classification of infantile hepatic hemangiomas and related lesions

Christison-Lagay et al. classification (2007)	
	Synonym
Focal	Solitary
Multifocal	Multinodular
Diffuse	Disseminated
Mo et al. classification (2004)	
Hepatic infantile hemangioma (HIH), GLUT1 positive	
Hepatic vascular malformation with capillary proliferation (HVMCP), GLUT1 negative	

IHEs have also been classified according to their angiographic phenotype. Based on angiograms obtained in 15 infants with a diagnosis of hepatic hemangioma, Kassarjian and coworkers (2002) distinguished five types of these vascular tumors. Type 1 was defined as the classic appearance with early filling of abnormal vascular channels, stagnation of contrast medium, and no evidence of a direct shunt; type 2 showed high-flow nodules without direct shunts; type 3 was characterized by direct arteriovenous shunts, type 4 by direct portovenous shunts, and type 5 by both direct arteriovenous and portovenous shunts.

A further classification of these hepatic lesions relates to tumors sensu strictiori versus congenital vascular malformations, an issue that has previously been discussed (Boon et al. 1996; Prokurat et al. 2002). A refined version of this distinction or classification was proposed by Mo et al. (2004). They distinguished multifocal hepatic lesions with features of IHE (termed, by the authors, hepatic infantile hemangioma (HIH)) from solitary angiomatous hepatic lesions (termed hepatic vascular malformation with capillary proliferation (HVMCP)). Apart from the clearly different macroscopic presentation and growth pattern, IHI differed from HVMCP that IHI was GLUT1 positive and HVMCP not, suggesting that the two groups represent two fundamentally different hepatic vascular lesions in infants and young children.

Epidemiology

IHE accounts for about 12–20 % of all childhood hepatic tumors and is the most common symptomatic liver tumor during the first 6 months of life. Altogether, 85 % of patients with IHHE are diagnosed before the age of 2 months, and the tumor is rarely diagnosed beyond the age of 3 years. The tumor may develop during the fetal period and may be manifest as a congenital neoplasm (Schiavon et al. 1982; de Bievre et al. 1994; Sheu et al. 1994; Dreyfus et al. 1996; Morris et al. 1999; Gembruch et al. 2002; Morimura et al. 2003; Pott Bartsch et al. 2003; Ritter et al. 2003; Walsh et al. 2004; Chou et al. 2005; Govender et al. 2006; De Paoli et al. 2007; Schmitz et al. 2009; Franchi-Abella et al. 2012).

In a review of 30 patients, 20 were female (McLean et al. 1972). Prenatal sonographic appearances of (early) lesions (Gonen et al. 1989; Abuhamad et al. 1993; Sepulveda et al. 1993; Chuileannain et al. 1999; Meirowitz et al. 2000; Chou et al. 2005; Schmitz et al. 2009) and features in fetal MRI (Dong et al. 2010) have been reported. Such studies are of particular interest because they have described the dynamic evolution of the complex vascularization of IHE, including feeding arteries with altering flow patterns and characteristics of the continuously changing umbilical-placental circulation (Abuhamad et al. 1993; Meirowitz et al. 2000). IHE can result in fetal hydrops (Skopec and Lakatua 1989; Gonen et al. 1989). In one investigation, hepatic hemangioma was detected prenatally in 30 % of patients with the focal type (Kulungowski et al. 2012). Even though most IHEs occur, as the term implies, in the infantile period, the majority being manifest in the first 6 months, rare instances of such tumors in adolescence (18 years; Selby et al. 1994) and adult patients are known (Diment et al. 2001). The tumor has also been observed in heterotopic intrathoracic liver (Shah et al. 1987).

Clinical Features

General Features

The majority of focal/solitary IHEs are asymptomatic, most symptoms and signs therefore being associated with multifocal or diffuse lesions (Christon-Lagay et al. 2007). The dominant clinical features of multifocal IHE comprise hepatomegaly (83 %); an enlarging upper abdominal mass (66 %); sequelae of the shunting vascular mass, such as cardiovascular failure and coagulopathy; and jaundice. In case of multiple or diffuse lesions, hepatomegaly can be massive (Cohen and Myers 1986; De Paoli et al. 2007). In a study of 19 patients surveyed by the Japanese Infantile Hepatic Hemangioma Study Group, abdominal distention (47.4 %), high-output

cardiac failure (47.4 %), coagulopathy (42.1 %), and respiratory distress (31.6 %) were the major presentations (Kuroda et al. 2011). Solitary lesions exert symptoms and signs in relation to their size and the shunting volume (McGahon et al. 1964; Mortele et al. 2002). In regard to frequency, mass effects and shunt effects are followed by less common manifestations such as vomiting (Bay et al. 2005), splenomegaly, jaundice, ascites, gastrointestinal bleeding, anemia, feeding difficulties, and hepatic bruit (Pellerin et al. 1971; Smith et al. 1978). Vomiting, in particular projectile vomiting, is a rather uncommon sign of IHE (Bay et al. 2005). Obstructive jaundice has been observed in IHE located to the hepatic hilar region (Hase et al. 1995).

Selected References Fox and Cella 1951; Crocker and Cleland 1957; Sommacal 1957; Dachman et al. 1983; Hanchard et al. 1983; Holcomb et al. 1988; Becker and Heitler 1989; Cornelius et al. 1989; Samuel and Spitz 1995; Woltering et al. 1997; Amonkar et al. 1999; Daller et al. 1999; Robben et al. 1999; Lu et al. 2002; Kasahara et al. 2003; Walsh et al. 2004; Riley et al. 2006; Dickie et al. 2009; Moon et al. 2009; Van der Meijs et al. 2009; Zenzen et al. 2009; Marsciani et al. 2010

Cardiac and Circulatory Complications

Multifocal, but usually not focal or diffuse, IHE can result in congestive heart failure (due to arteriovenous shunting), and cardiac failure may even be the initial manifestation, suggesting congenital heart disease (38.5–58 % of the patients) (Levick and Rubic 1953; Cleland 1959; Bredon and Baker 1969; Leonidas et al. 1973; Braun et al. 1975; Slovis et al. 1975; Rocchini et al.1976; Prabhu and Purandare 1977; Rotman et al. 1980; Vorse et al. 1983; Zavota et al. 1984; Burrows et al. 1985; Becker and Heitler 1989; Stanley et al. 1989; Davenport et al. 1995; Pethe et al. 1995; Iyer et al. 1996; Lu et al. 2002; Chen et al. 2003; Sidwell et al. 2004; Jothilakshmi et al. 2006). The relative incidences of these manifestations vary considerably among different reports. In the series reported by Chen et al. (2003), 50 % had abdominal distention, 38.8 % congestive heart failure, 38.8 % abdominal mass, 30 % jaundice, and 23 % skin hemangiomas. In another report, the most common presenting features among 16 patients were high-output cardiac failure (69 %), consumptive coagulopathy (75 %), and anemia (75 %) (Samuel and Spitz 1995). In a recent study on 13 patients (median age, 14 days), congestive heart failure and abdominal mass were predictive of 5-month mortality rates, and patients who underwent resection surgery, with or without OLT, had a lower 5-month mortality rate and a greater 2-year survival rate than those who underwent hepatic artery ligation or embolization (Daller et al. 1999). The severe cardiac complications of IHE can clinically present as acute asystole (Malvy et al. 1978) and may cause sudden unexpected death (Dempers et al. 2011). The arteriovenous shunting depends on the formation of feeding vessels that are perfused by blood from the hepatic artery. High-output failure of infants with IHE can dramatically be controlled by hepatic artery ligation (de Lorimier et al. 1967; Rake et al. 1970; Mattioli et al. 1974; Laird et al. 1976; Malvy et al. 1978; Moazam et al. 1983). Cardiac decompensation and circulatory failure can already occur in patients with fetal IHE. Among 16 fetuses with focal IHE, four had associated cardiomegaly and five had cardiac failure. Eight of the nine fetuses with cardiac disorders were symptomatic at birth. Prenatal cardiac abnormality, enlargement of more than one hepatic vein, and large volume of the hepatic lesion were associated with symptomatic disease (Franchi-Abella et al. 2012).

Coagulopathy

Coagulopathy is a complication of multifocal IHE and is caused by consumption mechanisms and activation of the coagulation cascade within the large vascular network (Nöller and Freundt 1958; Haferland 1961; Linderkamp et al. 1976; Hase et al. 1995; Jayanthi et al. 2000). This complication may already develop in fetal hepatic hemangioendothelioma (Gembruch et al. 2002). Similar to

other highly vascularized tumors, IHE may, therefore, induce the Kasabach-Merritt phenomenon or syndrome (Kasabach and Merritt 1940; Sevinir and Özkan 2007). Skopec and Lakatua 1989). Large tumors may cause obstructive jaundice (Linderkamp et al. 1976). IHE may undergo a rapid course ending up with coagulopathy, liver insufficiency, and cardiac failure (Grabhorn et al. 2009; van der Meijs et al. 2009).

Other Complications

Further complications mainly include tumor rupture and/or hepatic rupture, followed by hematoperitoneum and hemorrhagic shock. Sudden death may ensue (Caussade et al. 1954; Karbel' et al. 1990; Lunetta et al. 2004).

Consumptive Hypothyroidism

Interestingly, IHE can cause disorders of thyroid hormone function, specifically hypothyroidism caused by iodothyronine deiodinases, a disorder termed consumptive hypothyroidism. This complication almost exclusively occurs in the diffuse form of IHE. Hypothyroidism occurring in patients with IHE is caused by increased thyroxine catabolism by the tumor and was first reported in 2000 (Huang et al. 2000). To normalize the serum TSH levels in IHE patients, unusually high doses of intravenous liothyronine and LT4 are required. In the autopsy case of Huang et al. (2000), samples revealed that the IHE tissue had high D3 iodothyronine deiodinase, showing that IHE can produce type 3 iodothyronine deiodinase which converts T4 and T3 to inactive metabolites, i.e., reverse T3 and 3,3′-diiodothyronine, respectively (review: Huang 2005). Several other cases of IHE-induced consumptive hypothyroidism have been reported (Mason et al. 2001; Konrad et al. 2003; Güven et al. 2005; Ho et al. 2005; Kalpatthi et al. 2006; Cho et al. 2008; Mouat et al. 2008; Cetinkaya et al. 2010; Peters et al. 2010; Jassam et al. 2011; Imteyaz et al. 2012). In patients with regression of hepatic IHE associated with consumptive hypothyroidism, the hormonal disorder also regresses (Konrad et al. 2003), as it does following liver transplantation for IHE (Lee et al. 2006; Balazs et al. 2007). Consumptive hypothyroidism can occur in recurrent IHE after steroid therapy, caused by increased type 3 iodothyronine deiodinase activity (Bessho et al. 2010). There is a relationship between the incidence of hypothyroidism and the growth pattern of IHE. In a study of 121 patients, hypothyroidism was documented in all patients with diffuse hepatic hemangioma and 21.4 % in patients with multifocal hepatic hemangioma, but not in patients with focal hepatic hemangioma (Kulungowski et al. 2012). Consumptive hypothyroidism caused by increased deiodinase activity has also been found in adults with hepatic vascular tumors (Huang et al. 2002; Howard et al. 2011). The disorder has also been noted in non-angiomatous tumors, e.g., malignant solitary fibrous tumor, as a manifestation of a paraneoplastic syndrome (Ruppe et al. 2005). In one infant, both increased activity of the tumor for type 3 iodothyronine deiodinase and an increased production of a TSH-like hormone were detected (Ho et al. 2005).

Production of Thyrotropin

Ayling et al. (2001) reported on seven with IHE showing increased thyrotropin levels. The serum thyroxine level was decreased in 4 and increased in 2. Immunohistochemistry of the tumors exhibited positive staining of tumor tissue, but of normal liver tissue, for thyrotropin, suggesting the synthesis and secretion of a thyrotropin-like factor by some IHE.

Elevation of Serum AFP Levels

IHE can be associated with elevated serum AFP (sometimes several thousand ng/ml) leading to the suspicion of hepatoblastoma, but probably not related to the tumor as such (Urbach et al. 1987; Han et al. 1998; Herman and Siegel 2001; Lu et al. 2002; Zenge et al. 2002; Sari et al. 2006;

Moon et al. 2009; Kim et al. 2010; Seok and Kim 2010). Among 16 patients with IHE, two patients with bilobar disease showed elevated levels of serum AFP at presentation (Moon et al. 2009). In an immunohistochemical study, it was demonstrated that, in two cases of IHE, hepatocytes near or entrapped within the tumors were the source of AFP (Kim et al. 2010). An elevated serum AFP has also been reported to occur in the mother in case of a fetal IHE (Meirowitz et al. 2000; Mhanni et al. 2000), and maternal AFP may be the first manifestation of the developing tumor (Meirowitz et al. 2000).

Associations

Extrahepatic Hemangioendotheliomas

Hepatic IHE can occur in conjunction with splenic IHE (hepatosplenic IHE; Kumar et al. 2000; Ng et al. 2003; Wang et al. 2009). Association of IHE with a paraspinal hemangioendothelioma was described (Wood et al. 1977).

Skin Angiomas

IHE is known to come together with other angiomatous lesions, particularly hemangiomas of the skin, the latter apparently being detectable in up to 50 % of the patients (Sween and Weinberg 1950; Prabhu and Purandare 1977; Robinson and Hambleton 1977; Berman and Lim 1978; Dehner 1987; Douri 2005; Mendiratta et al. 2008; Dickie et al. 2009; Horii et al. 2010; Tan et al. 2011; Yeh et al. 2011). In a series of 91 patients, skin hemangiomas were noted in 11 % (Selby et al. 1994). The incidence of accompanying cutaneous hemangiomas is correlated with the type of growth pattern of IHE. Of 121 patients studied within a hemangioma registry, cutaneous hemangiomas accompanied 77.4 % of multifocal hepatic hemangioma, 53.3 % of diffuse hepatic hemangioma, and 15.3 % of focal hepatic hemangioma (Kulungowski et al. 2012). There is a relationship between the number of cutaneous hemangiomas and the probability of associated hepatic hemangiomas. A multicenter prospective study of children with cutaneous infantile hemangiomas conducted at pediatric dermatology clinics at Hemangioma Investigator Group sites in the United States, Canada, and Spain between 2005 and 2008 revealed that 24 of 151 infants (16 %) with five or more cutaneous infantile hemangiomas had hepatic hemangiomas identified by abdominal ultrasound, versus none of the infants with fewer than five (Horii et al. 2011).

Placental Lesions

The tumor has been observed together with chorangioma (Meirowitz et al. 2000), with placental tumor manifestations (Marton et al. 1997), or with anomalous dilated and tortuous vessels on the placental surface (Kanai et al. 1998), suggesting a generalized anomaly of vascular morphogenesis. IHE was found in association with congenital circumscribed choroidal hemangioma/chorangioma (Shturman-Ellstein et al. 1978; Shaikh et al. 2001). IHE is also commonly associated with non-tumoral placental pathologies. In a group of 13 infants who developed IHE, gross lesions with disturbance of the uteroplacental circulation were found in all placentas from children who developed IHE, including retroplacental hematoma in two infants, extensive ischemic infarction in seven, and large dilated vascular communications, severe vasculitis, chorioamnionitis, and funiculitis in four. It was suggested that such abnormalities may cause fetal hypoxic stress followed by release of vascular endothelial growth factors and placental growth factor, potentially playing a role in hepatic vasoproliferation (Lopez Gutiérrez et al. 2007).

Non-angiomatous Tumors

A very rare association is IHE combined with hepatic mesenchymal hamartoma (Bejarano et al. 2003; Hsiao et al. 2007; Behr et al. 2012), sometimes causing elevated serum AFP levels (Hsiao et al. 2007). In a 6-month-old child, continuously shrinking IHE after interventional

therapy was followed by focal nodular hyperplasia (FNH) at the site of the former IHE (Turowski et al. 2009). Similar to other situations, FNH may have been induced by the focal circulatory disorder connected with the shunting vascular tumor. Multicentric IHE was found in association with a large brain hemangioma (Bar-Sever et al. 1994).

Other Associations

A vertical association of IHE with biliary atresia has been suggested (Sharp et al. 2008). In one patient, IHE was associated with congenital hemihypertrophy (Wood et al. 1977). IHE has been found in association with congenital absence of the pericardium and congenital diaphragmatic hernia (Terbruegge et al. 2005) and with agenesis of the corpus callosum with interhemispheric cyst and trisomy 21 (Murphy et al. 2006).

Imaging Features

IHE has characteristic sonographic features, characterized by complex heterogeneous masses that usually reveal hypoechoic components. Calcifications may be seen, and Doppler evaluation may uncover shunting (Abuhamad et al. 1993; Kardorff et al. 2001; Zenge et al. 2002; Ng et al. 2003; Kassarjian et al. 2004; Breysem et al. 2008). Sonographically, the lesions may initially present as a roundish solitary lesion predominantly consisting of markedly perfused and tortuous cavities, whereas multifocal type 2 lesions may present as solid tumors. Fetal IHE can be suspected and monitored by sonography (Meirowitz et al. 2000). Sonography is also useful for the monitoring of the treatment response (Warmann et al. 2003). Non-contrast CT images show several or multiple hypoattenuating masses or nodules of lower density than the surrounding liver, while postcontrast images reveal intense enhancement of the lesions. Many IHEs show a characteristic dense peripheral nodular enhancement. The typical enhancement patterns are similar to those seen in adult hemangiomas (Presedo et al. 1996; Robben et al. 1999; Herman and Siegel 2000; Parmar et al. 2001; Kaniklides et al. 2000; Ng et al. 2003; Kassarjian et al. 2004; Singh et al. 2008; Feng et al. 2010). In a large series of patients, contrast-enhanced CT showed a peripheral rim (51.6 %), uniform (48.4 %), fibrillary (33.3 %), and nodular (28.8 %) contrast enhancement in the hepatic arterial phase. Homogeneous (100 %), rim (98.2 %), and mixed enhancement patterns were noted in tumors <1.0 cm, >2.0 cm, and 1.0–2.0 cm in diameter, respectively, in the hepatic arterial phase (Feng et al. 2010). Rarely, ringlike calcifications on CT and MRI have been found (Mavili et al. 2006). MRI with or without gadolinium enhancement reveals mostly hypointense masses in T1-weighted images, with an isointense and sometimes irregular border, and hyperintense masses in T2-weighted images. In case of tumor necrosis, contrast material is absent in the tumor center (Chung et al. 1996; Presedo et al. 1996; Mortele et al. 2002; Kassarjian et al. 2004; Halefoglu 2007; Feng et al. 2010). Angiography findings of IHE are rather complex and characterized by early filling of abnormal vascular channels with or without extensive shunts (Jackson et al. 1977; Mortensson and Pettersson 1979; Burke et al. 1986; Kassarjian et al. 2002). As complex and heterogeneous tumors, IHEs show considerable variations in the vascular supply (Burrows 1991; Park et al. 1996). In particular, part of the tumors reveal portal vein-hepatic vein fistulas and extensive systemic arterial supply with formation of a complex collateral circulation (Burrows 1991; McHugh and Burrows 1992). The diagnosis and evolution of IHE can be confirmed and followed by technetium-99 m-labeled red blood cell scans (Kristidis et al. 1991; Hertleb et al. 1994), and dynamic and static hepatic scintigraphy will demonstrate the vascularity and size of the liver masses and provide distinction from other tumors (Cruveiller et al. 1965; review: Stanley et al. 1977).

Regression/Involution of IHE

Part of infantile hemangiomas, particularly those in the skin, show a distinct sequence of

developmental stages, characterized as a proliferation or growth phase, followed by an involuting phase, and complete involution itself. Early growth of infantile hemangiomas seems to be influenced by endothelial progenitor cells (Yu et al. 2004). Involution depends on finely tuned apoptosis of endothelial cells (Razon et al. 1998). As their cutaneous counterpart, IHE can undergo involution, but this phenomenon is mainly seen in the multifocal form of IHE. Similar to its cutaneous counterpart, IHE may undergo rapid involution (RICH; Sakamoto et al. 2011; Roebuck et al. 2012), sometimes associated with hepatic failure (Zenzen et al. 2009). It is not yet known whether involuting IHE displays the same or similar features in the involution pattern in comparison with hemangiomas of the skin. The histologic appearance of RICH differs from that of non-involuting tumors (NICH) and common hemangiomas, but there are important overlaps. RICH was composed of small to large lobules of capillaries with moderately plump endothelial cells, the lobules being surrounded by fibrous tissue. Involuting zones are visualized as centrolobular atrophy, fibrosis, and draining channels, associated with hemosiderosis and/or calcifications. The endothelia in RICH were not GLUT1 positive (Berenguer et al. 2003). Involuting lesions differ from hepatic vascular malformations in that they express GLUT1 and, by activation of apoptotic pathways, are associated with expression of the Wilms tumor 1 gene/WT1 (Lawley et al. 2005).

Pathology

Macroscopy

Macroscopically, three growth patterns can be distinguished, i.e., solitary (focal; single focus), multifocal (multinodular), and diffuse phenotypes (Figs. 1 and 2). In multifocal tumors, the lesions may be scattered throughout the liver or may be clustered within one lobe (Dehner and Ishak 1971), resulting in a gross pattern resembling metastatic liver disease. In most cases, the tumor nodules are lighter in color than the surrounding liver tissue, and in cut sections the lesions usually

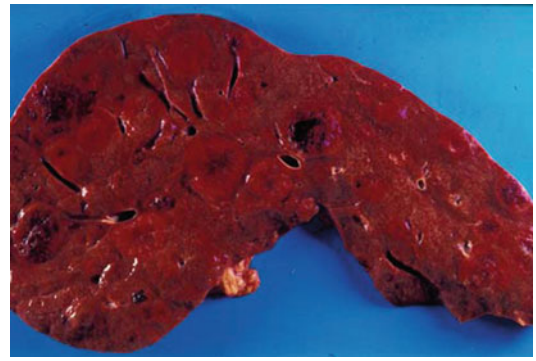

Fig. 1 Infantile hepatic hemangioma. The liver exhibits numerous tumor nodules with central hemorrhage (unfixed necropsy specimen)

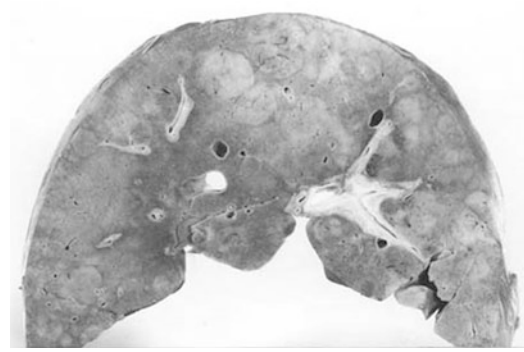

Fig. 2 Infantile hepatic hemangioma. Numerous, in part confluent tumor nodules in both liver lobes (fixed necropsy specimen)

reveal a dark-red center surrounded by a lighter-colored ring (Foote 1919; McLean et al. 1972). In cases with a high content of blood in the lesions, the liver surface is covered with purple to bluish-red nodules varying in size from a marble to a ping-pong ball. When the remaining liver shows fatty change, these nodules stand on a dull yellow background of liver substance (Goodale 1930). The subcapsular nodules are flat or umbilicated and are usually soft on palpation. In the diffuse form of IHE, almost the entire liver is densely occupied by nodules of IHE which may touch each other and which leave only a small amount of functioning parenchyma. The nodules are usually well circumscribed, not encapsulated, relatively soft and spongy, or discretely firm, with a reddish-brown or gray to white cut surface

(Dachman et al. 1983; Lunetta et al. 2004). Solitary (focal) lesions tend to be more solid and gray, whereas multifocal lesions tend to be soft and yellowish red, with small hemorrhages. In one study, the tumor nodules ranged from 0.2 to 15 cm in diameter, and there was no significant difference in size between solitary and multifocal forms (Dehner and Ishak 1971). The tumors tend to grow by compression rather than invasion. Pedunculated lesions are uncommon. Central parts of large masses may show evidence of infarction, hemorrhage, necrosis, fibrosis, and/or focal dystrophic calcification.

There is evidence that the gross growth pattern is related to a specific cell lineage or differentiation pathway involved. GLUT1-positive tumors were shown to form multiple white-tan nodules showing central regressive changes in some cases (Mo et al. 2004). These were the tumors representing the classical IHEs or, as proposed by the authors, infantile hepatic hemangiomas (IHIs). Patients with GLUT1-negative lesions usually had a single large mass with a mean diameter of 8 cm, typically with a central infarcted and hemorrhagic area. These lesions were termed hepatic vascular malformation with capillary proliferation/HVMCP (Mo et al. 2004).

Histopathology

As already specified above, Dehner and Ishak (1971) subdivided this tumor histologically into types 1 and 2. The histopathology of the former type I lesions has been described in detail (Figs. 3, 4, 5, and 6; Touloukian 1970; Dehner and Ishak 1971; Dehner 1978). These nodules show irregularly dilated and usually rather small, compressed vascular channels lined by a single layer or, less commonly, several layers of flat endothelial cells with only minor structural anomalies. The channels are outlined by a reticulin fiber sheath. In highly vascular areas, the extracellular space is not well developed and contains only few fibroblastoid cells and very few lymphoid cells. Part of the tumors contain areas with more stromal elements, sometimes with myxoid features resembling mesenchymal hamartoma (Dehner and Ishak 1971). Areas of central fibrosis are seen in part of the tumors, mainly in solitary/focal lesions. Some cases show a cavernous differentiation or arteriovenous structures, probably representing shunts. In the study of Dehner and Ishak (1971), ten out of 17 type I lesions had cavernous hemangiomatous foci. Rarely, extramedullary hemopoiesis was detected (Orzechowski 1928; Sigameni et al. 2010). Solitary IHE can undergo extensive cystic necrosis (Herman and Siegel 2001). The tumors often contain clusters of biliary ductules and may contain entrapped, cytokeratin 7-positive small bile ducts (Bhattacharyya et al. 2007).

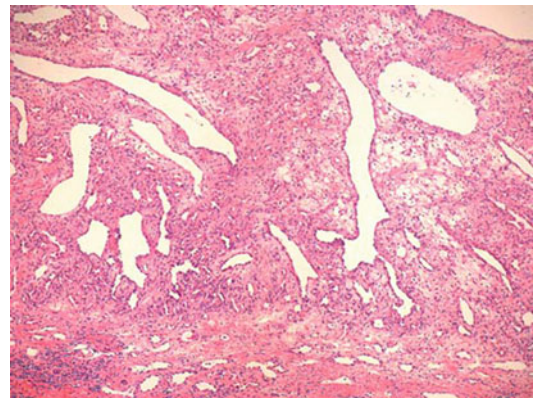

Fig. 3 Infantile hepatic hemangioma, type 1. *Solid* areas with small vascular spaces alternate with cavernous spaces. The interface to the adjacent liver is at the bottom of the figure (hematoxylin and eosin stain)

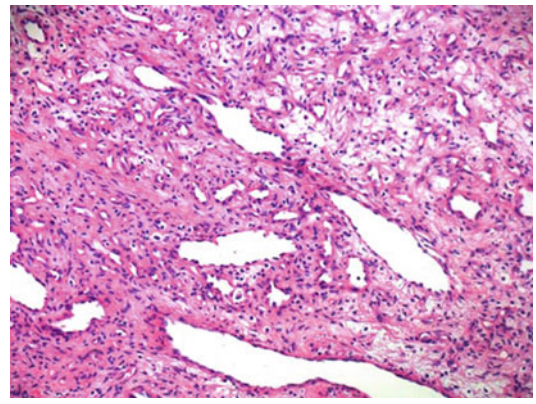

Fig. 4 Infantile hepatic hemangioma. The small and also the larger vascular channels are lined with flat endothelial cells. The intervascular tissue has a fibrous or myxoid aspect (hematoxylin and eosin stain)

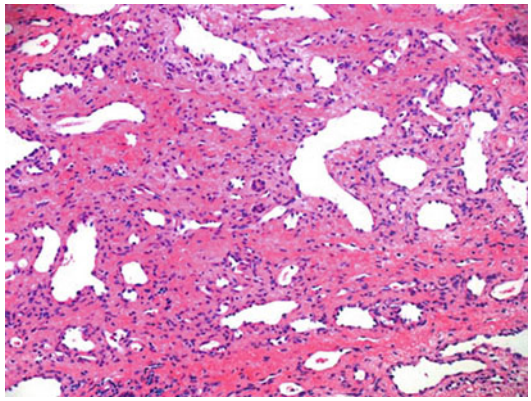

Fig. 5 Infantile hepatic hemangioma, type 1. Older lesions may undergo fibrosclerotic change. Note the portal tract with small bile ducts in the center. Infantile hepatic hemangiomas can integrate preexisting structures of the liver (hematoxylin and eosin stain)

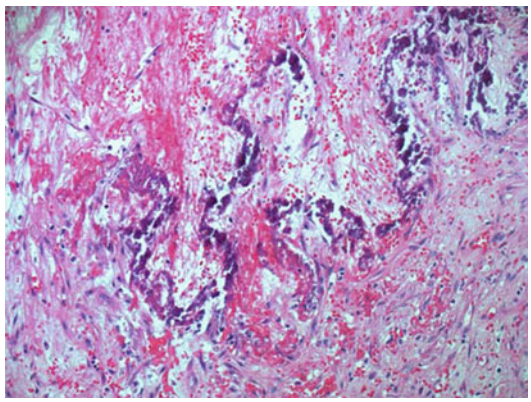

Fig. 6 Infantile hepatic hemangioma, type 1. In this tumor, regressive changes are associated with calcifications (hematoxylin and eosin stain)

Hepatic infantile hemangiomas (IHIs) as defined by Mo et al. (2004) and being GLUT1-positive multiple lesions are histologically characterized by closely packed small capillary-sized vessels with interspersed pericytes and collagen fibers, resembling cutaneous infantile hemangioma and corresponding to type 1 IHE according to Dehner and Ishak's classification. The second group of lesions defined by Mo et al. (2004) is the solitary large masses that are GLUT1 negative and called hepatic vascular malformation with capillary proliferation (HVMCP). These lesions show a central zone of hemorrhage and necrosis/infarction and a peripheral zone with congested and dilated thin-walled vessels lined by flattened epithelium, associated with vascular thrombi and calcifications. This zone is surrounded by a rim of myxoid stroma containing numerous capillary-type blood vessels, with an indistinct demarcation between the lesion and adjacent liver (Mo et al. 2004).

The former type 2 lesions show a very vascular and in part hypercellular neoplasm composed of atypical, anastomosing vascular channels admixed with necrosis and hemorrhage (Andries and Kaump 1944; Dehner and Ishak 1971). That such lesions differ in biology and histology from the more common type 1 lesions was first worked out by Andries and Kaump in 1944. These authors underlined the absence of encapsulation and an infiltrative growth with whorls of spindle-shaped cells. The irregularly shaped lumina are lined by atypical, flattened polygonal endothelial cells, sometimes with hobnail-like formations, similar to those noted in angiosarcomas. Polygonal cells may form multilayered structures and show cytoplasmic microlumina. Part of the vascular spaces display papillary intraluminal projections covered with one of the several layers of enlarged endothelial cells. Mainly in areas with necrosis, structures resembling Schiller-Duval bodies of yolk sac tumors may be observed (Ganguly and Mukherjee 2010). Mitotic activity is brisk, sometimes with atypical and tetrapolar mitotic figures. The vascular spaces contain erythrocytes, at some places with pooling of blood in cavernous or peliosis-like spaces. Erythrophagocytosis by the abnormal endothelial cells is found. The same or a similar histology was found in lymph node metastases or remote metastases of the hepatic tumors (Ganguly and Mukherjee 2010). The nodules may contain foci of extramedullary erythropoiesis. Ductular biliary profiles and hepatocytes are intermingled with vascular channels in the majority of cases.

Cytology

Fine needle aspiration cytology smears revealed clusters of and isolated cuboidal, round cells with benign-looking features (Kumar et al. 2010).

Spindle-shaped cells with scant cytoplasm and wavy, kinked, and indented nuclear outlines were also found (Sigamani et al. 2010).

Ultrastructure

Electron microscopically, type 1 IHE showed large numbers of vascular channels of varying sizes lined by abnormal endothelial cells. An incomplete basement membrane separated endothelial cells from extracellular matrix, in the absence of pericytes. The interstitium contained fibroblastoid cells, microfibrils, and collagen fibers (Feldman et al. 1978). No pericytes were observed in another study (Selby et al. 1994). However, another EM investigation of type 1 IHE had uncovered a high density of pericytes in the walls of vascular channels, and these cells may play a role in vessel contractility and the establishment of shunting (Zerbini et al. 1991). In type 2 I.E. electron microscopy revealed that tumor endothelial cells appeared less differentiated and more disorganized than in type 1 tumors. Marked thickening and duplication of basement membranes were noted (Chan et al. 1986).

Immunohistochemistry

Immunohistochemically, endothelial cells of the abnormal vascular channels are reactive to von Willebrand factor, CD31, CD34 (Fig. 7), Ulex europaeus I lectin, an endothelial cell marker (EC), and vimentin and are lined by a continuous basement membrane (Yasunaga et al. 1989; Selby et al. 1994; Cerar et al. 1996; Amonkar et al. 1999; Lunetta et al. 2004; Riley et al. 2006; Ganguly and Mukherjee 2010; Zhang et al. 2010). Subendothelial cells, enveloped with basement membrane, express smooth muscle actin, but not desmin, and appear to represent a pericyte phenotype (Cerar et al. 1996), also detectable by use of EM (Zerbini et al. 1991). Focal IHEs are not reactive for GLUT1, an erythrocyte-type glucose transporter protein (North et al. 2000), whereas

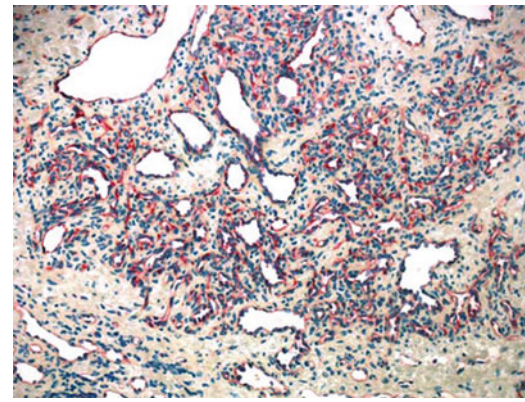

Fig. 7 Infantile hepatic hemangioma, type 1. The endothelial lining is CD34 positive (CD34 immunostain)

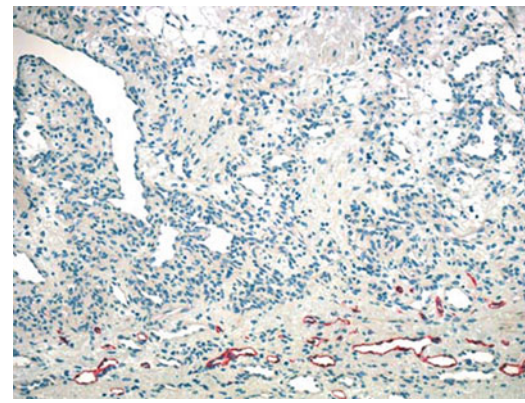

Fig. 8 Infantile hepatic hemangioma, type 1. Lymph vessels are detectable in liver tissue adjacent to the tumor (*bottom*), while the neoplasm itself does not contain lymphatics (D2-40 immunostain)

the endothelial cells of multifocal lesions and diffuse lesions are typically GLUT1 positive, like typical cutaneous hemangiomas of this age group (Drut and Drut 2004; Hernandez et al. 2005; Christison-Lagay et al. 2007). Reactivity for GLUT1 distinguishes IHE from other types of hepatic angiomatous tumors, in particular congenital hepatic vascular malformations (Mo et al. 2004). In contrast to cutaneous hemangiomas, nuclei of IHE are not reactive for p57KIP2 (Drut and Drut 2005). D2-40-reactive lymph vessels are not present within the tumors (Fig. 8).

Differential Diagnosis

IHE must be distinguished from other hepatic vascular tumors occurring in the pediatric age group, in particular angiosarcoma, cavernous hemangioma, capillary hemangioma, and epithelioid hemangioendothelioma. Angiosarcoma of the adult type occurs in the pediatric liver and shows the characteristic histology of highly atypical and sometimes large or pleomorphic endothelial cells that often reveal the hobnail phenomenon and line markedly abnormal and often slit-like spaces. Bizarre and giant cells with massively abnormal mitotic figures are a typical feature, as are solid sarcomatous foci with spindle cells. Cavernous hemangioma of the liver is much less common in infants and children than IHE and is histologically characterized by widely dilated, thin-walled vascular channels lined with flat endothelial cells and by an intervening stroma that may contain lymphoid cells. Capillary hepatic hemangioma is a very rare tumor in infants and children, but its histology may be very close to that of type 1 I.E. However, in contrast to IHE, capillary hemangioma of the liver is usually a small and solitary tumor. Epithelioid hemangioendothelioma is an intermediate-grade invasively growing vascular tumor with medium-sized to large cells forming strands and clusters within a stroma and displaying vacuole-like intracellular lumina. In case mutlifocal IHE is associated with splenic or retroperitoneal hemangioma, neuroblastoma with liver metastases may be suspected on clinical and radiological grounds (Wang et al. 2009).

Biology of Disease: Type 2 IHE as a Low-Grade Angiosarcoma

Two histologic types (type 1 and type 2; Dehner and Ishak 1971; see below) have been recognized, their identification possibly being of importance insofar as IHE1 eventually regresses, and type 2 IHE has been proposed to show a more aggressive phenotype and has been reported to undergo malignant change, i.e., to angiosarcoma or related lesions (Orzechowski 1928; Andries and Kaump 1944; Schwartz 1945; Kauffman and Stout 1961; Kirchner et al. 1981; Noronha and Gonzales-Crussi 1984; Strate et al. 1984; Dehner 1987; Selby et al. 1992; Nazir and Pervez 2006; Ganguly and Mukherjee 2010). One of the first reported cases referred to a 2.5-month-old girl, who was markedly icteric and had a hepatic hemangioendothelioma which had metastasized to the lung and the skin (Orzewchowski 1928). Type 2 IHE may show a fulminant course with extrahepatic extension affecting intestine, lung, skin, and soft tissues, hence being clinically confounded with neuroblastoma (Garcia-Rodriguez et al. 2010). However, the histologic distinction between these two lesions may be difficult, and the prediction of the ultimate course is not easy and often not possible (Dehner an Ishak 1971; Awan et al. 1996; Prokurat et al. 2002), all the more so because the patterns may coexist in the same lesion (Noronha and Gonzalez-Crussi 1984). Even in the case of a benign-looking histology (type 1), multifocality, rapid growth, poor treatment response, and of course metastatic disease indicate malignancy characteristic for at least part of the tumors classified as type 2 (Zurcher et al. 1982). On the other hand, part of the cases, and probably those with a type 1 histology, may show spontaneous regression within 12–18 months (Araujo et al. 2008). Although type 2 IHE thus appears to be associated with a poorer outcome in part of cases, some series have not substantiated this observation (Selby et al. 1994; Cerar et al. 1996). In the large series (91 patients) of Selby et al. (1994), 87 % were first seen before the age of 6 months; the 6-month-survival rate, based on 71 patients, was 70 %, all deaths occurring during the initial presentation/hospitalization of infants, with the exception of two patients who died 3 months and 7 months after diagnosis. Significant factors predicting death 6 months after diagnosis included the presence of congestive heart failure, jaundice, multiple tumor nodules, and absence of cavernous differentiation (Selby et al. 1994). The issue of type 2 lesions as angiosarcoma is further discussed in the chapter of pediatric hepatic angiosarcoma.

References

Abuhamad AZ, Lewis D, Inati MN, Johnson DR, Copel JA (1993) The use of color flow Doppler in the diagnosis of fetal hepatic hemangioma. J Ultrasound Med 12:223–226

Amonkar P, Desai S, Deb R, Kane S, Kurkure P, Deshpande RK, Chinoy R (1999) Infantile hemangioendothelioma of the liver. Med Pediatr Oncol 32:392–394

Andries GH, Kaump DH (1944) Multiple malignant hemangiomas of the liver. Am J Clin Pathol 14(suppl):489

Araujo AR, Maciel I, Costa JC, Vieira A, Enes C, Santos Silva E (2008) Infantile hepatic hemangioendothelioma. A multifocal, bilobular and asymptomatic case with spontaneous regression (in Spanish). An Pediatr (Barc) 68:507–510

Arcardi J, Nezelof C (1963) L'hémangiomatose multinodulaire du foie du nourrisson. Commentaires anatomocliniques à propos de quatre observations. Arch Fr Pédiatr 20:933

Awan S, Davenport M, Portmann B, Howard ER (1996) Angiosarcoma of liver in children. J Pediatr Surg 31:1729–1732

Ayling RM, Davenport M, Hadzic N, Metcalfe R, Buchanan CR, Howard ER, Mieli-Vergani G (2001) Hepatic hemangioendothelioma associated with production of humoral thyrotropin-like factor. J Pediatr 138:932–935

Balazs AE, Athanassaki I, Gunn SK, Tatevian N, Huang SA, Haymond MW, Karaviti LP (2007) Rapid resolution of consumptive hypothyroidism in a child with hepatic hemangioendothelioma following liver transplantation. Ann Clin Lab Sci 37:280–284

Bar-Sever Z, Horev G, Lubin E, Kornreich L, Naor N, Ziv N, Shimoni A, Grunebaum M (1994) A rare coexistence of a multicentric hepatic hemangioendothelioma with a large brain hemangioma in a preterm infant. Pediatr Radiol 24:141–142

Bay A, Oner AF, Etlik O, Koseoglu B, Kaya A (2005) Unusual presentation of infantile hemangioendothelioma. Pediatr Blood Cancer 44:267–269

Becker JM, Heitler MS (1989) Hepatic hemangioendothelioma in infancy. Surg Gynecol Obstet 168:189–200

Behr GG, Fishman SJ, Caty MG, Kulungowski AM, Paltiel HJ, Alomari AI (2012) Hepatic mesenchymal hamartoma and infantile hemangioma: a rare association. J Pediatr Surg 47:448–452

Bejarano PA, Serrano MF, Casillas J, Dehner LP, Kato T, Mitral N, Rodriguez MM, Tzakis A (2003) Concurrent infantile hemangioendothelioma and mesenchymal hamartoma in a developmentally arrested liver of an infant requiring hepatic transplantation. Pediatr Dev Pathol 6:552–557

Bellini F, Beltrame A (1965) On a case of hepatic hemangioendothelioma in an infant (in Italian). Arch Ital Chir 91:594–602

Berdon WE, Baker DH (1969) Giant hepatic hemangioma with cardiac failure in the newborn infant. Value of high-dosage intravenous urography and umbilical angiography. Radiology 92:1523–1528

Berenguer B, Mulliken JB, Enjolras O, Boon LM, Wassef M, Josset P, Burrows PE et al (2003) Rapidly involuting congenital hemangioma: clinical and histopathologic features. Pediatr Dev Pathol 6:495–510

Berezin SW, Sharnoff JG, Stein JD (1948) Primary hemangioendothelioma of the liver in infancy. N Engl J Med 238:906

Berman B, Lim HWP (1978) Concurrent cutaneous and hepatic hemangiomata in infancy: report of a case and a review of the literature. J Dermatol Surg Oncol 4:869–873

Berman JK, Kirkhoff P, Levene N (1955) Hepatic lobectomy for hemangioma of the liver in a five-day-old infant. AMA Arch Surg 71:249–253

Bessho K, Etani Y, Ichimori H, Miyoshi Y, Namba N, Yoneda A, Ooue T, Chihara T et al (2010) Increased type 3 iodothyronine deiodinase activity in a regrown hepatic hemangioma with consumptive hypothyroidism. Eur J Pediatr 169:215–221

Bhattacharyya NK, Chatterjee U, Sen S, Sarkar S (2007) Infantile hemangio-endothelioma of liver: report of two cases. Indian J Pathol Microbiol 50:340–342

Blauel I (1942) Ueber das Hämangioendotheliom der Leber bei Kindern. Monatsschr F Kinderheilkde 91:345

Blumenfeld TA, Fleming ID, Johnson WW (1969) Juvenile hemangioendothelioma of the liver. Report of a case and review of the literature. Cancer 24:853–857

Bohm N, Jacobi H (1976) Infantile hemangiomatosis of liver (in German). Med Welt 27:1887–1891

Bondy J (1911) Angiosarcoma of the liver in an infant. JAMA 56:873

Boon LM, Burrows PE, Paltiel HJ, Lund DP, Ezekowitz RA, Folkman J, Mulliken JB (1996) Hepatic vascular anomalies in infancy: a twenty-seven-year experience. J Pediatr 129:346–354

Braun P, Ducharme JC, Riopelle JL, Davignon A (1975) Hemangiomatosis of the liver in infants. J Pediatr Surg 10:121–126

Breysem L, Allewaet S, Claus F, De Beer A, Van Geet C, Rayyan M, Smet MH (2008) The use of duplex doppler ultrasound in a case of multifocal hepatic hemangioma. JBR-BTR 91:145–148

Burke DR, Verstandig A, Edwards O, Meranze SG, McLean GK, Stein EJ (1986) Infantile hemangioendothelioma: angiographic features and factors determining efficacy of hepatic artery embolization. Cardiovasc Intervent Radiol 9:154–157

Burman D, Mansell PWA, Warin R (1967) Miliary hemangiomata in the newborn. Arch Dis Child 42:193

Burrows PE (1991) Variations in the vascular supply to infantile hepatic hemangio-endothelioma. Radiology 181:631–632

Burrows PE, Rosenberg HC, Chuang HS (1985) Diffuse hepatic hemangiomas: percutaneous transcatheter

embolization with detachable silicone balloons. Radiology 156:85–88
Caussade L, Neimann N, Tridon P (1954) Hémangioendothéliome du foie chez un nouveau-né mort par rupture du foie. Arch Fr Pédiatr 11:514
Cerar A, Dolenc-Strazar ZD, Bartenjev D (1996) Infantile hemangioendothelioma of the liver in a neonate. Immunohistochemical observations. Am J Surg Pathol 20:871–876
Cetinkaya S, Peltek Kendirici HN, Yilmaz Agladioglu S, Bas VN, Ozdemir S, Bozkurt C et al (2010) Hypothyroidism due to hepatic hemangioendothelioma: a case report. J Clin Res Pediatr Endocrinol 2:126–130
Chabalko JJ, Fraumeni JF (1975) Blood-vessel neoplasms in children: epidemiological aspects. Med Pediatr Oncol 1:135–141
Chan YF, Choi AC, Ma L, Leung MP (1986) Infantile hemangioendothelioma of the liver: ultrastructural study of a type II case. Pathology 18:463–468
Chen CC, Kong MS, Yang CP, Hung IJ (2003) Hepatic hemangioendothelioma in children: analysis of thirteen cases. Acta Paediatr Taiwan 44:8–13
Cho YH, Taplin C, Mansour A, Howman-Giles R, Hardwick R, Lord D, Howard NJ (2008) Case report: consumptive hypothyroidism consequent to multiple infantile hepatic haemangiomas. Curr Opin Pediatr 20:213–215
Chou SY, Chiang HK, Chow PK, Wu CF, Liang SJ, Hsu CS (2005) Fetal hepatic hemangioma diagnosed prenatally with ultrasonography. Acta Obstet Gynecol Scand 84:301–302
Christiaens L, Demaille A, Clay A, Farriaux JP (1964) Multinodular hemangiomatosis of the liver in an infant (in French). Lille Med 35:484–487
Christison-Lagay, Burrwos PE, Alomari A, Dubois J, Kozakewich HP, Lane TS, Paltiel HJ et al (2007) Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. J Pediatr Surg 42:62–67
Chuileannain FN, Rowlands S, Sampson A (1999) Ultrasonographic appearances of fetal hepatic hemangioma. J Ultrasound Med 18:379–381
Chung T, Hoffer FA, Burrows PE, Paltiel HJ (1996) MR imaging of hepatic hemangiomas of infancy and changes seen with interferon alpha-2a treatment. Pediatr Radiol 26:341–348
Cleland RS (1959) Benign and malignant tumors of the liver. Pediatr Clin North Am 6:427–447
Cohen RC, Myers NA (1986) Diagnosis and management of massive hepatic hemangiomas in childhood. J Pediatr Surg 21:6–9
Cornelius AS, Womer RB, Jakacki R (1989) Multiple hemangioendotheliomas of the liver. Med Pediatr Oncol 17:501–504
Crocker DW, Cleland RS (1957) Infantile hemangioendothelioma of the liver; report of three cases. Pediatrics 19:596–606
Cruveiller J, Lafourcade J, Vallée G, Bocquet L, Laurent M, Turpin R (1965) Congenital hepatic hemangiomatosis. Clinical and scintigraphic study of a case with a favorable outcome (in French). Sem Hop 41:3049–3063
Dachman AH, Lichtenstein JE, Friedman AC, Hartman D (1983) Infantile hemangioendothelioma of the liver: a radiologic-pathologic-clinical correlation. AJR Am J Roentgenol 140:1093–1096
Daller JA, Bueno J, Gutierrez J, Dvorchik I, Towbin RB, Dickman PS, Mazariegos G, Reyes J (1999) Hepatic hemangioendothelioma: clinical experience and management strategy. J Pediatr Surg 34:98–105
Daudet M (1965) Reflections apropos of a case of hepatic hemolymphangioma of the infant. Operation recovery (in French). Pediatrie 20:445–451
Davenport M, Hansen L, Heaton ND, Howard ER (1995) Hemangioendothelioma of the liver in infants. J Pediatr Surg 30:44–48
de Bièvre P, Dufour P, Lefèbvre C, Vinatier D, Bernardi C, Depret S, Monnier JC (1994) Prenatal diagnosis of hepatic hemangioendothelioma. Apropos of a case (in French). J Gynécol Obstet Biol Reprod (Paris) 23:435–439
de Lorimier AA, Simpson EB, Baum RS, Carlsson E (1967) Hepatic-artery ligation for hepatic hemangiomatosis. N Engl J Med 277:33–337
De Paoli AG, Williams M, Parsons SJ, Long E, Brothers L, Dargaville PA (2007) Massive hepatic congenital haemangioma: clinical dilemmas. J Paediatr Child Health 43:321–314
Dehner LP (1978) Hepatic tumors in the pediatric age group: a distinctive clinicopathologic spectrum. Perspect Pediatr Pathol 4:217–268
Dehner LP (1987) Liver, gallbladder and extrahepatic biliary tract. In: Dehner LP (ed) Pediatric surgical pathology, 2nd edn. Williams and Wilkins, Baltimore, pp 483–523
Dehner LP, Ishak KG (1971) Vascular tumors of the liver in infants and children. Arch Pathol 92:101–111
Dempers J, Wadee SA, Boyd T, Wright C, Odendaal HJ, Sens MA, Prenatal Alcohol and SIDS and Stillbirth (PASS) network (2011) Hepatic hemangioendothelioma presenting as sudden unexpected death in infancy: a case report. Pediatr Dev Pathol 14:71–74
Desbaillets P (1963) Hémangioendothéliome du foie à symptomatologie avant tout cardiaque. Radiol Clin 32:301
Diaz P, Ferrada C, Gonzales G, Espinoza J, Lopez I (1970) Hepatic diffuse hemangiomatosis (in Spanish). Rev Chil Pediatr 41:130–136
Dickie B, Dasgupta R, Nair R, Alonso MH, Ryckman FC, Tiao GM, Adams DM, Azizkhan RG (2009) Spectrum of hepatic hemangiomas: management and outcome. J Pediatr Surg 44:125–133
Diment J, Yurim O, Pappo O (2001) Infantile hemangioendothelioma of the liver in an adult. Arch Pathol Lab Med 125:931–932

Dodrick JR (1938) Multiple malignant hemangioendotheliomas in an infant. Am J Dis Child 55:559

Dong KR, Zheng S, Xiao X (2009) Conservative management of neonatal hepatic hemangioma: a report from one institute. Pediatr Surg Int 25:493–498

Dong SZ, Zhu M, Zhong YM, Yin MZ (2010) Use of foetal MRI in diagnosing hepatic hemangioendotheliomas: a report of four cases. Eur J Radiol 75:301–305

Douri T (2005) Multiple cutaneous hemangiomas accompanied by hepatic hemangiomas. Dermatol Online 11:21

Dreyfus M, Baldauf JJ, Dadoun K, Becmeur F, Berrut F, Ritter J (1996) Prenatal diagnosis of hepatic hemangioma. Fetal Diagn Ther 11:57–60

Drut RM, Drut R (2004) Extracutaneous infantile haemangioma is also Glut1 positive. J Clin Pathol 57:1197–1200

Drut R, Drut RM (2005) Expression of p57KIP2 in infantile hemangioma. J Mol Hist 36:195–197

Falcone DM, Friedman S, Peker H (1965) Precordial murmurs in high cardiac output states: differentiation from murmurs of congenital heart disease in infancy. J Pediatr 66:729

Feldman PS, Shneidman D, Kaplan C (1978) Ultrastructure of infantile hemangioendothelioma of the liver. Cancer 42:521–527

Feng ST, Chan T, Ching AS, Sun CH, Guo HY, Fan M, Meng QF, Li ZP (2010) CT and MR imaging characteristics of infantile hepatic hemangioendothelioma. Eur J Radiol 76:e24–e29

Foote J (1919) Hemangio-endothelioma of liver. JAMA 73:1042

Fox PF, Cella LE (1951) Hemangioendothelioma of the liver. Ann Surg 134:1042–1047

Franchi-Abella S, Gorincour G, Avni F, Guibaud L, Chevret L, Pariente D, SFIPP-GRRIF (2012) Hepatic haemangioma – prenatal imaging findings, complications and perinatal outcome in a case series. Pediatr Radiol 42:298–307

Ganguly R, Mukherjee A (2010) Infantile hemangioendothelioma: a case report and discussion. Pathol Res Pract 206:53–58

Garcia-Rodriguez E, Calderon-Lopez G, Salinas-Martin V, Ferrari-Cortes A, Pavon-Delgado A et al (2010) Neonatal fulminant type 2 infantile hepatic hemangioendothelioma involving skin, viscera and soft tissue. Fetal Pediatr Pathol 29:338–343

Gembruch U, Baschat AA, Gloeckner-Hoffmann K, Gortner L, Germer U (2002) Prenatal diagnosis and management of fetuses with liver hemangiomata. Ultrasound Obstet Gynecol 19:454–460

Gonen R, Fong K, Chiasson DA (1989) Prenatal sonographic diagnosis of hepatic hemangioendothelioma with secondary nonimmune hydrops fetalis. Obstet Gynecol 73:485

Gonzales-Crussi F, Reyes-Mugica M (1991) Cellular hemangiomas ("hemangioendotheliomas") in infants. Light microscopic, immunohistochemical, and ultrastructural observations. Am J Surg Pathol 15:769–778

Goodale RH (1930) Hemangio-endothelioma of the liver. Arch Pathol 9:528–533

Govender L, Panday S, Moodley J (2006) Prenatal diagnosis of congenital hepatic haemangioma. J Obstet Gynaecol 26:69–70

Grabhorn E, Richter A, Fischer L, Krebs-Schmitt D, Ganschow R (2009) Neonates with severe infantile hepatic hemangioendothelioma: limitations of liver transplantation. Pediatr Transplant 13:560–564

Graivier L, Votteler TP, Dorman GW (1967) Hepatic hemangiomas in newborn infants. J Pediatr Surg 2:299–307

Güven A, Aygun C, Ince H, Aydin M, Pinarli FG, Baysal K, Küçüködük S (2005) Severe hypothyroidism caused by hepatic hemangioendothelioma in an infant of a diabetic mother. Horm Res 63:86–89

Haferland W (1961) Hämangiomatose im Pfortadergebiet als Kasabach-Merrittsches Syndrome. Z Kinderheilkde 85:125–140

Halefoglu AM (2007) Magnetic resonance imaging of infantile hemangioendothelioma. Turk J Pediatr 49:77–81

Han SJ, Tsai CC, Tsai HM, Chen YJ (1998) Infantile hemangioendothelioma with a highly elevated serum alpha-fetoprotein level. Hepatogastroenterology 45:459–461

Hanchard B, Persuad V, Kerr G, Baum P (1983) Primary infantile haemangioendothelioma of the liver. West Indian Med J 32:44–47

Hase T, Kodama M, Kishida A, Matsushita M, Kurumi Y, Mizukuro T, Okabe H, Uno M, Ohta S (1995) Successful management of infantile hepatic hilar hemangioendothelioma with obstructive jaundice and consumption coagulopathy. J Pediatr Surg 30:1485–1487

Hendrick JG (1948) Hemangioma of the liver causing death in a newborn infant. J Pediatr 32:309–310

Herman TE, Siegel MJ (2000) Special imaging casebook. Infantile hepatic hemangioendothelioma. J Perinatol 20:447–449

Herman TE, Siegel MJ (2001) Solitary hepatic hemangioendothelioma with extensive cystic necrosis and markedly elevated alpha-fetoprotein. J Perinatol 21:568–570

Hernandez F, Navarro M, Encinas JL, Lopez Gutierrez JC, Lopez Santamaria M, Leal N et al (2005) The role of GLUT1 immunostaining in the diagnosis and classification of liver vascular tumors in children. J Pediatr Surg 40:801–804

Hertleb M, Sliwinski Z, Boldys H, Kloc T, Baron J (1994) Angiomatosis of the liver (in Polish). Wiad Lek 47:138–141

Ho J, Kendrick V, Dewey D, Pacaud D (2005) New insight into the pathophysiology of severe hypothyroidism in an infant with multiple hepatic hemangiomas. J Pediatr Endocrinol Metab 18:511–514

Holcomb GW, O'Neill JA, Mahboubi JR, Bishop HC (1988) Experience with hepatic hemangioendothelioma in infancy and childhood. J Pediatr Surg 23:661–666

Horii KA, Drolet BA, Baselga E, Frieden IJ, Metry DW, Morel KD, Newell BD, Nopper AJ et al (2010) Risk of

hepatic hemangiomas in infants with large hemangiomas. Arch Dermatol 146:201–203
Horii KA, Drolet BA, Frieden IJ, Baselga E, Chamlin SL, Haggstrom AN, Holland KE et al (2011) Prospective study of the frequency of hepatic hemangiomas in infants with multiple cutaneous infantile hemangiomas. Pediatr Dermatol 28:245–253
Howard WA (1936) Multiple hemangio-endotheliomas of the liver. J Pediatr 8:588
Howard D, La Rosa FG, Huang S, Salvatore D, Mulcahey M, Sang-Lee J, Wachs M et al (2011) Consumptive hypothyroidism resulting from hepatic vascular tumors in an athyreotic adult. J Clin Endocrinol Metab 96:1966–1970
Hsiao KH, Lin LH, Chen DF, Huang SH (2007) Hepatic mesenchymal hamartoma combined with infantile hepatic hemangioendothelioma in an infant. J Formos Med Assoc 106(suppl):S1–S4
Huang SA (2005) Physiology and pathophysiology of type 3 deiodinase in humans. Thyroid 15:875–881
Huang SA, Tu HM, Harney JW et al (2000) Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. N Engl J Med 343:185–189
Huang SA, Fish SA, Dorfman DM, Salvatore D, Kozakewich HP, Mandel SJ, Larsen PR (2002) A 21-year-old woman with consumptive hypothyroidism due to a vascular tumor expressing type 3 iodothyronine deiodinase. J Clin Endocrinol Metab 87:4457–4461
Hurmuzache E, Barbuta R, Haimovici M, Bogdan A (1968) Congenital multiple hepatic hemangioma in an infant, with favorable evolution (in Romanian). Pediatr (Bucur) 17:41–44
Imteyaz H, Karnsakul W, Levine MA, Burrwos PE, Benson J, Hsu S, Schwarz KB (2012) Unusual case of hypothyroidism in an infant with hepatic hemangioma. J Pediatr Gastroenterol Nutr 54:692–695
Iyer CP, Stanley P, Mahour GH (1996) Hepatic hemangiomas in infants and children: a review of 30 cases. Am Surg 62:356–360
Jackson C, Greene HL, O'Neill J, Kirchner S (1977) Hepatic hemangioendothelioma. Angiographic appearance and apparent prednisone responsiveness. Am J Dis Child 131:74–77
Jassam N, Visser TJ, Brisco T, Bathia D, McClean P, Barth JH (2011) Consumptive hypothyroidism: a case report and review of the literature. Ann Clin Biochem 48:186–189
Jayanthi V, Shankar TR, Ravindarn C, Sudalaimuthu S, Chandrasekar TS (2000) Diffuse hepatic hemangiomatosis: case report. Trop Gastroenterol 21:188–189
Jothilakshmi K, Matthai J, Paul S, Singal AK (2006) Symptomatic hepatic hemangioendothelioma in a newborn. Indian Pediatr 43:908–910
Kalpatthi R, Germak J, Mizelle K, Yeager N (2006) Thyroid abnormalities in infantile hepatic hemangioendothelioma. Pediatr Blood Cancer 49:1021–1024
Kanai N, Saito K, Homma Y, Makino S (1998) Infantile hemangioendothelioma of the liver associated with anomalous dilated and tortuous vessels on the placental surface. Pediatr Surg Int 13:175–176
Kaniklides C, Dimopoulos PA, Bajic D (2000) Infantile hemangioendothelioma. A case report. Acta Radiol 41:161–164
Karbel' GG, Lebedev DV, Iastrebov II (1990) Hemangioendothelioma of the liver as the cause of sudden death (in Russian). Sud Med Ekspert 33:57–58
Kardorff R, Fuchs J, Peuster M, Rodeck B (2001) Infantile hemangioendothelioma of the liver – sonographic diagnosis and follow-up (in German). Ultraschall Med 22:258–264
Kasabach HA, Merritt KK (1940) Capillary hemangioma with extensive purpura: report of case. Am J Dis Child 59:1063–1070
Kasahara M, Kiuchi T, Haga H, Uemoto S, Uryuhara K, Fujimoto Y, Ogura Y, Oike F et al (2003) Monosegmental living-donor liver transplantation for infantile hepatic hemangioendothelioma. J Pediatr Surg 38:1108–1111
Kassarjian A, Dubois J, Burrows PE (2002) Angiographic classification of hepatic hemangiomas in infants. Radiology 222:693–698
Kassarjian A, Zurakowski D, Dubois J (2004) Infantile hepatic hemangiomas: clinical and imaging findings and their correlation with therapy. AJR Am J Roentgenol 182:785–795
Kauffman SL, Stout AP (1961) Malignant hemangioendothelioma in infants and children. Cancer 14:1186–1196
Kim TJ, Lee YS, Song YS, Park CK, Shim SI, Kang CS, Lee KY (2010) Infantile hemangioendothelioma with elevated serum alpha fetoprotein: report of two cases with immunohistochemical analysis. Hum Pathol 41:763–767
Kirchner SG, Heller RM, Kasselberg AG, Greene HL (1981) Infantile hepatic hemangioendothelioma with subsequent malignant degeneration. Pediatr Radiol 11:42–45
Konrad D, Ellis G, Perlman K (2003) Spontaneous regression of severe acquired infantile hypothyroidism associated with multiple liver hemangiomas. Pediatrics 112:1424–1426
Kothny K (1912) Über ein Hämangioendotheliom in zirrhotischer Leber. Frankfurt Z Pathol 10:20–40
Kristidis P, de Silva M, Howman-Giles R, Gaskin KJ (1991) Infantile hepatic haemangioma: investigation and treatment. J Paediatr Child Health 27:57–61
Kulungowski AM, Alomari AI, Chawla A, Christison-Lagay ER, Fishman SJ (2012) Lessons from a liver hemangioma registry: subtype classification. J Pediatr Surg 47:165–170
Kumar R, Gupta R, dasan BJ, Khullar S, Marwah A (2000) Infantile hemangioendothelioma of the liver, spleen and anterior abdominal wall. Clin Nucl Med 25:938
Kumar PV, Salimi A, Ahmadi J (2010) Infantile hepatic hemangioendothelioma: report of a case with fine needle aspiration findings. Acta Cytol 54(suppl):807–810

Kunstadter RH (1933) Hemangioendothelioma of the liver in infancy. Am J Dis Child 46:803

Kuroda T, Kumagai M, Nosaka S, Nakazawa A, Takimoto T, Hoshino K, Infantile Hepatic Hemangioma Study Group, Japan (2011) Critical infantile hepatic hemangioma: results of a nationwide survey by the Japanese Infantile Hepatic Hemangioma Study Group. J Pediatr Surg 46:2239–2243

Laird WP, Friedman S, Koop CE, Schwartz GJ (1976) Hepatic hemangiomatosis. Successful management by hepatic artery ligation. Am J Dis Child 130:657–659

Lawley LP, Cerimele F, Weiss SW, North P, Cogen C, Kozakewich HP, Mulliken JB et al (2005) Expression of Wilms tumor 1 gene distinguishes vascular malformations from proliferative endothelial lesions. Arch Dermatol 141:1297–1300

Lee TC, Barshes NR, Agee EE, O'Mahoney CA, Karpen SJ, Carter BA, Bristow JD et al (2006) Resolution of medically resistant hypothyroidism after liver transplantation for hepatic hemangioendothelioma. J Pediatr Surg 41:1783–1785

Leonidas JC, Strauss L, Beck AR (1973) Vascular tumors of the liver in newborns. Am J Dis Child 125:507–510

Levick CB, Rubic J (1953) Hemangioendothelioma of the liver simulating congenital heart disease in an infant. Arch Dis Child 28:49–51

Linderkamp O, Hopner F, Klose H, Riegel K, Hecker WC (1976) Solitary hepatic hemangioma in a newborn infant complicated by cardiac failure, consumption coagulopathy, microangiopathic hemolytic anemia, and obstructive jaundice. Case report and review of the literature. Eur J Pediatr 124:23–29

Lopez Gutiérrez JC, Avila LF, Sosa G, Patron M (2007) Placental anomalies in children with infantile hemangioma. Pediatr Dermatol 24:353–355

Lu CC, Ko SF, Liang CD, Kuo HW, Tiao MM (2002) Infantile hepatic hemangioendothelioma presenting as early heart failure: report of two cases. Chang Gung Med J 25:405–410

Lunetta P, Karikoski R, Penttila A, Sajantila A (2004) Sudden death associated with a multifocal type II hemangioendothelioma of the liver in a 3-month-old infant. Am J Forensic Med Pathol 25:56–59

Malvy P, Leborgne J, Le Neel JC, Bouhour JB, Petitier H, Lefèvre M (1978) Diffuse multinodular haemangioma of the liver in the infant presenting as acute asystole and treated by ligation of the hepatic artery (in French). Chirurgie 104:506–511

Marsciani A, Pericoli R, Alaggio R, Brisigotti M, Vergine G (2010) Massive response of severe infantile hepatic hemangioma to propranolol. Pediatr Blood Cancer 54:176

Marton T, Silhavy M, Csapo Z, Szende B, Papp Z (1997) Multifocal hemangioendothelioma of the fetus and placenta. Hum Pathol 28:866–869

Mason KP, Koka BV, Eldredge EA, Fishman SJ, Burrows PE (2001) Perioperative considerations in a hypothyroid infant with hepatic haemangioma. Pediatr Anaesth 11:228–232

Matolo NM, Johnson DG (1973) Surgical treatment of hepatic hemangioma in the newborn. Arch Surg 106:725–727

Mattioli L, Lee KR, Holder TM (1974) Hepatic artery ligation for cardiac failure due to hepatic hemangioma in the newborn. J Pediatr Surg 9:859–862

Mavili E, Kahriman G, Tuna IS, Coskun A (2006) Atypical imaging findings of infantile hemangioendothelioma: a case report. Acta Radiol 47:1091–1093

McGahon JJ, Crellin PR, Whittinghill JA, Swenson OA (1964) Solitary infantile hemangioendothelioma of the liver: report of one case. Rocky Mt Med J 61:38–39

McHugh K, Burrows PE (1992) Infantile hepatic hemangioendotheliomas: significance of portal venous and systemic collateral arterial supply. J Vasc Interv Radiol 3:337–344

McLean RH, Moller JH, Warwick WJ, Satran L, Lucas RV (1972) Multinodular hemangiomatosis of the liver in infancy. Pediatrics 49:563–573

Meirowitz NB, Guzman ER, Underberg-Davis SJ, Pellegrino JE, Vintzileos AM (2000) Hepatic hemangioendothelioma: prenatal sonographic findings and evolution of the lesion. J Clin Ultrasound 28:258–263

Mendiratta V, Anand R, Chander R, Harjai B, Gupta T (2008) Multiple neonatal haemangiomatosis with liver haemangiomas and anaemia. Australas J Dermatol 49:42–43

Mhanni AA, Chodirker BN, Evans JA, Menticouglou S, Wiseman N, MacDonald N, Chudley AE (2000) Fetal hepatic haemangioendothelioma: a new association with elevated maternal serum alpha-fetoprotein. Prenat Diagn 20:432–435

Mo JQ, Dimashkieh HH, Bove KE (2004) GLUT1 endothelial reactivity distinguishes hepatic infantile hemangioma from congenital hepatic vascular malformation with associated capillary proliferation. Hum Pathol 35:200–209

Moazam F, Rodgers BM, Talbert JL (1983) Hepatic artery ligation for hepatic hemangiomatosis of infancy. J Pediatr Surg 18:120–123

Moon SB, Kwon HJ, Park KW, Yun WJ, Jung SE (2009) Clinical experience with infantile hepatic hemangioendothelioma. World J Surg 33:597–602

Morimura Y, Fujimori K, Ishida T, Ito A, Nomura Y, Sato A (2003) Fetal hepatic hemangioma representing non-reassuring pattern in fetal heart rate monitoring. J Obstet Gynaecol Res 29:347–350

Morris J, Abbott J, Burrwos P, Levine D (1999) Antenatal diagnosis of fetal hepatic hemangioma treated with maternal corticosteroids. Obstet Gynecol 94:813–815

Mortele KJ, Vanzieleghem B, Mortele B, Benoit Y, Ros PR (2002) Solitary hepatic infantile hemangioendothelioma: dynamic gadolinium-enhanced MR imaging findings. Eur Radiol 12:862–865

Mortensson W, Pettersson H (1979) Infantile hepatic haemangioendothelioma. Angiographic considerations. Acta Radiol Diagn (Stockh) 20:161–169

Mouat F, Evans HM, Cutfield WS, Hofman PL, Jefferies C (2008) Massive hepatic hemangioendothelioma and consumptive hypothyroidism. J Pediatr Endocrinol Metab 21:701–703

Murphy AM, Brenner C, Ann Lynch S (2006) Agenesis of the corpus callosum with interhemispheric cyst, hepatic hemangioma and trisomy 21. Clin Dysmorphol 15:149–151

Nazir and Pervez (2006) Pub Med PMID 16410090

Ng WH, Ching AS, Chan KF, Fung WT (2003) Clinics and diagnostic imaging (89). Infantile hepatosplenic haemangioendotheliomas. Singapore Med J 44:491–495

Nöller HG, Freundt KJ (1958) A case of thrombopenia-hemangioma syndrome in a young infant, Kasabach-Merritt disease (in German). Arch Kinderheilkd 157:258–270

Noronha R, Gonzales-Crussi F (1984) Hepatic angiosarcoma in childhood: a case report and review of the literature. Am J Surg Pathol 8:863–871

North PE, Waner M, Miteracki A, Mihm MC (2000) GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 31:11–22

Orzechowski G (1928) Hämangioendothelioma der Leber. Virchows Arch 267:63

Othersen HB, Watanatittan S (1978) Giant hemangiomatosis of the liver in infancy. Am Surg 44:20–25

Packard GB, Palmer HD (1955) Primary neoplasms of the liver in infants and children. Ann Surg 142:214

Park CH, Hwang HS, Hong J, Pak MS (1996) Giant infantile hemangioendothelioma of the liver. Scintigraphic diagnosis. Clin Nucl Med 21:293–295

Parmar RC, Bavdekar SB, Borwankar SS, Muranjan MN, Shenoy A (2001) Infantile hemangioendothelioma. Indian J Pediatr 68:459–461

Pavlenishvili IV, Nemsadze KP (1978) Disseminated hemangiomatosis of the liver in a newborn infant (in - Russian). Vopr Okhr Materin Det 23:85–87

Pellerin D, Alagille D, Bertin P (1971) Retentional jaundice and hepatic angiomatosis in a newborn (in French). Arch Fr Pediatr 28:1093–1100

Peters C, Langham S, Mullis PE, Dattani MT (2010) Use of combined liothyronine and thyroxine therapy for consumptive hypothyroidism associated with hepatic haemangiomas in infancy. Horm Res Paediatr 74:149–152

Pethe VV, Kalgutkar AD, Mondkar J, Oak SN, Deodhar KP, Deshmukh SS (1995) Hepatic hemangioendothelioma of infancy with congestive heart failure – report of a case. Indian J Cancer 32:186–188

Pollice L, Pagliarulo G (1975) Primary hepatic infantile hemangioendothelioma (in Italian). Tumori 61:565–574

Pott Bartsch EM, Peak BW, Yoshizawa J, Goldstein RB, Ferrell LD, Coakley FV et al (2003) Giant fetal hepatic hemangioma. Case report and literature review. Fetal Diagn Ther 18:59–64

Prabhu SR, Purandare SM (1977) Infantile hemangioendothelioma of the liver with congestive cardiac failure. Indian J Cancer 14:370–373

Presedo A, Martinez-Ibanez V, Castellote A, Lucaya X, Sanchez de Toledo J, Marques A, Boix-Ochoa J (1996) Infantile hepatic hemangioendothelioma of the liver: report of 11 cases (in Spanish). Cir Pediatr 9:51–54

Prokurat A, Kluge P, Chrupek M et al (2002) Hemangioma of the liver in children: proliferating vascular tumor or congenital vascular malformation? Med Pediatr Oncol 39:524–529

Rake MO, Liberman MM, Dawson JL, Evans R, Raftery EB, Laws J, Williams R (1970) Ligation of the hepatic artery in the treatment of heart failure due to hepatic haemangiomatosis. Gut 11:512–515

Razon MJ, Kraling BM, Mulliken JB, Bischoff J (1998) Increased apoptosis coincides with onset of involution in infantile hemangioma. Microcirculation 5:189–195

Riley MR, Garcia MG, Cox KL, Berquist WE, Kerner JA (2006) Hepatic infantile hemangioendothelioma with unusual manifestations. J Pediatr Gastroenterol Nutr 42:109–113

Ritter S, Jorn H, Ahaus M, Rath W (2003) Prenatal diagnosis of hepatic hemangioendothelioma and peripartual management 8 in German). Z Geburtshilfe Neonatol 207:29–32

Robben SG, Meradji M, Woltering MC, Egeler RM (1999) Infantile hepatic hemangioendothelioma. JBR-BTR 82:123

Robbins BH, Castle RF (1965) Hemangiomas, hepatic involvement, congestive failure. Letter to the editor. Pediatrics 35:868

Robinson D, Hambleton G (1977) Cutaneous and hepatic haemangiomata. Arch Dis Child 52:155–157

Rocchini AP, Rosenthal A, Issenberg HJ, Nadas AS (1976) Hepatic hemangioendothelioma: hemodynamic observations and treatment. Pediatrics 57:131–135

Roebuck D, Sebire N, Lehmann E, Barnacle A (2012) Rapidly involuting congenital haemangioma (RICH) of the liver. Pediatr Radiol 42:308–314

Rotman M, John M, Stowe S, Inamdar S (1980) Radiation treatment of pediatric hepatic hemangiomatosis and coexisting cardiac failure. N Engl J Med 302:852

Ruppe MD, Huang SA, Jan de Beur SM (2005) Consumptive hypothyroidism caused by paraneoplastic production of type 3 iodothyronine deiodinase. Thyroid 15:1369–1372

Sakamoto S, Kasahara M, Shigeta T, Fukuda A, Kakiuchi T, Miyasaka M, Nosaka S et al (2011) Living donor liver transplantation for multiple intrahepatic portosystemic shunts after involution of infantile hepatic hemangiomas. J Pediatr Surg 46:1288–1291

Samuel M, Spitz L (1995) Infantile hepatic hemangioendothelioma: the role of surgery. J Pediatr Surg 30:1425–1429

Sari N, Yalcin B, Akyüz C, Haliloglu M, Büyükpamukçu M (2006) Infantile hepatic hemangioendothelioma with elevated serum alpha-fetoprotein. Pediatr Hematol Oncol 23:639–647

Schiavon G, Dal Pozzo A, Alessandrini H (1982) Hepatic hemangioma in the neonate: description of a case treated surgically with favorable outcome (in Italian). Pediatr Med Chir 4:571–573

Schmitz R, Heinig J, Klockenbusch W, Kiesel L, Steinhard J (2009) Antenatal diagnosis of a giant fetal hemangioma and treatment with maternal corticosteroid. Ultraschall Med 30:223–226

Schneegans E, Korn R, Haarscher A, Alt J (1964) Multinodular hemangiomatosis of the liver (in French). Pediatrie 19:799–805

Schumann HD (1941) Beitrag zur Kasuistik des primären Hämangioendotheliomas der Leber. Frankfurt Z Pathol 55:1

Schwartz AR (1945) Multiple malignant hemangioendothelioma in infant: report of a case. Arch Pediatr 62:1

Selby DM, Stocker JT, Ishak KG (1992) Angiosarcoma of the liver in childhood: a clinicopathologic and follow-up study of 10 cases. Pediatr Pathol 12:485–498

Selby DM, Stocker JT, Waclawiw MA, Hitchcock CL, Ishak KG (1994) Infantile hemangioendothelioma of the liver. Hepatology 20:39–45

Selke AC, Cornell SH (1969) Infantile hepatic hemangioendothelioma. Am J Roentgenol Radium Ther Nucl Med 106:200–203

Seok JY, Kim YB (2010) Infantile hemangioendothelioma with increased serum alpha-fetoprotein (in Korean). Korean J Hepatol 16:192–196

Sepulveda WH, Donetch G, Giuliano A (1993) Prenatal sonographic diagnosis of hepatic hemangioma. Eur J Obstet Gynecol Reprod Biol 48:73–76

Sevinir B, Özkan TB (2007) Infantile hepatic hemangioendothelioma: clinical presentation and treatment. Turk J Gastroenterol 18:182–187

Shah KD, Beck R, Jhaveri MK, Keohane M, Weinberg B, Gerber MA (1987) Infantile hemangioendothelioma of heterotopic intrathoracic liver associated with diaphragmatic hernia. Hum Pathol 18:754–765

Shaik S, Sanislo S, O'Brien JM, Alcorn D (2001) Congenital circumscribed choroidal haemangioma associated with infantile hepatic haemangioendothelioma. Br J Ophthalmol 85:626

Sharp L, Makin E, Davenport M (2008) Hepatic haemangioendothelioma: a vertical association with biliary atresia? Eur J Pediatr Surg 18:277–279

Sheu BC, Shyu MK, Lin YF, Lee CN, Hsieh FJ, Chou YH, Yau KI, Huang SF (1994) Prenatal diagnosis and corticosteroid treatment of diffuse neonatal hemangiomatosis: case report. J Ultrasound Med 13:495–499

Shturman-Ellstein R, Greco MA, Myrie C, Goldman EK (1978) Hydrops fetalis, hydramnios and hepatic vascular malformation associated with cutaneous hemangioma and chorangioma. Acta Paediatr Scand 67:239–243

Siderys H, Moore TC, Shumacker HB (1962) Left hepatic lobectomy for hemangioma of the liver in the newborn. Surgery 52:502–504

Sidwell RU, Daubeney PE, Porter W, Roberts NM (2004) Neonatal hemangiomatosis and atrial septal defect: a rare cause of right heart failure in infancy. Pediatr Dermatol 21:66–69

Sigamani E, Iyer VK, Agarwala S (2010) Fine needle aspiration cytology of infantile haemangioendothelioma of the liver: a report of two cases. Cytopathology 21:398–402

Singh S, Chowdhury V, Prakash A, Aggarwal A (2008) Infantile haemangio-endothelioma of liver: a case report. J Indian Med Assoc 106:120

Skopec LL, Lakatua DJ (1989) Non-immune fetal hydrops with hepatic hemangioendothelioma and Kasabach-Merritt syndrome: a case report. Pediatr Pathol 9:87–93

Sloane CE, Baek SM, Beck AR (1977) Solitary neonatal hepatic hemangioendothelioma: case report and discussion. Mt Sinai J Med 44:234–240

Slovis TL, Berdon WE, Holler JO, Casarella WJ, Baker DH (1975) Hemangiomas of the liver in infants. AJR Am J Roentgenol 123:791–801

Smith GG, Lohr JA, Malcolm BS, Kelser RW (1978) Hepatic hemangioendothelioma and hyperbilirubinemia. South Med J 71:1439–1441

Sommacal D (1957) A case of multiple hemangiomatosis in infants (in German). Helv Paediatr Acta 12:666–678

Stanley P, Gates GF, Eto RT, Miller SW (1977) Hepatic cavernous hemangiomas and hemangioendotheliomas in infancy. AJR Am J Roentgenol 129:317–321

Stanley P, Geer GD, Miller JH, Gilsanz V, Landing BH, Boechat IM (1989) Infantile hepatic hemangiomas. Clinical features, radiologic investigations, and treatment of 20 patients. Cancer 64:936–949

Stone HH, Nielson IC (1965) Hemangioma of the liver in the newborn. Report of a successful outcome following hepatic lobectomy. Arch Surg 90:319–322

Stovis TL, Berdon WE, Holler JO et al (1975) Hemangiomas of the liver in infants. AJR Am J Roentgenol 123:791

Strate SM, Rutlddge JC, Weinberg AG (1984) Delayed development of angiosarcoma in multinodular infantile hepatic hemangioendothelioma. Arch Pathol Lab Med 108:943–944

Sweed A, Weinberg T (1950) Hemangioendothelioma of the liver in infancy. Am J Dis Child 80:436–441

Tan ST, Itinteang T, Leadbitter P (2011) Low-dose propranolol for multiple hepatic and cutaneous hemangiomas with deranged liver function. Pediatrics 127:e772–e776

Tawes RL, Nelson JA, Hyde GA (1971) Hepatic hemangioma: successful resection in a neonate. Surgery 70:782–785

Taylor AC, Moore E (1933) Multiple hemangiomas showing certain malignant characteristics in an infant. Am J Cancer 19:31

Terbruegge MO, Rennie JM, Haugen SE (2005) Congenital absence of the pericardium associated with congenital diaphragmatic hernia and hepatic hemangioendothelioma: case report and review of the literature. Pediatr Surg Int 21:557–559

Touloukian RJ (1970) Hepatic hemangioendothelioma during infancy: pathology, diagnosis and treatment with prednisone. Pediatrics 45:1–6

Turowski C, Feist H, Alzen G, Glüer S, Petersen C (2009) Conversion of a neonatal hepatic hemangioma to focal nodular hyperplasia. Pathol Int 59:251–254

Urbach AH, Zitelli BJ, Blatt J et al (1987) Elevated alpha-fetoprotein in a neonate with a benign hemangioendothelioma of the liver. Pediatrics 80:596–597

Van Acker P, Derom F, De Gendt G, Berzsenyi G (1975) Haemangioma of the liver in newborn infant (in Dutch). Acta Chir Belg 74:545–550

Van der Meijs BB, Merks JH, de Haan TR, Tabbers MM, van Rijn RR (2009) Neonatal hepatic haemangioendothelioma: treatment options and dilemmas. Pediatr Radiol 39:277–281

Veeder BS, Austin JH (1913) Multiple congenital hemangio-endotheliomas of the liver. Am J Med Sci 143:102–107

Verger P, Guillard JM, Cixous P, Laigle JL (1972) Case of multinodular hemangiomatosis of the liver with favorable outcome (in French). Arch Fr Pédiatr 29:1115–1116

Videback A (1946) Haemangio-endothelioma of the liver. Acta Paediatr 33:129–143

Vorse HB, Smith EI, Luckstead EF, Fraser JJ (1983) Hepatic hemangiomatosis of infancy. Am J Dis Child 137:672–673

Walsh R, Harrington J, Beneck D, Ozkaynak MF (2004) Congenital infantile hemangioendothelioma type II treated with orthotopic liver transplantation. J Pediatr Hematol Oncol 26:121–123

Wang J, Pei G, Yan J, Zhang G (2009) Coexistence of a giant splenic hemangioma and multiple hepatic hemangiomas mimicking a left adrenal neuroblastoma accompanied with multifocal hepatic metastases: pyrite answer. J Pediatr Hematol Oncol 31:983–984

Warmann S, Bertram H, Kardorff R, Sasse M, Hausdorf G, Fuchs J (2003) Interventional treatment of infantile hepatic hemangioendothelioma. J Pediatr Surg 38:1177–1181

Weinberg AG, Finegold MJ (1983) Primary hepatic tumors of childhood. Hum Pathol 14:512–537

Winters RW, Robinson SJ, Bates G (1954) Hemangioma of the liver with heart failure. A case report. Pediatrics 14:117

Woltering MC, Robben S, Egeler RM (1997) Hepatic hemangioendothelioma of infancy: treatment with interferon alpha. J Pediatr Gastroenterol Nutr 24:348–351

Wood BP, Putnam TC, Chacko AK (1977) Infantile hepatic hemangioendotheliomas associated with hemihypertrophy. Pediatr Radiol 5:242–245

Yasunaga C, Sueishi K, Ohgami H, Suita S, Kawanami T (1989) Heterogeneous expression of endothelial cell markers in infantile hemangioendothelioma. Immunohistochemical study of two solitary cases and one multiple one. Am J Clin Pathol 91:673–681, Curr. Opin. Pediatr. 14, 99-102

Yeh I, Bruckner AL, Sanchez R, Jeng MR, Newell BD, Frieden IJ (2011) Diffuse infantile hepatic hemangiomas: a report of four cases successfully managed with medical therapy. Pediatr Dermatol 28:267–275

Yu Y, Flint AF, Mulliken JB, Wu JK, Bischoff J (2004) Endothelial progenitor cells in infantile hemangioma. Blood 103:1373–1375

Zavota L, Bini F, Carano N, Agnetti A, Squarcia U (1984) Hepatic hemangiomatosis with congestive cardiac failure and development into a cholestatic hepatopathy (in Italian). Pediatr Med Chir 6:621–624

Zenge JP, Fenton L, Lovell MA, Grover TR (2002) Case report: infantile hemangioendothelioma. Curr Opin Pediatr 14:99–102

Zenzen W, Perez-Atayde AR, Elisofon SA, Kim HB, Alomari AI (2009) Hepatic failure in a rapidly involuting congenital hemangioma of the liver: failure of embolotherapy. Pediatr Radiol 39:1118–1123

Zerbini et al. (1991) Pub Med PMID 2036623

Zhang Z, Chen HJ, Yang WJ, Bu H, Wei B, Long XY, Fu J, Zhang R, Ni YB, Zhang HY (2010) Infantile hepatic hemangioendothelioma: a clinicopathologic study in a Chinese population. World J Gastroenterol 16:4549–4557

Zürcher B, Caflisch U, Hofer B, Schärli A, Laissue J (1982) Hemangio-endothelioma of the liver (case report). Z Kinderchir 35:26–31

Variants of Hemangioendotheliomas of the Hepatobiliary Tract

53

Contents

Abstract

Apart from epithelioid hepatic hemangioendothelioma and infantile hepatic hemangioendothelioma/hepatic infantile hemangioma, there are few other endotheliomas that can manifest as primary neoplasms of the liver. Kaposiform hemangioendothelioma is a rare, locally aggressive, vascular spindle-cell tumor that resembles Kaposi's sarcoma. This neoplasm most commonly develops in the skin and the retroperitoneal space of infants and children, but is also observed in the hepatobiliary tract in rare instances. Kaposiform hemangioendothelioma is a well-known cause of Kasabach-Merritt syndrome. Histologically, the neoplasm is characterized by nodules or lobules of rather bland-looking spindle cells which encircle slit-like, CD31- and CD34-positive vascular channels. A further hemangioendotheliomatous neoplasm that develops in the liver as a primary tumor is polymorphous hemangioendothelioma.

Kaposiform Hemangioendothelioma

Introduction

Kaposiform hemangioendothelioma (KFE) is a rare, locally aggressive (borderline), vascular spindle-cell tumor with resemblance to Kaposi's sarcoma, first described in 1993 (Zukerberg et al. 1993). Before the definition as KFH, the

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_53

lesion has anecdotically been described under various names, such as hemangioendothelioma, congenital hemangioendothelioma, Kaposi's-like infantile hemangioendothelioma, and hemangioma with Kaposi's sarcoma-like features (Niedt et al. 1989). The neoplasm seems to be closely related to tufted angioma (TA), and both KFE and TA are now considered neoplasms of intermediate malignancy because of infiltrative growth, local aggressiveness, and variable prognosis. Tumors exhibiting features that are transitional between KFE and TA have been described even in the same specimen of some patients (Brasanac et al. 2003), and a dynamic transformation between both tumors has been reported (Chu et al. 2003), suggesting that KFE and TA may reflect different stages in the evolution of a single entity (Arai et al. 2006). Most commonly, KFE develops in the skin and in the retroperitoneal space of infants and children. The development of KFE in adolescents or in adults is rare (Mentzel et al. 1997; review: Fernandez et al. 2009).

Epidemiology

In a study of 163 patients from North America, the prevalence of KFE in Massachusetts was 0.91 case per 100,000 children (Croteau et al. 2013). Most of KFH present during early childhood (first year of life), and the lesion is more common in males. In the Boston study, KFE manifested in infancy in 93 % of cases, with 60 % as neonate (Croteau et al. 2012). Cases in adults are rare (Mentzel et al. 1997) and may in part have been diagnosed as TA.

Clinical Manifestations and Imaging Features

Apart from the classical sites, i.e., skin and retroperitoneal space, KFH can also occur in visceral locations. Multifocal and particularly internal lesions may, depending on their extension, cause severe complications. Retroperitoneal extensions or manifestations occur in 18 % of the patients. Owing to its distinct angioarchitecture and vascular composition, KFH has a tendency to bleed and to sometimes cause life-threatening hemorrhage. In contrast to infantile and juvenile hemangiomas, KFH shows no tendency to spontaneously regress and involute. Untreated KFH is associated with a rather high mortality rate (up to 30 %), mainly caused by locally invasive effects, large and irresectable visceral manifestations, massive hemorrhage, and KMS (review: Fernandez et al. 2009).

KFH is a well-known cause of Kasabach-Merritt syndrome/KMS (synonym: Kasabach-Merritt phenomenon) (Zukerberg et al. 1993; Walker et al. 2002; Hauer et al. 2007; Drucker et al. 2009; Fahrtash et al. 2010; Veening et al. 2010; Garcia-Monaco et al. 2012), mainly in case of large retroperitoneal lesions. In fact, KMS is closely associated with KFH and TA and not with common infantile hemangioma (Enjolras et al. 1997; Sarkar et al. 1997). KMS was described in 1940 (Kasabach and Merritt 1940) and is characterized by a complex vascular tumor coagulopathy with profound thrombocytopenia (<20,000) and consumptive coagulopathy and hypofibrinogenemia with fibrin degradation products (reviews: Maguiness and Guenther 2002; Rodriguez et al. 2009). KMS in KFH usually develops in the first months of life. The pathogenesis of KMS has not been clarified and is complex, because KMS is not related to the lesion mass or the clinical extent since many large and very large juvenile hemangiomas, vascular malformations with a large internal vessel surface, and disseminated Kaposi's sarcoma never lead to this complication. There is some evidence that KMS preferentially evolves in vascular tumors and tumor-like lesions that have a lymphatic contribution. KMS was found in advanced Kaposi's sarcoma, multifocal lymphangioendotheliomatosis, and TA (Alvarez-Mendoza et al. 2000). KFH was observed to develop on the background of a capillary-lymphatic vascular malformation, followed by Kasabach-Merritt syndrome. KFH may be associated with lymphangiomatosis, characterized by the presence of either diffusely infiltrating lymphangiomas or as lymphangioma involving multiple sites (Zukerberg et al. 1993; Vetter-Kauczok et al. 2008). This association is usually seen in children and only exceptionally in adults (Mentzel et al. 1997).

KFH Involvement of the Hepatobiliary Tract

The liver can be involved by KFH in situations of multifocal tumors, whereby sometimes one dominant extrahepatic lesion is found (Nakaya et al. 2014). KFH has been observed in the choledochus of a 5-month-old male infant with cholestatic jaundice. CT revealed a vascular tumor in the hepatic portal region causing biliary obstruction. The tumor was successfully resected followed by hepatoportoenterostomy (Terui et al. 2010). KFH occurs in the kidney and can invade the inferior vena cava to reach the retrohepatic space (Indolfi et al. 2010).

Pathology

Histologically, KFH is characterized by nodules, solid sheets, or lobules of morphologically rather bland-looking spindle cells, ranging in size from small to large, that are grouped to fascicles and which encircle slit-like capillary channels at the periphery of nodules and lobules. Small areas with densely packed spindle cells may be noted. Dense spindle-cell areas are mainly noted at the periphery of vascular lobules, where the spindle cells stream into the vascular compartment. Central portions of the lobules (the so-called glomeruloid islands), in contrast to the cellular periphery, are composed of hemovascular channels with surrounding clusters of small or epithelioid-looking SMA-positive cells (possibly pericyte-like cells; Lyons et al. 2004). The vascular spaces may look empty, but also contain red blood cells and sometimes microthrombi. Extravasation of erythrocytes and focal hemosiderosis are found.

Immunohistochemically, the endothelial cells of the vascular channels are in part reactive for CD31 and CD34. Staining of these two endothelial markers is diffuse across the vascular lobules, including the circumferential spindle cells at the periphery and the small vascular channels in the center. The endothelial cells of KFH are GLUT1 negative (North et al. 2000; Lyons et al. 2004). More than 90 % of KFH are positive for D2-40 (podoplanin), a marker of lymphatic endothelium (Debelenko et al. 2005; Galambos and Nodit 2005; Arai et al. 2006). D2-40 stains the neoplastic spindle cells and lymphatic channels adjacent to vascular lobules. The staining is typically concentrated at the peripheral part of vascular lobules where D2-40 highlights spindle cells that stream between the lobules and circumscribe the glomeruloid cores. This results in "dark" rings encircling "pale" centers of the vascular lobules. D2-40 staining was observed in 20–70 % of the cellular component of the lesions and 70–90 % of the large spindled cells (Debelenko et al. 2005). Similar to Kaposi's sarcoma and Dabska-type hemangioendotheliomas which have features of lymphatic differentiation, KFH is positive for vascular endothelial growth factor receptor-3 (VEGFR-3), a lymphatic endothelial marker (Folpe et al. 2000; Saito et al. 2009). Part of the cells of KFH express the lymphatic endothelial nuclear transcription factor, Prox1, with a distinct pattern; the mainly peripherally located spindle cells are positive for Prox1, podoplanin, CD31, and CD34, and also the endothelial cells in the glomeruloid foci are Prox1 positive (Le Huu et al. 2010; Miettinen and Wang 2012). It has been proposed that both VEGFR-3 and Prox1 might be superior to D2-40 in identifying endothelial cells of a lymphatic lineage (Castro and Galambos 2009). Prox1 has been found to promote invasion of KFH cells in an experimental murine model (Dadras et al. 2008). In contrast to Kaposi's sarcoma, human herpesvirus 8 was not detected in KFH (Cheuk et al. 2004; Lyons et al. 2004; Robin et al. 2004; Deraedt et al. 2006).

Polymorphous Hemangioendothelioma

Introduction

Polymorphous hemangioendothelioma (PHE) was originally described as a distinctive vasoproliferative lesion developing in lymph nodes, characterized by solid, primitive vascular, and angiomatous patterns and relatively bland cytologic features (Chan et al. 1992). These

authors reported a series of 39 patients with primary vascular tumors of lymph nodes other than Kaposi's sarcoma and identified three cases with the novel phenotype of PHE. The term polymorphous was chosen to emphasize the great variability of histological patterns present in this tumor. PHE is a neoplasm of borderline malignant potential and has both nodal and extranodal manifestations (Rehring et al. 1999; Tadros et al. 2003; Moreno-Ramirez et al. 2004; Falleti et al. 2009). PHE is histologically characterized by a complex mixture of intermingled solid, spindled, retiform, epithelioid, and angiomatous components. The tumor cells are immunoreactive for CD31, CD34, and factor VIII-associated antigen (Nascimento et al. 1997).

Polymorphous Hemangioendothelioma of the Liver

PHE may occur as primary hepatic neoplasm (Cobianchi et al. 2009). A large hepatic mass was detected in 47-year-old female patient suffering from abdominal pain and anemia. Sonography and MRI of the abdomen revealed a large heterogeneous mass ($9 \times 7 \times 7$ cm) in the left lateral hepatic segments (segments II, III, and partially IV). The hepatic resection specimen was almost completely replaced by a nodular, hemorrhagic mass with an expanding growth pattern without encapsulation. Cut sections showed a variegated color from red to yellowish. On histology the tumor displayed a thin inflammatory pseudocapsule and a composite pattern, consisting of angiomatous, retiform, and solid areas. The angiomatous areas showed clefts, branching channels, and dilated vascular spaces lined by plump cuboidal and often hobnailed cells. Pseudopapillary structures were noted, and there were areas mimicking the pattern seen in retiform hemangioendothelioma. The solid areas consisted of oval to spindle cells with vacuolated nuclei and an indistinct, slightly eosinophilic cytoplasm, these cells being arranged in a trabecular to vaguely fascicular pattern. The intervening stroma was sclerotic to fibrocellular to edematous. Only occasional mitotic figures were found. Areas of tumor necrosis were observed. Immunohistochemically, cells of the angiomatous and spindled areas were positive for vimentin, CD31, and factor VIII-associated antigen, but not CD34. The growth fraction (Ki-67) was less than 1 %.

References

Alvarez-Mendoza A, Lourdes TS, Ridaura-Sanz C, Ruiz-Maldonado R (2000) Histopathology of vascular lesions found in Kasabach-Merritt syndrome: review based on 13 cases. Pediatr Dev Pathol 3:556–560

Arai E, Kuramochi A, Tsuchida T, Tsuneyoshi M, Kage M, Fukunaga M, Ito T et al (2006) Usefulness of D2-40 immunohistochemistry for differentiation between kaposiform hemangioendothelioma and tufted angioma. J Cutan Pathol 33:492–497

Brasanac D, Janic D, Boricic I, Jovanovic N, Dokmanovic L (2003) Retroperitoneal kaposiform hemangioendothelioma with tufted angioma-like features in an infant with Kasabach-Merritt syndrome. Pathol Int 53:627–631

Castro EC, Galambos C (2009) Prox-1 and VEGFR3 antibodies are superior to D2-40 in identifying endothelial cells of lymphatic malformations – a proposal of a new immunohistochemical panel to differentiate lymphatic from other vascular malformations. Pediatr Dev Pathol 12:187–194

Chan JK, Frizzera G, Fletcher CD, Rosai J (1992) Primary vascular tumors of lymph nodes other than Kaposi's sarcoma. Analysis of 39 cases and delineation of two new entities. Am J Surg Pathol 16:335–350

Cheuk W, Wong KO, Wong CS, Dinkel JE, Ben-Dor D, Chan JK (2004) Immunostaining for human herpesvirus 8 latent nuclear antigen-1 helps distinguish Kaposi sarcoma from its mimickers. Am J Clin Pathol 121:335–342

Chu CY, Hsiao CH, Chiu HC (2003) Transformation between kaposiform hemangioendothelioma and tufted angioma. Dermatology 206:334–337

Cobianchi L, Lucioni M, Rosso R, Zonta S, Fiandrino G, Alessiani M, Doni M, Ferrari A et al (2009) Unique vascular tumor primary arising in the liver and exhibiting histopathological features consistent with so-called polymorphous hemangioendothelioma. Pathol Int 59:890–894

Croteau SE, Liang MG, Kozakewich HP, Alomari AI, Fishman SJ, Mulliken JB, Trenor CC (2013) Kaposiform hemangioendothelioma: atypical features and risk of Kasabach-Merritt phenomenon in 107 referrals. J Pediatr 163:142–147

Dadras SS, Skrzypek A, Nguyen L, Shin JW, Schulz MM, Arbiser J, Mihm MC, Detmar M (2008) Prox-1 promotes invasion of kaposiform hemangioendotheliomas. J Invest Dermatol 128:2798–2806

Debelenko LV, Perez-Atayde AR, Mulliken JB, Liang MG, Archibald TH, Kozakewich HP (2005) D2-40 immunohistochemical analysis of pediatric vascular tumors reveals positivity in kaposiform hemangioendothelioma. Mod Pathol 18:1454–1460

Deraedt et al. (2006) Pub Med PMID 16596383

Drucker et al. (2009) Pub Med PMID 19426625

Enjolras O, Wassef M, Mazoyer E, Frieden IJ, Rieu PN, Drouet L, Taieb A, Stalder JF et al (1997) Infants with Kasabach-Merritt syndrome do not have "true" hemangiomas. J Pediatr 130:631–640

Fahrtash F, McCahon E, Arbuckle S (2010) Successful treatment of kaposiform hemangioendothelioma and tufted angioma with vincristine. J Pediatr Hematol Oncol 32:506–510

Falleti J, Siano M, De Cecio R, Somma A, Pettinato G, Insabato L (2009) Nodal and extranodal soft tissue polymorphous hemangioendothelioma: a case report and review of the literature. Tumori 95:94–97

Fernandez Y, Bernabeu-Wittel M, Garcia-Morillo JS (2009) Kaposiform hemangioendothelioma. Eur J Intern Med 20:106–113

Folpe AL, Veikkola T, Valtola R, Weiss SW (2000) Vascular endothelial growth factor receptor-3 (VEGFR-3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi's sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. Mod Pathol 13:180–185

Galambos C, Nodit L (2005) Identification of lymphatic endothelium in pediatric vascular tumors and malformations. Pediatr Dev Pathol 8:181–189

Garcia-Monaco R, Giachetti A, Peralta O, Napoli N, Lobos P, Gioseffi L, Mariani G (2012) Kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon: successful treatment with embolization and vincristine in two newborns. J Vasc Interv Radiol 23:417–422

Hauer et al. (2007) PubMed PMID 16411198

Indolfi et al. (2010) Pub Med PMID 20588198

Kasabach HH, Merritt KK (1940) Capillary hemangioma with extensive purpura: report of a case. Am J Dis Child 59:1063

Le Huu AR, Jokinen CH, Ruben BP, Mihm MC, Weiss SW, North PE, Dadras SS (2010) Expression of Prox1, lymphatic endothelial nuclear transcription factor, in kaposiform hemangioendothelioma and tufted angioma. Am J Surg Pathol 34:1563–1573

Lyons LL, North PE, Mac-Moune Lai F, Stoler MH, Folpe AL, Weiss SW (2004) Kaposiform hemangioendothelioma: a study of 33 cases emphasizing its pathologic, immunophenotypic, and biologic uniqueness from juvenile hemangioma. Am J Surg Pathol 28:559–568

Maguiness S, Guenther L (2002) Kasabach-Merritt syndrome. J Cutan Med Surg 6:335–339

Mentzel T, Mazzoleni G, Dei Tos AP, Fletcher CD (1997) Kaposiform hemangioendothelioma in adults. Clinicopathologic and immunohistochemical analysis of three cases. Am J Clin Pathol 108:450–455

Miettinen M, Wang ZF (2012) Prox1 transcription factor as a marker for vascular tumors – evaluation of 314 vascular endothelial and 1086 nonvascular tumors. Am J Surg Pathol 36:351–359

Moreno-Ramirez D, Gonzalez-Campora R, Escudero AG et al (2004) Recurrent polymorphous hemangioendothelioma. Histopathology 45:196–197

Nakaya T, Morita K, Kurata A, Ushiku T, Igarashi T, Kuroda M, Fukayama M (2014) Multifocal kaposiform hemangioendothelioma in multiple visceral organs: an autopsy of 9-day-old female baby. Hum Pathol 45:1773–1777

Nascimento AG, Keeney GL, Sciot R, Fltecher CD (1997) Polymorphous hemangioendothelioma: a report of two cases, one affecting extranodal soft tissues, and review of the literature. Am J Surg Pathol 21:1083–1089

Niedt GW, Greco MA, Wieczorek R, Blanc WA, Knowles DM (1989) Hemangioma with Kaposi's sarcoma-like features: report of two cases. Plast Reconstr Surg 9:567–575

North PE, Waner M, Mizeracki A, Mihm MC (2000) GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 31:11–22

Rehring TF, Deutchman A, Cross JS (1999) Polymorphous hemangioendothelioma. Ann Thor Surg 68:1396–1397

Robin YM, Guillou L, Michels JJ, Coindre JM (2004) Human herpesvirus 8 immunostaining: a sensitive and specific method for diagnosing Kaposi sarcoma in paraffin-embedded sections. Am J Clin Pathol 121:330–334

Rodriguez V, Lee A, Witman PM, Anderson PA (2009) Kasabach-Merritt phenomenon: case series and retrospective review of the Mayo clinic experience. J Pediatr Hematol Oncol 31:522–526

Saito M, Gunji Y, Kashii Y, Odaka J, Yamauchi T, Kanai N, Momoi MY (2009) Refractory kaposiform hemangioendothelioma that expressed vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3: a case report. J Pediatr Hematol Oncol 31:194–197

Sarkar M, Mulliken JB, Kozakewich HP, Robertson RL, Burrows PE (1997) Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with Kaposiform hemangioendothelioma and not with common infantile hemangioma. Plast Reconstr Surg 100:1377–1386

Tadros M, Rizk SS, Opher E, Thompson LD (2003) Polymorphous hemangioendothelioma of the neck. Ann Diagn Pathol 7:165–168

Terui K, Nakatani Y, Kambe M, Fukunaga M, Hishiki T, Saito T, Sato Y, Takenouchi A et al (2010) Kaposiform hemangioendothelioma of the choledochus. J Pediatr Surg 45:1887–1889

Veening MA, Verbeke JI, Witbreuk MM, Kaspers GJ (2010) Kaposiform (spindle cell) hemangioendothelioma in a child with an unusual presentation. J Pediatr Hematol Oncol 32:240–242

Vetter-Kauczok CS, Ströbel P, Bröcker EB, Becker JC (2008) Kaposiform hemangioendothelioma with distant lymphangiomatosis without an association to Kasabach-Merritt-syndrome in a female adult. Vasc Health Risk Manag 4:263–266

Walker et al. (2002) Pub Med PMID 11984805

Zukerberg et al. (1993) Pub Med PMID 8494101

Angiosarcoma of the Liver

54

ICD-O code 9120/3

Contents

Abstract

Angiosarcoma is a high-grade (grade 3) sarcoma that consists of a proliferation of atypical endothelial cells. Angiosarcoma develops in various organs and tissues and is the most important hepatic sarcoma, albeit it amounts to only 2 % of all primary hepatic malignancies. There is a male predominance, probably linked to risk factors related to chemical industries. The peak incidence of hepatic angiosarcoma is in the sixth to seventh decades of life, but the tumor also occurs in the pediatric age group. Seventy percent of hepatic angiosarcomas are sporadic lesions, and 30 % are associated with agents known to play a role in this neoplasm, particularly vinyl chloride monomer, pesticides, arsenicals, androgenic steroids, external ionizing radiation, and formerly thorotrast. Macroscopically, angiosarcoma presents in various growth patterns, ranging from massive tumors to diffuse micronodular lesions. Histopathology resembles that of angiosarcomas in other locations. Two main cell types prevail, i.e., highly abnormal endothelial cells lining abortive vascular spaces and interstitial spindle cells. Polymorphous elements and giant cells may occur, and part of tumor cells exhibit erythrophagocytosis. Hepatic angiosarcoma is a very aggressive, metastasizing neoplasm associated with poor outcome.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_54

Introduction

Angiosarcoma is defined as highly malignant (grade 3) soft tissue sarcoma composed of atypical endothelial cells with complex genetic and genomic changes. Hepatic angiosarcoma is a rare primary malignancy of the liver that usually affects adults, but rarely also affects the pediatric liver. Hepatic angiosarcoma has been described in the older literature under various names, including hemangiosarcoma, hemangioendothelial sarcoma, malignant endothelioma, and retothel sarcoma (Nazari 1906). The first reported case of hepatic angiosarcoma was probably that of von Frerichs (von Frerichs 1861). The term, primary angiosarcoma of the liver, has already been employed in 1890, based on two observations (Arnold 1890). After the definition of hepatic angiosarcoma, a series of detailed descriptions of this tumor have been published, sometimes under the alternative and now obsolete terms, hemangioendothelial sarcoma, hemangioendotheliosarcoma, angioendothelioma, reticuloendothelioma, angioblastic reticuloendothelioma, sarcome angioplastique, and Kupffer cell sarcoma (Arnold 1890; Peyser 1893; Israil 1894; Bramwell and Leith 1896; D'Urso 1896; Pepere 1900; De Haan 1903; Marx 1904a, b; Jores 1908; Kothny 1912; Fischer 1913; Hachfeld 1914; Kahle 1919; Schlesinger 1920; Blumberg 1926; Puhr 1931; Matturi and Rossi 1963; Rakov et al. 1963). Important aspects of hepatic angiosarcoma have been reviewed (Alrenga 1975; Locker et al. 1979; Buetow et al. 1994). Hepatic angiosarcoma is sometimes listed in the group of malignant vascular tumors (MVT) of the liver, also including hemangioendothelioma and its epithelioid variant, and tumors formerly classified as hemangiopericytoma (Groeschl et al. 2014).

Epidemiology

Angiosarcomas account for only 2 % of all primary hepatic malignant neoplasms, but are the most common primary hepatic sarcoma. This high-grade hepatic sarcoma has an estimated incidence of 0.14–0.25 per million (Mani and van Thiel 2001). There is male predominance (male/female ratio of 3:1), probably related to the direct link with industrial chemical exposure; however, the male predominance persists even in idiopathic hepatic angiosarcoma at a rate of 4:1 (Baxter 1981). In an autopsy study from Japan, the male/female ratio in patients with thorotrast-induced hepatic angiosarcoma was 27:2, because most of the male patients were ex-servicemen who had received thorium dioxide injections during radiologic examinations for war-related wounds (Kojiro et al. 1985). The peak incidence is in the sixth and seventh decades of life, although true hepatic angiosarcoma also occurs in the pediatric age group (Geramizadeh et al. 2011; Wang and Wei 2013). Among 161 angiosarcomas reviewed from the files of the French Sarcoma Group from 1980 to 2004, 7 tumors were primary hepatic angiosarcomas (4 %; Fayette et al. 2007). Among 11,939 patients diagnosed with primary hepatic tumors from 1985 to 2007 at 2 South Korean centers, 5 patients were diagnosed with primary hepatic angiosarcoma (Kim et al. 2009).

About 70 % of hepatic angiosarcomas are sporadic, i.e,. without recognizable cause (Fiechtner and Reyes 1976), and the remaining 30 % are associated with agents known to induce this type of tumor, in particular vinyl chloride monomer, pesticides, arsenical compounds, use of androgenic steroids, hepatic iron overload, external radiation, and, formerly, thorotrast (Falk et al. 1979a, 1981a; Baxter 1981; Buetow et al. 1994; Timaran et al. 2000; Mani and Van Thiel 2001; Budd 2002; Koyama et al. 2002; Molina and Hernandez 2003; Bonaccorsi-Riani and Lerut 2010; Huang et al. 2011). A minority of hepatic angiosarcomas have been found in association with liver cirrhosis (Kothny 1912; Kahle 1919). Very rarely, hepatic angiosarcoma develops in pre-existing liver tumors, such as adult mesenchymal hamartoma (Kulkarni et al. 2010).

Clinical and Imaging Presentation

The clinical features of hepatic angiosarcoma are nonspecific and include abdominal pain, hepatomegaly, abdominal distension, weakness,

weight loss, ascites, and eventually jaundice with or without fever.

Selected References Giacomelli 1950; Fontaine et al. 1954; Miller et al. 1964; Barjon et al. 1965; Yamagiwa et al. 1967; Ansari and Weigent 1971; Sugahara et al. 1974; Alrenga 1975; Locker et al. 1979; Wang et al. 1983; Roester et al. 1985; Lelbach 1996; Molina and Hernandez 2003; Kim et al. 2009; Zhou et al. 2010; Chi et al. 2011; Duan and Li 2012; Poggi Machuca et al. 2012; Yang et al. 2012.

In one series of 103 patients, jaundice or ascites (usually hemorrhagic) were found on presentation in 24 % and 28 %, respectively, of the patients (Locker et al. 1979). In rare situations, hepatic angiosarcoma was detected incidentally, during routine imaging procedures (Kajihara et al. 2013). Owing to the rapid growth, necrosis, and/or bleeding, hepatic angiosarcomas are known to undergo "spontaneous" rupture (Ho et al. 2004; Chien et al. 2012). Disseminated intravascular coagulopathy may ensue (Tordjman et al. 1995), and up to one fourth of the patients may present with sometimes severe intra-abdominal bleeding. Massive tumor involvement of the liver may cause liver failure in up to 31 % and portal hypertension (Locker et al. 1979; Rojter et al. 1995; Akdogan et al. 2002; Bhati et al. 2008), but signs of significant liver disease were not detected in other studies (Makk et al. 1976; El Zayadi et al. 1986; Dannaher et al. 1981). Massive tumor burden can create extensive arteriovenous shunting followed by congestive heart failure (Harrison et al. 2001). Due to invasive growth and formation in tumor thrombus, angiosarcoma can induce portal vein thrombosis (Pimentel Cauduro et al. 2002).

Complications

A severe complication of hepatic angiosarcoma is rupture of large hemorrhagic tumors, causing rupture of the liver and often massive intra-abdominal bleeding (Mahony et al. 1982; Azodo et al. 1993; Burke and Opeskin 2000; Horger 2003; Ho et al. 2004; Ikeda et al. 2006; Leowardi et al. 2006). Rupture is promoted by the high density of abnormal vascular structures and the extensive necrosis of these neoplasms. Acute intra-abdominal hemorrhage is a well-known complication and may occur in up to one fourth of the patients (Locker et al. 1979; Tordjman et al. 1995; Lelbach 1996; Stambo and Guiney 2007). Some hepatic angiosarcomas may primarily manifest as recurrent hemoperitoneum (Lee et al. 2008). Other, less common complications include consumption coagulopathy and microangiopathic hemolytic anemia (Michot et al. 1987), congestive heart failure (Harrison et al. 2001), and fulminant liver failure due to diffuse tumor infiltration (Montell Garcia et al. 2012; Olson et al. 2014). Hepatic angiosarcoma is a very rare cause of Kasabach-Merritt syndrome (Alliot et al. 2001; Gonzalez Rodriguez et al. 2012). Hepatic angiosarcoma can rarely be associated with veno-occlusive disease and mimick sinusoidal obstruction syndrome. This change probably represents secondary alterations due to injury to the hepatic sinusoids by the invasive/angioinvasive malignant neoplasm (Wiland et al. 2012).

Imaging

Most patients with hepatic angiosarcoma present with hepatic mass lesions identified on imaging examinations (Vasile et al. 1983; Ross and Rasmussen 1989; Fajadet et al. 1990; Ohtomo et al. 1992; Rademaker et al. 2000). Contrast-enhanced ultrasound of hepatic mesenchymal malignancies reveal as peripheral nodular enhancement, chaotic central vascularization, and absence of contrast enhancement in the late phase (Trojan et al. 2010). On contrast-enhanced CT images, hepatic angiosarcomas present as nonspecific hypoattenuating masses with heterogeneous enhancement, lesions that cannot easily be distinguished from other invasive malignant primary or metastatic liver tumors (Silverman et al. 1983; Fajadet et al. 1990; White et al. 1993; Buetow et al. 1994;

Ohmoto et al. 2000; Koyama et al. 2002; Yu et al. 2003; Chiu et al. 2005; Kim et al. 2006; Maeda et al. 2007; Yu et al. 2008; Park et al. 2009; Wang et al. 2012). Small tumors (e.g., 15 cmm) may be difficult to differentiate from hemangioma (Okano et al. 2012). Diffuse forms of angiosarcoma, a heterogeneous appearance on contrast-enhanced CT, have been described (Vasile et al. 1983; Rademaker et al. 2000). Some reports state that angiosarcomas with a large dominant mass can mimick hepatic hemangioma (Vasile et al. 1983; Itai and Teraoka 1989; Yamanaka et al. 2002). Hepatic angiosarcoma may not be difficult to distinguish from hepatic hemangioma on CT (Peterson et al. 2000), but in more complex cases, it has been shown that early central enhancement and arterioportal shunting on dynamic CT might be helpful for distinguishing hepatic angiosarcoma with a solid growth pattern from benign vascular neoplasms (Ohmoto et al. 2000). In general, early central enhancement, numerous hepatic lesions, and arterioportal shunting suggest angiosarcoma rather than hemangioma. Hepatic angiosarcoma with a portal venous supply may mimick hemangiomatosis of the liver (Kitami et al. 2003). In some cases, the tumors have been undetectable with US or CT (Locker et al. 1979; Silverman et al. 1983; Kanel et al. 1987), sometimes owing to predominantly intrasinusoidal growth (Thomas et al. 1975). Angiography of liver illustrates the rich and complex vascularization of the neoplasms. In some case, the tumors were shown to be supplied by both the hepatic artery and portal vein (Hoshi et al. 2006).

Association with Other Liver Tumors

Exceptionally, hepatic angiosarcomas develop in conjunction with other liver tumors, e.g., adult mesenchymal hamartoma (Li et al. 2007; Kulkarni et al. 2010). It has also been suggested that angiosarcoma of the liver may emerge from pre-existing other vascular tumors, e.g., epithelioid hemangioendothelioma (Cioffi-Pretti et al. 2009).

Pathology

Macroscopy

Hepatic angiosarcoma presents in the form of several growth patterns (Ito et al. 1988; Table 1).

Angiosarcoma can present as a large circumscribed or ill-defined tumor that involves large parts of liver lobes or almost the entire liver (massive form; Fig. 1). These neoplasms often show a central necrosis and multiple hemorrhages, while the periphery of the tumor displays a dark-red spongy texture. The massive lesions may contain isolated remnants of liver substance and often show invaded or thrombosed entrapped veins. Large tumors can be accompanied by satellite nodules that develop through intravascular metastatic spread. The multinodular form is characterized by small- to medium-sized, isolated or

Table 1 Macroscopic growth patterns of hepatic angiosarcoma (Ito et al. 1988)

Massive pattern
Multinodular pattern
Diffuse micronodular pattern
Mixed multinodular and massive pattern
Solitary nodular pattern
Giant hemangioma-like pattern
Cystic pattern

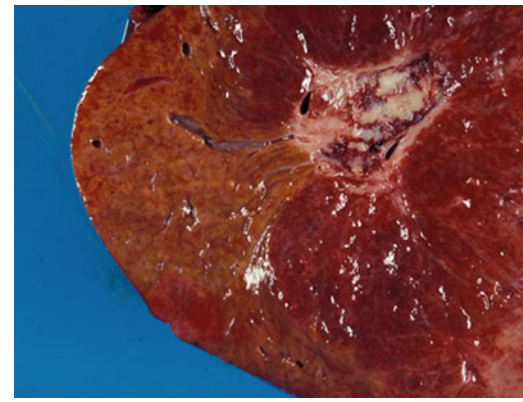

Fig. 1 Primary angiosarcoma of the liver. A massive, hemorrhagic invasive tumor contains a central necrotic area. Preserved hepatic parenchyma is seen to the left as a cuneiform tan structure

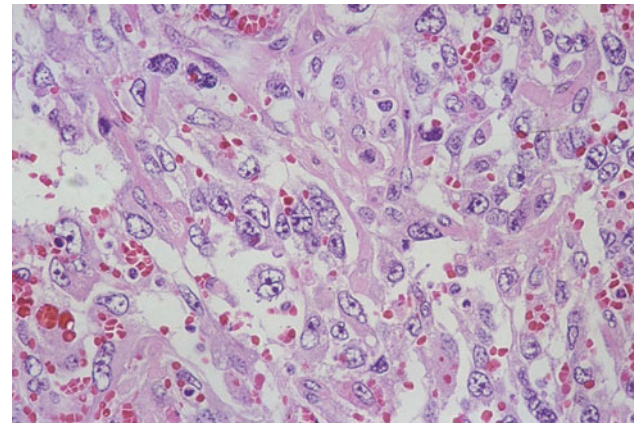

Fig. 2 Primary hepatic angiosarcoma. Abnormal and in part slit-like vascular spaces are lined by highly atypical endothelial cells with large nuclei (hematoxylin and eosin stain)

coalescent spongy hemorrhagic nodules that may involve large parts of the organ or almost the entire liver. These lesions can be identified during laparoscopy (Yasunaka et al. 2012). Less frequently, the liver is diffusely occupied by small to tiny hemorrhagic tumor foci, a presentation resembling peliosis hepatis or diffuse hemangiomatosis (the diffuse micronodular pattern). In these cases, the cut surface of the liver is speckled with small dark-red spots, sometimes on a yellowish steatotic parenchyma (Rojter et al. 1995). Massive tumors can be associated with areas of multinodular growth (mixed forms). Less commonly, the initial presentation is that of a small solitary nodule that may be confounded with small hemangioma (Heo et al. 2007). Rarely, the initial presentation is that of a large, circumscribed angiomatous, large tumor that macroscopically closely mimics giant hepatic hemangioma (Kirschstein et al. 2000). Part of the tumors form cystic structures (Ludwig and Hoffman 1975). In some tumors, the center of the lesion is occupied by a large hemorrhagic cyst filled with liquid or clotted blood, while the tumor periphery shows a rim of hemorrhagic tissue, associated with small dark-red satellite lesions.

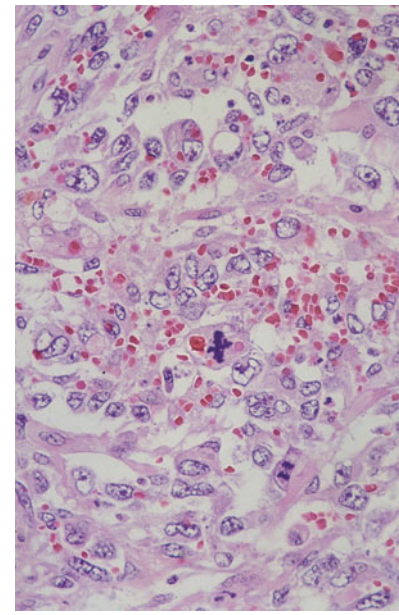

Fig. 3 Primary hepatic angiosarcoma with atypical mitotic figure (*center*) and signs of erythrophagocytosis (hematoxylin and eosin stain)

Histopathology

Diagnosis by needle biopsy of the tumor is possible, but this diagnostic procedure may be treacherous, nondiagnostic, and even dangerous, as at least one lethal complication following image-guided percutaneous liver biopsy has been reported (Drinkovic and Brkljacic 1996). The histopathology resembles in many aspects that known from soft tissue angiosarcomas (Ludwig and Hoffman 1975; Thomas and Popper 1975; Kojiro et al. 1985; Ito et al. 1988; Saleh and Tao 1998). Generally, angiosarcomas reveal four main histologic patterns, i.e., vasoformative, spindled, epithelioid, and mixed (Figs. 2, 3, 4, 5, 6, 7, 8,

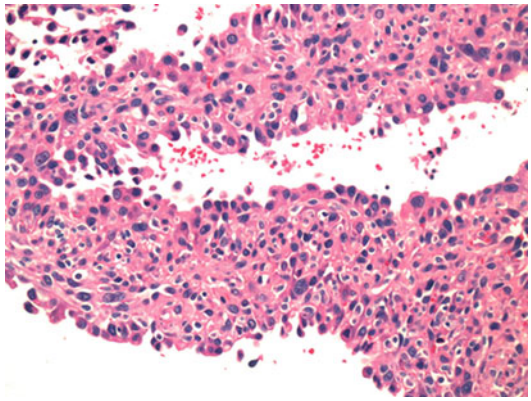

Fig. 4 Primary hepatic angiosarcoma with so-called hobnail cells protruding into the lumen of vascular spaces (hematoxylin and eosin stain)

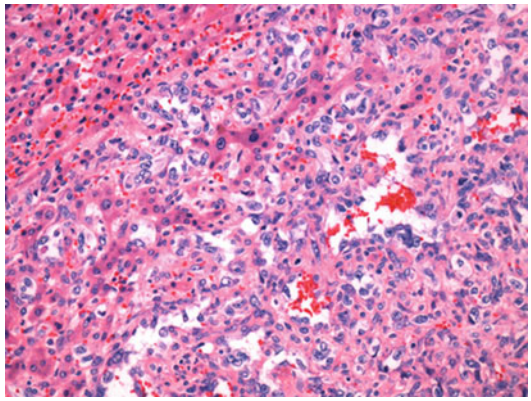

Fig. 5 Invasive pattern of hepatic angiosarcoma. Sarcoma cells have invaded the parenchyma and induced dissociation of atrophic hepatocyte plates (*upper half of figure*; hematoxylin and eosin stain)

and 9). In hepatic angiosarcomas, the tumor mainly consists of two cellular components, i.e., spindle cells and highly abnormal endothelial cells that line irregular vascular spaces, the vasoformative pattern. The spindle-shaped cells somewhat resemble fibroblasts or myofibroblasts, and these cells contain elongate nuclei with one or two nucleoli. The endothelial cells vary much in their shape, ranging from flat cells with enlarged, hyperchromatic nuclei, enlarged protruding cells forming the hobnail pattern, to highly polymorphous cells or multinucleated tumor giant cells. The large and atypical endothelial cells may show

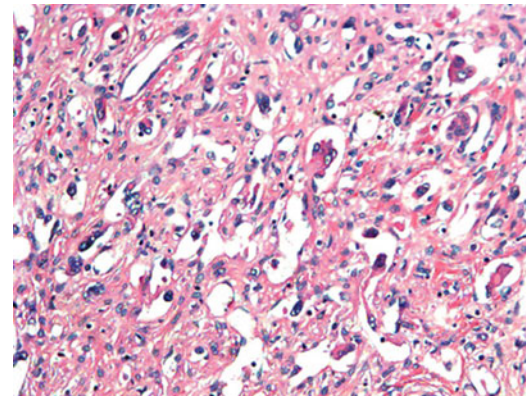

Fig. 6 Primary hepatic angiosarcoma with endovascular pseudopapillary growths (hematoxylin and eosin stain)

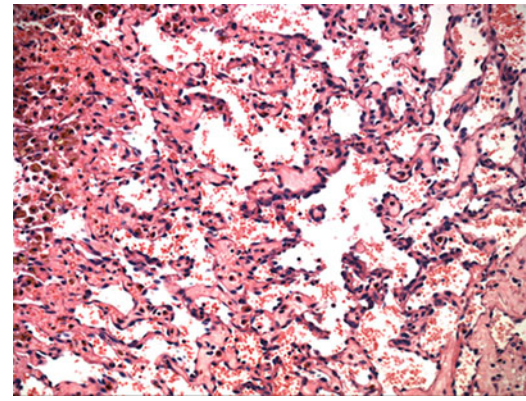

Fig. 7 Hemangioma-like hepatic angiosarcoma. The overall pattern mimics cavernous hemangioma, but vascular channels are lined by highly atypical endothelial cells (hematoxylin and eosin stain)

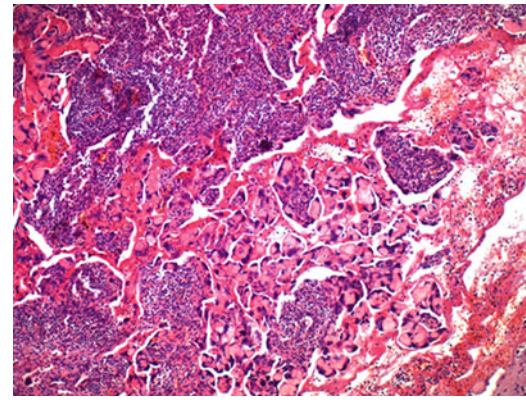

Fig. 8 Hepatic angiosarcoma with stromal cores and dense lymphocytic infiltrates (hematoxylin and eosin stain)

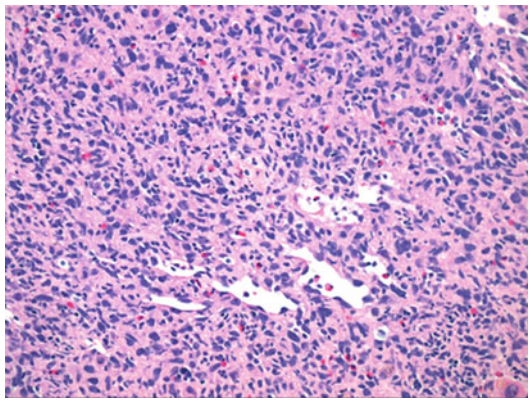

Fig. 9 Hepatic angiosarcoma, spindle cell type (hematoxylin and eosin stain)

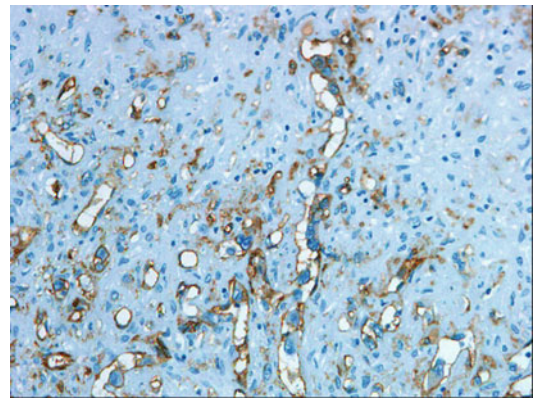

Fig. 10 Hepatic angiosarcoma. The tumor cells are reactive for CD34. Note the highly atypical nuclei of the tumor cells (CD34 immunostain)

erythrophagocytosis, later associated with hemosiderosis of tumor tissue. According to Kojiro and coworkers (1985), two main growth patterns of hepatic angiosarcoma can be distinguished. The first, the sinusoidal or intrasinusoidal growth pattern (Thomas et al. 1975; Kojiro et al. 1985), is characterized by a proliferation of single or multilayered tumor cells along sinusoid-like vascular channels with variable degrees of vascular dilatations and atrophy of the intervening liver cell plates. The tumor cells may completely fill the vascular channels, including small- and medium-sized branches of the portal venous system. The second pattern, the solid pattern, is characterized by solid tumor nests consisting mostly of spindle-shaped cells and fewer polyhedral cells, with a poorly developed vascular network. The solid areas tend to undergo extensive necrosis. In both growth patterns, secondary changes may occur, including extramedullary hemopoiesis, fibrosis, and hyalinosis. The liver tissue surrounding the tumor nodules exhibits atrophy, fatty change, hepatocyte apoptosis, focal and sometimes peliosis like sinusoidal dilatations, fibrosis, and ductular proliferations (Scherer et al. 1996).

Immunohistochemistry

Angiosarcoma cells are immunoreactive for the endothelial cell lineage markers, FVIII-associated antigen, CD31, and CD34 (Figs. 10 and 11; Saleh and Tao 1998). Strong expression of vascular endothelial growth factor A and C as well as p-AKT, p-4EBP11, and elF4E was detected in human angiosarcomas (Lahat et al. 2010). Angiosarcomas are reactive for claudin-5, mostly with a diffuse cytoplasmic staining (Miettinen et al. 2011). The stromal tissue surrounding angiosarcoma expresses decorin, while the tumor itself is negative (Salomäki et al. 2008). Part of angiosarcomas may show immunoreactivity for the neuroendocrine markers synaptophysin and/or chromogranin A, a potential diagnostic pitfall (Tessier Cloutier et al. 2014). The highly

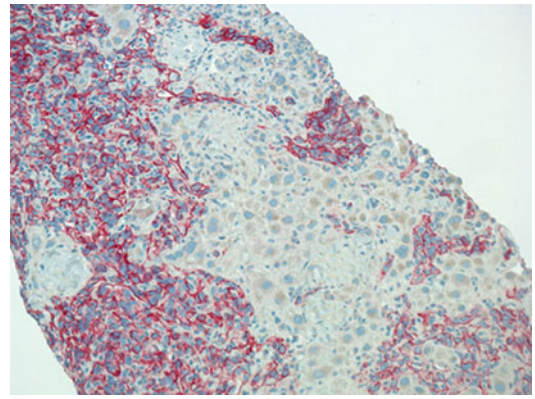

Fig. 11 CD34-positive cells of hepatic angiosarcoma (in *red*) have invaded the hepatic parenchyma (CD34 immunostain)

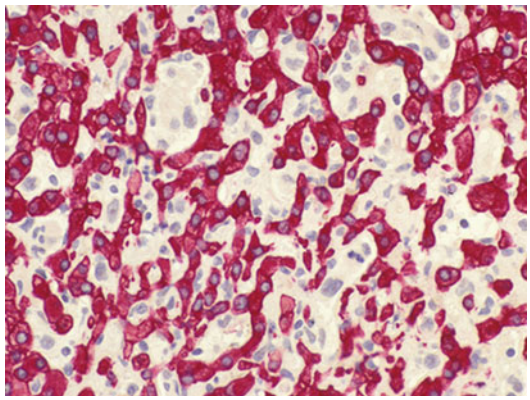

Fig. 12 Hepatic angiosarcoma. Cytokeratin-positive hepatocyte plates are atrophic and separated by sarcoma cells with mitotic activity (CAM 5.2 immunostain)

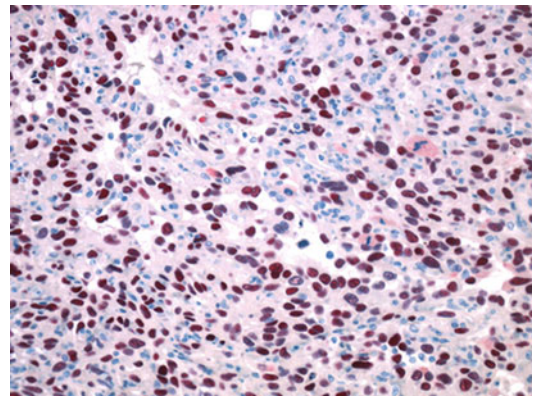

Fig. 14 High proliferative activity of hepatic angiosarcoma as a grade 3 neoplasm (MIB1 immunostain)

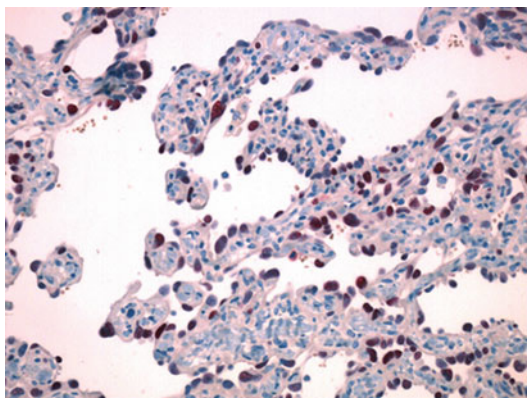

Fig. 13 Nuclear reactivity for p53 protein in hepatic angiosarcoma (p53 immunostain)

invasive phenotype of angiosarcoma in the liver is impressively visualized in cytokeratin stains depicting the invaded hepatocyte population (Fig. 12). Hepatic angiosarcoma, similar to angiosarcomas in other locations, can express p53 protein in the nuclei (Fig. 13). As a grade 3 sarcoma, hepatic angiosarcoma exhibits a high to very high proliferative activity (Fig. 14).

Pathology of Thorotrast-Induced Hepatic Angiosarcoma

Thorotrast-induced hepatic angiosarcoma is, in the whole, very similar to angiosarcomas induced by other agents (Umezu 1984; Kojiro et al. 1982, 1985; Ito et al. 1988). Based on 29 autopsy cases, Kojiro and coworkers (1985) studied the macroscopy and histopathology of thorotrast-induced hepatic angiosarcoma in detail. These authors divided the macroscopic growth patterns into four types, i.e., diffuse micronodular, multinodular, massive, and mixed multinodular and massive, diffuse micronodular and multinodular types being the most common. In the diffuse micronodular type, ill-defined hemorrhagic macular and/or micronodular lesions were scattered throughout the liver. In the multinodular type, fingertip- to walnut-sized hemorrhagic nodules are found. In the massive type, a confluent hemorragic mass measuring more than 10 cm in diameter is detected. In the mixed multinodular and massive type, varying-sized hemorrhagic nodules coexist with a large confluent hemorrhagic mass (Kojiro et al. 1985). Thorotrast deposition is already visualized in H&E-stained sections, in the form of a grayish-white particulate matter that may form clusters with fibrotic areas containing macrophages. The material is also located within the macrophages themselves (thorotrast phagocytosis).

Autoradiography, using the technique of overlayering tissue sections with photoemulsion (Yamamoto et al. 2010), shows the typical high-LET particle tracts radiating from thorotrast grains situated in tissues. These tracts form starlike

profiles, and the length of the tracts nicely shows how many cells are in the damaging reach of the alpha-type ionizing radiation.

Angiosarcoma as a Component of Mixed Hepatic Tumors

Very rarely, angiosarcoma has been observed as a component of mixed malignant liver tumors or atypical "carcinosarcomas." L'Esperance (1915) described the case of a 27-year-old female patient who had died of acute abdominal hemorrhage. Autopsy revealed an immensely enlarged liver measuring 30 cm across both lobes and weighing 6 kg. The organ was studded with numerous nodules measuring up to 6 cm, in part hemorrhagic, and projecting above the surface of the liver. Other nodules were necrotic rather than hemorrhagic, and still others were bile stained. Similar tumor tissue was found in the enlarged hilar lymph nodes. Histology showed a mixture of angiosarcoma ("perithelioma"), hemangioma, and hepatocellular carcinoma.

Differential Diagnosis

An important differential diagnosis is hepatic metastasis of soft tissue, skin, and skeletal angiosarcoma (Meis-Kindblom and Kindblom 1998; Tateishi et al. 2003; Yamashita et al. 2012; Blackmon et al. 2014), but also primary visceral angiosarcomas are known to often metastasize to the liver (Chami et al. 1994; Brown et al. 2004; Yoshida et al. 2009; Ni et al. 2013), in particular those arising in the spleen (Kishikawa et al. 1977; Ferreira et al. 2012; Duan et al. 2013; Kamocki et al. 2013). Involvement of the liver by the rare primary angiosarcoma of the gallbladder was reported (Odashiro et al. 2005). Angioblastic meningioma/hemangiopericytoma, which tends to metastasize to the liver, may be confounded with angiosarcoma (Petito and Porro 1971). In rare instances, hepatocellular carcinoma exhibits an angiosarcoma-like morphology, but the tumor cells lack expression of CD31 and CD34 (Suzuki et al. 2010). Squamous cell carcinomas are also known to sometimes develop a pseudoangiosarcomatous pattern (Conde-Taboada et al. 2005). Anastomosing hemangioma of the liver, further discussed in another paragraph, can histologically mimic angiosarcoma (Lin et al. 2013).

Biology of Disease

Hepatic angiosarcoma is a highly aggressive grade 3 sarcoma that massively invades the liver substance and adjacent tissue, and which widely metastasizes, also to unusual sites such as the spleen, small intestine, or stomach (Casado Martin et al. 1994; Vennarecci et al. 1997; Kim et al. 2005; Ahmad et al. 2008). The tumor has generally a poor outcome, this histology being worse than any other primary hepatic sarcoma (Matthaei et al. 2009), although long-term survivors have been reported after resection, but mainly in case of solitary lesions (Louagie et al. 1984; Timaran et al. 2000; Özden et al. 2003; Arima-Iwasa et al. 2007; Zhou et al. 2010). In a meta-analysis covering 25 articles published from January 2000 to December 2012, the median survival time was 5 months. Local excision alone or combination with adjuvant chemotherapy was the optical choice, with a median survival time of 17 months (Zheng et al. 2014). Palliative chemotherapy in metastasizing hepatic angiosarcoma is potentially useful to improve survival (Kim et al. 2009). Most cases of hepatic angiosarcoma are discovered at an advanced stage, and less than 20 % of patients have received surgery with liver resection. The results of liver transplantation for angiosarcoma are disastrous with a universal tumor recurrence within 6 months (Maluf et al. 2005; Castaldo and Wright Pinson 2007; Bonaccorsi-Riani and Lerut 2010), and in fact, hepatic angiosarcoma is now an absolute contraindication to liver transplantation (Orlando et al. 2013). So far, there is no standardized treatment for hepatic angiosarcoma, but surgery still seems to be the treatment of choice for selected patients. When the lesion is still confined to one lobe of the liver without extrahepatic disease, hepatic resection has in fact proven to be beneficial (preoperative interventional embolization of

the tumor-supplying vessels reduces the risk of pre- and intraoperative hemorrhage (Matthaei et al. 2007). Up to 40 % of patients with hepatic angiosarcoma have liver fibrosis or liver cirrhosis, but the causal relationship between this tumor and fibrosing liver disease is still unknown.

Etiology and Pathogenesis of Hepatic Angiosarcoma

Main causative agents of hepatic angiosarcoma comprise vinyl chloride monomer, thortrast, arsenical salts, aromatic steroids, and a range of other chemical agents. A retrospective epidemiologic study of deaths from hepatic angiosarcoma in the USA revealed that, during 1964–1974, there were 168 such cases, of which 22 % were associated with vinyl chloride, thorotrast, or arsenical salts (Falk et al. 1979a).

Vinyl Chloride

Vinyl chloride (VC) monomer is used for the manufacture of polyvinyl chloride, an important plastic resin for the production of tubes and pipes and for construction and siding. In 1974, VC had been shown to be a human carcinogen, first demonstrated by Professor Cesare Maltoni (Mehlman 2002), inducing angiosarcoma of the liver (Block 1974; Creech and Johnson 1974; Lee and Harry 1974; Maltoni 1974; Wallnöfer and Zinnagl 1977; reviews: Lewis 1999; Bosetti et al. 2003; Bolt 2005; Sherman 2009). The carcinogenic role of VC was also demonstrated on the basis of experimental evidence in rodents. In the light of this carcinogenicity, the exposure levels were drastically reduced arriving at a level of $\leq$1 ppm (review: Dogliotti 2006). Since 1974, numerous reports from several countries have confirmed the role of VC as a hepatic carcinogen (Delorme and Makk 1975; Heath et al. 1975; Lilis et al. 1975; Thomas and Popper 1975; Thomas et al. 1975; Baxter 1976; Makk et al. 1976; Waxweiler et al. 1976; Brady et al. 1977; Delorme 1978; Delorme and Theriault 1978; Popper et al. 1978; Roche et al. 1978; Spirtas and Kamenski 1978; Dannaher et al. 1981; Vianna et al. 1981; Louagie et al. 1984; Falk 1987; Brugnami et al. 1988; Paliard et al. 1991; Riordan et al. 1991; Lee et al. 1996; Lelbach 1996; Elliot and Kleinschmidt 1997; Hozo et al. 2000; Lewis and Rempala 2003; Di Lorenzo et al. 2012). VC also palys a role in causing non-tumorous liver lesions, such as steatohepatitis (toxicant-associated steatohepatitis, TASH; Cave et al. 2010). Among 7,000 men who were at some time between 1940 and 1974 exposed to VC monomer in the manufacture of polyvinyl chloride, four cases of liver cancer were found, of these two were hepatic angiosarcomas (Fox and Collier 1977). VC-associated cases of angiosarcoma have been tabulated in the hepatic angiosarcoma register of the Association of Plastic Manufacturers in Europe (Forman et al. 1985). Among 61 patients with angiosarcoma of the liver registered in England and Wales (1979–1986) and in Scotland (1975–1987), ten cases were found among VC workers (Elliott and Kleinschmidt 1997). During the follow-up of 12,700 male workers in the VC industry in four European countries, a total of 53 deaths from primary liver cancer and 18 incident cases of liver cancer were identified, including 37 angiosarcomas, 10 hepatocellular carcinomas, and 24 liver cancers of other and unknown histology (Ward et al. 2001). Two pooled analyses of worker cohorts from 56 VC plants in North America and Europe included over 22,000 workers; overall, a total of 1,778 cancer deaths were observed, with 71 confirmed angiosarcomas and a standardized mortality ratio of 0.97 (Bosetti et al. 2003). Hepatic angiosarcoma has not only been noted in workers exposed to VC monomer gas in the course of polyvinyl chloride manufacture but also in other situations, such as polyvinyl chloride autoclave cleaning (Riordan et al. 1991), or among hairdressers and barbers using hair spray containing VC propellant (Infante et al. 2009). Vinyl chloride-induced hepatic angiosarcoma may later be followed by peliosis hepatis (Paliard et al. 1991). Vinyl chloride-induced hepatic angiosarcoma was found in association with hepatocellular carcinoma (Delorme 1978).

The toxicity of VC and pathogenic mechanisms have been studied in animal experimentation (Holmberg et al. 1976; Winell et al. 1976;

Suzuki 1983; Maltoni and Cotti 1988; review: Williamson 1976). In mice and rats treated with vinyl chloride, hepatic angiosarcoma developed (Radike et al. 1977; Gehring et al. 1979; Hong et al. 1980; Spit et al. 1981; Suzuki 1981; Saito et al. 1997). In one experimental study, one mouse has shown hepatic angiosarcoma 56 weeks after exposure to 600 ppm vinyl chloride for 4 weeks. Ultrastructurally, two neoplastic cell types, a mesenchymal and a well-differentiated endothelial cell type, were identified, and a pericyte-like cell was also present (Suzuki 1981). The molecular mechanisms of carcinogenesis by VC have been reviewed (Dogliotti 2006). VC is rapidly metabolized to generate reactive metabolites reacting with proteins, DNA, and RNA. In particular, cholorethylene oxide and its derivatives, chloroacetaldehyde and chloroethanol, react with nucleic acids, the reaction being most rapid with chloroethyleneoxide (Malaveille et al. 1975). Chloroethylene oxide, which is the most relevant toxic product of VC, is produced by the action of cytochrome P450 isoenzyme CYP2E1 (El Ghissassi et al. 1998) and is degraded by epoxide hydrolase and glutathione-S-transferase. A major type of modified nucleic acid base is 7-(2-oxoethyl)-guanine, which constitutes 98 % of total adducts but which is not mutagenic. In contrast, the less copiously produced etheno-adducts are mutagenic/miscoding agents, particularly 1,N6-ethenoguanine, 3,N4-ethenocytosine, N2,3-ethenoguanine, and 1,N2,ethenoguanine (review: Barbin 2000). Mutagenic etheno-adducts are recognized and eliminated from DNA by the action of DNA glycosylases which are the key enzymes in this repair pathway (review: Gros et al. 2003). These enzymes remove the etheno-adducts from DNA by hydrolizing the N-glycosidic bond between the altered base and deoxyribose, thus leaving an abasic site in the DNA. A second repair mechanism involves the DNA helicase encoded by the XPD gene, which shows polymorphisms that are thought to play a role in differential susceptibility for VC-induced DNA damage (Zhu et al. 2005). Etheno-adducts alter genes involved in growth regulation and also the genes for DNA polymerases (Guengerich et al. 1999). Non-repaired mutagenic etheno-adducts have been shown to cause Ras gene mutations (Marion et al. 1991; Marion and Boivin-Angele 1999; Boivin-Angele et al. 2000). In particular, G>A transitions were observed at codon 13 in part of the tumor cases (Marion et al. 1991; Weihrauch et al. 2002). The adducts also cause p53 gene mutations, all A>T transitions (Hollstein et al. 1994). VC-induced hepatic angiosarcomas have shown p53 mutations at A/T base pairs (Hollstein et al. 1994; Smith et al. 1998).

Arsenic

Chronic arsenic exposure (chronic arsenosis) leads to several disorders of the liver, including cirrhosis, hepatoportal sclerosis, hepatocellular carcinoma, and angiosarcoma (Cowlishaw et al. 1979; Calmus and Poupon 1982). Inorganic arsenic is a well-known human carcinogen inducing skin cancer and tumors of several inner organs, such as the lung, urinary bladder, and liver (Jackson and Grainge 1975). The liver is a distinct target of arsenic carcinogenesis (review: Liu and Waalkes 2008). Hepatic angiosarcoma has numerous times been associated with arsenic salt exposure, either through treatments or by contact and intake in the environment. Also brief arsenic therapy (e.g., with Fowler's solution, potassium arsenite) has been observed to be followed by the development of this tumor (Roth 1957; Regelson et al. 1968; Lander et al. 1975; Popper et al. 1978; Falk et al. 1981b; Roat et al. 1982; Kasper et al. 1984; Kadas et al. 1985; Salgado et al. 1995; Dueñas et al. 1998; Tsai et al. 1998; Ho et al. 2004). Hepatic angiosarcoma and other arsenic-induced pathologies have been registered in the International Tissue and Tumor Repository for Chronic Arsenosis (ITTRCA; Centeno et al. 2002). The delay between arsenic ingestion and diagnosis of hepatic angiosarcoma may exceed 30 years (Roat et al. 1982).

Arsenic is in the nitrogen group of the periodic system and is a transitional or metalloid element. Pure metallic arsenic is rarely found in nature. Elemental arsenic has zero oxidation state, but

arsenic can occur in trivalent or pentavalent states. In more detail, arsenic occurs in five different valence states, i.e., +V (arsenate), +III (arsenite), +I (arsonium metal), 0 (arsenic), and –III (arsine). Arsenic readily reacts with diverse metals, oxygen, sulfur, carbon, and hydrogen. The three most important inorganic forms are red arsenic (realgar, As4S4), yellow arsenic (orpiment or opperment, As2S3), and white arsenic (arsenic trioxide, As2O3). The most toxic arsenicals (the arsenites) are those which contain trivalent arsenic, in particular the very poisonous arsenic trioxide, derived from arsenious acid (H2As2O3). But the most toxic arsenical is the volatile hydride, arsine (AsH3). Organic arsenicals (mostly several forms of methylated arsenic compounds) contain trivalent or pentavalent arsenic linked to a carbon atom by a covalent bond.

Arsenic is widely present in soil, water, air, and components of the biomass. It is estimated that the natural global emission of arsenic and of arsenic-containing components amounts to 8,000 tons per year, and emissions from man-made sources 23,600 tons per year, one major source being arsenic-containing pesticides such as dimethylarsinic acid (DMA) (review: Huang et al. 2004). Arsenic (from Greek, arsenikon, meaning "potent") in various galenic forms has been employed as a drug for more than 2,000 years (review: Jolliffe 1993). In the eighteenth century, Fowler's solution (1 % potassium arsenite) was used for the relief of various ailments, including Sydenham's chorea (Fowler 1994), and remained popular for over 150 years. This arsenic solution was introduced by Thomas Fowler in 1786 as a flavored solution to mainly treat headaches, remittent fevers, anemia, and rheumatism. As reviewed in the interesting article by Jolliffe (1993), Fowler with the apothecary Hughes had identified arsenic as the major constitutent of the "ague drops" patented by Thomas Wilson, a London chemist, in 1781. By the early 1900s, Ehrlich's experiments showed that arsphenamine was active in syphilis, and arsenicals remained the most important antiluietic treatment for almost 40 years. Until recently, arsenicals have been ingested for the treatment of sleeping sickness. Today, arsenic trioxide is used for the treatment of acute promyelocytic leukemia (PML). Besides exposure to arsenic-containing medical drugs, nonoccupational exposure to arsenic can take place through ingestion of contaminated food and water. One well-known example of waterborne intoxication is contamination of well water with arsenic leached from underground sediments in large areas of India and Bangladesh, with hundreds of thousands of people having developed precancerous skin lesion due to arsenic ingestion (NRC 1999). Inhalational exposure to arsenic occurs in industrial settings such as lead, copper and zinc smelting, from fossil fuel combustion in power plants, in the semiconductor industry, and in pesticide production.

What Is the Biochemistry of Arsenic in Normal Prokaryotic and Eukaryotic Cells?

The oxidation status of arsenic markedly affects the toxicity of arsenic (review: Huang et al. 2004). Arsenite is taken up by mammalian cells by passive diffusion, whereas arsenate competes with phosphate for cellular uptake. Arsenite strongly interacts with thiol group-containing molecules (thiols and dithiols) and thus affects enzyme activities by binding to cysteinyl residues. Conversely, arsenate in its structure resembling that of phosphate interferes with oxidative phosphorylation via formation of unstable arsenate esters, causing ATP deficiency. Arsenate is rapidly reduced to arsenite in blood via reaction with glutathione. In the cytosol of hepatocytes, arsenite undergoes methylation by the action of arsenic methyltransferase (encoded by the As3mt gene) to monomethylarsonic acid (MMA) and then to dimethylarsinic acid (DMA). The methyl donor is S-adenosyl-L-methionine. MDA and DMA are more cytotoxic and more genotoxic than the parent arsenic oxides. Arsenic is rapidly excreted in urine as a mixture of arsenate, arsenite, MMA, and DMA, DMA being the major component accounting for 60–80 % of total arsenic. Arsenate is excreted more rapidly than arsenite, this being a main reason for the greater toxicity and carcinogenicity of arsenite. In prokaryotes and

eukaryotes, resistance to arsenical compounds is mediated by several members of the Acr3 family of cell membrane As and Sb antiporters/permeases that facilitate efflux of trivalent arsenic and antimony, dependent on the electrochemical potential gradient of protons generated by plasma membrane H(+)-translocating P-type ATPase/ArsA ATPase (Maciaszczyk et al. 2011). In prokaryotes, the trivalent metalloids, As(III) and Sb (III), are transferred to the ArsA ATPase, the catalytic subunit of the arsenic efflux pump, by the ArsD metallochaperone (Yang et al. 2011). The ars operon encoded by *E. coli* plasmid R773 has arsD and arsA genes, where ArsA is the arsenic ATPase unit of the pump and ArdD the gene for the As(III) metallochaperone (Abdul Ajees et al. 2011).

What Are the Carcinogenic Pathways of Arsenic ?

Arsenic is an atypical carcinogen, because it is neither an initiator nor a promoter (Barrett et al. 1989; review: Huang et al. 2004). Arsenic exerts direct effects on chromosomes, the genome, and the replication machinery. Unlike other carcinogens, arsenic fails to cause point mutations, but instead causes large multilocus deletion mutations leading to cell death. Arsenic exposure induces chromosome aberrations, aneuploidy and formation of micronuclei (similar to ionizing radiation), DNA-protein cross-linking, and sister chromatid exchange. Arsenite inhibits DNA ligase and hence DNA repair. Arsenic, even at low doses, affects the expression of several cellular pathways in part shared by toxic effects of cadium (Benton et al. 2011; review; Huang et al. 2004). Oxidative stress, altered DNA repair, and altered DNA methylation patterns seem to play a major role in arsenic-mediated carcinogenesis (Kitchin 2001; Huang et al. 2004; Kitchin and Conolly 2010). Arsenic induces the production of reactive oxygen species (ROS) during its metabolism in cells, countreracted by cellular superoxide dismutase. Arsenic also increases the production of hydrogen peroxide in the extracellular space. Cells deficient in catalase are hypersentitive to arsenic cytotoxicity, supporting the pathogenic role of ROS. ROS themselves are known to play a role in the initiation and promotion processes of carcinogenesis and to be involved in signaling of the cell transformation response . Induction of p-ERK and cell proliferation by arsenite is mediated by oxidative stress, since antioxidants can inhibit arsenite-induced cell transformation (Li et al. 2011). Arsenic alters gene expression via activation of signal transduction pathways. Arsenite is a potent stimulator of c-fos and c-jun expression and AP-1 transactivational activity. Induction of AP-1 is mediated by activation of protein kinase C and MAPKs family members. Both arsenate and arsenite induce the activation of the transcription factor, NFkappaB, in an ERK-dependent pathway (review: Huang et al. 2004). Arsenic is found to target and degrade a class of proteins with high levels of cysteine residues and vicinal thiol groups, such as zinc finger proteins, promyelocytic leukemia protein (PML), and PML-retinoic acid receptor alpha (PML-RARalpha) fusion protein. Arsenite interacts selectively with zinc finger proteins containing C3H1 or C4 motifs (Zhou et al. 2011), and arsenic directly binds the C3HC4 zinc finger motif in the RBCC domain of PML and PML-RAR (retinoic acid receptor) alpha, induces their homodimerization and multimerization, and enhances their interaction with the SUMO E2 conjugase Ubc9, thus facilitating proteasomal degradation (Zhang et al. 2010; Chen et al. 2011). Wild-type p53 protein accumulates in cells treated with arsenic, while mutant p53 protein is a target of arsenic trioxide in that its degradation is promoted by arsenicals (Yan et al. 2011). Arsenic affects apoptotic pathways. Apoptosis induced by arsenic oxide in PML cells depends on the presence of the expression of PML-RARalpha, not the PLZF-RARalpha fusion protein. Redistribution of PML nuclear bodies upon As2O3 treatment is accompanied by recruitment of PIC-1/SUMO-1 into PML nuclear bodies, and this modified PML-RARalpha is involved in the induction of apoptosis (Sternsdorf et al. 1999). Arsenic oxide (As(2)O(3) targets the stem cell marker, CD133/

prominin-1, to gallbladder carcinoma cells and via this mechanism induces apoptosis (Ai et al. 2011).

Thorotrast (Thorium Dioxide)

Thorotrast and Umbrathor are thorium-containing roentgenographic contrast media that had been introduced into market in 1929. Thorotrast is a 25 % colloidal solution of thorium 232 dioxide. Thorium nuclide 232 is slighty unstable and decays through the emission of alpha particles which exert high-LET ionizing radation. Thorotrast was widely used until 1955. It was intensively employed owing to its excellent contrast characteristics and almost inexistent acute toxicity and had wide indications for cerebral angiography, cholangiography, and urographic techniques. It is estimated that up to ten million persons received thorotrast for a wide variety of examinations. About 10 years after its introduction, reports of thorotrast-related cancers started to appear, but thorotrast was still used until the mid-1950s. The most common liver tumors induced by this high-LET radiation source are cholangiocarcinomas, hepatocellular carcinoma, angiosarcoma, and squamous cell carcinoma (review: Lipshutz et al. 2002) . Thorium 232 is a radioactive isotope that naturally emits alpha and beta particles and gamma rays. Around 90 % of the emitted ionizing radiation is in the form of alpha particles. Thorium 232 has a half-life of 14 billion years. After injection, the particulate matter contained in thorotrast is taken up by cells of phagocytic system (mainly macrophages) and other cells and is stored in the body for life, particularly in the spleen, the liver (the Kupffer cell system) and the bone marrow. For more details, see the chapter on liver involvement in pneumokonioses and other dust-induced disorders.

The first report of hepatic angiosarcoma related to thorotrast dates from 1947 (MacMahon et al. 1947). Since then, numerous reports have documented the causal relationship between thorotrast exposure and the emergence of hepatic angiosarcoma (Da Horta 1956; Batzenschlager et al. 1961; Vellenga 1962; Rakov et al. 1963; Hohenstatt 1965; Leitner 1965; Underwood and Huck 1978; Falk et al. 1979a; Telles et al. 1979; Winberg and Ranchod 1979; Baxter et al. 1980; Hiraoka et al. 1981; Manning et al. 1983; Silverman et al. 1983; Mohr et al. 1984; Umezu 1984; Bruguera et al. 1985; Kojiro et al. 1985; Abe and Wakasa 1987; Azodo et al. 1993; Ishikawa et al. 2001; Arteche et al. 2007; Van Kampen et al. 2007). Thorotrast-induced hepatic angiosarcoma is well known to occur after delays of many years after exposure (Underwood and Huck 1978; Abe and Wakasa 1987). In one study of 29 cases examined by autopsy, the tumors were diagnosed after a latent period after thorium dioxide injection ranging from 27 to 49 years, with a mean of 36.2 years (Kojiro et al. 1985). Hepatic angiosarcoma induced by thorotrast was produced experimentally in rats, which however also developed hepatic Kupffer cell sarcomas (Wesch et al. 1984). In the German Thorotrast study, covering 2,326 patients that had been compared with 1890 nonexposed controls, the latent period of all liver cancers ranged from 16 years to more than 50 years; in comparison, the first cases of acute myeloid leukemia were seen 5 years after thorotrast injection. Two thirds of the 454 hepatic cancers observed in the thorotrast group were classified as carcinomas (predominantly cholangiocarcinomas), and one third as angiosarcomas (Van Kaick et al. 1999).

Other Etiopathogenetic Relations

Diverse aromatic sex steroids are considered to play an etiologic role in hepatic angiosarcoma. They include androgenic-anabolic steroids (Daneshmend and Bradfield 1979; Falk et al. 1979b; Nordsten 1985), oral contraceptives (Monroe et al. 1993; Shi et al. 1981), and diethylstilbestrol (Hoch-Ligeti 1978). Among 131 deaths from hepatic angiosarcoma not induced by VC, thorotrast, or arsenic, observed between 1964 and 1974 in the USA, 4 (3.1 %) were associated with the use of androgenic-anabolic steroids (Falk et al. 1979). Other chemical substances that were

associated with the development of hepatic angiosarcoma include cyclophosphamide (Rosenthal et al. 2000), urethane (Cadranel et al. 1993), and pesticides (El Zayadi et al. 1986). There is a rare correlation between hemochromatosis and hepatic angiosarcoma (Sussman et al. 1974; Timaran et al. 2000; Mani and Van Thiel 2001; Özden et al. 2003; Stambo and Guiney 2007).

Pathogenic Pathways

Whereas etiologic factors playing a significant role in the development of hepatic angiosarcoma are well recognized (see above), pathogenic mechanisms are only starting to be better understood. In what follows, a selection of pathways probably important in pathogenesis is briefly summarized.

Angiosarcomas exhibit recurrent mutations of PTPRB and PLCG1, factors intimately linked to angiogenesis (Behjati et al. 2014). PTPRB is protein tyrosine phosphatase, receptor type B that regulates various cellular processes, including regulation of growth. PLCG1 is a signal transducer of tyrosine kinases and phospholipase centrally involved in inositol phosphate signaling. Sporadic and thorotrast-induced hepatic angiosarcomas show frequent and multiple point mutations in the K-ras-2 gene (Przygodski et al. 1997). Mutations of K-ras-2 have also been detected in hepatic angiosarcoma caused by vinyl chloride exposure (Weihrauch et al. 2002). P53 gene mutations are well-known and frequent events in angiosarcomas caused by vinyl chloride monomer and alpha-particle radiation (Hollstein et al. 1994; Andersson et al. 1995; Wada et al. 1999). In the absence of such etiologic factors, the status of p53 gene mutations is less clear, as the published results vary considerably regarding the frequency of p53 mutations, either found to be uncommon in extrahepatic angiosarcomas (Inohara 1994; Naka et al. 1997) or rather common (Zietz et al. 1998). Whereas TP53 mutations are, e.g., frequent in leiomyosarcoma and undifferentiated pleomorphic sarcoma, these aberrations are rarely involved in the pathogenesis of angiosarcoma (Italiano et al. 2012). Few cases of p53 mutations have been reported for hepatic angiosarcomas not related to vinyl chloride or thorotrast (Soini et al. 1995). P53 mutations in primary hepatic angiosarcomas have also been detected in tumors not associated with vinyl chloride exposure (Soini et al. 1995).

References

Abdul Ajees A, Yang J, Rosen BP (2011) The Ars(III) metallochaperone. Biometals 24:391–399

Abe M, Wakasa H (1987) Thorotrast-induced hepatic angiosarcoma with 39 years latency. A pathologic and immunohistochemical study. Acta Pathol Jpn 37:1653–1660

Ahmad Z, Nisa A, Idrees R, Minhas K, Pervez S, Mumtaz K (2008) Hepatic angiosarcoma with metastasis to small intestine. J Coll Physicians Surg Pak 18:50–52

Ai Z, Pan H, Suo T, Lv C, Tong S, Liu H (2011) Arsenic oxide targets stem cell marker CD133/prominin-1 in gallbladder carcinoma. Cancer Lett 310:181–187

Akdogan M, Gurakar A, Sharago S, El-Sahwi K, Carlson J, Sebastian A, Ahmed U et al (2002) Unusual presentation of hepatic vascular tumors as fulminant hepatic failure. Turk J Gastroenterol 13:216–220

Alliot C, Tribout B, Barrios M, Gontier MF (2001) Angiosarcoma variant of Kasabach-Merritt syndrome. Eur J Gastroenterol Hepatol 13:731–734

Alrenga DP (1975) Primary angiosarcoma of the liver. Int Surg 60:198–203

Andersson M, Jönsson M, Nielsen LL, Vyberg M, Visfeldt J, Storm HH, Wallin H (1995) Mutations in the tumor suppressor gene p53 in human liver cancer induced by alpha-particles. Cancer Epidemiol Biomarkers Prev 4:765–770

Ansari A, Weigent CE (1971) Hemangioendothelial sarcoma of the liver: a clinicopathological study of an 81-year- old male veteran. Am J Gastroenterol 56:420–427

Arima-Iwasa S, Chijiiwa K, Makino I, Tanabe R, Ohuchida J, Kondo K (2007) A case of hepatic angiosarcoma surviving for more than 16 months after hepatic resection. Hepatogastroenterology 54:533–535

Arnold J (1890) Zwei Fälle von primärem Angiosarcom der Leber. Beitr Pathol Anat Allg Pathol 8:123–139

Arteche E, Ostiz S, de Miguel C (2007) Case 2. Diffuse hepatic angiosarcoma secondary to thorotrast deposit (Spanish). Radiologia 48:29

Azodo MV, Gutierrez OH, Greer T (1993) Thorotrast-induced ruptured hepatic angiosarcoma. Abdom Imaging 18:78–81

Barbin A (2000) Etheno-adduct-forming chemicals from mutagenicity testing to tumor mutation spectra. Mutat Res 462:55–69

Barjon P, Pages A, Fourcade JC (1965) Hepatic hemangioendotheliosarcoma. Coexistence of a renal polycystosis (in French). Presse Med 73:2233–2235

Barrett JC, Lamb PW, Wang TC, Lee TC (1989) Mechanisms of arsenic-induced cell transformation. Biol Trace Elem Res 21:421–429

Batzenschlager A, Reville P, Weill-Bousson M (1961) Cavernous angioplastic endothelial sarcoma of the liver and hepatic throrotrastosis (in French). Bull Assoc Fr Etud Cancer 48:347–364

Baxter PJ (1976) Epidemiological studies of PVC manufacturers and fabricators, and primary angiosarcoma of the liver. Proc Roy Soc Med 69:297–299

Baxter PJ (1981) The British hepatic angiosarcoma register. Environ Health Perspect 41:115–116

Baxter PJ, Langlands AO, Anthony PP, Macsween RN, Scheuer PJ (1980) Angiosarcoma of the liver: a marker tumour for the late effects of Thorotrast in Great Britain. Br J Cancer 41:446–453

Behjati S, Tarpey PS, Sheldon H, Martincorena I, Van Loo P, Gundem G, Wedge DC, Ramakrishna M et al (2014) Recurrent PTPRB and PLCG1 mutations in angiosarcoma. Nat Genet 46:376–379

Benton MA, Rager JE, Smeester L, Fry RC (2011) Comparative genomic analyses identify common molecular pathways modulated upon exposure to low doses of arsenic and cadmium. BMC Genomics 12:173

Bhati CS, Bhatt AN, Starkey G, Hübscher SG, Bramhall SR (2008) Acute liver failure due to primary angiosarcoma: a case report and review of literature. World J Surg Oncol 6:104

Blackmon J, Rajpara A, Patel V, Gilroy R, Aires D, Fraga G (2014) Primary scalp angiosarcoma with metastasis to the liver in an orthotopic liver transplant patient. Exp Clin Transplant 12:269–272

Block JB (1974) Angiosarcoma of the liver following vinyl chloride exposure. JAMA 229:53–54

Blumberg A (1926) Hämangioendotheliom der Leber. Virchows Arch Pathol Anat Physiol Klin Med 261:82–86

Boivin-Angele S, Lefrançois L, Froment O, Spiethoff A, Bogdanffy MS, Wegener K, Wesch H et al (2000) Ras gene mutations in vinyl chloride-induced liver tumours are carcinogen-specific but vary with cell type and species. Int J Cancer 85:223–227

Bolt HM (2005) Vinyl chloride – a classical industrial toxicant of new interest. Crit Rev Toxicol 35:307–323

Bonaccorsi-Riani E, Lerut J (2010) Liver transplantation and vascular tumours. Transpl Int 23:686–691

Bosetti C, La Vecchia C, Lipworth L, McLaughlin JK (2003) Occupational exposure to vinyl chloride and cancer risk: a review of the epidemiological literature. Eur J Cancer Prev 12:427–430

Brady J, Liberatore F, Harper P, Greenwald P, Burnett W, Davies JN, Bishop M, Polan A et al (1977) Angiosarcoma of the liver: an epidemiologic survey. J Natl Cancer Inst 59:1383–1385

Bramwell J, Leith M (1896) Enormous primary sarcoma of the liver. Edinb Med J 42:52

Brown CJ, Falck VG, MacLean A (2004) Angiosarcoma of the colon and rectum: report of a case and review of the literature. Dis Colon Rectum 47:2202–2207

Brugnami G, Abbritti G, Morelli A, Maltoni C, Solinas A, Pelliccioli G (1988) Liver angiosarcoma in a vinyl chloride polymerization plant worker. Report of the seventh Italian case. Med Lav 79:34–41

Bruguera M, Mas A, Rodes J (1985) Hepatic cholangiocarcinoma and angiosarcoma after the administration of thorotrast (in Spanish). Med Clin (Barc) 85:516

Budd GT (2002) Management of angiosarcoma. Curr Oncol Rep 4:515–519

Buetow PC, Maj MC, Buck JL, Ros PR, Goodman ZD (1994) Malignant vascular tumors of the liver: radiologic-pathologic correlation. Radiographics 14:153–166

Burke M, Opeskin K (2000) Spontaneous rupture of the liver associated with a primary angiosarcoma: case report. Am J Forensic Med Pathol 21:134–137

Cadranel JF, Legendre C, Desaint B, delamarre N, Florent C, Levy VG (1993) Liver disease from surreptitious administration of urethane. J Clin Gastroenterol 17:52–56

Calmus Y, Poupon R (1982) The liver and arsenic (in French). Gastroenterol Clin Biol 6:933–941

Casado Martin M, Aguirre Losada A, Rodriguez Laiz JM, Clemente Ricote G, Banares Canizares R et al (1994) Hepatic angiosarcoma with splenic metastasis (in Spanish). Rev Esp Enferm Dig 85:51–54

Castaldo ET, Wright Pinson C (2007) Liver transplantation for non-hepatocellular carcinoma malignancy. HPB (Oxford) 9:98–103

Cave M, Falkner KC, Ray M, Joshi-Barve S, Brock G, Khan R, Bon Homme M, McClain CJ (2010) Toxicant-associated steatohepatitis in vinyl chloride workers. Hepatology 51:474–481

Centeno JA, Mullick FG, Martinez L, Page NP, Gibb H, Longfellow D, Thompson C, Ladish ER (2002) Pathology related to chronic arsenic exposure. Environ Health Perspect 110(Suppl 5):883–886

Chami TN, Ratner LE, Henneberry J, Smith DP, Hill G, Katz PO (1994) Angiosarcoma of the small intestine: a case report and literature review. Am J Gastroenterol 89:797–800

Chen SJ, Zhou GB, Zhang XW, Mao JH, de Thé H, Chen Z (2011) From an old remedy to a magic bullet: molecular mechanisms underlying the therapeutic effects of arsenic in fighting leukemia. Blood 117:6425–6437

Chi TY, Yang ZY, Xue HD, Lü K, Feng RE, Xu HF, Yang XB, Sang XT, Lu X et al (2011) Diagnosis and treatment of primary hepatic angiosarcoma: a report of 7 cases with a literature review (in Chinese). Zhonghua Yi Xue Za Zhi 91:1694–1697

Chien CY, Hwang CC, Yeh CN, Chen HY, Wu JT, Cheung CS, Lin CL, Yen CL et al (2012) Liver angiosarcoma, a rare liver malignancy, presented with intraabdominal

bleeding due to rupture – a case report. World J Surg Oncol 10:23
Chiu O, Frank JD, Dow CA (2005) Hepatic angiosarcoma: detection with computed tomography. Australas Radiol 49:163–165
Cioffi-Pretti JL, Kalof AN, Ebert G, McCahill LE (2009) Hepatic angiosarcoma five years following spontaneous intraperitoneal bleed of a hepatic mass. Rare Tumors 1:e33
Conde-Taboada A, Florez A, De la Torre C, Feal C, Garica-Doval I, Cruces M (2005) Pseudoangiosarcomatous squamous cell carcinoma of skin arising adjacent to decubitus ulcers. Am J Dermatopathol 27:142–144
Cowlishaw JL, Ollard EJ, Cowen AE, Powell LW (1979) Liver disease associated with chronic arsenic ingestion. Aust NZ J Med 9:310–313
Creech JL, Johnson MN (1974) Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med 16:150–151
D'Urso L (1896) Endothelioma primario del fegato. Atti R Acc Med Chir Napilo 4:120
Da Horta JS (1956) Late lesions in man caused by colloidal thorium dioxide (thorotrast); a new case of sarcoma of the liver twenty-two years after the injection. AMA Arch Pathol 62:403–418
Daneshmend TK, Bradfield JW (1979) Hepatic angiosarcoma associated with androgenic-anabolic steroids. Lancet 2:1249
Dannaher CL, Tamburro CH, Yam LT (1981) Occupational carcinogenesis: the Louisville experience with chloride-associated hepatic angiosarcoma. Am J Med 70:279–287
De Haan J (1903) Primäres Angiosarcoma alveolare multiplex der Leber. Zieglers beitr 34:210
Delorme F (1978) Association d'un angiosarcome du foie et d'un hépatome, chez un ouvrier du chlorure de vinyle. Ann Anat Pathol (Paris) 23:105–114
Delorme F, Makk L (1975) Angiosarcome du foie chez des ouvriers ayant été en contact prolongé avec le chlorure de vinyle. Description morphologique des lésions. Un Med Canada 104:1836–1844
Delorme F, Theriault G (1978) Ten cases of angiosarcoma of the liver in Shawinigan. Quebec J Occup Med 20:338–340
Di Lorenzo L, Corfiati M, Catacchio T (2012) Liver angiosarcoma from past exposure to vinyl chloride: a case report (in Italian). Med Lav 103:459–465
Dogliotti E (2006) Molecular mechanisms of carcinogenesis by vinyl chloride. Ann Ist Super Sanita 42:163–169
Drinkovic I, Brkljacic B (1996) Two cases of lethal complications following ultrasound-guided percutaneous fine-needle biopsy of the liver. Cardiovasc Intervent Radiol 19:360
Duan XF, Li Q (2012) Primary hepatic angiosarcoma: a retrospective analysis of 6 cases. J Dig Dis 13:381–385
Duan YF, Jiang Y, Wu CX, Zhu F (2013) Spontaneous rupture of primary splenic angiosarcoma: a case report and literature review. World J Surg Oncol 11:53
Dueñas C, Perez-Alvarez JC, Busteros JI, Saez-Royuela F, Martin-Lorente JL, Yuguero L, Lopez-Morante A (1998) Idiopathic portal hypertension and angiosarcoma associated with arsenical salts therapy. J Clin Gastroenterol 26:303–305
El Ghissassi F, Barbin A, Bartsch H (1998) Metabolic activation of vinyl chloride by rat liver microsomes: low-dose kinetics and involvement of cytochrome P450 2E1. Biochem Pharmacol 55:1445–1452
El Zayadi A, Khalil A, El Sammy N, Hamza MR, Selim O (1986) Hepatic angiosarcoma among Egyptian farmers exposed to pesticides. Hepatogastroenterology 33:148–150
Elliott P, Kleinschmidt I (1997) Angiosarcoma of the liver in Great Britain in proximity to vinyl chloride sites. Occup Environ Med 54:14–18
Fajadet P, Poey C, Giron J, Maquin P, Railhac JJ, Voigt JJ, Bardet D (1990) Hepatic angiosarcoma. CT and MRI aspects. A case report and review of the literature (in French). Ann Radiol (Paris) 33:260–263
Falk H (1987) Vinyl chloride-induced hepatic angiosarcoma. Princess Takamatsu Symp 18:39–46
Falk H, Telles NC, Ishak KG, Thomas LB, Popper H (1979a) Epidemiology of thorotrast-induced hepatic angiosarcoma in the United States. Environ Res 18:65–73
Falk H, Thomas LB, Popper H, Ishak KG (1979b) Hepatic angiosarcoma associated with androgenic-anabolic steroids. Lancet 2:1120–1123
Falk H, Herbert J, Crowley S, Ishak KG, Thomas LB, Popper H, Caldwell GG (1981a) Epidemiology of hepatic angiosarcoma in the United States: 1964–1974. Environ Health Perspect 41:107–113
Falk H, Caldwell GG, Ishak KG, Thomas LB, Popper H (1981b) Arsenic-related hepatic angiosarcoma. Am J Ind Med 2:43–50
Fayette J, Martin E, Piperno-Neumann S, Le Cesne A, Robert C, Bonvalot S, Ranchère D et al (2007) Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol 18:2030–2036
Ferreira BP, Rodler ET, Loggers ET, Pollack SM, Jones RL (2012) Systemic therapy in primary angiosarcoma of the spleen. Rare Tumors 4:e55
Fiechtner JJ, Reyes CN (1976) Angiosarcoma of the liver in a rural population. Four cases diagnosed in 29-month period. JAMA 236:1704–1706
Fontaine R, Frank P, Legal Y, Sibilly A, Kieny R (1954) Partial hepatectomy in successfully surgery of endothelial sarcoma of the liver (in French). Presse Med 62:1839–1841
Forman D, Bennett B, Stafford J, Doll R (1985) Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases. Br J Ind Med 42:750–753
Fowler PBS (1994) A history of the use of arsenicals in man (comment). J R Soc Med 87:183
Fox AJ, Collier PF (1977) Mortality experience of workers exposed to vinyl chloride monomer in the manufacture

of polyvinyl chloride in Great Britain. Br J Ind Med 34:1–10
Gehring PJ, Watanabe PG, Park CN (1979) Risk of angiosarcoma in workers exposed to vinyl chloride as predicted from studies in rats. Toxicol Appl Pharmacol 49:15–21
Geramizadeh B, Safari A, Bahador A, Nikeghballan S, Salahi H, Kazemi K, Deghani SM et al (2011) Hepatic angiosarcoma of childhood: a case report and review of literature. J Pediatr Surg 46:e9–e11
Giacomelli V (1950) Clinical, operative and histological evaluations in a case of angiosarcoma of the liver invading the stomach (in Italian). G Sci Mediche 5:221–224
Gonzalez Rodriguez FJ, Dominguez Comesaña E, Portela Serra JL, Lede Fernandez A et al (2012) Urgent surgery in a Kasabach-Merrit syndrome associated with a giant hepatic angiosarcoma. Cir Esp
Groeschl RT, Miura JT, Oshima K, Gamblin TC, Turaga KK (2014) Does histology predict outcome for malignant vascular tumors of the liver ? J Surg Oncol, 109:483–486
Gros L, Ishchenko AA, Saparbaev M (2003) Enzymology of repair of etheno-adducts. Mutat Res 531:219–229
Guengerich FP, Langouet S, Mican AN, Akasaka S, Müller M, Persmark M (1999) Formation of etheno adducts and their effects on DANN polymerases. IARC Sci Publ 150:137–145
Hachfeld M (1914) Primärer Leberkrebs nach zirrhotischer Schrumpfung. Primäres malignes Endotheliom der Leber. Thesis, Halle
Harrison JR, Faust TW, Blackstone MO (2001) Hepatic angiosarcoma: an unusual cause of congestive heart failure. South Med J 94:336–338
Heath CW, Falk H, Creech JL (1975) Characteristics of cases of angiosarcoma of the liver vinyl chloride workers in the United States. Ann NY Acad Sci 246:231–236
Heo SH, Jeong YY, Shin SS, Chung TW, Kang HK (2007) Solitary small hepatic angiosarcoma: initial and follow-up imaging findings. Korean J Radiol 8:180–183
Hiraoka T, Kambara T, Morinaga T, Nakagaw HS (1981) Hemangioendothelial sarcoma of the liver after thorotrast injection. Acta Pathol Jpn 31:853–861
Ho SY, Tsai CC, Tsai YC, Guo HR (2004) Hepatic angiosarcoma presenting as hepatic rupture in a patient with long-term ingestion of arsenic. J Formos Med Assoc 103:374–379
Hoch-Ligeti C (1978) Angiosarcoma of the liver associated with diethylstilbestrol. JAMA 240:1510–1511
Hohenstatt H (1965) Multiple hemangiosarcomas of the liver following cerebral angiography with thorotrast (in German). Hippokrates 36:227–228
Hollstein M, Marion MJ, Lehman T, Welsh J, Harris CC, Martel-Planche G, Kusters I, Montesano R (1994) p53 mutations at A:T base pairs in angiosarcomas of vinyl chloride-exposed factory workers. Carcinogenesis 15:1–3
Holmberg B, Kronevi T, Winell M (1976) The pathology of vinyl chloride exposed mice. Acta Vet Scand 17:328–342
Hong CB, Winston JM, Lee CC (1980) Hepatic angiosarcoma. Animal model: angiosarcoma of rats and mice induced by vinyl chloride. Am J Pathol 101:737–740
Horger MS (2003) Spontaneously ruptured hemangiosarcoma of the liver (in German). Rofo 175:307–308
Hoshi N, Mukai S, Oishi M, Takano M, Shinzawa J, Watanabe S, Yamazaki S, Sakuma H et al (2006) A case of hepatic angiosarcoma supplied by both hepatic artery and portal vein. Fukushima J Med Sci 52:13–19
Hozo I, Miric D, Bojic L, Giunio L, Lusic I, Culic V, Simunic M (2000) Liver angiosarcoma and hemangiopericytoma after occupational exposure to vinyl chloride monomer. Environ Health Perspect 108:793–795
Huang C, Ke Q, Costa M, Shi X (2004) Molecular mechanisms of arsenic carcinogenesis. Mol Cell Biochem 255:57–66
Huang NC, Wann SR, Chang HT, Lin SL, Wang JS, Guo HR (2011) Arsenic, vinyl chloride, viral hepatitis, and hepatic angiosarcoma: a hospital-based study and review of literature in Taiwan. BMC Gastroenterol 11:142
Ikeda K, Maehara M, Ohmura N, Kurokawa H, Koda K, Yokoyama H, Sawada S (2006) Spontaneous rupture of a necrotic hepatic angiosarcoma: findings on dual-phase computed tomography and angiography. Radiat Med 24:369–372
Infante PF, Petty SE, Groth DH, Markowitz G, Rosner D (2009) Vinyl chloride propellant in hair spray and angiosarcoma of the liver among hairdressers and barbers: case reports. Int J Occup Environ Health 15:36–42
Inohara S (1994) Immunohistochemical localization of p53 protein in malignant hemangioendothelioma. Acta Derm Venereol 74:161–162
Ishikawa Y, Wada I, Fukumoto M (2001) Alpha-particle carcinogenesis in Thorotrast patients: epidemiology, dosimetry, pathology, and molecular analysis. J Environ Pathol Toxicol Oncol 20:311–315
Israil B (1894) Operation eines primären Lebersarkoms. Dtsch Med Wschr 20:669
Itai Y, Teraoka T (1989) Angiosarcoma of the liver mimicking cavernous hemangioma on dynamic CT. J Comput Assist Tomogr 13:910–912
Italiano A, Chen CL, Thomas R, Breen M, Bonnet F, Sevenet N, Longy M, Maki RG et al (2012) Alterations of the p53 and PIK3CA/AKT/mTOR pathways in angiosarcomas: a pattern distinct from other sarcomas with complex genomics. Cancer 188:5878–5887
Ito Y, Kojiro M, Nakashima T, Mori T (1988) Pathomorphologic characteristics of 102 cases of thorotrast-related hepatocellular carcinoma, cholangiocarcinoma, and hepatic angiosarcoma. Cancer 62:1153–1162
Jackson R, Grainge JW (1975) Arsenic and cancer. Can Med Assoc J 113:396–401
Jolliffe DM (1993) A history of the use of arsenicals in man. J R Soc Med 86:287–289
Jores H (1908) Ein Fall von sarkomatösem Angiom der Milz und der Leber. Zentralbl Allg Pathol Pathol Anat 19:342

Kadas I, Balasz L, Par A, Barna K (1985) Angiosarcoma of the liver following brief arsenic therapy (in German). Zentralbl Allg Pathol 130:539–543

Kahle H (1919) Über ein Hamogonien and Leukozyten erzeugendes Angiosarkom in zirrhotischer Leber. Virchows Arch Pathol Anat Physiol Klin Med 226:44–63

Kajihara J, Wada H, Tomimaru Y, Hama N, Akita H, Kawamoto K, Kobayashi S, Eguchi H et al (2013) Successful liver resection of a rapidly growing hepatic angiosarcoma – a case report (in Japanese). Gan To Kagaku Ryoho 40:1801–1803

Kamocki Z, Steward A, Zareba KP, Kuklinski A, Kedra B (2013) Primary splenic angiosarcoma – the same diagnosis yielding two different clinical pictures. Case report. Contemp Oncol (Pozn) 17:218–221

Kanel GC, Korula J, Liew CT, Peters RL (1987) Atypical diffuse angiosarcoma of the liver. West J Med 146:482–485

Kasper ML, Schoenfield L, Strom RL, Theologides A (1984) Hepatic angiosarcoma and bronchioloalveolar carcinoma induced by Fowler's solution. JAMA 252:3407–3408

Kim TO, Kim GH, Heo J, Kang DH, Song GA, Cho M (2005) Metastasis of hepatic angiosarcoma to the stomach. J Gastroenterol 40:1003–1004

Kim KA, Kim KW, Park SH, Jang SJ, Park MS, Kim PN, Lee MG, Ha HK (2006) Unusual mesenchymal liver tumors in adults: radiologic-pathologic correlation. AJR Am J Roentgenol 187:W481–W489

Kim HR, Rha SY, Cheon SH, Roh JK, Park YN, Yoo NC (2009) Clinical features and treatment outcomes of advanced stage primary hepatic angiosarcoma. Ann Oncol 20:780–787

Kirschstein T, Aeberli D, Zimmermann A, Uhl W, Büchler MW (2000) Metastatic angiosarcoma of the liver preoperatively presenting as giant hemangioma. Digestion 62:280–283

Kishikawa T, Numaguchi Y, Tokunaga M, Matsuura K (1977) Hemangiosarcoma of the spleen and liver metastases: angiographic manifestations. Radiology 123:31–35

Kitami M, Yamada T, Sato A, Matsuhashi T, Saito H, Ishibashi T, Takahashi S, Endoh M (2003) Diffuse hepatic angiosarcoma with a portal venous supply mimicking hemangiomatosis. J Comput Assist Tomogr 27:626–629

Kitchin KT (2001) Recent advances in arsenic carcinogenesis: modes of action, animal model systems, and methylated arsenic metabolites. Toxicol Appl Pharmacol 172:249–261

Kitchin KT, Conolly R (2010) Arsenic-induced carcinogenesis – oxidative stress as a possible mode of action and future research needs for more biologically based risk assessment. Chem Res Toxicol 23:327–335

Kojiro M, Kawano Y, Kawasaki H, Nakashima T, Ikezaki H (1982) Thorotrast-induced hepatic angiosarcoma and combined hepatocellular and cholangiocarcinoma. Cancer 49:2161–2164

Kojiro M, Nakashima T, Ito Y, Ikezaki H (1985) Pathomorphological study on thorotrast-induced hepatic malignancies. Strahlentherapie Sonderb 80:119–122

Kothny K (1912) Über ein Hämangioendotheliom in zirrhotischer Leber. Frankf Zschr Pathol 10:135

Koyama T, Fletcher JG, Johnson CD, Kuo MS, Notohara K, Burgart LJ (2002) Primary hepatic angiosarcoma: findings at CT and MR imaging. Radiology 222:667–673

Kulkarni MP, Agashe SR, Singh RV, Sulhyan KR (2010) Hepatic angiosarcoma arising in an adult mesenchymal hamartoma. Indian J Pathol Microbiol 53:322–324

Lahat G, Dhuka AR, Hallevi H, Xiao L, Zou C, Smith KD, Phung TL, Pollock RE et al (2010) Angiosarcoma: clinical and molecular insights. Ann Surg 251:1098–1106

Lander JJ, Stanley RJ, Sumner HW, Boswell DC, Aach RD (1975) Angiosarcoma of the liver associated with Fowler's solution (potassium arsenite). Gastroenterology 68:1582–1586

Lee FI, Harry DS (1974) Angiosarcoma of the liver in a vinyl chloride worker. Lancet 29:1316–1318

Lee FI, Smith PM, Bennett B, Williams DMJ (1996) Occupationally related angiosarcoma of the liver in the United Kingdom 1972–1994. Gut 39:312–318

Lee SW, Song CY, Gi YH, Kang SB, Kim YS, Nam SW, Lee DS, Kim JO (2008) Hepatic angiosarcoma manifested as recurrent hemoperitoneum. World J Gastroenterol 14:2935–2938

Leitner ZA (1965) Sequelae of thorotrast. Br Med J 2:1062–1063

Lelbach W (1996) A 25-year follow-up study of heavily exposed vinyl chloride workers in Germany. Am J Ind Med 29:446–456

Leowardi C, Hormann Y, Hinz U, Wente MN, Hallscheidt P, Flechtenmacher C, Büchler MW et al (2006) Ruptured angiosarcoma of the liver treated by emergency catheter-directed embolization. World J Gastroenterol 12:804–808

L'Esperance (1915) Pub PMID 19972230

Lewis R (1999) Vinyl chloride and polyvinyl chloride. Occup Med 14:719–742

Lewis R, Rempala G (2003) A case-cohort study of angiosarcoma of the liver and brain cancer at a polymer production plant. J Occup Environ Med 45:538–545

Li Q, Wang J, Sun Y, Cui Y, Hao X (2007) Hepatic angiosarcoma arising in an adult mesenchymal hamartoma. Int Sem Surg Oncol 4:3

Li G, Lee LS, Li M, Tsao SW, Chiu JF (2011) Molecular changes during arsenic-induced cell transformation. J Cell Physiol. doi:10.1002/cp.22683

Lilis R, Anderson H, Nicholson WJ, Daum S, Fischbein AS, Selikoff IJ (1975) Prevalence of disease among vinyl chloride and polyvinyl chloride. Ann NY Acad Sci 246:22–41

Lin J, Bigge J, Ulbright TM, Montgomery E (2013) Anastomosing hemangioma of the liver and gastrointestinal tract: an unusual variant histologically mimicking angiosarcoma. Am J Surg Pathol 37:1761–1765

Lipshutz GS, Brennan TV, Warren RS (2002) Thorotrast-induced liver neoplasia: a collective review. J Am Coll Surg 195:713–718

Liu J, Waalkes MP (2008) Liver as a target of arsenic carcinogenesis. Toxicol Sci 105:24–32

Locker GY, Doroshow JH, Zwelling LA, Chabner BA (1979) The clinical features of hepatic angiosarcoma: a report of four cases and a review of the English literature. Medicine (Baltimore) 58:48–64

Louagie YA, Gianello P, Kestens F, Bonbled F, Haot JG (1984) Vinylchloride induced hepatic angiosarcoma. Br J Surg 71:322–323

Ludwig J, Hoffman HN (1975) Hemangiosarcoma of the liver. Spectrum of morphologic changes and clinical findings. Mayo Clin Proc 50:255–263

Maciaszczyk-Dziubinska E, Migocka M, Wysocki R (2011) Acr3 is a plasma membrane antiporter that catalyzes As(III)/H(+) and Sb(III)/H(+) exchange in *Saccharomyces cerevisiae*. Biochim Biophys Acta 1808:1855–1859

MacMahon E, Murphy AS, Bates MI (1947) Endothelial cell sarcoma of the liver following Thorotrast injection. Am J Pathol 23:585–611

Maeda T, Tateishi U, Hasegawa T, Ojima H, Arai Y, Sugimura K (2007) Primary hepatic angiosarcoma on coregistered FDG PET and CT. AJR Am J Roentgenol 188:1615–1617

Mahony B, Jeffrey RB, Federle MP (1982) Spontaneous rupture of hepatic and splenic angiosarcoma demonstrated by CT: AJR Am. J Roentgenol 138:965–966

Makk L, Delorme F, Creech JL, Ogden LL, Fadell EH, Songster CL et al (1976) Clinical and morphologic features of hepatic angiosarcoma in vinyl chloride workers. Cancer 37:149–163

Malaveille C, Bartsch H, Barbin A, Camus AM, Montesano R, Croisy A, Jacquignon P (1975) Mutagenicity of vinyl chloride chloroethyleneoxide, chloroacetaldehyde and chloroethanol. Biochem Biophys Res Commun 63:363–370

Maltoni C (1974) Angiosarcoma epatico in operai esposti a cloruro di vinile. resoconte dei primi due casi riscontrati in Italia. Med Lavoro 65:445–450

Maltoni C, Cotti G (1988) Carcinogenicity of vinyl chloride in Sprague-Dawley rats after prenatal and postnatal exposure. Ann NY Acad Sci 534:145–159

Maluf D, Coterell A, Clark B, Stravitz T, Kauffman HM, Fisher RA (2005) Hepatic angiosarcoma and liver transplantation: case report and literature review. Transplant Proc 37:2195

Mani H, Van Thiel DH (2001) Mesenchymal tumors of the liver. Clin Liver Dis 5:219–257

Manning JT, Ordonez NG, Barton JH (1983) Endothelial cell origin of thorium oxide-induced angiosarcoma of liver. Arch Pathol Lab Med 107:456–458

Marion MJ, Boivin-Angele S (1999) Vinyl chloride-specific mutations in humans and animals. IARC Sci Publ 150:315–324

Marion MJ, Froment O, Trepo C (1991) Activation of Ki-ras gene by point mutation in human liver angiosarcoma associated with vinyl chloride exposure. Mol Carcinog 4:450–454

Marx H (1904a) Primäres Sarkom der Leber. Zentralbl Allgem Pathol Pathol Nat 15:110

Marx H (1904b) Über einen eigenartigen primären Tumor der Leber nebst bemerkungen zur Chorionepitheliomfrage. Beitr Pathol Anat Allg Pathol 36:585–605

Matthaei H, Boelke E, Eisenberger CF, Alldinger I, Krieg A, Schmelzle M, Poremba C et al (2007) Interdisciplinary treatment of primary hepatic angiosarcoma: emergency tumor embolization followed by elective surgery. Eur J Med Res 12:591–594

Matthaei H, Krieg A, Schmelzle M, Boelke E, Poremba C, Rogiers X, Koefel WT, Peiper M (2009) Long-term survival after surgery for primary hepatic sarcoma in adults. Arch Surg 144:339–344

Matturi L, Rossi L (1963) Angioblastic reticuloendotheliomas of the liver (Kupffer cell sarcomas). Presentation of two cases and review of the literature (in Italian). Fegato 9:127–148

Mehlman MA (2002) Remembering Professor Cesare Maltoni. Ann NY Acad Sci 982:1–25

Meis-Kindblom JM, Kindblom LG (1998) Angiosarcoma of soft tissue: a study of 80 cases. Am J Surg Pathol 22:683–697

Michot F, Bruggisser D, Fehr H, Yurtsever H, Anabitarte M (1987) Microangiopathic hemolytic anemia, erythrophagocytosis and consumption coagulopathy in vinyl chloride-induced hemangiosarcoma of the spleen and liver (in German). Schweiz Med Wochenschr 117:990–995

Miettinen M, Sarlomo-Rikala M, Wang ZF (2011) Claudin-5 as an immunohistochemical marker for angiosarcoma and hemangioendotheliomas. Am J Surg Pathol 35:1848–1856

Miller EA, Richards WG, Reed WH (1964) Hemangioendothelial sarcoma of the liver (Kupffer cell sarcoma). Case report. Wis Med J 63:471–475

Mohr CP, Kaup FG, Gossmann HH, Teschke R (1984) Hemangioendothelioma of the liver 38 years after administration of thorium dioxide (in German). Z Gastroenterol 22:153–157

Molina E, Hernandez A (2003) Clinical manifestations of primary hepatic angiosarcoma. Dig Dis Sci 48:677–682

Monroe PS, Riddell RH, Siegler M, Baker AL (1993) Hepatic angiosarcoma. Possible relationship to long-term oral contraceptive ingestion. JAMA 246:64–65

Montell Garcia M, Romero Cabello R, Romero Feregrino R, Atri Moises M, Trejo Estrada R et al (2012) Angiosarcoma of the liver as a cause of fulminant liver failure. MBJ Case Rep pii: 6cr2012006417 (Pub med PMID 22865805)

Naka N, Tomita Y, Nakanishi H, Araki N, Hongyo T, Ochi T, Aozasa K (1997) Mutations of p53 tumor-suppressor gene in angiosarcoma. Int J Cancer 71:952–955

Nazari A (1906) Contributo allo studio dei sarcoma primitivi del fegato. Il Policlinico (Sezione Medica, Roma) 8:360–369

Ni Q, Shang D, Peng H, Roy M, Liang G, Bi W, Gao X (2013) Primary angiosarcoma of the small intestine with metastasis to the liver: a case report and review of the literature. World J Surg Oncol 11:242

Nordsten M (1985) Hemangiosarcoma of the liver associated with administration of androgenic steroid (in Danish). Ugeskr Laeger 147:2615–2616

NRC (1999) National Research Council Report: arsenic in the drinking water. National Academy Press, Washington, DC

Odashiro AN, Pereira PR, Odashiro Miiji LN, Nguyen GK (2005) Angiosarcoma of the gallbladder: case report and review of the literature. Can J Gastroenterol 19:257–259

Ohmoto K, Hirokawa M, Takesue M, Yamamoto S (2000) Hepatic angiosarcoma with early central enhancement and arterioportal shunt on dynamic CT. Hepatogastroenterology 47:1717–1718

Ohtomo K, Araki T, Itai Y, Monzawa S, Ohba H, Nogata Y et al (1992) MR imaging of malignant mesenchymal tumors of the liver. Gastrointest Radiol 17:58–62

Okano A, Sonoyama H, Masano Y, Taniguchi T, Ohana M, Kusumi F, Nabeshima M (2012) The natural history of hepatic angiosarcoma that was difficult to differentiate from cavernous hemangioma. Intern Med 51:2899–2904

Olson TS, Chan ES, Paessler ME, Sullivan KE, Frantz CN, Russo P, Bessler M (2014) Liver failure due to hepatic angiosarcoma in an adolescent with dyskeratosis congenita. J Pediatr Hematol Oncol 36:312–315

Orlando G, Adam R, Mirza D, Soderdahl G, Porte RJ, Paul A, Burroughs AK, Seiler CA et al (2013) Hepatic hemangiosarcoma: an absolute contraindication to liver transplantation – The European Liver Transplant Registry Experience. Transplantation 95:872–877

Özden I, Bilge O, Erkan M, Cevikbas U, Acarli K (2003) Five years and 4 months of recurrence-free survival in hepatic angiosarcoma. J Hepato-Biliary Pancreat Surg 10:250–252

Paliard P, Valette PJ, Berger F, Contassot JC, Partensky C (1991) Peliosis hepatis of late onset in a patient exposed to vinyl chloride and treated for hepatic angiosarcoma (in French). Gastroenterol Clin Biol 15:445–448

Park YS, Kim JH, Kim KW, Lee IS, Yoon HK, Ko GY, Sung KB (2009) Primary hepatic angiosarcoma: imaging findings and palliative treatment with transcatheter arterial chemoembolization or embolization. Clin Radiol 64:779–785

Pepere G (1900) Ricerche istogenetice degli epitheliomi ed endotheliomi primarii del fegato. Il Policlinico Suppl 7

Peterson MS, Baron RL, Rankin SC (2000) Hepatic angiosarcoma: findings on multiphasic contrast-enhanced helical CT do not mimic hepatic hemangioma. AJR Am J Roentgenol 175:165–170

Petito CK, Porro RS (1971) Angioblastic meningioma with hepatic metastasis. J Neurol Neurosurg Psychiatry 34:541–545

Peyser K (1893) Ein Fall von Angiosarkom der Leber und des Magens. Thesis, München

Pimentel Cauduro SK, Petrovic LM, Sodeman TC, Ishitani MB, Menon KV, hay JE (2002) Unsuspected primary hepatic angiosarcoma associated with portal vein thrombosis complicating cirrhosis. Liver Transpl 8:1080–1081

Poggi Machuca L, Ibarra Chirinos O, Lopez Del Aguila J, Villanueva Pflucker M, Camacho Zacarias F et al (2012) Hepatic angiosarcoma: case report and review of the literature (in Spanish). Rev Gastroenterol Peru 32:317–322

Popper H, Thomas LB, Telles NC, Falk H, Selikoff IJ (1978) Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast, and arsenic. Comparison with cases of unknown etiology. Am J Pathol 92:349–376

Przygodski RM, Finkelstein SD, Keohavong P, Zhu D, Bakker A, Swalsky PA, Soini Y et al (1997) Sporadic and thorotrast-induced angiosarcomas of the liver manifest frequent and multiple point mutations in K-ras-2. Lab Invest 76:153–159

Puhr L (1931) Über das sogenannte primäre Hämangioendotheliom der Leber. Zschr Krebsforsch 34:503–517

Rademaker J, Widjaja A, Galanski M (2000) Hepatic hemangiosarcoma: imaging findings and differential diagnosis. Eur Radiol 10:129–133

Radike MJ, Stemmer KL, Brown PG, Larson E, Bingham E (1977) Effect of ethanol and vinyl chloride on the induction of liver tumors: preliminary report. Environ Health Perspect 21:153–155

Rakov HL, Smalldon TR, Derman H (1963) Hepatic hemangioendotheliosarcoma. Report of a case due to Thorium. Arch Intern Med 112:173–178

Regelson W, Kim U, Ospina J, Holland JF (1968) Hemangioendothelial sarcoma of liver from chronic arsenic intoxication by Fowler's solution. Cancer 21:514–522

Riordan SM, Loo CK, Haber RW, Thomas MC (1991) Vinyl chloride related hepatic angiosarcoma in a polyvinyl chloride autoclave cleaner in Australia. Med J Aust 155:125–128

Roat JW, Wald A, Mendelow H, Pataki KI (1982) Hepatic angiosarcoma associated with short-term arsenic ingestion. Am J Med 73:933–936

Roche J, Fournet J, Hostein J, Panh M, Bonnet-Eymard J (1978) Hepatic angiosarcoma due to vinyl chloride. Report of 4 cases (in French). Gastroenterol Clin Biol 2:669–678

Roesler A, Schreyer T, Keller E, Storkel S (1985) Hemangiopericytoma of the liver (in German). Roentgenblätter 38:58–59

Rojter S, Villamil FG, Petrovic LM, Silverman JM, Woolf GM, Podesta LG, Makowka L, Vierling JM (1995) Malignant vascular tumors of the liver presenting as liver failure and portal hypertension. Liver Transplant Surg 1:156–161

Rosenthal AK, Klausmeier M, Cronin ME, McLaughlin JK (2000) Hepatic angiosarcoma occurring after cyclophosphamide therapy: case report and review of the literature. Am J Clin Oncol 23:581–583

Ross P, Rasmussen JF (1989) Malignant liver tumors. Curr Probl Diagn Radiol 18:95–124

Roth F (1957) Arsenic, liver and tumors: hemangioendothelioma (in German). Z Krebsforsch 61:468–503

Saito et al. (1997) Pub Med PMD 9012458

Saleh HA, Tao LC (1998) Hepatic angiosarcoma: aspiration biopsy cytology and immunocytochemical contribution. Diagn Cytopathol 18:208

Salgado M, Sans M, Forns X, Bruguera M, Castells A, Nvasa M, Rodés J (1995) Hepatic angiosarcoma: a report of a case associated with treatment with arsenic salts and a review of the literature (in Spanish). Gastroenterol Hepatol 18:132–135

Salomàki HM, Sainio AO, Söderström M, Pakkanen S, Laine J, Järveläinen HT (2008) Differential expression of decorin by human malignant and benign vascular tumors. J Histochem Cytochem 56:639–646

Scherer G, Roeren T, Hofmann W, Brado M, Kauffmann GW (1996) Surprising finding of a hepatic hemangiosarcoma with concomitant peliosis hepatis (in German). Rofo Fortschr Geb Roentgenstr Neuen Bildgeb Verfahr 165:305–308

Schlesinger K (1920) Primäres malignes Angioendotheliom der cirrhotischen Leber. Thesis, Frankfort

Sherman M (2009) Vinyl chloride and the liver. J Hepatol 51:1074–1081

Shi EC, Fischer A, Crouch R, Ham JM (1981) Possible association of angiosarcoma with oral contraceptive agents. Med J Aust 1:473–474

Silverman PM, Ram PC, Korobkin M (1983) CT appearance of abdominal thorotrast deposition and throtrast-induced angiosarcoma of the liver. J Comput Assist Tomogr 7:655–658

Smith SJ, Li Y, Whitley R, Marion MJ, Partilo S, Carney WP, Brandt-Rauf PW (1998) Molecular epidemiology of p53 protein mutations in workers exposed to vinyl chloride. Am J Epidemiol 147:302–308

Soini Y, Welsh JA, Ishak KG, Bennett WP (1995) P53 mutations in primary hepatic angiosarcomas not associated with vinyl chloride exposure. Carcinogenesis 16:2879–2881

Spirtas R, Kaminski R (1978) Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. 1977 update of the NIOSH register. J Occup Med 20:427–429

Spit BJ, Feron VJ, Hendriksen CF (1981) Ultrastructure of hepatic angiosarcoma in rats induced by vinyl chloride. Exp Mol Pathol 35:277–284

Stambo GW, Guiney MJ (2007) Hepatic angiosarcoma presenting as an acute intraabdominal haemorrhage treated with transarterial chemoembolization. Sarcoma 2007:90169

Sternsdorf T, Puccetti E, Jensen K, Hoelzer D, Will H, Ottmann OG, Ruthardt M (1999) PIC-1/SUMO-1-modified PML-retinoic acid receptor alpha mediates arsenic trioxide-induced apoptosis in acute promyelocytic leukemia. Mol Cell Biol 19:5170–5178

Sugahara K, Shirakura T, Kawano N, Kino I (1974) Primary malignant haemangioendothelioma of the liver. Am J Gastroenterol 62:240–244

Sussman EB, Nydick I, Gray GF (1974) Hemangioendothelial sarcoma of the liver and hemochromatosis. Arch Pathol 97:39–42

Suzuki Y (1981) Electron microscopic observations of hepatic and subcutaneous hemangiosarcomas induced in mice exposed to vinyl chloride monomer. Am J Ind Med 2:103–117

Suzuki Y (1983) Neoplastic effect of vinyl chloride in mouse lung – lower doses and short-term exposure. Environ Res 32:91–103

Suzuki H, Komatsu A, Fujioka Y, Yamashiro K, Takeda H, Hamada T (2010) Angiosarcoma-like metastatic carcinoma of the liver. Pathol Res Pract 206:484–488

Tateishi U, Hasegawa T, Muramatsu Y, Moriyama N (2003) Hepatic metastases of soft tissue angiosarcoma: CT and MR imaging findings. Abdom Imaging 28:660–664

Telles NC, Thomas LB, Popper H, Ishak KG, Falk H (1979) Evolution of thorotrast-induced hepatic angiosarcomas. Environ Res 18:74–87

Tessier Cloutier B, Costa FD, Tazelaar HD, Folpe AL (2014) Aberrant expression of neuroendocrine markers in angiosarcoma: a potential diagnostic pitfall. Hum Pathol 45:1618–1624

Thomas LB, Popper H (1975) Pathology of angiosarcoma of the liver among vinyl chloride-polyvinyl chloride workers. Ann NY Acad Sci 246:268–277

Thomas LB, Popper H, Berk PD, Selikoff I, Falk H (1975) Vinyl-chloride-induced liver disease. From idiopathic portal hypertension (Banti's syndrome) to angiosarcoma. N Engl J Med 292:17–22

Timaran CH, Grandas OH, Bell JL (2000) Hepatic angiosarcoma: long-term survival after complete surgical removal. Am Surg 66:1153–1157

Tordjman R, Eugene C, Clouet O, Wesenfelder L, Collet C, Bergue A (1995) Hepatosplenic angiosarcoma complicated by hemoperitoneum and disseminated intravascular coagulation. Treatment by arterial embolization and chemotherapy (in French). Gastroenterol Clin Biol 19:625–628

Trojan J, Hammerstingl R, Engels K, Schneider AR, Zeuzem S, Dietrich CF (2010) Contrast-enhanced ultrasound in the diagnosis of malignant mesenchymal liver tumors. J Clin Ultrasound 38:227–231

Tsai MH, Chien RN, Hsieh SY, Hung CF, Chen TC, Sheen IS (1998) Primary hepatic angiosarcoma: report of a case involving environmental arsenic exposure. Changgeng Yi Xue Za Zhi 21:469–474

Umezu T (1984) Pathomorphological study, on Thorotrast-induced hepatic angiosarcoma. J Kurume Med Assoc 47:62–73

Underwood JC, Huck P (1978) Thorotrast associated hepatic angiosarcoma with 36 years latency. Cancer 42:2610–2612

Van Kaick G, Dalheimer A, Hornik S, Kaul A, Liebermann D, Lührs H, Spiethoff A, Wegener K et al (1999) The German Thorotrast Study: recent results and assessment of risks. Radiat Res 152: S64–S71

Van Kampen RJW, Erdkamp FLG, Peters FPJ (2007) Thorium dioxide-related haemangiosarcoma of the liver. Neth J Med 65:279–282
Vasile N, Larde D, Zafrani S, Bernard H, Mathieu D (1983) Hepatic angiosarcoma. J Comput Assist Tomogr 7:899–901
Vellenga R (1962) A case of hemangiosarcoma of the liver 25 years after thorotrast injection for cerebral angiography (in Dutch). J Belge Radiol 45:682–688
Vennarecci G, Ismail T, Gunson B, McMaster P (1997) Primary angiosarcoma of the liver (in Italian). Minerva Chir 52:1141–1146
Vianna NJ, Brady J, Haprer P (1981) Angiosarcoma of the liver: a signal lesion of vinyl chloride exposure. Environ Health Perspect 41:207–210
Von Frerichs FT (1861) Klinik der Leberkrankheiten, viehweg f and son braunschweig vol 2. p 319
Wada I, Horiuchi H, Mori M, Ishikawa Y, Fukumoto M, Mori T, Kato Y, Kitagawa T et al (1999) High rate of small TP53 mutations and infrequent loss of heterozygosity in malignant liver tumors associated with thorotrast: implications for alpha-particle carcinogenesis. Radiat Res 152(Suppl 6):S125–S127
Wallnöfer H, Zinnagl N (1977) Hämangiosarkomatose nach Polyvinylchloridexposition. Med Klein 72:410–413
Wang ZB, Wei LX (2013) Primary hepatic angiosarcoma: a clinical and pathological analysis (in Chinese). Zhonghua Bing Li Xue Za Zhi 42:376–380
Wang YT, Wong SC, Thomas A (1983) Locally invasive hepatic angiosarcoma: an unusual cause of massive haemothorax. Thorax 38:558–559
Wang L, Lv K, Chang XY, Xia Y, Yang ZY, Jiang YX, Dai Q, Tan L, Li JC (2012) Contrast-enhanced ultrasound study of primary hepatic angiosarcoma: a pitfall of non-enhancement. Eur J Radiol 81:2054–2059
Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, De Santis M, Engholm G et al (2001) Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. Epidemiology 12:710–718
Waxweiler RJ, Stringer W, Wagoner JK, Jones J, Falk H, Carter C (1976) Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 271:40–48
Weihrauch M, Bader M, Lehnert G, Koch B, Wittekind C, Wrbitzky R, Tannapfel A (2002) Mutation analysis of K-ras-2 in liver angiosarcoma and adjacent nonneoplastic liver tissue from patients occupationally exposed to vinyl chloride. Environ Mol Mutagen 40:36–40
Wesch H, Wegener K, Riedel W (1984) Follow-up animal experimental study. In: Van Kaick G, Muth A, Kaul A (eds) The German thorotrast study. Commission of the European Communities, Luxembourg
White PG, Adams H, Smith PM (1993) The computed tomographic appearances of angiosarcoma of the liver. Clin Radiol 48:321–325
Wiland HO, Pai RK, Purysko AS (2012) Hepatic angiosarcoma mimicking sinusoidal obstruction syndrome/venoocclusive disease: a pathologic-radiologic correlation. Ann Diagn Pathol 16:275–279
Williamson KS (1976) Vinyl chloride: review of animal studies. Proc R Soc Med 69:281–283
Winberg CD, Ranchod M (1979) Thorotrast induced hepatic cholangiocarcinoma and angiosarcoma. Hum Pathol 10:108–112
Winell M, Holmberg B, Kronevi T (1976) Biological effects of vinyl chloride: an experimental study. Environ Health Perspect 17:211–216
Yamagiwa H, Mizutani T, Yamazaki I (1967) Malignant hemangioendothelioma of the liver with metastases to the kidneys and adrenals. Mie Med J 16:221–227
Yamamoto Y, Chikawa J, Uegaki Y, Usuda N, Kuwahara Y, Fukumoto M (2010) Histological type of Thorotrast-induced liver tumors associated with the translocation of deposited radionuclides. Cancer Sci 101:336–340
Yamanaka T, Shiraki K, Ito T, Sugimoto K, Sakai T, Ohmori S, Takase K, Nakano T et al (2002) Hepatic angiosarcoma mimicking cavernous hemangioma on angiography. Hepatogastroenterology 49:1425–1427
Yamashita H, Endo K, Teshima R (2012) Angiosarcoma of the proximal humerus: a case report and review of the literature. J Med Case Rep 6:347
Yan W, Zhang Y, Zhang J, Liu S, Cho SJ, Chen X (2011) Mutant p53 protein is targeted by arsenic for degradation and plays a role in arsenic-mediated growth suppression. J Biol Chen 286:17478–17486
Yang J, Salam AA, Rosen BP (2011) Genetic mapping of the interface between the ArsD metallochaperone and the ArsA ATPase. Mol Microbiol 79:872–881
Yang KF, Leow VM, Hasnan MN, Manisekar KS (2012) Primary hepatic angiosarcoma: difficulty in clinical., radiological, and pathological diagnosis. Med J Malaysia 67:127–128
Yasunaka T, Ikeda F, Kobashi H, Miyake Y, Takaki A, Iwasaki Y, Hada H, Yamamoto K et al (2012) Hepatic angiosarcoma with characteristic laparoscopic findings. Dig Endosc 24:124
Yoshida K, Ito F, Nakazawa H, Maeda Y, Tomoe H, Aiba M (2009) A case of primary renal angiosarcoma. Rare Tumors 1:e28
Yu R, Zhang S, Hua J (2003) Hepatic angiosarcoma: CT findings. Chin Med J (Engl) 116:318–320
Yu RS, Chen Y, Jiang B, Wang LH, Xu XF (2008) Primary hepatic sarcomas: CT findings. Eur Radiol 18:2196–2205
Zhang XW, Yan XJ, Zhou ZR, Yang FF, Wu ZY, Sun HB, Liang WX, Song AX et al (2010) Arsenic trioxide controls the fate of the PML-RARalpha oncoprotein by directly binding PML. Science 328:240–243
Zheng YW, Zhang XW, Zhang JL, Hui ZZ, Du WJ, Li RM, Ren XB (2014) Primary hepatic angiosarcoma and potential treatment options. J Gastroenterol Hepatol 29:906–911
Zhou YM, Li B, Yin ZM, Xu F, Wang B, Xu W, Liu P, Yang JM (2010) Results of hepatic resection for primary hepatic angiosarcoma in adults. Med Sci Monit 16: CR61–CR66

Zhou X, Sun X, Cooper KL, Wang F, Liu KJ, Hudson LG (2011) Arsenite interacts selectively with zinc finger proteins containing C3H1 and C4 motifs. J Biol Chem 286:22855–22863

Zhu S, Wang A, Xia Z (2005) Polymorphisms of DNA repair gene XPD and DNA damage of workers exposed to vinylchloride monomer. Int J Environ Health 208:383–390

Zietz C, Rössle M, Haas C, Sendelhofert A, Hirschmann A, Stürzl M, Löhrs U (1998) MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. Am J Pathol 153:1425–1433

Pediatric Hepatic Angiosarcomas 55

Contents

Abstract

Distinct variants of hepatic angiosarcoma occur in the pediatric age group. Overall, these are very rare neoplasms. Infantile type of hepatic angiosarcoma, at least part of which was previously classified as type 2 of infantile hepatic hemangioendothelioma, is a rapidly growing neoplasm that commonly involves both liver lobes and causes marked hepatomegaly. The tumor may be associated with respiratory distress but does not induce congestive heart failure. The histology is different from adult-type hepatic angiosarcoma and characterized by a complex network of anastomosing and sometimes slit-like vascular channels lined by plump, often spindle-shaped endothelial cells with atypical nuclei. Whorls of sarcomatoid cells and kaposiform spindle cells are observed. Irregular budding and branching structures are a typical feature. Infantile hepatic angiosarcoma can metastasize, mainly to the lungs, and is associated with rapid progression. Very rarely, pediatric hepatic angiosarcoma displays the morphology of adult-type angiosarcoma. These neoplasms develop in children older than 3 years of age and are sporadic lesions.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_55

Pediatric Hepatic Angiosarcoma, Infantile Type

Introduction

As discussed in the respective chapter, infantile hepatic hemangioendotheliomas of type 1 are vascular tumors that characteristically appear in infancy and, subsequently, involute, thus displaying a relatively benign behavior. Rarely, such lesions behave in an aggressive way and in such a setting have metastatic potential, hence showing the features of angiosarcomas. Less than 50 of such malignancies have been reported in the literature so far. Most of such tumors have previously been classified as infantile hepatic hemangioendothelioma type 2 (Dehner and Ishak 1971). In brief, Dehner and Ishak defined the type 1 as a pattern predicting a benign course, the histology closely resembling that of hemangioendotheliomas developing at other site, mainly characterized by irregularly arranged and dilated vascular channels lined by a single layer of cytologically bland-looking endothelial cells. In contrast, type 2 is associated with an aggressive course, including metastatic disease, and exhibits irregularly budding and branching vascular structures with larger and atypical endothelial cells. The latter variant of hepatic hemangioendothelioma is now generally interpreted to be an angiosarcoma, also based on the aggressive clinical course (Ishak et al. 2001). Dehner and Ishak (1971) already emphasized that the histologic pattern as such is not an absolute predictor of the clinical behavior. This difficulty is further enhanced by the fact that benign-looking (type 1) hepatic hemangioendotheliomas may with time transform into lesions histologically representing low-grade angiosarcomas, an evolution discussed in more detail below. In the present context, this type of low-grade hepatic angiosarcoma occurring in infancy and early childhood is termed infantile-type hepatic angiosarcoma (pediatric hepatic angiosarcoma of infantile type). Much rarer are hepatic angiosarcomas that histologically reflect the features of hepatic angiosarcomas of adult patients. These adult-type pediatric hepatic angiosarcomas are treated in a separate chapter.

Epidemiology

Since the reports of de Haan (1903) and Dehner and Ishak (1971), relatively few cases of infantile-type hepatic angiosarcoma have been described (Chabalko and Fraumeni 1975; Falk et al. 1981; Kirchner et al. 1981; Moazam et al. 1982; Noronha and Gonzalez-Crussi 1984; Strate et al. 1984; Alt et al. 1985; Selby et al. 1992; Awan et al. 1996; Dimashkieh et al. 2004; Premalata et al. 2005; Nazir and Pervez 2006; Ackermann et al. 2011; Geramizadeh et al. 2011).

Pediatric hepatic angiosarcoma is among the most uncommon types of childhood hepatic vascular tumors. In the series of Dehner and Ishak (1971), the age at diagnosis ranged from 13 days to 4 years, and 87 % of the tumors were diagnosed before the patients reached the age of 6 months. Patients with angiosarcoma are older at diagnosis than those with type 1 hepatic hemangioendothelioma (Chabalko and Fraumeni 1975; Selby et al. 1992; Dimashkieh et al. 2004). In a series of ten cases, the range of age at diagnosis was 18 months to 7 years, with a mean of 3.7 years (Selby et al. 1992), and in a series of four cases, the mean age at diagnosis was 38 months (Awan et al. 1996). Among 41 cases reported in the literature, about half of the patients were older than 2 years at diagnosis (Dimashkieh et al. 2004). In contrast to adult hepatic angiosarcoma, pediatric hepatic angiosarcoma affects females more than males, with an overall female to male ratio of about 2:1.

Clinical and Imaging Features

Similar to type 1 hepatic hemangioendothelioma (see the respective chapter), infantile-type hepatic angiosarcoma usually presents as hepatomegaly, which is in fact the most frequent physical finding. The abdominal enlargement caused by tumor-induced hepatomegaly may develop rapidly, and involvement of both liver lobes is common from the outset. Hepatomegaly may be accompanied by abdominal pain, vomiting, fever, jaundice, respiratory distress, and anemia. In contrast to

type 1 hemangioendothelioma, patients with angiosarcoma do not show congestive heart failure (Selby et al. 1992), and consumption coagulopathy has not been noted. Metastases, especially in the lungs, are a common early occurrence.

It has been suggested that this type of neoplasm may arise via malignant transformation of type 1 infantile hepatic hemangioendothelioma, based on observations that angiosarcoma became histologically evident on repeat biopsy, in liver resection specimens, or on autopsy, requiring ample biopsy in patients where the clinical course is suspicious of malignancy (Dehner and Ishak 1971; Falk et al. 1981; Kirchner et al. 1981; Strate et al. 1984; Alt et al. 1985; Awan et al. 1996). Patient 15 (2 months of age) listed in the publication of Dehner and Ishak (1971) showed a mixture of type 1 and type 2 lesions, but the biology of tumor disease is unknown as the patient died during cardiac surgery for patent ductus arteriosus. Falk and coworkers (1981) described three infantile hepatic vascular tumors that were histologically benign on the initial biopsy, but subsequently (i.e., within 2–20 months) transformed into an aggressive-looking histology associated with a malignant clinical course. All three malignant tumors consisted of remnants of type 1 hemangioendothelioma, foci of low-grade angiosarcoma, and multiple nodular areas composed of loose mesenchymal tissue with scattered malignant cells and embedded small bile ducts. The 6-month-old infant described by Kirchner et al. (1981) had multiple hepatic hemangioendothelioma that regressed after steroid therapy, but recurred at 4 years of age as a neoplasm with an angiosarcoma histology. In the case reported by Strate et al. (1984), a 3-month-old male infant presented with multiple hepatic nodules interpreted, also based on a biopsy, as benign hemangioendothelioma. After an unsuccessful steroid therapy of several weeks duration, the liver gradually decreased in site during a 6-month period, and the child was well at 2.5 years of age, with a normal liver radionuclide scan, but reappeared at 5 years with painful hepatomegaly and hepatic filling defects. Following progressive abdominal distention, anemia, and fever, the patient died. Autopsy revealed a markedly enlarged liver (2,620 g) with ruptured and in part cystic, hemorrhagic tumor masses histologically showing angiosarcoma with a prominent spindle cell component.

Abdominal CT displays low-attenuating vascular lesions forming masses of variable diameters, typically around 2–4 cm (Awan et al. 1996). There are no clear features to differentiate pediatric angiosarcoma from type 1 hemangioendothelioma (Awan et al. 1996). Doppler flow studies showed an increase in hepatic arterial blood flow and sometimes reverse flow in portal venous branches secondary to tumor infiltration (Awan et al. 1996).

Pathology

Macroscopy

Similar to type 1 lesions, infantile-type pediatric hepatic angiosarcoma presents as either solitary or multiple nodular masses without predilection for the right or the left liver lobe. The tumors are more or less well delineated, sometimes with infiltrating borders, but are unencapsulated. The cut surface is gray to red or tan, sometimes with hemorrhage, friable necrotic areas, or cystic alterations. In part of the cases, most tumor revealed cysts filled with a hemorrhagic fluid (de Haan 1903). In contrast to solitary nodules, which tend to be more solid, multiple nodules are more often soft and hemorrhagic or hyperemic.

Histopathology

The histology of infantile-type pediatric hepatic angiosarcoma is different from that of adult-type angiosarcoma. In the infantile type, most cases representing the former infantile hepatic hemangioendothelioma type 2, histology displays a complex network of irregular and in part anastomosing vascular channels, some of them slit-like, lined by plump, often spindle-shaped, endothelial cells with eosinophilic cytoplasm and

large, oval, and vesicular nuclei with prominent nucleoli. In contrast to adult-type angiosarcoma, hypercellular whorls of sarcomatoid cells or kaposiform spindle cell areas can be found (Dimashkieh et al. 2004). In cells lining vascular spaces, the nuclei appear pushed to the side. A typical feature, already described for type 2 hemangioendothelioma (Dehner and Ishak 1971), is the presence of "irregular budding and branching structures, in part giving the impression of lying free within tortuous vascular spaces." The budding structures sometimes form endoluminal polypoid formations covered by several layers of highly atypical endothelial cells. Sometimes, very few endothelial cells surround an erythrocyte-containing space, resulting in the appearance of capillary-like vessels lined by tumor cells (Falk et al. 1981). In some areas, anaplastic endothelial cells seem to line preexisting sinusoidal vessels with interposed atrophic liver cell plates (so-called trabecular angiosarcoma; Falk et al. 1981). Angiosarcoma tissue can invade subterminal veins and tributaries of the hepatic veins. Within larger vascular spaces, angiosarcoma typically forms filiform, fibrous stalks covered by neoplastic endothelial cells (Falk et al. 1981). There are areas where the vascular spaces are poorly developed or look collapsed. Such areas are often occupied by a solid growth of spindle cells with entrapped atrophic hepatic parenchymal cells and small bile duct and ductules, this pattern somewhat resembling Kaposi's sarcoma or kaposiform hemangioendothelioma of soft tissues (Ishak et al. 2001). In these areas, mitotic figures may be more frequent than in the clearly vascular components. At the periphery of the tumor nodules, arterioles with muscle cells and small feeding arteries may be in evidence. Sometimes, such feeding vessels are abundant and traverse the connective tissue sheath of the tumor nodules. Cavernous vascular spaces may occur, but are less prominent than in type 1 lesions, although they were detected in five out of six cases in one study (Dehner and Ishak 1971). The tumor may also show hypercellular whorls of sarcomatoid cells or glomeruloid foci. Pleomorphic cells or multinucleated giant cells are usually sparse, in contrast to adult-type angiosarcoma. Intracellular eosinophilic, PAS-positive globules are present in most cases and may be abundant, specifically within kaposiform spindle cells (Selby et al. 1982; Dvorak 1993). These globules are not immunoreactive for alpha-1 antitrypsin. Part of the tumors show foci of extramedullary hematopoiesis (five out of six patients; Dehner and Ishak 1971). The tumors usually show necrosis and hemorrhage, sometimes prominent. Granulation tissue and fibrosis may develop around necrotic components of the tumor. In this connective tissue, thick collagen bundles may develop, and the adjacent liver substance can show perifocal atrophy, ductular proliferations, and cholestasis. In one case, electron microscopy revealed plump cells lining vascular spaces showing multiple free ribosomal helices together with a well-developed smooth endoplasmic reticulum and small mitochondria. The tumor cells often contained myelin figures, membrane-bound inclusions (lysosomes), and lipid droplets. Typical Weibel-Palade bodies were not detected (Noronha and Gonzalez-Crussi 1984).

Immunohistochemistry

The endothelial cells lining the vascular channels are reactive for CD31, CD34, and factor VIII-associated antigen (Selby et al. 1992; Dimashkieh et al. 2004). Also part of the (kaposiform) spindle cells is positive for CD31 and CD34 (Dimashkieh et al. 2004). The proliferative activity assessed in MIB1 immunostains ranged from 0.4 % to 6 % (Dimashkieh et al. 2004).

Hepatic Angiosarcoma Associated with Other Angiomatous Tumors

It is well known that cutaneous hemangiomas can be associated with internal vascular tumors. Specifically, the presence of more than five cutaneous lesions seems to be a marker of possible internal hemangiomatosis, with the liver being the most often involved site. Hepatic angiosarcoma (type 2 hemangioendothelioma) was found in conjunction with multiple cutaneous infantile

hemangiomas in neonates, infants, and children up to 4 years of age (Dehner and Ishak 1971; Chabalko and Fraumeni 1975; Falk et al. 1981; Kirchner et al. 1981; Alt et al. 1985; Selby et al. 1992; Awan et al. 1996; Walsh et al. 2004; Nord et al. 2006). Infantile-type hepatic angiosarcoma has also been observed associated with other visceral vascular tumors, e.g., jejunal angiosarcoma (Ganguly and Mukherjee 2010).

Biology of Disease

Infantile-type hepatic angiosarcoma has a very poor prognosis, with an average survival of 16 months (Dimashkieh et al. 2004). The often multicentric tumor grows rapidly and is usually unresectable. Metastases occur early in the course of disease, especially metastases to the lung (Kaufmann and Stout 1961; Falk et al. 1981; Selby et al. 1992; Awan et al. 1996).

Etiopathogenic Pathways

In one case of infantile-type hepatic angiosarcoma, exposure to arsenic was found, and etiologic factor known to play a role in hepatic angiosarcomas of adult patients (Falk et al. 1981), but in the other reported cases, there was no clear association with environmental cancerogens.

Adult-Type Pediatric Hepatic Angiosarcoma

Introduction

As in adults, angiosarcoma in children is one of the rarest soft tissue tumors, representing fewer than 1 % of soft tissue sarcomas, and visceral forms of this tumor are even much less common. Adult-type pediatric hepatic angiosarcoma is a highly aggressive tumor that is histologically different from infantile-type hepatic angiosarcoma (type 2 infantile hepatic hemangioendothelioma; see above), in that it does not occur in conjunction with hepatic hemangioendothelioma and its histology closely resembles that of hepatic angiosarcoma of adult patients.

Epidemiology and Presentation

Relatively few adult-type angiosarcomas have been reported (Nielsen 1951; Davis 1961; Sugahara et al. 1974; Adam et al. 1975; Falk et al. 1981; Selby et al. 1992; Hernandez et al. 1999; Premalata et al. 2005; Gunawardena et al. 1997; Bien et al. 2009; Deyrup et al. 2009; Geramizadeh et al. 2011; van den Brand et al. 2011). Hepatic angiosarcomas not associated with infantile hepatic hemangioma/hemangioendothelioma are diagnosed in children of an older age group than infantile hemangioma, i.e., with a mean age of 3.7 years at diagnosis (Selby et al. 1992).

Sugahara et al. (1974) described a large liver angiosarcoma in a 15-year-old male; this tumor was particularly large, the right hepatic lobectomy specimen weighing 3,550 g. A primary hepatic tumor observed in a 3-year-old girl (Adam et al. 1975) was associated with cachexia, ascites, abdominal wall edema, venous congestion, and bilateral pleural metastases, the malignancy rapidly leading to death. At autopsy, the right liver lobe was replaced by a huge, in part yellowish gray, in part hemorrhagic tumor with the histology of angiosarcoma. The case of Gunawardena et al. (1997) was a 3-year- and 11-month-old female with a large nodular and firm liver tumor which histologically consisted of a grade 3 pleomorphic cell angiosarcoma. The patient reported by Hernandez and coworkers (1999) was a 3-year-old boy presenting with a large hepatic tumor and pulmonary nodules representing metastases. CT of the liver showed a tumor mass that was centrally liquefied with a hemorrhagic component. An exophytic component of the tumor protruded through the diaphragm at the level of the right cardiophrenic angle. Biopsy of the tumor revealed angiosarcoma characterized by haphazard slit-like spaces lined by highly atypical endothelial cells. Among ten children with angiosarcoma studied by the Polish Pediatric Rare Tumors Study, one

2.5-year-old male child had hepatic angiosarcoma (stage T2N1M0), and this patient died with regional relapse after R1 liver resection (Bien et al. 2009). In a study of 15 high-grade angiosarcomas in the soft tissues and viscera of children, tumors arose in both sexes (8 males, 7 females), and the age at diagnosis ranged from 3 months to 19 years (median, 11 years). Only two tumors were located in the liver. Eight cases showed an epithelioid morphology and seven cases were primarily spindled. One case was positive for podoplanin (Deyrup et al. 2009). Hepatic pediatric angiosarcoma has been observed in association with the ICF syndrome (immunodeficiency, centromeric region instability, facial anomalies; a disorder caused by defective DNA methylation; van den Brand et al. 2011). In contrast to hepatic angiosarcoma in adult patients, the role of cancerogenic environmental factors is less prominent in pediatric angiosarcoma. In one patient, exposure to elevated levels of arsenic in the environment may have played an important role (Falk et al. 1981).

Pathology

The tumors present large nodular masses with invasive borders. On cut surfaces, the neoplastic tissue is gray to white, sometimes with necroses, hemorrhages, and cyst formation (Hernandez et al. 1999).

Histologically, the neoplasm reported by Sugahara et al. (1974) revealed a mixture of pleomorphic angiosarcoma with marked nuclear atypia and mitotic activity and areas consisting of spindle cells, blood lakes with lining endothelial cells, and irregular capillary-like channels. Erythrophagocytosis was in evidence. The hepatic tumor described by Gunawardena et al. (1997) consisted of CD34-positive pleomorphic tumor cells with an eosinophilic cytoplasm, large nuclei, and numerous mitotic figures, including abnormal ones. A solid growth prevailed, but small dilated channels lined by plump cells were also noted. The tumor cells contained numerous eosinophilic, PAS-positive globules that stained for alapha-1 antitrypsin. In the systematic study of Deyrup et al. (2009), two histologic patterns were observed either individually or in combination: (1) a racemose vasculature dissecting through adjacent normal tissue and (2) solid sheets and nests of cells (Deyrup et al. 2009). Most tumors display at least focal vasoformative areas, characterized by the formation of vascular channels lined by endothelial cells with hyperchromatic nuclei. Solid areas show dense tissue consisting of elongated spindle cells forming fascicles and whorls, with a variable admixture of epithelioid cells. In one study, an epithelioid component was detected in 53 % of the tumors (Deyrup et al. 2009). A hobnail morphology was seldom seen and was not associated with podoplanin expression (Deyrup et al. 2009). The mitotic activity is usually high to very high, with up to more than 60 mitotic figures per 10 HPFs.

The neoplastic cells are immunoreactive for the endothelial cell lineage markers, CD31, CD34, and FVIII-associated antigen. Positivity for podoplanin is an exceptional finding (Deyrup et al. 2009).

Differential Diagnosis

The main differential diagnosis is low-grade hepatic angiosarcoma occurring in conjunction with infantile hepatic hemangioma/hemangioendothelioma. In these tumors, the histology is different from adult-type angiosarcoma in that hypercellular whorls and "kaposiform" spindle cells prevail.

References

Ackermann O, Fabre M, Franchi S, Pariente D, Debray D, Jacquemin E, Gauthier F et al (2011) Widening spectrum of liver angiosarcoma in children. J Pediatr Gastroenterol Nutr 53:615–619

Adam YG, Huvos AG, Hajdu SI (1975) Malignant vascular tumors of the liver. Ann Surg 175:375–383

Alt B, Hafez GR, Trigg M, Shahidi NT, Gilbert EF (1985) Angiosarcoma of the liver and spleen in an infant. Pediatr Pathol 4:331–339

Awan S, Davenport M, Portmann B, Howard ER (1996) Angiosarcoma of the liver in children. J Pediatr Surg 31:1729–1732

Bien E, Stachowicz-Stencel T, Balcerska A, Godzinski J, Kazanowska B, Perek-Polnik M et al (2009) Angiosarcoma in children – still uncontrollable oncological problem. The report of the Polish Paediatric Rare Tumours Study. Eur J Cancer 1:411–420

Chabalko JJ, Fraumeni JF (1975) Blood-vessel neoplasms in children: epidemiologic aspects. Med Pediatr Oncol 1:135–141

Davis GM (1961) Hemangioendothelioma of the liver with unusual roentgenologic findings. Report of a case. Gastroenterology 40:253–258

De Haan J (1903) Primäres Angiosarcoma alveolare multiplex der Leber bei einem 4 Monate alten Kinde. Beitr Pathol Anat Allg Pathol 34:215–219

Dehner LP, Ishak KG (1971) Vascular tumors of the liver in infants and children: a study of 30 cases and review of the literature. Arch Pathol 92:101–111

Deyrup AT, Miettinen M, North PE, Khoury JD, Tighiouart M, Spunt SL, Parham D et al (2009) Angiosarcomas arising in the viscera and soft tissue of children and young adults: a clinicopathologic study of 15 cases. Am J Surg Pathol 33:264–269

Dimashkieh HH, Mo JQ, Wyatt-Ashmead J, Collins MH (2004) Pediatric hepatic angiosarcoma: case report and review of the literature. Pediatr Dev Pathol 7:527–532

Dvorak AM (1993) Abundant eosinophilic globules in a series of cases of angiosarcoma of the liver in childhood. Pediatr Pathol 13:541–545

Falk H, Herbert JT, Edmonds L, Heath CW, Thomas LB, Popper H (1981) Review of four cases of childhood hepatic angiosarcomas: elevated environmental arsenic exposure in one case. Cancer 47:382–391

Ganguly R, Mukherjee A (2010) Infantile hemangioendothelioma: a case report and discussion. Pathol Res Pract 206:53–58

Geramizadeh B, Safari A, Bahador A, Nikeghbalian S, Salahi H, Kazemi K, Dehghani SM et al (2011) Hepatic angiosarcoma of childhood: a case report and review of literature. J Pediatr Surg 46:e9–e11

Gunawardena SW, Trautwein LM, Finegold MJ, Ogden AK (1997) Hepatic angiosarcoma in a child: successful therapy with surgery and adjuvant chemotherapy. Med Pediatr Oncol 28:139–143

Hernandez E, Escalon EA, Pefkarou AC, Fort J, Khatib Z, Brathwaite CD (1999) Hepatic angiosarcoma in children: review and presentation of one case. Int Pediatr 14:121–124

Ishak KG, Goodman ZD, Stocker JT (2001) Malignant mesenchymal tumors, vol 3, Tumors of the Liver and Intrahepatic Bile Ducts. American Registry of Pathology, Washington, DC, pp 301–306, Fascicle 13

Kaufmann SL, Stout AP (1961) Malignant hemangioendothelioma in infants and children. Cancer 14:1186–1196

Kirchner SG, Heller RM, Kasselberg AG, Greene HL (1981) Infantile hepatic hemangioendothelioma with subsequent malignant degeneration. Pediatr Radiol 11:42–45

Moazam F, Talbert JL, Rodgers BM (1982) Primary tumors of the liver in infancy and childhood. J Fla Med Assoc 69:991–996

Nazir Z, Pervez S (2006) Malignant vascular tumors of liver in children. J Pediatr Surg 41:e49–e51

Nielsen OS (1951) Primary hemangio-endotheliosarcoma in the liver of children. Acta Paediatr 40:431–438

Nord KM, Kandel J, Lefkowitch JH, Lobritto SJ, Morel KD, North PE, Garzon MC (2006) Multiple cutaneous infantile hemangiomas associated with hepatic angiosarcoma: case report and review of the literature. Pediatrics 118:e907–e913

Noronha R, Gonzalez-Crussi F (1984) Hepatic angiosarcoma in childhood: a case report and review of the literature. Am J Surg Pathol 8:863–871

Premalata CS, Kumar RV, Appaji L, Prabhakaran PS (2005) Childhood hepatic angiosarcoma – a case report. Indian J Pathol Microbiol 48:487–498

Selby DM, Stocker JT, Ishak KG (1992) Angiosarcoma of the liver in childhood: and clinicopathologic and follow-up study of 10 cases. Pediatr Pathol 12:485–498

Strate SM, Rutledge JC, Weinberg AG (1984) Delayed development of angiosarcoma in multinodular infantile hepatic hemangioendothelioma. Arch Pathol Lab Med 108:943–944

Sugahara K, Shirakura T, Kawano N, Kino I (1974) Primary malignant hemangioendothelioma of the liver. Report of a successful case of resection and review of the Japanese literature. Am J Gastroenterol 62:240–244

van den Brand M, Flucke UE, Bult P, Weemaes CM, van Deuren M (2011) Angiosarcoma in a patient with immunodeficiency, centromeric region instability, facial anomalies (ICF) syndrome. Am J Med Genet A 155A:622–625

Walsh R, Harrington J, Beneck D, Ozkaynak MF (2004) Congenital infantile hepatic hemangioendothelioma type II treated with orthotopic liver transplantation. J Pediatr Hematol Oncol 26:121–123

Hepatic Kaposi's Sarcoma

56

ICD-O code 9140/3

Contents

Abstract

Kaposi's sarcoma (KS) is a malignant tumor composed of spindle cells and slit-like, frequently abortive vascular structures. KS mainly occurs in the skin and several internal organs and exists in the form of four main types, i.e., classical, endemic, immunosuppression-associated, and epidemic or AIDS-associated KS. KS is associated with herpesvirus or herpesvirus type 8 infection. KS primary to the liver almost always develops in the setting of AIDS. Lesions restricted to the liver are very uncommon, most patients also showing KS lesions elsewhere, but hepatic KS is a well-known tumor that was already documented in Kaposi's own patients. The liver neoplasms are usually multiple and are visualized as red-brown and hemorrhagic nodules that may reach more than 5 cm in diameter. The histologic picture is dominated by spindle cells that are reactive for the endothelial markers CD31 and CD34, but are also positive for D2-40. In fact, KS cells seem to originate from a lymphatic endothelial cell lineage. Apart from KS apparently developing in the liver, this organ is also involved by metastatic KS.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_56

Introduction

Kaposi's sarcoma (KS) is a malignant neoplasm composed of spindle cells and angioid slit-like vascular structures. KS can present with cutaneous lesions with or without internal tumors, but primary deep organ KS in the absence of cutaneous involvement also occurs. KS has a strong etiologic relationship with a human gammaherpesvirus, KSHV, or human herpesvirus 8 (HHV8) (Fig. 1).

Kaposi described the lesion in 1872 (Kaposi 1872). Moriz Kohn Kaposi (1837–1902) was an internationally respected dermatologist and is also credited with the first description of xeroderma pigmentosum. In regard to the pigmented sarcoma he described, he emphasized that this new disease was incurable and rapidly lethal. Among the five patients he described, three were dead within 12–16 months of presentation. As his autopsy findings showed also visceral involvement, Kaposi said that " [one] must postulate, for this scourge, that there is a generalized disease (dyscrasia) pre-existing from the beginning" (Breimer 1994; Zantinga and Coppes 1996; reviews: Orfanos et al. 1995; Antman and Chang 2000; Szajerka and Jablecki 2007). KS was first regarded as a hyperplastic process with features of reversibility (Brooks 1986), but is now established to be a neoplastic process.

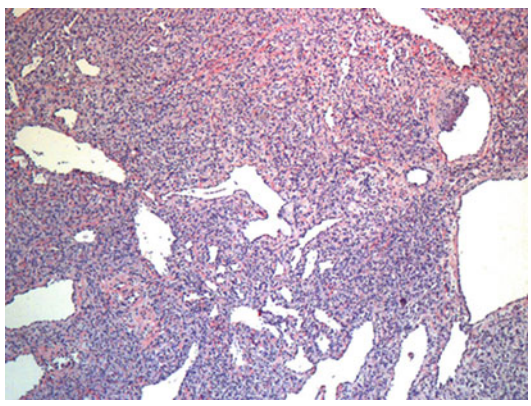

Fig. 1 Kaposi's sarcoma of the liver. A highly cellular neoplasm consisting of spindle cells and polygonal cells contains relatively few vascular spaces hematoxylin and eosin stain

Based on distinct clinical settings and manifestations, KS can be separated into several forms (Table 1).

Being previously a rare and little studied condition, the AIDS epidemic drew much attention to this complex tumor. The disease is caused by a transmissible agent, Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus type 8 (HHV8) (Chang et al. 1994; Schalling et al. 1995; Moore et al. 1996), a member of the gamma-herpesviridae.

Epidemiology

KS occurs in four forms, i.e., classic, endemic (African), posttransplant, and epidemic (AIDS-related) forms. Classic KS is rare and occurs predominantly in Mediterranean and Middle Eastern men. Among 438 classic KS patients studied in the USA, the tumor was more common in men with a mean age of 74 years; the lesions presented predominantly in the lower extremities, in the nodular stage, and KSHV was detected in the majority of patients. Classic KS is a rather indolent disease and rarely accounts, as such, for patient demise, but a second, non-classic KS malignancy was present in 42 %, 73 % with a

Table 1 Classification of Kaposi's sarcoma (KS)

Classic KS
The originally described disease affecting elderly men in Mediterranean populations of Eastern European descent. Clinical course relatively indolent
Endemic KS
Endemic KS occurs in two types, i.e., African cutaneous KS and African lymphadenopathic KS. Endemic KS affects young African persons, mainly from sub-Saharan Africa. This disease is a cutaneous disorder not related to HIV infection, with a more aggressive course
Immunosuppression-associated KS
This form of KS was increasing in frequency in the era of solid organ transplantation, mainly before the advent of calcineurin inhibitors. It is related to KSHV infection, either of the recipient or the graft
AIDS-associated KS or epidemic KS
This is the most aggressive form of KS that is 300 times more common in AIDS patients than in solid organ transplant recipients. It is caused by sexually transmitted KSHV

higher incidence over the general population (Hiatt et al. 2008). In AIDS-associated KS, there was also a male predominance, and a more aggressive behavior, with higher rates of visceral and disseminated disease (Hiatt et al. 2008).

The epidemic form is associated with immunosuppression-induced KSHV infection (reviews: Beral et al. 1990; Beral 1991). Sexual contacts are the most important mode of transmission of the agent, although transmission by blood and perinatally may also occur. KS became an epidemic among male homosexuals and foreshadowed the AIDS epidemic. HIV-induced immunosuppression allows KS to manifest itself in individuals who are normally asymptomatic carriers of KSHV, and this is the main reason why the combined infection with HIV and KSHV promotes the frequent development of KS in AIDS. KS is often the first manifestation of AIDS. KS rarely occurs in heterosexuals from Europe or North America, but occurs frequently among heterosexuals from Africa, because the prevalence of KSHV among the population is much higher in Africa (Beral. 1991). Up to 1998, nearly 5,000 cases of morphologically confirmed classic KS have been reported in Europe, the Mediterranean Basin, and the Americas (review: Iscovich et al. 2000). In the era of highly active antiretroviral therapy (HAART), the incidence of AIDS-KS has considerably declined, probably due to enhanced immune reconstitution and anti-KSHV-specific immune responses (review: Hengge et al. 2002). KSHV is also associated with a recently described disorder, KSHV inflammatory cytokine syndrome (KICS), characterized by systemic illness as a result of systemic, lytic KSHV infection (Tamburro et al. 2012).

By 1989, 15 % of all reported AIDS cases in the USA had KS as the primary AIDS-defining illness (Beral et al. 1990). Subsequent to the introduction of highly effective antiretroviral therapy, the incidence of AIDS-KS has declined, but the prevalence of KS remains high in untreated HIV patients, particularly in sub-Saharan Africa. Cases of KS in antiretrovirally treated HIV patients may be linked to the development of the immune reconstitution inflammatory syndrome (Bower et al. 2005; Leidner and Aboulafia 2005; Hofman and Nelson 2006). KS is the most common gastrointestinal malignancy in AIDS, seen in about 40 % of patients, and is often asymptomatic. KS may involve the stomach, the small and large bowels, and rarely the appendix (review: Arora and Goldberg 2010).

KS is a well-known complication after organ transplantation (Serraino et al. 2005; review: Lebbé et al. 2008); its incidence ranges between 2 % and 5.5 %, according to different centers worldwide. Among 1,721 Italian solid organ transplant recipients, the risk for KS was about 100 times greater compared to the general population, especially during the first 2 years after transplantation. Age older than 30 years at transplantation and a more aggressive immunosuppressive regimen were both independent risk factors for the disease (Tessari et al. 2006). KS has been observed to develop subsequent to liver transplantation (Aseni et al. 2001; review: Di Benedetto et al. 2008), also in the liver graft itself (Colina et al. 1996; Mazza et al. 1996).

Primary and Secondary Hepatic Kaposi's Sarcoma

Introduction

KS of the liver almost always evolves in the context of AIDS, and lesions restricted to the liver are very rare, most patients in fact having KS lesions elsewhere (Hasan et al. 1989; Kumar et al. 1989; Gonzalez-Lopez et al. 1996; Ikezaki et al. 2011). Liver involvement by KS, seen at autopsy, was already noted among the first five patients described by Kaposi (1872). However, there are relatively few reports documenting primary hepatic KS (Defalque et al. 1988; Luburich et al. 1990; Towers et al. 1991; Valls et al. 1991; Gottesman et al. 1993; Tanaka et al. 1995). In a patient with AIDS, ultrasonography (US) revealed several small (5–10 mm) hyperechoic nodules and dense periportal bands. Autopsy showed primary hepatic KS (Luburich et al. 1990). In the AIDS patient reported by Tanaka et al. (1995), hepatic KS was detected by US and CT, US showing multiple hyperechoic tumors

along the portal vein and CT showing low density and delayed enhancement by contrast material. Hepatic KS was confirmed in the setting of an autopsy. As the hepatic KS lesions are very hypervascular, tumor biopsy can cause massive bleeding (Gottesman et al. 1993). Primary hepatic KS occurs in the pediatric age group (Moore et al. 2008). Multiple hepatosplenic KS has been reported in an HIV-infected child (Hsieh et al. 2007).

Pathology

Tumors are usually multiple and present as red-brown, spongiform, and hemorrhagic nodules, ranging in diameter from few millimeters to more than 7 cm. Lesions with infiltrating borders occur.

The four clinical forms of KS display very similar histopathological features, with the proliferation of spindle cells considered as the KS tumor cells, associated with inflammation and neo-angiogenesis. This distinct pattern, which is also in evidence in early lesions and precursor lesions of KS, has led to a model of KS's histogenesis, including both a spindle cell and a frankly endothelial cell lineage (Russell-Jones and Wilson-Jones 1988). The KS spindle cells seem to originate from a lymphatic endothelial cell lineage (review: Gessain and Duprez 2005). KSHV is expressed in these spindle cells at all stages of the disease, with latency gene expression clearly predominating, while cells expressing markers of lytic infection form a minority. Spindle cell areas contain large numbers of slit-like spaces which lack endothelial lining but are stuffed with erythrocytes (Dorfman 1984; Holzhausen et al. 1988; Ioachim et al. 1995). Areas rich in red cells may contain hemosiderin granules. The angiomatoid areas show a capillary-like meshwork or sinusoidal patterns lined by atypical endothelial cells. In the liver tissue surrounding KS lesions, peliotic foci may develop. Ultrastructurally, part of the endothelial cells shows Weibel-Palade bodies (Holzhausen et al. 1988; Orenstein 2008), and the spindle cells show erythrophagocytosis (Orenstein 2008).

KS tumor cells are immunoreactive for the endothelial markers, CD31 and CD34 (Miettinen et al. 1994; Russell Jones et al. 1995), CD31 staining being present in endothelial cells but not spindle cells (DeYoung et al. 1995). KS endothelia are reactive for ICAM-1, thrombomodulin, and tissue factor (Zhang et al. 1994) and for CD40 (Pammer et al. 1996). The tumor cells are podoplanin/D2-40 antibody-positive (Weninger et al. 1999; Kahn et al. 2002; Fukunaga 2005; Kalof and Cooper 2009) and are reactive for another lymphatic endothelial marker, hyaluronan receptor/LYVE-1 (Xu et al. 2004). The endothelioid cells also express VEGFR3, all these findings suggesting a lymphatic endothelial cell lineage (Jussila et al. 1998; Weninger et al. 1999; Folpe et al. 2000). KS of the GIT may morphologically mimic GIST, and like GIST, a fraction of GIT-KS are reactive for CD117 (Parfitt et al. 2008).

Metastatic Hepatic Kaposi's Sarcoma and Disseminated Kaposi's Sarcoma

Liver involvement in disseminated KS is well known and also occurs in AIDS-related KS (Dhrif et al. 2007). Subsequent to cutaneous KS, hepatosplenic manifestations are well-known complications, but mainly based on autopsy findings (Gonzalez-Lopez et al. 1996). Whether these hepatosplenic manifestations represent metastatic disease or de novo disease has not been formally clarified.

References

Antman K, Chang Y (2000) Kaposi's sarcoma. N Engl J Med 342:1027–1038

Arora M, Goldberg EM (2010) Kaposi sarcoma involving the gastrointestinal tract. Gastroenterol Hepatol (NY) 6:459–462

Aseni P, Vertemati M, Minola E, Arcieri K, Bonacina E, Camozzi M, Osio C, Forti D (2001) Kaposi's sarcoma in liver transplant recipients: morphological and clinical description. Liver Transpl 7:816–823

Beral V (1991) Epidemiology of Kaposi's sarcoma. Cancer Surv 10:5–22

Beral V, Peterman TA, Berkelman RL et al (1990) Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection ? Lancet 335:123–128

Bower M, Nelson M, Young AM, Thirlwell C, Newsom-Davis T, Mandalia S, Dhillon T et al (2005) Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol 23:5224–5228

Breimer L (1994) Original description of Kaposi's sarcoma. BMJ 308:1303–1304

Brooks JJ (1986) Kaposi's sarcoma: a reversible hyperplasia. Lancet 2:1309–1310

Chang et al. (1994) Pub Med PMID 7997879

Colina F, Lopez-Rios F, Lumbreras C, Martinez-Laso J, Garcia IG, Moreno-Gonzalez E (1996) Kaposi's sarcoma developing in a liver graft. Transplantation 61:1779–1781

Defalque D, Menu Y, Matheron S, Girard PM, Nahum H (1988) Hepatic Kaposi's sarcoma and AIDS. Ultrasonographic and x-ray computed tomographic aspects (in French). J Radiol 69:617–620

DeYoung BR, Swanson PE, Argenyi ZB, Ritter JH, Fitzgibbon JF, Stahl DJ, Hoover W, Wick MR (1995) CD31 immunoreactivity in mesenchymal neoplasms of the skin and subcutis: report of 145 cases and review of putative immunohistologic markers of endothelial differentiation. J Cutan Pathol 22:215–222

Dhrif AS, Kilani B, Ammari L, Kanoun F, Tiouri H, Ben Chaaben T (2007) AIDS-associated Kaposi's sarcoma: 22 cases (in French). Tunis Med 85:494–499

Di Benedetto F, Di Sandro S, De Ruvo N, Berretta M, Masetti M, Montalti R, Ballarin R et al (2008) Kaposi's sarcoma after liver transplantation. J Cancer Res Clin Oncol 134:653–658

Dorfman RF (1984) Kaposi's sarcoma revisited. Hum Pathol 15:1013–1017

Folpe AL, Veikkola T, Valtola R, Weiss SW (2000) Vascular endothelial growth factor receptor-3 (VEGFR-3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi's sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. Mod Pathol 13:180–185

Fukunaga M (2005) Expression of D2-40 in lymphatic endothelium of normal tissues and in vascular tumors. Histopathology 46:396–402

Gessain and Duprez (2005) Pub Med PMID 16188485

Gonzalez-Lopez A, Fernandez-Martin JI, Gordillo I, Dronda F (1996) Disseminated Kaposi's sarcoma with hepatosplenic involvement in AIDS (in Spanish). Med Clin (Barc) 106:622–623

Gottesman D, Dyrszka H, Abarran J, Hilfer J (1993) AIDS-related hepatic Kaposi's sarcoma: massive bleeding following liver biopsy. Am J Gastroenterol 88:762–764

Hasan FA, Jeffers LJ, Welsh SW, Reddy KR, Schiff ER (1989) Hepatic involvement as the primary manifestation of Kaposi's sarcoma in the acquired immune deficiency syndrome. Am J Gastroenterol 84:1449–1451

Hengge UR, Ruzicka T, Tyring SK, Stutschke M, Roggendorf M, Schwartz RA, Seeber S (2002) Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 1: epidemiology, environmental predispositions, clinical manifestations, and therapy. Lancet Infect Dis 2:281–292

Hiatt KM, Nelson AM, Lichy JH, Fanburg-Smith JC (2008) Classic Kaposi sarcoma in the United States over the last two decades: a clinicopathologic and molecular study of 438 non-HIV-related Kaposi sarcoma patients with comparison to HIV-related Kaposi sarcoma. Mod Pathol 21:572–582

Hofman P, Nelson AM (2006) The pathology induced by highly active antiretroviral therapy against human immunodeficiency virus: an update. Curr Med Chem 13:3121–3132

Holzhausen HJ, Stiller D, Sachs M (1988) Morphological pathology of classic Kaposi's sarcoma. Ultrastructural studies and reflections on histogenesis (in German). Zbl Allg Pathol 134:435–447

Hsieh MC, Chiu NC, Chi H, Huang FY (2007) Hepatosplenic Kaposi's sarcoma as the initial presentation in a Taiwanese child with human immunodeficiency virus infection. Acta Paediatr Taiwan 48:84–88

Ikezaki H, Ogawa E, Murata M, Ihara T, Toyoda K, Taniai H, Otaguro S, Kaunuma M et al (2011) A case of AIDS-associated Kaposi's sarcoma with systemic invasion (in Japanese). Kansenshogaku Zasshi 85:54–58

Ioachim HL, Adsay V, Giancotti FR, Dorset B, Melamed J (1995) Kaposi's sarcoma of internal organs. Cancer 75:1376–1385

Iscovich J, Boffetta P, Franceschi S, Azizi E, Sarid R (2000) Classic Kaposi sarcoma: epidemiology and risk factors. Cancer 88:500–517

Jussila et al. (1998) Pub Med PMID 9563467

Kahn HJ, Bailey D, Marks A (2002) Monoclonal antibody D2-40, a new marker of lymphatic endothelium, reacts with Kaposi's sarcoma and a subset of angiosarcomas. Mod Pathol 15:434–440

Kalof AN, Cooper K (2009) D2-40 immunohistochemistry – so far ! Adv Anat Pathol 16:62–64

Kaposi M (1872) Idiopathisches multiples Pigmentsarcom der Haut. Arch Dermatol Res 4:265–273

Kumar S, Schade RR, Peel R, Lehar SC, Joyce R, Van Thiel DH (1989) Kaposi's sarcoma with visceral involvement in a young heterosexual male without evidence of the acquired immune deficiency syndrome. Am J Gastroenterol 84:318–321

Lebbé C, Legendre C, Francès C (2008) Kaposi sarcoma in transplantation. Transplant Rev (Orlando) 22:252–261

Leidner RS, Aboulafia DM (2005) Recrudescent Kaposi's sarcoma after initiation of HAART: a manifestation of immune reconstitution syndrome. AIDS Patient Care STDS 19:635–644

Luburich P, Bru C, Ayuso MC, Azon A, Condom E (1990) Hepatic Kaposi sarcoma in AIDS: US and CT findings. Radiology 175:172–174

Mazza D, Gugenheim J, Toouli J, Baldini E, Mouiel J (1996) Hepatic localisation of an aggressive Kaposi's sarcoma leading to liver graft failure. Gastroenterol Clin Biol 20:1136

Miettinen et al. (1994) PubMed PMID 7512718

Moore PS, Gao SJ, Dominguez G, Cesarman E, Lungu O, Knowles DM, Garber R et al (1996) Primary

characterization of a herpesvirus agent associated with Kaposi's sarcoma. J Virol 70:549–558
Moore SW, Davidson A, Hadley GP, Kruger M, Poole J, Stones D, Wainwright L, Wessels G (2008) Malignant liver tumors in South African children: a national audit. World J Surg 32:1389–1395
Orenstein JM (2008) Ultrastructure of Kaposi sarcoma. Ultrastruct Pathol 32:211–220
Orfanos CE, Husak R, Wolfer U, Garbe C (1995) Kaposi's sarcoma: a reevaluation. Recent Results Cancer Res 139:275–296
Pammer et al. (1996) Pub Med PMID 8623911
Parfitt JR, Rodriguez-Justo M, Feakins R, Novelli MR (2008) Gastrointestinal Kaposi's sarcoma: CD117 expression and the potential for misdiagnosis as gastrointestinal stromal tumour. Histopathology 52:816–823
Russell Jones R, Orchard G, Zelger B, Wilson Jones E (1995) Immunostaining for CD31 and CD34 in Kaposi sarcoma. J Clin Pathol 48:1011–1016
Russell-Jones R, Wilson-Jones E (1988) The histogenesis of Kaposi's sarcoma. Am J Dermatopathol 8:369–370
Schalling et al .(1995) Pub Med PMID 7585156
Serraino D, Angeletti C, Carrieri MP, Longo B, Piche M, Piselli P, Arbustini E, Burra P et al (2005) Kaposi's sarcoma in transplant and HIV-infected patients: an epidemiologic study in Italy and France. Transplantation 80:1699–1704
Szajerka and Jablecki (2007) Pub Med PMID 18219366
Tamburro KM, Yang D, Poisson J, Fedoriw Y, Roy D, Lucas A, Sin SH, Malouf N et al (2012) Vironome of Kaposi sarcoma associated herpesvirus-inflammatory cytokine syndrome in an AIDS patient reveals co-infection of human herpesvirus 8 and human herpesvirus 6A. Virology 422:220–225
Tanaka T, Masuda G, Takechi A, Kobayashi H, Tanaka S, Koike M, Hattori N (1995) A case of AIDS-related hepatic Kaposi's sarcoma. J Gastroenterol 30:268–272
Tessari G, Naldi L, Boschiero L, Cordiano C, Piaserico S, Fortina AB, Cerimele D et al (2006) Incidence and clinical predictors of Kaposi's sarcoma among 1721 Italian solid organ transplant recipients: a multicenter study. Eur J Dermatol 16:553–557
Towers MJ, Withers CE, Rachlis AR, Pappas SC, Kolin A (1991) Ultrasound diagnosis of hepatic Kaposi sarcoma. J Ultrasound Med 10:701–703
Valls C, Canas C, Turell LG, Pruna X (1991) Hepatosplenic AIDS-related Kaposi's sarcoma. Gastrointest Radiol 16:342–344
Weninger W, Partanen TA, Breiteneder-Geleff S, Mayer C, Kowalski H, Mildner M et al (1999) Expression of vascular endothelial growth factor receptor-3 and podoplanin suggests a lymphatic endothelial cell origin of Kaposi's sarcoma tumor cells. Lab Investig 79:243–251
Xu H, Edwards JR, Espinosa O, Banerji S, Jackson DG, Athanasou NA (2004) Expression of a lymphatic endothelial cell marker in benign and malignant vascular tumors. Hum Pathol 35:857–861
Zantinga AR, Coppes MJ (1996) Moriz Kaposi (1837–1902): great master of the Viennese school of dermatology. Med Pediatr Oncol 27:128–131
Zhang et al.(1994) Pub med PMID 7507301

Glomus Tumor and Glomangiopericytic Tumors of the Liver

57

ICD-O code 8711/0

Contents

Abstract

Glomus tumor is a distinct neoplasm derived from pericyte-like cells normally present in neuromyoarterial structures with the morphology of specialized arteriovenous anastomosis in the skin. These cells normally form glomus bodies involved in thermoregulation and control of hemodynamic features. Glomus tumors are usually benign neoplasms that usually occur in the skin in the vasculature of inner organs and exceptionally in the liver. A distinct neoplasm originating from perivascular myoid cells is termed myopericytoma, glomangiopericytoma, and myofibroma. Most of these unusual neoplasms develop in soft tissues and the skin of children and mid-adult individuals. The tumors very rarely occur in the hepatobiliary tract and the periampullary region, sometimes associated with Epstein-Barr virus infection.

Glomus Tumor

Introduction

Glomus tumors derived from a distinct pericyte-like cell type normally present in a distinct neuromyoarterial structure with the morphology of a specialized arteriovenous anastomosis and involve in the regulation of hemodynamic mechanisms, in particular thermal regulation (glomus body or glomus organ; organ of Hoyer and

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_57

Grosser). Glomus bodies chiefly occur in the subungual dermis and in the lateral areas of the digits, in the palm, and in the precoccygeal soft tissue (glomus coccygeum), but may also occur in the vascular system of internal organs. Normally, the glomus body has an afferent arteriole branching into two or four preglomic arterioles, which blend into a distinct segment with an irregular lumen and harboring the AV anastomosis proper, the canal of Suquet and Hoyer, which then drains into collecting veins. Glomangiomas derived from these specialized organs of skin soft tissue are also termed glomuvenous malformations (Boon et al. 2004; Solovan et al. 2012). Syndromatic, hereditary multiple glomuvenous malformations (familial glomangiomas) are caused by mutations of glomulin, a protein that inhibits cullin-RING ligases (Brouillard et al. 2005; Hristova et al. 2012; Tron et al. 2012). The term glomus tumor was formerly employed to denote tumors arising from sensor cells of glomera such as the glomus jugulare, but these neoplasms are now termed paraganglioma. Glomus tumors or glomangiomas are neoplasms with a usually benign course, albeit malignant variants also occur (Folpe et al. 2001). Visceral glomus tumors have been observed in the lung, small intestine, colon, kidney, and liver.

Glomus Tumor/Glomangioma of the Liver

Primary hepatic glomus tumors (glomangiomas) are very rare neoplasms (Gassel et al. 2002; Kenn et al. 2002; Jaiswal et al. 2004; Amoueian et al. 2011; Geramizadeh et al. 2011; Kihara et al. 2014). The clinical presentation is nonspecific, with upper abdominal discomfort or pain due to a mass effect. The size of hepatic glomus tumors at presentation varies considerably. In one patient, glomangioma of the liver presented as a 4.5-cm subcapsular tumor in a 61-year-old male patient (Gassel et al. 2002). In an another case, a 50-year-old woman showed a large, hypervascular, and cystic lesion of 15 cm diameter, suggesting the presence of hepatic vascular tumor (Geramizadeh et al. 2011). In other patients, the tumor appeared as a cystic hepatic mass (Amoueian et al. 2011; Kihara et al. 2014).

Histologically, hepatic glomus tumors are composed of small uniform round to oval cells, separated by thin fibrovascular stromal components. The cytoplasm is slightly eosinophilic, with indistinct borders, and nuclei show an open chromatin. Immunohistochemically, the tumor cells are reactive for vimentin, CD34, and smooth muscle actin (Amoueian et al. 2011; Geramizadeh et al. 2011). In one case, tumor cells were focally positive for calponin (Jaiswal et al. 2004).

Differential Diagnosis

A rare differential diagnosis is liver metastases of malignant glomus tumor (Dasaev and Stepanov 1985; Brathwaite and Poppiti 1996).

Hepatic Myopericytoma, Glomangiopericytoma, and Myofibroma

Introduction

Myopericytoma (MPC) is term proposed to describe a group of neoplasms that originate from perivascular myoid cells. These tumors show a range of histologic growth patterns and mainly occur in the soft tissues (Folpe AL 2002; Dray et al. 2006; Mentzel et al. 2006; Fisher 2013). In 1998, Granter and coworkers formally used the term MPC and defined a spectrum of tumors showing perivascular myoid differentiation, comprising myofibromatosis in adults, myofibroma (MF), glomangiopericytoma (GPC), and myopericytoma (Granter et al. 1998). The entities have been endorsed by the WHO classification, where myopericytoma and myofibroma are listed as separate entities and glomangiopericytoma as a subtype of myopericytoma (Folpe AL 2002). The cell lineages involved in this tumor group share features of both smooth muscle cells and glomus cells, but the cell of

origin of these lineages and their eventual relation to the perivascular epithelioid cell (PEC) are still unknown.

Clinical and Imaging Features

MPC occurs mainly in childhood and to mid-adult years, with a male predominance (Folpe AL 2002; Dray et al. 2006). The vast majority of the tumors arise in the soft tissues and the skin (Mentzel et al. 2006), but few intracranial cases have been observed (Rousseau et al. 2005), and there are patients who presented with solitary or multiple pulmonary nodules (Cao et al. 2009; Lau et al. 2009; Song et al. 2012), tumor of the heart (Orlandi et al. 2004), myopericytoma of the kidney (Lau et al. 2010; Dhingra et al. 2012), and parotid gland (Kuczkowski et al. 2010). The MPC group of tumors is usually benign lesions, but malignant variants of MPC have been reported (McMenamin and Fletcher 2002). Part of the MPCs have been shown to develop in conjunction with EBV infection in patients with AIDS (Calderaro et al. 2008; Lau et al. 2009).

MPC, GMP, and MF of the Hepatobiliary Tract

Calderaro and coworkers described multifocal MPC occurring in a 34-year-old male patient with AIDS and EBV infection, the tumor being located intracranially, in the spine, and in the liver. Tumor cells were positive for EBV by the use of EBER (Calderaro et al. 2008). In a second patient, a 42-year-old man with HIV infection, the neoplastic process started in the orolaryngeal mucosa, followed by tumor manifestations in the frontal lobe of the brain and in the liver. Again, the tumor was EBV positive (Lau et al. 2009). Periampullary EBV-associated myopericytoma was reported in a patient with AIDS who presented with obstructive jaundice. Based on the presence of cellular pleomorphism and increased mitotic activity, a malignant variant was favored (Ramdial et al. 2011).

General Histopathology

Myopericytoma

MPC is characterized by plump spindle cells, some with a myofibroblast appearance, arranged in sheets and fascicles and focally arranged around blood vessels in a concentric pattern, resulting in a hemangiopericytoma-like vascular pattern. The perivascular cells may have a glomoid appearance. The mitotic count is low (<1 per 10 high power fields). Some of the spindle cells exhibit features resembling smooth muscle cells, albeit with less cytoplasmic eosinophilia. Part of the tumors show hyalinization and hyalinized nodules protruding into vascular spaces similar to the pattern seen in myofibromatosis (Dray et al. 2006). Immunohistochemically, the cells are positive for vimentin, smooth muscle actin, and, in a patchy pattern, for desmin, but usually not for vimentin (Dray et al. 2006). The tumor cells are not reactive for HMB45, S-100 protein, CD99, or CD34.

Glomangiopericytoma

Glomangiopericytoma is a rare tumor that almost only occurs in the sinonasal region, mid-facial structures, and the pterygopalatine fossa (sinonasal glomangiopericytoma, sinonasal-type hemangiopericytoma; Thompson 2004). It is histologically characterized by pericytes and myoid cells surrounding a dense network of capillary-type vascular channels (Arpaci et al. 2012).

Myofibroma

The histology of myofibroma reveals an overlap with that of myopericytoma, but a biphasic zonation pattern composed of fascicles of spindle-shaped cells with abundant eosinophilic cytoplasm that resemble smooth muscle cells in the peripheral zones of the lesion prevails. In the central areas, one notes clusters of more primitive-looking, round to polygonal, or small spindle cells with less and amphophilic cytoplasm and some nuclear pleomorphism. These cells were typically arranged in a hemangiopericytoma-like vascular pattern. Hyalinized areas with nodular

intravascular bulging are present. The immunohistochemical phenotype is similar to that of MPC, but desmin staining is less prominent.

References

Amoueian S, Meibodi NT, Tavoosi H, Ekramifard VR, Attaranzadeh A, Montazer M (2011) Primary glomus tumor of the liver. Arch Iran Med 14:294–295

Arpaci RB, Kara T, Vayisoglu Y, Özgur A, Özcan C (2012) Sinonasal glomangiopericytoma. J Craniofac Surg 23:1194–1196

Boon LM, Mulliken JB, Enjolars O, Vikkula M (2004) Glomuvenous malformation (glomangioma) and venous malformation: distinct clinicopathologic and genetic entities. Arch Dermatol 140:971–976

Brathwaite and Poppiti 1996. http://www.ncbi.nlm.nih.gov/pubmed/8554113

Brouillard P, Ghassibé M, Penington A, Boon LM, Dompmartin A, Temple IK, Cordisco M et al (2005) Four common glomulin mutations cause two thirds of glomuvenous malformations ("familial glomangiomas"): evidence for a founder effect. J Med Genet 42:e13

Calderaro J, Polivka M, Gallien S, Bertheau P, Thiebault JB, Molina JM, Gray F (2008) Multifocal Epstein Barr virus (EBV)-associated myopericytoma in a patient with AIDS. Neuropathol Appl Neurobiol 34:115–117

Cao JH, Xu JP, Li YC, Lai J, Li Q (2009) Pulmonary myopericytoma: a case report and review of the literature. Chin Med J (Engl) 122:755–757

Dasaev and Stepanov 1985. http://www.ncbi.nlm.nih.gov/pubmed/2987610

Dhingra S, Ayala A, Chai H, Moreno V, Zhao B (2012) Renal myopericytoma: case report and review of literature. Arch Pathol Lab Med 136:563–566

Dray MS, McCarthy SW, Palmer AA, Bonar SF, Stalley PD, Marjoniemi V, Millar E et al (2006) Myopericytoma: a unifying term for a spectrum of tumours that show overlapping features with myofibroma. A review of 14 cases. J Clin Pathol 59:67–73

Fisher C (2013) Unusual myoid, perivascular, and postradiation lesions, with emphasis on atypical vascular lesion, postradiation cutaneous angiosarcoma, myoepithelial tumors, myopericytoma, and perivascular epithelioid cell tumor. Semin Diagn Pathol 30:73–84

Folpe AL (2002) Glomus tumours. In: Fletcher CD, Unni KK, Mertens F (eds), Pericytic (perivascular) tumours (chapter 5), Pathology and Genetics of Tumours of soft Tissue and Bone. World Health Organisation classification of tumours, IARCC Press, Lyon, pp 135–139

Folpe AL, Fanburg-Smith JC, Miettinen M, Weiss SW (2001) Atypical and malignant glomus tumors: analysis of 52 cases, with a proposal for the reclassification of glomus tumors. Am J Surg Pathol 25:1–12

Gassel HJ, Klein I, Timmermann W, Kenn W, Gassel AM, Thiede A (2002) Presentation of an unusual benign liver tumor: primary hepatic glomangioma. Scand J Gastroenterol 37:1237–1240

Geramizadeh B, Nikehblaian S, Shamsaifar A, Kazemi K, Tavoosi H, Sefidbakht S et al (2011) Primary glomus tumor of the liver: a rare case report and review of the literature. Indian J Pathol Microbiol 54:584–587

Granter SR, Badizadegan K, Fletcher CD (1998) Myofibromatosis in adults, glomangiopericytoma, and myopericytoma: a spectrum of tumors showing perivascular myoid differentiation. Am J Surg Pathol 22:513–525

Hristova VA, Stringer DK, Weissman AM (2012) Cullin RING ligases: glommed by glomulin. Mol Cell 47:331–332

Jaiswal VR, Champine JG, Sharma S, Molberg KH (2004) Primary glomangioma of the liver: a case report and review of the literature. Arch Pathol Lab Med 128: e46–e49

Kenn W, Klein I, Gassel HJ, Gattenloehner S, Gassel AM, Hahn D (2002) Primary glomangioma of the liver: imaging findings. Abdom Imaging 27:716–719

Kihara A, Fukushima J, Horiuchi H (2014) Glomus tumor of the liver presenting as a cystic lesion. Pathol Int 64:295–297

Kuczkowski J, Rzepko R, Szurwska E (2010) Myopericytoma of the parotid gland – a pathological conundrum. J Craniomaxillofac Surg 38:595–596

Lau PP, Wong OK, Lui PC, Cheung OY, Ho LC, Wong WC, To KF, Chan JK (2009) Myopericytoma in patients with AIDS: a new class of Epstein-Barr virus-associated tumor. Am J Surg Pathol 33:1666–1672

Lau SK, Klein R, Jiang Z, Weiss LM, Chu PG (2010) Myopericytoma of the kidney. Hum Pathol 41:1500–1504

McMenamin ME, Fletcher CD (2002) Malignant myopericytoma: expanding the spectrum of tumours with myopericytic differentiation. Histopathology 41:450–460

Mentzel T, Dei Tos AP, Sapi Z, Kutzner H (2006) Myopericytoma of skin and soft tissues: clinicopathologic and immunohistochemical study of 54 cases. Am J Surg Pathol 30:104–113

Orlandi A, Ferlosio A, Ciucci A, Pellgrino A, Spagnoli LG (2004) Unusual cardiac tumour with perivascular myoid differentiation: a case report. J Clin Pathol 57:1338–1340

Ramdial PK, Sing Y, Deonarain J, Singh B, Allopi L, Moodley P (2011) Periampullary Epstein-Barr virus-associated myopericytoma. Hum Pathol 42:1348–1354

Rousseau A, Kujas M, van Effenterre R, Boch AL, Carpentier A, Leroy JP, Poirier J (2005) Primary intracranial myopericytoma: report of three cases and review of the literature. Neuropathol Appl Neurobiol 31:641–648

Solovan C, Chiticariu E, Beinsan D, Zurac S, Baderca F (2012) Multiple disseminated glomuvenous

malformations: do we know enough ? Rom J Morphol Embryol 53:1077–1080

Song XL, Sun XY, Zhang GL, Yu YW, Wang CH (2012) Myopericytoma presenting as multiple pulmonary nodules. Intern Med 51:639–642

Thompson LD (2004) Sinonasal tract glomangiopericytoma (hemangiopericytoma). Ear Nose Throat 83:807

Tron AE, Arai T, Duda DM, Kuwabara H, Olszewski JL, Fujiwara Y, Bahamon BN et al (2012) The glomuvenous malformation protein glomulin binds Rbx1 and regulates cullin RING ligase-mediated turnover of Fbw7. Mol Cell 46:67–78

Tumor-Like Vascular Malformations 58

Contents

Abstract

Vascular malformations represent a broad and complex spectrum of in part congenital and tumor-like conditions that occur either as systemic disorders or organ-specific pathologies. Hemodynamically, vascular malformations are classified as slow flow, high flow, and mixed malformations. The slow-flow disorders, Klippel-Trenaunay syndrome, Sturge-Weber syndrome, and unilateral nevoid telangiectatic syndrome, rarely involve the liver, where they manifest as abnormal vessels, mainly venous abnormalities, angiectases, and angioma-like lesions, sometimes associated with focal nodular hyperplasia or related changes. A distinct group of disorders is congenital and acquired venovenous malformations of the liver and patent ductus venosus, resulting in portosystemic shunts and associated parenchymal changes.

Introduction

Several vascular lesions are currently classified as malformations, although a generally accepted classification has still to be awaited, owing to the lack of criteria, the use of eponymic terms, and the problems arising when defining what a malformation is (Breugem et al. 2001). Of importance is that a distinction has to be made between blood vessel tumors/neoplasms and vascular malformations (Mulliken and Glowacki 1982; Mulliken 1997), although the latter may clinically

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_58

produce a tumor-like tissue. However, the growth of vascular malformations is commensurate with the growth of the patient (Cohen 2000), what is clearly not the case with neoplasms. The biologic classification of vascular malformations is based on the observation that they may predominantly involve a single type of channel anomaly (arterial, capillary, lymphatic, venous) or that they come as complex/combined lesions (Mulliken 1993; Cohen 2000). The Mulliken classification, which relates to clinical presentation and cellular features of the lesions, has been accepted by the International Society for the Study of Vascular Anomalies (ISSVA; Enjolras and Mulliken 1997; Cohen 2000). In regard to hemodynamic features and consequences, vascular malformations and vasomalformative syndromes are classified into slow-flow or high-flow disorders (review: Garzon et al. 2007). Slow-flow or high-flow disorders with known structural involvement of the liver are listed in Table 1.

Molecular Features

Recent progress relating to the identification of molecular mechanisms operational in vascular morphogenesis had its impact on the understanding of vascular malformations, and this will also modify our view of those lesions developing in the liver (reviews: Timur et al. 2005; Wang 2005; Dompmartin et al. 2010; Frigerio et al. 2012; Table 2). Here, we briefly discuss those malformations which can be accepted as such, hepatic lesions evolving in the setting of hereditary hemorrhagic telangiectasia being addressed in a separate chapter.

Table 1 Slow-flow and high-flow vascular malformations and mixed malformations, with liver involvement

Slow-flow disorders
Klippel-Trenaunay syndrome
Sturge-Weber syndrome
Congenital portosystemic venous shunts
Unilateral nevoid telangiectatic syndrome
Adams-Oliver syndrome
Rubinstein-Taybi syndrome
Proteus syndrome
High-flow disorders
Capillary malformation-arteriovenous malformation syndrome
Parkes Weber syndrome
Malformation syndromes with venous, lymphatic, or mixed features
Blue rubber bleb nevus syndrome
Maffucci syndrome
Gorham-Stout syndrome

Extracranial Non-syndromatic Vascular Malformations

Vascular malformations located to the liver are much less common than hemangiomas and may manifest at an early age (Boon et al. 1996; Burrows et al. 2001). Arteriovenous malformations (AVM) sometimes result in congestive heart failure already in the newborn. AVM observed in later childhood are usually seen in the context of hereditary hemorrhagic telangiectasia (HHT), which is discussed in more detail below. The spectrum of lesions is relatively broad and ranges from arterioportal fistulas to complex and shunting anomalies of portal and hepatic veins, to portomesenteric venous malformations, and to pure venous and venolymphatic malformations. Most of the intrahepatic arterioportal fistulas

Table 2 Molecular features of vascular malformations and associated syndromes

Malformation	Molecule/gene involved
Klippel-Trenaunay syndrome	AGGF1
Capillary malformation syndrome	RASA1
Rhodoid nevus	RASA1
Sporadic Sturge-Weber syndrome	RASA1
Cutaneous/mucosal venous malformations	TIE2
Hereditary hemorrhagic telangiectasia	ENG, ACVRLK1, MADH4
CADASIL	Notch3
Cerebral cavernous malformations	KRIT1, MGC4607, PDCD10
Coats' disease	NDP
Proteus syndrome	PTEN

(arterioportal fistula syndrome) are sporadic (Lu et al. 1996; Vauthey et al. 1997), but they are also known to occur in HHT and Ehlers-Danlos syndromes. The fistulas can result in portal hypertension (Billing and Jamieson 1997), in heart failure, and in intestinal ischemia (Vauthey et al. 1997). A congenital presentation was detected in only 13 % in a series of 76 patients (Vauthey et al. 1997). Most congenital arterioportal fistulas present with a large intrahepatic varix, sometimes with multiple connecting arteries (Burrows et al. 2001). Owing to shunt-induced shearing stress, intimal damage of the venous part with subsequent portal vein thrombosis may ensue (Maeda et al. 1997). At imaging, the lesions may be confused with hepatic hemangiomas, which can show arterioportal shunting (Kim et al. 2001). Portovenous shunting is known to occur in infantile hepatic hemangiomas and in galactosemia (Ono et al. 1998), but may also manifest as isolated portovenous fistulas. It can develop in Osler-Weber-Rendu disease (Matsuo et al. 2001). Pure venous hepatic anomalies are mostly observed in the blue rubber bleb nevus syndrome, which is discussed below.

Klippel-Trenaunay Syndrome (KTS)

KTS (synonym: angioosteohypertrophy syndrome; OMIM 149000; Vollmar 1974), a rare so-called mesodermal phakomatosis, has been defined to consist of combined vascular malformations of capillary, venous, and lymphatic vessels and varicosities of unusual distribution observed during infancy and childhood and has an early onset (in particular the lateral venous anomaly) and limb enlargement (Klippel and Trenaunay 1900; in the original article not spelt with an é; Servelle 1985; Jacob et al. 1998; Cohen 2000, 2002; Breugem et al. 2001).

Although several reports bring KTS together with Parkes Weber syndrome (frequently written as Parkes-Weber syndrome, which is not correct: Frederick Parkes Weber, 1863–1962, is written without a hyphen) and even combine the eponyms within the designation of a syndrome (e.g., Klippel-Trenaunay-Weber syndrome), it had been emphasized that KTS and Parkes Weber syndrome are two different entities, the latter being a high-flow malformation and always manifesting arteriovenous fistulas (not present in KTS) and lacking the lymph vessel involvement typical for KTS. There is no bona fide overlap between KTS and Sturge-Weber syndrome (Cohen 2000; Jay 2000), although features of Sturge-Weber syndrome can occur in combination with KTS and phakomatosis pigmentovascularis (Chhajed et al. 2010; Finklea et al. 2010). The study of such combination within a familial setting has led to the view that KTS and SWS might represent different manifestations of the same affliction (Pereira de Godoy and Fett-Conte 2010). KTS occurs sporadically or as a hereditary disorder linked to a locus on chromosome 8q22.3 (Lindenauer 1965; Cohen 2002), and males and females are equally affected. In KTS associated with a genetic defect, variants of the angiogenic factor AGGF1 gene have been found (Tian et al. 2004; Hu et al. 2008). Experimentally, AGGF1 is involved in establishing venous identity in zebra fish embryos, overexpression of AGGF1 leads to increased angiogenesis and increased lumen diameter of veins via an AKT pathway, whereas knockdown of AGGF1 resulted in defective vasculogenesis and angiogenesis, with a loss of venous identity (Chen et al. 2013). The expression of AGGF1 is regulated GATA1 (Fan et al. 2009).

Hepatic manifestations of Klippel-Trenaunay syndrome reported so far are sparse and, in part, difficult to judge because it is not always clear whether the patients in fact suffered from KTS. Silent hepatic manifestations of KTS may present as multiple low-attenuation areas in the liver at imaging, representing abnormal vascular structures (Fig. 1; Jafri et al. 1983). A patient with KTS developed multiple focal nodular hyperplasia/FNH (Bathgate et al. 1999), lesions known to be caused by a hepatic circulation disorder. Other alterations comprise venous anomalies, with large abdominal veins draining from the dome of the liver into the hepatic veins (Haber et al. 1995). Such anomalies may result in portal hypertension (Grundfest-Broniatowski et al. 1982). Visceral hemangiomas in KTS have been reported,

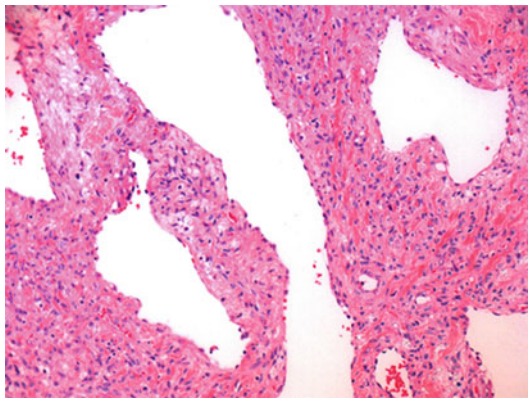

Fig. 1 Thick-walled dilated vascular anastomoses seen in hepatic manifestations of Klippel-Trenaunay syndrome (hematoxylin and eosin stain)

including the liver (Alpay et al. 1996). In patients with KTS, focal nodular hyperplasia of the liver has been observed (Haber et al. 1995; Bathgate et al. 1999). Similar to other circulation disorders of the liver, this change may develop in response to an altered intrahepatic blood distribution owing to vascular anomalies.

Sturge-Weber Syndrome

Sturge-Weber syndrome (SWS, encephalofacial angiomatosis, craniofacial angiomatosis, OMIM 185300) is characterized by an intracranial vascular abnormality, leptomeningeal angiomatosis, usually involving the occipital and posterior parietal lobes, associated with facial cutaneous vascular malformations (port-wine stains), seizures, and glaucoma. Leptomeningeal angiomatosis can cause a derangement of superficial cortical perfusion, with laminar cortical necrosis and calcifications (Baselga 2004; Manivannan et al. 2012). A variant of SWS is Shapiro Shulman syndrome, characterized by cutaneous vascular nevi, abnormal intracranial venous drainage, and hydrocephalus (Prats Viñas et al. 2011). Sporadic SWS showed a RASA1 mutation (Zhou et al. 2011). There are few reports of manifestations of SWS outside the classical manifestation sites. In very rare instances, SWS is associated with hepatic angiomas, sometimes extensively (Billson and Gillam 1984). A persistent hepatic venous plexus has been found in a patient with SWS (Gajinov et al. 2008), characterized by three additional vessels arising from the inferior vena cava, circulating between liver segments, forming a common trunk in the suprahepatic region that flowed into the right atrium.

Unilateral Nevoid Telangiectatic (Telangiectasia) Syndrome (UNTS)

UNTS was first described in 1899 and is chiefly characterized by a dermatomal distribution of telangiectases developing mostly in the upper and middle dermis. The disorder may be congenital, but in other instances, it is related, e.g., to high estrogen levels, UNTS occurring in pregnancy, during puberty, and in chronic liver disease (Uhlin and McCarty 1983; Wilken 1984). Rarely, visceral manifestations in UNTS have been described, one patient exhibiting gastric involvement with hemorrhages (Anderton and Smith 1975). Liver involvement seems to occur in the form of multiple dilated vascular channels associated with portal fibrosis, suggesting that UNTS may produce an abnormal hepatic vascular morphogenesis (Capron et al. 1981).

Congenital and Acquired Venovenous Malformations of the Liver

Congenital extrahepatic portosystemic shunt (CEPS) was first described by John Abernethy in 1793 (Abernethy 1793). This is the reason why extrahepatic portosystemic shunts are also termed Abernethy malformations (reviews: Gallego et al. 2004; Stringer 2008). Morgan and Superina (1994) classified extrahepatic portosystemic shunts into two types (Table 3). The more common CEPS type I is the side-to-end anastomosis or congenital absence of the portal vein, resulting in complete diversion of portal blood into the vena cava inferior. The malformations are further subdivided into those in which the superior mesenteric and splenic veins end up separately at the systemic veins and those in which these two

Table 3 Classification of venovenous malformations of the liver

***Extrahepatic portosystemic shunts* (*Morgan-Superina classification and Abernethy classification*)**
Abernethy type I
Abernethy type II
***Intrahepatic portosystemic shunts* (*Park* et al. *classification*)**
Type 1
Single large channel connects the right portal vein to the IVC
Type 2
Localized peripheral shunt in which one or more communications exist in a single hepatic segment
Type 3
Portosystemic shunt through a venous aneurysm
Type 4
Multiple communications between peripheral portal and hepatic veins in several segments
Persistent ductus venosus
***Absent ductus venosus* (*agenesis of ductus venosus*)**

venous systems join to form a common trunk that ends up at the inferior vena cava, the iliac veins, or the right atrium. Type I is usually observed in girls and is often associated with other malformations, including cardiac abnormalities, malrotation, and polysplenia. CEPS type II or side-to-side anastomosis with portal vein supply partially conserved has no gender predilection and no associated malformations (Witters et al. 2008). Pathogenetically, it has been suggested that congenital absence of the portal vein is attributed to an excessive involution of the peri-intestinal vitelline venous loop or to failure of vitelline veins to generate anastomoses with umbilical veins or hepatic sinusoids. Both forms of extrahepatic CEPS have a number of hepatic associations, the most common being nodular hyperplastic lesions of parenchyma (Yonemitsu et al. 2000; Murray et al. 2003), clear-cut nodular regenerative hyperplasia (Peker et al. 2009), and liver cell adenomas (Kawakatsu et al. 1994). The patients can show liver calcifications (Avila et al. 2006).

Congenital intrahepatic portosystemic shunts are defined as abnormal intrahepatic connections between branches of the portal vein and the hepatic veins (Jabra and Taylor 1991; Kakitsubata et al. 1996; Caiulo et al. 2001; Senocak et al. 2008; Bernard et al. 2012). These intrahepatic shunts have been classified into four morphologic types by Park and coworkers (1990), as summarized in Table 3.

Acquired (spontaneous) intrahepatic portosystemic venous shunts (SIPSVS) are relatively rare lesions of unknown etiology that are characterized by communications between portal and hepatic veins, mostly occur in cirrhotic livers, and can undergo aneurysmatical change. Patients may suffer from shunt-induced hepatic encephalopathy and/or glucoregulation problems (Villar et al. 2000; Yamagami et al. 2000; Oguz et al. 2003; Pocha and Mallakkal 2004; Filik and Boyacioglu 2006). Intrahepatic portosystemic shunts can be associated with focal liver lesions, e.g., multiple hemangioma-like lesions (Matsumoto et al. 1990). Focal nodular hyperplasia (FNH) of the liver has also been found in the setting of intrahepatic porto-portal communication, characterized by the absence of the horizontal segment of the left portal vein with portal supply between the anterior segmental branch of the right portal vein and the umbilical portion of the left portal vein (Mignon et al. 1996).

Irrespective of the cause and the anatomical differences, any portosystemic shunt can result in atrophic-hyperplastic changes (atrophy-hypertrophy complex/AHC of the liver) of the liver, often with formation of nodular lesions. Hyperplastic liver nodules were found following portal systemic shunt surgery (Guérin et al. 2009). Experimentally, portocaval anastomosis in the rat caused hyperplastic liver nodules (Weinbren and Washington 1976), these nodules in rats developing in the background of an atrophic liver (Dubuisson et al. 1985).

Patent Ductus Venosus as a Cause of Intrahepatic Portosystemic Shunt

The ductus venosus (DV; Ductus venosus Arantii; discovered by Giulio Cesare Aranzio, Bologna, 1530–1589) is a transitory vascular channel that shunts approximately half of the blood flow of the fetal umbilical vein directly into the inferior vena cava and oxygenated blood

from the placenta, thus bypassing the liver. The DV naturally closes during the first week of life in the majority of full-term neonates. In an ultrasonographic study of 50 healthy neonates, the DV was closed in 94 % of the infants before day 3, whereas the DV was closed in only 12 % at the same time, in 76 % before day 7, and in all infants before day 18 (Fugelseth et al. 1997). The DV shows a delayed closure in preterm infants, with no significant correlation to the closure of the ductus arteriosus or the condition of the infant (Fugelseth et al. 1998). After closure of DV, a fibrous strand called ligamentum venosum remains, usually attached to the left branch of the portal vein, and it may be continuous with the ligamentum teres hepatis. Patent (persistent) ductus venosus (PDV) is a very rare condition characterized by persistence of a large shunt connecting the portal vein with hepatic veins (Zientarski 1976; Nagano et al. 1999). Congenital intrahepatic portosystemic shunt due to PDV can cause progressive liver dysfunction with hepatic steatosis (Uchino et al. 1996). In adult patients with persistent DV, partial nodular transformation of the liver was found (Wanless et al. 1985), probably a hyperplastic reaction similar to that observed in other shunt situations.

Absence of the Ductus Venosus as a Cause of Portosystemic Venous Shunts

Agenesis of the DV is a rare condition that causes extra- or intrahepatic venous shunts and is often associated with hydrops and cardiac and extracardiac anomalies (Krutsay 1959; Contratti et al. 2001; Langman et al. 2001; Berg et al. 2006; Acherman et al. 2007). The absence of DV may be a feature of Down syndrome (Pipitone et al. 2003). Among 23 fetuses studied by Doppler techniques, 19 fetuses with agenesis of DV showed that the umbilical vein connected to the portal sinus, while the remaining four fetuses had extrahepatic umbilical venous drainage (Berg et al. 2006). Three main patterns of abnormal venous circulation were found, i.e., (1) umbilical vein bypassing the liver and connecting directly to right atrium (46 %); (2) umbilical vein bypassing the liver and connecting to the inferior vena cava, mostly through one of the iliac veins (25 %); and (3) umbilical vein connecting to the portal circulation without giving rise to a ductus venosus (21 %; Contratti et al. 2001). In the extrahepatic shunt variant, the development of the portal venous system depends on the size of the shunt. If the shunt is narrow, the portal system will develop normally. In contrast, a wide shunt is associated with hypoplasia or the absence of the portal system, hepatic dysfunction, tricuspid regurgitation, and poor outcome (Shen et al. 2011). The abnormal venous flow in DV agenesis is sometimes associated with hepatic vascular wall changes, including proliferation of the hepatic arterioles with reduction of portal venules (Langman et al. 2001).

Adams-Oliver Syndrome

Adams-Oliver syndrome (OMIM 100300) is a rare genetic disorder assigned to chromosome locus 3q13.33 and characterized by congenital absence of skin/aplasia cutis congenita (in particular scalp vertex defects), transverse limb defects, congenital cardiac malformations, and cutis marmorata telangiectatica congenita. It is suggested that the disorder results from an early ontogenetic vascular abnormality. There is an association between the syndrome and portal hypertension due to hepatoportal sclerosis and extrahepatic portal vein obstruction, associated with nodular regenerative hyperplasia (Girard et al. 2005; Silva et al. 2012).

Proteus Syndrome

Proteus syndrome (OMIM 176920) is a highly variable, severe malformative overgrowth disorder characterized by disproportionate overgrowth of body parts (the phenotype of the “elephant man”), connective tissue nevi, epidermal nevi, exostoses and hyperostoses, visceral hamartomas

and lipomas, and vascular malformations. Proteus syndrome is caused by a mosaic somatic activating mutation in AKT1 (Lindhurst et al. 2011). Proteus syndrome patients can show hepatomegaly (Ahmetoglu et al. 2003), probably caused by hemolymphangiomas occupying the liver and other visceral organs (Eberhard 1994).

Blue Rubber Bleb Nevus Syndrome (BRBNS)

BRBNS (OMIM 112200; synonym : Bean's syndrome), described in 1860 (Gascoyen 1860) and defined in 1958 (Bean 1958), is a rare disease characterized by distinct venous malformations in the skin, in the gastrointestinal tract, and less frequently elsewhere (Kisu et al. 1986; Moodley and Ramdial 1993; Fernandes et al. 1999; Giordano et al. 2004; Deng et al. 2008; Ng et al. 2009; Das et al. 2013). It occurs as a sporadic or autosomal-dominant disorder, with a responsible locus situated on chromosome 9p (Boon et al. 1994), where the gene for Tie2 kinase is located. The lesions mostly appear at birth or in early childhood, with a tendency to increase in number and size with age. The BRBNS skin lesions are blue and soft nodules histologically consisting of dysplastic venous channels with a flattened endothelium and lacking smooth muscle cells (Robinowitz and Esterly 1995). The cells of the small vascular channels express c-kit (Mogler et al. 2010). Angioma-like and in part polypoid lesions with a similar histology (Ertem et al. 2001) predominate in the intestinal tract, resulting in occult or overt hemorrhage, e. g., originating from ampullary lesions (Badran et al. 2007). Other visceral organs include the parotid gland, the urinary bladder, and the liver. Hepatic venous malformations in BRBNS have been suspected (Hashimoto et al. 1989), suggested based on multiple small poolings in angiography (Kisu et al. 1986), or found on CT images (Giordano et al. 2004; Deng et al. 2008; Krishnappa and Padmini 2010), but systematic studies on the morphology of liver manifestations are not yet available, with the exception that the venous malformations may contain phleboliths.

Maffucci Syndrome

Maffucci syndrome (OMIM 166000) is a rare condition typically including enchondromas at various sites, the presence of cutaneous and visceral vascular malformations/angiomas, and a tendency to develop spindle cell hemangioendothelioma (review: Superti-Furga et al. 2012). Both Ollier disease (multiple enchondromatosis) and Maffucci syndrome are caused by somatic mosaic mutations of isocitrate dehydrogenases 1 (IDH1) and 2 (IDH2) (Amary et al. 2011). In a pediatric patient with this syndrome, a hepatic hemangioma with a diameter of 11 cm was detected (Pezzilli et al. 2009).

Gorham-Stout Syndrome

Gorham-Stout syndrome (Gorham's disease, vanishing bone disease, massive osteolysis with lymphangioma and/or hemangioma, invasive lymphhemangiomatosis) is a rare vasomalformative disorder characterized by multiple destructive and progressive bone defects thought to be caused by invasive systemic lymphangiomas/hemangiomas. The syndrome can be associated with visceral hemangiomas, including hepatic hemangiomas (Takahashi et al. 2005).

Other Syndromatic Vascular Malformations Involving the Liver

An overlap syndrome characterized by multiple anomalous venous channels, persistent primitive hepatic venous plexus, interrupted inferior vena cava, and renal lymphangiomatosis has been described (Watson et al. 2012). Hepatic vascular malformations have been found in a patient with Simpson-Golabi-Behmel syndrome. A 1-year-old

boy showed a hypervascular lesion in the right posterior liver. The resection specimen showed an unencapsulated lesion measuring up to 1.7 cm in diameter, composed of multiple variably sized vessels with intervening fibrous stroma, consistent with a hemangiomatous vascular malformation (Cureton et al. 2007). A large hepatic cavernous vascular malformation was diagnosed in a patient with nevus vascularis mixtus (cutaneous vascular twin nevi) associated with intracranial vascular malformation of the Dyke-Davidoff-Masson/homolateral hypertrophy of skull and sinuses type (Ruggieri et al. 2012). Focal nodular hyperplasia (FNH) of the liver was observed in children with hemihypertrophy and multiple cutaneous vascular malformations (Everson et al. 1976; Al-Attar et al. 2004). Hepatic vascular lesions characterized by clusters of dilated endothelial channels and vascularized cysts are found in Mulibrey nanism, the lesions having a diameter of 5 mm to 7 cm and associated with hepatomegaly. Part of the lesions are histologically hemangiomas or peliotic foci and are associated with abnormal sinusoidal patterns and central veins with unusually thick walls (Karlberg et al. 2009). Mulibrey nanism (muscle-liver-brain-eye nanism, OMIM 253250) is a monogenic disorder caused by recessive mutations in the TRIM37 gene encoding the peroxisomal Trim37 protein with E3 RING ubiquitin ligase activity. Patients with the syndrome reveal prenatal-onset growth failure, fibrous dysplasia of long bones, J-shaped sella, cutaneous nevi flammei, perimyocardial cardiopathy, and severe insulin resistance with metabolic syndrome as young adults.

Hepatic Angiomas, Angioma-Like Lesions, and Telangiectases in Osler's Disease

Osler's disease (Rendu-Osler-Weber disease, hereditary hemorrhagic telangiectasia, HHT) is an autosomal dominant vascular dysplasia characterized by telangiectasias and arteriovenous anastomoses in several organs and tissues, including visceral organs. Arteriovenous malformations, a hallmark of HHT, occur predominantly in the lungs (50 %), liver (30–70 %), and brain (10 %) (review: Govani and Shvlin 2009). In HHT, arterial aneurysms occur with high prevalence.

So far, five types of HHT have been identified. The mutated gene in type 1 Osler's disease/HHT (OMIM 187300) is assigned to chromosome 9q34.11 and involves endoglin (HHT1), while HHT2 is caused by mutations of ALK1, both abnormalities affecting the TGF-beta signaling pathway which is crucial in angiogenesis (review: Fernandez et al. 2006). Specifically, endoglin as a transmembrane auxiliary receptor for TGF-beta expressed in proliferating endothelial cells plays a central role in endoglin-mediated vascular remodeling linked to TGF-beta signaling pathways (Lebrin and Mummery 2008; ten Dijke et al. 2008). HHT2 (OMIM 600376; chromosome 12q11-q14) is caused by mutations of Alk-1/activin receptor-like kinase involved in TGF-beta signaling. HHT3 and HHT4 (OMIM 601101 and 610655, respectively) are assigned to chromosomes 5q31 and 7p14, respectively, but the defects are not yet specified. The fifth type is termed JPHT or juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome. JPHT (OMIM 175050, chromosome 18q21.1) is caused by mutations of the MADH4 gene encoding Smad4, a component of the TGF receptor signaling pathway. A vascular anomaly syndrome with phenotypic overlap with HHT is associated with BMP (bone morphogenetic protein 9) mutations (Wooderchak-Donahue et al. 2013).

Hepatic involvement in HHT occurs in 8–31 % of cases and is characterized by small telangiectases, discrete blood vessel dysplasias, and vascular anastomoses, including portovenous, arteriovenous, and arterioportal anastomoses causing complex shunts. These anomalies may result in high-output cardiac failure, biliary tract ischemia, and portal hypertension (Buscarini et al. 1994, 2006; Garcia-Tsao 2007; Khalid and Garcia-Tsao 2008; Coremans et al. 2015). Part of large anastomoses may mimic vascular tumors and other hepatic neoplasms. In Osler's disease, multiple telangiectatic lesions may develop in the liver

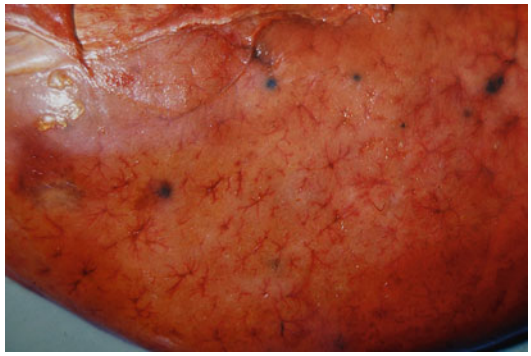

Fig. 2 Small hepatic hemangiomas and spider-shaped or stellate subcapsular telangiectasias in Osler's disease (non-fixed necropsy specimen)

(Fig. 2). Exceptionally, hepatic hemangiomatosis with formation of calcified lesions develops in the setting of Osler's disease (Selmaier et al. 1993) liver involvement.

References

Abernethy J (1793) Account of two instances of uncommon formations, in the viscera of the human body. Communicated by Sir Joseph Banks. Bart PRS Philos Trans R Soc Lond 83:59–66

Acherman RJ, Evans WN, Galindo A, Collazos JC, Rothman A, Mayman GA, Luna CF et al (2007) Diagnosis of absent ductus venosus in a population referred for fetal echocardiography: association with a persistent portosystemic shunt requiring postnatal device occlusion. J Ultrasound Med 26:1077–1082

Ahmetoglu A, Isik Y, Aynaci O, Bahadir S, Aynaci FM (2003) Proteus syndrome associated with liver involvement: case report. Genet Couns 14:221–226

Al-Attar M, Verma R, Shannon RS, McKeever PA, Rickett A (2004) Focal nodular hyperplasia in a child with hemihypertrophy and multiple cutaneous vascular malformations. Australas Radiol 48:77–79

Alpay F, Kurekci AE, Gunesli S, Gokcay E (1996) Klippel-Trenaunay-Weber syndrome with hemimegalencephaly. Report of a case. Turk J Pediatr 38:277–280

Amary MF, Damato S, Halai D, Eskandarpour M, Berisha F, Bonar F, McCarthy S et al (2011) Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. Nat Genet 43:1262–1265

Anderton RL, Smith JG (1975) Unilateral nevoid telangiectasia with gastric involvement. Arch Dermatol 111:617–621

Avila LF, Luis AL, Encinas JL, Hernandez F, Olivares P, Fernandez Cuadrado J, Hierro L et al (2006) Congenital portosystemic shunt. The Abernethy malformation (in Spanish). Cir Pediatr 19:204–209

Badran AM, Vahedi K, Berrebi D, Catana D, De Lagausie P, Drouet L, Ferkadji F, Mougenot JF (2007) Pediatric ampullar and small bowel blue rubber bleb nevus syndrome diagnosed by wireless capsule endoscopy. J Pediatr Gastroenterol Nutr 44:283–286

Baselga E (2004) Sturge-Weber syndrome. Sem Cutan Med Surg 23:87–98

Bathgate A, MacGilchrist A, Piris J, Garden J (1999) Multiple focal nodular hyperplasia in Klippel-Trenaunay syndrome. Gastroenterology 117:284–285

Bean WB (1958) Blue rubber bleb nevi of the skin and gastrointestinal tract. In: Vascular spiders and related lesions of the skin (Bean WB, ed.). Charles C. Thomas, Springfield, pp 178–185

Berg C, Kamil D, Geipel A, Kohl T, Knöpfle G, Hansmann M, Gembruch U (2006) Absence of ductus venosus – importance of umbilical venous drainage. Ultrasound Obstet Gynecol 28:275–281

Bernard O, Franchi-Abella S, Brancherau S, Pariente D, Gauthier F, Jacquemin E (2012) Congenital portosystemic shunts in children: recognition, evaluation, and management. Semin Liver Dis 32:273–287

Billing JS, Jamieson NV (1997) Hepatic arterioportal fistula: a curable cause of portal hypertension in infancy. HPB Surg 10:311–314

Billson VR, Gillam GL (1984) An unusual case of Sturge-Weber syndrome. Pathology 16:462–465

Boon LM, Mulliken JB, Vikkula M, Watkins H, Seidman J, Olsen BR, Warman ML (1994) Assignment of locus for dominantly inherited venous malformations to chromosome 9p. Hum Mol Genet 3:1583–1587

Boon LM, Burrows PE, Paltiel HJ, Lund DP, Ezekowitz RA, Folkman J, Mulliken JB (1996) Hepatic vascular anomalies in infancy: a twenty-seven-year experience. J Pediatr 129:346–354

Breugem CC, van der Horst CMAM, Hennekam RCM (2001) Progress toward understanding vascular malformations. Plast Reconstr Surg 107:1509–1523

Burrows PE, Dubois J, Kassarjian A (2001) Pediatric hepatic vascular anomalies. Pediatr Radiol 31:533–545

Buscarini E, Buscarini L, Civardi G, Arruzzoli S, Bossalini G, Piantanida M (1994) Hepatic vascular malformations in hereditary hemorrhagic telangiectasia: imaging findings. AJR Am J Roentgenol 163:1105–1110

Buscarini E, Plauchu H, Garcia Tsao G, White RI, Sabba C, Miller F, Saurin JC, Pelage JP, Lesca G et al (2006) Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. Liver Int 26:1040–1046

Caiulo VA, Presta G, Latini G, Mattioli G, Jasonni V (2001) Diagnostic and follow-up of congenital intrahepatic portosystemic venous shunt by ultrasounds. Acta Paediatr 90:1209–1210

Capron JP, Kantor G, Dupas JL, Degott C, Locquet MC (1981) Unilateral nevoid telangiectasia and chronic

liver disease. Report of a case and review of the literature. Am J Gastroenterol 76:47–51
Chen D, Li L, Tu X, Yin Z, Wang Q (2013) Functional characterization of Klippel-Trenaunay syndrome gene AGGF1 identifies a novel angiogenic signaling pathway for specification of vein differentiation and angiogenesis during embryogenesis. Hum Mol Genet 22:963–976
Chhajed M, Pandit S, Dhawan N, Jain A (2010) Klippel-Trenaunay and Sturge-Weber overlap syndrome with phakomatosis pigmentovascularis. J Pediatr Neurosci 5:138–140
Cohen MM (2000) Klippel-Trenaunay syndrome. Am J Med Genet 93:171–175
Cohen MM (2002) More on vascular malformations. Plast Reconstr Surg 109:2591–2595
Contratti G, Banzi C, Ghi T, Perolo A, Pilu G, Visentin A (2001) Absence of the ductus venosus: report of 10 new cases and review of the literature. Ultrasound Obstet Gynecol 18:605–609
Coremans L, Van den Bossche B, Colle I (2015) Hepatic involvement in hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome. Acta Gastroenterol Belg 78:319–326
Cureton E, Guo H, Idowu O, Kim S (2007) Hepatic vascular malformation in a patient with Simpson-Golabi-Behmel syndrome. Am J Med Genet A 143:1379–1381
Das KJ, Sharma P, Naswa N, Soundararajan R, Kumar R, Bal C, Malhotra A (2013) Hybrid SPECT-CT with 99mTc-labeled red blood cell in a case of blue rubber bleb nevus syndrome: added value over planar scintigraphy. Diagn Interv Radiol 19:41–43
Deng ZH, Xu CD, Chen SN (2008) Diagnosis and treatment of blue rubber bleb nevus syndrome in children. World J Pediatr 4:70–73
Dompmartin A, Vikkula M, Boon LM (2010) Venous malformation: update on aetiopathogenesis, diagnosis and management. Phlebology 25:224–235
Dubuisson L, Vonnahme FJ, Stzark F, Bioulac-Sage P, Balabaud C (1985) Hyperplastic foci in the atrophic liver of rats after portacaval anastomosis. Liver 5:21–28
Eberhard DA (1994) Two-year-old boy with Proteus syndrome and fatal pulmonary thromboembolism. Pediatr Pathol 14:771–779
Enjolras O, Mulliken JB (1997) Vascular tumors and vascular malformations (new issues). Adv Dermatol 13:375–423
Ertem D, Acar Y, Kotiloglou E, Yucelten D, Pehlivanoglu E (2001) Blue rubber bleb nevus syndrome. Pediatrics 107:418–421
Everson RB, Muesles M, Henson DE (1976) Focal nodular hyperplasia of the liver in a child with hemihypertrophy. J Pediatr 88:985–987
Fan C, Ouyang P, Timur AA, He P, You SA, Hu Y, Ke T, Driscoll DJ, Chen Q, Wang QK (2009) Novel roles of GATA1 in regulation of angiogenic factor AGGF1 and endothelial cell function. J Biol Chem 284:23331–23343
Fernandes C, Silva A, Coelho A, Campos M, Pontes F (1999) Blue rubber bleb nevus: case report and literature review. Eur J Gastroenterol Hepatol 11:455–457
Fernandez-L A, Sanz-Rodriguez F, Blanco FJ, Bernabeu C, Botella LM (2006) Hereditary hemorrhagic telangiectasia, a vascular dysplasia affecting the TGF-beta signaling pathway. Clin Med Res 4:66–78
Finklea LB, Mohr MR, Warthan MM, Darrow DH, Williams JV (2010) Two reports of phacomatosis pigmentovascularis type IIb, one in association with Sturge-Weber syndrome and Klippel-Trenaunay syndrome. Pediatr Dermatol 27:303–305
Frigerio A, Stevenson DA, Grimmer JF (2012) The genetics of vascular anomalies. Curr Opin Otolaryngol Head Neck Surg 20:527–532
Fugelseth D, Lindemann R, Liestel K, Kiserud T, Langslet A (1997) Ultrasonographic study of ductus venosus in healthy neonates. Arch Dis Child Fetal Neonatal Ed 77: F131–F134
Fugelseth D, Lindemann R, Liestel K, Kiserud T, Langslet A (1998) Postnatal closure of ductus venosus in preterm infants < or = 32 weeks. An ultrasonographic study. Early Hum Dev 53:163–169
Gajinov Z, Misic-Pavkov G, Matic M, Duran V, Adic O, Duran B, Ivkov M, Poljacki M (2008) Persistent hepatic venous plexus in a patient with Sturge-Weber syndrome. Pediatr Dermatol 25:452–454
Gallego C, Miralles M, Marin C, Muyor P, Gonzalez G, Garcia-Hidalgo E (2004) Congenital hepatic shunts. RadioGraphics 24:755–772
Garcia-Tsao G (2007) Liver involvement in hereditary hemorrhagic telangiectasia (HHT). J Hepatol 46:499–507
Garzon MC, Huang JT, Enjolras O, Frieden IJ (2007) Vascular malformations. Part II: associated syndromes. J Am Acad Dermatol 56:541–564
Gascoyen GG (1860) Case of nevus involving the parotid gland and causing death from suffocation: nevi of the viscera. Trans Pathol Soc Lond 11:267
Giordano C, Battagliese A, di Gioia CR, Campagna D, Benedetti F, Travaglini C, Gallo P et al (2004) Blue rubber bleb nevus syndrome and pulmonary hypertension: an unusual association. Cardiovasc Pathol 13:317–322
Girard M, Amiel J, Fabre M, Pariente D, Lyonnet S, Jacquemin E (2005) Adams-Oliver syndrome and hepatoportal sclerosis: occasional association or common mechanism ? Am J Med Genet A 135:186–189
Govin FS, Shovlin CL (2009) Hereditary haemorrhagic telangiectasia: a clinical and scientific review. Eur J Hum Genet 17:860–871
Grundfest-Broniatowski S, Carey WD, Sivak MV, Feldman B (1982) Klippel-Trenaunay-Weber syndrome with visceral involvement and portal hypertension. Ann Surg 183:418–428
Guérin F, Porras J, Fabre M, Guettier C, Pariente D, Bernard O, Gauthier F (2009) Liver nodules after portal

systemic shunt surgery for extrahepatic portal vein obstruction in children. J Pediatr Surg 44:1337–1343
Haber M, Reuben A, Burrell M, Oliverio P, Salem RR, West AB (1995) Multiple focal nodular hyperplasia of the liver associated with hemihypertrophy and vascular malformations. Gastroenterology 108:1256–1262
Hashimoto et al. 1989. http://www.ncbi.nlm.nih.gov/pubmed/2752649
Hu Y, Li L, Seidelmann SB, Timur AA, Shen PH, Driscoll DJ, Wang QK (2008) Identification of association of common AGGF1 variants with susceptibility for Klippel-Trenaunay syndrome using the structure association program. Ann Hum Genet 72:636–643
Jabra AA, Taylor GA (1991) Ultrasound diagnosis of congenital intrahepatic portosystemic venous shunt. Pediatr Radiol 21:529–530
Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P (1998) Klippel-Trénaunay syndrome: spectrum and management. Mayo Clin Proc 73:28–36
Jafri SZ, Bree RL, Glazer GM, Francis IR, Schwab RE (1983) Computed tomography and ultrasound findings in Klippel-Trenaunay syndrome. J Comput Assist Tomogr 7:457–460
Jay V (2000) Sturge-Weber syndrome. Pediatr Dev Pathol 3:301–305
Kakitsubata Y, Kakitsubata S, Kiyomizu H, Ogawa T, Kato K, Watanabe K (1996) Intrahepatic portal-hepatic venous shunts demonstrated by US, CT, and MR imaging. Acta Radiol 37:680–684
Karlberg N, Karlberg S, Karikoski R, Mikkola S, Lipsanen-Nyman M, Jalanko H (2009) High frequency of tumours in Mulibrey nanism. J Pathol 218:163–171
Kawakatsu M, Vilgrain V, Belghiti J, Flejou JF, Nahum H (1994) Association of multiple liver cell adenomas with spontaneous intrahepatic portohepatic shunt. Abdom Imaging 19:438–440
Khalid SK, Garcia-Tsao G (2008) Hepatic vascular malformations in hereditary hemorrhagic telangiectasia. Semin Liver Dis 28:247–258
Kim et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11396258
Kisu T, Yamaoka K, Uchida Y, Mori H, Nakama T, Hisatsugu T, Miyaji H, Motooka M (1986) A case of blue rubber bleb nevus syndrome with familial onset. Gastroenterol Jpn 21:262–266
Klippel M, Trénaunay P (1900) Du naevus variqueux ostéohypertrophique. Arch Gén Med Paris 3:611
Krishnapa A, Padmini J (2010) Blue rubber bleb nevus syndrome. Indian J Pathol Microbiol 53:168–170
Krutsay M (1959) On atresia of the ductus venosus Arantius (in German). Zbl Allg Pathol 100:233–236
Langman G, Wainwright H, Matthews L (2001) Absence of the ductus venosus with direct connection between the umbilical vein and right atrium. Pediatr Dev Pathol 4:298–303
Lebrin F, Mummery CL (2008) Endoglin-mediated vascular remodeling: mechanisms underlying hereditary hemorrhagic telangiectasia. Trends Cardiovasc Med 18:25–32
Lindenauer SM (1965) The Klippel-Trenaunay-Weber syndrome: varicosity, hypertrophy and hemangioma with no arteriovenous fistula. Ann Surg 162:303
Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, Peters K, Turner J, Cannons JL et al (2011) A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med 365:611–619
Lu DSK, Lin J, Kadell BM (1996) Congenital or idiopathic hepatic vascular malformations. CT findings. AJR Am J Roentgenol 167:1155–1157
Maeda N, Horie Y, Koda M, Suou T, Andachi H, Nakamura K, Kawasaki H (1997) Extrahepatic portal obstruction without hepatopetal pathways associated with congenital arterioportal fistula : a case report. Hepatogastroenterology 44:1317–1320
Manivannan N, Gokulanathan S, Ahathya RS, Gubernath, Daniel R, Shanmugasundaram (2012) Sturge-Weber syndrome. J Pharm Bioallied Sci 4(suppl 2): S349–S352
Matsumoto R, Izutsu M, Kobayashi S, Kusano S (1990) A case of multiple intrahepatic portosystemic venous shunts associated with multiple hemangioma-like lesions of the liver (in Japanese). Rinsho Horshasen 35:1085–1088
Matsuo M, Kanematsu M, Kato H, Kondo H, Sugisaki K, Hoshi H (2001) Osler-Weber-Rendu disease: visualizing portovenous shunting with three-dimensional sonography. AJR Am J Roentgenol 176:919–920
Mignon F, Mesurolle B, Cazaban A, Lemeste J (1996) Focal nodular hyperplasia and spontaneous intrahepatic porto-portal communication (in French). J Radiol 77:1233–1236
Mogler C, Beck C, Kulozik A, Penzel R, Schirmacher P, Breuhahn K (2010) Elevated expression of c-kit in small venous malformations of blue rubber bleb nevus syndrome. Rare Tumors 2:e36
Moodley M, Ramdial P (1993) Blue rubber bleb nevus syndrome: case report and review of the literature. Pediatrics 92:160–162
Morgan G, Superina R (1994) Congenital absence of the portal vein: two cases and a proposed classification system for portasystemic vascular anomalies. J Pediatr Surg 29:1239–1241
Mulliken JB (1993) Cutaneous vascular anomalies. Semin Vasc Surg 6:204–218
Mulliken JB (1997) Vascular anomalies. In: Aston SJ, Beasley RW, Thorne CHM (eds) Grabb and Smith's plastic surgery, 5th edn. Lippincott-Raven, Philadelphia, pp 191–203
Mulliken JB, Glowacki J (1982) Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 69:412–420
Murray CP, Yoo SJ, Babyn PS (2003) Congenital extrahepatic portosystemic shunts. Pediatr Radiol 33: 614–620

Nagano K, Hoshino H, Nishimura D, Katada N, Sano H, Kato K (1999) Patent ductus venosus. J Gastroenterol Hepatol 14:285–288

Ng EK, Cheung FK, Chiu PW (2009) Blue rubber bleb nevus syndrome: treatment of multiple gastrointestinal hemangiomas with argon plasma coagulator. Dig Endosc 21:40–42

Oguz B, Akata D, Balkanci F, Akhan O (2003) Intrahepatic portosystemic venous shunt: diagnosis by colour/power Doppler imaging and three-dimensional ultrasound. Br J Radiol 76:487–490

Ono H, Mawatari H, Mizoguchi N, Eguchi T, Sakura N (1998) Clinical features and outcome of eight infants with intrahepatic portovenous shunts detected in neonatal screening for galactosaemia. Acta Paediatr 87:631–634

Park JH, Cha SH, Han JK, Han MC (1990) Intrahepatic portosystemic venous shunt. AJR Am J Roentgenol 155:527–528

Peker A, Ucar T, Kuloglu Z, Ceyhan K, Tutar E, Fitoz S (2009) Congenital absence of portal vein associated with nodular regenerative hyperplasia of the liver and pulmonary hypertension. Clin Imaging 33:322–325

Pereira de Godoy JM, Fett-Conte AC (2010) Dominant inheritance and intra-familial variations in the association of Sturge-Weber and Klippel-Trenaunay-Weber syndromes. Indian J Hum Genet 16:26–27

Pezzilli R, Serra C, Tomassetti P, Brocchi E, Campana D, Corinaldesi R (2009) Maffucci syndrome with hemangioma of the liver. Case Rep Gastroenterol 3:1–4

Pipitone S, Garofalo C, Corsello G, Mongiovi M, Piccione M, Maresi E, Sperandeo V (2003) Abnormalities of the umbilico-portal venous system in Down syndrome: a report of two new patients. Am J Med Genet A 120A:528–532

Pocha C, Mallakkal B (2004) Spontaneous intrahepatic portal-systemic venous shunt in the adult: case report and review of the literature. Dig Dis Sci 49:1201–1206

Prats Viñas JM, Suinaga Errasti I, Blanco Lago R (2011) Shapiro Shulman syndrome: a forgotten condition. Pediatr Neurol 44:308–310

Robinowitz LE, Esterly NB (1995) Blue rubber bleb nevus syndrome. In: Schachner LA, Hansen RC (eds) Pediatric dermatology, 2nd edn. Churchill Livingstone, New York, pp 969–970

Ruggieri M, Milone P, Pavone P, Falsaperla R, Polizzi A, Caltabiano R, Fichera M et al (2012) Nevus vascularis mixtus (cutaneous vascular twin nevi) associated with intracranial vascular malformation of the Dyke-Davidoff-Masson type in two patients. Am J Med Genet A 158A:2870–2880

Selmaier M, Cidlinsky K, Ell C, Hahn EG (1993) Liver hemangiomatosis in Osler's disease (in German). Dtsch Med Wochenschr 118:1015–1019

Senocak E, Oguz B, Edgüer T, Cila A (2008) Congenital intrahepatic portosystemic shunt with variant inferior right hepatic vein. Diagn Interv Radiol 14:97–99

Servelle M (1985) Klippel and Trenaunay's syndrome: 768 operated cases. Ann Surg 201:365–373

Shen O, Valsky DV, Messing B, Cohen SM, Lipschuetz M, Yagel S (2011) Shunt diameter in agenesis of the ductus venosus with extrahepatic portosystemic shunt impacts on prognosis. Ultrasound Obstet Gynecol 37:184–190

Silva G, Braga A, Leitao B, Mesquita A, Reis A, Duarte C, Barbot J, Silva ES (2012) Adams-Oliver syndrome and portal hypertension: fortuitous association or common mechanism ? Am J Med Genet A 158A:648–651

Stringer MD (2008) The clinical anatomy of congenital portosystemic venous shunts. Clin Anat 21:147–157

Superti-Furga A, Spranger J, Nishimura G (2012) Enchondromatosis revisited: new classification with molecular basis. Am J Med Genet C: Semin Med Genet 160C:154–164

Takahashi A, Ogawa C, Kanazawa T, Watanabe H, Suzuki M, Suzuki N, Tsuchida Y et al (2005) Remission induced by interferon alfa in a patient with massive osteolysis and extension of lymph-hemangiomatosis: a severe case of Gorham-Stout syndrome. J Pediatr Surg 40:E47–E50

ten Dijke P, Goumans MJ, Pardali E (2008) Endoglin in angiogenesis and vascular diseases. Angiogenesis 11:79–89

Tian XL, Kadaba R, You SA, Liu M, Timur AA, Yang L, Chen Q, Szafranski P, Rao S et al (2004) Identification of an angiogenic factor that when mutated causes susceptibility to Klippel-Trenaunay syndrome. Nature 427:640–645

Timur AA, Driscoll DJ, Wang Q (2005) Biomedicine and diseases: the Klippel-Trenaunay syndrome, vascular anomalies and vascular morphogenesis. Cell Mol Life Sci 62:1434–1447

Uchino T, Endo F, Ikeda S, Shiraki K, Sera Y, Matsuda I (1996) Three brothers with progressive hepatic dysfunction and severe hepatic steatosis due to a patent ductus venosus. Gastroenterology 110:1964–1968

Uhlin SR, McCarty KS (1983) Unilateral nevoid telangiectatic syndrome: the role of estrogen and progesterone receptors. Arch Dermatol 119:226

Vauthey JN, Tomczak RJ, Helmberger T, Gertsch P, Forsmark C, Caridi J, Reed A, Langham MR, Lauwers GY, Goffette P, Lerut J (1997) The arterioportal fistula syndrome: clinicopathologic features, diagnosis, and therapy. Gastroenterology 113:1390–1401

Villar F, Goria O, Hervé S, Lestrat JP, Perrot S, Scotté M (2000) Intrahepatic portocaval shunt: review of the literature, apropos of 1 case (in French). Gastroenterol Clin Biol 24:582–584

Vollmar J (1974) Zur Geschichte und Terminologie der Syndrome nach F.P. Weber and Klippel-Trénaunay. VASA 3:231–241

Wang QK (2005) Update on the molecular genetics of vascular anomalies. Lymphat Res Biol 3:226–233

Wanless IR, Lentz JS, Roberts EA (1985) Partial nodular transformation of liver in an adult with persistent ductus venosus. Review with hypothesis on pathogenesis. Arch Pathol Lab Med 109:427–432

Watson T, Martinez E, Crabbe D, Chetcuti P, Kraft JK (2012) Renal lymphangiomatosis, interrupted IVC with persistent primitive hepatic venous plexus and multiple anomalous venous channels: parts of an overlap syndrome ? Pediatr Radiol 42:253–256

Weinbren K, Washington SL (1976) Hyperplastic nodules after portacaval anastomosis in rats. Nature 264:440–442

Wilken JK (1984) Unilateral dermatomal superficial telangiectasia. Arch Dermatol 120:579

Witters P, Maleux G, George C, Delcroix M, Hoffman I, Gewillig M, Verslype C, Monbaliu D et al (2008) Congenital veno-venous malformations of the liver: widely variable clinical presentations. J Gastroenterol Hepatol 23:e390–e394

Wooderchak-Donahue WL, McDonald J, O'Fallon B, Upton PD, Li W, Roman BL, Young S et al (2013) BMP9 mutations cause a vascular-anomaly syndrome with phenotypic overlap with hereditary hemorrhagic telangiectasis. Am J Hum Genet 93:530–537

Yamagami T, Nakamura T, Tokiwa K, Ohno K, Itoh H, Maeda T (2000) Intrahepatic portosystemic venous shunt associated with biliary atresia: a case report. Pediatr Radiol 30:489–491

Yonemitsu H, Mori H, Kimura T, Kagawa K, Tsuda T, Yamada Y, Kiyosue H, Matsumoto S (2000) Congenital extrahepatic portocaval shunt associated with hepatic hyperplastic nodules in a patient with Dubin-Johnson syndrome. Abdom Imaging 25:572–575

Zhou Q, Zheng JW, Yang XJ, Wang HJ, Ma D, Qin ZP (2011) Detection of RASA1 mutations in patients with sporadic Sturge-Weber syndrome. Childs Nerv Syst 27:603–607

Zientarski B (1976) Persistent ductus venosus Arantii. Folia Morphol (Warsz) 35:169–172

Bacillary Angiomatosis and Peliosis Hepatis

59

Contents

Abstract

Bacillary angiomatosis is a reactive vascular disorder associated with *Bartonella* (*B.*) infection, specifically *B. henselae* and suspectedly *B. clarridgeiae*. The lesions are characterized by hemangioma-like endothelial proliferations. In the liver, bacillary angiomatosis (bacillary peliosis) may be associated with *Bartonella*-induced granulomatous hepatitis. Foci of hepatic bacillary angiomatosis can mimic neoplastic processes, because the lesions may exceed few centimeters in diameter. In contrast to neoplastic lesions, bacillary peliosis regresses upon antibiotic therapy. Some of the lesions contain stainable *Bartonella* organisms. Pathogenetically, *Bartonella* modulate vascular morphogenesis and induce endothelial cell migration and proliferation. Peliosis hepatis, another reactive vascular process which radiologically resembles liver tumors, is characterized by focal or diffuse cystic blood-filled spaces mainly localized in parenchyma. Peliotic lesions show a loss of endothelial lining and an effacement of the perisinusoidal reticulin network. Peliosis hepatis can be induced by a wide array of factors, including infections and drugs.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_59

Bacillary Angiomatosis

Introduction

Bartonella organisms are Gram-negative, oxidase-negative, fastidious bacteria belonging to the a2 subclass of Proteobacteria, which are usually transmitted by numerous arthropod vectors, employ mammalian host reservoirs, and reveal a distinct natural history (Jacomo et al. 2002). *Bartonella* ssp. evoke persistent infections in several wild and domestic animals producing a substantial reservoir in nature being the source of inadvertent human infections (Breitschwerdt and Kordick 2000). By studying vascular, hemangioma-like proliferations in patients with AIDS, clusters of bacteria exhibiting the structure of Gram-negative, Warthin-Starry-positive rods and thus showing the staining profile of Bartonella have been detected (LeBoit et al. 1988). These lesions had an epithelioid appearance and regressed after antibiotic therapy in several patients. The histomorphologic features of what was then termed bacillary or epithelioid angiomatosis were described in detail (Walford et al. 1990).

The genus, *Bartonella*, has been extended by the inclusion of the genera *Rochalimaea* and *Grahamella*. Members of the genus *Bartonella* are involved in a broad array of human diseases, including Carrion's disease, trench fever, cat-scratch disease, bacillary angiomatosis-peliosis, endocarditis, and bacteremia. At least 14 species with several strains are currently recognized, and 7 out these are implicated to play a role in human infections. Phylogenetic data based on the analysis of 16S rDNA, 16S–23S rRNA intergenic spacers, citrate synthase, and 60 kDa heat shock proteins have first resulted in the identification of six significant evolutionary clusters (Houpikian and Raoult 2001), and by comparison of groEL sequences, a reliable classification of species and subspecies has recently been proposed (Zeaiter et al. 2002b). Cat-scratch disease and the associated vascular lesions are caused by *Bartonella* (B.) *henselae* and, suspectedly, by *B. clarridgeiae* (Kordick et al. 1997). *B. henselae* manifests in the form of several genotypes, however not exhibiting different epidemiological or clinical characteristics (Zeaiter et al. 2002a). Starting from a still enigmatic niche, *Bartonella* spp. typically parasite erythrocytes of mammalian hosts in a distinct seeding rhythm and by use of a type IV secretion system (Baron et al. 2002; Seubert et al. 2002; Dehio 2004; Devio 2005; Raoult 2007) encoded by *Bartonella* virB operon genes (Schmiederer et al. 2001) and thus produce long-lasting hemotropic infections. *Bartonella* organisms evoke a distinct immune response in hosts, involving both humoral and cellular reactions and having an impact on the manifestations of several disease phenotypes (Karem et al. 1999; Karem 2000; Bonatti et al. 2006).

Hepatobiliary Manifestations

The main liver lesions induced by *Bartonella* include granulomatous hepatitis and a variant of peliosis. Granulomas, also well-known from other organs in bartonellosis, may grow to considerable size (more than 3 cm; (Murano et al. 2001; Florin et al. 2008), i.e., lesions which may be confounded with tumors at imaging. With respect to peliosis of the liver, nomenclature of such lesions in bartonellosis is somewhat ambiguous, the range of terms employed including *Bartonella*-positive peliosis hepatis, bacillary peliosis, and parenchymal bacillary peliosis, all terms apparently denoting the same type of lesion. In what follows, the term bacillary peliosis will be used throughout (Alkan and Orenstein 1991; Carucci and Halvorsen 2006). In a study of liver tissue from eight HIV-infected patients, peliotic lesions showed clumps of a granular purple material that on Warthin-Starry staining and electron microscopy proved to be bacilli, morphologically identical to those found in skin lesions of bacillary angiomatosis. It was found that this bacillary peliosis responded to antibiotic therapy (Perkocha et al. 1990). Later, *Rochalimaea henselae* (now *Bartonella henselae*) was identified in both bacillary peliosis and bacillary angiomatosis by use of immunocytochemistry and lipid chemical and molecular biology methods (Reed et al. 1992;

Slater et al. 1992; Welch et al. 1992). At electron microscopy, the organisms were observed in sinusoidal endothelial cells, but also extracellularly (Leong et al. 1992). In an epidemiological study of *Bartonella* infections employing molecular techniques, it has been demonstrated that bacillary peliosis was associated exclusively with *B. henselae* (Koehler et al. 1997).

Some of the mechanisms involved in the pathogenesis of *Bartonella*-induced vascular changes have been studied. Generally, *Bartonella* appear to cause or to modulate vascular morphogenesis including endothelial cell migration and proliferation (Conley et al. 1994; Schmid et al. 2004; Scheidegger et al. 2009), but *B. henselae* can attach and invade several cell systems, including erythrocytes and epithelial cells apart from endothelial cells. Vascular colonization in vitro by *B. henselae* requires a close contact between the leading lamella of endothelial cells resulting in a bacterial aggregate which is afterward internalized via the so-called invasome. This actin-dependent invasion process, which is operational for clinical isolates of *B. henselae* but not for a mutant, by-passes the ordinary phagosomal pathway (Devio et al. 1997; Devio 2001). The contact between the organisms and endothelial cells seems to depend on outer membrane proteins (OMPs) of *B. henselae*. Out of nine members of OMPs characterized so far, the 43 kD variant (Omp43) has been shown to be the major adhesin for human umbilical vein endothelial cells (Burgess and Anderson 1998). The cloned Omp43 gene has an ORF of 1,206 nucleotides coding for a protein of 402 amino acids, and this Omp43 gene product is predicted to exist as a 16 stranded beta barrel protein similar to the Omp2b *Brucella abortus* porin, even though it is not yet known whether Omp43 protein also functions as a porin in *B. henselae* (Burgess et al. 2000). Adhesion of piliated *B. henselae* strains to human endothelial cells results in a protracted upregulation of E-selectin and ICAM-1, ICAM-1 upregulation being dependent on a heat-stable component (Maeno et al. 2002) and mediated by the activation of NF-kappaB, and this mechanism is dependent on OMPs, but not on lipopolysaccharides (Fuhrmann et al. 2001). Endothelial cell reaction to *B. henselae* is complex insofar as the proliferation response of these cells does not depend on a direct contact with the germ, and a proliferative response also ensues upon exposure to non-piliated bacterial strains unable to attach to endothelia (Maeno et al. 1999), suggesting that a humoral signal is involved. Upon interaction of *B. henselae* with viable host endothelia, bacterial rRNA synthesis and replication are rapidly induced, suggesting a specific interaction (Kempf et al. 2000). It has recently been shown that *B. henselae* induces host cell production of the angiogenic factor, vascular endothelial growth factor (VEGF), resulting in the proliferation of endothelial cells (Kempf et al. 2001).

Is there, in immunocompromised hosts, a coinfection-based relationship between *Bartonella*-induced angiomatoid lesions and Kaposi sarcoma (KS)? In fact, epithelioid angiomatosis can develop together with KS in patients with AIDS (Schwartzman et al. 1990). However, it has been reported that KS-associated herpes virus DNA is, expectedly, absent in bacillary angiomatosis-peliosis lesions (Relman et al. 1999), suggesting that the two lesion patterns emerge independently.

Peliosis and Lipopeliosis Hepatis

Introduction

Peliosis hepatis is defined as the presence of focal or diffuse cystic blood-filled spaces in the liver, chiefly localized to the parenchyma. Peliosis hepatis was first mentioned in the literature in 1861 as “blood cysts of the liver” (Wagner 1861) and was for a long time judged to just represent some sort of a strange liver lesion. In a report of 1900, the condition was termed cavernous degeneration of the liver (Fabris 1900). Hedrén coined the designation telangiectasia hepatis disseminata (Hédren 1909). The term peliosis appears in 1916 (Schönlank 1916). But it took a long time until peliosis was consistently employed to denote the changes. In particular, the concept that peliosis is characterized by hepatic hemorrhage appeared for decades after peliosis was defined, e.g., using

terms such as "miliary hepatic hemorrhages" (Senf 1939). The term peliosis (from Greek, pelios) originally denotes a macroscopic change meaning purple or dusky. This distinct gross feature, i.e., reddish-purple areas, is particularly detectable on the liver surface at laparoscopy (Solis-Herruzo et al. 1983). Peliosis chiefly occurs in the liver but, e.g., also in spleen, lymph nodes, lung, parathyroids, and pancreatic islet cell adenomas.

Epidemiology

Numerous cases of hepatic peliosis have been described in the literature since the appearance of the initial defining reports (Burger and Marcuse 1952; Hamilton and Lubitz 1952; Kent and Thompson 1961; Taxy 1978; Trites 1957; Winkler and Poulsen 1975; Yanoff and Rawson 1964; Yap et al. 1993; Young 1953; Zak 1950). The condition mainly develops in adults, but pediatric cases have also been reported (Bank et al. 1978; Nuernberger and Ramos 1975; Pautard et al. 1986; Samyn et al. 2004; Usatin and Wigger 1976), and it has even been observed in a neonate (Kawamoto and Wakabayashi 1980).

Clinical and Imaging Features

Most cases of peliosis hepatic are asymptomatic, and patients usually suffer from underlying disease associated with peliosis. Rarely, hepatic peliosis causes portal hypertension and contributes to progressive hepatic insufficiency and to fatal complications including intrahepatic or peritoneal hemorrhage (Toth et al. 2002). It leads to hemorrhagic hepatic necrosis in some patients, can result in life-threatening or fatal hepatic rupture, and sometimes initially presents as acute hepatic failure and intraperitoneal hemorrhage. In children, space-occupying peliosis was found to cause inferior vena cava compression Hiorns et al. 2005.

Selected References: Chawla et al. 1980; Okuda et al. 1981; Smathers et al. 1984; Adam et al. 1991; Berzigotti et al. 2006; Fidelman et al. 2002; Hayward et al. 1991; Jacquemin et al. 1999; Karger et al. 2005; Marechal et al. 2005; Oriordan et al. 2000; Vignaux et al. 1999; Wang et al. 2001; Toth et al. 2002; Kim et al. 2007b; Khadikar et al. 2008; Buelow et al. 2012; Choi et al. 2009.

Peliosis hepatis can be diagnosed at liver imaging, based on characteristic features of focal to diffuse vascular lesions (Battal et al. 2010; Iannaccone et al. 2006; Jamadar et al. 1994; Kleinig et al. 2003; Nougaret et al. 2009; Saatci et al. 1995; Steinke et al. 2003; Tsukamoto et al. 1984; Yekeler et al. 2004). The peliotic lesions may reach several cm in diameter and can therefore, on sonography and CT images, mimic hepatic tumors (Ferrozzi et al. 2001; Vreswijvel et al. 2003; Atila et al. 2007; Han and Kim 2007a; Savastano et al. 2005; Kim et al. 2007a; Bexten et al. 2012).

Peliosis Hepatis Can Mimic Liver Tumors

Large foci of peliosis can simulate a hemorrhagic hepatic cancer on CT images (Dai and Zhong 2013; (Huang and Wang 2013). In case of multiple lesions, peliosis hepatis can resemble metastatic liver tumor (Liu et al. 2014; Tateishi et al. 1998; Wannesson et al. 2009; Xiong et al. 2012). In rare instances, peliosis-associated hemorrhage presents, on CT and MR, as a pseudotumoral lesion (Ferrozzi et al. 2001).

Pathology

Macroscopy

Macroscopically, major and minor forms of hepatic peliosis are distinguished. Macroscopic (major) peliosis is in evidence as sharply delineated, dark cavities of frequently spherical shape seen both from the liver's capsular surface and, as confluent and clustered, spongy cystic lesions, on the cut surface, sometimes grossly resembling a cavernous hemangioma. The lesions vary in

size from less than 1 mm to several cm in diameter and are usually multiple, single lesions being rare. Microscopic (minor) peliosis hepatis is characterized by smaller lesions detectable at histologic examination.

Histopathology

In contrast to sinusoidal dilatation or evacuation of liver cell plates owing to hepatocyte drop out, the histologic definition of peliosis requires the observation of a breakdown of the perisinusoidal reticulin fiber network and, at least in early lesions, the loss of an endothelial lining of the cavities, even though re-endothelization may occur in later stages (Tsokos and Erbersdobler 2005; Wold and Ludwig 1981; Tzirogiannis et al. 2006). Peliotic cavities are usually poor in Kupffer cells or may even lack them. In liver tissue adjacent to peliotic lesions, sinusoids may show dilatation (Zafrani et al. 1984a; Wold and Ludwig 1981), and perifocal hepatocytes may exhibit cholestatic change. Peliosis hepatic can result in intrahepatic calcifications (Muradali et al. 1996). Peliotic cavities have been classified into phlebectatic and parenchymal variants (Yanoff and Rawson 1964), which may coexist in the same liver (Wakabayashi et al. 1984). In the former variant, vascular spaces with regular contour and uniform size have been described, mainly in zone 3, and communicating with central/terminal veins. These spaces were lined by fibrin and layered blood elements, with an incomplete endothelial or fibrous wall. The latter variant was characterized by irregularly shaped blood-filled channels in a diffuse distribution, without endothelial lining, no communication with central veins, and no thrombi (Yanoff and Rawson 1964). Several reports have later employed this classification (McGiven 1970; Naeim et al. 1973). However, others were unable to confirm this distinction (Bagheri and Boyer 1974; Taxy 1978; Wold and Ludwig 1981). Wold and Ludwig (1981) studied five autopsy cases of incidentally detected hepatic peliosis, including scanning electron microscopy, and observed that all cases presented a mixture of the patterns previously proposed, thus rendering the classification into two variants not useful.

Ultrastructure

Ultrastructurally, sinusoidal endothelial cells show signs of damage (swelling, blebs, clear cell change) or regeneration, large areas of communication between the sinusoidal and the perisinusoidal space, and the formation of multicellular endothelial layers (Zafrani et al. 1984a).

Immunohistochemistry

In dilated sinusoids and cavities, expression of the cell adhesion molecules, ICAM-1, LFA-1, and VLA-4 was found, involving endothelial cells, Kupffer cells, and hepatocytes, suggesting a complex interaction of these cell types in peliosis (Gulubova 2005). Within the lesion, deposition of collagen types II and IV, tenascin, and alpha-SMA was found, suggesting activation of myofibroblasts as a secondary event (Gulubova 2002).

Peliosis in Tumors or in the Vicinity of Liver Tumors

Peliosis-like alterations also occur in liver cell adenomas, adult-type hepatocellular carcinoma, fibrolamellar carcinoma, and angiomyolipoma (Akatsu et al. 2004), but it is not known whether the ectatic vessels observed under these circumstances are bona fide peliosis or a lesion morphologically mimicking it. Peliosis can also evolve together with other tumors in the liver, including angiosarcoma (Cadranel et al. 1993; Scherer et al. 1996), where peliotic cysts are lined by atypical or malignant endothelial cells. Hepatic peliosis has been observed in association with hepatocellular carcinoma/HCC (Herrera et al. 1981). Rarely, HCC itself undergoes prominent peliotic change. In this situation, HCC contains multiple blood-filled cystic spaces and dilated sinusoid-like vascular channels (pelioid-type HCC; (Ikeda et al. 2011; Ji et al. 2001).

Causes and Associations

Peliosis hepatis has been observed in numerous conditions and associations (Table 1).

It is of interest to note that all 32 cases reported in the literature between the first descriptions in 1861 (Wagner 1861) and 1947 (Weber 1947) were found in patients with tuberculosis (Schrohe 1899; Swetschnikow 1910; Hedrén 1909; (Geisler 1931; Grätzer 1928; Lunghetti 1914; Meusburger 1934; Mittasch 1920; Peltason 1921). Peliosis hepatic can occur as a congenital lesion (Bracero et al. 1995; Kawamoto and Wakabayashi 1980), e.g., in association with congenital portal vein aneurysm (Mungan et al. 2009), and is sometimes observed in infants (Cragg et al. 1984), in one report as a focal lesion thought to be related to asphyxial death (Selby and Stocker 1995). In children, peliosis hepatis has been repeatedly found in X-linked myotubular myopathy (Terlizzi et al. 2013). Is there a relationship between the phenotype of peliosis hepatis and its etiology? There appears to be a tendency for macroscopic peliosis to occur more frequently as complication of anabolic, estrogenic, or glucocorticoids, in certain chronic infections (tuberculosis and leprosy), in vasculitis, in leukemia, and in AIDS, whereas microscopic forms are more frequently seen in kidney- or liver-transplanted patients and in malignancies. Why this seems to be so is currently unknown. In some situations, no association had been identified, leading to the term idiopathic peliosis hepatis (Brochard et al. 1981; Hyodo et al. 2004).

Selected References (Naeim et al. 1973; Madell and Kosek 1977; Bagheri and Boyer 1974; Bain et al. 1982; Degott et al. 1978; Dejgaard et al. 1984; Furuta et al. 1982; Hillion et al. 1983; Loomus et al. 1983; Okuda et al. 1981; Paradinas et al. 1977; Puppala and Ro 1979; Wakabayashi et al. 1984; Willen et al. 1979; Zafrani et al. 1984b, 1987; (Bjork et al. 1985; Bonnet et al. 1987; Czapar et al. 1986; Garnier et al. 1986; Hankey and Saker 1987; Mourad et al. 1987; Nesher et al. 1985; Pautard et al. 1986; Larrey et al.

Table 1 Peliosis hepatis: causes and associations

Infections
Tuberculosis
Bartonella henselae
Gummous syphilis
Lepromatous leprosy
Bacterial endocarditis
HIV
Autoimmune conditions
Systemic lupus erythematodes
Autoimmune vasculitis
Endocrine disorders
Glucocorticoid-producing tumors
Metabolic disorders
Glycogenosis type I
Chronic hypervitaminosis A
Neoplastic disease
Hodgkin's disease
Hairy cell leukemia
Diverse B-cell non-Hodgkin's lymphomas
Multiple myeloma
Renal cell carcinoma
Nephroblastoma
Systemic mastocytosis
Castleman's disease
Drugs
Anabolic steroids
Danazol
Diethylstilbestrol
Oral contraceptives
Immunosuppressive drugs (e.g., following transplantation)
Tamoxifen
Azathioprin
Urethan
6-Mercaptopurin
Nucleoside analogs
Methotrexate
Other associations
Hemodialysis
Hereditary hemorrhagic telangiectasia
Retroperitoneal abscess
Systematic amyloidosis
X-linked myotubular myopathy
Cardiopathy
Ionizing radiation (including thorotrast)
Marasmus

1988; Saimot et al. 1988; Scoazec et al. 1988; Simon et al. 1988; van Erpecum et al. 1988; Van Schil et al. 1988: Brick et al. 1989; Voinchet et al. 1988; Cadranel et al.,1990; (Cadranel et al. 1993; Cavalcanti et al. 1994; Chen et al. 2008; Corpa et al. 2004; Eising et al. 1990, 2007; Fine et al. 1995; Gushiken 2000; Hung et al. 2004; Kleger et al. 2009; Lorcerie et al. 1990; Matsumoto et al. 1992; Molina et al. 1995; Omori et al. 2004; Otani et al. 1992; Paliard et al. 1991; Pavlatos et al. 2001; Radin and Kanel 1991; Romagnuolo et al. 1998; Saritas et al. 2006; Scheuer et al. 1990; Sherman et al. 1992; Soe et al. 1992; Staub and Leibowitz 1996; Tsirigotis et al. 2007; Yoshioka et al. 1998).

Differential Diagnosis

Peliosis hepatis should not be confounded with simple congestive sinusoidal dilatation and with red blood cell extravasation (the so-called red blood cell-trabecular lesion; RBCTL), even though transfer of erythrocytes into the perisinusoidal space may occur in peliosis as well. RBCTL is morphologically characterized by accumulation of red blood cells in the space of Disse, frequently associated with hepatocyte plate atrophy and/or hepatocyte dropout. It is seen in hepatic venous outflow disorders (e.g., acute Budd-Chiari syndrome), liver graft harvesting injury, acute liver graft failure, left-sided heart failure without hypotension, and myeloproliferative disorders, adjacent to liver masses, and as a side effect of drugs.

Pathogenesis

The pathogenesis of peliosis hepatis has not yet been fully clarified. It has been proposed that lesions may form through cystic expansion of sinusoids or the space of Disse, in some way representing an extreme variant of sinusoidal dilatation. Whether this is so or whether peliosis is something more complex than dilatation remains to be clarified. Endothelial cell damage with cell loss and formation of gaps even enabling erythrocytes to pass into the perisinusoidal space may play an important role (Zafrani et al. 1984a). Of particular pathogenic interest is the fact that a whole spectrum of aromatic steroids and derivatives or analogs thereof can result in peliosis. Periportal sinusoidal dilatation has also been reported in pregnancy (Fisher and Neiman 1984; Perarnau and Bacq 2008). In an electron microscopic study of liver tissue with sinusoidal dilatation of patients under oral contraceptives, proliferation and an enhanced activity of sinusoidal endothelial cells were observed, but blood cell extravasation was lacking, this constellation being different from peliosis induced by androgenic steroids (Balasz 1988). This may indicate that a complex interplay between damage with gap formation and a proliferative/regenerative response may be involved, probably modulated by factors produced by adjacent hepatocytes, Kupffer cells, hepatic stellate cells, Pit cells, and intrasinusoidal leukocytes. In the rat liver, activation of Kupffer cells results in the generation and release of superoxide anion which can induce sinusoidal endothelial cell injury (SEC) (Hasegawa et al. 2001). Under several circumstances, neutrophils can accumulate in the sinusoids and produce variable degrees of SEC (Gong et al. 2002). Leakiness of sinusoids via induction of gaps as large as to allow the transit of nucleated cells can result from cell loss induced by cytostatic drugs such as cyclophosphamide (Malhi et al. 2002).

In some situations, peliosis appears to result from sinusoidal wall injury induced by neoplastic cells; this has been proposed for hairy cell leukemia (Zafrani et al. 1987). Hairy cells express nonretractable cell surface projections, in part organized by an actin-binding, leukocyte-specific phosphoprotein, pp52/LSP1 (Miyoshi et al. 2001), and resulting in intravascular cell convolutes contacting endothelial surfaces. The homing of these abnormal leukemic cells into sinusoids and their interaction with endothelial cells is

mediated by the expression of vascular adhesion molecule-1 (VCAM-1) receptors on these endothelia, whereas hyaluronan triggers the homing of hairy cells to portal tracts in the liver, but not to sinusoids, where hyaluronan expression is lacking (Aziz et al. 2000). The endothelium-damaging mechanisms are not clarified so far. Hairy cells express the interleukin (IL)-3 receptor a chain (CD123) in a characteristic pattern (Munoz et al. 2001) and produce tartrate-resistant acid phosphatase (TRAP; (Lamp and Drexler 2000). Local activity of TRAP results in the production of reactive oxygen species (ROS) which may directly damage contacting endothelial cells of the sinusoids. On the other hand, hairy cell leukemia can be associated with vasculitis (Hasler et al. 1995), eventually mediated by autoantibodies to hairy cells cross-reacting with endothelial cells (Gabriel et al. 1986), and this mechanism may be operational in hepatic peliosis. In lymphoproliferative disorders with immunoglobulin chain production, sinusoidal damage may be related to the deposition of light chains, e.g., in Waldenström's disease (Voinchet et al. 1988). Regenerative overshoot of endothelial cells may play a role in the abnormal configuration of these vascular channels in peliosis.

Are there animal models of hepatic peliosis? Aged male Long-Evans Cinnamon (LEC) rats (an animal model of Wilson's disease) develop severe lesions of peliosis hepatis, together with hepatic dysplastic/neoplastic lesions (Onaya et al. 2000). In a conditional H-RAS/V12G transgenic mouse tumor (melanoma) model with engineered VEGF tumor expression, it was found that mice harboring VEGF-expressing tumors developed a fatal liver syndrome resembling peliosis hepatis, and the severity of liver lesions was correlated with serum levels of VEGF. These interesting observations suggest that one of the main angiogenic factors, VEGF, may play a significant role in the pathogenesis of peliosis

Lipopeliosis of the Liver

The term lipopeliosis was originally coined to denote a novel form of preservation injury in a grafted liver of a 51-year-old man and superficially resembling peliosis hepatis, however with accumulation of fat within the peliotic cavities instead of blood (Ferrell et al. 1992), and later described in more detail based on five grafted livers (Cha et al. 1994). This change occurred as early as 3 days after grafting and may be associated with poor allograft function. Histologically, in four of five patients originally reported by Cha and coworkers (Cha et al. 1994), grafts exhibited in zero-time biopsies a mild or moderate fatty change. All five first post-OLT liver biopsies obtained between days 3 and 8 after grafting showed a striking dilatation of the sinusoidal spaces, shown by immunohistochemistry to represent sinusoids. Oil red O stains confirmed that these spaces were filled with fat. Lipopeliosis can be cleared within 25 days via elimination of fat by the action of the hepatic macrophage/Kupffer cell system (Cha et al. 1994). Pathogenetically, it was suggested that injured, fat-laden hepatocytes may discharge their accumulated neutral fat into the sinusoidal space; therefore, lipopeliosis may not only occur after grafting of fatty livers but also in other situations of steatosis with subsequent liver cell damage. In fact, neutral fat may leave the compartment of a steatotic liver to enter, in droplet form, the bloodstream, as exemplified by the occurrence of fat embolism in case of massive steatosis of the liver in pregnancy (Jones 1993) or in acute hepatic necrosis with steatosis (Schulz et al. 1996). However, this view as to pathogenic mechanisms involved may need revision, based on the recent observation that, in transplanted steatotic livers, large fat globules accumulate mainly outside sinusoids, thus requiring an alternate hypothesis as to how fat then may get access to the circulation (Bioulac-Sage et al. 2002). The authors propose that fat, discharged from damaged or necrotic hepatocytes, may accumulate in the extrasinusoidal space, hence mimicking dilated sinusoids, be surrounded by hepatic macrophages, and to then be cleared by macrophages. Therefore, the term lipopeliosis, previously criticized (Yokoo 1995), may in fact seem inappropriate and is replaced by pseudopeliotic steatosis (Bioulac-Sage et al. 2002).

References

Adam G, Lesser T, Neumann R (1991) Liver rupture in peliosis hepatis (in German). Zentralbl Chir 116:399–403

Akatsu T, Sakamoto M, Shimazu M, Kitajima M (2004) Pedunculated angiomyolipoma of the liver with a predominant pelioid pattern. Virchows Arch 444:467–469

Alkan S, Orenstein JM (1991) Bacillary peliosis hepatis. N Engl J Med 324:1513–1514

Atila K, Coker A, Uçar D, Karademir S, Sagol O, AStarcioglu H, Astarcioglu I (2007) A rare clinical entity misdiagnosed as a tumor: peliosis hepatis. Ulus Travma Acil Cerrahi Derg 13:149–153

Aziz KA, Till KJ, Zuzel M, Cawley JC (2000) Involvement of CD44-hyaluronan interaction in malignant cell homing and fibronectin synthesis in hairy cell leukemia. Blood 96:3161–3167

Bagheri SA, Boyer J (1974) Peliosis hepatis associated with androgenic-anabolic steroid therapy: a severe form of hepatic injury. Ann Intern Med 81:610

Bain BJ, Chong KC, Coghlan SJ, Roberts SJ (1982) Hepatic sinusoidal ectasia in association with Hodgkin's disease. Postgrad Med J 58:182–184

Balasz M (1988) Sinusoidal dilatation of the liver in patients on oral contraceptives. Electron microscopical study of 14 cases. Exp Pathol 35:231–237

Bank J, Lykkebo D, Hagerstrand I (1978) Peliosis hepatis in a child. Acta Paediatr Scand 67:105–107

Baron C, OCallaghan D, Lanka E (2002) Bacterial secrets of secretion: EuroConference on the biology of type IV secretion processes. Mol Microbiol 43:1359–1365

Battal B, Kocaoglu M, Atay AA, Bulakbasi N (2010) Multifocal peliosis hepatis. MR and diffusion-weighted MR-imaging findings of an atypical case. Ups J Med Sci 115:153–156

Berzigotti A, Magalotti D, Zappoli P, Rossi C, Callea F, Zoli M (2006) Peliosis hepatis as an early histological finding in idiopathic portal hypertension: a case report. World J Gastroenterol 12:3612–3615

Bexten T, Burck I, Bechstein WO, Moench C (2012) Hepatic peliosis – a rare liver tumor and challenge for diagnostic investigation plus therapy (in German). Dtsch Med Wochenschr 137:1505–1509

Bioulac-Sage P, Balabaud C, Ferrell L (2002) Lipopeliosis revisited: should we keep the term? Am J Surg Pathol 26:134–135

Bjork O, Eklof O, Willi U, Ahstrom L (1985) Veno-occlusive disease and peliosis of the liver complicating the course of Wilms' tumour. Acta Radiol Diagn (Stockh) 26:589–597

Bonatti H, Mendez J, Guerrero I, Krishna M, Ananda-Michel J, Yao J, Steers JL, Hellinger W et al (2006) Disseminated Bartonella infection following liver transplantation. Transpl Int 19:683–687

Bonnet P, Smadja C, Szekely AM, Delage Y, Calmus Y, Poupon R, Franco D (1987) Intractable ascites in systemic mastocytosis treated by portal diversion. Dig Dis Sci 32:209–213

Bracero LA, Gambon TB, Evans R, Beneck D (1995) Ultrasonographic findings in a case of congenital peliosis hepatis. J Ultrasound Med 14:483–486

Breitschwerdt EE, Kordick DL (2000) Bartonella infection in animals: carriership, reservoir potential, pathogenicity, and zoonotic potential for human infection. Clin Microbiol Rev 13:428–438

Brick JE, Moreland LW, Al-Kawas F, Chang WWL, Layne RD, DiBartolomeo AG (1989) Prospective analysis of liver biopsies before and after methotrexate therapy in rheumatoid patients. Semin Arthritis Rheum 19:31–44

Brochard P, Lejonc JL, Schaefer A, Portos JL (1981) Idiopathic peliosis hepatis: case report and review of the literature. Ann Med Interne 132:195–199

Buelow B, Otjen J, Sabath AP, Harruff RC (2012) Peliosis hepatis presenting as liver rupture in a vulnerable adult: a case report. Am J Forensic Med Pathol 33:307–310

Burger RA, Marcuse PM (1952) Peliosis hepatis; report of case. Am J Clin Pathol 22:569–573

Burgess AW, Anderson BE (1998) Outer membrane proteins of *Bartonella henselae* and their interaction with human endothelial cells. Microb Pathog 25:157–164

Burgess AWO, Paquet J-Y, Letesson J-J, Anderson BE (2000) Isolation, sequencing and expression of *Bartonella henselae* omp43 and predicted membrane topology of the deduced protein. Microb Pathog 29:73–80

Cadranel JF, Cadranel J, Buffet C, Fabre M, Pelletier G, d'Agay MF, Ink O, Roche A, Milleron B, Etienne JP (1990) Nodular regenerative hyperplasia of the liver, peliosis hepatis, and perisinusoidal fibrosis. Association with angioimmunoblastic lymphadenopathy and severe hypoxemia. Gastroenterology 99:268–273

Cadranel JF, Legendre C, Desaint B, Delamarre N, Florent C, Levy VG (1993) Liver disease from surreptitious administration of urethane. J Clin Gastroenterol 17:52–56

Carucci LR, Halvorsen RA (2006) Hepatic peliosis (bacillary angiomatosis) in AIDS: CT findings. Abdom Imaging 31:253

Cavalcanti R, Pol S, Carnot F, Campos H, Degott C, Driss F, Legendre C, Kreis H (1994) Impact and evolution of peliosis hepatis in renal transplant recipients. Transplantation 58:315–316

Cha I, Bass N, Ferrell L (1994) Lipopeliosis. An immunohistochemical and clinicopathologic study of five cases. Am J Surg Pathol 18:789–795

Chawla SK, Patel HD, Mahadevia SS, LoPresti PA (1980) Portal hypertension in peliosis hepatis. Report of the first case. Am J Proctol Gastroenterol Colon Rectal Surg 31:11–12

Chen JF, Chen WX, Zhang HY, Zhang WY (2008) Peliosis and gummatous syphilis of the liver: a case report. World J Gastroenterol 14:1961–1963

Choi SK, Jin JS, Cho SG, Choi SJ, Kim CS, Choe YM, Lee KY (2009) Spontaneous liver rupture in a patient with peliosis hepatis: a case report. World J Gastroenterol 15:5493–5497

Conley T, Slater L, Hamilton K (1994) Rochalimaea species stimulate human endothelial cell proliferation and migration in vitro (see comments). J Lab Clin Med 124:521–528

Corpa MV, Bacchi MM, Bacchi CE, Coelho KI (2004) Peliosis hepatis associated with lymphoplasmacytic lymphoma: an autopsy case report. Arch Pathol Lab Med 128:1283–1285

Cragg A, Castaneda-Zuniga W, Lund G, Salomonowitz E, Amplatz K (1984) Infantile peliosis hepatis. A case report. Pediatr Radiol 14:340–342

Czapar CA, Weldon-Linne CM, Moore DM et al (1986) Peliosis hepatis in the acquired immunodeficiency syndrome. Arch Pathol Lab Med 110:611–613

Dai and Zhang 2013. http://www.ncbi.nlm.nih.gov/pubmed/24137445

Degott C, Rueff B, Kreis H, Duboust A, Potet F, Benhamou JP (1978) Peliosis hepatis in recipients of renal transplants. Gut 19:748–753

Dehio C (2004) Molecular and cellular basis of Bartonella pathogenesis. Annu Rev Microbiol 58:365–390

Dejgaard A, Krogsgaard K, Jacobsen M (1984) Veno-occlusive disease and peliosis of the liver after thorotrast administration. Virchows Arch A Pathol Anat Histopathol 403:87–94

Devio C (2001) Bartonella interactions with endothelial cells and erythrocytes. Trends Microbiol 9:279–285

Devio C (2005) Bartonella-host-cell interactions and vascular tumour formation. Nat Rev Microbiol 3:621–631

Devio C, Meyer M, Berger J, Schwarz H, Lanz C (1997) Interaction of *Bartonella henselae* with endothelial cells results in bacterial aggregation on the cell surface and the subsequent engulfment and internalisation of the bacterial aggregate by a unique structure, the invasome. J Cell Sci 110:2141–2154

Eising EG, Auffermann W, Peters PE, Schmidt H, Ullrich K (1990) Focal peliosis of the adult liver in combination with glycogenosis type I (v.Gierke). A case report and review of the recent literature (in German). Radiologe 30:428–432

Elsing C, Placke J, Herrmann T (2007) Alcohol binging causes peliosis hepatis during azathioprine therapy in Crohn's disease. World J Gastroenterol 13:4646–4648

Fabris A (1900) Cavernöse Degeneration der Leber. Beitr Path Anat Allgem Path 28:349–362

Ferrell L, Bass N, Roberts J, Ascher N (1992) Lipopeliosis: fat-induced sinusoidal dilatation in transplanted liver mimicking peliosis hepatis. J Clin Pathol 45:1109–1110

Ferrozzi F, Tognini G, Zuccoli G, Cademartiri F, Pavone P (2001) Peliosis hepatis with pseudotumoral and hemorrhagic evolution: CT and MR findings. Abdom Imaging 26:197–199

Fidelman N, LaBerge JM, Kerlan RK (2002) SCVIR 2002 Film Panel case 4: massive intraperitoneal hemorrhage caused by peliosis hepatis. J Vasc Intwrv Radiol 13:542–545

Fine KD, Solano M, Polter DE, Tillery GW (1995) Malignant histiocytosis in a patient presenting with hepatic dysfunction and peliosis hepatis. Am J Gastroenterol 90:485–488

Fisher MR, Neiman HL (1984) Periportal sinusoidal dilatation associated with pregnancy. Cardiovasc Intervent Radiol 7:299–302

Florin TA, Zaoutis TE, Zaoutis LB (2008) Beyond cat scratch disease: widening spectrum of *Bartonella henselae* infection. Pediatrics 121:e1413–e1425

Fuhrmann O, Arvand M, Gohler A, Schmid M, Krull M, Hippenstiel S, Seybold J, Dehio C, Suttorp N (2001) *Bartonella henselae* induces NF-kappaB-dependent upregulation of adhesion molecules in cultured human endothelial cells: possible role of outer membrane proteins as pathogenic factors. Infect Immun 69:5088–5097

Furuta M, Asamoto H, Kitaichi M, Harada N, Obara A, Matsumoto S (1982) A case of peliosis hepatis appearing in a patient with lepromatous leprosy (in Japanese). Nippon Rai Gakkai Zasshi 51:22–27

Gabriel SE, Conn DT, Phyliky RL, Pittelkow MR, Scott RE (1986) Vasculitis in hairy cell leukemia: review of literature and consideration of possible pathogenic mechanisms. J Rheumatol 13:1167

Garnier T, Parelon G, Bauret P, Ampelas M, Bories P, Michel H (1986) Peliosis hepatis associated with pulmonary tuberculosis simulating acute alcoholic hepatitis (in French). Gastroenterol Clin Biol 10:774–775

Geisler W (1931) Über die sogenannte Peliosis der Leber. Virchows Arch Path Anat 280:565–578

Gong JP, Wu CX, Liu CA, Li SW, Shi YJ, Li XH, Peng Y (2002) Liver sinusoidal endothelial cell injury by neutrophils in rats with acute obstructive cholangitis. World J Gastroenterol 8:342–345

Grätzer G (1928) Über sogenannte "Peliosis hepatis". Frankfurt Ztschr Pathol 36:134–145

Gulubova M (2002) Immunohistochemical localization of collagen type III and type IV, laminin, tenascin and alpha-smooth muscle actin (alpha SMA) in the human liver in peliosis. Pathol Res Pract 198:803–812

Gulubova MV (2005) Expression of cell adhesion molecules and their beta1 and beta2 integrin ligands in human liver peliosis. Pathol Res Pract 201:503–511

Gushiken FC (2000) Peliosis hepatis after treatment with 2-chloro-3′-deoxyadenosine. South Med J 93:625–626

Hamilton FT, Lubitz JM (1952) Peliosis hepatis. report of three cases, with discussion of pathogenesis. Arch Pathol 54:564–572

Han JK, Kim SH (2006) Focal peliosis hepatis mimicking hepatocellular carcinoma (in Korean). Korean J Hepatol 12:460–463

Hankey GJ, Saker BM (1987) Peliosis hepatis in a renal transplant recipient and in a haemodialysis patient. Med J Aust 19:102–105

Hasegawa T, Nakano M, Hashimoto T, Hiraishi K, Suzuki K, Kuwano H (2001) Sinusoidal endothelial cell injury by superoxide anion and iron in the Propionibacterium acnes-pretreated and lipopolysaccharide-stimulated rat liver. Liver 21:415–424

Hasler P, Kistler H, Gerber H (1995) Vasculitides in hairy cell leukemia. Sem Arthritis Rheumatol 25:134
Hayward SR, Lucas CE, Ledgerwood AM (1991) Recurrent spontaneous intrahepatic haemorrhage from peliosis hepatis. Arch Surg 126:782–783
Hedren G (1909) Telangiectasia hepatis disseminata und ihre Pathogenese. Beitr Path Anat Allgem Path 45:306–324
Herrera LO, Glassman CI, Teixido RA, Oglesby JT, Andrade EL, Rodrigue RB (1981) Peliosis hepatis associated with cavernous hemangioma and hepatocarcinoma. Am Surg 47:502–506
Hillion D, De Viel E, Bergue A, Bruet A, Dongradi G, Fendler JP (1983) Peliosis hepatis in a chronic hemodialysis patient. Nephron 35:205–206
Hiorns MP, Rossi UG, Roebuck DJ (2005) Peliosis hepatis causing inferior vena cava compression in a 3-year-old child. Pediatr Radiol 35:209–211
Houpikian and Raoult 2001. http://www.ncbi.nlm.nih.gov/pubmed/11473990
Huang CY, Wang ZW (2013) Peliosis hepatis mimicking hepatic malignancy: a case report. J Dig Dis 14:272–275
Hung NR, Chantrain L, Dechambre S (2004) Peliosis hepatis revealed by biliary colic in a patient with oral contraceptive use. Acta Chir Belg 104:727–729
Hyodo M, Mellon MA, Larsen PN, Wettergren A, Rasmussen A, Kirkegaard P et al (2004) Idiopathic extensive peliosis hepatis treated with liver transplantation. J Hepatobiliary Pancreat Surg 11:371–374
Iannaccone R, Federle MP, Brancatelli G, Matsui O, Fishman EK, Narra VR, Grazioli L et al (2006) Peliosis hepatis: spectrum of imaging findings. AJR Am J Roentgenol 187:W43–W52
Ikeda N, Oka K, Yonekawa N, Takaku H, Suzuki T, Saitoh T, Nagakura S, Nakano M (2011) Pelioid-type well-differentiated hepatocellular carcinoma in a patient with a history of taking oral contraceptives: report of a case. Surg Today 41:1270–1274
Jacomo V, Kelly PJ, Raoult D (2002) Natural history of Bartonella infections (an exception to Koch's postulate). Clin Diagn Lab Immunol 9:8–18
Jacquemin E, Pariente D, Fabre M, Huault G, Valayer J, Bernard O (1999) Peliosis hepatis with initial presentation as acute hepatic failure and intraperitoneal hemorrhage in children. J Hepatol 30:1146–1150
Jamadar DA, D'Souza SP, Thomas EA, Giles TE (1994) Case report: radiological appearances in peliosis hepatis. Br J Radiol 67:102–104
Ji EK, Ryu JS, Kang GH, Moon DH, Auh YH, Lee HK (2001) Pelioid-type hepatocellular carcinoma masquerading as a hepatic hemangioma on technetium-99m red blood cell scintigraphy. Clin Nucl Med 26:33–35
Jones MB (1993) Pulmonary fat embolism associated with acute fatty liver of pregnancy. Am J Gastroenterol 88:791–792
Karem KL (2000) Immune aspects of Bartonella. Crit Rev Microbiol 26:133–145
Karem KL, Dubois KA, McGill SL, Regnery RL (1999) Characterization of *Bartonella henselae*-specific immunity in BALB/c mice. Immunology 97:352–358
Karger B, Varchmin-Schultheiss K, Fechner G (2005) Fatal hepatic haemorrhage in a child-peliosis hepatis versus maltreatment. Int J Legal Med 119:44–46
Kawamoto S, Wakabayashi T (1980) Peliosis hepatis in a newborn infant. Arch Pathol Lab Med 104:444–445
Kempf VA, Schaller M, Behrendt S, Volkmann B, Aepfelbacher M, Cakman I, Autenrieth IB (2000) Interaction of *Bartonella henselae* with endothelial cells results in rapid bacterial rRNA synthesis and replication. Cell Microbiol 2:431–441
Kempf VA, Volkmann B, Schaller M, Sander CA, Alitalo K, Riess T, Autenrieth IB (2001) Evidence of a leading role for VEGF in *Bartonella henselae*-induced endothelial cell proliferations. Cell Micobiol 3:623–632
Kent G, Thompson JR (1961) Peliosis hepatis; involvement of reticuloendothelial system. Arch Pathol 72:658–664
Khadikhar UN, Prabhu S, Sharma D (2008) Peliosis hepatis presenting as hemoperitoneum. Indian J Med Sci 62:236–237
Kim SH, Lee JM, Kim WH, Han JK, Lee JY, Choi BI (2007a) Focal peliosis hepatis as a mimicker of hepatic tumors: radiological-pathological correlation. J Comput Assist Tomogr 31:79–85
Kim EA, Yoon KH, Joen SJ, Cai QY, Lee YW, Yoon SE, Yoon KJ, Juhng SK (2007b) Peliosis hepatis with hemorrhagic necrosis and rupture: a case report with emphasis on the multi-detector CT findings. Korean J Radiol 8:64–69
Kleger A, Bommer M, Kunze M, Klaus J, Leithaeuser F, Wegener M, Adler G, Dikopoulos N (2009) First reported case of disease: peliosis hepatis as cardinal symptom of Hodgkin's lymphoma. Oncologist 14:1088–1094
Kleinig P, Davies RP, Maddern G, Kew J (2003) Peliosis hepatis: central "fast surge" ultrasound enhancement and multislice CT appearances. Clin Radiol 58:995–998
Koehler JE, Sanchez MA, Garrido CS, Whitfeld MJ, Chen FM, Berger TG, Rodriguez-Barradas MC, LeBoit PE, Tappero JW (1997) Molecular epidemiology of bartonella infections in patients with bacillary angiomatosis-peliosis. N Engl J Med 337:1876–1883
Kordick DL, Hilyard EJ, Hadfield TL, Wilson KH, Steigerwalt AG, Brenner DJ, Breitschwerdt EB (1997) *Bartonella clarridgeiae*, a newly recognized zoonotic pathogen causing inoculation papules, fever, and lymphadenopathy (cat scratch disease). J Clin Microbiol 35:1813–1818
Lamp EC, Drexler HG (2000) Biology of tartrate-resistant acid phosphatase. Leuk Lymphoma 39:477–484
Larrey D, Freneaux E, Berson A, Babany G, Degott C, Valla D, Pessayre D, Benhamou JP (1988) Peliosis hepatis induced by 6-thioguanine administration. Gut 29:1265–1269

LeBoit PE, Berger TG, Egbert BM, Yen TS, Stoler MH, Bonfiglio TA, Strauchen JA, English CK, Wear DJ (1988) Epithelioid haemangioma-like vascular proliferation in AIDS: manifestation of cat scratch disease bacillus infection? Lancet 1(8592):960–963

Leong SS, Cazen RA, Yu GS, LeFevre L, Carson JW (1992) Abdominal visceral peliosis associated with bacillary angiomatosis. Ultrastructural evidence of endothelial destruction by bacilli. Arch Pathol Lab Med 116:866–871

Liu C, Pasupathy A, Weltman M (2014) Multifocal peliosis hepatis simulating metastatic malignancy. Dig Liver Dis 46:862–863

Loomus GN, Aneja P, Bota RA (1983) A case of peliosis hepatis associated with tamoxifen therapy. Am J Clin Pathol 80:881–883

Lorcerie B, Grobost O, Lalu-Fraisse A, Piard F, Camus P, Portier H, Martin F (1990) Peliosis hepatis in dermatomyositis treated with azathioprine and corticoids (in French). Rev Med Interne 11:25–28

Lunghetti A (1914) Über eine Fall von disseminierter Telangiektasie oder kavernomatöser Entartung der Leber. Zentralbl Allgem Path Path Anat 25:790

Maeno N, Oda H, Yoshiie K, Wahid MR, Fujimura T, Matayoshi S (1999) Live *Bartonella henselae* enhances endothelial cell proliferation without direct contact. Microb Pathog 27:419–427

Maeno N, Yoshiie K, Matayoshi S, Fujimura T, Mao S, Wahid MR, Oda H (2002) A heat-stable component of *Bartonella henselae* upregulates intercellular adhesion molecule-1 expression on vascular endothelial cells. Scand J Immunol 55:366–372

Malhi H, Annamaneni P, Slehria S, Joseph B, Bhargava KK, Palestro O, Novikoff PM, Gupta S (2002) Cyclophosphamide disrupts hepatic sinusoidal endothelium and improves transplanted cell engraftment in rat liver. Hepatology 36:112–121

Marechal R, Taccone FS, Bourgeois N, Hittelet A (2005) Spontaneous intrahepatic haemorrhage due to peliosis hepatis (in French). Rev Med Brux 26:451–454

Matsumoto T, Yoshimine T, Shimouchi K, Shiotu H, Kuwabara N, Fukuda Y, Hoshi T (1992) The liver in systemic lupus erythematosus: pathologic analysis of 52 cases and review of Japanese Autopsy Registry Data. Hum Pathol 23:1151–1158

McGiven AR (1970) Peliosis hepatis: case report and review of pathogenesis. J Pathol 101:283

Meusburger A (1934) Telangiectasia hepatis disseminata beim Menschen. Ztschr Kreislaufforsch 26:877–879

Mittasch G (1920) Über Leberblutungen bei Lungentuberkulose. Virchows Arch Path Anat 228:476–482

Miyoshi EK, Stewart PL, Kincade PW, Lee MB, Thompson AA, Wall R (2001) Aberrant expression and localization of the cytoskeleton-binding pp 52 (LSP1) protein in hairy cell leukemia. Leuk Res 25:57–67

Molina T, Delmer A, Le Tourneau A, Texier P, Degott C, Audoin J, Zittoun R, Diebold J (1995) Hepatic lesions of vascular origin in multicentric Castleman's disease, plasma cell type: report of one case with peliosis hepatis and another with perisinusoidal fibrosis and nodular regenerative hyperplasia. Pathol Res Pract 191:1159–1164

Mourad G, Bories P, Berthelemy C, Barneon G, Michel H, Mion C (1987) Peliosis hepatis and nodular regenerative hyperplasia of the liver in renal transplants. Is cytomegalovirus the cause of this severe disease? Transplant Proc 19:3697–3698

Mungan Z, Pinarbasi B, Bakir B, Gulluoglu M, Baran B, Akyuz F, Demir K, Kaymakoglu S (2009) Congenital portal vein aneurysm associated with peliosis hepatis and intestinal lymphangiectasia. Gastroenterol Res Pract 2009:479264

Munoz L, Nomdedeu JF, Lopez O, Carnicer MJ, Bellido M, Aventin A, Brunet S, Sierra J (2001) Interleukin-3 receptor a chain (CD123) is widely expressed in hematologic malignancies. Haematologica 86:1261–1269

Muradali D, Wilson SR, Wanless IR, Greig PD, Cattral M, Cameron RO, Levy GA (1996) Peliosis hepatis with intrahepatic calcifications. J Ultrasound Med 15:257–260

Murano I, Yoshii H, Kurashige H, Sugio Y, Tsukahara M (2001) Giant hepatic granuloma caused by *Bartonella henselae*. Pediatr Infect Dis J 20:319–320

Naeim F, Copper P, Semion AA (1973) Peliosis hepatis: possible etiologic role of anabolic steroids. Arch Pathol 95:284

Nesher G, Dollberg L, Zimran A, Hershko C (1985) Hepatosplenic peliosis after danazol and glucocorticoids for ITP. N Engl J Med 312:242–243

Nougaret S, Aufort S, Ramos J, Pierredon MA, Delhom E, Colleau J, Ragu N, Gallix B et al (2009) Hepatic peliosis: an entity to remember (in French). J Radiol 90:1745–1749

Nuernberger S, Ramos C (1975) Peliosis hepatis in an infant. J Pediatr 87:424–426

Okuda K, Omata M, Itoh Y, Ikezaki H, Nakashima T (1981) Peliosis hepatis as a late and fatal complication of thorotrast liver disease. Report of five cases. Liver 1:110–122

Omori H, Asahi H, Irinoda T, Takahashi M, Kato K, Saito K (2004) Peliosis hepatis during postpartum period: successful embolization of hepatic artery. J Gastroenterol 39:168–171

Onaya H, Itai Y, Yoshioka H, Doy M, Mitsumori F (2000) Peliosis hepatis and neoplastic/dysplastic lesions in aged male Long-Evans Cinnamon rats: MR imaging with pathologic correlation. Magn Reson Imaging 18:143–150

Oriordan K, Blei A, Vogelzang R, Nemcek A, Abecassis M (2000) Peliosis hepatis with intrahepatic hemorrhage: successful embolization of the hepatic artery. HPB Surg 11:353–358

Otani M, Ohaki Y, Nakatani Y, Ito E, Shimoyama K, Misugi K (1992) An autopsy case of renal cell carcinoma associated with extensive peliosis hepatis. Acta Pathol Jpn 42:62–68

Paliard P, Valette PJ, Berger F, Contassot JC, Partensky C (1991) Peliosis hepatis of late onset in a patient exposed

to vinyl chloride and treated for hepatic angiosarcoma (in French). Gastroenterol Clin Biol 15:445–448
Paradinas FJ, Bull TB, Westaby D, Murray-Lyon IM (1977) Hyperplasia and prolapse of hepatocytes into hepatic veins during long-term methyltestosterone therapy: possible relationships of these changes to the development of peliosis hepatis and liver tumours. Histopathology 1:225–246
Pautard JC, Baculard A, Boccon-Gibod L, Carlioz H, Tournier G (1986) Hepatic peliosis in bacterial endocarditis in a child with Marfan disease (in French). Presse Med 15:1973–1974
Pavlatos AM, Fultz O, Monberg MJ, Vootkur A (2001) Review of oxymetholone: a 17alpha-alkylated anabolic-androgen steroid. Clin Ther 23:789–801
Peltason F (1921) Über multiple Leberblutungen bei Miliartuberkulose. Virchows Arch Path Anat 230:230–259
Perarnau JM, Bacq Y (2008) Hepatic vascular involvement related to pregnancy, oral contraceptives, and estrogen replacement therapy. Semin Liver Dis 28:315–327
Perkocha LA, Geaghan SM, Yen TS, Nishimura SL, Chan SP, Garcia-Kennedy R, Honda G, Stoloff AC, Klein HZ, Goldman RL et al (1990) Clinical and pathological features of bacillary peliosis hepatis in association with human immunodeficiency virus infection. N Engl J Med 323:1581–1586
Puppala AR, Ro JA (1979) Possible association between peliosis hepatis and diethylstilbestrol: report of two cases. Postgrad Med 65:280–281
Radin DR, Kanel GC (1991) Peliosis hepatis in a patient with human immunodeficiency virus infection. AJR Am J Roentgenol 156:91–92
Raoult D (2007) From cat scratch disease to *Bartonella henselae* infection. Clin Infect Dis 45:1541–1542
Reed JA, Brigati DJ, Flynn SD, McNutt NS, Min KW, Welch DF, Slater LN (1992) Immunocytochemical identification of Rochalimaea henselae in bacillary (epithelioid) angiomatosis, parenchymal bacillary peliosis, and persistent fever with bacteremia. Am J Surg Pathol 16:650–657
Relman DA, Fredricks DN, Yoder KE, Mirowski G, Berger T, Koehler J (1999) Absence of Kaposi's sarcoma-associated herpes virus DNA in bacillary angiomatosis-peliosis lesions. J Infect Dis 180:1386–1389
Romagnuolo J, Sadowski DC, Lalor E, Jewell L, Thomson AB (1998) Cholestatic hepatocellular injury with azathioprine: a case report and review of the mechanisms of hepatotoxicity. Can J Gastroenterol 12:479–483
Saatci I, Coskun M, Boyvat F, Cila A, Gürgey A (1995) MR findings in peliosis hepatis. Pediatr Radiol 25:31–33
Saimot AG, Benhamou J-P, Feldmann G (1988) Peliosis hepatis and sinusoidal dilation during infection by the human immunodeficiency virus (HIV). An ultrastructural study. Am J Pathol 131:38–47
Samyn M, Hadzic N, Davenport M, Verma A, Karani J, Portmann B, Mieli-Vergani G (2004) Peliosis hepatis in childhood: case report and review of the literature. J Pediatr Gastroenterol Nutr 39:431–434
Saritas U, Ustundaq Y, Isitan G, Bastugrul S, Erekul S (2006) Abdominal Castleman disease with mixed histopathology in a patient with iron deficiency anemia, growth retardation and peliosis hepatis. Am J Med Sci 331:51–54
Savastano S, San BO, Velo E, Rettore C, Altavilla G (2005) Pseudotumoral appearance of peliosis hepatis. AJR Am J Roentgenol 185:558–559
Scheidegger F, Ellner Y, Guye P, Rhomberg TA, Weber H, Augustin H, Dehio C (2009) Distinct activities of *Bartonella henselae* type IV secretion effector proteins modulate capillary-like sprout formation. Cell Microbiol 11:1088–1101
Scherer G, Roeren T, Hofmann W, Brado M, Kauffmann GW (1996) Surprising finding of a hepatic hemangiosarcoma with concomitant peliosis hepatis (in German). Rofo Fortschr Geb Roentgenstr Neuen Bildgeb Verfahr 165:305–308
Scheuer PJ, Schachtler LA, Mathur S, Burroughs AK, Rolles K (1990) Peliosis hepatis after liver transplantation. J Clin Pathol 43:1036–1037
Schmid MC, Schulein R, Dehio M, Denecker G, Carena I, Dehio C (2004) The VirB type IV secretion system of *Bartonella henselae* mediates invasion, proinflammatory activation and antiapoptotic protection of endothelial cells. Mol Microbiol 52:81.92
Schmiederer M, Arcenas R, Widen R, Valkov N, Anderson B (2001) Intracellular induction of the *Bartonella henselae* virB operon by human endothelial cells. Infect Immun 69:6495–6502
Schönlank FW (1916) Ein Fall von Peliosis hepatis. Virchows Arch (Pathol Anat) 222:358–364
Schrohe T (1899) Teleangiektasien der Leber. Virchows Arch Pathol Anat 156:37–61
Schulz F, Trubner K, Hildebrand E (1996) Fatal fat embolism in acute hepatic necrosis with associated fatty liver. Am J Forensic Med Pathol 17:264–268
Schwartzman WA, Marchevsky A, Meyer RD (1990) Epithelioid angiomatosis or cat scratch disease with splenic and hepatic abnormalities in AIDS: case report and review of the literature. Scand J Infect Dis 22:121–133
Scoazec et al. 1988. http://www.ncbi.nlm.nih.gov/pubmed/3354642
Selby and Stocker 1995. http://www.ncbi.nlm.nih.gov/pubmed/8597845
Senf HW (1939) Über die Entstehung der verschiedenen Formen miliarer Leberblutungen (Peliosis hepatis). Virchows Arch Pathol Anat 304:539–554
Seubert A, Schulein R, Dehio C (2002) Bacterial persistence within erythrocytes: a unique pathogenic strategy of Bartonella spp. Int J Med Microbiol 291:555–560
Sherman D, Ramsay B, Theodorou NA, Woodrow D, Paradinas FP, Cream JJ, Murray-Lyon IM (1992) Reversible plane xanthoma, vasculitis, and peliosis hepatis in giant lymph node hyperplasia (Castleman's disease): a case report and review of the cutaneous

manifestations of giant lymph node hyperplasia. J Am Acad Dermatol 26:105–109
Simon DM, Krause R, Galambos JT (1988) Peliosis hepatis in a patient with marasmus. Gastroenterology 95:805–809
Slater LN, Welch DF, Min KW (1992) Rochalimaea henselae causes bacillary angiomatosis and peliosis hepatis. Arch Intern Med 152:602–606
Smathers RL, Heiken JP, Lee JK, Press GA, Balfe DM (1984) Computed tomography of fatal hepatic rupture due to peliosis hepatis. J Comput Assist Tomogr 8:768–769
Soe KL, Soe M, Gluud C (1992) Liver pathology associated with the use of anabolic-androgenic steroids. Liver 12:73–79
Solis-Herruzo JA, Colina F, Munoz-Yague MT, Castellano G, Morillas JD (1983) Reddish-purple areas on the liver surface: the laparoscopic picture of peliosis hepatis. Endoscopy 15:96–100
Staub PG, Leibowitz CB (1996) Peliosis hepatis associated with oral contraceptive use. Australas Radiol 40:172–174
Steinke K, Terraciano L, Wiesner W (2003) Unusual cross-sectional imaging findings in hepatic peliosis. Eur Radiol 13:1916–1919
Swetschnikow WA (1910) Über eigentümliche Teleangiektasien der Leber. Zbl Allg Pathol Pathol Anat 21:1085
Tateishi T, Machi J, Morioka WK (1998) Focal peliosis hepatis resembling metastatic liver tumor. J Ultrasound Med 17:581–584
Taxy JB (1978) Peliosis: a morphologic curiosity becomes a iatrogenic problem. Hum Pathol 9:331–340
Terlizzi JP, Azizi R, Chow MD, Underberg-Davis S, Nosher JL, Stafford PW, Pierre J (2013) Peliosis hepatis in a child with myotubular myopathy: successful treatment using hepatic artery embolization. J Pediatr Surg 48:e9–e12
Toth P, Takacs I, Kerekes L, Sapy P (2002) Chirurgische Behandlung der intraabdominellen Blutung bei Peliose der Leber. Chirurg 73:83–85
Trites AE (1957) Peliosis hepatis; report of a case. AMA Arch Pathol 63:183–186
Tsirigotis P, Sella T, Shapira MY, Bitan M, Bloom A, Kiselgoff D, Levin M, Libster D et al (2007) Peliosis hepatis following treatment with androgen-steroids in patients with bone marrow failure syndromes. Haematologica 92:e106–e110
Tsokos M, Erbersdobler A (2005) Pathology of peliosis. Forensic Sci Int 149:25–33
Tsukamoto Y, Nakata H, Kimoto T, Noda T, Kuroda Y, Haratake J (1984) CT and angiography of peliosis hepatis. AJR Am J Roentgenol 142:539–540
Tzirogiannis KN, Papadimas GK, Kondyli VG, Kourentzi KT, Demonakou MD, Kyriakou LG et al (2006) Peliosis hepatis: microscopic and macroscopic type, time pattern, and correlation with liver cell apoptosis in a model of toxic liver injury. Dig Dis Sci 51:1998–2006
Usatin M, Wigger H (1976) Peliosis in a child. Arch Pathol Lab Med 100:419–421
van Erpecum KJ, Janssens AR, Kreuning J, Ruiter DJ, Kroon HM, Grond AJ (1988) Generalized peliosis hepatis and cirrhosis after long-term use of oral contraceptives. Am J Gastroenterol 83(572–575):1988
Van Schil P, Mortelmans L, Schoofs E, Bourgeois N, Van Hee R, Vaneerdweg W, Vereycken H, Heytens L (1988) Peliosis hepatis associated with liver and retroperitoneal abscesses. Digestion 41:55-–60
Verswijvel G, Janssens F, Colla P, Mampaey S, Verheist H, Van Eycken P, Erven W (2003) Peliosis hepatis presenting as a multifocal hepatic pseudotumor: MR findings in two cases. Eur Radiol 13(suppl 4):L40–L44
Vignaux O, Legmann P, de Pinieux G, Chaussade S, Spaulding C, Couturier D, Bonnin A (1999) Hemorrhagic necrosis due to peliosis hepatis: imaging findings and pathological correlation. Eur Radiol 9:454–456
Voinchet O, Degott C, Scoazec JY, Feldmann G, Benhamou JP (1988) Peliosis hepatis, nodular regenerative hyperplasia of the liver, and light-chain deposition in a patient with Waldenstrom's macroglobulinemia. Gastroenterology 95:482–486
Wagner E (1861) Ein Fall von Blutcysten der Leber. Arch Heilkd 2:369–370
Wakabayashi T, Onda H, Tada T, Iijima M, Itoh Y (1984) High incidence of peliosis hepatis in autopsy cases of aplastic anemia with special reference to analbolic steroid therapy. Acta Pathol Jpn 34:1079–1086
Walford N, Van der Wouw PA, Das PK, Ten Velden JJ, Hulsebosch HJ (1990) Epithelioid angiomatosis in the acquired immunodeficiency syndrome: morphology and differential diagnosis. Histopathology 16:83–88
Wang SY, Ruggles S, Vade A, Newman BM, Borge MA (2001) Hepatic rupture caused by peliosis hepatis. J Pediatr Surg 36:1456–1459
Wannesson L, Chigrinova E, Raditchkova M, Mazzucchelli L, Ghielmini M (2009) Peliosis hepatis in cancer patients mimicking infection and metastases. Onkologie 32:54–56
Weber HW (1947) Beitrag zur Morphologie und Pathogenese der Peliosis hepatis. Frankfurt Ztschr Pathol 59:52–58
Welch DF, Pickett DA, Slater LN, Steigerwalt AG, Brenner DJ (1992) Rochalimaea henselae sp.nov., a cause of septicemia, bacillary angiomatosis, and parenchymal bacillary peliosis. J Clin Microbiol 30:275–280
Willen H, Willen R, Gad A, Thorstensson S (1979) Peliosis hepatis as a result of endogenous steroid hormone production. Virchows Arch A Pathol Anat Histol 383:233–240
Winkler K, Poulsen H (1975) Liver disease with periportal sinusoidal dilatation. A possible complication to contraceptive steroids. Scand J Gastroenterol 10:699–704
Wold LE, Ludwig J (1981) Peliosis hepatis: two morphologic variants? Hum Pathol 12:388–389
Xiong WJ, Hu LJ, Jian YC, He Y, Zhou W, Guo XL, Zheng YX (2012) Focal peliosis hepatis in a colon cancer

patient resembling metastatic liver tumor. World J Gastroenterol 18:5999–6002
Yanoff M, Rawson AJ (1964) Peliosis hepatis: an anatomic study with demonstration of two variants. Arch Pathol 77:159–165
Yap I, Yeoh KG, Wee A, Kang JY, Tan L (1993) Peliosis hepatis: a case report. Ann Acad Med Singap 22:381–383
Yekeler E, Dursun M, Tunaci A, Cevikbas U, Rozanes I (2004) Diagnosing of peliosis hepatis by magnetic resonance imaging. J Hepatol 41:351
Yokoo H (1995) Lipopeliosis. Am J Surg Pathol 19:971
Yoshioka K, Sato T, Ishii T, Tanaka S, Kioka K, Harihara S, Imamoto S, Haze K, Inoue T, Fujii S (1998) Peliosis hepatis associated with idiopathic restrictive cardiomyopathy. Intern Med 37:51–55
Young JM (1953) Peliosis hepatis; report of two cases. Am Rev Tuberc 67:385–390
Zafrani ES, Cazier A, Baudelot A-M, Feldmann G (1984a) Ultra-structural lesions of the liver in human peliosis: a report of 12 cases. Am J Pathol 114:349–359
Zafrani ES, Bernuau D, Feldmann G (1984b) Peliosis-like ultrastructural changes of the hepatic sinusoids in human chronic hypervitaminosis A: report of three cases. Hum Pathol 15:1166–1170
Zafrani et al. 1987. http://www.ncbi.nlm.nih.gov/pubmed/3610131
Zak FG (1950) Peliosis hepatis. Am J Pathol 26:1–15
Zeaiter Z, Fournier PE, Raoult D (2002a) Genomic variation of *Bartonella henselae* strains detected in lymph nodes of patients with cat scratch disease. J Clin Microbiol 40:1023–1030
Zeaiter Z, Fournier PE, Ogata H, Raoult D (2002b) Phylogenetic classification of Bartonella species by comparing groEL sequences. Int J Syst Evol Microbiol 52:165–171

Part VI

Tumors and Tumor-Like Lesions of Lymph Vessels of the Hepatobiliary Tract

Lymph Vessel Tumors of the Hepatobiliary Tract

60

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_60

Abstract

In contrast to hepatic blood vessel tumors, tumors and tumor-like lesions of hepatic lymph vessels are very rare conditions. Primary lymph vessel tumors of the liver present as multifocal or solitary tumorous lesions. A multifocal process is lymphangiomatosis, a disorder occurring both in children and adults. Predilection sites include lungs, skeletal muscle, and bone, whereas visceral organs are rarely involved. In the liver, lesions form large and in part confluent masses that consist of densely packed lymphatic channels and cystic structures. The process can rapidly progress and recur after resection. Solitary and localized hepatic lymph vessel tumors comprise cystic lymphangioma, non-cystic lymphangioma, capillary lymphangioma, and the very rare lymphangioma of bile ducts. Tumor-like lymphatic vessel lesions of the liver include hepatic lymphangiectasis, hepatic lymphocele, and primary lymphatic dysplasia of the liver.

Introduction

A broad array of clinical disorders of lymphangiogenesis are currently known (review: Witte et al. 2001), and some of them can manifest in the liver. In contrast to the morphogenesis of blood vessels, still less is known about mechanisms involved in normal, dysplastic, and neoplastic lymphangiogenesis, but similar pathways employing an analogous biochemical machinery may be operational (Witte et al. 2001). Overall, lymph vessel tumors of the liver are rare and unusual lesions. They comprise lymphangiomatosis, lymphangiomas, which are traditionally divided into three groups (capillary, cavernous, and cystic forms), lymphangiomyomatosis, and few other lesions characterized by an increase of abnormal lymph vessels, but of doubtful neoplastic character. Lymphangiomyomatosis is discussed in the context of tumors of the perivascular epithelioid cell system. Are clinically benign lymph vessel tumors neoplastic disorders? According the modern concepts, part of the lesions are now classified as lymphatic malformations, sometimes with a progressive character (Salazard et al. 2006; Perkins et al. 2010), and their pathogenesis has been reviewed in detail (Wiegand et al. 2008).

Lymphangiomatosis

Lymphangiomatosis is a rare disorder occurring in children and adults without gender predilection, characterized by the multifocal occurrence of lymphangiomas, and in some way reflecting the counterpart of angiomatosis (Ozeki et al. 2007). This unique lesion mostly manifests in children and is rare after age 20, but even though congenitality is suggested in systemic forms, the diagnosis is usually not common at birth, the tumor requiring a latent developmental period until it will be detectable. In the systemic variant, predilection sites are the lungs, soft tissues (particularly skeletal muscle), and bone, multiple bone lesions being observed in more than three-fourth of the patients, whereas visceral manifestations are less frequent (Jain et al. 2007; Kim et al. 2010). Apart from the extent of disease, the main localization bears an impact on prognosis, liver, spleen, lung, and thoracic duct involvement usually being associated with a poorer outcome. Lymphangiomatosis exceptionally develops in the liver, either as a manifestation of a systemic disorder or as an isolated, nonsystemic organ manifestation This process, which has alternatively been termed lymphangioendothelioma (Peters et al. 1989), is characterized by a pathologic proliferation of lymphatic channels involving soft tissues, bone, and solid organs. The abnormal growth of lymphatics can present as capillary-like/cavernous, cavernous, or cystic phenotypes. The cystic variant is also called cavernous lymphangiomatosis and may clinically and radiologically mimic polycystic liver disease (O'Sullivan et al. 1998). Diffuse hepatic lymphangiomatosis can undergo massive progression after liver resection (Datz et al. 2001) and recur after orthotopic liver transplantation

(Ra et al. 2007). Some of the cases involve infants and small children, suggesting that at least part of lymphangiomatoses are congenital malformations rather than a bona fide neoplastic process.

Selected References Shennan 1915; Parson and Ebbs 1940; Paden and Mantz 1955; Hambach and Hendrich 1959; Fischer and Roeckl 1961; Harshman et al. 1961; Deloore and Buyssens 1965; Asch et al. 1974; McQuown et al. 1975; Shuster and Gang 1980; Van Steenbergen et al. 1985; Miller et al. 1988; Cutillo et al. 1989; Schmid et al. 1991; Haratake et al. 1992; Ramani and Shah 1993; Haratake et al. 1995; Tepetes et al. 1995; de Souza et al. 1996; O'Sullivan et al. 1998; Datz et al. 2001; Ra et al. 2007; Ooi et al. 2011.

Macroscopy

In the liver, the lesions can grow to large and in part confluent, grayish-white masses causing sometimes massive hepatomegaly (Schmid et al. 1991; Ra et al. 2007). From the outside, the liver can show a nodular surface with several to numerous blue-dome cysts having a diameter ranging from few mm to more than 2 cm. The capsule between these cystic structures is either gray or mottled brown to dark red. In cut surfaces, clusters of cystic spaces with a clear to turbid fluid are seen, and in advanced cases, the hepatic parenchyma is mostly replaced by a network of cystic spaces with zones of fibrosis. Large areas of fibrosis developing in cystic areas can form stellate scars similar to those seen in focal nodular hyperplasia (Schmid et al. 1991).

Histopathology

Histologically, abnormal and sometimes densely packed lymphatic channels may predominate in the portal tracts and around bile ducts and ductules. Cystic lymphatic spaces are often noted, filled with an eosinophilic proteinaceous fluid and showing a flat endothelial lining. At the border of the cyst lumen, a rim of vacuoles similar to those seen in thyroid gland follicles can be seen, sometimes with confluence to form a halo (Asch et al. 1974). In later phases, the lymph vessel proliferation is accompanied by associated fibrotic changes resulting in septal structures which may reach the capsular surface and produce externally visible stellate capsular scars. The 3D network of fibrous septa or scars (Schmid et al. 1991) can lead to the separation of the liver substance into rather large nodule-like masses and to hepatocyte hyperplasia, visualized at gross examination and at imaging and not to be confounded with liver cirrhosis or regenerative nodular hyperplasia. In some cases, sinusoids of preserved hepatic lobules are dilated, and particularly in the periportal zone 1, it may be difficult to distinguish these structures from adjacent lymph vessels. By the use of silver impregnation, it has been observed that the lymph-draining perisinusoidal space of Disse is dilated, and it has been suggested that, in hepatic lymphangiomatosis, some of these spaces may be directly connected with lymph vessels in the portal tracts (Haratake et al. 1992).

Immunohistochemistry

Immunohistochemically, the cells lining the abnormal lymphatic channels are reactive, to variable degrees, for Ulex Europaeus agglutinin 1, von Willebrand factor (factor VIII-related antigen), and CD31 (Schmid et al. 1991; Haratake et al. 1992; Ramani and Shah 1993), whereas one group was unable to detect CD31 and CD34 in the abnormal endothelial cells (Datz et al. 2001). The cystic variant is characterized by large and apparently communicating cystic spaces identifiable at imaging (Cutillo et al. 1989) and which may under rare circumstances be extremely abundant, thus mimicking polycystic liver disease (O'Sullivan et al. 1998). Even though the growth of the abnormal lymphatic channels appears to be a benign or non-neoplastic process, the sometimes rapid and massive increase of lymphatic mass, in few cases

almost entirely replacing the liver substance (Peters et al. 1989), can cause severe morbidity, organ failure, and even death, in particular when the lungs are diffusely involved. Isolated manifestations in the liver may be clinically silent and incidentally detected, or they may rarely result in massive growth (massive hepatic lymphangiomatosis) requiring surgery or, in case of liver failure, even liver transplantation (Miller et al. 1988; Tepetes et al. 1995; Datz et al. 2001). Owing to the observation of acute and chronic pericholangiolitis in association with pediatric multifocal hepatic lymphangiomatosis, it has been suggested that some of these lesions may represent a reactive, pseudoneoplastic dilatation of liver lymphatics subsequent to an inflammatory response (Sathyavagiswaran and Sherwin 1989). Hepatic cystic lymphangiectasis has been reported to occur within a syndromatic setting, e.g., with the VACTERL association (vertebral anomalies, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or segmental atresia, reno-urinary anomalies, and limb defects; Distefano et al. 1998).

Cystic Lymphangioma of the Liver

ICD-O code 9170/0

Introduction

In situations where small lymphatic channels are lacking or are not readily detectable, hepatic lymphangiomatous lesions with a predominantly cystic component pose a differential diagnostic problem. In some reports, such tumors have been classified as variants of lymphangiomatosis (Singh et al. 1971; Rumpf and Mannfeld 1972). However, *cystic lymphangiomas* (synonym: cystic hygroma) morphologically very similar or indistinguishable from respective tumors at other sites occur in the liver as well, both in children and adults, albeit as an uncommon condition. Based on a series of 139 patients, only about 9 % of pediatric lymphangiomas have been reported to occur in the intra-abdominal compartment (Hancock and Dickens 1992), whereas in another study, intra-abdominal lymphangiomas accounted for less than 5 % of cases (Kosir and Sannino 1991). Lymphangioma of the liver usually presents as an isolated lesion not associated with other disorders, but the hepatic tumor can develop together with splenic lymphangioma (Dupuy et al. 1984), and a patient with intra-abdominal and hepatic lymphangiomas associated with diffuse venous hemangiomas of the skin and visceral organs has been described (Canataroglu et al. 2003). Cystic lymphangioma can rarely develop in the hepatic ligaments, e.g., the ligamentum teres (Zaev 1989).

Selected References Maresch 1903; Rocke 1933; Symmers and Ward-McQuaid 1950; Prochiantz et al. 1951; Serio and Marini 1965; Dagradi et al. 1968; Rumpf and Mannfeld 1972; Jovanovic et al. 1980; Tramonti et al. 1982; Moran Penco et al. 1983; Dupuy et al. 1984; Karkavitsas et al. 1985; Clerici et al. 1989; Ottonello et al. 1990; Stavropoulos et al. 1994; Koh and Sheu 2000; Bartelheimer et al. 2001; Canataroglu et al. 2003; Chan et al. 2005; Allen et al. 2006; Nzegwu et al. 2007; Zeidan and Delarue 2008; Shahi et al. 2009; Stunell et al. 2009; Huang et al. 2010; Matsumoto et al. 2010; Gonidec et al. 2011; Kochin et al. 2011; Soares Junior et al. 2011; Ak et al. 2012.

Macroscopy

Cystic lymphangiomas of the liver are usually solitary lesions with a diameter of few cm, but giant tumors have also been described (Symmers and Ward-McQuaid 1950; Zeidan and Delarue 2008; Stunell et al. 2009; Huang et al. 2010). In the 1.5 year-old-boy described by Rumpf and Mannfeld (1972), a cystic tumor measuring more than 15 cm in diameter was attached to the right liver lobe through a stalk. Similar to the respective soft tissue tumors, hepatic cystic lymphangiomas consist of cystic spaces, sometimes interconnected, which contain a serous, serosanguinous, or chylous fluid. The clustering

of cysts with intervening fibrous septa often results in a lobulated morphology of the tumors. The cyst walls may contain calcifications, sometimes extensive. The lining of the cysts is smooth, and the cyst walls are usually thin. The lesions can grow as multilocular and pedunculated masses extending beyond the liver surface (Koh and Sheu 2000), and the tumors can also develop within the hepatic ligaments (Zaev 1989).

Histopathology

Histologically, the cysts contain an eosinophilic, proteinaceous fluid with marginal vacuoles and are lined by a flat endothelium of the lymphatic type, and the wall of the channels or cysts may contain lymphoid tissue, smooth muscle cells, and foam cells (Enzinger and Weiss 1995; De Perrot and Rostan 1998¸ Figs. 1, 2, 3, and 4). Outside the liver, regression of lymphangiomas has been reported to occur spontaneously (Hancock and Dickens 1992), but progressive growth may also ensue (Saiji and Munro 1975; Hancock and Dickens 1992). Lymphangiomas may show focally dense lymphocytic infiltrations (mainly T lymphocytes) and sometimes abundant tissue mast cell infiltrates, the latter being much less evident in lymphangiomatosis. Some lymphangiomas exhibit hemorrhage between the vascular

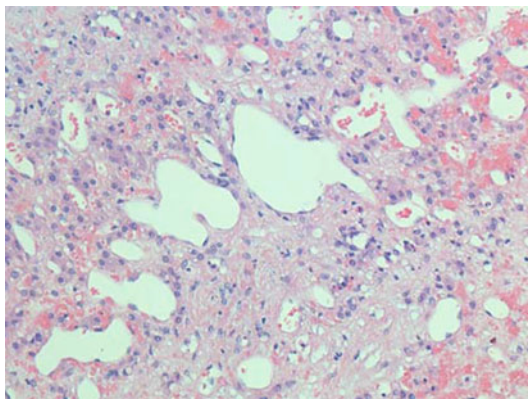

Fig. 1 Lymphangioma of the liver. Dilated lymphatic channels with a flat cellular lining are intertwined with hepatocyte plates (hematoxylin and eosin stain)

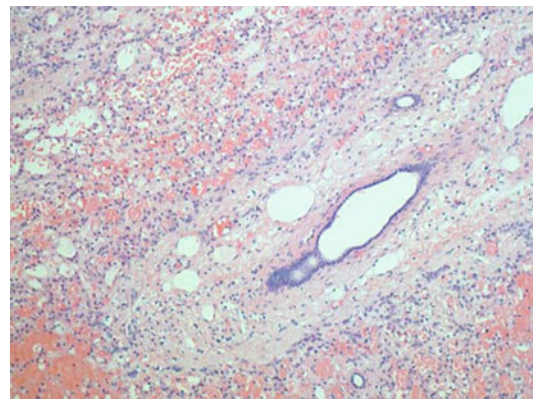

Fig. 3 Hepatic lymphangiectasis with involvement of a portal tract (hematoxylin and eosin stain)

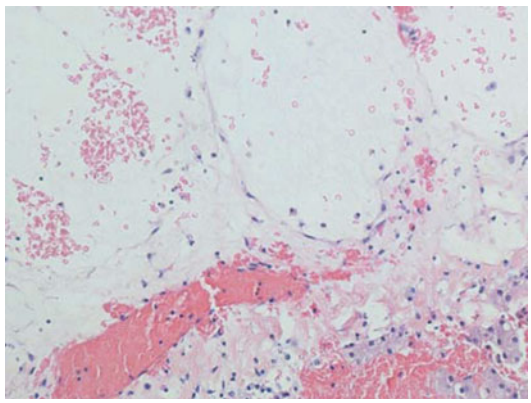

Fig. 2 Markedly dilated lymphatic channels in cystic lymphangioma of the liver (hematoxylin and eosin stain)

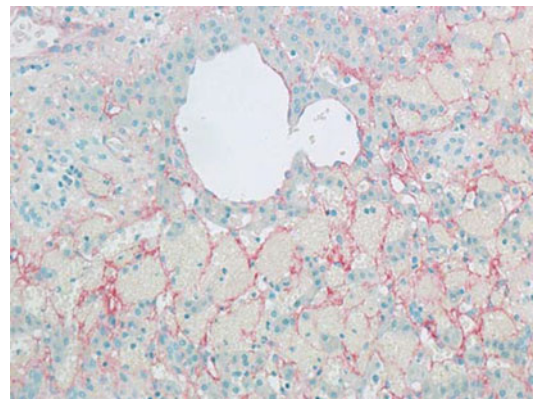

Fig. 4 Lymphangioma of the liver with a meshwork of abnormal lymphatic channels (D2-40 immunostain)

channels and even blood within the vascular spaces, but whether this qualifies such changes to employ the term hemangiolymphangioma is doubtful, even though this term has been used for tumors with these features, also in the liver (Damascelli et al. 1984).

Differential Diagnosis

Cystic lymphangiomas might be confounded, at imaging, with lymphoceles. Lymph cysts, e.g., in topographical association with bile ducts (Nishino et al. 1988), may emerge without foregoing trauma. Finally, cystic hamartomas of the hepatic pedicle can contain dilated lymph vessels and may be confounded with cystic lymphangiomas (Bugnon et al. 1987).

Non-cystic Lymphangioma of the Liver

Hepatic non-cystic lymphangiomas not related to congenital lymphangiomatosis have also been observed, including cavernous variants (Serio and Marini 1965; Delamarre et al. 1990 (with a literature review); Stavropoulos et al. 1994; Nikhinson 1994; Bartelheimer et al. 2001). A lymphangiomatous component can also emerge within the manifestations of systemic angiomatosis, e.g., in pregnancy (Bardeguez et al. 1990).

Capillary Lymphangioma of the Liver

Capillary lymphangioma, i.e., non-cystic lymphangioma of the liver, is a very unusual condition, and we are aware of only few published cases, observed in neonatal and adult patients (Van Steenbergen et al. 1985; Peters et al. 1989). In the neonate reported by Peters et al. (1989), the tumor almost entirely replaced the liver substance; no other organs were involved. The adult patient described by Van Steenbergen and coworkers (1985) showed an unusual, diffuse lymphangiomatous infiltration of the liver, whereby the numerous lesions were not distinguishable from necrotic metastases by the use of ultrasonography and CT.

Lymphangioma of the Bile Ducts

Introduction

Lymphangiomas are very rare tumor lesions of the biliary tract and are considered to either be neoplasms or tumor-like lymph vessel malformations. So far, the majority of lymphangiomas were located to the ampullary region and Vater's papilla (Artaza et al. 1995; Friedrich et al. 1985; Sriram et al. 2000; Targarona Modena et al. 2005). Lymphangioma of Vater's papilla results in stenosis, sometimes followed by obstructive jaundice (Friedrich et al. 1985) or acute pancreatitis (Sriram et al. 2000).

Pathology

Lymphangiomas are usually cystic and circumscribed nodular lesions with thin-walled cystic spaces. Following dissection, a clear fluid escapes from the cysts, sometimes with signs of previous hemorrhage. Lymphangioma cysts are lined by a flat complete or incomplete lymphatic endothelium. The septa between the cystic spaces consist of hypocellular connective tissue with focal lymphocytic infiltration. Cysts contain an eosinophilic, lymph-like fluid rich in proteins, sometimes containing clusters of lymphocytes and monocytoid cells. At the border of the cysts, vacuoles may be seen in the proteinaceous material.

Differential Diagnosis

Apart from true lymphangioma, para-bile duct lymphatic cysts have been described (Nishino et al. 1988). Retroperitoneal multiple lymphangioma can grow toward the extrahepatic

bile ducts and cause stenosis with biliary dilatation (Adachi et al. 2001).

Multifocal Lymphangioendotheliomatosis with Thrombocytopenia

Introduction

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MFLAM) is a rare form of congenital vascular anomaly involving the skin and the gastrointestinal tract. MFLAM is characterized by numerous angiomatous skin lesions, gastrointestinal tract (GIT) lesions, GIT hemorrhage, and thrombocytopenia. In the original report, the three patients presented with hundreds of congenital red-brown to violaceous skin plaques (macules and papules) as large as a few centimeters, with similar lesions throughout the gastrointestinal tract with severe GI tract bleeding. One patient had synovial involvement. All had significant refractory thrombocytopenia. Histology of the skin lesions showed thin-walled vessels in the dermis and subcutis lined by hobnailed, proliferative endothelial cells co-expressing the hyaluronan receptor LYVE-1 and CD31, most vessels displaying intraluminal papillary, hypercellular, and sometimes glomeruloid projections. The lesions were similar to benign lymphangioendothelioma (North et al. 2004). Other reports confirmed the uniqueness of this entity (Piggott et al. 2006; Yeung et al. 2006; Maronn et al. 2009; Campbell et al. 2010; Noel et al. 2012; Zegpi et al. 2012). The skin lesions progressively grow in size and number. The sometimes indurated skin papules may show central pallor and others central scar-like areas. GIT hemorrhage may be present since birth up to the first 2–3 years of age. The pathogenesis of refractory thrombocytopenia in MFLAM is not clarified, but consumptive loss of thrombocytes in the abnormal vascular channels, associated with coagulopathy, has been suggested. Thrombocytosis in MFLAM worsens with transfusions (Piggott et al. 2006; Maronn et al. 2009). A disorder similar to MFLAM was described in a later report, based on ten children (Prasad et al. 2005).

Hepatic Manifestations of MFLAM

Few reports have documented multiple lymphangioendotheliomatic lesions in the liver in the setting of generalized MFLAM (Prasad et al. 2005; Maronn et al. 2009).

Differential Diagnosis

The presentation of MFLAM in some respects resembles that of kaposiform hemangioendothelioma (K-HE), first described in 1993 as a vascular neoplasm with local aggressiveness (Zukerberg et al. 1993). K-HE mainly involves the skin and retroperitoneal space and, in contrast to MFLAM, also develops deep nodules and papules with telangiectasias. Gastrointestinal involvement has so far only been observed as an exceptional finding (Burgos et al. 2009).

Lymphangiectases of the Liver

Hepatic lymphangiectases have been identified at autopsy in an infant with congenital pulmonary lymphangiectasis. The markedly dilated lymph vessels spaces were localized to the portal tracts (Hirano et al. 2004). The latter disorder is a rare disease characterized by dilatation of the pulmonary lymphatic vessels and exists as congenital and acquired (secondary) form (Laurence 1955). The congenital form may present as a familial disorder (Scott-Emuakpor et al. 1981; OMIM 265300).

Hepatic Lymphocele

A lymphocele (chylous lymphocele) is a circumscribed and sometimes cystic accumulation of lymph following inflammation or

traumatic injury and subsequential to lymph vessel traumatism, e.g., post-surgery. Lymphocele is a rare condition in the liver and occurs at the hepatic hilum, within the liver substance proper, in a perihepatic compartment, or in a subcapsular position (Jahne et al. 1988; Bauer and McLeod 1998; Rao et al. 2000). It has been observed as a subcapsular extension of pelvic lymphocele after pelvic surgery (Bauer and Mcleod 1998).

Primary Lymphatic Dysplasia of the Liver

Primary lymphatic dysplasia (PLD) is a rare disorder which can present with lymphedema, chylothorax, and chylous ascites and is sometimes manifest in the newborn period already (Hanssler et al. 1990). Together with other causes, primary lymphangiectatic or lymphatic dysplastic disorders may therefore clinically be classified as so-called primary chylous disorders (PCDs; Noel et al. 2001).

Primary lymphangiectasia of the gastrointestinal tract does not appear to directly involve the liver, but the intestinal form has been observed to occur together with congenital liver fibrosis, eventually representing a novel syndrome (Chagnon et al. 1982; Pelletier et al. 1986).

Cellular and Tissual Origins of Hepatic Lymphatic Tumors

It is a current view that hepatic lymph vessel tumors take their origin from pre-existing lymphatic vessels and lymphatic channels of the liver. However, an origin from lymphatogenic mesenchymal stem cells giving rise to lymphatic endothelial cells has also to be considered. Small lymph vessels are present in portal tracts of the liver and show a distinct spatial relationship to blood vessels (Clain and McNulty 1968). Hepatic lymphatics can easily be visualized by means of podoplanin immunostaining (Yokomori et al. 2010). In situations with significant hepatic outflow obstruction, liver lymphatics become more prominent (Rajaram and Subramanian 1978).

The Identification of Lymph Vessel Endothelia

The identification of tumor cells as lymphatic endothelia is difficult and in some way still enigmatic, owing to a considerable overlap between blood and lymph vessel endothelial phenotypes, differences being related to quantitative aspects rather than qualitative ones, and the fact that levels of gene expression in these cell lineages are markedly influenced by physiologic and pathologic conditions (Sleeman et al. 2001). Ultrastructurally, endothelial cells of lymphatics can be identified owing to their lack of Weibel-Palade bodies (Ghadially 1988), but electron microscopy will not be available in the majority of cases analyzed. Although some of the factors expressed in lymph vessel endothelia briefly discussed below have been claimed to be "specific," we still are in a situation where a combined approach may result in reliable cell identification, but in some circumstances, the cells of interest will so far remain indistinguishable at histologic and immunohistochemical examination (also in tumors), until novel and truly specific cellular components will be identified. Molecules analyzed so far include factor VIII-related antigen, CD31, CD34, PECAM, desmoplakin, podoplanin, LYVE-1 (a homologue of the hyaluronan receptor, CD44), basement membrane proteins (laminin and type IV collagen), and certain enzymes (alkaline phosphatase and 5′ endonuclease), results obtained differing from one study to the other.

Conventional Markers

Employing immunoelectron microscopy, an expression of CD31, CD34, and type IV collagen has been demonstrated in lymphangiomas (Sauter et al. 1998), but CD34 is not always detectable using light microscopic immunohistochemistry

(Paal et al. 1998). Lymphangiomas can also express cytokeratins, including K7 and K18 (Miettinen and Fetsch 2000). In a recent study on lymphangiomas (LA) and congenital pulmonary lymphangiomatosis (CPL), which make part of a spectrum of lymphatic disorders, there was evidence that LA and CPL shared a similar immunohistochemical profile for vimentin, factor VIII-related protein/von Willebrand factor, CD31, CD34, and, to a lesser extent, CD45RO (Brown et al. 1999). However, these are features which are also expressed in other vascular tumors thus not being useful for distinguishing lymphatic from other lesions. LYVE-1, a CD44 analogue, has been proposed to be restricted to endothelia of lymph vessels (Banerji et al. 1999; Jackson et al. 2001), but has recently been shown to be expressed in endothelia of normal liver blood sinusoids in mice and humans (Mouta Carreira et al. 2001). Promising results for lymph vessel tumor identification may be expected via assessment of the expression of Prox-1, a homeobox transcription factor expressed in lymphangioblasts and lymphatic endothelium (see above; Wigle and Oliver 1999; Rodriguez-Niedenfuhr et al. 2001).

Podoplanin

A further useful marker is podoplanin, a 43- or 38-kDa membrane protein controlling the shape of glomerular podocytes (Matsui et al. 1999) and staining lymphatic but not blood vessel endothelial cells, together with VEGFR-3. Podoplanin is present in small but not in large lymphatics (Breiteneder-Geleff et al. 1999). Podoplanin has also been shown to be expressed in endothelia of benign lymphatic tumorous lesions (Breiteneder-Geleff et al. 1999). It has been shown that the beta-chemokine receptor D6 is expressed by the lymphatic endothelium in a subset of vessels of the skin, intestine, and lymphoid tissues, but not in others (Nibbs et al. 2001), suggesting a heterogeneity of the lymph vessel system in the body.

Vascular Endothelial Growth Factors and Their Receptors

Furthermore, the identification of distinct vascular growth factors may, in the future, have a larger impact on the definition of cells in tumors suspected to be of lymph vessel origin, including those developing in the liver. VEGFR-3 is expressed in lymphatic endothelial cells, but it is also expressed in a subset of fenestrated blood vessels in humans (Partanen et al. 2000). VEGFR-3 mRNA has been localized to human lymphangioma (Kaipainen et al. 1995), and both VEGFR-2 and VEGFR-3 have been detected in a mouse model of lymphangioma (Mancardi et al. 1999). In a study on 29 cases of lymphangioma, employing RNA in situ hybridization, endothelial cells of these tumors co-expressed transcripts of VEGF-C and its receptors, VEGFR-3 (Flt4) and VEGFR-2 (Flk1), whereas there was little or no expression of VEGF-C and the two receptors in endothelial cells of hemangiomas or angiosarcomas (Huang et al. 2001), suggesting that VEGF-C and its receptors may have a role in lymphatic tumor growth via autocrine or paracrine regulation. VEGF-C expression was detected in 36 % of adult cystic hygromas, while VEGFR-3 expression was found in 72 % of cavernous lymphangiomas and 71 % of cystic hygromas (Itakura et al. 2009).

Other Lymphatic Endothelial Markers

D6 is detectable in a subset of vascular tumors with a lymphatic endothelial cell lineage (Nibbs et al. 2001). Prox-1, which plays a decisive role in lymphangiogenesis, can be detected in lymphatics, but it is also expressed in non-endothelial cells such as the heart, liver, and pancreas. By the use of phage-displayed peptide libraries and phage-screening procedures, a peptide (LyP-1) was recently identified and shown to co-localize with three other markers to lymphatic vessel cells, suggesting that LyP-1 is a novel marker for this cell lineage (Laakkonen et al. 2002).

References

Adachi S, Maruyama T, Suetomi T, Morishita Y, Otsuka M, Todoroki T, Fukao K (2001) Retroperitoneal multiple lymphangioma with differential cyst contents causing hydronephrosis and biliary dilatation. Hepatogastroenterology 48:397–400

Ak SJ, Park SK, Park HU (2012) A case of isolated hepatic lymphangioma (in Korean). Korean J Gastroenterol 59:189–192

Allen JG, Riall TS, Cameron JL, Askin FB, Hruban RH, Campbell KA (2006) Abdominal lymphangioma in adults. J Gastrointest Surg 10:746–751

Artaza T, Potenciano JM, Legaz M, Munoz C, Talavera A, Sanchez E (1995) Lymphangioma of vater's ampulla: a rare cause of obstructive jaundice. Endoscopic therapy. Scand J Gastroenterol 30:804–806

Asch MJ, Cohen AH, Moore TC (1974) Hepatic and splenic lymphangiomatosis with skeletal involvement: report of a case and review of the literature. Surgery 76:334–339

Banerji S, Ni J, Wang SX, Clasper S, Su J, Tammi R, Jones M, Jackson DG (1999) LYVE-1, a new homologue of the CD44 glycoprotein, is a lymph-specific receptor for hyaluronan. J Cell Biol 144:789–801

Bardeguez A, Chatterjee M, Tepedino M, Sicuranza B (1990) Systemic cystic angiomatosis in pregnancy: a case presentation and review of the literature. Am J Obstet Gynecol 163:42–45

Bartelheimer MW, Schlegel HM, Picolin K (2001) Solitary adult lymphangioma of the liver as very rare variant of benign space-occupying lesion of the liver (in German). Rofo 173:771–772

Bauer JJ, McLeod DG (1998) Hepatic subcapsular extension of pelvic lymphocele after radical retropubic prostatectomy. Urology 51:846–848

Breiteneder-Geleff S, Soleiman A, Horvat R, Amann G, Kowalsi H, Kerjaschki D (1999) Podoplanin – a specific marker for lymphatic endothelium expressed in angiosarcoma (in German). Verh Dtsch Ges Pathol 83:270–275

Brown M, Pysher T, Coffin CM (1999) Lymphangioma and congenital pulmonary lymphangiectasis: a histologic, immunohistochemical, and clinicopathologic comparison. Mod Pathol 12:569–575

Bugnon PY, Martinot JC, Servais B, Lecomte-Houcke M, Gautier-Benoit C (1987) Hamartome kystique du pédicule hépatique chez l'adulte. Un cas et revue de la littérature. Chirurgie (Paris) 113:906–909

Burgos L, Gutiérrez JC, Barrena S, De la Torre C, Suarez O, Luis AL (2009) Atypical vascular tumors of the gastrointestinal tract: four uncommon cases. Cir Pediatr 22:125–127

Campbell CM, Beckum KM, Hammers YA, North PE, Drolet BE, Theos A (2010) Multiple congenital red-brown macules, thrombocytopenia, and gastrointestinal bleeding. Diagnosis. Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT). Pediatr Dermatol 27:395–396

Canataroglu A, Gumurdulu Y, Gumurdulu D, Balal M, Tuncer I, Sagliker Y (2003) Coexistence of cystic intra-abdominal lymphangiomas and diffuse venous haemangiomas in adult life. Neth J Med 61:95–97

Chagnon JP, Barge J, Hay JM, Devars du Mayne JF, Ricahrd JP, Hardouin JP (1982) Congenital hepatic fibrosis, multiple renal cysts and primary intestinal lymphangiectasia (in French). Gasteroenterol Clin Biol 6:326–332

Chan SC, Huang SF, Lee WC, Wan YL (2005) Solitary hepatic lymphangioma – a case report. Int J Clin Pract Suppl 147:100–102

Clain D, McNulty J (1968) A radiological study of the lymphatics of the liver. Br J Radiol 41:662

Clerici D, Griffa B, Ceppi M, Basilico V, Milvio E (1989) Cystic lymphangioma of the liver. Presentation of a clinical case (in Italian). Minerva Chir 44:1139–1141

Cutillo DP, Swayne LC, Cucco J, Dougan H (1989) CT and MR imaging in cystic abdominal lymphangiomatosis. J Comput Assist Tomogr 13:534–536

Dagradi A, Pizzecco E, Dagradi V (1968) Zystisches Lymphangioma des rechten Leberlappens. Z Kinderchir 6:343–349

Damascelli B, Spagnoli I, Garbagnati F, Ceglia E, Milella M, Masciadri N (1984) Massive lymphorrhoea after fine needle biopsy of the cystic haemolymphangioma of the liver. Eur J Radiol 4:107–109

Datz C, Graziadei IW, Dietze O, Jaschke W, Konigsrainer A, Sandhofer F, Margreiter R (2001) Massive progression of diffuse hepatic lymphangiomatosis after liver resection and rapid deterioration after liver transplantation. Am J Gastroenterol 96:1278–1281

De Perrot M, Rostan O (1998) Abdominal lymphangioma in adults and children. Br J Surg 85:395–397

De Souza LM, Bentlin MR, De Abreu ES, Bacchi CE (1996) Systemic congenital lymphangiomatosis. Rev Paul Med 114:1278–1281

Delamarre J, Lamblin G, Sevestre H, Deschepper B, Jouet-Gondry C, Davion T, Capron JP (1990) Cavernous lymphangioma of the liver. A report of 2 cases and review of the literature (in French). Gastroenterol Clin Biol 14:576–580

Deloore F, Buyssens N (1965) Lymphangiomatosis of the liver (in Dutch). Belg Tijschr Geneesk 21:273–278

Distefano G, Rodono A, Smilari P, Saporito A, Di Bella D, Magro G, Sanges G, Romeo MG (1998) The VACTERL association: a report of a clinical case with hepatic cystic lymphangiectasis (in Italian). Pediatr Med Chir 20:223–226

Dupuy JP, Catanzano G, Bouchet JB, Le Goff JJ (1984) Cystic hepatosplenic lymphangioma (in French). Ann Radiol (Paris) 27:417–420

Enzinger FM, Weiss SW (1995) Tumors of lymph vessels. In: Enzinger FM, Weiss SW (eds) Soft tissue tumors. Mosby, St. Louis, pp 679–700

Fischer C, Roeckl H (1961) A case of systematized hemangiomatosis. Hautarzt 12:79

Friedrich HJ, Schramm H, Peckholz I (1985) Cavernous lymphangioma of Vater's papilla as a cause of

occlusive icterus. Case report (in German). Zentralbl Chir 110:1263–1265
Ghadially FN (1988) Ultrastructural pathology of the cell and matrix, 3rd edn. Butterworths, London, pp 827–837
Gonidec S, Guibal A, Pilleul F (2011) Solitary hepatic lymphangioma of the adult: MRI findings (in French). J Radiol 92:729–731
Hambach R, Hendrich F (1959) Ein Fall von generalisierter Haemangio-matose. Zbl Allg Pathol 100:236
Hancock BJ, Dickens SV (1992) Complications of lymphangiomas in children. J Pediatr Surg 27:270–276
Hanssler L, Metz KA, Roll C, Hennecke KH (1990) Primary lymphatic dysplasia in a newborn infant (in German). Monatsschr Kinderheilk 138:772–774
Haratake J, Koide O, Takeshita H (1992) Hepatic lymphangiomatosis: report of two cases, with an immunohistochemical study. Am J Gastroenterol 87:906–909
Haratake J, Makino H, Arai K (1995) Hepatic lymphangiomatosis and its related tumors and tumor-like conditions (in Japanese). Ryoikibetsu Shokogun Shirizu 7:292–294
Harshman JA, Smith EB, Evans PV (1961) Cystic lymphangiectasis of the spleen. Arch Pathol 71:344
Hirano H, Nishigami T, Okimura A, Nakasho K, Uematsu K (2004) Autopsy case of congenital pulmonary lymphangiectasis. Pathol Int 54:532–536
Huang HY, Ho CC, Huang PH, Hsu SM (2001) Co-expression of VEGF-C and its receptors, VEGFR-2 and VEGFR-3, in endothelial cells of lymphangioma. Implication in autocrine or paracrine regulation of lymphangioma. Lab Invest 81:1729–1734
Huang L, Li J, Zhou F, Yan J, Liu C, Zhou AY, Tang A, Yan Y (2010) Giant cystic lymphangioma of the liver. Hepatol Int 4:784–787
Itakura E, Yamamoto H, Oda Y, Furue M, Tsuneyoshi M (2009) VEGF-C and VEGFR-3 in a series of lymphangiomas: is superficial lymphangioma a true lymphangioma? Virchows Arch 454:317–325
Jackson DG, Prevo R, Clasper S, Banerji S (2001) LYVE-1, the lymphatic system and tumor lymphangiogenesis. Trends Immunol 22:317–321
Jahne J, Meyer HJ, Milbradt H, Pichlmayr R (1988) Chylous lymphocele: a rare complication after gastrectomy for non-Hodgkin's lymphoma of the stomach (in German). Dtsch Med Wochenschr 113:1440–1442
Jain M, Aggarwal S, Singh S (2007) Intra-abdominal cavernous lymphangiomatosis in Siamese twins: a case report. Indian J Pathol Microbiol 50:570–571
Jovanovic DM, Opric M, Milovanovic B, Radojkovic P (1980) Cystic lymphangioma of the liver (in Serbo-Croatian). Acta Chir Iugosl 27:71–76
Kaipainen A, Korhonen J, Mustonen T, van Hinsbergh VW, Fang GH, Dumont D et al (1995) Expression of the fms-like tyrosine kinase 4 gene becomes restricted to lymphatic endothelium during development. Proc Natl Acad Sci U S A 92:3566–3570
Karkavitsas N, Farschidpur D, Lieber H (1985) CT of a rare benign liver lymphangioma (in German). Digitale Bilddiagn 5:142–144
Kim DH, Seo HS, Seo J, Kim HK, Her K, Suk EH (2010) Lymphangiomatosis involving the inferior vena cava, heart, and pulmonary artery and pelvic cavity. Korean J Radiol 11:115–118
Kochin IN, Miloh TA, Amon R, Iyer KR, Suchy FJ, Kerkar N (2011) Benign liver masses and lesions in children: 53 cases and 12 years. Isr Med Assoc J 13:542–547
Koh CC, Sheu JC (2000) Hepatic lymphangioma – a case report. Pediatr Surg Int 16:515–516
Kosir MA, Sannino RE (1991) Pediatric abdominal lymphangiomas: a plea for early recognition. J Pediatr Surg 26:1309–1313
Laakkonen P, Porkka K, Hoffman JA, Ruoslahti E (2002) A tumor-homing peptide with a targeting specificity related to lymphatic vessels. Nat Med 8:751–755
Laurence KM (1955) Congenital pulmonary cystic lymphangiectasis. J Pathol Bacteriol 70:325–333
Mancardi et al (1999) http://www.ncbi.nlm.nih.gov/pubmed/9925752
Maresch R (1903) Ueber ein Lymphangiom der Leber. Z Heilk 24:39–50
Maronn M, Catrine K, North P, Browning MB, Kerschner JE, Noel R, Drolet BA, Kelly M (2009) Expanding the phenotype of multifocal lymphangioendotheliomatosis with thrombocytopenia. Pediatr Blood Cancer 52: 531–534
Matsui K, Breiteneder-Geleff S, Soleiman A, Kowalsi H, Kerjaschki D (1999) Podoplanin, a novel 43-kDa membrane protein, controls the shape of podocytes. Nephrol Dial Transplant 14(Suppl):9–11
Matsumoto T, Ojima H, Akishima-Fukasawa Y, Hiraoka N, Onaya H, Shimada K, Mizuguchi Y et al (2010) Solitary hepatic lymphangioma: report of a case. Surg Today 40:883–889
McQuown DS, Fishbein MC, Moran ET, Hoffman RB (1975) Abdominal cystic lymphangiomatosis: report of a case involving the liver and spleen and illustration of two cases with origin in the greater omentum and root of the mesentery. J Clin Ultrasound 3:291–296
Miettinen M, Fetsch JF (2000) Distribution of keratins in normal endothelial cells and a spectrum of vascular tumors: implications for tumor diagnosis. Hum Pathol 31:1062–1067
Miller C, Mazzaferro V, Makowka L, Chap Chap P, Demetris J, Tzsakis A, Esquivel CO et al (1988) Orthotopic liver transplantation for massive hepatic lymphangiomatosis. Surgery 103:490–495
Moran Penco JM, Borella F, Garibaldi L, Toma P, Dodero P (1983) Hepatic hemangiolymphangioma in an infant. An Esp Pediatr 19:411–413
Mouta Carreira et al (2001) http://www.ncbi.nlm.nih.gov/pubmed/11719431
Nibbs RJ, Kriehuber E, Ponath PD, Parent D, Qin S, Campbell JD, Henderson A et al (2001) The beta-chemokine receptor D6 is expressed by lymphatic endothelium and a subset of vascular tumors. Am J Pathol 158:867–877
Nikhinson RA (1994) Hepatic lymphangioma (in Russian). Khirurgiia (Mosk) 3:59–60

Nishino M, Ezumi A, Tei H, Hirose J, Yamamoto K, Ohashi M, Tanaka M, Kishida T et al (1988) A case of para bile duct lymphatic cyst with polycystic disease treated with pure ethanol injection after ultrasonic drainage (in Japanese). Nippon Naika Gakkai Zasshi 77:1446–1449

Noel AA, Gloviczki P, Bencer CE, Whitley D, Stanson AW, Deschamps C (2001) Treatment of symptomatic primary chylous disorders. J Vasc Surg 34:785–791

Noel RJ, Duffy KJ, Kelly ME, Tondravi N, Northe PE, Drolet BA (2012) Endoscopic management of gastrointestinal bleeding from multifocal lymphangioendotheliomatosis with thrombocytopenia: limited efficacy and complications. J Pediatr Gastroenterol Nutr 54:822–824

North PE, Kahn T, Cordisco MR, Dadras SS, Detmar M, Frieden IJ (2004) Multifocal lymphangioendotheliomatosis with thrombocytopenia: a newly recognized clinicopathological entity. Arch Dermatol 140:599–606

Nzegwu MA, Ekenze SO, Okafor OC, Anyanwu PA, Odetunde OA, Olusina DB (2007) Solitary hepatic lymphangioma in an infant. J Perinat Med 35:164–165

O'Sullivan DA, Torres VE, de Groen PC, Batts KP, King BF, Vockley J (1998) Hepatic lymphangiomatosis mimicking polycystic liver disease. Mayo Clin Proc 73:1188–1192

Ooi CY, Brody D, Wong R, Moroz S, Ngan BY, Navarro OM, Fecteau A, Grant D, Ng VL (2011) Liver transplantation for massive hepatic lymphangiomatosis in a child. J Pediatr Gastroenterol Nutr 52:366–369

Ottonello R, Cadoni S, Maxia G, Cocco P, Gemini S (1990) A case of cystic lymphangioma of the liver (in Italian). Minerva Chir 45:1407–1409

Ozeki M, Funato M, Kanda K, Ito M, Teramoto T, Kaneko H, Fukao T, Kondo N (2007) Clinical improvement of diffuse lymphangiomatosis with pegylated interferon alfa-2b therapy: case report and review of the literature. Pediatr Hematol Oncol 24:513–524

Paal E, Thompson LD, Heffess CS (1998) A clinicopathologic and immunohistochemical study of ten pancreatic lymphangiomas and a review of the literature. Cancer 82:2150–2158

Paden PA, Mantz FA (1955) Benign systemic hemangiomatosis without cutaneous involvement. Radiology 64:252

Parson LS, Ebbs JH (1940) Generalized angiomatosis presenting the clinical characteristics of storage reticulosis with some observations on the reticuloendo-theliosis. Arch Dis Child 15:129

Partanen TA, Alitalo K, Miettinen M (1999) Lack of lymphatic vascular specificity of vascular endothelial growth factor receptor 3 in 185 vascular tumors. Cancer 86:2406–2412

Partanen et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/11023993

Pelletier VA, Galeano N, Brochu P, Morin CL, Weber AM, Roy CC (1986) Secretory diarrhea with protein-losing enteropathy, enterocolitis cystica superficialis, intestinal lymphangiectasia, and congenital hepatic fibrosis: a new syndrome. J Pediatr 108:61–65

Perkins JA, Manning SC, Tempero RM, Cunningham MJ, Edmonds JL, Hoffer FA, Egbert MA (2010) Lymphatic malformations: current cellular and clinical investigations. Otolaryngol Head Neck Surg 142:789–794

Peters ME, Gilbert-Barness EF, Rao B, Odell GB (1989) Lymphangioendothelioma of the liver in a neonate. J Pediatr Gastroenterol Nutr 9:115–118

Piggott KD, Riedel PA, Baron HI (2006) Multifocal lymphangioendotheliomatosis with thrombocytopenia: a rare cause of gastrointestinal bleeding in the newborn period. Pediatrics 117:e810–e813

Prasad V, Fishman SJ, Mulliken JB, Fox VL, Liang MG, Klement G, Kieran MW, Burrows PE et al (2005) Cutaneovisceral angiomatosis with thrombocytopenia. Pediatr Dev Pathol 8:407–419

Prochiantz A, Aupinel C, Sabatier L (1951) Lymphangiome du foie poéré et guéri. Arch Franç Pédiatr 8:282–286

Ra SH, Bradley RF, Fishbein MC, Busuttli RW, Lu DS, Lassman CR (2007) Recurrent hepatic lymphangiomatosis after orthotopic liver transplantation. Liver Transpl 13:1593–1597

Rajaram PC, Subramanian R (1978) Lymphatic dynamics of liver by hepatic lymphography using lipiodol ultra fluid. Lymphology 11:93–100

Ramani P, Shah A (1993) Lymphangiomatosis. Histologic and immunohistochemical analysis of four cases. Am J Surg Pathol 17:329–335

Rao AR, Chui AK, Shi LW, Verran DJ, Sheil AG (2000) Technique for repair of lymphocele after liver transplantation using patent blue dye. Transplant Proc 32:2221–2222

Rocke J (1933) Specimen: lymphangioma of liver. Proc R Soc Med 27:123–124

Rodriguez-Niedenfuhr M, Papoutsi M, Christ B, Nicolaides KH, von Kaisenberg CS et al (2001) Prox1 is a marker of ectodermal placodes, endodermal compartments, lymphatic endothelium and lymphangioblasts. Anat Embryol (Berl) 204:399–406

Rumpf P, Mannfeld U (1972) Cystic lymphangioma of the liver in childhood (in German). Zentralbl Chir 97:1060–1063

Saiji M, Munro IR (1975) Lymphangioma: a long-term follow-up study. Plast Reconstr Surg 56:642–651

Salazard B, Londner J, Casanova D, Bardot J, Magalon G (2006) The lymphatic malformations: clinical aspects and evolution (in French). Ann Chir Plast Esthet 51:412–422

Sathyavagiswaran L, Sherwin RP (1989) Acute and chronic pericholangiolitis in association with multifocal hepatic lymphangiomatosis. Hum Pathol 20:601–603

Sauter et al (1998) http://www.ncbi.nlm.nih.gov/pubmed/9446823

Schmid C, Beham A, Uranus S, Melzer G, Aubock L, Seewann HL, Klimpfinger M (1991) Non-systemic

diffuse lymphangiomatosis of spleen and liver. Histopathology 18:478–480
Scott-Emuakpor AB, Warren ST, Kapur S, Quiachon EB, Higgins JV (1981) Familial occurrence of congenital pulmonary lymphangiectasis. Am J Dis Child 135:532–534
Serio G, Marini F (1965) Lymphangioma of the liver. Apropos of a case treated by typical right lobectomy (in Italian). Chir Ital 17:783–800
Shahi KS, Geeta B, Rajput P (2009) Solitary hepatic lymphangioma in a 22-day-old infant. J Pediatr Surg 44:E9–E11
Shennan T (1915) Histologically non-malignant angioma with numerous metastases. J Pathol Bacteriol 19:139
Shuster SR, Gang DR (1980) Case record of the Massachusetts General Hospital. An 11-year-old girl with multiple osteolytic lesions and a mediastinal mass. N Engl J Med 303:270–276
Singh SS, Baboo ML, Pathak IC (1971) Cystic lymphangioma in children: report of 32 cases including lesions at rare sites. Surgery 69:947–951
Sleeman JP, Krishnan J, Kirkin V, Baumann P (2001) Markers for the lymphatic endothelium: in search for the holy grail? Microsc Res Tech 55:61–69
Soares Junior AW, Tajra CE, Soares VY, Soares JL, Costa JA (2011) Hepatectomy of lymphangioma in situs inversus totalis – case report (in Portuguese). Rev Col Bras Cir 38:450–451
Sriram PV, Weise C, Seitz U, Brand B, Schröder S, Soehendra N (2000) Lymphangioma of the major duodenal papilla presenting as acute pancreatitis: treatment by endoscopic snare papillectomy. Gastrointest Endosc 51:733–736
Stavropoulos M, Vagianos C, Scopa CD, Dragotis C, Androulakis J (1994) Solitary hepatic lymphangioma. A rare benign tumour: a case report. HPB Surg 8:33–36
Stunell H, Ridgway PF, Torreggiani WC, Crotty P, Conlon KC (2009) Hepatic lymphangioma: a rare cause of abdominal pain in a 30-year-old female. Ir J Med Sci 178:93–96
Symmers W, Ward-McQuaid J (1950) Successful resection of a large cavernous lymphangiomatoid lesion of the liver of a child aged 19 months. Br J Surg 38:12–17
Targarona Modena J, Rosamedina JL, Garatea R, Romero C, Lora A, Contardo C, Mantila L et al (2005) Transduodenal ampullectomy: an useful alternative for the treatment of Vater's ampulla lesions. Case reports of an unfrequent surgical technique (in Spanish). Rev Gastroenterol Peru 25:106–111
Tepetes K, Selby R, Webb M, Madariaga JR, Iwatsuki S, Starzl TE (1995) Orthotopic liver transplantation for benign hepatic neoplasms. Arch Surg 130:153–156
Tramonti M, Parisi L, Del Moro J, Dal Pozzo G (1982) A case of cystic lymphangioma of the liver studied by ultrasonography and tomodensitometry (in Italian). Radiol Med (Torino) 68:667–668
Van Steenbergen W, Joosten E, Marchal G, Baert A, Vanstapel MJ, Desmet V, Wijnants P, De Groote J (1985) Hepatic lymphangiomatosis. Report of a case and review of the literature. Gastroenterology 88:1968–1972
Wiegand S, Eivazi B, Barth PJ, Berens von Rautenfeld D, Folz BJ, Mandic R, Werner JA (2008) Pathogenesis of lymphangiomas. Virchows Arch 453:1–8
Wigle JT, Oliver G (1999) prox1 function is required for the development of the murine lymphatic system. Cell 98:769–778
Witte MH, Bernas MJ, Martin CP, Witte CL (2001) Lymphangiogenesis and lymphangiodysplasia: from molecular to clinical lymphology. Miscrosc Res Tech 55:122–145
Yeung J, Somers G, Viero S, Pope E (2006) Multifocal lymphangioendotheliomatosis with thrombocytopenia. J Am Acad Dermatol 54(Suppl 5):S214–S217
Yokomori H, Oda M, Kaneko F, Kawachi S, Tanabe M, Yoshimura K, Kitagawa Y, Hibi T (2010) Lymphatic marker podoplanin/D2-40 in human advanced cirrhotic liver – re-evaluations of microlymphatic abnormalities. BMC Gastroenterol 10:131
Zaev KN (1989) Multi-chamber cyst-like lymphangioma of the round ligament of the liver in a child (in Russian). Vestn Khir Im I I Grek 142:81–82
Zegpi MS, Zavala A, del Puerto C, Cardenas C, Gonzalez S (2012) Newborn with multifocal lymphangioendotheliomatosis with thrombocytopenia. Indian J Dermatol Venereol Leprol 78:409
Zeidan S, Delarue A (2008) Uncommon etiology of a cystic hepatic tumor. Dig Surg 25:10–11
Zukerberg LR, Nickoloff BJ, Weiss SW (1993) Kaposiform hemangioendothelioma of infancy and childhood. An aggressive neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. Am J Surg Pathol 17:321–328

Part VII

Solitary Fibrous Tumor and Tumors with a Hemangiopericytoma-Like Pattern

Solitary Fibrous Tumor/ Hemangiopericytoma of the Liver

61

Contents

Abstract

Solitary fibrous tumors form a complex spectrum of neoplasms, at least part of which were previously related to perivascular cells and thus termed hemangiopericytomas. The classical solitary fibrous tumor, occurring in the form of several variants, typically develops in the pleuropulmonary compartment, but also exists in certain visceral organs, including the liver. Rare variants are those which contain components with hemangiopericytoma-like features. In addition to these lesions, there still exist so-called true hemangiopericytomas, neoplasms that typically occur in the meninges and the sinonasal space. In the liver, primary solitary fibrous presents as well-circumscribed and expanding lesions with fibroma-like features. Histologically, the neoplasms are cellular tumors composed of spindle cells looking different from fibroblasts and myofibroblasts. These cells are arranged in a storiform pattern or form dense sheaths surrounding slit-like vascular channels. The origin of the cells is not yet elucidated. Solitary fibrous tumors show recurrent breakpoints in 12q13, associated with frequent deletions affecting STAT6, caused by somatic fusions of two genes, NAB2 and STAT6.

ICD-O codes:

Solitary fibrous tumor	8815/1
Hemangiopericytoma including lipomatous hemangiopericytoma	9150/1

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_61

Introduction

This group of tumors was previously thought to be derived from specialized cells supporting blood vessels, i.e., pericytes and glomus cells, leading to the term hemangiopericytoma. The lesion was first described in 1942 as a vascular tumor featuring Zimmermann's pericytes (Stout and Murray 1942). In 2002, the WHO tumor classification system reclassified soft tissue tumors known so far as hemangiopericytomas as a variant of solitary fibrous tumor. In particular, cellular solitary fibrous tumor is regarded as a synonym of hemangiopericytoma (Park and Araujo 2009). Solitary fibrous tumors represent a heterogeneous group of spindle cell neoplasms with a biological behavior varying between benign and low-grade malignant phenotypes. The term, solitary fibrous tumor (SFT), is now preferred to the former term, hemangiopericytoma, all the more so because the cell of origin is still disputed (Penel et al. 2012). In the WHO classification, solitary fibrous tumor is listed in the intermediate (rarely metastasizing) category, characterizing neoplasms that are often locally aggressive but may have the capability to give rise to distant metastases in some patients, the risk of such a metastatic phenotype being less than 2 % and not predictable from the histologic presentation. Solitary fibrous tumor has several subgroups, comprising fibrous, cellular, fat cell-containing, and giant cell variants. The cellular variant, showing a hypercellular component exceeding 90 % of the tumor, covers most of the "classical" hemangiopericytomas (Knösel et al. 2010). The fat cell-containing variant was previously termed lipomatous hemangiopericytoma, and the variant rich in giant cells is equivalent to giant cell angiofibroma.

Currently, a small spectrum of tumors with a hemangiopericytoma-like pattern may be considered (Table 1). However, recent molecular genetic findings suggest that the entire spectrum of lesions may be separated into two major groups, i.e., classic pleuropulmonary SFT showing the most common NAB2-STAT6 fusion variant, mainly occurring in older patients and having a more favorable course, and deep-seated hemangiopericytomas showing the second most common NAB2-STAT6 fusion variant, occurring in much younger patients, and having a more aggressive phenotype (Barthelmess et al. 2014).

Table 1 Tumors with a hemangiopericytoma-like pattern

Solitary fibrous tumor (classical pleuropulmonary SFT and several variants, in part in other visceral organs)
True hemangiopericytomas (meningeal hemangiopericytoma, deep-seated hemangiopericytomas, myopericytoma, glomangiopericytoma, and the sinonasal hemangiopericytoma group)
Tumors with occasional hemangiopericytoma-like features

Hemangiopericytoma was described in 1942 as a relatively uncommon distinctive vascular tumor thought to be derived from Zimmermann's pericapillary pericytes (Stout and Murray 1942). Pericytes, identified in 1873 already (Rouget 1873) and analyzed in detail in 1923 (Zimmermann 1923), are dendritic or arborizing cells with multilineage features, arranged along capillaries and venules. In addition to their cases, Stout and Murray cite one or possibly two cases of hemangiopericytoma in a group of vascular tumors described in 1937 (Schmidt 1937) which this author, following the suggestion of Orsos (1934), termed gemmangiomata (gemmangiomas). The features of this neoplasm were characterized in more detail in the following years (Stout 1949; 1956; McMaster et al. 1975; Enzinger and Smith 1976; Mentzel et al. 1994; Nappi et al. 1995; Spitz et al. 1998), also in context with related tumors and the question as to the true entity of hemangiopericytoma (Gengler and Guillou 2006; Park and Araujo 2009). Pericytes can differentiate along fibroblastoid, myoid, osseous, and adipocyte lineages, what is of importance for the understanding of tumors derived thereof, because some pericytomas can develop a myoid component or produce neoplastic adipocytes (lipomatous hemangiopericytomas) (fat-forming solitary fibrous tumors; Lee and Fletcher 2011). Related tumors comprise myofibromatosis and the so-called infantile hemangiopericytoma, glomangiopericytoma, myopericytoma, and perivascular myoma. As most of the hepatic primary manifestations of this tumor category were

described under the term hemangiopericytoma, this label will sometimes be used in addition to solitary fibrous tumor in the following paragraphs.

Epidemiology

Solitary fibrous tumor typically presents in adult individuals. Among 106 cases analyzed, the mean age at presentation was 45 years. The tumors were usually deep-seated lesions (Enzinger and Smith 1976). The tumors occupy clinically and biologically characteristic anatomical locations, including meningeal, cerebral, orbital, sinunasal, osseous, pulmonary, pleural, soft tissue, and visceral tumors. The tumors also occur in the pediatric age group (Fernandez-Pineda et al. 2011), including the entity of multicentric infantile hemangiopericytoma (Sulit et al. 2011). For hepatic SFT, the tumors develop more frequently in females, and the mean age at diagnosis was 55.8 years (Vennarecci et al. 2005). In an earlier study of nine patients, seven patients were female and two male, with an age range at presentation of 32–83 years (mean, 57.5 years; Moran et al. 1998). A recent review of 38 published cases listed 26 female and 12 male patients (Liu et al. 2013). In one investigation, hepatic hemangiopericytoma was associated with occupational exposure to vinyl chloride monomer (Hozo et al. 2000). Most reports concerning primary hepatic SFT described single cases or very small series of this neoplasm.

Selected References Kim and Damjanov 1983; Kottke-Marchant et al. 1989; Kasano et al. 1991; Bost et al. 1995; Barnoud et al. 1996; Chan 1997; Khalifa et al. 1997; Levine and Rose 1997; Lecesne et al. 1998; Guglielmi et al. 1998; Moran et al. 1998; Fuksbrumer et al. 2000; Vaswani et al. 2000; Yilmaz et al. 2000; Lin et al. 2001; Saint-Marc et al. 2002; Chithriki et al. 2004; Neeff et al. 2004; Vennarecci et al. 2005; Moser et al. 2005; Changku et al. 2006; Ji et al. 2006; Jia et al. 2006; Lehmann et al. 2006; Nath et al. 2006; Terkivatan et al. 2006; Kwak et al. 2007; Obuz et al. 2007; Weitz et al. 2007; Chen et al. 2008; El-Khouli et al. 2008; Kandpal et al. 2008; Korkolis et al. 2008; Perini et al. 2008; Novais et al. 2010; Huanca et al. 2011; Güray Durak et al. 2013; Liu et al. 2013.

Hemangiopericytoma/Solitary Fibrous Tumor of the Liver

Clinical Features

Primary SFTs exhibit a clinical presentation that is non-characteristic in most patients, but particularly in the case of large tumors, abdominal distension, right upper quadrant or periumbilical pain, nausea, weight loss, and abnormal liver tests may occur. Hepatic SFT is a rare lesion, and metastatic disease may be difficult to exclude in a given patient owing to the peculiar biology of these neoplasms (Balouet and Destombes 1967; Bergnach 1967; Weitzner 1970; Klein et al. 1971; Wyrick and Wren 1975; Roesler et al. 1985; Thapa et al. 1986; Sano et al. 1991; Zornig et al. 1992; Maeda and Nakaba 1995; Noda et al. 1995; Flores-Stadler et al. 1997; Campion et al. 1999; Hozo et al. 2000; Kruskal and Kane 2002; Ghiur et al. 2003; Plikat et al. 2003; Caruso et al. 2009; Bokshan et al. 2012). In one series, tumor size ranged from 2 to 32 cm in diameter, and the largest weight of a published tumor was 4725 g (Vennarecci et al. 2005). The tumors can grow to such a large size that resection is not feasible, even in the absence of remote disease (Bergnach 1967). Primary hepatic SFT/hemangiopericytoma can present as a multicentric tumor with cystic cavernoma-like areas (Klein et al. 1971).

Part of the hepatic lesions have been reported to show an aggressive course (malignant hemangiopericytoma; Thapa et al. 1986; Sano et al. 1991; Yilmaz et al. 2000; Ghiur et al. 2003; Plikat et al. 2003; Chan et al. 2007; Seijas et al. 2009; Peng et al. 2011; Jakob et al. 2013). These lesions exhibit an invasive phenotype, can traverse the liver capsule, infiltrate the abdominal wall, and give rise to metastasis either in the liver

or in extrahepatic sites. Frankly malignant variants may present with abdominal hemorrhage due to tumor rupture. In one patient SFT of the liver exhibited local recurrence 6 years after resection, and histologic examination of the recurrent tumor displayed features of an aggressive form of SFT (Brochard et al. 2010). In a given case, it is difficult to judge what the biologic course will probably be, although hypercellular parts with increased nuclear atypia and elevated proliferative activity have been observed, suggesting low-grade malignant transformation (Fuksbrumer et al. 2000).

Several observations document an association between SFT/hemangiopericytomas and sometimes severe hypoglycemia, a syndrome called non-islet cell tumor hypoglycemia (NICTH), tumor-associated hypoglycemia (TAH), and the Doege-Potter syndrome (Paullada et al. 1968; Wegmann et al. 1994; Adams et al. 1999), a phenomenon also known for primary SFT/hemangiopericytoma of the liver (Weitzner 1970; Guglielmi et al. 1998; Campion et al. 1999; Kruskal and Kane 2002; Plikat et al. 2003; Bokshan et al. 2012), related to the production of insulin-like growth factor II (ILGF-II) and caused by loss of imprinting of the respective gene (Sohda and Yun 1996; Grunenberger et al. 1999), or by ILGF-II- and ILGF-binding protein 6 (Hoekman et al. 1999), by these neoplasms. Tumor-associated hypoglycemia has also been detected in a patient with hepatic fibrosarcoma (Immerman et al. 1982).

Imaging Features

Hepatic solitary fibrous tumors/hemangiopericytomas are usually solitary lesions, but multicentricity has also been reported (Klein et al. 1971). Sonographically, a complex mass with hyper-isoechoic solid components and hypoechoic cystic areas was described (Caruso et al. 2009). Speckled calcifications may be found. Administration of contrast media in CT and MR imaging reflects the high vascularization of the lesions, showing early, intense, and prolonged enhancement (Caruso et al. 2009). Scintigraphically, large cold nodules in the liver have been reported in a patient with multifocal tumor (Klein et al. 1971). In MR pictures, solid tumor masses prevail, sometimes with a large central necrosis (Plikat et al. 2003).

Macroscopic Pathology

Similar to tumors in other locations, the neoplasms form well-circumscribed and expanding lesions and usually form solid masses of gray to reddish or tan color. The tissue is firm, similar to that of fibromas. The tumors often exhibit partial or apparently complete encapsulation, sometimes with a typically shiny capsule, or formation of a pseudocapsule with perifocal liver atrophy. The cut surface is lobulated. Part of the tumors exhibit whorled and fasciculated cut surface (Korkolis et al. 2008). Hemorrhages may occur, while gross necrosis is unusual, at least in primary tumors. However, very large tumors have shown extensive geographic and sometimes infarctoid central necrosis (Moran et al. 1998). Both gross necrosis and hemorrhage have been encountered (Guglielmi et al. 1998). Some primary hepatic tumors grow to large or huge size (Kottke-Marchant et al. 1989; Guglielmi et al. 1998; Fuksbrumer et al. 2000), and masses up to 22 cm in diameter have been seen (Weitzner 1970), with a weight exceeding 4 kg (Chan et al. 2007). Central cystic cavities have been reported (Barnoud et al. 1996), and the hepatic lesions rarely present as a cyst containing a hemorrhagic fluid and mural tumor nodules of varying size (Klein et al. 1971). SFT with a multiloculated cystic appearance has also been described (Güray Durak et al. 2013). An expanding growth mode prevails, with the adjacent liver showing marked compression atrophy and signs of vascular engorgement. Secondary vascular and/or bile duct compression is sometimes found, and local invasive growth can be encountered, including invasion of intrahepatic veins (Fuksbrumer et al. 2000). Rarely, a pedunculated growth pattern has been seen (Moran

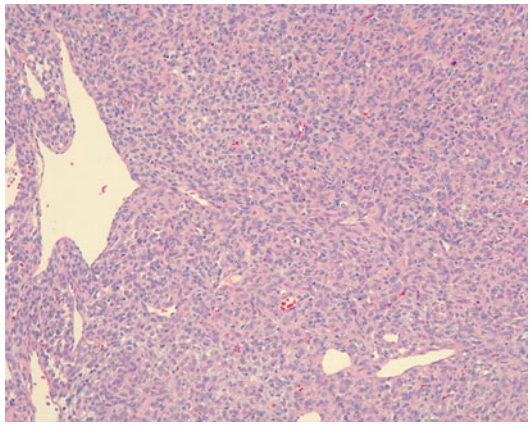

Fig. 1 Primary solitary fibrous tumor of the liver. Part of the tumor cells are associated with vascular spaces (hemangiopericytoma-like pattern; hematoxylin and eosin stain)

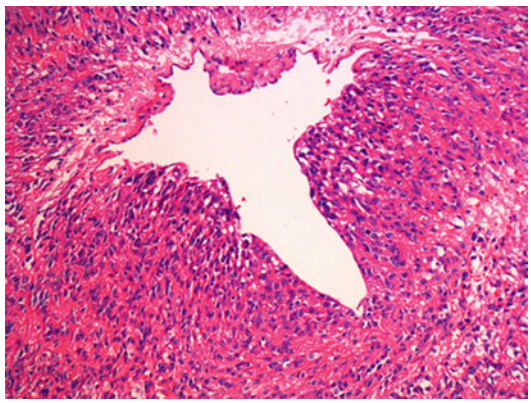

Fig. 2 Solitary fibrous tumor of the liver. The perivascular cellular cuff results in a pericytomatous pattern (hematoxylin and eosin stain)

et al. 1998; Park et al. 2011). Hepatic SFT belongs to the category of liver neoplasm causing capsular retraction (Blachar et al. 2009).

Histopathology

SFTs are often cellular tumors composed of spindle cells with a rather poorly developed and only slightly eosinophilic cytoplasm. These cells, which look different from both fibroblasts and myofibroblasts, either form a short storiform

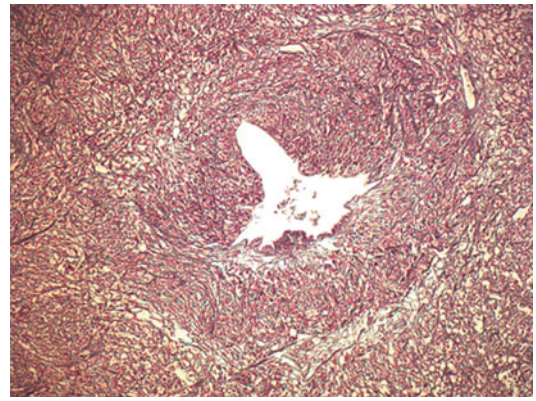

Fig. 3 Solitary fibrous tumor of the liver with a dense network of reticulin fibers (Gomori silver stain)

(so-called patternless) pattern or dense sheaths surrounding slit-like vascular channels (Figs. 1, 2, and 3). The latter pattern previously raised the suspicion that the cells might represent a pericyte or a pericyte-like cell. In most cells, the cytoplasm is not well delineated, and the nuclei are hyperchromatic and either spindled in shape or plump. Mitotic figures are usually rare, but one may find areas with 5–10 mitoses per ten high-power fields. The cellular lesions are traversed by a characteristic vascular ramifying tree showing a "staghorn" pattern. In silver stains, the tumor displays a very dense network of reticulin fibers, which encircle groups of spindle cells or even single cells, and is usually more dense in proximity of blood vessels (the pericapillary reticulin sheath; Stout 1949). In part of cases, an inflammatory response with lymphocytes and mast cells may be encountered. Focal myxoid change may occur (Korkolis et al. 2008), an alteration that can dominate SFT presentation in extrahepatic tumors (myxoid SFT; Lau et al. 2009).

Electron Microscopy

Electron microscopically, the tumor cells are closely apposed, but show poor development of cell-to-cell junctions. The organelle content of cells is highly variable and non-characteristic. Flocculent basement membrane material is

deposited linearly along the surface of many tumor cells (Flores-Stadler et al. 1997).

Immunohistochemistry

Immunohistochemically, the majority of the tumor cells are markedly reactive for vimentin, and staining for BCL-2, CD99, and alpha-1 antitrypsin is at least focally present (Patra et al. 2012; Liu et al. 2013). Endothelia of the intervening vessels and part of the spindle cells are CD34 positive (Fig. 4; Hanau and Miettinen 1995; Barnoud et al. 1996; Kwak et al. 2007; Korkolis et al. 2008; Peng et al. 2011). CD34 reactivity is considered characteristic for SFT (Brunnemann et al. 1999). Part of hepatic SFT expressed VEGF in a pattern resembling that of proliferating hemangiomas, and some of the cells were reactive for factor XIIIa, similar to the interstitial cells of cellular hemangiomas of infancy (Flores-Stadler et al. 1997). A subpopulation of factor XIIIa-positive cells was identified, similar to the "interstitial cells" of cellular hemangiomas of infancy (Flores-Stadler et al. 1997). At least part of the tumors exhibit nuclear reactivity for STAT6 (Doyle et al. 2013; Schweizer et al. 2013; Barthelmess et al. 2014), linked to NAB2-STAT6 fusion (see below). Immunoreactivity for cytokeratins, epithelial membrane antigen (EMA), desmosomal proteins, S-100 protein, smooth muscle actin, and desmin is usually lacking, although keratin positivity has been reported in one instance (Kim and Damjanov 1983).

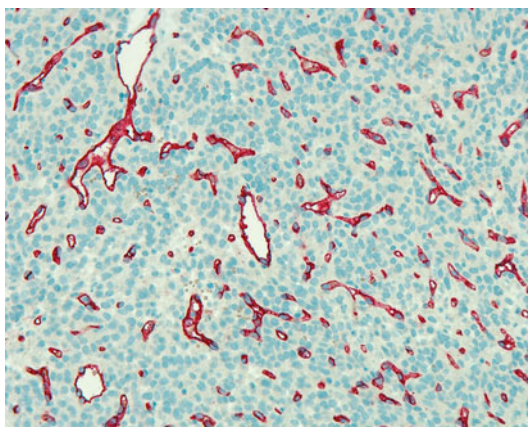

Fig. 4 Solitary fibrous tumor of the liver. The highly cellular neoplastic tissue is strongly vascularized (CD34 immunostain)

Solitary Fibrous Tumor/ Hemangiopericytoma of Hepatic Ligaments

Hemangiopericytoma/SFT rarely develops in the ligamentum teres of the liver (Majnarich and Stout 1960) and in the falciform ligament (Gidwani et al. 2004).

Differential Diagnosis

SFTs/hemangiopericytomas primary to diverse locations can extensively metastasize to the liver (van Assendelft et al. 1984; Chakravarty et al. 1991; Nakamura et al. 2005; Alberti et al. 2006; Balaji et al. 2008; Cheng et al. 2008; Zalinski et al. 2009; Balibrea et al. 2013). Among these neoplasms, meningeal hemangiopericytoma is particularly prone to metastasize to the liver (Buccauw et al. 2011). The metastases can cause paraneoplastic non-islet cell hypoglycemia due to production of IGF-II (Bell and Buist 1981; Sohda and Yun 1996; Lawson et al. 2009). Intra-abdominal SFT/hemangiopericytoma located close to the liver and/or extensively spreading may mimic hepatic localizations of this tumor, e.g., peritoneal spread (Prakash et al. 2009; Reicks and Wilkinson 2011).

Molecular Genetic Alterations

In SFT, chromosome banding and FSH showed recurrent breakpoints in 12q13, associated with frequent deletions affecting STAT6. This feature is associated with somatic fusions of the two genes, NGFI-A-binding protein 2 (NAB2) and STAT6, and nuclear expression of the C-terminal part of STAT6 (Chmielecki et al. 2013; Mohajeri et al. 2013; Robinson et al. 2013; Schweizer et al. 2013; Barthelmess et al. 2014; Koelsche

et al. 2014). In a series of 52 cases of SFT, 12 different NAB2-STAT6 fusion variants were detected in 92 % of cases. Immunohistochemically, all tumors showed strong and diffuse nuclear reactivity for STAT6 (Barthelmess et al. 2014). The NAB2-STAT6 fusion was also found in meningeal hemangiopericytomas (Schweizer et al. 2013). NAB2 is the transcriptional regulator NGFI-A-binding protein 2, a protein which functions in the nucleus to activate or repress transcription, in part through interaction with nucleosome remodeling and deacetylase complexes. NAB2 regulates and modulates the expression levels of the tumor necrosis factor (TNF) family member TNF-related apoptosis inducing ligand/TRAIL (Balzarolo et al. 2013). SFT also strongly expresses the GRIA2 gene (Vivero et al. 2014), encoding a protein of the ionotropic AMPA glutamate receptor.

Putative Cellular Origins

The cell of origin and the histogenesis of solitary fibrous tumors have not been elucidated so far, but putative mesothelial or primitive mesenchymal cells have been suggested. What is the evidence for the involvement of a mesenchymal progenitor cell? One argument is based on the finding of several lines of differentiation in solitary fibrous tumors: (1) fibrous variant, (2) cellular variant (more than 90 % cellularity), (3) adipocyte-forming variant (fat-forming SFT; lipomatous hemangiopericytoma), (4) giant cell-rich variant (giant cell angiofibroma with floret cells, including the vascular variant), (5) myxoid SFT, (6) synchronous pleuro-renal and renal solitary tumor, and (7) malignant solitary fibrous tumors. Based on electron microscopic investigations showing a mixture of mesenchymal cells and cells with features of mesothelia, a submesothelial origin of the tumor has been proposed (Kottke-Marchant et al. 1989; Barnoud et al. 1996). However, the convincing demonstration of SFTs at extrapleural sites strongly argues against its mesothelial or submesothelial origin. Parts of the cells are reactive for CD99 and CD34, and ultrastructurally the dominant cell population exhibits some degree of myofibroblastic differentiation, focal smooth muscle features, and undifferentiated cells in a perivascular location (Ide et al. 2005; Rodriguez-Gil et al. 2009). The involvement of a perivascular cell is also supported by the fact that solitary fibrous tumors may show transition to hemangiopericytomas (the hemangiopericytoma/solitary fibrous spectrum; Park and Araujo 2009). In fact, soft tissue with hemangiopericytoma-like growth patterns can now be divided into three categories, as summarized in the Table, and one of these categories is the solitary fibrous tumor group (Knösel et al. 2010). Therefore, a CD34-reactive fibroblastoid and vessel-associated progenitor cell may histogenetically be involved, but such a putative mesenchymal stem cell has not yet been identified in the normal liver. A common or characteristic cytogenetic anomaly has not been detected so far (Torabi et al. 2008; Torres-Olivera et al. 2009).

References

Adams J, Lodge JP, Parker D (1999) Liver transplantation for metastatic hemangiopericytoma associated with hypoglycemia. Transplantation 67:488–489

Alberti C, Benea G, Kopf B, De Giorgi U (2006) Hepatic metastases of hemangiopericytoma: contrast-enhanced MRI, contrast-enhanced ultrasonography and angiography findings. Cancer Imaging 6:56–59

Balaji R, Khoo JB, Sittampalam K, Chee SK (2008) CT imaging of malignant metastatic hemangiopericytoma of the parotid gland with histopathologic correlation. Cancer Imaging 8:186–190

Balibrea JM, Rovira-Argelaques M, Otero-Pineiro AM, Julian JF, Carrato C, Navinés J et al (2013) Multifocal hepatic cystic mass as first manifestation of metastatic spinal hemangiopericytoma. Int J Surg Case Rep 4:15–18

Balouet G, Destombes P (1967) Apropos of several apparently primary hepatic mesenchymatous tumours. Trial classification and diagnosis of spindle cell tumours of the liver (in French). Ann Anat Pathol (Paris) 12:273–286

Balzarolo M, Watzl C, Medema JP, Wolkers MC (2013) NAB2 and EGR-1 exert opposite roles in regulating TRAIL expression in human natural killer cells. Immunol Lett 151:61–67

Barnoud R, Arvieux C, Pasquier D, Pasquier B, Letoublon C (1996) Solitary fibrous tumour of the liver with CD34 expression. Histopathology 28:551–554

Barthelmess S, Geddert H, Boltze C, Moskalev EA, Bieg M, Suîrbu H, Brors B, Wiemann S et al (2014)

Solitary fibrous tumors (SFTs)/hemangiopericytomas (HPCs) with different variants of the NAB2-STAT6 gene fusion are characterized by specific histomorphology and distinct clinicopathological features. Am J Pathol 184:1209–1218

Bell GM, Buist TA (1981) Arterial embolization in the management of liver tumour with recurrent hypoglycaemia. Postgrad Med J 57:534–536

Bergnach A (1967) On a case of perithelioma of the liver (in Italian). Friuli Med 22:1037–1048

Blachar A, Federle MP, Sosna J (2009) Liver lesions with hepatic capsular retraction. Semin Ultrasound CT MR 30:426–435

Bokshan SL, Doyle M, Becker N, Nalbantoglu I, Chapman WC (2012) Hepatic hemangioendothelioma/solitary fibrous tumor: a review of our current understanding and case study. J Gastrointest Surg 16:2170–2176

Bost F, Barnoud R, Peoc'h M, Le Marc'hadour F, Pasquier D, Pasquier B (1995) CD34 positivity in solitary fibrous tumor of the liver. Am J Surg Pathol 19:1334–1335

Brochard C, Michalak S, Aubé C, Singeorzan C, Fournier HD, Laccourreye L, Calès P et al (2010) A not so solitary fibrous tumor of the liver. Gastroenterol Clin Biol 34:716–720

Brunnemann RB, Ro JY, Ordonez NG, Mooney J, El-Naggar AK, Ayala AG (1999) Extrapleural solitary fibrous tumor: a clinicopathologic study of 24 cases. Mod Pathol 12:1034–1042

Buccauw K, Sciot R, Wolter P, Aerts R, Claus F (2011) Delayed liver metastasis of a meningeal solitary fibrous tumor. Acta Gastroenterol Belg 74:567–569

Campion JP, Gerard O, Dien F, Ramee MP, Turlin B (1999) Primary liver hemangiopericytoma associated with hypoglycemia: report of a second case. Hepatogastroenterology 46:1944–1948

Caruso S, Gruttadauria S, Mivervini MI, Miraglia R, Milazzo M, Luca A, Gridelli B (2009) Primary hemangiopericytoma of the liver: sonographic findings. J Clin Ultrasound 37:305–307

Chakravarty BJ, Munn S, Lane MR (1991) Hepatic metastasis from a meningeal haemangiopericytoma. Aust N Z J Med 21:884–885

Chan JKC (1997) Solitary fibrous tumor of the liver: everywhere, and a diagnosis in vogue. Histopathology 31:568–576

Chan G, Horton PJ, Thyssen S, Lamarche M, Nahal A, Hill DJ, Marliss EB, Metrakos P (2007) Malignant transformation of a solitary fibrous tumor of the liver and intractable hypoglycemia. J Hepatobiliary Pancreat Surg 14:595–599

Changku J, Shaohua S, Zhicheng Z, Shusen Z (2006) Solitary fibrous tumor of the liver: retrospective study of reported cases. Cancer Invest 24:132–135

Chen JJ, Ong SL, Richards C, Garcea G, Pollard C, Berry D, Dennison A (2008) Inaccuracy of fine-needle biopsy in the diagnosis of solitary fibrous tumour of the liver. Asian J Surg 31:195–198

Cheng NY, Chen RC, Chen TY, Tu HY (2008) Contrast-enhanced ultrasonography of hepatic metastasis of hemangiopericytoma. J Ultrasound Med 27:667–671

Chithriki M, Jaibaji M, Vandermolen R (2004) Solitary fibrous tumor of the liver with presenting symptoms of hypoglycemic coma. Am Surg 70:291–293

Chmielecki J, Crago AM, Rosenberg M, O'Connor R, Walker SR, Ambrogio L, Auclair D et al (2013) Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. Nat Genet 45:131–132

Doyle LA, Vivero M, Fletcher CD, Mertens F, Hornick JL (2013) Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. Mod Pathol. doi:10.1038/modpathol.2013.164

El-Khouli RH, Geschwind JF, Bluemke DA, Kamel IR (2008) Solitary fibrous tumor of the liver: magnetic resonance imaging evaluation and treatment with transarterial chemoembolization. J Comput Assist Tomogr 32:769–771

Enzinger FM, Smith BH (1976) Hemangiopericytoma. An analysis of 106 cases. Hum Pathol 7:61–82

Fernandez-Pineda I, Parida L, Jenkins JJ, Davidoff AM, Rao BN, Rodriguez-Galindo C (2011) Childhood hemangiopericytoma: review of St Jude Children's Research Hospital. J Pediatr Hematol Oncol 33:356–359

Flores-Stadler EM, Chou P, Walterhouse D, Bourtsos E, Gonzalez-Crussi F (1997) Hemangiopericytoma of the liver: immunohistochemical observations, expression of angiogenic factors, and review of the literature. J Pediatr Hematol Oncol 19:449–454

Fuksbrumer MS, Klimstra D, Panicek DM (2000) Solitary fibrous tumor of the liver: imaging findings. AJR Am J Roentgenol 175:1683–1687

Gengler and Guillou 2006. http://www.ncbi.nlm.nih.gov/pubmed/16359538

Ghiur M, Serbanoiu D, Nicolescu D, Ghiur L, Zbuchea A (2003) Malignant liver hemangiopericytoma ruptured after an abdominal traumatism (in Romanian). Chirurgia (Bucur) 98:249–251

Gidwani AL, Mullan FJ, Kenny B (2004) Solitary fibrous tumour of the falciform ligament containing multiple foci of malignant transformation. J Clin Pathol 57:546–547

Grunenberger F, Bachellier P, Chenard MP, Massard G, Caraman PL, Perrin E, Zapf J et al (1999) Hepatic and pulmonary metastases from a meningeal hemangiopericytoma and severe hypoglycemia due to abnormal secretion of insulin-like growth factor: a case report. Cancer 85:2245–2248

Guglielmi A, Frameglia M, Iuzzolino P, Martignoni G, De Manzoni G, Laterza E, Veraldi GF et al (1998) Solitary fibrous tumor of the liver with CD34 positivity and hypoglycemia. J Hepatobiliary Pancreat Surg 5:212–216

Güray Durak M, Sagol Ö, Tuna B, Ertener Ö, Ünek T, Karademir S, Dicle O (2013) Cystic solitary fibrous

tumor of the liver: a case report. Turk Patoloji Derg 29:217–220
Hanau CA, Miettinen M (1995) Solitary fibrous tumor: histological and immunohistochemical spectrum of benign and malignant variants presenting at different sites. Hum Pathol 26:440–449
Hoekman K, van Doorn J, Gloudemans T, Maassen JA, Schuller AG, Pinedo HM (1999) Hypoglycaemia associated with the production of insulin-like growth factor II and insulin-like growth factor binding protein 6 by a haemangiopericytoma. Clin Endocrinol (Oxf) 51:247–253
Hozo I, Miric D, Bojic L, Giunio L, Lusic I, Culic V, Simunic M (2000) Liver angiosarcoma and hemangiopericytoma after occupational exposure to vinyl chloride monomer. Environ Health Perspect 108:793–795
Huanca L, Webb P, Ruiz E (2011) Hepatic solitary fibrous tumor (in Spanish). Rev Gastroenterol Peru 31:376–380
Ide F, Obara K, Mishima K, Saito I, Kusama K (2005) Ultrastructural spectrum of solitary fibrous tumor: a unique perivascular tumor with alternative lines of differentiation. Virchows Arch 446:646–652
Immerman SC, Sener SF, Khandekar JD (1982) Causes and evaluation of tumor-induced hypoglycemia. Arch Surg 117:905–908
Jakob M, Schneider M, Hoeller I, Laffer U, Kaderli R (2013) Malignant solitary fibrous tumor involving the liver. World J Gastroenterol 19:3354–3357
Ji Y, Fan J, Xu Y, Zhou J, Zeng HY, Tan YS (2006) Solitary fibrous tumor of the liver. Hepatobiliary Pancreat Dis Int 5:151–153
Jia C, Shi S, Zhao Z, Zhen S (2006) Solitary fibrous tumor of the liver: retrospective study of reported cases. Cancer Invest 24:132–135
Kandpal H, Sharma R, Gupta SD, Kumar A (2008) Solitary fibrous tumour of the liver: a rare imaging diagnosis using MRI and diffusion-weighted imaging. Br J Radiol 81:e282–e286
Kasano Y, Tanimura H, Tabuse Y, Nagai Y, Mori K, Minami K (1991) Giant fibrous mesothelioma of the liver. Am J Gastroenterol 86:379–380
Khalifa MA, Montgomery EA, Azumi N, Gomes MN, Zeman RK, Min KW, Lack EE (1997) Solitary fibrous tumors: a series of lesions, some in unusual sites. South Med J 90:793–799
Kim H, Damjanov I (1983) Localized fibrous mesothelioma of the liver. Report of a giant tumor studied by light and electron microscopy. Cancer 52:1662–1665
Klein W, Marx E, Hurter J, Huth F (1971) Multicentric hemangiopericytoma of the liver with cystic cavernoma-like areas (in German). Zentralbl Chir 96:387–391
Knösel T, Schulz B, Katenkamp K, Katenkamp D, Petersen I (2010) Solitary fibrous tumor and hemangiopericytoma: what is new ? (in German). Pathologe 31:123–128
Koelsche C, Schweizer L, Renner M, Warth A, Jones DTW, Sahm F, Euss DE, Capper D, Knösel T et al (2014) Nuclear relocation of STAT6 reliably predicts NAB2-STAT6 fusion for the diagnosis of solitary fibrous tumour. Histopathology 65:613–622
Korkolis DP, Apostolaki K, Aggeli C, Plataniotis G, Gontikakis E, Volanaki D, Sebastiadou M et al (2008) Solitary fibrous tumor of the liver expressing CD34 and vimentin: a case report. World J Gastroenterol 14:6261–6264
Kottke-Marchant K, Hart WR, Broughan T (1989) Localized fibrous tumor (localized fibrous mesothelioma) of the liver. Cancer 64:1096
Kruskal JB, Kane RA (2002) Paraneoplastic hypoglycemia associated with a hepatic hemangiopericytoma. J Ultrasound Med 21:927–932
Kwak SY, Gwak GY, Yun WK, Kim HJ, Do IG, Joh JW, Park CK (2007) A case of solitary fibrous tumor of the liver (in Korean). Korean J Hepatol 13:560–564
Lau SK, Weiss LM, Chu PG (2009) Myxoid solitary fibrous tumor: a clinicopathologic study of three cases. Virchows Arch 454:189–194
Lawson EA, Zhang X, Crocker JT, Wang WL, Klibanski A (2009) Hypoglycemia from IGF2 overexpression associated with activation of fetal promoters and loss of imprinting in a metastatic hemangiopericytoma. J Clin Endocrinol Metab 94:2226–2231
Lecesne R, Drouillard J, Le Bail B, Saric J, Balabaud C, Laurent F (1998) Localized fibrous tumor of the liver: imaging findings. Eur Radiol 8:36–38
Lee JC, Fletcher CD (2011) Malignant fat-forming solitary fibrous tumor (so-called "lipomatous hemangiopericytoma"): clinicopathologic analysis of 14 cases. Am J Surg Pathol 35:1177–1185
Lehmann C, Mourra N, Tubiana JM, Arrivé L (2006) Solitary fibrous tumor of the liver (in French). J Radiol 87:139–142
Levine TS, Rose DS (1997) Solitary fibrous tumor of the liver. Histopathology 30:396–397
Lin YT, Lo GH, Lai KH, Tsai CC, Pan HB, Tseng HH, Lo YS (2001) Solitary fibrous tumor of the liver. Zhonghua Yi Xue Za Zhi (Taipei) 64:305–309
Liu Q, Liu J, Chen W, Mao S, Guo Y (2013) Primary solitary fibrous tumors of liver: a case report and literature review. Diagn Pathol 8:195
Maeda S, Nakaba H (1995) Hemangiopericytoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:339–341
Majnarich G, Stout AP (1960) Hemangiopericytoma of the ligamentum teres of the liver; report of a case. Am J Surg 100:740–743
McMaster MJ, Soule EH, Ivins JC (1975) Hemangiopericytoma. A clinicopathologic study and long-term followup of 60 patients. Cancer 36:2232–2244
Mentzel T, Calonie E, Nascimento AG, Fletcher CD (1994) Infantile hemangiopericytoma versus infantile myofibromatosis. Study of a series suggesting a continuous spectrum of infantile myofibroblastic lesions. Am J Surg Pathol 18:922–930
Mohajeri A, Tayebwa J, Collin A, Nilsson J, Magnussen L, von Steyern FV, Brosjö O et al (2013) Comprehensive

genetic analysis identifies a pathognomonic NAB2/STAT6 fusion gene, non-random secondary genomic imbalances, and a characteristic gene expression profile in solitary fibrous tumor. Genes Chromosomes Cancer 52:873–886

Moran CA, Ishak KG, Goodman ZD (1998) Solitary fibrous tumor of the liver: a clinicopathologic and immunohistochemical study of nine cases. Ann Diagn Pathol 2:19–24

Moser T, Nogueira TS, Neuville A, Riehm S, Averous G, Weber JC, Veillon F (2005) Delayed enhancement pattern in a localized fibrous tumor of the liver. AJR Am J Roentgenol 184:1578–1580

Nakamura S, Fukui M, Takeshita H, Tsuji Y, Murata H, Kubo T (2005) Malignant solitary fibrous tumor of the thigh accompanied by hypoglycemic coma. A case report. Anticancer Res 25:2461–2464

Nappi O, Ritter JH, Pettinato G, Wick MR (1995) Hemangiopericytoma: histopathological pattern or clinicopathologic entity? Semin Diagn Pathol 12:221–232

Nath DS, Rutzik AD, Sielaf TD (2006) Solitary fibrous tumor of the liver. AJR Am J Roentgenol 187: W187–W190

Neeff H, Obermaier R, Technau-Ihling K, Werner M, Kurtz C, Imdahl A, Hopt UT (2004) Solitary fibrous tumour of the liver: case report and review of the literature. Langenbecks Arch Surg 389:293–298

Noda N, Hasegawa H, Kanai M, Shimizu Y, Yoshida H, Matsumoto T, Akita M (1995) Recurrent hemangiopericytoma of the liver: report of a case. Surg Today 25:72–75

Novais P, Robles-Medranda C, Pannain VL, Barbossa D, Biccas B, Fogaça H (2010) Solitary fibrous tumor: is surgical approach the best option ? J Gastrointest Liver Dis 19:81–84

Obuz F, Secil M, Sagol O, Karademir S, Topalak O (2007) Ultrasonography and magnetic resonance imaging of solitary fibrous tumor of the liver. Tumori 93:100–102

Orsos F (1934) Gefässsprossgeschwulst (Gemmangioma). Beitr Path Anat 93:121

Park MS, Araujo DM (2009) New insights into the hemangiopericytoma/solitary fibrous tumor spectrum of tumors. Curr Opin Oncol 21:327–331

Park HS, Kim YK, Cho BH, Moon WS (2011) Pedunculated hepatic mass. Liver Int 31:541

Patra S, Vij M, Venugopal K, Rela M (2012) Hepatic solitary fibrous tumor: report of a rare case. Indian J Pathol Microbiol 55:236–238

Paullada JJ, Lisci-Garmilla A, Gonzales-Angulo A, Jurado-Mendoza J, Quijano-Narezo M, Gomez-Peralta L, Doria-Medina M (1968) Hemangiopericytoma associated with hypoglycemia. Metabolic and electron microscopic studies of a case. Am J Med 44:990–999

Penel N, Amela EY, Decanter G, Robin YM, Marec-Berard P (2012) Solitary fibrous tumors and so-called hemangiopericytoma. Sarcoma 2012:690251

Peng L, Liu Y, Ai Y, Liu Z, He Y, Liu Q (2011) Skull base metastases from a malignant solitary fibrous tumor of the liver. A case report and literature review. Diagn Pathol 6:127

Perini MV, Herman P, D'Albuquerque LA, Saad WA (2008) Solitary fibrous tumor of the liver: report of a rare case and review of the literature. Int J Surg 6:396–399

Plikat K, Reichle A, Elmlinger MW, Schölmerich J (2003) Hypoglycemia associated with the production of insulin-like growth factor (IGF)-II by a hemangiopericytoma (in German). Dtsch Med Wochenschr 128:257–260

Prakash M, Mumtaz HA, Sodhi KS, Kapoor R, Khandelwal N (2009) Hemangiopericytoma: an unusual cause of peritoneal carcinomatosis. Cancer Imaging 9:32–34

Reicks M, Wilkinson N (2011) Recurrent peritoneal hemangiopericytoma. Am Surg 77:E65–E66

Robinson DR, Wu YM, Kalyana-Sundaram S, Cao X, Lonigro RJ, Sung YS, Chen CL et al (2013) Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 45:180–185

Rodriguez-Gil Y, Gonzalez MA, Carcavilla CB, Santamaria JS (2009) Lines of cell differentiation in solitary fibrous tumor: an ultrastructural and immunohistochemical study of 10 cases. Ultrastruct Pathol 33:274–285

Roesler A, Schreyer T, Keller E, Storkel S (1985) Hemangiopericytoma of the liver (in German). Roentgenblätter 38:58–59

Rouget C (1873) Mémoire sur le développement, la structure et propriétés physiologiques des capillaires sanguins et lymphatiques. Arch Physiol Norm Pathol 5:603

Saint-Marc O, Pozzo A, Causse X, Heitzmann A, Debillon G (2002) Solitary fibrous liver tumor: clinical, radiological and pathological characteristics (in French). Gastroenterol Clin Biol 26:171–173

Sano T, Terada T, Hayashi F, Kiribuchi Y, Setoyama R, Kawano N, Hatakeyama S (1991) Malignant hemangiopericytoma of the liver: report of a case. Jpn J Surg 21:462–465

Schmidt H (1937) Zur Kenntnis des Gemmangioms und seiner Beziehungen zum Angiosarkom. Frankfurt Ztschr Path 51:43

Schweizer L, Koelsche C, Sahm F, Piro RM, Capper D, Reuss DE, Pusch S, Habel A et al (2013) Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein. Acta Neuropathol 125:651–658

Seijas R, Ares O, Sierra J, Pérez-Dominguez M (2009) Oncogenic osteomalacia: two case reports with surprisingly different outcomes. Arch Orthop Trauma Surg 129:533–539

Sohda T, Yun K (1996) Insulin-like growth factor II expression in primary meningeal hemangiopericytoma and its

metastasis to the liver accompanied by hypoglycemia. Hum Pathol 27:858–861
Spitz FR, Bouvet M, Pisters PW, Pollock RE, Feig BW (1998) Hemangiopericytoma: a 20-year single-institution experience. Ann Surg Oncol 5:350–355
Stout AP (1949) Hemangiopericytoma: a study of 26 cases. Cancer 2:1027–1054
Stout AP (1956) Tumors featuring pericytes: glomus tumor and hemangiopericytoma. Lab Invest 5:217–223
Stout AP, Murray MR (1942) Hemangiopericytoma: a vascular tumor featuring Zimmermann's pericytes. Ann Surg 116:26–33
Sulit DJ, Tom WL, Willert JR, Nespeca MP, Friedlander SF (2011) Multicentric infantile hemangiopericytoma: case report and review of the literature. J Pediatr Hematol Oncol 33:e166–e170
Terkivatan T, Kliffen M, de Witt JH, van Geel AN, Eggermont AM, Verhoef C (2006) Giant solitary fibrous tumour of the liver. World J Surg Oncol 4:81
Thapa BR, Narasimharao KL, Marwaha RK, Walia BN, Bannerjee CK, Mitra SK, Pathak IC (1986) Malignant hemangiopericytoma of liver. Indian Pediatr 23:551–553
Torabi A, Leie SM, DiMaio D, Pinnt JC, Hess MM, Nelson M, Bridge JA (2008) Lack of a common or characteristic cytogenetic anomaly in solitary fibrous tumor. Cancer Genet Cytogenet 181:60–64
Torres-Olivera FJ, Vargas MT, Torres-Gomez FJ, Trigo I, Diaz M, Gonzalez-Campora R (2009) Cytogenetic, fluorescence in situ hybridization, and immunohistochemistry studies in a malignant pleural solitary fibrous tumor. Cancer Genet Cytogenet 189:122–126
van Assendelft AH, Strengell-Usanov L, Kastarinen S (1984) Pulmonary haemangiopericytoma with multiple metastases. Eur J Respir Dis 65:380–383
Vaswani K, Guttikonda S, Vitellas KM (2000) Localized fibrous tumor of the liver. AJR Am J Roentgenol 175:875–876
Vennarecci G, Ettorre GM, Giovanelli L, Del Nonno F, Perracchio L, Visca P, Corazza V et al (2005) Solitary fibrous tumor of the liver. J Hepatobiliary Pancreat Surg 12:341–344
Vivero M, Doyle LA, Fletcher CDM, Mertens F, Hornick JL (2014) GRIA2 is a novel diagnostic marker for solitary fibrous tumour identified through gene expression profiling. Histopathology 65:71–80
Wegmann W, Vonesch HJ, Kamber J, Kiss D (1994) Recurrent and metastasizing hemangiopericytoma of the meninges with paraneoplastic hypoglycemia (in German). Schweiz Med Wochenschr 124:146–151
Weitz J, Klimstra DS, Cymes K, Jarnagin WR, D'Angelica M, La Quaglia MP, Fong Y et al (2007) Management of primary liver sarcomas. Cancer 109:1391–1396
Weitzner S (1970) Primary hemangiopericytoma of liver associated with hypoglycemia. Report of a case. Am J Dig Dis 15:673–678
Wyrick WJ, Wren HB (1975) Primary hepatic intra-abdominal hemangiopericytoma. J Ark Med Soc 71:247–248
Yilmaz S, Kirimlioglu V, Ertas E, Hilmioglu F, Yildirim B, Katz D, Mizrak B (2000) Giant solitary fibrous tumor of the liver with metastasis to the skeletal system successfully treated with trisegmentectomy. Dig Dis Sci 45:168–174
Zalinski S, Goumard C, Scatton O, Terris B, Plantier F, Dupin N, Soubrane O (2009) Liver recurrence of a subcutaneous temporal hemangiopericytoma: the index case. J Gastrointest Surg 13:1155–1159
Zimmermann KW (1923) Der feinere Bau der Blutkapillaren. Z Anat Entwicklungsgesch 68:29
Zornig C, Kremer B, Henne-Bruns D, Weh HJ, Schröder S, Brölsch CE (1992) Primary sarcoma of the liver in the adult. Report of five surgically treated patients. Hepatogastroenterology 39:319–321

Part VIII

Mesenchymal Tumors of the Hepatobiliary Tract

Fibroblastoid and Myofibroblastoid Tumors of the Liver and Bile Ducts

62

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_62

Abstract

Primary neoplasms of the liver originating from fibroblasts and myofibroblasts are very rare lesions. Few cases of hepatic fibroma have been reported in the literature, but part of them may have been solitary fibrous tumors. True fibromas of the liver can grow to a very large size and had weight exceeding 4 kg. The tumors consist of a fibroblastoid tissue similar to that in extrahepatic fibromas. Very few fibromas were observed in the biliary tract. Fibrosarcoma is defined as a malignant mesenchymal tumor composed of neoplastic fibroblasts. The neoplasm can occur as a primary lesion in the liver, but part of older published cases would now be classified as other sarcomas or metastatic disease. Hepatic fibrosarcoma may be associated with paraneoplastic hypoglycemia. The neoplasms are usually solitary lesions of high cellularity. Very rarely, congenital and infantile fibrosarcoma manifests in the liver. Generalized infantile hepatic myofibromatosis can involve the hepatobiliary tract. Other primary hepatic neoplasms containing fibroblastoid cells include desmoid tumors, tumors with myxoid features, and tumors derived from stellate cells.

Fibroma of the Liver

These are unusual tumors which, owing to their rarity, have so far not been analyzed in detail by use of modern methods (Fig. 1). The first case may have been described by Chiari (1877), and only few cases have since been reported (Yokota 1944; Ishak 1976; Craig et al. 1989; Craig 1994; Tameda and Shiraki 1995). In Chiari's patient, an egg-shaped tumor was detected in the right liver lobe, microscopically consisting of a hypocellular fibrous tissue. Bona fide fibromas should be distinguished from solitary fibrous tumors, which occur in the liver (see below), but make part of the group of mesothelial neoplasms. As more specific immunohistochemistry was not available in previously described cases, it is difficult to judge which examples in fact correspond to

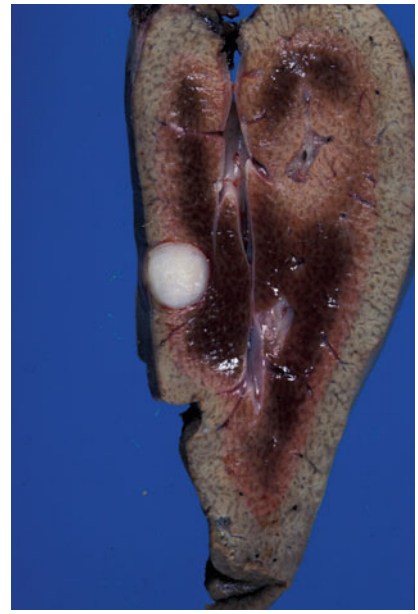

Fig. 1 Fibroma of the liver. The tumor appears as a well-delineated, white, and firm nodule in a non-cirrhotic liver

fibroma or to solitary fibrous tumor. As far as can be judged with the few examples, hepatic fibromas occur both in younger and older individuals. The cases reported in the AFIP atlas (Craig et al. 1989) are striking by their size, the maximum diameter observed being 27 cm and the weights ranging from 860 to 4,500 g. Hepatic fibromas are either expanding or pedunculated lesions and exhibit a polycyclic contour, the cut surface showing a whitish color, a nodular structure, and a fibrous texture with whorls and fibrous septa separating the nodules (Craig et al. 1989). Central necroses and cysts may occur. The histologic presentation is variable, ranging from hypocellular and bland-looking fibrous tissue to more cellular parts. The typical cell is spindle shaped and fibroblast- or myofibroblast-like, and these cells are embedded in a matrix consisting of collagen fibers. Mitotic figures may be encountered.

A unique case was reported from Japan (Yokota 1944). A 33-year-old male patient presenting with a history of upper abdominal pain showed on abdominal X ray a tree-like "stony" shadow in the gallbladder region. Under the preoperative diagnosis of gallstone disease,

laparotomy was performed. Exploration revealed a tumor mass in the right liver lobe, close to the anterior margin, adherent to gallbladder, transverse colon, and omentum. The lesion was resected and left a concave depression in the liver substance. Grossly, the tumor measured up to 6 cm in diameter and had a weight of 41 g. Strikingly, the nodular mass was as hard as a stone. Histologically, the tumor consisted of partly hyalinized bundles of connective tissue cells with associated matrix, focally with necrosis. The overall cellularity and vascularity were low. Extensive mineralization was noted, sometimes with heterotopic ossification, the bony tissue being devoid of osteoblasts. The diagnosis was fibroma ossificans (ossifying fibroma; "osteofibroma").

Fibroma of the Biliary Tract

Only few reports document primary fibroma of the biliary tract (Albers 1862; Holzinger 1901; Chu 1950; Taute et al. 1988; Shiga 1996). Fibroma may arise anywhere along the extrahepatic bile ducts, including the common bile duct (Albers 1862), the common hepatic duct (Chu 1950), and the hepatic ducts (Holzinger 1901). Pedunculated fibroma of the common hepatic duct can cause biliary obstruction (Taute et al. 1988). The lesion described by these authors measures about 6 mm and was associated with a massively dilated gallbladder. Histology showed a tumor consisting of fibroblastoid cells somewhat resembling a neurofibroma, and focal sclerohyalinosis was noted.

Fibromas of the bile ducts are mass-forming lesions that may lead to duct stenosis. In the case reported by Chu (1950), a 45-year-old male patient was examined due to progressive jaundice and clay-colored stools. The patient deceased and necropsy showed a tumor 2.5 cm proximal to the junction of the cystic and common hepatic ducts, presenting a firm ovular nodule, measuring up to 1 cm in diameter and located to the lateral wall of the common hepatic duct, causing compression of the lumen. The nodular lesion described by Holzinger (1901) was very similar to the case of Chu and also had led to massive biliary obstruction, including marked hydrops of the gallbladder. Pedicled (pedunculated) fibroma of the extrahepatic bile duct causing obstructive jaundice has been reported (Taute et al. 1988). In the latter case (female patient of 33 years of age), laparotomy showed, in the opened common hepatic duct, a cherry-sized pedunculated tumor which had obturated the lumen completely.

The morphologic features of biliary fibroma are those of fibromas located elsewhere, although relatively few descriptions are available. In the case of Chu (1950), the lesion situated in the wall of the common hepatic duct showed a circumscribed mass of closely arranged, elongated, thin, spindle-shaped cells suggesting fibroblasts/fibrocytes. They were disposed in interlacing bundles and were of regular size, shape, and staining. No mitotic figures were evident. The mucosa of the duct overlying the nodule exhibited necrosis and atrophy. Their muscular layer was not apparent, and a thin, compressed fibrous capsule surrounded the nodule. In the case of the pedunculated fibroma described by Taute et al. (1988), histology showed a lesion composed of fibroblastoid cells arranged in the form of interlacing bundles, sometimes with a wave-like pattern. The nuclei were elongated, but palisading was not noted, although the neoplasm somewhat resembled a neurogenic tumor.

Fibrosarcoma of the Liver

ICD-O Code 8810/3

Introduction

Fibrosarcoma is defined as a malignant mesenchymal tumor composed of neoplastic fibroblasts and fibrocytes, with variable amount of connective tissue fibers. Primary fibrosarcoma of the liver is, apart from malignant fibrous histiocytoma, one of the more frequent hepatic sarcomas in adult patients. In early reports, however, it is difficult to judge whether the sarcoma was in fact primary to the liver, and whether the

lesion was bona fide fibrosarcoma, because of the frequently used term, spindle cell sarcoma. A compilation of numerous cases published in 1909 listed 113 cases (Costantini 1909), but it is likely that only about 40 of these were primary hepatic sarcomas. Herxheimer analyzed these and other cases and published the results in 1930 (Herxheimer 1930). In his table, a subset of hepatic sarcomas was identified as spindle cell sarcoma, and at least part of them may represent fibrosarcomas primary to the liver (Orth 1885; Windrath 1885; Podrouzek 1888; Bramwell and Leith 1897; Cesaris-Demel 1900; Scheidemandel 1903; Marx 1904; Pater 1905; Bertelli 1908; Dominici and Merle 1909; Costantini 1909; Saltykov 1914; Dubs 1916; Goldstein 1921; Jaffe 1924). Several cases from the older literature, however difficult to classify from the respective reports, are cited by Thöhle is his, in those days, seminal book on the surgery of liver tumors (Thöhle 1913). From the second half of the twentieth century onwards, more detailed and/or reliable reports of true hepatic fibrosarcoma are available. In part of the cases, the primary localization to the liver has been confirmed at autopsy (Bodker and Boiesen 1981; Nakahama et al. 1989; Ito et al. 1990). In very few instances, primary hepatic fibrosarcoma occurred in combination with carcinoma in the liver (Dominici and Merle 1909; Saltykov 1914; Jaffe 1924). A subset of hepatic fibrosarcomas have been observed in cirrhotic livers (Dominici and Merle 1909; Jaffe 1924; Steiner 1960; Alrenga 1975).

Similar to other mesenchymal tumors, some hepatic fibrosarcomas were associated with (sometimes severe) hypoglycemia (Snapper et al. 1964; Gen et al. 1983; Kameya et al. 1985; Kotani et al. 1993). This form of tumor-associated hypoglycemia is termed syndrome of extrapancreatic tumor hypoglycemia (EPTH) or non-islet-cell tumor hypoglycemia (NICTH), and is caused by the paraneoplastic secretion of insulin-like growth factor II (Fukuda et al. 2006). In one case of hepatic fibrosarcoma with hypoglycemia, production of insulin-like growth factor II (IGF-II) was proposed to have induced hypoglycemia, based on the detection of IGF-II reactivity in the Golgi area of the neoplastic cells (Kotani et al. 1993).

Selected References Shallow and Wagner 1947; Simpson et al. 1955; Steiner 1960; Ojima et al. 1964; Snapper et al. 1964; Totzke and Hutcheson 1965; Balouet and Destombes 1967; Cavallo et al. 1968; Smith and Rele 1972; Walter et al. 1972; Chudacek 1973; Alrenga 1975; Papazian et al. 1978; Bodker and Boiesen 1981; Gen et al. 1983; Kameya et al. 1985; Bremondy et al. 1989; Nakahama et al. 1989; Ito et al. 1990; Kotani et al. 1993; Tameda and Shiraki 1995; Kelle et al. 2005; Ali et al. 2008; Zhao et al. 2008.

Pathology

Macroscopy

At gross examination, the mostly solitary tumors may grow to a size exceeding 15 cm diameter (Bramwell and Leith 1897; Dubs 1916; Jaffe 1924; Alrenga 1975; Nakahama et al. 1989). The size of the large or very large hepatic sarcomas was not always specified; sometimes only descriptions such as "enormous primary sarcoma" are found in the reports (Bramwell and Leith 1897). Saltykov (1914) reported on a 62-year-old male with liver cirrhosis, where necropsy revealed two primary liver tumors: the larger tumor, measuring 20 by 16 by 9 cm, was a hepatic spindle cell sarcoma, while the smaller tumor (3 cm) was hepatocellular carcinoma. A similar situation was reported by Jaffe (1924), who described a double synchronous liver tumor observed in a 64-year-old man who had liver cirrhosis. One tumor was located in the right lobe, measured 17 by 12 by 14 cm, and was spindle cell sarcoma; the other tumor was much smaller, was located to the left lobe, and was hepatocellular carcinoma. Dubs (1916) reported on a spindle cell sarcoma measuring 30 by 30 by 25 cm diagnosed in a 26-year-old female. Exceptionally, the tumors involve both liver lobes and

form conglomerates of firm nodules (Ali et al. 2008). The tumor appearance varies from firm and gray to white masses to myxoid lesions and those with hemorrhagic necroses, sometimes with marked central softening (Ito et al. 1990). The tumors are grossly well-delineated from the surrounding liver substance and usually form more or less spherical masses with or without satellite nodules. Lobulated morphologies are also known (sometimes termed "sarcoma phyllodes" in the older literature, in analogy to the respective breast tumor; Thöhle 1913). Macroscopic invasion of the portal vein has been noted (Alrenga 1975).

Histopathology

Histologically, the neoplasms are composed of interlacing bundles of fibroblastoid spindle cells. The nuclei are elongated, with pointed ends, and show minor pleomorphism and hyperchromasia. Mitotic figures are found, albeit usually in rather low numbers. A moderate amount of stainable collagen is seen between the neoplastic cells.

Immunohistochemistry

As in other locations, hepatic fibrosarcoma is markedly vimentin positive (Nakahama et al. 1989; Ito et al. 1990; Kelle et al. 2005). A subset of the tumor cells may be reactive for alpha-SMA. By use of podoplanin immunostaining, fibrosarcomas lack typical lymph vessels, a finding which is consistent with the infrequent occurrence of sarcoma metastasis to lymph nodes (Mahendra et al. 2008).

Differential Diagnosis

The main differential diagnosis is fibrosarcoma metastatic to the liver (Franseen and McCort 1948; Hall and Amin 1981; Yamaguchi et al. 1989; Isobe et al. 1997). Tumor-induced hypoglycemia was also detected in metastatic fibrosarcoma of the liver (Bousvaros 1960).

Sclerosing Epithelioid Fibrosarcoma

Introduction

Sclerosing epithelioid fibrosarcoma (SEF) is a variant of fibrosarcoma that had been first described in 1995 (Meis-Kindblom et al. 1995). This rare tumor is characterized by epithelioid neoplastic cells arranged in cords, sheets, strands, or nests embedded within a sclerotic collagenous matrix, whereby a picture resembling carcinoma may result.

There is some histologic overlap between SEF and low-grade fibromyxoid sarcoma/LGFMS. SEF is a low-grade sarcoma, but about 50 % of patients are estimated to develop local recurrence and/or metastases (review: Ossendorf et al. 2008). SEF involves the soft tissues of upper and lower extremities, limb girdles, head and neck area and trunk (mainly the chest), and rarely deep-seated organs and structures. Part of SEF cases have shown rearrangement of the FUS locus by FISH (Rekhi et al 2011; Wang et al. 2012). FUS rearrangements are typical for low-grade fibromyxoid sarcoma (Patel et al. 2011), further discussed in the respective chapter. MUC4, which was identified as a sensitive and specific marker for LGFMS, was also expressed in 78 % of cases of SEF, and FUS rearrangement was detected in 38 % of MUC4-positive SEF cases, showing that MUC4 reactivity is more common in SEF than FUS rearrangement. MUC4-positive SEFs with FUS rearrangement are likely closely related to LGFMS (Doyle et al. 2012).

Primary Sclerosing Epithelioid Fibrosarcoma of the Liver

SEF primary to the liver was observed in a 39-year-old male patient presenting with general fatigue and abdominal discomfort (Tomimaru

et al. 2009). CT and MRI revealed a large liver tumor measuring about 7 cm in diameter located in segment 1. Invasion of the inferior vena cava was noted, and extended left hepatectomy with resection of caudate lobe, diaphragm, right lower lung lobe, and pericardium was performed. In the resection specimen, the tumor measured up 68 mm in diameter and presented as a lobulated neoplasm that had also caused a tumor thrombus in the left portal vein. Histologically, the tumor showed round or polygonal, vimentin- and CD99-positive, cytokeratin-negative cells with a morphology typical for SEF. The cells were negative for EMA, desmin, alpha-SMA, and HMB45, and t (X;18), often found in synovial sarcoma, was not observed. The neoplastic ells were embedded in an abundant collagenous and partially hyalinized matrix (a sclerosing tumor). Peripheral part of the neoplasm showed spindle cells in a fascicular arrangement. The mitotic rate was low.

Congenital and Infantile Fibrosarcoma

Introduction

Congenital or infantile fibrosarcoma (CFS) was identified as a distinct entity by Stout in 1962 (Stout 1962). The majority of CSF affects patients younger than 5 years, and about 90 % are diagnosed in infants. The congenital variant proper is defined as a fibrosarcoma occurring within 3 months after birth (Kempson et al. 2001). CSF has a much less aggressive behavior than fibrosarcoma in adults, and it rarely metastasizes (Soule and Pritchard 1977; Coffin et al. 1994). The tumors mostly occur in several soft tissue compartments, but may rarely develop in visceral organs, e.g., the colon (Buccoliero et al. 2008).

Liver Involvement

Metastasis of a paraspinal CFS to the liver was observed in a fetus of 26 weeks of gestation (Nonaka and Sun 2004). At necropsy, the liver was congested and exhibited multiple, well-circumscribed, small, tan metastatic tumor nodules of up to 4 mm diameter, histologically showing the same fascicular pattern with herringbone appearance and marked mitotic activity as the primary tumor. At the periphery of the nodules, the tumor tissue interdigitated with liver parenchyma. The cellular variant of congenital mesoblastic nephroma, having the same chromosomal translocation as CFS, has also been found to rarely metastasize to the liver (Patel et al. 2003).

Etiology and Pathogenesis

The cell of origin of CFS is not known so far (Coffin et al. 1994). It is assumed to be a primitive mesenchymal cell which may give rise to several differentiation lineages, including vascular cells. CFS can come as a hemangiopericytomatous hypervascular tumor which, with time, may regress to hemangiomatous remnant (Miura et al. 2002). It has been shown that CFS has a characteristic cytogenetic alteration, i.e., t(12;15)(p13;q25), causing the fusion ETV6-NTRK3 (ETS variant gene 6 in band 12p13; neurotrophic tyrosine kinase receptor type 3 in band 15p15; Knezevich et al. 1998; Wai et al. 2000), detectable by PCR (Argani et al. 2000; Sheng et al. 2001) and fluorescence in situ hybridization (Adem et al. 2001) and identical to that found in the cellular variant of congenital mesoblastic nephroma (Sandberg and Bridge 2002). The same chromosomal translocation has been detected in secretory breast carcinoma (Lambros et al. 2009). A different translocation may also occur in bland-looking variants of CFS, i.e., 3-way t(12;15;19) translocations involving chromosome bands 12p13.2, 15q25.3, and 19p13.1, associated with trisomies 8, 11, and 20 (Mariño-Enriquez et al. 2008).

The ETS (E-twenty-six) family member ETV6/TEL is a phosphoprotein and transcriptional repressor active in the nucleus that can inhibit Ras-dependent cell growth and induce cellular aggregation of Ras-transformed cells. ETV6/TEL is, however, also actively exported from the nucleus. This exit from the nucleus is accomplished by posttranslational modification by sumoylation at lysin 99 in a highly conserved

ETV6 domain, a regulating mechanism assumed to play a role in cellular growth control (Wood et al. 2003). ETV6/TEL possesses several putative mitogen-activated protein (MAP) kinase phosphorylation sites; it becomes phosphorylated by p38 activated by cellular stress, but not by JNK1 (Arai et al. 2002; Hanson et al. 2008). Neurotrophins and their receptors have a central role in development, growth, and differentiation (Bernd 2008). The ETV6-NTRK3 fusion gene encodes the sterile alpha motif oligomerization domain of the ETV6 (TEL) transcription factor linked to the protein tyrosine kinase domain of the neurotrophin receptor 3. The resulting chimeric oncoprotein links to multiple signaling cascades including Ras-MAP kinase and PI3K-AKT through the insulin-like growth factor 1 receptor (IRS-I) adaptor protein and seems to act on several cell lineages (Lannon and Sorensen 2005). ETV6 is a fusion partner of more than 20 partner and is involved in leukemogenesis (Bohlander 2005).

Infantile Hepatic Myofibromatosis

Introduction

Infantile myofibromatosis (IM) is a rare mesenchymal tumor involving musculoskeletal, subcutaneous, and visceral fibrous tissues (Stout 1954; Chung and Enzinger 1981; Roggli et al. 1980; Wiswell et al. 1988; Jones et al. 2007; literature review: Ang et al. 2004; historic perspective: Matthews and Cockerell 2006; recent review of literature: Hausbrandt et al. 2010). This type of tumor was previously diagnosed as hamartomas, mesenchymal hamartomatosis, multiple vascular leiomyomas of the newborn, or hemangiopericytomas. Stout first described this entity (Stout 1954). Based on a review of 61 pathologic specimens, the term, IM, was then coined in 1981 (Chung and Enzinger 1981), as the cells involved have features of both differentiated fibroblasts and smooth muscle cells or myofibroblasts. IM represents the most common type of fibrous tumor in infancy, may be congenital or familial, and is sometimes associated with congenital anomalies (Inamadar et al. 2005). IM is more common in girls, is manifest at birth or in early infancy, and almost 90 % of the cases present by age two (Coffin and Dehner 1991), but few cases in older children have been reported (Franzese and Carron 2005). Multicentric IM may cause fetal death (Pelluard-Nehmé et al. 2007).

IM occurs in several variants, solitary myofibromatosis and congenital multicentric (multiple) myofibromatosis, the latter with or without involvement of visceral organs (Chung and Enzinger 1981; Coffin et al. 1995). Fewer than 25 % of all patients with IM have visceral involvement, including the intestine, colon, the spleen, and the lungs, but for those patients the mortality may be elevated (Wiswell et al. 1988; Jones et al. 2007; Dhall et al. 2008; Muraoka et al. 2008; Short et al. 2008). Solitary and multiple variants and apparently also generalized lesions may show the phenomenon of spontaneous regression or self-healing (self-healing IM), in that after the proliferative phase during the first months of life, spontaneous regression of the nodules occurs (Schaffzin et al. 1972; Chung and Enzinger 1981 Zeller et al. 1997; Hatzidaki et al. 2001; Martin et al. 2008), probably via apoptosis (Fukasawa et al. 1994). Although in principle non-malignant, the generalized lesion is unique in presentation by its pressure effects on different visceral organs and thus carries a high mortality rate (approaching 75 %, Wiswell et al. 1988). Furthermore, IM may involve blood vessels and be associated with generalized fibromuscular dysplasia of arteries, lesions that may add to poor outcome (Wright et al. 2004). Systemic complications usually arise during the proliferative phase of the disease. Apart from sporadic cases, hereditary IM is now well recognized (OMIM 228550). In some families, an autosomal dominant trait has been identified (Jennings et al. 1984; Ikediobi et al. 2003; Zand et al. 2004), while other families revealed autosomal recessive inheritance (Salamah et al. 1988; Narchi 2001). The gene(s) and gene product (s) involved have not been identified. IM has rarely been observed in patients with constitutional mismatch-repair deficiency (CMMR-D) syndrome (Lynch syndrome), caused by germline mutations in the mismatch-repair genes MLH1,

MSH2, MSH6, or PMS2 (Kruger et al. 2008; Wimmer and Etzler 2008).

Both vimentin-positive tumor cells and endothelial cells express connective tissue growth factor (CTGF) in IM (Kasaragod et al. 2001). The ETV6-NTRK3 gene fusion recognized in congenital fibrosarcoma has not been detectable in IM (Bourgeois et al. 2000), although there is histologic overlap between the two lesion types (Alaggio et al. 2008). In contrast to deep fibromatoses, nuclear beta-catenin expression has not been observed in IM (Bhattacharya et al. 2005; Thway et al. 2008).

Hepatobiliary Involvement

Involvement of the liver occurs almost exclusively in the generalized variant of IM and has been documented several times, sometimes with multiple liver lesions (Coffin et al. 1995; Leaute-Labreze et al. 2001; Day et al. 2002; Spadola et al. 2002; Gandhi et al. 2003). In an autopsy case of an infant with congenital generalized IM, nodules around the common bile duct were observed in addition to hepatic nodules (Coffin et al. 1995). Solitary hepatic IM has been described only twice (Hastier et al. 1998). The first case reported involved an 11-year-old girl with obstructive jaundice and dilated intrahepatic bile ducts. Exploratory laparotomy revealed the presence of a fibrous mass histologically compatible with IM behind the hilum, extending into the right and left liver lobes (Bosc et al. 1987). In a second case, a solitary hepatic myofibromatosis was diagnosed in a 16-year-old girl presenting with cholestatic jaundice. The tumor was localized at the hilum and measured 3–4 cm in diameter. The potential local invasiveness of the neoplasm was evidenced by the destruction of the bile ducts (Hastier et al. 1998). In a neonate with congenital generalized IM with marked visceral involvement (albeit not in the liver), the process was associated with neonatal hemochromatosis (Aksoy et al. 2000). Solitary IM (termed infantile myofibroma by the authors) was detected as a large mass contiguous with the liver in a female infant of 37-week gestational age (Schurr and Moulsdale 2008).

Pathology

Macroscopy

The hepatic manifestations either occur in the form of multiple small nodules reminiscent of metastatic disease, or present as rather large and circumscribed nodes with a pushing border and a low-density mass in CT (Sty et al. 1996). Macroscopically, IM lesions are described as spherical, non-mobile, firm, rubbery, flesh to purple-colored nodules. In a fetus with multicentric IM, manifestations have been found at the hepatic portal (Pelluard-Nehmé et al. 2007).

Histopathology

Histology is characterized by whorled nodules of eosinophilic, biphasic, and plump spindle cells embedded in a more or less collagenous ECM. The lesion generally has a zonal architectural pattern with more immature-looking cells in the center of the lesions and spindle cells with a more myoid appearance at the periphery of the nodules, but a monophasic cellular variant has also been recognized (Zelger et al. 1995). In regard to cells involved, there is a broad spectrum of morphologies ranging from immature-looking spindle cells via myofibroblast-like cells to a hemangiopericytoma-like vascular pattern, suggesting that IM and so-called infantile hemangiopericytomas represent different stages of maturation of the same entity (Mentzel et al. 1994). The complex pattern of the lesions is already in evidence at low magnification, with areas showing the characteristic staghorn pattern of vascular channels typical for the hemangiopericytoma-like component, and other areas exhibiting fascicles of elongated spindle cells, with an overall moderate to high cellularity.

Focal necrosis is commonly seen. Immunohistochemically, reactivity for alpha-SMA chiefly involves the spindled myofibroblasts, while the cells situated between the dilated vascular channels in the hemangiopericytoma-like parts are usually not SMA-positive, rendering the origin of this cell type difficult. However, the vascular channels in these parts show a thin rim of SMA-positive cells between the endothelium and the perivascular neoplastic cells. There is no reactivity for desmin, but this stain may help to identify invasion of adjacent muscular tissue structures. In the CD34 immunostain, the neoplastic cells are negative, but the dense vascular network is visualized. Interestingly the vascular lining of the pericytoma-like areas stains much less for CD34 than the vessels in the myofibroblastic parts. In the Ki-67 stain, the marked proliferative activity is obvious. In regressing lesions, fatty change of spindle cells has been found (Iijima et al. 1999). Further characteristic features comprise necrosis and mineralizations/calcifications, chiefly in central parts of the lesions. A typical cellular component is a myofibroblast-like cell reactive for vimentin and alpha-SMA, but negative for desmin (Fisher 1996). In one report, congenital generalized IM (not involving the liver) was associated with neonatal hemochromatosis (Aksoy et al. 2000).

Hepatic Desmoid Tumor

Intrahepatic Desmoid Tumor in Association with Familial Adenomatous Polyposis

Desmoid tumors (desmoids; aggressive fibromatosis) are fibrous proliferations that occur sporadically or in association with familial adenomatous polyposis (FAP) and Gardner syndrome (see below; Kotiligam et al. 2008). Patients with FAP have a thousand-fold risk of developing a desmoid tumor, usually in an intra-abdominal location (Gurbuz et al. 1994). Desmoids may behave aggressively, but do not metastasize. One case of hepatic manifestation has been described in a patient with familial adenomatous polyposis (Middleton et al. 2000): a 14-year-old female patient with a strong family history of desmoid disease in the context of FAP. During abdominal surgery, she was found to have at least four intra-abdominal desmoids, one of which was contained entirely in the substance of the liver. The tumor in the liver presented, in CT, as a roundish well-delineated mass of more than 10 cm size, and a core biopsy confirmed desmoid tumor (Middleton et al. 2000).

"Angiofibroma" of the Liver

Very few cases of so-called angiofibroma have been observed in the liver (Gmunder and Schmid 1972) or hepatic ligaments (Spay et al. 1973). In one of these mesenchymal lesions interpreted to be an angiofibroma, hypoglycemia was noted (Gmunder and Schmid 1972). It is likely that these rare lesions would be classified in a different manner today. Part of the tumors may have been solitary fibrous tumors. The lesion should not be confounded with cellular angiofibroma (angiomyofibroblastoma-like tumor), a neoplasm originally described to almost exclusively occur in the vulva, perineum, and pelvis of women (review: Iwasa and Fletcher 2004; Koo et al. 2009; Tardio 2009).

Myxoid Mesenchymal Tumors of the Liver (Myxoma, Myxosarcoma, Myxofibrosarcoma, Fibromyxoid Sarcoma, and Other Myxoid Mesenchymal Neoplasms)

Myxoma and Myxosarcoma

Myxomas and myxosarcomas (the latter probably an obsolete term) are not single entities, but rather form a heterogeneous group of complex lesions that, at least in part, await precise definitions. Myxoid neoplasms or lesions are classified as

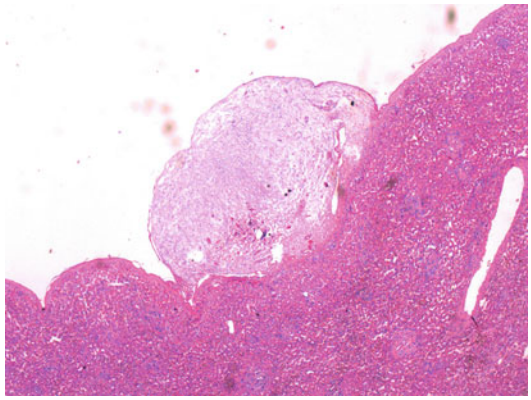

Fig. 2 Capsular myxofibroma of the liver (hematoxylin and eosin stain)

myxomas of soft tissues, myxomas located outside soft tissues, inadequately substantiated myxomas, myxoid soft tissue tumors not regarded as true myxomas, myxoid fatty conditions, other soft tissue lesions and neoplasms that are markedly myxoid, other soft tissue tumors having myxoid components, and non-neoplastic myxoid mesenchymal lesions (review: Allen 2000). Distinct and more common types of soft tissue myxomas consist of intramuscular myxoma, juxta-articular myxoma, superficial angiomyxoma (cutaneous myxoma), aggressive (deep) angiomyxoma, and myxoid neurothekeoma/myxoma of nerve sheaths. The WHO classification includes distinct categories of malignant soft tissue tumors with a myxoid component, such as myxoinflammatory fibroblastic sarcoma (ICD-O 8811/3), myxofibrosarcoma (ICD-O 8811/3), low-grade fibromyxoid sarcoma (ICD-O 8811/3), and malignant ossifying fibromyxoid tumor (ICD-O 8842/3). Well-recognized visceral myxomas include sino-orbital myxoma, renal myxoma, and myxoma of the small intestine. Few fibroblastoid neoplastic lesions occurring in the liver contain a marked myxoid component (Fig. 2).

Apparently, "true" myxoma has not been observed in the liver or biliary tract. Very few cases of so-called myxosarcoma primary to the liver have been reported. One case has been observed in childhood (Sarra and Bertolini 1968).

Involvement of the Liver in Cardiac Myxoma

Cardiac myxoma is the most common primary cardiac tumor, constituting about 50 % of all benign heart tumors in adults. Three-fourths of these lesions are located to the left atrium. Although benign lesions, cardiac myxomas can cause sudden death owing to coronary or systemic tumor embolism or to obstruction of blood flow at the mitral or tricuspid valve. Right atria myxoma can cause chronic congestion associated with dysfunction of the liver (Kluge et al. 1971), or hepatomegaly, jaundice and liver failure (Campisi et al. 1981). Myxoma of the right atrium can block the atrioventricular ostium or prolapse into the inferior vena cava, eventually followed by Budd-Chiari syndrome (Cujec et al. 1987; Anagnostopoulos et al. 2004). Right atrial myxoma can also induce portal and splenic vein thrombosis (Onan et al. 2011). Giant right atrial myxoma may radiologically mimic hepatic cirrhosis (Tok et al. 2007). Left atrial myxoma can embolize to the arterial tree, cerebral emboli being a severe and sometimes lethal complication. Embolization of myxoma was also found in the hepatic artery tree (Matsuoka et al. 1992). Embolization to the liver might cause metastatic disease. In one patient, two highly echogenic liver masses were detected 2 years after cardiac myxoma resection, suggestive of hepatic metastasis (Silaruks et al. 1999).

Differential Diagnosis

The differential diagnosis comprises few other hepatic mesenchymal tumors that have a myxoid tissue component, including primary hepatic myxoid leiomyosarcoma (Tsiatis et al. 2008), primary myxoid leiomyoma (Choi et al. 2014), and primary myxoid liposarcoma (Binesh et al. 2012). Right atrial metastasis of hepatocellular carcinoma can mimic atrial myxoma (Chua et al. 1986; Anwar et al. 2010).

Tumors with a Hepatic Stellate Cell Lineage (Spongiotic Pericytoma and Other Putative Hepatic Perisinusoidal Stellate Cell Tumors)

Introduction

Hepatic stellate cells (HSC; Ito cells) form an important perisinusoidal cell system in the liver. Activated HSCs differentiate into smooth muscle actin-positive myofibroblasts and play a central role in hepatic remodeling and fibrogenesis. The cell of origin of HSCs is not yet known. Although hepatic stellate cells (HSCs) have originally been described within the pericyte concept (Zimmermann 1923), their lineage appears to be more complex, with a purported derivation from the neural crest. It has also been suggested that HSCs are derived from mesothelial cells via mesothelial-mesenchymal transition in liver injury (Li et al. 2013). Notwithstanding the fact, that the liver contains a significant fraction of HSC, these cells do not seem to give rise to neoplastic lesions frequently.

Pure Hepatic Stellate Cell Tumors of the Liver (Spongiotic Pericytoma)

An interesting hepatic tumor apparently derived from hepatic stellate (perisinusoidal) cells and termed spongiotic pericytoma has been observed in the liver of N-nitrosomorpholine-treated rats (Stroebel et al. 1995). Ten years later, a similar lesion has been reported in a human. A 35-year-old woman showed a polycyclic liver tumor containing multiple nodular cell aggregates. The tumor cells were fusiform, with extensive cytoplasmic processes, a prominent Golgi apparatus, and fat droplets. Immunohistochemically, the cells were reactive for vimentin, CD34, CD105, CD99, CD56, and smooth muscle actin. This phenotype was interpreted as a neoplasm of hepatic stellate cells, i.e., a spongiotic pericytoma (Kaiserling and Müller 2005).

Hepatic Tumors Thought to Contain Hepatic Stellate Cells (HSCs) or HSC-Like Cells

Based on the expression of CD56, alpha-SMA and adipophilin in neoplastic cells of an undifferentiated embryonal sarcoma (UES) of the liver, it was suggested that UES may perhaps derive from HSCs or differentiating HSCs (Tanaka et al. 2012). HSCs or HSC-like cells have also been detected in cases of mesenchymal hamartoma of the liver (von Schweinitz et al. 1999). In one tumor, there were spindle cells positive for vimentin, alpha-smooth muscle actin, tenascin, alpha-crystallin, and desmin, a phenotype suggesting activated HSC (Shintaku and Watanabe 2010).

References

Adem C, Gisselsson D, Dal Cin P, Nascimento AG (2001) ETV6 rearrangements in patients with infantile fibrosarcomas and congenital mesoblastic nephromas by fluorescence in situ hybridization. Mod Pathol 14:1246–1251

Aksoy F, Göksel S, Ilvan S, Dervisoglu S, Ramazanoglu R (2000) Congenital generalized infantile myofibromatosis and neonatal hemochromatosis. An autopsy case report. Turk J Pediatr 42:334–337

Alaggio R, Barisani D, Ninfo V, Rosolen A, Coffin CM (2008) Morphologic overlap between infantile myofibromatosis and infantile fibrosarcoma: a pitfall in diagnosis. Pediatr Dev Pathol 11:355–362

Albers JFH (1862) Atlas der pathologischen Anatomie für praktische Aerzte, vol 4. Henry and Cohen, Bonn, p 490

Ali S, Shah P, Shah UJ, Shah A, Zargar S, Bashir A, Dhar S, Ali M (2008) Primary fibrosarcoma of the liver: we don't know much: a case report. Case Rep Gastroenterol 2:384–389

Allen PW (2000) Myxoma is not a single entity: a review of the concept of myxoma. Ann Diagn Pathol 4:99–123

Alrenga DP (1975) Primary fibrosarcoma of the liver. Case report and review of the literature. Cancer 36:446–449

Anagnostopoulos GK, Margantinis G, Kostopoulos P, Papadopoulou G, Roulias A, Sakorafas G et al (2004) Budd-Chiari syndrome and portal vein thrombosis due to right atrial myxoma. Ann Thorac Surg 78:333–334

Ang P, Tay YK, Walford NQ (2004) Infantile myofibromatosis: a case report and review of the literature. Cutis 73:229–231

Anwar AM, Nosir YF, Chamsi-Pasha MA, Ajam A, Chamsi-Pasha H (2010) Right atrial metastasis mimicking myxoma in advanced hepatocellular carcinoma. Echocardiography 27:80–83

Arai H, Maki K, Waga K, Sasaki K, Nakamura Y, Imai Y, Kurokawa M, Hirai H, Mitani K (2002) Functional regulation of TEL by p38-induced phosphorylation. Biochem Biophys Res Commun 299:116–125

Argani P, Fritsch M, Kadkol SS, Schuster A, Beckwith JB, Perlman EJ (2000) Detection of the ETV6-NTRK3 chimeric RNA of infantile fibrosarcoma/cellular congenital mesoblastic nephroma in paraffin-embedded tissue: application to challenging pediatric renal stromal tumors. Mod Pathol 13:29–36

Balouet G, Destombes P (1967) Apropos of several apparently primary mesenchymal tumors – trial classification and diagnosis of spindle cell tumors of the liver. Ann Anat Pathol (Paris) 12:273–286

Bernd P (2008) The role of neurotrophins during early development. Gene Expr 14:241–250

Bertelli (1908) Contribuzione allo studio dei sarcomi primitivi del fegato. Policlinico 15:20–21

Bhattacharya B, Dilworth HP, Iacobuzio-Donahue C, Ricci F, Weber K, Furlong MA et al (2005) Nuclear beta-catenin expression distinguishes deep fibromatosis from other benign and malignant fibroblastic and myofibroblastic lesions. Am J Surg Pathol 29:653–659

Binesh F, Akhavan A, Kargar S, Navabil H (2012) Primary liposarcoma of liver: a rare case and literature review. BMJ Case Rep. doi:10.1136/bcr-01-2012-5711

Bodker A, Boiesen PT (1981) A primary fibrosarcoma of the liver. Hepatogestroenterology 28:218–220

Bohlander SK (2005) ETV6: a versatile player in leukemogenesis. Semin Cancer Biol 15:162–174

Bosc O, Galifer RB, Barnon G, Marchal J, Margueritte G (1987) Fibromatose infantile à forme intra-abdominale isolée. A propos de 2 cas. Chir Pediatr 28:182–184

Bourgeois JM, Knezevich SR, Mathers JA, Sorensen PH (2000) Molecular detection of the ETV6-NTRK3 gene fusion differentiates congenital fibrosarcoma from other childhood spindle cell tumors. Am J Surg Pathol 24:937–946

Bousvaros GA (1960) Hypoglycemia in metastatic fibrosarcoma of the liver. Br Med J 1:836–838

Bramwell and Leith (1897) A case of enormous primitive sarcoma of the liver. Lancet 1:170

Bremondy A, Faulques B, Grimaud JC, Thervet L, Michotev G, Salducci J (1989) A case of primary hepatic fibrosarcoma (in French). Ann Chir 43:846

Buccoliero AM, Castiglione F, Degl'Innocenti DR, Maio V, Taddei A, Sardi I, Noccioli B et al (2008) Congenital/infantile fibrosarcoma of the colon: morphologic, immunohistochemical, molecular, and ultrastructural features of a relatively rare tumor in an extraordinary localization. J Pediatr Hematol Oncol 30:723–727

Campisi DJ, McElry CR, Criley JM, Gilkey F (1981) Jaundice, hepatosplenomegaly and liver failure in a 60-year-old woman. UCLA School of medicine (Clinicopathologic Conference). West J Med 134:27–33

Cavallo T, Lichewitz B, Rozov T (1968) Primary fibrosarcoma of the liver. Report of a case. Rev Hosp Clin Fac Sao Paulo 23:44–49

Cesaris-Demel (1900) Sul sarcoma primitivo del fegato. Arch Sci Med 24:273–278

Chiari H (1877) Ueber ein Fibrom der Leber. Wien. Med. Wochenschr. 365

Choi HS, Jung CW, Cho SY, Kim SB, Park S (2014) Primary myxoid leiomyoma of the liver. Kor J Pathol 48:54–57

Chu PT (1950) Benign neoplasms of the extrahepatic biliary ducts: review of the literature and report of a case of fibroma. Arch Pathol 50:84–97

Chua SO, Chiang CW, Lee YS, Lin SH, Liaw F (1986) Moving right atrial mass associated with hepatoma. Two cases detected by echocardiography. Chest 89:148–150

Chudacek Z (1973) Combination of primary fibroblastic liver sarcoma and gallbladder carcinoma (in German). Fortschr Geb Rontgenstr Nuklearmed 118:344–345

Chung EB, Enzinger FM (1981) Infantile myofibromatosis. Cancer 48:1807–1818

Coffin CM, Dehner LP (1991) Fibroblastic-myofibroblastic tumors in children and adolescents: a clinicopathologic study of 108 examples in 103 patients. Pediatr Pathol 11:569–588

Coffin CM, Jaszcz W, O'Shea PA, Dehner LP (1994) So-called congenital-infantile fibrosarcoma: does it exist and what is it? Pediatr Pathol 14:133–150

Coffin CM, Neilson KA, Ingels S, Frank-Gerszberg R, Dehner LP (1995) Congenital generalized myofibromatosis: a disseminated angiocentric myofibromatosis. Pediatr Pathol Lab Med 15:571–587

Costantini (1909) Sui sarcomi primitivi del fegato. Bull Sci Med Bologna 9:8–11

Craig JR (1994) Mesenchymal tumors of the liver. Diagnostic problems for the surgical pathologist. Pathology (Phila) 3:141–160

Craig JR, Peters RL, Edmondson HA (1989) Tumors of the liver and intrahepatic bile ducts, Atlas of tumor pathology, second series, fascicle 26. Armed Forces Institute of Pathology, Washington, DC, pp 92–94

Cujec B, Ulmer B, McKaigney JP, Bharadwaj B (1987) Right atrial myxoma presenting as Budd-Chiari syndrome. Ann Thorac Surg 44:658–659

Day M, Edwards AO, Weinberg A, Leavey PJ (2002) Successful therapy of a patient with infantile generalized myofibromatosis. Med Pediatr Oncol 38:371–373

Dhall D, Frykman PK, Wang HL (2008) Colorectal infantile myofibromatosis: an unusual cause of rectal prolapse and sigmoid colo-colonic intussusception: a case report. Case J 1:397

Dominici H, Merle P (1909) Composite tumor of liver – carcinoma and sarcoma following cirrhosis. Arch Med Exp Anat Pathol 21:136–153

Doyle LA, Wang WL, Dal Cin P, Lopez-Terrada D, Mertens F, Lazar AJ, Fletcher CD, Hornick JL (2012) MUC4 is a sensitive and extremely useful marker for sclerosing epithelioid fibrosarcoma: association with FUS gene rearrangement. Am J Surg Pathol 36:1444–1451

Dubs (1916) Ueber ein angebliche nach Trauma entstandenes primäres Sarkom der Leber. Dtsch Zeitschr Chirurg 138:1–6

Fisher C (1996) Fibromatosis and fibrosarcoma in infancy and childhood. Eur J Cancer 32:2094–2100

Franseen CC, McCort JJ (1948) Metastatic fibrosarcoma of liver and lungs. N Engl J Med 239:787–790

Franzese CB, Carron J (2005) Infantile myofibromatosis: unusual diagnosis in an older child. Int J Pediatr Otorhinolaryngol 69:865–868

Fukasawa Y, Ishikura H, Takada A, Yokoyama S, Imamura M, Yoshiki T, Sato H (1994) Massive apoptosis in infantile myofibromatosis. A putative mechanism of tumor regression. Am J Pathol 144:480–485

Fukuda I, Hizuka N, Ishikawa Y, Yasumoto K, Murakami Y, Sata A, Morita J, Kurimoto M et al (2006) Clinical features of insulin-like growth factor II producing non-islet-cell tumor hypoglycemia. Growth Horm IGF Res 16:211–216

Gandhi MM, Nathan PC, Weitzman S, Levitt GA (2003) Successful treatment of life-threatening generalized infantile myofibromatosis using low-dose chemotherapy. J Pediatr Hematol Oncol 25:750–754

Gen E, Kusuyama Y, Saito K, Nagasaki Y, Nakatani T, Yataka I, Oku A (1983) Primary fibrosarcoma of the liver with hypoglycemia. Acta Pathol Jpn 33:177–182

Gmunder U, Schmid M (1972) A benign mesenchymal tumor (angiofibroma) of the liver with hypoglycemia (in German). Acta Hepatogastroenterol (Stuttg) 19:425–430

Goldstein (1921) Primary sarcoma of the liver with the report of a case. Int Clin 2:73

Gurbuz AK, Giardiello FM, Petersen GM, Krush AJ, Offerhaus GJA, Booker SV et al (1994) Desmoid tumours in familial adenomatous polyposis. Gut 35:377–381

Hall JS, Amin UF (1981) Fibrosarcoma of the vulva: case reports and discussion. Int Surg 66:185–187

Hanson CA, Wood LD, Hiebert SW (2008) Cellular stress triggers TEL nuclear export via two genetically separable pathways. J Cell Biochem 104:488–498

Hastier P, Caroli-Bose FX, Harris AG, Sanit-Paul MC, Zaroukian ST, Arpurt JP et al (1998) Solitary hepatic infantile myofibromatosis in a female adolescent. Dig Dis Sci 43:1124–1128

Hatzidaki E, Korakaki E, Voloudaki A, Daskaloyannaki M, Manoura A, Giannakopoulou C (2001) Infantile myofibromatosis with visceral involvement and complete spontaneous regression. J Dermatol 28:379–382

Hausbrandt PA, Leithner A, Beham A, Bodo K, Raith J, Windhager R (2010) A rare case of infantile myofibromatosis and review of the literature. J Pediatr Orthop B 19:122–126

Herxheimer G (1930) Das sarkom. In: Henke F, Lubarsch O (eds) Leber. Handbuch der speziellen pathologischen anatomic und Histologie. Julius Springer Verlag, Berlin, pp 902–921

Holzinger J (1901) Dissertation, Munich, cited by Konjetzny GE (1910) Ergeb Allgem Path Path Anat 14, 714

Iijima S, Suzuki R, Otsuka F (1999) Solitary form of infantile myofibromatosis: a histologic, immunohistochemical, and electronmicroscopic study of a regressing tumor over a 20-month period. Am J Dermatopathol 21:375–380

Ikediobi NI, Iyengar V, Hwang L, Collins WE, Metry DW (2003) Infantile myofibromatosis: support for autosomal dominant inheritance. J Am Acad Dermatol 49(2 suppl case reports):S148–S150

Inamadar AC, Palit A, Athanikar SB, Sampagavi VV, Deshmukh NS (2005) Infantile myofibromatosis with multiple congenital anomalies. Pediatr Dermatol 22:281–282

Ishak KG (1976) Mesenchymal tumors of the liver. In: Okuda K, Peters R (eds) Hepatocellular carcinoma. Wiley, New York, pp 260–262

Isobe H, Wada Y, Ryo J, Mtasushita T, Makino T, Satoh B, Kanaya S, Katayama T et al (1997) An effective chemotherapy regimen for liver metastasis from retroperitoneal fibrosarcoma: report of a case. Surg Today 27:463–465

Ito Y, Uesaka Y, Takeshita S, Fujino H, Uta Y, Yasuda H, Oshima M, Kawabe T, Tagawa K et al (1990) A case report of primary fibrosarcoma of the liver. Gastroenterol Jpn 25:753–757

Iwasa Y, Fletcher CD (2004) Cellular angiofibroma: clinicopathologic and immunohistochemical analysis of 51 cases. Am J Surg Pathol 28:1426–1435

Jaffe RH (1924) Sarcoma and carcinoma of the liver following cirrhosis. Arch Intern Med 33:330–342

Jennings TA, Duray PH, Collins FS, Sabetta J, Enzinger FM (1984) Infantile myofibromatosis: evidence for an autosomal-dominant disorder. Am J Surg Pathol 8:529–538

Jones VS, Philip C, Harilal KR (2007) Infantile visceral myofibromatosis – a rare cause of neonatal intestinal obstruction. J Pediatr Surg 42:732–734

Kaiserling E, Müller H (2005) Neoplasm of hepatic stellate cells (spongiotic pericytoma): a new tumor entity in human liver. Pathol Res Pract 201:733–743

Kameya S, Sato R, Tamada M, Watanabe T, Ikuta K (1985) A case of liver fibrosarcoma associated with hypoglycemia (in Japanese). Nippon Shokakibyo Gakkai Zasshi 82:513–517

Kasaragod AB, Lucia MS, Cabirac G, Grotendorst GR, Stenmark KR (2001) Connective tissue growth factor expression in pediatric myofibroblastic tumors. Pediatr Dev Pathol 4:37–45

Kelle S, Paetsch I, Neuss M, Gebker R, Niesporek S, Meyer R, Fleck E, Nagel E (2005) Primary fibrosarcoma of the liver infiltrating the right atrium of the heart. Int J Cardiovasc Imaging 21:655–658

Kempson RL, Fletcher CD, Evans HL et al (2001) Atlas of tumor pathology, vol 3, Fascicle 30, Tumors of the Soft Tissues. Armed Forces Institute of Pathology, Washington, DC, pp 95–99

Kluge TH, Ulal SR, Gerbode F (1971) Dysfunction of the liver in cardiac myxoma. Surg Gynecol Obstet 134:288–290

Knezevich SR, McFadden DE, Tao W, Lim JF, Sorenson PH (1998) A novel ETV6-NTRK3 gene fusion in congenital fibrosarcoma. Nat Genet 18:184–187

Koo PJ, Goykhman I, Lembert L, Nunes LW (2009) MRI features of cellular angiomyofibroma with pathologic correlation. J Magn Reson Imaging 29:1195–1198

Kotani K, Tsuji M, Oki A, Kashihara T, Yamada K, Kawakami F, Tako H, Okuno G, Hizuka N et al (1993) IGF-II producing hepatic fibrosarcoma associated with hypoglycemia. Intern Med 32:897–901

Kotiligam D, Lazar AJ, Pllock RE, Lev D (2008) Desmoid tumor: a disease opportune for molecular insights. Histol Histopathol 23:117–126

Kruger S, Kinzel M, Walldorf C, Gottschling S, Bier A, Tinschert S, von Stackelberg A et al (2008) Homozygous PMS2 germline mutations in two families with early-onset haematological malignancy, brain tumours, HNPCC-associated tumours, and signs of neurofibromatosis type 1. Eur J Hum Genet 16:62–72

Lambros MB, Tan DS, Jones RL, Vatcheva R, Savage K, Tamber N, Fenwick K et al (2009) Genomic profile of a secretory breast cancer with an ETV6-NTRK3 duplication. J Clin Pathol 62:604–612

Lannon CL, Sorensen PH (2005) ETV6-NTRK3: a chimeric protein tyrosine kinase with transformation activity in multiple cell lineages. Semin Cancer Biol 15:215–223

Leaute-Labreze C, Labarthe MP, Blanc JF, Sanyas P, Dosquet C, Taieb A (2001) Self-healing generalized infantile myofibromatosis with elevated urinary bFGF. Pediatr Dermatol 18:305–307

Li Y, Wang J, Asahina K (2013) Mesothelial cells give rise to hepatic stellate cells and myofibroblasts via mesothelial-mesenchymal transition in liver injury. Proc Natl Acad Sci U S A 110:2324–2329

Mahendra G, Kliskey K, Williams K, Hollowood K, Jackson D, Athanasou NA (2008) Intratumoural lymphatics in benign and malignant soft tissue tumours. Virchows Arch 453:457–464

Mariño-Enriquez A, Li P, Samuelson J, Rossi MR, Reyes-Mugica M (2008) Congenital fibrosarcoma with a novel complex 3-way translocation t(12;15;19) and unusual histologic features. Hum Pathol 39:1844–1848

Martin JM, Jorda E, Calduch L, Monteagudo C, Pereda C, Villalon G (2008) Self-healing generalized infantile myofibromatosis. J Eur Acad Dermatol Venereol 22:236–238

Marx G (1904) Über das primäre Sarkom der Leber. Zbl Allg Pathol Pathol Anat 15:433

Matsuoka S, Ito M, Shinonome T, Yoshitoshi M, Tanimura A (1992) An autopsy case of cerebral embolism caused by atrial myxoma (in Japanese). No Shinkei Geka 20:255–259

Matthews MR, Cockerell CJ (2006) An historic perspective of infantile myofibromatosis. Adv Dermatol 22:279–305

Meis-Kindblom JM, Kindblom LG, Enzinger FM (1995) Sclerosing epithelioid fibrosarcoma. A variant of fibrosarcoma simulating carcinoma. Am J Surg Pathol 19:979–993

Mentzel T, Calonje E, Nascimento AG, Fletcher CD (1994) Infantile hemangiopericytoma versus infantile myofibromatosis. Study of a series suggesting a continuous spectrum of infantile myofibroblastic lesions. Am J Surg Pathol 18:922–930

Middleton SB, Fidler K, Hyer W, Phillips RK (2000) Familial adenomatous polyposis complicated by an intrahepatic desmoid tumor: report of a case. Dis Colon Rectum 43:1012–1014

Miura K, Han G, Sano M, Tsutsui Y (2002) Regression of congenital fibrosarcoma to hemangiomatous remnant with histological and genetic findings. Pathol Int 52:612–618

Muraoka I, Ohno Y, Kamitaari A, Okada M, Moriuchi H, Kanematsu T (2008) Congenital occurrence of solitary infantile myofibromatosis of the spleen. J Pediatr Surg 43:227–230

Nakahama M, Takansahi R, Yamazaki I, Machinami R (1989) Primary fibrosarcoma of the liver. Immunohistochemical and electron microscopic studies. Acta Pathol Jpn 39:814–820

Narchi H (2001) Four half-siblings with infantile myofibromatosis: a case for autosomal-recessive inheritance. Clin Genet 59:134–135

Nonaka D, Sun CC (2004) Congenital fibrosarcoma with metastasis in a fetus. Pediatr Dev Pathol 7:187–191

Ojima A, Sugiyama T, Takeda T, Hazama F, Nakayuki K, Uesugi Y, Miyazaki A, Suzuki Y, Fukushima M (1964) Six cases of rare malignant tumors of the liver. Acta Pathol Jpn 14:95–102

Onan B, Bayramoglu Z, Onan IS, Akpinar B (2011) Right atrial myxoma associated with portal and splenic vein thrombosis in a patient with Budd-Chiari syndrome. Turk Kardiyol Dern Ars 39:320–324

Orth M (1885) Über primäres Lebersarkom. Inaug Dissertation. (Thesis), University of Strassburg

Ossendorf C, Studer GM, Bode B, Fuchs B (2008) Sclerosing epithelioid fibrosarcoma: case presentation and a systematic review. Clin Orthop Relat Res 466:1485–1491

Papazian A, Capron JP, Gontier MF, Remond A, Dupas JL, Pietri J, Lorriaux A (1978) Fibrosarcoma of the liver. Report of two cases and review of the literature (in French). Gastroenterol Clin Biol 2:689–695

Patel Y, Mitchell CD, Hitchcock RJ (2003) Use of sarcoma-based chemotherapy in a case of congenital

mesoblastic nephroma with liver metastases. Urology 61:1260
Patel RM, Downs-Kelly E, Dandekar MN, Fanburg-Smith JC, Billings SD, Tubbs RR et al (2011) FUS (16p11) gene rearrangement as detected by fluorescence in-situ hybdridization in cutaneous low-grade fibromyxoid sarcoma: a potential diagnostic tool. Am J Dermatopathol 33:140–143
Pater (1905) Examen histologique d'un sarcome primaire du foie à type fusocellulaire. Bull Mém Soc Anat Paris 80:25–32
Pelluard-Nehmé F, Coatleven F, Carles D, Albnerti EM, Briex M, Dallay D (2007) Multicentric infantile myofibromatosis: two perinatal cases. Eur J Pediatr 166:997–1001
Podrouzek J (1888) Beiträge zur Kasuistik der primären Lebersarkome. Prague Med Wochenschr 36:341–345
Rekhi B, Folpe AL, Deshmukh M, Jambhekar NA (2011) Sclerosing epithelioid fibrosarcoma – a report of two cases with cytogenetic analysis of FUS gene rearrangement by FISH technique. Pathol Oncol Res 17:145–148
Roggli VL, Han-Seob K, Hawkins E (1980) Congenital generalized fibromatosis with visceral involvement. A case report. Cancer 45:954–960
Salamah MM, Hammoudi SM, Sadi ARM (1988) Infantile myofibromatosis. J Pediatr Surg 23:975–977
Saltykov S (1914) Sarcoma and carcinoma of liver. Cor Bl Schweiz Aerzte 44:385–396
Sandberg AA, Bridge JA (2002) Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors: congenital (infantile) fibrosarcoma and mesoblastic nephroma. Cancer Genet Cytogenet 132:1–13
Sarra A, Bertolini A (1968) Primary hepatic myxosarcoma in childhood (in Italian). Clin Pediatr (Bologna) 50:825–838
Schaffzin EA, Chung SMK, Kaye R (1972) Congenital generalized fibromatosis with complete spontaneous regression. J Bone Joint Surg 54(A):657–662
Scheidemandel K (1903) Ein Fall von primärem Sarkom der Leber. Inaug Dissertation Erlangen
Schurr P, Moulsdale W (2008) Infantile myofibroma: a case report and review of the literature. Adv Neonatal Care 8:13–20
Shallow TA, Wagner FB (1947) Primary fibrosarcoma of the liver. Ann Surg 125:439–446
Sheng WQ, Hisaoka M, Okamoto S, Tanaka A, Meis-Kindblom JM, Kindblom LG et al (2001) Congenital-infantile fibrosarcoma. A clinicopathologic study of 10 cases and molecular detection of the ETV6-NTRK3 fusion transcripts using paraffin-embedded tissues. Am J Clin Pathol 115:348–355
Shiga J (1996) Fibroma and fibrosarcoma of the extrahepatic bile ducts (in Japanese). Ryoikibetsu Shokogun Shirizu 9:40–42
Shintaku M, Watanabe K (2010) Mesenchymal hamartoma of the liver. A proliferative lesion of possible hepatic stellate cell (Ito cell) origin. Pathol Res Pract 206:532–536
Short M, Dramis A, Ramani P, Parikh DH (2008) Mediastinal and pulmonary infantile myofibromatosis: an unusual surgical presentation. J Pediatr Surg 43: e29–e31
Silaruks S, Kiatchoosakul S, Tatsanavivat P, Tontisirin C, Kuptarnond C, Prathanee S et al (1999) Atrial myxoma: a review of clinical experience at Srinagarind Hospital. J Med Assoc Thai 82:107–114
Simpson HM, Baggenstoss AH, Stauffer MH (1955) Primary sarcoma of the liver – a report of three cases. South Med J 48:1177–1182
Smith D, Rele SR (1972) A case of primary fibrosarcoma of the liver. Postgrad Med J 48:62–63
Snapper I, Schraft WC, Ginsberg DM (1964) Severe hypoglycemia due to fibrosarcoma of the liver. Maandschr Kindergeneeskd 32:337–347
Soule EH, Pritchard DJ (1977) Fibrosarcoma in infants and children: a review of 110 cases. Cancer 40:1711–1721
Spadola L, Anooshiravanti M, Sayegh Y, Jequier S, Hanquinet S (2002) Generalized infantile myofibromatosis with intracranial involvement: imaging findings in a newborn. Pediatr Radiol 32:872–874
Spay G, Toure P, Diouf AB (1973) Angiofibroma of the hepatic round ligament (in French). Bull Soc Med Afr Noire Lang Fr 18:201–203
Steiner PE (1960) Cancer of the liver and cirrhosis in Trans-Saharan Africa and the United States of America. Cancer 13:1085–1166
Stout AP (1954) Juvenile fibromatosis. Cancer 7:953–978
Stout AP (1962) Fibrosarcoma in infants and children. Cancer 15:1028–1040
Stroebel P, Mayer F, Zerban H, Bannasch P (1995) Spongiotic pericytoma: a benign neoplasm deriving from the perisinusoidal (Ito) cells in rat liver. Am J Pathol 146:903–913
Sty JR, Ruiz ME, Carmody TJ (1996) Congenital generalized fibromatosis: extraosseous accumulation of bone seeking radiopharmaceutical. Clin Nucl Med 21:413–414
Tameda Y, Shiraki K (1995) Primary fibroma of the liver, primary fibrosarcoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:384–386
Tanaka S, Takasawa A, Fukasawa Y, Hasegawa T, Sawada N (2012) An undifferentiated embryonal sarcoma of the liver containing adipophilin-positive vesicles in an adult with massive sinusoidal invasion. Int J Clin Exp Pathol 5:824–829
Tardio JC (2009) Leiomyomatous nodule in a cellular angiofibroma: a hitherto unreported finding. Virchows Arch 454:595–598
Taute BM, Zipprich B, Hoffmann G, Saul W (1988) Pedicled fibroma of the extrahepatic bile ducts (in German). Z Ges Inn Med 43:624–627
Thöhle F (1913) Chirurgie der Lebergeschwülste (Surgery of liver tumors). In: von Bruns P (ed) Der Neue Deutsche Chirurg, vol 7. Verlag Ferdinand Enke, Stuttgart

Thway K, Gibson S, Ramsay A, Sebire NJ (2008) Beta-catenin expression in pediatric fibroblastic and myofibroblastic lesions: a study of 100 cases. Pediatr Dev Pathol 12:292–296

Tok M, Oc M, Ucar HI, Dogan OF, Ozyuksel A, Kaya B, Farsak MB, Yorgancioglu AC (2007) Giant right atrial myxoma mimicking hepatic cirrhosis :a case report. Heart Surg Forum 10:E107–E109

Tomimaru Y, Nagano H, Marubashi S, Kobayashi S, Eguchi H, Takeda Y, Tanemura M et al (2009) Sclerosing epithelioid fibrosarcoma of the liver infiltrating the inferior vena cava. World J Gastroenterol 15:4204–4208

Totzke HA, Hutcheson JB (1965) Primary fibrosarcoma of the liver – case report. South Med J 58:236–238

Tsiatis AC, Atkinson JB, Wright JK, Cates JM (2008) Primary hepatic myxoid leiomyosarcoma: a case report and review of the literature. Ultrastruct Pathol 32:25–28

Von Schweinitz D, Dammeier BG, Glüer S (1999) Mesenchymal hamartoma of the liver – new insight into histogenesis. J Pediatr Surg 34:1269–1271

Wai DH, Knezevich SR, Lucas T, Jansen B, Kay RJ, Sorensen PH (2000) The ETV6-NTRK3 gene fusion encodes a chimeric protein tyrosine kinase that transforms NIH3T3 cells. Oncogene 19:906–915

Walter E, Bodner E, Lederer B (1972) Primary fibrosarcoma of the liver (in German). Wien Klin Wochenschr 24:808–813

Wang WL, Evans HL, Meis JM, Liegl-Atzwanger B, Bovee JV, Goldblum JR, Billings SD et al (2012) FUS rearrangements are rare in 'pure' sclerosing epithelioid fibrosarcoma. Mod Pathol 25:846–853

Wimmer K, Etzler J (2008) Constitutional mismatch repair-deficiency syndrome: have we so far seen only the Tipp of an iceberg? Hum Genet 124:105–122

Windrath (1885) Ueber die Sarkombildung in der Leber mit Beschreibung eines Falles von primärem Spindelzellensarkom der Leber. Inaug Dissertation, Freiburg (Germany)

Wiswell TE, Davis J, Cunningham BE, Solenberger R, Thomas PJ (1988) Infantile myofibromatosis: the most common fibrous tumor of infancy. J Pediatr Surg 23:314–318

Wood LD, Irvin BJ, Nucifora G, Luce KS, Hiebert SW (2003) Small ubiquitin-like modifier conjugation regulates nuclear export of TEL, a putative tumor suppressor. Proc Natl Acad Sci U S A 100:3257–3262

Wright C, Corbally MT, Hayes R, McDermott MB (2004) Multifocal infantile myofibromatosis and generalized fibromuscular dysplasia in a child: evidence for a common pathologic process ? Pediatr Dev Pathol 7:385–390

Yamaguchi T, Ogawa K, Furuhata A, Uekusa T, Nakagome H (1989) A case of retroperitoneal fibrosarcoma (in Japanese). Hinyokika Kiyo 35:465–468

Yokota H (1944) Ein ganz seltener Fall von steinartiger Tumorbildung in der Leber. Acta Med Okayama 7:351–356

Zand DJ, Huff D, Everman D, Russell K, Saitta S, McDonald-McGinn D, Zackai EH (2004) Autosomal dominant inheritance of infantile myofibromatosis. Am J Med Genet 126:261–266

Zelger BW, Calonje E, Sepp N, Fink FM, Zelger BG, Schmid KW (1995) Monophasic cellular variant of infantile myofibromatosis. An unusual histopathologic pattern in two siblings. Am J Dermatopathol 17:131–138

Zeller et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9392395

Zhao H, Cai JQ, Bi XY, Zhao JJ, Huang Z, Lu HZ, Zhou HT (2008) Diagnosis, treatment, and prognostic of liver sarcoma: analysis of 16 cases (in Chinese). Zhonghua Yi Xue Za Zhi 88:1537–1539

Zimmermann KW (1923) Der feinere Bau der Blutkapillaren. Z Anat Entwicklungsgesch 68:29–109

Leiomyomatous Tumors of the Hepatobiliary Tract

63

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_63

Abstract

Leiomyoma, composed of smooth muscle cells, is a rare primary tumor of the liver. Part of these lesions develop in immunosuppressed patients, in particular HIV-infected individuals and following organ transplantation, and there is an association with Epstein-Barr virus infection. Hepatic leiomyomas are solitary or multiple lesions that can grow to large size with cystic change. Leiomyoma can develop in the biliary tract and large veins of the liver. The malignant counterpart, leiomyosarcoma, is a very uncommon primary hepatic malignancy. These are usually solitary nodular masses, sometimes exceeding 20 cm in diameter, with a tendency for necrosis and hemorrhage. In contrast to high-grade sarcomas, the mitotic activity may be low, but undergoes significant increase as a function tumor progression and intrahepatic metastasis. One variant of hepatic leiomyosarcoma is characterized by a myxoid component.

Hepatic Leiomyoma

Introduction and Epidemiology

Leiomyoma is a benign neoplasm derived from and composed of smooth muscle cells. Primary leiomyoma of the liver is rare, with only relatively few cases having been reported in immunocompetent hosts.

Selected References Demel 1926; Rios-Dalenz 1965; Ishak 1976; Hawkins et al. 1980; Stark 1988; Rummeny et al. 1989; Hollands et al. 1989; Herzberg et al. 1990; Iwatsuki et al. 1990; Bartoli et al. 1991; Reinertson et al. 1992; Shiraki and Tameda 1995; Yoon et al. 1998; Mesenas et al. 2000; Belli et al. 2001; Kanazawa et al. 2002; Beuzen et al. 2004; Clarke et al. 2004; Imasato et al. 2005; Urizono et al. 2006; Kalil et al. 2009.

A more significant fraction of hepatic smooth muscle tumors (both benign and malignant) has recently been encountered in immunosuppressed

patients, in particular HIV-infected individuals (Wachsberg et al. 1994; Prévot et al. 1994; McClain et al. 1995; Wang et al. 2000), and following organ transplantation (Doyle et al. 1991; Ha et al. 1993; Le Bail et al. 1996; Brichard et al. 2001; Sclabas et al. 2002) HIV-infected immunocompromised hosts include both children (Ross et al. 1992; Mueller et al. 1992; Levin et al. 1994) and adults (Prévot et al. 1994; Wachsberg et al. 1994; Wang et al. 2000), although generally children seem to be more frequently involved (Prévot et al. 1994).

Of specific biologic interest is the now well-documented association between hepatic leiomyomatous tumors and Epstein-Barr virus (EBV) infection in immunosuppressed subjects. Prevot and coworkers reported the first case of EBV in hepatic smooth muscle neoplastic cells in an HIV-infected adult patient in 1994 (Prévot et al. 1994). Views concerning the possible causal relationship between immunosuppression, EBV infection, and the emergence of smooth muscle cell growths in several organs, including the liver, are briefly discussed below.

Clinical and Imaging Features

Clinically, some of the patients do not show symptoms, and the lesions are detected by imaging performed for other purposes, whereas other patients disclose upper abdominal pain or a palpable mass. Most cases reported so far were solitary tumors, sometimes more than 10 cm in diameter, large lesions resulting in compression of adjacent tissues or organs. In ultrasonography, hepatic leiomyoma presents as a low echoic mass with a clearly defined boundary, and contrast-enhanced CT is characterized by a hypovascular, sharply delineated nodule with peripheral enhancement during the equilibrium phase (Mueller et al. 1992; Wachsberg et al. 1994; Mesenas et al. 2000; Kanazawa et al. 2002; Sclabas et al. 2002). On MR imaging, the lesion has been shown to be hypointense by T1-weighted imaging and isointense with central hyperintensity by T2-weighted imaging (Sclabas et al. 2002; Kanazawa et al. 2002).

Macroscopic Pathology

At gross examination, hepatic leiomyomas are usually solitary lesions, but multiplicity has also been described (Wachsberg et al. 1994; Sclabas et al. 2002). Some solitary lesions may grow to very large size (giant leiomyoma of the liver; in one case with a diameter of 30 cm, Belli et al. 2001). The tumors exhibit an expanding growth pattern, with formation of a liver compression/atrophy zone at their periphery resulting in a sharply demarcated and roughly spherical lesion. On the cut surface, the usually firm neoplasms exhibit a whitish to gray color and may show a fibrous texture, similar to uterine leiomyomas (Fig. 1). Large tumors can develop cystic changes (Yoon et al. 1998; Sclabas et al. 2002), but gross necrosis or hemorrhage is usually lacking.

Histopathology

Histologically, the pattern is similar to leiomyomas occurring in other locations, although the cellularity may vary considerably. The key cell is a spindled leiomyocyte with elongated nuclei and a slightly eosinophilic cytoplasm (Fig. 2). The neoplastic cells are arranged in the form of fascicles, sometimes with a crisscross pattern. In most cases, nuclear atypia is slight,

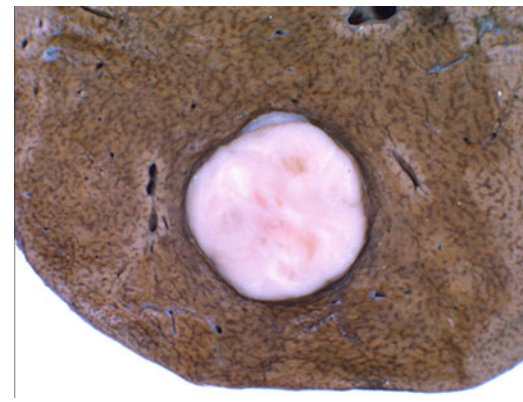

Fig. 1 Primary leiomyoma of the liver. Note the fasciculated structure of the lesion, similar to uterine leiomyoma. There is peritumoral atrophy of the liver, caused by expanding growth of the tumor

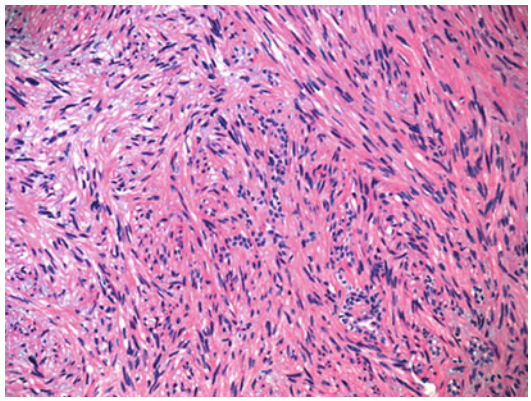

Fig. 2 Primary leiomyoma of the liver. Eosinophilic neoplastic smooth muscle cells with characteristic nuclei-form interlacing bundles (hematoxylin and eosin stain)

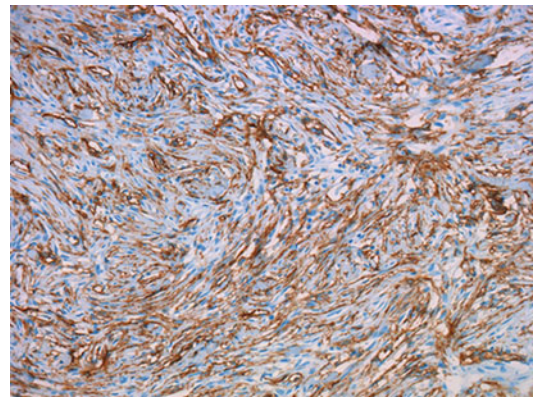

Fig. 3 Leiomyoma of the liver with strong reactivity of tumor cells for smooth muscle actin (alpha-SMA immunostain)

and only few mitotic figures are discernible (less than 1 per 20 HPFs). Some visceral leiomyomas, including those of the liver, occurring in immunosuppressed individuals may show a rather high cellularity and/or nuclear atypia, resulting in terms such as "cellular leiomyoma" or "atypical leiomyoma." In fact, it may sometimes be difficult to decide, by use of histology alone, whether the tumor in question is bona fide benign or malignant. In case of doubt, the neutral term, smooth muscle tumor of unknown dignity, may be preferable. In between the cells, a rich network of reticulin fibers is found, whereas a band of collagen fibers may be seen at the periphery of the lesion, indicating expansive growth, however without formation of a fibrous capsule. At the tumor-liver interface, a narrow zone of fibrovascular tissue is observed, containing an increased density of vessels running from the periphery to inner parts, probably illustrating the vascular pattern suggesting tumor angiogenesis seen at imaging (Kanazawa et al. 2002; see above). Immunohistochemically, there is marked reactivity for alpha-SMA (Fig. 3) and less for vimentin, whereas desmin is slightly expressed or lacking. In typical leiomyoma, there is no reactivity for CD34, S-100 protein, and HMB 45. In the tumors reported by us, the proliferative activity as based on Ki-67 immunostaining was low, i.e., less than 5 % (Sclabas et al. 2002).

Myxoid Leiomyoma of the Liver

In a minority of primary hepatic leiomyomas, neoplastic myocytes are embedded in a myxoid matrix. Such neoplasms are termed myxoid leiomyoma of the liver (Yoon et al. 1998; Choi et al. 2014). The neoplasms are uniformly hypocellular and consist of scattered, spindled smooth muscle cells with blunt-ended, cigar-shaped nuclei. The background tissue appears edematous, but is characterized by myxoid features with abundant intercellular substance.

Hepatic Leiomyoma and Epstein-Barr Virus Infection

An interesting feature of hepatic leiomyomas is their association with Epstein-Barr virus (EBV) infection. In EBV infection ensuing in immunocompromised hosts and transplanted patients in particular (Collins et al. 2001), benign and malignant smooth muscle tumors have now been detected, apart from the liver, in several organs (EBV-associated smooth muscle tumors, EBV-SMT; reviews: Deyrup 2008; Moore Dalal et al. 2008). The phenomenon of an association between EBV infection and the emergence of smooth muscle tumors (EBV-SMT) has now been documented also for the liver several times.

The tumors have in part be designated as leiomyoma (Prévot et al. 1994; Lee et al. 1995; Le Bail et al. 1996; Davidoff et al. 1996; Wang et al. 2000; Cheuk et al. 2002; Sclabas et al. 2002), whereas other studies employed the term leiomyosarcoma (McClain et al. 1995; Rogatsch et al. 2000; Brichard et al. 2001; Monforte-Munoz et al. 2003; Nur et al. 2007). Based on the distinctive clinicopathologic and biologic features, it is now proposed to term these lesions, EBV-associated smooth muscle tumors, also for those arising in the liver (Le Bail et al. 1996; Sadahira et al. 1996; Cheuk et al. 2002; Salamanca and Massa 2009). In several reports, more than one or even multiple synchronous hepatic lesions were detected (Lee et al. 1995; Sadahira et al. 1996; Rogatsch et al. 2000; Brichard et al. 2001; Sclabas et al. 2002; Gallien et al. 2008), and also EBV-associated multifocal leiomyosarcoma can present with multiple liver nodules (Nur et al. 2007). Morphologically, there seems to be a difference between EBV-associated hepatic smooth muscle tumors and those which do not exhibit such an association. EBV-SMT are typically well-differentiated smooth muscle tumors with little atypia and usually a low level of mitotic activity. They are consistently alpha-SMA positive, but less often positive for desmin. The tumors may contain primitive round cell areas and prominent intratumoral T lymphocyte infiltrations (Deyrup et al. 2006).

What is striking is the marked expression of EBV early antigen (EBER) in the nuclei of numerous tumor cells, already documented in the first reports by use of in situ hybridization/ISH (leiomyoma:Prévot et al. 1994; leiomyosarcoma: McClain et al. 1995). Nuclear EBER-ISH signals have subsequently been described in these hepatic lesions (Sadahira et al. 1996; Le Bail et al. 1996; Cheuk et al. 2002; Sclabas et al. 2002), and also viral DNA was demonstrated in the tumors by use of Southern blot analysis (Le Bail et al. 1996). We have seen two hepatic leiomyomas in a renal transplant recipient where EBV-LMP was not detectable, similar to a previous study (Lee et al. 1995), whereas there were marked ISH signals for EBV early antigen (EBER) (Sclabas et al. 2002). In patients with AIDS developing EBV-associated leiomyosarcomas (including hepatic tumors), the human EBV receptor (CD21) was expressed on tumor cells, more so on cells from HIV-infected individuals than on cells from HIV-negative individuals, suggesting that immunodeficiency may result in upregulation of CD21, which may be a prerequisite for EBV infection of smooth muscle cells (McClain et al. 1995). In the same study, quantitative PCR demonstrated high levels of EBV in tumor tissues, with as many as 4.3 genome copies per cell (McClain et al. 1995). In the three patients described by Lee and coworkers (1995), one of which had a hepatic lesion; molecular genetic analysis showed the EBV genome to be clonal in all three. Thus, hepatic EBV-associated smooth muscle tumors exhibit, with respect to EBV expression, molecular biologic features similar to the tumors that have been detected elsewhere, and the results obtained so far suggest that EBV can infect smooth muscle cells and may contribute to the pathogenic pathway of leiomyomas and leiomyosarcomas in immunocompromised hosts.

Leiomyoma of Bile Ducts

Introduction

Biliary leiomyomas mostly occur in the extrahepatic bile ducts, including the junction/bifurcation area (Mandeville and Stawski 1991), the common bile duct (Archambault and Archambault 1952; Kune and Polgar 1976; Lagun et al. 1993; Saito 1996), the distal common bile duct (Yamaoka et al. 1993; Goo et al. 2006; Kalaitzakis and Sturgess 2011), and, somewhat more commonly, the ampullo-papillary region (Nemsmann und Schroder 1984; Octavio de Toledo et al. 1991; Tseng et al. 2003).

Clinical Features

Lesions in the common bile duct almost always cause obstruction with intermittent jaundice,

prestenotic duct dilatation, and obstruction-induced secondary sclerosing cholangitis (Archambault and Archambault 1952; Kune and Polgar 1976; Lagun et al. 1993; Yamaoka et al. 1993; Goo et al. 2006). Biliary obstruction is also documented for leiomyomas located to the ampullo-papillary compartment (Tseng et al. 2003).

Pathology

Leiomyomas of the most proximal parts of the extrahepatic bile ducts, and particularly of the bifurcation area, may grossly and clinically mimic Klatskin tumor (Mandeville and Stawski 1991). In a case with pancreatoduodenectomy, the resected specimen showed a small hard tumor about 4 mm in diameter projecting into the lumen from the wall of the intrapancreatic portion of the common bile duct (Yamaoka et al. 1993).

Histology showed the features known for leiomyomas situated elsewhere (Yamaoka et al. 1993). The nodules are composed of interlacing bundles of bland looking, slightly eosinophilic spindle cells with elongated nuclei lacking atypia (Fig. 4). Mitotic figures are absent. The tumor cells are markedly reactive for vimentin and alpha-smooth muscle actin.

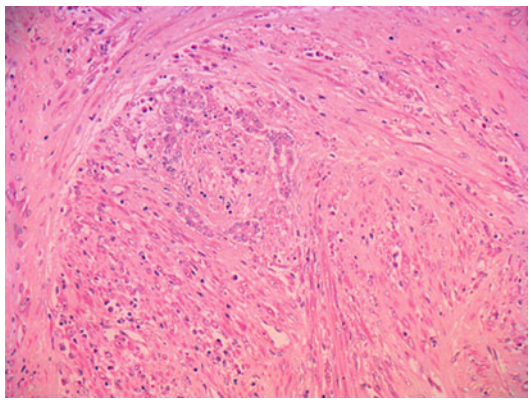

Fig. 4 Leiomyoma developing in a bile duct (hematoxylin and eosin stain)

Angioleiomyoma of the Bile Duct

Angioleiomyoma of the common bile duct has been observed in an 80-year-old woman presenting with obstructive jaundice (Ponka et al. 1983).

Pathogenic Pathways

It is assumed that the rare bile duct leiomyomas take their origin from preexisting smooth muscle cells located in the duct wall. The equipment of extrahepatic bile ducts with myocytes has been analyzed in detail since the first comprehensive study of bile duct anatomy by Kiernan (1833). It has been reported several times that the subepithelial connective tissue layer of the common duct may contain scant smooth muscle cells (Jordan 1952; Gray 1959; Bloom and Fawcett 1962; Arey 1963; Hess 1965); however, the different texts reveal some paucity of accurate information on the presence or absence of muscle cells in the different segments of the ducts. Conversely, few systematic studies provided more detailed informations, albeit with controversial results what may in part be related to methodological constraints and limitations. In a study of 24 normal common bile ducts, the authors reported complete absence of muscle cells, based on the dynamics of bile flow (Myers et al. 1962). In contrast, other reports documented the histologically proven presence of myocytes in the wall of the common bile duct (Hendrickson 1898; Burden 1925; Daniels et al. 1961; Burnett et al. 1964; Ludwick 1966; Watts and Dunphy 1966; Karski 1974a). It was observed that myocytes of the duodenal muscularis are in connection with myocyte bundles of the terminal segment of the common bile duct (Karski 1974b). In a systematic analysis of 100 common bile ducts obtained at necropsy of individuals with a normal hepatobiliary system, covering an age range of 13 years to 94 years, 88 % had no smooth muscle fibers whatsoever in the duct wall when studied in H&E, van Gieson's, and Masson trichrome stains, while 12 % of the

specimens had smooth muscle clearly demonstrated in the wall of the duct (Mahour et al. 1967). The quantity of smooth muscle cells varied among specimens, but, except for one specimen, such cells were always seen in sections from both the distal and the proximal segments. The myocytes were scattered in the fibroelastic tissue of the wall, in both circular and longitudinal directions, but in no instance did they form layers or muscular sheaths around the duct. There was no relationship between the age of the subject and the presence or absence of smooth muscle in the ducts. In another necropsy study (20 subjects), well-defined layers of smooth muscle did not exist in the common bile duct, but there were clusters of myocytes. In the upper third of the duct, there were only sparse longitudinally oriented cells, while in the midportion of the duct, the myocytes became more prominent, the cells then becoming a longitudinal layer toward the sphincter of Oddi (Ludwick 1966). A longitudinal orientation of myocytes was found to vary in man according to age, a more irregular arrangement of the cells being prevalent at higher age (Kialian and Aznaurian 1995).

The presence of intramural smooth myocytes in the supraduodenal portion of the common bile duct has been confirmed by use of immunohistochemistry (anti-actin), and the immunoreactive cells were predominantly oriented in a longitudinal direction (Walsh and Akoglu 1979). In a systematic study of 101 consecutive Whipple-type pancreatoduodenectomies and 21 autopsy specimens, extrahepatic bile ducts were analyzed immunohistochemically (desmin stain) in regard to the presence of smooth muscle cells. The pattern of smooth muscle distribution was categorized as continuous, interrupted, scattered, or lacking. The predominant patterns of the lower third of the common bile duct were interrupted (49 %) and continuous (43 %), those of the middle third were scattered (63 %) and interrupted (23 %), and those of the upper third have no muscle cells (58 %) and were scattered (39 %), suggesting a typical gradient of duct musculature both with respect to cell density and distribution. Because scattered muscle fibers or no muscle fibers were the main features of the upper third of the duct, understanding of this pattern may also be helpful for the assessment of the depth of invasion of bile duct cancer (Hong et al. 2000).

Other Hepatic Tumors with a Smooth Muscle Cell Lineage

Apart from leiomyomas evolving in the hepatic substance, this tumor can also develop in large liver veins, including the portal vein and the hepatic vein. Portal vein leiomyoma is exceedingly rare, one report documenting an increased proliferative activity of the tumor suggesting "semimalignancy" (Kremer et al. 1976). In one instance, an atypical leiomyoma of the hepatic vein occurring in a 14-year-old boy extended in the inferior vena cava and the right atrium and induced Budd-Chiari syndrome, suggesting the sometimes complex growth pattern of vascular leiomyomas (Dunlap and Udjus 1990; Lee et al. 1990). A similar situation of hepatic venous outflow tract obstruction has been observed in primary smooth muscle tumor of the inferior caval vein (Lintner et al. 1978).

A smooth muscle cell lineage is rarely involved in vascular tumors of the liver (see above), and one such lesions has been termed hepatic angiomyoma (Beissert et al. 2002). In an autopsy case, multiple hepatic benign smooth muscle cell tumors had been observed together with lesions representing cavernous hemangioma, and these composite tumors have been termed leiomyomatous hemangiomas of the liver (Key and Rao 1986). It may be surmised that a vascular progenitor cell of leiomyocytes may be involved in such an unusual situation. Hepatic angiomyolipomas, which are described in the respective chapter on perivascular cell tumors, may predominantly be composed of smooth muscle cells, which can then result in a difficult differential diagnosis (Nonomura et al. 1998).

Interestingly, neoplastic smooth muscle components may arise in hepatic tumors with a

non-mesenchymal cell lineage, including hepatoblastomas (see the respective chapter) and other epithelial neoplasms. Of particular theoretical interest is the observation of a primary smooth muscle tumor of the liver encasing a hepatobiliary cystadenoma without mesenchymal stroma (Yanase et al. 1999). In this tumor detected in a 59-year-old female, a solid and hypervascular mass consisting of neoplastic smooth muscle cells may have developed from cells involved in the mesenchymal component of hepatobiliary cystadenoma.

Leiomyomas of Large Liver-Associated Veins

The literature documents few cases of vascular tumors interpreted as leiomyomas. Most of these lesions were described in a time when modern diagnostic methods and criteria for smooth muscle cell tumor malignancy were not yet elaborated. Therefore, it is difficult to judge whether all of these neoplasm were bona fide leiomyomas of rather low-grade malignancy leiomyosarcomas. The majority of tumors interpreted as primary venous leiomyomas originated from the inferior vena cava (Abdullaeva 1951; Macek 1960; Hachisuka et al. 1963; Hoffmann 1963; Salaquarda 1964; Mandelbaum et al. 1974). Rarely, leiomyoma of the inferior vena cava was of the symplastic type (symplastic leiomyoma; Kahveci et al. 2012). Symplastic or atypical leiomyoma is characterized by moderate to severe cellular atypia in the absence of necrosis and a mitotic count of less than ten mitotic figures per ten HPFs. There is a single report on a leiomyoma of the portal vein (Kremer et al. 1976). The authors described a 34-year-old female patient who showed, at cholecystectomy, well-delineated tumor of 16 cm diameter at the pancreatic head. At surgery, this tumor was seen arise from the anterior portal vein wall. Histology showed a cellular leiomyoma. The postoperative follow-up revealed no evidence of disease at 12 months. An atypical leiomyoma, with a histology intermediate between benign and malignant features, was diagnosed in the hepatic vein of a 14-year-old male patient. The tumor extended into the right atrium and had caused Budd-Chiari syndrome (Lee et al. 1990).

Vascular Leiomyoblastoma of the Liver

Introduction

Leiomyoblastomas are epithelioid smooth muscle tumors that consist of a cell lineage with immature smooth muscle differentiation. The tumors chiefly occur in the uterus and the neoplastic cells mimic smooth muscle cells of the fetal uterus (Modafferi 2002; Watanabe et al. 2003). A morphologically somewhat similar but genetically different type of uterine tumor is plexiform leiomyoma, characterized by a neoplasm with ribbons and nests of smooth muscle cells that have an epithelioid shape and are entrapped in an abundant extracellular matrix (Hodge et al. 2008).

Leiomyoblastoma has been reported to occur in the stomach (rare tumors different from gastrointestinal stromal tumors; Huang et al. 2004, with review), the greater omentum (Tsurumi et al. 1991), the lesser omentum (Pizzimbono et al. 1973), the tongue (Sancho Alvarez et al. 2001), and the urethra (Sakai et al. 2000). Histologically, these tumors are composed of epithelioid, rhabdoid, and large vacuolated cells intermingled with spindle-shaped cells. Prominent nuclear atypia is usually lacking. Immunohistochemically, the tumor cells are intensively positive for desmin and alpha-smooth muscle actin (SMA) and sometimes for non-muscle myosin heavy chain, whereas positivity for heavy molecular weight caldesmon is restricted. Ultrastructurally, some of the cells contain dense aggregates of intermediate filaments as typically seen in rhabdoid cells (Watanabe et al. 2003). It seems that smooth muscle cells in some leiomyomatous tumors have the ability to transform in a rhabdoid or rhabdoid-like cell lineage (Parker et al. 2005). A subset of epithelioid smooth muscle tumors have a relation to blood vessels and are termed vascular leimyoblastoma. Based on the distinct distribution of epithelioid cells around blood vessels, the lesions may mimic PEComas (Zamecnik and Michal 2001) or glomangiomyomas (Sakai 2007).

Vascular Leiomyoblastoma of the Liver

This rare lesion has been observed in the liver of a 57-year-old male patient with a mass in the upper abdomen. Ultrasonography revealed a tumor of 8 cm diameter in the left liver lobe. The tumor was noteworthy for the associated paroxysmal pain attacks. Liver resection revealed an encapsulated tumor in the peripheral part of the left hepatic lobe and being in contact with the gastric wall. Histologically, the neoplasm consisted of globoid or epithelioid cells associated with a rich vasculature. These cells were positive for actin (Bianchi and Comino 1989).

Intravascular Leiomyomatosis

Introduction

Intravascular leiomyomatosis (IVL; intravenous leiomyoma) is a principally benign smooth muscle tumor (leiomyoma), usually originating from the myometrium and characterized by intrusive growth in uterine, ovarian, and other pelvic veins, sometimes causing worm-like plugs of tumor within uterine veins and macroscopically visible nodules in extrauterine vessels involved (Norris and Parmley 1975; Mulvany et al. 1994). IVL recurs in about 10 % of the patients and must be distinguished from low-grade endometrial stromal sarcoma and leiomyosarcoma with vascular invasion. IVL may be associated with so-called benign metastasizing leiomyoma, a lesion complex thought to be caused by embolic dislodgment of IVL leiomyomatous tissue to remote organs, mainly the lung (Arif et al. 2006; Garcia Rinaldi et al. 2007; Lee et al. 2008).

Involvement of the Hepatic Venous Outflow Tract

Involvement of the venous outflow tract of the liver may be expected in those cases where IVL extends from uterine and/or pelvic veins to the cavoatrial system, with extension of the tumors into the heart cavities, which is a well-known complication of this tumor and may cause cardiac failure and death via valvular obstruction (Mandelbaum et al. 1974; Saitoh et al. 2004; Vallejo et al. 2005; Demirkiran et al. 2013; Xu et al. 2013). The tumor may show extensive intracaval attachment in these situations (Nam et al. 2003) and the sometimes large tumor plug may obturate hepatic vein entry in the caval vein (Vallejo et al. 2005). Direct involvement of the hepatic veins has been described in a 66-year-old woman (Bahary et al. 1982) and in a patient who had developed Budd-Chiari syndrome (Kuenen et al. 1996). In rare instances, an equivalent oncological situation is produced by uterine leiomyosarcoma invading the large abdominal veins and extending along the inferior vena cava to the atrium (intravenous uterine leiomyosarcomatosis; Moorjani et al. 2005). Caval extension has also been found in a variant of IVL, intravascular lipoleiomyomatosis (Brescia et al. 1989). Exceptionally, leiomyomatosis peritonealis disseminata can also show intravascular extension (Haberal et al. 2007).

Pathology

Histology displays richly vascularized leiomyomatous tissue with typically constructed bundles of slender myocytes and very low mitotic activity (Bertrand et al. 1998). It has been reported that IVL occurs in several morphotypes, including cellular IVL, epithelioid IVL, IVL with bizarre nuclei, myxoid IVL, IVL with endometrial component, and intravascular lipoleiomyomatosis (Clement et al. 1988).

Pathogenesis

IVL is characterized by chromosomal aberrations, such as der(14)t(12;14)(q15;q24), suggesting that IVL arises from uterine leiomyoma with the same aberration (Quade et al. 2002; Dal Cin et al. 2003). Skewed X chromosome inactivation was observed in tumor samples, but not in myometrium, and in each tumor sample, the lower molecular weight allele of HUMARA was

nonrandomly inactivated, a finding most consistent with origin of IVL from a single transformation event (Quade et al. 2002). In contrast to preexisting vessel wall components, the intravascular leiomyomatous tumor tissue expresses estrogen and progesteron receptors, supporting intravascular tumor transport rather than novel tumorigenesis in situ (Kir et al. 2004).

Leiomyomatous Hamartomas/ Hamartosis

Introduction

Hamartomas with a leiomyomatous component are lesions well recognized to occur in the breast, albeit an uncommon tumor (myoid hamartoma; Stafyla et al. 2007; Bayar et al. 2010). Such lesions also occur in the lung, mostly in middle-aged women and commonly multiple (diffuse fibro-leiomyomatous hamartosis; multiple pulmonary leiomyomatous hamartomas; Cruickshank and Harrison 1953). The lesions may regress during pregnancy, suggesting hormonal dependency of these growths (Horstmann et al. 1977). Rarer locations of leiomyomatous hamartomas or hamartosis include the oral cavity (Nava-Villalba et al. 2008), the breast (Magro and Bisceglia 1998), and the intestinal tract (e.g., with congenital jejunoileal atresia; Rosenmann et al. 1980).

Myoid Hamartomas of the Liver

In a first report of this rare lesion, the tumor was termed mesenchymal, predominantly leiomyomatous, differentiated hamartoma of the liver (Leipner et al. 1984). In a later observation, a similar tumor was observed in a 17-year-old male patient (Gornicka et al. 2004). This patient had presented with jaundice and light stools and was admitted with suspicion of Klatskin's tumor, irrespective of his young age. Imaging demonstrated a solid lesion about 3 cm in diameter, situated in liver segment IV, associated with widening of the hepatic ducts. Diagnosed with perihilar malignancy, the patient underwent right-sided hemihepatectomy. The resection specimen showed a single, vaguely delineated and unencapsulated solid hilar tumor of cream color, measuring $5 \times 3.5 \times 3$ cm. Histologically, the lesion consisted of elongated spindle-shaped cells with eosinophilic cytoplasm and long, blunt-ended nuclei. The cells were arranged in tight bundles intersecting focally. The nodule contained numerous bile ductules, sometimes associated with arterioles. The border of the lesion was ill defined, with blending into liver parenchyma and perifocal liver atrophy. Immunohistochemically, most of the spindle cells were markedly reactive for alpha-smooth muscle actin, whereas only few cells were CD34 and desmin positive. The proliferation activity, based on Ki67 staining, was less than 5 % (Gornicka et al. 2004).

Leiomyomatous Hemangiomas of the Liver

This unique lesion was described in an autopsy report (Key and Rao 1986). A 74-year-old man died of cardiac arrest secondary to severe coronary artery atherosclerosis. At necropsy, the cut surface of the liver (1530 g) revealed several white, solid tumors in both lobes. These nodules ranged in size from 0.3 to 0.6 cm in diameter and had a firm texture. Histologically, the tumors were well circumscribed and consisted of interlacing bundles of spindle-shaped cells. These cells had the appearance of smooth muscle cells with fusiform nuclei. Small areas of hemorrhage were present in some of the tumors, but there was no necrosis. Bile ducts could be identified within the tumor in some sections. Some of the lesions seemed to arise from smooth muscle of intrahepatic veins, as tumor cells blended with the veins' tunica media. In addition to these myoid tumors, the liver also contained two cavernous hemangiomas. Intramural leiomyomas were found in this patients in parts of the gastrointestinal tract, including the proximal jejunum and the prepyloric region of the stomach (Key and Rao 1986).

Hamartoma-Associated Smooth Muscle Tumors of the Liver

This term is based on the observation of two patients who had hepatic tumors of long duration interpreted as hamartomas in whom, after many years, widespread metastases of malignant smooth muscle cells developed in a pattern of "carcinomatous lymphangiosis" in the lungs. In one patient (59-year-old male), autopsy revealed several firm nodules in the liver, lobulated like hamartomas, composed of a hypocellular matrix that contained collagen, reticulin, and elastin. The lesions were calcified and partially ossified. The nodules containing atypical myoid cells invaded vessels and were of the same morphology as those forming the pulmonary and lymphonodal metastatic deposits. The smooth muscle cell lineage was defined by electron microscopy. This patient also showed hypertrophic pneumatic osteoarthropathy of bones of the ankles and wrists. The second patient (46-year-old female) showed a similar lesion pattern, with a large hamartoma-like tumor in the liver and numerous pulmonary myoid nodules interpreted as leiomyosarcomatosis (Echevarria et al. 1978).

Leiomyosarcoma of the Liver

ICD-O code 8890/3

Introduction

Leiomyosarcomas are an important group of malignant mesenchymal tumors that chiefly occur in the uterus, certain soft tissue regions, and gastrointestinal tract (reviews: Fletcher et al. 2002; Miettinen and Fetsch 2006). Primary hepatic leiomyosarcoma is a very rare tumor of the liver, accounting for less than 1 % of primary liver malignancies. As malignant neoplasms derived from smooth muscle cells, hepatic leiomyosarcoma may arise from intrahepatic vascular structures, bile ducts, or myoid cells located to the hepatic ligaments.

Epidemiology

Following early reports on spindle cell sarcomas observed in the liver, a long series of reports have documented to existence of primary leiomyosarcoma of the liver, although earlier reports could not prove the diagnosis by use of immunohistochemistry. Hepatic leiomyosarcoma is typically a neoplasm of aged patients, most of them being diagnosed in patients older than 60 years. There are very few cases of pediatric hepatic leiomyosarcoma; one tumor was found in an infant (Surendrababu et al. 2006) and few others in children with acquired immunodeficiency syndrome (Ross et al. 1992). One report from Lebanon described three cases of primary hepatic leiomyosarcoma with unusually young age distribution (i.e., 20, 30, and 39 years at presentation; Shamseddine et al. 2010). A 25-year-old male patient with hepatic leiomyosarcoma has been described (Iordanidis et al. 2002). There is no gender preference.

Selected References Watanuki and Kusama 1955; Robert et al. 1964; Yamaguchi 1968; Mel'nikov and Sukharev 1970; Wilson et al. 1971; Fong and Ruebner 1974; Fujioka et al. 1974; Masur et al. 1975; Yoshikawa et al. 1977; Bloustein 1978; Von Ebert 1978; Echevarria et al. 1978; O'Leary et al. 1982; Chen 1983; Kunieda et al. 1984; Morente et al. 1984; Carvajal-Dosamentes and Reyes 1986; Maki et al. 1987; Peng et al. 1987; Qifang et al. 1987; Shurbaji et al. 1987; Kinoshita et al. 1988; Principe et al. 1988; Shimo et al. 1989; Spagliardi et al. 1990; Ischii et al. 1991; Korbi et al. 1991; Paraskevopoulos et al. 1991; Watanabe et al. 1991; Ohtomo et al. 1992; Pi 1992; Ross et al. 1992; Baur et al. 1993; Saint-Paul et al. 1993; Pinson et al. 1994; Smith et al. 1994; Dominguez Iglesias et al. 1995; Gandhi et al. 1995; Gates et al. 1995; Higuchi et al. 1995; Hiyama 1995; Soyer et al. 1995, 1996; Abdelli et al. 1996; Cioffi et al. 1996; Civardi et al. 1996; Ferrozzi et al. 1996; Holloway et al. 1996; Ahn et al. 1997; Ennoki et al. 1999; Péquignot et al. 1999; Tsuji et al. 2000; Nishiguchi et al. 2001; Baek et al. 2002;

Iordanidis et al. 2002; Lee et al. 2002, 2005; Linares Torres et al. 2002; Usandivaras 2002; Almogy et al. 2004; Maruta et al. 2004; Kwon et al. 2005; Sicaja et al. 2006; Jeong et al. 2008; Yu et al. 2008; Giuliante et al. 2009; Liang et al. 2009; Matthaei et al. 2009; Morris and Ghanta 2010; Shamseddine et al. 2010; Shivathirthan et al. 2011.

Clinical and Imaging Features

As other primary hepatic sarcomas, leiomyosarcomas of the liver present a clinical dilemma in so far as they are often asymptomatic until they become large, and even then they produce nonspecific symptoms (Gates et al. 1995; Yu et al. 2008). About half of the patients have abdominal pain and/or weight loss. In case of large and very large lesions, vomiting and jaundice may ensue. Most patients have no evidence of hepatitis or liver cirrhosis. Jaffe reported that hepatic neoplasms of mesenchymal origin were associated with cirrhosis in only 29 % of cases (Jaffe 1924). Some patients may show abnormal liver function tests, but serum AFP is consistently normal. Complications include acute bleeding and IVC obstruction (Jeong et al. 2008). Leiomyosarcoma of the liver was reported to mimic hepatic abscess (Gates et al. 1995). The tumor was found in conjunction with other tumors, including gastric lymphoma (Linares Torres et al. 2002) and von Recklinghausen's neurofibromatosis (Maruta et al. 2004). Hepatic leiomyosarcoma was identified together with cholangiocarcinoma in a liver showing thorotrastosis (Shurbaji et al. 1987).

Hepatic leiomyosarcoma has been found to metastasize within the liver (Baur et al. 1993; Tsuji et al. 2000; Kwon et al. 2005). Extrahepatic metastases have also been analyzed during autopsy (Von Ebert 1978) and have been reported for the hepatopancreatic and retroperitoneal locoregional lymph nodes, peritoneal seeding, lungs, pleura, skin, and kidneys. In case the tumor can be completely resected, the course may be favorable, with long-term survival described several times (Pinson et al. 1994; Poggio et al. 2000; Matthaei et al. 2009). As hepatic leiomyosarcoma tends to metastasize within the liver, early resection in low-stage disease is mandatory.

CT findings of primary hepatic leiomyosarcoma have been described as a large, well-defined, heterogeneous hypodensity mass with internal and peripheral enhancement or cystic mass with an enhancing thick wall. Large tumors may show a central markedly hypoattenuating area corresponding to tumor necrosis (Paraskevopoulos et al. 1991; Gandhi et al. 1995; Gates et al. 1995; Soyer et al. 1995; Ferrozzi et al. 1996; Fujita et al. 2002; Yu et al. 2008; Liang et al. 2009). Some tumors may show capsular retraction and internal small punctuate calcifications (Soyer et al. 1995). On contrast-enhanced CT scans, tumor enhancement is predominantly peripheral, but heterogeneous internal and peripheral enhancement and pseudocystic patterns may also occur. On T1-weighted images, the tumors are well defined and slightly heterogeneous, with hypointensity to the adjacent liver substance. T2-weighted images show heterogeneous, hyperintense lesions (Ohtomo et al. 1992; Soyer et al. 1996). In case of large central hemorrhage and necrosis, the presentation may mimic hemorrhagic hepatocarcinoma (Morris and Ghanta 2010). Angiography has revealed that the tumors are fed by vessels originating from the hepatic artery (Paraskevopoulos et al. 1991). Leiomyosarcoma was detected by high F-18 fluorodeoxyglucose positron emission tomographic uptake (Nishiguchi et al. 2001).

Macroscopic Pathology

Hepatic leiomyosarcomas are usually solitary nodular, nonencapsulated masses which are soft and hemorrhagic and may grow to large size, with reported diameters of 20 cm or even more (Fig. 5). The tumors are sharply delineated from the liver, with signs of perifocal liver atrophy. Large tumors may show central necrosis and hemorrhage.

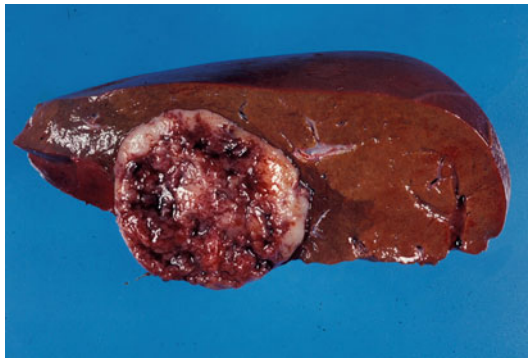

Fig. 5 Primary leiomyosarcoma of the liver. Large and friable tumor with marked hemorrhage and necrosis in a non-cirrhotic liver

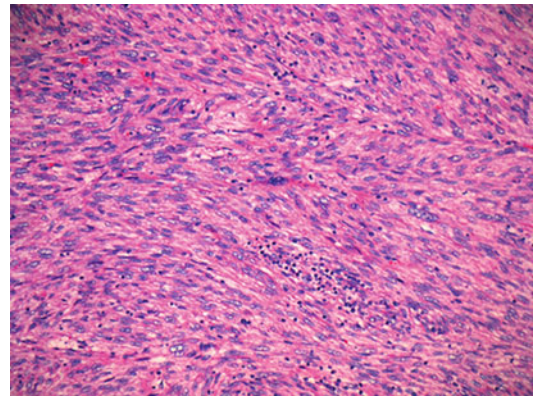

Fig. 6 Primary leiomyosarcoma of the liver (grade 3). The hypercellular tumor consists of abnormal smooth muscle cells with enlarged nuclei and shows focal necrosis with nuclear debris (hematoxylin and eosin stain)

Histopathology

The tumors exhibit a variable cellularity with little fibroblastic tissue and rather inconspicuous blood vessels. The cells are spindle shaped and arranged in fascicles. The cytoplasm is eosinophilic, pale, or clear, and the nuclei are typically blunt ended and elongated (Figs. 6 and 7). Nuclear pleomorphism varies from very slight to marked. The mitotic activity may be low (one per ten HPF), but it may undergo a significant increase in progressing tumors and in intrahepatic metastases (Baur et al. 1993). Apart from cellular and nuclear features, the most important criterion of diagnosing leiomyosarcoma appears to be the presence of mitotic figures, and the presence of one mitosis per two high-power fields is generally a marker for aggressiveness (Lee 1983). Primary hepatic leiomyosarcoma was diagnosed by use of fine-needle aspiration cytology (Smith et al. 1994). Ultrastructurally, the tumor cells contain myofilaments along with cytoplasmic dense bodies and marginal dense plaques, the more distinctive subcellular markers of smooth muscle cells. Mitochondria are sometimes numerous and diffusely distributed in the cell body (Bloustein 1978; Paraskevopoulos et al. 1991).

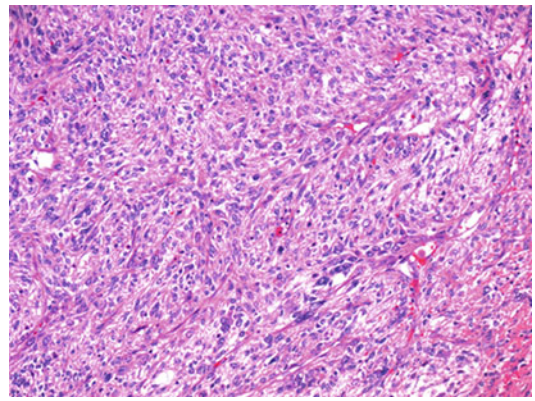

Fig. 7 Primary hepatic leiomyosarcoma (grade 3) with increased pleomorphic and a vague fascicular structure (hematoxylin and eosin stain)

Immunohistochemistry

The tumor cells are reactive for muscle-specific actin, alpha-SMA, desmin, and vimentin (Fig. 8; Watanabe et al. 1991; Saint-Paul et al. 1993; Dominguez Iglesias et al. 1995; Higuchi et al. 1995; Maruta et al. 2004; Sicaja et al. 2006). Smooth muscle tumors also express a unique pattern of gamma-smooth muscle isoactin gene expression (Brittingham et al. 1997). Desmin reactivity is seen in only part of the cases and in heterogeneous distribution in a given tumor, in one study involving only 20 % of the tumor cells (Korbi et al. 1991). The tumors also variably express SM1/SM2 myosin isoforms and non-muscle myosin. SM1/SM2 and

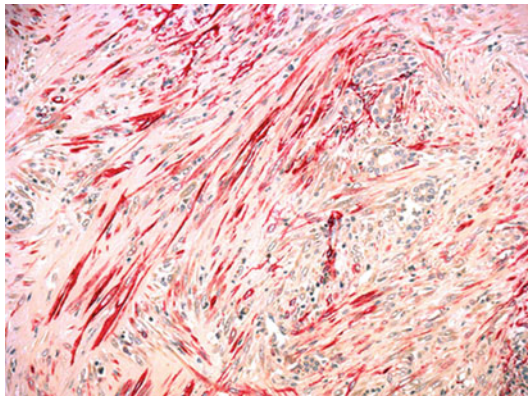

Fig. 8 Primary leiomyosarcoma of the liver. The atypical spindle cells express smooth muscle actin (alpha-SMA immunostain)

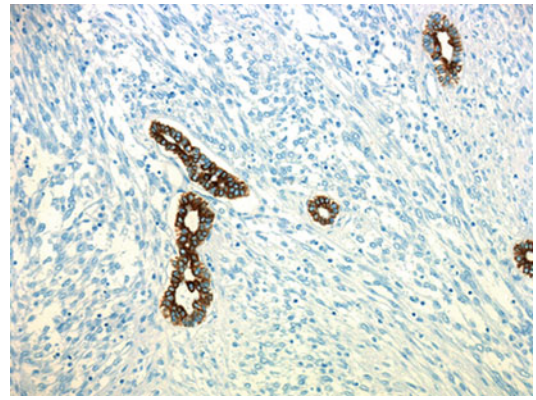

Fig. 9 Strongly invasive leiomyosarcoma of the liver with entrapment of small bile ducts (cytokeratin 19 immunostain)

non-muscle myosin expression pattern are not paralleled by different proliferation or apoptosis levels (Valenti et al. 1998). Smooth muscle cells and tumors derived thereof express h-caldesmon, which is a lineage marker for smooth myocytes (Watanabe et al. 1999, 2000). H-caldesmon is a protein which is combined with actin and tropomyosin and which is involved in contraction and cell motility. A novel marker that characterizes smooth muscle cell differentiation in sarcomas is transgelin (Robin et al. 2013). Leiomyosarcoma cells are markedly positive for p16, a finding which serves to distinguish this tumor from leiomyoma and its variants, where p16 staining is weak or lacking (Gannon et al. 2008; Hakverdi et al. 2011). In contrast to certain other sarcomas, leiomyosarcomas do not show nuclear p63 reactivity (Jo and Fletcher 2011). The highly invasive features of leiomyosarcoma with entrapment of small bile ducts can be visualized by cytokeratin immunostaining (Fig. 9). High-grade leiomyosarcomas exhibit an elevated proliferative activity as seen in MIB1 immunostains (Fig. 10).

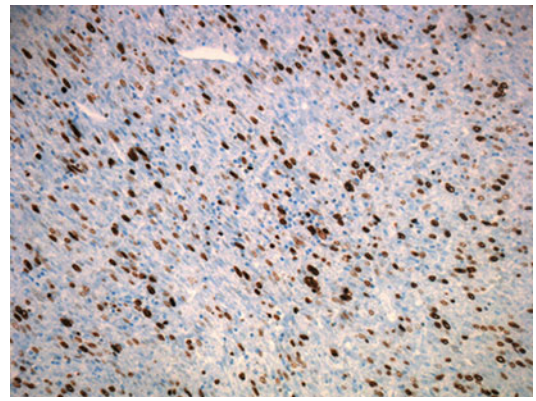

Fig. 10 High proliferative activity in grade 3 leiomyosarcoma of the liver (MIB1 immunostain)

Myxoid Leiomyosarcoma of the Liver

One variant of hepatic leiomyosarcoma is characterized by smooth muscle cells with a clear cytoplasm suspended in a myxoid stroma (hepatic myxoid leiomyosarcoma). Hepatic myxoid leiomyosarcoma was found in normal liver (Lee et al. 2002; Tsiatis et al. 2008) or in cirrhotic liver (Sicaja et al. 2006). Myxoid leiomyosarcoma had originally been described as a distinct subtype in the uterus (King et al. 1982). Subsequently, similar tumors were identified in extrauterine sites, including soft tissues, gastrointestinal tract, and vulva. The tumor diameters in the cases described ranged from 2.9 to 16 cm. Histologically, the spindled myocytes form interlacing bundles embedded in a rich, Alcian blue-positive myxoid matrix. The mitotic activity was reported to be low (one per ten HPFs; Sicaja et al. 2006). The clear aspect of the cytoplasm in one case was due to glycogen accumulation, as seen in electron microscopy (Sicaja et al. 2006). Immunohistochemically, the

tumor cells were positive for alpha-SMA and muscle-specific actin (HHF-35). In one case, strong and diffuse nuclear staining for estrogen receptor-b was observed (Tsiatis et al. 2008).

Epithelioid Leiomyosarcoma of the Liver

Epithelioid leiomyosarcoma is a rare subtype of malignant smooth muscle tumors. It has been reported as multiple primary lesion in the liver (Cioffi et al. 1996). The differentiation pathways of these neoplasms may be complex. For example, an oncocytic variant of primary epithelioid leiomyosarcoma of the liver has been reported (Delecluse et al. 1992).

Lipoleiomyosarcoma of the Liver

Lipoleiomyosarcoma (well-differentiated liposarcoma with leiomyosarcomatous differentiation) is a rare type of sarcoma that chiefly occurs in the retroperitoneal space, the paratesticular-inguinal region, the mediastinum, abdomen, and popliteal fossa. The tumor is histologically characterized by a multifocal, gradual transition of well-differentiated liposarcoma into smooth muscle areas (Folpe and Weiss 2002).

Inflammatory Leiomyosarcoma of the Liver

Inflammatory leiomyosarcoma denotes a leiomyosarcoma with a marked infiltration of lymphocytes, macrophages, and sometimes plasma cells. In one case, it was characterized by specific near-haploid chromosome changes (Dal Ci et al. 1998).

Hamartomatous Leiomyosarcoma of the Liver

This is an unusual lesion which has been described based on two patients (Echevarria et al. 1978). In the livers, lobulated nodules with a mesenchymal hamartoma-like configuration were found, histologically characterized by a hypocellular hyaline matrix with focal calcifications and ossifications. Atypical cells were embedded in the matrix, and at the periphery of the nodules, vascular proliferations and proliferated bile ducts were in evidence. Progression of the process was characterized by metastatic spread in the lungs and mediastinal lymph nodes of a cell lineage ultrastructurally showing the features of smooth muscle cells.

Leiomyosarcoma of the Bile Ducts

Introduction

Primary leiomyosarcomas of the biliary tract are very rare neoplasms that have been observed in the common bile duct (Schuppler 1934; Whitcomb et al. 1967; Jin et al. 1990), the ampullary region (Nitshe and Suckle 1947), and the duodenal papilla (Kefalas et al. 2004).

Pathology

There are few published pathology findings. In a 62-year-old female patient suffering from obstructive jaundice, surgical intervention showed that the proximal portion of the common bile duct was markedly dilated to a diameter of 5 cm and contained a solid green, fleshy, outwardly avascular tumor which extended into the right and left hepatic ducts and was attached to the wall of the common hepatic duct (Whitcomb et al. 1967).

In the case reported by Whitcomb et al. (1967), the tumor showed a well-vascularized tissue characterized by palisading and interlacing bundles of spindle-shaped cells with blunt-ended nuclei, reminiscent of abnormal smooth muscle cells. There was considerable cellular and nuclear polymorphism throughout the tumor, with many bizarre and occasionally multinucleated anaplastic cells. Abnormal mitoses were numerous and varied from two to eight per HPF (Whitcomb et al. 1967).

Differential Diagnosis

The histology of well-differentiated leiomyosarcoma may be confounded with leiomyoma of the bile ducts (Mandeville and Stawski 1991; Yamaoka et al. 1993; Saito 1996). Leiomyosarcoma enters the differential diagnosis of other spindle cell tumors occurring in the biliary tract (Yuan et al. 1995), including rhabdomyosarcoma of the adult (Aldabagh et al. 1986). Visceral leiomyosarcoma may metastasize to the extrahepatic bile ducts (e.g., leiomyosarcoma of the pancreas; Del Gallo et al. 1997). Based on biopsy sampling effects, the spindle cell-myoid component of biliary tract carcinosarcoma (Loud et al. 1997; Yoon and Choi 2004) may be misinterpreted.

Leiomyosarcoma of the Porta Hepatis

This is a rare primary location of this tumor and has been described as a hypervascular tumor (Balthazar 1981).

Leiomyosarcoma of the Hepatic Ligaments

Malignant mesenchymal tumors primary to the hepatic ligaments are very rare tumors. Leiomyosarcoma was observed in both the ligamentum falciforme (Morita et al. 1987) and the ligamentum teres hepatis (Mital and Bazaz-Malik 1971; Adachi et al. 1979; Yamaguchi et al. 1996). In sarcoma originating in the falciform ligament, supply of the tumor by the hepatic falciform artery has been demonstrated (Morita et al. 1987).

Differential Diagnosis

The most important differential diagnosis is certainly liver metastasis of primary extrahepatic leiomyosarcoma (Bowden and Murphy 1955; Kershner 1969; Soyer et al. 1997; Lang et al. 2000). The majority of the tumors have their primary site mostly in the viscera (Chen et al. 1998). In a series of 65 patients with hepatic sarcoma metastases, 61 patients had an intra-abdominal primary site, with 85 % being high-grade leiomyosarcomas (Jacques et al. 1995).

In a study of 34 patients undergoing hepatic resection for metastatic leiomyosarcoma, the site of the primary tumor was the stomach (31 %), small bowel (15 %), vena cava (4 %), kidney (4 %), colon (4 %), upper abdomen (19 %), and retroperitoneum (19 %) (Lang et al. 2000). Among 331 patients who had hepatic resection for sarcoma metastatic to liver, 61 % had gastrointestinal stromal tumors or leiomyosarcomas of the GI tract (DeMatteo et al. 2001). In contrast, metastatic leiomyosarcomas originating in the uterus are much rarer (Rose et al. 1989; Jacques et al. 1995; Soyer et al. 1997; Pawlik et al. 2006; Kuwahara et al. 2011; Lorenzo-Zuniga et al. 2011). In the study of 65 cases reported by Jacques et al. (1995), only one gynecologic primary tumor was found. The primary tumor may be situated close to the liver, e.g., the pancreas (Nobili et al. 2010), greater omentum (Koga et al. 2002), or the inferior vena cava (Hashimoto et al. 2012). Leiomyosarcomas metastatic to the liver differ from primary tumors on CT imaging. They are commonly large and circumscribed so-called cannonball lesions that distort the normal hepatic architecture. The larger metastases are still sharply defined and often show a central necrosis and are accentuated by contrast enhancement of normal surrounding liver. Smaller perfused metastases often become isodense following contrast medium administration (Noon et al. 1980). On MR images, a hemangioma-like pattern was the most common feature on T2-weighted images (Soyer et al. 1997). Leiomyosarcoma of the inferior vena cava, a well-known entity, may invade or metastasize into the liver (Huguet et al. 1992; Thompson et al. 1993; Hashimoto et al. 2012). Also retroperitoneal leiomyosarcoma situated behind the liver has been confounded with a primary liver tumor (Wada et al. 1994). A second group of tumors that enter differential diagnosis are EBV-associated hepatic smooth muscle tumors, which are discussed in another chapter. Leiomyosarcoma

can occur as a primary lesion in the gallbladder (Kumar et al. 1993; Tocchi et al. 1993; Danikas et al. 2001). Primary or secondary GIST of the liver and other non-myoid hepatic spindle cell tumors may be confounded with leiomyosarcoma, correct diagnosis requiring immunohistochemistry. Kit analysis serves to distinguish GIST from other spindle cell tumors. However, up to 5 % of GISTs can be completely negative for Kit on immunohistochemistry. Conversely, leiomyosarcomas may rarely express Kit, but are virtually never associated with an activating Kit mutation (Trent et al. 2007). Rarely, primary carcinosarcomas of the liver may contain a leiomyosarcomatous component, which may dominate the pattern in a needle biopsy.

Leiomyosarcoma of the Inferior Vena Cava and the Hepatic Veins

Introduction

Leiomyosarcoma of the inferior vena cava with or without involvement of associated veins is a rare neoplasm arising from smooth muscle cells of the venous wall; it represents only 0.5 % of all adult soft tissue sarcomas (Hollenbeck et al. 2003). However, the inferior vena cava is the most common site of origin for venous leiomyosarcomas, followed by major veins of the extremities.

Clinical and Imaging Features

The original description of a primary leiomyosarcoma of the inferior vena cava was published in 1871 (Perl 1871). Since then, numerous cases have been reported, either being restricted to distinct segments of the caval vein or concomitantly involving its large associated veins (Hallock et al. 1940; Deutsch et al. 1968; Wray and Dawkins 1971; Parrilla et al. 1992; Hollenbeck et al 2003; Dew et al. 2005; Hardwigsen et al. 2005; Sokolich et al. 2008; Krüger et al. 2010; Laskin et al. 2010; Sessa et al. 2010; Huang et al. 2011; Ulla et al. 2011). Leiomyosarcoma of the inferior vena cava occurs in patients usually older than 40 years; in a study of 25 patients, the age range was 41–79 years, with a median age of 56 years (Hollenbeck et al. 2003). The tumor may involve the hepatic veins and the renal vein confluences, sometimes combined (Lygidakis et al. 2007; Spinelli et al. 2008). Rarely, the process involves the infrarenal or the suprahepatic segments of the caval vein (Dew et al. 2005; Delis et al. 2008; Tameo et al. 2010). But caval leiomyosarcoma is most common in the retrohepatic portion of the inferior vena cava, between the renal and hepatic veins (Kulaylat et al. 1997; Mingoli et al. 1997; Hardwigsen et al. 2005). This is a complex and distinct localization for this malignancy, with a characteristic clinical presentation and biology of disease (Praseedom et al. 2007). Generally, the signs and symptoms are so nonspecific and mainly comprise abdominal pain and sometimes a flank mass (Wray and Dawkins 1971; Hardwigsen et al. 2005), but tumors encroaching upon the liver may mimic a primary hepatic tumor (Sokolich et al. 2008). In markedly symptomatic tumors, the initial presentation is dominated by inferior vena cava syndrome, Budd-Chiari syndrome, and thrombosis (Pollanen et al. 1987; Arraztoa et al. 1994; Mingoli et al. 1997).

Budd-Chiari syndrome, characterized by rapidly evolving hepatomegaly, jaundice and ascites, has a poor prognosis. The first case of leiomyosarcoma of the IVC associated with Budd-Chiari syndrome was reported in 1940 already (Hallock et al. 1940). Since then, there have been many further cases reported in the literature. Tumors in this compartment sometimes exhibit distinct and clinically important growth patterns. Leiomyosarcoma of the retrohepatic portion of the vena cava has been shown to grow through the venous wall and to infiltrate the right liver lobe (Huguet et al. 1992) or extend into the right atrium (Deutsch et al. 1968; Thompson et al. 1993; Fonseca et al. 2002), sometimes with dominant obstruction of the tricuspid valve (Hoffbrand and Lloyd-Thomas 1964). This can cause sudden death from pulmonary tumor embolization (Gowda et al. 2004). Primary embolization of caval leiomyosarcoma into the pulmonary artery has also been reported (Krüger et al. 2010).

In case of expanding growth, the tumor may displace segment I of the liver, mimicking a hepatic tumor (Schwarzbach et al. 1997).

Previously, 44 % of the cases have not been diagnosed until at autopsy and 50 % not until surgery (Chauhan et al. 1981). But recent advances in imaging techniques have enabled a more accurate diagnosis prior to surgical resection (Peh et al. 1993; Sessa et al. 2010; Huang et al. 2011), including direct-MDCT cavography where the injection of contrast agent through both lower limbs achieves maximum enhancement of the inferior vena cava (Ulla et al. 2011).

Apart from acute complications such as those related to Budd-Chiari syndrome, atrial involvement, and embolism, the biology of disease is positively influenced by combined surgical and chemotherapeutic therapies (Mingoli et al. 1997; Hollenbeck et al. 2003; Dew et al. 2005; Reges et al. 2008). As many of the tumors are large or very large at diagnosis, the lesions are often unresectable. The liver and the lungs are most often involved in hematogenous metastatic dissemination (Pollanen et al. 1987; Sokolich et al. 2008). Mingoli and coworkers (1997) reported that, up to August 1994, 218 patients were enrolled into The International Registry of Inferior Vena Cava Leiomyosarcomas. Among 120 patients where radical resection of the IVC tumor was performed, tumor recurrence was observed in 57.3 % at a mean follow-up of 32 ± 4 months, with a 5-year survival rate of 55 % (caval wall resection) and 37 % (caval segmental resection). These findings were largely confirmed in later investigations. In a study of 25 patients, 84 % underwent complete resection of the tumor; local recurrence occurred in 33 % and distant recurrence in 48 % of patients. Patients with complete resection had 3-year and 5-year disease-free specific survival rates of 76 % and 33 %, respectively (Hollenbeck et al. 2003). In a report on the experience with 22 patients, the 3-and 5-year mean actuarial survival rates in patients who underwent resection were 52.0 % and 34.8 %, respectively. Eleven patients died after a mean follow-up period of 43.7 months due to local recurrence and/or distant metastasis in nine cases and complications of chemotherapy in two (Kieffer et al. 2006). In a recent study of 40 patients, the 5-year and 10-year survival rates after resection without documented residual macroscopic disease were 50 % and 22 %, respectively. Suprahepatic vena caval and right atrial involvement by tumor, predominant intraluminal tumor growth, and residual postsurgical macroscopic disease were factors that correlated with death within 2 years. By univariate analysis, intraluminal tumor, compromised liver, and moderate to poor tumor differentiation were associated with increased tumor-related mortality, whereas a compromised liver (liver injury or failure) was the only factor correlated with mortality by multivariate analysis (Laskin et al. 2010).

The biology of leiomyosarcoma of the inferior vena cava is difficult to predict, as some tumors grow slowly within the luminal space of the vein, sometimes with nonspecific signs and symptoms of ten or more years' duration (Rosch et al. 2002). The difficulty in estimating biology of disease was mainly based on the small case series, until many patients could be evaluated in the context of The International Registry of Inferior Vena Cava (IVC) Leiomyosarcomas, established in 1992 (Mingoli et al. 1996). There is evidence that the prognosis after complete resection likely depends on the histologic features of the primary tumor. Factors such as tumor differentiation, mitotic index, and tumor size affect long-term prognosis. In a detailed description of vascular leiomyosarcomas, it was concluded that the mitotic index was the most important pathological feature on which a prognostic evaluation for a vascular leiomyosarcoma could be the bases. Patients with a mitotic index greater than 35/10 HPFs had a poor prognosis (Varela-Duran et al. 1979).

Pathology

Leiomyosarcoma of the inferior vena cava can grow to large size. In a study of 40 cases, the tumors ranged in size from 3.5 to 15.0 cm (median: 8.5 cm), and most involved the middle segment of the vessel and grew extraluminally (Laskin et al. 2010). The nodular masses can

grow into the hepatic vein inlets. In case of Budd-Chiari syndrome, the sometimes necrotic intraluminal tumors are associated with thrombotic material attached to the neoplastic nodules. Retrohepatic tumors can invade the venous wall and infiltrate the posterior part of the liver. In such situations, a primary liver malignancy with secondary involvement of the caval vein may be suspected macroscopically.

The sarcomas show a proliferation of atypical smooth muscle cells with increased grades of nuclear atypia and presence of mitotic figures. In a series of 40 patients, tumor grade was grade I in 11, grade II in 21, and grade III in 5 patients (Laskin et al. 2010). Caval leiomyosarcoma has been diagnosed by intraluminal biopsy (Shimoda et al. 1998), fine-needle aspiration cytology (Al-Rikabi et al. 2007), or endoscopic ultrasound-guided fine-needle aspiration biopsy (Jenssen et al. 2008).

Differential Diagnosis

Metastatic leiomyosarcoma may encroach upon the hepatic veins and induce a Budd-Chiari-like syndrome (Fortner et al. 1977).

Leiomyosarcoma of the Portal Vein and Its Tributaries

Introduction

Leiomyosarcomas originating from a vein wall are rare lesions. In the liver-related venous system, most of these neoplasms arise in the retrohepatic part of the inferior vena cava and the hepatic veins, whereas leiomyosarcoma of the portal venous system is a much more exceptional finding. The reason of this striking difference is currently unknown.

Clinical and Imaging Findings

Leiomyosarcoma primary to the portal vein is a rare cause of portal vein block (Wilson and Hine 1987; Sundaresan et al. 1990; Madariaga et al. 1995). The venous block causes portal hypertension with extensive collateral circulation and congestive splenomegaly (Madariaga et al. 1995). CT imaging shows well-defined heterogeneously enhancing solid masses, sometimes with areas of hypoattenuation representing cystic or necrotic changes. In contrast to benign thrombosis of the portal vein, which is associated with a moderate vessel enlargement at sonography (Van Gansbeke et al. 1985), involvement of the vein by a malignant tumor causes a marked and sometimes tremendous enlargement of the caliber of the vein (Wilson and Hine 1987). The vascular primary tumor may spread to the liver substance, with formation of intrahepatic metastases (Sundaresan et al. 1990). Leiomyosarcoma may also develop in the wall of large veins draining into the portal vein, specifically the superior mesenteric vein (Goldin et al. 2002).

Pathology

Leiomyosarcoma of the portal vein can grow to very large size. In one case, the resected tumor was 30 cm in diameter and weighed 1880 g (Sundaresan et al. 1990). Macroscopically, the tumor is similar to leiomyosarcomas of other locations, with an expanding growth pattern, a bosselated surface, and a cut surface with a whorled appearance. Histologically, the neoplasm consists of interlacing fascicles of eosinophilic spindle cells with elongated, blunt-ended nuclei. Usually, there are marked nuclear pleomorphism and numerous mitotic figures, the mitotic index sometimes exceeding 30/10 HPFs (Sundaresan et al. 1990).

Differential Diagnosis

Among tumor-induced portal vein block, hepatocellular carcinoma is the most common event (Mathieu et al. 1984). Extrahepatic tumorous portal vein obstruction has been shown to be caused by a wide array of malignancies, e.g., gastric and pancreatic carcinomas, Hodgkin's disease, and

malignant non-Hodgkin lymphomas. Gastric leiomyosarcoma can involve and block the extrahepatic portion of the vein (Sharma et al. 1996).

Leiomyosarcomatosis

Multicentric leiomyosarcomatosis is a very rare disorder that may involve both intra-abdominal and extra-abdominal organs (Case et al. 1973; Akata et al. 1999). Diffuse leiomyosarcomatosis has been noted in the gastrointestinal tract, with numerous tumors in the colon, stomach, or the entire GI tract from the stomach to the jejunum or even to the colon (Korman et al. 1997).

The liver may be involved in this complex process. In one reported patient, synchronous leiomyosarcoma nodules not considered to be metastatic deposits were observed in the gastrointestinal tract, liver, lungs, diaphragm, parathyroid gland, bone marrow of the vertebrae, and subcutaneous tissue (Fridie et al. 1992). Tumor manifestations in the ligamentum teres have been found in another patient with widespread organ involvement, again with tumors also in the bones (Akata et al. 1999).

Oncocytic Smooth Muscle Tumors

There are very few reports of malignant epithelioid smooth muscle tumors of the uterus and gastrointestinal tract showing oncocytic cell change (Nance and Reddick 1987; Nguyen et al. 2001). A primary and large hepatic epithelioid leiomyosarcoma treated by liver transplantation showed extensive oncocytic change, this feature having first led to the suspicion of a neuroendocrine tumor (Delecluse et al. 1992).

References

Abdelli N, Thiefin G, Diebold MD, Bouche O, Aucouturier JP, Zeitoun P (1996) Primary leiomyosarcoma of the liver 37 years after successful treatment of hereditary retinoblastoma (in French). Gastroenterol Clin Biol 20:502–505

Abdullaeva DA (1951) Leiomyoma of the inferior vena cava (in Russian). Arkh Patol 13:79–81

Adachi M, Sugita T, Maehara M, Sugaya H, Ihori M, Hisauchi T, Harada T, Kogure H, Tajima Y (1979) A case report of leiomyosarcoma originating in the ligamentum teres of the liver. Gastroenterol Jpn 14:238–242

Ahn HJ, Lee JH, Lee JK et al (1997) A case of primary leiomyosarcoma of the liver. Korean J Gastroenterol 31:691–695

Akata D, Aralasmak A, Ozmen MN, Akhan O, Altundag K, Güllü I (1999) US and CT findings of multicentric leiomyosarcomatosis. Eur Radiol 9:711–714

Aldabagh SM, Shibata CS, Taxy JB (1986) Rhabdomyosarcoma of the common bile duct in an adult. Arch Pathol Lab Med 110:547–550

Almogy G, Lieberman S, Gips M, Pappo O, Edden Y, Jurim O, Simon Slasky B, Uzieli B, Eid A (2004) Clinical outcomes of surgical resections for primary liver sarcoma in adults; results from a single centre. Eur J Surg Oncol 30:421–427

Al-Rikabi A, Hussain AA, Buchler M, Al-Muzrakchi A, Jyothi CR (2007) Primary leiomyosarcoma of the inferior vena cava: report of a case diagnosed by fine needle aspiration cytology and confirmed by histopathologic examination. Acta Cytol 51:477–479

Archambault H, Archambault R (1952) Leiomyoma of the common bile duct. Arch Surg 64:531–534

Arey LB (1963) Human histology, 2nd edn. W.B. Saunders, Philadelphia

Arif S, Ganesan R, Spooner D (2006) Intravascular leiomyomatosis and benign metastasizing leiomyoma: an unusual case. Int J Gynecol Cancer 16:1448–1450

Arraztoa J, Oddo D, Trujillo C, San Martin S, Veloso L (1994) Leiomyo-sarcoma of the inferior vena cava. Presentation of 1 case of autopsy and review of the literature (in Spanish). Rev Med Chil 122:82–87

Baek I, Kim JH, Lee MS, Baik GH, Hahn T, Park HJ, Park SH, Chang WK, Kim WJ, Park CK (2002) A case of primary leiomyosarcoma of the liver (in Korean). Taehan Kan Hakhoe Chi 8:481–485

Bahary CM, Gorodeski IG, Nilly M, Neri A, Avidor I, Garti IJ (1982) Intravascular leiomyomatosis. Obstet Gynecol 59(6 Suppl):73S

Balthazar EJ (1981) Gastrointestinal leiomyosarcoma – unusual sites: esophagus, colon and porta hepatis. Gastrointest Radiol 6:295–303

Bartoli S, Alo P, Leporelli P, Puce E, Di Tondo U, Thau A (1991) Primary hepatic leiomyoma (in Italian). Minerva Chir 46:777–779

Baur M, Potzi R, Lochs H, Neuhold N, Walgram M, Gangl A (1993) Primary leiomyosarcoma of the liver – a case report. Z Gastroenterol 31:20–23

Bayar S, Düsünceli E, Heper AO, Güner R, Genç V, Demirkazik A (2010) Myoid hamartoma of the breast: a very rare entity. Breast J 16:86–88

Beissert M, Kenn W, Schultz G, Keberle M, Eck M, Hahn D (2002) Hepatic angiomyoma: CT and MRI findings. Abdom Imaging 27:40–42

Belli G, Ciciliano F, Lannelli A, Marano I (2001) Hepatic resection for primary giant leiomyoma of the liver, vol 3. HPB, Oxford, pp 11–12

Bertrand P, Amabile P, Hardwigsen J, Campan P, Le Treut YP (1998) Intravenous leiomyomatosis with caval involvement: report of a case with radical resection and venous replacement. Arch Surg 133:460–462

Beuzen F, Roudie J, Moali I, Maitre S, Barthelemy P, Smadja C (2004) Primary leiomyoma of the liver: a rare benign tumor (in French). Gastroenterol Clin Biol 28:1169–1172

Bianchi C, Comino A (1989) Vascular leiomyoblastoma of the liver. A personal case (in Italian). Minerva Med 80:495–496

Bloom W, Fawcett DW (1962) A textbook of histology, 8th edn. W.B. Saunders, Philadelphia

Bloustein PA (1978) Hepatic leiomyosarcoma: ultrastructural study and review of the differential diagnosis. Hum Pathol 9:713–715

Bowden L, Murphy AI (1955) Right hepatic lobectomy: report of a case complicated by postoperative homologous serum hepatitis. Gastroenterology 28:288

Brescia RJ, Tazelaar HD, Hobbs J, Miller AW (1989) Intravascular lipoleiomyomatosis: a report of two cases. Hum Pathol 20:252–256

Brichard B, Smets F, Sokal E, Clapuyt P, Vermylen C, Cornu G, Rahier J, Otte JB (2001) Unusual evolution of an Epstein-Barr virus-associated leiomyosarcoma occurring after liver transplantation. Pediatr Transpl 5:365–369

Brittingham J, Liaw D, Liddell R, McHugh M, McCue P, McHugh KM (1997) Comparative analysis of smooth muscle isoactin gene expression in normal and neoplastic tissues. Pathobiology 65:113–122

Burden VG (1925) Observations on the histologic and pathologic anatomy of the hepatic, cystic and common bile ducts. Ann Surg 82:584

Burnett W, Gairns FW, Bacsich P (1964) Some observations on innervation of the extrahepatic biliary system in man. Ann Surg 159:8

Carvajal-Dosamentes A, Reyes E (1986) Hepatic leiomyosarcoma. Report of 2 cases (in Spanish). Rev Invest Clin 38:193–197

Case TC, Gianelli S, Conkin EF, Camer S (1973) Disseminated leiomyosarcomatosis: case report. J Am Geriatr Soc 21:92–96

Chauhan MA, Smith PL, Ferris EJ, Murphy K, Westbrook K, Slayden JE (1981) Leiomyosarcoma of the inferior vena cava: angiographic and computed tomography findings. Report of two cases and review of imaging criteria. Cardiovasc Intervent Radiol 4:209–214

Chen KT (1983) Hepatic leiomyosarcoma. J Surg Oncol 24:325–328

Chen H, Pruitt A, Nicol TL, Gorgulu S, Choti MA (1998) Complete hepatic resection of metastases from leiomyosarcoma prolongs survival. J Gastrointest Surg 2:151–155

Cheuk W, Li PC, Chan JK (2002) Epstein-Barr virus-associated smooth muscle tumour: a distinctive mesenchymal tumour of immunocompromised individuals. Pathology 34:245–249

Choi HS, Jung CW, Cho SY, Kim SB, Park S (2014) Primary myxoid leiomyoma of the liver. Korean J Pathol 48:54–57

Cioffi U, Quattrone P, De Simone M, Bonavina L, Segalin A, Masini T, Montorsi M (1996) Primary multiple epithelioid leiomyosarcoma of the liver. Hepatogastroenterology 43:1603–1605

Civardi G, Cavanna L, Iovine E, Buscarini E, Vallisa D, Buscarini L (1996) Diagnostic imaging of primary hepatic leiomyosarcoma: a case report. Ital J Gastroenterol 28:98–101

Clarke D, Currie E, Madhayan K, Parks R, Garden O (2004) Hepatic resection for benign non-cystic liver lesions. HPB (Oxford) 6:115–119

Clement PB, Young RH, Scully RE (1988) Intravenous leiomyomatosis of the uterus. A clinicopathological analysis of 16 cases with unusual histologic features. Am J Surg Pathol 12:932–945

Collins MH, Montone KT, Leahey AM, Hodinka RL, Salhany KE, Clark BJ, Duhaime AC, Spray TL, Tomaszewski JE (2001) Metachronous Epstein-Barr virus-related smooth muscle tumors in a child after heart transplantation: case report and review of the literature. J Pediatr Surg 36:1452–1455

Cruickshank DB, Harrison GK (1953) Diffuse fibroleiomyomatous hamartosis of the lung. Thorax 8:316–318

Dal Cin P, Sciot P, Fletcher CD, Samson I, De Vos R, Mandahl N, Willén H, Larsson O, Van den Berghe H (1998) Inflammatory leiomyosarcoma may be characterized by specific near-haploid chromosome changes. J Pathol 185:112–115

Dal Cin P, Quade BJ, Neskey DM, Kleinman MS, Weremowicz S, Morton CC (2003) Intravenous leiomyomatosis is characterized by a der(14)t(12;14)(q15;q24). Genes Chromosomes Cancer 36:205–206

Daniels BT, McGlone FB, Job H, Sawyer RB (1961) Changing concepts of common bile duct anatomy and physiology. JAMA 178:394

Danikas D, Theodorou SJ, Singh R, Camal DE (2001) Leiomyosarcoma of the gallbladder: a case report. Am Surg 67:873–874

Davidoff AM, Hebra A, Clark BJ, Tomaszewski JE, Montone KT, Ruchelli E, Lau HT (1996) Epstein-Barr virus-associated hepatic smooth muscle neoplasm in a cardiac transplant recipient. Transplantation 61:515–517

Del Gallo G, Scotté M, Goria O, Hémet J, Michot F, Ténière P (1997) Bile duct metastasis of pancreatic leiomyosarcoma (in French). Gastroenterol Clin Biol 21:233–234

Delecluse HJ, Berger G, Vauzelle JL, Berger F (1992) Oncocytic presentation of a primary epithelioid leiomyosarcoma of the liver (in French). Ann Pathol 12:109–113

Delis S, Triantopoulou C, Bakoyiannis A, Tassopoulos N, Dervenis C (2008) Leiomyosarcoma of the infrarenal portion of the inferior vena cava in a cirrhotic patient with hepatitis C. Abdom Imaging 33:222–224

DeMatteo RP, Shah A, Fong Y, Jarnagin WR, Blumgart LH, Brennan MF (2001) Results of hepatic resection for sarcoma metastatic to liver. Ann Surg 234:540–547

Demel R (1926) Ein operierter Fall von Lebermyom (An operated case of hepatic myoma). Virchows Arch 261:881–884

Demirkiran F, Sal V, Kaya U, Alhan C, Tokgozoglu N (2013) Intravenous leiomyoma with extension to the heart: a case report and review of the literature. Case Rep Obstet Gynecol 2013:602407

Deutsch V, Fraenkel O, Frand U, Hulu N (1968) Leiomyosarcoma of the inferior vena cava propagating into the right atrium. Br Heart J 30:571–574

Dew J, Hansen K, Hammon J, McCoy T, Levine EA, Shen P (2005) Leiomyosarcoma of the inferior vena cava: surgical management and clinical results. Ann Surg 71:497–501

Deyrup AT (2008) Epstein-Barr virus-associated epithelial and mesenchymal neoplasms. Hum Pathol 39:473–483

Deyrup AT, Lee VK, Hill CE, Cheuk W, Toh HC, Kesavan S, Chan EW, Weiss SW (2006) Epstein-Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events: a clinicopathologic and molecular analysis of 29 tumors from 19 patients. Am J Surg Pathol 30:75–82

Dominguez Iglesias F, Riera Velasco JR, Junco Petrement P, Calleja Iglesias M, Dias-Faes Cervero M (1995) Primary leiomyosarcoma of the liver (in Spanish). Rev Esp Enferm Dig 87:163–167

Doyle H, Tzakis AG, Yunis E, Starzl TE (1991) Smooth muscle tumor arising de novo in a liver allograft: a case report. Clin Transplant 5:60–62

Dunlap HJ, Udjus K (1990) Atypical leiomyoma arising in an hepatic vein with extension into the inferior vena cava and right atrium. Report of a case in a child. Pediatr Radiol 20:202–203

Ebert et al. 1978. http://www.ncbi.nlm.nih.gov/pubmed/716654

Echevarria RA, Arean VM, Galindo L (1978) Hepatic tumors of long duration with eventual metastases. Two cases of leiomyosarcomatosis possibly arising from hamartomas of liver. Am J Clin Pathol 69:624–631

Ennoki T, Hayashi D, Inokuchi T et al (1999) Combined right hepatic and retrohepatic caval resection with reconstruction using a polytetrafluoroethylene graft for primary leiomyosarcoma of the liver: report of a case. Surg Today 29:485–497

Ferrozzi F, Bova D, Zangrandi A, Garlaschi G (1996) Primary liver leiomyosarcoma: CT appearance. Abdom Imaging 21:157–160

Fletcher CDM, Unni KK, Mertends F (eds) (2002) WHO classification of tumours; pathology and genetics: tumours of soft tissue and bone. IARC Press, Lyon

Folpe AL, Weiss SW (2002) Lipoleiomyosarcoma (well-differentiated liposarcoma with leiomyosarcomatous differentiation): a clinicopathologic study of nine cases including one with dedifferentiation. Am J Surg Pathol 26:742–749

Fong JA, Ruebner BH (1974) Primary leiomyosarcoma of the liver. Hum Pathol 5:115–119

Fonseca N, Silvestre I, Bernardino L, Augusto F, Ferreira M, Nogueira A, Canada A et al (2002) Leiomyosarcoma of the inferior vena cava – a very rare case report. Rev Port Cardiol 21:1469–1478

Fortner et al. 1977. http://www.ncbi.nlm.nih.gov/pubmed/193461

Fridie IL, Hong IS, Green WR (1992) Multicentric gastrointestinal and extraintestinal leiomyosarcomatosis: a case report. J Natl Med Assoc 84:629–631

Fujioka Y, Inoue K, Oikawa I et al (1974) Autopsy case of hepatic tumor with interesting morphological findings. Hokkaido Igaku Zasshi 49:75–77

Fujita H, Kiriyama M, Kawamura T, Ii T, Takegawa S, Dohba S, Kojima Y, Yoshimura M, Kobayashi A et al (2002) Primary hepatic leiomyosarcoma in a woman after renal transplantation: report of a case. Surg Today 32:446–449

Gallien S, Zuber B, Polivka M, Lagrange-Xelot M, Thiebault JB, Bertheau P, Gray F, Molina JM (2008) Multifocal Epstein-Barr virus-associated smooth muscle tumor in adults with AIDS: case report and review of the literature. Oncology 74:167–176

Gandhi MR, Wong DC, Wood DJ (1995) Ultrasound and computed tomography appearances of primary hepatic leiomyosarcoma. Australas Radiol 39:289–291

Gannon BR, Manduch M, Childs TJ (2008) Differential immunoreactivity of p16 in leiomyosarcomas and leiomyoma variants. Int J Gynecol Pathol 27:68–73

Garcia Rinaldi R, Pérez Hernandez J, Corbala AR, Aponte HR, Dayan V, Plaza M (2007) Surgical treatment of multiple intracardiac and pulmonary artery tumor implants embolic from uterine intravascular leiomyomatosis. Bol Asoc Med PR 99:51–55

Gates LK, Cameron AJ, Nagorney DM, Goellner JR, Farley DR (1995) Primary leiomyosarcoma of the liver mimicking liver abscess. Am J Gastroenterol 90:649–652

Giuliante F, Sarno G, Ardito F, Pierconti F (2009) Primary hepatic leiomyosarcoma in a young man after Hodgkin's disease: diagnostic pitfalls and therapeutic challenge. Tumori 95:374–377

Goldin SB, Webb TH, Lillemoe KD (2002) Leiomyosarcoma arising from the superior mesenteric vein. Surgery 132:108–109

Goo JC, Yi MY, Jeon WJ, Seo JC, Chae HB, Park SM, Youn SJ, Kim SH, Choi JW (2006) A case of leiomyoma in the common bile duct (in Korean). Korean J Gastroenterol 47:77–81

Gornicka B, Ziarkiewicz-Wroblewska B, Wroblewski T, Koperski L, Pawlak J, Nychowski P et al (2004) Myoid hamartoma of the liver – a novel variant of hamartoma

developing in the hilar region and imitating a malignant liver tumor. Med Sci Monit 10:CS23–CS26
Gowda RM, Gowda MR, Mehta NJ et al (2004) Right atrial extension of primary venous leiomyosarcoma: pulmonary embolism and Budd-Chiari syndrome at presentation: a case report. Angiology 55:213–216
Gray H (1959) Anatomy of the human body, 27th edn. Lea and Febiger, Philadelphia
Ha C, Haller JO, Rollins NK (1993) Smooth muscle tumors in immunocompromised (HIV negative) children. Pediatr Radiol 23:413–414
Haberal A, Kavikcioglu F, Caglar GS, Cavusoglu D (2007) Leiomyomatosis peritonealis disseminata presenting with intravascular extension and coexisting with endometriosis: a case report. J Reprod Med 52:422–424
Hachisuka K, Ito I, Osada S, Kato K, Usizima H (1963) Leiomyoma of the inferior vena cava. Nagoya J Med Sci 25:93–98
Hakverdi S, Güngören A, Yaldiz M, Hakverdi AU, Toprak S (2011) Immunohistochemical analysis of p16 expression in uterine smooth muscle tumors. Eur J Gynaecol Oncol 32:513–515
Hallock P, Watson CJ, Berman L (1940) Primary tumor of the inferior vena cava with clinical features suggestive of Chiari's disease. Arch Intern Med 66:50
Hardwigsen J, Balandraud P, Ananian P, Saisse J, Le Treut YP (2005) Leiomyosarcoma of the retrohepatic portion of the inferior vena cava: clinical presentation and surgical management in five patients. J Am Coll Surg 200:57–63
Hashimoto M, Kobayashi T, Tashiro H, Amano H, Oshita A, Tanimoto Y, Kuroda S, Tazawa H et al (2012) A huge metastatic liver tumor from leiomyosarcoma of the inferior vena cava: report of a case. Surg Today 42:505–508
Hawkins EP, Jordan GL, McGavran MH (1980) Primary leiomyoma of the liver. Successful treatment by lobectomy and presentation of criteria for diagnosis. Am J Surg Pathol 4:301–304
Hendrickson WF (1898) A study of the musculature of the entire extra-hepatic biliary system including that of the duodenal portion of the common bile-duct and the sphincter. Bull Johns Hopkins Hosp 9:221
Herzberg AJ, MacDonald JA, Tucker JA, Humphrey PA, Meyers WC (1990) Primary leiomyoma of the liver. Am J Gastroenterol 85:1642–1645
Hess W (1965) Surgery of the biliary passages and the pancreas. Van Nostrand, Princeton
Higuchi T, Kikuchi M, Yamada Y (1995) Aggressive hepatic leiomyosarcoma – an immunohistochemical evaluation of malignant potential using monoclonal antibody MIB1. Acta Oncol 34:970–971
Hiyama Y (1995) Primary hepatic leiomyosarcoma and rhabdomyosarcoma (in Japanese). Ryokibetsu Shokogun Shirizu 7:463–466
Hodge JC, Quade BJ, Rubin MA, Stewart EA, Dal Cin P, Morton CC (2008) Molecular and cytogenetic characterization of plexiform leiomyomata provide further evidence for genetic heterogeneity underlying uterine fibroids. Am J Pathol 172:1403–1410
Hoffbrand AV, Lloyd-Thomas HG (1964) Leiomyosarcoma of the inferior vena cava leading to obstruction of the tricuspid valve. Br Heart J 26:709–715
Hoffmann E (1963) Ein Leiomyom der Vena cava inferior. Chirurg 34:85
Hollands MJ, Jaworski R, Wong KP, Little JM (1989) A leiomyoma of the liver. HPB Surg 1:337–343
Hollenbeck ST, Grobmyer SR, Kent KC, Brennan MF (2003) Surgical treatment and outcomes of patients with primary inferior vena cava leiomyosarcoma. J Am Coll Surg 197:575–579
Holloway H, Walsh CB, Thomas R, Fielding J (1996) Primary hepatic leiomyosarcoma. J Clin Gastroenterol 23:131–133
Hong SM, Kang GH, Lee HY, Ro JY (2000) Smooth muscle distribution in the extrahepatic bile duct: histologic and immunohistochemical studies of 122 cases. Am J Surg Pathol 24:660–667
Horstmann JP, Pietra GG, Harman JA, Cole NG, Grinspan S (1977) Spontaneous regression of pulmonary leiomyomas during pregnancy. Cancer 39:314–321
Huang XF, Wang CM, Pan BR, Dai XW, Fang L, Yang JJ, Yu H, Ren J (2004) Pathological characteristics of gastric leiomyoblastoma. World J Gastroenterol 10:3182–3184
Huang J, Liu Q, Lu JP, Wang F, Wang L, Jin AG (2011) Primary intraluminal leiomyosarcoma of the inferior vena cava: value of MRI with contrast-enhanced MR venography in diagnosis and treatment. Abdom Imaging 36:337–341
Huguet C, Harb J, Gavelli A, Riberi A (1992) Leiomyosarcoma of the inferior vena cava invading into the liver. Complete resection with venous reconstruction (in French). Gastroenterol Clin Biol 16:714–717
Imasato M, Tono T, Kano T, Kimura Y, Iwazawa T, Onishi T, Nakano Y, Yano H, Okamoto S, Monden T (2005) Primary leiomyoma of the liver: a case report (in Japanese). Nippon Geka Gakkai Zasshi 106:725–729
Iordanidis F, Hytiroglou P, Drevelgas A, Kodonas F, Ioannidis I, Nenopoulou H, Papadimitriou CS (2002) A 25-year-old man with a large hepatic tumor and multiple nodular lesions. Semin Liver Dis 1:97–102
Ischii H, Nakayama T, Hiyama Y (1991) Primary hepatic leiomyosarcoma: the investigation of domestic and foreign 34 cases (in Japanese). Nippon Shokakibyo Gakkai Zasshi 88:1256–1263
Ishak KG (1976) Mesenchymal tumors of the liver. In: Okuda K, Peters R (eds) Hepatocellular carcinoma. Wiley, New York, pp 260–262
Iwatsuki S, Todo S, Starzl TE (1990) Excisional therapy for benign hepatic lesions. Surg Gynecol Obstet 171:240–246
Jacques DP, Coit DG, Casper ES, Brennan MF (1995) Hepatic metastases from soft-tissue sarcoma. Ann Surg 221:392–397

Jaffe RH (1924) Sarcoma and carcinoma of the liver following cirrhosis. Arch Intern Med 33:330–335

Jenssen C, Siebert C, Bartho S (2008) Leiomyosarcoma of the inferior vena cava. Diagnosis using endoscopic ultrasound-guided fine-needle aspiration biopsy (in German). Dtsch Med Wochenschr 133: 769–772

Jeong TY, Kim YS, Park KJ, Lee JS, Huh JG, Ryu SH, Lee JH, Moon JS (2008) A case of primary leiomyosarcoma of the liver presenting with acute bleeding (in Korean). Korean J Gastroenterol 51:194–198

Jin J, Wei QY, Zhuang ZG, Zhong DX, Huang GX (1990) Leiomyosarcoma of the common bile duct. Chin Med J 103:778–780

Jo VY, Fletcher CD (2011) p63 immunohistochemical staining is limited in soft tissue tumors. Am J Clin Pathol 136:762–766

Jordan HE (1952) Textbook of histology, 9th edn. Appleton-Century-Crofts, New York

Kahveci V, Ogur T, Cipe G, Ozdemir S, Hazinedaroglu S (2012) Symplastic leiomyoma in the suprarenal inferior vena cava. Iran J Radiol 10:33–36

Kalaitzakis E, Sturgess R (2011) Biliary leiomyoma diagnosed by Spyglass cholangioscopy (with video). Gastrointest Endosc 74:409–410

Kalil AN, Ferreira MT, Ressler F, Zetter C (2009) Hepatic leiomyoma in an immunocompetent patient (in Portuguese). Rev Col Bras Cir 36:362–363

Kanazawa N, Izumi N, Tsuchiya K, Sakurai K, Hamano K, Itakura J, Asahina Y, Noguchi O, Uchihara M, Miyake S, Miyakawa N, Kawachi Y et al (2002) A case of primary leiomyoma of the liver in a patient without evidence of immunosuppression. Hepatol Res 24:80–88

Karski J (1974a) Smooth muscle of the common bile duct and pancreatic ducts in man. Folia Morphol (Warsz) 33:317–325

Karski J (1974b) Fibers connecting the duodenal muscularis with the muscularis of the terminal segments of the common bile duct and pancreatic duct in man. Folia Morphol (Warsz) 33:399–407

Kefalas CH, Altrabulsi B, Milvenan JS, Goldschmiedt M (2004) Endoscopic electrosurgical snare resection of leiomyosarcoma of main duodenal papilla. Gastrointest Endosc 59:743–745

Kershner D (1969) Leiomyosarcoma of the stomach with hepatic metastasis; radical resection with surgical recovery. Gastroenterology 18:456

Key RD, Rao RN (1986) Leiomyomatous hemangiomas of the liver mimicking primary leiomyomas. Arch Pathol Lab Med 110:658–659

Kialian GP, Aznaurian AV (1995) The age-related characteristics of the muscular layer of the common bile duct (in Russian). Morfologiia 108:10–12

Kieffer E, Alaoui M, Piette JC, Cacoub P, Chiche L (2006) Leiomyosarcoma of the inferior vena cava: experience in 22 cases. Ann Surg 244:289–295

Kiernan F (1833) The anatomy and physiology of the liver. Proc R Soc Lond Phil Trans 133:711

King ME, Dickersin GR, Scully RE (1982) Myxoid leiomyosarcoma of the uterus. A report of six cases. Am J Surg Pathol 6:589–598

Kinoshita A, Sakon M, Monden M, Gotoh M, Kobayashi K, Okuda H, Sakurai M, Okamura J, Mori T (1988) Triple synchronous malignant tumors. Hepatic leiomyosarcoma, splenic hemangiosarcoma and sigmoid colon cancer. Case report. Acta Chir Scand 154:477–479

Kir G, Kir M, Gurbuz A, Karateke A, Aker F (2004) Estrogen and progesterone expression of vessel walls with intravascular leiomyomatosis; discussion of histogenesis. Eur J Gynaecol Oncol 25:362–366

Koga T, Kusumoto T, Kakeji Y, Kishikawa K, Maehara Y, Yonemura T, Irie K, Sugimachi K (2002) Leiomyosarcoma of the greater omentum with liver metastasis: report of a case. Surg Today 32:434–438

Korbi S, Aouini MT, Remadi S, el Aimi S, Mokni M, Ben Aved F, Gannouni A (1991) Primary hepatic leiomyosarcoma. A case report with immunohistochemical studies and review of the literature. J Submiscrosc Cytol Pathol 23:643–647

Korman U, Ersavasti G, Kurugoglu S, Uygun NT, Akman C (1997) Radiologic evaluation of gastrointestinal leiomyosarcomatosis. Eur Radiol 7:1332–1334

Kremer K, Palomba PP, Sandmann W (1976) Leiomyoma of the portal vein (in German). Chirurg 47:214–220

Krüger T, Mustafi M, Nadalin S, Aebert H (2010) Vena cava sarcoma with tumor embolus in the pulmonary artery: surgical treatment. Ann Thorac Surg 90:642–644

Kuenen BC, Slee PH, Seidenrijk CA, Wagenaar SS (1996) Intravenous leiomyomatosis complicated by Budd-Chiari syndrome. Postgrad Med J 72:686–688

Kulaylat MN, Karakousis CP, Doerr RJ, Karamanoukian HL, O'Brien J, Peer R (1997) Leiomyosarcoma of the inferior vena cava: a clinicopathologic review and report of three cases. J Surg Oncol 65:205–217

Kumar S, Gupta A, Shrivastava UK, Bhargava SK (1993) Leiomyosarcoma of gallbladder: a case report. Indian J Pathol Microbiol 36:78–80

Kune GA, Polgar V (1976) Leiomyoma of the common bile duct causing obstructive jaundice. Med J Aust 1:698–699

Kunieda M, Okuyama T, Miyamoto T, Kato M, Masuzwa M, Matsuo S, Endo S, Kawahara T et al (1984) A case of primary leiomyosarcoma of the liver (in Japanese). Nippon Shokakibyo Gakai Zasshi 81:1858–1862

Kuwahara M, Hamada T, Kawakami T, Makimoto K, Iwasaki A (2011) Simultaneous resection of lung and liver metastases due to uterine leiomyosarcoma; report of a case (in Japanese). Kyobu Geka 64:509–511

Kwon KM, Jang BK, Chung WJ, Park KS, Cho KB, Hwang JS, Kang KJ, Kang YN, Kwon JH (2005) A case of primary hepatic leiomyosarcoma with intrahepatic and abdominal subcutaneous metastasis in Behçet's disease (in Korean). Korean J Hepatol 11:386–391

Lagun MA, Bluvshtein GA, Baranov DV (1993) Obturating leiomyoma of the common bile duct (in - Russian). Vestn Khir Im I I Grek 150:50–51

Lang H, Nussbaum KT, Kaudel P, Frühauf N, Flemming P, Raab R (2000) Hepatic metastases from leiomyosarcoma: a single-center experience with 34 liver resections during a 15-year period. Ann Surg 231:500–505

Laskin WB, Fanburg-Smith JC, Burke AP, Kraszewska E, Fetsch JF, Miettinen M (2010) Leiomyosarcoma of the inferior vena cava: clinicopathologic study of 40 cases. Am J Surg Pathol 34:873–881

Le Bail B, Morel D, Merel P, Comeau F, Merlio JP, Carles J, Trillaud H, Bioulac-Sage P (1996) Cystic smooth-muscle tumor of the liver and spleen associated with Epstein-Barr virus after renal transplantation. Am J Surg Pathol 20:1418–1425

Lee YT (1983) Leiomyosarcoma of the gastro-intestinal tract: general pattern of metastasis and recurrence. Cancer Treat Rev 10:91–101

Lee PK, Teixeira OH, Simons JA, Goodman RL, Brais MP, Barber GG, Dunlap HJ et al (1990) Atypical hepatic vein leiomyoma extending into the right atrium: an unusual cause of the Budd-Chiari syndrome. Can J Cardiol 6:107–110

Lee ES, Locker J, Nalesnik M, Reyes J, Jaffe R, Alashari M, Nour B, Tzakis A, Dickman PS (1995) The association of Epstein-Barr virus with smooth-muscle tumors occurring after organ transplantation. N Engl J Med 332:19–25

Lee HJ, Lee JL, Choi WH (2002) A case of primary myxoid leiomyosarcoma of the liver. Korean J Intern Med 17:278–282

Lee HL, Sohn JH, Kim JB, Han DS, Jeon YC, Hahm JS, Lee DH, Kee CS, Park YW (2005) A case of primary hepatic leiomyosarcoma presenting with multiple subcutaneous scalp mass (in Korean). Korean J Gastroenterol 46:233–236

Lee HJ, Choi J, Kim KR (2008) Pulmonary benign metastasizing leiomyoma associated with intravenous leiomyomatosis of the uterus: clinical behavior and genomic changes supporting a transportation theory. Int J Gynecol Pathol 27:340–345

Leipner N, Engel C, Stiens R (1984) Mesenchymal, predominantly leiomyomatous, differentiated hamartoma of the liver (in German). Rofo 140:608–610

Levin TL, Adam HM, van Hoeven KH, Goldman HS (1994) Hepatic spindle cell tumors in HIV positive children. Pediatr Radiol 24:78–79

Liang X, Xiao-Min S, Jiang-Ping X, Jie-Yu Y, Xiao-Jun Z, Zhi-Ren F, Guo-Shan D, Rui-Dong L (2009) Liver transplantation for primary hepatic leiomyosarcoma: a case report and review of the literature. Med Oncol 27:1269–1272

Linares Torres P, VIvas Alegre S, Castanon Lopez C, Dominguez Carbajo AB, Honrado Franco E et al (2002) Primary hepatic leiomyosarcoma in a patient with gastric non-Hodgkin lymphoma (in Spanish). Gastroenterol Hepatol 25:452–454

Lintner F, Faust U, Nowotny C (1978) Malignant degeneration of a primary leiomyoma of the inferior vena cava (leiomyosarcoma) with the clinical picture of the Chiari-Budd syndrome (in German). Wien Klin Wochenschr 90:485–489

Lorenzo-Zuniga V, Moreno de Vega V, Boix J (2011) Upper gastrointestinal bleeding from liver metastases of uterine leiomyosarcoma. Surg Laparosc Endosc Percutan Tech 21:e284–e285

Loud PA, Warshauer DM, Woosley JT, Hartmann TM (1997) Carcinosarcoma of the extrahepatic bile ducts: cholangiographic and CT appearance. Abdom Imaging 22:85–86

Ludwick JR (1966) Observations on the smooth muscle and contractile activity of the common bile duct. Ann Surg 164:1041–1050

Lygidakis NJ, Bhagat AD, Sharma SK, Kefalourous H, Porfiris T, Grigorakos L, Vrachnos P et al (2007) Leiomyosarcoma of the inferior vena cava – an unusual case. Hepatogastroenterology 54:710–715

Macek M (1960) Leiomyoma of the caudal vena cava (in Czech). Cas Lek Cesk 22:975–976

Madariaga JR, Nalesnik MA, Iwatsuki S, Starzl TE, Fung JJ (1995) Spindle cell tumor of the portal vein. J Surg Oncol 59:139–141

Magro G, Bisceglia M (1998) Muscular hamartoma of the breast. Case report and review of the literature. Pathol Res Pract 194:349–355

Mahour GH, Wakim KG, Soule EH, Ferris DO (1967) Structure of the common bile duct in man: presence or absence of smooth muscle. Ann Surg 166:91–94

Maki HS, Hubert BC, Saijad SM, Kirchner JP, Kuehner ME (1987) Primary hepatic leiomyosarcoma. Arch Surg 122:1193–1196

Mandelbaum I, Pauletto FJ, Nasser WK (1974) Resection of a leiomyoma of the inferior vena cava that produced tricuspid valvular obstruction. J Thorac Cardiovasc Surg 67:561–567

Mandeville GA, Stawski WS (1991) Obstructing leiomyoma of the common hepatic duct bifurcation simulating Klatskin tumor. Am Surg 57:676–678

Maruta K, Sonoda Y, Saigo R, Yoshioka T, Fukunaga H (2004) A patient with von Recklinghausen's disease associated with polymyositis, asymptomatic pheochromocytoma, and primary hepatic leiomyosarcoma (in Japanese). Nippon Ronen Igakkai Zasshi 41:339–343

Masur H, Sussman EB, Molander DW (1975) Primary hepatic leiomyosarcoma: a report of two cases. Gastroenterology 69:994–997

Mathieu D, Grenier P, Lardé D, Vasile N (1984) Portal vein involvement in hepatocellular carcinoma: dynamic CT features. Radiology 152:127–132

Matthaei H, Krieg A, Schmelzle M, Boelke E, Poremba C, Rogiers X, Knoefel WT, Peiper M (2009) Long-term survival after surgery for primary hepatic sarcoma in adults. Arch Surg 144:339–344

McClain KL, Leach CT, Jenson HB, Joshi VV, Pollock BH, Parmley RT, DiCarlo FJ, Chadwick EG, Murphy

SB (1995) Association of Epstein-Barr virus with leiomyosarcomas in young people with AIDS. N Engl J Med 332:12–18
Mel'nikov RA, Sukharev VF (1970) Leiomyosarcoma of the liver (in Russian). Vopr Onkol 16:73–75
Mesenas SJ, Ng KY, Raj P, Ho JM, Ng HS (2000) Primary leiomyoma of the liver. Singapore Med J 41:129–131
Miettinen M, Fetsch JF (2006) Evaluation of biological potential of smooth muscle tumours. Histopathology 48:97–105
Mingoli A, Cavallaro A, Sapienza P, Di Marzo L, Feldhaus RJ, Cavallari N (1996) International registry of inferior vena cava leiomyosarcoma: analysis of a world series on 218 patients. Anticancer Res 16:3201–3205
Mingoli A, Sapienza P, Cavallero A et al (1997) The effect of extent of caval resection in the treatment of inferior vena cava leiomyosarcoma. Anticancer Res 17:3877–3881
Mital RN, Bazaz-Malik G (1971) Leiomyosarcoma of the ligamentum teres of the liver. Am J Gastroenterol 56:48–51
Modafferi F (2002) Epithelioid cell's uterine leiomyoma uteri. A case report with immunohistochemical study. J Exp Clin Cancer Res 21:295–298
Monforte-Munoz H, Kapoor N, Saavedra JA (2003) Epstein-Barr virus-associated leiomyomatosis and posttransplant lymphoproliferative disorder in a child with severe combined immunodeficiency: case report and review of the literature. Pediatr Dev Pathol 6:449–457
Moore Dalal K, Antonescu CR, Dematteo RP, Maki RG (2008) EBV-associated smooth muscle neoplasms: solid tumors arising in the presence of immunosuppression and autoimmune diseases. Sarcoma 2008:859407
Moorjani et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/15985146
Morente M, Rodriguez R, Gil B et al (1984) Leiomiosarcoma hepatico primario. Gastroenterol Hepatol 7:77
Morita Y, Saito H, Okushiba S, Shinohara M, Satoh N, Uchino J (1987) A case report of leiomyosarcoma of the hepatic falciform ligament – clinical significance of the hepatic falciform artery (in Japanese). Rinsho Hoshasen 32:1613–1616
Morris CJ, Ghanta R (2010) Masquerading primary liver leiomyosarcoma as a hemorrhagic hepatoma. Clin Gastroenterol Hepatol 8:e26
Mueller BU, Butler KM, Higham MC, Husson RN, Montrella KA, Pizzo PA, Feuerstein IM, Manjunath K (1992) Smooth muscle tumors in children with human immunodeficiency virus infection. Pediatrics 90:460–463
Mulvany NJ, Slavin JL, Ostor G, Fortune DW (1994) Intravenous leiomyomatosis of the uterus: a clinicopathologic study of 22 cases. Int J Gynecol Pathol 13:1–9
Myers RN, Haupt GJ, Birkhead NC, Deaver JM (1962) Cinefluorographic observations of common physiology. Ann Surg 156:442
Nam MS, Jeon MJ, Kim YT, Kin JW, Park KH, Hong YS (2003) Pelvic leiomyomatosis with intracaval and intracardiac extension: a case report and review of the literature. Gynecol Oncol 89:175–180
Nance K, Reddick RL (1987) Epithelioid leiomyosarcoma of the small intestine with oncocytic change. Arch Pathol Lab Med 111:1181–1182
Nava-Villalba M, Ocampo-Acosta F, Seamanduras-Pacheco A, Aldape-Barrios BC (2008) Leiomyomatous hamartoma: report of two cases and review of the literature. Oral Surg Oral Med Oral Pathol Radiol Endod 105:e39–e45
Nemsmann B, Schroder D (1984) Juxtapapillary leiomyoma – a rare papillary tumor. Presentation of an unusual disease picture (in German). Fortschr Med 102:565–566
Nguyen GK, Russell L, Honoré L, Vriends R (2001) Epithelioid leiomyosarcoma of the uterus with oncocytic change. Pathol Res Pract 197:643–646
Nishiguchi S, Shiomi S, Ofuji S, Ishizu H, Iwata Y, Sasaki N, Minamitani S (2001) Leiomyosarcoma of the liver detected by high F-18 fluorodeoxyglucose positron emission tomographic uptake. Clin Nucl Med 26:798–799
Nitshe GA, Suckle HM (1947) Leiomyosarcoma of ampulla of Vater associated with tumor of eight nerve and neurogenic perforation of the duodenum; report of case and review of literature. Am J Clin Pathol 17:827–833
Nobili C, Lesevic V, Marzano E, Casnedi S, Greget M, Bachellier P, Pessaux P (2010) Primary pancreatic sarcoma with liver metastases: is there a place for radical surgery? (in French). Gastroenterol Clin Biol 34:227–230
Nonomura A, Minato H, Kurumaya H (1998) Angiomyolipoma predominantly composed of smooth muscle cells: problems in histological diagnosis. Histopathology 33:20–27
Noon MA, Young SW, Castellino RA (1980) Leiomyosarcoma metastatic to the liver: CT appearance. J Comput Assist Tomogr 4:527–530
Norris HJ, Parmley T (1975) Mesenchymal tumors of the uterus. V. Intravenous leiomyomatosis. A clinical and pathological study of 14 cases. Cancer 36:2164–2178
Nur S, Rosenblum WD, Katta UD, Islam H, Brown K, Ramaswamy G (2007) Epstein-Barr virus-associated multifocal leiomyosarcomas arising in a cardiac transplant recipient: autopsy case report and review of the literature. J Heart Lung Transplant 26:944–952
O'Leary MR, Hill RB, Levine RA (1982) Peritoneoscopic diagnosis of primary leiomyosarcoma of liver. Hum Pathol 13:76–78
Octavio de Toledo JM, Gomez Lorenzo F, Santiago MP, Figuerela B, Sierra JA, Dominguez J (1991) Upper digestive hemorrhage cause by ulcerated periampullary leiomyoma (in Spanish). Rev Esp Enferm Dig 79:156–159
Ohtomo K, Araki T, Itai Y, Monzawa S, Ohba N, Nogata Y, Hibara T, Koizumi K, Uchiyama G (1992) MR imaging of malignant mesenchymal tumors of the liver. Gastrointest Radiol 17:58–62

Paraskevopoulos JA, Stephenson TJ, Dennison AR (1991) Primary leiomyosarcoma of the liver. HPB Surg 4:157–162

Parker RL, Young RH, Clement PB (2005) Skeletal muscle-like and rhabdoid cells in uterine leiomyomas. Int J Gynecol Pathol 24:319–325

Parrilla M, Montilla Y, Alvarez C et al (1992) Leiomyosarcoma of the vena cava inferior. The correlation: ultrasound and fine-needle puncture biopsy. Gen 46:336–340

Pawlik TM, Vauthey JN, Abdalla EK, Pollock RE, Ellis LM, Curley SA (2006) Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. Arch Surg 141:537–544

Peh WCG, Cheung DLC, Ngan H (1993) Smooth muscle tumors of the inferior vena cava and right heart. Clin Imaging 17:117–123

Peng OF, Yan LN, Ran RT, Yao XY (1987) Clinicopathologic manifestations in 2 cases of primary leiomyosarcoma of the liver (in Chinese). Hua Xi Yi Ke Da Xue Xue Bao 18:90–92

Péquignot R, Thévenot T, Permal S, Tulliez M, Legman P, Dhote R, Christoforov B (1999) Hepatic leiomyosarcoma revealed by cutaneous metastasis (in French). Gastroenterol Clin Biol 23:991–992

Perl L (1871) Ein Fall von Sarkom der Vena cava inferior (A case of sarcoma of the vena cava inferior). Virchows Arch Pathol Anat 53:378

Pi ZM (1992) Twenty rare primary hepatic malignant tumors. Zhonghua Zhong Liu Za Zhi 14:210–212

Pinson CW, Lopez RR, Ivancev K, Ireland K, Sawyers JL (1994) Resection of hepatic malignant fibrous histiocytoma, fibrosarcoma, and leiomyosarcoma. South Med J 87:384–391

Pizzimbono CA, Higa E, Wise L (1973) Leiomyoblastoma of the lesser sac: case report and review of the literature. Am Surg 39:692–699

Poggio JL, Nagorney DM, Nascimento AG et al (2000) Surgical treatment of adult primary hepatic sarcoma. Br J Surg 87:1500–1505

Pollanen M, Butany J, Chiasson D (1987) Leiomyosarcoma of the inferior vena cava. Arch Pathol Lab Med 111:1085–1087

Ponka A, Laasonen L, Strengell-usanov L (1983) Angioleiomyoma of the common bile duct. Acta Med Scand 213:407–410

Praseedom RK, Dhar P, Jamieson NV, Wallwork J, Bergman I, Lomas DJ (2007) Leiomyosarcoma of the retrohepatic vena cava treated by excision and reconstruction with an aortic homograft: a case report and review of the literature. Surg Innov 14:287–291

Prévot S, Neris J, de Saint Maur PP (1994) Detection of Epstein Barr virus in an hepatic leiomyomatous neoplasm in an adult human immunodeficiency virus 1-infected patient. Virchows Arch 425:321–325

Principe F, Ferreira JS, Sobrinho-Simoes M (1988) Acute myeloid leukemia followed by hepatic leiomyosarcoma. A case report. Acta Med Port 1:87–89

Qifang P, Lunan Y, Ruiti R, Xianying Y (1987) Clinicopathologic manifestations in 2 cases of primary leiomyosarcoma of the liver (in Chinese). Hua Xi Yi Ke Da Xue Xue Bao 18:90–92

Quade BJ, Dal CP, Neskey DM, Weremowicz S, Morton CC (2002) Intravenous leiomyomatosis: molecular and cytogenetic analysis of a case. Mod Pathol 15:351–356

Reges R, Denardi F, Matheus W, Ferreira U, Netto NR, Billis A (2008) Primary leiomyosarcoma of the inferior vena cava: how should it be treated and the vein anatomy re-established? Int J Urol 15:259–260

Reinertson TE, Fortune JB, Peters JC, Pagnotta I, Baliut JA (1992) Primary leiomyoma of the liver. Dig Dis Sci 37:622–627

Rios-Dalenz JL (1965) Leiomyoma of the liver. Arch Pathol 79:54–56

Robert HG, Vayre P, De Brux J (1964) Muscle tumor of the rectum and hepatic leiomyosarcoma (in French). Concours Med 19:13–15

Robin YM, Penel N, Pérot G, Neuville A, Vélasco V, Ranchère-Vince D, Terrier P, Coindre JM (2013) Transgelin is a novel marker of smooth muscle differentiation that improves diagnostic accuracy of leiomyosarcomas: a comparative immunohistochemical reappraisal of myogenic markers in 900 soft tissue tumors. Mod Pathol 26:502–510

Rogatsch H, Bonatti H, Menet A, Larcher C, Feichtinger H, Dirnhofer S (2000) Epstein-Barr virus-associated multicentric leiomyosarcoma in an adult patient after heart transplantation. Am J Surg Pathol 24:614–621

Rosch R, Junge K, Töns C, Chalabi K, Klosterhalfen B, Schumpelick V (2002) Weakly malignant leiomyosarcoma of the inferior vena cava. A case report (in German). Chirurg 73:950–953

Rose PG, Piver MS, Tsukada Y, Lau T (1989) Patterns of metastasis in uterine sarcoma. An autopsy study. Cancer 63:935–938

Rosenmann E, Maayan C, Lernau O (1980) Leiomyomatous hamartosis with congenital jejunoileal atresia. Isr J Med Sci 16:775–779

Ross JS, Del Rosario A, Bui HX, Sonbati H, Solis O (1992) Primary hepatic leiomyosarcoma in a child with the acquired immunodeficiency syndrome. Hum Pathol 23:69–72

Rummeny E, Weissleder R, Stark DD, Saini S, Compton CC, Bennet W, Hahn PF, Wittenberg J, Malt RA, Ferrucci JT (1989) Primary liver tumors: diagnosis by MR imaging. AJR Am J Roentgenol 152:63–72

Sadahira Y, Moriya T, Shirabe T, Matsuno T, Manabe T (1996) Epstein-Barr virus-associated post-transplant primary smooth muscle tumor of the liver: report of an autopsy case. Pathol Int 46:601–604

Saint-Paul MC, Gugenheim J, Hofman P, Arpurt JP, Fabiani P, Michiels JF, Fujita N, Goubeaux B et al (1993) Leiomyosarcoma of the liver: a case treated by transplantation (in French). Gastroenterol Clin Biol 17:218–222

Saito K (1996) Smooth muscle tumors of the extra-hepatic bile duct (in Japanese). Ryoikibetsu Shokogun Shirizu 9:64–67

Saitoh M, Hayasaka T, Nakahara K, Ohmichi M, Shimazaki Y, Kurachi H (2004) Intravenous leiomyomatosis with cardiac extension. Gynecol Obstet Invest 58:168–170

Sakai Y (2007) Epithelioid vascular leiomyoma of the uterus mimicking glomangiomyoma. Arch Gynecol Obstet 275:59–61

Sakai Y, Yamada T, Fukuda H, Ichiyanagi N, Kamata S, Nagahama K, Tanizawa A, Watanabe T et al (2000) A case of epithelioid leiomyoma (leiomyoblastoma) of the urethra. Hinyokika Kiyo 46:41–43

Salamanca J, Massa DS (2009) EBV-associated hepatic smooth muscle tumor after lung transplantation: report of a case and review of the literature. J Heart Lung Transplant 28:1217–1220

Salaquarda F (1964) Leiomyoma of the inferior vena cava (in German). Zbl Allg Pathol Pathol Anat 105:405

Sancho Alvarez A, Poncela Blanco M, Morais Perez D, Martin Siguenza G, Peral Martinez JI (2001) Leiomyoblastoma of the tongue. Acta Otorrinolaringol Esp 52:70–73

Schuppler V (1934) Ein primäres Myosarkom des Ductus choledochus. Wien Klin Wochenschr 47:395–396

Schwarzbach M, Willeke F, Hoffmann V, Mechtersheimer G, Otto G (1997) Leiomyosarcoma of the inferior vena cava (in German). Dtsch Med Wochenschr 122:439–444

Sclabas GM, Maurer CA, Wente MN, Zimmermann A, Büchler MW (2002) Case report: hepatic leiomyoma in a renal transplant recipient. Transplant Proc 34:3200–3202

Sessa B, Iannicelli E, Caterino S, D'Angelo F, Milione M, Ziparo V, David V (2010) Imaging of leiomyosarcoma of the inferior vena cava: comparison of 2 cases and review of the literature. Cancer Imaging 10:80–84

Shamseddine A, Faraj W, Mukherji D, El Majzoub N, Khalife M, Siubra A, Shamseddine A (2010) Unusually young age distribution of primary hepatic leiomyosarcoma: case series and review of the adult literature. World J Surg Oncol 8:56

Sharma BC, Saraswat VA, Dhiman RK, Ghoshal UC, Puri AS, Sikora SS (1996) Unusual tumors causing extrahepatic portal venous obstruction. HPB Surg 9:165–167

Shimo M, Mutakami T, Endou H et al (1989) A clinicopathologic study of two cases of leiomyosarcoma of the liver. Rinsho Byori 7:635–642

Shimoda H, Oka K, Otani S, Hakozaki H, Yoshimura T, Okazaki H, Nishida S, Tomita S et al (1998) Vascular leiomyosarcoma arising from the inferior vena cava diagnosed by intraluminal biopsy. Virchows Arch 433:97–100

Shiraki K, Tameda Y (1995) Primary leiomyoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:432–434

Shivathirthan N, Kita J, Iso Y, Hachiya H, Kyunghwa P, Sawada T, Kubota K (2011) Primary hepatic leiomyosarcoma: case report an literature review. World J Gastrointest Oncol 3:148–152

Shurbaji MS, Olson JL, Kuhajda FP (1987) Thorotrast-associated hepatic leiomyosarcoma and cholangiocarcinoma in a single patient. Hum Pathol 18:524–526

Sicaja M, Namiq A, Forster J, Damjanov I (2006) Myxoid leiomyosarcoma of the liver. Pathol Res Pract 202:43–46

Smith MB, Silverman JF, Raab SS, Towell BD, Geisinger KR (1994) Fine-needle aspiration cytology of hepatic leiomyosarcoma. Diagn Cytopathol 11:321–327

Sokolich J, Mejia A, Cheng S, Dunn E (2008) Retroperitoneal leiomyosarcoma of the inferior vena cava mimicking a liver tumor. Am Surg 74:433–436

Soyer P, Bluemke DA, Riopel M, Hruban RH, Fishman EK (1995) Hepatic leiomyosarcomas: CT features with pathologic correlation. Eur J Radiol 19:177–182

Soyer P, Blanc F, Vissuzaine C, Marmuse JP, Menu Y (1996) Primary leiomyosarcoma of the liver: MR findings. Clin Imaging 20:273–275

Soyer P, Riopel M, Bluemke DA, Scherrer A (1997) Hepatic metastases from leiomyosarcoma: MR features with histopathologic correlation. Abdom Imaging 22:67–71

Spagliardi E, Longo A, Blanco GF, Ruggeri C, Buscaglia M, Torelli P (1990) Rare primary hepatic neoplasms. Our experience in 2 cases: a primary lymphoma and a leiomyosarcoma of the liver (in Italian). Minerva Chir 45:95–102

Spinelli A, Schumacher G, Benckert C, Sauer IM, Schmeding M, Glanemann M, Neumann UP et al (2008) Surgical treatment of a leiomyosarcoma of the inferior vena cava involving the hepatic and renal veins confluences: technical aspects. Eur J Surg Oncol 34:831–835

Stafyla V, Kotsifopoulos N, Grigoriadis K, Bakoyannis CN, Peros G, Sakorafas GH (2007) Myoid hamartoma of the breast: a case report and review of the literature. Breast J 13:85–87

Stark DD (1988) Benign hepatic leiomyoma. In: Stark DD, Bradley WG (eds) Magnetic resonance imaging. Mosby, St. Louis, pp 972–973

Sundaresan M, Kelly SB, Banjamin IS, Akosa AB (1990) Primary hepatic vascular leiomyosarcoma of probable portal vein origin. J Clin Pathol 43:1036

Surendrababu NR, Rao A, Samuel R (2006) Primary hepatic leiomyosarcoma in an infant. Pediatr Radiol 36:366

Tameo MN, Calligaro KD, Antin L, Dougherty MJ (2010) Primary leiomyosarcoma of the inferior vena cava: reports of infrarenal and suprahepatic caval involvement. J Vasc Surg 51:221–224

Thompson MM, Graham TR, Bolia AA, Firmin RK, Bell PR (1993) Intrahepatic leiomyosarcoma of the inferior

vena cava with extension into the right atrium. Eur J Vasc Surg 7:204–207
Tocchi A, Codacci-Pisanelli M, Costa G, Lepre L, Agostini N, Maggiolini F (1993) Leiomyosarcoma of the gallbladder: a clinical case (in Italian). G Chir 14:443–445
Trent JC, Lazar AJ, Zhang W (2007) Molecular approaches to resolve diagnostic dilemmas: the case of gastrointestinal stromal tumor and leiomyosarcoma. Future Oncol 3:629–637
Tseng LJ, Jao YT, Mo LR (2003) Leiomyoma of the major papilla. Gastrointest Endosc 57:717–718
Tsiatis AC, Atkinson JB, Wright JK, Cates JMM (2008) Primary hepatic myxoid leiomyosarcoma: a case report and review of the literature. Ultrastruct Pathol 32:25–28
Tsuji M, Takenaka R, Kashihara T, Hdama T, Terada N, Mori H (2000) Primary hepatic leiomyosarcoma in a patient with hepatitis C virus-related liver cirrhosis. Pathol Int 50:41–47
Tsurumi H, Okada S, Koshino Y, Oyama M, Higaki H, Shimokawa K, Yamauchi O, Moriwaki H, Muto Y (1991) A case of leiomyoblastoma (epithelioid leiomyosarcoma) of the greater omentum. Gastroenterol Jpn 26:370–375
Ulla M, Kohan A, Pekolj J, Isola M, Garcia-Monaco R (2011) Direct 64-row MDCT venography in the diagnosis of an inferior vena cava leiomyosarcoma. Abdom Imaging 36:333–336
Urizono Y, Ko S, Kanehiro H, Hisanaga M, Aomatsu Y, Nagao M, Ikeda N, Yamada T, Nakajima Y (2006) Primary leiomyoma of the liver: report of a case. Surg Today 36:629–632
Usandivaras JR (2002) Liver leiomyosarcoma (in Spanish). Acta Gastroenterol Latinoam 32:91–94
Valenti MT, Azzarello G, Vinante O, Manconi R, Balducci E, Guidolin D, Chiavegato A, Sartore S (1998) Differentiation, proliferation and apoptosis levels in human leiomyoma and leiomyosarcoma. J Cancer Res Clin Oncol 124:93–105
Vallejo JM, Ballester C, Sorribas F (2005) Intravascular leiomyomatosis: the surgical challenge of tumors with cavoatrial extension (in Spanish). Rev Esp Cardiol 58:1246–1247
Van Gansbeke D, Avni EF, Delcour C, Engelholm L, Struyven J (1985) Sonographic features of portal vein thrombosis. AJR Am J Roentgenol 144:749–752
Varela-Duran J, Oliva H, Rosai J (1979) Vascular leiomyosarcoma. Cancer 44:1684–1691
Von Ebert W (1978) Primary leiomyosarcoma of the liver. Zentralbl Allg Pathol 122:341–346
Wachsberg RH, Cho KC, Adekosan A (1994) Two leiomyomas of the liver in an adult with AIDS: CT and MR appearance. J Comput Assist Tomogr 18:156–157
Wada T, Ishigaki H, Akiyama M, Takemura T, Kawabe H, Matsuda K, Saito H (1994) A case of retroperitoneal leiomyosarcoma mimicking primary hepatic tumor (in Japanese). Nippon Shokakibyo Gakkai Zasshi 91:1141–1145
Walsh TH, Akoglu T (1979) The muscle content and contractile capability of the common bile duct. Ann R Coll Surg Engl 61:206–209
Wang MH, Wu CT, Hung CC, Liang JD, Chen PJ (2000) Hepatic leiomyomatous neoplasm associated with Epstein Barr virus infection in an adult with acquired immunodeficiency syndrome. J Formos Med Assoc 99:873–875
Watanabe K, Saito A, Wakabayashi H, Kawaguchi T, Suzuki T (1991) Two autopsy cases of primary leiomyosarcoma of the liver. Superiority of muscle-specific actin immunoreactivity in diagnosis. Acta Pathol Jpn 41:461–465
Watanabe K, Kusakabe T, Hoshi N, Saito A, Suzuki T (1999) H-caldesmon in leiomyosarcoma and tumors with smooth muscle cell-like differentiation: its specific expression in the smooth muscle cell tumor. Hum Pathol 30:392–396
Watanabe K, Tajino T, Sekiguchi M, Suzuki T (2000) h-Caldesmon as a specific marker for smooth muscle tumors. Comparison with other smooth muscle markers in bone tumors. Am J Clin Pathol 113:663–668
Watanabe K, Ogura G, Suzuki T (2003) Leiomyoblastoma of the uterus: an immunohistochemical and electron microscopic study of distinctive tumours with immature smooth muscle differentiation mimicking fetal uterine myocytes. Histopathology 42:379–386
Watanuki K, Kusama K (1955) A case of leiomyosarcoma of the liver. Nipon Ika Daigaku Zasshi 22:552
Watts JM, Dunphy JE (1966) The role of the common bile duct in biliary dynamics. Surg Gynecol Obstet 122:1207
Whitcomb FF, Corley GJ, Babigian DN, Colcock BP (1967) Leiomyosarcoma of the bile ducts. Gastroenterology 52:94–97
Wilson SR, Hine AL (1987) Leiomyosarcoma of the portal vein. AJR Am J Roentgenol 149:183–184
Wilson SE, Braitman H, Plested WG, Longmire WP (1971) Primary leiomyosarcoma of the liver. Ann Surg 174:232–237
Wray RC, Dawkins H (1971) Primary smooth muscle tumors of the inferior vena cava. Ann Surg 174:1009–1018
Xu ZF, Yong F, Chen YY, Pan AZ (2013) Uterine intravenous leiomyomatosis with cardiac extension: imaging characteristics and literature review. World J Clin Oncol 4:25–28
Yamaguchi T (1968) Case of primary leiomyosarcoma in the liver. Naika 22:1492
Yamaguchi J, Azuma T, Fujioka H, Tanaka K, Furui J, Tomioka T, Kanematsu T (1996) Leiomyosarcoma occurring in the ligamentum teres of the liver: a case report and a review of seven reported cases. Hepatogastroenterology 43:1051–1056

Yamaoka K, Tozuka S, Ikeda T, Kobayashi F, Noguchi O, Sakamoto S, Nagabori M et al (1993) Leiomyoma of the common bile duct. Am J Gastroenterol 88:469–470

Yanase M, Ikeda H, Ogata I, Ohno A, Moriya A, Miura N, Kimura S, Mori M, Oka T, Ohtomo K et al (1999) Primary smooth muscle tumor of the liver encasing hepatobiliary cystadenoma without mesenchymal stroma. Am J Surg Pathol 23:854–859

Yoon GS, Choi DL (2004) Sarcomatoid carcinoma of common bile duct: a case report. Hepatogastroenterology 51:106–109

Yoon GS, Kang GH, Kim OJ (1998) Primary myxoid leiomyoma of the liver. Arch Pathol Lab Med 122:1112–1115

Yoshikawa K, Satake K, Kinoshita H, Umeyama K, Hoto K (1977) Primary leiomyosarcoma of the liver. Clin Oncol 3:197–202

Yu RS, Chen Y, Jiang B, Wang LH, Xu XF (2008) Primary hepatic sarcomas: CT findings. Eur Radiol 18:2196–2205

Yuan CY, Lo HW, Tseng CH, Takasaki T, Hanyu F (1995) A case of spindle cell sarcomatous change of hepatic ducts manifesting as obstructive jaundice. J Gastroenterol 30:264–267

Zamecnik M, Michal M (2001) HMB45+ hyalinized epithelioid tumor of the uterus is linked to epithelioid leiomyoma rather than to PEC-omas. Int J Surg Pathol 9:341–343

Tumors of the Striated Muscle Cell Lineage: Hepatobiliary Rhabdomyosarcoma and Rhabdomyoma

64

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_64

Abstract

Rhabdomyosarcomas (RMS) are a group of aggressive malignancies derived from a skeletal muscle cell lineage. These neoplasms occur in several distinct body regions in children and adults. One subset of RMA develops in the hepatobiliary tract, mainly in the pediatric age group, associated with a distinct clinical and radiological syndrome. Hepatobiliary RMS is defined as a mucosal-type RMS arising from the wall of intrahepatic or extrahepatic bile ducts. This neoplasm is the most common biliary tract tumor in children, but is overall rare, accounting for only 0.8 % of all RMS and 1.3 % of malignant liver tumors in childhood. The neoplasm can form polypoid masses that protrude into the bile ducts. Histologically, most hepatobiliary RMS are embryonal RMA, whereas alveolar RMS is a very rare hepatic malignancy. Histologically, embryonal RMA of the liver shows a loose neoplastic tissue with desmin-positive stellate cells and cells resembling rhabdomyoblasts. Frequently, a cellular layer is found underneath the biliary tract epithelium, the so-called cambium. RMS of the hepatobiliary tract can rarely also occur in adults.

Pediatric Hepatobiliary Rhabdomyosarcoma

ICD-O codes:

Embryonal rhabdomyosarcoma	8910/3
Alveolar rhabdomyosarcoma	8920/3
Pleomorphic rhabdomyosarcoma	8901/3

Introduction

Rhabdomyosarcomas (RMS) are a group of aggressive mesenchymal malignancies well known to occur in several distinct body regions of children and histologically characterized by a growth of immature muscle cells with or without detectable cross-striation. Several types of RMS are now recognized, including embryonal RMS, alveolar RMS, pleomorphic RMS, spindle cell RMS, and anaplastic forms (Parham and Barr 2013).

Hepatobiliary rhabdomyosarcoma (HBRMS) is defined as a mucosal-type RMS arising from the wall of the intra- or extrahepatic bile ducts. This RMS is almost always an embryonal RMS. The lesion has first been described in 1875 (Wilks and Moxon 1875) and has later also been described as embryonic tumor with striated muscle (Sheehan 1930), a malignant mixed tumor of the choledochal duct (Goeters 1941), and a cystic liver tumor of the mixed type (Williams 1953). The case of Sheehan (1930), a 6-year-old girl, was described in great detail, and the author already pointed out that this type of tumor may present in the form of intrahepatic cysts representing dilated bile ducts obstructed by the intraluminally growing tumor. The lesion was further specified by Willis (1962).

Malignant muscle tumors have already been identified in the nineteenth century. The first case of RMS may have been described by the famous Viennese pathologist, Karl Freiherr von Rokitansky, who noted a tumor consisting of striated muscle cells in the tunica albuginea of the testis (von Rokitansky 1849). The first pediatric case might have been observed in a 3-year-old child by the Czech physician, Vilém Dusan Lambl, who called the tumor "muscle carcinoma" (Lambl 1860). Lambl is best known for his detection of an intestinal parasite which he called *Cercomonas intestinalis* (however, first observed by Anton van Leeuwenhoek) and which is now termed *Giardia lamblia*, an eponym based on Lambl and the French biologist, Alfred Mathieu Giard (1846–1908). Several classifications of RMS have been proposed (reviews: Parham 2001; Caillaud et al. 2006), and attempts for molecular classification have been undertaken (Davicioni et al. 2009).

Epidemiology

HBRMS is the most common biliary tract tumor in the pediatric age group and is, e.g., clearly more common as pediatric cholangiocarcinoma. But the

tumor is, overall, rare, and it accounts for only 0.8 % of all rhabdomyosarcomas and 1.3 % of all malignant liver tumors in childhood. At the time of diagnosis, 75 % of the children are under 5 years of age, and the tumor most often occurs in children aged 3–4 years. Girls are generally more frequently involved (5:1). However, in a review of 26 patients reported between 1875 and 1981 (Lack et al. 1981), 13 were male, 12 were female, and in 1 patient, the sex was not specified. Rarely, HBRMS occurs in adolescents (Haider et al. 2013).

Clinical Features

Clinical signs and symptoms are rather nonspecific and include upper abdominal pain, abdominal distention, nausea with vomiting, and hepatomegaly The clinical presentation is closely linked to the distinct growth pattern of the tumor, which grows along and within the bile ducts, causing biliary obstruction and cholestatic jaundice. Jaundice with or without associated leukocytosis was found as the presenting sign in 60–80 % of cases and critically depends on the level of bile duct involvement, being common in RMS located to the porta hepatis and obligatory in RMS of the ampullary region. Jaundice is commonly associated with marked hepatomegaly, and this combination may be confused with forms of icteric and cholestatic hepatitis. Obstructive jaundice occurs relatively late in the course of the disease, i.e., when the tumors are adequately large and then obturating the lumina, because bile flow continues between the intraluminal tumor projections. As in other malignancies (Staalman and Umans 1993), HBRMS may be associated with the paraneoplastic syndrome, hypertrophic osteoarthropathy (Geary et al. 2004). Radiologically, HBRMS may mimic choledochal cyst (Zampieri et al. 2006; Rebollo Guelar et al. 2013; Margain-Deslandes et al. 2013).

Selected References Goeters 1941; Gaubert 1965; Hays and Snyder 1965; Virenque et al. 1966; Soper and Dunphy 1968; Davis et al. 1969; Akers and Needham 1971; Corbineau et al. 1975; Babut et al. 1976; Taira et al. 1976; Nagaraj et al. 1977; Isaacson 1978; Cannon et al. 1979; Hashimoto et al. 1980; Coronado Perez and Angulo Hernandez 1981; Lack et al. 1981; Martinez et al. 1982; Mulet et al. 1982; Friedburg et al. 1984; Shamis et al. 1985; Arnaud et al. 1987; Horowitz et al. 1987; Shimada et al. 1987; Caty et al. 1990; Mann et al. 1990; Perisic et al. 1991; Gururangan et al. 1992; Babin-Boilletot et al. 1993; Lee et al. 1996; Pollono et al. 1998; Balkan et al. 1999; Hunt et al. 2002; Kebudi et al. 2003; Aggarwal et al. 2004; Zampieri et al. 2006; Huber et al. 2008; Zhao et al. 2011; Kumar et al. 2012; Diaconescu et al. 2013.

HBRMS of the Intrahepatic Bile Ducts

The intrahepatic biliary tree is the second most common manifestation of HBRMS, this tumor being more common in the extrahepatic duct system (see below). Sonography, conventional radiology, and CT display rather typical and, sometimes, pathognomonic changes. They comprise intrahepatic masses of heterogeneous structures with cystic areas and septations and bile duct stenosis with prestenotic duct dilatation (Witcombe 1979; Ruymann et al. 1985; Williams and Sheward 1986; Arnaud et al. 1987; Lee et al. 1996; Donnelly et al. 1998). MRI of the lesions show high signal intensity with heterogeneous enhancement in T2-weighted single-shot fast spin-echo axial MR images (Geary et al. 2004).

HBRMS of the Extrahepatic Bile Ducts

HBRMS involvement of the common bile duct is rare, but important pathology of the lower biliary tract in children, and is the most common site of HBRMS. Leriche (1934) reported the first case. The patient was a 4.5-year-old boy who presented with jaundice and a huge abdominal mass. At laparotomy, an enormous cystic dilatation of the common bile duct was seen. RMS of the large bile

duct can mimic a choledochal cyst (Nemade et al. 2007; Ali et al. 2009). The dilated duct contained copious bloody, mucoid fluid and a tumor the size of a child's head (Leriche 1934). Several other cases were reported since.

Selected References Goeters 1941; Willis 1948; Werner 1951; Horn et al. 1955; Farinacci et al. 1956; Bernheim et al. 1962; Delany et al. 1966; Gout et al. 1974; Majmudar and Kumar 1976; Sarrazin et al. 1977; Taura et al. 1977; Phatak and Prabhu 1982; Friedburg et al. 1984; von der Oelsnitz et al. 1991; Verstandig et al. 1991; Sanz et al. 1997; Berghoff et al. 1998; Prasad et al. 2003; Aggarwal et al. 2004; Kirli et al. 2012.

Ultrasonography typically shows biliary dilatation (Friedburg et al. 1984; Arnaud et al. 1987; Geoffray et al. 1987) and a space-occupying process or intraductal mass within the common duct, usually surrounded by fluid which may reflect necrosis (Friedburg et al. 1984; Geoffray et al. 1987). The portal vein may be displaced by large lesions, but portal vein thrombosis has not been noted (Geoffray et al. 1987). Color Doppler imaging has revealed numerous abnormal tumor arteries with low resistive index (Roebuck et al. 1998). CT images disclose low-density irregularly shaped masses within the dilated duct, with hypodense and heterogeneous attenuation patterns (Geoffray et al. 1987). Low attenuation areas within the tumor have been reported (Miller and Greenspan 1985; Caty et al. 1990; Patil et al. 1992; Linstedt-Hilden and Brambs 1994). With contrast enhancement, the tumors show four patterns: strong heterogeneous, incomplete globular, mild, and none (Roebuck et al. 1998). The masses may be surrounded by fluid collections which represent bile fluid between the duct wall and the protruding tumor masses (Roebuck et al. 1998). This pattern is also seen in cholangiograms, showing irregular luminal defects (Friedburg et al. 1984), a large mass in the duct lumen (Sanz et al. 1997), or the replacement of the common duct by a multilocular cystic lesion associated with prestenotic marked bile duct dilatation (Kitagawa and Aida 2007). This lesion pattern has been described as early as 1979 by the use of percutaneous transhepatic cholangiography (Cannon et al. 1979). In the case of RMS located to the hepatic hilum, multilocular cystic lesions are seen in US and CT (Kitagawa and Aida 2007). The characteristic luminal alterations caused by RMS can also be demonstrated by use of endoscopic retrograde cholangiopancreatography (ERCP; Himes et al. 2008). In case of marked bile duct dilatation caused by stenosis, choledochal cyst was a frequent diagnosis before surgery (Ruymann et al. 1985; Caty et al. 1990; von der Oelsnitz et al. 1991; Tireli et al. 2005). It has been reported that coronal CT sections were particularly useful in demonstrating the complex relationship of common bile duct RMS to the porta hepatis, pancreas, and duodenum (Verstandig et al. 1991). In MR images, the tumors show predominantly low signal intensity on T1-weighted images with intense but inhomogeneous contrast enhancement. On T2-weighted images, the tumors are moderately to markedly hyperintense (Roebuck et al. 1998).

Pediatric Rhabdomyosarcoma of the Ampullary Region

Embryonal RMS located to the ampullary region is a very rare variant of hepatobiliary RMS causing biliary obstruction. This pathology was first described in 1968 based on autopsy findings on a 6-year-old child (Isaacson 1978). In another case, a 3-year-old boy, exploratory laparotomy performed for obstructive jaundice and a cystic ampullary mass at imaging showed a cystic tumor within the posterior aspect of the pancreatic head, contiguous with the distal common bile duct. The cystic mass was opened, and botryoid, gelatinous material was spontaneously extruded from the cavity. Histology displayed embryonal RMS. Pancreaticoduodenectomy followed by adjuvant chemotherapy and irradiation resulted in long-term survival (Caty et al. 1990). A third case related to a 20-month-old baby girl who presented with 1-month history of progressive jaundice. Contrast-enhanced CT showed a large heterogeneous mass which appeared to arise from the

ampullary region causing biliary dilatation. Endoscopy revealed a large ulcerated lesion in the second part of the duodenum. In the resection specimen, an exophytically growing tumor of 11 cm diameter centered on the ampulla was found. Histology showed ampullary embryonal RMS with invasion of the distal common bile duct, duodenal wall, and pancreas (Perera et al. 2009).

HBRMS in Choledochal Cyst

Choledochal botryoid RMS was described in a 22-month-old boy who developed obstructive jaundice. Imaging first suggested cystic lymphangioma, but the cystic space was found at surgery to be a choledochal cyst harboring RMS (Sassi et al. 2008). A second reported patient was a 6-year-old girl who presented with recurrent jaundice and loss of weight. A large abdominal mass was palpable, and US and CT revealed a large subhepatic mass with multiple septations. The common bile duct opened directly into the mass, and the mass was continuous with the intrahepatic radicles. The resection specimen showed that the mass was choledochal cyst with secondary RMS (Patil et al. 1992).

Pediatric Rhabdomyosarcoma of the Liver Not Related to the Biliary Tract

Primary intrahepatic rhabdomyosarcoma not related to the biliary tract is extremely rare in children. Pack and Miller (1956) reported on a 14-year-old girl with a large tumor in the right liver lobe. Almost the entire lobe was replaced by a cystic thick-walled mass (up to 15.5 cm diameter) filled with amorphous necrotic brown-stained material and thin blood-tinged fluid. The histology showed embryonal RMS. Scheiden et al. (1988) described a 7-year-old boy who had presented with painful hepatomegaly and huge tumor in the left liver lobe. Surgical resection revealed an 18 cm-sized tumor in the left lobe, with extensive central regressive and cystic change. Histology showed embryonal RMS with immature-looking, desmin-positive tumor cells. The patient of Huang and coworkers (2003) was an 8-year-old boy presenting with abdominal pain, spiking fever, and a rapidly growing abdominal mass. Imaging revealed a large solid tumor in the right liver lobe, and the mass was removed by an extended right hepatectomy. Histology showed pleomorphic RMS. The patient died 2 months after resection due to tumor recurrence and massive internal hemorrhage. A second report described a 10-year-old boy who had a voluminous tumor at the inferior face of the right liver lobe, associated with thrombosis of the retrohepatic part of the inferior caval vein. The histology was embryonal rhabdomyosarcoma (Chat et al. 2007).

Rhabdomyosarcoma of the Hepatic Pedicle

In the pediatric age group, the hepatic pedicle or porta region represents an anatomical compartment where unusual tumors may arise, including liposarcoma and rhabdomyosarcoma. Embryonal RMS was observed in the mesenchyme of the liver pedicle in a 10-year-old child (Ferlicot et al. 1999).

Macroscopic Pathology

Most HBRMS exhibit a growth pattern centered on the intrahepatic bile ducts. Apart from this main pattern, RMS may also show a predominantly invasive growth pattern, with marked infiltration of the liver substance (Linstedt-Hilden and Brambs 1994). The tumor may present in the form of a mass filled with hemorrhagic and necrotic material (Kebudi et al. 2003). In resection specimens, one may note polypoid tumor masses that take their origin in the bile duct wall and protrude into the dilated bile duct lumen, sometimes resulting in the typical grape-like morphology that gave this RMS its name (botryoid meaning, grape-like). Resected polypoid, botryoid growths show a striking resemblance to nasal polyps. This

botryoid pattern may result in voluminous papillary-polypoid growths (Leriche 1934; Davis et al. 1969). Smaller resection specimens may only consist of soft, polypoid, gelatinous, and/or transparent tissue fragments. In RMS mainly showing an intrahepatic growth pattern, the cut surface of resection specimens may show, within the mass, bulging tumor nodules representing the polypoid intraductal lesions (Lack et al. 1981).

Histopathology

The histopathology of HBRMS is, as such, the same for intra- and extrahepatic tumors and is therefore summarized for both paragraphs (Figs. 1, 2, and 3; Bässler and Voth 1962). Non-necrotic tumors have an intact surface toward the biliary lumen. Already Sheehan (1930), in his report of a large intrahepatic HBRMS, emphasized that "the mucous columnar epithelium of the included cysts and the bile ducts remained intact and healthy. Thus in the extension down the common bile-duct the large mass of tumour cells had spread underneath the epithelium which it had raised undamaged on its surface." The intact biliary epithelium (with some degrees of epithelial disarray and/or atrophy) is expectedly positive for cytokeratins 7 and 19 and seems to play a significant role for the botryoid growth pattern. The subepithelial tumor generally shows a low cellularity, except a characteristic subepithelial zone of high cellularity, the so-called cambium layer well known from other mucosal sites of RMS. This layer contains most frequently embryonal rhabdomyoblasts, round cells with a myogenic cytoplasm, and racquet and strap cells. The latter possess large nuclei and dark, clumped chromatin and may show cross-striations. Within the cambium, foamy macrophages laden with lipids are not infrequently found (Davis et al. 1969). Interspersed among these neoplastic cells is a myxoid tissue component which becomes more prominent toward deeper layers of the tumor, where the neoplastic cells are more commonly stellate or spindled. The loose aspect of this tissue component may pose considerable differential diagnostic difficulties, because it may be misinterpreted as reactive edematous tissue in biopsies. This myxoid tissue may grow around septal and interlobular bile duct, producing a characteristic tissue sheath. Small bile ducts are usually surrounded by a hypercellular cambium which is in turn surrounded by a looser myxoid tissue (Davis et al. 1969). This tumor tissue induces stenotic changes with the formation of small bile duct cysts.

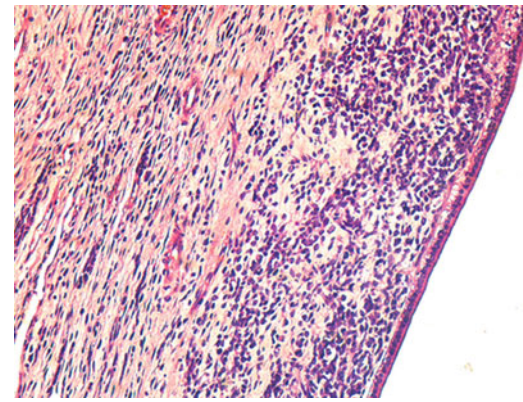

Fig. 1 Hepatobiliary rhabdomyosarcoma, embryonal type. Immature tumor cells form a hypercellular subepithelial layer in a bile duct, the so-called cambium layer (hematoxylin and eosin stain)

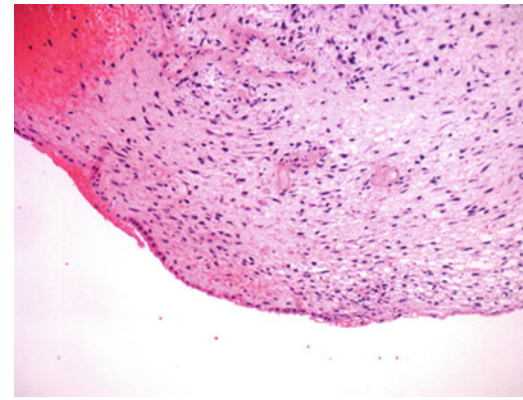

Fig. 2 Hepatobiliary rhabdomyosarcoma, embryonal type. Some of these neoplasms produce polypoid lesions with a loose hypocellular tumor tissue, protruding into bile ducts (botryoid rhabdomyosarcoma; hematoxylin and eosin stain)

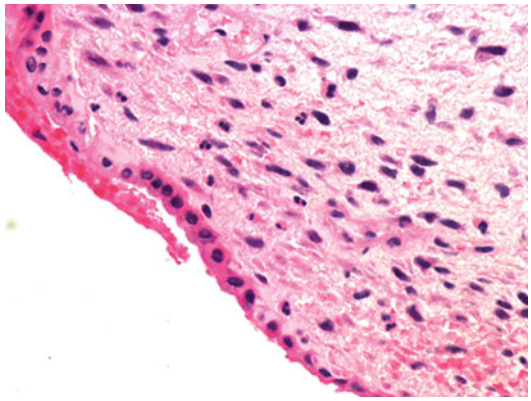

Fig. 3 Botryoid hepatobiliary rhabdomyosarcoma. The embryonal rhabdomyosarcoma consists of slender rhabdomyoblasts. The lesion is covered by damaged biliary epithelium. Botryoid rhabdomyosarcomas may lack a cambium layer (hematoxylin and eosin stain)

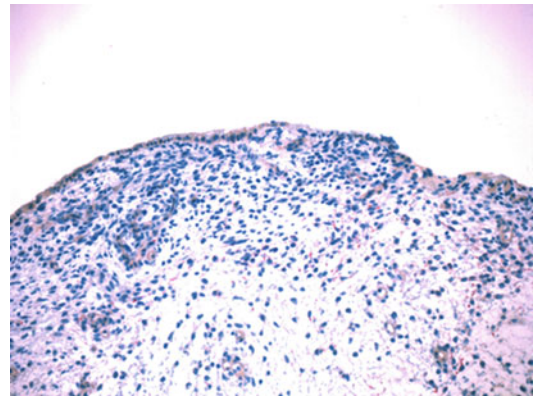

Fig. 4 Hepatobiliary rhabdomyosarcoma, embryonal type. Tumor cells in the cambium layer and stellate cells deeper in the loose tissue are desmin positive (desmin immunostain)

Immunohistochemistry

Immunohistochemistry has been considered to be the decisive diagnostic method in more than 20 % of RMS. RMS cells are consistently reactive for vimentin, and they express the skeletal muscle cell lineage markers, desmin, myogenin, and myogenic regulatory protein D1/MyoD1 (Fig. 4; Dias et al. 1990; Parham et al. 1991; Cessna et al. 2001; Sebire and Malone 2003). In a study of 956 cases (the majority of course being extrahepatic tumors), it was found that myogenin and MyoD1 were equally sensitive (positive for 97 % of RMS cases), with both also showing similar specificity (90 % vs. 91 % of cases), but expression was more consistent in alveolar RMS (ARMS) than embryonal RMS/ERMS (Morotti et al. 2006). In particular, nuclear myogenin expression is more pronounced in ARMS than in ERMS (Morgenstern et al. 2008). In pediatric liver tumors, polyclonal desmin and muscle-specific actin were variably immunoreactive in undifferentiated embryonal sarcoma (UES) and RMS; however, myogenin and MyoD1 were uniformly negative in UES and routinely positive in the majority of hepatobiliary RMS (Nicol et al. 2007). Embryonal RMS did not stain for the paired box transcription factor, PAX5, while 67 % of alveolar RMS were positive (Sullivan et al. 2009). It has been reported that diffuse myogenin expression in soft tissue pediatric RMS is an independent marker of poor survival (Heerema-McKenney et al. 2008). RMS with a component of round cells may be difficult to distinguish from other blue small cell tumors, e.g., neuroblastoma. Peripherin and alpha-internexin are specifically expressed in neuroblastoma but not in RMS. Microtubule-associated protein 1B (MAP1B) is strongly and diffusely expressed in all neuroblastomas but is also detectable in RMS. Nestin is diffusely expressed in RMA but also (multifocally) in a fraction of neuroblastomas (Willoughby et al. 2008). Part of RMS (more commonly ARMS than ERMS) may express anaplastic lymphoma kinase (ALK), most likely independent of the chromosomal fusion status (Corao et al. 2009). The intraluminal polypoid tumor masses in botryoid hepatobiliary RMS are lined by the preexisting cholangiocyte population (Fig. 5).

Ultrastructure

At electron microscopy, cells remote from the biliary mucosal surface are usually separated by a greater amount of loose ground substance containing few scattered collagen fiber bundles. Small aggregates of tumor cells may be partially surrounded by basement membrane. Many tumor

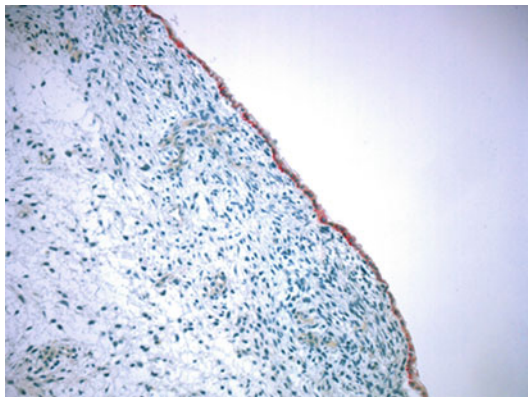

Fig. 5 Hepatobiliary rhabdomyosarcoma, embryonal type. A cytokeratin 19-positive cholangiocyte lining covers the bulging tumor. Note the vague cambium layer and the loose tumor tissue with stellate cells in the deeper part of the duct (CK19 immunostain)

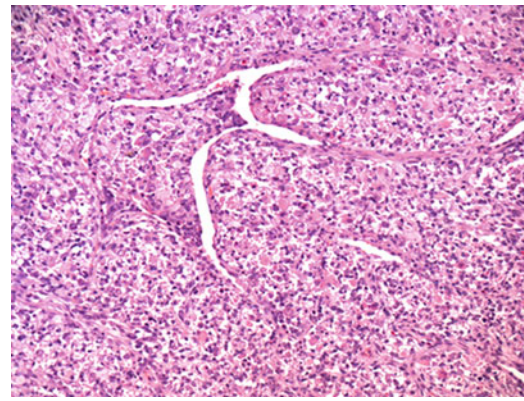

Fig. 6 Alveolar rhabdomyosarcoma of the liver (hematoxylin and eosin stain)

cells are so immature that a proper ultrastructural classification is not possible, but there are also rhabdomyoblasts with variable degrees of differentiation and sometimes well-defined, transversely oriented electron-dense areas and/or incomplete or deformed sarcomeres (Lack et al. 1981). In one electron microscopic study, the neoplasm was shown to consist of three types of cells: polygonal, elongated, and small cells. In contrast to the first two cell types, which revealed moderate to large amounts of myofibrils and occasional A, I, and Z bands, the small cell population was poor in myofibrils, but had dilated ER profiles (Taura et al. 1977).

Biology of Disease

HBRMS is an aggressive lesion that may infiltrate the liver substance and cause local and remote tumor spread, although this type of RMS is more prone to invasion of contiguous structures (Davis et al. 1969; Ruymann et al. 1985). In about 30 % of cases, metastases to the peritoneum, omentum, and locoregional lymph nodes occur. Distant metastases have been found in the lungs, pericardium, and bones of skull and extremities (Davis et al. 1969).

HBRMS remained incurable for a very long time period, until a child was cured by partial surgical resection, radiotherapy, and chemotherapy in 1971 (Akers and Needham 1971). In 1985, the Intergroup Rhabdomyosarcoma Study Group (IRSG) reported ten cases of HBRMS treated on the IRS I and IRS II protocols (Ruymann et al. 1985). Four of these ten patients survived, showing that, at that time, outcome was still poor. Aggressive surgery had been proposed (Martinez et al. 1982; Schweizer et al. 1994), but an analysis of 25 eligible patients with HBRMS enrolled in IRSG studies I through IV from 1972 to 1998 showed that gross total resection is rarely possible despite aggressive surgery and that outcome is good despite residual disease after surgery (Spunt et al. 2000). The signs and sequelae of obstructive jaundice/cholestasis may be relieved by external and internal-external biliary drainage (Roebuck and Stanley 2000). RMS located in soft tissues and classical sites will more and more be stratified for risk, e.g., via immunohistochemical marker expression or gene expression profiling (metagene patterns; Bortoluzzi et al. 2005). This has not yet been accomplished with hepatobiliary RMS, owing to the rarity of these lesions.

Hepatobiliary Alveolar Rhabdomyosarcoma

Hepatobiliary alveolar RMS is a very rare neoplasm (Fig. 6). Only in two reports there is evidence of an alveolar component. In a pediatric

hepatic rhabdomyosarcoma with striated tumor cells and associated with mucin-producing cysts reported in 1930 (Sheehan 1930), one figure of the publication depicts what seem to be alveolar rhabdomyosarcoma. The other patient with an alveolar hepatic RMS was an adult male (68 years) with a tumor in the right liver lobe (Shibata et al. 1987).

Primary Rhabdomyosarcoma of the Bile Ducts in Adults

Primary RMS of the large bile ducts in adults is extremely rare and has been described in the common bile duct (Aldabagh et al. 1986). The 40-year-old female patient presented with jaundice of short duration. A transhepatic percutaneous cholangiogram revealed an obstructive lesion involving the common bile duct with marked dilatation of the biliary system. At laparotomy, the tumor grossly involved the wall of the choledochus and extended into the cystic duct and common hepatic duct. Histologically, one noted an infiltration of the full thickness of the wall and the surrounding fatty tissue by a desmin- and myoglobin-reactive RMS with a distinct cambium layer. Elsewhere, the cells infiltrated in a single-file pattern with a desmoplastic reaction around normal structures (Aldabagh et al. 1986). Rhabdomyosarcoma may also develop in choledochal cysts. Pleomorphic RMS within a choledochal cysts has been described as a cause of obstructive jaundice (Tufail et al. 2006).

Primary Rhabdomyosarcoma of the Liver in Adults Not Clearly Related to the Biliary Tract

Adult-type rhabdomyosarcoma has been classically defined as a pleomorphic sarcoma with desmin expression occurring in the extremities and the trunk of adult patients. Classification of these lesions has been complex until a consensus was found (Palmer, SIOP, NCI, and International Classifications; review: Parham 2001). Histologically, these neoplasms occur in three categories, i.e., spindle cell RMS, pleomorphic RMS, and mixed forms (Stock et al. 2009). Spindle cell RMS seems to be a variant of embryonal RMS, and this tumor also occurs in the form of sclerosing spindle cell RMS (Gavino et al. 2010). Alveolar RMS is a distinct entity different in many aspects from classical adult-type RMS and shows up in a classical form and variants, including the clear cell variant. RMS occurring in the adult liver as a primary tumor seems to have complex features, in that also embryonal-type RMS and variants thereof have been reported.

Selected References Miller and Pack 1956; Mori et al. 1979; Hatanaka et al. 1983; Watanabe et al. 1983; Morimoto et al 1986; McArdle et al. 1989; Cote and Urmacher 1990; Hayakawa et al. 1990; Zornig et al. 1992; Bürrig and Knauer 1994; Hiyama 1995; Tominaga et al. 1995; Meyer-Pannwitt et al. 1996; McRae and Lee 2005.

Two tumors were reported to be alveolar RMS (Shibata et al. 1987; Schoofs et al. 2011). In one of these neoplasms, FISH analysis revealed PAX3/FOXO1A fusion (Schoofs et al. 2011). The hepatic cell of origin for these sarcomas is not known. Hepatic RMS in the adult may coexist with synchronous hepatocellular carcinoma in the same liver (Hatanaka et al. 1983; Morimoto et al. 1986; Hayakawa et al. 1990).

Pathology

Macroscopically, the tumors were described to be mass lesion with a nodular border, whitish to yellowish, and either soft or firm. Sometimes, hemorrhage and necrosis occur (Watanabe et al. 1983). Embryonal RMS classically consists of small, undifferentiated round to spindled or stellate cells that may resemble embryonic skeletal muscle cells. These cells are embedded in a myxoid matrix, causing a typical "loose" aspect of the tissue, with hypocellular and hypercellular areas. Differentiation of the cell lineage presents as an increasing number of cells with eosinophilic cytoplasm ("tadpole cells" and "strap cells"). These cells contain myofibrils, may show cross-

striation, and are rhabdomyoblasts. This phenotype is the classical variant of embryonal RMS. Part of the tumor cells may show distinct angulation of the muscle fibers – the so-called broken straw sign. The spindle cell variant has not been found in the liver so far. Immunohistochemically, more than 95 % of the tumor cells are reactive for desmin (Altmannsberger et al. 1985) and for HHF35, a monoclonal antibody directed against muscle actins (Schmidt et al. 1988). Nuclear positivity for myogenin is also diagnostically very useful (Cessna et al. 2001).

Rhabdomyosarcoma in/of the Inferior Vena Cava

Sarcoma of the inferior vena cava is usually leiomyosarcoma, with or without associated Budd-Chiari syndrome (see the respective chapter). More than 100 cases of this distinct entity have been reported. In contrast, other sarcomas are exceptional findings in this location. In particular, this refers to vascular RMS, which is mainly known from the pulmonary trunk and the pulmonary artery (Watanabe et al. 1985). A 63-year-old male patient had obstruction of the inferior vena cava caused by intraluminal pleomorphic RMS. This tumor was resected, but the patient died of local recurrence. Autopsy revealed RMS extending from the inferior vena cava just above the right renal vein to the right atrium and involving the caudate lobe of the liver. The tumor was associated with Budd-Chiari syndrome. It was difficult to decide whether the tumor took its origin in the vena cava or the liver (Fujita et al. 1993).

Intraperitoneal Involvement in Pediatric Rhabdomyosarcoma

Peritoneal manifestations of pediatric malignancy chiefly relate to desmoplastic small round cell tumors, lymphoma, germ cell tumors, neuroblastoma, Wilms tumor, and secondary seeding of intracranial tumors by ventriculoperitoneal shunts. Intraperitoneal neoplastic involvement in RMS is not common but may get into differential diagnostic considerations in case the lesions develop on the liver surface. It has been reported that approximately 10 % of children with abdominopelvic RMS may have intraperitoneal involvement either at the time of diagnosis or subsequently. The manifestations of intraperitoneal involvement comprise enhancing nodules or masses, a pseudomyxoma peritonei-like appearance, omental caking, and ascites (Chung et al. 1998). Intraperitoneal involvement has been observed in pelvic RMS, with enhanced nodular lesions in CT also located around the liver and in the lesser sac (Oto et al. 2001).

Liver Metastasis in Pediatric and Adult Rhabdomyosarcoma

RMS may metastasize to almost all organs, but there are instances where patients with RMS present with a distinct mode of diffuse metastasis. These cases may be called the leukemic variant of RMS, because the children can have fever, generalized malaise, bone pain due to marrow involvement, and circulating RMS cells in the peripheral blood smear resembling leukemia (Cohen 1992). Hepatic metastases have also been described for sclerosing RMS (Kikuchi et al. 2013).

Hepatic Rhabdomyomatous Tumors

In the pediatric age group, rhabdomyomas typically occur in the heart and here mostly in the context of tuberous sclerosis. In 1862, Friedrich Daniel von Recklinghausen reported pigeon egg-sized myomas found in the heart of a newborn (von Recklinghausen 1862), and these lesions were termed rhabdomyoma by the German physician and pathologist, Friedrich Albert von Zenker (1864). In childhood, rhabdomyomatous tumors may arise in the liver as a late sequela of fetal rhabdomyomatous nephroblastoma. This lesion is considered to be a predominantly monophasic mesenchymal variant of Wilms tumor, sometimes bilateral, which has not been seen in patients older than 4 years. It exhibits a less aggressive biology than standard

Wilms tumor despite its usually much larger size (Wigger 1976; Eble 1983; Joseph et al. 2003). Primary and metastatic lesions of this nephroblastoma variant can undergo maturation (Ishikawa et al. 2001). In a 14-year-old boy, a tumor with the features of a fetal rhabdomyoma arose in the liver 13 years after treatment for fetal rhabdomyomatous nephroblastoma (van der Kwast et al. 1992).

Other Liver Tumors with a Rhabdomyocytic/ Rhabdomyoblastic Differentiation

In the pediatric age group, hepatoblastoma may develop rhabdomyoblastic components within the spectrum of mixed epithelial and mesenchymal hepatoblastoma with teratoid features (Shabanov et al. 1981). However, there are also pediatric liver tumors with a rhabdomyoid component that cannot easily be allocated to mixed hepatoblastomas. Williams (1953) described, in 2-year-old boy, a neoplasm which he termed liver tumor of mixed type. The tumor presented as a cystic mass located in the right liver lobe. At necropsy, the mass consisted of cysts with a diameter ranging from 1 to 3 cm and solid components. The largest cystic mass had a fibrous capsule and contained thin leaves of tissue separated by a glairy mucous substance. Microscopically, the cysts were lined by a mucus-secreting cuboid or flattened epithelium. The cysts were separated by a mesenchyme that showed embryonic features and hypercellular areas, containing round cells, spindle cells, or strap-like cells and focally immature muscle cells with cross-striation. A similar tumor had been described by Sheehan (1930). A 6-year-old girl showed, at necropsy, a liver tumor of 12 cm diameter. This tumor grossly consisted of whitish tissue and was fairly soft, but showed little necrosis and no hemorrhage. It had a well-defined but not encapsulated edge. An extension had spread down the bile duct, with formation of a bulging and bulbous intraluminal mass. Histology in part corresponded to rhabdomyosarcoma, with striated tumor cells. In addition, however, there were clusters of cysts associated with the tumor, measuring up to 2 cm in diameter. The cysts were lined by single layer of columnar epithelium which secreted mucin. There are primary hepatic tumors which co-express features of both, hepatocellular carcinoma and rhabdomyosarcoma (so-called rhabdomyosarco-hematoma; Goldman and Friedman 1969), or features of combined cholangiocarcinoma and rhabdomyosarcoma. These carcinosarcomas are discussed in a separate chapter. Gastrointestinal stromal tumors (GIST) can show, both in the primary tumor and liver metastasis, rhabdomyosarcomatous differentiation after tyrosine kinase inhibitor therapy (Liegl et al. 2009). Schmid and coworkers reported a liver tumor observed in a 36-year-old female patient who had developed intermittent fever and increasing asthenia (Schmid et al. 1979). In a right hepatectomy specimen, they found a spherical, well-circumscribed tumor of 8.5 cm diameter, composed of a whitish-gray, moderately firm tissue with small cystic areas. Histologically, the tumor did not invade the surrounding liver tissue, but rather caused perifocal tissue compression. The interface between the tumor and the liver was characterized by a dense inflammatory infiltration. The neoplasm itself consisted of elongated spindle cells and large and pleomorphic, often multinucleated cells with only rare mitotic figures. Some of the cells displayed a ribbon-shaped appearance like skeletal muscle fibers, however without cross-striation. Also the interior of the tumor showed an inflammatory reaction. These findings suggested a rhabdomyoblastic origin, but ultrastructurally, the tumor cells shared features with hepatocytes. Hence, this neoplasm may represent an example of epithelial-mesenchymal transition.

References

Aggarwal K, Pahuja S, Chadha R (2004) Botryoid rhabdomyosarcoma of common bile duct. Indian J Pediatr 71:363–364

Akers RD, Needham ME (1971) Sarcoma botryoides of the bile ducts with survival. J Pediatr Surg 6:474–479

Aldabagh SM, Shibata CS, Taxy JB (1986) Rhabdomyosarcoma of the common bile duct in an adult. Arch Pathol Lab Med 110:547–550

Ali S, Russo MA, Margraf L (2009) Biliary rhabdomyosarcoma mimicking choledochal cyst. J Gastrointestin Liver Dis 18:95–97

Altmannsberger et al (1985) http://www.ncbi.nlm.nih.gov/pubmed/3881039

Arnaud O, Boscq M, Asquier E, Michel J (1987) Embryonal rhabdomyosarcoma of the biliary tree in children: a case report. Pediatr Radiol 17:250–251

Babin-Boilletot A, Flamant F, Terrier-Lacombe MJ, Marsden B, van Unnik A, Deméocq F et al (1993) Primitive malignant nonepithelial hepatic tumors in children. Med Pediatr Oncol 21:634–639

Babut JM, Ferrand B, Bracq H, Feuillu J, Mention J, Lecornu M (1976) Rhabdomyosarcome hépatique chez l'enfant. Ann Chir 30:251–255

Balkan E, Kiristioglu I, Gurpinar A, Sinmaz K, Ozkan T, Dogruyol H (1999) Rhabdomyosarcoma of the biliary tree. Turk J Pediatr 41:245–248

Bässler R, Voth D (1962) Pathologie und submikroskopische Morphologie des sogenannten Sarcoma botryoides der grossen Gallengänge. Krebsforschung 65:44–55

Berghoff R, Drut R, Urrutia A, Cedola J (1998) Rhabdomyosarcoma of the extrahepatic biliary tree: initial treatment with chemotherapy and conservative surgery. Med Pediatr Oncol 30:290–293

Bernheim M, Feroldi J, Larbre F, Sterlin M (1962) Botryoid sarcoma of the common bile duct. Apropos of a personal case (in French). Pediatrie 17:243–250

Bortoluzzi S, Bisognin A, Romualdi C, Danieli GA (2005) Novel genes, possible relevant for molecular diagnosis or therapy of human rhabdomyosarcoma, detected by genomic expression profiling. Gene 348:65–71

Bürrig KF, Knauer S (1994) Rhabdomyosarcoma of the liver in adulthood. Case report and review of the literature (in German). Pathologe 15:54–57

Caillaud JM, Gérard-Marchant R, Marsden HB, Van Unnik AJM, Rodary C, Rey A, Flamant F (2006) Histopathological classification of childhood rhabdomyosarcoma: a report from the international society of pediatric oncology pathology panel. Med Pediatr Oncol 17:391–400

Cannon PM, Legge DA, O'Donnell B (1979) The use of percutaneous transhepatic cholangiography in a case of embryonal rhabdomyosarcoma. Br J Radiol 52:326–327

Caty MG, Oldham KT, Prochownik EV (1990) Embryonal rhabdomyosarcoma of the ampulla of Vater with long-term survival following pancreaticoduodenectomy. J Pediatr Surg 25:1256–1258

Cessna MH, Zhou H, Perkins SL, Tripp SR, Layfield L, Daines C, Coffin CM (2001) Are myogenin and MyoD1 expression specific fo rhabdomyosarcoma? A study of 150 cases, with emphasis in spindle cell mimics. Am J Surg Pathol 25:1150–1157

Chat L, Mahi M, Chellaoui M, Khattab M, Benamour-Ammar H (2007) Embryonal rhabdomyosarcoma of the liver: an unusual site of origin (in French). J Radiol 88:72–74

Chung CJ, Fordham L:, Little S, Rayder S, Nimkin K, Kleinman PK, Watson C (1998) Intraperitoneal rhabdomyosarcoma involvement in children: incidence and imaging characteristics on CT. AJR Am J Roentgenol 170:1385–1387

Cohen MD (1992) Imaging of children with cancer, 1st edn. Mosby Year Book, St. Louis, pp 308–337

Corao DA, Biegel JA, Coffin CM, Barr FG, Wainwright LM, Ernst LM, Choi JK, Zhang PJ, Pawel BR (2009) ALK expression in rhabdomyosarcomas: correlation with histologic subtype and fusion status. Pediatr Dev Pathol 12:275–283

Corbineau D, Bertrand G, Simard C, Plane P, Delaitre R (1975) Sarcoma botryoide des voies biliares chez l'enfant. Ann Pediatr 22:735

Coronado Perez H, Angulo Hernandez O (1981) Liver neoplasms in children (in Spanish). Bol Med Hosp Infant Mex 38:723–740

Cote RJ, Urmacher C (1990) Rhabdomyosarcoma of the liver associated with long-term oral contraceptive use. Possible role of estrogens in the genesis of embryologically distinct liver tumors. Am J Surg Pathol 14:784–790

Davicioni et al (2009) http://www.ncbi.nlm.nih.gov/pubmed/19147825

Davis GL, Kissane JM, Ishak KG (1969) Embryonal rhabdomyosarcoma (sarcoma botryoides) of the biliary tree. Cancer 24:333–342

Delany HM, Driscoll PJ, Ainsworth H (1966) Sarcoma botryoides of the common bile duct. Report of a case and review of the literature. J Pediatr Surg 1:571–578

Diaconescu S, Burlea M, Miron I, Aprodu SG, Mihaila D, Olaru C, Miron L (2013) Childhood rhabdomyosarcoma. Anatomo-clinical and therapeutic study on 25 cases. Surgical implications. Rom J Morphol Embryol 54:531–537

Dias P, Parham DM, Shapiro DN, Webber BL, Houghton PJ (1990) Myogenic regulatory protein (MyoD1) expression in childhood solid tumors: diagnostic utility in rhabdomyosarcoma. Am J Pathol 137:1283–1291

Donnelly LF, Bisset GS, Frush DP (1998) Diagnosis please. Case 2: embryonal rhabdomyosarcoma of the biliary tree. Radiology 208:621–623

Eble JN (1983) Fetal rhabdomyomatous nephroblastoma. J Urol 130:541–543

Farinacci CJ, Fairchild JP, Sulak MH, Gilpatrick CW (1956) Sarcoma botryoides (a form of embryonal rhabdomyosarcoma) of the common bile duct: a report of two cases. Cancer 9:408–417

Ferlicot S, Quillard J, Chardot C, Caillou B, Oberlin O, Gauthier F, Fabre M (1999) Unusual site of an embryonal rhabdomyosarcoma of the mesenchymal hepatic pedicle (in French). Ann Pathol 19:521–524

Friedburg H, Kauffmann GW, Bohm N, Fiedler L, Jobke A (1984) Sonographic and computed tomographic features of embryonal rhabdomyosarcoma of the biliary tract. Pediatr Radiol 14:436–438

Fujita H, Kawata K, Sawada T, Mizutani T, Iwasaki Y, Shirono K, Kounosu H, Shirakata S (1993)

Rhabdomyosarcoma in the inferior vena cava with secondary Budd-Chiari syndrome. Intern Med 32:67–71
Gaubert J (1965) Les tumeurs malignes du tube digestif et de ses annexes chez l'enfant. Pediatrie 20:545–554
Gavino AC, Spears MD, Peng Y (2010) Sclerosing spindle cell rhabdomyosarcoma in an adult: report of a new case and review of the literature. Int J Surg Pathol 18:394–397
Geary TR, Maclennan AC, Irwin GJ (2004) Hypertrophic osteoarthropathy in primary liver rhabdomyosarcoma. Pediatr Radiol 34:250–252
Geoffray A, Couanet D, Montagne JP, Leclère J, Flamant F (1987) Ultrasonography and computed tomography for diagnosis and follow-up of biliary duct rhabdomyosarcoma in children. Pediatr Radiol 17:127–131
Goeters W (1941) Bösartige Mischgeschwulst des Duktus choledochus bei einem Kleinkind. Arch Kinderheilk 122:217
Goldman RL, Friedman NB (1969) Rhabdomyosarcohepatoma in an adult and embryonal hepatoma in a child. Am J Clin Pathol 51:137–143
Gout JP, Pont J, Pasquier B, Sarrazin R, Rossignol AM, Roget J (1974) Botryoid sarcoma of the choledochus (in French). Pediatrie 29:689–702
Gururangan S, O'Meara A, MacMahon C, Guiney EJ, O'Donnell B, Fitzgerald RJ, Breatnach F (1992) Primary hepatic tumours in children: a 26-year review. J Surg Oncol 50:30–36
Haider N, Nadim MS, Piracha MN (2013) Primary embryonal rhabdomyosarcoma of the liver in a young male. J Coll Physicians Surg Pak 23:750–751
Hashimoto S, Tanike K, Eto T et al (1980) Botryoid sarcoma of the bile ducts. Rinsho Hashasen 25:507–510
Hatanaka S, Sawada S, Midorikawa O (1983) Autopsy case of hepatoma associated with rhabdomyosarcoma of a probable hepatic origin (in Japanese). Nippon Rinsho 41:895–900
Hayakawa K, Shibata T, Yamashita K, Hamanaka D, Tanigawa N, Uarata Y, Hosokawa Y et al (1990) Computed tomography and angiogram of primary hepatic rhabdomyosarcoma: report of two adult cases. Radiat Med 8:35–39
Hays DM, Snyder WH (1965) Botryoid sarcoma (rhabdomyosarcoma) of the bile ducts. Am J Dis Child 110:595–605
Heerema-McKenney A, Wijnaendts LC, Pulliam JF, Lopez-Terrada D, McKenney JK, Zhu S et al (2008) Diffuse myogenin expression by immunohistochemistry is an independent marker of poor survival in pediatric rhabdomyosarcoma: a tissue microarray study of 71 primary tumors including correlation with molecular phenotype. Am J Surg Pathol 32:1513–1522
Himes RW, Raijman I, Finegold MJ, Russell HV, Fishman DS (2008) Diagnostic and therapeutic role of endoscopic retrograde cholangiopancreatography in biliary rhabdomyosarcoma. World J Gastroenterol 14:4823–4825
Hiyama Y (1995) Primary hepatic leiomyosarcoma and rhabdomyosarcoma (in Japanese). Ryoikibetsu Shokogun Shirizu 7:463–466
Horn RC, Yakovac WC, Kaye R, Koop CE (1955) Rhabdomyosarcoma (sarcoma botryoides) of the common bile duct; report of a case. Cancer 8:468–477
Horowitz ME, Etcubanas E, Webber BL, Kun LE, Rao BN, Rao BN, Vogel RJ, Pratt CB (1987) Hepatic undifferentiated (embryonal) sarcoma and rhabdomyosarcoma in children. Results of therapy. Cancer 59:396–402
Huang FC, Eng HL, Chen CL, Ko SF (2003) Primary pleomorphic rhabdomyosarcoma of the liver: case report. Hepatogastroenterology 50:73–76
Huber J, Sovinz P, Freidl T, Jahnel J, Lackner H, Höllwarth M, Otte JB, Urban C (2008) Long term survival in two children with rhabdomyosarcoma of the biliary tract. Klin Padiatr 220:378–379
Hunt GC, Corless CL, Terry AB, Katon RM (2002) Embryonal rhabdomyosarcoma in a 3-year-old child diagnosed at ERCP: case report and review. Gastrointest Endosc 56:445–447
Isaacson C (1978) Embryonal rhabdomyosarcoma of the ampulla of Vater. Cancer 41:466–468
Ishikawa K, Toyoda Y, Fukuzato Y, Kato K, Ijiri R, Tanaka Y (2001) Maturation in the primary and metastatic lesions of fetal rhabdomyomatous nephroblastoma. Med Pediatr Oncol 37:62–63
Joseph JM, Suter OC, Nenadov-Beck M, Gudinchet F, Frey P, Meagher-Villemure K (2003) Repeated surgical excision for an unusual variant of nephroblastoma: case report and review of the literature. J Pediatr Surg 38: E13
Kebudi R, Görgun Ö, Ayan I, Cosar R, Bilgiç B (2003) Rhabdomyosarcoma of the biliary tree. Pediatr Int 45:469–471
Kirli AE, Parlak E, Oguz B, Talim B, Akçören Z, Karnak I (2012) Rhabdomyosarcoma of the common bile duct: an unusual cause of obstructive jaundice in a child. Turk J Pediatr 54:654–657
Kitagawa N, Aida N (2007) Biliary rhabdomyosarcoma. Pediatr Radiol 37:1059
Kumar V, Chaudhary S, Kumar M, Gangopadhyay AN (2012) Rhabdomyosarcoma of biliary tract – a diagnostic dilemma. Indian J Surg Oncol 3:314–316
Lack EE, Perez Atayde A, Schuster SR (1981) Botryoid rhabdomyosarcoma of the biliary tract. Am J Surg Pathol 5:643–652
Lambl VD (1860) Carcinoma tibiae mit Neubildung von quergestreiften Muskelnfassern. Aus dem Franz-Josef-Kinderhospitale in Prag. Theil I, p 191
Lee MJ, Chang ML, Huang PH, Lue WC (1996) Biliary tree rhabdomyosarcoma: report of one case. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 37:458–460
Leriche MR (1934) Volumineuse tumeur papillomateuse du choledoque chez un enfant. Soc Chir Lyon 31:598–602
Liegl B, Hornick JL, Antonescu CR, Corless CL, Fletcher CD (2009) Rhabdomyosarcomatous differentiation in gastrointestinal stromal tumors after tyrosinase

inhibitor therapy: a novel form of tumor progression. Am J Surg Pathol 33:218–226
Linstedt-Hilden M, Brambs HJ (1994) Two different manifestations of botryoid sarcoma (embryonal rhabdomyosarcoma) of the biliary tree. Bildgebung 61:40–43
Majmudar B, Kumar VS (1976) Embryonal rhabdomyosarcoma (sarcoma botryoides) of the common bile duct: a case report. Hum Pathol 7:705–708
Mann JR, Kasthuri N, Raafat F, Pincott JR, Parkes SE, Muir KR, Ingram LC, Cameron AH (1990) Malignant hepatic tumours in children: incidence, clinical features and aetiology. Paediatr Perinat Epidemiol 4:276–289
Margain-Deslandes L, Gelas T, Bergeron C, Pracros JP, Collardeau-Frachon S, Lachaux A et al (2013) A botryoid rhabdomyosarcoma diagnosed as a choledochal cyst. Pediatr Blood Cancer 60:2089–2090
Martinez FLA, Haase GM, Koep LJ, Akers DR (1982) Rhabdomyosarcoma of the biliary tree: the case for aggressive surgery. J Pediatr Surg 17:508–511
McArdle JP, Hawley I, Sheyland J, Brain T (1989) Primary rhabdomyosarcoma of the adult liver. Am J Surg Pathol 13:961–965
McRae BL, Lee JR (2005) Pathologic quiz case: right upper quadrant abdominal mass in a young woman. Primary hepatorenal embryonal rhabdomyosarcoma with differentiation. Arch Pathol Lab Med 129: e51–e52
Meyer-Pannwitt U, Kummerfeldt K, Broelsch CE (1996) Primary pleomorphic rhabdomyosarcoma of the liver (in German). Langenbeck's Arch Chir 381:75–81
Miller JH, Greenspan BS (1985) Integrated imaging of hepatic tumors in childhood. Part I: malignant lesions (primary and metastatic). Radiology 154:83–90
Miller TR, Pack GT (1956) Total right hepatic lobectomy for rhabdomyosarcoma. AMA Arch Surg 73:1060–1062
Morgenstern DA, Rees H, Sebire NJ, Shipley J, Anderson J (2008) Rhabdomyosarcoma subtyping by immunohistochemical assessment of myogenin: tissue array study and review of the literature. Pathol Oncol Res 14:233–238
Mori H, Matsubara N, Fujii M, Kawai T, Tanaka T, Takahashi M (1979) Alphafetoprotein producing rhabdomyosarcoma of the adult liver. Acta Pathol Jpn 29:485–491
Morimoto H, Takada Y, Akita T, Kato Y, Tanigawa N, Muraoka R, Urata Y (1986) A resected case of collision tumor of hepatocellular carcinoma and primary liver rhabdomyosarcoma (in Japanese). Nippon Geka Gakkai Zasshi 87:456–463
Morotti RA, Nicol KK, Parham DM, Teot LA, Moore J, Hayes J, Meyer W, Qualman SJ (2006) An immunohistochemical algorithm to facilitate diagnosis and subtyping of rhabdomyosarcoma: the children's Oncology Group experience. Am J Surg Pathol 30:962–968
Mulet JF, Illa J, Mainou C, Ros J, Claret I (1982) Rhabdomyosarcoma of the bile ducts (in Spanish). An Esp Pediatr 17:65–70
Nagaraj HS, Kmetz DR, Leitner C (1977) Rhabdomyosarcoma of the bile ducts. J Pediatr Surg 12:1071–1074
Nemada B, Talapatra K, Shet T, Banavali S, Muckaden MA, Laskar S (2007) Embryonal rhabdomyosarcoma of the biliary tree mimicking a choledochal cyst. J Cancer Res Ther 3:40–42
Nicol K, Savell V, Moore J, Teot L, Spunt SL, Qualman S, Children's Oncology Group, Soft Tissue Sarcoma Committee (2007) Distinguishing undifferentiated embryonal sarcoma of the liver from biliary tract rhabdomyosarcoma: a Children's Oncology Group study. Pediatr Dev Pathol 10:89–97
Oto A, Basgün N, Kutluk T, Eryilmaz M, Oran M, Besim A (2001) Intraperitoneal involvement in rhabdomyosarcoma. CT findings in a child. Turk J Pediatr 43:342–344
Pack GT, Miller TR (1956) Total right lobectomy for rhabdomyosarcoma. AMA Arch Surg 73:1060–1062
Parham DM (2001) Pathologic classification of rhabdomyosarcomas and correlations with molecular studies. Mod Pathol 14:506–514
Parham DM, Barr FG (2013) Classification of rhabdomyosarcoma and its molecular basis. Adv Anat Pathol 20:387–397
Parham DM, Kelly DR, Donnelly WH, Douglass EC (1991) Immunohistochemical and ultrastructural spectrum of hepatic sarcomas of childhood: evidence for a common histogenesis. Mod Pathol 4:648–653
Patil KK, Omojola MF, Khurana P, Iyengar JK (1992) Embryonal rhabdomyosarcoma within a choledochal cyst. Can Assoc Radiol J 43:145–148
Perera MT, McKiernan PJ, Brundler MA, Hobin DA, Mayer DA, Mirza DF, Sharif K (2009) Embryonal rhabdomyosarcoma of the ampulla of Vater in early childhood: report of a case and review of literature. J Pediatr Surg 44:e9–e11
Perisic VN, Howard ER, Mihailovic T, Vujanic G, Milovanovic D, Ivanovsky P (1991) Cholestasis caused by biliary botryoid sarcoma. Eur J Pediatr Surg 1:242–243
Phatak AM, Prabhu SR (1982) Sarcoma botryoides of the common bile duct. A case report. Indian J Cancer 19:170–172
Pollono DG, Tomarchio S, Berghoff R, Drut R, Urrutia A, Cedola J (1998) Rhabdomyosarcoma of extrahepatic biliary tree: initial treatment with chemotherapy and conservative surgery. Med Pediatr Oncol 30:290–293
Prasad A, Chadha R, Choudhury SR (2003) Embryonal rhabdomyosarcoma of the common bile duct. Indian J Pediatr 70:91–92
Rebollo Guelar J, Lafont A, Garcia de Davila MT, Solemou V, Rose A, Bignon H (2013) Rhabdomyosarcoma of the biliary tree. Case report (in Spanish). Arch Argent Pediatr 111:e94–e96
Roebuck DJ, Stanley P (2000) External and internal-external biliary drainage in children with malignant obstructive jaundice. Pediatr Radiol 30:659–664
Roebuck DJ, Yang WT, Lam WW, Stanley P (1998) Hepatobiliary rhabdomyosarcoma in children: diagnostic radiology. Pediatr Radiol 28:101–108

Ruymann BF, Raney B, Crist W, Lawrence W, Lindberg R, Soule E, For the Intergroup Rhabdomyosarcoma Study Committee of CCSG and POG (1985) Rhabdomyosarcoma of the biliary tree in childhood. Cancer 56:575–581

Sanz N, de Mingo L, Florez F, Rollan V (1997) Rhabdomyosarcoma of the biliary tree. Pediatr Surg Int 12:200–201

Sarrazin R, Dyon JF, Brabant A, Pont J, Gout JP (1977) Botryoid sarcoma of the choledochus. Reflections apropos of a case and review of the literature (in French). Med Chir Dig 6:45–50

Sassi SH, Charfi L, Abes I, Mrad K, Dhouib R, Hamida NB, Oubiche F, Barsaoui S, Romdhane KB (2008) Cholestasis caused by a choledochal botryoid rhabdomyosarcoma in a 22-month-old boy (in French). Ann Pathol 28:45–48

Scheiden R, Kiesler J, Breitfellner G (1988) Primary embryonal rhabdomyosarcoma of the liver simulating malignant liver mesenchymoma (in German). Pathologe 9:37–41

Schmid C, Lombardi L, Giordano F, Delgrossi S (1979) Unusual morphologic features of a primary liver neoplasm. Tumori 65:649–655

Schmidt et al (1988) http://www.ncbi.nlm.nih.gov/pubmed/3354641

Schoofs G, Braeye L, Vanheste R, Verswijwel G, Debiec-Rychter M, Sciot R (2011) Hepatic rhabdomyosarcoma in an adult: a rare primary malignant liver tumor. Case report and literature review. Acta Gastroenterol Belg 74:576–581

Schweizer P, Schweizer M, Wehrmann M (1994) Major resection for embryonal rhabdomyosarcoma of the biliary tree. Pediatr Surg Int 9:268–273

Sebire NJ, Malone M (2003) Myogenin and MyoD1 expression in paediatric rhabdomyosarcomas. J Clin Pathol 56:412–416

Shabanov MA, Pokrovskaia NN, Iasonov AV (1981) Congenital hepatoblastoma with a rhabdomyoblastic component (in Russian). Arkh Patol 43:73–77

Shamis AI, Movchan VI, Lapina SP (1985) Rhabdomyoblastoma of the biliary tract in children (in Russian). Vestn Khir Im I I Grek 135:99–100

Sheehan HL (1930) An embryonic tumor of the liver containing striated muscle. J Pathol Bacteriol 33:251258

Shibata T, Hayakawa K, Yamashita K, Hamanaka D, Odori T, Ishii Y (1987) Two cases of primary hepatic rhabdomyosarcoma in adults (in Japanese). Rinsho Hoshasen 32:653–656

Shimada H, Newton WA, Soule EH, Beltangady MS, Maurer HM, For the Intergroup Rhabdomyosarcoma Study Committee (1987) Pathology of fatal rhabdomyosarcoma. Report from Intergroup Rhabdomyosarcoma Study (IRS-I and IRS-II). Cancer 59:459–465

Soper RT, Dunphy DL (1968) Sarcoma botryoides of the biliary tree. Surgery 63:1005–1011

Spunt SL, Lobe TE, Pappo AS, Parham DM, Wharam MD, Arndt C, Anderson JR, Crist WM et al (2000) Aggressive surgery is unwarranted for biliary tract rhabdomyosarcoma. J Pediatr Surg 35:309–316

Staalman CR, Umans U (1993) Hypertrophic osteoarthropathy in childhood malignancy. Med Pediatr Oncol 21:676–679

Stock N, Chibon F, Binh MB, Terrier P, Michels JJ, Valo I, Robin YM, Guillou L et al (2009) Adult-type rhabdomyosarcoma: analysis of 57 cases with clinicopathologic description, identification of 3 morphologic patterns and prognosis. Am J Surg Pathol 33:1850–1859

Sullivan LM, Atkins KA, LeGallo RD (2009) PAX immunoreactivity identifies alveolar rhabdomyosarcoma. Am J Surg Pathol 33:775–780

Taira Y, Nakayama I, Moriuchi A, Takahara O, Ito T, Tsuchiya R et al (1976) Sarcoma botryoides arising from the bile duct of children. Acta Pathol Jpn 26:709–718

Taura S, Taura M, Tanaka N, Ito T, Tsuchiya R (1977) Ultrastructure of botryoid sarcoma of the common bile duct. Gastroenterol Jpn 12:305–310

Tireli GA, Sander S, Dervisoglu S, Demiralo O, Unal M (2005) Embryonal rhabdomyosarcoma of the common bile duct mimicking choledochal cyst. J Hepatobiliary Pancreat Surg 12:263–265

Tominaga J, Kawase S, Ochi T, Yoshida M, Izawa M (1995) A case of primary rhabdomyosarcoma of liver at autopsy – literature review of 7 cases reported in Japan (in Japanese). Nippon Shokakibyo Gakkai Zasshi 92:255–258

Tufail M, Rizwan MM, Majid HJ (2006) Pleomorphic rhabdomyosarcoma within a choledochal cyst; a rare cause of obstructive jaundice. J Pak Med Assoc 56:379–381

Van der Kwast TH, ten Kate FJ, Vuzevski VD, Madern GC, Terpstra OT (1992) Hepatic rhabdomyomatous tumor: late sequel of a fetal rhabdomyomatous nephroblastoma. Pediatr Pathol 12:449–456

Verstandig A, Bar-Ziv J, Abu-Dalu KI, Granot E, Schiller M (1991) Sarcoma botryoides of the common bile duct: preoperative diagnosis by coronal CT and PTC. Pediatr Radiol 21:152–153

Virenque J, Gaubert J, Bouissou H, Fabre MT (1966) A case of botryoid sarcoma of the bile ducts (in French). Ann Chir Infant 7:25–38

Von der Oelsnitz G, Spaar HJ, Lieber T, Münchow B, Booss D (1991) Embryonal rhabdomyosarcoma of the common bile duct. Eur J Pediatr Surg 1:161–165

Von Recklinghausen FD (1862) Verhandlung der Gesellschaft für Geburtshülfe in Berlin; Sitzung vom 25. März, 1862. Monatsschr. Geburtskunde 20, 1

Von Rokitansky K (1849) Ein aus quergestreiften Muskelfasern constituirtes Aftergewebe. Zschr Gesellsch Wiener Aerzte 331

Von Zenker FA (1864) Ueber die Veränderungen der willkürlichen Muskeln im Typhus abdominalis. Leipzig

Watanabe A, Motoi M, Mizobuchi K, Hara I, Nishimura K, Nagashima H (1983) An adult case with rhabdomyosarcoma of the liver. Jpn J Med Sci Biol 22:240–244

Watanabe K, Yasuda M, Inoue T et al (1985) A case of primary rhabdomyosarcoma of the pulmonary trunk (in Japanese). Nichikyoushitsukaishi 23:739

Werner E (1951) Primary sarcoma of the common bile duct as cause of obstructive jaundice (in German). Kinderarztl Prax 19:122–124

Wigger HJ (1976) Fetal rhabdomyomatous nephroblastoma – a variant of Wilms' tumor. Hum Pathol 7:613–623

Wilks S, Moxon W (1875) Lectures on pathologic anatomy, 2nd edn. Brown Green, Longmans Roberts, London, pp 465–466

Williams AW (1953) Liver tumour of the mixed type. Br J Surg 41:13–15

Williams AG, Sheward SE (1986) Ultrasound appearance of biliary rhabdomyosarcoma. J Clin Ultrasound 14:63–65

Willis RA (1948) Pathology of tumours. Butterworth, London

Willis RA (1962) The pathology of tumors of children. Charles C. Thomas, Springfield, pp 67–75

Willoughby V, Sonowala A, Werland-Perurena A, Donner LR (2008) A comparative immunohistochemical analysis of small round cell tumors of childhood: utility of peripherin and alpha-internexin as markers for neuroblastomas. Appl Immunohistochem Mol Morphol 16:344–348

Witcombe JB (1979) Biliary rhabdomyosarcoma of childhood. Br J Radiol 52:1005–1006

Zampieri N, Camoglio F, Corroppolo M, Cecchetto M, Ornis S, Ottolenghi A (2006) Botryoid rhabdomyosarcoma of the biliary tract in children: a unique case report. Eur J Cancer Care (Engl) 15:463–466

Zhao M, Feng C, Wang JW, Liu Y, Tang SQ (2011) Childhood rhabdomyosarcoma: a retrospective review of 23 cases (in Chinese). Zhongguo Dang Dai Er Ke Za Zhi 13:657–660

Zornig C, Kremer B, Henne-Bruns D, Weh HJ, Schröder S, Brölsch CE (1992) Primary sarcoma of the liver in the adult. Report of five surgically treated patients. Hepatogastroenterology 39:319–321

Lipomatous Tumors, Liposarcoma, Benign Adipocyte-Containing Nonneoplastic Lesions, and Focal Fatty Changes of the Liver

65

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_65

Abstract

In the liver several adipocytic tumors and fatty lesions mimicking these neoplasms can develop. Primary lipomas of the liver are rare lesions that are either incidental findings or may produce mass effects, because these tumors can grow to very large size. Histologically, they consist of mature adipocytes. Hepatic lipoma has to be distinguished from adipocyte-rich angiomyolipoma, a tumor of the PEComa group, and from pseudolipoma of Glisson's capsule. Other benign hepatic tumors with an adipocyte or adipocyte-like component include myelolipoma and hibernoma. The malignant counterpart of lipoma, liposarcoma, is an exceedingly rare primary hepatic malignancy. Most liposarcomas found in the liver are in fact metastases. Primary hepatic liposarcomas are often large lesions. Histologically, the diverse patterns known for soft tissue liposarcomas are also observed in the respective liver tumors. Adipocytic neoplasms of the liver can be mimicked by other fat-rich lesions, including focal fatty change and focal fatty sparing of the liver.

Lipoma of the Liver

Introduction

Hepatic lipomas are unusual lesions, which previously have been found as incidental findings at autopsy, but have been detected in recent times more frequently in vivo, chiefly owing to refined imaging techniques. Descriptions date from as early as 1938 (Afekowna 1938) and are difficult to judge with respect to the true nature of the lesion, but more cases have been reported from about 1950 onwards. Most hepatic lipomas have been reported individually, four cases were reviewed in 1976 (Ishak 1976), and a larger series of 12 lesions was published in 1984 (Goodman and Ishak 1984). Since 1951, more than 30 cases have been reported.

Selected references: (Dirschmid and Kiester 1979; Hoeffel et al. 1977; Hübener and Hippeli 1980; Kampmann and Allmendinger 1983; Ramchand et al. 1970; Young 1951; Pounder 1983a; Bugovics 1988; Fulcheri 1987; Garant and Reinhold 1996; Liessi 1987; Mathieu et al. 1997; Pham et al. 1986; Prayer et al. 1992; Scapati et al. 1994; Shima et al. 1986; Souz 1984; Takagi et al. 1994; Takayasu 1987; Tarasiuk et al. 1991; Horton et al. 1999; Delis et al. 2008; Martin-Benitez et al. 2012; Nakamura et al. 2009; Petri et al. 2003; Puljiz et al. 2012; Szentpali et al. 2000).

Clinical Features

Clinically, hepatic lipomas are usually incidental findings at imaging or at autopsy, but large lesions may produce hepatic mass effects. The age range of these tumors is large, and there is no sex predilection, as far as can be judged from the cases reported so far. The clinical course is benign; in particular there is no evidence that hepatic lipomas have changed into a malignant tumor. Hepatic lipomas are usually not associated with preexisting liver disease, with the exception of hepatic steatosis. In a study of 92 benign hepatic lesions analyzed with MR imaging, a statistically significant relationship between hepatic lipomas and liver steatosis was found, a relationship suggested to be related to a common insulin resistance mechanism (Martin-Benitez et al. 2012).

Pathology of Hepatic Lipoma

Macroscopy

Hepatic lipomas occur as a usually solitary mass that grossly presents as circumscribed but not completely encapsulated tumors typically with a diameter of few mm to few cm (Figs. 1 and 2), but they can grow to considerable size (giant hepatic lipoma; 15 cm, (Bornstein-Quevedo et al. 2000); 21 cm, (Sonsuz et al. 1994). Multiple hepatic lipomas are exceptional findings (Delis et al. 2008). Most lipomas exhibit a more or less spherical shape and are situated deeply within the organ, but pedunculated variants have also been observed. Hepatic lipoma may occur together

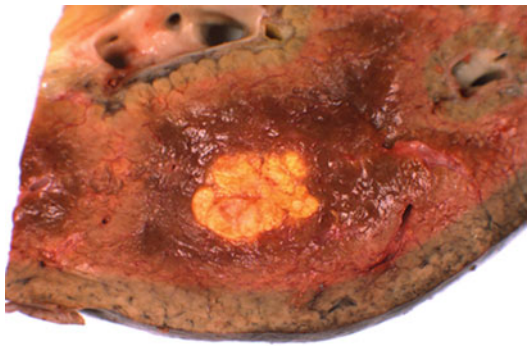

Fig. 1 Primary lipoma of the liver. A *yellow* lobulated tumor displays an expanding growth pattern

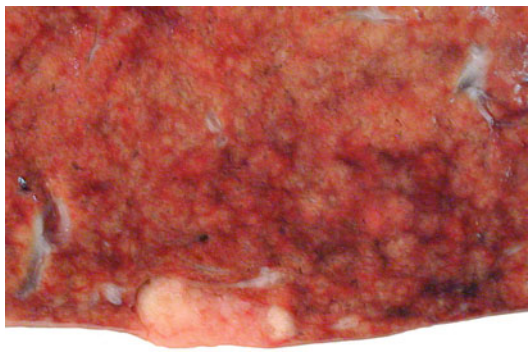

Fig. 2 Small subcapsular lipoma of the liver

with other liver tumors, such as hepatocellular carcinoma (Jover et al. 2001), but this may rather be a coincidental finding than a causal relationship.

Histopathology

Histologically, hepatic lipomas chiefly consist of mature-looking adipocytes, similar to lipomas in other locations. In large lesions one may note small regression foci with accumulation of foamy macrophages. At the border between the tumor and the adjacent liver substance, there is usually not a complete pseudocapsule, and adipocytes are mostly in direct contact to parenchyma, with relatively few cells interdigitating with the lobular tissue. However, there are instances where an incomplete fibrous interface had been observed (Szentpali et al. 2000). Particularly in case of large lesions, there is perifocal atrophy of adjacent liver tissue. Diagnosis of hepatic lipoma can be achieved by aspiration cytology (Langsteger et al. 1990).

Hepatic Lipomas vs. Fat-Rich Angiomyolipoma

A distinct situation are hepatic adipose tissue tumors developing in the context of tuberous sclerosis (Hirasaki et al. 1999; Schneider-Monteiro et al. 2003). It is difficult to judge whether the lesions classified as hepatic lipoma were in fact true lipomas or rather fat-rich hepatic angiomyolipomas. However, in one case a liver tumor was removed, histologically shown to be lipoma and being HMB-45 negative, in contrast to renal angiomyolipoma found in the same patient (Schneider-Monteiro et al. 2003). In a 30-year-old female patient with renal angiomyolipoma associated with tuberous sclerosis, abdominal sonography revealed multiple high echoic round tumors with acoustic shadows in the liver. Subsequent dynamic CT showed that these multiple lesions had contrast enhancement suggesting that these tumors were more likely angiomyolipoma than lipoma. A liver biopsy specimen appeared to have only adipose tissue, resulting in the diagnosis of hepatic lipomatous tumor (Hirasaki et al. 1999). However, it cannot be excluded that these lesions were adipose-predominant angiomyolipomas (see the chapter on these tumors).

Differential Diagnosis

The clinicopathologic differential diagnosis of hepatic lipoma includes fat-rich hepatic angiomyolipoma, hepatic pseudolipoma, the exceedingly rare lipoma of Glisson's capsule, and lipomas located close to the liver, e.g., lipoma of the inferior vena cava (Chou et al. 2001; Grassi et al. 2002; Ubrig-von Barany et al. 2002). The latter is a controversial lesion, because "lipoma" of the inferior vena cava, particularly in its intrahepatic portion, may in at least part of the

cases represent a pericaval and probably normal adipose tissue accumulation rather than a neoplasm. In fact, several cases of a fat mass-like lesion adjacent to and/or projecting into the inferior vena cava, superior vena cava, brachiocephalic vein, and femoral vein have been described, based on diverse imaging procedures, first in 1992 based on 11 cases (Gibo et al. 2001; Han et al. 1997; Hines et al. 1999; Katz and Goffner 2002; McClure et al. 2001; Miyake et al. 1992; Pan et al. 1995; Perry et al. 1994; Raju and Austin 2001; Sheafor et al. 1998; Thorogood and Maskell 1996; Tobias and Berkowitz 1992; Trabut et al. 1999; Vinnicombe et al. 1994). Between 1992 and 1999, more than 30 cases of such lesions spatially related to the subdiaphragmatic portion of the intrahepatic segment of the inferior vena cava have been reported, and some have termed these benign fat tissue structures as intravascular lipoma (McClure et al. 2001; Pan et al. 1995; Perry et al. 1994). A localized fat collection adjacent to the subdiaphragmatic inferior vena cava may mimic intracaval fat on axial CT scans owing to acute angulation of the IVC, probably as a result of anatomic variation (Han et al. 1997).

Lipoma of the Bile Ducts

Benign and malignant lipomatous tumors represent one of the most uncommon neoplastic lesion groups in the biliary tract. In a review on benign tumors of the extrahepatic bile ducts reported in the literature over 100 years, only four lipomatous lesions were identified (reviewed in Chu 1950). Three cases cited as lipomatous tumors that had developed in the extrahepatic bile ducts were associated with biliary retention and jaundice. However, none of these lesions was confirmed by histologic studies (Bouisson 1843; Ehrmann 1843); Dieckman as cited by Devic and Gallavardin 1901). The fourth reported case referred to a girl 3 years of age who clinically manifested progressive jaundice, clay-colored stools, and dark saffron urine characteristic of biliary obstruction. The child deceased and postmortem examination revealed a small "fatty growth" at the junction of the cystic and common bile ducts which was of the size of a large "horsebean." It was described to be a yellowish white, homogeneous, nonvascular growth "which gave a greasy stain to paper." The introduction of a probe showed the cystic and common ducts to be obstructed. The gallbladder "was small and flaccid and contained some grayish seromucoid secretion, which was very unlike its ordinary contents" (Wardell 1869).

Apart from lipoma, liposarcoma of the extrahepatic bile ducts has also been described (Fukusato and Machinami 1996). Lipomas located to the most distal compartment of the large bile duct, or specifically the juxtapapillary region (juxtapapillary lipoma), have been reported somewhat more frequently (Butters 1998; Koninger et al. 1994). The differential diagnosis would include an increase of mural adipose tissue of extrahepatic ducts seen in general obesity and an expansion of the adipose tissue around ducts (peribiliary fat; Shaub et al. 1975). It should be kept in mind that a distinct compartment of adipose tissue is physiologically present at the hepatic hilus (the hilar fat pad; Belloir et al. 1982). Hilar adipose tissue undergoes changes subsequent to corticosteroid therapy (Dietrich et al. 1997).

Lipoma (True Lipoma) of Glisson's Capsule

The first case of apparently true lipoma occurring in Glisson's capsule was reported in 1990 (Sossai and Barbazza 1990). In this 75-year-old female patient with fatal stroke and pneumonia, autopsy showed, on the anterior border of the left liver lobe and incorporated within Glisson's capsule, a yellow mass measuring 3.3 cm in maximum diameter. Histologically, this nodule had a distinct multilobular pattern consisting throughout of mature fat cells, showing only slight variation in size and shape. The lesion was divided by thin trabeculae of fibrous tissue and had a clear vascular network. Importantly for the differential diagnosis with pseudolipoma of Glisson's capsule (see below), the adjacent liver capsule was

populated by small clusters of mature adipocytes.

Pseudolipoma of the Hepatic (Glisson's) Capsule

Introduction

Pseudolipomas of the hepatic capsule, first described in 1929 (Rolleston and McNee 1929), are nonneoplastic solitary lesions consisting of damaged adipose tissue, localized to the hepatic capsule and usually not exceeding 2 cm in diameter (mean diameter for 18 cases reported in the literature, 1.14 cm) (Sasaki et al. 1994). Pseudolipomas were mostly observed as incidental findings in elderly or old individuals. In a review on 18 cases, age at diagnosis ranged from 33 to 86 years (mean, 57 years), and 16 were in male patients (Sasaki et al. 1994). Their significance lies in the risk of being confounded with other fat-containing mass lesions at imaging, in particular true lipoma, hence the terms, pseudolipoma of Glisson's capsule or hepatic pseudolipoma (Fievez and Courtoy 1978; Persaud 1969; Dirschmid and Kiesler 1979; Pounder 1983b; Benbow and Reid 1986; Karhunen 1985; Bruneton et al. 1987; Inoue et al. 1989; Redondo Martinez and Rey Lopez 1990; Quinn and Guzman-Hartman 2003; Sasaki et al. 1994; Shin et al. 2010). Until 1983, only nine cases had been reported (Pounder 1983b), but the prevalence of pseudolipoma was given as 0.2 % in a series of 1,300 consecutive autopsies (Karhunen 1985). Hepatic pseudolipoma has been reported to be missed in sonography, CT being required for detection (Bruneton et al. 1987). CT demonstrates a subcapsular low-density nodule with or without a high-density spot (Sasaki et al. 1994).

Pathology

Macroscopically, the lesions present as polypoid, white to yellowish, encapsulated masses situated on the liver capsule, the nodule being separated from the capsular surface by a more or less prominent peritoneal cleft (Fig. 3; Quinn and Guzman-Hartman 2003), but sometimes they manifest as rather flat lesions, intraoperatively being confounded with metastatic disease. A frozen section will bring the correct diagnosis in such situations. The center of the lesions may consist of friable, slightly granular, or flocculent masses demarcated by a thick capsule-like structure. Histologically, one notes a hypovascular fibrous capsule-like structure surrounding adipose tissue lobules of varying size, frequently with fat necrosis with "shadow adipocytes" (sometimes producing a honeycomb pattern on section), inflammatory reaction (lipophages), calcifications or even ossification, and scarring. Calcium deposits may also occur in the capsule of the lesion. Among 18 reported cases, calcifications within the substance of the nodule were detected in eight and ossification in two, and a central calcification may produce, in CT, a high-density spot resembling a bull's eye within the low-density nodule (Sasaki et al. 1994).

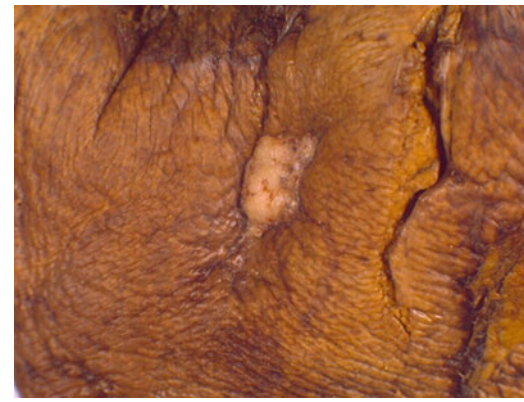

Fig. 3 Pseudolipoma of Glisson's capsule

Pathogenesis

Pathogenically it has been suggested that necrotic or inflamed epiploic appendices or other intraabdominal adipose structures may, via an exudative reaction, adhere to the hepatic capsular surface, subsequently being vascularized by capsular blood vessels (eventually via the induction of an inflammatory granulation tissue) and the

surviving portion then forming an encapsulated adipose tissue nodule. Fat necrosis, e.g., subsequent to strangulation, may induce a repair reaction with formation of a granulation tissue envelope, providing the feeding vessels for the nodule, later changing into a fibrous capsule (circumferential scar). Such a mechanism is supported by the observation that pseudolipomas are more frequently encountered on the anterior aspect of the hepatic capsule, a localization to the posteroinferior aspect being rare (Sasaki et al. 1994). Reattachment and vascularization of amputated fat tissue (migrating loose bodies) may also play a role (Karhunen 1985), but in this study, there was no correlation with previous abdominal surgery or obesity.

It has also been theorized that coelomic mesenchyme originally fated to become omentum or mesentery may ectopically develop in the hepatic capsule to then form what has therefore been termed *coelomic fat ectopia* (Wheeler and Edmondson 1985). Whether this pedunculated lesion, which consisted of mature adipose tissue, was contained in a mesothelial-lined sac, and exhibited numerous bundles of smooth muscle cells, is related to pseudolipoma or represents a different type of lesion is not clear.

Accumulation of Adipose Tissue in Hepatic Fissures and in the Region of the Liver Hilus (the Fat Pad of the Hepatic Hilus)

Fat tissue can develop within hepatic fissures, producing imaging signs of a pseudotumor (Halber and Daffner 1979). Physiologically, adipose tissue is located to the hepatic hilar compartment and here encircles blood and lymph vessels, lymph nodes, and bile ducts. Perihilar fat makes part of the hilar plate, bounded above by segment S4a (the inferior part of the medial segment), on the right by the Rouvière sulcus (a landmark demarcating the division between S6 and S5) and the cystic plate, and on the left is continuous with the umbilical plate (Gadzijev 2002; Kawarada et al. 2000). The adipose tissue located to the hepatic hilus may sometimes grow to larger nodular lesions, in particular in obese individuals. They consist of mature adipocytes and radiologically present as a pseudotumor. These lesions, termed fat pad of the hilus, are usually situated close to the gallbladder infundibulum and have been shown to regress after weight loss of the patient (Belloir et al. 1982). An echo-poor band of fat is seen between the anterior surface of the left lobe of the liver and the anterior abdominal wall in 25 % of patients undergoing an abdominal scan (Vijayaraghavan 1989). Obese patients may show subphrenic adipose tissue causing an increased distance between the diaphragm and the liver (Lindenbraten 1979; Villari et al. 1985). A hepatic/perihepatic adipose tissue pseudotumor can be produced by anteriorly displaced retroperitoneal fat, e.g., in association with pedunculated hepatic hemangioma (Ellis et al. 1985).

Hepatic Hibernoma

Introduction

Hibernomas are rare, benign, and slow-growing neoplasms consisting of brown adipose tissue (Brines and Johnson 1949; Merkel 1906). Typical sites include the thigh, the neck compartment, the scapular region, and soft tissues of the extremities and mediastinal and retroperitoneal spaces. The occurrence of multiple hibernomas has been reported (Baskurt et al. 2004). The classical diagnosis of hibernoma is made by histopathologic examination and finding of characteristic brown fat cells with granular and multivacuolated cytoplasm. However, the percentage of multivacuolated adipocyte-like cells (MVA) varies from one lesion to the other, and this phenomenon has led to the definition of two histologic hibernoma subgroups (Furlong et al. 2001; Ritchie et al. 2006), i.e., lipoma-like hibernoma (<70 % MVA) and non-lipoma-like hibernoma (>70 % MVA). It has been reported that lipoma-like lesions tend to be larger and are well defined, whereas non-lipoma-like lesions tended to be smaller and were unencapsulated (Ritchie et al. 2006).

Primary Hepatic Hibernoma

We are aware of only one reported observation describing a hibernoma component in a primary lipomatous tumor of the liver (Ishak 1976; morphology also reproduced in Craig et al. 1989, Fig. 114). In this situation, two hepatic lipomatous tumors were detected in a 39-year-old female patient. A pedunculated and encapsulated large (8 cm) angiolipoma, grossly presenting as a gritty mass, contained large and granular cells typical for brown adipose tissue, together with focal calcifications. The hibernoma component exhibited apparent transitions from granular cells to large vacuolated adipocytes.

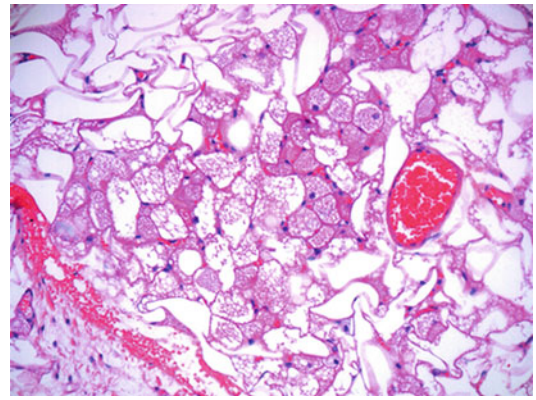

Fig. 4 Hibernoma. The large tumor cells exhibit a foamy, microvesicular cytoplasm (hematoxylin and eosin stain)

General Pathologic Features of Hibernomas

At gross examination, hibernomas vary in their color from brown or tan to yellow, depending on the amounts of granular cells vs. mature adipocytes. Histologically, the tumors exhibit a lobular texture and consist of three principal cell types, i.e., granular eosinophilic, polygonal multivacuolated, and univacuolated cells, and their transition forms (Fig. 4; Gaffney et al. 1983). This has led, as outlined above, to the recognition of two main variants of hibernoma, i.e., lipoma-like and non-lipoma-like forms (Ritchie et al. 2006). A myxoid variant of (Chirieac et al. 2006; Furlong et al. 2001) and a spindle cell variant of hibernoma (Furlong et al. 2001) have been described. Ultrastructurally, there is an inverse relationship between lipid droplet size and the spatial density of mitochondria; the cells exhibit the morphologic signs of marked micropinocytosis, and overall the ultrastructure of normal brown adipose tissue is very similar to that of hibernomas (Gaffney et al. 1983). Immunohistochemically, 85 % of the lesions are positive for S-100 protein (Furlong et al. 2001), and hibernomas express a protein unique to brown adipocyte mitochondria, the uncoupling protein (UCP, see below; Zancanaro et al. 1994). In addition, normal and neoplastic cells of brown adipose tissue express the adhesion molecule, CD31 (platelet-endothelial cell adhesion molecule-1), a member of the immunoglobulin superfamily commonly expressed in endothelial cells and involved in angiogenesis (Rosso and Lucioni 2006).

Hepatic Myelolipoma

Introduction

Myelolipoma is defined as a benign lipomatous tumor that contains variable amounts of normal-looking hematopoietic tissue. Myelolipoma is an unusual neoplasm which mostly occurs in the adrenal gland (review of the literature: Patel et al. 2006), but extra-adrenal sites (extra-adrenal myelolipoma, EAML) are known, including the retroperitoneal space, pelvic region, renal hilum or sinus, parietal pleura, lung, mediastinum, thoracic spine, stomach, and liver, and even generalized variants have been reported (Arzanian et al. 2006; Sawhney et al. 2006). EAML occurs more frequently in females (M:F = 1:2), with a median age at diagnosis of 66.5 years. A strong association of EAML with underlying inflammatory disorders, diabetes mellitus, and cardiovascular disease has been described, similar to that seen with adrenal myelolipomas. Adrenal myelolipoma (in particular the bilateral form) may be associated with endocrine dysfunction (Oliva et al. 1988), specifically adrenogenital syndrome (Miyazaki et al. 1990; Sakaki et al. 2006; Treska et al. 2006), e.g., congenital adrenal hyperplasia

due to 21-hydroxylase deficiency (Umpierrez et al. 1997) and combined 17-alpha-hydroxylase/17,20-lyase deficiency (Patocs et al. 2005). In contrast to the adrenal tumors, extra-adrenal myelolipomas are more frequently associated with hematopoietic disorders of various types. A clonal origin of myelolipoma components has been suggested based on the finding of nonrandom X chromosome inactivation in the hemopoietic elements (Bishop et al. 2006). On the other hand, hemopoietic tissue may accumulate in a tumorous mesenchymal compartment owing to marrow deficiency, as EAML can occur in conjunction with a markedly hypocellular bone marrow (Sawhney et al. 2006). The hemopoietic tissue may be the site of homing for lymphohematologic neoplasms, e.g., Hodgkin's lymphoma (Hagspiel 2005).

Hepatic Myelolipoma

Myelolipoma can occur in the liver as a primary neoplasm originating from an unknown cell type.

Selected references: (Grosdidier et al. 1973; Kaurich et al. 1988; Le Neel et al. 1984; Mali et al. 1986; Nishizaki et al. 1989; Rubin et al. 1984); Moreno Gonzales et al. 1991; (Fauchery et al. 1998; Imaoka et al. 1995; Orlandi et al. 1994; Pavon et al. 2009; Radhi 2010; Savoye-Collet et al. 2000; Takizawa et al. 1995).

As far as can be judged from the few reports, hepatic myelolipomas mostly occur in older individuals, and may be more frequent in females. In a review of six cases, five tumors occurred in females (Nishizaki et al. 1989). In this series, the tumor diameters ranged from 2 to 15 cm. In one report, hepatic myelolipoma developed in a hepatocellular carcinoma, with formation of a central nodule of 1.4 cm diameter in an HCC of 12 cm size (Van Hoe et al. 1994), and bone marrow was also once detected in a liver cell adenoma (Renaldi et al. 1993).

Hepatic myelolipoma was detected incidentally by the use of echography performed after the onset of a nonspecific painful symptomatology (Orlandi et al. 1994). CT examination revealed characteristic features of a fat-enriched mass (Nishizaki et al. 1989). In one case, abdominal MR showed heterogeneous low signal intensity on T1-weighted images, and the mass was initially hypointense after administration of a gadolinium bolus, and on the delayed-phase images, peripheral enhancement was observed (Savoye-Collet et al. 2000). Selective hepatic arteriography depicts myelolipoma as a hypervascular mass with a less vascular center, and unenhanced computed tomograms show a mass of low attenuation due to accumulation of fat (Nishizaki et al. 1989; Rubin et al. 1984).

The tumors may grow to impressive size, diameters of up to 17 cm and a weight of 880 g having been reported (Savoye-Collet et al. 2000). Macroscopically, myelolipomas are circumscribed and lobulated but usually nonencapsulated masses and are typically yellow to tan, the color range being dependent on the relative amounts of adipose tissue vs. hemopoietic tissue (Fig. 5). Large areas of myeloid tissue produce dark-red or purple foci on

Fig. 5 Myelolipoma of the liver. The bulging, well-delineated yellow tumor developed in a liver with secondary biliary fibrosis/cirrhosis

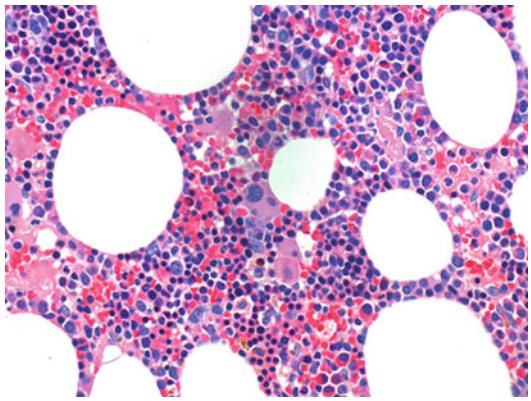

Fig. 6 Myelolipoma of the liver. Hematopoietic tissue intermingled with large adipocytes is the salient histologic feature (hematoxylin and eosin stain)

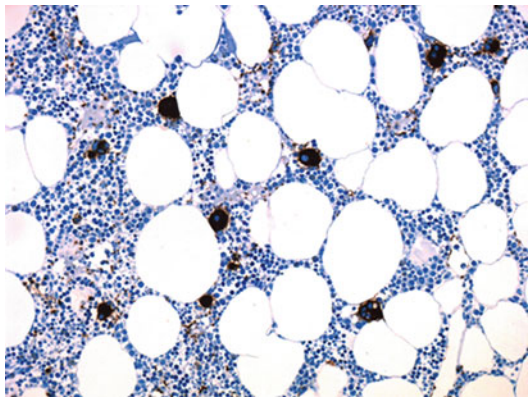

Fig. 7 In myelolipoma, megakaryocytes are typical component (CD61 immunostain)

a yellow background. Histologically, the hepatic tumors exhibit the same pattern as the adrenal ones, including the presence of megakaryocytes in the hemopoietic islands (Figs. 6 and 7; Rubin et al. 1984). The adipose component may be fibrotic, and in the hemopoietic tissue, lipid-laden macrophages may be present, suggesting lipid pinocytosis after decay of adipocytes. In one report, lipoblasts have been observed in the adipose component (Orlandi et al. 1994). The adjacent liver substance shows some atrophy owing to the expansive growth of the lesion, but hyperplastic hepatocyte changes in the tumor's vicinity have also been recognized (Orlandi et al. 1994). Exceptionally, myelolipoma was inside another hepatic mass, e.g., focal nodular hyperplasia (Suarez-Peñaranda et al. 2014).

Hepatobiliary Liposarcoma

Introduction

Liposarcoma primary to the liver is an exceedingly rare tumor. Wolloch and coworkers were apparently the first to describe such a lesion (Wolloch et al. 1973). In this study, the index patient with myxoid liposarcoma of the liver underwent a right hemihepatectomy and survived for 46 days only after surgery. Only a few bona fide cases were subsequently reported.

Selected references: (Aribal and Berberoglu 1993; Chen et al. 1988; Enterlaine et al. 1960; Golebiowski and Abycht 1987; Kim and Reyes 1985; Kim et al. 1987, 2007; Soares et al. 1989; Wolloch et al. 1973; Wright et al. 1993; Khan et al. 2001; Binesh et al. 2012; Gajda et al. 2007; Kuo et al. 2006; Lee et al. 2008; Naik et al. 2013; Nelson et al. 2001; Yu et al. 2002, 2008).

Classification

The WHO classification of liposarcomas is summarized in Table 1.

Epidemiology

In the light of the rarity of this hepatic malignancy, the known epidemiologic features are still fragmentary. Most patients were older than 30 years at the time point of diagnosis, but the tumor also occurs in infants and children, in this age group restricted to the hepatic hilar region (Chen et al. 1988; Soares et al. 1989; Wright et al. 1993).

Table 1 Classification of liposarcomas

	ICD-O code
Intermediate (*locally aggressive*)	
Well-differentiated liposarcoma	8851/3
Malignant	
Dedifferentiated liposarcoma	8858/3
Myxoid liposarcoma	8852/3
Round cell liposarcoma	8853/3
Pleomorphic liposarcoma	8854/3
Mixed-type liposarcoma	8855/3
Liposarcoma, not otherwise specified (NOS)	8850/3

Clinical and Imaging Features

Clinically, patients may present with upper abdominal pain, nausea, fever, and eventually jaundice. Radiological and sonographic examinations disclose a usually large hepatic mass, however with variable patterns at imaging. The masses can be located to the parenchyma of the liver or to the hilar area. In one case, sonography showed a poorly defined, lobulated, infiltrating echogenic lesion with shadowing, with hyperechogenic and hypoechogenic parts representing hemorrhage and necrosis (Khan et al. 2001), and similar observations have been reported for other tumors (Aribal and Berberoglu 1993; Kim et al. 1987), whereas CT has demonstrated low-attenuation masses of fat density (Khan et al. 2001; Kim et al. 2007) or a cystic mass (Kuo et al. 2006).

Pathology

Gross Pathology

Macroscopy reveals a usually large and more or less circumscribed mass. In one case, the tumor diameter was 27 cm (Nelson et al. 2001). The lesions may be pedunculated or exophytically growing in some instances. The cut surface is typically lobular and shows myxoid or tan to gray to yellowish tissue, sometimes with marked necrosis and hemorrhage. In fresh state, the tumor tissue may protrude from the cut surface. Hepatic liposarcomas may present as a huge cystic mass with multiple septa (Kuo et al. 2006).

Histopathology

As in liposarcomas located elsewhere, several patterns of differentiation have been described, including well-differentiated, myxoid, and pleomorphic types. Myxoid liposarcoma can present in the form of a multicentric neoplasm that also involves the liver (Cho et al. 2010).

Liposarcoma of the Biliary Tract

Primary liposarcoma has been observed in the extrahepatic bile ducts (Fukusato and Machinami 1996) and in the gallbladder (Hamada et al. 2006) and may be confounded with liposarcoma primary to the liver. Other primary locations around the liver compartment can result in differential diagnostic difficulties, including liposarcomas in the omentum (McAvoy et al. 1978; Ohi et al. 1992).

Differential Diagnosis

Differential diagnosis of primary hepatic liposarcoma comprises metastasis of this tumor to the liver. The primary tumors have been identified in peripheral soft tissues, the retroperitoneal space, breast, and visceral organs other than the liver.

Selected references: (Brasfield and Das Gupta 1970; Elwood et al. 2007; Ferrari et al. 2007; Garces et al. 2008; Huang et al. 2005; Maluccio et al. 2006; Merimsky et al. 1999; Mohandas et al. 1972; Prakash et al. 2008; Sheah et al. 2008; Teas et al. 1978; Wada et al. 2012).

However, visceral and retroperitoneal liposarcomas are those which most often cause liver metastasis, as it is uncommon for extremity soft tissue sarcomas to spread to the liver (less than 0.5 %; Estourgie et al. 2002; Jaques et al. 1995). Among metastasizing myxoid

liposarcoma, the liver was involved in 33 % of patients (Sheah et al. 2008). Also fat-rich, well-differentiated liposarcomas are known to metastasize to the liver, causing multiple fat-rich hepatic lesions (Prakash et al. 2008). Large retroperitoneal liposarcomas can grow toward the liver, push it aside, or invade it, resulting in a hepatic space-occupying lesion (Teng et al. 2012).

Pathogenic Pathways

The etiology and pathogenesis of hepatic liposarcomas are only partially known. It has been suggested that these neoplasms may originate from immature malignantly transformed mesenchymal cells via differentiated along an adipoblast lineage or from mesenchymal stem cells primed to become preadipoblasts/preadipocytes.

Part of liposarcomas show characteristic cytogenetic and molecular alterations (Table 2; review: Conyers et al. 2011).

There is evidence that certain molecular alterations in liposarcoma directly or indirectly affect features of growth, invasion, and spread. For example, the FUS-CHOP fusion protein interacts with the matrix metalloproteinase-2/MMP-2 promoter and can, via this pathway, facilitate metastasis through transcriptional activation of proteases (Patil et al. 2014).

Table 2 Molecular genetic features of liposarcomas

WDLPS and DDLPS	Supernumerary ring and/or giant rod chromosomes, with amplified segments from the 12q13-15 region; often MDM2 amplification (negative regulator of p53)
MLPS	FUS-CHOP/DDIT3 gene fusion in more than 95 %, through translocation t(12;16)(q13;p11)
PLPS	Complex arrangements of several chromosomes including gains and losses; often deletion of 13q14.2-q14.3; some with amplification of mitotic arrest deficient, MAD2

WDLPS well-differentiated liposarcoma, *DDLPS* dedifferentiated liposarcoma, *MLPS* myxoid liposarcoma, *PLPS* pleomorphic liposarcoma

Hilar Liposarcoma in Infancy and Childhood

Liposarcoma is a very rare tumor in the pediatric age group (Bouche-Pillon et al. 1989; Castleberry et al. 1984; Shmookler and Enzinger 1983). A review of previously published cases revealed that the peak incidence is during infancy and early adolescence, the extremities to be the most common site of origin (51 %), a predominance of myxoid histology (76 %), and a lower overall recurrence rate when compared with adult cases (37 % vs. 72 %, respectively) (Castleberry et al. 1984).

Only a few cases of primary hepatic liposarcoma developing in childhood are known, but interestingly part of them emerged in the region of the porta hepatis, where a distinct situation with respect to mesenchyme is present. An obstructive hilar tumor was first reported in 1989 in a 2-year and 4-month-old Caucasian male child presenting with fever and jaundice and resulting in death. The diagnosis of liposarcoma was confirmed at autopsy (Soares et al. 1989). A second case was a myxoid liposarcoma arising at the porta hepatis of a 3-year-old boy, with initially favorable response to surgery combined with radio- and chemotherapy, but with fatal recurrence about 12 years later, i.e., at age 15 years (Wright et al. 1993). A further case of pediatric hepatic liposarcoma was reported in a series of 55 malignant tumors of the liver studied in Taiwan (Chen et al. 1988).

Distinct Patterns of Hepatic Fatty Change Mimicking Tumor Masses: Focal Fatty Change and Focal Fatty Sparing of the Liver

Focal Fatty Change of the Liver

Introduction

Hepatic steatosis is a well-defined entity which is associated with a variety of disorders. Diagnosis and characterization of fat in the liver is a diagnostic challenge in daily practice, owing to the

rather broad differential diagnosis. It has long been known that fatty change of the liver may assume a nonuniform distribution (Mulhern et al. 1979; Scott et al. 1980). Focal fatty change (FFC; synonyms: focal fatty infiltration of the liver, focal hepatic fatty metamorphosis, focal fatty pseudotumor, geographic steatosis) makes part of a whole spectrum of fatty infiltration (FIL) of the liver, first described in 1934 (Simon 1934). According to the radiologic classification of Jain and McGahan (1993), focal hepatic changes related to fat include FFC, where gross areas with marked steatosis arise in an otherwise non-steatotic liver but also skip lesions defined as non-steatotic areas occurring in a diffuse fatty liver (see above Becher et al. 1988; Marchal et al. 1986). It has to be kept in mind that certain regions of the liver are commonly involved by fatty infiltration, such as the medial segment of the left lobe adjacent to the falciform ligament (Yoshikawa et al. 1987). FFC can be associated with a variety of conditions, including obesity, starvation, parenteral nutrition, diabetes mellitus, alcohol toxicity, disorders of blood supply, and drugs (specifically, cancer chemotherapy). It has to be emphasized that alcohol toxicity is not always associated with diffuse hepatic steatosis, but may present as FFC (Tang-Barton et al. 1985). FFC is mostly a disorder found in adults but may also occur in children (Brawer et al. 1980; Igarashi et al. 1994; Yoon et al. 1987). Pathogenetically, several observations suggest that a local disorder of hepatic blood circulation can result in a deranged hepatocytic triglyceride metabolism ending up in neutral fat storage.

Imaging Findings

There is a wealth of informations regarding the imaging features of FFC, related to the fact that FCC can closely mimic malignancy, in particular metastatic disease, and that FCC can produce a significant mass effect (Bashir 1990; Chong and Fan 1994; Gariballa et al. 1997; Martinez Alvarez et al. 1998; Yates and Streight 1986). FFC may be manifest with various appearances on ultrasonography, CT, MRI, and at gross examination (Basaran et al. 2005; Brawer et al. 1980; Kudo et al. 1989; Paulson et al. 1993; Prasad et al. 2005; Shah and Bellon 1986; Yoshikawa et al. 1987). On CT, FFC is identified as a low-density, usually nonspherical lesion usually lacking a mass effect (Halvorsen et al. 1982); however, FFC lesions with an important mass effect have also been reported (Verhille et al. 1994).

Pathology

Macroscopy

At gross examination, FFC manifests as sometimes large and usually sharply delimitated areas of clearly yellow tissue on the background of liver substance showing normal features (Figs. 8 and 9). The border of the lesion may be curved or sawtooth-like. In a postmortem study on lesions incidentally detected in ten patients, areas of FFC were measured up to 4 cm in diameter and were predominantly subcapsular in location (Brawer et al. 1980).

As summarized in Table 3, FFC manifests in the form of several morphotypes. Apart from FFC occupying large areas of a segment or lobe as a solitary lesion, there are instances where FFC are multiple or multinodular lesions (Baker and Silverman 1985; Flournoy et al. 1984; Plasencia Martinez and Corral de la Calle 2009; Van Vlierberghe et al. 1998). In case this pattern is

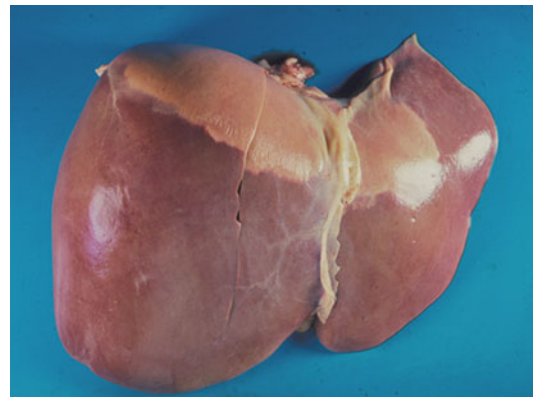

Fig. 8 Focal fatty change of the liver. A *large yellow*, geographic, and sharply delineated lesion occupies the superior aspect of both liver lobes

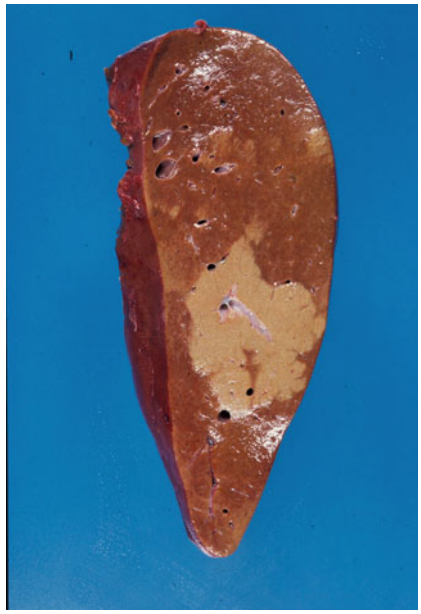

Fig. 9 Focal fatty change of the liver. A *yellow* zone of steatosis produces a mass-like effect

Table 3 Morphotypes of focal fatty change of the liver

Lobar/segmental type
Nodular type
Multifocal type
Subcapsular (wedge-shaped) type
FFC adjacent to the falciform ligament
Hilar/periportal type
Focal steatosis of the gallbladder fossa

diffuse, it closely mimics metastatic disease (diffuse multinodular hepatic steatosis; Amoyal et al. 1989).

Many cases of FFC show a lobar or segmental type of distribution, then mostly presenting with rather large lesions. Part of the FFC may have a nonrandom distribution: in a series of five cases of surgically confirmed FFC, all lesions were located at the anterolateral edge of the medial segment of the liver and were found adjacent to the falciform ligament (Middleton 1989; Yoshikawa et al. 1987). It has been suggested that focal steatosis around the falciform ligament is related to divergence of the portal vein or unusual blood supply (Liu et al. 2008), as outlined in a later paragraph. Apart from the strikingly frequent location near the falciform ligament, FFC were observed at other sites in the frequency sequence, anteromedial portion of segment IV, hilar side of segment IV, anterolateral portion of segment III, and around the hepatic hilum other than segment IV. FFC at the porta hepatis is correlated with aberrant venous drainage (Liu et al. 2008); see below). FFC has also been found in an intrahepatic sequestered segment located to the anterior part of segment IVB, fed by an abnormal transcapsular vascular tract (Battaglia et al. 1995). Foci of FFC may either be wedge shaped (in a subcapsular location) or have multiple lesions that may assume a nodular shape, these nodules sometimes exceeding a diameter of 10 cm (nodular focal fatty change). Further morphotypes of circumscribed fatty infiltration of the liver include periportal FFC (Salmonson et al. 1993), circumscribed steatosis of the gallbladder fossa or adjacent to the falciform ligament (Yoshikawa et al. 1987), and multifocal steatosis (El-Hassan et al. 1992; Sterling et al. 1997; Kemper et al. 2002; Van Vlierberghe et al. 1998). In a study on 1,425 patients, radiological evidence of fatty change of the liver was present in 9.7 %; among these patients, a diffuse fatty change was found in 68 %, FFC in 9 %, and multifocal fatty change in 22 % (El-Hassan et al. 1992).

Histopathology

Histologically, the liver parenchyma occupying the area of FFC preserved a lobular architecture and shows a type of predominantly macrovesicular hepatocyte change which is not distinguishable from that of diffuse fatty change of the liver (Gariballa et al. 1997). The subcapsular variant of FFC appears as a wedge-shaped rim of liver cells with fatty change, with the broad base facing the liver capsule (Glisson's capsule; Brawer et al. 1980). In biopsy, FFC lesions may show Mallory-Denk bodies and leukocytic infiltration, i.e., showing a pattern suggesting steatohepatitis ("focal steatohepatitis"). By the use of fine needle aspiration biopsy, this change may help in the differential diagnostic approach in

those instances, where malignancy is suspected (Layfield 1994; Zeppa et al. 2002). The cytologic features of FFC are characteristic. Aspirates show numerous hepatocytes in a background of blood, and these cells display a single or multiple clear vacuoles (Layfield 1994).

Focal Fatty Change in CARD

A particular distribution of steatosis has been observed in diabetic patients on continuous ambulatory peritoneal dialysis (CARD) treated with intraperitoneal insulin: these patients are known to develop a distinct type of hepatic subcapsular steatosis (Burrows and Jones 1994; Grove et al. 1991; Kallio et al. 2001; Nevalainen et al. 2000; Wanless et al. 1989). Wanless and colleagues were the first to report a postmortem study on 11 diabetic CAPD patients receiving intraperitoneal insulin; ten of these patients exhibited a subcapsular fatty rim measuring 0.05–12 mm in thickness and involving 5–80 % of the surface (Wanless et al. 1989). Grove and coworkers (Grove et al. 1991) observed on the posteroinferior surface of the right lobe a 10 × 8 cm sharply delineated subcapsular area of bright-yellow tissue, 4–6 mm in thickness. In the study of Kallio et al. (2001), subcapsular steatosis was detected in seven out of eight CARD patients receiving intraperitoneal insulin; the steatotic lesions were mostly located at the cranial segments of the liver, and the maximum thickness of the fatty rim ranged from 6.4 to 17.0 mm, visualized as a bright echogenic rim on the liver surface. In some patients there were discontinuous areas of subcapsular steatosis. In two necropsy cases, the gross features were characterized by yellowish subcapsular islands in an otherwise unaltered liver (Kallio et al. 2001). In regard to the possible pathogenic pathways, it has been theorized that insulin as such may play a significant role, the subcapsular location of fatty change in these patients being caused by the locally elevated insulin concentration secondary to its intraperitoneal administration (Wanless et al. 1989).

Focal Fatty Sparing

Introduction

Focal fatty sparing (FFS; skip lesions) denotes the circumscribed lack of detectable fatty change on a background of diffuse hepatic steatosis (Kissin et al. 1986; Marchal et al. 1986; Sauerbrei and Lopez 1986; White et al. 1987; Arai et al. 1988; Becher et al. 1988; Kreft et al. 1995; Yoshioka et al. 1994). It has significance in a clinical-radiologic setting because FFS may be interpreted as a focal tumoral lesion (pseudotumor, pseudolesion, pseudomass) (Fujikawa et al. 2002; Kreft et al. 1995; Vaidyanathan and Horrow 2007; Zezos et al. 2006). FFS is more frequent than focal fatty change (see below) and is typically localized to the liver segments IV and V near the gallbladder fossa, the area adjacent to the falciform ligament, subcapsular liver areas, and to the porta hepatis (Sarti et al. 1993; Chong and Fan 1994; Rubaltelli et al. 1997). The side of the medial segment of the left lobe which is adjacent to the portal vein is commonly spared when the remainder of the liver has significant fatty change (Berland 1986; Sauerbrei and Lopez 1986; White et al. 1987). This area often has decreased portal flow compared to the remainder of the liver (Fernandez and Bernardino 1991). Less commonly, FFS presents as multiple nodular lesions outside the typical locations of FFS (Tom et al. 2004). These lesions may mimic tumors (in particular, adenoma) even more frequently than those in the other locations.

Differential Diagnosis

Tumor metastatic to the liver can mimic sparing in irregular fatty liver (Onaya et al. 1994).

Pathogenesis

Similar to FCC, FFS is thought to be caused by abnormal blood supply to the liver areas involved in part of the cases. This is supported by situations

where abnormal or aberrant venous supply to the liver is associated with FFS in these segments, e.g., in the presence of aberrant gastric veins (Gabata et al. 1997; Terayama et al. 2004; Yoshioka et al. 1994). A focally spared area fatty liver was caused by arterioportal shunt (Arita et al. 1996). Based on biopsy findings it has been suggested that focal sparing is caused by inflammatory changes taking place in the liver area involved (Kreft et al. 1995).

Focal Fatty Sparing Around Liver Tumors

Introduction

Peritumoral sparing of hepatic fatty change is defined as a rim-like zone of liver substance around focal lesions, lacking fat accumulation in contrast to the remaining liver. This phenomenon has been found with several types of liver tumors, both epithelial and mesenchymal, but particularly in tissue surrounding hepatic colorectal cancer metastases and liver hemangiomas.

Clinical Presentation and Imaging Findings

On non-contrast CT scans, one notes a hyperattenuating rim having an attenuation similar to the spleen, a circular or semicircular shape, a width of a few millimeters, a clearly peritumoral localization, and an exhibiting loss of visualization with contrast enhancement. No such rims are seen around hepatic tumors unassociated with fatty infiltration (Itai et al. 1996). It has been reported that opposed-phase gradient-echo MRI is the best method for depicting peritumoral sparing of steatosis (Chung et al. 2003; Gabata et al. 2001; Xu et al. 2000; Chen et al. 2005). Grossholzer and coworkers (Grossholzer et al. 1998) separated focal fatty sparing around tumors into several types. *Peripheral sparing* (fan or wedge shaped) is observed in the liver substance between a peripherally situated nodule (commonly metastasis or HCC) and the overlying liver surface. The latter may be retracted, reflecting both the decrease in volume of the area involved and the increase in volume of the surrounding steatotic liver. *Segmental sparing* is observed when the underlying mass is located near, but not at, the liver hilus. Pathogenetically, it is suggested that the tumor compressed a portal venous branch and hence compromising the dependent parenchyma. *Lobar sparing* is seen when a tumor at the liver hilus causes sparing of an entire lobe by obstructing the left or right main portal vein branch. This alteration may be associated with biliary obstruction, as is, e.g., caused by hilar cholangiocarcinoma (Klatskin tumor).

Peritumoral sparing in hepatic hemangiomas appears as a hypoechoic lesion with or without a geographic hyperechoic rim in sonography (Kim et al. 2008), a hyperattenuating rim on unenhanced CT (Itai et al. 1996), and a hyperintense peritumoral rim on chemical shift MRI (Chen et al. 2005; Xu et al. 2000; Kim et al. 2006). Hepatic hemangiomas are known to have arterioportal shunts (Naganuma et al. 1999; Yu et al. 1998; Kim et al. 2006). Dilution of portal vein blood flow by arterial blood through the arterioportal shunts is considered to be the cause of peritumoral sparing (Kim et al. 2008). In contrast to the high frequency of arterioportal shunts in hepatic hemangioma, the shunt is rare in hepatocellular carcinomas, but a deranged local portal venous flow is thought to cause perilesional sparing in this tumor (Kim et al. 2008).

Pathology

Macroscopically, a pale rim separating a tumorous lesion from the yellowish liver substance is noted. This rim is usually only very thin, but may reach a thickness of 5 mm. Histologically, there is a rather sharp peripheral delimitation between the low-fat parenchymal rim and the surrounding steatotic liver, although some degree of interdigitation may occur (Chung et al. 2003). At the interface between the two areas, some hepatocyte ballooning and/or leukocytic infiltration may be seen

("steatohepatitic interface"). The rim may show some degree of liver atrophy (Chung et al. 2003).

References

Afekowna M (1938) Lipoma of the liver: case. Medycyne 7:848–849

Amoyal P, Bauret P, Bories P, Michel H (1989) Diffuse multinodular hepatic steatosis of metastatic appearance. A case description. Endoscopy 21:193–194

Arai et al (1988) http://www.ncbi.nlm.nih.gov/pubmed/3293374

Aribal E, Berberoglu L (1993) Primary liposarcoma of the liver. AJR Am J Roentgenol 161:1331–1332

Arita T, Matsunaga N, Honma Y, Nishikawa E, Nagaoka S (1996) Focally spared area of fatty liver caused by arterioportal shunt. J Comput Assist Tomogr 20:360–362

Arzanian MT, Khalghnejad-Tabari A, Shamsian BS, Jadali F, Gharib A, Esfahani H (2006) Generalized myelolipoma. Arch Iran Med 9:274–276

Baker ME, Silverman PM (1985) Nodular focal fatty infiltration of the liver: CT appearance. AJR Am J Roentgenol 145:79–80

Basaran C, Karcaaltincaba M, Akata D, Karabulut N, Akinci D, Ozman M, Akhan O (2005) Fat-containing lesions of the liver: cross-sectional imaging findings with emphasis on MRI. AJR Am J Roentgenol 184:1103–1110

Bashir Y (1990) Focal fatty infiltration of the liver mimicking metastatic disease. Postgrad Med J (Engl) 66:290–291

Baskurt E, Padgett DM, Matsumoto JA (2004) Multiple hibernomas in a 1-month-old female infant. AJNR Am J Neuroradiol 25:1443–1445

Battaglia DM, Wanless IR, Brady AP, Mackenzie RL (1995) Intrahepatic sequestered segment of liver presenting as focal fatty change. Am J Gastroenterol 90:2238–2239

Becher H, Scholmerich J, Volk BA, Gerok W (1988) Pseudotumor in steatosis hepatis – focal absence of fatty liver (in German). Med Klin 83:488–489

Belloir A, Bagni P, Veillon F, Weill F (1982) Hepatic echography. A misleading image: the fat pad of the hilus (in French). J Radiol 63:509–511

Benbow EW, Reid H (1986) Pseudolipoma of Glisson's capsule simulating metastatic tumour. J Clin Pathol 39:345–346

Berland LL (1986) Focal areas of decreased echogenicity in the liver at the porta hepatis. J Ultrasound Med 5:157–159

Binesh F, Akhavan A, Kargar S, Navabii H (2012) Primary liposarcoma of liver: a rare case and literature review. BMJ Case Rep. pii: bcr0120125711

Bishop et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/16819325

Bornstein-Quevedo L, Aviles-Salas A, Laguna M, Mercado MA, Gamboa-Dominguez A (2000) Primary lipoma of the liver (in Spanish). Rev Gastroenterol Mex 65:175–178

Bouche-Pillon MA, Behar C, Munzer M, Gaillard D, Lefebvre F, Lefort G, Daoud S (1989) Liposarcoma in children. Apropos of 3 cases and a review of the literature (in French). Chir Pediatr 30:181–184

Bouisson EF (1843) De la bile, de ses variétés physiologiques, et de ses altérations morbides. L. Castel, Paris, p 305

Brasfield RD, Das Gupta TK (1970) Liposarcoma. CA Cancer J Clin 20:3–8

Brawer MK, Austin GE, Lewin KJ (1980) Focal fatty change of the liver, a hitherto poorly recognized entity. Gastroenterology 78:247–252

Brines OA, Johnson MH (1949) Hibernoma: a special fatty tumor. Am J Pathol 25:467–479

Bugovics E (1988) Benign lipomatous tumor of the liver (in Hungarian). Orv Hetil 129:2195–2197

Bruneton et al (1987) http://www.ncbi.nlm.nih.gov/pubmed/33005127

Burrows CJ, Jones AW (1994) Hepatic subcapsular steatosis in a patient with insulin dependent diabetes receiving dialysis. J Clin Pathol 47:274–275

Butters M (1998) What is your diagnosis ? Juxtapapillary lipoma (in German). Schweiz Rundsch Med Prax 87:131–133

Castleberry RP, Kelly DR, Wilson ER, Cain WS, Salter MR (1984) Childhood liposarcoma. Report of a case and review of the literature. Cancer 54:579–584

Chen WJ, Lee JC, Hung WT (1988) Primary malignant tumor of liver in infants and children in Taiwan. J Pediatr Surg 23:457–461

Chen RC, Li CS, Lii JM, Chen WT, Tu HY (2005) Peritumoral fat-spared area is well correlated with the presence of temporal peritumoral enhancement in hepatic hemangioma in fatty liver. J Magn Reson Imaging 22:86–91

Chirieac LR, Dekmezian RH, Ayala AG (2006) Characterization of the myxoid variant of hibernoma. Ann Diagn Pathol 10:104–106

Cho SH, Rhim SC, Hyun SJ, Bae CW, Khang SK (2010) Intradural involvement of multicentric myxoid liposarcoma. J Korean Neurosurg Soc 48:276–280

Chong VFH, Fan YF (1994) Ultrasonographic hepatic pseudolesions: normal parenchyma mimicking mass lesions in fatty liver. Clin Radiol 49:326–329

Chou YH, Chiou HJ, Tiu CM, Chiang JH, Chang CY, Yu C (2001) Sonographic appearance of lipoma of the inferior vena cava. J Clin Ultrasound 29:359–362

Chu PT (1950) Benign neoplasms of the extrahepatic biliary ducts. Review of the literature and report of a case of fibroma. Arch Pathol 50:84–97

Chung JJ, Kim MJ, Kim JH, Lee JT, Yoo HS (2003) Fat sparing of surrounding liver from metastasis in patients with fatty liver: MR imaging with histopathologic correlation. AJR Am J Roentgenol 180:1347–1350

Conyers R, Young S, Thomas DM (2011) Liposarcoma: molecular genetics and therapeutics. Sarcoma. Article ID 483154

Craig JR, Peters RL, Edmondson HA (1989) Tumors of the liver and intrahepatic bile ducts. Atlas of tumor pathology, second series, fascicle 26. Armed Forces Institute of Pathology, Washington, DC

Delis S, Triantopoulou C, Kyzas PA, Dervenis C (2008) Multiple primary liver lipomas in a patient with chronic hepatitis B: a case report. Eur J Gastroenterol Hepatol 19:807–809

Devic, Gallavardin (1901) Rev Méd Orig Bibliogr Méd 21:570

Dietrich CF, Schall H, Kirchner J, Seifert H, Herrmann G, Caspary WF, Lembcke B (1997) Sonographic detection of focal changes in the liver hilus in patients receiving corticosteroid therapy. Z Gastroenterol 35:1051–1057

Dirschmid K, Kiesler J (1979) Lipom und Pseudolipom der Leber. Med Klin 74:997–999

Ehrmann CH (1843) Musée de la Faculté de Médicine de Strasbourg. Berger-Levrault, Strasbourg, p 1

El-Hassan AY, Ibrahim EM, al-Mulhim FA, Nabhan AA, Chammas MY (1992) Fatty infiltration of the liver: analysis of prevalence, radiological and clinical features and influence on patient management. Br J Radiol 65:774–778

Ellis JV, Salazar JE, Gavant ML (1985) Pedunculated hepatic hemangioma: an unusual cause for anteriorly displaced retroperitoneal fat. J Ultrasound Med 4:623–624

Elwood H, Parwani A, Cai G (2007) Fine-needle aspiration biopsy of myxoid liposarcoma metastatic to the liver: cytomorphologic and cytogenetic features. Diagn Cytopathol 35:734–737

Enterlaine HT, Culberson JD, Rochlin DB, Brady LW (1960) Liposarcoma. A clinical and pathological study of 53 cases. Cancer 13:932–950

Estourgie SH, Nielsen GP, Ott MJ (2002) Metastatic patterns of extremity myxoid liposarcoma and their outcome. J Surg Oncol 80:89–93

Fauchery A, Michel F, Rat P, Depret O, Kallee R, Justrabo E (1998) Isolated leiomyomatosis of the right adrenal vein associated with hepatic myelolipoma: diagnostic and therapeutic problems (in French). Prog Urol 8:398–403

Fernandez MP, Bernardino ME (1991) Hepatic pseudolesion: appearance of focal low attenuation in the medial segment of the left lobe at CT arterial portography. Radiology 181:809–812

Ferrari A, Besana-Ciani I, Rovera F, Siesto G, Dionigi G, Boni L, Dionigi R (2007) An unusual case of breast liposarcoma with liver metastases: the role of radical surgery. Breast J 13:324–325

Fievez M, Courtoy P (1978) Pseudo-lipoma of Glisson's capsule (in French). Gastroenterol Clin Biol 2:273–277

Flournoy JG, Potter JL, Sullivan BM, Gerza GB et al (1984) Case report. CT appearance of multifocal hepatic steatosis. Comput Assist Tomogr 8:1192–1194

Fujikawa K, Shiraki K, Ito T, Takase K, Nakano T (2002) Focal spared area in fatty liver mimicking a tumor. Hepatogastroenterology 49:1253–1254

Fukusato T, Machinami R (1996) Lipoma and liposarcoma of the extrahepatic bile ducts (in Japanese). Ryoikibetsu Shokogun Shirizu 9:34–36

Fulcheri E (1987) Lipoma of the liver. Pathologica 79:659–662

Furlong MA, Fanburg-Smith JC, Miettinen M (2001) The morphologic spectrum of hibernoma: a clinicopathologic study of 170 cases. Am J Surg Pathol 25:809–814

Gabata T, Matsui O, Kadoya M, Ueda K, Kawamori Y, Yoshikawa J, Takashima T (1997) Aberrant gastric venous drainage in a focal spared area of segment IV in fatty liver: demonstration with color Doppler sonography. Radiology 203:461–463

Gabata T, Kadoya M, Matsui O, Ueda K, Kawamori Y, Terayama N, Sanada J, Kobayashi S (2001) Peritumoral spared area in fatty liver: correlation between opposed-phase gradient-echo MR imaging and CT arteriography. Abdom Imaging 26:384–389

Gadzijev EM (2002) Surgical anatomy of hepatoduodenal ligament and hepatic hilus. J Hepato-Biliary-Pancreat Surg 9:531–533

Gaffney EF, Hargreaves HK, Semple E, Vellios F (1983) Hibernoma: distinctive light and electron microscopic features and relationship to brown adipose tissue. Hum Pathol 14:677–687

Gajda M, Hommann M, Böttcher J, Henning K, Kaiser WA, Settmacher U, Katenkamp D (2007) Primary liposarcoma of the liver (in German). Z Gastroenterol 45:1241–1244

Garant M, Reinhold C (1996) Resident's corner. Answer to case of the month #36. Hepatic lipoma. Can Assoc Radiol J 47:140–142

Garces CA, Reith JD, Grobmyer SR, Hochwald SN (2008) Isolated metastatic extremity liposarcoma to the liver, an uncommon and transient finding. World J Surg Oncol 6:108

Gariballa SE, Woods DJ, Davidson AR (1997) Case report: focal fatty liver infiltration causing mass effect. Clin Radiol 52:630–632

Gibo M, Murata S, Kuroki S (2001) Pericaval fat collection mimicking an intracaval lesion on CT in patients with chronic liver disease. Abdom Imaging 26:492–495

Golebiowski L, Abycht K (1987) Primary liposarcoma of the liver (in Polish). Wiad Lek 40:1064–1066

Goodman, Ishak (1984). http://www.ncbi.nlm.nih.gov/pubmed/6496843

Grassi R, Di Mizio R, Barberi A, Severini S, Del Vecchio A, Cappabianca S (2002) Case report. Ultrasound and CT findings in lipoma of the inferior vena cava. Br J Radiol 75:69–71

Grosdidier J, Boissel P, Macinot C, Drouin P (1973) Hepatic myelolipoma. Apropos of a case (in French). Nouv Press Med 2:1777–1779

Grossholzer M, Terrier F, Rubia L, Stoupis C, Hadengue A, Mentha G (1998) Focal sparing in the fatty liver as a

sign of an adjacent space-occupying lesion. AJR Am J Roentgenol 171:1391–1395
Grove A, Vyberg B, Vyberg M (1991) Focal fatty change of the liver. A review and a case associated with ambulatory peritoneal dialysis. Virchows Arch A Pathol Anat Histol 419:69–75
Hagspiel KD (2005) Manifestation of Hodgkin's lymphoma in an adrenal myelolipoma. Eur Radiol 15:1757–1759
Halber MD, Daffner RH (1979) Fat in the intrahepatic fissures. AJR Am J Roentgenol 132:842–843
Halvorsen RA, Korobkin M, Ram PC, Thompson WM (1982) CT appearance of focal fatty infiltration of the liver. AJR Am J Roentgenol 139:277–281
Hamada T, Yamagiwa K, Okanami Y, Fujii K, Nakamura I, Mizuno S, Yokoi H, Isaji S et al (2006) Primary liposarcoma of gallbladder diagnosed by preoperative imagings: a case report and review of literature. World J Gastroenterol 12:1472–1475
Han BK, Im JG, Jung JW, Chung MJ, Yeong KM (1997) Pericaval fat collection that mimics thrombosis of the inferior vena cava: demonstration with use of multidirectional reformation CT. Radiology 203:105–108
Hines J, Katz DS, Goffner L, Rubin GD (1999) Fat collection related to the intrahepatic inferior vena cava on CT. AJR Am J Roentgenol 172:409–411
Hirasaki S, Koide N, Ogawa H, Ujike K, Shinji T, Tsuji T (1999) Tuberous sclerosis associated with multiple hepatic lipomatous tumors and hemorrhagic renal angiomyolipoma. Intern Med 38:345–348
Hoeffel JC, Etzel JC, Drouin P, Boissel P (1977) Direct image of hepatic lipoma. Can Assoc Radiol J 28:153–155
Horton et al (1999) http://www.ncbi.nlm.nih.gov/pubmed/10194789
Huang HY, Brennan MF, Singer S, Antonescu CR (2005) Distant metastasis in retroperitoneal dedifferentiated liposarcoma is rare and rapidly fatal: a clinicopathological study with emphasis on the low-grade myxofibrosarcoma-like pattern as an early sign of dedifferentiation. Mod Pathol 18:976–984
Hübener KH, Hippeli R (1980) Das Leberlipom. Aussagewert von Sonographie, Szintigraphie, Computertomographie, und Angiographie bei der Diagnostik dieses seltenen Tumors. Röfo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 133:176–179
Igarashi M, Akiyama Y, Nakamura T, Ohtsuki S, Nakashima Y (1994) Focal fatty liver change in a 12-year-old Japanese boy. Eur J Pediatr 153:429–431
Imaoka S, Sasaki Y, Nakano H, Iwanaga T (1995) Lipomatous tumors (lipoma, angiomyolipoma, myelolipoma, focal fatty change) in the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:288–291. Inferior vena cava: a normal variant ? Clin Radiol 49:341–342
Inoue T, Shiga J, Machinami R (1989) Hepatic pseudolipoma: a hitherto undescribed hyperechoic hepatic nodule – direct correlation between ultrasonography and histology (in Japanese). Acta Hepatol Jpn 30:1533–1536
Ishak KG (1976) Mesenchymal tumors of the liver. In: Okuda K, Peters R (eds) Hepatocellular carcinoma. Wiley, New York, pp 260–262
Itai Y, Maeda M, Echigo J, Pan X, Saida Y, Kurosaki Y, Atai Y (1996) Hyperattenuating rim on noncontrast CT of the liver: probable peritumoral sparing of fatty infiltration. Clin Radiol 51:406–410
Jain KA, McGahan JP (1993) Spectrum of CT and sonographic appearance of fatty infiltration of the liver. Clin Imaging 17:162–168
Jaques DP, Coit DG, Casper ES, Brennan MF (1995) Hepatic metastases from soft-tissue sarcoma. Ann Surg 221:392–397
Jover JM, Carabias A, Ramos JL, Ortega P, Ruiz de Adana JC, Moreno AM (2001) Lipoma of the liver associated with hepatocellular carcinoma and polycystic liver disease. Dig Surg 18:323–324
Kallio T, Nevalainen PI, Lahtela JT, Mustonen J, Pasternack A (2001) Hepatic subcapsular steatosis in diabetic CARD patients treated with intraperitoneal insulin. Acta Radiol 42:323–325
Kampmann H, Allmendinger G (1983) Lipomas of the liver: differential diagnosis of liver metastasis by computerized tomography (in German) Z. Gastroenterology 21:521–525
Karhunen PJ (1985) Hepatic pseudolipoma. J Clin Pathol 38:877–879
Katz DS, Goffner L (2002) "Lipoma" of the inferior vena cava is actually a pericaval fat collection. J Clin Ultrasound 30:57–58
Kaurich JD, Coombs RJ, Zeiss J (1988) Myelolipoma of the liver: CT features. J Comput Assist Tomogr 12:660–661
Kawarada Y, Das BC, Taoka H (2000) Anatomy of the hepatic hilar area: the plate system. J Hepato-Biliary-Pancreat Surg 7:580–586
Kemper J, Jung G, Poll LW, Jonkmanns C, Luthen R, Moedder U (2002) CT and MRI findings of multifocal hepatic steatosis mimicking malignancy. Abdom Imaging 27:708–710
Khan et al (2001) http://www.ncbi.nlm.nih.gov/pubmed/11180184
Kim TW, Reyes CV (1985) Myxoid liposarcoma mimicking fluid density. J Surg Oncol 30:80–82
Kim YI, Yu ES, Lee KW, Park EU, Song HG (1987) Dedifferentiated liposarcoma of the liver. Cancer 60:2785–2790
Kim MJ, Kim KW, Won HJ et al (2006) Hepatic hemangiomas with peritumoral sparing of fatty infiltration in hepatic steatosis: findings on contrast-enhanced MR imaging and on sonography. J Korean Radiol Soc 55:571–577
Kim JL, Woo JY, Lee MJ, Kim KR, Jung JP, Lee NJ, Choi SH, Kim HD, Yang I et al (2007) Imaging findings of primary well-differentiated liposarcoma of the liver: a case report. Acta Radiol 48:1061–1065

Kim KW, Kim MJ, Lee SS, Kim HJ, Shin YM, Kim PN, Lee MG (2008) Sparing of fatty infiltration around focal hepatic lesions in patients with hepatic steatosis: sonographic appearance with CT and MRI correlation. AJR Am J Roentgenol 190:1018–1027

Kissin CM, Bellamy EA, Cosgrove DO, Slack N, Husband JE (1986) Focal sparing in fatty infiltration of the liver. Br J Radiol 59:25–28

Koninger J, Butters M, Roos U, Bittner R (1994) Juxtapapillary intraduodenal lipoma as a rare cause of jaundice and acute pancreatitis (in German). Z Gastroenterol 32:157–159

Kreft B, Stark D, Schild H (1995) Atypical focal fatty liver disease (in German). Aktuelle Radiol 5:372–373

Kudo M, Ikekubo K, Yamamoto K, Hino M, Ibuki Y, Tomita S, Kmori H, Orino A, Todo A (1989) Focal fatty infiltration of the liver in acute alcoholic liver injury: hot spots with radiocolloid SPECT scan. Am J Gastroenterol 84:948–952

Kuo LM, Chou HS, Chan KM, Yu MC, Lee WC (2006) A case of huge primary liposarcoma in the liver. World J Gastroenterol 12:1157–1159

Langsteger W, Lind P, Schneider GH, Koltringer P, Beham A, Eber O (1990) Lipoma of the liver: computed tomographic, ultrasonographic, and cytologic findings. Scand J Gastroenterol 25:302–306

Layfield LJ (1994) Focal fatty change of the liver: cytologic findings in a radiographic mimic of metastases. Diagn Cytopathol 11:385–387

Le Neel JC, Gasquet C, Lenne Y, Moulin S, Heloury Y, Leborgne J (1984) Myelolipoma of the liver (in French). Gastroenterol Clin Biol 8:682–683

Lee SY, Kim HJ, Park SY, Park YH, Chung SK (2008) Myxoid liposarcoma involving the liver, subcutaneous tissue, and epidural space in a polycystic disease patient. Clin Nucl Med 33:507–509

Liessi G (1987) Lipoma and angiomyolipoma of the liver. Description of 2 cases (in Italian). Radiol Med (Torino) 74:471–473

Lindenbraten LD (1979) The radiograph of a fat-layer under the right diaphragm (in German). Radiol Diagn (Berlin) 20:38–42

Liu LP, Dong BW, Yu XL, Zhang DK, Kang CS, Zhao XH (2008) Evaluation of focal fatty infiltration of the liver using color Doppler and contrast-enhanced sonography. J Clin Ultrasound 36:560–566

Mali SP, Gratama S, Mulder H (1986) Myelolipoma of the liver. ROFO Fortschr Geb Rontgenstr Nuklearmed 144:610–611

Maluccio MA, Covey AM, Schubert J, Brody LA, Sofocleus CT, Getrajdman GI et al (2006) Treatment of metastatic sarcoma to the liver with bland embolization. Cancer 107:1617–1623

Marchal G, Tshibwabwa-Tumba E, Verbeken E, Van Roost W, Van Steenbergen W, Baert A, Lauwerijns J (1986) "Skip areas" in hepatic steatosis: a sonographic-angiographic study. Gastrointest Radiol 11:151–157

Martin-Benitez G, Marti-Bonmati L, Barber C, Vila R (2012) Hepatic lipomas and steatosis: an association beyond chance. Eur J Radiol 81:e491–e494

Martinez Alvarez RM, Garcia LS, Solanilla P, Martin-Mir ML (1998) Focal hepatic steatosis simulating liver metastasis (in Spanish). Rev Esp Enferm Dig 90:195–196

Mathieu D, Vilgrain V, Mahfouz AE, Anglade MC, Vullierme MP, Denys A (1997) Benign liver tumors. Magn Reson Imaging Clin N Am 5:255–288

McAvoy JM, Fee HJ, Roth JA, Dainko EA (1978) Primary liposarcoma of the omentum. Arch Surg 113:870.872

McClure MJ, Sarrazin J, Kapusta L, Murphy J, Arenson AM, Geerts W (2001) Intravascular femoral vein lipoma: an unusual cause of lower limb venous obstruction. AJR Am J Roentgenol 176:463–464

Merimsky O, Terrier P, Stanca A, Le Chevalier T, Spielmann M, Tursz T, Le Cesne A (1999) Liver metastases from extremity soft tissue sarcoma. Am J Clin Oncol 22:70–72

Merkel H (1906) Ueber ein Pseudolipom der Mamma (on a pseudolipoma of the breast). Beitr Pathol Anat 39:152–157

Middleton WD (1989) Focal hepatic fatty infiltration adjacent to falciform ligament. AJR Am J Roentgenol 152:1326–1327

Miyake H, Suzuki K, Ueda S, Yamada Y, Takeda H, Mori H (1992) Localized fat collection adjacent to the intrahepatic portion of the inferior vena cava: a normal variant on CT. AJR Am J Roentgenol 158:423–425

Miyazaki Y, Yoshida M, Doi J (1990) A case of adrenal myelolipoma associated with adrenogenital syndrome (in Japanese). Hinyokika Kiyo 36:35–39

Mohandas D, Chandra RS, Srinivasan V, Bhaskar AG (1972) Liposarcoma of the ileum with secondaries in the liver. Am J Gastroenterol 58:172–176

Moreno GE, Seoane Gonzalez JB, Bercedo MJ, Santoyo SJ, Gomez SR, Vargas CJ, Ballestin CC, Garcia Maurino ML, Colina Ruiz-Delgado F (1991) Hepatic myelolipoma: new case and review of the literature. Hepatogastroenterology 38:60–63

Mulhern CB, Arger PH, Coleman BG, Stein GN (1979) Nonuniform attenuation in computed tomography of the cirrhotic liver. Radiology 132:399–402

Naganuma H, Ishida H, Konno K, Hamashima Y, Komatsuda T, Ishida J, Masamune O (1999) Hepatic hemangioma with arterioportal shunts. Abdom Imaging 24:42–46

Naik PR, Kumar P, Kumar PV (2013) Primary pleomorphic liposarcoma of liver: a case report and review of the literature. Case Rep Hepatol 2013:398910

Nakamura N, Kudo A, Ito K, Tanaka S, Arii S (2009) A hepatic lipoma mimicking angiomyolipoma of the liver: report of a case. Surg Today 39:825–828

Nelson V, Fernandes NF, Woolf GM, Geller SA, Petrovic LM (2001) Primary liposarcoma of the liver. A case report and review of the literature. Arch Pathol Lab Med 125:410–412

Nevalainen PI, Kallio T, Lahtela JT, Mustonen J, Pasternack AI (2000) High peritoneal permeability predisposes to hepatic steatosis in diabetic continuous ambulatory peritoneal dialysis patients receiving intraperitoneal insulin. Perit Dial Int 20:637–642

Nishizaki T, Kanematsu T, Matsumata T, Yasunaga C, Kakizoe S, Sugimachi K (1989) Myelolipoma of the liver. A case report. Cancer 63:930–934

Ohi M, Yutani C, Shimomukai H, Nishikawa M, Kishikawa N, Kuroda K, Nakayama M (1992) Primary round cell liposarcoma of the omentum. A case report. Acta Cytol 36:722–726

Oliva A, Duarte B, Hammadeh R et al (1988) Myelolipoma and endocrine dysfunction. Surgery 103:711–715

Onaya H, Itai Y, Kurosaki Y, Saida Y, Ebihara R, Kuramoto K (1994) Metastatic tumors in irregular fatty liver mimicking focal sparing. Radiat Med 12:69–73

Orlandi A, Marino B, De Dona G, Cefaro A, Spagnoli LG (1994) Clinico-pathological considerations about a case of hepatic myelolipoma (in Italian). Ann Ital Chir 65:253–256

Pan X, Saida Y, Kurosaki Y, Onaya H, Itai Y (1995) Fatty mass in the inferior vena cava at CT: lipoma or normal variant ? Radiat Med 13:251–253

Patel VG, Babalola OA, Fortson JK, Weaver WL (2006) Adrenal myelolipoma: report of a case and review of the literature. Am Surg 72:649–654

Patil N, Ahmed Kabeer Rasheed S, Abba M, Hendrik LJ, Schwarzbach M, Allgayer H (2014) A mechanistic study on the metastasis inducing function of FUS-CHOP fusion protein in liposarcoma. Int J Cancer 134:2808–2819

Patocs A, Liko I, Varga I, Gergics P, Boros A, Futo L, Kun I, Bertalan R, Toth S, Pazmany T et al (2005) Novel mutation of the CYP17 gene in two unrelated patients with combined 17alpha-hydroxylase/17,20-lyase deficiency: demonstration of absent enzyme activity by expressing the mutant CYP17 gene and by three-dimensional modeling. J Steroid Biochem Mol Biol 97:257–265

Paulson EK, Baker ME, Spritzer CE, Leder RA, Gulliver DJ, Meyers WC (1993) Focal fatty infiltration: a case of nontumorous defects in the left hepatic lobe during CT arterial portography. J Comput Assist Tomogr 17:590–595

Pavon CJ, Llodra GP, Cuadrado JF, Artero SM, Rodriguez AC, Cao RB, Fernandez FP (2009) Hepatic myelolipoma. Diagnosis and treatment (in Spanish). Gastroenterol Hepatol 32:349–352. Pericaval fat collection. J Clin Ultrasound 30:57–58

Perry JN, Williams MP, Dubbins PA, Farrow R (1994) Lipomata of the inferior vena cava: a normal variant? Clin Radiol 49:341–342

Persaud V (1969) Pseudolipoma of Glisson's capsule. Arch Pathol 88:555–556

Petri A, Hohn J, Wolfard A, Laszlo KE, Kocsis SG, Boros M, Balogh A (2003) Surgery of benign liver tumors: indications for treatment. Personal experience and review of the literature (in Hungarian). Magyar Onkológia 47:391–395

Pham DH, Manley PN, Nguyen KT (1986) Lipoma of the liver. Can Assoc Radiol J 37:283–284

Plasencia Martinez JM, Corral de la Calle MA (2009) Cases for diagnosis. Solution to case 5: multinodular focal fatty infiltration of the liver (in Spanish). Radiologia 51:333–336

Pounder DJ (1983a) Fatty tumours primary in the liver. Histopathology 7:801–802

Pounder DJ (1983b) Hepatic pseudolipoma. Pathology 15:83–84

Prakash M, Vyas S, Shanbhogue AK, Kang M, Dey P, Khandelwal N (2008) Case report: fat-containing liver metastases from retroperitoneal liposarcoma. Indian J Radiol Imaging 18:230–231

Prasad SR, Wang H, Rosas H, Menias CO, Narra VR, Middleton WD, Heiken JP (2005) Fat-containing lesions of the liver: radiologic-pathologic correlation. Radiographics 25:321–331

Prayer LM, Schurawitzki HJ, Wimberger DM (1992) Case report: lipoma of the liver – ultrasound, CT and MR imaging. Clin Radiol 45:353–354

Puljiz Z, Petricevic M, Branatic A, Barisic I, Puljiz M, Karin Z (2012) An unusually large liver lipoma. Med Glas (Zenica) 9:411–414

Quinn AM, Guzman-Hartman G (2003) Pseudolipoma of Glisson capsule. Arch Pathol Lab Med 127:503–504

Radhi J (2010) hepatic myelolipoma. J Gastrointest Liver Dis 19:106–107

Raju NL, Austin JH (2001) Case 37: Juxtacaval fat collection – mimic of lipoma in the subdiaphragmatic inferior vena cava. Radiology 220:471–474

Ramchand S, Ahmed Y, Baskerville L (1970) Lipoma of the liver. Arch Pathol 90:331–333

Redondo ME, Rey LA (1990) Hepatic pseudolipoma (in Spanish). Rev Esp Enferm Dig 78:326–327

Renaldi R, Rezae B, Brancorsini D, Bearzi I (1993) Hepatocellular adenoma with areas of bone marrow: report of a case. Am J Surg Pathol 17:952–953

Ritchie et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/16642344

Rolleston H, McNee JW (1929) Diseases of the liver, gallbladder and bile duct. Macmillan, London, p 487

Rosso R, Lucioni M (2006) Normal and neoplastic cells of brown adipose tissue express the adhesion molecule CD31. Arch Pathol Lab Med 130:480–482

Rubaltelli L, Savastano S, Cellini L, Zambotti B, Marchioro U (1997) Hyperechoic pseudotumors in segment IV of the liver. J Ultrasound Med 16:569–572

Rubin E, Russinovich NA, Luna RF, Tishler JM, Wilkerson JA (1984) Myelolipoma of the liver. Cancer 54:2043–2046

Sakaki M, Izaki H, Fukumori T, taue R et al (2006) Bilateral adrenal myelolipoma associated with adrenogenital syndrome. Int J Urol 13:801–802

Salmonson EC, Lundstedt C, Holmin T, Hagerstrand I (1993) Focal periportal liver steatosis. Abdom Imaging 18:39–41

Sarti DA, Fleihser DR, Rosenthal P (1993) Hepatic pseudomass on ultrasound in children with fatty infiltration of the liver. J Pediatr Gastroenterol Nutr 16:186

Sasaki M, Harada K, Nakanuma Y, Watanabe K (1994) Pseudolipoma of Glisson's capsule. Report of six cases and review of the literature. J Clin Gastroenterol 19:75–78

Sauerbrei EE, Lopez M (1986) Pseudotumor of the quadrate lobe in hepatic sonography: a sign of generalized fatty infiltration. AJR Am J Roentgenol 147:923–927

Savoye-Collet C, Goria O, Scotte M, Hemet J (2000) MR imaging of hepatic myelolipoma. AJR Am J Roentgenol 174:574–575

Sawhney R, McRae B, Lazarchick J (2006) A rare case of multifocal extra-adrenal myelolipoma with markedly hypocellular bone marrow. Ann Clin Lab Sci 36:208–211

Scapati A, Scapati C, De Marco S Jr, De Marco S (1994) Liver lipoma. Anatomo-histologic and radiologic study (in Italian). Pathologica 86:94–97

Schneider-Monteiro ED, Lucon AM, de Figueiredo AA, Rodrigues Junior AJ, Arap S (2003) Bilateral giant renal angiomyolipoma with hepatic lipoma in a patient with tuberous sclerosis. Rev Hosp Clin Fac Med Sao Paulo 58:103–108

Scott WW, Sanders RC, Siegelman SS (1980) Irregular fatty infiltration of the liver. AJR Am J Roentgenol 135:67–71

Shah ZR, Bellon EM (1986) The changing pattern in focal fatty change of the liver: a case report. J Comput Tomogr 10:261–262

Shaub MS, Birnbaum WW, Meyers HI (1975) Peribiliary fat: a new roentgenographic finding. Am J Roentgenol Radium Ther Nucl Med 123:330–337

Sheafor DH, Foti TM, Vaslef SN, Nelson RC (1998) Fat in the inferior vena cava with caval injury. AJR Am J Roentgenol 171:181–182

Sheah K, Oellette HA, Torriani M, Nielsen GP, Kattapuram S, Bredella MA (2008) Metastatic myxoid liposarcomas: imaging and histopathologic findings. Skelet Radiol 37:251–258

Shima Y, Moriyama N, Takayasu K, Muramatsu Y, Gotoh H, Yamada T, Hasegawa H, Hirohashi N (1986) Primary lipoma and angiomyolipoma of the liver diagnosed by CT scan: report of two resected cases (in Japanese). Rinsho Hoshasen 31:1457–1460

Shin NY, Kim MJ, Chung JJ, Chung YE, Choi JY, Park YN (2010) The differential imaging features of fat-containing tumors in the peritoneal cavity and retroperitoneum: the radiologic pathologic correlation. Korean J Radiol 11:333–345

Shmookler BM, Enzinger FM (1983) Liposarcoma occurring in children. An analysis of 17 cases and review of the literature. Cancer 52:567–574

Simon MA (1934) Focal fat infiltration in the liver. Am J Pathol 10:799–803

Soares FA, Magnani Landell GA, Peres LC, Olivera MA, Vincente Y, Tone LG (1989) Liposarcoma of hepatic hilum in childhood: report of a case and review of literature. Med Pediatr Oncol 17:239–243

Sonsuz A, Ozdemir S, Akdogan M, Senturk H, Ozbay G, Akin P, Gurakar M (1994) Lipoma of the liver. Z Gastroenterol 32:348–350

Sossai P, Barbazza R (1990) True lipoma of Glisson's capsule. J Clin Pathol 43:780

Souz A (1984) Lipoma of the liver. Z Gastroenterol 32:348–350

Sterling et al (1997) http://www.ncbi.nlm.nih.gov/pubmed/9382073

Suarez-Peñaranda JM, Bermudez-Naveira A, Fraga M, Aliste-Santos C, Cordeiro C, Muñoz-Barus JI (2014) Unusual forms of adrenal and extra-adrenal myelolipomas. Int J Surg Pathol 22:473–477

Szentpali K, Petri A, Olah T, Szendrenyi V, Ivanyi B, Balogh A (2000) Lipoma of the liver: a differential-diagnostic problem. Langenbeck's Arch Surg 385:31–33

Takagi H, Aizawa M, Son E, Kitano H, Yoshiyasu K, Kurooka K, Koh K, Yasutomi M (1994) A case of hepatic lipoma (in Japanese). Nippon Shokakibyo Gakkai Zasshi 91:105–108

Takayasu K (1987) Imaging characteristics of large lipoma and angiolipoma of the liver. Cancer 57:916–921

Takizawa H, Takikawa S, Koike M, Hirose S, Kusama A, Okamura N (1995) A case of hepatic myelolipoma (in Japanese). Nippon Shokakibyo Gakkai Zasshi 92:1882–1885

Tang-Barton P, Vas W, Weissman J, Salimi Z, Patel R, Morris L (1985) Focal fatty liver lesions in alcoholic liver disease: a broadened spectrum of CT appearances. Gastrointest Radiol 10:133–137

Tarasiuk BA, Diubenko TK, Tumasova EP (1991) A case of hepatic lipoma (in Russian). Klin Khir 5:70–71

Teas S, Ronan SG, Ghosh L (1978) Solitary metastatic liposarcoma of the liver. Arch Pathol Lab Med 102:605

Teng JF, Zeng X, Shi J, Xie WF, Lin Y (2012) A huge retroperitoneal liposarcoma presenting as a hepatic space-occupying lesion: a case report. J Dig Dis 13:120–122

Terayama N, Matsui O, Tatsu H, Gabata T, Kinoshita A, Hasatani K (2004) Focal sparing of fatty liver in segment II associated with aberrant left gastric vein. Br J Radiol 77:150–152

Thorogood SV, Maskell GF (1996) Intravascular lipoma of the superior vena cava – CT and MRI appearances. Br J Radiol 69:963–964

Tobias ME, Berkowitz I (1992) Fat-containing collection adjacent to intrahepatic inferior vena cava: sonographic detection and characterization. AJR Am J Roentgenol 159:1346

Tom WW, Yeh BM, Cheng JC, Qayyum A, Joe B, Coakley FV (2004) Hepatic pseudotumor due to nodular fatty sparing: the diagnostic role of opposed-phase MRI. AJR Am J Roentgenol 183:721–724

Trabut JB, Duong Van Huyen JP, Artru B, Bruneval P (1999) Intravascular lipoma of the superior vena cava (in French). Ann Pathol 19:529–531

Treska V, Wirthova M, Hadravska S, Mukensnabl P, Kuntscher V, Kreuzberg B, Lisa L, Kozak K (2006) Giant bilateral adrenal myelolipoma associated with congenital adrenal hyperplasia (in German). Zentralbl Chir 131:80–83

Ubrig-von BR, Braun C, Erlemann R (2002) Tumor of the inferior vena cava ? Lipoma of the inferior vena cava (in German). Radiologe 42:485–488

Umpierrez MB, Fackler S, Umpierrez GE, Rubin J (1997) Adrenal myelolipoma associated with endocrine dysfunction: review of the literature. Am J Med Sci 314:338–341

Vaidyanathan S, Horrow MM (2007) Case 6: diagnosis: "focal fatty sparing" of the caudate lobe mimicking a mass. Ultrasound Q 23:79–80

Van Hoe L, Gryspeerdt S, Van Eycken P, Baert AL, Marchal G (1994) Myelolipoma in a hepatocellular carcinoma: CT-pathologic correlation. AJR Am J Roentgenol 163:1111–1112

Van Vlierberghe H, Duyck P, Bernard P, Braxel C, Versieck J, Elewaut A (1998) Multifocal fatty infiltration of the liver; an aspecific presentation form of hepatitis C infection. Acta Gastroenterol Belg 61:379–381

Verhille R, Marchal G, Baert AL, Fevery J (1994) Focal fatty infiltration of the liver associated with important mass effect. JBR-BTR 77:10–12

Vijayaraghavan SB (1989) Fat pad vs. anterior subphrenic abscess: a new real-time sign. J Clin Ultrasound 17:653–655

Villari V, Pisciotta R, Biondi V, Palumbo P, Pinto R (1985) Subphrenic adipose tissue, an unfrequent cause of increased distance between the diaphragm and liver. Radiological study and echographic comparison (in Italian). Radiol Med (Torino) 71:582–586

Vinnicombe S, Wilson AG, Morgan R, Saunders K (1994) Intravascular lipomas of the superior vena cava: CT features. J Comput Assist Tomogr 18:824–827

Wada Y, Ebisui C, Okada K, Kato R, Makino S, Nishigaki T, Owada Y, Murakami T et al (2012) A case of rapidly progressing retroperitoneal differentiation type liposarcoma (in Japanese). Gan To Kagaku Ryoho 39:2429–2431

Wanless IR, Bargman JM, Oreopoulos DG, Vas SI (1989) Subcapsular steatonecrosis in response to peritoneal insulin delivery: a clue to the pathogenesis of steatonecrosis in obesity. Mod Pathol 2:69–74

Wardell Dr (Tunbridge Wells Infirmary) (1869) Small fatty growths obstructing cystic and common ducts. Lancet 2:407

Wheeler DA, Edmondson HA (1985) Coelomic fat ectopia of the liver. Arch Pathol Lab Med 109:783–785

White EM, Simeone JF, Mueller PR, Grant EG, Choyke PL, Zeman RK (1987) Focal periportal sparing in hepatic fatty infiltration: a cause of hepatic pseudomass on US. Radiology 162:57–59

Wolloch Y, Dintsman M, Garti I (1973) Primary malignant tumors of the liver. Isr J Med Sci 9:6–11

Wright NB, Skinner R, Lee RE, Craft AW (1993) Myxoid liposarcoma of the portal hepatis in childhood. Pediatr Radiol 23:620–621

Xu H, Jiang D, Yang L, Xiong Y, Yang F, Kong X (2000) The value of in-phase and opposed-phase T1-weighted breath-hold FLASH sequences for hepatic imaging. J Tongji Med Univ 20:290–293

Yates CK, Streight RA (1986) Focal fatty infiltration of the liver simulating metastatic disease. Radiology 159:83–84

Yoon JH, Park CI, Chung KS (1987) Focal fatty change of the liver. Yonsei Med J 28:322–325

Yoshikawa J, Matsui O, Takashima T, Sugiura H, Katayama K, Nishida Y, Tsuji M (1987) Focal fatty change of the liver adjacent to the falciform ligament: CT and sonographic findings in five surgically confirmed cases. AJR Am J Roentgenol 149:491–494

Yoshioka H, Saika A, Tsujiuchi K et al (1994) Focal spared area in fatty liver caused by anomalous return of right gastric vein. Jpn J Med Imaging 13:293–300

Young S (1951) A case of lipoma of the liver. J Path Bact 63:336

Yu JS, Kim MJ, Kim MW (1998) Intratumoral blood flow in cavernous hemangioma of the liver: radiologic-pathologic correlation. Radiology 208:549–550

Yu R, Wei J, Li R, Zhang S (2002) CT manifestations of primary hepatic sarcoma (in Chinese). Zhonghua Yi Xue Za Zhi 82:541–545

Yu RS, Chen Y, Jiang B, Wang LH, Xu XF (2008) Primary hepatic sarcomas: CT findings. Eur Radiol 18:2196–2205

Zancanaro C, Pelosi G, Accordini C, Balercia G, Sbabo L, Cinti S (1994) Immunohistochemical identification of the uncoupling protein in human hibernoma. Biol Cell 80:75–78

Zeppa P, Anniciello A, Vetrani A, Palombini L (2002) Fine needle aspiration biopsy of hepatic focal fatty change. A report of two cases. Acta Cytol 46:567–570

Zezos P, Tatsi P, Nakos A, Pachiadakis I, Kosmatopoulos F, Zafiriadou E, Molyvas E, Patsiaoura K (2006) Focal fatty liver sparing lesion presenting as a "pseudotumour": case report. Acta Gastroenterol Belg 69:323–326

Tumors of Osseous and Chondroid Cell Lineages

66

Contents

Abstract

Apart from mixed epithelial and mesenchymal hepatoblastomas, which commonly produce osteoid, hepatic neoplasms with osteogenic or chondroid differentiation are very rare lesions. True osteoma of the liver has apparently not been documented. In contrast, primary osteosarcoma of the liver is a well-documented, albeit rare malignancy that is diagnosed in older patients. It presents as pure neoplasms or mixed tumors (carcinosarcomas) with osteoid components. Pure hepatic osteosarcoma forms tumor of very large size, lesions sometimes exceeding a weight of 3000 g. Histology corresponds to that of skeletal osteosarcoma, with variable amounts of calcified tumor osteoid. Part of the neoplasms contain multinucleated tumor giant cells. Primary chondroma of the liver is an exceptional neoplasm, while primary hepatic tumors with a chondrosarcomatous component have more often been described. The differential diagnosis of these lesions mainly consists of metastatic liver disease, both osteosarcomas and chondrosarcomas metastasizing to the liver.

Osteoma of the Liver

Primary osteoma of the liver has apparently not yet been documented in the literature.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_66

Primary Osteosarcoma of the Liver

ICD-O Code 9180/3

Introduction

Relatively few osteosarcomas primary to the liver have been described, the first published observation dating from 1930, and the overall number of cases identifiable in the literature is rather low (Ogawa 1930). The diagnosis of primary osteosarcoma of the liver requires the fulfillment of the criteria for extraosseous osteosarcoma, i.e., the lack of a neoplastic epithelial component, the reliable detection of osteoid with or without mineralization, and of course the exclusion of metastatic disease (Ojima et al. 1964; Maynard and Fone 1969; Allan and Soule 1971; Sumiyoshi and Niho 1971; von Hochstetter et al. 1987; Craig et al. 1989; Liony et al. 1990; Kitayama et al. 1995; Govender and Rughubar 1998; Boldt et al. 1999; Phelip et al. 2007; Nawabi et al. 2009; Park et al. 2009).

Epidemiology

The female/male ratio in these eight tumors was 1/7, and the age range of presentation was 52–75 years. In the majority of cases, the tumor involved the right liver lobe, in three both liver lobes (no information in one case). Several patients had liver cirrhosis, including one patient, where hepatic osteosarcoma developed in cirrhosis associated with hemochromatosis (Maynard and Fone 1969).

Clinical and Imaging Features

The clinical presentation includes abdominal pain, an abdominal mass, signs of intestinal obstruction, or hepatic failure in patients with cirrhosis. CT scans show a rather dense, inhomogeneous mass revealing calcifications (Boldt et al. 1999), and angiography was characterized by a hypervascularized lesion (Liony et al. 1990). The clinical course of hepatic osteosarcoma is highly unfavorable. In four out of seven patients, remote metastatic disease was present at the time-point of diagnosis, and the tumor resulted in death in 7/7, the survival time after diagnosis ranging from 7 days to 4 months. The metastatic spread may involve both blood and lymph vessels. In an autopsy study, lymphatic spread to the hepatoduodenal ligament was observed, but the tumor also spread to the parietal and visceral peritoneum and the subjacent structures (von Hochstetter et al. 1987).

Pathology

Macroscopy

Macroscopically, hepatic osteosarcomas are large to very large lesions (in part more than 3000 g), with a diameter of 10 (Kitayama et al. 1995) to 25 cm (von Hochstetter et al. 1987; Govender and Rughubar 1998). The masses have a whitish to gray color, show a sandsoap consistency (depending on the amount of tumor bone), and may show large necroses.

In the first report on hepatic osteosarcoma, a 66-year-old female patient, the large tumor was located to the right lobe, with metastases to lymph nodes at the hepatic hilum and in the omentum (Ogawa 1930). An early autopsy report (male, 64-year-old) described a tumor of up to 13 cm size in the right lobe of a cirrhotic liver with hemochromatosis. The tumor had a fungating anterior surface and invaded the under surface of the right hemidiaphragm and the adjacent peritoneal surface. The cut surface of the neoplasm had the consistency of sandsoap, was white in color, and had a small area of necrosis (Maynard and Fone 1969). In a further autopsy report of 72-year-old female patient, a non-cirrhotic liver contained a large tumor (3350 g) measuring 25 × 19 × 14 cm and involving both liver lobes. The lesion was gray-white to pale yellow in color and had a gritty consistency on sectioning. There were large areas of necrosis. Tumor thrombi were present in the hepatic veins and hepatic portion of the inferior vena cava, and there was direct extension of tumor

into the porta hepatis. No lymph node or remote metastases were noted (Govender an Rughubar 1998). In a second necropsy of a 52-year-old male patient with liver cirrhosis, a tumor of about 10 cm in diameter bulged from the superior surface of the right lobe. The cut surface of the mass disclosed a yellowish-brown, focally whitish tumor with a partly fibrous capsule. The central area of the neoplasm showed marked necrosis and hemorrhage. In this patient, osteosarcoma was combined with a minute hepatocellular carcinoma (Kitayama et al. 1995). A further autopsy report referred to 75-year-old male patient, again with liver cirrhosis, showing a 6 cm multilobated and firm tumor in the right lobe. The tumor substance was yellowish and revealed hemorrhage and necrosis. Several nodular metastases were detected in the epiploon (Liony et al. 1990). Liver cirrhosis in conjunction with primary hepatic osteosarcoma was also described in an early Japanese report (Sumiyoshi and Niho 1971). In this 52-year-old male, the liver was enlarged (1700 g) and nodular, and the right lobe contained several firm, large, nodular tumor masses bulging from the interior surface. The cut surface disclosed a huge, yellowish-gray, multinodular tumor mass containing a small hemorrhagic or necrotic area. Extensive infiltrating growth into the branches of the portal vein was observed, and the inferior vena cava was completely occluded by a continuous growth of the tumor. A metastatic lesion was found in the septal wall of the right atrium, and few polypoid metastatic foci were present in the mucosa of the small bowel (Sumiyoshi and Niho 1971). On the cut surface, a grayish to red or speckled tissue is in evidence, sometimes with gritty features owing to the presence of calcified components. Gross necrosis may be impressive, and large tumors may contain a cystic cavity caused by tissue breakdown (Craig et al. 1989). The sarcoma has been reported to invade large veins of the hepatic outflow tract and the caval vein (the latter in three out of eight reported cases; Sumiyoshi and Niho 1971; Govender and Rughubar 1998; Boldt et al. 1999), eventually producing a tumor thrombus reaching the right atrium (Boldt et al. 1999).

Histopathology

Histology corresponds to standard osteosarcoma of the skeletal system. Most neoplastic cells are polymorphous or spindle-shaped elements, the latter sometimes arranged in the form of fascicles or whorls. However, predominantly osteoblastic lesions have also been noted (Govender and Rughubar 1998). Osteoid with or without mineralization in a lace-like pattern and a chondroid matrix with atypical chondroblast-like cells are regularly noted, even though the elaboration of osteoid may be heterogeneous or sparse (Fig. 1). In some of the lesions, chondroid differentiation (or chondrosarcoma) was noted (Ogawa 1930; Ojima et al. 1964; Sumiyoshi and Niho 1971; Kitayama et al. 1995; Boldt et al. 1999). One case showed numerous osteoclast-like giant cells, present mainly in the osteoblastic areas (Govender and Rughubar 1998). Some of the neoplasms contain multinucleated tumor giant cells. In part atypical mitotic figures are frequent, amounting to more than five mitoses per 10 HPF at $\times 40$ magnification in one study (Boldt et al. 1999). Expectedly, the neoplastic cells were immunoreactive for vimentin (Kitayama et al. 1995; Govender and Rughubar 1998; Boldt et al. 1999). Ultrastructurally, the neoplastic cells in one case exhibited the features of collagen-producing cells, showing indented nuclei with coarse heterochromatin along the inner membrane of the nuclear envelope, extensive labyrinthine spaces of dilated rough endoplasmic reticulum,

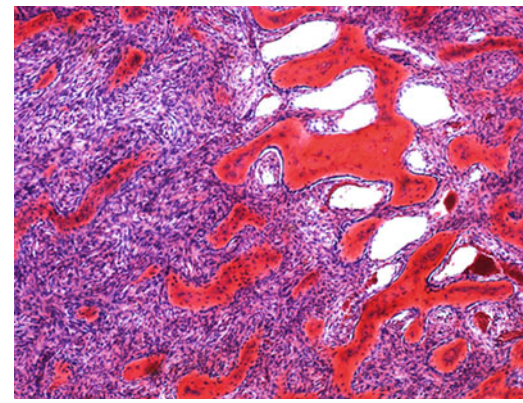

Fig. 1 Primary osteosarcoma of the liver with formation of immature tumor osteoid (hematoxylin and eosin stain)

numerous mitochondria, and small Golgi fields. In the pericellular maze of collagen fibrils, mineralization was detectable in the form of membrane-bound vesicles containing crystalline needles (von Hochstetter et al. 1987).

Differential Diagnosis

Skeletal osteosarcoma is known to metastasize to the liver (Shapiro et al. 1988). Also extraskeletal osteosarcomas can metastasize to the liver, including tumors arising in the mesentery or the omentum majus (Hussain et al. 2011; Tao et al. 2011). Histological difficulties arise in case of metastasis of small cell osteosarcoma to the liver (Ali et al. 2014), because other small cell malignancies may be mimicked. In the absence of evidence for metastatic disease, the main differential diagnosis of primary hepatic osteosarcoma is mixed hepatocellular carcinoma with osteosarcomatous components (hepatic carcinosarcoma with osseous components, Celikbilek et al. 2011; see the respective chapter). Histologically distinguishing these two lesion groups markedly depends on the sampling strategy employed, for this reason, one group of investigators prepared 155 tissue blocks to exclude an epithelial neoplastic component (Kitayama et al. 1995), but, similar to other situations of suspected mixed tumors, no reproducible sampling guidelines have been proposed so far. In addition, other tumors primary to the liver may contain osteoid, including malignant fibrous histiocytoma, malignant mesenchymoma, malignant teratomas, and adult-type hepatoblastoma.

Chondroma of the Liver

Primary cartilaginous tumors (chondromas and chondrosarcomas) of the liver are exceedingly rare, albeit pathogenically very interesting lesions. We are aware of only one report describing a large hepatic chondroma diagnosed in a 44-year-old woman, successfully removed at surgery, and showing the typical morphology of a benign cartilage tumor (Fried et al. 1992). This hepatic mass had been detected incidentally, and she had been followed up for 6 years with serial computed tomograms. Two liver biopsy specimens obtained by laparoscopy 3 and 6 years earlier showed only benign cartilaginous tissue, and the patient remained asymptomatic over this time period. After detection of an increase in mass, a preoperative MRI showed a large hepatic mass occupying the entire right liver lobe and extending into the caudate lobe. The mass contained numerous calcifications and measured approximately 16 cm in maximum diameter. Visceral angiography showed the mass to be hypovascular. Liver resection showed a histologically benign cartilage tumor with a non-aneuploid DNA content at flow cytometry (Fried et al. 1992).

Primary Hepatic Tumors with a Chondrosarcomatous Component

Primary chondrosarcoma of the liver has apparently been published only once so far. In 67-year-old male patient, synchronous occurrence of hepatocellular carcinoma and primary chondrosarcoma at two different places of the liver was observed (Sonoda et al. 1984). Cartilaginous components have been observed in mixed tumors or carcinosarcomas of the liver in adult patients, mostly associated with hepatocellular carcinoma (for more details, see ▶ Chap. 46, "Hepatobiliary Carcinosarcomas and Related Neoplasms"). The neoplastic cartilage component exhibits the features of chondrosarcoma (Imholz and Noltenius 1977; Kishimoto et al. 1984; Kawarada et al. 1985; Ooi et al. 1987; Leger-Ravet et al. 1996; Kinoshita and sakurai 1998; Nomura et al. 2000; Fu et al. 2000). These tumors are discussed in more detail in the respective chapter. Of special interest in the present context is the observation of Sonoda and coworkers, who reported on a 67-year-old male who showed hepatocellular carcinoma and chondrosarcoma arising from different areas of a cirrhotic liver, i.e., presenting as two independent tumors (Sonoda et al. 1984). Primary hepatic chondrosarcoma has been observed in mammals, e.g., the dog (Chikata et al. 2006). In few reports,

chondrosarcoma has been described to be located close to the liver, e.g., between the chest wall and liver (Cao et al. 2011), or in the right inferior aspect of the liver in case of costal chondrosarcoma (Nagata et al. 2012).

Metastases of Chondrosarcoma to the Liver

Rare metastases from skeletal and extraskeletal chondrosarcoma (mostly the myxoid variant) to the liver have been reported (Ryan et al. 2000; Mehanna et al. 2004).

Differential Diagnosis

Apart from metastases of chondrosarcomas (Ryan et al. 2000; Mehanna et al. 2004) and of chondroid salivary gland tumors (Youngs and Scheuer 1973; Chen 1978), the differential diagnosis may comprise chondroma of the diaphragm (Itakura et al. 1990).

References

Ali RH, Lee CH, Hayes MM (2014) Metastatic small cell osteosarcoma to the liver. A diagnostic pitfall for fine-needle aspiration cytology. Diagn Cytopathol 42:161–164

Allan CA, Soule EH (1971) Osteogenic sarcoma of the somatic soft tissues. Clinicopathologic study of 26 cases and review of the literature. Cancer 27:1121–1133

Boldt C, Pabst U, Nitsche R, Bürrig KF (1999) Primary osteosarcoma of the liver. Case report and literature review (in German). Pathologe 20:359–364

Cao D, Shah A, Liu Y (2011) Extraskeletal chondrosarcoma between chest wall and liver. Clin Gastroenterol Hepatol 9:e92–e93

Celikbilek M, Deniz K, Torun E, Artis T, Ozaslan E, Karahan OI, Patiroglu TE, Ozbakir O (2011) Primary hepatic carcinosarcoma. Hepatobiliary Pancreat Dis Int 10:101–103

Chen KTK (1978) Metastasizing pleomorphic adenoma of the salivary gland. Cancer 42:2407–2411

Chikata S, Nakamura S, Katayama R, Yanagisawa S, Matsuo Y, Yamane I, Takahashi K (2006) Primary chondrosarcoma in the liver of a dog. Vet Pathol 43:1033–1036

Craig JR, Peters RL, Edmondson HA (1989) Tumors of the liver and intrahepatic bile ducts. Atlas of tumor pathology, second series, fascicle 26. Armed Forces Institute of Pathology, Washington, DC, pp 246–248

Fried RH, Wardzala A, Willson RA, Sinanan MN, Marchioro TL, Haggitt R (1992) Benign cartilaginous tumor (chondroma) of the liver. Gastroenterology 103:678–680

Fu Y, Kobayashi S, Kushida Y, Saoo K, Haba R, Mori S, Miki H, Ohmori M (2000) Sarcomatoid hepatocellular carcinoma with chondroid variant: case report with immunohistochemical findings. Pathol Int 50:919–922

Govender D, Rughubar KN (1998) Primary osteosarcoma: case report and literature review. Pathology 30:323–325

Hussain MI, Al-Akeely MH, Alam MK, Jasser NA (2011) Extraskeletal osteosarcoma, telangiectatic variant arising from the small bowel mesentery. Saudi Med J 32:958–961

Imholz and Noltenius 1977. http://www.ncbi.nlm.nih.gov/pubmed/?term=197744

Itakura M, Shiraishi K, Kadosaka T, Matsuzaki S (1990) Chondroma of the diaphragm – report of a case. Endoscopy 22:276–278

Kawarada Y, Uehara S, Noda M, Yatani R, Mizumoto R (1985) Nonhepatocytic malignant mixed tumor primary in the liver: report of two cases. Cancer 55:1790–1798

Kinoshita H, Sakurai M (1998) Hepatocellular carcinoma with chondrosarcomatous variation: case report with immunohistochemical findings, and review of the literature. J Hepatobiliary Pancreat Surg 5:217–220

Kishimoto Y, Hijiya S, Nagasako R (1984) Malignant mixed tumor of the liver in adults. Am J Gastroenterol 79:229–235

Kitayama Y, Sugimura H, Arai T, Nagamatsu K, Kino I (1995) Primary osteosarcoma arising from cirrhotic liver. Pathol Int 45:320–325

Leger-Ravet MB, Borgonovo G, Amato A, Lemaigre G, Franco D (1996) Carcinosarcoma of the liver with mesenchymal differentiation: a case report. Hepatogastroenterology 43:255–259

Liony C, Lemarchand P, Manchon ND, Becret A, Bercroff E, Pellerin A, Tayot J, Bourreille J (1990) A case of primary osteosarcoma of the liver (in French). Gastroenterol Clin Biol 14:1003–1006

Maynard JH, Fone DJ (1969) Haemochromatosis with osteogenic sarcoma in the liver. Med J Aust 2:1260–1263

Mehanna D, Abu-Zidan FM, Rao S (2004) Liver metastasis in renal chondrosarcoma. Singapore Med J 45:183–185

Nagata Y, Shiraishi K, Matsuyama H (2012) A case of primary chondrosarcoma difficult to differentiate from retroperitoneal tumor (in Japanese). Hinyokika Kiyo 58:605–608

Nawabi A, Rath S, Nissen N, Forscher C, Colquhoun S, Lee J, Geller S, Wong A, Klein AS (2009) Primary

hepatic osteosarcoma. J Gastrointest Surg 13:1550–1553
Nomura K, Aizawa S, Ushigome S (2000) Carcinosarcoma of the liver. Arch Pathol Lab Med 124:888–890
Ogawa E (1930) Report of a case having both a squamous cell carcinoma of the gall bladder and an osteocartilaginous sarcoma of the liver (in Japanese). Hokuetsu Med J 45:703–709
Ojima A, Sugiyama T, Takeda T, Hazama F, Nakakuki K, Uesugi Y, Miyazaki A, Suzuki Y, Fukushima M (1964) Six cases of rare malignant tumors of the liver. Acta Pathol Jpn 14:95–102
Ooi A, Katsuda S, Nakanishi I, Nakamura N, Matsushita F, Tanaka N, Kobayashi K (1987) Hepatocellular carcinoma with chondrosarcomatous variation. A case report and review of the literature. Acta Pathol Jpn 37:1165–1173
Park SH, Choi SB, Kim WB, Song TJ (2009) Huge primary osteosarcoma of the liver presenting an aggressive recurrent pattern following surgical resection. J Dig Dis 10:231–235
Phelip JM, Sturm N, Roblin X, Baconnier M, Rebischung C, Chevallier C, Zarski JP (2007) Osteosarcoma: a rare cause of primary liver tumor (in French). Gastroenterol Clin Biol 31:836–837
Ryan JM, Dupuy DE, Pitman M, Boland GW, Hahn PF, Mueller PR (2000) Metastases to the liver from extraskeletal myxoid chondrosarcoma and successful treatment with percutaneous ethanol injection. Clin Radiol 55:314–317
Shapiro RS, Mendelson DS, Norton KN, Janus C, Gendal ES, Hermann G (1988) Case report: calcified liver metastases from osteosarcoma. J Comput Assist Tomogr 12:196–198
Sonoda T, Toyoshima S, Enjoji M, Kanematsu T, Inokuchi K (1984) Simultaneous occurrence of primary carcinoma and chondrosarcoma in the liver. A case report and review of the literature. Acta Pathol Jpn 34:919–924
Sumiyoshi A, Niho Y (1971) Primary osteogenic sarcoma of the liver – report of an autopsy case. Acta Pathol Jpn 21:305–312
Tao SX, Tian GQ, Ge MH, Fan CL (2011) Primary extraskeletal osteosarcoma of omentum majus. World J Surg Oncol 9:25
Von Hochstetter AR, Hattenschwiler J, Vogt M (1987) Primary osteosarcoma of the liver. Cancer 60:2312–2317
Youngs GR, Scheuer PJ (1973) Histologically benign mixed parotid tumor with hepatic metastasis. J Pathol 109:171–172

Gastrointestinal Stromal Tumors (GISTs) of the Liver

67

Contents

Abstract

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors with distinct clinical, morphologic, immunohistochemical, and molecular genetic features. GISTs account for 1–3 % of all gastrointestinal tumors, mainly occur in older adults, and are associated with specific KIT and PDGFRA mutations. Most GISTs immunohistochemically express KIT/CD117. GIST can involve the entire gastrointestinal tract, with a predilection for the stomach and the small intestine, whereas the liver is an uncommon primary location. Primary hepatic GISTs are well-circumscribed, firm tumors that may show central necrosis and satellite lesions. The histologic presentation corresponds to that of GISTs in other sites. Much more common than primary hepatic GIST are metastatic lesions, the liver being one of the most common metastatic sites of gastric and intestinal GIST. Liver metastases of GIST can undergo a distinct cystic change upon therapy with imatinib. Radiologically, part of these cysts closely mimic simple nonparasitic liver cysts.

ICD-O code 8936:

Benign GIST, prognostic groups 1, 2, 3a	8936/0
GIST with uncertain malignant potential, prognostic group 4	8936/1
Malignant GIST, prognostic groups 3b, 5, 6a, 6b	8936/3

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_67

Introduction

Gastrointestinal stromal tumors (GISTs) form a group of mesenchymal neoplasms with distinct clinical, morphologic, immunohistochemical, and molecular genetic features and a biologic behavior ranging from benign to malignant (reviews: Miettinen et al. 1999; Miettinen and Lasota 2001; Koh et al. 2004; Blay et al. 2005; Miettinen and Lasota 2006a, b; Biasco et al. 2009; Saleem and Ahmed 2009; Steigen and Eide 2009; Laurini and Carter 2010; Liegl-Atzwanger et al. 2010; Corless et al. 2011). They represent the most common primary mesenchymal tumor of the gastrointestinal tract, with roughly 1–3 % of all gastrointestinal tumors, but approximately 2000 cases of GIST are diagnosed annually in the United States.

Owing to some histologic resemblance, GISTs have formerly been mistaken to be smooth muscle tumors of the GI tract. GISTs were first described by Mazur and Clark in 1983 and are now the most common mesenchymal tumors of the human gastrointestinal tract (reviews: Miettinen et al. 2002; Koh et al. 2004). Today, neoplasms previously termed gastrointestinal autonomic nerve tumors (GANT) and gastrointestinal pacemaker cell tumors (GIPACT) are now regarded as belonging to the spectrum of GIST (Lee et al. 2001).

Epidemiology

GIST is typically a tumor of older adults, such neoplasms in young adults, adolescents, and children being very rare and more heterogeneous (Miettinen et al. 2005; Prakash et al. 2005). In the pediatric age group, GISTs mainly affect girls, and the tumors differ from those in adults in several respects. Pediatric GISTs typically arise in the stomach as multifocal tumors with a multinodular growth pattern, epithelioid morphology, lymph node metastases, and absence of KIT or PDGFRA mutations. One subset of adult GISTs present with almost the same pattern and are called “pediatric-type” GISTs in adults (Rege et al. 2011).

GISTs can involve the entire GI tract, but the majority develop in the stomach (60–70 %) and the small intestine (25–35 %), other locations being more uncommon, such as the colorectum (up to 5 %), the duodenum (up to 4 %), and the esophagus (2 %). GIST rarely develops in the periampullary region of the duodenum (Cavallini et al. 2005) or in the papilla Vateri itself (Wellmann et al. 2004). Lesion sites unrelated to the tubular GIT include the omentum, the mesentery, the retroperitoneal space, the pancreas, and the liver. GISTs are usually sporadic tumors, but they rarely occur in the setting of syndromes such as Carney triad (GIST, pulmonary chondroma, paraganglioma) or Carney-Stratakis syndrome (GIST plus paraganglioma). Syndromic GISTs are diagnosed in younger individuals, including children, and are more common in females (Postow and Robson 2012). Multiple GISTs may be associated with a very rare inherited condition, autosomal dominant familial GIST with germ line c-Kit mutations, of which around 20 families have been observed (Kim et al. 2005; Li et al. 2005).

General Histologic Features of GISTs

The histopathologic features characteristic of GIST have been extensively reviewed (Miettinen et al. 2002; Miettinen and Lasota 2006; Foo et al. 2012), and the histologic criteria of GIST have been defined by a consensus conference (Blay et al. 2005). GISTs vary from cellular spindle cell neoplasms to epithelioid or mixed, epithelioid, and spindle cell variants. Apart from the typical cellular and histologic features, few GISTs exhibit aberrant patterns, e.g., pseudopapillary structures in epithelioid variants or the formation of osteoclast-like giant cells (Leung et al. 2002) or the development of rhabdoid features (Richmond et al. 2004). In addition, some GISTs show epithelioid cells characterized by round to oval cells exhibiting a less cohesive pattern of growth and eosinophilic cytoplasm. A subtype of GIST with a myxoid and epithelioid differentiation and mast cell infiltration is associated with mutations of the PDGF receptor alpha gene (Sakurai et al. 2004). PDGFRA-mutated

GISTs were significantly more often epithelioid and had a higher PDGFRA expressed compared to c-Kit mutants (Agaimy et al. 2013). Rarely, GIST can undergo histologic dedifferentiation, e.g., to an anaplastic KIT-negative phenotype (Antonescu et al. 2013). Treatment with tyrosine kinase inhibitor (imatinib) can induce several changes in histology and immunohistochemistry. GISTs treated with imatinib can undergo cystic change (see below). Rhabdomyosarcomatous change has been found (Liegl et al. 2009). Remarkably, the immunophenotype of GIST may change upon treatment with imatinib, in that part of the tumors lose KIT positivity (even in continuing c-Kit mutations), and a subset of these also lose reactivity for CD34 (Pauwels et al. 2005).

Immunohistochemically, most GISTs express Kit (CD117; Sarlomo-Rikala et al. 1998; Hasegawa et al. 2002), although Kit-negative GISTs are known, and part of those have PDGFRA mutations (Debiec-Rychter et al. 2004; Medeiros et al. 2004). Up to 70 % of the lesions are immunoreactive for CD34 (more frequently in gastric tumors; Emile et al. 2004), and there is variable expression of smooth muscle actins (20–30 %), while only very few percent of the cases show desmin positivity. Differential diagnostically important is the low frequency of reactivity for S 100 protein, i.e., 10 % or less (review: Miettinen et al. 2002). cDNA microarray techniques may uncover other markers for GIST. By such an approach, a hypothetical protein termed DOG1 has been found to be expressed by GIST, irrespective of c-Kit or PDGFRA mutations (West et al. 2004).

Primary GIST of the Hepatobiliary Tract

Introduction

Rarely, GISTs are tumors primary to the liver (Hu et al. 2003; Park 2004a; De Chiara et al. 2006; Luo et al. 2009; Ochiai et al. 2009; Terada 2009; Yamamoto et al. 2010; Alecu et al. 2011; Li et al. 2012; Zhou et al. 2014). CT images showed hypoattenuation of the lesion in all three phases, and ultrasound with contrast revealed a hypervascular lesion in the arterial phase and hypoechoic features during portal and late phases (Luo et al. 2009). Malignant GIST rarely develops in the gallbladder (Park et al. 2004b), sometimes with evidence of interstitial cells of Cajal phenotype (Mendoza-Marin et al. 2002). Very rarely, GIST is associated with other hepatic tumors, e.g., inflammatory pseudotumor of the liver (Lo et al. 2004). In one patient with primary hepatic GIST, a PDGFRA gene mutation was found (Yamamoto et al. 2010).

Pathology

Macroscopy

In one patient with a malignant primary hepatic GIST, the mass measured 15 cm in diameter. It was a circumscribed tumor which, on cross section, revealed a firm and homogeneous, brownish-tan mass with large central necrosis, accompanied by three smaller satellite nodules (Hu et al. 2003). In a second patient, the solitary primary hepatic GIST had a diameter of 5 × 4 cm (Alecu et al. 2011).

Histopathology

The histopathology of hepatic GIST reflects that of GISTs located elsewhere, i.e., with predominance of a spindle cell population. However, an epithelioid morphology has also been described (Yamamoto et al. 2010). In few cases which had been immunohistochemically analyzed, the neoplastic tissue was markedly reactive for CD117 and vimentin and focally for CD34 (Hu et al. 2003; Luo et al. 2009; Ochiai et al. 2009). In one patient, metastases showed multinucleated giant cells that were not seen in the primary lesion (Hu et al. 2003). In another patient, a KIT-positive GIST primary to the liver metastasizes to the lung, and it was hypothesized that the liver tumor might be related to extra-GIT cells with a pacemaker cell phenotype (De Chiara et al. 2006).

Immunohistochemistry

Immunohistochemically, most GISTs express Kit (CD117; Sarlomo-Rikala et al. 1998; Hasegawa et al. 2002), although Kit-negative GISTs are known, and part of those have PDGFRA

mutations (Debiec-Rychter et al. 2004; Medeiros et al. 2004). Up to 70 % of the lesions are immunoreactive for CD34 (more frequently in gastric tumors; Emile et al. 2004), and there is variable expression of smooth muscle actins (20–30 %), while only very few percent of the cases show desmin positivity. Differential diagnostically important is the low frequency of reactivity for S 100 protein, i.e., 10 % or less (review: Miettinen et al. 2002). cDNA microarray techniques may uncover other markers for GIST. By such an approach, a hypothetical protein termed DOG1 has been found to be expressed by GIST, irrespective of c-Kit or PDGFRA mutations (West et al. 2004).

Secondary GIST of the Liver (Metastases)

Much more commonly, the liver manifestations of GIST are metastatic (DeMatteo et al. 2000; Sandrasegaran et al. 2005; Cheung et al. 2014). Among 94 patients with GIST metastases, 61 showed liver metastases, 51 of these liver only (DeMatteo et al. 2000). In one study, liver metastases amounted to 32 % (Sandrasegaran et al. 2005). In another study with follow-up, 38/53 patients with metastases had metastases to the liver (Burkill et al. 2003). Liver metastases of GIST may be a delayed phenomenon in some patients, e.g., found after 11 years (Ballarini et al. 1998). The imaging features of hepatic GIST metastases after chemotherapy have been specified (Sandrasegaran et al. 2005; Yang et al. 2005; Patnaik et al. 2012). In patients with recurrence of GIST following complete surgical resection, relapse commonly occurs in the liver (Plumb et al. 2013).

Therapy-Associated Cysts in GIST Metastases

It is important to note that liver metastases of GIST respond to imatinib therapy by rapidly showing cystic change (Fig. 1; Chen et al. 2002), and some of these treated lesions are almost indistinguishable from simple hepatic cysts (Sandrasegaran et al. 2005). This phenomenon is unusual, as imatinib induces not tumor necrosis but tumor cell apoptosis. Cystic degeneration of GIST following imatinib treatment is related to lack of CD34 expression (Koh et al. 2012). There are, however, rare instances of cystic liver metastases of GIST prior to the imatinib treatment era or before any treatment (Zonios et al. 2003; Jain et al. 2009; Colovic et al. 2013). Part of GISTs, mainly those with a high-risk mitotic status, show vasculogenic mimicry, characterized by the formation of fluid-conducting channels by highly invasive and genetically dysregulated tumor cells. GISTs having vasculogenic mimicry are prone to develop liver metastases (Sun et al. 2008). Not much information is available regarding molecular features that might favor liver metastases of GIST. In a recent study, GIST patients with loss of the succinate dehydrogenase subunit A, due to germ line mutations, show a slow course of disease, but have a slightly higher rate of liver metastases (Miettinen et al. 2013).

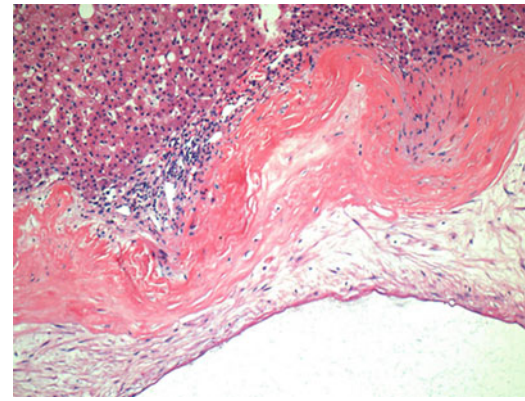

Fig. 1 Hepatic metastasis of gastrointestinal stromal tumor (GIST) post-therapy. Therapy has induced a cystic lesion. The cyst wall has an interior loose, slightly myxoid connective tissue, followed to the periphery by a waved band of collagenous tissue (hematoxylin and eosin stain)

Differential Diagnosis

Differential diagnosis mainly involves other spindle cell tumors primary to the liver or hepatic metastases of spindle cell sarcomas. In the

pre-immunohistochemistry area, many tumors now classified as GIST may have been diagnosed as benign or malignant smooth muscle tumors.

Biology of Disease

In contrast to earlier views, GISTs are to date regarded as non-benign lesions in principle, any such tumor having the potential of malignancy (Fletcher et al. 2002). The frequency of overtly malignant GIST has been estimated as 20–30 % of the frequency of all soft tissue sarcomas, but small, still not overtly malignant tumors are probably much more common (Miettinen et al. 2002). It is estimated that 25 % of gastric GISTs (not counting minimal incidental lesions) are malignant. In the GI tract, the most useful and best analyzed prognostic factors comprise tumor size and mitotic count, the latter expressed as the number of mitotic figures per 50 high-power fields (HPFs), with a total area of 5 mm2. In the TNM classification, grading is based on the mitotic rate. A low mitotic rate is <5 mitoses/50 HPFs; a high mitotic rate is >5 mitoses/50 HPFs. The prognostic groups employed in GIST (groups 1, 2, 3a, 3b, 4, 5, 6a, and 6b) are constructed from the two parameters, tumor size (diameter) and mitotic rate (review: Hou et al. 2009a, b). These prognostic systems have proven to be efficient, mainly in primary GISTs located in the gastrointestinal tube. For tumors located elsewhere, the prediction of malignancy is still difficult. Several informations that have increased our knowledge on the behavior of GIST are here briefly summarized. Prognosis of GIST has been related with tumor size and gender (Hasegawa et al. 2002; Singer et al. 2002; Bai et al. 2005). Among 48 studied patients with GIST, 5-year recurrence-free survival with tumors less than 5 cm, 5–10 cm, and more than 10 cm were 82 %, 45 %, and 27 %, respectively (Singer et al. 2002). In one study, frankly malignant GISTs have been found to be typically large (mean primary tumor size: 13 cm), well-circumscribed (86 %), heterogeneous, centrally necrotic tumors that arise in the wall of the small bowel or stomach, despite their size rarely obstructing the viscera involved (Burkill et al. 2003). An analysis of the predictors of survival in 38 curatively resected GISTs (23 tumors of the stomach 13 tumors of the small bowel and 2 in the color) in the pre-imatinib era showed that the overall 5-year survival rate was 70 % and that the presence of distant metastases, the proliferative index, and deletional mutations of KIT exon 11 correlated significantly with poor outcome, while none of the tumors with a PDGFRA mutant relapsed (Iesalnieks et al. 2005). PDGFRA-mutated GISTs of low or no malignant potential are usually located in the stomach (Lasota et al. 2004).

There is a clear relation between the proliferative activity of GIST and outcome (Hasegawa et al. 2002; Singer et al. 2002; Yokoi et al. 2005), and recent findings confirm that mitotic activity remains the strongest prognostic factor in GIST patients (Demir et al. 2013). The 5-year recurrence-free survival for patients with tumors that had 3 mitoses or fewer per 30 high-power fields, more than 3 but less than 15, and more than 15 mitoses per 30 fields was 89 %, 49 %, and 16 %, respectively (Singer et al. 2002). Pathologically, tumors larger than 5 cm (Yokoi et al. 2005) and/or those that have a mitotic activity count exceeding 5 per 50 high-power fields have a high frequency of intra-abdominal recurrence and liver metastasis. Conversely, tumors smaller than 2 cm and those with mitotic activity counts less than 5 per 50 high-power fields are likely to be benign (review: Miettinen et al. 2002). The histologic phenotype is also a predictor of GIST biology. A spindle cell histology is a favorable feature, while tumors with an epithelioid or mixed histology do worse (Singer et al. 2002), but this furthermore depends on the site of the tumors and their mutational status. There is evidence for a prognostic effect of the mutational status in GIST. Deletions affecting codons 557–558 of the c-Kit gene indicate poor prognosis in patients with completely resected GIST (Martin et al. 2005). In some studies, parameters have been combined in order to assess malignancy in GIST, higher risk being generally related to larger tumor size together with an elevated proliferative activity (Fletcher et al. 2002). In an investigation on 22 patients,

the tumor features were first broken down into the presence or absence of necrosis, each of these groups then further broken down into tumors with 5 cm or less than 5 cm, or more than 5 cm diameter, and finally separated in regard to the proliferation index (< = >3 %). It turned out that malignant GIST either had necrosis and a diameter of 5 or more than 5 cm or had necrosis with a diameter of less than 5 cm but a proliferation index exceeding 3 % (Yokoi et al. 2005).

Progression of GIST is also linked to expression patterns of growth and regulatory factors. Increased KIT signaling with upregulation of cyclin D correlates to accelerated proliferation and shorter disease-free survival in GIST with KIT exon 11 deletions (Haller et al. 2008). The CDKN2A tumor suppressor network (Haller et al. 2005) and the p16 locus are involved consistently in chromosomal losses found in malignant GIST. In fact, p16/INK4a downregulation, partly due to p16 promoter methylation, is implied in GIST progression, and reduced p16 protein immunostaining is associated with clinical malignancy (Ricci et al. 2004; Schmieder et al. 2008). For gastric GIST, CD26/dipeptidyl-peptidase IV seems to be a reliable biomarker of malignancy (Yamaguchi et al. 2008). Overexpression of fascin-1 was found to predict an aggressive behavior, including larger tumor size, higher mitotic counts, and blood vessel invasion (Yamamoto et al. 2013).

Therapy with imatinib has dramatically changed to prognosis of GIST (Croom and Perry 2003; Duffaud and Blay 2003; Chacon et al. 2005; Peshwe et al. 2005; Sanborn and Blanke 2005). Imatinib interferes with cellular availability of key substrates, via interference with glucose transport, glucose oxidation for RNA ribose synthesis in the pentose cycle, and de novo long-chain fatty acid synthesis. Acquired resistance to imatinib is increasing, and development of resistance can be assessed by metabolic profiling (Serkova and Boros 2005). Detailed analyses of the genetic status of GIST having developed resistance to imatinib have demonstrated that changes in the mutational pattern of the c-Kit gene, loss of KIT expression, and secondary PDGFRA mutations play a role (Debiec-Rychter et al. 2005).

Pathogenic Pathways

GISTs seem to be derived from a distinct cell of the GIT, the interstitial cell of Cajal, a cell type that is reactive for the KIT protein and regarded as a pacemaker cell (see below). Central to the tumorigenesis of GIST are activating mutations in the proto-oncogene tyrosine protein kinase c-Kit encoding the KIT protein (Hirota et al. 1998; Kitamura and Hirota 2004; Lasota and Miettinen 2006; review: Barnett et al. 2013), or platelet-derived growth factor receptor alpha (PDGFRA), which are regarded as alternative and mutually exclusive (Duensing et al. 2004a).

KIT Mutations

Generally, tumors with c-Kit mutations tend to develop in the small intestine, while those with PDGFRA mutations originate in the stomach (Penzel et al. 2005). Mutations of the c-Kit oncogene, causing changes in the KIT protein expression, are highly characteristic of GIST and are found in 80–85 % of GIST, while KIT immunoreactivity in the absence of mutations can also be detected in a growing list of other solid tumors, e.g., small cell lung cancer and germ cell tumors (Sihto et al. 2005). c-Kit mutations are also common in incidental GIST 1 cm or less in size, suggesting that activating c-Kit mutations are acquired very early in the GIST development pathway (Corless et al. 2002). GISTs in children with neurofibromatosis 1 (NF1) do not show KIT or PDGFRA mutations. Key mutations of c-Kit gene chiefly occur in exon 11, followed by exons 9, 13, and 17 (Hirota et al. 1998; Corless et al. 2004; Penzel et al. 2005), and such mutations do not occur in smooth muscle tumors of the GIT, with which GIST may be confounded (Lasota et al. 1999). In a subset of so-called wild-type GIST, no mutations of these two genes were found (Corless et al. 2004). There is a connection between mutations of these genes and morphotype, tumor biology, and responsiveness to imatinib. This may be due to distinct gene expression profiles, but there

is also evidence for a complex relationship between differential expression of mutant isoforms in epithelioid and mixed variants of GIST and the tumor site (Wasag et al. 2004). The signal transduction pathways stimulated by activated KIT involve AKT, MAPK, and STATs (Paner et al. 2003; Duensing et al. 2004b). Differentially expressed genes include ezrin, p70S6K, and protein kinases C/PKC, which are known to have important roles in KIT and PDGFRA signaling (Subramanian et al. 2004). However, one PKC species, PKC theta, is a marker of many GISTs, including those that lack c-Kit expression and/or contain PDGFRA mutations (Duensing et al. 2004a).

The correlation between c-Kit mutations and outcome is still controversial. Prognostic associations were found with particular c-Kit mutation types, and patients with missense exon 11 mutations had a higher rate of 5-year recurrence-free survival than those with GIST showing other mutation types. Exon 9 mutations of c-Kit per se did not have prognostic relevance, albeit these mutations are relevant and have direct therapeutic implications (Künstlinger et al. 2013). Moreover, an independent predictor for disease-free survival was the presence of deletion/insertion exon 11 mutations (Singer et al. 2002). In line with these findings is the observation that c-Kit mutations in GIST occur preferentially in the spindle cell rather than in the epithelioid cell variant, the spindle cell variant having a better prognosis (Wardelmann et al. 2002). On the other hand, Exon 11 c-Kit mutations are more common in malignant versus benign GIST (Lasota et al. 1999), and a recent study found that the presence of any c-Kit and PDGFRA mutations and the presence of c-Kit mutations alone were significantly associated with high-risk/malignant GIST (Penzel et al. 2005). It also surfaced that the type of deletional c-Kit mutations affects biology of disease in that they confer worse prognosis (Martin et al. 2005). In contrast, internal tandem duplications in 3′ end of c-Kit juxtamembrane domain occur predominantly in gastric tumors and generally seem to confer a favorable course (Lasota et al. 2003).

PDGFRA Mutations

A subset of GIST (up to 8 %; Corless et al. 2004) contains mutations in the homologous kinase, platelet-derived growth factor receptor alpha (PDGFRA) gene (chiefly exons 18 and 12), and the most common of these mutations is resistant to imatinib in vitro. In more detail, isoforms with a substitution involving codon D842 in exon 18 are resistant to the drug, while other mutations in exon 18 and mutations in exons 12 and 14 confer imatinib sensitivity (Corless et al. 2005). In a study of epithelioid-/mixed-type GIST, activating mutations of c-Kit were found in 50 % (mostly exon 11), while 25 % with no detectable c-Kit mutations demonstrated PDGFRA mutant isoforms. In contrast to other GISTs, neoplasms with PDGFRA mutations had an epithelioid phenotype and had more commonly multinuclear giant cells (Yi et al. 2005; Pauls et al. 2005). Most of the c-Kit mutant epithelioid/mixed tumors originated from non-gastric sites, whereas all GIST with mutant PDGFRA isoforms originated from the stomach (Wasag et al. 2004). That a great majority of GIST with PDGFRA mutations represent gastric tumors (usually with low or no malignant potential) has been found in another study (Lasota et al. 2004). A third situation where GIST develops in the context of a genetic anomaly is neurofibromatosis type 1, where GISTs show CD117 reactivity (even in the absence of c-Kit mutations), whereas nerve sheath tumors do not (Cheng et al. 2004; Andersson et al. 2005). GISTs also make part of Carney's triad characterized by GIST, pulmonary chondromas, and paragangliomas.

Germ Line Mutations of Succinate Dehydrogenase Subunit A or B (SDHA, SDHB)

A subset of about 75–10 % of GISTs reveals loss of succinate dehydrogenase (SDH) subunit B (SDHB), associated with loss of function of this mitochondrial SDH complex. Patients with such losses are wild type in regard to KIT and PDGFRA, and some of the patients have germ line mutations of the SDH subunit genes SDHB, SDHC, or SDHD, known as Carney-Stratakis

syndrome (GIST plus paraganglioma) (Pasini et al. 2008; Lodish et al. 2010; Miettinen et al. 2011; Celestino et al. 2012; Gill 2012). Thirty percent of patients who are SDH function deficient reveal loss of the SDHA unit signaling germ line mutations. SDHA-deficient patients are older than SDHB-mutated individuals and show a slow course of disease in most cases, despite a slightly higher rate of liver metastases (Dwight et al. 2013; Miettinen et al. 2013). SSDH mutations are strongly associated with paraganglioma of the organ of Zuckerkandl (Lodish et al. 2010). SDH-deficient GISTs are characterized by overexpression of insulin-like growth factor receptor 1/IGFR1, due to unknown reasons (Chou et al. 2012; Nannini et al. 2013).

Neurofibromatosis Type 1

Patients affected by neurofibromatosis type 1 (NF1) have an increased risk of developing GIST. NF1-associated GISTs are usually wild type for c-Kit and PDGFRA (Mussi et al. 2008) and can be associated with pheochromocytoma (Ozcinar et al. 2013; Vlenterie et al. 2013).

References

Agaimy A, Otto C, Braun A, Geddert H, Schaefer IM, Haller F (2013) Value of epithelioid morphology and PDGFRA immunostaining pattern for prediction of PDGFRA mutated phenotype in gastrointestinal stromal tumors (GISTs). Int J Clin Exp Pathol 6:1839–1846

Alecu L, Tulin A, Ursut B, Ursut B, Oproiu A, Obrocea F, Ionescu M (2011) Gastrointestinal stromal tumor with primary hepatic unique location – clinical case (in Romanian). Chirurgia (Bucur) 106:677–681

Andersson J, Sihto H, Meis-Kindblom JM, Joensuu H, Nupponen N, Kindblom LG (2005) NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. Am J Surg Pathol 29:1170–1176

Antonescu CR, Romaoe S, Zhang L, Nafa K, Hornick JL, Nielsen GP, Mino-Kenudson M et al (2013) Dedifferentiation in gastrointestinal stromal tumor to an anaplastic KIT-negative phenotype: a diagnostic pitfall: morphologic and molecular characterization of 8 cases occurring either de novo or after imatinib therapy. Am J Surg Pathol 37:385–392

Bai YK, Shao YF, Shi SS, Gao YN, Sun YT, Wan YL (2005) Analysis of prognostic factors in gastrointestinal stromal tumors of the small intestine (in Chinese). Zhonghua Wei Chang Wai Ke Za Zhi 8:213–216

Ballarini C, Intra M, Ceretti AP, Prestipino F, Bianchi FM, Sparacio F, Berti E, Perrone S et al (1998) Gastrointestinal stromal tumors: a “benign” tumor with hepatic metastasis after 11 years. Tumori 84:78–81

Barnett CM, Corless CL, Heinrich MC (2013) Gastrointestinal stromal tumors: molecular markers and genetic subtypes. Hematol Oncol Clin N Am 27:871–888

Biasco G, Velo D, Angriman I, Astorino M, Baldan A, Baseggio M, Basso U, Battaglia G et al (2009) Gastrointestinal stromal tumors: report of an audit and review of the literature. Eur J Cancer Prev 18:106–116

Blay JY, Bonvalot S, Casali P, Choi H, Debiec-Rychter M, Dei Tos AP, Emile JF, Gronchi A, Hogendoorn PC et al (2005) Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20–21 March 2004, under the auspices of ESMO. Ann Oncol 16:566–578

Burkill GJ, Badran M, Al-Muderis O, Meirion TJ, Judson IR, Fisher C, Moskovic EC (2003) Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. Radiology 226:527–532

Cavallini M, Cecera A, Ciardi A, Caterino S, Ziparo V (2005) Small periampullary duodenal gastrointestinal stromal tumor treated by local excision: report of a case. Tumori 91:264–266

Celestino R, Lima J, Faustino A, Vinagre J, Maximo V, Gouveia A, Soares P, Manuel Lopes J (2012) Molecular alterations and expression of succinate dehydrogenase complex in wild-type KIT/PDGFRA/BRAF gastrointestinal stromal tumors. Eur J Hum Genet 21:503–510

Chacon M, Roca E, Huertas E, Loria FS, Domenichini E (2005) Complete remission with imatinib in metastatic gastrointestinal stromal tumors. J Clin Oncol 23:6801–6802

Chen MY, Bechtold RE, Savage PD (2002) Cystic change in hepatic metastases from gastrointestinal stromal tumors (GISTs) treated with Gleevec (imatinib mesylate). AJR Am J Roentgenol 179:1059–1062

Cheng SP, Huang MJ, Yang TL, Tzen CY, Liu CL, Liu TP, Hsiao SC (2004) Neurofibromatosis with gastrointestinal stromal tumors: insights into the association. Dig Dis Sci 49:1165–1169

Cheung TT, Chok KS, Chan AC, Yau TC, Chan SC, Poon RT, Fan ST, Lo CM (2014) Analysis of long-term survival after hepatectomy for isolated liver metastasis of gastrointestinal stromal tumour. ANT J Surg 84(11):827–831

Chou A, Chen J, Clarkson A, Samra JS, Clifton-Bligh RJ, Hugh TJ, Gill AJ (2012) Succinate dehydrogenase-deficient GISTs are characterized by IGF1R overexpression. Mod Pathol 25:1307–1313

Colovic R, Micev M, Matic S, Colovic N, Grubor N, Atkinson HD (2013) Malignant stromal tumor of the

stomach with giant cystic liver metastases prior to treatment with imatinib mesylate. Vojnosanit Pregl 70:225–228

Corless CL, McGreevey L, Haley A, Town A, Heinrich MC (2002) KIT mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. Am J Pathol 160:1567–1572

Corless CL, Fletcher JA, Heinrich MC (2004) Biology of gastrointestinal stromal tumors. J Clin Oncol 22:3813–3825

Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, Shiraga S, Bainbridge T et al (2005) PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 23:5357–5364

Corless CL, Barnett CM, Heinrich MC (2011) Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer 11:865–878

Croom KF, Perry CM (2003) Imatinib mesylate: in the treatment of gastrointestinal stromal tumors. Drugs 63:513–522

De Chiara A, De Rosa V, Lastoria S, Lastoria S, Franco R, Botti G, Iaffaioli VR, Apice G (2006) Primary gastrointestinal stromal tumor of the liver with lung metastases successfully treated with STI-571 (imatinib mesylate). Front Biosci 11:498–501

Debiec-Rychter M, Wasag B, Stul M, De Wever I, van Oosterom A, Hagemeijer A, Sciot R (2004) Gastrointestinal stromal tumours (GISTs) negative for KIT (CD117 antigen) immunoreactivity. J Pathol 202:430–438

Debiec-Rychter M, Cools J, Dumez H, Sciot R, Stul M, Mentens N, Vranckx H, Wasag B et al (2005) Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology 128:270–279

DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF (2000) Two hundred gastrointestinal stromal tumors. Recurrence patterns and prognostic factors for survival. Ann Surg 231:51–58

Demir L, Ekinci N, Erten C, Kucukzeybek Y, Alacacioglu A, Somali I, Can A, Dirican A et al (2013) Does immunohistochemistry provide additional prognostic data in gastrointestinal stromal tumors? Asian Pac J Cancer Prev 14:4751–4758

Duensing A, Heinrich MC, Fletcher CD, Fletcher JA (2004a) Biology of gastrointestinal stromal tumors: KIT mutations and beyond. Cancer Invest 22:106–116

Duensing A, Medeiros F, McConarty B, Joseph NE, Panigrahy D, Singer S, Fletcher CD et al (2004b) Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). Oncogene 23:3999–4006

Duensing A, Joseph NE, Medeiros F, Smith F, Hornick JL, Heinrich MC, Corless CL et al (2004c) Protein kinase C theta (PKCtheta) expression and constitutive activation in gastrointestinal stromal tumors (GISTs). Cancer Res 64:5127–5131

Duffaud F, Blay JY (2003) Gastrointestinal stromal tumors: biology and treatment. Oncology 65:187–197

Dwight T, Benn DE, Clarkson A, Vilain R, Lipton L, Robinson BG, Clifton-Bligh RJ, Gill AJ (2013) Loss of SDHA expression identifies SDHA mutations in succinate dehydrogenase-deficient gastrointestinal stromal tumors. Am J Surg Pathol 37:226–233

Emile JF, Theou N, Tabone S, Cortez A, Terrier P, Chaumette MT, Julie C, Bertheau P et al (2004) Clinicopathologic, phenotypic, and genotypic characteristics of gastrointestinal mesenchymal tumors. Clin Gastroenterol Hepatol 2:597–605

Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ et al (2002) Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 33:459–465

Foo WC, Liegl-Atzwanger B, Lazar AJ (2012) Pathology of gastrointestinal stromal tumors. Clin Med Insights Pathol 5:23–33

Gill AJ (2012) Succinate dehydrogenase (SDH) and mitochondrial driven neoplasia. Pathology 44:285–292

Haller F, Gunawan B, von Heydebreck A, Schwager S, Schulten HJ, Wolf-Salgo J et al (2005) Prognostic role of E2F1 and members of the CDKN2A network in gastrointestinal stromal tumors. Clin Cancer Res 11:6589–6597

Haller F, Löbke C, Ruschhaupt M, Schulten HJ, Schwager S, Gunawan B, Armbrust T et al (2008) Increased KIT signaling with up-regulation of cyclin D correlates to accelerated proliferation and shorter disease-free survival in gastrointestinal stromal tumours ((GISts) with KIT exon 11 deletions. J Pathol 216:225–235

Hasegawa T, Matsuno Y, Shimoda T, Hirohashi S (2002) Gastrointestinal stromal tumor: consistent CD117 immunostaining for diagnosis, and prognostic classification based on tumor size and MIB-1 grade. Hum Pathol 33:669–676

Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M et al (1998) Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279:577–580

Hou YY, Lu SH, Zhou Y, Xu JF, Ji Y, Hou J, Qi WD, Shi Y, Tan YS, Zhu XZ (2009a) Predictive values of clinical and pathological parameters for malignancy of gastrointestinal stromal tumors. Histol Histopathol 24:737–747

Hou YY, Lu SH, Zhou Y, Qi WD, Shi Y, Tan YS, Zhu XZ (2009b) Stage and histological grade of gastrointestinal stromal tumors based on a new approach are strongly associated with clinical behaviors. Mod Pathol 22:556–569

Hu X, Forster J, Damjanov I (2003) Primary malignant gastrointestinal stromal tumor of the liver. Arch Pathol Lab Med 127:1606–1608

Jain P, Jha AK, Rai RR (2009) Cystic hepatic metastasis from gastrointestinal stromal tumor prior to imatinib mimicking a liver abscess. J Gastrointest Liver Dis 18:121–122

Kim HJ, Lim SJ, Park K, Yuh Y, Jang SJ, Choi J (2005) Multiple gastrointestinal stromal tumors with a germline c-kit mutation. Pathol Int 55:655–659

Kitamura Y, Hirota S (2004) Kit as a human oncogenic tyrosine kinase. Cell Mol Life Sci 61:2924–2931

Koh JS, Trent J, Chen L, El-Naggar A, Hunt K, Pollock R, Zhang W (2004) Gastrointestinal stromal tumors: overview of pathologic features, molecular biology, and therapy with imatinib mesylate. Histol Histopathol 19:565–574

Koh Y, Lee HE, Oh DY, Kim JH, Lee SH, Kim SH, Im SA, Kim TY, Heo DS, Kim WH et al (2012) The lack of CD34 expression in gastrointestinal stromal tumors is related to cystic degeneration following imatinib use. Jpn J Clin Oncol 42:1020–1027

Künstlinger H, Huss S, Merkelbach-Bruse S, Binot E, Kleine MA, Loeser H, Mittler J et al (2013) Gastrointestinal stromal tumors with KIT exon 9 mutations: update on genotype-phenotype correlation and validation of high-resolution melting assay for mutational testing. Am J Surg Pathol 37(11):1648–1659

Lasota J, Miettinen M (2006) KIT and PDGFRA mutations in gastrointestinal stroma tumors (GISTs). Semin Diagn Pathol 23:91–102

Lasota J, Jasinski M, Sarlomo-Rikala M, Miettinen M (1999) Mutations in exon 11 of c-Kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. Am J Pathol 154:53–60

Lasota J, Dansonka-Mieszkowska A, Stachura T, Schneider-Stock R, Kallajoki M, Steigen SE et al (2003) Gastrointestinal stromal tumors with internal tandem duplications in 3′ end of KIT juxtamembrane domain occur predominantly in stomach and generally seem to have a favorable course. Mod Pathol 16:1257–1264

Lasota J, Dansonka-Mieszkowska A, Sobin LH, Miettinen M (2004) A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. Lab Invest 84:874–883

Laurini JA, Carter JE (2010) Gastrointestinal stromal tumor. A review of the literature. Arch Pathol Lab Med 134:134–141

Lee JR, Joshi V, Griffin JW, Lasota J, Miettinen M (2001) Gastrointestinal autonomic nerve tumor: immunohistochemical and molecular identity with gastrointestinal stromal tumor. Am J Surg Pathol 25:979–987

Lesalnieks I, Rummele P, Dietmaier W, Jantsch T, Zulke C, Schlitt HJ, Hofstadter F, Anthuber M (2005) Factors associated with disease progression in patients with gastrointestinal stromal tumors in the pre-imatinib era. Am J Clin Pathol 124:1–9

Leung KM, Wong S, Chow TC, Lee KC (2002) A malignant gastrointestinal stromal tumor with osteoclast-like giant cells. Arch Pathol Lab Med 126:972–974

Li FP, Fletcher JA, Heinrich MC, Garber JE, Sallan SE, Curiel-Lewandrowski C et al (2005) Familial gastrointestinal stromal tumor syndrome: phenotype and molecular features in a kindred. J Clin Oncol 23:2735–2743

Li ZY, Liang QL, Chen GQ, Zhou Y, Liu QL (2012) Extragastrointestinal stromal tumor of the liver diagnosed by ultrasound-guided fine needle aspiration cytology: a case report and review of the literature. Arch Med Sci 8:392–397

Liegl B, Hornick JL, Antonescu CR, Corless CL, Fletcher CD (2009) Rhabdomyosarcomatous differentiation in gastrointestinal stromal tumors after tyrosine kinase inhibitor therapy: a novel form of tumor progression. Am J Surg Pathol 33:218–226

Liegl-Atzwanger B, Fletcher JA, Fletcher CDM (2010) Gastrointestinal stromal tumors. Virchows Arch 456:111–127

Lo OS, Poon RT, Lam CM, Fan ST (2004) Inflammatory pseudotumor of the liver in association with a gastrointestinal stromal tumor: a case report. World J Gastroenterol 10:1841–1843

Lodish MB, Adams KT, Huynh TT, Prodanov T, Ling A, Chen C, Shusteman S, Jimenez C et al (2010) Succinate dehydrogenase gene mutations are strongly associated with paraganglioma of the organ of Zuckerkandl. Endocrinol Relat Cancer 17:581–588

Luo XL, Liu D, Yang JJ, Zheng MW, Zhang J, Zhou XD (2009) Primary gastrointestinal stromal tumor of the liver: a case report. World J Gastroenterol 15:3704–3707

Martin J, Poveda A, Llombart-Bosch A, Ramos R, Lopez-Guerrero JA, Garcia del Muro J, Maurel J et al (2005) Deletions affecting codons 557–558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). J Clin Oncol 23:6190–6198

Mazur MT, Clark HB (1983) Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 7:507–519

Medeiros F, Corless CL, Duensing A, Hornick JL, Oliveira AM, Heinrich MC, Fletcher JA, Fletcher CD (2004) KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. Am J Surg Pathol 28:889–894

Mendoza-Marin M, Hoang MP, Albores-Saavedra J (2002) Malignant stromal tumor of the gallbladder with interstitial cells of Cajal phenotype. Arch Pathol Lab Med 126:481–483

Miettinen M, Lasota J (2001) Gastrointestinal stromal tumors – definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 438:1–12

Miettinen M, Lasota J (2006a) Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 23:70–83

Miettinen M, Lasota J (2006b) Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 130:1466–1478

Miettinen M, Sarlomo-Rikala M, Lasota J (1999) Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 30:1213–1220

Miettinen M, Majidi M, Lasota J (2002) Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): a review. Eur J Cancer 38(suppl 5):S39–S51

Miettinen M, Lasota J, Sobin LH (2005) Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol 29:1373–1381

Miettinen M, Wang ZF, Sarlomo-Rikala M, Osuch C, Rutkowski P, Lasota J (2011) Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. Am J Surg Pathol 35:1712–1721

Miettinen M, Killian JK, Wang ZF, Lasota J, Lau C, Jones L, Walker R, Pineda M et al (2013) Immunohistochemical loss of succinate dehydrogenase subunit A (SDHA) in gastrointestinal stromal tumors (GISTs) signals SDHA germline mutation. Am J Surg Pathol 37:234–240

Mussi C, Schildhaus HU, Gonchi A, Wardelmann E, Hohenberger P (2008) Therapeutic consequences from molecular biology for gastrointestinal stromal tumor patients affected by neurofibromatosis type 1. Clin Cancer Res 14:4550–4555

Nannini M, Astolfi A, Paterini P, Urbini M, Santini D, Catena F, Indio V, Casadio R et al (2013) Expression of IGF-1 receptor in KIT/PDGF receptor-α wild-type gastrointestinal stromal tumors with succinate dehydrogenase complex dysfunction. Future Oncol 9:121–126

Ochiai T, Sonoyama T, Kikuchi S, Ikoma H, Kubota T, Nakanishi M, Ichikawa D, Kikuchi S et al (2009) Primary large gastrointestinal stromal tumor of the liver: report of a case. Surg Today 39:633–636

Ozcinar B, Aksakal N, Agcaoglu O, Tukenmez M, Ozemir IA, Barnaros U, Colak N et al (2013) Multiple gastrointestinal stromal tumors and pheochromocytoma in a patient with von Recklinghausen's disease. Int J Surg Case Rep 4:216–218

Paner GP, Silberman S, Hartman G, Micetich KC, Aranha GV, Alkan S (2003) Analysis of signal transducer and activator of transcription 3 (STAT3) in gastrointestinal stromal tumors. Anticancer Res 23:2253–2260

Park SH, Kim MK, Kim H, Song BJ, Chi JG (2004a) Ultrastructural studies of gastrointestinal stromal tumors. J Korean Med Sci 19:234–244

Park JK, Choi SH, Lee S, Min KO, Yun SS, Jeon HM (2004b) Malignant gastrointestinal stromal tumor of the gallbladder. J Korean Med Sci 19:763–767

Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, Boikos SA et al (2008) Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. Eur J Hum Genet 16:79–88

Patnaik S, Jyotsnarani Y, Rammurti S (2012) Radiological features of metastatic gastrointestinal stromal tumors. J Clin Imaging Sci 2:43

Pauls K, Merkelbach-Bruse S, Thal D, Buttner R, Wardelmann E (2005) PDGFRalpha-and c-kit-mutated gastrointestinal stromal tumors (GISTs) are characterized by distinctive histological and immunohistochemical features. Histopathology 46:166–175

Pauwels P, Debiec-Rychter M, Stul M, De Wever I, van Oosterom AT, Sciot R (2005) Changing phenotype of gastrointestinal stromal tumours under imatinib mesylate treatment: a potential diagnostic pitfall. Histopathology 47:41–47

Penzel R, Aulmann S, Moock M, Schwarzbach M, Rieker RJ, Mechtersheimer G (2005) The location of KIT and PDGFRA gene mutations in gastrointestinal stromal tumours is site and phenotype associated. J Clin Pathol 58:634–639

Peshwe HB, Chatni S, Basu S (2005) Imatinib mesylate as therapy for gastrointestinal stromal tumor. Indian J Gastroenterol 24:188

Postow MA, Robson ME (2012) Inherited gastrointestinal stromal tumor syndromes: mutations, clinical features. and therapeutic implications. Clin Sarcoma Res 2:16

Prakash S, Sarran L, Socci N, DeMatteo RP, Eisenstat J, Greco AM, Maki RG, Wexler LH et al (2005) Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature. J Pediatr Hematol Oncol 27:179–187

Plumb AA, Kochhar R, Leahy M, Taylor MB (2013) Patterns of recurrence of gastrointestinal stromal tumour (GIST) following complete resection: implications for follow-up. Clin Radiol 68:770–775

Rege TA, Wagner AJ, Corless CL, Heinrich MC, Hornick JL (2011) "Pediatric-type" gastrointestinal stromal tumors in adults: distinctive histology predicts genotype and clinical behavior. Am J Surg Pathol 35:495–504

Ricci R, Arena V, Castri F, Martini M, Maggiano N, Murazio M, Pacelli F, Potenza AE et al (2004) Role of p16/INK4a in gastrointestinal stromal tumor progression. Am J Clin Pathol 122:35–43

Richmond JA, Mount SL, Schwarz JE (2004) Gastrointestinal stromal tumor of the stomach with rhabdoid phenotype: immunohistochemical, ultrastructural, and immunoelectron microscopic evaluation. Ultrastruct Pathol 28:165–170

Sakurai S, Hasegawa T, Sakuma Y, Takazawa Y, Motegi A, Nakajima T, Saito K, Fukayama M, Shimoda T (2004) Myxoid epithelioid gastrointestinal stromal tumor (GIST) with mast cell infiltrations: a subtype of GIST with mutations of platelet-derived growth factor receptor alpha gene. Hum Pathol 35:1223–1230

Saleem TB, Ahmed I (2009) Gastrointestinal stromal tumour – evolving concepts. Surgeon 7:36–41

Sanborn RE, Blanke CD (2005) Gastrointestinal stromal tumors and the evolution of targeted therapy. Clin Adv Hematol Oncol 3:647–657

Sandrasegaran K, Rajesh A, Rushing DA, Rydberg J, Akisik FM, Henley JD (2005) Gastrointestinal stromal tumors: CT and MRI findings. Eur Radiol 15:1407–1414

Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, Miettinen M (1998) CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol 11:728–734

Schmieder M, Wolf S, Danner B, Stoehr S, Juchems MS, Wuerl P, Henne-Bruns D et al (2008) p16 expression differentiates high-risk gastrointestinal stromal tumor and predicts poor outcome. Neoplasia 10:1154–1162

Serkova N, Boros LG (2005) Detection of resistance to imatinib by metabolic profiling: clinical and drug development implications. Am J Pharmacogenomics 5:293–302

Sihto H, Sarlomo-Rikala M, Tynninen O, Tanner M, Andersson LC, Franssila K, Nupponen NN, Joensuu H (2005) KIT and platelet-derived growth factor receptor alpha tyrosine kinase gene mutations and KIT amplification in human solid tumors. J Clin Oncol 23:49–57

Singer S, Rubin BP, Lux ML, Chen CJ, Demetri GD, Fletcher CD, Fletcher JA (2002) Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. J Clin Oncol 20:3898–3905

Steigen SE, Eide TJ (2009) Gastrointestinal stromal tumors (GISTs): a review. APMIS 117:73–86

Subramanian S, West RB, Corless CL, Ou W, Rubin BP, Chu KM, Leung SY, Yuen ST et al (2004) Gastrointestinal stromal tumors (GISTSs) with KIT and PDGFRA mutations have distinct gene expression profiles. Oncogene 23:7780–7790

Sun B, Qie S, Zhang S, Sun T, Zhao X, Gao S, Ni C, Wang X, Liu Y, Zhang L (2008) Role and mechanism of vasculogenic mimicry in gastrointestinal stromal tumors. Hum Pathol 39:444–451

Terada T (2009) Gastrointestinal stromal tumor of the digestive organs: a histopathologic study of 31 cases in a single Japanese institute. Int J Clin Exp Pathol 3:162–168

Vlenterie M, Flucke U, Hofmauer LC, Timmers HJ, Gastmeier J, Aust DE, van der Graaf WT et al (2013) Pheochromocytoma and gastrointestinal stromal tumors in patients with neurofibromatosis type I. Am J Med 126:174–180

Wardelmann E, Neidt I, Bierhoff E, Speidel N, Manegold C, Fischer HP, Pfeifer U, Pietsch T (2002) c-kit mutations in gastrointestinal stromal tumors occur preferentially in the spindle rather than in the epithelioid cell variant. Mod Pathol 15:125–136

Wasag B, Debiec-Rychter M, Pauwels P, Stul M, Vranckx H, Oosterom AV, Hagemeijer A, Sciot R (2004) Differential expression of KIT/PDGFRA mutant isoforms in epithelioid and mixed variants of gastrointestinal stromal tumors depends predominantly on the tumor site. Mod Pathol 17:889–894

Wellmann K, Gohla G, Wenk H (2004) Malignant gastrointestinal stromal tumor (GIST) of the papilla vateri. A rare tumor entity (in German). Chirurg 75:196–199

West RB, Corless CL, Chen X, Rubin BP, Subramanian S, Montgomery K, Zhu S, Ball CA et al (2004) The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am J Pathol 165:107–113

Yamaguchi U, Nakayama R, Honda K, Ichikawa H, Hasegawa T, Shitashige M, Ono M et al (2008) Distinct gene expression-defined classes of gastrointestinal stromal tumor. J Clin Oncol 26:4100–4108

Yamamoto H, Miyamoto Y, Nishihara Y, Kojima A, Imamura M, Kishikawa K, Takase Y et al (2010) Primary gastrointestinal stromal tumor of the liver with PDGFRA gene mutation. Hum Pathol 41: 605–609

Yamamoto H, Kohashi K, Fujita A, Oda Y (2013) Fascin-1 overexpression and miR-133b downregulation in the progression of gastrointestinal stromal tumor. Mod Pathol 26(4):563–571

Yang DM, Kim H, Kang JH, Park CH, Kim HS, Shin DB (2005) Computed tomography and sonographic findings of hepatic metastases from gastrointestinal stromal tumors after chemotherapy. J Comput Assist Tomogr 29:592–595

Yi ES, Strong CR, Piao Z, Perucho M, Weidner N (2005) Epithelioid gastrointestinal stromal tumor with PDGFRA activating mutation and immunoreactivity. Appl Immunohistochem Mol Morphol 13:157–161

Yokoi K, Tanaka N, Shoji K, Ishikawa N, Seya T, Horiba K, Kanazawa Y, Yamashita K et al (2005) A study of histopathological assessment criteria for assessing malignancy of gastrointestinal stromal tumor, from a clinical standpoint. J Gastroenterol 40:467–473

Zhou B, Zhang M, Yan S, Zheng S (2014) Primary gastrointestinal stromal tumor of the liver: report of a case. Surg Today 44(6):1142–1146

Zonios D, Soula M, Archimandritis AJ, Revenas K (2003) Cystlike hepatic metastases from gastrointestinal stromal tumors could be seen before any treatment. AJR Am J Roentgenol 181:282

Tumors and Tumor-Like Lesions of the Schwann Cell Lineage and the Nerve Sheath

68

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_68

Abstract

Schwannoma (neurinoma) is a benign nerve sheath tumor composed of neoplastic Schwann cells. These neoplasms have a wide distribution and also occur in the hepatobiliary tract. Primary hepatobiliary schwannomas are mainly diagnosed in older individuals, with equal gender distribution. Hepatic schwannomas take their origin from cells of hepatobiliary nerves which in turn originate from the hepatic plexus, nerves accompanying blood vessels and bile ducts, and nerves of hepatic ligaments. The tumor can grow to large size and may reach a diameter of 20 cm. Large lesions show hemorrhage and necrosis, notwithstanding their benign features, and may undergo cystic change. Histologically, spindle cells form interlacing bundles, sometimes with tapered nuclei and palisading and formation of Verocay bodies. The tumor cells are reactive for S100 protein. A malignant variant, malignant schwannoma, is a well-known soft tissue sarcoma, but is a very rare primary hepatic neoplasm. Also malignant peripheral nerve sheath tumor can occur in the hepatobiliary tract, sometimes in association with neurofibromatosis type 1. Rare benign hepatic tumors of the hepatobiliary tract include neurofibroma and benign hepatic nerve sheath tumor. An important differential diagnosis is amputation neuroma.

Schwannoma of the Liver

Introduction

Schwannoma (synonyms: neurilemmoma; neurinoma) is a benign nerve sheath tumor composed of neoplastic Schwann cells. The neoplasm had first been described by Verocay under the name neurinoma (Verocay 1910). Hepatic schwannomas are thought to take their origin from cells of hepatobiliary nerves, which originate from the hepatic plexus, the largest branch of the celiac plexus, and the nerves accompany the hepatic artery, the portal vein, the bile ducts, and their respective intrahepatic branches. In addition, nerves enter the liver from the ligaments and the peritoneal foldings. Along the nerve network located within the hepatoduodenal ligament, Schwann cell growths occur as well and may cause biliary obstruction.

Epidemiology

Primary hepatic schwannoma has been reported several times, albeit it is a rare lesion (Bialik and Del'tsova 1966; Pereira Filho et al. 1978; Tuder and Moraes 1984; Hytiroglou et al. 1993; Heffron et al. 1993; Yoshida et al. 1994; Nakajima 1995; Wada et al. 1998; Flemming et al. 1998; Kapoor et al. 2005, Lee et al. 2008; Momtahen et al. 2008; Akin et al. 2009; Kim and Park 2010, Ozkan et al. 2010; Hayashi et al. 2012; Ota et al. 2012). Females and males seem to be equally involved. Most of the patients reported so far were old, age at diagnosis ranging from 38 to 74 years, similar to malignant liver schwannomas not associated with neurofibromatosis, whereas malignant liver schwannomas in NF1 usually occur in younger age groups. Hepatic schwannomas can evolve in the context of NF1, but several cases have also been observed in patients without evidence of neurofibromatosis (Heffron et al. 1993; Wada et al. 1998).

Clinical and Imaging Features

Clinically, primary hepatic schwannomas are solitary and expansively growing tumors ranging in size from 4 to 20 cm. Plain CT images show nonhomogeneous masses, with enhanced CT depicting clear margins and an irregularly structured tumor center. Hepatic schwannoma may undergo cystic changes, resulting in a cystic mass mimicking hydatid disease (Flemming et al. 1998). In large tumors, arteries and portal vein branches may be encased, a finding that does not imply malignancy. On MR images, the tumors are hypointense on T1-weighted images and mixed hypo-and hyperintense on T2-weighted images. On serial contrast-enhanced images, the

lesions revealed gradually increasing centrilobular enhancement (Momtahen et al. 2008; Ota et al. 2012).

Pathology

Macroscopy

At gross examination, these are usually firm tumors showing a gray cut surface, which may display geographic necroses and foci of hemorrhage, particularly in large tumors. Hepatic schwannomas may grow to large size (15 cm: Wada et al. 1998; 16 cm: Yoshida et al. 1994). Benign schwannoma of the liver has been reported to undergo extensive cystic change (Hytiroglou et al. 1993; Yoshida et al. 1994), with the risk of being misinterpreted as hydatid disease (Flemming et al. 1998). Sometimes, multiple cystic nodules containing a gelatinous material were noted (Pereira Filho et al. 1978).

Histopathology

Histology is characterized by the phenotype known for schwannomas located in other organs and tissue (Figs. 1 and 2). The leading tumor cell is an elongated spindle cell that forms bundles arranged in an interlacing fashion. The nuclei vary widely in shape and size, but ovoid or elongated forms prevail, with a rather uniform chromatin structure and only mild atypia. The mitotic count is very low, and in many areas mitotic figures are not in evidence. Cellular areas display interwoven fascicles of spindle cells with tapered nuclei and occasional palisading, a feature typical for schwannomas. In tumors with an Antoni A pattern, Verocay bodies are seen. Verocay bodies are nodular or ovoid cellular areas showing prominent palisading of spindle cells at high density, present as a fascicular or turbinate cellular accumulation. Rarely, myxoid areas with or without cystic change are seen.

Electron Microscopy

Tumor cells exhibit long interdigitations surrounded by a discrete basal lamina. Long-spacing collagen (Luse bodies) was not detected (Wada et al. 1998).

Immunohistochemistry

Similar to schwannomas in other locations, the neoplastic cells are markedly reactive for S100 protein (Hayashi et al. 2012).

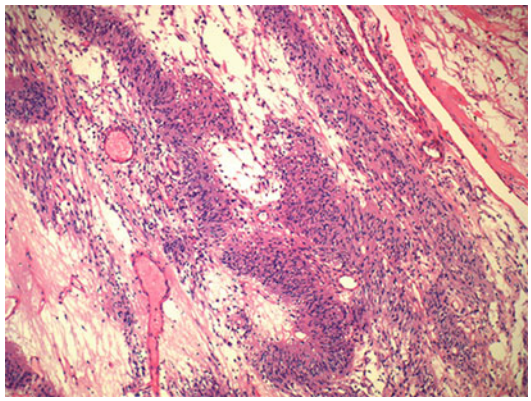

Fig. 1 Primary hepatobiliary schwannoma (neurinoma). Cellular bands with palisading are in evidence. There is focal myxoid change (hematoxylin and eosin stain)

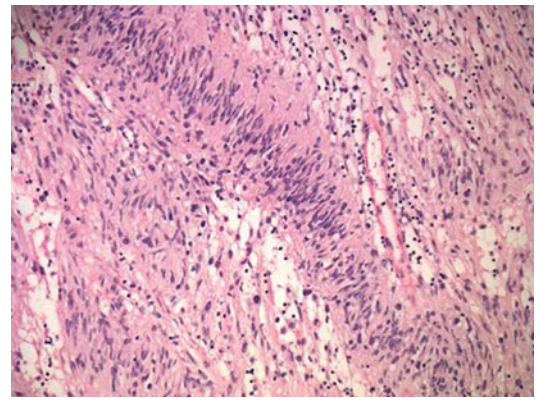

Fig. 2 Primary hepatobiliary schwannoma (neurinoma). Cell palisading at higher magnification (hematoxylin and eosin stain)

Differential Diagnosis

The histologic differential diagnoses mainly include leiomyomatous tumors, stromal tumors, and solitary fibrous tumor, all known to rarely occur in the liver as primary lesions. Schwannoma arising in the diaphragm can clinical mimic a liver tumor (Ikegami et al. 2004).

Primary Schwannoma of the Porta Hepatis

Besides schwannomas located within the liver substance proper, schwannoma arising in the porta hepatis has been described, this tumor apparently taking its origin from tissues of the hepatic artery (Choi et al. 2001; Park et al. 2006; Panait et al. 2011).

Primary Schwannoma of the Bile Ducts

Primary schwannoma can very rarely develop in the intra-and extrahepatic bile ducts (De Sena et al. 2009; Madhusuhan et al. 2009). Schwannomas of the extrahepatic bile ducts are clinically nonspecific. They can become symptomatic as soon as they cause bile duct compression or stenosis owing to intraluminal (polypoid) growth. Painless and progressive obstructive jaundice may ensue (Jakobs et al. 2003; Vyas et al. 2006). Most cases have been identified in the common bile duct (Oden 1955; Dowdy et al. 1962; Ronchetti and Zanniello 1962; Prevot et al. 1999; Honjo et al. 2003; Jakobs et al. 2003; Vyas et al. 2006; Fenoglio et al. 2007; Jung et al. 2007). Schwannoma can develop at the porta hepatis (Park et al. 2006; Kamani et al. 2007) and may clinically and radiologically mimic Klatskin tumor. Schwannoma was also identified in choledochal cyst (Otani et al. 2005).

Bile duct schwannomas show the histology of neurinomas known from other locations, often with Antoni A pattern and palisading of tumor cells (Jakobs et al. 2003; Kamani et al. 2007).

Primary Schwannomas of Hepatic Ligaments

Schwannoma has been observed as a primary tumor in the hepatoduodenal ligament (Pinto et al. 2011).

Primary Schwannoma of Hepatic Blood Vessels

Schwannomas can very rarely take their origin from hepatic blood vessels, e.g., the proper hepatic artery (Huang et al. 2011).

Primary Malignant Hepatic Schwannoma

Whereas malignant schwannoma is one of the most common soft tissue sarcomas in adults, accounting for about 10 % of all such lesions, primary malignant schwannoma of the liver is extremely rare and occurs with or without associated neurofibromatosis (Young 1975; Shmurun and Chibisov 1977; Tuder and Moraes 1984; Lederman et al. 1987; Morikawa et al. 1995; Fiel et al. 1996; Sheikh et al. 1996). In the five cases reviewed by Morikawa et al. (1995), all males, the mean age at the time of diagnosis was 68.7 years for those without associated NF1; the two patients with NF1 were much younger, i.e., 21 and 23 years, respectively. Primary hepatic malignant schwannomas are usually large (diameter of 20 cm, Shmurun and Chibisov 1977; 21 cm, Tuder and Moraes 1984) and solitary lesions, sometimes occupying a whole liver lobe (Morikawa et al. 1995). Among four reported cases, widespread metastasis had been found in two cases. At imaging, typical features include a well-demarcated hypodense mass on CT (Sheikh et al. 1996), and hypovascularity on angiograms, which is rather unusual.

Histology is characterized by a hypercellular neoplasm consisting mainly of spindle and polymorphic cells with hyperchromatic nuclei and numerous mitotic figures. The neoplastic cells are mostly arranged in the form of ill-defined,

sweeping fascicle-like structures. At the tumor-liver interface, the cells clearly invade the parenchyma and may grow into sinusoidal spaces, with atrophy of the adjacent hepatocyte plates. The spindle cells are immunoreactive for S-100 protein and vimentin. Particularly in large tumors, extensive necrosis is in evidence.

Pathogenesis

A critical step for the development of schwannomas is the non-expression of normal schwannomin/merlin by the Schwann cells involved. Merlin is the product of the NF2 gene and is an ezrin-moesin protein that normally localizes underneath the plasma membrane at cell-cell junctions and other cell surfaces sites that are rich in actin and actin-associated proteins and acts as a cytoskeleton organizer (McClatchey and Giovannini 2005; Denisenko et al. 2008). Merlin regulates contact inhibition of proliferation by limiting the delivery of several growth factor receptors at the plasma membrane of Schwann cells (Lallemsand et al. 2009). In mitogen-stimulated cells, p21-activated kinase (Pak) phosphorylates serine 518 in the C-terminal portion of merlin, inactivating the growth suppressive function of the protein (Okada et al. 2007; Roche et al. 2008; Chang and Welling 2009). This phosphorylation process is stimulated by neuregulin and laminin (Thaxton et al. 2008). Merlin/schwannomin phosphorylation requires binding to paxillin and targeting to the plasma membrane. Phosphorylated schwannomin is enriched in the peripheral-most parts of membrane specializations where paxillin, activated Pak, and Cdc42 but not Rac are highly expressed (Thaxton et al. 2007). Merlin was found to be expressed in 98 % of vestibular schwannomas and was inversely correlated with cyclin D1 in regard to intracellular localization. Merlin locates in the cytoplasm during the G0/G1 phase, moves to the nucleus at S phase, and accumulates in the cytoplasm at S phase after phosphorylation on serine 518 (Lü et al. 2008). Point mutation in the NF2 gene in schwannoma cells is associated with the expression of a merlin isoform with attenuated growth suppressive activity (Lepont et al. 2008). Deficiency of merlin, which normally binds to beta1 integrin and focal adhesion kinase, results in pathological adhesion to the extracellular matrix with increased numbers of mature and stable focal contacts, associated with activation of Rac1 (Flaiz et al. 2009). Merlin itself is regulated at the Roc1-cullin4A-DDB1-dependent level, and merlin is recruited to the E3 ligase complex through direct interaction with the WD40-containing adaptor protein VprBP (Huang and Chen 2008). Another protein involved in schwannomagenesis is PRKAR1A which is lost via inactivating mutations in the syndrome, Carney complex. Tissue-specific ablation of Prkar1a in murine neural crest precursor cells (TEC3KO mice) causes schwannomas with nearly 80 % penetrance. This is caused by almost complete loss of both NF proteins (Jones et al. 2008). A subset of patients with schwannomatosis reveal mutations in SMARCB1 (INI1, Hulsebos et al. 2007) or in both SMARCB1 and NF2 (Hadfield et al. 2008). Cell proliferation of differentiated Schwann cells is controlled by several factors and signaling pathways. Schwann cells are derived from neural crest cell precursors which are known to possess considerable plasticity. This is one reason why derivatives of neural crest cells can undergo transdifferentiation. Schwann cells can be transdifferentiated into myofibroblasts by downregulation of Sox10 (Roh et al. 2006).

Malignant Peripheral Nerve Sheath Tumor

ICD-O 9540/3

Introduction

Malignant peripheral nerve sheath tumor (MPNST) is defined as a malignant neoplasm arising from or differentiating toward cells intrinsic to peripheral nerve sheath and probably derived from the neural crest. The tumors often develop in association with neurofibromatosis type 1 (NF1). MPNSTs account for 5–10 % of

soft tissue sarcomas (Stark et al. 2001). Patients with neurofibromatosis type 1 (NF1) carry a 10 % lifetime risk of developing MPNST, this transition thought to be caused by complex genomic alterations (Mantripragada et al. 2009). In patients with NF1 and MPNSTs, survival rates are low and time to death is often less than 2 years (Zhou et al. 2009).

Primary Malignant Peripheral Nerve Sheath Tumors of the Liver and Biliary Tract

MPNST primary to the hepatobiliary tract has been reported several times (Young 1975; Schmurun and Chibisov 1977; Morikawa et al. 1995; Fiel et al. 1996; Iddings et al. 2008; Kobori et al. 2008; Subramaniam et al. 2012). In at least two instances, the tumors were associated with neurofibromatosis (Young 1975; Fiel et al. 1996). Grossly, the tumors resemble those seen in the soft tissues, i.e., firm tumors with central necrosis. The neoplasms may grow to very large size (e.g., diameter of 26 cm, Kobori et al. 2008). The tumor can invade almost entire liver lobes (Morikawa et al. 1995).

Histologically, the tumors are characterized by monomorphic or polymorphic spindle cells with hyperchromatic nuclei and the presence of mitotic figures, the majority of the cells being reactive for vimentin and S100 protein. CD10 is positive in MPNST, in contrast to benign neurofibromas (Cabibi et al. 2009). In the basement membrane component, laminin shows a prominent positivity. This phenomenon is reflected by the ultrastructurally detected presence of amorphous basement membrane-like material in the tumor interstitium (Kobori et al. 2008). Part of the spindle cells may assume a more prominent cytoplasm, causing an epithelioid morphology. Few giant cells may be noted. The mitotic rate varies considerably, ranging from very few mitotic figures to 13–14/10 HPFs (Kobori et al. 2008).

The differential diagnosis includes other primary hepatic spindle cell sarcomas and in particular liver metastasis of extrahepatic MPNST (Tomica et al. 2011; Meng et al. 2013).

Hepatic Schwannomas Undergoing Transformation into MPNST

There are few reports on tumors that seem to have developed from preexisting hepatic schwannomas, with formation of a malignant cell lineage of Schwann cells or perineural cells (Tuder and Moraes 1984; Woodruff et al. 1994).

Combined Hepatic Sarcomas in Neurofibromatosis

Schwannoma with angiosarcomatous change is a rare soft tissue neoplasm that affects older adults and mainly men. The angiosarcomatous component is usually of the epithelioid type and reveals solid or vessel-like cellular structures with CD31 and CD34 positivity (Rückert et al. 2000). In a young man with neurofibromatosis and known hepatic neurofibromas, a combined malignancy developed in the liver, consisting of both malignant schwannoma and angiosarcoma (Lederman et al. 1987).

Malignant Melanotic Schwannoma

A very rare subset of malignant nerve sheath tumors or schwannomas are characterized by the melanin deposition. These highly aggressive neoplasms occur in various organs and can metastasize to the liver (Janzer and Makek 1983), causing differential diagnostic problems with respect to melanoma metastasis. Malignant melanoma can undergo Schwannian differentiation, mimicking malignant melanotic schwannoma. Also this tumor type metastasizes to the liver (Schadendorf et al. 1993).

Malignant Triton Tumors of the Liver and Biliary Tract

Malignant triton tumor forms is a group of malignant tumors with a pluridirectional differentiation. These neoplasms are sometimes classified as subtypes of MPNST. They can express rhabdomyosarcomatous, osteoid, and chondroid components

(Kurtkaya-Yapicier et al. 2003; Ballas et al. 2009), and exceptionally even lipomatous lineages (Suresh et al. 2009).

Pathogenesis

Main molecular alterations include RAS/RAF/MAPK and/or PTEN/PI3K/AKT signaling pathways, PTEN being lost in both murine and human MPNST in NF1 (Gregorian et al. 2009). Eighteen percent of sporadic MPNSTs displayed RAS gene mutations (Perrone et al. 2009). P53 protein is expressed in part of MPNST and is an independent predictor of outcome (Brekke et al. 2009). MPNSTs show expression of PDGFRA, PDGFRB, and epidermal growth factor receptor (EGFR), with higher levels of EGFR expression seen in tumors associated with NF-1 (Holtkamp et al. 2008; Perrone et al. 2009). Overexpression of EGFR was correlated with worse prognostic variables and course. MPNST has a complex cell lineage with features reflecting neural crest/Schwann cell lineage-derived cells or perineural cells, and the tumors reveal deregulated signal cascades involving several pathways (review: Katz et al. 2009). Part of MPNST have typical EMA-positive perineural cells and have been proposed to be termed malignant perineurioma (Rosenberg et al. 2002). The cells express, apart from S100 protein, the erbB kinases mediating neuregulin-1 beta-isoform responses, which promote Schwann cell proliferation and migration during development and tumorigenesis (Stonecypher et al. 2005). The complex lineage pattern of MPNST cells is visualized by a strong reactivity for podoplanin in epithelioid MPNST (Jokinen et al. 2008).

Benign Hepatic Nerve Sheath Tumor

Benign nerve sheath tumor is a very rare neoplasm exceptionally developing in the liver. It was detected in a middle-aged female patient with a progressively enlarging epigastric lump of 8-month duration. CT revealed a 20 cm-sized tumor involving segments 2, 3, and 4 of the liver. The tumor was resected under the diagnosis of liver cell adenoma. The resection specimen disclosed two tumor nodules of 17 cm and 7.5 cm diameter, respectively, soft to firm in consistency. The larger nodule had a central area of necrosis. Histology revealed a spindle cell tumor with cells arranged in whorls and a storiform pattern, surrounded by a fibrous capsule. The cytoplasm of the tumor cells was eosinophilic, with indistinct borders, the nuclei being elongated or irregular. Mitotic figures were absent. The cells were immunoreactive for S100 protein, but were negative for c-kit and alpha-SMA.

Neurofibroma of the Liver

Introduction

Neurofibromatosis (NF; von Recklinghausen's disease) is a hereditary disorder which occurs in two types: type 1 (NF1) and type 2 (NF2). Autosomal dominant NF1 (assigned to chromosome 17q11.2) is primarily a disorder of nerves and astrocytes, with an incidence of about 1: 2000–3000. Conversely, autosomal dominant NF2 (assigned to chromosome 22q11.2) is a disease of the coverings of the central nervous system, intracranial manifestations chiefly including meningiomas and schwannomas, with an incidence of about 1: 50,000. Individuals with NF1 are predisposed to the development of benign and malignant neoplasms that arise primarily in cells derived from the embryonal neural crest (Skuse et al. 1989; Menon et al. 1990; DeClue et al. 1992; Legius et al. 1993; Johnson et al. 1993). The two main peripheral nerve tumors found in patients with NF1 are neurofibromas, a benign tumor, and malignant peripheral nerve sheath tumor (MPNST). The pathology of these lesions in NF1 has recently been reviewed (Woodruff 1999). Apart from nerve tumors, NF1 is associated with a rather broad array of other neoplastic lesions, including gastrointestinal stromal tumors (Giuly et al. 2003), pheochromocytomas, neuroblastomas, and mixed neuroendocrine and neural tumors. Children with NF1 are also predisposed to juvenile myelomonocytic leukemia, and some

heterozygous Nf1 mutant mice develop a similar myeloproliferative disorder. Overall, the risk of malignant myeloid disorders in young children with NF1 is 200–500 times the normal risk. In this chapter, hepatic tumorous manifestations of NF1 are discussed. Schwannomas primary to the liver are reviewed in another chapter.

Hepatic Neurofibromas

Neurofibromas involving the liver are rare and are specifically associated with type 1 neurofibromatosis. The majority of these tumors have been described as plexiform neurofibromas (Ghalib et al. 1995). Plexiform neurofibromas can produce large or even diffuse intrahepatic tumors, e.g., scattered throughout the entire liver around portal radicles. Most tumors have been observed in adults, but pediatric cases are also known. In part of the cases, neurofibromas have involved the compartment of the hepatic hilum, with encasement of vascular branches situated in this region (Poon et al. 2008; Hoshimoto et al. 2009). Plexiform neurofibromas also occur in the large bile ducts and are treated in a separate chapter. Plexiform neurofibroma of the liver may synchronously be associated with other tumors of the hepatobiliary tract, e.g., carcinoid of the ampulla of Vater (Samonakis et al. 2005).

Selected References Tesseraux and Zachmann 1954; Russomanno 1968; Bekker 1982; Meyer et al. 1982; Delacourt et al. 1987; Lederman et al. 1987; Partin et al. 1990; Chen et al. 1992; Hra et al. 1992; Gossios and Guy 1993; Rodriguez et al. 1993; Kakitsubata et al. 1994; Ghalib et al. 1995; Guzman Toro et al. 1995; Nakajima 1995; Andreu et al. 1997; Vilas Ferrol et al. 1998; Gallego et al. 1998; Cardinale et al. 2000; Fenton et al. 2001; Malagari et al. 2001; Imbert et al. 2002; Rui et al. 2002; Samonakis et al. 2005.

Clinical and Imaging Features

The gross presentation of hepatic manifestations of plexiform neurofibroma varies considerably. They produce infiltrative hypoechoic masses at sonography, the tumors being located around the porta hepatis and along the intrahepatic portal branches. On CT images, the masses are usually ill defined and hypoattenuating (Kakitsubata et al. 1994). Hepatic plexiform neurofibromas can grow to impressive size (7 cm; Malagari et al. 2001), and MRI images present them as circumscribed or ill-defined lesions with a multinodular configuration, showing low signal intensity on T1-weighted in- and out-of-phase images and hyperintensity on T2-weighted images (Gallego et al. 1998; Malagari et al. 2001). A periportal distribution of the lesions at imaging may reflect the development of the tumors along preexisting nerve structures located within Glisson's triads. The neurofibromas may grow along the vascular bundles, sometimes resulting in the encasement of the hepatic artery or the portal vein, with an eventual extension to the celiac trunk and into the hepatoduodenal ligament, rendering complete surgical resection difficult in such situations. Large tumors with intratumoral hemorrhage may evolve and have led to death in one young male patient (Lederman et al. 1987). However, in the latter case, neurofibroma lesions were present in portal tracts, and they were associated with malignant schwannoma and angiosarcoma, which is known to occur in the setting of von Recklinghausen's disease (Millstein et al. 1981; Riccardi et al. 1984; Png et al. 1996), even in children (Prasad 1983). A combination of plexiform neurofibromatosis and angiosarcoma of the liver has been described in a further report (Andreu et al. 1997).

Pathology

Macroscopically, hepatic neurofibromas are ill-defined, grayish-white masses that interdigitate with adjacent tissue. Plexiform lesions may show firm, white extensions that follow the intrahepatic portal tract sheaths.

Histology closely reflects the phenotype known for NF1-associated neurofibromas in other organs. Proliferations of all cellular elements of peripheral nerves are noted, including Schwann cells, the latter sometimes predominating and being the

chief cellular component, fibroblasts, perineural spindle cells, and axons. The cellular infiltrate may contain mast cells. Hepatic neurofibromas are nonencapsulated and, at their periphery, mainly grow along the portal tracts, sometimes effacing the portal vascular bundle and the septal or interlobular bile ducts. Abnormal growth of peribiliary nerves, associated with a considerable increase in extracellular matrix, may result in biliary obstruction and subsequent cholestasis (Hernandez Alvarez et al. 1991).

Neurofibroma of the Bile Ducts

Introduction

In contrast to schwannoma, neurofibroma of the biliary tract is a very rare lesion. It has been observed in the common hepatic duct (Chu 1950; Lovasz 1970; Mitchell et al. 1995; Taylor et al. 2001), the common bile duct (Claudon et al. 1988; Carbia et al. 1995; Bajor et al. 2002; Li et al. 2005; Béchade et al. 2010; Jiang et al. 2011), and the ampullary region (Simmons 1988). Most cases are sporadic non-syndromic lesions, but few cases have been found in association with neurofibromatosis type 1 (see below).

Clinical and Imaging Features

Bile duct neurofibroma can cause biliary obstruction with obstructive jaundice (Claudon et al. 1988; Carbia et al. 1995; Bajor et al. 2002; Li et al. 2005; Jiang et al. 2011). The lesions produce a circumscribed filling defect on MRI images (Li et al. 2005), but they may also cause complex structures with several submucosal tumor nodules (Taylor et al. 2001).

Biliary Tract Neurofibromas in Neurofibromatosis

The extrahepatic biliary tract, including the ampulla, is well known to be involved in neurofibromatosis von Recklinghausen (Meyer et al. 1982, Mendes Ribeiro and Woodham 2000). The most common neurofibromatosis-associated tumor in this anatomical compartment is somatostatinoma of the ampullary region, discussed in a separate chapter. In contrast, biliary tract neurofibroma is an exceptional finding in von Recklinghausen's disease (Relles et al. 2010). Multiple submucosal neurofibromas causing stricture of the proximal common hepatic duct have been described (Taylor et al. 2001). A collision tumor consisting of ampullary somatostatinoma and a neurofibroma has been observed (Varikatt et al. 2006).

Pathology

In one patient presenting with biliary obstruction, neurofibroma was manifest as a gray, rubbery, hard, and firm tumor with a smooth surface, measuring 1.5 cm in greatest diameter, arising from interior part of the common bile duct.

In neurofibromatosis type 1, bile duct neurofibroma has been observed to be of the plexiform type (Bajor et al. 2002) or to produce multiple neurofibromatous nodules in the submucosa of the bile duct (Taylor et al. 2001). However, plexiform bile duct neurofibroma has also been noted in the absence of neurofibromatosis (Mitchell et al. 1995).

Neurofibrosarcoma of the Liver

In rare instances, signs of malignancy are detectable, both on clinical grounds and histologically, resulting in the diagnosis of neurofibrosarcoma of the liver (Neumaier et al. 1997).

Other Liver Lesions Caused by Neurofibromatosis

Hepatoblastoma has been observed in association with NF1 (Uçar et al. 2007). A 72-year-old female with NF1 developed primary hepatic leiomyosarcoma (Maruta et al. 2004). Angiopathy with potentially catastrophic complications occurs in 1–3 % of patients with NF1 (Von Recklinghausen's vasculopathy; Zochodne 1984;

Oderich et al. 2007). Small, medium, and large arterial vessels are involved, including visceral arteries and the abdominal aorta (middle aortic syndrome), and the lesions are characterized by stenosis, occlusions, aneurysms, pseudoaneurysms, arteriovenous fistulas, and ruptures. Vascular disease associated with NF1 rarely manifests in the liver, e.g., as hepatic artery aneurysm (Hassen-Khodia et al. 1997) and spontaneous rupture of the hepatic artery (Rao et al. 2007). Congenital intrahepatic portosystemic venous shunt has been found in NF1 (Digilio et al. 2005).

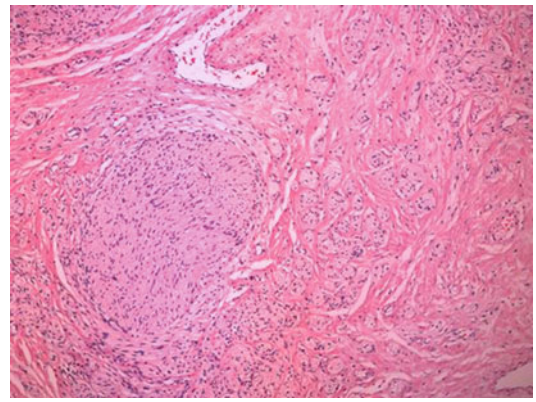

Fig. 3 Amputation neuroma of the biliary tract. The preexistent nerve (left half of figure) is associated with numerous newly formed nerve fibers embedded in collagenous scar tissue (to the right; hematoxylin and eosin stain)

Neuroma of Bile Ducts

Introduction

Neuroma (traumatic neuroma) are reactive lesions that almost always develop at the distal ends of the proximal segments of severed nerves. They are characterized by a neural enmeshment of a disorganized overgrowth of axons, Schwann cells, and perineural cells, forming fascicles of variable dimension embedded in a fibrocollagenous tissue (Figs. 3 and 4; Masson 1942).

Neuroma nodules are not neoplasms but represent thwarted attempts by the damaged nerves to regenerate (Stembridge 1951). Neuromas of the biliary tract derive from the sympathetic and parasympathetic fibers arising from the greater and lesser splanchnic nerves (Shafiroff and Hinton 1950; Loeweneck 1971; Zeff et al. 1976). It has been shown that the area of the common bile duct bifurcation with the cystic duct is a particularly nerve-rich region (Raigorodsky 1928; Womack and Crider 1947).

Traumatic neuroma, called "amputation neuroma," was described in detail in 1920 (Huber and Lewis 1920), but these authors reported that Odier at the beginning of the nineteenth century was the first to record the development of these growths (Odier 1811). Neuroma of the bile ducts was first described in 1928. The author described what he called a growth (Wucherung) of nerve tissue following repeated bile duct surgery (Husseinoff 1928). Neuromas of the cystic duct and common bile duct after cholecystectomy and

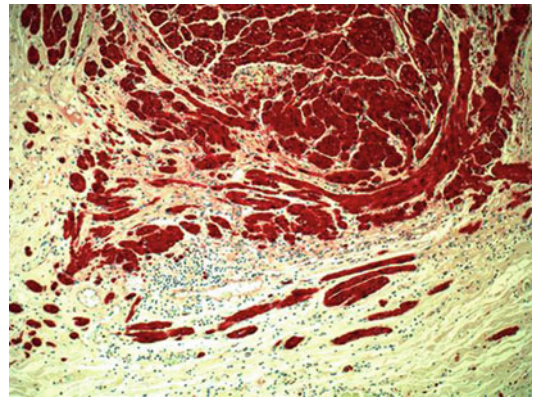

Fig. 4 Amputation neuroma of the biliary tract. In the S100 protein stain, the perineural accumulation of nerve fibers is clearly seen. The original nerve is located to the top of the figure (S100 protein immunostain)

being associated with jaundice were later reported in 1931 (Comfort and Walters 1931; Shapiro and Lifvendahl 1931), followed by a report in 1946 (Cieslack and Stout 1946) and the publication of six cases of post-cholecystectomy bile duct neuromas in 1947 (Womack and Crider 1947).

Epidemiology

Neuromas most commonly develop in the cystic duct after cholecystectomy, both open and laparoscopic, and are the best known example of

traumatic biliary tract neuroma (Berge and Haeger 1967). They develop with a highly variable delay following trauma, after cholecystectomy ranging from several months to more than 40 years (in one patient 45 years; Paquette et al. 2009). How frequent are posttraumatic biliary neuromas? The lesions have been demonstrated in up to 10 % of post-cholecystectomy patients at autopsy in one study (Pickens et al. 1999). But the vast majority of these patients remain asymptomatic for life.

Neuromas of the Cystic Duct

Neuroma of the cystic duct stump is a typical post-cholecystectomy lesion and is a known cause of post-cholecystectomy pain/post-cholecystectomy syndrome (Rosenberg and Matzner 1957; Loutsch 1961; Palagiano and D'Addato 1963; Mattler et al. 1965; Silvestri 1965; Joske and Finlay-Jones 1966; Maheshwari and Agarwal 1969; Zeff et al. 1976; Prinz et al. 1979). However, there are also rare instances of neuroma in the absence of previous surgery (Shapiro and Lifvendahl 1931; Peison and Benisch 1985). Post-cholecystectomy traumatic neuroma of the cystic duct may extend into the wall of the large extrahepatic bile ducts and thus cause biliary obstruction (Iannelli et al. 2003). Neuroma protruding from the cystic stump into the large ducts can be visualized by intraductal ultrasonography (Shimura et al. 2001).

Neuromas of the Hepatic Ducts

Neuroma of the right hepatic has been observed following right hemihepatectomy (Choi et al. 2009). Neuromas of the hepatic ducts can mimic hepatic duct carcinoma (Shumate et al. 1992; Koike et al. 2000) or Klatskin tumor (Martinez Ordaz et al. 1999; Pickens et al. 1999).

Neuromas of the Common Bile Duct

The first report (in German) of neuroma of the common bile duct referred to a patient who had undergone cholecystectomy owing to symptomatic cholecystolithiasis, studied at the Institute of Pathologic Anatomy of the University of Baku, now in Azerbaijan (Husseinoff 1928). It is suggested that neuroma of the extrahepatic large bile ducts produce signs and symptoms only in a very small proportion of patients, common bile duct neuroma being one cause of post-cholecystectomy syndrome (Stibenz et al. 1984). Symptomatic patients tend to present with intermittent right upper quadrant pain. Part of the patients develop jaundice owing to biliary obstruction. The causes of common bile duct neuroma comprise the post-cholecystectomy status, and the lesions also occur after liver transplantation (Colina et al. 1994; Mentha et al. 1999; Herrera et al. 2009), after innocent blunt abdominal trauma (Katsinelos et al. 2002), and in patients without known trauma or surgery (so-called "spontaneous" neuroma; Sugahara et al. 1985; Knapen et al. 1994; Akiyama et al. 1995; Tsitouridis et al. 1998).

Selected References Stembridge 1951; Bartlett and McDermott 1954; Hume and Buxton 1954; Cattell and Ville 1961; Takahara et al. 1981; Kopolovic et al. 1984; Larson and Storsteen 1984; Hochain et al. 1988; Rush et al. 1988; Turani et al. 1988; Van Gulik et al. 1989; Hofmann-Wackersreuther et al. 1991; Saint-Paul et al. 1993; Nagata et al. 1995; Nagafuchi et al. 1998; Chantranuwat and Shuangshoti 1999; Gavelli et al. 1999; Mentha et al. 1999; Watanabe et al. 2001; Wysocki et al. 2002; Capovilla et al. 2005; Cimaschi et al. 2006; Paquette et al. 2009.

In most cases, jaundice occurred late after surgery, the latest development of jaundice occurring 29 years after surgery. The patients sometimes show a slight to moderate elevation of serum CA 19-9, usually around 100 U/ml (normal: $<$34.9 U/ml), what may be a misleading finding in the differential diagnostic work-up (Hyman et al. 2003). The vast majority of patients are diagnosed in retrospect when the surgical pathology specimen is examined (Pickens et al. 1999; Hotta et al. 2004; Ueno et al. 2008; Paquette

et al. 2009). In part of the patients, the lesion may mimic biliary tract cancer (Koh et al. 2008).

Imaging reveals an irregularly shaped mass on CT and MRI scans, sometimes with bulging into the bile duct lumen or circumscribed thickening of the wall (Ueno et al. 2008; Paquette et al. 2009). MR imaging showed a dilatation of the bile ducts and a nodule or nodules with well-defined high-intensity nodules on T2-weighted images, while T1-weighted images showed iso-intense nodules with a low-intensity capsule (Ueno et al. 2008). Cholangiography shows a smooth stricture and a prestenotic duct dilatation (Ueno et al. 2008).

Pathology

A detailed pathologic description of post-cholecystectomy biliary tract neuroma is found in an instructive report as of 1931 (Comfort and Walters 1931). The authors describe a firm resection specimen of the cystic duct stump showing on cross section a central canal whose walls contained the typical interlacing nerve bundles in a groundwork of connective tissue. Neuromas located to the cystic stump may show ulceration of the overlying mucosa (Watanabe et al. 2001). Some neuromas exhibit an exophytic growth and may produce polypoid lesions, e.g., in the gallbladder (Sano et al. 1985).

Histology shows a predominantly eccentric thickening of the duct wall and variable narrowing of the lumen. Are there alterations in the nerves and ganglia that serve the structures giving rise to neuromas? Husseinoff (1928), in his case of a post-cholecystectomy neuroma of the common bile duct, noted fibrosis and a cellular infiltration of the stellate ganglion.

Pathogenesis

Regeneration of injured peripheral nerves involves complex and intimate interactions between axons, Schwann cells, perineural cells, fibroblasts, and components of the extracellular matrix. Neuroma formation is thought to be induced by posttraumatic nerve cell growth after surgery (Zeff et al. 1976; Pickens et al. 1999; Hyman et al. 2003; Hotta et al. 2004; Ueno et al. 2008; Hilliard 2009). The mode of nerve transection plays a role in neuromagenesis, as, e.g., oblique transection prevents neuromas (Marcol et al. 2006).

Axon growth is promoted by nerve growth factor (NGF), Sox11, and matrix proteins, specifically laminin (Tucker and Mearow 2008; Gordon 2009; Jankowski et al. 2009). Axonal guidance and neurite outgrowth are regulated by collapsing response mediator protein-2/CRMP-2, which is a calmodulin-binding protein (Zhang et al. 2009). On the other hand, axon outgrowth is controlled by axon regeneration inhibitors, including myelin-associated glycoprotein, Nogo and Nogo receptor, and chondroitin sulfate proteoglycans (McGee and Strittmatter 2003; Atwal et al. 2008; Yang and Schnaar 2008). Schwann cell proliferation in the regenerating nerve is mediated by ERK1/2 (Seo et al. 2009) and MMP-9 (Chattopadhyay and Shubayev 2009), while stromelysin generates a fibronectin fragment that inhibits Schwann cell proliferation (Muir and Manthorpe 1992). Growing Schwann cells express the receptor for, and are stimulated by, locally synthesized calcitonin gene-related peptide (Toth et al. 2009). Nerve fibroblasts affect the migratory behavior of Schwann cells, via neuregulin (Dreesmann et al. 2009). Schwann cells in regenerating nerves produce glial fibrillary acidic protein, induced by STAT3 which in turn depends on interleukin-6 (Lee et al. 2009). Myelinating Schwann cells express glucose-dependent insulinotropic polypeptide (GIP) and its receptor, GIPR, forming an autocrine and paracrine system regulating Schwann cell function. Schwann cell differentiation in regenerating nerves is regulated by meltrin-beta/ADAM 19, which functions as a modulator of juxtacrine signaling from axons that activate the Akt pathway and the Kros-20 expression, prerequisites of Schwann cell differentiation (Yumoto et al. 2008; Wakatsuki et al. 2009). Brain-derived growth factor (BDNF) is involved in local neuropathic pain development in neuromas, but seems to promote experimental neuroma formation (Marcol et al. 2007). The cells involved in regeneration of damaged nerves also include mononuclear cells

derived from the bone marrow and homing to the injury site. These cells have been shown secrete NGF (Ribeiro-Resende et al. 2009).

Neuromatosis of Bile Ducts

Neuromatosis is a condition characterized by neural hypertrophy and hyperplasia unassociated with ganglion cells, generally found in patients with multiple endocrine neoplasia type IIb (MEN IIb) caused by RET gene mutations and usually located in the gastrointestinal tract (Sachdev 1990; Lee and Norton 2000; Prabhu et al. 2004). Less commonly, neuromatosis has been observed in neurofibromatosis type 1, Cowden's disease, PTEN hamartoma-tumor syndrome, juvenile polyposis coli, Hirschsprung's disease, and colonic adenoma with or without adenocarcinoma (Schaffer et al. 2006; Gustafson et al. 2007). Multiple mucocutaneous neuromas have also been described as an idiopathic entity, i.e., in the absence of MEN IIb or the other conditions listed above (Truchot et al. 2001). There are very few reports on non-MEN IIb-associated neuromatosis of the biliary tract. In 64-year-old women without signs of MEN IIb, a history of cholelithiasis and biliary colic was investigated by ultrasound and CT, showing severe dilatation of the intra-and extrahepatic bile ducts as well as a scleroatrophic gallbladder with numerous calculi. Cholangiography revealed an abrupt blockage of the right hepatic duct without evidence of lithiasis. Based on the suspicion of malignancy, resection of the gallbladder and of part of the bile ducts was performed. The cystic duct contained a white, elastic, well-demarcated nodule of 4 mm diameter. Microscopy showed diffuse neural hypertrophy in the wall of the bile ducts, with the presence of numerous markedly thickened and highly branched nerve bundles. The cystic duct nodule was mucosal neuroma containing proliferated Schwann cells and numerous axons, in the absence of ganglionic cells. The morphology closely resembled that of gastrointestinal neuromatosis in MEN IIb (Tardio 2007). Neuromatosis has been diagnosed in the gallbladder (Cosmacini et al. 1967).

References

Akin M, Bozkirili B, Leventoglu S, Unal K, Kapucu LO, Akyurek N, Sare M (2009) Liver schwannoma incidentally discovered in a patient with breast cancer. Bratisl Lek Listy 110:298–300

Akiyama T, Saito H, Kiriyama M, Tomita F, Kosaka T, Kita I, Takashima S, Matsunou H (1995) A case of gallbladder cancer associated with a common bile duct neuroma, and a cystic lesion of the liver with histologic findings similar to those of an inflammatory pseudotumor. J Gastroenterol 30:408–412

Andreu V, Elizalde I, Mallafre C, Caballeria J, Salmeron JM, Sans M, Mas A, Bruguera M, Rods J (1997) Plexiform neurofibromatosis and angiosarcoma of the liver in von Recklinghausen disease. Am J Gastroenterol 92:1229–1230

Atwal JK, Pinkston-Gosse J, Syken J, Stawicki S, Wu Y, Shatz C, Tessier-Lavigne M (2008) PirB is a functional receptor for myelin inhibitors of axonal regeneration. Science 322:967–970

Bajor J, Garamszegi M, Grexa E, Anga B, Papp G, Bero T (2002) Bile duct obstruction caused by neurofibroma in a patient with Recklinghausen's disease (in Hungarian). Orv Hetil 143:1947–1950

Ballas K, Kontoulis TM, Papavasiliou A, Pissas D, Pavlidis T, Katsiki E, Venizelos I, Sakadamis A (2009) A rare case of malignant triton tumor with pluridirectional differentiation. South Med J 102:435–437

Bartlett MK, McDermott WV (1954) Amputation neuroma of the bile ducts with obstructive jaundice. N Engl J Med 251:213–216

Béchade D, Boulanger T, Palazzo L, Algayres JP (2010) Primary neurofibroma of the common bile duct. Gastrointest Endosc 72:895–897

Bekker GM (1982) Neurofibroma of the liver (in Russian). Sov Med 10:120–121

Berge T, Haeger K (1967) Clinical significance of the amputation neuroma and length of the cystic duct remnant. Acta Chir Scand 133:55–60

Bialik IR, Del'tsova GA (1966) Resection of the left lobe of the liver in extensive neurinoma (in Russian). Vestn Khir Im I I Grek 97:107–108

Brekke HR, Kolberg M, Skotheim RI, Hall KS, Bierkehagen B, Risberg B, Domanski HA et al (2009) Identification of p53 as a strong predictor of survival for patients with malignant peripheral nerve sheath tumors. Neuro Oncol 11:514–528

Cabibi D, Zerilli M, Caradonna G, Schillaci L, Belmonte B, Rodolico V (2009) Diagnostic and prognostic value of CD10 in peripheral nerve sheath tumors. Anticancer Res 29:3149–3155

Capovilla M, Lazure T, Lorand I, Carton E, Rocher L, Pelletier G, Cucherousset J, Bedossa P (2005) Post-cholecystectomy amputation neuroma of the common bile duct with obstructive jaundice (in French). Gastroenterol Clin Biol 29:79–81

Carbia S, Pagola J, Flaster N, Guida A, Jufe L, Gonzalez B, Caniparoli A (1995) Isolated neurofibroma of the common bile duct (in Spanish). Medicina (B Aires) 55:689–692

Cardinale L, Castoldi MC, Mattai Del Moro R, Sangermani R (2000) Intrahepatic neurofibromatosis in childhood. 2 cases (in Italian). Radiol Med (Torino) 100:84–86

Cattell RB, St Ville J (1961) Amputation neuromas of the biliary tract. Arch Surg 83:242–246

Chang LS, Welling DB (2009) Molecular biology of vestibular schwannomas. Methods Mol Biol 493:163–177

Chantranuwat C, Shuangshoti S (1999) Traumatic neuroma as a cause of obstructive jaundice. J Med Assoc Thai 82:619–622

Chattopadhyay S, Shubayev VI (2009) MMP-9 controls Schwann cell proliferation and phenotypic remodeling via IGF-1 and ErbB receptor-mediated activation of MEK/ERK pathway. Glia 57:1316–1325

Chen TC, Kuo WR, Chai CY, Juan KH (1992) Huge plexiform neurofibroma of the head and liver – case report. Gaoxiong Yi Xue Ke Xue Za Zhi 7:650–656

Choi H, Whitman G, Ro J, Charnsangavej C (2001) Benign schwannoma in the porta hepatis. AJR Am J Roentgenol 177:652

Choi SB, Park YN, Kim KS (2009) Traumatic neuroma of the right hepatic duct undertaken right hemihepatectomy. ANZ J Surg 79:91–92

Chu PT (1950) Benign neoplasms of the extrahepatic biliary ducts; review of the literature and report of a case of fibroma. Arch Pathol (Chicago) 50:84–97

Cieslak AK, Stout AP (1946) Traumatic and amputation neuromas. Arch Surg 53:646

Cimaschi D, De Cesare V, Pulcini G, Cervi E, Belloni M, Liserre B, Cervi GC (2006) A case of amputation neuroma of the bile duct following video-laparoscopic cholecystectomy (in Italian). G Chir 27:31–36

Claudon M, Floquet J, Boissel P, Aymard B, Bresler L, Regent D (1988) Obstructive jaundice and portal hypertension caused by isolated neurofibroma of the common bile duct (in French). Gastroenterol Clin Biol 12:765–767

Colina F, Garcia-Prats MD, Moreno E, Garcia-Munoz H, Ballestin C, Mayordomo JI, Gomez-Sanz R, Gonzalez-Pinto I (1994) Amputation neuroma of the hepatic hilum after orthotopic liver transplantation. Histopathology 25:151–157

Comfort MW, Walters W (1931) Intermittent jaundice due to neuroma of cystic and common bile ducts. Ann Surg 93:1142–1145

Cosmacini G, Costa F, Limentani A (1967) So-called neuromatosis of the gallbladder (in Italian). Radiol Med 53:1108–1114

De Sena G, Molino C, De Riitis MR, Candela S, Cifarelli V, Di Maio V, Chianese F, Rossetti DA et al (2009) Surgical management of schwannoma of biliary tract (in Italian). Chir Ital 61:119–121

DeClue JE, Papageorge AG, Fletcher JA (1992) Abnormal regulation of mammalian p21ras contributes to malignant tumor growth in von Recklinghausen' (type 1) neurofibromatosis. Cell 69:265–273

Delacourt C, Le Bourgeois M, Blanc P, de Blic J, Danel C, Brunelle F, Scheinmann P (1987) Diffuse mediastinal, retroperitoneal and hepatic neurofibromatosis in 4-year-old child. Value of puncture biopsy guided by computerized tomography (in French). Arch Fr Pediatr 44:601–603

Denisenko N, Cifuentes-Diaz C, Inironpoulou T, Carnaud M, Benoit E, Niwa-Kawakita M et al (2008) Tumor suppressor schwannomin/merlin is critical for the organization of Schwann cell contacts in peripheral nerves. J Neurosci 28:10472–10481

Digilio MC, Capolino R, Marino B, Darkozy A, Dallapiccola B (2005) Congenital intrahepatic portosystemic venous shunt: an unusual feature in LEOPARD syndrome and in neurofibromatosis type 1. Am J Med Genet A 134:457–458

Dowdy GS, Olin WG, Shelton EL, Waldron GW (1962) Benign tumors of the extrahepatic bile ducts. Arch Surg 85:503–512

Dreesmann L, Mittnacht U, Lietz M, Schlosshauer B (2009) Nerve fibroblast impact on Schwann cell behavior. Eur J Cell Biol 88:285–300

Fenoglio L, Severini S, Cena P, Migliori E, Bracco C, Pomero F, Panzone S, Cavallero GB et al (2007) Common bile duct schwannoma: a case report and review of literature. World J Gastroenterol 13:1275–1278

Fenton LZ, Foreman N, Wyatt-Ashmead J (2001) Diffuse, retroperitoneal mesenteric and intrahepatic periportal plexiform neurofibroma in a 5-year-old boy. Pediatr Radiol 31:637–639

Fiel MI, Schwartz M, Min AD, Sung MW, Thung SN (1996) Malignant schwannoma of the liver in a patient without neurofibromatosis: a case report and review of the literature. Arch Pathol Lab Med 120:1145–1147

Flaiz C, Ammoun S, Biebl A, Hanemann CO (2009) Altered adhesive structures and their relation to RhoGTPase activation in merlin-deficient schwannoma. Brain Pathol 19:27–38

Flemming P, Frerker M, Klempnauer J, Pichlmayr R (1998) Benign schwannoma of the liver with cystic changes misinterpreted as hydatid disease. Hepatogastroenterology 45:1764–1766

Gallego JC, Galindo P, Suarez I, Garcia-Rodriguez JF (1998) MR of hepatic plexiform neurofibroma. Clin Radiol 53:389–390

Gavelli A, Mainguené C, Greco A, Marmorale A, Ambrosiani N, Huguet C (1999) Bile duct amputation neuroma: a possible cause of postoperative stenosis (in French). Ann Chir 53:251–253

Ghalib R, Howard T, Lowell J, Huettner P, Whelan A, Teefey S, Peters M, White H (1995) Plexiform neurofibromatosis of the liver: case report and review of the literature. Hepatology 22:1154–1157

Giuly JA, Picand R, Giuly D, Monges B, Nguyen-Cat R (2003) Von Recklinghausen disease and gastrointestinal stromal tumors. Am J Surg 185:86–87

Gordon T (2009) The role of neurotrophic factors in nerve regeneration. Neurosurg Focus 26:E3

Gossios KJ, Guy RL (1993) Case report: imaging of widespread plexiform neurofibromatosis. Clin Radiol 47:211–213

Gregorian C, Nakashima J, Dry SM, Nghiemphu PL, Smith KB, Ao Y, Dang J, Lawson G et al (2009) PTEN dosage is essential for neurofibroma development and malignant transformation. Proc Natl Acad Sci U S A 106:19479–19484

Gustafson S, Zbuk KM, Scacheri C, Eng C (2007) Cowden syndrome. Semin Oncol 34:428–434

Guzman Toro F, Hinestroza D, Colmenares D (1995) Von Recklinghausen disease and hepatic neurofibromatosis (in Spanish). Gen 49:303–306

Hadfield KD, Newman WG, Bowers NL, Wallace A, Bolger C, Colley A, McCann E et al (2008) Molecular characterisation of SMARCB1 and NF2 in familial and sporadic schwannomatosis. J Med Genet 45:332–339

Hassen-Khodia R, Declemy S, Batt M, Castanet J, Perrin C, Ortonne JP, Le Bas P (1997) Visceral artery aneurysms in Von Recklinghausen's neurofibromatosis. J Vasc Surg 25:572–575

Hayashi M, Takeshita A, Yamamoto K, Tanigawa N (2012) Primary hepatic benign schwannoma. World J Gastrointest Surg 4:73–78

Heffron TG, Coventry S, Bedendo F, Baker A (1993) Resection of primary schwannoma of the liver not associated with neurofibromatosis. Arch Surg 128:1396–1398

Hernandez Alvarez G, Ayala Landa R, Hernandez Adrian G, Benarroch C (1991) Biliary obstruction in von Recklinghausen disease (in Spanish). Gen 45:55–60

Herrera L, Martino E, Rodriguez-Sanjuan JC, Castillo J, Casafont F, Gonzalez F, Figols J et al (2009) Traumatic neuroma of extrahepatic bile ducts after orthotopic liver transplantation. Transplant Proc 41:1054–1056

Hilliard MA (2009) Axonal degeneration and regeneration: a mechanistic tug-of-war. J Neurochem 108:23–32

Hochain P, Duranton Y, Manchon ND, Peillon C, Métayer J, Michot F, Testart J, Bercoff E, Bourreille J (1988) Neuroma of the common bile duct: a rare cause of jaundice (in French). Gastroenterol Clin Biol 12:576–578

Hofmann-Wackersreuther G, Ortloff-Kittredge P, Wünsch PH (1991) Amputation neuroma of the common bile duct after cholecystectomy. Lethal hepatic complications (in German). Zentralbl Pathol 137:82–85

Holtkamp et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18650488

Honjo Y, Kobayashi Y, Nakamura T, Takehira Y, Kitagawa M, Ikematsu Y, Ozawa T, Nakamura H (2003) Extrahepatic biliary schwannoma. Dig Dis Sci 48:2221–2226

Hoshimoto S, Morise Z, Takeura C, Ikeda M, Kagawa T, Tanahashi Y, Okabe Y, Mizoguchi Y, Sugioka A (2009) Plexiform neurofibroma in the hepatic hilum associated with neurofibromatosis type 1: a case report. Rare Tumors 1:e23

Hotta T, Kobayashi Y, Taniguchi K, Naka T, Johata K, Sahara M, Watanabe T, Tanimura H, Tsubota YT (2004) A traumatic neuroma of the bile duct: a case report. Hepatogastroenterology 51:39–42

Hra E, Sodeyama Y, Tanaka E, Nakano Y, Kiyosawa K, Furuta S (1992) A case of Recklinghausen's disease followed by intra-hepatic neurofibroma (in Japanese). Nippon Naika Gakkai Zasshi 81:913–914

Huang J, Chen J (2008) VprBP targets merlin to Roc1-Cul4A-DDB1 E3 ligase complex for degradation. Oncogene 27:4056–4064

Huang J, Zeng Y, Yan L (2011) Schwannoma originating from the proper hepatic artery. Dig Liver Dis 43:e15

Huber GC, Lewis D (1920) Amputation neuromas, their development and prevention. Arch Surg 1:85

Hulsebos TJ, Plomp AS, Wolterman RA, Robanus-Maandag EC, Baas F, Wesseling P (2007) Germline mutation of INI1/SMARCB1 in familial schwannomatosis. Am J Hum Genet 80:805–810

Hume RH, Buxton RW (1954) Postcholecystectomy amputation neuroma. Am Surg 20:698–708

Husseinoff D (1928) Ueber einen Fall von Wucherung des Nervengewebes nach wiederholten Operationen der Gallengänge. Zbl Allg Pathol 43:344–348

Hyman J, Wilczynski SP, Schwarz RE (2003) Extrahepatic bile duct stricture and elevated CA 19–9: malignant or benign? South Med J 96:89–92

Hytiroglou P, Linton P, Klion F, Schwartz M, Miller C, Thung SN (1993) Benign schwannoma of the liver. Arch Pathol Lab Med 117:216–218

Ianelli A, Fabiani P, Karimdjee BS, Converset S, Saint-Paul MC, Gugenheim J (2003) Traumatic neuroma of the cystic duct with biliary obstruction. Report of a case. Acta Gastroenterol Belg 66:28–29

Iddings DM, Wright BE, Bilchik A (2008) A rare cause of primary hepatic neoplasm: malignant peripheral nerve sheath tumor in the age of modern liver surgery. Am Surg 74:47–50

Ikegami T, Ezaki T, Ishida T, Kohno H, Fujihara M, Mori M (2004) Neurilemmoma of the diaphragm mimicking a liver tumor: case report. Abdom Imaging 29:85–86

Imbert JP, Pilleul F, Valette PJ (2002) Value of MRI in hepatic plexiform neurofibromatosis. Case report (in French). Gastroenterol Clin Biol 26:791–793

Jakobs R, Albert J, Schilling D, Nuesse T, Riemann JF (2003) Schwannoma of the common bile duct: a rare cause of obstructive jaundice. Endoscopy 35:695–697

Jankowski MP, McIlwrath SL, Jing X, Cornuet PK, Salerno KM, Koerber HR, Albers KM (2009) Sox11 transcription factor modulates peripheral nerve regeneration in adult mice. Brain Res 1256:43–54

Janzer RC, Makek M (1983) Intraoral malignant melanotic schwannoma. Ultrastructural evidence for melanogenesis by Schwann's cells. Arch Pathol Lab Med 107:298–301

Jiang L, Yan L, Cheng N, Jiang L (2011) Obstructive jaundice due to primary neurofibroma of the common bile duct. Dig Liver Dis 43:85

Johnson MR, Look AT, DeClue JE, Valentine MB, Lowy DR (1993) Inactivation of the NF1 gene in human melanoma and neuroblastoma cell lines without impaired regulation of GTP. Ras Proc Natl Acad Sci U S A 90:5539–5543

Jokinen CH, Dadras SS, Goldblum JR, van de Rijn M, West RB, Rubin BP (2008) Diagnostic implications of podoplanin expression in peripheral nerve sheath neoplasms. Am J Clin Pathol 129:886–893

Jones GN, Tep C, Towns WH, Mihai G, Tonks ID, Kay GF, Schmalbrock PM, Stemmer-Rachamimov AO et al (2008) Tissue-specific ablation of Prkar1a causes schwannomas by suppressing neurofibromatosis protein production. Neoplasia 10:1213–1221

Joske RA, Finlay-Jones LR (1966) Amputation neuroma of the cystic-duct stump. Br J Surg 53:766–768

Jung JH, Joo KR, Chae MJ, Jang JY, Lee SG, Dong SH, Kim HJ, Kim BH, Chang YW et al (2007) Extrahepatic biliary schwannoma: a case report. J Korean Med Sci 22:549–552

Kakitsubata Y, Kakitsubata S, Sonoda T, Watanabe K (1994) Neurofibromatosis type 1 involving the liver: ultrasound and CT manifestations. Pediatr Radiol 24:66–67

Kamani F, Dorudinia A, Goravanchi F, Rahimi F (2007) Extrahepatic bile duct neurilemmoma mimicking Klatskin tumor. Arch Iran Med 10:264–267

Kapoor S, Tevatia MS, Dattagupta S, Chattopadhyay TK (2005) Primary hepatic nerve sheath tumor. Liver Int 25:458–459

Katsinelos P, Dimiropoulos S, Galanis I, Tsolkas P, Paroutoglu G, Arvaniti M, Katsiba D et al (2002) Biliary stricture due to neuroma after an innocent blunt abdominal trauma. Surg Endosc 16:1494

Katz D, Lazar A, Lev D (2009) Malignant peripheral nerve sheath tumour (MPNST): the clinical implications of cellular signaling pathways. Expert Rev Mol Med 11: e30

Kim YC, Park MS (2010) Primary hepatic schwannoma mimicking malignancy on fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography. Hepatology 51:1080–1081

Knapen P, Ponette E, Marchal G, Baert AL, Van Steenbergen W, Fevery J, Geboes K et al (1994) Three cases of non-tumoural tight stenosis of the bifurcation of the hilar bile ducts. Röfo 161:561–563

Kobori L, Nagy P, Mathé Z, Hartmann E, Doros A, Paku S, Dezso K, Sapi Z (2008) Malignant peripheral nerve sheath tumor of the liver: a case report. Pathol Oncol Res 14:329–332

Koh DW, Lee WJ, Kim JH, Choi JI, Kim SH, Hong EK, Park JW, Kim CM (2008) Amputation neuroma mimicking common bile duct cancer: a case report (in Korean). Korean J Gastroenterol 52:32–36

Koike N, Todoriki T, Kawamoto T, Inagawa S, Yoshida S, Fukao K (2000) Amputation neuroma mimics common hepatic duct carcinoma. Hepatogastroenterology 47:639–643

Kopolovic J, Rivkind A, Rabinovici R, Klein B, Eyal Z (1984) Amputation neuroma of common bile duct with obstructive jaundice: a case report. Appl Pathol 2:292–294

Kurtkaya-Yapicier O, Scheithauer BW, Woodruff JM, Wenger DD, Cooley AM, Dominique D (2003) Schwannoma with rhabdomyoblastic differentiation: a unique variant of malignant triton tumor. Am J Surg Pathol 27:848–853

Lallemand D, Manent J, Couvelard A, Watilliaux A, Siena M, Charevre F, Lampin A, Niwa-Kawakita M et al (2009) Merlin regulates transmembrane receptor accumulation and signaling at the plasma membrane in primary mouse Schwann cells and in human schwannomas. Oncogene 28:854–865

Larson DM, Storsteen KA (1984) Traumatic neuroma of the bile ducts with intrahepatic extension causing obstructive jaundice. Hum Pathol 15:287–289

Lederman SM, Martin EC, Laffey KT, Lefkowitch JH (1987) Hepatic neurofibromatosis, malignant schwannoma, and angiosarcoma in von Recklinghausen's disease. Gastroenterology 92:234–239

Lee NC, Norton JA (2000) Multiple endocrine neoplasia type 2B – genetic basis and clinical expression. Surg Oncol 9:111–118

Lee WH, Kim TH, You SS, Choi SP, Min HJ, Kim HJ, Lee OJ, Ko GH (2008) Benign schwannoma of the liver: a case report. J Korean Med Sci 23:727–730

Lee HK, Seo IA, Suh DJ, Hong JI, Yoo YH, Park HT (2009) Interleukin-6 is required for the early induction of glial fibrillary acidic protein in Schwann cells during Wallerian degeneration. J Neurochem 108:776–786

Legius E, Marchuk DA, Collins FS, Glover T (1993) Somatic deletion of the neurofibromatosis type 1 gene in a neurofibrosarcoma supports a tumour suppressor gene hypothesis. Nat Genet 3:122–126

Lepont P, Stickney JT, Foster LA, Meng JJ, Hennigan RF, Ip W (2008) Point mutation in the NF2 gene of HEI-193 human schwannoma cells results in the expression of a merlin isoform with attenuated growth suppressive activity. Mutat Res 637:142–151

Li FY, Cheng JQ, He S, Li N, Zhang MM, Zhang XL, Jiang LS, Cheng NS, Xiong XZ (2005) Primary neurofibroma of the common bile duct as an unusual cause of obstructive jaundice: a case report. Dig Dis Sci 50:1166–1168

Loeweneck H (1971) Vagotomie und Choledochusinnervation (Vagotomy and innervation of the choledochus). Teil I: Die Gefässnervenstrassen zum supraduodenalen Choledochusabschnitt. Chirurg 42:178–180

Loutsch H (1961) Apropos of a case of amputation neuroma of the cystic stump (in French). Mem Acad Chir (Paris) 87:324–330

Lovasz L (1970) Neurofibromas of the choledochus causing jaundice (in Hungarian). Orv Hetil 111:513–514
Lü J, Zou J, Wu H, Cai L (2008) Compensative shuttling of merlin to phosphorylation on serine 518 in vestibular schwannoma. Laryngoscope 118:169–174
Madhusudhan KS, Srivastava DN, Dash NR, Gupta C, Gupta SD (2009) Case report: Schwannoma of both intrahepatic and extrahepatic bile ducts: a rare case. Br J Radiol 82:e212–e215
Maheshvari VK, Agarwal GP (1969) Post-cholecystectomy cystic duct neuroma. A case report. Indian J Pathol Bacteriol 12:126–127
Malagari K, Drakopoulos S, Brountzos E, Sissopulos A, Efthimidadou A, Hadjiyiannakis E, Kelekis DA (2001) Plexiform neurofibroma of the liver: findings on MR imaging, angiography, and CT portography. Am J Roentgenol 176:493–495
Mantripragada KK, de Stahl TD, Patridge C, Menzel U, Andersson R, Chuzhanova N et al (2009) Genome-wide high-resolution analysis of DNA copy number alterations in NF1-associated malignant peripheral nerve sheath tumors using 32K BAC array. Genes Chromosomes Cancer 48:897–907
Marcol W, Kotulska K, Larysz-Brysz M, Bierzynska-Macyszyn G, Wlaszczuk P, Lewin-Kowalik J (2006) Prevention of painful neuromas by oblique transection of peripheral nerves. J Neurosurg 104:285–289
Marcol W, Kotulska K, Larysz-Brysz M, Kowalik JL (2007) BDNF contributes to animal model neuropathic pain after peripheral nerve transection. Neurosurg Rev 30:235–243
Martinez Ordaz JL, Gomez Jimenez LM, Blanco Benavides R (1999) Bile duct neuroma. A benign neoplasm resembling Klatskin's tumor. Report of a case (in Spanish). Rev Gastroenterol Mex 64:146
Maruta K, Sonoda Y, Saigo R, Yoshioka T, Fukunaga H (2004) A patient with von Recklinghausen's disease associated with polymyositis, asymptomatic pheochromocytoma, and primary hepatic leiomyosarcoma (in Japanese). Nippon Ronen Igakkai Zasshi 41:339–343
Masson P (1942) Tumours encapsulées et benignes des nerfs (Encapsulated and benign tumors of nerves). Rev Canad Biol 1:209
Mattler EA, Barberis CR, Salama AA, Rossai J (1965) Postcholecystectomy syndrome – amputation neuroma of the cystic duct (in Spanish). Rev Argent Cir 8:93–94
McClatchey AI, Giovannini M (2005) Membrane organization and tumorigenesis – the NF2 tumor suppressor, merlin. Genes Dev 19:2265–2277
McGee AW, Strittmatter SM (2003) The Nogo-66 receptor: focusing myelin inhibition of axon regeneration. Trends Neurosci 26:193–198
Mendes Ribeiro HK, Woodham C (2000) CT demonstration of an unusual cause of biliary obstruction in a patient with peripheral neurofibromatosis. Clin Radiol 55:796–798
Meng ZH, Yang YS, Cheng KL, Chen GQ, Wang LP, Li W (2013) A huge malignant peripheral nerve sheath tumor with hepatic metastasis arising from retroperitoneal ganglioneuroma. Oncol Lett 5:123–126
Menon AG, Anderson KM, Riccardi VM (1990) Chromosome 17p deletions and p53 gene mutations associated with the formation of malignant neurofibrosarcomas in von Recklinghausen neurofibromatosis. Proc Natl Acad Sci U S A 87:5435–5439
Mentha G, Rubbia-Brandt L, Orci L, Becker C, Giostra E, Maino P, Borisch B, Handengue A, Morel P (1999) Traumatic neuroma with biliary duct obstruction after orthotopic liver transplantation. Transplantation 67:177–179
Meyer GW, Griffiths WJ, Welsh J, Cohen L, Johnson L, Weaver MJ (1982) Hepatobiliary involvement in von Recklinghausen's disease. Ann Intern Med 97:722–723
Millstein DI, Tang CK, Campbell EW (1981) Angiosarcoma developing in a patient with neurofibromatosis (von Recklinghausen's disease). Cancer 47:950–954
Mitchell DI, Char G, McDonald A, Scott P (1995) Plexiform neurofibroma: a rare cause of obstructive jaundice. West Indian Med J 44:146–147
Momtahen AJ, Akduman EI, Balci NC, Fattahi R, Haylioglu N (2008) Liver schwannoma: findings on MRI. Magn Reson Imaging 26:1442–1445
Morikawa Y, Ishihara Y, Matsuura N, Miyamoto H, Kakudo K (1995) Malignant schwannoma of the liver. Dig Dis Sci 40:1279–1282
Muir D, Manthorpe M (1992) Stromelysin generates a fibronectin fragment that inhibits Schwann cell proliferation. J Cell Biol 116:177–185
Nagafuchi Y, Katuki M, Hisatome K, Higure A, Asami S, Itoh H (1998) A traumatic neuroma associated with obstructive jaundice after laparoscopic cholecystectomy. Hepatogastroenterology 45:424–427
Nagata Y, Tomioka T, Chiba K, Kanematsu T (1995) Traumatic neuroma of the common hepatic duct after laparoscopic cholecystectomy. Am J Gastroenterol 90:1887–1888
Nakajima M (1995) Neurofibroma of the liver, schwannoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:381–383
Neumaier CE, Onetto F, Delucchi S, Cittadini G, Silvestri E (1997) Case report: isolated neurofibrosarcoma of the liver: US, CT and MR findings. Clin Radiol 52:310–311
Oden B (1955) Neurinoma of the common bile duct; report of a case. Acta Chir Scand 108:393–397
Oderich GS, Sulivan TM, Bower TC, Gloviczki P, Miller DV, Babovic-Vuksanovic D, Macedo TA et al (2007) Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. J Vasc Surg 46:475–484
Odier L (1811) Manuel de medicine pratique. J.J. Pachoud, Geneva, p 362
Okada T, You L, Giancotti FG (2007) Shedding light on Merlin's wizardry. Trends Cell Biol 17:222–229
Ota Y, Aso K, Watanabe K, Einama T, Imai K, Karasaki H, Sudo R, Tamaki Y, Okada M, Tokusashi Y et al (2012)

Hepatic schwannoma: imaging findings on CT. MRI and contrast-enhanced ultrasonography. World J Gastroenterol 18:4967–4972

Otani T, Shiori T, Mishima H, Ishihara A, Maeshiro T, Matsuo A, Umekita N, Warabi M (2005) Bile duct schwannoma developed in the remnant choledochal cyst – a case associated with total agenesis of the dorsal pancreas. Dig Liver Dis 37:705–708

Ozkan EE, Guldur ME, Uzunkoy A (2010) A case report of benign schwannoma of the liver. Intern Med 49:1533–1536

Palagiano V, D'Addato M (1963) Amputation neuroma of the cystic duct (in Italian). Acta Chir Ital 19:581–597

Panait L, Learn P, Dimaio C, Klimstra D, Do KG, Schwarz T, D'Angelica M, Dematteo R, Kingham P et al (2011) Resection of perihilar biliary schwannoma. Surg Oncol 20:e157–e159

Paquette IM, Suriawinata AA, Ornvold K, Gardner TB, Axelrod DA (2009) Neuroma of the bile duct: a late complication after cholecystectomy. J Gastrointest Surg 13:1517–1519

Park MK, Lee KT, Choi YS, Shin DH, Lee JY, Lee JK, Paik SW, Ko YH, Rhee JC (2006) A case of benign schwannoma in the porta hepatis (in Korean). Korean J Gastroenterol 47:164–167

Partin et al. 1990. http://www.ncbi.nlm.nih.gov/pubmed/2119333

Peison B, Benisch B (1985) Traumatic neuroma of the cystic duct in the absence of previous surgery. Hum Pathol 16:1168–1169

Pereira Filho RA, Souza SA, Oliveira Filho JA (1978) Primary neurilemmal tumour of the liver: case report. Arq Gastroenterol 15:136–138

Perrone F, Da Riva L, Orsenigo M, Losa M, Jocolle G, Millefanti C, Pastore E, Gronchi A et al (2009) PDGFRA, PDGFRB, EGFR, and downstream signalling activation in malignant peripheral nerve sheath tumor. Neuro Oncol 11:725–736

Pickens A, Vickers SM, Brown KL, Reddy VV, Thompson JA (1999) An unusual etiology of biliary hilar obstruction and the potential role of acidic fibroblast growth factor in the development of a biliary neuroma. Am Surg 65:47–51

Pinto J, Afonso M, Veloso R, Tente D, Fernandes S, Proença L, Carvalho J, Pontes JM, Fraga J (2011) Benign schwannoma of the hepatoduodenal ligament. Endoscopy 43(Suppl 2):E195–E196

Png MA, The HS, Poh WT (1996) Case report: angiosarcoma in a patient with von Recklinghausen's disease. Clin Radiol 51:521–523

Poon JC, Ogilvie T, Dixon E (2008) Neurofibroma of the porta hepatis. J Hepatobiliary Pancreat Surg 15:327–329

Prabhu M, Khouzam RN, Insel J (2004) Multiple endocrine neoplasia type 2 syndrome with bowel obstruction caused by intestinal neuroma: case report. South Med J 97:1130–1132

Prasad SB (1983) Von Recklinghausen's disease with angiosarcoma in a child. J Indian Med Assoc 81:138

Prevot S, Bienvenu L, Vaillant JC, Saint-Maur PP (1999) Benign schwannoma of the digestive tract: a clinicopathologic and immunohistochemical study of five cases; including a case of esophageal tumor. Am J Surg Pathol 23:431–436

Prinz RA, Greenlee HB, Caporale FS (1979) Amputation neuroma of the cystic duct: a treatable cause of postcholecystectomy pain. Am Surg 45:543–544

Raigorodsky JL (1928) Die Nerven der Leberpforte des Menschen (The nerves of the hepatic porta of man). Zschr F Anat Und Entwg 86:698–730

Rao V, Day CP, Manimaran N, Hurlow RA, Orme R (2007) Spontaneous rupture of the hepatic artery in a patient with type 1 neurofibromatosis treated by embolization: a case report. Cardiovasc Intervent Radiol 30:124–125

Relles D, Baek J, Witkiewicz A, Yeo CJ (2010) Periampullary and duodenal neoplasms in neurofibromatosis type 1: two cases and an updated 20-year review of the literature yielding 76 cases. J Gastrointest Surg 14:1052–1061

Ribeiro-Resende VT, Pimentel-Coelho PM, Mesentier-Louro LA, Mendez RM, Mello-Silva JP et al (2009) trophic activity derived from bone marrow mononuclear cells increases peripheral nerve regeneration by acting on both neuronal and glial cell populations. Neuroscience 159:540–549

Riccardi VM, Wheeler TM, Pickard LR, King B (1984) The pathophysiology of neurofibromatosis. II. Angiosarcoma as a complication. Cancer Genet Cytogenet 12:275–280

Roche PH, Bouvier C, Chinot O, Figarella-Branger D (2008) Genesis and biology of vestibular schwannomas. Prog Neurol Surg 21:24–31

Rodriguez E, Pombo F, Rodriguez I, Vazquez Iglesias JL, Galed I (1993) Diffuse intrahepatic periportal plexiform neurofibroma. Eur J Radiol 16:151–153

Roh J, Cho EA, Seong I, Limb JK, Lee S, Han SJ, Kim J (2006) Down-regulation of Sox10 with specific small interfering RNA promotes transdifferentiation of Schwannoma cells into myofibroblasts. Differentiation 74:542–551

Ronchetti A, Zanniello JM (1962) Schwannoma of the common bile duct. Comments on a case (in Spanish). Dia Med 34:1365–1371

Rosenberg J, Matzner MJ (1957) Neuroma in a dilated stump of the cystic duct; preoperative visualization by intravenous cholangiography. Am J Gastroenterol 27:471–478

Rosenberg AS, Langee CL, Stevens GL, Morgan MB (2002) Malignant peripheral nerve sheath tumor with perineurial differentiation: "malignant perineurioma". J Cutan Pathol 29:362–367

Rückert RI, Fleige B, Rogalla P, Woodruff JM (2000) Schwannoma with angiosarcoma. Report of a case and comparison with other types of nerve tumors with angiosarcoma. Cancer 89:1577–1585

Rui JA, Zhou L, Wang SB, Chen SG, Wei X, Han K, Zhang N, Zhao HT, Yang X (2002) Hepatic

trisegmentectomy for 29 patients with huge liver neoplasms. Hepatobiliary Pancreat Dis Int 1:187–190
Rush BF, Stefaniwsky AB, Sasso A, Dumitrescu I, Wexler D (1988) Neuroma of the common bile duct. J Surg Oncol 39:17–21
Russomanno E (1968) Hepatic neurofibromatosis: anatomo-clinical description of a case (in Italian). Bull Sci Med (Bologna) 140:401–408
Sachdev Y (1990) Multiple mucosal neuromatosis. Indian Pediatr 27:27–32
Saint-Paul MC, Benchimol D, Dumas R, Michiels JF, Hofman P, Van den Broucke X et al (1993) Neuroma of the common bile duct (in French). Ann Gastroenterol Hepatol (Paris) 29:65–67
Samonakis DN, Quaglia A, Joshi NM, Tibballs JM, Nagree A, Triantos CK, Davies N, Standish R et al (2005) Obstructive jaundice secondary to neuroendocrine tumour in a patient with von Recklinghausen's disease. Eur J Gastroenterol Hepatol 17:1229–1232
Sano T, Hirose T, Kagawa N, Hizawa K, Saito K (1985) Polypoid traumatic neuroma of the gallbladder. Arch Pathol Lab Med 109:574–576
Schadendorf D, Haas N, Worm M, Ostemeier H, Kohlmus C, Gottschalk J, Algermissen B et al (1993) Amelanotic malignant melanoma presenting as malignant schwannoma. Br J Dermatol 129:609–614
Schaffer JV, Kamino H, Witkiewicz A, McNiff JM, Orlow SJ (2006) Mucocutaneous neuromas: an underrecognized manifestation of PTEN hamartoma-tumor syndrome. Arch Dermatol 142:625–632
Schmurun RI, Chibisov VN (1977) Malignant neurinoma of the liver (in Russian). Ark Pathol 39:69–71
Seo TB, Oh MJ, You BG, Kwon KB, Chang IA, Yoon JH, Lee CY, Namgung U (2009) ERK1/2-mediated Schwann cell proliferation in the regenerating sciatic nerves by treadmill training. J Neurotrauma 26:1733–1744
Shafiroff BG, Hinton JW (1950) Surgical anatomy of the choledochal nerves. Arch Surg 60:944–948
Shapiro PF, Lifvendahl RA (1931) Tumors of the extrahepatic bile-ducts. Ann Surg 94:61–79
Sheikh MY, Husen YA, Pervez S, Khalid TR, Jaffer N, Afzal M (1996) Computed tomographic appearance of malignant schwannoma of the liver. Can Assoc Radiol J 47:183–185
Shimura K, Tamada K, Asada M, Watabiki N, Wada I, Tanaka N, Suzuki Y (2001) Intraductal ultrasonography of traumatic neuroma of the bile duct. Abdom Imaging 26:632–634
Shumate CR, Curley SA, Cleary KR, Ames FC (1992) Traumatic neuroma of the bile duct causing cholangitis and atrophy of the right hepatic lobe. South Med J 85:425–427
Shumurun RI, Chibisov VN (1977) Malignant neurinoma of the liver. Ark Pathol 39:69–71
Silvestri F (1965) Neuroma of the common bile duct stump (in Italian). Chir Ital 17:19–75
Simmons TC (1988) Ampullary neurofibroma. Dig Dis Sci 33:1500–1501
Skuse GR, Kosciolek BA, Rowley PT (1989) Molecular genetic analysis of tumors in von Recklinghausen neurofibromatosis: loss of heterozygosity for chromosome 17. Genes Chromosomes Cancer 1:36–41
Stark AM, Buhl R, Hugo HH, Mehdorn HM (2001) Malignant peripheral nerve sheath tumours – report of 8 cases and review of the literature. Acta Neurochir (Wien) 143:357–363
Stembridge VA (1951) Amputation neuroma following cholecystectomy. Ann Surg 134:1048–1051
Stibenz J, Kretzschmar U, Künzel W, Dittrich H (1984) Amputation neuroma as a rare cause of so-called postcholecystectomy syndrome (in German). Z Ges Inn Med 39:206–208
Stonecypher MS, Byer SJ, Grizzle WE, Carroll SL (2005) Activation of the neuregulin-1/ErbB signaling pathway promotes the proliferation of neoplastic Schwann cells in human malignant peripheral nerve sheath tumors. Oncogene 24:5589–5605
Subramaniam K, Dessauvagie B, Hardie M, Weber D, Adams L, Macquillan G, Jeffrey G et al (2012) Malignant peripheral nerve sheath tumour of the liver. Pathology 44:265–267
Sugahara K, Yamamoto M, Iizuka H, Yoshioka M, Miura K (1985) Spontaneous neuroma of the bile duct: a case report. Am J Gastroenterol 80:807–809
Suresh TN, Harendra Kumar ML, Prasad CS, Kalyani R, Borappa K (2009) Malignant peripheral nerve sheath tumor with divergent differentiation. Indian J Pathol Microbiol 52:74–76
Takahara N, Saito S, Yoshida M, Ohshima S, Okayasu I (1981) A case of amputation neuroma of the biliary tract with obstructive jaundice. Gastroenterol Jpn 16:521–526
Tardio JC (2007) Neuromatosis of the bile ducts: a previously un-reported location. Histopathology 50:523–525
Taylor MA, Loughrey MB, Toner PG, Regan MC (2001) An unusual cause of biliary stricture in a patient with neurofibromatosis type 1. Eur J Gastroenterol Hepatol 13:199–201
Tesseraux H, Zachmann L (1954) Recklinghausen's neurofibromatosis with enormous neoplastic formation in the right lungs and in liver (in German). Zentalbl Allg Pathol 91:190–196
Thaxton C, Lopera J, Bott M, Baldwin ME, Kalidas P, Fernandez-Valle C (2007) Phosphorylation of the NF2 tumor suppressor in Schwann cells is mediated by Cdc42-Pak and requires paxillin binding. Mol Cell Neurosci 34:231–242
Thaxton C, Lopera J, Bott M, Fernandez-Valle C (2008) Neuregulin and laminin stimulate phosphorylation of the NF2 tumor suppressor in Schwann cells by distinct protein kinase A and p21-activated kinase-dependent pathways. Oncogene 27:2705–2715
Tomica D, Danolic D, Puljiz M, Alvir I, Mamic I, Milas I, Knezevic F, Banovic M (2011) Aggressive intestinal

schwannoma malignum mimicking gynecological pathology – a case report. Coll Antropol 35(Suppl 1):339–343

Toth CC, Willis D, Twiss JL, Walsh S, Martinez JA, Liu WQ, Midha R, Zochodne DW (2009) Locally synthesized calcitonin gene-related peptide has a critical role in peripheral nerve regeneration. J Neuropathol Exp Neurol 68:326–337

Truchot F, Grézard P, Wolf F, Balme B, Perrot H (2001) Multiple idiopathic mucocutaneous neuromas: a new entity? Br J Dermatol 145:826–829

Tsitouridis J, Kouklakis G, Xiarhos P, Patakuita F (1998) Nontraumatic neuroma of the bile duct: report of a case. Dig Endosc 10:323–326

Tucker BA, Mearow KM (2008) Peripheral sensory axon growth: from receptor binding to cellular signaling. Can J Neurol Sci 35:551–566

Tuder RM, Moraes CF (1984) Primary semimalignant schwannoma of the liver. Light and electron microscopic studies. Pathol Res Pract 178:345–348

Turani H, Chaimoff C, Lurie B (1988) Amputation neuroma after cholecystectomy. A cause of intermittent obstructive jaundice. J Clin Gastroenterol 10:101–103

Uçar C, Caliskan U, ToY H, Günel E (2007) Hepatoblastoma in a child with neurofibromatosis type I. Pediatr Blood Cancer 49:357–359

Ueno Y, Ikeda K, Maehara M, Sakaida N, Omura N, Kurokawa H, Sawada S (2008) Traumatic neuroma of the bile duct. Abdom Imaging 33:560–562

Van Gulik TM, Brummelkamp WH, Lygidakis NJ (1989) Traumatic neuroma giving rise to biliary obstruction after reconstructive surgery for iatrogenic lesions of the biliary tract – a report of three cases. Hepatogastroenterology 36:255–257

Varikatt W, Yong JL, Killingsworth MC (2006) Somatostatinoma: collision with neurofibroma and ultrastructural features. Histol Histopathol 21:1171–1180

Verocay J (1910) Zur Kenntnis der 'Neurofibrome'. Beitr Pathol Anat 48:69–78

Vilas-Ferrol I, Hernandez-Gimenez M, Moya-Garcia MI, Menargues-Irles MA, Munoz-Nunez C, Poblet-Martinez E (1998) Intrahepatic plexiform neurofibroma in neurofibromatosis 1. Pediatr Radiol 28:733

Vyas FL, Jesudason MR, Samuel R, Govil S, Jesudason SR (2006) Schwannoma of bile duct – a case report. Trop Gastroenterol 27:50–51

Wada Y, Jimi A, Nakashima O, Kojiro M, Kurohiji T, Sai K (1998) Schwannoma of the liver: report of two surgical cases. Pathol Int 48:611–617

Wakatsuki S, Yumoto N, Komatsu K, Araki T, Sehara-Fujisawa A (2009) Roles of meltrin-beta/ADAM19 in progression of Schwann cell differentiation and myelination during sciatic nerve regeneration. J Biol Chem 284:2957–2966

Watanabe O, Haga S, Okabe T, Kumazawa K, Shiozawa S, Tsuchiya A, Kajiwara T, Hirotani T, Aiba M (2001) Amputation neuroma of common bile duct with obstructive jaundice. J Gastroenterol Hepatol 16:945–946

Womack NA, Crider RL (1947) The persistence of symptoms following cholecystectomy. Ann Surg 126:31–55

Woodruff JM (1999) Pathology of tumors of the peripheral nerve sheath in type 1 neurofibromatosis. Am J Med Genet 89:23–30

Woodruff JM, Selig AM, Crowley K, Allen PW (1994) Schwannoma (neurilemmoma) with malignant transformation. Am J Surg Pathol 18:882–895

Wysocki A, Papla B, Budzynski P (2002) Neuroma of the extrahepatic bile ducts as a cause of obstructive jaundice. Eur J Gastroenterol Hepatol 14:573–576

Yang LJ, Schnaar RL (2008) Axon regeneration inhibitors. Neurol Res 30:1047–1052

Yoshida M, Nakashima Y, Tanaka A, Mori K, Yamaoka Y (1994) Benign schwannoma of the liver: a case report. Nippon Geka Hokan 63:208–214

Young SJ (1975) Primary malignant neurilemmoma (schwannoma) of the liver in a case of neurofibromatosis. J Pathol 117:151–153

Yumoto N, Wakatsuki S, Kurisaki T, Hara Y, Osumi N, Frisén J, Sehara-Fujisawa A (2008) Meltrin beta/ADAM19 interacting with EphA4 in developing neural cells participates in formation of the neuromuscular junction. PLoS One 3:e3322

Zeff RH, Pfeffer RB, Adams PX, Ruoff M (1976) Reoperation for amputation neuroma of the cystic duct. Am J Surg 131:369–370

Zhang Z, Majava V, Greffier A, Hayes RL, Kursula P, Wang KK (2009) Collapsin response mediator protein-2 is a calmodulin-binding protein. Cell Mol Life Sci 66:526–536

Zhou C, Smith KD, Liu J, Lahat G, Myers S, Wang WL, Zhang W, McCutcheon IE et al (2009) Clinical, pathological, and molecular variables predictive of malignant peripheral nerve sheath tumor outcome. Ann Surg 249:1014–1022

Zochodne D (1984) Von Recklinghausen's vasculopathy. Am J Med Sci 287:64–65

Tumors of a Granular Cell Lineage

69

Contents

Abstract

Granular cell tumor (granular cell schwannoma) is a benign tumor characterized by the proliferation of distinct cells with a granular cytoplasm and unknown histogenesis. The cells are reactive for S100 protein and inhibin-alpha. These neoplasms occur almost ubiquitously in the body, but most lesions are diagnosed in the tongue, oral mucosa, and skin. Hepatobiliary granular cell tumor is a very rare tumor and most cases were detected in the walls of bile ducts. Less than 1 % of all these neoplasms originate from bile ducts. Here, they more often develop in the large extrahepatic ducts, gallbladder, and cystic duct, and there is a predominance in female patients. The lesions are mostly solitary and rarely multifocal. Large solitary lesions can cause biliary obstruction. The histologic presentation is the same for granular cell tumors located elsewhere. There exists a very rare malignant variant. A further rare malignancy with granular tumor cells is alveolar soft part sarcoma.

Hepatobiliary Granular Cell Tumors

ICD-O 9580/0 (malignant granular cell tumor: 9580/3)

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_69

Introduction

Granular cell tumor (GCT, synonyms: granular cell myoblastoma, granular cell schwannoma, Abrikossoff's tumor) represents a benign tumor mostly occurring in patients in their second to sixth decades, characterized by a growth of distinct cells with a markedly granular cytoplasm, occurring almost ubiquitously in the body, albeit with certain predilections, most lesions developing in the tongue, oral mucosa, and skin. Although a myogenic origin has been found to be wrong, the histogenesis of GCT is still unknown.

GCT was originally identified in the skeletal muscle of the tongue and termed myoblastic myomata (Abrikossoff 1926). Previous apparent observations of GCT by Virchow (1854) and Weber (1854) as cited by Ordonez (Ordonez 1999) represent, when one reads the original articles, early observations of either true lingual rhabdomyoma (see ▶ Chap. 64, "Tumors of the Striated Muscle Cell Lineage: Hepatobiliary Rhabdomyosarcoma and Rhabdomyoma") or a hamartoma-like hypertrophy of the tongue. Weber described, in his publication written in German, the case of 21-year-old man with a massive enlargement of the tongue ("size of a hand"), leading to displacement of the jaw teeth. Histologically, lingual hypertrophy with interposed adipose tissue, abnormal vascularization, and immature-looking myocytes/myoblasts were found (Weber 1854). Aleksei Ivanovich Abrikossoff (1875–1955) was a Russian pathologist who, from 1918 onwards, worked as a professor of pathological anatomy at the first and second Moscow State University. In his publication of 1926, he proposed that the "myoma" he described originated from the skeletal muscles. In his 1931 publication, he then called the lesion "myoblastic myoma" (Abrikossoff 1931), a term which was modified to "myoblastoma" and widely used in the years to come. The granular cell feature of the lesion was first employed as a diagnostic term in 1927 ("rhabdomyome granulocytaire"; Diss 1927), a term still used in 1952 in one report ("rabdomioma granuloso"; Fialho and Hilario 1952).

A distinct site of GCT is the upper oro-respiratory tract (Strong et al. 1970; Lack et al. 1980), where two groups of GCT develop, i.e., the gingival tumors of infancy (congenital epulis of the granular cell type) and the group of non-gingival tumors (tongue, larynx, bronchi, and trachea). GCT also has a striking predilection for the gastrointestinal tract, 5–10 % of GCT occurring in this system, but specifically in the esophagus. There are more than 100 reported cases of colorectal GCTs, more commonly occurring in men in the 5th decade. Gastrointestinal GCTs also occur with descending frequency in the anal region, stomach, and small bowel.

General Morphological Features of Granular Cell Tumors

As specified in more detail below, the main histologic feature of GCT is the proliferation of medium-sized to rather large cells with a remarkably granular cytoplasm and usually small and dark nuclei. These cells form ill-defined nodular lesions with sometimes invasive-looking borders. Immunohistochemically, GCT is reactive for S100 protein (Stefansson and Wollmann 1982; Dhillon and Rode 1983) and sometimes for a lysosome-associated protein detected by the CD68 antibody (Filie et al. 1996), but S100 protein-negative GCT is also recognized, e.g., the congenital variants (Filie et al. 1996) and GCT in the meninges (Vang et al. 2000). Other and more variable immunoreactivities include vimentin, neuron-specific enolase (NSE), CD57, Leu-7, alpha-1-antitrypsin, alpha-1-antichymotrypsin, inhibin-alpha, and osteopontin (review: Ordonez and Mackay 1999).

Granular Cell Tumors of the Bile Ducts

Epidemiology

The first case of GCT involving the bile duct system was reported in 1952 and involved a 25-year-old black female with obstructive jaundice secondary to GCT located to the distal intrapancreatic part of the choledochus (Coggins 1952). The first reported case of GCT of the cystic duct (albeit interpreted to be a granular

rhabdomyoma) also goes back to 1952 (Fialho and Hilario 1952). GCT of the biliary tract is rare; it has been estimated that less than 1 % of all GCT originate in this compartment (Karakozis et al. 2000). Despite its rarity, granular cell tumor is the most common benign non-epithelial tumor of the extrahepatic bile ducts and occurring more commonly in the bile duct than in the gallbladder. A predilection for large extrahepatic bile ducts is evident from the published observations: most of the tumors were observed either in the common bile duct or the cystic duct, followed by the hepatic ducts and the gallbladder (less than 5 %). Among 77 cases reviewed in 2010, 39 were located to the common bile duct, 19 to the cystic duct (25 when combined with other locations), and 18 to the hepatic ducts (including combinations) (Patel and Jakate 2010). Biliary tract granular cell tumor clearly predominates in female patients. In a review of 77 cases reported in the literature, 65 patients were female, 12 were male (Patel and Jakate 2010). When screening the literature, it is striking to note that about two thirds of the cases have been observed in black women, at a median age of 32 years (Te Boekhorst et al. 2000). Adults are predominantly involved, of rather young age (mean and median based on a review of 42 cases: 40 and 34 years, respectively; Lafreniere et al. 1991), but biliary tract GCT also occurs in the pediatric age group (Reynolds et al. 2000). From the cases reported so far, it is striking to note that more than 90 % developed in female patients, with a preponderance of blacks. Overall, more than 70 reports are found in the literature.

Selected References Coggins 1952; Fialho and Hilario 1952; Duncan and Wilson 1957; Serpe et al. 1960; Goldman et al. 1967; Mackay et al. 1968; Whitmore et al. 1969; Christensen and Ishak 1970; Abt et al. 1971; Livolsi et al. 1973; Whisnant et al. 1974; Dursi et al. 1975; Kittredge and Baer 1975; Reul et al. 1975; Ishii et al. 1977; Savage and Devitt 1977; Raia et al. 1978; Zvargulis et al. 1978; Assor 1979; Farris and Faust 1979; Jain et al. 1979; Bocquet et al. 1980; Dewar et al. 1981; Manstein et al. 1981; Mauro and Jaques 1981; Aisner et al. 1982; Penalba et al. 1982; Balart et al. 1983; Barber 1984; Chandrasoma and Fitzgibbons 1984; Orenstein et al. 1984; Yamashina and Stemmermann 1984; Yamaguchi et al. 1985; Cheslyn-Curtis et al. 1986; Kienzle et al. 1986; Hobbiss et al. 1987; Butterly et al. 1988; Timberlake and Tachovsky 1988; Eisen et al. 1991; Lafreniere et al. 1991; Sanchez and Nauta 1991; Mulhollan et al. 1992; Lewis et al. 1993; Yang and Ortiz 1993; Yazdanpanah et al. 1993; Ferri Romero et al. 1994; Foulner 1994; Mackenzie et al. 1994; Butler and Brown 1998; Aubert et al. 1999; Dusoleil et al. 1999; Fairchild et al. 1999; Karakozis et al. 2000; Martin and Stulc 2000; Pongtippan et al. 2000; Reynolds et al. 2000; Te Boekhorst et al. 2000; Murakata and Ishak 2001; Principe et al. 2003; Altavilla et al. 2004; Heuer et al. 2004; Itkin and Trerotola 2004; Hoda et al. 2005; Lochan et al. 2006; Tonsi et al. 2006; Zaidi et al. 2007; Bilanovic et al. 2008; Bot et al. 2008; Patel and Jakate 2010; Saito et al. 2012; Kamaoui and Pilleul 2013.

Clinical and Imaging Features

Commonly, the lesions are solitary; in addition, multifocal biliary tract GCT has been found (Martin and Stulc 2000). Most cases present with signs of biliary stenosis, sometimes associated with right upper quadrant pain, jaundice, fatigue, and hepatomegaly. In a review, signs of biliary obstruction were identified in 41 out of 42 reported cases (Lafreniere et al. 1991). This stenosis can mimic cholangiocarcinoma, in particular when the tumor occupies a bile duct in the hilar/perihilar region of the liver, where the lesion may resemble Klatskin tumor (Sanchez and Nauta 1991; Te Boekhorst et al. 2000; Hoda et al. 2005; Lochan et al. 2006; Bilanovic et al. 2008). The sometimes marked dilatation of the bile duct may be confounded with choledochal cyst. Long-standing biliary obstruction by GCT can induce biliary cirrhosis (Fairchild et al. 1999). In part of the cases, GCT of the biliary system occurred concomitantly with calculous disease of the biliary tract (Goldman et al. 1967; Ishii et al. 1977; Mackenzie et al. 1994; Butler and Brown 1998).

Topography of Biliary Tract Granular Cell Tumors

Most biliary GCT develops in the common bile duct. GCT has been observed to originate from the most distal part of the distal common bile duct, sometimes in its intrapancreatic part (Coggins 1952; Manstein et al. 1981; Chandrasoma and Fitzgibbons 1984; Mackenzie et al. 1994; Aubert et al. 1999; Altavilla et al. 2004; Heuer et al. 2004; Hoda et al. 2005; Zaidi et al. 2007; Bot et al. 2008). Marked stenosis of the most distal segment of the common duct may mimic cholangiocarcinoma (Tonsi et al. 2006). Rarely, the tumor location is even more distal, involving the ampullary region (Khalid et al. 2005). In case GCT develops at the hepatic duct confluence, the stenosing lesion may mimic a hilar cholangiocarcinoma (Klatskin tumor) leading to extended duct or hilar resection (Sanchez and Nauta 1991; Te Boekhorst et al. 2000). Several observations document the occurrence of GCT in the cystic duct (Fialho and Hilario 1952; Serpe et al. 1960; Goldman et al. 1967; Mackay et al. 1968; Reul et al. 1975; Hobbiss et al. 1987; Timberlake and Tachovsky 1988). Cystic duct stenosis caused by GCT can induce cholecystitis (Barber 1984), gallbladder hydrops (Reul et al. 1975), or mucocele (Serpe et al. 1960; Mackay et al. 1968; Yamashina and Stemmermann 1984). GCT also develops in the gallbladder itself (Aisner et al. 1982).

Pathology

Macroscopic Features

Biliary GCT is characteristically small and lack a discrete capsule. When sectioned, they are whitish with a rubbery consistency. The lesions vary greatly in size. In a review of 31 cases where the tumor size was identifiable from the reports, 65 % measured less than 1 cm, 20 % were between 1 and 2 cm, 13 % were between 2 and 3 cm, and 3 % were between 3 and 4 cm in diameter. Larger tumors, i.e., those exceeding 2 cm, were localized to the common bile duct or the common hepatic duct (Lafreniere et al. 1991). The local duct extension of the tumor is mostly sectorial, but lesions encircling the duct are also encountered. The intramural growth can cause bile duct obstruction (Altavilla et al. 2004) followed by prestenotic duct dilatation (Chandrasoma and Fitzgibbons 1984). The mucosal surface may be eroded.

Histopathology

Histologically, the duct wall involved is infiltrated by rather large and round to ovoid tumor cells forming nests, fascicles, or sheets, sometimes separating the smooth muscle bundles of the duct wall (Fig. 1). These cells contain numerous small and large eosinophilic granules in the cytoplasm and sometimes PAS-positive granular aggregates. The tumor cells can show longitudinal stripes or streaks in the cytoplasm. These strings, already depicted in Abrikossoff's original in Fig. 3, may have led to the interpretation of a myogenic origin of the cells ("myoblasts" or "sarkoblasts"). These strings represent a distinct cytoplasmic alignment of lysosomes. This view is supported by ultrastructural findings of aligned membrane-limited and lysosome-containing compartments in granular cells (see Fig. 8 on p. 196 in Ordonez 1999 and Fig. 8 on p. 215 in Ordonez and Mackay 1999). More uncommonly, spindle cells are encountered. The nuclei are round and centrally placed; they contain 2–3 small nucleoli. Mitotic figures are not found. The tissue components encircling the GCT cell nests contain the

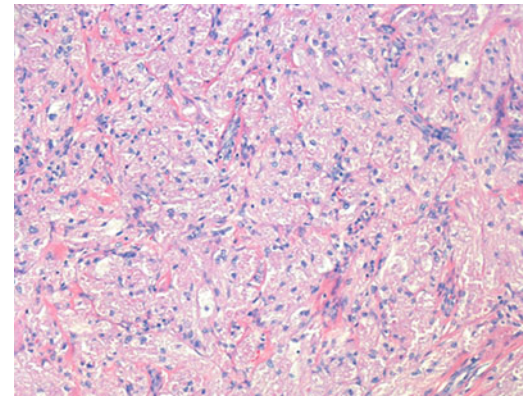

Fig. 1 Granular cell tumor of the bile duct. Nests of large tumor cells show a finely granular texture of the cytoplasm (hematoxylin and eosin stain)

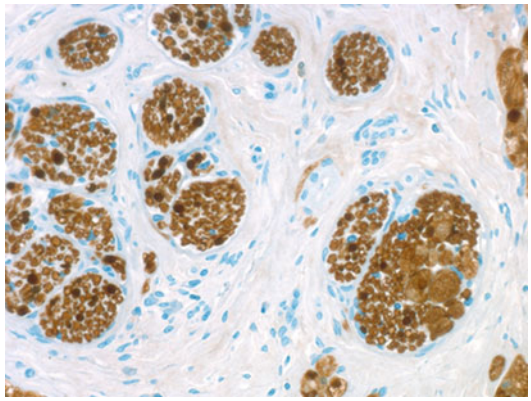

Fig. 2 Granular cell tumor of the bile duct with strong reactivity of the tumor cells for S100 protein (S100 protein immunoreactivity)

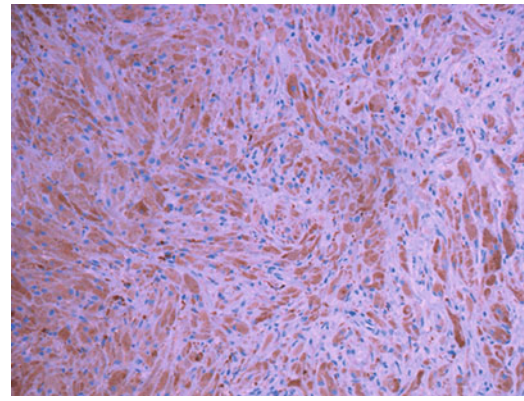

Fig. 3 Granular cell tumor of the bile duct. The neoplastic cells are consistently positive for inhibin-alpha (inhibin-alpha immunostain)

matrix proteins, laminin, and collagen IV (Miettinen et al. 1984; Reibel et al. 1985; Nathrath et al. 1986). In some instances, tumor cells are closely associated with small nerves and seem to invade perineural spaces (Altavilla et al. 2004).

Immunohistochemistry

The cells of granular cell tumors typically express S100 protein in a diffusely granular staining pattern in the cytoplasm and within the nuclei (Fig. 2). GCTs of the extrahepatic bile ducts and the gallbladder are diffusely positive for inhibin-alpha (Fig. 3; Murakata and Ishak 2001). The tumors also express the intermediate filament, nestin, in the cytoplasm and often with prominent membranous enhancement (Parfitt et al. 2006). Part of GCTs is reactive for CD68 (Filie et al. 1996).

Invasive Phenotype in Granular Cell Tumor

Although most GCTs are regarded to be benign, a locally invasive phenotype may be encountered. In a case analyzed by autopsy, the distal portion of the common bile duct displayed an ill-defined yellow homogeneous and rubbery area of thickening measuring up to 3.5 cm, with an intact overlying mucosa. Histologically, the growth occupied the entire wall of the duct and extended beyond the wall of the duct into the interstitial connective tissue of the pancreas, causing focal pancreatic atrophy (Coggins 1952).

Epithelial Hyperplasia Associated with Granular Cell Tumors

GCT developing beneath squamous epithelium of the skin is well known to induce a so-called pseudoepitheliomatous hyperplasia (PEH) of the overlying epithelium (Lack et al. 1980). PEH is sometimes mistaken to be a squamous cell carcinoma. Interestingly, PEH may involve non-squamous epithelial surfaces, in that it was found in the bronchial mucosa in a case of endobronchial GCT (Scala et al. 1999). Is there evidence that, similar to the situation in the skin, bile duct GCT induces a hyperplastic cholangiocyte reaction at the mucosal surface? In few situations, reactive atypia of the overlying epithelium and metaplastic pyloric glands may be observed.

Malignant Granular Cell Tumor: One or Several Entities

The first example of malignant GCT (localized to the urinary bladder) was described in 1945 (Ravich et al. 1945), and numerous cases have

since been reported, albeit not all of these are acceptable as malignant GCT. In a review from 1955 of the earlier reports, Gamboa stated that there were ten acceptable cases and rejected 21 cases that probably were rhabdomyosarcomas or alveolar soft part sarcomas (Gamboa 1955). Malignant GCT developing in the biliary tract has not been reported so far.

Differential Diagnosis

Nests of GCT can be confounded with accumulations of large macrophages/histiocytes with granular cytoplasm, collections of granular carcinoma cells, or amelanotic melanoma. Immunohistochemistry with the strong positivity for S100 protein in case of GCT will avoid interpretational errors.

Tumors with a Granular Cell Phenotype: Histogenetic Considerations, Do Granular Neoplastic Cells Involve a Lysosomal Disorder (Lysosomopathy)?

The cell of origin and the histogenesis of GCT have been a source of controversy (Abrikossoff 1926; Azzopardi 1956; Sobel and Churg 1964; Sobel et al. 1973; reviews: Ordonez 1999; Ordonez and Mackay 1999). The initial interpretation was that of a myogenic origin ("myoblasts" or "sarkoblasts"; Abrikossoff 1926, 1931; see below), but Abrikossoff already noted in his work of 1926 that, irrespective of the term he used ("myomas derived from the cross-striated musculature"), the five tumors he described were in part lacking cross-striation of the cells, in contrast to rhabdomyomas. He used the designation, rhabdomyoma nonstriocellulare ("non-cross-striated rhabdomyoma") to denote such lesions, and suggested a loss of cross-striation in myoblastic growths (Abrikossoff 1926).

Already in 1935, it was suggested that GCT might have a neural origin (Feyrter 1935). These authors and others emphasized the relationship between granular cells and peripheral nerves, resulting in the terms granular cell neuroma and granular cell neurofibroma (Fust and Custer 1948, 1949; Feyrter 1949, 1952). A derivation from (degenerated?) perineural fibroblastoid cells (Pearse 1950) or from neural crest cells (Buley et al. 1988) has also been discussed. Based on ultrastructural studies and on S100 protein reactivity, a Schwann cell origin has been suggested (Fisher and Wechsler 1962; Stefansson and Wollmann 1982; Armin et al. 1983; Mukai 1983), leading to one of the terms used to denote these lesions, i.e., granular cell schwannoma (Fisher and Wechsler 1962). A Schwannian cell derivation was also suggested by the finding of PGP 9.5 reactivity (Mahalingam et al. 2001) and Leu-7 reactivity in GCT cells (Smolle et al. 1985). Leu-7 is directed against a myelin-associated glycoprotein. On the other hand, other authors have suggested that GCT may rather be derived from uncommitted and possibly nerve-related mesenchymal cells (Miettinen et al. 1984).

Ultrastructural studies have found the cause of the light microscopic granularity of the cells' cytoplasm: the cells are rich in abnormally large lysosomes and myelin-like figures and may, albeit inconstantly, contain the so-called angulate bodies (Okada et al. 1990; Carstens and Yacoub 1993). Angulate bodies or lysosomes are, however, not restricted to a certain cell type, or, specifically, to Schwann cells, but occur in many situations and several cell types where the glycolipid composition of lysosomal membranes is changed. A further argument against a consistent role of Schwann cells is the marked reactivity of GCT cells for osteopontin, which is not detectable in schwannomas (Hoshi et al. 2005). It has been suggested that a distinct and possibly nerve sheath-related, CD34/vimentin-positive cell may also be involved (Maiorano et al. 2000).

Alveolar Soft Part Sarcoma

ICD-O code 9581/3

Introduction

Alveolar soft part sarcoma (ASPS) is a tumor entity first described in 1952 (Christopherson et al. 1952). Notwithstanding the characteristic histology, the cell lineage involved in this neoplasm is still unknown. There is no benign counterpart of this tumor. ASPS is rare; only about 0.5–1.0 % of all soft tissue sarcomas are ASPS. The neoplasm occurs predominantly in adolescents and young adults, more frequently in females, specifically in the age group under 25 years. The female predominance of ASPS has been proposed to be related to female possession of an extra X chromosome/non-inactivation of the ASPS X: autosome translocation fusion gene (Bu and Bernstein 2005; Folpe and Deyrup 2006). A little more than two thirds of the lesions have been observed in the buttock/thigh, legs, and chest wall or trunk, all other regions being clearly less common, apart from the tongue, which is relatively often involved in younger patients. About 3 % of the tumors develop in the retroperitoneal space (Weiss and Goldblum 2001; Anderson et al. 2005). ASPS is a malignancy with a characteristic metastatic pattern. Early metastasis to the lung, brain, and bone is common and has occurred in 21–65 % of patients by the time of initial presentation. Typically, the lungs are the first site to shoe metastatic disease, followed by the brain and bone, and other localizations, including the viscera, liver, heart, breast, and kidney. In particular for ASPS with unusual histology and/or locations, the detection of the ASPL/ASPSCR1-TFE3 transcript by the use of RT-PCR has been recommended (Williams et al. 2011). The translocation breakpoint can be identified by FISH, in particular dual-color, break-apart FISH (Zhong et al. 2010).

ASPS of the Hepatobiliary Tract

Primary hepatic ASPS was detected in a 47-year-old woman in whom abdominal imaging was induced by the observation of continuously elevated alkaline phosphatase levels. First CT and MR images showed a 5.1 × 2.8 cm-sized liver mass in the left lobe at the level of the portal hilum. During the next 3 months, CT images showed that the mass nearly doubled in size. Resection was planned but was deemed impossible because of involvement of the hepatic veins and the common hepatic duct. A surgical biopsy revealed the histology of ASPS (see below). Fluorescent ISH assays confirmed a translocation on Xp11.2 (TFE3 gene) in 75 % of tumor cells, consistent with an ASPL/TFE3 fusion. Comprehensive CT and PET studies did not show a lesion outside the liver, and MR findings of both lower extremities were also negative. In a later work-up, the tumor was regarded resectable. The hepatectomy specimen showed a 14.2 × 12.4 × 6.2 cm tan-to-pink, centrally necrotic and focally hemorrhagic tumor of the same histologic presentation as previously. Disease progressed, with metastases, and the patient died 22 months after resection (Shaddix et al. 2008).

General Histologic Features of Alveolar Soft Part Sarcoma

Histologically, the pattern is uniform and characterized by groups or compartments of cells, these structures being separated from each other by thin-walled vascular channels and matrix septa, resulting in a (pseudo)alveolar-like image giving the tumor its name. This alveoloid pattern is furthermore promoted by loss of cell adhesion and thus gap formation caused by regressive changes commonly occurring in the center of the cellular compartments (Weiss and Goldblum 2001; Khanna et al. 2008). At the periphery of the lesion, abnormal and dilated blood vessels are a typical feature, and angioinvasion is typical for this neoplasm. The neoplastic cells are large and rounded, sometimes polygonal, with distinct cell borders and one or more large vesicular nuclei with usually small nucleoli. A part of the cells is diffusely PAS-positive owing to an elevated glycogen content. The mitotic count is rather low.

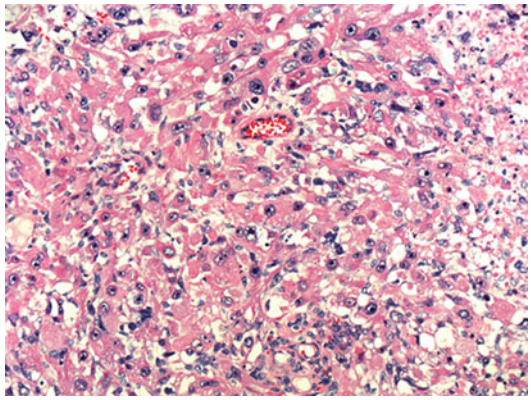

Fig. 4 Hepatic metastasis of alveolar soft part sarcoma. Large and highly atypical neoplastic cells with nuclei having prominent nuclei exhibit an eosinophilic and granular cytoplasm (hematoxylin and eosin stain)

In PAS stains, a fraction of the cells contain PAS-positive, diastase-resistant rhomboid or rod-shaped crystalloid inclusions, originally recognized and described in 1959 (Masson 1959). This phenomenon is found in about 80 % of ASPS (Weiss and Goldblum 2001). A similar type of crystalloids has been observed in large epithelioid smooth muscle cells of angiomyolipoma (Mukai et al. 1992). Apart from crystalloids, uncrystallized granules are found in ASPS cells, consisting of an aggregation of uncrystallized filaments with a diameter of 6 nm (Mukai et al. 1990). The precrystalline cytoplasmic inclusions have been shown to contain monocarboxylate transporter 1 (MCT1) and CD147 (see below; Ladanyi et al. 2002; comment: Weiss 2002). Immunohistochemically, reactivity for vimentin, muscle-specific actin, and desmin seems to be established (Rekhi et al. 2012), but part of the cells may be positive for S100 protein and/or neuron-specific enolase, while cytokeratins are negative. Immunohistochemical positivity for TFE3 (transcription factor E3, see below) is a useful marker for the diagnosis of ASPS (Williams et al. 2011; Rekhi et al. 2012). CD147 (basigin, EMMPRIN) can also serve as a diagnostic marker for ASPS. ASPS harboring the TFE3 gene fusions is immunohistochemically positive for cathepsin K (Martignoni et al. 2011).

Differential Diagnosis

The only pathologic differential diagnosis is ASPS metastatic to the liver (Fig. 4; Font et al. 1982; Casanova et al. 2000; Portera et al. 2001; Pennacchioli et al. 2010; Silas et al. 2010). Liver metastases of ASPS are, however, uncommon events, as this neoplasm usually metastasizes to the lungs, bones, brain, and lymph nodes.

References

Abrikossoff AI (1926) Ueber Myome, ausgehend von der quergestreiften willkürlichen Muskulatur. Virchows Arch Anat Physiol Klin Med 260:215–233

Abrikossoff AI (1931) Weitere Untersuchungen über Myoblastenmyome. Virchows Arch Pathol Anat 280:723–740

Abt AB, Feinberg E, Kunitz S (1971) Granular cell myoblastoma of the extrahepatic biliary tract. Mt Sinai J Med 38:457–461

Aisner SC, Khaneja S, Ramirez O (1982) Multiple granular cell tumors of the gallbladder and biliary tree. Report of a case. Arch Pathol Lab Med 106:470–471

Altavilla G, Brotto M, Busatto G, Boccu C, Ragni L (2004) Granular cell tumor of the intrapancreatic common bile duct: one case report and review of the literature. Ultrastruct Pathol 28:171–176

Anderson ME, Hornicek FJ, Gebhardt MC, Raskin KA, Mankin HJ (2005) Alveolar soft part sarcoma: a rare and enigmatic entity. Clin Orthop Relat Res 438:144–148

Armin A, Connelly EM, Rowden G (1983) An immunoperoxidase investigation of S-100 protein in granular cell myoblastomas: evidence for Schwann cell derivation. Am J Clin Pathol 79:37–44

Assor D (1979) Granular cell myoblastoma involving the common bile duct. Am J Surg 137:673–675

Aubert A, Palazzo L, Meduri B, Lasser P, Chiche R, De Baecque C (1999) Granular cell tumor of the common bile duct. Contribution of endoscopic ultrasonography in 2 cases (in French). Gastroenterol Clin Biol 23:10190–11093

Azzopardi JG (1956) Histogenesis of the granular-cell myoblastoma. J Pathol Bacteriol 71:85–94

Balart LA, Hines C, Mitchell W (1983) Granular cell schwannoma of the extrahepatic biliary system. Am J Gastroenterol 78:297–300

Barber CJ (1984) Granular cell tumour of the cystic duct. A cause of cholecystitis. JR Coll Surg Edinb 29:56–57

Bilanovic D, Boricic I, Zdravkovic D, Randjelovic T, Stanislavljevic N, Tokovic B (2008) Granular cell tumor of the common hepatic duct presenting as

cholangiocarcinoma and acute acalculous cholecystitis. Acta Chir Iugosl 55:99–101
Bocquet L, Vissuzaine C, Grossin M, Boutelier P (1980) Granular cell tumor of the common bile duct (in French). Arch Anat Cytol Pathol 28:360–364
Bot J, Wartel F, De Beauce S, Maunoury V, Mariette C (2008) Granular cell tumor of the common bile duct (in French). J Chir 145:374–375
Bu X, Bernstein L (2005) A proposed explanation for female predominance in alveolar soft part sarcoma. Noninactivation of X: autosome translocation fusion gene? Cancer 103:1245–1253
Buley et al. 1988. http://www.ncbi.nlm.nih.gov/pubmed/2452781
Butler JD, Brown KM (1998) Granular cell tumor of the extrahepatic biliary tract. Am Surg 64:1033–1036
Butterly LF, Schapiro RH, LaMuraglia GM, Warshaw AL (1988) Biliary granular cell tumor: a little-known curable bile duct neoplasm of young people. Surgery 103:328–334
Carstens PH, Yacoub O (1993) Importance of angulate bodies in the diagnosis of granular cell tumors (schwannomas). Ultrastruct Pathol 17:271–278
Casanova M, Ferrari A, Bisogno G, Cecchetto G, Basso E, De Bernardi B, Indolfi P et al (2000) Alveolar soft part sarcoma in children and adolescents: a report from the Soft-Tissue Sarcoma Italian Cooperative Group. Ann Oncol 11:1445–1449
Chandrasoma P, Fitzgibbons P (1984) Granular cell tumor of the intrapancreatic common bile duct. Cancer 53:2178–2182
Cheslyn-Curtis S, Russell RC, Rode J, Dhillon AP (1986) Granular cell tumour of the common bile duct. Postgrad Med J 62:961–963
Christensen AH, Ishak KG (1970) Benign tumors and pseudotumors. Report of 180 cases. Arch Pathol 90:423–432
Christopherson WM, Foote FW, Stewart FW (1952) Alveolar soft-part sarcomas: structurally characteristic tumors of uncertain histogenesis. Cancer 5:10–111
Coggins RP (1952) Granular-cell myoblastoma of common bile duct; report of a case with autopsy findings. AMA Arch Pathol 54:398–402
Dewar J, Dooley JS, Lindsay I, George P, Sherlock S (1981) Granular cell myoblastoma of the common bile duct treated by biliary drainage and surgery. Gut 22:70–76
Dhillon AP, Rode J (1983) Immunohistochemical studies of S100 protein and other neural characteristics expressed by granular cell tumour. Diagn Histopathol 6:23–28
Diss A (1927) Un nouveau type de tumeur musculaire; le rhabdomyome granulocytaire. Bull Cancer 16:862–865
Duncan JT, Wilson H (1957) Benign tumor of the common bile duct. Ann Surg 145:271–274
Dursi JF, Hirschl S, Gomez R, Mersheimer WL (1975) Granular cell myoblastoma of the common bile duct: report of a case and review of the literature. Rev Surg 32:305–310
Dusoleil A, Lahoud S, Condat B, Bellanger J, Fritsch J, Berthelot P, Bedossa P, Pelletier G, Buffet C (1999) Granular cell tumor of the biliary tract and bile ducts (in French). Gastroenterol Clin Biol 23:993–994
Eisen RN, Kirby WM, O'Quinn JL (1991) Granular cell tumor of the biliary tree. A report of two cases and a review of the literature. Am J Surg Pathol 15:460–465
Fairchild RB, Freeman R, Salah Hammad EM, Rohrer R (1999) Granular cell tumor with cirrhosis and transplantation. Transplantation 68:315–317
Farris KB, Faust BF (1979) Granular cell tumors of biliary ducts. Report of two cases and review of the literature. Arch Pathol Lab Med 103:510–512
Ferri Romero J, Carrion Tomas A, Estrada Caballero JL, Fernandez Gimenez F, Ceballos GS, Camunas MF (1994) Granular cell tumor of the bile duct: an infrequent location (in Spanish). Rev Esp Enferm Dig 85:217–219
Feyrter F (1935) Ueber eine eigenartige Geschwulstform des Nervengewebes im menschlichen Verdauungsschlauch. Virchows Arch Pathol Anat Physiol 285:480–501
Feyrter F (1949) Ueber die granulären neurogenen Gewächse. Beitr Pathol Anat 110:181
Feyrter F (1952) Ueber die granulären Neurome (sogenannte Myoblastome). Virchows Arch Pathol Anat 322:66–72
Fialho F, Hilario J (1952) Rabdomioma granuloso do cistico. Rev Bras Med 9:616–618
Filie AC, Lage JM, Azumi N (1996) Immunoreactivity of S100 protein, alpha-1-antitrypsin, and CD68 in adult and congenital granular cell tumors. Mod Pathol 9:888–892
Fisher ER, Wechsler H (1962) Granular cell myoblastoma – a misnomer. Electron microscopic and histochemical evidence concerning its Schwann cell derivation and nature (granular cell schwannoma). Cancer 15:936–954
Folpe AL, Deyrup AT (2006) Alveolar soft-part sarcoma: a review and update. J Clin Pathol 59:1127–1132
Font RL, Jurco S, Zimmerman LE (1982) Alveolar soft-part sarcoma of the orbit: a clinicopathologic analysis of seventeen cases and a review of the literature. Hum Pathol 13:569–579
Foulner D (1994) Case report: granular cell tumour of the biliary tree – the sonographic appearance. Clin Radiol 49:503–504
Fust JA, Custer RP (1948) Granular cell "myoblastoma" and granular cell "neurofibromas"; separation of neurogenous tumors from the myoblastoma group. Am J Pathol 24:674
Fust JA, Custer RP (1949) On neurogenesis of so-called granular cell myoblastoma. Am J Clin Pathol 19:522–535
Gamboa LG (1955) Malignant granular-cell myoblastoma. AMA Arch Pathol 60:663–668

Goldman LI, Lemole G, Ellis R, Rosemond GP (1967) Granular cell myoblastoma of the cystic duct. JAMA 200:1185–1186

Heuer T, Lahrtz HJ, Gerards H, Berkovic D, Kania U, Reis HE (2004) Posthepatic icterus caused by a solitary granular cell tumor of the common bile duct (in German). Z Gastroenterol 42:323–325

Hobbiss JH, Hasleton P, Kahn MK, Turner L (1987) Granular cell myoblastoma of the cystic duct: a case report and review of the literature. J R Coll Surg Edinb 32:117–118

Hoda RS, Minamiguchi S, Lewin DN, Foody W, Weselow G, Wildi SM (2005) Granular cell tumor of the biliary system: a report of 2 cases with cytologic diagnosis on endoscopic brushing. Acta Cytol 49:199–203

Hoshi et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/15998396

Ishii T, Iri H, Yamamoto S, Shinowawa Y, Sudoh M (1977) Granular cell myoblastoma of the gallbladder. Am J Gastroenterol 68:38–44

Itkin M, Trerotola SO (2004) SIR 2004 film panel case: multicentric granular cell tumor with biliary, subcutaneous, and breast involvement. J Vasc Interv Radiol 15:1021–1023

Jain KM, Hastings OM, Rickert RR, Swaminathan AP, Lazaro EJ (1979) Granular cell tumor of the common bile duct. Case report and review of the literature. Am J Gastroenterol 71:401–407

Kamaoui I, Pilleul F (2013) Granular cell tumour of the common bile duct: a condition to be aware of. Diagn Interv Imaging 94:24–326

Karakozis S, Gongora E, Zapas JL, He P, Krishnan J, Kirkpatrick JR (2000) Granular cell tumors of the biliary tree. Surgery 128:113–115

Khalid K, Alam MK, Wafaa AA, Ibrahim AT (2005) Granular cell tumour of the ampulla of Vater. J Postgrad Med 51:36–38

Khanna P, Paidas CN, Gilbert-Barness E (2008) Alveolar soft part sarcoma: clinical, histopathological, molecular, and ultrastructural aspects. Fetal Pediatr Pathol 27:31–40

Kienzle HF, Bahr R, Stolte M (1986) Granular cell tumor of the common bile duct (in German). Dtsch Med Wochenschr 111:197

Kittredge RD, Baer JW (1975) Percutaneous transhepatic cholangiography. Problems in interpretation. Am J Radiol 125:35–46

Lack EE, Worsham GF, Callihan MD, Crawford BE, Klappenbach S, Rowden G, Chun B (1980) Granular cell tumor: a clinicopathologic study of 110 patients. J Surg Oncol 33:301–316

Ladanyi M, Antonescu CR, Drobnjak M, Baren A, Lui MY, Golde DW, Cordon-cardo C (2002) The precrystalline cytoplasmic granules of alveolar soft part sarcoma contain monocarboxylate transporter 1 and CD147. Am J Pathol 160:1215–1221

Lafreniere R, Demetrick DJ, Benediktsson H (1991) Granular cell neoplasm of the extrahepatic biliary tree: morphological, ultrastructural, and immunohistochemical study and review of the literature. J Surg Oncol 46:60–66

Lewis WD, Buell JF, Jenkins RL, Burke PA (1993) Biliary duct granular cell tumor: a rare but surgically curable benign tumor. HPB Surg 6:311–317

Livolsi VA, Perzin KH, Badder EM, Price JB, Porter M (1973) Granular cell tumors of the biliary tract. Arch Pathol 95:13–17

Lochan R, Balupuri S, Bennett MK, Manas DM (2006) Granular cell tumor as an unusual cause of obstruction at the hepatic hilum: report of a case. Surg Today 36:934–936

Mackay B, Elliott GB, Path FC, MacDougall JA (1968) Granular cell myoblastoma of the cystic duct: report of a case with electron microscope observations. Can J Surg 11:44–51

Mahalingam M, LoPiccolo D, Byers HR (2001) Expression of PGP 9.5 in granular cell nerve sheath tumors: an immunohistochemical study of six cases. J Cutan Pathol 28:282–286

Maiorano et al. 2000. http://www.ncbi.nlm.nih.gov/pubmed/10890560

Manstein ME, McBrearty FX, Pellechia PE, Paskin DL (1981) Granular cell tumor of the common bile duct. Dig Dis Sci 26:938–942

Martignoni G, Gobbo S, Camparo P, Brunelli M, Munari E, Segala D, Pea M, Bonetti F et al (2011) Differential expression of cathepsin K in neoplasms harboring TFE3 gene fusions. Mod Pathol 24:1313–1319

Martin RC, Stulc JP (2000) Multifocal granular cell tumor of the biliary tree: case report and review. Gastrointest Endosc 51:238–240

Masson P (1959) Tumeurs Humaines: histologie, diagnostic, et techniques, 2nd edn. Librairie Maloine, Paris

Mauro MA, Jaques PF (1981) Granular-cell tumors of the esophagus and common bile duct. J Can Assoc Radiol 32:254–256

Miettinen M, Lehtonen E, Lehtola H, Ekblom P, Lehto VP, Virtanen I (1984) Histogenesis of granular cell tumour – an immunohistochemical and ultrastructural study. J Pathol 142:221–229

Mukai M (1983) Immunohistochemical localization of S-100 protein and peripheral nerve myelin proteins (P2 protein, P0 protein) in granular cell tumors. Am J Pathol 112:139–146

Mukai M, Torikata C, Iri H (1990) Alveolar soft part sarcoma: an electron microscopic study especially of uncrystallized granules using a tannic acid-containing fixative. Ultrastruct Pathol 14:41–50

Mukai M, Torikata C, Iri H, Tamai S, Sugiura H, Tanaka Y, Sakamoto M, Hirohashi S (1992) Crystalloids in angiomyolipoma. 1. A previously unnoticed phenomenon of renal angiomyolipoma occurring at a high frequency. Am J Surg Pathol 16:1–10

Mulhollan TJ, Ro JY, el-Naggar AK, Sahin AA, Ayala AG (1992) Granular cell tumor of the biliary tree. Am J Surg Pathol 16:204–206

Murakata LA, Ishak KG (2001) Expression of inhibin-alpha by granular cell tumors of the gallbladder and extrahepatic bile ducts. Am J Surg Pathol 25:1200–1203

Nathrath et al. 1986. http://www.ncbi.nlm.nih.gov/pubmed/3004014

Okada H, Yamamoto H, Kawana T, Katoh T, Kozawa Y, Izumi H (1990) Granular cell tumor of the tongue: an electron microscopical and immunohistochemical study. J Nihon Univ Sch Dent 32:35–43

Ordonez 1999. http://www.ncbi.nlm.nih.gov/pubmed/10410172

Ordonez and Mackay 1999. http://www.ncbi.nlm.nih.gov/pubmed/10503740

Orenstein HH, Brenner LH, Nay HR (1984) Granular cell myoblastoma of the extrahepatic biliary system. Am J Surg 147:827–831

Parfitt JR, Mclean CA, Joseph MG, Streutker CJ, Al-Haddad S, Driman DK (2006) Granular cell tumours of the gastrointestinal tract: expression of nestin and clinicopathological evaluation of 11 patients. Histopathology 48:424–430

Patel AJ, Jakate SM (2010) Granular cell tumor of the biliary tract. Gastroenterol Hepatol 6:331–336

Pearse AGE (1950) The histogenesis of granular-cell myoblastoma (? granular-cell perineural fibroblastoma). J Path Bact 62:351–362

Penalba C, Vallot T, Cerf M, de Mestier P, Gouerou H (1982) Granular cell tumor of the biliary tract. Apropos of a case (in French). Ann Chir 36:723–726

Pennacchioli E, Fiore M, Collini P, Radaelli S, Dileo P, Stacchiotti S, Casali PG, Gronchi A (2010) Alveolar soft part sarcoma: clinical presentation, treatment, and outcome in a series of 33 patients at a single institution. Ann Surg Oncol 17:3229–3233

Pongtippan A, Suyabodha T, Wongmeekiat A, Kositchaiwat S, Bunyaratvej S (2000) Granular cell tumor of the common bile duct: a case report. J Med Assoc Thai 83(suppl 1):S7–S11

Portera CA, Ho V, Patel SR, Hunt KK, Feig BW, Respondek PM, Yasko AW, Benjamin RS et al (2001) Alveolar soft part sarcoma: clinical course and patterns of metastasis in 70 patients treated at a single institution. Cancer 91:585–591

Principe A, Ercolani G, Bassi F, Paolucci U, Raspadori A, Turi P, Beltempo P, Grazi GL, Cavallari A (2003) Diagnostic dilemmas in biliary strictures mimicking cholangiocarcinoma. Hepatogastroenterology 50:1246–1249

Raia AA et al (1978) Mioblastoma de coledoco. Rev Assoc Med Brasil 24:379–380

Ravich A, Stout AP, Ravich RA (1945) Malignant granular cell myoblastoma involving the urinary bladder. Ann Surg 121:361–372

Reibel J, Wewer U, Albrechtsen R (1985) The pattern of distribution of laminin in neurogenic tumors, granular cell tumors, and nevi of the oral mucosa. Acta Pathol Microbiol Immunol Scand A 93:41–47

Rekhi B, Ingle A, Agarwal M, Puri A, Laskar S, Jambhekar NA (2012) Alveolar soft part sarcoma 'revisited': clinicopathological review of 47 cases from a tertiary cancer centre, including immunohistochemical expression of TFE3 in 22 cases and 21 other tumours. Pathology 44:11–17

Reul GJ, Rubio PA, Berkman NL (1975) Granular cell myoblastoma of the cystic duct. A case report with hydrops of the gallbladder. Am J Surg 129:583–584

Reynolds EM, Tsivis PA, Long JA (2000) Granular cell tumor of the biliary tree in a pediatric patient. J Pediatr Surg 35:652–654

Saito J, Kitagawa M, Kusanagi H, Kano N, Ishii E, Nakaji S, Hirata N, Hoshi K (2012) Granular cell tumor of the common bile duct: a Japanese case. World J Gastroenterol 18:6324–6327

Sanchez JA, Nauta RJ (1991) Resection of a granular cell tumor at the hepatic confluence. A precarious location for a benign tumor. Am Surg 57:446–450

Savage A, Devitt P (1977) Granular cell myoblastoma of the biliary tree. Postgrad Med 53:574–577

Scala R, Naldi M, Fabianelli F, Coniglio G, Guadagni G, Archinucci I, Rossi M (1999) Endobronchial granular cell tumor. Monaldi Arch Chest Dis 54:404–406

Serpe SJ, Todd D, Baruch H (1960) Cholecystitis due to granular cell myoblastoma of the cystic duct. Am J Dig Dis 5:824–826

Shaddix KK, Fakhre C-P, Nields WW, Steers JL, Hewitt WR, Menke DM (2008) Primary alveolar soft-part sarcoma of the liver: anomalous presentation of a rare disease. Am Surg 74:43–46

Silas OA, Adoga AA, Manasseh AN, Echejoh GO, Vhriterhire RA, Mandong BM (2010) Persistent alveolar soft-part sarcoma with liver metastasis: a case report. J Med Case Reports 4:233

Smolle et al. 1985. http://www.ncbi.nlm.nih.gov/pubmed/2581359

Sobel HJ, Churg J (1964) Granular cells and granular cell lesions. Arch Pathol 77:132–141

Sobel HJ, Schwarz R, Marquet E (1973) Light-and electron-microscope study of the origin of granular-cell myoblastoma. J Pathol 109:101–111

Stefansson K, Wollmann RL (1982) S-100 protein in granular cell tumors (granular cell myoblastomas). Cancer 49:1834–1838

Strong EW, McDivitt RW, Brasfield RD (1970) Granular cell myoblastoma. Cancer 25:415–422

Te Boekhorst DS, Gerhards MF, van Gulik TM, Gouma DJ (2000) Granular cell tumor at the hepatic duct confluence mimicking Klatskin tumor. A report of two cases and a review of the literature. Dig Surg 17:299–303

Timberlake GA, Tachovsky TJ (1988) Granular cell myoblastoma of the cystic duct. Mil Med 153:98–99

Tonsi A, Standish R, Desai C, Davidson BR (2006) Granular cell tumour of the bile duct mimicking distal cholangiocarcinoma: one case report and review of the literature. Minerva Chir 61:247–255

Vang R, Heck K, Fuller GN, Medeiros LJ (2000) Granular cell tumor of intracranial meninges. Clin Neuropathol 19:41–44

Weber CO (1854) Anatomische Untersuchung einer hypertrophischen Zunge nebst Bemerkungen über die Neubildung quergestreifter Muskulatur. Arch Pathol Anat Physiol Klin Med 7:115–126

Weiss SW (2002) Alveolar soft part sarcoma. Are we at the end or just the beginning of our quest? Am J Pathol 160:1197–1199

Weiss SW, Goldblum JR (2001) Enzinger and Weiss's soft tissue tumors, 4th edn. Mosby, St Louis

Whisnant DJ, Bennett SE, Huffman SR, Weiss DL, Parker JC, Griffen WO (1974) Common bile duct obstruction by granular cell tumor (Schwannoma). Am J Dig Dis 19:471–476

Whitmore JT, Whitley JP, LaVerde P, Cerda JJ (1969) Granular cell myoblastoma of the common bile duct. Am J Dig Dis 14:516–520

Williams A, Bartle G, Sumathi VP, Meis JM, Mangham DC, Grimer RJ, Kindblom LG (2011) Detection of ASPL/TFE3 fusion transcriptions and the TFE3 antigen in formalin-fixed, paraffin-embedded tissue in a series of 18 cases of alveolar soft part sarcoma: useful diagnostic tools in cases with unusual histologic features. Virchows Arch 458:291–300

Yamaguchi K, Kuroki S, Daimaru Y, Hashimoto H, Enjoji M (1985) Granular cell tumor of the gallbladder. Report of a case. Acta Pathol Jpn 35:687–691

Yamashina M, Stemmermann GN (1984) Granular cell tumor: unusual cause for mucocele of gallbladder. Am J Gastroenterol 79:701–703

Yang KL, Ortiz L (1993) Granular cell myoblastoma involving multiple organs. South Med J 86:478–479

Yazdanpanah Y, Maunoury V, Saudemont A, Bouchind'Homme B, Houcke P, Lecomte-Houcke M, Paris JC (1993) Granular cell tumor of the choledochus (in French). Gastroenterol Clin Biol 17:607

Zaidi AH, Ashraf M, Mamoon N, Amin MU (2007) Granular cell tumour of the common bile duct. J Coll Physicians Surg Pak 17:572–573

Zhong M, De Angelo P, Osborne L, Keane-Tarchichi M, Goldfischer M, Edelmann L et al (2010) Dual-color, break-apart FISH assay on paraffin-embedded tissues as an adjunct to diagnosis of Xp11 translocation renal cell carcinoma and alveolar soft part sarcoma. Am J Surg Pathol 34:757–766

Zvargulis JE, Keating JP, Askin FB, Ternberg JL (1978) Granular cell myoblastoma. A case of biliary obstruction. Am J Dis Child 132:68–70

Synovial-Like Neoplasms (Synovial Sarcoma) of the Liver

70

Contents

Abstract

Synovial sarcoma is an aggressive soft tissue sarcoma of uncertain histogenesis with a predilection for the deep soft tissues of paraarticular regions of the extremities. The tumor predominantly develops in younger adults and accounts for 5–10 % of all soft tissue sarcomas. Apart from extremities, this sarcoma also occurs in various other sites, including visceral organs, the heart and large blood vessels. Most instances of hepatic manifestations of this neoplasm are metastases. However, few cases of monophasic primary hepatic synovial sarcoma have been reported. The tumors are sometimes large and hemorrhagic. Histologically, spindle cells and hemangiopericytoma-like cells prevail, with variable admixtures of epithelioid cells. The tumors are associated with the typical SYT-SSX1 or SYT-SSX2 rearrangement and the corresponding fusion proteins, as in soft tissue synovial sarcomas. Very rarely, synovial sarcoma develops as a primary lesion in the biliary tract.

Synovial Sarcoma of the Liver

ICD-O code 9040/3

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_70

Introduction

Synovial sarcoma is a clinically and morphologically well-defined malignant neoplasm of still uncertain histogenesis that develops chiefly in younger adults (median age, 30 years), with a predilection for the deep soft tissues of paraarticular regions of the extremities. The tumor represents 5–10 % of all soft tissue sarcomas. Other important primary locations include the oropharyngeal area, parapharynx and larynx, abdominal and chest walls, skeletal system, retroperitoneal space, heart and blood vessels, genital tract, salivary glands, and several visceral organs, in particular lungs and kidneys.

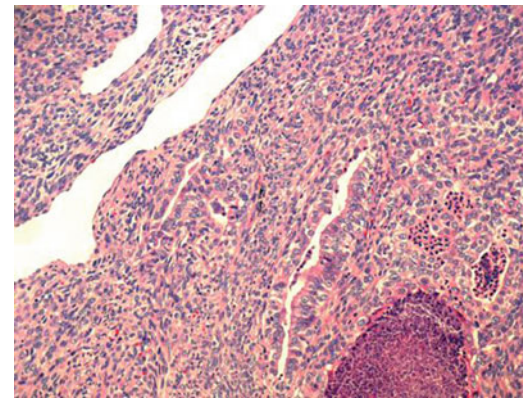

Fig. 1 Synovial sarcoma of the liver. This hypercellular spindle cell sarcoma contains several foci of epithelial formation with a slit-like lumen. Focal necrosis, typical for grade 3 sarcomas, is present (*right bottom* corner; hematoxylin and eosin stain)

Synovial Sarcoma Primary to the Liver

Intra-abdominal synovial sarcoma is a rare manifestation of this neoplasm, accounting to about 3–4 % of the cases (Fisher et al. 2004). Most instances of hepatic manifestations of synovial sarcoma are metastases. In the literature, few cases of monophasic primary hepatic synovial sarcomas are found (Srivastava et al. 2005; Holla et al. 2006; Romeo et al. 2015; Zajak et al. 2015). Hepatic synovial sarcomas show the same histologic and immunohistochemical phenotypes as extrahepatic tumors (Figs. 1, 2, and 3). A female patient (60 years of age) presented with a dominant tumor mass of 10 cm diameter in the right liver lobe, associated with multiple satellite nodules (Srivastava et al. 2005). The resection specimen of the right lobe shows five relatively well-circumscribed, diffusely hemorrhagic, tan-gray nodules, the largest measuring 10 cm in its greatest diameter. Some of the nodules exhibited gross necrosis. Histologically, the nodules were unencapsulated and had a well-defined expansile margin compressing the adjacent liver substance. The tumor was composed of hypercellular neoplastic tissue with spindle cells arranged in a fascicular or storiform pattern. Hypocellular areas with myxoid features and areas with a hemangiopericytoma-like vascular pattern were also in evidence. The tumor revealed a high proliferative activity, with about 20 mitotic figures

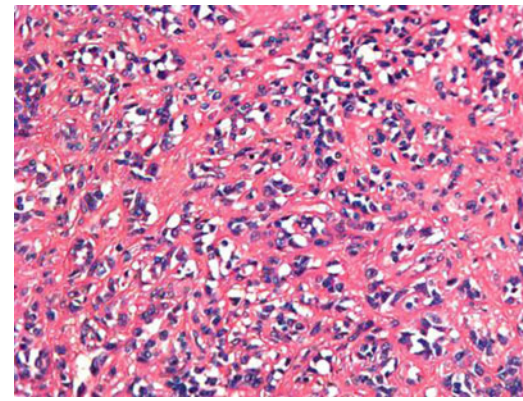

Fig. 2 Synovial sarcoma of the liver. In this case, only abortive epithelial structures are recognizable (hematoxylin and eosin stain)

per 10 HPs, and vascular invasion was detectable. Immunohistochemically, the cells are reactive for vimentin and Bcl-2, and weakly for muscle-specific and smooth muscle actin, but not for desmin, CD34, S-100 protein, and epithelial markers. Cytogenetic analysis showed several clonal abnormalities, among them an abnormal chromosome X due to a translocation of chromosomes X and 18, with the breakpoints in the SSX1 and SSX2 (band Xp11) and SYT (band 18q11) gene regions, confirming the diagnosis of a monophasic synovial sarcoma. The primary location to the liver was based on a detailed physical

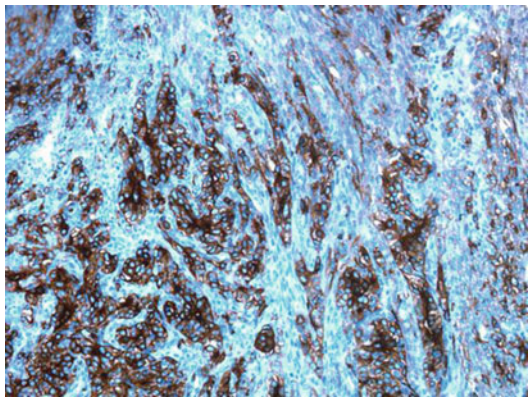

Fig. 3 Synovial sarcoma of the liver. Solid formations of epithelial cells, but not the spindle cells, are strongly cytokeratin reactive (AE1/AE3 cytokeratin immunostain)

examination and imaging workup that failed to reveal a primary tumor elsewhere, but an autopsy was not performed (Srivastava et al. 2005). A second case was that of 18-year-old female patient presenting with a history of fatigue, nausea, vomiting, and abdominal fullness. A CT scan and an angiogram showed a large mass extending from the left lobe of the liver. Liver resection revealed a mass of up to 21 cm diameter. Histology displayed a monophasic synovial sarcoma. Cytogenetic study revealed a reciprocal translocation between the short arm of the X chromosome and the long arm of chromosome 18 with breakpoints at band Xp11.2 and band 18q11.2 (Holla et al. 2006). Primary synovial sarcoma can also develop in ligaments associated with the liver, e.g., the triangular ligament on the superior surface of the liver (Rao et al. 2013).

Primary Synovial Sarcoma of the Biliary Tract

A 51-year-old male patient presented with a 1-month history of obstructive jaundice, and ERCP revealed an irregular mass in the common bile duct. MRCP showed an intraluminal mass in the common bile duct with likely extension into the neck of the gallbladder. The tumor was resected through pylorus-preserving pancreaticoduodenectomy and showed to by synovial sarcoma. No other manifestation of this malignancy was detectable (Qayum et al. 2008).

Visceral Synovial Sarcoma in the Pediatric and Adolescent Age Groups

Synovial sarcoma is a malignancy that also develops in infants, children, and adolescents (Kerouanton et al. 2014; Soole et al. 2014; Ferrari et al. 2015). In infants, this malignancy is extremely rare, with an annual incidence of 0.5 per million (Köse et al. 2014). Pediatric synovial sarcoma can metastasize to the liver. Primary monophasic synovial sarcoma of the liver was diagnosed in 13-year-old boy presenting with a painful mass in the right liver lobe, the tumor having a SS18-SSX1 fusion transcript (Xiong et al. 2013).

Synovial Sarcoma Metastatic to the Liver

Synovial sarcoma is known to metastasize to the liver, both from primary tumors in soft tissues and visceral organs, including primaries in the kidneys or prostate (Wang et al. 2010; Zhang et al. 2014). Soft tissue synovial sarcoma metastasizing to the liver was observed in a premature newborn (Köse et al. 2014).

Differential Diagnosis

The liver may secondarily be involved in those exceptional instances where intravascular synovial sarcoma develops in the inferior vena cava (Shaw and Lais 1993). Synovial sarcoma can develop in structures around the liver compartment, such as the gastrocolic ligament (Ko et al. 1998), the stomach (Billings et al. 2000; Makhlouf et al. 2008), the duodenum (Company Campins et al. 2009), the omentum (sometimes with involvement of the liver substance; Wang et al. 2006), and the retroperitoneal space (Shmookler 1982).

General Histologic and Immunohistochemical Features of Synovial Sarcoma

Synovial sarcoma has a characteristic histologic presentation. The neoplastic cell lineage involves two main types of cells, i.e., epithelial cells resembling those of carcinomas and fibrosarcoma-like spindle cells. Transitions between the two are well recognized and suggest a morphogenetic relationship. Depending on the relative representation of the cell types, synovial sarcoma is classified into (a) a biphasic type, with epithelial and spindle cell components in varying proportions; (b) a monophasic fibrous type; and (c) a very rare monophasic epithelial type. There also exists a poorly differentiated variant, termed poorly differentiated or round cell synovial sarcoma (Weiss and Goldblum 2001). The epithelial components consist of cells rich in a commonly pale cytoplasm and with large vesicular, round to ovoid nuclei. The shape of these cells varies from cuboidal to columnar. The growth patterns of epithelial-type cells include solid cords or nests, glandular profiles, and sometimes papillary structures. Squamous metaplasia may occur. The spindle cell component consists of plump and fusiform, fibroblast-like cells with usually darker nuclei, arranged in the form of compact sheets, resulting in a phenotype resembling that of fibrosarcoma, although long fascicles and a herringbone pattern are rarely seen (Weiss and Goldblum 2001). Hypocellular areas of synovial sarcoma may show hyaline areas, mineralization/calcification, or a myxoid change. While focal myxoid change is well known to occur in synovial sarcoma, there is a subset of these tumors where a myxoid pattern predominates (myxoid synovial sarcoma; Krane et al. 1999). The poorly differentiated or round cell variant is thought to represent a form of tumor progression superimposed on any other type of synovial sarcoma (Weiss and Goldblum 2001). It occurs on one of three patterns, namely, a large cell or epithelioid pattern, a small cell pattern (mimicking other small round cell tumors), and a high-grade spindle cell pattern composed of spindle-shaped cells with pleomorphic nuclei and a high mitotic count. Some tumors exhibit a prominent vascular phenotype, resembling hemangiopericytoma. Few monophasic synovial sarcomas show marked epithelioid features (Weidner et al. 1993), rhabdoid features (Jun et al. 2004), or impressive ossification (Hara et al. 2003). Synovial sarcoma may histologically mimic primitive neuroectodermal tumor (Masui et al. 1999). There are also variants with unique growth patterns, such as a predominantly intravascular growth pattern (intravascular synovial sarcoma (Shaw and Lais 1993) and intraneural synovial sarcoma (Zenmyo et al. 2001; Chu et al. 2004)).

Immunohistochemically, most synovial sarcomas are reactive for cytokeratins and epithelial membrane antigen (EMA), cytokeratin positivity amounting to at least 90 % of all tumors, but reactivity for epithelial markers is more prominent and frequent in epithelial types than in monophasic fibrous or poorly differentiated types. It is important to note that, in contrast to other spindle cell sarcomas, the cells of synovial sarcoma express cytokeratins 7 and 19. Up to 30 % of synovial sarcomas show focal immunoreactivity for S-100 protein, and the cells involved frequently co-express epithelial markers. Furthermore, 60–70 % of synovial sarcomas express CD99, and 75–100 % express bcl-2, while CD34 is consistently negative (Weiss and Goldblum 2001). Synovial sarcoma cells show a reduced expression of SMARCB1/INI1 based on a post-transcriptional regulatory mechanism (Kohashi et al. 2010; Rekhi and Vogel 2015).

Cytogenetic and Molecular Features of Synovial Sarcomas

Based on a frequent and distinct molecular genetic change and the possibility to generate cell lines with self-renewal capacity, synovial sarcoma has been proposed to be a stem cell malignancy (Naka et al. 2010). Cytogenetically, synovial sarcoma is characterized by translocation t(X;18) (p 11.2; q11.2) found in more than 95 % of the neoplasms (reviews: Lazar et al. 2006; Thway and Fisher 2014; Trautmann et al. 2014; Nielsen et al. 2015; murine models: Haldar et al. 2008). This results in

a fusion protein called synovial sarcoma X breakpoint 2 interacting protein or SSX2IP, which is a reliable diagnostic marker (review: Sun et al. 2008), also for extraskeletal synovial sarcomas (Fukuoka 2006) and detectable in paraffin-embedded material (Thway et al. 2010). In most cases, the translocation involves juxtaposition of the SYT (for synovial sarcoma translocation or translocated gene; synonym, SS18) gene on chromosome 18 to the SSX1 or SSX2 genes on chromosome X, thus creating SYT-SSX1 or SYT-SSX2 rearrangements and the respective chimeric fusion proteins. SYT/SSX1 translocations are seen in nearly three times as many synovial sarcomas as SYT/SSX2 translocations. SYT is highly conserved among species. Alternative splicing produces at least four isoforms of SYT, the most prominent being the long (SYT/L) and short (SYT/S) isoforms, which differ by inclusion of exon 8 in SYT/L. In synovial sarcoma, the SYT-SXX1 translocation is correlated with the expression of the differentially expressed gene, transducin-like enhancer of split (TLE1) belonging to the Groucho/TLE family (Knösel et al. 2010). SYT-SSX1 fusion gene expression has also been observed in epithelioid sarcoma (De Torres et al. 2005), but is not present in other sarcomas (Van de Rijn et al. 1999).

The oncoprotein SYT has a conserved N-terminal domain (SNH domain), which interacts with the hBRM and BRG1 chromatin-remodeling proteins, and a C-terminal transactivating sequence rich in glutamine, proline, glycine, and tyrosine (QPGY domain), which interacts with the ribonucleoprotein SIP/CoAA (Iwasaki et al. 2005; Perani et al. 2005), a human nuclear receptor co-activator with similarity to EWS and TLS/FUS family proteins. The latter interaction stimulates estrogen and glucocorticoid receptor-dependent transcriptional activation (Perani et al. 2005). The C-terminal region of SSX1, comprising the SSX1 portion of the SYT-SSX1 fusion protein, binds strongly to core histones and oligonucleosomes and directs nuclear localization of the fusion protein. The chimeric oncoprotein SYT-SSX1 is also capable to induce the cyclin-dependent kinase inhibitor p21 (WAF1/CIP1) by activation of the p21 gene promoter (Tsuda et al. 2005). SYT also interacts with a component of the histone deacetylase complex, mSin3A (Ito et al. 2004). There is also evidence that SYT-SSX1 induces insulin-like growth factor II (IGF2) expression and that SYT-SSX2 is necessary for maintaining IGF2 expression in a synovial sarcoma cell line (Sun et al. 2006). The SYT-SSX2 oncogene antagonizes the polycomb complex protein Bmi1: the fusion protein destabilizes the polycomb subunit Bmi1, resulting in impairment of polycomb-associated histone H2A ubiquitination and reactivation (desilencing) of polycomb target genes (Barco et al. 2009).

The SYT-SSX fusion type has important effects on the biology of synovial sarcoma. The fusion type is associated with sex, reflecting a 1:1 male-to-female ratio for SYT-SSX1 and a 1:2 ratio for SYT-SSX2 cases. SYT-SSX1 cases are more often peripheral or free limb, while there was an excess of SYT-SSX2 tumors among axial sarcomas.

In regard to adhesion and spread of synovial sarcoma cells, it is important to note that the SYT-SSX fusion protein interacts with components of the cytoskeleton and the adhesion protein network. SYT is essential for early embryonic development through the regulation of cell migration (Kimura et al. 2009). Activation of beta1 integrins is associated with formation of SYT/p300 complexes (Eid et al. 2000). Cytosolic isoforms of SYT bind F-actin and are involved in cytoskeletal reorganization. The association of SYT with F-actin bundles is extensive but stops short of the distal ends at focal adhesions. As ablation of SYN causes markedly impaired adhesion and spreading on fibronectin and laminin, but not on collagen types I and IV, SYN affects the tumor cells' ability to bind and react to the extracellular matrix (Kim et al. 2009). Downregulation of SYT-SSX expression in synovial sarcoma cells by small interfering RNA enhances the focal adhesion pathway and inhibits anchorage-independent growth (Takenaka et al. 2010). SYT-SSX2 remodels the cytoskeleton through activation of the ephrin pathway. Synovial sarcoma cells show mutual repulsion in vitro, cell repulsion being a well-known effect

of ephrin (Barco et al. 2007). The SYT protein also interacts with a global transcriptional activator, the SNF/SWI complex, which has been characterized as a chromatin-remodeling factor that enhances accessibility of the transcriptional machinery to DNA within a repressive chromatin structure. SYT has a unique QPGY domain, which is also present in the largest subunits, p250 and the homolog p250R, of the corresponding SNF/SWI complexes (Kato et al. 2002). Moreover, SYT interacts with another important co-activator, p300. The multifunctional co-activator p300 is a member of the Sox9 (Sry-type high mobility group box 9)-related transcriptional apparatus. p300 potentiates Sox9-dependent transcription on chromatinized DNA and is associated with hyperacetylated histones (Furumatsu et al. 2005). p300 and associated factors act as a histone acetyltransferase targeting specific lysine residues in substrate proteins (Dormeyer et al. 2005). Histone acetyltransferase activities of proteins such as p300, CBP, and P/CAF play important roles in activation of gene expression. This activity of p300 is itself promoted via Ser-1834 phosphorylation of p300 by Akt, Akt being activated and translocated to the nucleus in response to tumor necrosis factor-alpha (Huang and Chen 2005). SYT/p300 complex formation promotes cell adhesion to a fibronectin matrix (Eid et al. 2000), via promotion of E-cadherin expression (Liu et al. 2005). The SS18-SSX fusion protein mediates attenuation of a network consisting of EGR1 (early growth response-1) and PTEN that regulates cell survival. EGR1 and PTEN induce apoptosis of synovial sarcoma cells. The fusion protein maintains EGR1 expression at low levels, hence deceasing tumor cell death (Su et al. 2010).

The impact of the fusion type on metastatic spread was controversial in the past (Kawai et al. 1998; Ladanyi et al. 2002; Guillou et al. 2004). There is a relation between the SYT-SSX fusion type and the tumor's morphology. All biphasic synovial sarcomas seem to be associated with SYT-SSX1 fusion, while all monophasic neoplasms appear to be associated with the SYT-SSX2 fusion (Antonescu et al. 2000). Recent analyses showed that tumor stage and tumor grade are clearly superior as prognosticators in comparison with the SYT-SSX status (Guillou et al. 2004; Takenaka et al. 2008; ten Heuvel et al. 2009).

There are several other molecular features identified in synovial sarcoma. A subset of synovial sarcomas show Her-2/neu (ERBB2) oncogene expression, restricted to tumors with the SYT/SSX1 translocation (Allander et al. 2002; Nuciforo et al. 2003; Thomas et al. 2005), a phenomenon associated with epithelial differentiation (Allander et al. 2002) and lower risk of developing metastasis (Sapi et al. 2005).

The Wnt signaling pathway seems to be involved in synovial sarcoma, in that 28 % of the tumors were found to express high level nuclear beta-catenin expression (Saito et al. 2001; Ng et al. 2005), with or without associated beta-catenin gene mutations (Saito et al. 2000; Sato et al. 2001). In synovial sarcoma, nuclear beta-catenin expression correlates with cyclin D1 expression (Horvai et al. 2006), not confirmed in another study (Saito et al. 2006). Nuclear beta-catenin accumulation in synovial sarcoma is caused by recruitment of this protein by the SYT-SSX2 translocation protein (Pretto et al. 2006). The frizzled homologue 10 (FZD10), a member of the Wnt signal receptor family, is highly and specifically upregulated in synovial sarcoma and induces enhanced phosphorylation of the Disheveled (Dvl)2/Dvl3 complex as well as activation of the Rac1-JNK cascade. Activation of this pathway causes lamellipodia formation and enhanced anchorage-independent growth of synovial sarcoma cells (Fukukawa et al. 2009).

Differential expression of E-cadherin seems to affect the differentiation along an epithelial lineage in synovial sarcomas (Sato et al. 1999; Laskin and Miettinen 2002). Mutations of the gene for E-cadherin, participation in the beta-catenin network, frequently occur in this tumor, are correlated with the SYT-SSX fusion, and are correlated with a spindle cell/monophasic phenotype and the absence of epithelial/glandular differentiation (Saito et al. 2001, 2004). Expression of E-cadherin in synovial sarcoma is also associated

with expression of matrix metalloproteinase-2 (MMP-2), the latter having an important role in the epithelial differentiation of this neoplasm (Saito et al. 2002).

References

Allander SV, Illei PB, Chen Y, Antonescu CR, Bittner M, Ladanyi M, Meltzer PS (2002) Expression profiling of synovial sarcoma by cDNA microarrays: association of ERBB2, IGFBP2, and ELF3 with epithelial differentiation. Am J Pathol 161:1531–1534

Antonescu CR, Kawai A, Leung DH, Lonardo F, Woodruff JM, Healey JH, Ladanyi M (2000) Strong association of SYT-SSX fusion type and morphologic epithelial differentiation in synovial sarcoma. Diagn Mol Pathol 9:1–8

Barco R, Hunt LB, Frump AL, Garcia CB, Benesh A, Caldwell RL, Eid JE (2007) The synovial sarcoma SYT-SSX2 oncogene remodels the cytoskeleton through activation of the ephrin pathway. Mol Biol Cell 18:4003–4012

Barco R, Garcia CB, Eid JE (2009) The synovial sarcoma-associated SYT-SSX2 oncogene antagonizes the polycomb complex protein Bmi1. PLoS One 4:e5060

Billings SD, Meisner LF, Cummings OW, Tejada E (2000) Synovial sarcoma of the upper digestive tract: a report of two cases with demonstration of the X;18 translocation by fluorescence in situ hybridization. Mod Pathol 13:68–76

Chu PG, Benhattar J, Weiss LM, Meaghar-Villemure K (2004) Intraneural synovial sarcoma: two cases. Mod Pathol 17:258–263

Company Campins M.M., Morales R, Dolz C, Garcia-Bonafe M, Vilella A, Huguet P (2009) Primary monophasic synovial sarcoma of the duodenum confirmed by cytogenetic analysis with demonstration of t (X;18): a case report. J Gastrointestin Liver Dis 18:89–93

De Torres C, Cardesa TM, Rodriguez-Perales S, Cigudosa JC, Mora J (2005) Epithelioid sarcoma with SYT-SSX1 fusion gene expression: molecular and cytogenetic analysis. Cancer Genet Cytogenet 162:50–56

Dormeyer W, Ott M, Schnolzer M (2005) Analysis of p300 acetyltransferase substrate specificity by MALDI TOF mass spectrometry. Methods 36:376–382

Eid JE, Kung AL, Scully R, Livingstone DM (2000) p300 interacts with the nuclear proto-oncoprotein SYT as part of the active control of cell adhesion. Cell 102:839–848

Ferrari A, De Salvo GL, Brennan B, van Noesel MM, De Paoli A, Casanova M, Francotte N et al (2015) Synovial sarcoma in children and adolescents: the European Pediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005). Ann Oncol 26:567–572

Fisher C, Folpe AL, Hashimoto H, Weiss SW (2004) Intra-abdominal synovial sarcoma: a clinicopathological study. Histopathology 45:245–253

Fukukawa C, Nagayama S, Tsunoda T, Toguchida J, Nakamura Y, Katagiri T (2009) Activation of the non-canonical Dvl-Rac1-JNK pathway by Frizzled homologue 10 in human synovial sarcoma. Oncogene 28:1110–1120

Fukuoka K (2006) Molecular detection of SYT-SSX fusion gene transcripts currently represents the most specific and sensitive tool for diagnosing intrathoracic synovial sarcoma. Intern Med 45:881–882

Furumatsu T, Tsuda M, Yoshida K, Taniguchi N, Ito T, Hashimoto M, Ito T, Asahara H (2005) Sox9 and p300 cooperatively regulate chromatin-mediated transcription. J Biol Chem 280:35203–35208

Guillou L, Benhattar J, Bonichou F, Gallagher G, Terrier P, Stauffer E, Somerhausen NS et al (2004) Histologic grade, but not SYT-SSX fusion type, is an important prognostic factor in patients with synovial sarcoma: a multicenter, retrospective analysis. J Clin Oncol 22:4040–4050

Haldar M, Randall RL, Capecchi MR (2008) Synovial sarcoma: from genetics to genetic-based animal modeling. Clin Orthop Relat Res 466:2156–2167

Hara S, Hatori M, Hosaka M, Komatsu T, Tsuchiya T, Kimura N (2003) Synovial sarcoma with massive ossification – a case report. Ups J Med Sci 108:239

Holla P, Hafez GR, Slukvin I, Kalayoglu M (2006) Synovial sarcoma, a primary liver tumor – a case report. Pathol Res Pract 202:385–387

Horvai AE, Kramer MJ, O'Donnell R (2006) Beta-catenin nuclear expression correlates with cyclin D1 expression in primary and metastatic synovial sarcoma: a tissue microarray study. Arch Pathol Lab Med 130:792–798

Huang WC, Chen CC (2005) Akt phosphorylation of p300 at Ser-1834 is essential for its histone acetyltransferase and transcriptional activity. Mol Cell Biol 25:6592–6602

Ito T, Ouchida M, Ito S, Jitsumori Y, Morimoto Y, Ozaki T, Kawai A, Inoue H, Shimizu K (2004) SYT, a partner of SYT-SSX oncoprotein in synovial sarcomas, interacts with mSin3A, a component of histone deacetylase complex. Lab Invest 84:1484–1490

Iwasaki T, Koibuchi N, Chin WW (2005) Synovial sarcoma translocation (SYT) encodes a nuclear receptor coactivator. Endocrinology 146:3892–3899

Jun SY, Choi J, Kang GH, Park SH, Avala AG, Ro JY (2004) Synovial sarcoma of the kidney with rhabdoid features: report of three cases. Am J Surg Pathol 28:634–637

Kato H, Tjernberg A, Zhang W, Krutchinsky AN, An W, Takeuchi T, Ohtsuki Y, Sugano S et al (2002) SYT associates with human SNF/SWI complexes and the C-terminal region of its fusion partner SSX1 targets histones. J Biol Chem 277:5498–5505

Kawai A, Woodruff J, Healey JH, Brennan MF, Antonescu CR, Ladanyi M (1998) SYT-SSX gene fusion as a

determinant of morphology and prognosis in synovial sarcoma. N Engl J Med 338:153–160

Kerouanton A, Jimenez I, Cellier C, Laurence V, Helfre S, Pannier S, Mary P, Freneaux P et al (2014) Synovial sarcoma in children and adolescents. J Pediatr Hematol Oncol 36:257–262

Kim J, Swee M, Parks WC (2009) Cytosolic SYT/SS18 isoforms are actin-associated proteins that function in matrix-specific adhesion. PLoS One 4:e6455

Kimura T, Sakai M, Tabu K, Wang L, Tsunematsu R, Tsuda M, Sawa H, Nagashima K et al (2009) Human synovial sarcoma proto-oncogene Syt is essential for early embryonic development through the regulation of cell migration. Lab Invest 89:645–656

Knösel T, Heretsch S, Altendorf-Hofmann A, Richter P, Katenkamp K, Katenkamp D, Berndt A, Petersen I (2010) TLE1 is a robust diagnostic biomarker for synovial sarcomas and correlates with t(X;18): analysis of 319 cases. Eur J Cancer 46:1170–1176

Ko SF, Chou FF, Huang CH, Ng SH, Wan YL, Lee TY, Lin JW et al (1998) Primary synovial sarcoma of the gastrocolic ligament. Br J Radiol 71:438–440

Kohashi K, Yamamoto H, Tamiya S, Matono H, Iwamoto Y, Taguchi T, Tsuneyoshi M (2010) Reduced expression of SMARCB1/INI1 protein in synovial sarcoma. Mod Pathol 23:981–990

Köse D, Annagür A, Erol C, Ugras S, Köksal Y (2014) Synovial sarcoma in a premature newborn. Pediatr Int 56:e17–e20

Krane JF, Bertoni F, Fletcher CD (1999) Myxoid synovial sarcoma: an underappreciated morphologic subset. Mod Pathol 12:456–462

Ladanyi M, Antonescu CR, Leung DH et al (2002) Impact of SYT-SSX fusion type on the clinical behavior of synovial sarcoma: a multi-institutional retrospective study of 243 patients. Cancer Res 62:135–140

Laskin WB, Miettinen M (2002) Epithelial-type and neural-type cadherin expression in malignant noncarcinomatous neoplasms with epithelioid features that involve the soft tissues. Arch Pathol Lab Med 126:425–431

Lazar A, Abruzzo LV, Pollock RE, Lee S, Czerniak B (2006) Molecular diagnosis of sarcomas: chromosomal translocations in sarcomas. Arch Pathol Lab Med 130:1199–1207

Liu YN, Lee WW, Wang CY, Chao TH, Chen Y, Chen JH (2005) Regulatory mechanisms controlling human E-cadherin gene expression. Oncogene 24:8277–8290

Makhlouf HR, Ahrens W, Agarwal B, Dow N, Marshalleck JJ, Lee EL, Dotto JE, Hui P et al (2008) Synovial sarcoma of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 10 cases. Am J Surg Pathol 32:275–281

Masui F, Matsuno Y, Yokoyama R, Nakanishi Y, Hasegawa T, Kanai Y, Beppu Y, Hirohashi S et al (1999) Synovial sarcoma, histologically mimicking primitive neuroectodermal tumor/Ewing's sarcoma at distant sites. Jpn J Clin Oncol 29:438–441

Naka N, Takenaka S, Araki N, Miwa T, Hashimoto N, Yoshioka K, Joyama S, Hamada KI et al (2010) Synovial sarcoma is a stem cell malignancy. Stem Cells 28:1119–1131

Ng TL, Gown AM, Barry TS, Cheang MC, Chan AK, Turbin DA, Hsu FD, West RB, Nielsen TO (2005) Nuclear beta-catenin in mesenchymal tumors. Mod Pathol 18:68–74

Nielsen TO, Poulin NM, Ladanyi M (2015) Synovial sarcoma: recent discoveries as a roadmap to new avenues for therapy. Cancer Discov 5:124–134

Nuciforo PG, Pellegrini C, Fasani R, Maggioni M, Coggi G, Parafioriti A, Bosari S (2003) Molecular and immunohistochemical analysis of HER2/neu oncogene in synovial sarcoma. Hum Pathol 34:639–645

Perani M, Antonson P, Hamoudi R, Ingram CJ, Cooper CS, Garrett MD, Goodwin GH (2005) The proto-oncoprotein SYT interacts with SIP/CoAA a human nuclear receptor co-activator with similarity to EWS and TLS/FUS family of proteins. J Biol Chem 280:42863–42876

Pretto D, Barco R, Rivera J, Neel N, Gustavson MD, Eid JE (2006) The synovial sarcoma translocation protein SYT-SSX2 recruits beta-catenin to the nucleus and associates it in an active complex. Oncogene 25:3661–3669

Qayum A, Riall TS, Srinivasan R, Salazar FA (2008) A patient with synovial sarcoma primary to the gallbladder and common bile duct. J Gastrointest Surg 12:609–611

Rao L, Jaiprakash P, Palankar N, Gowda V (2013) Intra-abdominal primary monophasic synovial sarcoma with hemangiopericytoma-like areas. J Cancer Res Ther 9:102–104

Rekhi B, Vogel U (2015) Utility of characteristic 'weak to absent' INI1/SMARCB1/BAF47 expression in diagnosis of synovial sarcomas. APMIS. doi:10.1111/apm.12395

Romeo S, Rossi S, Acosta MM, Canal F, Sbaraglia M, Laurino L, Mazzoleni G et al (2015) Primary synovial sarcoma (SS) of the digestive system: a molecular and clinicopathological study of fifteen cases. Clin Sarcoma Res 5:7

Saito T, Oda Y, Sakamoto A, Tamiya S, Kinukawa N, Hayashi K, Iwamoto Y, Tsuneyoshi M (2000) Prognostic values of the preserved expression of the E-cadherin and catenin families of adhesion molecules and of beta-catenin mutations in synovial sarcoma. J Pathol 192:342–350

Saito T, Oda Y, Sugimachi K, Kawaguchi K, Tamiya S, Tanaka K, Matsuda S, Sakamoto A et al (2001) E-cadherin gene mutations frequently occur in synovial sarcoma as a determinant of histological features. Am J Pathol 159:2117–2124

Saito T, Oda Y, Sakamoto A, Tamiya S, Iwamoto Y, Tsuneyoshi M (2002) Matrix metalloproteinase-2 expression correlates with morphological and immunohistochemical epithelial characteristics in synovial sarcoma. Histopathology 40:279–285

Saito T, Oda Y, Kawaguchi K, Sugimachi K, Yamamoto H, Tateishi N, Tanaka K, Matsuda S et al (2004) E-cadherin mutation and Snail overexpression as alternative mechanisms of E-cadherin inactivation in synovial sarcoma. Oncogene 23:8629–8638

Saito T, Oda Y, Yamamoto H, Kawaguchi K, Tanaka K, Matsuda S, Iwamoto Y, Tsuneyoshi M (2006) Nuclear beta-catenin correlates with cyclin D1 expression in spindle and pleomorphic sarcomas but not in synovial sarcoma. Hum Pathol 37:689–697

Sapi Z, Papai Z, Hruska A, Antal I, Bodo M, Orosz Z (2005) Her-2 oncogene amplification, chromosome 17 and DNA ploidy status in synovial sarcoma. Pathol Oncol Res 11:133–138

Sato H, Hasegawa T, Abe Y, Sakai H, Hirohashi S (1999) Expression of E-cadherin in bone and soft tissue sarcomas: a possible role in epithelial differentiation. Hum Pathol 30:1344–1349

Sato H, Hasegawa T, Kanai Y, Tsutsumi Y, Osamura Y, Abe Y, Sakai H, Hirohashi S (2001) Expression of cadherins and their undercoat proteins (alpha-, beta-, and gamma-catenins and p120) and accumulation of beta-catenin with no gene mutations in synovial sarcoma. Virchows Arch 438:23–30

Shaw GR, Lais CJ (1993) Fatal intravascular synovial sarcoma in a 31-year-old woman. Hum Pathol 24:809–810

Shmookler BM (1982) Retroperitoneal synovial sarcoma: a report of four cases. Am J Clin Pathol 77:669–673

Soole F, Maupain C, Defachelles AS, Taque S, Minard-Colin V, Bergeron C, De Rycke Y et al (2014) Synovial sarcoma relapses in children and adolescents: prognostic factors, treatment, and outcome. Pediatr. Blood Cancer 61:1387–1393

Srivastava A, Nielsen PG, Dal CP, Rosenberg AE (2005) Monophasic synovial sarcoma of the liver. Arch Pathol Lab Med 129:1047–1049

Su L, Cheng H, Sampaio AV, Nielsen TO, Underhill TM (2010) EGR1 reactivation by histone deacetylase inhibitors promotes synovial sarcoma cell death through the PTEN tumor suppressor. Oncogene 29:4352–4361

Sun Y, Gao D, Liu Y, Huang J, Lessnick S, Tanaka S (2006) IGF2 is critical for tumorigenesis by synovial sarcoma oncoprotein SYT-SSX1. Oncogene 25:1042–1052

Sun B, Sun Y, Wang J, Zhao X, Zhang S, Liu Y, Li X, Feng Y, Zhou H, Hao X (2008) The diagnostic value of SYT-SSX detected by reverse transcriptase-polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) for synovial sarcoma: a review and prospective study of 255 cases. Cancer Sci 99:1355–1361

Takenaka S, Ueda T, Naka N, Araki N, Hashimoto N, Myoui A, Ozaki T, Nakayama T et al (2008) Prognostic implication of SYT-SSX fusion type in synovial sarcoma: a multi-institutional retrospective analysis in Japan. Oncol Rep 19:467–476

Takenaka S, Naka N, Araki N, Hashimoto N, Ueda T, Yoshioka K, Yoshikawa H, Itoh K (2010) Downregulation of SS18-SSX1 expression in synovial sarcoma by small interfering RNA enhances the focal adhesion pathway and inhibits anchorage-independent growth in vitro and tumor growth in vivo. Int J Oncol 36:823–831

Ten Heuvel SE, Hoekstra HJ, Bastiaannet E, Suurmeijer AJ (2009) The classic prognostic factors tumor stage, tumor size, and tumor grade are the strongest predictors of outcome in synovial sarcoma: no role for SSX fusion type or ezrin expression. Appl Immunohistochem Mol Morphol 17:189–195

Thomas DG, Giordano TJ, Sanders D, Biermann S, Sondak VK, Trent JC, Yu D et al (2005) Expression of receptor tyrosine kinases epidermal growth factor receptor and HER-2/neu in synovial sarcoma. Cancer 103:830–838

Thway K, Fisher C (2014) Synovial sarcoma: defining features and diagnostic evolution. Ann Diagn Pathol 18:369–380

Thway K, Rockcliffe S, Gonzalez D, Swansbury J, Min T, Thompson L, Fisher C (2010) Utility of sarcoma-specific fusion gene analysis in paraffin-embedded material for routine diagnosis at a specialist centre. J Clin Pathol 63:508–512

Trautmann M, Sievers E, Aretz S, Kindler D, Michels S, Friedrichs N, Renner M, Kirfel J et al (2014) SS18-SSX fusion protein-induced Wnt/β-catenin signaling is a therapeutic target in synovial sarcoma. Oncogene 33:5006–5016

Tsuda M, Watanabe T, Seki T, Kimura T, Sawa H, Minami A, Akagi T, Isobe KI, Nagashima K, Tanaka S (2005) Induction of p21 (WAF1/CIP1) by human synovial sarcoma-associated chimeric oncoprotein SYT-SSX1. Oncogene 24:7984–7990

Van de Rijn M, Barr FG, Collins MH, Xiong QB, Fisher C (1999) Absence of SYT-SSX fusion products in soft tissue tumors other than synovial sarcoma. Am J Clin Pathol 112:43–49

Wang YJ, Wen SC, Chien ST, Sheu JW, Hsuea CW, Feng NH (2006) Primary intra-abdominal synovial sarcoma. J Chin Med Assoc 69:492–495

Wang ZH, Wang XC, Xue M (2010) Clinicopathologic analysis of 4 cases of primary renal synovial sarcoma. Chin J Cancer 29:212–216

Weidner N, Goldman R, Johnston J (1993) Epithelioid monophasic synovial sarcoma. Ultrastruct Pathol 17:287–294

Weiss SW, Goldblum JR (2001) Enzinger and Weiss's soft tissue tumors, 4th edn. Mosby, St Louis, pp 1483–1509

Xiong B, Chen M, Ye F, Zhang Z, Yin L, Huang H, Chen H, Zhang H (2013) Primary monophasic synovial sarcoma of the liver in a 13-year-old boy. Pediatr Dev Pathol 16:353–356

Zajak J, Hladik P, Lischke R (2015) Synovial sarcoma of the liver – case report (in Czech). Rozhl Chir 94:78–81

Zenmyo M, Komiya S, Hamada T, Hiraoka K, Nagata K, Tsuji S, Hashimoto H, Inoue A (2001) Intraneural monophasic synovial sarcoma: a case report. Spine 26:310–313

Zhang Q, Wang H, Ren L, Qi X, Liu F, Zhang D (2014) Primary synovial sarcoma of the prostate metastatic to the liver and lung: a case report. World J Surg Oncol 12:194

Malignant Fibrous Histiocytoma of the Liver: A Neoplasm of the Undifferentiated High-Grade Pleomorphic Sarcoma Group

71

ICD-O code 8830/3

Contents

Abstract

The term malignant fibrous histiocytoma (MFH) previously denoted a malignancy suggested to originate from histiocytes. Later, it was realized that MFH represents a heterogeneous group of sarcomas of variable cell lineages. The current WHO classification includes MFH as subtypes of undifferentiated high-grade polymorphous sarcoma (UPS). The tumors exist in the form of five histologic patterns, i.e., storiform-pleomorphic, myxoid, giant cell, angiomatoid, and inflammatory MFH/UPS. Primary MFH in its original sense is a very rare liver neoplasm that occurs in older individuals. Hepatic MFH can be associated with paraneoplastic syndromes, including hypoglycemia due to secretion of ILF-II, and prominent leukocytosis and leukemoid reactions due to ectopic production of granulocyte colony-stimulating factor. Hepatic MFH/UPS presents as solitary or multiple irregular tumor masses and exhibits the same histologic patterns as its extrahepatic counterparts. MFH/UPS of the liver is an aggressive neoplasm with a high recurrence rate.

Introduction

The term malignant fibrous histiocytoma (MFH) was coined in the 1960s to encompass a group of aggressive soft tissue sarcomas then suggested to originate from "histiocytes" (Ozello et al. 1963;

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_71

O'Brien and Stout 1964). By the mid-1980s, MFH represented the most common sarcoma diagnosis in adults (review: Dei Tos 2006). Later, it was realized that MFH is a collection of malignant neoplasms that are related to liposarcomas, fibrosarcomas, and other sarcomas, rendering the term MFH controversial and signifying a pattern rather than a distinct entity (Enzinger 1986; Hollowood and Fletcher 1995; Meister 1995; Akerman 1997; Erlandson and Antonescu 2004; Al-Agha and Igbokwe 2008). Ultrastructurally, MFH has features of an unusual fibrosarcoma (Orenstein 2014). The current WHO classification no longer includes MFH as a distinct diagnostic category, but rather as subtypes of an undifferentiated high-grade polymorphous sarcoma (UPS; reviews: Dei Tos 2006; Fletcher 2006; Murphey 2007). The term "pleomorphic sarcoma" seems to include, apart from tumors previously classified as MFH, also other sarcomas than can now be more precisely attributed to a distinct cell lineage, probably requiring a further reappraisal of these neoplasms in the future (Goldblum 2014). So far, undifferentiated pleomorphic sarcoma still is an inclusive term, but in particular novel molecular features will subclassify the lesions into, e.g., dedifferentiated liposarcomas, smooth muscle neoplasms, and variants of fibrosarcomas (Kelleher and Viterbo 2013; Toda et al. 2013; Le Guellec et al. 2014; Martin-Broto et al. 2014). In what follows, MFH is discussed as group of neoplasms under its original meaning, without referring to the "true" status of this disease. The reason for doing so is related to the fact that a large proportion of hepatic malignancies classified as "MFH" have been published prior to the redefinition of this tumor group and that many clinicians are still familiar with "MFH" (Orenstein 2014).

The "MFH Patterns"

Histologically, storiform-pleomorphic, myxoid, giant cell, angiomatoid, and inflammatory variants of MFH have been recognized, now allocated to other WHO categories (Table 1), although the variants have prognostic significance (Fletcher et al. 2001). In a large group of tumors formerly classified as MFH (159 cases) reviewed after applying modern diagnostic methods, only 13 % were re-diagnosed as MFH (Fletcher 1992).

The patterns described in Table 1 often show transitions from areas having a highly ordered storiform pattern to less differentiated areas with a pleomorphic appearance (Weiss and Enzinger 1978; Dehner 1988; Fanburgh-Smith and Miettinen 1999; Hasegawa et al. 2000; Coindre et al. 2004; Fisher 2004; Idbaih et al. 2005; Adrien et al. 2010; Chen et al. 2013; Xiang et al. 2013; Kao et al. 2014; Schaefer and Fletcher 2014). Immunohistochemically, the majority of the previous "MFHs" display variable and in part marked reactivities for vimentin, CD68, factor-XIIIa, and antiproteases (Nemes and Thomazy 1988; Binder et al. 1992). Myofibroblastoid cells with SMA reactivity are often noted (Hasegawa et al. 2003).

Primary MFH/UPS of the Liver

Introduction and Epidemiology

Primary MFH in its original sense is a very rare liver neoplasm that was first reported in 1985 (Conran and Stocker 1985). In this first case, a primary location in the liver was confirmed at autopsy. Male patients were slightly more often involved, and the age range at diagnosis was 27–79 years (mean, 51 years; Anagnosto-poulos et al. 2005). In a subsequent review of 27 published cases as of 2008, age at diagnosis ranged from 34 to 87 years (average, 57 years), and there were 16 men and 11 women (Li et al. 2008). In a Chinese study on 76 cases, among 50 were men (male: female = 1.9:1), the mean age of the patients was 51 years, and more than 85 % were older than 40 years at the time point of diagnosis (Yao and Dai 2012). There is evidence that tumors classified as MFH account for a majority of primary hepatic sarcomas (Tan and Xiao 2013). There is no relationship with liver cirrhosis. However, in one patient hepatic MFH was associated with cirrhosis and a synchronous small hepatocellular carcinoma (Hwang et al. 2011).

Table 1 "Classical" histopathologic MFH patterns and WHO interpretation

Storiform-pleomorphic MFH
Up to 70 % of previously reported cases. The high-grade lesions show spindle cells admixed with rounded or polygonal cells, mostly with a storiform pattern. Cells with bizarre, giant cells and mitoses are common
WHO interpretation:
The diagnosis of the neopleomorphic MFH requires the exclusion of any other sarcoma lineage. The tumor is in 2002 still classified under fibrohistiocytic tumors, but is renamed undifferentiated high-grade pleomorphic sarcoma
Myxoid MFH
The second most common pattern (10–20 % of cases). Spindled or stellate cells embedded in an abundant myxoid matrix
WHO interpretation:
The myxoid lesions are no longer an MFH subtype, but are classified as myxofibrosarcoma. As the tumors exhibit myoid cell differentiation, the neoplasms are listed under myofibroblastic tumors
Giant cell MFH
About 10–15 % of cases. Numerous multinucleated giant cells resembling osteoclasts, but with high-grade nuclear atypias
WHO interpretation:
Most cases of the former giant cell MFH are other sarcomas or anaplastic giant cell carcinomas, giant cell being a nonspecific feature. The few cases of giant cell MFH that are left after exclusion of other malignancies are termed undifferentiated pleomorphic sarcoma with giant cells
Angiomatoid MFH
Tumors consist of benign-looking eosinophilic cells arranged in sheets and whorls, with a spindled, oval, or round cell morphology with only slight pleomorphism. Fibrous pseudocapsules and lymphocytic cuffs may be present. There are pseudovascular spaces filled with blood. Part of the tumor cells show myoid or schwannoid features. A subset of the neoplasm presents as myxoid tumors. The tumor most commonly occurs in the extremities of children and young adults, but rare visceral forms are also known. Part of tumors showed EWSR1 gene rearrangements, EWSR1-CREB1 fusion, or EWSR1-ATF1 fusion
WHO interpretation:
This is no longer a subtype of MFH, but is termed angiomatoid fibrous histiocytoma. As these neoplasms have an intriguing immunophenotype, with coexpression of desmin, EMA, and CD99, they are classified under tumors of uncertain differentiation
Inflammatory MFH
The rarest pattern (around 5 %). The neoplasms show a dense inflammatory infiltrate in and around the tumor, consisting of neutrophils, lymphocytes, plasma cells, and macrophages
WHO interpretation:
A significant part is now classified as dedifferentiated liposarcoma with a prominent inflammatory reaction. In case no distinct lineage can be identified, inflammatory MFH is now called undifferentiated pleomorphic sarcoma with prominent inflammation

Selected references: (Alberti-Flor et al. 1985; Dehner 1986; Fukayama and Koike 1986; Lengyel et al. 1986; Arens et al. 1987; Bruneton et al. 1988; Honda et al. 1988; Katsuda et al. 1988; Ohyama et al. 1989; Hamasaki et al. 1991; Akifuji et al. 1992; McGrady and Mirakhur 1992; Zornig et al. 1992; Lieu et al. 1993; Reed et al. 1993; Pinson et al. 1994; Shi et al. 1994; Arakawa et al. 1995; Tamaki et al. 1995; Schima et al. 1997; Ferrozzi and Bova 1998; Fujita and Lauwers 1998; Wunderbaldinger et al. 1998; Maekawa et al. 1999; Yu et al. 1999; Poggio et al. 2000; Schweyer et al. 2000; Colovic et al. 2001; Chou et al. 2002; Liu et al. 2004; Chen and Li 2006; Ding et al. 2006; Ye et al. 2007; Li et al. 2008; Yu et al. 2008; Sugitani et al. 2009; Caldeira et al. 2010; Cong and Gong 2011; Yin et al. 2011; Karki et al. 2012; Yao and Dai 2012; Das et al. 2013; Tan and Xiao 2013; Dong et al. 2014).

Clinical and Imaging Features

In a large review, the major clinical presentation (78.4 %) was abdominal pain or discomfort,

sometimes associated with malaise, anorexia, weight loss, and/or fever. 14.9 % of patients were asymptomatic (Yao and Dai 2012). MFH of the liver can present as hepatomegaly. Uncommon signs and symptoms include jaundice and chest pain (Li et al. 2008). The rare inflammatory variant may mimic a pyogenic liver abscess (Hu et al. 2013) and can be associated with an elevated peripheral white blood cell count. Similar to other hepatic mesenchymal tumors, MFH can be associated with hypoglycemia, probably due to secretion of insulin-like growth factor II (ILF-II) of the big isoform (Kageyama et al. 2003). Exceptionally, MFH is associated with prominent leukocytosis/paraneoplastic leukemoid reaction caused by production of granulocyte colony-stimulating factor (Mayumi et al. 2001), but this has not yet been observed in hepatic MFH. The prognosis of hepatic MFH depends primarily on tumor size and stage at the time of diagnosis. After hepatic resection of MFH in 12 patients, local recurrence had occurred in 6 patients and local recurrence plus distant metastasis in 3 at a median follow-up of 11.3 months. The median survival for the R0 liver resection group carried out in patients without extrahepatic metastases was 8.5 months, while the median survival of the debulking group was 7 months (Yin et al. 2011).

Pathology

Macroscopy

Primary MFH of the liver presents as solitary or multiple roundish to irregularly shaped tumor masses. In a study of 27 cases, the lesion was located in the right liver lobe in 9, in the left lobe in 9, and in both lobes in 6 analyzable cases (Li et al. 2008), i.e., without clear lobe predilection. Among 76 cases, 82.9 % were solitary lesions, with tumor diameter ranging from 2.5 to 23.5 cm (average, 10.3 cm; Yao and Dai 2012). In a minority of cases (9 %), hepatic MFHs initially present as multiple liver nodules of variable size, with the largest nodule ranging in diameter from 2 to 9 cm (Li et al. 2008). A single large nodule can be accompanied by several smaller daughter nodules. The tumors usually form circumscribed, but unencapsulated lesions with a form consistency. Less often the neoplasms have a rubbery consistency, and least common is a fleshy phenotype. The cut surface shows a gray to white tissue (seldom yellowish), sometimes with a fascicular texture or a whorly pattern. Hemorrhage is common, and large necroses are noted. Large foci of necrosis can undergo liquefaction, leaving a cystic space. Some MFHs initially present as cystic or multicystic masses. Direct invasion of adjacent organs was noted in almost a third of cases, and tumor thrombi are found in the inferior vena cava (Schweyer et al. 2000). In a review of 34 cases, 32 % of the neoplasms showed local invasion, most often into the diaphragm and lung (Li et al. 2008). Distant metastasis, mainly to lungs, was detected in less than 10 % of patients.

Histopathology

Histopathologically, hepatic MFH reflects all the patterns listed in Table 1. In most cases, however, spindled cells with pleomorphic nuclei predominate, these cells arranged in small fascicles in an often storiform pattern. Myxoid patterns seem to be very uncommon in the liver. In a small series of hepatic MFH, a myxoid variant was seen only once, and this tumor did not show necrosis (Li et al. 2008). Multinucleated giant cells or mononucleated giant cells with highly abnormal or even bizarre nuclei are common. Few tumor cells may reveal a rhabdoid morphology (Li et al. 2008). Necrosis and apoptosis are frequently found. The mitotic count varies considerably and ranged from less 5/10 HPFs to more than 20/10 HPFs (reviewed in Li et al. 2008). MFH may entrap intrahepatic bile duct, which then can undergo cystic change (Fukuyama and Koike 1986).

Ultrastructure

Electron microscopically, three types of tumor cells were identified, viz., cells with prominent endoplasmic reticulum and some with filaments, overall resembling fibroblastoid or myofibroblastoid cells. Other cells resembled histiocytes/macrophages, myoid cells, or undifferentiated

mesenchymal cells (Fukuyama and Koike 1986; Hamasaki et al. 1991; Wunderbaldinger et al. 1998; Li et al. 2008).

Immunohistochemistry

As in extrahepatic MFHs, neoplastic cells of hepatic MFHs are consistently positive for vimentin. Many cells are reactive for CD68 and antiproteases, and part of them stain for lysozyme. MFHs with myoid cells express alpha-SMA and/or desmin (review: Li et al. 2008), and part of the tumors were positive for ezrin (Li et al. 2008; Sugitani et al. 2009), and more than 50 % of MFHs have shown reactivity for promyelocytic leukemia body/PML components (63.9 %; Matsuo et al. 2008).

Liver Metastases of MFH/UPS

MFH as an aggressive neoplasm can metastasize to the liver, sometimes with large metastatic nodules (Ohmori et al. 1996; Atmatzidis et al. 2003; Suzuki et al. 2013; Thomas and Koshi 2013). Apart from spindle cell tumors with a storiform pattern, also neoplasms with myxoid, giant cell, or angiomatoid components metastasize to the liver (Ben Jilani et al. 1993; Chow et al. 1998).

MFH/UPS of the Bile Ducts

There are few observations on MFH taking its origin in the biliary tract, including the hepatic duct, with formation of a stenosing tumor (Kim et al. 2006). Primary MFH has also been observed in the papilla of Vater (Giuliani 2013).

MFH/UPS of the Gallbladder

Several reports have documented MFH primary to the gallbladder. This localization was first reported in 1983 (Kristofferson et al. 1983). Several reports of single cases or small series followed (Sasada et al. 1988; Sreekantaiah et al. 1992; Miyakawa and Hamano 1996; Orii et al. 1998; Tomono et al. 1998; Gruttadauria et al. 2001; Kato et al. 2002; Al-Daraji et al. 2009; Husain et al. 2009). Among seven reported patients, five were female and two were male, with an age range at presentation of 41–75 years. Several of the known histologic phenotypes have been detected in gallbladder MFH, but most of the lesions belonged to the spindle cell-storiform category. An inflammatory variant was found in one patient (Kato et al. 2002), while another study also documented an unusual fibromyxoid sarcoma-like (Evans-like) neoplasm and one tumor which presented a pleomorphic hyalinizing angiectatic tumor-like mixture (Al-Daraji et al. 2009). Most patients died of local recurrence and/or metastases.

MFH/UPS of the Hepatic Ligaments

MFH has been found as a primary neoplasm of the falciform ligament (Toughrai et al. 2007).

Differential Diagnosis

Generally, hepatic MFH has to be distinguished from other rare hepatic sarcomas with a spindle cell component. Intrahepatic cholangiocarcinoma with extensive sarcomatous change may histologically mimic MFH. Multicystic hepatic MFH resembles other cystic liver tumors, in particular cystadenomas, cystadenocarcinomas, or mucinous cystic tumors (Ding et al. 2006). Inflammatory MFH of the liver may clinico-radiologically be confounded with pyogenic liver abscess.

References

Adrien D, Ludger KH, Ingo S, Oliver M, Cornelius K, Michael CA, Lars S, Ole G et al (2010) Malignant fibrous histiocytoma-pleomorphic sarcoma, NOS. Gene expression, histology, and clinical course. A pilot study. Langenbecks Arch Surg 395:261–275

Akerman M (1997) Malignant fibrous histiocytoma- the commonest soft tissue sarcoma or a nonexistent entity? Acta Orthop Scand Suppl 273:41–46

Akifuji Y, Honjo I, Katayama S, Ishitobi S, Ueki J, Kishi K, Kato K, Nakamoto S (1992) Malignant fibrous

histiocytoma of the liver: a case report and review of the literature. Intern Med 31:284–288
Al-Agha OM, Igbokwe AA (2008) Malignant fibrous histiocytoma: between the past and the present. Arch Pathol Lab Med 132:1030–1035
Alberti-Flor et al (1985) http://www.ncbi.nlm.nih.gov/pubmed/2993091
Al-Daraji WI, Makhlouf HR, Miettinen M, Montgomery EA, Goodman ZD, Marwaha JS et al (2009) Primary gallbladder sarcoma: a clinicopathologic study of 15 cases, heterogeneous sarcomas with poor outcome, except pediatric botryoid rhabdomyosarcoma. Am J Surg Pathol 33:826–834
Anagnostopoulos G, Sakorafas GH, Grigoriadis K, Kostopoulos P (2005) Malignant fibrous histiocytoma of the liver: a case report and review of the literature. Mt Sinai J Med 72:50–52
Arakawa Y, Moriyama M, Sugitani M (1995) Histiocytoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:392–394
Arends JW, Willebrand D, Blaauw AM, Bosman FT (1987) Primary malignant fibrous histiocytoma of the liver – a case report with immunocytochemical observations. Histopathology 11:427–431
Atmatzidis KS, Pavlidis TE, Galanis IN, Papaziogas BT, Papaziogas TB (2003) Malignant fibrous histiocytoma of the abdominal cavity: report of a case. Surg Today 33:794–796
Ben Jilani S, el Mezni F, Dziri C, Khatteche A, Zermani R, Najeh N (1993) Primary malignant histiocytofibroma of the pancreas. Apropos of a case (in French). Arch Anat Cytol Pathol 41:167–170
Binder SW, Said JW, Shintaku IP, Punkus GS (1992) A histiocyte-specific marker in the diagnosis of malignant fibrous histiocytoma. Use of monoclonal antibody KP-1 (CD68). Am J Clin Pathol 97:759–763
Bruneton et al (1988) http://www.ncbi.nlm.nih.gov/pubmed/2844619
Caldeira A, Martin-Carreras F, Pereira E, Sousa R, Gonçalves R, Tristan J, Banhudo A (2010) Malignant fibrous histiocytoma – a rare hepatic tumor. Rev Esp Enferm Dig 102:146–147
Chen Q, Li Q (2006) Primary malignant fibrous histiocytoma of the liver: an analysis of 3 cases (in Chinese). Zhonghua Gan Zang Bing Za Zhi 14:313
Chen W, Shi H, Liu Y, Ke Z, Han A (2013) Endotracheal angiomatoid 'malignant' fibrous histiocytoma: EWSR1 gene rearrangement. Pathology 45:506–508
Chou YC, Lin CP, Cheng JS (2002) Primary malignant fibrous histiocytoma of the liver. Report of a case and review of the literature. J Intern Med (Taiwan) 13:94–98
Chow LT, Allen PW, Kumta SM, Grifith J, Li CK, Leung PC (1998) Angiomatoid malignant fibrous histiocytoma: report of an unusual case with highly aggressive clinical course. J Foot Ankle Surg 37:235–238
Coindre JM, Hostein I, Maire G, Derre J, Guillou L, Leroux A, Ghnassia JP, Collin F et al (2004) Inflammatory malignant fibrous histiocytoma and dedifferentiated liposarcomas: histological review, genomic profile, and MDM2 and CDK4 status favor a single entity. J Pathol 203:822–830
Colovic N, Cemerikic-Martinovic V, Colovic R, Zogovic S (2001) Primary malignant fibrous histiocytoma of the spleen and liver. Med Oncol 18:293–297
Cong Z, Gong J (2011) Primary malignant fibrous histiocytoma of the liver: CT findings in five histopathological proven patients. Abdom Imaging 36:552–556
Conran RM, Stocker JT (1985) Malignant fibrous histiocytoma of the liver: a case report. Am J Gastroenterol 80:813–815
Das A, Arya SV, Soni N, Gowda GG, Kalwaniya DS (2013) A rare presentation of hepatic and splenic cystic malignant fibrous histiocytoma: a case report and literature review. Int J Surg Case Rep 4:139–141
Dehner LP (1986) Malignant fibrous histiocytoma arising in the liver. Arch Pathol Lab Med 110:773–774
Dehner LP (1988) Malignant fibrous histiocyte. Nonspecific morphologic pattern, specific pathologic entity, or both? Arch Pathol Lab Med 112:236–237
Dei Tos AP (2006) Classification of pleomorphic sarcomas: where are we now? Histopathology 48:51–62
Ding GH, Wu MC, Yang JH, Cheng SQ, Li N, Dai BH, Cong WM (2006) Primary hepatic malignant fibrous histiocytoma mimicking cystadenocarcinomas: case report. Hepatobiliary Pancreat Dis Int 5:620–623
Dong J, An W, Ma W, Guo X, Gao Y, Liu C, Li Y (2014) Primary hepatic malignant fibrous histiocytoma mimicking hepatocellular carcinoma: a report of two cases. Oncol Lett 8:2150–2154
Enzinger FM (1986) Malignant fibrous histiocytoma 20 years after Stout. Am J Surg Pathol 10(suppl 1):43–53
Erlandon RA, Antonescu CR (2004) The rise and fall of malignant fibrous histiocytoma. Ultrastruct Pathol 28:283–289
Fanburg-Smith JC, Miettinnen M (1999) Angiomatoid "malignant" fibrous histiocytoma: a clinicopathologic study of 158 cases and further exploration of the myoid phenotype. Hum Pathol 30:1336–1343
Ferrozzi F, Bova D (1998) Hepatic malignant fibrous histiocytoma: CT findings. Clin Radiol 53:699–701
Fisher C (2004) Myofibroblastic malignancies. Adv Anat Pathol 11:190–201
Fletcher CD (1992) Pleomorphic malignant fibrous histiocytoma: fact or fiction? A critical reappraisal based on 159 tumors diagnosed as pleomorphic sarcoma. Am J Surg Pathol 16:213–228
Fletcher CD (2006) The evolving classification of soft tissue tumours: an update based on the new WHO classification. Histopathology 48:3–12
Fletcher CD, Gustafson P, Rydholm A, Willen H, Akerman M (2001) Clinicopathologic re-evaluation

of 100 malignant fibrous histiocytomas: prognostic relevance of subclassifications. J Clin Oncol 19:3045–3050

Fujita S, Lauwers GY (1998) Primary hepatic malignant fibrous histiocytoma: report of a case and review of the literature. Pathol Int 48:225–229

Fukayama M, Koike M (1986) Malignant fibrous histiocytoma of the liver. Arch Pathol Lab Med 110:203–206

Giuliani J (2013) Primary malignant fibrous histiocyte of Vater's papilla: first reported case. J Gastrointest Cancer 44:366–367

Goldblum JR (2014) An approach to pleomorphic sarcomas: can we subclassify, and does it matter? Mod Pathol 27(suppl1):S39–S46

Gruttadauria S, Doria C, Minervini MI, Doyle HR, Mandala L, Foglieni CS, Panarello G et al (2001) Malignant fibrous histiocytoma of the gallbladder: case report and review of the literature. Am Surg 67:714–717

Hamasaki K, Mimura H, Sato S, Sakai H, Miyashima T, Gochi A, Orita K (1991) Malignant fibrous histiocytoma of the liver – a case report. Gastroenterol Jpn 26:666–673

Hasegawa T, Seki K, Ono K, Hirohashi S (2000) Angiomatoid (malignant) fibrous histiocytoma: a peculiar low-grade tumor showing immunophenotypic heterogeneity and ultrastructural variations. Pathol Int 50:731–738

Hasegawa T, Hasegawa F, Hirose T, Sato T, Matsuno Y (2003) Expression of smooth muscle markers in so called malignant fibrous histiocytoma. J Clin Pathol 56:666–671

Hollowood K, Fletcher CD (1995) Malignant fibrous histiocytoma: morphologic pattern or pathologic entity? Semin Diagn Pathol 12:210–220

Honda H, Nakamura Y, Kajwara T, Muranaka T, Yoshida K, Tomooka K, Oshiumi Y et al (1988) Malignant fibrous histiocytoma of the liver. Comput Med Imaging Graph 12:131–134

Hu JS, Gupta S, Chang SK (2013) Primary hepatic inflammatory malignant fibrous histiocytoma: report of a rare entity and diagnostic pitfall mimicking a liver abscess. Pathology 45:430–432

Husain EA, Prescott RJ, Haider SA, Al-Mahmoud RW, Zelger BG, Zelger B, Al-Daraji WI (2009) Gallbladder sarcoma: a clinicopathological study of seven cases from the UK and Austria with emphasis on morphological subtypes. Dig Dis Sci 54:395–400

Hwang HS, Ha ND, Jeong YK, Suh JH, Choi HJ, Kim YM, Cha HJ (2011) Simultaneous occurrence of malignant fibrous histiocytoma and hepatocellular carcinoma in cirrhotic liver: a case report. World J Hepatol 3:256–261

Idbaih A, Coindre JM, Derre J, Mariani O, Terrier P, Ranchere D, Mairal A, Aurias A (2005) Myxoid malignant fibrous histiocytoma and pleomorphic liposarcoma share very similar genomic imbalances. Lab Invest 85:176–181

Kageyama K, Moriyama T, Hizuka N, Sakihara S, Takayasu S, Tamasawa N, Suda T (2003) Hypoglycemia associated with big insulin-like growth factor II during development of malignant fibrous histiocytoma. Endocr J 50:753–758

Kao YC, Lan J, Tai HC, Li CF, Liu KW, Tsai JW, Fang FM, Yu SC, Huang HY (2014) Angiomatoid fibrous histiocytoma: clinicopathological and molecular characterization with emphasis on variant histomorphology. J Clin Pathol 67:210–215

Karki B, Xu YK, Wu YK, Zhang WW (2012) Primary malignant fibrous histiocytoma of the abdominal cavity: CT findings and pathologic correlation. World J Radiol 4:151–158

Kato T, Kojima T, Shimizu T, Sasaki H, Abe M, Okushiba S, Kondo S, Kato H, Sato H (2002) Inflammatory malignant fibrous histiocytoma of the gallbladder: report of a case. Surg Today 32:81–85

Katsuda S, Kawahara E, Matsui Y, Ohyama S, Nakanishi I (1988) Malignant fibrous histiocytoma of the liver: a case report and review of the literature. Am J Gastroenterol 83:1278–1282

Kelleher FC, Viterbo A (2013) Histologic and genetic advances in refining the diagnosis of "undifferentiated pleomorphic sarcoma". Cancers (Basel) 5:218–233

Kim MH, Chung JJ, Choi YJ, Park KS, Park S, Yang HC (2006) Malignant fibrous histiocytoma of the common hepatic duct: a case report. J Comput Assist Tomogr 30:903–905

Kristofferson AO, Domellof L, Emdin SO, Kullenberg K (1983) Malignant fibrous histiocytoma of the gallbladder. A case report. J Surg Oncol 23:56–59

Le Guellec S, Chibon F, Ouali M, Perot G, Decouvelaere AV, Robin YM, Larousserie F et al (2014) Are peripheral purely undifferentiated pleomorphic sarcomas with MDM2 amplification dedifferentiated liposarcomas? Am J Surg Pathol 38:293–304

Lengyel G, Megyesi K, Vallent K, Mohacsy J (1986) Primary malignant histiocytoma of the liver (in Hungarian). Orv Hetil 127:2509–2511

Li YR, Akbari E, Tretiakova MS, Hart J, Akbari M, Urbanski SJ, Gao ZH (2008) Primary hepatic malignant fibrous histiocytoma: clinicopathologic characteristics and prognostic value of ezrin expression. Am J Surg Pathol 32:1144–1158

Lieu PK, Ho J, Ng HS (1993) Primary malignant fibrous histiocytoma of the spleen and liver – a case report. Ann Acad Med Singapore 22:390–392

Liu CL, Fan ST, Lo CM, Chan SC, Tso WK, Ng IO, Wong J (2004) Hepatic resection for incidentaloma. J Gastrointest Surg 8:785–793

Maekawa T, Yabuki K, Sato K, Tamasaki Y, Maekawa H, Ogawa K, Hirano A, Eguchi M et al (1999) A case of fibrous histiocytoma of the liver. Nippon Geka Hokan 68:14–23

Martin-Broto J, Gutierrez AM, Ramos RF, Lopez-Guerrero JA, Ferrari S, Stacchiotti S et al (2014) MRP1 overexpression determines poor prognosis in prospectively treated patients with localized high-risk soft tissue sarcoma of limbs and trunk wall: an ISG/GEIS study. Mol Cancer Ther 13:249–259

Matsuo T, Sugita T, Shimose S, Kubo T, Ishikawa M, Yasunaga Y, Ochi M (2008) Immunohistochemical expression of promyelocytic leukemia body in soft tissue sarcomas. J Exp Clin Cancer Res 27:73

Mayumi E, Okuno T, Ogawa T, Kurata K, Ishioka H, Hamamoto H, Ishiki K, Maga T et al (2001) Malignant fibrous histiocytoma of soft tissue producing granulocyte colony-stimulating factor. Intern Med 40:536–540

McGrady BJ, Mirakhur MM (1992) Recurrent malignant fibrous histiocytoma of the liver. Histopathology 21:290–292

Meister P (1995) Malignant fibrous histiocytoma: a "fibrohistiocytic" or primitive, fibroblastic sarcoma. Curr Top Pathol 89:193–214

Miyakawa R, Hamano K (1996) Malignant fibrous histiocytoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:243–244

Murphey MD (2007) World Health Organization classification of bone and soft tissue tumors: modifications and implications for radiologists. Semin Musculoskelet Radiol 11:201–214

Nemes Z, Thomazy V (1988) Factor XIIIa and the classic histiocytic markers in malignant fibrous histiocytoma: a comparative immunohistochemical study. Hum Pathol 19:822–829

O'Brien JE, Stout AP (1964) Malignant fibrous xanthomas. Cancer 17:1445–1458

Ohmori K, Matsui H, Kanamori M, Yudoh K, Yasuda T, Terahata S (1996) Malignant fibrous histiocytoma secondary to fibrous dysplasia. A case report. Int Orthop 20:385–388

Ohyama S, Asano K, Sasaki M, Katuta S (1989) Malignant fibrous histiocytoma of the liver (in Japanese). Nippon Geka Gakkai Zasshi 90:306–309

Orenstein JM (2014) The so called "malignant fibrous histiocytoma" is actually an unusual fibrosarcoma. Ultrastruct Pathol 38:52–54

Orii K, Umemura T, Matsuzawa M, Yoshiw T, Tamura Y, Yamamura N, Iijima Y, Nagata A et al (1998) A case of primary malignant fibrous histiocytoma of the gallbladder and a review of the cases in Japan (in Japanese). Nihon Shokakibyo Gakkai Zasshi 95:161–166

Ozello L, Stout AP, Murray MR (1963) Cultural characteristics of malignant histiocytomas and fibrous xanthomas. Cancer 16:331–344

Pinson CW, Lopez RR, Ivancev K, Ireland K, Sawyers JL (1994) Resection of primary hepatic malignant fibrous histiocytoma, fibrosarcoma, and leiomyosarcoma. South Med J 87:384–391

Poggio JL, Nagorney DM, Nascimento AG, Rowland C, Kay P, Young RM, Donohue JH (2000) Surgical treatment of adult primary hepatic sarcoma. Br J Surg 87:1500–1505

Reed JG, Goodman P, Soloway RD (1993) Primary malignant fibrous histiocytoma of the liver MRI findings. Magn Res Imaging 11:139–143

Sasada A, Yanagawa M, Hayashi S, Kita Y, Yoshimura M (1988) primary malignant fibrous histiocytoma of the gallbladder: a case report (in Japanese). Nippon Geka Gakkai Zasshi 89:1306–1309

Schaefer IM, Fletcher CD (2014) Myxoid variant of so-called angiomatoid "malignant fibrous histiocytoma": clinicopathologic characterization in a series of 21 cases. Am J Surg Pathol 38:816–823

Schima W, Saini S, Echeverri JA, Hahn PF, Harisinghani M, Mueller PR (1997) Focal liver lesions: characterization with conventional spin-echo versus fast spin-echo T2-weighted MR imaging. Radiology 202:389–393

Schweyer S, Meyer-Venter R, Lorf T, Sattler B, Fayyazi A (2000) Malignant fibrous histiocytoma of the liver (in German). Z Gastroenterol 38:243–248

Shi SS, Liu FS, Li TS (1994) Primary sarcoma of the liver (in Chinese). Zhonghua Zhong Liu Za Zhi 16:228–230

Sreekantaiah C, Rao UN, Karakousis CP, Sandberg AA (1992) Cytogenetic findings in a malignant fibrous histiocytoma of the gallbladder. Cancer Genet Cytogenet 59:30–34

Sugitani M, Aramaki O, Kikuchi K, Sheikh A, Oinuma T, Mamiya T, Takayama T, Nemoto N (2009) Two cases of primary malignant fibrous histiocytoma of the liver: immunohistochemical expression of ezrin and its relationship with prognosis. Acta Histochem Cytochem 42:83–88

Suzuki S, Watanabe S, Kato H, Inagaki H, Hattori H, Morita A (2013) A case of cutaneous malignant fibrous histiocytoma with multiple organ metastases. Kaohsiung J Med Sci 29:111–115

Tamaki H, Sanda T, Kawamura K, Ohhashi N, Muneyuki T, Yuasa H (1995) Malignant fibrous histiocytoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirzu 7:295–298

Tan Y, Xiao EH (2013) Rare hepatic malignant tumors: dynamic CT, MRI, and clinicopathologic features: with analysis of 54 cases and review of the literature. Abdom Imaging 38:511–526

Thomas ME, Koshi R (2013) Electron microscopy in the diagnosis of malignant fibrous histiocytoma of the lung presenting as metastasis to the maxillary gingiva. Int J Oral Maxillofac Surg 42:99–101

Toda M, Kawamoto T, Ueha T, Kishimoto K, Hara H, Fukase N, Onishi Y, Harada R et al (2013) 'Decoy' and 'non-decoy' functions of DcR3 promote malignant potential in human malignant fibrous histiocytoma cells. Int J Oncol 43:703–712

Tomono H, Fujika S, Kato K, Yoshida K, Nimura Y (1998) Malignant fibrous histiocytoma of the gallbladder. Hepatogastroenterology 45:1468–1472

Toughrai T, Errougani A, Elabssi M, M'bida R, Amraoui M, Chkoff R (2007) Malignant fibrous

histiocytoma of the falciform ligament (in French). J Chir (Paris) 144:173–175

Weiss SW, Enzinger FM (1978) Malignant fibrous histiocytoma: an analysis of 200 cases. Cancer 41:2250–2266

Wunderbaldinger P, Schima W, Harisinghani M, Saini S (1998) Primary malignant fibrous histiocytoma of the liver: CT and MR findings. AJR Am J Roentegenol 171:900–901

Xiang L, Zhou J, Gu W, Yang B (2013) Retroperitoneal angiomatoid fibrous histiocytoma: a case report and review of the literature. Oncol Lett 5:1833–1835

Yao D, Dai C (2012) Clinical characteristics of the primary hepatic malignant fibrous histiocytoma in China: case report and review of the literature. World J Surg Oncol 10:2

Ye MF, Zheng S, Xu JH, Chen LR (2007) Primary hepatic malignant fibrous histiocytoma: a case report and review of the literature. Histol Histopathol 22:1337–1342

Yin L, Lai CH, Li AJ, Pan ZY, Fu SY, Lau WY, Zhou WP, Meng-Chaowu (2011) Primary hepatic malignant fibrous histiocytoma: diagnostic pitfalls and therapeutic challenge. Hepatogastroenterology 58:887–891

Yu JS, Kim KW, Kim CS, Yoon KH, Jeong HJ, Lee DG (1999) Primary malignant fibrous histiocytoma of the liver: imaging features of five surgically confirmed cases. Abdom Imaging 24:386–391

Yu RS, Chen Y, Jiang B, Wang LH, Xu XF (2008) Primary hepatic sarcomas: CT findings. Eur Radiol 18:2196–2205

Zornig C, Kremer B, Henne-Bruns D, Weh HJ, Schröder S, Brolsch CE (1992) primary sarcoma of the liver in the adult. Report of five surgically treated patients. Hepatogastroenterology 39:319–321

Part IX

Tumors of the Mesothelial Lineage

Hepatic Mesotheliomas and Related Neoplasms

72

Contents

Abstract

Mesotheliomas form a complex group of neoplasms with a biologic behavior that ranges from benign to malignant. Apart from pleural mesothelioma, which has a strong association with asbestos exposure, these neoplasms also develop in other serosal surfaces, including the liver capsule, and in some inner organs, e.g., the heart and liver. Benign cystic mesothelioma, a neoplasm mainly occurring in middle-aged women with a previous history of gynecological surgery, rarely develops in the liver. Few cases of malignant epithelial monophasic mesothelioma of the liver have been reported. Also mesothelioma with a biphasic pattern was observed in the liver, in part associated with asbestos exposure. A second type of mesothelial neoplasm is adenomatoid tumor. This tumor typically occurs in the genital tract, but several extragenital sites have been found, including the heart, the mediastinum and the gastrointestinal tract. Few observations document primary adenomatoid tumor of the liver.

Hepatic Mesothelioma

ICD-O codes 9050/3-9053/3 (9050/0 for benign neoplasms)

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_72

Introduction

Mesotheliomas form a spectrum of neoplastic mesothelial lesions ranging in biological behavior from benign to highly malignant (review: Mott 2012). The incidence of malignant pleural mesotheliomas has rapidly increased from a rare tumor to the current 2500–3000 cases per year in the USA (review: Yang et al. 2008). In about 80–90 % of patients with pleural mesothelioma, the tumor is related to occupational exposure to asbestos in the air. The latent development period is usually long, about 25–40 years after initial exposure. There are certain differences in asbestos toxicity and induction of cancerogenesis, in that, e. g., occupational exposure to relatively pure chrysotile (a component of asbestos cement) within permissible levels was not associated with a significant increase in lung cancer or with mesothelioma (Sichletidis et al. 2008). Mesothelioma can occur in extrapleural localizations, including the peritoneal and pericardial surfaces (Chua et al. 2009) and, much more rarely, some inner organs. Diffuse malignant mesothelioma typically has a poor clinical course, with death occurring in most patients without 2 years after diagnosis. General morphologic features and classification of mesothelioma are added at the end of the chapter.

Benign Cystic Mesothelioma of the Liver

Benign cystic mesotheliomas (synonym, multicystic peritoneal mesothelioma) occur mainly in adults, predominantly middle-aged females with a previous history of gynecological surgery, and are considered to be benign and curable. They commonly develop in the compartment of the peritoneum, where they have also been termed multilocular peritoneal inclusion cysts (Mennemeyer and Smith 1979; Cusatelli et al. 1997; Datta and Paty 1997; review: Häfner et al. 2002). They are infrequently found after castration or menopause, suggesting some degree of hormonal dependence. However, estrogen and/or progesterone receptors were detected by the use of immunohistochemistry in a minority of lesions only (Sawh et al. 2003). Cystic mesotheliomas have a significant tendency for local recurrence after resection. In a report of 15 cases, recurrence was found to be 26.7 % (Katsube et al. 1982). In another study, 17/38 patients with at least 1 year of follow-up had postsurgical recurrences (Ross et al. 1989). Malignant transformation has been reported, but is an uncommon event (Gonzalez-Moreno et al. 2002). Cystic peritoneal mesothelioma can cause progressive abdominal distension in the pediatric age group, suggesting massive ascites (McCullagh et al. 1994).

Cystic mesotheliomas very rarely occur in the liver (Antropoli et al. 2002; Flemming et al. 2002; Di Blasi et al. 2004). An unusual case of such a tumor has been reported in 2002 (Flemming et al. 2002). A left-sided lobectomy specimen from a 51-year-old female exhibited an 8-cm diameter, gray-brownish, partially cystic, encapsulated mass with a soft-glistening surface. Histopathology revealed a partially cystic, highly vascular, and well-encapsulated neoplasm. Anastomosing, loosely arranged cords of tumor cells were separated by medium-sized and large vessels with a varying thickness of vessel walls, simulating a vascular neoplasm. The cystic spaces were populated by tumor cells which exhibited a hobnail morphology. Immunohistochemically, the neoplastic cells were reactive for pankeratin, cytokeratin 8/18, HBME-1, calretinin, epithelial membrane antigen, and vimentin. About a third of the tumor cell nuclei were positive for estrogen receptor. The estimated proliferation fraction was less than 1 %. Electron microscopy confirmed the mesothelial phenotype of the cells, these elements showing microvilli and desmosomes, and focally tonofibril-like filaments. A similar case was reported in 2004, a multicystic mesothelioma of the liver with secondary involvement of peritoneum and the inguinal region (Di Blasi et al. 2004).

Primary Malignant Mesothelioma of the Liver Capsule

This very unusual lesion has been reported in a 54-year-old female patient presenting with acute

abdominal pain and a heterogeneous mass in the right liver lobe, considered to be hepatocellular carcinoma and presented as a 12-cm-sized tumor arising from Glisson's capsule of the right lobe of the liver (Leonardou et al. 2003).

Hepatic Tubulopapillary Mesothelioma

In one patient, mesothelioma of the liver consisted of papillary and tubular structures and of spindle cell areas, and it was suggested that such tumors may originate from hepatic submesothelial connective tissue (Rout et al. 1999).

Intrahepatic Malignant Epithelial (Epithelioid, Monophasic) Mesothelioma

Relatively few cases of epithelial monophasic mesothelioma primary to the liver have been reported (Fig. 1; Rout et al. 1999; Imura et al. 2002; Leonardou et al. 2003; Gütgemann et al. 2006; Kim et al. 2008; Buchholz et al. 2009). In the case of Imura and coworkers (Imura et al. 2002), a tumor was detected in the right lobe of the cirrhotic liver of a 64-year-old male patient. Histologically, the neoplasm was predominantly composed of single glandular or branching tubules embedded in a desmoplastic stroma. Furthermore, scattered, irregularly arranged, dilated tubules or gland-like spaces were present. Dilated spaces with papillary ingrowths were also recognized. The epithelioid cells were immunoreactive for cytokeratins (including cytokeratin 8), epithelial membrane antigen (EMA), calretinin, and HBME-1, thus reflecting a pattern known for other epithelial mesotheliomas (Ordonez 1999). Tubular together with papillary structures have been noted in another case of epithelial hepatic mesothelioma (see above; Rout et al. 1999). Leonardou et al. (2003) reported on a 54-year-old female patient presenting with a cystic tumor with areas of hemorrhage within the center. Histologically, the tumor was composed of sheets of cytologically bland polygonal cells. The lesion was largely solid, but also contained multiple gland-like spaces and microcysts lined by cuboidal to columnar cells. Immunohistochemistry revealed positivity for vimentin, cytokeratin AE1/AE3, cytokeratin 8, and calretinin. There was no evidence of extrahepatic spread, but the tumor was regarded as malignant. A third case was reported in 2006, based on a 62-year-old male patient showing a 5.8-cm mass in the right liver lobe at incidental CT (Gütgemann et al. 2006). Histologically, the neoplasm consisted of numerous epithelioid cells arranged in cords, solid, and papillary patterns. On higher magnification, the tumor contained islands and cords composed of round to polygonal cells with abundant pale eosinophilic cytoplasm. Other areas showed a more solid proliferation of epithelioid cells containing large atypical nuclei. The immunophenotype was characterized by positivity for pancytokeratin, CK7, D2-40, WT-1, CA 12-5, calretinin, vimentin, and thrombomodulin. In a case reported by Buchholz and coworkers, the tumor had metastasized to periaortic lymph nodes, thus confirming its malignant behavior. A study of lymph node metastases revealed that the vascular endothelial growth factor receptor-1-expressing mesothelioma cells in the lymph nodes were associated with a dense D2-40-positive lymphangiovascular network, suggesting the induction of lymphangiogenesis by the tumor metastases (Buchholz et al. 2009).

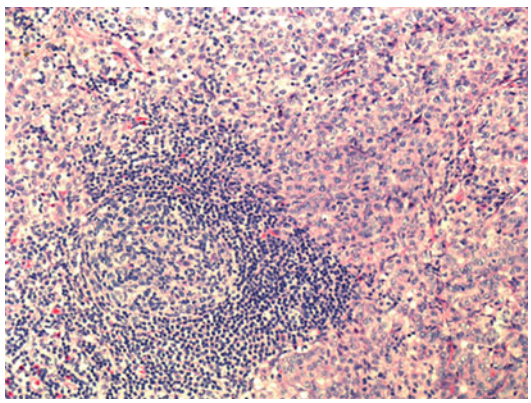

Fig. 1 Epithelial mesothelioma of the liver with lymph follicle formation (hematoxylin and eosin stain)

Intrahepatic Malignant Biphasic Mesothelioma

Similar to mesotheliomas developing in the pleural compartment, very rare cases of hepatic mesotheliomas can show the typical biphasical pattern (Sasaki et al. 2009). In the patient described by Sasaki and coworkers (Sasaki et al. 2009), the tumor was associated with asbestos exposure and presented as a 4.4-cm nodule in the right liver lobe of a 66-year-old male patient. The hepatic resection specimen showed a yellowish-white tumor with well-defined borders and central necrosis. Histologically, this mesothelioma was a mixture of papillary epithelioid structures, microcystic and adenomatoid parts, and sarcomatoid components. Immunohistochemically, the tumor cells were reactive for WT-1, calretinin, D2-40, mesothelin, and thrombomodulin.

Primitive Cystic Neoplasm of the Liver with Mesothelial Differentiation

This is a rare entity characterized by features resembling those of benign cystic peritoneal mesotheliomas (DeStephano et al. 1985; Shing et al. 1997). The patient of DeStephano et al. was a 6-month-old girl with a partially cystic liver tumor. Histologically, a differentiated cystic component had features of cystic peritoneal mesothelioma. Alpha-fetoprotein and alpha-1 antitrypsin were demonstrated in solid, anaplastic portions of the recurrent tumor. Recurrence occurred after surgical resection. Despite chemotherapy, the outcome was fatal after 11 months (DeStephano et al. 1985). A similar case of a malignant epithelial neoplasm consistent with a primitive cystic neoplasm was observed in the liver of a 3-year-old boy, the tumor showing mesothelial differentiation (Shing et al. 1997).

Mesothelioma of the Hepatic Ligaments

Malignant mesothelioma can develop in the falciform ligament, with subsequent metastasis to the liver (Marubayashi et al. 1998). These tumors are discussed in more detail in the chapter on neoplasms of the hepatic ligaments.

Mesothelial Cell Nests and Mesothelial Cysts of the Liver

There are few instances of non-neoplastic mesothelial formations primary to the liver. This includes mesothelial cell nests and mesothelial cysts (Komori et al. 2008; Silva et al. 2009). Mesothelial cysts are known to occur in several organs (spleen, pancreas, adrenal gland, ovary, vaginal process of the testis, and mesentery). Familial occurrence of multiple mesothelial spleen cysts has been reported (Iwanaka et al. 1995). Hepatic mesothelial cyst is characterized by a solitary or multilobular, thin-walled cyst of variable size which exhibits a unicellular lining of normal-looking mesothelial cells. Mesothelial cyst has been observed in a neonate (Komori et al. 2008). In this patient, routine antenatal ultrasound examination had shown an intra-abdominal cystic mass, which increased in size after birth to reach a diameter of 8 cm and became symptomatic, requiring surgical removal. The cyst was located in the anterior part of the liver and protruded into an omphalocele sac. The mesothelial lining of the cyst was positive for calretinin and D2-40. In other observations, mesothelial cysts were detected at the porta hepatis (Augustine et al. 2001), in an accessory liver lobe situated in an omphalocele (Rougemont et al. 2007), and in a supradiaphragmatic accessory liver (Luoma and Raboei 2003). In the latter case, the supradiaphragmatic liver part was surrounded by a collection of multilocular mesothelial cysts mimicking hydrothorax and causing respiratory distress of the neonate. In two neonates described by Rougemont et al. (2007), accessory liver lobes found in the setting of omphalocele showed multilocular cystic lesions, intricately admixed to the liver parenchyma. These cysts were lined by a single layer of cytokeratin-, calretinin-, and podoplanin-positive cells exhibiting a focal hobnail appearance. Mesothelial cyst of the gallbladder has been reported (Hoffman et al. 1989).

Mesothelial cysts also occur in the hepatic ligaments (see the respective ▶ Chap. 116, "Tumors and Tumor-Like Lesions of the Hepatic Ligaments").

Differential Diagnosis

Malignant pleural mesothelioma can metastasize to the liver. In a postmortem study of 318 patients, extrapleural dissemination of tumor was found in 87.7 % of cases, and tumor dissemination in extrathoracic sites was common (55.4 % of patients), involvement of the liver amounting to 31.9 % (Finn et al. 2012). The liver and in particular the liver's capsular surface may be involved in malignant diffuse peritoneal mesotheliomas (Samedi et al. 2010; Nagata et al. 2011), and in some instances this mode of growth may initially suggest primary hepatic malignancy (Matsukuma et al. 1996) and can cause recurrent ascites (Samedi et al. 2010). Rarely, peritoneal mesothelioma produces an omental mass close to the liver (Takeuchi et al. 2008), which may pose differential diagnostic problems. Liver involvement has been noted in peritoneal multicystic mesothelioma (Antropoli et al. 2002), and in well-differentiated papillary mesothelioma (Gong et al. 2005), an uncommon subtype of mesothelioma that typically occurs in the peritoneum of women without a history of asbestos exposure and usually follows an indolent course. There are also instances where pleural or pericardial malignant mesotheliomas metastasized to the liver (Cimbaluk et al. 2006; Doval et al. 2007). Benign cystic mesothelioma is often confused with multicystic abdominal lymphangioma, which is, however, mainly found in males, 60 % of whom are younger than 5 years old. Hepatocellular carcinoma very rarely exhibits a mesothelioma-like dissemination, with extended spread to the abdominal serosal surfaces (Otsuki et al. 2005). As such, HCC rarely metastasizes to the peritoneum (with or without carcinomatosis peritonei; Edmondson and Steiner 1954; Patton and Horn 1964; Anthony 1973; Nakashima et al. 1983; Yuki et al. 1990), and a peritoneal spreading mode masquerading mesothelioma is certainly exceptional. Asbestos fibers have been identified in squamous cell carcinoma of the cystic duct in a patient with asbestos occupational exposure of 5-year duration (Szendröi et al. 1983).

General Remarks on Mesotheliomas: Histological Types

The pathology of mesothelioma has recently been reviewed (Corson 2004; Tischoff et al. 2011). Mesotheliomas occur in several, now well-defined morphotypes (Table 1) that have been defined in the WHO classification of tumors. The most aggressive but the least common variant is sarcomatoid mesothelioma (Klebe et al. 2010). In addition, several

Table 1 Histological types of mesothelioma

WHO classification of mesothelioma	
Diffuse malignant mesothelioma	9050/3
Epithelioid mesothelioma	9052/3
Sarcomatoid mesothelioma	9051/3
Desmoplastic mesothelioma	9051/3
Biphasic mesothelioma	9053/3
Localized malignant mesothelioma	9050/3
Other tumors of mesothelial origin	
Well-differentiated papillary mesothelioma	9052/1
Adenomatoid tumor	9054/0
Variants of mesothelioma (in alphabetical order)	
Adenoid cystic mesothelioma	
Deciduoid mesothelioma	
Diffuse mesothelioma – NOS	
Gaucher cell-like mesothelioma	
Glandular mesothelioma	
Glomeruloid mesothelioma	
Histiocytoid mesothelioma	
In situ mesothelioma	
Macrocystic mesothelioma	
Microcystic mesothelioma	
Mucin-positive mesothelioma	
Pleomorphic mesothelioma	
Signet ring cell mesothelioma	
Single file mesothelioma	
Small cell mesothelioma	
Papillary mesothelioma	
Pleomorphic mesothelioma	
Tubulopapillary mesothelioma	
Vacuolated cell mesothelioma	

and usually rare variants of mesothelioma have been described, listed in the table.

Immunohistochemical Phenotype of and Markers for Mesothelioma

Mesotheliomas display a distinct expression pattern of several proteins belonging to various families and consequently a typical immunophenotype now allowing a more reproducible morphologic diagnosis (Davidson 2008; Greillier et al. 2008; Addis and Roche 2009; Betta et al. 2012). Mesothelioma cells express C-ERC/mesothelin and soluble mesothelin-related Peptides (SMRP), CEA, Ber-EP4, calretinin, osteopontin-1, megakaryocyte potentiating factor (MPF), Wilms tumor protein-1 (WT-1), HBME 1, podoplanin/D2-40, h-caldesmon, N-cadherin, CD138, intelectin, HMGB1, and vascular endothelial growth factor receptor-1 (VEGFR1; Ohta et al. 1999), thought to play an important role in angiogenesis and lymphangiogenesis in mesothelioma. In addition, asbestos-related malignant pleural mesotheliomas frequently express semaphorin-6D and its receptor plexin-A1, and plexin-A1 forms a complex with vascular endothelial factor receptor-2 (Catalano et al. 2009). A novel immunocytochemical marker that can distinguish between benign and malignant mesothelial lineages is termed IMP3/L523S, a monoclonal antibody directed against KOC, an oncofetal RNA-binding protein (Ikeda et al. 2010). Expression of the chaperone, CD147, has been found to discriminate between reactive mesothelial cells and malignant mesothelioma (Pinheiro et al. 2012). In a meta-analysis of literature data, the most frequently investigated serum marker was soluble mesothelin-related peptide (SMRP), and for noninvasive diagnosis, the markers CEA, Ber-EP4, and calretinin were most valuable in discriminating mesothelioma from other malignancies (van der Bij et al. 2011). In a multicenter study, SMRP and MPF were more closely associated with disease course than osteopontin and are expected to be useful in monitoring patient response in mesothelioma (Hollevoet et al. 2011).

Adenomatoid Tumor of the Liver

9054/0

Introduction

Adenomatoid tumor, first described in 1945 (Golden and Ash 1945), is a benign biphasic tumor now thought to be of mesothelial origin. These nodular and mostly circumscribed lesions typically occur in the female and male genital tracts and mesothelial surfaces, but are also known from extragenital sites, including the adrenal gland (Isotalo et al. 2003; Garg et al. 2005), pancreas (Overstreet et al. 2003), appendix (Hanada et al. 2003), mesocolon and omentum (Yeh et al. 2008), mesentery (Honore and Korn 1976), heart (Natarajan et al. 1997), pleura (Kaplan et al. 1996; Minato et al. 2009), mediastinum (Plaza et al. 2004), and peritoneum (Wang et al. 2005). Adenomatoid tumors may develop as composite lesions, in the adrenal gland, e.g., associated with myelolipoma (Timonera et al. 2008). The relationship between adenomatoid tumor and mesothelioma is underlined by immunohistochemical parallels between the neoplasms (Satoh et al. 1998; Delahunt et al. 2000; Schwartz and Longacre 2004) and the observations that localized malignant mesothelioma may accompany adenomatoid tumor-like lesions (Umezu et al. 2002), that papillary mesothelioma of the omentum can develop in conjunction with adenomatoid tumor (Hanrahan 1963), and that composite multicystic mesothelioma and adenomatoid tumor of the female genital tract have been reported (Zamecnik and Gomolcak 2000).

Morphology of Adenomatoid Tumors

Histologically, the lesions consist of slit-like or gland-like cystic spaces or irregularly shaped spaces lined by flattened cells. There are also solid components composed of similar cells or tubules by cuboidal cells. Distinct thread-like bridging strands crossing the glandular or pseudotubular spaces are a

typical morphologic feature of adenomatoid tumor (Hes et al. 2003). These formations are embedded in a fibrous matrix that shows signs of elastogenesis (Akhtar et al. 1976). The (epi/meso)thelioid cells are either pale or eosinophilic and rarely markedly oxyphilic (oxyphilic adenomatoid tumor; Phillips et al. 2007). Some adenomatoid tumors contain cells with prominent cytoplasmic vacuoles which, similar to the glandular space lumina, contain an Alcian blue-positive material rich in hyaluronic acid. This is also a typical feature of mesothelioma, adding to the striking histologic resemblance between the two tumor types. Adenomatoid tumor can, similar to mesothelioma, produce papillary structures (Glatz and Wegmann 2000). Mitotic figures are almost never seen. The tumors may undergo extensive necrosis (infarcted adenomatoid tumor; Skinnider and Young 2004). Immunohistochemically, adenomatoid tumors, similar to mesotheliomas, are positive for broad-spectrum cytokeratins, cytokeratins 5/6, epithelial membrane antigen (EMA), calretinin, mesothelin, HBME1, Wilms tumor suppressor gene product (WT1), podoplanin, and D2-40, but negative for BerEP4, claudin 5, CD31, and CD34 (review: Marchevsky 2008). Adenomatoid tumors may show a striking resemblance to lymphangiomas, particularly in cases with markedly flattened cells lining the thin spaces. Positivity for D2-40 may be misleading in such cases (Kuroda et al. 2007), and this antibody should, hence, be complemented by calretinin and cytokeratins 5/6, as D2-40 is also a marker for mesothelial cells.

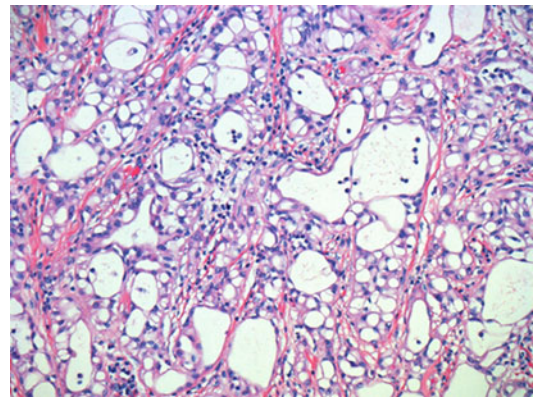

Fig. 2 Adenomatoid tumor of the liver. Epithelioid cell nests embedded in a stroma show marked vacuolar change (hematoxylin and eosin stain)

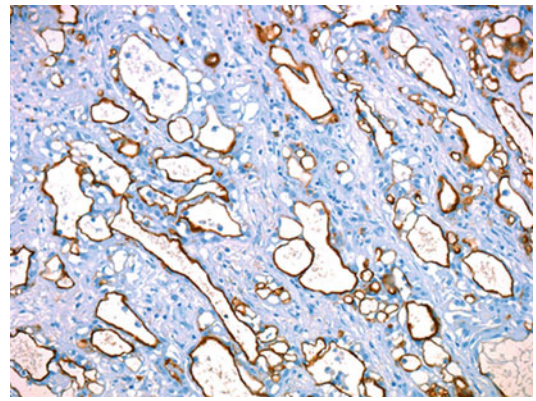

Fig. 3 Adenomatoid tumor of the liver. The epithelioid cells are reactive for podoplanin (podoplanin immunostain)

Solitary Adenomatoid Tumor of the Liver

Adenomatoid tumor can occur in as a primary tumor of the liver, with a histology and immunohistochemical phenotype as in other locations of these lesions (Figs. 2, 3, and 4). The first report of primary solitary adenomatoid tumor of the liver is from 2008 (Nagata et al. 2008). A 39-year-old male patient showed a 2.0-cm hypervascular hepatic tumor in liver segment V, found by ultrasonography during a routine checkup. There was no evidence for another tumor. Abdominal CT demonstrated that the tumor was hypointense in pre-enhancement and highly enhanced in the arterial phase with early washout. In MRI, the tumor was hypointense on T1-weighted images and highly hyperintense on T2-weighted images. Angiography showed the tumor as a hypervascular mass fed by A5 from an arterioportal shunt. Hepatic segmentectomy was performed. The specimen revealed a 1.5-cm nonencapsulated soft mass in the subcapsular region, with a hemorrhagic cut surface with numerous microcystic spongiotic structures. The

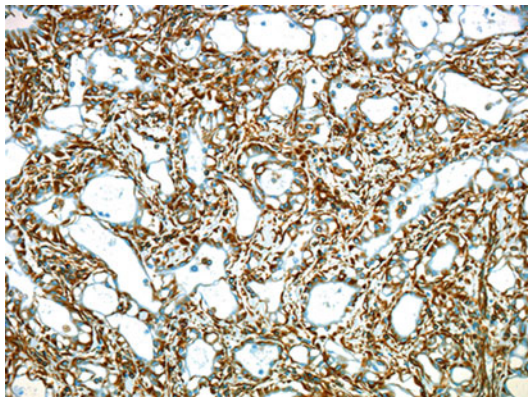

Fig. 4 Adenomatoid tumor of the liver. Intervening stromal spindle cells strongly reactive for smooth muscle actin are myofibroblasts (alpha-SMA immunostain)

interface of the lesion with the adjacent liver substance exhibited a micronodular interdigitation pattern. Histologically, the nodular tumor comprises cystic spaces within a collagenous stroma, lined with cuboidal, low-columnar, or flattened epithelioid cells, the spaces being filled with a colloid-like substance. The lining cells displayed small- to large-sized vacuoles and round to oval nuclei. Mitotic figures or atypias were not seen. Immunohistochemically, the epithelioid cells were reactive for pancytokeratin (AE1/AE3), epithelial membrane antigen (EMA), CAM 5.2, cytokeratins 7 and 19, calretinin, WT1, and D2-40. The adjacent stromal cells had the features of myofibroblasts, with marked positivity or alpha-SMA (Nagata et al. 2008). Since this case report, few other observations have been published (Adachi et al. 2012; Kim et al. 2012). Cystic adenomatoid tumor was detected at the porta hepatis (Grosse-Holz et al. 2013).

Multiple Abdominal Adenomatoid Tumors Involving the Liver

In an old female patient, several left-sided peritoneal adenomatoid tumor nodules located below the dome of the diaphragm (each measuring 0.2 cm) were associated with a further such tumor (0.5 cm) located to the posterior aspect of the left lobe of the liver. This nodule appeared pale yellow and well circumscribed, unencapsulated in the frozen section. The two lesion groups shared the morphologic and immunohistochemical features of adenomatoid tumor, the liver tumor being calretinin positive and negative for BerEP4. Ultrastructural examination performed on the liver lesion showed prominent desmosomes, long microvilli on the luminal surface of tumor acini, and a collagenous stroma typical of an adenomatoid tumor (Hayes et al. 2007).

References

Adachi S, Yanagawa T, Furumoto A, Fujino S, Doi R, Dono K, Kitada M (2012) Adenomatoid tumor of the liver. Pathol Int 62:153–154

Addis B, Roche H (2009) Problems in mesothelioma diagnosis. Histopathology 54:55–68

Akhtar M, Reyes F, Young I (1976) Elastogenesis in adenomatoid tumor: histochemical and ultrastructural observations. Cancer 37:338–345

Anthony PP (1973) Primary carcinoma of the liver: a study of 282 cases in Ugandan Africans. J Pathol 110:37–48

Antropoli M, Freda F, Apicella A, Nunziata L, Cutolo PP, Antropoli C, Petronella P (2002) Peritoneal multicystic mesothelioma: unusual case of localization in the left lobe of the liver (in Italian). Chir Ital 54:897–902

Augustine AJ, Pai RK, Pai R, Diaz EA, Prabhu HS, Swaroop R (2001) Mesothelial cyst at porta hepatis. Indian J Gastroenterol 20:35–36

Betta PG, Magnani C, Bensi T, Trincheri NF, Orecchia S (2012) Immunohistochemical and molecular diagnostics of pleural malignant mesothelioma. Arch Pathol Lab Med 136:253–261

Buchholz BM, Gütgemann I, Fischer HP, Gorschlüter M, Türler A, Kalff JC, Hirner A, Standop J (2009) Lymph node dissection in primary intrahepatic malignant mesothelioma: case report and implication for diagnosis and therapy. Langenbecks Arch Surg 394:1123–1130

Catalano et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19176370

Chua TC, Yan TD, Morris DL (2009) Surgical biology for the clinician: peritoneal mesothelioma :current understanding and management. Can J Surg 52:59–64

Cimbaluk D, Kasuganti D, Kluskens L, Reddy V, Gattuso P (2006) Malignant biphasic pleural mesothelioma metastatic to the liver diagnosed by fine-needle aspiration. Diagn Cytopathol 34:33–36

Corson JM (2004) Pathology of mesothelioma. Thorac Surg Clin 14:447–460

Cusatelli P, Altavilla G, Merchetti M (1997) Benign cystic mesothelioma of the peritoneum: a case report. Eur J Gynaecol 18:124–126

Datta RU, Paty PB (1997) Cystic mesothelioma of the peritoneum. Eur J Surg Oncol 23:461–462

Davidson B (2008) New diagnostic and molecular characteristics of malignant mesothelioma. Ultrastruct Pathol 32:227–240

Delahunt B, Eble JN, King D, Bethwaite PB, Nacey JN, Thornton A (2000) Immunohistochemical evidence for mesothelial origin of paratesticular adenomatoid tumour. Histopathology 36:109–115

DeStephano DB, Wesley JR, Heidelberger KP, Hutchinson RJ, Blane CE, Coran AG (1985) Primitive cystic hepatic neoplasm of infancy with mesothelial differentiation: report of a case. Pediatr Pathol 4:291–302

Di Blasi A, Boscaino A, De Dominicis G, Marino Marsilia G, D'Antonio A, Nappi O (2004) Multicystic mesothelioma of the liver with secondary involvement of peritoneum and inguinal region. Int J Surg Pathol 12:87–91

Doval DC, Pande SB, Sharma JB, Rao SA, Prakash N, Vaid AK (2007) Report of a case of pericardial mesothelioma with liver metastases responding well to pemetrexed and platinum-based chemotherapy. J Thorac Oncol 2:780–781

Edmondson HA, Steiner PE (1954) Primary carcinoma of the liver: a study of 100 cases among 48900 necropsies. Cancer 7:462–503

Finn et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22576637

Flemming P, Becker T, Klempnauer J, Hogemann D, Kreft A, Kreipe HH (2002) Benign cystic mesothelioma of the liver. Am J Surg Pathol 26:1523–1527

Garg et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/15692945

Glatz K, Wegmann W (2000) Papillary adenomatoid tumour of the adrenal gland. Histopathology 37:376–377

Golden A, Ash J (1945) Adenomatoid tumour of the genital tract. Am J Pathol 21:63–79

Gong Y, Ren R, Ordonez NG, Sun X, Sneige N (2005) Fine needle aspiration cytology of well-differentiated papillary mesothelioma: a case report. Acta Cytol 49:537–542

Gonzalez-Moreno S, Yan H, Alcorn KW, Sugarbaker PH (2002) Malignant transformation of "benign" cystic mesothelioma of the peritoneum. J Surg Oncol 79:243–251

Greillier L, Baas P, Welch JJ, Hasan B, Passioukov A (2008) Biomarkers for malignant pleural mesothelioma: current status. Mol Diagn Ther 12:375–390

Grosse-Holz M, Streitberg V, Thies J, Lenhart M, Seitz G (2013) Cystic tumor on the porta hepatis (in German). Pathologe 34:463–465

Gütgemann I, Standop J, Fischer HP (2006) Primary intrahepatic malignant mesothelioma of epithelioid type. Virchows Arch 448:655–658

Häfner M, Novacek G, Herbst F, Ullrich R, Gangl A (2002) Giant benign cystic mesothelioma: a case report and review of literature. Eur J Gastroenterol Hepatol 14:77–80

Hanada et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12959144

Hanrahan JB (1963) A combined papillary mesothelioma and adenomatoid tumor of the omentum; report of a case. Cancer 16:1497–1500

Hayes SJ, Clark P, Mathias R, Formela L, Vickers J, Armstrong GR (2007) Multiple adenomatoid tumours in the liver and peritoneum. J Clin Pathol 60:722–725

Hes O, Perez-Montiel DM, Alvarado Cabrero I, Zamecnik M, Podhola M, Sulc M, Hora M, Mukensnabl P et al (2003) Thread-like bridging strands: a morphologic feature present in all adenomatoid tumors. Ann Diagn Pathol 7:273–277

Hoffman CJ, Hales ED, Malachowski ME, Pietrafitta JJ (1989) Mesothelial cyst of the gallbladder. J Clin Ultrasound 17:50–52

Hollevoet K, Nackaerts K, Gosselin R, De Wever W, Bosquée L, De Vuyst P, Germonpré P et al (2011) Soluble mesothelin, megakaryocyte potentiating factor, and osteopontin as markers of patient response and outcome in mesothelioma. J Thorac Oncol 6:1930–1937

Honore and Korn 1976. http://www.ncbi.nlm.nih.gov/pubmed/1003400

Ikeda K, Tate G, Suzuki T, Kitamura T, Mitsuya T (2010) IMP3/L523S, a novel immunocytochemical marker that distinguishes benign and malignant cells: the expression profiles of IMP3/L523S in effusion cytology. Hum Pathol 41:745–750

Imura J, Ichikawa K, Takeda J, Iwasaki Y, Tomita S, Kubota K, Fujimori T (2002) Localized malignant mesothelioma of the epithelial type occurring as a primary hepatic neoplasm: a case report with review of the literature. APMIS 110:789–794

Isotalo et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12826889

Iwanaka T, Nakanishi H, Tsuchida Y, Oka T, Honna T, Shimizu K (1995) Familial multiple mesothelial cysts of the spleen. J Pediatr Surg 30:1743–1745

Kaplan et al. 1996. http://www.ncbi.nlm.nih.gov/pubmed/8827028

Katsube et al. 1982. http://www.ncbi.nlm.nih.gov/pubmed/7116294

Kim et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18705333

Kim JB, Yu E, Shim JH, Song GW, Kim GU, Jin YJ, Park HS (2012) Concurrent hepatic adenomatoid tumor and hepatic hemangioma: a case report. Clin Mol Hepatol 18:229–234

Klebe S, Brownlee NA, Mahar A, Burchette JL, Sporn TA, Vollmer RT, Roggli VL (2010) Sarcomatoid mesothelioma: a clinical-pathologic correlation of 326 cases. Mod Pathol 23:470–479

Komori et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/17598115

Kuroda N, Toi M, Hiroi M, Lee GH (2007) Diagnostic pitfall of D2-40 in adenomatoid tumour. Histopathology 51:719–721

Leonardou P, Semelka RC, Kanematsu M, Braga L, Woosley JT (2003) Primary malignant mesothelioma of the liver: MR imaging findings. Magn Reson Imaging 21:1091–1093

Luoma R, Raboei E (2003) Supradiaphragmatic accessory liver: a rare cause of respiratory distress in a neonate. J Pediatr Surg 38:1413–1414

Marchevsky AM (2008) Application of immunohistochemistry to the diagnosis of malignant mesothelioma. Arch Pathol Lab Med 132:397–401

Marubayashi S, Ohdan H, Asahara T, Ikeda M, Hinoi T, Fukuma K, Maeda T, Oshiro Y, Shimamoto F, Dohi K (1998) Malignant mesothelioma originating in the hepatic falciform ligament: report of a case. Surg Today 28:929–931

Matsukuma S, Aida S, Hata Y, Sugiura Y, Tamai S (1996) Localized malignant peritoneal mesothelioma containing rhabdoid cells. Pathol Int 46:389–391

McCullagh M, Keen C, Dykes E (1994) Cystic mesothelioma of the peritoneum: a rare cause of 'ascites' in children. J Pediatr Surg 29:1205–1207

Mennemeyer R, Smith M (1979) Multicystic peritoneal mesothelioma: a case report with electron microscopy of a case mimicking intra-abdominal cystic hygroma (lymphangioma). Cancer 44:692–698

Minato et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19627540

Mott FE (2012) Mesothelioma: a review. Ochsner J 12:70–79

Nagata S, Aishima S, Fukuzawa K, Takagi H, Yonematsu H, Iwashita Y, Kinoshita T, Wakasugi K (2008) Adenomatoid tumour of the liver. J Clin Pathol 61:777–780

Nagata S, Tomoeda M, Kubo C, Yoshizawa H, Yuki M, Kitamura M, Takenaka A, Nakanishi K et al (2011) Malignant mesothelioma of the peritoneum invading the liver and mimicking metastatic carcinoma: a case report. Pathol Res Pract 207:395–398

Nakashima T, Okuda K, Kojiro M et al (1983) Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. Cancer 51:863–877

Natarajan et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9351577

Ohta Y, Shridhar V, Bright RK, Kalemkerian GP, Du W, Carbone M et al (1999) VEGF and VEGF type C play an important role in angiogenesis and lymphangiogenesis in human malignant mesothelioma tumours. Br J Cancer 81:54–61

Ordonez NG (1999) The immunohistochemical diagnosis of epithelial mesothelioma. Hum Pathol 30:313–323

Otsuki Y, Shimizu S, Hosoda Y, Nagasawa M, Sato Y, Kobayashi H (2005) Hepatocellular carcinoma with mesothelioma-like dissemination. Pathol Int 55:738–744

Overstreet et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12808068

Patton RB, Horn RC (1964) Primary liver carcinoma. Autopsy study of 60 cases. Cancer 17:757–768

Phillips V, McCluggage WG, Young RH (2007) Oxyphilic adenomatoid tumor of the ovary: a case report with discussion of the differential diagnosis of ovarian tumors with vacuoles and related spaces. Int J Gynecol Pathol 26:16–20

Pinheiro C, Longatto-Filho A, Soares TR, Pereira H, Bedrossian C, Michael C, Schmitt FC et al (2012) CD147 immunohistochemistry discriminates between reactive mesothelial cells and malignant mesothelioma. Diagn Cytopathol 40:478–483

Plaza et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/14707875

Ross MJ, Welch WR, Scully RE (1989) Multilocular peritoneal inclusion cysts (so-called cystic mesotheliomas). Cancer 64:1336–1346

Rougemont AL, Sartelet H, Oligny LL, Bensoussan A, Yazbeck S, Fournet JC (2007) Accessory liver lobe with mesothelial inclusion cysts in an omphalocele: a new malformative association. Pediatr Dev Pathol 10:224–228

Rout P, Rameshkumar K, Srikrishna NV (1999) Hepatic mesothelioma. Indian J Gastroenterol 18:176–177

Samedi V, White S, Zimarowski MJ, Harris A, Saffitz J, Wang HH (2010) Metastatic peritoneal mesothelioma in the setting of recurrent ascites: a case report. Diagn Cytopathol 38:675–681

Sasaki et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19195066

Satoh Y, Hiraguchi M, Matuura T, Takasu K (1998) Immunohistochemical evidence of the mesothelial histogenesis of a uterine adenomatoid tumor. J Obstet Gynaecol Res 24:91–101

Sawh RN, Malpica A, Deavers MT, Liu J, Silva EG (2003) Benign cystic mesothelioma of the peritoneum: a clinicopathologic study of 17 cases and immunohistochemical analysis of estrogen and progesterone receptor status. Hum Pathol 34:369–374

Schwartz EJ, Longacre TA (2004) Adenomatoid tumors of the female and male genital tracts express WT1. Int J Gynecol Pathol 23:123–128

Shing HP, Wu TT, Hwang B, Chin TW, Wei CF, Tasy SH (1997) Malignant epithelial neoplasm consistent with primitive cystic hepatic neoplasm with mesothelial differentiation: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 59:265–268

Sichletidis L, Chloros D, Spyratos D, Haidich AB, Fourkiotou I, Kakoura M, Patakas D (2008) Mortality from occupational exposure to relatively pure chrysotile: a 39-year study. Respiration 78:63–68

Silva AR, Fragoso AC, Oliveira M, Costa-Maia J, Estevao-Costa A, Bessa-Monteiro A, Campos M (2009) Laparoscopic excision of a hepatic mesothelial cyst (in Spanish). Cir Pediatr 22:229–232

Skinnider BF, Young RH (2004) Infarcted adenomatoid tumor: a report of five cases of a facet of a benign neoplasm that may cause diagnostic difficulty. Am J Surg Pathol 28:77–83

Szendröi M, Németh L, Vajta G (1983) Asbestos bodies in a bile duct cancer after occupational exposure. Environ Res 30:270–280

Takeuchi N, Nakai M, Sato M (2008) A case of omental mesothelioma presenting with laminar thickening of omentum-appearance of diffuse malignant peritoneal mesothelioma (in Japanese). Gan To Kagaku Ryoho 35:677–681

Timonera ER, Paiva ME, Lopes JM, Eloy C, van der Kwast T, Asa SL (2008) Composite adenomatoid tumor and myelolipoma of adrenal gland: report of 2 cases. Arch Pathol Lab Med 132:265–267

Tischoff I, Neid M, Neumann V, Tannapfel A (2011) Pathohistological diagnosis and differential diagnosis. Recent Results Cancer Res 189:57–78

Umezu H, Kuwata K, Ebe Y, Yamamoto T, Naito M, Yamato Y, Ishiyama T, Tsuchida M, Okuizumi M, Ishikawa H, Koizumi N (2002) Microcystic variant of localized malignant mesothelioma accompanying an adenomatoid tumor-like lesion. Pathol Int 52:416–422

van der Bij S, Schaake E, Koffijberg H, Burgers JA, de Mol BA, Moons KG (2011) Markers for the non-invasive diagnosis of mesothelioma: a systematic review. Br J Cancer 104:1325–1333

Wang et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/15854561

Yang et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18709470

Yeh et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/19133002

Yuki K, Hirohashi S, Sakamoto M, Kanai T, Shimosato Y (1990) Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. Cancer 66:2174–2179

Zamecnik M, Gomolcak P (2000) Composite multicystic mesothelioma and adenomatoid tumor of the ovary: additional observation suggesting common histogenesis of both lesions. Cesk Patol 36:160–162

Part X

Tumors of the Perivascular Epithelioid Cell (PEC) System

Perivascular Epithelioid Cell Tumors 73

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_73

Abstract

Perivascular epithelioid cell (PEC) tumors form a complex group of neoplasms that share the presence of a unique cell type of still unknown lineage and source. PEC tumors or PEComas develop in numerous organs, including the hepatobiliary tract. In the liver, primary PEComa exclusively composed of PEC in the absence of heterologous elements is a rare neoplasm that sometimes presents as a large tumor mimicking other primary hepatic neoplasms. Although the course of PEComa is often favorable, tumor recurrence and even metastatic spread may occur. A second hepatic tumor of the PEComa group is angiomyolipoma, well known as a renal tumor occurring in the setting of tuberous sclerosis. Angiomyolipoma is composed of epithelioid cells of the PEC type, adipocytes, myoid cells, and abnormal blood vessels, in variable proportions. Some tumors are predominantly epithelioid, while others almost entirely consist of fat cells and thus mimic lipomas. Very rare hepatobiliary PEC tumors include clear cell myomelanocytic tumors, other clear cell and "sugar" tumors, and lymphangiomyomatosis.

PEComa Family of Tumors and the Concept of Perivascular Epithelioid Cells (PEC)

Perivascular epithelioid cells (PECs) have first been described in 1944 by Apitz in his work on tumors and malformations of the renal cortex (Apitz 1944). This author noted that, in renal angiomyolipomas, myoid cells revealed a particular spatial relationship to proliferated tumor vessels (page 318 and Figs. 11 and 12 of the work of 1944). Figure 11 of Apitz's publication shows a distinct array of medium-sized spindle cells sometimes separating the blood vessels from the lipomatous tumor components. The immature-looking myoid cells had some resemblance to epithelial tumor cells. The author noted this cell type in angiomyolipomas exclusively and argued that these myoid cells were not of angiomatous origin but rather got secondarily involved with the blood vessels. Apitz also found that angiomyolipomas with this specific feature were those with the most prominent growth behavior (Apitz 1944). In 1968, Masson described the cells in more detail, again for renal myolipomas and angiomyolipomas, and noted the distinct relationship between vessels and myoid cells (" . . .les éléments myoides ayant tendance à se grouper sans ordre au pourtour de nombreux vaisseaux") and the epithelioid aspect of some of these cells ("Il arrive enfin qu'à ces éléments faciles à identifier s'en ajoutent d'autres, épithélioides, plus ou moins volumineux, acidophiles, groupés en amas ou en cordons, qu'Apitz considère come des myoblastes anormaux"; although Apitz did not use the term, myoblasts, in his work).

The concept of PEC has been reviewed (Pea et al. 1996; Bonetti et al. 1997). PECs do not seem to have a normal counterpart. Morphologically, PECs occurring in several neoplasms commonly have a medium size with a pale eosinophilic to clear cytoplasm and a centrally located round nucleus showing only slight atypia. But PEC may also occur as spindled cells with an elongated nucleus and thus may reveal a myoid phenotype. Other PEC lineages show a markedly eosinophilic cytoplasm and more prominent epithelioid aspect. Immunohistochemically, the prominent phenotype is that of a coexpression of muscle cell and melanotic cell markers, chiefly HMB-45 (directed against a 46 kD melanosome glycoprotein), Melan-A/MART-1, tyrosinase, microphthalmia transcription factor (MITF), and smooth muscle actin (SMA). PECs are usually not reactive for S-100 protein, cytokeratins, and vimentin. In regard to these key markers, there is considerable variation among several PEC populations, with sometimes only focal reactivity for either HMB-45 or SMA (Bonetti et al. 1997). In contrast to melanomas and clear cell sarcomas, PEComas are reactive for MUM-1, a known lymphocyte marker (Ferenczi et al. 2012). It has also been suggested that PECs have a neural crest origin (Fernandez-Flores 2011) or be derived from telocytes (Ardeleanu and Bussolati 2011).

The neoplastic offspring of PEC comprises a family of neoplasms, termed PEC tumors (Table 1;

Table 1 Classification of PEC tumors

Perivascular epithelioid cell tumor sensu *stricto* (PEComa)
Clear cell myomelanocytic tumor (CCMT)
Clear cell sugar tumor (CCST)
Angiomyolipoma (AML)
Monotypic epithelioid angiomyolipoma (renal epithelioid oxyphilic neoplasm, REON)
Renal microhamartoma (related to AML)
Renal capsular neoplasms (RCN, renal capsulomas)
Pediatric epithelioid renal neoplasm with HMB-45 reactivity
Pulmonary clear cell nodules (CCN)
Lymphangioleiomyomatosis (LAM)
Intranodal palisading leiomyoblastoma
Abdominopelvic sarcoma of perivascular epithelioid cells

review: Armah and Parwani 2009). The WHO defines PEC tumors or PEComas as mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells (PECs). PEC as a neoplastic lineage in both angiomyolipomas and clear cell sugar tumor was first noted in 1991 (Pea et al. 1991). In 1992, the concept of a distinct PEC tumor family was advanced, based on the detection of cellular links between angiomyolipoma, clear cell sugar tumors, and lymphangioleiomyomatosis and the recognition that the cells of these tumors were reactive with melanocyte markers, an epithelioid morphology, and a perivascular distribution (Bonetti et al. 1992).

The term, PEComa, to denote neoplasms of "pure" PEC composition was suggested in 1996 (Zamboni et al. 1996) and has since gained wide acceptance. Later, the PEComa family of tumors has grown to comprise a considerable number of entities, including perivascular epithelioid clear cell tumor (PEComa), the closely related clear cell myomelanocytic tumors (CCMT), angiomyolipoma (AML), monotypic epithelioid angiomyolipoma (renal epithelioid oxyphilic neoplasm, REON), renal microhamartomas (related to AML), renal capsular neoplasms (RCN, capsulomas), pediatric epithelioid renal neoplasm with HMB-45 reactivity, pulmonary and extrapulmonary clear cell (sugar) tumors, pulmonary clear cell nodules (CCN), lymphangioleiomyomatosis (pulmonary and extrapulmonary variants, LAM), intranodal palisading leiomyoblastoma, and abdominopelvic sarcoma of perivascular epithelioid cells. In the female genital tract and retroperitoneum, a sclerosing variant of PEComa occurs, which may have an aggressive course (Hornick and Fletcher 2008; Yamada et al. 2011; Santi et al. 2012). In a review, PEComas outside the kidney, lung, and liver, there tended to be a female predominance (Pan et al. 2003), with a wide age distribution. PEC tumors show a wide range of biologic behavior, most lesions being benign or of intermediate behavior, but frankly malignant forms also exist (Bleeker et al. 2012).

Patients with tumors of the PEC family may exhibit lesions of the tuberous sclerosis complex (TSC; Vang and Kempson 2002). In fact, the majority of neoplastic lesions composed of PEC have been suggested to be related to TSC (Bonetti et al. 1997). In addition, a distinct subset of PEComas harbors fusions involving the transcription factor E3 (TFE3). TFE3-expressing PEComas tend to prevail in young age, are not associated with tuberous sclerosis, and tend to show a predominant alveolar architecture and epithelioid features (Argani et al. 2010; Matkowskyj et al. 2013; Shen et al. 2014). Reactivity for TFE3 was not detected in PEComa of the liver (Xia et al. 2013).

Primary PEComa of the Hepatobiliary Tract

Introduction

PEComas sensu stricto, i.e., without cellular elements typical for angiomyolipoma (such as adipose tissue and smooth muscle cells), are very rare hepatic neoplasms. The first case was probably reported in 2006 (Parfitt et al. 2006), followed by several other descriptions.

Selected References Fang et al. 2007; Larbcharoensub et al. 2007; Svajdler et al. 2007;

Della Vigna et al. 2008; Paiva et al. 2008; Stenram 2008; Zimmermann et al. 2008; Akitake et al. 2009; Priola et al. 2009; Sanchez Pérez et al. 2009; Strzelczyk et al. 2009; Ahn and Bang 2011; Selvaggi et al. 2011; Durczynski et al. 2012; Tan and Xiao 2012; Cheung et al. 2013; Jafari et al. 2013; Khaja et al. 2013; Shen et al. 2013; Tay et al. 2013; Yu and Tang 2013; Zhao et al. 2013; Liu et al. 2014; Ameurtesse et al. 2014; Bergamo et al. 2014; Khan et al. 2014; Tan et al. 2014; Zhang et al. 2014.

Clinical and Imaging Features

The clinical presentation of PEComas of the liver is nonspecific and similar to other primary hepatic neoplasms with slow growth and low aggressivity. Generally, abdominal discomfort, indigestion, loss of appetite, nausea, and intermittent colic pain have been noted. Laboratory tests have no diagnostic utility. Most primary hepatic PEComas have been described as solid tumors with an expanding growth pattern. Several of the reported lesions measured few cm in diameter, but these neoplasms may also grow to larger size, e.g., with a diameter of 7 cm (Zimmermann et al. 2008) to 17 cm (Strzelczyk et al. 2009), causing clinically manifest hepatomegaly. In one series of seven cases, the maximum diameters ranged from 2.5 to 8.5 cm (mean = 4 cm; Tan and Xiao 2012). Rarely, hepatic PEComas may undergo intratumoral hemorrhage and cause acute abdomen (Priola et al. 2009). In one patient, a large (15 cm) hepatic PEComa was synchronously associated with multiple focal nodular hyperplasia (Durczynski et al. 2012). The biologic behavior of hepatic PEComas is, similar, the PEComas situated elsewhere, difficult to predict. In one patient, metastases to multiple sites developed nearly 9 years after diagnosis (Parfitt et al. 2006). A second malignant hepatic PEComa was associated with multiple lobulated nodules containing hemorrhagic fluid on the liver surface, peritoneum and omentum, and led to the patient's death 25 days after hospital admission (Selvaggi et al. 2011).

On CT images, the tumors were in some cases centrally hypodense, with enhancement in the arterial phase (Sanchez-Pérez et al. 2009; Selvaggi et al. 2011; Tan and Xiao 2012). In non-enhanced MR, the tumors showed low intensity on T1-weighted images and a high intensity on T2-weighted images (Akitake et al. 2009; Sanchez-Pérez et al. 2009). Fat-suppressive MR did not show suppression of hyperintensity of the tumor, indicating poor or absent fat component (Akitake et al. 2009). Some of the reported tumors resembled focal nodular hyperplasia, hemangioma, or hepatocellular carcinoma at imaging (Parfitt et al. 2006; Fang et al. 2007; Larbcharoensub et al. 2007; Svajdler et al. 2007; Paiva et al. 2008; Zimmermann et al. 2008). Contrast-enhanced ultrasonography demonstrated early-phase enhancement of the tumor and rapid drainage of the contrast agent to veins (Akitake et al. 2009).

Pathology

Macroscopy

At gross examination, hepatic PEComas are nodular and well-circumscribed masses with a grayish-white, yellow-tan to pink cut surface (Fig. 1). Larger tumors may be friable in central parts, have a fragile consistency, and may undergo cystic change (Zimmermann et al. 2008; Strzelczyk et al. 2009), while hemorrhage and necrosis are rare observations.

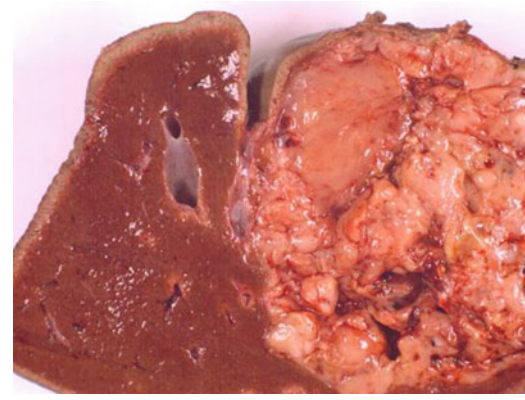

Fig. 1 Primary perivascular epithelioid cell tumor (PEComa) of the liver (non-fixed resection specimen)

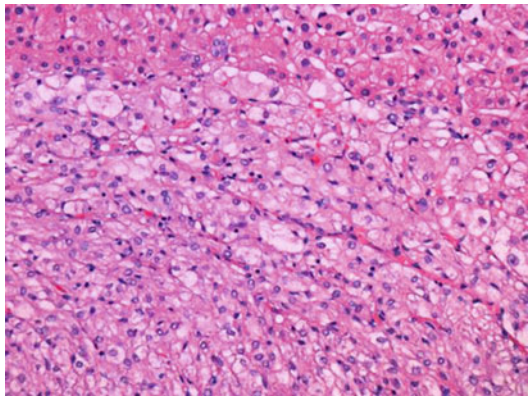

Fig. 2 Primary perivascular epithelioid cell tumor (PEComa) of the liver. The neoplasm consists of large, pale cells with small round and regular nuclei. At the interface with the liver, no stromal interposition is present (hematoxylin and eosin stain)

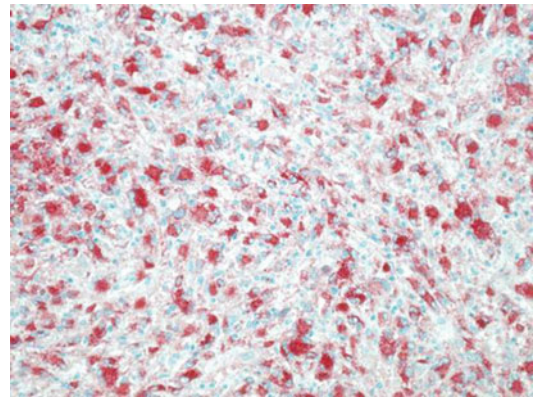

Fig. 3 Primary perivascular epithelioid cell tumor (PEComa) of the liver. The neoplastic cells show strong cytoplasmic reactivity for HMB-45 (HMB-45 immunostain)

Histopathology

Most of the tumor mass is composed of medium-sized polygonal or slightly elongated cells with an epithelioid appearance, showing an eosinophilic, pale, or clear cytoplasm (Fig. 2). These cells form nests, bundles, tiny nodules, or platelike (trabeculum-like) arrangements with intervening, thin-walled vascular channels, a pattern that sometimes mimics hepatocellular carcinoma. Apart from epithelioid cells, spindle cells in variable quantities also occur. These cells display a faintly eosinophilic cytoplasm and ovoid to elongated nuclei, forming bundles and at some places palisade-like structures (Zimmermann et al. 2008). A smaller component is represented by large eosinophilic or pale cells with sometimes pleomorphic nuclei. Mitotic figures are usually rare or not detectable. Reticulin fibers predominate in the spindle cell areas. Part of the lesions display a predominance of clear cells, resulting in the presentation of a clear cell "sugar" tumor (Strzelczyk et al. 2009). Some of the tumors show a high degree of vascularity and the presence of dilated vascular channels (Strzelczyk et al. 2009). A clear cell component similar to that of clear cell myomelanocytic tumors of hepatic ligaments (see below) has also been described (Larbcharoensub et al. 2007). The histology of hepatic PEComas may not serve well to predict the biologic behavior. In a patient with a histologically benign hepatic PEComa, metastases to multiple sites occurred 9 years later (Parfitt et al. 2006).

Ultrastructure

Ultrastructurally, part of the tumor cells (mainly the clear cells) exhibit abundant glycogen. Other cells showed a well-developed rough endoplasmic reticulum, thin filaments, microtubules, and aberrant melanosomes (Larbcharoensub et al. 2007).

Immunohistochemistry

Immunohistochemically, the tumors reported were consistently positive for HMB-45 (Fig. 3) and other melanoma markers (Melan-A, melanoma antigen/PNL2, microphthalmia transcription factor, tyrosinase). Usually, granular cytoplasmic reactivity for HMB-45 prevails, whereas Melan-A is less strongly expressed (Zimmermann et al. 2008). Melanoma antigen/PNL2 was mostly found in larger, epithelioid cells (Zimmermann et al. 2008). The tumors may contain SMA-positive myoid cells (Fig. 4). SMA reactivity is heterogeneous and mainly involves

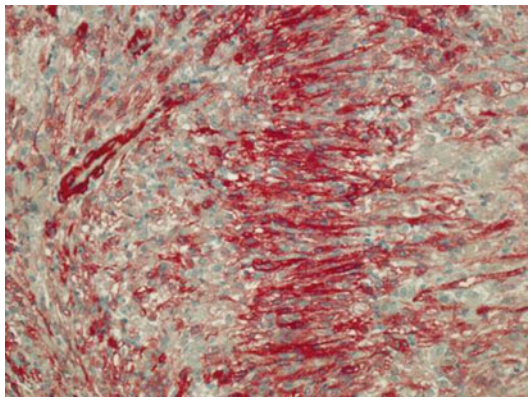

Fig. 4 Primary perivascular epithelioid cell tumor (PEComa) of the liver. Apart from epithelioid cells (*left half of figure*), this tumor contains smooth muscle actin-positive palisading spindled cells (alpha-SMA immunostain)

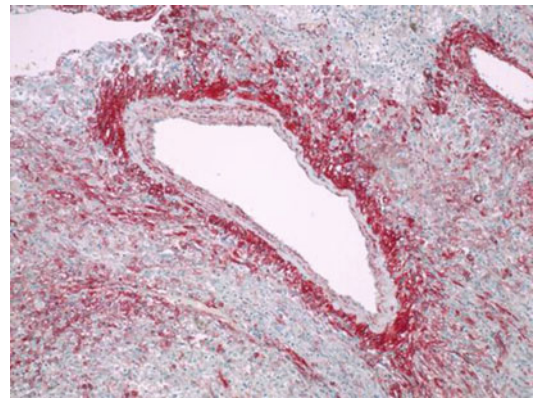

Fig. 5 In hepatic PEComa, smooth muscle cell-positive smooth muscle cells may predominate as perivascular cells, forming a cellular corona (alpha-SMA immunostain)

the slender spindle cells that are arranged in bundles. Sometimes, SMA-positive smooth muscle cells are closely associated with blood vessels, apparently engaging with the vessels' adventitia (Fig. 5; Zimmermann et al. 2008). At contacts of the tumor with portal tracts of the adjacent liver substance, strongly SMA-positive tumor spindle cells being less or not reactive for HMB-45 and Melan-A form a tight interface with the outer contour of arteries and veins, sometimes completely encircling these vessels in a radial fashion (Zimmermann et al. 2008). Beta-catenin is expressed in a mixed cytoplasmic and membranous staining pattern, being more prominent in the epithelioid cell population. This beta-catenin reactivity was more marked in tumor tissue near the tumor boundaries next to the normal hepatic tissue (Zimmermann et al. 2008). In a review of immunohistochemical findings observed in nine published cases, the typical diagnostic constellation was a positivity of the tumor cells for HMB-45, Melan-A, MITF, tyrosinase, HHF35, SMA, h-caldesmon, NKI/C3, and calponin (Strzelczyk et al. 2009). A minority of PEComas are weakly reactive for the lymphocyte marker, MUM-1 expression, while angiomyolipomas are negative (Ferenczi et al. 2012). Reactivity for S100 protein is highly variable and was found in some and not in other reports (Svajdler et al. 2007). Some authors described aberrant

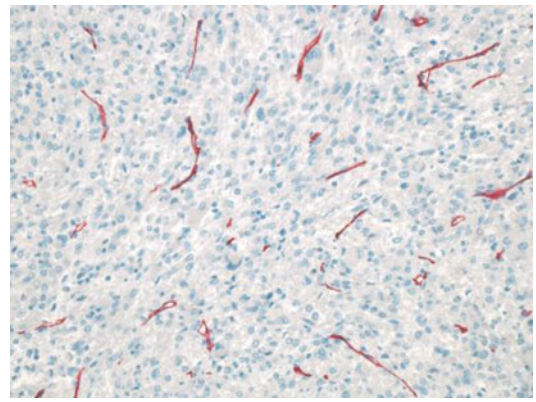

Fig. 6 Vascularization pattern of primary hepatic PEComa (CD31 immunostain)

cytoplasmic reactivity for CD1a in PEComas (Adachi et al. 2006; Adachi et al. 2008; Fadare and Liang 2008), but a more recent investigation emphasized that these tumors fail to show membranous immunostaining and do not truly express CD1a (Ahrens and Folpe 2011). PEComas display a characteristic vascular pattern that is well visualized by CD31 immunostaining (Fig. 6).

Melanotic Hepatic PEComa

Few hepatic PEComas may contain cells with a finely granular dark brown and iron-negative pigment, these cells showing a positive granular,

black cytoplasmic staining in the Fontana-Masson stain, suggesting a melanocytic component (melanotic hepatic PEComa; Zimmermann et al. 2008). A later case was characterized by a huge hepatic PEComa with a diameter of 24 cm showing brownish back areas on the cut surface. Histologically, the tumor revealed abundant melanin pigment in epithelioid neoplastic cells, but otherwise exhibiting epithelioid and spindle cells with clear to eosinophilic cytoplasm (Patra et al. 2013).

PEComa of the Bile Ducts

Primary PEComa of the common bile duct was detected in a 51-year-old male patient who had acute inset of epigastric pain. A CT of the abdomen with contrast showed a soft tissue density extending into the common bile duct at the level of the pancreatic head. ERCP revealed an intraluminal mass causing duct dilatation. The resection specimen showed a tumor within the common bile duct measuring 2.4 cm in greatest dimension. Microscopic examination revealed a well-circumscribed but unencapsulated mass composed of plum epithelioid cells with abundant clear to lightly eosinophilic cytoplasm, arranged in a nested growth pattern with a rich vascular network. Rarely, tumor cells contained a light brown melanin-type pigment. Immunohistochemically, the neoplastic cells were strongly positive for HMB-45 and neuron-specific enolase, but negative for cytokeratin, vimentin, Melan-A, and smooth muscle actin (Sadeghi et al. 2004).

Differential Diagnosis

The most important histological differential diagnosis are variants of hepatic angiomyolipomas with a very low adipocyte content. These monotypic epithelioid forms of angiomyolipoma may present with a more aggressive biology and are very difficult to distinguish from classical PEComa. Metastases of amelanotic melanomas, mainly those with a clear cell component, may be almost undistinguishable from PEComas, because they share a very similar immunophenotype. A careful patient history, also with exclusion of visceral melanomas and ocular melanoma, is mandatory. Very rare instances of liver metastases of extrahepatic PEComas have been reported (Houlle et al. 2010; Nagata et al. 2011).

Perivascular Epithelioid Clear Cell Tumors of the Hepatobiliary Tract: Clear Cell Myomelanocytic Tumors of the Hepatic Ligaments

This is a small group of very rare tumors that have mostly been detected to arise in the falciform ligament. In a report on seven patients, all tumors occurred in or immediately adjacent to the ligamentum teres or ligamentum falciforme and were termed clear cell myomelanocytic tumors (Figs. 7 and 8; Folpe et al. 2000). There were six females and one male, with an age range of 3–21 years (median, 11 years). Macroscopically, the tumors were well-circumscribed masses with a diameter ranging from 5 to 20 cm (median, 11 cm). Histologically, the neoplasms consisted of fascicles and nests of faintly eosinophilic spindle cells with a low mitotic activity. Immunohistochemically, all tumors were reactive for

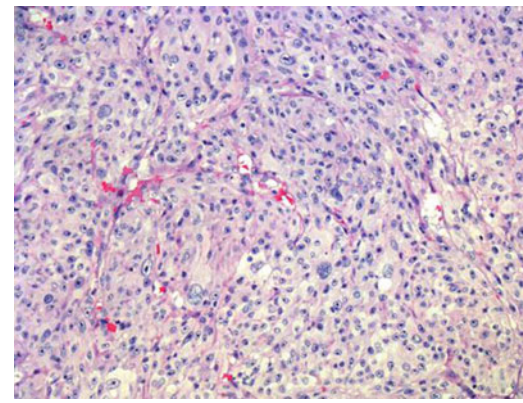

Fig. 7 Clear cell myomelanocytic tumor of the hepatic ligaments (hematoxylin and eosin stain)

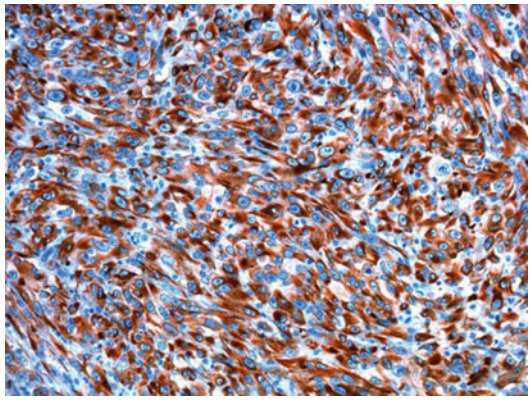

Fig. 8 Clear cell myomelanocytic tumor of the hepatic ligaments, reactivity for HMB-45 (HMB-45 immunostain)

HMB-45 (gp100 protein), and part of the neoplasms were positive for Melan-A, microphthalmia transcription factor (MITF), alpha-SMA, and myosin, but not desmin and S100 protein. Three tumors were analyzed for tuberin expression, with a negative result. Follow-up in six patients revealed that five patients were free of disease and one patient had a presumed lung metastasis. In the same year, Tanaka et al. (2000) reported a similar tumor occurring in the ligamentum teres hepatis of a 13-year-old Japanese girl. The authors used the term HMB-45/Melan-A and smooth muscle actin-positive clear cell epithelioid tumor to denote this lesion. The liver tumor measured up to 9 cm in diameter and was completely removed. Macroscopically, the tumor tissue was homogeneous and tan-white, without necrosis or hemorrhage. Histologically, polygonal or oval-shaped cells with a granular or clear cytoplasm were arranged in nests or sheets. There was moderate nuclear atypical, but mitotic figures were absent. Immunohistochemically, most of the neoplastic cells were reactive for HMB-45, Melan-A, and smooth muscle actin, but were negative for desmin, cytokeratin, CD34, CD68, or CD99. The tumor was interpreted to represent a member of the clear cell "sugar tumors." A similar neoplasm was reported in a 36-year-old woman presenting with acute abdomen caused by intralesional hemorrhage (Priola et al. 2009).

PEComas of the Hepatic Ligaments in Adults

Few cases of PEComas arising in the hepatic ligaments of adults have been reported, both in the falciform ligament (Choi et al. 2009) and the ligamentum teres (Sotiropoulos et al. 2009). In the case of Choi and coworkers (2009), a 30-year-old woman presented with a growing periumbilical mass. A CT scan of the abdomen showed an intra-abdominal, well-enhanced, and focally calcified mass measuring 7.5 cm supposed to originate from the falciform ligament. The resected specimen revealed a uniloculated cystic tumor with a solid portion, and histology was characterized by a population of spindled to epithelioid cells with a clear to eosinophilic cytoplasm and immunoreactivity for HMB-45 and SMA. Also a variant of PEC neoplasms, clear cell myomelanocytic/myomelanocytic tumor, was observed in the hepatic ligaments (Folpe et al. 2000; Priola et al. 2009; Coker et al. 2013), a type of neoplasm further discussed in a separate paragraph.

Angiomyolipoma of the Liver

ICD-O 8693/1

Introduction

The term angiomyolipoma was first used by Morgan and coworkers in 1951 to denote a distinct renal tumor (Morgan et al. 1951). Angiomyolipomas (AMLs) are rare neoplasms and have been detected in only 0.07 % of an autopsy series. The detection of the expression of melanoma-associated markers has shown that AML belongs to the PEComa family of tumors. AML is most often located in the kidneys, almost always follows a benign course, and occurs both sporadically and in association with the tuberous sclerosis complex (TSC; reviews: Blute et al. 1988; Eble 1998). AMLs mostly share a common histologic pattern in all the organs they

arise, characterized by a mixture of epithelioid or spindled perivascular cells, myoid elements/smooth muscle cells, and adipose tissue to variable amounts. However, AML also occurs in a rather broad spectrum of histological variants.

The monotypic epithelioid variant of AML has recently been differentiated as a distinct entity from typical AML. Few cases of AML with locally aggressive behavior and distant metastases have been described, considered malignant variants of AML (multicentric aggressive angiomyolipoma). These tumors are usually multicentric lesions with associated renal AML and are histologically of the epithelioid-predominant type (review: Lai et al. 2006). One variant of AML is composed exclusively or predominantly of smooth muscle cells (smooth muscle cell-predominant AML), and tumors with this phenotype were observed in the liver and in the renal capsule (Nonomura et al. 1998). Renal angiomyolipoma with epithelial cysts (AMLEC) is a recently recognized entity characterized by three distinct histologic components.

Angiomyolipoma of the liver (hepatic angiomyolipoma, HAML) is a rare lesion that has first been reported in 1922 at the scientific session of the association of middle-German pathologists in Dresden (Mittasch 1922). The tumor was again described in 1976 based on two tumors incidentally found at autopsy (Ishak 1976). However, it appears that the liver is the second most common site of AML. The first clinical case was presented in 1983 (Kawarada and Mizumoto 1983). Since then, more than 200 cases have been described in the literature (reviews: Nonomura et al. 1994a; Chung et al. 2002; Petrolla and Xin 2008; Ding et al. 2011; Yang et al. 2013). In about 20 % of the patients, an association with the tuberous sclerosis complex (TSC) has been identified, similar to AML occurring in other organs (Compton et al. 1976; Dumortier et al. 2010).

Epidemiology

In a retrospective study of eight female patients with HAML, age ranged from 30 to 66 years (mean, 45.3 years) (Yeh et al. 2001). In a review of 74 cases reported in the literature, HAMLs were noted between the first and eight decade, and the lesions ranged from 0.3 to 36 cm in diameter (Hoffman et al. 1997). Among 156 patients with angiomyolipoma originating from different organs, the liver was involved in 14 % (Yang et al. 2012). In a study on 30 patients with HAML, female patients were diagnosed as having this lesion more often than males (5:1), and mean age at diagnosis was 48.7 years (range, 29–68 years). Among 26 other patients, the female predominance was 21:5 (Ren et al. 2003), while in a more recent analysis of 51 patients, 41 were female (Li et al. 2009), and in a study on 79 patients, there were 58 women and 21 men (Ding et al. 2011). A clear predominance of female subjects was observed in another recent study (54 females vs. 20 males; Hu et al. 2011).

Clinical Features

Most tumors are located to the right liver lobe (in 56.8 % of 169 patients; Yu et al. 2010), and there is a clear female predominance. Similar to renal AML, HAML may manifest in the form of multiple angiomyolipomas, more often in patients with tuberous sclerosis (Kyokane et al. 1995; Nonomura et al. 1995; Arblade et al. 1996; Strotzer et al. 1999; Fricke et al. 2004; Saito et al. 2004; Takamura et al. 2005), but multiple HAMLs, sometimes with up to 15 nodules of variable diameter, have also been observed in the absence of tuberous sclerosis (Tang et al. 2002; Saito et al. 2004; Dumortier et al. 2010). Hepatic AML may be associated with unilateral or bilateral renal AML (Kimura et al. 1994; Hirasaki et al. 1999; Chao et al. 2004; Mongha et al. 2008). In a study on 205 patients with tuberous sclerosis complex, the presence of HAML was significantly associated with the presence of renal AML (Black et al. 2012). In one review, 13 of 60 cases of HAML were associated with concurrent renal AML (Hoffman et al. 1997). HAML has been observed in association with pulmonary angiomyolipoma (Garcia and Mestre de Juan 2002), pulmonary

lymphangioleiomyomatosis (Kim et al. 2003), focal nodular hyperplasia, bile duct adenoma and cavernous hemangioma of the liver (Langner et al. 2001), splenic hamartoma (Irie et al. 2002), hepatocellular carcinoma (Chang et al. 2001; Yang et al. 2008), and high-grade sarcoma of the liver (Bralet et al. 2000).

In a series of 52 cases (Nonomura et al. 1994a), the disease was symptomatic in 60 % of the patients, with abdominal pain or distress found in 37 % of the patients, followed by malaise and upper abdominal mass or hepatomegaly. Among ten patients from China, HAML was detected incidentally via routine examinations in eight patients (Ji et al. 2001). Among 26 patients (18 females), most patients presented no significant symptoms except for one who had spontaneous rupture hemorrhage (Zhou et al. 2008). Among 94 Chinese patients from four institutions, 52 patients (55.3 %) showed no significant clinical symptoms (Chang et al. 2011). Complications of HAML are seldom encountered. This is contrast to renal AML, where spontaneous and sometimes massive retroperitoneal hemorrhage from the tumor (Wunderlich's syndrome) can occur in up to 10 % of the patients. HAML complications comprise acute abdomen induced by intratumoral hemorrhage (Priola et al. 2009), rupture (Zhou et al. 2008; Ding et al. 2011), and Budd-Chiari syndrome (Kelleher et al. 2004). All of 26 patients of one series that had hepatic resection of HAML showed a benign course with no signs of recurrence (Ren et al. 2003). In a series of 25 cases, all patients underwent partial hepatectomy, and there was no evidence of recurrence after a median follow-up of 43 months (Li et al. 2008). Follow-up analysis of 94 Chinese patients with HAML and treatment with surgical resection (follow-up rate, 91.5 %) showed no signs of recurrence or metastasis (Chang et al. 2011). HAML may show progressive growth, but this is slow and usually does not indicate a transition to malignancy. It was found that particularly the adipose tissue component can undergo a considerable increase in mass with time (Rimola et al. 2003). However, late recurrence of HAML has been reported, usually in cases with an epithelioid morphology and sometimes several years after surgical treatment (Croquet et al. 2000; Dalle et al. 2000; Deng et al. 2008; Nguyen et al. 2008). Epithelioid HAML may show macroscopic angioinvasion, with invasion and thrombosis of the portal vein. In one patient with this alteration, no tumor recurrence following resection was noted during the subsequent 24-month follow-up (Rouquie et al. 2006). Aggressive HAML with fatal progressive disease has also been observed in the pediatric age group (McKinney et al. 2005).

Pathology

Macroscopy

Commonly, HAMLs are sharply demarcated masses without a capsule. The cut surface of resected HAML is whitish yellow to yellow or tan and relatively homogeneous. The tumor tissue is mostly soft and sometimes friable. Calcification is an exceptional finding. The majority of the tumors have no fibrous pseudocapsule, but such a structure may be mimicked macroscopically by the rim of peritumoral liver atrophy. Necrosis and hemorrhagic foci may be in evidence (Yuan et al. 2001). Rarely, HAMLs are pedunculated lesions (Akatsu et al. 2004). In HAML developing in the context of tuberous sclerosis, hepatic tumors are more often multiple and smaller lesions (Mittasch 1922; Fricke et al. 2004; Saito et al. 2004), sometimes clustered in subcapsular parts of the liver.

Histopathology

The histopathology of HAML has been described in detail (Nonomura et al. 1994a; Tsui et al. 1999; Yuan et al. 2001; Shao et al. 2003). The pathologic diagnosis of HAML is mostly made based on the recognition of the four major components of AML, i.e., abnormal blood vessels, PEC cells, smooth muscle cells, and adipose tissue (Figs. 9 and 10). These tissue elements of HAML are, however, highly variable in expression from case to case and even between different areas of the same tumor. In one series, the most common pattern was solid sheets of myoid cells intermixed

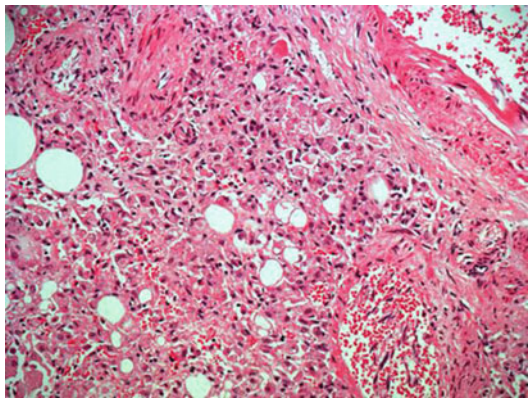

Fig. 9 Angiomyolipoma of the liver. This tumor consists of a complex mixture of macrovesicular adipose cells, epithelioid cells, spindle cells, and abnormal blood vessels (hematoxylin and eosin stain)

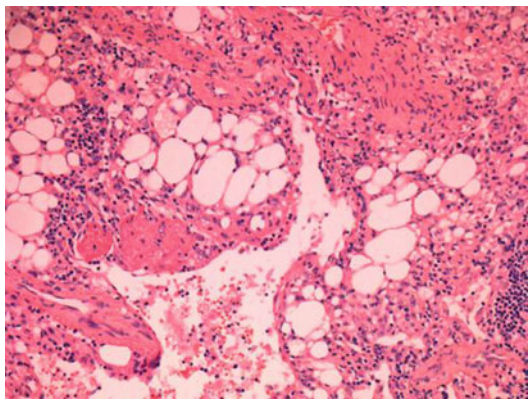

Fig. 10 Angiomyolipoma of the liver with ectatic blood vessels and myoid cell nests (hematoxylin and eosin stain)

with adipose cells and decorated by abnormal thick-walled vessels, the myoid cells being either epithelioid, spindled, or intermediate (Yuan et al. 2001). The epithelioid cells may be large and polygonal shaped or may represent so-called spider-web cells. The cytoplasm of epithelioid cells is eosinophil and granular or clear and vacuolated at the periphery, and the nucleus is commonly eccentrically placed. Nuclear atypias of epithelioid cells are usually slight, but markedly pleomorphic and hyperchromatic nuclei had been found in the rare cases of HAML with a malignant behavior (Deng et al. 2008). The epithelioid cells may contain PAS-positive, diastase-resistant cytoplasmic granules, and part of the cells show nuclear pseudoinclusions. In contrast, spindled myoid cells show a usually clear and slightly vacuolated cytoplasm and oval to fusiform nuclei. The characteristic blending of myoid cells into the walls of abnormal vessels, already described in 1944 for renal AML (Apitz 1944; see above), has also been described in HAML (Yuan et al. 2001). Intermediate cells are smaller, ovoid, or short spindle cells intermingled with polygonal epithelioid cells and present in mostly small areas as sheets of loosely arranged whorled and interlaced fascicles (Yuan et al. 2001). Adipose cells are morphologically mature and are arranged in sheets or as individual cells isolated between myoid cells, but lipoma-like lesions or angiolipomatous lesions sometimes occupying more than 80 of the tumor also occur. Within the lipomatous areas, lipoblast-like cells with multivacuolated, Oil red O-positive cytoplasm and indented nuclei have been recognized (Yuan et al. 2001). Mitotic figures are usually sparse. The development of the vascular component may be variable, but frequently one notes conspicuous tortuous and partially abnormal thick-walled blood vessels that commonly lack an elastic lamella. Large HAMLs (diameter more than 5 cm) showed a significantly increased microvessel density and lymph vessel density as compared with smaller tumors (Xian et al. 2011). The blood vessels may be cuffed by SMA-positive myoid cells which typically blend into the peripheral part of the vascular wall, as originally described by Apitz (1944). Reactive changes include focal lymphocytic infiltrations (Nonomura et al. 2012), foamy macrophages (sometimes lipogranulomas), and cholesterol crystal clefts and cholesterol granulomas.

Most HAMLs are histologically expanding lesions, with peritumoral atrophy of the liver substance. However, HAML can show microscopic invasive growth at the tumor periphery, with growth of epithelioid tumor cells into sinusoidal vascular channels, suggesting malignancy. Also other normal hepatic structures may be invaded. In a systematic study of 39 cases, an invasive growth pattern into surrounding hepatic parenchyma, portal triads, and/or around hepatic veins

was found in 62 % of the cases, invasion usually presenting as perivascular growth. Distant metastases were not found in any of the cases within the mean follow-up period of 6.8 years (Nonomura et al. 2006). The significance of this intriguing phenomenon is currently unknown, and it is not clear, whether this distinct growth pattern in fact represents invasion as seen in frankly malignant neoplasms.

Electron Microscopy

In HAML, epithelioid cells were ultrastructurally found to be in close association with endothelial cells and characterized by unusual cytoplasmic organelles such as myofilaments having focal densities and dense attachments, numerous large electron-dense bodies, and a large number of glycogen particles and lipid droplets, suggesting that these cells may represent immature mesenchymal cells having the ability to differentiate toward both smooth muscle and adipose cells (Okada et al. 1989). Epithelioid cells also contain electron-dense granules with transverse striations like those found in melanosomes (Weeks et al. 1991).

Immunohistochemistry

It is now well established that, similar to PEC tumors, HAMLs express reactivity for HMB-45 (Weeks et al. 1991; Yuan et al. 2001; Ren et al. 2003; Saito et al. 2004; Yeh et al. 2005), chiefly in the myoid cell component. HMB-45 (human melanoma, black) is an organelle membrane-specific marker related to the pmel 17 gene product (review: Bacchi et al. 1996). HAML cell is also reactive for Melan-A (Nonomura et al. 1996). Myoid/smooth muscle cells expressed HMB-45 in 100 % of cases, Melan-A in 14/15 lesions, MITF in 5/12, and tyrosinase in 3/12 hepatic AML, immunoreactivity being generally stronger in the epithelioid component (Makhlouf et al. 2002a). Part of the spindled cells express vimentin and/or smooth muscle actin (Yuan et al. 2001). Angiomyolipomas, including those of the liver, express KIT (CD117) in epithelioid, spindle, and intermediate round cells in a diffuse cytoplasmic staining pattern (Makhlouf et al. 2002b). In 12 patients with HAML, no reactivity for estrogen and progesterone receptors was found (Yeh et al. 2005). This is in contrast to renal AML, where both estrogen and progesterone receptor have been observed in some investigations.

Variants of Hepatic Angiomyolipoma

Fat-Predominant HAML

A subset of HAML is characterized by predominance of adipose tissue, resembling hepatic lipoma and sometimes occurring as multiple lesions (Shima et al. 1986; Blumgart et al. 1987; Nonomura et al. 1996; Hirasaki et al. 1999). The absence of adipose tissue in HAML may be associated with the epithelioid phenotype (Kimura et al. 1994). Hepatic lipoma may radiologically mimic fat-rich HAML (Nakamura et al. 2009). A very rare variant of HAML with a significant fat cell component displays myelolipoma-like features (Agaimy et al. 2012).

Monotypic Epithelioid HAML

The epithelioid variant of AML (monotypic epithelioid AML) has been observed in the liver (Kimura et al. 1994; Koide et al. 1998; Flemming et al. 2000; Leenman et al. 2009) and may account for 50 % or more of the tumor cells (Shao et al. 2003). In few cases, the epithelioid phenotype was associated with lack of adipose tissue (Kimura et al. 1994). In a study of 15 hepatic AML, the tumors exhibited a predominance of the epithelioid smooth muscle cell component, in contrast to renal counterparts which were more frequently spindled (Makhlouf et al. 2002a). Very rarely, the epithelioid phenotype may result in a trabecular growth pattern mimicking hepatocellular carcinoma (trabecular angiomyolipoma; Tsui et al. 1992). Resemblance to hepatocellular carcinoma is also encountered in those variants of

HAML that produce a polygonal epithelioid cell component (Koide et al. 1998).

Smooth Muscle Cell-Predominant HAML

A further variant observed in the liver is smooth muscle cell-predominant HAML (Nonomura et al. 1998). In most HAMLs, the morphology and frequency of smooth muscle cells are quite variable (Nonomura et al. 2012). But there are rare HAMLs with an impressive smooth muscle component. The so-called myomatous HAML has distinct imaging features, being hypoechoic on US and hypointense in MR images (Boraschi et al. 2012). Histologically, these lesions show a prominent component of SMA-positive myoid cells forming fascicles and bundles intermingled with clear cells and sometimes fat-storing cells. Few cases have shown pleomorphic histological features (Nonomura et al. 1994b).

Clear Cell HAML

This extremely rare variant, characterized by a high content of clear cells mimicking clear cell hepatocellular carcinoma, has been observed in the liver of a 47-year-old Chinese women (Chen et al. 2009). The lesion was resected, and macroscopy revealed a white, oval mass which had now a diameter of 3 cm. Histology showed HAML with variable proportions of adipose tissue, smooth muscle cells, and large epithelioid cells with a clear cytoplasm, many cells with peripheral clearing and radiating strands of cytoplasm adhering to the nucleus producing a spider cell appearance. Immunohistochemically, the tumor cells were positive for HMB-45.

Oncocytic HAML

Similar to other AMLs with oncocytic features (Martignoni et al. 2002; Sironi and Spinelli 2003), HAML may present with an oncocytic phenotype (oncocytic HAML; Salisbury and Portmann 1987; Tsui et al. 1999; Yuan et al. 2001). In a series of 30 HAML, the oncocytic variant was detected in three cases (Tsui et al. 1999).

Giant Cell HAML

HAML with numerous giant cells was observed in a 23-year-old female with tuberous sclerosis and multiple masses throughout the liver, measuring from 4 to 11 cm. A CT-guided fine-needle aspiration biopsy was performed, and cytology smears revealed epithelioid, HMB-45-positive HAML with a contribution of numerous large, multinucleated epithelioid cells, which also were HMB-45 positive (Alatassi and Sahoo 2009).

Inflammatory HAML

Rarely, HAML histologically presents as a lesion with a dense leukocytic infiltration, resembling inflammatory pseudotumor of the liver (Kojima et al. 2004; Liu et al. 2012). This HAML with HMB-45-positive epithelioid, myoid, and adipose cells exhibited a histologic picture resembling an inflammatory pseudotumor, with a dense infiltrate consisting of small lymphocytes, macrophages, and plasma cells. In a series of five cases without signs of tuberous sclerosis, the patients were four females and one male, with an age range of 21–48 years at diagnosis (mean, 39.2 years). The tumor size was from 5.5 to 10 cm in the greatest dimension (mean, 7.46 cm). Histology was a mixture of epithelioid, myoid, and scattered adipose cells. More than 50 % of the tumor areas showed a heavy inflammatory infiltration. The patients had no evidence of disease during a follow-up period from 3 to 9 years (Shi et al. 2010).

Malignant HAML

A malignant potential of HAML is difficult to judge. This is in part due to the fact that HAML can show significant cellular atypia, seen in up to 25 % of cases. In addition, signs of invasive

growth were noted in 69 % of cases (Nonomura et al. 2012). All of the few examples of HAML with a malignant behavior were histologically characterized by increased nuclear atypia, sometimes with pleomorphic tumor cells, and the development of hemorrhagic and coagulative necrosis (Dalle et al. 2000; Nguyen et al. 2008). All tumors exhibited only a low mitotic rate. In one report, spindle cells displayed rectangular, hyperchromatic nuclei, and part of the epithelioid cells showed enlarged vesicular nuclei with macronucleoli. Few cells had a Reed-Sternberg cell-like appearance. In this case, tumor cells invaded the sinusoids between the adjacent hepatocyte plates (Nguyen et al. 2008). It has, however, been shown that an invasive behavior of HAML is not correlated with a malignant phenotype (see above; Nonomura et al. 2006).

Differential Diagnosis

Fat-predominant HAML may be confounded with rare hepatic lipomas, while variants with a predominant smooth muscle cell component can mimic leiomyomatous tumors of the liver. In rare situations, extrahepatic malignant epithelioid angiomyolipomas can metastasize to the liver, e.g., renal AMLs (Vicens et al. 2014).

Pathogenesis

AML has been recognized as a clonal neoplasm, based on the finding of nonrandom inactivation of the X chromosome. Clonality of AML has also been documented for those tumors primary to the liver (Flemming et al. 2000). DNA flow cytometric studies revealed a diploid DNA pattern in HAML (Terris et al. 1996). Methylation pattern analysis of the human androgen receptor gene on chromosome Xq11-12 has shown that adipose tissue and smooth muscle cells of renal AML are both monoclonal but may arise independently, suggesting the coexistence of tumor subclones in these lesions (Cheng et al. 2001). However, another study observed clonal smooth muscle and blood vessel cell populations, while adipose tissue was polyclonal and thought to be metaplastic or reactive (Saxena et al. 1999).

Extrapulmonary Clear Cell ("Sugar") Tumors of the PEC Type

Introduction

Clear cell "sugar" tumors were described in the lung (Liebow and Castleman 1963, 1971) and are related to angiomyolipoma and other PEC tumors (Bonetti et al. 1994), but may also occur in extrapulmonary sites (primary extrapulmonary sugar tumor, PEST), including the skin, breast, rectum, vulva, heart, and pancreas (Zamboni et al. 1996; Govender et al. 2002; Tazelaar et al. 2001; de Saint Aubain Somerhausen et al. 2005; Baez et al. 2009). The cell of origin and direction of differentiation of these neoplasms remains enigmatic, but recognition of HMB-45 immunoreactivity and identification of melanosomes have suggested a relationship to angiomyolipoma of the kidney or liver and lymphangiomyomatosis. The potential relationship between clear cell sugar tumor and lymphangiomyomatosis, a lesion connected to tuberous sclerosis, is underlined by the observation of clear cell proliferations of the lung with lymphangiomyomatosis-like change (Pileri et al. 2004).

Clear Cell ("Sugar") Tumors of the Hepatobiliary Tract

"Sugar" clear cell tumors of PEC lineage are very uncommon in the liver and biliary tract. Alexandrakis and Klinge (1998) described a 10 cm-sized tumor incidentally found in the right liver lobe of a 32-year-old man. Histology revealed a clear cell tumor characterized by a uniform population of large epithelioid cells with a mostly water-clear and sometimes also eosinophilic and granular cytoplasm. In the clear cells, the rough endoplasmic reticulum (ergastoplasm) was concentrated in a perinuclear compartment, forming threads leading from the nuclei to the

periphery of the clear cytoplasm. The cytoplasm contained granular PAS-positive material, digestible with diastase treatment, while melanin granules were not detected. Very few univacuolated or multivacuolated adipocyte-like cells were found within the neoplasm. Groups of cells or single cells were surrounded by a network of reticulin fibers. In addition to clear epithelioid cells, spindle-shaped cells were also noted, forming whorl-like formations around small blood vessels. The tumor contained foci of erythroblasts and of foamy macrophages and lymphocytes. Immunohistochemically, the neoplastic cells were reactive for HMB-45, and spindle cells were in part reactive for smooth muscle actin. It is possible that this neoplasm was related to angiomyolipoma variants.

Differential Diagnosis

In the alimentary tract, EPSG should be distinguished from other lesions with a clear cell phenotype, including gastric clear cell carcinoma; clear cell carcinomas of the bowel, biliary tract, liver, and pancreas; clear cell well-differentiated neuroendocrine carcinomas; and clear cell variants of alimentary tract melanoma (review: Ritter et al. 1997).

Extrapulmonary Lymphangiomyomatosis

Introduction

Lymphangiomyomatosis (lymphangioleiomyomatosis, LAM) is a proliferative lesion of smooth muscle cells from lymphatic vessel origin. The process is well recognized in the lung (pulmonary lymphangiomyomatosis, PLAM), in lymphatic trunks, and in lymph nodes and seems to be restricted to female patients usually during their reproductive age. In the lungs, LAM is characterized as the cystic destruction of pulmonary parenchyma; obstruction of airways, blood vessels, and lymphatics; and loss of pulmonary function. The disease is a partial presentation of tuberous sclerosis (reviews: Zhang and Travis 2010; Cottin et al. 2011; Harari et al. 2011). This is supported by the observation that renal angiomyolipomas, of which at least 40 % occur in the setting of tuberous sclerosis, are often detected in patients with LAM. Both lesions are characterized by the involvement of HMB-45-reactive myoid cells (Chan et al. 1993; Hironaka and Fukayama 1999). In LAM, the proliferating myoid cells are benign looking, but they may undergo metastatic spread. The smooth muscle cells coexpress muscle cell markers (SMA and desmin), melanocyte markers (HMB-45, Melan-A/MART-1, and microphthalmia transcription factor), steroid hormone receptors, and a member of the Wnt signaling pathway, beta-catenin. Disseminated LAM cells have been shown to exhibit TSC2 LOH in about half of the patients examined (Crooks et al. 2004). LAM or LAM-like lesions are known to develop in extrapulmonary compartments (extrapulmonary LAM), most often in the retroperitoneal space (Hamada et al. 1997; Jaiswal et al. 2003). Other extrapulmonary sites comprise the pelvic cavity (Kim et al. 2005) and the uterus (Torres et al. 1995) and very uncommonly other organs and tissues.

Lymphangiomyomatosis of the Hepatobiliary Tract

Involvement of the liver by LAM has been observed in female patient with pulmonary LAM, bilateral renal angiomyolipomas, and LAM manifestations in the ovaries and periadrenal vessels (Lack et al. 1986). In this case, the pattern of LAM manifestations suggests metastatic spread from pulmonary LAM. Retroperitoneal extrapulmonary LAM was found to infiltrate the papilla of Vater, causing biliary tract obstruction (De Groot et al. 2008). In this patient, a 23-year-old, otherwise healthy woman, a CT scan of the abdomen showed a large retroperitoneal mass, up to 16 cm in diameter, with cystic and solid components in the lower right abdomen which extended around the abdominal aorta and inferior vena cava. Later examinations revealed pulmonary LAM. In the course of the disease, the process extended to the ampullary region, causing bile duct stenosis

and dilated bile ducts. An ampullary biopsy displayed a lymphangiectatic pattern typical for LAM.

Lymphangiomyomatosis Associated with Other Liver Tumors

Pulmonary LAM is well known to be associated with renal angiomyolipomas, in some studies in more than 50 % of cases (Valensi 1973; Monteforte and Kohnen 1974; Lack et al. 1986; Bernstein et al. 1995; Torres et al. 1995; Maziak et al. 1996). A less common emerging entity is pulmonary LAM associated with the synchronous development of hepatic angiomyolipoma (Kim et al. 2003; Ciftci et al. 2007; Lu et al. 2009; Ishitobi et al. 2011). In a series of 14 cases of LAM, hepatic angiomyolipoma was noted in 7.14 % of patients (Lu et al. 2009). One patient with pulmonary LAM was found to have a large hepatic hemangioma (Cagnano et al. 1991).

Lymphangiomyomatosis Associated with Nonneoplastic Liver Lesions

Extrapulmonary LAM located to the retroperitoneal space, with formation of a large cystic tumor, was associated with peliosis hepatis (Hamada et al. 1997).

Peritoneal PEComatosis

This alteration was first described in a 70-year-old female patient and was characterized by a diffuse myomelanocytic tumor of the peritoneum clinically simulating peritoneal malignant mesothelioma. Exploratory laparoscopy revealed diffuse encasing of the peritonealized organs by a fleshy tissue rind, and scattered nodules were also present. One of the tumor masses measured 6 cm and was considered as the dominant lesion. The cells were of the epithelioid type and positive for HMB-45, Melan-A, and SMA, but negative for S-100 protein (Salviato et al. 2006).

Hepatic Hamartomas in Tuberous Sclerosis

The older literature reveals several reports of hepatic nodular lesions occurring in the context of tuberous sclerosis and termed liver hamartomas (Viamonte et al. 1966; Compton et al. 1976; Fleury et al. 1987; Jozwiak et al. 1992; Cheung et al. 1993). In most reports, no histologic diagnosis was performed. Based on the radiological descriptions, emphasizing the similarity between these "hamartomas" and renal angiomyolipomas, it can safely be assumed that most of these "hamartomas" were in fact hepatic angiomyolipomas. Cheung et al. (1993) specify in their discussion of three observations that, although the imaging features of the lesions on CT and US images are similar in many ways to renal angiomyolipomas, there has been a lack of pathological evidence that (some) of the liver lesions in tuberous sclerosis are indeed angiomyolipomas. Thus, these liver nodules were widely referred to as hamartomas. As hepatic angiomyolipomas can present as homogeneously enhancing masses that are nearly isodense to normal liver tissue on plain CT scans, focal nodular hyperplasia of the liver may be assumed in such cases (Strotzer et al. 1999).

Hepatic Dysplastic Lesions in Tuberous Sclerosis

In a minority of pediatric patients with tuberous sclerosis, unusual hepatocyte alterations characterized by cytomegaly and/or dysplastic changes have been observed (Grasso et al. 1982; Drut 1990; Ruggieri et al. 1997). Necropsy of an 8-month-old male infant with tuberous sclerosis showed microscopic collections of large cells having a pale, faintly eosinophilic cytoplasm and a large nucleus located in the liver, thymus, lungs, and heart (Drut 1990). Some of these highly atypical cells formed clusters in the liver parenchyma, resembling a sympathetic neuronal ganglion, associated with smaller, satellite-like cells. A 3-day-old male patient with tuberous sclerosis

complex showed, at necropsy, a liver disorganized in some places by the presence of a few to as many as 50 rounded hepatocytes, 80 μm in diameter, with an eosinophilic cytoplasm and containing one or two vesicular nuclei with a prominent nucleolus. Some of these hepatocytes were irregularly shaped and extremely vacuolated, morphologically resembling the glycogenated "spider cells" of cardiac rhabdomyoma (Ruggieri et al. 1997).

The dysplastic large and giant cells of the liver described in these reports resemble the splenic "histiocytoid" cells (so-called splenic histiocytosis) found mostly in newborns and rarely in adults with tuberous sclerosis, sometimes forming nodules or tumor-like lesions in the spleen (Ostor and Fortune 1978; Bender and Yunis 1981; Bender and Yunis 1982; Tunali et al. 2004; Rudzki et al. 2005). The pathogenesis of these peculiar hepatocyte changes is currently unknown.

References

Adachi Y, Kitamura Y, Nakamura H, Taniguchi Y, Miwa K, Horie Y, Hayashi K (2006) Benign clear (sugar) cell tumor of the lung with CD1a expression. Pathol Int 56:453–456

Adachi Y, Horie Y, Kitamura Y, Nakamura H, Taniguchi Y, Miwa K, Fujioka S et al (2008) CD1a expression in PEComas. Pathol Int 58:169–173

Agaimy A, Vassos N, Croner RS, Strobel D, Lell M (2012) Hepatic angiomyolipoma: a series of six cases with emphasis on pathological-radiological correlations and unusual variants diagnosed by core needle biopsy. Int J Clin Exp Pathol 5:512–521

Ahn JH, Bang H (2011) Primary perivascular epithelioid cell tumor (PEComa) of the liver: a case report and review of the literature. Kor J Pathol 45:93–97

Ahrens WA, Folpe AL (2011) CD1a immunopositivity in perivascular epithelioid cell neoplasms: true expression or technical artifact? A streptavidin-biotin and polymer-based detection system immunohistochemical study of perivascular epithelioid cell neoplasms and their morphologic mimics. Hum Pathol 42:369–374

Akatsu T, Sakamoto M, Shimazu M, Kitajima M (2004) Pedunculated angiomyolipoma of the liver with a predominant pelioid pattern. Virchows Arch 444:467–469

Akitake R, Kimura H, Sekoguchi S, Nakamura H, Seno H, Chiba T, Fujimoto S (2009) Perivascular epithelioid cell tumor (PEComa) of the liver diagnosed by contrast-enhanced ultrasonography. Intern Med 48:2083–2086

Alatassi H, Sahoo S (2009) Epithelioid angiomyolipoma of the liver with striking giant cell component: fine-needle aspiration biopsy findings of a rare neoplasm. Diagn Cytopathol 37:192–194

Alexandrakis E, Klinge O (1998) Clear cell tumour of the liver – morphological spectrum and pathogenesis (in German). Verh Dtsch Ges Pathol 82:460–468

Ameurtesse H, Chbani L, Bennani A, Toughrai I, Beggui N, Kamaoui I, Elfatemi H, Harmouch T et al (2014) Primary perivascular epithelioid cell tumor of the liver: new case report and literature review. Diagn Pathol 9:149

Apitz K (1944) Die Geschwülste und Gewebsmissbildungen der Nierenrinde.II. Mitteilung. Die mesenchymalen Neubildungen. Virchows Arch 311:306–327

Arblade S, Vilgrain V, Terris B, Zins M, Vullierme MP, Flejour JF, Belghiti J, Menu Y (1996) Hepatic angiomyolipoma simulating hepatocytic tumor. 3 cases (in French). Gastroenterol Clin Biol 20:1022–1026

Ardeleanu C, Bussolati G (2011) Telocytes are the common cell of origin of both PEComas and GISTs: an evidence-supported hypothesis. J Cell Mol Med 15:2569–2574

Argani P, Aulmann S, Illei PB, Netto GJ, Ro J, Cho HY, Dogan S, Ladanyi M, Martignoni G et al (2010) A distinctive subset of PEComas harbors TFE3 gene fusions. Am J Surg Pathol 34:1395–1406

Armah HB, Parwani AV (2009) Perivascular epithelioid cell tumor. Arch Pathol Lab Med 133:648–654

Bacchi CE, Bonetti F, Pea M, Martignoni G, Gown AM (1996) HMB-45. A review. Appl Immunohistochem 4:73–85

Baez JC, Landry JM, Saltzman JR, Qian X, Zinner MJ, Mortelé KJ (2009) Pancreatic PEComas (sugar tumor). MDCT EUS JOP 10:679–682

Bender BL, Yunis EJ (1981) Splenic involvement in tuberous sclerosis. Report of three cases. Virchows Arch (Pathol Anat) 391:363–369

Bender BL, Yunis EJ (1982) The pathology of tuberous sclerosis. Pathol Ann 17:339–382

Bergamo F, Maruzzo M, Basso U, Montesco MC, Zagonel V, Gringeri E, Cillo U (2014) Neoadjuvant sirolimus for a large hepatic perivascular epithelioid cell tumor (PEComa). World J Surg Oncol 12:46

Bernstein SM, Newell JD, Adamczyk D, Mortenson RL, King TE, Lynch DA (1995) How common are renal angiomyolipomas in patients with pulmonary lymphangiomyomatosis? Am J Respir Crit Care Med 152:2138–2143

Black et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22251200

Bleeker JS, Quevedo JF, Folpe AL (2012) "Malignant" perivascular epithelioid cell neoplasm: risk stratification and treatment strategies. Sarcoma 2012:541626

Blumgart RL, Payne M, Rhodes AH (1987) Angiomyolipoma of the liver. Clin Radiol 38:329–330

Blute ML, Malek RS, Segura JW (1988) Angiomyolipoma: clinical metamorphosis and concepts for management. J Urol 139:20–24

Bonetti F, Pea M, Martignoni G, Zamboni G (1992) PEC and sugar. Am J Surg Pathol 16:307–308

Bonetti F, Pea M, Martignoni G, Doglioni C, Zamboni G, Capelli P, Rimondi P, Andrion A (1994) Clear cell ("sugar") tumor of the lung is a lesion strictly related to angiomyolipoma – the concept of a family of lesions characterized by the presence of the perivascular epithelioid cells (PEC). Pathology 26:230–236

Bonetti F, Pea M, Martignoni G, Zamboni G, Manfrin E, Colombari R, Mariuzzi GM (1997) Review article. new unifying concept. The perivascular epithelioid cell and related lesions. Adv Anat Pathol 4:343–358

Boraschi P, Donati F, Gherarducci G (2012) Imaging findings in myomatous angiomyolipoma of the liver. Diagn Interv Radiol 18:387–390

Bralet MP, Terris B, Valla D, Belghiti J, Degott C (2000) Angiomyolipoma and high-grade sarcoma of the liver. Histopathology 37:570–572

Cagnano M, Benharroch D, Geffen DB (1991) Pulmonary lymphangioleiomyomatosis. Report of a case with associated multiple soft-tissue tumors. Arch Pathol Lab Med 115:1257–1259

Chan JKC, Tsang WYW, Pau MY, Tang MC, Pang SW, Fletcher CDM (1993) Lymphangiomyomatosis and angiomyolipoma: closely related entities characterized by hamartomatous proliferation of HMB-45-positive smooth muscle. Histopathology 22:445–455

Chang YC, Tsai HM, Chow NH (2001) Hepatic angiomyolipoma with concomitant hepatocellular carcinomas. Hepatogastroenterology 48:253–255

Chang Z, Zhang JM, Ying JQ, Ge YP (2011) Characteristics and treatment strategy of hepatic angiomyolipoma: a series of 94 patients collected from four institutions. J Gastroenterol Liver Dis 20:65–69

Chao CH, Lin CY, Chan SC, Chen KS (2004) Concurrent hepatic and ruptured renal angiomyolipoma in tuberous sclerosis complex. Chang Gung Med J 27:696–700

Chen P, Yuan T, Liu H (2009) Hepatic angiomyolipoma mimicking hepatic clear cell carcinoma. J Int Med Res 37:257–263

Cheng L, Gu J, Eble JN, Bostwick DG, Younger C, MacLennan GT, Abdul-Karim FW, Geary WA et al (2001) Molecular genetic evidence for different clonal origin of components of human renal angiomyolipomas. Am J Surg Pathol 25:1231–1236

Cheung H, Ambrose RE, Lee PO (1993) Liver hamartomas in tuberous sclerosis. Clin Radiol 47:421–423

Cheung TT, Trendell-Smith N, Poon RT (2013) Primary perivascular epithelioid cell tumour (PEComa) of the liver. BMJ Case Rep. doi:10.1136/bcr-2013-008706

Choi CW, Kim TO, Kim KY, Lee SM, Kim GH, Kang DH, Song GA, Kim S, Kim DH (2009) Perivascular epithelioid cell tumor (PEComa) of abdominal cavity from falciform ligament: a case report. J Korean Med Sci 24:346–349

Chung AY, Ng SB, Thng CH, Chow PK, Ooi LP (2002) Hepatic angiomyolipoma mimicking hepatocellular carcinoma. Asian J Surg 25:251–254

Ciftci AO, Sanlialp I, Tanyel FC, Buyukpamukçu N (2007) The association of pulmonary lymphangioleiomyomatosis with renal and hepatic angiomyolipomas in a prepubertal girl: a previously unreported entity. Respiration 74:335–337

Coker D, Kench J, Ansari N, Zhou R, Sandroussi C (2013) Education and imaging: hepatobiliary and pancreatic: clear cell myomelanotic tumor of ligamentum teres. J Gastroenterol Hepatol 28:381

Compton WR, Lester PE, Kyaw MM, Madsen JA (1976) Abdominal angiographic spectrum of tuberous sclerosis. AJR Am J Roentgenol 126:807–812

Cottin V, Archer F, Leroux C, Mornex JF, Cordier JF (2011) Milestones in lymphangioleiomyomatosis research. Eur Respir Rev 20:3–6

Crooks DM, Pacheco-Rodriguez G, DeCastro RM, McCoy JP, Wang JA, Kumaki F et al (2004) Molecular and genetic analysis of disseminated neoplastic cells in lymphangioleiomyomatosis. Proc Natl Acad Sci U S A 101:17462–17467

Croquet V, Pilette C, Aube C, Bouju B, Oberti F, Cervi C, Arnaud JP, Rousselet MC, Boyer J, Cales P (2000) Late recurrence of a hepatic angiomyolipoma. Eur J Gastroenterol Hepatol 12:579–582

Dalle I, Sciot R, de Vos R, Aerts R, van Damme B, Desmet V, Roskams T (2000) Malignant angiomyolipoma of the liver: a hitherto unreported variant. Histopathology 36:443–450

De Groot JW, Vecht J, van den Bergen HA, Coenen JL (2008) Extrapulmonary lymphangioleiomyomatosis: an unusual cause of biliary tract obstruction. Neth J Med 66:31–34

De Saint Aubain Somerhausen N, Gomez Galdon M, Bouffioux B, Courtin C, Theunis A, Vogeleer MN, Myant N (2005) Clear cell 'sugar' tumor (PEComa) of the skin: a case report. J Cutan Pathol 32:441–444

Della Vigna P, Preda L, Montfardini L, Gorone MS, Maffini FA, Bellomi M (2008) Growing perivascular epithelioid cell tumor of the liver studied with contrast-enhanced ultrasonography and magnetic resonance imaging. J Ultrasound Med 27:1781–1785

Deng YF, Lin Q, Zhang SH, Ling YM, He JK, Chen XF (2008) Malignant angiomyolipoma in the liver: a case report with pathological and molecular analysis. Pathol Res Pract 204:911–918

Ding GH, Liu Y, Wu MC, Yang GS, Yang JM, Cong WM (2011) Diagnosis and treatment of hepatic angiomyolipoma. J Surg Oncol 103:807–812

Drut R (1990) Multivisceral dysplastic lesions in a patient with tuberous sclerosis and Langerhans cell histiocytosis. Pediatr Pathol 10:633–639

Dumortier J, Guillaud O, Walter T, Ber CE, Partensky C, Boilot O, Scoazec JY (2010) Liver transplantation for

multiple angiomyolipomas complicating tuberous sclerosis complex. Gastroenterol Clin Biol 34:494–498
Durczynski A, Hogendorf P, Szymanski D, Sporny S, Strelczyk J (2012) Synchronous occurrence of multiple focal nodular hyperplasia an huge hepatic perivascular epithelioid cell tumor (PEComa) in young woman after oral contraceptive use – is there a common pathogenesis? Pol Przegl Chir 84:457–460
Eble 1998. http://www.ncbi.nlm.nih.gov/pubmed/9503504
Fadare O, Liang SX (2008) Epithelioid smooth muscle tumors of the uterus do not express CD1a: a potential immunohistochemical adjunct in their distinction from uterine perivascular epithelioid cell tumors. Ann Diagn Pathol 12:401–405
Fang SH, Zhou LN, Jin M, Hu JB (2007) Perivascular epithelioid cell tumor of the liver: a report of two cases and review of the literature. World J Gastroenterol 13:5537–5539
Ferenczi K, Lastra RR, Farkas T, Elenitsas R, Xu X, Roberts S, Brooks JS, Zhang PJ (2012) MUM-1 expression differentiates tumors in the PEComa family from clear cell sarcoma and melanoma. Int J Surg Pathol 20:29–36
Fernandez-Flores A (2011) Evidence on the neural crest origin of PEComas. Rom J Morphol Embryol 52:7–13
Flemming P, Lehmann U, Becker T, Klempnauer J, Kreipe H (2000) Common and epithelioid variants of hepatic angiomyolipoma exhibit clonal growth and share a distinctive immunophenotype. Hepatology 32:213–217
Fleury P, Smits N, van Baal S (1987) The incidence of hepatic hamartomas in tuberous sclerosis. Evaluation by ultrasonography. ROFO 146:694–696
Folpe AL, Goodman ZD, Ishak KG, Paulino AF, Taboada EM, Meehan SA, Weiss SW (2000) Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres. A novel member of the perivascular epithelioid clear cell family of tumors with a predilection for children and young adults. Am J Surg Pathol 24:1239–1246
Fricke BL, Donnelly LF, Casper KA, Bissler JJ (2004) Frequency and imaging appearance of hepatic angiomyolipomas in pediatric and adult patients with tuberous sclerosis. AJR Am J Roentgenol 182:1027–1030
Garcia TR, Mestre de Juan MJ (2002) Angiomyolipoma of the liver and lung: a case explained by the presence of perivascular epithelioid cells. Pathol Res Pract 198:363–367
Govender D, Sabaratnam RM, Essa AS (2002) Clear cell 'sugar' tumor of the breast: another extrapulmonary site and review of the literature. Am J Surg Pathol 26:670–675
Grasso S, Manusia M, Sciacca F (1982) Unusual liver lesion in tuberous sclerosis. Arch Pathol Lab Med 106:49
Hamada K, Nakaya M, Shirayama R, Kobayashi H, Kasuga H, Narita N, Mishima K et al (1997) Autopsy findings of retroperitoneal cystic tumor and peliosis hepatis in lymphangioleiomyomatosis (in Japanese). Nihon Kyobu Shikkan Gakkai Zasshi 35:437–441
Harari S, Torre O, Moss J (2011) Lymphangioleiomyomatosis: what do we know and what are we looking for? Eur Respir Rev 20:34–44
Hirasaki S, Koide N, Ogawa H, Ujike K, Shinji T, Tsui T (1999) Tuberous sclerosis associated with multiple hepatic lipomatous tumors and hemorrhagic renal angiomyolipoma. Intern Med 38:345–348
Hironaka M, Fukayama M (1999) Regional proliferation of HMB-45-positive clear cells of the lung with lymphangioleiomyomatosis-like distribution, replacing the lobes with multiple cysts and nodules. Am J Surg Pathol 23:1288–1293
Hoffman AL, Emre S, Verham RP, Petrovic LM, Eguchi S, Silverman JL, Geller SA, Schwartz ME et al (1997) Hepatic angiomyolipoma: two case reports of caudate-based lesions and review of the literature. Liver Transpl Surg 3:46–53
Hornick JL, Fletcher CD (2008) Sclerosing PEComa: clinicopathologic analysis of a distinctive variant with a predilection for the retroperitoneum. Am J Surg Pathol 32:493–501
Houlle S, Lemoine F, François A, Michot C, Sabourin JC (2010) PEComas: report of five abdominopelvic cases (in French). Ann Pathol 30:350–356
Hu WG, Lai EC, Liu H, Zhou WP, Fu SY, Pan ZY, Huang G, Lei Y, Lau WY, Wu MC (2011) Diagnostic difficulties and treatment strategy of hepatic angiomyolipoma. Asian J Surg 34:158–162
Irie H, Tamagaki T, Takeda N, Hiranuma O, Kono Y, Higaki T, Yoshizumi M, Tanaka M et al (2002) hepatic angiomyolipoma associated with splenic hamartoma. Intern Med 41:191–198
Ishak KG (1976) Mesenchymal tumors of the liver. In: Okuda K, Peters RL (eds) Hepatocellular carcinoma. Wiley, New York, pp 247–304
Ishitobi F, Fukuma A, Shibata H, Nagai A (2011) Case of tuberous sclerosis complex with pulmonary lymphangioleiomyomatosis and angiomyolipomas of the liver and kidney (in Japanese). Rinsho Byori 59:571–576
Jafari A, Fischer HP, von Websky M, Hong GS, Kalff JC, Manekeller S (2013) Primary perivascular epithelioid cell tumour (PEComa) of the liver: case report and review of the literature. Z Gastroenterol 51:1096–1100
Jaiswal VR, Baird J, Fleming J, Miller DS, Sharma S, Molberg K (2003) Localized retroperitoneal lymphangioleiomyomatosis mimicking malignancy. A case report and review of the literature. Arch Pathol Lab Med 127:879–882
Ji Y, Zhu X, Zhou J, Tan Y, Wang J, Fan J, Zhou Y (2001) Hepatic angiomyolipoma: a clinicopathologic study of 10 cases. Chin Med J (Engl) 114:280–285
Jozwiak S, Pedich M, Rajszys P, Michalowicz R (1992) Incidence of hepatic hamartomas in tuberous sclerosis. Arch Dis Child 67:1363–1365

Kawarada Y, Mizumoto R (1983) Angiomyolipoma of the liver. Am J Gastroenterol 78:434–439

Kelleher T, Staunton M, Malone D, Geoghan J, McCormick A (2004) Budd Chiari syndrome associated with angiomyolipoma of the liver. J Hepatol 40:1048–1049

Khaja F, Carilli A, Baidas S, Sriharan A, Norford S (2013) PEComa: a perivascular epithelioid cell tumor in the liver – a case report and review of the literature. Case Rep Med 2013:904126

Khan HM, Katz SC, Libbey NP, Somasundar PS (2014) Hepatic PEComa: a potential pitfall in the evaluation of hepatic neoplasms. BMJ Case Rep. doi:10.1136/bcr-2014-204122

Kim NR, Chung MP, Park CK, Lee KS, Han J (2003) Pulmonary lymphangioleiomyomatosis and multiple hepatic angiomyolipomas in a man. Pathol Int 53:231–235

Kim HS, Park MI, Suh KS (2005) Lymphangiomyomatosis arising in the pelvic cavity: a case report. J Korean Med Sci 20:904–907

Kimura N, Kubota M, Nagura H (1994) A hepatic tumor associated with bilateral renal angiomyolipomas: a variant of angiomyolipoma? Pathol Int 44:540–547

Koide O, Matsuzaka K, Tanaka Y (1998) Multiple giant angiomyolipomas with a polygonal epithelioid cell component in tuberous sclerosis: an autopsy case report. Pathol Int 48:998–1002

Kojima M, Nakamura S, Ohno Y, Sugihara S, Sakata N, Masawa N (2004) Hepatic angiomyolipoma resembling an inflammatory pseudotumor of the liver. A case report. Pathol Res Pract 200:713–716

Kyokane T, Akita Y, Katayama M, Sato T, Shichino S, Nimura Y (1995) Multiple angiomyolipomas of the liver (case report). Hepatogastroenterology 42:510–515

Lack EE, Dolan MF, Finisio J, Grover G, Singh M, Triche TJ (1986) Pulmonary and extrapulmonary lymphangiomyomatosis: report of a case with bilateral renal angiomyolipomas, multifocal lymphangiomyomatosis, and a glial polyp of the endocervix. Am J Surg Pathol 10:650–657

Lai HY, Chen CK, Lee YH, Tsai PP, Chen JH, Shen WC (2006) Multicentric aggressive angiomyolipomas: a rare form of PEComas. AJR Am J Roentgenol 186:837–840

Langner C, Homayounfar K, Ruten B, Fass J, Ruschoff J (2001) Concomitant occurrence of angiomyolipoma, focal nodular hyperplasia, bile duct adenoma, and cavernous hemangioma in the liver (in German). Pathologe 22:417–423

Larbcharoensub N, Karnsombut P, Jatchavala J, Wasutit Y, Nitiyanant P (2007) Primary hepatic clear cell myomelanocytic tumor. Case report and review of the literature. APMIS 115:1454–1459

Leenman EE, Mukhina MS, Nasyrov AR (2009) Monophasic angiomyolipoma (PEComa) of the liver (in Russian). Arkh Patol 71:44–46

Li et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18516533

Li T, Fan J, Qin LX, Zhou J, Sun HC, Wang L, Ye QH, Qiu SJ, Tang ZY (2009) A clinicopathologic study of hepatic angiomyolipoma (in Chinese). Zhomghua Wai Ke Za Zhi 47:1536–1539

Liebow AA, Castleman B (1963) Benign "clear cell tumors" of the lung. Am J Pathol 43:13a–14a

Liebow AA, Castleman B (1971) Benign clear cell ("sugar") tumors of the lung. Yale J Biol Med 43:213–222

Liu Y, Wang J, Lin XY, Xu HT, Qiu XS, Wang EH (2012) Inflammatory angiomyolipoma of the liver: a rare hepatic tumor. Diagn Pathol 7:122

Liu D, Shi D, Xu Y, Cao L (2014) Management of perivascular epithelioid cell tumor of the liver: a case report and review of the literature. Oncol Lett 7:148–152

Lu SH, Hou YY, Tan YS, Xu JF, Zeng HY, Sujie AK, Wang XD, Bai CX (2009) Clinical and histopathological alterations of lymphangioleiomyomatosis in 14 Chinese patients. Chin Med J (Engl) 122:1895–1900

Makhlouf HR, Ishak KG, Shekar R, Sesterhenn IA, Young DY, Fanburg-Smith JC (2002a) Melanoma markers in angiomyolipoma of the liver and kidney: a comparative study. Arch Pathol Lab Med 126:49–55

Makhlouf HR, Remotti HE, Ishak KG (2002b) Expression of KIT (CD117) in angiomyolipoma. Am J Surg Pathol 26:493–497

Martignoni et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/11958671

Matkowskyj KA, Rao MS, Raparia K (2013) Transcription factor E3 protein-positive perivascular epithelioid cell tumor of the appendix presenting as acute appendicitis: a case report and review of the literature. Arch Pathol Lab Med 137:434–437

Maziak DE, Kesten S, Rappaport DC, Maurer J (1996) Extrathoracic angiomyolipomas in lymphangioleiomyomatosis. Eur Respir J 9:402–405

McKinney CA, Geiger JD, Castle VP, Ruiz RE, Strouse PJ (2005) Aggressive hepatic angiomyolipoma in a child. Pediatr Hematol Oncol 22:17–24

Mittasch L (1922) Demonstration eines Angiomyolipoms der Leber bei tuberöser Hirnsklerose (Demonstration of an angiomyolipoma of the liver in tuberous brain sclerosis). Centralbl Allgem Pathol Pathol Anat 33:67

Mongha R, Bansal P, Dutta A, Das RK, Kundu AK (2008) Wunderlich's syndrome with hepatic angiomyolipoma in tuberous sclerosis. Indian J Cancer 45:64–66

Monteforte WJ, Kohnen PW (1974) Angiomyolipomas in a case of lymphangiomyomatosis syndrome: relationships to tuberous sclerosis. Cancer 34:317–321

Morgan GS, Straumjord JV, Hall EJ (1951) Angiomyolipoma of the kidney. J Urol 65:525–527

Nagata S, Yuki M, Tomoeda M, Kubo C, Yoshizawa H, Kitamura M, Uehara H, Katayama K et al (2011) Perivascular epithelioid cell neoplasm (PEComa)

originating from the pancreas and metastasizing to the liver. Pancreas 40:1155–1157
Nakamura N, Kudo A, Ito K, Tanaka S, Arii S (2009) A hepatic lipoma mimicking angiomyolipoma of the liver: report of a case. Surg Today 39:825–828
Nguyen TT, Gorman B, Shields D, Goodman Z (2008) Malignant hepatic angiomyolipoma: report of a case and review of literature. Am J Surg Pathol 32:793–798
Nonomura A, Mizukami Y, Kadova M (1994a) Angiomyolipoma of the liver: a collective review. J Gastroenterol 29:95–105
Nonomura A, Mizukami Y, Muraoka K, Yajima M, Oda K (1994b) Angiomyolipoma of the liver with pleomorphic histological features. Histopathology 24:279–281
Nonomura A, Mizukami Y, Kadova M, Takayanagi N, Hirono T (1995) Multiple angiomyolipoma of the liver. J Clin Gastroenterol 20:248–251
Nonomura A, Mizukami Y, Shimizu K, Kadoya M, Matsui O (1996) Angiomyolipoma mimicking true lipoma of the liver: report of two cases. Pathol Int 46:221–227
Nonomura A, Minato H, Kurumaya H (1998) Angiomyolipoma predominantly composed of smooth muscle cells: problems in histological diagnosis. Histopathology 33:20–27
Nonomura A, Enomoto Y, Takeda M, Tamura T, Kasai T, Yoshikawa T, Nakamine H (2006) Invasive growth of hepatic angiomyolipoma; a hitherto unreported ominous histological feature. Histopathology 48:831–835
Nonomura A, Enomoto Y, Takeda M, Takano M, Morita K, Kasai T (2012) Angiomyolipoma of the liver: a reappraisal of morphological features and delineation of new characteristic histological features from the clinicopathological findings of 55 tumours in 47 patients. Histopathology 61:863–880
Okada K, Yokoyama S, Nakayama I, Tada I, Kobayashi M (1989) An electron microscopic study of hepatic angiomyolipoma. Acta Pathol Jpn 39:743–749
Ostor AG, Fortune DW (1978) Tuberous sclerosis initially seen as hydrops fetalis: report of a case and review of the literature. Arch Pathol Lab Med 102:34–39
Paiva CE, Moraes Neto FA, Agaimy A, Custodio Domingues MA, Rogatto SR (2008) Perivascular epithelioid cell tumor of the liver coexisting with gastrointestinal stromal tumor. World J Gastroenterol 14:800–802
Pan CC, Yang AH, Chiang H (2003) Malignant perivascular epithelioid cell tumor involving the prostate. Arch Pathol Lab Med 127:E96–E98
Parfitt JR, Bella AJ, Izawa JI, Wehrli BM (2006) Malignant neoplasm of perivascular epithelioid cells of the liver. Arch Pathol Lab Med 130:1219–1222
Patra S, Vij M, Kota V, Kancherla R, Rela M (2013) Pigmented perivascular epithelioid cell tumor of the liver: report of a rare case with brief review of literature. J Cancer Res Ther 9:305–307
Pea M, Bonetti F, Zamboni G, Martignoni G, Fiore-Donati-L, Doglioni C (1991) Clear cell tumor and angiomyolipoma. Am J Surg Pathol 15:199–202
Pea M, Martignoni G, Zamboni G, Bonetti F (1996) Perivascular epithelioid cell. Am J Surg Pathol 20:1149–1153
Petrolla AA, Xin W (2008) Hepatic angiomyolipoma. Arch Pathol Lab Med 132:1679–1682
Pileri SA, Cavazza A, Schiavina M, Zompatori M, Pederzoli M, Goldfischer M, Sabattini E et al (2004) Clear-cell proliferation of the lung with lymphangioleiomyomatosis-like change. Histopathology 44:156–163
Priola AM, Priola SM, Cataldi A, Marci V, Fava C (2009) Acute abdomen as an unusual presentation of hepatic PEComas. A case report. Tumori 95:123–128
Ren N, Qin LX, Tang ZY, Wu ZQ, Fan J (2003) Diagnosis and treatment of hepatic angiomyolipoma in 26 cases. World J Gastroenterol 9:1856–1858
Rimola J, Martin J, Puig J, Darnell A, Gil D (2003) Hepatic angiomyolipoma: progressive changes in size and tumor composition. Abdom Imaging 28:665–667
Ritter JH, Mills SE, Gaffey MJ, Nappi O, Wick MR (1997) Clear cell tumors of the alimentary tract and abdominal cavity. Semin Diagn Pathol 14:213–219
Rouquie D, Eggenspieler P, Algayres JP, Bechade D, Camparo P, Baranger B (2006) Malignant-like angiomyolipoma of the liver: report of one case and review of the literature (in French). Ann Chir 131:338–341
Rudzki Z, Wilk W, Smigielski M (2005) Splenic tumors in an adult with tuberous sclerosis: the giant "histiocytoid" cells are dysplastic histiocytes. Virchows Arch 447:672–674
Ruggieri M, Carbonara C, Magro G, Migone N, Grasso S, Tinè A, Pavone L, Gomez MR (1997) Tuberous sclerosis complex: neonatal deaths in three of four children of consanguineous, non-expressing parents. J Med Genet 34:256–260
Sadeghi S, Krigman H, Maluf H (2004) Perivascular epithelioid clear cell tumor of the common bile duct. Am J Surg Pathol 28:1107–1110
Saito M, Tsukamoto T, Takahashi T, Sai K, Fujii H, Nagashima K (2004) Multifocal angiomyolipoma affecting the liver and lung without tuberous sclerosis. J Clin Pathol 57:221–224
Salisbury JR, Portmann BC (1987) Oncocytic liver cell adenoma. Histopathology 11:533–539
Salviato T, Altavilla G, Busatto G, Pizzolitto S, Falconieri G (2006) Diffuse intra-abdominal clear cell myomelanocytic tumor: report of an unusual presentation of "PEComatosis" simulating peritoneal mesothelioma. Ann Diagn Pathol 10:352–356
Sanchez Pérez B, Suarez Munoz MA, Aranda Narvaez JM, Fernandez Aguilar JL, Santoyo Santoyo J (2009) Perivascular epithelioid cell tumour (PEComa) of the liver (in Spanish). Cir Esp 85:184–186
Santi R, Franchi A, Villari D, Paglierani M, Pepi M, Danielli D, Nicita G, Nesi G (2012) Sclerosing variant of PEComa: report of a case and review of the literature. Histol Histopathol 27:1175–1181

Saxena A, Alport EC, Custead S, Skinnider LF (1999) Molecular analysis of clonality of sporadic angiomyolipomas. J Pathol 189:79–84

Selvaggi F, Risio D, Claudi R, Cianci R, Angelucci D, Pulcini D, D'Aulerio A, Legnini M et al (2011) Malignant PEComa: a case report with emphasis on clinical and morphological criteria. BMC Surg 11:3

Shao Y, Zhong DR, Li XH (2003) Differences in morphology and immunohistochemistry between hepatic angiomyolipoma and renal angiomyolipoma (in Chinese). Zhonghua Yi Xue Za Zhi 83:1142–1145

Shen HQ, Chen DF, Sun XH, Li X, Xu J, Hu XB, Li MQ, Wu T, Zhang RY, Li KZ (2013) MRI diagnosis of perivascular epithelioid cell tumor (PEComa) of the liver. Rom J Morphol Embryol 54:643–647

Shen Q, Rao Q, Xia QY, Yu B, Shi QL, Zhang RS, Zhou XJ (2014) Perivascular epithelioid cell tumor (PEComa) with TFE3 gene rearrangement: clinicopathological, immunohistochemical, and molecular features. Virchows Arch 465:607–613

Shi H, Cao D, Wei L, Sun L, Guo A (2010) Inflammatory angiomyolipomas of the liver: a clinicopathologic and immunohistochemical analysis of 5 cases. Ann Diagn Pathol 14:240–246

Shima Y, Moriyama N, Takayasu K, Muramatsu Y, Gotoh H, Yamada T, Hasegawa H, Hirohashi N (1986) Primary lipoma and angiomyolipoma of the liver diagnosed by CT scan: report of two resected cases (in Japanese). Rinsho Hoshasen 31:1457–1460

Sironi M, Spinelli M (2003) Oncocytic angiomyolipoma of the kidney: a case report. Int J Surg Pathol 11:229–234

Sotiropoulos GC, Moskalenko V, Lang H (2009) Clinical challenges and images in GI. Image 2. Perivascular epithelioid cell (PEC) tumor of the ligamentum teres. Gastronterology 136:2065

Stenram U (2008) Perivascular epithelioid cell tumor of the liver. World J Gastroenterol 14:3105

Strotzer M, Paetzel C, Feuerbach S (1999) Multiple hepatic angiolipomas: a case report and review of literature. Eur Radiol 9:259–261

Strzelczyk JM, Durczynski A, Szymanski D, Jablkowski M, Dworniak D, Sporny S (2009) Primary perivascular epithelioid cell tumor (PEComa) of the liver: report of a case. Surg Today 39:916–921

Svajdler M, Bohus P, Goc V, Tkacova V (2007) Perivascular epithelioid cell tumor (PEComa) of the liver: a case report and review of the literature (in Czech). Cesk Patol 43:18–22

Takamura K, Miyake H, Fujii M, Nishi M, Tashiro S, Shimada M (2005) Multiple hepatic angiomyolipomas with a solitary omental angiomyolipoma. J Med Invest 52:218–222

Tan Y, Xiao EH (2012) Hepatic perivascular epithelioid cell tumor (PEComa): dynamic CT. MRI, ultrasonography, and pathologic features – analysis of 7 cases and review of the literature. Abdom Imaging 37:781–787

Tan Y, Zhang H, Wang XC (2014) Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres. Indian J Pathol Microbiol 57:453–455

Tanaka Y, Ijiri R, Kato Y, Misugi K, Nakatani Y, Hara M (2000) HMB-45/melan-A and smooth muscle actin-positive clear-cell epithelioid tumor arising in the ligamentum teres hepatis: additional example of clear cell "sugar" tumors. Am J Surg Pathol 24:1295–1299

Tang LH, Hui P, Garcia-Tsao G, Salem RR, Jain D (2002) Multiple angiomyolipomata of the liver: a case report. Mod Pathol 15:167–171

Tay S, Lao WT, Chen CL, Chan WP (2013) Contrast-enhanced CT and angiographic findings in hepatic perivascular epithelioid cell tumor. JBR-BTR 96:308–310

Tazelaar HD, Batts KP, Srigley JR (2001) Primary extrapulmonary sugar tumor (PEST): a report of four cases. Mod Pathol 14:87–90

Terris B, Flejou JF, Picot R, Belghiti J, Henin D (1996) Hepatic angiomyolipoma. A report of four cases with immunohistochemical and DNA-flow cytometric studies. Arch Pathol Lab Med 120:68–72

Torres VE, Björnsson J, King BF, Kumar R, Zincke H, Edell ES, Wilson TO, Hattery RR et al (1995) Extrapulmonary lymphangioleiomyomatosis and lymphangiomatous cysts in tuberous sclerosis complex. Mayo Clin Proc 70:641–648

Tsui WM, Yuen AK, Ma KF, Tse CC (1992) Hepatic angiomyolipomas with a deceptive trabecular pattern and HMB-45 reactivity. Histopathology 21:569–573

Tsui WM, Colombari R, Portmann BC, Bonetti F, Thung SN, Ferrell LD, Nakanuma Y et al (1999) Hepatic angiomyolipoma: a clinicopathologic study of 30 cases and delineation of unusual morphologic variants. Am J Surg Pathol 23:34–48

Tunali N, Gümürdülü D, Zorludemir S (2004) Splenic involvement in a stillborn fetus with tuberous sclerosis and multiple cardiac rhabdomyomas. Turk J Pediatr 46:357–361

Valensi QJ (1973) Pulmonary lymphangiomyomatosis, a probable forme fruste of tuberous sclerosis. A case report and survey of the literature. Am Rev Res Dis 108:1411–1415

Vang R, Kempson RL (2002) Perivascular epithelioid cell tumor ('PEComa') of the uterus: a subset of HMB-45-positive epithelioid mesenchymal neoplasms with an uncertain relationship to pure smooth muscle tumors. Am J Surg Pathol 26:1–13

Viamonte M, Ravel R, Politano V, Bridges B (1966) Angiographic findings in a patient with tuberous sclerosis. AJR Am J Roentgenol 98:723–733

Vicens RA, Jensen CT, Korivi BR, Bhosale PR (2014) Malignant renal epithelioid angiomyolipoma with liver metastasis after resection: a case report with multimodality imaging and review of the literature. J Comput Assist Tomogr 38:574–577

Weeks DA, Malott RL, Arnesen M, Zuppan C, Aitken D, Mierau G (1991) Hepatic angiomyolipoma with striated granules and positivity with melanoma-specific

antibody (HMB-45): a report of two cases. Ultrastruct Pathol 15:563–571

Xia QY, Rao Q, Shen Q, Liu B, Shi QL, Shi SS, Yu B, Zhang RS, Ma HH, Lu ZF et al (2013) Immunohistochemical study of perivascular epithelioid cell neoplasms (in Chinese). Zhonghua Bing Li Xue Za Zhi 42:381–385

Xian ZH, Cong WM, Lu XY, Yu H, Wu MC (2011) Angiogenesis and lymphangiogenesis in sporadic hepatic angiomyolipoma. Pathol Res Pract 207:403–409

Yamada Y, Yamamoto H, Ohishi Y, Nishiyama K, Fukuhara M, Saitou T, Tsuneyoshi M et al (2011) Sclerosing variant of perivascular epithelioid cell tumor in the female genital organs. Pathol Int 61:768–772

Yang B, Chen WH, ShI PZ, Xiang JJ, Xu RJ, Liu JH (2008) Coincidence of hepatocellular carcinoma and hepatic angiomyolipomas in tuberous sclerosis complex: a case report. World J Gastroenterol 14:812–814

Yang L, Feng XL, Shen S, Shan L, Zhang HF, Liu XY, Lv N (2012) Clinicopathologic analysis of 156 patients with angiomyolipoma originating from different organs. Oncol Lett 3:586–590

Yang X, Li A, Wu M (2013) Hepatic angiomyolipoma: clinical, imaging and pathological features in 178 cases. Med Oncol 30:416

Yeh CN, Chen MF, Hung CF, Chen TC, Chao TC (2001) Angiomyolipoma of the liver. J Surg Oncol 77:195–200

Yeh CN, Lee KF, Chen MF (2005) Immunohistochemical study of hepatic angiomyolipoma. Hepatogastroenterology 52:1151–1153

Yu D, Tang S (2013) Hepatic perivascular epithelioid cell tumor: a case report and review of the literature. Intern Med 52:1333–1336

Yu F, Wang K, Yan ZL, Zhang XF, Li J, Dong H, Cong WM, Shi LH, Shen F, Wu MC (2010) Clinical study of 169 patients with hepatic angiomyolipoma (in Chinese). Zhonghua Wai Ke Za Zhi 48:1621–1624

Yuan JI, Zhu X, Xu J, Zhou J, Tan Y, Wang J, Fan J, Zhou Y (2001) Hepatic angiomyolipoma: a clinicopathologic study of 10 cases. Chinese Med J 114:280–285

Zamboni G, Pea M, Martignoni G, Zancanaro C, Faccioli G, Gilioli E, Pederzoli P, Bonetti F (1996) Clear cell "sugar" tumor of the pancreas. A novel member of the family of lesions characterized by the presence of perivascular epithelioid cells. Am J Surg Pathol 20:722–730

Zhang X, Travis WD (2010) Pulmonary lymphangioleiomyomatosis. Arch Pathol Lab Med 134:1823–1828

Zhang X, Wang L, Jiang Y, Wan Z, Li W, Yao C, Geng Z, Lv Y (2014) Hepatic perivascular epithelioid cell tumors – not otherwise specified: a case report. Nan Fang Yi Ke Da Xue Xue Bao 34:1–4

Zhao LJ, Yang YJ, Wu H, Huang SM, Liu K (2013) Perivascular epithelioid cell tumor of the liver: a case report and literature review. Eur Rev Med Pharmacol Sci 17:1665–1668

Zhou YM, Li B, Xu F, Wang B, Li DQ, Zhang XF, Liu P, Yang JM (2008) Clinical features of hepatic angiomyolipoma. Hepatobiliary Pancreat Dis Int 7:284–287

Zimmermann A, von der Brelie C, Berger B, Kappeler A, Candinas D (2008) Primary perivascular epithelioid cell tumor of the liver not related to hepatic ligaments: hepatic PEComa as an emerging entity. Histol Histopathol 23:1185–1193

Part XI

Hepatobiliary Tumors of Neuroendocrine Lineages

Paraganglioma of the Hepatobiliary Tract

74

Contents

Abstract

Extra-adrenal paragangliomas are a group of neoplasms that derive from extra-adrenal sympathetic and parasympathetic paraganglia and related neuroendocrine cell systems in various organs. The biological behavior of these neoplasms ranges from a relatively benign course to frankly malignant behavior. Primary hepatic paraganglioma is a very rare neoplasm that is usually situated within the liver substance and is nonfunctional. The tumors can grow to a size exceeding 5 cm in diameter, may show a fibrous capsule, and can undergo cystic change. Hepatic paraganglioma can metastasize to locoregional lymph nodes. Histologically, the leading cell type is the large eosinophilic cell that forms paraganglia. These cells are strongly reactive for chromogranin A and synaptophysin. The complex stroma of paragangliomas contains S100 protein-positive sustentacular cells. Paraganglioma can also develop in extrahepatic bile ducts and cause biliary obstruction. Exceptionally, paraganglioma synchronously involves liver and bile ducts. The tumor was also observed in the gallbladder and hepatic ligaments.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_74

ICD-O 8693/1

Introduction

Pheochromocytomas, intra-adrenal paraganglioma, and extra-adrenal sympathetic and parasympathetic paragangliomas are neuroendocrine tumors derived from adrenal chromaffin cells or similar cells in extra-adrenal sympathetic and parasympathetic paraganglia, respectively (Chen et al. 2010). The term, paraganglioma, is a generic one applied to tumors arising from paraganglia regardless of location. The 2004 WHO classification of endocrine tumors defines pheochromocytoma as a tumor arising from chromaffin cells in the adrenal medulla. Closely related neoplasms in extra-adrenal sympathetic and parasympathetic paraganglia are classified as extra-adrenal paragangliomas; hence, a pheochromocytoma is an intra-adrenal paraganglioma (Tischler et al. 2006; Tischler 2008). The current strategies for the biochemical diagnosis of this tumor group have recently been reviewed (Eisenhofer et al. 2008; Joynt et al. 2009).

General Clinicopathologic Features

Extra-adrenal paragangliomas have nearly identical imaging features as the adrenal counterparts, including a homogeneous or heterogeneous hyperenhancing soft tissue mass at CT, multiple areas of signal void interspersed with hyperintense foci (salt-and-pepper appearance) within the tumor masses at MRI, and an intense tumor blush with enlarged feeding arteries at angiography (Lee et al. 2006). It has been observed that diffusion-weighted imaging (DWI) was superior to FDG-PET in the detection of lymph node and liver metastases of malignant paraganglioma and pheochromocytoma (Takano et al. 2008).

The pathology of paragangliomas has been described in detail, also in regard to the identification of potentially malignant variants (McNicol 2006; Tischler et al. 2006). In an analysis of 120 adrenal and extra-adrenal cases, features noted more frequently in malignant tumors included male predominance, extra-adrenal location, greater tumor weight, coarse nodularity of the primary tumor, confluent tumor necrosis, and the presence of vascular invasion and/or extensive local invasion. Intracytoplasmic hyaline globules were more frequently found in benign than in malignant tumors (Linnoila et al. 1990). In an immunohistochemical study, assessment of the proliferative activity by use of the MIB-1 antibody was found to be a useful adjunct marker to predict malignant behavior (Kumaki et al. 2002). In particular, MIB-1 (Ki-67) immunostaining combined with hTERT expression analysis aided in the distinction between benign and malignant forms (Elder et al. 2003). At the molecular level, recent studies suggest that methylation of the p16INK4A promoter is associated with malignant behavior of abdominal extra-adrenal paragangliomas but not pheochromocytomas (Kiss et al. 2008). Part of paragangliomas show the features of a CpG island methylator phenotype (CIMP), defined as concerted hypermethylation in three or more genes, and the CIMP phenotype in abdominal paragangliomas was associated with malignant behavior (Geli et al. 2008).

Paraganglioma of the Liver

Hepatic paragangliomas have been reported to be nonfunctional and show the typical histology of paragangliomas located elsewhere (Fig. 1; Ferrell et al. 1990; Kang et al. 1991; Corti et al. 2002;

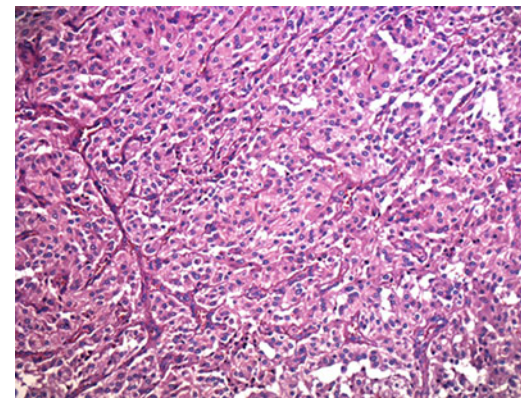

Fig. 1 Primary paraganglioma of the liver. Numerous cell nests ("zellballen") with strongly granular cytoplasm are recognized (hematoxylin and eosin stain)

Hong et al. 2013; Koh et al. 2013) or functional (Chang et al. 2006; Roman and Sosa 2007) and are usually situated within the liver substance. In one case, primary paraganglioma simultaneously involved the liver, gallbladder, and common bile duct. The tumor had metastasized to portal and celiac lymph nodes (Ferrell et al. 1990). In one patient (a 16-year-old girl), paraganglioma was localized to the falciform ligament of the liver (Delbridge and Connolly 1982).

Paraganglioma of Bile Ducts

Primary paraganglioma also takes its origin from the hepatic duct and at the hepatic hilum, sometimes causing biliary obstruction (Sarma et al. 1980; Hitanant et al. 1984; Albores-Saavedra et al. 2000; Caceres et al. 2001; Sarma 2006). One patient was a 28-year-old otherwise healthy woman with a history of abdominal pain and cholelithiasis. At laparoscopy, a round, 3-cm mass was detected encircling the median portion of the common bile duct. Examination of the resection specimen showed a mass attached to the junction of the cystic and common bile ducts. Microscopic study revealed a tumor composed of clustered, uniform small round cells, separated by capillaries and packed with dense granules positive for chromogranin (Caceres et al. 2001).

Paraganglioma of the Gallbladder

Rarely, paraganglioma of the gallbladder has been described (Miller et al. 1972; Wolff 1973; Ferrell et al. 1990; Freschi and Sassi 1990; Hirano 2000; Cho et al. 2001; Rodriguez-Merchan et al. 2006). It may occur in the context of multiple endocrine neoplasia syndrome (Mehra and Chung-Park 2005). Among eight cases of gallbladder paragangliomas, five patients were female, and the age at presentation ranged from 32 to 67 years. The diameter of the lesions varied from 1.3 to 3 cm. In at least one case, the hemorrhagic tumor has been suggested to have caused acute cholecystitis (Cho et al. 2001).

Paraganglioma of the Ampullary/Periampullary Region

Classical paraganglioma has been observed in the ampullary/periampullary region of the duodenum. More than 130 cases are found in the literature (Carter et al. 2008; Sankot and Svarcova 2008). An intriguing lesion of the periampullary region is a tumor termed gangliocytic paraganglioma. About 20 % of duodenal-ampullary paragangliomas belong to this category (Parini et al. 2007), and this distinct tumor variety is further discussed in a separate chapter.

Pathology

Macroscopy of Classical Hepatic Paraganglioma

Primary hepatic paragangliomas reach 6 cm (Chang et al. 2006) to 8 cm (Corti et al. 2002) in diameter. In the 46-year-old male patient reported by Corti et al. (2002), the right hepatic lobe presented an 8-cm resiliently firm nodular mass. The cut surface was pale gray, with a large central area of fibrosis. A thin fibrous capsule separated the tumor from the surrounding liver tissue, which showed no evidence of fibrosis or cirrhosis. Cystic variants, radiologically mimicking a liver cyst, have been reported (Laca et al. 2008).

Histopathology and Immunohistochemistry of Classical Hepatic Paraganglioma

The histological and immunohistochemical features of paragangliomas are well established (review: Kliewer and Cochran 1989). Paragangliomas display a characteristic vascular architecture, and these lesions have also been described as highly vascular at imaging (Chang et al. 2006). The leading cell type of paraganglioma reflects the chief cell found in normal paraganglia. These are polygonal eosinophilic cells with round nuclei lacking conspicuous nucleoli. S100 protein-positive sustentacular cells

are found in variable numbers. Immunohistochemically, the neoplastic cells are strongly positive for chromogranin A, synaptophysin, neuron-specific enolase, and IGF-II protein, but negative for vimentin, CD10, and keratins. The expression of IGF-II transcripts has also been demonstrated by use of in situ hybridization (Corti et al. 2002). The stroma of paragangliomas is a complex tissue that contains several classes of stromal cells. One stromal cell component consists of typical fibroblastoid cells. A second group is represented by alpha-SMA-positive cells that may correspond to the myofibroblast lineage and mainly occur in fibrous bands and the tumor capsule (Kuroda et al. 2008). A third category of cells is spindle cells that are caldesmon positive. Within the stroma of paragangliomas, sustentacular (reactive for S100 protein; Schröder and Johannsen 1986) and dendritic cells (reactive for HLA-DR; Furihata and Ohtsuki 1991) are typically observed.

Variants of Classical Paraganglioma

Some variants of paraganglioma have been described. Composite paraganglioma-ganglioneuroma is characterized by the presence of neuronal cells in the tumor. These neoplasms have been found more frequently in the ampullary region of the duodenum (see above). The melanin-containing pigmented paraganglioma variant (melanotic paraganglioma) has been identified in the retroperitoneal space, the heart, the urinary bladder, the uterus, and the nodose vagal ganglion (Tavassoli 1986; Küchemann 1995; Moran et al. 1997; Lack et al. 1998; Mikolaenko et al. 2001; Dundr et al. 2003; Reddy et al. 2003), but has not yet been detected in the hepatobiliary tract. These special features of paraganglioma differentiation support the hypothesis that these neoplasms may be derived from neural crest cells.

Gangliocytic Paraganglioma

This tumor is briefly discussed in a separate paragraph, because it deviates considerably from the concept of classical paraganglioma and shows a distinct anatomical distribution. First described in 1962 (Taylor and Helwig 1962), this is a rare tumor of the gastrointestinal tract of still unknown histogenesis. In particular, it is not yet clear whether this neoplasm in fact belongs to the paraganglioma group, irrespective of the term employed to denote this lesion. The significance of this neoplasm in the context of the present chapter refers to the fact that gangliocytic paraganglioma almost always occurs in the second part of the duodenum and often in the ampulla of Vater or the periampullary region. This tumor has a slight male predominance, with a male-female ratio of 1.6:1. It is usually diagnosed in the fifth or sixth decade of life, and in about 60 % the clinical presentation is that of gastrointestinal bleeding, but patients with biliary obstruction have also been reported (Gemer and Feuchtwanger 1966; Reed et al. 1977; Babaryka 1978; Williams et al. 1980; Anders et al. 1987; Barbareschi et al. 1989; Evans et al. 1996; Sakhuja et al. 2001; Girgis and Henthorne 2002; Hüffer et al. 2003; Ghouti et al. 2004; Sankot and Svarcova 2008; Von Loga et al. 2010). Most gangliocytic paragangliomas seem to undergo a benign course, but several of these tumors have shown malignant spread with locoregional lymph node metastases (Büchler et al. 1985; Korbi et al. 1987; Burke and Helwig 1989; Inai et al. 1989; Hashimoto et al. 1992; Dookhan et al. 1993; Sundararajan et al. 2003; Bucher et al. 2004; Wong et al. 2005; Witkiewicz et al. 2007).

Histologically, gangliocytic paraganglioma is characterized by a complex admixture of epithelioid cells, spindle cells, carcinoid tumor-like cells, and ganglion cells of varying levels of differentiation/maturation, all these lineages emerging in highly variable proportions within a given tumor. The lesions are usually not encapsulated and reveal a rather infiltrating tumor border. The immunohistochemical phenotype is also complex, in that the epithelioid cells may be reactive for neuroendocrine markers (chromogranin A, synaptophysin, and NSE) and for several hormones, including serotonin, pancreatic polypeptide, somatostatin, vasoactive intestinal peptide, and Leu-enkephalin. The spindle cells are reactive

for S100 protein and vimentin and sometimes for NSE and neurofilament proteins. The ganglion cells stain for neurofilaments and NSE (Perrone et al. 1985; Scheithauer et al. 1986; Anders et al. 1987; Barbareschi et al. 1989; Watanabe et al. 1995; Furihata et al. 1996; Altavilla et al. 2001; Ohtsuki et al. 2009).

Differential Diagnosis

The differential diagnosis includes liver metastases of malignant paragangliomas (in case of carotid body tumors, there may be delay of many years; Prados et al. 1981; Mall et al. 2000; Christie et al. 2006; Oakes et al. 2014). Also, periampullary gangliocytic paraganglioma can metastasize to the liver (Amin et al. 2013). Paragangliomas located close to the liver may be confounded with hepatic primary tumors, e.g., greater omentum (Archontovasilis et al. 2007) and mesenterium (Jaffer and Harpaz 2002; Canda et al. 2004).

Normal Hepatobiliary Paraganglia as a Potential Source of Paragangliomas

Kohn (1903) coined the term paraganglia paraganglioma to denote anatomic structures formed by collections of neuroendocrine cells spatially and functionally related to ganglia of the autonomic nervous system (Kuo et al. 1974). Paraganglia are a neuroendocrine cell system near or in the autonomic nervous system, with a roughly symmetric distribution with extension from the skull base to the pelvic floor. All paraganglia have a similar histologic appearance characterized by well-defined cell nests (zellballen) consisting of chief cells (type 1 cells) and a thin layer of sustentacular cells (type 2 cells). Chief cells contain membrane-bound, electron-dense secretory granules that contain catecholamines. Abdominal nonchromaffin paraganglia (glomera) have been noted principally in close proximity to major branches of the aorta, superior mesenteric and celiac arteries in man and animals, and along the vagus nerve branches mainly in animals. The liver is innervated by aminergic, cholinergic, peptidergic, and nitrergic nerves (review: McCuskey 2004). In the normal situation, paraganglia in the subdiaphragmatic compartment closely follow the ramifications of the vagus nerve. In the rat a mean of eight paraganglia were found to be associated with branches of the subdiaphragmatic vagus, and 94 % of the paraganglia were located at nerve branch points. Some of the larger paraganglia contained at their central poles one to six neurons (Prechtl and Powley 1985). Retrograde and anterograde tracing studies in the rat have shown that only a minor portion of the common hepatic vagal branch innervates the liver area proper, but hepatic paraganglia, bile ducts, and portal vein branches receive the densest vagal afferent innervation (Berthoud 2004). The clusters of hepatic paraganglia are nestled between and within the fascicles of the common hepatic vagal branch as it travels along the hepatoesophageal artery from the subdiaphragmatic vagal trunk on the esophagus toward the hepatic artery proper. Most of these glomus cells are clustered around capillary spaces (Prechtl and Powley 1987; Berthoud et al. 1992; Berthoud and Patterson 1996; Goehler et al. 1997). Hepatic vagus-associated paraganglia contain catecholamines, mainly norepinephrine and dopamine, but also epinephrine (Pinon et al. 1999). The vagal paraganglia, including those at the hepatic hilum and in the liver, may cooperate in an immune-to-brain communication, in that these vagal glomus cells bind IL-1 receptor antagonist (Goehler et al. 1997).

Nonneoplastic paraganglionic tissue in the gallbladder wall has been described in several reports (Kuo et al. 1974; Fine and Raju 1980; Raju and Fine 1980; McDonald 1990; Kawabata 1999) and also in textbooks (Weidner and Goldman 1996; Fierson 1997; Tischler 1997). In the case described by Kuo et al. (1974), a gallbladder resected because of stones showed, within the perimuscular connective tissue, a 0.3-mm sharply circumscribed, round and highly vascularized structure composed of nests of large cells having a central nucleus and a moderate amount of granular amphophilic cytoplasm. The

cells had the same features as the cells of the carotid body and the organ of Zuckerkandl. In the analysis of Fine and Raju (1980), one to five glomera were observed in nine of ten gallbladder specimens examined. The glomera were situated in the subserosal space in intimate association with blood vessels and small nerves, but in only one instance was a single ganglion cell found adjacent to a paraganglion. Their size ranged from about 60 to 200 mm. The nests were similar regardless of size, being composed on two types of cells arranged as poorly defined lobules in close association with a delicate capillary network. The chief cell was characterized as large and uniform cell with a round or oval vesicular nucleus and an eosinophilic, finely granular cytoplasm containing silver-positive (Bodian Protargol) granules. The second cell type is more seldom and is spindle-shaped supporting cells (Fine and Raju 1980). In the two observations of Kawabata (1999), paraganglionic tissue nests were seen in the subserosal connective tissue of gallbladders. The chief cells were positive for chromogranin A and in part for dopamine beta-hydroxylase and enkephalins, and there were typical S100 protein-positive sustentacular cells. Ultrastructurally, gallbladder paraganglia are identical to that of other nonchromaffin paraganglia featuring granule-bearing chief cells with many axons ensheathed by supporting cells (Raju and Fine 1980).

Genetic and Molecular Features

The majority of paragangliomas are sporadic lesions. In addition, there are several paraganglioma syndromes caused by alterations in the following genes: VHL, RET, NF-1, SDHB, SDHC, SDHD, SDHAF2, KIF1Bbeta, PHD2, and TMEM127 (reviews: Chetty 2010; Opocher and Schiavi 2010). About 10–15 % of paragangliomas are associated with germline mutations of the mitochondrial succinate dehydrogenase A, B, C, or D genes (SDHB, SDHC, and SDHD mutations; Astuti et al. 2001; Neumann et al. 2004; Schiavi et al. 2005; Benn et al. 2006; Ogawa et al. 2006; Papaspyrou et al. 2008; Bayley et al. 2009; Pasini and Stratakis 2009; Oishi et al. 2010; Schimke et al. 2010). The mitochondrial succinate-coenzyme Q reductase (complex II) consists of four succinate dehydrogenase subunits which are assumed to be involved in deranged mitochondrial respiration in tumors, according to Otto Warburg's hypothesis ("Warburg tumors"; Bayley and Devilee 2010a). A heterozygous germline SDHA mutation was found in a female patient suffering from a catecholamine-secreting abdominal paraganglioma (Burnichon et al. 2010). SDHB mutations predispose to paraganglioma syndrome type 4 (PGL-4), and SDHD mutations predispose to paraganglioma syndrome type 1 (PGL-1). In both syndromes, pheochromocytomas as well as head and neck paragangliomas occur. In contrast with SDHD mutation carriers (PGL-1) who have more frequent multifocal paragangliomas, SDHB mutation carriers (PGL-4) are more likely to develop malignant disease and possibly extraparaganglial neoplasms, including renal cell and thyroid carcinomas (Neumann et al. 2004; Ricketts et al. 2008). SDH gene mutations are also strongly associated with paragangliomas of the organ of Zuckerkandl (Lodish et al. 2010). There is also a paraganglioma syndrome caused by SDHAF2 (SDH5) mutations. The SDHAF2 gene encodes an SDH cofactor related to the function of the SDHA subunit and required for SDH flavination and is currently exclusively associated with head and neck paragangliomas (Hao et al. 2009; Bayley et al. 2010b).

Apart from pheochromocytomas and paragangliomas, other tumors have been associated with SDH mutations, such as gastrointestinal stromal tumors (GISTs), specifically in the context of the Carney triad and the Carney-Stratakis syndrome. Carney triad describes the association of paragangliomas with GISTs and pulmonary chondroma. A number of other lesions have been reported in this condition including pheochromocytomas, esophageal leiomyoma, and adrenocortical adenomas (Carney 2009). Carney-Stratakis syndrome is characterized by

the combination of GISTs/gastric stromal sarcomas and paragangliomas and is inherited as an autosomal dominant trait. In this syndrome, germline mutations of the SDHB, SDHC, and SDHD genes have been found (Stratakis and Carney 2009). Germline mutations and variants of succinate dehydrogenase genes have also been found in PTEN mutation-negative patients with Cowden syndrome or Cowden-like syndromes (Ni et al. 2008).

TMEM127 is a new pheochromocytoma susceptibility gene associated with LOH 2q11. Germline TMEM127 mutations are associated with pheochromocytoma, including bilateral forms. Transcriptome and immunohistochemical analyses showed that TMEM127-related pheochromocytoma clustered with NF1-related and RET-related tumors in a large series of pheochromocytomas and paragangliomas. TMEM127 associates with the endomembrane system and co-localizes with perinuclear (activated) mTOR, suggesting that it is a negative regulator of mTOR (Qin et al. 2010; Burnichon et al. 2011).

References

Albores-Saavedra J, Henson DE, Klimstra DS (2000) Tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater. N . Atlas of tumor pathology, Fascicle 27, third series. Armed Forces Institute of Pathology, Washington, DC

Altavilla G, Chiarelli S, Fassina A (2001) Duodenal periampullary gangliocytic paraganglioma: report of two cases with immunohistochemical and ultrastructural study. Ultrastruct Pathol 25:137–145

Amin SM, Albrechtsen NW, Forster J, Damjanov I (2013) Gangliocytic paraganglioma of duodenum metastatic to lymph nodes and liver and extending into the retropancreatic space. Pathologica 105:90–93

Anders KH, Glasgow BJ, Lewin KJ (1987) Gangliocytic paraganglioma associated with duodenal adenocarcinoma. Case report with immunohistochemical evaluation. Arch Pathol Lab Med 111:49–52

Archontovasilis F, Markogiannakis H, Dikoglou C, Drimousis P, Totouzas KG, Theodorou D, Katsaragakis S (2007) Paraganglioma of the greater omentum: case report and review of the literature. World J Surg Oncol 5:87

Astuti D, Latif F, Dallol A, Dahia PL, Douglas F, George E, Sköldberg F, Husebye ES et al (2001) Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. Am J Hum Genet 69:49–54

Babaryka I (1978) Polypoid nonchromaffin paraganglioma of the duodenum. Virchows Arch A Pathol Anat Histol 377:181–187

Barbareschi M, Frigo B, Aldovini D, Leonardi E, Cristina S, Falleni M (1989) Duodenal gangliocytic paraganglioma: report of a case and review of the literature. Virchows Arch A Pathol Anat Histopathol 416:81–89

Bayley JP, Devilee P (2010) Warburg tumours and the mechanisms of mitochondrial tumour suppressor genes. Barking up the right tree? Curr Opin Genet Dev 20:324–329

Bayley JP, Weiss M, Grimbergen A, van Brussel B, Hes F, Jansen J, Verhoef S, Devilee P et al (2009) Molecular characterization of novel germline mutations affecting SDHD and SDHC in pheochromocytoma and paraganglioma patients. Endocr Relat Cancer 16:929–937

Bayley JP, Kunst HP, Cascon A, Sampietro ML, Gaal J, Kopershoek E, Hinojar-Gutierrez A et al (2010) SDHAF2 mutations in familial and sporadic paraganglioma and phaeochromocytoma. Lancet Oncol 11:366–372

Benn DE, Gimenez-Roqueplo AP, Reilly JR, Bertherat J, Burgess J, Byth K, Croxson M et al (2006) Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab 91:827–836

Berthoud HR (2004) Anatomy and function of sensory hepatic nerves. Anat Rec A Discov Mol Cell Evol Biol 280:827–835

Berthoud HR, Patterson LM (1996) Innervation of rat abdominal paraganglia by calretinin-like immunoreactive nerve fibers. Neurosci Lett 210:115–118

Berthoud HR, Kressel M, Neuhuber WL (1992) An anterograde tracing study of the vagal innervation of rat liver, portal vein and biliary system. Anat Embryol (Berlin) 186:431–442

Bucher P, Mathe Z, Buhler L, Chilcott M, Gervaz P, Egger JF, Morel P (2004) Paraganglioma of the ampulla of Vater: a potential malignant neoplasm. Scand J Gastroenterol 39:291–295

Büchler M, Malfertheimer P, Baczako K, Krautzberger W, Beger HG (1985) A metastatic endocrine-neurogenic tumor of the ampulla of Vater with multiple endocrine immunoreaction – malignant paraganglioma? Digestion 31:54–59

Burke AP, Helwig EB (1989) Gangliocytic paraganglioma. Am J Clin Pathol 92:1–9

Burnichon N, Brière JJ, Libé R, Vescovo L, Rivière J, Tissier F, Jouanno E et al (2010) SDHA is a tumor suppressor gene causing paraganglioma. Hum Mol Genet 19:3011–3020

Burnichon N, Lepoutre-Lussey C, Laffaire J, Gadessaud N, Molinié V, Hemigou A, Plouin PF et al (2011) A novel TMEM127 mutation in a patient

with familial bilateral pheochromocytoma. Eur J Endocrinol 164:141–145
Caceres M, Mosquera LF, Shih JA, O'leary JP (2001) Paraganglioma of the bile duct. South Med J 94:515–518
Canda AE, Sis B, Sökmen S, Füzün M, Canda MS (2004) An unusual mesenteric paraganglioma producing human chorionic gonadotropin. Tumori 90:249–252
Carney JA (2009) Carney triad: a syndrome featuring paraganglionic, adrenocortical, and possibly other endocrine tumors. J Clin Endocrinol Metab 94:3656–3662
Carter JT, Grenert JP, Rubenstein L, Stewart L, Way LW (2008) Tumors of the ampulla of Vater: histopathologic classification and predictors of survival. J Am Coll Surg 207:210–218
Chang H, Xu L, Mu Q (2006) Primary functioning hepatic paraganglioma: a case report. Adv Ther 23:817–820
Chen H, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak K, North American Neuroendocrine Tumor Society (NANETS) (2010) The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas 39:775–783
Chetty R (2010) Familial paraganglioma syndromes. J Clin Pathol 63:488–491
Cho YU, Kim JY, Choi SK, Hur YS, Lee KY, Kim SJ, Ahn SI, Hong KC, Woo ZH et al (2001) A case of hemorrhagic gallbladder paraganglioma causing acute cholecystitis. Yonsei Med J 42:352–356
Christie N, Parsons AM, Behrns KE (2006) Metastatic hepatic paraganglioma 6 years after carotid body tumor resection. Clin Gastroenterol Hepatol 4:XXIV
Corti B, D'Errico A, Pierangeli F, Fiorentino M, Altimari A, Grigioni WF (2002) Primary paraganglioma strictly confined to the liver and mimicking hepatocellular carcinoma: an immunohistochemical and in situ hybridization study. Am J Surg Pathol 26:945–959
Delbridge L, Connolly J (1982) Paraganglioma of the falciform ligament: a case report. Aust NZ J Surg 52:315–317
Dookhan DB, Miettinen M, Finkel G, Gibaz Z (1993) Recurrent duodenal gangliocytic paraganglioma with lymph node metastasis. Histopathology 22:399–401
Dundr P, Dudorkinova D, Povysil C, Pesl M, Babjuk M, Dvoracek J, Zelinka T (2003) Pigmented composite paraganglioma-ganglioneuroma of the urinary bladder. Pathol Res Pract 199:765–769
Eisenhofer G, Siegert G, Kotzerke J, Bornstein SR, Pacak K (2008) Current progress and future challenges in the biochemical diagnosis and treatment of pheochromocytomas and paragangliomas. Horm Metab Res 40:329–337
Elder EE, Xu D, Höög A, Enberg U, Hou M, Pisa P, Gruber A, Larsson C, Bäckdahl M (2003) KI-67 and hTERT expression can aid in the distinction between malignant and benign pheochromocytoma and paraganglioma. Mod Pathol 16:246–255
Evans JD, Wilson PG, Barber PC (1996) Duodenal gangliocytic paraganglioma presenting as an ampullary tumor. Int J Pancreatol 20:131–134
Ferrell KD, Ng A, Rouch D, Chua GT (1990) Nonfunctioning paraganglioma of the liver, gallbladder and common bile duct. Indiana Med 83:822–824
Fierson HF (1997) Gallbladder and extrahepatic biliary system. In: Sternberg SS (ed) Histology for pathologists, 2nd edn. Lippincott-Raven, Philadelphia, pp 593–611
Fine G, Raju UB (1980) Paraganglia in the human gallbladder. Arch Pathol Lab Med 104:265–268
Freschi M, Sassi I (1990) Paraganglioma of the gallbladder (in Italian). Pathologica 82:459–463
Furihata M, Ohtsuki Y (1991) Immunohistochemical characterization of HLA-DR-antigen positive dendritic cells in pheochromocytomas and paragangliomas as a prognostic marker. Virchows Arch A Pathol Anat 418:33–39
Furihata M, Sonobe H, Iwata J, Ido E, Ohtsuki Y, Ohnishi S (1996) Immunohistochemical characterization of a case of duodenal gangliocytic paraganglioma. Pathol Int 46:610–613
Geli J, Kiss N, Karimi M, Lee JJ, Bäckdahl M, Ekström TJ, Larsson C (2008) Global and regional CpG methylation in pheochromocytomas and abdominal paragangliomas: association to malignant behavior. Clin Cancer Res 14:2551–2559
Gemer M, Feuchtwanger MM (1966) Ganglioneuroma of the duodenum. Gastroenterology 51:689–693
Ghouti L, Moutardier V, Hassoun J, Delpero JR (2004) Periampullary gangliocytic paraganglioma resected by surgical ampullectomy: a case report (in French). Gastroenterol Clin Biol 28:494–496
Girgis PA, Henthorne WA (2002) Pathologic quiz case. Mass at the ampulla of Vater in a 43-year-old man. Gangliocytic paraganglioma. Arch Pathol Lab Med 126:1239–1240
Goehler LE, Relton JK, Dripps D, Kiechle R, Tartaglia N, Maier SF, Watkins LR (1997) Vagal paraganglia bind biotinylated interleukin-1 receptor antagonist: a possible mechanism for immune-to-brain communication. Brain Res Bull 43:357–364
Hao HX, Khalimonchuk O, Schraders M, Dephoune N, Bayley JP, Kunst H, Devilee P et al (2009) SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma. Science 325:1139–1142
Hashimoto S, Kawasaki S, Matsuzawa K, Harada H, Makuuchi M (1992) Gangliocytic paraganglioma of the papilla of Vater with regional lymph node metastasis. Am J Gastroenterol 87:1216–1218
Hirano T (2000) Paraganglioma of the gallbladder: report of a rare case. Am J Gastroenterol 95:1607–1608
Hitanant S, Sriumpai S, Na-songkla S, Pichyangkula C, Sindhavananda K, Viranuvatti V (1984)

Paraganglioma of the common hepatic duct. Am J Gastroenterol 79:485–488
Hong SW, Lee WY, Lee HK (2013) Hepatic paraganglioma and multifocal gastrointestinal stromal tumor in a female: incomplete Carney triad. World J Gastrointest Surg 5:229–232
Hüffer M, Riechmann M, Müller J, Bürrig KF, Richter A (2003) Gangliocytic paraganglioma of the ampulla of Vater (in German). Zentralbl Chir 128:232–235
Inai K, Kobuke T, Yonehara S, Tokuoka S (1989) Duodenal gangliocytic paraganglioma with lymph node metastasis in a 17-year-old boy. Cancer 63:2540–2545
Jaffer S, Harpaz N (2002) Mesenteric paraganglioma: a case report and review of the literature. Arch Pathol Lab Med 126:362–364
Joynt KE, Moslehi JJ, Baughman KL (2009) Paragangliomas: etiology, presentation, and management. Cardiol Rev 17:159–164
Kang YS, Kuhlman JE, Fishman EK, Zerhouni EA (1991) Nonfunctional paraganglioma of the liver. Clin Imaging 15:216–219
Kawabata K (1999) Paraganglia of the gallbladder: a report of two cases with an immunohistochemical study. Pathol Res Pract 195:781–786
Kiss NB, Geli J, Lundberg F, Avci C, Velazquez-Fernandez D, Hashemi J, Weber G, Höög A et al (2008) Methylation of the p16INK4A promoter is associated with malignant behavior in abdominal extra-adrenal paragangliomas but not pheochromocytomas. Endocr Relat Cancer 15:609–621
Kliewer KE, Cochran AJ (1989) A review of the histology, ultrastructure, immunohistology, and molecular biology of extra-adrenal paragangliomas. Arch Pathol Lab Med 113:1209–1218
Koh PS, Koong JK, Westerhout CJ, Yoong BK (2013) Education and imaging. Hepatobiliary and pancreatic: a huge liver paraganglioma. J Gastroenterol Hepatol 28:1075
Kohn H (1903) Die Paraganglien. Arch Mikr Anat 62:263–365
Korbi S, Kapanci Y, Widgren S (1987) Malignant paraganglioma of the duodenum. Immunohistochemical and ultrastructural study of a case (in French). Ann Pathol 7:47–55
Küchemann K (1995) A rare case of pigmented paraganglioma. Virchows Arch 427:111–112
Kumaki N, Kajiwara H, Kameyama K, DeLellis RA, Asa SL, Osamura RY, Takami H (2002) Prediction of malignant behavior of pheochromocytomas and paragangliomas using immunohistochemical techniques. Endocr Pathol 13:149–156
Kuo T, Anderson CB, Rosai J (1974) Normal paraganglia in the human gallbladder. Arch Pathol 97:46–47
Kuroda N, Tamura M, Ohara M, Hirouchi T, Mizuno K, Miyazaki E, Hayashi Y, Lee GH (2008) Possible identification of third stromal component in extraadrenal paraganglioma: myofibroblast in fibrous band and capsule. Med Mol Morphol 41:59–61
Laca L, Fani M, Janik J, Miklusica J, Adamik M, Hosala M (2008) Cystic feochromocytoma, mimicing a liver cyst. A case review (in Slovak). Rozhl Chir 87:306–310
Lack EE, Kim H, Reed K (1998) Pigmented ("black") extraadrenal paraganglioma. Am J Surg Pathol 22:265–269
Lee KY, Oh YW, Noh HJ, Lee YJ, Yong HS, Kang EY, Kim KA, Lee NJ (2006) Extraadrenal paragangliomas of the body: imaging features. AJR Am J Roentgenol 187:492–504
Linnoila RI, Keiser HR, Steinberg SM, Lack EE (1990) Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. Hum Pathol 21:1168–1180
Lodish MB, Adams KT, Huynh TT, Prodanov T, Ling A, Chen C, Shusterman S, Jimenez C et al (2010) Succinate dehydrogenase gene mutations are strongly associated with paraganglioma of the organ of Zuckerkandl. Endocr Relat Cancer 17:581–588
Mall J, Saclarides T, Doolas A, Eibl-Eibesfeld B (2000) First report of hepatic lobectomy for metastatic carotid body tumor. J Cardiovasc Surg (Torino) 41:759–761
McCuskey RS (2004) Anatomy of efferent hepatic nerves. Anat Rec A Discov Mol Cell Evol Biol 280:821–826
McDonald EC (1990) Nonneoplastic paraganglionic tissue in the gallbladder wall. J Tenn Med Assoc 83:225–226
McNicol AM (2006) Histopathology and immunohistochemistry of adrenal medullary tumors and paragangliomas. Endocr Pathol 17:329–336
Mehra S, Chung-Park M (2005) Gallbladder paraganglioma: a case report with review of the literature. Arch Pathol Lab Med 129:523–526
Mikolaenko I, Galliani CA, Davis GG (2001) Pigmented cardiac paraganglioma. Arch Pathol Lab Med 125:680–682
Miller TA, Weber TR, Appelman HD (1972) Paraganglioma of the gallbladder. Arch Surg 105:637–639
Moran CA, Albores-Saavedra J, Wenig BM, Mena H (1997) Pigmented extraadrenal paraganglioma. A clinicopathologic and immunohistochemical study of five cases. Cancer 79:398–402
Neumann HP, Pawlu C, Peczkowska M, Bausch B, McWhinney SR, Muresan M, Buchta M et al (2004) Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. JAMA 292:943–951
Ni Y, Zbuk KM, Sadler T, Patocs A, Lobo G, Edelman E, Platzer P, Orloff MS, Waite KA, Eng C (2008) Germline mutations and variants of succinate dehydrogenase genes in Cowden and Cowden-like syndromes. Am J Hum Genet 83:261–268
Oakes A, Witt B, Adler DG (2014) Metastatic carotid body paraganglioma detected during evaluation for biliary stone disease. Diagn Cytopathol 42:868–871
Ogawa K, Shiga K, Saijo S, Ogawa T, Kimura N, Horii A (2006) A novel G106D alteration of the SDHD gene in

a pedigree with familial paraganglioma. Am J Med Genet A 140:2441–2446
Ohtsuki Y, Watanabe R, Kimura M, Okamoto T, Murakami S, Mizukami Y, Takeji M et al (2009) Immunohistochemical and electron microscopic studies of a case of duodenal gangliocytic paraganglioma. Med Mol Morphol 42:245–249
Oishi Y, Nagai S, Yoshida M, Fujisawa S, Sazawa A, Shinohara N, Nonomura K, Matsuno K, Shimizu C (2010) Mutation analysis of the SDHB and SDHD genes in pheochromocytomas and paragangliomas: identification of a novel nonsense mutation (Q168X) in the SDHB gene. Endocr J 57:745–750
Opocher G, Schiavi F (2010) Genetics of pheochromocytomas and paragangliomas. Best Pract Res Clin Endocrinol Metab 24:943–956
Papaspyrou K, Rossmann H, Fottner C, Weber MM, Mann W, Lackner KJ, Helling K (2008) Malignant paraganglioma caused by a novel germline mutation of the succinate dehydrogenase D-gene – a case report. Head Neck 30:964–969
Parini U, Nardi M, Loffredo A, Fabozzi M, Roveroni M (2007) Laparoscopic resection of duodenal gangliocytic paraganglioma. A case report. Chir Ital 59:551–558
Pasini B, Stratakis CA (2009) SDH mutations in tumorigenesis and inherited endocrine tumours: lesson from the phaeochromocytoma-paraganglioma syndromes. J Intern Med 266:19–42
Perrone T, Sibley RK, Rosai J (1985) Duodenal gangliocytic paraganglioma. An immunohistochemical and ultrastructural study and a hypothesis concerning its origin. Am J Surg Pathol 9:31–41
Pinon M, Racotta IS, Ortiz-Butron R, Racotta R (1999) Catecholamines in paraganglia associated with the hepatic branch of the vagus nerve: effects of 6-hydroxydopamine and reserpine. J Auton Nerv Syst 75:131–135
Prados M, Byrd M, Suarez A (1981) Paraganglioma of the liver seven years following the resection of a carotid body tumor – a case report. J La State Med Soc 133:186–188
Prechtl JC, Powley TL (1985) Organization and distribution of the rat subdiaphragmatic vagus and associated paraganglia. J Comp Neurol 235:182–195
Prechtl JC, Powley TL (1987) A light and electron microscopic examination of the vagal hepatic branch of the rat. Anat Embryol (Berlin) 176:115–126
Qin Y, Yao L, King EE, Buddavarapu K, Lenci RE, Chocron ES, Lechleiter JD, Sass M et al (2010) Germline mutations in TMEM127 confer susceptibility to pheochromocytoma. Nat Genet 42:229–233
Raju UB, Fine G (1980) Ultrastructure of the gallbladder paraganglia. Arch Pathol Lab Med 104:379–383
Reddy CE, Panda NK, Vaiphei K, Powari M (2003) Pigmented vagal paraganglioma. J Laryngol Otol 117:584–587
Reed RJ, Caroca PJ, Harkin JC (1977) Gangliocytic paraganglioma. Am J Surg Pathol 1:207–216
Ricketts C, Woodward ER, Killick P, Morris MR, Astuti D, Latif F, Maher ER (2008) Germline SDHB mutations and familial renal cell carcinoma. J Natl Cancer Inst 100:1260–1262
Rodriguez-Merchan B, Lozoya R, Allende E, Mesa J (2006) Paraganglioma of the gallbladder (in Spanish). Med Clin Barc 127:158
Roman SA, Sosa JA (2007) Functional paragangliomas presenting as primary liver tumors. South Med J 100:195–196
Sakhuja P, Malhotra V, Gondal R, Dutt N, Choudhary A (2001) Periampullary gangliocytic paraganglioma. J Clin Gastroenterol 33:154–156
Sankot J, Svarcova I (2008) Periampullary gangliocytic paraganglioma (in Czech). Rozhl Chir 87:38–41
Sarma DP (2006) Paraganglioma of the hepatic duct: a personal commentary. South Med J 99:785–786
Sarma DP, Rodriguez FH, Hoffmann EO (1980) Paraganglioma of the hepatic duct. South Med J 73:1677–1678
Scheithauer BW, Nora FE, LeChago J, Wick MR, Crawford BG, Weiland LH, Carney JA (1986) Duodenal gangliocytic paraganglioma. Clinicopathologic and immunohistochemical study of 11 cases. Am J Clin Pathol 86:559–565
Schiavi F, Boedeker CC, Bausch B, Peczowska M, Gomez CF, Strassburg T, Pawlu C et al (2005) Predictors and prevalence of paraganglioma syndrome associated with mutations of the SDHC gene. JAMA 294:2057–2063
Schimke RN, Collins DL, Stolle CA (2010) Paraganglioma, neuroblastoma, and a SDHB mutation: resolution of a 30 year-old mystery. Am J Med Genet A 152A:1531–1555
Schröder HD, Johannsen L (1986) Demonstration of S-100 protein in sustentacular cells of pheochromocytoma and paragangliomas. Histopathology 10:1023–1033
Stratakis CA, Carney JA (2009) The triad of paragangliomas, gastric stromal tumours and pulmonary chondromas (Carney triad), and the dyad of paragangliomas and gastric stromal sarcomas (Carney-Stratakis syndrome): molecular genetics and clinical implications. J Intern Med 266:43–52
Sundararajan V, Robinson-Smith TM, Lowy AM (2003) Duodenal gangliocytic paraganglioma with lymph node metastasis: a case report and review of the literature. Arch Pathol Lab Med 127:139–141
Takano A, Oriuchi N, Tsushima Y, Taketomi-Takahashi A, Nakajima T, Arisaka Y, Higuchi T et al (2008) Detection of metastatic lesions from malignant pheochromocytoma and paraganglioma with diffusion-weighted magnetic resonance imaging: comparison with 18-FDG positron emission tomography and 123I-MIBG scintigraphy. Ann Nucl Med 22:395–401
Tavassoli FA (1986) Melanotic paragangliona of the uterus. Cancer 58:942–948

Taylor HB, Helwig EB (1962) Benign nonchromaffin paragangliomas of the duodenum. Virchows Arch A Pathol Anat Histopathol 335:356–366

Tischler AS (1997) Paraganglioma. In: Sternberg SS (ed) Histology for pathologists, 2nd edn. Lippincott-Raven, Philadelphia, pp 1153–1172

Tischler AS (2008) Pheochromocytoma and extra-adrenal paraganglioma: updates. Arch Pathol Lab Med 132:1272–1284

Tischler AS, Kimura N, McNicol AM (2006) Pathology of pheochromocytoma and extra-adrenal paraganglioma. Ann NY Acad Sci 1073:557–570

Von Loga K, König A, Zustin J (2010) Periampullary gangliocytic paraganglioma: a case report. In Vivo 24:321–324

Watanabe K, Hasegawa H, Sakuma H, Tsuboi M, Ito S, Suzuki T (1995) Two cases of duodenal gangliocytic paraganglioma: immunocytochemical characteristics. Fukushina J Med Sci 41:141–152

Weidner N, Goldman RL (1996) Triviomas. In: Weidner N (ed) The difficult diagnosis in surgical pathology. W.B. Saunders Company, Philadelphia, pp 912–918

Williams SJ, Lucas RJ, McCaughey RS (1980) Paraganglioma of the duodenum: a case report. Surgery 87:454–458

Witkiewicz A, Galler A, Yeo CJ, Gross SD (2007) Gangliocytic paraganglioma: case report and review of the literature. J Gastrointest Surg 11:1351–1354

Wolff M (1973) Paraganglioma of the gallbladder. Arch Surg 107:493

Wong A, Miller AR, Metter J, Thomas CR (2005) Locally advanced duodenal gangliocytic paraganglioma treated with adjuvant radiation therapy: case report and review of the literature. World J Surg Oncol 3:15

Neuroendocrine Tumors of the Hepatobiliary Tract

75

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_75

Abstract

Neuroendocrine neoplasms of the hepatobiliary tract are rare neoplasms that derive from neuroendocrine cells located in the bile duct mucosa and several compartments of the liver proper. These neoplasms are divided into neuroendocrine tumors (NET) and neuroendocrine carcinomas (NEC). Well-differentiated NET (G1) have previously been termed carcinoid tumors. Most of neuroendocrine neoplasms that are known from extrahepatic organs and tissues also develop in the hepatobiliary tract, except tumors that originate from distinct specialized neuroendocrine/endocrine cell types that do not exist in this organ. The bile ducts are a well-known primary location of well-differentiated carcinoid-type NETs. Neuroendocrine carcinomas can also develop in bile ducts and the liver, but are unusual lesions. Intriguing primary neuroendocrine neoplasms of the liver are undifferentiated small cell and large cell carcinomas, which have to be distinguished from the more common liver metastases of extrahepatic tumors with this morphology.

ICD-O codes:

Neuroendocrine tumor (NET)	
NET G1 (carcinoid)	**8240/3**
NET G2	**8249/3**
Neuroendocrine carcinoma (NEC)	**8246/3**
Large cell NEC	**8013/3**
Small cell NEC	**8041/3**
Mixed adenoneuroendocrine carcinoma (MANEC)	**8244/3**

Introduction

Neuroendocrine tumors of the hepatobiliary tract are rare neoplasms that derive from neuroendocrine cells located in the bile duct mucosa and probably in certain parts of the liver parenchyma. These tumors are now divided into

neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs). Part of NETs (the NET G1 variants) have previously been termed carcinoid tumors or argentaffinomas (reviews: DeLellis and Osamura 2006; Chetty 2008). In the WHO classification, the term carcinoid tumor has been replaced with the term endocrine tumor to designate all gastrointestinal neoplasms with evidence of endocrine differentiation. It comprises the entire spectrum from well-differentiated (previously known as carcinoid tumors) to poorly differentiated tumors with endocrine features, particularly small cell and large cell carcinomas. Specifically, the term carcinoid tumor has been replaced by the term well-differentiated neuroendocrine tumor (now NET G1) by Capella et al. (2000) in the WHO classification of tumors.

Apparently, Langerhans seems to be the first to have described carcinoid tumor (Ogilvie 1947). The low-grade malignancy of carcinoids led Lubarsch (1888) to call them "little carcinomas." The term carcinoid ("carcinoma-like") was coined in 1907 in the first volume of the Frankfurter *Zeitschrift für Pathologie*, based on tumors found in the small intestine which, by using this novel term, the author wished to distinguish from cecal adenocarcinomas (Oberndorfer 1907). Seven years later, Gosset and Masson reported the presence of silver-reducing granules in the cytoplasm of carcinoid tumor cells (Gosset and Masson 1914). The carcinoid syndrome, found in patients with metastases of a carcinoid tumor, was first described in 1953 (Isler and Hedinger 1953). Endocrine/neuroendocrine tumors originate from neural crest-derived neuroendocrine cells that migrated to the foregut, midgut, and hindgut during embryogenesis. These cells are or were also termed enterochromaffin cells or, owing to distinct histochemical features, amine precursor uptake and decarboxylation (APUD) cells. The last mentioned name has led to the designation APUDOMA for neoplasms derived from APUD cells and are so-called type A carcinoids. APUDOMA is a terminology that is now obsolete. The cells are normally detectable along the entire digestive tract (from the oral cavity to the anal region) and in the associated inner organs, most of the cells being located in the appendix and small intestine (Kulke and Mayer 1999). There is a striking difference between the pancreas and the hepatobiliary tract in regard to the amount and diversity of endocrine cells. The pancreas contains large numbers and highly diverse types of these cells, while the biliary tract contains relatively few, and in the liver substance proper, the cells are hardly detectable (see below).

Epidemiology and Localizations

Overall, NETs account for only 0.2–2 % of all gastrointestinal malignancies. The change in our understanding of biology and terminology of the lesions in question has altered figures about the anatomical distribution and incidence of these neoplasms. Formerly, it was estimated that around 90 % of carcinoids were located to the appendix (Van Weel 1962), but this figure has now dropped to 54 % (Kinley and Penner 1962), the remaining carcinoids being found in other parts of the gastrointestinal tract, the bronchopulmonary system (30.1 %), pancreas (2.3 %), reproductive system (1.2 %), biliary tract (1.1 %), head and neck (0.4 %) (Kinley and Penner 1962; Maggard et al. 2004), and other endocrine /neuroendocrine tumors with a histology different from classical carcinoids being found in the pancreas and other internal organs (review: Soga 2003). NETs and NECs of the hepatobiliary system are very rare lesions. Gallbladder NETs represent 0.2 % and bile duct NETs 0.01 % of the cases. Bile duct NETs are equally distributed between males and females, while gallbladder NETs show a slight female preponderance (F/M = 1.8/1). The average age at presentation is about 60 years for bile duct NETs and 65 years for gallbladder NETs.

Classification and Grading of Neuroendocrine Tumors

Introduction

The more complex classifications of neuroendocrine tumors and the redefinitions of carcinoid tumors are mainly based on the recognition that

neuroendocrine tumors, and particularly those derived from foregut cells, are heterogeneous in regard to their morphologic and biologic features. Several systems to standardize diagnosis, classification, staging, and care of neuroendocrine tumors have been developed. TNM staging and grading of foregut neuroendocrine tumors has been standardized by a consensus panel of the European Neuroendocrine Tumor Society/ENETS (Rindi et al. 2006; Klöppel et al. 2009, 2010). In the ENETS publication as of 2010, specific staging of neuroendocrine tumors of the hepatobiliary tract was specified (Rindi 2010).

Classification

The novel classification proposed in the 2010 WHO classification (Rindi et al. 2010) is shown in Table 1. It is seen that the lesions are divided into five categories, similar to the WHO 2000 classification, but with a change in nomenclature.

According to this novel classification, a NET is defined as "a well-differentiated neuroendocrine neoplasm composed of cell with features similar to those of the normal gut endocrine cells, expressing general markers of neuroendocrine differentiation and hormones according to site, with mild-to-moderate nuclear atypia and a low number of mitoses (<20 per 10 HPF)" (Rindi et al. 2010). The neoplasms are graded as shown below. G1 lesions are the former carcinoid tumors or carcinoids. In contrast to NET, a NEC is defined as a poorly differentiated, high-grade neuroendocrine neoplasm composed of large, small, or intermediate cells. Some of the tumors may show organoid features similar to NET. NECs diffusely express general neuroendocrine markers, have an elevated mitotic rate (>20 per 10 HPF), and are G3 lesions (Rindi et al. 2010).

Table 1 WHO 2010 classification of neuroendocrine neoplasms of the digestive system (transition scheme, Rindi et al. 2010, modified), compared with the 2000 system

WHO 2010	WHO 2000
1. NET G1 (carcinoid)	Well-differentiated endocrine tumor
2. NET G2	Well-differentiated endocrine carcinoma
3. NEC (large cell or small cell)	Poorly differentiated endocrine carcinoma
4. Mixed adenoneuroendocrine	Mixed exocrine-endocrine carcinoma (MANEC)
5. Hyperplastic and preneoplastic	Tumor-like lesions

Grading

The grading system was developed in the light of the findings that proliferative activity can be employed to stratify the tumors in regard to their potential behavior (Table 2).

Generally, G1 and G2 should refer to well-differentiated neuroendocrine tumors showing diffuse positivity for chromogranin A and synaptophysin. Punctate necrosis is per se regarded as an indication for a more aggressive tumor, pointing at a G2 situation. G3 is a poorly differentiated, highly proliferative neuroendocrine carcinoma, which may have more extensive necrosis and shows an irregular and variable staining for chromogranin A and synaptophysin. The pathology reporting of neuroendocrine tumors has also been standardized by a consensus procedure employing the Delphic consensus process (Klimstra et al. 2010).

General Macroscopic Pathology of Neuroendocrine Neoplasms of the Liver and Biliary Tract

Most neuroendocrine neoplasms primary to the liver and biliary tract display a macroscopic pathology that is nonspecific, although some of the tumor may show a yellowish or tan color, in particular well-differentiated NETs (carcinoids).

Table 2 ENETS grading of neuroendocrine tumors (Rindi et al. 2006)

Grade	Mitotic count (10 HPF)	Ki-67 index (%)
G1	<2	<=2
G2	2–20	3–20
G3	>20	>20

Fig. 1 Primary neuroendocrine carcinoma of the liver with multiple intrahepatic metastases

Fig. 2 Primary neuroendocrine tumor of the liver manifesting as a well-circumscribed white nodule

Depending on their differentiation, the growth patterns of the lesions ranges from well-circumscribed spherical nodules to ill-defined and highly invasive neoplasms with satellite lesions and signs of intrahepatic spread (Figs. 1, 2, and 3).

Intrahepatic Well-Differentiated Neuroendocrine Tumors (NET G1): Carcinoid-Type Variants

Introduction

Primary intrahepatic carcinoid tumor (IHNET) is a rare neoplasm arising in the liver itself (review: DeLellis and Osamura 2006). Intrahepatic

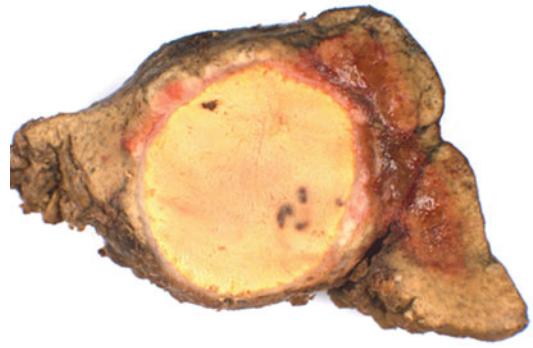

Fig. 3 Liver metastasis of neuroendocrine tumor with extensive necrosis. Only a thin peripheral rim of preserved tumor tissue is present

carcinoid was first described in 1958 (Edmondson 1958). As carcinoid tumors of the gastrointestinal tract frequently metastasize to the liver, the liver in fact being the most frequently involved organ due to metastatic disease from extrahepatic neuroendocrine neoplasms, diagnosis of primary hepatic carcinoid must exclude extrahepatic primary disease. In fact, a meticulous follow-up is required in order to rule out occult extrahepatic malignancy to confirm the primary nature of the hepatic tumor. Traditionally, these tumors have been classified as typical carcinoids (amounting to 80 % of the lesions), atypical carcinoids, and variant types (Soga and Tazawa 1971).

Primary intrahepatic lesions are much rarer than hepatic metastases of carcinoid tumors located elsewhere. One group examined 2837 consecutive patients with carcinoid tumors without identifying a single primary tumor of the liver (Godwin 1975). Among 184 liver tumors, 46 resections were performed, and 1 of them was a carcinoid tumor (Holbrook et al. 1996). Recent reports presented surveys of 95 cases (Modlin et al. 2005a, b). Notwithstanding the rarity of primary hepatic carcinoid, numerous reports have described lesions that were classified or interpreted as primary well-differentiated hepatic neuroendocrine tumors or, in most publications, as carcinoid tumors. Few cases have been reported in the pediatric age group (Foley et al. 2008).

Selected References (Edmondson 1958; Cruikshank 1961; Ali et al. 1978; Walter et al. 1978,

1980; Gould et al. 1981; Maros and Hecser 1982; Norgaard and Bardram 1985; Yamashita et al. 1986; Hodgson and Maton 1987; Miura and Shirasawa 1988; Derizhanova and Miroshnikov 1989; Andreola et al. 1990; Taghy et al. 1990; Sioutos et al. 1991; Takayasu et al. 1992; Wang et al. 1992; Imaoka et al. 1993; Inoue et al. 1993; Moriura et al. 1993; Yasoshima et al. 1993; Shima and Ota 1995; Holbrook et al. 1996; Krishnamurty et al. 1996; Mehta et al. 1996; Cianchi et al. 1997; Fujino et al. 1998; Oh et al. 1998; Asakawa et al. 1999; Kehagias et al. 1999; Nemes et al. 1999; Pilichowska et al. 1999; Rückert et al. 1999; Sano et al. 1999; Mizuno et al. 2000; Furrer et al. 2001; Iwao et al. 2001; Tagliabue et al. 2001; Iimuro et al. 2002; Kim et al. 2002; Soga 2002; Knox et al. 2003; Fenwick et al. 2004; Iribarren Diaz et al. 2004; Nikfarjam et al. 2004a, b; Kohashi et al. 2005; Komatsu et al. 2005; Modlin et al. 2005a, b; Nishimori et al. 2005; Shih et al. 2005; Tohyama et al. 2005; Ulasan et al. 2005; Abdel Wahab et al. 2006; Donadon et al. 2006; Lau et al. 2006; Mrabet et al. 2006; Lingamfelter et al. 2007; Nagamura et al. 2007; Shah et al. 2007; Gravante et al. 2008; Jarboui et al. 2008; Schwartz et al. 2008; Touloumis et al. 2008; Yeung et al. 2008; Zhang et al. 2008; De Liguori Carino et al. 2009; Fenoglio et al. 2009; Lin et al. 2009; Landen et al. 2014).

Epidemiology and Clinical Features

In a review of 69 published cases (Gravante et al. 2008), 40.6 % were male, and the median age at diagnosis was 50 years (range: 8–83 years). The clinical presentation is often nonspecific, either without symptoms (23.2 %) or with upper abdominal pain (33.3 %), but patients with large tumors that secrete 5-HIAA may show flushing and diarrhea (the carcinoid syndrome; Mehta et al. 1996; Furrer et al. 2001; Touloumis et al. 2008; Zhang et al. 2008). In the review of Gravante et al. (2008), 18.9 % of the patients revealed symptoms of carcinoid syndrome. Few instances of carcinoid heart disease have been reported (Tohyama et al. 2005). Carcinoid syndrome, characterized by paroxysmal vasomotor disorders, flush, diarrhea, tachycardia, hypotension, salivation, and tremor, is caused by the secretion of the active substances, 5-hydroxytryptamine (serotonin), 5-hydroxytryptophane, kallikrein, bradykinin, histamine, and prostaglandin E. Carcinoid heart disease is characterized by right-sided endocardial fibrosis of atrium and ventricle and fibrous thickening of tricuspid and pulmonary valves, causing valvular stenosis and regurgitation (Pellikka et al. 1993; Bernheim et al. 2007). Part of the patients may present other endocrine syndromes, such as severe hypoglycemia caused by insulin secretion (Ali et al. 1978; Furrer et al. 2001), or Cushing's syndrome (Shah et al. 2007). Hepatic carcinoids have been shown to produce gastrin (Larriva-Sahd et al. 1992; Inoue et al. 1993; Moriura et al. 1993; Krishnamurty et al. 1996; Kehagias et al. 1999; see below) or pancreatic polypeptide (Warner et al. 1980). Primary hepatic carcinoid tumor may be detected as an incidentaloma (Liu et al. 2004).

Primary hepatic carcinoid tumors are usually solitary lesions, single nodules having been identified in 69 % of patients. The tumors are usually heterogeneous solid masses at ultrasound and on CT images (Takayasu et al. 1992; Ulasan et al. 2005; Yeung et al. 2008), but they may also present as a large solitary cystic lesion (Lemaire et al. 1995) or as large multicystic lesions of the liver (Shih et al. 2005). CT with intravenous contrast shows enhancing, but often poorly marginated masses. MRI is advocated as the imaging modality of choice, with improved visualization of the tumors on T2-weighted images (Takayasu et al. 1992; Imaoka et al. 1993; Fujino et al. 1998; Yeung et al. 2008). Some of the tumors reveal calcifications and/or fibrous scarring. Angiography shows, owing to the high vascularity of the lesions, a tumor blush, usually without malignant neovascularity (Walter et al. 1978; Takayasu et al. 1992; Inoue et al. 1993). Part of the tumors exhibit a centrally located radiolucent area in angiography (Modlin et al. 2005a). The tumors and their spread can be successfully assessed by the use of 111 In-pentetreotide/octreotide scintigraphy (Octreoscan imaging) analyzing high

somatostatin analog uptake by the tumor cells (Nemes et al. 1999; Fenoglio et al. 2009). Octreotide binds with high affinity to the somatostatin subtype 2 receptor/SSTR2, which is widely expressed on the cell surface of neuroendocrine cell systems. Nuclear medicine imaging utilizing technetium-99m isotopes may be helpful in diagnosis (Shih et al. 2005; Schwartz et al. 2008).

Pathology

Macroscopically, the tumors are either solitary, roundish, and well-delineated nodules, or they form complex lobulated masses that may show one to several daughter nodules. In solitary lesions, a study reviewing 61 cases found an average diameter of 11.1 cm (Nikfarjam et al. 2004b). In another study of 88 cases, the mean tumor diameter was 9.5 cm (Soga 2002). The color of the cut surface ranges from light-gray or white-yellowish to yellow-orange or tan. Extensive necrosis and/or hemorrhage can occur, mainly in the center of large tumors.

Histologically, the tumors show the characteristic features known for other NETs/carcinoids, i.e., nests of small- to medium-sized round to ovoid cells with a finely granular cytoplasm and centrally placed, round nuclei with a rather dense chromatin and very small nucleoli (Fig. 4). Mitotic figures are typically rare, less than 20 per 10 HPF. Many cells are positive in the Grimelius and Fontana-Masson stains, but this reaction is not positive in all tumors. The tumor stroma is delicate, sometimes fibroblastic. Stromal hyalinization may occur (Schwartz et al. 2008). Similar to extrahepatic carcinoids, the neoplasms show scattered nests and cells outside the main contour of the tumor, whereby it is often difficult to decide whether this represents true invasion. However, true sinusoidal invasion in liver parenchyma can occur (Lingamfelter et al. 2007). Immunohistochemically, the cells are reactive for neuroendocrine lineage markers, i.e., chromogranin A (Fig. 5), synaptophysin, and neuron-specific enolase. Part of the tumors are reactive for serotonin. The tumors show a low level of proliferative activity (Fig. 6).

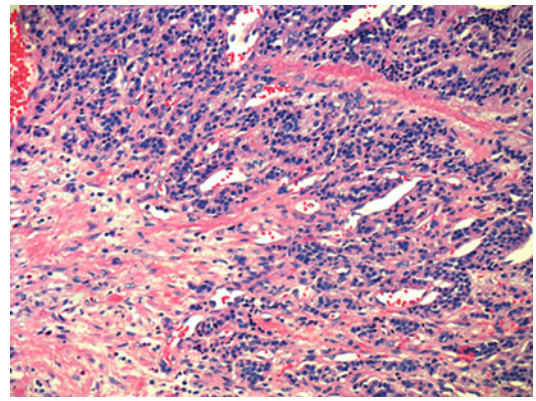

Fig. 4 Carcinoid tumor (well-differentiated neuroendocrine tumor) of the liver. Nests of medium-sized neoplastic cells exhibit round, "endocrine" nuclei (hematoxylin and eosin stain)

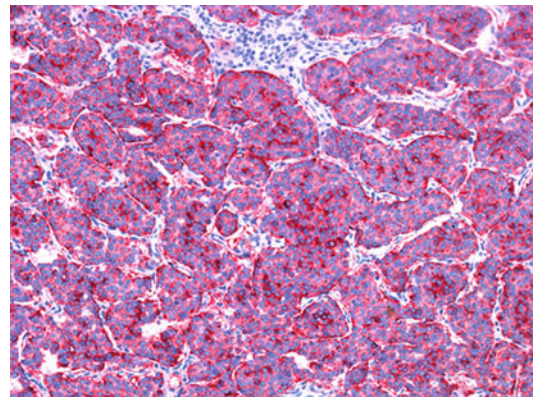

Fig. 5 Chromogranin A reactivity of a hepatic well-differentiated neuroendocrine tumor (chromogranin A immunostain)

Biology of Disease and Characteristics of Tumor Spread

The clinical course of PHCT is generally less aggressive than that of several other types of neuroendocrine tumors. However, it is well established that, in principle, carcinoids have a malignant potential, as this also holds true for primary carcinoid tumors of the liver. Among 69 patients that had been reviewed (Gravante et al. 2008), 39.1 % of the patients had died and 52.2 % had survived, 63.8 % having undergone hepatic resection and 4.3 % liver transplantation.

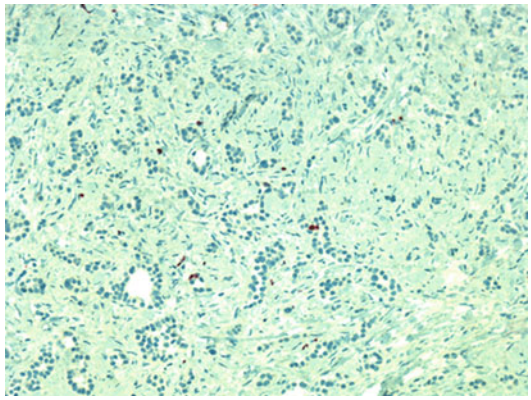

Fig. 6 Proliferative activity of well-differentiated neuroendocrine tumor of the hepatobiliary tract (MIB1 immunostain)

A study of 2003 revealed a favorable prognosis at 5 years in 74 % of surgically treated patients, with an 18 % recurrence rate (Knox et al. 2003). Tumor recurrence, sometimes causing death, may occur more than 10 years after the first intervention (Nishimori et al. 2005; Abdel Wahab et al. 2006).

As a general principle for prognostication or stratification in regard to risk, tumors smaller than 1 cm of diameter, in any anatomical location, usually are favorable lesions with only rare local recurrence or distant spread, whereas those exceeding 2 cm in diameter are often more aggressive (Graeme-Cook 2003). However, this general rule may not be applicable to carcinoid tumors of the liver, or only with modifications, because hepatic carcinoid tumors generally tend to be diagnosed when they have larger sizes (not rarely exceeding 15 cm in diameter), and large tumor sizes have either been associated with a favorable course (Fenwick et al. 2004) or with poor outcome (Pilichowska et al. 1999), hence requiring a refinement of prognostic stratification. In an analysis of 64 cases, extrahepatic metastases were detected in 16 % of patients, either at the time point of diagnosis or after the establishment of non-surgical therapies. Bone and lung are the most common sites of remote metastases (review: Nikfarjam et al. 2004b). One study (88 cases) found extrahepatic metastases more often in primary tumors being >5 cm in diameter, lymph node, bone, and lung metastases being identified in 22 % of cases (Soga 2002). PHCTs are known to metastasize to locoregional lymph nodes. In a study of 53 cases of PHCT reported in the English literature, lymph node involvement occurred in 60 % of the cases (Iwao et al. 2001). Post-resection perihepatic lymph node involvement has been infrequently observed in the absence of hepatic involvement, but metachronous lymph node metastasis was detected after a 5-year follow-up in one case of surgically treated PHCT (Iimuro et al. 2002).

Intrahepatic Neuroendocrine Tumors (NETs): Special Types

Primary Intrahepatic Somatostatinoma

Somatostatinomas are rare neuroendocrine tumors that account for approximately 1 % of all gastrointestinal neuroendocrine neoplasms. The neoplasms may be sporadic lesions or associated with neurofibromatosis type 1, MEN1, or von Hippel-Lindau disease. Hormonally inactive somatostatinomas are asymptomatic or oligosymptomatic, while functional somatostatinomas secrete large amounts of somatostatin which suppresses gallbladder motility and inhibits the secretory activity of several endocrine cell systems. This may cause the somatostatinoma/inhibitory syndrome, which is characterized by the triad, mild diabetes mellitus, cholelithiasis, and diarrhea/steatorrhea. Very few primary intrahepatic somatostatinomas have been described (Grundmann et al. 1985; Ohwada et al. 2003; Morisawa et al. 2006). The few patients reported had nonspecific symptoms and signs of a primary liver tumor. In one patient, the tumor has developed in the context of von Recklinghausen's disease (Morisawa et al. 2006). Primary intrahepatic somatostatinoma has to be distinguished from hepatic metastases (Do Cao et al. 2010).

Primary Intrahepatic Gastrinoma

Gastrinomas are rare NETs that produce gastrin, a peptide that is secreted into circulation in at least part of cases, inducing Zollinger-Ellison syndrome.

Only 5.6 % of gastrinomas occur in extraduodenal, extrapancreatic, and extranodal locations. Genetically, nonhereditary (sporadic) gastrinomas are distinguished from hereditary gastrinomas, the latter being associated with multiple endocrine neoplasia type 1 (MEN1) syndrome. In about 75 % of the patients with gastrinoma, this tumor is a solitary lesion (sporadic gastrinoma), and sporadic gastrinomas occur mainly in the duodenum and pancreas, while the hereditary gastrinomas almost all occur in the duodenum (review: Anlauf et al. 2006). As other carcinoid-type tumors, gastrinomas have a malignant potential. It is estimated that about 65 % of gastrinomas will show signs of malignancy, and up to 40 % of the patients will show metastatic disease at the time point of diagnosis, but even metastatic lesions may show a slow and protracted growth.

Primary intrahepatic gastrinoma is a very rare neoplasm of the liver. Relatively few reports have convincingly documented gastrinoma primary to the liver (Smith and Auldist 1984; Larriva-Sahd et al. 1992; Inoue et al. 1993; Moriura et al. 1993; Smyrniotis et al. 1994; Krishnamurty et al. 1996; Tiomny et al. 1997; Kehagias et al. 1999; Bello Argues et al. 2001; Chien et al. 2001; Deol et al. 2003; Shibata et al. 2006; Ishikawa et al. 2008; Denève et al. 2009; Rascarachi et al. 2009; Tsalis et al. 2011; Naoe et al. 2012; Ogawa et al. 2014). It is of special interest because it may, as gastrinomas in other locations, be associated with Zollinger-Ellison syndrome (Naoe et al. 2012). . Intrahepatic gastrinoma is a diagnostic challenge because, apart from its rarity, the tumor may be small, difficult to detect even with advanced imaging techniques, and has to be distinguished from the much more frequent extrahepatic gastrinomas. Furthermore, the liver is a very common site of gastrinoma metastases (Massironi et al. 2014; Sun et al. 2014). Histopathologically, gastrinomas are composed of compact groups of medium-sized to rather large cells with a granular eosinophilic cytoplasm and large nuclei with some atypia and sometimes intranuclear inclusions. The tumor cells are embedded in a fibrous stroma forming thin septa and are arranged in a so-called insular pattern. Intrahepatic tumors with calcifications have been described (Chien et al. 2001). Immunohistochemically, the tumor cells are reactive, apart from neuroendocrine lineage markers (chromogranin A, NSE, synaptophysin), for gastrin.

Primary Intrahepatic Glucagonoma

Glucagonoma is a NET arising from alpha-cells of the pancreas or analogous neuroendocrine cells in other organs, with extrapancreatic glucagonomas accounting for less than 1 % of all cases. It can be associated with a typical endocrine syndrome, i.e., weight loss, anemia, stomatitis, thromboembolism, and necrolytic migratory erythema (NME), a paraneoplastic dermatosis (the glucagonoma syndrome). NME occurs in only about 50 % of glucagonoma patients, but its presence is highly suggestive of glucagonoma. Primary hepatic glucagonoma is very rare, while pancreatic glucagonoma is well known to metastasize to the liver (Sheehan-Dare et al. 1988). A 37-year-old male patient was found to have a liver mass identified as a glucagon-producing tumor, in the absence of another extrahepatic manifestation (De Giorgio et al. 1998). In a 73-year-old female patient with necrolytic migratory erythema and hyperglucagonemia, autopsy revealed a large hepatic tumor measuring up to 8 cm in diameter with a macroscopic pattern of white and dark brown stripes located in the left lobe, while two smaller white nodules were also found in the right lobe. No other tumor was observed. Histology and immunohistology identified the tumor as malignant hepatic glucagonoma (possibly NET G2). The tumor consisted mainly of cords or a cobblestone-like pattern of medium-sized cells with moderate nuclear atypia and two to five mitosis per ten HPFs. Hemorrhage and necrosis were noted. Immunohistochemically, the cells were positive for glucagon, chromogranin A., and synaptophysin (Obi et al. 2009).

Primary Intrahepatic VIPoma

Vasoactive intestinal peptide (VIP)-producing tumor (VIPoma) causing Verner-Morrison

syndrome (so-called pancreatic cholera; WDHA syndrome) is a very rare neuroendocrine tumor of the gastrointestinal tract, with an estimated incidence of 0.1 per million per year. 70–80 % of these neoplasms arise in the pancreas, where VIPoma accounts for less than 10 % of islet cell tumors. The distinct endocrine syndrome is characterized by profuse watery diarrhea, hypokalemia, hypercalcemia, and metabolic acidosis. The syndrome is usually induced by the secretion of VIP by the tumor cells, but other cosecreted peptides may also be involved, including pancreatic polypeptide (PP), the oligopeptide histidine isoleucine, neurotensin, or gastric inhibitory peptide.

Primary hepatic VIPoma is an exceptional finding, with only few reports available (Ayub et al. 1993; Lundstedt et al. 1994; Hachicha et al. 2003). Primary VIPoma of the liver has been found to cause typical Verner-Morrison syndrome, which disappeared after resection of the tumor (Ayub et al. 1993; Hachicha et al. 2003). Histologically, VIPoma is composed of uniform small to medium-sized cells that form nests or trabecular structures, with few pseudorosettes. The cells are variably immunoreactive for VIP, in addition to general neuroendocrine markers. Differential diagnostically, gastrointestinal and pancreatic VIPoma is known to metastasize to the liver (Johnston et al. 2010; Li et al. 2010; Abu-Zaid et al. 2014). In hepatic metastases, an increased expression of CXCR4 was found, suggesting a role in the metastatic process (Müller et al. 2012).

Primary Intrahepatic Signet-Ring Cell Carcinoid (Primary Intrahepatic Signet-Ring Cell NET)

Primary hepatic signet-ring cell carcinoid is an unusual variant of carcinoid tumor, characterized by cytoplasmic mucin-negative keratin aggregate inclusions that mimic the cytologic features of other signet-ring cells. The paranuclear inclusions are pale, vacuole-like structures on an eosinophilic cytoplasmic background (Aoki et al. 1992; Zhu et al. 2010).

Primary Well-Differentiated Intrahepatic Neuroendocrine Carcinoma (NET G2; WHO 2000: WDEC)

Relatively few intrahepatic neoplasms corresponding to NET G2/WDEC have been observed (Figs. 7, 8, 9, 10, 11, 12, 13, and 14; Hsueh et al. 1993; Fukunaga 1998; Yasuda et al. 2006; Chen et al. 2014; Masunaga et al. 2014; Rocca et al. 2014; review: Shinkawa et al. 2013), with few detailed pathology findings. In the course of the autopsy of a 71-year-old man with dermatomyositis, multiple tumors were detected in his noncirrhotic liver. These tumors were composed of small- to medium-sized cells with clear cytoplasm, arranged in nests, sheets, and rosettes. Immunohistochemically, the tumor cells were reactive for CK7, CK19, epithelial membrane antigen (EMA), chromogranin A, NSE, and CD56, but not for synaptophysin. The tumor had metastasized to locoregional lymph nodes, the gallbladder, and the lung (Yasuda et al. 2006). Primary WDEC can produce important mass lesions in the liver, sometimes exceeding a diameter of 20 cm, so-called giant tumors (Rocca et al. 2014; Sotiropoulos et al. 2014). In fact, WDECs/NET G2 tumors typically manifest as a large dominant hypervascular mass at imaging, often accompanied by satellite nodules (Li et al. 2013).

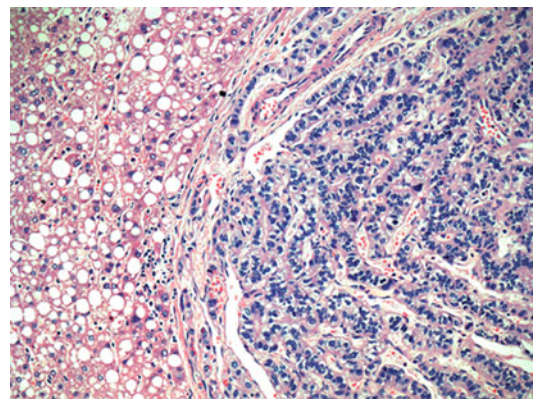

Fig. 7 Neuroendocrine carcinoma of the liver with moderate degree of differentiation (hematoxylin and eosin stain)

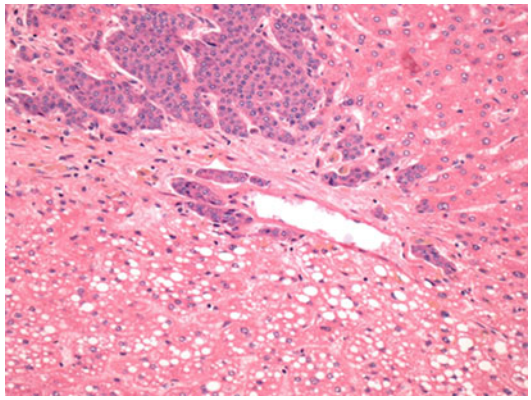

Fig. 8 Invasion of neuroendocrine carcinoma of the liver. The tumor invades dilated sinusoids and is present in perivascular lymphatics (*center*; hematoxylin and eosin stain)

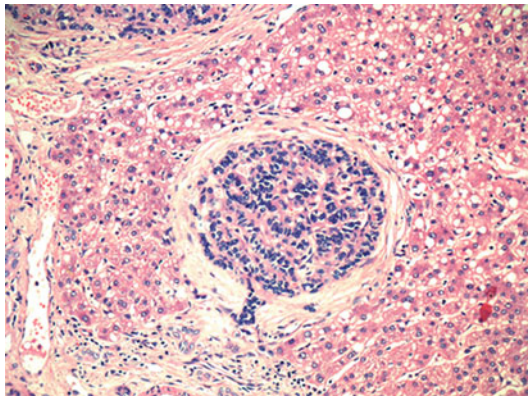

Fig. 9 Intravenous invasion (small portal venous branch) of hepatic neuroendocrine carcinoma (hematoxylin and eosin stain)

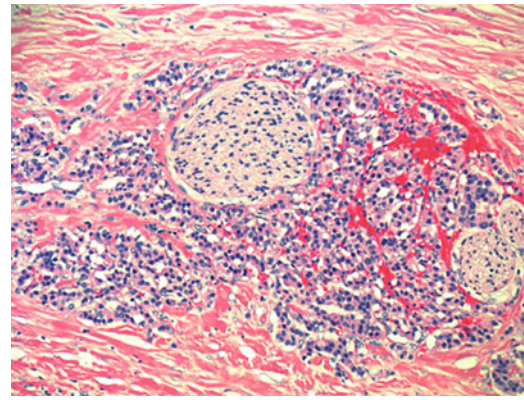

Fig. 10 Perineural invasion of hepatic neuroendocrine carcinoma (hematoxylin and eosin stain)

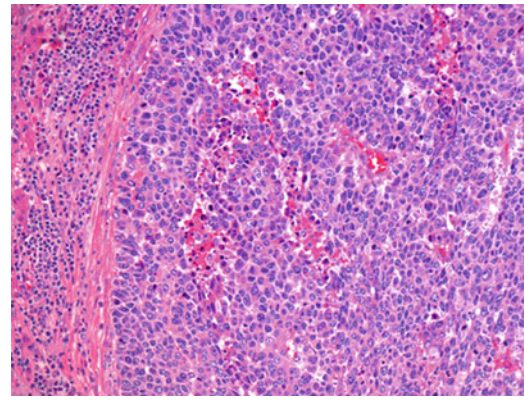

Fig. 11 Poorly differentiated variant of hepatobiliary neuroendocrine carcinoma with focal necrosis (hematoxylin and eosin stain)

Poorly Differentiated Intrahepatic Neuroendocrine Carcinoma (NEC)

In contrast to extrahepatic bile ducts, intrahepatic NEC is an exceptional observation. Primary hepatic small cell carcinoma of the neuroendocrine type (PHSCC-NE) forms the poorly differentiated end of the spectrum of neuroendocrine carcinomas (Balta et al. 2008). Immunohistochemically, the tumors are reactive for CD56 and focally for cytokeratins 8, 18, and w0, but are negative for TT1 and CDX2 (Balta et al. 2008).

Mixed Intrahepatic Adenoneuroendocrine Carcinoma (MANEC)

Very rarely, hepatic carcinoid arises as a composite tumor consisting of a neuroendocrine tumor and an adenocarcinoma/cholangiocarcinoma (Hidaka et al. 2000; Koplin and Agni 2009). The cases histologically present as well-differentiated adenocarcinoma with components of argyrophil carcinoid tumor cells, the latter sometimes being immunohistochemically positive for serotonin.

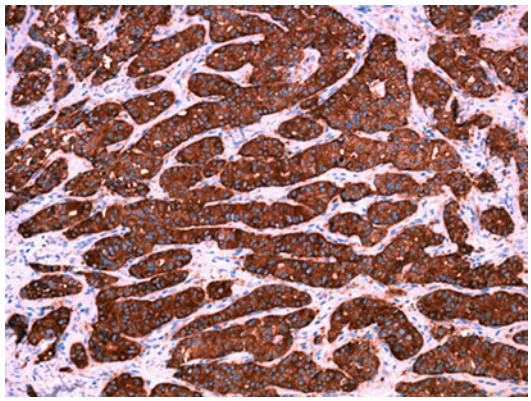

Fig. 12 Hepatic neuroendocrine carcinoma with diffuse expression of synaptophysin (synaptophysin immunostain)

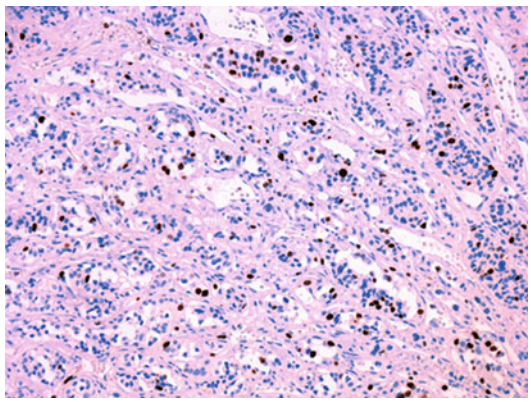

Fig. 13 Proliferative activity of hepatic neuroendocrine carcinoma (MIB1 immunostain)

Well-Differentiated Neuroendocrine Tumors (NET G1; Carcinoid Tumors) of the Extrahepatic Bile Ducts

Introduction and Epidemiology

Well-differentiated endocrine tumors (carcinoids) of the common bile duct are relatively uncommon lesions, the first example having been reported in 1959 (Davies 1959). Since, more than 50 cases have been reported. Carcinoid tumor of the common bile duct has also been observed in adolescents (Volpe et al. 2003) and in the pediatric age group

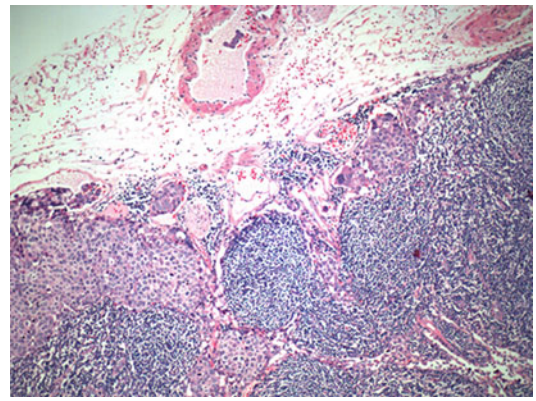

Fig. 14 Locoregional lymph node metastasis of hepatic neuroendocrine carcinoma (hematoxylin and eosin stain)

(Tonnhofer et al. 2009; Song et al. 2011). Most of the tumors were detected in the common bile duct and the cystic duct, and the lesions are less commonly encountered in the hepatic ducts. In a review of 44 cases, 34 tumors were located in the common bile duct (Nesi et al. 2006). In this review, tumors were more often diagnosed in female patients (25 F, 16 M). Up to 2009, about 55 primary carcinoid tumors of the cystic duct were reported (review: Felekouras et al. 2009).

Clinical Features

The most frequent clinical signs observed in these patients were jaundice, right upper quadrant pain, biliary colic, nausea, and vomiting. In a more recent review of 62 cases, 36 were women and 24 men, and their mean age at presentation was 47.5 years (range 12–79 years). The most common sign was painless jaundice (42 of 58 patients), followed by right upper quadrant pain (16 of 58 patients). Eighteen patients showed metastases to the liver, pancreas, gallbladder, and regional lymph nodes, while 40 had disease confined to the bile ducts. Thirty-six tumors were located in the common bile duct, 16 to the perihilar region, 7 to the cystic duct, and only 3 to the common hepatic duct. In these reviewed cases, most tumors were nonfunctioning (Felekouras et al. 2009). Carcinoid tumor has also developed in the wall

of a congenital bile duct cyst (Ueyama et al. 1992). Tumors located at the confluence may mimic Klatskin tumor (Chan et al. 2000). Rarely, carcinoids of the extrahepatic bile ducts may be associated with distinct endocrine syndromes. ACTH production causing Cushing's syndrome has been reported (Dahm et al. 1993). Carcinoid tumor of the common bile duct or the common hepatic duct has been observed as a complication of von Hippel-Lindau syndrome (Fellows et al. 1990; Nafidi et al. 2008). Numerous cases have been compiled in the literature, with in part detailed descriptions of clinical, imaging, and histologic features.

Selected References (Pilz 1961; Shiffman and Juler 1963; Warren et al. 1964; Little et al. 1968; Godwin 1975; Bergdahl 1976; Judge et al. 1976; Schwesinger 1978; Gerlock and Mühletaler 1979; Machado et al. 1981; Vittaux et al. 1981; Abe et al. 1983; Goodman et al. 1984; Alexander et al. 1986; Nicolescu and Popescu 1986; Bickerstaff and Ross 1987; Gastinger et al. 1987; Jutte et al. 1987; Reinhardt et al. 1988; Chittal and Ra 1989; Fujita et al. 1989; Brown et al. 1990; Bumin et al. 1990; Fellows et al. 1990; Angeles-Angeles et al. 1991; Barron-Rodriguez et al. 1991; Besznyak et al. 1991; Dixon et al. 1992; Newman et al. 1992; Rugge et al. 1992; Dahm et al. 1993; Gembala et al. 1993; Sankary et al. 1995; Belli et al. 1996; Kopelman et al. 1996; Bembenek et al. 1998; Nahas et al. 1998; Shah et al. 1998; Aronsky et al. 1999; Chamberlain and Blumgart 1999; Hermina et al. 1999; Perakath et al. 1999; Ross et al. 1999; Chan et al. 2000; Juturi et al. 2000; Maitra et al. 2000; Turrion et al. 2002; Pawlik et al. 2003; Podnos et al. 2003; Volpe et al. 2003; El Rassi et al. 2004; Menezes et al. 2004; Hubert et al. 2005; Ligato et al. 2005; Pithawala et al. 2005; Caglikulekci et al. 2006; Honda et al. 2006; John et al. 2006; Kim et al. 2006; Nesi et al. 2006; Colombo et al. 2007; Ferrone et al. 2007; Sethi et al. 2007; Stavridi et al. 2007; Gusani et al. 2008; Nafidi et al. 2008; Schmitt et al. 2008; Felekouras et al. 2009; Noronha and Raza 2010; Lee et al. 2011).

Pathology

Macroscopically, biliary tract carcinoids have been found to measure 1.1–5.5 cm in diameter at diagnosis (Felekouras et al. 2009). The tumors have a whitish to yellow to tan color and are circumscribed nodules with usually well-defined borders. The histology and immunohistochemistry are those of other carcinoids.

Differential Diagnosis

Hepatic metastases (so-called carcinoidosis) are common complications of neuroendocrine tumors of the gastrointestinal tract. It has been reported that the neoplasms metastasize to the liver in 5–10 % of the cases (Dejong et al. 2002). In fact, most hepatic carcinoids are metastases rather than primary tumors. The most common primary sites in the GIT are the appendix (35 %), small intestine (25 %), and rectum (12 %).

Neuroendocrine Tumors (NETs) of the Extrahepatic Bile Ducts: Special Types

Gastrinoma

The majority of the rare hepatobiliary gastrinomas are observed within the liver substance (see above), but few tumors were detected in the walls of the extrahepatic bile ducts (Mandujano-Vera et al. 1995; Hao et al. 1996; Martignoni et al. 1999; Price et al. 2009; Tarçin et al. 2011). As with intrahepatic gastrinomas, these neoplasms may cause Zollinger-Ellison syndrome. In the patient described by Mandujanovera et al. (1995), a 53-year-old woman, a stenosing small tumor was found in the lower third of the common bile duct, showing diffuse gastrin production and focal reactivity for serotonin and pancreatic polypeptide. The ulcerogenic syndrome ceased after resection of the tumor. Bile duct gastrinomas can grow to large size. One patient had a solitary, well-encapsulated mass of 8 cm

diameter in the common bile duct (Tarçin et al. 2011). Among three patients reported by Price et al. (2009), two had MEN1 syndrome. An association of biliary tract gastrinoma and MEN1 was confirmed by a later report (Tonelli et al. 2013).

Somatostatinoma

One case of somatostatinoma of the cystic duct was reported (Goodman et al. 1984).

Clear Cell Carcinoid Tumor

This rare tumor was detected in the most distal (intrapancreatic) portion of the common bile duct in a 73-year-old man suffering from epigastric pain (Todoraki et al. 2007). CT revealed a slight dilatation of the extra- and intrahepatic bile ducts and a slightly protruding nodular lesion in the distal common duct. The resection specimen showed a golden-yellowish polypoid mass measuring up to 1.2 cm in diameter. Histologically, the neoplasm consisted of uniformly sized polygonal cells with small round nuclei and a clear, abundant cytoplasm. Mitotic figures were not in evidence, but there were signs of perineural and vascular invasion. Immunohistochemically, the tumor cells were reactive for chromogranin A, synaptophysin, NSE, and pancreatic polypeptide, but not for CD56, somatostatin, serotonin, or cytokeratin.

Well-Differentiated Neuroendocrine Carcinoma (NET G2, WDEC, "Malignant Carcinoid") of the Extrahepatic Bile Ducts

This still incompletely defined group of neuroendocrine tumors is characterized by features of atypical carcinoid tumor with clear signs of invasion and metastasis at diagnosis (Yamamoto et al. 1986; Oikawa et al. 1998; Yamaguchi et al. 2009; Squillaci et al. 2010). In one 79-year-old male patient, the tumor was located to the bile duct confluence and was histologically composed of a well-differentiated tubular carcinoma, numerous tumor cells being argyrophil and/or argentophil and immunoreactive for serotonin, somatostatin, and gastrin (Yamamoto et al. 1986). In two other patients, the tumors showed transmural invasion, lymph node metastasis, and subcapsular liver tissue infiltration (Squillaci et al. 2010). In one case, reactivity for gastrin-releasing peptide was the prominent immunohistochemical feature (Oikawa et al. 1998). NET G2 was also observed in the cystic duct (Felekouras et al. 2009). These authors reviewed six previously reported cases.

Mixed Adenoneuroendocrine Carcinoma (MANEC) of the Biliary Tract

Neuroendocrine carcinoma of the bile ducts can very rarely occur as mixed adenoneuroendocrine carcinoma/MANEC (Yamamoto et al. 1998).

Poorly Differentiated Neuroendocrine Carcinomas (PDEC; WHO 2010: NEC) of the Extrahepatic Bile Ducts

Small Cell Neuroendocrine Carcinoma (SCNEC)

Small cell neuroendocrine carcinoma (SCNEC) of the extrahepatic bile duct system is a rare high-grade malignancy morphologically resembling in many aspects the counterpart so often arising in the bronchopulmonary tract (Fig. 15). Only around 4 % of the small cell carcinomas arise in organs other than the lung. When SCNEC occurs in the biliary tract, it develops mainly in the gallbladder, while relatively few cases have been reported for the common bile duct (Sabanathan et al. 1988; Van der Wal et al. 1989; Nishihara et al. 1993; Miyashita et al. 2001; Hazama et al. 2003; Kuraoka et al.

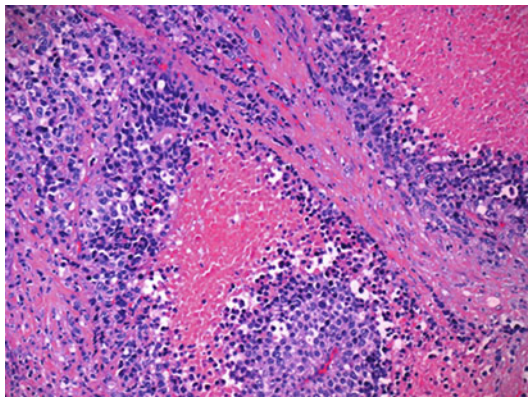

Fig. 15 Small cell undifferentiated neuroendocrine carcinoma of the hepatobiliary tract with coagulation necrosis (hematoxylin and eosin stain)

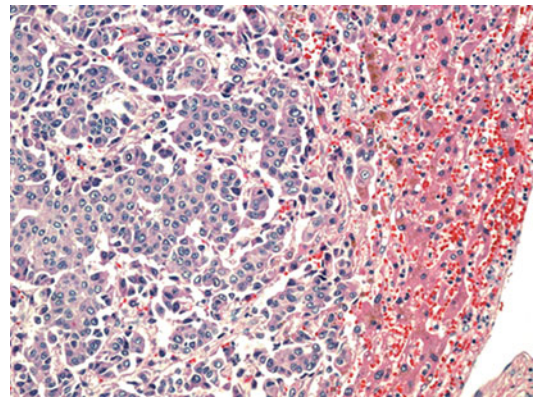

Fig. 16 Large cell undifferentiated hepatobiliary neuroendocrine carcinoma (hematoxylin and eosin stain)

2003; Kaiho et al. 2005; Nassar et al. 2005; Jeon et al. 2006; Jun et al. 2006; Hosonuma et al. 2008; Albores-Saavedra et al. 2009; Cho et al. 2009; Okamura et al. 2009). In a SEER study (Albores-Saavedra et al. 2009), the mean age at diagnosis was 68.4 years, while it was 58.2 years in bile duct carcinoids. The 10-year survival was 0 %. In a review of 17 cases of small cell carcinoma of bile ducts, nine tumors were located to the distal part of the common bile duct and eight tumors in its middle portion, 14/17 patients presented with jaundice (Hosonuma et al. 2008). SCNEC of the extrahepatic bile ducts can show a stenosing growth pattern resembling that of cholangiocarcinomas, e.g., with irregular luminal narrowing situated at the confluence of the common bile duct, cystic duct, and common hepatic duct (Hosonuma et al. 2008). The prognosis of biliary tract SCNEC is very poor, the longest reported survival being 23 months after initial diagnosis and 20 months after combined surgery, radiotherapy, and chemotherapy (Okamura et al. 2009). Histologically, the presentation is characterized by an almost diffuse growth of small-sized, round, Grimelius-positive cells with scant cytoplasm and hyperchromatic, oval nuclei. The mitotic count is high. Part of the tumors may develop glandular or squamous epithelia, or may be composite tumors of SCNEC, adenocarcinoma, or squamous cell carcinoma (Hosonuma et al. 2008). Immunohistochemically, most cells are variably positive for cytokeratins, EMA, NSA, Leu-7, CD56, synaptophysin, and chromogranin A.

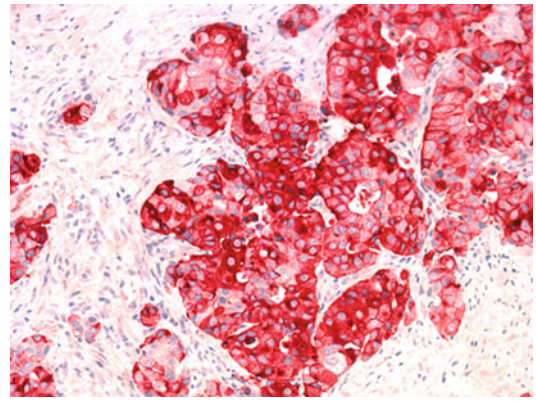

Fig. 17 Large cell undifferentiated hepatobiliary carcinoma; expression of chromogranin A (chromogranin A immunostain)

Large Cell Neuroendocrine Carcinoma (LCNEC)

Only few examples of LCNEC of the extrahepatic bile ducts have been described in the literature (Figs. 16 and 17; Jun et al. 2006; Carter et al. 2009; Demoreuil et al. 2009). Composite

large cell neuroendocrine carcinoma and adenocarcinoma has been observed (Sato et al. 2006).

Bile Duct Adenoma with Neuroendocrine Features

In one case of bile duct adenoma, there were periductular nests and clusters of uniform round cells, suggestive of a neuroendocrine cell proliferation. Immunohistochemistry showed decoration of these cells with several neuroendocrine markers, while neuroendocrine marker expression was not found in the epithelial cells of the ductules (O'Hara et al. 1992).

Combined Hepatic Tumors

Amphicrine Carcinoma of the Liver

Amphicrine tumors are defined as neoplasms that display both glandular and neuroendocrine differentiation in the same cell system. A single case of this type of tumor has been reported for the liver. A 47-year-old man presented with abdominal pain and MR revealed a 5.2 × 4.4 × 4 cm mass in the medial segment of the left liver lobe. Ultrasound showed a focal well-circumscribed lesion with heterogeneous echogenicity, while CT showed a solitary hyperenhancing lesion. On MR, the tumor was hyperintense relative to surrounding parenchyma on T2-weighted images. In the resection specimen, the well-delimitated tumor had a maximum diameter of 5 cm and histologically consisted of sheets of poorly cohesive malignant cells separated by thin fibrous septa. The cytoplasm was rich and eosinophilic, with many prominent intracytoplasmic vacuoles, imparting a signet-cell phenotype. These vacuoles were focally PASD and mucicarmine positive. However, no glandular structures were noted. Focal vascular invasion was found. Immunohistochemically, the neoplastic cells were reactive for synaptophysin and chromogranin, and for cytokeratins 7 and 20. Furthermore, the tumor was strongly positive for villin and pancytokeratin (Ganesan et al. 2011).

Combined Primary Neuroendocrine and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) with neuroendocrine components is an extremely rare tumor (Barsky et al. 1984; Artopoulos and Destuni 1994). In the case of Barsky et al. (1984), the tumor ultrastructurally consisted of HCC cells, carcinoid tumor cells, and cells showing both of these features. In an HCC arisen in a patient with MEN1, HCC cells with expression of chromogranin A were detected (Nakajima et al. 2000). Aboelenen and coworkers reported on a large (20 cm) hepatic tumor that consisted of a combination of neuroendocrine tumor cells and cells reactive for Hep Par1, however without glypican-3 staining (Aboelenen et al. 2014). Combined neuroendocrine and hepatocellular carcinomas can also contain a poorly differentiated neuroendocrine lineage (NEC), mostly of small cell type (Yamaguchi et al. 2004; Yang et al. 2009). In a rapidly growing HCC, the moderately differentiated HCC component contained nests of small cell NEC expressing several neuroendocrine lineage markers (Yamaguchi et al. 2004).

Collision Tumors

A collision tumor of the liver was composed of a small cell high-grade neuroendocrine carcinoma and hepatocellular carcinoma, the two tumors separated by fibrous bands (Garcia et al. 2006). Extrahepatic collision tumors containing a neuroendocrine component can metastasize to the liver (Mroz et al. 2009). Neuroendocrine collision tumors should not be confounded with situations in which hepatic neuroendocrine tumor is synchronously associated with HCC located elsewhere in the liver (Ishida et al. 2003).

Hepatobiliary Cellular Sources of Neuroendocrine Tumors

Neuroendocrine Cells in the Biliary Tract Mucosa

Endocrine cells present in the epithelial lining of the normal human intrahepatic biliary tract are mostly argyrophilic cells and are found both in children and adults. These cells are mostly immunoreactive for somatostatin (Kurumaya et al. 1989). Also the mucosa of the extrahepatic bile ducts and of the ampulla of humans, but not the gallbladder, harbors somatostatin-containing cells detectable with immunohistochemistry (Dancygier et al. 1984).

Neuroendocrine Features of Cholangiocytes and the Neurobiliary Interactome

Proliferating cholangiocytes can acquire the phenotype of neuroendocrine cells. Particularly, cells of human ductular proliferations display neuroendocrine features, and neuroendocrine factors themselves regulate cholangiocyte proliferation (Roskams et al. 1990, 2004; Alvaro et al. 2007; Mancino and Alvaro 2007; Marzioni et al. 2009; Munshi et al. 2011). Cholangiocytes express the neural cell adhesion molecule, N-CAM (CD56), including the cells of ductular proliferations (Roskams et al. 1991; Fabris et al. 2000). Cells located to ductular proliferations express parathyroid hormone-related peptide (Roskams et al. 1993).

Cholangiocytes express several hormone and neurohormone receptor systems. They possess serotonin 1A and 1B receptors. The activation of these receptors inhibits the growth and choleretic activity of the biliary tree in bile duct-ligated rats, associated with enhanced protein kinase C signaling. Cholangiocytes also secrete the ligand, serotonin, suggesting an autocrine/paracrine regulation of cholangiocyte growth and function (Marzioni et al. 2005). Glucagon-like peptide-1 (GLP-1) induces the neuroendocrine transdifferentiation of pancreatic ductal cells and also plays a role in cholangiocyte turnover in the course of cholestasis. Cholangiocytes express the GLP-1 receptor which is upregulated during cholestasis. GLP-1 and its receptor agonist exendin-4 increase cholangiocyte growth both in vivo and in vitro, whereby the GLP-1 signaling is mediated by phosphatidyl-inositol-3-kinase, cAMP/protein kinase A, and Ca^{2+}-CamKII alpha. Proliferating cholangiocytes themselves secrete GLP-1, suggesting an autocrine/paracrine loop (Marzioni et al. 2007). Normal and diseased cholangiocytes express components of the neurotrophin-neurotrophin receptor system. Both nerve growth factor (NGF) and its TrkA receptor are expressed by normal rat cholangiocytes, and these proteins are upregulated in bile duct-ligated rats. Normal cholangiocytes secrete NGF and this secretion is increased in proliferating cholangiocytes. In vitro, NGF and estrogens have an additive effect on cholangiocyte proliferation by acting on phosphorylated TrkA and p-ERK1/2 (Gigliozzi et al. 2004). The proliferation of cholangiocytes is coordinatively controlled by the parasympathetic and sympathetic innervation of the liver and biliary tract. The sensory neuropeptides, alpha and beta calcitonin gene-related peptide (alpha-CGRP and beta-CGRP), stimulate the proliferation of cholangiocytes, induce elevated cAMP levels, and stimulate the activation of cAMP-dependent protein kinase A and cAMP response element-binding protein DNA binding (Glaser et al. 2007). Murine cholangiocytes express the neurokinin-1 receptor (NK-1R) with expression upregulated following bile duct ligation. In NK-1R knockout mice, the number of CK19-positive cholangiocyte decreases and enhanced cholangiocyte apoptosis ensues (Glaser et al. 2011). The observation that many hormones, neuropeptides, and neurotransmitters regulate the homeostasis of normal cholangiocytes and affect the behavior of cholangiocellular carcinoma cells suggests the

existence of a distinct neurobiliary network or a neurobiliary interactome.

Neuroendocrine Cells in Metaplastic Lesions of the Biliary Tract

In metaplastic lesions of the extrahepatic bile ducts (the most common lesion being pseudopyloric gland metaplasia), endocrine cells were detected in 56 % of metaplastic areas (Hoang et al. 2001). In the liver with hepatolithiasis, pseudopyloric gland metaplasia and intestinal metaplasia may be prominent in intrahepatic bile ducts, and the metaplastic lesions contained endocrine cells, including argyrophil, argentaffin, and gut hormone-containing cells in 59 % of the cases. The occurrence of these endocrine cells was closely associated with intestinal metaplasia, although there were a few endocrine cells in metaplastic pseudopyloric glands (Kurumaya et al. 1990).

Development and Morphogenesis of Hepatobiliary Neuroendocrine Cells

In vitro, adult hepatic stem cells of the rat are capable to transdifferentiate into pancreatic endocrine hormone-producing cells. These differentiated cells can self-assemble to form three-dimensional islet cell-like clusters that express pancreatic islet cell differentiation-related transcripts, such as PDX-1, PAX-4, PAX-6, Nkx2, Nkx6, insulin I and II, glucose transporter 2 and glucagon, while these cells lose the expression of the hepatocyte lineage marker, Hep-Par (Yang et al. 2002).

Biliary epithelium explants cultured in vitro have been shown to undergo transdifferentiation into pancreatic-type endocrine cells. These cholangiocyte-born cells express the pancreatic transcription factors Pdx1, HNF6, and Sox9, while the expression of Ngn3, a proendocrine transcription factor, is transient, consistent with an early stage of endocrine cell differentiation (Eberhard et al. 2008).

What drives the neuroendocrine-like transdifferentiation of cholangiocytes?

The mechanisms driving cholangiocytes to a neuroendocrine-like phenotype are only partially known. The transcription factor pancreatic duodenal homeobox-1 (PDX-1) is required for pancreatic development and induces neuroendocrine-like transition of pancreatic ductal cells. Cholangiocytes of bile duct-ligated rats, but not normal rat cholangiocytes, express PDX-1. The expression and nuclear translocation of PDX-1 is promoted by GLP-1, which is secreted by proliferating cholangiocytes in obstructive cholestasis. The de novo expression of PDX-1 by cholangiocytes allows these cells to synthesize IGF-1 and VEGF (Marzioni et al. 2010).

References

Abdel Wahab M, Fathy O, Elghwalby N, Sultan A, Mostafa M, El-Baz M, Elsaadany M et al (2006) Primary hepatic carcinoid tumor: one Egyptian center experience. Hepatogastroenterology 53:33–38

Abe V, Itoh H, Yoshida M (1983) Carcinoid tumor of the common bile duct: report of a case. Stomach Intestine 18:543–548

Aboelenen A, El-hawary AK, Megahed N, Zalata KR, El-Salk EM, Fattah MA, Sorogny ME et al (2014) Right hepatectomy for combined primary neuroendocrine and hepatocellular carcinoma. A case report. Int J Surg Case Rep 5:26–29

Abu-Zaid A, Azzam A, Abudan Z, Algouhi A, Almana H, Amin T (2014) Sporadic pancreatic vasoactive intestinal peptide-producing tumor (VIPoma) in a 47-year-old male. Hematol Oncol Stem Cell Ther 7:109–115

Albores-Saavedra J, Batich K, Hossain S, Henson DE, Schwartz AM (2009) Carcinoid tumors and small-cell carcinomas of the gallbladder and extrahepatic bile ducts: a comparative study based on 221 cases from the Surveillance, Epidemiology, and End Results Program. Ann Diagn Pathol 13:378–383

Alexander IA, Thomson KR, Kune GA (1986) Primary common bile duct carcinoid: demonstration by computed tomography, ultrasonography and angiography. Australas Radiol 30:34–37

Ali M, Fayemi AO, Braun EV (1978) Malignant apudoma of the liver with symptomatic intractable hypoglycemia. Cancer 42:686–692

Alvaro D, Mancino MG, Glaser S, Gaudio E, Marzioni M, Francis H, Alpini G (2007) Proliferating cholangiocytes: a neuroendocrine compartment in the diseased liver. Gastroenterology 132:415–431

Andreola S, Lombardi L, Audisio RA et al (1990) A clinicopathologic study of primary hepatic carcinoid tumors. Cancer 65:1211–1218

Angeles-Angeles A, Quintanilla-Martinez L, Larriva-Sahd J (1991) Primary carcinoid of the common bile duct. Immunohistochemical characterization of a case and review of the literature. Am J Clin Pathol 96:341–344

Anlauf M, Garbrecht N, Henopp T, Schmitt A, Schlenger R, Raffel A, Krausch M, Gimm O et al (2006) Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinicopathological and epidemiological features. World J Gastroenterol 12:5440–5446

Aoki K, Sakamoto M, Mukai K, Kosuge T, Takayama T, Hirohashi S (1992) Signet-ring cell carcinoid: a primary hepatic carcinoid tumor with cytoplasmic inclusions comprising of aggregates of keratin. Jpn J Clin Oncol 22:54–59

Aronsky D, Z'graggen K, Stauffer E, Lange J, Klaiber C (1999) Primary neuroendocrine tumors of the cystic duct. Digestion 60:493–496

Artopoulos JG, Destuni C (1994) Primary mixed hepatocellular carcinoma with carcinoid characteristics. A case report. Hepatogastroenterology 41:442–444

Asakawa T, Tomioka T, Abe K, Yamaguchi T, Tsunoda T, Kanematsu T (1999) Primary hepatic carcinoid tumor. J Gastroenterol 34:123–127

Ayub A, Zafar M, Abdulkareem A, Ali MA, Lingawi T, Harbi A (1993) Primary hepatic vipoma. Am J Gastroenterol 88:958–961

Balta Z, Sauerbruch T, Hirner A, Büttner R, Fischer HP (2008) Primary neuroendocrine carcinoma of the liver. From carcinoid tumor to small-cell hepatic carcinoma: case reports and review of the literature (in German). Pathologe 29:53–60

Barron-Rodriguez LP, Manivel JC, Méndet-Sanchez N, Jessurun J (1991) Carcinoid tumor of the common bile duct: evidence for its origin in metaplastic endocrine cells. Am J Gastroenterol 86:1073–1076

Barsky SH, Linnoila I, Triche TJ, Costa J (1984) Hepatocellular carcinoma with carcinoid features. Hum Pathol 15:892–894

Belli G, Rotondano G, D'Agostino A, Marano I (1996) Primary extrahepatic bile duct carcinoids. HPB Surg 9:101–105

Bello Argues P, Hervas Benito I, Mateo Navarro A (2001) Scintigraphy with 111In-octreotide in a case of primary hepatic gastrinoma (in Spanish). Rev Esp Med Nucl 20:381–385

Bembenek A, Lotterer E, Machens A et al (1998) Neuroendocrine tumor of the common hepatic duct: a rare cause of extrahepatic jaundice in adolescence. Surgery 123:712–715

Bergdahl (1976) http://www.ncbi.nlm.nih.gov/pubmed/1067071

Bernheim AM, Connolly HM, Pellikka PA (2007) Carcinoid heart disease. Curr Treat Options Cardiovasc Med 9:482–489

Besznyak I, Tasnadi G, Hirsch T et al (1991) Hepatolobectomy for carcinoid tumor of the hepatic duct. Orv Hetil 132:591–594

Bickerstaff DR, Ross WB (1987) Carcinoid of the biliary tree: a case report and review of the literature. J R Coll Surg Edinb 32:48–51

Brown WM, Henderson JM, Kennedy JC (1990) Carcinoid tumor of the bile duct. A case report and literature review. Am Surg 56:343–346

Bumin C, Ormeci N, Dolapçi M, Güngör S (1990) Carcinoid tumor of the biliary duct. Int Surg 75:262–264

Caglikulekci M, Dirlik M, Aydin O, Ozer C, Colak T, Dag A, Canbaz H, Aydin S (2006) Carcinoid tumour of the common bile duct: report of a case and a review of the literature. Acta Chir Belg 106:112–115

Capella C, Sobin LH, Arnold R (2000) Endocrine tumors of the gallbladder and extrahepatic bile ducts. In: Hamilton RAL (ed) Pathology and genetics of tumors of the digestive system. WHO Classification of Tumors, IARC Press, Lyon

Carter et al (2009) http://www.ncbi.nlm.nih.gov/pubmed/19528385

Chamberlain RS, Blumgart LH (1999) Carcinoid tumors of the extrahepatic bile duct: a rare cause of malignant biliary obstruction. Cancer 86:1959–1965

Chan C, Medina-Franco H, Bell W, Lazenby A, Vickers S (2000) Carcinoid tumor of the hepatic duct presenting as a Klatskin tumor in an adolescent and review of world literature. Hepatogastroenterology 47:519–521

Chen Z, Xiao HE, Ramchandra P, Huang HJ (2014) Imaging and pathological features of primary hepatic neuroendocrine carcinoma: an analysis of nine cases and review of the literature. Oncol Lett 7:956–962

Chetty R (2008) Requiem for the term 'carcinoid tumour' in the gastrointestinal tract? Can J Gastroenterol 22:357–358

Chien RN, Chen TC, Chiu CT, Tsai SL, Jen LB, Liaw YF (2001) Primary calcified gastrinoma of the liver. Dig Dis Sci 46:370–375

Chittal SM, Ra PM (1989) Carcinoid of the cystic duct. Histopathology 15:643–646

Cho SB, Park SY, Joo YE (2009) Small cell carcinoma of the extrahepatic bile duct presenting with hemobilia (in Korean). Korean J Gastroenterol 54:186–190

Cianchi F, Carassale G, Palomba A, Pucciani F, Messerini L (1997) A case of primary hepatic carcinoid. A report of its surgical resolution (in Italian). Minerva Chir 52:433–437

Colombo F, Carrara B, Rosato S, Rück F, Simonetti A, Soccio M, Taverniti G, Zeppieri MC (2007) Carcinoid tumors of the bile ducts (in Italian). Chir Ital 59:405–410

Cruikshank AH (1961) The pathology of 111 cases of primary hepatic malignancy collected in the Liverpool region. J Clin Pathol 14:120–131

Dahm M, Steegmüller KW, Beyer J, Küstner E, Schinzel H, Lang J, Junginger T (1993) Cushing

syndrome in ACTH-producing neuroendocrine tumor of the hepatic duct (in German). Chirurg 64:662–665
Dancygier H, Klein U, Leuschner U, Hübner K, Classen M (1984) Somatostatin-containing cells in the extrahepatic biliary tract in humans. Gastroenterology 86:892–896
Davies AJ (1959) Carcinoid tumors (argentaffinomata). Ann R Coll Surg Engl 25:277–280
De Giorgio R, Migliori M, Lalli S, Montini GC, Gullo L, Corinaldesi R, Bordi C, Tomassetti P (1998) Asymptomatic glucagonoma presenting with isolated hepatic nodule. Hepatogastroenterology 45:1093–1096
De Liguori Carino N, Manzia TM, Tariciotti L, Berlanda M, Orlando G, Tisone G (2009) Liver transplantation in primary hepatic carcinoid tumor: case report and literature review. Transplant Proc 41:1386–1389
Dejong CH, Parks RW, Currie E, Piris J, Redhead DN, Garden OJ (2002) Treatment of hepatic metastases of neuroendocrine malignancies: a 10-year experience. J R Coll Surg Edinb 47:495–499
DeLellis RA, Osamura RY (2006) Neuroendocrine tumors: an overview. Pathol Case Rev 11:229–234
Demoreuil C, Thirot-Bidault A, Dagher C, Bou-farah R, Benbrahem C, Lazure T, Dayral F, Buffet C (2009) Poorly differentiated large cell endocrine carcinoma of the extrahepatic bile ducts (in French). Gastroenterol Clin Biol 33:194–198
Denève E, Hamoui M, Chalançon A, Blanc PM, Aufort S, Fabre JM, Nocca D (2009) A case of intrahepatic gastrinoma (in French). Ann Endocrinol (Paris) 70:242–245
Deol ZK, Frezza E, DeJong S, Pickleman J (2003) Solitary hepatic gastrinoma treated with laparoscopic radiofrequency ablation. JSLS 7:285–289
Derizhanova IS, Miroshnikov VP (1989) Primary carcinoid of the liver (in Russian). Vopr Onkol 35:736–739
Dixon J, Lisehora G, Lee MY (1992) Carcinoid tumour of the common bile duct. Contemp Surg 41:37–40
Do Cao C, Mekinian A, Ladsous M, Aubert S, D'Herbomez M, Pattou F, Bourdelle-Hego MF et al (2010) Hypercalcitoninemia revealing a somatostatinoma. Ann Endocrinol (Paris) 71:553–557
Donadon M, Torzilli G, Palmisano A, Del Fabbro D, Panizzo V, Maggioni M, Santambroglio R, Montorsi M (2006) Liver resection for primary hepatic neuroendocrine tumours: report of three cases and review of the literature. Eur J Surg Oncol 32:325–328
Eberhard D, Tosh D, Slack JM (2008) Origin of pancreatic endocrine cells from biliary duct epithelium. Cell Mol Life Sci 65:3467–3480
Edmondson HA (1958) Carcinoid tumor. In: Edmondson HA (ed) Tumors of the liver and intrahepatic bile ducts, Atlas of tumor pathology. Armed Forces Institute of Pathology, Washington, DC, pp 105–111
El Rassi ZS, Mohsine RM, Berger F, Thierry P, Partensky CC (2004) Endocrine tumors of the extrahepatic bile ducts. Pathological and clinical aspects, surgical management and outcome. Hepatogastroenterology 51:1295–1300
Fabris L, Strazzabosco M, Crosby HA, Ballardini G, Hubscher SG, Kelly DA, Neuberger JM et al (2000) Characterization and isolation of ductular cells coexpressing neural cell adhesion molecule and Bcl-2 from primary cholangiopathies and ductal plate malformations. Am J Pathol 156:1599–1612
Felekouras E, Petrou A, Bramis K, Prassas E, Papaconstantinou I, Dimitrou N, Pazaiti A et al (2009) Malignant carcinoid tumor of the cystic duct: a rare cause of bile duct obstruction. Hepatobiliary Pancreat Dis Int 8:640–646
Fellows IW, Leach IH, Smith PG, Toghill PJ, Doran J (1990) Carcinoid tumor of the common bile duct – a novel complication of von Hippel-Lindau syndrome. Gut 31:728–729
Fenoglio LM, Severini S, Ferrigno D, Gollè G, Serraino C, Bracco C, Castagna E et al (2009) Primary hepatic carcinoid: a case report and literature review. World J Gastroenterol 15:2418–2422
Fenwick SW, Wyatt JI, Toogood GJ, Lodge JP (2004) Hepatic resection and transplantation for primary carcinoid of the liver. Ann Surg 239:210–219
Ferrone CR, Tang LH, D'Angelica M, DeMatteo RP, Blumgart LH, Klinstra DS, Jarnagin WR (2007) Extrahepatic bile duct carcinoid tumors: malignant biliary obstruction with a good prognosis. J Am Coll Surg 205:357–361
Foley DS, Sunil I, Debski R, Ignacio RC, Nagaraj HS (2008) Primary hepatic carcinoid tumor in children. J Pediatr Surg 43:e25–e28
Fujino K, Koito K, Sano S et al (1998) A primary hepatic carcinoid tumor: evaluation by computed tomography and magnetic resonance imaging. Radiat Med 16:371–373
Fujita N, Mochizuki F, Lee S, Satoh K, Kobayashi G, Yano A, Shimoda T (1989) Carcinoid tumour of the bile duct: case report. Gastrointest Radiol 14:151–154
Fukunaga M (1998) Neuroendocrine carcinoma of the liver: an autopsy case. Pathol Int 48:481–485
Furrer J, Hattenschwiler A, Komminoth P, Pfammatter T, Wiesli P (2001) Carcinoid syndrome, acromegaly, and hypoglycemia due to an insulin-secreting neuroendocrine tumor of the liver. J Clin Endocrinol Metab 86:2227–2230
Ganesan K, Achmad E, Sirlin CB, Bouvet M, Datnow B, Weidner N, Peterson MR (2011) Amphicrine carcinoma of the liver. Ann Diagn Pathol 15:355–357
Garcia MT, Bejarano PA, Yssa M, Buitrago E, Livingstone A (2006) Tumor of the liver (hepatocellular and high grade neuroendocrine carcinoma): a case report and review of the literature. Virchows Arch 449:376–381
Gastinger I, Schütze U, Beetz G, Lippert H (1987) Obstructive jaundice caused by a carcinoid tumor of the hepatocholedochal duct (in German). Zentralbl Chir 112:1170–1175
Gembala et al (1993) http://www.ncbi.nlm.nih.gov/pubmed/8508084
Gerlock AJ, Mühletaler CA (1979) Primary common bile duct carcinoid. Gastrointest Radiol 4:263–264

Gigliozzi A, Alpini G, Baroni GS, Marucci L, Metalli VD, Glaser SS, Francis H, Mancino MG et al (2004) Nerve growth factor modulates the proliferative capacity of the intrahepatic biliary epithelium in experimental cholestasis. Gastroenterology 127:1198–1209

Glaser SS, Ueno Y, DeMorrow S, Chiasson VL, Katki KA, Venter J, Francis HL et al (2007) Knockout of alpha-calcitonin gene-related peptide reduces cholangiocyte proliferation in bile duct ligated mice. Lab Invest 87:914–926

Glaser S, Gaudio E, Renzi A, Mancinelli R, Ueno Y, Venter J, White M, Kopriva S et al (2011) Knockout of the neurokinin-1 receptor reduces cholangiocyte proliferation in bile duct ligated mice. Am J Physiol Gastrointest Liver Physiol 301:G297–G305

Godwin (1975) http://www.ncbi.nlm.nih.gov/pubmed/1157019

Goodman ZD, Albores-Saavedra J, Lundblad DM (1984) Somatostatinoma of the cystic duct. Cancer 53:498–502

Gosset A, Masson P (1914) Tumeurs endocrines de l'appendice. Press Méd 22:237–240

Gould VE, Banner BF, Baerwaldt M (1981) Neuroendocrine neoplasms in unusual primary sites. Diagn Histopathol 4:263–277

Graeme-Cook F (2003) Neuroendocrine tumors of the GI tract and appendix. In: Odze R (ed) Surgical pathology of the GI tract, liver, biliary tract, and pancreas, 1st edn. Elsevier Saunders, Philadelphia, pp 485–486

Gravante G, De Liguori Carino N, Overton J, Manzia TM, Orlando G (2008) Primary carcinoids of the liver: a review of symptoms, diagnosis and treatments. Dig Surg 25:364–368

Grundmann R, Thul P, Krestin GP, Krueger GR (1985) Somatostatinoma of the liver (in German). Leber Magen Darm 15:81–84

Gusani NJ, Marsh JW, Nalesnik MA, Tublin ME, Gamblin TC (2008) Carcinoid of the extra-hepatic bile duct: a case report with long-term follow-up and review of literature. Am Surg 74:87–90

Hachicha I, Zayene A, Mnif Hachicha L, Ben Ali A, Mokni M, Derbel F, Dahmene Y et al (2003) Primary hepatic vipoma (in French). Gastroenterol Clin Biol 27:551–554

Hao L, Friedman AL, Navarro VJ, West B, Robert ME (1996) Carcinoid tumor of the common bile duct producing gastrin and serotonin. J Clin Gastroenterol 23:63–65

Hazama K, Suzuki Y, Takahashi M, Yoshioka T, Takano S, Kondoh S, Katoh H (2003) Primary small cell carcinoma of the common bile duct, in which surgical treatment was performed after neoadjuvant chemotherapy: report of a case. Surg Today 33:870–872

Hermina M, Starling J, Warner TF (1999) Carcinoid tumor of the cystic duct. Pathol Res Pract 195:707–709

Hidaka H, Kuwao S, Kokubu S, Yanagimoto K, Satomichi A, Takada M, Nakazawa T, Saigenji K (2000) Mixed carcinoid-adenocarcinoma of the liver. Intern Med 39:910–913

Hoang MP, Murakata LA, Padilla-Rodriguez AL, Albores-Saavedra J (2001) Metaplastic lesions of the extrahepatic bile ducts: a morphologic and immunohistochemical study. Mod Pathol 14:1119–1125

Hodgson HJ, Maton PN (1987) Carcinoid and neuroendocrine tumours of the liver. Baillieres Clin Gastroenterol 1:35–61

Holbrook RF, Koo K, Ryan JH (1996) Resection of malignant primary liver tumors. Am J Surg 171:453–455

Honda H, Hayashi S, Sekiguchi Y, Tsukadaira T, Nakamura T (2006) A case of the extrahepatic bile duct carcinoid tumor (in Japanese). Nippon Shokakibyo Gakkai Zasshi 103:1169–1175

Hosonuma K, Sato K, Honma M, Kashiwabara K, Takahashi H, Takagi H, Mori M (2008) Small-cell carcinoma of the extrahepatic bile duct: a case report and review of the literature. Hepatol Int 2:129–132

Hsueh C, Tan XD, Gonzalez-Crussi F (1993) Primary hepatic neuroendocrine carcinoma in a child. Morphologic, immunocytochemical, and molecular biologic studies. Cancer 71:2660–2665

Hubert C, Sempoux C, Berquin A, Deprez P, Jamar F, Gigot JF (2005) Bile duct carcinoid tumors: an uncommon disease but with a good prognosis? Hepatogastroenterology 52:1042–1047

Iimuro Y, Deguchi Y, Ueda Y et al (2002) Primary hepatic carcinoid tumor with metachronous lymph node metastasis after long-term follow up. J Gastroenterol Hepatol 17:1119–1124

Imaoka I, Sugimura K, Tamura K (1993) Case report: MR imaging of a carcinoid tumor of the liver. Clin Radiol 47:287–289

Inoue Y, Nakamura H, Mizumoto S, Mori H, Yamaski K (1993) Primary hepatic carcinoid with production of gastrin: a case report. Radiat Med 11:102–106

Iribarren Diaz M, de Castro Parga G, Freiria Barreiro G, Fernandez Martin R, Meléndez Villar R et al (2004) Solitary hepatic carcinoid tumor in a man with prior treatment for rectal adenocarcinoma. Rapid growth without carcinoid syndrome (in Spanish). Gastroenterol Hepatol 27:125–128

Ishida M, Seki K, Tatsuzawa A, Katayama K, Hirose K, Azuma T, Imamura Y, Abraham A, Yamaguchi A (2003) Primary hepatic neuroendocrine carcinoma coexisting with hepatocellular carcinoma in hepatitis C liver cirrhosis: report of a case. Surg Today 33:214–218

Ishikawa Y, Yoshida H, Mamada Y, Taniai N, Matsumoto S, Bando K, Mizuguchi Y et al (2008) Curative resection of primary hepatic gastrinoma. Hepatogastroenterology 55:2224–2227

Isler P, Hedinger C (1953) Metastasierendes Dünndarmcarcinoid mit schweren, vorwiegend das rechte Herz betreffenden Klappenfehlern und Pulmonalstenose – ein eigenartiger Symptomenkomplex? Schweiz Med Wochenschr 83:4–7

Iwao M, Nakamuta M, Enjoji M et al (2001) Primary hepatic carcinoid tumor: case report and review 53 cases. Med Sci Monit 7:746–750

Jarboui S, Jerraya H, Moussi A, Daldoul S, Morched Abdesselem M, Zaouche A (2008) Primary carcinoid hepatic tumour: a case report (in French). Tunis Med 86:386–388

Jeon WJ, Chae HB, Park SM, Youn SJ, Choi JW, Kim SH (2006) A case of primary small cell carcinoma arising from the common bile duct (in Korean). Korean J Gastroenterol 48:438–442

John BM, Song MH, Park YS, Jo YJ, Kim SH, Lee HH, Kim SK, Jung SH, Kim DH, Kim DH (2006) A case of carcinoid tumor of the common bile duct (in Korean). Korean J Gastroenterol 47:320–323

Johnston PC, Ardill JE, Johnston BT, Mc Cance DR (2010) Vasoactive intestinal polypeptide secreting pancreatic tumour with hepatic metastases: long term survival after orthotopic liver transplantation. Ir J Med Sci 179:439–441

Judge DM, Dickman PS, Trapukdi BS (1976) Nonfunctioning argyrophilic tumour (APUDoma) of the hepatic duct: simplified methods of detecting biogenic amines in tissue. Am J Clin Pathol 66:40–45

Jun SR, Lee JM, Han JK, Choi BI (2006) High-grade neuroendocrine carcinomas of the gallbladder and bile duct: report of four cases with pathological correlation. J Comput Assist Tomogr 30:604–609

Jutte DL, Bell RH, Penn I, Powers J, Kolinjivadi J (1987) Carcinoid tumor of the biliary system. Case report and literature review. Dig Dis Sci 32:763–769

Juturi JV, Maghfoor I, Doll DC, Evans ML (2000) A case of biliary carcinoid presenting with pancreatitis and obstructive jaundice. Am J Gastroenterol 95:2973–2974

Kaiho T, Tanaka T, Tsuchiya S, Yanagisawa S, Takeuchi O, Miura M, Saigusa N et al (2005) A case of small cell carcinoma of the common bile duct. Hepatogastroenterology 52:363–367

Kehagias D, Moulopoulos L, Smirniotis V, Pafiti A, Ispanopoulos S, Vlahos L (1999) Imaging findings in primary carcinoid tumour of the liver with gastrin production. Br J Radiol 72:207–209

Kim SR, Imoto S, Maekawa Y, Matsuoka T, Hayashi Y, Ando K, Mita K, Shintani S et al (2002) CEA producing primary hepatic carcinoid. Hepatol Res 22:313–321

Kim DH, Song MH, Kim DH (2006) Malignant carcinoid tumor of the common bile duct: report of a case. Surg Today 36:485–489

Kinley CE, Penner DW (1962) Carcinoid tumors: a review and clinicopathological study of 52 cases. Can J Surg 51:138–147

Klimstra DS, Modlin IR, Adsay NV, Chetty R, Deshpande V, Gönen M, Jensen RT et al (2010) Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. Am J Surg Pathol 34:300–313

Klöppel G, Couvelard A, Perren A, Komminoth P, McNicol AM, Nilsson O, Scarpa A et al (2009) ENETS consensus guidelines for the standards, of care in neuroendocrine tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. Neuroendocrinology 90:162–166

Klöppel G, Rindi G, Perren A, Komminoth P, Klimstra DS (2010) The ENETS and UICC TNM classification of neuroendocrine tumors of the gastrointestinal tract and the pancreas: comment (in German). Pathologe 31:353–354

Knox CD, Anderson CD, Lamps LW, Adkins RB, Pinson CW (2003) Long-term survival after resection for primary hepatic carcinoid tumor. Ann Surg Oncol 10:1171–1175

Kohashi T, Itamoto T, Katayama K, Nakahara H, Onoe T, Matsugu Y, Nakatsuka H et al (2005) Primary hepatic carcinoid tumor (a case report). Hepatogastroenterology 52:1218–1220

Komatsu T, Ishida H, Furukawa K, Miyauchi T et al (2005) Primary carcinoid tumor of the liver: report of a case with an emphasis on contrast-enhanced ultrasonographic findings. J Clin Ultrasound 33:302–304

Kopelman D, Schein M, Kerner H, Bahuss H, Hashmonai M (1996) Carcinoid tumor of the common bile duct. HPB Surg 10:41–43

Koplin S, Agni R (2009) Hepatic composite tumor in a patient with primary sclerosing cholangitis. Pathol Res Pract 205:361–364

Krishnamurty SC, Dutta V, Pai SA et al (1996) Primary carcinoid tumor of the liver: report of four resected cases including one with gastrin production. J Surg Oncol 62:218–221

Kulke MH, Mayer RJ (1999) Carcinoid tumors. N Engl J Med 340:858–868

Kuraoka K, Taniyam K, Fujitaka T et al (2003) Small cell carcinoma of the extrahepatic bile duct: case report and immunohistochemical analysis. Pathol Int 53:887–891

Kurumaya H, Ohta G, Nakanuma Y (1989) Endocrine cells in the intrahepatic biliary tree in normal livers and hepatolithiasis. Arch Pathol Lab Med 113:143–147

Kurumaya H, Terada T, Nakanuma Y (1990) 'Metaplastic lesions' in intrahepatic bile ducts in hepatolithiasis: a histochemical and immunohistochemical study. J Gastroenterol Hepatol 5:530–536

Landen S, Elens M, Vrancken C, Nuytens F, Meert T, Delugeau V (2014) Giant hepatic carcinoid: a rare tumor with a favorable prognosis. Case Rep Surg 2014:456509

Larriva-Sahd J, Angeles-Angeles A, Hernandez-Pando R et al (1992) Ultrastructural and immunocytochemical study of a primary gastrinoma of the liver. Ultrastruct Pathol 16:667–672

Lau PP, Tint KA, Tse GM, Lui PC (2006) Primary hepatic carcinoid tumours: report of two cases. Pathology 38:458–461

Lee JH, Lee KG, Oh YH, Paik SS, Park HK, Lee KS (2011) Carcinoid tumors of the extrahepatic biliary tract: report of four cases. Surg Today 41:430–435

Lemaire LC, Pols HA, Tilanus HW (1995) Carcinoid tumour presenting as a giant hepatic cyst. Br J Surg 82:133

Li JT, Fang HQ, Liu XL, Tang Z, Xu J, Zhang SZ, Ma R, Zhang LY, Wang JW et al (2010) Is radiofrequency ablation justified for liver metastatic VIPoma patient undergoing Whipple procedure? Chin Med J (Engl) 123:2151–2154

Li RK, Zhao J, Rao SX, Chen CZ, Zeng MS, Qiang JW (2013) Primary hepatic neuroendocrine carcinoma: MR imaging findings including preliminary observation on diffusion-weighted imaging. Abdom Imaging 38:1269–1276

Ligato S, Furmaga W, Cartun RW, Hull D, Tsongalis GJ (2005) Primary carcinoid tumor of the common hepatic duct: a rare case with immunohistochemical and molecular findings. Oncol Rep 13:543–546

Lin CW, Lai CH, Hsu CC, Hsu CT, Hsieh PM, Hung KC, Chen YS (2009) Primary hepatic carcinoid tumor: a case report and review of the literature. Cases J 2:90

Lingamfelter D, Hoffman L, Verma A, Depond W, Lankachandra K (2007) Giant atypical carcinoid of the liver with vascular metastases and local sinusoidal invasion: a case report. J Med Case Reports 1:47

Little JM, Gibson AA, Kay AW (1968) Primary common bile-duct carcinoid. Br J Surg 55:147–149

Liu CL, Fan ST, Lo CM, Chan SC, Tso WK, Ng IO, Wong J (2004) Hepatic resection for incidentaloma. J Gastrointest Surg 8:785–793

Lubarsch O (1888) Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberculose. Virchows Arch Pathol Anat 111:280–317

Lundstedt C, Linjawi T, Amin T (1994) Liver VIPoma: report of two cases and literature review. Abdom Imaging 19:433–437

Machado MC, Penteado S, Bacchella T, Bettarello A, da Cunha JE, Faintuch J, Lopes HL, Raia A (1981) Carcinoid tumor (apudoma) of the junction of the main hepatic ducts (in Portuguese). Rev Hosp Clin Fac Med Sao Paulo 36:139–142

Maggard MA, O'Connell JB, Ko CY (2004) Updated population-based review of carcinoid tumors. Ann Surg 240:117–122

Maitra A, Krueger JE, Tascilar M et al (2000) Carcinoid tumors of the extrahepatic bile ducts: a study of seven cases. Am J Surg Pathol 24:1501–1510

Mancino MG, Alvaro D (2007) Pathophysiology of cholangiocytes: recent advances (in Italian). Recenti Prog Med 98:583–588

Mandujano-Vera G, Angeles-Angeles A, de la Cruz-Hernandez J, Sansores-Perez M, Larriva-Sahd J (1995) Gastrinoma of the common bile duct. immunohistochemical and ultrastructural study of a case. J Clin Gastroenterol 20:321–324

Maros T, Hecser L (1982) Primary carcinoid of the liver (in Romanian). Rev Chir Oncol Radiol ORL Oftalmol Stomatol Chir 31:299–302

Martignoni ME, Friess H, Lübke D, Uhl W, Maurer C, Müller M, Richard H, Reubi JC, Büchler MW (1999) Study of a primary gastrinoma of the common bile duct – a case report. Digestion 60:187–190

Marzioni M, Glaser S, Francis H, Marucci L, Benedetti A, Alvaro D, Taffetani S, Ueno Y et al (2005) Autocrine/paracrine regulation of the growth of the biliary tree by the neuroendocrine hormone serotonin. Gastroenterology 128:121–137

Marzioni M, Alpini G, Saccomanno S, Candelaresi C, Venter J, Rychlicki C, Fava G et al (2007) Glucagon-like peptide-1 and its receptor agonist exendin-4 modulate cholangiocyte adaptive response to cholestasis. Gastroenterology 133:244–255

Marzioni M, Fava G, Alvaro D, Alpini G, Benedetti A (2009) Control of cholangiocyte adaptive responses by visceral hormones and neuropeptides. Clin Rev Allergy Immunol 36:13–22

Marzioni M, Saccomanno S, Candelaresi C, Rychlicki C, Agostinelli L, Shanmukhappa K et al (2010) Pancreatic duodenal homeobox-1 de novo expression drives cholangiocyte neuroendocrine-like transdifferentiation. J Hepatol 53:663–670

Massironi S, Zilli A, Rossi RE, Cavalcoli F, Conte D, Peracchi M (2014) Gastrinoma and neurofibromatosis type 2: the first case report and review of the literature. BMC Gastroenterol 14:110

Masunaga A, Inoue K, Mizukami H, Hayashi T, Mitsuya T (2014) Neuroendocrine carcinoma arising in a hepatitis C virus-infected liver: mechanism of the tumor development may be similar to that of development of pancreatic neuroendocrine cells. Pathol Int 64:81–85

Mehta DC, Warner RR, Parnes I, Weiss M (1996) An 18-year follow-up of primary hepatic carcinoid with carcinoid syndrome. J Clin Gastroenterol 23:60–62

Menezes AAC, Diver AJ, Mccance D, Diamond T (2004) Carcinoid tumor of the extrahepatic bile duct – report of a case and literature review. Ulster Med J 73:59–62

Miura K, Shirasawa H (1988) Primary carcinoid tumor of the liver. Am J Clin Pathol 89:561–564

Miyashita T, Konishi K, Noto M et al (2001) A case of small cell carcinoma of the common bile duct (in Japanese). Nippon Shokakibyo Gakkai Zasshi 98:1195–1198

Mizuno Y, Ohkohchi N, Fujimori K et al (2000) Primary hepatic carcinoid tumor: a case report. Hepatogastroenterology 47:528–530

Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD (2005a) Current status of gastrointestinal carcinoids. Gastroenterology 128:1717–1751

Modlin IM, Shapiro MD, Kidd M (2005b) An analysis of rare carcinoid tumors: clarifying these clinical conundrums. World J Surg 29:92–101

Morisawa Y, Tanaka A, Yamamoto T, Uegaki S, Takamori Y, Ishii T, Kuyama Y, Fukusato T et al (2006) Primary hepatic somatostatinoma developed in a patient with von Recklinghausen's disease. J Gastroenterol 41:389–391

Moriura S, Ikeda S, Hirai M et al (1993) Hepatic gastrinoma. Cancer 72:1547–1550

Mrabet N, Houissa H, Bellil K, Bellil S, Mekni A, Haouet S, Sebai F, ZitounaMohamed M, Kchir N (2006) Primary hepatic carcinoid tumor: a case report (in French). Tunis Med 84:198–200

Mroz A, Kiedrowski M, Malinowska M, Sopylo R (2009) Collision tumour of the stomach – adenocarcinoma and neuroendocrine carcinoma: case report and review of the literature. Pol J Pathol 60:94–97

Müller S, Kupka S, Königsrainer I, Northoff H, Sotlar K, Bock T, Kandolf R, Traub F et al (2012) MSH2 and CXCR4 involvement in malignant VIPoma. World J Surg Oncol 10:264

Munshi MK, Priester S, Gaudio E, Yang F, Alpini G, Mancinelli R, Wise C, Meng F et al (2011) Regulation of biliary proliferation by neuroendocrine factors: implications for the pathogenesis of cholestatic liver diseases. Am J Pathol 178:472–484

Nafidi O, Nguyen BN, Roy A (2008) Carcinoid tumor of the common bile duct: a rare complication of von Hippel-Lindau syndrome. World J Gastroenterol 14:1299–1301

Nagamura N, Andou M, Toyokawa T, Ohnishi T, Nakatu M, Suwaki K, Hirohata M (2007) Primary liver carcinoid tumor complicated with colon cancer (in Japanese). Nippon Naika Gakkai Zasshi 96:1473–1475

Nahas SC, Lourencao JL, Gazoni E, Mott CB, Borba MR, Pinto Filho JO, Lopes LH et al (1998) Carcinoid tumor of the common bile duct: a case report (in Portuguese). Rev Hosp Clin Fac Med Sao Paulo 53:26–28

Nakajima K, Sakurai A, Katai M, Yajima H, Mori J, Katakura M, Tsuchiya S, Hashizume K (2000) Chromogranin A expression in hepatocellular carcinoma in a patient with germline MEN1 gene mutation. Intern Med 39:20–24

Naoe H, Iwasaki H, Kawasaki T, Ozaki T, Tsutsumi H, Okuda A, Konoe T, Nonaka K et al (2012) Primary hepatic gastrinoma as an unusual manifestation of Zollinger-Ellison syndrome. Case Rep Gastroenterol 6:590–595

Nassar et al (2005) http://www.ncbi.nlm.nih.gov/pubmed/15832081

Nemes B, Podder H, Jaray J et al (1999) Primary hepatic carcinoid in a renal transplant patient. Pathol Oncol Res 5:67–69

Nesi G, Lombardi A, Batignani G, Ficari F, Rubio CA, Tonelli F (2006) Well-differentiated endocrine tumor of the distal common bile duct: a case study and literature review. Virchows Arch 449:104–111

Newman K, Vates T, Duffy L, Anderson K (1992) Pancreatoduodenectomy with preservation of the stomach and pylorus: a safe and effective alternative in children. J Pediatr Surg 27:1334–1335

Nicolescu PG, Popescu A (1986) Carcinoid tumor of the cystic duct. Morphol Embryol (Bucur) 32:275–277

Nikfarjam M, Evans P, Muralidharan V, Christophi C (2004a) Not all hepatic carcinoids are metastases. J Gastroenterol Hepatol 19:232–233

Nikfarjam M, Muralidharan V, Christophi C (2004b) Primary hepatic carcinoid tumors. HPB (Oxford) 6:13–17

Nishihara K, Tsuneyoshi M, Niiyama H et al (1993) Composite glandular-endocrine cell carcinoma of the extrahepatic bile duct: immunohistochemical study. Pathology 25:90–94

Nishimori H, Tsuji K, Miyamoto N, Sakurai Y, Mitsui S, Kang JH, Yoshida M, Nomura M et al (2005) Recurrence of primary hepatic carcinoid tumor in the remnant liver 13 yr after resection. Int J Gastrointest Cancer 35:147–151

Norgaard T, Bardram L (1985) Endocrine liver tumour differential diagnosis from hepatocellular carcinoma. Histopathology 9:777–781

Noronha YS, Raza AS (2010) Well-differentiated neuroendocrine (carcinoid) tumors of the extrahepatic bile ducts. Arch Pathol Lab Med 134:1075–1079

O'Hara BJ, McCue PA, Miettinen M (1992) Bile duct adenomas with endocrine component. Immunohistochemical study and comparison with conventional bile duct adenomas. Am J Surg Pathol 16:21–25

Oberndorfer S (1907) Karzinoide Tumoren des Dünndarms. Frankf Z Path 1:426–432

Obi N, Katabami T, Obi R, Odanaka M, Sasano K, Tanaka Y (2009) Primary malignant hepatic glucagonoma: an autopsy case. Endocr J 56:715–719

Ogawa S, Wada M, Fukushima M, Shimeno N, Inoue S, Chung H, Fujita M, Suginoshita Y et al (2014) Case of primary hepatic gastrinoma: diagnostic usefulness of the selective arterial calcium injection test. Hepatol Res. doi:10.1111/hepr.12404

Ogilvie RF (1947) Pathological histology, 3rd edn. Livingstone, Edinburgh

Oh YH, Kang GH, Kim OJ (1998) Primary hepatic carcinoid tumor with a paranuclear clear zone: a case report. J Korean Med Sci 13:317–320

Ohwada S, Joshita T, Ishihara T, Oyama T, Inui Y, Aoki J (2003) Primary liver somatostatinoma. J Gastroenterol Hepatol 18:1218–1219

Oikawa I, Hirata K, Katsuramaki T, Mukaiya M, Sasaki K, Satoh M (1998) Neuroendocrine carcinoma of the extrahepatic biliary tract with positive immunostaining for gastrin-releasing peptide: report of a case. Surg Today 28:1192–1195

Okamura Y, Maeda A, Matsunaga K, Kanemoto H, Boku N, Furukawa H, Sasaki K, Uesaka K (2009) Small-cell carcinoma in the common bile duct treated with multidisciplinary management. J Hepatobiliary Pancreat Surg 16:575–578

Pawlik TM, Shah S, Eckhauser FE (2003) Carcinoid tumor of the biliary tract: treating a rare cause of bile duct obstruction. Am Surg 69:98–101

Pellikka PA, Tajik AJ, Khandheria BK, Seward JB, Callahan JA, Pitot HC, Kvols LK (1993) Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. Circulation 87:1188–1196

Perakath B, Chandran BS, Srivastava VM, Nair A, Sitaram V (1999) Carcinoid tumor of common hepatic duct. Indian J Gastroenterol 18:127

Pilichowska M, Kimura N, Ouchi A, Lin H, Mizuno Y, Nagura H (1999) Primary hepatic carcinoid and neuroendocrine carcinoma: clinicopathological and immunohistochemical study of five cases. Pathol Int 49:318–324

Pilz E (1961) Über ein Karzinoid des Ductus choledochus (On a carcinoid of the choledochal duct). Zentralbl Chir 86:1588–1590

Pithawala M, Mittal G, Prabhu RY, Kantharia CV, Joshi A, Supe A (2005) Carcinoid tumor of bile duct. Indian J Gastroenterol 24:262–263

Podnos YD, Jimenez JC, Zainabadi K, Ji P, Cooke J, Busuttil RW, Imagawa DK (2003) Carcinoid tumors of the common bile duct: report of two cases. Surg Today 33:553–555

Price TN, Thompson GB, Lewis JT, Lyoyd RV, Young WF (2009) Zollinger-Ellison syndrome due to primary gastrinoma of the extrahepatic biliary tree: there case reports and review of literature. Endocr Pract 15:737–749

Rascarachi et al (2009) http://www.ncbi.nlm.nih.gov/pubmed/19918579

Reinhardt D, Thiele H, Weber JC, Hofmann WJ (1988) Carcinoid of the ductus choledochus. A rare cause of obstructive jaundice (in German). Chirurg 59:683–687

Rindi G (2010) The ENETS guidelines: the new TNM classification system. Tumori 96:806–809

Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Eriksson B et al (2006) TNM staging of foregut (neuro)endocrine tumors: a consensus panel including a grading system. Virchows Arch 449:395–401

Rindi G, Arnold R, Bosman FT, Capella C, Klimstra DS, Klöppel G, Komminoth P et al (2010) Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds) WHO classification of tumours of the digestive system, 4th edn. IARC, Lyon, pp 13–14

Rocca A, Calise F, Marino G, Montagnani S, Cinelli M, Amato B, Guerra G (2014) Primary giant hepatic neuroendocrine carcinoma: a case report. Int J Surg 12(Suppl 1):S218–S221

Roskams T, van den Oord JJ, De Vos R, Desmet VJ (1990) Neuroendocrine features of reactive bile ductules in cholestatic liver disease. Am J Pathol 137:1019–1025

Roskams T, De Vos R, van den Oord JJ, Desmet V (1991) Cells with neuroendocrine features in regeneration human liver. APMIS Suppl 23:32–39

Roskams T, Campos RV, Drucker DJ, Desmet VJ (1993) Reactive human bile ductules express parathyroid hormone-related peptide. Histopathology 23:11–19

Roskams T, Cassiman D, De Vos R, Libbrecht L (2004) Neuroregulation of the neuroendocrine compartment of the liver. Anat Rec A Discov Mol Cell Evol Biol 280:910–923

Ross AC, Hurley JB, Hay WB, Rusnak CH, Petrunia DM (1999) Carcinoids of the common bile duct: a case report and literature review. Can J Surg 42:59–63

Rückert RI, Rückert JC, Dorffel Y, Rudolph B, Müller JM (1999) Primary hepatic neuroendocrine tumor: successful hepatectomy in two cases and review of the literature. Digestion 60:110–116

Rugge M, Sonega F, Militello C, Guido M, Ninfo V (1992) Primary carcinoid tumor of the cystic and common bile ducts. Am J Surg Pathol 16:802–807

Sabanathan S, Hashimi H, Nicholson G et al (1988) Primary oat cell carcinoma of the common bile duct. J R Coll Surg Edinb 33:285–286

Sankary HN, Foster P, Frye E, Williams JW (1995) Carcinoid tumors of the extrahepatic bile duct: an unusual cause of bile duct obstruction. Liver Transpl Surg 1:122–123

Sano K, Kosuge T, Yamamoto J et al (1999) Primary hepatic carcinoid tumors confirmed with long-term follow-up after resection. Hepatogastroenterology 46:2547–2550

Sato K, Waseda R, Tastuzawa Y, Fujinaga H, Wakabayashi T, Ueda Y, Katsuda S (2006) Composite large cell neuroendocrine carcinoma and adenocarcinoma of the common bile duct. J Clin Pathol 59:105–107

Schmitt TM, Bonatti H, Hagspiel KD, Iezzoni J, Northup P, Pruett TL (2008) Carcinoid of the bile duct bifurcation. J Am Coll Surg 206:399

Schwartz G, Colanta A, Gaetz H, Olichney J, Attiyeh F (2008) Primary carcinoid tumors of the liver. World J Surg Oncol 6:91

Schwesinger G (1978) Carcinoid tumor of the bile ducts (in German). Z Ärztl Fortbild (Jena) 72:796–798

Sethi H, Madanur M, Srinivasan P, Portmann B, Heaton N, Rela M (2007) Non-functioning well-differentiated neuroendocrine tumor of the extrahepatic bile duct: an unusual suspect? Hepatobiliary Pancreatol Dis Int 6:549–552

Shah IA, Schlageter MO, Wong SX, Gani OS (1998) Carcinoid tumor of the cystic duct. Dig Surg 15:372–373

Shah NA, Urusova IA, D'Agnolo A, Colquhoun SD, Rosenbloom BE, Vener SL, Geller SA et al (2007) Primary hepatic carcinoid tumor presenting as Cushing's syndrome. J Endocrinol Invest 30:327–333

Sheehan-dare RA, Simmons AV, Cotterill JA, Janke PG (1988) Hepatic tumors with hyperglucagonemia. Response to treatment with human lymphoblastoid interferon. Cancer 62:912–914

Shibata C, Naito H, Funayama Y, Fukushima K, Takahashi K, Unno M, Sasaki I (2006) Diagnosis and surgical treatment for primary liver gastrinoma: report of a case. Dig Dis Sci 51:1122–1125

Shiffman, Juler (1963) http://www.ncbi.nlm.nih.gov/pubmed/14208462

Shih WJ, Samayoa L, Shih GL, Milan P (2005) Primary hepatic carcinoid tumor presenting as a large multicystic lesion of the liver and on Tc-99m RBC abdominal imaging showing photopenic areas. Clin Nucl Med 30:530–531

Shima K, Ota G (1995) Primary hepatic carcinoid tumor (in Japanese). Ryoikibetsu Shokogun Shirizu 7:450–452

Shinkawa H, Takatsuka S, Kaizaki R, Fujiwara Y, Kurai O, Yamazaki O (2013) Postoperative outcomes of primary

hepatic neuroendocrine carcinomas: review article. Osaka City Med J 59:105–113
Sioutos N, Virta S, Kessimian N (1991) Primary hepatic carcinoid tumor. An electron microscopic and immunohistochemical study. Am J Clin Pathol 95:172–175
Smith AL, Auldist AW (1984) Successful surgical resection of an hepatic gastrinoma in a child. J Pediatr Gastroenterol Nutr 3:801–804
Smyrniotis V, Kehagias D, Kostopanagiotou G et al (1994) Primary hepatic gastrinoma. Am J Gastroenterol 94:3380–3381
Soga J (2002) Primary hepatic endocrinomas (carcinoids and variant neoplasms). A statistical evaluation of 126 reported cases. J Exp Clin Cancer Res 21:457–468
Soga J (2003) Carcinoids and their variant endocrinomas. An analysis of 11842 reported cases. J Exp Clin Cancer Res 22:517–530
Soga J, Tazawa K (1971) Pathologic analysis of carcinoids. Histologic reevaluation of 62 cases. Cancer 28:990–998
Song LY, Hu XL, Zhao LS, Ning PR (2011) Carcinoid tumor of common bile duct: report of a case in pediatric patient (in Chinese). Zhonghua Bing Li Xue Za Zhi 40:54–55
Sotiropoulos GC, Charalampoudis P, Delladetsima I, Stamopoulos P, Dourakis S, Kouraklis G (2014) Surgery for giant primary neuroendocrine carcinoma of the liver. J Gastrointest Surg 18:839–841
Squillaci S, Matchione R, Piccolomini M, Colombo F, Bucci F, Bruno M, Bisceglia M (2010) Well-differentiated neuroendocrine carcinoma (malignant carcinoid) of the extrahepatic biliary tract: report of two cases and literature review. APMIS 118:543–556
Stavridi F, Chong H, Chan S, Goldsmith C, Reddy M, Glees J, Benepal T (2007) Neuroendocrine tumour of the cystic duct: a case report and literature review. Gastrointest Cancer 38:32–33
Sun QK, Wang W, Zhou H, Lv Y, Yu JH, Ma JL, Jia WD, Xu GL (2014) Misdiagnosed gastrinoma: a case report. Oncol Lett 7:2089–2092
Taghy A, Belmahl AM, Belmahl A (1990) Carcinoid liver tumors. Apropos of a case (in French). J Chir (Paris) 127:290–293
Tagliabue L, Tarolo GL, Bestetti A, Di Leo C, Del Sole A (2001) I. A rare case of hepatic carcinoid. Clin Nucl Med 26:893
Takayasu K, Muramatsu Y, Sakamoto M et al (1992) Findings in primary hepatic carcinoid tumor: US, CT, MRI, and angiography. J Comput Assist Tomogr 16:99–102
Tarçin Ö, Yazici D, Ince Ü, Deyneli O, Sancak S, Aydin H, Yavuz D, Akalin S (2011) Bulky gastrinoma of the common bile duct: unusual localization of extrapancreatic gastrinoma – case report. Turk J Gastroenterol 22:219–223
Tiomny E, Brill S, Baratz M, Messer G, Greif F, Moshkowitz M, Gilat T (1997) Primary liver gastrinoma. J Clin Gastroenterol 24:188–191
Todoraki T, Sano T, Yamada S, Hirahara N, Toda N, Tsukada K, Motojima R, Motojima T (2007) Clear cell carcinoid tumor of the distal common bile duct. World J Surg Oncol 5:6
Tohyama T, Matsui K, Kitagawa K (2005) Primary hepatic carcinoid tumor with carcinoid syndrome and carcinoid heart disease: a case report of a patient on long-term follow-up. Intern Med 44:958–962
Tonelli F, Giudici F, Nesi G, Batignanu G, Brandi ML (2013) Biliary tree gastrinoma in multiple endocrine neoplasia type 1 syndrome. World J Gastroenterol 19:8312–8320
Tonnhofer U, Balassy C, Reck CA, Koller A, Horcher E (2009) Neuroendocrine tumor of the common hepatic duct, mimicking a choledochal cyst in a 6-year-old child. J Pediatr Surg 44:E23–E25
Touloumis Z, Delis SG, Triantopoulou C, Giannakou N, Avgerinos C, Dervenis C (2008) Primary hepatic carcinoid; a diagnostic dilemma: a case report. Cases J 1:314
Tsalis K, Vrakas G, Vradelis S, Dimoulas A, Pilavaki M, Papaemmanouli S, Micheli A et al (2011) Primary hepatic gastrinoma: report of a case and review of literature. World J Gastrointest Pathophysiol 2:26–30
Turrion et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/11959276
Ueyama T, Ding J, Hashimoto H et al (1992) Carcinoid tumor arising in the wall of a congenital bile duct cyst. Arch Pathol Lab Med 116:291–293
Ulasan S, Kizilkilic O, Yildirim T, Tercan F, Bolat F, Yildirim S (2005) Primary hepatic carcinoid tumor: dynamic CT features. Abdom Imaging 30:281–285
Van der Wal AC, Van Leeuwen DJ, Walford N (1989) Small cell neuroendocrine (oat cell) tumour of the common bile duct. Histopathology 16:398–400
Van Weel (1962) http://www.ncbi.nlm.nih.gov/pubmed/14005545
Vittaux J, Salmon RJ, Languille O, Buffet C, Martin E, Chaput JC (1981) Carcinoid tumor of the common bile duct. Am J Gastroenterol 76:360–362
Volpe CM, Pryor JP, Caty M, Doerr RJ (2003) An adolescent with bile duct carcinoid tumor. Med Pediatr Oncol 40:137–138
Walter JF, Appelman HD, Reuter SR (1978) Angiographic and pathologic features of probably primary carcinoid-like hepatic tumors. Gastrointest Radiol 3:397–400
Wang CY, Chen A, Tseng HH, Tu YC, Chen VT, Hsieh HF (1992) Carcinoid tumor localized in the liver – two cases report: immunohistochemical and ultrastructural studies. Zhonghua Yi Xue Za Zhi (Taipei) 49:365–400
Warner TF, Seo IS, Madura JA, Polak JM, Pearse AG (1980) Pancreatic-polypeptide-producing apudoma of the liver. Cancer 46:1146–1151
Warren et al (1964) http://www.ncbi.nlm.nih.gov/pubmed/14218555
Yamaguchi R, Nakashima O, Ogata T, Hanada K, Kumabe T, Kojiro M (2004) Hepatocellular carcinoma with an unusual neuroendocrine component. Pathol Int 54:861–865
Yamaguchi Y, Shimizu H, Yoneda E (2009) A case of recurrent endocrine carcinoma of the common bile

duct successfully treated by hepatic artery infusion with CPT-11 and CDDP (in Japanese). Gan To Kagaku Ryoho 36:823–825

Yamamoto M, Nakajo S, Tahara E, Miyoshi N (1986) Endocrine cell carcinoma of extrahepatic bile duct. Acta Pathol Jpn 36:587–593

Yamamoto J, Abe Y, Nishihara K, Katsumoto F, Takeda S, Abe R, Toyoshima S (1998) Composite glandular-neuroendocrine carcinoma of the hilar bile duct: report of a case. Surg Today 28:758–762

Yamashita Y, Takahashi M, Tsuji A, Korogi Y, Uozumi H, Kimura Y (1986) Primary carcinoid tumor of the liver: a case report. J Comput Tomogr 10:313–317

Yang L, Li S, Hatch H, Ahrens K, Cornelius JG, Petersen BE, Peck AB (2002) In vitro trans-differentiation of adult hepatic stem cells into pancreatic endocrine hormone-producing cells. Proc Natl Acad Sci U S A 99:8078–8083

Yang CS, Wen MC, Jan YJ, Wang J, Wu CC (2009) Combined primary neuroendocrine carcinoma and hepatocellular carcinoma of the liver. J Chin Med Assoc 72:430–433

Yasoshima H, Uematsu K, Sakurai K et al (1993) Primary hepatic carcinoid tumor. Acta Pathol Jpn 43:783–789

Yasuda E, Takeshita A, Murata S, Ihaku Y, Nitta T, Akuagawa H, Egashira Y, Shibayama Y (2006) Neuroendocrine carcinoma of the liver associated with dermatomyositis: autopsy case and review of the literature. Pathol Int 56:749–754

Yeung YP, Sau S, Chiu H, Chong KA, Li VK (2008) Primary hepatic carcinoid tumour: a detailed account of imaging findings. Hepatogastroenterology 55:663–665

Zhang A, Xiang J, Zhang M, Zheng S (2008) Primary hepatic carcinoid tumours: clinical features with an emphasis on carcinoid syndrome and recurrence. J Int Med Res 36:848–859

Zhu H, Sun K, Ward SC, Schwartz M, Thung SN, Qin L (2010) Primary hepatic signet ring cell neuroendocrine tumor: a case report with literature review. Semin Liver Dis 30:422–428

Part XII

Hepatobiliary Tumors with a Small Cell Undifferentiated Lineage

Undifferentiated Small Cell Tumors of the Hepatobiliary Tract

76

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_76

Abstract

A small group of primary hepatobiliary tumors is characterized by the presence of morphologically undifferentiated small cells. These small cell tumors (SCTs), which histologically appear as "small cell blue tumors" due to the dense crowding of nuclei together with poorly developed cytoplasm, have several cell lineage courses that can only be identified by means of immunohistochemistry and molecular methods. One type of hepatic SCT is a member of the complex family of neuroectodermal tumors that predominantly occur in the skeleton and soft tissues of adolescents and young adults (primitive neuroectodermal tumors or PNETs). Hepatic PNETs are very rare neoplasms with an aggressive course, and the tumor also develops in the biliary tract. Other hepatobiliary SCTs include desmoplastic small round cell tumor, NUT midline carcinoma, and hepatic neuroblastoma and its variants. As all hepatobiliary SCTs are very rare neoplasms, they have to be distinguished from the more common metastatic lesions of these tumors.

Primitive Neuroectodermal Tumors (PNETs) of the Liver

ICD-O code 9364/3

Introduction

Primitive neuroectodermal tumors (PNETs) constitute a family of malignant neoplasms of presumed neuroectodermal origin that predominantly present as bone and soft tissue tumors in adolescents and young adults, but also occurs in adults of more advanced age. The Ewing's family of tumors (EFTs) comprises Ewing's sarcoma of the bone (which was formerly believed to be of reticulum cell or perivascular cell origin), extraosseous Ewing's sarcoma, PNET (extraosseous Ewing-like neoplasms that have progressively been allocated to tumors with a neuroectodermal lineage), and malignant small cell tumor of the thoracopulmonary region, also called Askin's tumor (reviews: Carvajal and Meyers 2005; Khoury 2005, 2008; Armbruster et al. 2008).

While Ewing's sarcoma is a primary bone tumor and follows osteosarcoma as the second most common malignant bone tumor in children, PNETs either occur in the CNS (CNS-PNET) or develop in soft tissues of the thoracopulmonary region, pelvis, and lower extremities and rarely in visceral organs, the myocardium, and the skin (peripheral PNET, pPNET). Most PNET family members are diagnosed before the age of 35 years, with a slight male predominance. Once considered to be uncommon, PNET now accounts for almost 20 % of malignant soft tissue tumors in children. Increased recognition of PNET is due to advances in definition of the diagnostic features, immunohistochemistry, and molecular diagnostics, which have led to the identification of the tumor in nonclassical sites. These neoplasms all exhibit a neural phenotype, express the MIC2 protein (CD99), and display the chromosomal translocation t(11;22)(q24;q12), causing the EWS-FLI1 fusion transcript in about 90 % of the cases. Many, if not all, of the remaining cases of PNET are associated with translocations resulting in the fusion of the EWS gene to other members of the ETS family (reviews: Seth and Watson 2005; Maire et al. 2008). Apart from the bone and soft tissue, PNETs occur in several internal organs, including the lung, myocardium, stomach, pancreas, and hepatobiliary tract. After the lung, the kidney is now the most common visceral site of PNET. In the pediatric age group, primary cutaneous PNET represents a distinct clinical entity (Lee et al. 1995).

Primary PNET of the Liver

Few examples of primary hepatobiliary PNET have been reported (Sarangarajan et al. 2001; Song et al. 2004; Ousadden et al. 2005; Mani et al. 2010; Cambruzzi et al. 2011). For the liver, one tumor was detected in a 58-year-old female who complained of right-sided hypochondrial

pain of 1 year duration. Sonography revealed a cystic tumor of 10 cm diameter in segments VII and VIII, confirmed by CT. Serum AFP was normal (Ousadden et al. 2005). A second reported patient was a 20-year-old lady presenting with massive hepatomegaly. Liver biopsy revealed nests of small round tumor cells expressing MIC2 and Fli-1, compatible with PNET. Extensive search regarding any possible different site of origin was negative (Mani et al. 2010). A third patient with PNET primary to the liver was an 18-year-old male with clinical complaints of pain in the right upper abdominal quadrant, due to a large tumor in the right liver lobe. The hepatic resection specimen showed that the right lobe was replaced by a yellow-red solid mass measuring up to 21 cm in diameter. Histology showed typical PNET with immunoreactivity for CD99 and vimentin (Cambruzzi et al. 2011).

PNET can also develop in the biliary tract. A 14-year-old female patient developed obstructive jaundice caused by a pedunculated submucosal tumor of 1.5 cm size located to the common hepatic duct. Histology was typical for PNET, part of the cells having a moderate amount of clear cytoplasm that was PAS positive. The cells were markedly positive for CD99, and PCR revealed the EWS-FLI1 fusion (Sarangarajan et al. 2001). PNET also takes its origin from the gallbladder. A 53-year-old female showed, in the fundus of the gallbladder, a polypoid mass measuring 7 × 4 × 3.5 cm, whitish tan, friable, and mostly necrotic. The tumor cells were MIC2 positive (Song et al. 2004).

Pathology

The histological picture is characterized by a diffuse growth of small cells with scant, amphophilic, or clear cytoplasm. In the silver stain, groups or nests of tumor cells are surrounded by delicate reticulin fibers (Figs. 1, 2, and 3). Tumor cell rosettes may be encountered. Small areas with discrete desmoplastic stroma may be noted, but not of the type observed in desmoplastic round cell tumors discussed below.

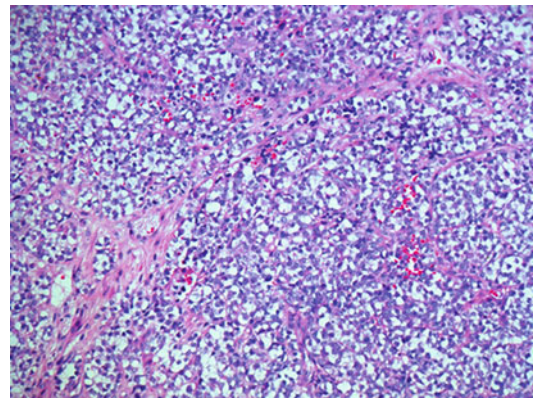

Fig. 1 Primary PNET of the liver. There is a diffuse growth of small- to medium-sized poorly differentiated tumor cells (hematoxylin and eosin stain)

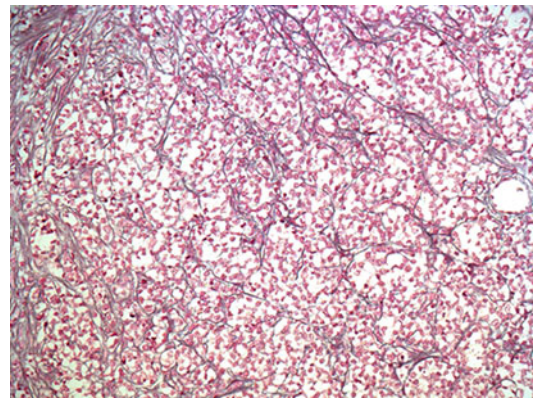

Fig. 2 Primary PNET of the liver. Nests and strands of small tumor cells are separated from each other by reticulin fibers, whereas reticulin is not detectable within nests or strands themselves (Gomori silver stain)

Immunohistochemistry

The typical diagnostic feature is the presence of marked positivity for MIC2 (CD99 antibody), in a predominantly membranous staining pattern (Fig. 4). It is important to note that other mesenchymal tumors may express MIC2, including poorly differentiated synovial sarcoma and rhabdomyosarcoma. Immunohistochemical expression of the FLI-1 protein may be valuable in confirming the diagnosis of EWS/PNET in cases where molecular genetic evaluation is not feasible (Folpe et al. 2000).

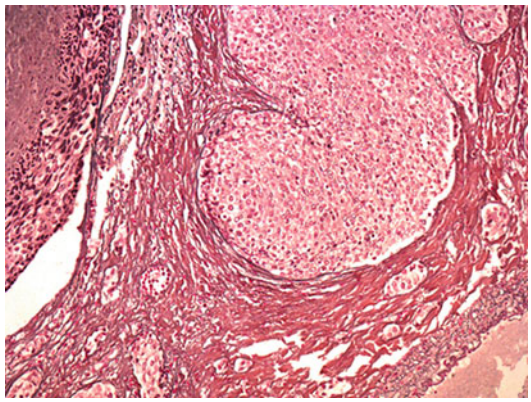

Fig. 3 In this reticulin stain, lack of fibers within the PNET nodule is in evidence (Gomori silver stain)

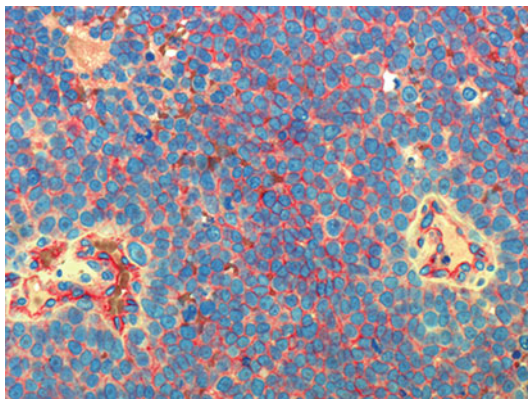

Fig. 4 Primary PNET of the liver. The neoplastic cells exhibit strong membranous staining for CD99 (CD99 immunostain)

PNET Metastatic to the Liver

PNET and Ewing's sarcoma are known to metastasize to the liver (Centenera Fondon et al. 1952; Mackenzie et al. 1992). Metastatic PNET of the liver may present of cystic lesions (Shah and McHugh 2000) or masquerade as liver abscess (Hyun et al. 2002). Ultrasound of cystic metastases showed multiple anechoic cystic lesions with posterior enhancement, and CT confirmed multiple cysts of varying size, sometimes with a rim of calcification (Shah and McHugh 2000). Ewing's sarcoma of the ribs was found to have metastasized into a focal nodular hyperplasia (FNH) of the liver (Hagay et al. 1986).

Desmoplastic Small Round Cell Tumors

Introduction

Desmoplastic small round cell tumor (DSRCT) is an uncommon, highly aggressive (high-grade) malignancy usually arising in the abdomen of young males, forming intraperitoneal and peritoneal masses, often with numerous peritoneal implants. This distinct tumor type was first described in 1989 (Gerald and Rosai 1989) and then in 1991 (Layfield and Lenarsky 1991), specified in detail 1 year later based on 19 cases (Gerald et al. 1991). The typical abdominal presentation is in the form of numerous nodules growing out of the peritoneal surface, these nodules ranging in diameter from few millimeters to more than 10 cm (mean diameter in one study of 14 patients, 5 cm; Pickhardt et al. 1999). DSRCT also occurs in abdominal internal organs, including the pancreas, and extraabdominal tumors have been reported, such as the kidney (Eaton and Cendron 2006; Janssens et al. 2009), soft tissues, ovary, heart, lung, central nervous system, and major salivary glands.

DSRCT is immunohistochemically characterized by the polyphenotypic expression of vimentin, cytokeratins, desmin (dot pattern), WT-1, neuron-specific enolase, CD15, Ber-EP4, and CD99 (about one fifth of cases) (Ordonez 1998; Zhang et al. 2003; Chang 2006; Lee and Hsiao 2007) and ultrastructurally by signs of divergent differentiation and a characteristic paranuclear aggregate of intermediate filaments (Wills 1993). A rare subset of DSRCT is characterized by the lack of epithelial differentiation, i.e., without cytokeratin staining (Trupiano et al. 1999). Similar to other small cell tumors, such as neuroblastoma and medulloblastoma, a large cell variant of EWS/WT1 translocation-positive DSRCT is known (Pasquinelli et al. 2000).

Epidemiology

In a review of 32 cases, there were 29 male and 3 female patients, with ages at diagnosis from 6 to 54 years (mean, 25 years). 88 % of the tumors were

located in the abdominal cavity; others involved soft tissues and ethmoid sinus (Lae et al. 2002).

DSRCT of the Liver

Among 28 DSRCTs located to the abdominal cavity, nine tumors also involved the liver (Lae et al. 2002). DSRCT of the liver can be associated with multiple intraperitoneal tumors (Li et al. 2014). A further published case was located in the perihepatic space (Chouli et al. 2005). In many situations of the liver involved, metastatic disease from primary tumor outside the liver is present (Arra et al. 2013; Hirano et al. 2013). Among 62 patients with primary intraabdominal disease, 40 % presented liver metastases (Arra et al. 2013).

Macroscopy

DSRCTs are typically solid, multilobated, firm, and focally fleshy masses with a gray-white cut surface. However, cystic lesions have also been found (Li et al. 2014). Hemorrhages and necroses are often noted.

Histopathology

The neoplasms consist of solid sheets, clusters, cords, or large nests of small round, ovoid, or spindled cells with a scanty, ill-defined, and slightly eosinophilic to amphophilic cytoplasm. The nuclei are hyperchromatic, round to elongated, with small nucleoli and coarse, clumped chromatin. These cells are embedded in a hypocellular, desmoplastic stroma. Rarely, the tumor cells form tubules, rosettes, or gland-like structure. The mitotic count is usually high to very high. Necroses, sometimes with small calcifications, are often seen.

Pathogenic Pathways

The tumors reveal a translocation of chromosomes 11 and 22 [t(11;22)(p13;q12)] (Sawyer et al. 1992) resulting in the formation of the chimeric EWS-WT1 fusion gene (Ladanyi and Gerald 1994; Brodie et al. 1995; Gerald et al. 1998; Lee and Hsiao 2007; review: Gerald and Haber 2005). Most chimeric genes consist of the first seven exons of EWS and the last three exons (zinc finger domains) of WT1. WT1 immunohistochemistry reliably differentiates DSRCT from PNET (Barnoud et al. 2000; Hill et al. 2000) and reflects the EWS-WT1 fusion transcript in most DSRCT, but some cases express full-length WT1 or have variant transcripts, resulting in atypical staining patterns (Murphy et al. 2008).

EWS-WT1 chimeras are heterogeneous as a result of fusions at different regions of the EWS gene to the WT1 gene (Kim et al. 1998; Chan et al. 1999; Liu et al. 2000), which leads to the expectation of different targets of the fusion transcripts. Two isoforms of the EWS-WT1 fusion product transcriptionally activate the adenosine transporter ENT4, which is highly expressed in DSRCT (Li et al. 2008), and platelet-derived growth factor-A/PDGFA, a potent secreted mitogen (Lee et al. 1997). EWS-WT1(-KTS), a variant which lacks three amino acid residues (Lys-Thr-Ser) in the DNA-binding domain and which transforms NIH3T3 cells, induces a tetraspanin-family protein, TALLA-1 (T-cell acute lymphoblastic leukemia-associated antigen 1), a protein which regulates cell adhesion, migration, and metastasis (Ito et al. 2003). A rare fusion variant, EWS-WT1 5/10, is a potential transactivator of the insulin-like growth factor-I receptor gene (Werner et al. 2007). Unusual instances of so-called hybrid tumors in the abdominal cavity of young males, showing a combination of PNET morphology, immunophenotype of DSRCT, and EWS/FLI-1 fusion instead of EWS/WT1 fusion, have been observed (Katz et al. 1997).

NUT Midline Carcinoma

Introduction

NUT midline carcinoma (NMC) is a rare and aggressive malignant neoplasm of the upper aerodigestive tract, mainly occurring in children

and young adults and characterized by a rearrangement on the nuclear protein in testis (NUT; HUGO symbol, C15orf55) gene on chromosome 15q14. This rearrangement results in distinct fusion oncogenes, whereby NUT engages in a balanced translocation with BRD4 (bromodomain-containing protein 4) located on chromosome 19p13.1 (BRD4-NUT fusion oncogene) in up to 75 % of cases, while the remaining cases exhibit rearrangement of NUT with various other fusion partners, such as BRD3 and NSD3 (French et al. 2014). NMC is predominantly located to the midline structures, i.e., the nasopharynx, orbit, salivary glands, mediastinum, thymus, and other compartments of the thoracic cavity, including the trachea and lung. Very rarely, the upper abdominal cavity and its organs are involved (Kees et al. 1991; Kubonishi et al. 1991; French et al. 2001, 2004, 2008; Stelow and French 2009; French 2010a, b, 2013; Stelow 2011; Bauer et al. 2012; Fang et al. 2013; French 2013; Thompson-Wicking et al. 2013).

Epidemiology

From the relatively few patients reported so far, it surfaced that NMC mainly occurs in a young age group, but patients older than 70 years have been described. In a review of 28 patients, 14 were female and 14 male. Twenty-five out of twenty-eight patients had tumors in the head and neck or chest regions (Stelow 2011). Shehata and coworkers found an age range at presentation of 0–78 years, with a mean of 23 years (Shehata et al. 2010).

Clinical Features

In most patients, NMC presents as a mass lesion in midline structures, i.e., the head, neck, mediastinum, and chest (French 2010a; Hsieh et al. 2011; Evans et al. 2012). In a study of 114 poorly differentiated carcinomas or unclassified malignancies of the mediastinum, 3.5 % of cases showed nuclear NUT expression (Evans et al. 2012). In a minority of patients, the neoplasm mainly manifests below the diaphragm or shows a multifocal distribution (French et al. 2004; Shehata et al. 2010; Polsani et al. 2012). Advanced local disease is frequently accompanied by distant hematogenous metastases (Kees et al. 1991; Vargas et al. 2001; Toretsky et al. 2003; Mertens et al. 2006; den Bakker et al. 2009; Engleson et al. 2006; Stelow et al. 2008; Nelson et al. 2010; Ziai et al. 2010; Hsieh et al. 2011; review: Stelow and French 2009).

Liver Involvement

A primary localization in the liver or pancreas with subsequent metastatic disease is very rare (Shehata et al. 2010). Metastatic liver involvement by NMC was found in patients with extensive multiorgan disease. Similar to other metastatic sites, liver metastases of NMC present as bulky masses of friable tumor tissue with marked necrosis.

The main histologic features of NMC are that of a poorly differentiated small cell blue tumor with variable degrees of squamous cell differentiation. The cells grow in sheets or show nested pattern in a desmoplastic stroma. The cytoplasm is scant, amphophilic, or eosinophilic. The nuclei are mostly uniform, but nuclei with irregular shape also occur. Nucleoli are prominent, and mitotic figures are abundant (Fig. 5).

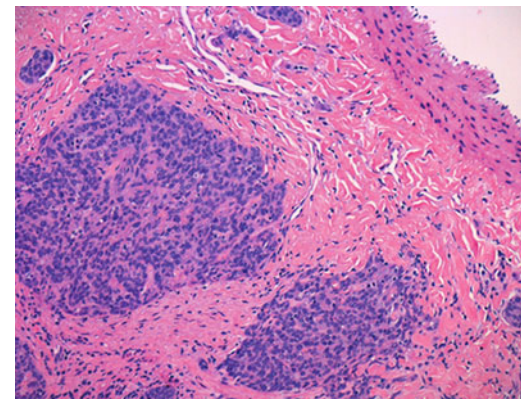

Fig. 5 Metastasis of NUT carcinoma in the liver (hematoxylin and eosin stain)

Transition from the small cell population to squamous cell areas is typically abrupt. The tumor usually shows extensive necrosis and sometimes numerous apoptotic bodies. Ultrastructurally, the tumor cells displayed prominent bundles of tonofilaments, clusters of pleomorphic granules, stubby microvillous projections, desmosomal-type junctions, and junctional complexes (Wartchow et al. 2012).

NMC cells are epithelial and are reactive for cytokeratins, mainly CK7 and focally CK20. The squamous differentiation is seen as reactivity for p63 (Stelow 2011). The NUT fusion protein is visualized in NMC tumor tissue with a monoclonal antibody (Haack et al. 2009; French 2010a). NUT rearrangement can be detected by fluorescent in situ hybridization (Shehata et al. 2010) and by reverse transcriptase PCR (French 2010b).

Molecular Pathways

The NUT-BRD fusion proteins induce uncontrolled growth of cells associated with a block in differentiation (French et al. 2008; French 2010a, 2012; Yan et al. 2011). BRD4 is a member of the BET (bromodomains and extraterminal) family that includes mammalian BRD2 to BRD7, BRDT, *Drosophila* fsh, yeast Bdf1, Bdf2, and corresponding homologs in other species. The BRD partner of the fusion oncogene contains two bromodomains (bromo and extra C-terminal domain/BET family of bromodomains) that bind to acetylated histones. Generally, bromodomains are acetyl-lysine-binding modules (acetyl-lysine recognition motifs) that promote the establishment of nucleosome acetylation in a wide array of organisms. BRD4 is a chromatin adaptor containing tandem bromodomains (BD1 and BD2) binding to acetylated histones H3 and H4. This molecular recognition allows BRD4 to associate with acetylated chromatin throughout the cell cycle and to regulate transcription of targeted loci, affecting cell cycle control in normal and neoplastic cells. Bromodomains found in chromatin-associated proteins and almost all histone acetyltransferases function as the sole protein module known to bind acetyl-lysine motifs/lysine-acetylated peptides and represent an evolutionarily conserved epigenetic regulator system (reviews: Zeng and Zhou 2002; Mujtaba et al. 2007). BRD4 directly interacts with a member of a subfamily of H3K36 methyltransferases, NSD3. One isoform of NSD3 is an adaptor protein that couples BRD4 to the CHD8 chromatin remodeler (Shen et al. 2015).

Histone acetylation is central to the epigenetic control of transcription, and here bromodomains are operational as epigenetic "writers and erasers" (Sanchez and Zhou 2009). BRD4 is found in several transcription complexes, including the general cofactor mediator and the P-TEFb elongation factor (Chiang 2009). In its fusion with NUT, BRD4 becomes a member of a potent chromatin regulator that drives aberrant transcription within large topological domains (Alekseyenko et al. 2015). The dual bromodomains and a p300-binding portion of BRD4-NUT cause sequestering of p300 to distinct regions of chromatin, thus promoting global transcriptional repression (review: French 2013). BRD4 also affects the metabolism of microRNAs and controls the essential epigenetic regulators, long noncoding RNA, e.g., HOTAIR (Pastori et al. 2015).

BRD4 localizes to chromosomes during mitosis ad is implicated in holding mitotic memory. Throughout mitosis, BRD4 remains bound to the transcription start sites of many M/G1 genes that are programmed to be expressed at the end of, or immediately after, mitosis. BRD4 binding to M7G1 genes increases at telophase, goes in line with recruitment of P-TEFb, and coincides with increased acetylation of histones H3 and H4 (Dey et al. 2009). At late mitosis, BRD4 also functions as an associated factor and positive regulator of P-TEFb (positive transcription elongation factor b), a Cdk9-cyclin T1 heterodimer that stimulates transcriptional elongation by phosphorylating the C-terminal domain of RNA polymerase II, via phosphorylation of serine 2 (Devaiah et al. 2012). The cyclin-dependent kinase 9 (Cdk9) is activated by T-type cyclins and cyclin K-generating P-TEFs. Phospho-Cdk9 displays a punctate distribution throughout the nucleoplasm and co-localizes with cyclin T1 within nuclear speckle domains, and phospho-Cdk9 also co-localizes with the hyperphosphorylated form of

RNA polymerase II, suggesting that nuclear speckles are the resident site of active P-TEFb (Dow et al. 2010). The BRD4-P-TEFb interaction increases in cells progressing from late mitosis to early G1 phase. Concurrently, P-TEFb is recruited to chromosomes, beginning around mid- to late anaphase and before nuclear lamina formation and nuclear import of other transcription factors. BRD4 recruitment to chromosomes at late mitosis marks those genes whose active transcription mode must be preserved across cell division (Yang et al. 2008). The recruitment of P-TEFb through BRD4 induces the release of the promoter-proximal paused RNA polymerase II and the increase of its processivity. The nucleosome platform allowing the binding of BRD4 and its interaction with P-TEFb is constructed by a histone cross talk between H3S10ph and H4K16ac to generate a nucleosomal histone recognition code (Zippo et al. 2009). Therefore, BRD4 marks select genes on mitotic chromatin, directs postmitotic transcription, and is implicated in transmitting epigenetic memory through mitosis. The downstream targets of BRD-NUT are highly enriched for genes upregulated by MYC. BRD4-NUT associates with the MYC promoter and is required for maintaining MYC expression in NMC cells, suggesting that MYC is an important factor for the maintenance of a proliferative state in NMC (Grayson et al. 2014).

In interphase, BRD4 interacts with P-TEFb and functions as a global transcriptional coactivator. Expression of BRD4 is associated with globally decreased histone acetylation and transcriptional repression, and experimental restoration of bulk chromatin acetylation engages a program of squamous differentiation (Schwartz et al. 2011), suggesting a mechanism for the typical squamous differentiation in NUT midline carcinomas. NUT can also fuse to other genes, such as NSD3, the NSD3-NUT fusion oncogene binding to BRD4 and thus blocking cell differentiation and maintaining proliferation (French et al. 2014).

Through its important role in the regulation of transcription, BRD4 affects the expression of numerous proteins that are involved in programming pathways in stem cells and neoplastic cells. The BRD4-NUT fusion oncogene is required for an abnormal activation of SOX2, a pathway that drives stem cell-like growth and cellular transformation of NMC (Wang et al. 2014a). BRD4 is involved in the behavior of cancer cells other than NUT, including acute myeloid leukemia and hepatocellular carcinomas (HCCs). In HCC, BRD4 induces cell migration and invasion through activation of matrix metalloproteinases 2 and 9 (Wang et al. 2015) and promotes tumor growth and epithelial-mesenchymal transition (Zhang et al. 2015).

Hepatic Neuroblastoma and Related Neoplasms (Manifestations of Peripheral Neuroblastic Tumors)

ICD-O codes:

Neuroblastoma	9500/3
Ganglioneuroblastoma	9490/3
Ganglioneuroma	9490/0

Introduction

Peripheral neuroblastic tumors (NTs), which include neuroblastomas, ganglioneuroblastomas, and ganglioneuromas, are defined as embryonal tumors of the sympathetic nervous system and originate from immature sympathetic neuroblasts derived from the neural crest. NT chiefly arises in the adrenal medulla, paravertebral sympathetic ganglia, and sympathetic paraganglia, such as the organ of Zuckerkandl. The concept of neuroblastoma is based on the seminal works of James Homer Wright, William Pepper, and Robert Hutchinson (review: Rothenberg et al. 2009). NTs clearly show the capability to undergo neuronal differentiation and are, therefore, neoplasms different from peripheral primitive neuroectodermal tumors/PNETs, irrespective of certain morphologic similarities. NTs typically exhibit deletion of chromosome 1p parts and N-Myc amplification, but lack the EWS/ETS translocation of PNET. NTs show a broad spectrum of lineages, ranging from primitive neuroblasts, resembling cells of other small cell blue tumors, to differentiating neuroblasts and mature-looking ganglionic cells, and part of the tumors display Schwannian stromal development. Clinical and basic research has shown that NTs

form a heterogeneous group of neoplasms with favorable and unfavorable biologies. Biologically unfavorable NTs (high-risk NTs) reveal an aggressive course and still often cause fatal outcome (reviews: Shimada 2006; Maris et al. 2007; Bell et al. 2014).

Liver involvement by NTs is metastatic in the large majority of cases, the liver being a frequent metastatic site of neuroblastoma. Exceptionally, neuroblastoma was detected in the liver in the absence of (proven) extrahepatic NT, lesions therefore thought to be primary hepatic neuroblastoma.

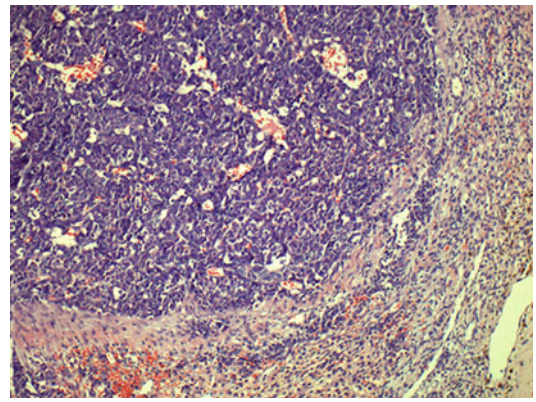

Fig. 6 Metastatic neuroblastoma of the liver (hematoxylin and eosin stain)

Primary Neuroblastoma of the Liver

There are very rare instances of neuroblastoma apparently primary to the liver. Hepatomegaly caused by metastases was found as the presenting sign of stage pattern 4S neuroblastoma in the absence of a primary site outside of the liver (Bujanover et al. 1990). Apparently primary neuroblastoma has been found in adults (Ouakaa-Kchaou et al. 2010; Jung and Kim 2011). In one case, a female patient of age 51 years presented with 9 cm-sized hypodense hepatic tumor with a histology of differentiated neuroblastoma and lymph node metastasis (Ouakaa-Kchaou et al. 2010). In a second patient, a 29-year-old woman, the neoplasm manifested as a solitary hepatic mass. Grossly, this mass was a large, creamy, rubbery form with focal hemorrhage and central cavitation. Despite a thorough systemic survey, including CT scans, no extrahepatic mass was detected. Histology, immunohistochemistry, and electron microscopy revealed a neuroblastic neoplasm. Liver and bone manifestations of neuroblastoma may occur in adults in whom no primary site was determined (Mackay et al. 1976).

Neuroblastoma Metastasis of the Liver: Pepper Type of Neuroblastoma

Liver metastases of neuroblastoma are a typical feature of this neoplasm, particularly in stage pattern 4S (Fig. 6; Bond 1976; Franken et al. 1986).

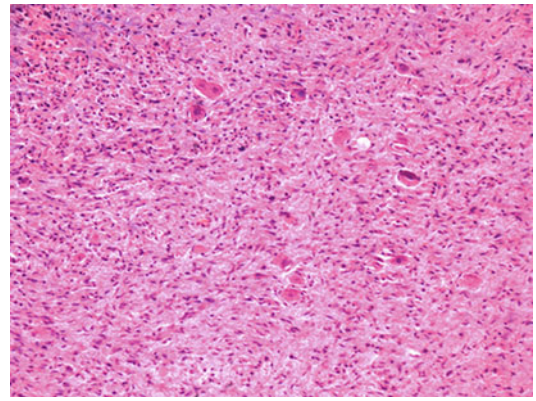

Fig. 7 Metastatic ganglioneuroma of the liver. In a Schwannian stromal background, several ganglionic cells are seen (hematoxylin and eosin)

A predominantly hepatic metastasis pattern is called the Pepper type of neuroblastoma. The most characteristic feature of the Pepper type is the often excessive hepatomegaly (Pepper 1901). In the Hutchinson type, on the other hand, metastases in the skeleton, and particularly the skull, predominate (Hutchinson 1907). Several authors emphasized the significance of these two major metastasis patterns, while other refused to attach any special importance to these types of metastasis. The pathogenic mechanisms involved in these two spreading patterns are still unknown.

Apart from stroma-poor neuroblastoma, also stroma-rich variants, including ganglioneuroma, can metastasize to the liver (Fig. 7).

Metastases are often multiple and thus cause a rapidly enlarging liver (Wyatt and Farber 1941; Schnaufer and Koop 1975; Bond 1976; Halperin 1987). The lesions may later undergo calcification (Ross 1965). Extensive metastatic deposits to the liver have been observed in congenital neuroblastoma (Gupta and Bansal 2012). In one patient with congenital adrenal neuroblastoma and liver metastases, the disease process was associated with Hashimoto-Pritzker disease, a congenital self-healing cutaneous reticulohistiocytosis (Jacob et al. 2009). Liver metastasis of neuroblastoma may also occur via transplacental twin-to-twin metastasis in monozygotic twins (Tajiri et al. 2010). There is a correlation between the frequency of hepatic neuroblastoma metastases and patient age. Analysis of data compiled in early years (Scott et al. 1933; Redman et al. 1938) revealed that the frequency of hepatic metastases above the age of 6 months shows only slight variation, while below that age there is a strong increase in frequency up to birth, reaching the highest values in neonates (Wieberdink 1957). In fact, typical "Pepper patients" are very young. In Pepper's own autopsy series, the age of patients with liver metastases ranged from 1.5 to 16 weeks. This frequency distribution pattern also holds true for extensive hepatic metastasis. After age 6 months, extensive hepatic metastasis is clearly less frequent than metastases in the liver in general (Wieberdink 1957). A rare variant of neuroblastoma prone to produce liver metastases, or bilateral adrenal cystic neuroblastoma, is a distinct phenotype associated with MYCN amplification. The tumors, which are sometimes diagnosed prenatally, present as masses that contain macrocysts and a histology characterized by multiple microcysts (Herman and Siegel 1995; Lee et al. 1998; Chou and Lin 1999; Petit et al. 2001; Pederiva et al. 2007; Haberal et al. 2008). The majority of unilateral cystic neuroblastomas are favorable stage, stroma-poor, but with low or intermediate mitotic-karyorrhectic indices, MYCN amplification negative, and with a favorable outcome (Kozakewich et al. 1998), while bilateral forms show MYCN amplification and marked hepatic spread. Typically, the cystic morphology can be recapitulated in the hepatic metastases (Chacko et al. 2007). Cystic neuroblastoma can undergo massive intracystic hemorrhage (Lee et al. 1998). Due to intratumoral hemorrhage, both primary tumors and their metastases may reveal a three-layer fluid level (Chou and Lin 1999). In part of patients, liver metastases of neuroblastoma may undergo spontaneous regression (D'Angio et al. 1971; Schwartz et al. 1974). It was suggested that congenital neuroblastoma might have the greatest propensity for regression (Komuro et al. 1998).

The metastatic potential of neuroblastomas is regulated by distinct factors and mechanisms. It is well known that amplification of N-myc in untreated human neuroblastoma correlates with advanced disease stage (Brodeur et al. 1984; Schwab 1994; Tsuchida et al. 1996). N-myc enhances cell growth, IGF-IR expression, and tumorigenicity in combination with Bcl-2 (Castle et al. 1993; Ikegaki et al. 1995). N-myc repression of beta1-integrin expression may result in a less differentiated phenotype (van Golen et al. 2003). In a multivariate analysis, it surfaced that N-Myc amplification and Shimada UH both emerged as independent prognostic factors and that most N-myc-amplified tumors had in fact an unfavorable histology and a poorer prognosis (George et al. 2001). In aggressive N-myc-amplified neuroblastomas, the c-kit receptor and its stem cell factor (SCF) ligand are preferentially expressed, and their signaling is active in promoting neuroblastoma cell proliferation (Vitali et al. 2003). Expression of full-length trkB (p145; BDNF/neurotrophin-4/5 receptor) can be found in some highly aggressive neuroblastomas with N-myc amplification, and trkB expression is induced by all-trans retinoic acid (Edsjo et al. 2003). Activation of the PI3K/AKT pathway correlates with poor prognosis in these neoplasms and requires expression of the N-myc oncogene. Specifically, N-myc expression is regulated by the AKT2 isoform of AKT. AKT2 promotes migration and invasion of neuroblastoma cells and induces hepatic metastasis (Qiao et al. 2013). Metastasis of neuroblastoma to the liver is also linked to the expression of gastrin-releasing peptide receptor (GRP-R) expression in neuroblastoma cells. Focal adhesion kinase/FAK is a critical

downstream target of GRP-R. FAK and GRP-R are co-expressed in neuroblastoma, and their overexpression promotes flattening of tumor cells, migration, and metastasis (Lee et al. 2012b). Inhibition of FAK decreases cell invasion, migration, and metastasis in N-Myc-amplified neuroblastoma (Megison et al. 2013). Anaplastic lymphoma kinase (ALK), the gene of which is a predisposition gene for familial neuroblastoma (Mossé et al. 2008), plays a role in neuroblastoma growth and may be involved in tumor spread. As hepatic metastasis in neuroblastoma is a predominant feature of poorly differentiated neuronal phenotypes of tumors, factors affecting differentiation pathways may influence metastatic spread. Certain microRNAs define distinct neuroblastoma cell phenotypes. MicroRNA-124 induces terminal neuronal differentiation with reduced malignancy, while increased levels of microRNA-21, microRNA-221, and microRNA-335 characterized nonneuronal, nonmalignant phenotypes by blocking neuronal differentiation (Samaraweera et al. 2014). The metastatic features of neuroblastoma are also modulated by tumor-associated inflammatory cells. Metastatic neuroblastomas showed higher infiltration levels of tumor-associated macrophages/TAMs than locoregional tumors (Asgharzadeh et al. 2012).

Neuroblastoma as a Component of Mixed Hepatic Tumors

A large hepatic tumor detected in a 3-year-old child displayed a mixture of hepatoblastoma, neuroblastoma, and malignant teratoma with rhabdomyosarcomatous differentiation (Moll et al. 2009).

Focal Nodular Hyperplasia (FNH) of the Liver in Patients with Neuroblastoma

Similar to other solid pediatric tumors treated with chemotherapy, long-term survivors of neuroblastoma can develop focal nodular hyperplasia (FNH) of the liver, FNH being regarded as a late effect of cytotoxic therapies (Bouyn et al. 2003; Joyner et al. 2005; Freidl et al. 2008; Marabelle et al. 2008; Benz-Bohm et al. 2010; Sugito et al. 2011). In a retrospective study of 14 cases of FNH found in children following chemotherapy of malignancy, FNH was discovered by chance during routine examination in 78 % of patients (Bouyn et al. 2003). In an analysis of four pediatric patients with neuroblastoma, nephroblastoma, and GISTs, FNH developed 2, 2.5., 3, and 8 years after successful treatment of their primary malignancies (Freidl et al. 2008). Pathogenetically, it has been proposed that high doses of alkylating agents, veno-occlusive disease, and hepatic radiotherapy may be responsible for vascular injury favoring the development of hepatocyte hyperplasia and FNH (Bouyn et al. 2003). The overall incidence of FNH in this target population of patients varied markedly, being 0.45 % in one (Bouyn et al. 2003) and 9.4 % in another study (Sugito et al. 2011).

Hypervascular Hepatic Nodules in Childhood Neuroblastoma Survivors

Children with a history of solid tumors treated with chemotherapy, including neuroblastoma, can develop hypervascular hepatic nodules (HHNs) in their livers. The time interval between therapy and the diagnosis of HHNs ranged from 3.2 to 8.5 years, and HHNs present as small and often multiple hypo-or isoechoic nodules, showing a strong enhancement on sequential early-phase postcontrast CT images, turning to isoattenuated lesions during the later phase (Lee et al. 2012a; Yoo et al. 2013).

Morphology of Neuroblastic Tumors

Neuroblastoma tumors (NTs) and cell lines are heterogeneous in regard to cell lineages and differentiation patterns. Basically, neuroblastomas consist of a tumorigenic neuroblastic phenotype and a nonneuronal non-tumorigenic phenotype (S-cells). Neuroblastic cells can undergo neuronal differentiation and include stem cells (I-cells) and neuronal cells (N-cells).

Morphology of Neuroblastic/Neuronal Lineages

Cells of the neuroblastic lineage are mostly small elements with scant cytoplasm, indistinct cell borders, and a high nuclear-to-cytoplasmic ratio. The cells resemble those of other small cell blue tumors. The nuclei are small and round and display a stippled ("salt-and-pepper") chromatin. Undifferentiated and poorly differentiated neuroblastomas may show larger cells with prominent nucleoli. The neuroblastic cells form solid cellular masses, with necroses and sometimes calcifications. Neuroblastomas exhibit variable infiltrates of lymphocytes, indicating an antitumor immune response. Differentiating neuroblastic tumors form focal eosinophilic neuropil clusters, around which the tumor cells may be arranged in a radiating pattern. These structures are termed Homer Wright rosettes or, more correctly, Homer Wright pseudorosettes, as true rosettes, such as Flexner-Wintersteiner rosettes, contain an empty lumen. Note that Homer Wright should be written without a hyphen: James Homer Wright (1869–1928; Massachusetts General Hospital) described the structures in 1910 and is well known for the Wright stain in hematology (Wright 1910; reviews: Yanoff 1990; Lee et al. 2002; Rothenberg et al. 2009). Immunohistochemically, the tumor cells are reactive for synaptophysin, neuron-specific enolase, chromogranin A, and, as a function of neuronal differentiation, neurofilaments. Early members of the NT lineage can be identified by positivity for PHOX2B. Ganglioneuroblastomas and ganglioneuromas contain differentiating or differentiated neuronal/ganglionic cells with abundant cytoplasm containing basophilic Nissl substance (rough endoplasmic reticulum) and large round-to-oval nuclei with prominent nucleoli.

The differentiation pathways leading from stem-like undifferentiated cells (I-cells) to mature neuronal cells have in part been elucidated and are currently tested in the light of future treatment strategies. The self-renewal of tumor-initiating I-cells is linked to kit expression (Lau et al. 2014). Factors promoting neuroblast formation and differentiation comprise N-Myc expression (Guglielmi et al. 2014) and certain cell adhesion molecules (exendin-4; Luciani et al. 2013). N-Myc/MYCN promotes the expansion of PHOX2B-positive neuronal progenitors to become N-cells (Alam et al. 2009). A central role in differentiation is played by the homeobox protein HOXC9 (Wang et al. 2014b). Neuronal differentiation associated with cell cycle exit is induced by the Down syndrome-related protein kinase, DYRK1A, which phosphorylates p27 (KIP1) and cyclin D1 (Soppa et al. 2014). Differentiation of neuroblastoma cells is also programmed by distinct sets of microRNAs (Zhao et al. 2014).

Morphology of Nonneuronal Cell Lineages

Schwannian stromal cells (S-cells) are pale or eosinophilic spindled elements that form a cellular background or clusters of cells interspersed with neuronal cells. Cells of this Schwannian stroma are S100 protein positive. A Schwannian cell component varies markedly among NTs, ranging from complete lack of such cells to Schwannian stroma-rich neoplasms. S-cells modulate the behavior of N-cells in a complex fashion (Liu et al. 2005). There is evidence that S-cells prevent the activation of fibroblasts in NTs (Zeine et al. 2009). The cellular origin of nonneuronal S-cells that form a Schwannian stromal component is not yet fully clarified, but there is evidence that these cells form the stromal component recruited by the neuroblastic tumor cells (review: Shimada 2006). In vitro, neuroblastoma cells can promote Schwann cell proliferation (Ambros et al. 2001). It was proposed that N-cells and S-cells originate from a tumor progenitor cell (Mora et al. 2001), but a later study showed that S-cells do not harbor the genetic alterations of N-cell but may share the same clonal origin (Bourdeaut et al. 2008). Gene expression profiling revealed that N-cells differ from S-cells with respect to the degree of DNA imbalance (Coco et al. 2005). In a human neuroblastoma cell line model, transitions between N-cells and S-cells were found, S-cell formation being induced by

depletion kinase D-interacting substrate of 220kD/Kidins220 (Rogers and Schor 2013).

Classifications of Neuroblastic Tumors

The classification of the International Neuroblastoma Pathology Committee (the International Neuroblastoma Pathology Classification (INPC); Shimada et al. 1999a, b) is shown in Table 1. This classification was found to have prognostic value (Burgues et al. 2006).

Schwannian stroma-poor neuroblastoma (NB) has a more favorable subgroup (favorable histology, FH) and an unfavorable subgroup (unfavorable histology, UH). The favorable subgroup in <1.5 year patients consists of poorly differentiated or differentiating and low or intermediate MKI tumors and in 1.5–5 year patients of differentiating and low MKI tumors. The unfavorable group in <1.5 year patients consists of (a) undifferentiated tumor (a rare subtype) and (b) high MKI tumor; in 1.5–5 year patients, it consists of (a) undifferentiated or poorly differentiated tumor and (b) intermediate or high MKI tumor; and in >5 year patients, all tumors. The Schwannian stroma-rich NT represents ganglioneuroblastoma, intermixed (GNBi), while the Schwannian stroma-dominant NT includes ganglioneuroma (GN), maturing and mature. The composite Schwannian stroma-rich/stroma-dominant and stroma-poor tumors form ganglioneuroblastoma, nodular (GNBn). The only differences between the original Shimada classification and the INPC are (1) to subdivide the "undifferentiated" subtype in the former classification into two subtypes or undifferentiated and poorly differentiated in the latter classification and (2) to change the name of "stroma rich, well differentiated" in the former classification to " ganglioneuroma, maturing" in the latter classification.

Table 1 International Neuroblastoma Pathology Classification (INPC)

Four basic categories of NTs
Neuroblastoma (Schwannian stroma poor), NB
Ganglioneuroblastoma, intermixed (Schwannian stroma rich), GNBi
Ganglioneuroma (Schwannian stroma dominant), GN
Ganglioneuroblastoma, nodular (composite, Schwannian stroma rich/stroma dominant and stroma poor), GNBn
Subcategories (subtypes) of neuroblastoma/NB (grade of neuroblastic differentiation)
Undifferentiated
Poorly differentiated
Differentiating
Subcategories of ganglioneuroma/GN (complete or incomplete stage of final maturation)
Maturing
Mature
Subcategories of ganglioneuroblastoma, nodular/ GNBn
Favorable
Unfavorable

In an analysis of the morphologic features in clinically favorable and unfavorable groups of Schwannian stroma-poor neuroblastomas, it turned out that nuclear size, cellularity, prominent nucleoli in undifferentiated or poorly differentiated neuroblasts, and the number of mitotic or karyorrhectic cells (MKI) showed a significant correlation with clinical groups, identifying an unfavorable clinical course (Ambros et al. 2002). Subsequently it turned out that the combination of histopathologic evaluation and N-myc status distinguished four clinical and biologic tumor subsets in patients with NT. Expression of N-myc, which is known to cause DNA instability, in an amplified state can be a powerful driving force for preventing neuroblastic differentiation age independently and for increasing mitotic and karyorrhectic activities age dependently (Goto et al. 2001).

References

Alam G, Cui H, Shi H, Yang L, Ding J, Mao L, Maltese WA, Ding HF (2009) MYCN promotes the expansion of Phox2B-positive neuronal progenitors to drive neuroblastoma development. Am J Pathol 175:856–866

Alekseyenko AA, Walsh EM, Wang X, Grayson AR, His PT, Kharchenko PV, Kurosa MI, French CA (2015) The oncogenic BRD4-NUT chromatin regulator drives aberrant transcription within large topological domains. Genes Dev 29:1507–1523

Ambros IM, Attarbaschi A, Rumpler S, Luegmayr A, Turkof E, Gadner H, Ambros PF (2001)

Neuroblastoma cells provoke Schwann cell proliferation in vitro. Med Pediatr Oncol 36:163–168

Ambros IM, Hata JI, Joshi VV, Roald B, Dehner LP, Tüchler H, Pötschger U, Shimada H (2002) Morphologic features of neuroblastoma (Schwannian stroma-poor tumors) in clinically favorable and unfavorable groups. Cancer 94:1574–1583

Armbruster C, Huber M, Prosch H, Dworan N, Attems J (2008) Ewing's sarcoma and peripheral primitive neuroectodermal tumor in adults: different features of a rare neoplasm. Onkologie 31:179–184

Arra VC, Price AP, Fleming S, Sohn MJ, Magnan H, LaQuaglia MP, Abramson S (2013) Characteristic imaging features of desmoplastic small round cell tumour. Pediatr Radiol 43:93–102

Asgharzadeh S, Salo JA, Ji L, Oberthuer A, Fischer M, Berthold F, Hadjidaniel M et al (2012) Clinical significance of tumor-associated inflammatory cells in metastatic neuroblastoma. J Clin Oncol 30:3525–3532

Barnoud R, Sabourin JC, Pasquier D, Ranchère D, Bailly C, Terrier-Lacombe MJ, Pasquier B (2000) Immunohistochemical expression of WT1 by desmoplastic small round cell tumor: a comparative study with other small round cell tumors. Am J Surg Pathol 24:830–836

Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB, Lüer SC, Muhammed S et al (2012) Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res 18:5773–5779

Bell E, Chen L, Viprey VF, Blanchard GB (2014) Meeting report – 3rd neuroblastoma research symposium, Liverpool, 6–7th November, 2013. Pediatr Blood Cancer 61:1711–1713

Benz-Bohm G, Hero B, Grossmann A, Simon T, Körber F, Bethold F (2010) Focal nodular hyperplasia of the liver in longterm survivors of neuroblastoma. How much diagnostic imaging is necessary? Eur J Radiol 74:e1–e5

Bond JV (1976) Neuroblastoma metastatic to the liver in infants. Arch Dis Child 51:879–882

Bourdeaut F, Ribeiro A, Paris R, Pierron G, Couturier J, Peuchmaur M, Delattre O (2008) In neuroblastic tumours, Schwann cells do not harbour the genetic alterations of neuroblasts but may nevertheless share the same clonal origin. Oncogene 27:3066–3071

Bouyn CI, Leclere J, Raimondo G, le Pointe HD, Couanet D, Valteau-Couanet D, Hartmann O (2003) Hepatic focal nodular hyperplasia in children previously treated for a solid tumor. Incidence, risk factors, and outcome. Cancer 97:3107–3113

Brodeur GM, Seeger RC, Schwab M, Varmus HE, Bishop JM (1984) Amplification of N-myc in untreated human neuroblastoma correlates with advanced disease stage. Science 224:1121–1124

Brodie SG, Stocker SJ, Wardlaw JC, Duncan MH, McConnell TS, Feddersen RM, Williams TM (1995) EWS and WT-1 gene fusion in desmoplastic small round cell tumor of the abdomen. Hum Pathol 26:1370–1374

Bujanover Y, Hareel A, Burstein Y (1990) Hepatomegaly as a single presenting sign of stage IV-S neuroblastoma. J Pediatr Gastroenterol Nutr 11:545–548

Burgues O, Navarro S, Noguera R, Pellin A, Ruiz A, Castel V, Llombart-Bosch A (2006) Prognostic values of the International Neuroblastoma Pathology Classification in neuroblastoma (Schwannian stroma-poor) and comparison with other prognostic factors: a study of 182 cases from the Spanish Neuroblastoma Registry. Virchows Arch 449:410–420

Cambruzzi E, Guerra EE, Hilgert HC, Schmitz HJ, Silva VL, Milani DM, Cruz RP et al (2011) Primitive neuroectodermal tumor of the liver: a case report. Case Rep Med 2011:748194

Carvajal R, Meyers P (2005) Ewing's sarcoma and primitive neuroectodermal family of tumors. Hematol Oncol Clin N Am 19:501–525

Castle VP, Heidelberger KP, Bromberg J, Ou X, Dole M, Nunez G (1993) Expression of the apoptosis-suppressing protein bcl.2, in neuroblastoma is associated with unfavorable histology and N-myc amplification. Am J Pathol 143:1543–1550

Centenera Fondon D, Paniagua Rodriguez G, Lopez Garcia E (1952) Ewing tumor (osseous reticulosarcoma) with cardiac and hepatic metastasis (in Spanish). Rev Clin Esp 46:171–176

Chacko J, Karl S, Sen S, Eapen A, Mathai J (2007) Bilateral cystic adrenal neuroblastoma with cystic metastasis in the liver. J Pediatr Surg 42:E11–E13

Chan AS, MacNeill S, Thorner P, Squire J, Zielenska M (1999) Variant EWS-WT1 chimeric product in the desmoplastic small round cell tumor. Pediatr Dev Pathol 2:188–192

Chang F (2006) Desmoplastic small round cell tumors: cytologic, histologic, and immunohistochemical features. Arch Pathol Lab Med 130:728–732

Chiang CM (2009) Brd4 engagement from chromatin targeting to transcriptional regulation: selective contact with acetylated histone H3 and H4. F100 Biol Rep 1:98

Chou HC, Lin KH (1999) Cystic neuroblastoma with hepatic metastasis: report of one case. Acta Paediatr Taiwan 40:277–279

Chouli M, Viala J, Dromain C, Fizazi K, Duvillard P, Vanel D (2005) Intra-abdominal desmoplastic small round cell tumors: CT findings and clinicopathological correlations in 13 cases. Eur J Radiol 54:438–442

Coco S, Defferrari R, Scaruffi P, Cavazzana A, Di Cristofano C, Longo L, Mazzocco K et al (2005) Genome analysis and gene expression profiling of neuroblastoma and ganglioneuroblastoma reveal differences between neuroblastic and Schwannian stromal cells. J Pathol 207:346–357

D'Angio GJ, Evans AE, Koop CE (1971) Special pattern of widespread neuroblastoma with favourable prognosis. Lancet 1:1046

Den Bakker MA, Beverloo BH, van den Heuvel-Eibrink MM, Meeuwis CA, Tan LM et al (2009) NUT midline

carcinoma of the parotid gland with mesenchymal differentiation. Am J Surg Pathol 33:1253–1258
Devaiah BN, Lewis BA, Cherman N, Hewitt MC, Albrecht BK, Robey PG, Ozato K et al (2012) BRD4 is an atypical kinase that phosphorylates serine2 of the RNA polymerase II carboxy-terminal domain. Proc Natl Acad Sci U S A 109:6927–6932
Dey A, Nishiyama A, Karpova T, Mcnally J, Ozato K (2009) Brd4 marks select genes on mitotic chromatin and directs postmitotic transcription. Mol Biol Cell 20:4899–4909
Dow EC, Liu H, Rice AP (2010) T-loop phosphorylated Cdk9 localizes to nuclear speckle domains which may serve as sites of active P-TEFb function and exchange between the Brd4 and 7SK/HEXIM1 regulatory complexes. J Cell Physiol 224:84–93
Eaton and Cendron 2006. http://www.ncbi.nlm.nih.gov/pubmed/18947596
Edsjo A, Lavenius E, Nilsson H, Hoehner JC, Simonsson P, Culp LA, Martinsson T et al (2003) Expression of trkB in human neuroblastoma in relation to MYCN expression and retinoic acid treatment. Lab Invest 83:813–823
Engleson J, Soller M, Panagopoulos I, Dahlén A, Dictor M, Jerkeman M (2006) Midline carcinoma with t(15;19) and BRD4-NUT fusion oncogene in a 30-year-old female with response to docetaxel and radiotherapy. BMC Cancer 6:69
Evans AG, French CA, Cameron MJ, Fletcher CD, Jackman DM, Lathan CS, Sholl LM (2012) Pathologic characteristics of NUT midline carcinoma arising in the mediastinum. Am J Surg Pathol 36:1222–1227
Fang W, French CA, Cameron MJ, Han Y, Liu H (2013) Clinicopathological significance of NUT rearrangements in poorly differentiated malignant tumors of the upper respiratory tract. Int J Surg Pathol 21:102–110
Folpe AL, Hill CE, Parham DM, O'Shea PA, Weiss SW (2000) Immunohistochemical detection of FLI-1 protein expression: a study of 132 round cell tumors with emphasis on CD99-positive mimics of Ewing's sarcoma/primitive neuroectodermal tumor. Am J Surg Pathol 24:1657–1662
Franken EA, Smith WL, Cohen MD, Kisker CT, Platz CE (1986) Hepatic imaging in stage IV-S neuroblastoma. Pediatr Radiol 16:107–109
Freidl T, Lackner H, Huber J, Sovinz P, Moser A, Schroettner B, Schwinger W, Urban C (2008) Focal nodular hyperplasia in children following treatment of hemato-oncologic diseases. Klin Padiatr 220:384–387
French CA (2010a) NUT midline carcinoma. Cancer Genet Cytogenet 203:16–20
French CA (2010b) Demystified molecular pathology of NUT midline carcinomas. J Clin Pathol 63:492–496
French CA (2012) Pathogenesis of NUT midline carcinoma. Annu Rev Pathol 7:247–265
French CA (2013) The importance of diagnosing NUT midline carcinoma. Head Neck Pathol 7:11–16
French CA (2014) NUT midline carcinoma. Nat Rev Cancer 14:149–150
French CA, Miyoshi I, Aster JC, Kubonishi I, Kroll TG, Dal CP, Vargas SO, Perez-Atayde AR et al (2001) BRD4 bromodomain gene rearrangement in aggressive carcinoma with translocation t(15;19). Am J Pathol 159:1987–1992
French CA, Kutok JL, Faquin WC, Toretsky JA, Antonescu CR, Griffin CA, Nose V et al (2004) Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol 22:4135–4139
French CA, Ramirez CL, Kolamkova J, Hickman TT, Cameron MJ, Thyne ME, Kutok JL et al (2008) BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene 27:2237–2242
French CA, Rahman S, Walsh EM, Kühnle S, Grayson AR, Lemieux ME, Grunfeld N et al (2014) NSD3-NUT fusion oncoprotein in NUT midline carcinoma: implications for a novel oncogenic mechanism. Cancer Discov 4:928–941
George RE, Variend S, Cullinane C, Cotterill SJ, McGuckin AG, Ellershaw C, Lunec J, Pearson AD, United Kingdom Children Cancer Study Group (2001) Relationship between histopathological features, MYCN amplification, and prognosis: a UKCCSG study. United Kingdom Children Cancer Study Group. Med Pediatr Oncol 36:169–176
Gerald WL, Haber DA (2005) The EWS-WT1 gene fusion in desmoplastic small round cell tumor. Semin Cancer Biol 15:197–205
Gerald WL, Rosai J (1989) Case 2. Desmoplastic small round cell tumor with divergent differentiation. Pediatr Pathol 9:177–183
Gerald WL, Miller HK, Battifora H, Miettinen M, Silva EG, Rosai J (1991) Intra-abdominal desmoplastic small round-cell tumor. Report of 19 cases of a distinctive type of high-grade polyphenotypic malignancy affecting young individuals. Am J Surg Pathol 15:499–513
Gerald WL, Ladanyi M, de Alaya E, Cuatrecases M, Kushner BH, LaQuaglia MP, Rosai J (1998) Clinical, pathologic, and molecular spectrum of tumors associated with t(11;22)(p13;q12): desmoplastic small round-cell tumor and its variants. J Clin Oncol 16:3028–3036
Goto S, Umehara S, Gerbing RB, Stram DO, Brodeur GM, Seeger RC, Lukens JN et al (2001) Histopathology (International Neuroblastoma Pathology Classification) and MYCN status in patients with peripheral neuroblastic tumors. A report from the Children's Cancer Group. Cancer 92:2699–2708
Grayson AR, Walsh EM, Cameron MJ, Ashworth T, Ambrose JM, Aserlind AB, Wang H et al (2014) MYC, a downstream target of BRD-NUT, is necessary and sufficient for the blockade of differentiation in NUT midline carcinoma. Oncogene 33:1736–1742

Guglielmi L, Cinnella C, Nardella M, Maresca G, Valentini A, Mercanti D, Felsani A et al (2014) MYCN gene expression is required for the onset of the differentiation programme in neuroblastoma cells. Cell Death Dis 5:e1081

Gupta K, Bansal A (2012) Congenital neuroblastoma: an autopsy report. Fetal Pediatr Pathol 31:331–335

Haack H, Johnson LA, Fry CJ, Crosby K, Polakiewicz RD, Stelow EB, Hong SM et al (2009) Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol 33:984–991

Haberal M, Ozcay F, Sevmis S, Karakayali H, Moray G, Torgay A, Coskun M, Demirhan B et al (2008) Liver transplant in an infant with bilateral cystic neuroblastoma complicated by hepatic metastases and life-threatening consumption coagulopathy. Pediatr Transplant 12:358–362

Hagay ZJ, Zirkin HJ, Moses M, Khodadadi J (1986) Ewing's sarcoma metastatic to focal nodular hyperplasia of liver. J Surg Oncol 32:100–105

Halperin EC (1987) Hepatic metastasis from neuroblastoma. South Med J 80:1370–1373

Herman TE, Siegel MJ (1995) Special imaging casebook. Neonatal cystic adrenal neuroblastoma with massive hepatomegaly. J Perinatol 15:78–80

Hill DA, Pfeifer JD, Marley EF, Dehner LP, Humphrey PA, Zhu X, Swanson PE (2000) WT1 staining reliably differentiates desmoplastic small round cell tumor from Ewing sarcoma/primitive neuroectodermal tumor. An immunohistochemical and molecular diagnosis study. Am J Clin Pathol 114:345–353

Hirano G, Irie M, Nakashima Y, Shakado S, Sohda T, Tanaka T, Takamatsu Y, Aoki M et al (2013) Desmoplastic small round cell tumors in a young man. Intern Med 52:1909–1914

Hsieh MS, French CA, Liang CW, Hsiao CH (2011) NUT midline carcinoma: case report and review of the literature. Int J Surg Pathol 19:808–812

Hutchinson R (1907–1908) Suprarenal sarcoma in children with metastasis in the skull. Q J Med 1:33

Hyun CB, Lee YR, Bemiller TA (2002) Metastatic peripheral primitive neuroectodermal tumor (PNET) masquerading as liver abscess: a case report of liver metastasis in orbital PNET. J Clin Gastroenterol 35:93–97

Ikegaki N, Katsumata M, Tsujimoto Y, Nakagawara A, Brodeur GM (1995) Relationship between bcl-2 and myc gene expression in human neuroblastoma. Cancer Lett 91:161–168

Ito E, Honma R, Imai J, Azuma S, Kanno T, Mori S, Yoshie O, Nishio J, Iwasaki H et al (2003) A tetraspanin-family protein, T-cell acute lymphoblastic leukemia-associated antigen 1, is induced by the Ewing's sarcoma-Wilms' tumor 1 fusion protein of desmoplastic small round-cell tumor. Am J Pathol 163:2165–2172

Jacob ES, Varghese RG, Toi PC, Bhaskaran R, Rai R (2009) Congenital neuroblastoma with liver metastasis presenting with Hashimoto Pritzker disease. Indian J Pathol Microbiol 52:374–376

Janssens et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19358490

Joyner BL, Levin TL, Goyal RK, Newman B (2005) Focal nodal hyperplasia of the liver: a sequela of tumor therapy. Pediatr Radiol 35:1234–1239

Jung G, Kim J (2011) Primary hepatic neuroblastoma. A case report. Korean J Pathol 45:423–427

Katz RL, Quezado M, Senderowicz AM, Villalba L, Laskin WB, Tsokos M (1997) An intra-abdominal small round cell neoplasm with features of primitive neuroectodermal and desmoplastic round cell tumor and a EWS/FLI-1 fusion transcript. Hum Pathol 28:502–509

Kees UR, Mulcahy MT, Willoughby ML (1991) Intrathoracic carcinoma in an 11-year-old girl showing a translocation t(15;19). Am J Pediatr Hematol Oncol 13:459–464

Khoury JD (2005) Ewing sarcoma family of tumors. Adv Anat Pathol 12:212–220

Khoury JD (2008) Ewing sarcoma family of tumors: a model for the new era of integrated laboratory diagnostics. Expert Rev Mol Diagn 8:97–105

Kim J, Lee K, Pelletier J (1998) The desmoplastic small round cell tumor t(11;22) translocation produces EWS/WT1 isoforms with differing oncogenic properties. Oncogene 16:1973–1979

Komuro H, Imaizumi S, Hirata A, Matsumoto M, Kikuchi A, Hanada R, Yamamoto K (1998) Congenital mediastinal dumbbell neuroblastoma with spontaneous regression of liver metastases. Pediatr Surg Int 14:86–88

Kozakewich HP, Perez-Atayde AR, Donovan MJ, Fletcher JA, Estroff JA, Shamberger RC et al (1998) Cystic neuroblastoma: emphasis on gene expression, morphology, and pathogenesis. Pediatr Dev Pathol 1:17–28

Kubonishi I, Takehara N, Iwata J, Sonobe H, Ohtsuki Y, Abe T, Miyoshi I (1991) Novel t(15;19)(q15;p13) chromosome abnormality in a thymic carcinoma. Cancer Res 51:3327–3328

Ladanyi M, Gerald W (1994) Fusion of the EWS and WT1 genes in the desmoplastic small round cell tumor. Cancer Res 54:2837–2840

Lae ME, Roche PC, Jin L, Lloyd RV, Nascimento AG (2002) Desmoplastic small round cell tumor: a clinicopathologic, immunohistochemical, and molecular study of 32 tumors. Am J Surg Pathol 26:823–835

Lau ST, Hansford LM, Chan WK, Chan GC, Wan TS, Wong KK, Kaplan DR, Tam PK et al (2014) Prokineticin signaling is required for the maintenance of a de novo population of c-KIT+ cells to sustain neuroblastoma progression. Oncogenesis. doi:10.1038/onc.2014.24

Layfield LJ, Lenarsky C (1991) Desmoplastic small cell tumors of the peritoneum coexpressing mesenchymal and epithelial markers. Am J Clin Pathol 96:536–543

Lee and Hsiao 2007. http://www.ncbi.nlm.nih.gov/pubmed/17964965

Lee CS, Southey MC, Slater H, Auldist AW, Chow CW, Venter DJ (1995) Primary cutaneous Ewing's sarcoma/

peripheral primitive neuroectodermal tumors in childhood. A molecular, cytogenetic, and immunohistochemical study. Diagn Mol Pathol 4:174–181

Lee SB, Kolquist KA, Nichols K, Englert C, Maheswaran S, Ladanyi M, Gerald WL, Haber DA (1997) The EWS-WT1 translocation product induces PDGFA in desmoplastic small round-cell tumour. Nat Genet 17:309–313

Lee SY, Chuang JH, Huang CB, Hsiao CC, Wan YL, Ng SH, Lee TY, Ko SF (1998) Congenital bilateral cystic neuroblastoma with liver metastases and massive intracystic haemorrhage. Br J Radiol 71:1205–1207

Lee RE, Young RH, Castleman B (2002) James Homer Wright: a biography of the enigmatic creator of the Wright stain on the occasion of its centennial. Am J Surg Pathol 26:88–96

Lee MH, Yoo SY, Kim JH, Eo H, Jeon TY, Kim SH, Ko EY, Yoon HK, Sung KW et al (2012a) Hypervascular hepatic nodules in childhood cancer survivors: clinical and imaging features. Clin Imaging 36:301–307

Lee S, Qiao J, Paul P, O'Connor KL, Evers MB, Chung DH (2012b) FAK is a critical regulator of neuroblastoma liver metastasis. Oncotarget 3:1576–1587

Li H, Smolen GA, Beers LF, Xia L, Gerald W, Wang J, Haber DA, Lee SB (2008) Adenosine transporter ENT4 is a direct target of EWS/WT1 translocation product and is highly expressed in desmoplastic small round cell tumor. PLoS ONE 3:e2353

Li X, Yu J, Fang S, Xing X, Zhao J (2014) Desmoplastic small round cell tumor: a case report and review of the literature. World J Surg 12:9

Liu J, Nau MM, Yeh JC, Allegra CJ, Chu E, Wright JJ (2000) Molecular heterogeneity and function of EWS-WT1 fusion transcripts in desmoplastic small round cell tumors. Clin Cancer Res 6:3522–3529

Liu S, Tian Y, Chlenski A, Yang Q, Salwen HR, Cohn SL (2005) 'Cross-talk' between Schwannian stroma and neuroblasts promotes neuroblastoma tumor differentiation and inhibits angiogenesis. Cancer Lett 228:125–131

Luciani P, Deledda C, Benvenuti S, Squecco R, Cellai I, Fibbi B, Marone IM, Giuliani C et al (2013) Exendin-4 induces cell adhesion and differentiation and counteracts the invasive potential of human neuroblastoma cells. PLoS ONE 8:e71716

Mackay B, Luna MA, Butler JJ (1976) Adult neuroblastoma. Electron microscopic observations in nine cases. Cancer 37:1334–1351

Mackenzie DJ, James B, Geller SA, Sackier JM (1992) Laparoscopic diagnosis of Ewing's sarcoma metastatic to the liver: case report and review of the literature. J Pediatr Surg 27:93–95

Maire G, Brown CW, Bayani J, Pereira C, Gravel DH, Bell JC, Zielenska M, Squire JA (2008) Complex rearrangement of chromosomes 19, 21, and 22 in Ewing sarcoma involving a novel reciprocal inversion-insertion mechanism of EWS-ERG fusion gene formation: a case analysis and literature review. Cancer Genet Cytogenet 181:81–92

Mani S, Dutta D, De BK (2010) Primitive neuroectodermal tumor of the liver: a case report. Jpn J Clin Oncol 40:258–262

Marabelle A, Campagne D, Déchelotte P, Chipponi J, Deméocq F, Kanold J (2008) Focal nodular hyperplasia of the liver in patients previously treated for pediatric neoplastic diseases. J Pediatr Hematol Oncol 30:546–549

Maris JM, Hogarty MD, Bagatell R, Cohn SL (2007) Neuroblastoma. Lancet 369:2106–2120

Megison ML, Stewart JE, Nabers HC, Gillory LA, Beierle EA (2013) FAK inhibition decreases cell invasion, migration and metastasis in MYCN amplified neuroblastoma. Clin Exp Metastasis 30:555–568

Mertens F, Wiebe T, Adlercreutz C, Mandahl N, French CA (2006) Successful treatment of a child with t(15;19)-positive tumor. Pediatr Blood Cancer 49:1015–1017

Moll A, Krenauer A, Bierbach U, Till H, Hirsch W, Leuschner I, Schmitz N, Wittekind C et al (2009) Mixed hepatoblastoma and teratoma of the liver in a 3-year-old child: a unique combination and clinical challenge. Diagn Pathol 4:37

Mora J, Cheung NK, Juan G, Illei P, Cheung I, Akram M, Chi S, Ladanyi M, Cordon-Cardo C et al (2001) Neuroblastic and Schwannian stromal cells of neuroblastoma are derived from a tumoral progenitor cell. Cancer Res 61:6892–6898

Mossé YP, Laudenslager M, Longo L, Cole KA, Wood A, Attiyeh EF, Laquaglia MJ et al (2008) Identification of ALK as a major familial neuroblastoma predisposition gene. Nature 455:930–935

Mujtaba S, Zeng L, Zhou MM (2007) Structure and acetyl-lysine recognition of the bromodomain. Oncogene 26:5521–5527

Murphy AJ, Bishop K, Pereira C, Chilton-MacNeill S, Ho M, Zielenska M, Thorner PS (2008) A new molecular variant of desmoplastic small round cell tumor: significance of WT1 immunostaining in this entity. Hum Pathol 39:1763–1770

Nelson BA, Lee EY, French CA, Bauer DE, Vargas SO (2010) BRD4-NUT carcinoma of the mediastinum in a pediatric patient: multidetector computed tomography imaging findings. J Thorac Imaging 25:W93–W96

Ordonez 1998. http://www.ncbi.nlm.nih.gov/pubmed/9808123

Ouakaa-Kchaou A, Khalfallah T, Kharrat J, Romani M, Kilani A, Kochlef A, Gargouri D et al (2010) Liver neuroblastoma in an adult (in French). Tunis Med 88:682

Ousadden A, Mazaz K, Amraoul A, Kettani F, Chefchaouni MC, Ait Taleb K (2005) Primary hepatic localization of the PPNET (primitive peripheral neuroectodermal tumors). Case report (in French). Ann Chir 130:254–256

Pasquinelli G, Montanaro L, Martinelli GN (2000) Desmoplastic small round-cell tumor: a case report on the large cell variant with immunohistochemical, ultrastructural, and molecular genetic analysis. Ultrastruct Pathol 24:333–337

Pastori C, Kapranov P, Penas C, Peschansky V, Volmar CH, Sarkaria JN, Bregy A, Komotar R, St. Laurent G et al (2015) The bromodomain protein BRD4 controls HOTAIR, a long noncoding RNA essential for glioblastoma proliferation. Proc Natl Acad Sci U S A 112:8326–8331

Pederiva F, Andres A, Sastre A, Alves J, Martinez L, Tovar JA (2007) Bilateral adrenal neuroblastoma is different. Eur J Pediatr Surg 17:393–396

Pepper W (1901) A study of congenital sarcoma of the liver and suprarenals. Am J Med Sci 121:287

Petit T, de Lagausie P, El Ghoneimi A, Garel C, Aigrain Y (2001) Postnatal management of cystic neuroblastoma. Eur J Pediatr Surg 11:411–414

Pickhardt PJ, Fisher AJ, Balfe DM, Dehner LP, Huettner PC (1999) Desmoplastic small round cell tumor of the abdomen: radiologic-histopathologic correlation. Radiology 210:633–638

Polsani A, Braithwaite KA, Alazraki AL, Abramowsky C, Shehata BM (2012) NUT midline carcinoma: an imaging case series and review of the literature. Pediatr Radiol 42:205–210

Qiao J, Lee S, Paul P, Qiao L, Taylor CJ, Schlegel C, Colon NC, Chung DH (2013) Akt2 regulates metastatic potential in neuroblastoma. PLoS ONE 8:e56382

Redman JL, Agerty HA, Barthmajer OF, Fisher HR (1938) Adrenal neuroblastoma. Report of a case and review of the literature. Arch Pediatr Adolesc Med 56:1097–1112

Rogers DA, Schor NF (2013) Kidins220/ARMS depletion is associated with the neural-to-Schwann-like transition in a human neuroblastoma cell line model. Exp Cell Res 319:660–669

Ross P (1965) Calcification in liver metastases from neuroblastoma. Radiology 85:1074–1079

Rothenberg AB, Berdon WE, D'Angio GJ, Yamashiro DJ, Cowles RA (2009) Neuroblastoma – remembering the three physicians who described it a century ago: James Homer Wright, William Pepper, and Robert Hutchinson. Pediatr Radiol 39:155–160

Samaraweera L, Grandinetti KB, Huang R, Spengler BA, Ross RA (2014) MicroRNAs define distinct human neuroblastoma cell phenotypes and regulate their differentiation and tumorigenicity. BMC Cancer 14:309

Sanchez R, Zhou MM (2009) The role of human bromodomains in chromatin biology and gene transcription. Curr Opin Drug Discov Dev 12:659–665

Sarangarajan R, Hill DA, Humphrey PA, Hitchcock MG, Dehner LP, Pfeifer JD (2001) Primitive neuroectodermal tumors of the biliary and gastrointestinal tracts: clinicopathologic and molecular diagnostic study of two cases. Pediatr Dev Pathol 4:185–191

Sawyer JR, Tryka AF, Lewis JM (1992) A novel reciprocal chromosome translocation t(11;22)(p13;q12) in an intraabdominal desmoplastic small round-cell tumor. Am J Surg Pathol 16:411–416

Schnaufer L, Koop CE (1975) Silastic abdominal patch for temporary hepatomegaly in stage IV-S neuroblastoma. J Pediatr Surg 10:73–76

Schwab M (1994) Where pathology meets molecular biology: N-myc amplification in human neuroblastoma as a paradigm for the clinical use of an oncogene alteration. Verh Dtsch Ges Pathol 78:26–33

Schwartz AD, Dadash-Zadeh M, Lee H, Swaney JJ (1974) Spontaneous regression of disseminated neuroblastoma. J Pediatr 85:760–764

Schwartz BE, Hofer MD, Lemieux ME, Bauer DE, Cameron MJ, West NH, Agoston ES et al (2011) Differentiation of NUT midline carcinoma by epigenomic reprogramming. Cancer Res 71:2686–2696

Scott E, Oliver MG, Oliver MH (1933) Sympathetic tumors of the adrenal medulla. Am J Cancer 17:396–433

Seth A, Watson DK (2005) ETS transcription factors and their emerging roles in human cancer. Eur J Cancer 41:2462–2478

Shah BK, McHugh K (2000) Cystic liver metastases from extracranial primitive neuroectodermal tumour: a case report. Pediatr Radiol 30:834–836

Shehata BM, Steelman CK, Abramowsky CR, Olson TA, French CA, Saxe DF, Ricketts RR et al (2010) NUT midline carcinoma in a newborn with multiorgan disseminated tumor and a 2-year-old boy with a pancreatic/hepatic primary. Pediatr Dev Pathol 13:481–485

Shen C, Ipsaro JJ, Shi J, Milazzo JP, Wang E, Roe JS, Suzuki Y, Pappin DJ, Joshua-Tor L, Vakoc CR (2015) NSD3-short is an adaptor protein that couples BRD4 to the CHD8 chromatin remodeler. Mol Cell 60:847–859.

Shimada H (2006) Pathology of peripheral neuroblastic tumors. Lab Med 37:684–698

Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B (1999a) Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. Cancer 86:349–363

Shimada H, Ambros IM, Dehner LP, Hata JI, Joshi VV, Roald B, Stram DO, Gerbing RB, Lukens JN, Matthay KK, Castleberry RP (1999b) The International Neuroblastoma Pathology Classification (the Shimada system). Cancer 86:364–372

Song DE, Choi G, Jun SY, Ro JY (2004) Primitive neuroectodermal tumor of the gallbladder. Arch Pathol Lab Med 128:571–573

Soppa U, Schumacher J, Florencio Ortiz V, Pasqualon T, Tejedor FJ, Becker W (2014) The down syndrome-related protein kinase DYRK1A phosphorylates p27 (Kip1) and cyclin D1 and induces cell cycle exit and neuronal differentiation. Cell Cycle 13:2084–2100

Stelow EB (2011) A review of NUT midline carcinoma. Head Neck Pathol 5:31–35

Stelow EB, French CA (2009) Carcinomas of the upper aerodigestive tract with rearrangement of the nuclear protein of the testis (NUT) gene (NUT midline carcinomas). Adv Anat Pathol 16:92–96

Stelow EB, Bellizzi AM, Taneja K, Mills SE, Legallo RD, Kutok JL, Aster JC, French CA (2008) NUT rearrangement in undifferentiated carcinomas of the

upper aerodigestive tract. Am J Surg Pathol 32:828–834
Sugito K, Uekusa S, Kawashima H, Furuya T, Ohashi K, Inoue M, Ikeda T, Koshinaga T et al (2011) The clinical course in pediatric solid tumor patients with focal nodular hyperplasia of the liver. Int J Clin Oncol 16:482–487
Tajiri T, Souzaki R, Kinoshita Y, Tanaka S, Koga Y, Suminoe A, Hara T, Kohashi K et al (2010) Concordance for neuroblastoma in monozygotic twins: case report and review of the literature. J Pediatr Surg 45:2312–2316
Thompson-Wicking K, Francis RW, Stirnweiss A, Ferrari E, Welch MD, Baker E, Murch AR et al (2013) Novel BRD4-NUT fusion isoforms increase the pathogenic complexity in NUT midline carcinoma. Oncogene 32:4664–4674
Toretsky JA, Jenson J, Sun CC, Eshkenazi AE, Campbell A, Hunger SP et al (2003) Translocation (11; 15;19): a highly specific chromosome rearrangement associated with poorly differentiated thymic carcinoma in young patients. Am J Clin Oncol 26:300–3006
Trupiano JK, Machen SK, Barr FG, Goldblum JR (1999) Cytokeratin-negative desmoplastic small round cell tumor: a report of two cases emphasizing the utility of reverse transcriptase-polymerase chain reaction. Mod Pathol 12:849–853
Tsuchida Y, Hemmi H, Inoue A, Obana K, Yang HW, Hayashi Y, Kanda N, Shimatake H (1996) Genetic clinical markers of human neuroblastoma with special reference to N-myc oncogene: amplified or not amplified ? – an overview. Tumour Biol 17:65–74
Van Golen CM, Soules ME, Grauman AR, Feldman EL (2003) N-myc overexpression leads to decreased beta1 integrin expression and increased apoptosis in human neuroblastoma. Oncogene 22:2664–2673
Vargas SO, French CA, Faul PN, Fletcher JA, Davis IJ, Dai Cin P et al (2001) Upper respiratory tract carcinoma with chromosomal translocation 15;19: evidence for a distinct disease entity of young patients with a rapidly fatal course. Cancer 92:1195–1203
Vitali R, Cesi V, Nicotra MR, McDowell HP, Donfrancesco A, Mannarino O, Natali PG, Raschella G, Dominici C (2003) c-Kit is preferentially expressed in MYCN-amplified neuroblastoma and its effect on cell proliferation is inhibited in vitro by STI-571. Int J Cancer 106:147–152
Wang R, Liu W, Helfer CM, Bradner JE, Hornick JL, Janicki SM, French CA, You J (2014a) Activation of SOX2 expression by BRD4-NUT oncogenic fusion drives neoplastic transformation in NUT midline carcinoma. Cancer Res 74:3332–3343
Wang X, Yangl L, Choi JH, Kitamura E, Chang CS, Ding J, Lee EJ, Cui H, Ding HF (2014b) Genome-wide analysis of HOXC9-induced neuronal differentiation of neuroblastoma cells. Genom Data 2:50–52
Wang YH, Sui XM, Sui YN, Zhu QW, Yan K, Wang LS, Wang F, Zhou JH (2015) BRD4 induces cell migration and invasion in HCC cells through MMP-2 and MMP-9 activation mediated by the Sonic hedgehog signaling pathway. Oncol Lett 10:2227–2232
Wartchow EP, Moore TS, French CA, Mierau GW (2012) Ultrastructural features of NUT midline carcinoma. Ultrastruct Pathol 36:280–284
Werner H, Idelman G, Rubinstein M, Pattee P, Nagalla SR, Roberts CT (2007) A novel EWS-WT1 gene fusion product in desmoplastic small round cell tumor is a potent transactivator of the insulin-like growth factor-I receptor (IGF-IR) gene. Cancer Lett 247:84–90
Wieberdink J (1957) Foetal haemic metastasis. An explanation of the "Pepper-type" of metastasis in adrenal neuroblastoma. Br J Cancer 11:378–383
Wills 1993. http://www.ncbi.nlm.nih.gov/pubmed/8266595
Wright JH (1910) Neurocytoma or neuroblastoma, a kind of tumor not generally recognized. J Exp Med 12:556–561
Wyatt GM, Farber S (1941) Neuroblastoma sympatheticum. Roentgenological appearances and radiation treatment. Am J Roentgenol Radium Ther 46:485–492
Yan J, Diaz J, Jiao J, Wang R, You J (2011) Perturbation of BRD4 protein function by BRD4-NUT protein abrogates cellular differentiation in NUT midline carcinoma. J Biol Chem 286:27663–27675
Yang Z, He N, Zhou Q (2008) Brd4 recruits P-TEFb to chromosomes at late mitosis to promote G1 gene expression and cell cycle progression. Mol Cell Biol 28:967–976
Yanoff M (1990) The rosettes of James Homer Wright. Arch Ophthalmol 108:167
Yoo SY, Kim JH, Eo H, Jeon TY, Sung KW, Kim HS (2013) Dynamic MRI findings and clinical features of benign hypervascular hepatic nodules in childhood-cancer survivors. AJR Am J Roentgenol 201:178–184
Zeine R, Salwen HR, Peddinti R, Tian Y, Guerrero L, Yang Q, Chlenski A, Cohn SL (2009) Presence of cancer-associated fibroblasts inversely correlates with Schwannian stroma in neuroblastoma tumors. Mod Pathol 22:950–958
Zeng L, Zhou MM (2002) Bromodomain: an acetyl-lysine binding domain. FEBS Lett 513:124–128
Zhang PJ, Goldblum JR, Pawel BR, Fisher C, Pasha TL, Barr FG (2003) Immunophenotype of desmoplastic small round cell tumors as detected in cases with EWS-WT1 gene fusion product. Mod Pathol 16:229–235
Zhang P, Dong Z, Cai J, Zhang C, Shen Z, Ke A, Gao D, Fan J, Shi G (2015) BRD4 promotes tumor growth and epithelial-mesenchymal transition in hepatocellular carcinoma. Int J Immunopathol Pharmacol 28:36–44
Zhao Z, Ma X, Hsiao TH, Lin G, Kosti A, Yu X, Suresh U, Chen Y, Tomlinson GE et al (2014) A high-content

morphological screen identifies novel microRNAs that regulate neuroblastoma cell differentiation. Oncotarget 5:2499–2512

Ziai J, French CA, Zambrano E (2010) NUT gene rearrangement in a poorly-differentiated carcinoma of the submandibular gland. Head Neck Pathol 4:163–168

Zippo A, Serafini R, Rocchigiani M, Pennacchini S, Krepelova A, Oliviero S (2009) Histone crosstalk between H3S10ph and H4K16ac generates a histone code that mediates transcription elongation. Cell 138:1122–1136

Part XIII

Hepatobiliary Melanotic Tumors

Primary and Secondary Malignant Melanoma, and Other Melanotic Tumors, of the Hepatobiliary Tract

77

ICD-O code 8720/3

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_77

Abstract

Malignant melanoma (MM) is an aggressive malignancy that frequently involves the hepatobiliary tract, due to the frequent metastases to the liver. Therefore, most of malignant melanotic lesions detected in the liver and bile ducts are metastases of skin melanomas. But there is a small group of MM that takes its origin in the hepatobiliary tract, albeit the cell of origin is not yet known, possibly a neural crest cell that homed to this organ during embryogenesis. Primary MM is well documented for extrahepatic bile ducts and the gallbladder, where primary MMs have been described since long. In particular, primary gallbladder MM is a recognized entity with characteristic growth patterns. In contrast, primary hepatic MM is less well defined and numerous cases published in the old literature may be misinterpretations because metastatic disease is difficult to exclude in many cases, because the primary tumor may have been missed or had regressed. A distinct situation is ocular MM which is known to produce liver metastases after a long time delay. There are rare other melanotic tumors that can manifest in the liver, including melanotic progonoma. A tumor related to MM and known to have visceral manifestations is clear cell sarcoma or melanoma of soft parts.

Primary Malignant Melanoma of the Liver

Introduction

In contrast to primary malignant melanomas of the bile ducts and the gallbladder, which are well-recognized entities and are discussed in the following paragraphs, melanoma primary to the liver not related to the biliary tract is an exceptional finding. As with other melanomas in this anatomical compartment, diagnosis of a primary localization to the liver requires careful exclusion of metastatic disease, in particular metastasis of uveal melanoma, which is known to produce liver metastasis after long delays (see below). The difficulty in excluding extrahepatic primary melanoma renders at least part of the older reports questionable. In a study on 473 extraorbital malignant melanomas published in 1900, 362 tumors had taken their origin in the skin, 65 were related to the intestinal tract and the genital organs, and 46 to inner organs. Among the latter, a primary site to the liver was regarded as possible in seven cases (Luther 1900). At the end of this chapter, the older literature referring to well-documented or purported primary malignant melanomas is summarized.

Selected References von Frerichs 1861; Block 1875; Hanot and Gilbert 1888; Nencki and Sieber 1888; Luther 1900; Nazari 1906; Mansson 1926; Smith 1926; Koch 1930; Konschegg and Hada 1937; Lence 1937; Boj 1954; Tacquet et al. 1959; Ogan et al. 1961; Vido et al. 1964; Adel'shinova 1969; Furuta et al. 1995; Zhang and Zhao 1995; Li et al. 2003; Wang et al. 2005; Hu 2006; Gong et al. 2008.

Pathology

Malignant melanoma primary to the liver shares histopathology and immunohistochemistry with extrahepatic melanomas (Figs. 1, 2, 3, 4, and 5).

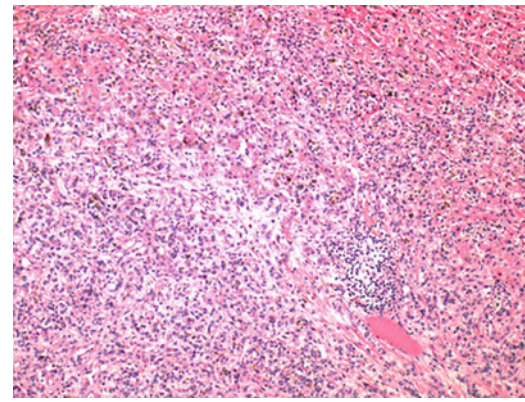

Fig. 1 Malignant melanoma with apparent primary localization to the liver. The pigment-containing tumor cells have partially destroyed the liver parenchyma (hematoxylin and eosin stain)

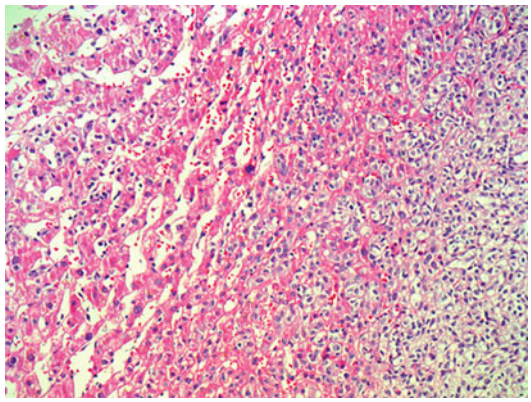

Fig. 2 Metastasis of malignant melanoma in the liver. Neoplastic cells invade the hepatic sinusoids (hematoxylin and eosin stain)

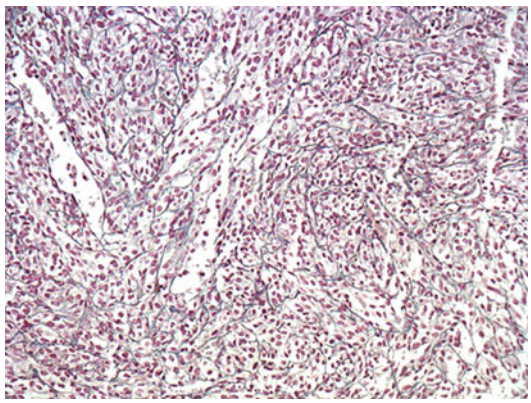

Fig. 3 Malignant melanoma in the liver. Clusters and nests of melanoma cells are surrounded by reticulin fibers (Gomori silver stain)

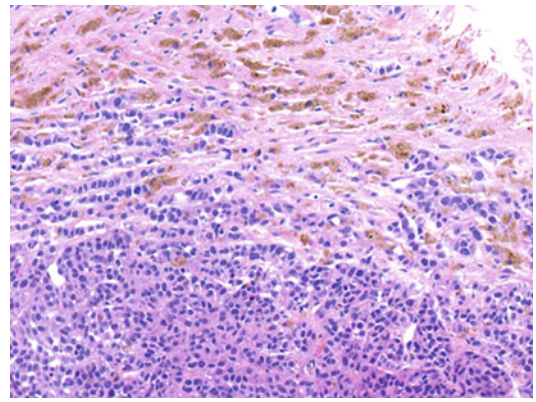

Fig. 4 Malignant melanoma in the liver. The tumor has a low level of melanin pigmentation, but melanin has accumulated in tumor-associated macrophages (melanophores, upper part of figure; hematoxylin and eosin stain)

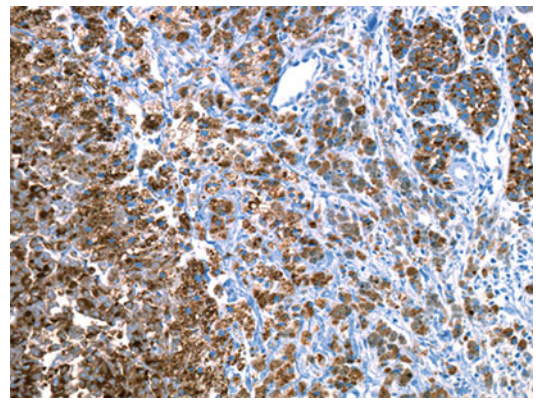

Fig. 5 Malignant melanoma in the liver. Tumor cells are strongly HMB-45 reactive (HMB-45 immunostain)

An autopsy report described the lesion as a large black mass surrounded by fibrous tissue (Furuta et al. 1995). In another patient who had undergone liver resection, the oval and well-delineated tumor, measuring up to 12 cm in diameter, had grayish-yellow cut surface, reflecting hypomelanotic melanoma (Gong et al. 2008).

Histopathology

In the case described by Gong et al. (2008), the histology was characterized by typical spindled and pleomorphic melanoma cells with or without pigment, immunoreactive for HMB-45, and showing few melanosomes in electron micrographs.

Malignant Melanoma of the Bile Ducts

Introduction

Primary malignant melanoma of the bile duct system is very rare, and certainly much less common than gallbladder melanomas. As outlined in more detail in the paragraph on melanoma of the gallbladder, identification of the bile duct as a

primary site of melanoma may be difficult to distinguish from metastatic disease. Similar to the gallbladder, careful exclusion of melanoma situated elsewhere and the observation of junctional activity in the biliary mucosa are important criteria (Wagner et al. 2000). The first case reported was a melanoma located in the distalmost common bile duct and Vater's diverticulum (Duval 1908), followed by the description of an apparently isolated tumor in the common duct only 55 years later (Zaide 1963). The 47-year-old male patient described by Zaide presented with a 3-month history of obstructive jaundice, and common duct resection showed typical melanoma.

Localizations and Clinical Features

Primary malignant melanoma of the biliary tract has been detected in all parts of the extrahepatic duct system, i.e., involving the bifurcation (confluens) of the large duct (Washburn et al. 1995; Gonzalez et al. 2001), hepatic and common bile ducts combined (Deugnier et al. 1991), the common bile duct (Duval 1908; Shepherd 1908; Zaide 1963; Breatnach et al. 1985; Carstens et al. 1986; Wright and Brewer 1988; Cohen et al. 1990; Zhang et al. 1991; Gates et al. 1996; Wagner et al. 2000; Medina et al. 2003; Bejarano Gonzalez et al. 2005), and the ampulla of Vater (Duval 1908; Washburn et al. 1995; Fléchon et al. 2002). Melanoma of the common bile duct may be combined with melanoma in the gallbladder (Zhang et al. 1991; Medina et al. 2003).

The first case, reported in 1908 (Duval 1908), is instructive owing to its morphology and was described as melanoma of Vater's diverticulum and lower portion of the common bile duct. The neoplasm ("melanophoroma") had developed in a 44-year-old man who presented with deep jaundice. It had caused complete obstruction of the distal common duct and was a dark-brown cylindrical mass of 2.5 cm in diameter. A careful search during autopsy failed to establish the metastatic nature of this growth. Interestingly, this melanoma revealed a papillary growth pattern, described as showing "innumerable densely arranged flattened fingerlike projections which floated free in their distal extremities, but remained firmly attached at their bases".

Both common bile duct and ampullary melanoma may, expectedly, cause obstructive jaundice (Zaide 1963; Wright and Brewer 1988; Washburn et al. 1995; Bejarano Gonzalez et al. 2005), and complete obstruction was already described in 1908 (Duval 1908). Sonography and CT usually display dilatation of intra- and extrahepatic bile ducts caused by tumor-induced stenosis (Wagner et al. 2000; Van Bokhoven et al. 2006). Melanoma primary to the common bile duct has low signal intensity on T2-weighted images and high signal intensity on unenhanced T1-weighted images (Medina et al. 2003). Endoscopic retrograde cholangiopancreatography (ERCP) has revealed lobulated filling defects in the common duct (Wagner et al. 2000).

Pathology

Macroscopy

Relatively few cases contained a documentation of gross findings. Zaide (1963) described a cauliflowered, friable, black tumor in the common bile duct. In the case of Carstens and coworkers (1986), the Whipple resection specimen disclosed a brown polypoid mass of the common bile duct, measuring up to 1.3 cm. The tumor may infiltrate the common duct wall over longer distances, over a length of 10 cm in one patient (Deugnier et al. 1991). Zhang et al. described a 58-year-old man with a 1-cm, lobulated, soft black mass of the common bile duct, as well as a concurrent mass involving the gallbladder (Zhang et al. 1991). In the case reported by Wagner and coworkers, the resected specimen (Whipple procedure) demonstrated a dilated common bile duct that contained a large, fungating and polypoid, pediculated, white-tan to gray-brown mass located to the midportion of the duct and measuring 4.0 × 2.0 × 1.9 cm (Wagner et al. 2000). The lesions developing in the common bile duct have been described as polypoid, similar to primary melanoma of the gallbladder, in another report (Medina et al. 2003),

Histopathology

Primary common duct and ampullary melanomas show polypoid, mucosal, and/or submucosal tumor nodules of variable size, immunoreactive for HMB-45 and Melan-A (Wagner et al. 2000; Fléchon et al. 2002). Electron microscopy demonstrated premelanosomes type I, electron-dense granules consistent with melanin pigment, and coiled, vesicular, and spiral filaments in the cytoplasm (Wagner et al. 2000).

Immunohistochemistry

Malignant melanoma cells express a characteristic spectrum of markers (reviews: Ohsie et al. 2008; Prieto and Shea 2011). More than 90 % of the tumors are positive for S100 protein. Both polyclonal and monoclonal anti-S100 protein antibodies label melanocytic lesions, with a cytoplasmic and nuclear pattern. HMB-45 antibody detects gp100, a glycoprotein that is fairly specific for cells of the melanocyte linage and melanomas (Rothberg et al. 2008), but HMB-45 also stains perivascular epithelioid cells and their tumors (PEComas). An important marker is MART1 (melanoma antigen recognized by T cells-1; Busam et al. 1998). This antigen is detected by two antibodies, Melan-A and A-103. MART1 is expressed by both benign and malignant melanocytic cells. It has to be noted that MART1 is also expressed by PEComas (similar to HMB-45) and that A-103 also stains cells of steroid hormone-producing tumors. Tyrosinase is expressed in cells of the melanocyte lineage. Microphthalmia transcription factor (MITF) is a nuclear protein involved in the development of melanocytic cells and synthesis of melanin. It is expressed in melanomas with a nuclear staining pattern, but it may also be expressed by macrophages, lymphocytes, and fibroblasts. Schwann cells and smooth muscle cells. Melastatin-1 (MLSN1, TPRM1) is highly expressed in melanocytic nevi, but it is absent from melanoma metastases. The expression of MLSN1 inversely correlated with tumor thickness (review: Dadras 2011).

Malignant Melanoma Metastatic to the Bile Ducts

An autopsy study demonstrated that patients with metastasizing melanoma had biliary duct metastases in 6 %, in contrast to 15 % with metastases to the gallbladder (Das Gupta and Brasfield 1964). The metastatic sites involve the common bile duct (Armbruster 1973; Cole and Freston 1973; Bowdler and Leach 1982; Daunt and King 1982; McArthur and Teergarden 1983; O'Connell et al. 1984; Kohler and Riemann 1987; Cohen et al. 1990; England and Sarr 1990; Parquier et al. 1991; Thompson et al. 1993; Garas et al. 2000; Grasso et al. 2003; Uchikov et al. 2004; Cardot-Leccia et al. 2005; Van Bokhoven et al. 2006; Colovic et al. 2007; Rezanko et al. 2008), the cystic duct (O'Connell et al., 1984), and the ampullary region (Sans et al. 1996; Van Bokhoven et al. 2006). Metastasis to the common bile duct may cause obstructive jaundice with marked cholestasis, sometimes combined with hemobilia (Cole and Freston 1973; McArthur and Teergarden 1983; Kohler and Riemann 1987; England and Sarr 1990; Parquier et al. 1991; Thompson et al. 1993; Brankamp et al. 2007).

Metastasis-induced common bile duct stenosis can be demonstrated by the use of endoscopic retrograde cholangiopancreatography, showing filiform stenosis in one reported patient (Brankamp et al. 2007) and a complex filling defect in another (Garas et al. 2000). The lesions are also demonstrated by intraoperative cholangiography (Colovic et al. 2007). Expectedly, also melanoma metastatic to the ampulla may cause massive stenosis and obstructive jaundice (Sans et al. 1996; Caballero-Mendoza et al. 1999). At imaging, metastatic melanoma of the common bile duct may appear as a vegetating lesion on CT images (Grasso et al. 2003) or produce a spherical filling defect (Thompson et al. 1993). Retrograde cholangiopancreatography (ERCP) shows bile duct compression and intraluminal impressions that resist removal with a basket or balloon (Garas et al. 2000), lobulated filling defects (Van Bokohoven et al. 2006), or large intraductal masses (Garas et al. 2000). During ERCP, cell material can be obtained. It has been reported that metastatic melanoma of the common bile duct can be diagnosed with brush cytology

(Brankamp et al. 2007; Rezanko et al. 2008). In case of ampullary metastasis, endoscopy has revealed a dark-brown, easily bruising lesion bulging from the mucosal surface (Van Bokhoven et al. 2006).

Few gross findings are available from the literature. In one patient, the choledochal resection specimen revealed a large lobulated and polypoid mass stenosing the duct (Brankamp et al. 2007).

Primary Malignant Melanoma of the Gallbladder

Introduction

The gallbladder is one of the rarest sites of visceral malignant melanoma. The first case was reported in 1907 under the term melanoblastoma of the gallbladder (Wieting and Hamdi 1907). In this 40-year-old female patient, generalized metastases owing to melanoma were found, caused by primary gallbladder melanoma. Relatively few cases have since been described. As with other mucosal malignant melanomas, most of the patients are in the fourth of fifth decade of life at the time point of diagnosis (Velez et al. 1995). Among 29 cases reviewed from the literature, age at presentation ranged from 25 to 74 years, with 17 males and 12 females (Ricci et al. 2001). Primary gallbladder melanoma has been observed in conjunction with dysplastic nevus syndrome (Ricci et al. 2001).

Selected references Rosenthal 1931; Pautler and Gallavan 1951; Thayer et al. 1955; Kazmann and Zukaukas 1956; Walsh 1956; Larmi 1960; Jones 1961; Raffensberger et al. 1963; Simard et al. 1966; Das Gupta et al. 1969; Balthasar and Javors 1975; Peison and Rabin 1976; Sierra-Calejas and Warecka 1976; Hatae et al. 1978; Carle et al. 1981; Anderson et al. 1983; Borja et al. 1984; Naguib and Aterman 1984; Seul and Lüchtrath 1984; Rudolph et al. 1985; Verbanck et al. 1986; Heath and Womack 1988; Guerini et al. 1990; Zhang et al. 1991; Habeck 1993; Hatanake et al. 1993; Higgins and Strutton 1995; Velez et al. 1995; Longwitz et al. 1996; Saoshiro et al. 1996; Dong et al. 1999; De Simone et al. 2000; Ricci et al. 2001; Medina et al. 2003; Rea and van Heerden 2004; Safioleas et al. 2006; Martel et al. 2009.

It is difficult to judge whether all the reported cases were in fact bona fide primary tumors or rather melanoma metastases, which are well known to occur in the gallbladder (see below; Higgins and Strutton 1995; Safioleas et al. 2006). Heath and Womack (1988) suggested that certain criteria should be fulfilled before primary melanoma is diagnosed: (1) tumors must be solitary and arise from the mucosal surface of the gallbladder; (2) they must either by papillary or polypoid; and (3) they must either display junctional activity or have any other primary sites excluded by history taking, examination, and investigation. Using these guidelines, these authors have identified 15 cases in the literature that did not fulfill the required criteria. Ricci and coworkers (2001) proposed the following criteria: (1) the exclusion of a previous primary melanoma, (2) the absence of synchronous involvement of sites other than the considered one, (3) the unicity of the lesion, (4) its polypoid or papillary shape, and (5) the presence of a junctional melanocytic component. However, the authors emphasized that these criteria are weak, particularly if singly taken. It is, e.g., known that melanoma metastatic to the gallbladder can be polypoid or show intraepithelial spread with junctional activity (Murphy et al. 1987; Dong et al. 1999). In case all of the mentioned criteria must be fulfilled, the number of bona fide primary gallbladder melanomas would probably be reduced to less than 10.

Clinical and Imaging Features

Clinically, this lesion may mimic gallstone disease and/or may present as acute acalculous cholecystitis (Peison and Rabin 1976; Dong et al. 1999; De Simone et al. 2000). Ultrasound demonstrates hyperdense intraluminal strands of tumor, sometimes with hyperechogenic intraluminal "school of fish" reflections (Longwitz et al. 1996). CT often reveals solid intraluminal masses with a hypodense and partially hyperdense reticular structure, reflecting

the common polypoid growth pattern of these melanomas. Gallbladder melanoma often gives rise to metastatic disease (in 9/13 cases reviewed by Carle et al. 1981). Primary gallbladder melanoma may metastasize to the common bile duct, eventually via mucosal implants (Verbanck et al. 1986). Information about the metastatic involvement of the cystic duct lymph node is very sparse. In one report, it was specified as not involved (Ricci et al. 2001).

Pathology

Macroscopy

Primary malignant melanoma of the gallbladder shows several distinct growth patterns (Table 1).

In the first reported case, gallbladder melanoma presented as a polypoid tumor sitting on a rather broad base and measuring up to 2 cm. The surface of the polyp was irregularly nodular, and the mucosal covering was missing. This melanoma was much lighter in color than the numerous metastases (Wieting and Hamdi 1907). Polypoid growth with formation of sometimes black polyps has subsequently been observed several times (e.g., Rosenthal 1931; Peison and Rabin 1976; Carle et al. 1981; Borja et al. 1984; Habeck 1993; Ricci et al. 2001). Polypoid melanoma is probably the most common pattern encountered: in a compilation of 13 cases of primary gallbladder melanoma (Carle et al. 1981), 11 tumors showed a polypoid growth pattern. In a study of 29 patients collected from the literature, 24 lesions were polypoid or papillary, and 13 were described as single polypoid (Ricci et al. 2001).

Of differential diagnostic importance is the size of primary gallbladder melanomas. In the five cases reviewed by Walsh (1956), the size of the exclusively polypoid lesions ranged from 2 to 7.5 cm in length and 2–4 cm in width, what is in contrast to the few millimeters given by Willis for the usual size of metastatic deposits (Willis 1952). Beneath the melanoma polyp, smaller tumor nodules may penetrate deeper layers of the gallbladder wall (Borja et al. 1984). Gallbladder melanoma may also show a diffuse mucosal growth. A further morphotype is the presentation as brown to black patches and slightly raised plaques (Rosenthal 1931). Nodular or mass-forming melanoma has also been noted (Pautler and Gallavan 1951; Walsh 1956). The case of Walsh (1956) was a 45-year-old male patient admitted for biliary colic. Under suspicion of stones cholecystectomy was performed. The patient had a small scar in the center of the forehead, but there was no history of cutaneous melanoma and no evidence of ocular melanoma. The resection specimen showed a mottled yellow-brown trilobulated tumor mass extending from the midportion of the gallbladder almost to the fundus, measuring 7.5 × 2.5 × 1.0 cm.

Table 1 Gross growth patterns of gallbladder melanoma

Diffuse pattern
Growth as plaques or patches
Polypoid (exophytic) pattern
Nodular pattern
Mass-forming pattern

Histopathology

In the few available reports, the histology of gallbladder melanoma is more or less the same as that in other visceral locations. The lesions may be surrounded by clusters of melanin-containing macrophages (melanophores, melanophages; Hatae et al. 1978). The gallbladder epithelium overlaying the melanoma nodules may be infiltrated by lymphocytes (Borja et al. 1984). Of interest is the observation of active junctional changes in scattered foci of altered mucosa overlying a melanoma: in one case, large round cells with hyperchromatic nuclei and spongy cytoplasm were scattered at or near the basal layer of the gallbladder mucosa, at one place associated with squamous metaplasia of the surface epithelium. In this multilayered squamous epithelium, a pagetoid pattern of large atypical melanocytes was seen (Walsh 1956). Small clusters as well as individual tumor cells containing fine granular pigment within the columnar epithelium or forming a junctional component were seen in other cases (Peison and Rabin 1976; Carle

et al. 1981; Borja et al. 1984; Heath and Womack 1988; Ricci et al. 2001). In one case, a focus of active junctional changes was found in normal mucosa at a distance from the tumor, and the melanocytes, which appeared wedged between the columnar cells, showed no nuclear atypia (Peison and Rabin 1976). In Fig. 8 of their report, it is seen that slender and highly pigmented cells are intercalated between epithelial cells, sometimes occupying the entire space between two neighboring columnar cells from their basal to apical portions. At other places, larger but again markedly melanized cells occupy the junctional area, but rather at locations lacking intercalated melanocytes. These findings suggest changes derived from preexisting mucosal melanocytic cells or neural crest cells. It has been argued that an activated junctional nevus is a prerequisite of mucosal melanoma (Allen and Spitz 1953). Walsh (1956) who noted the combination of a squamous metaplasia and junctional activity thought that melanoma may have developed in this squamous cell epithelium of the gallbladder. This is worth considering because a squamous epithelium may represent a homing site for melanocyte precursors. Taken together, junctional activity has been suggested to be an important criterion for the diagnosis of primary melanoma of the gallbladder (Heath and Womack 1988). The apical portion of columnar mucosal epithelial cells may contain melanin pigment granules, probably representing shedded melanosomes phagocytosed from the gallbladder lumen (Hatae et al. 1978; Carle et al. 1981).

Malignant Melanoma Metastatic to the Gallbladder

The most important differential diagnosis of primary gallbladder melanoma is malignant melanoma metastatic to the gallbladder, a metastasis pattern that is well recognized in the literature. It has been reported that involvement of the gallbladder occurs in about 15 % of all gastrointestinal metastatic localizations in postmortem case records (Das Gupta and Brasfield 1964). In a study of 19 patients, the median age at presentation was 46.7 years; ten of the primary cutaneous melanomas were of the superficial spreading type, three were nodular, and most lesions showed Clark levels of either III or IV (Dong et al. 1999). Both abdominal CT and right upper quadrant ultrasonography are useful in uncovering the presence of gallbladder metastases. Metastatic melanoma lesions are usually smaller than primary tumors of the gallbladder and often present as flat intramural nodules in addition to the well-known polypoid lesions. Involvement of the gallbladder seldom produces symptoms, but melanoma metastases in the gallbladder may rarely cause acute cholecystitis (Henriques 1955; Ostick and Haqqani 1976; Langley et al. 1997) or masquerade cholelithiasis (Herrington 1965).

Selected references Das Gupta and Brasfield 1964; Zemlyn 1966; Shimkin et al. 1972; McFadden et al. 1979; Bundy and Ritchie 1982; Murphy et al. 1987; Stutte et al. 1989; Goldin 1990; Hahn et al. 1993; Avila et al. 1994; Gawenda et al. 1995; Abdelli et al. 1996; Bedo et al. 1996; Holloway and King 1997; Seelig and Schönleben 1997; Dong et al. 1999; Hallal et al. 1999; Paolini et al. 1999; Cellerino et al. 2000; Köhler et al. 2000; Guida et al. 2002; Gogas et al. 2003; Crippa et al. 2004; Gassler et al. 2004; Uchikov et al. 2004; Rehani et al. 2006; Romero et al. 2006; Varsamidakis et al. 2006; Katz et al. 2007; Marone et al. 2007; Nelms et al. 2007; Takayama et al. 2007; Tuveri and Tuveri 2007; Samplaski et al. 2008.

Macroscopy

The majority of the metastatic lesions are serosal implants. Mucosal metastases were seen in 7/19 patients at autopsy (Das Gupta and Brasfield 1964). A polypoid, intraluminal growth pattern has also been noted in metastatic gallbladder melanoma, but is a rare finding, in contrast to primary gallbladder melanoma (Henriques 1955; Das Gupta and Brasfield 1964; Ostick and Haqqani 1976). In one case, this metastatic growth pattern

was associated with cholecystitis, probably cause by obstruction (Henriques 1955). Gallbladder metastasis may develop in association with melanoma metastasis to the common bile duct (Uchikov et al. 2004).

Liver Metastases of Cutaneous and Visceral Melanomas

Introduction and Epidemiology

The liver is a major metastasis-susceptible site and is thought to possess a distinct prometastatic microenvironment (Vidal-Vanaclocha 2008). Malignant melanoma frequently metastasizes widely to many organs, and the liver is involved in at least 10–20 % of cases (Rose et al. 2001) and, probably, in up to one third of cases. However, these figures markedly depend on the methods employed to detect metastasis and on the stage of disease at the moment of metastasis assessment. Among a total of 652 patients with malignant melanoma treated between 1935 and 1960 at a North American center, only 27 or 4 % presented with evidence of the liver as the first site of metastasis, initial clinical evidence of metastasis being hepatomegaly and abnormal liver tests. In contrast, 84 out of 124 patients (60 %) with stage III disease (melanomatosis) had hepatomegaly and 44 % of this group (37 patients) had laboratory evidence of liver malfunction, but only 7 (8 %) of the 84 patients had clinical jaundice. Among 125 autopsy cases, the incidence of metastasis to the liver was 68 % (Das Gupta and Brasfield 1964).

Clinical Features

Hepatic melanoma metastases cause sometimes massive hepatomegaly associated with ascites. They may rupture and cause massive bleeding (Cooperman et al. 1976; Dousei et al. 1991). In cases with massive tumor load and tumor cell decay, diffuse melanosis and melanuria (Virchow) may occur. Typically, the urine darkens with time and may then turn deeply black, with a positive melanogen test (Thormälen's test; Feigl and Querner 1917). Liver metastasis of malignant melanoma has been shown to portend a grave prognosis, with a median survival time of about 4 months. Most cases of melanoma liver metastases have their primary tumor in the skin, but primary visceral melanomas also metastasize to the liver, and metastases are sometimes caused by melanoma of unknown primary site (MUP), MUP accounting for 3.7–6 % of all incident melanomas (Dasgupta et al. 1963; Milton et al. 1977; Katz et al. 2005).

Pathology

Macroscopy

Enlargement of the liver due to multiple metastatic melanoma nodules is common, and sometimes a gigantic enlargement of the liver is noted (Das Gupta and Brasfield 1964). The common type of metastasis pattern is multiple, with nodules ranging from few mm to more than 10 cm in diameter, with no predilection for any liver lobe among 125 autopsy cases (Das Gupta and Brasfield 1964). Rare cases show a diffuse infiltration of the organ, with nodules being hardly visible. A predilection for the hepatic capsular compartment may occur, with liver parenchyma remaining remarkably normal.

Histopathology

As in other melanoma metastases in parenchymal organs, the melanoma cells seen in hepatic metastases are often spherical, smaller cells forming nests with alveolar features. These alveolar formations contain a network of reticulin and collagen fibers. Nests of small to medium-sized melanoma cells may grow within the sinusoidal channels, but they are sometimes also intercalated with liver cell plates. Marked involvement of the sinusoidal vascular compartment may cause liver atrophy and portal hypertension (Block 1875). There are metastases with a predominant growth of melanoma cells in portal tracts and septa. In the center of larger cell nests, apoptosis and/or

necrosis is found, with melanin granules situated in the intercellular space and signs of melanosome phagocytosis (melanophagy) by Kupffer cells (melanophores). Similar to situations with massive iron overload of the liver, dark-brown melanin-containing Kupffer cell nodules occur. In case of large necrosis, the involved area is overpigmented at low magnification and reveals heaps and coarse granular masses of condensed melanin pigment. Large and pleomorphic cells or cells reminiscent of poorly differentiated sarcoma may occur, large cells sometimes forming syncytia. An alveolar pattern is not seen in large cells, and syncytial cells often have less melanin than the smaller cells (Konschegg and Hada 1937). Some metastases contain melanin-containing spindle cells as found in part of primary malignant melanomas. Apart from apoptosis and necrosis, melanoma cells in metastases may undergo other secondary changes, in particular fatty change. Neutral fat is more commonly noted in large tumor cells than in small ones. The stainable fat droplets are usually present in close association with pigment granules.

Liver Metastases of Choroidal (Uveal) Melanoma

Introduction

Choroidal (uveal) melanoma is a distinct entity with considerable differences in regard to skin melanomas (Laver et al. 2010). It is the most common intraocular malignant neoplasm, with an incidence of about six cases per million population per year in the Caucasian population (Singh and Topham 2003). Uveal melanoma may be associated with an increased incidence of other neoplasms. Choroidal melanoma has a characteristic chromosomal configuration. Monosomy 3 is an early event present in 50–60 % of tumors, often associated with the long arm of chromosome 8. Ocular melanoma has a complex biology in regard to local recurrence and metastasis, only partly related to the histologic type. Uveal melanomas are typically slow-growing tumors that show local infiltrative properties but little tendency to produce metastatic disease unless extraocular extension is present or enucleation has taken place, which has an adverse effect on prognosis (Zimmerman and McLean 1979; McLean et al. 1980). In regard to biology of disease, two classes of ocular melanoma are distinguished, Class 1 tumors having low risk and Class 2 having a high risk for metastatic death (Onken et al. 2004). In metastatic disease, the liver is frequently involved. In contrast to choroidal melanoma, iris melanoma has a much lesser tendency to metastasize.

Liver Metastasis of Uveal Melanoma

Liver metastases of ocular (choroidal; uveal) melanoma are a well-recognized event and may develop with considerable delay (Newton 1965; Lorigan et al. 1991). Cases manifesting 15 years or more after ocular melanoma diagnosis have been reported (Hosonuma et al. 2005). Sometimes, a long delay may camouflage the fact that ocular melanoma was present many years ago, e.g., until examination and inquiry reveal the presence of a glass eye post enucleation (Lubarsch 1920). Hence, ocular melanoma is one of the tumors that may produce hepatic CUP (cancer of unknown primary). However, in a study on 40 patients with hepatic melanoma metastasis undergoing liver resection (16 ocular and 24 cutaneous melanomas), the median disease-free interval from the time of primary tumor treatment to hepatic metastasis was the same for both groups, but patients with primary ocular melanoma were more likely to experience recurrence within the liver after hepatic resection, whereas patients with a cutaneous primary tumor more often developed extrahepatic involvement (Pawlik et al. 2006). For many patients, the liver is the primary and only site involved at the time of detection of systemic metastases (Patel et al. 1978). Ocular melanoma may occasionally metastasize to the liver before enucleation (Wilhelm and Zakov 1982).

What determines the risk of uveal melanoma metastatic disease and hence outcome in general? In a very large study of 3,432 cases of malignant melanoma of the choroid and ciliary body,

mortality from metastasis 15 years after enucleation was 46 % (McLean et al. 1982). Well-known risk factors comprise tumor size, epithelioid tumor cell type (see below), mitotic activity, vascular loops, lymphocytic infiltration, extraocular extension (scleral invasion), and enucleation (Singh et al. 2001; McLean et al. 2004; Coupland et al. 2008).

What are more refined parameters predicting metastatic disease? Extraocular spread via aqueous channels, ciliary arteries, vortex veins, ciliary nerves, optic nerve, and a variety of other routes occurred in 124/847 patients analyzed. This extraocular extension correlated with anterior tumor extension, large basal tumor diameter, epithelioid cell type, closed loops, high mitotic rate, and monosomy 3, and was a significant predictor of metastatic disease and death (Coupland et al. 2008). In the liver, an infiltrative growth pattern is associated with ciliary body involvement and extrascleral tumor extension of the primary ocular tumor (Dayani et al. 2009).

There are distinct molecular changes affecting invasion and spread in uveal melanoma (Bakalian et al. 2008). Cyclooxygenase-2 (COX-2) is expressed in more than 50 % of uveal melanomas, and it correlates with markers of poor prognosis, such as an epithelioid cell type, the presence of lymphocytic infiltration, and vascular closed loops. In addition, mixed-cell tumors are further subdivided into two subclasses by the presence and absence of COX-2 expression, expression of COX-2 having an adverse effect on outcome (Figueiredo et al. 2003). The histologic detection of laminin-rich vasculogenic mimicry patterns in uveal melanoma is associated with death from metastasis, although uveal melanoma cells forming a vasculogenic mimicry pattern in a laminin-containing three-dimensional microenvironment upregulate genes associated with differentiation and downregulate proliferation- and invasion-associated genes (Folberg et al. 2006). Class 2 tumors prone to liver metastasis and poor outcome show loss of the helix-loop-helix inhibitor ID2, and this downregulation triggers upregulation of E-cadherin, which in turn promotes anchorage-independent growth as a likely antecedent to metastasis (Onken et al. 2006). Class 2 tumors possess a distinct signature in gene expression profiling (Onken et al. 2004; Worley et al. 2007; Chang et al. 2008; Van Gils et al. 2008; Trolet et al. 2009) and reveal distinct patterns of microRNA expression (Radhakrishnan et al. 2009), and a classifier that includes six microRNA discriminators accurately distinguishes Class 1 from Class 2 tumors (Worley et al. 2008).

Ocular melanoma metastasis in the liver has a poor prognosis, despite improvement of therapeutic measures (Class 2 ocular melanoma). Commonly, median survival is reported to be less than 1 year. Among 201 studied patients, serum alkaline phosphatase, total bilirubin, and lactic dehydrogenase plus response to treatment showed a strong relation to survival, but not patient age and gender, metastasis-free interval, presence of extrahepatic metastases, and type of therapy (Bedikian et al. 1995). In a more recent study, prolonged survival was correlated with an interval from primary tumor diagnosis to liver metastasis >24 months and with the absence of a military metastasis mode (Mariani et al. 2009). In another study, two independent favorable prognostic factors were fewer than ten liver metastases at screening and, for the primary ocular tumor, absence of ciliary body involvement (Kodjikian et al. 2005). Metastatic tumor burden in the liver has an impact on outcome. In addition, the metastases may induce local vascular complications. The tumor can induce Budd-Chiari syndrome in the absence of chemotherapy (Caya et al. 1983). Today, hepatic arterial chemoembolization of ocular or cutaneous melanoma liver metastases results in longer survival, and patients with lesions that have a nodular tumor appearance on angiography survive longer than patients with infiltrative lesions (Sharma et al. 2008; Dayani et al. 2009). However, this procedure may be complicated by post-necrotic giant hemorrhagic cysts and eventually hepatic failure (Ataergin et al. 2009). Hyperthermic isolated hepatic perfusion with melphalan leads to immediate changes in tumor gene expression. In pre-therapy tumors, the Ras GTPase activator, ecotropic viral integration site 5 (EVI5), and several other melanoma-associated genes are overexpressed.

Pathology

Macroscopy

Liver metastasis of choroidal melanoma comes in three main patterns, viz., large mass lesions, nodular lesions, and infiltrative lesions.

Histopathology

Primary tumors of ocular melanoma are histologically described by the Callender-Wilder classification or modified versions of it (Callender 1931; Callender and Wilder 1935). The histologic patterns of ocular melanoma may be recapitulated in its hepatic metastases. But how are the distinct cytologic and histopathologic features reflected in liver metastases of ocular melanoma? In a study of 29 uveal melanomas and their metastases, a significant difference in cell type was found. The metastases revealed 82.5 % epithelioid or nonclassifiable cells. Cells in metastases have a similar reactivity for HMB-45, but show more frequently NKI-3 expression than the primary tumor. The findings suggest that metastases consist of a greater fraction of high-grade malignant melanoma cells (Luyten et al. 1996).

Diffuse Liver Infiltration by Melanoma: A Cause of Liver Failure

Multiple metastases of malignant melanoma causing diffuse hepatic infiltration (miliary melanoma metastases) is a well-known clinicopathologic entity (Pichon et al. 2004; Shan et al. 2009). The patient may present with anorexia and abdominal distension, and both sonography and CT reveal an enlarged liver without detectable nodules. Liver biopsy usually shows an almost diffuse infiltration of the sinusoidal spaces with melanoma cells. This massive hepatic involvement can result in liver failure with striking elevations of liver tests, particularly lactate dehydrogenase, and causing death in part of the patients (Bouloux et al. 1986; Lesur et al. 1992; Te et al. 1999; Jose et al. 2002; Montero et al. 2002; Tanaka et al. 2004; Kaplan et al. 2005; Rubio et al. 2005; De Castro et al. 2007). Melanomas involved in this catastrophic event are usually skin melanomas, but the syndrome has also been found in ocular melanoma (Lesur et al. 1992). Liver failure has also been observed in marked hepatic melanoma metastasis of the non-diffuse type (Muehlenberg and Wardelmann 1992). There are, however, situations where even marked diffuse hepatic metastasis is not associated with hepatocellular disease and shows normal serum liver enzyme levels (Donoso et al. 1985). Such differences have not been pathophysiologically clarified, but one may assume that there is a relevant pathogenic difference between the mere presence of multiple but circumscribed metastases and massive and, in particular, intrasinusoidal infiltration, the latter severely compromising hepatocyte metabolism. Hepatocyte malfunction caused by sinusoidal tumor cell infiltration has been observed in lymphomas, leukemias, and carcinomas (Martelli et al. 2000; Ihara et al. 2001), and also in plasmacytoma (Rahhal et al. 2009), but is probably a rare event, observed in 18 patients among 4,020 admissions of acute liver failure in on study (Rowbotham et al. 1998).

Congenital Metastasizing Malignant Melanoma

Congenital melanoma is a very rare neoplastic process that is often associated with giant melanocytic nevi (Coe 1925; Sweet and Connerty 1941; Schneiderman et al. 1987; Koyama et al. 1996; Richardson et al. 2002). Congenital melanoma can develop in the eye (Greer 1966; Palazzi et al. 2005). The fetus can also be affected by melanoma metastases derived from malignant melanoma of the mother (transplacental metastases; Holland 1949; Brodsky et al. 1965). The relation between congenital nevi and the development of melanocyte malignancy is not clarified, because metastasis alone is not a reliable criterion for malignancy in these lesions. A congenital giant but bland-looking melanocytic nevus may be associated with placental metastasis showing the same bland cellular features, and the infant suffering no ill effects (Holaday and Castrow

1968; Mancianti et al. 1990; Carroll et al. 1994). Congenital melanoma may give rise to multiple prenatal or postnatal metastases, including the lymph nodes and liver (Naraysingh and Busby 1986; Campbell et al. 1987; Schneiderman et al. 1987; Ishii et al. 1991). In the case of Schneiderman and coworkers (1987), a huge dorsal malignant melanoma found in a fetus delivered at 33 weeks' gestation had given rise to multiple pulmonary and placental metastases and to two liver metastases, one subcapsular and the other internally. The authors emphasized that the liver metastases contained scant melanin, whereas the placental metastases contained abundant melanin.

Animal-Type/Equine-Type Melanoma

A minority of pigmented skin neoplasms in humans, characterized by nodules of heavily melanized cells and low mitotic rate, resemble melanocytic neoplasms observed in horses and laboratory animals. The primary tumors are asymmetrical, predominantly intradermal neoplasms formed of deeply pigmented, round or short, spindle-shaped dendritic melanocytes with some degree of nuclear hyperchromatism and a single nucleolus, but with only minor nuclear atypia and low mitotic count. A prominent population of pigment-containing macrophages (melanophages/melanophores) is invariably present. The biology of disease of these animal-type melanomas is complex and unpredictable (Crowson et al. 1999; Kazakov et al. 2004; Ludgate et al. 2010). They show a long indolent phase, but may then metastasize. Liver metastasis has been reported (Levene 1979; Crowson et al. 1999; Anthony et al. 2006; Ludgate et al. 2010).

Pigmented Epithelioid Melanocytoma (PEM)

PEM is a low-grade melanocytic tumor (or a unique variant of low-grade melanoma) with a distinct locoregional metastatic potential (Zembowicz et al. 2004). PEM occurs sporadically or in the context of the Carney complex (complex of spotty skin pigmentation, myxomas, endocrine hyperactivity, and schwannomas; reviews: Boikos and Stratakis 2006; Boikos and Stratakis 2007) caused by mutations of the protein kinase A regulatory subunit type 1 alpha, coded by the PRKAR1A gene (Stratakis 2002). Loss of expression of this PKA subunit has been found in PEM, but not in malignant melanoma or other melanocytic lesions (Zembowicz et al. 2007). The lesions chiefly occur in the skin of the extremities, and the sometimes ulcerated tumors are formed by deep dermal proliferation of heavily pigmented epithelioid and/or spindled melanocytes. PEM tends to produce lymph node metastases, but the clinical course is usually indolent. In a series of 41 consecutive PEM, only one patient developed liver metastases (Zembowicz et al. 2004).

Neurocutaneous Melanosis

Neurocutaneous melanosis (NCM; OMIM 249400) is a rare phakomatosis characterized by a focal or diffuse proliferation of melanin-containing cells in both the skin and the leptomeninges, with a high risk of melanoma formation, mainly in the CNS (review: Di Rocco et al. 2004). NCM is thought to be caused by a migration disorder of neural crest-derived progenitor cells. About two thirds of patients with NCM have giant congenital melanocytic nevi; the remaining third exhibits numerous nevoid lesions but no giant nevi. In a study of 39 reported cases, most patients presented in the first 2 years of life with neurologic manifestations of CNS mass lesions, increased intracranial pressure, or spinal cord compression. Leptomeningeal melanoma was found in 62 % of the cases, but even in the absence of melanoma, symptomatic NCM had an extremely poor prognosis (Kadonaga and Frieden 1991). In an adult man with NCM, multiple primary intracranial melanomas developed, and autopsy showed numerous hepatic melanoma metastases (Arunkumar et al. 2001).

Melanotic Neuroectodermal Tumors of Infancy (Melanotic Progonoma)

Melanotic neuroectodermal tumor of infancy (MNTI; synonyms: melanotic progonoma; retinal anlage tumor; pigmented neuroectodermal tumor of infancy; pigmented epulis; melanotic ameloblastoma/adamantinoma; melanotic epithelial odontoma), first described 1918 (Krompecher 1918), is a rare neoplasm affecting infants, with a peak between the second and sixth month of age. A small number of cases have been reported in older children and adults. Only 8.9 % of the manifestations of MNTI were found at an age more than 12 months (Kruse-Lösler et al. 2006).

In the oldest reports, the lesion was termed melanotic epithelial odontoma (Mummery and Pitts 1926), congenital melanocarcinoma of the jaw (Dudits and Szabo 1935), and unusual melanoma of the alveolus and maxilla (Söderberg and Padgett 1941). Stowens (1957) believed that the tumor resembled the vomeronasal organ of Jacobson and assumed that the tumor may represent an atavism of sensory neuroectodermal origin, therefore proposing the term melanotic progonoma. In a first detailed literature covering reported cases until 1981, 139 patients with MNTI were identified (Hupp et al. 1981). Between 1900 and 2004, 140 patients could be reviewed, and the authors identified a total of 355 cases reported between 1918 and 2004 (Kruse-Lösler et al. 2006). This tumor is discussed in the present chapter owing to its likely derivation, similar to melanoma, from neural crest cells.

Most commonly the neoplasms affect the maxilla of infants during the first year of life (68–80 %), but it may also develop in the mandible (5.8 %), other regions of the skull (10.8 %), dura, brain, pineal gland, epididymis, ovary, uterus, mediastinum, and long bones. MNTI is commonly slow-growing and appears benign, but the tumors show a rapid expansile growth and a rather high rate of recurrence, and a minority of the lesions have a frankly malignant potential, with metastatic spread.

Histologically, the tumor cells resemble abnormal and often heavily melanized melanocytes, with variable complements of melanosomes, but there is also a subset of cells resembling neuroblasts. The pigmented cells are arranged either as strands or clusters often forming the lining of small cleft-like or tubular spaces, or as alveolar structures surrounded by a fibrovascular stroma. Ultrastructurally, the pigment corresponds to the cutaneous type of neural crest-type melanin (Stiller et al. 1983). Many tumor cells contain a single cilium. The blast-like cells are immunoreactive for synaptophysin and neuron-specific enolase, whereas the larger, and in part pigmented, epithelioid cells are positive for HMB-45 and vimentin.

Malignant varieties of MNTI may metastasize, including the lymph nodes (De Chiara et al. 1992) and liver (Schulz 1957; Lindahl 1970; Dehner et al. 1979; Block et al. 1980). Hepatic metastases histologically show small and dark, blast-like cells and thus resemble those of neuroblastoma (Dehner et al. 1979; Block et al. 1980). In the patient described by Block and coworkers (1980), locally recurrent tumor started to spread first to cervical lymph nodes, followed by lymph node metastasis to nearly all major lymph node groups above and below the diaphragm and to the visceral pleura, the bone marrow, and the liver. At autopsy, the liver showed multiple grayish to hemorrhagic metastatic nodules. Histologically, clusters and clumps of small, nonpigmented cells were also found outside the gross metastases, mainly within sinusoids. A hepatic intrasinusoidal growth pattern was also reported by Dehner et al. (1979).

Differential Diagnosis of Metastatic Liver Melanoma: Rare Other Melanotic Neoplasms Metastasizing to the Liver

Apart from malignant melanoma, other tumors may contain melanin, and part of them have been found to metastasize to the liver, giving rise to differential diagnostic problems in biopsies. They include pigmented squamous cell carcinoma (Jurado et al. 1998), pigmented mucoepidermoid carcinoma (Takeda and Kurose 2006), heavily pigmented renal cell carcinoma (Rossi et al. 2009), pigmented neuroendocrine tumors

(Iihara et al. 2002), primary clear cell sarcoma (Taminelli et al. 2005), melanotic schwannoma (Janzer and Makek 1983), and meningeal melanocytoma (Wang et al. 2007).

Historical Outline of Melanotic Liver Tumors

The 50-year-old female patient reported by von Frerichs exhibited hepatic melanoma, the other melanoma manifestations being restricted to the retroperitoneal lymph nodes, lung, and pleura (von Frerichs 1861). Nencki and Sieber reported on a patient with exclusive localization of a sarcomatoid melanoma to the liver, with formation of an enormous liver tumor, but had to admit that the orbits were not examined (Nencki and Sieber 1888). Hanot and Gilbert, in their monograph on diseases of the liver (1888), mention a case of melanoma apparently primary to the liver. An early case (53-year-old male) by Nazari (1906) was described as a primary melanosarcoma of the liver. Autopsy revealed a partly melanized tumor with nut- to orange-sized nodes mainly in the left liver lobe and a granite-like aspect of the right liver lobe. The carefully performed necropsy did not show any other potential primary tumor, but there is no information regarding the eyes. Ewing, in his *Neoplastic Diseases*, quotes Rolleston as referring to nine cases reported as primary melanoma of the liver. He also mentions a case of Johnston's of a large pigmented tumor of the liver with no demonstrable primary tumor found elsewhere. Early observations reveal the sometimes unique gross aspect of liver melanoma, which impressed the authors. Mansson (1926) described a 4-year-old boy with signs of Addison's disease who had, based on autopsy findings, a multinodular malignant melanoma primary to the liver, with coal-black nodules having destroyed most of the parenchyma, associated with massive ascites. If this patient really suffered from primary hepatic melanoma, this would be the youngest patient reported. This boy, however, suffered from extensive skin pigmentations, which were interpreted to be due to Addison's disease, but a skin biopsy is not reported, leaving the question of a melanotic disorder open. The 68-year-old female patient described by Smith (1926) had atrophic liver cirrhosis in the final stage, with rapidly evolving jaundice and death. Necropsy showed a cirrhotic liver with an extraordinary color, which "was a mottled yellowish-greenish black resembling granite. The cut section of the liver presented the same mottled granite surface. Throughout the organ there were areas of black or gray which resembled the anthracosis usually in the lungs and mediastinal lymph nodes. The retroperitoneal lymph nodes, which were enlarged to almond size, in the region of the bile ducts, showed similar pigmented changes." The gross features resembled the change termed Welch's cirrhosis hepatis anthracotica (Welch 1891). Histologically, the tumor cells were epithelioid or spindled and contained large amounts of melanin pigment, representing malignant melanoma. At no time did the physical examination of the patient or the subsequent examination at necropsy reveal any potential tumor nodule or pigmented nevus which could be considered as a possible primary focus. Part of the neoplastic cells had assumed an alveolar growth pattern. The patient of Brandt had a tumor in the liver termed melanocytoblastoma, without any other pigmented lesion at autopsy (Brandt 1930). Koch described the case of 35-year-old female patient with massive hepatomegaly owing to liver melanoma in the absence of nevi or any other melanoma manifestations, including the eyes. At necropsy, the liver weighed 7,990 g and contained numerous blackish nodules (Koch 1930). An autopsy case described in 1937 (Konschegg and Hada 1937) was interpreted as primary "melanotic liver carcinoma" but was clearly a malignant melanoma. Lence's case (1937) was 31-year-old female having died of endometritis puerperalis suppurativa. Autopsy revealed a melanotic liver tumor ("melanosarcoma hepatis cum necrosi disseminata textus hepatici"), i.e., malignant melanoma. No other melanotic lesions were seen, and there were neither nevi, skin scars, or ocular findings (Lence 1937). The 58-year-old patient died of metastasizing melanoma with involvement of all internal organs, except the brain, adrenals, and

spleen. The liver as a primary site of the melanoma was purported based on the fact that the liver manifestations were exceedingly large and that the liver cells contained a brown and coarse pigment showing the same histochemical features as the pigment in the melanoma cells, in the absence of generalized melanosis, suggesting a transition from pigmented hepatocytes to the tumor. However, when carefully reading the original report, including the histochemical appendix written by Hada, there is strong suspicion that this patient may have had Dubin-Johnson's syndrome with liver metastases of a malignant melanoma having arisen elsewhere. The case of Gong and coworkers (2008) was a 36-year-old male patient with a well-defined, solitary and oval, low-dense liver mass (right lobe) in CT, measuring 12.8 × 10.1 cm. This mass had been detected in a routine checkup. The mass was resected and shown to be a rather hypomelanotic malignant melanoma.

Visceral Clear Cell Sarcomas (Melanoma of Soft Parts)

Introduction

Clear cell sarcoma (CCS; previously also termed melanoma of soft parts) is a distinctive soft tissue malignancy that shows melanocytic differentiation. CCS also develops in the skin and causes difficulties in the differential diagnosis from primary malignant melanoma (Hantschke et al. 2010). CCS differs from malignant melanoma in the expression of mismatch repair proteins (Garcia et al. 2006a), and in contrast to malignant melanoma, CCS cells are CD117-negative (Garcia et al. 2006b), and CCS differs from malignant melanoma in the expression of mismatch repair proteins (Garcia et al. 2006b).

CCS has a specific genetic background that includes the chromosomal translocations, t(12;22)(q13;q12), causing an EWSR1/ATF1 chimeric gene, or t(2;22)(q34;q12), causing an EWSR1/CREB1 fusion gene (Zucman et al. 1993; Antonescu et al. 2002; Panagopoulos et al. 2002; Jishage et al. 2003; Wang et al. 2009; Song et al. 2010). Four types of EWS-ATF1 chimeric transcripts, termed types 1–4, have been identified. The most frequent chimeric transcript (type 1) is an in-frame fusion of exon 8 of EWS with exon 4 of ATF1. The type 2 transcript of EWS-ATF1 is an in-frame fusion of exon 7 of EWS with exon 5 of ATF1, that of type 3 an in-frame fusion of EWS exon 10 with ATF1 exon 5, while type 4 is an in-frame fusion of EWS exon 7 with ATF1 exon 7 (Panagopoulos et al. 2002). The EWS-CREB1 fusion characterized CCS located in the gastrointestinal tract (Antonescu et al. 2006).

CCS rarely occurs in the gastrointestinal tract, including the stomach, jejunum, ileum, and colon (Donner et al. 1998; Fukuda et al. 2000; Taminelli et al. 2005; Antonescu et al. 2006; Granville et al. 2006; Marcon et al. 2007; Lagmay et al. 2009; Terazawa et al. 2009) and has been reported to have either the EWS-ATF1 fusion (Granville et al. 2006) or the EWS-CREB1 fusion (Antonescu et al. 2006). It may occur in association with IgG4-related sclerosing disease (Joo et al. 2009). A subset of GIT tumors resembling malignant melanoma in fact show t(12;22)(q13;q12) translocation causing the EWS-ATF1 fusion and are therefore visceral CCS (Covinsky et al. 2005).

Clear Cell Sarcoma Metastasis of the Liver

Primary CCS of the liver has not yet been reported, but metastatic liver disease was described. Primary CCS of the small intestine metastasized to the liver (Taminelli et al. 2005; Joo et al. 2009). Multiple liver metastases were also observed following resection of CCS of the rectus sheath (Xu et al. 2007). Extensive metastasis to liver and lung was noted in a young patient with CCS primary to the kidney (Rubin et al. 1999). Histologically, CCS is characterized by diffuse sheet-like or nested patterns of usually large and round cells with a pale, slightly eosinophilic to clear cytoplasm and nuclear pleomorphism. Nuclei are vesicular with prominent nucleoli, and numerous mitotic figures are in

evidence. The nests or sheets are separated from each other by a delicate vascularized connective tissue. Immunohistochemically, the cells are reactive for vimentin, Melan-A, HMB-45, calponin, and S100 protein.

Clear cell sarcoma-like tumor with osteoclast-like giant cells of the gastrointestinal tract (osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts): A malignant tumor spreading to the liver

In 2003, six cases of a novel tumor entity has been reported, characterized by CCS associated with osteoclast-like multinuclear giant cells (Zambrano et al. 2003). Five of the cases were located in the small bowel and one in the stomach. The age of patients ranged from 13 to 37 years. The neoplasms behaved aggressively, with metastases to the locoregional lymph nodes, liver, and other intraabdominal sites. The neoplasms consist of medium-sized, predominantly oval, relatively monomorphic cells that are diffusely immunoreactive for S-100 protein, but are negative for CD117 and HMB-45. The giant cells are positive for CD68, a macrophage marker. The tumor displays t(12;22)(q13;q12), as in CCS of the soft parts (Zambrano et al. 2003; Friedrichs et al. 2005). The lesion has been described in a later reports, the tumor being situated in the stomach or the small bowel (Friedrichs et al. 2005; Huang et al. 2006; review: Kosemehmetoglu and Folpe 2010). In contrast to the original description, a later case was HMB-45 positive and Melan-A positive (Friedrichs et al. 2005).

References

Abdelli N, Thiefin G, Diebold MD, Rodriguez JD, Varini E, Zeitoun P (1996) Endoscopic retrograde cholangiography in a metastatic melanoma of the gallbladder presenting as a gallstone migration. Endoscopy 28:402

Adel'shinova SA (1969) Melanoma of the liver (in Russian). Ter Arkh 41:120–121

Allen AC, Spitz S (1953) Malignant melanoma – a clinicopathological analysis of the criteria for diagnosis and prognosis. Cancer 6:1–45

Anderson JB, Hughes RG, Williamson RC (1983) Malignant melanoma of the gallbladder. Postgrad Med J 59:390–391

Antonescu CR, Tschernyavsky SJ, Woodruff JM, Jungbluth AA, Brennan MF, Ladanyi M (2002) Molecular diagnosis of clear cell sarcoma: detection of EWS-ATF1 and MITF-M transcripts and histopathological and ultrastructural analysis of 12 cases. J Mol Diagn 4:44–52

Antonescu CR, Nafa K, Segal NH, Dal Cin P, Ladanyi M (2006) EWS-CREB1: a recurrent variant fusion in clear cell sarcoma – association with gastrointestinal location and absence of melanocytic differentiation. Clin Cancer Res 12:5356–5362

Antony FC, Sanclemente G, Shaikh H, Trelles AS, Calonje E (2006) Pigment synthesizing melanoma (so-called animal type melanoma): a clinicopathological study of 14 cases of a poorly known distinctive variant of melanoma. Histopathology 48:754–762

Armbruster C (1973) Pancreatocephaloduodenectomy for melanoma metastasis in the terminal ductus choledochus (in German). Zentralbl Chir 98:681–682

ArunKumar et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/1129238

Ataergin S, Tasar M, Solchaga L, Ozet A, Arpaci F (2009) Unusual severe complication following transarterial chemoembolization for metastatic malignant melanoma: giant intrahepatic cysts and fatal hepatic failure. Cardiovasc Intervent Radiol 32:361–364

Avila NA, Shawker TH, Fraker D (1994) Color-flow ultrasonography in metastatic melanoma of the gallbladder. J Clin Ultrasound 22:342–347

Bakalian S, Marshall JC, Logan P, Faingold D, Maloney S, Di Cesare S, Martins C, Fernandes BF, Burnier MN (2008) Molecular pathways mediating liver metastasis in patients with uveal melanoma. Clin Cancer Res 14:951–956

Balthazar EJ, Javors B (1975) The radiology corner. Malignant melanoma of the gallbladder. Am J Gastroenterol 64:332–335

Bedikian AY, Legha SS, Mavligit G, Carrasco CH, Khorana S, Plager C, Papadopoulos N, Benjamin RS (1995) Treatment of uveal melanoma metastatic to the liver: a review of the M.D. Anderson Cancer Center experience and prognostic factors. Cancer 76:1665–1670

Bedo F, Hoffer L, Bély M, Fekete G (1996) Isolated metastasis in the gallbladder from malignant cutaneous melanoma discovered by ultrasound (in Hungarian). Orv Hetil 137:1427–1428

Bejarano Gonzalez N, Garcia Moforte N, Darnell Martin A, Dinares Fernandez MC, Laporte Rosello E, Navarro Soto S (2005) Primary malignant melanoma of the common bile duct: a case report and literature review. Gastroenterol Hepatol 28:382–384

Block A (1875) Ueber ein primäres melanotisches Endotheliom der Leber. Arch Heilfd 16:412–418
Block et al. 1980. http://www.ncbi.nlm.nih.gov/pubmed/6244526
Boikos SA, Stratakis CA (2006) Carney complex: pathology and molecular genetics. Neuroendocrinology 83:189–199
Boikos SA, Stratakis CA (2007) Carney complex. The first 20 years. Curr Opin Oncol 19:24–29
Boj E (1954) Case of primary malignant melanoma of the liver according to world literature; review and critical evaluation of cases of primary malignant pigmented tumors of the liver (in Polish). Patol Pol 5:17–24
Borja SR, Meyer WR, Cahill JP (1984) Malignant melanoma of the gallbladder. Report of a case. Cancer 54:929–931
Bouloux PM, Scott RJ, Goligher JE, Kindell C (1986) Fulminant hepatic failure secondary to diffuse liver infiltration by melanoma. J R Soc Med 79:302–303
Bowdler DA, Leach RD (1982) Metastatic intrabiliary melanoma. Clin Oncol 8:251–255
Bramkamp M, Dedes KJ, Strobel K, Pahnke J, Breitenstein S, Clavien PA (2007) Cholestasis from malignant melanoma. J Clin Oncol 25:725–726
Brandt M (1930) Melano cytoblastom der leber zeitschrf krebsforsch 31:254–262
Breatnach E, Luna R, Rubin E, Alexander B (1985) Malignant melanoma presenting as a mass obstructing the common bile duct. J Comput Tomogr 9:177–180
Brodsky I, Baren M, Kahn SB, Lewis G, Tellem M (1965) Metastatic malignant melanoma from other to foetus. Cancer 18:1048–1054
Bundy AL, Ritchie WG (1982) Ultrasonic diagnosis of metastatic melanoma of the gallbladder presenting as acute cholecystitis. J Clin Ultrasound 10:285–287
Busam KJ, Chen YT, Old LJ, Stockert E, Iversen K, Coplan KA, Rosai J, Barnhill RL, Jungbluth AA (1998) Expression of melan-A (MART1) in benign melanocytic nevi and primary cutaneous malignant melanoma. Am J Surg Pathol 22:976–982
Caballero-Mednoza E, Gallo-Reynoso S, Arista-Nasr J, Angeles-Angeles A (1999) Obstructive jaundice as the first clinical manifestation of a metastatic malignant melanoma in the ampulla of Vater. J Clin Gastroenterol 29:188–189
Callender GR (1931) Malignant melanotic tumors of the eye: a study of histological types in 111 cases. Trans Am Acad Ophthalmol Otolaryngol 36:131–142
Callender GR, Wilder HC (1935) Melanoma of the choroid: the prognostic significance of argyrophil fibers. Am J Cancer 25:251–258
Campbell WA, Storlazzi E, Vintzileos AM, Wu A, Schneiderman H, Nochimson DJ (1987) Fetal malignant melanoma: ultrasound presentation and review of the literature. Obstet Gynecol 70:434–439
Cardot-Leccia N, Dahman M, Effi B, Chevallier A, Sejor E, Michiels JF, Saint-Paul MC (2005) A solitary tumor of the common bile duct: case report of a metastatic melanoma (in French). Gastroenterol Clin Biol 29:1177–1179
Carle G, Lessells AM, Best PV (1981) Malignant melanoma of the gallbladder: a case report. Cancer 48:2318–2322
Carroll CB, Ceballos P, Perry AE, Mihm MC, Spencer SK (1994) Severely atypical medium-sized congenital nevus with widespread satellitosis and placental deposits in a neonate: the problem of congenital melanoma and its stimulants. J Am Acad Dermatol 30:825–828
Carstens HB, Ghazi C, Carnighan RH, Brewer MS (1986) Primary malignant melanoma of the common bile duct. Hum Pathol 17:1282–1285
Caya JG, Spivey M, Tieu TM, Hansen R, Wollenberg NJ (1983) Budd-Chiari syndrome complicating metastatic ocular melanoma in a patient not receiving chemotherapy. Am J Gastroenterol 78:826–829
Cellerino P, Corsi F, Morandi E, Foschi D, Trabucchi E (2000) Metastatic melanoma of the gallbladder. Eur J Surg Oncol 26:815–816
Chang SH, Worley LA, Onken MD, Harbour JW (2008) Prognostic biomarkers in uveal melanoma: evidence for a stem cell-like phenotype associated with metastasis. Melanoma Res 18:191–200
Coe HE (1925) Malignant pigmented mole in an infant. Northwest Med 24:181–182
Cohen AJ, Thompson LD, Jaques DP, d'Avis JC (1990) Biliary tract melanoma. Mil Med 155:5–8
Cole HS, Freston JW (1973) Recurrent melanoma presenting with obstructive jaundice. Report of two cases. Rocky Mt Med J 70:42–46
Colovic RB, Grubor NM, Jovanovic MD, Micev MT, Colovic NR (2007) Metastatic melanoma to the common bile duct causing obstructive jaundice: a case report. World J Gastroenterol 13:813–815
Cooperman AM, Weiland LH, Welch JS (1976) Massive bleeding from a ruptured metastatic hepatic melanoma treated by hepatic lobectomy. Case report an review of the literature. Mayo Clin Proc 51:167–170
Coupland SE, Campbell I, Damato B (2008) Routes of extraocular extension of uveal melanoma: risk factors and influence on survival probability. Ophthalmology 115:1778–1785
Covinsky M, Gong S, Rajaram V, Perry A, Pfeifer J (2005) EWS-ATF1 fusion transcripts in gastrointestinal tumors previously diagnosed as malignant melanoma. Hum Pathol 36:74–81
Crippa S, Bovo G, Romano F, Mussi C, Uggeri F (2004) melanoma metastatic to the gallbladder and small bowel: report of a case and review of the literature. Melanoma Res 14:427–430
Crowson AN, Magro CM, Mihm MC (1999) Malignant melanoma with prominent pigment synthesis: "animal type" melanoma – a clinical and histological study of six cases with a consideration of other melanocytic neoplasms with prominent pigment synthesis. Hum Pathol 30:543–550

Dadras SS (2011) Molecular diagnostics in melanoma. Current status and perspectives. Arch Pathol Lab Med 135:860–869

Das Gupta T, Brasfield R (1964) Metastatic melanoma: a clinicopathological study. Cancer 17:1323–1339

Das Gupta TK, Brasfield RD, Paglia MA (1969) Primary melanoma in unusual sites. Surg Gynecol Obstet 128:841

Das Gupta T, Bowden L, Berg JW (1963) Malignant melanoma of unknown primary origin. Surg Gynecol Obstet 117:341–345

Daunt N, King DM (1982) Metastatic melanoma in the biliary tree. Br J Radiol 55:873–874

Dayani PN, Gould JE, Brown DB, Sharma KV, Linette GP, Harbour JW (2009) Hepatic metastasis from uveal melanoma: angiographic pattern predictive of survival after hepatic arterial chemoembolization. Arch Ophthalmol 127:628–632

De Castro ML, Tardio A, Hernandez V, Martinez A, Dominguez F, Clofent J (2007) Acute liver failure secondary to malignant infiltration by melanoma (in Spanish). Rev Esp Enferm Dig 99:49–50

De Chiara A, Van Tomout JM, Hachitanda Y, Ortega JA, Shimada H (1992) Melanotic neuroectodermal tumor of infancy. A case report of paratesticular primary with lymph node involvement. Am J Pediatr Hematol Oncol 14:356–360

Dehner et al. 1979. http://www.ncbi.nlm.nih.gov/pubmed/221089

De Simone P, Mainente P, Bedin N (2000) Gallbladder melanoma mimicking acute acalculous cholecystitis. Surg Endosc 14:593

Deugnier Y, Turlin B, Léhry D, Pennarun JR, Verger P, Launois B, Ramée MP (1991) Malignant melanoma of the hepatic and common bile ducts. A case report and review of the literature. Arch Pathol Lab Med 115:915–917

Di Rocco et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/14576958

Dong XD, DeMatos P, Prieto VG, Seigler HF (1999) Melanoma of the gallbladder: a review of cases seen at Duke University Medical Center. Cancer 85:32–39

Donner LR, Trompler RA, Dobin S (1998) Clear cell sarcoma of the ileum: the crucial role of cytogenetics for the diagnosis. Am J Surg Pathol 22:121–124

Donoso LA, Shields JA, Augsburger JJ, Orth DH, Johnson P (1985) Metastatic uveal melanoma: diffuse hepatic metastasis in a patient with concurrent normal serum liver enzyme levels and liver scan. Arch Ophthalmol 103:758

Dousei T, Miyata M, Yamaguchi T, Nagaoka M, Takahashi E, Kawashima Y (1991) Rupture of liver metastasis of malignant melanoma – a case of hepatic resection. Jpn J Surg 21:480–484

Dudits A and Szabo B (1935) Kongenitales melano karzinom des oberkiefers. Monatsschr Kinderh 63:294–302

Duval CW (1908) Melanoma of Vater's diverticulum and lower portion of common bile duct causing complete obstruction. J Exp Med 10:465–475

England MD, Sarr MG (1990) Metastatic melanoma: an unusual cause of obstructive jaundice. Surgery 107:595–596

Feigl J, Querner E (1917) Untersuchungen über Melanurie. Dtsch Arch Klin Med 123:107

Figueiredo A, Caissie AL, Callejo SA, McLean IW, Gold P, Burnier MN (2003) Cyclooxygenase-2 expression in uveal melanoma: novel classification of mixed-cell-type tumours. Can J Ophthalmol 38:352–356

Fléchon A, Lombard-Bohas C, Saurin JC, Ponchon T, Partensky C, Scoazec JY (2002) Malignant melanoma presenting as an ampullary tumour. Histopathology 41:562–563

Folberg et al. 2006. http://www.ncbi.nlm.nih.gov/pubmed/1698855

Friedrichs N, Testi MA, Moiraghi L, Modena P, Paggen E, Plötner A, Wiechmann V et al (2005) Clear cell sarcoma-like tumor with osteoclast-like giant cells in the small bowel: further evidence for a new tumor entity. Int J Surg Pathol 13:313–318

Fukuda T, Kakihara T, Baba K, Yamaki T, Yamaguchi T, Suzuki T (2000) Clear cell sarcoma arising in the transverse colon. Pathol Int 50:412–416

Furuta M, Suto H, Nakamoto S, Suzuki R, Hirai Y, Asanuma K (1995) MRI of malignant melanoma of the liver. Radiat Med 13:143–145

Garas G, Bramston B, Edmunds SE (2000) Malignant melanoma metastatic to the common bile duct. J Gastroenterol Hepatol 15:1348–1351

Garcia JJ, Kramer MJ, O'Donnell RJ, Horvai AE (2006a) Mismatch repair protein expression and microsatellite instability: a comparison of clear cell sarcoma of soft parts and metastatic melanoma. Mod Pathol 19:950–957

Garcia JJ, Kramer MJ, Mackey ZB, O'Donnell RJ, Horvai AE (2006b) Utility of CD117 immunoreactivity in differentiating metastatic melanoma from clear cell sarcoma. Arch Pathol Lab Med 130:343–348

Gassler N, Banafsche M, Quentmeier A, Otto HF, Helmke BM (2004) Secondary malignant melanoma of the gallbladder. A contribution to the differential diagnosis of pigmented lesions of the gallbladder (in German). Pathologe 25:155–159

Gates J, Kane RA, Hartnell GG (1996) Primary biliary tract malignant melanoma. Abdom Imaging 21:453–455

Gawenda M, Franzen D, Lorenzen J, Müller U (1995) Brain and gallbladder metastases 10 years after local excision of a cutaneous malignant melanoma (in German). Dtsch Med Wochenschr 120:289–292

Gogas J, Mantas D, Gogas H, Kouskos E, Markopoulos C, Vgenopoulou S (2003) Metastatic melanoma in the gallbladder: report of a case. Surg Today 33:135–137

Goldin EG (1990) Malignant melanoma metastatic to the gallbladder. Case report and review of the literature. Am Surg 56:369–373

Gong et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18756609

Gonzalez QH, Medina-Franco H, Aldrete JS (2001) Melanoma of bile ducts. Report of a case and review of the literature (in Spanish). Rev Gastroenterol Mex 66:150–152

Granville L, Hicks J, Popek E, Dishop M, Tatevian N, Lopez-Terrada D (2006) Visceral clear cell sarcoma of soft tissue with confirmation by EWS-ATF1 fusion detection. Ultrastruct Pathol 30:11–118

Grasso RF, Bonomo G, Chiappa A, Orsi F, Zbar AP, Mazzarol G, Bellomi M (2003) Malignant metastatic melanoma of common bile duct: virtual CT cholangioscopy. Hepato-Gastroenterology 50: 1333–1335

Greer CH (1966) Congenital melanoma of the anterior uvea. Arch Ophthalmol 76:77–78

Guerini A, Gottardi D, Galassi A, Armani A, Biondani L, Candiani V, Venza E (1990) Malignant melanoma of the gallbladder. Case report and review of the literature. Arch Anat Cytol Pathol 38:168–170

Guida M, Cramarossa A, Gentile A, Benvestito S, De Fazio M, Sanbiasi D, Crucitta E, De Lena M (2002) Metastatic malignant melanoma of the gallbladder: a case report and review of the literature. Melanoma Res 12:619–625

Habeck JO (1993) Primary malignant melanoma of the gallbladder. Case report and literature review (in German). Zentralbl Pathol 139:367–371

Hahn ST, Park SH, Choi HS, Kim CY, Shinn KS, Kim CS (1993) Ultrasonographic features of metastatic melanoma of the gallbladder. J Clin Ultrasound 21:542–546

Hallal H, Vilaplana-Garcia R, Garcia-Solano J, Perez-Mila L (1999) Metastatic melanoma in the gallbladder (in Spanish). Gastroenterol Hepatol 22:161–162

Hanot V, Gilbert A (1888) Etude sur les maladies du foie. Asselin and Houzeau, Paris

Hantschke M, Mentzel T, Rütten A, Palmedo G, Calonje E, Lazar AJ, Kutzner H (2010) Cutaneous clear cell sarcoma: a clinicopathologic, immunohistochemical, and molecular analysis of 12 cases emphasizing its distinction from dermal melanoma. Am J Surg Pathol 34:216–222

Hatae Y, Kikuchi M, Segawa M, Yonemitsu K (1978) Malignant melanoma of the gallbladder. Pathol Res Pract 163:281–287

Hatanaka N, Miyata M, Kamiike W, Okumura K, Hashimoto T, Yamaguchi T, Kishino Y, Sakurai M, Matsuda H (1993) Radical resection of primary malignant melanoma of the gallbladder with multiple metastases: report of a case. Surg Today 23:1023–1026

Heath DI, Womack C (1988) Primary malignant melanoma of the gall bladder. J Clin Pathol 41:1073–1077

Henriques C (1955) A case of secondary melanoma of the gall-bladder presenting as acute cholecystitis. Br J Surg 42:663–665

Herrington JL (1965) Metastatic malignant melanoma of the gallbladder masquerading as cholelithiasis. Am J Surg 109:676–678

Higgins CM, Strutton GM (1995) Malignant melanoma of the gall bladder – does primary melanoma exist ? Pathology 27:312–314

Holaday WJ, Castrow FF (1968) Placental metastasis from a fetal giant pigmented nevus. Arch Dermatol 98:486–488

Holland E (1949) A case of transplacental metastases of malignant melanoma from mother to foetus. J Obstet Gynaecol Br Emp 56:529

Holloway BJ, King DM (1997) Ultrasound diagnosis of metastatic melanoma of the gallbladder. Br J Radiol 70:1122–1125

Hosonuma K, Sato K, Takagi H, Mashimo T, Saruya T, Takahashi H, Horiuchi K, Honma M, Mori M (2005) Hepatic metastasis from choroidal malignant melanoma developing 15 years after enucleation (in Japanese). Nippon Shokakibyo Gakkai Zasshi 102:1201–1206

Hu XR (2006) A case of primary malignant melanoma of the liver. Zhonghua Fangshexue Zazhi 40:1115

Huang W, Zhang X, Li D, Chen J, Meng K, Wang Y, Lu Z, Zhou X (2006) Osteoclast-rich tumor of the gastrointestinal tract with features resembling those of clear cell sarcoma of soft parts. Virchows Arch 448:200–203

Hupp et al. 1981. http://www.ncbi.nlm.nih.gov/pubmed/6286519

Ihara N, Yashiro N, Kinoshita T, Yoshigi J, Ouchi T, Narita M, Hattori C, Kaneko N (2001) Diffuse intrasinusoidal liver metastasis of small cell lung cancer causing fulminant hepatic failure: CT findings – a case report. Radiat Med 19:275–277

Iihara K, Yamaguchi K, Fujioka Y, Uno S (2002) Pigmented neuroendocrine tumor of the lung, showing neuromelanin. Pathol Int 52:734–739

Ishii N, Ichiyama S, Saito S, Kurosawa T, Nakajima H (1991) Congenital malignant melanoma. Br J Dermatol 124:492–494

Janzer RC, Makek M (1983) Intraoral malignant melanotic schwannoma. Ultrastructural evidence for melanogenesis by Schwann's cells. Arch Pathol Lab Med 107:298–301

Jishage M, Fujino T, Yamazaki Y, Kuroda H, Nakamura T (2003) Identification of target genes for EWS/ATF-1 chimeric transcription factor. Oncogene 22:41–49

Jones CH (1961) Malignant melanoma of the gall-bladder. J Pathol Bacteriol 81:423–430

Joo M, Chang SH, Kim H, Gardner JM, Ro JY (2009) Primary gastrointestinal clear cell sarcoma: report of 2 cases, one case associated with IgG4-related sclerosing disease, and review of literature. Ann Diagn Pathol 13:30–35

Jose L, Montero JM, Sivia DL, Heras RO, Enrique F, Manuel DM (2002) Acute liver failure caused by diffuse hepatic melanoma infiltration. J Hepatol 37:540–541

Jurado I, Saez A, Luelmo J, Diaz J, Mendez I, Rey M (1998) Pigmented squamous cell carcinoma of the skin: report of two cases and review of the literature. Am J Dermatopathol 20:578–581

Kadonaga and Frieden 1991. http://www.ncbi.nlm.nih.gov/pubmed/1869648
Kaplan GG, Medlicott S, Culleton B, Laupland KB (2005) Acute hepatic failure and multi-system organ failure secondary to replacement of the liver with metastatic melanoma. BMC Cancer 5:67
Katz KA, Jonasch E, Hodi FS (2005) Melanoma of unknown primary: experience at Massachusetts General Hospital and Dana-Farber Cancer Institute. Melanoma Res 15:77–82
Katz SC, Bowne WB, Wolchok JD, Busam KJ, Jaques DP, Coit DG (2007) Surgical management of melanoma of the gallbladder: a report of 13 cases and review of the literature. Am J Surg 193:493–497
Kazakov DV, Rütten A, Kempf W, Michel M (2004) Melanoma with prominent pigment synthesis (animal-type melanoma): a case report with ultrastructural studies. Am J Dermatopathol 26:290–297
Kazmann HA, Zukaukas CL (1956) Malignant melanoma of the gallbladder. Am J Surg 92:469–471
Koch R (1930) Primäres Lebermelanom (primary melanoma of the liver). Virchows Arch Pathol Anat Histopathol 277:489–497
Kodjikian L, Grange J-D, Baldo S, Baillif S, Garweg JG, Rivoire M (2005) Prognostic factors of liver metastases from uveal melanoma. Graefe's Arch Clin Exp Ophthalmol 243:985–993
Kohler B, Riemann JF (1987) Obstructive jaundice due to an intraductal melanoma metastasis. Endoscopy 19:79–80
Köhler U, Jacobi T, Sebastian G, Nagel M (2000) Laparoscopic cholecystectomy in isolated gallbladder metastasis of malignant melanoma. Chirurg 71:1517–1520
Konschegg T, Hada A (1937) Malignes primäres Lebermelanom (primary malignant melanoma of the liver). Zeitschr Pathol 51:499–508
Kosemehmetoglu K, Folpe AL (2010) Clear cell sarcoma of tendons and aponeuroses, and osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: a review and update. J Clin Pathol 63:416–423
Koyama T, Murakami M, Nishihara O, Masuda T (1996) Congenital melanoma: a case suggesting rhabdomyogenic differentiation. Pediatr Dermatol 13:389–393
Krompecher E (1918) Zur Histogenese und Morphologie der Adamantinome und sonstiger Kiefergeschwülste. Beitr Path Anat 64:165–197
Kruse-Lösler B, Gaertner C, Bürger H, Seper L, Joos U, Kleinheinz J (2006) Melanotic neuroectodermal tumor of infancy: systematic review of the literature and presentation of a case. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102:204–216
Labver NV, McLaughlin ME, Duker JS (2010) Ocular melanoma. Arch Pathol Lab Med 134:1778–1784
Lagmay JP, Ranalli M, Arcilla M, Baker P (2009) Clear cell sarcoma of the stomach. Pediatr Blood Cancer 53:214–216
Langley RG, Bailey EM, Sober AJ (1997) Acute cholecystitis from metastatic melanoma to the gall-bladder in a patient with a low-risk melanoma. Br J Dermatol 136:279–282
Larmi TK (1960) Malignant melanoma of the gallbladder. Report of a case resulting in an external biliary fistula. Acta Chir Scand 119:502–505
Lence P (1937) Über seltene primäre Lokalisationen melanotischer Tumoren. Ergebn Allgem Path Pathol Anat Menschen Tiere 32:48–90
Lesur et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1463316
Levene A (1979) Disseminated dermal melanocytosis terminating in melanoma. Br J Dermatol 101:197
Li HC, Xu HB, Wang HM (2003) A case of malignant melanoma of the liver showing an enormous cystic occupy (sic; in Chinese). Zhonghua Zhongliu Zazhi 25:110
Lindahl 1970. http://www.ncbi.nlm.nih.gov/pubmed/4320020
Longwitz D, Schulz HG, Bosse A (1996) Malignant melanoma of the gallbladder (in German). Ultraschall Med 17:195–198
Lorigan JG, Wallace S, Mavligit GM (1991) The prevalence and location of metastases from ocular melanoma: imaging study in 110 patients. AJR Am J Roentgenol 157:1279–1281
Lubarsch O (1920) Zur vergleichenden Pathologie der melanotischen Gewächse. Med Klin (Wochenschr f prakt Ärzte) 14(8):195–199
Ludgate MV, Fullen DR, Lee J, Rees R, Sabel MS, Wong SL, Johnson TM (2010) Animal-type melanoma: a clinical and histopathological study of 22 cases from a single institution. Br J Dermatol 162:129–136
Luther A (1900) Ueber melanotische Geschwülste (On melanotic tumors). Thesis, Leipzig 1900/01
Luyten et al. 1996. http://www.ncbi.nlm.nih.gov/pubmed/8621261
Mancianti et al. 1990. http://www.ncbi.nlm.nih.gov/pubmed/1877645
Mansson PA (1926) Ett fall av melanosarcom I levern, som kliniskt företedde bilden av Morbus Banti + Morbus Addisonii. Hygieia Medicinsk Tidskrift (Stockholm) 88:359–364
Marcon N, Montagne K, Corby S, Ayav A, Plénat F, Champigneulle J (2007) Primary clear cell sarcoma of the ileum (in French). Ann Pathol 27:369–372
Mariani P, Piperno-Neumann S, Servois V, Berry MG, Dorval T, Plancher C, Couturier J, Levy-Gabriel C et al (2009) Surgical management of liver metastases from uveal melanoma: 16 years' experience at the Institute Curie. Eur J Surg Oncol 35:1192–1197
Marone U, Caraco C, Losito S, Daponte A, Chiofalo MG, Mori S, Cerra R, Pezzullo L, Mozzillo N (2007) Laparoscopic cholecystectomy for melanoma metastatic to the gallbladder: is it an adequate surgical procedure? Report of a case and review of the literature. World J Surg Oncol 5:141

Martel JP, Mclean CA, Rankin RN (2009) Melanoma of the gallbladder. Radiographics 29:291–296

Martelli O, Coppola L, De Quarto AL, Palma M, Sarmiento R, Foggi CM (2000) Fulminant hepatic failure caused by diffuse intrasinusoidal metastatic liver disease: a case report. Tumori 86:424–427

McArthur MS, Teergarden DK (1983) Metastatic melanoma presenting as obstructive jaundice with hemobilia. Am J Surg 145:830–832

McFadden PM, Krementz ET, McKinnon WM, Pararo LL, Ryan RF (1979) Metastatic melanoma of the gallbladder. Cancer 44:1802–1808

McLean IW, Foster WD, Zimmerman LE, Martin DG (1980) Inferred natural history of uveal melanoma. Invest Ophthalmol Vis Sci 19:760–770

McLean IW, Foster WD, Zimmerman LE (1982) Uveal melanoma: location, size, cell type, and enucleation as risk factors in metastasis. Hum Pathol 13:123–132

McLean IW, Saraiva VS, Burnier MN (2004) Pathological and prognostic features of uveal melanomas. Can J Ophthalmol 39:343–350

Medina V, Darnell A, Bejarano N, Falco J, Musulen E, Martin J (2003) Primary biliary tract malignant melanoma: US, CT, and MR findings. Abdom Imaging 28:842–846

Milton GW, Shaw HM, McCarthy WH (1977) Occult primary malignant melanoma: factors influencing survival. Br J Surg 64:805–808

Montero JL, Muntané J, de las Heras S, Ortega R, Fraga E, De la Mata M (2002) Acute liver failure caused by diffuse hepatic melanoma infiltration. J Hepatol 37:540–541

Muehlenberg K, Wardelmann E (1992) Acute liver failure in metastatic melanoma (in German). Leber Magen Darm 22:192–194

Mummery and Pitts 1926. http://www.ncbi.nlm.nih.gov/pubmed/19985112

Murphy MN, Lorimer SM, Glennon PE (1987) Metastatic melanoma of the gallbladder: a case report and review of the literature. J Surg Oncol 34:68–72

Naguib SE, Aterman K (1984) Presumed primary malignant melanoma of the gallbladder. Report of a case and a review of the literature. Am J Dermatopathol 6 (suppl):231–243

Naraysingh V, Busby GO (1986) Congenital malignant melanoma. J Pediatr Surg 21:81–82

Nazari A (1906) Contributo allo studio dei sarcomi primitivi del fegato (contribution to the study of primary sarcomas of the liver). Il Policlinico. Periodico di Medicina. Chirurgia e Igiene (Roma) 13:360–369

Nelms JK, Patel JA, Atkinson DP, Raves JJ (2007) Metastatic malignant melanoma of the gallbladder presenting as biliary colic: a case report and review of literature. Am Surg 73:833–835

Nencki M, Sieber N (1888) Weitere Beiträge zur Kenntnis der tierischen Melanine. Arch Exp Pathol 24:17

Newton FH (1965) Malignant melanoma of choroid. Report of a case with clinical history of 36 years and follow up of 32 years. Arch Ophthalmol 73:198–199

O'Connell JB, Whittemore DM, Russell JC, Ellis WA, Becker DR (1984) Malignant melanoma metastatic to the cystic and common bile ducts. Cancer 53:184–186

Ogan H, Sirmaci N, Alyanak S, Goral S (1961) Melanoblastoma of the liver presenting with melanuria (in Turkish). Turk Tip Cemiy Mecm 27:591–594

Ohsie SJ, Sarantopoulos GP, Cochran AJ, Binder SW (2008) Immunohistochemical characteristics of melanoma. J Cutan Pathol 35:433–444

Onken MD, Worley LA, Ehlers JP, Harbour JW (2004) Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. Cancer Res 64:7205–7209

Onken MD, Ehlers JP, Worley LA, Makita J, Yokota Y, Harbour JW (2006) Functional gene expression analysis uncovers phenotypic switch in aggressive uveal melanomas. Cancer Res 66:4602–4609

Ostick DG, Haqqani MT (1976) Obstructive cholecystitis due to metastatic melanoma. Postgrad Med J 52:710–712

Palazzi MA, Ober MD, Abreu HF, Cardinalli IA, Isaac CR, Odashiro AN, Burnier MN (2005) Congenital uveal malignant melanoma: a case report. Can J Ophthalmol 40:611–615

Panagopoulos I, Mertens F, Débiec-Rychter M, Isaksson M, Limon J, Kardas I, Domanski HA et al (2002) Molecular genetic characterization of the EWS/ATF1 fusion gene in clear cell sarcoma of tendons and aponeuroses. Int J Cancer 99:560–567

Paolini O, Rampal A, Caroli-Bosc FX, Desruelles F, Ortonne JP, Delmont JP (1999) Vesicular metastasis of malignant melanoma revealed by recurrent hepatic colic crises (in French). Gastroenterol Clin Biol 23:412–414

Parquier JN, Peetrons P, Liénard D, Maisonnier H, Jeanmart L (1991) Jaundice secondary to a metastasis of a malignant melanoma at the level of the common bile duct (in French). J Belg Radiol 74:201–204

Patel JK, Didolkar MS, Pickren JW, Moore RH (1978) Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. Am J Surg 135:807–810

Pautler EE, Gallavan EM (1951) Melanoma of brain and gallbladder. AMA Arch Pathol 51:238–245

Pawlik TM, Zorzi D, Abdalla EK, Clary BM, Gershenwald JE, Ross MI, Alioa TA, Curley SA et al (2006) Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease. Ann Surg Oncol 13:712–720

Peison B, Rabin L (1976) Malignant melanoma of the gallbladder: report of three cases and review of the literature. Cancer 37:2448–2454

Pichon N, Delage-Corre M, Paraf F (2004) Hepatic metastatic miliaria from a malignant melanoma: 2 case reports (in French). Gastroenterol Clin Biol 28:593–595

Prieto and Shea 2011. http://www.ncbi.nlm.nih.gov/pubmed/21732774

Radhakrishnan A, Badhrinarayanan N, Biswas J, Krishnakumar S (2009) Analysis of chromosomal

aberration (1,3, and 8) and association of microRNAs in uveal melanoma. Mol Vis 15:2146–2154
Raffensperger EC, Brason FW, Triano G (1963) Primary melanoma of the gallbladder. Am J Dig Dis 8:356–363
Rahhal FE, Schade RR, Nayak A, Coleman TA (2009) Hepatic failure caused by plasma cell infiltration in multiple myeloma. World J Gastroenterol 15:2038–2040
Rea DJ, van Heerden JA (2004) Image of the month. Malignant melanoma of the gallbladder (primary vs. secondary). Arch Surg 139:1383–1384
Rehani B, Strohmeyer P, Jacobs M, Mantil J (2006) Gallbladder metastasis from malignant melanoma: diagnosis with FDG PET/CT. Clin Nucl Med 31:812–813
Rezanko T, Bolat B, Gelai F, Ekinci N, Aksoz K (2008) Metastatic melanoma of the common bile duct diagnosed with brush cytology. Cytopathology 19:200–201
Ricci R, Maggiano N, Martini M, Mulé AM, Pierconti F, Capelli A, Larocca LM (2001) Primary malignant melanoma of the gallbladder in dysplastic naevus syndrome. Virchows Arch 438:159–165
Richardson SK, Tannous ZS, Mihm MC (2002) Congenital and infantile melanoma: a review of the literature and report of an uncommon variant, pigment-synthesizing melanoma. J Am Acad Dermatol 47:77–90
Romero M, Bianchi L, Vilana R (2006) Melanoma metastasis to the gallbladder (in Spanish). Radiologia 48:321–323
Rose et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11485537
Rosenthal SR (1931) Primary melanocarcinoma of the gallbladder. Am J Cancer 15:2288–2300
Rossi G, Cadioli A, Costantini M, Grazia Del Buono M, Oleari G (2009) Heavily pigmented renal cell carcinoma: a case report, with review of the literature and differential diagnosis. Int J Surg Pathol 17:167–169
Rothberg BE, Moeder CB, Kluger H, Halaban R, Elder DE, Murphy GF, Lazar A, Prieto V et al (2008) Nuclear to non-nuclear Pmel17/gp100 expression (HMB45 staining) as a discriminator between benign and malignant melanocytic lesions. Mod Pathol 21:1121–1129
Rowbotham D, Wendon J, Williams R (1998) Acute liver failure secondary to hepatic infiltration: a single center experience of 18 cases. Gut 42:576–580
Rubin BP, Fletcher JA, Renshaw AA (1999) Clear cell sarcoma of soft parts: report of a case primary in the kidney with cytogenetic confirmation. Am J Surg Pathol 23:589–594
Rubio S, Barbero-Villares A, Reina T, Nieto S, Mendoza J, Garcia-Buey L (2005) Rapidly-progressive liver failure secondary to melanoma infiltration. Gasteroenterol Hepatol 28:619–621
Rudolph A, Bothe J, Bonk U (1985) Malignant melanoma of the gallbladder (in German). Chirurg 56:469–471
Safioleas M, Agapitos E, Kontzoglou K, Stamatakos M, Safioleas P, Mouzopoulos G, Kostakis A (2006) Primary melanoma of the gallbladder: does it exist? Report of a case and review of the literature. World J Gastroenterol 12:4259–4261
Samplaski MK, Rosato EL, Witkiewicz AK, Mastrangelo MJ, Berger AC (2008) Malignant melanoma of the gallbladder: a report of two cases and review of the literature. J Gastrointest Surg 12:1123–1126
Sans M, Llach J, Bordas JM, Andreu V, Campo A, Castells A, Mondelo E, Teres J, Rodes J (1996) Metastatic malignant melanoma of the papilla of Vater: an unusual case of obstructive cholestasis treated with biliary prostheses. Endoscopy 28:791–792
Saoshiro T, Negishi M, Hayashi A, Etou T (1996) Malignant melanoma of the gallbladder (in Japanese). Ryokibetsu Shokogun Shirizu 9:240–242
Schneiderman H, Wu AY, Campbell WA, Forouhar F, Yamase H, Greenstein R, Grant-Kels JM (1987) Congenital melanoma with multiple prenatal metastases. Cancer 60:1371–1377
Schulz D (1957) A malignant melanotic neoplasm of the uterus resembling the retinal anlage tumor. Am J Clin Pathol 28:524–532
Seelig MH, Schönleben K (1997) Laparoscopic cholecystectomy for a metastasis of a malignant melanoma in the gallbladder. Z Gastroenterol 35:673–675
Seul B, Lüchtrath H (1984) Malignant melanoma of the gallbladder (in German). Chirurg 55:179–181
Shan GD, Xu GQ, Chen LH, Wang ZM, Jin EY, Hu FL, Li YM (2009) Diffuse liver infiltration by melanoma of unknown primary origin: one case report and literature review. Intern Med 48:2093–2096
Sharma KV, Gould JE, Harbour JW, Linette GP, Pilgram TK, Dayani PN, Brown DB (2008) Hepatic arterial chemoembolization for management of metastatic melanoma. AJR Am J Roentgenol 190:99–104
Shepherd FJ (1908) XI. Melanotic sarcoma of the common bile duct, etc. Ann Surg 47:948–952
Shimkin PM, Soloway MS, Jaffe E (1972) Metastatic melanoma of the gallbladder. Am J Roentgenol Radium Ther Nucl Med 116:393–395
Sierra-Callejas JL, Warecka K (1976) Primary malignant melanoma of the gallbladder. Virchows Arch A Pathol Anat Histol 370:233–238
Simard C, George P, Caulet T, Diebold J (1966) Les mélanomes malins de la vésicule biliaire. J Chir (Paris) 92:51
Singh AD, Topham A (2003) Incidence of uveal melanoma in the United States: 1973–1997. Ophthalmology 110:956–961
Singh AD, Shields CL, Shields JA (2001) Prognostic factors in uveal melanoma. Melanoma Res 11:255–263
Smith LW (1926) Four unusual malignant tumors of the liver. With four plates. Arch Pathol Lab Med 1:365–382
Söderberg NB, Padgett EC (1941) Two unusual melanomas of the alveolus and maxilla. Am J Orthodont Oral Surg 27:A270–A274
Song JS, Choi J, Kim JH, Jang SJ, Cho KJ (2010) Diagnostic utility of EWS break-apart fluorescence in situ hybridization in distinguishing between non-cutaneous melanoma and clear cell sarcoma. Pathol Int 60:608–613

Stiller D, Herrmann P, Holzhausen HJ (1983) Melanotic ectodermal tumor of infancy (melanotic progonoma) – an unusual soft tissue tumor (in German). Zentralbl Allg Pathol 128:307–316

Stowens D (1957) A pigmented tumor of infancy: the melanotic progonoma. J path 73:43–51

Stratakis CA (2002) Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit (PRKAR1A) in patients with the "complex of spotty skin pigmentation, myxomas, endocrine hyperactivity, and schwannomas " (Carney complex). Ann NY Acad Sci 968:3–21

Stutte H, Müller PH, d'Hoedt B, Stroebel W (1989) Ultrasonographic diagnosis of melanoma metastasis in liver, gallbladder, and spleen. J Ultrasound Med 8:541–547

Sweet LK, Connerty HV (1941) Congenital melanoma: report of a case in which antenatal metastasis occurred. Am J Dis Child 62:1029–1040

Tacquet A, Clay A, Guerrin F, Demaille A (1959) Case of probably primary melanoma of the liver (in French). Arch Mal Appar Dig Mal Nutr 48:89–92

Takayama Y, Asayama Y, Yoshimitsu K, Irie H, Tajima T, Hirakawa M, Ishigami K, Kakihara D et al (2007) Metastatic melanoma of the gallbladder. Comput Med Imaging Graph 31:469–471

Takeda Y, Kurose A (2006) Pigmented mucoepidermoid carcinoma, a case report and review of the literature on melanin-pigmented salivary gland tumors. J Oral Sci 48:253–256

Taminelli L, Zaman K, Gengler C, Peloponissios N, Bouzourene H, Coindre JM, Histein I, Guillou L (2005) Primary clear cell sarcoma of the ileum: an uncommon and misleading site. Virchows Arch 447:772–777

Tanaka M, Watanabe S, Masaki T, Kurokohchi K, Kinekawa F, Inoue H, Uchida N, Kuriyama S (2004) Fulminant hepatic failure caused by malignant melanoma of unknown primary origin. J Gastroenterol 39:804–806

Te HS, Schiano TD, Kahaleh M, Lissoos TW, Baker AL, Hart J, Conjeevaram HS (1999) Fulminant hepatic failure secondary to malignant melanoma: case report an review of the literature. Am J Gastroenterol 94:262–266

Terazawa K, Otsuka H, Morita N, Yamashita K, Nishitani H (2009) Clear-cell sarcoma of the small intestine detected by FDG-PET/CT during comprehensive examination of an inflammatory reaction. J Med Invest 56:70–75

Thayer KH, Williams OO, Rowe D (1955) Malignant melanoma of the gallbladder; report of a case and review of the literature. Ariz Med 12:15–18

Thompson JF, Mathur MN, Coates AS (1993) Common bile duct obstruction due to intraluminal metastatic melanoma. Aust NZ J Surg 63:502–504

Trolet J, Hupé P, Huon I, Lebigot I, Decraene C, Delattre O, Sastre-Garau X, Saule S, Thiéry JP et al (2009) Genomic profiling and identification of high-risk uveal melanoma by array CGH analysis of primary tumors and liver metastases. Invest Ophthalmol Vis Sci 50:2572–2580

Tuveri M, Tuveri A (2007) Isolated metastatic melanoma to the gallbladder: is laparoscopic cholecystectomy indicated?: a case report and review of the literature. Surg Laparosc Endosc Percutan Tech 17:141–144

Uchikov A, Genova S, Dimitrov I, Entchev A, Dimov R, Stefanov C (2004) A case of melanoma metastatic to the gallbladder and the common bile duct with clinical presentation of obstructive jaundice and bilirubinemia. J BUON 9:317–319

Van Bokhoven MM, Arntzen EH, Tan AC (2006) Metastatic melanoma of the common bile duct and ampulla of Vater. Gastrointest Endosc 63:873–874

Van Gils et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18552379

Varsamidakis N, Panagiotou P, Yettimis E (2006) Isolated gallbladder metastatic melanoma. HPB (Oxford) 8:73

Velez AF, Penetrante RB, Spellman JE, Orozco A, Karakousis CP (1995) Malignant melanoma of the gallbladder: report of a case and review of the literature. Am Surg 61:1095–1098

Verbanck JJ, Rutgeerts LJ, van Aelst FJ, Tytgat JH, Decoster JM, Noyez DN, Theunynck PJ, Geboes KJ (1986) Primary malignant melanoma of the gallbladder, metastatic to the common bile duct. Gastroenterology 91:214–218

Vidal-Vanaclocha F (2008) The prometastatic microenvironment of the liver. Cancer Microenviron 1:113–129

Vido I, Hupka S, Brixova E (1964) Melanoblastoma of the liver. Case report. Acta Hepatosplenol 11:102–106

Von Frerichs FTh (1861) Klinik der Leberkrankheiten, 2nd edn, 2 vols. Friedrich Vieweg and son, Braunschweig

Wagner MS, Shoup M, Pickleman J, Yong S (2000) Primary malignant melanoma of the common bile duct: a case report and review of the literature. Arch Pathol Lab Med 124:419–422

Walsh TS (1956) Primary melanoma of the gallbladder with cervical metastasis and fourteen and a half year survival; first histologically proved case. Cancer 9:518–522

Wang CF, An DJ, Zhang C (2005) A case of primary malignant melanoma of the liver. Zhonghua Gandanyi Waike Zazhi 11:480

Wang et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17542513

Wang WL, Mayordomo E, Zhang W, Hernandez VS, Tuvin D, Garcia L, Jev DC et al (2009) Detection and characterization of EWSR1/ATF1 and EWSR1/CREB1 chimeric transcripts in clear cell sarcoma (melanoma of soft parts). Mod Pathol 22:1201–1209

Washburn WK, Noda S, Lewis WD, Jenkins RL (1995) Primary malignant melanoma of the biliary tract. Liver Transpl Surg 1:103–106

Welch WH (1891) A case of cirrhosis hepatis anthracotica. Bull Johns Hopkins Hosp 2:32

Wieting H, Hamdi B (1907) Ueber die physiologische und pathologische Melaninpigmentierung und den epithelialen Ursprung der Melanoblastome. Ein

primäres Melanoblastom der Gallenblase. Beitr Pathol Allg Pathol 42:24–84

Wilhelm JL, Zakov ZN (1982) Choroidal malignant melanoma with liver metastasis before enucleation. Ann Ophthalmol 14:789–791

Willis RA (1952) The spread of tumours in the human body, 2nd edn. Butterworth & Co., London, p 219

Worley LA, Onken MD, Person E, Robirds D, Branson J, Char DH, Perry A, Harbour JW (2007) Transcriptomic versus chromosomal prognostic markers and clinical outcome in uveal melanoma. Clin Cancer Res 13:1466–1471

Worley LA, Long MD, Onken MD, Harbour JW (2008) Micro-RNAs associated with metastasis in uveal melanoma identified by multiplexed microarray profiling. Melanoma Res 18:184–190

Wright RA, Brewer M (1988) Primary melanoma of the common bile duct. South Med J 81:396–397

Xu GG, Chong YL, Cheong MO (2007) Clear cell sarcoma of the rectus sheath. Singap Med J 48:e203–e205

Zaide EC (1963) Malignant melanoma of the choledochus (in Portuguese). Arg Oncol 26:254–255

Zambrano E, Reyes-Mugica M, Franchi A, Rosai J (2003) An osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: reports of 6 cases of a GIST simulator. Int J Surg Pathol 11:75–81

Zembowicz A, Carney JA, Mihm MC (2004) Pigmented epithelioid melanocytoma: a low-grade melanocytic tumor with metastatic potential indistinguishable from animal-type melanoma and epithelioid blue nevus. Am J Surg Pathol 28:31–40

Zembowicz A, Knoepp SM, Bei T, Stergiopoulos S, Eng C, Mihm MC, Stratakis CA (2007) Loss of expression of protein kinase A regulatory subunit 1alpha in pigmented epithelioid melanocytoma but not in melanoma or other melanocytic lesions. Am J Surg Pathol 31:1764–1775

Zemlyn S (1966) Metastatic melanoma of the gallbladder. Radiology 87:744–745

Zhang H, Zhao JM (1995) Primary enormous malignant melanoma of the liver: a case report. Zhongguo Yike Daxue Xuebao 24:93

Zhang ZD, Myles J, Pai RP, Howard JM (1991) Malignant melanoma of the biliary tract: a case report. Surgery 109:323–328

Zimmerman LE, Mclean IW (1979) Metastatic disease from untreated uveal melanomas. Am J Ophthalmol 88:524–534

Zucman J, Delattre O, Desmaze C, Epstein AL, Stenman G, Speleman F, Fletcher CD et al (1993) EWS and ATF-1 gene fusion induced by t(12;22) translocation in malignant melanoma of soft parts. Nat Genet 4:341–345

Part XIV

Hepatobiliary Tumors with a Rhabdoid Cell Lineage

Malignant Rhabdoid Tumors and Tumors with Rhabdoid Features

78

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_78

Abstract

Several tumors are characterized by the presence of a distinct cell type, the rhabdoid cell. This cell of still unknown origin shows a striking cytoskeletal inclusion that is visualized as an eosinophilic eccentrically placed cell body. Certain neoplasms, malignant rhabdoid tumors, are entirely composed of rhabdoid cells, while numerous other tumors contain subsets of rhabdoid cells or rhabdoid-like cells (neoplasms with rhabdoid features). The presence of rhabdoid cells generally confers a highly malignant phenotype. Rhabdoid tumors consistently show absence of nuclear reactivity for the chromatin-remodeling factor, SRF5/INI1. Malignant rhabdoid tumor is a well-known cancer of the kidney, but it also rarely occurs as a primary tumor in the liver of infants and children and exceptionally in adolescents and adults. The liver can also be involved in a rare and fatal condition of early infancy, congenital disseminated malignant rhabdoid tumor. There are few other complex pediatric liver neoplasms with rhabdoid cell elements. In adults, several hepatobiliary neoplasms, including cholangiocarcinoma, can exhibit rhabdoid features.

The Rhabdoid Tumor Family

Malignant rhabdoid tumor (MRT) is a rare and high-grade neoplasm chiefly occurring in infants and very young children and more uncommonly in adults. MRT was first described as an aggressive, rhabdomyosarcomatoid variant of Wilms' tumor (Beckwith and Palmer 1978) and later confirmed to be a distinct clinicopathologic entity of pediatric renal tumors, under the term rhabdoid tumor (Palmer and Sutow 1983; Weeks et al. 1989a; Berry and Vujanic 1992; Beckwith 2002; Tomlinson et al. 2005). Early, the term "rhabdomyoblastoma" has been used as synonymous with RT (Hajdu 1986), but there is no evidence of a myoblast lineage involved in these neoplasms. All of these lesions are characterized by a distinct, albeit intriguing, cell, the rhabdoid cell. Cancer cells showing morphologic changes resembling a rhabdoid cell are termed cells with rhabdoid features.

The Rhabdoid Cell, Hallmark of Rhabdoid Tumors

The term, rhabdoid cell, may have been chosen to suggest some resemblance to an immature rhabdomyoid cell, but it correctly derives from the Greek word *rhabdoides*, which means shaped like a rod or striped, and is thus a misleading term for describing the morphologically distinct cell found in RT. The rhabdoid cell, whether being the leading cell type of a neoplasm or only representing one tumor cell type among others (tumors with rhabdoid features), is now known to act as a highly aggressive indicator of many malignant tumors. The characteristic cytoskeletal inclusion has been analyzed on a molecular level. By investigating the complete human CK8 gene, it surfaced that all MRT samples have missense mutations in the human KRT 8 gene, none of which was found in any control samples. Remarkably, some of these mutations involve domains known to be important for lateral protofilament-protofilament interactions, mutations in MRT thus probably causing conformational changes of cytokeratins in RT (Shiratsuchi et al. 2002). There are cytoplasmic structures which mimic the inclusions seen in RT. "Pseudo-rhabdoid cells" have, e.g., been found in pancreatic endocrine neoplasms (Chetty and Asa 2004), and these inclusions are characterized by whorls of intermediate filaments with entrapped neurosecretory granules (Shia et al. 2004). The cells of RT seem to be capable to undergo epithelial differentiation, with production of a basal lamina and convergent tight junctions (Seo et al. 1988).

Classifications of Rhabdoid Tumors and Tumors with Rhabdoid Features

Apart from the "classical" renal RT, the first example of an RT, several extrarenal tumors containing rhabdoid cells have been described (Weeks

et al. 1989b). Extrarenal RT is now conceived as a counterpart of RT of the kidney and had formerly been defined as a distinct tumor type based largely or entirely on the cytological resemblance of its constituent cells to those of classical renal RT, characterized by the typical cytoplasmic inclusions (Parham et al. 1994). Later, the concept of extrarenal RTs has been modified, based on the observation of so-called rhabdoid cells (Sobrinho-Simoes 1991; or "hyaline cells") in numerous neoplasms not obviously directly related RT. Malignant tumors containing variable amounts of rhabdoid cells commonly exhibit a more aggressive biology. Therefore, the identification of rhabdoid features is an important diagnostic procedure.

The nomenclature of the lesions is not yet standardized. Several terms have been employed to denote the presence of rhabdoid cells or rhabdoid-like cells in neoplasms, including rhabdoid tumors, tumors with rhabdoid features, rhabdoid phenotype, rhabdoid differentiation, rhabdoid transformation, rhabdoid areas, and rhabdoid as an adjective preceding the name of the tumor (such as rhabdoid adenocarcinoma). Widely used are the terms extrarenal rhabdoid tumors (ERRT; related to the fact that malignant rhabdoid tumor was first described in the kidney) or malignant extrarenal rhabdoid tumors (MERT). ERRT and MERT as a discrete pathologic entity have been a controversial issue despite rather frequent reports of their occurrence (Ogino et al. 2000). Based on the heterogeneity of ERRT, it has been proposed that the term, ERRT, is not valid as representing a specific diagnostic entity and that the term "poorly differentiated neoplasm with rhabdoid features" would be preferable for these undifferentiated tumors (Parham et al. 1994). Generally, the uncertainty as to what a rhabdoid tumor might be is furthered by the observation that the leading identifier, the rhabdoid cell, is expressed in such lesions in a highly variable way, ranging from "purely" rhabdoid tumors to those with only focal rhabdoid features, raising the still open question where the cutoff value for the definition of a bona fide rhabdoid tumor might be. The conceptual discussion referring to these questions has been reviewed (Wick et al. 1995). Apart from the "classical" renal malignant rhabdoid tumor (RRT), one may tentatively group, as a working formulation (Table 1), the remaining lesions into (a) malignant extrarenal rhabdoid tumors (MERT; or ERRT, as they are also termed) which should morphologically closely reflect the renal counterpart in its original definition; (b) composite extrarenal rhabdoid tumors (CERT) in which recognizable parent neoplasms are admixed with MERT; (c) congenital disseminated RT (with or without the features of the rhabdoid tumor disposition syndrome; White et al. 1999; Fernandez et al. 2002); (d) small cell undifferentiated hepatoblastoma with rhabdoid features; and (e) tumors (usually in adults) with rhabdoid features, comprising a growing spectrum of neoplasms that have subsets of cells resembling, or corresponding to, rhabdoid or rhabdoid-like cells.

Table 1 Working formulation for the classification of malignant rhabdoid tumors (MRTs)

Renal malignant rhabdoid tumor (RMRT)
Malignant extrarenal rhabdoid tumors (MERT)
Composite extrarenal rhabdoid tumors (CERT)
Congenital disseminated RT and rhabdoid tumor disposition syndrome
Small cell undifferentiated hepatoblastoma with rhabdoid features
Intrahepatic cholangiocarcinoma with rhabdoid features
Malignancies with rhabdoid features in adults

MERT have been described at several different sites including the central nervous system (atypical teratoid tumors rhabdoid tumor/AT/RT), orbit, lung, esophagus, liver, colon, bladder, female genital tract (vulva, uterus, ovary), paratesticular area, pelvis, soft tissues, mesentery, and chest (Frierson et al. 1985; Sotelo-Avila et al. 1986; Gururangan et al. 1993; Hsueh and Chang 1996; Marcus et al. 1996; Rubenchik et al. 1996; Gunduz et al. 1998; Figarola and Khader 1999; Brand and Covert 2001; Leath et al. 2003; Ng et al. 2003; Ohgaki et al. 2003; Chang et al. 2004; Salamanca et al. 2004; Gottlieb et al. 2005; Garces-Iñigo et al. 2009). Soft tissue rhabdoid tumor (STRT) was defined as a tumor

composed of noncohesive single cells, clusters, or sheets of large tumor cells with abundant glassy eosinophilic cytoplasm, an eccentric vesicular nucleus, positivity for vimentin and/or cytokeratin or other epithelial markers, and exclusion of other neoplasms with rhabdoid inclusions (Fanburg-Smith et al. 1998). Some of the MERT are fetal or congenital tumors (Maschek et al. 1992; Pizer et al. 1997; Stidham et al. 1999; White et al. 1999; Hosli et al. 2001; Fernandez et al. 2002; Leader et al. 2002; Sajedi et al. 2002; Gottlieb et al. 2005).

Tumors with rhabdoid features, i.e., with a variable component of neoplastic cells with a rhabdoid phenotype as defined above, form a very heterogeneous group of lesions. It has not yet been defined what the minimum requirements to place such tumors into this category are. These lesions do not seem related to renal and extrarenal true rhabdoid tumors and are generally poorly differentiated tumors, the presence of cells with rhabdoid features being a hallmark of a dedifferentiated state of the neoplastic cell population, albeit with some exceptions. Neoplasms with rhabdoid features include, among others, meningiomas (Perry et al. 1998), rhabdoid glioblastoma (Kleinschmidt-DeMasters et al. 2010; Momota et al. 2011), thyroid carcinomas, including the differentiated follicular variant (Chetty and Govender 1999; Lai et al. 2005; Agarwal et al. 2006), lung carcinomas (Miyagi et al. 2000; Kaneko et al. 2002), esophagus carcinomas (Varghese et al. 2005), stomach cancer (Ueyama et al. 1993; Pinto et al. 1997), small intestinal carcinoma (Amrikachi et al. 2002), colorectal cancer (a distinct entity with a very aggressive behavior; Chetty and Bhathal 1993; Remo et al. 2012), pancreatic carcinoma (Al-Nafussi and O'Donell 1999; Kuroda et al. 2000; Cho et al. 2006), neuroendocrine tumors (Perez-Montiel et al. 2003), gastrointestinal stromal tumor (Richmond et al. 2004), renal cell carcinomas (Gokden et al. 2000; Humphrey 2011), malignant melanoma (Chang et al. 1994), squamous cell carcinomas (Aoyagi et al. 2009), proximal-type epithelioid sarcoma with rhabdoid features (Guillou et al. 1997), and other certain sarcomas (Kim et al. 2010).

Malignant Rhabdoid Tumor of the Liver in Infants and Children

Introduction

The first infant with a primary hepatic RT (hepatic MERT) was described in 1982 as a form of infantile sarcoma (Gonzalez-Crussi et al. 1982). In this work, the characteristic intracytoplasmic inclusions were recognized, but it was discussed whether the neoplasm was of histiocytic origin. Since then, several examples of infantile and childhood hepatic RT have been reported, and the majority of the lesions occurred in patients less than 1 year of age.

Selected References Sotelo-Avila et al. 1986; Parham et al. 1988, 1994; Hunt and Anderson 1990; Mann et al. 1990; Foschini et al. 1992; Maschek et al. 1992; Di Cori et al. 1993; Gururangan et al. 1993; Weyman et al. 1993; Scheimberg et al. 1996; Jimenez-Heffernan et al. 1998; Kelly et al. 1998; Donner et al. 2000; Ravindra et al. 2002; Rosito et al. 2002; Katzenstein et al. 2003; Halasz et al. 2004; Yuri et al. 2004; Kuroda et al. 2005; Clairotte et al. 2006; Jayaram et al. 2007; Wu et al. 2008; Abe et al. 2009; Abdullah et al. 2010; Trobaugh-Lotrario et al. 2011; Martelli and Liu 2013.

From these reports, it is difficult to judge whether these lesions form a distinct entity or rather a heterogeneous group of neoplasms sharing the phenomenon of a variable contribution of rhabdoid cells. This difficult issue had already been addressed in an early report (Parham et al. 1994). These authors found three hepatic tumors among 42 cases of ERRT, and each of the three was in some way different from the others. One rhabdoid lesions displayed epithelial features with a striking accumulation of tonofilaments and reactivity for epithelial markers. The second tumor had the cytohistologic features of renal RT but with areas of desmoplasia, and it was discussed whether this lesion might represent a tumor of the intra-abdominal desmoplastic small cell tumor group. The third neoplasm again shared morphologic features with renal RT, but expressed epithelial markers (Parham et al. 1994).

Clinical Features

The tumor usually presents as a right upper quadrant mass (Scheimberg et al. 1996). The serum AFP is consistently normal. Imaging shows large, homogeneous or lobulated, hypodense tumors with blurred margins, sometimes with calcifications (Jimenez-Heffernan et al. 1998). In some children with hepatic RT, hypercalcemia was observed (Jimenez-Heffernan et al. 1998; Donner et al. 2000). Hypercalcemia is known to be associated with certain pediatric renal tumors, in particular rhabdoid tumor and congenital mesoblastic nephroma, and thought to be caused by ectopic production of parathyroid hormone-related peptide (Mayes et al. 1984; Jayabose et al. 1988; Rousseau-Merck et al. 1988; McKay and Furman 1993; Papadakis et al. 1995; Amar et al. 2001). In one study, renal rhabdoid tumor was associated with hypercalcemia in 23 % of the patients (Amar et al. 2001). It has also been found that hepatic RT may secrete vasointestinal peptide causing watery diarrhea (Weyman et al. 1993). Local complications of hepatic RT include spontaneous rupture and hemorrhage (Kelly et al. 1998; Ravindra et al. 2002; Clairotte et al. 2006).

Biology of Disease

Hepatic RTs are highly aggressive neoplasms which often present with metastases at the time of diagnosis and which are difficult to treat and to cure. In a recent review of 34 patients with a median age at presentation of 8 months, 30 patients died of disease or treatment complications. Most deaths occurred within 12 months after diagnosis. Of the four patients alive without disease, all were treated with chemotherapy, and three had surgery or liver transplantation (Trobaugh-Lotrario et al. 2011).

Pathology

Macroscopy

Hepatic RTs are often large tumors, sometimes with a diameter of more than 15 cm. The masses are solitary (Kelly et al. 1998) or multinodular (Yuri et al. 2004) and present as friable, grayish white tumors with necroses and hemorrhages. The necrosis may predominate in the tumor's center, with radiating streaks of necrosis to the periphery and sometimes with formation of cystic cavities. In some cases, the main tumor mass is associated with few to numerous satellite nodules probably representing intrahepatic metastases. The cut surface is typically variegated in appearance, sometimes with pseudocyst formation. It may show a lobulated texture (Hunt and Anderson 1990). The margins of the tumor are ill-defined and infiltrative, always without capsule formation, but perifocal liver atrophy is in evidence. The tumor may breach the liver capsule and invade adjacent organs, the diaphragm, or the abdominal wall and/or surround the gallbladder, the extrahepatic biliary tract, and the inferior vena cava (Scheimberg et al. 1996). Subcapsular hematoma was noted in some cases (Kelly et al. 1998; Yuri et al. 2004). Larger tumors may undergo spontaneous rupture (Kelly et al. 1998; Ravindra et al. 2002). In one patient, a long capsular tear of the involved liver lobe was detected at laparotomy, associated with free intraperitoneal blood having caused shock (Kelly et al. 1998).

Histopathology

RTs are highly cellular neoplasms that show somewhat monotonous noncohesive or poorly cohesive sheets of cells. The neoplastic cells of RT are medium-sized to large, and round, ovoid to polygonal in shape. They may be embedded in a sometimes myxoid stroma rich in glycosaminoglycans. The cells have a vesicular or sometimes irregularly shaped nucleus showing one to several prominent nucleoli, typically with a rather clear blue color in H&E sections. At least part of the cells contain the characteristic paranuclear inclusion body which may be hyaline (Figs. 1 and 2). This paranuclear inclusion displaces the nucleus into an eccentric position. The rhabdoid features of the neoplastic cells are particularly well recognizable in aspiration cytology specimens (Akhtar et al. 1994; Yusuf et al. 1996; Pogacnik and Zidar 1997; Barroca et al. 2003). Part of the neoplastic

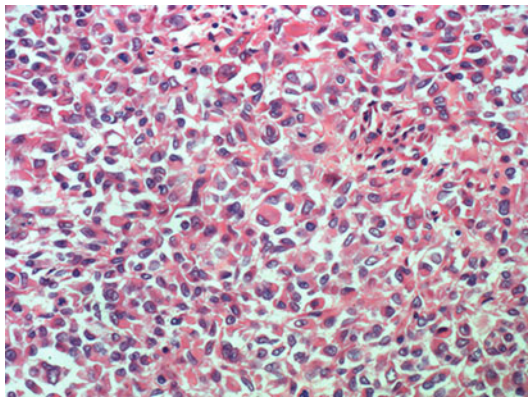

Fig. 1 Malignant rhabdoid tumor of the liver. A diffuse growth consists of mostly medium-sized cells which sometimes reveal an eccentrical eosinophilic cytoplasmic part (hematoxylin and eosin stain)

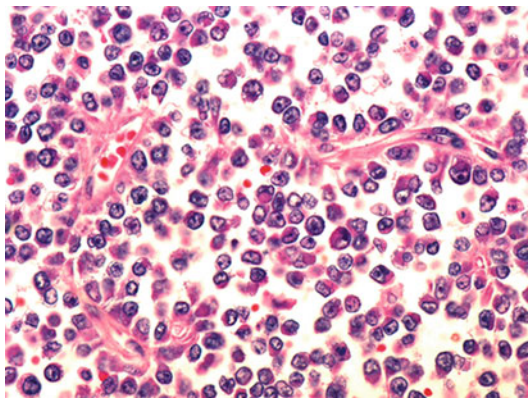

Fig. 2 Malignant rhabdoid tumor of the liver. Part of the tumor cells display a small eosinophilic paranuclear body (hematoxylin and eosin stain)

cells may reveal signs of epithelial differentiation (Parham et al. 1988). In silver stains, the neoplastic cells are grouped to nests or small clusters by reticulin fibers. The growth is markedly invasive, with intrasinusoidal invasion and entrapment of hepatocytes and small bile ducts and ductules within the tumor.

Electron Microscopy

Ultrastructurally, the cytoplasmic paranuclear inclusions are composed of whorled filaments measuring 10 nm in diameter, representing (modified) intermediate filaments of the cytoskeleton (Haas et al. 1981; Yuri et al. 2004). The dense aggregation of intermediate filaments seems to indent the adjacent nucleus, but without obliteration of the nuclear lamina and without visible alterations of peripheral chromatin structures in this region. The area containing the intermediate filament condensation displays few organelles, whereas mitochondria, elements of the SER and RER, and glycogen particles are interposed between the inclusion and the nucleus or the cytoplasmic membrane (Hunt and Anderson 1990). In peripheral part of the filament aggregate, small vesicles of the SER, mitochondria, or lipid droplets may be trapped. As an indication of epithelial differentiation, hemidesmosomes or desmosome-like structures, focal tonofilament-like condensations, and primitive junctional complexes may be encountered (Maschek et al. 1992; White et al. 1999).

Immunohistochemistry

The paranuclear inclusion bodies of renal and extrarenal RT rhabdoid cells express both CK8 and CK18 (Fig. 3; Shiratsuchi et al. 2001; Yuri et al. 2004), which seems to be a rather constant feature, and sometimes CK 7 and CK19 (Kaiserling et al. 1996; Foschini et al. 1992; Shiratsuchi et al. 2001; Yuri et al. 2004), while other cytokeratins are rarely, weakly, questionably or not expressed. There is almost constant reactivity for vimentin (Fig. 4), but not desmin and AFP. S-100 protein, neuron-specific enolase, CD99, Leu-7, GFAP, neurofilament, muscle-specific actin, alpha-1-antitrypsin, and epithelial membrane antigen (EMA) may be expressed in a variable fashion, reflecting the so-called "polyantigenic" character of RTs (Parham et al. 1988; Scheimberg et al. 1996; Machado et al. 2010). About two thirds of RT express E-cadherin, while these tumors are not reactive for beta-catenin (Saito et al. 2001). Some RT reveal immunohistochemical features of stem cells, including positivity for SALL4 and/or Lin28 (Deisch et al. 2011). RT cells are often reactive for claudin-6, which is a nonspecific

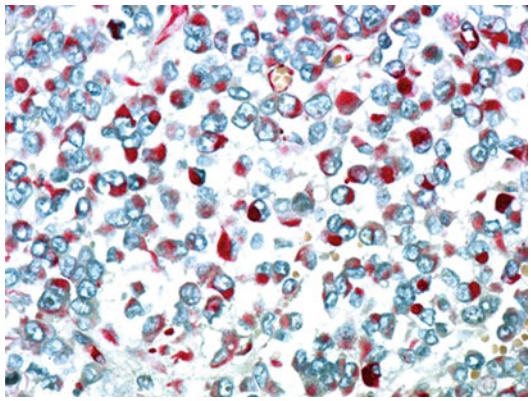

Fig. 3 Malignant rhabdoid tumor of the liver. In this cytokeratin stain, paranuclear bodies appear as *red eccentrical dots* (CAM5.2 immunostain)

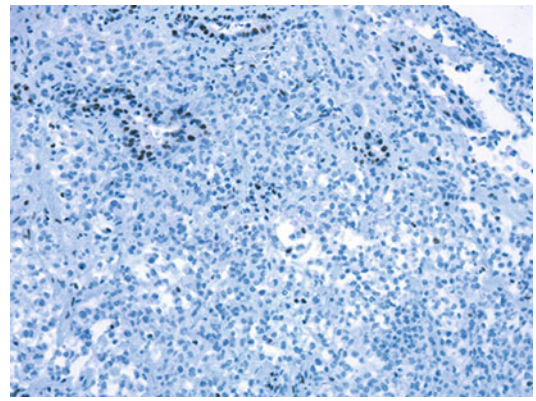

Fig. 5 Malignant rhabdoid tumor of the liver. In contrast to nuclei in normal cholangiocytes and endothelial cells, tumor cell nuclei are INI1 negative (INI1/BAF47 immunostain)

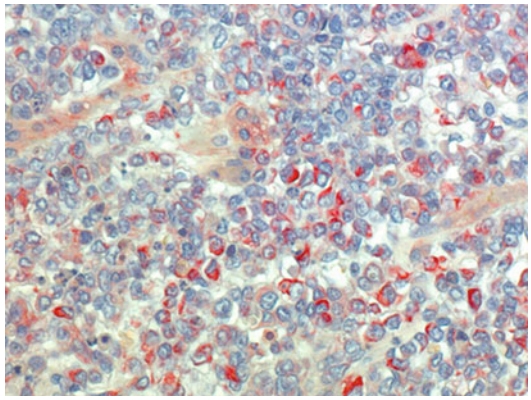

Fig. 4 Malignant rhabdoid tumor of the liver. Paranuclear bodies as visualized by vimentin expression (vimentin immunostain)

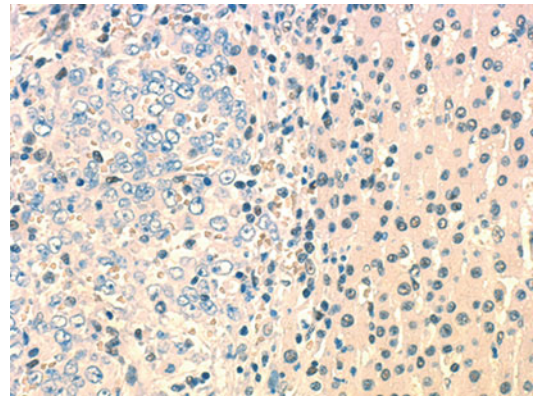

Fig. 6 Malignant rhabdoid tumor of the liver, INI1 expression pattern at higher magnification. INI1-negative tumor cells are seen to the left. Note the nuclear INI1 positivity of normal hepatocytes (to the *right*), endothelial cells, and infiltrating lymphocytes (INI1/BAF47 immunostain)

marker for malignant RT and other pediatric tumors (Sullivan et al. 2012). At least part of hepatic RT cell are reactive for glypican-3 (Kohashi et al. 2013; Chan et al. 2014).

As a central feature of pediatric rhabdoid tumor is the truncation of the hSNF5/INI1 gene (see below), nuclear expression of the respective protein has been analyzed by immunohistochemistry in such tumors. Typically, RT cells lack nuclear immunostaining for SRF5/INI1 (Figs. 5 and 6). The lacking nuclear expression of INI1 contrasts clearly with adjacent normal cells and infiltrating leukocytes, with their positive nuclear signals. The loss of the INI1 protein was observed in all RT tested, in contrast to a positive nuclear signal in non-rhabdoid neoplasms (Hoot et al. 2004; Al Nassan et al. 2010).

Differential Diagnosis

Primary hepatic RT has to be distinguished from liver metastases of RT primarily located elsewhere, predominantly in the kidney. Metastasis of rhabdoid meningioma to the liver has been reported (Wang et al. 2011).

Congenital Disseminated Malignant Rhabdoid Tumor

Congenital disseminated malignant rhabdoid tumor (CDMRT) is a rare, highly aggressive and fatal tumor of early infancy, with tumor manifestations in the CNS, kidney, liver, head and neck region, and placenta and sometimes a dominant tumor mass in various body regions. CDMRT is associated with 22q11.2 deletions or translocations (White et al. 1999; Fernandez et al. 2002; Gottlieb et al. 2005; Yurdakul et al. 2007). In a series of nine patients, five neonates had tumor evident at birth, and two of these had placental metastases (White et al. 1999).

Malignant Rhabdoid Tumor of the Liver in Adolescents and Adults

Malignant hepatic RT is a very rare neoplasm in adults (Marzano et al. 2009; Sibileau et al. 2011; Kang et al. 2013). The first two cases were observed in a 27-year-old male and a 15-year-old male, both with a heterogeneous liver tumor of 17 cm and 15 cm diameter, respectively. The tumor histology was typical for rhabdoid tumor, associated with lack of nuclear INI1 expression (Marzano et al. 2009). A young adult showed a voluminous heterogeneous, partially necrotic mass in the left liver lobe, measuring up to 17 cm in diameter, displaying RT histology, lack of INI1 expression, and a molecular analysis highly suggestive of INI1 biallelic mutation. The patient was treated with resection and chemotherapy and was alive without signs of recurrence 41 months after therapy (Sibileau et al. 2011). The patient reported by Kang and coworkers (2013) was a 50-year-old male presenting with a large hepatic mass. CT showed a very large multinodular hypoattenuating tumor with rim enhancement in the entire left lobe of the liver. A needle biopsy yielded a hypercellular tumor with necrosis and hemorrhage, composed of loosely cohesive cell clusters separated by intervening fibrous septa. The neoplastic cells showed the typical features of rhabdoid cells and were immunoreactive for cytokeratin 19 and vimentin and focally for cytokeratin 7. These cells displayed partial loss of INI1 reactivity (Kang et al. 2013).

Congenital Primitive Epithelial Tumor of the Liver with Rhabdoid Features

This is a rare congenital malignancy characterized by an immature, non-hepatocyte epithelial cell lineage with rhabdoid features and clinical manifestations mimicking disseminated neuroblastoma, with placental metastases. Autopsy of the index patient who had died at the age of 4 days showed a 6-cm yellowish tumor with marked hemorrhage in the left liver lobe and up to 2-cm multiple hemorrhagic lesions distributed in both liver lobes. Histologically, this tumor consisted of large atypical cells which often formed glandular or tubular structures and lacked blastemal features. Bizarre giant cells were scattered through the neoplasm. About 5 % of the tumor cells displayed rhabdoid features, with cytokeratin- and vimentin-positive inclusions, which showed the typical arrangement of intermediate filament aggregates in electron micrographs. Tumor emboli with occasional extravascular extension were noted in the liver, lung, heart, intestine, adrenal glands, and brain. The placenta was infiltrated by the same or similar tumor cells, often with invasion of the villous stroma and extending into the marginal sinus (Ohyama et al. 2000).

Fatal Primitive Childhood Tumor with Rhabdoid Features

Fatal primitive childhood tumor with rhabdoid features is a novel malignancy characterized by a small round cell neoplastic process with focal expression of rhabdoid features, a stromal reaction, and the potential for differentiation along different cell lineages (Gaffney and Breatnach 1989).

Hepatoblastomas with Rhabdoid Features

Part of hepatoblastomas of the small cell undifferentiated (SCUD) type show rhabdoid-like cells. These neoplasms have been termed small cell undifferentiated hepatoblastomas with rhabdoid features or SCUD-HB with rhabdoid features (Zimmermann and SIOPEL Group 2003, 2011). Later, malignant hepatic rhabdoid tumor being INI1 negative and morphologically mimicking hepatoblastoma was reported (Wagner et al. 2007). This variant of hepatoblastoma makes part of the group of hepatoblastomas with a low serum AFP level at diagnosis, a high-risk biology, poor response to chemotherapy, and poor outcome (De Ioris et al. 2008). Within a group of 11 patients with SCUD hepatoblastoma, all patients with reported AFP results exhibited normal or minimally increased serum AFP levels. None of these patients survived. Immunostaining revealed that tumors from six of six patients tested were INI1 negative (Trobaugh-Lotrario et al. 2009). Therefore, at least a subset of SCUD hepatoblastomas share morphologic and molecular features and a very aggressive course, with malignant rhabdoid tumors of the liver. Hepatoblastomas with rhabdoid features show SMARCB+/INI1 alterations (Russo and Biegel 2009).

Intrahepatic Cholangiocarcinoma with Rhabdoid Features

Intrahepatic cholangiocarcinoma with rhabdoid features (rhabdoid cholangiocarcinoma; intrahepatic cholangiocarcinoma with rhabdoid transformation) is so far classified as a rare variant of sarcomatoid cholangiocarcinoma characterized by the presence of neoplastic cells with a rhabdoid phenotype (Honda et al. 1996; Lim et al. 2004; Sugano et al. 2013). Similar to other sarcomatoid cholangiocarcinomas (Nakajima et al. 1993), the variant with rhabdoid features reveals a very aggressive course (Lim et al. 2004). In one patient, a 61-year-old female with multiple liver masses at imaging, the tumor consisted of two distinct components, i.e., a tubular adenocarcinoma and a sarcomatous component showing rhabdoid cells expressing both vimentin and cytokeratins (Honda et al. 1996). In the patient reported by Lim and coworkers (2004), a huge intrahepatic tumor in the left liver lobe measuring up to 17 cm was detected, showing extensive necrosis and hemorrhage and an infiltrative border. Viable tumor, found only in the peripheral portion of the mass, was reddish yellow to tan and hemorrhagic. Histologically, the entire neoplasm was composed of loosely cohesive, round to polygonal cells with abundant eosinophilic, glassy cytoplasm and eccentrically placed, vesicular nuclei. Close to the nuclei, the cytoplasmic bodies typical for rhabdoid cells were noted. Immunohistochemically, the tumor cells co-expressed both vimentin and epithelial markers. Some of the cells had mucin-containing vacuoles, but, in contrast to the tumor described by Honda and coworkers, a carcinomatous component was not found in this lesion.

Primary Rhabdoid Tumor of the Gallbladder

In a 46-year-old male patient, the gallbladder showed a slight thickening in the body wall, measuring 1 cm. The lesion was located on the peritoneal side, i.e., away from the liver bed. Sections from this area revealed collections of loosely arranged plump cells with the features of rhabdoid cells, which showed the typical eccentric paranuclear positivity for vimentin (Suri et al. 2003). A second case of gallbladder carcinoma with a rhabdoid component, but associated with sarcomatoid features, was reported in a 61-year-old female patient. This tumor of 4.5-cm size was situated in the neck portion of the gallbladder (Kim et al. 2003).

Intra-abdominal Tumors with Rhabdoid Features Mimicking Hepatic Neoplasms

Localized malignant peritoneal mesothelioma with rhabdoid cells appearing as a liver neoplasm has been reported (Matsukuma et al. 1996).

Pathogenesis

Distinct Presentation Patterns of RT and Their Relation to Distinct Chromosomal Changes

Apart from isolated MRT occurring in a variety of organs, there are distinct clinical MRT entities that have opened the way for the identification of molecular pathogenic pathways. As discussed below, germline mutations of the hSNF5/INI1 gene predispose children to the development of RT. However, familial cases are extremely rare. Pedigrees in which two or more individuals carry germline mutations of this gene characterize the rhabdoid predisposition syndrome (RPS). The term, RPS, was first coined in 1999 (Sevenet et al. 1999). The tumors associated with RPS include AT/RT, choroid plexus carcinoma, medulloblastoma, extrarenal RT, and rarely renal RT (Sevenet et al. 1999; Taylor et al. 2000; Lee et al. 2002a; Janson et al. 2006; review: Roberts 2006). There is evidence for a favorable outcome of patients affected by RT due to RPS (Kordes et al. 2014). The genetic causes of RPS are complex in that not all patients show mutations of the hSNF5/INI1 locus. In fact, non-linkage of familial RT to hSNF5/INI1 (SMARCB1) has implied a second locus for RPS (Frühwald et al. 2006). The complexity of RPS is furthermore illustrated by the finding of unaffected carriers in a family segregating a germline mutation of INI1 and RT, supporting the hypothesis that there may be variable risks of development of RT in the context of a germline mutation and suggesting that there may be a developmental window in which most RT occur (Janson et al. 2006).

Atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system is a distinct entity among malignant pediatric brain tumors (Briner et al. 1985; Rorke et al. 1995; Ho et al. 2000; Lee et al. 2002b; Packer et al. 2002; Wharton et al. 2003; review: Tekkok and Sav 2005). AT/RT commonly develops in the posterior fossa, similar to medulloblastoma. The tumor's incidence is still undefined, but may comprise as high as one in four primitive CNS tumors in infants (report on a workshop; Packer et al. 2002). AR/RT occurs almost exclusively in children, most of whom are 5 years old or less, but the neoplasm can also develop in adults (Raisanen et al. 2005). Histologically, AT/RT is defined as a polymorphous malignant neoplasm often featuring rhabdoid, PNET, epithelial, and mesenchymal components (Oka and Scheithauer 1999; Ho et al. 2000), these various features having led to the term, teratoid, but of course AT/RT is not a germ cell tumor. The lesion has been shown to involve aberrations of chromosome 22q (Biegel et al. 1989, 1990, 1992; Lee et al. 2002b; Wharton et al. 2003), also in adult cases (Raisanen et al. 2005), and the gene involved in this situation is hSNF5/INI1, as discussed below. Histologically, AT/RT is rarely mimicked by another unusual pediatric cerebellar tumor with rhabdoid cells and unique cytoplasmic inclusions in the presence of INI1 gene product (Sasaki et al. 2005).

Cytogenetic Features of RT and the Identification of a Relevant Rhabdoid Tumor Gene

As discussed above, numerous reports have documented anomalies of chromosome 22 in RT, chiefly deletions, translocations, and monosomy involving 22q and a chromosomal site encoding a tumor suppressor gene (Biegel et al. 1989, 1990, 1992; Schofield et al. 1996; Rosty et al. 1998; White et al. 1999; Roberts and Orkin 2004; Halliday et al. 2009; Roberts and Biegel 2009; Stojanova and Penn 2009), although other translocation partners have also been identified (Donner et al. 2000). The gene located on 22q11.2 is called hSNF5 or INI1 (BAF47; SMARCB1: SWI/SNF-related, matrix-

associated, actin-dependent regulator of chromatin). Mutations of this gene are detectable in about 75 % of patients with RT (Biegel et al. 2000; Bourdeaut et al. 2011; Hollmann and Hornick 2011). The gene product is a member of the ATP-dependent SWI/SNF chromatin-remodeling complex that was first identified as a homologue of the yeast Snf5 protein and as a protein that interacts with the HIV integrase protein (hence the alternative term, integrase interactor 1; Kalapan et al. 1994; Muchardt et al. 1995). Its role as a tumor suppressor gene in the pathogenesis of rhabdoid tumors has been reviewed (Biegel et al. 2002). However, deficient hSNF5/INI1 gene function is not restricted to rhabdoid tumors but also occurs in other neoplastic processes, including choroid plexus carcinoma, medulloblastoma, and central primitive neuroectodermal tumors (Sevenet et al. 1999) and chronic myeloid leukemia (Grand et al. 1999). In rhabdoid tumors, hSNF5/INI1 inactivation is mainly associated with homozygous deletions and mitotic recombination causing truncated gene products (Versteege et al. 1998; Rousseau-Merck et al. 1999; Uno et al. 2002; Eaton et al. 2011; Kosho et al. 2013; Shain and Pollack 2013). Gene targeting experiments confirmed that INI1 also functions as a tumor suppressor in mice. While INI1-null mice are embryonic lethal, 15–30 % of mice heterozygous for INI1 develop malignant tumors with variable rhabdoid features (Roberts et al. 2000; Guidi et al. 2001, 2004). The effects of mutationally changed INI1 on cellular functions are complex. The nuclear export of INI1 depends on a masked nuclear export signal (NES) in the highly conserved repeat 2 domain of INI1 that mediates regulated hCRM1/exportin1-dependent nuclear export, and mutations in this region cause mislocalization in the cytoplasm (Craig et al. 2002). Interestingly, rhabdoid tumors with biallelic loss of SMARCB1 have these features as almost the sole recurrent event, otherwise showing an extremely low rate of mutations (Lee et al. 2012). SMARCB1-deficient neoplasms showed downregulation of the BIN1 tumor suppressor through epigenetic mechanisms, thus identifying BIN1 as and SNF5 target gene (McKenna et al. 2012).

What Is hSNF5/INI1?

The hSNF5/INI1 (SMARCB1/Baf47) tumor suppressor is an integral component of mammalian SWI/SNF chromatin-remodeling enzymes that contain more than ten proteins, including SNF2 family ATPases BRM (Brahma in Drosophila) or BRG1 (Brahma-related gene 1; BRM), hSNF5/INI1 (BAF47), BAF155, BAF170, BAF60, and BAF57, and that contribute to the regulation of many genes (reviews: Hargreaves and Crabtree 2011; Euskirchen et al. 2012). This multisubunit machine utilizes ATP hydrolysis to modulate chromatin structure and to regulate promoter nucleosome. Generally, BAF complexes establish nucleosome occupancy patterns, which are crucial to epigenetic regulation. SMARCB1 is responsible for generating nucleosome-depleted regions or NDRs (Montecino et al. 2007; Sims et al. 2007; Lu and Roberts 2013; Tolstorukov et al. 2013; You et al. 2013). During carcinogenesis, the functions of chromatin regulators are often disrupted by genetic mutations and/or epigenetic alterations, causing genome-wide derangements of gene function (Wilson and Roberts 2011; Shu et al. 2012; reviews: Lee and Roberts 2013; Oike et al. 2013; Wang et al. 2014). The expression levels of these core SWI/SNF subunits are stoichiometric, with few or no unbound molecules in the cell. The subunit levels are regulated through protein-protein interactions and via proteasomal degradation (Chen and Archer 2005). The SWI/SNF complex also makes part of a protein complex associated with regulatory DNA sequences (locus control regions, LCR) that protect transgenes from position-effect variegation and heterochromatinization and also promote copy-number dependence of the levels of transgene expression. This LCR-associated remodeling complex (LARC) contains, apart from SWI/SNF, heterogeneous nuclear ribonucleoprotein C1/C2 and the gene silencer, nucleosome remodeling and deacetylating protein (NuRD)/MeCP1 (Mahajan et al. 2005). Truncation of INI1 causes deficient gene function, but SWI/SNF enzyme complex formation as such and the expression of many BRG1-dependent genes are independent of INI1

(Doan et al. 2004), indicating the complex construction features of this protein network. SWI/SNF chromatin-remodeling enzymes utilize the energy of ATP hydrolysis to alter histone-DNA contacts, resulting in an altered nucleosome structure that can lead to repositioning, or sliding, of nucleosomes along the DNA (Becker 2002; Becker and Horz 2002; Narlikar et al. 2002). But the entire protein network of the complexes also depends on the differential functions of single proteins involved, apart from hSNF5/INI1. Human Brahma (hBRM), a catalytic component of the SWI/SNF complex, associates with the methyl-CpG-binding protein, MeCP2, which mediates transcriptional repression of methylated genes, BRM thus being functionally linked to gene silencing (Harikrishnan et al. 2005). BRM-deficient mice also show methylation and silencing of gene promoters (Banine et al. 2005). The chromatin-remodeling and mRNA splicing functions of the Brahma complex are mediated by the SMARCB1 subunit (Zraly and Dingwall 2012).

BAF57 is a subunit in the SWI/SNF complex that is required for maintaining the proper subunit composition of the complex (Hah et al. 2010). It is associated with the BRG1 ATPase and with hBRM (human Brahma) ATPase and regulates cell cycle progression through the transcriptional regulation of certain cell cycle-related genes. Furthermore, it induces apoptosis by stimulating CYLD, the tumor suppressor involved in familial cylindromatosis, an autosomal dominant predisposition syndrome of multiple tumors of skin appendages (Wang et al. 2005). Mutations in the CYLD gene are also involved in two other disorders, Brooke-Spiegler syndrome and multiple familial trichoepithelioma (Salhi et al. 2004), all of which might however represent phenotypic variation of a single entity (Bowen et al. 2005). CYLD is a deubiquitinating enzyme (Trompouki et al. 2003) which attenuates NF-kappaB signaling by selectively removing K63-linked polyubiquitin chains (deubiquitination) that activate IkappaB kinase (IKK) which phosphorylates IkappaB, via interaction of CYLD with NEMO, the regulatory subunit of IKK (Kovalenko et al. 2003; Saito et al. 2004). CYLD also deubiquinates other proteins, including TNF receptor-associated factor 2 (TRAF2; Trompouki et al. 2003). The deubiquinating activity of CYLD is regulated via IkappaB kinase gamma-dependent phosphorylation (Reiley et al. 2005). BAF60a (BRG1-associated factor 60a) mediates critical interactions between nuclear glucocorticoid receptors and the BRG1 chromatin-remodeling complex (Hsiao et al. 2003). As other proteins, the expression of chromatin-remodeling proteins is subject to the action of distinct types of microRNAs. Studies on the differential microRNA expression profiles between malignant rhabdoid tumor and epithelioid sarcoma uncovered that microRNA193a-5p seems to downregulate SMARCB1 mRNA expression (Kohashi et al. 2014).

What Are the Cellular Actions of SWI/SNF?

Via several mechanisms, components of the SWI/SNF protein system including hSNF5/INI1 affect several cellular biochemical pathways and associated functions. Main cellular function pathways regulated by this system are the cell division cycle, cell differentiation, cytoskeletal functions, and epigenomic effects. In addition to cellular structures and components, SMARCB1 can also interact with foreign proteins, including the cytomegalovirus proteins UL114 and UL44 (Ranneberg-Nilsen et al. 2012).

Cell Division and Cell Survival

The cell cycle arrest machinery generally depends on components of SWI/SNF-related complexes (Ae et al. 2002; Betz et al. 2002; Versteege et al. 2002; Sansam and Roberts 2006; Kuwahara et al. 2010). The loss of hSNF5/INI1 function in RT-derived cells leads to polyploidization and chromosomal instability by compromising the mitotic checkpoint of the cell cycle (Imbalzano and Jones 2005; Vries et al. 2005). hSNF5/INI1 represses cyclin D1 transcription in rhabdoid cells

by directly recruiting histone deacetylase 1 complex to its promoter, and genetic ablation of cyclin D1 abrogates the genesis of rhabdoid tumors resulting from INI1 loss in INI1 heterozygous mice with targeted INI1 disruption (Tsikitis et al. 2005). Apart from the enzymatically active hSNF5/INI1, the complexes contain noncatalytic subunits, including p270/ARID1A and ARID1B. It has been shown that the p270 (ARID1A/SMARCF1) subunit is essential for normal cell cycle arrest (Nagl et al. 2005). The tumor suppressor activity of SNF5/INI1 depends on its regulation of cell cycle progression, where it interacts and cooperates with retinoblastoma protein (Chai et al. 2007). Its inactivation leads to aberrant upregulation of E2F targets and increased levels of p53 that are accompanied by apoptosis, polyploidy, and cell cycle progression or cell cycle arrest (Isakoff et al. 2005; Kato et al. 2007). One downstream target of SNF5 is Aurora kinase A. SNF5/INI1 represses Aurora A transcription in a cell-specific manner, and the loss of SNF5 function as found in RT leads to aberrant overexpression of Aurora A in these neoplasms, required for survival (Lee et al. 2011). The loss of SMARCB1, as found in rhabdoid tumor cells, is associated with persistent AKT activation, contributing to proliferation and survival (Darr et al. 2014). In RT, the core component of SNF5 can block the Hedgehog signaling effector, glioma-associated family member-1/GLI1, which promotes malignant RT growth when SNF5 is lost (Jagani et al. 2010; Reiter 2010). The loss of SNF5 phenocopied beta-catenin hyperactivation and was essential for regulating Wnt/beta-catenin pathway target expression (Mora-Blanco et al. 2014).

Cell Differentiation

Chromatin modifiers, apart from a broad array of transcription factors, are important for cell differentiation pathways (Albanese et al. 2006). In an animal model, it was shown that hepatic SNF5 deletion caused neonatal death and the formation of a hepatic epithelium was also affected in SNF5-deficient livers, due to gene misexpression, suggesting a role of chromatin remodeling in hepatic cell lineage differentiation (Gresh et al. 2005).

Cell Size, Cell Shape, Nuclear Shape, and Cell Motility

hSNF5/INI11 modulates cell growth and actin cytoskeleton organization.

It has been shown that this tumor suppressor induces marked modifications of the cell shape including complete disruption of the actin stress fiber network and disappearance of focal adhesions associated with upregulation of genes involved in the organization of the actin cytoskeleton (Medjkane et al. 2004). The chromatin-remodeling ATPase, BRG1, contributes to the regulation of overall cell size and shape. BRG1 also affects nuclear morphology. Knockdown of BRG1 induced groves in the nuclear periphery of epithelial cells, an alteration independent of cytoskeletal connections (Imbalzano et al. 2013). SMARCB1 interacts with SCAI (suppressor of cancer cell invasion), a transcriptional modulator regulating cancer cell motility through suppression of MAL-/SRF-dependent gene transcription (Kressner et al. 2013). SNF5/INI1 regulates cell migration in a RhoA-dependent manner (Caramel et al. 2008).

Endocytosis

The SMARCB1 subunit of the SNF complex interacts with dynamin-2 in the cytoplasm, a large GTPase involved in endocytosis and vesicle dynamics. SMARCB1 inhibits assembly stimulated dynamin-2 GTPase activity and thus modulates endocytosis (Alfonso-Pérez et al. 2014).

Epigenetic Mechanisms

Due to its functions as a chromatin-remodeling protein, SMARCB1 affects epigenomic mechanisms linked to DNA methylation (review: Weichenhan and Plass 2013).

Other Chromatin-Remodeling Proteins

Apart from SWI/SNF and the associated protein network, other proteins act as chromatin remodelers and can potentially cause disease when altered in function. The nucleosome-binding family of high mobility group proteins (HMGN), which facilitate the formation of critical chromatin structures more conducive for transcription, seem to act independently of SWI/SNF (Hill et al. 2005). Chromatin remodeling is affected by the evolutionarily conserved Swi3p, Rsc8p, and Moira (SWIRM) domain that is found in many chromosomal proteins involved in chromatin modifications (Qian et al. 2005). The SWI/SNF-like chromatin remodeler ATRX is involved in the regulation of histone variant deposition. ATRX is mutated at high percentages in multiple tumor types, and its mutations are also found in a syndrome after which it is named, alpha thalassemia/mental retardation, X-linked (Ratnakumar and Bernstein 2013). Chromatin remodeling in mammals is also mediated by proteins of the hINO80 family (human inositol auxotrophy 80) which catalyze ATP-dependent nucleosome remodeling (Bakshi et al. 2006; Chen et al. 2011), including the mammalian Tip49a and Tip49b proteins belonging to the conserved RVB family of ATPases (Jin et al. 2005). The hINO80 SNF2 ATPAase is subject to regulation at multiple levels in the INO80 chromatin-remodeling complex (Chen et al. 2013). hINO80 exhibits complex interactions with cytoskeletal proteins. Its chromatin-remodeling complex interacts with nuclear actin which acts as a monomer in the nucleus (actin-containing chromatin-modifying complexes; Kapoor and Shen 2014). Human INO80 binds to microtubules through the E-hook of tubulin and thus affects spindle assembly (Park et al. 2011). A factor involved in chromatin remodeling is called the "facilitates chromatin transcription (FACT) complex" which affects chromatin function during transcription, replication, and DNA repair. Via selective chromatin remodeling of genes that stimulate proliferation, inhibit cell death, and regulate cellular stress responses, FACT complex is an accelerator of tumor transformation (Garcia et al. 2013). The chromatin-remodeling complex NoRC silences a fraction of rRNA genes and promotes a repressive heterochromatin structure at centromeres and telomeres, a structure required for sustaining genomic integrity (Postepska-Igielska et al. 2013).

Neoplasms Other Than Rhabdoid Tumors Associated with Alterations and Mutations of Chromatin-Remodeling Factors

Deficiency of SNF5/INI1 is characteristic for RT, but it also occurs in other neoplastic processes (Bourdeaut et al. 2007). Whereas the loss of SMARCB1 is a typical feature of RT, mutations of BRG1/SMARCA4 were found in diverse cancers (Medina et al. 2008), including hepatocellular carcinoma (Endo et al. 2013). Genetic changes in the SMARCB1 gene have been detected in families with schwannomatosis (familial schwannomatosis; Hulsebos et al. 2007; Swensen et al. 2009; Brennan et al. 2011; Melean et al. 2012; Rizzo et al. 2012; Smith et al. 2012a, 2012b; Plotkin et al. 2013; Val-Bernal et al. 2013). Schwannomatosis, characterized by schwannomas synchronously occurring at several sites in the absence of bilateral vestibular schwannomas, is the third major form of neurofibromatosis and may be associated with meningiomas and meningiomatosis (Bacci et al. 2010). These neoplasms seem to develop through a mechanism that is distinct from that of rhabdoid tumors in which the SMARCB1 protein is completely absent (Smith et al. 2012a). Apart from SMARCB1 mutations, multiple diffuse schwannomas also develop in the setting of germline KRAS mutations as a RASopathy phenotype (Bertola et al. 2012), and an autosomal dominant form of multiple schwannomas is caused by germline loss of function in LZTR1 (Piotrowski et al. 2014).

Roles of Deranged Chromatin-Remodeling Factor Functions in Nonneoplastic Disorders

Heterozygous germline mutations in components of the SWI/SNF chromatin-remodeling

complexes were observed in patients with non-syndromic intellectual disability and in Coffin-Siris syndrome and Nicolaides-Baraitser syndrome, disorders associated with severe speech delay (review: Santen et al. 2012). In particular, germline variants in the ARID1A (p270) complex of BAF, involving a protein essential for normal cell cycle arrest, and mutations in SMARCB1, SMARCA4, and ARID1B were observed in patients with Coffin-Siris syndrome.

Other Genes and Gene Products Involved in the Pathogenesis of Rhabdoid Tumors

In AT/RT, aberrant methylation of the RASSF1A gene promoter has been found and suggested to play a role in origination and progression of these tumors (Mühlisch et al. 2006). What is RASSF1A? It is a tumor suppressor gene (RAS association domain family 1 gene) assigned to chromosome 3p21.3 in humans. The isoforms RASSF1, RASSF1A, and RASSF1C are distinguished by alternative NH(2)-terminal exons and the transcripts initiate separate CpG islands as methylation targets. Homologues of RASSF1, however located on other chromosomes, are the RASSF3 and NORE1 genes (Tommasi et al. 2002). The loss of RASSF1A (but not RASSF1C) expression by either promoter silencing or loss of heterozygosity (LOH) is a frequent event in several human cancers, and this holds particularly true for epigenetic inactivation of the gene's promoter via methylation mechanisms (Pfeifer et al. 2002; Dammann et al. 2003, 2005; Pfeifer and Dammann 2005). In other tumors, overexpression of RASSF1A is involved (Agathanggelou et al. 2005). RASSF1A-knockout mice exhibit increased susceptibility to spontaneous and carcinogen-induced tumors (Tommasi et al. 2005). RASSF1A has several known actions. It can delay cell cycle progression at the G1/S checkpoint by association with the cyclin A transcription repressor, p120E4F (Fenton et al. 2004), and can cause mitotic arrest through interaction with cdc20 and the inhibition of the anaphase-promoting complex (Song et al. 2004). It furthermore promotes apoptosis mediated through interaction with NORE1, MST1, and MST2 (Dammann et al. 2003). The RASSF1A gene product also associates with microtubules in a paclitaxel-like manner (Dallol et al. 2005), and the centrosomal RASSF1A-binding protein 1 regulates mitotic progression by recruiting RASSF1A to spindle poles (Song et al. 2005), these mechanisms affecting cytokinesis and cell migration. With respect to the microtubule cytoskeleton, RASSF1A interacts with a microtubule-associated protein (MAP-1) homologue, C19ORF5, which specifically associates with microtubules stabilized by RASSF1A, and can cause mitochondrial aggregation and genome destruction (MAGD; Liu et al. 2005). On the other hand, RASSF1A and MAP-1 link death receptor signaling to Bax conformational change and cell death (Baksh et al. 2005), illustrating that RASSF1A is involved in both cell cycle regulation and apoptosis. A rhabdoid morphology in gastrointestinal stromal tumors is associated with PDGFRA mutations (Schaefer et al. 2014).

References

Abdullah A, Patel Y, Lewis TJ, Elsamaloty H, Strobel S (2010) Extrarenal malignant rhabdoid tumors: radiologic findings with histopathologic correlation. Cancer Imaging 10:97–101

Abe T, Oguma E, Nozawa K, Sato Y, Arakawa A, Kikuchi A, Kishimoto H, Minami M (2009) Malignant rhabdoid tumor of the liver: a case report with US and CT manifestation. Jpn J Radiol 27:462–465

Ae K, Kobayashi N, Sakuma R, Ogata T, Kuroda H, Kawaguchi N, Shinomiya K, Kitamura Y (2002) Chromatin remodeling factor encoded by ini1 induces G1 arrest and apoptosis in ini1-deficient cells. Oncogene 21:3112–3120

Agarwal S, Sharma MC, Aron M, Sarkar C, Agarwal N, Chumber S (2006) Poorly differentiated thyroid carcinoma with rhabdoid phenotype: a diagnostic dilemma – report of a rare case. Endocr Pathol 17:399–405

Agathanggelou A, Cooper WN, Latif F (2005) Role of the RAS association domain family 1 (RASSF1) tumor suppressor genes in human cancers. Cancer Res 65:3497–3508

Akhtar M, Kfoury H, Haider A, Sackey K, Ali MA (1994) Fine-needle aspiration biopsy diagnosis of extrarenal malignant rhabdoid tumor. Diagn Cytopathol 11:271–276

Al Nassan A, Sughayer M, Matalka I, Ghandour K, Masarveh M, Zimmermann A, Sultan I (2010) INI1

(BAF 47) immunohistochemistry is an essential diagnostic tool for children with hepatic tumors and low alpha fetoprotein. J Pediatr Hematol Oncol 32:e79–e81

Albanese P, Belin MF, Delattre O (2006) The tumour suppressor hSNF5/INI1 controls the differentiation potential of malignant rhabdoid cells. Eur J Cancer 42:2326–2334

Alfonso-Pérez T, Dominguez-Sanchez MS, Garcia-Dominguez M, Reyes JC (2014) Cytoplasmic interaction of the tumour suppressor protein hSNF5 with dynamin-2 controls endocytosis. Oncogene 33:3064–3074

Al-Nafussi A, O'Donnell M (1999) Poorly differentiated adenocarcinoma with extensive rhabdoid differentiation: clinicopathological features of two cases arising in the gastrointestinal tract. Pathol Int 49:160–163

Amar AM, Tomlinson G, Green DM, Breslow NE, de Alarcon PA (2001) Clinical presentation of rhabdoid tumors of the kidney. J Pediatr Hematol Oncol 23:105–108

Amrikachi M, Ro JY, Ordonez NG, Ayala AG (2002) Adenocarcinomas of the gastrointestinal tract with prominent rhabdoid features. Ann Diagn Pathol 6:357–363

Aoyagi S, Hata H, Iitani MM, Homma E, Inokuma D, Shimizu H (2009) Squamous cell carcinoma of the auricle with rhabdoid features. J Cutan Pathol 36:919–921

Bacci C, Sestini R, Provenzano A, Paganini I, Mancini I, Porfirio B, Vivarelli R, Genuardi M et al (2010) Schwannomatosis associated with multiple meningiomas due to a familial SMARCB1 mutation. Neurogenetics 11:73–80

Baksh S, Tommasi S, Fenton S, Yu VC, Martins LM, Pfeifer GP, Latif F, Downward J, Neel BG (2005) The tumor suppressor RASSF1A and MAP-1 link death receptor signaling to bax conformational change and cell death. Mol Cell 18:637–650

Bakshi R, Mehta AK, Sharma R, Maiti S, Pasha S, Brahmachari V (2006) Characterization of a human SWI2/SNF2 like protein hINI80: demonstration of catalytic and DNA binding activity. Biochem Biophys Res Commun 339:313–320

Banine F, Bartlett C, Gunawardena R, Muchardt C, Yaniv M, Knudsen ES, Weissman BE, Sherman LS (2005) SWI/SNF chromatin-remodeling factors induce changes in DNA methylation to promote transcriptional activation. Cancer Res 65:3542–3547

Barroca HM, Costa MJ, Carvalho JL (2003) Cytologic profile of rhabdoid tumor of the kidney. A report of three cases. Acta Cytol 47:1055–1058

Becker PB (2002) Nucleosome sliding: facts and fiction. EMBO J 21:4749–4753

Becker PB, Horz W (2002) ATP-dependent nucleosome remodeling. Annu Rev Biochem 71:247–273

Beckwith JB (2002) Revised SIOP working classification of renal tumors of childhood. Med Pediatr Oncol 38:77–78

Beckwith JB, Palmer NF (1978) Histopathology and prognosis of Wilms tumor: results from the First National Wilms' Tumor Study. Cancer 41:1937–1948

Berry PJ, Vujanic GM (1992) Malignant rhabdoid tumour. Histopathology 20:189–193

Bertola DR, Pereira AC, Brasil AC, Suzuki L, Leite C, Falzoni R, Tannuri U, Poplawski AB et al (2012) Multiple, diffuse schwannomas in a RASopathy phenotype patient with germline KRAS mutation: a causal relationship? Clin Genet 81:595–597

Betz BL, Strobeck MW, Reisman DN, Knudsen ES, Weissman BE (2002) Re-expression of hSNF5/INI1/BAF47 in pediatric tumor cells leads to G1 arrest associated with induction of p16ink4a and activation of RB. Oncogene 21:5193–5203

Biegel JA, Rorke LB, Emanuel BS (1989) Monosomy 22 in rhabdoid or atypical teratoid tumors of the brain. N Engl J Med 321:906

Biegel JA, Rorke LB, Packer RJ, Emanuel BS (1990) Monosomy 22 in rhabdoid or atypical tumors of the brain. J Neurosurg 73:710–714

Biegel JA, Burk CD, Parmiter AH, Emanuel BS (1992) Molecular analysis of a partial deletion of 22q in a central nervous system rhabdoid tumor. Genes Chromosomes Cancer 5:104–108

Biegel JA, Fogelgren B, Zhou JY, James CD, Janss AJ, Allen JC, Zagzag D, Raffel C, Rorke LB (2000) Mutations of the INI1 rhabdoid tumor suppressor gene in medulloblastomas and primitive neuroectodermal tumors of the central nervous system. Clin Cancer Res 6:2759–2763

Biegel JA, Kalpana G, Knudsen E, Packer RJ, Roberts C, Thiele CJ, Weissman B, Smith M (2002) The role of INI1 and the SWI/SNF complex in the development of rhabdoid tumors: meeting summary from the workshop on childhood atypical teratoid/rhabdoid tumors. Cancer Res 62:323–328

Bourdeaut F, Fréneaux P, Thuille B, Lellouch-Tubiana A, Nicolas A, Couturier J, Pierron G et al (2007) hSNF5/INII-deficient tumours and rhabdoid tumours are convergent but not fully overlapping entities. J Pathol 211:323–330

Bourdeaut F, Lequin D, Brugières L, Reynaud S, Dufour C, Doz F, André N, Sephan JL et al (2011) Frequent hSNF5/INI1 germline mutations in patients with rhabdoid tumor. Clin Cancer Res 17:31–38

Bowen S, Gill M, Lee DA, Fisher G, Geronemus RG, Vazquez ME, Celebi JT (2005) Mutations in the CYLD gene in Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma: lack of genotype-phenotype correlation. J Invest Dermatol 124:919–920

Brand A, Covert A (2001) Malignant rhabdoid tumor of the vulva: case report and review of the literature with emphasis on clinical management and outcome. Gynecol Oncol 80:99–103

Brennan PM, Barlow A, Geraghty A, Summers D, Fitzpatrick MM (2011) Multiple schwannomatosis caused by the recently described INI1 gene – molecular

pathology, and implications for prognosis. Br J Neurosurg 25:330–332
Briner J, Bannwart F, Kleihues P, Odermatt B, Janzer R, Willi U, Boltshauser E (1985) Malignant small cell tumor of the brain with intermediate filaments – a case of a primary cerebral rhabdoid tumor. Pediatr Pathol 3:117–118
Caramel J, Quignon F, Delattre O (2008) RhoA-dependent regulation of cell migration by the tumor suppressor hSNF5/INI1. Cancer Res 68:6154–6161
Chai J, Lu X, Godfrey V, Fletcher C, Roberts CW, Van Dyke T, Weissman BE (2007) Tumor-specific cooperation of retinoblastoma protein family and Snf5 inactivation. Cancer Res 67:3002–3009
Chan ES, Pawel B, Corao D, Venneti S, Russo P, Santi MR, Sullivan LM (2014) Immunohistochemical expression of glypican-3 in pediatric tumors: an analysis of 414 cases. Pediatr Dev Pathol 16:272–277
Chang et al. 1994. http://www.ncbi.nlm.nih.gov/pubmed/7942598
Chang JH, Dikranian AH, Johnston WH, Storch SK, Hurwitz RS (2004) Malignant extrarenal rhabdoid tumor of the bladder: 9-year survival after chemotherapy and partial cystectomy. J Urol 171:820–821
Chen J, Archer TK (2005) Regulating SWI/SNF subunit levels via protein-protein interactions and proteasomal degradation: BAF155 and BAF170 limit expression of BAF57. Mol Cell Biol 25:9016–9027
Chen et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21303910
Chen L, Conaway RC, Conaway JW (2013) Multiple modes of regulation of the human Ino80 SNF2 ATPase by subunits of the INO80 chromatin-remodeling complex. Proc Natl Acad Sci U S A 110:20497–20502
Chetty R, Asa SL (2004) Pancreatic endocrine tumour with cytoplasmic keratin whorls. Is the term "rhabdoid" appropriate? J Clin Pathol 57:1106–1110
Chetty R, Bhathal PS (1993) Caecal adenocarcinoma with rhabdoid phenotype: an immunohistochemical and ultrastructural analysis. Virchows Arch A Pathol Anat Histopathol 422:179–182
Chetty R, Govender D (1999) Follicular thyroid carcinoma with rhabdoid phenotype. Virchows Arch 435:133–136
Cho YM, Choi J, Lee OJ, Lee HI, Han DJ, Ro JY (2006) SMARCB1/INI1 missense mutations in mucinous carcinoma with rhabdoid features. Pathol Int 56:702–706
Clairotte A, Ringenbach F, Laithier V, Aubert D, Kantelip B (2006) Malignant rhabdoid tumor of the liver with spontaneous rupture: a case report (in French). Ann Pathol 26:122–125
Craig E, Zhang ZK, Davies KP, Kalpana GV (2002) A masked NES in INI1/hSNF5 mediates hCRM1-dependent nuclear export: implications for tumorigenesis. EMBO J 21:31–42
Dallol A, Agathanggelou A, Tommasi S, Pfeifer GP, Mahler ER, Latif F (2005) Involvement of the RASSF1A tumor suppressor gene in controlling cell migration. Cancer Res 65:7653–7659
Dammann R, Schagdarsurengin U, Strunnikova M, Rastetter M, Seidel C, Liu L, Tommasi S, Pfeifer GP (2003) Epigenetic inactivation of the Ras-association domain family 1 (RASSF1A) gene and its function in human carcinogenesis. Histol Histopathol 18:665–677
Dammann R, Schagdarsurengin U, Seidel C, Strunnikova M, Rastetter M, Baier K, Pfeifer GP (2005) the tumor suppressor RASSF1A in human carcinogenesis: an update. Histol Histopathol 20:645–663
Darr J, Klochendler A, Isaac S, Eden A (2014) Loss of IGFBP7 expression and persistent AKT activation contribute to SMARCB1/Snf5-mediated tumorigenesis. Oncogene 33:3024–3032
De Ioris M, Brugières L, Zimmermann A, Keeling J, Brock P, Maibach R, Pritchard J, Shafford L, Zsiros J, Czauderna P, Perilongo G (2008) Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: the SIOPEL group experience. Eur J Cancer 44:545–550
Deisch J, Raisanen J, Rakheija D (2011) Immunohistochemical expression of embryonic stem cell markers in malignant rhabdoid tumors. Pediatr Dev Pathol 14:353–359
Di Cori S, Oudjhane K, Neilson K (1993) Primary malignant rhabdoid tumour of the liver. Can Assoc Radiol J 44:52–54
Doan DN, Veal TM, Yan Z, Jones SN, Imbalzano AN (2004) Loss of the INI1 tumor suppressor does not impair the expression of multiple BRG1-dependent genes or the assembly of SWI/SNF enzymes. Oncogene 23:3462–3473
Donner LR, Rao A, Truss LM, Dobin SM (2000) Translocation (8;13)(q24.2;q33) in a malignant rhabdoid tumor of the liver. Cancer Genet Cytogenet 116:153–157
Eaton KW, Tooke LS, Wainwright LM, Judkins AR, Biegel JA (2011) Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. Pediatr Blood Cancer 56:7–15
Endo M, Yasui K, Zen Y, Gen Y, Zen K, Tsuji K, Dohi O, Mitsuyoshi H, Tanaka S et al (2013) Alterations of the SWI/SNF chromatin remodeling subunit-BRG1 and BRM in hepatocellular carcinoma. Liver Int 33:105–117
Euskirchen G, Auerbach RK, Snyder M (2012) SWI/SNF chromatin-remodeling factors: multiscale analyses and diverse functions. J Biol Chem 287:30897–30905
Fanburg-Smith JC, Hengge M, Hengge UR, Smith JS, Miettinen M (1998) Extrarenal rhabdoid tumors of soft tissue: a clinicopathologic and immunohistochemical study of 18 cases. Ann Diagn Pathol 2:351–362
Fenton SL, Dallol A, Agathanggelou A, Hesson L, Ahmed-Choudhury J, Baksh S, Sardet C et al (2004) identification of the E1A-regulated transcription factor p120 E4F as an interacting partner of the RASSF1A candidate tumor suppressor gene. Cancer Res 64:102–107
Fernandez C, Bouvier C, Sevenet N, Liprandi A, Coze C, Lena G, Figarella-Branger D (2002) Congenital disseminated malignant rhabdoid tumor and cerebellar tumor mimicking medulloblastoma in monozygotic

twins: pathologic and molecular diagnosis. Am J Surg Pathol 26:266–270
Figarola MS, Khader SM (1999) pediatric case of the day. Extrarenal rhabdoid tumor of the pelvis. Radiographics 19:1693–1695
Foschini MP, van Eycken P, Brock PR, Casteels-Van Daele M, de Vos R, Dal Cin P, Van den Berghe H, Desmet VJ (1992) Malignant rhabdoid tumour of the liver. A case report. Histopathology 20:157–165
Frierson HF, Mills SE, Innes DJ (1985) Malignant rhabdoid tumor of the pelvis. Cancer 55:1963–1967
Frühwald MC, Hasselblatt M, Wirth S, Kohler G, Schneppenheim R, Subero JI, Siebert R et al (2006) Non-linkage of familial rhabdoid tumors to SMARCB1 implies a second locus for the rhabdoid tumor predisposition syndrome. Pediatr Blood Cancer 47:273–278
Gaffney EF, Breatnach F (1989) Diverse immunoreactivity and metachronous ultrastructural variability in fatal primitive childhood tumor with rhabdoid features. Arch Pathol Lab Med 113:1322
Garces-Iñigo EF, Leung R, Sebire NJ, McHugh K (2009) Extrarenal rhabdoid tumours outside the central nervous system in infancy. Pediatr Radiol 39:817–822
Garcia H, Miecznikowski JC, Safina A, Commane M, Ruusulehro A, Kilpinen S, Leach RW et al (2013) Facilitates chromatin transcription complex is an "accelerator" of tumor transformation and potential marker and target of aggressive cancers. Cell Rep 4:159–173
Gokden et al. 2000. http://www.ncbi.nlm.nih.gov/pubmed/11023094
Gonzalez-Crussi F, Goldschmidt RA, Hsueh W, Trujillo Y (1982) Infantile sarcoma with intracytoplasmic inclusions. A distinctive tumor of possible histiocytic origin. Cancer 49:2365–2375
Gottlieb C, Nijhawan N, Chorneyko K, O'Grady KF, Harney JT (2005) Congenital orbital disseminated extrarenal malignant rhabdoid tumor. Ophthal Plast Reconstr Surg 21:76–79
Grand F, Kulkarni S, Chase A, Goldman JM, Gordon M, Cross NC (1999) Frequent deletion of hSNF5/INI1, a component of the SWI/SNF complex, in chronic myeloid leukemia. Cancer Res 59:3870–3874
Gresh L, Bourachot B, Reimann A, Guigas B, Fiette L, Garbay S, Muchardt C, Hue L et al (2005) The SWI/SNF chromatin-remodeling complex subunit SNF5 is essential for hepatocyte differentiation. EMBO J 24:3313–3324
Guidi CJ, Sands AT, Zambrowicz BP, Turner TK, Demers DA, Webster W, Smith TW et al (2001) Disruption of Ini1 leads to peri-implantation lethality and tumorigenesis in mice. Mol Cell Biol 21:3598–3603
Guidi CJ, Veal TM, Jones SN, Imbalzano AN (2004) Transcriptional compensation for loss of an allele of the Ini1 tumor suppressor. J Biol Chem 279:4180–4185
Guillou L, Wadden C, Coindre JM, Krausz T, Fletcher CD (1997) "Proximal-type" epithelioid sarcoma, a distinctive aggressive neoplasm showing rhabdoid features. Clinicopathologic, immunohistochemical, and ultrastructural study of a series. Am J Surg Pathol 21:130–146
Gunduz K, Shields JA, Eagle RC, Shields CL, De Potter P, Klombers L (1998) Malignant rhabdoid tumor of the orbit. Arch Ophthalmol 116:243–246
Gururangan S, Bowman LC, Parham DM, Wilimas JA, Rao B, Pratt CB, Douglass EC (1993) Primary extracranial rhabdoid tumors. Clinicopathologic features and response to ifosfamide. Cancer 71:2653–2659
Haas JE, Palmer NF, Weinberg AG, Beckwith JB (1981) Ultrastructure of malignant rhabdoid tumor of the kidney. A distinct renal tumor of children. Hum Pathol 12:646–657
Hah N, Kolkman A, Ruhl DD, Pijnappel WW, Heck AJ, Timmers HT, Kraus WL (2010) A role for BAF57 in cell cycle-dependent transcriptional regulation by the SWI/SNF chromatin remodeling complex. Cancer Res 70:4402–4411
Hajdu SI (1986) Differential diagnosis of soft tissue and bone tumors. Lea and Febiger, Philadelphia, pp 28–29
Halasz J, Kovacs M, Illyes G, Mattyus I, Szolnoki J, Szabo A, Verebely T, Schaff Z (2004) Malignant rhabdoid tumour in the liver (in Hungarian). Orv Hetil 145:1439–1443
Halliday GM, Bock VL, Moloney FJ, Lyons JG (2009) SWI/SNF: a chromatin-remodelling complex with a role in carcinogenesis. Int J Biochem Cell Biol 41:725–728
Hargreaves DC, Crabtree GR (2011) ATP-dependent chromatin remodeling: genetics, genomics and mechanisms. Cell Res 21:396–420
Harikrishnan KN, Chow MZ, Baker EK, Pal S, Bassal S, Brasacchio D, Wang L, Craig JM, Jones PL, Sif S, El-Osta A (2005) Brahma links the SWI/SNF chromatin-remodeling complex with MeCP2-dependent transcriptional silencing. Nat Genet 37:254–264
Hill DA, Peterson CL, Imbalzano AN (2005) Effect of HMGN1 on chromatin structure and SWI/SNF-mediated chromatin remodeling. J Biol Chem 280:41777–41783
Ho DM, Hsu CY, Wong TT, Ting LT, Chiang H (2000) Atypical teratoid/rhabdoid tumor of the central nervous system: a comparative study with primitive neuroectodermal tumor/medulloblastoma. Acta Neuropathol (Berlin) 99:482–488
Hollmann TJ, Hornick JL (2011) INI1-deficient tumors: diagnostic features and molecular genetics. Am J Surg Pathol 35:e47–e63
Honda M, Enjoji M, Sakai H, Yamamoto I, Tsuneyoshi M, Nawata H (1996) Case report: intrahepatic cholangiocarcinoma with rhabdoid transformation. J Gastroenterol Hepatol 11:771–774
Hoot AC, Russo P, Judkins AR, Perlman EJ, Biegel JA (2004) Immunohistochemical analysis of hSNF5/INI1 distinguishes renal and extra-renal malignant rhabdoid tumors from other pediatric soft tissue tumors. Am J Surg Pathol 28:1485–1491

Hosli I, Holzgreve W, Danzer E, Tercanli S (2001) two case reports of rare fetal tumors: an indication for surface rendering? Ultrasound Obstet Gynaecol 17:522–526

Hsiao PW, Fryer CJ, Trotter KW, Wang W, Archer TK (2003) BAF60a mediates critical interactions between nuclear receptors and the BRG1 chromatin-remodeling complex for transactivation. Mol Cell Biol 23:6210–6220

Hsueh S, Chang TC (1996) Malignant rhabdoid tumor of the uterine corpus. Gynecol Oncol 61:142–146

Hulsebos TJ, Plomp AS, Wolterman RA, Robanus-Maandaq EC, Baas F, Wesseling P (2007) Germline mutation of INI1/SMARCB1 in familial schwannomatosis. Am J Hum Genet 80:805–810

Humphrey PA (2011) Renal cell carcinoma with rhabdoid features. J Urol 186:675–676

Hunt SJ, Anderson WD (1990) Malignant rhabdoid tumor of the liver. A distinct clinicopathologic entity. Am J Clin Pathol 94:645–648

Imbalzano AN, Jones SN (2005) Snf5 tumor suppressor couples chromatin remodeling, checkpoint control, and chromosomal stability. Cancer Cell 7:294–295

Imbalzano KM, Cohet N, Wu Q, Underwood JM, Imbalzano AN, Nickerson JA (2013) Nuclear shape changes are induced by knockdown of the SWI/SNF ATPase BRG1 and are independent of cytoskeletal connections. PLoS One 8:e55628

Isakoff MS, Sansam CG, Tamayo P, Subramanian A, Evans JA, Fillmore CM, Wang X et al (2005) Inactivation of the Snf5 tumor suppressor stimulates cell cycle progression and cooperates with p53 loss in oncogenic transformation. Proc Natl Acad Sci U S A 102:17745–17750

Jagani Z, Mora-Blanco EL, Sansam CG, McKenna ES, Wilson B, Chen D, Klekota J et al (2010) Loss of the tumor suppressor Snf5 leads to aberrant activation of the Hedgehog-Gli pathway. Nat Med 16:1429–1432

Janson K, Nedzi LA, David O, Schorin M, Walsh JW, Bhattacharjee M, Pridjian G, Tan L et al (2006) Predisposition to atypical teratoid/rhabdoid tumor due to an inherited INI1 mutation. Pediatr Blood Cancer 47:279–284

Jayabose S, Iqbal K, Newman L, San Filippo JA, Davidian MM, Noto R, Sagel I (1988) hypercalcemia in childhood renal tumors. Cancer 61:788–791

Jayaram A, Finegold MJ, Parham DM, Jasty R (2007) Successful management of rhabdoid tumor of the liver. J Pediatr Hematol Oncol 29:406–408

Jimenez-Heffernan JA, Lopez-Ferrer P, Burgos E, Viguer JM (1998) Pathological case of the month. Primary hepatic malignant tumor with rhabdoid features. Arch Pediatr Adolesc Med 152:509–510

Jin J, Cai Y, Yao T, Gottschalk AJ, Florens L, Swanson SK, Gutierrez JL, Coleman MK et al (2005) A mammalian chromatin remodeling complex with similarities to the yeast INO80 complex. J Biol Chem 280:21915–21923

Kaiserling E, Ruck P, Handgretinger R, Leipoldt M, Hipfel R (1996) Immunohistochemical and cytogenetic findings in malignant rhabdoid tumor. Gen Diagn Pathol 141:327–337

Kalpana GV, Marmon S, Wang W, Crabtree GR, Goff SP (1994) Binding and stimulation of HIV-1 integrase by a human homolog of yeast transcription factor SNF5. Science 266:2002–2006

Kaneko et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12445136

Kang YN, Kim SP, Jang BK (2013) A primary malignant rhabdoid tumor in adult liver. Kor J Pathol 47:486–488

Kapoor P, Shen X (2014) Mechanisms of nuclear actin in chromatin-remodeling complexes. Trends Cell Biol 24:238–246

Kato H, Honma R, Sanda T, Fujiwara T, Ito E, Yanagisawa Y, Imai J, Okamaoto T et al (2007) Knock down of hSNF5/Ini1 causes cell cycle arrest and apoptosis in a p53-dependent manner. Biochem Biophys Res Commun 361:580–585

Katzenstein HM, Kletzel M, Reynolds M, Superina R, Gonzalez-Crussi F (2003) Metastatic malignant rhabdoid tumor of the liver treated with tandem high-dose therapy and autologous peripheral blood stem cell rescue. Med Pediatr Oncol 40:199–201

Kelly DM, Jones M, Humphreys S, Howard ER (1998) Spontaneous rupture of a malignant rhabdoid tumor of the liver. Pediatr Surg Int 14:111–112

Kim MJ, Yu E, Ro JY (2003) Sarcomatoid carcinoma of the gallbladder with a rhabdoid tumor component. Arch Pathol Lab Med 127:e406–e408

Kim JY, Cho YM, Ro JY (2010) Prostatic stromal sarcoma with rhabdoid features. Ann Diagn Pathol 14:453–456

Kleinschmidt-DeMasters BK, Alassiri AH, Birks DK, Newell KL, Moore W, Lillehei KO (2010) Epithelioid versus rhabdoid glioblastomas are distinguished by monosomy 22 and immunohistochemical expression of INI-1 but not claudin 8. Am J Surg Pathol 34:341–354

Kohashi K, Nakatsura T, Kinoshita Y, Yamamoto H, Yamada Y, Tajiri T, Taguchi T et al (2013) Glypican 3 expression in tumors with loss of SMARCB1/INI1 protein expression. Hum Pathol 44:526–533

Kohashi K, Yamamoto H, Kumagai R, Yamada Y, Hotokebuchi Y, Taguchi T, Iwamoto Y et al (2014) Differential microRNA expression profiles between malignant rhabdoid tumor and epithelioid sarcoma: miR193a-5p is suggested to downregulate SMARCB1 mRNA expression. Mod Pathol 27:832–839

Kordes U, Bartelheim K, Modena P, Massimino M, Biassoni V, Reinhard H, Hasselblatt M et al (2014) Favorable outcome of patients affected by rhabdoid tumors due to rhabdoid tumor predisposition syndrome (RTPS). Pediatr Blood Cancer 61:919–921

Kosho T, Okamoto N, Ohashi H, Tsurusaki Y, Imai Y, Hibi-Ko Y, Kawame H, Homma T et al (2013) Clinical correlations of mutations affecting six components of the SWI/SNF complex: detailed description of 21 patients and a review of the literature. Am J Med Genet A 161:1221–1237

Kovalenko A, Chable-Bessia C, Cantarella G, Israel A, Wallach D, Courtois G (2003) The tumour suppressor CYLD negatively regulates NF-kappaB signalling by deubiquitination. Nature 424:801–805

Kressner C, Nollau P, Grosse R, Brandt DT (2013) Functional interaction of SCAI with the SWI/SNF complex for transcription and tumor cell invasion. PLoS One 8:e69947

Kuroda N, Saweda T, Miyazaki E, Hayashi Y, Toi M, Naruse K, Fukui T, Nakayama H et al (2000) Anaplastic carcinoma of the pancreas with rhabdoid features. Pathol Int 50:57–62

Kuroda H, Moritake H, Sawada K, Kuwahara Y, Imoto I, Inazawa J, Sugimoto T (2005) Establishment of a cell line form a malignant rhabdoid tumor of the liver lacking the function of two tumor suppressor genes, hSNF5/INI11 and p16. Cancer Genet Cytogenet 158:172–179

Kuwahara Y, Charboneau A, Knudsen ES, Weissman BE (2010) Reexpression of hSNF5 in malignant rhabdoid tumor cell lines causes cell cycle arrest through a p21 (CIP1/WAF1)-dependent mechanism. Cancer Res 70:1854–1865

Lai et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/15737050

Leader J, Carlan SJ, Blum J (2002) Congenital malignant extrarenal rhabdoid tumor: prenatal ultrasound findings. Obstet Gynecol 99:949–951

Leath CA, Huh WK, Conner M, Barnes MN (2003) Primary extrarenal rhabdoid tumor of the ovary. A case report. J Reprod Med 48:283–286

Lee RS, Roberts CW (2013) Rhabdoid tumors: an initial clue to the role of chromatin remodeling in cancer. Brain Pathol 23:200–205

Lee HY, Yoon CS, Sevenet N, Rajalingam V, Delattre O, Walford NQ (2002a) Rhabdoid tumor of the kidney is a component of the rhabdoid predisposition syndrome. Pediatr Dev Pathol 5:395–399

Lee MC, Park SK, Lim JS, Jung S, Kim JH, Woo YJ, Lee JS, Kim HI, Jeong MJ, Choi HY (2002b) Atypical teratoid/rhabdoid tumor of the central nervous system: clinico-pathologic study. Neuropathology 22:252–260

Lee S, Cimica V, Ramachandra N, Zagzag D, Kalpana GV (2011) Aurora A is a repressed effector target of the chromatin remodeling protein INI1/hSNF5 required for rhabdoid tumor cell survival. Cancer Res 71:3225–3235

Lee RS, Stewart C, Carter SL, Ambrogio L, Cibulskis K, Sougnez C, Lawrence MS et al (2012) A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. J Clin Invest 122:2983–2988

Lim BJ, Kim KS, Lim JS, Kim MJ, Park C, Park YN (2004) Rhabdoid cholangiocarcinoma: a variant of cholangiocarcinoma with aggressive behavior. Yonsei Med J 45:543–546

Liu L, Vo A, Liu G, McKeehan WL (2005) Putative tumor suppressor RASSF1 interactive protein and cell death inducer C19ORF5 is a DNA binding protein. Biochem Biophys Res Commun 332:670–676

Lu P, Roberts CW (2013) The SWI/SNF tumor suppressor complex: regulation of promoter nucleosomes and beyond. Nucleus 4:374–378

Machado I, Noguera R, Santonja N, Donat J, Fernandez-Delgado R, Acevedo A, Baragano M et al (2010) Immunohistochemical study as a tool in differential diagnosis of pediatric malignant rhabdoid tumor. Appl Immunohistochem Mol Morphol 18:150–158

Mahajan MC, Narlikar GJ, Boyapaty G, Kingston RE, Weissman SM (2005) heterogeneous nuclear ribonucleoprotein C1/C2, MeCP1, and SWI/SNF form a chromatin remodeling complex at the beta-globin locus control region. Proc Natl Acad Sci U S A 102:15012–15017

Mann JR, Kasthuri N, Raafat F, Pincott JR, Parkes SE, Muir KR, Ingram LC, Cameron AH (1990) Malignant hepatic tumours in children: incidence, clinical features and aetiology. Paediatr Perinat Epidemiol 4:276–289

Marcus VA, Viloria J, Owen D, Tsao MS (1996) Malignant rhabdoid tumor of the colon. Report of a case with molecular analysis. Dis Colon Rectum 39:1322–1326

Martelli MG, Liu C (2013) Malignant rhabdoid tumour of the liver in a seven-month-old female infant: a case report and literature review. Afr J Paediatr Surg 10:50–54

Marzano E, Lermite E, Nobili C, Teyssedou C, Bachellier P, Arnaud JP, Pessaux P (2009) Malignant rhabdoid tumour of the liver in the young adult: report of first two cases. HPB Surg 2009:628206

Maschek H, Werner M, Busche G, Weinel P (1992) Congenital rhabdoid tumor in the mediastinum and liver. Case report and review of the literature (in German). Pathologe 13:172–178

Matsukuma S, Aida S, Hata Y, Sugiura Y, Tamai S (1996) Localized malignant peritoneal mesothelioma containing rhabdoid cells. Pathol Int 46:389–391

Mayes LC, Kasselberg AG, Roloff JS, Lukens JN (1984) Hypercalcemia associated with immunoreactive parathyroid hormone in a malignant rhabdoid tumor of the kidney (rhabdoid Wilms' tumor). Cancer 54:882–884

McKay C, Furman WL (1993) Hypercalcemia complicating childhood malignancies. Cancer 72:256–260

McKenna ES, Tamayo P, Cho YJ, Tillman EJ, Mora-Blanco EL, Sansam CG, Koellhoffer EC et al (2012) Epigenetic inactivation of the tumor suppressor BIN1 drives proliferation of SNF5-deficient tumors. Cell Cycle 11:1956–1965

Medina PP, Sanchez-Cespedes M (2008) Involvement of the chromatin-remodeling factor BRG1/SMARCA4 in human cancer. Epigenetics 3:64–68

Medjkane S, Novikov E, Versteege I, Delattre O (2004) The tumor suppressor hSNF5/INI11 modulates cell growth and actin cytoskeleton organization. Cancer Res 64:3406–3413

Melean G, Velasco A, Hernandez-Imaz E, Rodriguez-Alvarez FJ, Martin Y, Valero A et al (2012) RNA-based analysis of two SMARCB1 mutations associated with familial schwannomatosis with meningiomas. Neurogenetics 13:267–274

Miyagi J, Tsuhako K, Kinjo T, Iwamasa T, Hashimoto H, Ishikawa S (2000) Rhabdoid tumour of the lung is a dedifferentiated phenotype of pulmonary adenocarcinoma. Histopathology 37:37–44

Momota H, Iwami K, Fujii M, Motomura K, Natsume A, Ogino J, Hasegawa T, Wakabayashi T (2011) Rhabdoid glioblastoma in a child: case report and literature review. Brain Tumor Pathol 28:65–70

Montecino M, Stein JL, Stein GS, Lian JB, van Wijnen AJ, Cruzat F, Gutierrez S et al (2007) Nucleosome organization and targeting of SWI/SNF chromatin-remodeling complexes: contributions of the DNA sequence. Biochem Cell Biol 85:419–425

Mora-Blanco EL, Mishina Y, Tillman EJ, Cho YJ, Thom CS, Pomeroy SL, Shao W et al (2014). Activation of b-catenin/TCF targets following loss of the tumor suppressor SNF5. Oncogene 33:933–938

Muchardt C, Sardet C, Bourachot B, Onufryk C, Yaniv M (1995) A human protein with homology to Saccharomyces cerevisiae SNF5 interacts with the potential helicase hbrm. Nucleic Acids Res 23:1127–1132

Mühlisch J, Schwering A, Grotzer M, Vince GH, Roggendorf W, Hagemann C, Sorensen N et al (2006) Epigenetic repression of RASSF1A but not CASP8 in supratentorial PNET (sPNET) and atypical teratoid/rhabdoid tumors (AT/RT) of childhood. Oncogene 25:1111–1117

Nagl NG, Patsialou A, Haines DS, Dallas PB, Beck GR, Moran E (2005) The p270 (ARID1A/SMARCF1) subunit of mammalian SWI/SNF-related complexes is essential for normal cell cycle arrest. Cancer Res 65:9236–9244

Nakajima T, Tajima Y, Sugano I, Nagao K, Kondo Y, Wada K (1993) Intrahepatic cholangiocarcinoma with sarcomatous change. Clinicopathologic and immunohistochemical evaluation of seven cases. Cancer 72:1872–1877

Narlikar GJ, Fan HY, Kingston RE (2002) Cooperation between complexes that regulate chromatin structure and transcription. Cell 108:475–487

Ng WC, Leong HT, Ma KF, Yip WL, Suen WM (2003) Malignant rhabdoid tumour of the oesophagus: a case report. J Clin Pathol 56:713–714

Ogino S, Ro JY, Redline RW (2000) Malignant rhabdoid tumor: a phenotype? An entity? A controversy revisited. Adv Anat Pathol 7:181–190

Ohgaki M, Higuchi A, Chou H, Takashina K, Kawakami S, Fujita Y, Hagiwara A, Yamagishi H (2003) An extrarenal malignant rhabdoid tumor suspected to originate from the mesentery in an adult: report of a case. Surg Today 33:556–559

Ohyama M, Ijiiri R, Tanaka Y, Kato K, Aida N, Ohnuma K, Sho N, Masuno M, Misugi K (2000) Congenital primitive epithelial tumor of the liver showing focal rhabdoid features, placental involvement, and clinical features mimicking multifocal hemangioma or stage 4S neuroblastoma. Hum Pathol 31:259–263

Oike T, Ogiwara H, Nakano T, Yokota J, Kohno T (2013) Inactivating mutations in SWI/SNF chromatin remodeling genes in human cancer. Jpn J Clin Oncol 43:849–855

Oka H, Scheithauer BW (1999) Clinicopathological characteristics of atypical teratoid/rhabdoid tumor. Neurol Med Chir (Tokyo) 39:510–517

Packer RJ, Biegel JA, Blaney S, Finlay J, Geyer JR, Heideman R, Hilden J, Janss AJ et al (2002) Atypical teratoid/rhabdoid tumor of the central nervous system: report of a workshop. J Pediatr Hematol Oncol 24:337–342

Palmer NF, Sutow W (1983) Clinical aspects of the rhabdoid tumor of the kidney: a report of the National Wilms' Tumor Study Group. Med Pediatr Oncol 11:242–245

Papadakis V, Vlachopapadopoulou EA, Levine L (1995) Rhabdoid tumor of the kidney with humoral hypercalcemia and parathyroid hormone-related protein production. Med Pediatr Oncol 24:133–136

Parham DM, Peiper SC, Robicheaux G, Ribeiro RC, Douglass EC (1988) Malignant rhabdoid tumor of the liver. Evidence for epithelial differentiation. Arch Pathol Lab Med 112:61–64

Parham DM, Weeks DA, Beckwith JB (1994) The clinicopathologic spectrum of putative extrarenal rhabdoid tumors. An analysis of 42 cases studied with immunohistochemistry or electron microscopy. Am J Surg Pathol 18:1010–1029

Park EJ, Hur SK, Lee HS, Lee SA, Kwon J (2011) The human Ino80 binds to microtubule via the E-hook of tubulin: implications for the role in spindle assembly. Biochem Biophys Res Commun 416:416–420

Perez-Montiel MD, Frankel WL, Suster S (2003) Neuroendocrine carcinomas of the pancreas with 'rhabdoid' features. Am J Surg Pathol 27:642–649

Perry et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9850174

Pfeifer GP, Dammann R (2005) Methylation of the tumor suppressor gene RASSF1A in human tumors. Biochemistry (Mosc) 70:576–583

Pfeifer GP, Yoon JH, Liu L, Tommasi S, Wilczynski SP, Dammann R (2002) Methylation of the RASSF1A gene in human cancers. Biol Chem 383:907–914

Pinto JA, Gonzalez Alfonso JE, Gonzalez L, Stevenson N (1997) Well differentiated gastric adenocarcinoma with rhabdoid areas: a case report with immunohistochemical analysis. Pathol Res Pract 193:801–805

Piotrowski A, Xie J, Liu YF, Poplawski AB, Gomes AR, Madanecki P, Fu C, Crowley MR et al (2014) Germline loss-of-function mutations in LZTR1 predispose to an inherited disorder of multiple schwannomas. Nat Genet 46:182–187

Pizer BL, Ashworth M, Berry PJ, Foreman NK (1997) Congenital malignant rhabdoid tumour of the gum margin. Oral Oncol 33:447–450

Plotkin SR, Blakeley JO, Evans DG, Hanemann CO, Hulsebos TJ, Hunter-Schaedle K et al (2013) Update from the 2011 International Schwannomatosis Workshop: from genetics to diagnostic criteria. Am J Med Genet A 161A:405–416

Pogacnik A, Zidar N (1997) Malignant rhabdoid tumor of the liver diagnosed by fine needle aspiration cytology. A case report. Acta Cytol 41:539–543

Postepska-Igielska A, Krunic D, Schmitt N, Greulich-Bode KM, Boukamp P, Grummt I (2013) The chromatin remodelling complex NoRC safeguards genome stability by heterochromatin formation at telomeres and centromeres. EMBO Rep 14:704–710

Qian C, Zhang Q, Li S, Zeng L, Walsh MJ, Zhou MM (2005) Structure and chromosomal DNA binding of the SWIRM domain. Nat Struct Mol Biol 12:1078–1085

Raisanen J, Biegel JA, Hatanpaa KJ, Judkins A, White CL, Perry A (2005) Chromosome 22q deletions in atypical teratoid/rhabdoid tumors in adults. Brain Pathol 15:23–28

Ranneberg-Nilsen T, Rollag H, Slettebakk R, Backe PH, Olsen O, Luna L, Bjoras M (2012) The chromatin remodeling factor SMARCB1 forms a complex with human cytomegalovirus proteins UL114 and UL44. PLoS One 7:e34119

Ratnakumar K, Bernstein E (2013) ATRX: the case of a peculiar chromatin remodeler. Epigenetics 8:3–9

Ravindra KV, Cullinane C, Lewis IJ, Squire BR, Stringer MD (2002) Long-term survival after spontaneous rupture of a malignant rhabdoid tumor of the liver. J Pediatr Surg 37:1488–1490

Reiley W, Zhang M, Wu X, Granger E, Sun SC (2005) Regulation of the deubiquitinating enzyme CYLD by IkappaB kinase gamma-dependent phosphorylation. Mol Cell Biol 25:3886–3895

Reiter JF (2010) Crippling SWI-SNF makes tumors GLI-ful. Nat Med 16:1374–1376

Remo A, Zanella C, Molinari E, Talamini A, Tollini F, Piacentini P, Battaglia P, Baritono E et al (2012) Rhabdoid carcinoma of the colon: a distinct entity with a very aggressive behavior: a case report associated with a polyposis coli and review of the literature. Int J Surg Pathol 20:185–190

Richmond et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15471430

Rizzo D, Fréneaux P, Brisse H, Louvrier C, Lequin D, Nicolas A, Ranchère D, Verkarre V et al (2012) SMARCB1 deficiency in tumor from the peripheral nervous system: a link between schwannomas and rhabdoid tumors? Am J Surg Pathol 36:964–972

Roberts CW (2006) Genetic causes of familial risk in rhabdoid tumors. Pediatr Blood Cancer 47:235–237

Roberts CWM, Biegel JA (2009) The role of SMARCB1/INI1 in development of rhabdoid tumor. Cancer Biol Ther 8:412–416

Roberts CWM, Orkin SH (2004) The SWI/SNF complex – chromatin and cancer. Nat Rev 4:133–142

Roberts CW, Galusha SA, McMenamin ME, Fletcher CD, Orkin SH (2000) Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. Proc Natl Acad Sci U S A 97:13796–13800

Rorke LB, Packer R, Biegel J (1995) Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood. J Neurooncol 24:21–28

Rosito P, Mancini AF, Semeraro M, Paone G, Lima M, Federici S, Domini M, Burnelli R et al (2002) Malignant primary tumors of the liver in childhood (in Italian). Pediatr Med Chir 24:200–207

Rosty C, Peter M, Zucman J, Validire P, Delattre O, Aurias A (1998) Cytogenetic and molecular analysis of a t (1;22)(p36;q11) in a rhabdoid tumor with a putative homozygous deletion of chromosome 22. Genes Chromosomes Cancer 21:82–89

Rousseau-Merck MF, de Keyzer Y, Bourdeau A, Cournot G, Mercier F, Nezelof C (1988) PTH mRNA transcription analysis in infantile tumors associated with hypercalcemia. Cancer 62:303–308

Rousseau-Merck MF, Versteege I, Legrand I, Couturier J, Mairal A, Delattre O, Aurias A (1999) hSNF5/INI1 inactivation is mainly associated with homozygous deletions and mitotic recombinations in rhabdoid tumors. Cancer Res 59:3152–3156

Rubenchik I, Dardick I, Auger M (1996) Cytopathology and ultrastructure of primary rhabdoid tumor of lung. Ultrastruct Pathol 20:355–360

Russo P, Biegel JA (2009) SMARC1/INI1 alterations and hepatoblastoma: another extrarenal rhabdoid tumor revealed? Pediatr Blood Cancer 52:312–313

Saito T, Oda Y, Itakura E, Shiratsuchi H, Kinoshita Y, Oshiro Y, Tamiya S, Hachitanda Y, Iwamoto Y, Tsuneyoshi M (2001) Expression of intercellular adhesion molecules in epithelioid sarcoma and malignant rhabdoid tumor. Pathol Int 51:532–542

Saito K, Kigawa T, Koshiba S, Sato K, Matsuo Y, Sakamoto A, Takagi T, Shirouzu M et al (2004) The CAP-Gly domain of CYLD associates with the proline-rich sequence in NEMO/IKKgamma. Structure (Camb) 12:1719–1728

Sajedi M, Wolff JE, Egeler RM, Pinto A, Hughes R, Anderson RA, Coppes MJ (2002) Congenital extrarenal non-central nervous system malignant rhabdoid tumor. J Pediatr Hematol Oncol 24:316–320

Salamanca J, Rodriguez-Peralto JL, Azorin D, Ballestin C, De Agustin P (2004) Paratesticular congenital malignant rhabdoid tumor diagnosed by fine-needle aspiration cytology. A case report. Diagn Cytopathol 30:46–50

Salhi A, Bornholdt D, Oeffner F, Malik S, Heid E, Happle R, Grzeschik KH (2004) Multiple familial trichoepithelioma caused by mutations in the cylindromatosis tumor suppressor gene. Cancer Res 64:5113–5117

Sansam CG, Roberts CWM (2006) Altered chromatin remodeling via Snf5 loss leads to aberrant cell cycle regulation. Cell Cycle 6:621–624

Santen GW, Kriek M, van Attikum H (2012) SWI/SNF complex in disorder: SWItching from malignancies to intellectual disability. Epigenetics 7:1219–1224

Sasaki A, Kurihara H, Ishiuchi S, Hirato J, Saito N, Nakazato Y (2005) Pediatric embryonal tumor of the cerebellum with rhabdoid cells and novel intracytoplasmic inclusions: distinction from atypical teratoid/rhabdoid tumor. Acta Neuropathol (Berl) 110:69–76

Schaefer IM, Ströbel P, Cameron S, Beham A, Otto C, Schildhaus HU and Agaimy A (2014). Rhabdoid morphology in gastrointestinal stromal tumours (GISTs) is associated with PDGFRA mutations but does not imply aggressive behaviour. Histopathology 64:421–430

Scheimberg I, Cullinane C, Kelsey A, Malone M (1996) Primary hepatic malignant tumor with rhabdoid features. A histological, immunocytochemical, and electron microscopic study of four cases and a review of the literature. Am J Surg Pathol 20:1394–1400

Schofield DE, Beckwith JB, Sklar J (1996) Loss of heterozygosity at chromosome regions 22q11-12 and 11p15.5 in renal rhabdoid tumors. Genes Chromosomes Cancer 15:10–17

Seo IS, Min KW, Brodhecker C, Mirkin LD (1988) Malignant renal rhabdoid tumour. Immunohistochemical and ultrastructural studies. Histopathology 13:657–666

Sevenet N, Sheridan E, Amram D, Schneider P, Handgretinger R, Delattre O (1999) Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. Am J Hum Genet 65:1342–1348

Shain AH, Pollack JR (2013) The spectrum of SWI/SNF mutations, ubiquitous in human cancers. PLoS One 8:e55119

Shia J, Erlandson RA, Klimstra DS (2004) Whorls of intermediate filaments with entrapped neurosecretory granules correspond to "rhabdoid" inclusions seen in pancreatic endocrine neoplasms. Am J Surg Pathol 28:271–273

Shiratsuchi H, Oshiro Y, Saito T, Itakura E, Kinoshita Y, Tamiya S, Oda Y, Komiyama S, Tsuneyoshi M (2001) Cytokeratin subunits of inclusion bodies in rhabdoid cells: immunohistochemical and clinicopathological study of malignant rhabdoid tumor and epithelioid sarcoma. Int J Surg Pathol 9:37–48

Shiratsuchi H, Saito T, Sakamoto A, Itakura E, Tamiya S, Oshiro Y, Oda Y, Toh S et al (2002) Mutation analysis of human cytokeratin 8 gene in malignant rhabdoid tumor: a possible association with intracytoplasmic inclusion body formation. Mod Pathol 15:146–153

Shu XS, Li L, Tao Q (2012) Chromatin regulators with tumor suppressor properties and their alterations in human cancers. Epigenomics 4:537–549

Sibileau E, Moroch J, Teyssedou C, Aubé C (2011) Malignant rhabdoid tumors of the liver: an exceptional tumor in adults – a case report and literature review. Eur J Gastroenterol Hepatol 23:104–108

Sims HI, Lane JM, Ulyanova NP, Schnitzler GR (2007) Human SWI/SNF drives sequence-directed repositioning of nucleosomes on C-myc promoter DNA minicircles. Biochemistry 46:11377–11388

Smith MJ, Walker JA, Shen Y, Stemmer-Rachamimov A, Gusella JF, Plotkin SR (2012a) Expression of SMARCB1 (INI1) mutations in familial schwannomatosis. Hum Mol Genet 21:5239–5245

Smith MJ, Wallace AJ, Bowers NL, Rustad CF, Woods CG, Leschziner GD, Ferner RE et al (2012b) Frequency of SMARCB1 mutations in familial and sporadic schwannomatosis. Neurogenetics 13:141–145

Sobrinho-Simoes M (1991) The saga of rhabdoid cells and rhabdoid tumors. Ultrastruct Pathol 15:I–V

Song MS, Song SJ, Ayad NG, Chang JS, Lee JH, Hong HK, Lee H, Choi N, Kim J et al (2004) The tumour suppressor RASSF1A regulates mitosis by inhibiting the APC-Cdc20 complex. Nat Cell Biol 6:129–137

Song MS, Chang JS, Song SJ, Yang TH, Lee H, Lim DS (2005) The centrosomal protein RAS association domain family protein 1A (RASSF1A)-binding protein 1 regulates mitotic progression by recruiting RASSF1A to spindle poles. J Biol Chem 280:3920–3927

Sotelo-Avila C, Gonzalez-Crussi F, deMello D, Vogler C, Gooch WM, Gale G, Pena R (1986) Renal and extrarenal rhabdoid tumors in children: a clinicopathologic study of 14 patients. Semin Diagn Pathol 3:151–163

Stidham DB, Burgett RA, Davis MM, Plager DA (1999) Congenital malignant rhabdoid tumor of the orbit. J AAPOS 3:318–320

Stojanova A, Penn LZ (2009) The role of INI1/hSNF5 in gene regulation and cancer. Biochem Cell Biol 87:163–177

Sugano I, Senda T, Hayashi S, Okaya T, Yamazaki K, Ishida Y (2013) A rhabdoid-mimicking intrahepatic cholangiocarcinoma. Pathol Int 63:422–424

Sullivan LM, Yankovich T, Le P, Martinez D, Santi M, Biegel JA, Pawel BR, Judkins AR (2012) Claudin-6 is a nonspecific marker for malignant rhabdoid and other pediatric tumors. Am J Surg Pathol 36:73–80

Suri VS, Gondal R, Agarwal A, Malhotra V, Sakhuja P, Singhal S (2003) Primary rhabdoid tumor of the gallbladder: report of a case. Surg Today 33:464–466

Swensen JJ, Keyser J, Coffin CM, Biegel JA, Viskochil DH, Williams MS (2009) Familial occurrence of schwannomas and malignant rhabdoid tumour associated with a duplication in SMARCB1. J Med Genet 46:68–72

Taylor MD, Gokgoz N, Andrulis IL, Mainprize TG, Drake JM, Rutka JT (2000) Familial posterior fossa tumors of infancy secondary to germline mutations of the hSNF5 gene. Am J Hum Genet 66:1403–1406

Tekkok IH, Sav A (2005) Primary malignant rhabdoid tumor of the central nervous system – a comprehensive review. J Neurooncol 73:241–252

Tolstorukov MY, Sansam CG, Lu P, Koellhoffer EC, Helming KC, Alver BH, Tillman EJ et al (2013) Swi/Snf chromatin remodeling/tumor suppressor complex establishes nucleosome occupancy at target promoters. Proc Natl Acad Sci U S A 110:10165–10170

Tomlinson GE, Breslow NE, Dome J, Guthrie KA, Norkool P, Li S, Thomas PR, Perlman E et al (2005) Rhabdoid tumor of the kidney in the National Wilms' Tumor Study: age at diagnosis as a prognostic factor. J Clin Oncol 23:7641–7645

Tommasi S, Dammann R, Jin SG, Zhang XF, Avruch J, Pfeifer GP (2002) RASSF3 and NORE1: identification and cloning of the human homologues of the putative tumor suppressor gene RASSF1. Oncogene 21:2713–2720

Tommasi S, Dammann R, Zhang Z, Wang Y, Liu L, Tsark WM, Wilczynski SP, Li J et al (2005) Tumor susceptibility of Rassf1a knockout mice. Cancer Res 65:92–98

Trobaugh-Lotrario AD, Tomslinson GE, Finegold MJ, Gore L, Feusner JH (2009) Small cell undifferentiated variant of hepatoblastoma: adverse clinical and molecular features similar to rhabdoid tumors. Pediatr Blood Cancer 52:328–334

Trobaugh-Lotrario AD, Finegold MJ, Feusner JH (2011) Rhabdoid tumors of the liver: rare, aggressive, and poorly responsive to standard cytotoxic chemotherapy. Pediatr Blood Cancer 57:423–428

Trompouki E, Hatzivassiliou E, Tsichritzis T, Farmer H, Ashworth A, Mosialos G (2003) CYLD is a deubiquinating enzyme that negatively regulates NF-kappaB activation by TNRF family members. Nature 424:793–796

Tsikitis M, Zhang Z, Edelman W, Zagzag D, Kalpana GV (2005) Genetic ablation of Cyclin D1 abrogates genesis of rhabdoid tumors resulting from Ini1 loss. Proc Natl Acad Sci U S A 102:12129–12134

Ueyama T, Nagai E, Yao T, Tsuneyoshi M (1993) Vimentin-positive gastric carcinoma with rhabdoid features. A clinicopathologic and immunohistochemical study. Am J Surg Pathol 17:813–819

Uno K, Takita J, Yokomori K, Tanaka Y, Ohta S, Shimada H, Gilles FH, Sugita K, Abe S et al (2002) Aberrations of the hSNF5/INI1 gene are restricted to malignant rhabdoid tumors or atypical teratoid/rhabdoid tumors in pediatric solid tumors. Genes Chromosomes Cancer 34:33–41

Val-Bernal JF, Mayorga M, Sedano-Tous MJ (2013) Schwannomatosis presenting as pancreatic and submandibular gland schwannoma. Pathol Res Pract 209:817–822

Varghese LR, Stanley MW, Lucido ML, Mallery S, Lai R, Bardales RH (2005) Esophageal carcinoma with a rhabdoid phenotype: a case report of diagnosis by endoscopic ultrasound-guided fine-needle aspiration. Diagn Cytopathol 33:407–411

Versteege I, Sevenet N, Lange J, Rousseau-Merck MF, Ambros P, Handgretinger R et al (1998) Truncating mutations of HSNF5/INI1 in aggressive pediatric cancer. Nature 394:203–206

Versteege I, Medjkane S, Rouillard D, Delattre O (2002) A key role of the hSNF5/INI1 tumour suppressor in the control of the G1-S transition of the cell cycle. Oncogene 21:6403–6412

Vries RG, Bezrookove V, Zuijderduijn LM, Kia SK, Houweling A, Oruetxebarria I, Raap AK, Verrijzer CP (2005) Cancer-associated mutations in chromatin remodeler hSNF5 promote chromosomal instability by compromising the mitotic checkpoint. Genes Dev 19:665–670

Wagner LM, Garrett JK, Ballard ET, Hill DA, Perry A, Biegel JA, Collins MH (2007) Malignant rhabdoid tumor mimicking hepatoblastoma: a case report and literature review. Pediatr Dev Pathol 10:409–415

Wang L, Baiocchi RA, Pal S, Mosialos G, Caligiuri M, Sif S (2005) The BRG1-and hBRM-associated factor BAF57 induces apoptosis by stimulating expression of the cylindromatosis tumor suppressor gene. Mol Cell Biol 25:7953–7965

Wang Z, Kong M, Li J, Xiao W, Zheng S (2011) Intraspinal rhabdoid meningioma metastasis to the liver. J Clin Neurosci 18:714–716

Wang X, Haswell JR, Roberts CW (2014) Molecular pathways: SWI/SNF (BAF) complexes are frequently mutated in cancer – mechanisms and potential therapeutic insights. Clin Cancer Res 20:21–27

Weeks DA, Beckwith JB, Mierau GW, Luckey DW (1989a) Rhabdoid tumor of the kidney: a report of 111 cases from the national Wilms' Tumor Study Pathology Center. Am J Surg Pathol 13:439–458

Weeks DA, Beckwith JB, Mierau GW (1989b) Rhabdoid tumor: an entity or a phenotype. Arch Pathol Lab Med 113:113–114

Weichenhan D, Plass C (2013) The evolving epigenome. Hum Mol Genet 22:R1–R6

Weyman C, Dolson L, Kedar A (1993) Secretion of vasointestinal peptide by a primary liver tumor with rhabdoid features. J Surg Oncol 54:267–270

Wharton SB, Wardle C, Ironside JW, Wallace WH, Royds JA, Hammond DW (2003) Comparative genomic hybridization and pathological findings in atypical teratoid/rhabdoid tumour of the central nervous system. Neuropathol Appl Neurobiol 29:254–261

White FV, Dehner LP, Belchis DA, Conard K, Davis MM, Stocker JT, Zuppan CW et al (1999) Congenital disseminated malignant rhabdoid tumor: a distinct clinicopathologic entity demonstrating abnormalities of chromosome 22q11. Am J Surg Pathol 23:249–256

Wick MR, Ritter JH, Dehner LP (1995) Malignant rhabdoid tumors: a clinicopathologic review and conceptual discussion. Semin Diagn Pathol 12:233–248

Wilson BG, Roberts CW (2011) SWI/SNF nucleosome remodelers and cancer. Nat Rev Cancer 11:481–492

Wu X, Dagar V, Algar E, Muscat A, Bandopadhayay P, Ashley D, Wo Chow C (2008) Rhabdoid tumour: a malignancy of early childhood with variable primary site, histology and clinical behaviour. Pathology 40:664–670

You JS, De Carvalho DD, Dai C, Liu M, Pandiyan K, Zhou XJ, Liang G, Jones PA (2013) SNF5 is an essential executor of epigenetic regulation during differentiation. PLoS Genet 9:e1003459

Yurdakul Z, Berrak SG, Bilgen H, Altuncu E, Akman I, Canpolat C, Demiryont M, Ozek E (2007) Congenital disseminated malignant rhabdoid tumor of the soft tissue. Pediatr Blood Cancer 49:364–365

Yuri T, Danbara N, Shikata N, Fujimoto S, Nakano T, Sakaida N, Uemura Y, Tsubura A (2004) Malignant rhabdoid tumor of the liver: case report and literature review. Pathol Int 54:623–629

Yusuf Y, Belmonte AH, Tchertkoff V (1996) Fine needle aspiration cytology of a recurrent malignant tumor of

the kidney with rhabdoid features in an adult. A case report. Acta Cytol 40:1313–1316

Zimmermann A (2011) Liver tumors of childhood. In: Saxena R (ed) Practical hepatic pathology. A diagnostic approach. Elsevier Saunders, Philadelphia, pp 522–525

Zimmermann A, SIOPEL Group (2003) Liver tumors in childhood and adolescence: an expanding spectrum of intriguing lesions. Bangladesh J Child Health 27: S36–S55

Zraly CB, Dingwall AK (2012) The chromatin remodeling and mRNA splicing functions of the Brahma (SWI/SNF) complex are mediated by the SNR1/SNF5 regulatory subunit. Nucleic Acid Res 40:5975–5987

Part XV

Hepatobiliary Germ Cell Tumors

Germ Cell Tumors of the Liver

79

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_79

Abstract

Most germ cell tumors develop in the gonads, but, due to germ cells misplaced during embryogenesis, these neoplasms can arise in numerous extragonadal sites, including the hepatobiliary tract. Primary teratomas of the liver are known for a long time and can present as liver tumors in the prenatal period already. Hepatic teratomas diagnosed in adults must be distinguished from germ cell tumor metastases that underwent differentiation into teratoma. Furthermore, hepatic teratomas have to be distinguished from mixed tumors and teratoid hepatoblastomas.

Yolk sac tumor can develop in the liver both in the pediatric age group and in adults. This neoplasm is frequently associated with elevated serum levels of alpha-fetoprotein. Non-gestational and extragonadal choriocarcinoma very rarely develops in the liver of children and adult patients. A distinct condition is infantile choriocarcinoma syndrome, where gestational placental choriocarcinoma spreads to the fetus. Other rare hepatobiliary germ cell tumors include mixed germ cell tumors and dermoid cyst.

Introduction

ICD-O codes:

Yolk sac tumor	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/3
Dermoid cyst	9084/0
Teratoma with somatic-type malignancies	9084/3
Mixed germ cell tumors	9085/3

Germ cell tumors represent a complex group of neoplasms derived from germ cells located in various organs and tissues. Most germ cell tumors develop in the gonads, mainly in the testis, but they also originate from misplaced germ cells that occur in extragonadal locations, mostly along the central body axis, beginning in the CNS (pineal gland area) and ending in the sacrococcygeal region. Testicular germ cell tumors represent the most common solid organ malignancy afflicting young adult men with peak incidences ranging between 25 and 35 years of age. A report of the SEER Program revealed that its incidence has increased by 44 % between 1973 and 1998, including a 24 % rise in the incidence of non-seminomatous tumors and a 64 % rise in seminomas (McGlynn et al. 2003).

With few exceptions, almost all types of germ cell tumors listed below have been diagnosed in the liver and/or biliary tract either as primary neoplasms or metastatic disease. A part of germ cell tumors cause solitary liver masses, while others, especially choriocarcinoma, often present as multiple hepatic lesions. Similar to gonads and certain extragonadal sites, germ cell tumors, and in particular teratomas, are manifest in the form of cystic liver lesions that may mimic other cystic processes of the liver, both in adults and children.

Classifications

Mainly in a clinical-oncological setting, the tumors are classified into two major histological types: seminoma and non-seminomatous germ cell tumors, with seminomas comprising about 40–50 % of germ cell tumors (reviews: Ulbright 2005; van de Geijn et al. 2009). A different classification systems divided germ cell tumors into five types. Type I germ cell tumors include the teratomas and yolk sac tumors that occur in neonates and infants. Besides the testis, these neoplasms also occur in the sacrococcygeal region, head and neck, liver and other visceral organs, and midline of the brain. The cell of origin is thought to be an embryonal germ cell with a partially erased pattern of genomic imprinting. Type II germ cell tumors comprise seminomatous and non-seminomatous tumors. The seminomas are termed dysgerminoma in the ovary, gonadoblastoma in dysgenetic gonads, and germinoma in the brain. Seminomas are composed of malignant cells resembling gonocytes (Culty 2009). The non-seminomatous tumors can consist of undifferentiated cells, forming embryonal carcinoma, whose cells are the malignant counterpart of the pluripotent stem cells of the embryonal inner cell mass, which can differentiate into yolk sac tumor, choriocarcinoma, and

Table 1 WHO classification of germ cell tumors (Eble et al. 2004)

Intratubular germ cell neoplasia, unclassified type (IGCNU; ICD-O code 9064/2)
Tumors of one histological type
Seminoma (ICD-O code 9061/3)
Variants: cribriform, pseudoglandular, and tubular variants; seminoma with high
Mitotic rate; seminoma with syncytiotrophoblastic cells
Spermatocytic seminoma (ICD-O code 9063)
Spermatocytic seminoma with sarcoma
Embryonal carcinoma (ICD-O code 9070/3)
Yolk sac tumor (ICD-O code 9071/3)
Choriocarcinoma (ICD-O code 9100/3)
Teratoma (ICD-O 9080/3)
Dermoid cyst (ICD-O code 9084/0)
Teratoma with somatic-type malignancies (ICD-O code 9084/3)
Tumors with more than one histological type (mixed forms)
Mixed germ cell tumors (ICD-O code 9085/3)
Polyembryoma (ICD-O code 9072/3)

teratoma. Type III germ cell tumors consist of spermatocytic seminoma, only found in the testis of elderly men. Type IV and V germ cell tumors are the dermoid cysts found predominantly in the ovary and hydatiform moles, respectively. These two tumor forms are characterized by their exclusively somatic and trophoblastic differentiation, respectively. This previous classification has now been revised and changes in significant parts, resulting in the current 2004 WHO classification (Eble et al. 2004). The WHO classification is summarized in Table 1.

A distinct entity is teratoma with a malignant somatic component (TMSC), a rare disorder diagnosed when a somatic-type malignancy occurs in the context of a germ cell tumor. TMSC predominantly occurs in adults (with a mean age at presentation of 31 years in one study of testis tumors; Colecchia et al. 2011) and exceptionally in the pediatric age group.

In 1997, the International Germ Cell Consensus Classification (IGCCC) was published, having two prognostic categories (good and intermediate) for seminomas and three prognostic categories (good, intermediate, poor) for non-seminomatous germ cell tumors. The classification is based on the following independent prognostic variables: histology of the primary tumor, site of the primary tumor, degree of pretreatment tumor marker elevation (AFP, beta-HCG, LDH), and the presence of nonpulmonary visceral metastases (International Germ Cell Cancer Collaborative Group 1997).

Teratoma of the Liver (ICD-O Code 9080/3)

Introduction

Teratomas are germ cell neoplasms that develop from the three embryonic germ layers (teratoma triphyllicum) and are characterized by virtually any tissue type. Mature teratomas are benign tumors which are usually cystic. Dermoid cyst (type IV germ cell tumor) is often regarded as a special form of mature teratoma with a predominantly ectodermal derivation but seems to be a distinct entity. Immature teratomas are always potentially malignant, but their biology and prognosis depend on the anatomic site of the tumor, patient age, and the fraction of immature elements within the tumor.

Teratoma has been described to arise as a primary tumor in the liver. A first report appeared in 1898 under the term teratoma hepatis (Misick 1898). However, an analysis of this case report shows that this lesion has now be reclassified as mixed epithelial and mesenchymal hepatoblastoma. True teratoma of the liver is a rare lesion. In a review of 70,000 consecutive surgical specimens, only one such tumor was found (Pollice 1973). Among the cases reported, there is, as in other teratomas, a female preponderance. Hepatic teratomas occasionally present as tumors prenatally, including one case observed in an anencephalic fetus (Robinson and Nelson 1986). At necropsy, the liver contained a solid, gray-brown, firm, irregular, and in part nodular mass situated predominantly in the midportion of the right liver lobe. Histologically, the tumor consisted of small to medium spaces lined by biliary-type epithelium, a cystic focus of

squamous epithelium, striated muscle cells, and fascicles of peripheral nerves. The tumors can grow to large size during the fetal period and cause an absolute obstacle to delivery (Froboese 1952). True teratomas of the liver can occur in infants and children.

Selected References Misick 1898; Nissel 1928; Yarbrough 1944; Hartz and Van der Sar 1945; Froboese 1952; Yarbrough and Evashwick 1956; Potter 1962; Misugi and Reiner 1965; Kiryabwire and Mugerwa 1967; Dehner 1968; Nikaidoh et al. 1970; Grave 1972; Pear and Boline 1972; Pollice 1973; Clatworthy et al. 1974; Fabre et al. 1977; Dische and Gardner 1978; Witte et al. 1983; Kraudel and Williams 1984; Robinson and Nelson 1986; Rao et al. 1987; Schnater et al. 2005; Dong et al. 2009; Gupta et al. 2013.

Several cases of hepatic teratomas have been observed in adults.

Selected References Sissoew 1922; Ehrich 1924; Imai 1934; Leschke 1959; Weis and Luechtrath 1964; Marennyi 1971; Ishak 1976; Todani et al. 1977; Watanabe et al. 1978; Gonzalez-Crussi 1982; Teleshov 1989; Winter and Freeny 1993; Kobayashi and Inoue 1995; Alam et al. 1998; Theegarten et al. 1998; Cöl 2003; Nirmala et al. 2003; Martin et al. 2004; Strunk et al. 2005; Rahmat et al. 2006; Certo et al. 2008; Dong et al. 2009; Madan et al. 2010; Zhao et al. 2010.

Clinical and Imaging Features

The common initial sign was abdominal enlargement, although obstructive jaundice and anemia were also reported. Many germ cell tumors secrete AFP, in particular yolk sac tumor. Also immature teratomas often secrete AFP (Arai et al. 1997; Cöl 2003). Lectin-reactive AFP (L3) may be employed as a discriminator, as hepatoblastomas and yolk sac tumors have a high or very high L3 fraction, whereas immature teratomas show an L3 fraction that is around 10 % (Kinoshita et al. 2008). Hepatic teratomas can very rarely give rise to secondary neoplasms, such as squamous cell carcinoma (Imai 1934). The typical X-ray feature of benign hepatic teratomas is a liver mass with focal calcifications. Benign teratomas of the liver are usually cystic lesions which show a mixed echo pattern in US. Hypo- or anechoic components represent the cystic portions of the masses. Hyperechoic foci could represent either calcifications or macroscopic fat. These components are differentiated by the abrupt posterior acoustic shadowing behind calcifications but gradual attenuation of the sound beam behind fat. Fat-fluid levels occurring owing to the presence of sebum are pathognomonic findings (Martin et al. 2004). CT reveals semisolid heterogenic structures with multiple low-density cystic and solid elements. However, this pattern has also been observed in immature hepatic teratomas (Cöl 2003). Hepatic teratomas are usually well-delineated lesions that are easily resectable from the surrounding hepatic parenchyma.

Pathology

Macroscopy

Immature teratomas are bulky and usually have a smooth external surface. On section they exhibit a solid or predominantly solid structure, large cystic spaces being less prominent than in mature teratomas. But as in the mature variants, grossly visible adipose tissue, bone, mineralized parts, sticky masses within cysts, and even hair may be noted. The viscous, yellowish masses found within cysts grossly resemble the contents of epidermoid cysts and may contain glittering crystals of cholesterol and few to numerous hairs.

Histopathology, Immunohistochemistry, and Ultrastructure

The typical tissual and cellular composition of hepatic teratomas reflects that teratomas located elsewhere (Figs. 1 and 2). The features of a triphyllic teratoma have been illustratively described in a report from 1945 already

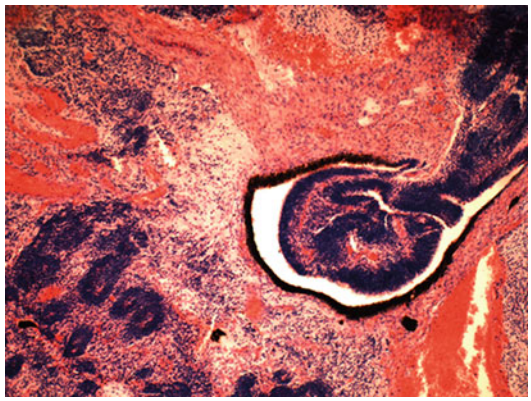

Fig. 1 Mature teratoma of the liver. In the *right half* of the figure, an abortive eye equivalent with a pigment epithelium layer is seen (hematoxylin and eosin stain)

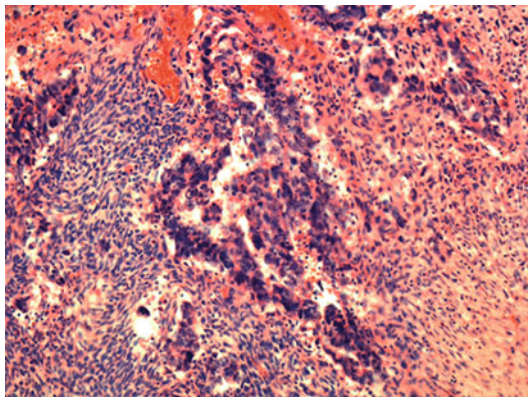

Fig. 2 Immature teratoma of the liver. There is a complex mixture of primitive mesenchyme and highly atypical epithelial structures (hematoxylin and eosin stain)

(Hartz and van der Sar 1945; see above). Neuroectodermal tissues including the brain and melanin-producing cells have been reported several times (Imai 1934; Hartz and van der Sar 1945; Froboese 1952; Watanabe et al. 1978). A part of hepatic teratomas showed distinct histologic patterns. The 32-year-old male patient described by Imai (1934) is of special interest insofar as a tumor in the epigastric region was known since infancy. The tumor had increased in size in the last year. The tumor was unresectable and the patient died. Autopsy revealed a large globular tumor on the inferior surface of the right lobe. Histologically, the tumor was a mature triphyllic teratoma containing the skin, bone, cartilage, bronchial mucosa, salivary glands, nerve fibers, and an eye anlage. The mature teratoma had now started to grow because a squamous carcinoma had arisen in it. The case described by Yarbrough (1944) was a 6-week-old female infant presenting with irritability, vomiting, constipation, and a rapidly enlarging abdomen. Imaging revealed a large abdominal tumor, and surgery revealed a partially cystic tumor mass at the margin of the liver, weighing 3.5 lb. Histology disclosed a mixture of connective tissue, adipose tissue, cartilage and bone, skin with hair follicles, intestinal and bronchial mucosa, liver, pancreas, cysts with squamous epithelium, brain tissue with choroid plexus, and hypophyseal tissue. The presence of hypophysis in this case is remarkable, as pituitary tissue is almost never found in teratomas. Choroid plexus components are also rare; in the figure published of Yarbrough, we note typical papillary fronds covered by the one-layered epithelium characteristic of choroid plexus. A further exemplary case of neonatal hepatic teratoma is the patient described by Hartz and Van der Sar (1945). The medial part of the right liver lobe was occupied by a large, nodular soft tumor, measuring $8 \times 6 \times 5$ cm. On sections it appeared that the nodes were really thin-walled cysts, giving the cut surface a honeycombed appearance. The tissue between the cysts contained few islands of cartilage. Histologically, the tumor was composed of tissues, derived from the three germ layers. One of the cysts was lined by skin with hair follicles and sebaceous glands. Other cysts contained gastric mucosa with parietal cells or colonic-type mucosa. Between the cysts, one noted salivary gland tissue, glioneural tissue, striated muscle tissue, cartilage, and adipose tissue. The fetus with hepatic teratoma reported by Dische and Gardner (1978) had trisomy 13 and an additional teratoma in the neck region. At autopsy, the liver weighed 7 g and grossly was not remarkable except for a few discrete pale areas in both lobes. Histology disclosed parenchyma intimately mixed with squamous epithelium, hair, and clusters of glomeruloid structures with adjacent tubules. Connective tissue components containing large nerve trunks, skeletal muscle cells, ducts with sloughed lining cells, and dystrophic calcifications were present. The case of a 20-year-old female patient, reported by Watanabe et al. (1978), having

a true teratoma of the liver is difficult to judge because she had had dysgerminoma of her left ovary resected 8 years prior to the resection of the liver tumor. Problematic is the case described by Misugi and Reiner (1965). A hepatic tumor found in two-and-a-half-year-old boy and fully analyzed based on autopsy was diagnosed as being malignant true teratoma. However, most of the tumor consisted of polyhedral epithelial cells with eosinophilic cytoplasm, associated with extramedullary hematopoiesis, and Fig. 1 of the publication clearly shows the features of fetal-type hepatoblastoma. The remaining tumor components revealed ciliated epithelial lumens with cartilage (resembling bronchial structures), mucoid epithelia, keratinizing squamous epithelium, osteoid, striated muscle cells, and central nervous tissue with ganglion cells. Therefore, this tumor today qualifies for mixed epithelial and mesenchymal hepatoblastoma, with teratoid features.

Immunohistochemistry

A part of hepatic germ cell tumors, including immature components of teratomas, express germ cell markers, including nuclear labeling for SALL4 (Trinh et al. 2012; Bai et al. 2013; Camparo and Comperat 2013), NANOG (Bai et al. 2013), and CD133. SALL4 is typically positive in yolk sac tumors and yolk sac tumor components, as is CD117 (Trinh et al. 2012). The tumors can contain glypican-3-positive cells (Bai et al. 2013). Mature teratomas may contain neuroendocrine cell lineages with neurosecretory granules expressing neuron-specific enolase and chromogranin A. Focal expression of pancreatic polypeptide and somatostatin has been observed (Nirmala et al. 2003). Ultrastructurally, these cells show dense-core granules (Nirmala et al. 2003).

Calcified Mature Teratoma of the Liver with Bone and Tooth Formation

Whereas the bone and cartilage are often seen in hepatic teratomas, tooth-forming teratoma is a very rare primary tumor in the liver (Froeboese 1952; Leschke 1959; Kalinin 1964; Kiyabwire and Mugerwa 1967; Han 1970; Watanabe et al. 1978; Gupta et al. 2013). Kalinin (1964) reported a 25-year-old female with a cyst in the right liver lobe, showing an egg shell-like calcification and teeth at radiography. In the case described by Han (1970), a 46-year-old man showed a 10 cm-sized calcified mass in the right upper quadrant near the midline. Two rows of teeth partially embedded into a plaque of bone were seen. At surgery, a 10 cm cystic mass was found in the quadrate lobe of the liver. On exploration of the common bile duct, several hairs were noted within it ("trichophilia"), and a probe could be easily passed from the common duct into the cyst. Compression of the cyst resulted in the extrusion of a yellowish fluid mixed with hairs through the common bile duct (Han 1970). In a mature hepatic cystic teratoma diagnosed in a 4-year-old boy, tooth enamel and pulp, but no fully developed teeth, were detected (Gupta et al. 2013).

Teratoma with Somatic-Type Malignant Component in the Liver (ICD-O Code 9084/3)

Teratoma with a malignant somatic component (TMSC) is rare variant of teratoma characterized by the evolution of a somatic malignant neoplasm in connection with a germ cell tumor. TMSC mainly develops in adults (Hong et al. 2013; Oosterhuis et al. 2013; Paliwal et al. 2013; Schaefer et al. 2013). Sarcomatous components are rare in germ cell tumors; they have been observed more often in mediastinal germ cell tumors than those of other locations. It has been proposed that they evolve via malignant transformation of a mesenchymal lineage in the germ cell tumor, from a primitive germ cell, or through dedifferentiation. TMSC was also found as hepatocellular carcinoma arising in testicular teratoma (Jain et al. 2013). In the liver, the only observations that may represent TMSC are hepatoblastoma associated with cystic teratoma (Conrad et al. 1993), squamous cell carcinoma arising in hepatic teratoma (Imai 1934), and

mixed hepatic germ cell tumor with sarcomatous components (Xu et al. 2010).

Dermoid Cyst of the Liver (ICD-O Code 9084/0)

This denotes tumors exclusively consisting of skin components, i.e., keratinizing epidermis and associated adnexal structures. This is an excessively rare lesion in the liver (Meckel 1894; Caroli et al. 1963; Yong Hin Nam 1970). In one case, the cyst was filled with the typical fatty and sticky, sebum- and hair-containing mass but histologically also showed a focus of cartilage (Meckel 1894). A second case, referring to a 25-year-old male patient, was characterized by a partly calcified mass of the retroperitoneal space that was in connection with the left hepatic duct. Upon incision of the common hepatic duct, a large amount of sebum-like material and a mèche of long hair could be extracted, this material having been discharged from the cavity of the dermoid cyst (Caroli et al. 1963).

Primary Yolk Sac Tumor (Endodermal Sinus Tumor) of the Liver (ICD-O Code 9071/3)

Introduction

Yolk sac tumor (YST; endodermal sinus tumor, EST) is a rare malignant tumor which usually arises in the gonads, but in 10–15 % of cases occurs in extragonadal sites, mostly in the anterior mediastinum, the retroperitoneal space, and the sacrococcygeal region. Unusual primary sites are the cerebrum and cerebellum, the pineal gland, the eye, the thymus, the stomach, the uterus, the vulva, the urinary bladder, the prostate gland, and the liver.

YST belongs to the group of tumors that can secrete AFP. AFP has three isoforms (L1, L2, and L3), and the L3 fraction is a well-established diagnostic marker for hepatocellular carcinoma. Similar to hepatoblastomas, YST reveals elevation of both total AFP and the L3 fraction (Kinoshita et al. 2008). YSTs have been shown to secrete an AFP isoform (AFP-C) that is normally produced by fetal liver. This AFP mRNA isoform lacks exon 1 and is transcribed form the intron A, the intron between exons 1 and 2. It is assumed that AFP-C located in the cytoplasm plays functional roles different from those of common AFP (Fukusawa et al. 2005). The production of plasma proteins, and in particular of AFP, by YST is regulated by a transcription factor implicated in the regulation of plasma protein production in the liver, CCAAT/enhancer binding protein (C/EBP)-beta (Hirashiki et al. 2005).

Yolk Sac Tumor of the Liver

A primary localization to the liver (hepatic yolk sac tumor) is uncommon but is known both for the pediatric age group and adults. Most of the neoplasms grow within the liver substance. Yolk sac tumor also occurs in the common bile duct (Munghate et al. 2011), in combination with benign teratoma in the common bile duct (Kim et al. 1993b) and in conjunction with hepatocellular carcinoma (Morinaga et al. 1996). The first observation has been published in 1975 (Hart 1975): the tumor was detected in an 18-month-old boy who had an elevated AFP concentration in the preoperative serum sample; after extended right hepatectomy, widespread metastases developed, resulting in death 6 and a half months after resection. Since then, relatively few cases of this lesion have been reported for the liver, both in children and in adults, and most of them presented, and had a similar outcome, as the case originally described in 1975, albeit successful treatment by chemotherapy and liver transplantation has been reported (Abramson et al. 2005). Primary hepatic YST has been observed in patients as old as 64 years (Lenci et al. 2008). In reviewing the literature which we could consult, 7/13 were female and 6/13 male patients; 4/13 were small children (6–27 months) and 9/13 adults, the age at presentation for adults ranging from 24 to 62 years, however, 6/9 being within their 20s. In the 12 patients where serum AFP had been determined, the levels were elevated

throughout, sometimes exceedingly high (up to 255,000 ng/ml; Wakely et al. 1991). The clinical signs are nonspecific and comprise increasing abdominal girth, mass effect with gradually increasing upper abdominal swelling and hepatomegaly, and chest pain. US and CT usually show a well-circumscribed solid and spherical mass.

Selected References Hart 1975; Okamatsu et al. 1980; Yan 1982; Natori et al. 1983; Narita et al. 1988; Wakely et al. 1991; Villaschi and Balistreri 1991; Whelan et al. 1992; Cross and Variend 1992; Higuchi and Kikuchi 1993; Morinaga et al. 1996; Wong et al. 1998; Gunawardena et al. 2002; Toumi et al. 2004; Abramson et al. 2005; Gilbert et al. 2006; Lenci et al. 2008; Moore et al. 2008; Kajo et al. 2009; Warren and Thompson 2009.

The diagnosis of primary hepatic YST obviously requires the exclusion of metastatic disease of a YST located to a more typical compartment, and one may argue that a small extrahepatic primary tumor may have been missed, but at least one autopsy study documented the absence of a primary tumor remote to the liver, resulting in the proof or at least a very high likelihood that primary hepatic YST does in fact exist (Natori et al. 1983). This is further underlined by the two observations where hepatic YST was directly associated with two certainly hepatic primaries, i.e., hepatoblastoma (Cross and Variend 1992) or hepatocellular carcinoma (Morinaga et al. 1996). The 6-month-old boy described by Cross and Variend (1992) had a large tumor of the right hepatic lobe consisting of mixed epithelial and mesenchymal hepatoblastoma (epithelial component mixed fetal-embryonal, osteoid formation) and of yolk sac tumor with typical Schiller-Duval bodies.

Macroscopy

Macroscopically, YSTs of the liver are solitary lesions of mostly large size (reported diameters ranging from 10 to 17 cm). The tumors show gross necroses and hemorrhages and are mostly solid, but hepatic YST may also present as a cystic lesion (Wong et al. 1998). Gross invasion of large portal vein and hepatic vein branches may occur (Morinaga et al. 1996).

Histopathology

The histology of hepatic YST reflects the patterns typical for this tumor (Fig. 3; Wold et al. 1984; Eble et al. 2004). It shows a reticular cellular pattern characterized by a meshwork of communicating spaces mixed with solid sheets of medium-sized to large cells, intermingled with glandular structures and canalicular profiles (the reticular-microcystic pattern). A macrocystic pattern may also occur. About 10 % of the tumors contain, to a variable degree, components with a polyvesicular vitelline pattern, consisting of small cysts embedded in a loose connective tissue and lined by a flat or cuboidal epithelium. Furthermore, papillary structures lined by neoplastic cells arranged around a fibrovascular core are observed, the so-called Schiller-Duval bodies (the endodermal sinus pattern). Parietal yolk sac differentiation denotes the presence of an abundant and hyaline extracellular matrix representing basement membrane-type material. Less frequent components include solid (5 %), papillary (5 %), spindle cell, myxoid, enteric, and hepatoid patterns. Hepatoid YSTs form a distinct subset of

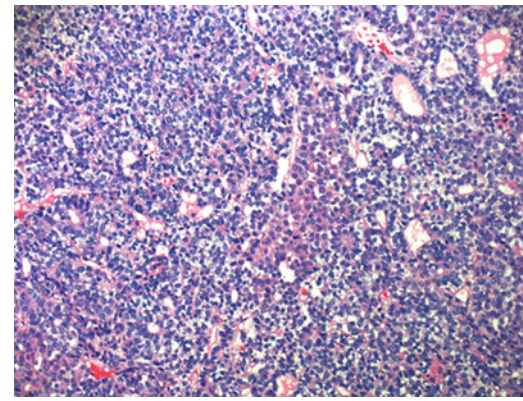

Fig. 3 Yolk sac tumor of the liver. The neoplasm shows several acinar-like structures, but Schiller-Duval bodies are not found (hematoxylin and eosin stain)

YSTs. The possible liver cell differentiation in YST (Jacobsen and Jacobsen 1983; Nakashima et al. 1987) is of particular interest in the present context and is further discussed below. Very rarely, hepatic YST is combined with other components of germ cell tumors, e.g., mature teratoma (Verma et al. 2003) or immature teratoma (Xu et al. 2010). In at least part of the tumor (and in roughly 85 % of cases), hyaline globules of varying size are observed both, intracellularly and extracellularly, chiefly in the areas of a reticular and solid growth pattern, whereas they are rarer in polyvitelline regions. The globules are PAS positive and diastase resistant and may be reactive for alpha-1-antitrypsin and AFP.

Immunohistochemistry

Immunohistochemically, YST cells can express AFP (Fig. 4), alpha-1-antitrypsin, and PLAP in a cytoplasmic pattern but are negative for hCG and Ki-1. Most YSTs are markedly positive for glypican-3 (Esheba et al. 2008). Glypican-3 has a higher sensitivity than AFP for yolk sac tumors (Zynger et al. 2010). SALL4, a stem cell marker, is expressed in the majority of YSTs and is very reliable marker also for metastatic disease of these tumors (Cao et al. 2009). Another marker of embryonic stem cells, the RNA-binding protein LIN28, is also expressed in YSTs and their metastases (Cao et al. 2011). Carcinoembryonic antigen (CEA) and glutathione S-transferase p reactivities can be found in cells of the glandular components but not in other cells.

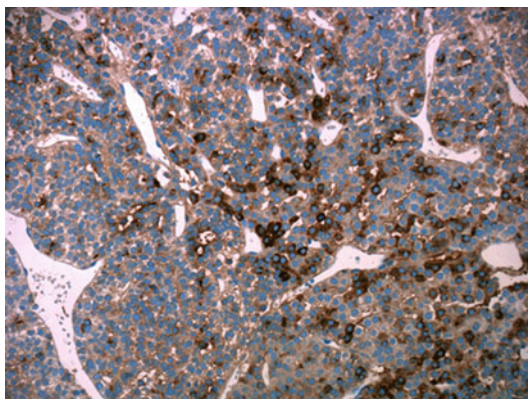

Fig. 4 Focal alpha-fetoprotein (AFP) reactivity in hepatic yolk sac tumor (AFP immunostain)

Yolk Sac Tumor in Other Parts of the Hepatobiliary Tract

YST has been found as a primary tumor in the common bile duct (Munghate et al. 2011) and in the falciform ligament of the liver (Atkinson et al. 1992).

Differential Diagnosis

As the histological presentation of YST is unique, the only relevant differential diagnosis is hepatic metastatic disease, mainly from primary gonadal, retroperitoneal, or sacrococcygeal tumors (Chen et al. 1999; Yalcin et al. 2002). Also the rare gastric and pancreatic YSTs have been found to metastasize to the liver (Tahara et al. 2008; Zhang et al. 2010). As hepatic YST sometimes develops in the cirrhotic liver of an older patient (e.g., 64 years; Lenci et al. 2008) and is associated with elevated serum AFP, this tumor may be misinterpreted as hepatocellular carcinoma.

Primary Choriocarcinoma of the Liver in Adult Patients (ICD-O Code 9100/3)

Non-gestational and extragonadal choriocarcinomas are unusual in adult individuals and, e.g., include primary sites in the esophagus, the stomach, the colon, the lung, and the liver (Fig. 5).

Primary hepatic choriocarcinomas in adults are not only exceedingly rare, but also enigmatic lesions, because it is very difficult to exclude an eventually occult placental or gonadal primary tumor in such situations. Furthermore, a choriocarcinoma phenotype may be mimicked by other tumors occurring in the liver, including the production of hCG. The respective observations have, therefore, raised some criticisms (Anthony 1992), and it remains to be proven in part of the cases whether such neoplasms really occurred primary

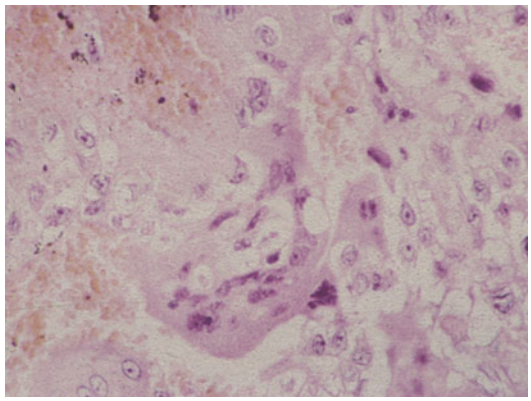

Fig. 5 Choriocarcinoma in the liver. The *center* shows multinucleated syncytiotrophoblastic cells (hematoxylin and eosin stain)

to the liver in these adult patients. To our knowledge, less than 20 cases of primary hepatic choriocarcinomas have been reported (Guretwitsch 1911; Fischer 1913; Stoy 1921; Christeller and Oppenheimer 1925; De Zalka 1927; Benitz 1950; Fine et al. 1962; Heaton et al. 1986; Fernandez-Alonso et al. 1992; Arai et al. 2001; Sekine et al. 2013). Gurewitsch (1911) described the case of a 31-year-old woman who had died 18 months after a hydatiform mole. Tumor nodules were detected in the liver, one nodule invading the small intestine. There was no evidence of tumor in the uterus, but decidual changes and lutein cysts of the ovaries were present. A second instance was reported in 1913 (Fischer 1913). The author described a 45-year-old female who had had two deliveries, the last 18 months prior to admission. At autopsy, numerous hepatic nodules measuring 2–6 cm in diameter were noted, and there was tumor invasion of the hepatic veins. Histology revealed choriocarcinoma. The uterus did not show any tumor tissue. In 1925, a 52-year-old woman was reported with a history of ten normal deliveries, that last of which dating back 12 years. At autopsy, the liver weighed 2,000 g and was filled with choriocarcinoma nodules, the largest having a diameter of 6 cm. Smaller tumor nodules were present in the lungs and intestinal wall. The uterus showed no tumor but displayed decidual change, and lutein cysts were seen in the ovaries (Christeller and Oppenheimer 1925).

In a 40-year-old male, chorionepitheliomatous nodules were observed in the liver, in the absence of any testicular tumor but with nodules regarded as metastatic foci in the lungs, gastric and intestinal mucosa, spleen, and perihepatic lymph nodes (Stoy 1921). The case of De Zalka (1927) was that of 46-year-old woman who had had five pregnancies. She later observed a small tumor in the right abdominal region which about 10 months later occupied the entire right abdomen. In hospital, a liver mass was detected, and she died the following month. Autopsy revealed a liver weight exceeding 4 kg, and the organ was studded with brownish to blue, soft, fragile, and spongy nodules up to 7 cm in diameter. The uterus was normal (also histologically), as were the ovaries, except a hemorrhagic cyst. Histology of the liver nodules disclosed choriocarcinoma. The case of Fernandez Alonso et al. (1992) is important insofar as necropsy was performed, with no evidence of a testicular primary tumor in a detailed workup. The tumors observed in the cirrhotic liver of this 62-year-old male patient were typically hemorrhagic and partially necrotic, and the histologic pattern was characterized by cells with the features of both cytotrophoblast and syncytiotrophoblast, the latter with immunoreactivity for hCG. In a 52-year-old with a large hepatic mass and elevated serum AFP and beta-HCG levels, autopsy revealed multilocular primary hepatic choriocarcinoma combined with embryonal carcinoma (Theegarten et al. 1998). In a group of five males having primary hepatic choriocarcinoma, the average age at diagnosis was 41.6 years, and all patients presented with a large hepatic mass on ultrasonography measuring 11 cm in diameter on average. Three patients showed extrahepatic metastases. None of the patients had evidence of a testicular tumor or a testicular scar (Shi et al. 2010).

Liver Tumors with So-Called Choriocarcinomatous Metaplasia

In exceptional situations, non-germ cell malignancies localized to the liver can contain choriocarcinoma components. Liver metastases of

colorectal adenocarcinoma can undergo so-called choriocarcinomatous metaplasia (Kiran et al. 2001).

Metastatic Choriocarcinoma and the Choriocarcinoma Syndrome

In adult patients, liver metastases of gestational choriocarcinoma (Kang et al. 2002; Lok et al. 2005; Mousavi and Behnamfer 2009), gonadal choriocarcinoma (Stärk 1917; Blanke et al. 2000; Worster et al. 2002), and extragonadal choriocarcinoma (Walthard 1907; Ebisawa et al. 2007; Waseda et al. 2012) have been described. In rare cases, choriocarcinoma metastases in the retroperitoneal space encroach on the hepatic hilum and/or the extrahepatic bile ducts, causing obstructive jaundice (Ahsaini et al. 2012). In part of patients with metastatic choriocarcinoma, including liver metastases, massive tumor hemorrhage followed by sometimes fatal hemorrhagic shock can ensue. This condition is termed choriocarcinoma syndrome (Lok et al. 2005; Baagar et al. 2013; Nakamura et al. 2013).

Primary Choriocarcinoma of the Liver in Infants and Children

Pediatric Gestational Choriocarcinoma

Pure gonadal or extragonadal choriocarcinoma (synonym: malignant teratoma, trophoblastic; MTT) presenting in the pediatric age group is a rare entity, and non-gestational extragonadal choriocarcinoma in children has chiefly been observed in the pineal gland, the region of the third brain ventricle, and the anterior mediastinum. Apart from these non-gestational forms, pediatric gestational choriocarcinoma occurs in few situations, including girls of reproductive age and neonates or infants with visceral manifestations of this tumor. Neonatal/infantile choriocarcinoma is a distinct variant of gestational choriocarcinoma (*infantile choriocarcinoma syndrome*; Witzleben and Bruninga 1968; Belchis et al. 1993), and the placenta is the site of origin of this trophoblastic neoplasm, with subsequent spread into the fetus. The "syndromatic" features are characterized by a presentation at 5 weeks to 7 months of age, an acute illness, anemia and/or pallor, and hepatomegaly (Blohm and Gobel 2004). Further signs comprise a complex hemorrhagic disorder, including hemoperitoneum (rupture of hepatic tumor); multiple pulmonary hemorrhages with hemoptysis, hematemesis, melena, or hematuria; and CNS malfunction (Lazure et al. 2003). Idiopathic massive fetomaternal hemorrhage may occur (Blackburn 1976; Kruseman et al. 1977; Tsukamoto et al. 1986; Chou et al. 2002). The uniform overproduction of b-HCG by the neoplastic trophoblastic cells (chiefly hyperglycosylated hCG, playing a role in invasion; Bahado-Singh et al. 2002), sometimes associated with high serum levels, may result in signs and symptoms of precocious puberty. Infantile choriocarcinoma has an aggressive biology, with only few surviving children reported among patients described in the earlier literature.

Selected References Emery 1952; Kay and Reed 1953; Buckell and Owen 1954; Mercer et al. 1958; Daamen et al. 1961; Witzleben and Bruninga 1968; Kruseman et al. 1977; Nieuwenhuizen Krusemann et al. 1977; Feldman 1977; Aozosa et al. 1981; Kalifa et al. 1981; Tsukamoto et al. 1986; Fraser et al. 1992; Hongo et al. 1992; Belchis et al. 1993; Shitara et al. 1993; Szavay et al. 2000; Blohm et al. 2001; Heath and Tiedemann 2001; Chou et al. 2002; Dumesnil et al. 2005.

Neonatal gestational choriocarcinoma has also been described several times (Kelly et al. 1971; Avril et al. 1986; Flam et al. 1989; Chandra et al. 1990; Belchis et al. 1993; Kim et al. 1993a; Moon et al. 1993; Picton et al. 1995; Sashi et al. 1996; Andreitchouk et al. 1996; Kishkurno et al. 1997). Involvement of the liver in neonatal or infantile gestational choriocarcinoma has been well documented (Hongo et al. 1992; Kim et al. 1993a; Sashi et al. 1996; Andreitchouk et al. 1996; Kishkurno et al. 1997; Szavay et al. 2000; Blohm et al. 2001; Chou et al. 2002;

Liu and Guo 2006; Getrajdman et al. 2012), also in neonates (Moon et al. 1993). In fact the liver is the most frequently involved organ in neonates. In a review of 26 patients reported until 2001, 19 (73 %) showed hepatic tumors (Blohm et al. 2001), and the liver neoplasms are considered as hematogenous metastases of a placental primary tumor, even though one report also considered a primary liver tumor, in the absence of gross placental disease; however, the placenta was not histologically examined (Kim et al. 1993a). The primary placental tumor can be microscopic in size and may be missed on inspection of the placenta (Szavay et al. 2000). At MR imaging, hemorrhage within the hepatic tumors is suggested by the finding of hyperintense T2-weighted images, whereas central portions were hypointense on T1-weighted images and bright on T2-weighted images. T1-weighted postgadolinium imaging showed peripheral enhancement of tumor nodules (Moon et al. 1993; Van der Hoef et al. 2004).

Primary Hepatic Choriocarcinoma in the Pediatric Age Group

Primary infantile hepatic choriocarcinoma (solitary infantile choriocarcinoma of the liver) is a very rare tumor that has first been reported in 1993, based on the observation of an infant with hepatic choriocarcinoma in the absence of gross placental involvement, however, without placental histology (Kim et al. 1993a). Since then, few other infantile or neonatal patients with this intriguing disease have been described, usually with massive liver involvement in the absence of extrahepatic germ cell tumor (van der Hoef et al. 2004; Yoon et al. 2007; Hanson et al. 2011).

Pathology

Macroscopically, hepatic choriocarcinomas are solitary or multiple, sometimes large tumors with characteristically highly vascularized, hemorrhagic, and very friable features (Kim et al. 1993a; Sashi et al. 1996), therefore lesions prone to rupture with fatal intra-abdominal hemorrhage and difficult respectability. Histologically, hepatic manifestations of choriocarcinoma closely reflect the morphologic phenotype known for other malignant trophoblastic tumors. Usually, the tumor is mainly composed of two cell types, syncytiotrophoblasts and cytotrophoblasts, but mononucleated cells intermediate between these two may also occur which, in case syncytiotrophoblasts are rare, result in a monophasic pattern of the tumor. The syncytiotrophoblastic giant and multinucleated cells typically cap or wrap the cytotrophoblastic cells, this configuration sometimes producing villus-like structures. Immunohistochemically, both trophoblastic cell types are reactive for cytokeratins; in particular, and similar to partial and complete moles, cytokeratin 20 is a biomarker of neoplastic gestational trophoblastic disease (Stackievicz et al. 2002). CEA may be positive, but vimentin is negative. All three trophoblast cell types are reactive for CD10 (common acute lymphoblastic leukemia antigen, CALLA), a monomeric type II integral membrane peptidase (Ordi et al. 2003). b-hCG is expressed in syncytiotrophoblasts and intermediate cells. Human placental lactogen is also positive, albeit less markedly so. Alpha-inhibin is expressed in both syncytiotrophoblasts and intermediate cells but not in cytotrophoblasts (Shih and Kurman 1999).

Pathogenesis

What is the evidence that infantile choriocarcinoma derives via spread from overt or occult placental trophoblastic disease? How frequently is a primary placental tumor detectable? In an analysis of 26 reported neonatal/infantile choriocarcinoma patients, maternal gestational trophoblastic disease was present in 16 (62 %; Blohm et al. 2001). However, only in 2 of these 26 cases was the placenta histologically examined, and a placental choriocarcinoma could not be detected (Nieuwenhuizen Krusemann et al. 1977; Tsukamoto et al. 1986).

In case a primary trophoblastic tumor is not found in the placenta, occult gestational

choriocarcinoma or a primary hepatic lesion has been suggested (Kim et al. 1993a). In fact, primary choriocarcinoma of the liver has been proposed to occur (Fernandez Alonso et al. 1992). The concept that infantile choriocarcinoma syndrome may originate from focal placental trophoblastic disease is supported by the finding of Y chromosomes in the tumors (Blohm et al. 2001). What are the cytogenetic patterns in such neoplasms? Germ cell tumors from adult male patients frequently show isochromosome 12i (12q) or gain of the short arm of chromosome 12 (Samaniego et al. 1990), whereas chromosome 12 anomalies are less frequent in the respective tumors of female patients (Rodriguez et al. 1995) and, in contrast to other anomalies, are much less frequent in pediatric germ cell tumors (Perlman et al. 1994). The majority of pediatric embryonal carcinomas and yolk sac tumors display deletions at 1p36 or imbalances of the short and long arms of chromosome 1 (Perlman et al. 1994, 1996; Stock et al. 1994), but the 1p36.33 deletion/imbalance has only once been found in pediatric choriocarcinoma (Blohm et al. 2001), suggesting differences regarding the differentiation along the cell lineages involved. So far, there are no sufficient cytogenetic or molecular data available for successfully tracing the spreading pathway from overt or putative placental disease to neonatal/infantile choriocarcinoma syndrome.

Mixed Germ Cell Tumors of the Liver (ICD-O Code 9085/3)

This is the most exceptional form of hepatic germ cell tumors. In a two-and-a-half-year-old boy with a gradual increase in abdominal distension, ultrasonography and CT of the abdomen revealed a large hepatic mass. Serum AFP was elevated. The left hepatic lobectomy specimen showed a combined yolk sac tumor and mature teratoma. Despite chemotherapy, widespread intrahepatic metastasis developed and the patient died due to liver dysfunction after 6 months (Verma et al. 2003). Another case was observed in a 34-year-old man, this mixed germ cell tumor (immature teratoma and yolk sac tumor) having a sarcomatous component with rhabdomyoblasts, interphase cytogenetics revealing that both the germ cell tumor and the sarcomatous tissue were positive for i(12p) and 12p overrepresentation (Xu et al. 2010).

Germ Cell Tumors of the Biliary Tract

Germ cell tumors (in first-line teratomas) arising as primary tumors from the biliary tract are extremely rare neoplasms (Pfefferkorn and Commichau 1955; Frexes et al. 1986; Kim et al. 1993b; Demircan et al. 2004). The 54-year-old female patient described by Pfefferkorn and Commichau (1955) presented with upper abdominal pain and progressive jaundice with acholic stools. Laparotomy revealed in intraluminal tumor extending from the common bile duct to the cystic duct. Choledochotomy uncovered a large intraluminal, form tumor mass that originated from the posterior common duct wall, where it was attached as a pedunculated mass. Histology showed an immature teratoma with epithelial cysts and osteoid and chondroid components. The tumor showed a transition to osteochondrosarcoma and therefore contained a component of teratoma with a malignant somatic component (MSC). In the patient of Frexes et al. (1986), a teratoma was located to the common hepatic duct. In the 5-year-old boy described by Kim and coworkers (1993b), a benign cystic teratoma of the common bile duct was associated with an endodermal sinus tumor. Demircan and colleagues (2004) reported on a benign cystic teratoma arising from the distal common hepatic duct of a 4-month-old girl with anomalous common bile ducts, where the common bile duct originated from the apex of the gallbladder and reached the duodenum passing over the tumor. The latter presented as 15 cm-sized cystic mass with solid components.

The differential diagnosis of biliary tract germ cell tumors includes germ cell tumors of the retroperitoneal space secondarily invading the ampullary or biliary region (Caroli et al. 1963; Simpson et al. 2005), metastatic germ cell tumors (Rentsch et al. 1977), epidermoid cysts of the

intrahepatic ducts (Chiu et al. 2005), and pseudoepidermoid cysts arising from squamous metaplasia of the gallbladder (Teo et al. 2005). Infantile epidermoid cyst of the intrahepatic bile ducts is a very rare disorder where an epidermoid cyst is in direct communication with bile ducts and drains via the common bile duct (Chiu et al. 2005).

Germ Cell Tumors of the Hepatic Hilar Region

Mature cystic teratoma has been observed at the porta hepatis, preoperatively sometimes diagnosed as a choledochal cyst (Marennyi 1971; Brown et al. 2008). In one patient, a 10-month-old girl, laparotomy revealed a thick-walled cyst obscuring the entire subhepatic space and displacing the bowel medially. A small tubular structure was noted running from the cyst to the distal common bile duct. This was found to leak bile when the cyst was excised. Histologically, the cyst was lined by respiratory epithelium, intestinal epithelium, skin and skin adnexa, pancreatic tissue, and lymphoid tissue. The second patient, a 14-month-old girl, had a cystic mass attached to the portal vein, splenic vein, common hepatic duct, common bile duct, and cystic artery. Histology disclosed a mature teratoma lined with intestinal and respiratory epithelium, with the cartilage, bone, pancreatic tissue, skeletal muscle, and lymphoid tissue (Brown et al. 2008).

Teratomas of the Hepatic Ligaments

Few reports described teratomas arising in the falciform ligament (Bowen et al. 1987; Atkinson et al. 1992; Ayyappan et al. 2007; Gangopadhyay et al. 2009; Srivastava et al. 2011). In the case reported by Srivastava et al. (2011), a congenital mature cystic teratoma of the falciform ligament was situated within an omphalocele. Teratoma has also been diagnosed in the ligamentum teres (Abe et al. 1976). Primary germ cell tumors also occur in the hepatoduodenal ligament, e.g., mature teratoma/dermoid cyst (Akimov 1989; Wang and Dong 2004; Sasaki et al. 2005; Souftas et al. 2008).

Germ Cell Tumors of the Liver Synchronously Combined with Other Hepatic Neoplasms

Teratoma of the liver has seldom been observed in conjunction with a synchronous other hepatic tumors, e.g., combined cystic teratoma and hepatoblastoma (Conrad et al. 1993). Hepatocellular carcinoma associated with hepatic yolk sac tumor has been observed (Morinaga et al. 1996).

Growing Teratoma Syndrome

Introduction

The growing teratoma syndrome (GTS) refers to the phenomenon whereby germ cell tumors enlarge after chemotherapy despite apparently complete eradication of malignant cells and normalization of serum tumor markers (Logothetis et al. 1982). Previously, the phenomenon of benign distant metastases appearing during follow-up was designated, "chemotherapeutic retroconversion" (DiSaia et al. 1977). Specifically, the criteria for the diagnosis of growing teratoma syndrome include non-seminomatous germ cell gonadal or extragonadal mature or immature teratomatous elements; normalization of elevated serum AFP, beta-HCG, and lactate dehydrogenase after therapy; evidence of enlarging metastases, despite chemotherapy and normalization of serum markers; and exclusively mature teratomatous elements on histopathology of the metastases (review: Gorbatiy et al. 2009). The mature elements may consist of few cell lineages and may, e.g., exclusively consist of glial elements, causing military or nodular gliomatosis peritonei (Hsieh and Liu 2009). The syndrome appears in 1.9–7.6 % of the patients after treatment for non-seminomatous germ cell tumors (Jeffery et al. 1991). In men who develop growing teratoma syndrome, the testis is the primary site of origin in as many as 93 % of the patients, followed by the mediastinum and the pineal gland. Growing teratoma syndrome is also known from teratomas of the ovaries. The most common site of growing metastases is the retroperitoneal space. The pathogenesis of growing

teratoma syndrome is not clarified, but hypotheses include selective survival and growth of the mature teratoma component of a germ cell tumor after chemotherapy and differentiation of the cells of the original germ cell tumor into a more benign mature teratoma (Andre et al. 2000). Mature teratoma may present as pelvic and abdominal masses many years after treatment of a gonadal teratoma (Djordjevic et al. 2007).

Manifestations of Growing Teratoma Syndrome in the Liver

Growing teratoma syndrome may manifest in the liver, with sometimes rapidly growing teratomatous hepatic masses (Lentini et al. 1986; Connor and Guest 1999; Eghtesad et al. 2003; Kapoor et al. 2003; Lorusso et al. 2011). The hepatic metastases may form fatty and cystic structures at CT, suggesting maturation of the tumor (Connor and Guest 1999). One patient who had been operated because of testicular mixed germ cell tumor developed marked hepatomegaly from numerous masses with cystic, solid, and calcified components replacing almost the entire liver (Kapoor et al. 2003).

Germ Cell Tumors Metastatic to the Liver

General Remarks

All malignant gonadal and extragonadal germ cells can metastasize to the liver, albeit with variable preponderances for the diverse types of germ cell tumors, also depending on the efficacy of treatments. Hepatic metastases were described for gonadal and extragonadal seminomas (Stomper et al. 1986; Bokemeyer et al. 2001; Chung et al. 2004; Pectasides et al. 2008; Ng et al. 2010), mature components of immature teratomas (Barwad et al. 2011), yolk sac tumors (Tahara et al. 2008; Zhang et al. 2010; Barman et al. 2013; Littooij et al. 2014), embryonal carcinoma (Yano et al. 1983; Abdel-Dayem et al. 1984; Cunningham et al. 1989; Uekado et al. 1994), choriocarcinoma (Alvarado-Cabrero et al. 2014), and teratoma with malignant transformation (Wang and Kazmi 2011). Also extrahepatic germ cell tumors with somatic-type malignant component can metastasize to the liver (Kobayashi et al. 2010).

Struma Ovarii Metastatic to the Liver

Between 15 % and 20 % of ovarian tumors are germ cell in origin, and approximately 10 % of these contain thyroid cells. A much smaller fraction contain sufficient thyroid tissue (50 %) to be classified as a struma ovarii. Most struma ovarii are benign and it has been estimated that less than 3 % are malignant, although malignancy of struma ovarii, in the absence of metastasis, is more difficult to diagnose than orthotopic thyroid carcinoma. Malignant struma ovarii can metastasize to the peritoneum, produce nonmalignant ascites and hydrothorax (pseudo-Meigs syndrome), and occasionally metastasize to distant organs (metastatic ovarian strumosis; review of the literature: Mattucci et al. 2007). Overall, 5–6 % of malignant struma ovarii metastasize. The targets of dissemination of struma ovarii are different from those of orthotopic thyroid carcinoma. Thyroid carcinomas most commonly spread to regional lymph nodes of the neck and less often via hematogenous dissemination to the lung, bone, and brain. In contrast, malignant struma ovarii can spread by regional lymphatics to pelvic and paraaortic lymph nodes; direct spread to the omentum, the peritoneal surface, and the contralateral ovary; and hematogenous spread to the bone, lung, and liver. Struma ovarii is well known to metastasize to the liver (sometimes with functioning metastases) and has to be distinguished from metastasis of follicular or papillary thyroid carcinoma (Kempers et al. 1970; De Graaff et al. 1983; O'Connell et al. 1990; Thomas and Batty 1992; Balasch et al. 1993; Dardik et al. 1999; Konez et al. 2000; Rotman-Pikielny et al. 2000; DeSimone et al. 2003; Cherng et al. 2005; McDougall 2006; Salvatori et al. 2008; Marcy et al. 2010). In order to increase I131 uptake by hepatic metastases, recombinant human thyrotropin has been employed (Rotman-Pikielny

et al. 2000). Within struma ovarii, follicular or papillary thyroid-type carcinoma can develop (Roth et al. 2008; Zhang and Axiotis 2010), which may metastasize, including to the liver (Garg et al. 2009).

Hepatic Tissue in Germ Cell Tumors

It is well known that a hepatocyte lineage can develop in diverse forms of germ cell tumors. Among 516 germ cell tumors, hepatic tissue was observed in 48 cases (9.3 %). The incidence of hepatic tissue was low in tumors of the ovary (5 %), high in both retroperitoneal (27 %) and sacrococcygeal (24 %) tumors, and low in both mature (0.3 %) and immature teratomas (11 %). The frequency was very high in yolk sac tumors >(48 %) and mixed germ cell tumors (52 %). Many hepatic cell nests were found in polyembryoma. In yolk sac tumors, the hepatocyte-like cells resemble more frequently cells of hepatocellular carcinoma (Nakashima et al. 1987). Teratomas may also contain bile ducts and ductules. In a study of 45 teratomas of different localizations, bile duct-like tubules were found in 24 % of the cases, one tumor being almost entirely composed of such elements (Roma and Humphrey 2010).

Cystic Lesions of the Hepatobiliary Tract Mimicking Teratomas: Epidermoid Cyst of the Liver and the Bile Ducts

Together with dermoid cyst (see below), this is the most uncommon form of a lesion that may be related to teratomas (Schullinger et al. 1983; Lombardi et al. 1995; Fernandez-Castroagudin et al. 2001). The lesion was diagnosed in the pediatric age group, e.g., in a 4-year-old girl who had presented with biliary cirrhosis (Schullinger et al. 1983). Hepatic epidermoid cysts may be large and mimic hydatid disease (Fernandez-Castroagudin et al. 2001). In one case, hepatic epidermoid cyst showed microscopic foci of squamous cell carcinoma (Lombardo et al. 1995).

Epidermoid cyst has been identified in the intrahepatic duct system. In one case, the cyst was located at the confluence of the right and left hepatic ducts and involved all of the common hepatic duct (Chiu et al. 2005).

Extrahepatic Non-germ Cell Neoplasms with Germ Cell Tumor-like Components Metastasizing to the Liver

Extrahepatic carcinomas can contain germ cell tumor or germ cell tumor-like components (Wang et al. 2000; Abe et al. 2008; Satake et al. 2011). These components may metastasize to the liver. In a patient with gastric adenocarcinoma, this tumor showed yolk sac tumor differentiation and liver metastasis of the yolk sac tumor component (Bihari et al. 2013).

Differential Diagnosis

Gonadal germ cell tumors are well known to metastasize to the liver. Post-chemotherapy resection of liver metastases is a successful therapeutic approach (Yokoi et al. 2003; You et al. 2009). The probability of hepatic metastasis of pure immature ovarian teratoma is significantly related to chemotherapy. In one study, the hepatic metastatic rate was 16.7 % in the standard adjuvant chemotherapy group but increased markedly to 31.2 % in the irregular chemotherapy group (Fan et al. 2001). Retroperitoneal teratomas, particularly those which have a close relationship to the inferior vena cava, may mimic a mass lesion in the posterior part of the liver. Retroperitoneal twin fetus in fetu associated with immature teratoma has been described (Pourang et al. 2009).

References

Abdel-Dayem HM, Motawi S, Jahan S, Kubasik H (1984) Liver metastasis from embryonal carcinoma of the ovary with complete situs inversus. First reported case and review of the literature. Clin Nucl Med 9:558–560

Abe H, Ikeda K, Watanabe I (1976) Teratoma of the ligamentum teres of the liver – a case report. Fukushima J Med Sci 23:1–10

Abe A, Furumoto H, Yoshida K, Nishimura M, Irihara M, Kudo E, Sano T (2008) A case of ovarian endometrioid adenocarcinoma with a yolk sac tumor component. Int J Gynecol Cancer 18:168–172

Abramson LP, Oillai S, Acton R, Melin-Aldana H, Superina R (2005) Successful liver transplantation for treatment of a hepatic yolk sac tumor. J Pediatr Surg 40:1185–1187

Ahsaini M, Tazi F, Mellas S, Elammari J, Khalouk A, Stuurman-Wieringa R, Elfassi MJ, Farih MH et al (2012) Pure choriocarcinoma of the testis presenting with jaundice: a case report and review of the literature. J Med Case Rep 6:269

Akimov OV (1989) Hepatoduodenal ligament teratoma followed by hypertensive syndrome of the portal vein. Arkh Patol 51:60–62

Alam K, Maheshwari V, Aziz M, Ghani I (1998) Teratoma of the liver – a case report. Indian J Pathol Microbiol 41:457–459

Alvarado-Cabrero I, Hernandez-Toriz N, Paner GP (2014) Clinicopathologic analysis of choriocarcinoma as a pure or predominant component of germ cell tumor of the testis. Am J Surg Pathol 38:111–118

Andre F, Fizazi K, Culine S, Droz J, Taupin P, Lhommé C, Terrier-Lacombe M, Théodore C (2000) The growing teratoma syndrome: results of therapy and long-term follow-up of 33 patients. Eur J Cancer 36:1389–1394

Andreitchouk AE, Takahashi O, Kodama H, Morita M, Sankawa T, Saito K, Enomoto K, Tanaka T (1996) Choriocarcinoma in infant and mother: a case report. J Obstet Gynaecol Res 22:585–588

Anthony PP (1992) Letter to the case. Pathol Res Pract 188:378

Aozosa K, Ito H, Kohro T, Ha K, Nakamura M, Okada A (1981) Choriocarcinoma in infant and mother. Acta Pathol Jpn 31:317–322

Arai K, Ohta S, Suzuki M, Suzuki H (1997) Primary immature mediastinal teratoma in adulthood. Eur J Surg Oncol 23:64–67

Arai M, Oka K, Nihei T, Hirota K, Kawano H, Kawasaki T, Hakozaki H (2001) Primary hepatic choriocarcinoma – a case report. Hepatogastroenterology 48:424–426

Atkinson JB, Foster CE, Lally KP, Isaacs H, Siegel SE (1992) Primary endodermal sinus (yolk sac) tumor of the falciform ligament. J Pediatr Surg 27:105–107

Avril MF, Mathieu A, Kalifa C, Caillou C (1986) Infantile choriocarcinoma with cutaneous tumors. An additional case and review of the literature. J Am Acad Dermatol 14:918–927

Ayyappan AP, Singh SE, Shah A (2007) Mature cystic teratoma in the falciform ligament of the liver. J Postgrad Med 53:48–49

Baagar K, Khan FY, Alkuwari E (2013) Choriocarcinoma syndrome: a case report and a literature review. Case Rep Oncol Med 2013:697251

Bahado-Singh RO, Oz AU, Kingston JM, Shahabi S, Hsu CD, Cole L (2002) The role of hyperglycosylated hCG in trophoblast invasion and the prediction of subsequent pre-eclampsia. Prenat Diagn 22:478–481

Bai S, Wei S, Pasha TL, Yao Y, Tomaszewski JE, Bing Z (2013) Immunohistochemical studies of metastatic germ-cell tumors in retroperitoneal dissection specimens: a sensitive and specific panel. Int J Surg Pathol 21:342–351

Balasch J, Pahisa J, Marquez M, Odi J, Fabregues F, Puerto B, Vanrell JA (1993) Metastatic ovarian strumosis in an in-vitro fertilization patient. Hum Reprod 8:2075–2077

Barman DC, Halder A, Bhattacharya S, Mandal K, Mallick SK (2013) Yolk sac tumour of the cryptorchid testis, with an unusual presentation – diagnosed by fine needle aspiration cytology. J Clin Diagn Res 7:1444–1446

Barwad A, Dey P, Shivalingam J (2011) Metastatic of mature component in a treated case of immature teratoma diagnosed on fine-needle aspiration cytology of the liver. Diagn Cytopathol 39:711–713

Belchis DA, Mowry J, Davis JH (1993) Infantile choriocarcinoma. Re-examination of a potentially curable entity. Cancer 72:2028–2032

Benitz KF (1950) Über das sogenannte primäre Chorionepitheliom der Leber, mit einer eigenen Beobachtung (On the so-called primary chorionepithelioma of the liver, with an own observation). Thesis, Hamburg

Bihari C, Rastogni A, Chandan KN, Yadav V, Panda D (2013) Gastric adenocarcinoma with yolk sac tumor differentiation and liver metastasis of yolk sac tumor component. Case Rep Oncol Med 2013:923596

Blackburn GK (1976) Massive fetomaternal haemorrhage due to choriocarcinoma of the uterus. J Pediatr 89:680–681

Blanke CD, Hemmer MP, Witte RS (2000) Acute tumor lysis syndrome with choriocarcinoma. South Med J 93:916–919

Blohm ME, Gobel U (2004) Unexplained anemia and failure to thrive as initial symptoms of infantile choriocarcinoma: a review. Eur J Pediatr 163:1–6

Blohm MEG, Calaminus G, Gnekow AK, Heidemann PH, Bolkenius M, Weinel P, von Schweinitz D, Ambros PF et al (2001) Disseminated choriocarcinoma in infancy is curable by chemotherapy and delayed tumour resection. Eur J Cancer 37:72–78

Bokemeyer C, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Schmoll HJ, Kanz L et al (2001) Extragonadal seminoma: an international multicenter analysis of prognostic factors and long term treatment outcome. Cancer 91:1394–1401

Bowen B, Ros PR, McCarthy MJ, Olmsted WW, Hjermstad BM (1987) Gastrointestinal teratomas: CT and US appearance with pathologic correlation. Radiology 162:431–433

Brown B, Khalil B, Batra G, Rampersad B, Bruce J (2008) Mature cystic teratoma arising at the porta hepatis: a diagnostic dilemma. J Pediatr Surg 43:e1–e3

Buckell EWC, Owen TK (1954) Chorioepithelioma in mother and infant. J Obstet Gyncecol Br Emp 61:329–333

Camparo P, Comperat EM (2013) SALL4 is a useful marker in the diagnostic work-up of germ cell tumors in extra-testicular locations. Virchows Arch 462:337–341

Cao D, Guo S, Allan RW, Molberg KH, Peng Y (2009) SALL4 is a novel sensitive and specific marker of ovarian primitive germ cell tumors and is particularly useful in distinguishing yolk sac tumor from clear cell carcinoma. Am J Surg Pathol 33:894–904

Cao D, Liu A, Wang F, Allam RW, Mei K, Peng Y, Du J, Guo S, Abel TW, Lane Z, Ma J et al (2011) RNA-binding protein LIN28 is a marker for primary extragonadal germ cell tumors: an immunohistochemical study of 131 cases. Mod Pathol 24:288–296

Caroli J, Hepp J, Phocas E, Beauchant J (1963) Perforated retroperitoneal teratoma (dermoid cyst?) in the left hepatic duct and the stomach. Contribution to the study of the complications of retroperitoneal teratoma (in French). Sem Hop 39:1499–1508

Certo M, Franca M, Gomes M, Machado R (2008) Liver teratoma. Acta Gastroenterol Belg 71:275–279

Chandra SA, Gilbert EF, Viseskul C, Strother CM, Haning RV, Javis MJ (1990) Neonatal intracranial choriocarcinoma. Arch Pathol Lab Med 114:1079–1082

Chen CL, Wang PH, Ng HT, Yuan CC (1999) Transhepatic artery chemoembolization for liver metastases of primary retroperitoneal endodermal sinus tumor. A case report. J Reprod Med 44:559–562

Cherng SC, Wang YF, Fan YM, Chen CY, Yuan YN, Cheng CY (2005) Malignant struma ovarii with peritoneal implants and pelvic structures and liver metastases demonstrated by I-131 SPECT and low-dose CT. Clin Nucl Med 30:797–798

Chiu B, Melin-Aldana H, Superina RA (2005) Management of an epidermoid cyst of the intrahepatic ducts. J Pediatr Surg 40:e31–e33

Chou HC, Chen RL, Yau KI, Huang SF, Ni YH, Tang JR (2002) Infantile choriocarcinoma with idiopathic massive fetomaternal hemorrhage. Med Pediatr Oncol 38:203–204

Christeller E, Oppenheimer P (1925) Über ein ektopisches Chorionepitheliom der Leber (On an ectopic chorionepithelioma of the liver). Virchows Arch Pathol Anat Physiol Klin Med 257:691–708

Chung PW, Gospodarowicz MK, Panzarella T, Jewett MA, Sturgeon JF, Tew-George B, Bayley AJ et al (2004) Stage II testicular seminoma: patterns of recurrence and outcome of treatment. Eur Urol 45:754–759

Clatworthy HW, Schiller M, Grosfeld JL (1974) Primary liver tumors in infancy and childhood. 41 cases variously treated. Arch Surg 109:143–147

Cöl C (2003) Immature teratoma in both mediastinum and liver of a 21-year-old female patient. Acta Med Austriaca 30:26–28

Colecchia M, Necchi A, Paolini B, Nicolai N, Salvioni R (2011) Teratoma with somatic-type malignant components in germ cell tumors of the testis: a clinicopathologic analysis of 40 cases with outcome correlation. Int J Surg Pathol 19:321–327

Connor S, Guest P (1999) Conversion of multiple solid testicular teratoma metastases to fatty and cystic liver masses following chemotherapy: CT evidence of "maturation". Br J Radiol 72:1114–1116

Conrad RJ, Gribbin D, Walker NI, Ong TH (1993) Combined cystic teratoma and hepatoblastoma of the liver. Probable divergent differentiation of an uncommitted hepatic precursor cell. Cancer 72:2910–2913

Cross SS, Variend S (1992) Combined hepatoblastoma and yolk sac tumor of the liver. Cancer 69:1323–1326

Culty M (2009) Gonocytes, the forgotten cells of the germ cell lineage. Birth Defects Res C Embryo Today 87:1–26

Cunningham LN, Ginsberg P, Manfrey S, Finkelstein LH (1989) Massive hemorrhage secondary to metastatic testicular carcinoma. J Am Osteopath Assoc 89:341–344

Daamen CBF, Bloem GWD, Westerbeck AJ (1961) Chorioepithelioma in mother and child. J Obstet Gynecol Br Common 68:144–149

Dardik RB, Dardik M, Westra W, Montz FJ (1999) Malignant struma ovarii: two case reports and a review of the literature. Gynecol Oncol 73:447–451

De Graaff J, van Vliet MA, Miseree SC (1983) Malignant struma ovarii. Eur J Obstet Gynecol Reprod Biol 16:31–35

De Zalka E (1927) Concerning ectopic chorionepithelioma. Am J Pathol 4:59–74

Dehner LP (1968) Hepatic tumors in the pediatric age group: a distinctive clinicopathologic spectrum. Perspect Pediatr Pathol 4:217–268

Demircan M, Uguralp S, Mutus M, Kutlu R, Mizrak B (2004) Teratoma arising from anomalous common bile ducts: a case report. J Pediatr Surg 39:e1–e2

DeSimone CP, Lele SM, Modesitt SC (2003) Malignant struma ovarii: a case report and analysis of cases reported in the literature with focus on survival and I131 therapy. Gynecol Oncol 89:543–548

Disaia PJ, Saltz A, Kagan AR, Morrow CP (1977) Chemotherapeutic retroconversion of immature teratoma of the ovary. Obstet Gynecol 49:346–350

Dische MR, Gardner HA (1978) Mixed teratoid tumors of the liver and neck in trisomy 13. Am J Clin Pathol 69:631–637

Djordjevic B, Euscher ED, Malpica A (2007) Growing teratoma syndrome of the ovary: review of literature and first report of a carcinoid tumor arising in a growing teratoma of the ovary. Am J Surg Pathol 31:1913–1918

Dong Q, Jiang B, Lu Y, Zhang H, Jiang Z, Lu H, Yang C, Zhao J, Hao X (2009) Surgical management of giant liver tumors involving the hepatic hilum of children. World J Surg 33:1520–1525

Dumesnil C, Gatbois E, Leverger G (2005) Infantile choriocarcinoma: an uncommon and curable tumor (in French). Arch Pediatr 12:1721–1725

Ebisawa S, Yamazaki S, Yasuo M, Urushihata K, Tsushima K, Hanaoka M, Koizumi T, Fujimoto K et al (2007) Multiple hepatic metastases due to germ cell tumor on initial clinical presentation (in Japanese). Nihon Kokyuki Gakkai Zasshi 45:318–323

Eble JN, Sauter G, Epstein JI, Sesterhenn IA (2004) Pathology and genetics of tumours of the urinary system and male genital organs. WHO classification of tumours. IARC Press, Lyon

Eghtesad B, Marsh WJ, Cacciarelli T, Geller D, Reves J, Jain A, Fontes P, Devera M, Fung J (2003) Liver transplantation for growing teratoma syndrome: report of a case. Liver Transpl 9:1222–1224

Ehrich W (1924) Beitrag zur Kenntnis der Mischgeschwülste der Leber. Thesis, Rostock University, Germany

Emery JL (1952) Chorioepithelioma in the newborn male: child with hyperplasia of the interstitial cells of the testis. J Pathol Bacteriol 64:735–739

Esheba GE, Pate LL, Longacre TA (2008) Oncofetal protein glypican-3 distinguishes yolk sac tumor from clear cell carcinoma of the ovary. Am J Surg Pathol 32:600–607

Fabre C, Gregoire A, Scheiner C, Basbous D, Lebreuil G (1977) Hepatic dysembryoma. Report of a case in the child (in French). Arch Anat Cytol Pathol 25:209–212

Fan Q, Huang H, Lian L, Lang J (2001) Characteristics, diagnosis and treatment of hepatic metastases of pure immature ovarian teratoma. Chin Med J (Engl) 114:506–509

Feldman K (1977) Choriocarcinoma with neonatal anemia. N Engl J Med 296:880

Fernandez Alonso J, Saez C, Perez P, Montaño A, Japon MA (1992) Primary pure choriocarcinoma of the liver. Pathol Res Pract 188:375–377

Fernandez-Castroagudin J, Bustamante Montalvo M, Delgado Blanco M, Gonzalez-Quintela A, Pintos Martinez E, Varo Pérez E (2001) Epidermoid cyst: a rare cause of cystic liver disease. Gastroenterol Hepatol 24:247–249

Fine G, Smith RW, Pachter MR (1962) Primary extragenital choriocarcinoma in the male subject. Am J Med 32:776–794

Fischer B (1913) Primäres Chorionepitheliom der Leber (Primary chorionepithelioma of the liver). Frankfurter Z Pathol 12:462–480

Flam F, Lundström V, Silfverswärd C (1989) Choriocarcinoma in mother and child. Case report. Br J Obstet Gynaecol 96:241–244

Fraser GC, Blair GK, Hemming A, Murphy JJ, Rogers P (1992) The treatment of simultaneous choriocarcinoma in mother and baby. J Pediatr Surg 27:1318–1319

Frexes M, Neblett WW, Holcomb GW (1986) Spectrum of biliary disease in childhood. South Med J 79:1342–1349

Froboese C (1952) Teratoma triphyllicum polycysticum congenitum hepatis having a size of child's head and being an absolute obstacle to delivery (in German). Zentralbl Allg Pathol 89:364–379

Fukusawa et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/15914041

Gangopadhyay AN, Srivastava P, Upadhyaya VD, Hasan Z, Vijayendra KR, Sharma SP (2009) Mature cystic teratoma in falciform ligament of the liver in an infant. Afr J Paediatr Surg 6:132–133

Garg K, Soslow RA, Rivera M, Tuttle MR, Ghossein RA (2009) Histologically bland "extremely well differentiated" thyroid carcinomas arising in struma ovarii can recur and metastasize. Int J Gyncecol Pathol 28:222–230

Getrajdman J, Kolev V, Body E, Chuang L (2012) Case of maternal and infantile choriocarcinoma following normal pregnancy. Gynecol Oncol Case Rep 2:102–104

Gilbert KL, Bergman S, Dodd LG, Volmar KE, Creager AJ (2006) Cytomorphology of yolk sac tumor of the liver in fine-needle aspiration: a pediatric case. Diagn Cytopathol 34:421–423

Gonzalez-Crussi F (1982) Extragonadal teratomas. In: Hartmann WH (ed) Atlas of tumor pathology, 2nd series, fascicle 18. Armed Forces Institute of Pathology, Washington, DC

Gorbatiy V, Spiess PE, Pisters LL (2009) The growing teratoma syndrome: current review of the literature. Indian J Urol 25:186–189

Grave GF (1972) Teratoma of the liver. S Afr J Surg 10:121–123

Gunawardena SA, Siriwardana HP, Wickramasingha SY, Madurawe MN, Fernando R (2002) Primary endodermal sinus (yolk sac) tumour of the liver. Eur J Surg Oncol 28:90–91

Gupta R, Bansal K, Manchanda V, Gupta R (2013) Mature cystic teratoma of liver. ASPS J Case Rep 4:13

Gurewitsch R (1911) Ein ektopisches Chorionepitheliom der Leber nach Blasenmole. Kindt Publisher, Munich

Han SY (1970) Dermoid cyst of the liver. Report of case. Am J Roentgenol Radium Ther Nucl Med 109:842–843

Hanson D, Walter AW, Dunn S, Rittenhouse DW, Griffin G (2011) Infantile choriocarcinoma in a neonate with massive liver involvement cured with chemotherapy and liver transplant. J Pediatr Hematol Oncol 33: e258–e260

Hart WR (1975) Primary endodermal sinus (yolk sac) tumor of the liver. First reported case. Cancer 35:1453–1458

Hartz P, Van der Sar A (1945) Teratoma of the liver in an infant. Am J Clin Pathol 15:159–162

Heath JA, Tiedemann K (2001) Successful management of neonatal choriocarcinoma. Med Pediatr Oncol 36:497–499

Heaton GE, Matthews TH, Cristopherson WH (1986) Malignant trophoblastic tumors with massive hemorrhage presenting as liver primary. Am J Surg Pathol 10:342–347

Higuchi T, Kikuchi M (1993) Yolk sac tumor of the liver treated with transcatheter arterial embolization. Am J Gastroenterol 88:1125–1126

Hirashiki K, Kishimoto T, Ishiguro H, Nagai Y, Furuya M, Sekiya S, Ishikura H (2005) Regulatory role of CCAAT/enhancer binding protein-beta in the production of plasma proteins in yolk sac tumor. Exp Mol Pathol 78:247–256

Hong W, Dumoff KL, Torigian DA, Bing Z (2013) Primary retroperitoneal mature cystic teratoma with focal enteric type adenocarcinoma in a post-partum woman: report of a case with literature review. Rare Tumors 5: e1

Hongo T, Fujii Y, Fukuoka T, Iijima S, Matsushita T, Nakagawa Y, Igarashi Y (1992) Long-term treatment in infantile choriocarcinoma. Acta Paediatr Jpn 34:52–59

Hsieh YL, Liu CS (2009) Progression from an immature teratoma with military gliomatosis peritonei to growing teratoma syndrome with nodular gliomatosis peritonei. Pediatr Neonatol 50:78–81

Imai T (1934) Ein Fall von zystischem Teratoma der Leber, in welchem Plattenepithelkrebs entstand (A case of cystic teratoma of the liver, in which squamous cell carcinoma developed). Trans Soc Pathol Jpn 24:578–580

International Germ Cell Cancer Collaborative Group (1997) International Germ cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 15:594–603

Ishak KG (1976) Primary hepatic tumors in childhood. Prog Liver Dis 5:636–667

Jacobsen GK, Jacobsen M (1983) Possible liver cell differentiation in testicular germ cell tumors. Histopathology 7:537–548

Jain D, Mittal S, Gupta M (2013) Hepatocellular carcinoma arising in a testicular teratoma: a distinct and unrecognized secondary somatic malignancy. Ann Diagn Pathol 17:367–371

Jeffery GM, Theaker JM, Lee AH, Blaquière RM, Smart CJ, Mead GM (1991) The growing teratoma syndrome. Br J Urol 67:195–202

Kajo K, Machalekova K, Laca L (2009) Unusual clinical presentation of hepatic yolk sac tumour in periappendical region. A case report and review of the literature (in Slovak). Cesk Patol 45:113–116

Kalifa C, Brule F, Baillif P, Caillaud JM, Schweisguth O (1981) Metastases chez un nourisson d'un choriocarcinome placentaire. Arch Fr Pediatr 38:351–352

Kalinin VN (1964) Case of dermoid cyst of liver. Vest Rentgen Radiol 39:62–63

Kang YJ, Oh JH, Yoon Y, Kim EJ, Kim DY, Kang HS (2002) Hepatic metastasis from choriocarcinoma: angiographic findings in two cases. Korean J Radiol 3:260–263

Kapoor V, Ferris JV, Rajendiran S (2003) Growing teratoma syndrome of the liver: treatment with living related donor liver transplantation. AJR Am J Roentgenol 181:839–841

Kay S, Reed WG (1953) Chorioepithelioma of the lung in a female infant seven months old. Am J Pathol 29:555–561

Kelly DL, Kushner J, McLean WT (1971) Neonatal intracranial choriocarcinoma: case report. J Neurosurg 35:465–471

Kempers RD, Dockerty MB, Hoffman DL, Bartholomew LG (1970) Struma ovarii – ascetic, hyperthyroid, and asymptomatic syndromes. Ann Intern Med 72:883–893

Kim SN, Chi JG, Kim YW, Dong ES, Shin HY, Ahn HS, Kim CW (1993a) Neonatal choriocarcinoma of liver. Pediatr Pathol 13:723–730

Kim WS, Choi BI, Lee YS, Chi JG, Park HR, Kim I, Yeon KM, Han MC (1993b) Endodermal sinus tumour associated with benign teratoma of the common bile duct. Pediatr Radiol 23:59–60

Kinoshita Y, Tajiri T, Souzaki R, Tatsuta K, Higashi M, Izaki T, Takahashi Y, Taguchi T (2008) Diagnostic value of lectin reactive alpha-fetoprotein for neoinfantile hepatic tumors and malignant germ cell tumors: preliminary study. J Pediatr Hematol Oncol 30:447–450

Kiran RP, Visvanathan R, Simpson CG (2001) Eur J Surg Oncol 27:436–437

Kiryabwire JW, Mugerwa JW (1967) Teratoma of the liver in an African child. Br J Surg 54:585–587

Kishkurno S, Ishida A, Takahashi Y, Arai H, Nakajima W, Abe T, Takada G (1997) A case of neonatal choriocarcinoma. Am J Perinatol 14:79–82

Kobayashi Y, Inoue T (1995) Hepatic teratoma, malignant teratoma (in Japanese). Ryoikibetsu Shokogun Shirizu 7:329–332

Kobayashi N, Koizumi T, Eguchi T, Hyogotani A, Saito G, Hamanaka K, Shiina T, Kurai M et al (2010) A mediastinal somatic-type germ cell tumor with hepatic metastasis successfully treated by multiple modalities. Anticancer Res 30:5117–5120

Konez O, Hanelin LG, Jenison EL, Goyal M, Randolph W (2000) Functioning liver metastases of an I-131 whole-body scan: a case of malignant struma ovarii. Clin Nucl Med 25:465–496

Kraudel K, Williams CH (1984) Ultrasound case report of hepatic teratoma in newborn. J Clin Ultrasound 12:98–101

Kruseman AC, van Lent M, Blom AH, Lauw GP (1977) Choriocarcinoma in mother and child, identified by immunoenzyme histochemistry. Am J Clin Pathol 67:279–283

Lazure T, Durand P, Chevret L, Cuilliere P, Pariente D, Bui M, Lhomme C, Fabre M (2003) Infantile and maternal choriocarcinoma (in French). Ann Pathol 23:153–156

Lenci I, Tariciotti L, Baiocchi L, Manzia TM, Toti L, Craboledda P, Callea F, Angelico M, Tisone G (2008) Primary yolk sac tumor of the liver: incidental finding in a patient transplanted for hepatocellular carcinoma. Transpl Int 21:598–601

Lentini JF, Love MB, Ritchie WG, Sedlacek TV (1986) Computed tomography in retroconversion of hepatic metastases from immature ovarian teratoma. J Comput Assist Tomogr 10:1060–1062

Leschke W (1959) Liver teratoma in an adult (in German). Zentralbl Allg Pathol 99:255–258
Littoji AS, McHugh K, McCarville MB, Sebire NJ, Bahrami A, Roebuck DJ (2014) Yolk sac tumour: a rare cause of raised serum alpha-foetoprotein in a young child with a large liver mass. Pediatr Radiol 44:18–22
Liu J, Guo L (2006) Intraplacental choriocarcinoma in a term placenta with both maternal and infantile metastases: a case report and review of the literature. Gynecol Oncol 103:1147–1151
Logothetis CJ, Samuels ML, Trindade A, Johnson DE (1982) The growing teratoma syndrome. Cancer 50:1629–1635
Lok CA, Reekers JA, Westermann AM, Van der Velden J (2005) Embolization for hemorrhage of liver metastases from choriocarcinoma. Gynecol Oncol 98:506–509
Lombardo FP, Hertford DE, Tan LK, Kazam E, Ramirez de Arellaro E (1995) Epidermoid cyst of the liver complicated by microscopic squamous cell carcinoma: CT, ultrasound, and pathology. J Comput Assist Tomogr 19:131–134
Lorusso D, Malaguti P, Trivellizzi IN, Scambia G (2011) Unusual liver locations of growing teratoma syndrome in ovarian malignant germ cell tumors. Gynecol Oncol Case Rep 1:24–25
Madan M, Arora R, Singh J, Kaur A (2010) Mature cystic teratoma of the liver in an adult female. Indian J Pathol Microbiol 53:872–873
Marcy PY, Thariat J, Benisvy D, Azuar P (2010) Lethal, malignant, metastatic struma ovarii. Thyroid 20:1037–1040
Marennyi VM (1971) Teratoma of the hepatic portal (in - Russian). Klin Khir 3:56
Martin LC, Papadatos D, Michaud C, Thomas J (2004) Best cases from the AFIP: liver teratoma. Radiographics 24:1467–1471
Mattucci ML, Dellera A, Guerriero A, Barbieri F, Minnelli L, Furlani L (2007) Malignant struma ovarii: a case report and review of the literature. J Endocrinol Invest 30:517–520
McDougall IR (2006) Metastatic struma ovarii: the burden of truth. Clin Nucl Med 31:321–324
McGlynn KA, Devesa SS, Sigurdson AJ et al (2003) Trends in the incidence of testicular germ cell tumors in the United States. Cancer 97:63–70
Meckel H (1894) Chirurgie der Leber und Gallenblase. Cit. by Langenbeck. Dtsch Chir 45, Lief. 1/2
Mercer RD, Lammert AC, Anderson R, Hazard JB (1958) Choriocarcinoma in mother and infant. J Am Med Assoc 166:482–483
Misick OS (1898) A case of teratoma hepatis. J Path Bact 5:128–136
Misugi K, Reiner CB (1965) A malignant true teratoma of liver in childhood. Arch Pathol 80:409–412
Moon WK, Kim WS, Kim IO, Hong JH, Yeon KM, Han MC, Chi JG, Ahn HS, Shin HY (1993) Hepatic choriocarcinoma in a neonate: MP appearance. J Comput Assist Tomogr 17:653–655
Moore SW, Davidson A, Hadley GP, Kruger M, Poole J, Stones D, Wainwright L, Wessels G (2008) Malignant liver tumors in South African children: a national audit. World J Surg 32:1389–1395
Morinaga S, Nishiya H, Inafuku T (1996) Yolk sac tumor of the liver combined with hepatocellular carcinoma. Arch Pathol Lab Med 120:687–690
Mousavi SA, Behnamfer F (2009) Gestational trophoblastic tumor with liver metastasis after misoprostol abortion. Arch Gynecol Obstet 279:587–590
Munghate GS, Agarwala S, Bhatnagar V (2011) Primary yolk sac tumor of the common bile duct. J Pediatr Surg 46:1271–1273
Nakamura M, Hanai T, Sanjyo H, Yasuda K, Takamoto D, Gohbara A, Teranishi J, Yumura Y et al (2013) A suspected case of extra-gonadal germ cell tumor complicated with choriocarcinoma syndrome (in Japanese). Hinyokika Kiyo 59:309–314
Nakashima N, Fukatsu T, Nagasaka T, Sobue M, Takeuchi J (1987) The frequency and histology of hepatic tissue in germ cell tumors. Am J Surg Pathol 11:682–692
Yong Hin Nam (1970) Dermoid cyst in the liver. Radiography 36:148–150
Narita T, Moriyama Y, Ito Y (1988) Endodermal sinus (yolk sac) tumor of the liver. A case report and review of the literature. J Pathol 155:41–47
Natori T, Teshima S, Kikuchi Y, Aizawa M, Konno T, Tamaki A, Kakita A, Shinada Y, Kasai Y (1983) Primary yolk sac tumor of the liver. An autopsy case with ultrastructural and immunopathological studies. Acta Pathol Jpn 33:555–564
Ng CF, Tsui TM, To KF, Hou SM, Yip SS (2010) Late recurrent seminoma: 18 years after bilateral orchidectomy in patient with bilateral stage one testicular seminoma. Int Urol Nephrol 42:69–72
Nieuwenhuizen Krusemann AC, van Lant M, Blom AH, Lauw GP (1977) Choriocarcinoma in mother and child, identified by immunoenzyme histochemistry. Am J Clin Pathol 67:279–283
Nikaidoh H, Boggs J, Swenson O (1970) Liver tumors in infants and children. Clinical and pathological analysis of 22 cases. Arch Surg 101:245–257
Nirmala V, Chopra P, Machado NO (2003) An unusual adult hepatic teratoma. Histopathology 43:306–308
Nissel W (1928) Die Mischgeschülste der Leber. Virchows Arch Pathol Anat Physiol Klin Med 269:446–457
O'Connell ME, Fisher C, Harmer CL (1990) Malignant struma ovarii: presentation and management. Br J Radiol 63:360–363
Okamatsu T, Nagai M, Lie U et al (1980) Yolk sac tumor of the liver. Report of a case. Pediatr Surg 12:821–826
Ooserhuis JW, Peeters SH, Smit VT, Stoop H, Looijenga LH, Elezvier HW, Osanto S (2013) Patient with two secondary somatic-type malignancies in a late recurrence of a testicular non-seminoma: illustration of potential and flaw of the cancer stem cell therapy concept. Int J Dev Biol 57:153–157
Ordi J, Romagosa C, Tavassoli FA, Nogales F, Palacin A, Condom E, Torne A, Cardesa A (2003) CD10

expression in epithelial tissues and tumors of the gynaecologic tract: a useful marker in the diagnosis of mesonephric, trophoblastic, and clear cell tumors. Am J Surg Pathol 27:178–186

Paliwal N, Gupta K, Dewan RK, Mullick S (2013) Adenocarcinoma (somatic-type malignancy) in mature teratoma of anterior mediastinum. Indian J Chest Dis Allied Sci 55:39–41

Pear BL, Boline JE (1972) Teratoma of the liver. Cancer Sem 4:229–233

Pectasides D, Nikolaou M, Pectasides E, Koumarianou A, Valavanis C, Economopoulos T (2008) Complete response after imatinib mesylate administration in a patient with chemoresistant stage IV seminoma. Anticancer Res 28:2317–2320

Perlman EJ, Cushing B, Hawkins E, Griffin CA (1994) Cytogenetic analysis of childhood endodermal sinus tumors: a Pediatric Oncology Group study. Pediatr Pathol 14:695–708

Perlman EJ, Valentine MB, Griffin CA, Look AT (1996) Deletion of 1p36 in childhood endodermal sinus tumors by two-color fluorescence in situ hybridization: a Pediatric Oncology Group Study. Genes Chromosomes Cancer 16:15–20

Pfefferkorn A, Commichau G (1955) Embryonic teratoma of the common bile duct with a transition into an osteochondrosarcoma (in German). Bruns Beitr Klin Chir 191:486–493

Picton SV, Bose-Haider B, Lendon M, Hancock BW, Campbell RH (1995) Simultaneous choriocarcinoma in mother and newborn infant. Med Pediatr Oncol 25:475–478

Pollice L (1973) Primary hepatic tumors in infancy and childhood. Am J Clin Path 60:512–521

Potter EL (1962) Pathology of the fetus and the infant, 2nd edn. Year Book Medical Publishers, Chicago

Pourang H, Sarmadi S, Mireskandari SM, Soleimani M, Mollaeian M, Alizadeh H, Alehosein SM (2009) Twin fetus in fetu with immature teratoma: a case report and review of the literature. Arch Iranian Med 12:507–510

Rahmat K, Vijayananthan A, Abdullah B, Amin S (2006) Benign teratoma of the liver: a rare cause of cholangitis. Biomed Imaging Interv J 2:e20

Rao PL, Venkatesh A, Murthy VS (1987) Cystic teratoma in the bare area of liver. Indian J Pediatr 54:275–278

Rentsch I, Gartner U, Muller P, Kerk L (1977) Endoscopic retrograde cholangiopancreatography (ERCP) in obstructive jaundice caused by metastatic testicular teratoma. Endoscopy 9:101–103

Robinson RA, Nelson L (1986) Hepatic teratoma in an anencephalic fetus. Arch Pathol Lab Med 110:655–657

Rodriguez E, Melamed J, Reuter V, Chaganti RS (1995) Chromosomal abnormalities in choriocarcinoma of the female. Cancer Genet Cytogenet 80:9–12

Roma AA, Humphrey PA (2010) Bile duct-like differentiation in teratoma: a clinicopathologic and immunohistochemical study. Ann Diagn Pathol 14:402–407

Roth LM, Miller AW, Taleman A (2008) Typical thyroid-type carcinoma arising in struma ovarii: a report of 4 cases and review of the literature. Int J Gynecol Pathol 27:496–506

Rotman-Pikielny P, Reynolds JC, Barker WC, Yen PM, Skarulis MC, Sarlis NJ (2000) Recombinant human thyrotropin for the diagnosis and treatment of a highly functional metastatic struma ovarii. J Clin Endocrinol Metab 85:237–244

Salvatori M, Dambra DP, D'Angelo G, Conte LL, Locantore P, Zannoni G, Campo V, Campo S (2008) A case of metastatic struma ovarii treated with ^{131}I therapy: focus on preservation of fertility and selected review of the literature. Gynecol Endocrinol 24:312–319

Samaniego F, Rodriguez E, Houldsworth J, Murty VV, Ladanyi M, Lele KP, Chen QG, Dmitrovsky E, Geller NL, Reuter V et al (1990) Cytogenetic and molecular analysis of human male germ cell tumors: chromosome 12 abnormalities and gene amplification. Genes Chromosomes Cancer 1:289–300

Sasaki H, Ajiki T, Takase S, Fujino Y, Suzuki Y, Tominaga M et al (2005) Images of interest. Hepatobiliary and pancreatic: mature cystic teratoma in the hepatoduodenal ligament. J Gastroenterol Hepatol 20:317

Sashi R, Sato K, Hirano H, Tomura N, Watarai J, Ishida A, Morita M (1996) Infantile choriocarcinoma: a case report with MRI, angiography and bone scintigraphy. Pediatr Radiol 26:869–870

Satake N, Chikakiyo M, Yagi T, Suzuki Y, Hirose T (2011) Gastric cancer with choriocarcinoma and yolk sac tumor components: case report. Pathol Int 61:156–160

Schaefer IM, Zardo P, Freermann S, Marx A, Ströbel P, Fischer S (2013) Neuroendocrine carcinoma in a mediastinal teratoma as a rare variant of somatic-type malignancy. Virchows Arch 463:731–735

Schnater JM, Kuijper CF, Zsiros J, Heij HA, Aroson DC (2005) Pre-operative diagnostic biopsy and surgery in paediatric liver tumours – the Amsterdam experience. Eur J Surg Oncol 31:1160–1165

Schullinger JN, Wigger HJ, Price JB, Benson M, Harris RC (1983) Epidermoid cysts of the liver. J Pediatr Surg 18:240–242

Sekine R, Hyodo M, Kojima M, Meguro Y, Suzuki A, Yokoyama T, Lefor AT, Hirota N (2013) Primary hepatic choriocarcinoma in a 49-year-old man: report of a case. World J Gastroenterol 19:9485–9489

Shi H, Cao D, Wei L, Sun L, Guo A (2010) Primary choriocarcinoma of the liver: a clinicopathological study of five cases in males. Virchows Arch 456:65–70

Shih IM, Kurman RJ (1999) Immunohistochemical localization of inhibin-alpha in the placenta and gestational trophoblastic lesions. Int J Gynecol Pathol 18:144–150

Shitara T, Oshima Y, Yugami S et al (1993) Choriocarcinoma in children. Am J Pediatr Hematol Oncol 15:268–269

Simpson L, Sundaresan R, Vohra M, Sheagren J, Cougar D, August C, Ali I (2005) Invasive choriocarcinoma involving the major duodenal papilla. Gastrointest Endosc 61:926–928

Sissoew T (1922) Wissenschaftliche Sammelschrift zum 50jährigen Jubiläum von Prof. A.A. Netschaew, cited in Nissel 1928

Souftas V, Polychronidis A, Giatromanolaki A, Perente S, Simopoulos C (2008) Dermoid cyst in the hepatoduodenal ligament: report of a case. Surg Today 38:959–961

Srivastava PK, Gangopadhyay AN, Gupta DK, Sharma SP, Kumar V (2011) Unusual content of omphalocele: a congenital mature cystic teratoma of falciform ligament of the liver. Pediatr Surg Int 27:1355–1356

Stackievicz R, Drucker L, Zemer R, Klein A, Markovitch O, Yarkon S (2002) Cytokeratin 20 as a biomarker of gestational trophoblastic disease: diagnostic and prognostic significance. Gynecol Oncol 87:34–38

Stärk A (1917) Malignes Chorionepitheliom bei einem 28jährigen Soldaten mit kleinem Embryom des Hodens. Inaugural-Dissertation, Frankfurt

Stock C, Ambros IM, Lion T, Haas OA, Zoubek A, Gadner H, Ambros PF (1994) Detection of numerical and structural chromosome abnormalities in pediatric germ cell tumors by means of interphase cytogenetics. Genes Chromosomes Cancer 11:40–50

Stomper PC, Jochelson MS, Friedman EL, Garnick MB, Richie JP (1986) CT evaluation of advanced seminoma treated with chemotherapy. AJR Am J Roentgenol 146:745–748

Stoy R (1921) Über ein primäres Chorionepitheliom der Leber bei einem Manne (On a primary chorionepithelioma of the liver in a man). Inaugural Dissertation, Frankfurt

Strunk H, Borner N, Stuckmann G, Fröhlich E, Hadizadeh D (2005) Contrast-enhanced ‚low MI real-time' sonography for the assessment of the malignancy of focal liver lesions (in German). Röfo 177:1394–1404

Szavay PO, Wermes C, Fuchs J, Schrappe M, Flemming P, von Schweinitz D (2000) Effective treatment of infantile choriocarcinoma in the liver with chemotherapy and surgical resection: a case report. J Pediatr Surg 35:1134–1135

Tahara H, Hirokawa T, Oyama T, Naganuma A, Maruta S, Ban S, Yoshida K, Takagi H, Mori M (2008) Gastric yolk sac tumor complicated with beta-human chorionic gonadotropin-producing metastases. Intern Med 47:2145–2149

Teleshov A (1989) Teratoma of the liver (in Russian). Klin Khir (9):61

Teo CH, Leow CK, Chang SA (2005) A pseudoepidermoid cyst arising from exuberant squamous metaplasia of the gallbladder. Arch Pathol Lab Med 129:e138–e140

Theegarten D, Reinacher A, Greaven U, Philippou S (1998) Mixed malignant germ cell tumour of the liver. Virchows Arch 433:93–96

Thomas RD, Batty VB (1992) Metastatic malignant struma ovarii. Two case reports. Clin Nucl Med 17:577–578

Todani T, Tabuchi K, Watanabe Y, Tsutsumi A (1977) True hepatic teratoma with high alpha fetoprotein in serum. J Pediatr Surg 12:591–592

Toumi N, Chaumette-Plankaert MT, Cherqui D, de Revel T, Duvillard P, Theodore C (2004) Germ cell tumors. Case 3. Primary yolk sac tumor of the liver. J Clin Oncol 22:1756–1758

Trinh DT, Shibata K, Hirosawa T, Umezu T, Mizuno M, Kajiyama H, Kikkawa F (2012) Diagnostic utility of CD117, CD133, SALL4, OCT4, TCL1 and glypican-3 in malignant germ cell tumors of the ovary. J Obstet Gynaecol Res 38:841–848

Tsukamoto N, Matsumura M, Matsukuma K et al (1986) Choriocarcinoma in mother and fetus. Gynec Oncol 24:113–119

Uekado Y, Sawada Y, Inagaki T, Hiroi A (1994) Effective chemoembolization for liver metastasis in a case of testicular cancer (in Japanese). Gan To Kagaku Ryoho 21:1673–1676

Ulbright TM (2005) Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. Mod Pathol 18(suppl 2):S61–S79

Van de Geijn GJ, Hersmus R, Looijenga LH (2009) Recent developments in testicular germ cell tumor research. Birth Defects Res C Embryo Today 87:96–113

Van der Hoef M, Niggli FK, Willi UV, Huisman TA (2004) Solitary infantile choriocarcinoma of the liver: MRI findings. Pediatr Radiol 34:820–823

Verma M, Agarwal S, Mohta A (2003) Primary mixed germ cell tumour of the liver – a case report. Indian J Pathol Microbiol 46:658–659

Vilaschi S, Balistreri P (1991) Endodermal sinus tumour of the liver. Histopathology 18:86–88

Wakely PE, Krummel TM, Johnson DE (1991) Yolk sac tumor of the liver. Mod Pathol 4:121–125

Walthard M (1907) Zur Ätiologie der Chorionepitheliome ohne Primärtumor im Uterus. Zschr f Geburtsh 59:443

Wang H, Dong J (2004) Teratoma in the hepatoduodenal ligament followed by portal hypertension syndrome. J Gastroenterol Hepatol 19:477–479

Wang J, Kazmi SA (2011) Teratoma with malignant transformation: a case report with pathological, cytogenetic, and immunohistochemistry analysis. Sarcoma 2011:450743

Wang L, Tabbarah HJ, Gulati P, Rice S, French SW (2000) Gastric adenocarcinoma with a yolk sac component: a case report and review of the literature. J Clin Gastroenterol 31:85–88

Warren M, Thompson KS (2009) Two cases of primary yolk sac tumor of the liver in childhood: case reports and literature review. Pediatr Dev Pathol 12:410–416

Waseda Y, Komai Y, Yano A, Fujii Y, Noguchi N, Kihara K (2012) Pathological complete response and two-year disease-free survival in a primary gastric choriocarcinoma patient with advanced liver metastases treated with germ cell tumor-based chemotherapy: a case report. Jpn J Clin Oncol 42:1197–1201

Watanabe I, Kasai M, Suzuki S (1978) True teratoma of the liver: report of a case and review of the literature. Acta Hepatogastroenterol 25:40–44

Weis J, Luechtrath H (1964) Embryonal teratoma of the liver (in German). Virchows Arch Pathol Anat Physiol Klin Med 338:45–50

Whelan JS, Stebbings W, Owen RA, Calne R, Clark PI (1992) Successful treatment of a primary endodermal sinus tumour of the liver. Cancer 70:2260–2262

Winter TC, Freeny P (1993) Hepatic teratoma in an adult. Case report with review of the literature. J Clin Gastroenterol 17:308–310

Witte DP, Kissane JM, Askin FB (1983) Hepatic teratomas in children. Pediatr Pathol 1:81–92

Witzleben CL, Bruninga G (1968) Infantile choriocarcinoma: a characteristic syndrome. J Pediatr 73:374–378

Wold LE, Kramer SA, Farrow GM (1984) Testicular yolk sac and embryonal carcinomas in pediatric patients: comparative immunohistochemical and clinicopathologic study. Am J Clin Pathol 81:427–435

Wong NA, D'Costa H, Barry RE, Alderson D, Moorghen M (1998) Primary yolk sac tumor of the liver in adulthood. J Clin Pathol 51:939–940

Worster et al. (2002) http://www.ncbi.nlm.nih.gov/pubmed/17612431

Xu AM, Gong SJ, Song WH, Li XW, Pan CH, Zhu JJ, Wu MC (2010) Primary mixed germ cell tumor of the liver with sarcomatous components. World J Gastroenterol 16:652–656

Yalcin B, Kutluk MT, Ariyürek M, Gögüs S, Büyükpamukçu M (2002) Metastatic endodermal sinus tumor: CT appearances. Turk J Pediatr 44:343–345

Yan QH (1982) Primary endodermal sinus tumor of the liver: a case report with a discussion on embryogenesis. Chung Hua Chung Liu Tsa Chih 4:224–225

Yano T, Miyamoto U, Mukai T, Noda K, Eto Y, Uchida T, Oya I, Kaji M (1983) A case of alpha-fetoprotein producing embryonal carcinoma of the stomach (in Japanese). Gan No Rinsho 29:A-23

Yarbrough SM (1944) Report of a case of teratoma of the liver in an infant. Texas J Med 40:426–427

Yarbrough SM, Evashwick G (1956) Case of teratoma of the liver, with fourteen-year postoperative survival. Cancer 9:848–850

Yokoi Y, Suzuki S, Baba S, Ohzeki T, Yajima S, Okada S, Okumura T, Konno H, Nakamura S (2003) Aggressive hepatectomy for complete remission of metastatic germ cell tumor following chemotherapy: report of a case. Hepatogastroenterology 50:1136–1139

Yoon JM, Burns RC, Malogolowkin MH, Mascarenhas L (2007) Treatment of infantile choriocarcinoma of the liver. Pediatr Blood Cancer 49:99–102

You YN, Leibovitch BC, Que FG (2009) Hepatic metastasectomy for testicular germ cell tumors: is it worth it? J Gastrointest Surg 13:595–601

Zhang X, Axiotis C (2010) Thyroid-type carcinoma of struma ovarii. Arch Pathol Lab Med 134:786–791

Zhang B, Gao S, Chen Y, Wu Y (2010) Primary yolk sac tumor arising in the pancreas with hepatic metastasis: a case report. Korean J Radiol 11:472–475

Zhao JG, Cai B, Qiu B, Sun L (2010) A case report of immature hepatic teratoma (in Chinese). Zhonghua Gan Zang Bing Za Zhi 18:72

Zynger DL, McCallum JC, Luan C, Chou PM, Yang XJ (2010) Glypican 3 has a higher sensitivity than alpha-fetoprotein for testicular and ovarian yolk sac tumor: immunohistochemical investigation with analysis of histological growth patterns. Histopathology 56:750–757

Part XVI

Hepatobiliary Myeloid Neoplasms

Myeloid Neoplasms with an Erythroid Cell Lineage

80

Contents

Abstract

Polycythemia vera (PV; polycythemia rubra vera) is a chronic myeloproliferative neoplasm characterized by increased red blood cell production independent of normal regulatory mechanisms. The majority of patients with PV show the JAK2V617F mutation or another functional similar JAK mutation. In fully developed disease, there is hepatomegaly associated with hyperemia and eventually signs of hepatic infarcts. Histologically, the sinusoids are dilated and filled with erythrocytes which can form stacks or "rouleaus." PV is complicated by hepatic venous outflow disorders, in particular hepatic vein thrombosis with Budd-Chiari syndrome, sometimes associated with factor V Leiden mutation. Portal vein thrombosis is a well-documented complication of PV. These hepatic blood flow disorders are frequently followed by nodular regenerative hyperplasia. PV can also cause perisinusoidal fibrosis with an increase in reticulin and fibrotic changes of the liver related to necrosis and infarction.

Polycythemia Vera

ICD-O Code 9950/3

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_80

Introduction

The 2008 WHO classification defines polycythemia vera (polycythemia rubra vera; PV; formerly also termed "plethora vera") as a chronic myeloproliferative neoplasm characterized by increased red blood cell production independent of normal regulatory mechanisms. Practically all patients with PV harbor the JAK2V617F mutation or another functional similar JAK mutation, resulting in proliferation of all hematopoietic cell lineages ("panmyelosis").

PV was first described by Vaquez, and Osler recognized it as a "new clinical entity" characterized by chronic cyanosis and polycythemia, hence using the term still employed today (Vaquez 1892; Osler 1903; review: Means 2008). PV is characterized by the insidious onset of erythroid proliferation (erythrocytosis) and secondary platelet and granulocyte overproduction; it can progress from a proliferative stage to a "metastatic" phase and further develop into a clinically malignant phase (Golden 2003; Gilbert 2003). In 1967, the Polycythemia Vera Study Group (PVSG) was organized to identify the optimal approach to diagnosis of PV (Table 1).

In modern classifications, three phases of PV may be recognized: (1) a prepolycythemic or prodromal phase with borderline to only mild erythrocytosis; (2) an overt polycythemic phase, characterized by a significantly increased red cell mass; and (3) a "spent" or post-polycythemic myelofibrosis phase, in which cytopenias, including anemia, are associated with bone marrow fibrosis, extramedullary hematopoiesis, and hypersplenism. PV can also evolve into myelodysplasia and acute leukemia.

Table 1 PVSG diagnostic criteria for PV

Category A
A1 increased red cell mass
M > = 36 mL/kg
F > = 32 mL/kg
A2 oxygen saturation > = 92 %
A3 splenomegaly
Category B
B1 platelets > = 400 × 10(9)/L
B2 white blood cell count > = 12 × 10(9)/L
B3 LAP score >100[a]
B4 serum B12 > 900 pg/mL (660 pM)
U B12 BC >2,200 pg/mL (1,620 pM)

U B12 BC indicates unbound vitamin B12 binding capacity

[a]In the absence of fever or infection

Adapted from: Peterson and Wasserman (1995)

Epidemiology

The disease is rare, with an estimated incidence of 2.3 per 100,000; it is more frequent in males and usually affects older individuals, although cases in young adults and children have been reported (Tefferi 2001). In a large retrospective study examining all in- and outpatient records of Olmsted County, Minnesota, over a period of 55 years, the incidence rate of PV was 1.9 per 100,000 persons and year, and incidence rates increased with advancing age for men up to 23.5 per 100,000 and year, the median age at presentation being 55–60 years (Ania et al. 1994).

Clinical Features

PV is a chronic myeloproliferative disorder characterized by panmyelosis, splenomegaly, and a predisposition to vascular thrombosis, myelofibrosis, and acute leukemia. Basically, it represents a clonal stem cell disease with persistently increased erythrocyte production and is the only known type of primary acquired polycythemia (reviews: Berlin and Wasserman 1997; Streiff et al. 2002; Golden 2003; Tefferi 2003).

Liver Pathology in Polycythemia Vera

Macroscopy

A part of patients with PV show hepatomegaly. In fully developed disease, the enlarged and engorged liver shows a cut surface which is dark-red or gray-blue, sometimes with small nodular regenerates. In fresh state, cutting through the

organ is followed by copious oozing of blood from the cut surface, sometimes intermingled with small granules of coagulated blood or thrombi (Hirschfeld 1906; Hamilton and Morse 1912; Mosse 1920). The liver capsule can show scarred depressions, probably sequelae of previous infarctions caused by venous thrombosis.

Histopathology

The sinusoids are markedly dilated and filled with erythrocytes which can form stacks or develop rouleau formation. A part of the sinusoids are so densely packed with red blood cells that the endothelial lining is no longer visible, the perisinusoidal space of Disse is effaced or compressed, and hepatocyte plates have undergone atrophy. Erythrocytes may enter the space of Disse, mimicking so-called Disse space hemorrhage. A slight increase of reticulin fibers may occur in the perisinusoidal space. Engorged vessels are also found in the portal tracts. In case of PV with myelofibrosis and myeloid metaplasia, there may be hepatic enlargement with extensive extramedullary hematopoiesis with dilatation of sinusoids, compression of hepatocyte plates, and hepatocyte atrophy and dysfunction, resulting in acute hepatic failure (McBrine et al. 1980).

Hepatic Venous Outflow Disorders in PV

Hepatic venous outflow disorders, and mainly Budd-Chiari syndrome (BCS), occur as a complication of several types of myeloproliferative disorders (Poreddy and DeLeve 2002). As they are specifically well known for patients suffering from PV, these disorders are discussed in this paragraph. The BCS results from thrombogenic conditions and is caused by stenosis or obstruction of the hepatic venous outflow at the level of the hepatic veins and/or of the suprahepatic part of the inferior caval vein (Sherlock and Dooley 1993; Dilawari et al. 1994; Mahmoud et al. 1996; Valla 2002). The level of obstruction is reflected by two chief forms of BCS. The acute syndrome is invariably associated with extensive blockage of the major hepatic veins, and in a small fraction of patients, the caval vein is also occluded. Acute BCS causes a characteristic liver pathology with massive congestion and necrosis. In contrast, the chronic form of BCS is characterized by portal venous hypertension and a variably abnormal vasculature (Dilawari et al. 1994; Tilanus 1995; Iwai et al. 1998). On the other hand, it has been proposed to classify hepatic venous outflow disorders caused by thrombosis into two groups, the first representing "classical" BCS that is more common in the West and the second representing an obliterative disease predominantly affecting the hepatic portion of the inferior vena cava ("obliterative hepatocavopathy"), the latter being predominant in developing countries and being "idiopathic" or then being associated with hepatocellular carcinoma (Okuda et al. 1995, 1998; Okuda 2002). A more recent expert panel classifies BCS on the one hand according to etiology (primary vs. secondary forms) and on the other hand according to the site of obstruction (small hepatic veins, large hepatic veins, inferior vena cava. and combined obstruction) (Janssen et al. 2003).

Pathogenically, BCS probably represents a spectrum of disease caused primarily by a hypercoagulable state and eventually promoted by vascular changes favoring local thrombosis, e.g., malignant tumors in the liver. Membranous obstruction (web) of the caval vein (MOVC) has formerly been regarded as a congenital alteration sometimes causing BCS, but is currently considered to be a sequela to thrombosis (Kage et al. 1992). However, a significant fraction of patients with BCS have no identifiable underlying condition, the percentage ranging from 13 % to 62 % in several studies (Hadengue et al. 1994; Slakey et al. 2001). Apart from PV, BCS developing as a complication of MPD is established for CML (Picardi et al. 2000).

The association of BCS and PV is well established for a long time (Chini 1954; Brown et al. 1955; Caroli and Soulier 1956; Cantwell et al. 1956; Chlumsky and Chlumska 1966; Siguier et al. 1967; Thomas and Caroli 1971; Retzlaff and Monge 1973; Balique 1981;

Fechtner and DelDuca 1994). In one study on BCS, overt PV was the underlying cause in about 10 % of the cases, and essential thrombocythemia and chronic idiopathic myelofibrosis in only a very few (De Stefano et al. 1997). BCS associated with PV has also been observed in children from families with familial PV (Cario et al. 2003). Hepatic venous thrombosis in patients with PV is induced by other disorders with a genetic background, such as the factor V Leiden mutation and other thrombophilic coagulation disorders (Janssen 2000; Mohanty et al. 2001). It was shown that the factor V Leiden mutation is in fact the second most common etiology associated with BCS (Mahmoud et al. 1997; Delarive and Gonvers 1998; Simsek et al. 2000; Janssen et al. 2000; Deltenre et al. 2001), whereas other genetic disorders of thrombophilic factors are rarer causes of BCS (e.g., the G20210A mutation of the prothrombin gene; Poort et al. 1996; Bucciarelli et al. 1998; De Stefano et al. 1998; Oner et al. 1999; Minnema et al. 2000; Brancaccio et al. 2002). It has been observed that fulminant BCS in PV was associated with factor V Leiden mutation (Akyildiz et al. 2006).

Portal Vein and/or Splanchnic Vein Thrombosis in Polycythemia Vera

The etiology of portal vein thrombosis (PVT) is heterogeneous, but important primary risk factors comprise cirrhosis, hepatobiliary malignancies, pancreatitis, and several disorders of the coagulation system (Mahmoud et al. 1997; review: Janssen 2000; Janssen et al. 2000). PVT is a well-documented complication of PV in its overt, masked, or early forms (Lommel 1906; Kratzeisen 1923; Alford et al. 1968; Valla et al. 1988; Drenou et al. 1992; Pati et al. 1998; Escher and Demarmels Biasiutti 1999; Randi et al. 2002). On the other hand, PVT is also known to be itself a complication of BCS that can be caused by PV. PVT, apart from its perfusion disorder of the liver, can cause compression of the bile duct in PV (Löhr et al. 1993). PV T in PV can be complicated by pylothrombophlebitis.

Why Is PV Associated with Thrombosis of Large Veins?

Thrombotic events are present in 20–50 % of patients with PCV at diagnosis and involve both large vessels and the microcirculation. It is estimated that the incidence of thrombosis is higher in PV than in essential thrombocythemia, and significant risk factors are increasing age and previous thrombosis (Orlandi et al. 1989; Pearson 2002). The pathogenic mechanisms underlying the increased incidence of thrombotic events in PV are still somewhat illusive. Prothrombotic factors such as an increased blood viscosity caused by an elevated hematocrit, abnormal platelet functions, and the procoagulative action of the cells involved have been proposed (Fields and Freeman 1993; Fiessinger 1994; Michiels 1997; Barbui and Finazzi 1997; Gumina et al. 2002; Friess et al. 2003). It has been shown that thrombocytes form heterotypic aggregates with leukocytes (platelet-neutrophil complexes; PNC) through platelet CD62P and leukocyte beta2-integrins, resulting in cell features with increased adhesion (Peters et al. 1999). A platelet-leukocyte conjugate formation occurring in myeloproliferative disorders, including PV, seems to indicate platelet activation, associated with platelet microparticle production serving as catalytic surfaces for thrombin generation (Villmow et al. 2002). In BCS or portal vein thrombosis, an increased expression of CD11b on neutrophils was detected, supporting a role for neutrophils in hepatic venous thrombosis (Alvarez-Larran et al. 2004). Increased CD11/CD18 expression on neutrophils is also found in essential thrombocythemia (Burgaleta et al. 2002). In addition, there is an "endothelial factor" in the pathogenic cascade of PV-associated thrombosis. PV seems to cause endothelial dysfunction in the preclinical phase of arterial disease, characterized by impaired flow-mediated vasodilatation (Neunteufl et al. 2001). On the other hand, there are findings indicating that hepatic erythropoietin production occurs in the acute phase of BCS and suggesting that, in some cases of BCS, erythrocytosis which resolves after the acute phase may be secondary to liver disease (Levy et al. 1985). A new line of

thinking in regard to factors promoting thrombogenesis in PV and other myeloproliferative disorders is the pathogenic role of the JAK2V617F mutation in PV (Patel et al. 2006; Sozer et al. 2009; Benedik-Dolnicar et al. 2012; de Grandis et al. 2012; Yonal et al. 2012). This issue is discussed in more detail in the chapter on essential thrombocythemia.

Nodular Regenerative Hyperplasia in PV

Subacute or chronic BCS can result in a distinct hepatocyte response characterized by the production of numerous hepatocyte nodules not encircled by collagen fibers, but compressing the adjacent parenchyma. This is *nodular regenerative hyperplasia* (NRH) of the liver, occurring in several myeloproliferative disorders associated with hepatic venopathies and being a cause of portal hypertension (Al-Mukhaizeem et al. 2004). NRH is characterized by multiple enhancing nodules in CT during the hepatic arterial and portal venous phases and by hyperintense nodules in MR on T1-weighted images and hypointense or isointense nodules on T2-weighted images (Castellano et al. 1989; De Sousa et al. 1991; Wanless 1994; Clouet et al. 1999; Rha et al. 2000; Soler et al. 2000). NRH is discussed in more detail in another chapter. Even though NRH with small regenerative nodules may mimic multiple small metastases in the liver or produce a pseudotumoral presentation (Casillas et al. 1997; Clouet et al. 1999), a more difficult differential diagnostic situation arises in case of larger nodular lesions developing in the liver in chronic BCS. They include large regenerative (macroregenerative) nodules (that are mostly smaller than 4 cm) (Tanaka and Wanless 1998; Vilgrain et al. 1999; Zhou et al. 2000; Brancatelli et al. 2002; Ibarrola et al. 2004), adenomatous hyperplastic nodules (according to the older nomenclature; Soyer et al. 1993), FNH and FNH-like lesions (Schilling et al. 2000; Maetani et al. 2002; Ibarrola et al. 2004), and hepatocellular carcinoma, whereby the latter seems to be more frequent in patients with MOVC (Simson 1982; Nakamura and Takezawa 1982; Kew et al. 1989; Takayasu et al. 1994; Katoh and Shigematsu 1999; Havlioglu et al. 2003; Jang et al. 2003). In BCS, tumorous hepatic lesions may be mimicked by hemorrhagic necroses producing a mass (Shapiro et al. 1993).

Hepatic Fibrosis in PV

Apart from nodular lesions sometimes mimicking neoplastic disease, the liver in PV-associated BCS can undergo marked remodeling associated with fibrosis (Gundling et al. 2004). Severe hepatic fibrosis develops in BCS with a variety of histologic patterns. First, a part of the livers show a pattern of cirrhosis in which there is fibrous bridging between hepatic veins and the portal tracts (the so-called veno-portal cirrhosis); second, some livers in BCS exhibit a pattern of so-called reversed-lobulation cirrhosis (*veno-centric cirrhosis*), in which fibrous bridging between hepatic veins and portal tracts is minimal (Tanaka and Wanless 1998). In one study, all livers with veno-portal cirrhosis had severe portal vein obliteration, not seen to this degree in the other type of cirrhosis or in mixed forms, suggesting that portal vein obliteration in BCS plays a role in the pathogenesis of veno-portal bridging fibrosis (Tanaka and Wanless 1998). In the latter study, 9/15 BCS livers with these types of cirrhosis also showed large regenerative nodules histologically resembling focal nodular hyperplasia, also reported in another study (Schilling et al. 2000). In addition, fibrogenesis in PV may be mediated by activated JAK2-induced expression of galectin-3, known to involved in fibrosis and angiogenesis (Koopmans et al. 2012).

Portal Hypertension in PV and Other Hematological Disorders

As in other myeloproliferative disorders, portal hypertension may occur in PV, and not only due to thrombosis of large hepatic veins. The pathogenic mechanisms have been discussed in detail (Al-Mukhaizeem et al. 2004). These authors

proposed to classify the pathogenic pathways as a function of the anatomical site(s) of the hematologic disorders' manifestations. A first prehepatic (presinusoidal) cause of portal hypertension is, above all, portal vein and other splanchnic vein thrombosis. A second presinusoidal cause includes nodular regenerative hyperplasia of the liver, occurring in myeloproliferative disorders. Intrahepatic or sinusoidal blockage resulting in portal hypertension in myeloproliferative disorders is caused by extramedullary hemopoiesis, infiltration by abnormal hematopoietic cells, perisinusoidal fibrosis induced by hemopoietic cells located to the sinusoidal compartment (particularly fibrogenic megakaryocytes), nodular regenerative hyperplasia, liver cirrhosis, and amyloidosis. Postsinusoidal causes of portal hypertension comprise hepatic venous outflow disorders, as discussed above, and heart failure, e.g., owing to cardiac iron overload or amyloidosis.

PV can be associated with, or cause, acute obliterative endophlebitis of hepatic veins, lesions that can cause sinusoidal blockade and non-cirrhotic portal hypertension (Mandelbaum et al. 1953).

Liver Cancer in Polycythemia Vera

Several reports document the association of erythrocytosis/polyglobulia with hepatocellular carcinoma (HCC). In fact, erythrocytosis is one of the most common of the paraneoplastic syndromes in HCC, with an estimated incidence ranging from 2.2 % to 12 % (McFadzean et al. 1958; Jacobson et al. 1978; Sawabe et al. 1993; Chu et al. 1999; Trotter et al. 2002; Argumanis et al. 2002). From the etiologic point of view, at least four situations of this association have to be considered. The first situation refers to patients having *bona fide* PV and HCC (Toth and Bilodeau 1980; Gensini and Conti 2002). The second situation is characterized by HCCs thought to produce, or have been documented to produce, erythropoietin with secondary erythrocytosis (direct evidence: Funakoshi et al. 1993; Sakisaka et al. 1993; Muta et al. 1994; Matsuyama et al. 2000); (indirect evidence: McFadzean et al. 1958; Kan et al. 1961; Conte et al. 1964; Baume et al. 1965; Brownstein and Ballard 1966; McFadzean et al. 1967; Santer et al. 1967; Ruvidic and Ivaneski 1970; Zlatkina and Shcherbak 1970; Gordon et al. 1970; Nakai et al. 1972; Lizzi et al. 1973; Scott and Theologides 1974; Davidson 1976; Cornet et al. 1978; Jacobson et al. 1978; Okazaki et al. 1979; Kawasaki et al. 1979; Watanobe 1988; Shchekochikhin and Osipova 1991; Sawabe et al. 1993; Huang et al. 1994; Argumanis et al. 2002; Cheng et al. 2002). Of pathophysiologic interest are those situations where both elevated serum erythropoietin and erythrocytosis regressed after HCC resection (Regimbeau et al. 1999). Furthermore, erythropoietin production by HCCs seems to increase in response to hypoxia, for example, hepatic release of erythropoietin increases subsequent to chemoembolization of HCC (Pirisi et al. 1995). It has to be emphasized that elevated erythropoietin levels in patients with HCC may also be due to decreased erythropoietin clearance caused by underlying liver disease (Malaguarnera et al. 1996). An excess synthesis of erythropoietin by tumors was demonstrated in mice with spontaneous HCCs (Horiouchi et al. 1997). The third situation are patients developing HCC in the context of a hepatic venous outflow disorder, including BCS induced by PV (Havlioglu et al. 2003). Overall, HCC is rare in cases of hepatic venous outflow obstruction without concurrent thrombosis of the vena cava (Valla 2002). In fact, it is well known that HCC is a sequela of MOVC, but the incidence of HCC in MOVC varies according to geography (Simson 1982; Okuda 1982; Nakamura and Takezawa 1982; Rector et al. 1985; Kew et al. 1989; Hautekeete et al. 1990; Kage et al. 1992; Shrestha et al. 1996; Seo et al. 1998; Okuda et al. 1998; Karia et al. 2000). The fourth situation is represented by patients with PV exhibiting HCC after treatment, e.g., with radioactive phosphorus (Chudecki 1972), although a causal relationship has not been proven. The clinical triad of *erythrocytosis*, *hemochromatosis*, and *hepatocellular carcinoma* has been reported several times, this combination principally being

found in elderly males (Lizzi et al. 1973; Scott and Theologides 1974; Raphael et al. 1979). Erythrocytosis in this situation has again been proposed to be caused by the action of erythropoietin derived from HCC. As HCC is a frequent complication of hemochromatosis, such a constellation might be expected to occur.

Cytogenetic and Molecular Features

About 20 % of patients show karyotypic abnormalities, including +8, +9, del(20q), del(13q), and del(9p). The most frequent molecular abnormality in PV is the gain-of-function mutation JAK2V617F, occurring in more than 95 % of PV patients (Scott et al. 2007; Scott 2011). This mutation is not specific for PV but also occurs in other myeloproliferative disorders, including idiopathic myelofibrosis and essential thrombocythemia. The reason for this is that the mutation is manifest in a hematopoietic stem cell and is therefore transmitted to all cell lineages derived thereof. The remaining few % of patients show other mutations of JAK with the same functional consequences. Activation of JAK2 (Janus kinase 2), which phosphorylates signal transducer activator of transcription (STAT), promotes overexpression of the cell cycle regulator CDC25A (Gautier et al. 2012) and upregulates a broad array of growth factors, including VEGF, which may be responsible for angiogenesis in PV and other myeloproliferative disorders.

Pathogenic Pathways

The pathogenic mechanisms of PV are not fully understood, but the defect seems to involve hyperresponsiveness of PV progenitor cells to several cytokines (Prchal 2001). Diagnostic criteria and aspects of classification and molecular biology have been reviewed (Michiels and Juvonen 1997; Pearson 1998; Messinezy and Pearson 1999; Prchal and Prchal 1999; Golden 2003; Prchal 2003). It is known that patients with PV exhibit higher levels of a hemopoietic receptor, polycythemia rubra vera-1 (PRV-1), in granulocytes/neutrophils, and it was proposed that this phenomenon provides a rapid, highly specific, and sensitive marker for the diagnosis of PV in comparison with nonneoplastic erythrocytoses (Klippel et al. 2003). However, another group found that the PRV-1 gene is constitutively expressed by bone marrow cells and does not discriminate PV from reactive and other chronic myeloproliferative disorders (Bock et al. 2003), whereas a more recent investigation confirmed that neutrophil PRV-1 upregulation is a characteristic feature of PV, although in itself not sufficient for the diagnosis of PV (Tefferi et al. 2004). One reason for this is that overexpression of the PRV-1 receptor is also found in other myeloproliferative disorders, e.g., essential thrombocythemia (Teofili et al. 2002). The PRV-1 gene encodes an open reading frame of 437 amino acids, containing a signal peptide and two cysteine-rich domains homologous to those found in the uPAR/Ly6/CD59/snake toxin-receptor superfamily, linked to the cell surface via a glycosylphosphatidylinositol (GPI) link (Temerinac et al. 2000; Klippel et al. 2002).

So-called Chronic Erythroid Leukemia

Introduction

This is a rare and heterogeneous group of intriguing disorders that have not yet been classified in a satisfactory way but has already been described by Di Guglielmo and a coworker (Di Guglielmo and Quattrin 1942). In fact, the term does not appear in modern classifications of leukemias and myeloproliferative disorders. The disorder is briefly discussed because the term appears in literature referring to liver involvement, and at least some of these leukemias seem to have a link to the respective acute leukemia forms. Based on the stem cell nature of the disorders, the beginning and evolution of this subset of leukemias are variable. For example, patients may first present with chronic erythroleukemia with refractory anemia, to later switch to acute erythroid leukemia (M6), and then to acute myeloid leukemia of the M0 type, also involving dysplastic features of

other hemopoietic lineages, and therefore suggesting a stage-by-stage trilineage continuum (Michiels et al. 1997). There are several synonyms to denote disorders that are, or have been, interpreted to be chronic neoplastic erythroproliferative diseases. They include chronic erythroleukemia, chronic erythremia, chronic erythremic myelosis, chronic erythremic disease, chronic erythromyelosis, chronic Di Guglielmo syndrome, Di Guglielmo's erythremia with prolonged course, primary chronic erythroblastosis, and Heilmeyer-Schöner disease (Heilmeyer and Schöner 1961; Starcich et al. 1963; Introzzi and Buscarini 1966; Thurm et al. 1967; Spremolla et al. 1970; Stewart 1971; Marsan et al. 1973; Kass 1975; Nunnensiek et al. 1976; Sroczynski and Hrycek 1976; Pivnik et al. 1987; Bindi et al. 1999). Heilmeyer and Schöner described the disorder having their eponyms under the term chronic pure erythroblastosis of the adult as a leukemic process going in parallel to the erythrocytic system (Heilmeyer and Schöner 1961). All or most of these manifestations of hematologic neoplasias seem to have in common a chronically persistent malignant proliferation of cell populations dominated by an erythroid lineage, although it has not been specified as to what percentage of erythroid cells must be involved and what exactly "chronic" means.

In chronic erythroid leukemia, the morphology of blast cells has been studied in detail, particularly in regard to the erythroblastic components. Erythroblasts can show several anomalies, including deviations between cytoplasmic baso- or eosinophilia and the nuclear chromatin features, and binucleated or trinucleated cells (Introzzi and Buscarini 1966). Ultrastructurally, the cells of interest may show cytoplasmic vacuolation and vesicular bodies and may display significant numbers of membrane-bound ferritin particles and also isolated ferritin crystals in the cytoplasm (Introzzi and Buscarini 1966).

Liver Involvement

There are only sparse data available in regard to liver involvement in chronic erythroid leukemia(s). In one patient, tumorous lesions containing erythroid cells ("erythrosarcomas") were found in several organs, including the liver (Pivnik et al. 1987). Another case was characterized by the development of, as it was called, "malignant erythroblastomas" (Goreczky and Toth 1967). The autopsy of a patient with acute erythroid leukemia transforming in chronic erythremia revealed hepatomegaly (2,700 g) with increased consistency of the organ and grayish or hemorrhagic areas. Histologically, the portal tracts and the sinusoids were densely infiltrated by abnormal blastic cells, causing atrophy and dissolution of the liver cell plates. In the portal tracts, blast also occupied alterations looking like interface lesions/piecemeal necroses. The hepatocytes showed iron overload (Starcich et al. 1963; with a histologic figure of the liver changes).

References

Akyildiz M, Karasu Z, Dheir H, Osmanoglu N, Akay S, Ilter T (2006) Fulminant Budd-Chiari syndrome associated with polycythemia rubra vera and factor V Leiden mutation. Eur J Intern Med 17:66–67

Alford FP, Myers KA, Syme J (1968) Portal hypertension and bleeding varices due to thrombosis in the portal venous system complicating polycythaemia vera. Med J Aust 2:64–66

Al-Mukhaizeem KA, Rosenberg A, Sherker AH (2004) Nodular regenerative hyperplasia of the liver: an under-recognized cause of portal hypertension in hematological disorders. Am J Hematol 75:225–230

Alvarez-Larran A, Garcia-Pagan JC, Abraldes JG, Arellano E, Reverter JC, Bosch J, Cervantes F (2004) Increased CD11b neutrophil expression in Budd-Chiari syndrome or portal vein thrombosis secondary to polycythemia vera. Br J Haematol 124:329–335

Ania BJ, Suman VJ, Sobell JL, Codd MB, Silverstein MN, Melton LJ (1994) Trends in the incidence of polycythemia vera among Olmsted County, Minnesota residents, 1935–1989. Am J Hematol 47:89–93

Argumanis E, Quispe D, Ruiz E (2002) Erythrocytosis associated with hepatocellular carcinoma. Two case reports (in Spanish). Rev Gastroenterol Peru 22:84–87

Balique JG (1981) Budd-Chiari syndrome. Physiopathogenic hypothesis for polycythemia (in French). Nouv Presse Med 10:907–908

Barbui T, Finazzi G (1997) Risk factors and prevention of vascular complications in polycythemia vera. Semin Thromb Hemost 23:455–461

Baume P, Piper DW, Cumberland VH, Jones KO (1965) Primary hepatoma associated with polycythemia:

report of a case with a study of tumour and urine erythropoietin levels. Med J Aust 2:833–835
Benedik-Dolnicar M, Homan M, Brecelj J (2012) JAK2V617F mutation in a 9-year-old girl with polycythemia vera and Budd-Chiari syndrome: a case report. J Pediatr Hematol Oncol 34:243–244
Berlin NI, Wasserman LR (1997) Polycythemia vera: a retrospective and reprise. J Lab Clin Med 130:365–373
Bindi M, Quartieri F, Siuti E, Stefanelli A, Mechelli S, Castiglioni MG (1999) Chronic erythremic myelosis (or chronic form of Di Guglielmo's disease). A case report (in Italian). Recenti Prog Med 90:213–215
Bock O, Serinsoz E, Neusch M, Schlue J, Kreipe H (2003) The polycythaemia rubra vera-1 gene is constitutively expressed by bone marrow cells and does not discriminate polycythaemia vera from reactive and other chronic myeloproliferative disorders. Br J Haematol 123:472–474
Brancaccio V, Iannaccone L, Margaglione M, Guardascione MA, Amitrano L (2002) Multiple thrombophilic factors in a patient with Budd-Chiari syndrome. Clin Lab Haematol 24:61–63
Brancatelli G, Federle MP, Grazioli L, Golfieri R, Lecnioni R (2002) Benign regenerative nodules in Budd-Chiari syndrome and other vascular disorders of the liver: radiologic-pathologic and clinical correlation. Radiographics 22:847–862
Brown RN, Pidgeon JW, Johnson HA (1955) The Budd-Chiari syndrome complicating a case of polycythemia vera. Calif Med 83:37–39
Brownstein MH, Ballard HS (1966) Hepatoma associated with erythrocytosis. Am J Med 40:204–210
Bucciarelli P, Franchi F, Alatri A, Bettini P, Moia M (1998) Budd-Chiari syndrome in a patient heterozygous for the G20210A mutation of the prothrombin gene. Thromb Hemost 79:445–446
Burgaleta C, Gonzalez N, Cesar J (2002) Increased CD11/Cd18 expression and altered metabolic activity on polymorphonuclear leukocytes from patients with polycythemia vera and essential thrombocythemia. Acta Haematol 108:23–28
Cantwell D, Fitzgerald O, Fitzgerald P, Mehigan JA (1956) Diagnosis and treatment of the Budd-Chiari syndrome in polycythaemia vera. Br Med J 44:1343–1345
Cario H, Pahl HL, Schwarz K, Galm C, Hoffmann M, Burdelski M, Kohne E, Debatin KM (2003) Familial polycythemia vera with Budd-Chiari syndrome in childhood. Br J Haematol 123:346–352
Caroli J, Soulier JP (1956) Polycythemia vera and the Budd-Chiari syndrome: clinical, biological and endoscopic study; traitement with P34 and tromexam; apparent recovery (in French). Rev Med Chir Mal Foie 31:39–48
Casillas C, Marti-Bonmati L, Galant J (1997) Pseudotumoral presentation of nodular regenerative hyperplasia of the liver: imaging in five patients including MR imaging. Eur Radiol 7:654–658
Castellano G, Canga F, Solis-Herruzo JA, Colina F, Martinez-Montiel MP, Morillas JD (1989) Budd-Chiari syndrome associated with nodular regenerative hyperplasia of the liver. J Clin Gastroenterol 11:698–702
Cheng TI, Tsou MH, Yang PS, Sung SM, Chuang VP, Sung JL (2002) Dermatomyositis and erythrocytosis associated with hepatocellular carcinoma. J Gastroenterol Hepatol 17:1239–1240
Chini V (1954) Deficiency picture and Budd-Chiari syndrome in polycythemia vera (in Italian). Rass Clin Sci 30:168–174
Chlumsky J, Chlumska A (1966) Liver and polycythemia vera (Vaquez-osler disease). (in German). Gastroenterologia 105:366–374
Chu CW, Hwang SJ, Luo JC, Tsay SH, Li CP, Chang FY, Lee SD, Lui WY, Chiang JH (1999) Manifestations of hypercholesterolaemia, hypoglycaemia, erythrocytosis and hypercalcaemia in patients with hepatocellular carcinoma: report of two cases. J Gastroenterol Hepatol 14:807–810
Chudecki B (1972) Primary cancer of the liver following treatment of polycythaemia vera with radioactive phosphorus. Br J Radiol 45:770–774
Clouet M, Boulay I, Boudiaf M, Soyer P, Nemeth J, Kiselman R, Rymer R (1999) Imaging features of nodular regenerative hyperplasia of the liver mimicking hepatic metastases. Abdom Imaging 24:258–261
Conte M, Fouet P, Jacobs C, Conte-Marti (1964) Primary liver cancer and polycythemia (in French). Bull Mem Soc Med Hop Paris 115:1011–1016
Cornet A, Barbier JP, Benisty H, Carnot F, Fraitag B (1978) Polyglobulia as a manifestation of a primary of the liver (in French). Ann Med Interne (Paris) 129:279–281
Davidson CS (1976) Hepatocellular carcinoma and erythrocytosis. Semin Hematol 13:115–119
De Grandis M, Cambot M, Wautier MP, Cassinat B, Chomienne C, Colin Y, Wautier JL et al (2012) JAK2V617F activates Lu/BCAM-mediated red cell adhesion in polycythemia vera through an EpoR-independent Rap1/Akt pathway. Blood 121:658–665
De Sousa JMM, Portmann B, Williams R (1991) Nodular regenerative hyperplasia of the liver and the Budd-Chiari syndrome. J Hepatol 12:28–35
De Stefano V, Teofili L, Leone G, Michiels JJ (1997) Spontaneous erythroid colony formation as the clue to an underlying myeloproliferative disorder in patients with Budd-Chiari syndrome or portal vein thrombosis. Semin Thromb Hemost 23:411–418
De Stefano V, Chiusolo P, Paciaroni K, Teofili L, Ortu La Barbera E, Casorelli I, Leone G (1998) Hepatic vein thrombosis in a patient with mutant 20210A allele. Thromb Hemost 80:519
Delarive J, Gonvers JJ (1998) Budd-Chiari syndrome related to factor V Leiden mutation. Am J Gastroenterol 93:651–652
Deltenre P, Denninger MH, Hillaire S, Guillin MC, Casadevall N, Briere J, Erlinger S, Valla DC (2001) Factor V Leiden related Budd-Chiari syndrome. Gut 48:264–268
Di Guglielmo G, Quattrin N (1942) Mielosi eritremica cronica. Haematologica 24:1

Dilawari JB, Bambery P, Chawla Y, Kaur U, Bhusnurmath SR, Malhotra HS, Sood GK, Mitra SK, Khanna SK, Walia BS (1994) Hepatic outflow obstruction (Budd-Chiari syndrome). Experience with 177 patients and a review of the literature. Medicine (Baltimore) 73:21–36

Drenou B, Le Prise PY, Poilane B, Bernard-Griffiths I, Ghandour C, Fauchet R (1992) Polycythaemia and portal vein thrombosis. Nouv Rev Fr Hematol 34:399–403

Escher R, Demarmels BF (1999) Fall 9. Eine 26jährige Frau mit splanchnischer Venenthrombose als Initialmanifestation einer Polycythaemia vera. Ther Umschau 56:505–508

Fechtner L, DelDuca V (1994) Diagnosis by MRI of Budd-Chiari syndrome presenting with new onset of polycythemia. Del Med J 66:554

Fields W, Freeman NJ (1993) The hypercoagulability of polycythemia vera. Hosp Pract (Off Ed) 28(9A):65–68, 72–73

Fiessinger JN (1994) Thrombotic complications of polycythemia. The venous and arterial risk factors. Nouv Rev Fr Hematol 36:179–181

Friess D, Lämmle B, Alberio L (2003) Qualitative platelet defect and thrombohaemorrhagic complications in a patient with polycythaemia vera. Case 10. Hamostaseologie 23:138–143

Funakoshi A, Muta H, Baba T, Shimizu S (1993) Gene expression of mutant erythropoietin in hepatocellular carcinoma. Biochem Biophys Res Commun 195:717–722

Gautier EF, Picard M, Laurent C, Marty C, Villeval JL, Demur C, Delhommeau F, Hexner E et al (2012) The cell cycle regulator CDC25A is a target for JAK2V617F oncogene. Blood 119:1190–1199

Gensini GF, Conti AA (2002) Association between hepatocellular carcinoma and polycythemia vera (in Italian). Recenti Prog Med 93:25–27

Gilbert HS (2003) Modern treatment strategies in polycythemia vera. Semin Hematol 40(suppl 2):26–29

Golden C (2003) Polycythemia vera: a review. Clin J Oncol Nurs 7:553–556

Gordon AS, Zanjani ED, Zalusky R (1970) A possible mechanism for the erythrocytosis associated with hepatocellular carcinoma in man. Blood 35:151–157

Goreczky L, Toth J (1967) A case of malignant erythroblastoma. A rare form of Di Guglielmo's syndrome (in German). Folia Haematol Int Mag Klein Morphol Blutforsch 88:45–53

Gumina RJ, Foley DA, Tefferi A, Rooke TW, Shields RC (2002) Polycythemia vera –a case report and discussion on pathogenic mechanisms of increased thrombosis. Angiology 53:587–591

Gundling F, Kreth F, Tröltzsch M, Tannapfel A, Bödeker H, Mössner J (2004) Unclear liver fibrosis in a 42-year-old patient with polycythemia vera (in German). Internist (Berl) 45:1293–1298

Hadengue A, Poliquin M, Vilgrain V et al (1994) The changing scene of hepatic vein thrombosis: recognition of asymptomatic cases. Gastroenterology 106:1042–1047

Hamilton A, Moise ME (1912) Erythrocythemia. Boston Med J 166:963–967

Hautekeete ML, Brenard R, Hadengue A, Degott C, Babany G, Arrive L, Lebrec D, Menu Y, Erlinger S, Benhamou JP (1990) membranous obstruction of the inferior vena cava and hepatocellular carcinoma in a Caribbean patient. J Clin Gastroenterol 12:214–217

Havlioglu N, Brunt EM, Bacon BR (2003) Budd-Chiari syndrome and hepatocellular carcinoma: a case report and review of the literature. Am J Gastroenterol 98:201–204

Heilmeyer L, Schöner W (1961) Die chronische reine Erythroblastose des Erwachsenen als Leukämieparalleler Prozess des erythrocytären Systems. Dtsch Arch Klin Med 187:225–248

Hirschfeld H (1906) Zur Pathologischen Anatomine der Plethora Vera. Med Klin 8:588–592

Horiouchi A, Hayashi S, Ando T, Nonoyama T (1997) Secondary polycythemia in male B6C3F1 mice with spontaneously occurring hepatocellular carcinomas. Toxikol Pathol 25:511–515

Huang SJ, Lee SD, Wu JC et al (1994) Clinical evaluation of erythrocytosis in patients with hepatocellular carcinoma. Chin Med J (Taipei) 53:262–269

Ibarrola C, Castellano VM, Colina F (2004) Focal hyperplastic hepatocellular nodules in hepatic venous outflow obstruction: a clinicopathological study of four patients and 24 nodules. Histopathology 44:172–179

Introzzi P, Buscarini L (1966) Contribution to the study of chronic erythremic disease (in Italian). Haematologica 51:1–14

Iwai M, Kitagawa Y, Nakajima T, Takeda M, Okanoue T, Nakajima T, Ogasawara T, Suyama Y, Miyoshi M, Kashima K (1998) Clinical features, image analysis, and laparoscopic and histological liver findings in Budd-Chiari syndrome. Hepato-Gastroenterology 45:2359–2368

Jacobson RJ, Lowenthal MN, Kew MC (1978) Erythrocytosis in hepatocellular cancer. S Afr Med J 53:658–660

Jang JW, Yoon SK, Bae SH, Choi JY, Chung KW, Sun HS (2003) Rapidly progressing Budd-Chiari syndrome complicated by hepatocellular carcinoma. Korean J Intern Med 18:191–195

Janssen HL (2000) Changing perspectives in portal vein thrombosis. Scand J Gastroenterol, (Suppl 232):69–73

Janssen HL, Meinardi JR, Vleggaar FP, van Uum SH, Haagsma EB, van Der Meer FJ, van Hattum J et al (2000) Factor V Leiden mutation, prothrombin gene mutation, and deficiencies in coagulation inhibitors associated with Budd-Chiari syndrome and portal vein thrombosis: results of a case-control study. Blood 96:2364–2368

Janssen HLA, Garcia-Pagan JC, Elias E, Mentha G, Hadengue A, Valla DC, European Group for the Study of Vascular Disorders of the Liver (2003)

Budd-Chiari syndrome: a review by an expert panel. J Hepatol 38:364–371
Kage M, Arakawa M, Kojiro M, Okuda K (1992) Histopathology of membranous obstruction of the inferior vena cava in the Budd-Chiari syndrome. Gastroenterology 102:2081–2090
Kan YW, McFadzean AJ, Todd D, Tso SC (1961) Further observations on polycythemia in hepatocellular carcinoma. Blood 18:592–598
Karia K, Mathur SK, Amarapurkar D, Punamiya SJ (2000) Hepatocellular carcinoma in association with membranous obstruction of inferior vena cava. Indian J Gastroenterol 19:90–91
Kass L (1975) Chronic erythremic myelosis profiling a refractory anemia. Postgrad Med 58:161–166
Katoh M, Shigematsu H (1999) Primary liver carcinoma complicating membranous obstruction of the inferior vena cava. Pathol Int 49:253–257
Kawasaki T, Taketa K, Ueda M, Watanabe A, Watanabe M, Shimamura J, Okazaki S, Mitani K, Nakata K, Endo H, Nagashima H, Ogawa K (1979) A case of hepatocellular carcinoma with hypercholesterolemia, erythrocytosis and hypoglycemia (in Japanese). Nippon Shokakibyo Gakkai Zasshi 76:1871–1877
Kew MC, McKnight A, Hodkinson J, Bukofzer S, Esser JD (1989) The role of membranous obstruction of the inferior vena cava in the etiology of hepatocellular carcinoma in Southern African blacks. Hepatology 9:121–125
Klippel S, Strunck E, Busse CE, Behringer D, Pahl HL (2002) Biochemical characterization of PRV-1, a novel hematopoietic cell surface receptor, which is overexpressed in polycythemia rubra vera. Blood 100:2441–2448
Klippel S, Strunck E, Temerinac S, Bench AJ, Meinhardt G, Mohr U, Leichtle R, Green AR, Griesshammer M et al (2003) Quantification of PRV-1 mRNA distinguishes polycythemia vera from secondary erythrocytosis. Blood 102:3569–3574
Koopmans SM, Bot FJ, Schouten HC, Janssen J, van Marion AM (2012) The involvement of galectins in the modulation of the JAK/STAT pathway in myeloproliferative neoplasia. Am J Blood Res 2:119–127
Kratzeisen E (1923) Polyzythämie und Pfortaderthrombose. Virchows Arch 244:467
Levy VG, Ruskone A, Baillou C, Theirman-Duffaud D, Najman A, Boffa GA (1985) Polycythemia and the Budd-Chiari syndrome: study of serum erythropoietin and bone marrow erythroid progenitors. Hepatology 5:858–861
Lizzi FA, Tartaglia AP, Adamson JW (1973) Hemochromatosis, hepatoma, erythrocytosis, and erythropoietin. N Y State J Med 73:1098–1100
Löhr JM, Kuchenreuter S, Grebmeier H, Hahn EG, Fleig WE (1993) Compression of the common bile duct due to portal-vein thrombosis in polycythemia vera. Hepatology 17:586–592
Lommel K (1906) Über Polyzythämie und Milztumor. Arch Klin Med 87:315
Maetani Y, Itoh K, Egawa H, Haga H, Sakurai T, Nishida N, Ametani F, Shibata T, Kubo T, Tanaka K, Konishi J (2002) Benign hepatic nodules in Budd-Chiari syndrome: radiologic-pathologic correlation with emphasis on the central scar. AJR Am J Roentgenol 178:869–875
Mahmoud AE, Mendoza A, Meshikhes AN, Olliff S, West R, Neuberger J, Buckels J, Wilde J, Elias E (1996) Clinical spectrum, investigations and treatment of Budd-Chiari syndrome. Q J M 89:37–43
Mahmoud AE, Elias E, Beauchamp N, Wilde JT (1997) Prevalence of the factor V Leiden mutation in hepatic and portal vein thrombosis. Gut 40:798–800
Malaguarnera M, bentivegna P, Di Fazio I, Laurino A, Romano M, Trovato BA (1996) Erythropoietin in hepatocellular carcinoma (in French). Bull Cancer 83:977–980
Mandelbaum H, Diamond D, Feldman F (1953) Acute obliterative endophlebitis of the hepatic veins secondary to polycythemia vera. N Y State J Med 53:2689–2692
Marsan C, Henon P, Boddaert A (1973) A case of chronic erythremic myelosis (in French). Arch Anat Pathol (Paris) 21:171–178
Matsuyama M, Yamazaki O, Horii K, Higaki I, Kawai S, Mikami S, Higashino M, Oka H, Nakai T, Inoue T (2000) Erythrocytosis caused by an erythropoietin-producing hepatocellular carcinoma. J Surg Oncol 75:197–202
McBrine PA, Miller A, Zimelman AP, Koff RS (1980) Polycythemia vera with myelofibrosis and myeloid metaplasia. Acute hepatic failure following splenectomy. Am J Clin Pathol 74:693–696
McFadzean AJ, Todd D, Tsang KC (1958) Polycythemia in primary carcinoma of the liver. Blood 13:427–435
McFadzean AJ, Todd D, Tso SC (1967) Erythrocytosis associated with hepatocellular carcinoma. Blood 29:808–811
Means RT (2008) Perspective: Osler's 1903 paper on polycythemia vera. Am J Med Sci 335:418–419
Messinezy M, Pearson TC (1999) The classification and diagnostic criteria of the erythrocytoses (polycytaemias). Clin Lab Haematol 21:309–316
Michiels JJ (1997) Erythromelalgia and vascular complications in polycythemia vera. Semin Thromb Hemost 23:441–454
Michiels JJ, Juvonen E (1997) Proposal for revised diagnostic criteria of essential thrombocythemia and polycythemia vera by the Thrombocythemia Vera Study Group. Semin Thromb Hemost 23:339–347
Michiels JJ, van der Meulen J, Brederoo P (1997) The natural history of trilinear myelodysplastic syndrome and erythroleukemia. Haematologica 82:452–454
Minnema MC, Janssen HLA, Niermeijer P, de Man RA (2000) Budd-Chiari syndrome: combination of genetic defects and the use of oral contraceptives leading to hypercoagulability. J Hepatol 33:509–512
Mohanty D, Shetty S, Ghosh K, Pawar A, Abraham P (2001) Hereditary thrombophilia as a cause of Budd-

Chiari syndrome: a study from Western India. Hepatology 34:666–670
Mosse E (1920) Die Polyglobulien. In: Kraus F, Brugsch T (eds) Handbuch der Specziellen Pathologie and Therapie. Urban and Schwarzenberg, Berlin, p 821
Muta H, Funakoshi A, Baba T, Uike N, Wakasugi H, Kozuru M, Jimi A (1994) Gene expression of erythropoietin in hepatocellular carcinoma. Intern Med 33:427–431
Nakai Y, Tamai Y, Minaguchi S, Yoshimi T, Hoshino T (1972) Primary hepatocellular carcinoma with polycythemia, hypercholesterolemia and various other clinical symptoms (in Japanese). Nippon Rinsho 30:2329–2334
Nakamura S, Takezawa Y (1982) Obstruction of the inferior vena cava in the hepatic portion and hepatocellular carcinoma. Tohoku J Exp Med 138:119–120
Neunteufl T, Heher S, Stefenelli T, Pabinger I, Gisslinger H (2001) Endothelial dysfunction in patients with polycythaemia vera. Br J Haematol 115:354–359
Nunnensiek C, Rössler R, Neumann G (1976) Chronic erythroleukemia in Di Guglielmo's syndrome (in German). Med Welt 27:1154–1156
Okazaki N, Ozaki H, Arima M, Hattori N, Kimura K (1979) Hepatocellular carcinoma associated with erythrocytosis. A nine year survival after successful chemotherapy and left lateral hepatectomy. Acta Hepatogastroenterology (Stuttg) 26:248–252
Okuda K (1982) Membranous obstruction of the inferior vena cava: etiology and relation to hepatocellular carcinoma. Gastroenterology 82:376–379
Okuda K (2002) Inferior vena cava thrombosis at its hepatic portion (obliterative hepatocavopathy). Semin Liver Dis 22:15–26
Okuda H, Yamagata H, Obata H, Iwata H, Sasaki R, Imai F, Okudaira M, Ohbu M, Okuda K (1995) Epidemiological and clinical features of Budd-Chiari syndrome in Japan. J Hepatol 22:1–9
Okuda K, Kage M, Shrestha SM (1998) Proposal of a new nomenclature for Budd-Chiari syndrome: hepatic vein thrombosis versus thrombosis of the inferior vena cava at its hepatic portion. Hepatology 28:1191–1198
Oner AF, Arslan S, Caksen H, Ceylan A (1999) Budd-Chiari syndrome in a patient heterozygous for both factor V Leiden and the G20210A mutation on the prothrombin gene. Thromb Hemost 82:1366–1367
Orlandi E, Castelli G, Brusamolino E, canevari A, Morra E, Lazzarino M, Bernasconi C (1989) Hemorrhagic and thrombotic complications in polycythemia vera. A clinical study. Haematologica 74:45–49
Osler W (1903) Chronic cyanosis, with polycythemia and enlarged spleen: a new clinical entity. Am J Med Sci 126:176–201
Patel RK, Lea NC, Heeghan MA, Westwood NB, Milojkovic D, Thanigaikumar M et al (2006) Prevalence of the activating JAK2 tyrosine kinase mutation V617F in the Budd-Chiari syndrome. Gastroenterology 130:2031–2038
Pati HP, Dayal S, Kashyap R, Padhy AK (1998) Masked polycythaemia vera in a patient with extrahepatic portal venous obstruction. Eur J Gastroenterol Hepatol 10:883–885
Pearson TC (1998) Diagnosis and classification of erythrocytoses and thrombocytoses. Baillieres Clin Haematol 11:695–720
Pearson TC (2002) The risk of thrombosis in essential thrombocythemia and polycythemia vera. Semin Oncol 29(suppl 10):16–21
Peters MJ, Dixon G, Kotowicz KT, Hatch DJ, Heyderman RS, Klein NJ (1999) Circulating platelet-neutrophil complexes represent a subpopulation of activated neutrophils primed for adhesion, phagocytosis and intracellular killing. Br J Haematol 106:391–399
Peterson P, Wasserman LR (1995) The natural history of polycythemia vera. In: Wasserman LR, Berk PD, Berlin NI (eds) Polycythemia vera and the myeloproliferative disorders. W.B. Saunders, Philadelphia, pp 14–21
Picardi M, Muretto P, Luciano L (2000) Budd-Chiari syndrome in chronic myeloid leukemia. Haematologica 85:429
Pirisi M, Fabris C, Soardo G, Falleti E, Gasparini D, Vitulli D, Toniutto P, Gonano F, Bartoli E (1995) Hepatic release of erythropoietin induced by transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 22:148–152
Pivnik AV, Idel'son LI, Ter-Grigorov VS, Gel'man VB, Khasenov BA (1987) Neoplastic form of chronic erythromyelosis (erythrosarcoma) with eosinophilia and cardiac lesions (in Russian). Ter Arkh 59:130–133
Poort SR, Rosendaal FR, Reitsma PH, Bertina RM (1996) A common genetic variation of the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 88:3698–3703
Poreddy V, DeLeve LD (2002) Hepatic circulatory diseases associated with chronic myeloid disorders. Clin Liver Dis 6:909–931
Prchal JT (2001) Pathogenetic mechanisms of polycythemia vera and congenital polycythemic disorders. Semin Hematol 38(suppl 2):10–20
Prchal JT (2003) Classification and molecular biology of polycythemias (erythrocytoses) and thrombocytosis. Hematol Oncol Clin N Am 17:1151–1158
Prchal JF, Prchal JT (1999) Molecular basis for polycythemia. Curr Opin Hematol 6:100–109
Randi ML, Fabris F, Ruzzon E, Pacquola E, Cella G, Girolami A (2002) Splenectomy after portal thrombosis in patients with polycythemia vera and essential thrombocythemia. Haematologica 87:1180–1184
Raphael B, Cooperberg AA, Niloff P (1979) The triad of hemochromatosis, hepatoma and erythrocytosis. Cancer 43:690–694
Rector WG, Xu YH, Goldstein L, Peters RL, Reynolds TB (1985) Membranous obstruction of the inferior vena cava in the United States. Medicine (Baltimore) 64:134–143

Regimbeau JM, Rain JD, Sauvanet A, Bai YS, Belghiti J (1999) Regression of polycythemia and elevated serum erythropoietin after resection of hepatocellular carcinoma (in French). Gastroenterol Clin Biol 23:532–533

Retzlaff K, Monge JJ (1973) Polycythemia vera with acute Budd-Chiari syndrome. Minn Med 56:60–62

Rha SE, Lee MG, Lee YS, Kang GH, Ha HK, Kim PN, Auh YH (2000) Nodular regenerative hyperplasia of the liver in Budd-Chiari syndrome: CT and MR features. Abdom Imaging 25:255–258

Ruvidic R, Ivaneski M (1970) Polyglobulism associated with primary liver cancer (in French). Nouv Rev Fr Hematol 10:261–265

Sakisaka S, Watanabe M, Tateishi H, Harada M, Shakado S, Mimura Y, Gondo K, Yoshitake M, Noguchi K, Hino T et al (1993) Erythropoietin production in hepatocellular carcinoma cells associated with polycythemia: immunohistochemical evidence. Hepatology 18:1357–1362

Santer MA, Waldmann TA, Fallon HJ (1967) Erythrocytosis and hyperlipemia as manifestations of hepatic carcinoma. Arch Intern Med 120:735–739

Sawabe Y, Iida S, Tabata Y, Yonemitsu H (1993) Serum erythropoietin measurements by a one-step sandwich enzyme linked immunosorbent assay in patients with hepatocellular carcinoma and liver cirrhosis. Jpn J Clin Oncol 23:273–277

Schilling MK, Zimmermann A, Redaelli C, Seiler CA, Buchler MW (2000) Liver nodules resembling focal nodular hyperplasia after hepatic venous thrombosis. J Hepatol 33:673–676

Scott LM (2011) The JAK2 exon 12 mutations: a comprehensive review. Am J Hematol 86:668–676

Scott D, Theologides A (1974) Hepatoma, erythrocytosis and increased serum erythropoietin developing in longstanding hemochromatosis. Am J Gastroenterol 61:206–211

Scott LM, Tong W, Levine RL, Scott MA, Beer PA, Stratton MR, Futreal PA, Erber WN et al (2007) JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med 356:459–468

Seo JB, Chung JW, Park JH, Kim SH, Kim TK, Han JK, Choi BI, Han MC (1998) Benign obstruction of the hepatic inferior vena cava complicated by hepatocellular carcinoma: combined interventional management. AJR Am J Roentgenol 170:655–659

Shapiro RS, Maldjian JA, Stancato-Pasik A, Ramos R (1993) Hepatic mass in Budd-Chiardrome: CT and MRI findings. Comput Med Imaging Graph 17:457–460

Shchekochikhin SM, Osipova MV (1991) A case of combined hepatocellular carcinoma and erythremia (in Russian). Ter Arkh 63:139–140

Sherlock S, Dooley J (1993) Budd-Chiari (hepatic venous obstruction) syndrome. In: Sherlock S, Dooley J (eds) Diseases of the liver and biliary system. Blackwell Scientific Publications, Oxford, pp 183–192

Shrestha SM, Okuda K, Uchida T, Maharjan KG, Shrestha S, Joshi BL, Larsson S, Vaidya Y (1996) Endemicity and clinical picture of liver disease due to obstruction of the hepatic portion of the inferior vena cava in Nepal. J Gastroenterol Hepatol 11:170–179

Siguier F, Godeau P, Delluc G, Sraer JD (1967) Budd-Chiari syndrome with polycythemia. Considerations on the pseudo-tumoral aspect (in French). Bull Mem Soc Med Hop Paris 118:1235–1238

Simsek S, Verheesen RV, Haagsma EB, Lourens J (2000) Subacute Budd-Chiari syndrome associated with polycythemia vera and factor V Leiden mutation. Neth J Med 57:62–67

Simson IW (1982) Membranous obstruction of the inferior vena cava and hepatocellular carcinoma in South Africa. Gastroenterology 82:171–178

Slakey DP, Klein AS, Venbrux AC et al (2001) Budd-Chiari syndrome. Current management options. Ann Surg 233:522–527

Soler R, Rodriguez E, Pombo F, Gonzalez J, Pombo S, Prada C (2000) Benign regenerative nodules with copper accumulation in a case of chronic Budd-Chiari syndrome: CT and MR findings. Abdom Imaging 25:486–489

Soyer P, Lacheheb D, Caudron C, Levesque M (1993) MRI of adenomatous hyperplastic nodules of the liver in Budd-Chiari syndrome. J Comput Assist Tomogr 17:86–89

Sozer S, Fiel MI, Schiano T, Xu M, Mascarenhas J, Hoffman R (2009) The presence of JAK2V617F mutation in the liver endothelial cells of patients with Budd-Chiari syndrome. Blood 113:5246–5249

Spremolla G, Tomei GP, Biancalana D (1970) Chronic erythremic myelosis: morphological and cytochemical data (in Italian). Haematologica 55:435–459

Sroczynski J, Hrycek A (1976) Primary chronic erythroblastosis (Heilmeyer-Schöner disease) (in Polish). Pol Tyg Lek 31:811–812

Starcich R, Tardini A, Vitali-Mazza L (1963) Di Guglielmo's erythremia with prolonged course (chronic erythremia): anatomoclinical and ultrastructural study (in Italian). Riv Anat Patol Oncol 24 (suppl):709–748

Stewart C (1971) Chronic Di Guglielmo disease. Med J Aust 27:480–482

Streiff MB, Smith B, Spivak JL (2002) The diagnosis and management of polycythemia vera in the era since the Polycythemia Vera Study Group: a survey of American Society of hematology members' practice patterns. Blood 99:1144–1149

Takayasu K, Muramatsu Y, Moriyama N, Wakao F, Makuuchi M, Takayama T, Kosuge T, Okazaki N, Yamada R (1994) Radiological study of idiopathic Budd-Chiari syndrome complicated by hepatocellular carcinoma. A report of four cases. Am J Gastroenterol 89:249–253

Tanaka M, Wanless IR (1998) Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the

histogenesis of venocentric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. Hepatology 27:488–496

Tefferi A (2001) Chronic myeloid disorders: classification and treatment overview. Semin Hematol 38:1–4

Tefferi A (2003) Polycythemia vera: a comprehensive review and clinical recommendations. Mayo Clin Proc 78:174–194

Tefferi A, Lasho TL, Wolanskyj AP, Mesa RA (2004) Neutrophil PRV-1 expression across the chronic myeloproliferative disorders and in secondary or spurious polycythemia. Blood 103:3547–3548

Temerinac S, Klippel S, Strunck E, Roder S, Lubbert M, Lange W, Azemar M, Meinhardt G, Schaefer HE, Pahl HL (2000) Cloning of PRV-1, a novel member of the uPAR receptor superfamily, which is overexpressed in polycythemia rubra vera. Blood 95:2569–2576

Teofili L, Martini M, Luongo M, Di Mario A, Leone G, De Stefano V, Larocca LM (2002) Overexpression of the polycythemia rubra vera-1 gene in essential thrombocythemia. J Clin Oncol 20:4249–4254

Thomas M, Caroli J (1971) Polycythemia and Budd-Chiari syndrome. Apropos of 17 cases (in French). Ann Med Interne (Paris) 122:1175–1186

Thurm RH, Casey MJ, Emerson CP (1967) Chronic Di Guglielmo syndrome. Am J Med Sci 253:399–405

Tilanus HW (1995) Budd-Chiari syndrome. Br J Surg 82:1023–1030

Toth J, Bilodeau B (1980) Polycythemia vera associated with hepatocellular carcinoma: apropos of a case (in French). Union Med Can 109:1638–1640

Trotter JF, Cohn A, Grant R (2002) Erythrocytosis in a patient with hepatocellular carcinoma. J Clin Gastroenterol 35:365–366

Valla D (2002) Hepatic vein thrombosis (Budd-Chiari syndrome). Semin Liver Dis 22:5–14

Valla D, Casadevall N, Huisse MG, Tulliez M, Grange JD, Muller O, Binda T, Varet B, Rueff B, Benhamou JP (1988) Etiology of portal vein thrombosis in adults. A prospective evaluation of primary myeloproliferative disorders. Gastroenterology 94:1063–1069

Vaquez H (1892) Sur une forme spéciale de cyanose s'accompagnant d' hyperglobulie excessive et persistante. CR Soc Biol (Paris) 44:384–388

Vilgrain V, Lewin M, Vons C, Denys A, Valla D, Flejou JF, Belghiti J, Menu Y (1999) Hepatic nodules in Budd-Chiari syndrome: imaging features. Radiology 210:443–450

Villmow T, Kemkes-Matthes B, Matzdorff AC (2002) Markers of platelet activation and platelet-leukocyte interaction in patients with myeloproliferative syndromes. Thromb Res 108:139–145

Wanless IR (1994) Regenerative nodules in Budd-Chiari syndrome. Hepatology 19:139I

Watanobe H (1988) Hepatocellular carcinoma associated with a rare combination of polycythemia and chronic thyroiditis. Hepato-Gastroenterology 35:14–16

Yonal I, Pinarbasi B, Hindilerden F, Hancer VS, Nalcaci M, Kaymakoglu S, Diz-Kucukkaya R (2012) The clinical significance of JAK2V617F mutation for Philadelphia-negative chronic myeloproliferative neoplasms in patients with splanchnic vein thrombosis. J Thromb Thrombolysis 34:388–396

Zhou H, Wolff M, Pauleit D, Fischer HP, Pfeifer U (2000) Multiple macroregenerative nodules in liver cirrhosis due to Budd-Chiari syndrome. Case reports and review of the literature. Hepato-Gastroenterology 47:522–527

Zlatkina AR, Shcherbak EM (1970) Erythrocytosis in primary cancer of the liver (in Russian). Probl Gematol Pereliv Krovi 15:55–56

Myeloproliferative Syndromes and Thrombocythemia

81

Contents

Abstract

Several types of myeloproliferative syndrome (MPS) can involve the hepatobiliary tract, with a wide array of pathologic conditions. In MPSs with infiltration of liver parenchyma, hepatomegaly is a general feature and may be massive, often in conjunction with marked splenomegaly. Primary myelofibrosis (agnogenic myeloid metaplasia) is a clonal myeloproliferative neoplasm characterized by a growth of predominantly granulocyte precursors and megakaryocytes. Involvement of the liver shows accumulation of these cells mainly within sinusoids. This intrahepatic proliferation is frequently associated with liver fibrosis, mainly perisinusoidal fibrosis. The neoplastic cells can also form myeloid tumors or granulocytic sarcomas in the liver. Chronic myelogenous leukemia can also cause proliferation of immature myeloid cells in the liver, with massive hepatomegaly, together with signs of extramedullary hepatic hematopoiesis. In chronic neutrophilic leukemia, maturing and mature neutrophils can accumulate in the liver. In essential thrombocythemia, a myeloproliferative neoplasm involves primarily the megakaryocyte lineage; abnormal megakaryocytes accumulate in hepatic sinusoids. In this MPS, thrombotic complications of liver veins are a well-known phenomenon.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_81

Primary Myelofibrosis

ICD-O code 9961/3

Introduction

According to the 2008 WHO classification, primary myelofibrosis (PMF; synonym: chronic idiopathic myelofibrosis, CIMF; agnogenic myeloid metaplasia, AMM; idiopathic myelofibrosis; myelofibrosis with myeloid metaplasia, osteomyelosclerosis) is defined as clonal myeloproliferative neoplasm (MPN) characterized by a proliferation of predominantly megakaryocytes and granulocyte precursors in the bone marrow that is in a fully developed state, associated with reactive bone marrow fibrosis and extramedullary hematopoiesis. In bone marrow, PMF shows a stepwise evolution, starting with a hypercellular marrow without fibrosis (the prefibrotic stage) and progressing to reticulin deposition, reticulin and collagen deposition, and often osteosclerosis in the final stage. The fibrotic stage is characterized by leukoerythroblastosis in the blood with teardrop-shaped erythrocytes, and patients in this stage usually show marked hepatosplenomegaly (Michiels et al. 2007; Tefferi 2012b). PMF can undergo leukemic transformation. The main causes of morbidity and mortality in PMF are bone marrow failure, thromboembolic events, portal hypertension, cardiac failure, and acute leukemia.

PMF as a clonal hemopoietic stem cell disease has first been described in 1879 (Heuck 1879), 13 years before Vasquez described polycythemia vera rubra, followed by reports in 1905 and 1908 (Hirschield 1905; Donhauser 1908) (historical review: Weinstein 1991; more recent reviews: Tefferi et al. 1995a; Spivak et al. 2003, 2011; Tefferi and Silverstein 1996, 1997; Tefferi 2003, 2012b, 2013). The primary or idiopathic form accounts for roughly 90 %, whereas secondary forms, following another chronic myeloproliferative disorder, account for 10 % of all cases. Criteria for the diagnosis of PMF were first proposed by the Polycythemia Vera Study Group (PVSG; Laszlo 1975), but a host of terms has been proposed for this disorder. A consensus conference had proposed to employ the term myelofibrosis with myeloid metaplasia, MMM (Barosi et al. 1999), but the official term of the WHO classification now generally is PMF. Together with polycythemia vera and essential thrombocythemia, PMF makes part of the Philadelphia chromosome-negative chronic myeloproliferative disorders (CMPD).

The primary pathogenic feature of PMF is a clonal expansion of stem cells resulting in chronic myeloproliferation and atypical megakaryocyte hyperplasia (review: Lataillade et al. 2008). Clonal studies have clearly shown that the trilineage proliferation (granulocytic, erythroid, and megakaryocytic) in PMF is monoclonal and has a stem cell origin, whereas the fibroblastoid/stromal cells producing fibrosis are polyclonal (reviews: Barosi et al. 1999). However, spontaneous growth of *megakaryocytes* and their progenitors is one of the biologic hallmarks of PMF, and, therefore, interest is focused at the mechanisms inducing such a growth response. Pertinent aspects of megakaryocyte development, expansion, and differentiation pathways, involving an intricate network of gene products, are briefly addressed, also in the context with what will be discussed in the paragraphs on polycythemia vera, essential thrombocythemia, acute megakaryoblastic leukemia, and TMD in Down syndrome.

Epidemiology

PMF most often affects individuals in their sixth or seventh decade of life, both sexes being equally involved. The overt fibrotic phase of PMF is estimated to occur at 0.5–1.5 per 100,000 persons per year. Pediatric PMF also occurs, but is a very rare condition. PMF which develops in children is different from adult PMF in that malignant transformation is not a feature, and mutations of JAK2V617F or MPLW515L were not found (DeLario et al. 2012). A subset of PMF shows, similar to other myeloproliferative disorders, hereditary features (review: Ranjan et al. 2013).

Clinical Features

Blood and bone marrow are always involved. In early-stage disease, up to 30 % of patients are asymptomatic, and the disease is suspected because of indolent splenomegaly. Leukoerythroblastosis in the peripheral blood is an important diagnostic element. Patients may first present with marked thrombocytosis, raising the suspicion of essential thrombocythemia. The main features of the disease comprise ineffective erythropoiesis, dysplastic megakaryocyte hyperplasia, an increase in the ratio of immature granulocytes to total granulocytes, substantial bone marrow fibrosis, extramedullary hemopoiesis, anemia, and hepatosplenomegaly (Tefferi et al. 2000). Myelofibrosis is frequently associated with osteosclerosis (Diamond et al. 2002; with a review of the literature). In later stages, extramedullary hematopoiesis becomes a prominent feature, the main cause of hepatosplenomegaly. The most common site of extramedullary hematopoiesis is the spleen, followed by the liver, and in both organs, megakaryocyte accumulation is often the most striking alteration. The prognosis of PMF depends on the stage in which PMF is firstly diagnosed and on leukemic transformation.

Involvement of the Liver

Extramedullary Hematopoiesis

In PMF, extramedullary hemopoiesis (EMH) occurs in several organs, particularly the spleen, the liver, and the lymph nodes, less frequently the kidney and adrenal, and others. Involvement of the liver can result in fatal outcome (Ruebner 1960). It is still a matter of debate as to what the features of the extramedullary hemopoietic tissue are. One view holds it that they represent a compensatory mechanism by which blood cells are formed outside the bone marrow when bone marrow cell production is insufficient to meet the body's demands, and this is underlined by observations of EMH occurring in nonneoplastic situations such as congenital hemolytic anemias (e.g., thalassemias) and severe hemolytic and ineffective erythropoietic states (hypochromic anemia, pernicious anemia, erythroblastosis fetalis, and others). Is, however, EMH occurring in CMPD, including PMF, reactive, or is it a manifestation of abnormal stem cells having homed to remote organs?

Non-tumorous Involvement of the Liver in PMF

The accumulation of hemopoietic cells in the liver (*hepatic EMH*), and particularly within the sinusoidal channels, is a frequent finding in PMF and is associated with hepatomegaly (Figs. 1, 2, and 3; Scheimberg et al. 1995). A clinicopathologic correlation was found between the sinusoidal

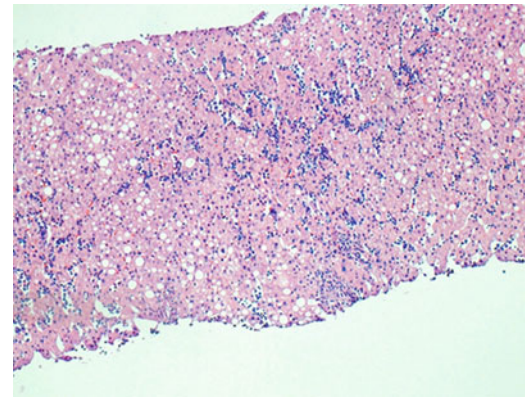

Fig. 1 Involvement of the liver in myeloproliferative syndrome. Immature myeloid cells focally infiltrate hepatic sinusoids (hematoxylin and eosin stain)

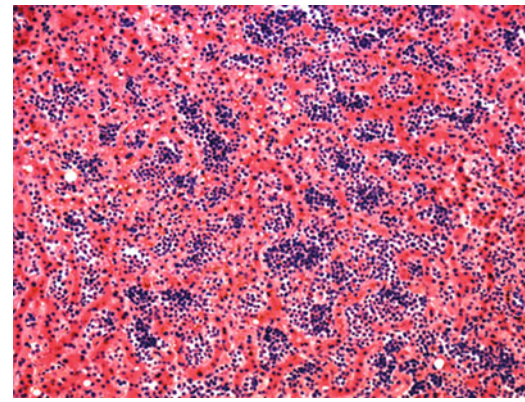

Fig. 2 Myeloproliferative syndrome, liver involvement. In this case, marked accumulation of neoplastic myeloid cells is observed in the sinusoids, causing atrophy of hepatocyte plates (hematoxylin and eosin stain)

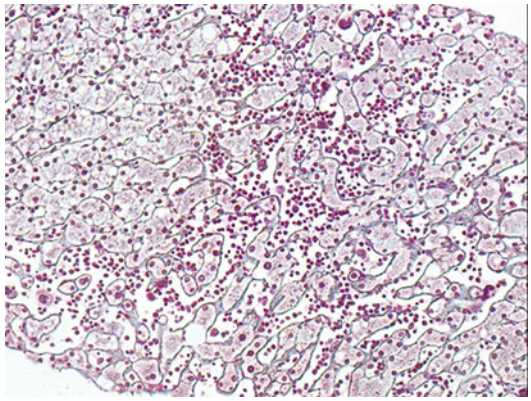

Fig. 3 Myeloproliferative syndrome, liver involvement. This reticulin stain illustrates that most myeloid cells are located within the intrasinusoidal compartment, only few cells being inside hepatocyte plates or in Disse's space. Few megakaryocytes are present (Gomori silver stain)

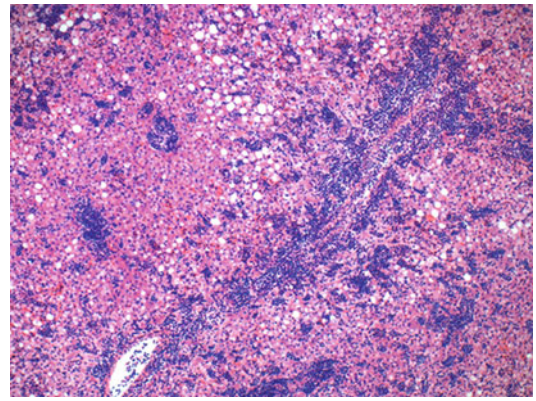

Fig. 4 Myeloproliferative syndrome in the blastic phase. Numerous immature myeloid elements (blasts) occupy both sinusoids and portal tracts (hematoxylin and eosin stain)

hemopoiesis and the number of white blood cell precursors in the peripheral blood, and erythroid hyperplasia in the bone marrow correlated negatively with white blood cell precursors and spleen and liver size (Ozen et al. 1997). In some situations, hepatomegaly is caused by a marked contribution of megakaryocytes (Nalbandian et al. 1968). EMH in PMF has also been reported to involve the wall of the gallbladder, mimicking cholecystitis (Thorns et al. 2002; Sahasrabudhe and Davenport 2005).

Liver Fibrosis

The growth of extramedullary hemopoietic elements in the liver is frequently associated with complex patterns of hepatic fibrosis (Fig. 4; Ruebner 1960; Glew et al. 1973; Degott et al. 1985; review: Le Bousse-Kerdilès 2012). Accumulation of hemopoietic cells and associated stromal elements in the sinusoidal compartment can lead to perisinusoidal fibrosis (Bioulac-Sage et al. 1986; Roux et al. 1987; Tsao 1989), which in turn may cause nodular regenerative hyperplasia of the liver and portal hypertension (Degott et al. 1985). In addition to PMF, perisinusoidal fibrosis can also be encountered in chronic myeloid leukemia, polycythemia vera, and essential thrombocythemia (see the respective paragraphs). Early-stage perisinusoidal fibrosis is revealed by the presence of collagen fiber bundles localized to Disse's space and surrounding liver cell plates, usually in areas where sinusoids are occupied by dense accumulations of hemopoietic elements (Tsao 1989), this distinct spatial relationship suggesting that there might be a pathogenic link between extramedullary hemopoiesis and fibrogenesis. In later stages, collagen deposition in the space of Disse is extensive, sometimes resulting in chicken-fence fibrosis, and associated with atrophy of hepatic plates. This perisinusoidal fibrosis is already visualized in the hematoxylin and eosin stain in the form of an eosinophilic fibrillar material, but is better seen in collagen stains. A variable contribution of reticulin fibers is in evidence. At the ultrastructural level, it has been observed that perisinusoidal fibrosis in CIMF is associated with a differentiation of quiescent stellate cells into myofibroblast-like, matrix-producing cells, i.e., as in other fibrogenic pathways in liver disease (Bioulac-Sage et al. 1986; Roux et al. 1987). Typically, these activated myofibroblasts are immunoreactive for alpha-smooth muscle actin (alphaSMA). Marked perisinusoidal fibrosis may cause a distortion of the lobular architecture, but nodular regenerative hyperplasia and even cirrhosis are rarely seen. In liver areas involved, Kupffer cells may show iron overload. Whether this iron accumulation

contributes to fibrogenesis in PMF is unknown. Perisinusoidal fibrosis with or without capillarization of the sinusoids causes portal hypertension through the establishment of a sinusoidal block and other mechanisms (see below).

Tumorous Hepatic Lesions in PMF

The extramedullary hemopoiesis in PMF occasionally forms tumorous masses in several organs, called *extramedullary myeloid tumors*. Focal intrahepatic extramedullary hemopoiesis (FIEH) occurring in PMF has repeatedly been documented, and also the imaging features have been described (Wiener et al. 1987; Abbitt and Teates 1989; Kobayashi et al. 1989; Warshauer and Schiebler 1991; Siniluoto et al. 1992; Aytaç et al. 1999; Kwak and Lee 2000; Navarro et al. 2000; Gupta et al. 2004; Cardoso et al. 2011). FIEH can manifest as solitary or multiple lesions (Abbitt and Teates 1989; Warshauer and Schiebler 1991). Reported masses had a diameter of 2.5–15 cm; in rare instances, these myeloid hepatic tumors may grow to giant masses (Navarro et al. 2000; Gil-Fernandez et al. 2001). Sonographically, FIEH presents in the form of two distinct patterns, i.e., (a) a well-defined homogeneously hypoechoic lesion or (b) a well-defined homogeneously hyperechoic mass encircling the portal vein and its main branches (Siniluoto et al. 1992).

The gross presentation of FIEH is characterized by rather sharply delineated tumorous masses with an either spheroid or lobulated contour, reflecting what is seen at imaging (Aytaç et al. 1999; Gupta et al. 2004). The lesion can grow to a size of 15 cm (Navarro et al. 2000). The cut surface of these either friable or firm masses (the consistency depending on the relation between cellularity and stromagenesis) is highly variable, ranging from whitish to tan or even dark-red. Histologically, the masses consist of usually mixed hemopoietic tissue that however typically contains a large proportion of megakaryoblasts and megakaryocytes, but lesions with predominance of erythroid elements are also recognized. It is of interest to note that megakaryocytes also prevail in hepatic manifestations of the transient myeloproliferative disorder occurring in patients with Down syndrome (see below). The hemopoietic cells in FIEH are chiefly localized to dilated hepatic sinusoids, but sometimes the cells also locate to Disse's space and to tissue spaces occupied by hepatocyte cords. The latter finding is intriguing, because hemopoietic cells do not usually home to extrasinusoidal spaces in the liver, owing to the homing and relocation mechanisms required. A distinct array of stromal cells accompanies the hemopoietic elements in FIEH. The density of these mesenchymal cells is, however, markedly variable, ranging from only a few and not easily detectable stromal cells to lesions presenting a sclerosing phenotype (see below). Similar to findings in myelofibrotic bone marrow, extramedullary hemopoiesis in the abdominal cavity may lead to the accumulation of pseudo-Gaucher cells in the peritoneal fluid (Lang and Uthman 1999). FIEH may be associated with nodular regenerative hyperplasia of the liver, a lesion known to also occur in patients with myeloproliferative disorders.

Fibrosing/sclerosing variants of hemopoietic tumors in PMF (sclerosing extramedullary hematopoietic tumor; SEMHT).

Part of the tumor-forming lesions in PMF and other chronic myeloproliferative disorders are characterized by a sometimes marked fibrogenesis, resulting in sclerosed masses. Previously, such lesions were also termed fibrous hematopoietic tumors (Beckman and Oehrle 1982). The term now currently employed is *sclerosing extramedullary hematopoietic tumor* (*SEMHT*; Remstein et al. 2000; Lane et al. 2000). SEMHT are solitary or multiple lesions that mostly form retroperitoneal or serosal-based masses, but they also develop in the breast, the lung, and the skin. The tumors may be mistaken for sarcomas, particularly sclerosing liposarcomas, other solid neoplasms, or lymphocyte-poor Hodgkin's lymphoma.

The anatomical compartment of the liver and associated structures can be involved by SEMHT. The lesion has been found in the liver (Waitz et al. 1978) and in the ligamentum teres hepatis (Kwon et al. 2004). Multiple sclerosing

hemopoietic tumors have been observed throughout the peritoneal surfaces (Tzankov et al. 2002). At gross examination, the tumor nodules are well circumscribed, up to several cm in diameter, firm, with a fibrous texture, and whitish. Histologically, SEMHT reveal a fibrosclerotic and myxoid background with usually thick collagen bundles, sometimes with interspersed groups of mature adipocytes. Within this matrix, there are clusters of trilineage hemopoiesis, with in part atypical megakaryocytes, granulocytes and their precursors, erythroid precursors, and only very few or no blasts.

Myeloid/Granulocytic Sarcoma of the Liver

Myeloid sarcomas are neoplasms of immature granulocytes, monocytes, or both involving extramedullary sites and occur in both leukemic and nonleukemic patients (Hang et al. 2011), also in PMF (Yoshiki et al. 2011; Morita et al. 2012). In rare instances, myeloid metaplasia of the liver may be followed by hepatic granulocytic sarcoma (Gangane et al. 2008), suggesting the focal outgrowth of transformed hematopoietic stem cells.

Portal Hypertension in PMF Patients with Hepatic Involvement

Portal hypertension occurs in 4–10 % of the patients with PMF (Shaldon and Sherlock 1962), and in at least 50 % of these patients, liver biopsies have uncovered extramedullary hemopoiesis as the only abnormality (Wyatt and Sommers 1950), while others show variable degrees of perisinusoidal fibrosis/capillarization or combined lesion patterns. The pathogenesis of portal hypertension arising in PMF has been difficult to understand because liver biopsy findings have often shown only minimal changes (Wanless et al. 1990). In a study of 97 patients with polycythemia vera and 48 patients with PMF (then termed agnogenic myeloid metaplasia), 10 patients without cirrhosis showed portal venous hypertension. All of these patients exhibited lesions in small- or medium-sized portal vein branches, and four had stenosis of the extrahepatic portion of the portal vein reflecting organized thrombi. Portal vein lesions were associated with nodular regenerative hyperplasia. In this autopsy study, there was no correlation between hepatic hemopoietic infiltration and signs of portal hypertension, and it was concluded that portal vein anomalies and subsequent nodular regenerative changes may play a pathogenic role for portal hypertension (Wanless et al. 1990).

Liver Changes Following Splenectomy in Patients with PMF

The risks and benefits of splenectomy in PMF have been studied in detail (Barosi et al. 1998; Tefferi et al. 2000). The postsplenectomy occurrence of extreme thrombocytosis, hepatomegaly, and leukemic transformation is of major concern (Mesa et al. 2000), even though the development of blast transformation after splenectomy may not affect overall survival and does not undermined the palliative role of the procedure for the other indications (Tefferi et al. 2000). In a large study, blast transformation was noted in 14.2 % of the patients, and substantial postsplenectomy hepatomegaly occurred in 16 % (Barosi et al. 1998). Subsequent to splenectomy, patients with CIMF may develop acute or chronic liver changes and rarely acute liver failure. In a recent analysis of numerous patients, liver failure was the direct cause of 7 % of the deaths (Barosi et al. 1998). Liver biopsies revealed extramedullary hepatic hemopoiesis, consisting of dysmorphic megakaryocytes primarily localized to the sinusoidal blood space, often accompanied by erythroid cells (Lopez-Guillermo et al. 1991). Subsequent to splenectomy, hepatomegaly (sometimes massive) can emerge (Grieco et al. 1988; Barosi et al. 1998). The secondary increase of hemopoietic elements in the liver after loss of the splenic compartment may be one of the reasons why the degree of hepatomegaly can increase, or hepatomegaly develop, after splenectomy in CIMF. In the rare complication characterized by acute liver failure with hepatic enlargement after splenectomy (McBrine et al. 1980; Perez-Villa et al. 1988), extensive extramedullary hemopoiesis dilating hepatic sinusoids and apparently compressing liver cells were the main pathologic findings (McBrine et al. 1980).

Differential Diagnosis

Mass-Forming Extramedullary Hematopoiesis

The biopsy differential diagnosis of mass-forming FIEH in CIMF includes focal hemopoiesis in benign hematologic disorders. FIEH can sometimes form large lesions (e.g., in thalassemia; Dewar et al. 1990; Wong et al. 1999) and hepatic myelolipoma (see ▶ Chap. 65, "Lipomatous Tumors, Liposarcoma, Benign Adipocyte-Containing Nonneoplastic Lesions, and Focal Fatty Changes of the Liver"). Rarely, multiple manifestations of FIEH of several cm diameter occur in patients without overt hematologic disease (Gupta et al. 2004). Liver involvement in CIMF may be associated with, or being complicated by, other hepatic tumors, e.g., hepatocellular carcinoma (Mitsuhashi et al. 1977).

Reactive Myelofibrotic Disorders Mimicking PMF

Myelofibrosis develops in one variant of hereditary primary hypertrophic osteoarthropathy (PHO), i.e., in PHO caused by mutations of the prostaglandin transporter SLCO2A1 (Diggle et al. 2012). Interestingly, gray platelet syndrome (GPS; alpha granule storage defect/deficiency) is sometimes associated with myelofibrosis, however usually with formation of increased reticulin fibers (Levy-Toledano et al. 1981). GPS is a rare bleeding disorder with thrombocytopenia, agranular gray platelets, and almost total absence of platelet alpha granules and their constituents (Raccuglia 1971). More than half of the reported cases are from a large family in Japan, and an autosomal dominant trait has been proposed (Mori et al. 1984). A hereditary platelet defect in the rat (Wistar Furth hereditary macrothrombocytopenic rat) resembles GPS of man. GPS belongs to a whole group of platelet disorders with abnormal alpha granule composition and function, also including factor V Quebec disorder (which leads to a degradation of most proteins continued within the alpha granules) and the Paris-Trousseau/Jacobsen-type dysmegakaryopoietic thrombocytopenia (associated with a chromosome 11q23.3 deletion, Fli-1 gene deletion, alpha granule deficiency, and abnormal, giant platelet alpha granules). Platelets in GPS display a markedly reduced concentration of the majority of alpha granule proteins that include platelet factor-4, beta-thromboglobulin, thrombospondin, fibrinogen, von Willebrand factor together with factor VIII, plasminogen activator inhibitor-1, TLT-1 (a TREM family member), PDGF C, glycoprotein (GP) VI, osteonectin, and fibronectin. Under normal conditions, these molecules are stored in alpha granules, and their secretion is mediated by or dependent on SNAP receptor (SNARE) complex formation between syntaxin, SNAP-25, and vesicle-associated membrane proteins.

Cytogenetic and Molecular Features

Cytogenetic abnormalities are detected in up to 30 % of patients (review: Hussein et al. 2009). The most common karyotypic features are del (20q) and partial trisomy 1q. No karyotype abnormality is proving the presence of PMF, but either del(13)(q12-22) or der (6)(1;6) is strongly suggestive (Hussein et al. 2009). Approximately half of patients with PMF show the JAK3V617F tyrosine kinase mutation, also found in other myeloproliferative disorders (Zhang and Li 2008; Kiladijan 2012; Tibes et al. 2012; Xia et al. 2012; Milosevic and Kralovics 2013; Nielsen et al. 2013). Among 30 patients with PMF, 50 % carried a JAK2V617F mutation (Xia et al. 2012). The presence of the JAK2V617F mutation does not seem to have an impact on leukemic transformation in PMF (Helbig et al. 2012). PMF patients can also show MPL/thrombopoietin receptor mutations (Tefferi 2008), but much less commonly than JAK2V617F mutations (Xia et al. 2012). The presence of MPL mutations has narrow and inconsistent phenotypic effects in PMF (Pardanani et al. 2011). The A3669G polymorphism of the glucocorticoid receptor is a susceptibility allele for PMF and contributes to phenotypic diversity and blast transformation (Poletto et al. 2012). Mutations in the isocitrate dehydrogenase (IDH) gene can occur in PMF and predict leukemic transformation and shortened survival (Tefferi et al. 2012b). Another mutational change that predicts poor survival in PMF is mutation in the EZH2 gene (Guglielmelli et al. 2011). EZH2 is

the PcG enhancer of zeste homolog 2, the catalytic component of the polycomb repressive complex 2, which serves to trimethylate histone H3 lysine 27. In PMF, mutations of the spliceosome components SF3B1 and SRSF2 occur, similar to other disorders with leukemogenesis (Malcovati et al. 2011; Makishima et al. 2012). Among 187 patients with PMF screened, 17 % harbored SRSF2 monoallelic mutations affecting residue P95, and mutations were associated with advanced age and shorter overall and leukemia-free survival (Lasho et al. 2012). TP53 mutation is rare in PMF (Greaves et al. 2013). PMF reveals a distinct methylome profile with both aberrant hyper- and hypomethylation gene patterns. Aberrant hypomethylation in PMF was seen to occur in non-CpG island loci, a pattern different from other myeloproliferative disorders (Nischal et al. 2013). Megakaryocytes in PMF show a decrease expression of proapoptotic genes such as BNIP3 (review: Kreipe et al. 2012).

Chronic Myelogenous Leukemia (CML, BCR/ABL1 Positive)

ICD-O code 9875/3

Introduction

In the WHO classification, chronic myelogenous leukemia (CML) is defined specifically as a myeloproliferative disorder that originates in an abnormal pluripotent bone marrow stem cell and is characterized by the invariable presence of the Ph chromosome or the *BCR*/*ABL* fusion gene. BCR/ABL1 is detectable in all myeloid lineages as well as in some lymphoid cells and endothelial cells in CML, although the initial presenting alteration as pathological neutrocytosis. Following an initial indolent chronic phase, CML can progress to accelerated and blast phases (CML accelerated phase (CML-AP) and CML blast phase (CML-BP)). The minimally invasive neoplastic cells in CML largely occupy the hemopoietic compartments and tissues, in particular the blood, bone marrow, and spleen, although the liver may be infiltrated as well.

Clinical Features

CML has an insidious onset, resulting in a largely asymptomatic onset in up to 40 % of patients. Diagnosis in these patients is done when an abnormal leukocyte count is detected in routine blood smears. Later symptoms and signs include fatigue, night sweats, weight loss, and splenomegaly. This phenotype is termed CML in chronic phase (CML-CP). Patients with the accelerated phase or blastic phases of CML, which may develop suddenly or after a transition phase, show the signs and sequelae of cytopenia and sometimes massive splenomegaly.

Morphology and Immunocytochemistry of the Leukemic Cells

In the chronic phase of CML, leukemic cells circulating in blood are neutrophils in different stages of maturation, always associated with absolute basophilia and often with monocytosis, with blasts accounting for less than 2 % of the cells. In the p190 BCR/ABL1 isoform, monocytosis is always present, resembling chronic myelomonocytic leukemia. The increased cell turnover causes the production of pseudo-Gaucher cells and sea-blue histiocytes in the bone marrow, cells derived from the neoplastic clone. The blast phase is characterized by the presence of 20 % or more of blast cells in the peripheral blood of nucleated cells in the bone marrow or by an extramedullary blast proliferation. A myeloid blast population (neutrophilic, eosinophilic, basophilic, monocytic, megakaryocytic, or erythroid blasts) is found around 70 % of patients, while 20–30 % of patients reveal a lymphoid blast lineage (precursor B cells or T lymphoblastic, with co-expression of myeloid antigens). Neutrophils in CML exhibit a markedly decreased neutrophil alkaline phosphatase. The blasts in myeloid blast phase may have strong,

weak, or no myeloperoxidase activity, but often express antigens associated with granulocytic, monocytic, megakaryoblastic, and/or erythroid differentiation.

Liver Involvement

Introduction

In part of patients with CML, the liver is infiltrated by the neoplastic cell populations (Hopps and Rucks 1948; Schwarze et al. 1975; Walz-Mattmüller et al. 1998). In addition, patients with CML may show "normal-looking" extramedullary hematopoiesis (Kajigaya et al. 1987). However, this type of extramedullary hematopoiesis seems to be more abnormal than marrow hematopoiesis (Baccarani et al. 1978).

Pathology

Macroscopy

In part of the patients, hepatomegaly is present, sometimes massive, with liver weights reaching 10 kg (Gruber 1930). The liver capsule is generally smooth, but circumscribed thickening was also noted. On cut surfaces of the liver, the lobular architecture may be blurred due to sinusoidal infiltration. These infiltrates can show confluence, resulting in a whitish network. A subset of patients display focal tumor-like lesions termed leukomas caused by marked focal accumulation of neoplastic cells. In case of strong expression of myeloperoxidase, a green enzyme, leukomas can turn to a greenish color, i.e., chloromas (the "leukemia with green tumors" or myeloid chloroleukemia of Fabian; Fabian 1908).

Histopathology

Histologically, in patients with neoplastic hepatic infiltration, the partially dilated sinusoids contain blood with an increased neutrophil cellularity and/or contain clusters of neutrophil precursors in different stages of maturation and erythroblasts. The neoplastic elements form clusters or are arranged within the sinusoids in the form of "Indian files." Part of the cells, mainly the myeloid cells, are in close relationship with sinusoidal endothelial cells, or seem to adhere to them. In part of the cases, the process infiltrates the portal tracts to variable degrees, however with predominance of immature cell forms with decreased cytoplasmic granularity (Butterfield 1908). Leukomas and chloromas consist of dense tumor-like accumulations of myeloid cells in various stages of differentiations, associated with expansive growth and perifocal atrophy of the hepatic parenchyma (Kchinologuer 1915). Liver biopsies from 15 untreated patients with CML showed that the proportion of erythroblasts was higher than in the bone marrow, and an increased frequency of basophilic leukocytes was recorded in the extramedullary sites. The mitotic indices of the granulocytopoietic and erythrocytopoietic precursor cells were lower in the spleen and liver than in bone marrow, suggesting marked differences in the biologic features of hepatic blood-forming cells in CML in comparison with the marrow. In the liver, also a considerable admixture of lymphoid cells was found (Sjögren and Brandt 1976). Intrasinusoidal normal-looking or abnormal CD61-positive megakaryocytes may also be in evidence. Part of the involved livers show perisinusoidal reticulin fibrosis, similar to that found in the bone marrow (Mikel et al. 1990). In the chronic phase of CML, extramedullary hemopoiesis can result in the emergence of multiple and in part hemorrhagic nodules of extramedullary hemopoiesis ("pseudochloromas") in the absence of blastic transformation (Barton et al. 1979). In the course of blastic transformation, the sinusoids and portal tract spaces are progressively infiltrated by large numbers of lysozyme- and CD34-positive myeloid or lymphoid blasts cells. In the parenchyma, these blasts may cause hepatocyte plate atrophy and effacement of the lobular architecture. Massive hepatic involvement has been observed CML showing monoblastic transformation (Ondreyco et al. 1981). Liver involvement in CML can be associated with hepatic vascular complications, specifically Budd-Chiari syndrome (Anger et al. 1989; Picardi et al. 2000).

Pathogenic Pathways

Ninety to ninety-five percent of CML have the t (9;22)(q34;q11.2) translocation at diagnosis, resulting in the Philadelphia (Ph) chromosome. This translocation fuses sequences of the BCR gene on chromosome 22 with regions of the ABL1 on chromosome 9 (reviews: Ernst and Hochhaus 2012; Gianfelici et al. 2012). The breakpoint in BCR is found in the major breakpoint cluster region M-BCR in the majority of cases. The fusion results in an abnormal fusion protein, p210, a kinase with increased tyrosine kinase activity and responsible for the constitutive activation of several signal transduction pathways. The BCR/ABL fusion directly downregulates the expression of c-Jun, a monopoiesis-promoting transcription factor, by activating the PI3-Akt pathway, thereby promoting neutrophil differentiation in chronic phase CML (Kobayashi et al. 2009). Much less commonly, the breakpoint involves exons 17–20, resulting in a larger fusion protein called p230. Patients with p230 have pronounced neutrophil maturation and/or marked thrombocytosis. CML is regarded as a stem cell disorder derived from a pluripotent bone marrow stem cell (review: Crews and Jamieson 2012). The clonal population of neoplastic cells exhibits marked heterogeneity in regard to proliferation and differentiation. The population contains stem cells with a high proliferative activity and marked self-renewal capacity not found in leukemic cells, and these cells maintain the leukemic process. In the course of CML in chronic phase (CML-CP), leukemia stem cells or their progeny may at some stage acquire additional genetic alterations that cause CML to transform further, from CML-CP to a more advanced phase, which is classified as either accelerated phase CMl (CML-AP) or blastic phase CML (CML-BP). CML-BP is characterized by a massive expansion of immature blasts or progenitor cells with myeloid or lymphoid features (review: Skorski 2012).

Apart from hematopoietic stem cells, other CML-initiating cells have been postulated, including fetal liver kinase-1-ppositive, BCR/ABL1 fusion gene-positive mesenchymal stem cells (Xishan et al. 2011). These findings are of interest in the light of the significant roles played by the stromal microenvironment and its signaling pathways in CML leukemogenesis (review: Seke Etet et al. 2012).

Chronic Neutrophilic Leukemia (CNL)

ICD-O code 9963/3

Introduction

Chronic neutrophilic leukemia (CNL) is a rare BCR/ABL/Ph1-negative chronic myeloproliferative disease mostly occurring in elderly patients of both sexes, characterized by persistent neutrophilia (mature neutrophilic leukocytosis), bone marrow granulocytic hypercellularity without evidence of myelodysplasia, splenomegaly/hepatosplenomegaly, and bearing a poor prognosis (Yam 1982; Zittoun et al. 1994; Elliot et al. 2001; Böhm and Schaefer 2002; Elliott 2004, 2006; Haferlach et al. 2008; Thiele 2009). In addition to the absence of BCR/ABl rearrangement, CNL has no rearrangement of PDGFRA, PDGFRB, or FGFR1.

The exact incidence of CNL is not known, but probably less than 200 cases have been reported in the literature, and of these, only 40 have been found to meet the WHO criteria in a detailed review (Elliott 2006). CNL can be distinguished from CML, neutrophilic-chronic myelogenous leukemia, and myelodysplastic syndromes, although a transition from polycythemia vera (Foa et al. 1991; Higuchi et al. 1999), or from a myelodysplastic syndrome (including CMMoL) (Zoumbos et al. 1989; Cervantes et al. 1990; Pascucci et al. 1997), to CNL has been reported. The criteria for CNL diagnosis have been worked out (You and Weisbrot 1979), but CNL is still in the process for improved definition, having led to the concept of "true" CNL (Reilly 2002). In fact, cases with CNL were not included in the FAB system (Bennett et al. 1994). The disorder has the potential for blastic transformation and progressive refractory neutrophilia (Elliott 2004; Amato et al. 2008).

Clinical Features

The most common reported clinical feature is splenomegaly, sometimes symptomatic. Patients with CNL often show hepatomegaly as well (You and Weisbrot 1979; Zittoun et al. 1994). CNL can be associated with elevated serum vitamin B12 levels and can present with Sweet's syndrome (Gan et al. 2007). As CML, CNL can undergo blastic transformation (Elliott 2004; Amato et al. 2008).

Morphology

Patients with CNL have a marked peripheral leukocytosis (WBC $\geq 25 \times 10(9)/L$), with segmented neutrophils and band forms accounting for more than 80 % of the WBCs, immature granulocytes being less than 10 % of WBCs, and myeloblasts less than 1 %. In the bone marrow, the neutrophil maturation pattern is normal, and myeloblasts amount less than 5 % of nucleated BM cells.

Liver Involvement in Chronic Neutrophilic Leukemia

Liver Infiltration by Leukemic Cells

Similar to CML, maturing and mature neutrophils have the capability to home to the hepatic vascular bed (You and Weisbrot 1979; Zittoun et al. 1994) and are chiefly found within sinusoids (Yamaya et al. 1982; Hayashi et al. 1983; Takenaka et al. 1986), where they are seen either in central parts of the vascular channels or then close to the endothelial lining, sometimes forming small clusters of cells. Similar to other hematologic neoplastic disorders, CNL may show Gaucher-like cells in the infiltrate (Tang et al. 1987).

Other Hepatic Lesions Associated with CNL

CNL has been described to be associated with nonalcoholic steatohepatitis (NASH), and it has been assumed that the hepatic infiltration in CNL may contribute to the pathogenesis of NASH (Yoshida et al. 2004).

Leukocytosis and Leukemoid Reactions in Hepatocellular Carcinoma: Alterations Mimicking CNL

Some patients with hepatocellular carcinoma (HCC) exhibit marked neutrophilic leukocytosis/neutrophilia with or without pyrexia, eventually leading to a hematologic presentation mimicking leukemia ("leukemoid reactions "; "pseudoleukemic hyperleukocytosis"; Ochoa 1981; Rosenfeld et al. 1982; Sylvain et al. 1985; Okuda et al. 1991; Manas Garcia et al. 2004). HCC cells can express and secrete colony-stimulating factor(s), in particular granulocyte CSF (G-CSF), suggested to cause the leukocytosis (Toyoda et al. 1989; Yamamoto et al. 1999). In addition to HCC, other tumors in the liver are capable to synthesize G-CSF inducing leukocytosis, including primary adenosquamous carcinoma of the liver (Hayashi et al. 2001) and primary liver squamous carcinoma (Koyama et al. 1990).

Pathogenic Pathways

Usually, none of the common cytogenetic anomalies characteristic of myeloid disorders are detectable. The clonal nature of CNL has been established (Kwong and Cheng 1993), and monosomy at 11q23 has been interpreted to be a marker for clonality in CNL (Froberg et al. 1998).

The exact cause of CNL is not known so far. Interestingly, several reports illustrate the association of CNL with monoclonal gammopathies/monoclonal gammopathy of uncertain significance (MGUS) and with plasmacytic proliferative disorders, including myeloma, which may even precede the onset of overt CNL (Tursz et al. 1974; Vorobiof et al. 1978; Watanabe et al. 1984; Zoumbos et al. 1987; Rovira et al. 1990; Standen et al. 1990; Masini et al. 1992; Cehreli et al. 1994; Ito et al. 1996; Tanaka et al. 1998; Nitta et al. 1999; Dincol et al. 2002; Hartley et al. 2010). An association with myeloma has also been noted for other types of leukemia and related disorders, such as myelomonocytic leukemia (Raz and Polliack 1984; Akashi et al. 1991), acute monocytic leukemia (Luca and Almanaseer 2003), myelodysplastic syndrome (Sato et al. 1992), and erythroleukemia (Barcos et al. 1979). The pathogenesis of these

associations is not clear. It was suggested that the two groups of disorders may go back to a common stem cell followed by an abnormal development in the sense of "lineage infidelity" (Akashi et al. 1991; Nitta et al. 1999), or that myeloma might induce a leukemoid reaction mimicking a myeloproliferative disorder (Ito et al. 1996). In fact, molecular studies have shown that, in at least part of these associations, the neutrophils were not clonal (Standen et al. 1993). On the other hand, myeloma may produce granulocyte colony-stimulating factor and induce a clinical situation mimicking CNL (Usuda et al. 1997; Kusaba et al. 2004).

Essential Thrombocythemia

ICD-O code 9962/3

Introduction

According to the 2008 WHO classification, essential thrombocythemia (ET) is defined as a chronic myeloproliferative neoplasm that involves primarily the megakaryocytic cell lineage. Synonyms of ET comprise primary thrombocytosis, idiopathic thrombocytosis, and hemorrhagic thrombocythemia. ET is also termed thrombocythemia vera. ET is hematologically characterized by persistent thrombocytosis $\geq 450 \times 10(9)/L$ in the peripheral blood, increased numbers of large, mature megakaryocytes in bone marrow, and clinically by episodes of thrombosis and/or hemorrhage (reviews: Michiels et al. 2007; Levine and Heaney 2008; Harrison 2010; Beer 2011; Tefferi 2012a).

ET was regarded as a "benign" myeloproliferative disorder with an, as such, normal life expectancy. However, the population-based Olmsted County Study suggested that survival among patients with ET was significantly worse than that among age- and sex-matched healthy control subjects (Mesa et al. 1999), and the reduced survival is chiefly caused by thrombotic and vascular complications and in fewer patients by the emergence of myelodysplasia, myelofibrosis, or acute leukemia (Harrison 2002; Cervantes et al. 2002; Bernasconi et al. 2002). As polycythemia vera, ET originates in the clonal expansion of a transformed pluripotential hemopoietic progenitor cell ("clonal thrombocytosis"; Tefferi et al. 1995b; Michiels 1996; Gilbert 2001; review: Schafer 2004). ET is, therefore, one of the chronic myeloproliferative disorders. The relationship of chronic hemopoietic stem cell disorders is underlined by the rare finding of ET following polycythemia vera (Randi et al. 1996) and by thrombocytosis occurring in the context of polycythemia vera. Moreover, thrombocytosis may also be associated with the myelodysplastic 5q- syndrome, a mixed myelodysplastic and myeloproliferative syndrome. The clonality of ET has been investigated by several methods (Schafer 2001; Liu et al. 2003); however, ET may not always be clonal, and these forms may be at lower risk of thrombotic complications (Harrison et al. 1999), suggesting that a non-clonal disease can progress to clonal disease and that ET may be a heterogeneous disorder (Schafer 2004).

Epidemiology

ET has an estimated incidence of 0.6–2.5 per 100,000 persons per year, according to the Polycythemia Vera Study Group (PVSG). Most patients are 50–60 years old at diagnosis, males and females being equally affected. A second age peak, mainly in women, is at about 30 years of age, and also children can develop ET (Michiels and Juvonen 1997; Michiels and Thiele 2002). More than half of patients are asymptomatic when markedly elevated thrombocyte numbers are detected in peripheral blood, the remaining patients usually presenting with thrombosis and signs of vascular occlusion.

Clinical Features

More than half of patients are asymptomatic at diagnosis. Symptomatic patients show signs and complications of vascular occlusion and/or hemorrhage (Falanga and Marchetti 2012).

Hemorrhages are common from mucosal surfaces. Thrombosis of medium-sized to large arteries may occur. About 50 % of patients show splenomegaly, and 15–20 % hepatomegaly. However, the prevalence of splenomegaly depends on the diagnostic criteria for ET used, in that splenomegaly more often occurs in patients who have thrombocytosis in the prefibrotic stage of myeloproliferative syndrome.

Morphology

The major alterations in ET are marked thrombocytosis in peripheral blood, with an abnormal platelet morphology and a prominent proliferation of megakaryocytes in the bone marrow. Large and even giant megakaryocytes predominate, usually with deeply lobulated and hyperlobulated nuclei (the so-called stag hornlike nuclei). ET usually shows an early-stage myeloproliferative bone marrow disorder, characterized by a proliferation of mature-looking enlarged megakaryocytes in the bone marrow with no or only slightly increased cellularity, and there is no progression of the myeloproliferative activity. Granulopoiesis and erythropoiesis are mostly normal in marrow, and no marrow fibrosis is in evidence in 99 % of the patients at the time of diagnosis. ET may pose differential diagnostic problems in comparison with CIMF, because also ET can be associated with an increase in bone marrow reticulin fibers, albeit in a minority of the patients. Initial and early idiopathic myelofibrosis (CIMF) mimicking ET is characterized by a reduction of life expectancy different from that of ET (Thiele and Kvasnicka 2003). The bone marrow in ET reveals an isolated (monolinear) proliferation of megakaryocytes without gross abnormalities of this cell lineage (Thiele et al. 1987), but with a marked expansion of megakaryocyte precursors (Thiele et al. 1990).

At EM examination, bone marrow megakaryocytes in ET were found to be in part large or even giant and characterized by a highly lobulated nucleus containing several nucleoli and an extensive intermediate zone of the cytoplasm with many Golgi fields, numerous profiles of the demarcation membrane system, and an abundance of alpha granules and some dense bodies, findings suggesting not a marked structural abnormality, but rather reflecting a state of markedly increased thrombocytopenic activity (Thiele et al. 1988).

Liver Involvement in Essential Thrombocythemia

Hepatic Infiltration

In ET, liver sinusoids may show an accumulation of megakaryocytes, either as single elements or in clusters, and/or of other hemopoietic elements (Fig. 5). It is not yet known how frequent megakaryocyte homing to the hepatic sinusoidal compartment is in ET. In the case of dense accumulations, sinusoidal plugging by megakaryocytes may ensue, similar to other organs, e.g., the lung (Hill et al. 1996).

Megakaryocytes located to the hepatic sinusoidal channels can contain entire other cells, mainly hematologic cells or fragments thereof in their cytoplasm, a phenomenon termed emperipolesis (Thiele et al. 1984; Tavassoli 1986). The homing, and eventual proliferation, of megakaryocytes and their progenitors to the hepatic sinusoidal vascular bed can induce fibrosis and in particular perisinusoidal fibrosis; this phenomenon is further discussed in the paragraphs on CIMF and TMD in Down

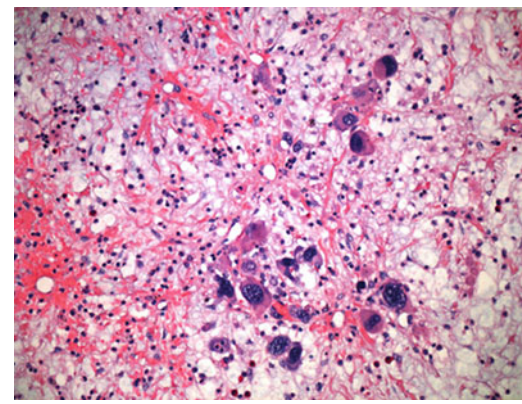

Fig. 5 Liver involvement in essential thrombocythemia. The parenchyma is destroyed and replaced by a tissue containing clusters of atypical megakaryocytes (hematoxylin and eosin stain)

syndrome. Furthermore, sinusoids harboring megakaryocytes may be dilated and distorted, which may be caused not only by a mass effect and/or stasis but also be distinctive effects of megakaryocytes on sinusoidal endothelial cells (see below). Extramedullary hemopoiesis in the liver was found in ET complicated by blastic transformation and acute myelofibrosis (Chen et al. 1987).

Thrombotic Complications of Liver Veins in Essential Thrombocythemia

ET is well known to be associated with diverse thrombotic and hemorrhagic manifestations, including platelet-mediated erythromelalgia, microvascular disturbances, (aspirin-responsive) arterial thrombophilia, coronary artery disease, atypical cerebral ischemic attacks, paradoxical thrombosis and bleeding, and thrombosis of visceral veins (Michiels et al. 1996, 2004). Hemorrhagic thrombocythemia is a clinical syndrome of recurrent spontaneous mucocutaneous and secondary hemorrhages associated with extremely high platelet counts far in excess of 1000 × 10 (9)/L; at increasing platelet counts in excess of 2000 × 10(9)/L, arterial thrombophilia of ET changes into a spontaneous bleeding tendency as a consequence of platelet-mediated increased proteolysis of the large von Willebrand factor multimers leading to a type 2 acquired von Willebrand syndrome (Michiels 2003; Michiels et al. 2004). Venous thromboses, including those of large visceral veins, are related to platelet effects, increased hematocrit, blood cell mass, and increased concomitant blood viscosity. Budd-Chiari syndrome (BCS; see above) occurs as a complication of ET, similar to other myeloproliferative disorders (Garza Trasobares et al. 1988; Corredoira et al. 1989; Brunerova et al. 2004; Karakulska-Prystupiuk et al. 2012). Furthermore, portal vein thrombosis with or without associated splenic vein thrombosis occurs in ET and other forms of thrombocytosis (Chiti et al. 1992; Teofili et al. 1992; Randi et al. 1993, 2002; Jimenez Saenz et al. 1998; Berk and Ahmed 2006). A latent form of ET has presented as portal cavernoma (Cai et al. 2009), and cavernous transformation of the portal vein was also noted in hemorrhagic thrombocythemia (Macpherson et al. 1957). Occlusive thrombotic lesions may also involve microvessels of the liver (Singh and Wetherley-Mein 1977).

In ET, multiple venous and arterial thrombosis of the gallbladder causing acute cholecystitis have been observed (Picon-Coronel et al. 2011). The pathogenesis of thrombotic events in ET and other myeloproliferative disorders has not yet been clarified. It was hypothesized that endothelial cell abnormalities associated with the hematological malignancy might contribute to the prothrombotic state. Budd-Chiari syndrome, splanchnic vein thrombosis, and portal vein thrombosis have been associated with JAK2V617F mutations (Patel et al. 2006; Xavier et al. 2010; Qi et al. 2011; Sozer and Hoffman 2011) and JAK2V617F-positive hematopoiesis, in particular latent myeloproliferative disorders and ET (Allegra et al. 2009; Smalberg et al. 2012; Yonal et al. 2012). In liver endothelial cells of patients with Budd-Chiari syndrome, JAK2V617F mutation has been demonstrated (Sozer et al. 2009). Expression of JAK2V617F may promote cell adhesion. It was demonstrated that it activates Lu/BCAM-mediated erythrocyte adhesion in polycythemia vera through an EpoR-independent Rap1/Akt pathway (De Grandis et al. 2013).

Essential Thrombocythemia and Liver Tumors or Tumor-like Lesions

Relatively few reports document the association of ET with hepatic tumors. Hepatic angiosarcoma has been observed in a patient with ET complicated by Budd-Chiari syndrome (Marichy et al. 1995). On the other hand, hepatocellular carcinomas can be associated with thrombocytosis (Yoshida et al. 2003) and can produce thrombopoietin (TPO) resulting in marked thrombocytosis (Ryu et al. 2003). The thrombocytosis observed in some patients with hepatoblastoma (Forouhar et al. 1984; Shafford and Pritchard 1993) seems to be caused by the same or a similar mechanism (Nickerson et al. 1980; Yamaguchi et al. 1996; Komura et al. 1998). Similar to what has been discussed in BCS occurring in polycythemia vera, hepatic venous disorders in ET may be followed by nodular regenerative hyperplasia of the liver, e.g., in

obliterative portal venopathy (Wanless et al. 1980; Fukai et al. 1992; Al-Mukhaizeem et al. 2004).

These findings are to be interpreted in the light of the role played by the liver for production of several hemopoietic hormones. The liver acts as the primary site of synthesis of erythropoietin (EPO) in the fetal stage, and it is the predominant TPO-producing organ for life (Jelkmann 2001). TPO is synthesized and expressed in hepatocytes in a constitutive way, and serum TPO levels reflect the total mass of functional liver (Sungaran et al. 1997; Okubo et al. 2000). In contrast to EPO and other hepatic export proteins, the hepatic synthesis of TPO is little influenced by external signals (with the exception of IL-6 that enhances hepatic TPO mRNA expression; Kaser et al. 2001), and the kinetics of serum TPO is mainly determined by megakaryocytes and platelets that remove TPO from blood by means of their high-affinity TPO receptors (Jelkmann 2001).

Pathogenic Mechanisms of Organ Infiltration in Essential Thrombocythemia

In the bone marrow, megakaryocytes hold a distinct, nonrandom position, in that they reside at a characteristic distance from the abluminal surface of the sinusal endothelium (Lichtman et al. 1978). There is structural evidence that megakaryocytes are motile (Leven 1987) and that entire megakaryocytes traverse the marrow-blood barrier and then enter the circulation (Thiele et al. 1994), and this passage occurs through apertures of 6 μm in diameter, located in the parajunctional areas of the bone marrow sinus endothelium (Tavassoli and Aoki 1981). In situations of matrix increase, e.g., myeloproliferative disorders with marrow fibrosis, transmural migration of megakaryocytes reveals a mole-like tunneling through the thickened sinusal wall (Thiele et al. 1997). It is not yet known whether megakaryocytes located to hepatic sinusoids in ET and other situation can traverse from the intrasinusoidal compartment into the perisinusoidal space.

The interactions between megakaryocytes and endothelial cells of sinus and sinus-like vascular channels are complex. In an ultrastructural study of the bone marrow in ET, it was found that two different kinds of megakaryocyte cytoplasmic processes are penetrating the marrow sinus wall. Megakaryocytes develop multiple, pseudopod-like projections derived from their peripheral zone and devoid of organelles, probably serving as anchors to keep the cells in a subendothelial position. The second type of cytoplasmic processes reaching into the vascular lumen consists of tentacle-like elongated protrusions rich in organelles, thought to represent either the beginning of megakaryocytes' egress into circulation or putative early platelets ("protruding platelet territories"; platelet fields; proplatelets) (Thiele et al. 1991). It has been suggested that megakaryocyte projections may, in addition to their proposed anchoring function, serve to monitor the circulation and to receive information as to the requirement of the body for platelet formation (Tavassoli and Aoki 1981). It has also been suggested that the distinct marrow position of megakaryocytes reflects their status as components of the barrier, in that megakaryocytes may offer a transmegakaryocytic route for other cells to enter circulation, via emperipolesis (Tavassoli 1986). Upon contact with subendothelial extracellular matrix, megakaryocytes adhere to proteins, spread, and undergo fragmentation, thus exhibiting a platelet-like behavior (Caine et al. 1986).

Megakaryocytes and the Hepatic Sinusoid

Megakaryocytes circulate in the peripheral blood and can home to the non-marrow microvascular bed, including hepatic sinusoids. This is accomplished by the expression and action of distinct adhesion molecules (Hagiwara et al. 1996). Circulating megakaryocytes, although >75 % positive for CD41, have, however, unlike platelets and bone marrow megakaryocytes, a reduced and remarkably heterogeneous labeling with antibodies against the alpha subunits of VLA2, VLA5, and VLA6 (Van Pampus et al. 1992). The lining of the liver sinusoids is different from that of bone marrow sinuses, and this will have an effect of the interaction with megakaryocytes. The endothelium of bone marrow sinuses is a

continuous, structurally polarized layer (the bone marrow microvascular endothelium, BMEC) with segmental surface differentiation and which is selective in cellular transport and can accomplish selective retention/homing of progenitor cells (Tavassoli 1981; Shirota and Tavassoli 1992; Papayannopoulou and Craddock 1997). Cell homing factors for this specialized surface comprise VEGF, vascular endothelial cadherin, VCAM-1, endothelial selectins, and the chemokine, stromal cell-derived factor-1alpha (SDF-1alpha), the latter being produced by bone marrow stromal cells and representing a chemotactic factor for hemopoietic cells (Jacobsen et al. 1996; Kim and Broxmeyer 1998; Frenette et al. 1998; Mohle et al. 1998; Jo et al. 2000; Van Buul et al. 2002). In contrast to normal hepatic sinusoids, bone marrow sinuses have a basement membrane and an endothelial fenestration mode that is different from that of sinusoidal endothelia, with only few fenestrations (Muto 1976). Liver sinusoids are also very distinct vascular channels with respect to their ontogenesis, as they partially derive from liver mesothelial cells and cells of the proepicardium, a mesothelial tissue anatomically continuous with liver mesothelium, in avian embryos (Perez-Pomares et al. 2004). Hepatic sinusoidal endothelial porosities and fenestrations are dynamical structures/phenomena that seem to affect transendothelial trafficking, also during regeneration (Wack et al. 2001).

The traffic of megakaryocytes between extravascular and intravascular compartments in the liver seems to be bidirectional, in that megakaryocytes in fetal hepatic megakaryocytopoiesis are partially located outside vascular channels of the liver and can then enter circulation (Enzan et al. 1980). The accumulation of megakaryocytes in the liver, and their local growth, may be modulated by the local availability of thrombopoietin that is chiefly produced in the liver and changes in function of liver mass and disease (Wolber and Jelkmann 2002; Freni et al. 2002). It has been demonstrated that sinusoidal endothelial cells constitutively co-express thrombopoietin and the thrombopoietin receptor, c-mpl (Cardier and Dempsey 1998). Stimulation of these cells with thrombopoietin in vitro induces the secretion of proinflammatory cytokines and promotes endothelial cell proliferation (Cardier 1999). Thrombopoietin, via its receptor, c-mpl, drives the expansion of megakaryocytes, while the priming, the early developmental steps, and the differentiation of these cells are controlled by several other genes and gene products, including Gfi-1b (Saleque et al. 2002), jumonji (Kitajima et al. 2001), interferon regulatory factor-2 (Stellacci et al. 2004), GATA-1 (Iwasaki et al. 2003), BUBR1 (Wang et al. 2004a), and the glutamate signaling/NMDA glutamate receptor pathways (Hitchcock et al. 2003). Furthermore, megakaryocyte maturation is associated with the expression of the CXC chemokine, connective tissue-activating peptide CTAP III, a chemokine that can support stem cell-derived hemopoiesis, but inhibits the proliferation of committed megakaryocyte progenitors (Deutsch et al. 2000). Platelet formation in turn depends on apoptotic processes, with caspase activation within megakaryocytes (Li and Kuter 2001; De Botton et al. 2002; Testa 2002).

It is not yet known whether sinusoidal and/or perisinusoidal hepatic cells, and in particular hepatic stellate cells, produce factors chemotactic for hemopoietic cells, e.g., stromal cell-derived factor-1, although hepatic stellate cells can secrete several cytokines and chemokines, including CCL2/monocyte chemoattractant protein-1 (Marra et al. 2004), and CCR5 and RANTES, probably allowing a cross talk between stellate cells and leukocytes (Schwabe et al. 2003). Platelet-activating factor (PAF) is predominantly produced in the liver and is released in an increased fashion in cirrhosis (Yang et al. 2004), but PAF plays a major role as a potent hepatic vasoconstrictor and systemic vasodilator. Cells of the megakaryocyte lineage and their platelet products can store and release vascular endothelial growth factor (VEGF; Mohle et al. 1997; Salgado et al. 2001), and megakaryocytes in myeloproliferative disorders can express the Tie-2 receptor (Zetterberg et al. 2003). The

autocrine-paracrine VEGF loops potentiate the maturation of megakaryocyte precursors through the Flt1 receptor (Casella et al. 2003). On the other hand, activated hepatic stellate cells produce cyclooxygenase-2 (COX-2) protein to induced VEGF production, and this response is regulated by vHL/HIF-1 alpha (Wang et al. 2004b). The network is further complicated by the observation that bone marrow cells can give rise to hepatic stellate cells in the mouse (Baba et al. 2004).

Cytogenetic and Molecular Features

Five to ten percent of ET patients reveal an abnormal karyotype, but no cytogenetic alterations specific for ET are known. Forty to fifty percent of the patients carry the Janus kinase 2 (JAK2) V617F or a functionally similar mutation, but these mutations are not specific for ET, because they are found in polycythemia vera and primary myelofibrosis as well (Cho et al. 2009; Deepak et al. 2011; Kiladjian 2012; Martinez-Avilez et al. 2012; Pich et al. 2012). One percent of ET patients show a gain of function mutation of MPL, MPL W515K/L. In patients with JAK2 V617F-positive ET with del(20q), haploinsufficiency of the nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2/NFATC2 seems to cooperate with activation of the JAK-STAT signaling pathway (Vieira et al. 2012). Mutations of TET2 (tet oncogene family member 2) were detected in both JAK-positive and JAK-negative ET, but only in a minority of cases and more often in older patients (Tefferi et al. 2009; Martinez-Aviles et al. 2012). Patients with ET have an increased incidence of acute myeloid leukemia. A predisposition to this evolution is related to a polymorphism in the XPD gene (Hernandez-Boluda et al. 2012). Hereditary thrombocythemia is an autosomal dominant disorder with clinical features resembling those of sporadic ET and caused by germline mutations in the genes for Thrombopoietin and its receptor, MPL (Rumi 2008; Ding et al. 2009).

References

Abbitt PL, Teates CD (1989) The sonographic appearance of extramedullary hematopoiesis in the liver. J Clin Ultrasound 17:280–282

Akashi K, Harada M, Shibuya T, Fukagawa K, Kimura N, Sagawa K, Yoshikai Y, Teshima T et al (1991) Simultaneous occurrence of myelomonocytic leukemia and multiple myeloma: involvement of common leukemic progenitors and their developmental abnormality of "lineage infidelity". J Cell Physiol 148:446–456

Allegra A, Alonci A, Penna G, D'Angelo A, Rizzotti P, Granata A, Musolino (2009) JAK2-positive latent essential thrombocythemia and splanchnic vein thrombosis: The role of bone marrow biopsy for the diagnosis of myeloproliferative disease. Acta Haematol 121:218–220

Al-Mukhaizeem KA, Rosenberg A, Sherker AH (2004) Nodular regenerative hyperplasia of the liver: an under-recognized cause of portal hypertension in hematological disorders. Am J Hematol 75:225–230

Amato D, Memon S, Wang C (2008) Myeloblastic transformation of chronic neutrophilic leukaemia. Br J Haematol 142:148

Anger BR, Seifried E, Scheppach J, Heimpel H (1989) Budd-Chiari syndrome and thrombosis of other abdominal vessels in the chronic myeloproliferative diseases. Klin Wochenschr 67:818–825

Aytaç S, Fitoz S, Akyar S, Atasoy C, Erekul S (1999) Focal intrahepatic extramedullary hematopoiesis: color Doppler US and CT findings. Abdom Imaging 24:366–368

Baba S, Fujii H, Hirose T, Yasuchika K, Azuma H, Hoppo T, Naito M, Machimoto T, Ikai I (2004) Commitment of bone marrow cells to hepatic stellate cells in mouse. J Hepatol 40:255–260

Baccarani M, Zaccaria A, Bagnara GP, Santucci MA, Brunelli MA, Tura S (1978) The relevance of extramedullary hemopoiesis to the staging of chronic myeloid leukemia. Boll Ist Sieroter Milan 57:257–270

Barcos M, Kim S, Seon BK, Nussbaum A, Gailani S, Henderson ES (1979) Idiotype in myeloma terminating in erythroleukemia. Med Pediatr Oncol 7:341–349

Barosi G, Ambrosetti A, Centra A, Falcone A, Finelli C, Foa P, Grossi A, Guarnone R, Rupoli S et al (1998) Splenectomy and risk of blast transformation in myelofibrosis with myeloid metaplasia. Italian Cooperative Study Group on Myeloid with Myeloid Metaplasia. Blood 91:3630–3636

Barosi G, Ambrosetti A, Finelli C, Grossi A, Leoni P, Liberato NL, Petti MC, Pogliani E, Ricetti M et al (1999) The Italian consensus conference on diagnostic criteria for myelofibrosis with myeloid metaplasia. Br J Haematol 104:730–737

Barton JC, Conrad ME, Poon MC (1979) Pseudochloroma: extramedullary hematopoietic nodules in chronic myelogenous leukemia. Ann Intern Med 91:735–738

Beckman EN, Oehrle JS (1982) Fibrous hematopoietic tumors arising in agnogenic myeloid metaplasia. Hum Pathol 13:804–810

Beer PA (2011) The pathogenesis of essential thrombocythemia. Curr Opin Hematol 18:323–329

Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick H et al (1994) The chronic myeloid leukemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid and chronic myelomonocytic leukemia. Proposals by the French-American-British Cooperative Leukaemia group. Br J Haematol 87:746–754

Berk DR, Ahmed A (2006) Portal, splenic, and superior mesenteric vein thrombosis in a patient with latent essential thrombocythemia and hyperhomocysteinemia. J Clin Gastroenterol 40:227–228

Bernasconi P, Boni M, Cavigliano PM et al (2002) Acute myeloid leukemia (AML) having evolved from essential thrombocythemia (ET): distinctive chromosome abnormalities in patients treated with pipobroman or hydroxyurea. Leukemia 16:2078–2083

Bioulac-Sage P, Roux D, Quinton A, Lamouliatte H, Balabaud C (1986) Ultrastructure of sinusoids in patients with agnogenic myeloid metaplasia. J Submicrosc Cytol 18:815–821

Böhm J, Schaefer HE (2002) Chronic neutrophilic leukaemia: 14 new cases of an uncommon myeloproliferative disease. J Clin Pathol 55:862–864

Brunerova L, Bartakova H, Jankovska M, Cieslarova B, Hulek P, Kozak T, Andel M (2004) The Budd-Chiari syndrome in a patient with primary thrombocythemia treated with interferon alfa and transjugular portosystemic shunt (in Czech). Cas Lek Cesk 143:198–201

Butterfield EE (1908) Über die ungranulierten Vorstufen der Myelozyten und ihre Bildung in Milz, Leber und Lymphdrüsen. Dtsch Arch Klin Med 92:336

Cai XY, Zhou W, Hong DF, Cai XJ (2009) A latent form of essential thrombocythemia presenting as portal cavernoma. World J Gastroenterol 15:5368–5370

Caine YG, Vlodavsky I, Hersh M, Polliack A, Gurfel D, Or R, Levine RF, Eldor A (1986) Adhesion, spreading and fragmentation of human megakaryocytes exposed to subendothelial extracellular matrix: a scanning electron microscopy study. Scan Electron Miscroc (Pt3):1087–1094

Cardier JE (1999) Effects of megakaryocyte growth and development factor (thrombopoietin) on liver endothelial cells in vitro. Microvasc Res 58:108–113

Cardier JE, Dempsey J (1998) Thrombopoietin and its receptor, c-mpl, are constitutively expressed by mouse liver endothelial cells: evidence of thrombopoietin as a growth factor for liver endothelial cells. Blood 91:923–929

Cardoso FS, Pires JV, Miranda JS, Araulo JM (2011) Hepatic nodule: a case of primary myelofibrosis. BMJ Case Rep 2011:bcr 0520114220

Casella I, Feccia T, Chelucci C, Samoggia P, Castelli G, Guerriero R, Parolini I, Petrucci E, Pelosi E et al (2003) Autocrine-paracrine VEGF loops potentiate the maturation of megakaryocytic precursors through Flt1 receptor. Blood 101:1316–1323

Cehreli C, Undar B, Akkoc N, Onvural B, Altungoz O (1994) Coexistence of chronic neutrophilic leukemia with light chain myeloma. Acta Haematol 91:32–34

Cervantes F, Rozman M, Vives-Corrons JL, Rozman C (1990) Chronic neutrophilic leukemia with dysplastic features. Acta Haematol 84:109

Cervantes F, Alvarez-Larran A, Talarn C, Gomez M, Montserrat E (2002) Myelofibrosis with myeloid metaplasia following essential thrombocythaemia: actuarial probability, presenting characteristics and evolution in a series of 195 patients. Br J Haematol 118:786–790

Chen YH, Mishoulam H, Mir JA, Choi YS, Schade SG (1987) Blastic transformation in a case of essential thrombocythemia. South Med J 80:1040–1043

Chiti A, Giovanella LC, Bestetti A, Castellani M, Gattoni F, Bossi MC, Tarolo GL (1992) Final scintigraphic diagnosis with [99mTc] HIDA in a case of focal nodular hyperplasia with essential thrombocythemia and portal thrombosis (in Italian). Radiol Med (Torino) 84:491–493

Cho YU, Chi HS, Lee EH, Jang S, Park CJ, Seo EJ (2009) Comparison of clinicopathologic findings according to JAK2 V617F mutation in patients with essential thrombocythemia. Int J Hematol 89:39–44

Corredoira JC, Gonzalez M, Casariego E, Perez R (1989) Budd-Chiari syndrome as a preceding phase of essential thrombocythemia (in Spanish). Sangre (Barc) 34:381

Crews LA, Jamieson CH (2012) Chronic myeloid leukemia stem cell biology. Curr Hematol Malig Rep 7:125–132

De Botton S, Sabri S, Daugas E, Zermati Y, Guidotti JE, Hermine O, Kroemer G, Vainchenker W, Debili N (2002) Platelet formation is the consequence of caspase activation within megakaryocytes. Blood 100:1310–1317

De Grandis M, Cambot M, Wautier MP, Cassinat B, Chomienne C, Colin Y, Wautier JL et al (2013) JAK2V617F activates Lu/BCAM-mediated red cell adhesion in polycythemia vera through an EpoR-independent Rap1/Akt pathway. Blood 121:658–665

Deepak A, Punamiya S, Patel N, Parekh S, Mehta S, Shah N (2011) Prevalence of JAK2(V617F) mutation in intra-abdominal venous thrombosis. Trop Gastroenterol 32:279–284

Degott et al. 1985. http://www.ncbi.nlm.nih.gov/pubmed/4079668

Delario et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22389089

Deutsch V, Bitan M, Friedmann Y, Eldor A, Vlodavsky I (2000) Megakaryocyte maturation is associated with expression of the CXC chemokine connective tissue-activating peptide CTAP III. Br J Haematol 111:1180–1189

Dewar G, Leung NW, Ng HK, Bradley M, Li AK (1990) Massive, solitary, intrahepatic, extramedullary hematopoietic tumor in thalassemia. Surgery 107:704–707

Diamond T, Smith A, Schnier R, Manoharan A (2002) Syndrome of myelofibrosis and osteosclerosis: a series of case reports and review of the literature). Bone 30:498–501

Diggle CP, Parry DA, Logan CV, Laissue P, Rivera C, Restrepo CM, Fonseca DJ et al (2012) Prostaglandin transporter mutations cause pachydermoperiostosis with myelofibrosis. Hum Mutat 33:1175–1181

Dincol G, Nalcaci M, Dogan O, Aktan M, Kucukkaya R, Agan M, Dincol K (2002) Coexistence of chronic neutrophilic leukemia with multiple myeloma. Leuk Lymphoma 43:649–651

Ding J, Komatsu H, Iida S, Yano H, Kusumoto S, Inagaki A, Mori F, Ri M, Ito A, Wakita A et al (2009) The Asn505 mutation of c-MPL gene, which causes familial essential thrombocythemia, induces autonomous homodimerization of the c-Mpl protein due to the strong amino acid polarity. Blood 114:3325–3328

Donhauser JL (1908) The human spleen as an haematoplastic organ, as exemplified in a case of splenomegaly with sclerosis of the bone marrow. J Exp Med 10:559–574

Elliott MA (2004) Chronic neutrophilic leukemia: a contemporary review. Curr Hematol Rep 3:210–217

Elliott MA (2006) Chronic neutrophilic leukemia and chronic myelomonocytic leukemia: WHO defined. Best Pract Res Clin Haematol 19:571–593

Elliott MA, Dewald GW, Tefferi A, Hanson CA (2001) Chronic neutrophilic leukemia (CNL): a clinical, pathologic and cytogenetic study. Leukemia 15:35–40

Enzan H, Takahashi H, Kawakami M, Yamashita S, Ohkita T, Yamamoto M (1980) Light and electron microscopic observations of hepatic hematopoiesis of human fetuses. II. Megakaryocytopoiesis. Acta Pathol Jpn 30:937–954

Ernst T, Hochhaus A (2012) Chronic myeloid leukemia: clinical impact of BCR-ABL1 mutations and other lesions associated with disease progression. Semin Oncol 39:58–66

Fabian E (1908) Über lymphatische und myeloische Chloroleukämie. Beitr Pathol Anat Allg Pathol 43:172

Falanga A, Marchetti M (2012) Thrombotic disease in the myeloproliferative neoplasms. Hematol Am Soc Hematol Educ Program 2012:571–581

Foa P, Iurlo A, Saglio G, Guerrasion A, Capsoni F, Malolo AT (1991) Chronic neutrophilic leukemia associated with polycythemia vera: pathogenetic implications and therapeutic approach. Br J Haematol 78:286–288

Forouhar FA, Quinn JJ, Cooke R, Foster JH (1984) The effect of chemotherapy on hepatoblastoma. Arch Pathol Lab Med 108:311–314

Frenette PS, Subbarao S, Mazo IB, von Adrian UH, Wagner DD (1998) Endothelial selectins and vascular cell adhesion molecule-1 promote hematopoietic progenitor homing to bone marrow. Proc Natl Acad Sci U S A 95:14423–14428

Freni MA, Spadaro A, Ajello A, Barbaro E, Scaffidi M, Alessi N, Resta ML, Ferrau O (2002) Serum thrombopoietin in chronic liver disease: relation to severity of the disease and spleen size. Hepatogastroenterology 49:1382–1385

Froberg MK, Brunning RD, Dorion P, Litz CE, Torlakovic E (1998) Demonstration of clonality in neutrophils using FISH in a case of chronic neutrophilic leukemia. Leukemia 12:623–626

Fukai T, Ishibashi H, Noda T, Dohmen K, Kudo J, Nagafuchi S, Sueishi K, Yamasaki T, Sameshima H (1992) Nodular regenerative hyperplasia of the liver with portal vein thrombosis and hyperplasia of the adrenal gland. Gastroenterol Jpn 27:108–114

Gan GG, Pasagna JF, Eow GI, Nadarajan VS (2007) Chronic neutrophilic leukaemia. Singapore Med J 48: e74–e76

Gangane N, Kamra H, Anshu, Joshi D, Gupta A (2008) Cytodiagnosis of granulocytic sarcoma of liver arising in a milieu of myeloid metaplasia: a case report. Acta Cytol 52:619–622

Garza Trasobares E, Gonzalez Sanz-Agero P, Villeta Caraballo E, Suarez Parga JM, Santamaria Blanco P, Quiles F (1988) Budd-Chiari syndrome in a case of essential thrombocythemia (in Spanish). Rev Esp Enferm Apar Dig 73:64–66

Gianfelici V, Lahortiga I, Cools J (2012) Chromosomal aberrations and fusion genes in myeloid malignancies. Expert Rev Hematol 5:381–393

Gilbert HS (2001) Diagnosis and treatment of thrombocythemia in myeloproliferative disorders. Oncology (Huntingt) 15:989–996

Gil-Fernandez JJ, Martinez-Chamorro C, Tomas JF (2001) The irreplaceable image: a giant hepatic mass of myeloid metaplasia in a patient without myelofibrosis. Haematologica 86:445

Glew RH, Haese WH, McIntyre PA (1973) Myeloid metaplasia with myelofibrosis: the clinical spectrum of extramedullary hematopoiesis and tumor formation. Johns Hopkins Med J 132:253

Greaves WO, Verma S, Bisrat T, Strati P, Rahimi H, Paladugu AV, Luthra R, Patel KP et al (2013) TP53 mutation is rare in primary myelofibrosis. Leuk Lymphoma 54:1552

Grieco A, Manna R, Mancini R, Gambassi G (1988) Massive hepatomegaly following splenectomy for myeloid metaplasia. Am J Med 84:797

Gruber GB (1930) Die Leber bei Erkrankungen des blut- und lymphbildenden Gewebs-Apparates. In: Henke F, Lubarsch O (eds) Handbuch der speziellen pathologischen Anatomie und Histologie, vol 5, Verdauungsdrüsen, Erster Teil, Leber, Julius. Springer, Berlin, pp 654–658

Guglielmelli P, Biamonte F, Score J, Hidalgo-Curtis C, Cervantes F, Maffioli M, Fanelli T et al (2011) EZH2

mutational status predicts poor survival in myelofibrosis. Blood 118:5227–5234
Gupta P, Naran A, Auh YH, Chung JS (2004) Focal intrahepatic extramedullary hematopoiesis presenting as fatty lesions. AJR Am J Roentgenol 182:1031–1032
Haferlach T, Bacher U, Kern W, Schnittger S, Haferlach C (2008) The diagnosis of BCR/ABL-negative chronic myeloproliferative diseases (CMPD): a comprehensive approach based on morphology, cytogenetics, and molecular markers. Ann Hematol 87:1–10
Hagiwara T, Nagasawa T, Nagahisa H, Takizawa M, Osada M, Abe T (1996) Expression of adhesion molecules on cytoplasmic processes of human megakaryocytes. Exp Hematol 24:690–695
Hang XF, Xin HG, Wang L, Xu WS, Wang JX, Ni W, Cai X, Zhang RQ (2011) Nonleukemic myeloid sarcoma of the liver: a case report and review of literature. Hepatol Int 5:747–750
Harrison CN (2002) Current trends in essential thrombocythaemia. Br J Haematol 117:796–808
Harrison C (2010) Rethinking disease definitions and therapeutic strategies in essential thrombocythemia and polycythemia vera. Hematol Am Soc Hematol Educ Program 2010:129–134
Harrison CN, Gale RE, Machin SJ, Linch DC (1999) A large proportion of patients with a diagnosis of essential thrombocythemia do not have a clonal disorder and may be at lower risk of thrombotic complications. Blood 93:417–424
Hartley MA, Sokol L, Caceres G, Hussein MA, List A, Pinilla-Ibarz J (2010) Monoclonal gammopathy of undetermined significance disguised as chronic neutrophilic leukemia. Mediterr J Hematol Infect Dis 2: e2010002
Hayashi K, Nakamura H, Ohnishi Y, Tamura K, Maruyama T, Tachibana N, Tsuda K et al (1983) A case of chronic neutrophilic leukemia accompanied by the infiltration of mature neutrophils in the liver sinusoids (in Japanese). Rinsho Ketsueki 24:600–606
Hayashi T, Mizuki A, Yamaguchi T, Hasegawa T, Kunihiro T, Tsukada N, Matsuoka K, Orikasa H et al (2001) Primary adenosquamous carcinoma of the liver which produces granulocyte-colony-stimulating factor and parathyroid hormone related peptide: association with leukocytosis and hypercalcemia. Intern Med 40:631–634
Helbig G, Wieczorkiewicz A, Wozniczka K, Wiesniewska-Piaty K, Rusek A, Kyrcz-Krzemien S (2012) The JAK2V617F tyrosine kinase mutation has no impact on overall survival and the risk of leukemic transformation in myelofibrosis. Med Oncol 29:2379–2384
Hernandez-Boluda JC, Pereira A, Cervantes F, Alvarez-Larran A, Collado M, Such E et al (2012) A polymorphism in the XPD gene predisposes to leukemic transformation and new nonmyeloid malignancies in essential thrombocythemia and polycythemia vera. Blood 119:5221–5228
Heuck G (1879) Zwei Fälle von Leukämie mit eigenthümlichem Blut- resp. Knochenmarksbefund Virchows Arch 78:475–481
Higuchi T, Oba R, Endo M, Harada H, Mori H, Niikura H, Omine M, Fujita K (1999) Transition of polycythemia vera to chronic neutrophilic leukemia. Leuk Lymphoma 33:203–206
Hill G, McClean D, Fraser R, Hart D, Crozier I, Snowden J, Gibbons S (1996) Pulmonary hypertension as a consequence of alveolar capillary plugging by malignant megakaryocytes in essential thrombocythemia. Aust NZ J Med 26:852–853
Hirschield H (1905) Zur Kenntnis der atypischen myeloiden Leukämie. Berlin Klin Wschr 42:1004–1008
Hitchcock IS, Skerry TM, Howard MR, Genever PG (2003) NMDA receptor-mediated regulation of human megakaryocytopoiesis. Blood 102:1254–1259
Hopps HC, Rucks WW (1948) Chronic myelogenous leukemia with very marked involvement of the spleen, liver and bone marrow. J Okla State Med Assoc 41:384–386
Hussein K, Van Dyke DL, Tefferi A (2009) Conventional cytogenetics in myelofibrosis: literature review and discussion. Eur Haematol 82:329–338
Ito T, Kojima H, Otani K, Komeno T, Mitsuhashi S, Hasegawa Y, Kobayashi T, Ninomyia H et al (1996) Chronic neutrophilic leukemia associated with monoclonal gammopathy of undetermined significance. Acta Haematol 95:140–143
Iwasaki H, Mizuno S, Wells RA, Cantor AB, Watanabe S, Akashi K (2003) GATA-1 converts lymphoid and myelomonocytic progenitors into the megakaryocyte/erythrocyte lineage. Immunity 19:451–462
Jacobsen K, Kravitz J, Kincade PW, Osmond DG (1996) Adhesion receptors on bone marrow stromal cells: in vivo expression of vascular cell adhesion molecule-1 by reticular cells and sinusoidal endothelium in normal and gamma-irradiated mice. Blood 87:73–82
Jelkmann W (2001) The role of the liver in the production of thrombopoietin compared with erythropoietin. Eur J Gastroenterol Hepatol 13:791–801
Jimenez Saenz JM, Gomez Berne J, Perez Layo A, Sanjuan Portugal F, Hermida Lazcano I (1998) Splenoportal thrombosis: form of presentation of essential thrombocythemia (in Spanish). An Med Interna 15:594–596
Jo DY, Rafii S, Hamada T, Moore MA (2000) Chemotaxis of primitive hematopoietic cells in response to stromal cell-derived factor-1. J Clin Invest 105:101–111
Kajigaya Y, Sasaki H, Ikuta K, Koiso Y, Fukazawa K, Matsuyama S, Tanaka Y, Misugi K et al (1987) An autopsy case of juvenile chronic myelogenous leukemia with extramedullary hematopoiesis in liver (in Japanese). Rinsho Ketsueki 28:939–944
Karakulska-Prystupiak E, Gierej B, Paszkowska-Kowalewska M, Wilkowojska U, Jedrzejczak WW (2012) Portal vein thrombosis as the main symptom of unclassified JAK2-positive myeloproliferative neoplasm – case report (in Polish). Pol Merkur Lek 33:29–31

Kaser A, Brandacher G, Steurer W, Kaser S, Offner FA, Zoller H, Theurl I, Widder W, Molnar C et al (2001) Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. Blood 98:2720–2725

Kchinologuer K (1915) Le chlorome une tumeur maligne. Thesis, University of Geneva

Kiladjian JJ (2012) The spectrum of JAK2-positive myeloproliferative neoplasms. Hematol Am Soc Hematol Educ Program 2012:561–566

Kim CH, Broxmeyer HE (1998) In vitro behavior of hematopoietic progenitor cells under the influence of chemoattractants: stromal cell-derived factor-1, steel factor, and the bone marrow environment. Blood 91:100

Kitajima K, Kojima M, Kondo S, Takeuchi T (2001) A role of jumonji gene in proliferation but not differentiation of megakaryocyte lineage cells. Exp Hematol 29:507–514

Kobayashi A, Sugihara M, Kurosaki M, Ishida Y, Takayanagi N, Matsui O, Takashima T (1989) CT characteristics of intrahepatic, periportal, extramedullary hematopoiesis. J Comput Assist Tomogr 13:354–356

Kobayashi S, Kimura F, Ikeda T, Osawa Y, Torikai H, Kobyashi A, Sato K, Motoyoshi K (2009) BCR-ABL promotes neutrophil differentiation in the chronic phase of chronic myeloid leukemia by downregulating c-Jun expression. Leukemia 23:1622–1627

Komura E, Matsumura T, Kato T, Tahara T, Tsunoda Y, Sawada T (1998) Thrombopoietin in patients with hepatoblastoma. Stem Cells 16:329–333

Koyama R, Segawa H, Nagai T, Matsumoto S, Koyanagi T, Matsuura M, Ito K, Sakamaki S et al (1990) A case of primary squamous cell carcinoma producing granulocyte colony stimulating factor (in Japanese). Nippon Naika Gakkai Zasshi 79:1732–1734

Kreipe H, Büsche G, Bock O, Hussein K (2012) Myelofibrosis: molecular and cell biological aspects. Fibrogenesis Tissue Repair 5(Suppl 1):S21

Kusaba N, Yoshida H, Ohkubo F, Mishima K, Shimamastu K, Okamura T, Sata M (2004) Granulocyte-colony stimulating factor-producing myeloma with clinical manifestations mimicking chronic neutrophilic leukemia (in Japanese). Rinsho Ketsueki 45:228–232

Kwak HS, Lee JM (2000) CT findings of extramedullary hematopoiesis in the thorax, liver and kidneys, in a patient with idiopathic myelofibrosis. J Korean Med Sci 15:460–462

Kwon Y, Yu E, Huh J, Lee SK, Ro JY (2004) Sclerosing extramedullary hematopoietic tumor involving lesser omentum and ligamentum teres in liver explant. Ann Diagn Pathol 8:227–232

Kwong YL, Cheng G (1993) Clonal nature of chronic neutrophilic leukemia. Blood 82:1035

Lane WJ, Dias S, Hattori K, Heissig B, Choy M, Rabbany SY, Wood J, Moore MA, Rafii S (2000) Stromal-derived factor-1-induced megakaryocyte migration and platelet production is dependent on matrix metalloproteinases. Blood 96:4152–4159

Lang E, Uthman M (1999) Pseudo-Gaucher cells in peritoneal fluid: an uncommon manifestation of extramedullary hematopoiesis. Diagn Cytopathol 20:379–381

Lasho TL, Jimma T, Finke CM, Patnaik M, Hanson CA, Ketterling RP, Pardanani A, Tefferi A (2012) SRSF2 mutations in primary myelofibrosis: significant clustering with IDH mutations and independent association with inferior overall and leukemia-free survival. Blood 120:4168–4171

Laszlo J (1975) Myeloproliferative disorders (MPD): myelofibrosis, myelosclerosis, extramedullary hematopoiesis, undifferentiated MPD, and hemorrhagic thrombocythemia. Semin Hematol 2:409–432

Lataillade JJ, Pierre-Louis O, Hasselbalch HC, Uzan G, Jasmin C, Martyre MC, Le Bousse-Kerdilès MC et al (2008) Does primary myelofibrosis involve a defective stem cell niche? From concept to evidence. Blood 112:3026–3035

Le Bousse-Kerdilès MC (2012) Primary myelofibrosis and the "bad seeds in bad soil" concept. Fibrogenesis Tissue Repair 5(Suppl 1):S20

Leven RM (1987) Megakaryocyte motility and platelet formation. Scanning Microsc 1:1701–1709

Levine RL, Heaney M (2008) New advances in the pathogenesis and therapy of essential thrombocythemia. Hematol Am Soc Hematol Educ Program 2008:76–82

Levy-Toledano S, Caen JP, Breton-Gorius J, Rendu F, Cywiner-Golenzer C, Dupuy E et al (1981) Gray platelet syndrome: alpha-granule deficiency. Its influence on platelet function. J Lab Clin Med 98:831–848

Li J, Kuter DJ (2001) The end is just the beginning: megakaryocyte apoptosis and platelet release. Int J Hematol 74:365–374

Lichtman MA, Chamberlain JK, Simon W, Santillo PA (1978) Parasinusoidal location of megakaryocytes in marrow: a determinant of platelet release. Am J Hematol 4:303–312

Liu E, Jelinek J, Pastore YD, Guan Y, Prchal JF, Prchal JT (2003) Discrimination of polycythemias and thrombocytoses by novel, simple, accurate clonality assays and comparison with PRV-1 expression and BFU-E response to erythropoietin. Blood 101:3294–3301

Lopez-Guillermo A, Cervantes F, Bruguera M, Pereira A, Feliu E, Rozman C (1991) Liver dysfunction following splenectomy in idiopathic myelofibrosis: a study of 10 patients. Acta Haematol 85:184–188

Luca DC, Almanaseer IY (2003) Simultaneous presentation of multiple myeloma and acute monocytic leukemia. Arch Pathol Lab Med 127:1506–1508

Macpherson AI, Ingram GI, Maclean N (1957) Haemorrhagic thrombocythaemia associated with cavernous transformation of the portal vein and hepatomegaly. J R Coll Surg Edinb 2:191–201

Makishima H, Visconte V, Sakaguchi H, Jankowska AM, Abu Kar S, Jerez A, Przychodzen B et al (2012)

Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. Blood 119:3203–3210

Malcovati L, Papaemmanueli E, Bowen DT, Boultwood J, Della Porta MG, Pascutto C et al (2011) Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. Blood 118:6239–6246

Manas Garcia MD, Marchan Carranza E, Galiana Gomez del Pulgar J, Ceres Alabau F (2004) Hepatocarcinoma with leukemoid reaction (in Spanish). An Med Interna 21:197–198

Marichy C, Dumontet C, Bastion Y, Rieux C, Blay JY, Salles G, Biron P, Coiffier B (1995) Hepatic angiosarcoma in a patient with essential thrombocythaemia and Budd-Chiari syndrome. Eur J Cancer 31A:423

Marra F, Delogu W, Petrai I, Pastacaldi S, Bonacchi A, Efsen E, Aleffi S, Bertolani C, Pinzani M, Gentilini P (2004) Differential requirement of members of the MAPK family for CCL2 expression by hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 287: G18–G26

Martinez-Aviles L, Alvarez-Larran A, Besses C, Navarro G, Torres E, Longaron R et al (2012) Clinical significance of clonality assessment in JAK2V617F-negative essential thrombocythemia. Ann Hematol 91:1555–1562

Martinez-Avilez L, Besses C, Alvarez-Larran A, Torres E, Serrano S, Bellisillo B (2012) TET2, ASXL1, IDH1, IDH2, and c-CBL genes in JAK2- and MPL-negative myeloproliferative neoplasms. Ann Hematol 91:533–541

Masini L, Salvarani C, Macchioni P, Baldi G, Rossi F, Croci G, Prandi S, Davoli C, Portioli I, Gobbi F (1992) Chronic neutrophilic leukemia (CNL) with karyotypic abnormalities associated with plasma cell dyscrasia: a case report. Haematologica 77:277–279

McBrine PA, Miller A, Zimelman AP, Koff RS (1980) Polycythemia vera with myelofibrosis and myeloid metaplasia. Acute hepatic failure following splenectomy. Am J Clin Pathol 74:693–696

Mesa RA, Silverstein MN, Jacobsen SJ, Wollan PC, Tefferi A (1999) Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County Study, 1976–1995. Am J Hematol 61:10–15

Mesa et al. 2000. http://www.ncbi.nlm.nih.gov/pubmed/10986148

Michiels JJ (1996) The myeloproliferative disorders. An historical appraisal and personal experience. Leuk Lymphoma 22(Suppl 1):1–14

Michiels JJ (2003) Platelet-mediated microvascular inflammation and thrombosis in thrombocythemia vera: a distinct aspirin-responsive arterial thrombophilia, which transforms into a bleeding diathesis at increasing platelet counts. Pathol Biol (Paris) 51:167–175

Michiels JJ, Juvonen E (1997) Proposal for revised diagnostic criteria of essential thrombocythemia and polycythemia vera by the thrombocythemia vera study group. Semin Thromb Hemost 23:339–347

Michiels JJ, Thiele J (2002) Clinical and pathological criteria for the diagnosis of essential thrombocythemia, polycythemia vera and idiopathic myelofibrosis (agnogenic myeloid metaplasia). Int J Hematol 76:133–145

Michiels JJ, van Genderen PJ, Lindemans J, van Vliet HH (1996) Erythromelalgic, thrombotic and hemorrhagic manifestations in 50 cases of thrombocythemia. Leuk Lymphoma 22(Suppl 1):47–56

Michiels JJ, Berneman ZN, Schroyens W, van Vliet HH (2004) Pathophysiology and treatment of platelet-mediated microvascular disturbances, major thrombosis and bleeding complications in essential thrombocythaemia and polycythaemia vera. Platelets 15:67–84

Michiels JJ, Bernema Z, Van Bockstaele D, De Raeve H, Schroyens W (2007) Current diagnosis criteria for the chronic myeloproliferative disorders (MPD) essential thrombocythemia (ET), polycythemia vera (PV) and chronic idiopathic myelofibrosis (CIMF). Pathol Biol (Paris) 55:92–104

Mikel JJ, Owen G, Lewis IJ (1990) Hepatic fibrosis in juvenile chronic granulocytic leukemia: an unusual finding in three cases. Pediatr Pathol 10:385–395

Milosevic JD, Kralovics R (2013) Genetic and epigenetic alterations of myeloproliferative disorders. Int J Hematol 97:183–197

Mitsuhashi T, Hojo K, Yamagata F, Sowa E (1977) An autopsy case of agnogenic myeloid metaplasia complicated by hepatic cell carcinoma. Nippon Ketsueki Gakkai Zasshi 40:519–528

Mohle R, Green D, Moore MA, Nachman RL, Rafii S (1997) Constitutive production and thrombin-mediated release of vascular endothelial growth factor by human megakaryocytes and platelets. Proc Natl Acad Sci U S A 94:663–668

Mohle R, Rafii S, Moore MA (1998) The role of endothelium in the regulation of hematopoietic stem cell migration. Stem Cells 16(Suppl 1):159–165

Mori et al. 1984. http://www.ncbi.nlm.nih.gov/pubmed/6484975

Morita K, Nakamine H, Inoue R, Takano M, Takeda M, Enomoto Y, Kasai T, Nonomura A et al (2012) Autopsy case of primary myelofibrosis in which myeloid sarcoma was the initial manifestation of tumor progression. Pathol Int 62:433–437

Muto M (1976) A scanning and transmission electron microscopic study on rat bone marrow sinuses and transmural migration of blood cells. Arch Histol Jpn 39:51–66

Nalbandian RM, Wilner FM, Blackall CJ (1968) Myeloid megakaryocytic hepatosplenomegaly. Case study with a proposed system of matrix classification of the myeloproliferative disorders. Am J Clin Pathol 49:535–555

Navarro M, Crespo C, Perez L, Martinez C, Galant J, Gonzalez I (2000) Massive intrahepatic extramedullary hematopoiesis in myelofibrosis. Abdom Imaging 25:184–186

Nickerson HJ, Silberman TL, McDonald TP (1980) Hepatoblastoma, thrombocytosis, and increased thrombopoietin. Cancer 45:315–317

Nielsen C, Birgens HS, Nordestgaard BG, Bojesen SE (2013) Diagnostic value of JAK2 V617F somatic mutation for myeloproliferative cancer in 49,488 individuals from the general population. Br J Haematol 160:70–79

Nischal S, Bhattacharyya S, Christopeit M, Yu Y, Zhou L, Bhagat TD, Sohal D, Will B et al (2013) Methylome profiling reveals distinct alterations in phenotypic and mutational subgroups of myeloproliferative neoplasms. Cancer Res 73:1076–1085

Nitta M, Tsuboi K, Yamashita S, Kato M, Hayami Y, Harada S, Komatsu H, Iida S, Banno S et al (1999) Multiple myeloma preceding the development of chronic myelogenous leukemia. Int J Hematol 69:170–173

Ochoa JF (1981) Hepatoma presenting as a single cavitary lung mass and leukemoid reaction. Chest 80:250

Okubo M, Shiota G, Kawasaki H (2000) Thrombopoietin levels in serum and liver tissue in patients with chronic viral hepatitis and hepatocellular carcinoma. Clin Sci (Lond) 99:207–214

Okuda K, Kondo Y, Nakano M, Kage M, Arakawa M, Kojiro M, Ohtsuki T, Shimokawa Y et al (1991) Hepatocellular carcinoma presenting with pyrexia and leukocytosis: report of five cases. Hepatology 13:695–700

Ondreyco SM, Kjeldsberg CR, Fineman RM, Vaninetti S, Kushner JP (1981) Monoblastic transformation in chronic myelogenous leukemia: presentation with massive hepatic involvement. Cancer 48:957–963

Ozen S, Ferhanoglu B, Senocak M, Tuzuner N (1997) Idiopathic myelofibrosis (agnogenic myeloid metaplasia): clinicopathological analysis of 32 patients. Leuk Res 21:125–131

Papayannopoulou T, Craddock C (1997) Homing and trafficking of hematopoietic progenitor cells. Acta Haematol 97:97–104

Pardanani A, Guglielmelli P, Lasho TL, Pancrazzi A, Finke CM, Vannuchi AM, Tefferi A (2011) Primary myelofibrosis with or without mutant MPL: comparison of survival and clinical features involving 603 patients. Leukemia 25:1834–1839

Pascucci M, Dorion P, Makary A, Froberg MK (1997) Chronic neutrophilic leukemia evolving from a myelodysplastic syndrome. Acta Haematol 98:163–166

Patel RK, Lea NC, Heneghan MA, Westwood NB, Milojkovic D, Thanigaikumar M et al (2006) Prevalence of the activating JAK2 tyrosine kinase mutation V617F in the Budd-Chiari syndrome. Gastroenterology 130:2031–2038

Perez-Villa et al. 1988. http://www.ncbi.nlm.nih.gov/pubmed/3172909

Perez-Pomares JM, Carmona R, Gonzalez-Iriarte M, Macias D, Guadix JA, Munoz-Chapuli R (2004) Contribution of mesothelium-derived cells to liver sinusoids in avian embryos. Dev Dyn 229:465–474

Picardi M, Muretto P, Luciano L (2000) Budd-Chiari syndrome in chronic myeloid leukemia. Haematologica 85:429

Pich A, Riera L, Beggiato E, Nicolino B, Godio L, Campisi P, Sismondi F, di Celle PF (2012) JAK2V617F mutation and allele burden are associated with distinct clinical and morphological subtypes in patients with essential thrombocythaemia. J Clin Pathol 65:953–955

Picon-Coronel G, Chablé-Montero F, Angeles-Angeles A, Albores-Saavedra J (2011) Multiple venous and arterial thromboses of the gallbladder causing acute cholecystitis. A previously undescribed complication of essential thrombocythemia. Ann Hepatol 10:365–369

Poletto V, Rosti V, Villani L, Catarsi P, Carolei A, Campanelli R, Massa M, Martinetti M et al (2012) A3669G polymorphism of glucocorticoid receptor is a susceptibility allele for primary myelofibrosis and contributes to phenotype diversity and blast transformation. Blood 120:3112–3117

Qi X, Yang Z, Bai M, Shi X, Han G, Fan D (2011) Meta-analysis: the significance of screening for JAK2V617F mutation in Budd-Chiari syndrome and portal venous system thrombosis. Aliment Pharmacol Ther 33:1087–1103

Raccuglia G (1971) Grey platelet syndrome. A variety of qualitative platelet disorders. Am J Med 51:818–828

Randi ML, Fabris F, Tison T, Barbone E, Rossi C, Girolami A (1993) Prevalence of specific thrombotic accidents in patients with thrombocytosis. Haematologia (Budap) 25:149–152

Randi ML, Barbone E, Zerbinati P, Soini B, Rossi C, Girolami A (1996) Essential thrombocythemia following polycythemia vera: an unusual sequence. J Med 27:363–368

Randi et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/1244348

Ranjan A, Penninga E, Jelsig AM, Hasselbalch HC, Bierrum OW (2013) Inheritance of the chronic myeloproliferative neoplasms. A systematic review. Clin Genet 83:99–107

Raz I, Polliack A (1984) Coexistence of myelomonocytic leukemia and monoclonal gammopathy or myeloma. Simultaneous presentation in three patients. Cancer 53:83–85

Reilly JT (2002) Chronic neutrophilic leukaemia: a distinct clinical entity ? Br J Haematol 116:10–18

Remstein et al. 2000. http://www.ncbi.nlm.nih.gov/pubmed/10632487

Rosenfeld CS, Sloan B, Egitto DJ (1982) Multiple hepatoma with leukemoid reaction. NY State J Med 82:359–361

Roux et al. 1987. http://www.ncbi.nlm.nih.gov/pubmed/3493936

Rovira M, Cervantes F, Nomdedeu B, Rozman C (1990) Chronic neutrophilic leukaemia preceding for seven years the development of multiple myeloma. Acta Haematol 83:94–95

Ruebner B (1960) Myelosclerosis with serosal myeloid metaplasia and fatal liver involvement. Ann Intern Med 53:1075–1088

Rumi E (2008) Familial chronic myeloproliferative disorders: the state of the art. Hematol Oncol 26: 131–138

Ryu T, Nishimura S, Miura H, Yamada H, Morita H, Miyazaki H, Kitamura S, Miura Y, Saito T (2003) Thrombopoietin-producing hepatocellular carcinoma. Intern Med 42:730–734

Sahasrabudhe N, Davenport A (2005) Myeloid metaplasia in the gall bladder: a case report. J Clin Pathol 58:998–999

Saleque S, Cameron S, Orkin SH (2002) The zinc-finger proto-oncogene Gfi-1b is essential for development of the erythroid and megakaryocytic lineages. Genes Dev 16:301–306

Salgado R, Benoy I, Bogers J, Weytjens R, Vermeulen P, Dirix L, Van Marck E (2001) Platelets and vascular endothelial growth factor (VEGF): a morphological and functional study. Angiogenesis 4:37–43

Sato S, Nagai T, Nishikiori Y, Inoue K, Nakagawa T, Ono Y, Yoshida Y, Okuma M (1992) Coexistence of myeloma and primary myelodysplastic syndrome (MDS). (in Japanese). Rinsho Ketsueki 33:58–62

Schafer AI (2001) Thrombocytosis and thrombocythemia. Blood Rev 15:159–166

Schafer AI (2004) Thrombocytosis. N Engl J Med 350:1211–1219

Scheimberg IB, Pollock DJ, Collins PW, Doran HM, Newland AC, van der Walt JD (1995) Pathology of the liver in leukemia and lymphoma. A study of 110 autopsies. Histopathology 26:311–321

Schwabe RF, Bataller R, Brenner DA (2003) Human hepatic stellate cells express CCR5 and RANTES to induce proliferation and migration. Am J Physiol Gastrointest Liver Physiol 285:G949–G958

Schwarze EW, Schwalbe P, Klein UE (1975) Pathoanatomical features of so-called Ph1-chronic myeloid leukemia. Virchows Arch A Pathol Anat Histol 367:137–148

Seke Etet PF, Vecchio L, Nwabo Kamdje AH (2012) Signaling pathway in chronic myeloid leukemia and leukemic stem cell maintenance: key role of stromal microenvironment. Cell Signal 24:1883–1888

Shafford EA, Pritchard J (1993) Extreme thrombocytosis as a diagnostic clue to hepatoblastoma. Arch Dis Child 69:171

Shaldon S, Sherlock S (1962) Portal hypertension in the myeloproliferative syndrome and the reticulosis. Am J Med 32:758–764

Shirota T, Tavassoli M (1992) Alterations of bone marrow sinus endothelium induced by ionizing irradiation: implications in the homing of intravenously transplanted marrow cells. Blood Cells 18:197–214

Singh AK, Wetherley-Mein G (1977) Microvascular occlusive lesions in primary thrombocythaemia. Br J Haematol 36:553–564

Siniluoto TM, Hyvarinen SA, Paivansalo MJ, Alavaikko MJ, Suramo IJ (1992) Abdominal ultrasonography in myelofibrosis. Acta Radiol 33:343–346

Sjögren U, Brandt L (1976) Different composition and mitotic activity of the haemopoietic tissue in bone marrow, spleen and liver in chronic myeloid leukaemia. Acta Haematol 55:73–80

Skorski T (2012) Genetic mechanisms of chronic myeloid leukemia blastic transformation. Curr Hematol Malig Rep 7:87–93

Smalberg JH, Arends LR, Valla DC, Kiladjian JJ, Janssen HL, Leebeek FW (2012) Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis. Blood 120:4921–4928

Sozer S, Hoffman R (2011) Laser-capture microdissection and analysis of liver endothelial cells from patients with Budd-Chiari syndrome. Methods Mol Biol 755:405–415

Sozer S, Fiel MI, Schiano T, Xu M, Mascarenhas J, Hoffman R (2009) The presence of JAK2V&+/F mutation in the liver endothelial cells of patients with Budd-Chiari syndrome. Blood 113:5246–5249

Spivak JL, Barosi G, Tognoni G, Barbui T, Finazzi G, Marchioli R, Marchetti M (2003) Chronic myeloproliferative disorders. Hematology (Am Soc Hematol Educ Program) 2003:200–224

Standen GR, Jasani B, Wagstaff M, Wardrop CA (1990) Chronic neutrophilic leukemia and multiple myeloma. An association with lambda light chain expression. Cancer 66:162–166

Standen GR, Steers FJ, Jones L (1993) Clonality of chronic neutrophilic leukaemia associated with myeloma: analysis using the X-lined probe M 27 b. J Clin Pathol 46:297–298

Stellacci E, Testa U, Petrucci E, Benedetti E, Orsatti R, Feccia T, Stafsnes M, Coccia EM, Marziali G, Battistini A (2004) Interferon regulatory factor-2 drives megakaryocyte differentiation. Biochem J 377:367–378

Sungaran R, Markovic B, Chong BH (1997) Localization and regulation of thrombopoietin mRNA expression in human kidney, liver, bone marrow, and spleen using in situ hybridization. Blood 89:101–107

Sylvain C, Guilhot F, Carretier M, Verneau A, Poncin E, Beauchant M (1985) Pseudoleukemic hyperleukocytosis disclosing hepatocellular carcinoma (in French). Gastroenterol Clin Biol 9:368–369

Takenaka T, Nakamine H, Hirano K, Tsujimoto M, Maeda J, Koridani T, Hara H (1986) An autopsy case of chronic neutrophilic leukemia – with special reference to the origin of leukemic cells (in Japanese). Rinsho Ketsueki 27:903–909

Tanaka M, Kimura R, Matsutani A, Zaitsu K, Oka Y, Oizumi K (1998) Coexistence of chronic myelogenous leukemia and multiple myeloma. Case report and review of the literature. Acta Haematol 99:221–223

Tang DJ, Yu ZF, Song JZ, Chen MC, Wang ZW (1987) Gaucher-like cells in chronic neutrophilic leukemia. A case report. Chin Med J (Engl) 100:988–989

Tavassoli M (1981) Structure and function of sinusoidal endothelium of bone marrow. Prog Clin Biol Res 59B:249–256

Tavassoli M (1986) Modulation of megakaryocyte emperipolesis by phlebotomy: megakaryocytes as a component of marrow-blood barrier. Blood Cells 12:205–216

Tavassoli M, Aoki M (1981) Migration of entire megakaryocytes through the marrow-blood barrier. Br J Haematol 48:25–29

Tefferi A (2003) The forgotten myeloproliferative disorder: myeloid metaplasia. Oncologist 8:225–231

Tefferi A (2008) JAK and MPL mutations in myeloid malignancies. Leuk Lymphoma 49:388–397

Tefferi A (2012a) Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol 87:285–293

Tefferi A (2012b) Myeloproliferative neoplasms 2012: the John M. Bennett 80th birthday anniversary lecture. Leuk Res 36:1481–1489

Tefferi A (2013) Primary myelofibrosis: 2013 update on diagnosis, risk-stratification, and management. Am J Hematol 88:141–150

Tefferi A, Silverstein MN (1996) Current perspective in agnogenic myeloid metaplasia. Leuk Lymphoma 22(Suppl 1):169–171

Tefferi A, Silverstein MN (1997) Agnogenic myeloid metaplasia. Cancer Invest 15:177–179

Tefferi A, Silverstein MN, Noel P (1995a) Agnogenic myeloid metaplasia. Semin Oncol 22:327

Tefferi A, Silverstein MN, Hoagland HC (1995b) Primary thrombocythemia. Semin Oncol 22:334–340

Tefferi A, Mesa RA, Nagorney DM, Schroeder G, Silverstein MN (2000) Splenectomy in myelofibrosis with myeloid metaplasia: a single-institution experience with 223 patients. Blood 95:2226–2233

Tefferi A, Pardanani A, Lim KH, Abdel-Wahab O, Lasho TL, Patel J, Gangat N, Finke CM et al (2009) TET2 mutations and their clinical correlates in polycythemia vera, essential thrombocythemia and myelofibrosis. Leukemia 23:905–911

Tefferi A, Jimma T, Gangat N, Vaidya R, Begna KH, Hanson CA, Van Dyke DL, Caramazza D et al (2011) Predictors of greater than 80 % 2-year mortality in primary myelofibrosis: a Mayo Clinic study of 884 karyotypically annotated patients. Blood 118:4595–4598

Tefferi A, Jimma T, Sulai NH, Lasho TL, Finke CM, Knudson RA, McClure RF, Pardanani A (2012) IDH mutations in primary myelofibrosis predict leukemic transformation and shortened survival: clinical evidence for leukemic collaboration with JAK2V617F. Leukemia 26:475–480

Teofili L, De Stefano V, Leone G, Micalizzi P, Iovino MS, Alfano G, Bizzi B (1992) Hematological causes of venous thrombosis in young people: high incidence of myeloproliferative disorder as underlying disease in patients with splanchnic venous thrombosis. Thromb Haemost 67:297–301

Testa U (2002) Platelet formation: a link between apoptosis and differentiation. Blood 100:1111–1112

Thiele J (2009) Philadelphia chromosome-negative chronic myeloproliferative disease. Am J Clin Pathol 132:261–280

Thiele J, Kvasnicka HM (2003) Chronic myeloproliferative disorders with thrombocythemia: a comparative study of two classification systems (PVSG, WHO) on 839 patients. Ann Hematol 82:148–152

Thiele J, Krech R, Choritz H, Georgii A (1984) Emperipolesis – a peculiar form of megakaryocytes as evaluated in chronic myeloproliferative diseases by morphometry and ultrastructure. Virchows Arch B Cell Pathol Incl Mol Pathol 46:253–263

Thiele J, Moedder B, Kremer B, Zankovich R, Fischer R (1987) Chronic myeloproliferative diseases with an elevated platelet count (in excess of 1,000,000/microliter): a clinicopathological study on 46 patients with special emphasis on primary (essential) thrombocythemia. Hematol Pathol 1:227–237

Thiele J, Jansen B, Orth KH, Orth H, Moedder B, Fischer R (1988) Ultrastructure of megakaryocytes in the human bone marrow of patients with primary (essential) thrombocythemia. J Submicrosc Cytol Pathol 20:671–681

Thiele J, Wagner S, Degel C, Dienemann D, Wienhold S, Zankovich R, Fischer R, Stein H (1990) Megakaryocyte precursors (pro-and megakaryoblasts) in bone marrow tissue from patients with reactive thrombocytosis, polycythemia vera and primary (essential) thrombocythemia. An immunomorphometric study. Virchows Arch B Cell Pathol Incl Mol Pathol 58:295–302

Thiele J, Galle R, Sander C, Fischer R (1991) Interactions between megakaryocytes and sinus wall. An ultrastructural study on bone marrow tissue in primary (essential) thrombocythemia. J Submicrosc Cytol Pathol 23:595–603

Thiele J, Kvasnicka HM, Amend T, Fischer R (1994) Megakaryocytes and sinus walls in primary osteomyelofibrosis: transendothelial migration as revealed by three-dimensional reconstruction of serial sections following sequential double-immunostaining. Virchows Arch 424:383–387

Thiele J, Kvasnicka HM, Fischer R, Diehl V (1997) Clinicopathological impact of the interaction between megakaryocytes and myeloid stroma in chronic myeloproliferative disorders: a concise update. Leuk Lymphoma 24:463–481

Thorns C, Rohrmoser B, Feller A, Horny HC (2002) Chronic cholecystitis and myeloid metaplasia. Histopathology 41:273–275

Tibes R, Bogenberger JM, Benson KL, Mesa RA (2012) Current outlook on molecular pathogenesis and treatment of myeloproliferative neoplasms. Mol Diagn Ther 16:269–283

Toyoda Y, Tonouchi T, Mimaya J (1989) Hemopoietic factor producing hepatocellular carcinoma in a child (in Japanese). Rinsho Ketsueki 30:94–98

Tsao MS (1989) Hepatic sinusoidal fibrosis in agnogenic myeloid metaplasia. Am J Clin Pathol 91:302–305

Tursz T, Frandrin G, Brouet JC, Seligmann M (1974) Coexistence of a myeloma and a granulocytic leukemia in the absence of any treatment. Study of 4 cases (in French). Nouv Rev Fr Hematol 14:693–704

Tzankov A, Krugmann J, Steurer M, Dirnhofer S (2002) Idiopathic myelofibrosis with nodal, serosal and parenchymatous infiltration. Case report and review of the literature. Acta Haematol 107:173–176

Usuda H, Naito M, Ohyach K, Iizumi T (1997) A case of multiple myeloma producing granulocyte colony-stimulating factor. Pathol Int 47:866–869

Van Buul JD, Voermans C, van den Berg V, Anthony EC, Mul FP, van Wetering S, van der Schoot CE, Hordijk PL (2002) Migration of human hematopoietic progenitor cells across bone marrow endothelium is regulated by vascular endothelial cadherin. J Immunol 168:588–596

Van Pampus EC, Denkers IA, van Geel BJ, Huijgens PC, Zevenbergen A, Ossenkoppele GJ, Langenhuijsen MM (1992) Expression of adhesion antigens of human bone marrow megakaryocytes, circulating megakaryocytes and blood platelets. Eur J Haematol 49:122–127

Vieira L, Vaz A, Matos P, Ambrosio AP, Nogueira M, Marques B, Pereira AM, Jordan P et al (2012) Three-way translocation (X; 20; 16)(p11; q13; q23) in essential thrombocythemia implicates NFATC2 in dysregulation of CSF2 expression and megakaryocyte proliferation. Genes Chromosomes Cancer 51:1093–1108

Vorobiof DA, Benjamin J, Kaplan H, Dvilansky A (1978) Chronic granulocytic leukemia, neutrophilic type, with paraproteinemia (IgA type K). Acta Haematol 60:316–320

Wack KE, Ross MA, Zegarra V, Sysko LR, Watkins SC, Stolz DB (2001) Sinusoidal ultrastructure evaluated during the revascularization of regenerating rat liver. Hepatology 33:363–378

Waitz R, Mayer G, Mayer S, Oberling F, Lang JM (1978) Myelosclerosis: pseudo-tumors forms (in French). Nouv Rev Fr Hematol 20:501–519

Walz-Mattmüller R, Horny HP, Ruck P, Kaiserling E (1998) Incidence and pattern of liver involvement in haematological malignancies. Pathol Res Pract 194:781–789

Wang Q, Liu T, Fang Y, Xie S, Huang X, Mahmood R, Ramaswamy G, Sakamoto KM et al (2004a) BUBR1 deficiency results in abnormal megakaryopoiesis. Blood 103:1278–1285

Wang YQ, Luk JM, Ikeda K, Man K, Chu AC, Kaneda K, Fan ST (2004b) Regulatory role of vHL/HIF-1alpha in hypoxia-induced VEGF production in hepatic stellate cells. Biochem Biophys Res Commun 317:358–362

Wanless IR, Godwin TA, Allen F, Feder A (1980) Nodular regenerative hyperplasia of the liver in hematologic disorders: a possible response to obliterative portal venopathy. A morphometric study of nine cases with an hypothesis on the pathogenesis. Medicine (Baltimore) 59:367–379

Wanless IR, Peterson P, Das A, Boitnott JK, Moore GW, Bernier V (1990) Hepatic vascular disease and portal hypertension in polycythemia vera and agnogenic myeloid metaplasia: a clinicopathological study of 145 patients examined at autopsy. Hepatology 12:1166–1174

Warshauer DM, Schiebler ML (1991) Intrahepatic extramedullary hematopoiesis: MR, CT, and sonographic appearance. J Comput Assist Tomogr 15:683–685

Watanabe A, Yoshida Y, Yamamoto H, Kimura S, Nagashima H, Kitajima K (1984) A case of chronic neutrophilic leukemia with paraproteinemia (IgG type lambda and IgA type K). Jpn J Med 23:39–44

Weinstein IM (1991) Idiopathic myelofibrosis: historical review, diagnosis and management. Blood Rev 5:98–104

Wiener MD, Halvorsen RA, Vollmer RT, Foster WL, Roberts L (1987) Focal intrahepatic extramedullary hematopoiesis mimicking neoplasm. AJR Am J Roentgenol 149:1171–1172

Wolber EM, Jelkmann W (2002) Thrombopoietin: the novel hepatic hormone. News Physiol Sci 17:6–10

Wong Y, Chen F, Tai KS, Yip LK, Tsang KW, Chan FL, Ooi GC (1999) Imaging features of focal intrahepatic extramedullary haematopoiesis. Br J Radiol 72:906–910

Wyatt and Sommers 1950. http://www.ncbi.nlm.nih.gov/pubmed/15411421

Xavier SG, Gadleha T, Pimenta G, Eugenio AM, Ribeiro DD, Gomes FM, Bonamino M et al (2010) JAK2V617F mutation in patients with splanchnic vein thrombosis. Dig Dis Sci 55:1770–1777

Xia J, Lu MZ, Jinag YQ, Yang GH, Zhuang Y, Sun HL, Shen YF (2012) JAK2 V617F, MPL W515L and JAK2 exon 12 mutations in Chinese patients with primary myelofibrosis. Chin J Cancer Res 24:72–76

Xishan Z, Guangyu A, Yuguang S, Hongmei Z (2011) The research on the immune-modulatory defect of mesenchymal stem cell from chronic myeloid leukemia patients. J Exp Clin Cancer Res 30:47

Yam LT (1982) Neutrophilic leukemia. South Med J 75:870

Yamaguchi H, Ishii E, Hayashida Y, Hirata Y, Sakai R, Miyazaki S (1996) Mechanism of thrombocytosis in hepatoblastoma: a case report. Pediatr Hematol Oncol 13:539–544

Yamamoto S, Takashima S, Ogawa H, Kuroda T, Yamamoto M, Takeda A, Nakmaura H (1999) Granulocyte-colony-stimulating factor-producing hepatocellular carcinoma. J Gastroenterol 34:640–644

Yamaya T, Kamata Y, Nagai K, Sawada Y (1982) An autopsy case of chronic neutrophilic leukemia and the review of the Japanese literature (in Japanese). Rinsho Ketsueki 23:1808–1815

Yang Y, Nemoto EM, Harvey SA, Subbotin VM, Gandhi CR (2004) Increased hepatic platelet activating factor (PAF) and PAF receptors in carbon tetrachloride induced liver cirrhosis. Gut 53:877–883

Yonal I, Pinarbasi B, Hindilerden F, Hancer VS, Nalcaci M, Kaymakoglu D, Diz-Kucukkaya R (2012) The clinical significance of JAK2V617F mutation for Philadelphia-negative chronic myeloproliferative neoplasms in patients with splanchnic vein thrombosis. J Thromb Thrombolysis 34:388–396

Yoshida S, Kohro S, Yamakage M, Nakayama M, Namiki A (2003) A case of suspected pulmonary thrombosis in a patient with reactive thrombocytosis who underwent liver subsegmentectomy (in Japanese). Masui 52:1320–1322

Yoshida C, Kojima H, Iijima T, Katsura Y, Shimizu S, Suzukawa K, Mukai HY, Hasegawa Y et al (2004) Association of non-alcoholic steatohepatitis (NASH) with chronic neutrophilic leukemia. Eur J Haematol 72:225–228

Yoshiki Y, Asai T, Ichikawa M, Hangaishi A, Ota S, Imai Y, Takahashi T, Kurokawa M (2011) A case of myeloid sarcoma with correlation to JAK2V617F mutation, complicated by myelofibrosis and secondary acute myeloid leukemia. Intern Med 50:2649–2652

You W, Weisbrot IM (1979) Chronic neutrophilic leukemia: report of two cases and review of the literature. Am J Clin Pathol 72:233–242

Zetterberg E, Lundberg LG, Palmblad J (2003) Expression of cox-2, tie-2 and glycodelin by megakaryocytes in patients with chronic myeloid leukaemia and polycythaemia vera. Br J Haematol 121:497–499

Zhang and Li 2008. http://www.ncbi.nlm.nih.gov/pubmed/19080367

Zittoun R, Rea D, Ngoc LH, Ramond S (1994) Chronic neutrophilic leukemia. A study of four cases. Ann Hematol 68:55–60

Zoumbos NC, Chrysanthopoulos C, Starakis J, Kapatais-Zoumbos K (1987) Kappa light chain myeloma developing in a patient with chronic neutrophilic leukaemia. Br J Haematol 65:504–505

Zoumbos NC, Symeonidis A, Kourakli-Symeonidis A (1989) Chronic neutrophilic leukemia with dysplastic features: a new variant of the myelodysplastic syndrome? Acta Haematol 82:156–160

Myeloid Neoplasms with Eosinophil Lineage

82

Contents

Abstract

The liver can be involved by several neoplastic and reactive disorders characterized by eosinophilia/hypereosinophilia. The common pathogenic pathway of liver damage induced by these conditions is the toxic action of eosinophil granulocyte proteins and eosinophil-associated immune reactions. The liver parenchyma and portal tracts can be infiltrated in the setting of the myeloproliferative neoplasia, chronic eosinophilic leukemia associated with FIP1L1-PDGFRA fusion. Other neoplastic eosinophil processes that may invade and damage the liver are disorders with PDGFRB rearrangement and the 8p11 myeloproliferative syndrome with FGFR1 rearrangement. There are also cases of idiopathic hypereosinophilia, characterized by peripheral eosinophilia with tissue damage in the absence of known cause of eosinophilia. Phenotypically, all these disorders may be associated with various hepatic pathologies, including mass-forming hepatic eosinophilic infiltrations, diffuse hepatic infiltration, eosinophilic granulocytoma/sarcoma, focal hepatic eosinophilic necrosis, eosinophilic hepatitis, eosinophilic cholangiopathy, eosinophilic sclerosing cholangitis, eosinophilic abscesses, eosinophilic hepatic vasculitis, hypereosinophilic hepatic venous thrombosis, and eosinophilic ascites.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_82

Introduction and Classification

Generally, hypereosinophilic states are classified into three major groups, namely, (1) *reactive* (*or non-clonal*) *eosinophilias* (e.g., *allergic reactions*, *infestations*, *infections*, *side effects of drugs*), (2) *clonal disorders of the hemopoietic system associated with eosinophilia*, and (3) *idiopathic hypereosinophilic syndrome* (*HES*) (review: Brito-Babapulle 2003). The clonal disorders with variable degrees of eosinophilia chiefly comprise acute and chronic eosinophilic leukemia (AEL and CEL, respectively), AML and CML with eosinophilia, polycythemia rubra vera with eosinophilia, essential thrombocythemia with eosinophilia, myelodysplastic disorders (MDS) with eosinophilia, eosinophilias in chromosome 16 variant disorders and in the 8p11 myeloproliferative syndrome (EMS), eosinophilic variants of systemic mast cell disease, and several lymphoproliferative disorders with eosinophilia (Brito-Babapulle 2003).

In regard to clonal disorders, the WHO classification distinguishes two major subgroups: (1) myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or fibroblast growth factor receptor 1 (FGFR1), and (2) chronic eosinophilic leukemia (CEL), not otherwise specified (reviews : Gotlib 2010, 2011; Klion et al. 2010; Klion 2011; Noel 2012; Noel and Mesa 2013).

Chronic Eosinophilic Leukemia, Not Otherwise Specified (NOS)

ICD-O Code 9964/3

According to the WHO classification, chronic eosinophilic leukemia (CEL) is defined as a myeloproliferative neoplasia in which autonomous clonal proliferation of eosinophil precursors results in persistently increased numbers of eosinophils in bone marrow, peripheral blood, and peripheral tissues. CEL, not otherwise specified (CEL, NOS) excludes cases with a Philadelphia chromosome, BCR-ABL1 fusion gene, or rearrangement of PDGFRA, PDGFRB, or FGFR1 (reviews: Gotlib 2011, 2012). In CEL, NOS, the eosinophil count in peripheral blood is $=> 1.5 \times 10(9)/L$, and there are less than 20 % blasts in bone marrow or peripheral blood. The proper diagnosis required the proof that the cell lineage is clonal. In case this proof is not available, the disorder should be termed idiopathic hypereosinophilic syndrome (HES). CEL, NOS is a multisystem disorder characterized by eosinophil tissue infiltrations in many organs, including the liver, and cytokine-mediated tissue damage. Evidence of splenic and hepatic involvement is found in 30–50 % of patients. CEL, NOS has a poor prognosis with a high risk of acute transformation (Helbig et al. 2012).

The main feature of morphology is the predominance of mature eosinophils in peripheral blood, with only few eosinophilic myelocytes or promyelocytes. Cytologic abnormalities of eosinophils may be encountered, such as cell enlargement, hyper- or hyposegmentation of nuclei, sparse cytoplasmic granulation, or cytoplasmic vacuolation. Eosinophilia may be accompanied by neutrophilia (a common finding), monocytosis, and mild basophilia. A similar morphologic presentation is found in bone marrow and peripheral infiltrated tissues, often with formation of Charcot-Leyden crystals.

Cytogenetic analyses are important for diagnosis of CEL; the most frequent aberrations have been reviewed (Oliver et al. 1998; Bain 2003). Typical cytogenetic abnormalities include trisomy 8, isochromosome 17, monosomy 7, and several translocations. A breakthrough for the understanding of both CEL and HES was achieved by the identification of a constitutively activated fusion tyrosine kinase assigned to chromosome 4q12, derived from an interstitial deletion, fusing the PDGFR alpha gene (PDGFRA) to an uncharacterized human gene, FIP1-like-1 (FIP1L1) (Cools et al. 2003a). The result of the fusion is called FIP1L1-PDGFRA, encoding a constitutively active receptor tyrosine kinase that is capable of transforming hemopoietic cells; the alteration causes responsiveness to the tyrosine kinase inhibitor, imatinib (Cools et al. 2003a, 2004; Gotlib et al. 2004; Stone et al. 2004; Vandenberghe et al. 2004; Cortes and Kantarjian

2004), and also in a murine model of FIP1L1-PDGFRA-induced CMPD (Cools et al. 2003b). As not all patients responding to imatinib exhibit this characteristic fusion, genetic heterogeneity of HES/CEL is suggested (Gotlib et al. 2004). The fusion of the two genes has also been detected in systemic mast cell disease with eosinophilia (Pardanani et al. 2003; Gilliland et al. 2004; Tefferi and Pardanani 2004; Tefferi et al. 2004), supporting a pathogenic role of the hybrid receptor kinase in eosinophil production (see below; mast cell disorders).

Myeloid and Lymphoid Neoplasms with Eosinophilia Associated with Abnormalities of PDGFRA, PDGFRB, or FGFR1 (ICD-O Codes 9965/3, 9966/3, and 9967/3, Respectively)

In the WHO classification, these three myeloproliferative and lymphoid neoplasms (MPNs) form a rare group of disorders with characteristic gene rearrangements and a distinct morphologic and clinical phenotype. Hypereosinophilia is a characteristic feature, but is not invariable.

MPN with PDGFRA rearrangement (synonym: chronic eosinophilic leukemia with FIP1L1-PDGFRA) is the most common form. The prevailing lesion is FIP1L1-PDGFRA resulting from a cryptic deletion at 4q12. The disorder, which is much more common in males than females (17:1), most often manifests as CEL, but AML, T-LBL, or both simultaneously also occur. The leukemia occurs in patients with a broad age range (7–77 years). Respiratory (interstitial fibrosis), cardiac (endomyocardial fibrosis), and/or gastrointestinal signs are common. The majority of patients have splenomegaly, while hepatomegaly is less common. In the course of CEL, acute transformation may ensue.

MPN with PDGFRB rearrangement (synonym: chronic myelomonocytic leukemia with eosinophilia associated with t(5;12)) is characterized by fusion of PDGFRB with ETV6, usually caused by t(5;12)(q31-33;p12). The hematologic presentation is mostly that of CMML, usually with eosinophilia. However, there are also patients presenting with atypical chronic myeloid leukemia, AML, or juvenile myelomonocytic leukemia. Males are slightly more often involved, and the disease prevails in middle-aged individuals. Splenomegaly is a common finding, whereas liver enlargement is rare. Cardiac involvement can develop. Acute transformation after a relatively short time period can occur.

MPN with FGFR1 rearrangement (synonyms: 8p11 myeloproliferative syndrome, 8p11 stem cell leukemia/lymphoma syndrome) is a heterogeneous group of disorders considered to be derived from a pluripotent hematopoietic stem cell. Several fusion partners of FGFR1 have been identified, all resulting in an abnormal tyrosine kinase. Most patients are young, with a medium onset age of 32 years. Clinically, the disorder presents as CEL, AML, T or B lymphoblastic lymphoma/leukemia, or mixed phenotype acute leukemia. In CEL, blastic transformation may take place. Depending on the type of lineage, there is involvement of the spleen, liver, lymph nodes, or other tissues.

Idiopathic Hypereosinophilic Syndrome (HES)

Introduction

Hypereosinophilia has been defined as a peripheral blood eosinophil count greater than 1,500/mm(3) that persists for at least 6 months, and may be associated with tissue damage, in the absence of other causes of eosinophilia (reviews: Gleich and Leiferman 2009; Gotlib 2012). Idiopathic hypereosinophilic syndromes represent a complex and heterogeneous group of disorders having in common that eosinophil granulocytes are persistently elevated in blood and tissues, eventually causing marked tissue injury with end-organ damage (HES; Hardy and Anderson 1968; reviews: Lin and Boyce 2003; Brito-Babapulle 2003; Bain 2004; Tefferi 2005; Tefferi et al. 2006; Pardanani and Verstovsek 2007; Gotlib 2008; Gleich and Leiferman 2009). Chronic eosinophilic leukemia, not otherwise specified (CEL, NOS) and myeloid and lymphoid

neoplasms with eosinophilia and distinct chromosomal rearrangements make part of this group. Classification criteria for the two disorders have been worked out (Oliver et al. 1998), and according to the new WHO classification, CEL is listed among the chronic myeloproliferative diseases (CMPDs; Haferlach et al. 2004).

In principle, HES and its proved clonal neoplasms comprise a spectrum of indolent to aggressive diseases characterized by persistent hypereosinophilia and that are BCR-ABL negative. Aggressiveness is causally linked to the damaging effects of eosinophils to the tissues that are infiltrated. However, production and release of potentially injurious eosinophil granule products may not suffice for aggressiveness of a given disease process. This is underlined by the observation that eosinophil-derived neurotoxin and major basic protein are elevated in patients with autosomal-dominant familial eosinophilia, but this disorder has a more benign course than typical HES (Klion et al. 2004). Chusid and coworkers have defined three criteria for the diagnosis of HES; they include: (1) eosinophilia of at least 1,500 eosinophils/mm^3 for longer than 6 months, or death before 6 months associated with signs and symptoms of hypereosinophilic disease; (2) lack of evidence for other causes of eosinophilia; and (3) presumptive signs and symptoms of organ involvement (Chusid et al. 1975). In the WHO classification, a diagnosis of HES or chronic eosinophilic leukemia (CEL) requires the exclusion of reactive causes of eosinophilia. However, the classification of HES remained confusing for a longer time period; in particular, "cases referred to an eosinophilic leukemia by many authors overlap with cases termed hypereosinophilic syndrome by others, and generally both fulfill the . . .criteria for HES" (Oliver et al. 1998). A common feature of all the disorders belonging to the large spectrum of diseases is of course the continuing eosinophilia, and, per definition, involvement of tissues and organs is a key alteration, albeit this is highly variable. The patients with these disorders are preferentially male (male-female ratio, 9:1), and HES is usually diagnosed between the ages of 20 and 50 years.

Classification

According to a classification proposal (Oliver et al. 1998), *four subgroups* of patients with HES can be distinguished (Table 1).

A further group of HES is characterized by the expansion of a clonal CD3(−)CD4(+) T-cell population. This is termed the lymphocytic variant of HES, a condition often associated with a pruritic

Table 1 Classification of hypereosinophilic syndromes

Subgroup 1 **patients** exhibit very mild clinical disease, frequently with urticaria and/or angioedema. Some of these patients may, in fact, not have an idiopathic form of HES, but rather a secondary eosinophilia that had not been identified as such
Subgroup 2 **patients** show more severe organ involvement, in particular of the heart, including Loeffler's endocarditis, the lung, the skin, and the CNS, but gastrointestinal, renal, and soft tissue involvement has also been reported
Subgroup 3 **patients** display a prominent hematologic syndrome associated with an unfavorable outcome, with anemia, thrombocytopenia, susceptibility to infections, and splenomegaly. Immature eosinophils are detectable, as is myelofibrosis, with a presentation typical for other chronic myeloproliferative disorders. Patients with this constellation are recommended to be diagnosed as *chronic eosinophilic leukemia* (CEL). Diagnostic for leukemia is the presence of a clonal cytogenetic anomaly, but also the detection of naphthol chloroacetate esterase in eosinophils seems to be specific for neoplastic eosinophils. Morphologic criteria for the diagnosis of CEL have been worked out (Oliver et al. 1998) and comprise the criteria of HES plus either a clonal cytogenetic abnormality or two of the following: immature eosinophil precursors accounting for >25 % of the differential count, myeloblasts accounting for >5 % of the differential count, and naphthol chloroacetate esterase-positive eosinophils. As cellular morphologic anomalies, including dysplasia, may be seen in HES in the absence of neoplastic lineage, these features are not regarded as reliable for the diagnosis of CEL
Subgroup 4 **patients** are those with CEL undergoing blastic transformation. Progression to blastic transformation is well known in patients that had stable disease for several years. This category is defined as CEL with the presence of >30 % of myeloblasts in the differential marrow or peripheral blood count (Oliver et al. 1998). This disease can be rapidly fatal

rash (Zaheri et al. 2010). The involved T-cells secrete IL-5 which is considered to be the cause of the accompanying eosinophilia (Gleich and Leiferman 2009). In some cases, chronic active EBV infection was identified as the driving mechanism of the disorder (Klion et al. 2013). Lymphocyte variant of HES can finally transform into a T-cell lymphoma (Ravoet et al. 2009; d'Elbée et al. 2013).

Liver Changes in HES and Chronic Eosinophilic Leukemia

Phenotypes

HES/CEL typically causes a broad spectrum of organ and tissue damage (Fauci et al. 1982; Weller and Bubley 1994), involving a multistep pathogenic cascade well studied in eosinophilic heart disease. Specific proteins released from eosinophils (e.g., major basic protein and eosinophilic cationic protein) can exert direct cellular damage resulting in necrosis, but some of the injuries are induced by vascular (endothelial) damage followed by local thrombosis and ischemia. Some forms of HES are associated with elevated numbers of T lymphocytes that may harm target tissues. Cell injury, necrosis, and vascular damage may be followed by progressive fibrosis, in particular in patients with myeloproliferative variants of HES and elevated serum tryptase levels (Klion et al. 2003).

A broad spectrum of causes induce eosinophil infiltration of the liver. One group is, similar to other organs, characterized by single-organ eosinophil infiltration without eosinophilia. The other group, discussed in this paragraph, consists of lesions developing in underlying clonal disorders of the hemopoietic system, viz., HES/CEL.

Several lesions are caused in the liver by HES/CEL (Table 2).

Table 2 Phenotypes of liver disease and associated alteration in HES/CEL

Eosinophilic infiltrations of the liver
Diffuse hepatic infiltration by eosinophils and/or their precursors
Focal eosinophilic infiltration of the liver (in part mass forming)
Eosinophilic granulocytoma/myelocytoma/myeloblastoma/granulocytic sarcoma
Focal hepatic eosinophil-related necrosis (FHERN; focal eosinophilic necrosis, FEN)
Eosinophilic hepatic inflammatory changes
Eosinophilic chronic active hepatitis
Eosinophilic lobular hepatitis
Eosinophilic hepatic abscess
Bile duct disease caused by eosinophils
Eosinophilic cholangiopathy
Eosinophilic sclerosing cholangitis
Hepatic vascular disorders in HES/CEL
Budd-Chiari syndrome and hepatic veno-occlusive disease
Hypereosinophilic thrombi in veins and/or arteries
Eosinophilic hepatic vasculitis
Other hepatic changes and associated alterations
Cholestatic hepatopathy
Eosinophilic ascites
Hepatocellular carcinoma in hypereosinophilia

Diffuse Eosinophilic Hepatic Infiltration

Hepatomegaly is a common feature in patients with HES/CEL (Chusid et al. 1975; Kim et al. 1993). At least part of this increase in liver mass is caused by eosinophilic infiltration of this organ, which may occur in up to 32 % of the patients with HES/CEL (Fauci et al. 1982) or, in one study, in all patients (Kim et al. 1993). Blast cells and eosinophils in all stages of maturation, including unusual atypical eosinophil precursors, have been reported to be located to the liver (Bianco et al. 1984; Yu et al. 1989; Take et al. 1990; Bartolomei et al. 1994; Valente et al. 1997; Kim et al. 2002; Reyes et al. 2005; Sun et al. 2005; Lai et al. 2008). In one reported patient, liver infiltration in HES was associated with sinus histiocytosis with massive lymphadenopathy of the Rosai-Dorfman type (Hernandez et al. 1987). The cells occupy both the portal tracts and the parenchyma, and at least part of the eosinophils may be reactive for chloroacetate esterase (Bianco et al. 1984), suggesting the contribution of a neoplastic eosinophil lineage.

Focal Eosinophilic Infiltration of the Liver and Eosinophilic Granulocytic Tumors

Focal eosinophilic infiltration of the liver (FEIL) occurs in both HES/CEL and benign causes of hypereosinophilia, such as parasitic infestations. FEIL should not be called eosinophilic abscess, because the latter almost exclusively occurs in secondary forms of tissue eosinophilia, mainly in parasitic disease. FEIL developing in the setting of HES/CEL has been described several times (Won et al. 1999; Oh et al. 2004; Kim et al. 2005; Lai et al. 2008; Park et al. 2009; Shatery and Sayyah 2011). FEIL may present as single mass of the liver, histologically characterized by marked eosinophilic infiltration of the area involved and centrilobular necrosis (Oh et al. 2004).

Aggressive forms of HES with formation of osteodestructive eosinophilic tumors ("eosinophilic myelocytomas," "myeloblastomas," "eosinophilic chloromas," " eosinophilic granulocytic sarcomas") have been described (Benvenisti and DeBellis 1969; Pardo-Peret et al. 1979; Ellman et al. 1979; Lynott et al. 2000; Adler and Schaefer 2001). Similar lesions may develop in the liver, although no biopsy data are available so far. However, liver sonography in 13 HES patients with liver involvement showed multiple round or oval hypoechoic or variably echogenic lesions in seven patients, and these lesions measured 1–2 cm with poorly defined margins. Four of these patients had one or two hypoechoic lesions 3–4 cm in size. The number of the lesions and the extent of diffuse lesions seemed to be proportional to the degree of eosinophilia (Nam et al. 1999). Similar changes have been described by the use of CT and other imaging techniques (White et al. 1981; Shiomi et al. 1991; Kim et al. 1993; Lim et al. 2000; Yoo et al. 2003).

Focal Eosinophilic Necrosis (FEN) of the Liver (Focal Hepatic Eosinophil-Related Necrosis, FHERN)

Focal eosinophilic necrosis (FEN) of the liver associated with HES is a unique alteration characterized by geographic, multiacinar areas of hepatic necrosis with eosinophilic inflammation, with other liver regions showing features of chronic hepatitis (Ung et al. 2000). In CT and MR images, FEN presents as focal hypoattenuating lesions and as focal hypoechoic lesions on sonography: Sometimes, numerous low-attenuation lesions disseminated throughout the entire liver are seen in CT scans (Yoo et al. 2003; Yu et al. 2005; Choi et al. 2009; Cho et al. 2010). The foci vary in size and are round or oval, and they tend to regress as peripheral blood eosinophil counts decrease (Lee et al. 1999). In contrast to metastases, FEN associated with visceral cancer and analyzed by CT imaging far more frequently showed a fuzzy margin, subtle hypoattenuation, and a nonspherical shape, and rim enhance is seldom encountered (Jang et al. 2002). Histologically, confluent parenchymal necrosis is in evidence, accompanied by a dense perifocal infiltrate rich in eosinophils (Ung et al. 2000). Smaller eosinophilic necroinflammatory foci may occur as well. FEN may be grossly visible, because the lesions can grow to 2 cm in diameter (Ung et al. 2000). Adjacent liver tissue reveals an eosinophil-predominant lobular hepatitis and signs of chronic active periportal hepatitis with accumulation of eosinophils in the interface lesions. The pathogenesis of FEN in HES has not yet been clarified, but cytotoxic effects of densely infiltrating eosinophils and their products have been suggested (Lee et al. 1999; Ung et al. 2000; Yoo et al. 2003).

Eosinophilic Hepatitis

A portal tract/periportal infiltration is regarded as typical for HES/CEL (Fauci et al. 1982; Croffy et al. 1988; Foong et al. 1991; Cha et al. 1998; Minola and Sonzogni 2005; Morgan-Rowe et al. 2011), resulting in the histologic phenotype of *eosinophilic chronic active hepatitis*. The eosinophils located to the widened portal tracts are variably intermingled with lymphocytes, plasma cells, and macrophages. Interface lesions/piecemeal necroses may also contain significant numbers of

eosinophils. Within the lobular parenchyma, eosinophils are mostly seen within the sinusoidal compartment, but some of the cells seem to stick to the endothelia, with endothelial damage and formation of microthrombi, and few eosinophils or eosinophil precursors are found between hepatocytes of damaged and in part even destructed liver cell plates (Cha et al. 1998), suggesting parenchymal injury. In case numerous eosinophils infiltrate the parenchyma, the descriptive histologic features are those of *eosinophilic lobular hepatitis*.

Bile Duct Disease Caused by Eosinophils

Eosinophilic cholangiopathy is a unique disorder of large bile duct characterized by a self-limited eosinophil infiltration of ducts. In eosinophilic cholangiopathy, eosinophils display a ductocentric distribution associated with biliary epithelial damage (Butler et al. 1985; Tenner et al. 1997; Valente et al. 1997; Abdalla and Vauthey 2002; Jimenez-Sanz et al. 2003; Duseja et al. 2005; Jeyamani et al. 2007; Sussman et al. 2008; Oh et al. 2012). Eosinophilic cholangiopathy can develop in conjunction with other eosinophilic gastrointestinal disorders, e.g., eosinophilic colitis (Schoonbrodt et al. 1995; Sussman et al. 2008). The eosinophils are accumulated in the connective tissue around the ducts and ductules, often with a transmural distribution and sometimes more prominently at the sites of the peribiliary plexus, and occasionally forming so-called microabscesses (Cha et al. 1998). The latter is a misnomer, because histology is characterized by dense accumulations of eosinophils not induced by an infectious process. Some of the cells are engaged with the biliary epithelium, with signs of epithelial infiltration and/or dislocation into the lumina. Cholangiocyte damage apparently caused by eosinophils is evident in the form of irregular epithelial lining, cholangiocyte vacuolation, karyopyknosis, and apoptosis. A similar process can develop in the gallbladder (eosinophilic cholecystitis; Jimenez-Sanz et al. 2003; Shakov et al. 2007). What is the biology of disease in eosinophilic cholangiopathy? In a review of 23 reported cases of eosinophilic cholangiopathy, 82.6 % remained disease-free, while among the remaining there may be patients requiring therapy because of biliary stenosis (Nashed et al. 2010). In some patients with eosinophilic infiltration of bile ducts, duct wall sclerosis ensues causing stenosis and mimicking bile duct cancer (Rodgers et al. 2001; Matsumoto et al. 2007; Chen et al. 2009). This lesion has been termed HES-associated *eosinophilic sclerosing cholangitis* (synonym: hypereosinophilic sclerosing cholangitis) (Kagawa et al. 1988; Neeman and Kadish 1987; Rosengart et al. 1990; Grauer et al. 1993; Ichikawa et al. 1997; Al-Abdulla et al. 2000; Pometta et al. 2000; Delevaux et al. 2002; Miura et al. 2009). In part of the patients with HES, sclerosing cholangitis is associated with chronic inflammatory bowel disease (Scheurlen et al. 1992). It is currently not clear, whether eosinophilic cholangiopathy without fibrosis/sclerosis and the sclerosing variant are the same disease in different stages of evolution or whether we deal with two diseases.

Histologically, involved bile ducts disclose a dense ductocentric eosinophil infiltration associated with fibrosclerosis as seen in primary sclerosing cholangitis (Miura et al. 2009). In PSC, eosinophils may occur in the periductal tissue compartment to variable degrees, and it has been suggested that eosinophils are related to the pathogenesis of PSC (Watanabe et al. 1995; Shimomura et al. 1996), similar to primary biliary cirrhosis. The bile duct inflammation with marked contribution of eosinophils may be accompanied by eosinophil infiltration of adjacent parenchyma, as specified above (*eosinophilic cholangiohepatitis*).

Pathogenetically, effects of eosinophil granule products, inducing cell damage and fibrogenesis, have been proposed. In a case of eosinophilic cholecystitis, deposition of secreted eosinophil cationic protein (ECP) and of major basic protein (MBP) has been detected (Noguchi et al. 1992; Tajima and Katagiri 1996).

Hepatic Vascular Disorders in HES/CEL

Veno-occlusive Disease and Budd-Chiari Syndrome in HES

Patients with HES/CEL can develop acute hepatic veno-occlusive disease (VOD Kojima and Sasaki 1995) or Budd-Chiari syndrome (Elouaer-Blanc et al. 1985; Walker 1987; Suenaga et al. 1991; Vargas et al. 1993; Zylberberg et al. 1996; Becker et al. 2006; Inoue et al. 2007; Mishchenko et al. 2012), sometimes followed by liver failure. Pathogenetically, local damaging effects of eosinophils on venous endothelial cells and/or a pro-coagulative action of eosinophils have been proposed, supported by regression of VOD subsequent to corticosteroid therapy (Kojima and Sasaki 1995). As in other forms of hepatic venous outflow disorders, nodular regenerative hyperplasia (NRH) of the liver may develop in HES (Baker et al. 1991; Nakamura et al. 1997).

Eosinophilic Hepatic Vasculitis

HES and CEL are known to be associated with necrotizing vasculitis (Jang et al. 2000; Gotlib et al. 2003). In one patient with HES, liver rupture occurred and was associated with eosinophilic necrotizing arteritis of the hepatic artery with fibrinoid necrosis (Cheung et al. 2009).

Other Hepatic Changes and Associated Alterations

Cholestatic Hepatopathy

HES is known to rarely be associated with cholestasis, sometimes with recurrent episodes of abdominal pain (Valente et al. 1997). In part of these instances, intrahepatic bile duct damage caused by toxic actions of eosinophils may be involved. On the other hand, cholestasis may be caused by stenosis of extrahepatic bile duct in case of pancreatic involvement in HES (eosinophilic pancreatitis; Eugene et al. 1984; Euscher et al. 2000).

Eosinophilic Ascites

HES with or without involvement of the liver can be associated with eosinophilic ascites, sometimes massive (Adams and Mainz 1977; Vandewiele et al. 1991; Rimbrot et al. 2001; de Carpi et al. 2007), but it also occurs in other situations of secondary eosinophilia, e.g., eosinophilic gastroenteritis (Leveque et al. 1998) or toxocariasis (Cruz et al. 2008). As such, eosinophilic ascites is a rare alteration and should therefore raise the suspicion of HES and related disorders.

Hepatocellular Carcinoma Associated with Eosinophilia/Hypereosinophilia

Hepatocellular carcinoma is known to sometimes be associated with paraneoplastic hypereosinophilia, occasionally of severe degree (Komai et al. 1984; Salame et al. 1988; Ranke 1965; Yuen et al. 1995; Chang et al. 1996; Balian et al. 2001; Bonaventure et al. 2003; Villas et al. 2003). Pathogenetically, the production of pro-eosinophilic cytokines, e.g., IL-5 (the most specific cytokine for the eosinophil lineage), by CD4+ T lymphocytes infiltrating the hepatic tumor has been proposed (Balian et al. 2001).

Charcot-Leyden Crystals in HES and Other Hypereosinophilic States

In several of these eosinophilic lesions described above, Charcot-Leyden crystals (CLC) are observed in histologic preparations, e.g., in eosinophilic hepatitis, in eosinophilic cholangiopathy, and in eosinophilic sclerosing cholangitis. In case of marked eosinophilia (e.g., severe HES), CLC can also circulate in the blood and then enter thrombotic material (Dincsoy et al. 1981). Apart from a cytoplasmic localization, CLC have been detected within nuclei, e.g., in refractory anemia with dysplastic eosinophils (Ma et al. 1995).

The crystals have a characteristic ultrastructural morphology (Carson et al. 1992). CLC are mainly composed of a lineage-specific protein

(the eosinophil/basophil Charcot-Leyden crystal protein, galectin-10) with human eosinophil lysophospholipase activity (the CLC protein; Weller et al. 1980, 1984; Calafat et al. 1997; Dyer and Rosenberg 2000). However, eosinophil lysophospholipase has no sequence similarities to any known lysophospholipases; rather, it has a moderate sequence similarity to members of the galectin superfamily of carbohydrate-binding proteins and has thus been termed galectin-10. The CLC protein interacts with (true) eosinophil lysophospholipases and known inhibitors of this lipolytic activity (Leonidas et al. 1995; Dyer et al. 1997; Swaminathan et al. 1999; Ackerman et al. 2002). In eosinophils, the CLC protein is confined to a distinct crystalloid-free granule population in mature cells (Dvorak et al. 1988).

CLC and their component are not exclusively found in eosinophils. CLC are formed by basophils (Ackerman et al. 1982), and lysophospholipase has been localized to human basophil granules (Dvorak and Ackerman 1989; Golightly et al. 1990; Calafat et al. 1997). This phenomenon is probably related to a common basophil-eosinophil progenitor (Denburg et al. 1985). CLC and CLC protein are furthermore detectable in the phagosomes of certain macrophage populations, indicating phagocytosis of crystals and their constituents (Dvorak et al. 1990b). The protein has been localized to intracytoplasmic crystals in neoplastic cells of pancreatic solid and papillary tumors (Dvorak et al. 1990a).

Systemic Mast Cell Disease with Eosinophilia

A subset of systemic mast cell disease (SMCD) is associated with marked eosinophilia. In particular, SMCD may be associated with HES more frequently than previously anticipated (McElroy et al. 1998; Gotlib and Akin 2012). It has recently been found that an early stem cell origin of the FIP1L1-PDGFRA mutation (see above) may be involved in the pathogenesis of hypereosinophilia in SMCD (Pardanani et al. 2003; Gilliland et al. 2004; Tefferi et al. 2004; Florian et al. 2006). These findings serve for a partial molecular classification of SMCD (Tefferi and Pardanani 2004). The liver alterations in the hypereosinophilic form of SMCD can be expected to be a mixture of the findings in HES and those in SMCD that are discussed in more detail in a separate chapter.

References

Abdalla EK, Vauthey JN (2002) Eosinophilic cholangiopathy. Surgery 131:237–238

Ackerman SJ, Weil GJ, Gleich GJ (1982) Formation of Charcot-Leyden crystals by human basophils. J Exp Med 155:1597–1609

Ackerman SJ, Liu L, Kwatia MA, Savage MP, Leonidas DD, Swaminathan GJ, Acharya KR (2002) Charcot-Leyden crystal protein (galectin-10) is not a dual function galectin with lysophospholipase activity but binds a lysophospholipase inhibitor in a novel structural fashion. J Biol Chem 277:14859–14868

Adams HW, Mainz DL (1977) Eosinophilic ascites. A case report and review of the literature. Am J Dig Dis 22:40–42

Adler CP, Schaefer HE (2001) Eosinophilic chloroma (eosinophilic granulocytic sarcoma). Histopathology 39:544–546

Al-Abdulla NA, Schulick RD, Regan F (2000) Hypereosinophilic sclerosing cholangitis: findings using half-Fourier magnetic resonance imaging. Hepatogastroenterology 47:359–361

Bain BJ (2003) Cytogenetic and molecular genetic aspects of eosinophilic leukemias. Br J Haematol 122:173–179

Bain B (2004) The idiopathic hypereosinophilic syndrome and eosinophilic leukemias. Haematologica 89:133–137

Baker BL, Axiotis C, Hurwitz ES, Leavitt R, Di Bisceglie AM (1991) Nodular regenerative hyperplasia of the liver in idiopathic hypereosinophilic syndrome. J Clin Gastroenterol 13:452–456

Balian A, Bonte E, Naveau S, Foussat A, Bouchet-Delbos-L, Berrebi D, Vons C, Capron F, Chaput JC, Emilie D (2001) Intratumoral production of interleukin-5 leading to paraneoplastic peripheral eosinophilia in hepatocellular carcinoma. J Hepatol 34:355–356

Bartolomei C, Arcabasso GD, Paoletti P, Baldacci S (1994) An unusual case of pulmonary infiltrates with hepatic involvement in a woman with eosinophilia (in Italian). Minerva Med 85:491–493

Becker V, Lersch C, Gaa J, Schmid RM (2006) Partial Budd-Chiari syndrome associated with a hypereosinophilic syndrome (in German). Z Gastroenterol 44:173–177

Benvenisti DS, DeBellis RH (1969) Carcinoma of the breast, chronic lymphocytic leukemia,

macroglobulinemia, eosinophilic chloroma and myelosclerosis – a unique association. Cancer 23:1204–1209

Bianco P, Papa G, Martelli M, Bonucci E (1984) Eosinophilic leukemia with prominent visceral involvement: histopathological and histochemical observations. Appl Pathol 2:247–254

Bonaventure C, Etienne-Mastroianni B, Alessio A, Scoazec JY, Boillot O, Dumortier J (2003) Paraneoplastic hypereosinophilia associated with hepatocellular carcinoma (in French). Gastroenterol Clin Biol 27:1167–1169

Brito-Babapulle F (2003) The eosinophilias, including the idiopathic hypereosinophilic syndrome. Br J Haematol 121:203–223

Butler TW, Feintuch TA, Caine WP (1985) Eosinophilic cholangitis, lymphadenopathy, and peripheral eosinophilia: a case report. Am J Gastroenterol 80:572–574

Calafat J, Janssen H, Knol EF, Weller PF, Egesten A (1997) Ultrastructural localization of Charcot-leyden crystal protein in human eosinophils and basophils. Eur J Haematol 58:56–66

Carson HJ, Buschmann RJ, Weisz-Carrington P, Choi YS (1992) Identification of Charcot-Leyden crystals by electron microscopy. Ultrastruct Pathol 16:403–411

Cha SH, Park CM, Cha IH, Kim HJ, Lee DH, Baek SY, Kim PN, Ha HK (1998) Hepatic involvement in hypereosinophilic syndrome: value of portal venous phase imaging. Abdom Imaging 23:154–157

Chang WC, Liaw CC, Wang PN, Tsai YH, Hsueh S (1996) Tumor-associated hypereosinophilia: report of four cases. Changgeng Yi Xue Za Zhi 19:66–70

Chen WH, Yu CC, Wu CC, Jan YJ (2009) Eosinophilic cholangitis with obstructive jaundice mimicking bile duct carcinoma. J Hepatobiliary Pancreat Surg 16:242–245

Cheung YS, Wong S, Lam PKN, Lee KF, Wong J, Lai PBS (2009) Spontaneous liver rupture in hypereosinophilic syndrome: a rare but fatal complication. World J Gastroenterol 15:5875–5878

Cho ES, Yu JS, Kim MJ, Chung JJ, Kim KW (2010) Focal eosinophilic necrosis on superparamagnetic iron oxide-enhanced MRI. AJR Am J Roentgenol 194:1296–1302

Choi JI, Lee JM, Kim SH, Lee JY, Lee MW, Han CJ, Han JK, Choi BI (2009) Differentiating focal eosinophilic necrosis of the liver from hepatic metastases using unenhanced and portal venous phase computed tomographic imagings: results of univariate and multivariate statistical analyses. J Comput Assist Tomogr 33:705–709

Chusid MJ, Dale DC, West BC, Wolff SM (1975) The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine 54:1–27

Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, Kutok J, Clark J, Galinsky I, Griffin JD et al (2003a) A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med 348:1201–1214

Cools J, Stover EH, Boulton CL, Gotlib J, Legare RD, Amaral SM, Curley DP, Duclos N, Rowan R, Kutok JL et al (2003b) PKC412 overcomes resistance to imatinib in a murine model of FIP1L1-PDGFRalpha-induced myeloproliferative disease. Cancer Cell 3:459–469

Cools J, Stover EH, Wlodarska I, Marynen P, Gilliland DG (2004) The FIP1L1-PDGFRalpha kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia. Curr Opin Hematol 11:51–57

Cortes J, Kantarjian H (2004) Beyond chronic myelogenous leukemia: potential role for imatinib in Philadelphia-negative myeloproliferative disorders. Cancer 100:2064–2078

Croffy B, Kopelman R, Kaplan M (1988) Hypereosinophilic syndrome. Association with chronic active hepatitis. Dig Dis Sci 33:233–239

Cruz AT, Franklin GY, Kaplan SL (2008) Toxocariasis causing eosinophilic ascites. Pediatr Infect Dis J 27:563–564

D'Elbée JM, Parrens M, Mercié P, Longy Boursier M, Dieval C, de Mascarel A, Duffau P et al (2013) Hypereosinophilic syndrome – lymphocytic variant transforming into peripheral T-cell lymphoma with severe oral manifestations. Oral Surg Oral Med Oral Pathol Oral Radiol 116:e185–190

de Carpi JM, Rives S, Parada F, Varea V (2007) Eosinophilic ascites as the first sign of idiopathic hypereosinophilic syndrome in childhood. J Clin Gastroenterol 41:864–865

Delevaux I, Andre M, Chipponi J, Milesi-Lecat AM, Dechelotte P, Aumaitre O (2002) A rare manifestation of idiopathic hypereosinophilic syndrome: sclerosing cholangitis. Dig Dis Sci 47:148–151

Denburg JA, Telizyn S, Messner H, Lim B, Jamal N, Ackerman SJ, Gleich GJ, Bienenstock J (1985) Heterogeneity of human peripheral blood eosinophil-type colonies: evidence for a common basophil-eosinophil progenitor. Blood 66:312–318

Dincsoy HP, Burton TJ, van der Bel-Kahn JM (1981) Circulating Charcot-leyden crystals in the hypereosinophilic syndrome. Am J Clin Pathol 75:236–243

Duseja A, Nada R, Dhiman RK, Chawla YK, Kalra N, Prashad S, Karwasra RK (2005) Eosinophilic cholangiopathy – a case report. Dig Dis Sci 50:1422–1425

Dvorak AM, Ackerman SJ (1989) Ultrastructural localization of the Charcot-Leyden crystal protein (lysophospholipase) to granules and intragranular crystals in mature human basophils. Lab Invest 60:557–567

Dvorak AM, Letourneau L, Login GR, Weller PF, Ackerman SJ (1988) Ultrastructural localization of the Charcot-Leyden crystal protein (lysophospholipase) to a distinct crystalloid-free granule population in mature human eosinophils. Blood 72:150–158

Dvorak AM, Letourneau L, Weller PF, Ackerman SJ (1990a) Ultrastructural localization of Charcot-Leyden crystal protein (lysophospholipase) to intracytoplasmic crystals in tumor cells of primary solid and papillary

epithelial neoplasm of the pancreas. Lab Invest 62:608–615

Dvorak AM, Weller PF, Monahan-Earley RA, Letourneau L, Ackerman SJ (1990b) Ultrastructural localization of Charcot-leyden crystal protein (lysophospholipase) and peroxidase in macrophages, eosinophils, and extracellular matrix of the skin in the hypereosinophilic syndrome. Lab Invest 62:590–607

Dyer KD, Rosenberg HF (2000) Shared features of transcription: mutational analysis of the eosinophil/basophil Charcot-Leyden crystal protein gene promoter. J Leukoc Biol 67:691–698

Dyer KD, Handen JS, Rosenberg HF (1997) The genomic structure of the human Charcot-leyden crystal protein gene is analogous to those of the galectin genes. Genomics 40:217–221

Ellman L, Hammond D, Atkins L (1979) Eosinophilia, chloromas and a chromosome abnormality in a patient with a myeloproliferative syndrome. Cancer 43:2410–2413

Elouaer-Blanc L, Zafrani ES, Farcet JP, Saint-Marc Girardin MF, Mathieu D, Dhumeaux D (1985) Hepatic vein obstruction in idiopathic hypereosinophilic syndrome. Arch Intern Med 145:751–753

Eugene C, Gury B, Bergue A, Quevauvilliers J (1984) Icterus disclosing pancreatic involvement in idiopathic hypereosinophilic syndrome (in French). Gastroenterol Clin Biol 8:966–969

Euscher E, Vaswani K, Frankel W (2000) Eosinophilic pancreatitis: a rare entity than can mimic a pancreatic neoplasm. Ann Diagn Pathol 4:379–385

Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH (1982) The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med 97:78–92

Florian S, Esterbauer H, Binder T, Mullauer L, Haas OA, Sperr WR, Sillaber C, Valent P (2006) Systemic mastocytosis (SM) associated with chronic eosinophilic leukemia (SM-CEL): detection of FIPL1L1/PDHGRalpha, classification by WHO criteria, and response to therapy with imatinib. Leuk Res 30:1201–1205

Foong A, Scholes JV, Gleich GJ, Kephart GM, Holt PR (1991) Eosinophil-induced chronic active hepatitis in the idiopathic hypereosinophilic syndrome. Hepatology 13:1090–1094

Gilliland G, Cools J, Stover EH, Wlodarska I, Marynen P (2004) FIP1L1-PDGFRalpha in hypereosinophilic syndrome and mastocytosis. Hematol J 5(suppl 3): S133–S137

Gleich GJ, Leiferman KM (2009) The hypereosinophilic syndromes: current concepts and treatments. Br J Haematol 145:271–285

Golightly LM, Thomas LL, Dvorak AM, Ackerman SJ (1990) Charcot-Leyden crystal protein in the degranulation and recovery of activated basophils. J Leukoc Biol 51:386–392

Gotlib J (2008) Chronic eosinophilic leukemia/hypereosinophilic syndrome. Cancer Treat Res 142:69–106

Gotlib J (2010) Eosinophilic myeloid disorders: new classification and novel therapeutic strategies. Curr Opin Hematol 17:117–124

Gotlib J (2011) World Health Organization-defined eosinophilic disorders: 2011 update on diagnosis, risk stratification, and management. Am J Heamtol 86:677–688

Gotlib J (2012) World Health Organization-defined eosinophilic disorders: 2012 update on diagnosis, risk stratification, and management. Am J Hematol 87:903–914

Gotlib J, Akin C (2012) Mast cells and eosinophils in mastocytosis, chronic eosinophilic leukemia, and non-clonal disorders. Semin Hematol 49:128–137

Gotlib V, Darji J, Bloomfield K, Chadburn A, Patel A, Braunschweig I (2003) Eosinophilic variant of chronic myeloid leukemia with vascular complications. Leuk Lymphoma 44:1609–1613

Gotlib J, Cools J, Malone JM, Schrier SL, Gilliland DG, Coutre SE (2004) The FIP1L1-PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. Blood 103:2879–2891

Grauer L, Padilla VM, Bouza L, Barkin JS (1993) Eosinophilic sclerosing cholangitis associated with hypereosinophilic syndrome. Am J Gastroenterol 88:1764–1769

Haferlach T, Kern W, Schnittger S, Schoch C (2004) Modern diagnostics in chronic myeloproliferative diseases (CMPDs). Ann Hematol 83(suppl 1):S59–S61

Hardy WR, Anderson RE (1968) The hypereosinophilic syndromes. Ann Intern Med 68:1220–1229

Helbig G, Soja A, Bartkowska-Chrobok A, Kyrcz-Krzemien S (2012) Chronic eosinophilic leukemia-not otherwise specified has a poor prognosis with unresponsiveness to conventional treatment and high risk of acute transformation. Am J Hematol 87:643–645

Hernandez D, Gutierret L, Duque H, Olavarria R, Muci R, Wunaii H (1987) Association of sinus histiocytosis with massive lymphadenopathy and idiopathic hypereosinophilic syndrome. Histol Histopathol 2:239–242

Ichikawa N, Taniguchi A, Akama H, Ishiguro H, Kurihara T, Terai C, Hara M, Kashiwazaki S (1997) Sclerosing cholangitis associated with hypereosinophilic syndrome. Intern Med 36:561–564

Inoue A, Michitaka K, Shigematsu S, Konishi I, Hirooka M, Hiasa Y, Matsui H, Matsuura B et al (2007) Budd-Chiari syndrome associated with hypereosinophilic syndrome. Intern Med 46:1095–1100

Jang KA, Lim YS, Choi JH, Sung KJ, Moon KC, Koh JK (2000) Hypereosinophilic syndrome presenting as cutaneous necrotizing eosinophilic vasculitis and Raynaud's phenomenon complicated by digital gangrene. Br J Dermatol 144:1087–1090

Jang HJ, Lee WJ, Lee SJ, Kim HK, Lim JH (2002) Focal eosinophilic necrosis of the liver in patients with

underlying gastric or colorectal cancer: CT differentiation from metastasis. Korean J Radiol 3:240–244
Jeyamani R, Ramakrishna BS, Kurian G (2007) Eosinophilic cholangiopathy – a report of two cases. Indian J Gastroenterol 26:190–191
Jimenez-Sanz M, Villar-Rodriguez JL, Torres Y, Carmona I, Salas-Herrero E, Gonzalez-Vilches J et al (2003) Biliary tract disease: a rare manifestation of eosinophilic gastroenteritis. Dig Dis Sci 48:624–627
Kagawa T, Suematsu M, Miura S et al (1988) A case of primary sclerosing cholangitis with eosinophilia (in Japanese). Sogorinsho 9:2339–2342
Kim GB, Kwon JH, Kang DS (1993) Hypereosinophilic syndrome: imaging findings in patients with hepatic involvement. AJR Am J Roentgenol 161:577–580
Kim YM, Lee YJ, Park JH, Lee JW, Lee CH (2002) A case of idiopathic hypereosinophilic syndrome with hepatic involvement in a 5-year-old boy (in Korean). Taehan Kann Hakhoe Chi 8:321–326
Kim YK, Kim CS, Moon WS, Cho BH, Lee SY, Lee JM (2005) MRI findings of focal eosinophilic liver diseases. AJR Am J Roentgenol 184:1541–1548
Klion AD (2011) Eosinophilic myeloproliferative disorders. Hematol Am Soc Hematol Educ Prog 2011:257–263
Klion AD, Noel P, Akin C, Law MA, Gilliland DG, Cools J, Metcalfe DD, Nutman TB (2003) Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. Blood 101:4660–4666
Klion AD, Law MA, Riemenschneider W, McMaster ML, Brown MR, Horne M, Karp B, Robinson M, Sachdev V, Tucker E et al (2004) Familial eosinophilia: a benign disorder? Blood 103:4050–4055
Klion AD, Meija R, Cowen EW, Dowdell KC, Dunleavy K, Fahle GA, Holland-Thomas N et al (2013) Chronic active Epstein-Barr virus infection: a novel cause of lymphocytic variant hypereosinophilic syndrome. Blood 121:2364–2366
Kojima K, Sasaki T (1995) Veno-occlusive disease in hypereosinophilic syndrome. Intern Med 34:1194–1197
Komai K, Wada K, Sakata Y, Okawa M, Sasaki D, Yoshida Y, Shiono T, Yanagiya S, Tanaka T (1984) Eosinophilia and hepatocellular carcinoma associated with von Recklinghausen's disease (in Japanese). Nippon Shokakibyo Gakkai Zasshi 81:3019–3022
Lai M, Afdhal N, Challies T (2008) Liver masses and eosinophilia. Liver Int 28:150
Lee WJ, Lim HK, Lim JH, Kim SH, Choi SH, Lee SJ (1999) Foci of eosinophil-related necrosis in the liver: imaging findings and correlation with eosinophilia. AJR Am J Roentgenol 172:1255–1261
Leonidas DD, Elbert BL, Zhou Z, Leffler H, Ackerman SJ, Acharya KR (1995) Crystal structure of human Charcot-leyden crystal protein, an eosinophil lysophospholipase, identifies it as a new member of the carbohydrate-binding family of galectins. Structure 3:1379–1393
Leveque L, Michiels C, Collet E, Jouve JL, Lorcerie B, Lambert D (1998) Eosinophilic ascites and urticaria (in French). Rev Med Interne 19:334–337
Lim JH, Lee WJ, Lee DH, Nam KJ (2000) Hypereosinophilic syndrome: CT findings in patients with hepatic lobar or segmental involvement. Korean J Radiol 1:98–103
Lin DA, Boyce JA (2003) The idiopathic hypereosinophilic syndrome. Allergy Asthma Proc 24:417–420
Lynott A, Ravandi-Kashani F, Giles FJ (2000) Malignancy: case report: hypereosinophilia progressing to granulocytic sarcoma and acute myelocytic leukemia with trisomy 8: a case report and review of the literature. Hematology 4:487–493
Ma SK, Wong KF, Chan JK, Kwong YL (1995) Refractory cytopenia with t(1;8),+8 abnormality and dysplastic eosinophils showing intranuclear Charcot-Leyden crystals: a fluorescence in situ hybridization study. Br J Haematol 90:216–218
Matsumoto N, Yokoyama K, Nakai K, Yamamoto T, Otani T, Ogawa M, Tanaka N et al (2007) A case of eosinophilic cholangitis: imaging findings of contrast-enhanced ultrasonography, cholangioscopy, and intraductal ultrasonography. World J Gastroenterol 13:1995–1997
McElroy EA, Phyliky RL, Li CY (1998) Systemic mast cell disease associated with the hypereosinophilic syndrome. Mayo Clin Proc 73:47–50
Minola E, Sonzogni A (2005) Chronic hepatitis in hypereosinophilic syndrome: report of an unusual case. Infez Med 13:182–186
Mishchenko E, Tadmor T, Schiff E, Attias D, Polliack A (2012) Hypereosinophilia, JAK2V617F, and Budd-Chiari syndrome: who is responsible for what ? Am J Hematol 86:223–224
Miura F, Asano T, Amano H, Yoshida M, Toyota N, Wada K, Kato K, Takada T, Fukushima J et al (2009) Resected case of eosinophilic cholangiopathy presenting with secondary sclerosing cholangitis. World J Gastroenterol 15:1394–1397
Morgan-Rowe LM, Pericleus M, Luong TV, Dooley JS, Burroughs AK (2011) Hepatobiliary disease associated with hypereosinophilia: a report of two patients and a review of the literature. Dig Dis Sci 56:3689–3694
Nakamura Y, Takeuchi T, Kanaoka H, Okanue T, Kashima K (1997) A case of nodular regenerative hyperplasia of liver with idiopathic hypereosinophilic syndrome (in Japanese). Nippon Shokakibyo Gakkai Zasshi 94:44–48
Nam KJ, Jung WJ, Choi JC, Koo BS, Park BH, Lee KN, Han SY, Shin WW, Han SS (1999) Hepatic involvement in hypereosinophilia: sonographic findings. J Ultrasound Med 18:475–479
Nashed C, Sakpal SV, Shusharina V, Chamberlain RS (2010) Eosinophilic cholangitis and cholangiopathy: a sheep in wolves clothing. HPB Surg 2010:906496

Neeman A, Kadish U (1987) Marked eosinophilia in a patient with primary sclerosing cholangitis. Am J Med 83:378–379

Noel P (2012) Eosinophilic myeloid disorders. Semin Hematol 49:120–127

Noel P, Mesa RA (2013) Eosinophilic myeloid neoplasms. Curr Opin Hematol 20:157–162

Noguchi et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1739138

Oh KC, Park SH, Baek SH, Park CH, Hahn TH, Lee DK, Yeon JE, Kim JH, Byun KS, Park CK, Lee CH (2004) Idiopathic hypereosinophilic syndrome presenting as a single mass in the liver (in Korean). Korean J Gastroenterol 43:61–65

Oh SR, Kim D, Kim TH (2012) Eosinophilic cholangiopathy. Gastrointest Endosc 75:669

Oliver JW, Deol I, Morgan DL, Tonk VS (1998) Chronic eosinophilic leukemia and hypereosinophilic syndromes. Proposal for classification, literature review, and report of a case with a unique chromosomal abnormality. Cancer Genet Cytogenet 107:111–117

Pardanani A, Verstovsek S (2007) Hypereosinophilic syndrome, chronic eosinophilic leukemia, and mast cell disease. Cancer J 13:384–391

Pardanani A, Ketterling RP, Brockman SR, Flynn HC, Paternoster SF, Shearer BM, Reeder TL et al (2003) CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. Blood 102:3093–3096

Pardo-Peret P, Sans-Sabrafen J, Buxo Costa J, Rosell Costa R, Woessner S (1979) Malignant hypereosinophilic syndrome. Report of an exceptional case (in Spanish). Med Clin (Barc) 72:189–194

Park MS, Kim MJ, Lim JS, Kim SH, Kim HS, Chung YE, Kim KW (2009) Metastasis versus focal eosinophilic infiltration of the liver in patients with extrahepatic abdominal cancer: an evaluation with gadobenate dimeglumine-enhanced magnetic resonance imaging. J Comput Assist Tomogr 33:119–124

Pometta R, Callea F, Mangano M, Zuccoli E, Conte D (2000) Recurrent cholestasis and hypereosinophilia in a young female. Dig Liver Dis 32:630–633

Ranke EJ (1965) Eosinophilia and hepatocellular carcinoma. Report of a case. Am J Dig Dis 10:548–553

Ravoet M, Sibille C, Gu C, Libin M, Haibe-Kains B, Sotitiou C, Goldman M, Roufosse F et al (2009) Molecular profiling of CD3-CD4+ T cells from patients with the lymphocytic variant of hypereosinophilic syndrome reveals targeting of growth control pathways. Blood 114:2969–2983

Reyes M, Abraham C, Abedi M, Carucci LR, Schwartz LB (2005) Hypereosinophilic syndrome with hepatobiliary masses and obstructive jaundice. Ann Aller Asthma Immunol 94:25–28

Rimbrot S, Bennett M, Komorovski M, Levy Y (2001) Eosinophilic ascites as a presenting symptom of the hypereosinophilic syndrome (in Hebrew). Harefuah 140:471–472

Rodgers M, Allen J, Koea J, McCall J (2001) Eosinophilic cholangitis: a case of 'malignant masquerade'. HPB (Oxford) 3:235–239

Rosengart TK, Rotterdam H, Ranson JHC (1990) Eosinophilic cholangitis: a self-limited biliary obstruction. Am J Gastroenterol 85:582–585

Salame M, Rickaert F, Deprez C, Van Gossum A, Cremer M (1988) Hépatocarcinome et hyperéosinophilie. Acta Gastroenterol Belg L1:169–172

Scheurlen M, Mork H, Weber P (1992) Hypereosinophilic syndrome resembling chronic inflammatory bowel disease with primary sclerosing cholangitis. J Clin Gastroenterol 14:59–63

Schoonbrodt D, Horsmans Y, Laka A, Geubel AP, Hoang P (1995) Eosinophilic gastroenteritis presenting with colitis and cholangitis. Dig Dis Sci 40:308–314

Shakov R, Simoni G, Villacin A, Baddoura W (2007) Eosinophilic cholecystitis, with a review of the literature. Ann Clin Lab Sci 37:182–185

Shatery K, Sayyah A (2011) Idiopathic hypereosinophilic syndrome presenting with liver mass. Report of two cases: idiopathic hypereosinophilic syndrome and liver mass. Hepat Mon 11:123–125

Shimomura I, Takase Y, Matsumoto S, Kuyama J, Nakajima T, Maeda H, Sugase T, Hata A, Hanada M, Okuno M (1996) Primary sclerosing cholangitis associated with increased peripheral eosinophils and serum IgE. J Gastroenterol 31:737–741

Shiomi S, Kuroki T, Ueda T, Ikeoka N, Kobayashi N, Ochi H (1991) Hypereosinophilic syndrome appearing as a focal defect on liver scan. Ann Nucl Med 5:171–173

Stone RM, Gilliland DG, Klion AD (2004) Platelet-derived growth factor receptor inhibition to treat idiopathic hypereosinophilic syndrome. Semin Oncol 31(suppl 6):12–17

Suenaga N, Hayashi F, Miyauhi N, Nakamura H, Kitada O, Sugita M, Uematsu K, Kitaichi M (1991) A case of hypereosinophilic syndrome associated with pulmonary infarction and hepatic vein obstruction (Budd-Chiari syndrome) (in Japanese). Nihon Kyobu Shikkan Gakkai Zasshi 29:239–244

Sun JS, Kim JK, Won JH, Lee KM, Cheong JY, Kim YB (2005) MR findings in eosinophilic infiltration of the liver. J Comput Assist Tomogr 29:191–194

Sussman DA, Bejarano PA, Regev A (2008) Eosinophilic cholangiopathy with concurrent eosinophilic colitis in a patient with idiopathic hypereosinophilic syndrome. Eur J Gastroenterol Hepatol 20:574–577

Swaminathan GJ, Leonidas DD, Savage MP, Ackerman SJ, Acharya KR (1999) Selective recognition of mannose by the human eosinophil Charcot-Leyden crystal protein (galectin-10): a crystallographic study at 1.8 A resolution. Biochemistry 38:13837–13843

Tajima K, Katagiri T (1996) Deposits of eosinophil granule proteins in eosinophilic cholecystitis and eosinophilic colitis associated with hypereosinophilic syndrome. Dig Dis Sci 41:282–288

Take M, Sekiguchi M, Hiroe M, Oshimi K, Mizoguchi H, Kaneta Y (1990) Clinicopathological analysis of a

patient with hypereosinophilic syndrome who demonstrated disseminated eosinophilic infiltration in various organs at autopsy. Heart Vessels Suppl 5:19–23

Tefferi A (2005) Modern diagnosis and treatment of primary eosinophilia. Acta Haematol 114:52–60

Tefferi A, Pardanani A (2004) Clinical, genetic, and therapeutic insights into systemic mast cell disease. Curr Opin Hematol 11:58–64

Tefferi A, Lasho TL, Brockman SR, Elliott MA, Dispenzieri A, Pardanani A (2004) FIP1L1-PDGFRA and c-kit D816V mutation-based clonality studies in systemic mast cell disease associated with eosinophilia. Haematologica 89:871–873

Tefferi A, Patnaik MM, Pardanani A (2006) Eosinophilia: secondary, clonal and idiopathic. Br J Haematol 133:468–492

Tenner S, Roston A, Lichtenstein D, Brooks D, Herlihy E, Carr-Locke D (1997) Eosinophilic cholangiopathy. Gastrointest Endosc 45:307–309

Ung KA, Remotti H, Olsson R (2000) Eosinophilic hepatic necrosis in hypereosinophilic syndrome. J Clin Gastroenterol 31:323–327

Valente AI, Pinto HC, Ramalho F, Cabrita PF, Catarino C, Serejo F, Baptista A, Saragoca A, Bordalo O, Moura MC (1997) Idiopathic hypereosinophilic syndrome presenting as cholestatic liver disease. Eur J Gastroenterol Hepatol 9:815–817

Vandenberghe P, Wlodarska I, Michaux L, Zachee P, Boogaerts M, Vanstraelen D, Herregods MC et al (2004) Clinical and molecular features of FIP1L1-PDGFRA(+) chronic eosinophilic leukemias. Leukemia 18:734–742

Vandewiele IA, Maeyaert BM, Van Cutsem EJ, Geboes KR, Knockaert DC (1991) Massive eosinophilic ascites: differential diagnosis between idiopathic hypereosinophilic syndrome and eosinophilic gastroenteritis. Acta Clin Belg 46:37–41

Vargas CA, Maldonado O, Botero RC, Jeffers LJ, Parker T, Reddy KR, Schiff ER (1993) Budd-Chiari syndrome associated with the hypereosinophilic syndrome. Am J Gastroenterol 88:1802–1803

Villas JM, Salah SA, Tovar JC, Carreter de Granda E, Guilen FS (2003) Peripheral hypereosinophilia in a patient with hepatocellular carcinoma. South Med J 96:326–327

Walker M (1987) Idiopathic hypereosinophilia associated with hepatic vein thrombosis. Arch Intern Med 147:2220–2221

Watanabe H, Ohira H, Kuroda M, Takagi T, Ishikawa H, Nishimaki T, Kasukawa R, Takahashi K (1995) Primary sclerosing cholangitis with marked eosinophilic infiltration in the liver. J Gastroenterol 30:524–528

Weller PF, Bubley GJ (1994) The idiopathic hypereosinophilic syndrome. Blood 83:2759–2779

Weller PF, Goetzl EJ, Austen KF (1980) Identification of human eosinophil lysophospholipase as the constituent of Charcot-Leyden crystals. Proc Natl Acad Sci U S A 77:7440–7443

Weller PF, Bach DS, Austen KF (1984) Biochemical characterization of human eosinophil Charcot-Leyden crystal protein (lysophospholipase). J Biol Chem 259:15100–15105

White WL, Wahner HW, Brown ML, James EM (1981) Sequential liver imaging in the hypereosinophilic syndrome: discordant images with scintigraphy, ultrasound, and computed tomography. Clin Nucl Med 6:75–77

Won JH, Kim MJ, Kim BM, Ji H, Chung JJ, Yoo HS, Lee JT, Park YN, Hong SW (1999) Focal eosinophilic infiltration of the liver: a mimick of hepatic metastasis. Abdom Imaging 24:369–372

Yoo SY, Han JK, Kim YH, Kim TK, Choi BI, Han MC (2003) Focal eosinophilic infiltration in the liver: radiologic findings and clinical course. Abdom Imaging 28:326–332

Yu IT, Chiang H, Wang JH (1989) Hypereosinophilic syndrome with Löffler's endomyocarditis: report of an autopsy case (in Chinese). Taiwan Yi Xue Hui Za Zhi 88:740–743

Yu JS, Yoon SW, Park MS, Lee JH, Kim KW (2005) Eosinophilic hepatic necrosis: magnetic resonance imaging and computed tomography comparison. J Comput Assist Tomogr 29:765–771

Yuen BH, Reyes CV, Rawal PA, Sosman J, Jensen J (1995) Severe eosinophilia and hepatocellular carcinoma: an unusual association. Diagn Cytopathol 13:151–154

Zaheri S, Alam A, Marks AJ, Wakelin S (2010) Lymphocytic variant of hypereosinophilic syndrome. Clin Exp Dermatol 35:634–636

Zylberberg H, Valla D, Viguie F, Casadevall N (1996) Budd-Chiari syndrome associated with 5q deletion and hypereosinophilia. J Clin Gastroenterol 23:66–68

Systemic Mastocytosis and Mast Cell Tumors

83

Contents

Abstract

Mastocytosis or mast cell disease is a clonal neoplastic proliferation of mast cells that accumulate in one or more organ systems. Depending on the predominant organ and tissue involvement, mastocytosis can present in the form of various clinic-pathologic conditions, including cutaneous mastocytosis, solitary mastocytoma, systemic mastocytosis, mast cell leukemia, and mast cell sarcoma. The hepatobiliary tract can be involved by several of these disorders. In systemic mastocytosis, focal, mass-forming, and diffuse infiltrations of neoplastic mast cells are observed in the liver. In this disorder, rare hepatic manifestations further include mast cell-induced hepatic fibrosis, obliterative venous disorders, mast cell cholangiopathy, solitary mastocytoma and mast cell sarcoma, intrahepatic cholestasis, and non-cirrhotic portal hypertension. Neoplastic hepatic mast cell infiltrates in systemic mastocytosis are mainly located within sinusoids and portal tracts but may also predominate around intrahepatic bile ducts. Dense portal tract infiltration sometimes causes extensive interface lesions (aggressive mastocytosis), one possible cause of fibrosis and hepatic remodeling. The liver is also involved in mast cell leukemia, an extremely rare disorder characterized by immature mast cells, inner organ damage, and a rapidly malignant course.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_83

ICD-O Codes

Cutaneous mastocytosis (urticaria pigmentosa)	9740/1
Diffuse cutaneous mastocytosis	9740/1
Solitary mastocytoma of skin	9740/1
Extracutaneous mastocytoma	9740/1
Indolent systemic mastocytosis	9741/1
Systemic mastocytosis	9741/3
Mast cell leukemia	9742/3
Mast cell sarcoma	9740/3

Introduction

According the WHO classification (2008), mastocytosis (synonym: mast cell disease) is due to a clonal, neoplastic proliferation of mast cells that accumulate in one or more organ systems. The disorder is heterogeneous, ranging from skin lesions (cutaneous mastocytosis) that may spontaneously regress to highly aggressive neoplasms associated with short survival. Systemic mast cell disease (SM) is a neoplastic process of multilineage, myelomastocytic, or mast cell-committed hematopoietic progenitor cells (Hartmann et al. 2001; Escribano et al. 2002; Sperr et al. 2002).

The mast cell has been identified by Paul Ehrlich in 1879 (Mastzellen; Ehrlich 1878; Beaven MA 2009; Ribatti and Crivellato 2014; Ghably et al. 2015), the term relating to the German word for "overfed" (Sagher and Even-Paz 1967). However, cutaneous mast cell disease had been discovered 10 years earlier and reported using the term, urticaria pigmentosa (Nettleship and Tay 1869).

Traditionally, mast cell proliferative disorders (MCPD) are divided into *cutaneous mastocytosis* (affecting only the skin) and *systemic mastocytosis* (SM; => organs; Horny et al. 1997; Valent et al. 1999; Pardanani 2011). Mastocytosis may occur in any age, whereby cutaneous mastocytosis (urticarial pigmentosa) is predominantly a disease of children and may be present at birth, while systemic mastocytosis is generally diagnosed after the second decade of life.

One of the most important histologic features of SM is the dense infiltrate of spindle-shaped or round mast cells in the bone marrow, whereas a slight increase in diffusely scattered ("polyclonal") bone marrow mast cells (BMMC) is a reactive process not to be termed, mastocytosis. It can, e.g., also occur in multilineage myeloid malignancies, such as myeloid leukemia, myelodysplastic syndromes, and myeloproliferative syndromes. However, a variable focal infiltration of BMMC without systemic involvement (mastocytosis of bone marrow) has also been reported (reviews: Valent et al. 1999; Pardanani 2012). In a significant subgroup of patients (10–35 %), an associated clonal hematologic non-mast cell lineage disorder (AHNMD) occurs; AHNMDs have been classified according to WHO criteria (see below). Most AHNMDs resemble myeloid malignancies such as AML, myeloproliferative disorders, or myelodysplastic syndromes, and patients with SM-AHNMD have a less favorable prognosis concerning survival when compared with indolent SM (Sperr et al. 2002; Stoecker and Wang 2012). SM has also been observed together with primary thrombocythemia (Le Tourneau et al. 1991). In most instances, SM is a disease of adults, but pediatric cases have been reported (Hartmann and Metcalfe 2000; Chemli et al. 2003), and SM can present as a congenital disorder (Date et al. 1989).

Classification of Mastocytosis

Several systems to classify mastocytosis have been proposed (Travis et al. 1988; Metcalfe 1991; Horny et al. 1993; Valent et al. 2001a; Arock and Valent 2010; Valent and Horny 2011; Chiu and Orazi 2012). Part of the classifications are listed in Table 1.

In addition to these clinical-morphologic classifications, attempts are undertaken to classify SM and related disorders according to mutational patterns of key genes. In fact, a partial molecular classification is now emerging, i.e., Asp816Val c-kit+, FIP1L1-PDGFRA +, and molecularly

Table 1 Classification of mastocytosis/mast cell diseases

(A) 2008 WHO classification of mast cell diseases (modified; comment: Sanchez-Muñoz et al. 2011)	
Cutaneous mastocytosis (including urticarial pigmentosa)	ICD-O code 9740/1
Diffuse cutaneous mastocytosis	ICD-O code 9740/1
Indolent systemic mastocytosis (ISM)	ICO-O code 9741/1
Systemic mast cell disease with associated clonal hematological non-mast cell lineage disease (SM-AHNMD)	ICD-O code 9741/3
Aggressive systemic mastocytosis (ASM)	ICD-O code 9741/3
Mast cell leukemia	ICD-O code 9742/3
Mast cell sarcoma	ICD-O code 9742/3
Extracutaneous mastocytoma	ICD-O code 9740/1
(B) Classification of mastocytosis as proposed by Travis et al. (1988) **and modified by Metcalfe (1991)**	
I. Indolent mastocytosis	
A. Skin only	
Urticaria pigmentosa (UP)	
Diffuse cutaneous mastocytosis	
B. Systemic	
Marrow	
Gastrointestinal tract with/without urticaria pigmentosa	
II. Mastocytosis with an associated hematologic disorder (± *UP*)	
III. Mast cell leukemia	
IV. Lymphadenopathic mastocytosis with eosinophilia (= *aggressive mastocytosis*; ± *UP*)	
(C) Classification of mastocytosis as proposed by et al. (1993)	
I. Cutaneous mastocytosis	
A. Urticaria pigmentosa (UP)	
B. Diffuse cutaneous "erythrodermic" mastocytosis	
C. Telangiectasia macularis eruptiva perstans	
D. Solitary mastocytoma	
II. Systemic (*benign or indolent*) *mastocytosis*; *usually with skin lesions of UP but no associated malignant hematologic disorder* (*bone marrow involvement very common*)	
III. Malignant (*aggressive*) *mastocytosis*; *usually without skin lesions of UP but associated with malignant hematologic disorders*	
IV. Mast cell leukemia	
V. Mast cell sarcoma	
(*continued*)	

Table 1 (continued)

(D) Classification of mastocytosis as proposed by Valent et al. (2001a)
Cutaneous mastocytosis
Urticaria pigmentosa (UP; maculopapular cutaneous mastocytosis; MPCM)
Subvariants:
Typical UP
Plaque form
Nodular
Telangiectasia macularis eruptiva perstans (TMEP)
Diffuse cutaneous mastocytosis (DCM)
Mastocytoma of the skin
Indolent systemic mastocytosis (*ISM*)
Provisional subvariants
(Isolated) bone marrow mastocytosis (BMM)
Smoldering systemic mastocytosis
Systemic mastocytosis with an AHNMD (*SM-AHNMD*)
Subvariants
SM-MDS
SM-MPS
SM-AML
SM-NHL
Aggressive systemic mastocytosis (*ASM*)
Subvariant
Lymphadenopathic mastocytosis with eosinophilia
Mast cell leukemia (*MCL*)
Aleukemic subvariant
Mast cell sarcoma
Extracutaneous mastocytoma

undefined cases, and it is expected that such molecular classifications are therapeutically relevant (Tefferi and Pardanani 2004).

Systemic Mastocytosis and Its Variants: A Brief Overview

Systemic mastocytosis (*SM*) and its variants can induce a common clinical syndrome called *systemic mast cell activation syndrome* (*SMCAS*), a spectrum of organ and tissue manifestations caused by activated mast cells and their released products. In principle, SMCAS comprises disorders characterized by the accumulation of genetically altered mast cells and/or abnormal release of

these cells' mediators, potentially affecting the function of numerous cells and tissues (review: Molderings et al. 2011). *Indolent systemic mastocytosis* (ISM) is a disorder characterized by fulfilled SM criteria, with a modestly elevated burden of mast cells, an indolent clinical course, and a good prognosis, in the absence of mast cell leukemia and AHNMD. Organ function impairment with C signs is lacking, although mast cell infiltration in several organs, including the liver, occurs. Circulating KIT D816V mutation-positive non-mast cells in peripheral blood are a characteristic feature of indolent systemic mastocytosis (Kristensen et al. 2012). In contrast, *aggressive systemic mastocytosis* shows C-findings as a sign of organ function impairment, due to infiltration by neoplastic mast cells and secretion of their products (reviews: Horny and Valent 2001; Patnaik et al. 2007; Pagano et al. 2008; Arock and Valent 2010; Ozdemir et al. 2011; Quintas-Cardama et al. 2011; Andersen et al. 2012; Pardanani 2012; Gotlib et al. 2013). In particular, patients exhibit one of the following: (1) abnormal myelopoiesis with significant blood count abnormalities; (2) hepatomegaly with impairment of liver function (often with ascites), (3) large osteolyses; (4) malabsorption due to GIT infiltration; (5) splenomegaly with hypersplenism; or (6) life-threatening impairment of organ function in other organ systems (Valent et al. 2001a, 2003). Aggressive systemic mastocytosis can be associated crystal-storing histiocytosis storing Charcot-Leyden crystals (Alayed et al. 2010). *Smoldering mastocytosis* is a novel subtype of systemic mastocytosis, characterized by the lack of aggressive disease, absence of associated hemopoietic neoplasias, and slow progression of disease. These patients show a high burden of mast cells, a hypercellular bone marrow, and organomegaly (Valent et al. 2002a). In some patients with smoldering systemic mastocytosis, cryptic life-threatening crises may occur (Shah et al. 2012). *Occult mastocytosis* has, e.g., been observed in AML with a t(8;21) translocation, the neoplastic mast cells being in part spindle shaped and showing an aberrant phenotype, including co-expression of tryptase, chymase, c-kit, and CD25 (Bernd et al. 2004).

Systemic mastocytosis with an AHNMD (SM with an *a*ssociated clonal *h*ematologic *n*on-*m*ast cell lineage *d*isease; SM-AHNMD; Stoecker and Wang 2012) denotes SM disorders associated with several types of hemopoietic or lymphoid neoplastic diseases. Thus, AHNMD are categorized as MDS (myelodysplasia), MPS (myeloproliferative syndrome), AML (acute myeloid leukemia), NHL (Hauswirth et al. 2008a), or malignant histiocytosis (Rudski et al. 2011). Most of the cases involve a myeloid progenitor cell, and SM is usually diagnosed concurrently with the myeloid malignancies. Part of the patients with SM-AHNMD exhibit activating c-kit mutations (Pullarkat et al. 2003).

Recently, a further group of mast cell disorders has been described under the term, *myelomastocytic overlap syndromes* (Valent et al. 2001b). These patients show large numbers of very immature mast cell lineage cells (metachromatically granulated blast-like cells), but the criteria to diagnose mastocytosis are not met. The patients have advanced myeloid neoplasms (myelodysplastic syndromes or myeloproliferative syndromes with blast cell increase, or AML) and variably suffer from mediator-related symptoms. These disorders may mimic mast cell leukemia or basophilic leukemia, but in contrast to basophilic leukemia, the cells involved are markedly Kit positive and tryptase positive, and in contrast to mast cell leukemia, CD25 expression and the c-kit Asp-816-Val mutation are lacking (Valent et al. 2001b). A further novel entity is myelomastocytic leukemia, a myeloid neoplasm characterized by partial differentiation of mast cell lineage cells (Valent et al. 2002b).

Mast cell leukemia is a manifestation of high-grade (malignant) mast cell disease with a significant number of leukemic mast cells circulating in the peripheral blood (Valent et al. 2001a; Georgin-Lavialle et al. 2013). Mast cell leukemia accounts for less than 1 % of all mastocytoses (review: Georgin-Lavialle et al. 2013). Mast cell leukemia is a rapidly fatal disease in contrast to non-leukemic variants; it is characterized by a substantial increase of atypical mast cells in the

peripheral blood, diffuse infiltration with atypical mast cells in the bone marrow, a strong association with peptic ulcer disease, marked constitutional symptoms, and hepatosplenomegaly (Travis et al. 1986). Systemic mastocytosis can undergo progressive evolution into fatal mast cell leukemia (Gülen et al. 2012). Aleukemic mast cell leukemia has replaced the former "malignant mastocytosis" and is an extremely rare form of leukemia (Horny et al. 2002). The relationship between mast cell leukemia and bone marrow progenitor cells is complex and not yet fully clarified. It has, e.g., been shown that mast cell leukemia can evolve from refractory anemia with excess of blasts in transformation (RAEB-T/5q syndrome), showing blast cells of the mast cell lineage (Sugita et al. 1996). Recently, a variant of mast cell leukemia with more mature neoplastic cells and a more favorable course has been defined as chronic mast cell leukemia (Cehreli et al. 2014; Valent et al. 2014). Chronic mast cell leukemia can exhibit KIT S476I and lacks inner organ damage. A rare transition form of immature mast cell leukemia is myelomonocytic leukemia (Horny et al. 2014).

It is known that up to one third of the patients with SM have some degree of peripheral blood and/or bone marrow eosinophilia, but SM is sometimes associated with an hypereosinophilia syndrome (HES) in its proper sense (*eosinophilic disorders and SM*/*SMCD*; Miranda et al. 1994; McElroy et al. 1998). Based on the detection of the index c-kit gene mutation (Asp816Val), it has been found that, in the SM/HS combination, eosinophils are derived from the neoplastic clone in some patients (Pardanani et al. 2003c). Therefore, the term *SM*/*SMCD-eos* has been proposed to denote this spectrum of lesions. An interesting group of lesions is formed by a subset of patients who have a myeloproliferative variant of idiopathic hyper-eosinophilic syndrome associated with increased bone marrow mast cells, tissue fibrosis, poor prognosis, and imatinib responsiveness. In these patients, serum tryptase levels are elevated, and this phenomenon is a sensitive marker of this myeloproliferative variant of HS, in addition showing the presence of the recently described fusion of the Fip1-like 1 (FIP1L1) gene to the platelet-derived growth factor receptor alpha (PDGFRA) gene (Klion et al. 2003). The fusion of the two genes results from an approximately 800-kb interstitial chromosomal deletion that includes the cysteine-rich hydrophobic domain 2/CHIc2 locus. FIP1L1-PDGFRA is a constitutively activated tyrosine kinase that transforms hematopoietic cells and is a therapeutic target for imatinib mesylate. The deletion of CHIC2, located to chromosome 4q12, is a surrogate marker of the FIP1L1-PDGFRA fusion, and this deletion has been found in HES/SM (Pardadani et al. 2003b). More recently, FIP1L1-PDGFRalpha has been directly detected in SMCD associated with HES (Gilliland et al. 2004; Tefferi et al. 2004), and, together with c-kit mutations, this fusion gene has been proposed for a partial molecular classification of SMCD (Tefferi and Pardanani 2004).

Tumorous growth of neoplastic mast cells (*mastocytoma*) is almost exclusively found in the skin and is very rare in other organ sites (Valent et al. 2001a).

Mast cell sarcoma is a very rare disorder. It is defined by a locally destructive (sarcoma-like) growth of a tumor consisting of highly atypical mast cells without systemic involvement, but secondary generalization can occur (Ryan et al. 2013). Bone marrow mastocytosis can be associated with immature extramedullary mast cell sarcoma (Sotlar et al. 1997).

Liver Involvement in Mastocytosis

Introduction

In SM, diffuse involvement of many organs and tissue occurs, including the skin, bone, lymph nodes, respiratory tract, gastrointestinal tract, spleen, and liver. Gastrointestinal manifestations are observed in at least 20 % of patients with SM (Mutter et al. 1963; Webb et al. 1982; Tharp 1985; Debeuckelaere et al. 1991; Metcalfe 1991; Karnam and Rogers 1999; Jensen 2000; Tharp and Chan 2003; Akin and Metcalfe 2004; Kirsch et al. 2008). Involvement of the alimentary canal may result in abdominal pain, diarrhea, peptic

Table 2 Spectrum/phenotypes of liver involvement in systemic mastocytosis

Hepatic mast cell infiltration as single change (slight, moderate, severe; severe with interface lesions = histologically "aggressive mastocytosis")
Hepatic mast cell infiltration with chronic fibrosing liver disease or cirrhosis
Mast cell-induced hepatic obliterative venous disorders with/without NRH (obliterative portal venopathy and hepatic venopathy)
Mast cell cholangiopathy
Mastocytoma of the liver
Mast cell sarcoma of the liver
Intrahepatic cholestasis
Non-cirrhotic portal hypertension

ulcer disease, and, in severe cases, malabsorption. GIT and other organ manifestations can be associated with hemorrhagic diathesis, which may complicate liver biopsy in SM (Adler et al. 1985). The manifestations of SM in the liver comprise several more or less defined pathologic and pathophysiologic constellations (Table 2). In addition to alterations caused by the mere presence of a tumorous infiltrate, the liver may also be involved in systemic mast cell activation syndrome (SMCAS). Patients with SMCAS have shown an elevation of plasma cholesterin in 75 %, elevations of serum transaminases and bilirubin in 40 % and 36 %, respectively, and elevation of hepatomegaly in 34 % (Alfter et al. 2009).

Clinical and Imaging Features

Clinically and radiologically, SM causes hepatomegaly (sometimes massive) with or without ascites in up to 77 % of the patients (Rohner and Rodermund 1981; Webb et al. 1982; Yam et al. 1986; Travis et al. 1988; Biersack 1988; Horny et al. 1989; Chemli et al. 2003; Kupfer et al. 2007), and liver involvement is sometimes evidenced by elevated serum alkaline phosphatase and, interestingly, in signs of portal hypertension in a subset of patients. Massive diffuse mast cell infiltration of the liver can cause cholestasis (Kupfer et al. 2007) or even hepatic failure (Wendum et al. 2004). Focal involvement of the liver presents as ill-defined areas of low attenuation in imaging (Kennedy et al. 1999). What is the prevalence of liver disease in SM ? In a large study involving 41 patients, a combination of clinical, radiologic, and serum biochemical criteria resulted in 61 % of the patients with SM having liver involvement. This included hepatomegaly in 24.4 %, ascites in 7 %, and elevated serum enzymes in 54 % (Mican et al. 1995).

SM rarely presents non-cirrhotic portal venous hypertension, complicated by esophageal variceal bleeding (NCPH; Capron et al. 1978; Grundfest et al. 1980; Sawers et al. 1982; Le Jeunne et al. 1986; Bonnet et al. 1987; Narayanan et al. 1989; Vincenzi et al. 1992; Fonga-Djimi et al. 1995; Kyriakou et al. 1998). This may result in shunting of mast cell-rich splenic blood into the systemic circulation (Sumpio et al. 1988). It is thought that a hepatic sinusoidal block caused by perisinusoidal fibrosis is the main pathogenic mechanism, but an impairment of microvascular liver blood flow owing to mast cell infiltration has also been considered (Grundfest et al. 1980). Furthermore, it has been proposed that the development of portal and/or hepatic venopathy with or without associated nodular regenerative hyperplasia of the liver can cause NCPH (Mican et al. 1995), because such changes have been observed in other disorders accompanied by NCPH, including myeloproliferative disorders (Wanless et al. 1980). NCPH in SM has been reported to simulate autoimmune cholangiopathy (Kyriakou et al. 1998).

Liver Pathology in Systemic Mastocytosis

Within the normal liver, mast cells are relatively scarce, with a density of about 1–2 to 3.9 mast cells per square millimeter in humans (Farrell et al. 1995; Armbrust et al. 1997). It has been reported that normal liver mast cells are mainly from the MC-TC type (Gulubova 2003). The morphology of liver involvement in SM as assessed by liver biopsy or after OLT has been reported several times (Hissard et al. 1950; Ende

and Chernis 1953; Mutter et al. 1963; Bureau et al. 1965; Burgoon et al. 1968; Campbell et al. 1979; Fishman et al. 1979; Hirschowitz and Groarke 1979; Bredfeldt et al. 1980; Grundfest et al. 1980; Abraham et al. 1992; Safyan et al. 1997; Mican et al. 1995; Maruyama et al. 1998; Pauls et al. 1999). Liver involvement in SM is dominated by mast cell infiltrations of variable densities.

Histologically, one pattern of involvement in SM presents as a diffuse infiltration of hepatic tissue, but predominantly the portal tracts, by abnormal mast cells, with or without associated changes (Demis 1963; Sawers et al. 1982; Ghandur-Mnyamneh and Gould 1985; Yam et al. 1986; Horny et al. 1989; Mican et al. 1995). The mast cells are frequently spindle shaped and hypogranular, thus requiring special stains as discussed above (Maruyama et al. 1998). In part of the patients, the mast cell infiltrate forms clusters of cells (Kyriakou et al. 1998). Mast cell numbers in liver involvement have been quantified and shown to be clearly higher than in normal livers or those with fibrotic changes or cirrhosis (Horny et al. 1989), even though a marked increase in mast cell numbers may very occasionally occur in some other liver disorders (Murata et al. 1973; Bardadin and Schuer 1986). The infiltrate is sometimes mixed, but there are situations where mast cells are the predominant infiltrating cell. In a mixed infiltration, toluidine blue staining will easily identify the cell of interest and has been shown to be crucial to detect mast cells otherwise masked by other cells (Mican et al. 1995). The mast cell nature of spindle cells localized to the portal tract in SM has been proved by the use of electron microscopy (Ghandur-Mnyamneh and Gould 1985). In some of the patients, mast cells hug bile ducts (ductocentric mast cell infiltrates). Although a portal tract infiltration may be impressive, intralobular infiltrates of mast cells are also frequently discernible, chiefly involving the sinusoids (more so in the periportal zone 1), amounting to 96 % of the cases in one study (Mican et al. 1995). Within portal tract spaces, an angiocentric localization of mast cells may be in evidence. Severe degrees of portal tract mast cell infiltration cause sometimes extensive interface lesions ("aggressive mastocytosis"). In regard to accompanying inflammatory changes, chronic portal inflammation was observed in all cases, and 60 % of biopsies showed accompanying eosinophilia of portal tracts (Mican et al. 1995). A usually low-grade eosinophil component in the infiltrates is recognized, but this may be expected to be more significant in those cases of SM associated with hypereosinophilia (see above). Marked infiltration of the liver by abnormal cells of the mast cell lineage have also been reported for mast cell leukemia (Yoshida et al. 2009) and aleukemic mast cell leukemia/malignant mastocytosis (Horny et al. 2002). In mast cell leukemia, extramedullary leukemic infiltrates are most commonly found in the spleen, liver and lymph nodes (Valentini et al. 2008).

Immunohistochemically, infiltrating mast cells can be detected by immunoreactivity for c-KIT (Wendum et al. 2004). Detection of aberrant expression of CD25 and CD2 on the surface of neoplastic mast cells but not their normal counterparts is an important diagnostic element (Sanchez-Munoz et al. 2011). CD203c is overexpressed in neoplastic mast cells in SM and is upregulated upon IgE receptor cross-linking (Hauswirth et al. 2008b). Immunoreactivity for CD25 in mast cells of the GIT is regarded as specific for SM (Hahn and Hornick 2007).

Liver Involvement in Mast Cell Leukemia

Mast cell leukemia is an extremely rare disorder characterized by immature mast cell forms, inner organ damage, and a rapidly malignant course (Lu et al. 2014). A variant, chronic mast cell leukemia has a more favorable biology and lacks inner organ damage (see above). In the setting of mast cell leukemia, neoplastic mast cells involve the liver circulation and may settle within sinusoids and portal tracts. Liver infiltration with abnormal cells can be massive and is then associated with marked infiltration of the bone marrow, spleen, and lymph nodes. At autopsy, the liver sinusoids, mainly in lobular zone 3, and central veins are clogged with mast cell tryptase-positive

cells, causing rapidly progressive non-cirrhotic portal hypertension (Yoshida et al. 2009). As in other organs, liver cells undergo damage induced by the neoplastic cells.

Mastocytoma of the Liver

Exceptionally, mast cell accumulation in the liver can result in a tumorous lesion, i.e., mastocytoma of the liver. In one report, a mass located to the quadrate liver lobe and isodense with liver substance on native CT imaging had a diameter of up to 3 cm. Needle biopsy of the lesion induced an anaphylactoid reaction (Klose and Skora 1990).

Liver Fibrosis in Systemic Mast Cell Disease

Mast cell infiltration in SM can be associated with liver fibrosis (Sawers et al. 1982; Brunning et al. 1983; Ghandur-Mnyamneh and Gould 1985; Yam et al. 1986; Horny et al. 1989; Mican et al. 1995) and has been reported to cause liver cirrhosis (Ghandur-Mnyamneh and Gould 1985; Horny et al. 1989), but no patient with cirrhosis has been detected in a large study of 41 patients (Mican et al. 1995). In the latter study, increased portal fibrosis was seen in 64 % of the biopsy specimens and correlated with mast cell infiltration and portal infiltration, whereas extensive bridging fibrosis was seen in 12 % (Mican et al. 1995). The pathogenesis of liver fibrosis in mastocytosis has not yet been clarified, but fibrokines such as TGF-beta and basic fibroblast growth factor secreted by mast cells may play a role (Choi and Claman 1987; Levi-Schaffer and Weg 1997; Marone et al. 1997; Li and Baek 2002; Baek et al. 2002). Mast cells can interact with myofibroblasts thought to play a role in the production of extracellular matrix (Akiyoshi and Terada 1998; Jeong et al. 2002), and it has also been shown that murine mast cells directly synthesize basement membrane components involved in early fibrosis responses (Thompson et al. 1991). For the pathogenesis of hepatic fibrosis, it is also of interest to note that human and rat hepatic stellate cells (HSC) can produce stem cell factor, a possible mechanism for fibrogenic mast cell recruitment (Gaca et al. 1999). On the other hand, mast cells and histamine did not appear to exert an important role in the induction of fibrosis under experimental conditions using mast cell-deficient Ws/Ws rates (Okazaki et al. 1998). What may furthermore influence the development of a fibrotic response is the capability of mast cells to induce angiogenesis; this has, e.g., been demonstrated in the bone marrow of patients with SM (Wimazal et al. 2002).

Mast Cell-Induced Obliterative Hepatic Venous Disorders

Mast cell hepatopathy is rarely associated with in part obliterative hepatic venous changes (*portal obliterative venopathy and/or veno-occlusive-like disease/hepatic venopathy*), possibly causing nodular regenerative hyperplasia (NRH) of the liver in a minority of patients (Mican et al. 1995). Histologically, portal venopathy in SM shows prominent hypertrophy of smooth muscle around markedly narrowed portal venous branches, whereas hepatic venopathy is visualized in the form of terminal veins showing almost complete occlusion by loose connective tissue infiltrated by mast cells, eosinophils, and lymphocytes (Mican et al. 1995).

Cholangiopathy and Chronic Cholangitis in SM ("Mast Cell Cholangiopathy")

Liver involvement in SM can result in a presentation indistinguishable from primary sclerosing cholangitis, associated with periductal/ductocentric mast cell infiltration. This lesion has been proposed to be termed *mast cell cholangiopathy* (Baron et al.1995). In SM cases presenting with *intrahepatic cholestasis*, mast cell infiltration of portal tracts, periductal portal tract edema, epithelial irregularities of the interlobular bile ducts, and centrizonal cholestasis have been noted (Safyan et al. 1997), suggesting an obstructive mechanism at the level of small intrahepatic bile ducts. It may be assumed that abnormal mast cells forming a

ductocentric infiltrate can damage cholangiocytes by secreted cytokines and other mast cell-derived components. Mast cell cholangiopathy can lead to bile duct fibrosis and show ductal changes compatible with those found in primary sclerosing cholangitis (Baron et al. 1995; Marbello et al. 2004; Papachristou et al. 2004).

Non-cirrhotic Portal Hypertension in SM

Few informations are still available for liver pathology in case of *SM-induced NCPH*. NCPH can be caused by dense hepatic infiltrates in systemic mastocytosis (Capron et al. 1978) or in mast cell leukemia (Yoshida et al. 2009). In one case, liver biopsy disclosed dense fibrosis of hepatic arterial and portal venule walls, resulting in complete obstruction of some portal radicles, and focal fibrosis of outflow venules and peliosis were also present (Bonnet et al. 1987).

The Liver in Mast Cell Activation Syndrome

Mast cell activation syndrome (MCAS) occurs in a number of different clinical conditions, such as IgE-dependent allergies, other forms of inflammatory reactions, and neoplastic mastocytosis (reviews: Haenisch et al. 2012; Valent 2013). The clinical presentation spectrum of MCAS is broad and ranges from mild symptoms and signs to a life-threatening disorder induced by mast cell products and depending on the number of degranulating mast cells and genetic predisposition factors. MCAS is classified into (1) primary MCAS in which KIT-mutated clonal mast cells are detectable, (2) secondary MCAS based on inflammatory and in particular IgE-mediated disorders, and (3) idiopathic MCAS. The liver may be involved in MCAS. In one study, an elevation of plasma cholesterol was found in 75 % of the patients, and elevations of transaminases and bilirubin were present in 40 % and 36 % of the patients, respectively. Thirty four percent had hepatomegaly (Alfter et al. 2009).

Differential Diagnosis: Mast Cells in the Liver in Disorders Other Than Systemic Mastocytosis

Mast cells form an important hepatic cell population involved in liver homeostasis and in several hepatic disorders (Benyon 1999). Mast cells have been shown to play a role in fibrotic and stromal reactions for several hepatic lesions, including acute inflammation (Grizzi et al. 2002), chronic inflammatory hepatobiliary diseases (Tsuneyama et al. 1999; Matsunaga and Terada 2000), hepatic fibrosis and cirrhosis (Kim 1971; Murata et al. 1973; Farrell et al. 1995; Armbrust et al. 1997; Yamashiro et al. 1998; Matsunaga et al. 1999; Sugihara et al. 1999), primary biliary cirrhosis (Nakamura et al. 1997), secondary biliary cirrhosis in rats (Rioux et al. 1996), granulomatous hepatitis (Celasun et al. 1992), hepatic radiation damage (Peng et al. 1994), the regulation of the peribiliary vascular plexus (Koda et al. 2000), perimetastatic reactions (Gulubova 2003), stroma and capillarization of HCC and intrahepatic CCC (Terada and Matsunaga 2000; Grizzi et al. 2003), sclerosing hepatic hemangiomas (Makhlouf and Ishak 2002), biliary atresia (Uddin Ahmed et al. 2000), and chronic liver graft rejection (O'Keeffe et al. 2002). Mast cell increase was more pronounced in primary biliary cirrhosis than in other forms of chronic liver disease (Farrell et al. 1995). Mast cells can also constitute a major cellular component of the infiltrate in inflammatory pseudotumors of the liver, hence the previous and now obsolete term, "solitary mast cell tumor" (Krech et al. 1995).

Differential diagnostically, most of these lesions will not be confounded with liver involvement in SM. However, difficulties may arose in chronic and in particular sclerosing cholangitis with mast cell infiltrates, because this may histologically mimic mast cell cholangiopathy.

The Phenotype of Normal Mast Cells and of Mast Cells in Systemic Mastocytosis

Mature normal mast cells are easily identifiable in hematoxylin and eosin-stained sections, but the reliable detection of immature forms requires

special staining techniques, such as Wright-Giemsa stain, toluidine blue stain, alcian blue/safranin stains, Unna's method (polychrome methylene blue with differentiation in glycerol ether), and other stains (Graham et al. 1994; Tomasi et al. 2003). It has also been emphasized that mast cells form a heterogeneous group of cells in regard to their formalin sensitivity (Marshall et al. 1987). Mast cells are identifiable by the use of cyto-/histochemistry (naphthol-AS-D chloroacetate esterase reaction; Horny et al. 1997) and immunohistochemistry with monoclonal antibodies directed against tryptase (Walls et al. 1990; Yamashiro et al. 1998). Human mast cells are categorized into mast cells positive for tryptase (MC-T) and those positive for both tryptase and chymase (MC-TC). MC-T are mainly mucosal-type mast cells, whereas connective tissue-type mast cells are chiefly MC-TC. Ultrastructurally, MC-T have granules with discrete scrolls and particulate and beaded pattern, while MC-TC have granules with finely granular or particulate material (Gulubova 2003). Normal mast cells express CD117 (c-kit/KIT; the receptor for stem cell factor) and CD68 (a marker for activated macrophages) but not CD25 or CD2 (Horny et al. 1990; Li et al. 1996; Escribano et al. 1999; Jordan et al. 2001; review: Tefferi and Pardanani 2004).

Mast cells from patients with SM display unique morphologic properties and aberrant immunophenotypic characteristics as compared with normal mast cells (Li et al. 1996; Horny and Valent 2001; Li 2001). Based on cytomorphologic features, four distinct cell types have been recorded, i.e., (1) typical tissue mast cells; (2) atypical mast cells exhibiting elongated cytoplasmic extensions, oval nuclei, and a hypogranular cytoplasm (atypical mast cells type I); (3) atypical mast cells with bi-or multilobed nuclei (atypical mast cells type II); and (4) metachromatically granulated blast-like cells ("metachromatic blasts"). Patients having more than 5 % atypical mast cells type II and/or "metachromatic blasts" showed a significantly shorter survival, suggesting that mast cell typing is a prognosticator in SM (Sperr et al. 2001). In contrast to normal mast cells, neoplastic mast cells in mastocytosis express the T-cell-associated antigen CD2 (Horny and Valent 2002), and they also express CD117/Kit and bcl-x(L) (Jordan et al. 2001). SM mast cells show aberrant expression of CD30 (Sotlar et al. 2011) and of CD25 (IL-2 receptor alpha chain) and abnormally high levels of the CD11c and CD35 complement receptors, the CD59 complement regulatory molecule, the CD63 lysosomal membrane antigen, and the CD69 early-activation antigen. In addition, SM mast cells express abnormally low levels of CD117 (Escribano et al. 2004; Lim et al. 2008). Of relevance for the tissual distribution of mast cells is the finding that neoplastic mast cells express the homing-associated cell adhesion molecule, CD44/HCAM (Horny et al. 1996). These distinct features are of relevance for the assessment of tissue involvement in SM, and strategies for immunophenotyping/quantitative multiparametric flow cytometry have recently been proposed by the Spanish Network on Mastocytosis (REMA; Escribano et al. 2004). In addition, soluble stem cell factor receptor (CD117) and CD25 levels in the plasma have been demonstrated to be surrogate markers of disease severity in mastocytosis (Akin et al. 2000). The complex function of normal and neoplastic mast cells is regulated by distinct transcriptional networks (Takemoto et al. 2008).

Molecular Features in Mastocytosis

A series of laboratory investigations has revealed that mast cell disease is a clonal stem cell disorder, with pathogenetically relevant mutations of the c-KIT being in the center of pathogenic pathways (Tefferi and Pardanani 2004; Sadrzadeh et al. 2011). Malignant variants of SM are therefore considered to be c-kit-driven disorders (Furitsu et al. 1993).

Most mastocytosis cases are associated with somatically acquired activating mutations of the tyrosine kinase domain of the KIT receptor for stem cell factor/SCF (reviews: Fuller 2012; Verstivsek 2013). Most of the patients with SM display the c-kit AL (Asp816Val; KITD816V) mutation, and this mutation is associated with advanced age, an aggressive clinical course,

increased bone marrow mast cell content, and sometimes CML (Valent et al. 2001a; Sotlar et al. 2002; Pardanani et al. 2003a, b; Laine et al. 2011). The somatic D816V KIT mutation has also been found in adult-onset familial mastocytosis (Zanotti et al. 2013). The KITD816V mutation results in ligand-independent activation of KIT tyrosine kinase and provides relative resistance to the tyrosine kinase inhibitor imatinib. The KITD816V mutation accounts for about 95 % or more of adults with SM. Rare other mutations include D816Y, D816H, and D816F. In children with mast cell disorders, the KITD816V mutation accounts for only about one third of cases of cutaneous mastocytosis. The mechanism leading from KIT mutations to mast cell disease involves a pathway where constitutively active mutant D816Vkit, even though not a transformant, induced increased differentiation of cells along cell lineages in the absence of factors and increased differentiation along the mast cell lineage in the presence of stem cell factor (SCF) (Ferrao et al. 2003). KIT regulation of mast cell proliferation has been linked to the activation of phosphatidylinositol 3-OH kinase/PI3K, in that the activating D816V mutation causes a robust activation of PI3K signaling. The proliferative mast cell response induced by the activation of this pathway is linked to PTEN downregulation (Furumoto et al. 2011). Oncogenic KIT signals are operational on endolysosomes and endoplasmic reticulum in order to promote neoplastic mast cell proliferation (Obata et al. 2014).

KIT gene mutations are a major driving force for common forms of SM, but the mechanisms involved in other phenotypes of mast cell disease are less clear. TET2, DNMT3A, and ASXL1 mutations are also present in mastocytosis and may have an impact on the biology of disease (Traina et al. 2012). It has been shown that TET2 mutations associate with aggressive forms of the disease. In murine mast cells, TET2 loss cooperates with c-KITD816V to transform mast cells (Soucie et al. 2012). In patients with SM-AHNMD, mutations other than those found in classical SM have been identified. SM associated with AML showed the RUNX1-RUNX1T fusion gene, while SM associated with myeloproliferative neoplasms revealed JAK2V617F. In patients with mast cell proliferation and eosinophilia, the FIP1L1-PDGFRA fusion gene has been found.

References

Abraham EK, Augustine J, Amma S, Nair K (1992) Malignant systemic mastocytosis. Indian J Cancer 29:192–197

Adler SN, Klein RA, Lyon DT (1985) Bleeding after liver biopsy in a patient with systemic mastocytosis and malabsorption. J Clin Gastroenterol 7:350–353

Akin et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/10942367

Akin C, Metcalfe DD (2004) Systemic mastocytosis. Annu Rev Med 55:419–432

Akiyoshi H, Terada T (1998) Mast cell, myofibroblast and nerve terminal complexes in carbon tetrachloride-induced cirrhotic rat livers. J Hepatol 29:112–119

Alayed KM, Alabdulaali MK, Alkhairy KS, Elnour S, Alhajjaj A (2010) Aggressive systemic mastocytosis with Charcot-Leyden crystals-associated crystal storing histiocytosis in bone marrow. Pathology 42:85–87

Alfter K, von Kügelgen I, Haenisch B, Frieling T, Hülsdonk A, Haars U, Rolfs A, Noe G et al (2009) New aspects of liver abnormalities as part of the systemic mast cell activation syndrome. Liver Int 29:181–186

Andersen CL, Kristensen TK, Severinsen MT, Moller MB, Vestergaard H, Bergmann OJ et al (2012) Systemic mastocytosis – a systematic review. Dan Med J 59: A4397

Armbrust T, Batusic D, Ringe B, Ramadori G (1997) Mast cells distribution in human liver disease and experimental rat liver fibrosis. Indications for mast cell participation in development of liver fibrosis. J Hepatol 26:1042–1054

Arock M, Valent P (2010) Pathogenesis, classification and treatment of mastocytosis: state of the art in 2010 and future perspectives. Expert Rev Hematol 3:497–516

Baek JY, Tefferi A, Pardanani A, Li CY (2002) Immunohistochemical studies of c-kit, transforming growth factor-beta, and basic fibroblast growth factor in mast cell disease. Leuk Res 26:83–90

Bardadin KA, Schuer PJ (1986) Mast cells in acute hepatitis. J Pathol 149:315–325

Baron TH, Koehler RE, Rodgers WH, Fallon MB, Ferguson SM (1995) Mast cell cholangiopathy: another cause of sclerosing cholangitis. Gastroenterology 109:1677–1681

Beaven (2009) http://www.ncbi.nlm.nih.gov/pubmed/19130582

Benyon RC (1999) Mast cells in the liver. Clin Exp Allergy 29:155–158

Bernd HW, Sotlar K, Lorenzen J, Osieka R, Fabry U, Valent P, Horny HP (2004) Acute myeloid leukaemia with t(8; 21) associated with "occult" mastocytosis.

Report of an unusual case and review of the literature. J Clin Pathol 57:324–328
Biersack HJ (1988) Liver and spleen scans in systemic mast-cell disease. Br J Radiol 61:651
Bonnet P, Smadja C, Szekely AM, Delage Y, Calmus Y, Poupou R, Franco D (1987) Intractable ascites in systemic mastocytosis treated by portal diversion. Dig Dis Sci 32:209–213
Bredfeldt JE, O'Laughlin JC, Durham JB, Blessing LD (1980) malabsorption and gastric hyperacidity in systemic mastocytosis. Results of cimetidine therapy. Am J Gastroenterol 74:133–137
Brunning RD, Mckenna RW, Rosai J, Parkin JL, Risdall R (1983) Systemic mastocytosis. Extracutaneous manifestations. Am J Surg Pathol 7:425–438
Bureau Y, Rodat G, Barrière H, Litoux P, Bureau B (1965) Mastocytose cutanée de l'adulte avec mastocytose hépatique, et monocytose sanguine. Bull Dermatol 72:850–853
Burgoon CF, Graham JH, McCaffree DL (1968) Mast cell disease – a cutaneous variant with multisystem involvement. Arch Dermatol 98:590–605
Campbell EW, Hector D, Gossain V (1979) Heparin activity in systemic mastocytosis. Ann Intern Med 90:940–941
Capron JP, Lebrec D, Degott C, Chivrac D, Coevoet B, Delobel J (1978) Portal hypertension in systemic mastocytosis. Gastroenterology 75:595–597
Cehreli C, Alacacioglu I, Piskin O, Ates H, Cehreli R, Calibasi G, Yuksel E, Ozkal S, Ozsan GH (2014) Mast cell leukemia associated with undefined morphology and chronic basophilic leukemia. BMC Hematol 14:17
Celasun B, Crow J, Scheuer PJ (1992) Mast cells in granulomatous liver disease. Pathol Res Pract 188: 97–100
Chemli J, Krid S, Tfefha A, Abroug S, Harbi A (2003) Systemic infantile mastocytosis: about a case with respiratory and digestive involvement (in French). Arch Pediatr 10:898–902
Chiu A, Orazi A (2012) Mastocytosis and related disorders. Semin Diagn Pathol 29:19–30
Choi KL, Claman HN (1987) Mast cells, fibroblasts, and fibrosis. New clues to the riddle of mast cells. Immunol Res 6:145–152
Date UG, Venugopal P, Kalgalwala TY, Rajani A, Parikh DA, Advani SH, Irani SF (1989) Congenital systemic mastocytosis. Indian Pediatr 26:286–290
Debeuckelaere S, Schoors DF, Devis G (1991) Systemic mast cell disease: a review of the literature with special focus on the gastrointestinal manifestations. Acta Lin Belg 46:226–232
Demis DJ (1963) The mastocytosis syndrome: clinical and biological studies. Ann Intern Med 59:194–206
Ehrlich P (1878) Beiträge fur theorie und praxis der histologischmen färbung. Thesis, Leipzig
Ende N, Chernis E (1953) Splenic mastocytosis. Blood 13:631–641
Escribano L, Diaz Agustin B, Bravo P et al (1999) Immunophenotype of bone marrow mast cells in indolent systemic mast cell disease in adults. Leuk Lymphoma 35:227–235
Escribano L, Akin C, Castells M, Orfao A, Metcalfe DD (2002) Mastocytosis: current concepts in diagnosis and treatment. Ann Hematol 81:677–690
Escribano L, Diaz-Agustin B, Lopez A, Nunez Lopez R, Garcia-Montero A, Almeida J et al (2004) Immunophenotypic analysis of mast cells in mastocytosis: when and how to do it. Proposals of the Spanish Network on Mastocytosis (REMA). Cytometry 58B:1–8
Farrell DJ, Hines JE, Walls AF, Kelly PJ, Bennett MK, Burt AD (1995) Intrahepatic mast cells in chronic liver diseases. Hepatology 22:1175–1181
Ferrao PT, Gonda TJ, Ashman LK (2003) Constitutively active mutant D816Vkit induces megakaryocyte and mast cell differentiation of early haemopoietic cells from murine foetal liver. Leuk Res 27:547–555
Fishman RS, Fleming CR, Li CY (1979) Systemic mastocytosis with review of gastrointestinal manifestations. Mayo Clin Proc 54:51–54
Fonga-Djimi HS, Gottrand F, Bonnevalle M, Farriaux JP (1995) A fatal case of portal hypertension complicating systemic mastocytosis in an adolescent. Eur J Pediatr 154:819–821
Fuller SJ (2012) New insights into the pathogenesis, diagnosis, and management of mastocytosis. Hematol Oncol Clin North Am 26:1143–1168
Furitsu T, Tsujimura T, Tono T et al (1993) Identification of mutations in the coding sequence of the protooncogene c-kit in a human mast cell leukemia cell line causing ligand-independent activation of c-kit product. J Clin Invest 92:1736–1744
Furumoto Y, Charles N, Olivera A, Leung WH, Dillahunt S, Sargent JL, Tinsley K et al (2011) PTEN deficiency in mast cells causes a mastocytosis-like proliferative disease that heightens allergic responses and vascular permeability. Blood 118:5466–5475
Gaca MD, Pickering JA, Arthur MJ, Benyon RC (1999) Human and rat hepatic stellate cells produce stem cell factor: a possible mechanism for mast cell recruitment in liver fibrosis. J Hepatol 30:850–858
Georgin-Lavialle S, Lhermitte L, Dubreuil P, Chandesris MO, Hermine O, Damaj G (2013) Mast cell leukemia. Blood 121:1285–1295
Ghably et al (2015) http://www.ncbi.nlm.nih.gov/pubmed/25388241
Ghandur-Mnyamneh L, Gould E (1985) Systemic mastocytosis with portal hypertension. Arch Pathol Lab Med 109:76–78
Gilliland G, Cools J, Stover EH, Wlodarska I, Marynen P (2004) FIP1L1-PDGFRalpha in hypereosinophilic syndrome and mastocytosis. Hematol J 3:S133–S137
Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, Kluin-Nelemans H et al (2013) International Working Group-myeloproliferative Neoplasms

Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood 121:2393–2401

Graham JS, Bryant MA, Kirkpatrick LJ, Moltrup DL (1994) Staining mast cells for morphometric evaluation on an image analysis system. Biotech Histochem 69:121–126

Grizzi F, Franceschini B, Barbieri B, Gagliano N, Arosio B, Chiriva-Internati M, Annoni G, Dioguardi N (2002) Mast cell density: a quantitative index of acute liver inflammation. Anal Quant Cytol Histol 24:63–69

Grizzi F, Franceschini B, Chiriva-Internati M, Liu Y, Hermonat PL, Dioguardi N (2003) Mast cells and human hepatocellular carcinoma. World J Gastroenterol 9:1469–1473

Grundfest S, Cooperman AM, Ferguson R, Benjamin S (1980) Portal hypertension associated with systemic mastocytosis and splenomegaly. Gastroenterology 78:370–373

Gülen T, Sander B, Nilsson G, Palmblad J, Sotlar K, Horny HP, Hägglund H (2012) Systemic mastocytosis: progressive evolution of an occult disease into fatal mast cell leukemia: unique findings on an unusual hematological neoplasm. Med Oncol 29:3540–3546

Gulubova MV (2003) Structural examination of tryptase- and chymase-positive mast cells in livers, containing metastases from gastrointestinal cancers. Clin Exp Metastasis 20:611–620

Haenisch B, Nöthen MM, Molderings GJ (2012) Systemic mast cell activation disease: the role of molecular genetic alterations in pathogenesis, heritability and diagnostics. Immunology 137:197–205

Hahn HP, Hornick JL (2007) Immunoreactivity for CD25 in gastrointestinal mucosal mast cells is specific for systemic mastocytosis. Am J Surg Pathol 31:1669–1676

Hartmann K, Metcalfe DD (2000) Pediatric mastocytosis. Hematol Oncol Clin North Am 14:625–640

Hartmann K, Bruns SB, Henz BM (2001) Mastocytosis review of clinical and experimental aspects. J Investig Dermatol Symp Proc 6:143–147

Hauswirth AW, Födinger M, Fritz M, Müllauer L, Simonitsch-Klupp I, Streubel B, Chott A et al (2008a) Indolent systemic mastocytosis associated with atypical small lymphocytic lymphoma: a rare form of concomitant lymphoproliferative disease. Hum Pathol 39:917–924

Hauswirth AW, Escribano L, Prados A, Nunez R, Mirkina I, Kneidinger M, Florian S et al (2008b) CD203c is overexpressed on neoplastic mast cells in systemic mastocytosis and is upregulated upon IgE receptor cross-linking. Int J Immunopathol Pharmacol 21:797–806

Hirschowitz BI, Groarke JF (1979) Effect of cimetidine on gastric hypersecretion and diarrhea in systemic mastocytosis. Ann Intern Med 90:769–771

Hissard R, Moncourier L, Jacquet J (1950) Une nouvelle affection hematodermique, la mastocytose. Compte Rendu Acad Sci 231:253–255

Horny HP, Valent P (2001) Diagnosis of mastocytosis: general histopathological aspects, morphological criteria, and immunohistochemical findings. Leuk Res 25:543–551

Horny HP, Valent P (2002) Histopathological and immunohistochemical aspects of mastocytosis. Int Arch Allery Immunol 127:115–117

Horny HP, Kaiserling E, Campbell M, Parwaresch MR, Lennert K (1989) Liver findings in generalized mastocytosis: a clinicopathologic study. Cancer 63:532–538

Horny HP, Schaumburg-Lever G, Bolz S et al (1990) Use of monoclonal antibody KP1 for identifying normal and neoplastic human mast cells. J Clin Pathol 43:719–722

Horny et al (1993) http://www.ncbi.nlm.nih.gov/pubmed/8491475

Horny HP, Menke DM, Kaiserling E (1996) Neoplastic human tissue mast cells express the adhesion molecule CD44/HCAM. Virchows Arch 429:91–94

Horny HP, Ruck P, Krober S, Kaiserling E (1997) Systemic mast cell disease (mastocytosis). General aspects and histopathological diagnosis. Histol Histopathol 12:1081–1089

Horny HP, Krokowski M, Feller AC, Hintze G, Sotlar K, Valent P (2002) Aleukemic mast cell leukemia (formerly: " malignant mastocytosis "): an extremely rare form of leukemia. A case report and simultaneously a contribution to revised classification of mastocytosis (in German). Wien Klin Wochenschr 114:222–228

Horny HP, Sotlar K, Reiter A, Valent P (2014) Myelomastocytic leukemia: histopathological features, diagnostic criteria and differential diagnosis. Expert Rev Hematol 7:431–437

Jensen RT (2000) Gastrointestinal abnormalities and involvement in systemic mastocytosis. Hematol Oncol Clin North Am 14:579–623

Jeong WI, Lee CS, Park SJ, Chung JY, Jeong KS (2002) Kinetics of macrophages, myofibroblasts and mast cells in carbon tetrachloride-induced rat liver cirrhosis. Anticancer Res 22:869–877

Jordan JH, Walchshofer S, Jurecka W, Mosberger I, Sperr WR, Wolff K, Chott A, Buhring HJ, Lechner K, Horny HP, Valent P (2001) Immuno-histochemical properties of bone marrow mast cells in systemic mastocytosis evidence for expression of CD2, CD117/Kit, and bcl-x (L). Hum Pathol 32:545–552

Karnam U, Rogers A (1999) Systemic mastocytosis. Dig Dis 17:299–307

Kennedy RJ, Scoffield JL, Garstin WIH (1999) An unusual presentation of systemic mastocytosis. J Clin Pathol 52:301–302

Kim U (1971) The role of mast cells in human liver cirrhosis. Nagoya J Med Sci 34:131–142

Kirsch R, Geboes K, Shepherd NA, de Hertogh G, Di Nicola N, Lebel S, Mickys U et al (2008) Systemic mastocytosis involving the gastrointestinal tract: clinicopathologic and molecular study of five cases. Mod Pathol 21:1508–1516

Klion AD, Noel P, Akin C, Law MA, Gilliland DG, Cools J, Metcalfe DD, Nutman TB (2003) Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. Blood 101:4660–4666

Klose KC, Skora T (1990) A mastocytoma of the liver – computed tomographic follow-up and biopsy (in German). Radiologe 30:81–83

Koda W, Harada K, Tsuneyama K, Kono N, Sasaki M, Matsui O, Nakanuma Y (2000) Evidence of the participation of peribiliary mast cells in regulation of the peribiliary vascular plexus along the intrahepatic biliary tree. Lab Invest 80:1007–1017

Krech RH, Erhardt-Domagalski M, Neumann H (1995) Inflammatory pseudotumor of the liver. Morphologic and cytophotometry studies and differential diagnosis (in German). Pathologe 16:415–420

Kristensen T, Broesby-Olsen S, Vestergaard H, Bindslev-Jensen C, Moller MB, Mastocytosis Centre Odense University Hospital (2012) Circulating KIT D816V mutation-positive non-mast cells in peripheral blood are characteristic of indolent systemic mastocytosis. Eur J Haematol 89:42–46

Kupfer SS, Hart J, Mohanty SR (2007) Aggressive systemic mastocytosis presenting with hepatic cholestasis. Eur J Gastroenterol Hepatol 19:901–905

Kyriakou D, Kouroumalis E, Konsolas J, Oekonomaki H, Tzardi M, Kanavaros P, Manoussos O, Eliopoulos GD (1998) Systemic mastocytosis: a rare cause of noncirrhotic portal hypertension simulating autoimmune cholangitis – report of four cases. Am J Gastroenterol 93:106–108

Laine E, Chauvot de Beauchêne I, Perahia D, Auclair C, Tchertanov L (2011) Mutation D816V alters the internal structure and dynamics of c-KIT receptor cytoplasmic region: implications for dimerization and activation mechanisms. PLoS Comput Biol 7, e1002068

Le Jeunne C, Hugues FC, Rolle G, Jaubert F, Dufat R (1986) Hepatomegaly with portal hypertension indicative of systemic mastocytosis (in French). Rev Med Interne 7:253–257

Le Tourneau A, Gaulard P, D'Agay MF, Vainchencker W, Cadiou M, Devidas A, Hainoun C, Clauvel JP, Andouin J, Diebold J (1991) Primary thrombocythaemia associated with systemic mastocytosis: a report of five cases. Br J Haematol 79:84–89

Levi-Schaffer F, Weg VB (1997) Mast cells, eosinophils and fibrosis. Clin Exp Allergy 27(suppl 1):64–70

Li CY (2001) Diagnosis of mastocytosis: value of cytochemistry and immunohistochemistry. Leuk Res 25:537–541

Li CY, Baek JY (2002) Mastocytosis and fibrosis role of cytokines. Int Arch Allergy Immunol 127:123–126

Li WV, Kapadia SB, Sonmez-Alpan E, Swerdlow SH (1996) Immunohistochemical characterization of mast cell disease in paraffin sections using tryptase, CD68, myeloperoxidase, lysozyme, and CD20 antibodies. Mod Pathol 9:982–988

Lim KH, Pardanani A, Tefferi A (2008) KIT and mastocytosis. Acta Haematol 119:194–198

Lu DY, Gau JP, Hong YC, Liu CY, Yu YB, Hsiao LT, Liu JH, Chen PM, Chiou TJ, Tzeng CH (2014) Mast cell leukemia: an extremely rare disease. J Chin Med Assoc 77:446–449

Makhlouf HR, Ishak KG (2002) Sclerosed hemangioma and sclerosing cavernous hemangioma of the liver: a comparative clinicopathologic and immunohistochemical study with emphasis on the role of mast cells in their histogenesis. Liver 22:70–78

Marbello L, Anghilieri M, Nosari A, Minola E, Cairoli R, Ricci F, Morra E (2004) Aggressive systemic mastocytosis mimicking sclerosing cholangitis. Haematologica 89:ECR35

Marone G, Casolaro V, Patella V, Florio G, Triggiani M (1997) Molecular and cellular biology of mast cells and basophils. Int Arch Allergy Immunol 114:207–217

Marshall JS, Ford GP, Bell EB (1987) Formalin sensitivity and differential staining of mast cells in human dermis. Br J Dermatol 117:29–36

Maruyama H, Sugihara S, Ishihara K, Sada K, Tsutsumi M, Tsujiuchi T, Nakae D, Konishi Y (1998) Systemic mast cell disease with splenic infarction: a case report. Pathol Int 48:403–411

Matsunaga Y, Terada T (2000) Mast cell subpopulation in chronic inflammatory hepatobiliary diseases. Liver 20:152–156

Matsunaga Y, Kawasaki H, Terada T (1999) Stromal mast cells and nerve fibers in various chronic liver diseases: relevance to hepatic fibrosis. Am J Gastroenterol 94:1923–1932

McElroy EA, Phyliky RL, Li CY (1998) Systemic mast cell disease associated with the hypereosinophilic syndrome. Mayo Clin Proc 73:47–50

Metcalfe DD (1991) The liver, spleen, and lymph nodes in mastocytosis. J Invest Dermatol 96:45S–46S

Mican JM, Di Bisceglie AM, Fong TL, Travis WD, Kleiner DE, Baker B, Metcalfe DD (1995) Hepatic involvement in mastocytosis: clinicopathologic correlations in 41 cases. Hepatology 22:1163–1170

Miranda RN, Esparza AR, Sambandam S, Medeiros LJ (1994) Systemic mast cell disease presenting with peripheral blood eosinophilia. Hum Pathol 25:727–730

Molderings GJ, Brettner S, Homann J, Afrin LB (2011) Mast cell activation disease a concise practical guide for diagnostic workup and therapeutic options. J Hematol Oncol 4:10

Murata K, Okudaira M, Akashio K (1973) Mast cells in human liver tissue. Increased mast cell number in relation to the components of connective tissue in the cirrhotic process. Acta Derm Venereol Suppl (Stockholm) 73:157–165

Mutter RD, Tannenbaum M, Ultman JE (1963) Systemic mast cell disease. Ann Intern Med 59:887–905

Nakamura A, Yamazaki K, Suzuki K, Sato S (1997) Increased portal tract infiltration of mast cells and eosinophils in primary biliary cirrhosis. Am J Gastroenterol 92:2245–2249

Narayanan MN, Liu Yin JA, Azzawi S, Warnes TW, Turck WP (1989) Portal hypertension and ascites in systemic mastocytosis. Postgrad Med J 65:394–396

Nettleship E, Tay W (1869) Rare forms of urficaria. Br Med J 2:323–325

O'Keeffe C, Baird AW, Nolan N, McCormick PA (2002) Mast cell hyperplasia in chronic rejection after liver transplantation. Liver Transpl 8:50–57

Obata Y, Toyoshima S, Wakamatsu E, Suzuki S, Ogawa S, Esumi H, Abe R (2014) Oncogenic Kit signals on endolysosomes and endoplasmic reticulum are essential for neoplastic mast cell proliferation. Nat Commun. doi:10.1038/ncomms6715

Okazaki T, Hirota S, Xu ZD, Maeyama K, Nakama A, Kawano S, Hori M, Kitamura Y (1998) Increase of mast cells in the liver and lung may be associated with but not a cause of fibrosis demonstration using mast cell-deficient Ws/Ws rats. Lab Invest 78:1431–1438

Ozdemir D, Dagdelen S, Erbas T (2011) Systemic mastocytosis. Am J Med Sci 342:409–415

Pagano L, Valentini CG, Caira M, Rondoni M, Van Lint MT, Candoni A, Allione B et al (2008) Advanced mast cell disease: an Italian hematological multicenter experience. Int J Hematol 88:483–488

Papachristou GI, Demetris AJ, Craig F, Lee KK, Rabinovitz M (2004) Cholestatic jaundice and bone lesions in an elderly woman. Nat Clin Pract Gastroenterol Hepatol 1:53–57

Pardanani A (2011) Systemic mastocytosis in adults: 2011 update on diagnosis, risk stratification, and management. Am J Hematol 86:362–371

Pardanani A (2012) Systemic mastocytosis disease overview, pathogenesis, and treatment. Hematol Oncol Clin North Am 26:1117–1128

Pardanani A, Reeder TL, Kimlinger TK, Baek JY, Li CY, Butterfield JH, Tefferi A (2003a) Flt-3 and c-kit mutation studies in a spectrum of chronic myeloid disorders including systemic mast cell disease. Leuk Res 27:739–742

Pardanani A, Ketterling RP, Brockman SR, Flynn HC, Paternoster SF, Shearer BM, Reeder TL et al (2003b) CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. Blood 102:3093–3096

Pardanani A, Reeder T, Li CY, Tefferi A (2003c) Eosinophils are derived from the neoplastic clone in patients with systemic mastocytosis and eosinophilia. Leuk Res 27:877–878

Pardanani A (2012) Systemic mastocytosis in adults: 2012 update on diagnosis, risk stratification, and management. Am J Hematol 87:401–411, 131, 784–791

Patnaik MM, Rindos M, Kouides PA, Tefferi A, Pardanani A (2007) Systemic mastocytosis: a concise clinical and laboratory review. Arch Pathol Lab Med 131:784–91

Pauls JD, Brems J, Pockros PJ, Saven A, Wagner RL, Weber R, Metcalfe D, Christiansen SC (1999) Mastocytosis: diverse presentations and outcomes. Arch Intern Med 159:401–405

Peng RY, Wang DW, Xu ZH, Gao YB, Yang RB, Liu P, Wang ZP, Li YP (1994) The changes and significance of mast cells in irradiated rat liver. J Environ Pathol Toxikol Oncol 13:11–116

Pullarkat VA, Bueso-Ramos C, Lai R, Kroft S, Wilson CS, Pullarkat ST, Bu X, Thein M, Lee M, Brynes RK (2003) Systemic mastocytosis with associated clonal hematological non-mast-cell lineage disease: analysis of clinicopathologic features and activating c-kit mutations. Am J Hematol 73:12–17

Quintas-Cardama A, Jain N, Verstovsek S (2011) Advances and controversies in the diagnosis, pathogenesis, and treatment of systemic mastocytosis. Cancer 117:5439–5449

Ribatti and Crivellato (2014) http://www.ncbi.nlm.nih.gov/pubmed/24534641

Rioux KP, Sharkey KA, Wallace JL, Swain MG (1996) Hepatic mucosal mast cell hyperplasia in rats with secondary biliary cirrhosis. Hepatology 23:888–895

Rohner HG, Rodermund OE (1981) Mastozytose und Gastrointestinaltrakt. Hautarzt 32:611–616

Rudski Z, Sotlar K, Kudela A, Starzak-Gwozdz J, Horny HP (2011) Systemic mastocytosis (SM) and associated malignant bone marrow histiocytosis – a hitherto undescribed form of SM-AHNMD. Pol J Pathol 62:101–104

Ryan RJ, Akin C, Castells M, Wills M, Selig MK, Nielsen GP, Ferry JA, Hornick JL (2013) Mast cell sarcoma: a rare and potentially under-recognized diagnostic entity with specific therapeutic implications. Mod Pathol 26:533–543

Sadrzadeh H, Abdel-Wahab O, Fathi AT (2011) Molecular alterations underlying eosinophilic and mast cell malignancies. Discov Med 12:481–493

Safyan EL, Veerabagu MP, Swerdlow SH, Lee RG, Rakela J (1997) Intrahepatic cholestasis due to systemic mastocytosis: a case report and review of the literature. Am J Gastroenterol 92:1197–1200

Sagher F, Even-Paz Z (1967) Mastocytosis and the mast cell. Year Book Publishers, Chicago

Sanchez-Munoz K, Teodosio C, Morgado JM, Escribano L (2011) Immunophenotypic characterization of bone marrow mast cells in mastocytosis and other mast cell disorders. Methods Cell Biol 103:333–359

Sanchez-Muñoz L, Alvarez-Twose I, Garcia-Montero AC, Teodosio C, Jara-Acevedo M et al (2011) Evaluation of the WHO criteria for the classification of patients with mastocytosis. Mod Pathol 24:1157–1168

Sawers AH, Davson J, Braganza J, Geary CG (1982) Systemic mastocytosis, myelofibrosis, and portal hypertension. J Clin Pathol 35:617–619

Shah M, Holyoake TL, Jackson B, Drummond M (2012) Smouldering systemic mastocytosis presenting with

cryptic life-threatening crises: case report and literature review. Scott Med J 57:60

Sotlar K, Horny HP, Lebherz J, Leser HG, Bultmann B (1997) Association of bone marrow mastocytosis with extremely immature extramedullary mast cell sarcoma (in German). Pathologe 18:252–256

Sotlar K, Fridrich C, Mall A, Jaussi R, Bultmann B, Valent P, Horny HP (2002) Detection of c-kit point mutation Asp-816➔Val in microdissected pooled single mast cells and leukemic cells in a patient with systemic mastocytosis and concomitant chronic myelomonocytic leukemia. Leuk Res 26:979–984

Sotlar K, Cerny-Reiterer S, Petat-Dutter K, Hessel H, Berezowska S, Müllauer L, Valent P et al (2011) Aberrant expression of CD30 in neoplastic mast cells in high-grade mastocytosis. Mod Pathol 24:585–595

Soucie E, Hanssens K, Mercher T, Georgin-Lavialle S, Damaj G, Livideanu C, Chandesris MO et al (2012) In aggressive forms of mastocytosis, TET2 loss cooperates with c-KITD816V to transform mast cells. Blood 120:4846–4849

Sperr WR, Escribano L, Jordan JH, Schernthaner GH, Kundi M, Horny HP, Valent P (2001) Morphologic properties of neoplastic mast cells: delineation of stages of maturation and implication for cytological grading of mastocytosis. Leuk Res 25:529–536

Sperr WR, Horny HP, Valent P (2002) Spectrum of associated clonal hematologic non-mast cell lineage disorders occurring in patients with systemic mastocytosis. Int Arch Allergy Immunol 127:140–142

Stoecker MM, Wang E (2012) Systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease: a clinicopathologic review. Arch Pathol Lab Med 136:832–838

Sugihara A, Tsujimura T, Fujita Y, Nakata Y, Terada N (1999) Evaluation of role of mast cells in the development of liver fibrosis using mast cell-deficient rats and mice. J Hepatol 30:859–867

Sugita K, Kaneko T, Sekine Y, Taguchi N, Miyauchi J (1996) Mast cell leukemia evolved from REAB-T (5q-syndrome) in a 12 year-old girl (in Japanese). Rinsho Ketsueki 37:430–436

Sumpio BE, O'Leary G, Gusberg RJ (1988) Variceal bleeding, hypersplenism, and systemic mastocytosis. Pathophysiology and management. Arch Surg 123:767–769

Takemoto CM, Lee YN, Jegga AG, Zablocki D, Brandal S, Shahlaee A, Huang S et al (2008) Blood Cells Mol Dis 41:82–90

Tefferi A, Pardanani A (2004) Clinical, genetic, and therapeutic insights into systemic mast cell disease. Curr Opin Hematol 11:58–64

Tefferi A, Lasho TL, Brockman SR, Elliott MA, Dispenzieri A, Pardanani A (2004) FIP1L1-PDGFRA and c-kit D816V mutation-based clonality studies in systemic mast cell disease associated with eosinophilia. Haematologica 89:871–873

Terada T, Matsunaga Y (2000) Increased mast cells in hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Hepatol 33:961–966

Tharp MD (1985) The spectrum of mastocytosis. Am J Med Sci 289:119–132

Tharp MD, Chan IJ (2003) Mastocytosis Adv Dermatol 19:207–236

Thompson HL, Burbelo PD, Gabriel G, Yamada Y, Metcalfe DD (1991) Murine mast cells synthesize basement membrane components: a potential role in early fibrosis. J Clin Invest 87:619–623

Tomasi VH, Orrea SC, Raimondi AR, Itoiz ME (2003) A new technique for staining mast cells using ferroin. Biotech Histochem 78:255–259

Traina F, Visconte V, Jankowska AM, Makishima H, O'Keefe CL, Elson P, Han Y et al (2012) Single nucleotide polymorphism array lesions, TET2, DNMT3A, SXL1 and CBL mutations are present in systemic mastocytosis. PLoS One 7, e43090

Travis WD, Li CY, Hoagland HC, Travis LB, Banks PM (1986) Mast cell leukemia: report of a case and review of the literature. Mayo Clin Proc 61:957–966

Travis WD, Li CY, Bergstralh EJ, Yam LT, Swee RG (1988) Systemic mast cell disease: analysis of 58 cases and literature review. Medicine 67:345–368

Tsuneyama K, Kono N, Yamashiro M, Kouda W, Sabit A, Sasaki M, Nakanuma Y (1999) Aberrant expression of stem cell factor on biliary epithelial cells and peribiliary infiltration of c-kit-expressing mast cells in hepatolithiasis and primary sclerosing cholangitis: a possible contribution to bile duct fibrosis. J Pathol 189:609–614

Uddin Ahmed AF, Ohtani H, Nio M, Funaki N, Sasaki H, Nagura H, Ohi R (2000) Intrahepatic mast cell population correlates with clinical outcome in biliary atresia. J Pediatr Surg 35:1762–1765

Valent P (2013) Mast cell activation syndromes: definition and classification. Allergy 68:417–424

Valent P, Horny HP (2011) Classification and response criteria in mast cell disorders: time to revise ? Int Arch Allergy Immunol 155:306–308

Valent P, Escribano L, Parwaresch RM, Schemmel V, Schwartz LB, Sotlar K, Sperr WR, Horny HP (1999) Recent advances in mastocytosis research. Summary of the Vienna mastocytosis meeting 198. Int Arch Allergy Immunol 120:1–7

Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, Marone G, Nunez R, Akin C, Sotlar K, Sperr WR, Wolff K et al (2001a) Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 25:603–625

Valent P, Sperr WR, Samorapoompichit P, Geissler K, Lechner K, Horny HP, Bennett JM (2001b) Myelomastocytic overlap syndromes: biology, criteria, and relationship to mastocytosis. Leuk Res 25:595–602

Valent P, Akin C, Sperr WR, Horny HP, Metcalfe DD (2002a) Smouldering mastocytosis: a novel subtype of systemic mastocytosis with slow progression. Int Arch Allergy Immunol 127:137–139

Valent P, Samorapoompichit P, Sperr WR, Horny HP, Lechner K (2002b) Myelomastocytic leukemia: myeloid neoplasm characterized by partial differentiation of mast cell-lineage cells. Hematol J 3:90–94

Valent P, Akin C, Sperr WR, Escribano L, Arock M, Horny HP, Bennett JM, Metcalfe DD (2003) Aggressive systematic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. Leuk Res 27:635–641

Valent P, Sotlar K, Sperr WR, Reiter A, Arock M, Horny HP (2014) Chronic mast cell leukemia: a novel leukemia-variant with distinct morphological and clinical features. Leuk Res. doi:10.106/j.leukres. 2014.09.010

Valentini CG, Rondoni M, Pogliani EM, Van Lint MT, Cattaneo C, Marbello L, Pulsoni A et al (2008) Mast cell leukemia: a report of ten cases. Ann Hematol 87:505–508

Verstivsek S (2013) Advanced systemic mastocytosis: the impact of KIT mutations in diagnosis, treatment, and progression. Eur J Haematol 90:89–98

Vincenzi V, Costan Biedo F, Carrabba E, Benvegnu B, Furlanetto A, Basevi A (1992) Systemic mastocytosis with portal hypertension and hepatocellular failure (in Italian). Minerva Med 83:563–565

Walls AF, Jones DB, Williams JH, Church MK, Holgate ST (1990) Immunohistochemical identification of mast cells in formaldehyde-fixed tissue using monoclonal antibodies specific for tryptase. J Pathol 162:119–126

Wanless IR, Godwin TA, Allen F, Feder A (1980) Nodular regenerative hyperplasia of the liver in hematologic disorders: a possible response to obliterative portal venopathy: a morphometric study of nine cases with an hypothesis of the pathogenesis. Medicine 59:367–379

Webb TA, Li CY, Yam LT (1982) Systemic mast cell disease. A clinical and hematopathologic study of 26 cases. Cancer 49:927–938

Wendum D, Prevot S, Poujol-Robert A, Rosmorduc O, Cabane J, Fouillard L, Flejou JF (2004) Liver involvement revealing systemic mastocytosis report of two cases (in French). Gastroenterol Clin Biol 28:80–83

Wimazal F, Jordan JH, Sperr WR, Chott A, Dabass S, Lechner K, Horny HP, Valent P (2002) Increased angiogenesis in the bone marrow of patients with systemic mastocytosis. Am J Pathol 160:1639–1645

Yam LT, Chan CH, Li CY (1986) Hepatic involvement in systemic mast cell disease. Am J Med 80:819–826

Yamashiro M, Kouda W, Kono N, Tsuneyama K, Matsui O, Nakanuma Y (1998) Distribution of intrahepatic mast cells in various hepatobiliary disorders. An immunohistochemical study. Virchows Arch 433:471–479

Yoshida M, Nishikawa Y, Yamamoto Y, Doi Y, Tokairin T, Yoshioka T, Omori Y, Watanabe A et al (2009) Mast cell leukemia with rapidly progressing portal hypertension. Pathol Int 59:817–822

Zanotti R, Simioni L, Garcia-Montero AC, Perbellini O, Bonadonna P, Caruso B, Jara-Acevedo M et al (2013) Somatic D816V KIT mutation in a case of adult-onset familial mastocytosis. J Allergy Clin Immunol 131:605–607

Acute Leukemias of Granulocytic, Erythroid, and Megakaryocytic Lineages

84

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_84

Abstract

In several types of acute leukemia, neoplastic cells infiltrate the liver parenchyma, portal tracts, and tissues accompanying bile ducts and blood vessels. Acute myeloid leukemia (AML), defined as a clonal expansion of myeloid blasts, frequently results in hepatic infiltrates that sometimes cause hepatomegaly. In massive infiltration, leukemic blasts induce liver damage and eventually hepatic failure. Dense bile duct infiltrates can cause obstructive jaundice. In AML, mass-forming hepatic lesions termed granulocytic sarcoma can develop. In contrast to AML, neoplastic cells in acute erythroid leukemia tend to accumulate in the lumens of hepatic blood vessels, but marked blastic infiltration of parenchyma also occurs. Acute megakaryoblastic leukemia is a neoplasia in which at least 50 % of cells are of the megakaryocyte lineage. Infiltration of the liver by cells of this leukemia is often associated with hepatic fibrosis. This neoplasm overlaps with the rapidly progressive disorder, acute panmyelosis with myelofibrosis. Blastic infiltration of the liver associated with fibrosis is also a feature of transient abnormal myelopoiesis in Down syndrome.

Acute Myeloid Leukemia (AML) and Related Precursor Neoplasms

Introduction

Acute myeloid leukemia (AML) is defined as a clonal expansion of myeloid blasts in the bone marrow, blood, or other tissues (reviews: Jaffe et al. 2001; Betz and Hess 2010; Estey 2013; Ferrara and Schiffer 2013; Puumala et al. 2013; Walter et al. 2013). AML exists in numerous variants, a part of which display recurrent genetic abnormalities.

Liver Involvement in Acute Myeloid Leukemia

Introduction

The findings of liver infiltration in AML are known from both biopsy and autopsy studies (Krishbaum and Preuss 1943; Ito 1970; Bross et al. 1975; Chi et al. 1976; Viadana et al. 1978; Ondreyco et al. 1981; Aviles Miranda et al. 1981; Ito et al. 1985; Barcos et al. 1987; Scheimberg et al. 1995; Walz-Mattmuller et al. 1998). In fact, the recognition of extramedullary dissemination by leukemia, also in the absence of overt marrow involvement, is documented in the old literature referring to this issue (Gruber 1930; Nies et al. 1965; Mathé et al. 1966). Infiltration of the liver by blasts may be clinically silent, may induce marked hepatomegaly and liver function abnormalities (Sharma Poudel and Karki 2007), or may cause jaundice and/or fulminant hepatic failure in case of massive blastic infiltration (Zafrani et al. 1983; Eisen et al. 2008). The majority of patients with AML-induced liver abnormalities display jaundice, a cholestatic picture, or obstructive jaundice at presentation (Mathews et al. 2008). In a large autopsy study on 585 patients with AML, 41 % exhibited organ involvement of the liver (the liver, spleen, and lymph nodes being the organs with the highest incidence of leukemic involvement), and the mean liver weight in these autopsied patients was 2253 g (Barcos et al. 1987). In another study of 127 liver specimens (2 biopsies and 125 autopsies), 60–70 % of the specimens showed liver infiltration in acute myeloid leukemia (Walz-Mattmüller et al. 1998). The hepatic infiltration pattern seen in AML may also be present in cases where chronic leukemia is followed by massive production of blasts, e.g., monoblasts (Ondreyco et al. 1981). Massive blastic infiltration of the liver can result in fulminant hepatic failure (Ondreyco et al. 1981; Zafrani et al. 1983).

Pathology

Patients with various forms of AML can show hepatomegaly, but in most cases, enlargement of the liver is slight to moderate, but can become marked in certain situations of blast crisis. Hepatomegaly can also be caused by disorders complicating AML, including generalized infection/septicemia, portal vein thrombosis, fatty change, and therapy-induced parenchymal damage. At

autopsy, the liver may show rounded margins, dilated subcapsular blood vessels, a grayish-red discoloration, and a flabby consistency. In cases of marked liver infiltration, mostly in blast crisis, the lobular architecture is effaced. In AML, myeloid cells infiltrate both the portal tracts and the parenchyma, with permeation of the sinusoids (Fig. 1; Scheimberg et al. 1995; Wandroo et al. 2004; Mathews et al. 2008; Nishihori et al. 2011), sometimes with a diffuse and marked infiltration pattern associated with the signs of cholestatic hepatitis (Sevinc et al. 2004; Wandroo et al. 2004). A diffuse accumulation of neutrophil precursors, maturing forms with more cytoplasmic granules, and blast cells can occur within the hepatic sinusoids (Wandroo et al. 2004), but there are situations where either the portal tract spaces or the parenchyma are almost exclusively involved. In some patients, a predominance of micromyeloblasts was noted. In the portal tracts, the leukemia cells appear to be randomly distributed, but sometimes an angiocentric or a ductocentric pattern is in evidence. That part of the leukemia cells that may be attracted by, or home to, distinct tissue components is further illustrated by a sometimes preferential localization of these cells to the periductular space or to interface lesions. The hepatic infiltrates in AML consist of cells displaying several size classes ranging from small- to medium-sized cells: The cytoplasmic features and the nuclear morphology vary from one type/variant of AML to the other (Ito 1970), therefore requiring immunohistochemical techniques. Hepatic infiltrates in AML with predominance of a neutrophil lineage exhibits cells expressing MPO, CD13, CD15, and/or CD33, while AML with monocytoid differentiation, or AMML and acute monoblastic/monocytic leukemias, display numerous cells, or a majority of cells, expressing monocyte lineage markers (Cd14, CD4, CD11b, CD11c, CD64, CD36, and lysozyme). Diagnostic difficulties arise in immature forms of AML (see above), where the cellular infiltrates may resemble non-Hodgkin's lymphoma, but immunohistochemical stains will usually solve these questions.

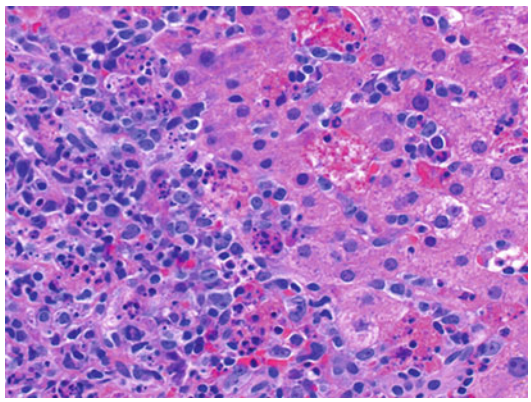

Fig. 1 Acute myeloid leukemia, infiltration of the liver. Basophilic and amphophilic blasts invade the sinusoids. Numerous nuclear debris are seen (hematoxylin and eosin stain)

Obstructive Jaundice in AML

Leukemic cells in AML can infiltrate the walls of large bile ducts, cause stenosis, and hence induce obstructive jaundice (Rajesh et al. 2006). In part of patients, large and dense infiltrates of immature myeloid cells have been observed in the hilar/perihilar area, with formation of thick sheaths engulfing hilar bile ducts and blood vessels (review: Gruber 1930). However, there are also patients with AML associated with signs of obstructive jaundice without bile duct infiltration at imaging (Goor et al. 2002; Mathews et al. 2008).

Granulocytic Sarcomas in AML

In AML or variants thereof, initial organ manifestation may be in the form of granulocytic sarcomas (GS; Liu et al. 1973; Alama Zaragoza et al. 2003; Best-Aguilera et al. 2005; Lee et al. 2007). Overall. GS was detected at autopsy in 8 % of patients with AML and in 4 % of those with CML (Liu et al. 1973). Involvement of the gastrointestinal tract is relatively rare, being reported in 7 % of 61 tumors (Neiman et al. 1981). GS in the liver, the hepatic ducts, at the porta hepatis, the common bile duct, or the pancreatic head are known to cause cholestasis

and obstructive jaundice, sometimes as the presenting feature of AML (McCord et al. 1973; Lillicrap et al. 1982; King et al. 1987; Gutierrez de Guzman et al. 1987; Case Records of the Massachusetts General Hospital 1988, 1990; Matsueda et al. 1998; Abe et al. 1999; Jaing et al. 2001; Alama Zaragoza et al. 2003; Mano et al. 2004). Lesions developing in the perihilar region have been reported to be as large as 2.5 cm (Matsueda et al. 1998) and may thus mimic a perihilar stenosing carcinoma/Klatskin tumor. In part of cases, chloroma-like nodular lesions can develop. AML cases with such features have previously been termed "chloroleukemic myeloblastosis" or "acute chloroleukemia."

Hepatic Extramedullary Hematopoiesis in AML

Extramedullary hemopoiesis can occur in both treated and untreated patients, but is rarer than in myeloproliferative disorders.

Hepatic Vascular Alterations in AML

AML cells can accumulate within microvascular lumina, thus forming aggregates and so-called leukocyte thrombi (McKee and Collins 1974). In the liver, this is sometimes in evidence within the sinusoidal channels, but is also found in the small vessels forming the peribiliary plexus. Targeting of leukemia cells to the sinusoidal compartment has been found to be induced by treatment with gemtuzumab ozogamicin (an immunoconjugate composed of recombinant humanized murine anti-CD33 antibody linked to calicheamicin) that targets CD33-positive cells (Rajvanshi et al. 2002). AML can cause thrombotic obstruction of hepatic veins, leading to Budd-Chiari syndrome and eventually liver failure (Amitrano et al. 2006).

Hepatic Fibrosis in AML

Hepatic fibrosis is known to develop in AML (Niedobietk 1968) and presents in several patterns, but it is more frequent or more severe in the chemotherapy and chemo-/radiotherapy groups (Scheimberg et al. 1995). In a minority of cases, hepatic fibrosis is associated with liver lobule remodeling, resulting in cirrhosis (Danopoulos and Angelopoulos 1953; "leukemic liver cirrhosis").

Other liver Alterations in AML

In rare instances, AML can cause bridging necrosis and reticulin bridging fibrosis, with distortion of liver lobules and associated with activation of hepatic stellate cells (Kuroda et al. 2006). Involvement of the liver in AML can be associated with macrovesicular or microvesicular steatosis, and/or with visible cholestasis (Scheimberg et al. 1995), however at least in part caused by chemotherapeutic measures. In particular, L-asparaginase is known to induce diffuse hepatic steatosis (due to asparagine deficiency) in 50–90 % of the treated patients and to increase in severity with increased duration of the treatment (Kitmacher et al. 1991; Halton et al. 1998; Sahoo and Hart 2003). L-asparaginase induces hypertriglyceridemia (Tozuka et al. 1997), eventually via a derangement of glutamine metabolism (Ollenschlager et al. 1988) which, apart from a direct toxic effect on hepatocytes, may be involved in the pathogenesis of liver steatosis. Necrosis of liver parenchyma was reported in patients with AML with or without therapy and has been proposed to be a consequence of leukemic infiltration and/or infection in the latter group (Scheimberg et al. 1995). Focal necrosis is sometimes associated with steatosis (Scheimberg et al. 1995). Hepatic iron overload is a frequent finding and is most marked in the bone marrow transplant group (Armand et al. 2011). AML cells are involved in an angiogenic phenotype (Schuch et al. 2002), and native human AML blasts have a pro-angiogenic phenotype involving the action of VEGF and IL-8 that are released at relatively high levels (Glenjen et al. 2003). Involvement of visceral organs in AML may result in release of leukemia cells into the abdominal cavity, with formation of so-called leukemic ascites (Simel and Weinberg 1985).

Therapy of AML can, as in other situations, cause alterations of hepatic veins. For example, probable veno-occlusive disease has been observed in AML treated with gemtuzumab ozogamicin (O'Boyle et al. 2003). There is an increased incidence of AML after liver transplantation (Camos et al. 2004; with a review of the literature). Veno-occlusive disease in patients with AML can be caused by treatment with gemtuzumab ozogamicin (Stadtmauer 2002; Giles 2002), in up to 2 % of the treated patients (Leopold et al. 2002), and even in the absence of previous stem cell transplantation (Giles et al. 2001). Apart from the accumulation of leukemic cells in the microvascular bed, AML may also be complicated by disseminated intravascular coagulation (Genova and Georgief 1974). This is mainly observed in patients with APL (acute promyelocytic leukemia).

A further group of hepatic lesions in acute non-lymphoblastic leukemia is directly or indirectly caused by therapy, sometimes with signs of chronic liver disease, including diverse forms of viral hepatitis (Aviles Miranda et al. 1981; Locasciulli et al. 1983) and direct sequelae of chemotherapy (Iqbal et al. 1996). Massive hepatic infarction caused by the almost complete obstruction of both the hepatic artery and portal vein by thrombi was observed as a complication developing after salvage chemotherapy such as FLAGM inducing marked myelosuppression (Saito et al. 2010). In addition, a significant proportion of patients with AML in remission display persisting liver function abnormalities of unknown pathogenesis, liver biopsies showing non-characteristic inflammatory changes of varying degrees (Armitage et al. 1978). The liver may also be involved in infections developing under, or subsequent to, therapy of acute leukemia, including septicemia (Chi et al. 1976).

Classification

Based on the numerous cytogenetic and molecular features of AML, classification of this disorder has become complex. The classification of AML comprises four major categories: (1) AML with recurrent genetic abnormalities; (2) AML with multilineage dysplasia; (3) AML, therapy-related; and (4) AML, not otherwise categorized/specified (NOS). AML NOS also contains rare acute myeloid leukemias including myelomonocytic, monoblastic/monocytic, erythroid, megakaryoblastic, and basophilic leukemias. These uncommon disorders are treated in separate paragraphs.

Morphology

The morphologic features of "classical" AML cells have been studied in detail, including electron microscopy (Schumacher et al. 1973). The cells of interest are best stained with Wright-Giemsa or May-Grünwald-Giemsa stains. By use of these stains, myeloblasts vary in their size from enlarged lymphocytes to monocytes (or even larger). The cytoplasm is usually basophilic to blue-gray, and the nuclei are mostly round to oval, with several nucleoli. The cells may disclose few azurophilic granules; Auer rods are lineage specific for myeloid cells (Jaffe et al. 2001). A further myeloid lineage-specific marker is myeloperoxidase (MPO) that can be detected by use of cytochemistry. The immunophenotype of myeloid leukemia cells is characterized by reactivity for CD13, CD33, CD15, MPO, and CD117 (Ball and Fanger 1983; Jaffe et al. 2001). The morphology exhibits some particularities in regard to the subtypes of AML. AML1/ETO (ICD-O code: 9896/3; AML1 = RUNX1 gene), which is an AML generally showing maturation in the neutrophil granulocyte lineage (Jaffe et al. 2001), consists of cells with the features of large blasts with more abundant cytoplasm, often numerous azurophilic granules, frequent Auer rods, and few cells with very large granules (pseudo-Chediak-Higashi granules). Smaller blasts in this variant occur mainly in the streaming blood. In addition to the lineage-specific immunophenotype, the cells typically express CD34, often express CD56, and a subset displays the lymphoid marker, CD19. The AML1/ETO translocation t(8;21)(q22;q22) involves the AML1/RUNX1 gene encoding CBFalpha and the ETO (8;21) gene. AML (CBFbeta/MYH11)

(ICD-O code: 9871/3) is an AML that mostly displays granulocytic and monocytic differentiation and a characteristically abnormal eosinophil component in the marrow (Jaffe et al. 2001). Acute myelomonocytic leukemia with abnormal eosinophils is also termed AMML Eo.

Acute Erythroid Leukemias

ICD-O code 9840/3

Introduction

In the 2008 WHO classification, acute erythroid leukemias (synonyms: erythremic myelosis; Di Guglielmo's disease; Di Guglielmo 1917, 1962) are acute leukemias characterized by a predominantly erythroid lineage. Today, two subtypes are recognized based on the presence or absence of a significant myeloid/granulocyte component: erythroleukemia (erythroid/myeloid) and pure erythroid leukemia (acute erythremic myelosis; true erythroleukemia; Hasserjian et al. 2001). Erythroleukemia (erythroid/myeloid) may present as a de novo neoplasm or evolve from MDS or chronic myeloproliferative disorder. The features of acute erythroid leukemias have been described and reviewed in detail (Domingo-Claros et al. 2002; Srinivas et al. 2007; Santos et al. 2009; Hasserjian et al. 2010; Kasyan et al. 2010; Zuo et al. 2010; Liu et al. 2011, 2012), as well as the issue of erythroid proliferations in myeloid neoplasms (Wang and Hasserjian 2012). Classifications of acute erythroid leukemia are briefly discussed at the end of this chapter.

Clinical Features and Morphology

Several reports document the hematologic presentation of erythroid leukemias, both in children and adults (Scott et al. 1964; Sondergaard-Petersen 1975; Roggli and Saleem 1982; Ruvidic et al. 1986; Griesser and Horny 1987; Atkinson et al. 1992; Day et al. 1997; Hasserjian et al. 2001). The most common presenting symptoms and signs are related to the moderate or profound anemia which is always present. Pure erythroid leukemia can be associated with hemophagocytosis (Kitagawa et al. 2009). Hemophagocytic lymphohistiocytosis is a recurrent and specific complication of acute erythroid leukemia (Yamazaki et al. 2011).

Morphology

In erythroleukemia (erythroid/myeloid), all maturation stages may be found, erythroid precursors being dysplastic, often with megaloblastoid nuclei, binucleated, and multinucleated forms. Myeloblasts are commonly of intermediate size, contain relatively few granules, and may show Auer rods. Dysplastic features also involve neutrophils and megakaryocytes. In pure erythroid leukemia, erythroblasts of medium to large size prevail, commonly with a deeply basophilic cytoplasm and round nuclei with a fine chromatin structure (proerythroblasts). Red cell maturation is blocked in acute erythroid leukemia (Blum and Angelillo-Scherrer 2012). In contrast to immature fetal erythroid cells that can undergo enucleation to produce pyrenocytes (McGrath et al. 2008), maturation with enucleation dependent on erythroblast macrophage protein/Emp (Soni et al. 2006) does not take place in acute erythroid leukemias.

In regard to the immunophenotype, erythroid cells in erythroleukemia (FAB M6a) usually lack myeloid markers and MPO, but are reactive for glycophorin A and hemoglobin A (Keifer et al. 1984; Jaffe et al. 2001). The expression of Hb A and the aberrant expression of Hb F in cells of acute erythroid leukemia have been described, in particular fetal hemoglobin-containing erythroblasts or "F blasts" (Omine et al. 1983; Markham et al. 1983; Sumitra et al. 1988; Choi et al. 2002), and these erythroid lineage markers can be detected by use of immunohistochemistry in tissues (Pinkus and Said 1981; Forni et al. 1983).

Liver Involvement in Acute Erythroid Leukemia

The immature erythroid cells in acute erythroid leukemias have a marked tendency to accumulate and grow within vascular lumina, i.e., showing an intravascular growth pattern (Hasserjian et al. 2001). Therefore, immature erythroid cells in these leukemias are capable to spread and to locate in the liver, resulting in hepatomegaly (Lazzaro 1933; Stodtmeister 1941; Mirchandani et al. 1983; Reiffers et al. 1985; Kowal-Vern et al. 1992; Tsuji et al. 1995; Mazzella et al. 1998; Hasserjian et al. 2001; Funakoshi et al. 2011). There is, however, marked variability in the reported incidence of hepatomegaly (0–18 %; review: Roggli and Saleem 1982). Infiltration of the liver had already been noted by Di Guglielmo in his first description of the disorder (Di Guglielmo 1926). Marked blastic infiltration of the liver in acute erythroid leukemia has been described in autopsy liver samples (Roggli and Saleem 1982; Iida et al. 1991; Tsuji et al. 1995). In the autopsy study of Roggli and Saleem, the organs involved in order of decreasing frequency were the bone marrow, spleen liver, lymph nodes, kidneys, dura, stomach, urinary bladder, skin, and choroid plexus (Roggli and Saleem 1982). In liver biopsy, a patchy intrasinusoidal and focal portal infiltrate of large, beta-sialoglycoprotein-positive, immature erythroid lineage cells were reported (Hasserjian et al. 2001). Rarely, erythroblastic islands are seen within sinusoids, similar to findings in the bone marrow (Taher et al. 1981). It is surmised that the cells involved express distinct adhesion molecules that mediate the homing mechanisms (Hasserjian et al. 2001). The erythroblasts may show erythrophagocytosis (Sondergaard-Petersen 1974). In a patient with the anerythremic variant of acute erythroid leukemia (described in the title as Di Guglielmo's syndrome), autopsy showed hepatomegaly (1800 g) and a diffuse infiltration of both the portal tracts and the sinusoids with blast cells that were immunohistochemically reactive for hemoglobin (Tsuji et al. 1995).

Erythroleukemia can present as a congenital disorder, both with erythremic and anerythremic manifestation. Congenital anerythremic erythroleukemia, is a very rare disorder (Bjure et al. 1960; Lasson and Goos 1981; Allan et al. 1989; Hadjiyannakis et al. 1998). Per definition, congenital leukemias originate in utero, and manifestations are present at birth or in the first four postnatal weeks. The disorder has been reported to present with connatal hepatosplenomegaly and abnormal liver tests, later resulting in death due to hepatic failure (Lazure et al. 2003). A premortem biopsy and the autopsy in this patient showed a blastic infiltration of organs, in the liver mainly within portal tracts, and these cells expressed only the erythroid markers, glycophorin A and C. In addition, the biopsy revealed extensive portal and perisinusoidal fibrosis without atrophic hepatocytes. At autopsy, the liver was enlarged (225 g; expected: 133 g) and grossly cholestatic and multinodular (numerous millimetric pink nodules), with hilar and portal lymph node swelling (Lazure et al. 2003). Histologic examination showed a diffuse and nodular blastic infiltration consisting of basophilic cells with round or multilobated nuclei; in addition, binuclear and giant blasts were noted. In an another report, congenital erythroleukemia was associated with liver failure of unknown pathogenesis (Allan et al. 1989).

Erythroblastomas and Erythroblastic Sarcomas

A distinct variant of acute erythroid leukemia is characterized by the formation of tumorous lesions rich in abnormal erythroblasts, described in the literature under several terms, including *erythroblastic sarcoma*, *erythroblastomatosis*, *erythroblastoma malignum*, and *erythroblastoma diffusum*. The recognition of these lesions goes back to 1934, based on the observation of a patient with abnormal erythropoietic foci (erythroblastoma; Limarzi and Levinson 1943), followed by several reports afterward (Birkle 1950; Siede and Rotter 1950; Harwerth 1952; Dubois-Ferrière et al. 1955; Böttiger and Hellström 1956; Rohr 1960; Goreczky and Toth 1967; Wang et al. 2011; Cornfield 2012; Riddle

and Olsen 2012). Morphologically, this disorder is characterized by a growth dominated by abnormal erythroblasts, including large or even giant, markedly basophilic forms, frequently with vacuolization of the cytoplasm ("paraerythroblasts"). Proerythroblasts and other maturing cells with denser nuclei and amphophilic or slightly eosinophilic cytoplasms occur in variable numbers.

Few data relate to manifestations of malignant erythroblastoma in the liver (Corwin and Nettleship 1959; Goreczky and Toth 1967). In a 66-year-old female patient, autopsy of the liver (2500 g) revealed a tumor-like growth ("erythroid metastases") of the cells described above, predominantly of the immature types (Goreczky and Toth 1967).

Differential Diagnosis

The differential diagnosis comprises AML with maturation and shift into a population of increased erythroid precursors and AML with multilineage dysplasia. Rarely, CML, idiopathic myelofibrosis, or polycythemia vera undergo erythroblastic transformation and may then mimic (or represent?) acute erythroid leukemia (Dammert and Kaipainen 1960; Bank et al. 1966; Garcia et al. 1989). On the other hand, acute erythroid leukemia may dedifferentiate and end up with a disorder compatible with AML-MO (Michiels et al. 1997). Pure erythroid acute leukemia may have poor erythroid maturation and is then difficult to distinguish from other types of AML, in particular acute megakaryoblastic leukemia. Most cases of acute erythroid leukemia are sporadic, but familial occurrence has also been reported (Siebert et al. 1995). Erythroleukemia has been identified following erythropoietin therapy in a patient with CIMF (Coleman et al. 2001). Of particular interest is the association of acute erythroid leukemia with the stem cell disorder, paroxysmal nocturnal hemoglobinuria (PNH; Carmel et al. 1970; Cowall et al. 1979; Luzzatto et al. 1979; Kiga et al. 1980; Shimano et al. 1983; Meletis and Terpos 2003).

Classifications of Acute Erythroid Leukemia

The 2008 WHO classification distinguishes erythroleukemia from pure erythroid leukemia. In the FAB classification system, these leukemias were classified as AML-M6 (AML6), with three subtypes, i.e., M6a, erythroid/myeloid; M6b, pure erythroid leukemia; and M6c, mixed (Table 1).

Acute and Chronic Basophilic Leukemia

Acute Basophilic Leukemia (ABL; ICD-O 9870/3)

Acute basophilic leukemia (ABL) is a very rare disorder (about 4–5 % of all acute nonlymphocytic leukemias; Chevallier and Marinone 1951; Shah et al. 1984; Peterson et al. 1991). Usually, ABL presents as a mixture of blasts from different lineages with a considerable but highly variable participation of mature or immature basophilic cells (Liso et al. 1978). Complete diagnostic criteria of ABL, therefore, remain to be worked out. Essential thrombocythemia can transform into ABL (Shah et al. 1984), and basophilic crisis has been observed in chronic myeloid leukemia (Ozaki et al. 1989). Furthermore, basophilic differentiation occurs in

Table 1 Classifications of acute erythroid leukemias

WHO classification (2008)
Erythroleukemia (erythroid/myeloid)
Defined by the presence in the bone marrow of =>50 % erythroid precursors in the entire nucleated population and =>20 % myeloblasts in the entire non-erythroid population
Pure erythroid leukemia
Defined as a neoplasia of immature cells (undifferentiated or proerythroblastic in appearance) exclusively committed to the erythroid lineage, accounting for =>80 % of bone marrow cells
FAB classification
M6a, erythroid/myeloid
M6b, pure erythroid leukemia
M6c, mixed

some patients with acute promyelocytic leukemia (Tallman et al. 1993).

Four ABL types have been recognized, i.e., (a) the basophilic terminal phase (basophilic blastic crisis) of chronic myeloid leukemia, (b) the mixed basophilic-eosinophilic types, (c) the promyelocytic basophilic type, and (d) the so-called histio-basoblastic type (Quattrin 1978). However, ABL does now no longer include the basophilic proliferation seen frequently in patients with chronic myeloid leukemia or other myeloproliferative disorders in either the chronic or the blastic stage (Dick 1991). Most frequently, the blast cells are morphologically undifferentiated, and the recognition of the presence of coarse basophilic granules may be the first step in diagnosis, although the number of blast cells with deep purple granules in May-Grünwald-Giemsa preparations is variable from case to case. These granules are metachromatic and MPO negative, although the results of the peroxidase reactivity are controversial and the typical toluidine blue metachromatic reaction is frequently equivocal (Shvidel et al. 2003).

Chronic Basophilic Leukemia

Evidence has accumulated that chronic basophilic leukemia represents a distinct clinicopathologic entity and a variant form of a chronic myeloproliferative neoplasm (Barlas 1954; Nasi et al. 1960; Anikin 1963; Rosenthal et al. 1977; Pardanani et al. 2003; Tang et al. 2009). Basophilia is recognized as a feature of chronic myeloid leukemia and is considered a prognosticator for poor outcome (Denburg and Browman 1988). The emergence of a basophil cell lineage is also known for the blastic phase of CML (Nissenblatt 1980; Li and Yam 1987; Peterson et al. 1991), and prominent basophilia is associated with blast crisis with the i(17q) anomaly (Alimena et al. 1987). In CML, basophilia is mostly found in the Ph+/bcr+ and Ph−/bcr+ configurations. Chronic basophilic leukemia, an aggressive disorder with a potential to transform into acute leukemia, is Ph negative and shows marked bone marrow hypercellularity with trilineage overgrowth, prominent basophilia, dysmegakaryopoiesis, and abnormal mast cells in part of the patients (Pardanani et al. 2003). Chronic myeloproliferative disorders with production of numerous basophils can present in an aleukemic form, with infiltration of internal organs, including the liver (Lertprasertsuke and Tsutsumi 1991).

Liver Involvement in Basophilic Leukemia

In basophilic leukemia, immature leukemic cells with variable signs of basophilic differentiation can infiltrate portal tracts or the liver and/or accumulate within hepatic sinusoids. A part of the cells correspond to immature blasts. In the Giemsa stain, purple metachromatic cytoplasmic granules are in evidence. Leukemic cells with coarse basophilic granules may represent a minority of infiltrate cells and can be missed without special staining or immunohistochemistry (CD9 and CD25). A disorder of liver function has been observed in acute basophilic leukemia in the absence of leukemic liver infiltration (Scolyer et al. 2000). In chronic myeloproliferative disorders with marked basophilia, immature basophils infiltrate, among other internal organs, the liver, associated with liver fibrosis and sometimes accumulation of abnormal mast cells (Lertprasertsuke and Tsutsumi 1991). Thus, the hepatic changes in part resemble those observed in systemic mastocytosis (see below).

Acute Megakaryocytic Leukemias: Acute Megakaryoblastic Leukemia and Acute Myeloid Leukemia (Megakaryoblastic) with t(1;22)(p13;q13)

ICD-O code 9910/3

Introduction

In the WHO classification of tumors, acute megakaryoblastic leukemia (AMKL; FAB: M7; ICD-O code 9910/3; "acute megakaryocytic leukemia"; "acute panmyelosis with myelofibrosis") is an acute leukemia with 20 % or more blasts of which at least 50 % are of the megakaryocyte lineage. The category excludes cases of AML with myelodysplasia-related changes, Down syndrome-related cases, AML with t(1;22)(p13;q13), AML with inv(3)(q21q26.2), and AMl with t(3;3)(q21;q26.2).

Acute Megakaryoblastic Leukemia (AMKL)

AMKL is an uncommon disease that was included in the FAB classification in 1985 (Bennett et al. 1985; Gassmann and Loffler 1995). The disorder occurs in both children and adults and accounts for 3–5 % of acute leukemias. Hematologically, the patients usually present with cytopenia, including thrombocytopenia, although thrombocytosis may also occur. Circulating leukemic blasts are usually rare or lacking, but there are patients with organomegaly and significant numbers of circulating blasts as well. The frequent finding of bone marrow fibrosis has led to the term "acute myelofibrosis" in some reports relating to AMKL, leading to some confusion. AMKL evolves de novo or, less frequently, in the context of a preexisting myeloproliferative disease, e.g., essential thrombocythemia (Radaelli et al. 2002) or chronic myeloid leukemia (Wu et al. 1996). The striking relationship with myeloproliferative disorders occurring in Down syndrome is discussed in a later paragraph (see below). The prognosis of AMKL is usually poor in adults when compared to other types of AML, but the outcome of AMKL in children with or without Down syndrome is more favorable (Hama et al. 2008).

Morphologically, megakaryoblasts are medium-sized or large elements with a round or slightly irregular nucleus and a basophilic, often agranular cytoplasm. In some patients, small cells reminiscent of lymphoid cells or lymphoblasts develop. The cells of interest are mostly reactive for one or more of the thrombocyte glycoproteins, CD41 and/or CD61, while CD42, characterizing more mature thrombocytes, is less frequently present. Typically, CD 36 is positive. In contrast, expression of CD13, CD33, and CD34 is rare or lacking, and MPO is, in most cases, not detectable (Koike 1984; Choate et al. 1988; Jaffe et al. 2001).

Liver Involvement in Acute Megakaryoblastic Leukemia

Hepatic leukemic infiltration in the setting of AMKL (Sato et al. 1990; Vargas et al. 2011) makes part of a distinct clinicopathologic entity, extramedullary AMKL (Chitragar et al. 2011). Similar to CIMF and other myeloproliferative disorders, AMKL can, probably through the action of its cells, induce fibrotic changes in the liver in case of hepatic involvement (Garel et al. 1991; Shibata et al. 1998). This leukemia is well known to exhibit bone marrow fibrosis ("acute myelofibrosis"), and this may be followed by progressive fibrosis in the liver (Shibata et al. 1998). In infantile AMKL (not associated with trisomy 21), hepatomegaly with hepatic fibrosis surrounding intrahepatic blast accumulations has been observed (Garel et al. 1991). It seems that cells of the megakaryocyte lineage play a key role in fibrogenic pathways in these disorders, further discussed in the paragraphs on CIMF and ET. This is exemplified by the observation of frequent and marked myelofibrosis in patients with Ph-positive CML undergoing megakaryoblastic transformation (Van Slyck et al. 1970) and the distinct position of the megakaryoblast in pediatric transitional myeloproliferative disorders (TMD). The megakaryocyte-mediated fibrotic reactions in the liver of children with Down syndrome (DS) is discussed in the paragraph on DS-TMD. The fibrotic liver reaction in the early phases is chiefly characterized by perisinusoidal fibrosis, apparently more pronounced in places where megakaryoblasts/

megakaryocytes have accumulated. There seems to be an intricate spatial relationship between megakaryoblasts and the sinusoidal wall, mature-looking megakaryocytes seemingly extending through the endothelium into the perisinusoidal space of Disse, where they may achieve contact with hepatic stellate cells. These putative biologic contact sites are of interest insofar as factors released by megakaryocytes and cells of AMKL comprise TGF-beta (mainly the isoforms 2 and 3) and PDGF-B (Terui et al. 1990; Reilly et al. 1993; Kitagawa et al. 1994; Wickenhauser et al. 1995; Hassan et al. 1995; Yoon et al. 2000). Furthermore, megakaryocytes express PDGFRbeta (Yoon et al. 2000). These findings suggest a fibrogenic action of megakaryocytes, as further discussed in the paragraphs on CIMF and TMD. It will be interesting to study whether megakaryoblasts/megakaryocytes can engage into distinct contacts with hepatic stellate cells, because HSC are able to form specific aggregates with partner cells of their vicinity, such as hepatocytes during certain phases of liver regeneration (Mabuchi et al. 2004).

Tumor Formation

The cells of AMKL can sometimes develop tumorous lesions as a result of their cohesive nature, and these masses may simulate metastatic disease (Pui et al. 1985; Dharmasena et al. 1986; Penchansky et al. 1989; Ashfaq et al. 1992; Kitagawa et al. 1994; Bozkurt et al. 2008). Such lesions also occur in AMKL developing in Down syndrome (see below; Nito et al. 1983; Hoshikawa et al. 1988). It has to be emphasized, however, that extramedullary megakaryoblastic tumors also occur in other stem cell disorders, e.g., chronic idiopathic myelofibrosis (CIMF) (Chubachi et al. 1995; Chan et al. 1996), probably reflecting a switch in priming of neoplastic progenitor cells. Conversely, megakaryoblastic sarcoma in CIMF can terminate as acute megakaryoblastic leukemia (Hirose et al. 2001). Histologically, the tumorous lesions are composed of a mixture of megakaryoblasts and spindle cells, sometimes with a significant desmoplastic reaction (Ashfaq et al. 1992).

Liver Involvement in Acute Myeloid Leukemia (Megakaryoblastic) with t(1;22)(p13;q13)

This type of acute leukemia seems to be more often associated with liver infiltration, sometimes massive and tumor forming. In a 4-week-old infant with this type of leukemia who had presented with ascites, massive infiltration of hepatic sinusoids by leukemic cells were found. Bone marrow fibrosis appeared after infiltrative disease in the liver and liver fibrosis (Lewis et al. 2008). Tumoral leukemic infiltration of the liver found at autopsy was reported in a neonate with congenital megakaryoblastic leukemia associated with t(1;22)(p13;q13). There was a massive, predominantly periportal leukemic infiltration extending into larger bile ducts and encasing the portal vein (Gong et al. 1999). A large tumor developing in the course of acute megakaryoblastic leukemia and consisting of leukemic cells associated with fibrosis was observed in the liver of a child who presented with a hepatic mass lesion that resembled hepatoblastoma. The child was later shown to have t(1;22)(p13;q13) (Amemiya et al. 2008). Severe liver dysfunction probably related to hepatic leukemic infiltration was observed in a child with putative variant of t(1;22)(p13;q13), i.e., acute megakaryoblastic leukemia with t(17;22)(q21;q13) (Chitlur et al. 2004).

Cytogenetic and Molecular Genetic Features of AMKL

There is no unique chromosomal abnormality associated with AMKL in adults. However, an AML with contribution of megakaryoblasts but not included among AMKL in the WHO classification is associated with at least two distinct cytogenetic abnormalities, i.e., trisomy of chromosome 21 and the reciprocal t(1;22)(p13;q13) chromosomal translocation. AMKL in adults frequently exhibits the cytogenetic abnormalities of secondary leukemia (Duchayne et al. 2003), while the genetic features are more restricted in children

(review: Hama et al. 2012). Rare chromosomal aberrations in AMKL comprise t(10;11)(p13;q14-21), resulting in the fusion of the gene CALM, encoding a clathrin assembly protein, to the gene AF10, a putative transcription factor (Jones et al. 2001); MNX1-ETV6 fusion (Taketani et al. 2008). Gene mutations identified in AMKL include mutations in the thrombopoietin receptor gene (Hussein et al. 2009) and a novel Janus kinase 3 P132A mutation (Riera et al. 2011).

Acute Panmyelosis with Myelofibrosis (APMF)

ICD-O code 9931/3

Introduction

Acute panmyelosis with myelofibrosis (APMF) is a rapidly progressing entity showing partial morphologic overlap with acute megakaryoblastic leukemia. The concept of APMF (acute or malignant myelofibrosis/myelosclerosis) originated from observations showing that part of patients with myeloproliferative disorders associated with myelofibrosis were characterized, in contrast to the usually chronic course, by a rapidly fatal outcome. It is still difficult to judge whether all cases previously assigned to so-called acute myelofibrosis are the same as APMF. The WHO classification defines APMF as an acute panmyeloid proliferation with increased blasts and accompanying fibrosis of the bone marrow that does not meet criteria for AML with myelodysplasia-related changes.

APMF is a disorder characterized by a multilineage myeloid proliferation with a less numerous population of blasts than acute megakaryoblastic leukemia, blasts always being CD34 positive, in contrast to the latter, where only part of the blasts are positive, and the blasts in APMF rarely express megakaryocytic antigens (Orazi et al. 2005). Most cases of APMF show a fibrotic bone marrow with an increased number of immature trilineage hematopoietic elements and dysplastic megakaryocytes predominantly of small size showing hypolobulated or non-lobulated nuclei. Foci of blasts are found in bone marrow, but the overall marrow blast content in APMF is difficult to assess. The cytogenetic patterns seem to be nonspecific (Suvajdzic et al. 2004).

Clinical Features

Patients with APMF often present acutely with symptoms and signs of severe illness, including fatigue and weakness, fever, and bone pain. Splenomegaly is not a feature. The patients always show pancytopenia and the course is characterized by the rapid development of bone marrow insufficiency and the transition to acute myelogenous leukemia in a high proportion of patients (Thiele et al. 2004).

Liver Involvement

In extramedullary disease, APMF can cause considerable diagnostic difficulties (Orazi 2007). In one patient with this disorder, autopsy revealed an infiltration of the liver (sinusoidal cell accumulation) by myeloid and erythroid cell and in part atypical megakaryocytes (Hayashi et al. 1989). This infiltration pattern can also occur in other myeloproliferative disorders and is therefore not specific for APMF. APMF can cause peritoneal hematopoiesis (Metzgeroth et al. 2005) which may involve the liver surface.

Myeloid Proliferations Related to Down Syndrome (Transient Abnormal Myelopoiesis/ Myeloproliferative Disorders in Trisomy 21): High Risk for Acute Megakaryoblastic Leukemia

Introduction

Down (or Down's) syndrome (trisomy 21) is a frequent condition associated with a variety of signs and symptoms. A major gene product that is overexpressed by chromosome 21 polysomy is

the dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (Dyrk1A), which participates in the mechanisms underlying the mental and other physical signs of Down syndrome (Park et al. 2009). In addition, overexpression of Dyrk1A is thought to be involved in leukemogenesis and in the reduced risk of epithelial cancers in these patients (Birger and Izraeli 2012).

A transient myelopoiesis/myeloproliferative disorder (TMD) can develop in newborns and infants with Down syndrome, characterized by a hematologic disorder resembling acute megakaryoblastic leukemia (Engel et al. 1964; Okada et al. 1972; Evans 1975; Weinstein 1978; Lewis et al. 1983; Wong et al. 1988; Homans et al. 1993; Zubizarretta et al. 1995; D'Angelo and Merlo 2003; Zipursky 2003; reviews: Brink 2006; Wiseman et al. 2009). TMD is characterized by an abundance of blasts within the peripheral blood and the liver. These blasts share expression megakaryocytic and erythroid phenotypes (Ito et al. 1995; Bozner 2002). A part of the patients with TMD will develop acute megakaryoblastic leukemia within 1–3 years. There is a complex causal relationship between chromosome 21, GATA1, and megakaryocytopoiesis, briefly discussed later.

Epidemiology and Clinical Presentation

TMD develops in approximately 10 % of Down syndrome newborns. It rarely occurs in newborns with trisomy 21 mosaicism. Newborns and infants with TMD usually present with thrombocytopenia, often associated with excess blasts in peripheral blood. Other cytopenias are less common. Hepatosplenomegaly may be found. Most patients show healing within a few months, but in around 20 % TMD is life-threatening or fatal. In the patient group with low-risk and hence solely observed, peripheral blasts and all other TMD signs cleared at a median of 36 and 49 days from diagnosis, respectively (Gamis et al. 2011). A fraction of the TMD patients undergoes progression (or transformation) to acute megakaryoblastic leukemia (Down syndrome-associated acute megakaryoblastic leukemia; DS-AMKL), with an estimated 30 % of TMD patients developing DS-AMKL within 1–3 years (Cosson et al. 1974; Lewis et al. 1983; Nito et al. 1983; Stoll et al. 1985; Suarez et al. 1985). Children with Down syndrome are 500 times more likely to develop AMKL, but also 20 times more likely to develop acute lymphoblastic leukemia (reviews: Bruwier and Chantrain 2012; Seewald et al. 2012). DS-AMKL post-TMD can be preceded by refractory anemia with excess of blasts (RAEB; Yokoyama et al. 1984), indicating the relation between MDS and TMD. Approximately 20 % of patients with TMD die at an early age due to failure of several organs, specifically also liver disease (Park et al. 2014).

Liver Involvement in TMD

Introduction

TMD is associated with a complex liver disorder mainly caused by blast infiltration and a distinct type of hepatic fibrosis. The disorder presents as hepatomegaly, cholestasis, and hyperbilirubinemia (predominantly conjugated) with minimal elevation of serum transaminases. Neonatal cholestasis develops in a significant percentage of patients with Down syndrome and is always associated with involvement of other organs (Arnell and Fischler 2012). Down syndrome with or without TMD can lead to severe perinatal liver disease with fatal outcome (Ruchelli et al. 1991). Early death is significantly correlated with the degree of transaminase elevation during the course of illness. TMD-associated hepatic fibrosis together with sinusoidal colonization by blasts and megakaryocytes can develop already during the fetal period (Vimercati et al. 2003). There is indirect evidence that liver involvement may develop between the 11th and 13th week of gestation already, in that liver volume determined by 3D ultrasound was increased in Down fetuses in comparison with euploid fetuses (Gielchinsky et al. 2011).

Liver Infiltration with Blastic Cells

In TMD, the liver may be infiltrated by numerous blasts with bilineage features and, sometimes, by a large number of megakaryocytes and their

precursors localized to the sinusoidal compartment (Ruchelli et al. 1991), causing hepatomegaly (Becroft 1993), sometimes already in the fetal period (Macones et al. 1995). Rarely, cells of the megakaryoblast/megakaryocyte lineage may grow in the form of tumors localized to several organs, including the liver (Nito et al. 1983), but megakaryoblastic/megakaryocytic tumor formation in the liver also occurs in those DS patients developing leukemia. In a 2-year-old DS patient with acute megakaryoblastic leukemia, autopsy showed an enlarged liver studded with numerous miliary yellowish nodules, histologically characterized by dense nodular infiltrates consisting of large immature megakaryoblasts. Many of these cells were detectable within sinusoidal lumina as well (Hoshikawa et al. 1988).

Liver Fibrosis

TMD is associated with a distinct type of infantile liver fibrosis in approximately 15–20 % of the patients (Becroft and Zwi 1990; Miyauchi et al. 1992; Yagihashi et al. 1995; Inoue et al. 1996; Villamour Zambrano et al. 1997; Schwab et al. 1998; Hongeng et al. 2000; Brink 2006; Tokairin et al. 2008; Hirabayshi et al. 2011). A diffuse pattern of a sometimes severe perisinusoidal fibrosis is a main alteration. The fibrosis can result in marked disarray of hepatocyte plates and in ductular proliferation with or without cholestasis (Schwab et al. 1998). In an autopsy study of four patients, diffuse intralobular fibrosis was a striking change in all patients (Miyauchi et al. 1992). Hepatic fibrosis in TMD can rarely result in liver cirrhosis (Urano et al. 1983). In one report, moderate iron deposits in hepatocytes were described (Schwab et al. 1998), whereas a heavy iron overload reflecting perinatal hemochromatosis syndrome was detected in the majority of patients with Down syndrome-associated severe perinatal liver disease (Ruchelli et al. 1991). In addition to the liver, the pancreas can also undergo fibrosis in TMD ("perinatal visceral fibrosis"; Becroft and Zwi 1990; Becroft 1993).

Molecular Features

TMD is initiated before birth when fetal liver hematopoietic cells trisomic for chromosome 21 acquire mutations in GATA1 (Roy et al. 2012). Mutations in the gene of the transcription factor GATA1 are associated with both TMD and DS-AMKL (Ito et al. 1995; Mundschau et al. 2003; Xu et al. 2003; Greene et al. 2003; reviews: Izraeli et al. 2007; Ciovacco et al. 2008; Shimizu et al. 2008; Gamis and Smith 2012; Toki et al. 2013). GATA1 is a member of a transcription factor family that affects growth and maturation of several cell systems, but is expressed primarily in hematopoietic cells, and is essential for the development of erythroid cells, megakaryocytes, eosinophils, and mast cells. Absence of GATA1 leads to differentiation arrest and apoptosis of erythroid progenitor cells and promotes the accumulation of immature megakaryocytes. GATA1 mutations are an early event in the pathway leading from latent TMD clones to AMKL (Hitzler et al. 2003; Rainis et al. 2003; Gurbuxani et al. 2004), but abnormal telomerase expression may also play a role in the malignant conversion of TMD cell lineages (Holt et al. 2002). Recently, GATA1 mutations have been identified in TMD blasts from every infant examined, supporting the view that GATA1 plays a crucial role in Down syndrome leukemogenesis (Mundschau et al. 2003). GATA1 mutations occur in utero in most DS-TMD and DS-AMKL; multiple separate GATA1 mutant clones can develop in an individual, and these mutations may occur without clinical signs of disease (Ahmed et al. 2004; Yoshida et al. 2013). A fetal origin of the GATA1 mutations has been verified in identical twins with TMD and DS-AMKL (Shimada et al. 2004). There are, however, also situations where polysomy of chromosome 21 is associated with AMKL in the absence of GATA1 mutations. For example, tetrasomy 21 as a sole acquired abnormality was found in pediatric AMKL without GATA1 mutations (Shin et al. 2008). In the pathways leading to megakaryocyte differentiation, GATA1 interacts with components of the transcriptional elongation factor, P-TEFb, a complex containing cyclin T1 and the cyclin-dependent kinase 9/Cdk9 (Elagib et al. 2008). GATA1 mutations in Down syndrome

may act in a genetic network also involving PML and SUMO3, as found by the detection of a 15q24 microdeletion in patients with TMD (Haemmerling et al. 2012). A part of Down patients with TMD and AMKL have acquired gain- or loss-of-function mutations of JAK3/Janus kinase 3 gene mutations (De Vita et al. 2007). Recent studies have also shown that the critical gene on chromosome 21, DYRK1A, is involved in leukemogenesis of AMKL (Malinge et al. 2012). Furthermore, Down syndrome critical region 1 (DSCR1), a member of the calcipressin family of calcineurin inhibitors, is overexpressed in Down syndrome. Overexpression of DSCR1 causes destabilization of the calcineurin/nuclear factor of activated T cells (NFAT) pathway, a mechanism that drives the proliferation of megakaryocyte precursors and may act in AMKL leukemogenesis (Kyttälä et al. 2009).

References

Abe Y, Takatsuki H, Okada Y, Saito A, Kimura T, Nishimura J (1999) Mucosa-associated lymphoid tissue type lymphoma of the gallbladder associated with acute myeloid leukemia. Intern Med 38:442–444

Ahmed M, Sternberg A, Hall G, Thomas A, Smith O, O'Marcaigh A, Wynn R, Stevens R, Addison M et al (2004) Natural history of GATA1 mutations in Down syndrome. Blood 103:2480–2489

Alama Zaragoza MA, Robles Iniesta A, Roca Adelantado I, Sales Maicas MA, Ferrandez Izquierdo A, Roman Sanchez P (2003) Hepatic granulocytic sarcoma: an unusual presentation (in Spanish). An Med Interna 20:141–144

Alimena G, De Cuia MR, Diverio D, Gastaldi R, Nanni M (1987) The karyotype of blastic crisis. Cancer Genet Cytogenet 26:39–50

Allan RR, Wadswoerth LD, Kalousek DK, Massing BG (1989) Congenital erythroleukemia: a case report with morphological, immunophenotypic, and cytogenetic findings. Am J Hematol 31:114–121

Amemiya S, Akahane M, Takita J, Igarashi T, Ohtomo K (2008) Imaging findings of upper abdominal involvement by acute megakaryoblastic leukaemia. Pediatr Radiol 38:457–461

Amitrano L, Guardascione MA, Schiavone EM, Brancaccio V, Antinolfi I, Iannaccone L et al (2006) Hepatic vein thrombosis leading to fulminant hepatic failure in a case of acute non-promyelocytic myelogenous leukemia. Blood Coagul Fibrinolysis 17:59–61

Anikin BS (1963) A case of chronic basophilic leukemia (in Russian). Probl Gematol Pereliv Krovi 8:50–51

Armand P, Kim HT, Rhodes J, Sainvil MM, Cutler C, Ho VT, Koreth J, Alyea P, Hearsey D et al (2011) Iron overload in patients with acute leukemia or MDS undergoing myeloablative stem cell transplantation. Biol Blood Marrow Transplant 17:852–860

Armitage et al. 1978. http://www.ncbi.nlm.nih.gov/pubmed/630548

Arnell H, Fischler B (2012) Population-based study of incidence and clinical outcome of neonatal cholestasis in patients with Down syndrome. J Pediatr 161:899–902

Ashfaq R, Weinberg AG, Argyle CA (1992) Acute megakaryoblastic leukemia simulating carcinoma. Am J Clin Pathol 98:55–60

Atkinson J, Hrisinko MA, Weil SC (1992) Erythroleukemia: a review of 15 cases meeting 1985 FAB criteria and survey of the literature. Blood Rev 6:204–214

Aviles Miranda et al. 1981. http://www.ncbi.nlm.nih.gov/pubmed/7336068

Ball ED, Fanger MW (1983) The use of myeloid-specific monoclonal antibodies in the diagnosis of leukemia. Diagn Immunol 1:90–95

Bank A, Larsen PR, Anderson HM (1966) Di Guglielmo's syndrome after polycythemia. N Engl J Med 275:489

Barcos M, Lane W, Gomez GA, Han T, Freeman A, Preisler H, Henderson E (1987) An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). Cancer 60:827–837

Barlas O (1954) A case of chronic basophilic leukemia. Sang 25:147–156

Becroft DM (1993) Fetal megakaryocytic dyshemopoiesis in Down syndrome: association with hepatic and pancreatic fibrosis. Pediatr Pathol 13:811–820

Becroft DM, Zwi LJ (1990) Perinatal visceral fibrosis accompanying the megakaryoblastic leukemoid reaction of Down syndrome. Pediatr Pathol 10:397–406

Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C (1985) Criteria for the diagnosis of acute leukemia of megakaryocyte lineage (M7). A report of the French-American-British Cooperative Group. Ann Intern Med 103:460–462

Best-Aguilera CR, Vazquez-Del Mercado M, Munoz-Valle JF, Herrera-Zarate L, Navarro-Hernandez RE et al (2005) Massive myeloid sarcoma affecting the central nervous system, mediastinum, retroperitoneum, liver, and rectum associated with acute myeloblastic leukaemia: a case report. J Clin Pathol 58:325–327

Betz BL, Hess JL (2010) Acute myeloid leukemia diagnosis in the 21st century. Arch Pathol Lab Med 134:1427–1433

Birger Y, Izraeli S (2012) DYRK1A in Down syndrome: an oncogene or tumor suppressor ? J Clin Invest 122:807–810

Birkle K (1950) Atypische chronische erythroblastose. Dtsch Arch Klin Med 197:428–437

Bjure J, Fichtelius KE, Ranström S (1960) On the problem of congenital hemopathies (congenital myeloid and erythremic blood picture). Acta Paediatr 49:358–370

Blum S, Angelillo-Scherrer A (2012) Block of red blood cell maturation in acute erythroid leukemia. Blood 120:1974

Böttiger LE, Hellström O (1956) Erythroblastomatosis. Acta Haematol 16:329–337

Bozkurt SU, Berrak SG, Tugtepe H, Canpolat C, Palanduz S, Tecimer T (2008) Acute megakaryoblastic leukemia mimicking small round cell tumor with novel t(1;5)(q21;p13). APMIS 116:163–166

Bozner P (2002) Transient myeloproliferative disorder with erythroid differentiation in Down syndrome. Arch Pathol Lab Med 126:474–477

Brink DS (2006) Transient leukemia (transient myeloproliferative disorder, transient abnormal myelopoiesis) of Down syndrome. Adv Anat Pathol 13:256–262

Bross ID, Viadana E, Pickren JW (1975) The metastatic spread of myeloma and leukemias in men. Virchows Arch A Pathol Anat Histol 365:91–101

Bruwier A, Chantrain CF (2012) Hematological disorders and leukemia in children with Down syndrome. Eur J Pediatr 171:1301–1307

Camos M, Esteve J, Rimola A, Grande L, Rozman M, Colomer D, Villamor N, Costa D, Montserrat E (2004) Increased incidence of acute myeloid leukemia after liver transplantation ? Description of three new cases and review of the literature. Transplantation 77:311–313

Carmel R, Coltman CA, Yatteau RF, Costanzi JJ (1970) Association of paroxysmal nocturnal hemoglobinuria with erythroleukemia. N Engl J Med 283:1329–1331

Case Records of the Massachusetts General Hospital (Case 32-1988) (1988) N Engl J Med 319:356–364

Case Records of the Massachusetts General Hospital (Case 22-1990) (1990) N Engl J Med 322:1585–1594

Chan AC, Kwong YL, Lam CC (1996) Granulocytic sarcoma of megakaryoblastic differentiation complicating chronic idiopathic myelofibrosis. Hum Pathol 27:417–420

Chevallier P, Marinone G (1951) Acute basophilic leukosis (in French). Sang 22:374–385

Chi CH, Lagerlof B, Lantz B, Reizenstein P (1976) Autopsy findings in leukaemia. Scand J Haematol 17:251–257

Chitlur MB, Bhambhani K, Mohamed AN, Ravindranath Y, Savasan S (2004) Acute megakaryoblastic leukemia with t(17;22)(q21;q13) and liver dysfunction. Cancer Genet Cytogenet 154:167–168

Chitragar S, Agarwal S, Iyer VK, Mathur SR, Karak AK, Chharchhodawala T, Sharma A et al (2011) Cytomorphological features of extramedullary acute megakaryoblastic leukemia on fine needle aspiration and cerebrospinal fluid cytology: a case report. Cytojournal 8:17

Choate JJ, Domenico DR, McGraw TP, Fareed J, Molanr Z, Schumacher HR (1988) Diagnosis of acute megakaryoblastic leukemia by flow cytometry and immunoalkaline phosphatase techniques. Utilization of new monoclonal antibodies. Am J Clin Pathol 89:247–253

Choi JW, Kim Y, Fujino M, Ito M (2002) Significance of fetal hemoglobin-containing erythroblasts (F blasts) and the F blast/F cell ratio in myelodysplastic syndromes. Leukemia 16:1478–1483

Chubachi A, Wakui H, Miura I, Saitoh M, Nishinari T, Nishimura S, Miura AB (1995) Extramedullary megakaryoblastic tumors following an indolent phase of myelofibrosis. Leuk Lymphoma 17:351–354

Ciovacco WA, Raskind WH, Kacena MA (2008) Human phenotypes associated with GATA-1 mutations. Gene 427:1–6

Coleman TA, Hamill RL, Ford SM (2001) Erythroleukemia following erythropoietin therapy, extramedullary hematopoiesis, and splenectomy in a patient with myelofibrosis and myeloid metaplasia. Am J Hematol 67:214–215

Cornfield DB (2012) Erythroblastic sarcoma: an extremely rare variant of myeloid sarcoma. Hum Pathol 43:2080–2083

Corwin WC, Nettleship A (1959) A solitary erythroblastoma of the liver; report of a case. J Lab Clin Med 53:882–887

Cosson A, Despress P, Gazengel C et al (1974) Syndrome leucémique singulier chez un nouveau-né trisomique 21: prolifération mégacaryocyto-plaquettaire: syndrome de coagulation intravasculaire diffuse. Nouv Rev Fr Hematol 14:181–198

Cowall DE, Pasquale DN, Dekker P (1979) Paroxysmal nocturnal hemoglobinuria terminating as erythroleukemia. Cancer 43:1914–1916

D'Angelo G, Merlo P (2003) Transient myeloproliferative syndrome/transient acute myeloid leukemia in a newborn with Down syndrome: a case report and literature review. Lab Hematol 9:38–41

Dammert K, Kaipainen WJ (1960) Acute erythremic myelosis as a terminal stage of polycythemia vera. Acta Pathol Microbiol Scand 50:156

Danopoulos E, Angelopoulos B (1953) Peculiar case of acute myeloid leukemia manifesting clinically as liver cirrhosis. Sang 24:280–282

Day DS, Gay JN, Kraus JS, Sabio H, Satya-Prakash KL, Russell B, Wanslyey WD (1997) Erythroleukemia of childhood and infancy: a report of two cases. Ann Clin Lab Sci 27:142–150

De Vita S, Mulligan C, McElwaine S, Dagna-Bricarelli F, Spinelli M, Basso G, Nizetic D et al (2007) Loss-of-function JAK3 mutations in TMD and AMKL of Down syndrome. Br J Haematol 137:337–341

Denburg JA, Browman G (1988) Prognostic implications of basophil differentiation in chronic myeloid leukemia. Am J Hematol 27:110–114

Dharmasena F, Wickham N, McHugh PJ, Catovsky D, Galton DA (1986) Osteolytic tumors in acute megakaryoblastic leukemia. Cancer 58:2273–2277

Di Guglielmo G (1917) Richerche di hematologia. I. Un caso di eritroleucemia. Folio Med 3:386

Di Guglielmo G (1926) Eritremia acute. Bolletino Soc Med Chir 1:665–673

Di Guglielmo G (1962) Le malattie eritremiche ed eritroleucemiche. In Pensiero Scientifico Ed., Roma
Dick FR (1991) Evolution of the French-American-British (FAB) proposals. Am J Clin Pathol 96:153–155
Domingo-Claros A, Larriba I, Rozman M, Irriguible D, Vallespi T, Aventin A, Ayats R et al (2002) Acute erythroid neoplastic proliferations. A biological study based on 62 patients. Haematologica 87:148–153
Dubois-Ferrière H, Chapnis-Hoffmann H, Hürni A, Crucheaud A (1955) Erythroblastomatose diffuse avec reaction monocytaire sanguine. Schweiz Med Wschr 85:46–947
Duchayne E, Fenneteau O, Pages MP, Sainty D, Arnoulet C, Dastugue N, Garand R, Flandrin G, Groupe Français d'Hématologie Cellulaire; Groupe Français de Cytogénétique Hématologique (2003) Acute megakaryoblastic leukaemia: a national clinical and biological study of 53 adult and childhood cases by the Groupe Français d'Hématologie Cellulaire (GFHC). Leuk Lymphoma 44:49–58
Eisen A, Dovrish Z, Hadari R, Lew S, Amital H (2008) Jaundice and acute liver failure as the first manifestation of acute myeloid leukemia. Isr Med Assoc J 10:733–735
Elagib KE, Mihaylov IS, Delehanty LL, Bullock GC, Ouma KD, Caronia JF, Gonias SL et al (2008) Cross-talk of GATA-1 and P-TEFb in megakaryocyte differentiation. Blood 112:4884–4894
Engel RR, Hammond D, Eitzman DV, Pearson H, Krivit W (1964) Transient congenital leukemia in 7 infants with mongolism. J Pediatr 65:303–305
Estey EH (2013) Acute myeloid leukemia: 2013 update on risk-stratification and management. Am J Hematol 88:318–327
Evans DI (1975) Acute myelofibrosis in children with Down's syndrome. Arch Dis Child 50:458–462
Ferrara F, Schiffer CA (2013) Acute myeloid leukaemia in adults. Lancet 381:484–495
Forni M, Meyer PR, Levy NB, Lukes RJ, Taylor CR (1983) An immunohistochemical study of hemoglobin A, hemoglobin F, muramidase, and transferrin in erythroid hyperplasia and neoplasia. Am J Clin Pathol 80:145–151
Funakoshi Y, Matsuoka H, Yamamoto K, Yakushijin K, Inui Y, Okamura A, Takeuchi M et al (2011) Therapy-related pure erythroid leukemia with hepatic infiltration and hemophagocytic syndrome. Intern Med 50:3031–3035
Gamis AS, Smith FO (2012) Transient myeloproliferative disorder in children with Down syndrome: clarity to this enigmatic disorder. Br J Haematol 159:277–287
Gamis AS, Alonzo TA, Gerbing RB, Hilden JM, Sorrell AD, Sharma M, Loew TW et al (2011) Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children's Oncology Group Study A2971. Blood 118:6752–6759
Garcia S, Miguel A, Miguel A, Linares M, Navarro M, Colomina P (1989) Idiopathic myelofibrosis terminating in erythroleukemia. Am J Hematol 32:70–71
Garel D, Mielot F, Gaulard P, Quillard J, Dommergues JP, Tchernia G (1991) Acute megakaryocytic leukemia (AMKL) with major myelofibrosis in an infant. Diagnosis by liver biopsy and response to treatment. Nouv Rev Fr Hematol 33:5–8
Gassmann W, Loffler H (1995) Acute megakaryoblastic leukemia. Leuk Lymphoma 18(Suppl 1):69–73
Genova V, Georgief Z (1974) Disseminated intravascular coagulation in blastic leukemia and certain other disorders (in French). Folia Haematol Int Mag Klein Morphol Blutforsch 101:300–312
Gielchinsky Y, Zvanca M, Minekawa R, Persico N, Nicolaides KH (2011) Liver volume in trisomy 21 and euploid fetuses at 11 to 13 weeks. Prenat Diagn 31:28–32
Giles FJ (2002) Gemtuzumab ozogamicin: promise and challenge in patients with acute myeloid leukemia. Expert Rev Anticancer Ther 2:630–640
Giles FJ, Kantarjian HM, Kornblau SM, Thomas DA, Garcia-Manero G, Waddelow TA, David CL, Phan AT et al (2001) Mylotarg (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. Cancer 92:406–413
Glenjen N, Hovland R, Wergeland L, Wendelbo O, Ernst P, Bruserud O (2003) The angioregulatory phenotype of native human acute myelogenous leukemia cells: influence of karyotype, Flt3 abnormalities and differentiation status. Eur J Haematol 71:163–173
Gong J, Jéquier S, Brundler MA, Gumy-Pausc F, Wacker P (1999) Hepatic involvement by congenital megakaryocytic leukemia in a neonate: sonographic features. AJR Am J 173:1063–1064
Goor Y, Goor O, Michalewitcz R, Cabili S (2002) Acute myeloid leukemia presenting as obstructive jaundice. J Clin Gastroenterol 34:485–486
Goreczky and Toth 1967. http://www.ncbi.nlm.nih.gov/pubmed/4173665
Greene ME, Mundschau G, Wechsler J, McDevitt M, Gamis A, Karp J, Gurbuxani S, Arceci R, Crispino JD (2003) Mutations in GATA 1 in both transient myeloproliferative disorder and acute megakaryoblastic leukemia of Down syndrome. Blood Cells Mol Dis 31:351–356
Griesser GH, Horny HP (1987) Hematopathological features of acute erythremia (morbus Di Guglielmo). A contribution to the classification and differential diagnosis of erythroid neoplasms. Acta Haematol 77:193–197
Gruber GB (1930) 6. Die Leber bei Erkrankungen des blut- und lymphbildenden Gewebs-Apparates. In: Henke F, Lubarsch O (eds) Handbuch der speziellen pathologischen Anatomie und Histologie, vol 5, Verdauungsdrüsen, Erster Teil, Leber. Julius Springer, Berlin, pp 661–663

Gurbuxani S, Vyas P, Crispino JD (2004) Recent insights into the mechanisms of myeloid leukemogenesis in Down syndrome. Blood 103:399–406

Gutierrez de Guzman J, Clavero C, Palomo MA, Oyonarte S, Maldonado J (1987) Obstructive jaundice caused by granulocytic sarcoma. An unusual presentation of an acute leukemia (in Spanish). Rev Clin Esp 180:309–310

Hadjiyannakis A, Fletcher WA, Lebrun DP, van Wylick RC, Dow KE (1998) Congenital erythroleukemia in a neonate with severe hypoxic ischemic encephalopathy. Am J Perinatol 15:689–694

Haemmerling S, Behnisch W, Doerks T, Korbel JO, Bork P, Moog U, Hentze S, Grasshoff U et al (2012) A 15q24 microdeletion in transient myeloproliferative disease (TMD) and acute megakaryoblastic leukaemia (AMKL) implicates PML and SUMO3 in the leukaemogenesis of TMD/AMKL. Br J Haematol 157:180–187

Halton JM, Nazir DJ, McQueen MJ, Barr RD (1998) Blood lipid profiles in children with acute lymphoblastic leukemia. Cancer 83:379–384

Hama A, Yagasaki H, Takahashi Y, Nishio N, Muramatsu H, Yoshida N, Tanaka M et al (2008) Acute megakaryoblastic leukaemia (AMKL) in children: a comparison of AMKL with and without Down syndrome. Br J Haematol 140:552–561

Hama A, Muramatsu H, Makishima H, Sugimoto Y, Szpurka H, Jasek M, O'Keefe C et al (2012) Molecular lesions in childhood and adult acute megakaryoblastic leukaemia. Br J Haematol 156:316–325

Harwerth HG (1952) Die acute erythroleukämie. Erg Inn Med 3:375–406

Hassan HT, Hanauske AR, Lux E, Kleine HD, Freund M (1995) A new fibroblast growth stimulating activity from the human megakaryoblastic leukaemia cell line ELF-153: in vitro and in vivo findings. Int J Exp Pathol 76:361–367

Hasserjian et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11253132

Hasserjian RP, Zuo Z, Garcia C, Tang G, Kasyan A, Luthra R, Abruzzo LV, Kantarjian HM et al (2010) Acute erythroid leukemia: a reassessment using criteria refined in the 2008 WHO classification. Blood 115:1985–1992

Hayashi Y, Tange T, Chi LC, Ishida T, Kitamura T, Kitamura K, Urano Y (1989) An autopsy case of myelodysplastic syndrome (MDS): diagnostic problems between MDS and the other haematopoietic disorders including acute myelofibrosis. Nihon Ketsueki Gakkai Zasshi 52:49–54

Hirabayashi K, Shiohara M, Takahashi D, Saito S, Tanaka M, Yanagisawa R, Sakashita K et al (2011) retrospective analysis of factors for development of liver dysfunction in transient leukemia of Down syndrome. Leuk Lymphoma 52:1523–1527

Hirose Y, Masaki Y, Shimoyama K, Sugai S, Nojima T (2001) Granulocytic sarcoma of megakaryoblastic differentiation in the lymph nodes terminating as acute megakaryoblastic leukemia in a case of chronic idiopathic myelofibrosis persisting for 16 years. Eur J Haematol 67:194–198

Hitzler JK, Cheung J, Li Y, Scherer SW, Zipursky A (2003) GATA1 mutations in transient leukemia and acute megakaryoblastic leukemia of Down syndrome. Blood 101:4301–4304

Holt SE, Brown EJ, Zipursky A (2002) Telomerase and the benign and malignant megakaryoblastic leukemias of Down syndrome. J Pediatr Hematol Oncol 24:14–17

Homans AC, Verissimo AM, Vlacha V (1993) Transient abnormal myelopoiesis of infancy associated with trisomy 21. Am J Pediatr Hematol Oncol 15:392–399

Hongeng S, Pakakasame S, Hathirat P, Phuapradid P, Worapongpaiboon S (2000) Diffuse hepatic fibrosis with transient myeloproliferative disorders in Down syndrome. J Pediatr Hematol Oncol 22:543–544

Hoshikawa N, Shirasawa K, Niino H, Hasegawa N, Fukuzumi N (1988) Acute leukemia of megakaryocyte lineage with tumor formation. An autopsy case of patient with Down's syndrome. Acta Pathol Jpn 38:193–207

Hussein K, Bock O, Theophile K, Schulz-Bischof K, Porwit A, Schlue J, Jonigk D, Kreipe H (2009) MPLW515L mutation in acute megakaryoblastic leukemia. Leukemia 23:852–855

Iida S, Takeuchi G, Komatsu H, Banno S, Wakita A, Nitta M, Takada K, Mitomo Y, Yamamoto M, Masuoka H et al (1991) Blastic form of acute erythremia: report of an autopsy case (in Japanese). Rinsho Ketsueki 32:1486–1491

Inoue T, Kobayashi Y, Kusuda S (1996) Unusual hepatic fibrosis in three cases of Down syndrome (in Japanese). Rinsho Byori 44:590–594

Iqbal et al. 1996. http://www.ncbi.nlm.nih.gov/pubmed/8722371

Ito E (1970) Histopathological studies on leukemic liver and spleen, with special reference to the sizes of leukemia cells infiltrating the liver. Yonago Acta Med 14:106–130

Ito et al. 1985. http://www.ncbi.nlm.nih.gov/pubmed/3897144

Ito E, Kasai M, Hayashi Y, Toki T, Arai K, Yokoyama S, Kato K, Tachibana N, Yamamoto M, Yokoyama M (1995) Expression of erythroid-specific genes in acute megakaryoblastic leukaemia and transient myeloproliferative disorder in Down's syndrome. Br J Haematol 90:607–614

Izraeli S, Rainis L, Hertzberg L, Smooha G, Birger Y (2007) Trisomy of chromosome 21 in leukemogenesis. Blood Cells Mol Dis 39:156–159

Jaffe ES, Harris NL, Stein H, Vardiman JW (eds) (2001) Pathology and genetics of tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours. IARC Press, Lyon

Jaing TH, Yang CP, Chang KW, Wang CJ, Chiu CH, Luo CC (2001) Extrahepatic obstruction of the biliary tract as the presenting feature of acute myeloid leukemia. J Pediatr Gastroenterol Nutr 33:620–622

Jones LK, Chaplin T, Shankar A, Neat M, Patel N, Samuel DP, Hill AS, Debernardi S et al (2001) Identification and molecular characterization of a CALM-AF10 fusion in acute megakaryoblastic leukaemia. Leukemia 15:910–914

Kasyan A, Medeiros LJ, Zuo Z, Santos FP, Ravandi-Kashani F, Miranda R, Vadhan-Raj S et al (2010) Acute erythroid leukemia as defined in the World Health Organization classification is a rare and pathogenetically heterogeneous disease. Mod Pathol 23:1113–1126

Keifer J, Zaino R, Ballard JO (1984) Erythroleukemic infiltration of a lymph node: use of hemoglobin immunohistochemical techniques in diagnosis. Hum Pathol 15:1090–1093

Kiga Y, Umeda M, Kaneko H, Hirahata T, Ishikawa I, Takatsuki Y, Mugitani H, Tsukahara T et al (1980) A case of paroxysmal nocturnal hemoglobinuria which occurred during the course of erythroleukemia (in Japanese). Rinsho Ketsueki 21:1193–1200

King DJ, Ewen SW, Sewell HF, Dawson AA (1987) Obstructive jaundice. An unusual presentation of granulocytic sarcoma. Cancer 60:114–117

Kitagawa M, Yoshida S, Ishige I, Minami J, Kuwata T, Tanizawa T, Kamiyama R (1994) Immunolocalization of platelet-derived growth factor, transforming growth factor.beta, and fibronectin in acute megakaryoblastic leukemia manifesting tumor formation. Hum Pathol 25:723–726

Kitagawa J, Hara T, Tsurumi H, Oyama M, Moriwaki H (2009) Pure erythroid leukemia with hemophagocytosis. Intern Med 48:1695–1698

Kitmacher P, Zarski JP, Barnoud D, Gressin R, Guignier M, Sotto JJ, Rachail M (1991) Acute severe steatosis following an acute necrotic, hemorrhagic pancreatitis after treatment with asparaginase (in French). Ann Gastroenterol Hepatol (Paris) 27:271–272

Koike T (1984) Megakaryoblastic leukemia: the characterization and identification of megakaryoblasts. Blood 64:683–692

Kowal-Vern A, Cotelingam J, Schumacher HR (1992) The prognostic significance of proerythroblasts in acute erythroleukemia. Am J Clin Pathol 98:34–40

Krishbaum JD, Preuss FS (1943) Leukemia: a clinical and pathologic study of one hundred and twenty-three fatal cases in a series of 14,000 necropsies. Arch Intern Med 71:777–792

Kuroda N, Mizobuchi M, Shimamura Y, Daibata M, Miyoshi I, Ohara M, Hirouchi T et al (2006) Bridging necrosis and reticulin bridging fibrosis induced by intrahepatic involvement of acute biphenotypic leukemia. APMIS 114:908–911

Kyttälä S, Habermann I, Minami T, Ehninger G, Kiani A (2009) Regulation of Down syndrome critical region 1 expression by nuclear factor of activated T cells in megakaryocytes. Br J Haematol 144: 395–408

Lasson U, Goos M (1981) Congenital erythroleukemia: a case report. Blut 43:237–241

Lazure T, Beauchamp A, Croisille L, Ferlicot S, Feneux D, Fabre M (2003) Congenital anerythremic erythroleukemia presenting as hepatic failure. Arch Pathol Lab Med 127:1362–1365

Lazzaro G (1933) Mielosi eritremica acuta. Haematologica 14:483

Lee JY, Lee WS, Jung MK, Jeon SW, Cho CM, Tak WY, Kweon YO, Kim SK et al (2007) Acute myeloid leukemia presenting as obstructive jaundice caused by granulocytic sarcoma. Gut Liver 1:182–185

Leopold LH, Berger MS, Feingold J (2002) Acute and long-term toxicities associated with gemtuzumab ozogamicin (mylotarg (r)) therapy of acute myeloid leukemia. Clin Lymphoma 2(Suppl 1): S29–S34

Lertprasertsuke N, Tsutsumi Y (1991) An unusual form of chronic myeloproliferative disorder. Aleukemic basophilic leukemia. Acta Pathol Jpn 41:73–81

Lewis DS, Thompson M, Hudson E, Liberman MM, Samson D (1983) Down's syndrome and acute megakaryoblastic leukaemia – case report and review of the literature. Acta Haematol 70:236–242

Lewis MS, Kaicker S, Strauchen JA, Morotti RA (2008) Hepatic involvement in congenital acute megakaryoblastic leukemia: a case report with emphasis on the liver pathology findings. Pediatr Dev Pathol 11:55–58

Li CY, Yam LT (1987) Cytochemical characterization of leukemic cells with numerous cytoplasmic granules. Mayo Clin Proc 62:978–985

Lillicrap DP, Ginsburg AD, Corbett WE (1982) Relapse of acute myelogenous leukemia presenting with extrahepatic obstruction of the biliary tract. Can Med Assoc J 127:1000–1001

Limarzi LR, Levinson SA (1943) An undescribed type of erythropoiesis observed in human sternal marrow. Arch Pathol 36:127–130

Liso V, Troccoli G, Specchia G (1978) Mast cell leukemia and acute basophilic leukemia. Cytochemical studies. Bibl Haematol 45:142–146

Liu PI, Ishimaru T, McGregor DH et al (1973) Autopsy study of granulocytic sarcoma (chloroma) in patients with myelogenous leukemia, Hiroshima-Nagasaki 1949–1969. Cancer 31:948–955

Liu W, Hasserjian RP, Zhang L, Miranda RN, Medeiros LJ, Wang SA (2011) Pure erythroid leukemia: a reassessment of the entity using the 2008 World Health Organization classification. Mod Pathol 24:375–383

Liu CJ, Hong YC, Yang CF, Liu SH, Gau JP, Liu JH, Hsiao LT, Liu CY, Yu YB et al (2012) Clinicopathologic features and outcome of acute erythroid leukemia based on 2008 revised World health Organization classification. Leuk Lymphoma 53:289–294

Locasciulli et al. 1983. http://www.ncbi.nlm.nih.gov/pubmed/6402922

Luzzatto L, Familusi JB, Williams CK, Junaid TA, Rotoli B, Alfinito F (1979) The PNH abnormality in myeloproliferative disorders: association of PNH and

acute erythremic myelosis in two children. Haematologica 64:13–30
Mabuchi A, Mullaney I, Sheard PW, Hessian PA, Mallard BL, Tawadrous MN, Zimmermann A, Senoo H, Wheatley AM (2004) Role of hepatic stellate cell/hepatocyte interaction and activation of hepatic stellate cells in the early phase of liver regeneration in the rat. J Hepatol 40:910–916
Macones GA, Johnson A, Tilley D, Wade R, Wapner R (1995) Fetal hepatosplenomegaly associated with transient myeloproliferative disorder in trisomy 21. Fetal Diagn Ther 10:131–133
Malinge S, Bliss-Moreau M, Kirsammer G, Diebold L, Chlon T, Gurbuxani S, Crispino JD (2012) Increased dosage of the chromosome 21 ortholog Dyrk1a promotes megakaryoblastic leukemia in a murine model of Down syndrome. J Clin Invest 122:948–962
Mano Y, Yokoyama K, Chen CK, Tsukada Y, Ikeda Y, Okamoto S (2004) Acute myeloid leukemia presenting with obstructive jaundice and granulocytic sarcoma of the common bile duct (in Japanese). Rinsho Ketsueki 45:1039–1043
Markham RE, Butler F, Goh K, Rowley PT (1983) Erythroleukemia manifesting delta beta-thalassemia. Hemoglobin 7:71–78
Mathé G, Schwarzenberg L, Mery AM et al (1966) Extensive histological and cytological survey of patients with acute leukemia in "complete remission". Br Med J 1:640–642
Mathews E, Laurie T, O'Riordan K, Nabhan C (2008) Liver involvement with acute myeloid leukemia. Case Rep Gastroenterol 2:121–124
Matsueda K, Yamamoto H, Doi I (1998) An autopsy case of granulocytic sarcoma of the porta hepatis causing obstructive jaundice. J Gastroenterol 33:428–433
Mazzella FM, Kowal-Vern A, Shrit MA, Wibowo AL, Rector JT, Cotelingam JD, Collier J, Mikhael A, Cualing H, Schumacher HR (1998) Acute erythroleukemia: evaluation of 48 cases with reference to classification, cell proliferation, cytogenetics, and prognosis. Am J Clin Pathol 110:590–598
McCord RG, Gilbert EF, Joo PJ (1973) Acute leukemia presenting as jaundice with acute liver failure. Clin Pediatr (Phila) 12:7A, passim
McGrath KE, Kingsley PD, Koniski AD, Porter RL, Bushnell TP, Palis J (2008) Enucleation of primitive erythroid cell generates a transient population of "pyrenocytes" in the mammalian fetus. Blood 111:2409–2417
McKee LC, Collins RD (1974) Intravascular leukocyte thrombi and aggregates as a cause of morbidity and mortality in leukemia. Medicine (Baltimore) 53:463–478
Meletis J, Terpos E (2003) Recent insights into the pathophysiology of paroxysmal nocturnal hemoglobinuria. Med Sci Monit 9:RA161–RA172
Metzgeroth G, Reiter A, Back W, Anders M, Hehlmann R, Hastka J (2005) Peritoneal haematopoiesis in acute panmyelosis with myelofibrosis. Br J Haematol 130:1
Michiels et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9299860
Mirchandani I, Palutke M, Dutcher TF, Bishop CR (1983) The value of immunoperoxidase studies in the diagnosis of two cases of acute leukemia. Scand J Haematol 30:207–210
Miyauchi J, Ito Y, Kawano T, Tsunematsu Y, Shimizu K (1992) Unusual diffuse liver fibrosis accompanying transient myeloproliferative disorder in Down's syndrome: a report of four autopsy cases and proposal of a hypothesis. Blood 80:1521–1527
Mundschau G, Gurbuxani S, Gamis AS, Greene ME, Arceci RJ, Crispino JD (2003) Mutagenesis of GATA1 ia an initiating event in Down syndrome leukemogenesis. Blood 101:4298–4300
Nasi C, Favero A, Testoni PP (1960) Chronic basophilic leukemia (in Italian). Minerva Med 51:527–531
Neiman RS, Barcos M, Berard C, Bonner H, Mann R, Rydell RE, Bennett JM (1981) Granulocytic sarcoma: a clinicopathologic study of 61 biopsied cases. Cancer 48:1426–1437
Niedobitek F (1968) Fibrosis of the liver in acute leucosis of children (in German). Verh Dtsch Ges Pathol 52:553–557
Nies BA, Bodey GP, Thomas LB, Brecher G, Freireich EJ (1965) The persistence of extramedullary leukemic infiltrates during bone marrow remission of acute leukemia. Blood 26:133–141
Nishihori T, Fernandez HF, Coppola D, Ochoa-Bayona JL, Lancet JE, Komrokji RS et al (2011) Hepatobiliary manifestations of acute myeloid leukemia. Leuk Res 35:e81–e83
Nissenblatt MJ (1980) Basophilic transformation of chronic myelogenous leukemia. South Med J 73:1316–1319
Nito T, Terashima K, Matsuda M, Imai Y, Yokoyama S, Hayashi T (1983) Transient abnormal myelopoiesis followed by acute megakaryoblastic leukemia with extramedullary tumors. An autopsied case of Down's syndrome. Acta Pathol Jpn 33:1027–1039
O'Boyle KP, Murigeppa A, Jain D, Dauber L, Dutcher JP, Wiernik PH (2003) Probable veno-occlusive disease after treatment with gemtuzumab ozogamicin in a patient with acute myeloid leukemia and a history of liver transplantation for familial hemochromatosis. Med Oncol 20:379–384
Okada H, Liu PI, Hoshino T, Yamamoto T, Yamaoka H, Murakami M (1972) Down's syndrome associated with a myeloproliferative disorder. Am J Dis Child 124:107–110
Ollenschlager G, Roth E, Linkesch W, Jansen S, Simmel A, Modder B (1988) Asparaginase-induced derangements of glutamine metabolism: the pathogenetic basis for some drug-related side-effects. Eur J Clin Invest 18:512–516
Omine M, Iwata N, Maekawa T, Ohba Y (1983) A case of juvenile erythroleukemia with uncoordinated

expression of fetal red cell markers. Acta Haematol 69:275–277
Ondreyco SM, Kjeldsberg CR, Fineman RM, Vaninetti S, Kushner JP (1981) Monoblastic transformation in chronic myelogenous leukemia: presentation with massive hepatic involvement. Cancer 48:957–963
Orazi A (2007) Histopathology in the diagnosis and classification of acute myeloid leukemia, myelodysplastic syndromes, and myelodysplastic/myeloproliferative diseases. Pathobiology 74:97–114
Orazi A, O'Malley DP, Jiang J, Vance GH, Thomas J, Czader M, Fang W, An C et al (2005) Acute panmyelosis with myelofibrosis: an entity distinct from acute megakaryoblastic leukemia. Mod Pathol 18:603–614
Ozaki M, Kanemitsu N, Yasukawa M, Fujita S (1989) Basophilic crisis of chronic myelogenous leukemia. Jpn J Med 28:67–71
Pardanani AD, Morice WG, Hoyer JD, Tefferi A (2003) Chronic basophilic leukemia: a distinct clinicopathologic entity? Eur J Haematol 71:18–22
Park J, Song WJ, Chung KC (2009) Function and regulation of Dyrk1A: towards understanding Down syndrome. Cell Mol Life Sci 66:3235–3240
Park MJ, Sotomatsu M, Ohki K, Arai K, Maruyama K, Kobayashi T, Nishi A, Sameshima K, Takagi T, Hayashi Y (2014) Liver disease is frequently observed in Down syndrome patients with transient abnormal myelopoiesis. Int J Hematol 99:154–161
Penchansky L, Taylor SR, Krause JR (1989) Three infants with acute megakaryoblastic leukemia simulating metastatic tumor. Cancer 64:1366–1371
Peterson LC, Parkin JL, Arthur DC, Brunning RD (1991) Acute basophilic leukaemia. A clinical, morphologic, and cytogenetic study of eight cases. Am J Clin Pathol 96:160–170
Pinkus GS, Said JW (1981) Intracellular hemoglobin-a specific marker for erythroid cells in paraffin sections. An immunoperoxidase study of normal, megaloblastic, and dysplastic erythropoiesis, including erythroleukemia and other myeloproliferative disorders. Am J Pathol 102:308–313
Pui CH, Rivera G, Mirro J, Stass S, Peiper S, Murphy SB (1985) Acute megakaryoblastic leukemia: blast cell aggregates simulating metastatic tumor. Arch Pathol Lab Med 109:1033–1035
Puumala SE, Ross JA, Aplenc R, Spector LG (2013) Epidemiology of childhood acute myeloid leukemia. Pediatr Blood Cancer 60:728–733
Quattrin N (1978) Follow-up of sixty two cases of acute basophilic leukemia. Biomedicine 28:72–79
Radaelli F, Mazza R, Curioni E, Ciani A, Pomati M, Maiolo AT (2002) Acute megakaryoblastic leukemia in essential thrombocythemia: an unusual evolution ? Eur J Haematol 69:108–111
Rainis L, Bercovich D, Strehl S, Teigler-Schlegel A, Stark B, Trka J, Amariglio N, Biondi A, Muler I et al (2003) Mutations in exon 2 of GATA1 are early events in megakaryocyte malignancies associated with trisomy 21. Blood 102:981–986
Rajesh G, Sadasivan S, Iran KR, Nandakumar R, Balakrishnan V (2006) Acute myeloid leukemia presenting as obstructive jaundice. Indian J Gastroenterol 25:93–94
Rajvanshi P, Shulman HM, Sievers EL, McDonald GB (2002) Hepatic sinusoidal obstruction after gemtuzumab ozogamicin (Mylotarg) therapy. Blood 99:3915
Reiffers J, Bernard P, Larrue J, Zachary D, David B, Boisseau M, Broustet A (1985) Acute erythroblastic leukemia presenting as acute undifferentiated leukemia: a report of two cases with ultrastructural features. Leuk Res 9:413–420
Reilly JT, Barnett D, Dolan G, Forrest P, Eastham J, Smith A (1993) Characterization of an acute micromegakaryocytic leukaemia: evidence for the pathogenesis of myelofibrosis. Br J Haematol 83:58–62
Richeli ED, Uri A, Dimmick JE, Bove KE, Huff DS, Duncan LM, Jennings JB, Witzleben CL (1991) Severe perinatal liver disease and Down syndrome: an apparent relationship. Hum Pathol 22:1274–1280
Riddle A, Olsen B (2012) Erythroblastic sarcoma. Leuk Res 36:e182–e184
Riera L, Lasorsa E, Bonello L, Sismondi F, Tondat F, Di Bello C, Di Celle PF, Chiarle R et al (2011) Description of a novel Janus kinase 3 P132A mutation in acute megakaryoblastic leukemia and demonstration of previously reported Janus kinase 3 mutations in normal subjects. Leuk Lymphoma 52:1742–1750
Roggli VL, Saleem A (1982) Erythroleukemia: a study of 15 cases and literature review. Cancer 49:101–108
Rohr K (1960) Das menschliche Knochenmark, 3rd edn. G. Thieme, Stuttgart
Rosenthal S, Schwartz JH, Canellos GP (1977) Basophilic chronic granulocytic leukemia with hyperhistaminaemia. Br J Haematol 36:367–372
Roy A, Roberts I, Vyas P (2012) Biology and management of transient abnormal myelopoiesis (TAM) in children with Down syndrome. Semin Fetal Neonatal Med 17:196–201
Ruvidic R, Pavlovic-Kentera V, Boskovic D, Biljanovic-Paunovic L, Mijovic A, Jovanovic V (1986) Acute erythremic myelosis (Di Guglielmo) following atypical aplastic anemia. Leuk Res 10:451–455
Sahoo S, Hart J (2003) Histopathological features of L-asparaginase-induced liver disease. Semin Liver Dis 23:295–299
Saito M, Mori A, Irie T, Tanaka M, Miorika M (2010) Massive hepatic infarction occurred during the myelosuppression after re-induction chemotherapy for acute myeloid leukemia (in Japanese). Rinsho Ketsueki 51:1789–1791
Santos FP, Faderl S, Garcia-Manero G, Koller C, Beran M, O'brien S, Pierce S, Freireich EJ et al (2009) Adult acute erythroleukemia: an analysis of 91 patients treated at a single institution. Leukemia 23:2275–2280
Sato K, Ushijima T, Ohbayashi Y, Sato H, Urabe A (1990) Atypical infiltration of megakaryocytes into the liver and spleen in a case of refractory anemia (in Japanese). Rinsho Ketsueki 31:1004–1007

Scheimberg IB, Pollock DJ, Collins PW, Doran HM, Newland AC, van der Walt JD (1995) Pathology of the liver in leukaemia and lymphoma. A study of 110 autopsies. Histopathology 26:311–321

Schuch G, Machluf M, Bartsch G, Nomi M, Richard H, Atala A, Soker S (2002) In vivo administration of vascular endothelial growth factor (VEGF) and its antagonist, soluble neuropilin-1, predicts a role of VEGF in the progression of acute myeloid leukemia in vivo. Blood 100:4622–4628

Schumacher HR, Szekely IE, Park SA, Rao UN, Fisher DR, Patel SB (1973) Acute leukemia cells. Qualitative and quantitative electron microscopy. Am J Pathol 73:27–46

Schwab M, Niemeyer C, Schwarzer U (1998) Down syndrome, transient myeloproliferative disorder, and infantile liver fibrosis. Med Pediatr Oncol 31:159–165

Scolyer RA, Brun M, D'Rozario J, Webb M (2000) Acute basophilic leukemia presenting with abnormal liver function tests and the absence of blast cells in the peripheral blood. Pathology 32:52–55

Scott RB, Ellison RR, Ley AB (1964) A clinical study of twenty cases of erythroleukemia (di Guglielmo's syndrome). Am J Med 37:162

Seewald L, Taub JW, Maloney KW, McCabe ER (2012) Acute leukemias in children with Down syndrome. Mol Genet Metab 107:25–30

Sevinc A, Buyukberber S, Camci C, Koruk M, Savas MC, Turk HM, Sari I, Buyukberber NM (2004) Granulocytic sarcoma of the colon and leukemic infiltration of the liver in a patient presenting with hematochezia. Digestion 69:262–265

Shah I, Lewkow LM, Koppitch F (1984) Acute basophilic leukemia. Am J Med 76:1097–1099

Sharma Poudel B, Karki L (2007) Abnormal hepatic function and splenomegaly on the newly diagnosed acute leukemia patients. JNMA J Nepal Med Assoc 46:165–169

Shibata K, Nakano S, Watanabe M, Yano H, Matsuzaki M, Sano M (1998) Acute megakaryocytic leukaemia (AML-M7) with myelofibrosis terminating in AML-M0 with concurrent liver fibrosis. Eur J Haematol 60:310–312

Shimada A, Xu G, Toki T, Kimura H, Hayashi Y, Ito E (2004) Fetal origin of the GATA1 mutation in identical twins with transient myeloproliferative disorder and acute megakaryoblastic leukemia accompanying Down syndrome. Blood 103:366.

Shimano S, Omine M, Yashiro K, Tsuchiya J, Maekawa T (1983) A case of paroxysmal nocturnal hemoglobinuria terminating in erythroleukemia after 22 years' observation. Nippon Ketsueki Gakkai Zasshi 46:30–34

Shimizu R, Engel JD, Yamamoto M (2008) GATA1-related leukemias. Nat Rev Cancer 8:279–287

Shin MG, Choi HW, Kim HR, Kim MJ, Baek HJ, Han DK, Kook H, Hwang TJ, Kim HJ et al (2008) Tetrasomy 21 as a sole acquired abnormality without GATA1 gene mutation in pediatric acute megakaryoblastic leukemia: a case report and review of the literature. Leuk Res 32:1615–1619

Shvidel L, Shaft D, Stark B, Shtalrid M, Berrebi A, Resnitzky P (2003) Acute basophilic leukaemia: eight unsuspected new cases diagnosed by electron microscopy. Br J Haematol 120:774–781, and jaundice. Digestion 69:262–265

Siebert R, Jhanwar S, Brown K, Berman E, Offit K (1995) Familial acute myeloid leukemia and DiGuglielmo syndrome. Leukemia 9:1091–1094

Siede W, Rotter W (1950) Das maligne Erythroblastom. Dtsch Arch Klin Med 197:326–352

Simel DL, Weinberg JB (1985) Leukemic ascites complicating acute myelomonoblastic leukemia. Arch Pathol Lab Med 109:365–367

Sondergaard-Petersen H (1974) Erythrophagocytosis by pathological erythroblasts in the Di Guglielmo syndrome. A study of 18 cases. Scand J Haematol 13:260–265

Sondergaard-Petersen H (1975) The Di Guglielmo syndrome: a study of 17 cases. I. Clinical and haematological manifestations. Acta Med Scand 198:165–174

Soni S, Bala S, Gwynn B, Sahr KE, Peters LL, Hanspal M (2006) Absence of erythroblast macrophage protein (Emp) leads to failure of erythroblast nuclear extrusion. J Biol Chem 281:20181–20189

Srinivas U, Kumar R, Pati H, Saxena R, Tyagi S (2007) Sub classification and clinic-hematological correlation of 40 cases of acute erythroleukemia – can proerythroblast/myeloblast and proerythroblast/total erythroid cell ratios help subclassify ? Hematology 12:381–385

Stadtmauer EE (2002) Gemtuzumab ozogamicin in the treatment of acute myeloid leukemia. Curr Oncol Rep 4:375–380

Stodtmeister R (1941) Akute Erythroblastose und erythroblastische Reaktion. Klein Wschr 20:441

Stoll C, Seiller F, Lutz P, Levy JM (1985) Leucémie mégacaryoblastique avec hypodiploidie chez un enfant trisomique 21. Ann Pediatr (Paris) 32:521–523

Suarez CR, Le Beau MM, Silberman S, Fresco R, Rowley JD (1985) Acute megakaryoblastic leukemia in Down's syndrome: report of a case and review of cytogenetic findings. Med Pediatr Oncol 13:225–231

Sumitra D, Kumar S, Neelam V, Sarode R, Verma S (1988) A case of erythroleukaemia with partial expression of fetal red cell markers. J Assoc Physicians India 36:620

Suvajdzic N, Marisavlievic D, Kraguljac N, Pantic M, Djordjevic V, Jankovic G, Cemerikic-Martinovic V et al (2004) Acute panmyelosis with myelofibrosis: clinical, immunophenotypic and cytogenetic study of twelve cases. Leuk Lymphoma 45:1873–1879

Taher A, Gilbert E, Shahidi NT (1981) Erythroblastic islands in erythroleukemia. Am J Pediatr Hematol Oncol 3:121–125

Taketani T, Taki T, Sako M, Ishii T, Yamaguchi S, Hayashi Y (2008) MNX1-ETV6 fusion in an acute megakaryoblastic leukemia and expression of the MNX1 gene in leukemia and normal B cell lines. Cancer Genet Cytogenet 186:115–119

Tallman MS, Hakimian D, Snower D, Rubin CM, Reisel H, Variakojis D (1993) Basophilic differentiation in acute promyelocytic leukemia. Leukemia 7:521–526

Tang G, Woods LJ, Wang SA, Brettler D, Andersen M, Miron PM, Pechet L, Woda BA et al (2009) Chronic basophilic leukemia: a rare form of chronic myeloproliferative neoplasm. Hum Pathol 40:1194–1199

Terui T, Niitsu Y, Mahara K, Fujisaki Y, Urushizaki Y, Mogi Y, Kohgo Y, Watanabe N, Ogura M, Saito H (1990) The production of transforming growth factor-beta in acute megakaryoblastic leukemia and its possible implications in myelofibrosis. Blood 75:1540–1548

Thiele J, Kvasnicka HM, Zerhusen G, Vardiman J, Diehl V, Luebbert M, Schmitt-Greaff A (2004) Acute panmyelosis with myelofibrosis: a clinicopathological study of 46 patients including histochemistry of bone marrow biopsies and follow-up. Ann Hematol 83:513–521

Tokairin et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18067644

Toki T, Kanezaki R, Kobayashi E, Kaneko H, Suzuki M, Wang R, Terui K, Kanegane H et al (2013) Naturally occurring oncogenic GATA1 mutants with internal deletions in transient abnormal myelopoiesis in Down syndrome. Blood 121:3181–3184

Tozuka M, Yamauchi K, Hidaka H, Nakabayashi T, Okumura N, Katsuyama T (1997) Characterization of hypertriglyceridemia induced by L-asparaginase therapy for acute lymphoblastic leukemia and malignant lymphoma. Ann Clin Lab Sci 27:351–357

Tsuji M, Tamai M, Terada N, Tako H (1995) Anerythremic form of acute erythremic myelosis (Di Guglielmo's syndrome) causing hepatosplenomegaly due to the infiltration of hemoglobin-bearing blast cells: an autopsy case. Pathol Int 45:310–314

Urano Y, Kondo M, Hayashi Y, Wakuya J, Nakata T, Tanaka K, Seo A (1983) Transitory abnormal myelopoiesis of the monoblastic form in a newborn infant with Down's syndrome and liver cirrhosis (in French). Ann Pathol 3:337–339

Van Slyck EJ, Weiss L, Dully M (1970) Chromosomal evidence for the secondary role of fibroblastic proliferation in acute myelofibrosis. Blood 36:729–735

Vargas AC, O'Brien B, Marquez ML, Ortiz-Hidalgo C, Lakhani SR (2011) Extramedullary megakaryoblastic leukaemia with massive generalised infiltration. Pathology 43:517–519

Viadana E, Bross ID, Pickren JW (1978) An autopsy study of the metastatic pattern of human leukemias. Oncology 35:87–96

Villamour Zambrano E, Alonso Ortiz T, Arizcun Pineda J, Moro Serrano M (1997) Diffuse liver fibrosis associated with transient myeloproliferative disorder in Down's syndrome (in Spanish). An Esp Pediatr 47:69–70

Vimercati A, Greco P, Gentile A, Ingravallo G, Loverro G, Selvaggi L (2003) Fetal liver hyperechogenicity on sonography may be a serendipitous sign of a transient myeloproliferative disorder. Prenat Diagn 23:44–47

Walter RB, Othus M, Burnett AK, Löwenberg B, Kantarjian HM, Ossenkoppele GJ et al (2013) Significance of FAB subclassification of "acute myeloid leukemia, NOS" in the 2008 WHO classification: analysis of 5848 newly diagnosed patients. Blood 121:2424–2431

Walz–Mattmüller et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9842637

Wandroo FA, Murray J, Mutimer D, Hubscher S (2004) Acute myeloid leukaemia presenting as cholestatic hepatitis. J Clin Pathol 57:544–545

Wang SA, Hasserjian RP (2012) Erythroid proliferations in myeloid neoplasms. Hum Pathol 43:153–164

Wang HY, Huang LJ, Liu Z, Garcia R, Li S, Galliani CA (2011) Erythroblastic sarcoma presenting as bilateral ovarian masses in an infant with pure erythroid leukemia. Hum Pathol 42:749–758

Weinstein HJ (1978) Congenital leukaemia and the neonatal myeloproliferative disorders associated with Down's syndrome. Clin Haematol 7:147–154

Wickenhauser C, Hillienhof A, Jungheim K, Lorenzen J, Ruskowski H, Hansmann ML, Thiele J, Fischer R (1995) Detection and quantification of transforming growth factor beta (TGF-beta) and platelet-derived growth factor (PDGF) release by normal human megakaryocytes. Leukemia 9:310–315

Wiseman FK, Alford KA, Tybulewicz VL, Fisher EM (2009) Down syndrome – recent progress and future prospects. Hum Mol Genet 18:R75–R83

Wong KY, Jones MM, Srivastava AK et al (1988) Transient myeloproliferative disorder and acute nonlymphoblastic leukemia in Down syndrome. J Pediatr 112:18–22

Wu CD, Medeiros LJ, Miranda RN, Mark HF, Rintels P (1996) Chronic myeloid leukemia manifested during megakaryoblastic crisis. South Med J 89:422–427

Xu G, Nagano M, Kanezaki R, Toki T, Hayashi Y, Taketani T, Taki T, Mitui T, Koike K, Kato K, Imaizumi M et al (2003) Frequent mutations in the GATA-1 gene in the transient myeloproliferative disorder of Down syndrome. Blood 102:2960–2968

Yagihashi N, Watanabe K, Yagihashi S (1995) Transient abnormal myelopoiesis accompanied by hepatic fibrosis in two infants with Down syndrome. J Clin Pathol 48:973–975

Yamazaki S, Nakamura F, Nasu R, Nannya Y, Ichikawa M, Kurokawa M (2011) Haemophagocytic lymphohistiocytosis is a recurrent and specific complication of acute erythroid leukaemia. Br J Haematol 153:669–672

Yokoyama S, Nito T, Irimada K, Yoshimura Y, Hayashi T (1984) Acute megakaryoblastic leukemia preceded by refractory anemia with excess blast cells: leukemic transformation in an infant of Down syndrome recovering from transient abnormal myelopoiesis. Nippon Ketsueki Gakkai Zasshi 47:62–70

Yoon SY, Tefferi A, Li CY (2000) Cellular distribution of platelet-derived growth factor, transforming growth

factor-beta, basic fibroblast growth factor, and their receptors in normal bone marrow. Acta Haematol 104:151–157

Yoshida K, Toki T, Okuno Y, Kanezaki R, Shiraishi Y, Sato-Otsubo A, Sanada M, Park MJ, Terui K, Suzuki H et al (2013) The landscape of somatic mutations in Down syndrome-related myeloid disorders. Nat Genet 45:1293–1299

Zafrani ES, Leclercq B, Vernant JP, Pinaudeau Y, Chomette G, Dhumeaux D (1983) Massive blastic infiltration of the liver: a cause of fulminant hepatic failure. Hepatology 3:428–432

Zipursky A (2003) Transient leukaemia – a benign form of leukaemia in newborn infants with trisomy 21. Br J Haematol 120:930–938

Zubizarretta P, Muriel FS, Barbieri MAF (1995) Transient myeloproliferative disorder associated with trisomy 21, a wide range syndrome: report of two cases with trisomy 21 mosaicism. Med Pediatr Oncol 25:60–64

Zuo Z, Polski JM, Kasyan A, Medeiros J (2010) Acute erythroid leukemia. Arch Pathol Lab Med 134:1261–1270

Myeloid Neoplasms with a Monocytoid Lineage

85

Contents

Abstract

Myeloid neoplasms with a monocytoid lineage can involve the hepatobiliary tract. In acute myelomonocytic leukemia, characterized by the proliferation of both neutrophil and monocyte precursors, the liver can show an increased number of monocytoid cells and neutrophils in sinusoids, but usually without blasts. Similar cells infiltrate portal tracts, often with monocytoid cells with nuclei of promonocytes. In juvenile myelomonocytic leukemia, hepatomegaly can develop due to infiltration of the liver with monocytoid cells and immature granulocytes, mainly in sinusoids. Hepatic involvement in acute monoblastic and monocytic leukemia is characterized by sometimes massive blastic infiltration of parenchyma, monoblasts occupying sinusoids and portal tracts, causing hepatomegaly and a whitish discoloration of the organ. The liver is often involved in chronic myelomonocytic leukemia, with myelomonocytic cells, erythroid precursors, and less commonly megakaryocytes mainly within sinusoids. Dense sinusoidal infiltration may result in sinusoidal obstruction and portal hypertension. This leukemia can be associated with hepatobiliary myeloid tumors.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_85

Acute Myelomonocytic Leukemia

ICD-O code 9867/3

Introduction

In the WHO classification of tumors, acute myelomonocytic leukemia (AMML; AML-M4) is defined as an acute leukemia characterized by the proliferation of both neutrophil and monocyte precursors. In peripheral blood and bone marrow, = >20 % blasts, including promonocytes, are found, and neutrophils and monocytes plus their respective precursors each comprise at least 20 % of bone marrow cells. AMML accounts for about 5–10 % of acute myeloid leukemias. It is slightly more common in males and is predominantly a disease of the elderly. Clinically, patients with AMML usually present with fatigue, fever, anemia, and thrombocytopenia.

Morphology

The morphology of AMML is characterized by monoblasts, large cells with abundant basophilic cytoplasm, which may contain vacuoles and scattered fine azurophilic granules. Monoblasts usually have roundish nuclei with prominent nuclei. Immunocytochemically, in contrast, promonocytes have a less basophilic and more granulated cytoplasm, sometimes with large azurophilic granules, and more irregular and slightly convoluted nuclei. Cells of AMML may show the pseudo-Chediak-Higashi anomaly (Rao et al. 2009). Immunocytochemically, AMML blasts variable express CD13, CD33, CD65, and CD15. Some of the blasts are immature precursor cells expressing CD34 and CD117. Subpopulations of blasts express monocyte lineage markers, including CD14, CD4, CD11b, CD11c, CD64, CD36, macrophage-restricted CD68 (PGM1), CD163, and lysozyme. Monocyte lineage differentiation is typically characterized by coexpression of CD15 and CD64. Cells of AMMl can undergo differentiation which was shown to be induced by thrombomodulin via JNK signaling (Yang et al. 2012). Posttranscriptional modulation of C/EBPalpha (CCAAT/enhancer-binding protein alpha), which induces monocyte differentiation in normal leukocytes, also prompts monocytic differentiation and apoptosis in AMML cells (Yoshida et al. 2012).

Liver Involvement

The liver of patients with AMML shows an increased number of neutrophils and monocytoid cells in the sinusoids, usually without blasts. The monocytoid elements have reniform or oval nuclei with a rather fine chromatin pattern. Similar cells infiltrate the portal tracts, sometimes with expansion of these structures. The infiltrate contains monocytoid cells with nuclei of the type found in promonocytes seen in blood and bone marrow smears. Inflammatory pseudotumor of the liver has been found in association with AMML (Isobe et al. 1991).

Cytogenetic and Molecular Genetic Features

Cytogenetically, an abnormal but nonspecific karyotype, in particular +8, is found in the majority of cases. Double supernumerary isochromosome 4p was detected in AMML (Soriani et al. 2010). Inversion of chromosome 16 in AMML was found to be associated with basophilia and bone marrow eosinophilia (Matsuura et al. 1987). CD7-positive AMML with trisomy 21 as a sole acquired chromosomal abnormality was observed in two adolescents (Kudo et al. 2011). The t(8;16)(p11;p13) translocation is a rare alteration involved in de novo and therapy-related AMML and acute monocytic leukemia. It fuses two genes encoding histone acetyltransferases MYST3 (MOZ) located at 8p11 to CREBBP (CBP) located at 16p13. Leukemias with 8p11 (MYST3) rearrangement were AMML in 7 % and monocytic (93 %), and the abnormality was associated with poor prognosis (Gervais et al. 2008). Genome profiling revealed that MYST3-linked cases of AMML (MYST3 located

at 8p11) show alteration of the MYB locus (Murati et al. 2009).

Juvenile Myelomonocytic Leukemia

ICD-O code 9946/3

Introduction

The WHO classification of tumors defines juvenile myelomonocytic leukemia (JMML; formerly juvenile chronic myeloid leukemia) as a clonal hematopoietic disorder characterized by the proliferation principally of the granulocytic and monocytic lineages. Blasts plus promonocytes account for less than 20 % of cells in the peripheral blood and bone marrow. Erythroid and megakaryocytic abnormalities are often present. The BCR-ABL1 fusion is absent, while gene mutations of the RAS/MAPK signaling pathway are characteristic (reviews: Emanuel 2008; Urs et al. 2009).

JMML is a rare disorder of infants and children, with about 1.3 cases per million children 0–14 years of age. It is expressed as a clonal, mixed panmyelopathy responding poorly to most standard chemotherapy regimens and showing an elevated relapse rate after stem cell transplantation, although this procedure can cure the disease (Shannon et al. 1994; Busque et al. 1995; Hess et al. 1996; Arico et al. 1997; Chang et al. 2004; Emanuel 2004). Together with pediatric myelodysplastic syndrome, JMML is classified as a pediatric myeloproliferative disorder (PMPD; Cotter 1998). JMML usually presents with leukocytosis with the presence of early myeloid and monocytic forms, thrombocytopenia, a skin rash, and hepatosplenomegaly. During the frequently rapid progression of disease, infiltration of organs and tissues other than the bone marrow ensues. About half the patients have lymphadenopathy, and leukemic infiltration can cause markedly enlarged tonsils. A distinct feature of JMML is that the majority of young individuals exhibit elevated levels of fetal hemoglobin (HbF), especially in those with an abnormal karyotype, sometimes producing an acquired Cooley's anemia-like phenotype, suggesting that cell systems in JMML may undergo a reversion to a fetal pattern (Weatherall et al. 1968; Maurer et al. 1972; Weinberg et al. 1990; Honig et al. 1998). The most common cytogenetic alteration is that of monosomy or deletion of the long arm of chromosome 7 occurring in up to 25 % of the individuals (Cotter 1998; Chang et al. 2004). Other abnormalities are found in 10 % of patients and a normal karyotype in 65 %.

Morphology

The peripheral blood generally exhibits leukocytosis, thrombocytopenia, and often anemia. The leukocytosis is dominated by neutrophils, with some promyelocytes and myelocytes as well as monocytes. Blasts are usually less than 5 % and always less than 20 %. Red cell macrocytosis may be seen, especially in patients with monosomy 7. In the bone marrow, which shows hypercellularity with granulocyte proliferation, monocytes are less impressive than in peripheral blood, usually accounting for 5–10 % of nucleated cells. Blasts are less than 20 % of bone marrow cells. Auer rods are never seen, and dysplasia is minimal in most cases.

Liver Involvement

Relatively few reports refer to liver changes in JMML. Patients with JMML typically show splenomegaly, whereas hepatomegaly is less common, occurring in about a third of patients in one series (Niemeyer et al. 1994). Enlargement of the liver is mainly due to infiltration of hepatic tissue by leukemic cells, as based on liver biopsy findings. The blood in the liver sinusoids show increased numbers of circulating cells, whereby granulocytes, including hyposegmented forms, predominate. Monocytoid cells may be noted in histologic sections mostly diagnosed based on the characteristic nuclear morphology. Few nests of erythroblasts may be found, and megakaryocytes are often found. The portal tracts may show dense

infiltrates mainly of mature granulocytes and their precursors, with a variable admixture of partly CD68-positive monocytoid cells. The infiltrate sometimes encroaches upon small intralobular bile ducts, and increased myeloid cells are also noted in the lumens of small portal vein branches (Honig et al. 1998). Hepatic fibrosis has been detected in patients with juvenile chronic granulocytic leukemia/JMML (Takanashi 1972; Kajigaya et al. 1987; Mikel et al. 1990). The liver histology is characterized by several features, including extramedullary hemopoiesis, both portal and bridging fibrosis, with fibrosis around terminal/central veins, and these alterations were proposed to be caused by leukemic infiltration.

Pathogenesis

The pathogenic pathways involved in JMML leukemogenesis have been elucidated in the course of the last years. Patients with JMML reveal characteristic alterations in several signaling pathways, whereby the RAS, NF1, and PTPN11 pathways have a central role (reviews: Koike and Matsuda 2008; Niemeyer and Kratz 2008; Loh 2010). There is a striking relationship between JMML and a dysregulation of factors involved in the Ras and neurofibromatosis 1/NF1 signaling pathways. Up to 75 % of cases of JMML have a disorder in the GM-CSF/Ras signal transduction pathway (Emanuel 2004). In fact, the most common myeloid malignancy in children with NF type 1 is JMML, which seems to develop in a stepwise fashion (Clark and Hutter 1982; Miles et al. 1996; Leung et al. 2003).

A further factor involved in the Ras pathway and altered in JMML is PTPN11 (Liu et al. 2009). The PTPN11 gene encodes a non-receptor protein tyrosine phosphatase, SHP-2 (Src homology 2 domain-containing protein tyrosine phosphatase), that acts as an upstream regulator of Ras via relaying signals from activated growth factor receptors to p21 ras and other signaling molecules. PTPN11 is mutated in approximately 35 % of patients with JMML. Compared with patients with RAS mutations or without any aberrations, patients with PTPN11 mutation were significantly older at diagnosis and had higher fetal Hb levels, both of which have been identified as poor prognosis factors.

Missense mutations of CBL, an E3 ubiquitin ligase and multi-adaptor protein that control proliferative signaling networks by downregulating growth factor receptor signaling cascades, have been detected in JMML (Loh et al. 2009; Makishima et al. 2009). Germ line mutations of the CBL gene cause a new genetic syndrome with predisposition to JMML (Pérez et al. 2010). This dominant disorder is characterized by impaired growth, developmental delay, cryptorchidism and a predisposition to JMML (Niemeyer et al. 2010).

A distinct translocation (t(5;17) (q33;p11.2)) causing the fusion of the PDGF B receptor and HCMOGT-1 has been detected in JMML (Morerio et al. 2004). The chromosome rearrangement site 5q31–33 harbors the PDGFRB gene, encoding a tyrosine kinase receptor, and this gene is known to fuse with at least six partner genes, i.e., ETV6, CEV14, HIP1, H4/D10S170, RAB5, and PDE4DIP (Morerio et al. 2004). Spliceosomal gene aberrations are rare in JMML (Hirabayashi et al. 2012).

Acute Monoblastic and Monocytic Leukemia

ICD-O code 9891/3

Introduction

Acute monoblastic leukemia and acute monocytic leukemia are defined as myeloid leukemias in which 80 % or more of the neoplastic cells are members of the monocyte lineage, including monoblasts, promonocytes, and monocytes. These two forms of leukemia are distinguished by the relative proportions of monoblasts and promonocytes, monoblasts accounting for 80 % or more of the cells in acute monoblastic leukemia, whereas the majority of cells in acute monocytic leukemia are promonocytes

Epidemiology

Among AMLs, acute monoblastic leukemia and acute monocytic leukemia are rare subsets, both accounting for less than 5 % of AMLs. The disorder is more common in younger individuals, although it may develop in any age group and can also occur as a congenital leukemia. Acute monocytic leukemia is more common in adults and is slightly more frequent in males than in females (M:F = 1.8:1).

Clinical Features and Morphology

Acute monoblastic leukemia and acute monocytic leukemia are clinically characterized by lymphadenopathy, gingival hypertrophy, coagulation disorders, and lysozymuria (Shaw 1978).

Monoblasts are large cells with abundant cytoplasm that is moderately to markedly basophilic, the cytoplasm containing scattered and discrete azurophilic granules and some clear vacuoles. Normal monoblasts usually show round nuclei with a delicate chromatin structure and one or more prominent nucleoli. In contrast, promonocytes have a less basophilic and more granulated cytoplasm and a more irregular and convoluted nuclear shape. The cytoplasm contains large azurophilic granules and vacuoles. Both of these cell types exhibit intense reactivity for nonspecific esterase, but 10–20 % of acute monoblastic leukemia lack nonspecific esterase activity or show only weak positivity. Monoblasts lack activity of myeloperoxidase, while promonocytes may show a weak activity in part of the cells. The immunophenotype of these cells is characterized by reactivity for the myeloid antigens CD13, CD33 (bright), CD15, and CD65. There is reactivity for at least two markers of the monocytoid lineage, i.e., CD14, CD4, CD11b, CD11c, CD64, CD68, CD36, lysozyme, and, in part, CD163.

Hepatobiliary Involvement

Massive blastic infiltration of the liver by monoblastic/monocytic cells in acute leukemia can cause hepatomegaly (Ondreyco et al. 1981). Macroscopically, dense and diffuse infiltrates lead to a whitish discoloration of the organ (Park et al. 2001).

In acute monoblastic leukemia with liver involvement, portal tracts and sinusoids are densely populated with monocytoid cells (Peterson et al. 1981; Ondreyco et al. 1981; Hayashida et al. 1992; Kontny et al. 1995; Park et al. 2001). These are characterized as small- to medium-sized cells with an amphophilic, finely granulated cytoplasm (azurophilic granules) and irregularly shaped, ovoid, and sometimes slightly indented nuclei with multiple nucleoli, features characteristic for acute monoblastic/monocytic leukemias (McKenna et al. 1975). The cytoplasm may show few clear vacuoles. The sinusoids can become markedly distended by massively proliferating intrasinusoidal leukemia cells. Adjacent hepatocytes are sometimes atrophic or are destroyed by invading leukemia cells. The cells may also accumulate in hepatic venules (Park et al. 2001). At the border between portal tracts and the lobular parenchyma, the leukemic cells may induce piecemeal-like lesions ("leukemic piecemeal necrosis"). The cytoplasm of the neoplastic cells is markedly positive for nonspecific esterase, a reaction inhibited after fluoride incubation (Ondreyco et al. 1981). In liver infiltrates, the monoblastic character of leukemia cells was confirmed by electron microscopy. The cells display a cluster of mitochondria at one side of the nucleus, slightly dilated ER profiles, characteristic lysosomal granules, and nuclei with course and peripheralized chromatin and some indentations of the nuclear contour (Ondreyco et al. 1981). These ultrastructural features have also been observed in other extramedullary manifestations of acute monoblastic/monocytic leukemias (Sultan et al. 1977; Peterson et al. 1981).

Monoblastic/Monocytoid Mass Lesions in the Liver ("Monocytomas"; Monoblastic Sarcomas; Monoblastic Tumors; Monoblastic Type of Myeloid Sarcoma)

In some patients with acute monoblastic or monocytic leukemia, extramedullary masses consisting

of leukemic cells can develop (Peterson et al. 1981). These mass lesions (monocytomas; monoblastic sarcomas; monoblastic tumors) may involve the skin and several visceral organs, including the gastrointestinal tract, liver, kidneys, and heart (Rappoport and Kugel 1947; Feichter et al. 1974; Miliauskas 1986; Sepp et al. 1993; Orts et al. 1996; Iwaka and Saikawa 2007; Zuo et al. 2008; Holloman et al. 2009). Several reports document nodular "monocytomas" of the liver (Rappoport and Kugel 1947; Bonnin 1951; Feichter et al. 1974; Wu et al. 2011). In the 64-year-old patient described by Feichter and coworkers (1974), necropsy revealed several cherry-sized whitish nodules in the liver histologically composed of monocytoid infiltrated in the setting of monoblastic leukemia. In a neonate with congenital monoblastic leukemia presenting as jaundice and ascites, CT showed several hypodense liver lesions (Wu et al. 2011).

Immunohistochemistry

The monocytoid leukemic cells are partly reactive for CD68, lysozyme, and CD31 (Park et al. 2001). Subsets of monocytoid leukemia cells are reactive for CD163. CD163 (hemoglobin scavenger receptor/HbSR) is a specific marker of the macrophage cell lineage (Lau et al. 2004). CD163 serves to identify the monocytoid character of cells in acute myeloid leukemia with monocytic differentiation (Walter et al. 2003; Garcia et al. 2008). The most specific monocyte lineage marker after CD68 and CD163 is Krüppel-like factor 4, while CD68 is the most sensitive monocyte marker (Klco et al. 2011).

Differential Diagnosis

The main differential diagnosis refers to other leukemias with mononuclear cells, including poorly differentiated forms of acute myeloid leukemia and acute lymphoblastic leukemias.

Pathogenic Pathways

Parts of leukemias show the involvement of the mixed lineage leukemia/MLL gene. MLL (MLL1, HRX, ALL1; the human homologue of the Drosophila gene trithorax) is frequently rearranged in leukemia, particularly in infantile leukemia and therapy-related leukemia. MLL-induced acute leukemias are often highly aggressive, frequently refractory to therapy, and markedly driven by epigenetic dysregulation (Bernt and Armstrong 2011; Muntean and Hess 2012). The MLL gene is localized at chromosome 11q23 and encodes a large histone methyltransferase that directly binds DNA and positively regulated gene transcription, including homeobox (HOX) genes. MLL regulates HOX gene expression through direct promoter binding and histone H3 Lys 4 methylation mediated by the intrinsic methyltransferase activity of the MLL SET domain (Hess 2004). Translocations involving chromosome band 11q23 and hence MLL are found in more than 70 % of infant leukemias, 5.2 % of acute myeloblastic leukemia, and 22 % of acute lymphoblastic leukemia (De Braekeleer et al. 2005). More than 25 fusion partners of MLL have been identified. The MLL-human gephyrin fusion gene was often found in leukemias with a chromosome 11 band q23 (11q23). Gephyrin (GPHN) is a rat glycine receptor-associated protein which forms submembranous complexes and anchor glycine or gamma-aminobutyric acid A receptors to microtubules. It is an organizer at GABAergic synapses where it forms oligomeric superstructures (Tretter et al. 2012). The small tubulin-binding oligomerization domain of gephyrin is sufficient to convert MLL to an oncogene (Eguchi et al. 2004). Patients with acute monoblastic leukemia or acute undifferentiated leukemia showed t(11;14)(q23;q24) translocation and revealed that a human homologue of gephyrin (human gephyrin) had fused with MLL (Eguchi et al. 2001; Kuwada et al. 2001). Other fusion partners for MLL comprise SEPTIN6 (associated with inv ins (X;11)(q24;q23q13; Kim et al. 2003); SEPTIN9 associated with t(11;17)(q23q25;

Kurosu et al. 2008); MYO1F, an unconventional myosin type 1F (Taki et al. 2005); AF3p21, a nuclear protein with SH3- and proline-rich domains (Sano 2001); AF9 (Li et al. 2008); MLLT10 (de Figueiredo et al. 2012); and ELL (De Braekeleer et al. 2012). In MLL-fused leukemia cells, the CCAAT/enhancer-binding proteins (C/EBPs), C/EBPalpha and C/EBPepsilon, induce monocytic differentiation of myelomonocytic cells through downregulation of Myc (Matsushita et al. 2008). It is known that C/EBPalpha also directs monocytic commitment of primary myeloid progenitor cells (Wang et al. 2006). MLL family proteins interact with menin, a nuclear protein mutated in the MEN1 multiple endocrine neoplasia syndrome and that interacts with many proteins and is involved in a variety of cellular processes. Menin acts as a hub recruiting both wild-type MLL and MLL-fusion proteins to target genes (Thiel et al. 2012). Menin is an essential oncogenic cofactor for MLL-associated leukemogenesis (Yokoyama et al. 2005). Menin binds to the N terminus of MLL and in cooperation with MLL regulates the expression of the cyclin-dependent kinase inhibitors, p27Kip1 and p18Ink4c, via a mechanism involving recruitment of MLL to the p27Kip1 and p18Ink4c promoters and coding regions (Milne et al. 2005). MLL also forms a SET1-like histone methyltransferase complex with menin to regulate HOX gene expression (Yokoyama et al. 2004). Menin also acts as an adaptor that physically links MLL with LEDGF (lens epithelium-derived growth factor), a chromatin-associated protein that is required for MLL-dependent transcription and leukemogenesis (Yokoyama and Cleary 2008). Menin binds the JUN family transcription factor JUND and inhibits its transcriptional activity. The menin molecule contains a deep pocket that binds short peptides of MLL or JUND in the same manner, but with opposite effects on transcription. The menin-JUND interaction blocks the JUN N-terminal kinase (JNK)-mediated JUND phosphorylation and suppresses JUND-induced transcription, while menin promotes gene transcription by binding the transcription activator MLL (Huang et al. 2012). Another DNA methyltransferase gene mutated in acute monocytic leukemia is DNMT3A, encoding the DNA methyltransferase 3A (Yan et al. 2011; Fried et al. 2012).

Other Antigens/Proteins Associated with Acute Monocytoid Leukemias

MLAA-34, a splice variant of the CAB39L gene, is an antigen characterizing acute monocytic leukemia. MLAA-34 is an anti-apoptotic protein closely related to monocytoid leukemogenesis (Zhang et al. 2009).

Chronic Myelomonocytic Leukemia

ICD-O code 9945/3

Introduction

The WHO classification defines chronic myelomonocytic leukemia (CMML) as a clonal hematopoietic malignancy derived from a hematopoietic stem cell that is characterized by features of both a myeloproliferative neoplasm and a myelodysplastic syndrome. The diagnostic criteria for CMML include persistent monocytosis $>1 \times 10(9)/L$ in peripheral blood, absence of a Philadelphia chromosome and BCR-ABL 1 fusion gene, no arrangement of PDGFRA or PDGFRB, fewer than 20 % in peripheral blood and bone marrow (promonocytes are considered to be blast equivalents), and dysplasia involving one or more myeloid lineages. In the absence of myelodysplasia, a diagnosis of CMML can be done if the other requirements are met, and an acquired clonal cytogenetic or molecular genetic abnormality is present in bone marrow cells, or if the monocytosis has persisted for at least 3 months, and all other causes of chronic monocytosis are excluded.

CMML is divided into two subsets, CMML-1 and CMML-2, in dependence of the number of blasts plus promonocytes in the bone marrow and the peripheral blood. CMML-1 has <5 % blasts in peripheral blood and <10 % blasts in bone marrow. CMML-2 has 5–19 % blasts in peripheral blood or 10–19 % blasts in bone marrow. The International Prognostic Scoring System for myelodysplastic syndrome cannot be used to risk stratify patients with CMML because this model excluded patients with a leukocyte count >12 × 10(9)/L (review: Parikh and Tefferi 2012).

Clinical Features

Clinically, the disorder presents as an atypical myeloproliferative disorder with usually elevated peripheral white blood cell counts. Nonspecific clinical features comprise fatigue, fever, night sweats, and weight loss. CMML often involves extramedullary sites, specifically the spleen, liver, skin, and lymph nodes. CMML can cause myeloid sarcomas in various organs (Taillan et al. 1990; Hancock et al. 1997; Suh and Shin 2000; Akiyama et al. 2002).

Morphology

The hallmark of CMML is peripheral blood monocytosis, with almost always monocytes representing more than 10 % of leukocytes. Monocytes in blood smears are mostly mature, but abnormal granulation, abnormal nuclear lobulation, and/or abnormal chromatin patterns may occur. Neutrophil precursors account for less than 10 % in typical cases. In most patients, dysgranulopoiesis is noted. The bone marrow is hypercellular in three quarters of patients, with prominent granulocytic proliferation an invariable monocytic proliferation. In up to 80 % of patients, microkaryocytes and megakaryocytes with abnormally lobulated nuclei are found. Up to 30 % of cases reveal an increase in reticulin fibers.

Involvement of the Liver and Biliary Tract

The liver is often involved in CMML and shows myelomonocytic infiltrates and sometimes erythroid precursor cells and few megakaryocytes mostly in the sinusoids and portal tracts (Thomas et al. 1981; Pamplona et al. 1996). Infiltration of myelomonocytic cells of the wall of a liver cyst has been described (Akai et al. 2007). Dense sinusoidal infiltration may result in a sinusoidal blockage and portal hypertension (Pamplona et al. 1996). Massive infiltration of the spleen and liver may cause death (Thomas et al. 1981). Involvement of the liver by pyoderma gangrenosum developing in the setting of CMML was reported (Vadillo et al. 1999). CMML was found to be associated with myeloid tumor of the gallbladder (Bartley et al. 2007).

Cytogenetic Features and Molecular Genetic Features

Nonspecific clonal cytogenetic abnormalities were previously found in 20–40 % of patients with CMML, mostly +8, −7/del(7q) and structural abnormalities of 12p. Up to 40 % reveal point mutations of RAS genes at diagnosis or during disease evolution, and an alteration of the RUNX1 gene has been detected (Gelsi-Boyer et al. 2008). Recently, characteristic molecular genetic changes have been identified in patients with CMML (review: Muramatsu et al. 2012), including TET2 mutations (Grossmann et al. 2011; Euba et al. 2012; Pérez et al. 2012) and recurrent spliceosomal gene mutations (SRSF2, U2AF1, SF3B1; Abu Kar et al. 2012; Makishima et al. 2012), and mutations of genes associated with epigenetic regulation (Jankowska et al. 2011). The ASXL1 mutation correlated with an evolution toward an acutely transformed state in patients with CMML (Gelsi-Boyer et al. 2010). Part of CMML patients show novel chimaeric fusion genes involving the RET gene, enhancing monocytic differentiation (BCR-RET and FGFR1OP-RET).

References

Abu Kar S, Jankowska AM, Makishima H, Visconte V, Jerez A, Sugimoto Y, Muramatsu H et al (2012) Spliceosomal gene mutations are frequent events in the diverse mutational spectrum of chronic myelomonocytic leukemia but largely absent in juvenile myelomonocytic leukemia. Haematologica 98:107–113

Akai T, Kikawada M, Kimura A, Kikukawa M, Kiuchi A, Hanyu H, Matsubayashi J, Iwamoto T (2007) An elderly autopsy case of chronic myelomonocytic leukemia with infiltration of a giant liver cysts and multiple organs (in Japanese). Nippon Ronen Igakkai Zasshi 44:507–512

Akiyama N, Ohwada A, Kajiwara K, Ohtake H, Hayama M, Kohri M, Taira M, Niitsu N et al (2002) Granulocytic sarcoma of the colon in chronic myelomonocytic leukemia (in Japanese). Rinsho Ketsueki 43:937–942

Arico M, Biondi A, Pui CH (1997) Juvenile myelomonocytic leukemia. Blood 90:479–488

Bartley AN, Nelson CL, Nelson DH, Fuchs DA (2007) Disseminated extramedullary myeloid tumor of the gallbladder without involvement of the bone marrow. Am J Hematol 82:65–68

Bernt KM, Armstrong SA (2011) Targeting epigenetic programs in MLL-rearranged leukemias. Hematol Am Soc Hematol Educ Program 2011:354–360

Bonnin JA (1951) Monocytic leukemia with chloroma-like tumours. Med J Aust 38:835–839

Busque L, Gilliland DG, Prchal JT, Sieff CA, Weinstein JJ, Sokol JM, Belickova M, Wayne AS et al (1995) Clonality in juvenile chronic myelogenous leukemia. Blood 85:21–30

Chang YH, Jou ST, Lin DT, Lu MY, Lin KH (2004) Differentiating juvenile myelomonocytic leukemia from chronic myeloid leukemia in childhood. J Pediatr Hematol Oncol 26:236–242

Clark RD, Hutter JJ (1982) Familial neurofibromatosis and juvenile chronic myelogenous leukemia. Hum Genet 60:230–232

Cotter FE (1998) Childhood myeloproliferative disorders. Baillieres Clin Haematol 11:875–898

De Braekeleer M, Morel F, Le Bris MJ, Herry A, Douet-Guilbert N (2005) The MLL gene and translocations involving chromosomal band 1qq23 in acute leukemia. Anticancer Res 25:1931–1944

De Braekeleer E, Douet-Guilbert N, Meyer C, Morel F, Marschalek R, De Braekeleer M (2012) MLL-ELL fusion gene in two infants with acute monoblastic leukemia and myeloid sarcoma. Leuk Lymphoma 53:1222–1224

De Figueiredo AF, Vieira TP, Liehr T, Bhatt S, de Souza MT, Binato R, Marques-Salles Tde J et al (2012) A rare cryptic and complex rearrangement leading to MLL-MLLT10 gene fusion masked by del(10)(p12) in a child with acute monoblastic leukemia (AML-M5). Leuk Res 36:e74–e77

Eguchi M, Eguchi-Ishimae M, Seto M, Morishita K, Suzuki K, Ueda R, Ueda K, Kamada N et al (2001) GPHN, a novel partner gene fused to MLL in a leukemia with t(11;14)(q23;q24). Genes Chromosomes Cancer 32:212–221

Eguchi M, Eguchi-Ishimae M, Greaves M (2004) The small oligomerization domain of gephyrin converts MLL to an oncogene. Blood 103:3876–3882

Emanuel PD (2004) Juvenile myelomonocytic leukemia. Curr Hematol Rep 3:203–209

Emanuel PD (2008) Juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia. Leukemia 22:1335–1342

Euba B, Vizmanos JL, Garcia-Granero M, Aranaz P, Hurtado C, Migueliz I, Novo FJ et al (2012) A meta-analysis of TET2 mutations shows a distinct distribution pattern in de novo acute myeloid leukemia and chronic myelomonocytic leukemia. Leuk Lymphoma 53:1230–1233

Feichter GE, Müller KA, Bolte JP (1974) Monocytic leukemia with multiple monocytomas and late hematological manifestations (in German). Zentralbl Allg Pathol 118:445–451

Fried I, Wölfler A, Quehenberger F, Hoefler G, Still H, Zebisch A (2012) Mutations in DNMT3A and loss of RKIP are independent events in acute monocytic leukemia. Haematologica 97:1936–1937

Garcia C, Gardner D, Reichard KK (2008) CD163: a specific immunohistochemical marker for acute myeloid leukemia with monocytic differentiation. Appl Immunohistochem Mol Morphol 16:417–421

Gelsi-Boyer V, Trouplin V, Adélaide J, Aceto N, Remy V, Pinson S, Houdayer C, Arnoulet C et al (2008) Genome profiling of chronic myelomonocytic leukemia: frequent alterations of RAS and RUNX1 genes. BMC Cancer 8:299

Gelsi-Boyer V, Trouplin V, Roquain J, Adélaide J, Carbuccia N, Esterni B, Finetti P et al (2010) ASXL1 mutation is associated with poor prognosis and acute transformation in chronic myelomonocytic leukaemia. Br J Haematol 151:365–375

Gervais et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18528428

Grossmann V, Kohlmann A, Eder C, Haferlach C, Kern W, Cross NC, Haferlach T, Schnittger S (2011) Molecular profiling of chronic myelomonocytic leukemia reveals diverse mutations in $>$ 80 % of patients with TET2 and EZH2 being of high prognostic relevance. Leukemia 25:877–879

Hancock JC, Prchal JT, Bennett JM, Listinsky CM (1997) Trilineage extramedullary myeloid cell tumor in myelodysplastic syndrome. Arch Pathol Lab Med 121:520–523

Hayashida T, Araki Y, Kawano K, Kamata T, Kawai Y, Takeuchi K, Watanabe K, Okamoto S et al (1992)

Extramedullary diseases as presenting features of aleukemic acute monocytic leukemia (in Japanese). Rinsho Ketsueki 33:1679–1684

Hess JL (2004) MLL: a histone methyltransferase disrupted in leukemia. Trends Mol Med 10:500–507

Hess JL, Zutter MM, Castleberry RP, Emanuel PD (1996) Juvenile chronic myelogenous leukemia. Am J Clin Pathol 105:238–248

Hirabayashi S, Flotho C, Moetter J, Heuser M, Hasle H, Gruhn B, Klingebiel T, Thol F et al (2012) Spliceosomal gene aberrations are rare, coexist with oncogenic mutations, and are unlikely to exert a driver effect in childhood MDS and JMML. Blood 119: e96–e99

Holloman D, Eberts P, Clark C, Lewin D, Lazarchick J, Stuart R, Comerford L (2009) Extensive involvement of the gastrointestinal tract by a de novo presentation of the monoblastic type of myeloid sarcoma: a case report of a rare entity that is often misdiagnosed. Am J Med Sci 338:513–516

Honig GR, Suarez CR, Vida LN, Lu SJ, Liu ET (1998) Juvenile myelomonocytic leukemia (JMML) with the hematologic phenotype of severe b thalassemia. Am J Hematol 58:67–71

Huang J, Gurung B, Wan B, Matkar S, Veniaminova NA, Wan K, Merchant JL, Hua X et al (2012) The same pocket in menin binds both MLL and JUND but has opposite effects on transcription. Nature 482:542–546

Isobe H, Nishi Y, Fukutomi T, Iwamoto H, Nakamuta M, Sakai H, Andoh B, Sakamoto S et al (1991) Inflammatory pseudotumor of the liver associated with acute myelomonocytic leukemia. Am J Gastroenterol 86:238–240

Iwaka Y, Saikawa Y (2007) Monoblastic sarcoma of the kidneys in an infant leukaemia. Eur J Haematol 78:181

Jankowska AM, Makishima H, Tiu RV, Szpurka H, Huang Y, Traina F, Visconte V et al (2011) Mutational spectrum analysis of chronic myelomonocytic leukemia includes genes associated with epigenetic regulation: UTX, EZH2, and DNMT3A. Blood 118:3932–3941

Kajigaya Y, Sasaki H, Ikuta K, Koiso Y, Fukazawa K, Matsuyama S, Tanaka Y, Misugi K, Shibuya T (1987) An autopsy case of juvenile chronic myelogenous leukemia with extramedullary hematopoiesis in liver (in Japanese). Rinsho Ketsueki 28:939–944

Kim HJ, Ki CS, Park Q, Koo HH, Yoo KH, Kim EJ, Kim SH (2003) MLL/SEPTIN6 chimeric transcript from inv ins (X;11)(q24;q23q13) in acute monocytic leukemia: report of a case and review of the literature. Genes Chromosomes Cancer 38:8–12

Klco JM, Kulkarni S, Kreisel FH, Nguyen TD, Hassan A, Frater JL (2011) Immunohistochemical analysis of monocytic leukemias: usefulness of CD14 and Krüppel-like factor 4, a novel monocyte marker. Am J Clin Pathol 135:720–730

Koike K, Matsuda K (2008) Recent advances in the pathogenesis and management of juvenile myelomonocytic leukaemia. Br J Haematol 141:567–575

Kontny U, Gutjahr P, Schumacher R (1995) Unusual pattern of gastric and hepatic infiltration in an infant with acute monocytic leukemia. Pediatr Radiol 25:19–20

Kudo K, Terui K, Sasaki S, Kamio T, Sato T, Ito E (2011) CD7-positive acute myelomonocytic leukemia with trisomy 21 as a sole acquired chromosomal abnormality in two adolescents. Leuk Res 35:e167–e168

Kurosu T, Tsuji K, Ohki M, Miki T, Yamamoto M, Kakihana K, Koyama T, Taniguchi S et al (2008) A variant-type MLL/SEPT9 fusion transcript in adult de novo acute monocytic leukemia (M5b) with t(11;17)(q23;q25). Int J Hematol 88:192–196

Kuwada N, Kimura F, Matsumura T, Yamashita T, Nakamura Y, Wakimoto N, Ikeda T et al (2001) t(11;14)(q23;q24) generates an MLL-human gephyrin fusion gene along with a de facto truncated MLL in acute monoblastic leukemia. Cancer Res 61:2665–2669

Lau SK, Chu PG, Weiss LM (2004) CD163: a specific marker of macrophages in paraffin-embedded tissue samples. Am J Clin Pathol 122:794–801

Leung EW, Vanek W, Abdelhaleem M, Freedman MH, Dror Y (2003) The evolution of juvenile myelomonocytic leukemia in a female patient with paternally inherited neurofibromatosis type I. J Pediatr Hematol Oncol 25:145–147

Li L, Liu LB, Wang L, Zou P (2008) Effect of MLL-AF9 fusion gene silence of acute monocytic leukemia cell line THP-1 on cyclin-dependent kinase inhibitor p27 expression (in Chinese). Zhonghua Xue Ye Xue Za Zhi 29:375–378

Liu YL, Catsleberry RP, Emanuel PD (2009) PTEN deficiency is a common defect in juvenile myelomonocytic leukemia. Leuk Res 33:671–677

Loh ML (2010) Childhood myelodysplastic syndrome: focus on the approach to diagnosis and treatment of juvenile myelomonocytic leukemia. Hematol Am Soc Hematol Educ Program 2010:357–362

Loh ML, Sakai DS, Flotho C, Kang M, Fliegauf M, Archambeault S, Mullighan CG et al (2009) Mutations in CBL occur frequently in juvenile myelomonocytic leukemia. Blood 114:1859–1863

Makishima H, Cazzolli H, Szpurka H, Dunbar A, Tiu R, Huh J, Muramatsu H, O'Keefe C et al (2009) Mutations of e3 ubiquitin ligase cbl family members constitute a novel common pathogenic lesion in myeloid malignancies. J Clin Oncol 27:6109–6116

Makishima H, Visconte V, Sakaguchi H, Jankowska AM, Abu Kar S, Jerez A, Przychodzen B et al (2012) Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. Blood 119:3202–3210

Matsushita H, Nakajima H, Nakamura Y, Tsukamoto H, Tanaka Y, Jin G, Yabe M et al (2008) C/EBPalpha and C/EBPepsilon induce the monocytic differentiation of myelomonocytic cells with the MLL-chimeric fusion gene. Oncogene 27:6749–6760

Matsuura Y, Sato N, Kimura F, Shimomura S, Yamamoto K, Enomoto Y, Takatani O (1987) An increase in basophils

in a case of acute myelomonocytic leukaemia associated with marrow eosinophilia and inversion of chromosome 16. Eur J Haematol 39:457–461

Maurer HS, Vida LN, Honig GR (1972) Similarities of the erythrocytes in juvenile chronic myeloid leukemia to fetal erythrocytes. Blood 39:778–784

McKenna RW, Bloomfield CD, Dick F, Nesbit ME, Brunning RD (1975) Acute monoblastic leukemia: diagnosis and treatment of ten cases. Blood 46:481–494

Mikel JJ, Owen G, Lewis IJ (1990) Hepatic fibrosis in juvenile chronic granulocytic leukemia: an unusual finding in three cases. Pediatr Pathol 10:385–395

Miles DK, Freedman MH, Stephens K, Pallavicini M, Sievers EL, Weaver M, Grunberger T, Thompson P, Shannon KM (1996) Patterns of hematopoietic lineage involvement in children with neurofibromatosis type 1 and malignant myeloid disorders. Blood 88:4314–4320

Miliauskas JR (1986) Dermal monocytic sarcoma/monoblastic tumour: report of two cases of acute monocytic leukemia with initial dermal manifestations only. Pathology 18:249–253

Milne TA, Hughes CM, Lloyd R, Yang Z, Rozenblatt-Rosen O, Dou Y, Schnepp RW et al (2005) Menin and MLL cooperatively regulate expression of cyclin-dependent kinase inhibitors. Proc Natl Acad Sci U S A 102:749–754

Morerio C, Acquila M, Rosanda C, Rapella A, Dufour C, Locatelli F, Maserati E, Pasquali F, Panarello C (2004) HCMOGT-1 is a novel fusion partner to PDGFRB in juvenile myelomonocytic leukemia with t(5;17)(q33;p11.2). Cancer Res 64:2649–2651

Muntean AG, Hess JL (2012) The pathogenesis of mixed-lineage leukemia. Annu Rev Pathol 7:283–301

Muramatsu H, Makishima H, Maciejewski JP (2012) Chronic myelomonocytic leukemia and atypical chronic myeloid leukemia: novel pathogenetic lesions. Semin Oncol 39:67–73

Murati A, Gervais C, Carbuccia N, Finetti P, Cervera N, Adélaide J, Struski S, Lippert E et al (2009) Genome profiling of acute myelomonocytic leukemia: alteration of the MYB locus in MYST3-linked cases. Leukemia 23:85–94

Niemeyer CM, Kratz CP (2008) Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia: molecular classification and treatment options. Br J Haematol 140:610–624

Niemeyer C, Arico M, Biondi A et al (1994) Chronic myelomonocytic leukemia in childhood. Leuk Res 18:6 (Abstract)

Niemeyer CM, Kang MW, Shin DH, Furlan I, Erlacher M, Bunin NJ, Bunda S, Finklestein JZ et al (2010) Germline CBL mutations cause developmental abnormalities and predispose to juvenile myelomonocytic leukemia. Nat Genet 42:794–800

Ondreyco SM, Kjeldsberg CR, Fineman RM, Vaninetti S, Kushner JP (1981) Monoblastic transformation in chronic myelogenous leukemia: presentation with massive hepatic involvement. Cancer 48:957–963

Orts M, Ribera JM, Calatrava A, Larrouse E, Catalan R, Navarro JT, Milla F, Feliu E (1996) Pseudotumorous cardiac infiltration in a patient with acute monoblastic leukemia (in Spanish). Med Clin (Barc) 106:545–547

Pamplona J, Sabat M, Sancho Poch FJ, Monés J (1996) Ascites caused by portal hypertension in a patient with chronic myelomonocytic leukemia (in Spanish). Rev Esp Enferm Dig 88:151–153

Parikh SA, Tefferi A (2012) Chronic myelomonocytic leukemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol 87:610–619

Park SY, Jang JJ, Kim CW, Cho HI, Chi JG (2001) Congenital monoblastic leukemia with 9;11 translocation in monozygotic twins: a case report. J Korean Med Sci 16:366–370

Pérez B, Mechinaud F, Galambrun C, Ben Romdhane N, Isidor B, Philip N, Derain-Court J et al (2010) Germline mutations of the CBL gene define a new genetic syndrome with predisposition to juvenile myelomonocytic leukaemia. J Med Genet 47:686–691

Pérez C, Martinez-Calle N, Martin-Subero JI, Segura V, Delabesse E, Fernandez-Mercado M et al (2012) TET2 mutations are associated with specific 5-methylcytosine and 5-hydroxymethylcytosine profiles in patients with chronic myelomonocytic leukemia. PLoS One 7:e31605

Peterson L, Dehner LP, Brunning RD (1981) Extramedullary masses as presenting features of acute monoblastic leukemia. Am J Clin Pathol 75:140–148

Rao S, Kar R, Saxena R (2009) Pseudo Chediak-Higashi anomaly in acute myelomonocytic leukemia. Indian J Pathol Microbiol 52:255–256

Rappoport AE, Kugel VH (1947) Monocytic leukemia. A case report illustrating variations in the clinical picture. Blood 2:332–355

Sano K (2001) Structure of AF3p21, a new member of mixed lineage leukemia (MLL) fusion partner proteins – implication for MLL-induced leukemogenesis. Leuk Lymphoma 42:595–602

Sepp N, Radaszkiewicz T, Meijer CJ, Smolle J, Seewann H, Fritsch P, Kerl H (1993) Specific skin manifestations in acute leukemia with monocytic differentiation. A morphologic and immunohistochemical study of 11cases. Cancer 71:124–132

Shannon KM, O'Connell P, Martin GA, Paderanga D, Olson K, Dinndorf P, McCormick F (1994) Loss of the normal *NF1* allele from the bone marrow of children with type I neurofibromatosis and malignant myeloid disorders. N Engl J Med 330:597–601

Shaw MT (1978) The distinctive features of acute monocytic leukemia. Am J Hematol 4:97–103

Soriani S, Marbello L, Colosimo A, Scarpati B, Grillo G, Cesana C (2010) Double supernumerary isochromosome 4p in acute myelomonocytic leukemia. Leuk Res 34:e342–e344

Suh YK, Shin HJ (2000) Fine-needle aspiration biopsy of granulocytic sarcoma: a clinicopathologic study of 27 cases. Cancer 90:364–372

Sultan C, Imbert M, Ricard MF, Sebaoun G, Marquet M, Brun B, Forgues L (1977) Pure acute monocytic leukemia. A study of 12 cases. Am J Clin Pathol 68:752–757

Taillan B, Vitetta A, Perrin C, Fuzibet JG, Lacour JP, Vinti H, Hastier P, Dujardin P (1990) Granulocytic sarcoma, disclosing myelomonocytic leukemia (in French). Ann Med Interne (Paris) 141:559–560

Takanashi R (1972) A pathological study on the juvenile type of chronic myeloid leukemia. Acta Pathol Jpn 22:489–508

Taki T, Akiyama M, Saito S, Ono R, Taniwaki M, Kato Y, Yuza Y, Eto Y, Hayashi Y (2005) The MYO1F, unconventional myosin type 1F, gene is fused to MLL in infant cause monocytic leukemia with a complex translocation involving chromosomes 7, 11, 19 and 22. Oncogene 24:5191–5197

Thiel AT, Huang J, Lei M, Hua X (2012) Menin as a hub controlling mixed lineage leukemia. Bioessays 34:771–780

Thomas WJ, North RB, Poplack DG, Slease RB, Duval-Arnould B (1981) Chronic myelomonocytic leukemia in childhood. Am J Hematol 10:181–194

Tretter V, Mukherjee J, Maric HM, Schindelin H, Sieghart W, Moss SJ (2012) Gephyrin, the enigmatic organizer at GABAergic synapses. Front Cell Neurosci 6:23

Urs L, Qualman SJ, Kahwash SB (2009) Juvenile myelomonocytic leukemia: report of seven cases and review of literature. Pediatr Dev Pathol 12:136–142

Vadillo M, Jucgla A, Podzamczer D, Rufi G, Domingo A (1999) Pyoderma gangrenosum with liver, spleen and bone marrow involvement in a patient with chronic myelomonocytic leukaemia. Br J Dermatol 141:541–543

Walter RB, Bächli EB, Schaer DJ, Rüegg R, Schoedon G (2003) Expression of the hemoglobin scavenger receptor (CD163/HbSR) as immunophenotypic marker of monocyte lineage in acute myeloid leukemia. Blood 101:3755–3756

Wang D, D'Costa J, Civin CI, Friedman AD (2006) C/EBPalpha directs monocytic commitment of primary myeloid progenitors. Blood 108:1223–1229

Weatherall DJ, Edwards JA, Donohoe WTA (1968) Haemoglobin and red cell enzyme changes in juvenile myeloid leukaemia. Br Med J 1:679–681

Weinberg RS, Leibowitz D, Weinblatt ME, Kochen J, Alter BP (1990) Juvenile chronic myelogenous leukaemia: the only example of truly fetal (not fetal-like) erythropoiesis. Br J Haematol 76:307–310

Wu X, Du L, Wang X (2011) Congenital monoblastic leukemia presenting as jaundice, pleural effusion, and ascites: case report and literature review. Fetal Pediatr Pathol 30:27–31

Yan XJ, Xu J, Gu ZH, Pan CM, Lu G, Shen Y, Shi JY, Zhu YM, Tanh L, Zhang XW et al (2011) Exome sequencing identifies somatic mutations of DNA methyltransferase gene DNMT3A in acute monocytic leukemia. Nat Genet 43:309–315

Yang J, Ikezoe T, Nishioka C, Honda G, Yokoyama A (2012) Thrombomodulin-induced differentiation of acute myelomonocytic leukemia cells via JNK signaling. Leuk Res 36:625–633

Yokoyama A, Cleary ML (2008) Menin critically links MLL proteins with LEDGF on cancer-associated targets. Cancer Cell 14:36–46

Yokoyama A, Wang Z, Wysocka J, Sanyal M, Aufiero DJ, Kitabayashi I, Herr W, Cleary ML (2004) Leukemia proto-oncoprotein MLL forms a SET1-like histone methyltransferase complex with menin to regulate Hox gene expression. Mol Cell Biol 24:5639–5649

Yokoyama A, Somervaille TC, Smith KS, Rozenblatt-Rosen O, Meyerson M, Cleary ML (2005) The menin tumor suppressor protein is an essential oncogenic cofactor for MLL-associated leukemogenesis. Cell 123:207–218

Yoshida H, Imamura T, Fujiki A, Hirashima Y, Miyachi M, Inukai T, Hosoi H (2012) Post-transcriptional modulation of C/EBPa prompts monocytic differentiation and apoptosis in acute myelomonocytic leukaemia cells. Leuk Res 36:735–741

Zhang PY, Zhang WG, He AL, Wang JL, Li WB (2009) Identification and functional characterization of the novel acute monocytic leukemia associated antigen MLAA-34. Cancer Immunol Immunother 58:281–290

Zuo Z, Lu WP, Yu JB, Li JM, Liao DY (2008) Extramedullary infiltration of acute monocytic leukemia/monoblastic sarcoma: a clinicopathologic and immunophenotype analysis of 5 cases (in Chinese). Zhonghua Bing Li Xue Za Zhi 37:27–30

Malignant and Benign Extramedullary Tumor-Forming Myeloid Proliferations

86

Contents

Abstract

Myeloid neoplasms can form extramedullary myeloid tumors or masses, also in the hepatobiliary tract. Granulocytic sarcoma (extramedullary myeloid tumor (EMMT)) is an uncommon extramedullary manifestation of myelogenous leukemias and other forms of myeloproliferation. The gastrointestinal tract is rarely involved, and most patients are under 18 years of age. EMMT is mainly associated with acute myeloid leukemia, the blastic phase of chronic myeloid leukemia, and several types of myeloproliferative syndromes. In the liver, EMMT produces solitary nodular masses or, less commonly, multiple nodular lesions. In tumors composed of neoplastic cells rich in myeloperoxidase, the nodules have a greenish color (chloroma). Histologically, the tumors are composed of a mixture of myeloid cells with diverse degrees of differentiation, including lesions that consist of myeloid blasts. EMMT can also present as neoplasms with predominance of eosinophilic precursors or megakaryoblasts/megakaryocytes. EMMT has to be distinguished from benign extramedullary myeloid proliferations (BEMMPs) that also occur in the hepatobiliary tract. These reactive lesions can grow to important size (tumefactive BEMMP). Rare BEMMPs are characterized by a prominent fibrous matrix (sclerosing variants).

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_86

Granulocytic Sarcoma (WHO: Myeloid Sarcoma; Extramedullary Myeloid Tumor (EMMT))

ICD-O code 9930/3

Introduction

Granulocytic sarcoma ((GS); extramedullary myeloid tumor (EMMT); chloroma) is an uncommon extramedullary manifestation of myelogenous leukemias and other forms of myeloproliferation (3–8 %) in which tumorous masses of immature cells of the myeloid lineage develop. The concept was subsequently expanded to include all forms of extramedullary myeloid leukemic infiltrates, and the more comprehensive term extramedullary myeloid tumor (EMMT) is more and more in use, although the term proposed in 1988 was "extramedullary myeloid *cell* tumor" (Davey et al. 1988). In what follows, however, the original term, granulocytic sarcoma (GS) (Rappaport 1966), will be employed throughout. A short history of definitions and terminology is found at the end of this chapter.

Epidemiology and Clinical Features

GS is most commonly situated in the bones, skull, orbit, soft tissues, skin, breast, serosal surfaces, and paranasal sinuses (Huber 1878; Muss and Moloney 1973; Libson et al. 1986; Binder et al. 2000). The gastrointestinal tract is rarely involved, being reported in 4/61 (7 %) lesions (Neiman et al. 1981). GS occurs typically in children (Reinhard and Creutzig 2002; Porto et al. 2004); in fact, 75 % of the reported cases were patients under 18 years of age. GS may present at any time during the course of disease and can even precede the clinical onset of leukemia (Mason et al. 1973; McCarty et al. 1980). However, GS arising in non-leukemic patients does not necessarily progress to AML; in one study, 7 of 16 patients presenting with GS without manifesting leukemia did not develop acute leukemia after 3.5–16 years of follow-up (Meis et al. 1986). The disorders where GS has been observed include AML (the major association), CML (in particular its blastic phase), myeloproliferative syndromes (chronic idiopathic myelofibrosis), essential thrombocythemia, myelodysplastic syndromes, and polycythemia vera. GS may be seen as a de novo lesion without marrow involvement, or as a neoplasm associated with overt leukemia in the marrow, or as a site of leukemia relapse. AML and MDS can relapse as GS/chloroma after bone marrow transplantation (Bekassy et al. 1996; Szomor et al. 1997). In the retrospective EBMT cohort study, 0.7 %, 0.3 %, and 0.2 % of patients transplanted, respectively, for AML, MDS, or CML relapsed with GS/chloroma after allogeneic bone marrow transplantation (Bekassy et al. 1996). It seems that the incidence of GS is rising, and this may be due to prolonged survival of patients with myeloid malignancies. Based on an autopsy series, GS was found in 8 % of patients with AML and in 4 % of those with CML (Liu et al. 1973). It has been proposed that certain features of the abnormal stem cell-derived lineages (e.g., t(8;21); morphology of FAB M2, M4, and M5; expression of CD56, CD2, CD4, CD 7) may be associated with a higher incidence of extramedullary myeloid tumors (Binder et al. 2000).

Granulocytic Sarcoma (GS) of the Liver

GS/chloroma of the liver has been documented in the early literature already (Gade 1884; Fabian 1908; Kchinowloguer 1915; Askanazy 1916), and few reports are available in the more recent literature (Suh and Shin 2000; Alama Zaragoza et al. 2003; Sedinc et al. 2004; Best-Aguilera et al. 2005; Gangane et al. 2008; Hang et al. 2011). In a historical study of 96 observed and reported cases of chloroma, the liver was the site of "chloromatous nodules" in 19 instances (Kchinowloguer 1915). GS of the liver may develop on the background of myeloid metaplasia, with formation of multiple nodules of variable size (Gangane et al. 2008). Clinically, hepatic GS may be silent, present as a space-occupying mass with sequelae as in other larger tumors, or is

seldom associated with important acute jaundice (Alama Zaragoza et al. 2003).

GSs of the liver are solitary nodular masses or develop in the form of multiple nodules. The gross features may vary, the green or greenish color not always being clearly in evidence. Apart from the techniques used to examine the tumors, heterogeneity of differentiation and expression of myeloperoxidase may play a role for such differences. For example, a case of myeloid leukemia has been reported where hepatic perihilar, enlarged lymph nodes were yellow to greenish, whereas numerous GS nodules within the liver substance were gray to yellow, with a "dry" inner zone, resembling caseous necrosis (Fabian 1908). In typical hepatic chloroma, the green color may already be seen in biopsy specimens (Alama Zaragoza et al. 2003).

Histologically, GS are composed of a mixture of myeloid cells exhibiting diverse degrees of differentiation. The lesions may be subdivided into well differentiated, poorly differentiated, and blastic, according to the cytologic criteria reported (Menasce et al. 1999). The myeloid cells may be admixed with stromal cells and cells of the macrophage lineage, sometimes resulting in a starry-sky-like picture due to the presence of phagocytes with tingible bodies. The cells of GS may contain crystalline inclusions that, ultrastructurally, are indistinguishable from Charcot-Leyden crystals (Strauchen and Gordon 2002).

Variant Patterns of GS: Eosinophil (Eosinophilic Granulocytic Sarcoma) and Megakaryocytic Lineages

There are variants of GS/chloroma with a distinct cellular differentiation pattern. One variant is characterized by a high content in eosinophils and their precursors, a lesion termed eosinophilic granulocytic sarcoma or "eosinophilic chloroma" (Benvenisti and DeBellis 1969; Adler and Schaefer 2001). These lesions show dense accumulations of eosinophilic granulocytes (Muller et al. 1987), myelocytes, and few promyelocytes combined with a background of nongranular blasts, accompanied by the presence of Charcot-Leyden crystals, in part phagocytosed by macrophages. Contrary to GS with a predominantly or exclusively neutrophil lineage, myeloperoxidase (MPO) and naphthol-AS-D-chloroacetate esterase (NACE) are absent from eosinophils. Instead, eosinophils contain a peroxidase different from MPO/verdoperoxidase; this eosinophil peroxidase fails to contribute any green color to the macroscopic aspect. Therefore, GS with predominance of eosinophils must not be called "eosinophilic chloroma," because they cannot be green cancers. In addition, the cells in GS can enter a megakaryoblast/megakaryocyte differentiation pathway (extramedullary megakaryoblastic tumors), eventually terminating as acute megakaryoblastic leukemia (Kobayashi et al. 1992; Chubachi et al. 1995; Chan et al. 1996; Hirose et al. 2001). GS in the liver may, similar to non-tumorous involvement in myeloid disorders, be associated with hepatic iron overload/hemosiderosis (Fabian, Butterfield, Fabian).

Table 1 Predominant immunohistochemical phenotype in granulocytic sarcoma

Positivity in high percentage for:
Myeloperoxidase (MPO)
CD 43
Lysozyme
CD117/c-Kit
CD45
CD56
CD13

The histologic identification of GS may be difficult, thus requiring immunohistochemical examinations (Table 1; Davey et al. 1988, 1990; Roth et al. 1995). Reliable markers for a differentiating myeloid cell lineage comprise myeloperoxidase (MPO), lysozyme, and CD13 (Roth et al. 1995; Quintanilla-Martinez et al. 1995; Eelnitoba-Johnson et al. 1996; Audouin et al. 2003). MPO is detectable by use of the monoclonal antibody, MPO-7 (Lepelley et al. 1993). GS cells are variably positive for CD45 (Hudock et al. 1994; Quintanilla-Martinez et al. 1995). Expression of CD56 is frequent in

GS, especially when the marrow blasts have monocytoid differentiation, and immature myeloid cells in GS are frequently reactive for HLA-DR, whereas CD34 positivity of immature myeloid cells is relatively uncommon in GS, except in cases with underlying myelodysplastic syndrome or CML (Chang et al. 2000). Myeloid progenitor cell antigens, CD31 and CD34, can be expressed in GS, and CD43 is expressed in the majority of cases (Hudock et al. 1994). Lysozyme and CD43 together seem to be potent markers for GS (Menasce et al. 1999), and the use of the combination of CD34, MPO, and Leder's chloroacetate esterase stain can help to reach a definitive diagnosis (Mourad et al. 2001). It has been shown that CD99 (MIC2) is commonly expressed in blasts in M1-, M3-, and HLA-DR-negative AML (Zhang et al. 2000) and may therefore show reactivity in a subset of GS cells. Other markers that are variable positive in the GS target cells include elastase, CD15, CD68, and c-Kit (Traweek et al. 1993; Chen et al. 2001). A study of 30 cases showed CD117/c-Kit reactivity in 87 %, MPO 97 %, lysozyme 93 %, CD34 47 %, CD45 84 %, CD43 97 %, TdT 37 %, CD79a 20 %, CD20 10 %, CD3 10 %, and CD10 1 % (Chen et al. 2001).

Granulocytic Sarcoma of the Biliary Tract

Stenosing lesions of intrahepatic bile ducts caused by GS (see below) have to be distinguished from those situations, where neoplastic myeloid cells locate to the tissues surrounding the bile ducts, including the large ducts and causing extrahepatic obstructive jaundice (Gutierret de Guzman et al. 1987; Nakamoto et al. 1987; Case Records of the Massachusetts General Hospital 1988; Mano et al. 2004; Gonzalez-Vela et al. 2006; Hourseau et al. 2006; Sung et al. 2006; Lee et al. 2007; Abid et al. 2010; Bartels et al. 2010; Hachicha et al. 2010; Hwang et al. 2010; Kawamura et al. 2010; Rajeswari et al. 2012). Obstructive jaundice caused by GS has been observed in a child with FLT3-internal tandem duplication with t(8;21) AML (Kawamura et al. 2010). GS of the bile ducts may be followed by AML with multilineage dysplasia and chromosomal abnormalities (Sung et al. 2006).

GS can develop in the main biliary ducts, both in AML and in CML, but obstructive jaundice caused by such lesions had only rarely been reported, and in several patients, GS causing biliary obstruction was related to AML (Lillicrap et al. 1982; King et al. 1987; Gutierret de Guzman et al. 1987; Case records 1988, 1990; Rotter et al. 1992; Fleming and Slone 1997; Matsueda et al. 1998; Jaing et al. 2001; Piccalunga et al. 2007; Table). However, obstructive jaundice in AML can also develop in the absence of a mass in the sense of GS (Goor et al. 2002). One patient developed overt AML 16 months after the onset of jaundice and 11 months after the diagnosis of GS (King et al. 1987). In part of the cases, GS involved the hilar/perihilar region and caused bile duct stenosis, sometimes mimicking Klatskin tumor (Pomeranz et al. 1985; Matsueda et al. 1998; Ascani et al. 2003; Kim et al. 2006). Obstruction of extrahepatic bile ducts with subsequent cholestasis can be caused by GS located to the pancreas (King et al. 1987; Ravandi-Kashani et al. 1999; Servin-Abad et al. 2003).

Histologically, biliary tract GS presents as a tumor-like stenosing mass or as a lesion with transmural infiltration of the duct by myeloid cells with medium-sized round nuclei with central nucleoli and an eosinophilic cytoplasm. Immunohistochemically, the cells are reactive for MPO, CD68, lysozyme, CD45, CD117, and CD43 (Gonzalez-Vela et al. 2006). In some instances, numerous myeloid cells infiltrate the periductal tissue and may form macroscopically greenish sheaths of up to 0.5 cm in diameter ("Glisson tract chlorosis"; Müller 1926). Histologically, the dense myeloid infiltrate fills the Glisson's spaces and can extend into the tissues adjacent to liver lobules, suggesting cirrhotic remodeling at low magnification (Figs. 26 and 27 in Gruber 1930). The myeloid cells may encroach upon intrahepatic bile ducts, associated with bile duct damage ("myeloid leukemic cholangiopathy"). An intricate spatial relationship between leukemia cells and the biliary epithelium has been shown by use of myeloperoxidase

immunohistochemistry, the leukemia cells also encircling the vessels of the peribiliary plexus (Fleming and Slone 1997).

Why Are Bona Fide Chloromas Green?

Myeloperoxidase (MPO; hydrogen peroxide oxidoreductase; EC 1.11.1.7) is a neutrophil lysosomal heme protein essential for optimal oxygen-dependent microbicidal activity of these phagocytes (Arnhold 2004). The importance of MPO is illustrated by an individual with a neutrophil function defect caused by hereditary MPO deficiency (Romano et al. 1997; Petrides 1998; Marchetti et al. 2004). The gene encoding MPO is assigned to human chromosome 17q21.3-q23 (van Tuinen et al. 1987; Inazawa et al. 1989), where it forms a gene cluster together with the lactoperoxidase and eosinophil peroxidase genes (Sakamaki et al. 2000). The three genes are also clustered in the mouse (on the murine chromosome 11; Sakamaki et al. 2002). MPO, itself subject to genetic promoter polymorphisms (Ritgers et al. 2003), is the most abundant neutrophil granule enzyme and catalyzes the two-electron oxidation of ubiquitous chloride to generate the potent bleaching oxidant, hypochlorous acid (HOCl), a halogenation cycle that is important in microbial killing (reviews: Jantschko et al. 2004; Arnhold et al. 2003). The enzyme is a unique peroxidase in having a globin-like standard reduction potential of the ferric/ferrous couple, and the kinetics of the reactivity of ferrous MPO with molecular oxygen has been studied in detail (Jantschko et al. 2004).

During biosynthesis of MPO, the luminal endoplasmic reticulum proteins, calreticulin and calnexin, act as molecular chaperones, associating reversibly with the heme-free glycosylated precursor, apo-Pro-MPO (Nauseef et al. 1998). Neutrophil *primary* granule release (neutrophil degranulation) is dependent on the Rho GTPase, Rac2, as based on studies employing rac2 (−/−) knockout mice, whereas secondary specific and tertiary granule release does not seem to depend on Rac2 (Abdel-Latif et al. 2004). For the identification of cell lineage features, MPO is an early-appearing and very reliable myeloid lineage marker. The protein is detectable in a subset of hemopoietic bone marrow progenitors as well as in granulo-/monocytopoietic cells, whereas other myeloid-related cells including epidermal Langerhans cells lack MPO expression. There is evidence that early myeloid progenitors lack MPO and then enter two pathways, one representing the origin of MPO-positive myeloid cells and the other remaining MPO-negative and delivering non-granulocytic/non-monocytic cells such as Langerhans cells (Scholz et al. 2004). MPO can be purified from freshly isolated blood cells, resulting in a protein preparation which is *green* and has an A430/A280 nm of 0.68 (Xu et al. 1990). This typical color, having led to the term verdoperoxidase (from Latin viridis, green), depends on the porphyrin moiety of MPO's heme component (Newton et al. 1965; Lee et al. 1967; Nichol et al. 1969; Mitsuoka 1969). Crystalline protoporphyrin has been isolated from cells of experimental chloroma (Schultz and Schwartz 1956).

The Concept of Granulocytic Sarcoma: Brief Historical Outline

The lesion has probably first been described in 1811 (Burns 1811). The association of GS and acute leukemia was established in 1893 (Dock 1893), while the term GS was first employed in 1966 (Rappaport 1966). Synonyms include chloroma, chloromyeloma, chloromyelosarcoma, granulocytic leukosarcoma, chloroleukemia, myeloblastoma, chloromyeloblastoma, myelocytoma, myelosarcoma, and leukoma. The 2001 tumor classification of the WHO employs the term myelosarcoma.

The term chloroma (from Greek chloros, green) was coined already in 1853 (King 1853). This author used this term based on the observation that the cut surface of the tumor appears temporarily green under light, owing to the tumor's high content in myeloperoxidase. Chloroma is the "green cancer of Aran" (Aran 1854; see also Turk 1903; Brannan 1926; Edgerton 1947; Ross 1955; Anonymous 1961; Reardon and Moloney 1961; Tran et al. 1962;

Kojima 1963; Wiernik and Serpick 1970; Mason et al. 1973) and is also known as Balfour's disease (Balfour 1835). Both Balfour and, later, Aran (who coined the term "cancer vert" ("green cancer")) described chloroma in the skull and dura. François-Amilcar Aran, born 1817 in Bordeaux (France), was a physician with widespread interests; in 1858, he published an influential book, entitled *Leçons cliniques sur les maladies de l'uterus et de ses annexes*. A major work, his planned *Dictionnaire de Thérapeutique*, remained unfinished owing to his untimely death in 1861 at the age of 44. John Hutton Balfour, born 1808 in Edinburgh, made his MD in 1831, but in 1840 he began giving lectures in botany and became botany professor already in 1841. In fact, he is much more known for his botanical studies, becoming head of the Royal Botanical Garden and Queen's botanist in Scotland. For 30 years, he was dean of the medical faculty in Edinburgh where he first introduced teaching in microscopy. The description of GS represents one of his relatively few medical articles, his opus being clearly dominated by botany, but his description of GS earned him the eponym Balfour's disease. Owing to his strong encouragement of the Palliser expedition, his name was also given to Balfour Pass and Mount Balfour (3,272 m/10,735 ft) in Canada. In 1916, Askanazy used, in addition to chloroma, the term "leukemia with green tumors" (Askanazy 1916).

Benign Extramedullary Myeloid Proliferations

Introduction

Extramedullary hematopoiesis (EMH) refers to the production of blood cells outside the bone marrow and is often a compensatory response to cope with bone marrow failure associated with marrow infiltration, marrow depletion, or marrow hyperactivity in certain chronic anemias (Kumar et al. 1995; review by O'Malley 2007). Benign extramedullary myeloid proliferations (BEMMPs; the so-called myeloid metaplasia) are reactive lesions occurring in diverse extramedullary compartments, consisting of reactive EMH. BEMPP can present as diffuse tissue infiltrations, microfocal alterations, or macronodular tumor-like lesions, the latter sometimes mimicking a neoplastic process. BEMMPs forming tumor-like masses are also termed tumefactive extramedullary hematopoiesis. Tumor-forming BEMMPs are rare lesions that were described in 1945 based on autopsy findings showing intrathoracic tumor-like lesions (Ask-Upmark 1945). A preference of intrathoracic BEMMP lesions was later confirmed by Verani et al. (1980) who collected 55 cases from the literature up to 1980, most cases seen in patients with thalassemia and spherocytosis, while sickle cell anemia as a cause of intrathoracic BEMMP was less often noted in comparison with other hemolytic disorders. Typical localizations of BEMMP include the intrathoracic/paravertebral compartment, skin, salivary and lacrimal glands, lung, spleen, kidney, and liver (see below). In part of tumor-forming BEMMP, the hematopoietic tissue undergoes marked production of extracellular matrix (ECM), with deposition of collagen and other ECM proteins (sclerosing extramedullary hematopoietic tumor (SEMHT)). The proliferations develop as a response to high demands for production of blood elements and are usually caused by hematologic disorders occupying bone marrow spaces, by increased destruction of blood cells, or by hematopoietic growth factors (reviews by Nappi et al. 2003; O'Malley 2007).

Benign Extramedullary Myeloid Proliferations in the Liver

The liver is a central site for early hematopoiesis and possesses a distinct stromal cell microenvironment for stem cell homing and priming for hematopoietic cell lineages. This stromal compartment is maintained in adult livers, and it is therefore not astonishing that the liver is a relatively common site for EMH. In infants, the presence of hepatic hemopoiesis is considered normal up to about 5 weeks of age. The stromal microenvironment is maintained in adult livers which are therefore a relatively common site for EMH. In

the adult liver, BEMMP usually presents as accumulations of hematopoietic cells within sinusoids. In fact, the hepatic parenchyma is one of the most common sites of diffuse BEMMP in patients with hemolytic anemias or myeloproliferative disorders (Ward and Block 1971). The cellular composition of these accumulations varies markedly and ranges from tiny erythropoietic foci with normoblasts to foci containing a mixture of immature and mature erythroid and granulocytopoietic cells, with or without associated megakaryocytes, the latter being rare findings. Apart from diffuse sinusoidal infiltrates, BEMMP can also present as microfocal lesions that are not macroscopically visible.

Nodular Extramedullary Hematopoiesis of the Liver (Tumefactive BEMMP)

Less commonly, BEMMP develops into larger focal lesions or even tumefactive lesions. These lesions, which are also termed nodular extramedullary hematopoiesis of the liver (NEMH-L), occur in the form of solitary or multiple lesions of variable size, involving one or both liver lobes (Kopecky et al. 1986; Wiener et al. 1987; Kopecky 1988; Dardi et al. 1990; Tamm et al. 1995; Lemos et al. 1997; Wong et al. 1999; Priola et al. 2012). Among eight cases with sufficient data compiled from the literature, five were multiple and three solitary lesions (Wong et al. 1999). NEMH-L can present as a solitary space-occupying lesion mimicking a primary liver neoplasm, mainly HCC (Lee et al. 2008), metastatic disease, FNH, or an atypical hemangioma (Wiener et al. 1987; Bradley and Metreweli 1990; Gil-Fernandez et al. 2001; Tamiolakis et al. 2004), thus promoting diagnostic fine needle aspiration (Dardi et al. 1990; Lemos et al. 1997). Metastatic disease may in particular be suspected in case NEMH-L produces several lesions with nodular hepatomegaly (Hervé et al. 2001).

Macroscopically, NEMH-Ls are generally described as nodular and sometimes bulky and rather well-defined lesions that are of medium consistency and show a cut surface that varies from red-brown or tan (in case of high vascularity and/or iron deposition) to grayish white. Sizes of the nodules range from tiny lesions mimicking microabscesses (Kopecky et al. 1986) to 1.5 cm (Hervé et al. 2001), 3 cm (Wong et al. 1999), or even 8 cm (Ma and Au 1999). Massive solitary NEMH-L has been observed in thalassemia (Dewar et al. 1990) and in myelofibrosis (Navarro et al. 2000). The masses may grow rather rapidly, particularly postsplenectomy; in one observation, the first hepatic manifestation was a 3 cm lesion, growing to 6 cm within 3 months (Wong et al. 1999). On the other hand, even very large lesions have been reported to remain unchanged for 4 years (Ma and Au 1999).

Histologically, NEMH-L is composed of normal-looking hematopoietic tissue consisting of all three lineages. Few small cells with a lymphoid morphology may be present. It is not yet known whether such cells may, in addition to a lymphocyte population, represent hematopoietic stem cells. Similar to bone marrow, the hematopoietic tissue contains scattered macrophages with or without stainable iron. In addition, cells with a spindle-shaped morphology are detectable in small numbers (an analogue to marrow stromal cells?). In larger lesions, extracellular matrix may be increased, sometimes with focal fibrosis or sclerosis. In fact, NEMH-L can produce stellate scars visible in MRI and CT (Wong et al. 1999). The adjacent liver substance is compressed in large lesions, and perifocal hepatocytes may show iron overload (Ma and Au 1999). Hematopoietic tissue in BEMMP lesions may undergo adipose transformation ("fatty marrow change"; "fatty replacement"; Yamato and Fuhrman 1987), similar to what can take place in bone marrow. This alteration was also noted in intrahepatic BEMMP (Gupta et al. 2004).

Sclerosing Extramedullary Hematopoietic Tumor of the Liver

Sclerosing extramedullary hematopoietic tumor (SEMHT) is a rare lesion that typically arises in patients with chronic myeloproliferative disorders

(Remstein et al. 2000; Sukov et al. 2009). It can develop in the abdominal cavity, where it can form large solitary masses or multiple nodular tumors (Yang et al. 2002). In one patient, SEMHT involved the lesser omentum and the ligamentum teres of the liver (Kwon et al. 2004). Histologically, elements of the myeloid lineage, including blasts, are embedded in a dense matrix rich in collagen fiber bundles and reticulin fibers. In some cases, the cells situated in the matrix are predominantly bizarre-looking giant cells with lobated nuclei, cells that mimic malignancy but representing megakaryocytes and megakaryoblasts morphologically altered by the sclerosed matrix.

Differential Diagnosis

The most important, and at the same time the most difficult, differential diagnosis of hepatic BEMMP is differentiated hemopoietic elements with a neoplastic character. On exclusively morphological grounds, it is not, or barely, possible to distinguish reactive myeloid proliferations and neoplastic ones in the setting of a malignant myeloproliferative disorder. Neoplastic myeloid disorders morphologically mimicking BEMPP may also develop in the biliary tract. A disseminated myeloproliferative lesion of the gallbladder has been observed in a 63-year-old female in the absence of bone marrow involvement. The patient subsequently developed a neoplastic myeloid disorder that was disseminated throughout inner organs at autopsy, but again with sparing of the bone marrow (Bartley et al. 2007).

References

Abdel-Latif D, Steward M, Macdonald DL, Francis GA, Dinauer MC, Lacy P (2004) Rac2 is critical for neutrophil primary granule exocytosis. Blood 104:832–839

Abid M, Belaj H, Mnif L, Cheikhrouhou H, Mdhafer M, Beyrouti MI (2010) Myeloid sarcoma of the main biliary duct (in French). Presse Med 39:402–404

Adler CP, Schaefer HE (2001) Eosinophilic chloroma (eosinophilic granulocytic sarcoma). Histopathology 39:544–546

Alama Zaragoza MA, Robles Iniesta A, Roca Adelantado I, Sales Maicas MA, Ferrandez Izquiredo A, Roman Sanchez P (2003) Hepatic granulocytic sarcoma: an unusual presentation (in Spanish). An Med Interna 20:141–144

Anonymous (1961) Chloroma. . .Aran's green cancer. Cancer Bull 13:5

Aran FA (1854) Notes sur une forme particulière et encore peu connue de cancer de la dure mère et des os du crâne (cancer vert). Arch Gen Med (Paris) 5(ser. 4):385

Arnhold J (2004) Properties, functions, and secretion of human myeloperoxidase. Biochemistry (Mosc) 69:4–9

Arnhold J, Furtmuller PG, Obinger C (2003) Redox properties of myeloperoxidase. Redox Rep 8:179–186

Ascani S, Piccaluga PP, Pileri SA (2003) Granulocytic sarcoma of main biliary ducts. Br J Haematol 121:534

Askanazy M (1916) Einiges zum Verständnis der Chlorome. Beitr Pathol Anat Allg Pathol 63:23

Ask-Upmark E (1945) Tumours simulating intrathoracic heterotopia of bone marrow. Acta Radiol 26:425–440

Audouin J, Comperat E, Le Tourneau A, Camilleri-Broet S, Adida C, Molina T, Diebold J (2003) Myeloid sarcoma: clinical and morphologic criteria useful for diagnosis. Int J Surg Pathol 11:271–282

Balfour JH (1835) Case of particular disease of the skull and dura mater. Edinb Med Surg J 43:319–325

Bartels M, Theergarten D, Metz KA, Dührsen U (2010) 56-year-old female patient with jaundice and paraparesis (in German). Dtsch Med Wochenschr 135:1861–1862

Bartley AN, Nelson CL, Nelson DH, Fuchs DA (2007) Disseminated extramedullary myeloid tumor of the gallbladder without involvement of the bone marrow. Am J Hematol 82:65–68

Bekassy AN, Hermans J, Gorin NC, Gratwohl A for the Acute and Chronic Leukemia Working Parties of the European Group for Blood and Marrow Transplant (1996) Granulocytic sarcoma after allogeneic bone marrow transplantation: a retrospective European multicenter survey. Bone Marrow Transplant 17:801–808

Benvenisti DS, DeBellis RH (1969) Carcinoma of the breast, chronic lymphocytic leukemia, macroglobulinemia, eosinophilic chloroma and myelosclerosis – a unique association. Cancer 23:1204–1209

Best-Aguilera CR, Vazquez-Del Mercado M, Munoz-Valle JF, Herrera-Zarate L, Navarro-Hernandez RE et al (2005) Massive myeloid sarcoma affecting the central nervous system, mediastinum, retroperitoneum, liver, and rectum associated with acute myeloblastic leukemia: a case report. J Clin Pathol 58:325–327

Binder C, Tiemann M, Haase D, Humpe A, Kneba M (2000) Isolated meningeal chloroma (granulocytic sarcoma) – a case report and a review of the literature. Ann Hematol 79:459–462

Bradley MJ, Metreweli C (1990) Sonography of extramedullary hematopoiesis of the liver. AJR Am J Roentgenol 154:900–901

Brannan D (1926) Chloroma. Johns Hopkins Hosp Bull 38:189

Burns A (1811) Observations on the surgical anatomy of the head and neck. 2nd ed, Wardlaw and Cunninghame, Glasgow

Case Records of the Massachusetts General Hospital (1988) N Engl J Med 319:356–364, case 32–1988

Case Records of the Massachusetts General Hospital (1990) N Engl J Med 322:1585–1594, case 22–1990

Chan AC, Kwong YL, Lam CC (1996) Granulocytic sarcoma of megakaryoblastic differentiation complicating chronic idiopathic myelofibrosis. Hum Pathol 27:417–420

Chang CC, Eshoa C, Kampalath B, Shidham VB, Perkins S (2000) Immunophenotypic profile of myeloid cells in granulocytic sarcoma by immunohistochemistry. Correlation with blast differentiation in bone marrow. Am J Clin Pathol 114:807–811

Chen J, Yanuck RR, Abbondanzo SL, Chu WS, Aguilera NS (2001) c-Kit (CD117) reactivity in extramedullary myeloid tumor/granulocytic sarcoma. Arch Pathol Lab Med 125:1448–1452

Chubachi A, Wakui H, Miura I, Saitoh M, Nishinari T, Nishimura S, Miura AB (1995) Extramedullary megakaryoblastic tumors following an indolent phase of myelofibrosis. Leuk Lymphoma 17:351–354

Dardi LE, Marzano M, Froula E (1990) Fine needle aspiration cytologic diagnosis of focal intrahepatic extramedullary hematopoiesis. Acta Cytol 34:567–569

Davey FR, Olson S, Kurec AS, Eastman-Abaya R, Gottlieb AJ, Mason DY (1988) The immunophenotyping of extramedullary myeloid cell tumors in paraffin-embedded tissue sections. Am J Surg Pathol 12:699–707

Davey FR, Elghetany MT, Kurec AS (1990) Immunophenotyping of hematologic neoplasms in paraffin-embedded tissue sections. Am J Clin Pathol 93(suppl 1):S17–S26

Dewar G, Leung NW, Ng HK, Bradley M, Li AK (1990) Massive, solitary, intrahepatic, extramedullary hematopoietic tumor in thalassemia. Surgery 107:704–707

Dock G (1893) Chloroma and its relation to leukemia. Am J Med Sci 106:152–157

Edgerton A (1947) Chloroma: report of a case and review of the literature. Trans Am Ophthalmol Soc 45:376–414

Eelnitoba-Johnson K, Hodges GF, King TC, Wu CD, Medeiros LJ (1996) Extramedullary myeloid cell tumors arising in the setting of chronic myelomonocytic leukemia. A report of two cases. Arch Pathol Lab Med 120:62–67

Fabian H (1908) Ueber lymphatische und myeloische Chloroleukämie. Beitr Pathol Anat Allg Pathol 43:172

Fleming DR, Slone SP (1997) CML blast crisis resulting in biliary obstruction following BMT. Bone Marrow Transplant 19:853–854

Gade J (1884) Bidrag til kundkabens ven klorom. Nord Med Ark 16 (nr. 9)

Gangane N, Kamra H, Anshu, Joshi D, Gupta A (2008) Cytodiagnosis of granulocytic sarcoma of liver in a milieu of myeloid metaplasia: a case report. Acta Cytol 52:619–622

Gil-Fernandez et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11325659

Gonzalez-Vela MC, Val-Bernal JF, Mayorga M, Cagigal ML, Fernandez F, Mazorra F (2006) Myeloid sarcoma of the extrahepatic bile ducts presenting as obstructive jaundice. APMIS 114:666–668

Goor Y, Goor O, Michalewitcz R, Cabili S (2002) Acute myeloid leukemia presenting as obstructive jaundice. J Clin Gastroenterol 34:485–486

Gruber GB (1930) 6. Die Leber bei Erkrankungen des blut- und lymphbildenden Gewebs-Apparates. In: Henke F, Lubarsch O (eds) Handbuch der Speziellen Pathologischen Anatomie und Histologie, vol 5. Julius Springer, Berlin, p 662, part 1

Gupta P, Naran A, Auh YH, Chung JS (2004) Focal intrahepatic extramedullary hematopoiesis presenting as fatty lesions. AJR Am J Roentgenol 182:1031–1032

Gutierret de Guzman J, Clavero C, Palomo MA, Oyonarte S, Maldonado J (1987) Obstructive jaundice caused by granulocytic sarcoma. An unusual presentation of an acute leukemia (in Spanish). Rev Clin Esp 180:309–310

Hachicha LM, Chaari C, Ellouze S, Gheriani M, Abid M, Boudawara TS (2010) A rare tumor of the main biliary duct (in French). Ann Pathol 30:470–472

Hang XF, Xin HG, Wang L, Xu WS, Wang JX, Ni W, Cai X, Zhang RQ (2011) Nonleukemic myeloid sarcoma of the liver: a case report and review of literature. Hepatol Int 5:747–750

Hervé S, Savoye G, Svoye-Collet C, Bahbahani A, Auliac JB, Bota S, François A, Lerebours E (2001) Intrahepatic extramedullary hematopoiesis as a manifestation of malignant thymoma: an unusual cause of nodular hepatomegaly (in French). Gastroenterol Clin Biol 25:711–713

Hirose Y, Masaki Y, Shimoyama K, Sugai S, Nojima T (2001) Granulocytic sarcoma of megakaryoblastic differentiation in the lymph nodes terminating as acute megakaryoblastic leukemia in a case of chronic idiopathic myelofibrosis persisting for 16 years. Eur J Haematol 67:194–198

Hourseau M, Zafrani ES, Bienvenu L, Habib E, Lusina D, Choudat L (2006) Myeloid sarcoma of the main biliary duct mimicking a bile duct carcinoma: report of one case (in French). Gastroenterol Clin Biol 30:159–160

Huber K (1878) Studien über das sogenannte Chlorom. Arch Heilkde 19:129

Hudock J, Chatten J, Miettinen M (1994) Immunohistochemical evaluation of myeloid leukemia infiltrates (granulocytic sarcoma) in formaldehyde-fixed, paraffin-embedded tissue. Am J Clin Pathol 102:55–60

Hwang DW, Lim CS, Jang JY, Lee SE, Yoon SO, Jeon YK, Uk Lee K, Kim SW (2010) Primary hematolymphoid malignancies involving the extrahepatic bile duct or gallbladder. Leuk Lymphoma 51:1278–1287

Inazawa J, Inoue K, Nishigaki H, Tsuda S, Taniwaki M, Misawa S, Abe T (1989) Assignment of the human

myeloperoxidase gene (MPO) to bands q21-3 – q23 of chromosome 17. Cytogenet Cell Genet 50:135–136
Jaing TH, Yang CP, Chang KW, Wang CJ, Chiu CH, Luo CC (2001) Extrahepatic obstruction of the biliary tract as the presenting feature of acute myeloid leukemia. J Pediatr Gastroenterol Nutr 33:620–622
Jantschko W, Furtmuller PG, Zederbauer M, Jakopitsch C, Obinger C (2004) Kinetics of oxygen binding to ferrous myeloperoxidase. Arch Biochem Biophys 426:91–97
Kawamura M, Kaku H, Ito T, Funata N, Taki T, Shimada A, Hayashi Y (2010) FLT3-internal tandem duplication in a pediatric patient with t(8;21) acute myeloid leukemia. Cancer Genet Cytogenet 203:292–296
Kchinowloguer J (1915) Le chlorome, une tumeur maligne. Thesis, Geneva
Kim HW, Choi SJ, Lee JH, Lee JH, Kim TS, Kim YG, Kang JM, Huh J, Park KM et al (2006) Nonleukemic granulocytic sarcoma in the bile duct: a case report. J Korean Med Sci 21:745–748
King A (1853) A case of chloroma. Mon J Med 17:97
King DJ, Ewen SW, Sewell HF, Dawson AA (1987) Obstructive jaundice. An unusual presentation of granulocytic sarcoma. Cancer 60:114–117
Kobayashi M, Imamura M, Soga R, Tsuda Y, Maeda S, Iwasaki H, Sugiura M, Ohizumi H, Musashi M et al (1992) Establishment of a novel granulocytic sarcoma line which can adhere to dermal fibroblasts from a patient with granulocytic sarcoma in dermal tissues and myelofibrosis. Br J Haematol 82:26–31
Kojima M (1963) Tumor-forming leukemia (including chloroma) (in Japanese). Nippon Ketsueki Gakkai Zasshi 26:62–68
Kopecky KK (1988) Intrahepatic extramedullary hematopoiesis. AJR Am J Roentgenol 150:1198–1199
Kopecky KK, Moriarty AT, Antony AC, Baker MK (1986) Extramedullary hematopoiesis in acute lymphocytic leukemia masquerading as hepatic renal, and splenic microabscesses. AJR Am J Roentgenol 147:846–847
Kumar A, Aggarwal S, de Tilly LN (1995) Case of the season. Thalassemia major with extramedullary hematopoiesis in the liver. Semin Roentgenol 30:99–101
Kwon Y, Yu E, Huh J, Lee SK, Ro JY (2004) Sclerosing extramedullary hematopoietic tumor involving lesser omentum and ligamentum teres in liver explant. Ann Diagn Pathol 8:227–232
Lee L, Richards JF, Beer CT (1967) Experimental chloroleukemia in Sprague Dawley rats. I. Isolation of protoporphyrin from the chloroma. Arch Biochem Biophys 118:585–589
Lee JY, Lee WS, Jung MK, Jeon SW, Cho CM, Tak WY, Kweon YO, Kim SK et al (2007) Acute myeloid leukemia presenting as obstructive jaundice caused by granulocytic sarcoma. Gut Liver 1:182–185
Lee IJ, Kim SH, Kim DS, Lee JM, Han JK, Choi BI (2008) Intrahepatic extramedullary hematopoiesis mimicking a hypervascular hepatic neoplasm on dynamic – and SPIO-enhanced MRI. Korean J Radiol 9(suppl): S34–S38
Lemos LB, Baliga M, Benghuzzi HA, Cason Z (1997) Nodular hematopoiesis of the liver diagnosed by fine-needle aspiration cytology. Diagn Cytopathol 16:51–54
Lepelley P, Preudhomme C, Sartiaux C, Ghevaert C, Lai JL, Iaru T, Fenaux P, Cosson A (1993) Immunological detection of myeloperoxidase in poorly differentiated acute leukemia. Eur J Haematol 50:155–159
Libson E, Bloom RA, Galun E, Polliack A (1986) Granulocytic sarcoma (chloroma) of bone: the CT appearance. Comput Radiol 10:175–178
Lillicrap DP, Ginsburg AD, Corbett WE (1982) Relapse of acute myelogenous leukemia presenting with extrahepatic obstruction of the biliary tract. Can Med Assoc J 127:1000–1001
Liu PI, Ishimaru T, McGregor DH, Yamamoto T, Steer A (1973) Autopsy study of granulocytic sarcoma (chloroma) in patients with myelogenous leukemia, Hiroshima-Nagasaki 1949–1969. Cancer 31:948–955
Ma SK, Au WY (1999) Images in haematology. Hepatic haemopoiesis in beta-thalassaemia trait. Br J Haematol 107:1
Mano Y, Yokoyama K, Chen CK, Tsukada Y, Ikeda Y, Okamoto S (2004) Acute myeloid leukemia presenting with obstructive jaundice and granulocytic sarcoma of the common bile duct (in Japanese). Rinsho Ketsueki 45:1039–1043
Marchetti C, Patriarca P, Solero GP, Baralle FE, Romano M (2004) Genetic characterization of myeloperoxidase deficiency in Italy. Hum Mutat 23:496–505
Mason TE, Demaree RS, Margolis CI (1973) Granulocytic sarcoma (chloroma), two years preceding myelogenous leukemia. Cancer 31:423–432
Matsueda K, Yamamoto H, Doi I (1998) An autopsy case of granulocytic sarcoma of the porta hepatis causing obstructive jaundice. J Gastroenterol 33:428–433
McCarty KS, Wortmen J, Daly J, Rundles RW, Hanker JS (1980) Chloroma without evidence of leukemia: facilitated light microscopic diagnosis. Blood 56:104–108
Meis JM, Butler JJ, Osborne BM, Manning JT (1986) Granulocytic sarcoma in nonleukemic patients. Cancer 58:2697–2709
Menasce LP, Banerjee SS, Beckett E, Harris M (1999) Extra-medullary myeloid tumour (granulocytic sarcoma) is often misdiagnosed: a study of 26 cases. Histopathology 34:391–398
Mitsuoka T (1969) Metabolism of porphyrin and heme on experimental chloroma (in Japanese). Nippon Naika Gakkai Zasshi 58:293–302
Mourad W, Kfoury H, Al Husseini H (2001) The value of CD34, myeloperoxidase and chloroacetate esterase (Leder) stain in the diagnosis of granulocytic sarcoma. Ann Saudi Med 21:287–291
Müller HW (1926) Ein Fall von Chlorom bei Myeloblastenleukämie. Frankfurt Zschr Pathol 34:3
Muller S, Crocker J, Smith PJ (1987) A quantitative study of eosinophil polymorphonuclear leucocytes in granulocytic sarcoma (chloroma). J Clin Pathol 40:1264
Muss HB, Moloney WC (1973) Chloroma and other myeloblastic tumors. Blood 42:721–728

Nakamoto H, Inagaki Y, Maruyama T, Masuda T, Kamiya T, Suzuki O, Ookawa H, Kiryu Y (1987) A case of chronic myeloblastic leukemia associated with extrahepatic obstructive jaundice due to leukemic cell infiltration in blast crisis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 84:1844–1849

Nappi O, Boscaino A, Wick MR (2003) Extramedullary hematopoietic proliferations, extraosseous plasmacytomas, and ectopic splenic implants (splenosis). Semin Diagn Pathol 20:338–356

Nauseef WM, McCormick SJ, Goedken M (1998) Coordinated participation of calreticulin and calnexin in the biosynthesis of myeloperoxidase. J Biol Chem 273:7107–7111

Navarro M, Crespo C, Pérez L, Martinez C, Galant J, Gonzalez I (2000) Massive intrahepatic extramedullary hematopoiesis in myelofibrosis. Abdom Imaging 25:184–186

Neiman RS, Barcos M, Berard C, Bonner H, Mann R, Rydell RE, Bennett JM (1981) Granulocytic sarcoma: a clinicopathologic study of 61 biopsied cases. Cancer 48:1426–1437

Newton N, Morelll DB, Clarke L (1965) Myeloperoxidase and associated porphyrins in rat chloroma tissue. I. Biochim Biophys Acta 96:463–475

Nichol AW, Morell DB, Thomson J (1969) Porphyrins derived from the prosthetic group of myeloperoxidase. Biochem Biophys Res Commun 36:576–581

O'Malley DP (2007) Benign extramedullary myeloid proliferations. Mod Pathol 20:405–415

Petrides PE (1998) Molecular genetics of peroxidase deficiency. J Mol Med 76:688–698

Piccalunga PP, Ascani S, Agostinelli C, Paolini S, Laterza C, Papayannidis C, Martinelli G et al (2007) Myeloid sarcoma of liver: an unusual cause of jaundice. Report of three cases and review of literature. Histopathology 50:802–805

Pomeranz SJ, Hawkins HH, Towbin R, Lisberg WN, Clark RA (1985) Granulocytic sarcoma (chloroma): CT manifestations. Radiology 155:167–170

Porto L, Kieslich M, Schwabe D, Zanella FE, Lanfermann H (2004) Granulocytic sarcoma in children. Neuroradiology 46:374–377

Priola AM, Gned D, Boccuzzi F, Priola SM (2012) Unusual focal intrahepatic extramedullary haematopoiesis in alpha-thalassemia. Liver Int 32:771

Quintanilla-Martinez L, Zukerberg LR, Ferry JA, Harris NL (1995) Extramedullary tumors of lymphoid or myeloid blasts. The role of immunohistology in diagnosis and classification. Am J Clin Pathol 104:431–443

Rajeswari B, Ninan A, Prasannakumara SN, Parukuttyamma K (2012) Acute myeloid leukemia presenting as obstructive jaundice. Indian Pediatr 49:414–416

Rappaport H (1966) Tumors of the hematopoietic system. Atlas of tumor pathology. Armed Forces Institute of pathology, Washington, DC, pp 241–243, section III, fascicle 8

Ravandi-Kashani F, Estey E, Cortes J, Medeirost LJ, Giles FJ (1999) Granulocytic sarcoma of the pancreas: a report of two cases and literature review. Clin Lab Haematol 21:219–224

Reardon G, Moloney WC (1961) Chloroma and related myeloblastic neoplasms. Arch Intern Med 108:864–871

Reinhard D, Creutzig U (2002) Isolated myelosarcoma in children – update and review. Leuk Lymphoma 43:565–574

Remstein ED, Kurtin PJ, Nascimento AG (2000) Sclerosing extramedullary hematopoietic tumor in chronic myeloproliferative disorders. Am J Surg Pathol 24:51–55

Ritgers A, Heeringa P, Giesen JE, Theunissen RT, Jacobs H, Tervaert JW (2003) Neutrophil myeloperoxidase activity and the influence of two single-nucleotide promoter polymorphisms. Br J Haematol 123:536–538

Romano M, Dri P, Dadalt L, Patriarca P, Baralle FE (1997) Biochemical and molecular characterization of hereditary myeloperoxidase deficiency. Blood 90:4126–4134

Ross RR (1955) Chloroma and chloroleukemia. Am J Med 18:671

Roth MJ, Medeiros LJ, Elenitoba-Johnson K, Kuchnio M, Jaffe ES, Stetler-Stevenson M (1995) Extramedullary myeloid cell tumors. An immunohistochemical study of 29 cases using routinely fixed and processed paraffin-embedded tissue sections. Arch Pathol Lab Med 119:790–798

Rotter AJ, O'Donnell MR, Radin DR, Marx HF (1992) Peribiliary chloroma: a rare cause of jaundice after bone marrow transplantation. AJR Am J Roentgenol 158:1255–1256

Sakamaki K, Kanda N, Ueda T, Aikawa E, Nagata S (2000) The eosinophil peroxidase gene forms a cluster with the genes for myeloperoxidase and lactoperoxidase on human chromosome 17. Cytogenet Cell Genet 88:246–248

Sakamaki K, Ueda T, Nagata S (2002) The evolutionary conservation of the mammalian peroxidase genes. Cytogenet Genome Res 98:93–95

Scholz W, Platzer B, Schumich A, Hocher B, Fritsch G, Knapp W, Strobl H (2004) Initial human myeloid/dendritic cell progenitors identified by absence of myeloperoxidase protein expression. Exp Hematol 32:270–276

Schultz J, Schwartz S (1956) The chemistry of experimental chloroma. II. Isolation of crystalline protoporphyrin, its origin and relation to other porphyrins. Cancer Res 16:565–568

Sedinc A, Buyukberber S, Camci C, Koruk M, Savas MC, Turk HM, Sari I, Buyukberber NM (2004) Granulocytic sarcoma of the colon and leukemic infiltration of the liver in a patient presenting with hematochezia and jaundice. Digestion 69:262–265

Servin-Abad L, Caldera H, Cardenas R, Casillas J (2003) Granulocytic sarcoma of the pancreas. A report of one case and review of the literature. Acta Haematol 110:188–192

Strauchen JA, Gordon RE (2002) Crystalline inclusions in granulocytic sarcoma. Arch Pathol Lab Med 126:85–86

Suh YK, Shin HJ (2000) Fine-needle aspiration biopsy of granulocytic sarcoma: a clinicopathologic study of 27 cases. Cancer 90:364–372

Sukov WR, Remstein ED, Nascimento AG, Sethi S, Lewin M (2009) Sclerosing extramedullary hematopoietic tumor: emphasis on diagnosis by renal biopsy. Ann Diagn Pathol 13:127–131

Sung CO, Ko YH, Park CK, Jang KT, Heo JS (2006) Isolated biliary granulocytic sarcoma followed by acute myelogenous leukemia with multilineage dysplasia: a case report and literature review. J Korean Med Sci 21:550–554

Szomor A, Passweg JR, Tichelli A, Hoffmann T, Speck B, Gratwohl A (1997) Myeloid leukemia and myelodysplastic syndrome relapsing as granulocytic sarcoma (chloroma) after allogeneic bone marrow transplantation. Ann Hematol 75:239–241

Tamiolakis D, Venizelos J, Prassopoulos P, Simopoulos S, Bolioti S, Tsiapali M, Papadopoulos N (2004) Intrahepatic extramedullary hematopoietic tumor mimicking metastatic carcinoma from a colonic primary. Onkologie 27:65–67

Tamm EP, Rabushka LS, Fishman EK, Hruban RH, Diehl AM, Klein A (1995) Intrahepatic, extramedullary hematopoiesis mimicking hemangioma on technetium-99m red blood cell SPECT examination. Clin Imaging 19:88–91

Tran HT, Nguyen N, Nguyen V (1962) Observations on chloroma or green cancer of Aran (in Russian). Vestn Otorinolaringol 24:96–97

Traweek ST, Arber DA, Rappaport H, Brynes RK (1993) Extramedullary myeloid cell tumors. An immunohistochemical and morphologic study of 28 cases. Am J Surg Pathol 17:1011–1019

Turk W (1903) Acute myeloide Leukämie mit Grünfärbung des Knochenmarks. Mitt Gesellsch Med Kinderheilk 2:39

Van Tuinen P, Johnson KR, Ledbetter SA, Nussbaum RL, Rovera G, Ledbetter DH (1987) Localization of myeloperoxidase to the long arm of human chromosome 17: relationship to the 15; 17 translocation of acute promyelocytic leukemia. Oncogene 1:319–322

Verani R, Olson J, Moak JL (1980) Intrathoracic extramedullary hematopoiesis: report of a case in a patient with sickle-cell disease-beta-thalassemia. Am J Clin Pathol 73:133–137

Ward HP, Block MH (1971) The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with the myeloproliferative syndrome. Medicine 50:357–420

Wiener MD, Halvorsen RA, Vollmer RT, Foster WL, Roberts L (1987) Focal intrahepatic extramedullary hematopoiesis mimicking neoplasm. AJR Am J Roentgenol 149:1171–1172

Wiernik and Serpick 1970. http://www.ncbi.nlm.nih.gov/pubmed/4908654

Wong Y, Chen F, Tai KS, Yip LK, Tsang KW, Chan FL, Ooi GC (1999) Imaging features of focal intrahepatic extramedullary haematopoiesis. Br J Radiol 72: 906–910

Xu L, Li C, Wu Q, Wang B (1990) Purification and identification of human leukocyte myeloperoxidase (in Chinese). Hua Xi Yi Ke Da Xue Xue Bao 21:256–258

Yamato M, Fuhrman CR (1987) Computed tomography of fatty replacement in extramedullary hematopoiesis. J Comput Assist Tomogr 11:541–542

Yang X, Bhuiya T, Esposito M (2002) Sclerosing extramedullary hematopoietic tumor. Ann Diagn Pathol 6:183–187

Zhang PJ, Barcos M, Stewart CC, Block AW, Sait S, Brooks JJ (2000) Immunoreactivity of MIC2 (CD99) in acute myelogenous leukemia and related diseases. Mod Pathol 13:452–458

Blastic Plasmacytoid Dendritic Cell Neoplasm

87

ICD-O 9727/3

Contents

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive tumor derived from precursors of plasmacytoid dendritic cells. Novel findings showed that BPDCN originate from myeloid-derived dendritic cells or are related to subtypes of acute myeloid leukemia. The neoplastic cells display a complex immunophenotype, with expression of natural killer cell markers, CD68, CD123, CD303, TCL1, cutaneous lymphocyte-associated antigen, and granzyme B. This is a rare malignancy that mainly occurs in elderly males and has a tendency to involve multiple sites, but almost all patients show skin involvement. The tumor can spread to internal organs and shows early liver metastasis. Hepatic involvement often causes significant hepatomegaly. Histologically, the medium-sized lymphoid-looking neoplastic cells form infiltrates that chiefly occupy portal tracts. The cells typically exhibit cytoplasmic microvacuoles that localized along the cell membrane.

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a clinically aggressive tumor which is derived from precursors of plasmacytoid dendritic cells, with a high frequency of cutaneous

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_87

and bone marrow involvement and leukemic dissemination. Synonyms of BPDCN include blastic NK-cell lymphoma, agranular CD4+ natural killer cell leukemia, blastic natural killer leukemia/lymphoma, and agranular CD4+CD56+ hematodermic neoplasm/tumor. Novel findings suggest that cells of BPDCN originate from myeloid-derived dendritic cells or are related to subtypes of acute myeloid leukemia (Menezes et al. 2014). BPDCN is a rare neoplasm that more often occurs in males, mostly in elderly patients, with a mean age at diagnosis of 61–67 years, but the tumor can also develop in children. The malignancy tends to involve multiple sites, but almost all patients show skin involvement, followed by bone marrow, lymph nodes, and overt leukemia (Petrella and Facchetti 2010; Pagano et al. 2013; Riaz et al. 2014; Shi and Wang 2014).

The patients commonly have asymptomatic solitary or multiple skin plaques or nodules, measuring from a few millimeters to up to 10 cm, often associated with locoregional lymphadenopathy. Low-level bone marrow and peripheral blood involvement are observed in up to 90 % of cases, and may dominate the clinical picture, sometimes in the absence of skin manifestations. Cytopenia is a common finding, sometimes associated with megaloblastic erythroid maturation and tumor-induced monocytosis. Systemic B symptoms are rare at presentation. After an initial phase of minor involvement, the bone marrow and peripheral blood are invariably affected in the course of the disease. In advanced disease, inner organs and the central nervous system are infiltrated. In most cases, a fulminant leukemic phase develops in the final segment of disease.

Morphology and Immunocytochemistry

The neoplasm is composed of a diffuse, monomorphous infiltrate of medium-sized blast cells, usually with a rather scant neoplasm that is agranular and gray blue on the Giemsa stain. The neoplastic cells display a lineage-negative CD4+/CD56+/CD43+/HLA-DR+ immunophenotype, initially suggesting an NK-cell derivation. Reactivity for the plasmacytoid dendritic cell-associated antigens CD123 (IL 3-alpha-chain receptor), BDCA-2/CD303, TCL1, CLA (cutaneous lymphocyte-associated antigen), and the interferon-dependent MxA (myxovirus A) protein is observed (Pilichowska et al. 2007; Hama et al. 2009; Cota et al. 2010). CD68 is expressed in about 50 % of cases, with a discrete dot-like reaction product, and at least part of the cells express granzyme B. Part of BPDCN cells are reactive for CD31/PECAM-1 (platelet endothelial cell adhesion molecule 1; Salva et al. 2014). In a systematic study, simultaneous expression of five markers, CD4, CD56, CD123, CD303, and TCL1, was found in only 46 % of patients (Julia et al. 2014). A novel marker for BPDCN cells is the protein, SPIB (Montes-Moreno et al. 2013).

What Are Plasmacytoid Dendritic Cells?

Immature dendritic cells (DCs) include plasmacytoid DCs, or so-called lymphoid DCs, and myeloid DCs and represent early-committed progenitor cells capable of differentiating into antigen-presenting DCs central to the initiation of primary T-cell-based immune responses.

Plasmacytoid DCs (pDCs; previously called, plasmacytoid T cells and plasmacytoid monocytes) are an immune cell type that forms the bridge between innate and adaptive immunity (Dzionek et al. 2002; Cao and Liu 2007; Cao 2009; Jegalian et al. 2009). These unique cells were observed initially in 1958 and called plasmacytoid T cells (Lennert and Remmele 1958). In 1997 it was shown that pDCs are able to differentiate into DCs and were given the additional name pre-DC2 cells (Grouard et al. 1997). DC2 differentiate from CD34+ progenitors and then plasmacytoid precursors which circulate in the blood as veiled cells and enter lymph nodes and mucosal tissues in response to immune activation (Brière et al. 2002). Less than 0.1 % of peripheral blood mononuclear cells are pDCs. They express BDCA-2, CD123 (but not the

markers of myeloid DCs, CD13, and CD33), and the adaptor protein CD2AP (Marafioti et al. 2008). In a recent study, CD56(+) dendritic-like cells were suggested to be the normal counterpart of cells characterizing blastic plasmacytoid dendritic cell tumors (Osaki et al. 2013). Analysis of a congenital BPDCN suggested that CLTC-ALK fusion is a primary event in a multipotent hematopoietic progenitor cells giving rise to plasmacytoid dendritic cells (Tokuda et al. 2014).

Liver Involvement

BPDCN can spread to internal organs and show early liver metastasis. Liver involvement may clinically present as hepatomegaly (Cui et al. 2014). In one patient, a liver scan revealed a 10 cm heterogeneous hypoechoic mass in the left liver lobe, and ultrasound-guided needle biopsy showed a well-demarcated, discrete infiltrate, mainly in portal tracts, of atypical lymphoid cells with an immunophenotype typical for BPDCN (Choi et al. 2010).

The infiltrate consists of medium-sized lymphoid-appearing cells that display a slightly irregular-shaped nucleus with smooth chromatin. The cytoplasm is mostly scant and never shows granulation. A minority of the cells are either small or large. Typically, the neoplastic cells show microvacuoles in the cytoplasm that localize along the cell membrane, resembling a string of pearls, and cytoplasmic pseudopodia.

Differential Diagnosis

Unusual forms of myeloid leukemia may mimic plasmacytoid dendritic cell leukemia (Sano et al. 2008). In fact, acute myeloid leukemia carrying cytoplasmic mutated nucleophosmin [NPMc (+) AML] shows considerable clinical and morphological overlap with CD4+/CD56+ neoplasms. However, cytoplasmic nucleophosmin is not detectable in blastic plasmacytoid dendritic cell neoplasias (Facchetti et al. 2009).

Pathogenesis, Cytogenetic Abnormalities, and Molecular Genetic Features

BPDCN is derived from precursor plasmacytoid dendritic cells (review: Riaz et al. 2014). Molecular profiling indicates that the neoplastic ells of BPDCN originate from the myeloid lineage and, in particular, from testing dendritic cells (Sapienza et al. 2014). About two thirds of patients with BPDCN have an abnormal karyotype, but specific chromosome aberrations are lacking so far. Several recurrent chromosomal abnormalities have been encountered, including 5q21 or 5q34 (the most common), 12p13 and 13q13–21 (both in two thirds of patients), 6q23–qter, 15q, and loss of chromosome 9. Recurrent deletions occurred in chromosomes 4 (4q34), 9 (9p13–p11), and 13 (13q12–q31). TET2 and TP53 mutations have frequently been observed in BPDCN (Jardin et al. 2011). BPDCN cells display aberrant activation of the NF-kappaB signaling pathway (Sapienza et al. 2014). TET2 (ten eleven translocation 2) mutations (Alayed et al. 2013) and EWSR1 gene rearrangement (Cao et al. 2014) have been detected in BPDCN. Recently, deleterious mutations in IKZF3, HOXB9, UBE2G2, and ZEB2 have been identified in BPDCN (Menezes et al. 2014).

References

Alayed K, Patel KP, Konoplev S, Singh RR, Routbort MJ, Reddy N, Pemmaraju N et al (2013) TET2 mutations, myelodysplastic features, and a distinct immunoprofile characterize blastic plasmacytoid dendritic cell neoplasm in the bone marrow. Am J Hematol 88:1055–1061

Brière F, Bendriss-Vermare N, Delale T, Burg S, Corbet C, Rissoan MC, Chaperot L et al (2002) Origin and filiation of human plasmacytoid dendritic cells. Hum Immunol 63:1081–1093

Cao W (2009) Molecular characterization of human plasmacytoid dendritic cells. J Clin Immunol 29:257–264

Cao W, Liu YJ (2007) Innate immunity functions of plasmacytoid dendritic cells. Curr Opin Immunol 19:24–30

Cao Q, Liu F, Niu G, Xue L, Han A (2014) Blastic plasmacytoid dendritic cell neoplasm with EWSR1 gene rearrangement. J Clin Pathol 67:90–92

Choi KW, Lee KY, Lee YK, Ku BS, Kim HS, Kim YH, Kim KH (2010) CD4-/CD56+/CD123+ hematodermic neoplasm showing early liver metastasis. Ann Dermatol 22:186–190

Cota C, Vale E, Viana I, Requena L, Ferrara G, Anemona L, Metze D, Fink-Puches R et al (2010) Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm – morphologic and phenotypic variability in a series of 33 patients. Am J Surg Pathol 34:75–87

Cui XB, Jin J, Pang XL, Li S, Liu CX, Li TT, Peng H, Zhang SM, Li L, Liang WH et al (2014) A case of blastic plasmacytoid dendritic cell neoplasm with ecchymotic lesions on the whole body. Int J Clin Exp Pathol 7:4391–4399

Dzionek A, Inagaki Y, Okawa K, Nagafune J, Röck J, Sohma Y, Winkels G, Zysk M, Yamaguchi Y et al (2002) Plasmacytoid dendritic cells: from specific surface markers to specific cellular functions. Hum Immunol 63:1133–1148

Facchetti F, Pileri SA, Agostinelli C, Martelli MP, Paulli M, Venditti A, Martelli MF, Falini B (2009) Cytoplasmic nucleophosmin is not detected in blastic plasmacytoid dendritic cell neoplasm. Haematologica 94:285–288

Grouard G, Rissoan MC, Filgueira L, Durand I, Banchereau J, Liu YJ (1997) The enigmatic plasmacytoid T cells develop into dendritic cells with interleukin (IL)-3 and CD40-ligand. J Exp Med 185:1101–1111

Hama A, Kudo K, Itzel BV, Muramatsu H, Nishio N, Yoshida N, Takahashi Y, Yagasaki H et al (2009) Plasmacytoid dendritic cell leukemia in children. J Pediatr Hematol Oncol 31:339–343

Jardin F, Ruminy P, Parmentier F, Troussard X, Vaida I, Stamatoullas A, Leprêtre S et al (2011) TET2 and TP53 mutations are frequently observed in blastic plasmacytoid dendritic cell neoplasm. Br J Haematol 153:413–416

Jegalian AG, Facchetti F, Jaffe ES (2009) Plasmacytoid dendritic cells: physiologic roles and pathologic states. Adv Anat Pathol 16:392–404

Julia F, Dalle S, Duru G, Balme B, Vergier B, Ortonne N, Vignon-Pennamen MD, Costes-Martineau V et al (2014) Blastic plasmacytoid dendritic neoplasms: clinico-immunohistochemical correlations in a series of 91 patients. Am J Surg Pathol 38:673–680

Lennert K, Remmele W (1958) Karyometric research on lymph node cells in man. I. Germinoblasts, lymphoblasts & lymphocytes (in German). Acta Haematol 19:99–113

Marafioti T, Paterson JC, Ballabio E, Reichard KK, Tedoldi S, Hollowood K, Dictor M, Hansmann ML et al (2008) Novel markers of normal and neoplastic human plasmacytoid dendritic cells. Blood 111:3778–3792

Menezes J, Acquadro F, Wiseman M, Gomez-Lopez G, Salgado RN, Talavera-Casañas JG et al (2014) Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendritic cell neoplasm. Leukemia 28:823–829

Montes-Moreno S, Ramos-Medina R, Martinez-Lopez A, Barrionuevo Cornejo C, Parra Cubillos A et al (2013) SPIB, a novel immunohistochemical marker for human blastic plasmacytoid dendritic cell neoplasms: characterization of its expression in major hematolymphoid neoplasms. Blood 121:643–647

Osaki Y, Yokohama A, Saito A, Tahara K, Yanagisawa K, Ogawa Y, Ishizaki T, Mitsui T et al (2013) Characterization of CD56+ dendritic-like cells: a normal counterpart of blastic plasmacytoid dendritic cell neoplasm? PLoS One 8:e81722

Pagano L, Valentini CG, Pulsoni A, Fisogno S, Carluccio P, Mannelli F, Lunghi M et al (2013) Blastic plasmacytoid dendritic neoplasm with leukemic presentation: an Italian multicenter study. Haematologica 98:239–246

Petrella T, Facchetti F (2010) Tumoral aspects of plasmacytoid dendritic cells: what do we know in 2009? Autoimmunity 43:210–214

Pilichowska ME, Fleming MD, Pinkus JL, Pinkus GS (2007) CD4+/CD56+ hematodermic neoplasm ("blastic natural killer cell lymphoma"): neoplastic cells express the immature dendritic cell marker BDCA-2 and produce interferon. Am J Clin Pathol 128:445–453

Riaz W, Zhang L, Horna P, Sokol L (2014) Blastic plasmacytoid dendritic cell neoplasm: update on molecular biology, diagnosis, and therapy. Cancer Control 21:279–289

Salva KA, Haemel AK, Pincus LB, Liu J, Sundram U, Guitart J, Longley BJ, Wood GS (2014) Expression of CD31/PECAM-1 (platelet endothelial cell adhesion molecule 1) by blastic plasmacytoid dendritic cell neoplasms. JAMA Dermatol 150:73–76

Sano F, Tasaka T, Nishimura H, Akiyama T, Kuba Y, Matsuhashi Y, Wada H, Sugihara T et al (2008) A peculiar case of acute myeloid leukemia mimicking plasmacytoid dendritic precursor cell leukemia. J Clin Exp Hematop 48:65–69

Sapienza MR, Fuligni F, Agostinelli C, Tripodo C, Righi S, Laginestra MA, Pileri A et al (2014) Molecular profiling of blastic plasmacytoid dendritic cell neoplasm reveals a unique pattern and suggests selective sensitivity to NK-kB pathway inhibition. Leukemia 28:1606–1616

Shi Y, Wang E (2014) Blastic plasmacytoid dendritic cell neoplasm: a clinicopathologic review. Arch Pathol Lab Med 138:564–569

Tokuda K, Eguchi-Ishimae M, Yagi C, Kawabe M, Moritani K, Niiya T, Tauchi H, Ishii E et al (2014) CLTC-ALK fusion as a primary event in congenital blastic plasmacytoid dendritic cell neoplasm. Genes Chromosomes Cancer 53:78–89

Part XVII

Hepatobiliary Hodgkin's Disease

Hodgkin Lymphoma of the Hepatobiliary Tract

88

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_88

Abstract

In most cases of classical Hodgkin lymphoma (HL), the neoplastic cells are derived from mature B lymphocytes at the germinal center stage of differentiation. The WHO classification separates nodular lymphocyte-predominant HL from classical HL, the latter subdivided into nodular sclerosis classical HL, lymphocyte-rich classical HL, mixed cellularity classical HL, and lymphocyte-depleted classical HL. All these forms of HL can occur in the hepatobiliary tract, either as rare primary lesions or as secondary manifestations of HL primarily located elsewhere. HL in the liver presents as one of several phenotypes, including miliary lesions, solitary or multiple nodular lesions, large masses, and rare diffuse patterns of involvement. In addition, HL can involve bile ducts and liver-associated lymph nodes with subsequent biliary obstruction mimicking primary bile duct cancer. The histologic presentation of hepatobiliary HD is the same as that in other organs. HL can be associated with several nonneoplastic hepatic alterations. These include a distinct type of vanishing small bile duct disease, granulomatous hepatitis, sclerosing cholangitis, and sinusoidal ectasias mimicking hepatic peliosis.

Introduction

Hodgkin lymphomas (HL) form a group of malignant lymphoproliferative disorders based on a neoplastic expansion mostly of a distinct type of B cells. In more than 98 % of classical HL, the neoplastic cells are derived from mature B cells at the germinal center stage of differentiation. HL presents in the form of several well-defined phenotypes that have an impact on the biology of disease. The principal clinical histologic features, their impact on the natural history of HL, and etiologic issues of HL have been elucidated and reviewed in detail. An outline referring to the history of the HL concept is added at the end of the chapter.

Table 1 2008 WHO histological classification of Hodgkin lymphoma

		ICD-O code
Nodular lymphocyte-predominant Hodgkin lymphoma	(NLPHL)	9659/3
Classical Hodgkin lymphoma	(CHL)	9650/3
Nodular sclerosis classical Hodgkin lymphoma	(NSHL)	9663/3
Lymphocyte-rich classical Hodgkin lymphoma	(LRCHL)	9651/3
Mixed cellularity classical Hodgkin lymphoma	(MCHL)	9652/3
Lymphocyte-depleted classical Hodgkin lymphoma	(LDHL)	9653/3

Selected References (Ziegler 1911; Favre and Croizat 1933; Jackson and Parker 1947; Harrison 1952; Lukes and Butler 1966; Lukes et al. 1966; Cross 1969; Lukes 1971; Jaffe et al. 2001; Thomas et al. 2004; Küppers and Hansmann 2005; Re et al. 2005; Schmitz et al. 2009; Smith 2010; Hjalgrim 2012; Küppers et al. 2012; Carbone et al. 2013; Gobbi et al. 2013; Ansell 2014).

The *WHO histological classification of HL* is shown in Table 1.

Epidemiology

HL accounts for 25–40 % of all lymphomas developing in Caucasians (much rarer in Orientals and persons from underdeveloped countries), with one peak of occurrence in the second to third decades and another in the sixth decade (Nakatsuka and Aozasa 2006). Involvement of the pediatric age group has been recognized early (von Hüttenbrenner 1871; Hübener 1893) and is an important manifestation of HF. The prevalences of the diverse subtypes of HL differ considerably. NLPHL accounts for approximately 5 % of all HL, patients being predominantly male and in the 30–50 years age group. Classical HL accounts for 95 % of all cases and hence is the

main form of HL. Classical HL shows a bimodal age distribution in Western countries, with a first peak at 15–35 years of age and a second peak in late life. NSCHL, the dominant subtype of classical HL, accounts for about 70 % of classical HL in Europe and North America and is more often encountered in resource-rich areas than in resource-poor areas. The incidence of NSCHL is similar in males and females and has its peak at 15–34 years of age. LRCHL is rare and comprises about 5 % of all classical HL. The majority of patients are male, with a higher age than in other forms of classical HL. MCCHL accounts for 20–25 % of classical HL and is more frequent in HIV-infected individuals and in developing countries. Seventy percent of the patients are male, with a mean age at diagnosis of 38 years. LDCHL forms the rarest subtype of classical HL, accounting for less than 1 % of cases in Western countries. Up to 75 % are male, with a median age at diagnosis of 30–37 years. LDCHL is often associated with HIV and is more often found in developing countries.

Epstein-Barr virus (EBV) infection has been associated with an increased risk of HL chiefly in young adults, based on the growing amount of evidence (Hjalgrim et al. 2003). The presence of EBV had a beneficial effect on the length of failure-free survival of patients with classical HL (Krugmann et al. 2003). Classical HL is a rare complication after solid organ transplantation (Hood et al. 1996). Lymphomas resembling HK developing after posttransplant lymphoproliferative disorder ("Hodgkin-like PTLD") have been reported (Stern et al. 2005). The relationship between bona fide posttransplant HL and the intriguing HL-like posttransplant disorders is not yet clarified.

Liver Involvement in Hodgkin Lymphoma

Introduction

Thomas Hodgkin described liver involvement incidentally (Hodgkin 1832); but in a critical analysis of Hodgkin's original cases, the diagnosis of HL involving the liver was accepted in only two cases (Fox 1936). Wilks noted hepatic involvement in 7 of his 13 cases (Wilks 1865). Manifestations of HL, albeit in a highly variable spectrum of patterns, were later reported and discussed many times.

Selected References (Murchison 1869; Barié 1875; Brauneck 1889; Reed 1902; Longcope 1903; Fabian 1911; Ziegler 1911; Rolleston 1912; Barron 1926; Coronini 1928; Gruber 1930; Chevallier and Bernard 1932; Foulon 1932; Hartfall 1932; Wallhauser 1933; Sternberg 1936; Baker and Mann 1939; Goldman 1940; Symmers 1944; Jackson and Parker 1944a, b; Newman and Pushkin 1951; Beatty 1954; Klein 1955; Levitan et al. 1961; Skovsgaard et al. 1982).

Liver involvement is uncommon in HL in early disease, but the incidence increases in the advanced phases of disease, becoming as high as 70 % in certain series (detailed review of the old literature, Wallhauser 1933; Givler et al. 1971; Bagley et al. 1973). In a study of 74 cases, the duration from diagnosis of HL to clinical evidence of liver abnormalities was 1–6 months in 23 %, 7–12 months in 10.8 %, 13–18 months in 10.8 %, and 19–24 months in 12.2 % and was then slowly decreasing as a function of time (Levitan et al. 1961). These data markedly depend on the clinical features, the patterns of liver involvement, and the choice of techniques for assessing liver involvement (radiology, peritoneoscopy, hepatic needle biopsy, autopsy). Direct hepatic involvement in visceral Hl is a frequent event (Cowan and Trounce 1973; Diebold and Temmim 1980; Urbano-Marquez et al. 1981; Kiewe et al. 2004) and may be the presenting manifestation of HL (Trewby et al. 1979). It seems that there is a correlation between splenic involvement and HL manifestations in the liver: The risk of hepatic involvement correlates closely with splenic involvement (Colby et al. 1981), and generally the liver is not involved when the spleen is not tumoral. In a study of 250 exploratory laparotomies for HL, hepatic tumoral localizations were disclosed by liver biopsies in 16 % of the patients with splenic involvement (Diebold and Temmim

1980). There are, however, exceptions to this "rule" where the liver has shown manifestations of HL in the absence of splenic involvement (Glatstein et al. 1969; Aisenberg 1971; Farrer-Brown et al. 1971; Piro et al. 1972; Michel et al. 1973; Spinelli et al. 1975; Fialk et al. 1979; Sulkes et al. 1979; Gordon et al. 1984). Among 472 liver biopsies performed within a large investigation, 11 biopsies from 10 patients (2.4 %) had infiltrates consisting of Reed-Sternberg cells and abnormal histiocytoid cells against the characteristic background of lymphocytes together with neutrophil and eosinophil granulocytes (Skovsgaard et al. 1982). In an autopsy study of 57 cases of malignant lymphoma, hepatic involvement was demonstrated in 67 % of HL versus 56 % in NHL (Okazaki et al. 1985). In another investigation of 112 consecutive patients with malignant lymphoma, hepatic lymphomatous involvement was found more frequently in NHL (16 %) than in HL (8 %) (Sans et al. 1998).

Involvement of the liver by HL often results in hepatomegaly. Hepatomegaly was observed clinically from 2.3 % to 80 % in a series reported before the modern treatment strategies of HL (Murray 1908; Burnam 1926; Uddströmer 1934; Baker und Mann 1939; Goldman 1940; Levitan et al. 1961; Biemer 1984). In a large study of 875 patients with HL, 32.5 % had hepatomegaly, and out of the 122/875 patients autopsied, hepatomegaly amounted to 79.6 % (Levitan et al. 1961). There are differences of opinion regarding the onset of hepatomegaly, some describing it as a sign of the terminal stages of disease (Ackerman and del Regato 1954), whereas others described hepatomegaly as a presenting feature, using the terms "*. . .forme hépatique et forme hépatosplénomégalique de la maladie de Hodgkin*" ("hepatic form and hepatosplenomegalic forms"; Pène 1952; Pène et al. 1955). Considering all types of HL, hepatomegaly seems to be infrequent in early HL and, when present, may represent a nonspecific reactive phenomenon (Biemer 1984). It is more frequently observed in LDCHL (Neiman et al. 1973). Some authors, basing their judgment on autopsy material primarily, claimed that hepatic involvement with organomegaly is a late manifestation of HL (Pène et al. 1955). In later phases of the disease, hepatomegaly can reflect direct, primary or secondary, organ involvement (Chim et al. 2000). Among 308 patients with HL analyzed in a more recent study, hepatomegaly was registered in 34, was more frequently encountered in stages III and IV versus I/II, and was more frequent in MCCHL and LDCHL than in LPCHL and NSCHL (Brinckmeyer et al. 1982).

Hepatic HL can be associated with jaundice and cholestasis. For example, in a study of 421 patients with HL presenting as a cholestatic febrile illness, 7.4 % of liver involvement was found (Cervantes et al. 1996). A icteric/cholestatic complication of HL has already been described in the end-nineteenth century and then in the 20th century (Brauneck 1889; Peiser 1913; Beatty 1954; Mac-Clure et al. 1959; Levitan et al. 1961; Bouroncle et al. 1962; Casirola and Dionigi 1966; Bombara et al. 1970; Barge and Potet 1971; Matsko and Zhukovets 1971; Perera et al. 1974; Piken et al. 1979; Liebermann 1986; Birrer and Young 1987; Marinone et al. 1989; Jansen and van der Lelie 1994; Warner and Whitcomb 1994; Cervantes et al. 1996; Yalcin et al. 1999; Gupta et al. 2002; Opeskin et al. 2003; Omidvari et al. 2004). Peiser described a patient with jaundice and histologic demonstration of HL infiltration mainly of the portal tracts and suggested to compress the small bile ducts as a mechanism of cholestasis (Peiser 1913). Cholestatic hepatitis may be mimicked in situations of massive hepatic infiltration by HL tissue resulting in hepatic failure (Lefkowitch et al. 1985). Cholestasis in patients with HL is sometimes caused by tumorous obstruction of extrahepatic bile ducts, in part also by enlarged perihilar or retroperitoneal lymph nodes (Michalitschke 1919; Diessner und Heck 1958; Razemon et al. 1961; Juniper 1963; Justin-Besançon et al. 1963; Sanbe and Shirato 1966; McNulty 1971; Pariente et al. 1981; Martin et al. 1992; Abe et al. 1997). Other causes of jaundice and/or cholestasis in HL comprise hemolysis, viral hepatitis, and drug toxicity. In the absence of any direct liver involvement by HL, a paraneoplastic cause of cholestasis has also been

postulated (Jansen and van der Leite 1994). The unique cholestatic syndrome caused by intrahepatic ductopenia in HL is discussed in a separate paragraph. HL can present as, or cause, acute hepatic failure (Gunasekaran et al. 1992; Weiner et al. 1994; Tornero et al. 1998; Rowbotham et al. 1998; Vadillo Serrano et al. 2002; Olnes et al. 2003; Vardarelli et al. 2004; Woolf et al. 2008; Hong et al. 2010). In part of these cases, hepatic insufficiency is caused by massive infiltration of the organ by HL (Tornero et al. 1998; Rowbotham et al. 1998; Karmacharya et al. 2014). Fulminant hepatic failure in HL has been described to be a paraneoplastic manifestation of HL (Dourakis et al. 1999), albeit of unknown mechanism.

What Are the Criteria for Involvement of the Liver in HL?

The involvement of the liver in HL is a key element for the success of abdominal pathologic HL staging for harvesting adequate liver samples, including laparoscopy, laparotomy, and/or hepatic needle biopsy, to date more and more assisted by modern imaging techniques. However, liver biopsy is still a standard in the assessment of hepatic involvement by HL, provided a reliable diagnosis can be done in a biopsy sample of the liver. But, as seen in the data given below, the highly variable figures of prevalence suggest, among true variances of involvement, differing types of criteria used to detect bona fide HL in contrast to nonspecific accompanying lesions (see below). Therefore, the question of suitable criteria has been addressed in the literature. In a now classical work by Lukes (1971), biopsies of the liver obtained at laparotomy have revealed three types of lesions: HL of nodular sclerosis, mixed, diffuse fibrosis, and reticular types (in accordance to the then employed nomenclature); the granulomas of uncertain origin (described in more detail in a later paragraph); and portal lymphocytic infiltration associated with proliferation of ductules, also of uncertain origin. Expectedly, difficulties in diagnosing HL mainly arise in small, microscopically detectable lesions. As emphasized by Lukes, the criteria for involvement in case of small hepatic lesions are the same or similar to those for small foci elsewhere. This author proposed that the evidence of a discrete lesion with features of one of the histologic types is essential as well as conclusive evidence of a Reed-Sternberg cell variant, although a diagnostic Reed-Sternberg cell is not required: a large, abnormal mononuclear cell with a huge nucleolus is an acceptable form. Lukes has it that particular caution must be used in interpreting small portal lymphocytic lesions in which there are a few abnormal mononuclear cells (Lukes 1971). It is advisable to perform numerous sections in order to search for the target cells (Dich et al. 1989). In case the large atypical cells are not evidence even after multiple sections, but the infiltrate and the configuration of the lesion nevertheless suggest HL, we propose to denote such lesions, suspicious of HL, not otherwise specified (NOS).

Selected References (Kadin et al. 1970; Givler et al. 1971; Bagley et al. 1972; Kaplan et al. 1973; Abt et al. 1974; Grieco and Cady 1980; Brown et al. 1981; Martin et al. 1982; Jaffe 1987; Pittman et al. 1988; Munker et al. 1995; Gupta et al. 1999; Martinet et al. 2000; Lieberz et al. 2000; Rueffer et al. 2003; van Spronsen and Veldhuis 2003); review Carde 2003.

Primary Hodgkin Lymphoma of the Liver

HL can develop as a primary extranodal disease (Padhi et al. 2012), of which the liver manifestation is an uncommon variant. HL limited to the liver has been rarely reported (Goia 1935; Symmers 1944; Guemes Diaz 1965; Gascard et al. 1970; Khapat'ko and Shestakova 1983; Zaman et al. 1991; Chim et al. 2000; Yokomori et al. 2008; Gota et al. 2009). Based on the biologic nature of HL, it is difficult to distinguish between a putative origin of HL primary to the liver in comparison with a secondary hepatic manifestation of HL originating elsewhere.

Macroscopic Features of the Liver in Hepatic HL Involvement

There have been attempts to classify the hepatic manifestations of HL. Coronini, Gruber, and Foulon distinguished the following types of hepatic involvement by HL: (1) capsular, (2) nodular or granulomatous lesions localized to the portal triad, (3) diffuse, and (4) encroachment upon or invasion of blood vessels (Coronini 1928; Gruber 1930; Foulon 1932).

Hepatic Nodular Manifestations of HL

Nodular involvement is manifest at laparoscopy in the form of white liver spots or nodules (Sans et al. 1998), and the nodular growth pattern is also grossly recognized in larger biopsy specimens (Fialk et al. 1979). In an autopsy study of HL and NHL patients, intrahepatic nodular lesions over 1 cm in diameter were macroscopically identified in 33 % of patients with HL, more frequent than in patients with NHL (22 %; Okazaki et al. 1985). In nodular hepatic HL, hypoechogenic foci have been observed, proved by biopsy to consist of HL tissue (Marjanska-Radziszewska et al. 1996). The macroscopically detectable lesions range in size from miliary foci to large nodules. The miliary pattern is characterized by tiny round lesions of gray to white color (Fraenkel and Much 1910a), easy to be confounded with granulomas. They may be grouped around intrahepatic bile ducts (Peiser 1913). When being cut, they are, however, more consistent than granulomas, and caseification is usually not seen in these small lesions. Similar to the spleen, these small lesions may reveal a characteristic bright color on a darker background, resulting in what has been called a "quartz splinter on granite" pattern (Dietrich 1908). These tiny nodules may grow to numerous, frequently very firm pea-sized lesions, sometimes with ill-defined borders (v. Hüttenbrenner 1871). Larger hepatic nodules may be solitary lesions, reaching up to 5 cm in diameter (Yamasaki 1904), or multiple (Sternberg 1898; Fabian 1911; Meyer 1911; Stahr and Synwoldt 1922; Barge and Potet 1971) and may then resemble metastases of other tumors (Peiser 1913; Russell 1914; Chim et al. 2000), all the more so as, in case they are located in peripheral parts of the liver, they may show a shallow central concavity (Barge and Potet 1971) or, rarely, typical umbilication (Fabian 1911). The coarse nodular manifestations of HL in the liver, resulting in markedly prominent nodular masses, were already recognized by Langhans (Langhans 1872), but intrahepatic tumorous manifestations in HL in progressive, and particularly non- or inadequately treated, disease are highly variegated.

This polymorphous gross picture is illustrated by an autopsy case of non-treated patient with HL, documented by Dr. Greenfield in 1876, showing the complex gross features of liver manifestations in this disease:

> On its (the liver's) surface were seen a number of irregular, somewhat prominent patches, either single or made up of a number of clustered nodules of small size, with surrounding injection. On sections these were found to be irregular infiltrating masses of new growth, which appeared to have become caseous. In addition to these nodules there were very marked thickeling and infiltration of the tela conjunctiva of the portal vein and bile ducts, extending into the liver; and here there were seen small patches or irregularly ramified infiltration of translucent, waxy-yellowish colour, apparently starting at the periphery of the lobules, these, with the caseous masses before described, being the most evident morbid appearances. (Greenfield 1876)

On the cut surface, medium-sized or large nodules are usually well delineated and exhibit a grayish-white, homogeneous, or spotted tissue, sometimes with central necrosis or hemorrhage (Russell 1914) resulting in a grossly visible central concavity (Barge and Potet 1971). Large nodules may be accompanied by much smaller but still grossly detectable foci, a part of which are located to the portal tracts. The large nodules may show a hyperemic and/or hemorrhagic rim of red-blue color (Meyer 1911). In HL lesions of high cellularity, the cut surface is pale gray to gray-red, said to resemble fish meat, and typically bulges (protuberant nodules of Sternberg; Sternberg 1913), whereas sclerosing forms of HL rather reveal a flat and firm cut surface of whitish color.

In case of marked sclerosis, the cut surface has been described to be "dry," and in such situations, the cut surface also reveals furrows and septa dividing the nodule into "acinar-like" compartments (Langhans 1872) or structures resembling "pseudolobules" (so-called secondary tuberculinization; Gilbert and Weil 1900). Intrahepatic septa-like structures have already been described by Masson and thought to follow the geometry of the portal fields ("*on constate que le foie est parcouru par des trainées fibreuses irrégulières qui suivent les bandelettes porte*" ["one notes that the liver is traversed by irregular fibrous tracts following the portal fields"]; Masson 1956). Other reports described that the firm linear lesions, or lesions like beads-on-a-string, seemed to follow the geometry of the intrahepatic bile ducts (Meyer 1911).

Old autopsy reports from the pre-chemotherapy period specify that HL masses in the liver are first smooth and elastic to become more and more firm with time, until the lesions may be very hard (the "hard lymphosarcoma"), producing a screeching sound when being cut with the knife (v. Hüttenbrenner 1871). In case of advanced fibrosclerosis of nodular lesions, these have been reported to resemble syphilitic gummas macroscopically (Jackson and Parker 1944b). This apparent evolution of the lesions, also reported several times in the old literature to occur in lymph nodes and other organs in Hodgkin disease not modified by therapy, is of interest insofar, as sclerosis, now regarded as a subtype of HL, may be part of the natural development of disease ("period of sclerosis"; Masson 1956). Particularly in larger nodules, necrosis may be seen with the naked eye, resulting in yellow-gray or dirty-looking, opaque masses. Dry granular necroses sometimes reminiscent of a caseification necrosis may be encountered and have been reported to form an arborizing network or a geographic pattern (Kaufmann 1909). Rarely, lardous necrotic lesions resembling those in the Hodgkin spleen are seen. The "red porphyry" appearance seen in the spleen involved by HL is not observed in the liver, owing to its different histologic architecture and composition. In lymphocyte-depleted HL, grayish and sometimes numerous nodules are seen scattered throughout the liver (Jackson and Parker 1944b).

Some presentation forms of hepatic HL are characterized by macroscopically yellow lesions caused by a complex mixture of infiltration, necrosis, and accumulation of lipid-laden macrophages (xanthomatous/xanthomatoid reaction). The lesions may present as miliary hepatic micronodules of brown-yellow color (Fraenkel and Much 1910b). One may encounter focal circumscribed cream-colored lesions or yellow streaks along the course of the portal areas (Jackson and Parker 1944b), likely to reflect a distinct pattern of spread of the disease. In case of a xanthomatoid/xanthogranulomatous reaction (accumulation of lipid-laden macrophages), yellow flecks are seen within the nodules or around the nodules in a yellow crescent-like structure, already recognized in other organs in the older literature (Dietrich 1908). This presentation may be modified by hemorrhagic spots or a focal brown discoloration owing to deposition of iron pigment, particularly after treatment. Rarely, the nodules show a greenish hue due to leakage of bile into the lesions. Superficially placed lesions may form confluent beds of coalescing nodules, thus forming plaque-like multinodular tumors that may occupy large areas of the capsular liver surface. The lesions may extend along the lymphatic drainage of the hepatic ligaments in a beads-on-a-string pattern, especially in the region of the round ligament. Although most of nodules have a spheroid shape, lesions with a streak-like or stellate morphology also occur (Hauck 1918; Kaufmann 1922). From the periphery of such nodules, furrows are seen to traverse the adjacent capsule of the liver, probably representing tissue retraction due to scarring. In addition, there may be streaky and in part arborizing lesions seen from the capsular surface of the organ (Sternberg 1913) or inside the organ, where they encircle atrophic parts of the lobular hepatic parenchyma (Langhans 1872). It has been suggested that grossly visible arborizing lesions may take their origin from the connective tissue sheath of portal and/or hepatic venous branches (Langhans 1872).

Diffuse Infiltration of the Liver

In contrast to miliary or macronodular forms, a diffuse pattern of liver infiltration by HL cells is a rare but severe form of disease that can cause fatal hepatic failure (Karmacharya et al. 2014).

Hepatic Capsular Manifestations of HL

These are rare lesions but have already been documented in old autopsy studies (Meyer 1911). In an autopsy study of 112 cases, an exclusively capsular manifestation was found in 2 cases only (Levitan et al. 1961).

Histopathology of Hepatic HL

The reliable diagnosis of HL in a liver biopsy is frequently difficult owing to the small sample size and the scarcity of diagnostic Reed-Sternberg cells and their variants (Gupta et al. 1999). It has, however, been emphasized that a primary diagnosis of HL involving the liver should only be made if diagnostic Reed-Sternberg cells are seen (Jaffe 1987), because nonspecific infiltrates are found in approximately 50 % of liver biopsies from patients with HL (Leslie and Colby 1984). If only a so-called inflammatory component is seen, the liver should not be considered to be involved with HL (Jaffe 1987).

Miliary Lesions

The miliary pattern of HL in the liver is histologically characterized by one of several types of lesions. Frequently, one notes collections consisting of atypical histiocytoid cells with prominent nucleoli, surrounded by small lymphocytes, in the absence of bona fide RS cells. The diagnostic significance of such lesions is questionable but has been proposed as being consistent with HL, provided that diagnostic evidence of the disease is present elsewhere (Kadin et al. 1971). In addition, small hepatic manifestations of HL may frequently defy classification of HL, even in cases where marked fibrosis suggesting nodular sclerosis is present. In a study of 51 *untreated* patients with HL, laparotomy staging revealed small foci of HL in liver biopsies of 9 patients. These lesions were largely confined to portal tracts and only rarely contained typical RS cells; they were registered as "unclassified" Hodgkin lesions (Kadin et al. 1971). Submiliary lesions, usually not detectable with the naked eye, are usually between 100 and 200 mm in size (Skovsgaard et al. 1982). Mixed portal tract infiltrates containing variable numbers of Reed-Sternberg cells and eosinophils are observed (Kiewe et al. 2004).

Portal Tract Infiltration

Portal tract involvement is rather typical for microscopic hepatic manifestations of HL and is characterized by an infiltration of the portal tract spaces by lymphocytes, atypical large mononuclear (nondiagnostic) cells, and diagnostic Reed-Sternberg cells (Chim et al. 2000), the pattern of the diagnostic cells depending on the type of HL. The HL tissue may extend from the portal tracts to the parenchyma of zone 1 (Davey and Doyle 1973). The lesions may then grow to a size to be recognized macroscopically as miliary-like micronodules (Peiser 1913). They can be associated with hepatocyte atrophy or necrosis, hepatocyte necrosis being found in up to 90 % in some studies (Davey and Doyle 1973) and the formation of lesions resembling interface lesions seen in active chronic hepatitis. Reed-Sternberg cells are capable to invade the parenchyma in these destructive lesions. As the lesions progress, the expanding infiltrates in the involved portal tracts may grow to the next portal tract, thus forming what may be called "lymphomatous bridging," and these lesions then become confluent and form larger tumor nodules (Davey and Doyle 1973). The portal tract infiltrate is sometimes accompanied by fibrosis, not only in NSHL lesions. However, a marked fibrosclerotic reaction in the portal triads seems to be more frequent and more prominent in hepatic NSHL. A contribution of eosinophils is regularly seen, also in the interface lesions,

but the density of eosinophil infiltrates is highly variable.

In the absence of diagnostic Reed-Sternberg cells, the combination of lymphocytes, eosinophils, and large atypical nondiagnostic cells in portal tracts should raise the suspicion of involvement by HL. Immunostaining for Reed-Sternberg cell markers may be helpful in these situations in order to uncover cells that are not easily identifiable in H&E sections. In some cases, several foci of HL are arranged in the portal tracts in the form of ductocentric, ringlike, or crescent-like structures that may compress the ducts (Peiser 1913; Coronini 1928). These ductocentric nodules may, in the larger intrahepatic ducts, be associated with fibrosis, resulting in a thick sheath encircling the ducts (Meyer 1911), somewhat resembling advanced primary sclerosing cholangitis. It has been suggested that portal tract infiltrates apparently encroaching upon small, interlobular bile ducts may cause cholestasis/jaundice (Peiser 1913), sometimes even with a clinical presentation simulating acute cholestatic hepatitis (Marinone et al. 1989). Old observation showed that small interlobular bile ducts embedded in HL tissue of portal tracts may resist destruction for longer time periods, epithelial necrosis being rather uncommon (Coronini 1928). Longer-standing involvement of the liver by HL may result in fibrosis of the liver (Mignot et al. 1979).

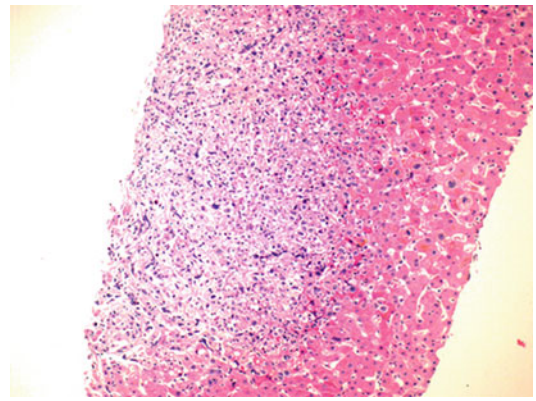

Fig. 1 Liver involvement in Hodgkin disease. A nodule consists of a mixed population of cells, with some large and atypical forms (needle biopsy; hematoxylin and eosin stain)

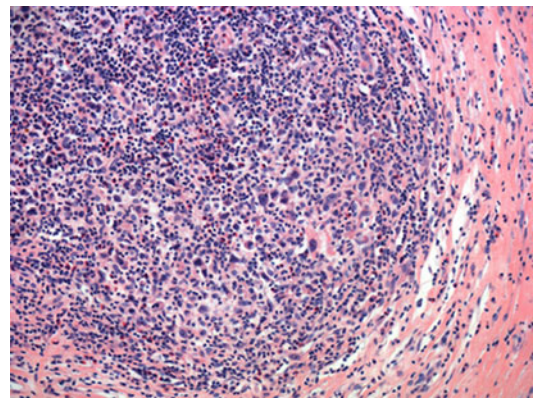

Fig. 2 Hodgkin lymphoma in the liver, mixed cellularity. Within a lymphocytic infiltrate, numerous Hodgkin cells are noted. The nodule is limited by slight fibrosis (hematoxylin and eosin stain)

Nodular Hepatic Lesions of HF

Nodular hepatic lesions histologically consist of dense infiltrates of lymphocytes, macrophages, eosinophils, Hodgkin/Reed-Sternberg cells, and Sternberg giant cells (Figs. 1, 2, 3, 4, and 5). There is recent evidence that giant cells in HL originate from mononucleated progenitors that divide and subsequently re-fuse (Rengstl et al. 2014). Plasma cells and mast cells may also be encountered in the infiltrate. The nodules may coalesce to conglomerates, thus effacing the liver architecture at these places. The cellularity of larger HL nodules is highly variegated, cellular areas and hypocellular, fibrosclerotic areas changing from one place to the other, sometimes interspersed with necroses containing nuclear debris (Russell 1914). Larger nodules are sometimes accompanied by miliary or submiliary foci of HL in their vicinity or may be connected by lymphoma tissue to infiltrated or non-infiltrated portal tracts. In the latter situation, a septal type of fibrosis may ensue, in particular in the nodular sclerosis variant of HL. Large HL nodules sometimes show few lymphocytes in their center, whereas dense lymphocytic infiltrations are seen at their periphery, mainly around small blood vessels (Russell 1914). Large nodules may integrate intrahepatic bile ducts, the contour of the ducts

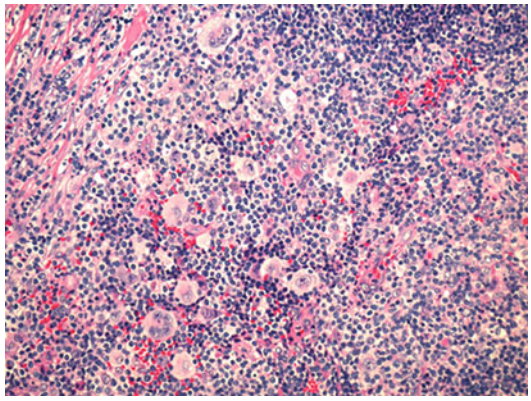

Fig. 3 Hodgkin lymphoma in the liver. Numerous Hodgkin cells and Reed-Sternberg cells are observed (hematoxylin and eosin stain)

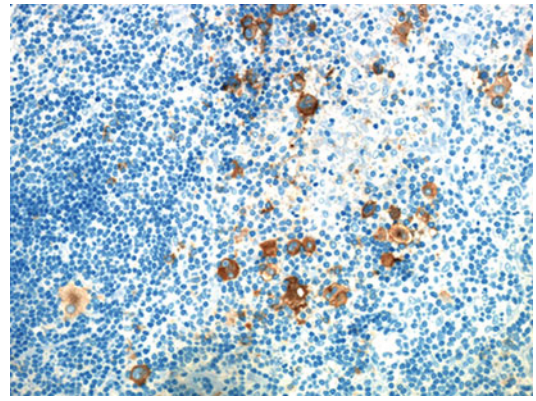

Fig. 5 Hodgkin lymphoma in the liver. Hodgkin cells and Reed-Sternberg cells show positivity for CD15 (CD15 immunostain)

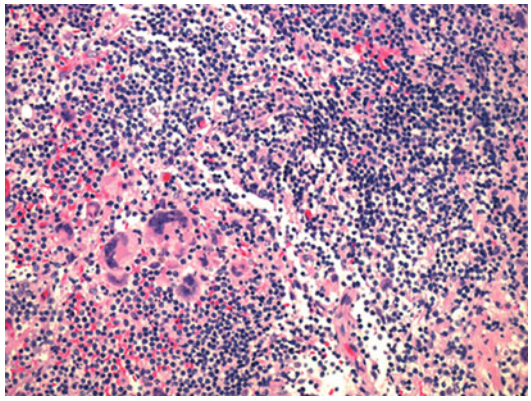

Fig. 4 Hodgkin lymphoma in the liver. In this case, Sternberg giant cells are found (*left half* of figure; hematoxylin and eosin stain)

being visible for some time, ending up with atrophy (with few remnants of cholangiocytes remaining) or even complete duct destruction with substitution by lymphoma tissue. In this situation, bile may leak out of the ducts and stain the HL tissue, particularly in case of lymphoma necrosis (Russell 1914). The neoplastic cell lineage of HL close interacts, within the tumor cell niche, with macrophages and dendritic cells, this interactome regulating a complex immune reaction (review: Tudor et al. 2014).

In addition to intrahepatic bile ducts, intrahepatic portal vein branches may be invaded, sometimes followed by portal vein thrombosis. In an autopsy study, this phenomenon was observed in 23 % of the cases, and this feature tended to occur more frequently with the lymphocyte-depleted type of HL (Davey and Doyle 1973). At the periphery of the nodular lesions, infiltration of hepatic parenchyma may occur, associated with hepatocyte plate atrophy and fatty change of hepatocytes (Russell 1914; Symmers 1944; Sherlock 1955) or even complete destruction of parenchyma. This atrophy has been observed already in old autopsy studies, described, e.g., as hepatocytic "spindle cells" or "spindle-shaped liver cells" (v. Hüttenbrenner 1871). Very rarely, HL may localize to lesions preexisting in the liver, e.g., hepatic angiomas (Toncini and Venzano 1981).

Hilar/Perihilar HL of the Liver and Large Bile Duct Involvement by HL

Involvement of the perihilar hepatic lymph nodes, together with those of the retroperitoneal space and/or the mesentery, causing compression of the large bile duct and thus jaundice, has been described in several reports, sometimes with formation of huge conglomerate masses (Fraenkel and Much 1910a; Meyer 1911; von Jaksch 1913; Weinberg 1917; Michalitschke 1919; Razemon et al. 1961; Martin et al. 1992). Interestingly, these clinical reports describe obstructive

jaundice and in part very large periductal lymphomas, but no prestenotic dilatation of the large hilar bile ducts. On the other hand, Russell described an autopsy case with nodular manifestations of HL in the liver, associated with impressive saccular dilatations of large bile ducts close to the hepatic hilum, these ducts being filled with a dark and viscous bile ("*dilatatio cystica circumscripta ductuum biliferorum*"), whereby some of these cystic structures seemed to follow the larger and infiltrated Glisson's tracts into the liver substance (Russell 1914). Rarely, periductal enlarged lymph nodes involved by HL may bulge into the duct lumen. That enlarged lymph nodes involved by HL exert obstructive effects is exemplified by nonvisualization of the gallbladder in HL of the cystic lymph node (Wee et al. 1970).

Seven patients with direct involvement in the perihilar/hilar tissue compartment were described in detail by Coronini (1928). In two patients, perihilar involvement with biliary obstruction was induced by involvement of hilar/perihilar lymph nodes by HL. In one patient, a perihilar lymphoma had led to kinking of the choledochal duct (Coronini 1928). Direct perihilar tissue involvement was detected in six patients of the extensive analysis of Coronini. Rarely, involvement of the large bile duct close to the hepatic hilum presents in the form of firm and flat nodes developing in the bile duct wall and causing stenosis (Meyer 1911; "Gallengangsgranulomatose"; Coronini 1928), thus clinically mimicking Klatskin's tumor. In other situations, a single bean-sized nodule of HL has been observed in the wall of the choledochal duct (Meyer 1911). Rarely, the entire mucosa of the large bile ducts is seeded by flat tumor nodules, separated from each other by clefts, causing lumenal stenosis (Stahr and Sywolt 1922). Histologically, the latter authors noted that these ductal wall lesions had a transmural extension and were rich in Reed-Sternberg cells, a HL tissue of high cellularity prevailing in the deeper parts of the lesions, while a tissue of lower cellularity was found more close to the mucosal surface. These ductal/periductal nodules may reach 1.5 cm in thickness, encircle the bile ducts, and induce filiform stenosis associated with prestenotic dilatation of the biliary tract (Coronini 1928), sometimes with sacculiform dilatations of the ducts close to the hilum (Russell 1914). Intramural growth of HL tissue in large bile ducts has later been confirmed (Ochoa and Keene 1970; Martin et al. 1992; Abe et al. 1997). In some patients, only duct strictures causing intermittent or persistent obstructive jaundice were found (Diessner and Heck 1958). Fibrotic HL lesions located to the bile ducts may produce imaging features indistinguishable from sclerosing cholangitis (Tartar and Balfe 1990). Biliary and portal vein strictures may also develop following HL therapy (Roberts et al. 2012).

Invasion and Spread of Hodgkin Lymphoma Within the Liver

Invasion of blood vessels and lymphatics by HL has been described by several authors (Reed 1902; Jeanselme and Marchal 1926; Coronini 1928; Callender 1930; Jackson and Parker 1944b; Sayhoun and Eisenberg 1949; Varadi 1960; Rappaport and Strum 1970; Strum et al. 1971; Rappaport et al. 1971; Naeim et al. 1974; Kirschner et al. 1974). But there are also informations in the literature showing the case against (Lamoureux et al. 1973). Rarely, HL reveals a nodal intrasinusoidal invasion pattern mimicking that of anaplastic large cell lymphoma (Lee et al. 2004), suggesting that HL cells can undergo a distinct homing pattern to, and expansion in, specific vascular channels. In the liver, several histopathologic patterns suggest an invasive phenotype of HL. The probably most early phases of involvement, when a specific infiltrate is found to partially occupy the portal tracts, are difficult to judge in regard to invasion, because it is currently still unknown as to how the neoplastic cells of HL reach the liver tissues. It is suggested that the distinct cells circulate in the blood and achieve access to the portal tracts or sinusoidal compartments of the liver by specific homing mechanisms followed by egress of the cells into the extravascular compartments.

In fact, some authors claimed that HL primarily invades the liver within the portal tract spaces

(Schmorl 1922; Sternberg 1936), whereas others proposed that HL extends along the periportal spaces (Fabian 1911; Ziegler 1911) or along the major intrahepatic bile ducts and the portal vein and its branches (Chevallier and Bernard 1932; Sternberg 1936). Spread along the portal tracts is suggested by the typical distribution of xanthomatous yellow streaks that follow the portal course in some cases of hepatic HL (Jackson and Parker 1944b). Dense accumulations of HL infiltrates containing Reed-Sternberg cells may be explained, at least at the beginning of the process, by proliferative expansion of the cells. That the apparently rather dense connective tissues located to the portal tracts allow a rapid infiltration by leukocytes is well known from diverse inflammatory processes (portal hepatitis), illustrating that lymphocytes are potently capable to invade the portal tract space. It may be surmised that the cells of HL can do the same thing, but the mechanisms are not known. On the other hand, expansion of the process beyond the limiting plate and thus into the liver lobules will require invasion rather than proliferative growth alone. Similarly, spread along the intrahepatic bile ducts and blood vessels necessarily involves an invasive phenotype of the neoplastic cells of HL. As described above, Reed-Sternberg cells can be observed within the lumina of hepatic sinusoids, and this will need specific homing and adhesion mechanisms. The fate of such cells in regard to later growth patterns (infiltration of the perisinusoidal space) is not established, but there is some morphologic (and thus indirect) evidence that miliary or submiliary HL growths found within the lobular parenchyma may take their origin from cells primarily settled in the sinusoids.

Invasion of lymph vessels, veins, and arteries by HL has been reported several times (Reed 1902; Jeanselme and Marchal 1926; Coronini 1928; Callender 1930; Jackson and Parker 1944b; Sayhoun and Eisenberg 1949; Varadi 1960). Vascular invasion by HL tissue/cells has been observed in lymph nodes, the incidence of vascular invasion in the original lymph node biopsies being highest in LDHL and decreasing in MCHL, NSHL, and LRCHL (Naeim et al. 1974). It is of importance to note that lymph node vascular invasion is associated more frequently with liver, lung, or bone marrow involvement, either initially or within 1 year in most of the cases analyzed in one study (Strum et al. 1971). Vascular invasion of lymph nodes or the spleen of patients with HL was associated with a high incidence of extranodal organ involvement in other investigations of several hundred tissue samples (Rappaport and Strum 1970; Rappaport et al. 1971). Similarly, HL vascular invasion in the spleen was associated with hepatic and bone marrow involvement, early relapse, and shortened survival (Kirschner et al. 1974). Simonds first noted HL lesions invading the portal vein (Simonds 1926), and this feature was confirmed in later studies (Davey and Doyle 1973). Other types of hepatic vessels have been found to be invaded in an autopsy study (Libansky et al. 1962). The most detailed histopathologic analysis found in the old literature is that of Coronini (Coronini 1928). He described several patterns of vascular lesions occurring in HL, also in the liver. The lesions comprise subendothelial granuloma-like proliferations, associated with endothelial damage, in portal vein branches, a ringlike phlebocentric granulomatosis (granulomatous phlebitis) of portal vein branches resulting in occluding venous thrombosis, and a massively stenosing lymphomatous invasion of large portal vein branches at the liver hilum (lymphomatous phlebopathy), sometimes with accumulation of Reed-Sternberg cells in the markedly thickened portal venous intima. In patients with hilar/perihilar involvement, he also observed an angiodestructive invasion of hepatic artery branches by HL, sometimes with impressive arrosion of the adventitia, a marked granulomatous reaction and/or arterial tissue and tumor necrosis, destruction of the elastica interna, and obliteration of the lumen and with accumulation of Reed-Sternberg cells within the altered media and intima (lymphomatous arteriopathy; Coronini 1928). These hepatic arterial lesions may be associated with necrosis of bile ducts (Coronini 1928), owing to ischemic cholangiopathy/cholangitis.

The neoplastic cells in HL, including cells with the features of Hodgkin and/or Reed-Sternberg cells, can circulate in the peripheral blood (Varadi

1955, 1960; Keiser 1960; Libansky et al. 1962; Hayhoe et al. 1978; Malfitano et al. 1980; Riccardi et al. 1980), sometimes in high numbers leading to what has been termed Reed-Sternberg cell leukemia (Cavalli et al. 1981). The source of these cells is not clear, but it has to be emphasized that peripheral blood mononuclear cells of patients with HL can give rise to permanently growing Hodgkin/Reed-Sternberg cells (Wolf et al. 1996). In regard to the liver, Reed-Sternberg cells have been observed within hepatic sinusoids (Priesel and Winkelbauer 1926; Coronini 1928; Barge and Potet 1971). In his extensive work in hepatic HL involvement, Coronini depicts three large elongated cells located in the sinusoids, most probably representing Sternberg giant cells (Coronini 1928; Fig. 2), a finding which is of interest in the light of target cell homing in HL. A very similar change is depicted in a work published 2 years earlier, again with huge cells with irregular or lobulated nuclei (not representing megakaryocytes) within the sinusoids (Priesel and Winkelbauer 1926). The preparations were from a small child with a generalized lymphomatous disease with numerous hepatic nodules; it is, based on the description, however not certain whether this child had bona fide HL. A convincing figure of Reed-Sternberg cells clearly situated within sinusoids is found in the work of Barge and Potet (Barge and Potet 1971; their Fig. 3).

How Frequent Are HL Infiltrates in the Liver in Extrahepatic HL?

This question has been addressed in rather large number of reports based on autopsies, but using highly variable criteria for identifying HL in the liver, with an incidence range of 10–70 % (Ziegler 1911; Wallhauser 1933; Sternberg 1936; Symmers 1944; Jackson and Parker 1944a; Ackerman and del Regato 1954; Davey and Doyle 1973; Colby et al. 1981). Detailed informations were obtained in a study of 875 patients with HL, 300 (34.3 %) presented with clinical evidence pointing at liver disease such as hepatomegaly and/or abnormal liver function tests. Of this group with clinical signs of liver disease and histologic proof of HL, 112 cases (44 %) were autopsied (Levitan et al. 1961). Of these 122 cases, 74 (66 %) revealed HL involving the liver and 38 (34 %) did not. In the latter group, however, all the livers exhibited some abnormality of major or minor degree. Of the cases with proven hepatic HL involvement, 86.5 % presented with diffuse infiltration, 10.8 % with nodular lesions, and 2.7 % exhibited mixed lesions. Both liver lobes were involved in most cases. Among 59 autopsies of patients with HL, intrahepatic HL was found in 41 or 70 % (Davey and Doyle 1973). In an autopsy study of 80 patients with HL from the time period 1972 to 1977, 54 patients had residual HL, and among 52 of these where the liver was autopsied, 33 had liver involvement (63 %; Colby et al. 1981). Different figures were obtained in liver biopsy studies, likely to be due to an earlier diagnostic approach in comparison with the late stages observed in autopsies. It has been maintained that silent liver involvement can be demonstrated early in the course of the disease by liver biopsy (Pène 1952). In a total of 472 liver biopsies performed in 308 patients with HL, only 2.4 % showed hepatic HL infiltrates consisting of Sternberg-Reed cells and abnormal lymphohistiocytic cells against a background of lymphocytes together with neutrophilic and eosinophilic granulocytes. These infiltrates formed foci of 100–200 mm diameter. This prevalence of bona fide HL involvement is somewhat lower than that in other studies (Rosenberg and Kaplan 1970; Glatstein et al. 1970; Kadin et al. 1971; Abt et al. 1974; Hellman 1974). In a further eight patients of the study of Skovsgaard and coworkers, infiltrates were found that had all the characteristic features of HL except the presence of Sternberg-Reed cells (Skovsgaard et al. 1982). In this large biopsy series, the most frequent finding was lymphocytic infiltration in portal tracts (in 56 % of biopsies), but was of moderate or severe degree in 20 % and 1 % only, respectively. This feature was followed in frequency by focal necrosis (24 %). It has been shown that changes found in liver biopsies taken at the end of staging operations instead at the beginning (a procedure preferred by many surgeons, because no further

manipulations are required) can readily be differentiated from the changes found in HL (Brown et al. 1981).

Is There a Preference of Certain HL Variants to Manifest in the Liver?

This question is difficult to answer due to the fact that the type of lesions found in the liver may or may not correspond to extrahepatic histologic patterns of HL. In an early autopsy study where access to histology was available for 39 cases, it was impossible to classify the intrahepatic HL infiltrates according to then used Lukes classification (Davey and Doyle 1973). This can, at least in part, be due to the phenomenon that extranodal spread, including the liver, is more prevalent in advanced disease and that there is convergence of the morphotypes of HL as a function of progression (Naeim et al. 1974). Nodular lymphocyte-predominant HL (NLPHL; nodular paragranuloma) is different clinically and also in regard to extranodal spread from other variants of HL (Bodis et al. 1997; Diehl et al. 1999). Clinically, most patients present with early stage disease (Ann Arbor I/II; Pappa et al. 1995), but 28 % of patients have presented with advanced stage disease and some of these cases have pursued an aggressive and even fatal clinical course (Hansmann et al. 1984; Trudel et al. 1987). Overall, liver involvement in NLPHL is regarded as rare (Pappa et al. 1995). Of 145 patients with NLPHL, 13 % of the involved sites were extranodal, 4 of them concerning the liver (Hansmann et al. 1984). Among 13 patients with NLPHL (10 with Ann Arbor stage III or IV), four exhibited liver involvement, in two patients with a macroscopic mass; the lesions were focal in two and multifocal in two patients, respectively (Siebert et al. 1995). Among 16 patients with NLPHL, six liver specimens were reviewed (needle or wedge biopsies), four having evidence for NLPHL involvement. None of the involved livers had grossly identifiable lesions. Small to large collections of mature-looking lymphocytes were present in the portal tracts of three of the cases, and varying numbers of LP cells with the immunophenotype typical for NLPHL were also present in this tissue compartment. The fourth case had intralobular and not portal tract involvement, and the numbers of L&H cells and of Reed-Sternberg cells were very low (Chang et al. 1995). The histopathologic differential diagnosis of NLPHL in the liver includes classical HL, T-cell-rich B-cell lymphoma involving the liver (Khan et al. 1993; Fraga et al. 2002), and B-lineage NHL. From a large autopsy study of 122 cases, it turned out that exactly half of the hepatic lesions were what was then termed Hodgkin granuloma (i.e., not LDHL), and of these 82.3 % showed almost exclusive involvement of the portal tracts (Levitan et al. 1961). For LDCHL, liver involvement has been documented by few liver biopsies (Neiman et al. 1973). In the setting of autopsies, liver involvement has been observed in eight out of nine necropsies (Neiman et al. 1973). It seems that portal vein invasion tends to be more frequent in LDCHL (Davey and Doyle 1973).

Hepatic Involvement by Variant Richter's Syndrome

Variant Richter's syndrome can involve the liver (Reddy and Thompson-Arildsen 2010). Hepatomegaly has been described as a feature of this disorder (Brecher and Banks 1990). A progressively enlarged liver has been reported in a patient who developed classical HL 4 years after the diagnosis of Rai stage II (Binet B) chronic lymphocytic leukemia, without liver histology (Nemets et al. 2003). Among nine patients with Richter's syndrome described by Foucar and Rydell, two showed a histology compatible with lymphocyte-depleted HL and were, therefore, likely to be variant Richter's syndrome. At autopsy, one of these two patients exhibited extensive hepatic infiltration with enlarged, confluent portal areas forming actual tumor nodules less than 5 mm in size (Foucar and Rydell 1980).

Differential Diagnosis

Histologically, the main differential diagnoses include lymphomatous lesions that produce cells resembling Hodgkin and Reed-Sternberg cells. These neoplasms mainly include T-cell-rich B-cell lymphoma and so-called Hodgkin-like peripheral T-cell lymphoma/PTCL (Mori et al. 2014). It has been suggested that nodular lymphocyte-predominant HL and T-cell/histiocyte-rich B-cell lymphoma might be endpoints of a spectrum of one disease (Hartmann et al. 2013).

Nonneoplastic Hepatic Manifestations of HL

Vanishing Bile Duct Syndrome in Hodgkin Lymphoma

A syndrome of "idiopathic" intrahepatic cholestasis occurs in some patients with HL, caused by a distinct ductopenic disorder. Secondary intrahepatic ductopenia (vanishing bile duct syndrome; VBDS) usually in the absence of direct HL infiltration of the liver is a rare but critical cause of cholestasis with or without jaundice in patients with HL; the disorder is thought to be a paraneoplastic manifestation of HL and may result in intractable fatal liver damage (review: Nader et al. 2013). Fatal liver failure due to VBDS can ensue despite HD remission (Aleem et al. 2013). The pathogenesis of HL-associated VBDS is not known. That HL as such is in some complex manner involved is supported by the observation that the small bile duct disorder may show resolution following successful therapy of HL (Crosbie et al. 1997). The differential diagnosis of cholestasis in HL due to VBDS/ductopenia comprises nonobstructive HL-associated cholestasis (see above), obstruction due to infiltration of the bile ducts by HL tissue (Ochoa and Keene 1970; Chaudhari et al. 2013), large extrahepatic bile duct obstruction by HL masses (Sanbe and Shirato 1966; McNulty 1971; Pariente et al. 1981; Martin et al. 1992; Abe et al. 1997), and extrahepatic biliary stricture subsequent to radiotherapy of the upper abdomen (Cherqui et al. 1994).

Selected References (Cavalli et al. 1979; Hubscher et al. 1993; Gottrand et al. 1997; de Medeiros et al. 1998; Ludwig 1998; Allory et al. 2000; Rossini et al. 2000; Yusuf et al. 2000; Ozkan et al. 2001; Ripoll et al. 2002; Liangpunsakul et al. 2002; Guliter et al. 2004; Ballonoff et al. 2008; Leeuwenburgh et al. 2008; Pass et al. 2008; Foramiti et al. 2011).

Sclerosing Cholangitis in Hodgkin Lymphoma

Apart from the well-established association with inflammatory bowel disease, primary sclerosing cholangitis (PSC) has been associated with other diseases, which are often cited as single case reports, including HL. Two patterns of bile duct disease resembling sclerosing cholangitis have been described. In the first pattern, fibrosing HL lesions situated in the walls of larger bile ducts produce a radiographic picture mimicking primary sclerosing cholangitis (PSC), with sometimes marked stenosis (Tartar and Balfe 1990; Gupta et al. 2002). The second pattern is characterized by PSC-like larger bile duct alterations in the absence of proven bile duct involvement by malignancy. In the adult age group, a first report concerned three men, of whom one patient had Crohn's disease of the colon. In these three patients, primary sclerosing cholangitis was diagnosed 2, 11, and 17 years before diagnosis of HL, and all three had then advanced biliary cirrhosis prompting referral for liver transplantation (Man et al. 1993). In a pediatric patient with HL involving the liver, biopsy disclosed a morphology compatible with sclerosing cholangitis (Gupta et al. 2002). The pathogenesis of the association of HL and PSC, if this is not a mere coincidence, is unknown. It has been suggested that immune suppression associated with long-standing and advanced liver disease or immunosuppressive drug therapy may predispose PSC patients to HL (Man et al. 1993).

Hepatic Granulomas in Hodgkin Lymphoma

Hodgkin lymphoma (HL) is well known to be associated with a granulomatous reaction in several organs and tissues (Brincker 1970; Kadin et al. 1970, 1971; Goldman 1970; Colby et al. 1981; Brooks 1982; Johnson et al. 1990; Arai et al. 1992), e.g., in the bone marrow, but also in the liver (Atwood et al. 1966; Brinker 1970; Stolzenbach et al. 1976; Sacks et al. 1978; Koene-Bogman 1978; Pak and Friedman 1981; Skovsgaard et al. 1982). In a study of 459 liver biopsies from 308 patients with HL, granulomas were detected in only 2 %, suggesting the rareness of this finding (Skovsgaard et al. 1982). The development of a marked granulomatous reaction can, similar to the situation of NHL, even be a prominent manifestation at the outset of HL (Lerza et al. 2002). In a study of 51 untreated patients, granulomas were detected in otherwise uninvolved tissues in 14 % of the patients (Kadin et al. 1971).

It was at first considered that hepatic granulomas in HL might be an early tissue expression of this neoplasm (Atwood et al. 1966; Brincker 1970); however, there is no evidence for this, with very few exceptions (Goldman 1970). HL, similar to NHL, may masquerade as "idiopathic" liver granulomas (Aderka et al. 1984), so that the presence of hepatic granulomas without clear cause should make one consider HL or NHL. Usually, the granulomas in HL present as noncaseating epithelioid cell nodules with or without a significant lymphocyte seam, but Langhans giant cells are usually sparse or lacking. Central fibrinoid necrosis was occasionally seen, whereas Schaumann and asteroid bodies were not observed (Kadin et al. 1971). A caseating reaction in the granulomas in the absence of mycobacterial infection is exceedingly rare (Johnson et al. 1990). In the liver, HL-associated granulomas are chiefly located to the portal tracts (Kadin et al. 1971). It is established that lymph nodes draining an area harboring malignancy can show epithelioid granulomas, sometimes to a degree histologically mimicking sarcoidosis and reflecting marked macrophage activation in conjunction with a cell-mediated immune reaction directed to tumor antigens (Nadel and Ackerman 1950). There is evidence that at least a part of the granulomas observed in conjunction with HD represent a reaction to oily radiographic contrast media used in lymphangiography (Pak and Friedman 1981), although it has been claimed that the granulomatous lesions in HL do not really resemble reactions to lymphangiography, mainly based on the observation that the heavily lipidized foreign body-type granulomas developing shortly after oily lymphangiography do not occur in HL (Kadin et al. 1970, 1971). But it has been shown that, as a function of time, lipid-rich lipogranulomas with vacuolated cells slowly transform into sarcoid-like granulomas of the type encountered in HL (Pak and Friedman 1981). A sarcoidosis-like granulomatous reaction has been observed following chemotherapy for HL (Merchant et al. 1994). The histiotype of granulomas occurring in HL may rarely deviate from the "standard" granuloma. Very rarely, hepatic granulomas of the liver in HL have been found to be of the caseating type, in the absence of tuberculosis (Johnson et al. 1990). Apart from typical epithelioid granulomas with a variably developed peripheral rim of lymphocytes, the fibrin-ring granuloma-type of lesion has also rarely been encountered in the liver in HL (in 4 % among 23 patients with such granulomas; Marazuela et al. 1991).

Whether the presence of epithelioid granulomas in HL, including granulomas in the liver, is of prognostic significance has been suggested and discussed in few reports, but a conclusive answer to this question requires more and prospective studies (O'Connell et al. 1975; Sacks et al. 1978; Chopra et al. 1995). In a larger analysis of 55 previously untreated patients with HL and associated granulomas, survival and relapse-free survival were significantly different in favor of the granuloma group in comparison with 553 patients without granulomas (Sacks et al. 1978). A later study revisiting the significance of granulomas (with one of the authors of the just mentioned 1978 study), involving 89 HL patients with granulomas and with a longer follow-up, resulted in a different conclusion: after long follow-up, the relapse-free survival advantage was no longer apparent (Abrams et al. 1988).

Lymphoid Hepatic Lobular Infiltration in the Absence of Bona Fide HL Infiltration of the Liver

The presence of lymphoma in the liver at staging may be difficult to confirm histologically when infiltrates are focal and/or nondiagnostic, i.e., without detectable Hodgkin or Reed-Sternberg cells. Focal lymphocytic infiltrations of the liver may, in the otherwise proven presence of HL, suggest hepatic manifestation of this disease. But how frequent are such infiltrates? In a study of wedge and needle liver biopsies from 123 consecutive staging laparotomies for HL, 12 biopsies revealed discrete lobular lymphoid aggregates. In this investigation, there were nine cases of hepatic involvement by HL and one of extensive portal infiltrates by inflammatory cells, but none of these specimens contained the distinctive parenchymal lymphoid aggregates. The lobular aggregates varied from a few lymphocytes clustered within sinusoids to large aggregates entrapping hepatocytes (Leslie and Colby 1984). The nature of these intralobular lymphoid infiltrations has not been clarified so far, but they may represent an immune reaction to unknown, eventually HL-associated antigens.

Nodular Regenerative Hyperplasia of the Liver

Infiltration of the liver substance by HL cells and tissue, associated with complex vascular abnormalities and a deranged blood flow, can result in nodular regenerative hyperplasia/NRH, a recurrent alteration of the liver in HL patients (Lopez et al. 2014).

Hepatic Sinusoidal Changes in Hodgkin Lymphoma

Hepatic sinusoidal dilatation (HSD) is characterized by the widening of sinusoids that may involve the entire liver lobule or predominate in periportal, midzonal, or pericentral areas. Peliosis hepatis, first described in 1916 under this term (Schoenlank 1916), differs from HSD by the formation of intraparenchymal blood-filled spaces ("lakes") without preferential location (Degott and Potet 1984), although there may be transitions or overlaps between the two lesions. Hepatic peliosis is characterized by oval or irregular, multiple blood-filled spaces within the liver parenchyma, the cavities ranging in size from less than 1 mm to several centimeters. In a study of 906 consecutive liver biopsies, sinusoidal dilatation unrelated to passive hepatic congestion was observed in 26 (2.9 %), and in 21 out of 26 the final diagnosis was a neoplastic or granulomatous disease, but in only half of them was there evidence of neoplastic or granulomatous infiltration of the liver (Bruguera et al. 1978). Sinusoidal dilatation (HSD; sinusoidal ectasia) occurring in the context of HL not associated with direct liver involvement has repeatedly been reported (Bain et al. 1982; Bruguera et al. 1987; Kakar et al. 2004). The examination of liver biopsy specimens from 46 patients with HL revealed sinusoidal dilatation with a predominantly centrilobular and mid-lobular localization in 50 %, more frequently in patients with (90 %) than in those without (20 %) systemic symptoms of disease. The prevalence of these alterations was not related to the stage of HL or the existence of hepatic infiltration by HL (Bruguera et al. 1987). From the descriptions, it is difficult to judge whether sinusoidal dilatation fulfilled the criteria of peliosis hepatis, but at least in part of the cases, these lesions may in fact represent, or may evolve to, bona fide peliosis hepatis (Pasquier et al. 1973; Iwai et al. 2002; Kleger et al. 2009), although peliosis in HL has been suggested to be an infrequent association (Bhaskar et al. 1990).

Cytogenetic and Molecular Features

LP cells in NLPHL show clonally rearranged immunoglobulin genes. The variable region of the immunoglobulin heavy chain genes have a high load of somatic mutations. In contrast to other forms of HL, latent EBV infection is consistently absent from LP cells but may be detectable in nonneoplastic lymphocytic bystander cells. In

80 % of NLPHL cases, aberrant somatic gene mutations have been found, involving PAX5, PIM1, RhoH/TTF, and MYC.

In classical HL, HRS cells contain clonal immunoglobulin gene rearrangements in more than 98 % of cases. In rare cases, T-cell receptor gene rearrangements had been detected. HRS cells have lost many of the typical B-cell lineage markers and express a host of aberrant markers. This is in part caused by a downregulation of early B-cell factor 1 (EBF1), a major B-cell transcription factor (Bohle et al. 2013). The transcription factor NF-kappaB is constitutively activated in HRS cells. There is recent evidence that HL is associated with genetic variations at both HLA and non-HLA loci, including loci at 2p16, 5q31, 6p31, 8q24, and 10p14. A susceptibility locus for HL is on chromosome 19p13.3, involving TCF3 (or E2A), a regulator of B- and T-cell lineage commitment (Cozen et al. 2014).

Both proliferation and survival of HL Reed-Sternberg cells require this activity, which is comprised of the p50 and relA subunits. It was shown that EBV-negative Reed-Sternberg cells reveal enhanced expression of NF-kappaB2/p52 and RelB-containing NF-kappaB DNA-binding activity and that CD30 triggers the noncanonical NF-kappaB activation pathway. Hodgkin cells and Reed-Sternberg cells display a disturbed cell cycle regulation with an abnormality short G1 phase (Tzankov et al. 2005). The p18INK4c gene, encoding a cyclin-dependent kinase (CDK) inhibitor interfering with the Rb-kinase activity of CDK6/CDK4, is silenced in HL through epigenetic promoter hypermethylation (Sanchez-Aguilera et al. 2004). Epigenetic inactivation of the putative tumor suppressor with proapoptotic activity, RASSF1 A, has been found in HL (Murray et al. 2004). Mutations of the JAK regulator SOC-1 occur and are associated with nuclear STAT5 accumulation in HRS cells. As discussed above, overexpression of CD30 is a typical feature of neoplastic cells in HL. CD30 is a member of the tumor necrosis factor/nerve growth factor receptor superfamily and is the receptor of the cytokine, CD30 ligand (CD30L; Gruss and Herrmann 1996). CD30 is expressed transiently on activated B and T cells and constitutively on several B- and T-cell NHLs and on HL. The major CD30 functions include participation in negative selection of thymocytes, costimulation of activated T cells, isotype switching of B cells, and regulation of the effector activity of cytotoxic lymphocytes. CD30 is expressed in Reed-Sternberg cells, and increased levels of serum CD30 are observed in HL patients and are a marker for predicting poor prognosis and poor treatment response. In fact, the CD30 antigen has been characterized as a marker for both primary and cultured Reed-Sternberg cells, but this antigen is also expressed in cells of anaplastic large cell lymphoma and of Burkitt lymphoma. Persistent expression of high levels of CD30 in HL cells, and in particular Reed-Sternberg cells, is thought to play a central role in growth regulation of the neoplastic cells involved. Reed-Sternberg cells, in contrast to cells of anaplastic large cell lymphoma, coexpress CD30 and CD30 ligand, suggesting an autocrine CD30L-CD30 cytokine receptor loop (Hsu and Hsu 2000). The differential expression patterns of downstream components of the CD30 signaling pathway, in particular TRAF1 and c-Rel, may prove a useful adjunct in distinguishing cases of classical HL from morphologically and immunophenotypically similar lymphomas (Rodig et al. 2005). CD30-mediated signals are involved in lymphoid cell homing to lymph nodes, and affect, in a complex network, apoptosis in that CD30 on the one hand upregulates Fas, death receptor 3, and TNF-related apoptosis-inducing ligand and on the other hand upregulates TNFR-associated factor 1 and cellular inhibitor of apoptosis 2, protecting cells from certain types of apoptosis (Muta et al. 2000). It has been found that expression of CD30 by neoplastic cells in HL is associated with inhibition of proliferation and activation of T cells (Su et al. 2004). Proteins that function in signaling events downstream of activated CD30 are also expressed in neoplastic cells of classical HL, including TRAF1 and activated c-Rel (Rodig et al. 2005), and CD30 ectodomain shedding affecting its biologic activity is mediated by TNF-alpha converting enzyme (TACE), is dependent on the availability of the

cysteine-rich domains (CRD) 2 and 5 of the CD30 ectodomain (Hansen et al. 2004), and is increased by depletion of cellular cholesterol and of lipid rafts (von Tresckow et al. 2004). TACE is itself a metalloproteinase, and inhibitors of this enzyme therefore affect the turnover of CD30 (Hansen et al. 2002).

Role of EBV Infection

HL is more often seen in patients with EBV infection (Khan 2006; Kapatai and Murray 2007; Martin et al. 2011; review: Mohamed et al. 2014). The highest frequency of EBV gene expression in HRS cells is found in MCCHL (around 75 %) and the lowest incidence in NSCHL (10–40 %). In Western countries, the EBV strain 1 prevails, whereas strain 2 prevails in resource-poor areas. EBV-encoded latent membrane protein 1 (LMP-1) gene exhibiting deletion mutants is highly associated with HIV-related HL, and these mutants accumulate in RS cells (Guidoboni et al. 2005). From a genome-wide association study of 1200 classical HL patients, it resulted that there were associations between EBV-positive classical HL and genetic variants within the class I region and between EBV-negative classical HL and the rs6903608 locus within the class II region, the latter association being confined to NSCHL (Urayama et al. 2012). In pediatric HL, tumor-associated macrophages are associated with EBV, suggesting that the macrophage microenvironment in pediatric classical HL is different from that of HL in adults (Barros et al. 2012). EBV contributes to the growth and survival of HRS cells. Expression of EBNA1 is associated with downregulation of the TGF-beta target gene, protein tyrosine phosphatase receptor kappa (PTPRK), conferring increased growth and survival to HRS cells (Flavell et al. 2008). EBV infection also affects the recruitment of accessory cells of HL tissue. Expression of the EBV-encoded EBV nuclear antigen 1 in HL neoplastic cells mediates the upregulation of the chemokine CCl20 and the migration of regulatory T cells (Baumforth et al. 2008).

Mechanisms Involved in Growth, Apoptosis, Invasion, and Spread of HL Cells

The Mummified Reed-Sternberg and Hodgkin Cells and Mechanisms of Para-apoptosis/Apoptosis in Hodgkin Lymphoma

The presence of degenerative or regressive changes occurring in the large neoplastic cells in HL had already been noted by Reed and by Sternberg, and these features were later specified in more detail (Jackson and Parker 1944b; Cross 1969; Lorenzen et al. 1997), in one instance described under the term "selective apoptotic necrosis (SAN)" (Kodousek et al. 1992). The phenomenon represents distinct stages of a cellular death process including para-apoptosis and apoptosis of Hodgkin/Reed-Sternberg cells, although it is established that the neoplastic cells in HL are characterized by a remarkable resistance to certain apoptotic stimuli. Histologically, the tissues of HL contain Reed-Sternberg cells with a condensed and markedly eosinophilic or amphophilic cytoplasm and basophilic and condensed nuclei lacking chromatin marginalization, termed mummified cells (Lorenzen et al. 1997). In certain stages of this decay process, the cells may be triangular or elongated. Although the nuclear chromatin undergoes condensation, the tortuous nuclear contour is retained for longer time periods. Similarly, immunoreactivity for CD30 and/or CD15 is retained in what has been termed para-apoptosis, while these markers are negative in cells with classical signs of apoptosis (Lorenzen et al. 1997). Para-apoptosis (nonclassical apoptosis) is a specific morphologic type of programmed, non-necrotic cell death, characterized by cytoplasmic vacuolization, condensed chromatin (but not early margination of the chromatin), and swollen mitochondria. In contrast to classical apoptosis, surface blebbing and the formation of typical apoptotic bodies do not occur (Asher et al. 1995). It seems that para-apoptosis is driven by an alternative caspase-9 activity that is Apaf-1-independent (Sperandio et al. 2000). Para-apoptosis, in addition to Hodgkin and Reed-Sternberg cells, has been observed

in several other cell systems, including lymphocytes (Asher et al. 1995) and the megakaryocyte lineage (Houwerzijl et al. 2004). It is sometimes noted that apoptosis and para-apoptosis are seen in classical HL, but in fact they may occur in any type and subtype of HL (Cross 1969). In a detailed study, the lowest incidence of mummified cells was found in NLPHL ("paragranuloma"), significantly different from the mixed cellularity subtype (Lorenzen et al. 1997). Mummified cells ("mummy cells") do not seem to exhibit DNA fragmentation, but the apoptotic cells are strongly reactive by in situ end labeling of DNA fragments (Benharroch et al. 1996, 1998), while abortive mitoses and nuclear DNA fragmentation were observed in CD30-reactive large cells of HL (Leoncini et al. 1996).

What are the mechanisms of apoptosis and para-apoptosis in HL? Several proteins known to regulate apoptosis and protection from apoptosis show an increased expression in HL tissue and/or Reed-Sternberg cells, including CD95/Fas (Vassallo et al. 2003; although the neoplastic cells show a remarkable resistance to Fas), Bcl-2 (Lauritzen et al. 1999; Kanavaros et al. 2000; Van Spronsen et al. 2000; Vassallo et al. 2003; Kim et al. 2003; Garcia et al. 2003; Kim et al. 2004), Bcl-x (Schlaifer et al. 1996; Chu et al. 1999; Lauritzen et al. 1999; Vassallo et al. 2003; Garcia et al. 2003; Kim et al. 2004), Bax (Brousset et al. 1996; Kanavaros et al. 2000; Vassallo et al. 2003), Bak (Brousset et al. 1999), CD40 ligand (Metkar et al. 2001), Mcl-1 (Vassallo et al. 2003), p53 protein and p53-binding protein MDM2 (Chilosi et al. 1994; Lauritzen et al. 1999), survivin (Garcia et al. 2003), and caspases (Smolewski et al. 2000). Bcl-2 protein reactivity is not usually found in NLPHL (Algara et al. 1991), but is observed in other types of HL to variable degrees (Gupta et al. 1994). Less is so far known about key mechanisms driving para-apoptosis which is an important pathway for the generation of typical mummified cells occurring in HL. A recent study has shown that IGFIR (insulin-like growth factor I receptor), as well as the IGFIR intracytoplasmic domain, induces non-apoptotic programmed cell death characterized by cytoplasmic vacuolation and resistance to apoptosis inhibitors, and this process requires transcription and the de novo synthesis of proteins. IGFIR-induced cell death is mediated by caspase-9 which is, as such, an inducer of apoptosis via cleavage and activation of caspase-3 zymogen and possibly other caspase zymogens, but in para-apoptosis, the caspase-9 effects are different from those in apoptosis owing to the effects of the caspase inhibitors, BAF, p53 protein, and XIAP (Sperandio et al. 2000).

What is the potential role of pro- and antiapoptotic mechanisms in the striking resistance of HL neoplastic cells to apoptosis? Deregulation of some of the factors seems to mediate rescue from apoptosis. There are differences in the expression patterns of Bcl-2 mRNA and Bcl-2 protein (Hell et al. 1995). HL-derived cell lines are resistant to Fas-mediated apoptosis and thus behave differently in comparison with normal germinal center B cells that are eliminated via a Fas pathway. The rescue mechanisms are not yet fully known, but Reed-Sternberg cells, although expressing Fas, exhibit a low frequency of Fas gene mutations, and part of these mutations may impair Fas/CD95 function in apoptotic pathways (Muschen et al. 2000; Maggio et al. 2003). Although expressed in HL cells, Fas does not seem to significantly affect apoptosis in these cells, because an inhibitor protein, cellular FLICE (FADD-like IL-1beta-converting enzyme)-inhibitory protein (c-FLIP), is expressed in the cells as well and protects them from autonomous Fas-mediated death (Dutton et al. 2004; Mathas et al. 2004). Inhibition of Fas-mediated apoptosis in Reed-Sternberg cells also seems to be mediated by constitutional expression of the Fas inhibitor operational in germinal B-cell survival, c-FLIP, in HL cells (Thomas et al. 2002). Furthermore, in regard to caspase effectors of apoptosis, one study did not find significant cytoplasmic staining for caspase-3 and caspase-8 in Reed-Sternberg cells (Xerri et al. 2000), whereas others did (Smolewski et al. 2000). The role of caspase activity in the light of the relative apoptosis resistance of at least some populations of neoplastic cells in HL is complex and is modified by other effectors. Cytochrome c fails to stimulate caspase-9 and

caspase-3 activation in HL-derived B cells, which is due to high level expression of the X-linked inhibitor of apoptosis (XIAP), apoptosis protease-activating factor-1, and caspase-3 being complexed (Kashkar et al. 2003). The expression of CD40 ligand in HL cells has been suggested to rescue these cells from apoptosis (Metkar et al. 2001). Soluble stem cell factor which interacts with the c-kit receptor expressed by Reed-Sternberg cells was able to partially rescue these cells from apoptosis (Aldinucci et al. 2002). On the other hand, some mechanisms seem to promote apoptosis of HL cells and therefore to be involved in pathways leading to mummified cells. Apoptosis of the neoplastic cells in HL is related to the expression of the cdk inhibitor, p27KIP1, suggesting that the p27 and possibly also the p21 pathways are involved in protection from apoptosis in HL (Kolar et al. 2000). The frequent expression in Reed-Sternberg cells of the proapoptotic proteins, Bax (Brousset et al. 1996) and Bak (Brousset et al. 1999), may be an important feature in the pathogenesis of mummified cells.

At least some of these factors seem to be correlated with the biology of disease. For example, a high percentage of Reed-Sternberg cells expressing Bcl-2 protein is associated with treatment failure and subsequent poor survival in young patients with nodular sclerosing HL (Van Spronsen et al. 2000). The simultaneous expression of Bcl-2, Mcl-1, and EBV-associated LMP-1 was shown to significantly and independently be correlated with excellent survival in classical HL (Vassallo et al. 2003). High numbers of active caspase 3-positive Reed-Sternberg cells predict a favorable clinical outcome (Dukers et al. 2002), although the action of caspases in these cell systems is complex, as briefly discussed above.

In contrast to pathogenic pathways promoting apoptosis in neoplastic HL lineages, there are mechanisms prolonging survival of these cells. Telomerase expression and telomere lengthening and inhibition of apoptosis by NF-kappaB expression and inhibitor of NF-kappaB mutations have been suggested to play a role in the possible immortalization of Hodgkin and Reed-Sternberg cells (Emmerich et al. 2003; Zheng et al. 2004). Survival of HL cells is also promoted by a Jagged1-activated Notch1 signaling pathway (Jundt et al. 2002).

Invasion and Spread

It may be anticipated that, similar to other malignant neoplasms, invasion and spread of HL cells markedly depend on cell-to-matrix interactions, all the more so as HL is characterized by a complex mixture of neoplastic cell lineages and nonneoplastic reactive tissues. It is well established that hematologic neoplasms derive from cell systems with an innate capacity of the expression of enzymes acting on the extracellular matrix, particularly metalloproteinases and gelatinases. MMP-9 levels are substantially increased in HL (Thorns et al. 2003; Hazar et al. 2004), and in HL, MMP-9 has been shown to be linked to an adverse prognosis (Kuittinen et al. 2002), similar to NHL (Sakata et al. 2004), suggesting a pathogenic effect promoting tumor cell spread in the matrix. It has been found that proteins associated with EBV (being involved in the development of HL) may affect the expression of metalloproteinase-9. This is of interest insofar as EBV, and specifically its LMP-1, seems to induce other invasion and metastasis factors, such as type IV collagenase, cyclooxygenase-2, and VEGF (Wakisaka and Pagano 2003). In fact, several reports have described an upregulating effect of LMP-1 on the expression of metalloproteinase-9 (Yoshizaki et al. 1998, 1999; Takeshita et al. 1999; Horikawa et al. 2000; Yoshizaki 2002; Wang et al. 2002). However, no correlation between the EBV status in HL and the expression of MMP-9 was found in another investigation (Flavell et al. 2000).

HL tissue also expresses proteins counteracting metalloproteinases, in particular tissue inhibitors of metalloproteinases (TIMPs), similar to NHL (Kuittinen et al. 2003). Expression of TIMP-1 has been detected in Reed-Sternberg cells and found to be an autocrine and paracrine survival factor, but also to be immunodepressant via inhibition of T-cell-mediated cytotoxicity (Oelmann et al. 2002). It has been shown that

the expression of TIMP-1 protein is strongly associated with the nodular sclerosis subtype and the existence of a bulky tumor in HL, while the expression of TIMP-2 is correlated with the occurrence of B symptoms, suggesting that TIMP-1 may promote growth of HL and linked to increased connective tissue turnover, whereas TIMP-2 may correlate with systemic effects of the disease (Pennanen et al. 2004). On the other hand, the expression of MMPs is induced by the extracellular MMP inducer (EMMPRIN). It was found that EMMPRIN and TIMP-1 were co-expressed in two thirds of HL (Thorns et al. 2002, 2003) and the interplay of these two factors may modulate the MMP activity in spread of HL. MMPs are also integrated in a complex network of other proteins, including CD30 that is expressed by a set of HL cells. It has been shown that CD signaling affects lymphoid cell trafficking and homing to lymph nodes (Muta et al. 2000). Furthermore, CD30 affects, via mediation of ICAM-1 upregulation, lymphocyte cluster formation in lymphoid tissues (lymphocyte self-aggregation; Nam et al. 2002). Apart from metalloproteinases, distinct components of the extracellular matrix (ECM) itself and cell surface molecules interacting with the ECM seem to affect the spreading mechanisms of HL cells. Syndecan-1 (CD 138) is a cell surface proteoglycan belonging to the syndecan family of cell surface transmembrane heparan sulfate proteoglycans participating in proliferation, cell migration, and cell-matrix interactions and thus is a multifunctional regulator of cell behavior within the microenvironment of normal cells and several tumors (Dhodapkar and Sanderson 1999; Conejo et al. 2000). Specifically, syndecan-1 has anti-invasive properties dependent on an invasion regulatory domain within the core protein (Langford et al. 2005). The cell-matrix relationship by syndecan-1 is also mediated by its ectodomain regulating alpha(v)beta(3) integrin activity (Beauvais et al. 2004), and shed ecodomains exert a proteolytic activity observed in a wound healing model of mice overexpressing syndecan-1 (Elenius et al. 2004). It is also involved in osteoprotegerin-induced chemotaxis in peripheral blood monocytes. The proteoglycan also makes part of mechanisms controlling vascular development, in that ephrinB2 and EphB4, its cognate receptor, upregulate syndecan-1 in inflammatory angiogenesis (Yuan et al. 2004). Syndecan-1 is associated with post-germinal center and terminal B-cell differentiation and is expressed by Reed-Sternberg cells (Carbone et al. 1997), but only in distinct subtypes of HL: it is not expressed by nodular sclerosis HL, but is, together with Bcl-6, expressed in classical mixed HL (Carbone et al. 1998); furthermore, the syndecan-1+MUM1/IRF4+Bcl-6- phenotype characterized HIV-HL (Carbone et al. 2001). In B-cell NHL, the expression of one of the hyaluronidases, HYAL2, acting on the substrate hyaluronan, was related with tumor aggressiveness (Bertrand et al. 2005), and it may be anticipated that this pathway is also active in the spread of HL.

The spread of HL is, furthermore, affected by the composition and amount of stroma and the local vascular geometry and thus by angiogenesis. The stromal response, which is a dominant feature in the NSHL subtype, is at least in part regulated by TGF-beta that is chiefly expressed in the nodular sclerosis variants (Kadin et al. 1990). It has been documented that vascular endothelial growth factor (VEGF) is expressed in HL (Foss et al. 1997) and specifically by neoplastic Hodgkin/Reed-Sternberg cells in HL but also by nonneoplastic cells (in particular macrophages) located to the stroma (Doussis-Anagnostopoulou et al. 2002)

History of the Hodgkin Disease Concept

Several synonyms of this disease were previously recognized, part of them integrating the observation that the progressive lymph node disorder was not associated with leukemia (lymphogranulomatosis maligna, lymphomatosis granulomatosa, malignant lymphogranuloma, pseudoleukemia, fibromyeloid medullary reticulosis, Paltauf-Sternberg disease, Hodgkin-Paltauf-Sternberg disease, Sternberg disease, Bonfils' disease, Bonfils' syndrome, Hodgkin granuloma, Hodgkin

syndrome, Pel-Ebstein fever, anemia sive cachexia lymphatica, cachexie sans leucémie, adénie, lymphadenoma, lymphome ganglionnaire anémique, progressive multiple lymph node hyperplasia, malignant aleukemic lymphadenoma). This goes back on a series of seminal reports describing the disorder (Hodgkin 1832; Bonfils 1857; Wilks 1865; Greenfield 1876; Pel 1885; Ebstein 1887; Paltauf 1897; Sternberg 1898; Fraenkel and Much 1910b). Thomas Hodgkin (1798–1866) was an English physician and pathologist. In 1825 he was elected member of the Royal College of Physicians in London, was appointed to a position as physician to The London Dispensary (comparable to present emergency unit), and became the curator of the pathology Museum at Guy's Hospital Medical School. Here, he started his career as a leading pathologist of his time and in 1827 became the first reader in England lecturing on pathological anatomy. He discovered the biconcavity of erythrocytes and the cross-striation of skeletal myocytes, but is of course best known for the description of the disease now bearing his name (Hodgkin 1832). At Guy's Hospital in London, Hodgkin was a colleague of Richard Bright and Thomas Addison. Unfortunately for him, he was denied professional advancement, and he later devoted most of his time to issues of social medicine, predominantly the medical problems of the poor and unprivileged, specifically American Indians and natives of black Africa. He was one of the founders of the British and Foreign Aborigines Protection Society, the later British and Foreign Anti-Slavery Society. Up to now, the seven original preparations of Hodgkin lymphogranulomatosis are kept in Guy's Hospital in London. The later analysis of these cases confirmed the diagnosis of the now Hodgkin disease in three of the seven, one designated as "cancer cerebriformis."

Carl Sternberg (Carl von Sternberg; 1872–1935) was working as assistant of pathology in the Viennese Rudolfspital, where he was influenced by professor Richard Paltauf (1858–1924). Several years after the first world war, where he earned great reputation for fighting for soldiers' rights, he became full professor in Vienna in 1926. His main research concerned tuberculosis and leukemia. In 1898, he published his work (in a Journal edited in Prague) on what is now known as Hodgkin disease, but regarded by him as a special form of tuberculosis ("*eigenartige Tuberkulose des lymphatischen Apparates*"), and described one of the cellular hallmarks of this disease (review: Sternberg 1936). HL, early thought to be a variant of tuberculosis, was then named, Sternberg disease or Paltauf-Sternberg lymphogranuloma, until Pappenheim coined the term lymphogranulomatosis.

Although Hodgkin and Sternberg are in the center of the recognition of the disease in question, others have contributed much to our understanding of Hodgkin disease. Another British physician, Samuel Wilks, independently described the same disease and with greater precision (Wilks 1856). But he recognized Hodgkin's priority and named the disease for Hodgkin in an article in Guy's Hospital Reports entitled "Cases of enlargement of the lymphatic glands and spleen (or, Hodgkin's disease) with remarks" (Wilks 1865). There is some evidence that a disease possibly representing Hodgkin disease was already described by Malpighi and Morgagni (in Birch-Hirschfeld 1878). Marcello Malpighi (1628–1694) is said to have described lesions corresponding to Hodgkin disease in 1666 (Malpighi 1666). Giovanni Battista Morgagni (1682–1771) presents a description of a disorder likely to be Hodgkin disease in his famous work entitled *De Sedibus et Causis Morborum per Anatomen Indagatis* (On the seats and causes of diseases investigated by anatomy) (Morgagni 1761). The view of Sternberg that HL may represent a unique form of tuberculosis was put into question several years after his descriptions only. Chiari had observed in several patients that the "granulomatous disease" can progress into a sarcomatous growth, with diffuse infiltration of organs adjacent to the lymph nodes initially involved, and already remarked that, in this situation, the cellularity of the lesions may increase (cited in Dietrich 1908), and these observations were confirmed later, leading to the term "granuloma-like sarcoma of lymph nodes" (Dietrich 1908).

An interesting history also relates to the giant cell that is such a typical feature of Hodgkin disease (the Reed-Sternberg cell). These characteristic giant and/or multinuclear cells were already registered by early authors (v. Hüttenbrenner 1871; Langhans 1872; Greenfield 1878; Dreschfeld 1891; Hübener 1893; Gilbert and Weil 1900; Dietrich 1908). Langhans, in his description of what was then termed "hard lymphosarcoma" (i.e., sclerosing forms of Hodgkin disease), noted scattered large cells with 2 or 3, and sometimes many more, nuclei of irregular shape ("*Hie und da finden sich zerstreut grössere dunkelkörnige Zellen, etwa von der Grösse der Schleimkörper, mit 2, 3 auch mehr Kernen, und ferner wahre Riesenzellen, grosse Haufen von dunkelkörniger Zellsubstanz mit 10, 20 Kernen, von länglich unregelmässiger Gesta*lt"). These cells do not represent the reactive multinuclear giant cells also detected by Langhans, but in fact a first description of the later Reed-Sternberg cell (Langhans 1872). Langhans refers, in his work, to a similar observation by v. Hüttenbrenner (1871), who described "multinuclear protoplasmic masses (giant cells)" and "*myeloplaques à plusieurs noyaux*." The striking giant cells were reported again in 1878 (Greenfield 1878). In his autopsy study on HL patients, Greenfield described the cells observed in enlarged lymph nodes as follows: "There were a large number of multinucleated cells adherent to the trabeculae, well seen on washing away the lymph cells. These multinucleated cells, containing from 4 to 8 or 12 nuclei, were often collected in clusters in the parts of the gland especially where the fibrous change was progressing" (Greenfield 1878). In his Fig. 2 (a drawing by the author), the typical large nuclei with the characteristic prominent nucleolus are nicely depicted. It is seen that this author already recognized that the cells in question occur in clusters, what is typical for certain variants of HL. Hübener described, based on the autopsy of a 5-year-old girl with typical HL, large cells in involved lymph nodes, characterized by the presence of two or more nuclei (Hübener 1893). The detailed description of the characteristic cells occurring in HL was performed by Sternberg (Sternberg 1898). Four years later appeared the work of Dorothy Reed Mendenhall (1874–1964) who not only produced more relevant information on the unique cells types but also separated Hodgkin disease from tuberculosis (Reed 1902). The so-called lacunar Reed-Sternberg cells chiefly observed in the nodular sclerosis variant of HL and characterized by cytoplasmic retraction in formalin-fixed samples have probably first been described in 1900 (Gilbert and Weil 1900; "*la très grosse majorité (des cellules) sont constituées par un gros noyau arrondi ou ovalaire, très clair, vésiculeux, que l'hématéine teinte à peine en violet clair et qui présente un ou deux nucléoles; on ne constate presque pas de protoplasme autour de ce noyau*"; the large majority of the cells exhibit a large, roundish, or ovoid nucleus, very clear, vesicular, that the hematein hardly stains violet, and that show one or two nucleoli; one detects almost no cytoplasm around these nuclei). A further characteristic feature in HL is the presence of a distinct type of Hodgkin cell apoptosis, resulting in so-called mummified cells (see below). It seems that this feature was first recognized in 1910 already. In an autopsy case of HL ("Sternberg's so-called peculiar tuberculosis of the lymphatic system") Graetz found large and giant cells in the bone marrow (with indented, reniform, or lobulated nuclei), part of these cells showing "marked pycnosis or other signs indicating cell decay" (Graetz 1910).

References

Abe H, Kubota K, Makuuchi M (1997) Obstructive jaundice secondary to Hodgkin's disease. Am J Gastroenterol 92:526–527

Abrams J, Pearl P, Moody M, Schimpff SC (1988) Epithelioid granulomas revisited: long-term follow-up in Hodgkin's disease. Am J Clin Oncol 11:456–460

Abt AB, Kirschner RH, Belliveau RE, O'Connell MJ, Sklandky BD, Greene WH, Wiernik PH (1974) Hepatic pathology associated with Hodgkin's disease. Cancer 33:1564–1571

Ackerman LV, del Regato JA (1954) Cancer: diagnosis, treatment and prognosis, 2nd edn. Mosby, St. Louis

Aderka D, Kraus M, Avidor I, Sidi Y, Weinberger A, Pinkhas J (1984) Hodgkin's and non-Hodgkin's lymphomas masquerading as "idiopathic" liver granulomas. Am J Gastroenterol 79:642–644

Aisenberg AC (1971) Letter. Ann Intern Med 75:322
Aldinucci et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/12199785
Aleem A, Al-Katari M, Alsaleh K, AlSwat K, Al-Sheikh A (2013) Vanishing bile duct syndrome in a Hodgkin's lymphoma patient with fatal outcome despite lymphoma remission. Saudi J Gastroenterol 19:286–289
Algara et al (1991) http://www.ncbi.nlm.nih.gov/pubmed/1916688
Allory Y, Metreau J, Zafrani E (2000) Paraneoplastic vanishing bile duct syndrome in a case of Hodgkin's disease (in French). Ann Pathol 20:52–55
Ansell SM (2014) Hodgkin lymphoma: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol 89:771–779
Arai N, Hara A, Umeda M, Sirai T (1992) Hodgkin's disease presenting with fever of unknown origin associated with granulomas of the bone marrow (in Japanese). Rinsho Ketsueki 33:1252–1256
Asher E, Payne CM, Bernstein C (1995) Evaluation of cell death in EBV-transformed lymphocytes using agarose gel electrophoresis, light microscopy and electron microscopy. II. Induction of non-classic apoptosis ("para-apoptosis") by tritiated thymidine. Leuk Lymphoma 19:107–119
Atwood WG, Miller RC, Nelson CT (1966) Sarcoidosis and the malignant lymphoreticular diseases. Arch Dermatol 94:144–151
Bagley CM, Roth JA, Thomas LB, Devita VT (1972) Liver biopsy in Hodgkin's disease. Clinicopathologic correlations in 127 patients. Ann Intern Med 76:219–225
Bagley CM, Thomas LB, Johnson RE, Chretien PB, de Vita VT (1973) Diagnosis of liver involvement by lymphoma: results in 96 consecutive peritoneoscopies. Cancer 31:840–847
Bain BJ, Chong KC, Coghlan SJ, Roberts SJ (1982) Hepatic sinusoidal ectasia in association with Hodgkin's disease. Postgrad Med J 58:182–184
Baker C, Mann WN (1939) Hodgkin's disease. A study of 65 cases. Guy's Hosp Rep 89:83–107
Ballonoff A, Kavanagh B, Nash R, Drabkin H, Trotter J, Costa L, Rabinovirch R (2008) Hodgkin lymphoma-related vanishing bile duct syndrome and idiopathic cholestasis: statistical analysis of all published cases and literature review. Acta Oncol 47:962–970
Barge J, Potet F (1971) Anatomopathological study of the liver in Hodgkin's disease (in French). Presse Med 79:565–568
Barié E (1875) Lymphadénie sans leucémie; hypertrophie généralisée des ganglions lymphatiques, tumeurs lymphoides du foie, de la rate, des reins, du coeur, de la peau, etc. Bull Soc Anat (Paris) 50(3 ser):711–719
Barron M (1926) Two rare cases of Hodgkin's disease: (a) chronic relapsing fever of Pel-Ebstein type; (b) Hodgkin's disease with extensive cutaneous manifestations. Arch Pathol (Chicago) 2:616
Barros MH, Hassan R, Niedobitek G (2012) Tumor-associated macrophages in pediatric classical Hodgkin lymphoma: association with Epstein-Barr virus, lymphocyte subsets, and prognostic impact. Clin Cancer Res 18:3762–3771
Baumforth KR, Birgersdotter A, Reynolds GM, Wei W, Kapatai G, Flavell JR, Kalk E, Piper K et al (2008) Expression of the Epstein-Barr virus-encoded Epstein-Barr virus nuclear antigen 1 in Hodgkin's lymphoma cells mediates up-regulation of CCL20 and the migration of regulatory T cells. Am J Pathol 173:195–204
Beatty (1954) http://www.ncbi.nlm.nih.gov/pubmed/113150006
Beauvais DM, Burbach BJ, Rapraeger AC (2004) The syndecan-1 ectodomain regulates alphavbeta3 integrin activity in human mammary carcinoma cells. J Cell Biol 167:171–181
Benharroch D, Prinsloo I, Goldstein J, Brousset P, Kachko L, Gopas J (1996) A comparison of distinct modes of tumor cell death in Hodgkin's disease using morphology and in situ DNA fragmentation. Ultrastruct Pathol 20:497–505
Benharroch D, Brousset P, Goldstein J, Gopas J (1998) Mummified Hodgkin cells and apoptosis. J Pathol 185:116
Bertrand P, Courel MN, Maingonnat C, Jardin F, Tilly H, Bastard C (2005) Expression of HYAL2 mRNA, hyaluronan and hyaluronidase in B-cell non-Hodgkin lymphoma: relationship with tumor aggressiveness. Int J Cancer 113:207–212. 8
Bhaskar KV, Joshi K, Banerjee CK, Rao RK, Verma SC (1990) Peliosis hepatis in Hodgkin's disease: an infrequent association. Am J Gastroenterol 85:628–629
Biemer JJ (1984) Hepatic manifestations of lymphomas. Ann Clin Lab Sci 14:252–260
Birch-Hirschfeld FV (1878) Leukämie und Pseudoleukämie, Hodgkinsche Krankheit. in: Gerhardts Handbuch der Kinderkrankheiten, Band 3, pp 301, 339
Birrer MJ, Young RC (1987) Differential diagnosis of jaundice in lymphoma patients. Semin Liver Dis 7:269–277
Bodis S, Kraus MD, Pinkus G, Silver B, Kadin ME, Canellos GP, Shulman LN, Tarbell NJ, Mauch PM (1997) Clinical presentation and outcome in lymphocyte-predominant Hodgkin's disease. J Clin Oncol 15:3060–3066
Bohle V, Döring C, Hansmann ML, Küppers R (2013) Role of early B-cell factor 1 (EBF1) in Hodgkin lymphoma. Leukemia 27:671–679
Bombara R, Cassi E, Pagliano F, Visca U (1970) On jaundice during hemoblastosis. Hodgkin's granuloma (in Italian). Minerva Med 61:4600–4660
Bonfils EA (1857) Quelques réflexions sur un cas d'hypertrophie ganglionaire générale: avec fistules lymphatiques et avec cachexie, sans leucémie. Clermont
Bouroncle BA, Old JW, Vazques AG (1962) Pathogenesis of jaundice in Hodgkin's disease. AMA Arch Intern Med 110:872–883
Brauneck H (1889) Ueber einen Fall von multipler Lymphombildung (Hodgkin'scher Krankheit), welcher unter hohem Fieber, Icterus und Nephritis zum Tode führte. Dtsch Arch Klin Med 44:297–310

Brecher, Banks (1990) http://www.ncbi.nlm.nih.gov/pubmed/1689938

Brincker H (1970) Epithelioid-cell granulomas in Hodgkin's disease. Acta Pathol Microbiol Scand A 78:19–32

Brinckmeyer LM, Skovsgaard T, Thiede T, Vesterager L, Nissen NI (1982) The liver in Hodgkin's disease – I. Clinico-pathological relations. Eur J Cancer Clin Oncol 18:421–428

Brooks JJ (1982) Granulomas in Hodgkin's disease. Hum Pathol 13:87

Brousset P, Benharroch D, Krajewski S, Laurent G, Meggetto F, Rigal-Huguet F, Gopas J, Prinsloo I et al (1996) Frequent expression of the cell death-inducing gene Bax in Reed-Sternberg cells of Hodgkin's disease. Blood 87:2470–2475

Brousset P, Krajewski S, Schlaifer D, Reed JC, Delsol G (1999) Detection of the cell death-inducing protein BAK in Reed-Sternberg cells of Hodgkin's disease. Leuk Lymphoma 34:581–584

Brown R, Gillett R, Stansfeld A, Irving M (1981) The timing of liver biopsy during staging laparotomy for Hodgkin's disease. Clin Oncol 7:99–103

Bruguera M, Aranguibel F, Ros E, Rodes J (1978) Incidence and clinical significance of sinusoidal dilatation in liver biopsies. Gastroenterology 75:474–478

Bruguera M, Caballero T, Carreras E, Aymerich M, Rodes J, Rozman C (1987) Hepatic sinusoidal dilatation in Hodgkin's disease. Liver 7:76–80

Burnam CF (1926) Hodgkin's disease, with especial reference to its treatment by irradiation. J Am Med Assoc 87:1445–1452

Callender GR (1930) The lymphatic tumor registry report. Am J Pathol 5:519

Carbone A, Gloghini A, Gattei V, Degan M, Improta S, Aldinucci D, Canzonieri V, Perin T, Volpe R et al (1997) Reed-Sternberg cells of classical Hodgkin's disease react with the plasma cell-specific monoclonal antibody B-B4 and express human syndecan-1. Blood 89:3787–3794

Carbone A, Gloghini A, Gaidano G, Franceschi S, Capello D, Drexler HG, Falini B, Dalla-Favera R (1998) Expression status of BCL-6 and syndecan-1 identifies distinct histogenetic subtypes of Hodgkin's disease. Blood 92:2220–2228

Carbone A, Gloghini A, Larocca LM, Capello D, Pierconti F, Canzonieri V, Tirelli U, Dalla-Favera R, Gaidano G (2001) Expression profile of MUM1/IRF4, BCL-6, and CD138/syndecan-1 defines novel histogenetic subsets of human immunodeficiency virus-related lymphomas. Blood 97:744–751

Carbone A, Spina M, Gloghini A, Ponzoni M, Doglioni C, Tirelli U (2013) Nodular lymphocytic predominant Hodgkin lymphoma with non-invasive or early invasive growth pattern suggests an early step of the disease with a highly favorable outcome. Am J Hematol 88:161–162

Carde P (2003) Staging Hodgkin's lymphoma: why and how? Haematologica 88:1176–1181

Casirola G, Dionigi R (1966) Jaundice in malignant granuloma. Clinical and statistic studies and etiopathogenic remarks (in Italian). Haematologica 51:817–835

Cavalli G, Casali AM, Lambertini F, Busachi C (1979) Changes in the small biliary passages in the hepatic localization of Hodgkin's disease. Virchows Arch A Pathol Anat Histol 384:295–306

Cavalli P, Cazzola M, Gobbi PG, Gorini M, Malfitano A, Riccardi A, Ascari E (1981) Reed-Sternberg cell leukaemia. Tumori 67:63–70

Cervantes F, Briones J, Bruguera M, Font C, Grau JM, Rozman C, Montserrat E (1996) Hodgkin's disease presenting as a cholestatic febrile illness: incidence and main characteristics in a series of 421 patients. Ann Hematol 72:357–360

Chang KL, Kamel OW, Arber DA, Horyd ID, Weiss LM (1995) pathologic features of nodular lymphocytes predominance Hodgkin's disease in extranodal sites. Am J Surg Pathol 19:1313–1324

Chaudhari D, Khan S, Saleem A, Taylor T, Teddy T, Reddy C, Borthwick T, Young M (2013) Obstructive jaundice as an initial manifestation of non-Hodgkin lymphoma: treatment dilemma and high mortality. Case Rep Med 2013:259642

Cherqui D, Palazzo L, Piedbois P, Charlotte F, Duvoux C, Duron JJ, Fagniez PL, Valla D (1994) Common bile duct stricture as a late complication of upper abdominal radiotherapy. J Hepatol 20:693–697

Chevallier P, Bernard J (1932) La maladie de Hodgkin. Masson, Paris

Chilosi M, Doglioni C, Menestrina F, Montagna L, Rigo A, Lestani M, Barbareschi M, Scarpa A et al (1994) Abnormal expression of the p53-binding protein MDM2 in Hodgkin's disease. Blood 84:4295–4300

Chim et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/11042525

Chopra R, Rana R, Zachariah A, Mahajan MK, Prabhakar BR (1995) Epithelioid granulomas in Hodgkin's disease – prognostic significance. Indian J Pathol Microbiol 38:427–433

Chu WS, Aguilera NS, Wei MQ, Abbondanzo SL (1999) Antiapoptotic marker Bcl-X (L), expression on Reed-Sternberg cells of Hodgkin's disease using a novel monoclonal marker, YTH-2H12. Hum Pathol 30:1065–1070

Colby TV, Hoppe RT, Warnke RA (1981) Hodgkin's disease at autopsy: 1972–1977. Cancer 47:1852–1862

Conejo JR, Kleeff J, Koliopanos A, Matsuda K, Zhu ZW, Goecke H, Bicheng N, Zimmermann A et al (2000) Syndecan-1 expression is up-regulated in pancreatic but not in other gastrointestinal cancers. Int J Cancer 88:12–20

Coronini C (1928) Ueber das Paltauf-Sternberg'sche Lymphogranulom, mit besonderer Berücksichtigung der veränderungen des verdauungsschlauches und solcher an der Leberpforte mit und ohne Gelbsucht. Zugleich ein Beitrag über lymphogranulomatöse Gefässveränderungen. Beitr Pathol Anat 80:405–478

Cowan R, Trounce JR (1973) Hodgkin's disease and the liver. Guys Hosp Rep 122:221–230
Cozen W, Timofeeva MN, Li D, Diepstra A, Hazelett D, Delahaye-Sourdeix M, Edlund CK et al (2014) A meta-analysis of Hodgkin lymphoma reveals 19p13.3 TCF3 as a novel susceptibility locus. Nat Commun 5:3856
Crosbie OM, Crown JP, Nolan NP, Murray R, Hegarty JE (1997) Resolution of paraneoplastic bile duct paucity following successful treatment of Hodgkin's disease. Hepatology 26:5–8
Cross JM (1969) Hodgkin's disease: histological classification and diagnosis. J Clin Pathol 22:165–182
Davey FR, Doyle WF (1973) Hepatic alterations in Hodgkin's disease. N Y State J Med 73:1981–1986
De Medeiros BC, Lacerda MA, Telles JE, da Silva JA, de Medeiros CR (1998) Cholestasis secondary to Hodgkin's disease: report of 2 cases of vanishing bile duct syndrome. Haematologica 83:1038–1040
Degott C, Potet F (1984) Peliosis hepatis and sinusoidal dilatation. Arch Anat Cytol Pathol 32:296–300
Dhodapkar MV, Sanderson RD (1999) Syndecan-1 (CD138) in myeloma and lymphoid malignancies: a multifunctional regulator of cell behavior within the tumor microenvironment. Leuk Lymphoma 34:35–43
Dich NH, Goodman ZD, Klein MA (1989) Hepatic involvement in Hodgkin's disease. Clues to histologic diagnosis. Cancer 64:2121–2126
Diebold J, Temmim L (1980) Anatomo-pathologic study of biopsies taken in 250 exploratory laparotomies for Hodgkin's disease (in French). Ann Anat Pathol (Paris) 25:341–352
Diehl V, Sextro M, Franklin J, Hansmann ML, Harris N, Jaffe E, Poppema S, Harris M, Franssila K et al (1999) Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on lymphocyte-predominant Hodgkin's disease. J Clin Oncol 17:776–783
Diessner GR, Heck FJ (1958) Intermittent obstructive jaundice in Hodgkin's disease: report of a case. J Lancet 78:99–102
Dietrich D (1908) Ueber granulomartiges Sarkom der Lymphdrüsen. Deut Med Wochenschr 27:1188–1189
Dourakis SP, Tzemanakis E, Deutsch M, Kafiri G, Hadziyannis SJ (1999) Fulminant hepatic failure as a presenting paraneoplastic manifestation of Hodgkin's disease. Eur J Gastroenterol Hepatol 11:1055–1058
Doussis-Anagnostopoulou IA, Talks KL, Turley H, Debnam P, Tan DC, Mariatos G, Gorgoulis V, Kittas C, Gatter KC (2002) Vascular endothelial growth factor (VEGF) is expressed by neoplastic Hodgkin-Reed-Sternberg cells in Hodgkin's disease. J Pathol 197:677–683
Dreschfeld J (1891) Ein Beitrag zur Lehre von den Lymphosarkomen. Dtsch Med Wochenschr 42:1175–1177
Dukers DF, Meijer CJ, ten Berge RL, Vos W, Ossenkoppele GJ, Oudejans JJ (2002) High numbers of active caspase 3-positive Reed-Sternberg cells in pretreatment biopsy specimens of patients with Hodgkin disease predict favorable clinical outcome. Blood 100:36–42
Dutton A, O'Neil JD, Milner AE, Reynolds GM, Starvzynski J, Crocker J, Young LS, Murray PG (2004) Expression of the cellular FLICE-inhibitory protein (c-FLIP) protects Hodgkin's lymphoma cells from autonomous Fas-mediated death. Proc Natl Acad Sci U S A 101:6611–6616
Ebstein W (1887) Das chronische Rückfallsfieber, eine neue Infektionskrankheit. Berl Klin Wochenschr 24:565–568
Elenius V, Gotte M, Reizes O, Elenius K, Bernfield M (2004) Inhibition of the soluble syndecan-1 ectodomains delays wound repair in mice overexpressing syndecan-1. J Biol Chem 279:41928–41935
Emmerich F, Theurich S, Hummel M, Haeffker A, Vry MS, Dohner K, Bommert K, Stein H, Dorken B (2003) Inactivating I kappa B epsilon mutations in Hodgkin/Reed-Sternberg cells. J Pathol 201:413–420
Fabian E (1911) Die Lymphogranulomatosis (Paltauf-Sternberg). Zbl f Allg Pathol Pathol Anat 22:145–186
Farrer-Brown G, Bennett MH, Harrison CV, Millett Y, Jelliffe AM (1971) The pathological findings following laparotomy in Hodgkin's disease. Br J Cancer 25:449–457
Favre M, Croizat A (1933) L'sadénie éosinophilique prurigène. Ann Dermat Syph 7:1918–1991
Fialk MA, Jarowski CI, Coleman M, Mouradian J (1979) Hepatic Hodgkin's disease without involvement of the spleen. Cancer 43:1146–1147
Flavell JR, Baumforth KR, Williams DM, Lukesova M, Madarova J, Noskova V, Prochazkova J et al (2000) Expression of the matrix metalloproteinase 9 in Hodgkin's disease is independent of EBV status. Mol Pathol 53:145–149
Flavell JR, Baumforth KR, Wood VH, Davies GL, Wei W, Reynolds GM, Morgan S, Boyce A et al (2008) Down-regulation of the TGF-beta target gene, PTPRK by the Epstein-Barr virus encoded EBNA1 contributes to the growth and survival of Hodgkin lymphoma cells. Blood 111:292–301
Foramiti S, Biondini E, Bigolin T, Pasca S, Rossi P (2011) Vanishing bile duct syndrome in non-Hodgkin lymphoma: a case report. Minerva Med 102:345–349
Foss HD, Araujo I, Demel G, Klotzbach H, Hummel M, Stein H (1997) Expression of vascular endothelial growth factor in lymphomas and Castleman's disease. J Pathol 183:44–50
Foucar, Rydell (1980) http://www.ncbi.nlm.nih.gov/pubmed/6770990
Foulon P (1932) A propos de quelques lésions extra-ganglionnaires de la lymphogranulomatöse. Ann Anat Path 9:725–744
Fox H (1936) Remarks on microscopical preparations made from some of the original tissue described by Thomas Hodgkin, 1832. Guy's Hosp Rep 86:11–16

Fraenkel E, Much H (1910a) Ueber die Hodgkin sche Krankheit [Lymphomatosis granulomatosa], insbesondere deren Aetiologie. Zschr Hyg Inf Krankh 67:160–199

Fraenkel E, Much H (1910b) Bemerkungen zur Aetiologie der Hodgkinschen Krankheit und der Leukaemia lymphatica. Münch Med Woschenschr 57:685–687

Fraga M, Sanchez-Verde L, Forteza J, Garcia—Rivero A, Piris MA (2002) T-cell/histiocyte-rich large-B-cell lymphoma is a disseminated aggressive neoplasm: differential diagnosis from Hodgkin's lymphoma. Histopathology 41:216–229

Garcia JF, Camacho FI, Morente M, Fraga M, Montalban C, Alvaro T, Bellas C, Castano A et al (2003) Hodgkin and Reed-Sternberg cells harbor alterations in the major tumor suppressor pathways and cell-cycle checkpoints: analyses using tissue microarrays. Blood 101:681–689

Gascard E, Ferrara A, Bizzari A (1970) Hepatic localization of Hodgkin's disease (apropos of a case simulating amebic abscess of the liver) (in French). Mars Med 107:605–615

Gilbert A, Weil E (1900) De la tuberculisation secondaire des ganglions néoplasiques. Arch Med Exp 12:257–268

Givler RL, Brunk SF, Hass CA, Gulesserian HP (1971) Problems of interpretation of liver biopsy in Hodgkin's disease. Cancer 28:1335–1342

Glatstein E, Guernsey JM, Rosenberg SA, Kaplan HS (1969) The value of laparotomy and splenectomy in the staging of Hodgkin's disease. Cancer 24:709–718

Glatstein E, Trueblood HW, Enright LP, Rosenberg SA, Kaplan HS (1970) Surgical staging of abdominal involved in unselected patients with Hodgkin's disease. Radiology 97:425–432

Gobbi PG, Ferreri AJ, Ponzoni M, Levis A (2013) Hodgkin lymphoma. Crit Rev Oncol Hematol 85:216–237

Goia I (1935) Contributions à la forme hépatique de la lymphogranulomatose maligne. Sang 9:367–374

Goldman LB (1940) Hodgkin's disease; an analysis of 212 cases. J Am Med Assoc 114:1611–1616

Goldman RL (1970) Granulomas in Hodgkin's disease. N Engl J Med 283:1410

Gordon CD, Sidawy MK, Talarico L, Kondi E (1984) Hodgkin's disease in the liver without splenic involvement. Arch Intern Med 144:2277–2278

Gota VS, Purandare NC, Gujral S, Shah S, Nair R, Rangarajan V (2009) Positron emission tomography/computerized tomography evaluation of primary Hodgkin's disease of liver. Indian J Cancer 46:237–239

Gottrand F, Cullu F, Mazingue F, Nelken B, Lecomte-Houcke M, Farriaux JP (1997) Intrahepatic cholestasis related to vanishing bile duct syndrome in Hodgkin's disease. J Pediatr Gastroenterol Nutr 24:430–433

Graetz F (1910) Fur Kenntnis von Sternbergs sog. "eigenartiger Tuberkulose des lymphatischen Apparates. Beitr z Klin Tuberk 15:110–132

Greenfield WS (1876) A case of lymphadenoma with tumours in the skin. Lancet 1:740

Greenfield WS (1878) Specimens illustrative of the pathology of lymphadenoma and leukocythaemia. Trans Pathol Soc London 29:272–304

Grieco MB, Cady B (1980) Staging laparotomy in Hodgkin's disease. Surg Clin North Am 60:369–379

Gruber GB (1930) Spezielle Infektionsfolgen der Leber. IX. Lymphogranulomatose. In: Henke F, Lubarsch O (eds) Handbuch der speziellen pathologischen Anatomie, vol 5, Part I. Springer, Berlin, pp 604–615

Gruss HJ, Herrmann F (1996) CD30 ligand, a member of the TNF ligand superfamily, with growth and activation control CD30+ lymphoid and lymphoma cells. Leuk Lymphoma 20:397–409

Guemes Diaz F (1965) Hepatic lymphogranuloma (in Spanish). Rev Esp Enferm Apar Dig 24:1210–1218

Guidoboni M, Ponzoni M, Caggiari L, Lettini AA, Vago L, De Re V, Gloghini A, Zancai P, Carbone A, Boiocchi M, Dolcetti R (2005) Latent membrane protein 1 deletion mutants accumulate in Reed-Sternberg cells of human immunodeficiency virus-related Hodgkin's lymphomas. J Virol 79:2643–2649

Guliter S, Erdem O, Isik M, Yamac K, Uluoglu O (2004) Cholestatic liver disease with ductopenia (vanishing bile duct syndrome) in Hodgkin's disease: report of a case. Tumori 90:517–520

Gunasekaran TS, Hassall E, Dimmick JE, Chan KW (1992) Hodgkin's disease presenting with fulminant liver disease. J Pediatr Gastroenterol Nutr 15:189–193

Gupta RK, Lister TA, Bodmer JG (1994) The t(14;18) chromosomal translocation and Bcl-2 protein expression in Hodgkin's disease. Leukemia 8:1337–1341

Gupta RK, Gospodarowicz MK, Lister TA (1999) Clinical evaluation and staging of Hodgkin's disease. In: Mauch PM, Armitage JO, Diehl V, Hoppe RT, Weiss LM (eds) Hodgkin's disease, 2nd edn. Lippincott Williams and Wilkins, Philadelphia, pp 223–240

Gupta A, Roebuck DJ, Michalski AJ (2002) Biliary involvement in Hodgkin's disease. Pediatr Radiol 32:202–204

Hansen HP, Matthey B, Barth S, Kisseleva T, Mokros T, Davies SJ, Beckett RP, Foelster-Holst R, Lange HH, Engert A, Lemke H (2002) Inhibition of metalloproteinases enhances the internalization of anti-CD30 antibody Ki-3 and the cytotoxic activity of Ki-3 immunotoxin. Int J Cancer 98:210–215

Hansen HP, Recke A, Reineke U, Von Tresckow B, Borchmann P, Von Strandmann EP, Lange H, Lemke H, Engert A (2004) The ectodomain shedding of CD30 is specifically regulated by peptide motifs in its cysteine-rich domains 2 and 5. FASEB J 18:893–895

Hansmann ML, Zwingers T, Boske A, Loffler H, Lennert K (1984) Clinical features of nodular paragranuloma (Hodgkin's disease, lymphocyte predominance type, nodular). J Cancer Res Clin Oncol 108:321–330

Harrison CV (1952) Benign Hodgkin's disease (Hodgkin's paragranuloma). J Pathol Bacteriol 64:513–518

Hartfall SJ (1932) Hodgkins disease of the lung. Guy's Hosp Rep 82:55–74
Hartmann S, Döring C, Jakobus C, Rengstl B, Newrzela S, Tousseyn T, Sagaert X, Ponzoni M et al (2013) Nodular lymphocyte predominant Hodgkin lymphoma and T cell/histiocyte rich large B cell lymphoma – endpoints of a spectrum of one disease? PLoS One 8:e78812
Hauck K (1918) Ein Beitrag zur Kenntnis der Lymphogranulomatose. Zbl f Allg Pathol Pathol Anat 29:225–232
Hayhoe FG, Burns GF, Cawley JC, Stewart JW (1978) Cytochemical, ultrastructural and immunological studies of circulating Reed-Sternberg cells. Br J Haematol 38:485–490
Hazar B, Polat G, Seyrek E, Bagdatoglglu O, Kanik A, Tiftik N (2004) Prognostic value of matrix metalloproteinases (MMP-2 and MMP-9) in Hodgkin's and non-Hodgkin's lymphoma. Int J Clin Pract 58:139–143
Hell K, Lorenzen J, Fischer R, Hansmann ML (1995) Hodgkin cells accumulate mRNA for bcl-2. Lab Invest 73:492–496
Hellman S (1974) Current studies in Hodgkin's disease. N Engl J Med 290:894–898
Hjalgrim H (2012) On the aetiology of Hodgkin lymphoma. Dan Med J 59:B4485
Hjalgrim H, Askling J, Rostgaard K, Hamilton-Dutoit S, Frisch M, Zhang JS, Madsen M, Rosdahl N et al (2003) Characteristics of Hodgkin's lymphoma after infectious mononucleosis. N Engl J Med 349:1324–1332
Hodgkin T (1832) On some morbid appearances of the absorbent glands and spleen. Medico-Chir Trans (London) 17:68–114 (reprint: Med Classics 1:741–770, 1937)
Hong FS, Smith CL, Angus PW, Crowley P, Ho WK (2010) Hodgkin lymphoma and fulminant hepatic failure. Leuk Lymphoma 51:947–951
Hood IM, Mahendra P, McNeil K, Marcus RE (1996) Hodgkin's disease after cardiac transplant: a report of two cases. Clin Lab Haematol 18:115–116
Horikawa T, Yoshizaki T, Sheen TS, Lee SY, Furukawa M (2000) Association of latent membrane protein 1 and matrix metalloproteinase 9 with metastasis in nasopharyngeal carcinoma. Cancer 89:715–723
Houwerzijl EJ, Blom NR, van der Want JJ, Esselink MT, Koornstra JJ, Smit JW, Louwes H et al (2004) Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. Blood 103:500–506
Hsu PL, Hsu SM (2000) Autocrine growth regulation of CD30 ligand in CD30-expressing Reed-Sternberg cells: distinction between Hodgkin's disease and anaplastic large cell lymphoma. Lab Invest 80:1111–1119
Hübener M (1893) Ein Fall von malignem Lymphom. Dtsch Zschr f Chir 37:368–372
Hubscher SG, Lumley MA, Elias E (1993) Vanishing bile duct syndrome: a possible mechanism for intrahepatic cholestasis in Hodgkin's lymphoma. Hepatology 17:70–77
Iwai M, Muramatsu A, Tanaka S, Morikawa T, Mori T, Harada Y, Okanoue T, Horishi M, Suyama Y, Kashima K (2002) Macroscopic and microscopic findings of livers in malignant hepatologic disorders, biopsied under peritoneoscopy. J Clin Gastroenterol 35:262–265
Jackson H, Parker F (1944a) Hodgkin's disease; I, general considerations. N Engl J Med 230:1–8
Jackson H, Parker F (1944b) Hodgkin's disease. II. Pathology. N Engl J Med 231:35–44
Jackson H, Parker F (1947) Hodgkin's disease and allied disorders. Oxford University Press, New York
Jaffe ES (1987) Malignant lymphomas: pathology of hepatic involvement. Semin Liver Dis 7:257–268
Jaffe ES, Harris NL, Stein H, Vardiman JW (2001) Pathology and genetics of tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours. IARC Press, Lyon
Jansen PL, van der Lelie H (1994) Intrahepatic cholestasis and biliary cirrhosis associated with extrahepatic Hodgkin's disease. Neth J Med 44:99–102
Jeanselme E, Marchal G (1926) Commentaires sur un cas de maladie de Hodgkin à évolution aigue. Ann Med 20:1–26
Johnson et al (1990) http://www.ncbi.nlm.nih.gov/pubmed/2227301
Jundt F, Anagnostopoulos I, Forster R, Mathas S, Stein H, Dorken B (2002) Activated Notch1 signaling promotes tumor cell proliferation and survival in Hodgkin and anaplastic large cell lymphoma. Blood 99:3398–3403
Juniper K (1963) Prolonged severe obstructive jaundice in Hodgkin's disease. Gastroenterology 44:199–204
Justin-Besançon L, Laroche C, Nenna A, Etienne JP (1963) Jaundice caused by choledochal obstruction in Hodgkin's disease. Surgical by-pass (in French). Sem Hop 39:2571–2574
Kadin ME, Donaldson SS, Dorfman RF (1970) Isolated granulomas in Hodgkin's disease. N Engl J Med 283:859–861
Kadin ME, Glatstein E, Dorfman RF (1971) Clinicopathologic studies of 117 untreated patients subjected to laparotomy for the staging of Hodgkin's disease. Cancer 27:1277–1294
Kadin ME, Agnarsson BA, Ellingsworth LR, Newcom SR (1990) Immunohistochemical evidence of a role for transforming growth factor beta in the pathogenesis of nodular sclerosing Hodgkin's disease. Am J Pathol 136:1209–1214
Kakar S, Kamath PS, Burgart LJ (2004) Sinusoidal dilatation and congestion in liver biopsy: is it always due to venous outflow impairment ? Arch Pathol Lab Med 128:901–904
Kanavaros P, Stefanaki K, Vlachonikolis J, Eliopoulos G, Kakolyris S, Rontogianni D, Gorgoulis V, Georgoulias V (2000) Expression of p53, p21/waf1, bcl-2, bax, Rb and Ki67 proteins in Hodgkin's lymphomas. Histol Histopathol 15:445–453
Kapatai, Murray (2007) http://www.ncbi.nlm.nih.gov/pubmed/18042690

Kaplan HS, Dorfman RF, Nelsen TS, Rosenberg SA (1973) Staging laparotomy and splenectomy in Hodgkin's disease: analysis of indications and patterns of involvement in 285 consecutive, unselected patients. Natl Cancer Inst Monogr 36:291–301

Karmacharya P, Bhandari N, Aryal MR, Pandit AA, Pathak R, Ghimire S, Shrestha P et al (2014) Before it crumbles: fulminant hepatic failure secondary to Hodgkin's lymphoma. J Comm Hosp Intern Med Perspect 4:25821

Kashkar H, Haefs C, Shin H, Hamilton-Dutiot SJ, Salvesen GS, Kronke M, Jurgensmeier JM (2003) XIAP-mediated caspase inhibition in Hodgkin's lymphoma-derived B cells. J Exp Med 198:341–347

Kaufmann E (1909) Lehrbuch der speziellen pathologischen Anatomie. Kapitel "Lymphogranulomatose", de Gruyter, Berlin, pp. 158–161

Kaufmann E (1922) Lehrbuch der speziellen pathologischen Anatomie, 7th edn, vol 1, de Gruyter, Berlin, p 205

Keiser G (1960) Tumor cell migration into peripheral blood in malignant tumors of the lymphatic and reticular system (in German). Acta Haematol 23:29–46

Khan G (2006) Epstein-Barr virus and the germinal center B cells. Exp Hematol 34:695–696

Khan SM, Cottrell BJ, Millward-Sadler GH, Wright DH (1993) T-cell-rich B-cell lymphoma presenting as liver disease. Histopathology 23:217–224

Khapat'ko TS, Shestakova NN (1983) Primary liver Hodgkin's disease (in Russian). Vrach Delo 8:98–100

Kiewe P, Korfel A, Loddenkemper C, Fischer L, Jahnke K, Notter M, Muhr-Wilkenshoff F, Stein H, Thiel E (2004) Unusual sites of Hodgkin's lymphoma: case 3. Cholemic nephrosis in Hodgkin's lymphoma with liver involvement. J Clin Oncol 22:4230–4231

Kim LH, Eow GI, Peh SC, Poppema S (2003) The role of CD30, CD40 and CD95 in the regulation of proliferation and apoptosis in classical Hodgkin's lymphoma. Pathology 35:428–435

Kim LH, Nadarajah VS, Peh SC, Poppema S (2004) Expression of Bcl-2 family members and presence of Epstein-Barr virus in the regulation of cell growth and death in classical Hodgkin's lymphoma. Histopathology 44:257–267

Kirschner RH, Abt AB, O'Connell MJ, Sklansky BD, Greene WH, Wiernik PH (1974) Vascular invasion and hematogenous dissemination of Hodgkin's disease. Cancer 34:1159–1162

Kleger A, Bommer M, Kunze M, Klaus J, Leithaeuser F, Wegener M, Adler G, Dikopoulos N (2009) First reported case of disease: peliosis hepatis as cardinal symptom of Hodgkin's lymphoma. Oncologist 14:1088–1094

Klein F (1955) Ueber einen Fall von akut verlaufender Lymphogranulomatose. Zbl Allg Pathol Pathol Anat 93:19–27

Kodousek R, Ticha V, Tichy M (1992) Selective apoptotic necrosis (SAN) of H/R-S cells in malignant lymphogranuloma, and their immunoreactivity with antinuclear antibodies. Scr Med 65:225–230

Koene-Bogman J (1978) Granulomas and the diagnosis of Hodgkin's disease. N Engl J Med 299:553

Kolar Z, Flavell JR, Ehrmann J, Rihakova P, Macak J, Lowe D, Crocker J, Vojtesek B, Young LS, Murray PG (2000) Apoptosis of malignant cells in Hodgkin's disease is related to expression of the cdk inhibitor p27KIP1. J Pathol 190:604–612

Krugmann J, Tzankov A, Gschwendtner A, Fischhofer M, Greil R, Fend F, Dirnhofer S (2003) Longer failure-free survival interval of Epstein-Barr virus-associated classical Hodgkin's lymphoma: a single-institution study. Mod Pathol 16:566–573

Kuittinen O, Soini Y, Turpeenniemi-Hujanen T (2002) Diverse role of MMP-2 and MMP-9 in the clinicopathological behavior of Hodgkin's lymphoma. Eur J Haematol 69:205–212

Kuittinen O, Apaja-Sarkkinen M, Turpeenniemi-Hujanen T (2003) Gelatinases (MMP-2 and MMP-9), TIMp-1 expression and the extent of neovascularization in aggressive non-Hodgkin's lymphomas. Eur J Haematol 71:91–99

Küppers R, Hansmann ML (2005) The Hodgkin and Reed/Sternberg cell. Int J Biochem Cell Biol 37:511–517

Küppers R, Engert A, Hansmann ML (2012) Hodgkin lymphoma. J Clin Invest 122:3439–3447

Lamoureux KB, Jaffe ES, Berard CW, Johnson RE (1973) Lack of identifiable vascular invasion in patients with extranodal dissemination of Hodgkin's disease. Cancer 31:824–825

Langford JK, Yang Y, Kieber-Emmons T, Sanderson RD (2005) Identification of an invasion regulatory domain within the core protein of syndecan-1. J Biol Chem 280:3467–3473

Langhans TH (1872) Das maligne Lymphosarkom (Pseudoleukämie). Virchows Arch 54:509–537

Lauritzen AF, Moller PH, Nedergaard T, Guldberg P, Hou-Jensen K, Ralfkiaer E (1999) Apoptosis-related genes and proteins in Hodgkin's disease. APMIS 107:636–644

Lee SS, Ryoo BY, Park YH, Park S, Kim MS, Park KH, Kim CW (2004) Hodgkin lymphoma with unusual intrasinusoidal pattern of infiltration. Leuk Lymphoma 45:2135–2141

Leeuwenburgh I, Lugtenburg EP, van Buuren HR, Zondervan PE, de Man RA (2008) Sever jaundice, due to vanishing bile duct syndrome, as presenting symptom of Hodgkin's lymphoma, fully reversible after chemotherapy. Eur J Gastroenterol Hepatol 20:145–147

Lefkowitch JH, Falkow S, Whitlock RT (1985) Hepatic Hodgkin's disease simulating cholestatic hepatitis with liver failure. Arch Pathol Lab Med 109:424–427

Leoncini L, Spina D, Close P, Megha T, Pacenti L, Tosi P, Pileri S, De Vivo A, Kraft R, Laissue JA, Cottier H (1996) Abortive mitoses and nuclear DNA fragmentation in CD30+ large cells of Hodgkin's disease. Leuk Lymphoma 22:119–124

Lerza R, Schenone E, Barsotti BP, Botta M, Arboscello E, Truini M, Bogliolo G, Pannacciulli I (2002) Epithelioid granulomas as main clinical manifestation at the outset of non-Hodgkin's lymphoma: report of two cases. Oncol Res 13:55–59

Leslie KO, Colby TV (1984) Hepatic parenchymal lymphoid aggregates in Hodgkin's disease. Hum Pathol 15:808–809

Levitan R, Henry T, Diamond D, Lloyd-Cravier LD (1961) Jaundice in Hodgkin's disease. Am J Med 30:99–111

Liangpunsakul S, Kwo P, Koukoulis GK (2002) Hodgkin's disease presenting as cholestatic hepatitis with prominent ductal injury. Eur J Gastroenterol Hepatol 14:323–327

Libansky J, Bednar B, Buzek J (1962) Sternberg cells (Reed cells) in the peripheral blood in a patient with Hodgkin's disease. Neoplasma 9:411–428

Liebermann DA (1986) Intrahepatic cholestasis due to Hodgkin's disease. An elusive diagnosis. J Clin Gastroenterol 8:304–307

Lieberz D, Sextro M, Paulus U, Franklin J, Tesch H, Diehl V (2000) How to restrict liver biopsy to high-risk patients in early-stage Hodgkin's disease. German Hodgkin's Lymphoma Study Group. Ann Hematol 79:73–78

Lopez R, Barrera L, Vera A, Andrade R (2014) Concurrent Hodgkin lymphoma and nodular regenerative hyperplasia on an explanted liver with clinical diagnosis of alcoholic cirrhosis at University Hospital fundacion santa fe de Bogota. Case Rep Pathol 2014:193802

Longcope WT (1903) On the pathological history of Hodgkin's disease, with a report of a series of cases. Bull Ayer Clin Lab 1:4–76

Lorenzen J, Thiele J, Fischer R (1997) The mummified Hodgkin cell: cell death in Hodgkin's disease. J Pathol 182:288–298

Ludwig J (1998) Idiopathic adulthood ductopenia: an update. Mayo Clin Proc 73:285–291

Lukes RJ (1971) Criteria for involvement of lymph node, bone marrow, spleen, and liver in Hodgkin's disease. Cancer Res 31:1755–1767

Lukes RJ, Butler JJ (1966) The pathology and nomenclature of Hodgkin's disease. Cancer Res 26:1063–1081

Lukes RJ, Butler JJ, Hicks EB (1966) Natural history of Hodgkin's disease as related to its pathologic picture. Cancer 19:317–344

Mac-Clure E, Lemos C, Ferreira CS, Leme MA (1959) Considerations on the pathogenesis of jaundice in Hodgkin's disease: presentation of two cases with hepatocanalicular jaundice (in Portuguese). Hospital (Rio J) 56:59–80

Maggio EM, Van den Berg A, De Jong D, Diepstra A, Poppema S (2003) Low frequency of FAS mutations in Reed-Sternberg cells of Hodgkin's lymphoma. Am J Pathol 162:29–35

Malfitano A, Cazzola M, Cavalli P, Gobbi PG, Gorini M, Ascari E, Perugini S (1980) Morphological and cytochemical studies of circulating Hodgkin's and Reed-Sternberg cells. Basic Appl Histochem 24:101–107

Malpighi M (1666) De viscerum structura exercitatio anatomica. Bologna

Man KM, Drejet A, Keeffe EB, Garcia-Kennedy R, Imperial JC, Esquivel CO (1993) Primary sclerosing cholangitis and Hodgkin's disease. Hepatology 18:1127–1131

Marazuela M, Moreno A, Yebra M, Cerezo E, Gomez-Gesto C, Vargas JA (1991) Hepatic fibrin-ring granulomas: a clinicopathologic study of 23 patients. Hum Pathol 22:607–613

Marinone G, Lazzari R, Pellizzari F, Marinone MG (1989) Acute cholestatic Hodgkin's lymphoma: an unusual clinical picture. Haematologica 74:293–296

Marjanska-Radziszewska J, Zawila K, Ciesla E (1996) A case of Hodgkin's disease with an uncommon clinical course. Predominant localization in the liver (in Polish). Przegl Lek 53:830–832

Martin JK, Clark SC, Beart RW, ReMine WH, White WL, Ilstrup DM (1982) Staging laparotomy in Hodgkin's disease: Mayo Clinic experience. Arch Surg 117:586–591

Martin KR, Moore TJ, Wright RA (1992) Obstructive jaundice secondary to primary biliary involvement with Hodgkin's disease. Am J Gastroenterol 87:1194–1195

Martin P, Gomez-Lozano N, Montes S, Salas C, Provencio M, Bellas C (2011) Epstein-Barr virus in the germinal centres of adenopathies affected by classic Hodgkin lymphoma. Histopathology 59:349–352

Martinet O, Bettschart V, Scholl B, Suter M (2000) Value of laparoscopic staging for Hodgkin disease. Surg Laparosc Endosc Percutan Tech 10:335–337

Masson P (1956) Tumeurs humaines. Histologie, diagnostics et techniques. Librairie Maloine, Paris, p 272

Mathas S, Lietz A, Anagnostopoulos I, Hummel F, Wiesner B, Janz M, Jundt F, Hirsch B, Johrens-Leder K et al (2004) c-FLIP mediates resistance of Hodgkin/Reed-Sternberg cells to death receptor-induced apoptosis. J Exp Med 199:1041–1052

Matsko GF, Zhukovets AV (1971) Jaundice in lymphogranulomatosis in children (in Russian). Pediatriia 50:40–43

McNulty JG (1971) Diagnosis of extrahepatic jaundice in Hodgkin's disease. Br Med J 4:26–27

Merchant TE, Filippa DA, Yahalom J (1994) Sarcoidosis following chemotherapy for Hodgkin's disease. Leuk Lymphoma 13:339–347

Metkar SS, Manna PP, Anand M, Naresh KN, Advani SH, Nadkarni JJ (2001) CD40 ligand – an anti-apoptotic molecule in Hodgkin's disease. Cancer Biother Radiopharm 16:85–92

Meyer O (1911) Beiträge zur Klinik, Pathogenese und pathologischen Anatomie des malignen Granuloms. Frankfurt Zschr Pathol 8:343–400

Michalitschke G (1919) Lymphogranulomatose und Ikterus. Wien Med Wochenschr 14:685–687

Michel J, Ardichvili D, Somerhausen M, Kenis Y, Heuson JC (1973) Hodgkin's disease with massive hepatic involvement and uninvolved spleen. Eur J Cancer 9:701–702

Mignot J, Bergue A, Baviera E, Malod-Panisset A (1979) Quantitative study of hepatic fibrosis i Hodgkin's disease (in French). Pathol Biol (Paris) 27:229–232

Mohamed G, Vrzalikova K, Cader FZ, Vockerodt M, Nagy E, Flodr P, Yap LF, Diepstra A et al (2014) Epstein-Barr virus, the germinal centre and the development of Hodgkin's lymphoma. J Gen Virol 95:1861–1869

Morgagni GB (1761) De sedibus et causis morborum per anatomen indagatis libri quinque, 2 vols, venice, typog. Remondiniana, 3 vols. edition in 1779, Yverdon (Ebroduni in Helvetia)

Mori D, Matsuishi E, Akashi M, Shibaki M, Hirano T, Ide M, Tsutsumi Y, Tsukiji H, Gondo H (2014) Hodgkin-like peripheral T-cell lymphoma (PTCL) with preserved Hodgkin-like lesions at autopsy: a case report with an interesting clinical course. Pathol Res Pract. doi:10.1016/j.prcp.2014.08.016

Munker R, Stengel A, Stabler A, Hiller E, Brehm G (1995) Diagnostic accuracy of ultrasound and computed tomography in the staging of Hodgkin's disease. Verification by laparotomy in 100 cases. Cancer 76:1460–1466

Murchison C (1869) "Lymphatic new formations" in the liver, with enlargement of the spleen and persistent jaundice, in a child aged 12. Trans Pathol Soc London 20:198–203

Murray GR (1908) Lymphadenoma. In: Allbutt C, Rolleston HD (eds) A system of medicine, vol 4, Part I. Macmillan, London, pp 459–481

Murray PG, Qiu GH, Fu L, Waites ER, Srivastava G, Heys D, Agathanggelou A, Latif F, Grundy RG et al (2004) Frequent epigenetic inactivation of the RASSF1A tumor suppressor gene in Hodgkin's lymphoma. Oncogene 23:1326–1331

Muschen M, Re D, Brauninger A, Wolf J, Hansmann ML, Diehl V, Küppers R, Rajewski K (2000) Somatic mutations of the CD95 gene in Hodgkin and Reed-Sternberg cells. Cancer Res 60:5640–5643

Muta H, Boise LH, Fang L, Podack ER (2000) CD30 signals integrate expression of cytotoxic effector molecules, lymphocyte trafficking signals, and signals for proliferation and apoptosis. J Immunol 165:5105–5111

Nadel EM, Ackerman LV (1950) Lesions resembling Boeck's sarcoid in lymph nodes draining an area containing a malignant neoplasm. Am J Clin Pathol 20:952–957

Nader K, Mok S, Kalra A, Harb A, Schwarting R, Ferber A (2013) Vanishing bile duct syndrome as a manifestation of Hodgkin's lymphoma: a case report and review of the literature. Tumori 99:e164–e168

Naeim F, Waisman J, Coulson WF (1974) Hodgkin's disease: the significance of vascular invasion. Cancer 34:655–662

Nakatsuka S, Aozasa K (2006) Epidemiology and pathologic features of Hodgkin lymphoma. Int J Hematol 83:391–397

Nam SY, Cho KS, Heo YM, Ha JC, Kim YH, Keun YH, Han HP, Kim HM, Podack ER (2002) Regulation of lymphocyte clustering by CD30-mediated ICAM-1 up-regulation. Cell Immunol 219:38–47

Nemets et al (2003) http://www.ncbi.nlm.nih.gov/pubmed/14959863

Neiman et al (1973) http://www.ncbi.nlm.nih.gov/pubmed/4688713

Newman B, Pushkin W (1951) Acute fulminating Hodgkin's disease. J Am Med Assoc 146:335–337

Ochoa JI, Keene WR (1970) Obstructive jaundice in Hodgkin's disease due to infiltration of the biliary ducts. J Fla Med Assoc 57:21–23

O'Connell MJ, Schimpff SC, Kirschner RH, Abt AB, Wiernik PH (1975) Epithelioid granulomas in Hodgkin disease. A favorable prognostic sign? JAMA 233:886–889

Oelmann E, Herbst H, Zuhlsdorf M, Albrecht O, Nolte A, Schmitmann C, Manzke O, Diehl V et al (2002) Tissue inhibitor of metalloproteinases 1 is an autocrine and paracrine survival factor, with additional immune-regulatory functions, expressed by Hodgkin/Reed-Sternberg cells. Blood 99:258–267

Okazaki A, Niibe H, Mitsuhashi N, Ito J, Nakajima N, Saito Y, Tamaki Y, Nagai T, Machinami R, Sakata N (1985) CT and pathologic studies on detecting hepatic involvement of malignant lymphoma (in Japanese). Gan No Rinsho 31:494–500

Olnes M, Alli P, Freedman A, Auster M, Erlich R (2003) Hematologic malignancies with extramedullary spread of disease. Case 3. Extra-nodal Hodgkin's disease presenting as rapidly progressive liver failure. J Clin Oncol 21:1890–1891

Omidvari SH, Khojasteh HN, Mohammadianpanah M, Monabati A, Mosalaei A, Ahmadloo N (2004) Long-term pruritus as the initial and sole clinical manifestation of occult Hodgkin's disease. Indian J Med Sci 58:250–252

Opeskin K, Burke M, McCaffrey G, Nandurkar H (2003) Hodgkin's disease associated cholestasis in a man with thymoma. Pathology 35:349–351

Ozkan A, Yoruk A, Celkan T, Apak H, Yildiz I, Ozbay G (2001) The vanishing bile duct syndrome in a child with Hodgkin disease. Med Pediatr Oncol 36:398–399

Padhi S, Paul TR, Challa S, Prayaga AK, Rajappa S, Raghunadharao D, Sarangi R (2012) Primary extra-nodal non Hodgkin lymphoma: a 5 year retrospective analysis. Asian Pac J Cancer Prev 13:4889–4895

Pak HY, Friedman NB (1981) Pseudosarcoid granulomas in Hodgkin's disease. Hum Pathol 12:832–837

Paltauf R (1897) Lymphosarkom (Lymphosarkomatose, Pseudoleukämie, Myelom, Chlorom). Ergebn Allg Pathol Pathol Anat Menschen Tiere 3:652–691

Pappa VI, Norton AJ, Gupta RK, Wilson AM, Rohatiner AZ, Lister TA (1995) Nodular type of lymphocyte

predominant Hodgkin's disease. A clinical study of 50 cases. Ann Oncol 6:559–565
Pariente D, Cornud F, Grenier P, Degos F, Nahum H (1981) Involvement of the common bile duct in Hodgkin's disease: report of three cases (in French). Sem Hop 57:2027–2030
Pasquier J, Pauchard J, Lesbros F, Descos L, Feroldi J, Scotto J (1973) Hodgkin's disease with principal hepatic localization and peliosis lesions. Apropos of a case (in French). Sem Hop 49:2301–2304
Pass AK, McLin VA, Rishton JR, Kearney DL, Hastings CA, Margolin JF (2008) Vanishing bile duct syndrome and Hodgkin disease: a case series and review of the literature. J Pediatr Hematol Oncol 30:976–980
Peiser H (1913) Zur Kasuistik der akuten Lymphogranulomatose. Med Klin 42:1719–1721
Pel PK (1885) Zur Symptomatologie der sogenannten Pseudo-Leukämie. Berl Klin Wochenschr 22:3–7
Pène P (1952) Foie et lymphogranulomatose de Hodgkin. Gaz Med Fr 59:1245–1250
Pène P, du Paquier P, Alium F, Pène JA (1955) Forme hépatosplénomégalique prédominante de la maladie de Hodgkin. Bordeaux Chir 2:93–94
Pennanen H, Kuittinen O, Soini Y, Turpeenniemi-Hujanen T (2004) Clinicopathological correlations of TIMP-1 and TIMP-2 in Hodgkin's lymphoma. Eur J Haematol 72:1–9
Perera DR, Greene ML, Fenster LF (1974) Cholestasis associated with extrabiliary Hodgkin's disease. Report of three cases and review of four others. Gastroenterology 67:680–685
Piken EP, Abraham GE, Hepner GW (1979) Investigation of a patient with Hodgkin's disease and cholestasis. Gastroenterology 77:145–147
Piro AJ, Hellman S, Moloney WC (1972) The influence of laparotomy on management decisions in Hodgkin's disease. Arch Intern Med 130:844–848
Pittman CE, Buss DH, Sterchi JM (1988) Detection of liver involvement in Hodgkin's disease. J Surg Oncol 38:265–266
Priesel A, Winkelbauer A (1926) Placentare Uebertragung des Lymphogranulomas. Virchows Arch Pathol Anat Physiol Klin Med 262:749–765
Rappaport H, Strum SB (1970) Vascular invasion in Hodgkin's disease: its incidence and relationship to the spread of the disease. Cancer 25:1304–1313
Rappaport H, Strum SB, Hutchison G, Allen LW (1971) Clinical and biological significance of vascular invasion in Hodgkin's disease. Cancer Res 31:1794–1798
Razemon P, Salembier Y, Meignie P (1961) Compression of the bile ducts by adenopathies in Hodgkin's disease (in French). Arch Mal Appar Dig Mal Nutr 50:374–376
Re D, Thomas RK, Behringer K, Diehl V (2005) From Hodgkin's disease to Hodgkin lymphoma: biological insights and therapeutic potential. Blood 105:4553–4560
Reddy N, Thompson-Arildsen MA (2010) Hodgkin's lymphoma: Richter's transformation of chronic lymphocytic leukemia involving the liver. J Clin Oncol 28: e543–e544
Reed D (1902) On the pathological changes in Hodgkin's disease, with especial reference to its relation to tuberculosis. Johns Hopkins Hosp Rep (Baltimore) 10:133–196
Rengstl B, Rieger MA, Newrzela S (2014) On the origin of giant cells in Hodgkin lymphoma. Community Integr Biol 7:e28602
Riccardi A, Montecucco CM, Cresci R, Mazzini G, Ascari E, Perugini S (1980) Cytokinetic studies on circulating neoplastic cells of Hodgkin's disease. Basic Appl Histochem 24:109–120
Ripoll C, Carretero L, Sabin P, Alvarez E, Marrupe D, Banares R (2002) Idiopathic cholestasis associated with progressive ductopenia in two patients with Hodgkin's disease (in Spanish). Gastroenterol Hepatol 25:313–315
Roberts KJ, Brown R, Patel JV, Toogood GJ (2012) Biliary and portal vein strictures following treatment of Hodgkin's lymphoma. Ann R Coll Surg Engl 94: e225–e226
Rodig SJ, Savage KJ, Nguyen V, Pinkus GS, Shipp MA, Aster JC, Kutok JL (2005) TRAF1 expression and c-Rel activation are useful adjuncts in distinguishing classical Hodgkin lymphoma from a subset of morphologically or immunophenotypically similar lymphomas. Am J Surg Pathol 29:196–203
Rolleston HD (1912) Diseases of the liver, gallbladder and bile-ducts, 2nd edn. Macmillan, London
Rosenberg SA, Kaplan HS (1970) Hodgkin's disease and other malignant lymphomas. Calif Med 113:23–28
Rossini MS, Lorand-Metze I, Oliveira GB, Souza CA (2000) Vanishing bile duct syndrome in Hodgkin's disease: case report. Sao Paulo Med J 118:154–157
Rowbotham D, Wendon J, Williams R (1998) Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. Gut 42:576–580
Rueffer U, Sieber M, Stemberg M, Gossmann A, Josting A, Koch T, Grotenhermen F, Diehl V, German Hodgkin's Lymphoma Study Group (GHSG) (2003) Spleen involvement in Hodgkin's lymphoma: assessment and risk profile. Ann Hematol 82:390–396
Russell BRG (1914) Drei bemerkenswerte Fälle von Lymphogranulomatose. Ziegler's Beitr Pathol Anat 58:516–553
Sacks EL, Donaldson SS, Gordon J, Dorfman RF (1978) Epithelioid granulomas associated with Hodgkin's disease: clinical correlations in 55 previously untreated patients. Cancer 41:562–567
Sakata K, Satoh M, Someya M, Asanuma H, Nagakura H, Oouchi A, Nakata K, Kogawa K, Koito K et al (2004) Expression of matrix metalloproteinase 9 is a prognostic factor in patients with non-Hodgkin lymphoma. Cancer 100:356–365
Sanbe K, Shirato E (1966) Case of common bile duct obstruction caused by Hodgkin's disease (in Japanese). Nippon Rinsho 24:1139–1142
Sanchez-Aguilera A, Delgado J, Camacho FI, Sanchez-Beato M, Sanchez L, Montalban C et al (2004) Silencing of the p18INK4c gene by promoter

hypermethylation in Reed-Sternberg cells in Hodgkin lymphomas. Blood 103:2351–2357
Sans M, Andreu V, Bordas JM, Llach J, Lopez-Guillermo-A, Cervantes F, Bruguera M, Mondelo F et al (1998) usefulness of laparoscopy with liver biopsy in the assessment of liver involvement at diagnosis of Hodgkin's and non-Hodgkin's lymphomas. Gastrointest Endosc 47:391–395
Sayhoun PF, Eisenberg S (1949) Hodgkin's disease, histopathological and clinical classification with radiotherapeutic response. Am J Roentgenol 61:369–379
Schlaifer D, Krajewski S, Rigal-Huguet F, Laurent G, Pris J, Delsol G, Reed JC, Brousset P (1996) Bcl-x gene expression in Hodgkin's disease. Leuk Lymphoma 23:143–146
Schmitz R, Stanelle J, Hansmann ML, Küppers R (2009) Pathogenesis of classical and lymphocyte-predominant Hodgkin lymphoma. Annu Rev Pathol 4:151–174
Schmorl K (1922) Case presentation before the Gesellschaft für Natur und Heilkunde zu Dresden, on 20 March 1922. Münch Med Wochenschr 69:908
Schoenlank FW (1916) Ein Fall von Peliosis hepatis. Virchows Arch [A] 222:358–364
Sherlock S (1955) Diseases of the liver and biliary system. Blackwell, Oxford
Siebert JD, Stuckey JH, Kurtin PJ, Banks PM (1995) Extranodal lymphocyte predominance Hodgkin's disease. Clinical and pathologic features. Am J Clin Pathol 103:485–491
Simonds JP (1926) Hodgkin's disease. Arch Pathol (Chicago) 1:394–430
Skovsgaard T, Brinckmeyer LM, Vesterager L, Thiede T, Nissen NI (1982) The liver in Hodgkin's disease – II. Histopathologic findings. Eur J Clin Oncol 18:429–435
Smith LB (2010) Nodular lymphocyte predominant Hodgkin lymphoma. Diagnostic peals and pitfalls. Arch Pathol Lab Med 134:1434–1439
Smolewski P, Niewiadomska H, Los E, Robak T (2000) Spontaneous apoptosis of Reed-Sternberg and Hodgkin cells; clinical and pathological implications in patients with Hodgkin's disease. Int J Oncol 17:603–609
Sperandio S, de Belle I, Bredesen DE (2000) An alternative, nonapoptotic form of programmed cell death. Proc Natl Acad Sci U S A 97:14376–14381
Spinelli P, Beretta G, Bajetta E, Tancini G, Castellani R, Rilke F, Bonadonna G (1975) Laparoscopy and laparotomy combined with bone marrow biopsy in staging Hodgkin's disease. Br Med J 4:554–556
Stahr H, Sywoldt I (1922) Ueber Lymphogranulomatose, insbesondere an den grossen Gallengängen. Med Klin (Berlin) 18:404–409
Stern M, Herrmann R, Rochlitz C, Dirnhofer S, Pless M (2005) A case of post-transplant lymphoproliferative disease presenting as CD20-expressing, Epstein-Barr-virus positive Hodgkin lymphoma. Eur J Haematol 74:267–270
Sternberg C (1898) Ueber eine eigenartige, unter dem Bilde der Pseudoleukämie verlaufende Tuberkulose des lymphatischen Apparates. Zschr Heilkunde (Prague) 19:21–90
Sternberg C (1913) XIII. Leber, Gallenblase und Gallenwege, Pankreas. In: Aschoff L (ed) Pathologische Anatomie. Ein Lehrbuch für Studierende und Aerzte, 3rd edn. Gustav Fischer, Jena, p 893
Sternberg C (1936) Lymphogranulomatose und Reticuloendotheliose. Ergebn AllgPathol Pathol Anat 30:1–76
Stolzenbach G, Garbrecht M, Mertelsmann R, Kastendieck H (1976) Coincidence of Hodgkin's disease and epithelioid-cell granulomatosis in liver and spleen (in German). Dtsch Med Wochenschr 101:709–711
Strum SB, Allen LW, Rappaport H (1971) Vascular invasion in Hodgkin's disease: its relationship to involvement of the spleen and other extranodal sites. Cancer 28:1329–1334
Su CC, Chiu HH, Chang CC, Chen JC, Hsu SM (2004) CD30 is involved in inhibition of T-cell proliferation by Hodgkin's Reed-Sternberg cells. Cancer Res 64:2148–2152
Sulkes A, Benjamin RS, Luna MA (1979) Liver replacement with Hodgkin's disease, lymphocyte-depletion type, with an uninvolved spleen. Eur J Cancer 15:373–377
Symmers D (1944) Clinical significance of the deeper anatomic changes in lymphoid diseases. Arch Intern Med 74:163–171
Takeshita H, Yoshizaki T, Miller WE, Sato H, Furukawa M, Pagano JS, Raab-Traub N (1999) Matrix metalloproteinase 9 expression is induced by Epstein-Barr virus latent membrane protein 1 C-terminal activation regions 1 and 2. J Virol 73:5548–5555
Tartar VM, Balfe DM (1990) Lymphoma in the wall of the bile ducts: radiologic imaging. Gastrointest Radiol 15:53–57
Thomas RK, Kallenborn A, Wickenhauser C, Schultze JL, Draube A, Vockerodt M, Re D, Diehl V, Wolf J (2002) Constitutive expression of c-FLIP in Hodgkin and Reed-Sternberg cells. Am J Pathol 160:1521–1528
Thomas RK, Re D, Wolf J, Diehl V (2004) Part I: Hodgkin's lymphoma – molecular biology of Hodgkin and Reed-Sternberg cells. Lancet Oncol 5:11–18
Thorns C, Feller AC, Merz H (2002) EMMPRIN (CD 174) is expressed in Hodgkin's lymphoma and anaplastic large cell lymphoma. An immunohistochemical study of 60 cases. Anticancer Res 22:1983–1986
Thorns C, Bernd HW, Hatton D, Merz H, Feller AC, Lange K (2003) Matrix-metalloproteinases in Hodgkin lymphoma. Anticancer Res 23:1555–1558
Toncini C, Venzano C (1981) Localization of Hodgkin's lymphoma in hepatic angiomas (in Italian). Pathologica 73:827–829
Tornero C, Laparra E, Jimenez A, Ricart C, Pastor A, Rull S (1998) Acute hepatic failure and Hodgkin's disease (in Spanish). An Med Interna 15:654–655
Trewby PN, Portmann B, Brinkley DM, Williams R (1979) Liver disease as presenting manifestation of Hodgkin's disease. Q J Med 48:137–150

Trudel MA, Krikorian JG, Neiman RS (1987) Lymphocyte predominance Hodgkin's disease: a clinicopathologic reassessment. Cancer 59:99–106

Tudor CS, Bruns H, Daniel C, Distel LV, Hartmann A, Gerbitz A, Buettner MJ (2014) Macrophages and dendritic cells as actors in the immune reaction of classical Hodgkin lymphoma. PLoS One 9:e114345

Tzankov A, Zimpfer A, Went P, Maurer R, Pileri SA, Geley S, Dirnhofer S (2005) Aberrant expression of cell cycle regulators in Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma. Mod Pathol 18:90–96

Uddströmer M (1934) On the occurrence of lymphogranulomatosis (Sternberg) in Sweden 1915–1931 and some considerations as to its relation to tuberculosis. Acta Tuberc Scand (Suppl 1):1–225

Urayama KY, Jarrett RF, Hjalgrim H, Diepstra A, Kamatani Y, Chabrier A, Gaborieau V, Boland A et al (2012) Genome-wide association study of classical Hodgkin lymphoma and Epstein-Barr virus status-defined subgroups. J Natl Cancer Inst 104:240–253

Urbano-Marquez A, Grau Junyent JM, Sala M, Estruch R, Bruguera M, Rozman C (1981) Hodgkin's disease presenting as a hepatic disease. Report of two cases (in Spanish). Med Clin (Barc) 76:255–258

Vadillo Serrano M, Las Heras G, Badia F, Puig I (2002) Hodgkin's disease presenting as severe acute liver failure (in Spanish). Med Clin (Barc) 119:677

Van Spronsen DJ, Veldhuis GJ (2003) New developments in staging and follow-up of patients with Hodgkin's lymphoma. Neth J Med 61:278–284

Van Spronsen DJ, Peh SC, Vrints LW, van Imhoff GW, Poppema S (2000) Clinical drug-resistant nodular sclerosing Hodgkin's lymphoma is associated with decreased bcl-2 expression in the surrounding lymphocytes and with increased bcl-2 expression in the Reed-Sternberg cells. Histopathology 37:420–426

Varadi S (1955) Hodgkin's disease: specific findings in sternal puncture material. Br J Haematol 1:184–188

Varadi S (1960) Reed-Sternberg cells in the peripheral blood and bone marrow in Hodgkin's disease. Br J Med 1:1239–1243

Vardarelli E, Dundar E, Aslan V, Gulbas Z (2004) Acute liver failure due to Hodgkin's lymphoma. Med Princ Pract 13:372–374

Vassallo J, Metze K, Traina F, de Sousa CA, Lorand-Metze I (2003) The prognostic relevance of apoptosis-related proteins in classical Hodgkin's lymphomas. Leuk Lymphoma 44:483–488

Von Hüttenbrenner A (1871) Zwei Fälle von harten Lymphomen bei Kinder. Jahrb Kinderheilk 4:157–165

Von Jaksch R (1913) Klinische Beiträge zur Kenntnis der Lymphogranulomatose. Dtsch Arch Klin Med 3:503–529

Von Tresckow B, Kallen KJ, von Strandmann EP, Borchmann P, Lange H, Engert A, Hansen HP (2004) depletion of cellular cholesterol and lipid rafts increases shedding of CD30. J Immunol 172:4324–4331

Wakisaka N, Pagano JS (2003) Epstein-Barr virus induces invasion and metastasis factors. Anticancer Res 23:2133–2138

Wallhauser A (1933) Hodgkin's disease. Arch Pathol 41:522–562

Wang C, Deng X, Li X, Gu H, Yi W, Wenig X, Xia L, Cao Y (2002) Matrix metalloproteinase 9 expression is induced by Epstein-Barr virus LMP1 via NF-kappa B or AP-1 signaling pathway in nasopharyngeal carcinoma cells (in Chinese). Zhongghua Zhong Liu Za Zhi 24:9–13

Warner AS, Whitcomb FF (1994) Extrahepatic Hodgkin's disease and cholestasis. Am J Gastroenterol 89:940–941

Wee GC, Hagen G, Torres A, Shieber W (1970) Hodgkin's disease of the cystic node as a cause of nonvisualization of the gallbladder. Am J Gastroenterol 54:272–276

Weinberg F (1917) Lymphogranuloma tuberculosum. Zschr Klin Med 85:99–166

Weiner G, Hoew SE, Mallory A (1994) hepatic failure from Hodgkin0s disease in a patient with HIV infection. J Clin Gastroenterol 18:88–89

Wilks S (1856) Cases of a peculiar enlargement of the lymphatic glands frequently associated with disease of the spleen. Guys Hosp Rep 2:114

Wilks S (1865) Cases of enlargement of the lymphatic glands and spleen (or, Hodgkin's disease) with remarks. Guys Hosp Rep 11:56

Wolf J, Kapp U, Bohlen H, Kornacker M, Schoch C, Stahl B, Mucke S, von Kalle C, Fonatsch C et al (1996) Peripheral blood mononuclear cells of a patient with advanced Hodgkin's lymphoma give rise to permanently growing Hodgkin-Reed Sternberg cells. Blood 87:3418–3428

Woolf KM, Wei MC, Link MP, Arber DA, Warnke RA (2008) Nodular-lymphocyte-predominant Hodgkin lymphoma presenting as fulminant hepatic failure in a pediatric patient: a case report with pathologic, immunophenotypic, and molecular findings. Appl Immunohistochem Mol Morphol 16:196–201

Xerri L, Palmerini F, Devilard E, Defrance T, Bouabdallah R, Hassoun J, Birg F (2000) Frequent nuclear localization of ICAD and cytoplasmic co-expression of caspase-8 and caspase-3 in human lymphomas. J Pathol 192:194–202

Yalcin S, Kars A, Sokmensuer C, Atahan L (1999) Extrahepatic Hodgkin's disease with intrahepatic cholestasis: report of two cases. Oncology 57:83–85

Yamasaki M (1904) Zur Kenntnis der Hodgkin'schen Krankheit und ihres uebergangs in Sarkom. Zschr Heilkde 25:268

Yokomori H, Kaneko F, Sato A, Takeuchi H, Tahara K, Motoori T, Sekiguchi Y, Mori S, Tamaru J et al (2008) Primary hepatic presentation of Hodgkin's lymphoma: a case report. Hepatol Res 38:1054–1057

Yoshizaki T (2002) Promotion of metastasis in nasopharyngeal carcinoma by Epstein-Barr virus latent membrane protein-1. Histol Histopathol 17:845–850

Yoshizaki T, Sato H, Furukawa M, Pagano JS (1998) The expression of matrix metalloproteinase 9 is enhanced by Epstein-Barr virus latent membrane protein 1. Proc Natl Acad Sci U S A 95:3621–3626

Yoshizaki T, Sato H, Murono S, Pagano JS, Furukawa M (1999) Matrix metalloproteinase 9 is induced by the Epstein-Barr virus BZLF1 transactivator. Clin Exp Metastasis 17:431–436

Yuan K, Hong TM, Chen JJ, Tsai WH, Lin MT (2004) Syndecan-1 up-regulated by ephrinB2/EphB4 plays dual roles in inflammatory angiogenesis. Blood 104:1025–1033

Yusuf MA, Elias E, Hubscher SG (2000) Jaundice caused by the vanishing bile duct syndrome in a child with Hodgkin lymphoma. J Pediatr Hematol Oncol 22:154–157

Zaman et al (1991) http://www.ncbi.nlm.nih.gov/pubmed/1885082

Zheng B, Georgakis GV, Li Y, Bharti A, McConkey D, Aggarwal BB, Younes A (2004) Induction of cell cycle arrest and apoptosis by the proteasome inhibitor PS-341 in Hodgkin disease cell lines is independent of inhibitor of nuclear factor-kappaB mutations or activation of the CD30, CD40, and RANK receptors. Clin Cancer Res 10:3207–3215

Ziegler K (1911) Die Hodgkinsche Krankheit. Gustav Fischer Verlag, Jena

Part XVIII

Hepatobiliary Non-Hodgkin's Lymphomas, Other Lymphoproliferative Disorders, and Neoplasms/Proliferations of the Dendritic and Histiocytic Systems

B-Cell Non-Hodgkin's Lymphomas with a Small Cell to Intermediate Cell Phenotype

89

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_89

Abstract

B-cell non-Hodgkin's lymphomas (B-cell NHLs) showing a proliferation of small- to medium-sized neoplastic cells have a strong tendency to infiltrate the liver. In particular, small lymphoma cells are capable to circulate and recirculate in the body and to leave the microcirculation in several organs. The most common B-cell NHL is chronic lymphocytic leukemia of the B-cell type. In this slowly progressing neoplasia, the liver is almost always involved. Accumulation of neoplastic cells causes hepatomegaly, a typical and frequent finding, with liver weights slowly increasing over time to sometimes reaching several kilograms. The exterior aspect of the liver may become grayish white, and the cut surface shows numerous small whitish nodules. The histologic substrate is markedly enlarged portal tracts which are densely infiltrated by small neoplastic lymphocytes. In long-standing disease, larger nodular lesions can develop, mimicking metastatic disease. A similar type of liver involvement is seen in the rare B-cell prolymphocytic leukemia. Focal and nodular hepatic infiltration is also observed in follicular NHL, mantle cell lymphoma, and extranodal marginal zone B-cell NHL of mucosa-associated lymphoid tissue/MALT.

Chronic B-Cell Lymphocytic Leukemia (Small B-Cell Lymphocytic Lymphoma; B-CLL/SLL)

ICD-O code 9823/3

Introduction

Based on the 2008 WHO classification, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is defined as a neoplasm composed of monomorphic small, round to slightly irregular B lymphocytes in the peripheral blood, bone marrow, spleen, lymph nodes, and other organs and tissues. CLL/SLL is often admixed with prolymphocytes and paraimmunoblasts and can form proliferation centers in tissue infiltrates. The general cytologic and histologic features of CLL are briefly discussed at the end of this chapter.

Chronic B-cell lymphocytic leukemia (B-CLL) and the underlying lymphoma, small B-cell lymphocytic lymphoma (SLL), belong to the group of so-called mature B-cell lymphoproliferative disorders (MBCLDs). SLL and its leukemic manifestation, B-CLL, are classified as one disorder, but in fact this apparent entity consists of several different B-cell diseases that are represented under this name. This phenotypic heterogeneity is reflected by a variability of chromosomal/genetic abnormalities, alterations in the expression of apoptosis-related proteins and other effectors, and mutations of growth factors (Caligaris-Cappio and Hamblin 1999; Wierda and Kipps 1999; Bannerji and Byrd 2000; Guipaud et al. 2003; Messmer et al. 2004).

Epidemiology

In Western countries, CLL is the most common leukemia of adults, with an incidence rate of approximately two to six cases per 100,000 persons per year, to reach 12.8 cases per 100,000 persons per year in the age group 65 years and more. CLL has a gender distribution of M/F = 1.5–2.0:1 (androtropy). The disease is much less common in Eastern countries, likely to be based on genetic factors, as the low incidence persists in migrants from such countries.

Clinical Features

CLL leads to a progressive expansion of small B lymphocytes in blood, bone marrow, and peripheral tissues. As the neoplastic cells, similar to their normal counterparts, circulate and recirculate in the organism, almost any tissue can be involved with time. Clinically relevant manifestations are mainly caused by bone marrow replacement and structural and functional disorders of inner organs such as the spleen. In the first and usually long

period of disease development, most patients are asymptomatic. Rare patients present with aleukemic tissue involvement.

Liver Pathology in Chronic B-Cell Lymphocytic Leukemia/Small B-Cell Lymphocytic Lymphoma

Macroscopy

Hepatomegaly is a typical and frequent finding, with liver weights caused by marked cellular infiltration range from little more than normal in early disease to several kilograms in advanced disease. In most patients, marked hepatomegaly is associated with splenomegaly, but splenic weight in B-CLL is usually less elevated than in myeloproliferative disorders. Due to sometimes massive infiltration, the liver capsule may be tense and the liver margins effaced. The exterior aspect of the unfixed liver may be grayish red or even grayish white. In a minority of cases, the liver capsule is mottled owing to multiple small hemorrhages. Moreover, the capsule may be turbid due to a serosal fibrinous reaction. The consistency of the tissue varies from firm to highly friable or flabby, depending on the density of lymphoma infiltration and the degree of tissue decay. The fresh cut surface typically shows numerous and mostly small whitish nodules reflecting the spacing of the densely infiltrated portal tracts. This location of the spots or dots to the lobular periphery has been recognized for a long time as being characteristic for CLL (Naegeli 1923). In the most typical situation, the lesions are miliar, i.e., one to about 3 or 4 mm in diameter, and may thus be confounded with granulomas. However, granulomas are never so regularly spaced all over the organ as are the lesions in CLL. In case of massive infiltration, these areas may show confluence or "lymphomatous bridging," resulting in a distinct network of grayish-white color. In other patients, and specifically in longer-standing disease and/or in case of blastic transformation, larger lesions can ensue, sometimes forming nodules of one or more cm diameter or even forming massive tumors occupying one or more segments of the liver. These patterns may mimic metastatic disease. Larger lesions are known to obstruct intrahepatic bile ducts, causing cholestasis with greenish discoloration of the entire organ or part of the organ, depending on the level of obstruction. Bile may leak from damaged bile ducts and then stain the lymphoma nodules yellow or greenish yellow. Liver organ changes in CLL not directly related to lymphoma cell infiltration include hemorrhages, abscesses, hepatic infarctions, and other rarer lesions.

The locoregional lymph nodes of the hepatic hilar/perihilar region are frequently enlarged. In most cases, this lymphadenomegaly is caused by lymph node infiltration, but other causes can contribute to node enlargement, including a cellular reaction to tissue breakdown in the liver, accumulation of iron-laden macrophages and of foamy cells subsequent to hepatic hemorrhage, granuloma formation, and immune reactions associated with accompanying liver inflammations (e.g., viral hepatitis).

Histopathology

B-CLL shares the patterns of liver infiltrations with other small cell non-Hodgkin's lymphomas (Barcos et al. 1987; Baumhoer et al. 2008). In the liver, B-CLL/SLL chiefly involves the portal tract spaces and, less so, the lumina of the sinusoids (Prinz 1951). The dense and often well-delineated portal tract infiltrates are typically monomorphic and already visualized at low magnification in the form of blue foci. In advanced disease, the entire portal tract space is occupied by the neoplastic cells, which cause expansion and rounding-up of the tracts, with or without spillover of cells into hepatic parenchyma (Figs. 1, 2, 3, and 4). In most cases, interface lesions are not prominent, and therefore, the boundary between portal tracts and parenchyma is rather sharp, in contrast to chronic active viral hepatitis. Due to dense infiltration, preexisting portal tract structures (blood vessels and bile ducts) are almost effaced, as the small round cells encircle these structures. More than 95 % of infiltrate cells are small B cells, and only a minor contribution of macrophages, plasma cells, and granulocytes is seen. The infiltrate is

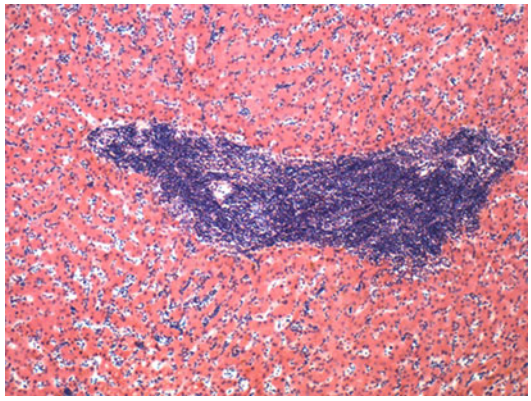

Fig. 1 Involvement of the liver in chronic B-cell lymphocytic leukemia. Small lymphoid cells are present within sinusoids (reflecting leukemia) and form a dense infiltrate in portal tracts. In contrast to infiltrates in chronic hepatitis, the portal tract infiltrate is highly monotonous (hematoxylin and eosin stain)

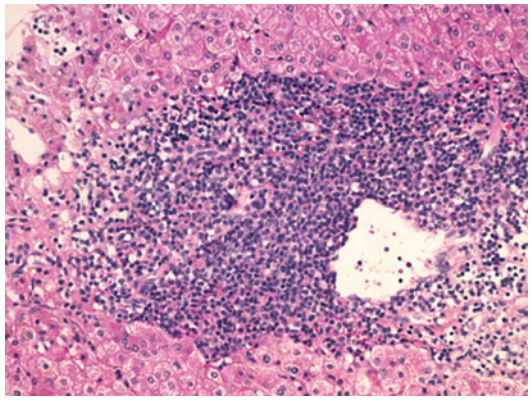

Fig. 2 Liver involvement in B-CLL. The monotonous dense portal tract infiltrate has led to destruction of the hepatic limiting plate ("leukemic/lymphomatous interface lesions or piecemeal necrosis"). The endothelium of the small portal vein branch is damaged by the lymphoma cells (hematoxylin and eosin stain)

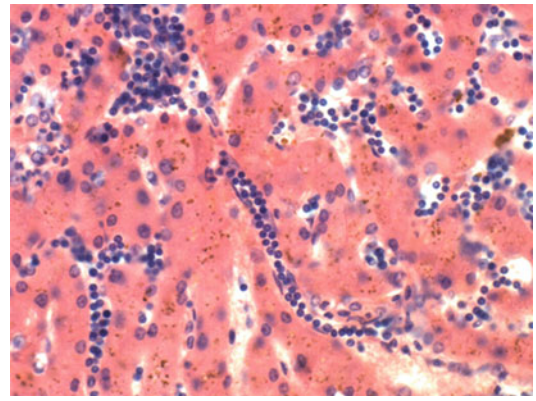

Fig. 3 Sinusoidal accumulation of cells in B-CLL. Tumor cells form rows and "Indian files" and are in close contact with the endothelial surface (hematoxylin and eosin stain)

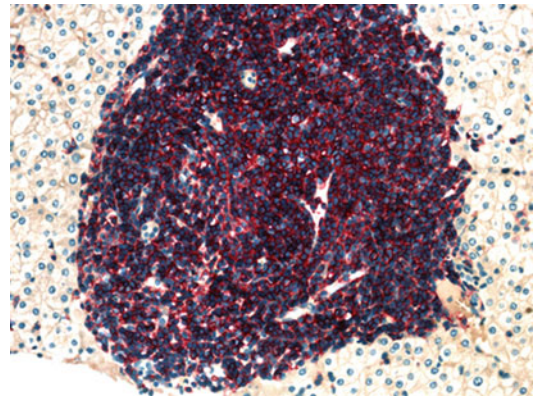

Fig. 4 Portal tract infiltrate in B-CLL. The neoplastic cells are strongly CD79a positive (CD79a immunostain)

dominated by small lymphocytes which are, however, somewhat larger than normal lymphocytes and are also larger than the leukemic lymphocytes circulating in blood. As in involved lymph nodes, so-called paraimmunoblasts or lymphoblasts are always seen, characterized as cells with a larger size, readily visible cytoplasm, oval nuclei with fine chromatin, and a single, centrally placed basophilic nucleolus. The neoplastic infiltrates also always contains few prolymphocytes, which are larger than small lymphocytes and have a nucleus with an open chromatin. The nucleus of prolymphocytes may be oval or irregular, resembling centrocyte nuclei. Paraimmunoblasts and prolymphocytes are the cell components showing mitotic figures. In situations where greater numbers of paraimmunoblasts are present, these cells are mostly clustered as proliferating aggregates, causing a pseudofollicular phenotype (so-called proliferation centers).

Immunohistochemically, a small component of T cells may be noted. Portal tract infiltrates may show a nodular configuration, but true lymph follicles or germinal centers are not found. An interesting phenomenon in some involved livers is parenchymal atrophy of lobular zone 1 and sometimes also 2, zone 3 being spared. The fact that the pericentral zone 3 is not or much less involved speaks against ischemia caused by blockage of sinusoidal entry sites, but effects of cytokines/chemokines may be considered. An increased number of small lymphocytes is seen in the sinusoids, but this feature is less prominent than portal tract infiltrates. The density of intrasinusoidal small B cells reflects leukemia, i.e., the number of neoplastic cells circulating in blood. A subset of patients will develop, usually in later phases of disease, tumorous nodules in the liver substance, mostly composed of prolymphocytes (intrahepatic small B-cell lymphoma; tumor-forming CLL). In tumor-forming CLL, the preexisting reticulin fiber network is effaced, and the cells have a tendency to infiltrate and destroy small- to medium-sized veins and to invade the adventitia of arteries, with splitting of the adventitia. The liver can also show tumorous hepatomegaly in patients with Richter syndrome (Tadmor et al. 2011).

Hepatic Failure in CLL

Marked hepatic infiltration leads to a variety of functional derangements of the organ. In rare instances, hepatic involvement in CLL results in severe hepatocyte injury and acute liver failure (Shehab et al. 1997; Costa et al. 1998; Hasuike et al. 2004; Esfahani et al. 2011). In one patient, this complication occurred in the setting of chronic hepatitis B, but autopsy revealed nodular and massive invasion of the liver by neoplastic lymphocytes associated with hepatocyte necrosis (Hasuike et al. 2004). Hepatocyte injury is probably not only caused by direct physical effects of infiltrating cells and ischemia due to sinusoidal obstruction but also by cytokines and chemokines delivered from immune and tumor cells.

Chronic Lymphocytic Leukemia-Associated Cholangiopathy

CLL-associated cholangiopathy is a recently described disorder (Mann et al. 2011). The index patient was a 41-year-old female with untreated CLL and with elevated liver enzymes in serum, including elevated alkaline phosphatase and gamma-glutamyl transferase. Autoimmune antibodies were negative. A liver biopsy showed that small bile ducts were pushed toward the periphery of infiltrated portal tracts. Some of these bile ducts displayed intraepithelial lymphocyte infiltration, resulting in significant narrowing of the duct lumen (cholangiopathy). The infiltrating lymphocytes had the same immunophenotype as leukemia cells.

Chronic Lymphocytic Leukemia and Portal Hypertension

Non-cirrhotic portal hypertension complicating CLL has been reported several times (Papadakis et al. 1986; Lindor et al. 1987; Rozman et al. 1989; Nakamura et al. 1989; Mouly et al. 1996; Pauwels et al. 2000). In part of the cases, hepatic infiltration was found to be the likely cause of intrahepatic block of blood flow (Rozman et al. 1989; Pauwels et al. 2000), in particular lymphocytic infiltration of the portal tracts that might impair blood flow from small portal venous branches into the sinusoidal vascular bed (Nakamura et al. 1989; Mouly et al. 1996), thus representing a pre-sinusoidal intrahepatic block. Another pathogenic mechanism is nodular regenerative hyperplasia induced by leukemic infiltration (Rozman et al. 1989). Portal hypertension in CLL can develop in the absence of liver infiltration and has been suggested to be caused by an increased spleno-portal flow (Wilputte et al. 2003). This view is supported by the observation of reversal of portal hypertension upon

resection of an involved spleen (Lindor et al. 1987).

Differential Diagnosis

Without immunohistochemistry, the morphologic presentation of B-CLL may be similar to four other lymphoproliferative diseases, i.e., lymphoplasmacytic lymphoma, lymphomas with a high proportion of centrocytes, prolymphocytic leukemia, and lymphocyte-rich forms of Hodgkin's lymphoma.

General Histopathology of Chronic B-Cell Lymphocytic Leukemia/Small B-Cell Lymphocytic Lymphoma)

The cellular and tissue features of B-CLL/SLL have recently been reviewed (Pileri et al. 2004). On a cellular level, the disorder is characterized by a distinct set of neoplastic lymphoid elements that can be classified into small lymphocytes (about 6 μm diameter), prolymphocytes, and paraimmunoblasts. It is of importance to note that the small lymphocyte component consists of cells that are slightly larger than small nonneoplastic lymphocytes. The basophilic cytoplasm is scant; the nuclei are usually spheroid, with a chromatin structure that is slightly more coarse than that of normal small lymphocytes. Cleaved nuclei resembling the nuclei of centrocytes may occur. Prolymphocytes exhibit an amphophilic or acidophilic cytoplasm and are clearly larger than small lymphocytes, and their nuclei display a small but easily evident nucleolus. Paraimmunoblasts have a diameter more than three times larger than small lymphocytes, a gray cytoplasm in the Giemsa stain, and a frequently ovoid nucleus with a prominent nucleolus.

Immunohistochemically, the cells of interest in B-CLL are reactive for CD19, CD45, CD79a, CD5, and CD23 but less consistently for CD20. CD20 is weakly or not expressed in the small cell component and is markedly expressed in prolymphocytes and paraimmunoblasts. The B-CLL cells are typically reactive for CD5 and CD23, usually more so in prolymphocytes and paraimmunoblasts. Furthermore, the neoplastic B cells usually express Bcl-2, being involved in the apoptosis protection in this long-lived cell population (see above). The cells are also positive for CD27, a typical memory B-cell marker: Small cells express the B-cell-specific activator protein (BSAP) encoded by the PAX-5 gene, while prolymphocytes and paraimmunoblasts gathering in proliferation centers/pseudofollicles express interferon-regulating factor 4 (IRF4) encoded by the MUM-1 gene (under normal conditions typically expressed in cells of the late germinal center cell pathway; cells leaving the germinal centers upon somatic hypermutation to become memory B cells or plasma cells; Pileri et al. 2004). B-CLL cells do not express CD27.

B-Cell Prolymphocytic Leukemia

ICD-O code 9833/3

Introduction

Prolymphocytic leukemia of B-cell subtype (B-PLL) is a very rare, highly aggressive disease with characteristic morphologic, immunocytochemical, cytogenetic, and molecular genetic features. About 1 % of all lymphocytic leukemias are B-PLL (reviews: Melo et al. 1987; Bolding and Jacobs 1988; Krishnan et al. 2006; Dungarwalla et al. 2008). The WHO classification of tumors defines B-PLL as a neoplasm of B prolymphocytes affecting the peripheral blood, bone marrow, and spleen. For diagnosis, prolymphocytes must exceed 55 % of lymphoid cells in the peripheral blood. According to WHO, cases of transformed chronic lymphocytic leukemia (CLL), with increased prolymphocytes, and lymphoid proliferations with relatively similar morphology but carrying the t(11;14)(q13;q32) translocation are excluded. CLL and B-PLL can occur as two concurrent lesions derived from two separate clones (Cao et al. 2011). Recently, B-PLL was considered as a specific subgroup of

leukemic mantle cell lymphoma (van der Velden et al. 2014).

Clinical Features

Clinically, patients with B-PLL experience rapid increase of B prolymphocytes in the peripheral blood and commonly show marked or even massive splenomegaly, with spleen weights sometimes exceeding 2000 g, while lymph node enlargement is not a prominent feature or even lacking (Bearman et al. 1978). In contrast to T-PLL, patients with B-PLL can have a prolonged progression-free survival under adequate therapy (review: Absi et al. 2005), and there is a subset of B-PLL patients who have a more indolent course (Shvidel et al. 1999). In a study of 41 patients with B-PLL, the median age at diagnosis was 67 years, with a male-female sex ratio of 2.4. A high level of surface IgM and/or IgD expression was found in all cases, FMC7+ in 76 %, and CD5+ in 67 %. The median overall survival time was 5 years and the event-free survival time was 37 months. No difference in outcome was found between primary BCPLL and secondary B-PLL derived from CLL (Hercher et al. 2001). Lymphocytic leukemia and B-PLL with MYC translocations are rare entities which seem to be associated with adverse prognostic features and unfavorable outcome (Put et al. 2012).

Morphology

The majority (more than 55 % per definition and often more than 90 %) of circulating cells are prolymphocytes. These are medium-sized cells, about twice the size of normal unstimulated lymphocytes, with a small amount of basophilic cytoplasm, round nuclei with condensed chromatin, and a prominent central nucleolus. Ultrastructurally, B-PLL is characterized by the predominance of a relatively large lymphoid cell with a prominent nucleolus, well-condensed peripheral nuclear chromatin, and a variable amount of heterochromatin in intranuclear clumps (Costello et al. 1980). The immunophenotype is characterized by strong expression of surface IgM and usually also IgD, the cells being positive for B-cell markers (CD19, CD20, CD22, CD79a and b, and FMC7). Twenty to thirty percent of cases show positivity for CD5 and 10–20 % for CD23.

Liver Involvement

Similar to the spleen, B-PLL can cause infiltration of the liver with prolymphocytes in a CLL-like distribution pattern (Lampert et al. 1980). These cells are present in the lumina of hepatic sinusoids, depending on the leukemic cell count in the peripheral blood. More impressive are often dense leukemic cell infiltrates occupying the expanded portal tracts, in a pattern often closely resembling that seen in B-CLL . The neoplastic cells first fill the portal tract space, encroaching upon small bile ducts and blood vessels. In the course of the disease, the cells leave the filled portal tract compartment and start to invade the periportal lobular zone 1, causing an ill-defined "blue" and highly cellular infiltrate effacing the portal tract structure. In case of massive hepatic infiltration, acute hepatic failure may ensue (Steidl et al. 1994).

Cytogenetic and Molecular Genetic Features

Complex karyotypes are common in B-PLL. Among these, del(17p) is detectable in 50 % of cases and is associated with p53 mutations. In cells of B-PLL, Ig genes are clonally rearranged with an unmutated heavy chain gene in about half of the cases. CLL and B-PLL have different and distinctive gene expression signatures (review: Del Giudice et al. 2009). B-PLL shows the highest rate of p53 mutations in B-cell malignancies and may be a major factor responsible for the aggressive course with frequent resistance to therapy (Lens et al. 1997). In a subset of B-PLL, BRAF V600E mutation has been detected (Langabeer et al. 2012). B-PLL and CLL with MYC gene

translocations form a subgroup with an aggressive disease course (Put et al. 2012).

Follicular Lymphoma of the Hepatobiliary Tract

ICD-O codes:

Follicular lymphoma	9690/3
Grade 1	9695.3
Grade 2	9691/3
Grade 3A	9698/3
Grade 3B	9698/3

Introduction

According to the definition of the WHO classification, follicular lymphoma (FL) is a neoplasm composed of follicle center (germinal center) B cells, typically both centrocytes and centroblasts/large transformed cells. This lymphoma typically produces a follicular pattern (at least partially). In case of complete formation of large follicular structures resembling giant follicles with germinal centers, the lesion is what has previously been termed Brill-Symmers disease (synonyms: giant follicular lymphoblastoma; giant follicular lymphoma, germinoblastoma; Brill et al. 1925; Symmers 1927). If diffuse areas of any size comprised predominantly or entirely of blastic lymphoid cells are present in any case of follicular lymphoma, a diagnosis of diffuse large B-cell lymphoma is also made (reviews: Klapper 2011; Roulland et al. 2011; Stevenson and Stevenson 2012).

Follicular lymphoma is a rather common lesion in the non-Hodgkin's lymphoma group, with about 20 % of all lymphomas. This high figure is, however, only valid for the USA and Western Europe; in Eastern Europe and Asia, FH is less common. FL is mainly a neoplasm of adults, most patients being diagnosed with FL in the sixth decade, with a slight female preponderance. In the pediatric age group, which is rarely involved, males clearly predominate. FL is mainly a disease of lymph nodes, but also the extranodal lymphatic tissues, including the spleen, are regularly involved. Infiltration of solid organs usually occurs in patients with extensive nodal disease, but (apparently) primary involvement of deep organs also occurs. Similar to other lymphomas, FL can transform to an aggressive lymphoma (Wong and Dickinson 2012).

Clinical Features

Patients commonly show widespread nodal involvement at diagnosis, often with splenomegaly, but the majority of patients are asymptomatic at diagnosis (Freedman 2012). Bone marrow involvement is found in 40–70 % of patients. Patients with FL are classified in regard to risk by use of the international prognostic index (FLIUPI) in the National LymphoCare Study (NLCS). FL in the pediatric age group differs in several respects from adult-type FL (Louissaint et al. 2012).

Morphology and Grading

The hallmark of FL is the presence of lesion mimicking lymphoid follicles that efface the preexisting lymphoid tissue or form a tumorous lesion in non-lymphoid tissues and organs. The follicles usually lack a well-defined mantle zone and typically lack macrophages with tingible bodies. In case of large follicular structures (Brill-Symmers pattern), a distinction between hyperplastic normal follicles and neoplastic lesions may be difficult, but immunostaining for follicular dendritic cells (Cd21/Cd23) will deliver the correct answer. Cytologically, FL is composed of two cell types of the B-cell lineage, i.e., small- to medium-sized cells with angulated or cleaved nuclei and scant cytoplasm (the centrocytes) and large cells, with round to oval nuclei and a thin rim of cytoplasm (the centroblasts). Centroblasts are always present, but usually form the minority. In part of the cases, FL cells may contain prominent Dutcher body formation (Wang et al. 2012a). Dutcher bodies (Dutcher and Fahey 1959) are intranuclear and intracytoplasmic, PAS-positive, Ig chain-related glycoprotein inclusions that were first recognized in patients with Waldenström's disease. The nuclear inclusions are in fact invaginations of cytoplasmic inclusions.

Table 1 Grading of follicular lymphoma (WHO classification 2008)

Grading	
Grade 1–2: Low grade	
Grade 1: 0–5 centroblasts per HPF	
Grade 2: 6–15 centroblasts per HPF	
Grade 3: High grade, >15 centroblasts per HPF	
Grade 3A: Centrocytes present	
Grade 3B: Solid sheets of centroblasts	
Reporting of pattern	***Proportion follicular***
Follicular	>75 %
Follicular and diffuse	25–75 %
Focally follicular	<25 %
Diffuse	0 %
Diffuse areas containing >15 centroblasts per HPF are diagnosed as diffuse large B-cell lymphoma with follicular lymphoma	

Grading of FL (Table 1), based on the proportion of centroblasts, has been advocated as a prognosticator, but the significance of FL grading is still debated. In principle, FL grading is based on counting or estimating the proportion or absolute number of centroblasts in ten neoplastic follicles at 40× magnification (high-power field, HPF), whereby at least ten HPFs within different follicles are evaluated.

Grade 3B is currently identified as a distinct entity by molecular analysis. Transformation to diffuse follicular lymphoma, characterized by a neoplastic proliferation of cells resembling centrocytes in the absence of a follicular pattern, occurs in about 30–40 % of patients, at a rate of around 3 % each year. Diffuse (or high-grade) transformations confer a more aggressive course (review: Takata et al. 2014). The cells must display immunohistochemical features of germinal center cells, and the diagnosis should only be made with an adequate tissue sample, as diagnosis is prone to considerable sampling error.

Immunohistochemically, the tumor cells express B-cell markers (CD19, CD20, CD22, CD79a). They are also reactive for BCL2, BCL6, and CD10, but negative for CD5, CD43, and IRF4/MUM1. The follicular areas may show sparse networks or meshworks of CD21-positive follicular dendritic cells. The tumor cells are usually positive for surface Igs. At least part of neoplastic cells express centerin (SERPINA9/GCEt1), a germinal center serpin variant (Frazer et al. 2000; Pan et al. 2003; Montes-Moreno et al. 2008). In part of FL, centerin is strongly expressed (Paterson et al. 2008).

Primary Follicular Lymphoma of the Hepatobiliary Tract

Primary follicular lymphoma of the liver has only been reported few times (Torres 1969; Michetti et al. 1978; Ryan et al. 1988; Ohsawa et al. 1992; Lei 1998; Yeshurun et al. 2001; Bronowicki et al 2003; Gomyo et al. 2007; Raimondo et al. 2012). It is estimated that only about 1–4 % of primary hepatic lymphomas are FL (Ohsawa et al. 1992). Primary FL of the liver may present as a solitary nodule or multiple nodules, sometimes mimicking a primary epithelial hepatic tumor. In a compilation of nine cases from the literature, five cases were solitary and four were multiple tumors (Gomyo et al. 2007). In case of multiple lesions, FL can cause marked hepatomegaly. In an autopsy case, the liver weighed 2240 g, and both the external and cut surfaces were studded by in part confluent nodules of tumor, some having a shallow central dimpling and measuring from 1.0 to 2.0 cm in diameter. Microscopically, the nodules consisted of lymphocytic NHL forming numerous and sometimes very large follicular aggregates that had effaced the liver structure, with some remaining small bile ducts reflecting previous portal tracts (Torres 1969). In case of marked hepatic infiltration, acute liver failure may be the initial manifestation of low-grade hepatic FL (Yeshurun et al. 2001). The follicular pattern may vary from one part of the hepatic tumors to the other, the more diffuse growth pattern of the lymphoma irregularly blending into the partly atrophic liver substance. The portal tract infiltrate can encroach upon damaged interlobular bile ducts, thus inducing a "lymphomatous bile duct lesion."

Primary FL has also been identified in extrahepatic bile ducts, in one patient mimicking a hilar cholangiocarcinoma (Sugawara et al. 2008; Christophides et al. 2009).

Secondary FL Involvement of the Liver

The liver can be involved in widespread FL (Fig. 5). Several cases have been described as liver involvement in Brill-Symmers disease or not otherwise specified lymphomas with formation of follicle-like structures (Terplan 1929; Symmers 1942; Cohen and Bergstrom 1946; Wells 1954; Wissmer et al. 1955; Fresen 1956; Baessler 1959). In the early report of Terpan (1929), the disorder is described as a "granuloma-like systemic disease," the giant follicles interpreted as granulomatous lesions. Symmers' patient (1942) showed, at autopsy, a markedly enlarged liver with tumor-like infiltrates measuring up to 1 cm in diameter. The patient of Cohen and Bergstrom (1946) showed white focal lesions of 1–2 mm size in the liver at autopsy. Among 31 patients with stage II–IV disease, 2 had liver involvement (Takagi et al. 1989).

Differential Diagnosis

An important histopathologic differential diagnosis of FL of the truly follicular type is nodular lymphoid hyperplasia of the liver (Jimenez et al. 2007). The much rarer diffuse variety may be confounded with other diffusely growing hepatic lymphomas.

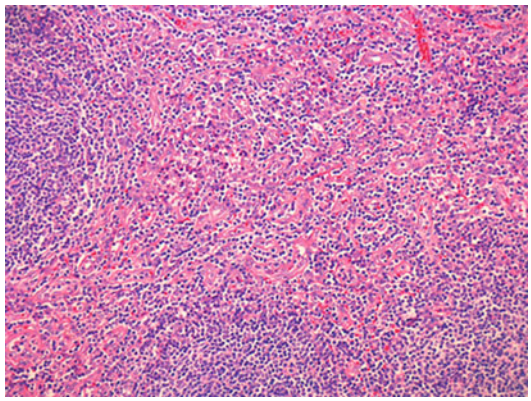

Fig. 5 Follicular non-Hodgkin's lymphoma of the liver. Abnormal follicular structures are found to the *left* and at the *bottom* of the figure (hematoxylin and eosin stain)

Cytogenetic and Molecular Features

Approximately 80 % of FL exhibit the translocation t(14;18)(q32;q21) and BCL2 gene rearrangements, mainly in low-grade lesions. This translocation is therefore a genetic hallmark of FL (review: Kishimoto and Nishikori 2014). BCL2 rearrangements are much less common in grade 3B FL. Five to fifteen percent of FL show abnormalities in 3q27-28 and/or BCL6 rearrangements, predominantly in low-grade lesions (grade 3B). Various other chromosomal and molecular abnormalities have been identified in FL (Oricchio et al. 2011; Kridel et al. 2012). Most patients with FL variably express BAFF (B-cell activation factor) and BAFF-RE, high expression of BAFF-R being an independent risk factor for overall survival (Li et al. 2012). Epigenetic inactivation of p16, p15, MGMT, and DAPK genes can take place in FL, concurrent hypermethylation of MGMT and DAPK genes being markers of chemoresistance and disease recurrence (Krajnovic et al. 2013). FL is characterized by a unique microRNA signature, whereby miR-20a/b and miR-194 targeting CDKN1A and SOCS2 potentially contribute to tumor cell proliferation and survival (Wang et al. 2012b). Apart from the neoplastic lymphoid B cells, the lymphoma's microenvironment is an important factor for tumor progression (Wahlin et al. 2012), and stromal cells associated with FL lymphoma cells play a significant pathogenic role (Mourcin et al. 2012). Furthermore, follicular helper T cells play a role for the survival of follicular neoplastic B cells (Amé-Thomas et al. 2012).

Mantle Cell Lymphoma of the Liver

ICD-O 9673/3

Introduction

According to the 2008 WHO classification, mantle cell lymphoma (MCL) is defined as a B-cell neoplasm composed of monomorphic small- to medium-sized lymphoid cells with irregular

nuclear contours and a CCND1 translocation. MCL is a rare lymphoma which account for about 3–10 % of all non-Hodgkin's lymphomas. The average age at diagnosis is 60 years, with a variable male predominance. The most common site of involvement is the lymph nodes, but the spleen and bone marrow also often participate, and the peripheral blood may be involved. A typical manifestation in the gastrointestinal tract is multiple lymphomatous polyposis. Clinically, many patients present with advanced stage at diagnosis, with lymphadenopathy, hepatosplenomegaly, and bone marrow and peripheral blood involvement (Weisenburger et al. 1982; Swerdlow et al. 1983; Decaudin et al. 1997; Lai and Medeiros 2000; Sander 2011; Kiel and Smith 2012; Shah et al. 2012; Vose 2013; Dreyling and European Mantle Cell Lymphoma Network 2014; Gordon et al. 2014).

Morphology

MCL is characterized by a monomorphic proliferation of small- to medium-sized lymphoid round cells with irregularly shaped nuclei, resembling centrocytes. Centroblast-like cells are absent. In nodes, these cells reveal a growth pattern with diffuse, vaguely nodular, mantle zone or rarely follicular areas. MCL often shows hyalinized small vessels. Large infiltrates may have interspersed pale histiocytes/macrophages, sometimes with a "starry sky" effect. MCL has few variants of prognostic significance, including blastoid and pleomorphic variants. Immunocytochemically, the cells express surface IgM/IgD, more often with a lambda than kappa light chain restriction. Cells are reactive for CD5, CD43, FMC-7, cyclinD1, and BCL2, but negative for CD10 and BCL6.

Liver Involvement

Primary Hepatic Mantle Cell Lymphoma

In rare instances, MCL was observed to develop as a primary liver lymphoma (Itoh et al. 1995; Lei et al. 1995; Zhang et al. 2010).

Secondary Involvement of the Liver

Involvement of the liver has been documented several times (Swerdlow et al. 1983; Franchi et al. 1995; Sousa et al. 1997). In a study of 102 patients, the liver was infiltrated in 22.64 % of cases (Ji et al. 2007). Also the blastic variant can involve the liver substance (Rodler et al. 2004). As in other small to intermediate cell lymphomas, the portal tract space is the preferential compartment for tumor cell proliferation and homing, with variable extension into the periportal lobular zone 1 ("lymphomatous piecemeal necrosis"; lymphomatous interface lesions). MCL can undergo peritoneal seeding (Bahat et al. 2010) and may thus involve the liver capsule.

Differential Diagnosis

As cyclinD1 is normally not expressed in B lymphocytes, cyclinD1 immunostaining is the key diagnostic marker for MCL and a chief discriminator in differential diagnoses of liver lymphomas.

Cytogenetic and Molecular Features

There is clonal rearrangement of Ig genes. Almost all cases show the translocation t(11;14)(q13;q32) juxtaposing IGH and cyclinD1/CCND1, considered as the primary genetic event in MCL lymphomagenesis (Jares et al. 2012; Royo et al. 2011; Dreyling and European Mantle Cell Lymphoma Network 2014). The translocation causes a reregulated overexpression of cyclinD1. In a simplified pathogenetic scheme, the cyclinD1/cyclin-dependent kinase 4/6 complex promotes phosphorylation of the retinoblastoma protein, Rb, leading to the release of the E2F transcription factors inducing progression through the cell cycle into S phase. The 4/6 complex is inhibited by p16INK4a. There are several molecular/cytogenetic variants of MCL, including cyclinD1-negative MCL, cases with trisomy 12, MYC translocation, and BCL6/3q27 translocation. In cyclinD1/CCND1-negative MCL,

CCDN2 rearrangements were the most frequent genetic events (Salaverria et al. 2013). Recently, several recurrent mutations were identified in MCL, including ATM, CCND1, MLL2, TP53, RB1, WHSC1, POT1, and SMARCA4 genes (Zhang et al. 2014). In addition, MCL shows a high number of nonrandom secondary chromosomal aberrations. Among molecular subsets of MCL, those defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features (Navarro et al. 2012). In MCL biology and progression, the composition and features of the microenvironment play a significant role, e.g., the production of IL-6, which is an MCL survival factor (Zhang et al. 2012).

Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma)

ICD-O: 9699/3

Introduction

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT; MALT lymphoma) is a low-grade extranodal NHL developing in several extranodal sites, including the gastrointestinal tract, thyroid gland, salivary glands, ocular adnexa, lung, breast, and liver. This type of lymphoma accounts for about 8 % of NHLs and 50 % of primary gastric lymphomas. Most cases develop in adults, with a median age at diagnosis of 61 years, with a slight female preponderance. MALT lymphomas belong to the group of marginal zone B-cell lymphomas (MZBL). Several features suggest that the three different clinicopathologic types of MZBL (nodal, extranodal, and splenic MZBL) are in fact three different diseases. Clinically, most patients present with stage I or stage II disease. Only a minority of patients show bone marrow involvement. Multiple extranodal sites may be affected in up to 25 % of patients with gastric MALT lymphoma and up to 45 % in those with extragastric disease (Isaacson and Du 2004; Zinzani 2012).

Morphology

In lymph nodes, the tumor cells of MALT lymphoma grow in a marginal zone distribution and spread out to form diffuse confluent areas. The cells are small to medium sized, with slightly irregular nuclei and inconspicuous nucleoli, part of the cells closely resembling centrocytes. The cytoplasm is rather abundant and pale, resulting in a monocytoid morphology. In gastric MALT lymphoma, up to a third of cases reveal plasmacytoid differentiation. A minority of cells exhibit a centroblast-like morphology. Where the tumor cells are in contact with epithelial surfaces or glandular structures, lymphoepithelial lesions develop. Small groups of lymphoma cells are in close association with epithelial cells, associated with epithelial disarray and signs of epithelial damage, such as eosinophilic degeneration. Immunocytochemically, the cells express IgM and less often IgA and IgG and are reactive for CD20, CD79a, CD21, CD35, and, rarely, CD5, negative for CD10 and CD23, and variably positive for CD43. A novel selectively expressed marker for MALT lymphoma is immunoglobulin superfamily receptor translocation-associated 1/IRTA1 (Falini et al. 2012).

Liver Involvement

Primary Hepatic Low-Grade MALT Lymphoma

Primary low-grade marginal zone B-cell lymphoma of MALT of the liver is very rare, less than 50 cases having been reported (Isaacson et al. 1995; Ueda et al. 1996; Maes et al. 1997; Prabhu et al. 1998; Ascoli et al. 1998; Kirk et al. 1999; Ye et al. 2000; Chen et al. 2000; Charton-Bain et al. 2000; Murakami et al. 2002; Yago et al. 2002; Golli et al. 2003; Mehrain et al. 2003; Takeshima et al. 2004; Gockel et al. 2005; Nart et al. 2005; Hamada et al. 2006; Shin et al 2006; Doi et al. 2008; Koubaa Mahjoub et al. 2008; Nakayama et al. 2010; Kiesewetter et al. 2012; Kikuma et al. 2012; Yu et al. 2013; Zhong et al. 2014). In most cases reported so far,

the hepatic NHL was identified incidentally, usually by imaging investigations for liver dysfunction or other diseases, including metastases (Chatelain et al. 2006). Nodules of MALT lymphoma can in fact closely mimic liver metastases. Among the 14 patients reviewed in a recent study (Murakami et al. 2002), nine patients were female, and this NHL involved elderly patients (median age: 64 years). Seven of the patients had preceding but variable liver disease. The lymphoma can be associated with HCV infection (Yago et al. 2002; Bronowicki et al. 2003; Orrego et al. 2005; Viswanatha and Dogan 2007; Arcaini et al. 2012), gastric *Helicobacter pylori* infection (Iida et al. 2007), or primary biliary cirrhosis (Prabhu et al. 1998; Ye et al. 2000; Nakayama et al. 2010). Primary hepatic MALT lymphoma c12/14 lesions were solitary. The dimensions of the hepatic masses ranged from less than 2 to 7.5 cm. Three of the patients reported so far suffered from primary biliary cirrhosis (Prabhu et al. 1998; Ye et al. 2000; Golli et al. 2003). This association had been suggested to eventually be related to an effect of chronic antigenic stimulation favoring the development of MALT-type NHL (Prabhu et al. 1998; Ye et al. 2000). Exceptionally, MALT lymphoma in the liver presents as high-grade lymphoma. In one patient, this lymphoma was diagnosed several years after complete remission of a gastric low-grade MALT lymphoma and was thought to have probably transformed from this gastric lymphoma (Chung et al. 2006).

Macroscopy

In the few cases that have been described, MALT NHL of the liver presented as ill-defined solid and firm masses of grayish-red color, sometimes in close relationship with vessels of bile ducts and with signs of necrosis and hemorrhage (Yu et al. 2013).

Histopathology

In more detail, the nodular hepatic growths in MALT lymphoma of the liver consist of small- to medium-sized cells that are slightly larger than normal small lymphocytes and that show centrocyte-like nuclei . In the Giemsa preparation, the moderate cytoplasm stains light or even clear. In addition to this main cell population, other cell types may occur, including elements with monocytoid features (with kidney-shaped nuclei) and cells resembling lymphoplasmacytoid cells. Similar to MALT NHL in the gastrointestinal tract, where about a third of the cases show cells with a plasma cell differentiation, plasma cells are also seen in hepatic lesions. The diffuse or nodular/follicular growth of NHL of the MALT type is intermingled with usually rather few large basophilic blasts of the immunoblast phenotype. Of particular interest for hepatic MALT lymphoma is the observation that the typical lymphoepithelial lesions are also found, but involving the epithelial lining of bile ducts. These *biliary lymphoepithelial lesions* have been reported in the literature (Maes et al. 1997; Charton-Bain et al. 2000; Ye et al. 2000; Iida et al. 2007; Baumhoer et al. 2008). This type of lesion is characterized by a disarray of involved small- to medium-sized bile ducts, with crowding of nuclei, loss of cholangiocytes, and intraepithelial infiltrates consisting of both tumor cells and normal-looking small lymphocytes. The lesions somewhat resemble the bile duct lesions seen in primary biliary cirrhosis and autoimmune cholangiopathy, and the epithelial damage is best visualized by use of biliary cytokeratin immunohistochemistry.

Immunohistochemistry

Immunohistochemically, the tumor cells express surface immunoglobulins (usually IgM), CD20, and CD79a, but not CD43 or CD45RO (Iida et al. 2007; Doi et al. 2008), the latter in cell subsets displaying varying degrees of plasmacytic differentiation, where also CD38 is positive. There is typically no immunoreactivity for CD23 and cyclin D1, but, in contrast to gastrointestinal NHL of the MALT type, extra-GIT lesions may express CD5. The nodular/follicular components

contain CD23- and CD35-positive follicular dendritic cells, however with variable colonization densities.

Nonparenchymal Involvement of the Hepatobiliary Tract

Extranodal marginal zone B-cell lymphoma of the MALT also occurs in the gallbladder and along the extrahepatic bile ducts to the papilla of Vater (Pelstring et al. 1991; Mosnier et al. 1992; McCluggage et al. 1996; Ventrucci et al. 1998; Bickel et al. 1999; Tsuchiya et al. 2001; Kang et al. 2001; Chim et al. 2002; Isomoto et al. 2003). This issue is further discussed in the part on biliary tumors.

Differential Diagnosis

MALT lymphoma of the liver has to be distinguished from other small B-cell lymphomas, either primary or secondary. Furthermore, hepatic pseudolymphomas may sometimes closely resemble MLAT lymphoma in conventional tissue sections (Willenbrock et al. 2006; Hayashi et al. 2011).

Pathogenic Pathways

The development of MALT lymphoma depends on antigen-driven T-cell-mediated stimulation, whereby, in gastric lymphomas, immune stimulation by *Helicobacter pylori* plays a significant role. MALT lymphoma bears specific translocations (reviews: Müller-Hermelink 2003; Bertoni and Zucca 2006). In the primary and most frequent t(11;18)(q21;q21) translocation, an inhibitor of apoptosis, API2 (apoptosis inhibitor-2), assigned to chromosome 11, and MALT1 are involved in this type of translocation, forming fusion transcripts of different lengths due to several breakpoints in the MALT1 gene and a rather constant breakpoint in the API2 gene. The second translocation, t(14;18)(q32;q21), fuses the immunoglobulin heavy chain gene (IGH) with MALT1. The latter translocation was detected most frequently in MALT lymphomas of the conjunctiva, liver, skin, parotid gland, and other salivary glands. It has furthermore observed that the t(14;18)(q32;q21) transcription can also involve fusion of IGH with bcl-2 in a subset of MALT lymphomas in patients with HCV infection (Libra et al. 2004). There are other translocations in MALT lymphoma, including the recently reported translocation t(X;14)(p11;q32), which deregulates expression of an orphan G-protein-coupled receptor, GPR34 (Ansell et al. 2012), and t(11;14)(q23;q32), involving IGh and DDX6 (Stary et al. 2013).

MALT1/paracaspase is a caspase-like protein making part of an evolutionarily conserved superfamily of caspase-like proteins, the paracaspases and metacaspases (Uren et al. 2000; Yu and Lenardo 2003; Hachmann et al. 2012; Kirchhofer and Vucic 2012; Wiesmann et al. 2012), that holds a central role in lymphocyte activation. This has been demonstrated by the use of paracaspase-deficient mice that are defective in antigen receptor-induced NF-kappaB activation and cytokine production (Ruefli-Brasse et al. 2003). MALT1 contains an N-terminal death domain, two immunoglobulin (Ig)-like domains, and a C-terminal caspase-like domain. MALT1 binds to bcl10 through its Ig-like domains and cooperates with bcl10 to activate NF-kappaB. Chimeric API2/MALT1 proteins are thought to function as oncogenes that bilaterally confer a proliferative advantage to the clone by activating the NF-kappaB signaling pathway and also inhibiting p53 protein-mediated apoptosis (Stoffel et al. 2004; Stoffel and Levine 2004). In fact, the chimeric protein binds to several protein partners that regulate apoptotic pathways, including Smac, HtrA2, and TRAF2 (Hosokawa et al. 2004). The NF-kappaB pathway is affected by a series of adaptor proteins, including MALT1/paracaspase (Hailfinger et al. 2011; Rosebeck et al. 2011), CARMA3 (a member of the membrane-associated guanylate kinase {MAGUK} family of scaffold proteins; Sun 2010; Jiang et al. 2011), BCAP, the E3 ubiquitin ligase mind bomb-2 (Stempin et al. 2011), and BCL10 (B-cell lymphoma 10) (Thome 2004), forming a protein

complex (the CARMA3-BCL10-MALT1 signalosome; Delekta et al. 2010; McAllister-Lucas et al. 2010), depending in its assembly on neuroepithelial transforming gene 1/Net1 (Vessichelli et al. 2012), in which BCL10 is thought to facilitate the oligomerization of MALT1 monomers (Simeoni et al. 2004). By this, the paracaspase MALT1 can potently activate NF-kappaB, suggesting that MALT1 might stimulate the kinase complex (IKK, inhibitor of NF-kappaB kinase) responsible for activating cytoplasmic NF-kappaB for translocation into the nucleus. The tripartite protein complex is also responsible for the ubiquitination of NEMO critical for NF-kappaB activation (Lynch and Gadina 2004). Specifically, BCL10 activates NF-kappaB through ubiquitination of NEMO (Zhou et al. 2004). On the other hand, the CARD domain of BCL10 can also activate NF-kappaB by its own, and both MALT1 and bcl10 seem to do so by a mediating action of TRAF6 ubiquitin ligase and TAK1.

The MALT1/paracaspase oligomers bind to TRAF6, induce TRAF6 oligomerization, and activate the ligase activity of TRAF6 to polyubiquitinate NEMO (Sun et al. 2004). The MALT1/paracaspase is also involved in T-cell receptor-induced NF-kappaB activation. MALT1 is required into the lipid rafts of the immunological synapse following activation of the T-cell receptor (TCR) and the CD28 coreceptor (CD3/CD28 costimulation). This recruitment of MALT1 is dependent on CARMA1, and MALT1 associates with CARMA1 in a bcl10-dependent manner (the tripartite/trimolecular complex; Che et al. 2004). It has recently been shown that expression of MALT1 in hematopoietic stem cells in mice recapitulates the pathogenesis of human lymphoma (Vicente-Duenas et al. 2012).

References

Absi A, His E, Kalaycio M (2005) Prolymphocytic leukemia. Curr Treat Options Oncol 6:197–208

Amé-Thomas P, Le Priol J, Yssel H, Caron G, Pangault C, Jean R, Martin N, Marafioti T et al (2012) Characterization of intratumoral follicular helper T cells in follicular lymphoma: role in the survival of malignant B cells. Leukemia 26:1053–1063

Ansell SM, Akasaka T, McPhail E, Manske M, Braggio E, Price-Troska T, Ziesmer S et al (2012) t(X;14)(p11;q32) in MALT lymphoma involving GPR34 reveals a role for GPR34 in tumor cell growth. Blood 120:3949–3957

Arcaini L, Merli M, Volpetti S, Rattotti S, Gotti M, Zaja F (2012) Indolent B-cell lymphomas associated with HCV infection: clinical and virological features and role of antiviral therapy. Clin Dev Immunol 2012:638185.

Ascoli V, Lo CF, Artini M, Levrero M, Martelli M, Negro F (1998) Extranodal lymphomas associated with hepatitis C virus infection. Am J Clin Pathol 109:600–609

Baessler R (1959) Liver changes in Brill-Symmers disease (in German). Virchows Arch Pathol Anat Physiol Klin Med 332:335–346

Bahat G, Saka B, Yenerel MN, Yilmaz E, Tascioglu C, Dogan O (2010) Peritoneal seeding and subsequent progression of mantle cell lymphoma after splenectomy for debulking. Curr Oncol 17:78–82

Banerji R, Byrd JC (2000) Update on the biology of chronic lymphocytic leukemia. Curr Opin Oncol 12:22–29

Barcos M, Lane W, Gomez GA, Han T, Freeman A, Preisler H, Henderson E (1987) An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). Cancer 60:827–837

Baumhoer D, Tzankov A, Dirnhofer S, Tornillo L, Terraciano LM (2008) Patterns of liver infiltration in lymphoproliferative disease. Histopathology 53:81–90

Bearman RM, Pangalis GA, Rappaport H (1978) Prolymphocytic leukemia: clinical, histopathological, and cytochemical observations. Cancer 42:2360–2372

Bertoni F, Zucca E (2006) Delving deeper into MALT lymphoma biology. J Clin Invest 116:22–26

Bickel A, Eitan A, Tsilman B, Cohen HI (1999) Low-grade B cell lymphoma of mucosa-associated lymphoid tissue (MALT) arising in the gallbladder. Hepatogastroenterology 46:1643–1646

Bolding E, Jacobs P (1988) B-cell prolymphocytic leukaemia – clinical and haematological features. S Afr Med J 73:470–472

Brill NE, Baehr G, Rosenthal N (1925) Generalized giant follicle hyperplasia of lymph nodes and spleen. A hitherto undescribed type. J Am Med Assoc 84:668–671

Bronowicki JP, Bineau C, Fugier P, Hermine O, Brousse N, Oberti F, Rousselet MC et al (2003) Primary lymphoma of the liver: clinical-pathological features and relationship with HCV infection in French patients. Hepatology 37:781–787

Caligaris-Cappio F, Hamblin TJ (1999) B-cell chronic lymphocytic leukemia: a bird of a different feather. J Clin Oncol 17:399–408

Cao F, Amato D, Wang C (2011) Concurrent chronic lymphocytic leukemia and prolymphocytic leukemia

derived from two separate B-cell clones. Am J Hematol 86:782

Charton-Bain MC, Lelong B, Bouabdallah R, Dubus P, Merlio JP, Hassoun J, Xerri L (2000) Hepatic MALT lymphoma disclosing a nodal extension (in French). Ann Pathol 20:137–141

Chatelain D, Maes C, Yzet T, Brevet M, Bounicaud D, Plachot JP, Verhaeghe P (2006) Primary hepatic lymphoma of MALT-type: a tumor that can simulate a liver metastasis (in French). Ann Chir 131:121–124

Che T, You Y, Wang D, Tanner MJ, Dixit VM, Lin X (2004) MALT1/paracaspase is a signaling component downstream of CARMA1 and mediates T cell receptor-induced NF-kappaB activation. J Biol Chem 279:15870–15876

Chen F, Ike O, Wada H, Hitomi S (2000) Pulmonary mucosa-associated lymphoid tissue lymphoma 8 years after resection of the same type of lymphoma of the liver. Jpn J Thorac Cardiovasc Surg 48:233–235

Chim CS, Liang R, Loong F, Chung LP (2002) Primary mucosa-associated lymphoid tissue lymphoma of the gallbladder. Am J Med 112:505–507

Christophides T, Samstein B, Emond J, Bhagat G (2009) Primary follicular lymphoma of the extrahepatic bile duct mimicking a hilar cholangiocarcinoma: case report and review of the literature. Hum Pathol 40:1808–1812

Chung YW, Sohn JH, Paik CH, Jeong JY, Han DS, Jeon YC, Oh YH (2006) High-grade hepatic mucosa-associated lymphoid tissue (MALT) lymphoma probably transformed from the low-grade gastric MALT lymphoma. Korean J Intern Med 21:194–198

Cohen S, Bergstrom V (1946) Giant follicular lymphoblastoma. Am J Clin Pathol 16:22

Costa F, Choy CG, Seiter K, Hann L, Thung SN, Michaeli J (1998) Hepatic outflow obstruction and liver failure due to leukemic cell infiltration in chronic lymphocytic leukemia. Leuk Lymphoma 30:403–410

Costello C, Catovsky D, O'Brien M, Galton DA (1980) Prolymphocytic leukaemia: an ultrastructural study of 22 cases. Br J Haematol 44:389–394

Decaudin D, Bosq J, Munck JN, Bayle C, Koscielny S, Boudjemaa S, Bennaceur A et al (1997) Mantle cell lymphomas: characteristics, natural history and prognostic factors of 45 cases. Leuk Lymphoma 26:539–550

Del Giudice I, Osuji N, Dexter T, Brito-Babaoulle V, Parry-Jones N, Chiaretti S, Messina M et al (2009) B-cell prolymphocytic leukemia and chronic lymphocytic leukemia have distinctive gene expression signatures. Leukemia 23:2160–2167

Delekta PC, Apel IJ, Gu S, Siu K, Hattori Y, McAllister-Lucas LM, Lucas PC (2010) Thrombin-dependent NF-{kappa}B activation and monocyte/endothelial adhesion are mediated by the CARMA3.Bcl10. MALT1 signalosome. J Biol Chem 285:41432–41442

Doi H, Horiike N, Hiraoka A, Koizumi Y, Yamamoto Y, Hasebe A, Ichikawa S, Yano M et al (2008) Primary hepatic marginal zone B cell lymphoma of mucosa-associated lymphoid tissue type: case report and review of the literature. Int J Hematol 88:418–423

Dreyling M, European Mantle Cell Lymphoma Network (2014) Mantle cell lymphoma: biology, clinical presentation, and therapeutic approaches. Am Soc Clin Oncol Educ Book 2014:191–198

Dungarwalla M, Matutes E, Dearden CE (2008) Prolymphocytic leukaemia of B- and T-cell subtype: a state-of-the-art paper. Eur J Haematol 80:469–476

Dutcher TF, Fahey JL (1959) The histopathology of the macroglobulinemia of Waldenström. J Natl Cancer Inst 22:887–917

Esfahani K, Gold P, Wakil S, Michel RP, Solymoss S (2011) Acute liver failure because of chronic lymphocytic leukemia: case report and review of the literature. Curr Oncol 18:39–42

Falini B, Agostinelli C, Bigerna B, Pucciarini A, Pacini R, Tabarrini A, Falcinelli F, Piccioli M et al (2012) IRTA1 is selectively expressed in nodal and extranodal marginal zone lymphomas. Histopathology 61:930–941

Franchi R, Abbiati C, Signaroldi A, Quadrelli G, Maggioni M, Sbalzarini G (1995) Primary lymphoma of the liver – a case report and a review of the literature. Oncol Rep 2:1017–1019

Frazer JK, Jackson DG, Gaillard JP, Lutter M, Liu YJ, Branchereau J, Capra JD et al (2000) Identification of centerin: a novel human germinal center B cell-restricted serpin. Eur J Immunol 30:3039–3048

Freedman A (2012) Follicular lymphoma: 2012 update on diagnosis and management. Am J Hematol 87:988–995

Fresen O (1956) Über Örtlichkeit und Wertigkeit des Morbus Brill-Symmers. Zbl Allg Path Pathol Anat 95:284

Gockel HR, Heidemann J, Lugering A, Mesters RM, Parwaresch R, Domschke W, Lugering N (2005) Stable remission after administration of rituximab in a patient with primary hepatic marginal zone B-cell lymphoma. Eur J Haematol 74:445–447

Golli L, Taieb J, Boleslawski E, Charlotte F, Taboury J, di Martino V, Poynard T, Hannoun L (2003) Mucosa-associated lymphoid tissue hepatic lymphoma with low-grade malignancy associated with primary biliary cirrhosis (in French). Gastroenterol Clin Biol 27:127–129

Gomyo H, Kagami Y, Kato H, Kawase T, Ohshiro A, Oyama T, Kamiya Y, Taji H, Nakamura S et al (2007) Primary hepatic follicular lymphoma: a case report and discussion of chemotherapy and favorable outcomes. J Clin Exp Hematop 47:73–77

Gordon LI, Bernstein SH, Jares P, Kahl BS, Witzig TE, Dreyling M (2014) Recent advances in mantle cell lymphoma: report of the 2013 Mantle Cell Lymphoma Consortium workshop. Leuk Lymphoma 55:2262–2270

Guipaud O, Deriano L, Salin H, Vallat L, Sabatier L, Merle-Beral H, Delic J (2003) B-cell chronic lymphocytic leukaemia: a polymorphic family unified by genomic features. Lancet Oncol 4:505–514

Hachmann J, Snipas SJ, van Raam BJ, Cancino EM, Houlihan EJ, Poreba M, Kasperkiewicz P et al (2012) Mechanism and specificity of the human paracaspase MALT1. Biochem J 443:287–295

Hailfinger S, Nogai H, Pelzer C, Jaworski M, Cabalzar K, Charton JE, Guzzardi M et al (2011) Malt1-dependent RelB cleavage promotes canonical Nf-kappaB activation in lymphocytes and lymphoma cell lines. Proc Natl Acad Sci U S A 108:14596–14601

Hamada M, Tanaka Y, Kobayashi Y, Takeshita E, Joko K (2006) A case of MALT lymphoma of the liver treated by RFA and Rituximab (in Japanese). Nippon Shokakibyo Gakkai Zasshi 103:655–660

Hasuike S, Hayashi K, Abe H, Sasaki H, Iwakiri H, Yamamoto S, Kato J, Uto H, Yamashita K, Hori T, Ido A, Tsubouchi H (2004) Acute hepatic failure due to hepatic involvement by chronic lymphocytic leukemic cells in a patient with chronic hepatitis B. J Gastroenterol 39:499–500

Hayashi M, Yonetani N, Hirokawa F, Asakuma M, Niyaji K, Takeshita A, Yamamoto K et al (2011) An operative case of hepatic pseudolymphoma difficult to differentiate from primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. World J Surg Oncol 9:3

Hercher C, Robain M, Davi F, Garand R, Flandrin G, Valensi F, Vandeputte H, Albert A et al (2001) A multicentric study of 41 cases of B-prolymphocytic leukemia: two evolutive forms. Leuk Lymphoma 42:981–987

Hosokawa et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15150097

Iida T, Iwahashi M, Nakamura M, Nakamori M, Yokoyama S, Tani M, Akamatsu H et al (2007) Primary hepatic low-grade B-cell lymphoma of MALT-type associated with Helicobacter pylori infection. Hepatogastroenterology 54:1898–1901

Isaacson PG, Du MQ (2004) MALT lymphoma: from morphology to molecules. Nat Rev Cancer 4:644–653

Isaacson PG, Banks PM, Best PV, McLure SP, Müller-Hermelink HK, Wyatt JI (1995) Primary low-grade hepatic B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)-type. Am J Surg Pathol 19:571–575

Isomoto H, Kamihira S, Matsuo E, Tawara M, Mizuta Y, Hayashi T, Maeda T, Kohno S, Tomonaga M (2003) A case of mucosa-associated lymphoid tissue lymphoma of the ampulla of Vater: successful treatment with radiation therapy. Eur J Gastroenterol Hepatol 15:1037–1041

Itoh Y, Moriyasu F, Okuma M, Ohno H (1995) Mantle cell lymphoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:299–301

Jares P, Colomer D, Campo E (2012) Molecular pathogenesis of mantle cell lymphoma. J Clin Invest 122:3416–3423

Ji H, Li GD, Li FY, Bai YQ, Chen Y, Yang MZ, Wang LJ, Tang Y, Zhang P, Xia T et al (2007) Mantle cell lymphoma: clinicopathological features and prognostic factors of 102 cases occurring in Chinese patients (in Chinese). Zhonghua Bing Li Xue Za Zhi 36:730–735

Jiang T, Grabiner B, Zhu Y, Jiang C, Li H, You Y, Lang J, Hung MC, Lin X (2011) CARMA3 is crucial for EGFR-induced activation of NF-kB and tumor progression. Cancer Res 71:2183–2192

Jimenez R, Beguiristain A, Ruiz-Montesinos I, Garnateo F, Echenique Elizondo M (2007) Nodular lymphoid hyperplasia of the liver. Pseudolymphoma (in Spanish). Cir Esp 82:241–243

Kang CS, Lee YS, Kim SM, Kim BK (2001) Primary low-grade B cell lymphoma of mucosa-associated lymphoid tissue type of the common bile duct. J Gastroenterol Hepatol 16:949–951

Kiel MJ, Smith LB (2012) Transformation of indolent mantle cell lymphoma to pleomorphic mantle cell lymphoma: case report and review of clinical and morphologic variants. Arch Pathol Lab Med 136:871–875

Kiesewetter B, Müllauer L, Streubel B, Agis H, Hirschl A, Makristathis A, Raderer M (2012) Primary mucosa-associated lymphoid tissue (MALT) lymphoma of the liver: clinical, molecular, and microbiological aspects. Ann Hematol 91:1817–1818

Kikuma K, Watanabe J, Oshiro Y, Shimogama T, Honda Y, Okamura S, Higaki K, Uike N et al (2012) Etiological factors in primary hepatic B-cell lymphoma. Virchows Arch 460:379–387

Kirchhofer D, Vucic D (2012) Protease activity of MALT1: a mystery unravelled. Biochem J 444:e3–e5

Kirk CM, Lewin D, Lazarchick J (1999) Primary hepatic B-cell lymphoma of mucosa-associated lymphoid tissue. Arch Pathol Lab Med 123:716–719

Kishimoto W, Nishikori M (2014) Molecular pathogenesis of follicular lymphoma. J Clin Exp Hematop 54:23–30

Klapper W (2011) Pathobiology and diagnosis of follicular lymphoma. Semin Diagn Pathol 28:146–160

Koubaa Mahjoub W, Chamette-Plnackaert MT, Murga Penas EM, Dierlamm J, Leroy K et al (2008) Primary hepatic lymphoma of mucosa-associated lymphoid tissue type: a case report with cytogenetic study. Int J Surg Pathol 16:301–307

Krajnovic M, Radojkovic M, Davidovic R, Dimitrijevic B, Krtolica K (2013) Prognostic significance of epigenetic inactivation of p16, p15, MGMT and DAPK genes in follicular lymphoma. Med Oncol 30:441

Kridel R, Sehn LH, Gascoyne RD (2012) Pathogenesis of follicular lymphoma. J Clin Invest 122:3424–3431

Krishnan B, Matutes E, Dearden C (2006) Prolymphocytic leukemias. Semin Oncol 33:257–263

Lai R, Medeiros LJ (2000) Pathologic diagnosis of mantle cell lymphoma. Clin Lymphoma 1:197–206

Lampert I, Catovsky D, Marsh GW, Child JA, Galton DA (1980) The histopathology of prolymphocytic leukaemia with particular reference to the spleen: a comparison with chronic lymphocytic leukaemia. Histopathology 4:3–19

Langabeer SE, Quinn F, O'Brien D, McElligot AM, Kelly J, Browne PV, Vandenberghe E (2012) Incidence of the BRAF V600E mutation in chronic lymphocytic leukaemia and prolymphocytic leukaemia. Leuk Res 36:483–484

Lei KI (1998) Primary non-Hodgkin's lymphoma of the liver. Leuk Lymphoma 29:293–299

Lei KI, Chow JH, Johnson PJ (1995) Aggressive primary hepatic lymphoma in Chinese patients. presentation, pathologic features, and outcome. Cancer 76:1336–1343

Lens D, De Schouwer PJ, Hamoudi RA, Addul-Rauf M, Farahat N, Matutes E, Crook T et al (1997) p53 abnormalities in B-cell prolymphocytic leukemia. Blood 89:2015–2023

Li YJ, Jiang WQ, Rao HL, Huang JJ, Xia Y, Huang HQ, Lin TY, Xia ZJ, Li S, Li ZM (2012) Expression of BAFF and BAFF-R in follicular lymphoma: correlation with clinicopathologic characteristics and survival outcomes. PLoS One 7:e50936

Libra M, De Re V, Gloghini A, Gasparotto D, Gragnani L, Navolanic PM, De Vita S, Mazzarino MC, Zignego AL, Carbone A, Boiocchi M (2004) Detection of bcl-2 rearrangement in mucosa-associated lymphoid tissue lymphomas from patients with hepatitis C virus infection. Haematologica 89:873–874

Lindor K, Rakela J, Perrault J, Van Heerden J (1987) Noncirrhotic portal hypertension due to lymphoma. Reversal following splenectomy. Dig Dis Sci 32:1056–1058

Louissaint A, Ackerman AM, Dias-Santagata D, Ferry JA, Hochberg EP, Huang MS et al (2012) Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood 120:2395–2404

Lynch OT, Gadina M (2004) Ubiquitination for activation: new directions in the NF-kappaB roadmap. Mol Interv 4:144–146

Maes M, Depardieu C, Dargent JL, Hermans M, Verhaeghe JL, Delabie J, Pittaluga S, Troufleau P, Verhest A, De Wolf-Peeters C (1997) Primary low-grade B-cell lymphoma of MALT-type occurring in the liver: a study of two cases. J Hepatol 27:922–927

Mann J, Urbanski S, Lategan J, Swain MG (2011) Chronic lymphocytic leukemia-associated cholangiopathy. Can J Gastroenterol 25:356–357

McAllister-Lucas LM, Jin X, Gu S, Siu K, McDonnell S, Ruland J, Delekta PC, Van Beek M et al (2010) The CARMA3-Bcl10-MALT1 signalosome promotes angiotensin II-dependent vascular inflammation and atherogenesis. J Biol Chem 285:25880–25884

McCluggage WG, Mackel E, Mckusker G (1996) Primary low grade malignant lymphoma of mucosa-associated lymphoid tissue of gallbladder. Histopathology 29:285–287

Mehrain S, Schima W, Ba-Ssalamah A, Kutaran A, Raderer M (2003) Primary MALT-lymphoma of the liver: multimodality imaging. Crit Rev Comput Tomogr 44:347–355

Melo JV, Catovsky D, Galton DA (1987) Chronic lymphocytic leukemia and prolymphocytic leukemia: a clinicopathological reappraisal. Blood Cells 12:339–353

Messmer BT, Albesiano E, Messmer D, Chiorazzi N (2004) The pattern and distribution of immunoglobulin VH gene mutations in chronic lymphocytic leukemia B cells are consistent with the canonical somatic hypermutation process. Blood 103:3490–3495

Michetti P, Rebizzo F, Volpi C (1978) A case of nodular lymphoma (so-called giant follicular lymphoma) diagnosed by laparoscopy and hepatic biopsy (in Italian). Pathologica 70:109–113

Montes-Moreno S, Roncador G, Maestre L, Martinez N, Sanchez-Verde L, Camacho FI et al (2008) Gcet1 (centerin), a highly restricted marker for a subset of germinal center-derived lymphomas. Blood 111:351–358

Mosnier JF, Brousse N, Sevestre C, Flejou JF, Delteil C, Henin D, Potet F (1992) Primary low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue arising in the gallbladder. Histopathology 20:273–275

Mouly S, Cochand-Priollet B, Halimi C, Bergmann JF (1996) Portal hypertension caused by intra-hepatic block in chronic lymphoid leukemia (in French). Presse Med 25:497–498

Mourcin F, Pangault C, Amin-Ali R, Amé-Thomas P, Tarte K (2012) Stromal cell contribution to human follicular lymphoma pathogenesis. Front Immunol 3:280

Müller-Hermelink HK (2003) Genetic and molecular genetic studies in the diagnosis of B-cell lymphomas: marginal zone lymphoma. Hum Pathol 34:336–340

Murakami J, Fukushima N, Ueno H, Saito T, Watanabe T, Tanosaki R, Kobayashi Y, Matsuno Y, Tobinai K (2002) Primary hepatic low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue type: a case report and review of the literature. Int J Hematol 75:85–90

Naegeli W (1923) Blutkrankheiten und Blutdiagnostik. Springer Verlag, Berlin

Nakamura N, Kume K, Mori M, Namiki M (1989) Portal hypertension in chronic lymphocytic leukemia (in Japanese). Rinsho Ketsueki 30:2169–2172

Nakayama S, Yokote T, Kobayashi K, Hirata Y, Akioka T, Miyoshi T, Oka S et al (2010) Primary hepatic MALT lymphoma associated with primary biliary cirrhosis. Leuk Res 34:e17–e20

Nart D, Ertan Y, Yilmaz F, Yüce G, Zeytunlu M, Kilic M (2005) Primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type in a liver transplant patient with hepatitis B cirrhosis. Transplant Proc 37:4408–4412

Navarro A, Clot G, Royo C, Jares P, Hadzidimitriou A, Agathangelidis A, Bikos V, Darzentas N et al (2012) Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features. Cancer Res 72:5307–5316

Ohsawa M, Aozasa K, Horiuchi K, Kataoka M, Hida J, Shimada H, Oka K, Wakata Y (1992) Malignant

lymphoma of the liver. Report of five cases and review of the literature. Dig Dis Sci 37:1105–1109
Oricchio E, Nanjangud G, Wolfe AL, Schatz JH, Mavrakis KJ, Jiang M, Liu X, Bruno J et al (2011) The Eph-receptor A7 is a soluble tumor suppressor for follicular lymphoma. Cell 147:554–564
Orrego M, Guo L, Reeder C, De Petris G, Balan V, Douglas DD, Byrne T, Harrison E et al (2005) Hepatic B-cell non-Hodgkin's lymphoma of MALT type in the liver explant of a patient with chronic hepatitis C infection. Liver Transpl 11:796–799
Pan Z, Shen Y, Du C, Zhou G, Rosenwald A, Staudt LM, Greiner TC, McKeithan TW et al (2003) Two newly characterized germinal center B-cell-associated genes, GCET1 and GCT2, have differential expression in normal and neoplastic B cells. Am J Pathol 163:135–144
Papadakis et al. 1986. http://www.ncbi.nlm.nih.gov/pubmed/3946451
Paterson MA, Hosking PS, Coughlin PB (2008) Expression of the serpin centerin defines a germinal center phenotypes in B-cell lymphomas. Am J Clin Pathol 130:117–126
Pauwels M, Pauwels S, Capron JP, Severstre H, Desablins B (2000) Portal hypertension caused by intra-hepatic block during chronic lymphocytic leukemia (in French). Gastroenterol Clin Biol 24:221–224
Pelstring RJ, Essell JH, Kurtin PJ, Cohen AR, Banks PM (1991) Diversity of organ site involvement among malignant lymphomas of mucosa-associated tissues. Am J Clin Pathol 96:738–745
Pileri SA, Sabattini E, Agostinelli C, Bodega L, Rossi M, Zinzani PL, Marafioti T (2004) Histopathology of B-cell chronic lymphocytic leukemia. Hematol Oncol Clin North Am 18:807–826
Prabhu RM, Medeiros LJ, Kumar D, Drachenberg CI, Papadimitriou JC, Appelman HD, Johnson LB et al (1998) Primary hepatic low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) associated with primary biliary cirrhosis. Mod Pathol 11:404–410
Prinz 1951. http://www.ncbi.nlm.nih.gov/pubmed/14836430
Put N, Van Roosbroeck K, Konings P, Meeus P, Brusselmans C, Rack K, Gervais C et al (2012) Chronic lymphocytic leukemia and prolymphocytic leukemia with MYC translocations: a subgroup with an aggressive disease. Ann Hematol 91:863–873
Raimondo L, Ferrara I, Stefano AD, Cella CA, D'Armiento FP, Ciancia G, Moretto R et al (2012) Primary hepatic lymphoma in a patient with previous rectal adenocarcinoma: a case report and discussion of etiopathogenesis and diagnostic tools. Int J Hematol 95:320–323
Rodler E, Welborn J, Hatcher S, Unger K, Larkin E, Gumerlock PH, Wun T, Richman C (2004) Blastic mantle cell lymphoma developing concurrently in a patient with chronic myelogenous leukemia and a review of the literature. Am J Hematol 75:231–238
Rosebeck S, Madden L, Jin X, Gu S, Apel IJ, Appert A, Hamoudi RA, Noels H, Sagaert X et al (2011) Cleavage of NIK by the API2-MALT1 fusion oncoprotein leads to noncanonical NF-kappaB activation. Science 331:468–472
Roulland S, Faroudi M, Mamessier E, Sungalee S, Salles G, Nadel B (2011) Early steps of follicular lymphoma pathogenesis. Adv Immunol 111:1–46
Royo C, Salaverria I, Hartmann EM, Rosenwald A, Campo E, Bea S (2011) The complex landscape of genetic alterations in mantle cell lymphoma. Semin Cancer Biol 21:322–334
Rozman M, Montserrat E, Bruguera M, Grau JM, Teres J, Rozman C (1989) Chronic lymphatic leukemia and portal hypertension: a causal association? (in Spanish). Med Clin (Barc) 92:26–28
Ruefli-Brasse AA, French DM, Dixit VM (2003) Regulation of NF-kappaB-dependent lymphocyte activation and development by paracaspase. Science 302:1581–1584
Ryan J, Straus DJ, Lange C, Filippa DA, Botet JF, Sanders LM, Shiu MH, Fortner JG (1988) Primary lymphoma of the liver. Cancer 61:370–375
Salaverria I, Royo C, Carvajal-Cuenca A, Clot G, Navarro A, Valera A, Song JY, Woroniecka R et al (2013) CCND2 rearrangements are the most frequent genetic events in cyclin D1-negative mantle cell lymphoma. Blood 121:1394–1402
Sander B (2011) Mantle cell lymphoma: recent insights into pathogenesis, clinical variability, and new diagnostic markers. Semin Diagn Pathol 28:245–255
Shah BD, Martin P, Sotomayor EM (2012) Mantle cell lymphoma: a clinically heterogeneous disease in need of tailored approaches. Cancer Control 19:227–235
Shehab TM, Kaminski MS, Lok ASF (1997) Acute liver failure due to hepatic involvement by hematologic malignancy. Dig Dis Sci 42:1400–1405
Shin SY, Kim JS, Lim JK, Hahn JS, Yang WI, Suh CO (2006) Longlasting remission of primary hepatic mucosa-associated lymphoid tissue (MALT) lymphoma achieved by radiotherapy alone. Korean J Intern Med 21:127–131
Shvidel L, Shtalrid M, Bassous L, Klepfish A, Vorst E, Berrebi A (1999) B-cell prolymphocytic leukemia: a survey of 35 patients emphasizing heterogeneity, prognostic factors and evidence for a group with an indolent course. Leuk Lymphoma 33:169–179
Simeoni L, Kliche S, Lindquist J, Schraven B (2004) Adaptors and linkers in T and B cells. Curr Opin Immunol 16:304–313
Sousa AE, Ventura F, Silva AC, Baptista A, Victorino RM, de Moura MC (1997) Centrocytic lymphoma presenting as a subphrenic abscess and a solitary liver nodule. Hepatogastroenterology 44:664–666
Stary S, Vinatzer U, Müllauer L, Raderer M, Birner P, Streubel B (2013) t(11;14)(q23;q32) involving IGH and DDX6 in nodal marginal zone lymphoma. Gene Chromosome Cancer 52:33–43
Steidl L, Rossi A, Comaggia M, Crippa G, Venco A (1994) Prolymphocytic B-cell leukemia with fatal acute liver

failure. A case report (in Italian). Recenti Prog Med 85:186–189
Stempin CC, Chi L, Giraldo-Vela JP, High AA, Häcker H, Redecke V (2011) The E3 ubiquitin ligase mind bomb-2 (MIB2) protein controls B-cell CLL/lymphoma 10 (BCL10)-dependent NF-kB activation. J Biol Chem 286:37147–37157
Stevenson FK, Stevenson GT (2012) Follicular lymphoma and the immune system: from pathogenesis to antibody therapy. Blood 119:3659–3667
Stoffel and Levine 2004. http://www.ncbi.nlm.nih.gov/pubmed/15280657
Stoffel A, Chaurushiya M, Singh B, Levine AJ (2004) Activation of NF-kappaB and inhibition of p53-mediated apoptosis by API2/mucosa-associated lymphoid tissue 1 fusions promote oncogenesis. Proc Natl Acad Sci U S A 101:9079–9084
Sugawara G, Nagino M, Oda K, Nishio H, Ebata T, Nimura Y (2008) Follicular lymphoma of the extrahepatic bile duct mimicking cholangiocarcinoma. J Hepato-Biliary-Pancreat Surg 15:196–199
Sun J (2010) CARMA3: a novel scaffold protein in regulation of NF-kB activation and diseases. World J Biol Chem 1:353–361
Sun L, Deng L, Ea CK, Xia ZP, Chen ZJ (2004) The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes. Mol Cell 14:289–301
Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press, Lyon
Swerdlow SH, Habeshaw JA, Murray LJ, Dhaliwal HS, Lister TA, Stansfeld AG (1983) Centrocytic lymphoma: a distinct clinicopathologic and immunologic entity. A multiparameter study of 18 cases at diagnosis and relapse. Am J Pathol 113:181–197
Symmers D (1927) Follicular lymphadenopathy with splenomegaly: a newly recognized disease of the lymphatic system. Arch Pathol 3:816–820
Symmers D (1942) Clinical significance of the pathologic changes in giant follicular lymphadenopathy. Arch Pathol 34:385
Tadmor T, Bejar J, Attias D, Polliack A (2011) Richter syndrome in chronic lymphocytic leukaemia manifesting only as tumorous hepatomegaly. Br J Haematol 155:135
Takagi T, Sampi K, Sawada U, Kuraishi Y, Takagi K, Mikata A (1989) Follicular lymphoma in Japan: retrospective study on natural history and therapeutic results in 50 cases collected from 4 institutions (in Japanese). Rinsho Ketsueki 30:2123–2128
Takata K, Miyata-Takata T, Sato Y, Yoshino T (2014) Pathology of follicular lymphoma. J Clin Exp Hematop 54:3–9
Takeshima F, Kunisaki M, Aritomi T, Osabe M, Akama F, Nakasone T, Nijno D, Katayama S et al (2004) Hepatic mucosa-associated lymphoid tissue lymphoma and hepatocellular carcinoma in a patient with hepatitis B virus infection. J Clin Gastroenterol 38:823–826
Terplan K (1929) Über eine eigenartige granulomähnliche Systemerkrankung. Verh Dtsch Ges Pathol 24:65
Thome M (2004) CARMA1, BCL-10 and MALT1 in lymphocyte development and activation. Nat Rev Immunol 4:348–359
Torres A (1969) Primary lymphocytic follicular lymphoma of liver. Cancer 23:1185–1189
Tsuchiya T, Shimokawa I, Higami Y, Ohtani H, Shigeoka Y, Ohshima K, Tanaka K, Ayabe H (2001) Primary low-grade MALT lymphoma of the gallbladder. Pathol Int 51:965–969
Ueda G, Oka K, Matsumoto T, Yatabe Y, Yamanaka K, Suyama M, Ariyama J, Futagawa S, Mori N (1996) Primary hepatic marginal zone B-cell lymphoma with mantle cell lymphoma phenotype. Virchows Arch 428:311–314
Uren AG, O'Rourke K, Aravind LA, Pisabarro MT, Seshagiri S, Koonin EV, Dixit VM (2000) Identification of paracaspases and metacaspases: two ancient families of caspase-like proteins, one of which plays a key role in MALT lymphoma. Mol Cell 6:961–967
Van der Velden VH, Hoogeven PG, de Ridder D, Schindler-van der Struijk M, van Zelm MC et al (2014) B-cell prolymphocytic leukemia: a specific subgroup of mantle cell lymphoma. Blood 124:412–419
Ventrucci M, Gherlinzoni F, Sabattini E, Cipolla A, Ubalducci GM, Pileri S (1998) Primary MALT-lymphoma of the papilla of Vater. Dig Dis Sci 43:214–216
Vessichelli M, Ferravante A, Zotti T, Reale C, Scudiero I, Picariello G, Vito P, Stilo R (2012) neuroepithelial transforming gene 1 (Net1) binds to caspase activation and recruitment domain (CARD)-and membrane-associated guanylate kinase-like domain-containing (CARMA) proteins and regulates nuclear factor kB activation. J Biol Chem 287:13722–13730
Vicente-Duenas C, Fontan L, Gonzalez-Herrero I, Romero-Camarero I, Segura V, Aznar MA et al (2012) Expression of MALT1 oncogene in hematopoietic stem/progenitor cells recapitulates the pathogenesis of human lymphoma in mice. Proc Natl Acad Sci USA 109:10534–10539
Viswanatha DS, Dogan A (2007) Hepatitis C virus and lymphoma. J Clin Pathol 60:1378–1383
Vose JM (2013) Mantle cell lymphoma: 2013 update on diagnosis, risk-stratification, and clinical management. Am J Hematol 88:1082–1088
Wahlin BE, Sander B, Christensson B, Ostenstad B, Holte H, Brown PD, Sundström C et al (2012) Entourage: the immune microenvironment following follicular lymphoma. Blood Cancer J 2:e52
Wang E, Stoecker M, Butchette J, Rehder C (2012a) Follicular lymphoma with prominent Dutcher body formation: a pathologic study of 3 cases in comparison with nodal or splenic lymphoplasmacytic lymphoma and marginal zone lymphoma. Hum Pathol 43:2001–2011
Wang W, Corrigan-Cummins M, Hudson J, Maric I, Simakova O, Neelapu SS, Kwak LW et al (2012b)

MicroRNA profiling of follicular lymphoma identifies microRNAs related to cell proliferation and tumor response. Haematologica 97:586–594

Weisenburger DD, Kim H, Rappaport H (1982) Mantle-zone lymphoma: a follicular variant of intermediate lymphocytic lymphoma. Cancer 49:1429–1438

Wells PO (1954) Giant follicular lymphoma. US Armed Forces Med J 5:725

Wierda and Kipps 1999. http://www.ncbi.nlm.nih.gov/pubmed/10400375

Wiesmann C, Leder L, Blank J, Bernardi A, Melkko S, Decock A, D'Arcy A, Villard F et al (2012) Structural determinants of MALT1 protease activity. J Mol Biol 419:4–21

Willenbrock K, Kriener S, Oeschger S, Hansmann ML (2006) Nodular lymphoid lesion of the liver with simultaneous focal nodular hyperplasia and hemangioma: discrimination from primary hepatic MALT-type non-Hodgkin's lymphoma. Virchows Arch 448:223–227

Wilputte JY, Martinet JP, Nguyen P, Damoiseaux P, Rahier J, Geubel A (2003) Chronic lymphocytic leukemia with portal hypertension and without liver involvement: a case report underlining the roles of increased spleno-portal blood flow and "protective" sinusoidal vasoconstriction. Acta Gastroenterol Belg 66:303–306

Wissmer B, Dubois-Ferrière H, Naz E, Wettstein P (1955) Maladie de Brill-Symmers à localisation splenohepatorectale. Arch Mal Appar Dig 44:273

Wong E, Dickinson M (2012) Transformation in follicular lymphoma: biology, prognosis, and therapeutic options. Curr Oncol Rep 14:424–432

Yago K, Shimada H, Itoh M, Ooba N, Itoh K, Suzuki M, Muro H, Nakamura S (2002) Primary low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) –type of the liver in a patient with hepatitis C virus infection. Leuk Lymphoma 43:1497–1500

Ye MQ, Suriawinata A, Black C, Min AD, Strauchen J, Thung SN (2000) Primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type in a patient with primary biliary cirrhosis. Arch Pathol Lab Med 124:604–608

Yeshurun M, Isnard F, Garderet L, Rambeloarisoa J, Prevot S, Carbonell N, Najman A (2001) Acute liver failure as initial manifestation of low-grade non-Hodgkin's lymphoma transformation into large-cell lymphoma. Leuk Lymphoma 42:555–559

Yu L, Lenardo MJ (2003) Immunlogy. The paracaspase connection. Science 302:1515–1516

Yu YD, Kim DS, Byun GY, Lee JH, Kim IS, Kim CY, Kim YC, Suh SO (2013) Primary hepatic marginal zone B cell lymphoma: a case report and review of the literature. Indian J Surg 75(suppl 1):331–336

Zhang ZK, Liu QR, Wu YQ, Hong CF, Li XX (2010) Clinicopathologic feature of primary hepatic mantle cell lymphoma: report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 39:418–420

Zhang L, Yang J, Qian J, Li H, Romaguera JE, Kwak LW, Wang M, Yi Q (2012) Role of the microenvironment in mantle cell lymphoma: IL-6 is an important survival factor for the tumor cells. Blood 120:3783–3792

Zhang J, Jima D, Moffitt AB, Liu Q, Czader M, Hsi ED, Fedoriw Y, Dunphy CH, Richards KL et al (2014) The genomic landscape of mantle cell lymphoma is related to the epigenetically determined chromatin state of normal B cells. Blood 123:2988–22996

Zhong Y, Wang X, Deng M, Fang H, Xu R (2014) Primary hepatic mucosa-associated lymphoid tissue lymphoma and hemangioma with chronic hepatitis B infection as an underlying condition. Biosci Trends 8:185–188

Zhou H, Wertz I, O'Rourke K, Ultsch M, Seshagiri S, Eby M, Xiao W, Dixit VM (2004) Bcl10 activates NF-kappaB pathway through ubiquitination of NEMO. Nature 427:167–171

Zinzani PL (2012) The many faces of marginal zone lymphoma. Hematol Am Soc Hematol Educ Program 2012:426–432

B-Cell Non-Hodgkin's Lymphomas with a Small Cell to Intermediate Cell Phenotype: Special Phenotypes

90

Contents

Abstract

The liver can be involved by several types of rare B-cell lymphoproliferative disorders. Hairy cell leukemia (HCL) is a rather indolent, rare chronic lymphoproliferative disorder that involves a distinct type of small B lymphocytes with oval nuclei and abundant cytoplasm with hairy projections. HCL accounts for 2–3 % of all adult-type leukemias. These neoplastic cells, arrested in a late stage of maturation, accumulate in peripheral blood and diffusely infiltrate bone marrow and inner organs, in particular the spleen. HCL can be associated with autoimmune disorders, such as rheumatoid arthritis and connective tissue diseases. The liver is frequently involved, but hepatomegaly is less common than in chronic lymphocytic leukemia. Histologically, hepatic infiltration ranges from focal cellular infiltrates, mainly in portal tracts, to massive diffuse parenchymal infiltration that may cause liver dysfunction. Rarely, HCL can cause tumoral nodular masses in the liver. The liver can be infiltrated in the setting of the rare disorder, T-cell/histiocyte-rich large B-cell lymphoma, in which scattered large B cells are embedded in a background of abundant T cells. Also, the rare lymphomatoid granulomatosis, defined as an angiocentric B-cell lymphoproliferative disorder associated with EBV infection, can extensively involve the liver.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_90

Hairy Cell Leukemia

ICD-O code 9940/3

Introduction

Hairy cell leukemia (HCL; earlier terms, leukemic reticuloendotheliosis, tricholeukocyte leukemia, trichocellular leukemia, lymphoid myelofibrosis, histio-lymphoctosis; Gosselin et al. 1956; Bouroncle et al. 1958; Duhamel and Guerra 1966; Flandrin et al. 1967; Plenderleith 1970; Ghadially and Skinnider 1972) is an unusual, rather indolent, chronic lymphoproliferative disorders involving a distinct type of small, mature B lymphocytes characterized by oval nuclei and abundant cytoplasm with "hairy" projections. No normal counterpart of this cell has been identified in the maturing B-cell lineage. These cells, which are arrested at a late stage of maturation, involve the peripheral blood and diffusely infiltrate the bone marrow, the spleen, and other inner organs. It is one of the rare NHL disorders, accounting for 2–3 % of all adult-type leukemias (Katayama and Finkel 1974; Staines and Cartwright 1993; Pettitt et al. 1999; Polliack 2002; Goodman et al. 2003; Hockley et al. 2012). Pathogenetically, BRAF V600E mutations are involved in part of the cases.

The term, HCL, refers to a unique morphologic feature of the cells involved, characterized by cytoplasmic projections seen in smears and, less so or not, in tissue sections. A second extraordinary feature of this B-cell neoplasm is the unusual sensitiveness of the disorder to therapy with the agents, interferon alpha and nucleosides. In principle, HCL is a variant of a chronic B-cell lymphoproliferative disorder with a variable propensity for blood involvement and bone marrow suppression. Similar to other chronic B-cell neoplasms, expansion of the abnormal cell population is related to the cells' longevity rather than to increased proliferation (Pettitt et al. 1999).

Clinical Features

The HCL cells have a distinct type of tissue distribution. In contrast to other chronic B-cell lymphoproliferative disease, HCL cells have little or no propensity to populate lymph nodes, whereas the spleen is more frequently, and more severely, involved (Forconi 2011; Galani et al. 2012; review by Cawley 2009). The disease mainly affects middle-aged and old males, with an overall male-to-female ratio of approximately 4:1. The median age of onset is 52 years (Cannon et al. 2008). Most patients show splenomegaly at presentation (mean spleen weight in a study of 16 patients is 1,700 g; Franssila 1983). Common hematological complications, i.e., anemia, neutropenia, monocytopenia, and thrombocytopenia, are mostly due to suppression of bone marrow hemopoiesis by the infiltrating, cytokine-producing HCL cells, to splenomegaly, and to the effects of the frequent infections (Kraut 2003). Infections are still a major cause of morbidity and mortality in HCL patients, possibly related to neutropenia and monocytopenia; a disordered defense is also indicated by the presence of unusual pathogens such as mycobacteria and *Listeria* (Thaker et al. 2001). Very rarely, HCL can undergo blastic transformation associated with the loss of TRAP expression (Nazeer et al. 1997). On the other hand, a nationwide investigation of the Italian Cooperative Group for the Study of HCL did not support the suspicion that patients with HCL are at increased risk for additional second malignancies, although the incidence of lymphoid neoplasms was significantly higher than expected (Federico et al. 2002). For example, it is known that HCL can transform into high-grade lymphomas (Adler et al. 1979; Franssila 1979; Downing et al. 1986; Arnalich et al. 1987; Huang et al. 1987; Sun et al. 2004).

HCL is sometimes associated with autoimmune disorders, including rheumatoid arthritis (Crofts et al. 1979; Zervas et al. 1991), connective tissue disease (Hasselbalch 1984), sclerodermapolymyositis overlap (Blanche et al. 1995), leukoclastic vasculitis (mainly of the skin, occasionally with cryoglobulinemia), systemic vasculitis, periarteritis nodosa, anticardiolipin syndrome, arthritis, rheumatism-like skin nodules, and chronic active hepatitis (Goedert et al. 1981; Dorsey and Penick 1982; Westbrook and Golde 1985; Begley et al. 1985; Farcet

et al. 1987; Salvarani et al. 1989; Shpilberg et al. 1989; Hasler et al. 1995). The recognition of such associations is also important in regard to eventual manifestations of visceral vasculitis in the liver. Less frequently, HCL is associated with sarcoidosis, the development of which may be favored by abnormal immunologic effector cell functions in HCL (Myers et al. 1979; Berthiot 1993; Schiller et al. 2003). However, granulomas can occur in both the liver and spleen in HCL in the apparent absence of sarcoidosis (Yam et al. 1983; Bendix-Hansen and Bayer Kristensen 1984).

Morphology of Leukemic Cells

The distinct features of the HCL cell have been reviewed (Domagala 1975). The unusual "hairy" surface of HCL cells is best recognized by phase microscopy and confirmed by transmission and scanning electron microscopy (Katayama et al. 1972; Fabre et al. 1974; Golomb et al. 1975). Both ruffles and microvilli have been detected in the HCL cells; cells with ruffled areas next to clumps of microvilli have been termed type A cells, while those cells displaying microvilli interspersed among ruffles are called type B cells (Gamliel and Golomb 1986). At EM examination, and sometimes also in light microscopy, the cytoplasm of HCL cells frequently contains so-called ribosome-lamella complexes (Katayama et al. 1972, 1973; Deegan et al. 1976). The production of the characteristic "hairs" or cytoplasmic projections is caused by an abnormal organization of the actin-containing cytoskeleton (Caligaris-Cappio et al. 1986). In HCL, the neoplastic cells circulate in the blood and infiltrate the bone marrow, but also several extramedullary organs, mainly the spleen and also the lymph nodes and the liver. In the marrow, early changes are sometimes characterized by a so-called spongy lymphoid myelofibrosis (Hasselbalch 1984).

Traditionally, expression of tartrate-resistant acid phosphatase (TRAP) is regarded as a characteristic marker of HCL cells. However, TRAP (Acp 5) is not restricted to HCL cells, but is detectable by immunohistochemistry and mRNA Northern blotting in diverse human tissues, particularly epithelial cells and dendritic cells (Hayman et al. 2001). TRAP isoenzyme 5 is detectable in paraffin sections by use of immunohistochemistry. Using a TRAP antibody, it has been shown that less than 50 % of the hairy cells were stained, whereas reactivity for CD20 and DBA.44 was 90 % and 50–60 %, respectively, suggesting that TRAP immunohistochemistry should be used in conjunction with other markers (Hoyer et al. 1997). As TRAP is not specific for the reliable identification of the neoplastic cell lineage in HCL, other markers are currently sought. It has been demonstrated that annexin A1 (ANXA1) is a gene that is upregulated in HCL and that immunocytochemistry using a monoclonal anti-ANX1 antibody is a specific tool for the diagnosis of HCL (Falini et al. 2004; Sherman et al. 2011). In contrast to classical HCL, variant HCL/HCLv cells do not express annexin A1 (Shao et al. 2013). HCL cells strongly express CD103 (Dong et al. 2009; Morgan et al. 2013), CD22, and CD11c and express the p55 chain of the IL-2 receptor (IL-2R) system recognized by anti-CD25 monoclonal antibodies (de Totero et al. 1994), binding IL-2 with low affinity, and p75 IL-2R chain that binds IL-2 with intermediate affinity. The presence of IL-2R on HCL cells confers a proliferative response to IL-15 (Trentin et al. 1997). There is a minority of HCL that does not express CD25 on the cell surface, but IL-2R receptor is detectable in the cytoplasm of the cells involved (Tison et al. 1995). Furthermore, HCL cells express CD52 in the majority of the neoplastic cells, providing a rationale for the use of anti-CD52 (alemtuzumab) in refractory HCL (Quigley et al. 2003). HCL cells express synaptojanin 2, a phosphatidylinositol 4,5-biphosphatase involved in cell growth and rearrangement of actin filaments; it was suggested that overexpression of this protein may correlate with the morphologic features of HCL (Spaenij-Dekking et al. 2003). A further surface marker that characterizes B-cell disorders with circulating hairy or villous cells is CD123 which identifies the alpha chain of the human IL-3 receptor (Del Giudice et al. 2004). A subset of HCL cells is reactive for T-cell

intracellular antigen-1 (TIA-1) in a small, dot-like, granular expression pattern, whereas other B-cell neoplasms are not (Mori et al. 2004).

Liver Changes in Hairy Cell Leukemia

General Features

In HCL, the liver is frequently involved, but the frequence of hepatomegaly is variably reported, either as a common or an uncommon finding. Participation of the liver in the disease process can occasionally cause liver dysfunction (Kraut 2003). In an autopsy study from 21 patients with HCL, liver involvement was present in 19 patients (Dedic 2003). Among 19 HCL patients, eight had hepatomegaly, although all of the 19 had evidence of liver infiltration in the biopsies (Yam et al. 1983).

Hepatic Infiltration with HCL Cells

Infiltration of the liver by the leukemic cells reveals diverse distribution patterns and variable degrees (Burke et al. 1974; Yam et al. 1983; Vardiman and Golomb 1984; Roquet et al. 1985; Zafrani et al. 1987; Itoh et al. 1989; Evans et al. 1992; Andrade et al. 1998; Dedic 2003). The infiltration ranges from focal cellular infiltrates, mainly in the portal tract spaces and cell accumulations within the lumina of sinusoids, to massive diffuse infiltration of almost the entire liver in advanced cases (Fig. 1; Dedic 2003). Massive hepatic infiltration can result in acute liver failure (Valero et al. 2007). Even in asymptomatic chronic liver disease associated with HCL, an extensive mononuclear accumulation in sinusoids was found (Andrade et al. 1998), a feature already emphasized in early reports (Fabre et al. 1974; Burke et al. 1974). It has been proposed that, in liver biopsies, a sinusoidal pattern of involvement is strongly in favor of HCL, in contrast to other types of NHL that preferentially infiltrate the portal tract spaces (Verdi et al. 1986). The accumulation of HCL cells in the sinusoids may be marked, leading to the effacement of the sinusoidal profiles and the perisinusoidal spaces

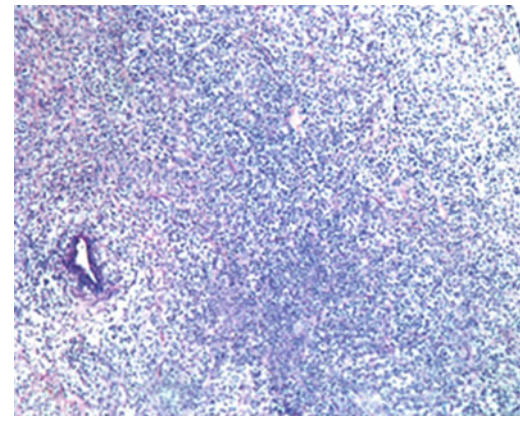

Fig. 1 Nodular infiltration of the liver in hairy cell leukemia (hematoxylin and eosin stain)

(Yam et al. 1983). The cellular features are usually those of a "mononuclear" infiltrate, typically with a so-called clear cell pattern, characterized by a "halo" appearance consisting of a clear rim of abundant cytoplasm surrounding uniform round or slightly indented nuclei. This phenomenon results in a peculiar pattern in case of sinusoidal accumulation of cells, characterized by variably sized, roundish, and clear areas containing the nuclei of the leukemic cells, the latter frequently in a marginal position of the clear areas (Yam et al. 1983; Roquet et al. 1985). The clear aspect of the cells is related to the shaggy cytoplasm which stains poorly with eosin and probably to the loose structures at the cells' periphery caused by the hairy projections (Yam et al. 1983). Interestingly, a hairy phenotype of the cells is more frequently in evidence within sinusoids, while cells forming a portal tract infiltrate more rarely exhibit cytoplasmic projections (Fabre et al. 1974).

The mechanisms of sinusoidal homing are not yet clear. Hairy cell homing seems to depend on CD44-hyaluronan interactions, but this is not relevant to hepatic sinusoids because in sinusoids, hyaluronan is largely absent (Aziz et al. 2000). The HCL cell features may be missed in paraffin sections (or may even not be suggestive of a neoplastic process; Yam et al. 1983), further cell typing requiring immunohistochemistry. The enzyme histochemical detection of HCL cell-related tartrate-resistant acid phosphatase in tissue

is possible in formalin-fixed and paraffin-embedded liver biopsy specimens (Grouls and Stiens 1984). TRAP immunohistochemistry also works in methacrylate-embedded sections (Yam et al. 1983). What is the clinical-biological significance of hepatic infiltration in HCL? In a study on 19 patients, the severity of HCL cell infiltration of the liver correlated poorly with the size of the liver or the spleen, the biochemical changes, or the number of hairy cells in the blood (Yam et al. 1983), confirmed in a later study on 22 patients (Vardiman and Golomb 1984). Very rarely, hepatic infiltration in HCL was associated with signs of fulminant hepatitis, probably caused by a damaging effect of HCL cells on the liver tissue (Evans et al. 1992).

Hepatic Masses Due To Focal HCL Infiltration

Hepatic infiltration in HCL can result in the formation of grossly visible, nodular lesions, ranging in size from 0.2 to 2.5 cm and mimicking a solid primary liver tumor (Katayama and Finkel 1974; Al-Za'abi et al. 2008; Sahar et al. 2009). In the 61-year-old male patient reported by Sahar and coworkers (2009), abdominal imaging and ultrasound first revealed two focal liver lesions presumed to be hemangiomas. Four years later, abdominal CT showed ten hepatic lesions of different sizes. On CT, the lesions had increased in size 3 years later, and two of the multiple lesions were verified to be hemangiomas by red blood cell scans. A tumor biopsy revealed a small-cell neoplasm consisting of cells that were identical to cells of HCL diagnosed in a bone marrow biopsy during the same period of investigation.

Hepatic Vascular Changes

Based on 14 cases of HCL, unique vascular lesions have been observed in splenectomy preparations and wedge biopsies of the liver. The splenic lesions were characterized by markedly distended and dilated sinusal vascular channels filled with erythrocytes (splenic pseudosinuses; Nanba et al. 1977). Interestingly, these channels were lined by HCL cells rather than endothelial cells. Similar changes were detected in the liver in the form of angiomatoid lesions mimicking peliosis hepatis in multifocal aggregates (Nanba et al. 1977; Berard and Nanba 1978). In the study of Nanba and coworkers (Nanba et al. 1977), three of five hepatic biopsies of HCL patients revealed portal tracts that were expanded by angiomatous lesions consisting of numerous dilated blood spaces resembling vascular channels in part extending into lobular zone 1 and thus causing a geographic picture at low magnification. Occasionally, these lesions connected with adjacent portal tracts in a linear fashion, conferring grossly a resemblance to a nutmeg liver (Nanba et al. 1977). Similar lesions were detectable within the lobular parenchyma. It was suggested that these distinct changes were caused by adherence of HCL cells to fibers of the ECM (Berard and Nanba 1978). Angiomatoid changes of sinusoids or sinusoid-like channels consist of intralobular cavities without zonal preference, and the cavities have marginated tumor cells or tumor cells filling the lumina. This angiomatoid lesion, which is apparently only found in HCL, was confirmed in later reports and was found in one study in 9 of 14 patients (Roquet et al. 1985).

The distinct relationship between HCL cells and the walls of sinusoids was investigated by electron microscopy. It was found that HCL cells adhere to the wall of the cavities that exhibited wide areas of communication between the sinusoidal lumen and Disse's space. These disruptions opened the way for HCL cells that were then sometimes in direct contact with hepatocytes. In a detailed ultrastructural investigation, three types of interactions between HCL cells and sinusoidal walls were described. In type I lesions, cytoplasmic processes of the leukemic cells traverse the endothelial lining through gaps ("bouton de chemise"), bifurcate outside, and extend into Disse's space; in type II, numerous projections (en "radicelles") seem to penetrate the endothelium through its fenestrations; and in type III, numerous but short projections slightly indent the endothelial cells (en "chenille," i.e., like a "caterpillar"). These findings illustrate the complexity of the cellular interactions,

suggesting a distinct series of highly ordered events (Fabre et al. 1974). It was suggested that sinusoidal vascular changes are directly caused by the tumor cells themselves (Zafrani et al. 1987). Novel approaches to the interaction of HCL cells with vessel walls are based on the tissue-homing features of all lymphoid cells. Using a human umbilical vein endothelial cell (HUVEC) model, it was found that the receptor-ligand pair, alpha4beta1/VCAM-1, is important for the adhesion of HCL cells to endothelia and accessory cells in tissues (Vincent et al. 1996). In one patient, a unique and large vascular tumorous lesion developed in HCL, causing marked hepatomegaly (Raz et al. 1984). In this patient, the diagnosis of cavernous hemangioma of the liver was done during splenectomy, but afterward, the large hepatic lesion was thought to be caused by the presence of large angiomatous lakes in the liver. Rarely, vasculitis-like lesions known to develop in HCL (see above), but of unknown pathogenesis, also involve hepatic blood vessels. In one report, arteries in the hepatic hilum formed gross nodular structures, causing compression of large bile ducts and hence obstructive jaundice. However, the histopathology of these vascular lesions was clearly different from polyarteritis nodosa: vascular walls exhibited marked edema and intimal fibrosis, but no necrosis, and the involved segments of the vessels were surrounded by leukemic infiltrates that penetrated the walls but infiltrated the entire thickness of the walls only rarely (Klima and Waddell 1984). A similar lesion was described in another report (Elkon et al. 1979).

Chronic Active Hepatitis

Chronic active hepatitis has been observed in HCL and proposed to belong to the spectrum of autoimmune disorders known to occur in this NHL (Begley et al. 1985).

Hepatic Granulomas

Manifestation of HCL in the liver seems to be rather frequently associated with formation of granulomas. In a study of 19 patients, 6 patients had histologically proven hepatic granulomas. These alterations were primarily located in the hepatic lobules, but were also detected within portal tracts in four patients (Yam et al. 1983). It was suggested that the elevation of serum alkaline phosphatase in HCL patients with liver involvement may be related to the presence of granulomas (Yam et al. 1983). In another study of 15 patients, hepatic granulomas were identified in 20 % (Bendix-Hansen and Bayer Kristensen 1984). HCL is known to sometimes be associated with sarcoidosis, another cause of granulomatous organ disease.

Hepatic Fibrosis in HCL

In case of hepatic infiltration in HCL, portal tract fibrosis was often present, but in one study, no patient had evidence of cirrhosis (Yam et al. 1983). Micronodular cirrhosis with "hemochromatosis" was noted in one patient in the series of Burke and coworkers (1974), but the authors did not specify whether the patient really had hereditary hemochromatosis or secondary hepatic overload.

Classification

The main features of HCL cells are their distinct morphology characterized by complex cytoplasmic projections and their particular activation status. However, there are other B-cell proliferative disorders exhibiting cells with projections, leading to the concept of "hairy cell lymphoproliferative disorders (LPD-HC)" (Yavorkovsky et al. 1990; Table 1). Apart from HCL, LPD-HC include splenic B-cell lymphoma with villous lymphocytes (SLVL; Melo et al. 1987), polyclonal B-cell chronic lymphoproliferative disease/hairy B-cell lymphoproliferative disorder (HBLD) (Matsue et al. 1996; Machii et al. 1997; Yagi et al. 2004), and, rarely, plasma cell leukemias (Tanioka et al. 2003). An immunophenotype scoring system has been proposed to distinguish the two probably related disorders, HCL and

Table 1 B-lymphocyte proliferative disorders with cellular/cytoplasmic projections ("hairy cell lymphoproliferative disorders, LPD-HC")

Hairy cell leukemia (HCL) and its variants (Table 2)
Splenic B-cell lymphoma with villous lymphocytes (SLVL)
Plasma cell leukemia with cytoplasmic projections
Polyclonal hairy B-cell lymphoproliferative disorder (HBLD, polyclonal B-cell chronic lymphoproliferative disease)

Table 2 Working classification of hairy cell leukemia (HCL) and its variants

Classic HCL (European-American-type HCL)
Variant HCL
Japanese variant of HCL
CD10+ HCL

SLVL (Matutes et al. 1994). The further subclassification of HCL is not yet universally recognized, but *three variants* have been described: (1) classic HCL (European-American-type HCL), (2) variant HCL, and (3) Japanese variant of HCL, each with distinct clinical and immunophenotype features. Variant HCL (HCLv) has validated diagnostic criteria (Shao et al. 2013) and has been accepted as a new entity in the WHO 2008 classification (Wang et al. 2011). *Classic HCL* is characterized by cells that are almost always positive for CD11c, CD25, and CD103. In contrast, *variant HCL* and *Japanese variant HCL* are CD11c(+), always CD25(−), and occasionally CD103(+). All three variants are typically CD10negative, with very few exceptions (Wu et al. 2000). There emerges a probable further subset of HCL expressing CD10 (CD10+-HCL; Jasionowski et al. 2003). A working classification of HCL is listed in Table 2.

The activation status of HCL cells is evident by the strong expression of cell surface molecules that are associated with normal B-lymphocyte activation, including CD22, CD25, CD72, and CD40. Furthermore, markers normally lost after B-cell activation, such as CD21 and CD24, are expressed only at low levels (review by Pettitt et al. 1999).

Cytogenetic and Molecular Features

There is no cytogenetic abnormality specific for HCL. More than 85 % of HCL cells reveal VH genes with somatic hypermutation indicating a post-germinal center stage of differentiation. By use of gene expression profiling and comparison of HCL cells with several subsets of normal purified B cells, it surfaced that HCL cells are more related to memory B cells (Basso et al. 2004), although the cells are negative for the germinal center-associated markers, CD27 and CD38 (Forconi et al. 2004). HCL commonly expresses multiple immunoglobulin isotypes, a feature rare in other B-lymphocyte malignancies, and genetic analyses have shown that the cells of origin are heterogeneous in terms of mutational status, but reveal common features of activation-induced cytidine deaminase expression and isotype switch events occurring prior to deletional recombination (Forconi et al. 2004). Possible oncogenic pathways in HCL may be related to the expression, in HCL cells, of a T-cell-associated transcription factor, T-bet, that is not expressed in the vast majority of reactive B cells (Dorfman et al. 2004). A BRAF (BRAF kinase) p.V600E mutation has recently been described as a molecular marker of HCL by whole exome sequencing (Tiacci et al. 2011). This BRAF mutation was found to be universally present in this leukemia (Tiacci et al. 2011; Andrulis et al. 2012; Ewalt et al. 2012; Schnittger et al. 2012; Verma et al. 2012). HCL cells express phosphorylated MEK and ERK as downstream targets of the BRAF kinase, and this activation of the RAF-MEK-ERK pathway is a diagnostic target (Tiacci et al. 2013). However, the BRAF mutation was not detected in cases of variant HCL (Xi et al. 2012; Shao et al. 2013). The "hairy" morphology of HCL cells is thought to be driven by overexpression of Rho family small GTPase members and upregulation of the growth arrest-specific molecule Gas7.

Pathophysiological Effects of HCL Cells

The neoplastic cells of HCL seem to affect bone marrow vascularity and to promote angiogenesis

in this tissue compartment. The generation of bone marrow microvessels in HCL seems to infer an increased risk of progression and INF-alpha treatment failure in HCL (Korkolopoulou et al. 2003). Patients with HCL are known to sometimes develop bone marrow reticulin fibrosis, and this seems to be related to a high expression of the fibrokine, TGF-beta1, in TCL cells (Shehata et al. 2004).

T-Cell/Histiocyte-Rich Large B-Cell Lymphoma

ICD-O code 9688/3

Introduction

In the 2008 WHO classification, T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL; synonyms, T-cell-rich B-cell lymphoma, histiocyte-rich/T-cell-rich large B-cell lymphoma) is defined as a neoplasm characterized by a limited number of scattered, large, atypical B cell embedded in a background of abundant T cells and frequently histiocytes. This NHL mainly involves middle-aged men (75 % are men) and accounts for less than 10 % of all diffuse large B-cell lymphomas. In comparison with large B-cell lymphoma, there is a higher incidence of B symptoms (62 %; Aki et al. 2004). THRLBCL mainly affects lymph nodes, but bone marrow and inner organs such as the spleen and liver are also involved in part of the patients, also as a function of disease progression. The lymphoma often presents with high stage at diagnosis (stage III–IV in 64 %; El-Weshi et al. 2007). There is evidence that the cellular composition of this heterogeneous group of lymphomas exerts an impact on tumor biology. Lesions with a high content of histiocytes behave aggressively and are more often resistant to therapy (Rodriguez et al. 1993; Achten et al. 2002; Lim et al. 2002; Bouabdallah et al. 2003; Abramson 2006; Pittaluga and Jaffe 2010; Tousseyn and De Wolf-Peeters 2011). The etiology and pathogenesis of THRLBCL are not known. Transcriptional features suggest a tolerogenic host immune response (Pittaluga and Jaffe 2010).

Morphology

This lymphoma predominantly grows with a diffuse growth pattern, although vague nodular structures may also be found. The typical histologic features are scattered and large B cells in tissues, and infiltrates of small T cells and non-epithelioid histiocytes/macrophages. The large B cells must represent less than 10 % of the cell population. The normal counterpart of the B cells is the germinal center B cell. A picture closely resembling lymphocyte-rich Hodgkin's lymphoma can develop, sometimes with highly atypical B cells, but bona fide Reed-Sternberg cells and eosinophils are lacking. TCRLBCL can be distinguished from classical Hodgkin's lymphoma by the presence of monoclonal IgH rearrangement and the CD30-CD15-CD45 +EMA+ immunophenotype (Fraga et al. 2002). In a minority of cases, the histiocyte component is poorly developed or almost lacking; these tumors may represent what has been termed T-cell-rich B-cell lymphoma. Immunohistochemically, the large scattered cells are reactive for pan B-cell markers and BCL6, and part of the cells express BCL2 and epithelial membrane antigen/EMA. Importantly, expression of CD15, CD30, and CD 138 is absent (Wang et al. 2005). The small lymphocytes are positive for CD3 and CD5 and the histiocytes for CD68. Part of the B cells in THRLBCL express the germinal center serpin, centerin (Montes-Moreno et al. 2008).

Liver Involvement

Primary Involvement of the Liver

Chambers and coworkers (1976) reported a necropsy case of a 55-year-old male patient who had succumbed to a primary hepatic lymphoma. At autopsy, the liver weighed 2,105 g and showed multiple pale nodules alternating with rather hemorrhagic areas almost throughout the liver substance. No tumor was found in the lymph nodes

or the spleen. Even in the absence of immunohistochemical examinations, the histologic description in the report and a histology figure were suggestive of TCRLBCL. The lymphomatous infiltrates were localized to expanded portal tracts and were characterized by scattered large and in part polymorphous lymphoid cells on a background of small lymphocytes and histiocytes with ovoid or reniform nuclei.

Secondary Involvement of the Liver

The liver is one of the deep-seated organs rather often infiltrated by TCRLBCL. The liver is involved in 13–70 % of the patients (Khan et al. 1993; Tajima et al. 1995; Dargent and De Wolf-Peeters 1998; Vidovic et al. 2001; Aki et al. 2004). In a liver biopsy series of eight cases, the main histologic features were a lymphohistiocytic or granulomatous infiltrate, usually centered on portal tracts, containing numerous small T cells and scattered large B cells with a blast-like morphology. In seven of the cases, liver involvement represented stage IV disease of the lymphoma (Khan et al. 1993). Clinically, TCRLBCL may mimic acute hepatitis, considered to be a nonneoplastic liver disease accompanying the lymphoma (Castroagudin et al. 1999).

Differential Diagnosis

The principal histopathologic differential diagnosis is lymphocyte-rich Hodgkin's lymphoma.

Lymphomatoid Granulomatosis

ICD-O code 9766/3

Introduction

Lymphomatoid granulomatosis (LYG) is defined as an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites and composed of EBV-positive B cells admixed with reactive T cells. The latter usually dominate the infiltrates. LYG is a rare condition that usually presents in adult life, although children with immunodeficiency disease can also be affected. Males are at least twice as often involved as females. Based on the first 40 cases that had been described, the disorder mainly involved the lung and usually spared the lymph nodes, spleen, and bone marrow. However, the skin is involved in about 45 %, and nodular renal lesions are encountered in 45 %, and central nervous system involvement occurs in at least 20 % (Liebow et al. 1972). Other common sites of involvement comprise the brain, kidney, and liver. Less common manifestation sites are the upper respiratory tract and gastrointestinal tract. Males predominate in a ratio of two to one, and the disorder usually affects patients in early middle age (Katzenstein et al. 2010). Pulmonary LYG or related disorders may occur as familial lymphoproliferative disorders (Rogers et al. 1992).

There is strong evidence that the pathogenesis of B-cell predominant LYG is related to EBV infection, suggesting that the mechanism of disease is based on a clonal population of EBV-infected B cells and that LYG may represent a T-cell-rich EBV-associated B-cell lymphoproliferative disease (Guinee et al. 1994; Myers et al. 1995; Wilson et al. 1996; Haque et al. 1998). EBV-positive forms of LYG seem to behave in an aggressive way (Nicholson et al. 1996). Patients with underlying immunodeficiency are at increased risk of attracting this EBV-driven B-cell lymphoproliferative disorder, mainly patients with allogeneic organ transplantation, HIV infection, and X-linked lymphoproliferative syndrome. LYG can progress to overt EBV-positive lymphoma (Stravodimou et al. 2012, reviews by Dunleavy et al. 2012 and Roschewski and Wilson 2012).

Clinical Features

As the lung is commonly affected, patients often present with symptoms and signs related to bronchopulmonary disease, such as cough, chest pain, and dyspnea. Constitutional signs, including fever, malaise, weight loss, and myalgias, are frequent. Patients with CNS involvement are either asymptomatic or show complex neurological

deficits. Overall, less than 5 % of patients with LYG are asymptomatic at the time point of diagnosis (Prapphal et al. 1991; Lucantoni et al. 2009; Melegh et al. 2009; Chung et al. 2011; Gonzalez-Darder et al. 2011; Bailie et al. 2012; Hare et al. 2012; Karabag et al. 2012).

Morphology

The histology of this unusual process has been reported in detail (Koss et al. 1986; Colby 2012). It seems that the proliferative process underlying LYG is based on a clonal expansion of B cells, which is also the reason why high-grade lymphomas developing from LYG are usually B-cell neoplasms. LYG is characterized by the presence of a usually small number of EBV-positive B cells, and these EBV+ cells usually show some atypia, resembling immunoblasts or, less frequently, pleomorphic Hodgkin-like cells. This B-cell-based lesion is accompanied by a prominent T-cell component, a phenomenon that may render the differential diagnosis to angiocentric T-cell lymphoma and related lesions difficult. This unique histologic presentation led to the identification of LYG as an angiocentric T-cell-rich B-cell lymphoproliferative disorder (McNiff et al. 1996), but LYG may be a heterogeneous process with subsets of different phenotypes. In fact, recent studies performing detailed phenotyping of cells involved have demonstrated that (1) B cells may represent a minor component, while T cells of the cytotoxic type predominate, and (2) that there are cases where B cells are not, or not easily, detectable, but the lesion is dominated by an expansion of CD3+ T cells of the CD8 type. This led the authors to identify a T-cell variant of LYG (T-cell LYG; Morice et al. 2002). In the LYG variant with B-cell predominance, the spectrum of B-cell proliferation roughly correlates with histologic grade (Guinee et al. 1998). The background contains, in addition to T cells, variable numbers of plasma cells, macrophages (without granuloma formation), and neutrophils. Blood vessels in the tumorous lesions reveal marked alterations, in particular lymphocytic vasculitis. This may lead to vascular obstruction, ischemia, and infarct-like necrosis. LYG is subject to malignancy grading, whereby the distinction of grade 3 vs. grades 1 and 2 is the most important feature. Grade 3 lesions are characterized by increased numbers of large atypical B cells identified as CD20+ elements in a cellular background that is generally less cellular than that in grades 1 and 2. Grade 1 shows only occasional large B cells, while in grade 2 they are more readily found and can form clusters (review by Katzenstein et al. 2010).

Liver Involvement in Lymphomatoid Granulomatosis

The liver is one of the organs that is regularly involved in the setting of generalized spread of LYG (Michaud et al. 1983; Bernstein et al. 1986; Pavlovskaia and Aikimbaev 1988; Nair et al. 1989; Donner et al. 1990). In the review of 40 patients by Liebow and coworkers (1972), clinical liver involvement was found in none, while among 22 necropsies, seven patients (31.5 %) revealed variable involvement.

Macroscopy

In the autopsy data published by Liebow et al. (1972), focal infiltration of the liver was observed in five patients. Gross liver changes were described in a later report (Schjolseth and Blom 1978). Autopsy revealed hepatomegaly, and the soft and yellow organ exhibited multiple grayish-white, irregular but well-demarcated infiltrates up to 1.5 cm in diameter. Another report refers to a 54-year-old male patient having died of abdominal manifestations of LYG (Chen 1977). Necropsy revealed ascites and marked hepatomegaly (2.5 kg), and both the external and the cut surfaces of the liver showed slightly bulging, firm, pale gray, irregular areas of up to 3 cm in diameter involving both liver lobes, interspersed with congested and mildly bile-stained parenchyma. In the case reported by Nair et al. (1989), autopsy showed multiple infarct-like lesions with erythematous borders in the liver.

Histopathology

The LYG infiltrates in the liver are sometimes rather massive and consist predominantly of atypical cells with occasional mitoses, sometimes with circumscribed foci of necrosis, but without the pattern of portal tract infiltrations seen in leukemias and lymphomas of other types. The infiltrates consist of elements similar to those seen in the classical pulmonary lesions, i.e., a mixture of atypical lymphoid cells, histiocytoid cells, and plasma cells. In two patients, the liver lesion was a thick encapsulated necrotic mass likely to represent previous tumor infiltration (Liebow et al. 1972). Some of the lesions mainly involve the portal tracts, exhibiting a variable infiltration by mononuclear cells, with a preponderance of large and bizarre forms. The vessels and the bile ducts were infiltrated as well in one study (Schjolseth and Blom 1978). In another autopsy report, the histology was characterized by irregular connecting areas of necrosis associated with focal density, in part angiocentric mononuclear cell infiltration consisting mainly of lymphocytes, scattered atypical large mononuclear cells, plasma cells, and macrophages. Apart from small hepatic vessels, the cellular infiltrate also involved the walls of medium-sized veins of the capsular area (Chen 1977).

Cytogenetic and Molecular Features

Most cases with grades 2 and 3 show clonality of immunoglobulin chains, based on the presence of neoplastic large B cells. Southern blot analysis displays clonality of EBV.

References

Abramson JS (2006) T-cell/histiocyte-rich B-cell lymphoma: biology, diagnosis, and management. Oncologist 11:384–392

Achten R, Verhoef G, Vanuytsel L, De Wolf-Peeters C (2002) Histiocyte-rich, T-cell-rich B-cell lymphoma: a distinct diffuse large B-cell lymphoma subtype showing characteristic morphologic and immunophenotypic features. Histopathology 40:31–45

Adler SS, Shetty J, Golomb HM (1979) Coexistence of leukemic reticuloendotheliosis and histiocytic lymphoma. Cancer 43:1872–1880

Aki H, Tuzuner N, Ongoren S, Baslar Z, Soysal T, Ferhanoglu B, Sahinler I, Aydin Y et al (2004) T-cell-rich B-cell lymphoma: a clinicopathologic study of 21 cases and comparison with 43 cases of diffuse large B-cell lymphoma. Leuk Res 28:229–236

Al-Za'abi AM, Boerner SL, Geddie W (2008) Hairy cell leukemia presenting as a discrete liver mass: diagnosis by fine needle aspiration biopsy. Diagn Cytopathol 36:128–132

Andrade RJ, Camargo R, Garcia E, Blanes A, Perez-Fernandez I, Ramirez G, Melgarejo F, Franquelo E (1998) A case of hairy cell leukemia resembling asymptomatic chronic liver disease on presentation. Acta Gastroenterol Belg 61:483–484

Andrulis M, Penzel R, Weichert W, von Deimling A, Capper D (2012) Application of a BRAF V600E mutation-specific antibody for the diagnosis of hairy cell leukemia. Am J Surg Pathol 36:1796–1800

Arnalich F, Camacho J, Jimenez C, Lahoz C, Patron M (1987) Occurrence of immunoblastic B-cell lymphoma in hairy cell leukemia. Cancer 59:1161–1164

Aziz KA, Till KJ, Zuzel M, Cawley JC (2000) Involvement of CD44-hyaluronan interaction in malignant cell homing and fibronectin synthesis in hairy cell leukemia. Blood 96:3161–3167

Bailie J, McNaughten B, Gray S, Hamilton J (2012) Unique presentation of testicular involvement in lymphomatoid granulomatosis. Onkologie 35:372–375

Basso K, Liso A, Tiacci E, Benedetti R, Pulsoni A, Foa R, Di Raimondo F, Amdrosetti A, Califano A et al (2004) Gene expression profiling of hairy cell leukemia reveals a phenotype related to memory B cells with altered expression of chemokine and adhesion receptors. J Exp Med 199:59–68

Begley CG, Mackay IR, Bhathal PS (1985) Another immune-mediated disease associated with hairy cell leukemia: chronic active hepatitis. Acta Haematol 73:104–105

Bendix-Hansen K, Bayer Kristensen I (1984) Granulomas of spleen and liver in hairy cell leukaemia. Acta Pathol Microbiol Immunol Scand A 92:157–160

Berard CW, Nanba K (1978) Hairy cell leukemia: vascular changes in spleen and liver. Recent Results Cancer Res 64:213

Bernstein ML, Reece ER, de Chadarévian JP, Koch PA (1986) Bone marrow transplantation in lymphomatoid granulomatosis. Report of a case. Cancer 58:969–972

Berthiot G (1993) Hairy-cell leukaemia and sarcoidosis. Eur J Med 2:61

Blanche P, Bachmeyer C, Mikdame M, Dreyfus F, Sicard D (1995) Scleroderma, polymyositis, and hairy cell leukemia. J Rheumatol 22:1384–1385

Bouabdallah R, Mounier N, Guettier C, Molina T, Ribrag V, Thieblemont C, Sonet A et al (2003) T-cell/histiocyte-rich large B-cell lymphomas and classical diffuse large B-cell lymphomas have similar outcome

after chemotherapy: a matched-control analysis. J Clin Oncol 21:1271–1277
Bouroncle BA, Wiseman BK, Doan CA (1958) Leukemic reticuloendotheliosis. Blood 13:609
Burke JS, Byrne GE, Rappaport H (1974) Hairy cell leukemia (leukemic reticuloendotheliosis). I. A clinical pathologic study of 21 patients. Cancer 33:1399–1410
Caligaris-Cappio F, Bergui L, Tesio L, Caorbascio G, Tousco F, Marchisio PC (1986) Cytoskeleton organization is aberrantly rearranged in the cells of B chronic lymphocytic leukemia and hairy cell leukemia. Blood 67:233–239
Cannon T, Mobarek D, Wegge J, Tabbara IA (2008) Hairy cell leukemia: current concepts. Cancer Invest 26:860–865
Castroagudin JF, Gonzalez-Quintela A, Fraga M, Forteza J, Barrio E (1999) Presentation of T-cell-rich B-cell lymphoma mimicking acute hepatitis. Hepatogastroenterology 46:1710–1713
Cawley J (2009) The biology of hairy cell leukemia. Leuk Lymphoma 50(suppl 1):8–11
Chambers TJ, O'Donohue DP, Stansfeld AG (1976) A case of primary lymphoma of the liver. J Clin Pathol 29:967–970
Chen KT (1977) Abdominal form of lymphomatoid granulomatosis. Hum Pathol 8:99–103
Chung JH, Wu CC, Gilman MD, Palmer EL, Hasserjian RP, Shepard JA (2011) Lymphomatoid granulomatosis: CT and FDG-PET findings. Korean J Radiol 12:671–678
Colby TV (2012) Current histological diagnosis of lymphomatoid granulomatosis. Mod Pathol 25(suppl 1):S39–S42
Crofts MA, Sharp JC, Joyner MV (1979) Rheumatoid arthritis and hairy-cell leukaemia. Lancet 2(8135): 203–204
Dargent JL, De Wolf-Peeters C (1998) Liver involvement by lymphoma: identification of a distinctive pattern of infiltration related to T-cell/histiocyte-rich B-cell lymphoma. Ann Diagn Pathol 2:363–369
De Totero D, Carcbone A, Tazzari PL, Raspadori D, Ventura A, Reato G, Lauria F, Foa R (1994) Expression of the IL2 receptor alpha, beta and gamma chains in hairy cell leukemia. Leuk Lymphoma 14(suppl 1): 27–32
Dedic K (2003) Hairy cell leukemia: an autopsy study. Acta Medica (Hradec Kralove) 46:175–177
Deegan MJ, Cossman J, Chosney BT, Schnitzer B (1976) Hairy cell leukemia. An immunologic and ultrastructural study. Cancer 38:1952–1961
Del Giudice I, Matutes E, Morilla R, Morilla A, Owusu-Ankomah K, Rafiq F, Hern R, Delgado J, Bazerbashi A, Catovsky D (2004) The diagnostic value of CD123 in B-cell disorders with hairy or villous lymphocytes. Haematologica 89:303–308
Domagala M (1975) Letter: the hairy cell. Hum Pathol 6:760
Dong HY, Weisberger J, Liu Z, Tugulea S (2009) Immunophenotypic analysis of CD103+ B-lymphoproliferative disorders: hairy cell leukemia and its mimics. Am J Clin Pathol 131:586–595
Donner LR, Dobin S, Harrington D, Bassion S, Rappaport ES, Peterson RF (1990) Angiocentric immunoproliferative lesion (lymphomatoid granulomatosis). A cytogenetic, immunophenotypic, and genotypic study. Cancer 65:249–254
Dorfman DM, Hwang ES, Shahsafaei A, Glimcher LH (2004) T-bet, a T-cell-associated transcription factor, is expressed in a subset of B-cell lymphoproliferative disorders. Am J Clin Pathol 122:292–297
Dorsey JK, Penick GD (1982) The association of hairy cell leukemia with unusual immunologic disorders. Arch Intern Med 142:902–903
Downing JR, Grossi CE, Smedberg CT, Burrows PD (1986) Diffuse large cell lymphoma in a patient with hairy cell leukemia: immunoglobulin gene analysis reveals separate clonal origins. Blood 67:739–744
Duhamel G, Guerra L (1966) Un syndrome hématologique difficile à définir: la myélosclérose lymphoide. Etude nosologique de six observations. Presse Med 74:585–590
Dunleavy K, Roschewski M, Wilson WH (2012) Lymphomatoid granulomatosis and other Epstein-Barr virus associated lymphoproliferative processes. Curr Hematol Malig Rep 7:208–215
Elkon KB, Hughes GR, Catovsky D, Clauvel JP, Dumont J, Seligmann M, Tannenbaum H, Esdaile J (1979) Hairy-cell leukaemia with polyarteritis nodosa. Lancet 2:280–282
El-Weshi A, Akhtar S, Mourad WA, Ajarim D, Adelsalam M, Khafaga Y, Bazarbashi S et al (2007) T-cell/histiocyte-rich B-cell lymphoma: clinical presentation, management and prognostic factors: report on 61 patients and review of literature. Leuk Lymphoma 48:1764–1773
Evans MA, Gastineau DA, Ludwig J (1992) Relapsing hairy cell leukemia presenting as fulminant hepatitis. Am J Med 92:209–212
Ewalt M, Nandula S, Phillips A, Alobeid B, Murty VV, Mansukhani MM, Bhagat G (2012) Real-time PCR-based analysis of BRAF V600E mutation in low and intermediate grade lymphomas confirms frequent occurrence in hairy cell leukaemia. Hematol Oncol 30:190–193
Fabre J, Delsol G, Fedou R, Pris J (1974) Study of liver biopsies by "hairy cell leukemia" (in French). Virchows Arch B Cell Pathol 15:139–156
Falini B, Tiacci E, Liso A, Basso K, Sabattini E, Pacini R, Foa R, Pulsoni A, Della Favera R, Pileri S (2004) Simple diagnostic assay for hairy cell leukaemia by immunocytochemical detection of annexin A1 (ANXA1). Lancet 363:1869–1870
Farcet JP, Weschsler J, Wirquin V, Divine M, Reyes F (1987) Vasculitis in hairy-cell leukemia. Arch Intern Med 147:660–664
Federico M, Zinzani PL, Frassoladati A, Vincenti M, Mode A, Annino L, Chisesi T et al (2002) Risk of second cancer in patients with hairy cell leukemia: long-term follow up. J Clin Oncol 20:638–646

Flandrin G, Boiron M, Lasneter J, Ripault J, Lortholary P, Tanzer J, Bernard J (1967) Etude par biopsie des infiltrations lymphocytaires de la moelle osseuse. Presse Med 75:2497–2502

Forconi F (2011) Hairy cell leukaemia: biological and clinical overview from immunogenetic insights. Hematol Oncol 29:55–66

Forconi F, Sahota SS, Raspadori D, Ippoliti M, Babbage G, Lauria F, Stevenson FK (2004) Hairy cell leukemia: at the crossroad of somatic mutation and isotype switch. Blood 104:3312–3317

Fraga M, Sanchez-Verde L, Forteza J, Garcia-Rivero A, Piris MA (2002) T-cell/histiocyte-rich large B-cell lymphoma is a disseminated aggressive neoplasm: differential diagnosis from Hodgkin's lymphoma. Histopathology 41:216–229

Franssila KO (1979) Coincidental hairy cell leukemia and large cell malignant lymphoma. Arch Pathol Lab Med 103:437–439

Franssila KO (1983) Hairy cell leukemia. A clinicopathologic study of 16 patients. Ann Clin Res 15:71–79

Galani KS, Subramanian PG, Gadage VS, Rahan K, Sshok Kumar MS, Shinde S et al (2012) Clinico-pathological profile of hairy cell leukemia: critical insights gained at a tertiary care center hospital. Indian J Pathol Microbiol 55:61–65

Gamliel H, Golomb HM (1986) Unique scanning electron microscopic features of hairy cells in hairy-cell leukemia. A review and current status. Scan Electron Microsc 96(Pt 4):1515–1521

Ghadially FN, Skinnider LF (1972) Ultrastructure of hairy cell leukemia. Cancer 29:444–452

Goedert JJ, Neefe JR, Smith FS, Stahl NI, Jaffe ES, Fauci AS (1981) Polyarteritis nodosa, hairy cell leukemia and splenosis. Am J Med 71:323–326

Golomb HM, Braylan R, Polliack A (1975) Hairy cell leukaemia (leukaemic reticuloendotheliosis): a scanning electron microscopic study of eight cases. Br J Haematol 29:455–460

Gonzalez-Darder JM, Vera-Roman JM, Pesudo-Martinez JV, Cerda-Nicolas M, Ochoa E (2011) Tumoral presentation of primary central nervous system lymphomatoid granulomatosis. Acta Neurochir (Wien) 153:1963–1970

Goodman GR, Bethel KJ, Saven A (2003) Hairy cell leukemia: an update. Curr Opin Hematol 10:258–266

Gosselin GR, Hanlon DG, Pease GL (1956) Leukemic reticuloendotheliosis. Can Med Assoc J 74:886–891

Grouls V, Stiens R (1984) Hepatic involvement in hairy cell leukemia: diagnosis by tartrate-resistant acid phosphatase enzyme histochemistry on formalin fixed and paraffin-embedded liver biopsy specimens. Pathol Res Pract 178:332–334

Guinee D, Jaffe E, Kingma D, Fishback N, Wallberg K, Krishnan J, Frizzera G, Travis W, Koss M (1994) Pulmonary lymphomatoid granulomatosis. Evidence for a proliferation of Epstein-Barr virus infected B-lymphocytes with a prominent T-cell component and vasculitis. Am J Surg Pathol 18:753–764

Guinee DG, Perkins SL, Travis WD, Holden JA, Tripp SR, Koss MN (1998) Proliferation and cellular phenotype in lymphomatoid granulomatosis: implications of a higher proliferation index in B cells. Am J Surg Pathol 22:1093–1100

Haque AK, Myers JL, Hudnall SD, Gelman BB, Lloyd RV, Payne D, Borucki M (1998) Pulmonary lymphomatoid granulomatosis in acquired immunodeficiency syndrome: lesions with Epstein-Barr virus infection. Mod Pathol 11:347–356

Hare SS, Souza CA, Bain G, Seely JM, Gomes MM, Quigley M (2012) The radiological spectrum of pulmonary lymphoproliferative disease. Br J Radiol 85:848–864

Hasler P, Kistler H, Gerber H (1995) Vasculitides in hairy cell leukemia. Semin Arthritis Rheum 25:134–142

Hasselbalch H (1984) Hairy-cell leukaemia simulating connective tissue disease. Scand J Haematol 32:457–460

Hayman AR, Macary P, Lehner PJ, Cox TM (2001) Tartrate-resistant acid phosphatse (Acp 5): identification in diverse human tissues and dendritic cells. J Histochem Cytochem 49:675–684

Hockley SL, Else M, Morilla A, Wotherspoon A, Dearden C, Catovsky D, Gonzalez D et al (2012) The prognostic impact of clinical and molecular features in hairy cell leukaemia variant and splenic marginal zone lymphoma. Br J Haematol 158:347–354

Hoyer JD, Li CY, Yam LT, Hanson CA, Kurtin PJ (1997) Immunohistochemical demonstration of acid phosphatase isoenzyme 5 (tartrate-resistant) in paraffin sections of hairy cell leukemia and other hematologic disorders. Am J Clin Pathol 108:308–315

Huang AT, Silverstein L, Gonias SL, Rundles RW, Raab-Traub N (1987) Transformation of hairy cell leukemia to EBV genome-containing aggressive B cell lymphoma. Leukemia 1:369–372

Itoh S, Matsuo S, Shimoji K, Oda T, Sasaki I, Katayama I (1989) The effect of alpha-interferon on the liver in a patient with hairy cell leukemia: light and electron microscopic studies. Am J Gastroenterol 84:942–947

Jasionowski TM, Hartung L, Greenwood JH, Perkins SL, Bahler DW (2003) Analysis of CD10+ hairy cell leukemia. Am J Clin Pathol 120:228–235

Karabag T, Aydin M, Barut F, Buyukates M, Dogan SM, Celik O, Sayin MR (2012) Epicardial mass causing cardiac compression: an unusual involvement in lymphomatoid granulomatosis. Tex Heart J 39:116–118

Katayama I, Finkel HE (1974) Leukemic reticuloendotheliosis: a clinicopathologic study with review of the literature. Am J Med 57:115–126

Katayama L, Li CY, Yam LT (1972) Ultrastructural characteristics of the 'hairy cells' of leukemic reticuloendotheliosis. Am J Pathol 67:361–366

Katayama I, Nagy GK, Balogh K (1973) Light microscopic identification of the ribosome-lamella complex in "hairy cells" of leukemic reticuloendotheliosis. Cancer 32:843–846

Katzenstein AL, Doxtader E, Narendra S (2010) Lymphomatoid granulomatosis: insights gained over 4 decades. Am J Surg Pathol 34:e35–e48

Khan SM, Cottrell BJ, Millward-Sadler GH, Wright DH (1993) T-cell-rich B-cell lymphoma presenting as liver disease. Histopathology 23:217–224

Klima M, Waddell CC (1984) Hairy cell leukemia associated with focal vascular damage. Hum Pathol 15:657–659

Korkolopoulou P, Gibabis DA, Kavantzas N, Angelopoulou MK, Siakantaris MP, Patsouris E, Androulaki A, Thymara I et al (2003) A morphometric study of bone marrow angiogenesis in hairy cell leukaemia with clinicopathological correlations. Br J Haematol 122:900–910

Koss MN, Hochholzer L, Langloss JM, Wehunt WD, Lazarus AA, Nichols PW (1986) Lymphomatoid granulomatosis: a clinicopathologic study of 42 patients. Pathology 18:283–288

Kraut EH (2003) Clinical manifestations and infectious complications of hairy-cell leukemia. Best Pract Res Clin Haematol 16:33–40

Liebow AA, Carrington CR, Friedman PJ (1972) Lymphomatoid granulomatosis. Hum Pathol 3:457–558

Lim MS, Beaty M, Sorbara L, Cheng RZ, Pittaluga S, Raffeld M, Jaffe ES (2002) T-cell/histiocyte-rich large B-cell lymphoma: a heterogeneous entity with derivation from germinal center B cells. Am J Surg Pathol 26:1458–1466

Lucantoni C, De Bonis P, Doglietto F, Esposito G, Larocca LM, Mangiola A, Martini M et al (2009) Primary cerebral lymphomatoid granulomatosis: report of four cases and literature review. J Neurooncol 94:235–242

Machii T, Yamaguchi M, Inoue R, Tokumine Y, Kuratsune H, Nagai H, Fukuda S, Furuyama K et al (1997) Polyclonal B-cell lymphocytosis with features resembling hairy cell leukemia-Japanese variant. Blood 89:2008–2014

Matsue K, Nishi H, Onozawa S, Itoh M, Tsukuda K, Yamaguchi M, Nakao S, Kashimura M (1996) Polyclonal B cell chronic lymphoproliferative disease with hairy cell morphology: a case report and clonal studies. Am J Hematol 51:141–146

Matutes E, Morilla R, Owusu-Ankomah K, Houliham A, Meeus P, Catovsyk D (1994) The immunophenotype of hairy cell leukemia (HCL). proposal for a scoring system to distinguish HCL from B-cell disorders with hairy or villous lymphocytes. Leuk Lymphoma 14(suppl 1):57–61

McNiff JM, Cooper D, Howe G, Crotty PL, Tallini G, Crouch J, Eisen RN (1996) Lymphomatoid granulomatosis of the skin and lung. An angiocentric T-cell-rich B-cell lymphoproliferative disorder. Arch Dermatol 132:1464–1470

Melegh Z, Sutak J, Whiteway A, Rooney N, Pawade J (2009) Lymphomatoid granulomatosis of the uterine cervix. Pathol Res Pract 205:371–374

Melo JV, Robinson DS, Gregory C, Catovsky D (1987) Splenic B cell lymphoma with "villous" lymphocytes in the peripheral blood: a disorder distinct from hairy cell leukemia. Leukemia 1:294–298

Michaud J, Banerjee D, Kaufmann JC (1983) Lymphomatoid granulomatosis involving the central nervous system: complication of a renal transplant with terminal monoclonal B-cell proliferation. Acta Neuropathol 61:141–147

Montes-Moreno S, Roncador G, Maestre L, Martinez N, Sanchez-Verde L, Camacho FI et al (2008) Gcet1 (centerin), a highly restricted marker for a subset of germinal center-derived lymphomas. Blood 111:351–358

Morgan EA, Yu H, Pinkus JL, Pinkus GS (2013) Immunohistochemical detection of hairy cell leukemia in paraffin sections using a highly effective CD103 rabbit monoclonal antibody. Am J Clin Pathol 139:220–230

Mori N, Murakami YI, Shimada S, Iwamizu-Watanabe S, Yamashita Y, Hasegawa Y, Kojima H, Nagasawa T (2004) TIA-1 expression in hairy cell leukemia. Mod Pathol 17:840–846

Morice WG, Kurtin PJ, Myers JL (2002) Expression of cytolytic lymphocyte-associated antigens in pulmonary lymphomatoid granulomatosis. Am J Clin Pathol 118:391–398

Myers TJ, Granville NB, Witter BA (1979) Hairy cell leukemia and sarcoid. Cancer 43:1777–1781

Myers JL, Kurtin PJ, Katzenstein AL, Tazelaae HD, Colby TV, Strickler JG, Lloyd RV, Isaacson PG (1995) Lymphomatoid granulomatosis. Evidence of immunophenotypic diversity and relationship to Epstein-Barr virus infection. Am J Surg Pathol 19:1300–1312

Nair BD, Joseph MG, Catton GE, Lach B (1989) Radiation therapy in lymphomatoid granulomatosis. Cancer 64:821–824

Nanba K, Soban EJ, Bowling MC, Berard CW (1977) Splenic pseudosinuses and hepatic angiomatous lesions: distinctive features of hairy cell leukemia. Am J Clin Pathol 67:415–426

Nazeer T, Burkart P, Dunn H, Jennings TA, Wolf B (1997) Blastic transformation of hairy cell leukemia. Arch Pathol Lab Med 121:707–713

Nicholson AG, Wotherspoon AC, Diss TC, Singh N, Butcher DN, Pan LX, Isaacson PG, Corrin B (1996) Lymphomatoid granulomatosis: evidence that some cases represent Epstein-Barr virus-associated B-cell lymphoma. Histopathology 29:317–324

Pavlovskaia AI, Aikimbaev KS (1988) Lymphomatoid granulomatosis: pathologoanatomical study of three cases with a review of the literature and differential diagnosis (in Russian). Arkh Patol 50:24–31

Pettitt AR, Zuzel M, Cawley JC (1999) Hairy-cell leukaemia: biology and management. Br J Haematol 106:2–8

Pittaluga S, Jaffe ES (2010) T-cell/histiocyte-rich large B-cell lymphoma. Haematologica 95:352–356

Plenderleith IH (1970) Hairy cell leukemia. Can Med Assoc J 102:1056–1060

Polliack A (2002) Hairy cell leukemia: biology, clinical diagnosis, unusual manifestations and associated disorders. Rev Clin Exp Hematol 6:366–388

Prapphal N, Limudompom S, Watana D, Yenrudee S, Viravaidya D, Chomdej S, Cutchavaree A (1991) Lymphomatoid granulomatosis with upper airway obstruction: a case report. J Med Assoc Thai 74:526–530

Quigley MM, Bethel KJ, Sharpe RW, Saven A (2003) CD52 expression in hairy cell leukemia. Am J Hematol 74:227–230

Raz I, Or R, Okon E, Leizerowitz R, Polliack A (1984) Hairy cell leukemia: report of an unusual case with hepatomegaly due to a large vascular tumor of the liver, mediastinal mass and pleural effusion containing hairy cells. Acta Haematol 71:393–399

Rodriguez J, Pugh WC, Cabanillas F (1993) T-cell-rich B-cell lymphoma. Blood 82:1586–1589

Rogers BB, Browning I, Rosenblatt H, McClain K, Kemp J, Glasser LL, Gresik MV, Sumaya C et al (1992) A familial lymphoproliferative disorder presenting with primary pulmonary manifestations. Am Rev Respir Dis 145:203–208

Roquet ML, Zafrani ES, Farcet JP, Reyes F, Pinaudeau Y (1985) Histopathological lesions of the liver in hairy cell leukemia: a report of 14 cases. Hepatology 5:496–500

Roschewski M, Wilson WH (2012) Lymphomatoid granulomatosis. Cancer J 18:469–474

Sahar N, Schiby G, Davidson T, Kneller A, Apter S, Farfel Z (2009) Hairy cell leukemia presenting as multiple discrete hepatic lesions. World J Gastroenterol 15:4453–4456

Salvarani C, Capozzoli N, Baricchi R, Macchioni PL, Rossi F, Ghirelli L, Bellelli A, Tumiati B, Portioli I (1989) Autoimmune disease in hairy-cell leukemia: systemic vasculitis and anticardiolipin syndrome. Clin Exp Rheumatol 7:329–330

Schiller G, Said J, Pal S (2003) Hairy cell leukemia and sarcoidosis: a case report and review of the literature. Leukemia 17:2057–2059

Schjolseth SA, Blom GP (1978) Lymphomatoid granulomatosis of the lung, liver and spleen. Scand J Haematol 21:104–108

Schnittger S, Bacher U, Haferlach T, Wendland N, Ulke M, Dicker F, Grossmann V et al (2012) Development and validation of a real-time quantification assay to detect and monitor BRAFV600E mutations in hairy cell leukemia. Blood 119:3151–3154

Shao H, Calvo KR, Grönborg M, Tembhare PR, Kreitman RJ, Stetler-Stevenson M, Yuan CM (2013) Distinguishing hairy cell leukemia variant from hairy cell leukemia: development and validation of diagnostic criteria. Leuk Res 37:401–409

Shehata M, Schwarzmeier JD, Hilgrath M, Hubmann R, Duechler M, Gisslinger H (2004) TGF-beta1 induces bone marrow reticulin fibrosis in hairy cell leukemia. J Clin Invest 113:676–685

Sherman MJ, Hanson CA, Hoyer JD (2011) An assessment of the usefulness of immunohistochemical stains in the diagnosis of hairy cell leukemia. Am J Clin Pathol 136:390–399

Shpilberg O, Ehrenfeld M, Berkovitz M, Maier MK, Samra Y (1989) Hairy cell leukemia with an autoimmune syndrome, paraproteinemia, and cryoglobulinemia. South Med J 82:1552–1554

Spaenij-Dekking EH, Van Delft J, Van Der Meijden E, Hiemstra HS, Falkenburg JH, Koning F, Drijfhout JW, Kluin-Nelemans JC (2003) Synaptojanin 2 is recognized by HLA class II-restricted hairy cell leukemia-specific T cells. Leukemia 17:2467–2473

Staines A, Cartwright RA (1993) Hairy cell leukaemia: descriptive epidemiology and a case-control study. Br J Haematol 85:714–717

Stravodimou A, Cairoli A, Rausch T, Du Pasquier R, Michel P (2012) PTLD Burkitt lymphoma in a patient with remote lymphomatoid granulomatosis. Case Rep Med 2012:239719

Sun T, Grupka N, Klein C (2004) Transformation of hairy leukemia to high-grade lymphoma: a case report and review of the literature. Hum Pathol 35:1423–1426

Tajima K, Fukase N, Shiono T, Katagiri T, Mito S (1995) An autopsied case of T-cell rich B-cell lymphoma with general involvement. Intern Med 34:243–246

Tanioka F, Tamashima S, Shimizu S, Kobayashi H, Kobayashi Y, Sugimura H (2003) A case of primary plasma cell leukemia with hairy-cell morphology and lambda-type Bence-Jones protein. Immunohistochemical and molecular analysis. Jpn J Clin Oncol 33:232–237

Thaker H, Neilly IJ, Saunders PG, Magee JG, Snow MH, Ong EL (2001) Remember mycobacterial disease in hairy cell leukaemia (HCL). J Infect 42:213–214

Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, Pucciarini A, Bigerna B et al (2011) BRAF mutations in hairy-cell leukemia. N Engl J Med 364:2305–2315

Tiacci E, Schiavoni G, Martelli MP, Boveri E, Pacini R, Tabarrini A, Zibellini S, Santi A et al (2013) Constant activation of the RAF-MEK-ERK pathway as a diagnostic and therapeutic target in hairy cell leukemia. Haematologica 98:635–639

Tison T, Dazzi F, Giacon C, Vianello F, Valente ML, Radossi P, Sgarabotto D, Girolami A, Pennelli N, Poletti A (1995) CD25-negative hairy cell leukaemia: intracytoplasmic detection of Tac antigen and interferon-induced surface expression. J Pathol 177:41–47

Tousseyn T, De Wolf-Peeters C (2011) T cell/histiocyte-rich large B-cell lymphoma: an update on its biology and classification. Virchows Arch 459:557–563

Trentin L, Zambello R, Benati C, Cassatella M, Agostini C, Bulian P, Adami F, Carra G, Pizzolo G, Trentin L, Zambello R, Sancetta R, Facco M, Cerutti A, Perin A, Siviero M, Basso U et al (1997) B lymphocytes from patients with chronic lymphoproliferative disorders are equipped with different costimulatory molecules. Cancer Res 57:4940–4947

Valero B, Pico Sala MD, Palazon JM, Paya A (2007) Acute liver failure in a patient with hairy cell leukemia (in Spanish). Gastroenterol Hepatol 30:338–339

Vardiman JW, Golomb HM (1984) Autopsy findings in hairy cell leukemia. Semin Oncol 11:370–380

Verdi CJ, Grogan TM, Protell R, Richter L, Rangel C (1986) Liver biopsy immunotyping to characterized lymphoid malignancies. Hepatology 6:6–13

Verma S, Greaves WO, Ravandi F, Reddy N, Bueso-Ramos CE, O'Brien S, Thomas DA et al (2012) Rapid detection and quantification of BRAF mutations in hairy cell leukemia using a sensitive pyrosequencing assay. Am J Clin Pathol 138:153–156

Vidovic A, Cemerikic V, Suvajdzic J, Petrovic M, Colovic M (2001) T-cell-rich B-cell lymphoma: a clinicopathologic study of eight cases. Haematologica (Budap) 31:17–24

Vincent AM, Burthem J, Brew R, Cawley JC (1996) Endothelial interactions of hairy cells: the importance of alpha 4 beta 1 in the unusual tissue distribution of the disorder. Blood 88:3945–3952

Wang J, Sun NC, Chen YY, Weiss LM (2005) T-cell/histiocyte-rich large B-cell lymphoma displays a heterogeneity similar to diffuse large B-cell lymphoma: a clinicopathologic, immunohistochemical, and molecular study of 30 cases. Appl Immunohistochem Mol Morphol 13:109–115

Wang X, Spielberger R, Huang Q (2011) Hairy cell leukemia variant, a new entity of the WHO 2008. J Clin Oncol 29:e864–e866

Westbrook CA, Golde DW (1985) Autoimmune disease in hairy-cell leukaemia: clinical syndromes and treatment. Br J Haematol 61:349–356

Wilson WH, Kingma DW, Raffeld M, Wittes RE, Jaffe ES (1996) Association of lymphomatoid granulomatosis with Epstein-Barr viral infection of B lymphocytes and response to interferon-alpha 2b. Blood 87:4531–4537

Wu ML, Kwaan HC, Goolsby CL (2000) Atypical hairy cell leukemia. Arch Pathol Lab Med 124:1710–1713

Xi L, Arons E, Navarro W, Calco KR, Stetler-Stevenson M, Raffeld M, Kreitman RJ (2012) Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation. Blood 119:33330–33332

Yagi Y, Sakabe H, Kakinoki R, Yoshikawa K, Inoue T, Fujiyama Y, Machii T (2004) A hairy B cell lymphoproliferative disorder resembling hairy cell leukemia (in Japanese). Rinsho Ketsueki 45:312–315

Yam LT, Janckila AJ, Chan CH, Li CY (1983) Hepatic involvement in hairy cell leukemia. Cancer 51:1497–1504

Yavorkovsky LL, Gipsh NM, Karminskaya NM, Udris O, Nikulshin SV, Yavorkovsky LI (1990) Hairy cell leukemia and other "hairy-cell" lymphoproliferative disorders (LPD-HC): the significance of morphologic, histologic and immunologic studies. Neoplasma 37:439–444

Zafrani ES, Degos F, Guigui B, Durand-Schneider AM, Martin N, Flandrin G, Benhamou JP, Feldmann G (1987) The hepatic sinusoid in hairy cell leukemia: an ultrastructural study of 12 cases. Hum Pathol 18:801–807

Zervas J, Vayopoulos G, Kaklamanis PH, Zerva CH, Fessas PH (1991) Hairy-cell leukaemia-associated polyarthritis: a report of two cases. Br J Rheumatol 30:157–158

B-Cell Non-Hodgkin's Lymphomas with a Blastic/Large Cell Phenotype

91

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_91

Abstract

Several distinct types of B-cell non-Hodgkin's lymphomas characterized by large or blastic cells can markedly infiltrate the liver. Diffuse large B-cell lymphoma (DLBCL), a neoplasm of large B lymphoid cells with a diffuse growth pattern, develops in the liver either as a primary neoplasm or a hepatic manifestation of a lymphoma located elsewhere. Due to the distinct growth pattern within the body, a diagnosis of primary DLBCL of the liver is, however, difficult to assume. Involvement of the liver can present in the form of voluminous tumors that can mimic primary hepatic carcinoma or other solid neoplasms. Hepatic DLBCL can cause portal vein thrombosis. Rarely, the liver is involved by other large B-cell neoplasms, including pyothorax-associated lymphoma, intravascular large B-cell lymphoma, the latter with predominantly intravascular growth of lymphoma cells, and primary effusion lymphoma. Burkitt lymphoma, of which the endemic variant is associated with EBV infection, can infiltrate the liver in part of patients, usually in the setting of widespread disease.

Diffuse Large B-Cell Lymphoma (DLBCL), NOS

ICD-O code: **9680/3**

Introduction

In the 2008 WHO Classification, diffuse large B-cell lymphoma (DLBCL) is defined as neoplasm of large B lymphoid cells with a diffuse growth pattern, with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte.

Morphology

Typical is a diffuse growth of B-cell with varying shapes and sizes, according to the variants listed in the Table. The most common variant is the centroblastic variant, composed of medium- to large-sized cells with oval to round, vesicular nuclei with a fine chromatin pattern and two to four nuclear membrane-bound nucleoli. The cytoplasm is amphophilic to basophilic. In the less common immunoblastic variant, more than 90 % of tumor cells are immunoblasts with a centrally placed nucleolus in the nucleus and basophilic cytoplasm. The anaplastic variant shows large to very large round to pleomorphic cells with bizarre, in part multilobed, nuclei and multinucleated giant cells. These cells may resemble Hodgkin cells or Reed-Sternberg cells. Rare variants include those with myxoid stroma, fibrillary matrix, pseudorosette formation, spindle cells, and signet-ring cells. Immunohistochemically, the cells are reactive for B-cell lineage markers (CD19, CD20, CD79a, and CD22). CD10 is found in 30–60 %, BCL6 in 60–90 %, and MUM1 in 35–65 %. Most of the cells express FOXP1. Surface immunoglobin is present in up to 75 % of cases, mostly IgM, followed by IgG and IgA. In tumor with a germinal center cell lineage, the GC-associated marker Jaw1/LRMP is positive (Tedoldi et al. 2006). The anaplastic variant is associated with CD30 expression, in the absence of ALK expression. Most cases lack EMA reactivity. This phenotype had previously been classified as a variant of anaplastic large-cell lymphoma, but is now recognized as a subtype of DLBCL. Similar to ALCL, this lymphoma can show a sinusoidal growth pattern (*CD30-positive sinusoidal large B-cell lymphoma*). In a study of 11 patients, the mean age was 63.2 years, with female/male ratio of 1.2: 1. The lymphomas tended to undergo extensive necrosis.

Anaplastic DLBCL may be associated with Epstein-Barr virus infection, in one case within a composite B-cell-T-cell lymphoma (Hirose et al. 2004). EBV infection in this lymphoma is in clear contrast to ALCL, where there is no evidence for an EBV association. An anaplastic lymphoma-like lymphoma of the B-cell lineage has been observed to be associated with HHV-8 infection in the absence of EBV (Huang et al. 2004).

Liver Involvement

Primary DLBCL of the liver has been reported several times, albeit it is difficult, from the biology of this disease, to assume that a visceral organ is really a primary site of DLBCL.

Selected References (Chabner et al. 1975; Osborne et al. 1985; Ryoo et al. 1986; Jaffe 1987; Lei et al. 1995; Brugière et al. 1996; Al-Fadda and Fashir 1998; Lei 1998; Sato et al. 1999; Chaib et al. 2002; Santos et al. 2003; Noronha et al. 2005; Balduzzi et al. 2010; Makhdoomi et al. 2010; Yeh et al. 2010; Ma et al. 2011; Zafar et al. 2012).

Fig. 1 Tumorous hepatic manifestation of diffuse large B-cell lymphoma ("lymphosarcoma" of the liver)

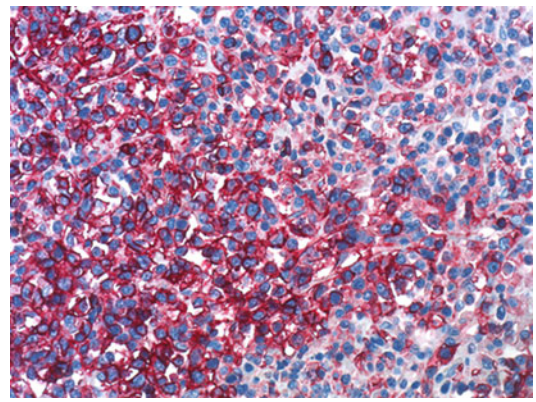

Fig. 2 In diffuse large B-cell lymphoma, neoplastic cells exhibit strong reactivity for CD20 (CD20 immunostain)

In most patients, liver involvement is a secondary phenomenon. In an older study of ten adult patients with large-cell lymphoma, several examinations (laparotomy in eight) revealed that the liver was the sole site of involvement initially, although subsequent staging procedures showed bone marrow involvement in three patients (Osborne et al. 1985). In this study, only one patient had hepatomegaly. Part of hepatic DLBCL are HCV-associated NHLs (Keller et al. 2010; Pellicelli et al. 2011). Primary and secondary DLBCL can form voluminous, whitish to yellowish tumor masses with an expanding growth pattern (Fig. 1). Sometimes, several large tumor nodules are centered around a central area of regression, with tumor collapse in the core area and formation of compressed parenchymal areas between the nodules (Chaib et al. 2002). In case of extensive infiltration, fulminant hepatic failure can ensue (Kheyri et al. 2013). Large tumors can mimic hepatocellular carcinoma radiologically. Tumors of enormous size have been reported, e.g., 18 cm diameter (Pereira et al. 1993). Histologically, cells with a centroblastic, immunoblastic, or anaplastic phenotype form a diffuse and monotonous infiltration, replacing the hepatic parenchyma. In rare variants, a predominantly intrasinusoidal and interstitial lymphomatous infiltration can occur (Kashimura et al. 2013). Immunohistochemistry reveals the immunophenotype found in other localizations of DLBCL, with a very high proliferative activity (Figs. 2 and 3). There is evidence that there is a difference in tumor biology between nodular and diffuse growth patterns, in that a tumor with a diffuse pattern has an unfavorable outcome (Emile et al. 2001). Hepatic DLBCL can cause portal vein thrombosis (Natsuizaka et al. 2009). In exceptional situations, hepatic DLBCL has infiltrated a preexisting other liver tumor, e.g., hepatocellular carcinoma (Utsunomiya et al. 2009). Dense hepatic infiltrates associated with hepatocyte injury, apoptosis, and/or necrosis can cause fulminant hepatic failure (Zafrani et al. 1983; Lettiere and Berg 2003) or biochemically mimic severe hepatitis (Harris and

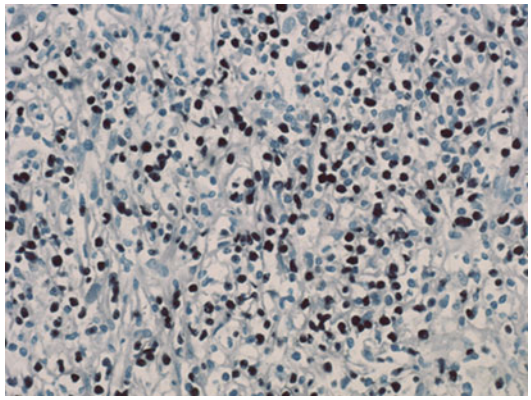

Fig. 3 Diffuse large B-cell lymphoma in the liver. The lymphoma cells reveal a very high proliferative activity (MIB1 immunostain)

Kornstein 1993). In case of large space-occupying lesions, portal hypertension can ensue (Bachmeyer et al. 2001).

Variants of DLBCL can also form primary hepatic neoplasms. De novo CD5-positive DLBCL accounts for about 10 % of DLBCLs, shows an aggressive course, and was found as a primary NHL of the liver and spleen (Zhang et al. 2013). Also EBV-driven DLBCL was diagnosed as a tumor confined to the liver (Dziadzio et al. 2013).

Classification

Several morphological and immunohistochemical variants and subgroups of DLBCL have been described, part of which have an impact on the biology of disease (Table 1; Pileri et al. 2002; Hans et al. 2004; Zinzani et al. 2005, 2010).

DLBCL accounts for 25–30 % of adult non-Hodgkin's lymphomas in western countries, more common in the elderly and median age at diagnosis being situated in the seventh decade, with a slight male preponderance. DLBCL is either a primary lymphoma or develops from a preexisting other B-cell lymphoma through transformation. Clinically, the tumor presents with nodal or extranodal disease, up to 40 % of patients initially having disease confined to extranodal sites, the most common extranodal compartment being the gastrointestinal tract. Other common sites are several visceral organs, including the liver, the bone, and the Waldeyer ring. Patients usually experience rapidly growing tumor masses, because DLBCL has a large proliferative fraction and usually reveals local growths (the former fast-growing tumors termed "lymphosarcomas"). A minority of patients with DLBCL enter a leukemic phase. Patients with DLBCL-associated leukemia present with high tumor burden and frequent involvement of extranodal sites (Muringampurath-John et al. 2012).

Table 1 Variants and subgroups of diffuse large B-cell lymphoma, NOS (According to the 2008 WHO Classification, modified)

Common morphologic variants
Centroblastic
Immunoblastic
Anaplastic
Rare morphologic variants
Myxoid stroma
Fibrillary matrix
Pseudorosette formation
Spindle cells
Signet-ring cells
Molecular subgroups
Germinal center B-cell-like (GCB)
Activated B-cell-like (ABC)
Immunohistochemical subgroups
CD5-positive DLBCL
Germinal center B-cell-like (GCB)
Non-germinal center B-cell-like (non-GCB)

Cytogenetic and Molecular Features

DLBCL shows clonally rearranged heavy- and light-chain genes. Up to a third of cases reveal abnormalities of the 3q27 region harboring the BCL6 gene, the most common translocation in DLBCL. BCL2 gene translocation is less frequently found. Up to 10 % show a MYC gene rearrangement. Aberrant somatic hypermutations involving several genes are seen in half of the cases.

Liver Involvement in DLBCL Associated with Chronic Inflammation (in Particular Pyothorax-Associated Lymphoma/PAL)

ICD-O code: **9680/3**

Introduction

Pyothorax-associated lymphoma (PAL) is a novel B-cell NHL entity that makes part of the rare primary pleural NHL developing in the setting of pyothorax, chronic pleuritis, and pneumopleural tuberculosis (Iuchi et al. 1989; Aozasa et al. 1993; Aozasa 1996; Nakatsuka et al. 2002; Narimatsu et al. 2007; Yamamoto et al. 2007; Sekine et al. 2010; Terada 2012). PAL is the prototypic form of the WHO lymphoma category, diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation. PAL involves the pleural space and the pleuropulmonary transition zone and, in part of the patients, peripheral parts of the lung and the chest wall. Most patients with this disorder have been reported from Japan. In a study of 37 cases, all patients were admitted after a 22–55 (mean 33)-year history of pyothorax caused by artifical pneumothorax for the treatment of lung tuberculosis or tuberculous pleuritis (Iuchi et al. 1989). In a more recent investigation on 106 cases, the median duration of pyothorax before admission was 37 years, and artificial pneumothorax for therapy of tuberculosis amounted to 80 % (Nakatsuka et al. 2002). In almost all studies, a diffuse proliferation of large B-cells predominated, i.e., the morphology of diffuse large B-cell lymphoma. One exception is Ki-1 (CD30)-positive anaplastic large-cell lymphoma of T-cell phenotype that has also been found to develop in long-standing tuberculous pyothorax (Nakamura et al. 1995). PAL is frequently, but not always, associated with EBV infection, with constant expression of the two latent membrane proteins, latent membrane protein (LMP)-1, and EBV-associated nuclear antigen (EBNA)-2 (Fukayama et al. 1993; Martin et al. 1994; Ohsawa et al. 1995; Takakuwa et al. 2008).

In situ hybridization showed that, in 106 patients, 70 % of the PAL were EBV-positive (Nakatsuka et al. 2002). The EBV load assessed by real-time PCR correlates with tumor mass (Shide et al. 2003). Proposed mechanisms for the pathogenesis of PAL in EBV infection include the production of an immunosuppressive cytokine from PAL cells, HLA class I alleles of patients with PAL, and mutations of cytotoxic lymphocyte epitopes in an EBV-latent antigen (Kanno and Aozasa 1998; Kanno et al. 1999). HHV-8 was not detected in PAL, in contrast to cavity-based high-grade lymphomas/BCBL (Taniere et al. 1998). The neoplasm consists of large lymphoid cells with frequent plasmacytoid differentiation, immunoreactive for CD20, CD79a, and/or CD138 B-cell antigens. Detailed immunophenotyping suggests that the cells derive from late germinal center (GC)/post-GC B-cells (Petitjean et al. 2002). Few cases exhibit aberrant expression of T-cell markers. The B-cell origin of lymphoma cells was confirmed by the demonstration of immunoglobulin light-chain restriction or clonal B-cell population (Petitjean et al. 2002). The differential diagnosis of pyothorax-associated B-cell lymphoma is the very rare T-cell counterpart of this lymphoma (Narimatsu et al. 2007; Santini et al. 2009).

Liver Involvement in Pyothorax-Associated Lymphoma

Involvement of the liver by PAL is exceptional. Extrathoracic dissemination to the liver was detected in a patient with PAL presenting a right basal calcified mass and parietal infiltration (Petitjean et al. 2002).

Intravascular Large B-Cell Lymphoma

ICD-O code: 9712/3

Introduction

In the 2008 WHO Classification, intravascular large B-cell lymphoma (IVLBCL) is defined as a rare type of extranodular large B-cell lymphoma showing selective growth of lymphoma cells within the lumina of blood vessels, in particular capillaries. Definition, diagnosis, and management of IVLBCL have been standardized in an international consensus meeting (Ponzoni et al. 2007).

IVLBCL is a rare and highly aggressive form of NHL that mainly occurs in adults, but pediatric and even congenital cases have been reported as well (median: 67 years at diagnosis), with an almost balanced gender distribution. The lymphoma has previously been described under several terms, including systemic endotheliomatosis, malignant angioendotheliosis, angioendotheliomatosis proliferans systemisata, neoplastic endotheliosis, intravascular lymphomatosis, and angiotropic large-cell lymphoma. The neoplasm was originally described in 1959 under the term systemic endotheliomatosis (Pfleger and Tappeiner 1959). As the term illustrates, this neoplasm was first thought to have an endothelial cell origin, but was about 30 years later identified to be a lymphoid cell growth (Wick et al. 1986; Otrakji et al. 1988). The hallmark of this high-grade B-cell lymphoma is its tendency to proliferate and spread within vascular lumina of several organs, however with predominant manifestations in the skin and in the central nervous system (Demirer et al. 1994; Conlin et al. 2001; Lui et al. 2003). In a clinicopathologic study of 38 HIV-negative patients diagnosed in western countries, two-thirds of the patients had disseminated disease at presentation (Ferreri et al. 2004). IVLBCL may disseminate to the heart, lungs, pancreas, liver, spleen, adrenals, genital tract, and, rarely, bone marrow and lymph nodes. About a fourth of the patients suffer from hepatosplenic involvement (Ferreri et al. 2004). A presence of lymphoma cells in the peripheral blood has only very occasionally been noted.

Clinical Features

Frequently, the first presentations are fever, neurologic symptoms, dementia, skin manifestations such as erythemas, nodules or plaques, and telangiectases, and/or shortness of breath and diffuse infiltrates in chest X-rays in those patients with pulmonary involvement (Hong et al. 2014). Rarely, humoral hypercalcemia associated with elevated serum parathyroid-related protein is a presenting symptom (Knobel et al. 2001). One variant of IVLBCL mainly occurring in Asian patients (the so-called Asian variant of IVLBCL) is characterized by early involvement of bone marrow and associated with hemophagocytic syndrome (IVL-HS; Hsieh et al. 2010; Fung et al. 2012). In addition to East Asian patients, individuals from Caucasian countries and Africa are rarely affected (Fung et al. 2012; Geyer et al. 2012). This variant has also been reported to be characterized by hepatosplenomegaly in the absence of neurologic or skin manifestations (Murase et al. 2002).

Morphology

Histologically, large and discohesive cells with a moderate rim of amphophilic cytoplasm and round to often bizarre nuclei with prominent nucleoli and mitotic figures accumulate in the lumina of capillaries, small veins, arterioles, and small arteries, but the cells may also occupy the perivascular spaces. It has even been observed that the cells of IVLBCL can colonize abnormal vascular compartments such as hemangiomas (Cerroni et al. 2004). The immunophenotype is that of a B-cell lineage (CD 20 and/or CD79a), with negative EMA staining. The cells express CD11a and CD49d (Kanda et al. 1999). A subset of IVLBCL (about 30 %) is reactive for CD5 (Khalidi et al. 1998; Murase et al. 2000), and there seems to be a variant with the same morphologic features but a T-cell phenotype (Au et al. 1997). IVLBCL may express myeloperoxidase, important for the differential diagnosis of granulocytic sarcoma (Conlin

et al. 2001). Furthermore, it has been reported that prostatic acid phosphatase is a possible tumor marker for IVLBCL (Seki et al. 2004; Kishi et al. 2004).

Liver Involvement in IVLBCL

IVLBCL usually undergoes an aggressive and sometimes fulminant course, spreading within vascular structures in numerous organs, including the liver.

Selected References for Liver Involvement (Kayano and Katayama 1990; Demirer et al. 1994; Rubin et al. 1997; Onishi et al. 1998; Tucker et al. 1999; Camidge et al. 2000; Murase et al. 2000; Yamashiro et al. 2001; Knobel et al. 2001; Fiegl et al. 2002; Goh et al. 2002; Lui et al. 2003; Terrier et al. 2005; Shiraki et al. 2007; Roshal et al. 2008; Xu et al. 2008; Higurashi et al. 2009; Szuba et al. 2010; Yasuda et al. 2010; Hishikawa et al. 2011; De Fino et al. 2012; Fung et al. 2012; Geyer et al. 2012; Gual-Tarrada et al. 2012; Yamada et al. 2012; Sekiguchi et al. 2013; Abe et al. 2014; Hoshi et al. 2014).

In a larger study, hepatosplenic involvement occurred in 26 % of the patients (Ferreri et al. 2004). Liver infiltration may cause abnormal liver function tests and jaundice, likely to be induced by direct hepatocyte damage by the lymphoma cells located to the vessels (Zeidman et al. 2004; Sekiguchi et al. 2013). In one patient with an unusual, mixed neurotropic and intravascular large B-cell lymphoma, the neoplasm had produced an ill-defined large and soft tumor mass in the right liver lobe (Yamada et al. 2012).

Liver histology shows large and in part highly atypical lymphoma cells, immunoreactive for CD45 and CD20, in several categories of vascular channels, including small portal venous branches and branches of the hepatic artery (DiGiuseppe et al. 1994; Demirer et al. 1994;). In particular, small portal veins in the portal tracts may be massively engorged with bizarre cells (Demirer et al. 1994). A preferential accumulation of the large cells may be found in the lumina of hepatic sinusoids (DiGiuseppe et al. 1994; Tucker et al. 1999; Camidge et al. 2000; Murase et al. 2000; Yagita et al. 2000; Conlin et al. 2001; Goh et al. 2002; Shimizu et al. 2007; Shiraki et al. 2007; Xu et al. 2008; Higurashi et al. 2009; Hishikawa et al. 2011). The intravascular cells may be enmeshed in fibrin or microthrombi, and associated endothelial proliferations may be seen. It is striking to note that, in IVLBCL, several categories of small blood vessels are involved, i.e., the terminal arterial segments, the capillary bed, and the draining veins, suggesting a distinct mode of neoplastic cell homing. In Asian variant IVLBCL, hepatomegaly is a typical feature, and hepatic infiltration is frequently accompanied by signs of hemophagocytosis (Onishi et al. 1998; Aoki et al. 2011). In addition to intravascular tumor cell accumulations, nodular or tumorous intrahepatic lesions have also been reported, showing that these lymphoma cells can also proliferate in extravascular compartments (Hashizume 2011).

Differential Diagnosis

The main differential diagnosis is sinusoidal accumulation of neoplastic cells in the course of lymphoid cell leukemias, e.g., plasmablastic leukemia.

Cytogenetic and Molecular Features

Few karyotypic abnormalities have been reported, without a specific recurrent pattern. IVLBCL is cytogenetically heterogeneous, but the most frequent alterations seen were -6 or 6q- and +18 or dup (18q) (Khoury et al. 2003). Immunoglobulin genes are clonally rearranged. The distinct intravascular localization of the lymphoma cells may be related to the differential expression of lymphoid homing receptors (Ferry et al. 1988) and/or deficiency or absence of the adhesion molecules

CDIia/CD18 (Jalkanen et al. 1989), CD29 (beta1-integrin), and CD54 (ICAM-1).

Primary Effusion Lymphoma (PEL)

ICD-O code: 9678/3

Introduction

Primary effusion lymphoma (PEL; synonym: body cavity-based lymphoma) is a large B-cell neoplasm usually presenting as serous effusions without detectable tumor masses. PEL is associated with human herpesvirus 8 (HHV8; Kaposi sarcoma-associated herpesvirus, KSHV) and most often develops in the setting of immunodeficiency (WHO 2008 Classification; reviews: Cousins and Nicholas 2014; Giffin and Damania 2014; Kim et al. 2014).

Lymphomatous effusions, often developing in the absence of solid tumor masses, were described since 1989 to occur in homosexual men with or without risk for AIDS (Knowles et al. 1989). The neoplastic cells of these lesions show clonal B-cell derivation and express CD45 and CD138, but lack the expression of other B-cell antigens. Many of the tumors show evidence of clonal EBV infection, and KSHV has been shown to be involved in the pathogenic pathways of most, but not all, cases of PEL (Cesarman et al. 1995; Buonaito et al. 2002; Sunil et al. 2010; Wang et al. 2011). The KSHV-positive lymphoma cells are in most cases coinfected by EBV, and they show mutated rearranged Ig genes, suggesting that the neoplastic cells originate from germinal center or post-germinal center B-cells (Hamoudi et al. 2004). The pathogenic pathways involving HHV8/KSHV in PEL are complex and only partially understood. HHV8 miRNA functions as a hijacking system that targets numerous cellular genes involved in proliferation and apoptosis in PEL (Gottwein et al. 2011; Gottwein 2012; Haecker et al. 2012), including the TGF-beta signaling pathway to promote cell survival (Lei et al. 2012), phosphorylation of PTEN on chromosome (Roy and Dittmer 2011), amplification of SELPLG and CORO1C genes encoding for proteins important for cell migration (Luan et al. 2010), and deletion of the suppressor genes FHIT and WWOX (Roy et al. 2011). PEL displays a highly complex transcriptome (Punj et al. 2012), which is modulated by HHV8 which also affects the immune system of the host (Lee et al. 2012). In cases being HHV8-negative, PAX-5 gene rearrangement has been detected (Ichinohasama et al. 1998). Characteristically, the majority of PELs occur exclusively as malignant neoplastic lymphomatous effusions, but part of the patients with PEL secondarily develop solid-tissue lymphoma masses. Clinically, the most common sites of PEL are the pleural, pericardial, and peritoneal cavities, whereby one body cavity is involved in most cases. However, multicavity involvement is also known (Hsieh et al. 2007), and prognosis is influenced by the number of body cavities involved (Castillo et al. 2012a). Extracavitary PEL involves the gastrointestinal tract, skin, lung, CNS, and lymph nodes. Furthermore, there are patients with this phenotype of neoplasm who initially present with a tissue mass and subsequently develop a malignant neoplastic effusion. There are also extracavitary HHV8-associated large B-cell lymphomas with a primarily solid growth pattern that may eventually represent a subtype of PEL (Giessen et al. 2012; Kim et al. 2012; Pan et al. 2012).

Liver Involvement

As the neoplastic cells in PEL are suspended in body cavity fluids without the formation of tumor masses, the liver is not expected to be involved by this NHL. However, PEL with formation of ascites may result in settling of lymphoma cells on the capsular surface of the liver. Similar to other serosal surfaces, the cells form a cellular layer of variable thickness, eventually associated with fibrinous and/hemorrhagic serositis. Within this epicapsular mass, the neoplastic cells seem to form cohesive structures consisting of large and in part highly polymorphous elements, with rather abundant and amphophilic cytoplasm, and large vesicular, partly deformed or indented nuclei

showing prominent nucleoli. The cells located to serosal surfaces and suspended in free fluid are usually CD138 (syndecan-1) reactive, and this expression may be important for the characteristic homing and location of the tumor cells, as syndecan-1 (normally also expressed in mature B-cells and plasma cells) is involved in adhesion of cells to the extracellular matrix. There seems to exist a relationship between chronic HCV infection and PEL. PEL developing in patients with HCV-related liver cirrhosis is exclusively manifest in the peritoneal cavity, usually with marked ascites, and is more frequently of the B-cell phenotype, in contrast to other PELs that are usually of the null phenotype (Ascoli et al. 1997; Ichinohasama et al. 1998; Hara et al. 2001; Paner et al. 2003; Makis and Stern 2010). PEL in HCV-related cirrhosis is usually HIV- and HHV-8 negative (Hara et al. 2001; Paner et al. 2003). The solid form of HHV8/KSHV-associated large B-cell lymphoma, whose relationship to PEL is not clarified, can also arise from the liver and spleen as multiple nodular lesions (Hasagawa et al. 2004).

There are other lymphomas characterized by serosal spreading consistent with PEL but not associated with KSHV infection (CD138-positive and KSHV-negative B-cell lymphomas with serosal spreading; Kuwabara et al. 2000). In an autopsy case, lymphoma manifestations were, in addition to body cavities and several lymph node stations, also detected in hepatic hilar nodes (Kuwabara et al. 2000).

Burkitt Lymphoma

ICD-O code: 9687/3

Introduction

According to the WHO classification, Burkitt lymphoma (BL) is a rapidly proliferating B-cell neoplasm with extremely short doubling times and a preference for extranodal sites. The tumor is named after Denis Parsons Burkitt, who graduated as a physician in 1935 from Trinity College in Dublin and served as a surgeon and lecturer in Africa during World War II, where he identified the endemic lymphoma (Burkitt and O'Conor 1961; Burkitt 1962; Smith 2012). Three forms of this lymphoma are known: endemic, sporadic, and immunodeficiency-associated BL (reviews: Magrath 2012; Molyneux et al. 2012). The endemic form is mainly known from equatorial Africa and Papua New Guinea. In Africa, the lymphoma chiefly involves children with a peak age between 4 and 7 years of age. In endemic BL, the EBV genome is present in virtually all tumor cells of patients, EBV-infected tumor cells being derived from memory B-cells, and there is a strong link with holoendemic malaria. The sporadic form is found throughout the world, mainly occurs in children and young adults, and is a rare type of NHL, accounting for only about 1–2 % of all lymphomas in western countries. However, BL accounts for 30–50 % of all childhood lymphomas. About 30 % of sporadic BLs show EBV infection, but the infection rate is higher in early EBV infection and in the presence of a low socioeconomic status. Immunodeficiency-associated BL chiefly develops in HIV-infected individuals, and 25–40 % of patients show EBV infection of neoplastic cells.

Morphologically, the neoplastic B-cells are medium sized and grow in a diffuse manner, with cell cohesion but often also cytoplasmic retraction in the sections. The cytoplasm is markedly basophilic; nuclei are round, with several basophilic, paracentrally placed nucleoli. Numerous mitotic figures are noted, and many apoptotic bodies are usually present. Part of BL shows plasmacytoid features or nuclear pleomorphism. A marked nuclear pleomorphism of BL cells is known following chemotherapy (Banks et al. 1975). A typical histologic feature is the "starry sky" pattern, characterized by numerous large and clear macrophages being dispersed in the tumor, these cells having phagocytosed apoptotic cells and/or nuclear fragments (so-called tingible bodies). Immunohistochemically, the tumor cells reveal reactivity for B-cell markers (CD19, CD20, CD22) CD38, BCL6, CD43, and CD77. The cells show expression of membrane IgM with light-chain restriction. More than 90 %

of cells are Ki-67 positive, reflecting the extremely high proliferation fraction.

Primary Burkitt Lymphoma of the Liver

Primary bona fide or probable Burkitt lymphoma of the liver is a very rare lesion; only less than 30 cases having been reported and only few of them with immunohistochemical verification (Siegel and Melson 1981; Miller et al. 1983; Rak et al. 1988; Wan et al. 1988; Adeodu et al. 1990; Scoazec et al. 1991; Ramos et al. 1997; Huang et al. 1997; Chim et al. 2001; Kuroda et al. 2001; Lee et al. 2008; Mantadakis et al. 2008; Mattar et al. 2010; Citak et al. 2011). Primary hepatic BL occurs in both endemic and sporadic forms of BL and was also detected, characterized by a hypervascular lesion, in a patient with HIV infection (Jacobs and Rozenblit 2006). Hepatic BL can develop in children with this type of lymphoma (Vade and Blane 1985; Huang et al. 1997; Hsu et al. 2003; Wammanda et al. 2004; Fikri and Dafiri 2006; Mantadakis et al. 2008). One case has been reported in a 14-year-old child, presenting a large solid mass confined to the right lobe of the liver, without evidence of involvement of other sites. The mass was resected and histologically proven to be Burkitt lymphoma (Huang et al. 1997). In two pediatric patients, hepatic BL manifested as obstructive jaundice (Hsu et al. 2003; Wammanda et al. 2004). In another child aged 8.5 years, primary hepatic BL presented as multifocal liver lesions (Mantadakis et al. 2008). One fully documented lesion of 6 cm diameter, including a detailed immunohistochemical work-up, was identified in an old patient having chronic hepatitis C. At autopsy, the mass was well delineated and showed, on the cut surface, geographical necroses and hemorrhage. The neoplasm was not associated with EBV infection (Kuroda et al. 2001). Primary hepatic BL can present with acute liver failure caused by dense hepatic infiltration associated with hepatocyte damage (Mattar et al. 2010).

Differential Diagnosis

The liver can be involved by BL situated elsewhere in the abdominal cavity (Durodola 1977; Anaissie et al. 1985; Glass et al. 1985; Park et al. 2004; Baumhoer et al. 2008; Kiresi et al. 2008). In a group of 19 pediatric patients with BL, the liver was involved in 12.1 % (Kamona et al. 2007). BL can also extensively involve the peritoneal surface (Wong et al. 2009).

Molecular Features

On the molecular level, around 90 % of cases show MYC oncogene translocation to Ig heavy-chain region (Soldini et al. 2013). In endemic BL, most of these translocations result from hypermutation, while in sporadic cases, the translocation mostly involves the Ig switch regions of the IgH locus at chromosome 14q32 (Greisman et al. 2012). BL can arise from lymphoplasmacytic lymphoma following acquisition of MYC translocation and loss of the ETV6 tumor suppressor gene (Peker et al. 2013). Other mutational events playing a role in BL pathogenesis comprise inactivating mutations of ID3, an inhibitor of the TCF3 transcription factor (Campo 2012; Leventaki et al. 2012; the ICGC MMML-Seq Project et al. 2012), and the GNA13, RET, PIK3R1, E2F4, and SWI/SNF-associated genes (Dave 2012; Giulino-Roth et al. 2012; Love et al. 2012; Molina-Privado et al. 2012). Expression of TCF3 activates the pro-survival PI3K pathway in BL (Schmitz et al. 2012). In fact, a strong survival signal for BL tumor cells is the PI3K signaling pathway, cooperating with MYC (Sander and Rajewski 2012). In childhood BL, EBV expression acts as a risk effect and independent prognosticator (Minnicelli et al. 2012). In memory B-cells, EBV nuclear antigen 1 induces expression of cellular microRNA has-miR-127, impairing B-cell differentiation and considered to play a pathogenic role in BL (Onnis et al. 2012). In BL, the extremely strong proliferative response is in part counteracted by cell loss via apoptosis, reflected not only by the presence of

apoptotic bodies, and karyorrhexis, but also by an increased expression of the apoptosis-associated proteins survivin, livin, and thrombospondin-1 (Kalungi et al. 2013).

Plasmablastic Lymphoma

ICD-O code: 9735/3

Introduction

Plasmablastic lymphoma (PBL) is defined as a diffuse proliferation of large neoplastic cells resembling B immunoblasts but which have the immunophenotype of plasma cells.

PBL is a rare and probably heterogeneous group of lymphomas (Colomo et al. 2004). The neoplasm prefers mostly extranodal sites and has the highest incidence in HIV-infected individuals, predominantly males, manifestations in the oral cavity being most common. It occurs also in other situations of immunosuppression. PBL has developed in the setting of Crohn's disease treated with azathioprine and infliximab (Plaza et al. 2011) and was found to arise in liver allografts. About half of patients with PBL have EBV infection. PBL prevails in elderly adults, but also occurs in the pediatric age group (Pather et al. 2013). A well-known site of PBL is the oral cavity, but it is also found in several other mucosae (including the sinonasal region), skin, bone, gastrointestinal tract, and soft tissues. Lymph node involvement is uncommon. At diagnosis, most patients present with advanced stage of disease (Corti et al. 2011; Hsi et al. 2011; review: Castillo and Reagan 2011). In a study of 50 patients with HIV-associated PBL, 90 % of patients had extranodal involvement at presentation, and 69 % had advanced stage disease (Castillo et al. 2012b). The biology of disease appears to differ as a function of the HIV status. In a series of elderly HIV-negative patients from Japan, the clinical behavior was more indolent than that of age-related EBV-associated lymphoproliferative disorders (Liu et al. 2012).

Morphology

The spectrum of cytomorphologies in PBL ranges from diffuse growths of immunoblast-like cells to cells resembling those in plasmablastic plasma cell myeloma. The nuclei of immunoblast-like cells show prominent nucleoli, whereas the nuclei of plasmacytoid components exhibit round nuclei with coarse chromatin and smaller or even unapparent nucleoli. Tumors with a high proportion of plasmablastic cells prevail in HIV-infected patients and in the oro-sinonasal region, while those with a plasmacytic differentiation tend to more often occur in other extranodal sites, but also in lymph nodes. Immunocytochemically, the cells express a plasmacytic phenotype, with reactivity for CD138, CD38, Vs38c, and MUM1. CD79a is expressed in 50–85 % of the cases. Typically, the tumor cells are negative or only weakly positive for CD20, CD45, and PAX5. Fifty to seventy percent of cases reveal expression of cytoplasmic immunoglobulins, most commonly IgG and either kappa or lambda light chains.

Liver Involvement

Few cases of apparently primary PBL of the liver have been reported (Metta et al. 2009; Tani et al. 2013). The HIV-infected adult patient reported by Metta et al. (2009) presented a nodular tumor lesion in the left lobe of the liver. Diagnosis of PBL was confirmed by liver biopsy. Morphology revealed a dense infiltrate composed of atypical and in part plasmacytoid lymphocytes expressing plasma cell markers (CD138, MUM1), but negative for CD20 and CD45. Immunohistochemistry and FISH showed the presence of EBV infection of tumor cells. There are no informations regarding infiltration pattern in secondary PBL involvement of the liver. The 79-year-old male HIV-negative patient described by Tani and coworkers (2013) presented with a very large liver mass. Autopsy showed a diffuse infiltration of the involved part of the liver with large-cell lymphoma with plasmacytoid features, the

neoplastic cells being reactive for CD30, EBV, Bob-1, and CD38.

Differential Diagnosis

The principal differential diagnoses are plasmablastic and pleomorphic plasma cell myelomas.

Cytogenetic and Molecular Features

There are no recurrent/specific karyotypic abnormalities. The tumor shows clonal IgH gene rearrangement. MYC rearrangement has been found in part of PBL cases (Slack and Gascoyne 2011; Castillo et al. 2012b).

Liver Cyst-Associated Non-Hodgkin's Lymphoma (CANHL)

Introduction

In very rare instances, non-Hodgkin's lymphomas (NHL) develop in preexisting cysts or organs with polycystic disease. We term these neoplasms cyst-associated NHL (CANHL).

CANHL of the Liver

In one old female patient, a hepatic cystic lesion suspicious of hepatobiliary cystadenoma was detected. Hepatic resection revealed a complex, but well-delineated cystic mass within parenchyma, having a diameter of 12 cm. It showed solid components, mural nodularity, and contained friable tissue masses with cystic spaces and clefts. Histology and immunohistochemistry showed primary diffuse large B-cell lymphoma (Valladolid et al. 2013). NHL was detected in a patient with isolated adult polycystic liver disease, forming nodular lesions among cysts (Cirasino et al. 1997). We observed hepatic CANHL in a female patient undergoing liver transplantation of primary hepatic polycystic disease. The massively enlarged organ was diffusely involved by numerous thin-walled cysts containing a clear fluid. On cut surfaces, one of these cysts did not contain fluid, but a soft matter of grayish-brown color which showed cracks after fixation suggesting a highly cellular tissue (Fig. 4). Histologically, most of the tissue was necrotic, with numerous shadow cells, but nucleated large round cells forming a homogeneous population were found at the periphery of the focus. These cells were positive for B-cell markers, were highly proliferative, and represented a monoclonal proliferation at PCR,

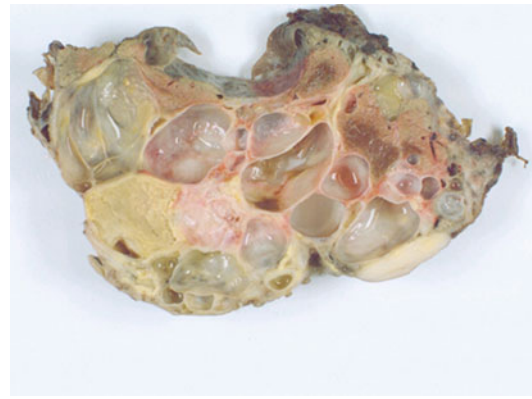

Fig. 4 Cyst-associated diffuse large B-cell lymphoma of the liver. In this specimen of adult polycystic liver disease, one of the cysts (*left lower* aspect of specimen) is filled with a yellowish mass representing necrotic tumor

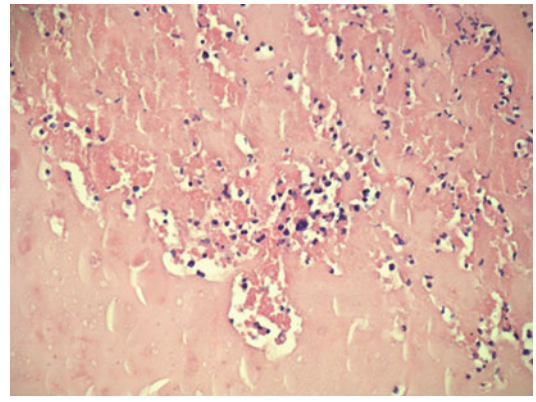

Fig. 5 Cyst-associated diffuse large B-cell lymphoma of the liver. The necrotic tissue, which completely filled the cyst, contains clusters of atypical large lymphoma cells (hematoxylin and eosin stain)

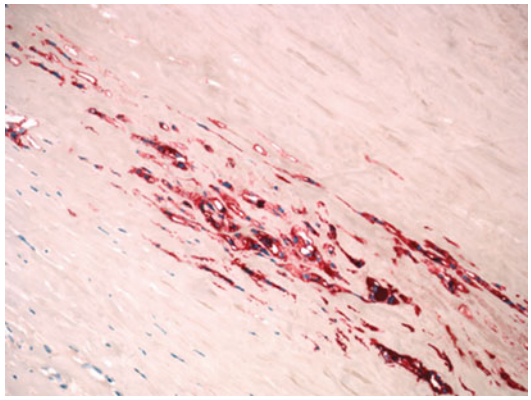

Fig. 6 Cyst-associated diffuse large B-cell lymphoma of the liver. The preserved lymphoma cells are diffusely reactive for CD20 (CD20 immunostain)

compatible with diffuse large B-cell lymphoma (Figs. 5 and 6). No other manifestations of an NHL were present in this patient, who survived without any chemotherapy.

Non-Hodgkin's Lymphoma Associated with Inflammatory Pseudocysts

Diffuse large B-cell lymphoma has been observed in association with pseudocysts probably arisen in the course of inflammation, e.g., in adrenals and in the paratesticular region. It was proposed to classify such NHLs in the WHO category of DLBCL developing in long-standing chronic inflammation, pyothorax-associated NHL being the prototype lesion (Boroumand et al. 2012). This type of lymphoma has not yet been described for the hepatobiliary tract.

Differential Diagnosis

In rare situations, NHLs can present as cystic or multicystic lesions, these cysts probably being secondary phenomena (Noguchi et al. 2013).

References

Abe H, Kamimura K, Mamizu M, Shibazaki Y, Ishiguro T, Katada S, Nishiyama YK, Takahashi Y, Hatano YY et al (2014) Early diagnosis of hepatic intravascular lymphoma: a case report and literature review. Intern Med 53:587–593

Adeodu OO, Nwosu SO, Odunusi OE (1990) Hepatic Burkitt lymphoma. Presentation with extremely rapid growth. Clin Pediatr 29:529–531

Al-Fadda M, Fashir BM (1998) Primary large cell lymphoma presenting as hilar mass and obstructive jaundice. Am J Gastroenterol 93:274–275

Anaissie E, Geha S, Allam C, Jabbour J, Khalyl M, Salem P (1985) Burkitt's lymphoma in the Middle East. A study of 34 cases. Cancer 56:2539–2543

Aoki Y, Takamiya M, Satoh T, Fujita S, Kato H, Maeno Y (2011) A fatal case of hematoperitoneum after ultrasound-guided liver biopsy in a patient with intravascular large B-cell lymphoma. Legal Med (Tokyo) 13:191–195

Aozasa K (1996) Pyothorax-associated lymphoma. Int J Hematol 65:9–16

Aozasa K, Ohsawa M, Iuchi K, Tajima K, Komatsu H, Shimoyama M (1993) Artificial pneumothorax as a risk factor for development of pleural lymphoma. Jpn J Cancer Res 84:55–57

Ascoli V, Lo Coco F, Artini M, Levrero M, Fruscalzo A, Mecucci C (1997) Primary effusion Burkitt's lymphoma with t(8;22) in a patient with hepatitis C virus-related cirrhosis. Hum Pathol 28:101–104

Au WY, Shek WH, Nicholls J, Tse KN, Todd D, Kwong YL (1997) T-cell intravascular lymphomatosis (angiotropic large cell lymphoma): association with Epstein-Barr viral infection. Histopathology 31:563–567

Bachmeyer C, Harry G, Cazier A, Bonnard P, Cadranel JF (2001) Portal hypertension due to intrahepatic obstruction in non-Hodgkin's lymphoma. Eur J Gastroenterol Hepatol 13:1491–1493

Balduzzi C, Yantorno M, Mosca I, Apraiz M, Velazquez MJ, Puente Mdel C, Moragrega V et al (2010) Primary hepatic lymphoma: an infrequent cause of focal hepatic lesion (in Spanish). Acta Gastroenterol Latinoam 40:361–366

Banks PM, Arseneau JC, Gralnick HR, Canellos GP, DeVita VT, Berard CW (1975) American Burkitt's lymphoma: a clinicopathologic study of 30 cases. II. Pathologic correlations. Am J Med 58:322–329

Baumhoer D, Tzankov A, Dirnhofer S, Tornillo L, Terraciano LM (2008) Patterns of liver infiltration in lymphoproliferative disease. Histopathology 53:81–90

Boroumand N, Ly TL, Sonstein J, Medeiros LJ (2012) Microscopic diffuse large B-cell lymphoma (DLBCL) occurring in pseudocysts: do these tumors belong to the category of DLBCL associated with chronic inflammation? Am J Surg Pathol 36:1074–1080

Brugière O, Pialoux G, Carnot F, Pol S, Fournier S, Deslandes P, Trotot P, Dupont B (1996) Primary non-Hodgkin's lymphomas of the liver in human immunodeficiency virus infected patients. Three cases (in French). Gastroenterol Clin Biol 20:307–311

Buonaito D:, Rossi D, Guidetti F, Vivenza D, Berra E, Deambrogi C, Ariatti C, Franceschetti S et al (2002) Human herpesvirus type 8-associated primary lymphomatous effusion in an elderly HIV-negative patient: clinical and molecular characterization. Ann Ital Med Int 17:54–59

Burkitt D (1962) A lymphoma syndrome in African children. Ann R Coll Surg Engl 30:211–219

Burkitt D, O'Conor GT (1961) Malignant lymphoma in African children. I. A clinical syndrome. Cancer 14:258–269

Camidge R, Ong E, Lucraft H (2000) An aggressive intrasinusoidal lymphoma presenting with marked systemic disturbance but normal imaging studies. Postgrad Med J 76:103–104

Campo E (2012) New pathogenic mechanisms in Burkitt lymphoma. Nat Genet 44:1288–1289

Castillo JJ, Reagan JL (2011) Plasmablastic lymphoma: a systematic review. Sci World J 11:687–696

Castillo JJ, Shum H, Lahijani M, Winer ES, Butera JN (2012a) Prognosis in primary effusion lymphoma is associated with the number of body cavities involved. Leuk Lymphoma 53:2378–2382

Castillo JJ, Furman M, Beltran BE, Bibas M, Bower M, Chen W, Diez-Martin JL, Liu JJ et al (2012b) Human immunodeficiency virus-associated plasmablastic lymphoma: poor prognosis in the era of highly active antiretroviral therapy. Cancer 118:5270–5277

Cerroni et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15316167

Cesarman et al. 1995. http://www.ncbi.nlm.nih.gov/pubmed/7700311

Chabner BA, Johnson RE, Chretien PB, Schein PS, Young RC, Canellos CP, Hubbard SH et al (1975) Percutaneous liver biopsy, peritoneoscopy and laparotomy: an assessment of relative merits in the lymphomata. Br J Cancer 31(Suppl 2):242–247

Chaib E, Leite KR, Saad WA, Gama-Rodrigues J (2002) Primary lymphoma of the liver treated by extended hepatectomy and chemotherapy: a case report (in Portuguese). Rev Hosp Clin Fac Med Sao Paulo 57:223–228

Chim CS, Choy C, Ooi GC, Liang R (2001) Primary hepatic lymphoma. Leuk Lymphoma 40:667–670

Cirasino L, Costantini MC, Canesi B, de Renzo A, Morra E (1997) Non-Hodgkin's lymphoma with rheumatism-like presentation and multiple cystic and nodular lesions in the liver. Recenti Prog Med 88:176–178

Citak EC, Sari I, Demirci M, Karakus C, Sahin Y (2011) Primary hepatic Burkitt lymphoma in a child and review of literature. J Pediatr Hematol Oncol 33: e368–e371

Colomo L, Loong F, Rives S, Pittaluga S, Martinez A, Lopez-Guilermo A, Ojanguren J et al (2004) Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. Am J Surg Pathol 28:736–747

Conlin PA, Orden MB, Hough TR, Morgan DL (2001) Myeloperoxidase-positive intravascular large B-cell lymphoma. Arch Pathol Lab Med 125:948–950

Corti M, Villafañe MF, Bistmans A, Campitelli A, Narbaitz M, Barè P (2011) Oral cavity and extra-oral plasmablastic lymphomas in AIDS patients: report of five cases and review of the literature. Int J STD AIDS 22:759–763

Cousins E, Nicholas J (2014) Molecular biology of human herpesvirus 8: novel functions and virus-host interactions implicated in viral pathogenesis and replication. Recent Results Cancer Res 193:227–268

Dave S (2012) Burkitt lymphoma : analysis of the genome. Clin Adv Hematol Oncol 10:54–55

De Fino C, Arena V, Hohaus S, Di Iorio R, Bozzoli V, Mirabella M (2012) Intravascular large B-cell lymphoma presenting as slowly progressive paraparesis with normal MRI features. J Neurol Sci 314:171–174

Demirer T, Dail DH, Aboulafia DM (1994) Four varied cases of intravascular lymphomatosis and a literature review. Cancer 73:1738–1745

DiGiuseppe et al. 1994. http://www.ncbi.nlm.nih.gov/pubmed/7989931

Durodola JI (1977) Pattern of organ involvement in Burkitt's lymphoma in Ibadan: a review. J Natl Med Assoc 69:319–323

Dziadzio M, Chee R, McNamara C, Deheragoda M, Wagner T, Seneviratne SL (2013) EBV-driven diffuse large B-cell lymphoma confined to the liver in a patient with a history of idiopathic CD4 lymphocytopenia. BMJ Case Rep. doi:10.1136/bcr-2013-009721

Emile JF, Azoulay D, Gornet JM, Lopes G, Delvart V, Samuel D, Reynes M, Bismuth H et al (2001) Primary non-Hodgkin's lymphomas of the liver with nodular and diffuse infiltration patterns have different prognoses. Ann Oncol 12:1005–1010

Ferreri AJ, Campo E, Seymour JF, Willemze R, Ilariucci F, Ambrosetti A, Zucca E et al (2004) Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol 127:173–183

Ferry JA, Harris NL, Picker LJ et al (1988) Intravascular lymphomatosis (malignant angioendotheliomatosis). A B-cell neoplasm expressing surface homing receptors. Mod Pathol 1:444–452

Fiegl et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12196378

Fikri M, Dafiri R (2006) Primary hepatic lymphoma: report of a pediatric case (in French). J Radiol 87:311–313

Fukayama M, Ibuka T, Hayashi Y, Ooba T, Koike M, Mizutani S (1993) Epstein-Barr virus in pyothorax-associated pleural lymphoma. Am J Pathol 143:1044–1049

Fung KM, Chakrabarty JH, Kern WF, Magharyous H, Gehrs BC, Li S (2012) Intravascular large B-cell lymphoma with hemophagocytic syndrome (Asian variant) in a Caucasian patient. Int J Clin Exp Pathol 5:448–454

Geyer H, Karlin N, Palen B, Mesa R (2012) Asian-variant intravascular lymphoma in the African race. Rare Tumors 4:e10

Giessen C, Di Gioia D, Huber B, Seppi B, Graser A, Duerr HR, Mayr D, Kirchner T et al (2012) Primary effusion lymphoma (PEL) without effusion: a patient case report of a PEL solid variant. J Clin Pathol 65:189–190

Giffin L, Damania B (2014) KSHV: pathways to tumorigenesis and persistent infection. Adv Virus Res 88:111–159

Giulino-Roth L, Wang K, Macdonald TY, Mathew S, Tam Y, Cronin MT, Palmer G et al (2012) Targeted genomic sequencing of pediatric Burkitt lymphoma identifies recurrent alterations in antiapoptotic and chromatin-remodeling genes. Blood 120:5181–5184

Glass RBJ, Fernbach SK, Conway JJ, Shkolnik A (1985) Gallium scintigraphy in American Burkitt lymphoma: accurate assessment of tumor load and prognosis. AJR Am J Roentgenol 145:671–676

Goh SG, Chuah KL, Tan PH (2002) Intravascular lymphomatosis of the lung and liver following eyelid lymphoma in a Chinese man and review of primary pulmonary intravascular lymphomatosis. Pathology 34:82–85

Gottwein E (2012) Kaposi's sarcoma-associated herpesvirus microRNAs. Front Microbiol 3:165

Gottwein E, Corcoran DL, Mukherjee N, Skalsky RL, Hafner M, Nusbaum JD, Shamulailatpam P et al (2011) Viral microRNA targetome of KSHV-infected primary effusion lymphoma cell lines. Cell Host Microbe 10:515–526

Greisman HA, Lu Z, Tsai AG, Greiner TC, Yi HS, Lieber MR (2012) IgH partner breakpoint sequences provide evidence that AID initiates t(11;14) and t(8;14) chromosomal breaks in mantle cell and Burkitt lymphomas. Blood 120:2864–2867

Gual-Tarrada N, Selva-O'Callaghan A, Ruiz-Marcellan C (2012) Intravascular large B-cell lymphoma, a cause of fever of unknown origin in the elderly. J Am Geriatr Soc 60:375–376

Haecker I, Gay LA, Yang Y, Hu J, Morse AM, NcIntyre LM, Renne R (2012) Ago HITS-CLIP expands understanding of Kaposi's sarcoma-associated herpesvirus miRNA function in primary effusion lymphomas. PLoS Pathog 8:e1002884

Hamoudi R, Diss TC, Oksenhendler E, Pan L, Carbone A, Ascoli V, Boshoff C, Isaacson P, Du MQ (2004) Distinct cellular origin of primary effusion lymphoma with and without EBV infection. Leuk Res 28:333–338

Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Müller-Hermelink HK et al (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103:275–282

Hara T, Nishi S, Horimoto A, Takenaka S, Ibata Y, Akamatsu H (2001) Primary effusion lymphoma in a patient with hepatitis C virus-related liver cirrhosis. J Gastroenterol Hepatol 16:948–949

Harris AC, Kornstein MJ (1993) Malignant lymphoma imitating hepatitis. Cancer 71:2639–2646

Hasagawa H, Katano H, Tanno M, Masuo S, Ae T, Sato Y, Takahashi H, Iwasaki T et al (2004) BCL-6-positive human herpesvirus 8-associated solid lymphoma arising from liver and spleen as multiple nodular lesions. Leuk Lymphoma 45:2169–2172

Hashizume Y (2011) Pathology of intravascular lymphoma (in Japanese). Brain Nerve 63:459–466

Higurashi T, Takahashi H, Inamori M, Iida H, Hosono K, Endo H, Sakamoto Y, Fujita K et al (2009) Intravascular lymphoma: usefulness of liver biopsy in the clinical setting. Intern Med 48:2155–2156

Hirose Y, Fukushima T, Masaki Y, Shimoyama K, Karasawa H, Ogawa N, Wano Y (2004) Epstein-Barr virus-associated composite lymphoma composed of peripheral T-cell lymphoma and an anaplastic variant of a diffuse large B-cell type of non-Hodgkin's lymphoma and strongly expressing p53 protein. Int J Hematol 79:260–265

Hishikawa N, Niwa H, Hara T, Hara K, Ito M, Shimada S, Yoshida M, Hashizume Y, Murakami N (2011) An autopsy case of lymphomatosis cerebri showing pathological changes of intravascular large B-cell lymphoma in visceral organs. Neuropathology 31:612–619

Hong JY, Kim HJ, Ko YM, Choi JY, Jung CW, Kim SJ, Kim WS (2014) Clinical features and treatment outcomes of intravascular large B-cell lymphoma: a single-center experience in Korea. Acta Haematol 131:18–27

Hoshi T, Fujii Y, Okuyama S, Tanaka Y, Kimura N, Mouri Y, Takaya H, Kajimura K (2014) Two cases of intravascular lymphoma diagnosed by random liver biopsy (in Japanese). Nihon Shokakibyo Gakkai Zasshi 111:1433–1440

Hsi ED, Lorsbach RB, Fend F, Dogan A (2011) Plasmablastic lymphoma and related disorders. Am J Clin Pathol 136:183–194

Hsieh PY, Huang SI, Li DK, Mao TL, Sheu JC, Chen CH (2007) Primary effusion lymphoma involving both pleural and abdominal cavities in a patient with hepatitis B virus-related liver cirrhosis. J Formos Med Assoc 106:504–508

Hsieh MS, Yeh YC, Chou YH, Lin CW (2010) Intravascular large B cell lymphoma in Taiwan: an Asian variant of non-germinal-center origin. J Formos Med Assoc 109:185–191

Hsu CF, Ko SF, Hsiao CC, Shieh CS, Huang CC, Huang FC (2003) Obstructive jaundice as the presenting manifestation of Burkitt's lymphoma in a 4-year-old boy. J Formos Med Assoc 102:105–108

Huang CB, Eng HL, Chuang JH, Cheng YF, Chen WJ (1997) Primary Burkitt's lymphoma of the liver: report of a case with long-term survival after surgical resection and combination chemotherapy. J Pediatr Hematol Oncol 19:135–138

Huang et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15105661

Ichinohasama R, Miura I, Kobayashi N, Saitoh Y, DeCoteau JF, Saiki Y, Mori S, Kadin ME, Ooya K (1998) Herpes virus type 8-negative primary effusion lymphoma associated with PAX-5 gene rearrangement and hepatitis C virus: a case report and review of the literature. Am J Surg Pathol 22:1528–1537

Iuchi K, Aozasa K, Yamamoto S, Mori T, Tajima K, Minato K, Mukai K, Komatsu H, Tagaki T, Kobayashi Y et al (1989) Non-Hodgkin's lymphoma of the pleural cavity developing from long-standing pyothorax. Summary of clinical and pathological findings in thirty-seven cases. Jpn J Clin Oncol 19:249–257

Jacobs SL, Rozenblit A (2006) HIV-associated hypervascular primary Burkitt's lymphoma of the liver. Clin Radiol 61:453–455

Jaffe ES (1987) Malignant lymphomas: pathology of hepatic involvement. Semin Liver Dis 7:257–268

Jalkanen et al. 1989. http://www.ncbi.nlm.nih.gov/pubmed/2573578

Kalungi S, Wabinga H, Bostad L (2013) Expression of apoptosis associated proteins Survivin, Livin and Thrombospondin-1 in Burkitt lymphoma. APMIS 12:239–245

Kamona AA, El-Khatib MA, Swaidan MY, Jarar MS, Suleiman AJ, Ali HM, Basharaheel AB et al (2007) Pediatric Burkitt's lymphoma: CT findings. Abdom Imaging 32:381–386

Kanno H, Aozasa K (1998) Mechanism for the development of pyothorax-associated lymphoma. Pathol Int 48:653–664

Kanno H, Ohsawa M, Hashimoto M, Iuchi K, Nakajima Y, Aozasa K (1999) HLA-A alleles of patients with pyothorax-associated lymphoma: anti-Epstein-Barr virus (EBV) host immune responses during the development of EBV latent antigen-positive lymphomas. Int J Cancer 82:630–634

Kashimura M, Murayama K, Kojima M (2013) Primary hepatic and hepatosplenic diffuse large B-cell lymphomas with intrasinusoidal and interstitial lymphomatous infiltration. Int J Surg Pathol 21:531–534

Keller BC, Nussensveig D, Dowell JE (2010) Diffuse large B-cell lymphoma in a hepatitis C virus-infected patient presenting with lactic acidosis and hypoglycemia. Am J Med Sci 339:202–204

Kayano and Katayama 1990. http://www.ncbi.nlm.nih.gov/pubmed/2189392

Kanda et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10492081

Khalidi et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9796727

Kheyri Z, Ali Asgari A, Zare Mehrjerdi A, Zamani F, Ajdarkosh H (2013) Fulminant hepatic failure due to primary hepatic lymphoma: a case report. Middle East J Dig Dis 5:168–170

Khoury et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12861069

Kim Y, Leventaki V, Bhaijee F, Jackson CC, Medeiros LJ, Vega F (2012) Extracavitary/solid variant of primary effusion lymphoma. Ann Diagn Pathol 16:441–446

Kim Y, Park CJ, Roh J, Huh J (2014) Current concepts in primary effusion lymphoma and other effusion-based lymphomas. Korean J Pathol 48:81–90

Kiresi D, Karabekmez LG, Koksal Y, Emlik D (2008) A case of Burkitt lymphoma re-presenting as periportal hepatic and multiple organ infiltration. Clin. Lymphoma Myeloma 8:59–61

Kishi et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15136242

Knobel B, Sommer I, Petchenko P, Lev D, Okon E (2001) Malignant humoral hypercalcemia associated with angiotropic large B cell lymphoma (in Hebrew). Harefuah 140:204–206

Knowles DM, Inghirami G, Ubriaco A, Dalla-Favera R (1989) Molecular genetic analysis of three AIDS-associated neoplasms of uncertain lineage demonstrates their B-cell derivation and the possible pathogenetic role of the Epstein-Barr virus. Blood 73:792–799

Kuroda J, Omoto A, Fujiki H, Okugawa K, Tamai H, Yamagishi H, Kobayashi Y, Yoshikawa T (2001) Primary hepatic Burkitt's lymphoma with chronic hepatitis C. Acta Haematol 105:237–240

Kuwabara H, Nagai M, Shibanushi T, Ohmori M, Kawakami K, Asakura H (2000) CD138-positive and Kaposi's sarcoma-associated herpesvirus (KSHV)-negative B-cell lymphoma with serosal spreading of the body cavity and lymphadenopathy: an autopsy case. Hum Pathol 31:1171–1175

Lee SH, Kim HJ, Mun JS, Oh HC, Lee HW, Choi CH, Kim JW, Do JH, Kim JG et al (2008) A case of primary hepatic Burkitt's lymphoma. Korean J Gastroenterol 51:259–264

Lee HR, Brulois K, Wong L, Jung JU (2012) Modulation of immune system by Kaposi's sarcoma-associated herpesvirus: lessons from viral evasion strategies. Front Microbiol 3:44

Lei 1998. http://www.ncbi.nlm.nih.gov/pubmed/9684927

Lei KI, Chow JH, Johnson PJ (1995) Aggressive primary hepatic lymphoma in Chinese patients. Presentation, pathologic features, and outcome. Cancer 76:1336–1343

Lei X, Zhu Y, Jones T, Bai Z, Huang Y, Gao SJ (2012) A Kaposi's sarcoma-associated herpesvirus microRNA and its variants target the transforming growth factor b pathway to promote cell survival. J Virol 86:11698–11711

Lettiere CJ, Berg BW (2003) Clinical features of non-Hodgkin's lymphoma presenting with acute liver failure: a report of five cases and review of published experience. Am J Gastroenterol 98:1641–1646

Leventaki V, Rodic V, Tripp SR, Bayerl MG, Perkins SL, Barnette P, Schiffman JD et al (2012) TP53 pathway analysis in paediatric Burkitt lymphomas reveals increased MDM4 expression as the only TP53 pathway abnormality detected in a subset of cases. Br J Haematol 158:763–771

Liu F, Asano N, Tatematsu A, Oyama T, Kitamura K, Suzuki K, Yamamoto K, Sakamoto N et al (2012) Plasmablastic lymphoma of the elderly: a

clinicopathological comparison with age-related Epstein-Barr virus-associated B cell lymphoproliferative disorder. Histopathology 61:1183–1197

Love C, Sun Z, Jima D, Li G, Zhang J, Miles R, Richards KL, Dunphy CH, Choi WW et al (2012) The genetic landscape of mutations in Burkitt lymphoma. Nat Genet 44:1321–1325

Luan SL, Boulanger E, Ye H, Chanudet E, Johnson N, Hamoudi RA, Bacon CM et al (2010) Primary effusion lymphoma: genomic profiling revealed amplification of SELPLG and CORO1C encoding for proteins important for cell migration. J Pathol 222:166–179

Lui PC, Wong GK, Poon WS, Tse GM (2003) Intravascular lymphomatosis. J Clin Pathol 56:468–470

Ma YJ, Chen EQ, Chen XB, Wang J, Tang H (2011) Primary hepatic diffuse large B cell lymphoma: a case report: primary hepatic diffuse large B cell lymphoma. Hepat Mon 11:203–205

Magrath I (2012) Epidemiology: clues to the pathogenesis of Burkitt lymphoma. Br J Haematol 156:744–756

Makhdoomi K, Ghaffari Moghaddam A, Aishi Oskue A, Mohammadi A, Ilkhanizadeh B et al (2010) Extranodal diffuse large B-cell lymphoma confined to liver in a kidney transplant recipient. Iran J Kidney Dis 4:336–339

Makis W, Stern J (2010) Hepatitis C-related primary effusion lymphoma of the pleura and peritoneum, imaged with F-18 FDG PET/CT. Clin Nucl Med 35:797–799

Mantadakis E, Raissaki M, Tzardi M, Katzilakis N, Chatzimichael A, Kalmanti M (2008) Primary hepatic Burkitt lymphoma. Pediatr Hematol Oncol 25:331–338

Martin A, Capron F, Liguory-Brunaud MD, De Frejacques C, Pluot M, Diebold J (1994) Epstein-Barr virus-associated primary malignant lymphomas of the pleural cavity occurring in longstanding pleural chronic inflammation. Hum Pathol 25:1314–1318

Mattar WE, Alex BK, Sherker AH (2010) Primary hepatic Burkitt lymphoma presenting with acute liver failure. J Gastrointest Cancer 41:261–263

Metta H, Corti M, Maranzana A, Schtirbu R, Narbaitz M, De Dios Soler M (2009) Unusual case of plasmablastic non-Hodgkin's lymphoma located in the liver. First case reported in an AIDS patient. Ann Hepatol 8:242–245

Miller ST, Wollner N, Meyers PA, Exelby P, Jereb B, Miller DR (1983) Primary hepatic or hepatosplenic non-Hodgkin's lymphoma in children. Cancer 52:2295–2298

Minnicelli C, Barros MH, Klumb CE, Romano SO, Zalcberg IR, Hassan R (2012) Relationship of Epstein-Barr virus and interleukin 10 promoter polymorphisms with the risk and clinical outcome of childhood Burkitt lymphoma. PLoS One 7:e46005

Molina-Privado I, Jimenez-P R, Montes-Moreno S, Chiodo Y, Rodriguez-Martinez M et al (2012) E2F4 plays a key role in Burkitt lymphoma tumorigenesis. Leukemia 26:2277–2285

Molyneux EM, Rochford R, Griffin B, Newton R, Jackson G, Menon G, Harrison CJ et al (2012) Burkitt's lymphoma. Lancet 379:1234–1244

Murase T, Nakamura S, Kawauchi K, Matsuzaki H, Sakai C, Inaba T, Nasu K, Tashiro K et al (2000) A Asian variant of intravascular large B-cell lymphoma: clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haematophagocytic syndrome. Br J Haematol 111:826–834

Murase et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/1186365

Muringampurath-John D, Jaye DL, Flowers CR, Saxe D, Chen Z, Lechowicz MJ, Weisenburger DD et al (2012) Characteristics and outcomes of diffuse large B-cell lymphoma presenting in leukemic phase. Br J Haematol 158:608–614

Nakamura et al. 1995. http://www.ncbi.nlm.nih.gov/pubmed/8522314

Nakatsuka S, Yao M, Hoshida Y, Yamamoto S, Iuchi K, Aozasa K (2002) Pyothorax-associated lymphoma: a review of 106 cases. J Clin Oncol 20:4255–4260

Narimatsu H, Ota Y, Kami M, Takeuchi K, Suzuki R, Matsuo K, Matsumura T, Yuji K et al (2007) Clinicopathological features of pyothorax-associated lymphoma; a retrospective survey involving 98 patients. Ann Oncol 18:122–128

Natsuizaka M, Kudo M, Suzuki M, Takano M, Tsuyuguchi M, Kawamura N, Noguchi S et al (2009) Diffuse large B-cell lymphoma with massive portal vein tumor thrombosis in a patient with alcoholic cirrhosis: a case report and literature review. Intern Med 48:805–808

Noguchi S, Yatera K, Kido T, Ogoshi T, Nagata S, Nishida C, Yamasaki K, Kawanami T et al (2013) Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma with multiple thin-walled pulmonary cysts: a case report and review of the literature. Intern Med 52:2325–2329

Noronha V, Shafi NQ, Obando JA, Kummar S (2005) Primary non-Hodgkin's lymphoma of the liver. Crit Rev Oncol Hematol 53:199–207

Ohsawa M, Tomita Y, Kanno H, Iuchi K, Kawabata Y, Nakajima Y, Komatsu H, Mukai K, Shimoyama M, Aozasa K (1995) Role of Epstein-Barr virus in pleural lymphomagenesis. Mod Pathol 8:848–853

Onishi Y, Hotta S, Iwamoto H, Kamoshida T, Takahashi A, Imai Y (1998) An autopsy case of intravascular malignant lymphomatosis with hemophagocytic syndrome, mental confusion and liver dysfunction (in Japanese). Rinsho Ketsueki 39:586–592

Onnis A, Navari M, Antonicelli G, Morettini F, Mannucci S, De Falco G, Vigorito E, Leoncini L (2012) Epstein-Barr nuclear antigen 1 induces expression of the cellular microRNA hsa-miR-127 and impairing B-cell differentiation in EBV-infected memory B cells. New insights into the pathogenesis of Burkitt lymphoma. Blood Cancer J 2:e84

Osborne BM, Butler JJ, Guarda LA (1985) Primary lymphoma of the liver. Ten cases and a review of the literature. Cancer 56:2902–2910

Otrakji CL, Voigt W, Amador A, Nadji M, Gregorios JB (1988) Malignant angioendotheliomatosis – a true lymphoma. A case of intravascular lymphomatosis studied by Southern blot hybridization analysis. Hum Pathol 19:475–478

Pan ZG, Zhang QY, Lu ZB, Quinto T, Rosenvald IB, Liu LT, Wilson D, Reddy V et al (2012) Extracavitary KSHV-associated large B-cell lymphoma: a distinct entity or a subtype of primary effusion lymphoma? Study of 9 cases and review of an additional 43 cases. Am J Surg Pathol 36:1129–1140

Paner GP, Jensen J, Foreman KE, Reyes CV (2003) HIV and HHV-8 negative primary effusion lymphoma in a patient with hepatitis C virus-related liver cirrhosis. Leuk Lymphoma 44:1811–1814

Park KY, Yu JS, Yoon SW, Park MS, Koo JS, Kim KW (2004) Burkitt's lymphoma representing periportal infiltrating mass on CT. Yonsei Med J 45:723–726

Pather S, Mackinnon D, Padayachee RS (2013) Plasmablastic lymphoma in pediatric patients: a clinicopathologic study of three cases. Ann Diagn Pathol 17:80–84

Peker D, Quigley B, Qin D, Papenhausen P, Zhang L (2013) Burkitt lymphoma arising from lymphoplasmacytic lymphoma following acquisition of MYC translocation and loss of the ETV6 tumor suppressor gene. Arch Pathol Lab Med 137:130–133

Pellicelli AM, Marignani M, Zoli V, Romano M, Morrone A, Nosotti L, Barbaro G, Picardi A et al (2011) Hepatitis C virus-related B cell subtypes in non-Hodgkin's lymphoma. World J Hepatol 3:278–284

Pereira FE, Goncalves CS, Musso C, de Menezes TM, Boni ES (1993) Primary non-Hodgkin's lymphoma of the liver: report of two cases and review of the literature (in Portuguese). Arq Gastroenterol 30:27–32

Petitjean B, Jardin F, Joly B, Martin-Garcia N, Tilly H, Picquenot JM, Briere J, Danel C, Mehaut S, Abd-Al-Samad I et al (2002) Pyothorax-associated lymphoma: a peculiar clinicopathologic entity derived from B cells at late stage of differentiation and with occasional aberrant dual B-and T-cell phenotype. Am J Surg Pathol 26:724–732

Pfleger VL, Tappeiner J (1959) Zur Erkenntnis der systemisierten Endotheliomatose der cutanen Blutgefässe (Reticuloendotheliose?). Hautarzt 10:359–363

Pileri SA, Dirnhofer S, Went P, Ascani S, Sabattini E, Marafioti T, Tzankov A, Leoncini L et al (2002) Diffuse large B-cell lymphoma: one or more entities? Present controversies and possible tools for its subclassification. Histopathology 41:482–509

Plaza R, Ponferrada A, Benito DM, Arevalo N, Foncillas MA, de Fuenmayor ML, Aldeguer M (2011) Plasmablastic lymphoma associated to Crohn's disease and hepatitis C virus chronic infection. J. Crohns Colitis 5:628–632

Ponzoni M, Ferreri AJ, Campo E, Facchetti F, Mazzucchelli L, Yoshino T, Murase T et al (2007) Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. J Clin Oncol 25:3168–3173

Punj V, Matta H, Chaudhary PM (2012) A computational profiling of changes in gene expression and transcription factors induced by vFLIP K13 in primary effusion lymphoma. PLoS One 7:e37498

Rak K, Hopper KD, Parker SH (1988) The "starry sky" liver with Burkitt's lymphoma. J Ultrasound Med 7:279–281

Ramos G, Murao M, De Oliveira BM, De Castro LPF, Viana MB (1997) Primary hepatic non-Hodgkin's lymphoma in children: a case report and review of the literature. Med Pediatr Oncol 28:370–372

Roshal M, Till BG, Fromm JR, Cherian S (2008) Intravascular large B cell lymphoma presenting in a liver explant. J Clin Pathol 61:877–878

Roy D, Dittmer DP (2011) Phosphatase and tensin homolog on chromosome 10 is phosphorylated in primary effusion lymphoma and Kaposi's sarcoma. Am J Pathol 179:2108–2119

Roy D, Sin SH, Damania B, Dittmer DP (2011) Tumor suppressor genes FHIT and WWOX are deleted in primary effusion lymphoma (PEL) cell lines. Blood 118:e32–e39

Rubin MA, Cossman J, Freter CE, Azumi N (1997) Intravascular large cell lymphoma coexisting within hemangiomas of the skin. Am J Surg Pathol 21:860–864

Ryoo JW, Manaligod JR, Walker MJ (1986) Primary lymphoma of the liver. J Clin Gastroenterol 8:308–311

Sander S, Rajewski K (2012) Burkitt lymphomagenesis linked to MYC plus PI3K in germinal center B cells. Oncotarget 3:1066–1067

Santini M, Fiorello A, Vicidomini G, Busiello L, Baldi A (2009) A surgical case of pyothorax-associated lymphoma of T-cell origin arising from the chest wall in chronic empyema. Ann Thorac Surg 88:642–645

Santos ES, Raez LE, Salvatierra J, Morgensztern D, Shanmugan N, Neff GW (2003) Primary hepatic non-Hodgkin's lymphomas: case report and review of the literature. Am J Gastroenterol 98:2789–2793

Sato S, Masuda T, Oikawa H, Satoh T, Suzuki Y, Takikawa Y, Yamazaki K, Suzuki K et al (1999) Primary hepatic lymphoma associated with primary biliary cirrhosis. Am J Gastroenterol 94:1669–1673

Schmitz R, Young RM, Ceribelli M, Jhavar S, Xiao W, Zhang M, Wright G, Shaffer AL et al (2012) Butkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. Nature 490:116–120

Scoazec JY, Degott D, Brousse N, Barge J, Molas G, Potet F, Benhamou JP (1991) Non-Hodgkin's lymphoma presenting as a primary tumor of the liver.

Presentation, diagnosis and outcome in eight patients. Hepatology 13:870–875
Seki et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15371756
Sekiguchi N, Joshita S, Yoshida T, Kurozumi M, Sano K, Nakagawa M, Ito T, Matsushita T, Komatsu D et al (2013) Liver dysfunction and thrombocytopenia diagnosed as intravascular large B-cell lymphoma using a timely and accurate transjugular liver biopsy. Intern Med 52:1903–1908
Sekine A, Hagiwara E, Hashiba Y, Ogura T, Takahashi H (2010) Clinical analysis of eight cases with pyothorax-associated lymphoma (in Japanese). Nihon Kokyuki Gakkai Zasshi 48:186–191
Shide K, Henzan H, Nagafuji K, Aoki K, Miyamoto T, Shimoda K, Kazuyama Y, Ohshima K, Gondo H, Harada M (2003) Dynamics of Epstein-Barr virus load in pyothorax-associated lymphoma. J Med Virol 70:137–140
Shimizu I, Ichikawa N, Yotsumoto M, Sumi M, Ueno M, Kobayashi H (2007) Asian variant of intravascular lymphoma: aspects of diagnosis and the role of rituximab. Intern Med 46:1381–1386
Shiraki K, Sugimoto K, Deguchi M, Ito N, Masuda C, Takei Y (2007) Hepatic intravascular large B cell lymphoma. Intern Med 46:1761–1762
Siegel MJ, Melson GL (1981) Sonographic demonstration of hepatic Burkitt's lymphoma. Pediatr Radiol 11:166–167
Slack GW, Gascoyne RD (2011) MYC and aggressive B-cell lymphomas. Adv Anat Pathol 18:219–228
Smith O (2012) Denis Parsons Burkitt CMG, MD, DSc, FRS, FRCS, FTCD (1911-93) Irish by birth, Trinity by the grace of god. Br J Haematol 156:770–776
Soldini D, Montagna C, Schüffler P, Martin V, Georgis A, Thiesler T, Curioni-Fontecedro A et al (2013) A new diagnostic algorithm for Burkitt and diffuse large B-cell lymphomas based on the expression of CSE1L and STAT3 and on MYC rearrangement predicts outcome. Ann Oncol 24:193–201
Sunil M, Reid E, Lechowicz MJ (2010) Update on HHV-8-associated malignancies. Curr Infect Dis Rep 12:147–154
Szuba A, Koba M, Rzeszutko M, Rzeszutko W, Dziegiel P, Loboda A, Dulak J, Andrzejak R (2010) Cutaneous angiogenesis in patient with intravascular lymphoma (IVL): a case report. Dermatol Online J 16:2
Takakuwa T, Tresnasari K, Rahadiani N, Miwa H, Daibata M, Aozasa K (2008) Cell origin of pyothorax-associated lymphoma: a lymphoma strongly associated with Epstein-Barr virus infection. Leukemia 22:620–627
Tani J, Miyoshi H, Nomura T, Yoneyama H, Kobara H, Mori H, Morishita A, Himoto T, Masaki T (2013) A case of plasmablastic lymphoma of the liver without human immunodeficiency virus infection. World J Gastroenterol 19:6299–6303
Taniere P, Manai A, Charpentier R, Terdjman P, Boucheron S, Cordier JF, Berger F (1998) Pyothorax-associated lymphoma: relationship with Epstein-Barr virus, human herpes virus-8 and body cavity-based high grade lymphomas. Eur Respir J 11:779–783
Tedoldi S, Paterson JC, Cordell J, Tan SY, Jones M, Manek S, Dei Tos AP, Roberton H et al (2006) Jaw1/LRMP, a germinal centre-associated marker for the immunohistochemical study of B-cell lymphomas. J Pathol 209:454–463
Terada T (2012) Acute onset pyothorax-associated lymphoma (PAL) with inflammatory features. Int J Clin Exp Pathol 5:163–166
Terrier B, Aouba A, Vasiliu V, Charlier C, Delarue R, Buzyn A, Hermine O (2005) Intravascular lymphoma associated with haemophagocytic syndrome: a very rare entity in western countries. Eur J Haematol 75:341–345
The ICGC MMML-seg Project, Richter J, Schlesner M, Hoffmann S, Kreuz M, Leich E et al (2012) recurrent mutation of the ID3 gene in Burkitt lymphoma identified by integrated genome, exome and transcriptome sequencing. Nat Genet 44:1316–1320
Tucker et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10506453
Utsunomiya T, Okamoto M, Tsujita E, Yamamoto M, Tsutsui S, Fujihara M, Ishida T (2009) Hepatocellular carcinoma infiltrated with non-Hodgkin's lymphoma: report of a case. Surg Today 39:1010–1012
Vade A, Blane CE (1985) Imaging of Burkitt lymphoma in pediatric patients. Pediatr Radiol 15:123–126
Valladolid G, Adams LL, Weisenberg E, Maker VK, Maker AV (2013) Primary hepatic lymphoma presenting as an isolated solitary hepatic cyst. J Clin Oncol 31:e21–e23
Wammanda RD, Ali FU, Adama SJ, Idris HW, Abubakar U (2004) Burkitt's lymphoma presenting as obstructive jaundice. Ann Trop Paediatr 24:103–106
Wan YL, Chen WJ, Huang SC, Lee TY, Tsai CC (1988) Solitary hepatic Burkitt lymphoma presenting as acute pancreatitis. Pediatr Radiol 18:160
Wang T, Nava VE, Schechter GP, Lichy JH, Liu ML (2011) Human herpes virus 8-unrelated primary effusion lymphoma-like lymphoma: a patient successfully treated with pleurodesis. J Clin Oncol 29:e747–e750
Wick MR, Mills SE, Scheitaner BW, Cooper PH, Davitz MA, Parkinson K (1986) Reassessment of malignant 'angioendotheliomatosis': evidence in favor of its reclassification as 'intravascular lymphomatosis'. Am J Surg Pathol 10:112–123
Wong S, Sanchez TR, Swischuk LE, Huang FS (2009) Diffuse peritoneal lymphomatosis: atypical presentation of Burkitt lymphoma. Pediatr Radiol 39:274–276
Xu X, Pang ZG, Liu WP, Zhang SF, Tang Y, Liao DY, Li GD (2008) Intravascular large B-cell lymphoma: report of two autopsy cases with literature review (in Chinese). Zhonghua Bing Li Xue Za Zhi 37:377–383
Yagita M, Tabata R, Konaka Y, Ohno T, Takatsuki K (2000) Intravascular large B-cell lymphoma associated with hypoalbuminemia and hypoxemia (in Japanese). Rinsho Ketsueki 41:1189–1194

Yamada S, Tanimoto A, Nabeshima A, Tasaki T, Wang KY, Kitada S, Noguchi H et al (2012) Diffuse large B-cell lymphoma presenting with neurolymphomatosis and intravascular lymphoma: a unique autopsy case with diverse neurological symptoms. Diagn Pathol 7:94

Yamamoto T, Masuda A, Sawada T, Nishikawa T, Yoshinaga K, Kazama H, Motoji T et al (2007) Pyothorax-associated lymphoma: a case showing transition from T-cell-rich polymorphic lesion to diffuse large B-cell lymphoma. Pathol Res Pract 203:605–611

Yasuda H, Ando J, Matsumoto T, Ogura K, Ozaki Y, Aritaka N, Aoki Y, Sugita M, Nomura T, Sekii H, Yamaguchi N et al (2010) Intravascular large B cell lymphoma with hepatic portal vein, splenic vein and mesenteric vein tumour embolism. Histopathology 57:648–650

Yamashiro et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/12080610

Yeh YM, Chang KC, Chen YP, Kao LY, Tsai HP, Ho CL, Wang JR, Jones D, Chen TY (2010) Large B cell lymphoma presenting initially in bone marrow, liver and spleen: an aggressive entity associated frequently with haemophagocytic syndrome. Histopathology 57:785–795

Zafar MS, Aggarwal S, Bhalla S (2012) Complete response to chemotherapy in primary hepatic lymphoma. J Cancer Res Ther 8:114–116

Zafrani ES, Leclerq B, Vernant JP, Pinaudeau Y, Chomette G, Dhumeaux D (1983) Massive blastic infiltration of the liver: a cause of fulminant hepatic failure. Hepatology 3:428–432

Zeidman et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15370227

Zhang X, Sun M, Zhang L, Shao H (2013) Primary hepatosplenic CD5-positive diffuse large B-cell lymphoma: a case report with literature review. Int J Clin Exp Pathol 6:985–989

Zinzani PL, Dirnhofer S, Sabattini E, Alinari L, Piccaluga PP, Stefoni V, Tani M et al (2005) Identification of outcome predictors in diffuse large B-cell lymphoma. Immunohistochemical profiling of homogeneously treated de novo tumors with nodal presentation on tissue micro-arrays. Haematologica 90:341–347

Zinzani PL, Broccoli A, Stefoni V, Musuraca G, Abruzzese E, De Renzo A, Cantonetti M et al (2010) Immunophenotype and intermediate-high international prognostic index score are prognostic factors for therapy in diffuse large B-cell lymphoma patients. Cancer 116:5667–5675

B-Cell Non-Hodgkin's Lymphomas with Lymphoplasmacytoid and Plasmacytic Features

92

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_92

Abstract

The liver can be infiltrated in lymphoplasmacytic lymphoma (LPL), a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, a disease usually involving bone marrow and less commonly lymph nodes and inner organs. LPL is often associated with production of a paraprotein, usually of the IgM type (Waldenström's disease). LPL of the liver may rarely be a primary process, but in most cases liver infiltration is the manifestation of generalized LPL. Hepatic infiltration is usually located to portal tracts, but rarely large tumor masses can develop, and compression of small blood vessels may cause portal hypertension. LPL is sometimes associated with peliosis hepatis. The liver is a known manifestation organ of plasmacytoma. In most cases, the liver participates in cases with systemic neoplastic disease. Diffuse, nodular, and mixed hepatic growth patterns of plasmacytoma are known. The rare disorder, plasma cell leukemia, can involve the liver, more frequently in primary plasma cell leukemia than in the secondary form that develops in the setting of plasmacytoma.

Lymphoplasmacytic Lymphoma and Waldenström's Macroglobulinemia

ICD-O code 9671/3

Introduction

Lymphoplasmacytic lymphoma (LPL) is, according to the 2008 WHO classification, defined as a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and the spleen and less commonly other tissues and organs. LPL often produces and secretes a paraprotein, usually of the IgM type, but this feature is not required for diagnosis, as there are nonsecretory forms of this disease. A significant fraction of LPL patients show Waldenström's macroglobulinemia, defined as LPL with bone marrow involvement and an IgM monoclonal gammopathy. LPL mostly occurs in adults with a median age in the sixth decade and a slight male predominance (reviews by Owen et al. (2003), Lin and Medeiros (2005), Vijay and Gertz (2007), Morel et al. (2009), Naderi and Yang (2013).

Waldenström's macroglobulinemia (WM, IgM paraproteinemia) is a disease that had been described by the great physician, scientist, and botany lover, Jan Gösta Waldenström (1906–1996), in 1944 under the term *incipient myelomatosis or essential hyperglobulinemia with fibrinogenopenia* (Waldenström 1944). Apart from macroglobulinemia (Waldenström's syndrome I), other eponyms associated with his name include a form of autoimmune hyperglobulinemia (Waldenström's syndrome II, not to be confounded with macroglobulinemia), Waldenström's disease (an acute form of thyrotoxicosis), Waldenström's chronic active hepatitis (a form of the now autoimmune hepatitis), Waldenström's syndrome (a hereditary disorder), and Waldenström's uveoparotitis (a disorder related to Heerfordt's syndrome). He also coined the term monoclonal gammopathy.

WM is characterized by the presence of a lymphoproliferative disorder (usually LPL) and of an elevated serum monoclonal IgM. Common clinical features include anemia, abnormal bleeding, hyperviscosity, lymphadenopathy, and splenomegaly (McDermott and Bell 1999). WM may represent the expression of several IgM-secreting, usually low-grade NHLs of the lymphocyte lineage and may thus not be a homogeneous disorder, but rather a clinicopathological entity (Pangalis et al. 2003; Owen et al. 2003). It is, therefore, important to recognize that WM can also occur in lymphomas different from LPL, including CLL, diffuse large B-cell lymphoma, follicular lymphoma,

mantle cell lymphoma, and extranodal marginal zone B-cell lymphoma (Owen et al. 2000). WM is also one feature of monoclonal gammopathy of undetermined significance (MGUS; Owen et al. 2000). Consensus recommendations for the clinicopathological definition of WM have been prepared in conjunction with the Second International Workshop on WM, referring to symptomatic WM, asymptomatic WM, MGUS, and so-called IGM-related disorders (Owen et al. 2003). LPL with WM is consistently composed of a spectrum or morphologic continuum of small lymphocytes, plasmacytoid lymphocytes, and plasma cells and occurs in at least two histologic variants, i.e., a more frequent lymphoplasmacytic or lymphoplasmacytoid variant and a less frequent group of lesions (monocytoid, signet ring cell, and hairy cell leukemia-like) (Remstein et al. 2003). Part of LPL cells show intranuclear inclusion containing IgM-kappa immunoglobulin, the Dutcher-Fahey intranuclear inclusion bodies (Boyd 1980).

All typical cases of LPL/WM express monoclonal surface immunoglobulin (predominantly kappa; k:l = 5:1) and the pan-B markers, CD19, CD20, CD22, and CD24, and slightly more than half of the neoplasms lack expression of CD5, CD10, and CD23 (San Miguel et al. 2003; Remstein et al. 2003). LPL/WM cells can show nuclear expression of BCL-10 (Merzianu et al. 2006). LPL is characterized by t(9;14)(p13;q32) in 50 % of patients who lack paraproteinemia. WM frequently shows 6q21 deletions (Schop et al. 2002) and is sometimes associated with 14q23 translocations and t(11;18)(q21;q21). Patients with WD can show somatic mutations in MYD88 and CXCR4 that are determinants of disease progression and outcome. These mutations are similar to nonsense and frameshift mutations found in the warts, hypogammaglobulinemia, infections, and myelokathexis/WHIM syndrome (Treon et al. 2012, 2014). MYD88 mutations were found in more than 90 % of WD patients and stimulate nuclear factor kappaB activity (Jimenez et al. 2013; Xu et al. 2013). Abnormal cytogenetic findings in LPL correlate with the polymorphous subtype and poor prognosis (Mansoor et al. 2001). LPL can transform into diffuse large B-cell lymphoma exhibiting plasmablastic/plasmacytoid features (Lin et al. 2003b; Simonitsch-Klupp et al. 2004).

Hepatic Manifestations of LPL/WM

Primary Lymphoplasmacytic Lymphoma of the Liver

Occasionally LPL has been reported as primary hepatic lymphoma, albeit such a primary organ manifestation is, similar to other NHLs with circulating lymphoma cells, difficult or even impossible to prove (Borgonovo et al. 1995). In two patients with primary hepatic LPL, a serum monoclonal peak of IgG kappa was identified (Borgonovo et al. 1995; Sekikawa et al. 1999).

Liver Infiltration in Extramedullary LPL/WM

Extramedullary involvement by Waldenström's macroglobulinemia occurs in a subset of patients. In a study on 44 patients, extramedullary involvements were, in decreasing order of frequency, the lymph nodes, the soft tissues, the spleen, the skin or lung, and rarely, each situation occurring only once, the tonsils, colon, liver, and gallbladder (Fig. 1). The lymphoplasmacytoid NHL phenotype was observed in 78 % (Lin et al. 2003a). On the other hand, another study on 45 patients found hepatomegaly in 44 % of patients, without specifying the cause of liver enlargement (Krajny and Pruzanski 1976). Rarely, infiltration of the liver in LPL is marked, resulting in tumorous lesions of the liver (Blatrix et al. 1973) or in massive sarcomatous infiltration that starts in sinusoids and portal tracts (Beau et al. 1984). Portal tract infiltration with compression of small portal venous branches may cause portal hypertension in LPL (Brooks 1976). Liver infiltration was detected in a patient with LPL associated with IgA

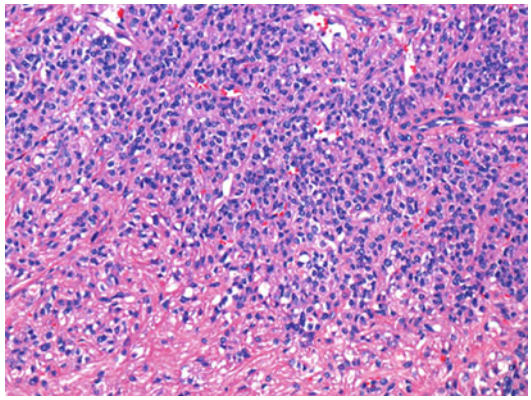

Fig. 1 Lymphoplasmacytoid infiltration of the liver in Waldenström's disease (hematoxylin and eosin stain)

hypergammaglobulinemia (Polprasert et al. 2009). Rarely, the liver is affected by high-grade immunoblastic lymphoma developing subsequent to WM, sometimes with jaundice and liver failure (Beau et al. 1984).

Peliosis Hepatis and Regenerative Changes of the Liver in WM

Peliosis hepatis has repeatedly detected in patients with WM (Ginestal-Cruz et al. 1979; Voinchet et al. 1988; Corpa et al. 2004). The peliotic foci may grow to a size rendering them grossly visible at autopsy (Corpa et al. 2004). In the patient of Corpa et al. (2004), the peliotic cavities were also irregularly filled with a monotonous population of CD20-positive neoplastic small lymphocytes, most with lymphoplasmacytic features (IgG/kappa). In contrast, the case reported by Ginestal-Cruz and coworkers (1979) showed a portal tract infiltrate by lymphoma cells, surrounded by typical peliotic cavities, which did not contain neoplastic cells. In this patient, peliosis might have been caused by oxymetholone therapy, a steroid known to induce peliosis hepatis (McDonald and Speicher 1978; Pavlatos et al. 2001), possibly via endothelial damage (Kosek and Smith 1980). Similarly, another patient with WM-associated peliosis hepatis did not display lymphoma cells within the peliotic lesions (Voinchet et al. 1988).

Nodular regenerative hyperplasia (NRH) of the liver in WM has been reported as a distinct association (Wanless et al. 1981). Pathogenetically, peliosis and nodular regenerative hyperplasia have been related to a disorder of hepatic microcirculation caused by light chain deposits in the sinusoidal walls (Voinchet et al. 1988). A similar or the same pathogenic pathway may be operational in liver peliosis rarely observed in multiple myeloma with production of Bence-Jones proteins (Kaise et al. 1982).

Amyloidosis and Light Chain Disease in LPL/WM

Primary systemic amyloidosis is a rare complication of immunoglobulin M monoclonal gammopathies and WM (Bedossa et al. 1988; Gertz et al. 1993, 2004; Gertz and Kyle 1988).

LPL/WM and Hepatocellular Carcinoma

There are few cases in the literature where WM was associated with hepatocellular carcinoma (Shimizu et al. 1982; Lotz et al. 1985; Lee et al. 1986; Yamamoto et al. 1990; Izumi et al. 1996; Hasegawa et al. 2000). This association may be related to chronic liver disease occurring in WM (Izumi et al. 1996), in particular the frequent infection of WM patients with HCV (Santini et al. 1993; Mussini et al. 1995; Mangia et al. 1996; Silvestri et al. 1998).

Differential Diagnosis

Monoclonal IgM gammopathy and hepatomegaly can occur in the absence of LPL/WM. Schnitzler's syndrome is a rare condition characterized by chronic urticarial, monoclonal IgM gammopathy,

intermittent fever, joint and/or bone pain with osteosclerosis, lymphadenopathy, hepatomegaly, splenomegaly, and leukocytosis. The etiology of this syndrome remains obscure (Lipsker et al. 2001; Kastritis et al. 2008). Schnitzler's syndrome can, similar to WD, be associated with nodular regenerative hyperplasia of the liver (Lauwers et al. 1999).

IgA-Type Lymphoplasmacytic Lymphoma with Liver Involvement

Introduction

Lymphoplasmacytic lymphoma with IgA hypergammaglobulinemia is a very rare variant of this type of lymphoma, which may clinically mimic Waldenström's disease (Hijmans 1975; Tursz et al. 1977; Hishitani et al. 1982; Askari et al. 1985; Basu et al. 2004). Histologically, a relatively high proportion of pleomorphic tumor cells is a feature in at least part of cases. The lymphoma is sometimes associated with autoimmune disorders (Askari et al. 1985) and can cause extranodal tumorous manifestations, involving the breast (Tsuji et al. 2009) and liver (see below).

Liver Involvement

Ig4-type lymphoplasmacytic lymphoma has been shown to involve the liver, clinically manifesting as abnormal liver function tests. This entity was first recognized in a 48-year-old female patient presenting with anemia and renal failure. Liver biopsy showed an infiltrate of small, atypical clonal cells with signs of plasmacytoid differentiation, associated with Ig4 hypergammaglobulinemia in serum (Polprasert et al. 2009).

Plasmacytoma of the Hepatobiliary Tract

ICD-O codes 9732/3 and 9734/3

Introduction

Both osseous plasmacytoma (plasmacytic multiple myeloma, PCM) and extraosseous plasmacytoma can manifest in the liver and biliary tract. In most cases, liver involvement occurs in the setting of myeloma, whereas primary hepatic plasmacytoma is very rare. In the 2008 WHO classification, extraosseous (extramedullary) plasmacytomas (EOPCs) are localized plasma cell neoplasms arising in tissues other than bone marrow. EOPCs account for about 3–5 % of all plasma cell neoplasms, with a medium age of patients at diagnosis of 55 years (Wiltshaw 1976; Knowling et al. 1983; Holland et al. 1992; Kremer et al. 2005). Two thirds are males. EOPC has a distinct frequency distribution pattern: About 80 % of the neoplasms arise in the upper respiratory tract, including the pharynx and larynx, but almost any other organ can be involved. Clinically, manifestations of EOPC depend on localization of the lesion and the tumor mass. Typically, the bone marrow is not involved. Approximately 20 % of patients show a small M-protein gradient, most often IgA (Shaheen et al. 2008; Lorsbach et al. 2011).

Liver Involvement in Plasmacytoma

Primary and Secondary EOPC of the Liver

In most cases of nodular hepatic manifestations of PCM, liver involvement makes part of extramedullary disease in systemic plasmacytoma (Fig. 2). In contrast, *primary hepatic nodular plasmacytoma* is exceedingly rare and usually presents as solitary plasmacytoma situated within the liver substance (Dohy et al. 1979; Abe et al. 1980; Weichhold et al. 1995; Loze et al. 1995; Demirhan et al. 1997; Petrucci et al. 2003; Lee et al. 2007; El Maaroufi et al. 2012). In one case, primary plasmacytoma of the liver had grown to the impressive size of 12 cm (Demirhan et al. 1997). Apart from the liver substance proper, PCM can develop at the hepatic hilus (Oyama et al. 2009) or in the gallbladder fossa (Majerovic et al. 2012).

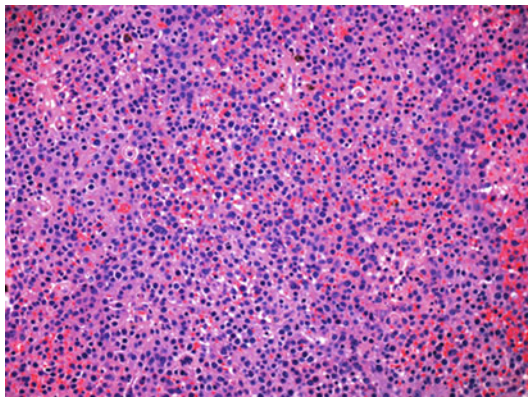

Fig. 2 Plasmacytoma in the liver. There is marked infiltration of the parenchyma with basophilic atypical plasma cells (hematoxylin and eosin stain)

Liver Involvement in Osseous/Medullary ("Classical") PCM

Extramedullary involvement of the liver of any form in PCM is seen at autopsy in 28–50 % of the patients (Walz-Mattmuller et al. 1998; Sucker et al. 2002), but diagnosis antemortem is chiefly based on presumptive clinical and laboratory findings and on imaging studies (Thomas et al. 1973; Kapadia 1980; Perez-Soler et al. 1985; Walz-Mattmuller et al. 1998; Oshima et al. 2001; Sucker et al. 2002; Malhotra et al. 2005; Bhandari et al. 2007; Poudel et al. 2012; Saboo et al. 2012). In a study of 869 cases, a palpable liver was detected in 21 % (Kyle 1975). In fact, hepatomegaly, sometimes massive (Jain et al. 2003), is the most frequent clinical sign of hepatic manifestations in some reported series of PCM and may cause compression signs and abdominal pain and sometimes portal hypertension (Solves et al. 1999). Hepatic involvement may also manifest as jaundice, with or without biliary obstruction (Pastor et al. 1996; Taarit et al. 2007) or caused by cholestatic hepatitis (Barth et al. 2005), or as liver failure (Rahhal et al. 2009; Coffey et al. 2012). Plasmacytoma nodules can rupture and mimic hepatocellular carcinoma (Ueda et al. 2010). Liver disease can rarely represent the primary manifestation of PCM (Solves et al. 1999). Biclonal multiple myeloma has also been observed in conjunction with preexisting liver disease, e.g., HCV-induced liver disease (Montella et al. 2000; Tashiro et al. 2003), which is of interest in the light of the pathogenic relationship between HCV infection and lymphomagenesis (see the respective paragraph).

Hepatic involvement mainly occurs in a *diffuse pattern*, a *nodular pattern*, and a *mixed pattern*. In the *diffuse pattern* of liver involvement, variable areas of the liver substance are more or less diffusely infiltrated by the abnormal plasma cells (Pasmantier and Azar 1969; Perez-Soler et al. 1985; Yoon et al. 1993; Sucker et al. 2002; Lopes da Silva et al. 2011), and nodular hepatic lesions are not visualized at imaging (Simmons et al. 1997). Among 21 histologically studied patients with liver involvement, diffuse infiltration of the liver was observed in ten patients (Perez-Soler et al. 1985). Diffuse liver infiltration can result in massive hepatomegaly (Jain et al. 2003) and, rarely, in hepatic failure (Fujii et al. 1998), but in a study of 21 patients, plasma cell infiltration of the liver did not appear to have a major prognostic significance (Perez-Soler et al. 1985). A reduced liver function thought to be caused by hepatic infiltration was detected in 13–58 % of the patients involved (Kyle 1975; Perez-Soler et al. 1985). Apart from the standard plasmacytic phenotype in PCM, liver infiltration has also been identified in the rarer signet ring-like light chain myeloma (Haidar et al. 2003). Plasmacellular neoplasms may also contain plasma cells with several to numerous variably PAS-positive intracytoplasmic globules or inclusions (Russell bodies) containing immunoglobulins stored in the smooth endoplasmic reticulum. Such cells have previously been termed morular cells by F.W. Mott in 1901 (from Latin morus, mulberry). Nowadays, these cells are often called Mott cells (Bavle 2013; McCormick et al. 2013). Histologically, large parts of liver tissue may be replaced by dense accumulations of plasma cells (producing low-attenuation areas at CT; Solves et al. 1999), sometimes only leaving partially atrophic bile ducts indicating the previous portal tracts (Simmons et al. 1997). The plasma cells are in close spatial contact with cholangiocytes, with

or without signs of plasma cell decay and occasionally with cholangiocyte apoptosis. Dense infiltration of portal tracts can induce cholestasis and jaundice (Thomas et al. 1973). In early phases of hepatic involvement, liver biopsies revealed a preferential infiltration of portal tracts by atypical plasma cells, with focal invasion of the adjacent zone 1 parenchyma (Kaur et al. 2000). However, there are also situations where monotypic light chain-expressing neoplastic cells preferentially accumulate in the sinusoids, associated with hepatocyte damage (Kapadia 1980; Kawano et al. 1991; Solves et al. 1999; Jain et al. 2003). Hepatocyte failure in these situations may lead to hyperammonemia and encephalopathy as the first signs of PCM (Kawano et al. 1991; Caminal et al. 1993).

In the *nodular pattern* of hepatic manifestation ("myelomatous nodules"), few to numerous, gray to white nodules resembling metastatic foci and consisting of dense accumulations of neoplastic plasma cells are observed at autopsy (Sucker et al. 2002). The lesions can reach a diameter of 2–3 cm. Ultrasound scans may reveal target lesions, with a hyperechoic center and peripheral hypoechoic haloes, whereas the lesions were reported to be slightly hypodense to the liver on non-contrast CT and slightly hyperdense during the arterial phase of contrast enhancement. On MRI the lesions were slightly hypointense to the liver on T1-weighted images and hyperintense on T2-weighted images, and they enhanced minimally with intravenous gadolinium (Mathieu et al. 1986; Caturelli et al. 1993; Curtis et al. 1995; Simmons et al. 1997; Ng et al. 1999). In case of abnormal angioarchitecture of the nodules, the lesions may mimic hypervascular hepatocellular carcinoma (Park et al. 2002). The histology is characterized by nodules composed of densely packed atypical plasmacytoid and plasma cells replacing the parenchyma and sometimes encroaching upon damaged bile ducts (Simmons et al. 1997). A rare manifestation of hepatic PCM is hepatic failure due to CD3+ plasma cell infiltration of the liver associated with light chain deposits (Yagci et al. 2002). Overall, involvement of the liver by PCM in the form of space-occupying lesions is less common than the diffuse form (Fernandez-Flores et al. 2003).

Selected References (Voet et al. 1983; Garfinkel et al. 1985; Mathieu et al. 1986; Thiruvengadam et al. 1990; Musto et al. 1992; Nguyen et al. 1992; Wajima 1992; Caturelli et al. 1993; Fautrel et al. 1993; Ganjoo et al. 1993; Curtis et al. 1995; Kelekis et al. 1997; Simmons et al. 1997; Chemlal et al. 1999; Hyun et al. 1999; Ng et al. 1999; Bangerter et al. 2000; Fernandez-Flores et al. 2003; Poggi et al. 2003; Galani et al. 2007; Invernizzi et al. 2007; Carneros et al. 2009; Wu et al. 2009; Gonzalez et al. 2010; Vazquez et al. 2010; Tan et al. 2011; de Vos et al. 2012; Husaric et al. 2013; Pal et al. 2014).

In a subset of cases with PCM, altered immunoglobulins and/or chains thereof are stored in histiocytic cells/macrophages in the form of crystalloid structures that can be detected by light microscopic examination (Takahashi et al. 1987; Jones et al. 1999; Lebeau et al. 2002; Papla et al. 2004). This condition is termed crystal-storing histiocytosis (CSH) and may also occur in other lymphomas, including those of the MALT type, and in transient polyclonal plasma cell hyperplasia following bone marrow transplantation. In CSH, large macrophages filled with oblong crystalline particles are found in ample quantities in several organs (mainly in the bone marrow), and the exact nature of the crystals may be unclear until immunohistochemical examinations are performed. Some of the macrophages resemble Gaucher cells or the pseudo-Gaucher cells seen in myelogenous leukemia, leading to the term "pseudo-pseudo-Gaucher cells" (Schaefer 1996). It has been suggested that Ig crystal accumulation in histiocytes/macrophages may be related to a possible pro-aggregation defect in Ig heavy chains (Papla et al. 2004). The liver may be involved by CSH developing in PCM, with accumulation of crystal-containing macrophages in the portal tracts and within liver lobules (Zioni et al. 2004; Papla et al. 2004). In one study, Ig heavy chain-derived crystals were not only identified in hepatic macrophages but, ultrastructurally, also within hepatocytes, the

crystals more frequently forming clusters in these parenchymal cells (Papla et al. 2004). The presence of Ig chain crystals in hepatocytes is most probably related to the expression of receptors for the Fc portion of Ig molecules on hepatocytes, also capable for binding immunoglobulin complexes or immunoglobulin aggregates, followed by endocytosis. Apart from crystalloid inclusions, immunoglobulin chains may, similar to normal plasma cells, accumulate in tumor cells in the form of numerous Russell bodies. Such lesions have been called Mott cell tumors (Brink et al. 1999; Fujiyoshi et al. 2001), in analogy to Mott cells that are plasma cells with abundant Russell bodies rendering the cell morula-like. We are not aware of such a lesion occurring in the liver.

Other Hepatic Manifestations of Plasmacytoma

Cholestasis

Cholestasis occurs in few patients that have extrahepatic large bile duct stenosis/obstruction due to plasmacytic tumor formation in perihilar lymph nodes, lymph nodes of the hepatoduodenal ligament, involvement of the bile ducts, or PCM manifestations in the pancreatic head area (Coban et al. 2004). However, few patients with extramedullary PCM develop jaundice in the absence of bile duct obstruction, in part associated with fever of unknown origin/FUO (Pastor et al. 1996; Vella et al. 2003; Mumoli et al. 2004). In part of the patients, this is related to the development of hepatic amyloidosis in plasmacytoma (Licht et al. 1999).

Hepatomegaly and Increased Hepatocyte Proliferation in POEMS Syndrome/Crow-Fukase Syndrome

POEMS is an acronym for polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes and denotes a distinct syndrome associated with neoplasms of the plasma cell lineage. Alternative terms to denote this syndrome are Crow-Fukase syndrome, Shimpo's syndrome, Takatsuki's syndrome, and PEP syndrome (Nakanishi et al. 1984; Rolon et al. 1989; Bisail et al. 1990; Soubrier et al. 1994; Koike and Sobue 2000; Takakura et al. 2003). The syndrome is sometimes associated with another group of lesions occurring in conjunction with plasmacytoma, namely, the AESOP (adenopathy and extensive skin patch overlying a plasmacytoma) syndrome (Lipsker et al. 2003). The minimal criteria to establish the diagnosis of POEMS syndrome are the presence of a demyelinating and axonal polyneuropathy associated with an IgA or IgG monoclonal gammopathy, the light chain being almost always lambda, and at least two of the following eight features: sclerosing plasmacytoma, endocrinopathy, skin changes, organomegaly, Castleman disease, anasarca, papillary edema, and thrombocytosis. Among these features, cutaneous glomeruloid angiomas are regarded as specific (Lagueny et al. 2004). Microvascular changes have also been described in the glomeruli of kidneys in patients with POEMS syndrome (Fukatsu et al. 1991). The cellular sources of M-proteins (i.e., lambda light chains and almost always alpha or gamma heavy chains) are typically osteosclerotic or, less frequently, mixed osteosclerotic and lytic myelomas or gammopathies of undetermined significance, while purely lytic multiple myeloma is rarely found (Nakasnishi et al. 1984; Soubrier et al. 1994). Crow-Fukase syndrome can develop with a long delay after plasmacytoma, in one case 18 years after the first manifestation of plasmacytoma (Sakemi and Okada 1992). The syndrome is, in addition to plasmacytoma, also associated with multicentric Castleman disease (Rolon et al. 1989). Pathogenetically, the syndrome is thought to be caused by increased levels of vascular endothelial growth factor (VEGF) produced by megakaryocytes and released from the increased thrombocytes, but independent of M-protein (Soubrier et al. 1997; Watanabe et al. 1998; Hashiguchi et al. 2000; Tokashiki et al. 2003; Lewerenz et al. 2003). However, several reports described a decrease of serum VEGF subsequent to the treatment of plasmacytoma

(Shinde et al. 2001; Yoritaka et al. 2004). Increased availability of VEGF may be related to the glomeruloid skin angiomas and other angiomatoid lesions occurring in POEMS syndrome, including arteriovenous fistulas and plexogenic pulmonary arteriopathy causing pulmonary arterial hypertension (Lewerenz et al. 2003). What are the pathogenic pathways causing hepatomegaly in POEMS syndrome? Liver biopsies suggest that hepatic enlargement is due to increased hepatocyte proliferation (Fushimi et al. 1995). Serum from patients with POEMS syndrome induced sustained proliferation of cultured murine hepatocyte by factors apparently different from hepatocyte growth factor (Fushimi et al. 1995, 1996). Increased serum levels of IL-6, a priming cytokine for hepatocyte proliferation, may play a role (Nakazawa et al. 1992; Hitoshi et al. 1992).

Liver Changes Related to PCM-Associated Hyperlipidemia

PCM and monoclonal gammopathies are sometimes associated with hyperlipidemia/type III hyperlipoproteinemia (Ansari 1992; Fukudome et al. 1996. The pathogenesis involves an autoimmune-like reaction mediated by inhibitory monoclonal immunoglobulin (frequently of the IgA class) directed against low-density lipoprotein binding to cellular receptors (Baudet et al. 1978; Cortese et al. 1982; Nozaki et al. 1997) or the formation of paraprotein-lipoprotein complexes (Taylor et al. 1978; Kilgore et al. 1985). The hyperlipidemia in plasmacytoma/myeloma is known to induce the development of xanthomatosis, with xanthomas consisting of lipid-laden, foamy macrophages (Moschella 1970; Marien and Smeenk 1975; Chelazzi and Uccella 1974; Roberts-Thomson et al. 1975; Wilson et al. 1975; Taylor et al. 1978). However, cutaneous xanthomas in association with paraproteinemia can also occur in the absence of hyperlipidemia (Feingold et al. 1989; Piccinno et al. 1990). In the liver, multiple xanthomatous collections of foamy macrophages as well as a sinusoidal accumulation of foam cells have been observed, resulting in xanthomas of the liver (Yim et al. 1995).

Vascular Complications in the Liver

Plasmacytoma can in rare instances involve small hepatic veins (Lazure et al. 2007). Rarely, PCM is associated with thrombotic venous complications in the liver, including Budd-Chiari syndrome (Tsuji et al. 1986, 1990).

Hepatic Tumors

An association of PCM with hepatocellular carcinoma (HCC) has rarely been reported (Inoue et al. 1986; Christou et al. 1998; Nakanishi et al. 2003). In a consecutive series of 317 patients with HCC, 32 (10.1 %) had 35 extrahepatic primary malignant neoplasms. Among these, ten were B-cell lymphoid neoplasms, these disorders therefore representing the most frequent associated malignancies (Di Stasi et al. 1994).

Differential Diagnosis

Several reactive disorders are associated with marked peripheral plasmacytosis, and some of them may lead to accumulation of increased numbers of plasma cells in organs and tissues, including the liver and the biliary tract. They include sickle cell anemia, certain infections (rubella, dengue, mononucleosis, parvovirus B19), serum sickness, drug therapy (e.g., sulfisoxazole or azathioprine), alcoholic liver disease, and hyperimmunization (review by Gawoski and Ooi 2003).

An unusual and etiologically unclarified plasma cell proliferative disorder of the upper aerodigestive tract has been reported, with plasma cell lesions typically producing a cobblestone or warty appearance of the upper aerodigestive tract mucosa including the larynx, pharynx, palate, lips, mouth, tongue, and trachea. Histologically,

all lesions were characterized by psoriasiform epithelial hyperplasia with dyskeratosis and dense subepithelial plasmacytosis (Ferreiro et al. 1994; Imbing et al. 1996; Khan et al. 1997; review by Bharti and Smith 2003).

Cytogenetic and Molecular Features

Cytogenetically, many cases of PCM and monoclonal gammopathy of undetermined significance (MGUS) are normal, but several chromosomal anomalies have been described for part of the lesions. A high frequency of chromosomal aberrations has in particular been detected by the use of direct chromosome preparations and with FISH (Nilsson et al. 2004). A subset of PCM exhibits a recurrent translocation t(14;20)(q32; q12) resulting in the aberrant expression of the transcription factor, MAFB, and there is evidence that this translocation has an adverse biologic effect (Boersma-Vreugdenhil et al. 2004). In the molecular level, primary chromosomal lesions cooperate with secondary genetic events, including gene mutations and epigenetic mechanisms (review by Boyd et al. 2012).

Plasma Cell Leukemia

Introduction

Plasma cell leukemia (PCL) is defined as a variant of plasma cell neoplasms with increased numbers of neoplastic plasma cells circulating in peripheral blood (synonyms, leukemic myelomatosis and myeloma cell leukemia). In case PCL is present at the time point of diagnosis of plasmacytic neoplasm, the diagnosis is that of primary PCL. Secondary PCL is the form that evolves as a late feature of plasma cell myeloma. Primary PCL is a rare disorder, accounting for only 2–5 % of cases of plasma cell neoplasms. It presents about one decade earlier than secondary PCL (Tiedemann et al. 2008). In PCL, the number of clonal plasma cells in peripheral blood exceeds $2 \times 10(9)/L$ or represents 20 % of the leukocyte differential count. Plasma cells infiltrate the bone marrow and are often also present in extramedullary tissues, including the spleen and liver. In contrast to plasma cell myeloma of IgD or IgA types, those with IgD, IgE, or light chains only are more often complicated by PCL.

Clinical Features

The clinical features are dominated by the sequelae of extensive bone marrow infiltration (bone marrow failure, anemia, thrombocytopenia), signs of osteolysis, and deep organ infiltration, sometimes with impaired renal function. Patients often show significant hepatosplenomegaly. Hyperviscosity syndrome has been observed. Patients with primary PCL show an aggressive course, with often abrupt onset of disease, with poor response to therapy, and with shorter median overall survival, progression-free survival, and complete response duration.

Liver Involvement

As both primary and secondary PCL tend to show extramedullary organ and tissue infiltration, the liver is expected to be involved, but hepatic infiltration is more frequent in primary PCL than in its secondary counterpart (Badhe et al. 2003; Majumdar et al. 2009; Islam and Anoop 2011). In a study of 64 patients with primary PCL, hepatomegaly was detected in 23 % of patients (Pagano et al. 2011). Atypical plasma cells mainly infiltrate the liver sinusoids (Sandri et al. 1976; Noguchi et al. 1985; Kawano et al. 1991), but portal tract infiltrates are seen in massive hepatic infiltrations, and part of patients develop tumorous plasmacellular masses in the liver substance in late phases of disease. Liver insufficiency is a rare complication (Lopez Guillermo et al. 1989).

Differential Diagnosis

The main differential diagnosis is infiltration of the liver in the setting of plasma cell myeloma.

Cytogenetic and Molecular Features

In primary PCL, IGH translocations were identified in 87 % of cases, with prevalence of t(11;14) (40 %) and t(14;16) (30.5 %), the translocations being more frequent than in plasma cell myeloma (Cho et al. 2011). The most frequent numerical alterations involved chromosomes 14q, 16q, 1p, 1q, 8p, 13q, and 17p (Chang et al. 2009, 2010; Peijing et al. 2009; Mosca et al. 2013). Among the genes activated and overexpressed in primary PCL are genes involved in hepatic stellate cell activation and hepatic fibrosis (Usmanl et al. 2012).

Immunoproliferative Small Intestinal Disease (IPSID)

Introduction

Immunoproliferative small intestinal disease (IPSID) is a variant of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), in which alpha immunoglobulin heavy chains are secreted. Owing to the latter phenomenon, the disorder is and was often called alpha heavy chain disease, but the 2008 WHO classification proposes the use of the term IPSID (reviews by Rappaport (1976), Nassar et al. (1978), Haghighi and Wolf (1986), Al-Saleem and Al-Mondhiry (2005), Salem and Estephan (2005).

The recognition of IPSID as an entity goes back to observations in the early to mid-1960s, when several reports appeared from Israel specifying a distinct primary small intestinal lymphoma associated with malabsorption in young adults (Frand and Ramot 1963; Ramot et al. 1965; Eidelman et al. 1966). This lesion is the previous so-called Mediterranean lymphoma that has now been recommended by the WHO to be termed IPSID. It is a variant of the B-cell lymphoma of MALT and a further member of infection-associated lymphoproliferative disorders. IPSID demonstrates an association with *Campylobacter jejuni*, is prevalent in the Middle and Far East and in Africa (and in immigrants thereof), and involves mainly the proximal small intestine resulting in malabsorption, diarrhea, and abdominal pain, with a remarkably uniform clinical presentation. In advanced disease, intestinal obstruction, abdominal masses, and ascites may be common (Doe 1975; WHO Report 1976; Kharazmi et al. 1976; Lewin et al. 1976; Tabbane et al. 1976; Seligman 1979; Kojasteh et al. 1983; Isaacson 1985; Salem et al. 1987; Takahashi et al. 1988; Kojasteh and Haghighi 1990; Price 1990; Martin and Aldoori 1994; Fine and Stone 1999; Swaroop 2000; Lecuit et al. 2004; Peek 2004; Peterson 2004; Economidou et al. 2006; Mrabti et al. 2011; Pervez et al. 2011; Huang and Sheu 2012; Mesnard et al. 2012). IPSID affects mainly older children and young adults, of low socioeconomic status in developing countries.

Many patients with IPSID were found to exhibit variable levels of abnormal immunoglobulin in serum or other body fluids, later identified to be truncated alpha heavy chains. Historically, a partial immunoglobulin heavy chain of the IgA class devoid of light chains in serum and other body fluids of some patients was reported in the late 1960s already (Seligmann et al. 1968, 1969; Rambaud et al. 1968). IPSID may, therefore, be regarded as an enteric form of alpha heavy chain disease (alpha HCD; WHO Report 1976; Seligmann 1979; Altuntas and Ensari 2000). Secretory forms (secreting IPSID/secretory alpha chain disease) and nonsecretory forms (nonsecreting IPSID/NS-IPSID/extensive small intestinal lymphomas without gammopathy) are recognized (Matuchansyk et al. 1989; Pai et al. 2005). There are also cases of IPSID that are alpha chain negative (Gilinsky et al. 1983; Cammoun et al. 1989).

Clinical Features

The natural history of the disease appears to be one of evolution from extensive lymphoid cell and plasma cell infiltration to overt malignant lymphoma. In stage A disease, the intestinal mucosa is diffusely and densely infiltrated by normal-looking lymphocytes and plasma cells, with

similar involvement of locoregional lymph nodes. Stage B is characterized by the emergence of atypical plasma cells and immunoblasts, and the infiltrate extends into the submucosa and the muscle layer. In stage C, an overt NHL involves the small intestine and locoregional lymph nodes (Galian et al. 1977). Apart from the Galian et al. staging system (1977), other staging systems are employed, including the WHO scheme (WHO Report 1976) and the Salem scheme (Salem et al. 1977). This evolution, which may take many years, apparently reflects a progression from the so-called "low-grade" IPSID to "high-grade" IPSID (Galian et al. 1977; Seligman and Rambaud 1983; Rogers et al. 1988; Kojasteh and Haghighi 1990; Androulaki et al. 2003). In Western patients with IPSID, the gross and histologic presentation may deviate from the pattern typically seen in Eastern patients, e.g., with the development of polypoid gastrointestinal lymphoma (Cohen et al. 1978).

Histopathology

In fully established IPSID, the intestinal mucosa is densely and diffusely infiltrated by lymphoid cells with a centrocyte-like morphology, by lymphoplasmacytoid cells, and by plasma cells, the entire mixed cell population forming a band-like and compact infiltrate in the mucosa, causing a grossly visible diffuse or sometimes nodular thickening of mucosal folds. Usually, long segments of the proximal small intestine are preferentially involved (Rappaport 1976; Galian et al. 1977; Haghighi et al. 1978; Nassar et al. 1978; Rambaud et al. 1990). This is the so-called "low-grade" IPSID. The dense infiltration leads to separation, infiltration, and partial or complete destruction of the crypts that look then sparse and splayed, whereas the surface enterocyte lining is mostly intact or only minimally altered, with intraepithelial lymphoid infiltration. Similar to MALT lymphomas, lymphoepithelial lesions are a typical morphologic feature of IPSID (Price 1990). In situations of heavy infiltration, the intestinal villi are shortened or even completely flattened. In some patients, micronodular aggregates are formed deep in the mucosa (so-called lympho-histiocytoid nodules; Nassar et al. 1978). In case of progression to lymphoplasmacytic and immunoblastic lymphoma of higher grade (Rogers et al. 1988; the so-called "high-grade" IPSID), lymphoid and plasmacytoid cells with increased atypia and pleomorphism emerge, and these cells may then leave the mucosal compartment to invade the submucosa and the muscularis propria.

Immunohistochemically, the centrocyte-like neoplastic cells forming the lymphoepithelial lesions show alpha 1 heavy chain, but no light chain, in the perinuclear space and cytoplasm. The plasma cells are reactive for alpha heavy chain and the J chain, but no light chains (Isaacson 1979; Isaacson et al. 1989). There is also a form of IPSID rich in reactive T cells (T-cell-rich alpha chain disease), mimicking T-cell lymphoma (Lavergne et al. 1997).

Liver Involvement in IPSID

Apart from the intestinal wall, locoregional lymph nodes and, rarely, other abdominal organs are involved (Galian et al. 1977; Nassar et al. 1978; Tabbane et al. 1988). Generalized lymphadenopathy and slight splenomegaly caused by lymphomatous infiltration have been reported (Takahashi et al. 1988). An involvement of the liver in IPSID occurs, but its prevalence is difficult to judge (Doe 1975; Plesnicar et al. 1975; Galian et al. 1977; Kahn and Novis 1977; Haghighi et al. 1978; Nassar et al. 1978; Asselah et al. 1983). Sparse informations on gross pathology of the liver are available. Among seven patients with either laparoscopy or necropsy findings, one patient showed miliary lesions throughout the liver, histologically corresponding to hepatic portal tract spaces uniformly expanded by a cell infiltrate identical to that noted in the involved small intestine and in locoregional lymph nodes, although a variable admixture with small lymphocytes was found. In addition, some of the plasmacytoid cells were seen in the sinusoids adjacent to the infiltrated portal tracts, i.e., within zone 1 (Haghighi et al. 1978). Among 16 patients having a liver

biopsy, none of the biopsies revealed malignant changes, but focal lymphocytic infiltrations were frequently observed in the portal tracts, and non-caseating granulomas were detected in two patients (Salem et al. 1977; Nassar et al. 1978). In contrast, liver localization of the lymphomatous infiltration was observed in other investigations. Liver infiltration was observed in four of six patients studied (Galian et al. 1977). In one patient having stage A intestinal and mesenteric lymph node disease, portal tract spaces were densely infiltrated by mature or sometimes atypical plasma cells and by some lymphocytes, and small foci of plasma cells were also scattered within the liver lobules. In another patient with intestinal and mesenteric lymph node stage B, surgical liver biopsies showed a portal space infiltrate made of lymphocytes, mature plasma cells, and regular immunoblast-like cells, and in a third patient, the infiltrate was seen to produce portal tract nodules formed by immunoblast-like cells and very rare mature plasma cells. A postmortem examination of a further patient revealed that portal tracts and the periportal tissue were occupied by a massive infiltration of large neoplastic cells identical to those found in the small intestine and mesenteric lymph nodes (Galian et al. 1977). In a large analysis of 22 patients, the liver histology was usually normal, but a slight or moderate lymphoplasmacytic infiltrate without evidence of atypia was found occasionally in the portal tracts. Portal and intralobular accumulations of atypical mononuclear cells were detected in three patients, while cells accumulating in the hepatic sinusoids were not found (Asselah et al. 1983). Among 17 patients with IPSID of the alpha chain disease type that had macroscopic and/or microscopic data, five showed neoplastic liver involvement, all with stage C disease according to Galian et al. (1977). Among 21 patients with nonsecreting IPSID, neoplastic liver involvement was identified in four patients, and four more patients had nonspecific portal tract infiltration (Tabbane et al. 1988).

Hepatic infiltration in progressive/advanced stage IPSID starts in the form of a sparse and mixed portal tract infiltration containing various numbers of plasma cells, requiring immunophenotyping for correct diagnosis, to then progress to dense infiltrates occupying the entire portal tract spaces, to nodular lesions, and finally to parenchymal involvement, mainly of periportal zone 1. A sparse lymphoid cell infiltrate may involve intrahepatic bile ducts (minimal biliary mucosal infiltration, MBMI).

Etiological and Pathogenetic Factors

The prevalence in certain geographic areas led to the supposition that an environmental infectious factor is responsible for initiating disease onset, previously supported by the observation that IPSID can occasionally respond to antimicrobial agents. Based on this phenomenon, a molecular strategy employing universal bacterial PCR primers in affected tissues resulted in the identification of *Campylobacter jejuni* as the likely factor (Lecuit et al. 2004). FISH signals for *C. jejuni* were most prominent within the mucosal lamina propria, in close apposition to capillaries. These observations supported the contention that *C. jejuni* may represent a hitherto undefined causative agent for IPSID (Puri et al. 1992; Lecuit et al. 2004; Peek 2004; Peterson 2004; Sellin 2004; Lecuit and Lortholary 2005). In addition, infection with *Helicobacter pylori* has been considered an etiological factor, as IPSID regressed in one patient upon *Helicobacter* eradication (Dutta et al. 2010).

References

Abe T, Dohy H, Takata N, Fujimura K, Okada K, Kuramoto A, Enzan H (1980) A case of solitary extramedullary plasmacytoma of the liver. Successful hepatectomy for gigantic tumor excreting massive Bence Jones protein in urine (in Japanese). Rinsho Ketsueki 21:1047–1053

Al-Saleem T, Al-Mondhiry H (2005) Immunoproliferative small intestinal disease (IPSID); a model for mature B-cell neoplasms. Blood 105:2274–2280

Altuntas B, Ensari A (2000) Alpha heavy chain disease in a child. Pediatr Int 42:306–309

Androulaki A, Lazaris AC, Papadimitriou K (2003) Lymphomatous category of immunoproliferative small intestinal disease. Br J Haematol 123:567

Ansari Z (1992) Hyperlipidemia in monoclonal gammopathy. N Y State J Med 92:496–497

Askari AD, Lagui CC, Rassiga AL, Hogrefe WR, Laipply TC (1985) Small-cell lymphoma and Sjögren's syndrome. Lymphoplasmacytic subvariant of small-cell lymphoma with IgA/kappa immunoglobulin surface markers. Arch Intern Med 145:935–937

Asselah F, Slavin G, Sowter G, Asselah H (1983) Immunoproliferative small intestinal disease in Algerians. I. Light microscopic and immunochemical studies. Cancer 52:227–237

Badhe et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/15025318

Bangerter M, Hidebrand A, Waidmann O, Griesshammer M (2000) Fine needle aspiration cytology in extramedullary plasmacytoma. Acta Cytol 44:287–291

Barth C, Bosse A, Andus T (2005) Severe acute cholestatic hepatitis by infiltration of monoclonal plasma cells in multiple myeloma. Z Gastroenterol 43:1129–1132

Basu D, Pathak D, Shyambabu C, Koner BC, Swaminathan RP (2004) Lymphoplasmacytic lymphoma with IgA paraproteinemia mimicking Waldenström's macroglobulinemia. Indian J Pathol Microbiol 47:515–517

Baudet et al. 1978. http://www.ncbi.nlm.nih.gov/pubmed/216434

Bavle RM (2013) Bizzare plasma cell – Mott cell. J Oral Maxillofac Pathol 17:2–3

Beau P, Touchard G, Lessard M, Moreau C, Druart F, Moricheau-Beauchant M, Tanzer J (1984) Massive sarcomatous infiltration of the liver disclosed by jaundice and hepatocellular failure in Waldenstrom's disease (in French). Gastroenterol Clin Biol 8:57–61

Bedossa P, Fabre M, Paraf F, Martin E, Lemaigre G (1988) Light chain deposition disease with liver dysfunction. Hum Pathol 19:1008–1014

Bhandari MS, Mazumder A, Vesole DH (2007) Liver involvement in multiple myeloma. Clin Lymphoma Myeloma 7:538–540

Bharti R, Smith DR (2003) Mucous membrane plasmacytosis: a case report and review of the literature. Dermatol Online J 9:15

Bisail et al. 1990. http://www.ncbi.nlm.nih.gov/pubmed/2276681

Blatrix C, Fine JM, Yeme D, Lambin P (1973) Tumoral forms of Waldenstrom's macroglobulinemia. Apropos of a case involving 2 localizations, orbital and hepatic (in French). Sem Hop 49:2847–2851

Boersma-Vreugdenhil et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15257707

Borgonovo G, d'Oiron R, Amato A, Leger-Ravet MB, Iseni MC, Smadja C, Lemaigre G et al (1995) Primary lymphoplasmacytic lymphoma of the liver associated with a serum monoclonal peak of IgG kappa. Am J Gastroenterol 90:137–140

Boyd JF (1980) Immunohistochemical staining of the Dutcher-Fahey intranuclear inclusion body in a case of Waldenström's macroglobulinaemia. J Pathol 132:81–91

Boyd KD, Pawlyn C, Morgan GJ, Davies FE (2012) Understanding the molecular biology of myeloma and its therapeutic implications. Expert Rev Hematol 5:603–617

Brink T, Wagner B, Gebbers JO (1999) Monoclonal plasma and Mott cells in a rectal adenoma. Histopathology 34:80–82

Brooks AP (1976) Portal hypertension in Waldenström's macroglobulinemia. Br Med J 1:689–690

Caminal L, Castellanos E, Mateos V, Astudillo A, Moreno C, Dieguez MA (1993) Hyperammonaemic encephalopathy as the presenting feature of IgD multiple myeloma. J Intern Med 233:277–279

Cammoun M, Jaafoura H, Tabbane F, Halphen M (1989) Immunoproliferative small intestinal disease without alpha-chain disease: a pathological study. Gastroenterology 96:750–763

Carneros JA, Piqueras B, Tomas E, Garcia-Duran F, Ciriza C, Bermejo F, Sanchez-Prudencio S et al (2009) Acute pancreatitis and space-occupying hepatic lesions in a patient with bone marrow transplant due to multiple myeloma (in Spanish) Gastroenterol Hepatol 32:410–414

Caturelli E, Squillante MM, Castelvetere M, Falcone A, Musto P (1993) Myelomatous nodular lesions of the liver: diagnosis by ultrasound-guided fine-needle biopsy. J Clin Ultrasound 21:133–137

Chang H, Qi X, Yeung J, Reece D, Xu W, Patterson B (2009) Genetic aberrations including chromosome 1 abnormalities and clinical features of plasma cell leukemia. Leuk Res 33:259–262

Chang H, Qi X, Jiang A, Xu W, Young T, Reece D (2010) 1p21 deletions are strongly associated with 1q21 gains and are an independent adverse prognostic factor for the outcome of high-dose chemotherapy in patients with multiple myeloma. Bone Marrow Transplant 45:117–121

Chelazzi G, Uccella R (1974) Hyperlipidemia and xanthomatosis in the course of multiple myeloma. Review of the literature and presentation of a case (in Spanish). Sangre (Barc) 19:295–300

Chemlal K, Couvelard A, Grange MJ, Marmuse JP, Charneau C, Launay O, Carbon C, Yeni P (1999) Nodular lesions of the liver revealing multiple myeloma. Leuk Lymphoma 33:389–392

Cho SY, Lim G, Oh SH, Lee HJ, Suh JT, Lee J, Lee WI, Lee HG, Yoon HJ, Park TS (2011) Primary plasma cell leukemia associated with t(6;14)(p21;q32) and IHG rearrangement: a case study and review of the literature. Ann Clin Lab Sci 41:277–281

Christou et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9700587

Coban S, Koklu S, Ertugrul I, Kuzu I, Bahar K (2004) Obstructive jaundice in a patient with multiple myeloma. J Gastroenterol Hepatol 19:837–838

Coffey D, Fain B, Thompson C, Chan ED, Nawaz S (2012) Liver failure as the only clinical manifestation of multiple myeloma. Ann Hematol 91:625–627

Cohen HJ, Gonzalvo A, Krook J, Thrompson TT, Kremer WB (1978) New presentation of alpha heavy chain disease: North American polypoid gastrointestinal lymphoma. Clinical and cellular studies. Cancer 41:1161–1169

Corpa MV, Bacchi MM, Bacchi CE, Coelho KI (2004) Peliosis hepatis associated with lymphoplasmacytic lymphoma: an autopsy case report. Arch Pathol Lab Med 128:1283–1285

Cortese C, Lweis B, Miller NE, Peyman MA, Rao SN, Slavin B, Sule U, Turner PR, Utermann G et al (1982) Myelomatosis with type III hyperlipoproteinemia: clinical and metabolic studies. N Engl J Med 307:79–83

Curtis JM, Pellegrini V, Tappin JA (1995) Case report: multiple myeloma – a rare presentation. Clin Radiol 50:63–64

De Vos M, Druez P, Nicaise M, Ngendahayo P, Sinapi I, Mineur P (2012) Multiple myeloma presenting as hepatic nodular lesion. Acta Clin Belg 67:378–380

Demirhan B, Sokmensuer C, Karakayali H, Gungen Y, Dogan A, Haberal M (1997) Primary extramedullary plasmacytoma of the liver. J Clin Pathol 50:74–76

Di Stasi et al. 1994. http://www.ncbi.nlm.nih.gov/pubmed/8052489

Doe WF (1975) Alpha chain disease: clinicopathological features and relationship to so-called Mediterranean lymphoma. Br J Cancer 31(Suppl 2):350–355

Dohy H, Abe T, Takata N, Fujimura K, Taketomi Y, Kuramoto A, Harada T, Hattori T et al (1979) Successful hepatectomy for solitary plasmacytoma. N Engl J Med 200:1218–1219

Dutta U, Udawat H, Noor MT, Sidhu GS, Kochar R, Vaiphei K, Singh K (2010) Regression of immunoproliferative small intestinal disease after eradication of Helicobacter pylori. J Gastrointest Cancer 41:212–215

Economidou I, Manousos ON, Triantafillidis JK, Vaslamatzis MM, Zafiropoulou R et al (2006) Immunoproliferative small intestinal disease in Greece: presentation of 13 cases including two from Albania. Eur J Gastroenterol Hepatol 18:1029–1038

Eidelman S, Parkins RA, Rubin CE (1966) Abdominal lymphoma presenting as malabsorption. A clinicopathologic study of nine cases in Israel and a review of the literature. Medicine 45:111–137

El Maaroufi H, Doghmi K, Rharrassi I, Mikdame M (2012) Extramedullary plasmacytoma of the liver. Hematol Oncol Stem Cell Ther 5:172–173

Fautrel et al. 1993. http://www.ncbi.nlm.nih.gov/pubmed/8332447

Feingold KR, Castro GR, Ishikawa Y, Fielding PE, Fielding CJ (1989) Cutaneous xanthoma in association with paraproteinemia in the absence of hyperlipidemia. J Clin Invest 83:796–802

Fernandez-Flores A, Fortes J, Smucler A, Orduna M, Pol A (2003) Involvement of the liver by multiple myeloma as nodular lesions: a case diagnosed by fine-needle aspiration and immunocytochemistry. Diagn Cytopathol 29:280–282

Ferreiro JA, Egorshin EV, Olsen KD, Banks PM, Weiland LH (1994) Mucous membrane plasmacytosis of the upper aerodigestive tract. A clinicopathologic study. Am J Surg Pathol 18:1048–1053

Fine KD, Stone MJ (1999) Alpha-heavy chain disease, mediterranean lymphoma, and immunoproliferative small intestinal disease: a review of clinicopathological features, pathogenesis, and differential diagnosis. Am J Gastroenterol 94:1139–1152

Frand VI, Ramot B (1963) Malignant lymphoma. An epidemiological study. Harefueh 65:23–28

Fujii S, Fukuda S, Sezaki T, Murakami M (1998) Clinicopathological study of multiple myeloma associated with hyperammonemia (in Japanese). Rinsho Ketsueki 39:27–33

Fujiyoshi Y, Inagaki H, Tateyama H, Murase T, Eimoto T (2001) Mott cell tumor of the stomach with helicobacter pylori infection. Pathol Int 51:43–46

Fukatsu A, Tamai H, Nishikawa K, Matsukawa W, Yoshida F, Matsuo S, Takeda A, Kodera K, Morozumi K, Ito Y (1991) The kidney disease of crow-Fukase (POEMS) syndrome: a clinicopathological study of four cases. Clin Nephrol 36:76–82

Fukudome K, Kato J, Ohashi T, Yamamoto Y, Eto T (1996) Hyperlipidemia associated with multiple myeloma. Intern Med 35:337–340

Fushimi T, Inoue A, Yahikozawa H, Koh CS, Yanagisawa N (1995) The detection of factors that may promote the hepatocyte proliferation in the serum of a patient with Crow-Fukase syndrome (in Japanese). Arerugi 44:1311–1316

Fushimi T, Inoue A, Koh CS, Yahikozawa H, Yanagisawa N (1996) A study on the pathogenesis of hepatomegaly in patients with Crow-Fukase syndrome (in Japanese). Rinsho Shinkeigaku 36:534–539

Galani Z, Vinou N, Kyrtsonis MC, Sachanas S, Antoniou T, Dimopoulou MN, Vassilakopoulos TP et al (2007) Hepatic and renal plasma cell lesions in a patient with multiple myeloma in hematological remission. Anticancer Res 27:571–574

Galian A, Lecestre MJ, Scotto J, Bognel C, Matuchansky C, Rambaud JC (1977) Pathological study of alpha-chain disease, with special emphasis on evolution. Cancer 39:2081–2101

Ganjoo RK, Malpas JS, Plowman PN (1993) Solitary plasmacytoma of bone: a rare disorder with an unusual evolution. Postgrad Med J 69:153–154

Garfinkel et al. 1985. http://www.ncbi.nlm.nih.gov/pubmed/4075676

Gawoski and Ooi 2003. http://www.ncbi.nlm.nih.gov/pubmed/12873179

Gertz MA, Kyle RA (1988) Hepatic amyloidosis (primary [AL], immunoglobulin light chain): the natural history in 80 patients. Am J Med 85:73–80

Gertz MA, Kyle RA, Noel P (1993) Primary systemic amyloidosis: a rare complication of immunoglobulin M monoclonal gammopathies and Waldenstrom's macroglobulinemia. J Clin Oncol 11:914–920

Gertz MA, Merlini G, Treon SP (2004) Amyloidosis and Waldenström's macroglobulinemia. Hematol Am Soc Hematol Educ Program 2004:257–282

Gilinsky NH, Novis BH, Mee AS, Wright JP, Price S, Marks IN (1983) Immunoproliferative small-intestinal disease: follow-up of an alpha-chain negative, lymphoma-free group. J Clin Gastroenterol 5:421–428

Ginestal-Cruz A, Correira JP, Batista A, Cardoso A, Monteiro E (1979) Recurrent upper gastro-intestinal bleeding, duodenal and gastric ulcer and peliosis hepatis in a patient with Waldenstrom's macroglobulinemia. Acta Med Port 1:721–727

Gonzalez GR, Navarro AM, Zambrano AR, Arrunatequi AM (2010) Nodular hepatic lesions secondary to myeloma IgA presenting as fever of unknown origin (in Spanish). Biomedica 30:478–481

Haghighi P, Wolf PL (1986) Alpha-heavy chain disease. Clin Lab Med 6:477–489

Haghighi P, Kharazmi A, Gerami C, Haghshenass M, Abadi P, Omidi H, Mostafavi N (1978) Primary upper small-intestinal lymphoma and alpha-chain disease. Report of 10 cases emphasizing pathological aspects. Am J Surg Pathol 2:147–157

Haidar et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12656751

Hasegawa K, Kubota K, Hirai H, Imai Y, Midorikawa Y, Makuuchi M (2000) Hepatocellular carcinoma followed by Waldenstrom's macroglobulinemia: a case report. Hepatogastroenterology 47:842–845

Hashiguchi et al. 2000. http://www.ncbi.nlm.nih.gov/pubmed/11212815

Hijmans W (1975) Waldenström's disease with an IgA paraprotein. Acta Med Scand 198:519–523

Hishitani Y, Yamamoto R, Nakamura Y, Mozai T, Kanoh T, Yashuda N (1982) A case of walder ström-like B cell neoplasm with monoclonal IgA secretion (in Japanese). Nippon Naika Gakkai Zasshi 71:830–836

Hitoshi S, Sato K, Suzuki K, Sato K, Sakuta M (1992) The role of interleukin-6 in Crow-Fukase syndrome (in Japanese). Rinsho Shinkeigaku 32:577–582

Holland J, Trenker DA, Wasserman TH, Fineberg B (1992) Plasmacytoma. Treatment results and conversion to myeloma. Cancer 69:1513–1517

Huang CG, Sheu CY (2012) A rare cause of lymphadenopathy near the terminal ileum: immunoproliferative small intestinal disease. Turk J Gastroenterol 23:91–93

Husaric S, Pasic J, Alic E, Kuljanin M (2013) Solitary extramedullary plasmocytoma of the liver. Acta Med Acad 42:85–86

Hyun DW, Park SW, Baik JH, Kim DH, Jung JT, Shin DG, Sohn SK, Lee KB (1999) A case of multiple myeloma with multiple intrahepatic extramedullary plasmacytomas. Korean J Hematol 34:143–147

Inoue et al. 1986. http://www.ncbi.nlm.nih.gov/pubmed/3031187

Imbing et al. 1996. http://www.ncbi.nlm.nih.gov/pubmed/8956764

Invernizzi R, Maffe GC, Travagkino E, Pagani E, Pieresca C (2007) Nodular lesions of the liver in multiple myeloma. Haematologica 92:e81

Isaacson P (1979) Middle East lymphoma and alpha-chain disease. An immunohistochemical study. Am J Surg Pathol 3:431–441

Isaacson PG (1985) Middle Eastern intestinal lymphoma. Semin Diagn Pathol 2:210–223

Isaacson PG, Dogan A, Price SK, Spencer J (1989) Immunoproliferative small-intestinal disease. An immunohistochemical study. Am J Surg Pathol 13:1023–1033

Islam MS, Anoop P (2011) Images in hematology. Transient erythrocyte changes caused by infiltration of liver by plasma cell leukemia. Am J Hematol 86:67–68

Izumi T, Sasaki R, Tsunoda S, Hatakeyama M, Koyama H, Shinohara N, Miura Y (1996) Sequential occurrence of hepatocellular carcinoma following Waldenstrom's macroglobulinemia: the pathogenetic role of chronic liver disease. Intern Med 35:416–418

Jain et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12696828

Jimenez C, Sebastian E, Chillon MC, Giraldo P, Hernandez Mariano J, Escalante F, Gonzalez-Lopez TJ et al (2013) MYD88 L265P is a marker highly characteristic of, but not restricted to, Waldenström's macroglobulinemia. Leukemia 27:1722–1728

Jones D, Bhatia VK, Krausz T, Pinkus GS (1999) Crystal-storing histiocytosis: a disorder occurring in plasmacytic tumors expressing immunoglobulin kappa light chain. Hum Pathol 30:1441–1448

Kahn LB, Novis BH (1977) Alpha-chain disease. A case report with autopsy findings. S Afr Med J 51:984–989

Kaise S, Nishimaki T, Morito T, Yoshida H, Kasukawa R, Asano S, Wakasa H (1982) An autopsy case of peliosis hepatis complicated by Bence-Jones lambda type multiple myeloma (in Japanese). Nippon Shokakibyo Gakkai Zasshi 79:1173–1177

Kapadia SB (1980) Multiple myeloma: a clinicopathologic study of 62 consecutively autopsied cases. Medicine 59:380–392

Kastritis E, Katoulis A, Terpos E, Pabayiotides I, Gavriotopoulopu M, Dimopopoulos MA (2008) Schnitzler's syndrome: increased levels of bone formation and angiogenesis factors are reduced after successful pefloxacin treatment. Clin Lymphoma Myeloma 8:359–362

Kaur J, Turner JR, Singh P, Al-Katib A (2000) Multiple myeloma in the liver. Am J Hematol 65:290

Kawano F, Tsukamoto A, Satoh M, Sanada I, Shido T, Miura K, Murakami T, Kaneko H et al (1991) Non-secretory primary plasma cell leukemia with hyperammonemia (in Japanese). Rinsho Ketsueki 32:399–403

Kelekis NL, Semelka RC, Warshauer DM, Sallah S (1997) Nodular liver involvement in light chain multiple myeloma: appearance on US and MRI. Clin Imaging 21:207–209

Khan NA, McKerrow WS, Palmer TJ (1997) Mucous membrane plasmacytosis of the upper aerodigestive tract. A case report with effective treatment. J Laryngol Otol 111:293–295

Kharazmi A, Haghighi P, Haghshenas M, Nasr K, Abadi P, Rezai HR (1976) Alpha-chain disease and its association with intestinal lymphoma. Clin Exp Immunol 26:124–128

Kilgore LL, Patterson BW, Parenti DM, Fisher WR (1985) Immune complex hyperlipidemia induced by an apolipoprotein-reactive immunoglobulin A paraprotein from a patient with multiple myeloma. Characterization of this immunoglobulin. J Clin Invest 76:225–232

Knowling M, Harwood A, Bergsagel D (1983) Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of the bone. J Clin Oncol 1:255–262

Koike and Sobue 2000. http://www.ncbi.nlm.nih.gov/pubmed/11037192

Kojasteh A, Haghighi P (1990) Immunoproliferative small intestinal disease: portrait of a potentially preventable cancer from the Third World. Am J Med 89:483–485

Kojasteh A, Haghshenass M, Haghighi P (1983) Current concepts: immunoproliferative small intestinal disease. A 'Third World' lesion. N Engl J Med 308:1401–1405

Kosek JC, Smith DL (1980) Cytotoxicity of oxymetholone to endothelial cells in vitro. Arch Pathol Lab Med 104:405–408

Krajny M, Pruzanski W (1976) Waldenström's macroglobulinemia: review of 45 cases. Can Med Assoc 114:899–900

Kremer M, Ott G, Nathrath M, Specht K, Stecker K, Alexiou C, Quintanilla-Martinez L, Fend F (2005) Primary extramedullary plasmacytoma and multiple myeloma: phenotypic differences revealed by immunohistochemical analysis. J Pathol 205:92–101

Kyle RA (1975) Multiple myeloma: review of 869 cases. Mayo Clin Proc 50:29–40

Lagueny et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15037841

Lauwers A, Chouvy V, Mosnier JF, Misery L, Alexandre C (1999) A case of Schnitzler's syndrome with nodular regenerative hyperplasia of the liver. Rev Rhum Engl Ed 66:281–283

Lavergne et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9147095

Lazure T, Miceli-Richard C, Sellam J, Fabre M, Mariette X, Guettier C (2007) Small hepatic vein involvement in IgG multiple myeloma: a very unusual of liver infiltration. Virchows Arch 450:127–129

Lebeau et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12176905

Lecuit M, Lortholary O (2005) Immunoproliferative small intestinal disease associated with Campylobacter jejuni (in French). Med Mal Infect 35(Suppl 2):S56–S58

Lecuit M, Suarez F, Lortholary O (2004) Immunoproliferative small intestinal disease associated with Campylobacter jejuni. N Engl J Med 350:1685–1686

Lee M, Sakai K, Kinoshita H, Hirohashi K, Tsuji Y, Suzuki N, Kobayashi Y (1986) Resected hepatocellular carcinoma with macroglobulinemia – a case report (in Japanese). Gan No Rinsho 32:401–406

Lee JY, Won JH, Kim HJ, Bae SB, Kim CK, Kim JH, Lee NS, Lee KT, Park SK et al (2007) Solitary extramedullary plasmacytoma of the liver without systemic monoclonal gammopathy. J Korean Med Sci 22:754–757

Lewerenz et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/14673584

Lewin KJ, Kahn LB, Novis BH (1976) Primary intestinal lymphoma of "Western" and "Mediterranean" type, alpha chain disease and massive plasma cell infiltration: a comparative study of 37 cases. Cancer 38:2511–2528

Licht et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10486860

Lin P, Medeiros LJ (2005) Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia: an evolving concept. Adv Anat Pathol 12:246–255

Lin P, Bueso-Ramos C, Wilson CS, Mansoor A, Medeiros LJ (2003a) Waldenstrom macroglobulinemia involving extramedullary sites: morphologic and immunophenotypic findings in 44 patients. Am J Surg Pathol 27:1104–1113

Lin P, Mansoor A, Bueso-Ramos C, Hao S, Lai R, Medeiros LJ (2003b) Diffuse large B-cell lymphoma occurring in patients with lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia. Clinicopathologic features of 12 cases. Am J Clin Pathol 120:246–253

Lipsker D, Veran Y, Grunenberger F, Cribier B, Heid E, Grosshans E (2001) The Schnitzler syndrome. Four new cases and review of the literature. Medicine (Baltimore) 80:37–44

Lipsker et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12544710

Lopes da Silva R, Monteira A, Veiga J (2011) Non-secretory multiple myeloma relapsing as extramedullary liver plasmacytomas. J Gastrointestin Liver Dis 20:81–83

Lopez Guillermo A, Marti JM, Bladé J, Nomdedeu B, Montserrat E, Rozman C (1989) Plasma cell leukemia. Study of 10 cases (in Spanish). Sangre (Barc) 34:28–31

Lorsbach RB, His ED, Dogan A, Fend F (2011) Plasma cell myeloma and related neoplasms. Am J Clin Pathol 136:168–182

Lotz JP, Colbert N, Degott C, Pariente EA (1985) Hepatocellular carcinoma related to hepatitis B virus in a patient with Waldenstrom's macroglobulinemia. J Clin Gastroenterol 7:438–440

Loze et al. 1995. http://www.ncbi.nlm.nih.gov/pubmed/8746064

Majerovic M, Bogdanic B, Drinkovic N, Kinda SB, Jakic-Razumovic J, Gasparovic V (2012) Extramedullary plasmacytoma imitating neoplasm of the gallbladder fossa after cholecystectomy. Coll Antropol 36:331–333

Majumdar N, Kumar R, Anand M, Kalita D, Ghara N, Chopra A, Medhi K, Sharma A et al (2009) Plasma cell leukemia – a study of 28 cases from India. Hematology 14:198–203

Malhotra P, Bhat P, Mahi S, Chauhan S, Rajwanshi A, Varma S (2005) Evolution of hepatosplenic plasmacytoma in a patient with multiple myeloma receiving chemotherapy. Am J Hematol 78:82–83

Mangia A, Clemente R, Musto P, Cascavilla I, La Floresta P, Sanpaolo G, Gentile R, Viglotti ML et al (1996) Hepatitis C virus infection and monoclonal gammopathies not associated with cryoglobulinemia. Leukemia 10:1209–1213

Mansoor A, Medeiros LJ, Weber DM, Alexanian R, Hayes K, Jones D, Lai R, Glassman A, Bueso-Ramos CE (2001) Cytogenetic findings in lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia. Chromosomal abnormalities are associated with the polymorphous subtype and an aggressive clinical course. Am J Clin Pathol 116:543–549

Marien KJ, Smeenk G (1975) Plane xanthomata associated with multiple myeloma and hyperlipoproteinaemia. Br J Dermatol 93:407–415

Martin IG, Aldoori MI (1994) Immunoproliferative small intestinal disease: Mediterranean lymphoma and alpha heavy chain disease. Br J Surg 81:20–24

Mathieu D, Elouaer-Blanc L, Diviné M, René E, Vasile N (1986) Hepatic plasmacytomas: sonographic and CT findings. J Comput Assist Tomogr 10:144–145

Matuchansky C, Cogné M, Lemaire M, Babin P, Touhrad G, Chamaret S, Preud'homme JL (1989) Nonsecretory alpha-chain disease with immunoproliferative small-intestinal disease. N Engl J Med 320:1534–1539

McCormick KA, Chen X, Walter RB (2013) Mott cells. Eur J Haematol 90:83

McDermott MK, Bell EM (1999) A review of Waldenstrom's macroglobulinemia. Clin J Oncol Nurs 3:107–111

McDonald EC, Speicher CE (1978) Peliosis hepatis associated with administration of oxymetholone. JAMA 240:243–244

Merzianu M, Jiang L, Lin P, Wang X, Weber DM, Vadhan-Raj S, Nguyen MH, Medeiros LJ et al (2006) Nuclear BCL-10 expression is common in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia and does not correlate with p65 NF-kappaB activation. Mod Pathol 19:891–898

Mesnard B, De Vroey B, Maunoury V, Lecuit M (2012) Immunoproliferative small intestinal disease associated with Campylobacter jejuni. Dig Liver Dis 44:799–800

Montella et al. 2000. http://www.ncbi.nlm.nih.gov/pubmed/10942947

Morel P, Duhamel A, Gobbi P, Dimopoulos MA, Dhodapkar MV, McCoy J, Crowley J et al (2009) International prognostic scoring system for Waldenström macroglobulinemia. Blood 113:4163–4170

Mosca L, Musto P, Todoerti K, Barbieri M, Agnelli L, Fabris S, Tuana G, Lionetti M et al (2013) Genome-wide analysis of primary plasma cell leukemia identifies recurrent imbalances associated with changes in transcriptional profiles. Am J Hematol 88:16–23

Moschella SL (1970) Xanthomatosis, associated with multiple myeloma. Arch Dermatol 102:121–123

Mrabti H, Raiss G, Raissouni S, el Tazi M, Inghaouen H, El Ghissassi I, Errihani H (2011) Intestinal non-Hodgkin lymphoma: "immunoproliferative small intestinal disease" (in French). Presse Med 40:995–1000

Mumoli N, Cei M, Incensati R, Verzuri S (2004) Multiple myeloma in a patient with fever of unknown origin and cholestasis. CMAJ 170:1809–1810

Mussini C, Ghini M, Mascia MT, Giovanardi P, Zanni G, Lattuada I, Moreali S, Longo G, Ferrari MG, Torelli G (1995) Monoclonal gammopathies and hepatitis C virus infection. Blood 85:1144–1145

Musto P, Falcone A, Caturelli E, Squillante MM, Castelvetere M, Carotenuto M (1992) Nodular lesions of the liver in multiple myeloma: a role for cytoadhesion molecules? Tumori 78:300–304

Naderi N, Yang DT (2013) Lymphoplasmacytic lymphoma and Waldenström macroglobulinemia. Arch Pathol Lab Med 137:580–585

Nakanishi T, Sobue I, Toyokura Y, Nishitani H, Kuroiwa Y, Satoyoshi E, Tsubaki T, Igata A, Ozaki Y (1984) The Crow-Fukase syndrome: a study of 102 cases in Japan. Neurology 34:712–720

Nakanishi et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/14748326

Nakazawa et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1476060

Nassar VH, Salem PA, Shahid MJ, Alami SY, Balikian JB, Salem AA, Nasrallah SM (1978) "Mediterranean abdominal lymphoma" or immunoproliferative small intestinal disease. Part II: pathological aspects. Cancer 41:1340–1354

Ng P, Slater S, Radvan G, Price A (1999) Hepatic plasmacytomas: case report and review of imaging features. Australas Radiol 43:98–101

Nguyen BD, Dash N, Lupetin AR (1992) MR imaging of hepatic plasmacytoma: a case report. Clin Imaging 16:98–101

Nilsson et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15287940

Noguchi K, Nagao T, Satoh Y, Kubota T, Shinizu M, Arimori S, Yamazaki H (1985) Plasma cell leukemia accompanied by polyclonal gammopathy and congenital tumor in the atrioventricular node. Tokai J Exp Clin Med 10:573–580

Nozaki et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9475252

Oshima K, Kanda Y, Nannya Y, Kaneko M, Hamaki T, Suguro M, Yamamoto R, Chizuka A, Matsuyama T et al (2001) Clinical and pathologic findings in 52 consecutively autopsied cases with multiple myeloma. Am J Hematol 67:1–5

Owen RG, Parapia LA, Higginson J, Misbah SA, Child JA, Morgan GJ, Jack AS (2000) Clinicopathological

correlates of IgM paraproteinemias. Clin Lymphoma 1:39–45
Owen RG, Treon SP, Al-Katib A, Fonseca R, Greipp PR, McMaster ML, Morra E, Pangalis GA, San Miguel JF et al (2003) Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol 30:110–115
Oyama N, Ise M, Mimura N, Tsujimura H, Sakai C, Kumagai K (2009) Hepatic hilus extramedullary plasmacytoma diagnosed by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) biopsy in a relapsed multiple myeloma (in Japanese). Rinsho Ketsueki 50:102–106
Pagano et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21252060
Pai RK, Snider WK, Starkey CR, Viswanatha D, Foucar MK, Wilson CS (2005) Nonsecretory variant of immunoproliferative small intestinal disease: a case report with pathologic, immunophenotypic, and molecular findings. Arch Pathol Lab Med 129:1487–1490
Pal S, Chattopadhyay B, Chatterjee A, Bhattacharya B (2014) Lambda light chain myeloma presenting as nodular hepatic lesion: a clinical rarity. J Cancer Res Ther 10:191–193
Pangalis GA, Kyrtsonis MC, Kontopidou FN, Vassilakopoulos TP, Siakantaris MP, Dimopoulou MN, Kittas C, Angelopoulou MK (2003) Differential diagnosis of Waldenstrom's macroglobulinemia from other low-grade B-cell lymphoproliferative disorders. Semin Oncol 30:201–205
Papla et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15278450
Park WK, Chang JC, Lee HZ, Kim HJ, Choi JH, Gu MJ (2002) A case of nodular hepatic involvement of multiple myeloma mimicking hypervascular hepatocellular carcinoma (in Korean). Taehan Kan Hakhoe Chi 8:490–494
Pasmantier MW, Azar HA (1969) Extra-skeletal spread in multiple plasma cell myeloma. Cancer 23:167–174
Pastor E, Perella M, Gomez A, Grau E, Pérez A, Escandon J (1996) Multiple myeloma of the liver presenting as nonobstructive jaundice. Am J Hematol 53:205–206
Pavlatos et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/1140282
Peek RM (2004) Intestinal malignancy and campylobacter jejuni. Gastroenterology 127:1266–1267
Peijing Q, Yan X, Yafei W, Dehui Z, Zengjun L, Junyyuan Q, Yaozhong Z, Lugul Q (2009) A retrospective analysis of thirty-one cases of plasma cell leukemia from a single center in China. Acta Haematol 121:47–51
Perez-Soler R, Esteban R, Allende E, Tornos Salomo C, Julia A, Guardia J (1985) Liver involvement in multiple myeloma. Am J Hematol 20:25–29
Pervez S, Mumtaz K, Ullah SS, Akhtar N, Ali N, Aagil H (2011) Immunoproliferative small intestinal disease (IPSID). J Coll Physicians Surg Pak 21:57–58
Peterson MC (2004) Immunoproliferative small intestinal disease associated with Campylobacter jejuni. N Engl J Med 350:1685–1686
Petrucci MT, Tirindelli MC, De Muro M, Martini V, Levi A, Mandelli F (2003) Extramedullary liver plasmacytoma a rare presentation. Leuk Lymphoma 44:1075–1076
Piccinno R, Menni S, Cavicchini S, Gianotti R (1990) Normolipemic plane xanthomas and IgG-k multiple myeloma. Description of a clinical case (in Italian). G Ital Dermatol Venereol 125:449–451
Plesnicar S, Sumi-Kriznik T, Golouh R (1975) Abdominal lymphoma with alpha-heavy chain disease. Isr J Med Sci 11:832–837
Poggi G, Teragni C, Scelsi M, Fratino P (2003) Ultrasound appearance of multiple myeloma in the liver. A case report. Radiol Med (Torino) 105:250–253
Polprasert C, Wongchitrat C, Assanasen T, Prayongratana K (2009) Lymphoplasmacytic lymphoma with IgA hypergammaglobulinemia and liver involvement. J Med Assoc Thai 92(Suppl 3):S65–S68
Poudel B, Mittal A, Shrestha R, Farooqui MS, Yadav NK, Shukla PS (2012) Liver involvement in multiple myeloma: a hospital based retrospective study. Asian Pac J Cancer Prev 13:2153–2155
Price SK (1990) Immunoproliferative small intestinal disease: a study of 13 cases with alpha heavy-chain disease. Histopathology 17:7–17
Puri AS, Aggarwal R, Khan EM, Naik S, Ayyagari A, Pandey R, Naik SR (1992) Explosive Campylobacter jejuni diarrhea in immunoproliferative small intestinal disease. Indian J Gastroenterol 11:141–143
Rahhal FE, Schade RR, Nayak A, Coleman TA (2009) Hepatic failure caused by plasma cell infiltration in multiple myeloma. World J Gastroenterol 15:2038–2040
Rambaud JC, Bognel C, Prost A, Bernier JJ, Le Quintrec Y, Lambling A, Danon F, Huez D, Seligmann M (1968) Clinico-pathological study of a patient with "Mediterranean" type of abdominal lymphoma and a new type of IgA abnormality ("alpha chain disease"). Digestion 1:321–336
Rambaud JC, Halphen M, Galian A, Tsapis A (1990) Immunoproliferative small intestinal disease (IPSID): relationships with alpha-chain disease and "Mediterranean" lymphomas. Springer Semin Immunopathol 12:239–250
Ramot B, Shahin N, Bubis JJ (1965) Malabsorption syndrome in lymphoma of small intestine. A study of 13 cases. Israel J Med Sci 1:221–226
Rappaport H (1976) The pathologic anatomy of alpha chain disease. Hamatol Bluttransfus 18:377–382
Remstein ED, Hanson CA, Kyle RA, San Miguel JF, Vidriales MB, Ocio E, Mateo G, Sanchez-Guijo F, Sanchez ML et al (2003) Immunophenotypic analysis of Waldenstrom's macroglobulinemia. Semin Oncol 30:187–195
Roberts-Thomson PJ, Venables GS, Onitri AC, Lewis B (1975) Polymeric IgA myeloma, hyperlipidaemia and xanthomatosis: a further case and review. Postgrad Med J 51:44–51

Rogers P, Hill I, Sinclair-Smith C, Bowie M (1988) Clinical and pathological evolution of alpha chain disease to immunoblastic lymphoma and response to COMP chemotherapy. Med Pediatr Oncol 16:128–131

Rolon et al. 1989. http://www.ncbi.nlm.nih.gov/pubmed/2602220

Saboo SS, Fennessy F, Benajiba L, Laubach J, Anderson KC, Richardson PG (2012) Imaging features of extramedullary, relapsed, and refractory multiple myeloma involving the liver across treatment with cyclophosphamide, lenalidomide, bortezomib, and dexamethasone. J Clin Oncol 30:e175–e179

Sakemi and Okada 1992. http://www.ncbi.nlm.nih.gov/pubmed/1568043

Salem PA, Estephan FF (2005) Immunoproliferative small intestinal disease: current concepts. Cancer J 11:374–382

Salem PA, Nassar VH, Shahid MJ et al (1977) "Mediterranean abdominal lymphoma" or immunoproliferative small intestinal disease. Part I: clinical aspects. Cancer 40:2941–2947

Salem P, el-Hashimi L, Anaissie E, Geha S, Habboubi N, Ibrahim N, Khalyl M, Allam C (1987) Primary small intestinal lymphoma in adults. A comparative study of IPSID versus non-IPSID in the Middle East. Cancer 59:1670–1676

Sandri R, Conte L, Piaserico PL (1976) Acute plasma-cell leukemia. Report of a case (in Italian). Minerva Med 67:2598–2604

San Miguel et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12720134

Santini GF, Crovatto M, Modolo ML, Martinelli P, Silvia C, Mazzi G, Franzin F, Moretti M, Tulissi P, Pozzato G (1993) Waldenstrom macroglobulinemia: a role of HCV infection? Blood 82:2932

Schaefer 1996. http://www.ncbi.nlm.nih.gov/pubmed/9122036

Schop RF, Kuehl WM, Van Wier SA, Ahmann GJ, Price-Troska T, Bailey RJ, Jalal SM, Qi Y et al (2002) Waldenstrom macroglobulinemia neoplastic cells lack immunoglobulin heavy chain locus translocations but have frequent 6q deletions. Blood 100:2996–3001

Sekikawa T, Iwase S, Takahara S, Ito K, Yamada J, Tada N, Mochizuki M (1999) Case of hepatic lymphoplasmacytoid lymphoma accompanied by IgG kappa-type M proteinemia (in Japanese). Nippon Naika Gakkai Zasshi 88:2471–2473

Seligmann M (1979) Heavy chain disease: current findings and concepts. Immunol Rev 48:145–167

Seligmann M, Rambaud JC (1983) Alpha chain disease. An immunoproliferative disease of the secretory immune system. Ann NY Acad Sci 403:478–485

Seligmann M, Danon F, Hurez D, Mihaesco E, Preud'homme JL (1968) Alpha-chain disease: a new immunoglobulin abnormality. Science 162:1396–1397

Seligmann M, Mihaesco E, Hurez D, Mihaesco C, Preud'homme JL (1969) Immunochemical studies in four cases of alpha chain disease. J Clin Invest 48:2374–2389

Sellin JH (2004) Immunoproliferative small intestinal disease associated with Campylobacter jejuni infection. Curr Gastroenterol Rep 6:353–354

Shaheen SP, Talwalkar SS, Medeiros LJ (2008) Multiple myeloma and immunosecretory disorders: an update. Adv Anat Pathol 15:196–210

Shimizu K, Kunii A, Ohnishi K, Hara K, Hirabayashi N, Kodama Y (1982) A case report of pleuropulmonary Waldenström's macroglobulinemia associated with hepatocellular carcinoma. Nihon Ketsueki Gakkai Zasshi 45:792–799

Shinde et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11481854

Signatories (no authors listed) (1976) Alpha-chain disease and related small-intestinal lymphoma: a memorandum. Bull World Health Organ 54:615–624. http://www.ncbi.nlm.nih.gov/pubmed/829415

Silvestri F, Barillari G, Fanin R, Salmaso F, Pipan C, Falasca E, Puglisi F, Mariuzzi L, Zaja F et al (1998) Impact of hepatitis C virus infection on clinical features, quality of life and survival of patients with lymphoplasmacytoid lymphoma/immunocytoma. Ann Oncol 9:499–504

Simmons MZ, Miller JA, Levine CD, Glucksman WJ, Wachsberg RH (1997) Myelomatous involvement of the liver: unusual ultrasound appearance. J Clin Ultrasound 25:145–148

Simonitsch-Klupp I, Hauser I, Ott G, Drach J, Ackermann J, Kaufmann J, Weltermann A, Greinix HT et al (2004) Diffuse large B-cell lymphomas with plasmablastic/plasmacytoid features are associated with TP53 deletions and poor clinical outcome. Leukemia 18:146–155

Solves P, de la Rubia J, Jarque I, Cervera J, Sanz GF, Vera-Sempera FJ, Sanz MA (1999) Liver disease as primary manifestation of multiple myeloma in a young. Leuk Res 23:403–405

Soubrier M, Dubost JJ, Sauvezie B (1994) POEMS syndrome: a study of 25 cases and a review of the literature. French Study Group on POEMS syndrome. Am J Med 97:543–553

Soubrier M, Dubost JJ, Serre AF, Ristori JM, Sauvezie B, Cathebras P, Piette JC, Chapman A et al (1997) Growth factors in POEMS syndrome: evidence for a marked increase in circulating vascular endothelial growth factor. Arthritis Rheum 40:786–787

Sucker C, Dolken G, Preuss J, Schwesinger G, Stockschlader M (2002) Plasma cell infiltration of the liver in multiple myeloma (in German). Dtsch Med Wochenschr 127:1469–1472

Swaroop VS (2000) Immunoproliferative small intestinal disease. Am J Gastroenterol 95:848

Taarit CB, Ajlani H, Fareh F, Zermani R, Jilani SB, Gharbi W, Maiz HB, Khedher A (2007) Multiple myeloma of the liver presenting as non-obstructive jaundice. Ann Hematol 86:529–530

Tabbane S, Tabbane F, Cammoun M, Mourali N (1976) Mediterranean lymphomas with alpha heavy chain monoclonal gammopathy. Cancer 38:1986–1996

Tabbane F, Mourali N, Cammoun M, Najjar T (1988) Results of laparotomy in immunoproliferative small intestinal disease. Cancer 61:1699–1706

Takahashi K, Naito M, Takatsuki K, Kono F, Chitose M, Ooshima S, Mori N, Sakuma H, Uchino F (1987) Multiple myeloma, IgA kappa type, accompanying crystal-storing histiocytosis and amyloidosis. Acta Pathol Jpn 37:141–154

Takahashi K, Naito M, Matsuoka Y, Takatsuki K (1988) A new form of alpha-chain disease with generalized lymph node involvement. Pathol Res Pract 183:717–723

Takakura et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12884826

Tan CH, Wang M, Fu WJ, Vikram R (2011) Nodular extramedullary multiple myeloma: hepatic involvement presenting as hypervascular lesions on CT. Ann Acad Med Singapore 40:329–331

Tashiro M, Tabaru A, Narita R, Sugihara Y, Otsuki M (2003) Biclonal multiple myeloma in liver cirrhosis due to hepatitis C virus infection. J Gastroenterol 38:1017–1018

Taylor JS, Lweis LA, Battle JD, Butkus A, Robertson AL, Deodhar S, Roenigk HH (1978) Plane xanthoma and multiple myeloma with lipoprotein-paraprotein complexing. Arch Dermatol 114:425–431

Thiruvengadam R, Penetrante RB, Goolsby HJ, Silk YN, Bernstein ZP (1990) Multiple myeloma presenting as space-occupying lesions of the liver. Cancer 65:2784–2786

Thomas FB, Clausen KP, Greenberger NJ (1973) Liver disease in multiple myeloma. Arch Intern Med 132:195–202

Tiedemann RE, Gonzalez-Paz N, Kyle RA, Santana-Davila R, Price-Troska T, Van Wier SA, Chng WJ, Ketterling RP et al (2008) Genetic aberrations and survival in plasma cell leukemia. Leukemia 22:1044–1052

Tokashiki et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/14714967

Treon SP, Xu L, Yang G, Zhou Y, Liu X, Cao Y, Sheehy P, Manning RJ, Patterson CJ et al (2012) MYD88 L265P somatic mutation in Waldenström's macrogobulinemia. N Engl J Med 367:826–833

Treon SP, Cao Y, Xu L, Liu X, Hunter ZR (2014) Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia. Blood 123:2791–2796

Tsuji et al. 1986. http://www.ncbi.nlm.nih.gov/pubmed/3723847

Tsuji et al. 1990. http://www.ncbi.nlm.nih.gov/pubmed/2083944

Tsuji T, Yamasaki H, Arima N, Tsuda H (2009) Lymphoplasmacytic lymphoma with a breast tumor and IgG+IgA+ type biclonal gammopathy (in Japanese). Rinsho Ketsueki 50:309–312

Tursz T, Brouet JC, Flandrin G, Danon F, Clauvel JP, Seligmann M (1977) Clinical and pathological features of Waldenström's macroglobulinemia in seven patients with serum monoclonal IgG or IgA. Am J Med 63:499–502

Ueda K, Matsui H, Watanabe T, Seki J, Ichinohe T, Tsuji Y, Matsumura K, Sawai Y et al (2010) Spontaneous rupture of liver plasmacytoma mimicking hepatocellular carcinoma. Intern Med 49:653–657

Usmanl et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22508408

Vazquez FJ, Funtowicz G, Rivello HG, Schutz N, Fantl D, Nucifora E (2010) Nodular hepatic lesions secondary to multiple myeloma (in Spanish). Medicina (B Aires) 70:311–315

Vella FS, Barbara S, Giannelli G, Pesolo MT, Ingravallo G, Gentile A et al (2003) Case of multiple myeloma mimicking an infectious disease with fever, intrahepatic cholestasis, renal failure, and pulmonary insufficiency. Am J Hematol 72:38–42

Vijay A, Gertz MA (2007) Waldenström macroglobulinemia. Blood 109:5096–5103

Voet D, Hamers J, Dendooven M, Nachtegaele P, Van Rattinghe R, Afschrift M, Kunnen M, Verdonk G (1983) Non excretory myeloma presenting as a liver nodule on ultrasound. Acta Clin Belg 38:384–387

Voinchet O, Degott C, Scoazec JY, Feldmann G, Benhamou JP (1988) Peliosis hepatis, nodular regenerative hyperplasia of the liver, and light-chain deposition in a patient with Waldenstrom's macroglobulinemia. Gastroenterology 95:482–486

Wajima 1992. http://www.ncbi.nlm.nih.gov/pubmed/1479181

Waldenström JG (1944) Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia – a new syndrome? Acta Med Scand 117:216–247

Walz-Mattmüller R, Horny HP, Ruck P, Kaiserling E (1998) Incidence and pattern of liver involvement in haematological malignancies. Pathol Res Pract 194:781–789

Wanless IR, Solt LC, Kortan P, Deck JH, Gardiner GW, Prokipchuk EJ (1981) Nodular regenerative hyperplasia of the liver associated with macroglobulinemia. A clue to the pathogenesis. Am J Med 70:1203–1209

Watanabe et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9771661

Weichhold W, Labouyrie E, Merlio JP, Masson B, de Mascarel A (1995) Primary extramedullary plasmacytoma of the liver. A case report. Am J Surg Pathol 19:1197–1202

Wilson DE, Floweres CM, Hershgold EJ, Eaton RP (1975) Multiple myeloma, cryoglobulinemia and xanthomatosis. Distinct clinical and biochemical syndromes in two patients. Am J Med 59:721–729

Wiltshaw E (1976) The natural history of extramedullary plasmacytoma and its relation to solitary myeloma of bone and myelomatosis. Medicine 55:217–238

Wu XN, Zhao XY, Jia JD (2009) Nodular liver lesions involving multiple myeloma: a case report and literature review. World J Gastroenterol 15:1014–1017

Xu L, Hunter ZR, Yang G, Zhou Y, Cao Y, Liu X, Morra E, Trojani A, Greco A, Arcaini L et al (2013) MYD88 L265P in Waldenström macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell

lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood 121:2051–2058

Yagci M, Sucak GT, Akyol G, Haznedar R (2002) Hepatic failure due to CD3+ plasma cell infiltration of the liver in multiple myeloma. Acta Haematol 107:38–42

Yamamoto K, Tohda S, Miki T, Suzuki T, Nagata K, Kamiyama T, Miura O, Imai Y, Murakami N, Katoh A et al (1990) Acute myeloblastic leukemia and hepatocellular carcinoma following Waldenstrom's macroglobulinemia (in Japanese). Rinsho Ketsueki 31:984–988

Yim H, Ahn HJ, Park C, Cheon JY (1995) Xanthoma of the liver in a patient with multiple myeloma associated with hyperlipidemia. A case report. J Korean Med Sci 10:453–456

Yoon YS, Min YH, Chon CY, Park C, Lee SJ, Hahn JS, Ko YW, Choi HJ (1993) Liver involvement in multiple myeloma proven by peritoneoscopy – a case report. Yonsei Med J 34:90–97

Yoritaka et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15293761

Zioni F, Giovanardi P, Bozzoli M, Artusi T, Bonacorsi G, Sighinolfi P (2004) Massive bone marrow crystal-storing histiocytosis in a patient with IgA-lambda multiple myeloma and extensive extramedullary disease. A case report. Tumori 90:348–351

Amyloidogenic Immunoglobulin Chain and Non-amyloidogenic Immunoglobulin Chain Diseases

93

Contents

Abstract

B-cell non-Hodgkin's lymphomas (NHL) can be associated with amyloidogenic immunoglobulin chain and non-amyloidogenic immunoglobulin chain disease. In both groups of disorders, the hepatobiliary tract can be involved in form of various patterns. Hepatic amyloidosis caused by NHL is termed amyloid light-chain or AL amyloidosis (primary amyloidosis) and develops in the setting of various B-cell neoplasms, most commonly with plasmacytoma. This form of amyloidosis induces an enlarged liver with increased transparency and elevated consistency. The predominant histological localization of amyloid is perisinusoidal and in portal tracts, associated with marked atrophy of hepatocyte plates. In a minority of cases of AL amyloidosis, tumor-like amyloid masses can develop (amyloidoma or amyloid tumor). This tumefactive hepatic amyloidosis is a very rare disorder. Amyloidosis can rarely involve intrahepatic and extrahepatic bile ducts. Among non-amyloidogenic immunoglobulin chain diseases, light-chain deposit disease can involve the liver. The liver is in fact the most frequent extrarenal localization of this disorder and is characterized by the deposition of granular or ribbonlike non-congophilic material along sinusoids.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_93

Hepatic Amyloidosis Caused by Non-Hodgkin's Lymphomas

Introduction

Amyloid light-chain (AL) amyloidosis (synonyms: primary systemic amyloidosis, primary amyloidosis, ICD-1o E85) is a form of amyloidosis caused by the deposition of abnormal monoclonal immunoglobulin light chains or light-chain fragments transformed into amyloid fibers with a beta-pleated structure (Husby 1983). AL is the most common form of amyloidosis in western countries and is typically associated with plasmacytoma/multiple myeloma, but also develops in other B-cell-derived malignancies, including lymphoplasmacytic lymphoma/Waldenström's disease (Gertz et al. 1993; Simmonds et al. 1997), diffuse and follicular B-cell lymphomas (Tschang 1976; Cohen et al. 2004), MALT lymphomas (Satani et al. 2007), and marginal zone lymphoma (Ryan et al. 2012), and in other monoclonal gammopathies. It is estimated that about 10–15 % of patients with multiple myeloma will develop overt AL amyloidosis. AL affects a wide range of organs and tissues and is therefore associated with highly variable clinical manifestations, but the kidney is the most commonly affected organ in AL amyloidosis.

Amyloidosis was and still is a very complex group of disorders. The unique gross and later histologic features of amyloidosis are known for a long time period. A sago spleen of amyloidosis has probably first been noted in 1639 by Nicolaus Fontanus, and lardaceous organ changes were reported in 1789 by Antoine Portal and later, in 1818, by Merat. A liver infiltration by a gelatinous substance in patients with tuberculosis or syphilis was described in 1842 by Rokitansky, the first description of the present secondary or AA amyloidosis (review: Kyle 2001). The term amyloid for these depositions goes back to "amyloid" used by Schleiden, a botanist, in 1838 to denote normal starch-containing material in plants. Rudolf Virchow first employed this term to describe the iodine-positive hyaline material characterizing amyloidosis. The characteristic apple-green birefringence when sections are stained with Congo red when viewed under polarized light was reported in 1927 (Divry and Florkin 1927). Electron microscopically, the non-branching fibrillar structure of amyloid was published in 1959 (Cohen and Calkins 1959). Apart from immunoglobulin light chains, up to 30 other proteins have been identified to cause diverse forms of amyloidosis. The pathogenesis of AL amyloidosis is not yet fully elucidated (Maniatis 1998; Merlini and Bellotti 2003; Pinney and Hawkins 2012; Ramirez-Alvarado 2012). A central step in the process is the partial lysosomal proteolysis of monoclonal light chains in macrophages, followed by tissue deposition of these altered chains or N-terminal chain fragments in the form of beta-pleated amyloid fibrils attached to a polysaccharide (so-called beta-fibrillosis; Glenner 1980). There are 40 kappa and 33 lambda germline genes that form a light-chain variable domain. In AL amyloidosis, there exists an overrepresentation of the germline light-chain genes, kappaI, lambda1, lambda2, lambda3, and lambda6. Each patient with AL amyloidosis reveals a unique amyloidogenic protein, because the phenomenon of somatic Ig hyper-mutation contributes to the complexity of AL amyloidosis.

Liver Involvement in AL Amyloidosis

Hepatic AL amyloidosis has most commonly been observed in the setting of multiple myeloma (Gertz and Kyle 1988; Yamamoto et al. 1995; Cross et al. 2006; Son et al. 2011b). Deposition of AL amyloid in the liver may induce significant functional derangements of this organ. AL amyloidosis of the liver can cause jaundice (Macias Robles et al. 1994) or cholestasis (Rubinow et al. 1978; Konikoff et al. 1987; Hoffman et al. 1988; Mohr et al. 1999; Ferreira et al. 2008). In part of patients with AL amyloidosis, cholestasis developed in the absence of visible hepatic amyloid involvement. In these cases, a toxic effect of abnormal light chains has been proposed

(Paudice et al. 2011). AL amyloidosis of the liver can cause hepatic failure (Dohmen et al. 1991; Yamamoto et al. 1995; Linardaki et al. 1997; Mainenti et al. 1997; Okabe et al. 1998; Berrios et al. 2003; Varela et al. 2003; Cross et al. 2006; Hydes and Aspinall 2012) and massive amyloid deposits resulting in atrophy and loss of hepatocytes, almost the entire liver substance being replaced by amyloid in some cases (Tabata et al. 2012). Livers occupied by amyloid may show increased tissue fragility and tend to hemorrhage and/or rupture (Naito et al. 2008; Tam et al. 2009; Szturz et al. 2013).

Marked hepatic amyloidosis is macroscopically characterized by either an enlarged liver with an increased transparency and elevated consistency (the "lardaceous liver"; Reuben 2004) or the presence of transparent deposits. In some cases, only a markedly atrophic liver with hyperemia is found. The histologic presentation of hepatic AL amyloidosis is different from that in AA amyloidosis (secondary amyloidosis). The predominant localization pattern in AA amyloidosis is vascular, whereas AL amyloidosis shows a perisinusoidal pattern in addition to portal tract and blood vessel involvement (Chopra et al. 1984; Smith and Malcolm 1986; Looi and Sumithran 1988; Iwata et al. 1995; Econimo et al. 2011; Sarsik et al. 2012). However, other studies arrived at different results (Chopra et al. 1984), e.g., showing that a sinusoidal deposition pattern also occurred in 29/78 cases of secondary (AA) amyloidosis (Buck and Koss 1991), suggesting that the hepatic amyloid distribution pattern will not help much in distinguishing the two forms of amyloidosis. Parenchymal involvement in AL amyloidosis often leads to atrophy of hepatocyte plates, sometimes associated with fatty change of liver cells. Perisinusoidal amyloid accumulation can narrow sinusoidal lumina and may cause complete effacement of the sinusoidal vascular channels.

Hepatic AL amyloid deposits more often show reactivity for lambda-type amyloid fibrils (Kuçi et al. 2007; Gioeva et al. 2009), but the inverse situation has also been reported in AL amyloidosis (Kebbel and Röcken 2006). In hepatic AL amyloidosis, the identification of amyloid deposits with anti-light-chain antibodies depends on the light-chain fragment regions to which antibodies had been raised. Amyloid deposits in the space of Disse tended to react weakly or partially with anti-lambda (118–134), but well with anti-lambda (159–175), while amyloid deposits in the portal vein wall reacted relatively well with both antibodies (Kiyama et al. 2007). Whether hepatic AL amyloidosis is reversible is currently unknown. Amyloid deposits can induce a macrophage reaction, sometimes with the formation of multinucleated giant cells of the foreign body type (amyloid granulomas), and small fragments of congophilic phagocytosed material may be seen within macrophages. Hepatic sinusoidal endothelial cells can store and metabolize serum immunoglobulin (Iwamura et al. 1995), but it is not established whether these cells can also metabolize AL amyloid fibrils.

Primary Hepatic Amyloidosis

Primary hepatic amyloidosis (PHA; synonym: hepatic AL amyloidosis) is a very rare disorder characterized by the abnormal deposition of monoclonal Ig light chains in the liver in the absence of overt myeloma or other B-cell neoplasms (Schmid et al. 1992; Park et al. 2003; Wang et al. 2012). The rarity of this disorder is illustrated by the observation that, in a study of 805 patients with clinically suspected or biopsy proven systemic amyloidosis, amyloidosis was never confined to the liver (Lovate et al. 1998), suggesting that at least part of cases with apparently primary hepatic AL amyloidosis are cases in the pre-gammopathy phase of disease. In PHA, AL amyloid deposition is predominantly found in the perisinusoidal space of Disse, but also occurs in portal tracts and in the walls of portal vein branches and central veins (Park et al. 2003; Wang et al. 2012). The pathogenesis of this unusual process is unknown. Patients with PHA often show marked hepatomegaly and elevated serum levels of alkaline phosphatase.

Mass-Forming Hepatic Amyloidosis (Amyloidoma, Amyloid Tumor)

In a minority of cases, AL amyloid presents in the form of tumor-like masses (amyloidoma, amyloid tumor, tumefactive liver infiltration in amyloidosis; Fig. 1). Amyloidomas have mostly been observed in the soft tissues, breast, urinary tract, muscles, lung, kidney, CNS, and lymph nodes (review: Westermark 2012). Amyloidomas were also observed following eradication of amyloid-containing lymphoma tissue by means of radiotherapy (Levitan et al. 1985). Amyloid tumors are very rare in the liver. Tumefactive hepatic amyloidosis was first described in detail based on a patient who had 15 × 8-cm-sized amyloid mass in the right liver lobe (Tötterman and Manninen 1982). In a 73-year-old female patient with multiple myeloma, dynamic CT of the abdomen revealed three high-density lobulating masses with central calcification in the dome and segment 3 of the liver, measuring up to 3 cm in diameter. Needle biopsy of a mass lesion showed diffuse, Congo red-positive amyloid deposits without viable hepatocytes (Son et al. 2011a). Localized pulmonary nodular amyloidosis can rarely extend through the diaphragm and reach the liver (Rosen et al. 2008).

Globular Hepatic Amyloid

A very rare form of hepatic amyloid that is sometimes associated with B-cell neoplasms is globular amyloid, a lesion mostly found in male patients. Histologically, round- to oval-shaped and sometimes laminated congophilic globules of 1–40 μm in diameter are found, sometimes with a transition to linear amyloid. The globules show the typical apple-green birefringence under polarized light. Most globules are found in portal tracts and within the hepatic parenchyma (French et al. 1981; Kanel et al. 1981; Pilgaard et al. 1993; Makhlouf and Goodman 2007). In rare forms of B-cell neoplasms, globular hepatic amyloid is an indicator of systemic AL amyloidosis (Agaram et al. 2005). Globular amyloid has also been detected in other tissues, e.g., the small bowel (Hemmer et al. 2007).

Biliary Tract Amyloidosis

A distinct and unique form of amyloidosis in the liver is the localization of amyloid around extra- and/or intrahepatic bile ducts (Fig. 2). Relatively few such situations have been reported (Sasaki et al. 1990; Terada et al. 1994). In one patient with multiple myeloma and obstructive jaundice, autopsy revealed the presence of amyloid

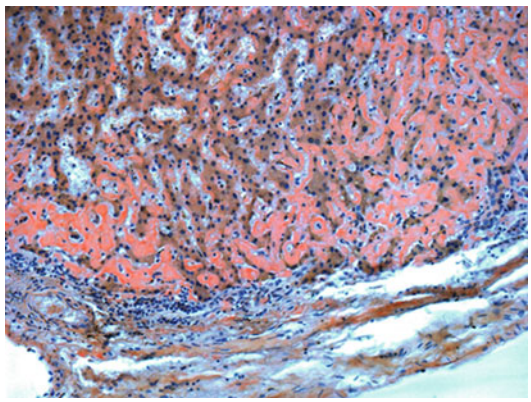

Fig. 1 Mass-forming amyloidosis (amyloidoma, amyloid tumor) of the liver in a patient with plasmacytoma. There is marked deposition of congophilic material in Disse's space, associated with atrophy of hepatocyte plates (Congo red stain)

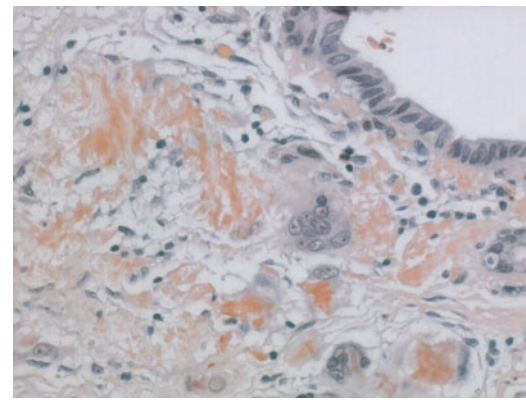

Fig. 2 Amyloidosis of the bile duct. The mucosa shows interstitial deposition of congophilic material, associated with a foreign body reaction mediated by giant cells (Congo red stain)

(ultrastructurally proven) in the walls of extra- and large intrahepatic bile ducts, associated with narrowing of the ducts involved (Terada et al. 1994). Amyloidosis was also diagnosed in the gallbladder (Remy et al. 1995; Kwon et al. 2007). In one patient, it presented as elevated nodular lesions mimicking gallbladder cancer and was histologically characterized by deposition of congophilic material in the walls of vessels within the gallbladder wall (Kwon et al. 2007).

Liver Involvement in Heavy-Chain Amyloidosis (AH)

Heavy-chain amyloidosis (AH) is a very unusual disease with few reported informations (Eulitz et al. 1990; Copeland et al. 2003; Mai et al. 2003; Gono et al. 2006). Whether amyloidosis that had been noted clinically in several patients with gamma heavy-chain disease (Frangione and Franklin 1973; Dickson et al. 1989) resulted from light – or heavy-chain deposition – has not been established (Eulitz et al. 1990). Based on the rarity of AH, only sparse data on liver involvement are available. In a first report of this disease, an enlarged, cirrhotic-appearing liver was detected at cholecystectomy, and a liver wedge biopsy revealed typically congophilic and birefringent amyloid diffusely involving the perisinusoidal spaces. At autopsy, additional amyloid deposits were found in the patient's kidney, heart, and spleen. Both serum and urine protein electrophoresis showed the presence of a whole and one fragment of IgG heavy chain, and both of these IgG heavy chains were associated with a kappa1-type light chain. In addition, urine analysis exhibited a further monoclonal gamma heavy-chain fragment that was also present in splenic amyloid showing an internally deleted IgG1 heavy chain (Eulitz et al. 1990).

Differential Diagnosis

The main histologic differential diagnosis of AL amyloidosis is AA amyloidosis. Hepatic amyloidosis is sometimes seen in hereditary amyloidosis (Harrison et al. 1996) and in the setting of amyloid-inducing hepatic tumors. AA amyloidosis has been reported to be associated with, or induced/caused by, liver cell adenoma several times (Thysell et al. 1986; Fievet et al. 1990; Melin et al. 1993; Cosme et al. 1995; Shibasaki et al. 1997). This is further discussed in the chapter of hepatocellular adenoma. An association between systemic amyloidosis and hepatocellular carcinoma has also been described (Delgado et al. 1999). The pathogenic mechanisms involved in these associations, which may not be coincidental in the case of liver cell adenoma, have not been clarified. It is, nevertheless, interesting to note that, in one reported patient, remission of nephrotic syndrome related to AA amyloidosis was achieved after hepatic adenomectomy (Melin et al. 1993). Furthermore, a patient with generalized amyloidosis and liver cell adenoma exhibited a decrease of highly elevated C-reactive serum protein and a complete normalization of the SAA level after resection of the adenoma. In this adenoma, amyloid deposition was detectable, and the tumor showed significantly elevated levels of tumor necrosis factor-alpha (TNF-alpha). It was suggested that this phenomenon, owing to the known SAA-inducing effect of TNF-alpha, might be linked to the pathogenesis of AA amyloidosis (Shibasaki et al. 1997).

Non-amyloid (Non-amyloidogenic) Immunoglobulin Chain Deposition Diseases

Introduction

Non-amyloidogenic monoclonal immunoglobulin-related diseases mainly include light-chain deposit (deposition) disease (LCDD, Randall disease), light- and heavy-chain deposition disease (LHCDD), and heavy-chain deposition disease (HCDD) (Buxbaum and Gallo 1999; Buxbaum et al. 1990). These disorders are plasma cell or, less commonly, lymphoplasmacytic neoplasias synthesizing and secreting abnormal clonal immunoglobulin light chains, heavy chains (less often), or both types of chains. These Ig chains are

deposited in the extracellular space of diverse tissues, where they cause tissue damage in the absence of amyloid formation or tumoral deposits ("aggregomas"). Immunoglobulin chain deposition diseases are rare disorders of adults, with a median age at presentation 56 years. Sixty-five percent of patients suffer from plasmacytoma/multiple myeloma.

Light-Chain Deposit Disease (Light-Chain Deposition Disease, LCDD)

Introduction

Light-chain deposit disease (LCDD; Randall et al. 1976; reviews: Buxbaum et al. 1990; Ronco et al. 2011; Jimenez-Zepeda 2012) is a rare monoclonal systemic gammopathy characterized by the presence of non-amyloidogenic monoclonal light chains in the serum and/or urine and deposition of kappa or lambda light chains in organs and tissues compromising organ function. The underlying diseases comprise plasmacytoma/myeloma; macroglobulinemia (lymphoplasmacytic lymphoma); several types of NHLs, including B-CLL; and monoclonal gammopathy of undetermined significance/MGUS (Okura et al. 2009). Only 5 % of patients with multiple myeloma will develop LLDD (Buxbaum et al. 1990). In patients without evident lymphoplasmacytic disorder (up to 40 % for periods of 2–17 years; Pozzi et al. 1995), LCDD is a frequent cause of diagnostic difficulty (Hall and Peat 2001).

Although light-chain amyloidosis (AL) is also a monoclonal immunoglobulin deposition disease, LCDD and AL differ in several ways, in that the *fibrillar* deposits in AL are congophilic, representing amyloid, and are more frequently derived from lambda than kappa light chains, whereas the *granular* deposits in LCDD are non-congophilic, are more frequently kappa than lambda, and exhibit a striking preference to be deposited along basement membranes in many organs (Randall et al. 1976; Ganeval et al. 1982). Light-chain deposition in LCDD is frequently present in the heart, kidneys, gastrointestinal tract, and liver. Renal manifestations include proteinuria, nephrotic syndrome, and progressive renal failure. End-stage kidney disease requiring dialysis is found in about 70 % of the patients with LCDD. The mean survival time is 34 months, i.e., significantly longer than in AL amyloidosis. But heart involvement can reduce survival to only 6 months, severe cardiac involvement thus being the most important prognostic factor. The deposits consist of an amorphous to granular, slightly eosinophilic material that is PAS positive and diastase resistant, but is typically negative for amyloid stains, including Congo red and thioflavin-T, and immunohistochemically stain for kappa or lambda light chains, but not for IgA, IgG, IgM, IgD, AA, or AL proteins, or amyloid P component (Michopoulos et al. 2002), and the deposits to not colocalize with apolipoprotein E. In contrast to light-chain amyloidosis (AL), where the deposits are ultrastructurally fibrillar, the deposits in LCDD exhibit a dense granular material usually located close to epithelial cells and/or the basal lamina of vascular walls (Hoffman-Guilaine et al. 1984). There is limited knowledge of the primary structure of light chains in LCDD, important for the deposition mechanisms, but amino acid substitutions caused by somatic mutations of the L12a gene have been detected, likely to cause increased hydrophobility with the potential for protein destabilization and disordered conformation (Vidal et al. 1999; including a review of the literature).

Liver Involvement in Light-Chain Deposit Disease

The liver is the most frequent extrarenal localization of LCDD, but has received less attention than the kidneys. The main manifestations of LCDD in the liver comprise hepatomegaly, abnormalities of liver function, portal hypertension, ascites, intrahepatic cholestatic jaundice, and eventually hepatic failure. Exceptionally, hepatic LCDD is associated with hepatic amyloidosis (Smith and Malcolm 1986; Casiraghi et al. 2000). LCDD can cause massive hepatomegaly, similar to amyloidosis (Pelletier et al. 1988; Nath et al. 2010). Mild or moderate abnormalities of liver function tests

are reported in approximately 20 % of patients; they most often accompany overt renal disease (Droz et al. 1984; Le Verger et al. 1985; Bedossa et al. 1988). Significant liver involvement is known to reduce the mean survival (Klinkenberg et al. 1991; Pozzi and Locatelli 2002). In a study of seven patients with liver involvement in LCDD, clinical renal involvement antedated liver light-chain deposits in all patients (Droz et al. 1984). LCDD of the liver sometimes results in cholestatic jaundice (Kumar et al. 2012), liver rupture (Croitoru et al. 2006), or liver failure (Faa et al. 1991; Casiraghi et al. 2000; Michopoulos et al. 2002; Mena-Duran et al. 2012), the latter probably due to marked impairment of hepatocyte function caused by obstruction of Disse's space by the protein deposits.

Selected References Mignon et al. 1980; Preud'homme et al. 1980; Case Records of the Massachusetts General Hospital 1981; Ganeval et al. 1981; Linder et al. 1983; Le Verger et al. 1985; Kirkpatrick et al. 1986; Bedossa et al. 1988; Pelletier et al. 1988; Toyoda et al. 1988; Faa et al. 1991; Girelli et al. 1998; Michopoulos et al. 2002; Croitoru et al. 2006; Samanez et al. 2006; Nath et al. 2010; Kwon et al. 2011; Kumar et al. 2012; Mena-Duran et al. 2012.

Macroscopic liver examination was obtained in two patients, with liver weights of 2,000 and 2,100 g, respectively, without other gross alterations. But hepatic light-chain deposition is also known to occur in LCDD without renal involvement (Michopoulos et al. 2002). Rarely, hepatic amyloidosis is associated with light-chain deposition disease (Smith and Malcolm 1986; Kirkpatrick et al. 1986; Pelletier et al. 1988; Faa et al. 1991; Girelli et al. 1998; Casiraghi et al. 2000), suggesting that LCDD and amyloidosis could be two expressions of the same disease. In a patient with multiple myeloma, the liver substance was involved by light-chain depositions, whereas amyloid was found in the wall of portal vein branches (Kirkpatrick et al. 1986).

Histologically, light-chain deposits are observed as a granular or compact, ribbonlike eosinophilic, variably PAS-positive, non-congophilic, and not birefringent material in the interstitial tissues spaces and in the space of Disse. This material is chromophilic on trichrome preparations and faintly red after picrosirius, but does not stain with Congo red, and is not metachromatic after crystal violet staining (Droz et al. 1984). The deposits are immunoreactive for light chains (kappa or lambda; Mignon et al. 1980; Droz et al. 1984; Le Verger et al. 1985; Faa et al. 1991; Girelli et al. 1998), and both portal tracts and the perisinusoidal space of Disse can be occupied (Droz et al. 1984; Michopoulos et al. 2002). It has been demonstrated that 15–20 % of LCDD have lambda light-chain deposits and a combination of light- and heavy-chain deposition is seen in less than 10 % of cases (Buxbaum et al. 1990). In the enlarged portal tracts, an increase of reticulin fibers and of collagen can be noted, together with light-chain deposition, and portal tract blood vessel walls may contain the deposits as well (Droz et al. 1984). Furthermore, the basement membranes of small bile ducts may be thickened owing to light-chain deposition (Droz et al. 1984). In the case of marked light-chain deposition, adjacent liver cell plates become atrophic. Electron microscopically, the light-chain deposits in the perisinusoidal space are visualized in the form of large and irregular mottles of granule dense material, spatially associated with a discontinuous or continuous basement membrane. Occasionally, the basement membrane material forms a double layer enclosing mottles of granular light-chain material. The adjacent hepatocytes reveal a lack of microvilli (Le Verger et al. 1985). In one study it has been demonstrated by an extraction procedure that the histologically visualized deposits in fact correspond to a deposition of kappa light chain, with a molecular weight of approximately 14–17 kDa (Toyoda et al. 1988). In lymph nodes and the lung, light-chain deposition may occur in the form of tumoral masses, termed "aggregomas" (Kijner and Yousem 1988; Stokes et al. 1997; Piard et al. 1998; Rostagno et al. 2002). So far, lesions of this type have not yet been described to occur in the liver.

Light-chain deposition along the sinusoidal profiles can also result in sinusoidal damage and the formation of peliosis or peliosis-like lesions

(Mignon et al. 1980; Droz et al. 1984; Le Verger et al. 1985). Moreover, perisinusoidal fibrosis (collagenization of Disse's space), and sometimes extensive liver fibrosis can develop (Droz et al. 1984; Bedossa et al. 1988), with an increase of immunoreactive collagens type I, III, and IV, laminin, and fibronectin in the space of Disse (Le Verger et al. 1985; Bedossa et al. 1988; Faa et al. 1991). Double immunostaining showed the co-deposition of large and thick deposits of light chain with thin and linear deposits of type IV collagen in the perisinusoidal space (Le Verger et al. 1985). Apart from the parenchymatous form of hepatic LCDD, a rare variant is characterized by light-chain deposits restricted to the hepatic artery tree, clinically associated with ischemic cholangitis due to stenosis of arteries feeding the bile ducts (Weisel et al. 2009).

Heavy-Chain Disease

Heavy chains or their fragments can be amyloidogenic, and the resulting amyloidosis shares the same morphologic features with other types of amyloidosis (Mai et al. 2003). In rare instances, monoclonal Ig heavy chains are deposited in tissues in the absence of formation of amyloidogenic beta-pleated sheets (heavy-chain deposition disease, HCDD; Katz et al. 1994; review: Kambham et al. 1999). HCDDs are caused by B-cell neoplasms that produce truncated monoclonal immunoglobulin heavy chains. In accordance with the diverse Ig heavy chain types, four types of HCDD are recognized, viz., alpha heavy-chain disease b (Seligmann's disease; mostly a digestive tract disorder), gamma heavy-chain disease (Franklin disease), mu heavy-chain disease, and delta heavy-chain disease. Gamma-type HCDD is chiefly characterized by lymphadenopathy, fever, anemia, hepatosplenomegaly, and renal glomerular and peritubular depositions of heavy chains without associated light chains (Oe et al. 2010). The gamma3 heavy chain seems to prevail (immunoglobulin gamma3 heavy-chain deposition disease; Kambham et al. 1999; Soma et al. 2004; Masai et al. 2009). Liver gamma heavy-chain deposits have not yet been reported.

References

Agaram N, Shia J, Klimstra DS, Lau N, Lin O, Erlandson RA, Filippa DA, Godwin TA (2005) Globular hepatic amyloid: a diagnostic peculiarity that bears clinical significance. Hum Pathol 36:845–849

Bedossa P, Fabre M, Paraf F, Martin E, Lemaigre G (1988) Light chain deposition disease with liver dysfunction. Hum Pathol 19:1008–1014

Berrios M, Armas-Merino R, Franco C, Parrochia E, Wolff C (2003) Acute liver failure in patient with liver amyloidosis associated to multiple myeloma (in Spanish). Rev Med Chil 131:1301–1303

Buck FS, Koss MN (1991) Hepatic amyloidosis: morphologic differences between systemic AL and AA types. Hum Pathol 22:904–907

Buxbaum J, Gallo G (1999) Nonamyloidotic monoclonal immunoglobulin deposition disease. Light-chain, heavy-chain, and light-and heavy-chain deposition diseases. Hematol Oncol Clin N Am 13:1235–1248

Buxbaum JN, Chuba JV, Hellman GC, Solomon A, Gallo GR (1990) Monoclonal immunoglobulin deposition disease: light chain and light and heavy chain deposition disease and their relation to light chain amyloidosis. Ann Intern Med 112:455–464

Case records of the Massachusetts General Hospital (case 1 – 1981) (1981) N Engl J Med 304:33

Casiraghi MA, De Paoli A, Assi A, Palladini G, Lavazza MT, Beretta A, Gualdoni G, Beretta R (2000) Hepatic amyloidosis with light chain deposition disease. A rare association. Dig Liver Dis 32:795–798

Chopra S, Rubinow A, Koff RS, Cohen AS (1984) Hepatic amyloidosis. A histopathologic analysis of primary (AL) and secondary (AA) forms. Am J Pathol 115:186–193

Cohen AS, Calkins E (1959) Electron microscopic observations on a fibrous component in amyloid of diverse origins. Nature 183:1202–1203

Cohen AD, Zhou P, Xiao Q, Fleisher M, Kalakonda N, Akhurst T, Chitale DA, Moscowitz C et al (2004) Systemic AL amyloidosis due to non-Hodgkin's lymphoma: an unusual clinicopathologic association. Br J Haematol 124:309–314

Copeland JN, Kouides PA, Grieff M, Nadasdy T (2003) Metachronous development of nonamyloidogenic l light chain deposition disease and IgG heavy chain amyloidosis in the same patient. Am J Surg Pathol 27:1477–1482

Cosme A, Horcajada JP, Vidaur F, Ojeda E, Torrado J, Areans JI (1995) Systemic AA amyloidosis induced by oral contraceptive-associated hepatocellular adenoma: a 13-year follow up. Liver 15:164–167

Croitoru AG, Hytiroglou P, Schwartz ME, Saxena R (2006) Liver transplantation for liver rupture due to light chain deposition disease: a case report. Semin Liver Dis 26:298–303

Cross TJ, Wendon JA, Quaglia A, Salisbury JR, Heneghan MA, Harrison PM (2006) Myeloma associated amyloidosis presenting as subacute liver failure. Postgrad Med J 82:e13

Delgado MA, Liu JY, Meleg-Smith S (1999) Systemic amyloidosis associated with hepatocellular carcinoma. Case report and literature review. J La State Med Soc 151:474–478

Dickson JR, Harth M, Bell DA, Komar R, Chodirker WB (1989) Gamma heavy chain disease and rheumatoid arthritis. Semin Arthritis Rheum 18:247–251

Divry P, Florkin M (1927) Sur les propriétés optiques de l'amyloide. CR Soc Biol (Paris) 97:1808–1810

Dohmen K, Nagano M, Iwakiri R, Yamano Y, Kikuchi Y, Mizoguchi M, Iwata Y, Mori Y, Ishibashi H (1991) A case of prominent hepatic cholestasis developing to hepatic failure in lambda-AL amyloidosis. Gastroenterol Jpn 26:376–381

Droz D, Noel LH, Carnot F, Degos F, Ganeval D, Grunfeld JP (1984) Liver involvement in nonamyloid light chain deposit disease. Lab Invest 50:683–689

Econimo L, Jeannin G, Biasi L, Mazzola G, Mendeni M, Presteni K, Gregorini G (2011) Liver involvement with rapidly progressive course in light chain (AL) amyloidosis: distinguishing features at presentation. Experience of a single center. Amyloid 18(suppl a):109–111

Eulitz M, Weiss DT, Solomon A (1990) Immunoglobulin heavy-chain associated amyloidosis. Proc Natl Acad Sci U S A 87:6542–6546

Faa G, Van Eyken P, De Vos R, Fevery J, Van Damme B, De Groote J, Desmet VJ (1991) Light chain deposition disease of the liver associated with AL-type amyloidosis and severe cholestasis. J Hepatol 12:75–82

Ferreira S, Baldaia C, Fatela N, Ramalho F, Costa MA, Brito D, Esteves G, Monteiro E (2008) Severe intrahepatic cholestasis, erythrocytosis and hypoglycemia: unusual presenting features of systemic AL amyloidosis. Scand J Gastroenterol 43:375–379

Fievet P, Sevestre H, Boudjelal M, Noel LH, Kemeny F, Franco D, Delamarre J, Capron JP (1990) Systemic AA amyloidosis induced by liver cell adenoma. Gut 31:361–363

Frangione B, Franklin EC (1973) Heavy chain diseases: clinical features and molecular significance of the disordered immunoglobulin structure. Semin Hematol 10:54–64

French SW, Schloss GT, Stillman AE (1981) Unusual amyloid bodies in human liver. Am J Clin Pathol 75:400–402

Ganeval D, Noel LH, Droz D, Leibowitch J (1981) Systemic lambda light- chain deposition in a patient with myeloma. Br Med J 282:681–683

Ganeval D, Mignon F, Preud'homme JL, Noel LH, Morel-Maroger L, Droz D, Brouet JC et al (1982) Visceral deposition of monoclonal light chains and immunoglobulins: a study of renal and immunopathologic abnormalities. Adv Nephrol 11:25–63

Gertz MA, Kyle RA (1988) hepatic amyloidosis (primary [AL], immunoglobulin light chain): the natural history in 80 patients. Am J Med 85:73–80

Gertz MA, Kyle RA, Noel P (1993) Primary systemic amyloidosis: a rare complication of immunoglobulin M monoclonal gammopathies and Waldenström's macroglobulinemia. J Clin Oncol 11:914–920

Gioeva Z, Kieninger B, Röcken C (2009) Amyloidosis in liver biopsies (in German). Pathologe 30:240–245

Girelli C, Giovanni L, Rocca F (1998) Light chain deposition disease of the liver. Eur J Gastroenterol Hepatol 10:429–430

Glenner GG (1980) Amyloid deposits and amyloidosis. The betafibrilloses (first of two parts). N Engl J Med 302:1283–1292

Gono T, Yazaki M, Fushimi T, Suzuki T, Uehara T, Sano K, Kametani F, Ito N, Matsushita M et al (2006) AH amyloidosis associated with lymphoplasmacytic lymphoma secreting a monoclonal gamma heavy chain carrying an unusual truncated D segment. Am J Kidney Dis 47:908–914

Hall CL, Peat DS (2001) The interesting case light chain deposit disease: a frequent cause of diagnostic difficulty. Nephrol Dial Transplant 16:1939–1941

Harrison RF, Hawkins PN, Roche WR, MacMahon RF, Hubscher SG, Buckels JA (1996) 'Fragile' liver and massive hepatic hemorrhage due to hereditary amyloidosis. Gut 38:151–152

Hemmer PR, Topazian MD, Gertz MA, Abraham SC (2007) Globular amyloid deposits isolated to the small bowel: a rare association with AL amyloidosis. Am J Surg Pathol 31:141–145

Hoffman-guilaine C, Nochy D, Tricottet V, Mallet L, Bariety J, Camilleri JP (1984) La maladie des dépots de chaines légères: une entité anatomopathologique. Ann Pathol 4:105–113

Hoffman MS, Stein BE, Davidian MM, Rosenthal WS (1988) Hepatic amyloidosis presenting as severe intrahepatic cholestasis: a case report and review of the literature. Am J Gastroenterol 83:783–785

Husby G (1983) Immunoglobulin-related (AL) amyloidosis. Clin Exp Rheumatol 1:353–358

Hydes TJ, Aspinall RJ (2012) Subacute liver failure secondary to amyloid light-chain amyloidosis. Gastroenterol Hepatol 8:205–208

Iwamura S, Enzan H, Saibara T, Onishi S, Yamamoto Y (1995) Hepatic sinusoidal endothelial cells can store and metabolize serum immunoglobulin. Hepatology 22:1456–1461

Iwata T, Hoshii Y, Kawano H, Gondo T, Takahashi M, Ishihara T, Yokota T, Ueta J, Uchino F (1995) Hepatic amyloidosis in Japan: histological and morphometric analysis based on amyloid proteins. Hum Pathol 26:1148–1153

Jimenez-Zepeda VH (2012) Light chain deposition disease: novel biological insights and treatment advances. Int J Lab Hematol 34:347–355

Kambham N, Markowitz GS, Appel GB, Kleiner MJ, Aucouturier P, D'Agati VD (1999) Heavy chain deposition disease: the disease spectrum. Am J Kidney Dis 33:954–962

Kanel GC, Uchida T, Peters RL (1981) Globular hepatic amyloid – an unusual morphologic presentation. Hepatology 1:647–652

Katz A, Zent R, Bargman JM (1994) IgG heavy-chain deposition disease. Mod Pathol 7:874–878

Kebbel A, Röcken C (2006) Immunohistochemical classification of amyloid in surgical pathology revisited. Am J Surg Pathol 30:673–683

Kijner CH, Yousem SA (1988) Systemic light chain deposition disease presenting as multiple pulmonary nodules: a case report an review of the literature. Am J Surg Pathol 12:405–413

Kirkpatrick CJ, Curry A, Galle J, Melzner I (1986) Systemic kappa light chain deposition and amyloidosis in multiple myeloma: novel morphological observations. Histopathology 10:1065–1076

Kiyama M, Hoshii Y, Cui D, Kawano H, Kanda T, Ishihara T (2007) Immunohistochemical and immunochemical study of amyloid in liver affected by systemic Alambda amyloidosis with antibodies against three different regions of immunoglobulin lambda light chain. Pathol Int 57:343–350

Klinkenberg N, Reis HE, Rakow L (1991) Liver involvement as leading symptom of a kappa light-chain deposit disease (in German). Med Klin (Munich) 86:394–398

Konikoff F, Mor C, Stern S, Shaklai M, Halevy J, Theodor E (1987) Cholestasis and liver failure with lambda-AL amyloidosis. Gut 28:903–906

Kuçi H, Ebert MP, Röcken C (2007) Anti-lambda-light chain-peptide antibodies are suitable for the immunohistochemical classification of AL amyloid. Histol Histopathol 22:379–387

Kumar PN, Sandhya V, Venkatakrishnan L, Krishnaveni J, Mohanakrishnan A, Nirmala V (2012) Light chain deposition disease presenting as cholestatic jaundice: a case report. Oman Med J 27:56–59

Kwon AH, Tsuji K, Yamada H, Okazaki K, Sakaida N (2007) Amyloidosis of the gallbladder mimicking gallbladder cancer. J Gastroenterol 42:261–264

Kwon JH, Jeong SH, Kim JW, Bang SM, Kim H, Kim YH, Song SH (2011) Case report: a case of light chain deposition disease involving liver and stomach with chronic hepatitis C virus infection and hepatocellular carcinoma. J Med Virol 83:810–814

Kyle RA (2001) Historical review. Amyloidosis: a convoluted story. Br J Haematol 114:529–538

Le Verger JC, Toulet R, Deugnier Y, Ramie MP (1985) Anomalies biologiques hépatiques au cours d'une maladie de chaines légères. Gastroenterol Clin Biol 9:184–185

Levitan N, Rubinow A, Bromer RH, Conlon CL, Doos WG, Hong WK (1985) Transformation of lymphoma to amyloidoma following radiation therapy. Hum Pathol 16:1072–1074

Linardaki G, Drivas G, Archimandritis A (1997) AL-type amyloidosis presenting with rapidly deteriorating liver involvement. J Clin Gastroenterol 24:297–298

Linder J, Croker BP, Vollmer RT, Shelburne J (1983) Systemic kappa light-chain deposition. An ultrastructural and immunohistochemical study. Am J Surg Pathol 7:85–93

Looi LM, Sumithran E (1988) Morphologic differences in the pattern of liver infiltration between systemic AL and AA amyloidosis. Hum Pathol 19:732–735

Lovat LB, Persey MR, Madhoo S, Pepys MB, Hawkins PN (1998) The liver in systemic amyloidosis: insights from 1231 serum amyloid P component scintigraphy in 484 patients. Gut 42:727–734

Macias Robles MD, Navia-Osorio Garcia-Braga JM, Menendez Caro JL, Velasco Alonso J, Lopez Lagunas I (1994) Jaundice secondary to intrahepatic deposit of light chains as a presenting form of multiple myeloma (in Spanish). An Med Interna 11:74–76

Mai HL, Sheikh-Hamad D, Herrera GA, Gu X, Truong LD (2003) Immunoglobulin heavy chain can be amyloidogenic: morphologic characterization including immunoelectron microscopy. Am J Surg Pathol 27:541–545

Mainenti PP, Petrelli G, Lamanda R, Amalfi G, Castiglione F (1997) Primary systemic amyloidosis with giant hepatomegaly and a swiftly progressive course. J Clin Gastroenterol 24:173–175

Makhlouf HR, Goodman ZD (2007) Globular hepatic amyloid: an early stage in the pathway of amyloid formation: a study of 20 new cases. Am J Surg Pathol 31:1615–1621

Maniatis A (1998) Pathophysiology of paraprotein production. Ren Fail 20:821–828

Masai R, Wakui H, Togashi M, Maki N, Ohtani H, Komatsuda A, Sawada K (2009) Clinicopathological features and prognosis in immunoglobulin light and heavy chain deposition disease. Clin Nephrol 71:9–20

Melin JP, Lecrique T, Wynckel A, Wong T, Noel LH, Belghiti J, Chanard J (1993) Remission of nephrotic syndrome related to AA amyloidosis after hepatic adenomectomy. Nephron 64:157–158

Mena-Duran A, Muñoz VE, Pareja LG, Sanchis CJ (2012) Liver failure caused by light chain deposition disease associated with multiple myeloma. Intern Med 51:773–776

Merlini G, Bellotti V (2003) Molecular mechanisms of amyloidosis. N Engl J Med 349:583–596

Michopoulos S, Petraki K, Petraki C, Dimopulos MA (2002) Light chain deposition disease of the liver without renal involvement in a patient with multiple myeloma related to liver failure and rapid fatal outcome. Dig Dis Sci 47:730–734

Mignon F, Morel-Maroger L, Cerf M, Preud'homme JL, Richet G (1980) Hepatic and renal deposits of kappa light chains revealing a dysglobulinemia (in French). Nephrologie 1:167–170

Mohr A, Miehlke S, Klauck S, Röcken C, Malfertheimer P (1999) hepatomegaly and cholestasis as primary clinical manifestations of an AL-kappa amyloidosis. Eur J Gastroenterol Hepatol 11:921–925

Naito KS, Ichiyama T, Kawakami S, Kadoya M, Tabata T, Matsuda M, Ikeda S (2008) AL amyloidosis with spontaneous hepatic rupture: successful treatment by transcatheter hepatic artery embolization. Amyloid 15:137–139

Nath SV, Peiris M, Bishton MJ, Maxwell E, Prince HM (2010) Light chain deposition disease presenting as massive hepatomegaly. Pathology 42:307–310

Oe Y, Nakaya I, Yahata M, Sakuma T, Sato H, Soma J (2010) A case of g1-heavy chain deposition disease successfully treated with melphalan and prednisolone therapy. Intern Med 49:1411–1415

Okabe M, Choi GH, Kudo M, Nakaya H, Kishimoto A, Suzuki H, Miyagishima T (1998) Hepatic failure due to myeloma-associated amyloidosis. J Gastroenterol 33:926–927

Okura T, Miyoshi K, Nagao T, Jotoku M, Enomoto D, Irita J, Kurata M, Higaki J (2009) Light chain deposition disease developing 15 years following the diagnosis of monoclonal gammopathy of undetermined significance. Intern Med 48:101–104

Park MA, Mueller PS, Kyle RA, Larson DR, Plevak MF, Gertz MA (2003) Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. Medicine (Baltimore) 82:291–298

Paudice N, Farsetti S, Caroti L, Ciuti G, Tempestini A, Perfetto F, Bergesio F (2011) Severe recurrent intrahepatic cholestasis in systemic AL amyloidosis without evident liver involvement. Unexplained hepatic toxicity or a case of misdiagnosed liver amyloidosis? Amyloid 18(suppl 1):142–144

Pelletier G, Fabre M, Attali P, Ladouch-Badre A, Ink O, Martin E, Etienne JP (1988) Light chain deposition disease presenting with hepatomegaly: an association with amyloid-like fibrils. Postgrad Med J 64:804–808

Piard F, Yaziji N, Jarry O, Assem M, Martin L, Bernard A, Jacquot JP, Justrabo E (1998) Solitary plasmacytoma of the lung with light chain extracellular deposits: a case report and review of the literature. Histopathology 32:356–361

Pilgaard J, Fenger C, Schaffalitzky de Muckadell OB (1993) Globular amyloid deposits in the liver. Histopathology 23:479–480

Pinney JH, Hawkins PN (2012) Amyloidosis. Ann Clin Biochem 49:229–241

Pozzi C, Locatelli F (2002) Kidney and liver involvement in monoclonal light chain disorders. Semin Nephrol 22:319–330

Pozzi C, Fogazzi GB, Banfi G, Strom EH, Ponticelli C, Locatelli F (1995) Renal disease and patient survival in light chain deposit disease. Clin Nephrol 43:281–287

Preud'homme JL, Morel-Maroger L, Brouet JC, Cerf M, Mignon F, Guglielmi P, Seligmann M (1980) Synthesis of abnormal immunoglobulins in lymphoplasmacytic disorders with visceral light chain deposition. Am J Med 69:703–710

Ramirez-Alvarado M (2012) Amyloid formation in light chain amyloidosis. Curr Top Med Chem 12:2523–2533

Randall RE, Williamson WC, Mullinax F, Tung MY, Still WJS (1976) Manifestations of systemic light chain deposition. Am J Med 60:293–299

Remy AJ, Perney P, Bourat L, Ramos J, Marty M, Cabaniols H, Durand L, Quenet F, Blanc F (1995) Amyloidosis of the gallbladder. An unusual localization (in French). Gastroenterol Clin Biol 19:215–217

Reuben A (2004) The legend of the lardaceous liver. Hepatology 40:763–766

Ronco P, Plaisier E, Aucouturier P (2011) Monoclonal immunoglobulin light and heavy chain deposition diseases: molecular models of common renal diseases. Contrib Nephrol 169:221–231

Rosen DJ, Stavropoulos C, Travis WD, Ashton RC, Bhora FY, Connery CP (2008) Transdiaphragmatic amyloidoma. Ann Thorac Surg 86:310–312

Rostagno A, Frizzera G, Ylagan L, Kumar A, Ghiso J, Gallo G (2002) Tumoral non-amyloidotic monoclonal immunoglobulin light chain deposits ('aggregoma'): presenting feature of B-cell dyscrasia in three cases with immunohistochemical and biochemical analyses. Br J Haematol 119:62–69

Rubinow A, Koff RS, Cohen AS (1978) Severe intrahepatic cholestasis in primary amyloidosis: a report of four cases and a review of the literature. Am J Med 64:937–946

Ryan RJ, Sloan JM, Collins AB, Mansouri J, Raje NS, Zukerberg LR, Ferry JA (2012) Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with amyloid deposition: a clinicopathologic case series. Am J Clin Pathol 137:51–64

Samanez C, Domingo A, Cibeira MT, Miquel R, Soler M, Bladé J (2006) Development of rapidly progressive liver light chain deposition under VAD chemotherapy in multiple myeloma. Eur J Haematol 76:83–85

Sarsik B, Sen S, Kirdok FS, Akarca US, Toz H, Yilmaz F (2012) Hepatic amyloidosis: morphologic spectrum of histopathological changes in AA and nonAA amyloidosis. Pathol Res Pract 208:713–718

Sasaki M, Nakanuma Y, Terada T, Hoso M, Saito K, Hayashi M, Kurumaya H (1990) Amyloid deposition in intrahepatic large bile ducts and peribiliary glands in systemic amyloidosis. Hepatology 12:743–746

Satani T, Yokose T, Kaburagi T, Asato Y, Itabashi M, Amemiya R (2007) Amyloid deposition in primary pulmonary marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Pathol Int 57:746–750

Schmid PA, Burger HR, Spycher MA, Bühler H, Heitz PU (1992) Primary amyloidosis of the liver (in German). Dtsch Med Wochenschr 117:1014–1018

Shibasaki T, Matsumoto H, Watabe K, Joh K, Nakano H, Matsuda H, Gomi H, Ohno I, Ishimoto F, Sakai O (1997) A case of renal amyloidosis associated with hepatic adenoma: the pathogenetic role of tumor necrosis factor-alpha. Nephron 75:350–353

Simmonds PD, Cottrell BJ, Mead GM, Wright DH, Whitehouse JM (1997) Lymphadenopathy due to amyloid deposition in non-Hodgkin's lymphoma. Ann Oncol 8:267–270

Smith NM, Malcolm AJ (1986) Simultaneous AL-type amyloid and light chain deposit disease in a liver biopsy: a case report. Histopathology 10:1057–1064

Soma J, Sato K, Sakuma T, Saito H, Sato H, Sato T, Abbas A, Aucouturier P (2004) Immunoglobulin gamma3-heavy-chain deposition disease: report of a case and relationship with hypocomplementemia. Am J Kidney Dis 43:E10–E16

Son RC, Chang JC, Choi JH (2011a) Primary hepatic amyloidosis: report of an unusual case presenting as a mass. Korean J Radiol 12:382–385

Son YM, Choi JY, Bak CH, Cheon M, Kim YE, Lee KH, Kim BT (2011b) 18F-FDG PET/CT in primary AL hepatic amyloidosis associated with multiple myeloma. Korean J Radiol 12:634–637

Stokes MB, Jagirdar J, Burchstin O, Kornacki S, Kumar A, Gallo G (1997) Nodular pulmonary immunoglobulin light chain deposits with coexistent amyloid and nonamyloid features in an HIV-infected patient. Mod Pathol 10:1059–1065

Szturz P, Kyclova J, Moulis M, Navratil M, Adam Z, Vanicek J, Mayer J (2013) Extensive AL amyloidosis presenting with recurrent liver hemorrhage and hemoperitoneum: case report and literature review. Klin Onkol 26:49–52

Tabata S, Kurata M, Takeda J, Funayama Y, Yamauchi N, Aoki K, Kato A, Ono Y et al (2012) Fatal hepatic failure due to AL amyloidosis in a patient with multiple myeloma. Rinsho Ketsueki 53:1906–1910

Tam M, Seldin DC, Forbes BM, Connors LH, Skinner M, Oran B, Quillen K, Sanchorawala V (2009) Spontaneous rupture of the liver in a patient with systemic AL amyloidosis undergoing treatment with high-dose melphalan and autologous stem cell transplantation: a case report with literature review. Amyloid 16:103–107

Terada T, Hirata K, Hisada Y, Hoshii Y, Nakanuma Y (1994) Obstructive jaundice caused by the deposition of amyloid-like substances in the extrahepatic and large intrahepatic bile ducts in a patient with multiple myeloma. Histopathology 24:485–487

Thysell H, Ingvar C, Gustafson T, Holmin T (1986) Systemic reactive amyloidosis caused by hepatocellular adenoma. A case report. J Hepatol 2:450–457

Tötterman KJ, Manninen V (1982) Tumefactive liver infiltration in amyloidosis. Ann Clin Res 14:11–14

Toyoda M, Kajita A, Kita S, Osamura Y, Shinoda T (1988) An autopsy case of diffuse myelomatosis associated with systemic kappa light chain deposition disease (LCDD). A patho-anatomical, immunohistochemical and immunobiological study. Acta Pathol Jpn 38:479–488

Tschang TP (1976) Nodular malignant lymphoma and amyloidosis. A case report. Cancer 38:2192–2196

Varela M, De Las Heras D, Miguel R (2003) Hepatic failure due to primary AL amyloidosis. J Hepatol 39:290

Vidal R, Goni F, Stevens F, Aucouturier P, Kumar A, Frangione B, Ghiso J et al. (1999) Somatic mutations of the LRA gene in V-kl light chain deposition disease. Potential effects on aberrant protein conformation and deposition. Am J Pathol 155:2009–2017

Wang YD, Zhao CY, Yin HZ (2012) Primary hepatic amyloidosis: a mini literature review and five cases report. Ann Hepatol 11:721–727

Weisel KC, Böckeler M, Bianchi L, Terracciano LM, Mayer F, Kanz L (2009) Development of rapid light-chain deposition disease in hepatic arteries with severe ischemic cholangitis in a multiple myeloma patient treated with melphalan, prednisone and lenalidomide. Int J Hematol 89:91–94

Westermark P (2012) Localized AL amyloidosis: a suicidal neoplasm? Upsala J Med Sci 117:244–250

Yamamoto T, Maeda N, Kawasaki H (1995) Hepatic failure in a case of multiple myeloma-associated amyloidosis (kappa-AL). J Gastroenterol 30:393–397

B-Cell Non-Hodgkin's Lymphomas Associated with Viral Infections

94

Contents

Abstract

A complex spectrum of lymphoproliferative disorders is associated with, or caused by, distinct viral infections. These infections include Epstein-Barr virus (EBV), human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus), human T-cell lymphotropic virus 1 (HTLV-1), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infections. EBV is long known to have associations with special forms of B-cell neoplasms, endemic Burkitt lymphoma being the most prominent example. But EBV infection is also involved in the pathogenesis of classical Hodgkin's lymphoma and plays a central role in posttransplant lymphoproliferative disorders. HHV-8 infection is, apart from Kaposi's sarcoma, associated with a broad array of rare lymphomas which in part develop in the setting of immunodeficiencies. HTLV-1 is involved in adult T-cell leukemia/lymphoma. HCV infection is a major worldwide cause of chronic liver disease, but is also associated with numerous extrahepatic manifestations, including B-cell neoplasms, suggested to be caused by chronic antigenic stimulation of the immune system. Lymphomas arising in patients with HIV infection are mostly related to the immunosuppression and concomitant infections known to promote lymphomagenesis, in particular EBV and HHV-8.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_94

Introduction

Several types of lymphoproliferative disorders are associated with, or caused by, distinct types of viral infections. Viruses involved include Epstein-Barr virus (EBV), human herpesvirus 8 (HHV-8; Kaposi's sarcoma-associated herpesvirus), human T-cell lymphotropic virus 1 (HTLV-1), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). These viruses are directly involved in the pathogenesis of lymphoproliferative disease or lymphomas, or cause conditions that favor the development of such disorders, mainly via generation of immunosuppression (Table 1).

Epstein-Barr Virus (EBV) Infections

As listed in Table 1, Epstein-Barr virus (EBV) infection is associated with a distinct group of lymphoproliferative diseases. The classification of these disorders was recently reviewed (Carbone et al. 2008). Part of these disorders can involve the hepatobiliary tract, either as a primary manifestation or as a secondary involvement in the setting of generalized disease. Apart from a direct action on lymphoid target cells, EBV is also capable to modulate cells of tumor microenvironments (Dolcetti 2015). It does so by hijacking the exosome pathway to excrete viral and cellular components, including Fas ligand to induce apoptosis in recipient cells (Ahmed et al. 2015).

Table 1 Viral infections associated with lymphoproliferative disorders

Virus	Lymphoproliferative disorder
Epstein-Barr virus (EBV)	Endemic Burkitt lymphoma
	EBV-positive large B-cell lymphoma (immunoblastic)
	EBV-associated primary CNS lymphoma
	EBV-associated polymorphic B-cell lymphoma with leukemia and congenital immunodeficiencies
	Lymphomatoid granulomatosis
	Senile EBV-associated B-cell lymphoproliferative disorder
	Classical Hodgkin's lymphoma
	Posttransplant lymphoproliferative disorder/PTLD
Human herpesvirus 8 (KSHV)	Primary effusion lymphoma (PEL)
	Multicentric Castleman disease (MCD)
	MCD-associated large B-cell lymphoma
	MCD-associated plasmablastic lymphoma
	MCD-associated PEL
	KSHV-associated solid lymphomas
	KSHV-associated plasmablastic lymphoma
	KSHV- and EBV-associated germinotropic lymphoproliferative disorder
	KSHV-associated anaplastic large cell lymphoma-like lymphoma
	KSHV- and EBV-associated anorectal lymphoma
	KSHV-related posttransplantation plasmacytic proliferation
EBV-HHV-8 co-positive lymphoproliferations	Various B-cell lymphomas
HTLV-1	Adult T-cell leukemia/lymphoma
Hepatitis C virus	Various B-cell non-Hodgkin's lymphomas
HIV	HIV-associated B-cell lymphoid malignancies
	EBV- and HHV-8-associated lymphomas in HIV infection

Abbreviations: *KSHV* Kaposi's sarcoma-associated herpesvirus, *HTLV-1* human T-cell lymphotropic virus 1, *HIV* human immunodeficiency virus

Endemic Burkitt Lymphoma

As specified in the respective chapter, endemic Burkitt lymphoma is primarily diagnosed in children in equatorial regions and is strongly associated with EBV infection and MYC gene translocations (review: Brady et al. 2007). A part of the patients also show molecular evidence for the participation of other infectious agents, in particular human herpesvirus 5 and HHV-8 (review: Abate et al. 2015).

B-Cell Lymphomas Other Than Burkitt Lymphoma

EBV infection is rarely associated with other B-cell lymphomas, including EBV-positive large B-cell lymphoma in young patients (Nicolae et al. 2015). Other B-cell neoplasms associated with EBV are primary central nervous system lymphomas and polymorphous lymphomas associated with leukemia and congenital immunodeficiencies.

EBV-Positive T-Cell Lymphoproliferative Diseases of Childhood

ICD-O codes (provisional) 9724/3 and 9725/3

In the 2008 WHO tumor classification, T-cell lymphoproliferative disorders of childhood that are associated with EBV are known as two distinct variants, both mainly occurring in Asians and in natives from Central and South America. The first form is Hydroa vacciniforme-like lymphoma, a cutaneous T-cell neoplasm with an indolent course over longer time periods. The second form is systemic EBV-positive T-cell lymphoproliferative disease (STLPD) of childhood, with a fulminant course (review: Hong et al. 2013). The latter is discussed here in some more detail, due to its prominent hepatic manifestations.

Hydroa vacciniforme-like lymphoma (ICD-O 9725/3) develops in children and adolescents in Asia and Central/South America and is related to sensitivity to insect (mosquito) bites and sunlight sensitivity. A defective immune response directed against EBV plays a pathogenetic role. Patients present with a papulovesicular eruption that proceeds to ulceration and scarring. Late in disease, systemic signs may develop, including hepatosplenomegaly and lymphadenopathy. The tumor cells are cytotoxic T-cells that reveal T-cell receptor rearrangement (Yachie et al. 2003; Wada et al. 2012).

Systemic EBV-positive T-cell lymphoproliferative disease of childhood (STLPD; ICD-O code 9724/3; synonyms: sporadic fatal infectious mononucleosis; severe chronic active EBV infection/CAEBV; Kimura 2006) is a severe and life-threatening systemic disease of children and young adults, predominantly males, characterized by an aggressive neoplastic proliferation of cytotoxic T-cells and EBV infection of B-cells. Most patients are from Japan and Taiwan, but few patients are from Western countries. Exceptionally, adult patients are affected (Abdul-Ghafar et al. 2011). Clinically, the patients show a rapidly progressive illness with multiorgan involvement and failure, often with sepsis, death occurring within days to weeks. One particularly aggressive variant reveals high fever, pancytopenia, marked lymphadenopathy, and hepatosplenomegaly. In contrast to the standard variant, EBV in this dangerous variant infects T-cells and NK cells, T-cells stimulated to become a monoclonal population and then a frankly malignant neoplastic cell population (Craig et al. 1992; Dolezal et al. 1995; Ohshima et al. 2008; Ohga et al. 2011; Rodriguez-Pinilla et al. 2011; Wang et al. 2012).

Infiltrating cells are small T-cells without relevant atypia. Few patients show larger and pleomorphic cell forms. The characteristic immunophenotype is a positive reaction for CD2, CD3, and, in forms secondary to acute primary EBV infection, CD8, whereas T-cells in patients with severe CAEBV are CD4 positive. The cells show T-cell receptor rearrangement. All cells contain EBV in a clonal episomal form.

Liver Involvement

In EBV-positive STLPD of childhood, the liver is the most commonly involved inner organ (review:

Yoshii et al. 2012). Prominent hepatomegaly, liver dysfunction, and eventually liver failure are typical features (Chan et al. 1992; Quintanilla-Martinez et al. 2000; Hauptmann et al. 2001; Liu et al. 2008; Salama et al. 2008; Rodriguez-Pinilla et al. 2011; Sevilla et al. 2011), followed by the spleen, lymph nodes, bone marrow, skin, and lung. Liver biopsies show CD3+ CD8+ lymphoid T-cells in sinusoids, sometimes in high numbers (Abdul-Ghafar et al. 2011). These sinusoidal lymphocytes are almost invariably EBER positive. Marked hemophagocytosis may be observed (Quintaneilla-Martinez et al. 2000).

Human T-Cell Lymphotropic Virus 1 (HTLV-1)

HTLV-1 is a central etiologic agent for adult T-cell leukemia/lymphoma (ATLL), as further discussed in the chapter on T-cell Non-Hodgkin's lymphomas, but does not suffice for neoplastic transformation of target T-cells to take place. HTLV-1 is a retrovirus of the *Retroviridae* family. In humans, HTLV-1 can infect several cell types, including T-lymphocytes, B-lymphocytes, dendritic cells, and fibroblasts. Persons with ATLL are exposed to HTLV-1 early in life, and the development of the lymphoproliferative process requires a long time period (reviews: Bangham and Ratner 2015; Utsch Gonçalves et al. 2010). Apart from its direct effects on gene expression in target cells, the virus affects epigenetic mechanisms, whereby its Tax and HBZ oncoproteins can both activate and silence cellular promoters by interaction with enzymes involved in histone modifications (Minarovits et al. 2016).

Lymphomas Associated with Kaposi's Sarcoma-Associated Herpesvirus (KHV)/Human Herpesvirus 8

Introduction

The Kaposi's sarcoma-associated herpesvirus (KSHV; human herpesvirus 8, HHV-8), detected in 1994 (Chang et al. 1994), belongs to the gamma human herpesvirus group, containing members of oncogenic viruses, specifically EBV and KSHV in man (Roizmann et al. 1992; Damania 2004). Gamma-herpesviruses, which have been identified in many animal species, are lymphotropic and can establish a lifelong period of latency in their host, with intermediate periods of lytic replication. The genome of KSHV is complex; apart from open reading frames (ROF) encoding enzymes and viral structural proteins, it contains several ORF that have been pirated during viral evolution from cellular genes. The gene products affect a host of cellular functions, including growth (Bcl-2 and cyclin homologs), signaling pathways, immune regulation (cytokine homologs), and angiogenesis (Boshoff and Weiss 1998; Sarid et al. 2002; Damania 2004; Schulz and Cesarman 2015). KSHV is found invariably in Kaposi's sarcoma (KS; Chang et al. 1994; Huang et al. 1995), and compelling evidence suggests that it is an etiologic agent of KS (Boshoff and Weiss 1998). This aspect is addressed in a separate chapter.

KSHV is lymphotropic (Mesri et al. 1996), and several lymphoproliferative disorders are known to be associated with KSHV infection (Ascoli et al. 1999, 2001; Matsushima et al. 1999; Du et al. 2001, 2002; Schulz 2001; Hengge et al. 2002; Navarro et al. 2003; Huang et al. 2004; Chadburn et al. 2004; Colomo et al. 2004; Cioc et al. 2004; Carbone et al. 2004; Carbone and Gloghini 2008; Bhutani et al. 2015; Elyamany et al. 2015; Huang and Low 2015). They are listed in Table 1. KSHV also induces a distinct pattern of inflammations, termed the KSHV inflammatory cytokine syndrome/KICS (Polizzotto et al. 2016).

KSHV (HHV-8) is common in sub-Saharan Africa and around the Mediterranean Sea, but is rare in most other countries. It is known to be transmitted in childhood within families in endemic regions and through sexual contacts among high-risk groups in Western countries. However, evidence is growing that transmission also occurs through heterosexual contact or injection drug use (Henke-Gendo and Schulz 2004). In contrast to PEL that is listed in the WHO classification, solid lymphomas developing in

association with KSHV infection have not yet been well characterized and classified. KSHV-associated solid lymphomas have been found to occur following resolution of PEL (Huang et al. 2002).

KSHV-Associated Lymphoma of the Liver

Few reports have described KSHV-associated lymphoproliferative disorders that were apparently primary to the liver. An AIDS patient showed BCL-6-positive B-cell lymphoma associated with KSHV, exclusively localized to the liver and spleen. The tumor cells were medium sized to large and were reactive for CD20, CD45, and BCL-6, but negative for CD30 and EMA, suggesting a neoplasm of germinal center cell origin (Hasegawa et al. 2004). Ferry and coworkers (2009) reported on a 59-year-old HIV-positive man who died after several weeks of fever, anemia, thrombocytopenia, hepatosplenomegaly, and multiorgan failure. Autopsy showed intravascular large B-cell lymphoma that had also involved the liver. The tumor cells were KSHV positive.

B-Cell Non-Hodgkin's Lymphomas Associated with Hepatitis C Virus Infection

Chronic infection with the hepatitis C virus (HCV) is not only responsible for a frequent liver disease worldwide, but is also associated with growing spectrum of extrahepatic manifestations (EHMs) involving the skin, kidneys, salivary glands, eyes, central nervous system, thyroid, and the immune system. Clinically, the most prominent EHMs of HCV infection include mixed cryoglobulinemia, cryoglobulinemic vasculitis, nephropathies, thyreopathies, cardiovascular diseases, type 2 diabetes mellitus, and neurocognitive and neuropsychiatric disorders. The term "HCV syndrome" has been coined to include both hepatic and extrahepatic manifestations of HCV infection (reviews: Ferri et al. 2007, 2015; Zignego et al. 2007; Monaco et al. 2015; Vigano and Colombo 2015). Furthermore, an increasing number of investigations have associated infection with HCV with the emergence of autoimmune disorders and NHL, mainly B-cell lymphomas.

Selected references: Ferri et al. 1994; De Rosa et al. 1997; Zuckerman et al. 1997; Luppi et al. 1998; Silvestri et al. 1998; Ohsawa et al. 1999; Kim et al. 2000; Mizorogi et al. 2000; Chindamo et al. 2002; Gasparotto et al. 2002; Fiorilli et al. 2003; Mele et al. 2003; Paydas et al. 2003; Tomita et al. 2003; Weng and Levy 2003; de Sanjose et al. 2004; Gisbert et al. 2004; Kitabayashi et al. 2004; Morton et al. 2004; Negri et al. 2004; Talamini et al. 2004; Viswanatha and Dogan 2007; Ito et al. 2011; Pellicelli et al. 2011; Tsutsumi et al. 2011; Arcaini et al. 2012; De Re et al. 2012; Hartridge-Lambert et al. 2012; Kikuma et al. 2012; Kedia et al. 2014; Carrier et al. 2015; Fiorino et al. 2015; Tasleem and Sood 2015.

In a study of 529 consecutive patients newly diagnosed with a lymphoid malignancy in Spain, a prevalence of 5.9 % HCV infection was found versus 3.8 % among controls, after exclusion of HIV-infected subjects and organ recipients (de Sanjose et al. 2004). Overall, the reported prevalence of HCV infection in patients with B-cell NHL is between 9 % and 32 %. In the DANVIR cohort study covering 11,975 HCV-infected patients, these patients had a 29.97-fold increased risk of NHL during the first year of follow-up and a 1.26-fold increased risk after the first year (Omland et al. 2012). In a recent population-based cohort study, chronic HCV infection was temporally associated with a twofold increased risk of lymphoid neoplasms, especially NHL in Asian patients (Su et al. 2015). But there are also reports not confirming such an association (King et al. 1998; Collier et al. 1999; Pioltelli et al. 2000; Hausfater et al. 2001; Aviles et al. 2003; Abe et al. 2015). It was suggested that these controversial data may reflect regional differences in the prevalence of HCV infection

(McColl et al. 1997). There is evidence that B-cell NHLs related to HCV infection exhibit certain types more frequently than others. For example, a study on 157 patients with de novo B-NHL showed that those with HCV infection had more frequently follicular, marginal zone, and diffuse large B-cell NHL (Luppi et al. 1998). On the other hand, there is evidence that the spectrum of B-cell NHL types is different in HCV-infected individuals in comparison with a noninfected population. In one investigation, B-cell NHLs in HCV-infected patients frequently presented at onset an extranodal localization with peculiar target organs of HCV infection (i.e., the liver and major salivary glands) being overrepresented, a diffuse large B-cell phenotype without prior history of low-grade B-cell NHL, and a weak association with a full-blown predisposing autoimmune disease (De Vita et al. 1997). Chronic HCV infection also seems to favor the evolution of plasma cell tumors/myelomas (Montella et al. 2000; Gharagozloo et al. 2001; Tashiro et al. 2003). In addition, HCV seems to be related to a subset of NHL primarily originating from the liver (Bronowicki et al. 2003), an issue discussed in more detail below.

What are the potential mechanisms involved in HCV-associated lymphomagenesis, provided that an association is accepted? So far, the molecular basis for HCV-induced lymphomagenesis is still unknown, but several findings may shed light on putative pathogenic pathways. One line of thinking is that the presence of HCV and/or the HCV genome (or parts of it) in target cells may be involved in lymphomagenic pathways. B-lymphocytes seem to have an important role in viral propagation of HCV (Muller et al. 1994). It was shown that HCV infects B-cells in vivo and in vitro, and cell lines can be derived from B-cell NHL that are persistently infected with HCV and display enhanced apoptosis (Sung et al. 2003). Few investigations suggest that the HCV genotype plays a role for the development of NHL, e.g., genotype 2ac might be more involved in the pathogenesis of lymphoproliferative disorders than others (Silvestri et al. 1997). In one study, the presence of components of the HCV genome has been detected in lymphoma cells of primary hepatic lymphoma (Ohsawa et al. 1998). Both positive-strand and negative-strand HCV RNA was detected in B-cell lymphomas, indicating viral replication (Karavattathayyil et al. 2000; Paydas et al. 2004). On the other hand, there is persistence of HCV in peripheral blood mononuclear cells in mixed cryoglobulinemia, a disorder thought to evolve into NHL in at least part of the cases (Zignego et al. 1997). The potential causal relationship between HCV and NHL is supported by observations from animal experimentation. Transgenic mice expressing the HCV core transgene develop malignant lymphoma of the follicular center cell type, and the livers of these animals express HCV core protein and mRNA (Ishikawa et al. 2003). Epigenetic mechanisms involving distinct patterns of microRNA expression in HCV-related malignancies have been discussed (review: Gragnani et al. 2015; Grewal et al. 2015).

A second pathogenic pathway that may play a significant role is HCV-mediated chronic immune stimulation promoting lymphomagenesis, a mechanism also discussed for NHLs arising in the setting of Helicobacter pylori infection (review: Suarez and Lecuit 2015).

Human Immunodeficiency Virus (HIV)

HIV infection is associated with an increased risk of B-cell lymphoid malignancies. Lymphomas occurring in patients with HIV infection are often EBV- or HHV-8-associated lesions (Mylona et al. 2008; Krishnan and Zaia 2014; Arvey et al. 2015; Carroll and Garzino-Demo 2015; Pinzone et al. 2015; Silverberg et al. 2015) or develop from EBV-HHV-8 co-positive cell systems. HIV-associated proteins, in particular tat and vpu, affect cell cooperation between lymphoid cells and cells of the microenvironment, including endothelial cells (De Paoli and Carbone 2015). On the other hand, microenvironments favoring the development of lymphomas exhibit EBV and/or HHV-8 coinfection (Pantanowitz et al. 2015).

References

Abate F, Amrosio MR, Mundo L, Laginestra MA, Fuligni F, Rossi M, Zairis S, Gazaneo S, De Falco G, Lazzi S et al (2015) Distinct viral and mutational spectrum of endemic Burkitt lymphoma. PLoS Pathog 11: e1005158

Abdul-Ghafar J, Kim JW, Park KH, Cho MY (2011) Fulminant Epstein-Barr virus-associated T-cell lymphoproliferative disorder in an immunocompetent middle-aged man presenting with chronic diarrhea and gastrointestinal bleeding. J Korean Med Sci 26:1103–1107

Abe SK, Inoue M, Swada N, Iwasaki M, Shimazu T, Yamaji T, Sasazuki S, Tanaka Y, Mizokami M, Tsugane S et al (2015) Hepatitis B and C virus infection and risk of lymphoid malignancies: a population-based cohort study (JPHC study). Cancer Epidemiol 39:562–566

Ahmed W, Philip PS, Attoub S, Khan G (2015) Epstein-Barr virus infected cells release Fas-ligand exosomal fractions and induce apoptosis in recipient cells via the extrinsic pathway. J Gen Virol. doi:10.1099/jgv.0.000313

Arcaini L, Merli M, Volpetti S, Rattotti S, Gotti M, Zaja F (2012) Indolent B-cell lymphomas associated with HCV infection: clinical and virological features and role of antiviral therapy. Clin Dev Immunol 2012:638185

Arvey A, Ojesina AI, Pedamallu CS, Ballon G, Jung J, Duke F, Leoncini F, De Falco G, Bressman E, Tam W et al (2015) The tumor virus landscape of AIDS-related lymphomas. Blood 125:e14–e22

Ascoli V, Sirianni MC, Mezzaroma I, Mastroianni CM, Vullo V, Andreoni M, Narciso P et al (1999) Human herpesvirus-8 in lymphomatous and nonlymphomatous body cavity effusions developing in Kaposi's sarcoma and multicentric Castleman's disease. Ann Diagn Pathol 3:357–363

Ascoli V, Signoretti S, Onetti-Muda A, Pescarmona E, Della-Rocca C, Nardi F, Mastroianni CM et al (2001) Primary effusion lymphoma in HIV-infected patients with multicentric Castleman's disease. J Pathol 193:200–209

Aviles A, Valdez L, Halabe J, Neri N, Nellen H et al (2003) No association between lymphoma and hepatitis C virus. Med Oncol 20:165–168

Bangham CR, Ratner L (2015) How does HTLV-1 cause adult T-cell leukemia/lymphoma (ATL)? Curr Opin Virol 14:93–100

Bhutani M, Polizzotto MN, Uldrick TS, Yarchoan R (2015) Kaposi sarcoma-associated herpesvirus-associated malignancies: epidemiology, pathogenesis, and advances in treatment. Semin Oncol 42:223–246

Boshoff C, Weiss RA (1998) Kaposi's sarcoma-associated herpesvirus. Adv Cancer Res 75:57–86

Brady G, MacArthur GJ, Farrell PJ (2007) Epstein-Barr virus and Burkitt lymphoma. J Clin Pathol 60:1397–1402

Bronowicki JP, Bineau C, Feugier P, Hermine O, Brousse N, Oberti F, Rousselet MC, Dharancy S, Gaulard P et al (2003) Primary lymphoma of the liver: clinical-pathological features and relationship with HCV infection in French patients. Hepatology 37:781–787

Carbone A, Gloghini A (2008) KSHV/HHV8-associated lymphomas. Br J Haematol 140:13–24

Carbone A, Gloghini A, Gaidano G (2004) Is plasmablastic lymphoma of the oral cavity an HHV-8-associated disease? Am J Surg Pathol 28:1251–1252

Carbone A, Gloghini A, Dotti G (2008) EBV-associated lymphoproliferative disorders: classification and treatment. Oncologist 13:577–585

Carrier P, Jaccard A, Jacques A, Jacques J, Tabouret T, Debette-Gratien M, Abraham J, Mesturoux L, Marquet P et al (2015) HCV-associated B-cell non-Hodgkin lymphomas and new direct antiviral agents. Liver Int 35:2222–2227

Carrol V, Garzino-Demo A (2015) HIV-associated lymphoma in the era of combination antiretroviral therapy: shifting the immunological landscape. Pathog Dis. doi:10.1093/femspd/ftv044. pii: ftv044

Chadburn A, Hyjek E, Mathew S, Cesarman E, Said J, Knowles DM (2004) KSHV-positive solid lymphomas represent an extra-cavitary variant of primary effusion lymphoma. Am J Surg Pathol 28:1401–1416

Chan LC, Srivastava G, Pittaluga S, Kwong YL, Liu HW, Yuen HL (1992) Detection of clonal Epstein-Barr virus in malignant proliferation of peripheral blood CD3+ CD8+ T cells. Leukemia 6:952–956

Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS (1994) Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 266:1865–1869

Chindamo et al. (2002) PubMed PMID 11956646

Cioc AM, Allen C, Kalmar JR, Suster S, Baiocchi R, Nuovo GJ (2004) Oral plasmablastic lymphomas in AIDS patients are associated with human herpesvirus 8. Am J Surg Pathol 28:41–46

Collier JD, Zanke B, Moore M, Kessler G, Krajden M, Shepherd F, Heathcote J (1999) No association between hepatitis C and B-cell lymphoma. Hepatology 29:1259–1261

Colomo L, Loong F, Rives S, Pittaluga S, Martinez A, Lopez-Guillermo A, Ojanguren J et al (2004) Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. Am J Surg Pathol 28:736–747

Craig FE, Clare CN, Sklar JL, Banks PM (1992) T-cell lymphoma and the virus-associated hemophagocytic syndrome. Am J Clin Pathol 97:189–194

Damania B (2004) Oncogenic gamma-herpesviruses: comparison of viral proteins involved in tumorigenesis. Nat Rev Microbiol 2:656–668

De Paoli P, Carbone A (2015) Microenvironmental abnormalities induced by viral cooperation: impact on lymphomagenesis. Semin Cancer Biol 34:70–80

De Re V, Caggiari L, Garziera M, De Zorzi M, Repetto O (2012) Molecular signature in HCV-positive lymphomas. Clin Dev Immunol 2012:623465

De Rosa G, Gobbo ML, De Renzo A, Notaro R, Garofalo S, Grimaldi M, Apuzzo A et al (1997) High prevalence of hepatitis C virus infection in patients with B-cell lymphoproliferative disorders in Italy. Am J Hematol 55:77–82

De Sanjose S, Nieters A, Goedert JJ, Domingo-Domenech-E, Fernandez de Sevilla A, Bosch R, Herrera P, Domingo A et al (2004) Role of hepatitis C virus infection in malignant lymphoma in Spain. Int J Cancer 111:81–85

De Vita et al. (1997) PubMed PMID 9226178

Dolcetti R (2015) Cross-talk between Epstein-Barr virus and microenvironment in the pathogenesis of lymphomas. Semin Cancer Biol 34:58–69

Dolezal MV, Kamel OW, van de Rijn M, Cleary ML, Sibley RK, Warnke RA (1995) Virus-associated hemophagocytic syndrome characterized by clonal Epstein-Barr virus genome. Am J Clin Pathol 103:189–194

Du MQ, Liu H, Diss TC, Ye H, Hamoudi RA, Dupin N, Meignin V, Oksenhendler E et al (2001) Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. Blood 97:2130–2136

Du MQ, Diss TC, Liu H, Ye H, Hamoudi RA, Cabecadas J, Dong HY, Harris NL, Chan JK et al (2002) KSHV- and EBV-associated germinotropic lymphoproliferative disorder. Blood 100:3415–3418

Elyamany G, Al Mussaed E, Alzahrani AM (2015) Plasmablastic lymphoma. A review of current knowledge and future directions. Adv Hematol 2015:315289

Ferri C, Caracciolo F, Zignego AL, La Civita L, Monti M, Longombardo G, Lombardini F, Greco F, Capochiani E et al (1994) Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Br J Haematol 88:392–394

Ferri C, Antonelli A, Mascia MT, Sebastiani M, Fallahi P, Ferrari D, Pileri SA, Zignego AL (2007) HCV-related autoimmune and neoplastic disorders: the HCV syndrome. Dig Liver Dis 39(Suppl 1):S13–S21

Ferri C, Sebastiani M, Giuggioli D, Colaci M, Fallahi P, Piluso A, Antonelli A, Zignego AL (2015) Hepatitis C virus syndrome: a constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer. World J Hepatol 7:327–343

Ferry JA, Sohani AR, Longtine JA, Schwartz RA, Harris NL (2009) HHV8-positive, EBV-positive Hodgkin lymphoma-like large B-cell lymphoma and HHV8-positive intravascular large B-cell lymphoma. Mod Pathol 22:618–626

Fiorilli M, Mecucci C, Farci P, Casato M (2003) HCV-associated lymphomas. Rev Clin Exp Hematol 7:406–423

Fiorino S, Bacchi-Reggiani L, de Biase D, Fornelli A, Masetti M, Tura A, Grizzi F, Zanello M, Mastrangelo L, Lombardi R, Acquaviva G et al (2015) Possible association between hepatitis C virus and malignancies different from hepatocellular carcinoma: a systematic review. World J Gastroenterol 21:12896–12953

Gasparotto D, De Re V, Boiocchi M (2002) Hepatitis C virus, B-cell proliferation and lymphomas. Leuk Lymphoma 43:747–751

Gharagozloo Z, Khoshnoodi J, Shokri F (2001) Hepatitis C virus infection in patients with essential mixed cryoglobulinemia, multiple myeloma and chronic lymphocytic leukemia. Pathol Oncol Res 7:135–139

Gisbert JP, Garcia-Buey L, Arranz R, Blas C, Pinilla I, Khorrami S, Acevedo A, Borque MJ et al (2004) The prevalence of hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Eur J Gastroenterol Hepatol 16:135–138

Gragnani L, Piluso A, Fognani E, Zignego AL (2015) MicroRNA expression in hepatitis C virus-related malignancies: a brief review. World J Gastroenterol 21:8562–8568

Grewal R, Cucuianu A, Swanepoel C, Dima D, Petrushev B, Pop B, Berindan-Neagoe I, Abayomi EA, Tomuleasa C (2015) The role of microRNAs in the pathogenesis of HIV-related lymphomas. Crit Rev Clin Lab Sci 52:232–241

Hartridge-Lambert SK, Stein EM, Markowitz AJ, Portlock CS (2012) Hepatitis C and non-Hodgkin lymphoma: the clinical perspective. Hepatology 55:634–641

Hasegawa H, Katano H, Tanno M, Masuo S, Ae T, Sato Y, Takahashi H, Iwasaki T et al (2004) BCL-6-positive human herpesvirus 8-associated solid lymphoma arising from liver and spleen as multiple nodular lesions. Leuk Lymphoma 45:2169–2172

Hauptmann S, Meru N, Schewe C, Jung A, Hiepe F, Burmester G, Niedobitek G, Buttgereit F (2001) Fatal atypical T-cell proliferation associated with Epstein-Barr virus infection. Br J Haematol 112:377–380

Hausfater P, Cacoub P, Sterkers Y, Thibault V, Amoura Z, Nguyen L, Ghillani P, Leblond V, Piette JC (2001) Hepatitis C virus infection and lymphoproliferative diseases: prospective study on 1576 patients in France. Am J Hematol 67:168–171

Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA, Seeber S (2002) Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: pathogenesis, Castleman's disease, and pleural effusion lymphoma. Lancet Infect Dis 2:344–352

Henke-Gendo C, Schulz TF (2004) Transmission and disease association of Kaposi's sarcoma-associated herpesvirus: recent developments. Curr Opin Infect Dis 17:53–57

Hong M, Ko YH, Yoo KH, Koo HH, Kim SJ, Kim WS, Park H (2013) EBV-positive T/NK-cell lymphoproliferative disease of childhood. Korean J Pathol 47:137–147

Huang G, Low G (2015) Human herpes virus-8-associated multicentric Castleman's disease in a human

immunodeficiency virus-positive patient with a previous history of Kaposi's sarcoma. J Clin Imaging Sci 5:59

Huang YQ, Li JJ, Kaplan MH, Poiesz B, Katabira E, Zhang WC, Feiner D, Friedman-Kein AE (1995) Human herpesvirus-like nucleic acid in various forms of Kaposi's sarcoma. Lancet 345:759–761

Huang Q, Chang KL, Gaal K, Arber DA (2002) Primary effusion lymphoma with subsequent development of a small bowel mass in an HIV-seropositive patient: a case report and literature review. Am J Surg Pathol 26:1363–1367

Huang Q, Chang KL, Gaal KK, Weiss LM (2004) KSHV/HHV8-associated lymphoma simulating anaplastic large cell lymphoma. Am J Surg Pathol 28:693–697

Ishikawa T, Shibuya K, Yasui K, Mitamura K, Ueda S (2003) Expression of hepatitis C virus core protein associated with malignant lymphoma in transgenic mice. Comp Immunol Microbiol Infect Dis 26:115–124

Ito M, Kusunoki H, Mochida K, Yamaguchi K, Mizuochi T (2011) HCV infection and B-cell lymphomagenesis. Adv Hematol 2011:835314

Karavattathayyil SJ, Kalkeri G, Liu HJ, Gaglio P, Krause JR, Dash S (2000) Detection of hepatitis C virus RNA sequences in B-cell non-Hodgkin lymphoma. Am J Clin Pathol 113:391–398

Kedia S, Bhatt VR, Rajan SK, Tandra PK, El Behery RA, Aktari M (2014) Benign and malignant hematological manifestations of chronic hepatitis C virus infection. Int J Prev Med 5(Suppl 3):S179–S192

Kikuma K, Watanabe J, Oshiro Y, Shimogama T, Honda Y, Okamura S, Higaki K, Uike N et al (2012) Etiological factors in primary hepatic B-cell lymphoma. Virchows Arch 460:379–387

Kim JH, Kim HY, Kang I, Kim YB, Park CK, Yoo JY, Kim ST (2000) A case of primary hepatic lymphoma with hepatitis C liver cirrhosis. Am J Gastroenterol 95:2377–2380

Kimura H (2006) Pathogenesis of chronic active Epstein-Barr virus infection: is this an infectious disease, lymphoproliferative disorder, or immunodeficiency? Rev Med Virol 16:251–261

King PD, Wilkes JD, Diaz-Arias AA (1998) Hepatitis C virus infection in non-Hodgkin's lymphoma. Clin Lab Haematol 20:107–110

Kitabayashi K, Hasegawa T, Uneo KI, Saito H, Kosaka T, Takeshima S, Kurose N et al (2004) Primary hepatic non-Hodgkin's lymphoma in a patient with chronic hepatitis C: report of a case. Surg Today 34:366–369

Krishnan A, Zaia JA (2014) HIV-associated non-Hodgkin lymphoma: viral origins and therapeutic options. Hematol Am Soc Hematol Educ Program 2014:584–589

Liu Y, Tang SQ, Liu LZ, Yang G, Feng C, Lei Q (2008) Characteristics of chronic active Epstein-Barr virus infection-associated hematological disorders in children (in Chinese). Zhongguo Shi Yan Xue Ye Xue Za Zhi 16:574–578

Luppi M, Longo G, Ferrari MG, Barozzi P, Marasca R, Morselli M, Valenti C, Mascia T, Vandelli L, Vallisa D, Cavanna L, Torelli G (1998) Clinico-pathological characterization of hepatitis C virus-related B-cell non-Hodgkin's lymphomas without symptomatic cryoglobulinemia. Ann Oncol 9:495–498

Matsushima AY, Strauchen JA, Lee G, Scigliano E, Hale EE, Weisse MT, Burstein D, Kamel O, Moore PS, Chang Y (1999) Posttransplantation plasmacytic proliferations related to Kaposi's sarcoma-associated herpesvirus. Am J Surg Pathol 23:1393–1400

McColl MD, Singer IO, Tait RC, McNeil IR, Cumming RL, Hogg RB (1997) The role of hepatitis C virus in the aetiology of non-Hodgkin's lymphoma – a regional association? Leuk Lymphoma 26:127–130

Mele A, Pulsoni A, Bianco E, Musto P, Szklo A, Sanpaolo MG, Iannitto E, De Renzo A, Martino B, Liso V et al (2003) Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. Blood 102:996–999

Mesri EA, Cesarman E, Arvanitakis L, Rafii S, Moore MA, Posnett DN, Knowles DM, Asch AS (1996) Human herpesvirus-8/Kaposi's sarcoma-associated herpesvirus is a new transmissible virus that infects B cells. J Exp Med 183:2385–2390

Minarivits J, Demcsak A, Banati F, Niller HH (2016) Epigenetic dysregulation in virus-associated neoplasms. Adv Exp Med Biol 879:71–90

Mizorogi F, Hiramoto J, Nozato A, Takekuma Y, Nagayama K, Tanaka T, Takagi K (2000) Hepatitis C virus infection in patients with B-cell non-Hodgkin's lymphoma. Intern Med 39:112–117

Monaco S, Mariotto S, Ferrari S, Calabrese M, Zanusso G, Gajofatto A, Sansonno D, Dammacco F (2015) Hepatitis C virus-associated neurocognitive and neuropsychiatric disorders: advances in 2015. World J Gastroenterol 21:11974–11983

Montella M, Crispo A, Russo F, Ronga D, Tridente V, Tamburini M (2000) Hepatitis C virus infection and new association with extrahepatic disease: multiple myeloma. Haematologica 85:883–884

Morton LM, Engels EA, Holford TR, Leaderer B, Zhang Y, Zahm SH, Boyle P, Zhang B, Flynn S et al (2004) Hepatitis C virus and risk of non-Hodgkin lymphoma: a population-based case-control study among Connecticut women. Cancer Epidemiol Biomarkers Prev 13:425–430

Muller HM, Kallinowski B, Sollbach C, Theilmann L, Goeser T, Pfaff E (1994) B-lymphocytes are predominantly involved in viral propagation of hepatitis C virus (HCV). Arch Virol Suppl 9:307–316

Mylona EE, Baraboutis IG, Lekakis LJ, Georgiou O, Papastamopoulos V, Skoutelis A (2008) Multicentric Castleman's disease in HIV infection: a systematic review of the literature. AIDS Rev 10:25–35

Navarro JT, Ribera JM, Junca J, Milla F (2003) Anorectal lymphoma without effusion associated with human herpesvirus-8 and type 1 Epstein-Barr virus in an HIV-infected patient. Hum Pathol 34:630

Negri E, Little D, Boiocchi M, La Vecchia C, Franceschi S (2004) B-cell non-Hodgkin's lymphoma and hepatitis C virus infection: a systematic review. Int J Cancer 111:1–8

Nicolae A, Pittalunga S, Abdullah S, Steinberg SM, Pham TA, Davies-Hill T, Xi L, Raffeld M, Jaffe ES (2015) EBV-positive large B-cell lymphomas in young patients: a nodal lymphoma with evidence for a tolerogenic immune environment. Blood 126:863–872

Ohga S, Ishimura M, Yoshimoto G, Miyamoto T, Takada H, Tanaka T, Ohshima K et al (2011) Clonal origin of Epstein-Barr virus (EBV)-infected T/NK-cell subpopulations in EBV-positive T/NK-cell lymphoproliferative disorders of childhood. J Clin Virol 51:31–37

Ohsawa M, Tomita Y, Hashimoto M, Kanno H, Aozasa K (1998) Hepatitis C viral genome in a subset of primary hepatic lymphomas. Mod Pathol 11:471–478

Ohsawa M, Shingu N, Miwa H, Yoshihara H, Kubo M, Tsukuma H, Teshima H, Hashimoto M, Aozasa K (1999) Risk of non-Hodgkin's lymphoma in patients with hepatitis C virus infection. Int J Cancer 80:237–239

Ohshima K, Kimura H, Yoshino T, Kim CW, Ko YH, Lee SS, Peh SC, Chan JK et al (2008) Proposed categorization of pathological states of EBV-associated T/natural killer-cell lymphoproliferative disorder (LPD) in children and young adults: overlap with chronic active EBV infection and infantile fulminant EBV T-LKPD. Pathol Int 58:209–217

Omland LH, Jepsen P, Krarup H, Christensen PB, Weis N, Nielsen L, Obel N, Sorensen HT et al (2012) Liver cancer and non-Hodgkin's lymphoma in hepatitis C virus-infected patients: results from the DANVIR cohort study. Int J Cancer 130:2310–2317

Pantanowitz L, Carbone A, Dolcetti R (2015) Microenvironment and HIV-related lymphomagenesis. Semin Cancer Biol 34:52–57

Paydas S, Kilic B, Yavuz S, Disel U, Tanriverdi K, Sahin B, Burgut R (2003) Anti-HCV and HCV-RNA prevalence and clinical correlations in cases with non-Hodgkin's lymphoma. Am J Hematol 74:89–93

Paydas S, Ergin M, Tanriverdi K, Yavuz S, Disel U, Kilic NB, Erdogan S, Sahin B, Tuncer I, Burgut R (2004) Detection of hepatitis C virus RNA in paraffin-embedded tissues from patients with non-Hodgkin's lymphoma. Am J Hematol 76:252–257

Pellicelli AM, Marignani M, Zoli V, Romano M, Morrone A, Nosotti L, Barbaro G, Picardi A et al (2011) Hepatitis C virus-related B cell subtypes in non-Hodgkin's lymphoma. World J Hepatol 3:278–284

Pinzone MR, Berretta M, Cacopardo B, Nunnari G (2015) Epstein-Barr virus-and Kaposi sarcoma-associated herpesvirus-related malignancies in the setting of human immunodeficiency virus infection. Semin Oncol 42:258–271

Pioltelli P, Gargantini L, Cassi E, Santoleri L, Bellati G, Magliano EM, Morra E (2000) Hepatitis C virus in non-Hodgkin's lymphoma. A reappraisal after a prospective case-control study of 300 patients Lombart Study group of HCV-Lymphoma. Am J Hematol 64:95–100

Polizzotto MN, Uldrick TS, Wyvill KM, Aleman K, Marshall V, Wang V, Whitby D, Pittalunga S, Jaffe E, Millo C et al (2016) Clinical features and outcomes of patients with symptomatic KSHV-associated inflammation: prospective characterization of the Kaposi sarcoma herpesvirus inflammatory cytokine syndrome (KICS). Clin Infect Dis 62:730–738

Quintanilla-Martinez L, Kumar S, Fend F, Reyes E, Teruya-Feldstein J, Kingma DW et al (2000) Fulminant EBV(+) T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. Blood 96:443–451

Rodriguez-Pinilla SM, Barrionuevo C, Garcia J, de los Angeles M, Pajares R, Casavilca S et al (2011) Epstein-Barr virus-positive systemic NK/T-cell lymphomas in children: report of six cases. Histopathology 59:1183–1193

Roizmann B, Desrosiers RC, Fleckenstein B, Lopez C, Minson AC, Studdert MJ (1992) The family Herpesviridae: an update. The Herpesvirus Study Group of the International Committee on Taxonomy of Viruses. Arch Virol 123:425–449

Salama ME, Parham DM, Perkins SL, Bahler DW, Ellison DA (2008) Fatal non-transplant-related Epstein-Barr virus-associated atypical lymphoid proliferations in infants and children: a clinicopathologic study. Pediatr Dev Pathol 11:443–449

Sarid R, Klepfish A, Schattner A (2002) Virology, pathogenetic mechanisms, and associated diseases of Kaposi sarcoma-associated herpesvirus (human herpesvirus 8). Mayo Clin Proc 77:941–949

Schulz TF (2001) KSHV/HHV8-associated lymphoproliferations in the AIDS setting. Eur J Cancer 37:1217–1228

Schulz TF, Cesarman E (2015) Kaposi sarcoma-associated herpesvirus: mechanisms of oncogenesis. Curr Opin Virol 14:116–128

Sevilla DW, El-Mallawany NK, Emmons FN, Alexander S, Bhagat G, Alobeid B (2011) Spectrum of childhood Epstein-Barr virus-associated T-cell proliferations and bone marrow findings. Pediatr Dev Pathol 14:28–37

Silverberg MJ, Lau B, Achenbach CJ, Jing Y, Althoff KN, D'Souza G, Engels EA, Hessol NA, Brooks JT, Burchell AN et al (2015) Cumulative incidence of cancer among persons with HIV in North America. A cohort study. Ann Intern Med 163:507–518

Silvestri F, Barillari G, Fanin R, Pipan C, Falasca E, Salmaso F, Zaja F, Infanti L, Patriarca F, Botta GA, Baccarani M (1997) The genotype of the hepatitis C virus in patients with HCV-related B cell non-Hodgkin's lymphoma. Leukemia 11:2157–2161

Silvestri F, Barillari G, Fanin R, Salmaso F, Pipan C, Falasca E, Puglisi F, Mariuzzi L, Zaja F et al (1998) Impact of hepatitis C virus infection on clinical features, quality of life and survival of patients with

lymphoplasmacytoid lymphoma/immunocytoma. Ann Oncol 9:499–504

Su TH, Liu CJ, Tseng TC, Chou SW, Liu CH, Yang HC, Wu SJ, Chen PJ, Chen DS, Chen CL, Kao JH (2015) Hepatitis C virus infection increases the risk of lymphoid-neoplasms: a population-based cohort study. Hepatology. doi:10.1002/hep.28387

Suarez F, Lecuit M (2015) Infection-associated non-Hodgkin lymphomas. Clin Microbiol Infect 21:991–997

Sung VM, Shimodaira S, Doughty AL, Picchio GR, Can H, Yen TS, Lindsay KL, Levine AM, Lai MM (2003) Establishment of B-cell lymphoma cell lines persistently infected with hepatitis C virus in vivo and in vitro: the apoptotic effects of virus infection. J Virol 77:2134–2146

Talamini R, Montella M, Crovatto M, Dal ML, Crispo A, Negri E, Spina M, Pinto A, Carbone A, Franceschi S (2004) Non-Hodgkin's lymphoma and hepatitis C virus: a case-control study from northern and southern Italy. Int J Cancer 110:380–385

Tashiro M, Tabaru A, Narita R, Sugihara Y, Otsuki M (2003) Biclonal multiple myeloma in liver cirrhosis due to hepatitis C virus infection. J Gastroenterol 38:1017–1018

Tasleem S, Sood GK (2015) Hepatitis C associated B-cell Non-Hodgkin lymphoma: clinical features and the role of antiviral therapy. J Clin Transpl Hepatol 3:134–139

Tomita N, Kodama F, Takabayashi M, Kawano T, Yamaji S, Fujimaki K, Fujisawa S et al (2003) Clinical features and outcome in HCV-positive aggressive non-Hodgkin's lymphoma. Leuk Lymphoma 44:1159–1164

Tsutsumi Y, Ito S, Ogasawara R, Kudo K, Tanaka J, Asaka M, Imamura M (2011) HCV virus and lymphoid neoplasms. Adv Hematol 2011:717951

Utsch GD, Proietti FA, Ramos Ribas JG, Grossi AM, Pinheiro SR, Guedes AC, Carneiro-Proietti ABF (2010) Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev 2010:577–589

Vigano M, Colombo M (2015) Extrahepatic manifestations of hepatitis C virus. Gastroenterol Clin N Am 44:775–791

Viswanatha DS, Dogan A (2007) Hepatitis C virus and lymphoma. J Clin Pathol 60:1378–1383

Wada T, Toga A, Sakakibara Y, Toma T, Hasegawa M, Takehara K, Shigemura T et al (2012) Clonal expansion of Epstein-Barr virus (EBV)-infected gd T cells in patients with chronic active EBV disease and hydroa vacciniforme-like eruptions. Int J Hematol 96:443–449

Wang W, Ti HJ, Nong L, Zhang S, Zhang Y, Li T (2012) Clinical and pathological analysis of three cases of childhood systemic EB virus positive T-cell lymphoproliferative disease (in Chinese). Beijing Da Xue Xue Bao 44:594–598

Weng WK, Levy S (2003) Hepatitis C virus (HCV) and lymphomagenesis. Leuk Lymphoma 44:1113–1120

Yachie A, Kanegane H, Kasahara Y (2003) Epstein-Barr virus-associated T-/natural killer cell lymphoproliferative diseases. Semin Hematol 40:124–132

Yoshii M, Ishida M, Hodohara K, Okuno H, Nakanishi R, Yoshida T, Okabe H (2012) Systemic Epstein-Barr virus-positive T-cell lymphoproliferative disease of childhood: report of a case with review of the literature. Oncol Lett 4:381–384

Zignego AL, Ferri C, Giannini C, La Civita L, Careccia G, Longombardo G, Bellesi G, Caracciolo F, Thiers V, Gentilini P (1997) Hepatitis C virus infection in mixed cryoglobulinemia and B-cell non-Hodgkin's lymphoma: evidence for a pathogenetic role. Arch Virol 142:545–555

Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB (2007) Extrahepatic manifestations of hepatitis C virus infection: a general overview and guidelines for a clinical approach. Dig Liver Dis 39:2–17

Zuckerman E, Zuckerman T, Levine AM, Douer D, Gutekunst K, Mizokami M, Qian DG, Velankar M, Nathwani BN, Fong TL (1997) Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Ann Intern Med 127:423–428

T-Cell Non-Hodgkin's Lymphomas 95

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_95

Abstract

Several types of T-cell non-Hodgkin's lymphomas are characterized by liver involvement, usually in the context of generalized lymphoma disease. The aggressive neoplasm, T-cell prolymphocytic leukemia, showing a proliferation of small- to medium-sized T cells, results in massive bone marrow infiltration and marrow failure but also infiltrates the lymph nodes, liver, and spleen. Hepatic infiltrates mostly involve portal tracts, causing hepatomegaly. Hepatic involvement is a common feature of T-cell large granular lymphocytic leukemia. Liver infiltration is also known for aggressive NK cell leukemia, a systemic proliferation of NK cells almost always associated with EBV infection. The liver may be densely infiltrated by large granular lymphocytes with azurophilic granules. The generalized neoplastic T-lymphocyte process, adult T-cell leukemia/lymphoma, is frequently complicated by focal t diffuse parenchymal or portal tract infiltration of the liver. Other T-cell neoplasms variably involving the liver comprise nasal-type extranodal NK/T-cell lymphoma, hepatosplenic T-cell lymphoma, mycosis fungoides, Sézary syndrome, and peripheral T-cell lymphomas.

T-Cell Prolymphocytic Leukemia

ICD-O Code 9834/3

Introduction

T-cell prolymphocytic leukemia (T-PLL) is an aggressive T-cell leukemia composed of small to medium-sized prolymphocytes having a mature post-thymic T-cell phenotype. The T-PLL cell population is mainly located in the bone marrow and peripheral blood, but other frequent sites are the lymph nodes, liver, and spleen. T-PLL is a rare lymphoproliferative disorder (about 2 %) that involves persons older than 30, with a median age of 65 years at diagnosis. It was first described in 1973 (Catovsky et al 1973). Clinically, most patients present with signs of bone marrow failure (anemia, thrombocytopenia), lymphadenopathy, and splenomegaly, and 20 % of patients have skin involvement. T-PLL rapidly progresses and is clearly more aggressive than B-PLL (Dearden 2009; Lim et al. 2009; Delgado et al. 2012; Tirado et al. 2012).

The tumor cells is a small- to medium-sized lymphoid round cell with a nongranular basophilic cytoplasm and round to ovoid (sometimes irregular) nuclei (Matutes et al. 1986). In 25 % of cases, the small lymphoid cells with nuclei without detectable nucleoli prevail (small cell variant of T-PLL). A small minority of cases (around 5 %) have highly irregular and even cerebriform nuclei. Cytoplasmic protrusions or blebs are characteristic alterations. The cells stain strongly for alpha-naphthyl acetate esterase and acid phosphatase with a dot-like reaction product in the region of the Golgi apparatus. Immunocytochemically, tumor cells express markers of mature peripheral T cells (CD2, CD3, CD7, CD52). In 60 % of patients, the cells are $CD4^+$, and 25 % of patients have $CD4^+/CD8^+$ cells. The oncogene TCL1 is overexpressed.

Liver Involvement

As in other leukemic forms of T-cell neoplasms, the liver can be infiltrated in patients with T-PLL, causing hepatomegaly (Valbuena et al. 2005). The pattern of infiltration in liver biopsies was mostly portal/periportal, with portal tract expansion and sometimes disruption of the limiting plate, while sinusoidal accumulations of leukemic cells were less prominent. In portal tracts, small portal venous branches may be distended with T-PLL cells, and interlobular bile ducts were buried in the dense leukemic infiltrate (Valbuena et al. 2005). In case of massive liver involvement and associated hepatocyte injury, acute hepatic failure can develop (McElreath et al. 2006).

Differential Diagnosis

The main histopathological differential diagnoses comprise hepatic infiltrates of other lymphomas

and leukemias with small- to intermediate-sized cells, such as B-CLL, and reactive lymphocytic lesions (pseudolymphomas; chronic active hepatitis).

Cytogenetic and Molecular Features

The cells of T-PLL belong to a mature post-thymic T-cell phenotype. T-cell receptor genes are clonally rearranged. The most common karyotypic abnormality is inversion of chromosome 14 with breakpoints in the long arm of q11 and q32. A minority of patients (10 %) show a reciprocal tandem translocation t(14;14)(q11;q32), juxtaposing the TRA locus with the oncogenes TCL1A and TCL1B at 14q32.1, associated with activation. TCL is an oncogene that can induce T-cell leukemia in murine models. A part of patients show mutations in ATM (ataxia telangiectasia mutated) on 11q23. In fact, T-PLL is a leukemia that occurs in ataxia telangiectasia. Patients with TCL1A-TCRAD juxtaposition have recurrent loss of the SMARCB1 tumor suppressor gene (Bug et al. 2009). Primary T-PLL exhibits recurrent JAK1 and JAK2 somatic mutations (Bellanger et al. 2014) and showed constitutive activation of the IL2RG-JAK1-JAK3-STAT5B axis promoting deregulation of DNA repair (Kiel et al. 2014).

T-Cell Large Granular Lymphocytic Leukemia

ICD-O Code 9831/3

Introduction

According to the 2008 WHO classification, T-cell large granular lymphocytic leukemia (T-LGL) represents a heterogeneous disorder that reveals persistent (>6 months) increase in the number of peripheral blood large granular lymphocytes (Brouet et al. 1975; McKenna et al. 1977). T-LGL accounts for 2–3 % of mature lymphocytic leukemias. There is no defined age peak, and genders are equally affected, but the disorder is rare before the age of 25 years. T-LGL mainly involves the bone marrow, peripheral blood, liver, and spleen. Conversely, lymph nodes are rarely affected. Most patients with T-LGL display an indolent clinical course, but sequelae may emerge due to the common signs of bone marrow failure, with severe neutropenia with or without anemia, while thrombocytopenia is uncommon. Neutropenia can cause severe infections. Splenomegaly is a frequent physical finding. A part of the patients develop autoimmune disorders such as rheumatoid arthritis (Sheridan et al. 1988; Nichols et al. 1994; Noguchi et al. 1997; Lamy and Loughran 2003; Osuji et al. 2005; Shah et al. 2009; Dearden 2011; Liu and Loughran 2011; Watters et al. 2011; Zhang and Loughran 2012).

Morphology

Normal natural killer cells (NK) are larger granular lymphocytes of the innate immune system and are widely distributed in lymphoid and nonlymphoid organs. Their precursors originate from the bone marrow and go through a complex differentiation process. From bone marrow and lymph nodes, they traffic to the blood, spleen, liver, lung, and other organs (Grégoire et al. 2007). The typical neoplastic cell in T-LGL is a cell with moderate to abundant cytoplasm which shows fine or coarse azurophilic cytoplasmic granules containing perforin and granzyme B. Ultrastructurally, these granules show parallel tubular arrays. Immunocytochemically, the cells are reactive for mature T-cell markers (CD3, CD8; seldom CD4). Over 80 % of cases express CD57 and CD16, and at least 50 % express members of the KIR family. Abnormally diminished or lost expression of CD5 and/or CD7 is common in T-LGL.

Liver Involvement

Involvement of the liver is a common feature of T-LGL and is characterized by infiltration with small- to intermediate-sized granular lymphocytes, which can expand portal tracts but mainly

accumulate in the sinusoidal lumina (Aisenberg et al 1981; Hooks et al. 1981; Kruskall et al. 1982; Pross et al 1982; Thien et al. 1982; Semenzato et al. 1984; Wallis et al. 1985; Vahancik et al. 1988; Agnarsson et al. 1989; Mizuki et al. 1996; Lamy and Loughran 2003). The combination of granular T-cell leukemia/lymphoma and hepatic sinusoidal infiltration was so typical that it was even classified as a "syndrome" (Kruskall et al. 1982). In a study of six liver biopsies (Agnarsson et al. 1989), all samples showed essentially similar features. A prominent intrasinusoidal accumulation of mononuclear cells with scant cytoplasm was identified. In case of dense infiltration, also the portal tracts were involved. The hepatocytes were not altered and not show signs of injury.

Molecular Features

T-LGL shows clonal rearrangement of the alpha/beta T-cell receptor, while gamma/delta T-cell receptor rearrangement is rare. There are no specific karyotypic abnormalities, but several activating pathways for the neoplastic cells have been identified, including pathways utilizing PDGF and IL-15 signaling (Leblanc et al. 2012). STAT3 mutations are highly specific for large granular lymphocytic leukemia (Fasan et al. 2012; Koskela et al. 2012; Jerez et al. 2012), whereby the SH2 dimerization ad activation of STAT3 is mutated. These mutational events lead to deregulation of STAT3 target genes (IFNGR2, BCL2L1, and JAK2), thought to be important elements in the pathogenic cascade of events (Koskela et al. 2012).

Aggressive NK Cell Leukemia

ICD-O Code 9948/3

Introduction

Aggressive natural killer (NK) cell leukemia (ANKL, aggressive NK cell leukemia/lymphoma) is a systemic neoplastic proliferation of NK cells almost always associated with EBV infection and clinically characterized by an aggressive course. It has been discussed whether ANKCL is the leukemic variant of extranodal NK/T-cell lymphoma.

The neoplasm chiefly involves young to middle-aged individuals, mainly in Asia and neotropical countries. The disease invariable involves the bone marrow and the peripheral blood, and the liver and spleen are the inner organs most commonly infiltrated. In part of the patients, the leukemic cell count in blood is low, and lymphomatous manifestations may predominate. Clinically, fever, a leukemic blood picture, signs of bone marrow failure, hepatosplenomegaly, and constitutional symptoms prevail. Coagulopathy, hemophagocytic syndromes, or multiorgan failure can develop (Chan et al. 1997; Cheung et al. 2003; Tse and Liang 2004; Nava and Jaffe 2005; Oshimi 2007; Ryder et al. 2007; Liang and Graham 2008; Semenzato et al. 2012; Lima 2013; Zhang et al. 2013). Etiology and pathogenesis of ANKL are unknown, but a significant role of EBV infection is considered in part of cases (Gogia et al. 2010; Okuno et al. 2012).

Bone marrow and inner organs are densely infiltrated by cells varying in morphology from typical large granular lymphocytes with fine or coarse azurophilic granules to highly atypical elements with irregularly folded nuclei. In the Wright-Giemsa stain, the cytoplasmic granules are prominent organelles. The cytoplasm ranges from pale to lightly basophilic. In bone marrow and inner organs, the tumor cells can form monotonous, cohesive infiltrates that destroy the background tissue. Apoptotic bodies and zonal necrosis are often found. Immunocytochemically, the neoplastic elements are positive for CD2, CD3epsilon, and CD56, and often CD16, but are CD3-negative. The cytoplasm expresses perforin, granzyme B, and granulysin, the latter being detectable in serum owing to elevated levels characterizing ANKL (Sekiguchi et al. 2012). and the majority of cells express Fas ligand. EBV virus can be detected in the tumor cells by various methods, whereby EBV early region protein is usually positive.

Liver Involvement

Focal to diffuse parenchymal infiltration or portal tract infiltration by neoplastic NK cells is a common finding in ANKL, associated with hepatomegaly, liver dysfunction, and jaundice (Boysen et al. 2011; Gao et al. 2013; Zhang et al. 2013; Park 2014). The cellular infiltrates are associated with numerous mitotic figures, apoptotic bodies, and necroses (Chan et al. 1997; Dunkley et al. 1998; Mori et al. 2000; Takai and Sanada 2001; Gao et al. 2013). The infiltrating cells express the typical immunophenotype and show marked apoptosis. Mainly in dense and large infiltrates, necroses develop, often with a zonal morphology. The infiltrates may contain macrophages with signs of erythrophagocytosis (hemophagocytic syndrome). Hemophagocytosis seems to be more frequent in ANKL patients with hepatic involvement. In part of the cases, an angiocentric growth pattern is seen. Multifocal to diffuse liver involvement is often associated with hepatocyte dysfunction and jaundice, the latter being a risk factor for early death (Zhang et al. 2013). In massive liver infiltration, acute liver failure due to hepatocyte loss can develop (Dellon et al. 2006). Apart from the effects of tissue infiltration, liver dysfunction in patients with ANKL is also supposed to be caused by interaction between Fas and Fas ligand (Makishima et al. 2007).

Cytogenetic and Molecular Features

T-cell receptor genes are in germline configuration and, therefore cannot be employed for clonality assessment. A part of the cases reveal clonal del (6)(q21q25) and 11q deletion.

Adult T-Cell Leukemia/Lymphoma

ICD-O Code 9827/3

Introduction

In the 2008 WHO classification, adult T-cell leukemia/lymphoma (ATLL) is defined as a peripheral T-cell neoplasm most frequently consisting of highly pleomorphic T lymphoid cells. ATLL, first described in 1977, is in part caused by the human T-cell leukemia virus type1 (official designation in viral taxonomy: human T-lymphotropic virus 1; HTLV-1), a retrovirus (Ohshima 2007). At diagnosis, ATLL is usually widely disseminated (high stage), with extensive nodal and organ involvement and leukemic presentation (review: Tsukasaki 2012). HTLV-1 (human T-cell lymphotropic virus 1) plays an important etiologic role in ATLL (see below).

Epidemiology and Clinical Features

Epidemiologically, ATLL prevails in certain endemic regions, above all Southwestern Japan, the Caribbean Basin, and Central Africa (Gessain and Cassar 2012). A nonendemic variant is known from Europe and North America (Foucar et al. 1985). The neoplastic cells infiltrate a wide range of tissues and organs, albeit lymph nodes and skin are the most commonly affected structures. Frequent additional sites are the bone marrow, spleen, liver, gastrointestinal tract, and central nervous system. Males are slightly more often affected, the age range at diagnosis being 20 to more than 80 years, with an average of 58 years. ATLL occurs in several clinical variants, i.e., acute, lymphomatous, chronic, and smoldering ATLL (Shimoyama 1991). In the acute phase of the disease, leukemia is frequent, associated with a skin rash, lymphadenomegaly, hepatosplenomegaly, and constitutional signs of disease.

In the acute variant of ATLL, hypercalcemia with or without lytic bone lesions is a common complication. A part of the patients display T-cell immunodeficiency with typical infections and infestations, such as *Pneumocystis carinii* and *Strongyloides stercoralis*. Lymphomatous ATLL is characterized by marked lymph node disease in the absence of leukemia. Ulcerated skin lesions are typical. The chronic form of ATLL is often accompanied by an exfoliative skin rash, and leukemia is rare. Patients with smoldering ATLL have an elevated percentage of peripheral blood T lymphocytes, but the WBC count is normal.

Skin and pulmonary lesions occur, but hypercalcemia is lacking.

ATLL is characterized by a broad range of neoplastic cell morphologies, comprising pleomorphic small, medium and large cell types, anaplastic morphology, and an uncommon form resembling angioimmunoblastic T-cell lymphoma. In most cases, neoplastic cells are medium-sized to large, frequently with marked nuclear pleomorphism, coarse chromatin structure, and prominent nucleoli. In part of the cases, highly atypical giant cells with polylobulated nuclei develop. These cells may resemble Reed-Sternberg cells with "kissing nuclei" (the Hodgkin-like ATLL), mostly seen in lymph nodes. Multilobated (polylobulated) tumor may circulate as leukemic cells (so-called flower cells). Immunohistochemically, the neoplastic cells express T-cell lineage markers (CD2, CD3, CD5) and often FOXP3 and CCR4, the latter two being markers of regulatory T cells. Most cases are $CD4^+/CD8^-$, but a minority show $CD8^+/CD4^-$ or $CD4^+/CD8^+$ phenotypes. Large transformed T cells may be CD30 positive, but they consistently lack ALK expression. ATLL cells show T-cell receptor rearrangement. Neoplastic cells display integration of HTLV-1, lacking in healthy carriers.

Liver Involvement

As ATLL is a generalized neoplastic disease, the liver is often involved (Hoshi et al. 1988; Taniguchi et al. 1993; Yamada et al. 1997; Tong et al. 2004; Kawamura et al. 2006; Powell et al. 2006; Takasaki et al. 2007). In ATLL, hepatic involvement is more frequent than in other lymphomas. There was a more frequent palpable hepatomegaly, higher total bilirubin, GOT, GPT, LDH, and alkaline phosphatase values, and among 36 autopsied cases out of 111, invasion of the liver was confirmed in 22 patients (Yamada et al. 1997). Concomitant involvement of bone marrow and visceral organs, including the liver, worsens prognosis (Takasaki et al. 2007). Hepatic infiltration is usually diffuse or multifocal, but a metastatic pattern also occurs (Tong et al. 2004). ATLL with blast crisis can be associated with acute liver failure (Kawamura et al. 2006; Powell et al. 2006). In this severe clinical situation, liver biopsy revealed massive infiltration with atypical T cells characteristic of ATLL and hepatic necrosis (Powell et al. 2006). It can be surmised that, similar to other situations with massive leukemic liver infiltration, dense accumulation of tumor cells in sinusoids and portal tracts can critically compromise portal venous inflow and hepatic sinusoidal microcirculation. In case of marked humoral hypercalcemia characterizing ATLL, extensive metastatic calcification of several organs may ensue, the liver being involved in 25 % (Senba and Kawai 1991). Multiorgan failure due to calcification may develop, including massive calcifications in the liver (Kumamoto et al. 1998). ATLL-associated hypercalcemia is related to upregulation and activation of several factors involved in bone demineralization, specifically the osteoclast differentiation factor receptor activator of nuclear factor-kB ligand (RANKL), its receptor RANK, and its decoy receptor osteoprotegerin/OPG. In very rare situations, adult T-cell lymphoma with anaplastic features can develop as an apparently primary tumor in the liver, forming nodular lesions mimicking metastatic disease (Cerban et al. 2012).

Etiology and Pathogenesis

Human T-cell lymphotropic virus 1 (HTLV-1) is a central etiologic agent for ATLL (Yamagishi and Watanabe 2012), but does not suffice for neoplastic transformation of target T cell to take place. HTLV-1 is a member of the viral genus *Deltaretrovirus*, subfamily *Orthoretrovirinae*, and family *Retroviridae*. Other members of *Deltaretrovirus* comprise HTLV-2, HTLV-3, and HTLV-4; the simian counterparts STLV-1,STLV-2, and STLV-3; and bovine leukemia virus (BLV). HTLV-1 and STLV-1, the latter causing disease in Old World monkeys and great apes, seem to have originated from a common ancestor. HTLV-1 contains an enveloped virion that is spherical to pleomorphic and is about 80–100 nm in diameter. HTLV-1 has a complex genome that contains,

apart from retroviral structural genes gag, pol, and env, several regulatory genes (Tax and Rex) and accessory genes (p12, p13, p30, and HBZ). HTLV-1 naturally infects humans, but experimental infections showed that also several rodents and New World monkeys can be infected. In tissue culture, HTLV-1 can infect several cell types, including T- and B-lymphocytes, dendritic cells, and fibroblasts, but only T cells can be transformed by this virus, mainly $CD4^+$ helper cells and much less efficiently $CD8^+$ cells. HTLV-1 exists in two subgroups in endemic Japan, i.e., the transcontinental and the Japanese subgroups (Otani et al. 2012). Persons with ATLL are exposed to HTLV-1 early in life, and lymphomagenesis requires a long time period. HTLV-1 is transmitted by breast milk, sexual transmission, and through contact with infected blood and blood products. It is estimated that about 20 million persons are infected by HTLV-1 worldwide. The lymphoma yield following viral infection is relatively low, in that ATLL is estimated to develop in 2.5 % of HTLV-1 carriers in Japan. Sporadic cases of ATLL often seem to refer to patients originally stemming from an endemic area.

Extranodal NK/T-Cell Lymphoma, Nasal Type

ICD-O Code 9719/3

Introduction

Extranodal NK/T-cell lymphoma of the nasal type (ENNKT-NT) is a predominantly extranodal neoplasm composed of either classical NK cells or cells with a cytotoxic T-cell phenotype. ENNKT-NT tends to induce vascular damage associated with often extensive necroses and is associated with EBV. Previously, the lymphoma had been termed ulceronecrotic proliferative lesion of the upper airways, progressive lethal granulomatous ulceration of the nose, granuloma gangraenescens, Stewart's granuloma, necrotizing granulomatous process of the midface, polymorphic reticulosis, non-healing midline granuloma, idiopathic midline destructive disease, malignant midline reticulosis, malignant medio-facial pseudogranuloma, lethal midline granuloma, centrofacial malignant granuloma, centrofacial reticulosarcoma with necrotic gangrenous evolution, and angiocentric immunoproliferative lesion. Stewart (1933) described ten such cases in detail, still the classical source on the subject. The lesion was suggested to lymphoma in 1966 (Eichel et al. 1966), confirmed in 1977 (Michaels and Gregory 1977).

The lymphoma predominantly occurs in Asian countries and in Meso- and South America, and males predominate. The most commonly involved tissues are those of the upper aerodigestive tract, particularly paranasal sinuses, nasal cavity, and nasopharynx. In addition, the skin, gastrointestinal tract, and testis are well-documented sites. In the nasal/midface region, the neoplasm can cause massive destruction followed by rapid spread to other tissues (extranasal NK/T-cell lymphomas). Patients usually have high-stage disease at diagnosis, with involvement of multiple sites.

Morphology

Typically, the neoplastic cells grow with an angiocentric and angiodestructive growth pattern, associated with fibrinoid vascular changes, apoptosis, and coagulative (infarctoid) necrosis caused by vascular obstruction/ischemia and cytokine/chemokine effects. In a series of 73 patients, an angiocentric and angiodestructive pattern was found in 69 % of patients (Li et al. 2013). The morphology of cells ranges from small cells to large and anaplastic cells. Tumors with intermediate cells and those with a mixture of small and large cells prevail. The cytoplasm is typically pale. Many tumor cells have irregularly shaped, folded, or elongated nuclei, with numerous mitotic figures. Nucleoli are usually small.

Immunohistochemically, the leading cell is positive for CD2, CD56, and cytoplasmic CD3 epsilon and negative for surface CD3. Many cells

express perforin and granzyme B. Few cases are positive for CD30 and CD7. The tumor typically express EBV.

Liver Involvement

In the course of the often rapid multiorgan spread, the liver can be involved (Michaels and Gregory 1977; Chappel and Powell 1981; Hatta et al. 1993; Ullrich et al. 1999; Chang et al. 2002; Ng et al. 2004; Kim et al. 2008). In a study of 18 patients, liver involvement was found in 92.8 % (Hatta et al 1993). Hepatic involvement may cause liver dysfunction (Monma et al. 2009). As far as it is known, the cells types infiltrating the liver are the same as those encountered in midfacial tumors, but it is unknown whether the angiodestructive phenotype is also seen in the liver. In one case reported by Michaels and Gregory (1977), the liver sinusoids showed infiltration by atypical lymphoid cells, some of them multinucleated. In a second case, the authors observed infiltration of portal tracts and parenchyma by groups of cells similar to those seen in lymph nodes and spleen.

Cytogenetic and Molecular Features

T-cell receptor gene is in germline configuration, but in a minority of cases, there is clonal T-cell receptor rearrangement, representing the cases with cytotoxic T-lymphocyte phenotype. A variety of nonspecific cytogenetic aberrations are known. By means of array-based comparative genomic hybridization, numerous chromosomal gains and losses were detected, with several critical candidate genes (Sun et al. 2014). Genes deregulated in this lymphoma include PRDM1/positive regulatory domain containing 1, ATG5, AIM1, FOXO3, and HACE1 (Huang et al. 2013; Liang et al. 2014).

Hepatosplenic T-Cell Lymphoma

ICD-O Code 9716/3

Introduction

In the 2008 WHO classification, hepatosplenic T-cell lymphoma (HSTL) is defined as an extranodal and systemic lymphoid neoplasm derived from cytotoxic T cells, most often of the gamma/delta T-cell receptor type. The leading neoplastic cell is a medium-sized element that tends to populate vascular sinusoids in the bone marrow, spleen, and liver. The skin is rarely affected. Overall, HSTL is a rare lymphoma that accounts for less than 1 % of all non-Hodgkin's lymphomas. Adolescents and young adults are most often affected (median: 35 years of age), with a male predominance. Up to 20 % of cases develop in the setting of chronic immune suppression, specifically long-term immunosuppressive therapy for solid organ transplantation. In children, HSTL has been reported following azathioprine therapy and infliximab therapy for Crohn's disease. Two main variants of HSTL can be distinguished, i.e., gamma/delta and the rarer alpha/beta HSTL (Wei et al. 2005; Vega et al. 2007; Shale et al. 2008; Falchook et al. 2009; Roelandt et al. 2009; Schmidt and Lim 2009; Thai and Prindiville 2010; Hocker et al. 2011; Kotlyar et al. 2011; Travert et al. 2012).

Hepatosplenic Gamma/Delta T-Cell Lymphoma

HSTL gamma/delta is recognized as a distinct subset of post-thymic peripheral T-cell lymphoma, characterized by the involvement of the spleen, liver, and often the bone marrow, but with no or little lymphadenopathy, usually following an aggressive course. Hepatosplenomegaly may be massive, due to dense tumor cell infiltration (Gaulard et al. 1986, 1990; Farcet et al. 1990; Wong et al. 1995; Cooke et al. 1996; Salhany et al. 1997a; Weidmann et al. 2000; Rossbach et al. 2002;; Ferreri et al. 2012; Qi et al. 2012; reviews: Sallah et al. 1997; Belhadj et al. 2003; Gaulard et al. 2003). Only few patients under 15 years of age have been reported (Weidmann et al. 2000; Rossbach et al. 2002; Gassas et al. 2004;). Bone marrow involvement is found

in approximately two thirds of the patients at diagnosis (Weidmann et al. 2000), but may be more frequent or even a constant feature as based on newer studies (Belhadj et al. 2003). The improvement of bone marrow diagnostics by use of efficient immunotyping has led to a decrease of splenectomies for diagnostic purposes (Belhadj et al. 2003). In a small number of patients, malignant cells are detectable in the peripheral blood either at presentation or later in the course of disease (Mastovich et al. 1994; Sallah et al. 1997). In contrast to other gamma/delta T-cell lymphomas, HSTL gamma/delta seems to be less heterogeneous (de Wolf-Peeters and Achten 2000). HSTL gamma/delta can occur as a complication of immunosuppression, e.g., subsequent to solid organ transplantation (Ross et al. 1994; Hanson et al. 1996; François et al. 1997; Salhany et al 1997b; Kraus et al. 1998; Roncella et al. 2000; Khan et al. 2001; Steurer et al. 2002; Belhadj et al. 2003). In part of these patients, HSTL gamma/delta manifests as late-onset posttransplant lymphoproliferative disorder (Wu et al. 2000). Very rarely, gamma/delta HSTL develops as a pregnancy-associated lymphoma (Niitsu et al. 2004); development of lymphoma during a pregnancy is as such rare, occurring in only 1 of 1,000–6,000 deliveries, the majority of these lesions being Hodgkin's lymphoma or B-cell lymphomas (Gelb et al. 1996; Pohlman and Macklis 2000; Glaser et al. 2012). Clinically, hepatosplenomegaly, sometimes marked, is a constant feature. Thrombocytopenia is frequent, and a part of the patients develop hemophagocytic syndrome (Kadin et al. 1981; Jaffe et al. 1983; Sun et al. 1990; Nosari et al. 1999; Côté-Daigneault and Bernard 2011). Thrombocytopenia may be associated with hemolytic anemia (Evans' syndrome; Motta et al. 2002). In a minority of patients, lymphoma-associated coagulopathy developed (Jahangiri and Mahesh 2010; Perini and Pro 2010). Apart from the now well-recognized, typical presentation, HSTL gamma/delta may come in variants with a different tissue expression or different evolution. Thus, this NHL may show an angiocentric growth pattern (Zabernigg et al. 1996) HSTL gamma/delta can undergo a blast-like terminal transformation (Mastovich et al. 1994), exhibit transformation into a prolymphocytic lineage (Sohn et al. 1997), or undergo a leukemic course after renal transplantation (Steurer et al. 2002).

Hepatosplenic Alpha/Beta T-Cell Lymphoma

In addition to the gamma/delta variant, there is a group of hepatosplenic T-cell lymphomas exhibiting an *alpha/beta lineage* (Lai et al. 2000; Suarez et al. 2000; Kumar et al. 2001; Macon et al. 2001; Dong et al. 2003; Nagai et al. 2010). The relative frequency and the prognostic relevance of the gamma/delta versus the alpha/beta phenotype in HSTL remain unknown, but the alpha/beta variant is thought to be rarer than its gamma/delta counterpart. This NHL may be associated with thrombocytopenia (similar to the gamma/delta variant) and with hemolytic anemia (Lai et al. 2000). In a study of 14 patients, 11 were female and 3 were male, with a median age of 36 years (HSTL gamma/delta: 34 years in one study). The clinical presentation was similar to that described previously for the gamma/delta variant of HSTL, except for the female preponderance and the different age distribution (5 patients younger than 13 years and 5 patients older than 50 years of age). The neoplastic cells in all these 14 NHLs were cytotoxic alpha/beta T cells. Three cases were associated with EBV, and alpha/beta HSTL has been observed following azathioprine therapy (Rashidi et al. 2012).

Liver Involvement in Hepatosplenic T-Cell Lymphomas

In liver biopsies, atypical small- to medium-sized cells occupy the sinusoids in variable density, mostly with sparing of the portal tract spaces (Farcet et al. 1990; Belhadj et al. 2003; Taguchi et al. 2004). The preferentially sinusoidal accumulation of the neoplastic cells has been highlighted in the original description of HSTL

gamma/delta already ("sinusal/sinusoidal localization of malignant cells"; Farcet et al. 1990), but sometimes this sinusoidal infiltration is sparse (Coventry et al. 1999). A sinusoidal pattern of infiltration also prevails in the alpha/beta variant of HSTL (Dong et al. 2003), but liver infiltration was largely periportal in four cases (Macon et al. 2001). In case of portal tract infiltration, a part of the neoplastic cells also infiltrate the periportal zone 1 of the liver lobule (Khan et al. 2001). The morphology of the cells is characterized by monomorphy and the presence of round or slightly irregular small- to medium-sized nuclei containing rather prominent nucleoli. A moderate amount of slightly basophilic or amphophilic cytoplasm is observed. In some of the patients, medium to large cells are found with signs of increased cellular pleomorphism, and predominantly large cell variants of HSTL gamma/delta have been reported (Khan et al. 2001). Probably caused by the cells' contact with the endothelia of the sinusoids, a part of the neoplastic cells display an elongated shape and dendritic projections. The density of neoplastic cells accumulating in the sinusoids is sometimes striking and leads to morphologic signs of a sinusoidal block. Small clusters of lymphoma cells sometimes seem to penetrate the perisinusoidal space and appear to locate within the suprajunctional space between two hepatocytes. Furthermore, tumor cells apparently situated in the perisinusoidal space are in close physical contact with hepatic stellate cells. As hepatic infiltration can be associated with a slight degree of perisinusoidal matrix increase, one may surmise that a signaling interaction might take place between the two cell systems involved.

The typical phenotype of the target cells is reactivity for CD2, CD3/CD3 epsilon, CD5, CD7, CD56, absence or presence of CD4 and/or CD8, absence of CD16 and CD57, and positivity for the gamma/delta TCR, mostly in the absence of an activated cytotoxic cell phenotype (Wong et al. 1995; Sadahira et al. 2003; Belhadj et al. 2003), although cases with a cytotoxic phenotype (expression of perforin, granzyme B, TIA-1) are known as well (Salhany et al. 1997). It has been shown that the cells in HSTL can express epithelial membrane antigen (EMA; Ohno et al. 1993) and CD26, the transmembrane serine aminopeptidase, dipeptidyl peptidase IV (Ruiz et al. 1998). This is of interest for the pathogenesis of lymphoma spread, because CD26 participates in ECM protein, and specifically collagen, interactions. Furthermore, the serine protease, granzyme M, is preferentially expressed in gamma/delta T-cell lymphomas (Krenacs et al. 2003).

The sinusoidal infiltration is sometimes associated with pericentral parenchymal necrosis (Khan et al. 2001). This may be caused by decreased sinusoidal blood flow owing to obstruction by lymphoma cells, i.e., an ischemic pericentral hepatocyte damage. HSTL gamma/delta can result in hepatic failure, eventually requiring liver transplantation (Blakolmer et al. 2000; Petersen-Benz et al. 2003). In one case of HSTL alpha/beta, biopsy revealed necrotizing hepatitis and the presence of a low-density infiltrate of atypical lymphocytes (Petersen-Benz et al. 2003). A similar situation has been reported by another group, again with extensive liver necrosis (Schwartz et al. 1998). Rarely, HSTL clinically mimics acute hepatitis, with markedly elevated serum aminotransferases and reduced prothrombin activity (Perfetto et al. 2003).

Cytogenetic Features, EBV Expression, and Molecular Mechanism

Cytogenetically, many patients reveal an isochromosome 7q as a primary and consistent aberration (Wang et al. 1995; Yao et al. 1996; Jonveaux et al. 1996; François et al. 1997; Alonsozana et al. 1997; Rossbach et al. 2002; Wlodarska et al. 2002), sometimes in association with trisomy 8 (Coventry et al. 1999; Chin et al. 2004). EBV infection is rarely encountered and may, if present, indicate a late event in posttransplant HSTL gamma/delta (Roncella et al. 2000). In a study of 21 patients, the median age at presentation was 34 years; 21/21 had splenomegaly, 15/21 hepatomegaly, and 20/21 showed thrombocytopenia. 18/21 of the patients were negative for EBV. 9/21 showed isochromosome arm 7q. Of these

21 patients, eight patients had previously undergone kidney transplantation or had a history of systemic lupus erythematodes, Hodgkin's disease, or malaria. The prognosis was poor; median survival time was 16 months, and all but two patients ultimately died despite consolidative or salvage high-dose therapy (Belhadj et al. 2003). The relationship between HSTL and EBV infection has been studied in detail (Ohshima et al. 2000).

Of four cases of alpha/beta HSTL analyzed cytogenetically, two revealed an isochromosome 7q (Macon et al. 2001). Isochromosome 7q in the alpha/beta variant has been detected in other reported patients (Lai et al. 2000; Suarez et al. 2000). The cells of alpha/beta HSTL may be immunoreactive for S100 protein (Dong et al. 2003).

Subcutaneous Panniculitis-Like T-Cell Lymphoma

ICD-O Code 9708/3

Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is defined as a T-cell lymphoma with a cytotoxic T-cell phenotype, predominantly infiltrating the subcutis of diverse body regions. Typically, the subcutaneous infiltrates are associated with adipose tissue necrosis (fat necrosis) with associated inflammatory reactions (panniculitis-like lesions; Gonzalez et al. 1991; Kumar et al. 1998). The neoplastic cells show T-cell receptor rearrangement, but lesions with rearrangement of the gamma/delta T-cell receptor are excluded from the SPTCL group and are now classified as cutaneous gamma/delta T-cell lymphoma (Go and Wester 2004; Hoque et al. 2003; Ghobrial et al. 2005; Willemze et al. 2008; Huang et al. 2009; Lü et al. 2010; Bakhshi et al. 2011).

SPTCL is rare and accounts for less than 1 % of all non-Hodgkin's lymphomas. 20 % of the patients are younger than 20 years at diagnosis, and females are slightly more often affected. Extremities and trunk are most frequently involved. The skin lesions are papules or nodules of up to several cm diameter, sometimes painful, usually without ulceration, as the lesions are deep-seated, but in case of large necrosis, upper parts of the skin undergo damage as well and become ulcerated. In addition to subcutaneous lesions, 20 % of the patients present with autoimmune features, most often system lupus erythematodes. Systemic signs of disease are common, as are abnormal liver function tests (Takeshita et al. 2004; Zhang et al. 2007). Among 21 patients with SPTCL, liver dysfunction with elevated serum enzymes was detectable in 52 % of patients (Ghobrial et al. 2005). Fifteen to 20 % of patients were reported to have hemophagocytic syndromes, which is an adverse prognosticator. A minority of patients show hepatosplenomegaly. Extranodal disease may involve the lung (Ma et al. 2005) and the liver (see below).

Morphology

The neoplastic T cells are of intermediate to large size and form an infiltrate within adipose lobules, without epidermotropism. The tumor cells are intermingled with histiocytes/macrophages containing apoptotic debris and lipid droplets, the latter from necrotic adipocytes. Nuclei are irregularly shaped and hyperchromatic, and the cytoplasm is usually pale. The tumor cells form typically rims around large adipocytes. Immunohistochemically, the cells are usually CD8-positive and contain perforin and granzyme B. They have a mature T-cell phenotype with expression of alpha/beta T-cell receptor.

Liver Involvement

From its subcutaneous sites, SPTCL can spread to lymph nodes and remote organs, including the liver. Extranodular organ involvement was identified in 7 out of 19 patients with SPTCL (Huang et al. 2009). In patients with advanced disease and extracutaneous and extranodal disease, the liver can be infiltrated (Huang et al. 2009; Babb

et al. 2011; Bakhshi et al. 2011). Tumor-associated hepatomegaly was observed part of patients with SPTCL (Yi et al. 2013). Liver involvement can present as small and multiple focal infiltrates or a diffuse infiltrate of atypical T cells, but it was also noted in the form of discrete nodules within the liver substance (Bakhshi et al. 2011).

Mycosis Fungoides

ICD-O Code 9700/3

Introduction

In the 2008 WHO classification, mycosis fungoides (MF; formerly also termed, "granuloma fungoides") is defined as an epidermotropic, primary cutaneous T-cell lymphoma composed of a neoplastic lineage of small- to medium-sized T cells with cerebriform nuclei. The postulated cell of origin is a mature skin-homing $CD4^+$ T-cell. MF accounts for about 50 % of all cutaneous lymphomas and mainly affects adults but also occurs in the pediatric age group and in adolescents. Males are twice as often affected than females. In the first stages of the disease, diverse cutaneous regions are involved, but in advanced stage disease, MF tends to spread to lymph nodes and inner organs, including the lung, spleen, and liver (Toro et al. 1997; Girardi et al. 2004; Zinzani et al. 2008; Beyer et al. 2011; Wong et al. 2011; Quaglino et al. 2012; Talpur et al. 2012; Vora et al. 2012). Stage-specific involvement of the blood occurs in high-stage disease. Mainly in the tumor stage, so-called transformation may ensue, defined as the presence of more than 25 % of large lymphoid cells in the dermal infiltrates. Large-cell transformation is associated with an aggressive course and shorter survival (Benner et al. 2012; Herrmann and Hughey 2012).

The classical form of MF is also termed Alibert-Bazin type of MF. Apart from this type, various other forms of MF or disorders related to MF are known. A rare variant of MF is pagetoid reticulosis with two distinct distribution patterns and clinical courses. One variant shows a localized patch or plaque, usually solitary on the extremities, containing intraepidermal proliferations of neoplastic T cells in a pagetoid distribution, typically affecting middle-aged and elderly men. This form of pagetoid reticulosis has a bland course and is called Woringer-Kolopp disease (Woringer and Kolopp 1939; Degreef et al. 1976; Braun-Falco et al. 1979; Oliver and Winkelmann 1989; Haghighi et al. 2000; Lee et al. 2008; Lichte et al. 2009; Matsuzaki et al. 2009; Martin et al. 2010; Koga et al. 2011; Mendese et al. 2012; review: Cribier 2005). The second variant reveals a more generalized presentation with diffuse cutaneous involvement and a more aggressive clinical course. This is Ketron-Goodman disease, which typically involves the trunk and extremities and probably represents an aggressive cutaneous T-cell lymphoma (Sullivan 1958; Mielke et al. 1989; Nakada et al. 2002; Carlesimo et al. 2009; review: Steffen 2005).

The pathogenetic pathways leading to MF are only partially elucidated. Malignant T cells forming the neoplastic population in MF have the capacity to home to the skin, a process facilitated by the expression of chemokines, cytokines, adhesion molecules, and defective apoptosis. The skin microenvironment with its epidermal-mesenchymal interactome and the presence of skin-associated immune cells, including cutaneous T cells, follicular helper T cells, and dendritic cells, play a supportive role for the development of MF (review: Jawed et al. 2014).

Clinical Features

Early disease if characterized by the development of cutaneous patches, papules, and plaques, later followed by tumor formation (the tumorous stage). In some patients, distinct exophytic tumor lesions develop (fungiform mycosis). This evolution, which may take years, had led to a clinical staging system.

In the stage of patches, papules, and plaques, layers of the epidermis show a band-like infiltrate of lymphocytes and histiocytes. In this stage, few lymphocytes typically display irregular, indented

(cerebriform) nuclei. In plaques, the epidermotropism is more pronounced, and in a minority of cases, small clusters of atypical T cells are situated within the epidermis (Pautrier microabscesses; in fact, these are not true abscesses, because the lesions consist of atypical T cells and not neutrophils). As the process continues, more and more infiltrates also occupy deeper layers of the skin, causing tumorous swellings (the tumorous stage). In this stage, greater numbers of highly atypical large tumor cells with cerebriform nuclei and blast cells with prominent nuclei are present (Berman 1940; Sausville et al. 1988). Clinically and histomorphologically, several subtypes or variants of MF have been defined, in addition to Woringer-Kolopp disease and Ketron-Goodman disease. They include hypopigmented MF, hyperpigmented MF, annular hypopigmented MF, erythrodermic MF, papular MF, erysipelas-like MF, interstitial MF, ichthyosis-like MF, poikilodermatous MF, purpuric MF, syringotropic MF, erythema annulare centrifugum-like MF, cutis laxa-like MF, invisible MF, granulomatous MF, pityriasis lichenoides-like MF, solitary (unilesional) MF, bullous MF, vesicular MF, and vesiculobullous MF(Abeldaño et al. 2011). These different presentations may be associated with patterns of biology of disease. For example, bullous MF (mycosis fungoides bullosa) represents a particularly aggressive form of MF and is associated with poor prognosis (Kneitz et al. 2010). Conversely, solitary MF (Ally et al. 2012) and annular hypopigmented MF (Uhlenhake and Mehregan 2012) appear to have a good prognosis. Folliculotropic MF can be combined with granulomatous slack skin. A part of the variants have demonstrated an abnormal immune phenotype of the neoplastic cells. Hyperpigmented MF is an unusual variant with a frequent $CD8^+$ phenotype (Pavlovsky et al. 2012). Folliculotropic MF was rarely found to undergo large-cell transformation with $CD30^+$ cells associated with eosinophilia and unfavorable course (Ishibashi et al. 2010). MF has been found in combination with lymphomatoid papulosis, and this associated seems to confer a more favorable outcome (Gallardo et al. 2004).

Liver Involvement

Generally, 75 % of patients with diverse types of cutaneous T-cell lymphomas, including MF, have extracutaneous disease, the most frequently infiltrated organs being the liver, spleen, and lung, which contain lymphoma in 38–66 % of autopsied patients (review: Huberman et al. 1980). In MF, visceral involvement is almost always associated with lymph node involvement and involvement of the spleen (Rappaport and Thomas 1974). In MF there was hepatic infiltration in an average of 45 % of these patients (Farber 1939; Epstein et al. 1972; Long and Mihm 1974; Rappaport and Thomas 1974; Variakojis et al. 1974; Griem et al. 1975; Levi and Wiernik 1975; Rodin et al. 1976; Rappaport 1977; Huberman et al. 1980; Doyle and Winkelmann 1981; Trope et al. 1985; Thomsen and Wantzin 1987; Liu et al. 2012). In part of the studies, the rate of liver involvement was higher (53 %; Rappaport and Thomas 1974). In a series of 49 consecutive cases of MF and Sézary syndrome, 18 % of the patients had visceral involvement (Bunn et al. 1980). Infiltration of the liver can cause hepatic failure (Albukerk and Duffy 1973; Shibata et al. 2009).

In an analysis of 17 MF patients who had microscopic evidence of MF infiltrates in the liver, 11 showed gross involvement. Seven of these had multiple nodules ranging from 0.1 to 5.5 cm, two patients had solitary nodules measuring 2 cm and 5 cm, and two were described as having tumor infiltrates. In 11 cases with gross liver involvement, the mean weight of the liver was 2004 g (range: 1,200–3,030 g), but liver weights exceeding 3 kg were also noted in cases with only microscopic involvement (Rappaport and Thomas 1974). MF of the liver presents in the form of whitish nodules with a size of dew mm to pea size. Sometimes, lentil-shaped nodules are noted close to the liver surface, often with a red, hyperemic rim. Peripheral nodules with radiating capsular folds have also been described (review of the old literature: Gruber 1930).

The liver is involved by circulating abnormal T cells in stages III and IV and parenchymal infiltration in stage IV (Table 1). The liver is characterized by a highly variable mode of tumor cell

Table 1 Patterns of liver involvement in mycosis fungoides

Accumulation of neoplastic circulating T cells in sinusoids and other hepatic vessels
Portal tract infiltrates with or without involvement of periportal zone 1
Tumorous nodular involvement
Diffuse hepatic infiltration

infiltration, more so than other involved visceral organs (Rappaport and Thomas 1974).

In part of patients, histology of the liver in MF involvement showed an infiltration of portal tracts, with encroachment upon the parenchyma of zone 1, with small atypical lymphocytes, sometimes admixed with neutrophils. Some of the lymphoid cells are larger and exhibit indented or cerebriform nuclei, as in the cutaneous/epidermal infiltrates (Rappaport 1977). In other patients, involvement is seen in the form of tumorous nodules that have no relation to portal tracts or other anatomical structures, and there are also patients who show a diffuse hepatic infiltration, similar to infiltrations seen in myeloproliferative disorders (Rappaport and Thomas 1974). Atypical T cells are also found in sinusoids and within hepatocyte plates (Albukerk and Duffy 1973). In several instances, only very rare tumor cells were found between liver cell plates, associated with sparse portal tract infiltrates containing few large cells with atypical dense nuclei (Variakojis et al. 1974). Diagnosis is difficult in such cases and requires detailed immunohistochemistry, even in the presence of rare atypical cells with indented or cerebriform nuclei. Microvascular changes of the liver have been observed in MF, including fibrinoid necrosis of central veins (Albukerk and Duffy 1973). MF can also infiltrate the walls of the extrahepatic bile ducts. In one case, mucosal infiltration of extrahepatic bile ducts caused biliary obstruction (Madsen et al. 1999).

Immunocytochemically, the tumor cells are $CD5^+$, $CD4^+$, and $CD8^-$. Only few cases are $CD8^+$ (Cho et al. 2012; Kasugai et al. 2012; Yamashita et al. 2012). Subsets of cells express clusterin, and this expression pattern correlates with stage and presence of large cells in MF (Chandra et al. 2009). A part of the cells have the features of follicular center helper T cells (Meyerson et al. 2013) and are reactive for PD-1 (Park et al. 2014). CD4/CD8 double-negative MF with CD279 expression has been suggested as disease of follicular helper cells (Kempf et al. 2012). Large cells in the transformation phase (see above) are $CD30^+$. In the Woringer-Kolopp variant of MF, T cells may be $CD4^+$ and $CD8^+$ (Zengin et al. 2008).

Cytogenetic and Molecular Features

Many cases show complex karyotypic aberrations, but above all in advanced stages, probably linked to increasing genomic instability of the neoplasm. Most abnormalities are, therefore, nonspecific. T-cell receptor genes are clonally rearranged. It was reported that constitutive activation of STAT3 and inactivation of PTEN and CDKN2A/p16INK4a are associated with disease progression. Tumor-stage MF has a characteristic molecular signature (van Kester et al. 2012). MF cells have a complex constellation of proliferative activity vs. cell loss through apoptosis. Almost all MF lesions were Fas ligand-negative, and in two thirds of lesions, Fas expression is low. Twenty five percent showed the phenotype, Fas high, and FLICE/Fas pathway inhibitor high, suggesting defective apoptotic pathways in MF (Stutz et al. 2012). Part of MF showed mutations in PLCG1 (phospholipase C gamma 1), associated with increased downstream signaling toward nuclear factor of activated T cells (NFAT) and nuclear NFAT immunostaining (Vaqué et al. 2014).

Sézary Syndrome

ICD-O Code 9701/3

Introduction

In the 2008 WHO classification, Sézary syndrome (SS) is defined by the triad of erythroderma,

generalized lymphadenopathy, and the presence of a neoplastic T-cell neoplasia with cerebriform nuclei (the Sézary cells) in the skin, lymph nodes, peripheral blood, and rarely inner organs. Additional diagnostic criteria are a Sézary cell count of at least 1,000 cells/mm^3, an expanded CD4$^+$ T-cell population with CD4/CD8 ratio of more than 10, and/or loss of one or more T-cell antigens. SS is rare, representing less than 5 % of all cutaneous T-cell lymphomas and is typically a disease of aged persons, usually over 60 years. Apart from erythroderma and lymphadenopathy, patients may show alopecia, palmar or plantar hyperkeratosis, and onychodystrophy. The loss of normal circulating CD4$^+$ cells causes an immunodeficiency state, with an increase of infections and secondary malignancies. SS is a progressive disease with a 5-year-survival rate of 10–20 %. Massively erythrodermic forms and cutaneous tumor load correlate with survival (Vonderheid and Bernengo 2003; Ogilvie et al. 2012; Yamashita et al. 2012; Booken et al. 2013).

Morphology

The neoplastic cells are small- to medium-sized and in part large lymphoid cells with a hyperconvoluted and deeply indented (cerebriform) nucleus, the Sézary cell. The histopathologic presentation is similar to that of mycosis fungoides, but infiltrates in SS are more often monotonous and less epidermotropic. In fact, epidermotropism is often absent. The architecture of enlarged lymph nodes is effaced by a dense infiltrate of Sézary cells. In contrast to lymph nodes, bone marrow usually displays only a sparse infiltration. Immunocytochemically, the tumor cells are reactive for CD2, CD3, and CD5, and most cases have a CD4$^+$ helper cell phenotype, CD8$^+$ Sézary syndrome being rare. Typically, SS shows heterogeneity of T-cell phenotypes, with differential antigen losses, e.g., regarding CD7 and CD26 (Steinhoff et al. 2009). T cells in Sézary syndrome are highly reactive for CD164 (a sialomucin) and FCRL3, a molecule present on a subset of human natural T regulatory cells (Wysocka et al. 2014).

Liver Involvement

In the terminal phase of the disease, almost all visceral organs can be involved by this lymphoma (Cohen et al. 1977; Hoppe et al. 1990), including the liver. Patients with generalized erythroderma had a higher frequency of visceral involvement (Bunn et al. 1980). Liver infiltration has been found in classical SS and is the most common extranodal site (Huberman et al. 1980), but also in variants presenting as T-cell leukemia (Dawkins et al. 1975). Sézary cells with the typical immunophenotype are mainly found in portal tracts, sometimes in high density, but in leukemic forms, also the sinusoids contain typical T cells with cerebriform nuclei. Circulating tumor cells appearing in the liver have a distinct phenotype, with co-expression of CD158k and vimentin (Ortonne et al. 2006). The mechanisms of hepatic homing of Sézary cells are not known, but homing to liver has been observed in a mouse model of SS (injection of Sézary cells into immunodeficient RAG2(–/–)yc(–/–) mice; van der Fits et al. 2012). Skin homing of Sézary cells involves SDF-1-CXCR4 signaling and downregulation of CD26/dipeptidyl peptidase IV (Narducci et al. 2006) and is related to expression of CCR4 and CCR10, while lymph node homing depends on CCR7 expression (Sokolowska-Wojdylo et al. 2005). Sézary cells migrate in response to stimulation by the chemokine, stromal cell-derived factor 1 alpha, but not the NT1 receptor (Magazin et al. 2004).

Cytogenetic and Molecular Features

SS shows several complex cytogenetic abnormalities, mainly of chromosomes 1p, 6q, 10q, 17p, and 19, reflecting marked progressive genomic instability, but there is no specific alteration known. Sézary cells show clonal T-cell receptor rearrangement. A part of cases show inactivation of TP53 and p16INK4a. As the Sézary cell transcriptome is studied in detail (Lee et al. 2012), more and more specific alterations are expected to be identified. Novel somatic missense mutations have been found in TBL1XR1,

EPHA7, and SLFN12 genes (Andersson et al. 2014). Furthermore, cutaneous T-cell lymphomas, including Sézary syndrome, showed PLCG1 mutations, eliciting increased downstream signaling toward NFAT/nuclear factor of activated T-cell activation (Vaqué et al. 2014).

Peripheral T-Cell Lymphoma (PTCL), NOS

ICD-O Code 9702/3

Introduction

According to the 2008 WHO classification, peripheral T-cell lymphoma (PTCL) forms a heterogeneous group of nodal or extranodal mature T-cell lymphomas which do not correspond to other, distinct categories of T-cell lymphomas. One variant of PTCL-NOS is characterized by epithelioid histiocytes and corresponds to Lennert's lymphoma (lymphoepithelioid variant). PTCL accounts for about 30 % of all peripheral T-cell lymphomas and is chiefly a disease of adults, with a male predominance. Patients usually show nodal involvement, but almost any tissue can be infiltrated. The typical patient shows generalized disease, with infiltration of the lymph nodes, bone marrow, spleen, liver, and other organs and tissues. Extranodal sites most often involved are gastrointestinal tract and skin. Leukemic presentation is uncommon, although the mature T cells can circulate and recirculate in blood and lymph. The cell of origin is an activated mature T lymphocyte, mostly of the $CD4^+$ central memory type of the immune system (Haioun et al. 1992; Foss et al. 2011; Piccaluga et al. 2011; Armitage 2012; Jaffe et al. 2013).

Morphology

Typically, neoplastic T cells in PTCL-NOS exhibit a highly variable phenotype, ranging from monomorphous medium-sized cells to large cells and highly polymorphic cells. Nuclei are often large, with prominent nuclei and numerous mitotic figures. A part of cases display large cells with a clear cytoplasm and/or cells resembling Reed-Sternberg cells. The neoplastic cells are situated in a tissue background that may contain significant numbers of nonneoplastic cells, including small T cells, plasma cells, B cells of variable size classes, and eosinophils. PTCL has been proposed to be divided into several categories or subtypes, viz., T-zone; pleomorphic, small; pleomorphic, medium; pleomorphic large; angiocentric; immunoblastic; and Lennert type (Shimizu et al. 1989). Lennert's lymphoma is a variant that has numerous epithelioid lymphohistiocytoid cells (the lymphoepithelioid cell variant). As Lennert's lymphoma appeared in numerous reports under this term, this variant of PTCL will be discussed in a separate paragraph for comparison reasons. One variant of PTCL is characterized by the presence of Reed-Sternberg-like cells of B-cell phenotype and genotype associated with EBV infection (Quintanilla-Martinez et al. 1999). Immunohistochemically, PTCL is characterized by an aberrant T-cell phenotype with common downregulation of CD5 and CD7. $CD4^+$ cells usually predominate. Some of the cases exhibit positivity for CD8, CD56, and mixed CD4/CD8 patterns.

Liver Involvement

Primary Liver Involvement

Peripheral T-cell lymphoma (PTCL) primarily manifesting in the liver is considered to be rather uncommon (Andreola et al. 1988; Sutton et al. 1989; Anthony et al. 1990; Shibata et al. 1991; Harris and Kornstein 1993; Bowman et al. 1994; Lei 1998; Kim et al. 2000; Schweiger et al. 2000; Levy 2002; Stancu et al. 2002; Leung et al. 2009; Miyashita et al. 2011; Hu et al. 2014). The tumor can present as a liver mass in the absence of lymphadenopathy, splenomegaly, or bone marrow disease (Hu et al. 2014). The hepatic manifestation may be a solitary lesion, multiple nodules, or

a diffuse infiltration (Levy 2002). Among three elderly men with this entity, two showed hepatomegaly and one jaundice. Imaging studies revealed marked hepatomegaly without focal lesions on one patient and multiple discrete tumor masses in two patients. Histology showed PTCL, with neoplastic cells situated in an inflammatory background and showing a monoclonal T-cell receptor gamma chain gene rearrangement, what is unusual (Stancu et al. 2002). These authors compiled eleven previous patients with apparently primary PTCL arising in the liver. Together with their 3 patients, 14 patients were evaluated, 11 being male and most patients older than 50. Eleven patients showed hepatomegaly, and seven were jaundiced. In the patient reported by Miyashita and coworkers (2011), liver biopsy showed portal tract infiltration of small- and intermediate-sized T cells with irregular nuclear contours. The cells were positive for CD3, CD8, and TIA-1, but negative for CD4, and showed T-cell receptor rearrangement. Portal tract infiltration may be massive and led to extensive lymphomatous infiltration of the entire liver (Harris and Kornstein 1993). Primary hepatic PTCL is sometimes associated with autoimmune disorders, including systemic lupus erythematodes (Sutton et al. 1989) and Felty's syndrome (Bowman et al. 1994).

Secondary Liver Involvement

The liver is one of the organs regularly infiltrated in generalized PTCL (Figs. 1 and 2; Shimizu et al. 1989; Tsutsumi et al. 1991; Lee et al. 2003; Mitarnun et al. 2004; Huang et al. 2012). In a study of 25 patients with PTCL, liver involvement was detected in 56 % (Shimizu et al. 1989). In one investigation, the morphology of T-cell infiltrates varied from mature small lymphocytes to larger, malignant-looking cells (Mitarnun et al. 2004). Peripheral T-cell lymphoma may cause hepatic failure (Schwartz et al. 1998). In one patient with acute liver failure requiring liver transplantation, the T-cell lymphoma recurred in the graft (Blakolmer et al. 2000).

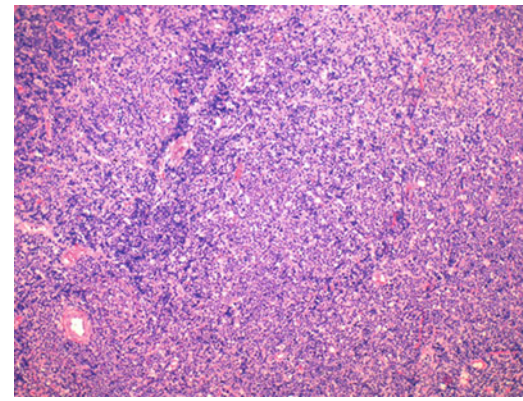

Fig. 1 T-cell lymphoma of the liver. The neoplastic lymphoid cells form vaguely nodular structure with intervening areas of smaller lymphocytes (hematoxylin and eosin stain)

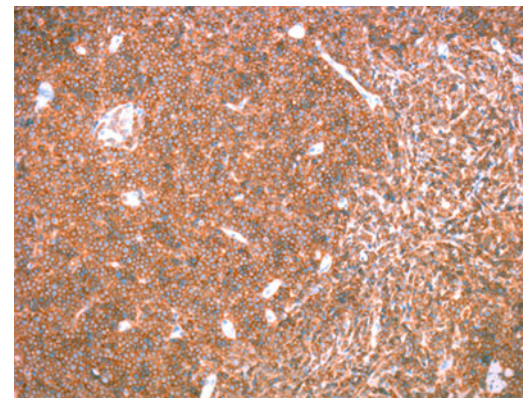

Fig. 2 T-cell lymphoma of the liver. The neoplastic cells are strongly CD3-positive (CD3 immunostain)

Other Liver Lesions Associated with PTCL-NOS

In a patient with PTCL, hemophagocytic syndrome presenting as hepatic failure has been observed (Hino et al. 1997).

Molecular Features

PTCL often show complex karyotypes. This is associated with alterations in gene expression of

numerous genes involved in proliferation, apoptosis, cell adhesion, and cell-matrix interactions. The molecular etiology of mature T-cell NHL has been studied in detail (Evens and Gartenhaus, 2003). T-cell receptor beta chain is usually expressed, in contrast to other T-cell lymphomas. PTCL show recurrent structural abnormalities of TP63 and other p53-related genes, involved in the disruption of p53-associated tumor suppressor functions (Vasmatzis et al. 2012). Similar to other T-cell lymphomas, the RHOA G17V gene mutation occurs frequently in PTCL (Manso et al. 2014; Palomero et al. 2014). Expression of small nucleolar RNAs (snoRNA) in PTCL cells was found to have diagnostic and prognostic significance (Valleron et al. 2012).

References

Abeldaño A, Arias M, Benedetti A, Ochoa K, Maskin M, Pellerano G, Kien MC, Chouela E (2011) Unusual variants of mycosis fungoides. Skinmed 9:218–222

Agnarsson BA, Loughran TP, Starkebaum G, Kadin ME (1989) The pathology of large granular lymphocytic leukemia. Hum Pathol 20:643–651

Aisenberg AC, Wilkes BM, Harris NL, Ault KA, Carey RW (1981) Chronic T-cell lymphocytosis with neutropenia: report of a case studied with monoclonal antibody. Blood 58:818–822

Albukerk J, Duffy JL (1973) Hepatic failure in a case of mycosis fungoides a case report and review of the literature. Am J Dig Dis 18:59–64

Ally MS, Pawade J, Tanaka M, Morris S, Mitchell T, Child F, Wain M, Whittaker S et al (2012) Solitary mycosis fungoides: a distinct clinicopathologic entity with a good prognosis: a series of 15cases and literature review. J Am Acad Dermatol 67:736–744

Alonsozana EL, Stamberg J, Kumar D, Jaffe ES, Medeiros LJ, Frantz C, Schiffer CA et al (1997) Isochromosome 7q: the primary cytogenetic abnormality in hepatosplenic gammadelta T cell lymphoma. Leukemia 11:1367–1372

Andersson et al. (2014) http://www.ncbi.nlm.nih.gov/pubmed/24689486

Andreola S, Audisio RA, Mazzaferro V, Doci R, Makowka L, Gennari L (1988) Primary lymphoma of the liver showing immunohistochemical evidence of T-cell origin. Successful management by right trisegmentectomy. Dig Dis Sci 33:1632–1636

Anthony PP, Sarsfield P, Clarke T (1990) Primary lymphoma of the liver: clinical and pathological features of 10 patients. J Clin Pathol 43:1007–1013

Armitage JO (2012) The aggressive peripheral T-cell lymphomas: 2012 update on diagnosis, risk stratification, and management. Am J Hematol 87:511–519

Babb A, Zerizer I, Naresh KN, Macdonald D (2011) Subcutaneous panniculitis-like T-cell lymphoma with extracutaneous dissemination demonstrated on FDG PET/CT. Am J Hematol 86:375–376

Bakhshi S, Das P, Puri K, Singhal M, Ramam M, Sharma A, Iyer VK, Gupta SD (2011) Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathologic study of 5 cases. Indian J Pathol Microbiol 54:318–322

Belhadj K, Reyes F, Farcet JP, Tilly H, Bastard C, Angonin R, Deconinck E, Charlotte F, Leblond V et al (2003) Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. Blood 102:4261–4269

Bellanger D, Jacquemin V, Chpon M, Pierron G, Bernard OA, Ghysdael J, Stern MH (2014) Recurrent JAK1 and JAK2 somatic mutations in T-cell prolymphocytic leukemia. Leukemia 28:417–419

Benner MF, Jansen PM, Vermeer MH, Willemze R (2012) Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood 119:1643–1649

Berman L (1940) Pathologic nature of mycosis fungoides. Arch Path 29:530–540

Beyer M, Möbs M, Humme D, Sterry W (2011) Pathogenesis of mycosis fungoides. J Dtsch Dermatol Ges 9:594–598

Blakolmer K, Gaulard P, Mannhalter C, Swerdlow S, Fassati LR, Rossi G, Maggi U, Conte D, Demetris AJ (2000) Unusual peripheral T cell lymphoma presenting as acute liver failure and reappearing in the liver allograft. Transplantation 70:1802–1805

Booken N, Nicolay JP, Weiss C, Klemke CD (2013) Cutaneous tumor cell load correlates with survival in patients with Sézary syndrome. J Dtsch Dermatol Ges 11:67–79

Bowman SJ, Levison DA, Cotter FE, Kingsley GH (1994) Primary T cell lymphoma of the liver in a patient with Felty's syndrome. Br J Rheumatol 33:157–160

Boysen AK, Jensen P, Johansen P, Dybkaer K, Nyegaard M (2011) Treatment of aggressive NK-cell leukemia: a case report and review of the literature. Case Rep Hematol 2011:818469

Braun-Falco O, Schmoeckel C, Burg G, Ryckmanns F (1979) Pagetoid reticulosis. A further case report with a report of the literature. Acta Derm Venereol Suppl (Stockh) 59:11–21

Brouet JC, Sasportes M, Flandrin G, Preud'Homme JL, Seligmann M (1975) Chronic lymphocytic leukaemia of T-cell origin. Immunological and clinical evaluation in eleven patients. Lancet 2:890–893

Bug S, Dürig J, Oyen F, Klein-Hitpass L, Martin-Subero JI, Harder L, Baudis M, Arnold N et al (2009) Recurrent loss, but lack of mutations, of the SMARCB1 tumor suppressor gene in T-cell prolymphocytic leukemia

with TCL1A-TCRAD juxtaposition. Cancer Genet Cytogenet 192:44–47
Bunn PA, Huberman MS, Whang-Peng J, Schechter GP, Guccion JG, Matthews MJ et al (1980) Prospective staging evaluation of patients with cutaneous T-cell lymphomas. Demonstration of a high frequency of extracutaneous dissemination. Ann Intern Med 93:223–230
Carlesimo M, Tammaro A, Cox C, Mari E, Fidanza L, Narcisi A, Cacchi C, Camplone G (2009) A case of Ketron-Goodman disease. Case Rep Dermatol 1:39–43
Catovsky D, Galetto J, Okos A, Galton GA, Wiltshaw E, Stathopoulos G (1973) Prolymphocytic leukaemia of B and T cell type. Lancet 2:232–234
Cerban et al. (2012) http://www.ncbi.nlm.nih.gov/pubmed/22720313
Chan JK, Sin VC, Wong KF, Ng CS, Tsang WY, Chan CH, Cheung MM, Lau WH (1997) Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood 89:4501–4513
Chandra P, Plaza JA, Zuo Z, Diwan AH, Koeppen H, Duvic M, Medeiros LJ et al (2009) Clusterin expression correlates with stage and presence of large cells in mycosis fungoides. Am J Clin Pathol 131:511–515
Chang SE, Lee SY, Choi JH, Sung KJ, Moon KC, Koh JK (2002) Cutaneous dissemination of nasal NK/T-cell lymphoma with bone marrow, liver and lung involvement. Clin Exp Dermatol 27:120–122
Chappel AG, Powell DE (1981) Malignant tumours of liver and lung with midline granuloma in an industrial worker. Br J Clin Pract 35:195–196
Cheung MM, Chan JK, Wong KF (2003) Natural killer cell neoplasms: a distinctive group of highly aggressive lymphomas/leukemias. Semin Hematol 40:221–232
Chin M, Mugishima H, Takamura M, Nagata T, Shichino H, Shimada T, Suzuki T, Harada K, Imashuku S, Yokota S (2004) Hemophagocytic syndrome and hepatosplenic gamma/delta T-cell lymphoma with isochromosome 7q and 8 trisomy. J Pediatr Hematol Oncol 26:375–378
Cho EB, Youn SH, Park EJ, Kwon IH, Kim KH, Kim KJ (2012) CD8-positive pityriasis lichenoides-like mycosis fungoides. Eur J Dermatol 22:415–416
Cohen MI, Widerlite LW, Schechter GP, Jaffe E, Fischmann AB, Schein PS, Macdonald JS (1977) Gastrointestinal involvement in the Sézary syndrome. Gastroenterology 73:145–149
Cooke CB, Krenacs L, Steler-Stevenson M, Greiner TC, Raffeld M, Kingma DW, Abruzzo L et al (1996) Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic gamma delta T-cell origin. Blood 88:4265–4274
Côté-Daigneault J, Bernard EJ (2011) Hepatosplenic lymphoma presenting initially as hemophagocytic syndrome in a 21-year-old man with Crohn's disease: a case report and literature review. Can J Gastroenterol 25:417–418
Coventry S, Punnett HH, Tomczak EZ, Casher D, Koehler M, Borowitz MJ, Griffin CA et al (1999) Consistency of isochromosome 7q and trisomy 8 in hepatosplenic gamma/delta T-cell lymphoma: detection by fluorescence In situ hybridization of a splenic touch-preparation from a pediatric patient. Pediatr Dev Pathol 2:478–483
Cribier B (2005) History: Frédéric Woringer (1903–1964) and Woringer-Kolopp disease. Am J Dermatopathol 27:534–545
Dawkins RL, Zilko PJ, Harper JM, Kimber RI, Keall DD (1975) Atypical Sézary syndrome: "T cell leukaemia" associated with reversible clubbing, acrolysis and infiltration of skin and liver. Aust J Dermatol 16:9–12
De Wolf-Peeters C, Achten R (2000) Gamma/delta T-cell lymphomas: a homogeneous entity ? Histopathology 36:294–305
Dearden CE (2009) T-cell prolymphocytic leukemia. 9(suppl 3):S239–S243
Dearden C (2011) Large granular lymphocytic leukaemia pathogenesis and management. Br J Haematol 152:273–283
Degreef H, Holvoet C, Van Vloten WA, De Wolf-Peeters C, Desmet V (1976) Woringer-Kolopp disease. An epidermotropic variant of mycosis fungoides. Cancer (5):2154–2165.
Delgado P, Starshak P, Rao N, Tirado CA (2012) A comprehensive update on molecular and cytogenetic abnormalities in T-cell prolymphocytic leukemia (T-pII). J Assoc Genet Thechnol 38:193–198
Dellon ES, Morris SR, Tang W, Dunphy CH, Russo MW (2006) Acute liver failure due to natural killer-like T-cell leukemia/lymphoma: a case report and review of the literature. World J Gastroenterol 12:4089–4092
Dong J, Chong YY, Meyerson HJ (2003) Hepatosplenic ab T-cell lymphoma. Arch Pathol Lab Med 127: e119–e122
Doyle JA, Winkelmann RK (1981) Staging laparotomy in cutaneous T-cell disease. Arch Dermatol 117:543–546
Dunkley S, Gibson J, Mackinlay N, Joshua D (1998) Aggressive natural killer cell leukemia/lymphoma. Pathology 30:157–159
Eichel BS, Harrison EG, Devine KD, Scanlon PW, Brown HA (1966) Primary lymphoma of the nose including a relationship to lethal midline granuloma. Am J Surg 112:597–605
Epstein EH, Levin DL, Croft JD, Lutzner MA (1972) Mycosis fungoides – survival prognostic features, response to therapy, and autopsy findings. Medicine 51:61–72
Evens and Garbenhaus 2003. http://www.ncbi.nlm.nih.gov/pubmed/12456315
Falchook GS, Vega F, Dang NH, Samaniego F, Rodriguez MA, Champlin RE, Hosing C et al (2009) Hepatosplenic gamma-delta T-cell lymphoma clinicopathological features and treatment. Ann Oncol 20:1080–1085

Farber V (1939) Mycosis fungoides in den inneren Organen ohne Hautveränderungen. Zentralbl Allg Pathol 72:152–153

Farcet JP, Gaulard P, Marolleau JP, Le Couedic JP, Henni T, Gourdin MF, Divine M et al (1990) Hepatosplenic T-cell lymphoma: sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor gamma delta. Blood 75:2213–2219

Fasan A, Kern W, Grossmann V, Haferlach C, Haferlach T, Schnittger S (2012) STAT3 mutations are highly specific for large granular lymphocytic leukemia. Leukemia

Ferreri AJ, Govi S, Pileri SA (2012) Hepatosplenic gamma-delta T-cell lymphoma. Crit Rev Oncol Hematol 83:283–292

Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K (2011) Peripheral T-cell lymphoma. Blood 117:6756–6767

Foucar K, Carroll TJ, Tannous R, Peterson L, Goeken JA, Binion S, Gajl-Peczalska J et al (1985) Nonendemic adult T-cell leukemia/lymphoma in the United States: report of two cases and review of the literature. Am J Clin Pathol 83:18–26

François A, Lesesve JF, Stamatoullas A, Comoz F, Lenormand B, Etienne I, Mendel I, Hemet J et al (1997) Hepatosplenic gamma/delta T-cell lymphoma: a report of two cases in immunocompromised patients, associated with isochromosome 7q. Am J Surg Pathol 21:781–790

Gallardo F, Costa C, Bellosillo B, Solé F, Estrach T, Servitje O, Garcia-Muret MP et al (2004) Lymphomatoid papulosis associated with mycosis fungoides: clinicopathological and molecular studies of 12 cases. Acta Derm Venereol 84:463–468

Gao LM, Liu WP, Yang QP, Li HF, Chen JJ, Tang Y, Zou Y, Liao DY, Liu YM et al (2013) Aggressive natural killer-cell leukemia with jaundice and spontaneous splenic rupture: a case report and review of the literature. Diagn Pathol 8:43

Gassas A, Kirby M, Weitzman S, Ngan B, Abla O, Doyle JJ (2004) Hepatosplenic gd T-cell lymphoma in a 10-year-old boy successfully treated with hematopoietic stem cell transplantation. Am J Hematol 75:113–114

Gaulard P, Zafrani ES, Mavier P, Rocha FD, Farcet JP, Divine M, Haioun C, Pinaudeau Y (1986) Peripheral T-cell lymphoma presenting as predominant liver disease: a report of three cases. Hepatology 6:864–868

Gaulard P, Bourquelot P, Kanavaros P, Haioun C, Le Couedic JP, Divine M, Goossens M, Zafrani ES, Farcet JP, Reyes F (1990) Expression of the alpha/beta and gamma/delta T-cell receptors in 57 cases of peripheral T-cell lymphomas. Identification of a subset of gamma/delta T-cell lymphomas. Am J Pathol 137:617–628

Gaulard P, Belhadj K, Reyes F (2003) Gammadelta T-cell lymphomas. Semin Hematol 40:233–243

Gelb AB, van de Rjin M, Warnke RA, Kamel OW (1996) Pregnancy-associated lymphomas. A clinicopathologic study. Cancer 78:304–310

Gessain A, Cassar O (2012) Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 3:388

Ghobrial IM, Weenig RH, Pittlekow MR, Qu G, Kurtin PJ, Ristow K, Ansell SM (2005) Clinical outcome of patients with subcutaneous panniculitis-like T-cell lymphoma. Leuk Lymphoma 46:703–708

Girardi M, Heald PW, Wilson LD (2004) The pathogenesis of mycosis fungoides. N Engl J Med 350:1978–1988

Glaser M, Goropevsek A, Kavalar R, Glaser A (2012) Hepatosplenic gamma-delta T-cell lymphoma in a female patient after delivery. Hematol Rep 4, e4

Go RS, Wester SM (2004) Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. Cancer 101:1404–1413

Gogia A, Kakar A, Byotra SP, Bhargav M (2010) Aggressive natural killer cell leukaemia: a rare and fatal disorder. J Assoc Physicians India 58:702–704

Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES (1991) T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. Am J Surg Pathol 15:17–27

Grégoire C, Chasson L, Luci C, Tomasello E, Geissmann F, Vivier E, Walzer T (2007) The trafficking of natural killer cells. Immunol Rev 220:169–182

Griem ML, Moran EM, Ferguson DS, Mettler FA, Griem SF (1975) Staging procedures in mycosis fungoides. Cancer 32:1385–1395

Gruber GB (1930) 5. Spezielle Infektionen der Leber. In: Henke F, Lubarsch O (eds) Handbuch der speziellen pathologischen Anatomie und Histologie, vol 5, Verdauungsdrüsen, Erster Teil, Leber, Julius. Springer, Berlin, pp 611–615

Haghighi B, Smoller BR, LeBoit PE, Warnke RA, Sander CA, Kohler S (2000) Pagetoid reticulosis (Woringer-Kolopp disease): an immunophenotypic, molecular, and clinicopathologic study. Mod Pathol 13:502–510

Haioun C, Gaulard P, Bourquelot P, Roudot-Thoraval F, Divine M, Lavaud A, Bagot M et al (1992) Clinical and biological analysis of peripheral T-cell lymphomas: a single institution study. Leuk Lymphoma 7:449–455

Hanson MN, Morrison VA, Peterson BA, Stieglbauer KT, Kubic VL, McCormick SR, McGlennen RC et al (1996) Posttransplant T-cell lymphoproliferative disorders – an aggressive, late complication of solid-organ transplantation. Blood 88:3626–3633

Harris AC, Kornstein MJ (1993) Malignant lymphoma imitating hepatitis. Cancer 71:2639–2646

Hatta C, Ishida M, Matsumoto T, Sugiyama Y, Makino N, Kotoh K (1993) Cases of lethal midline granuloma (polymorphic reticulosis) at our department in a recent 10-year period (in Japanese). Nihon Jibiinkoka Gakkai Kaiho 96:879–885

Herrmann JL, Hughey LC (2012) Recognizing large-cell transformation of mycosis fungoides. J Am Acad Dermatol 67:665–672

Hino T, Sata M, Arima N, Nouno R, Kumashiro R, Koga Y, Uchimura Y, Yoshitake M et al (1997) A case of malignant lymphoma with hemophagocytic syndrome presenting as hepatic failure. Kurume Med J 44:53–60

Hocker et al. (2011) http://www.ncbi.nlm.nih.gov/pubmed/21752051

Hooks JJ, Haynes BF, Detrick-Hooks B, Diehl LF, Gerrard TL, Fauci AS (1981) Gamma (immune) interferon produced by leukocytes from a patient with a T cell proliferation disease. Trans Assoc Am Physicians 94:198–203

Hoppe RT, Wood GS, Abel EA (1990) Mycosis fungoides and the Sézary syndrome: pathology, staging, and treatment. Curr Probl Cancer 14:293–371

Hoque SR, Child FJ, Whittaker SJ, Ferreira S, Orchard G, Jenner K, Spittle M, Russell-Jones R (2003) Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathological, immunophenotypic and molecular analysis of six patients. Br J Dermatol 148:516–525

Hoshi H, Jinnouchi S, Harada K, Watanabe K (1988) Gallium scintigraphy in patients with adult T-cell leukemia lymphoma. Eur J Nucl Med 14:177–179

Hu HJ, Liao MY, Qu YJ (2014) Primary hepatic peripheral T-cell lymphoma: a case report. Oncol Lett 8:258–262

Huang JJ, Cai MY, YeLi ZM, Huang HQ, Lin TY (2009) Clinical analysis of 19 cases of subcutaneous panniculitis T-cell lymphoma with literature review. Chin J Cancer 28:1–7

Huang H, Wan T, Chen C, Chen Y (2012) Peripheral T-cell lymphoma-unspecified with intestinal and liver involvement besides the lymph nodes: a case report (in Chinese). Nan Fang Yi Ke Da Xue Xue Bao 32:1381–1382

Huang Y, de Leval L, Gaulard P (2013) Molecular underpinning of extranodal NK/T-cell lymphoma. Best Pract Res Clin Hematol 26:57–74

Huberman MS, Bunn PA, Matthews MJ, Ihde DC, Gazdar AF, Cohen MH, Minna JD (1980) Hepatic involvement in the cutaneous T-cell lymphomas results of percutaneous biopsy and peritoneoscopy. Cancer 45:1683–1688

Ishibashi M, Ohshima K, Chen KR (2010) Folliculotropic mycosis fungoides with eosinophilia and $CD30^{+}$ large-cell transformation: a case with a fatal outcome presenting with multifocal lesions and leonine facies. Clin Exp Dermatol 35:e133–e136

Jaffe ES, Costa J, Fauci AS, Cossman J, Sokos M (1983) Malignant lymphoma and erythrophagocytosis simulating malignant histiocytosis. Am J Med 75:741–745

Jaffe ES, Nicolae A, Pittaluga S (2013) Peripheral T-cell and NK-cell lymphomas in the WHO classification: pearls and pitfalls. Mod Pathol 26(suppl 1):S71–S87

Jahangiri S, Mahesh S (2010) Hepatosplenic gamma-delta T-cell lymphoma presenting with disseminated intravascular coagulation and coexistent systemic mastocytosis. Clin Adv Hematol Oncol 8:690–694

Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C (2014) Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol 70:205.e1–205.16

Jerez A, Clemente MJ, Makishima H, Koskela H, Leblanc F, Peng NK, Olson T, Przychodzen B et al (2012) STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood 120:3048–3057

Jonveaux P, Daniel MT, Martel V, Maarek O, Berger R (1996) Isochromosome 7q and trisomy 8 are consistent primary, non-random chromosomal abnormalities associated with hepatosplenic T gamma/delta lymphoma. Leukemia 10:1453–1455

Kadin ME, Kamoun M, Lamberg J (1981) Erythrophagocytic T-g lymphoma: a clinicopathologic entity resembling malignant histiocytosis. N Engl J Med 304:648–658

Kasugai K, Yanagishita T, Takeo T, Takahashi E, Tamada Y, Matsumoto Y, Watanabe D (2012) CD8-positive mycosis fungoides bullosa. Eur J Dermatol 22:563–564

Kawamura E, Habu D, Kurooka H, Hayashi T, Oe A, Kotani J, Higashiyama S, Nakamae H et al (2006) Adult T-cell leukemia blast crisis in a patient with acute liver failure. Indian J Gastroenterol 25:49

Kempf W, Kazakov DV, Cipolat C, Kutzner H, Roncador G, Tomasini D (2012) CD4/CD8 double negative mycosis fungoides with PD-1 (CD279) expression – a disease of follicular helper T-cells ? Am J Dermatopathol 34:757–761

Khan WA, Yu L, Eisenbrey AB, Crisan D, Al Saadi A, Davis BH, Hankin RC, Mattson JC (2001) Hepatosplenic gamma/delta T-cell lymphoma in immunocompromised patients. Report of two cases and review of literature. Am J Clin Pathol 116:41–50

Kiel MJ, Velusamy T, Rolland D, Sahasrabuddhe AA, Chung F, Bailey NG, Schrader A, Li B, Li JZ, Ozel AB et al (2014) Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. Blood 124:1460–1472

Kim HS, Ko YH, Ree HJ (2000) A case report of primary T-cell lymphoma of the liver. J Korean Med Sci 15:240–242

Kim TM, Lee SY, Jeon YK, Ryoo BY, Cho GJ, Hong YS, Kim HJ, Kim SY, Kim CS et al (2008) Clinical heterogeneity of extranodal NK/T-cell lymphoma, nasal type: a national survey of the Korean Cancer Study Group. Ann Oncol 19:1477–1484

Kneitz H, Bröcker EB, Becker JC (2010) Mycosis fungoides bullosa: a case report and review of the literature. J Med Case Rep 4:78

Koga M, Imafuku S, Nakayama J (2011) Various skin manifestations of mycosis fungoides: histopathological features and prognosis. Fukuoka Igaku Zasshi 102:229–236

Koskela HL, Eldfors S, Ellonen P, van Andrichem AJ, Kuusanmäki H, Andersson EI et al (2012) Somatic STAT3 mutations in large granular lymphocytic leukemia. N Engl J Med 366:1905–1913

Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, Sampat S et al (2011) A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 9:36–41

Kraus MD, Crawford DF, Kaleem Z, Shenoy S, MacArthur CA, Longtine JA (1998) T gamma/delta hepatosplenic lymphoma in a heart transplant patient after an Epstein-Barr virus positive lymphoproliferative disorder: a case report. Cancer 82:983–992

Krenacs L, Smyth MJ, Bagdi E, Krenacs T, Kopper L, Rudiger T, Zettl A, Müller-Hermelink HK, Jaffe ES, Raffeld M (2003) The serine protease granzyme M is preferentially expressed in NK-cell, gamma delta T-cell, and intestinal T-cell lymphomas: evidence of origin from lymphocytes involved in innate immunity. Blood 101:3590–3593

Kruskall MS, Weitzman SA, Stossel TP, Harris N, Robinson SH (1982) Lymphoma with autoimmune neutropenia and hepatic sinusoidal infiltration: a syndrome. Ann Intern Med 97:202–205

Kumamoto H, Ichinohasama R, Sawai T, Naganuma H, Furukawa Y, Akiu N, Kano M et al (1998) Multiple organ failure associated with extensive metastatic calcification in a patient with an intermediate state of human T lymphotropic virus type I (HTLV-I) infection: report of an autopsy case. Pathol Int 48:313–318

Kumar S, Krenacs L, Medeiros J, Elenitoba-Johnson KS, Greiner TC, Sorbara L, Kingma DW et al (1998) Subcutaneous panniculitic T-cell lymphoma is a tumor of cytotoxic T lymphocytes. Hum Pathol 29:397–403

Kumar S, Lawlor C, Jaffe ES (2001) Hepatosplenic T-cell lymphoma of alphabeta lineage. Am J Surg Pathol 25:970–971

Lai R, Larratt LM, Etches W, Mortimer ST, Jewell LD, Dabbagh L, Coupland RW (2000) Hepatosplenic T-cell lymphoma of alphabeta lineage in a 16-year-old boy presenting with hemolytic anemia and thrombocytopenia. Am J Surg Pathol 24:459–463

Lamy T, Loughran TP (2003) Clinical features of large granular lymphocyte leukemia. Semin Hematol 40:185–195

Leblanc F, Zhang D, Liu X, Loughran TP (2012) Large granular lymphocyte leukemia: from dysregulated pathways to therapeutic targets. Future Oncol 8:787–801

Lee HJ, Im JG, Goo JM, Kim KW, Choi BI, Chang KH, Han JK, Han MH (2003) Peripheral T-cell lymphoma: spectrum of imaging findings with clinical and pathologic features. Radiographics 23:7–26

Lee J, Viakhireva N, Cesca C, Lee P, Kohler S, Hoppe RT, Kim YH (2008) Clinicopathologic features and treatment outcomes in Woringer-Kolopp disease. J Am Acad Dermatol 59:706–712

Lee CS, Ungewickell A, Bhaduri A, Qu K, Webster DE, Armstrong R, Wenig WK et al (2012) Transcriptome sequencing in Sezary syndrome identifies Sezary cell and mycosis fungoides-associated lncRNAs and novel transcripts. Blood 120:3288–3297

Lei KI (1998) Primary non-Hodgkin's lymphoma of the liver. Leuk Lymphoma 29:293–299

Leung VK, Lin SY, Loke TK, Chau TN, Leung CY, Fung TP, Lam SH (2009) Primary hepatic peripheral T-cell lymphoma in a patient with chronic hepatitis B infection. Hong Kong Med J 15:288–290

Levi JA, Wiernik PH (1975) Management of mycosis fungoides – current status and future prospects. Medicine 54:73–88

Levy AD (2002) Malignant liver tumors. Clin Liver Dis 6:147–164

Li et al. (2013) http://www.ncbi.nlm.nih.gov/pubmed/23232851

Liang X, Graham DK (2008) Natural killer cell neoplasms. Cancer 112:1425–1436

Liang L, Nong L, Zhang S, Zhao J, Ti H, Dong Y, Zhang B, Li T (2014) The downregulation of PRDM1/Blimp-1 is associated with aberrant expression of miR-223 in extranodal NK/T-cell lymphoma, nasal type. J Exp Clin Cancer Res 33:7

Lichte V, Ghoreschi K, Metzler G, Möhrle M, Geyer A, Röcken M, Schaller M (2009) Pagetoid reticulosis (Woringer-Kolopp disease). J Dtsch Dermatol Ges 7:353–354

Lim MS, de Leval L, Quintanilla-Martinez L (2009) Commentary on the 2008 WHO classification of mature T-and NK-cell neoplasms. J Hematopathol 2:65–73

Lima M (2013) Aggressive mature natural killer cell neoplasms: from epidemiology to diagnosis. Orphanet J Rare Dis 8:95

Liu X, Loughran TP (2011) The spectrum of large granular lymphocyte leukemia and Felty's syndrome. Curr Opin Hematol 18:254–259

Liu YQ, Zhu WY, Shu YQ, Gu YH (2012) A case of advanced mycosis fungoides with comprehensive skin and visceral organs metastasis: sensitive to chemical and biological therapy. Asian Pac J Trop Med 5:669–672

Long JC, Mihm M (1974) Mycosis fungoides with extracutaneous dissemination: a distinct clinicopathologic entity. Cancer 34:1745–1755

Lü Z, Shi YK, Zhou LQ, Qin Y, Dong M, Yang JL, Liu P, Zhang CG (2010) Primary subcutaneous panniculitis-like T-cell cutaneous lymphoma: clinical presentation, treatment and prognosis (in Chinese). Zhonghua Zhong Liu Za Zhi 32:350–353

Ma L, Bandarchi B, Glusac EJ (2005) Fatal subcutaneous panniculitis-like T-cell lymphoma with interface change and dermal mucin, a dead ringer for lupus erythematosus. J Cutan Pathol 32:360–365

Macon WR, Levy NB, Kurtin PJ, Salhany KE, Elkhalifa MY, Casey TT, Craig FE et al (2001) Hepatosplenic ab T-cell lymphomas: a report of 14 cases and comparison

with hepatosplenic gammadelta T-cell lymphomas. Am J Surg Pathol 25:285–296
Madsen JA, Tallini G, Glusac EJ, Salem RR, Braverman I, Robert ME (1999) Biliary tract obstruction secondary to mycosis fungoides: a case report. J Clin Gastroenterol 28:56–60
Magazin M, Poszepczynska-Guigné E, Bagot M, Boumsell L, Pruvost C, Chalon P et al (2004) Sézary syndrome cells unlike normal circulating T lymphocytes fail to migrate following engagement of NT1 receptor. J Invest Dermatol 122:111–118
Makishima H, Ito T, Momose K, Nakazawa H, Shimodaira S, Kamijo Y, Nakazawa Y, Ichikawa N, Ueno M et al (2007) Chemokine system and tissue infiltration in aggressive NK-cell leukemia. Leuk Res 31:1237–1245
Manso R, Sanchez-Beato M, Monsalvo S, Gomez S, Cereceda L, Llamas P, Rojo F et al (2014) The RHOA G17V gene mutation occurs frequently in peripheral T-cell lymphoma as is associated with a characteristic molecular signature. Blood 123:2893–2894
Martin SJ, Cohen PR, Cho-Vega JH, Tschen JA (2010) $CD8^+$ pagetoid reticulosis presenting as a solitary foot plaque in a young woman. J Clin Aesthet Dermatol 3:46–49
Mastovich S, Ratech H, Russel W et al (1994) Hepatosplenic T-cell lymphoma. An unusual case of a gd T-cell lymphoma with a blast-like terminal differentiation. Hum Pathol 25:102
Matsuzaki Y, Kimura K, Nakano H, Hanada K, Sawamura D (2009) Localized pagetoid reticulosis (Woringer-Kolopp disease) in early childhood. J Am Acad Dermatol 61:120–123
Matutes E, Garcia TJ, O'Brien M, Catovsky D (1986) The morphological spectrum of T-lymphocytic leukemia. Br J Haematol 64:111–124
McElreath DP, Angtuaco TL, Staggs B, Malik AH (2006) T cell prolymphocytic leukemia: a rare cause of acute liver failure. Dig Dis Sci 51:819–821
McKenna RW, Parkin J, Kersey JH, Gajl-Peczalska KJ, Peterson L, Brunning RD (1977) Chronic lymphoproliferative disorder with unusual clinical, morphologic, ultrastructural and membrane surface marker characteristics. Am J Med 62:588–596
Mendese GW, Beckford A, Krejci N, Mahalingam M, Goldberg L, Gilchrest BA (2012) Pagetoid reticulosis in a prepubescent boy successfully treated with photodynamic therapy. Clin Exp Dermatol 37:759–761
Meyerson HJ, Awadallah A, Pavlidakey P, Cooper K, Honda K, Miedler J (2013) Follicular center helper T-cell (TFH) marker positive mycosis fungoides/Sezary syndrome. Mod Pathol 26:32–43
Michaels L, Gregory MM (1977) Pathology of 'non-healing (midline) granuloma'. J Clin Pathol 30:317–327
Mielke V, Wolff HH, Winzer M, Sterry W (1989) Localized and disseminated pagetoid reticulosis: diagnostic immunophenotypical findings. Arch Dermatol 125:402–406
Mitarnun W, Saechan V, Suwiwat S, Pradutkanchana J, Takao S, Ishida T (2004) Hepatic cytotoxic T-cell infiltrates in patients with peripheral T-cell proliferative diseases/lymphomas: clinicopathological and molecular analysis. Pathol Int 54:819–829
Miyashita K, Tomita N, Oshiro H, Matsumoto C, Nakajima Y, Ito S, Matsumoto K, Fujita H et al (2011) Primary hepatic peripheral T-cell lymphoma treated with corticosteroid. Intern Med 50:617–620
Mizuki M, Tagawa S, Shibano M, Hirota T, Machi T, Kitani T, Ohsawa M, Aozasa K, Nojima J (1996) Large granular lymphocyte leukemia (in Japanese). Rinsho Byori 44:917–926
Monma F, Ueno S, Yamaguchi M, Tawara I, Miyazaki K, Nishii K, Nakase K, Katayama N (2009) Long-term remission of a nasal NK/T-cell lymphoma patient with massive involvement of the orbita and liver dysfunction. Rinsho Ketsueki 50:44–48
Mori N, Yamashita Y, Tsutzuki T, Nakayama A, Nakazawa M, Hasegawa Y, Kojima H et al (2000) Lymphomatous features of aggressive NK cell leukaemia/lymphoma with massive necrosis, haemophagocytosis and EB virus infection. Histopathology 37:363–371
Motta G, Vianello F, Menin C, De Nicolo A, Agata S, Altavilla G, Pietrogrande F, Girolami A (2002) Hepatosplenic gammadelta T-cell lymphoma presenting with immune-mediated thrombocytopenia and hemolytic anemia (Evans' syndrome). Am J Hematol 69:272–276
Nagai Y, Ikegama K, Mori M, Inoue D, Kimura T, Shimoji S, Togami K, Tabata S, Kurata M et al (2010) Hepatosplenic alphabeta T cell lymphoma. Int J Clin Oncol 15:215–219
Nakada T, Sueki H, Iijima M (2002) Disseminated pagetoid reticulosis (Ketron-Goodman disease): six-year follow-up. J Am Acad Dermatol 47(2 suppl): S183–S186
Narducci MG, Scala E, Bresin A, Caprini E, Picchio MC, Remotti D, Ragone G, Nasorri F et al (2006) Skin homing of Sézary cells involves SDF-1-CXCR4 signaling and down-regulation of CD26/dipeptidyl-peptidase IV. Blood 107:11108–11115
Nava VE, Jaffe ES (2005) The pathology of NK-cell lymphomas and leukemias. Adv Anat Pathol 12:27–34
Ng SB, Lai KW, Murugaya S, Lee KM, Loong SL, Fook-Chong S, Tao M, Sng I (2004) Nasal-type extranodal natural killer/T-cell lymphoma: a clinicopathologic and genotypic study of 42 cases in Singapore. Mod Pathol 17:1097–1107
Nichols GE, Normansell DE, Williams ME (1994) Lymphoproliferative disorder of granular lymphocytes: nine cases including one with features of CD56 (NKH1)-positive aggressive natural killer cell lymphoma. Mod Pathol 7:819–824
Niitsu N, Kohri M, Togano T, Nakamine H, Nakamura S, Iwabuchi K, Higashihara M (2004) Development of hepatosplenic gammadelta T-cell lymphoma with

pancytopenia during early pregnancy: a case report and review of the literature. Eur J Haematol 73:367–371
Noguchi M, Kawano Y, Sato N, Oshimi K (1997) T-cell lymphoma of $CD3^+CD4^+CD56^+$ granular lymphocytes with hemophagocytic syndrome. Leuk Lymphoma 26:349–358
Nosari A, Oreste PL, Biondi A, Costantini MC, Santoleri L, Intropido L, Muti G, Pungolino E, Gargantini L, Morra E (1999) Hepato-splenic gammadelta T-cell lymphoma: a rare entity mimicking the hemophagocytic syndrome. Am J Hematol 60:61–65
Ogilvie C, Jackson R, Leach M, McKay P (2012) Sézary syndrome: diagnosis and management. JR Coll Phys Edinb 42:317–321
Ohno T, Komada F, Yamaguchi M, Oka K, Nishii T, Tsuda M, Katsuta K, Yamaguchi T, Kita K, Shirakawa S (1993) Gamma/delta T-cell lymphoma with hepatosplenomegaly: report of a case. Int J Hematol 57:269–276
Ohshima K (2007) Pathological features of diseases associated with human T-cell leukemia virus type I. Cancer Sci 98:772–778
Ohshima K, Haraoka S, Harada N, Kamimura T, Suzumiya J, Kanda M, Kawasaki C, Sugihara M, Kikuchi M (2000) Hepatosplenic gammadelta T-cell lymphoma: relation to Epstein-Barr virus and activated cytotoxic molecules. Histopathology 36:127–135
Okuno Y, Tatetsu H, Nosaka K, Mitsuya H (2012) Three cases of aggressive natural killer cell leukemia with a lethal hemorrhagic complication. J Clin Exp Hematol 52:101–106
Oliver GF, Winkelmann RK (1989) Unilesional mycosis fungoides: a distinct entity. J Am Acad Dermatol 20:63–70
Ortonne N, Huet D, Gaudez C, Marie-Cardine A, Schiavon V, Bagot M, Musette P et al (2006) Significance of circulating T-cell clones in Sézary syndrome. Blood 107:4030–4038
Oshimi K (2007) Progress in understanding and managing natural killer-cell malignancies. Br J Haematol 139:532–544
Osuji N, Matutes E, Morilla A, Del Giudice I, Wotherspoon A, Catovsky D (2005) Prolonged treatment response in aggressive natural killer cell leukemia. Leuk Lymphoma 46:757–763
Otani M, Honda N, Xia PC, Eguchi K, Ichikawa T, Watanabe T, Yamaguchi K, Nakao K et al (2012) Distribution of two subgroups of human T-lymphotropic virus type 1 (HTLV-1) in endemic Japan. Trop Med Health 40:55–58
Palomero T, Couronné L, Khiabanian H, Kim MY, Ambesi-Impiombato A, Perez-Garcia A et al (2014) recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat Genet 46:166–170
Park JA (2014) 18F-FDG PET for diagnosis and response assessment for aggressive NK cell leukemia. Clin Nucl Med 39:e281–e282
Park JH, Han JH, Kang HY, Lee ES, Kim YC (2014) Expression of follicular helper T-cell markers in primary cutaneous T-cell lymphoma. Am J Dermatopathol 36:465–470
Pavlovsky L, Mimouni D, Amitay-Laish I, Feinmesser M, David M, Hodak E (2012) Hyperpigmented mycosis fungoides: an unusual variant of cutaneous T-cell lymphoma with a frequent $CD8^+$ phenotype. J Am Acad Dermatol 67:69–75
Perfetto F, Tarquini R, Mancuso F, Di Lollo S, Tozzini S, Bellesi G, Laffi G (2003) Hepato-splenic lymphoma: a rare entity mimicking acute hepatitis: a case report. World J Gastroenterol 9:1381–1384
Perini G, Pro B (2010) Hepatosplenic gamma-delta T-cell lymphoma, disseminated intravascular coagulation, and systemic mastocytosis: an unusual presentation for a rare disease. Clin Adv Hematol Oncol 8:693–694
Petersen-Benz C, Hoffmann N, Beckurts T, Goeser T, Steffen HM, Dries V (2003) Fulminant liver failure induced by hepatosplenic alphabeta T-cell lymphoma. Z Gastroenterol 41:1083–1086
Piccaluga PP, Agostinelli C, Tripodo C, Gazzola A, Bacci F, Sabattini E, Pileri SA et al (2011) Peripheral T-cell lymphoma classification: the matter of cellular derivation. Expert Rev Hematol 4:415–425
Pohlman B, Macklis RM (2000) Lymphoma and pregnancy. Semin Oncol 27:657–666
Powell N, Rusli F, Hübscher SG, Karanth M, Mutimer D (2006) Adult T-cell leukemia presenting with acute liver failure. Leuk Res 30:1315–1317
Pross HF, Pater J, Dwosh I, Giles A, Gallinger LA, Rubin P, Corbett WE, Galbraith P et al (1982) Studies of human natural killer cells. III. Neutropenia associated with unusual characteristics of antibody-dependent and natural killer cell-mediated cytotoxicity. J Clin Immunol 2:126–134
Qi X, Han G, He C, Guo W, Fan D (2012) Education and imaging. Hepatobiliary and pancreatic: hepatosplenic gamma-delta T-cell lymphoma. J Gastroenterol Hepatol 27:184
Quaglino P, Pimpinelli N, Berti E, Calzavara-Pinton P, Lombardo GA, Rupoli S, Alaibac M et al (2012) Mycosis fungoides: disease evolution of the "lion queen" revisited. G Ital Dermatol Venereol 147:523–531
Quintanilla-Martinez L, Fend F, Moguel LR, Spilove L, Beaty MW, Kingma DW, Raffeld M, Jaffe ES (1999) Peripheral T-cell lymphoma with Reed-Sternberg-like cells of B-cell phenotype and genotype associated with Epstein-Barr virus infection. Am J Surg Pathol 23:1233–1240
Rappaport HR (1977) The pathology of the extracutaneous lesions of mycosis fungoides. Bull Cancer 64:275–278
Rappaport H, Thomas LB (1974) Mycosis fungoides: the pathology of extracutaneous involvement. Cancer 34:1198–1229
Rashidi A, Lee ME, Fisher SI (2012) Hepatosplenic ab T-cell lymphoma associated with azathioprine therapy. Int J Hematol 95:592–594

Rodin et al. (1976) http://www.ncbi.nlm.nih.gov/pubmed/938250

Roelandt PR, Maertens J, Vandenberghe P, Verslype C, Roskams T, Aerts R, Nevens F et al (2009) Hepatosplenic gammadelta T-cell lymphoma after liver transplantation: report of the first 2 cases and review of the literature. Liver Transpl 15:686–692

Roncella S, Cutrona G, Truini M, Airoldi I, Pezzolo A, Valetto A, Di Martino D, Dadati P, De Rossi A et al (2000) Late Epstein-Barr virus infection of a hepatosplenic gamma delta T-cell lymphoma arising in a kidney transplant recipient. Haematologica 85:256–262

Ross et al. (1994) http://www.ncbi.nlm.nih.gov/pubmed/8085554

Rossbach HC, Chamizo W, Dumont DP, Barbosa JL, Sutcliffe MJ (2002) hepatosplenic gamma/delta T-cell lymphoma with isochromosome 7q, translocation t (7;21), and tetrasomy 8 in a 9-year-old girl. J Pediatr Hematol Oncol 24:154–157

Ruiz P, Mailhot S, Delgado P, Amador A, Viciana AL, Ferrer L, Zacharievich N (1998) CD26 expression and dipeptidyl peptidase IV activity in an aggressive hepatosplenic T-cell lymphoma. Cytometry 34:30–35

Ryder J, Wang X, Bao L, Gross SA, Hua F, Irons RD (2007) Aggressive natural killer cell leukemia: report of a Chinese series and review of the literature. Int Hematol 85:18–25

Sadahira Y, Notohara K, Manabe T (2003) Hepatosplenic T cell lymphoma with no expression of cytotoxic molecules. J Clin Pathol 56:631–633

Salhany KE, Feldman M, Kahn MJ, Peritt D, Schretzenmair RD, Wilson DM, DiPaola RS et al (1997a) Hepatosplenic gammadelta T-cell lymphoma: ultrastructural, immunophenotypic, and functional evidence for cytotoxic T lymphocyte differentiation. Hum Pathol 28:674–685

Salhany KE, Feldman M, Peritt D, Nowell PC (1997b) Cytotoxic T-lymphocyte differentiation and cytogenetic alterations in gammadelta hepatosplenic T-cell lymphoma and posttransplant lymphoproliferative disorders. Blood 89:3490–3491

Sallah S, Smith SV, Lony LC, Woodard P, Schmitz JL, Folds JD (1997) Gamma/delta T-cell hepatosplenic lymphoma: review of the literature, diagnosis by flow cytometry and concomitant autoimmune hemolytic anemia. Ann Hematol 74:139–142

Sausville EA, Eddy JL, Makuch RW, Fischmann AB, Schechter GP, Matthews M et al (1988) Histopathologic staging at initial diagnosis of mycosis fungoides and the Sézary syndrome. Definition of three distinctive prognostic groups. Ann Intern Med 109:372–382

Schmidt LA, Lim MS (2009) T cell lymphoproliferative disorders associated with anti-tumor necrosis factor alpha antibody therapy for ulcerative colitis: literature summary. J Hematop 2:121–126

Schwartz RA, Rezuke WN, Cartun RW, Hasson J (1998) Case report: an autopsy study of a rare T-cell lymphoma clinically misdiagnosed as fulminant hepatic disease. Conn Med 62:643–647

Schweiger F, Shinder R, Rubin S (2000) Primary lymphoma of the liver: a case report and review. Can J Gastroenterol 14:955–957

Sekiguchi N, Asano N, Ito T, Momose K, Momose M, Ishida F (2012) Elevated serum granulysin and its clinical relevance in mature NK-cell neoplasms. Int J Hematol 96:461–468

Semenzato G, Pizzolo G, Ranucci A, Agostini C, Chilosi M, Quinti I, De Sanctis G, Vercelli B et al (1984) Abnormal expansions of polyclonal large to small size granular lymphocytes : reactive or neoplastic process ? Blood 63:1271–1277

Semenzato G, Marino F, Zambello R (2012) State of the art in natural killer cell malignancies. Int J Lab Hematol 34:117–128

Senba M, Kawai K (1991) Metastatic calcification due to hypercalcemia in adult T-cell leukemia-lymphoma (ATLL). Zentralbl Pathol 137:341–345

Shah MV, Zhang R, Loughran TP (2009) Never say die : survival signaling in large granular lymphocyte leukemia. Clin Lymphoma Myeloma 9(suppl 3):S244–S253

Shale M, Kanfer E, Panaccione R, Ghosh S (2008) Hepatosplenic T cell lymphoma in inflammatory bowel disease. Gut 57:1639–1641

Sheridan W, Winton EF, Chan WC, Gordon DS, Vogler WR, Phillips C, Bongiovanni KF et al (1988) Leukemia of non-T lineage natural killer cells. Blood 72:1701–1707

Shibata M, Oki Y, Iwata M, Ogasawara B, Chujoh C, Ikeda H, Itoh G, Noda A (1991) A case of primary malignant lymphoma of the liver. Gastroenterol Jpn 26:769–773

Shibata S, Sugaya M, Minatani Y, Fujita H, Tsunemi Y, Miyagaki T, Saeki H, Kikuchi K et al (2009) Folliculotropic mycosis fungoides with severe hepatic failure due to hepatic involvement. Acta Derm Venereol 89:423–424

Shimizu K, Nagasaka T, Hara K, Ohnishi K, Hirano M, Kunii A (1989) Peripheral T-cell lymphoma: clinicopathologic analyses of 25 cases. Jpn J Med 28:569–576

Shimoyama M (1991) Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–87). Br J Haematol 79:428–437

Sohn SK, Ahn T, Kim DH, Jung JT, Hyun DW, Lee YH, Suh CS, Lee J, Lee KB (1997) hepatosplenic T-cell lymphoma: prolymphocytic transformation 18 months after splenectomy. Int J Hematol 66:227–232

Sokolowska-Wojdylo M, Wenzel J, Gaffal E, Lenz J, Speuser P, Erdmann S, Abuzahre F et al (2005) Circulating clonal CLA(+) and CD4(+) T cells in Sézary syndrome express the skin-homing chemokine receptors CCR4 and CCR10 as well as the lymph node-homing chemokine receptor CCR7. Br J Dermatol 152:258–264

Stancu M, Jones D, Vega F, Medeiros LJ (2002) Peripheral T-cell lymphoma arising in the liver. Am J Clin Pathol 118:574–581

Steffen C (2005) Ketron-Goodman disease, Woringer-Kolopp disease, and pagetoid reticulosis. Am J Dermatopathol 27:68–85

Steinhoff M, Schöpp S, Assaf C, Muche M, Beyer M, Sterry W, Lukowsky A (2009) Prevalence of genetically defined tumor cells in CD7 as well as CD56 positive and negative circulating T-cell subsets in Sézary syndrome. Leuk Res 33:88–99

Steurer M, Stauder R, Grunewald K, Gunsilius E, Duba HC, Gastl G, Dirnhofer S (2002) Hepatosplenic gammadelta-T-cell lymphoma with leukemic course after renal transplantation. Hum Pathol 33:253–258

Stewart JP (1933) Progressive lethal granulomatous ulceration of the nose. J Laryng 48:657–701

Stutz N, Johnson RD, Wood GS (2012) The Fas apoptotic pathway in cutaneous T-cell lymphomas: frequent expression of phenotypes associated with resistance to apoptosis. J Am Acad Dermatol 67:1327

Suarez F, Wlodarska I, Rigal-Huguet F, Mempel M, Martin-Garcia N, Farcet JP, Delsol G et al (2000) Hepatosplenic alphabeta T-cell lymphoma: an unusual case with clinical, histologic, and cytogenetic features of gammadelta hepatosplenic T-cell lymphoma. Am J Surg Pathol 24:1027–1032

Sullivan M (1958) Lloyd Warren Ketron: 1885–1958. AMA Arch Derm 78:766–767

Sun T, Brody J, Lichtman S, Boss E, Moskowitz L (1990) Extranodal T-cell lymphoma mimicking malignant histiocytosis. Am J Hematol 35:269–274

Sun L, Li M, Huang X, Xu J, Gao Z, Liu C (2014) High-resolution genome-wide analysis identified recurrent genetic alterations in NK/T-cell lymphoma, nasal type, wich are associated with disease progression. Med Oncol 31:71

Sutton E, Malatjalian D, Hayne OA, Hanly JG (1989) Liver lymphoma in systemic lupus erythematosus. J Rheumatol 16:1584–1588

Taguchi A, Miyazaki M, Sakuragi S, Shinohara K, Kamei T, Inoue Y (2004) Gamma/delta T cell lymphoma. Intern Med 43:120–125

Takai K, Sanada M (2001) Aggressive NK cell leukemia/lymphoma: an autopsy case (in Japanese). Rinsho Ketsueki 42:621–626

Takasaki Y, Iwanaga M, Tsukasaki K, Kusano M, Sugahara K, Yamada Y, Kamihira S et al (2007) Impact of visceral involvements and blood cell count abnormalities on survival in adult T-cell leukemia/lymphoma (ATLL). Leuk Res 31:751–757

Takeashita M, Okamura S, Oshiro Y, Imayama S, Okamoto S, Matsuki Y, Nakashima Y et al (2004) Clinicopathologic differences between 22 cases of CD56-negative and CD56-positive subcutaneous panniculitis-like lymphoma in Japan. Hum Pathol 35:231–239

Talpur R, Singh L, Daulat S, Liu P, Seyfer S, Trynosky T, Wei W, Duvic M (2012) Long-term outcomes of 1,263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009. Clin Cancer Res 18:5051–5060

Taniguchi S, Yamasaki K, Shibuya T, Asayama R (1993) Spontaneous remission of acute T-cell leukaemia with chromosomal abnormality infiltrating to skin and liver. Br J Haematol 85:413–414

Thai A, Prindiville T (2010) Hepatosplenic T-cell lymphoma and inflammatory bowel disease. J Crohns Colitis 4:511–522

Thien SL, Catovsky D, Oscier D, Goldman JM, van der Reijden HJ, Melief CJ, Rümke HC et al (1982) T-chronic lymphocytic leukaemia presenting as primary hypogammaglobulinaemia – evidence of a proliferation of T-suppressor cells. Clin Exp Immunol 47:670–676

Thomsen K, Wantzin GL (1987) Extracutaneous spreading with fatal outcome of mycosis fungoides in a patient treated with ciclosporin A: a word of caution. Dermatologica 174:236–238

Tirado CA, Starshak P, Delgado P, Rao N (2012) T-cell prolymphocytic leukemia (T-PLL), a heterogeneous disease exemplified by two cases and the important role of cytogenetics: a multidisciplinary approach. Exp Hematol Oncol 20:1

Tong GX, Hernandez O, Yee HT, Zheng SH, Yang GC (2004) Human T-lymphotropic virus type-1 related adult T-cell leukemia/lymphoma presenting as a parotid mass diagnosed by fine-needle aspiration biopsy. Diagn Cytopathol 31:333–337

Toro JR, Stoll HL, Stomper PC, Oseroff AR (1997) Prognostic factors and evaluation of mycosis fungoides and Sézary syndrome. J Am Acad Dermatol 37:58–67

Travert M, Huang Y, de Leval L, Martin-Garcia N, Delfau-Larue MH, Berger F, Bosq J et al (2012) Molecular features of hepatosplenic T-cell lymphoma unravels potential novel therapeutic targets. Blood 119:5795–5806

Trope BM, Schmidt JM, de Oliveira Neto AA, Pereira Junior AC, Marques AS et al (1985) Disseminated mycosis fungoides (in Portuguese). Med Cutan Ibero Lat Am 13:35–42

Tse E, Liang RH (2004) Natural killer cell neoplasms. Clin Lymphoma 5:197–201

Tsukasaki K (2012) Adult T-cell leukemia-lymphoma. Hematology 17(suppl 1):S32–S35

Tsutsumi Y, Deng YL, Uchiyama M, Kawano K, Ikeda Y (1991) OPD4-positive T-cell lymphoma of the liver in systemic lupus erythematosus. Acta Pathol Jpn 41:829–833

Uhlenhake EE, Mehregan DM (2012) Annular hypopigmentated mycosis fungoides: a novel ringed variant. J Cutan Pathol 39:535–539

Ullrich D, Wildfang I, Karstens, JH, Schröder M (1999). Nasal T-cell lymphoma of the lethal midline type. Case report and current aspects in the literature (in German). HNO 47:490–493

Vahancik A, Babusikova O, Ujhazy P, Klobusicka M, Jakubovsky J, Izakovic V (1988) Chronic

lymphoproliferative disease of large granular lymphocytes. Neoplasma 35:81–89
Valbuena JR, Herling M, Admirand JH, Padula A, Jones D, Medeiros LJ (2005) T-cell prolymphocytic leukemia involving extramedullary sites. Am J Clin Pathol 123:456–464
Valleron W, Ysebaert L, Berquet L, Fataccioli V, Quelen C, Martin A, Parrens M, Lamant L et al (2012) Small nucleolar RNA expression profiling identifies potential prognostic markers in peripheral T-cell lymphoma. Blood 120:3997–4005
Van der Fits L, Rebel HG, Out-Luiting JJ, Pouw SM, Smit F, Vermeer KG, van Zijl L et al (2012) A novel mouse model for Sézary syndrome using xenotransplantation of Sézary cells into immunodeficient RAG2(-/-) gc(-/-) mice. Exp Dermatol 21:706–709
Van Kester MS, Borg MK, Zoutman WH, Out-Luiting JJ, Jansen PM, Dreef EJ, Vermeer MH et al (2012) A meta-analysis of gene expression data identifies a molecular signature characteristic for tumor-stage mycosis fungoides. J Invest Dermatol 132:2050–2059
Vaqué JP, Gomez-Lopez G, Monsalvez V, Varela I, Martinez N, Pérez C, Dominguez O et al (2014) PLCG1 mutations in cutaneous T-cell lymphomas. Blood 123:2034–2043
Variakojis D, Rosas-Uribe A, Rappaport H (1974) Mycosis fungoides: pathologic findings in staging laparotomies. Cancer 33:1589–1600
Vasmatzis G, Johnson SH, Knudson RA, Ketterling RP, Braggio E, Fonseca R, Viswanatha DS et al (2012) Genome-wide analysis reveals recurrent structural abnormalities of TP63 and p53-related genes in peripheral T-cell lymphomas. Blood 120:2280–2289
Vega F, Medeiros LJ, Gaulard P (2007) Hepatosplenic and other gammadelta T-cell lymphomas. Am J Clin Pathol 127:869–880
Vonderheid EC, Bernengo MG (2003) The Sézary syndrome: hematologic criteria. Hematol Oncol Clin North Am 17:1367–1389
Vora R, Mubashir S, Talavia P, Anjaneyan G (2012) Mycosis fungoides: Tumour d'emblée. Indian Dermatol Online J 3:122–124
Wallis WJ, Loughran TP, Kadin ME, Clark EA, Starkebaum GA (1985) Polyarthritis and neutropenia associated with circulating large granular lymphocytes. Ann Intern Med 103:357–362
Wang CC, Tien HF, Lin MT, Su IJ, Wang CH, Chuang SM, Shen MC, Liu CH (1995) Consistent presence of isochromosome 7q in hepatosplenic T gamma/delta lymphoma: a new cytogenetic-clinicopathologic entity. Genes Chromosomes Cancer 12:161–164
Watters RJ, Liu X, Loughran TP (2011) T-cell and natural killer-cell large granular lymphocyte leukemia. Leuk Lymphoma 52:2217–2225
Wei SZ, Liu TH, Wang DT, Cao JL, Luo YF, Liang ZY (2005) Hepatosplenic gammadelta T-cell lymphoma. World J Gastroenterol 11:3729–3734
Weidmann E, Hinz T, Klein S, Schui DK, Harder S, Kriener S, Kabelitz D, Hoelzer D, Mitrou PS (2000) Cytotoxic hepatosplenic gammadelta T-cell lymphoma following acute myeloid leukemia bearing two distinct gamma chains of the T-cell receptor. Biologic and clinical features. Haematologica 85:1024–1031
Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C, Canninga-van Dijk MR et al (2008) Subcutaneous panniculitis-like T-cell lymphoma: definition, classification and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 111:838–845
Wlodarska I, Martin-Garcia N, Achten R, De Wolf-Peeters C, Pauwels P, Tulliez M, de Mascarel A et al (2002) Fluorescence in situ hybridization study of chromosome 7 aberrations in hepatosplenic T-cell lymphoma: isochromosome 7q as a common abnormality accumulating in forms with features of cytologic progression. Genes Chromosomes Cancer 33:243–251
Wong KF, Chan JK, Matutes E, McCarthy K, Ng CS, Chan CH, Ma SK (1995) Hepatosplenic gamma delta T-cell lymphoma. A distinctive aggressive lymphoma type. Am J Surg Pathol 19:718–726
Wong HK, Mishra A, Hake T, Porcu P (2011) Evolving insights in the pathogenesis and therapy of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). Br J Haematol 155:150–166
Woringer MF, Kolopp P (1939) Lésion erythémato-squameuse polycyclique de l'avant-bras évoluant depuis 6 ans chez un garçonnet de 13 ans, histologiquement infiltrate intraépidermique avec apparence tumorale. Ann Dermatol Venereol 10:945–958
Wu H, Wasik MA, Przybylski G, Finan J, Haynes B, Moore H, Leonard DG, Montone KT, Naji A et al (2000) Hepatosplenic gamma-delta T-cell lymphoma as a late-onset posttransplant lymphoproliferative disorder in renal transplant recipients. Am J Clin Pathol 113:487–496
Wysocka M, Kossenkov AV, Benoit BM, Troxel AB, Singer E, Schaffer A, Kim B, Dentchev T et al (2014) CD164 and FCRL3 are highly expressed on $CD4^{+}CD26$- T cell in Sézary syndrome patients. J Invest Dermatol 134:229–236
Yamada Y, Kamihira S, Murata K, Yamamura M, Maeda T, Tsukasaki K, Jubash T et al (1997) Frequent hepatic involvement in adult T cell leukemia: comparison with non-Hodgkin's lymphoma. Leuk Lymphoma 26:327–335
Yamagishi M, Watanabe T (2012) Molecular hallmarks of adult T cell leukemia. Front Microbiol 3:334
Yamashita T, Abbade LP, Marques ME, Marques SA (2012) Mycosis fungoides and Sézary syndrome: clinical, histopathological and immunohistochemical review and update. An Bras Dermatol 87:817–830
Yao M, Tien HF, Lin MT, Su IJ, Wang CT, Chen YC, Shen MC, Wang CH (1996) Clinical and hematological characteristics of hepatosplenic T gamma/delta lymphoma

with isochromosome for long arm of chromosome 7. Leuk Lymphoma 22:495–500

Yi L, Qun S, Wenjie Z, Wen Z, Jian L, Yan Z, Fengchun Z (2013) The presenting manifestations of subcutaneous panniculitis-like T-cell lymphoma and T-cell lymphoma and cutaneous γδ T-cell lymphoma may mimic those of rheumatic diseases: a report of 11 cases. Clin Rheumatol 32:1169–1175

Zabernigg A, Fend F, Thaler J, Gattringer C (1996) An unusual case of a splenic gamma/delta T-cell lymphoma with angiocentric tendency and haemophagocytic syndrome. Leuk Lymphoma 23:631–634

Zengin AY, Topkan E, Cimsit G, Yildiz K (2008) Woringer-Kolopp disease coexpressing CD4 and CD8 treated with radiation therapy: a case report. Tumori 94:754–757

Zhang D, Loughran TP (2012) Large granular lymphocytic leukemia: molecular pathogenesis, clinical manifestations, and treatment. Hematol Am Soc Hematol Educ Prog 2012:652–659

Zhang H, Gupta R, Wang JC, Lipton JF, Huang YW (2007) Subcutaneous panniculitis-like T-cell lymphoma in a patient with long-term remission with standard chemotherapy. J Natl Med Assoc 99:1190–1192

Zhang H, Meng Q, Yin W, Xu L, Lie L (2013) Adult aggressive natural killer cell leukemia. Am J Med Sci 346:56–63

Zinzani PL, Ferreri AJ, Cerroni L (2008) Mycosis fungoides. Crit Rev Oncol Hematol 65:172–182

T-Cell Non-Hodgkin's Lymphomas: Variant Forms

96

Contents

Abstract

There are several variant forms of T-cell non-Hodgkin's lymphomas that can involve the hepatobiliary tract. A distinct and highly aggressive variety of T-cell NHL is the lymphoepithelioid cell variant of peripheral T-cell lymphoma, also termed Lennert's lymphoma (LECL). LECL is characterized by a proliferation of CD4-positive T cells associated with high content of epithelioid macrophages/histiocytes. LECL exhibits a high incidence of generalized lymphadenopathy but rare extranodal disease. Liver involvement may occur, with variable degrees of hepatomegaly. A variant of peripheral T-cell NHL with a polymorphous T-cell lymphoproliferation and association with EBV infection and systemic disease is angioimmunoblastic T-cell lymphoma. This neoplasm accounts for 15–20 % of T-cell NHL. Hepatosplenomegaly is a frequent feature, and the liver shows infiltration by polymorphous lymphoid cells of the T-cell class associated with angiogenesis.

Lennert's Lymphoma (WHO Classification: Lymphoepithelioid Cell Variant of Peripheral T-Cell Lymphoma, Not Otherwise Specified)

ICD-O Code 9702/3

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_96

Introduction

A distinct and highly aggressive variety of ATL is lymphoepithelioid cell lymphoma (LECL; synonym: lymphohistiocytic lymphoma according to the Kiel classification) or Lennert's lymphoma. LECL is characterized by a T-cell NHL (CD4+ phenotype) with a high content of epithelioid histiocytes/macrophages (Lennert and Mestdagh 1968; Feller et al. 1986). Several cases with this NHL phenotype have since been reported, although the question as to whether LECL is a true entity has not been settled (Burke and Butler 1976; Klapper et al. 2008; Chihara et al. 2010; Savage et al. 2011). Lennert's lymphoma is characterized by a high incidence of generalized lymphadenopathy, but rare extranodal disease (Patsouris et al. 1993). A fraction of the patients with LECL show an aggressive course (Kitamura et al. 2005) and may exhibit transformation into a large-cell T-cell lymphoma without the prominent epithelioid cell component (Patsouris et al. 1988). Today, Lennert's lymphoma is classified as the lymphoepithelioid cell variant of PTCL-NOS (2008 WHO Classification). The reason for treating this lymphoma in a separate paragraph is, on the one hand, that several older reports of liver involvement employed the term, Lennert's lymphoma, instead of the now accepted term, lymphoepithelioid cell variant of PTCL. On the other hand, there is evidence that Lennert's lymphoma forms a rare but distinctive entity among epithelioid cell-rich lymphomas, differing from other PTCL subtypes (Hartmann et al. 2011). Lennert's lymphoma can show chromosomal abnormalities not found in other T-cell lymphomas, such as translocation t(14;19)(q11.2;q13.3) (Shin et al. 2012).

Morphology

Histologically and cytologically, LELC is characterized by a dense T-cell-dominated infiltrate, the usually CD4-positive T cells (Feller et al. 1986) ranging in morphology from small cells to large or even pleomorphic cells. The diagnostic feature of LELC is the presence of numerous histiocytes/macrophages, many of them having epithelioid features. Epithelioid cells may, in some cases, dominate the picture and even form small aggregates resembling microgranulomas (Lennert and Mestdagh 1968; Patsouris et al. 1988).

Liver Involvement

Relatively few data are available in regard to hepatic changes in patients with LECL, although liver involvement may occur, presenting as hepatomegaly (Staples and Getaz 1977). In an autopsy study of an old patient succumbing to LECL, liver weight was not increased, but histology sowed extensive infiltration of the portal tracts of the liver by a lymphoid cell population that, in contrast to lymph node biopsies, lacked the typical epithelioid cell component (MacGillivray and Macintosh 1978). Another patient revealed multiple low-density liver nodules, and biopsies thereof displayed an infiltration of neoplastic lymphoid cells with a CD3+, CD4−, CD8+ immunophenotype (Kojima et al. 2003). There are few reports describing hepatic failure in rapidly progressive LECL, likely due to massive hepatic infiltration (Kojima et al. 2003).

Angioimmunoblastic T-Cell Lymphoma

ICD-O Code 9705/3

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is defined as a peripheral T-cell lymphoma which is characterized by signs of systemic disease and a polymorphous T-cell lymphoproliferations mainly involving lymph nodes, but also several extranodal organs. AITL shows a nearly constant association with EBV infection; however, the neoplastic T cell themselves are EBV negative. The postulated cell of origin is the CD4+ follicular helper T cell. This lymphoma, which accounts for about 15–20 % of T-cell lymphomas, mainly

occurs in middle-aged and elderly individuals, males and females being equally affected. Apart from lymph nodes, the bone marrow, spleen, liver, and other organs and tissues can be involved (Ferry 2002).

AITL was formerly designated as angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), a rare clinical and pathologic entity defined as a malignant lymphoproliferative disorder, originally described under various terms, such as lymphogranulomatosis X, diffuse plasmacytic sarcomatosis, immunologic aberrations in idiopathic reticulosis, and immunoblastic lymphadenopathy (Lennert 1973; Lennert and Mohri 1974; Frizzera et al. 1974, 1975; Lukes and Tindle 1975; Radaszkiewicz and Lennert 1975). The original concept of AIDL was that of an atypical reactive process having an increased risk of progression to lymphoma. It is now evident that 80 % of cases of AIDL follow an aggressive course with short median survival and that the majority of cases are T-cell clonal disorders of still unknown etiology (Sallah and Gagnon 1998; Dogan et al. 2003). Therefore, most authors now accept that the disorder arises as a de novo peripheral T-cell lymphoma. In the WHO lymphoma classification, it is listed as a peripheral T-cell NHL, i.e., angioimmunoblastic T-cell lymphoma (AILT; ICD-O 9705/3), this term corresponding to AILD-TL, or angioimmunoblastic lymphadenopathy with dysproteinemia [AILD]-type T-cell lymphoma. AILT accounts for only 1–2 % of all NHL. The classification as a malignant T-cell NHL is also based on earlier reports showing malignant evolution of the disorder (Rubinstein and Dauber 1983). For example, about 10 years after the original description of AILD, a study on 172 patients (then with the diagnosis, "lymphogranulomatosis X") showed transformation into overtly malignant lymphoma proven at autopsy in 13.2 % of the cases (Knecht et al. 1985).

Clinical Features

Patients with this disorder present with frequently acute-onset fever, fatigue, rash (usually with pruritus), weight loss, generalized lymphadenopathy, hepatosplenomegaly, pleural effusion, ascites, arthritis, anemia (including anemia with positive Coombs test), quantitative changes in serum protein levels (polyclonal hypergammaglobulinemia), diverse immunologic disorders with signs of immunodeficiency, and sometimes hypocomplementemia (Frizzera et al. 1975; Pangalis et al. 1978; Cullen et al. 1979; Schauer et al. 1981; Ganesan et al. 1987; Higuchi et al. 1996; Ferry 2002; Dogan et al. 2003). In the setting of the International Peripheral T-Cell Lymphoma Project, it was found that, at presentation, generalized lymphadenopathy was present in 76 %, and 98 % of patients had stages III to IV disease (Federico et al. 2013). Immunodeficiency in patients with AILT is thought to be secondary to the malignant neoplastic process. Cells reactive for EBV antigen(s) are observed in the majority of cases and usually involve B cells (rarely in T cells as well); it is not yet known whether EBV plays a causal role in this lymphoma, or whether this infection follows the immunologic disorders associated with AITL.

Liver Involvement in AILT

As AILT is a generalized disorder, liver involvement is to be expected and in fact occurs in a significant proportion of the patients. However, exact quantitative data referring to prevalence are still sparse. Among 24 patients studied in an early report, hepatomegaly was present in 20 patients (Frizzera et al. 1975). Histologically, the liver is infiltrated by abnormal cells, but the morphology is usually less specific than that found in lymph nodes. In principle, the histologic appearance in extranodal sites are more unspecific but mimic some of the features seen in involved lymph nodes, including a polymorphous lymphoid cell infiltrate and, in particular, increased vascularity (Seehafer et al. 1980; Ghani and Krause 1985; Brown et al. 2001). The infiltrate may be difficult to interpret in some instances, diagnosis of involvement thus requiring specific methods including molecular clonality analysis (Murakami et al. 2001).

Infiltration of the liver tissue with atypical lymphoid cells with a T-cell immunophenotype is seen in part of the advanced cases (Knecht et al. 1985; Takai and Sanada 2000). As in lymph nodes, Reed-Sternberg-like cells representing large transformed blasts may occur in variable amounts. Based on 38 autopsy cases, liver involvement was found in 36.8 %. In addition to infiltrates of lymphocytes and plasma cells in a preferentially portal/periportal location, fibrosis and necrosis of liver tissue was occasionally seen. According to the previously employed subtyping, most of the liver lesions were either type II or type III (plasma cell predominant or mixed, respectively), while types I and IV (immunoblast predominant or epithelioid cell predominant, respectively) were rarer, and no case of type V infiltration (lymphocyte predominant) was found (Knecht et al. 1985).

The neoplastic cells are CD3+ and mostly phenotypically mature CD4+ T cells (Caulet et al. 1988; Lee et al. 2003b), usually admixed with normal CD4+ and CD8+ cells. The sometimes prominent plasmacytic component of the infiltrate is polytypic/polyclonal. A part of the neoplastic T cells are reactive for CD10 (Attygalle et al. 2004). Reactivity for CD10 (neutral endopeptidase, NEP; a cell surface metalloproteinase structurally related to CD26 and CD13) is very helpful in diagnosis, particularly in cases with low density of the neoplastic infiltrates, and in situations where the target cells are intermingled with numerous other cells, because CD10 is normally expressed in B cells with a typically high rate of apoptosis (Chu et al. 2000), but not by normal peripheral T cells or nodal peripheral T-cell lymphomas, whereas it is induced in T cells undergoing apoptosis, e.g., during HIV infection (Cutrona et al. 1999). Physiologically, CD10/NEP reduces the peptide concentration available for receptor binding and regulates a number of cell functions. In AILT, it seems that most, if not all, neoplastic T cells express CD10, but these CD10-reactive cells usually account for only a fraction of the infiltrate cells, ranging from about 5 % to about 30 %, depending on the infiltrate pattern type. The cells have an intricate spatial relation to CD21-positive dendritic cells, suggesting that the follicular dendritic cell network is important for lymphoma growth and expansion. However, in contrast to the lymph nodal lesions, CD21-reactive follicular dendritic cells are not easily detectable in hepatic infiltrates. If present, they prevail in infiltrated portal tract spaces. It may be added that the CD21+ cells occurring in AILT showing a dendritic morphology may not be "true" follicular dendritic cells, but rather fibroblastic reticulum cells expressing CD21 (Jones et al. 1998). This is, for the liver, of interest insofar as the cells sometimes found in portal tracts in AILT and showing a dendritic phenotype also express alpha SMA and/or desmin (myofibroblast-like cells), with or without cytokeratin expression. The lineage of these cells is not clear. Cytokeratin-positive reticulum cells, but of the extrafollicular interstitial type (CIRCs), have been described as a subset of fibroblastic reticulum cells (FBRCs) normally found in lymph nodes, and these cells co-express alpha SMA and desmin (Franke and Moll 1987; Gould et al. 1995). The relationship between these nodal cells and the hepatic cells has to be further studied.

As AILD-TL can be complicated by lymphoma-associated hemophagocytic syndrome (LAHS), hepatic macrophages having phagocytosed erythrocytes have been observed in this lymphoma (Takai and Sanada 2000). AILT is rarely associated with synchronous or metachronous Kaposi's sarcoma, with involvement of the liver (Diebold et al. 1980; Friedman-Birnbaum et al. 1985; Suster et al. 1987). Several other hepatic changes are known to be associated with AILT, including peliosis hepatis (Cadranel et al. 1990), nodular regenerative hyperplasia (NRH; Cadranel et al. 1990), perisinusoidal fibrosis (Sato et al. 1990; Cadranel et al. 1990), and sclerosing cholangitis (Wegerle et al. 1994). The pathogenesis of these associations is unknown. However, it has to emphasized that several agents that may be or have previously been administered in patients with AILT and other NHL are known to have peliosis and/or NRH as side effects, such as azathioprine (Lorcerie et al. 1990; Duvoux et al. 1991; Knudsen 2002), 6-thioguanine (Larrey et al. 1988). Peliosis hepatis also occurs in patients

with marasmus (Simon et al. 1988). AILT is, furthermore, sometimes associated with small- or large-vessel vasculitis with or without cryoglobulinemia (Simon et al. 1983; Molina Boix et al. 1984; Warlow et al. 1984; Sugaya et al. 2001). It is not yet known whether the liver may participate in these types of disorders.

Morphology of AILT

The term, angioimmunoblastic, is related to a specific lymph node histology generally characterized by a polymorphous T-cell infiltrate effacing the structure, prominent branching high-endothelial venules (so-called neovascularization), and a coarse network of CD21-reactive follicular dendritic cells (see below for more details) (Frizzera et al. 1974; Knecht et al. 1985; Feller et al. 1988; Leung et al. 1993; Jones et al. 1998). The origin of the neoplastic T-cell population seems to be a mature T-helper cell with variable expression of CD4 (Lee et al. 2003b). Typically, lymph node germinal centers can undergo regressive changes (burnt out germinal centers; Frizzera et al. 1974). Neoplastic T cells in AILT in most cases can be identified by the aberrant expression of CD10, also in cases with extranodal dissemination (Lee et al. 2003a; Attygalle et al. 2002; Attygalle et al. 2004). As in other types of NHL, a subset of cases show cells expressing the ZAP-70 protein (Admirand et al. 2004). Expression of CXCL13, a chemokine highly upregulated in germinal center T-helper cells, distinguishes AITL from other peripheral T-cell lymphomas (Grogg et al. 2006; Ortonne et al. 2007). Expression of nm23-H1, a gene involved in the regulation of tumor spread and metastasis, is detectable in part of AILT, and this expression is associated with poorer prognosis (Niitsu et al. 2003). It is important to recognize that AILT frequently harbors an expanded "monoclonal" B-cell population. Current evidence suggests that this phenomenon relates to B-cell clones that are driven by EBV infections that is found in over 95 % of all patients with AILT, i.e., representing a secondary change. In more detail, lymph node histology in AILT is characterized by the partial or complete effacement of architecture by a lymphoid infiltrate chiefly occupying the paracortical area. The sinuses are mostly spared, but an extranodal infiltrate component is frequently seen. Histology reflects a dynamic process leading from nodal lesions originally described as AILD, with diverse infiltrate components in addition to malignant T cells, to fully established T-cell lymphoma consisting of an almost pure cellular infiltrate. Depending on the time point of examination, several morphologic features can therefore be encountered. Based on histologic presentation, five subtypes had previously been distinguished, i.e., type I (immunoblastic predominance), type II (plasma cell predominance), type III (mixed cell type), type IV (epithelioid cell predominance), and type V (lymphocytic predominance) (Lennert et al. 1979). The histology of the lymph nodal lesions has been described in detail (Knecht et al. 1985). However, these categories may reflect some sort of observation windows in an ongoing evolution process of disease modified by secondary phenomena (such as recruitment of plasma cells and activated macrophages) and may therefore be rather artificial. In regard to the presence or absence of hyperplastic B-cell follicles/germinal centers previously emphasized to be important within a diagnostic setting, it is now recognized that the architectural changes in AILT seem to fall into three main patterns, i.e., *pattern I* (20 % of cases) with preservation of the lymph node architecture, hyperplastic B-cell follicles/germinal centers and an expanded paracortex harboring the abnormal T-cell population, a prominent vascular network, and increased numbers of macrophages, eosinophils, and plasma cells; *pattern II* (30 % of cases) with loss of nodal architecture, few depleted remnant follicles with concentrically arranged follicular dendritic cells, and a polymorphous nodal infiltrate; and *pattern III* (50 % of cases) with complete effacement of node architecture, lack of follicles, irregular proliferations of follicular dendritic cells, extensive neovascularization, and a polymorphous infiltrate (Ree et al. 1998, 1999; Attygalle et al. 2002; review: Dogan et al. 2003). These patterns again seem to represent dynamic

features of AILT, and phases with hyperplastic germinal centers may, therefore, indicate an earlier phase of disease rather than an unusual feature (Kojima et al. 2001). The marked vascular proliferative reaction seen in AILT, increasing over time, seems to be related to increased expression of vascular endothelial growth factor A both in lymphoma cells and endothelial cells (Zhao et al. 2004). Some cases of AITL show hyperplastic germinal centers (Ree et al. 1998). It has been suggested that this variant is a neoplasia with origin in the outer zone of the germinal center (Rodriguez-Justo et al. 2009).

Molecular Features

The neoplastic T cells in AITL show T-cell receptor rearrangement (Ren et al. 2008). AITL is associated with EBV infection, which may play a role in lymphomagenesis, although the neoplastic T cell does not express EBV. Histological progression of AITL has been shown to be associated with EBV and HHV6B viral load (Zhou et al. 2007). One subset of AITL apparently forming a distinct entity has been found to show clonal immunoglobulin gene rearrangement, associated with a component rich in large B cells and EBV infection (Abruzzo et al. 1993; composite AILD-TL and diffuse large B-cell lymphoma; AILD-TL rich in large B cells; Lome-Maldonado et al. 2002; Zettl et al. 2002; Battegay et al. 2004; Attygalle et al. 2007b). It has been proposed that EBV-associated large B-cell lymphoma may be a secondary event in AILD-TL via EBV infection or reactivation followed by clonal expansion of an immortalized EBV-infected B-cell clone (Willenbrock et al. 2007). AITL with a proliferation of large B cells shows CD10 expression (Attygalle et al. 2002, 2004, 2007a; Reichard et al. 2006). Recently, a recurrent inactivating mutation in RHOA GTPase, encoding p. Gly17Val, was detected in more than two thirds of AITL. The RHOA Gly17Val protein is thought to interfere with RHOA GTPase signaling (Palomero et al. 2014; Sakata-Yanagimoto et al. 2014; Yoo et al. 2014).

References

Abruzzo LV, Schmidt K, Weiss LM, Jaffe ES, Medeiros LJ, Sander CA, Raffeld M (1993) B-cell lymphoma after angioimmunoblastic lymphadenopathy: a case with oligoclonal gene rearrangements associated with Epstein-Barr virus. Blood 82:241–246

Admirand JH, Rassidakis GZ, Abruzzo LV, Valbuena JR, Jones D, Jeffrey Medeiros L (2004) Immunohistochemical detection of ZAP-70 in 341 cases of non-Hodgkin and Hodgkin lymphoma. Mod Pathol 17:954–961

Attygalle A, Al Jehani R, Diss TC, Munson P, Liu H, Du MQ, Isaacson PG, Dogan A (2002) Neoplastic T cells in angioimmunoblastic T-cell lymphoma express CD10. Blood 99:627–633

Attygalle AD, Diss TC, Munson P, Isaacson PG, Du MQ, Dogan A (2004) CD10 expression in extranodal dissemination of angioimmunoblastic T-cell lymphoma. Am J Surg Pathol 28:54–61

Attygalle AD, Kyriakou C, Dupuis J, Grogg KL, Diss TC, Wotherspoon AC, Chuang SS et al (2007a) Histologic evolution of angioimmunoblastic T-cell lymphoma in consecutive biopsies: clinical correlation and insights into natural history and disease progression. Am J Surg Pathol 31:1077–1088

Attygalle AD, Chuang SS, Diss TC, Du MQ, Isaacson PG, Dogan A (2007b) Distinguishing angioimmunoblastic T-cell lymphoma from peripheral T-cell lymphoma, unspecified, using morphology, immunophenotype and molecular genetics. Histopathology 50:498–508

Battegay M, Berger C, Rochlitz C, Hurwitz N, Hirsch HH, de Geyter C, Haque T, Nadal D (2004) Epstein-Barr virus load correlating with clinical manifestation and treatment response in a patient with angioimmunoblastic T-cell lymphoma. Antivir Ther 9:453–459

Brown HA, Macon WR, Kurtin PJ, Gibson LE (2001) Cutaneous involvement by angioimmunoblastic T-cell lymphoma with remarkable heterogeneous Epstein-Barr virus expression. J Cutan Pathol 28:432–438

Burke JS, Butler JJ (1976) Malignant lymphoma with a high content of epithelioid histiocytes (Lennert's lymphoma). Am J Clin Pathol 66:1–9

Cadranel JF, Cadranel J, Buffet C, Fabre M, Pelletier G, d'Agay MF, Ink O, Roche A, Milleron B, Etienne JP (1990) Nodular regenerative hyperplasia of the liver, peliosis hepatis, and perisinusoidal fibrosis. Association with angioimmunoblastic lymphadenopathy and sever hypoxemia. Gastroenterology 99:268–273

Caulet S, Audouin J, Le Tourneau A, Diebold J, Bernardou A, Zittoun R (1988) Angio-immunoblastic (AIL) or T-cell malignant lymphoma of AIL-type. A histopathological, immunohistochemical and ultrastructural study of 8 cases. Pathol Res Pract 183:724–734

Chihara T, Wada N, Kohara M, Matsui T, Masaya H, Maeda T, Shibayama H, Kanakura Y et al (2010) Peripheral T-cell lymphoma of Lennert type

complicated by monoclonal proliferation of large B-cells. Pathol Res Pract 206:185–190
Chu PG, Chang KL, Weiss LM, Arber DA (2000) Immunohistochemical detection of CD10 in paraffin sections of hematopoietic neoplasms: a comparison with flow cytometry detection in 56 cases. Appl Immunohistochem Mol Morphol 8:257–262
Cullen MH, Stansfeld AG, Oliver RT, Lister TA, Malpas JS (1979) Angio-immunoblastic lymphadenopathy: report of ten cases and review of the literature. Q J Med 48:151–177
Cutrona G, Leanza N, Ulivi M, Melioli G, Burgio VL, Mazzarelo G, Gabutti G, Roncella S et al (1999) Expression of CD10 by human T cells that undergo apoptosis both in vitro and in vivo. Blood 94:3067–3076
Diebold J, Tulliez M, Audouin J, Tricot G, Monsus M, Vilde F, Dubrisay J, Patri B, Arkwright S (1980) Visceral Kaposi sarcoma with angioimmunoblastic lymphadenopathy and latent sicca syndrome (in French). Bull Cancer 67:131–138
Dogan A, Attygalle AD, Kyriakou C (2003) Angioimmunoblastic T-cell lymphoma. Br J Haematol 121:681–691
Duvoux C, Kracht M, Lang P, Vernant JP, Zafrani ES, Dhumeaux D (1991) Nodular regenerative hyperplasia of the liver associated with azathioprine therapy (in French). Gastroenterol Clin Biol 15:968–973
Federico M, Rudiger T, Bellei M, Nathwani BN, Luminari S, Coiffier B, Harris NL, Jaffe ES et al (2013) Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the International Peripheral T-Cll Lymphoma Project. J Clin Oncol 31:240–246
Feller AC, Griesser GH, Mak TW, Lennert K (1986) Lymphoepithelioid lymphoma (Lennert's lymphoma) is a monoclonal proliferation of helper/inducer T cells. Blood 68:663–667
Feller AC, Griesser H, Schilling CV, Wacker HH, Dallenbach F, Bartels H, Kuse R, Mak TW, Lennert K (1988) Clonal gene rearrangement patterns correlate with immunophenotype and clinical parameters in patients with angioimmunoblastic lymphadenopathy. Am J Pathol 133:549–556
Ferry JA (2002) Angioimmunoblastic T-cell lymphoma. Adv Anat Pathol 9:273–279
Franke WW, Moll R (1987) Cytoskeletal components of lymphoid organs. I. Synthesis of cytokeratins 8 and 18 and desmin in subpopulations of extrafollicular reticulum cells of human lymph nodes, tonsils, and spleen. Differentiation 36:145–163
Friedman-Birnbaum R, Gilhar A, Carter A (1985) Coexistence of Kaposi's sarcoma and angioimmunoblastic lymphadenopathy. J Dermatol Surg Oncol 11:76–79
Frizzera G, Moran EM, Rappaport H (1974) Angioimmunoblastic lymphadenopathy with dysproteinemia. Lancet 866:1070–1073
Frizzera G, Moran EM, Rappaport H (1975) Angioimmunoblastic lymphadenopathy. Diagnosis and clinical course. Am J Med 59:803–818
Ganesan TS, Dhaliwal HS, Dorreen MS, Stansfeld AG, Habeshaw JA, Lister TA (1987) Angio-immunoblastic lymphadenopathy: a clinical, immunological and molecular study. Br J Cancer 55:437–442
Ghani AM, Krause JR (1985) Bone marrow biopsy findings in angioimmunoblastic lymphadenopathy. Br J Haematol 61:203–213
Gould VE, Bloom KJ, Franke WW, Warren WH, Moll R (1995) Increased numbers of cytokeratin-positive interstitial reticulum cells (CIRC) in reactive, inflammatory and neoplastic lymphadenopathies: hyperplasia or induced expression? Virchows Arch 425:617–629
Grogg KL, Attygalle AD, Macon WR, Remstein ED, Kurtin PJ, Dogan A (2006) Expression of CXCL13, a chemokine highly upregulated in germinal center T-helper cells, distinguishes angioimmunoblastic T-cell lymphoma from peripheral T-cell lymphoma, unspecified. Mod Pathol 19:1101–1107
Hartmann S, Agostinelli C, Klapper W, Korkolopoulou P, Koch K, Marafioti T, Piccaluga PP et al (2011) Revising the historical collection of epithelioid cell-rich lymphomas of the Kiel Lymph Node Registry: what is Lennert's lymphoma nowadays? Histopathology 59:1173–1182
Higuchi T, Mori H, Niikura H, Omine M (1996) Hypocomplementemia and hematological abnormalities in immunoblastic lymphadenopathy and immunoblastic lymphadenopathy-like T cell lymphoma. Acta Haematol 96:68–72
Jones D Jorgensen JL, Shahsafaei A, Dorfman DM (1998) Characteristic proliferations of reticular and dendritic cells in angioimmunoblastic lymphoma. Am J Surg Pathol 22:956-964 (PubMed PMID 9706975)
Kitamura A, Yamashita Y, Sato Y, Hasegawa Y, Kojima H, Nagasawa T, Mori N (2005) Aggressive Lennert's lymphoma: report of three cases in comparison to non-aggressive Lennert's lymphoma. Pathol Int 55:626–631
Klapper W, Böhm M, Siebert R, Lennert K (2008) Morphological variability of lymphohistiocytic variant of anaplastic large cell lymphoma (former lymphohistiocytic lymphoma according to the Kiel classification). Virchows Arch 452:599–605
Knecht H, Schwarze EW, Lennert K (1985) Histological, immunohistological and autopsy findings in lymphogranulomatosis X (including angio-immunoblastic lymphadenopathy). Virchows Arch 406:105–124
Knudsen AH (2002) Peliosis hepatis as the cause of liver affection in a patient treated with immunosuppressive agents (in Danish). Ugeskr Laeger 164:3215–3216
Kojima M, Nakamura S, Itoh H, Motoori T, Sugihara S, Shinkai H, Masawa N (2001) Angioimmunoblastic T-cell lymphoma with hyperplastic germinal centers: a clinicopathological and immunohistochemical study of 10 cases. APMIS 109:699–706

Kojima H, Shimizu S, Yoshida C, Katsura Y, Suzukawa K, Mukai HY, Hasegawa Y et al (2003) Rapidly progressive Lennert's lymphoma terminating in fulminant hepatic failure. Leuk Lymphoma 44:1409–1412

Larrey D, Freneaux E, Berson A, Babany G, Degott C, Valla D, Pessayre, Benhamou JP (1988) Peliosis hepatis induced by 6-thioguanine administration. Gut 29:1265–1269

Lee PS, Lin CN, Chuang SS (2003a) Immunophenotyping of angioimmunoblastic T-cell lymphomas by multiparameter flow cytometry. Pathol Res Pract 199:539–545

Lee SS, Rudiger T, Odenwald T, Roth S, Starostik P, Müller-Hermelink HK (2003b) Angioimmunoblastic T cell lymphoma is derived from mature T-helper cells with varying expression and loss of detectable CD4. Int J Cancer 103:12–20

Lennert K (1973) Pathologisch-histologische Klassifizierung der malignen Lymphoma. In: Stacher A (ed) Leukämien und maligne Lymphoma. Urban and Schwarzenberg, München, pp 181–194

Lennert, Mestdagh (1968) Pubmed PMID 4972336

Lennert K, Mohri N (1974) Histologische Klassifizierung und Vorkommen des M. Hodgkin. Internist 15:57–65

Lennert K, Knecht H, Burkert M (1979) Vorstadien maligner Lymphome. Verh Dtsch Ges Pathol 63:170–196

Leung CY, Ho FC, Srivastava G, Loke SL, Liu YT, Chan AC (1993) Usefulness of follicular dendritic cell pattern in classification of peripheral T-cell lymphomas. Histopathology 23:433–437

Lome-Maldonado C, Canioni D, Hermine O, Delabesse E, Damotte D, Raffoux E, Gaulard P, Macintyre E et al (2002) Angio-immunoblastic T cell lymphoma (AILD-TL) rich in large B cells and associated with Epstein-Barr virus infection. A different subtype of AILD-TL? Leukemia 16:2134–2141

Lorcerie B, Grobost O, Lalu-Fraisse A, Piard F, Camus P, Portier H, Martin F (1990) Peliosis hepatis in dermatomyositis treated with azathioprine and corticoids (in French). Rev Med Interne 11:25–28

Lukes, Tindle (1975) Pubmed PMID 1078547

MacGillivray JB, Macintosh WG (1978) A case of Lennert's lymphoma. J Clin Pathol 31:560–566

Molina Boix M, Ortega Gonzalez G, Perez Rigal V, Navarrete Montoya A, Lozano Garcia J, Alonso Lajara JD (1984) Vasculitis and cryoglobulinemia associated with an angioimmunoblastic lymphadenopathy. Study of 2 cases (in Spanish). Rev Clin Esp 175:117–118

Murakami T, Ohtsuki M, Nakagawa H (2001) Angioimmunoblastic lymphadenopathy-type peripheral T-cell lymphoma with cutaneous infiltration: report of a case and its gene expression profile. Br J Dermatol 144:878–884

Niitsu N, Nakamine H, Okamoto M, Akamatsu H, Honma Y, Higashihara M, Okabe-Kado J, Hirano M, Adult Lymphoma Treatment Study Group, ALTSG (2003) Expression of nm23-H1 is associated with poor prognosis in peripheral T-cell lymphoma. Br J Haematol 123:621–630

Ortonne N, Dupuis J, Plonquet A, Martin N, Copie-Bergman C, Bagot M, Delfau-Larue MH et al (2007) Characterization of CXCL13+ neoplastic T cells in cutaneous lesions of angioimmunoblastic T-cell lymphoma (AITL). Am J Surg Pathol 31:1068–1076

Palomero T, Couronné L, Khiabanian H, Kim MY, Ambesi-Impiombato A, Pereze-Garcia A et al (2014) Recurrent mutations in epigenetic regulators, RHO and FYN kinase in peripheral T cell lymphomas. Nat Genet 46:166–170

Pangalis GA, Moran EM, Rappaport H (1978) Blood and bone marrow findings in angioimmunoblastic lymphadenopathy. Blood 51:71–83

Patsouris E, Noel H, Lennert K (1988) Histological and immunohistological findings in lymphoepithelioid cell lymphoma (Lennert's lymphoma). Am J Surg Pathol 12:341–350

Patsouris E, Engelhard M, Zwingers T, Lennert K (1993) Lymphoepithelioid cell lymphoma (Lennert's lymphoma): clinical features derived from analysis of 108 cases. Br J Haematol 84:346–348

Radaszkiewicz T, Lennert K (1975) Lymphogranulomatosis X (immunoblastic adenopathy): clinical features, treatment and prognosis. Dtsch Med Wschr 21:1157–1163

Ree HJ, Kadin ME, Kikuchi M, Ko YH, Go JH, Suzumiya J, Kim DS (1998) Angioimmunoblastic lymphoma (AILD-type T-cell lymphoma) with hyperplastic germinal centers. Am J Surg Pathol 22:643–655

Ree HJ, Kadin ME, Kikuchi M, Ko YH, Suzumiya J, Go JH (1999) Bcl-6 expression in reactive follicular hyperplasia, follicular lymphoma, and angioimmunoblastic T-cell lymphoma with hyperplastic germinal centers: heterogeneity of intrafollicular T-cells and their altered distribution in the pathogenesis of angioimmunoblastic T-cell lymphoma. Hum Pathol 30:403–411

Reichard KK, Schwartz EJ, Higgins JP, Narasimhan B, Warnke RA, Natkunam Y (2006) CD10 expression in peripheral T-cell lymphomas complicated by a proliferation of large B-cells. Mod Pathol 19:337–343

Ren YL, Hong L, Nong L, Zhang S, Li T (2008) Clinicopathologic, immunohistochemical and molecular analysis in 15 cases of angioimmunoblastic T-cell lymphomas (in Chinese). Beijing Da Xue Xue Bao 40:352–357

Rodriguez-Justo M, Attygalle AD, Munson P, Roncador G, Marafioti T, Piris MA (2009) Angioimmunoblastic T-cell lymphoma with hyperplastic germinal centres: a neoplasia with origin in the outer zone of the germinal centre? Clinicopathological and immunohistochemical study of 10 cases with follicular T-cell markers. Mod Pathol 22:753–761

Rubinstein A, Dauber LG (1983) Lymphoma of cytotoxic/suppressor T cell phenotype (T8) following angioimmunoblastic lymphadenopathy. Oncology 40:195–199

Sakata-Yanagimoto M, Enami T, Yoshida K, Shiraishi Y, Ishii R, Miyake Y, Muto H, Tsuyama N et al (2014) Somatic RHOA mutation in angioblastic T cell lymphoma. Nat Genet 46:171–175

Sallah S, Gagnon GA (1998) Angioimmunoblastic lymphadenopathy with dysproteinemia: emphasis on pathogenesis and treatment. Acta Haematol 99:57–64

Sato I, Miura A, Yokomichi H, Suzuki C, Ichinohazama R (1990) Angio-immunoblastic lymphadenopathy with fibrosis of bone marrow, lymph node, liver and spleen, and proliferation of epithelioid cells in lymph nodes (in Japanese). Rinsho Ketsueki 31:958–962

Savage KJ, Ferreri AJ, Zinzani PL, Pileri SA (2011) Peripheral T-cell lymphoma – not otherwise specified. Crit Rev Oncol Hematol 79:321–329

Schauer PK, Straus DJ, Bagley CM, Rudolph RH, McCracken JD, Huff J, Glucksburg H, Bauermeister DE, Clarkson BD (1981) Angioimmunoblastic lymphadenopathy: clinical spectrum of disease. Cancer 48:2493–2498

Seehafer JR, Goldberg NC, Dicken CH, Su WP (1980) Cutaneous manifestations of angioimmunoblastic lymphadenopathy. Arch Dermatol 116:41–45

Shin SY, Jang S, Park CJ, Chi HS, Lee KH, Huh J, Seo EJ (2012) A rare case of Lennert's type peripheral T-cell lymphoma with t(14;19)(q11.2;q13.3). Int J Lab Hematol 34:328–332

Simon G, Faller JP, Carbillet JP (1983) Association of angioimmunoblastic lymphadenopathy and vasculitis (in French). Presse Med 12:2461–2462

Simon et al. (1988) Pubmed PMID 3135227

Staples WG, Gétaz EP (1977) Lympho-epithelioid cellular lymphoma (Lennert's lymphoma): a case report. S Afr Med J 51:555–556

Sugaya et al. (2001) Pubmed PMID 11280462

Suster S, Ronnen M, Bubis JJ (1987) Angioimmunoblastic lymphadenopathy following Kaposi's sarcoma. Am J Med Sci 294:249–252

Takai K, Sanada M (2000) Angioimmunoblastic T-cell lymphoma associated with hemophagocytic syndrome at onset and relapse (in Japanese). Rinsho Ketsueki 41:1260–1266

Warlow R, Vernea S, Mijch A (1984) Angioimmunoblastic lymphadenopathy associated with large-muscle arteritis. Hum Pathol 15:486–490

Wegerle W, Garbrecht M, Nerl C, Schmitt W (1994) Angioimmunoblastic lymphadenopathy with dysproteinemia and sclerosing cholangitis (in German). Dtsch Med Woschenschr 119:332–337

Willenbrock K, Bräuninger A, Hansmann ML (2007) Frequent occurrence of B-cell lymphomas in angioimmunoblastic T-cell lymphoma and proliferation of Epstein-Barr virus-infected cells in early cases. Br J Haematol 138:733–739

Yoo HY, Sung MK, Lee SH, Kim S, Lee H, Park S, Kim SC, Lee B, Rho K, Lee JE et al (2014) A recurrent inactivating mutation in RHOA GTPase in angioblastic T cell lymphoma. Nat Genet 46:371–375

Zettl A, Lee SS, Rudiger T, Starostik P, Marino M, Kirchner T, Ott M, Müller-Hermelink HK (2002) Epstein-Barr virus-associated B-cell lymphoproliferative disorders in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, unspecified. Am J Clin Pathol 117:386–379

Zhao WL, Mourah S, Mounier N, Leboef C, Daneshpouy ME, Legres L, Meignin V, Oksenhendler E et al (2004) Vascular endothelial growth factor-A is expressed both on lymphoma cells and endothelial cells in angioimmunoblastic T-cell lymphoma and related to lymphoma progression. Lab Invest 84:1512–1519

Zhou Y, Attygalle AD, Chuang SS, Diss T, Ye H, Liu H, Hamoudi RA, Munson P et al (2007) Angioimmunoblastic T-cell lymphoma: histological progression associated with EBV and HHV6B viral load. Br J Haematol 138:44–53

Posttransplant Lymphoproliferative Disorders (PTLDs)

97

Contents

Abstract

Posttransplant lymphoproliferative disorders (PTLDs) are lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in recipients of a solid organ, a bone marrow, or stem cell allografts. PTLDs include a broad spectrum of lesions that include early lesions (plasmacytic hyperplasia, infectious mononucleosis-like lesion), polymorphic PTLD, monomorphic PTLD (B-cell and T-cell variants), plasmacytoma-like lesions, and classical Hodgkin lymphoma-type PTLD. PTLD usually presents between 6 and 17 months posttransplantation, in most cases with signs of systemic illness. Following liver transplantation, PTLD may develop in the liver, but overall this is a rare complication. The spectrum of hepatic PTLD after hepatic transplantation ranges from polymorphic PTLD to high-grade lymphomas and is most often related to EBV-infected lymphoid cells. Growth patterns comprise discrete nodules to diffuse patterns involving the entire organ.

Introduction

Posttransplant lymphoproliferative disorders (PTLDs) are, as defined in the 2008 WHO classification, lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in recipients of a solid organ, a bone marrow, or stem cell allografts. PTLDs comprise a broad

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_97

Table 1 Classification of PTLD according to the 2008 WHO classification (modified)

Early lesions (ICD-O 9971/1)
Plasmacytic hyperplasia
Infectious mononucleosis-like lesion
Polymorphic PTLD (ICD-O 9971/3)
Monomorphic PTLD
(These forms of PTLD are classified according to the non-Hodgkin lymphoma they resemble)
B-cell neoplasms (monomorphic B-cell PTLD)
T-cell/NK-cell neoplasms (monomorphic T-cell PTLD)
Others
Plasmacytoma-like lesions
Classical Hodgkin lymphoma-type PTLD (including Hodgkin lymphoma-like PTLD)

spectrum of lesions that are listed in Table 1 (Knowles et al. 1995; Swerdlow 1997; Chadburn et al. 1998).

PTLD typically presents between 6 and 17 months posttransplantation, usually with the signs of a systemic illness. The epidemiology of PTLD depends on several factors, including the immunosuppression modalities, the EBV infection status, and genetic factors. In the group of adult solid organ recipients, the prevalence of PTLD in part corresponds with the intensity of immunosuppression required. This depends on the type of graft, in that recipients of renal grafts, bone marrow grafts, and stem cell grafts have a low frequency of PTLD (1 % or less) and those with heart-lung/lung grafts or intestinal grafts the highest. Generally, PTLD is more common in children, most cases being related to posttransplantation primary EBV infection (Chadburn et al. 1997; Cesarman et al. 1998; Knowles 1998; Hauke et al. 2001; Capello et al. 2004; Dhillon et al. 2007; Choi et al. 2010; Jagadeesh et al. 2012; Khedmat and Taheri 2012; Michonneau et al. 2013). In solid organ recipients, more than 90 % of PTLD are of host cell origin, but PTLD derived from donor cells is also well-documented (Cherqui et al. 1993; Armes et al. 1994; Strazzabosco et al. 1997; Capello et al. 2009). The majority of PTLDs are associated with EBV infection and are therefore through to represent EBV-driven monoclonal or polyclonal B-cell or monoclonal T-cell proliferations (Jones et al. 2010). Up to 30 % or more of PTLDs are EBV negative, with a tendency to increase. Relatively few EBV-negative PTLDs are caused by KSHV/HHV8 (e.g., primary effusion lymphoma), although expression of KSHV was not always confirmed (Chen et al. 2009). PTLDs developing after solid organ transplantation usually involve the lymph nodes, gastrointestinal tract, lungs, and liver, and the allograft itself is often involved, particularly in early EBV-associated lesions.

Liver Involvement

Following liver transplantation, PTLD may develop in the liver, but overall this is a rare complication (Barkholt et al. 1991; Mulvihill et al. 1994; Pickhardt and Siegel 1999; Nuckols et al. 2000; Wu et al. 2001; Jain et al. 2002; Gouya et al. 2006; Avolio et al. 2007; Ulu et al. 2007). Hepatic PTLD in a grafted liver may be of donor origin (Spiro et al. 1993). The spectrum of PTLD after liver transplantation ranges from polymorphic PTLD to high-grade lymphomas and is most often related to EBV-infected lymphoid cells (Chapchap et al. 1991; Kamdar et al. 2011). In a follow-up of 32 patients with PTLD, hepatic involvement was detected in 69 % (Pickhardt and Siegel 1998). In this study, hepatic involvement appeared as discrete nodules or a diffuse infiltration of the liver substance. The discrete lesions were well circumscribed solitary or multiple masses that were hypoechoic with variable through transmission on sonography and low attenuation on CT images. In diffuse hepatic infiltration, the process appeared as low-attenuation regions against a background of enhancing parenchyma and vessels. Among 51 patients with PTLD after solid organ transplantation, the liver involvement amounted to 53 % (Pickhardt and Siegel 1999). In a study of 18 cases of PTLD post-liver transplantation, the average time interval between transplant and diagnosis of PTLD was 50 months. Seven patients developed solitary or multiple liver/liver hilar masses, measuring in diameter from 5 to 9 cm (Dhillon et al. 2007). An

analysis of 17 consecutive cases of PTLD following adult liver transplantation revealed that the grafted liver was involved in 41 % of patients (Patel et al. 2007). The intrahepatic PTLD masses may become large tumors (Strouse et al. 1996), sometimes reaching a diameter of 12 cm (Wu et al. 2001). Burkitt lymphoma-like PTLD of the monomorphous type was observed in the grafted liver following OLT (Ulu et al. 2007). In child with liver transplantation, liver nodules of PTLD underwent primary calcification (Lecouvet et al. 1996). Plasmacytoma-like PTLD has also been observed to develop in the liver graft following liver transplantation (Vishnu et al. 2011).

Histologically, PTLD may be difficult to distinguish from marked acute rejection, the morphologic presentations sometimes being similar (Howard et al. 1992). In PTLD developing in the grafted liver, EBV expression and a high mitotic count were significantly more often found than in samples of acute rejection (Rizkalla et al. 1997).

Types of PTLD

Early Lesions (Plasmacytic Hyperplasia/PH and Infectious Mononucleosis/IM-Like PTLD)

Early lesions are lymphoid cell proliferations that preserve the architecture of involved tissues, mainly in the lymph nodes, and produce mass lesions. Both PH and IM-like lesions prevail in younger individuals, often in children and adult solid organ recipients who had no prior EBV infection. Morphologically, PH is characterized by an infiltrate that has abundant plasma cells, few bland immunoblasts, and numerous small lymphocytes. The IM-like variety has the typical histologic features of infectious mononucleosis, with numerous immunoblasts intermingled with T cells and plasma cells. Immunohistochemically and molecularly, the population of B cells is polytypic/polyclonal. EBV is expressed in many, but all cases. PL-PTLD may be followed by plasmacytic malignancy (Dunphy et al. 2002).

Polymorphic PTLD (P-PTLD)

P-PTLD is a more common type among all PTLD variants, frequency ranging from 20 % to over 80 % of the cases. In the pediatric age group, this is the most common form of PTLD, frequently following primary EBV infection. In contrast to early lesions, infiltrates in P-PTLD efface the structure of the involved tissues. The infiltrates consist of immunoblasts, plasma cells, and small- to medium-sized lymphocytes, with the full maturation program of B cells. In extranodal compartments, P-PTLD forms destructive masses. B cells show clonal rearrangement of Ig genes, but less prominently in monomorphic PTLD.

Monomorphic PTLD (M-PTLD)

This group of PTLD contains the cases which fulfill the criteria of B-cell or T-cell/NK-cell neoplasms and are subclassified as such.

Plasmacytoma-Like Lesion (Posttransplant Plasma Cell Proliferative Disorders (PT-PCPDs)

A recently described form of PTLD is PT-PCPD (Richendollar et al. 2009), in part associated with HCV infection, which is known to be related to essential mixed cryoglobulinemia and some non-Hodgkin lymphomas. In two patients having undergone liver transplantation, PCPDs developing in the grafted livers were associated with actively replicating HCV in neoplastic plasma cells. Liver biopsies showed a predominantly portal tract infiltration by plasma cells that were CD138 positive with kappa light chain restriction indicating the neoplastic feature of the target cells. ISH for EBV-encoded RNA in liver tissues was negative, while ISH for HCV RNA demonstrated a positive signal in hepatocytes and a stronger signal in the plasma cells. This post-OLT primary hepatic PCPD is different from other forms of posttransplant lymphoproliferative diseases and is associated with a high level of monoclonal proteins in the peripheral blood, negativity for EBV,

and replicating HCV in the proliferating plasma cells, suggesting that HCV was pathogenically involved (Tun et al. 2004; Vishnu et al. 2011).

Classical Hodgkin Lymphoma-Type PTLD (CHL-PTLD)

This is the least common of the major PTLD forms. It most commonly develops in renal graft recipients and is almost always EBV positive. Histologically, CHL-PTLD must fulfill the known criteria for classical Hodgkin disease, including the confirmation by immunohistochemistry (both CD15 and CD30 expression) (Nalesnik et al. 1993; Pitman et al. 2006; Semakula et al. 2006; Rohr et al. 2008; Krishnamurty et al. 2010). A part of these conditions are termed Hodgkin lymphoma-like PTLD (HL-like PTLD), due to cellular and immunohistochemical features different from those in classical Hodgkin lymphoma. HL-like PTLD is almost always EBV associated, similar to Hodgkin lymphoma developing in patients with HIV infection or immunosuppressed patients following chronic low-dose methotrexate administration. HL-like PTLD has been grouped together with CHL-PTLD, but there is still controversy as to whether it is truly a form of HL or whether it should rather be classified as a form B-cell PTLD (Ranganathan et al. 2004; Pitman et al. 2006). There is, in fact, recent evidence that HL-like PTLD represents a distinct clinicopathologic entity with an aggressive clinical course (Krishnamurthy et al. 2010).

EBV-Positive T-Cell Lymphoproliferative Diseases of Childhood

ICD-O codes (provisional) 9724/3 and 9725/3

Introduction

In the 2008 WHO tumor classification, T-cell lymphoproliferative disorders of childhood that are associated with EBV are known as two distinct variants, both mainly occurring in Asians and in natives from Central and South America. The first form is Hydroa vacciniforme-like lymphoma, a cutaneous T-cell neoplasm with an indolent course over longer time periods. The second form is systemic EBV-positive T-cell lymphoproliferative disease (STLPD) of childhood, with a fulminant course (review: Hong et al. 2013).

Hydroa vacciniforme-like lymphoma (ICD-O 9725/3) develops in children and adolescents in Asia and Central/South America and is related to sensitivity to insect (mosquito) bites and sunlight sensitivity. A defective immune response directed against EBV plays a pathogenetic role. Patients present with a papulovesicular eruption that proceeds to ulceration and scarring. Late in disease, systemic signs may develop, including hepatosplenomegaly and lymphadenopathy. The tumor cells are cytotoxic T cells that reveal T-cell receptor rearrangement (Yachie et al. 2003; Wada et al. 2012).

Systemic EBV-positive T-cell lymphoproliferative disease of childhood (STLPD; ICD-O code 9724/3; synonyms: sporadic fatal infectious mononucleosis; severe chronic active EBV infection/CAEBV; Kimura 2006) is a severe and life-threatening systemic disease of children and young adults, predominantly males, characterized by an aggressive neoplastic proliferation of cytotoxic T cells and EBV infection of B cells. Most patients are from Japan and Taiwan, but few patients are from Western countries. Exceptionally, adult patients are affected (Abdul-Ghafar et al. 2011). Clinically, the patients show a rapidly progressive illness with multiorgan involvement and failure, often with sepsis, death occurring within days to weeks. One particularly aggressive variant reveals high fever, pancytopenia, marked lymphadenopathy, and hepatosplenomegaly. In contrast to the standard variant, EBV in this dangerous variant infects T cells and NK cells, T cells stimulated to become a monoclonal population and then a frankly malignant neoplastic cell population (Craig et al. 1992; Dolezal et al. 1995; Ohshima et al. 2008; Ohga et al. 2011; Rodriguez-Pinilla et al. 2011; Wang et al. 2012).

Morphology

Infiltrating cells are small T cells without relevant atypia. Few patients show larger and pleomorphic cell forms. The characteristic immunophenotype is a positive reaction for CD2, CD3, and, in forms secondary to acute primary EBV infection, CD8, whereas T cells in patients with severe CAEBV are CD4 positive. The cells show T-cell receptor rearrangement. All cells contain EBV in a clonal episomal form.

Liver Involvement

In EBV-positive STLPD of childhood, the liver is the most commonly involved inner organ (review: Yoshii et al. 2012). Prominent hepatomegaly, liver dysfunction, and eventually liver failure are typical features (Chan et al. 1992; Quintanilla-Martinez et al. 2000; Hauptmann et al. 2001; Liu et al. 2008; Salama et al. 2008; Rodriguez-Pinilla et al. 2011; Sevilla et al. 2011), followed by the spleen, lymph nodes, bone marrow, skin, and lung. Liver biopsies show CD3+ CD8+ lymphoid T cells in sinusoids, sometimes in high numbers (Abdul-Ghafar et al. 2011). These sinusoidal lymphocytes are almost invariably EBER positive. Marked hemophagocytosis may be observed (Quintanilla-Martinez et al. 2000).

References

Abdul-Ghafar J, Kim JW, Park KH, Cho MY (2011) Fulminant Epstein-Barr virus-associated T-cell lymphoproliferative disorder in an immunocompetent middle-aged man presenting with chronic diarrhea and gastrointestinal bleeding. J Korean Med Sci 26:1103–1107

Armes JE, Angus P, Southey MC, Battaglia SE, Ross BC, Jones RM, Venter DJ (1994) Lymphoproliferative disease of donor origin in patients after orthotopic liver transplantation. Cancer 74:2436–2441

Avolio AW, Agnes S, Barbarino R, Magalini SC, Frongillo F, Pagano L, Larocca LM et al (2007) Posttransplant lymphoproliferative disorders after liver transplantation: analysis of early and late cases in a 255 patient series. Transplant Proc 39:1956–1960

Barkholt L, Billing H, Juliusson G, Porwit A, Ericzon BG, Groth CG (1991) B-cell lymphoma in transplanted liver. Clinical, histological and radiological manifestations. Transpl Int 4:8–11

Capello D, Berra E, Cerri M, Gaidano G (2004) Post-transplant lymphoproliferative disorders. Molecular analysis of histogenesis and pathogenesis. Minerva Med 95:53–64

Capello D, Rasi S, Oreste P, Veronese S, Cerri M, Ravelli E, Rossi D, Minola E, Colosimo A et al (2009) Molecular characterization of post-transplant lymphoproliferative disorders of donor origin occurring in liver transplant recipients. J Pathol 218:478–486

Cesarman E, Chadburn A, Liu YF, Migliazza A, Dalla-Favera R, Knowles DM (1998) BCL-6 gene mutations in posttransplantation lymphoproliferative disorders predict response to therapy and clinical outcome. Blood 92:2294–2302

Chachap P, Carone Filho E, Porta G, Miura I, Zerbini MC, Gayotto LC, Maksoud JG (1991) Posttransplant lymphoproliferative disease of the liver successfully treated by retransplantation. Transplantation 52:736–737

Chadburn A, Cesarman E, Knowles DM (1997) Molecular pathology of posttransplantation lymphoproliferative disorders. Semin Diagn Pathol 14:15–26

Chadburn A, Chen JM, Hsu DT, Frizzera G, Cesarman E, Garrett TJ, Mears JG et al (1998) The morphologic and molecular genetic categories of posttransplantation lymphoproliferative disorders are clinically relevant. Cancer 82:1978–1987

Chan LC, Srivastava G, Pittaluga S, Kwong YL, Liu HW, Yuen HL (1992) Detection of clonal Epstein-Barr virus in malignant proliferation of peripheral blood CD3+ CD8+ T cells. Leukemia 6:952–956

Chen W, Huang Q, Zuppan CW, Rowsell EH, Cao JD, Weiss LM, Wang J (2009) Complete absence of KSHV/HHV-8 in posttransplant lymphoproliferative disorders: an immunohistochemical and molecular study of 52 cases. Am J Clin Pathol 131:632–639

Cherqui D, Duvoux C, Plassa F, Gaulard P, Julien M, Fagniez PL, Dhumeaux D, Goossens M et al (1993) Lymphoproliferative disorder of donor origin in a liver transplant recipient: complete remission after drastic reduction of immunosuppression without graft loss. Transplantation 56:1023–1026

Choi JH, Park BB, Suh C, Won JH, Lee WS, Shin HJ (2010) Clinical characteristics of monomorphic post-transplant lymphoproliferative disorders. J Korean Med Sci 25:523–526

Craig FE, Clare CN, Sklar JL, Banks PM (1992) T-cell lymphoma and the virus-associated hemophagocytic syndrome. Am J Clin Pathol 97:189–194

Dhillon MS, Rai JK, Gunson BK, Olliff S, Olliff J (2007) Post-transplant lymphoproliferative disease in liver transplantation. Br J Radiol 80:337–346

Dolezal MV, Kamel OW, van de Rijn M, Cleary ML, Sibley RK, Warnke RA (1995) Virus-associated hemophagocytic syndrome characterized by clonal Epstein-Barr virus genome. Am J Clin Pathol 103:189–194

Dunphy CH, Galambos C, Polski JM, Evans HL, Gardner LJ, Grosso LE, Montone KT (2002) Extranodal

posttransplant plasmacytic hyperplasia with subsequent posttransplant plasmacytic malignancy: six-year interval case report and review of the literature. Arch Pathol Lab Med 126:351–356

Gouya G, Hartmann G, Faè P, Tauber M, Holzmüller H, Benzer W, Lang A, Schuster A et al (2006) A case of fulminant post-transplant lymphoproliferative disorder and septicemia. Clin Transplant 20:261–264

Hauke R, Smir B, Greiner T, Bierman P, Tarantola S, Anderson J, Shaw B, Armitage J (2001) Clinical and pathological features of posttransplant lymphoproliferative disorders: influence on survival and response to treatment. Ann Oncol 12:831–834

Hauptmann S, Meru N, Schewe C, Jung A, Hiepe F, Burmester G, Niedobitek G, Buttgereit F (2001) Fatal atypical T-cell proliferation associated with Epstein-Barr virus infection. Br J Haematol 112:377–380

Hong M, Ko YH, Yoo KH, Koo HH, Kim SJ, Kim WS, Park H (2013) EBV-positive T/NK-cell lymphoproliferative disease of childhood. Korean J Pathol 47:137–147

Howard TK, Klintmalm GB, Stone MJ, Cofer JB, Husberg BS, Goldstein RM, Gonwa TA (1992) Lymphoproliferative disorder masquerading as rejection in liver transplant recipients – an early aggressive tumor with atypical presentation. Transplantation 53:1145–1147

Jagadeesh D, Woda BA, Draper J, Evens AM (2012) Posttransplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. Curr Treat Options Oncol 13:122–136

Jain A, Nalesnik M, Reyes J, Pokharna R, Mazariegos G, Green M, Eghtesad B, Marsh W et al (2002) Posttransplant lymphoproliferative disorders in liver transplantation: a 20-year experience. Ann Surg 236:429–436

Jones K, Nourse JP, Morrison L, Nguyen-Van D, Moss DJ, Burrows SR, Gandhi MK (2010) Expansion of EBNA1-specific effector T cells in posttransplantation lymphoproliferative disorders. Blood 116:2245–2252

Kamdar KY, Rooney CM, Heslop HE (2011) Posttransplant lymphoproliferative disease following liver transplantation. Curr Opin Organ Transplant 16:274–280

Khedmat H, Taheri S (2012) Lymphoproliferative disorders in pediatric liver allograft recipients: a review of 212 cases. Hematol Oncol Stem Cell Ther 5:84–90

Kimura H (2006) Pathogenesis of chronic active Epstein-Barr virus infection: is this an infectious disease, lymphoproliferative disorder, or immunodeficiency? Rev Med Virol 16:251–261

Knowles DM (1998) The molecular genetics of posttransplantation lymphoproliferative disorders. Springer Semin Immunopathol 20:357–373

Knowles DM, Cesarman E, Chadburn A, Frizzera G, Chen J, Rose EA, Michler RE (1995) Correlative morphologic and molecular genetic analysis demonstrates three distinct categories of posttransplantation lymphoproliferative disorders. Blood 85:552–565

Krishnamurthy S, Hassan A, Frater JL, Paessler ME, Kreisel FH (2010) Pathologic and clinical features of Hodgkin lymphoma-like posttransplant lymphoproliferative disease. Int J Surg Pathol 18:278–285

Lecouvet F, Clapuyt P, Van Nieuwenhuyse JP, Everarts P, Baudrez V, Reding R, de Ville de Goyet J et al (1996) Primary calcification in post-transplantation lymphoproliferative disorder involving the hepatic graft: an exceptional finding. Pediatr Radiol 26:152–154

Liu Y, Tang SQ, Liu LZ, Yang G, Feng C, Lei Q (2008) Characteristics of chronic active Epstein-Barr virus infection-associated hematological disorders in children (in Chinese). Zhongguo Shi Yan Xue Ye Xue Za Zhi 16:574–578

Michonneau D, Suarez F, Lambert J, Adam J, Brousse N, Canioni D, Anglicheau D et al (2013) Late-onset posttransplantation lymphoproliferative disorders after kidney transplantation: a monocentric study over three decades. Nephrol Dial Transplant 28:471–478

Mulvihill DM, Munden MM, Edell D (1994) Lymphoproliferative disorder involving the liver following transplantation: CT appearance. J Comput Assist Tomogr 18:47–48

Nalesnik MA, Randhawa P, Demetris AJ, Casavilla A, Fung JJ, Locker J (1993) Lymphoma resembling Hodgkin disease after posttransplant lymphoproliferative disorder in a liver transplant recipient. Cancer 72:2568–2573

Nuckols JD, Baron PW, Stenzel TT, Olatidoye BA, Tuttle-Newhall JE, Clavien PA, Howell DN (2000) The pathology of liver-localized post-transplant lymphoproliferative disease: a report of three cases and a review of the literature. Am J Surg Pathol 24:733–741

Ohga S, Ishimura M, Yoshimoto G, Miyamoto T, Takada H, Tanaka T, Ohshima K et al (2011) Clonal origin of Epstein-Barr virus (EBV)-infected T/NK-cell subpopulations in EBV-positive T/NK-cell lymphoproliferative disorders of childhood. J Clin Virol 51:31–37

Ohshima K, Kimura H, Yoshino T, Kim CW, Ko YH, Lee SS, Peh SC, Chan JK et al (2008) Proposed categorization of pathological states of EBV-associated T/natural killer-cell lymphoproliferative disorder (LPD) in children and young adults: overlap with chronic active EBV infection and infantile fulminant EBV T-LKPD. Pathol Int 58:209–217

Patel H, Vogl DT, Agui N, Shaked A, Olthoff K, Markmann J, Reddy R, Stadtmauer EA et al (2007) Posttransplant lymphoproliferative disorder in adult liver transplant recipients: a report of seventeen cases. Leuk Lymphoma 48:885–891

Pickhardt PJ, Siegel MJ (1998) Abdominal manifestations of posttransplantation lymphoproliferative disorder. AJR Am J Roentgenol 171:1007–1013

Pickhardt PJ, Siegel MJ (1999) Posttransplantation lymphoproliferative disorder of the abdomen: CT evaluation in 51 patients. Radiology 213:73–78

Pitman SD, Huang Q, Zuppan CW, Rowsell EH, Cao JD, Berdeja JG, Weiss LM et al (2006) Hodgkin lymphoma-like posttransplant lymphoproliferative disorder (HL-like PTLD) simulates monomorphic B-cell

PTLD both clinically and pathologically. Am J Surg Pathol 30:470–476

Quintanilla-Martinez L, Kumar S, Fend F, Reyes E, Teruya-Feldstein J, Kingma DW et al (2000) Fulminant EBV(+) T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. Blood 96:443–451

Ranganathan S, Webber S, Ahuja S, Jaffe R (2004) Hodgkin-like posttransplant lymphoproliferative disorder in children: does it differ from posttransplant Hodgkin lymphoma? Pediatr Dev Pathol 7:348–360

Richendollar BG, His ED, Cook JR (2009) Extramedullary plasmacytoma-like posttransplantation lymphoproliferative disorders: clinical and pathological features. Am J Clin Pathol 132:581–588

Rizkalla KS, Asfar SK, Mclean CA, Garcia BM, Wall WJ, Grant DR (1997) Key features distinguishing posttransplantation lymphoproliferative disorders and acute liver rejection. Mod Pathol 10:708–715

Rodriguez-Pinilla SM, Barrionuevo C, Garcia J, de los Angeles M, Pajares R, Casavilca S et al (2011) Epstein-Barr virus-positive systemic NK/T-cell lymphomas in children: report of six cases. Histopathology 59:1183–1193

Rohr JC, Wagner HJ, Lauten M, Wacker HH, Jüttner E, Hanke C, Pohl M, Niemeyer CM (2008) Differentiation of EBV-induced post-transplant Hodgkin lymphoma from Hodgkin-like post-transplant lymphoproliferative disease. Pediatr Transplant 12:426–431

Salama ME, Parham DM, Perkins SL, Bahler DW, Ellison DA (2008) Fatal non-transplant-related Epstein-Barr virus-associated atypical lymphoid proliferations in infants and children: a clinicopathologic study. Pediatr Dev Pathol 11:443–449

Semakula B, Rittenbach JV, Wang J (2006) Hodgkin lymphoma-like posttransplantation lymphoproliferative disorder. Arch Pathol Lab Med 130:558–560

Sevilla DW, El-Mallawany NK, Emmons FN, Alexander S, Bhagat G, Alobeid B (2011) Spectrum of childhood Epstein-Barr virus-associated T-cell proliferations and bone marrow findings. Pediatr Dev Pathol 14:28–37

Spiro IJ, Yandell DW, Li C, Saini S, Ferry J, Powelson J, Katkov WN, Cosimi AB (1993) Brief report: lymphoma of donor origin occurring in the porta hepatis of a transplanted liver. N Engl J Med 329:27–29

Strazzabosco M, Corneo B, Iemmolo RM, Gerunda G, Bonaldi L, Merenda R, Neri D et al (1997) Epstein-Barr virus-associated post-transplant lympho-proliferative disease of donor origin in liver transplant recipients. J Hepatol 26:926–934

Strouse PJ, Platt JF, Francis IR, Bree RL (1996) Tumorous intrahepatic lymphoproliferative disorder in transplanted livers. AJR Am J Roentgenol 167:1159–1162

Swerdlow SH (1997) Classification of the posttransplant lymphoproliferative disorders: from the past to the present. Semin Diagn Pathol 14:2–7

Tun HW, Krishna M, Menke DM (2004) Hepatitis C-related posttransplant plasma cell proliferative disorder with hepatitis C virus in neoplastic plasma cells: a new posttransplant disease entity? Transplant Proc 36:2692–2696

Ulu EM, Tutar NU, Coskun M, Tore HG, Guvenc Z, Haberal M (2007) Abdominal computed tomography findings of malignant tumors in patients with solid organ transplants. Transplant Proc 39:1066–1070

Vishnu P, Jiang L, Cortese C, Menke DM, Tun HW (2011) Plasmacytoma-like posttransplant lymphoproliferative disorder following orthotopic liver transplantation: a case report. Transplant Proc 43:2806–2809

Wada T, Toga A, Sakakibara Y, Toma T, Hasegawa M, Takehara K, Shigemura T et al (2012) Clonal expansion of Epstein-Barr virus (EBV)-infected gd T cells in patients with chronic active EBV disease and hydroa vacciniforme-like eruptions. Int J Hematol 96:443–449

Wang W, Ti HJ, Nong L, Zhang S, Zhang Y, Li T (2012) Clinical and pathological analysis of three cases of childhood systemic EB virus positive T-cell lymphoproliferative disease (in Chinese). Beijing Da Xue Xue Bao 44:594–598

Wu L, Rappaport DC, Hanbidge A, Merchant N, Shepherd FA, Greig PD (2001) Lymphoproliferative disorders after liver transplantation: imaging features. Abdom Imaging 26:200–206

Yachie A, Kanegane H, Kasahara Y (2003) Epstein-Barr virus-associated T-/natural killer cell lymphoproliferative diseases. Semin Hematol 40:124–132

Yoshii M, Ishida M, Hodohara K, Okuno H, Nakanishi R, Yoshida T, Okabe H (2012) Systemic Epstein-Barr virus-positive T-cell lymphoproliferative disease of childhood: report of a case with review of the literature. Oncol Lett 4:381–384

Hepatobiliary Castleman Disease

98

Contents

Abstract

Castleman disease (CD), which can involve the hepatobiliary tract, is a complex spectrum of lymphoid proliferations that is divided into two clinical subtypes, i.e., localized CD (LCD) and multicentric CD (MCD). Both LCD and MCD can occur in one of several clinical and histological types or patterns. The main histologic presentations include the hyaline-vascular type of CD (a standard subtype and stroma-rich or angiomyoid subtype), a plasmacellular type of CD, and mixed patterns. MCD can also occur as an aggressive plasmablastic variant. Hepatomegaly is a common feature in patients with CD, but the histologic substratum is unknown in many cases. MCD produces atypical, mixed cellular infiltrates in the liver, consisting of lymphoid cells, macrophages, and plasma cells mainly located in portal tracts. Lymph follicles with germinal centers can develop. Localized CD can develop deeply in the liver substance or the porta hepatis. A very rare manifestation of hepatobiliary CD is a plasma cell-rich variant confined to the liver.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_98

Localized and Multicentric Castleman Disease (LCD and MCD)

Introduction

Lymph node disorders characterized by both follicular hyperplasia and increased vascularity were originally termed hypervascular follicular hyperplasia (HFH; Rywlin et al. 1966). In the fully developed form, this histologic pattern has received the eponymic designation Castleman disease. Castleman disease (CD) is a rare and still poorly understood, heterogeneous, so-called atypical proliferative disorder of the lymphatic system, first described in 1954 (Castleman and Towne 1954). Synonyms for at least part of the cases of CD comprise angiofollicular lymph node hyperplasia (ALNH), giant lymph node hyperplasia, follicular lymphoreticuloma, and giant lymphoid hamartoma (reviews: Frizzera 1988; Shahidi et al. 1995; McCarthy et al. 1995; Bowne et al. 1999; Palestro et al. 1999; Maslovsky et al. 2000; Van den Berge et al. 2002; Martino et al. 2004; McClain et al. 2004; reviews: Dham and Peterson 2007; Roca 2009). The lesions described in the early literature are now known as the hyaline-vascular type of CD, but later, a much rarer variant, the plasma cell type of CD, was identified that is also localized but bears very different clinical features. Later, it was recognized that CD can occur in a multicentric pattern, and more recently, an aggressive "plasmablastic" variant of multicentric CD was recognized.

CD has no predilection for either sex, and most patients are in the second and third decades of life, with rare occurrence in children younger than 15 years of age. CD is usually manifested as an asymptomatic, solitary mediastinal tumor (40–70 % of cases), but clinical manifestations of CD can vary from a localized mass (unicentric CD; see below) to a systemic disorder (multicentric CD; see below) with widespread lymphadenopathy, fever, autoimmune manifestations, and recurring infections (Herrada et al. 1998; Maslovsky et al. 2000; Talat and Schulte 2011; Dispenzieri et al. 2012). Meta-analytic data showed that peripheral lymphadenopathy is present in 100 %, abdominal lymphadenopathy in 53 %, mediastinal lymphadenopathy in 47 %, splenomegaly in 79 %, hepatomegaly in 63 %, edema or pleural effusions in 48 %, and skin rash in 37 % (Greiner et al. 2000). CD may, depending on the variant or form, remit, be chronic and nonprogressive, or may rapidly progress and be fatal, indicating the marked clinical heterogeneity of this group of disorders. Localized childhood CD may be associated with iron deficiency anemia, probably involving the IL-6/hepcidin pathway (Arlet et al. 2010).

Classification of CD

CD is divided into two clinical subtypes, i.e., *localized CD* (*LCD*) and *multicentric CD* (*MCD*) (McCarthy et al. 1995; McClain et al. 2004). LCD is also termed unicentric CD, and MCD, generalized CD. In some reports, MCD is listed under the term multicentric angiofollicular lymph node hyperplasia (MAFH). Both LCD and MCD can occur in one of several clinical and histologic types or patterns (Table 1). As the etiology and pathogenesis of these forms and variants differ considerably, this classification is not final and may undergo marked changes in the future. In particular, localized and multicentric forms may represent two different diseases. The histologic patterns of the subtypes are described in more detail below.

Table 1 Clinical and histologic subtypes of Castleman disease (CD)

Clinical subtypes
Localized (unicentric) CD (LCD)
Multicentric CD (MCD)
Not otherwise specified
Plasmablastic variant of MCD
Histologic subtypes
Hyaline-vascular type CD (HVCD)
"standard" subtype
Stroma-rich subtype (in part with angiomyoid proliferative lesion)
Plasma cellular type CD
Mixed histopathologic pattern

Hepatobiliary Pathology in Castleman Disease

Hepatomegaly and Diffuse Infiltration of the Liver

Hepatomegaly sometimes associated with hepatalgia is a frequent feature of CD, found in about two thirds of the cases (Bowne et al. 1999; Greiner et al. 2000; Maloisel et al. 2003; Mura et al. 2011), but the histologic substratum is unknown in most cases. MCD has been demonstrated to produce atypical, mixed infiltrates of the liver (Rais et al. 1990). They consist of accumulations of lymphocytes, macrophages (sometimes epithelioid cells) and plasma cells chiefly in the portal tracts (Fig. 1), with or without associated lymph follicles with large germinal centers.

Focal Hepatic Infiltration and Hepatic Tumors in CD

Localized CD may develop deeply in the liver substance or the porta hepatis as localized space-occupying and sometimes hypervascular lesions (Rahmouni et al. 1992; Mosnier et al. 1996; Peck and Lum 1996; Cirillo et al. 1998; Uzunlar et al. 2000; Meador and McLarney 2000; Maloisel et al. 2003; Przkora et al. 2003; Erkan et al. 2004; Jang et al. 2012; Miyoshi et al. 2013) that may mimic other tumorous hepatic lesions. Localized CD can develop in a hilar/perihilar location (Peck and Lum 1996; Karami et al. 2010; User et al. 2011) and can cause biliary obstruction (Przkora et al. 2003). In one patient, a hyaline-vascular CD of the liver produced a mass that mimicked hepatocellular carcinoma (Jang et al. 2012). CD can involve lymph nodes around the porta hepatis and along the common bile duct, causing biliary obstruction (Al-Salamah et al. 2005).

The plasma cell variant of CD confined to the liver has rarely been reported (Mosnier et al. 1996). In one young female patient with slight polyclonal hypergammaglobulinemia, ultrasonography and CT revealed a 2 cm diameter nodule in the liver. The resection specimen showed a gray-white, nodular, ill-defined lesion histologically composed of a stellate fibrous scar, which delimited small hepatocyte nodules without lobular organization. Numerous hyperplastic lymph follicles with large germinal centers were observed in the fibrotic areas. The interfollicular area was characterized by increased vascularity with short, closely spaced venules containing high endothelial cells and by a moderate to dense polytypic plasmacytic infiltration, some of the plasma cells exhibiting Russel bodies (Mosnier et al. 1996). Lesions of the liver in MCD may present in the form of multiple nodules visualized by ultrasound and CT. In an MCD patient with this pattern undergoing hepatic transplantation, the explant showed large fibrotic masses resembling the hyaline-vascular germinal centers that have previously been found in a lymph node involved with hyaline-vascular CD (Maloisel et al. 2003). In another female patient, a tumorous and partly calcified lesion of up to 13 cm diameter was detected in the porta hepatis, abutting the left lobe of the liver. Histology showed a mixed histologic pattern of CD (Cirillo et al. 1998). In a further case of tumorous CD localized to the porta hepatis, the histologic pattern was that of hyaline-vascular CD. The resected specimen revealed a partly nodular mass measuring up to 3.5 cm with a characteristic histology (Uzunlar et al. 2000). Localized

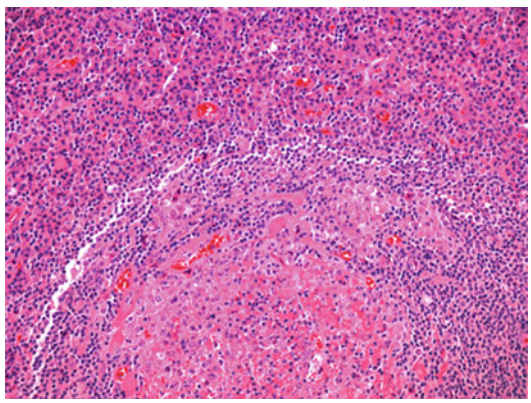

Fig. 1 Castleman disease of the liver. This case shows a focal epithelioid cell reaction (hematoxylin and eosin stain)

hyaline-vascular CD was also found as a nodule in the liver parenchyma (Miyoshi et al. 2013) and in the hepatoduodenal ligament (Sato et al. 2006).

Castleman Disease of the Bile Duct System

In very rare cases, CD manifests in the biliary tract. A case of hyaline-vascular CD of the extrahepatic bile duct, causing obstructive jaundice, was described. There was no evidence of disease elsewhere (Kalimuthu et al. 2013).

Vascular Neoplasia (VN) Complicating HVCD

The features of this unique tumor, which is different from Kaposi sarcoma (Gerald et al. 1990) have been described above. Among the seven patients described by the authors in 1990, two patients developed metastatic disease, in both instances involving the liver, with numerous nodules involving large areas of the liver (see Fig. 4 in the work of Gerald et al. 1990).

Microvascular and Regenerative Lesions of the Liver in CD

CD can be associated with marked hepatic sinusoidal dilatation causing hepatocyte plate atrophy (Featherstone et al. 1990; Curciarello et al. 1998; Kakar et al. 2004), with peliosis hepatis (Sherman et al. 1992) or peliosis hepatis combined with perisinusoidal fibrosis and nodular regenerative hyperplasia of the liver (Molina et al. 1995), a combination of lesions known to occur in several NHL (see the respective paragraphs). Interestingly, part of these changes may regress upon resection of the tumor, suggesting a humoral factor produced by CD lesions (Curciarello et al. 1998). In fact, it was shown that nodular regenerative hyperplasia of the liver in CD may be mediated by interleukin-6 (Kiyuna et al. 2005).

Amyloidosis in CD

The liver may be involved in those patients developing generalized amyloidosis in Castleman disease, causing hepatomegaly (Yamagata et al. 2006). By use of 123I-SAP scintigraphy and liver biopsy, hepatic accumulation of AA amyloid has been detected in such patients (Lachmann et al. 2002). A perihepatic manifestation of amyloidosis in Castleman disease has also been described (Ikeda et al. 1997).

Amyloidosis as a complication of CD is now well established and has been reported several times, but the pathogenic relationship has not yet been elucidated (West et al. 1989; Ordi et al. 1993; Tanaka et al. 1995; Ikeda et al. 1997; Curioni et al. 2001; Derici et al. 2002; Lachmann et al. 2002; review of the literature: Altiparmak et al. 2002; Gholam et al. 2003). Amyloidosis can develop in the localized form of CD and was found to regress following tumor removal (Androukali et al. 2007). One of the acute phase protein components of AA amyloid, SAA, has been shown to be elevated in Castleman disease (Ikeda et al. 1997) and to decrease after resection of the primary lesion (Perfetti al. 1994; Lachmann et al. 2002). In AA amyloidosis, a sustained high plasma concentration of SAA is a prerequisite for the development of amyloid accumulation, but it is not sufficient, because amyloid affects less than 10 % of those individuals with chronic inflammatory disease. One factor thought to modify amyloidogenic responses is IL-6, which is one of the major stimulants of acute phase protein synthesis by hepatocytes. The germinal centers of hyperplastic lymphoid follicles in the plasma cell variant of Castleman disease secrete large amounts of IL-6, and this response may affect pathways resulting in AA amyloidosis in this disorder.

Differential Diagnosis

Differential diagnosis includes lymphoid hyperplastic lesions other than CD, lymphocyte-predominant forms of Hodgkin disease, and several types of non-Hodgkin lymphomas.

Subtypes of CD and Their Histopathology

Localized (Unicentric) CD/LCD

LCD, the more common variant, manifests as a solitary mass that may be circumscribed or infiltrative, with associated lymphadenopathy confined to one lymph node or involving an entire nodal group/area. LCD of the hyaline-vascular type (HVCD) chiefly occurs in children and young adults (median age in the 30s), usually with manifestations in the mediastinum or the mesenteric area, sometimes with markedly enlarged peripheral or abdominal lymph nodes. More than 90 % of these patients do not have constitutional symptoms at presentation It usually follows a benign course after surgery (Bowne et al. 1999). LCD of the plasma cell type (PCCD) also preferentially occurs in children and young adults but overall in a younger age group (median age in the 20s). In contrast to HVCD, the mass usually consists of an aggregate of enlarged lymph nodes, most frequently in the mediastinum or the abdomen. Unlike HVCD, patients with PCCD often show constitutional symptoms and signs, and up to 90 % exhibit hematologic disorders, such as anemia and leukocytosis, and many develop hypergammaglobulinemia and hypoalbuminemia. It is the plasma cell variant of CD that, in contrast to HVCD, shows abnormal IL-6 expression by cells in the germinal centers and elsewhere in nodes, thought to hold an important position in pathogenic pathways.

Multicentric CD/MCD

MCD is rarer, and patients are older (median age in the 50s) and have multicentric manifestations. MCD is clinically characterized by cyclic episodes of lymphadenopathy, hepatosplenomegaly, fever, anemia, leukocytosis, hypergammaglobulinemia, hypoalbuminemia, skin rash, and rarely tumor lysis syndrome (Frizzera et al. 1983; Kessler 1985; Weisenburger et al. 1985; Peterson and Frizzera 1993; Lee et al. 2004). HIV-associated MCD is a rare lymphoproliferative disorder, the incidence of which seems to be increasing in the highly active antiretroviral therapy era (Bower et al. 2011; Reddy and Mitsuyasu 2011). It appears to occur more frequently in older HIV-positive individuals and well-preserved immune function (Powles et al. 2009). A significant fraction, or even most cases, of MCD are caused by KSHV/HHV8 (Polizzotto et al. 2012; Uldrick et al. 2012). It is a disease requiring chemotherapy and carries a worse prognosis, as subsequent infection of malignancy may lead to death (Herrada et al. 1998). Whereas LCD mainly presents with a mass effect, MCD is well known to manifest with constitutional symptoms and signs, multicentric lymphadenopathy, hepatosplenomegaly in many cases, and abnormal laboratory findings, including anemia and polyclonal hypergammaglobulinemia (Weisenburger et al. 1985). MCD follows one of four courses: relapse and remission, rapidly fatal disease, development of malignant lymphoma and/or Kaposi sarcoma, or stable and persistent disease (Weisenburger et al. 1985; Peterson and Frizzera 1993; Abdel-Reheim et al. 1996; Advani et al. 1999; Larroche et al. 2002 (with review of the literature); Oksenhendler et al. 2002). One subset of MCD is characterized by a "plasmablastic" cell population (plasmablastic-type MCD; PB-MCD) distinguished by the expression of HHV-8 latent nuclear antigen.

A disease occurring in Japan related to multicentric CD is characterized by thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly. The disorder shows myelofibrosis, microcytic anemia, signs of generalized inflammation, and renal dysfunction. Lymph nodes exhibited mixed or hyaline-vascular CD. This condition is termed TAFRO syndrome or Castleman-Kojima disease (Kawabata et al. 2013; Masaki et al. 2013).

Histologic Patterns of CD

Histologically, CD can be divided into three major patterns, i.e., the more common *hyaline-vascular type CD* (70–90 %), the less common *plasma*

cellular or plasma cell type CD, and a *mixed histopathologic pattern*. There is an association between these histologic patterns and the biology of disease. The histologic patterns can, in principle, occur both in localized and multicentric CD, however with some differences in prevalence.

Hyaline-Vascular CD

The hyaline-vascular type is commonly found in localized CD but has also been found in multicentric CD (Erkurt et al. 2009). This form of CD has been regarded as a reactive hyperplastic lesion, but recent studies have found monoclonality and cytogenetic abnormalities in part of these cases (Chang et al. 2014). In the hyaline-vascular type of CD (HVCD; synonym: Castleman disease of hyaline-vascular type, CDHV), the histologic hallmark consists of dense and in part venous vascular channels located to the interfollicular area and small, hyalinized follicles, in lymph nodes without distinction between cortical and medullary nodal architecture. The follicles are surrounded by circumferentially arranged layers of small lymphocytes, resulting in an "onion-skin" aspect in the mantle zone with radially arranged capillaries often penetrating the germinal centers. Frequently, the germinal centers contain deposits of hyaline connective tissue with a characteristic whorled appearance (Weisenburger et al. 1985; Carbone et al. 1986; Shahidi et al. 1995; Ghosh et al. 2010). A central stellate fibrosis visible in three-phase dynamic CT can occur in HVCD (Ota et al. 1997). In addition, this variant displays either an expanded, disrupted follicular dendritic cell network or multiple tight collections of follicular dendritic cells, whereas the arrangement and distribution of follicular dendritic cells in the plasma cell variant resemble those in normal follicles (Nguyen et al. 1994). The distinct features of follicular dendritic cells may be related to differential epidermal growth factor receptor expression in these cells, a shared feature of CD and follicular dendritic cell sarcoma (Sun et al. 2003). Whether the abnormally arranged follicular dendritic cells in CD express estrogen receptor alpha, as these cells do in lymph nodes (Sapino et al. 2003), is not yet known. Based on the distinct cellular composition of the interfollicular area in HVCD, resulting in considerable morphologic diversity of this tissue compartment (Danon et al. 1993), cells other than lymphocytes, plasma cells, and vascular cells have been studied in more detail. Specifically, a proliferation of dendritic-shaped or spindle cells was detected, a cell population divided into two types according to the immunostaining phenotype: CD68-reactive histiocytoid cells and smooth muscle actin-reactive myoid cells. Cases of HVCD with abundance of such cells were termed stroma-rich variants of HVCD (Danon et al. 1993). Similar proliferative lesions in the interfollicular area with either angiomyoid features or involving follicular dendritic cells were reported somewhat later and were predominantly found in female patients, and only in adults, frequently in an abdominal location (Lin and Frizzera 1997). Subsequently, cases of stroma-rich HVCD with marked and probably hyperplastic angiomyoid proliferative lesions consisting of SMA-positive but CD34- and desmin-negative spindle cells were reported (Izumi et al. 2002). HVCD is frequently associated with intra-lesion calcification, sometimes with a ramification or arborizing pattern (Sadamoto et al. 1998; Meador and McLarney 2000). In cases with marked fibrosis, a calcifying lesion (calcifying fibrous pseudotumor) may develop (Dargent et al. 1999). Most hyaline-vascular lesions are intrathoracic (Keller et al. 1972), with the anterior mediastinum as the most common site of occurrence. Although more than 90 % of the patients with hyaline-vascular CD are asymptomatic, symptoms caused by tracheobronchial compression may arise.

Plasma Cell Type CD

The plasma cell type of CD (PCCD) was first described in lymph nodes (Flendrig and Schillings 1969). It is characterized by normal to large germinal centers, no marked vascularization and hyalinization, occasional remnants of sinuses

between follicles, and a dense infiltration by plasma cells lying in sheets in the interfollicular areas (Keller et al. 1972). In PCCD associated with HHV8 infection, a distinct pattern of lymphoid follicle/germinal center dissolution, resulting from blurring of the mantle zone boundary where HHV8-infected lymphocytes are located, had been observed (Amin et al. 2003). The plasma cell type of CD is clinically more aggressive, commonly with involvement of multiple enlarged lymph nodes (Keller et al. 1972). Patients with the multicentric plasma cell variant of CD are generally older than those with plasma cellular LCD. In the localized plasma cell variant of CD, clonal cytogenetic abnormalities were detected, the clonal cells being non-lymphoid but rather stromal, dendritic, or endothelial in origin (Reichard et al. 2011).

A recently described clinicopathologic entity is the "plasmablastic" type of MCD (PB-MCD; Dupin et al. 2000). There is a clear association between PB-MCD and KSHV/HHV-8 infection. An increased pathogenicity of HHV-8 as well as an exacerbation of MCD have specifically been described in HIV-infected individuals and in the setting of AIDS (Suda et al. 2001; Schultz 2001; Aaron et al. 2002). The virally encoded production of IL-6 (vIL-6) in HHV-8 infection is regarded as an important driving force in the pathogenesis of this variant of MCD. vIL-6 not only contributes to plasmacytosis but can also induce VEGF and thus enhance angiogenesis (Aoki et al. 1999). In part of the patients, elevated levels of human IL-6 have been identified, apparently linked to increased IL-6 production in the interfollicular area in MCD and by dendritic cells located inside the enlarged follicular germinal centers (Yoshizaki et al. 1989; Leger-Ravet et al. 1991). Many of the HHV-8-infected cells also express the human IL-6 receptor, further supporting the significance of an IL-6-mediated pathway (Du et al. 2001). The expansion of target cell populations may also be affected by the function of HHV-8 K15 protein that can form a homodimer with an antiapoptotic protein, HAX-1 (Sharp et al. 2002). One variant of MCD is immunohistochemically characterized by numerous IgG4-positive plasma cells, resulting in a phenotype having overlapping features with IgG4-associated systemic sclerosing disease (Sato et al. 2010).

Neoplastic Lesions Associated with Castleman Disease

Lymphoproliferative Disorders

LCD and MCD are associated with the synchronous or metachronous development of a whole spectrum of tumorous lesions. LCD, including the plasma cell variant, can be complicated by NHL, albeit less commonly than the MCD counterpart, and a part of the NHL are plasma cell-rich marginal zone B-cell NHL resembling plasmacytoma (Kojima et al. 2002). Hypervascular follicular hyperplasia (HFH) associated with LCD can evolve into sometimes large angioproliferative and mass-producing lesions that may later behave aggressively (Gerald et al. 1990). It has been proposed that this vascular proliferative response in lymph nodes and in extranodal areas is related to increased production of vascular endothelial growth factor by cell systems of CD (VEGF; Nishi and Maruyama 2000).

MCD is more frequently associated with malignancy, especially Kaposi sarcoma (Dickson et al. 1985; De Rosa et al. 1989) and several types of NHL (Dickson et al. 1985; Vasef et al. 1992; Abdel-Reheim et al. 1996; Orcioni et al. 1998; Advani et al. 1999; Ascoli et al. 2001; Larroche et al. 2002 (with review of the literature); Oksenhendler et al. 2002; Nozawa et al. 2002; Theate et al. 2003; Vanizelos et al. 2004), including plasmacytoma (Schlosnagle et al. 1982; Kurihara and Hashimoto 1983; Wilkinson and Forrester-Wood 2003). NHL is clearly more often associated with MCD, its diagnosis being concurrent with CD diagnosis or occurring within 2 years. B-NHL is predominant (about 70 %), and mantle cell NHL represents about 40 % of the B-NHL. Hodgkin disease (HD) chiefly occurs in LCD of the plasma cell type, usually in the same nodal areas (Zarate-Osorno et al. 1994; Drut 1996). HD is of interfollicular or nodular sclerosis types, and its clinical course seems to be better than NHL (Larroche et al. 2002). Interestingly,

MCD can result in a population of immunoblastic/plasmablastic neoplastic cells (MCD-associated plasmablastic lymphoma) that localize to the body cavities, thus inducing the PEL phenotype (Ascoli et al. 2001). This observation suggests a link between MCD and PEL and suggests that MCD is a prelymphoma state. Further neoplastic lesions known to complicate CD, and more commonly the hyaline-vascular variant, are angiomyoid and follicular dendritic cell proliferative lesions, in particular follicular dendritic cell tumor, which is of specific interest in the light of the pathogenic involvement of follicular dendritic cells and other stromal cells in CD lesions (Chan et al. 1994, 2001; Saiz et al. 1997; Katano et al. 1997; Lin and Frizzera 1997; Fornelli et al. 1998; Perez-Ordonez and Rosai 1998; Desai et al. 2000; Yamamoto et al. 2004). A disorder sometimes regarded as identical to MCD is idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia (IPL). However, IPL has a significantly better 5-year survival rate than MCD, and none of 16 reported patients developed Kaposi sarcoma or a B-cell NHL or were KSHV positive, suggesting that IPL is distinct from MCD reported in Western countries (Kojima et al. 2004).

Vascular and Spindle Cell Tumors in Castleman Disease

The most well-established vascular tumor associated with CD is Kaposi sarcoma. Its histologic differential diagnosis comprises fibrovascular lymph node lesions mimicking hypervascular forms of CD, including angioproliferative lymphadenopathy developing in Epstein-Barr virus infection (Kojima et al. 2003). In addition to Kaposi sarcoma, the most intriguing vascular tumorous lesion evolving in CD is the so-called vascular neoplasia (VN; spindle cell sarcoma complicating Castleman disease; Gerald et al. 1990; Kakiuchi et al. 2002). It is characterized by a vascular neoplastic phenotype that is clearly different from Kaposi sarcoma. Based on seven cases (Gerald et al. 1990), the following features are characteristic of this distinct lesion: (1) combined features of HVCD/HFH and vascular neoplasia; (2) predominant location in the retroperitoneal space; (3) the vascular neoplastic component seems to arise from the interfollicular hypervascular regions of HVCD and is characterized by swirling fascicles of spindle, oval, and epithelioid cells, sometimes forming well-defined lumina with or without red blood cells, the lesions in part forming nodular structures; (4) constant presence of significant nuclear atypicality and pleomorphism in the absence of markedly elevated mitotic activity; (5) hemorrhage, fibrosis, and necrosis in most cases; and (6) recurrence of disease with metastases in the minority of the cases. Furthermore, lymphonodal spindle cell tumors occur in conjunction with mycobacterial infection in HIV-positive patients ("mycobacterial pseudotumors"; Logani et al. 1999), lesions not to be confounded with Kaposi sarcoma with mycobacteria. The abnormal vascular proliferative response in some of the lesions developing in HHV8-associated CD may be directly related to HHV-8 infection of target cells. It has been demonstrated that HHV-8 is localized to lymphonodal subcapsular spindle cell proliferations (where early intranodal Kaposi sarcoma initiates) and endothelial cells in CD (O'Leary et al. 2000). On the other hand, Kaposi sarcoma-associated herpesvirus-encoded interleukin-6 (vIL-6), a multifunctional cytokine that is elevated in HHV-8-associated CD, and IL-6 that may be increased in CD (Yoshizaki et al. 1989; Hsu et al. 1993; Foss et al. 1997) seem to exert a pro-angiogenic activity (Aoki et al. 1999) and are therefore thought to play an important role in the pathogenesis of certain HHV-8-associated disorders, including CD with hypervascular features and associated fibrovascular lesions. Furthermore, vascular endothelial growth factor (VEGF) is elevated in CD (Nishi and Maruyama 2000), and is mainly expressed in spindle cells, most likely myofibroblasts, located to follicular structures in CD, suggesting that vascularization of germinal centers in CD may be a consequence of abnormal local VEGF production (Foss et al. 1997). Secretion of VEGF and IL-6 was also observed in a distinct CD-associated vascular tumor, spindle cell sarcoma complicating Castleman disease, and so-called vascular neoplasia (Kakiuchi et al. 2002).

Apart from endothelial cells, distinct mesenchymal and/or myoid cell types are involved in a growing spectrum of fibrous, myoid, and vascular tumors and tumor-like lesions in several organs and tissues, and some of them may occur in the context of Castleman disease. They include (1) the so-called vascular neoplasia developing in CD (VN; spindle cell sarcoma complicating CD; Gerald et al. 1990); (2) pericyte-rich vascular neoplasms (Chan et al. 1994); (3) a group of lymphonodal myofibroblastic nodular lesions, comprising palisaded myofibroblastoma/intranodal hemorrhagic spindle cell tumor with amianthoid fibers/features (Michal et al. 1992; Padberg et al. 1994; Rossi et al. 1995; Rahimi et al. 1995; Creager and Garwacki 1999); (4) angiomyomatous lymphonodal hamartoma (Sakurai et al. 2000); (5) fibrohistiocytic nodular lesions developing in Castleman disease (Kurotaki et al. 1993); (6) angiomyoid proliferative lesions in stroma-rich HVCD (Izumi et al. 2002); (7) cutaneous glomeruloid hemangioma in Castleman disease associated with POEMS syndrome (Chan et al. 1990); (8) sclerosing angiomatoid nodular transformation (SANT) of the spleen (Martel et al. 2004), previously termed "cord capillary hemangioma" (Krishnan et al. 1993); and (9) a growing group of lesions consisting of cells probably belonging to a myofibroblast lineage, including pseudoangiomatous stromal hyperplasia (PASH) of the breast (Powell et al. 1995).

At least one cellular component involved in the pathogenesis of nodular spindle cell lesions of lymph nodes consists of a nodal stromal cell with myoid features, probably representing a subset of reticular cells in lymph nodes and the spleen. The true nature of such myoid cells still awaits characterization. One form of myoid cells is reactive for smooth muscle myosin and occurs mainly in lymph follicles and especially in germinal centers but is not present in the interfollicular area (Pinkus et al. 1986). Desmin negativity of interfollicular myoid cells has later been confirmed (Izumi et al. 2002). However, another study reported that the myoid cells in the interfollicular area and deep lymphonodal cortex were positive for both alpha-SMA and desmin, while myoid cells in the medulla were only positive for desmin (Toccanier-Pelte et al. 1987). A further lymphonodal spindle cell type originally termed "fibroblastic reticulum cell" and being reactive for smooth muscle actin and myosin (Müller-Hermelinck et al. 1981) most likely represents a myofibroblast or a myofibroblast-like cell. Therefore, at least some of the myoid and in part nodular lesions occurring in CD may in fact represent lesions consistent with myofibroblastic inflammatory pseudotumor (Izumi et al. 2002).

Pathogenesis

The pathogenesis of CD is still controversial and complex (reviews: Al-Maghrabi 2011; El-Osta and Kurzrock 2011). Overall, etiopathogenic pathways discussed include infections, autoimmune mechanisms, and dysregulated cytokine production. In particular, overproduction of interleukin-6 (IL-6), either by cells of the hyperplastic follicles or virally encoded (KSHV-induced, vIL-6) seems to be important for the progression of both. LCD and MCD, but predominantly in histologic variants characterized by high plasma cell density, i.e., the plasma cell types (Van den Berg et al. 2002; Day et al. 2003; Abe et al. 2006). There is increasing evidence that an abnormal proliferative response of mesenchymal/stromal cells, including follicular dendritic cells, may play a pathogenic role in CD and in particular its hyaline-vascular variant. It has, e.g., been shown that a rearrangement of a target gene located to 12q13–15 and encoding a member of the high mobility group protein family (HMGIC) is exclusively present in anti-CD21-reactive follicular dendritic cells in hyaline-vascular CD, suggesting a distinct molecular pathway promoting stromal cell overgrowth (Cokelaere et al. 2002). An abnormal vascular proliferative response in some of the lesions (see below) is thought to be mediated by increased release of VEGF (Nishi and Maruyama 2000).

The pathogenetic mechanisms involved in KSHV-induced CD are only partially elucidated. KSHV-encoded proteins determine or modulate cell proliferation, apoptosis, and differentiation,

acting on several types of target cells, including lymphoid cells, fibroblastoid spindle cells, and endothelial cells (review: Giffin and Damania 2014). In order to induce long-lasting effects on surviving host cells, lifelong latency of KSHV is important, but the mechanisms causing this latency are not well known. Latently infected cells have multiple extrachromosomal copies of covalently closed circular KSHV genomes (episomes) that are stably maintained in proliferating cells. The principle latency-associated factor is the latency-associated nuclear antigen, LANA, a protein which mediates episome persistence. It does so by promoting episome replication with each cell division (review: Ballestas and Kaye 2011). One regulatory loop is based on a feedback mechanism in which the viral replication and transcription activator (RTA) induces the expression of the latency-associated nuclear antigen (LANA) during early infection. LANA is expressed also in KSHV-induced tumor cells. LANA represses transcription and the function of RTA, thus establishing latency. For RTA repression, LANA interacts with the recombination signal sequence-binding protein Jk (RBP-Jk), a repressor of the Notch signaling pathway (Jin et al. 2012). For proliferation of KSHV-associated tumor cells, viral-encoded interleukin-6 (vIL-6) plays an important role (review: Nicholas 2010), regulated by a microRNA pathway (Kang et al. 2011). In addition, there is increasing evidence that not only factors produced during latent infection but also lytic phase viral gene products are involved in the regulation of host cell proliferation (review: Gantt and Casper 2011). The KSHV-encoded viral FLICE inhibitory protein (vFLIP) K13 protects against antibody-induced growth arrest and apoptosis in B lymphocytes in an NF-kB-dependent manner (Graham et al. 2013). KSHV is associated with angioproliferation as seen in Kaposi sarcoma. Several pathways seem to be involved in this angiogenic cascade. In Kaposi sarcoma, both hypoxia-inducible factor (HIF)-1alpha and HIF-2alpha were detected, suggesting a role of these oxygen sensors in tumoral angiogenesis. It appears that this oxygen-mediated influence on the actions of KSHV is regulated by a signaling network. The KSHV-associated ORF34 protein, a lytic gene product, is activated by hypoxia, and its transcription is upregulated by both HIFs. RF34 binds to HIF-1alpha and causes its degradation through the proteasome pathway (Haque and Kousoulas 2013). In MCD caused by KSHV/HHV8, the angiogenic response may be induced by the two KSHV-encoded factors, vMIP-I and vMIP-II. These proteins can be identified in MCD by use of monoclonal antibodies (Nakano et al. 2012). KSHV exerts profound effects on the host's immune system and alters the proliferation and differentiation of immunologic effector cells, important mechanisms in the pathogenesis of both CD and KSHV-associated lymphomas. Immune cells latently infected by KSHV downregulate genes involved in the host immune response, including genes for CD80, CD86, and the cytokines TNFalpha and IL-1beta, leading to a minimization of the viral immunological signature and evasion from host detection (Gregory et al. 2012).

Multicentric Giant Lymph Node Hyperplasia

Multicentric giant lymph node hyperplasia is a rare disorder of unknown etiology, characterized by the presence of lymphoid hyperplasia of lymph nodes at different sites, including cervical, axillary, and inguinal lymph nodes. Liver and bone marrow showed a moderate lymphocytic and plasmacellular infiltration. The patient has fever, skin rashes, and a polyclonal gammopathy and shows a rapidly progressive course (Bartoli et al. 1980).

Multicentric Abdominal Angiofollicular Hyperplasia

Multicentric abdominal angiofollicular hyperplasia is a very uncommon nonmalignant lymphoproliferative disorder of unknown etiology, characterized by fever, arthralgia, polyclonal gammopathy, presence of several autoantibodies, exclusively abdominal lymphadenopathy, and liver infiltration. Abdominal lymph nodes showed

reactive angiofollicular hyperplasia. Polyclonal lymphocytosis persisted in spate of steroid therapy (Montalban et al. 1989). The liver showed a portal tract infiltrate composed of small lymphocytes, plasma cells, and centrofollicular cells forming portal tract nodules, sometimes with intraepithelial lymphocytic infiltrates of small bile ducts, with lymphoepithelial lesions.

References

Aaron L, Lidove O, Viard JP, Troisvallet D, Piketty C, Vittecoq D, Zucman D, Bletry O, Dupont B (2002) Castleman's disease in patients infected with HIV. Rev Med Int 23:155–163

Abdel-Reheim FA, Koss W, Rappaport ES, Arber DA (1996) Coexistence of Hodgkin's disease and giant lymph node hyperplasia of the plasma-cell type (Castleman's disease). Arch Pathol Lab Med 120:91–96

Abe Y, Matsubara D, Gatanaga H, Oka S, Kimura S, Sasao Y, Saitoh K, Fujii T, Sato Y et al (2006) Distinct expression of Kaposi's sarcoma-associated herpesvirus-encoded proteins in Kaposi's sarcoma and multicentric Castleman's disease. Pathol Int 56:617–624

Advani R, Warnke R, Rosenberg S (1999) Treatment of multicentric Castleman's disease complicated by the development of non-Hodgkin's lymphoma with high-dose chemotherapy and autologous peripheral stem-cell support. Ann Oncol 10:1207–1209

Al-Maghrabi JA (2011) Castleman's disease. Update on pathogenesis. Saudi Med J 32:451–458

Al-Salamah SM, Khan IA, Khalid K, Al-Shakweer WA (2005) Castleman disease presenting as obstructive jaundice. Saudi Med J 26:111–113

Altiparmak MR, Pamuk GE, Pamuk ON, Dogusoy G (2002) Secondary amyloidosis in Castleman's disease: review of the literature and report of a case. Ann Hematol 81:336–339

Amin HM, Medeiros LJ, Manning JT and Jones D (2003) Dissolution of the lymphoid follicles is a feature of the HHV8+ variant of plasma cell Castleman's disease. Am J Surg Pathol 27: 91–100

Androulaki A, Giaslakiotis K, Giakoumi X, Aessopos A, Lzaris AC (2007) Localized Castleman's disease associated with systemic AA amyloidosis. Regression of amyloid deposits after tumor removal. Ann Hematol 86:55–57

Aoki Y, Jaffe ES, Chang Y, Jones K, Teruya-Feldstein J, Moore PS, Tosato G (1999) Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. Blood 93:4034–4043

Arlet JB, Hermine O, Darnige L, Ostland V, Westerman M, Badoual C, Pouchot J, Capron L (2010) Iron-deficiency anemia in Castleman disease: implication of the interleukin 6/hepcidin pathway. Pediatrics 126: e1608–e1612

Ascoli V, Signoretti S, Onetti-Muda A, Pescarmona E, Della-Rocca C, Nardi F, Mastroianni CM et al (2001) Primary effusion lymphoma in HIV-infected patients with multicentric Castleman's disease. J Pathol 193:200–209

Ballestas ME, Kaye KM (2011) The latency-associated nuclear antigen, a multifunctional protein central to Kaposi's sarcoma-associated herpesvirus latency. Future Microbiol 6:1399–1413

Bartoli E, Massarelli G, Soggia G, Tanda F (1980) Multicentric giant lymph node hyperplasia. A hyperimmune syndrome with a rapidly progressive course. Am J Clin Pathol 73:423–426

Bower M, Newsom-Davis T, Naresh K, Merchant S, Lee B, Gazzard B, Stebbing J et al (2011) Clinical features and outcome in HIV-associated multicentric Castleman's disease. J Clin Oncol 29:2481–2486

Bowne WB, Lewis JJ, Filippa DA, Niesvizky R, Brooks AD, Burt ME, Brennan MF (1999) The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. Cancer 85:706–717

Carbone A, Manconi R, Volpe R, Poletti A, De Paoli P, Tirelli U, Santini G (1986) Immunohistochemical, enzyme histochemical, and immunologic features of giant lymph node hyperplasia of the hyaline-vascular type. Cancer 58:908–916

Castleman B, Towne VW (1954) Case records of the Massachusetts General Hospital: case 32–1984. N Engl J Med 311:388–398

Chan JK, Fletcher CD, Hicklin GA, Rosai J (1990) Glomeruloid hemangioma. A distinctive cutaneous lesion of multicentric Castleman's disease associated with POEMS syndrome. Am J Surg Pathol 14:1036–1046

Chan JKC, Tsang WYW, Ng CS (1994) Follicular dendritic cell tumour and vascular neoplasm complicating hyaline-vascular Castleman's disease. Am J Surg Pathol 18:517–525

Chan AC, Chan KW, Chan JK, Au WY, Ho WK, Ng WM (2001) Development of follicular dendritic cell sarcoma in hyaline-vascular Castleman's disease of the nasopharynx: tracing its evolution by sequential biopsies. Histopathology 38:510–518

Chang KC, Wang YC, Hung LY, Huang WT, Tsou JH, Jones D, Song HL, Yeh YM, Kao LY, Medeiros LJ (2014) Monoclonality and cytogenetic abnormalities in hyaline vascular Castleman disease. Mod Pathol 27:823–831

Cirillo RL, Vitellas KM, Deyoung BR, Bennett WF (1998) Castleman disease mimicking a hepatic neoplasm. Clin Imaging 22:124–129

Cokelaere K, Debiec-Rychter M, De Wolf-Peeters C, Hagemeijer A, Sciot R (2002) Hyaline vascular Castleman's disease with HMGIC rearrangement in follicular dendritic cells: molecular evidence of mesenchymal tumorigenesis. Am J Surg Pathol 26:662–666

Creager AJ, Garwacki CP (1999) Recurrent intranodal palisaded myofibroblastoma with metaplastic bone formation. Arch Pathol Lab Med 123:433

Curciarello J, Castelletto R, Barbero R, Belloni P, Gelemur M, Castelletto E, Jmelnitzky A (1998) Hepatic sinusoidal dilatation associated to giant lymph node hyperplasia (Castleman's): a new case in a patient with periorbital xanthelasmas and history of celiac disease. J Clin Gastroenterol 27:76–78

Curioni S, D'Amico M, Quartagno R, Martino S, Dell'Antonio G, Cusi D (2001) Castleman's disease with nephrotic syndrome, amyloidosis and autoimmune manifestations. Nephrol Dial Transplant 16:1475–1478

Danon AD, Krishnan J, Frizzera G (1993) Morphoimmunophenotypic diversity of Castleman's disease, hyaline-vascular type: with emphasis on a stroma-rich variant and a new pathogenetic hypothesis. Virchows Arch A Pathol Anat Histol 423:369–382

Dargent JL, Delplace J, Roufosse C, Laget JP, Lespagnard L (1999) Development of a calcifying fibrous pseudotumour within a lesion of Castleman disease, hyaline-vascular subtype. J Clin Pathol 52:547–549

Day JRS, Bew D, Ali M, Dina R, Smith PLC (2003) Castleman's disease associated with myasthenia gravis. Ann Thorac Surg 75:1648–1650

De Rosa G, Barra E, Guarino M, gentile R (1989) Multicentric Castleman's disease in association with kaposi's sarcoma. Appl Pathol 7:105–110

Derici U, Arinsoy T, Ataoglu O, Bali M, Eroglu A, Goker B, Sindel S (2002) Localized Castleman's disease and nephrotic syndrome not responsive to resection plus colchicine therapy. Ann Hematol 81:399–401

Desai SB, Pradham SA, Chinoy RF (2000) Mediastinal Castleman's disease complicated by follicular dendritic cell tumour. Indian J Cancer 37:129–132

Dham A, Peterson BA (2007) Castleman disease. Curr Opin Hematol 14:354–359

Dickson D, Ben-Ezra JM, Reed J, Flax H, Janis R (1985) Multicentric giant lymph node hyperplasia, Kaposi's sarcoma, and lymphoma. Arch Pathol Lab Med 109:1013–1018

Dispenzieri A, Armitage JO, Loe MJ, Geyer SM, Allred J, Camoriano JK, Menke DM et al (2012) The clinical spectrum of Castleman's disease. Am J Hematol 87:997–1002

Drut R (1996) Coexistence of Hodgkin's disease and Castleman's disease. Arch Pathol Lab Med 120:1084

Du MQ, Liu H, Diss TC, Ye H, Hamoudi RA, Dupin N, Meignin V, Oksenhendler E et al (2001) Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. Blood 97:2130–2136

Dupin N, Diss TL, Kellam P, Tulliez M, Du MQ, Sicard D, Weiss RA, Isaacson PG, Boshoff C (2000) HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood 95:1406–1412

El-Osta HE, Kurzrock R (2011) Castleman's disease: from basic mechanisms to molecular therapeutics. Oncologist 16:497–511

Erkan N, Yildirim M, Selek E, Sayhan S (2004) Peripancreatic castleman disease. JOP 5:491–494

Erkurt MA, Aydogdu I, Kuku I, Kaya E, Mizrak B, Basaran Y (2009) A multicentric, hyaline vascular variant of Castleman's disease associated with B cell lymphoma: a case report. Cases J 2:8183

Featherstone T, Bayliss AP, Ewen SW, Brunt PW, Dawson AA (1990) Obscure anemia and hepatic dysfunction in Castleman's disease. Gut 31:834–837

Flendrig JA, Schillings PHM (1969) Benign giant lymphoma: the clinical signs and symptoms (Abstract). Folia Med Neerlandica 12:119

Fornelli A, Mureden A, Eusebi V (1998) Follicular dendritic cell tumor and unusual vascular lesion in lymph node with Castleman's disease. Description of a case. Pathologica 90:146–151

Foss HD, Araujo I, Demel G, Klotzbach H, Hummel M, Stein H (1997) Expression of vascular endothelial growth factor in lymphomas and Castleman's disease. J Pathol 183:44–50

Frizzera G (1988) Castleman's disease and related disorders. Semin Diagn Pathol 5:346–364

Frizzera G, Massarelli G, Banks PM, Rosai J (1983) A systemic lymphoproliferative disorder with morphologic features of Castleman's disease. Pathological findings in 15 patients. Am J Surg Pathol 7:211–231

Gantt S, Casper C (2011) Human herpesvirus 8-associated neoplasms: the roles of viral replication and antiviral treatment. Curr Opin Dis 24:295–301

Gerald W, Kostianovsky M, Rosai J (1990) Development of vascular neoplasia in Castleman's disease. Report of seven cases. Am J Surg Pathol 14:603–614

Gholam D, Vantelon JM, Al-Jijakli A, Bourhis JH (2003) A case of multicentric Castleman's disease associated with advanced systemic amyloidosis treated with chemotherapy and anti-CD20 monoclonal antibody. Ann Hematol 82:766–768

Ghosh A, Pradhan SV, Talwar OP (2010) Castleman's disease – hyaline vascular type – clinical, cytological and histological features with review of literature. Indian J Pathol Microbiol 53:244–247

Giffin L, Damania B (2014) KSHV: pathways to tumorigenesis and persistent infection. Adv Virus Res 88:111–159

Graham C, Matta H, Yang Y, Yi H, Suo Y, Tolani B, Chaudhary PM (2013) Kaposi's sarcoma-associated herpesvirus oncoprotein K13 protects against B cell receptor-induced growth arrest and apoptosis through NF-kB activation. J Virol 87:2242–2252

Gregory SM, Wang L, West JA, Dittmer DP, Damania B (2012) Latent Kaposi's sarcoma-associated herpesvirus infection of monocytes downregulates expression of adaptive immune response costimulatory receptors and proinflammatory cytokines. J Virol 86:3916–3923

Greiner T, Armitage JO, Gross TG (2000). Atypical lymphoproliferative disease. In: Schechter GP,

Berliner N, Telen MJ (eds) The American Society of Hematology (ASH) Education program book. 2000 no. 1, ASH, Washington D.C. pp 133–146

Haque M, Kousoulas KG (2013) The Kaposi's sarcoma-associated herpesvirus ORF34 protein binds to HIF-1a and causes its degradation via the proteasome pathway. J Virol 87:2164–2173

Herrada J, Cabanillas F, Rice L, Manning J, Pugh W (1998) The clinical behavior of localized and multicentric Castleman disease. Ann Intern Med 128:657–662

Hsu SM, Waldron JA, Xie SS, Barlogie B (1993) Expression of interleukin-6 in Castleman's disease. Hum Pathol 24:833–839

Ikeda S, Chisuwa H, Kawasaki S, Ozawa J, Hoshii Y, Yokota T, Aoi T (1997) Systemic reactive amyloidosis associated with Castleman's disease: serial changes of the concentrations of acute phase serum, amyloid A and interleukin 6 in serum. J Clin Pathol 50:965–967

Izumi M, Mochizuki M, Kuroda M, Iwaya K, Mukai K (2002) Angiomyoid proliferative lesion: an unusual stroma-rich variant of Castleman's disease of hyaline-vascular type. Virchows Arch 441:400–405

Jang SY, Kim BH, Kim JH, Ha SH, Hwang JA, Yeon JW, Kim KH, Paik SY (2012) A case of Castleman's disease mimicking a hepatocellular carcinoma: a case report and review of the literature. Korean J Gastroenterol 59:53–57

Jin Y, He Z, Liang D, Zhang Q, Zhang H, Deng Q, Robertson ES, Lan K (2012) Carboxy-terminal amino acids 1052 to 1082 of the latency-associated nuclear antigen (LANA) interact with RBP-Jk and are responsible for LANA-mediated RTA repression. J Virol 86:4956–4969

Kakar S, Kamath PS, Burgart LJ (2004) Sinusoidal dilatation and congestion in liver biopsy: is it always due to venous outflow impairment ? Arch Pathol Lab Med 128:901–904

Kakiuchi C, Ishida T, Sato H, Katano H, Ishiko T, Mukai H, Kogi M, Kasuga N, Takeuchi K et al (2002) Secretion of interleukin-6 and vascular endothelial growth factor by spindle cell sarcoma complicating Castleman's disease (so-called 'vascular neoplasia'). J Pathol 197:264–271

Kalimuthu SN, Traynor O, Albores-Saavedra J, Sheahan K, Gibbons D (2013) Hyaline vascular Castleman's disease involving the biliary tract. Ir Med J 106:86

Kang JG, Majerciak V, Uldrick TS, Wang X, Kruhlak M, Yarchoan R, Zheng ZM (2011) Kaposi's sarcoma-associated herpesviral IL-6 and human IL-6 open reading frames contain miRNA binding sites and are subject to cellular miRNA regulation. J Pathol 225:378–389

Karami H, Sahebpour AA, Ghasemi M, Karami H, Dabirian M, Vahidshahi K, Masiha F et al (2010) Hyaline vascular-type Castleman's disease in the hilum of liver: a case report. Cases J 3:74

Katano H, Kaneko K, Shimizu S, Saito T, Irie T, Mori S (1997) Follicular dendritic cell sarcoma complicated by hyaline-vascular type Castleman's disease in a schizophrenic patient. Pathol Int 47:703–706

Kawabata H, Takai K, Kojima M, Nakamura N, Aoki S, Nakamura S, Kinoshita T, Masaki Y (2013) Castleman-Kojima disease (TAFRO syndrome): a novel systemic inflammatory disease characterized by a constellation of symptoms, namely, thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly: a status report and summary of Fukushima (6 June, 2012) and Nagoya meetings (22 September, 2012). J Clin Exp Exp Hematop 53:57–61

Keller AR, Hocholzer L, Castleman B (1972) Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 29:670–683

Kessler E (1985) Multicentric giant lymph node hyperplasia. A report of seven cases. Cancer 56:2446–2451

Kiyuna A, Sunagaawa T, Hokama A, Touyama M, Tomiyama R, Sakugawa H, Kinjo F, Saito A (2005) Nodular regenerative hyperplasia of the liver and Castleman's disease: potential role of interleukin-6. Dig Dis Sci 50:314–316

Kojima M, Nakamura S, Motooti T, Shimano S, Murayama K, Tamaki Y, Shimizu K, Oyama T et al (2002) Primary marginal zone B-cell lymphoma of the lymph node resembling plasmacytoma arising from a plasma cell variant of Castleman's disease. A clinicopathological and immunohistochemical study of seven patients. APMIS 110:875–880

Kojima M, Yamane Y, Itoh H, Tanaka H, Sugihara S, Masawa N, Nakamura S (2003) Epstein-Barr virus-related lymph node lesion resembling autoimmune disease-like clinicopathological findings in elderly patients. Report of three cases. APMIS 111:1083–1088

Kojima et al. (2004) Pubmed PMID 14765269

Krishnan J, Danon A, Frizzera D (1993) Use of an anti-factor VIII-related antigen (F8) and QBEN10 (CD34) antibodies helps classify the benign vascular lesions of the spleen. Mod Pathol 6:94A

Kurihara K, Hashimoto N (1983) Extramedullary plasmacytoma associated with a Castleman's lesion of the cervical nodes. J Oral Pathol 12:131–138

Kurotaki H, Kaimori M, Nagai K (1993) Recurred Castleman's disease containing a fibrohistiocytic nodular lesion with vascular occlusion. Acta Pathol Jpn 43:603–607

Lachmann HJ, Gilbertson JA, Gillmore JD, Hawkins PN, Pepys MB (2002) Unicentric Castleman's disease complicated by systemic AA amyloidosis: a curable disease. QJM 95:211–218

Larroche C, Cacoub P, Soulier J, Oksenhendler E, Clauvel JP, Plette JC, Raphael M (2002) Castleman's disease and lymphoma: report of eight cases in HIV-negative patients and literature review. Am J Hematol 69:119–126

Lee KD, Lee KW, Choi IS, Yoon SS, Park S, Kim BK, Kim NK (2004) Multicentric Castleman's disease complicated by tumor lysis syndrome. Ann Hematol 83:722–725

Leger-Ravet MB, Peuchmaur M, Devergne O, Andouin J, Raphael M, Van Damme J et al (1991) Interleukin-6 gene expression in Castleman's disease. Blood 78:2923–2930

Lin O, Frizzera G (1997) Angiomyoid and follicular dendritic cell proliferative lesions in Castleman's disease of hyaline-vascular type: a study of 10 cases. Am J Surg Pathol 21:1295–1306

Logani S, Lucas DR, Cheng JD, Ioachim HL, Adsay NV (1999) Spindle cell tumors associated with mycobacteria in lymph nodes of HIV-positive patients: 'Kaposi sarcoma with mycobacteria' and 'mycobacterial pseudotumor'. Am J Surg Pathol 23:656–661

Maloisel F, Andres E, Chenard MP, Ellero B, Wolf P (2003) Treatment of hepatic relapse of multicentric Castleman's disease with transplantation. Am J Med 115:160–162

Martel M, Cheuk W, Lombardi L, Lifschitz-mercer B, Chan JK, Rosai J (2004) Sclerosing angiomatoid nodular transformation (SANT): report of 25 cases of a distinctive benign splenic lesion. Am J Surg Pathol 28:1268–1279

Martino G, Cariati S, Tintisona O, Veneroso S, De Villa F, Vergine M, Monti M (2004) Atypical lymphoproliferative disorders: Castleman's disease. Case report and review of the literature. Tumori 90:352–355

Masaki Y, Nakajima A, Iwao H, Kurose N, Sato T, Nakamura T, Miki M, Sakai T, Kawanami T, Sawaki T et al (2013) Japanese variant of multicentric Castleman's disease associated with serositis and thrombocytopenia – a report of two cases: is TAFRO syndrome (Castleman-Kojima disease) a distinct clinicopathological entity ? J Clin Exp Hematop 53:79–85

Maslovsky I, Uriev L, Lugassy G (2000) The heterogeneity of Castleman disease: report of five cases and review of the literature. Am J Med Sci 320:292–295

McCarthy MJ, Vukelja SJ, Banks PM, Weiss RB (1995) Angiofollicular lymph node hyperplasia (Castleman's disease). Cancer Treat Rev 21:291–310

McClain KL, Natkunam Y, Swerdklow SH (2004) Atypical cellular disorders. Hematol Am Soc Hematol Educ Program 2004:283–296

Meador TL, McLarney JK (2000) CT features of Castleman disease of the abdomen and pelvis. AJR Am J Roentgenol 175:115–118

Michal M, Chlumska A, Povysilova V (1992) Intranodal "amianthoid" myofibroblastoma. Report of six cases immunohistochemical and electron microscopical study. Pathol Res Pract 188:199–204

Miyoshi H, Mimura S, Nomura T, Tani J, Morishita A, Kobara H, Mori H, Yoneyama H et al (2013) A rare case of hyaline-type Castleman disease in the liver. World J Hepatol 5:404–408

Molina T, Delmer A, Le Tourneau A, Texier P, Degott C, Audoin J, Zittoun R, Diebold J (1995) Hepatic lesions of vascular origin in multicentric Castleman's disease, plasma cell type: report of one case with peliosis hepatis and another with perisinusoidal fibrosis and nodular regenerative hyperplasia. Pathol Res Pract 191:1159–1164

Montalban C, Bellas C, Brieva JA, Moreno A, Orte J, Ferro MT, Fernandez Muñoz R (1989) Multicentric abdominal angiofollicular hyperplasia: a clinical variant with exclusive involvement of the liver and abdominal lymph nodes (in Spanish). Sangre (Barc) 34:285–291

Mosnier JF, Flejou JF, Degos F, Belghiti J, Brouet JC, Benhamou JP, Degott C (1996) Plasma cell variant of Castleman's disease localized to the liver: a case report. Eur J Gastroenterol Hepatol 8:169–172

Müller-Hermelinck HK, Von Gaudecker B, Drenckhahn D, Jaworsky K, Feldmann C (1981) Fibroblastic and dendritic reticulum cells of lymphoid tissue. Ultrastructural, histochemical, and 3H-thymidine labeling studies. J Cancer Res Clin Oncol 101:149–164

Mura G, Tauceri F, Feri M, Verdecchia GM (2011) Report of two cases of Castleman's disease: a case of benign localized disease and a case of fast progressive multicentric disease. Acta Biomed 82:77–81

Nakano K, Katano H, Tadagaki K, Sato Y, Ohsaki E, Mori Y, Yamanishi K, Ueda K (2012) Novel monoclonal antibodies for identification of multicentric Castleman's disease; Kaposi's sarcoma-associated herpesvirus-encoded vMIP-I and vMIP-II. Virology 425:95–102

Nguyen DT, Diamond LW, Hansmann ML, Alavaikko MJ, Schröder H, Fellbaum C, Fischer R (1994) Castleman's disease. Differences in follicular dendritic network in the hyaline vascular and plasma cell variants. Histopathology 24:437–443

Nicholas J (2010) Human herpesvirus 8-encoded cytokines. Futur Virol 5:197–206

Nishi J, Maruyama I (2000) Increased expression of vascular endothelial growth factor (VEGF) in Castleman's disease: proposed pathomechanism of vascular proliferation in the affected lymph node. Leuk Lymphoma 38:387–394

Nozawa Y, Hirao M, Kamimura K, Hara Y, Abe M (2002) Unusual case of follicular lymphoma with hyaline-vascular follicles. Pathol Int 52:794–795

O'Leary J, Kennedy M, Howells D, Silva I, Uhlmann V, Luttich K, Biddolph S, Lucas S, Russell J et al (2000) Cellular localisation of HHV-8 in Castleman's disease: is there a link with lymph node vascularity ? Mol Pathol 53:69–76

Oksenhendler E, Boulanger E, Galicier L, Du MQ, Dupin N, Diss TC, Hamoudi R, Daniel MT et al (2002) High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. Blood 99:2331–2336

Orcioni GF, Mambelli V, Ascani S, Sabattini E, Piccioli M, Pieri F, Falini B, Pileri SA (1998) Concurrence of localized Castleman's disease and peripheral small B-lymphocytic lymphoma within the same lymph node. Gen Diagn Pathol 143:327–330

Ordi J, Grau JM, Junque A, Nomdedeu B, Palacin A, Cardesa A (1993) Secondary (AA) amyloidosis associated with Castleman's disease. Report of two cases and review of the literature. Am J Clin Pathol 100:394–397

Ota T, Mitsuyoshi A, Zaima M, Mizuno M, Morita R (1997) Visualization of central stellate fibrosis in hyaline vascular type Castleman's disease. Br J Radiol 70:1060–1062

Padberg BC, Holzhausen HJ, Weinland G, August C, Schröder S (1994) Primary hemorrhagic spindle tumor of the lymph node with amianthoid structures. Case report and review of the literature (in German). Pathologe 15:176–180

Palestro G, Turini F, Pagano M, Chiusa L (1999) Castleman's disease. Adv Clin Pathol 3:11–22

Peck D, Lum PA (1996) Castleman disease in the porta hepatis: biphasic helical computed tomography. Can Assoc Radiol J 47:410–412

Perez-Ordenez B, Rosai J (1998) Follicular dendritic cell tumor: review of the entity. Semin Diagn Pathol 15:144–154

Perfetti V, Bellotti MA, Arbustini E, De Benedetti F, Paulli M, Marinone MG, Merlini G (1994) Reversal of nephrotic syndrome due to reactive amyloidosis (AA-type) after excision of localized Castleman's disease. Am J Hematol 46:189–193

Peterson BA, Frizzera G (1993) Multicentric Castleman's disease. Semin Oncol 20:636–647

Pinkus GS, Warhol MJ, O'Connor EM, Etheridge CL, Fujiwara K (1986) Immunohistochemical localization of smooth muscle myosin in human spleen, lymph node, and other lymphoid tissues. Unique staining patterns in splenic white pulp and sinuses, lymphoid follicles, and certain vasculature, with ultrastructural correlations. Am J Pathol 123:440–453

Polizzotto MN, Uldrick TS, Hu D, Yarchoan R (2012) Clinical manifestations of Kaposi sarcoma herpesvirus lytic activation: multicentric Castleman disease (KSHV-MCD) and the KSHV inflammatory cytokine syndrome. Front Microbiol 3:73

Powell CM, Cranor ML, Rosen PP (1995) Pseudoangiomatous stromal hyperplasia (PASH). A mammary stromal tumor with myofibroblastic differentiation. Am J Surg Pathol 19:270–277

Powles T, Stebbing J, Bazeos A, Hatzimichael E, Mandalia S, Nelson M, Gazzard B et al (2009) The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. Ann Oncol 20:775–779

Przkora R, Bruns C, Zulke C, Heinkelein J, Rummele P, Schalhorn A, Jauch KW (2003) Castleman's disease causing obstructive jaundice. J Hepatol 38:548–549

Rahimi S, Onetti MA, Faraggiana T (1995) Multicentric intranodal myofibroblastoma in an infant. Histopathology 27:477–478

Rahmouni A, Golli M, Mathieu D, Anglade MC, Charlotte F, Vasile N (1992) Castleman disease mimicking liver tumor: CT and MR features. J Comput Assist Tomogr 16:699–703

Rais M, Ferrelli F, Avanteo MC, Murgia A, Pili P, Nicolosi A, Massidda B (1990) Histopathological study of a case of systemic angiofollicular hyperplasia (Castleman's disease). Pathologica 82:89–94

Reddy D, Mitsuyasu R (2011) HIV-associated multicentric Castleman disease. Curr Opin Oncol 23:475–481

Reichard KK, Robinett S, Foucar MK (2011) Clonal cytogenetic abnormalities in the plasma cell variant of Castleman disease. Cancer Genet 204:323–327

Roca B (2009) Castleman's disease. A review. AIDS Rev 11:3–7

Rossi A, Bulgarini A, Rondanelli E, Incensati R (1995) Intranodal palisaded myofibroblastoma: report of three new cases. Tumori 81:464–468

Rywlin AM, Recher L, Hoffman EP (1966) Lymphoma-like presentation of Kaposi's sarcoma. Arch Dermatol 93:554–561

Sadamoto Y, Abe Y, Higuchi K, Kato K, Matsumoto S, Arima N, Nawara H (1998) Retroperitoneal Castleman's disease of the hyaline vascular type presenting arborizing calcification. Intern Med 37:691–693

Saiz AD, Chan O, Strauchen JA (1997) Follicular dendritic cell tumor in Castleman's disease: a report of two cases. Int J Surg Pathol 5:25–30

Sakurai Y, Shoji M, Matsubara T, Imazu H, Hasegawa S, Ochiai M, Funabiki T, Mizoguchi Y et al (2000) Angiomyomatous hamartoma and associated stromal lesions in the right inguinal lymph node: a case report. Pathol Int 50:655–659

Sapino A, Cassoni P, Ferrero E, Bongiovanni M, Righi L, Fortunati N, Crafa P, Chiarle R, Bussolati G (2003) Estrogen receptor alpha is a novel marker expressed by follicular dendritic cells in lymph nodes and tumor-associated lymphoid infiltrates. Am J Pathol 163:1313–1320

Sato N, Kondo S, Saito K, Hirano S, Hara T, Tanaka E, Ootake S, Shichinohe T, Kawarada Y et al (2006) Hyaline vascular-type Castleman's disease in the hepatoduodenal ligament: report of a case. Surg Today 36:647–650

Sato Y, Kojima M, Takata K, Morito T, Mizobuchi K, Tanaka T, Inoue D, Shiomi H et al (2010) Multicentric Castleman's disease with abundant IgG4-positive cells: a clinical and pathological analysis of six cases. J Clin Pathol 63:1084–1089

Schlosnagle DC, Chan WC, Hargreaves HK, Nolting SF, Brynes RK (1982) Plasmacytoma arising in giant lymph node hyperplasia. Am J Clin Pathol 78:541–544

Schultz TF (2001) KSHV/HHV8-associated lymphoproliferations in the AIDS setting. Eur J Cancer 37:1217–1226

Shahidi H, Myers JL, Kvale PA (1995) Castleman's disease. Mayo Clin Proc 70:969–977

Sharp TV, Wang HW, Koumi A, Hollyman D, Endo Y, Ye H, Du MQ, Boshoff C (2002) K15 protein of Kaposi's sarcoma-associated herpesvirus is latently expressed and binds to HAX-1, a protein with antiapoptotic function. J Virol 76:802–816

Sherman D, Ramsay B, Theodorou NA, Woodrow D, Paradinas FP, Cream JJ, Murray-Lyon IM (1992) Reversible plane xanthoma, vasculitis, and peliosis hepatis in giant lymph node hyperplasia (Castleman's disease): a case report and review of the cutaneous manifestations of giant lymph node hyperplasia. J Am Acad Dermatol 26:105–109

Suda T, Katano H, Delsol G, Kakiuchi C, Nakamura T, Shiota M, Sata T, Higashihara M, Mori S (2001) HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. Pathol Int 51:671–679

Sun X, Chang KC, Abruzzo LV, Lai R, Younes A, Jones D (2003) Epidermal growth factor receptor expression in follicular dendritic cells: a shared feature of follicular dendritic cell sarcoma and Castleman's disease. Hum Pathol 34:835–840

Talat N, Schulte KM (2011) Castleman's disease: systematic analysis of 416 patients from the literature. Oncologist 16:1316–1324

Tanaka K, Horita M, Shibayama H, Seike M, Itoh Y, Hamaguchi K, Sato Y, Sakata T, Ishida T (1995) Secondary amyloidosis associated with Castleman's disease. Intern Med 34:122–126

Theate I, Michaux L, Squifflet JP, Martin A, Raphael M (2003) Human herpesvirus 8 and Epstein-Barr virus-related monotypic large B-cell lymphoproliferative disorder coexisting with mixed variant of Castleman's disease in a lymph node of a renal transplant recipient. Clin Transplant 17:451–454

Toccanier-Pelte MF, Skalli O, Kapanci Y, Gabbiani G (1987) Characterization of stromal cells with myoid features in lymph nodes and spleen in normal and pathologic conditions. Am J Pathol 129:109–118

Uldrick TS, Polizzotto MN, Yarchoan R (2012) Recent advances in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Curr Opin Oncol 24:495–505

User IR, Akçören Z, Karnak I (2011) Castleman disease: an unusual diagnosis of a portal mass in an 8-year-old boy. J Pediatr Surg 46:e9–e11

Uzunlar AK, Oezates M, Yaldiz M, Büyükbayram H, Oezaydin M (2000) Castleman's disease in the porta hepatis. Eur Radiol 10:1913–1915

Van den Berge M, Pawels P, Jakimowicz JJ, Creemers GJ (2002) Hyaline vascular Castleman's disease: a case report and brief review of the literature. Neth J Med 60:444–447

Vazef N, Katzin WE, Mendelsohn G, Reydman M (1992) Report of a case of localized Castleman's disease with progression to malignant lymphoma. Am J Clin Pathol 98:633–636

Venizelos I, Tamiolakis D, Simopoulos C, Nikolaidou S, Barbagadaki S, Lambropoulou M et al (2004) Diffuse large B-cell lymphoma arising from a multicentric mixed variant of Castleman's disease. Indian J Cancer 41:135–137

Weisenburger DD, Nathwani BN, Winberg CD, Rappaport H (1985) Multicentric angiofollicular lymph node hyperplasia: a clinicopathologic study of 16 cases. Hum Pathol 16:162–172

West KP, Morgan DR, Lauder I (1989) Angiofollicular lymph node hyperplasia with amyloidosis. Postgrad Med J 65:108–111

Wilkinson S, Forrester-Wood CP (2003) Surgical resection of a solitary plasmacytoma originating in a rib of a patient with Castleman's disease. Ann Thorac Surg 75:1018–1019

Yamagata N, Fujio J, Hirai R, Matsumaru M, Tanimaru S, Inokuchi C, Shikai T, Takezako N et al (2006) Marked hepatomegaly due to AA type amyloidosis in a case with Castleman's disease. Int J Hematol 84:70–73

Yamamoto K, Yoshida M, Yamamoto M, Ohki M, Miki T, Horiuchi T, Kurosaki M, Watanabe M, Miura O (2004) An abdominal follicular dendritic cell tumor in Castleman's disease (in Japanese). Rinsho Ketsueki 45:1033–1038

Yoshizaki K, Matsuda T, Nishimoto N, Kuritani T, Taeho L, Aozasa K, Nakahata T, Kawai H et al (1989) Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. Blood 74:1360–1367

Zarate-Osorno A, Medeiros LJ, Danon AD, Neiman RS (1994) Hodgkin's disease with coexistent Castleman-like histologic features. A report of three cases. Arch Pathol Lab Med 118:270–274

Lymphoid Hyperplasia and Pseudolymphomas of the Hepatobiliary Tract

99

Contents

Abstract

The hepatobiliary tract can show several types of lymphoid hyperplasia and so-called pseudolymphomas, reactive lesions that have to be distinguished from neoplastic lymphoproliferative processes. Reactive lymphoid hyperplasia of the liver is an unusual, benign hepatic mass lesion characterized by a dense circumscribed, expansively growing lymphocyte infiltrate with lymph follicles and sometimes germinal centers. These masses are usually incidental lesions and are symptomless. Etiology and pathogenesis are not clarified, but a long-standing local and uncontrolled immune reaction may play a role. This is underlined by an association of lymphoid hyperplasia with hepatitis C virus infection. Several cases of reactive lymphoid hyperplasia were observed to accompany malignant tumors situated elsewhere, including gastrointestinal tract cancers. Lesions can grow to several cm in size and may be confounded with primary hepatic cancers. The nodules are well circumscribed and nonencapsulated. Apart from the most common lymphocytic B-cell-predominant lesions, a rare histiocyte-rich variant is known. Reactive lymphoproliferations of the liver also develop in autoimmune lymphoproliferative syndromes.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_99

Reactive Lymphoid Hyperplasia

Introduction

Reactive lymphoid hyperplasia of the liver (synonyms: pseudolymphoma of the liver, nodular lymphoid lesion of the liver) is an unusual, benign hepatic mass lesion chiefly characterized by the presence of a reactive lymphocyte infiltrate with lymph follicles and an expanding growth pattern. Similar to reactive lymphoid hyperplasias in other organs, the etiology and pathogenesis have not been clarified, but an excessive local immune reaction to unknown antigen(s) may be involved.

Pseudolymphoma was first described in 1963 as a reactive lymphoproliferative lesion in the lung (Saltzstein 1963). The lesion can be found in various organs, including the gastrointestinal tract, orbit, thyroid gland, skin, and lung, but its occurrence in the liver is rare. Definitions available so far specify the lesion as propagation of lymph follicles constructed of lymphoid cells without cytological atypia, accompanied by conspicuous and sometimes hyperplastic germinal centers (Saltzstein 1963). Other authors have also proposed reactive lymphoid hyperplasia as a localized lesion well demarcated from surrounding tissue and characterized by the presence of hyperplastic lymphoid follicles with associated polyclonal population of small lymphocytes, mature plasma cells, macrophages, and stromal fibrosis (Katayanagi et al. 1994; Tanizawa et al. 1996).

Epidemiology

The first report of hepatic reactive lymphoid hyperplasia dates from 1981 (Snover et al. 1981), and less than 50 cases of reactive lymphoid hyperplasia of the liver have been reported so far, with most reports known from Japan. In most patients the lesion was symptomless and detected owing to routine examinations for other reasons. Incidental reactive lymphoid hyperplasia was found during back table examination of a donor liver (Sibulesky et al. 2010). In a review of 14 cases, the age range was 15–85 years (average 58 years; Zen et al. 2010); there is an impressive gynecotropy: among these 14 patients, 12 were female (Takahashi et al. 2006). 60 % of the lesions were located to the right liver lobe.

Selected References Grouls 1987; Fukuo et al. 1987; Tanabe et al. 1991; Isobe et al. 1993; Katayanagi et al. 1994; Ohtsu et al. 1994; Hiroshige and Tanabe 1995; Endou et al. 1996; Tanizawa et al. 1996; Fujinaga et al. 1997; Kim et al. 1997; Nishijima et al. 1998; Nagano et al. 1999; Sharifi et al. 1999; Okubo et al. 2001; Pantanowitz et al. 2001; Mori et al. 2002; Okuhama et al. 2003; Shiozawa et al. 2004; Maehara et al. 2006; Ota et al. 2006; Sato et al. 2006; Takahashi et al. 2006; Willenbrock et al. 2006; Jimenez et al. 2007, 2008; Machida et al. 2007; Matsumoto et al. 2007; Lin 2008; Park et al. 2008; Okada et al. 2009; Dominguez-Pérez and Castell-Monsalve 2010; Fukuo et al. 2010; Sibulesky et al. 2010; Watanabe et al. 2010; Zen et al. 2010; Hayashi et al. 2011; Kobayashi et al. 2011; Marchetti et al. 2011; Osame et al. 2011; Yoshikawa et al. 2011.

Several cases of hepatic reactive lymphoid hyperplasia accompanying malignant tumors have been reported, including colorectal carcinoma, gastric cancer, renal cell carcinoma, ovarian cancer, and multiple carcinomas in the same patient (Grouls 1987; Kim et al. 1997; Osame et al. 2011; Yoshikawa et al. 2011). Reactive lymphoid hyperplasia of the liver may be associated synchronously with other hepatic tumors, such as hemangioma and focal nodular hyperplasia (Willenbrock et al. 2006).

Imaging Features

Abdominal ultrasonography shows a homogeneous and hypoechoic lesion, sometimes with a hyperechoic rim (Tanabe et al. 1991; Nagano et al. 1999; Mori et al. 2002; Matsumoto et al. 2007; Hayashi et al. 2011). In CT images, a low-density area is detectable, which is not strongly enhancing in the arterial phase and

exhibits a vague low-density mass in the parenchymal and portal phases (Maehara et al. 2006). In one case, abdominal CT revealed a low-density area before contrast material injection, which was enhanced in the early arterial phase and subsequently washed out in the late phase (Hayashi et al. 2011). In case of extrahepatic malignancy, the CT features of reactive lymphoid hyperplasia can suggest metastatic disease (Marchetti et al. 2011). MR imaging showed a hyperintense T2 signaling nodular lesion and arterial phase enhancement with gadolinium injection (Matsumoto et al. 2007; Jimenez et al. 2008; Okada et al. 2009; Dominguez-Pérez and Castell-Monsalve 2010; Kobayashi et al. 2011). In a multinodular lesion, the masses showed slight T1 and T2 prolongation and restricted diffusion (Osame et al. 2011). In one case, a perfusion defect was seen during CT arterial portography (Maehara et al. 2006). The lesion has also been identified by use of FDG-PET (Lin 2008). Owing to expansive growth, the mass may cause narrowing of adjacent intrahepatic bile ducts.

Nodular Lymphoid Hyperplasia of the Liver

There are situations where large numbers of lymphoid follicles, also with prominent germinal centers, develop in the liver in the absence of hepatitis virus infection, sometimes forming macroscopically visible lesions. This is called *nodular lymphoid lesion of the liver* or *reactive lymphoid hyperplasia of the* liver and is thought to emerge via an immune-mediated process directed against so far unknown antigens. Clinically and radiologically, the lesions can closely mimic primary hepatic neoplasms or metastatic disease. The lesions have been observed in the setting of autoimmune disorders, including primary biliary cirrhosis (Okada et al. 2009; Fukuo et al. 2010; Ishida et al. 2010) and Sjögren's syndrome (Okubo et al. 2001). Rarely, nodular lymphoid lesion was associated with other tumorous lesions in the liver, i.e., focal nodular hyperplasia and hemangioma (Willenbrock et al. 2006).

Selected References Snover et al. 1981; Isobe et al. 1993; Katayanagi et al. 1994; Ohtsu et al. 1994; Tanizawa et al. 1996; Nagano et al. 1999; Sharifi et al. 1999; Okubo et al. 2001; Pantanowitz et al. 2001; Maehara et al. 2006; Sato et al. 2006; Takahashi et al. 2006; Willenbrock et al. 2006; Jimenez et al. 2007; Machida et al. 2007; Lin 2008; Okada et al. 2009; Dominguez-Pérez and Castell-Monsalve 2010; Fukuo et al. 2010; Ishida et al. 2010; Zen et al. 2010; Hayashi et al. 2011; Kobayashi et al. 2011; Marchetti et al. 2011; Tuckett et al. 2011; Yoshikawa et al. 2011; Amer et al. 2012; Yuan et al. 2012; Moon and Choi 2013.

In lesions that have been resected, the gross features were characterized by a well-circumscribed, nonencapsulated, mostly solitary nodule with a firm to rubbery consistency and a smooth or coarsely granular, whitish to yellowish or tan cut surface (Maehara et al. 2006; Jimenez et al. 2008; Zen et al. 2010). Some of the lesions may bulge from the fresh cut surface (Fig. 3 in Takahashi et al. 2006). The diameter of the reported lesions ranged from 0.9 to 5.5 cm (average: 1.7 cm; Zen et al. 2010). In another study of seven cases, the average size of the lesions was 45 mm (range: 15–105 mm; Yuan et al. 2012). Among eight reviewed lesions, six had a diameter between 15 and 20 mm (Maehara et al. 2006). The largest reported lesion (5.5 cm diameter) was observed in an 81-year-old male patient without preexisting liver disease (Zen et al. 2010). The macroscopic growth pattern is expanding causing perifocal atrophy of the liver substance, sometimes associated with perifocal nodular change and angiectases.

Histologically, reactive nodular lymphoid hyperplasia exists in two patterns, a lymphocyte-rich variant (Fig. 1) and a histiocyte-rich variant. In the lymphocyte-rich variant, the circumscribed nodules exhibit a dense lymphocytic infiltrate with formation of numerous lymph follicles, many of them with fully developed, normal-looking germinal centers containing the typical macrophages with tingible bodies/nuclear fragments. The infiltrate is also occupied by macrophages (mainly in

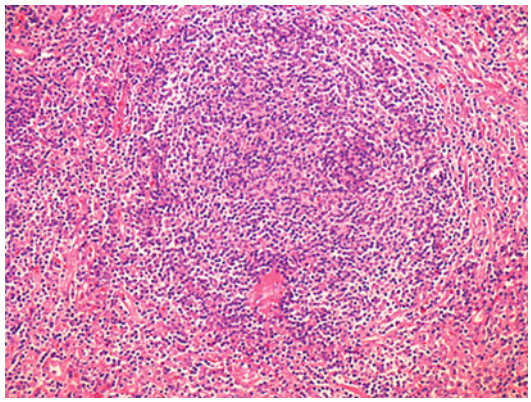

Fig. 1 Lymphoid hyperplasia of the liver with follicular structures (hematoxylin and eosin stain)

the interfollicular compartment; sometimes with an epithelioid morphology; Zen et al. 2010), immunoblasts, plasma cells, and other leukocytes, but these cells usually form a minority. Variable degrees of interfollicular hyalinosis have been noted (Tanizawa et al. 1996; Nagano et al. 1999; Sharifi et al. 1999; Pantanowitz et al. 2001; Sato et al. 2006; Machida et al. 2007). This sclerohyalinosis may rarely form fibrous nodular structures of various sizes (Machida et al. 2007). The edge of the lesions shows ductular proliferations which are CK7+ (Zen et al. 2010). Portal tracts in the vicinity of the lesion may show an increased lymphocytic infiltration (see below). Multinucleated giant cells in a granulomatous reaction containing cholesterol clefts have been noted (Zen et al. 2010). One lesion showed small calcifications (Zen et al. 2010).

Immunohistochemically, the lesion demonstrated B lymphocytes in the follicles (CD20+, CD79a+ and Bcl-6+, and Bcl-2 negative) along with CD3+ T lymphocytes (Matsumoto et al. 2007). Lymph follicles were found to be positive for CD10 (Hayashi et al. 2011). The plasma cells were polytypic, positive for both kappa and lambda light chains at a 3:1 ratio (Takahashi et al. 2006; Jimenez et al. 2008). Polyclonality of B cells/plasma cells was also confirmed by the use of in situ hybridization (Sato et al. 2006; Zen et al. 2010) and of Ig heavy chain analysis via PCR (Machida et al. 2007; Zen et al. 2010). IgG4+ cells were scarce in all lesions (Zen et al. 2010). Flow cytometric analysis of tumor cell suspensions disclosed a B:T cell ratio of 53.4 % CD3+ cells and 35.0 % CD20+ cells (Maehara et al. 2006). The lymphocyte population is immunohistochemically polytypic (Machida et al. 2007) and shows a polyclonal phenotype by the use of in situ hybridization for light chain restriction (Zen et al. 2010).

The histiocyte-rich variant its characterized by a high content of histiocytes, in addition to lymphoid cells. Park and coworkers (Park et al. 2008) reported a case of hepatic reactive lymphoid hyperplasia exhibiting unusual histiocyte-rich histologic features in a 47-year-old female patient in conjunction with a renal cell carcinoma. The well-circumscribed, yellowish-white, solitary nodule measured 1 cm in diameter. Histologically, two components were in evidence, the first being characterized by an infiltrate of CD68+ histiocytes, many of them epithelioid and sometimes forming granuloma-like structures, and the second by lymphocytes, lymph follicles, and germinal centers. The amount of histiocytes was the dominant feature, although few epithelioid macrophages and even sparse giant cells had been reported previously (Sharifi et al. 1999; Willenbrock et al. 2006). Most of the lymphoid follicles were present at the edge of the nodule, whereas ductular proliferations were noted. The mass also showed a focally marked hyalinosis. In the surrounding liver tissue, a prominent periductal lymphocyte infiltration with fibrosis was observed, but these changes were not found in more remote liver areas.

Another variant of nodular lymphoid lesion was characterized by epithelioid cell granulomas and Schaumann bodies in giant cells within the lesion (Nonomura et al. 1998). Rarely, the lesions may display an angiofollicular pattern, thus resembling Castleman's disease (Tanizawa et al. 1996).

Hepatic Pseudolymphoma

In case of large lesions that produce masses mimicking malignancy, the alterations have sometimes been allocated to the clinicopathologic category of *hepatic pseudolymphomas* (Grouls 1987; Katayanagi et al. 1994; Hiroshige

et al. 1995; Kim et al. 1997; Shiozawa et al. 2004; Ota et al. 2006; Matsumoto et al. 2007; Osame et al. 2011; Yang et al. 2013; Yoshida et al. 2013). Pseudolymphomas are mass lesions that may show the same or similar histologic pattern as nodular lymphoid lesion and may thus represent excessive forms of nodular lesions. Sometimes, complex multinodular lesions develop that can involve both liver lobes (Osame et al. 2011). It is, therefore, difficult to distinguish between the lesions in published reports, as the terminologies were sometimes not employed in a comparable manner. They are sometimes associated with conditions known to stimulate a lymphocyte-mediated immune reactions, e.g., chronic hepatitis C (Kim et al. 1997). But part of pseudolymphomas deviate from this lymphoid hyperplastic pattern and contain, e.g., increased numbers of plasma cells and histiocytes/macrophages. Such lesions show a histologic overlap with inflammatory pseudotumors, which are treated in separate chapters.

Non-nodular Lymphoid Hyperplasia of the Hepatobiliary Tract

Lymphoid Hyperplasia in Viral Hepatitis

One of the best known situations where lymph follicles emerge in the liver, and specifically in the portal tract spaces, is chronic hepatitis C (Hino et al. 1992; Mosnier et al. 1993; Freni et al. 1995; Murakami et al. 1999).

Portal Tract and Small Bile Duct Changes in Reactive Lymphoid Hyperplasia of the Liver

In the majority of the cases, the portal of the adjacent liver substance revealed a sometimes dense lymphocytic infiltration, which also involved the periductal tissue compartment (Isobe et al. 1993; Katayanagi et al. 1994; Sharifi et al. 1999; Pantanowitz et al. 2001; Maehara et al. 2006; Sato et al. 2006; Takahashi et al. 2006; Machida et al. 2007; Park et al. 2008; Zen et al. 2010). In at least two instances, these alterations were associated with lymphoepithelial lesions of small bile ducts (Sharifi et al. 1999; Willenbrock et al. 2006), and the periductal lymphocytic infiltration may be correlated with periductal fibrosis.

Lymphonodular Hyperplasia of Large Extra- and/or Intrahepatic Bile Ducts

The presence of numerous lymph follicles in the bile duct mucosa, resulting in bile duct stenosis, has rarely been observed and termed *follicular cholangitis* (Aoki et al. 2003). In the patient described by these authors, the mucosa of the common bile duct of a resection specimen showed a moderate stenosis by soft granular nodules with a "cobblestone-like" appearance, whereas the confluence of the hepatic ducts was whitish and firm upon palpation, and the right hepatic duct was completely obstructed. Histologically, the thickened duct wall contained numerous lymph follicles with richly formed germinal centers located to the outer layers, and, at the hepatic hilum, significant fibrosis and hyalinization in the interfollicular spaces were found.

Biology of Disease

Reactive lymphoid hyperplasia of the liver has a favorable outcome. Among five patients with a longer follow-up, the lesions did not recur after resection, and some nodules may regress spontaneously (Zen et al. 2010).

Differential Diagnosis

The main differential diagnosis is low-grade malignant follicular non-Hodgkin's lymphoma (NHL; Sharifi et al. 1999), in particular B-cell lymphoma of the MALT type (Sharifi et al. 1999; Willenbrock et al. 2006; Hayashi et al. 2011). In the presence of germinal centers, macrophages with tangible bodies are diagnostically helpful, because this feature is lacking in malignant lymphoma. In case of doubt and

particularly in needle biopsies, immunohistochemistry and molecular methods should be added to exclude NHL, which also occurs as a primary malignancy in the liver (see the respective chapter). Reactive lymphoid hyperplasia of the liver was found in at least two patients with colorectal cancer and first suspected to be metastases (Takahashi et al. 2006).

Etiology and Pathogenesis

An association between the development of hepatic reactive lymphoid hyperplasia and systemic or local pathologic immune reactions has been suggested. The lymphoid reaction has been observed in conjunction with chronic hepatitis C (Kim et al. 1997), a disorder known to be associated with autoimmune reactions and lymphoma; in conjunction with autoimmune thyroiditis (Nagano et al. 1999), primary biliary cirrhosis (Sharifi et al. 1999; Okada et al. 2009; Fukuo et al. 2010; Zen et al. 2010), Takayasu arteritis (Zen et al. 2010), or Sjögren's syndrome (Okubo et al. 2001); following interferon-alpha therapy for chronic hepatitis B (Ohtsu et all. 1994); and in a patient with primary immunodeficiency and polyglandular failure syndrome (Snover et al. 1981). In one patient, the histology of the lesion resembled an angiofollicular pattern as seen in Castleman's disease (Tanizawa et al. 1996).

Part of the lesions described were associated with a malignancy (see above). It may be hypothesized that the partly nodular reactive lymphoid lesions in the livers of these patients are local (and successful) immune reactions directed against small liver metastases of extrahepatic carcinomas.

Reactive Lymphoproliferative Disorders: Human Autoimmune Lymphoproliferative Syndrome

Introduction

Autoimmune lymphoproliferative syndrome (ALPS) denotes a disorder characterized by generalized reactive (non-neoplastic) lymphadenopathy, hypergammaglobulinemia, lymphocytosis, splenomegaly, sometimes hepatomegaly, and autoimmune features (Oliveira and Fleisher 2004; Deutsch et al. 2004). ALPS has originally been described as a chronic lymphadenopathy simulating malignant lymphoma in children (Canale and Smith 1967), resulting in the eponymic designation, Canale-Smith syndrome (Kellerer and Mutz 1976). A central feature of ALPS and its variants is a chronic reactive expansion of a distinct lymphocyte population, related to deranged lymphocyte apoptosis (reviews: Campagnoli et al. 2006; Rieux-Laucat and Magerus-Chatinet 2010; Madkaikar et al. 2011; Teachey 2010, 2011, 2012; Teachey et al. 2010). The involved lymphocyte population is dominated by T-cell receptor alphabeta CD4-CD8- (double-negative) T cells in the blood and in tissues (Sneller et al. 1992; Fisher et al. 1995; Lim et al. 1998; Price 2013). Apart from the TCR alphabeta phenotype typical for ALPS, TCR gammadelta has also been identified in double-negative T cells in ALPS (van den Berg et al. 2003). An increased risk for neoplasias of the lymphoid cell system has clearly been established but particularly so in patients having Fas gene mutations (see below; Straus et al. 2001; Oliveira and Fleisher 2004).

Liver Pathology in ALPS and Related Disorders

ALPS seems to be often associated with hepatomegaly (Koo et al. 1984; Le Deist et al. 1996; Avila et al. 1999). Hepatomegaly in ALPS seems to be caused by infiltration of the liver by lymphoid cells. One patient showed, in the liver biopsy, an infiltration of portal tracts and sinusoids by large lymphocytes and marked hemophagocytosis in the hepatic sinusoids (Le Deist et al. 1996). A pathologic study of ten patients with ALPS revealed marked paracortical hyperplasia of lymph nodes, the expanded interfollicular areas being dominated by T-cell receptor alphabeta CD3+, CD4-CD8- (double-negative) T cells and characterized by decreased apoptosis. The spleens were markedly enlarged, more than ten times normal size, with cellular expansion of both the red and white pulps.

Liver biopsies from two patients showed a lymphocytic infiltration of portal tracts ("triaditis") consisting again of predominantly double-negative T cells (more than 50 % of the cells). One of these patients developed chronic active hepatitis consistent with a form of autoimmune hepatitis (Lim et al. 1998). Type 2 autoimmune hepatitis developing in ALPS has been observed in another study (Pensati et al. 1997). The pathogenesis of hepatitis in apoptosis-deficient patients with ALPS is of particular interest, because there is evidence that Fas-mediated apoptosis is a critical step in the genesis of hepatitis (Kondo et al. 1997). It has been suggested that hepatitis emerging in failure of Fas-mediated lymphocyte pathways may be mediated by a hyperactivation of granzyme B counterbalancing Fas deficiency (André et al. 2004).

MRL/MP mice bearing the lymphoproliferative gene lpr (MRL/MP-lpr/lpr or MRL/lpr mice) are known to spontaneously develop severe autoimmune disease, including a form of chronic suppurative destructive cholangitis and antimitochondrial autoantibodies, mimicking human primary biliary cirrhosis (Tsuneyama et al. 2001). It is not yet known whether patients with ALPS or related disorders also tend to develop autoimmune disorders of the biliary tract.

Classification

There is now evidence that ALPS is not a single entity but makes part of a growing spectrum of disorders with overlapping phenotypes and different etiopathogenic pathways. A spectrum of symptoms and signs similar to ALPS may be seen in some patients with Evans syndrome, a hematologic disorder defined by autoimmune destruction of at least two hematologic cell types, associated with elevated double-negative T cells as in ALPS (Teachey et al. 2005). An ALPS-like clinical pattern in patients with decreased Fas function, but no Fas gene mutations, has been described under the terms autoimmune lymphoproliferative disease (ALD) and Dianzani autoimmune/lymphoproliferative disease (DALD) (Dianzani et al. 1997; Ramenghi et al. 2000; Chiocchetti et al. 2004). A further novel disorder of lymphocyte apoptosis is characterized by a combination of autoimmunity, infectious lymphadenopathy, double-negative T cells, and impaired activation-induced cell death in the absence of Fas or FasL gene mutations (Hundt et al. 2002).

ALPS bears striking similarities to respective diseases in the MRL and C3H/Hej strains of mice, showing mutations of the lpr and gld loci, respectively (Sneller et al. 1992). These gene loci encode for two proteins involved in the regulation of apoptosis, in humans representing CD95 (Fas/Apo-1) and CD95L (FasL; Fas ligand), respectively (Nagata 1996). Fas and its ligand have a central role in immune cell homeostasis and autoimmunity (Siegel et al. 2000), and Fas and FasL mutations are involved in several disorders of the immune system (Weintraub et al. 1998; Siegel and Fleisher 1999; Mullauer et al. 2001). In patients with ALPS, mutations of the CD95/Fas gene were identified (Fisher et al. 1995; Rieux-Laucat et al. 1995; Drappa et al. 1996; Bettinardi et al. 1997; Infante et al. 1998; Fleisher et al. 2001; Dowdell et al. 2010; Boggio et al. 2012; Fleisher and Oliveira 2012; Hsu et al. 2012; Lambotte et al. 2013; Magerus-Chatinet et al. 2013; Simesen de Bielke et al. 2012), indicating that ALPS is a group of mostly genetic disorders characterized by germline defects of apoptotic pathways in lymphoid cells (Puck and Sneller 1997; Dianzani et al. 2003), although sporadic somatic mutations of Fas gene have also been described (Holzelova et al. 2004). Variations in perforin expression are a susceptibility factor for ALPS development in subjects with defective Fas function (Clementi et al. 2006). There is a relation between the type of Fas mutations and the clinical phenotype (Rieux-Laucat et al. 1999). The pathogenic role of abnormal Fas expression in the pathogenesis of ALPS has also been studied in a transgenic mouse model of this disorder (Choi et al. 1999). Interestingly, targeted mutation of the Fas gene with loss of function in the mouse does not only promote massive lymphocyte expansion but also substantial liver hyperplasia (Adachi et al. 1995). The genetic basis of ALPS has since continued to expand with the identification of the much rarer Fas ligand gene mutations and defects in caspase-8 and caspase-10 (Grzela et al. 2004; review: Oliveira and Fleisher

Table 1 Proposed classifications of autoimmune lymphoproliferative syndromes (ALPS) and related disorders

Previous classification
ALPS
ALPS type I (Canale-Smith syndrome; OMIM 601859)
ALPS type Ia (ALPS-FAS; germline mutations in Fas)
ALPS type Ib (ALPS-FASLG; germline mutations in FasL)
ALPS type sFas (somatic mutations in Fas)
ALPS type II (mutations of caspase-10)
ALPS caused by mutations of caspase-8
DALD (Dianzani autoimmune/lymphoproliferative disease)
Evans syndrome with ALPS-like features (Teachey et al. 2005; Seif et al. 2010)
Hundt-type of ALPS-like disorder
Revised classification of ALPS proper (Oliveira et al. 2010)
ALPS type 0: germline homozygous mutations in Fas
ALPS type Ia: germline heterozygous mutations in Fas
ALPS type lm: somatic mutations in Fas
ALPS type Ib: germline mutations in Fas ligand
ALPS type IIa: germline mutations in caspase-10
ALPS type III: genetic defect undetermined

2004). In ALPS-like disorders without mutations of the Fas/FasL system, other factors involved in an apoptosis defect may play a role. In Dianzani autoimmune/lymphoproliferative disease (DALD), high levels of osteopontin associated with polymorphisms of its gene were found, suggesting that high osteopontin levels are involved in defective apoptosis (Chiocchetti et al. 2004). The diversity of ALPS and related disorders has led to a comprehensive classification, based on a 2009 NIH International Workshop (Oliveira et al. 2010), shown in Table 1.

Diffuse Infiltrative Lymphocytosis Syndrome

Introduction

Diffuse infiltrative lymphocytosis syndrome (DILS) is a reactive lymphoproliferative disorder that occurs in individuals infected with HIV-1. DILS is characterized by a persistent circulating CD8 lymphocytosis, marked salivary gland, and in particular parotid gland enlargement, sicca signs and symptoms, pulmonary insufficiency, a severe form of peripheral neuropathy, and an apparently antigen-driven CD8(+) T-cell lymphocytic infiltration of various organs and tissues, including a progressive visceral involvement also affecting the liver. The most dense CD8 cell infiltrates are observed in the salivary glands and lung. Specific associations with distinct MHC class I and II gene products suggest a pathogenic role of host immune responses to HIV (Itescu et al. 1989, 1993; Itescu 1991; Itescu and Winchester 1992; Franco-Paredes et al. 2002; Feller et al. 2007). Definitive DILS was found in 3 % of a large group of HIV-1-infected subjects, and patients with DILS had higher CD8 counts compared with those without DILS (Williams et al. 1998). DILS was more common in African Americans than in Caucasians and prevailed in persons with male-to-male transmission of HIV-1 (Kazi et al. 1996).

Liver Involvement

In patients with progressive DILS involvement of abdominal viscera, the liver shows an increasing parenchymal and portal tract infiltration with CD8 (+) T lymphocytes. This infiltration can be evident as hepatitis (Franco-Paredes et al. 2002). The hepatic infiltrative process has been distinguished from cellular infiltrations in the setting of T-cell non-Hodgkin's lymphomas which also tend to markedly involve the liver in part of patients.

References

Adachi et al. (1995) PubMed PMID 7581453

Amer A, Mafeld S, Saeed D, Al-Jundi W, Haugk B, Charnley R, White S (2012) Reactive lymphoid hyperplasia of the liver and pancreas. A report of two cases and a comprehensive review of the literature. Clin Res Hepatol Gastroenterol 36:e71–e80

André N, Roquelaure B, Thuret I, Ziol M, Rieux-Laucat F, Le Deist F (2004) Expression of granzyme B in viral hepatitis in patients with ALPS. Hepatology 39:864–865

Aoki T, Kubota K, Oka T, Hasegawa K, Hirai I, Makuuchi M (2003) Follicular cholangitis: another cause of benign biliary stricture. Hepatogastroenterology 50:639–642

Avila NA, Dwyer AJ, Dale JK, Lpoatin UA, Sneller MC, Jaffe ES, Puck JM, Straus SE (1999) Autoimmune lymphoproliferative syndrome: a syndrome associated with inherited genetic defects that impair lymphocytic apoptosis – CT and US features. Radiology 212:257–263

Bettinardi A, Brugnoni D, Quiros-Roldan E, Malagoli A, La Grutta S, Correra A, Notarangelo LD (1997) Missense mutations in the Fas gene resulting in autoimmune lymphoproliferative syndrome: a molecular and immunological analysis. Blood 89:902–909

Boggio E, Melensi M, Bocca S, Chiocchetti A, Comi C, Clemente N, Orilieri E, Soluri MF et al (2012) The -346T polymorphism of the SH2D1A gene is a risk factor for development of autoimmunity/lymphoproliferation in males with defective Fas function. Hum Immunol 73:585–592

Campagnoli MF, Garbarini L, Quarello P, Garelli E, Carando A, Baravalle V, Doria A et al (2006) The broad spectrum of autoimmune lymphoproliferative disease: molecular bases, clinical features and long-term follow-up in 31 patients. Haematologica 91:538–541

Canale VC, Smith CH (1967) Chronic lymphadenopathy simulating malignant lymphoma. J Pediatr 70:891–899

Chiocchetti A, Indelicato M, Bensi T, Mesturini R, Giordano M, Sametti S, Castelli L, Bottarei F et al (2004) High levels of osteopontin associated with polymorphisms in its gene are a risk factor for development of autoimmunity/lymphoproliferation. Blood 103:1376–1382

Choi Y, Ramnath VR, Eaton AS, Chen A, Simon-Stoos KL, Kleiner DE, Erikson J, Puck JM (1999) Expression in transgenic mice of dominant interfering Fas mutations: a model for human autoimmune lymphoproliferative syndrome. Clin Immunol 93:34–45

Clementi R, Chiocchetti A, Cappellano G, Cerutti E, Ferretti M, Orilieri E, Dianzani I et al (2006) Variations of the perforin gene in patients with autoimmunity/lymphoproliferation and defective Fas function. Blood 108:3079–3084

Deutsch M, Tsopanou E, Dourakis SP (2004) The autoimmune lymphoproliferative syndrome (Canale- Smith) in adulthood. Clin Rheumatol 23:43–44

Dianzani U, Bragardo M, DiFranco D, Alliaudi C, Scagni P, Buonfiglio D, Redoglia V, Bonissoni S et al (1997) Deficiency of the Fas apoptosis pathway without Fas gene mutations in pediatric patients with autoimmunity/lymphoproliferation. Blood 89:2871–2879

Dianzani U, Chiocchetti A, Ramenghi U (2003) Role of inherited defects decreasing Fas function in autoimmunity. Life Sci 72:2803–2824

Dominguez-Pérez AD, Castell-Monsalve J (2010) Pseudolymphoma of the liver. Contribution of double-contrast magnetic resonance imaging (in Spanish). Gastroenterol Hepatol 33:512–516

Dowdell KC, Niemela JE, Price S, Davis J, Hornung RL, Oliveira JB, Puck JM, Jaffe ES et al (2010) Somatic FAS mutations are common in patients with genetically undefined autoimmune lymphoproliferative syndrome. Blood 115:5164–5169

Drappa J, Vaishnaw AK, Sullivan KE, Chu JL, Elkon KB (1996) *Fas* gene mutations in the Canale-Smith syndrome, an inherited lymphoproliferative disorder associated with autoimmunity. N Engl J Med 335:1643–1649

Endou T, Isobe Y, Matsunaga K et al (1996) A case of pseudolymphoma of the liver (in Japanese). Clin Imagiol 12:1230

Feller L, White JP, Bouckaert M, Muthuphei MN (2007) Diffuse infiltrative CD8+ lymphocytosis syndrome: review of the literature and report of a case. SADJ 62:314–317

Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Lenardo MJ, Puck JM (1995) Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 81:935–946

Fleisher TA, Oliveira JB (2012) Monogenic defects in lymphocyte apoptosis. Curr Opin Allergy Clin Immunol 12:609–615

Fleisher TA, Straus SE, Bleesing JJ (2001) A genetic disorder of lymphocyte apoptosis involving the fas pathway: the autoimmune lymphoproliferative syndrome. Curr Allergy Asthma Rep 1:534–540

Franco-Paredes C, Rebolledo P, Folch E, Hernandez I, del Rio C (2002) Diagnosis of diffuse CD8+ lymphocytosis syndrome in HIV-infected patients. AIDS Read 12:408–413

Freni MA, Artuso D, Gerken G, Spanti C, Marafioti T, Alessi N, Spadaro A, Ajello A, Ferrau O (1995) Focal lymphocytic aggregates in chronic hepatitis C: occurrence, immunohistochemical characterization, and relation to markers of autoimmunity. Hepatology 22:389–394

Fujinaga Y, Matsui O, Shimizu K (1997) Reactive lymphoid hyperplasia of the liver (in Japanese). Jpn J Diagn Imaging 17:586

Fukuo Y, Shibuya T, Fukumura Y, Mizui T, Sai JK, Nagahara A, Tsukada A, Matsumoto T, Suyama M, Grouls V (1987) Pseudolymphoma (inflammatory pseudotumor) of the liver. Zbl Allg Pathol 133:565–568

Fukuo et al. (2010) PubMed PMID 20581780

Grouls (1987) PubMed PMId 3328445

Grzela T, Krauze A, Grzela K, Lazarczyk M, Niderla J, Brawura-Biskupski-Samaha R et al (2004) Impaired apoptosis of lymphocytes derived from patient with decreased expression of caspase-8 results in Alps-like phenotype. Int J Mol Med 14:937–942

Hayashi M, Yonetani N, Hirokawa F, Asakuma M, Miyaaji K, Takeshita A, Yamamoto K, Haga H et al (2011) An operative case of hepatic

pseudolymphoma difficult to differentiate from primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. World J Surg Oncol 9:3

Hino K, Okuda M, Konishi T, Yamashita A, Kayano K, Kubota M, Yasunaga M, Fukumoto Y, Okita K (1992) Analysis of lymphoid follicles in liver of patients with chronic hepatitis C. Liver 12:387–391

Hiroshige K, Tanabe Y (1995) Pseudolymphoma of the liver (in Japanese). Ryoikibetsu Shokogun Shirizu 7:333–335

Holzelova E, Vonarbourg C, Stolzenberg MC, Arkwright PD, Selz F, Prieur AM, Blanche S et al (2004) Autoimmune lymphoproliferative syndrome with somatic Fas mutations. N Engl J Med 351:1409–1418

Hsu AP, Dowdell KC, Davis J, Niemela JE, Anderson SM, Shaw PA, Rao VK, Puck JM (2012) Autoimmune lymphoproliferative syndrome due to FAS mutations outside the signal-transducing death domain : molecular mechanisms and clinical penetrance. Genet Med 14:81–98

Hundt M, Posovsky C, Schmidt RE (2002) A new disorder of lymphocyte apoptosis : combination of autoimmunity, infectious lymphadenopathy, double negative T cells, and impaired activation-induced cell death. Immunobiology 206:514–518

Infante AJ, Britton HA, DeNapoli T, Middelton LA, Lenardo MJ, Jackson CE, Wang J, Fleisher T, Straus SE, Puck JM (1998) The clinical spectrum in a large kindred with autoimmune lymphoproliferative syndrome caused by a Fas mutation that impairs lymphocyte apoptosis. J Pediatr 133:629–633

Ishida M, Nakahara T, Mochizuki Y, Tsujikawa T, Andoh A, Saito Y, Yamamoto H et al (2010) Hepatic reactive lymphoid hyperplasia in a patient with primary biliary cirrhosis. World J Hepatol 2:387–391

Isobe H, Sakamoto S, Sakai H, Masumoto A, Sonoda T, Adachi E et al (1993) Reactive lymphoid hyperplasia of the liver. J Clin Gastroenterol 16:240–244

Itescu S (1991) Diffuse infiltrative lymphocytosis syndrome in human immunodeficiency virus infection – a Sjögren's-like disease. Rheum Dis Clin N Am 17:99–115

Itescu S, Winchester R (1992) Diffuse infiltrative lymphocytosis syndrome: a disorder occurring in human immunodeficiency virus-1 infection that may present as a sicca syndrome. Rheum Dis Clin N Am 18:683–697

Itescu S, Brancato LJ, Winchester R (1989) A sicca syndrome in HIV infection: association with HLA-DR5 and CD8 lymphocytosis. Lancet 2:466–468

Itescu S, Dalton J, Zhang HZ, Winchester R (1993) Tissue infiltration in a CD8 lymphocytosis syndrome associated with human immunodeficiency virus-1 infection has the phenotypic appearance of an antigenically driven response. J Clin Invest 91:2216–2225

Jimenez R, Beguiristain A, Ruiz-Montesinos I, Villar F, Medrano MA, Garnateo F, Vaquero J et al (2007) Nodular lymphoid hyperplasia of the liver. Pseudolymphoma Rev Esp Enferm Dig 99:299–306

Jimenez R, Beguiristain A, Ruiz-Montesinos I, Villar F, Medrano MA, Garnateo F, Vaquero M et al (2008) Image of the moth: reactive lymphoid hyperplasia

Katayanagi K, Terada T, Nakanuma Y, Ueno T (1994) A case of pseudolymphoma of the liver. Pathol Int 44:704–711

Kazi S, Cohen PR, Williams F, Schempp R, Reveille JD (1996) The diffuse infiltrative lymphocytosis syndrome. Clinical and immunogenetic features in 35 patients. AIDS 10:385–391

Kellerer K, Mutz I (1976) Chronische pseudomaligne Immunoproliferation (Canale-Smith-Syndrome). Eur J Pediatr 121:203–213

Kim SR, Hayashi Y, Kang KB, Soe CG, Kim JH, Yang MK et al (1997) A case of pseudolymphoma of the liver with chronic hepatitis C. J Hepatol 26:209–214

Kobayashi A, Oda T, Fukunaga K, Sasaki R, Minami M, Ohkohchi N (2011) MR imaging of reactive lymphoid hyperplasia of the liver. J Gastrointest Surg 15:1282–1285

Kondo T, Suda T, Fukuyama H, Adachi M, Nagata S (1997) Essential role of the Fas ligand in the development of hepatitis. Nat Med 3:409–413

Koo CH, Nathwani BN, Winberg CD, Hill LR, Rappaport H (1984) Atypical lymphoplasmacytic and immunoblastic proliferation in lymph nodes of patients with autoimmune disease (autoimmune-disease-associated lymphadenopathy). Medicine (Baltimore) 63:274–290

Lambotte O, Neven B, Galicier L, Magerus-Chatinet A, Schleinitz N, Hermine O, Meyts I et al (2013) Diagnosis of autoimmune lymphoproliferative syndrome caused by FAS deficiency in adults. Haematologica 98:389–392

Lim MS, Straus SE, Dale JK, Fleisher TA, Steler-Stevenson M, Strober W, Sneller MC, Puck JM et al (1998) Pathological findings in human autoimmune lymphoproliferative syndrome. Am J Pathol 153:1541–1550

Lin E (2008) Reactive lymphoid hyperplasia of the liver identified by FDG PET. Clin Nucl Med 33:419–420

Machida T, Takahashi T, Itoh T, Hirayama M, Morita T, Horita S (2007) Reactive lymphoid hyperplasia of the liver: a case report and review of literature. World J Gastroenterol 13:5403–5407

Madkaikar M, Mhatre S, Gupta M, Ghosh K (2011) Advances in autoimmune lymphoproliferative syndromes. Eur J Haematol 87:1–9

Maehara N, Chijiwa K, Makino I, Ohuchida J, Kai M, Kondo K, Moriguchi S, Marutsuka K, Asada Y (2006) Segmentectomy for reactive lymphoid hyperplasia of the liver: report of a case. Surg Today 36:1019–1023

Magerus-Chatinet A, Stolzenberg MC, Lanzarotti N, Neven B, Daussy C, Picard C et al (2013) Autoimmune lymphoproliferative syndrome caused by a

homozygous null FAS ligand (FASLG) mutation. J Allergy Clin Immunol 131:486–490
Marchetti C, Manci N, Di Maurizio M, Di Tucci C, Burratti M, Iuliano M, Giorgini M, Salerno L et al (2011) Reactive lymphoid hyperplasia of liver mimicking late ovarian cancer recurrence: case report and literature review. Int J Clin Oncol 16:714–717
Matsumoto N, Ogawa M, Kawabata M, Tohne R, Hiroi Y, Furuta T, Yamamoto T, Gotoh I, Ishiwata H et al (2007) Pseudolymphoma of the liver: sonographic findings and review of the literature. J Clin Ultrasound 35:284–288
Moon WS, Choi KH (2013) Reactive lymphoid hyperplasia of the liver. Clin Mol Hepatol 19:87–91
Mori M, Koga Y, Dairaku K, Kishikawa M (2002) A case of pseudolymphoma of the liver (in Japanese). Acta Hepatol Jpa 43:376–380
Mosnier JF, Degott C, Marcellin P, Henin D, Erlinger S, Benhamou JP (1993) The intraportal lymphoid nodule and its environment in chronic active hepatitis C: an immunohistochemical study. Hepatology 17:366–371
Mullauer L, Gruber P, Sebinger D, Buch J, Wohlfart S, Chott A (2001) Mutations in apoptosis genes: a pathogenetic factor for human disease. Mutat Res 488:211–231
Murakami J, Shimizu Y, Kashii Y, Kato T, Minemura M, Okada K, Nambu S, Takahara T, Higuchi K et al (1999) Functional B-cell response in intrahepatic lymphoid follicles in chronic hepatitis C. Hepatology 30:143–150
Nagano K, Fukuda Y, Nakano I, Katano Y, Toyoda H, Nonami T et al (1999) Reactive lymphoid hyperplasia of the liver coexisting with chronic thyroiditis: radiographical characteristics of the disorder. J Gastroenterol Hepatol 14:163–167
Nagata S (1996) Apoptosis mediated by the Fas system. Prog Mol Subcell Biol 16:87–103
Nishijima K, Simizu Y, Oonishi K, Hasebe K, Tani S, Hashimoto T, Yagi M, Miwa K, Nonomura A (1998) A case of pseudolymphoma of the liver (in Japanese). Acta Hepatol Jpa 39:23–27
Nonomura A, Minato H, Shimizu K et al (1998) Pseudolymphoma (reactive lymphoid hyperplasia) of the liver containing epithelioid cell granulomas and Schaumann's bodies in giant cells. Int J Surg Pathol 6:101–108
Ohtsu T, Sasaki Y, Tanizaki H, Kawano N, Ryu M, Satake M et al (1994) Development of pseudolymphoma of liver following interferon-alpha therapy for chronic hepatitis B. Intern Med 33:18–22
Okada T, Mibayashi H, Hasatani K, Hayashi Y, Tsuji S, Kaneko Y, Yoshimitsu M, Tani K, Zen Y, Yamagishi M (2009) Pseudolymphoma of the liver associated with primary biliary cirrhosis: a case report and review of literature. World J Gastroenterol 28:4587–4592
Okubo H, Maekawa H, Ogawa K, Wada R, Sekigawa I, Iida N et al (2001) Pseudolymphoma of the liver associated with Sjögren's syndrome. Scand J Rheumatol 30:117–119
Okuhama Y, Kenjyo T, Oomine M, Kaneshiro T, Shikiya M (2003) A case of pseudolymphoma of the liver (in Japanese). Shoukakigeka 26:1557–1562
Oliveira JB, Bleesing JJ, Dianzani U, Fleisher TA, Jaffe ES, Lenardo MJ, Rieux-Laucat F et al (2010) Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. Blood 116:e35–e40
Osame A, Fujimitsu R, Ida M, Majima S, Takeshita M, Yoshimitsu K (2011) Multinodular pseudolymphoma of the liver: computed tomography and magnetic resonance imaging findings. Jpn J Radiol 29:524–527
Ota H, Isoda N, Sunada F, Kita H, Higashisawa T, Ono K, Sato S, Ido K, Sugano K (2006) A case of hepatic pseudolymphoma observed without surgical intervention. Hepatol Res 35:296–301
Pantanowitz L, Saldinger PF, Kadin ME (2001) Pathologic quiz case: hepatic mass in a patient with renal cell carcinoma. Arch Pathol Lab Med 125:577–578
Park HS, Jang KY, Kim YK, Cho BH, Moon WS (2008) Histiocyte-rich reactive lymphoid hyperplasia of the liver: unusual morphologic features. J Korean Med Sci 23:156–160
Price V (2013) Auto-immune lymphoproliferative disorder and other secondary immune thrombocytopenias in childhood. Pediatr Blood Cancer 60(Suppl 1):S12–S14
Puck JM, Sneller MC (1997) ALPS: an autoimmune human lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis. Semin Immunol 9:77–84
Ramenghi U, Bonissoni S, Migliaretti G, DeFranco S, Bottarel F, Gambaruto C, DiFranco D, Priori R et al (2000) Deficiency of Fas apoptosis pathway without Fas gene mutations is a familial trait predisposing to development of autoimmune diseases and cancer. Blood 95:3176–3182
Rieux-Laucat F, Magerus-Chatinet A (2010) Autoimmune lymphoproliferative syndrome: a multifactorial disorder. Haematologica 95:1805–1807
Rieux-Laucat F, Le Deist F, Hivroz C, Roberts IA, Debatin KM, Fischer A, de Villartay JP (1995) Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. Science 268:1347–1349
Rieux-Laucat F, Blachere S, Danielan S, De Villartay JP, Oleastro M, Solary E, Bader-Meunier B et al (1999) Lymphoproliferative syndrome with autoimmunity: a possible genetic basis for dominant expression of the clinical manifestations. Blood 94:2575–2582
Saltzstein SL (1963) Pulmonary malignant lymphomas and pseudolymphomas: classification, therapy, and prognosis. Cancer 16:928–932
Sato K, Ueda Y, Yokoi M, Hayashi K, Kosaka T, Katsuda S (2006) Reactive lymphoid hyperplasia of the liver in a patient with multiple carcinomas: a case report and brief review. J Clin Pathol 59:990–992
Seif AE, Manno CS, Sheen C, Grupp SA, Teachey DT (2010) Identifying autoimmune lymphoproliferative syndrome in children with Evans syndrome: a multi-institutional study. Blood 115:2142–2145

Sharifi S, Murphy M, Loda M, Pinkus GS, Khettry U (1999) Nodular lymphoid lesion of the liver: an immune-mediated disorder mimicking low-grade malignant lymphoma. Am J Surg Pathol 23:302–308

Shiozawa K, Kinoshita H, Tsuruta H, Nakazawa K, Naitou S, Koga M, Takeshima F, Omagari K et al (2004) A case of pseudolymphoma of the liver diagnosed before operation. Nippon Syoukakibyou Gakkai Zasshi 101:772–778

Sibulesky L, Satyanarayana R, Menke D, Nguyen JH (2010) Reactive nodular hyperplasia mimicking malignant lymphoma in donor liver allograft. Transplant Proc 42:1970–1972

Siegel RM, Fleisher TA (1999) The role of Fas and related death receptors in autoimmune and other disease states. J Allergy Clin Immunol 103:729–738

Siegel RM, Chan FK, Chun HJ, Lenardo MJ (2000) The multifaceted role of Fas in immune cell homeostasis and autoimmunity. Nat Immunol 1:469–474

Simesen de Bielke MG, Yancoski J, Rocco C, Pérez LE, Cantisano C, Pérez N, Oleastro M et al (2012) A missense mutation in the extracellular domain of fas: the most common change in argentinean patients with autoimmune lymphoproliferative syndrome represents a founder effect. J Clin Immunol 32:1197–1203

Sneller MC, Straus SE, Jaffe ES, Jaffe JS, Fleisher TA, Stetler-Stevenson M, Strober W (1992) A novel lymphoproliferative/autoimmune syndrome resembling murine *lpr*/*gld* disease. J Clin Invest 90:334–341

Snover DC, Filipovich AH, Dehner LP, Krivit W (1981) "Pseudolymphoma". A case associated with primary immunodeficiency disease and polyglandular failure syndrome. Arch Pathol Lab Med 105:46–49

Straus SE, Jaffe ES, Puck JM, Dale JK, Elkon KB, Rosen-Wolff A, Peteres AM, Sneller MC et al (2001) The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. Blood 98:194–200

Takahashi H, Sawai H, Matsuo Y, Funahashi H, Satoh M, Okada Y, Inagaki H, Takeyama H, Manabe T (2006) Reactive lymphoid hyperplasia of the liver in a patient with colon cancer: report of two cases. BMC Gastroenterol 6:25

Tanabe Y, Yano K, Yoshida Y, Sato T, Sakai K, Koyanagi N (1991) A respectable case of pseudolymphoma of the liver (in Japanese). Jpn J Gastroenterol 16:240

Tanizawa T, Eishi Y, Kamiyama R, Nakahara M, Abo Y, Sumita T et al (1996) Reactive lymphoid hyperplasia of the liver characterized by an angiofollicular pattern mimicking Castleman's disease. Pathol Int 46:782–786

Teachey DT (2010) Somatic ALPS: a FAScinating condition. Blood 115:5125–5126

Teachey DT (2011) Autoimmune lymphoproliferative syndrome: new approaches to diagnosis and management. Clin Adv Hematol Oncol 9:233–235

Teachey DT (2012) New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome. Curr Opin Pediatr 24:1–8

Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH, McMann JM et al (2005) Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). Blood 105:2443–2448

Teachey DT, Seif AE, Grupp SA (2010) Advances in the management and understanding of autoimmune lymphoproliferative syndrome (ALPS). Br J Haematol 148:205–216

Tsuneyama K, Nose M, Nisihara M, Katayanagi K, Harada K, Nakanuma Y (2001) Spontaneous occurrence of chronic non-suppurative destructive cholangitis and antimitochondrial autoantibodies in MRL/lpr mice: possible animal model for primary biliary cirrhosis. Pathol Int 51:418–424

Tuckett J, Hudson M, White S, Scott J (2011) Reactive lymphoid hyperplasia of the liver: a case report and review of imaging characteristics. Eur J Radiol Extra 79:e11–e14

Watanabe S (2010) Reactive lymphoid hyperplasia of the liver associated with primary biliary cirrhosis. Med Sci Monit 16:CS81–CS86

Weintraub JP, Godfrey V, Wolthusen PA, Cheek RL, Eisenberg RA, Cohen PL (1998) Immunological and pathological consequences of mutations in both Fas and Fas ligand. Cell Immunol 186:8–17

Williams FM, Cohen PR, Jumshyd J, Reveille JD (1998) Prevalence of the diffuse infiltrative lymphocytosis syndrome among human immunodeficiency virus type 1-positive outpatients. Arthritis Rheum 41:863–868

Willenbrock K, Kriener S, Oeschger S, Hansmann ML (2006) Nodular lymphoid lesion of the liver with simultaneous focal nodular hyperplasia and hemangioma: discrimination from primary hepatic MALT-type non-Hodgkin's lymphoma. Virchows Arch 448:223–227

Yang CT, Liu KL, Lin MC, Yuan RH (2013) Pseudolymphoma of the liver: report of a case and review of the literature. Asian J Surg. doi:10.1016/j.asjsur.2013.013

Yoshida K, Kobayashi S, Matsui O, Gabata T, Sanada J, Koda W, Minami T, Ryu Y, Kozaka K et al (2013) Hepatic pseudolymphoma: imaging-pathologic correlation with special reference to hemodynamic analysis. Abdom Imaging 38:1277–1285

Yoshikawa K, Konishi M, Kinoshita T, Takahashi S, Gotohda N, Kato Y, Kojima M (2011) Reactive lymphoid hyperplasia of the liver: literature review and 3 case reports. Hepatogastroenterology 58:1280–1285

Yuan L, Zhang Y, Wang Y, Cong W, Wu M (2012) Reactive lymphoid hyperplasia of the liver: a clinicopathological study of 7 cases. HPB Surg 2012:357694

Zen Y, Fujii T, Nakanuma Y (2010) Hepatic pseudolymphoma: a clinicopathological study of five cases and review of the literature. Mod Pathol 23:244–250

Tumors of the Langerhans Cell System

100

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_100

Abstract

Langerhans cell histiocytosis (LCH) is a rare proliferative disorder of bone marrow-derived antigen-presenting cells that home to diverse organs and tissues, predominantly the skin. LCH is a rare disease that mainly manifests in the pediatric age group, with several in part overlapping phenotypes. Clinically and morphologically, LCH is divided into unifocal LCH, single-system LCH, multifocal LCH, multiorgan/disseminated LCH, Langerhans cell sarcoma, and Langerhans tumors. All forms and variants are characterized by a progressive and monoclonal proliferation of medium-sized, CD1a-reactive, and langerin-/CD207-reactive cells that often contain Birbeck granules. Langerhans cell infiltrates are regularly accompanied by infiltrates of eosinophils, lymphoid cells, and macrophages. Lesions with a high density of eosinophils were previously termed eosinophilic granuloma. Hepatobiliary involvement in LCH presents with a characteristic spectrum of lesions that include a disseminated form, focal forms (microscopic and macroscopic), and a form associated with bile ducts (LCH cholangiopathy). A small subset of Langerhans cell proliferations present as tumorous lesions or Langerhans cell sarcoma. In addition to LCH, there are a group of so-called self-healing Langerhans cell and related disorders that can involve the hepatobiliary tract.

Langerhans Cell Histiocytosis (LCH)

ICD-O code 9751/3

Introduction

Langerhans cell histiocytosis (LCH) is a rare proliferative disorder of bone marrow-derived antigen-presenting cells that tend to chiefly infiltrate the skin, but also other organs and tissues, including the bone marrow, bone, liver, spleen, lymph nodes, gastrointestinal tract, lungs, and hypophysis (Arico and Egeler 1998; Broadbent et al. 1994; Herzog and Tubbs 1998; Ladisch 1998; Allen and McClain 2007; Windebank and Nanduri 2009; Abla et al. 2010; Minkow 2011; Munir et al. 2012; Xu et al. 2012a; Gadner et al. 2013; Haupt et al. 2013; Collin et al. 2015; El Demellawy et al. 2015). Synonymous terms that are currently regarded as obsolete are histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schüller-Christian disease, Langerhans cell granulomatosis, type II histiocytosis, and nonlipid reticuloendotheliosis (Komp 1987; Favara et al. 1997). These older terms reflect the first clinical descriptions of LCH and its variants by Hand (1893, 1921), by Schüller (1915), by Christian (1919), and later by Letterer (1924) and Siwe (1933), resulting in considerable confusion in nomenclature until it was recognized that the disease in each of these clinical syndromes was components of a spectrum of disease involving the LC (Lichtenstein 1953; Lieberman et al. 1969; Broadbent et al. 1994).

Epidemiology

The estimated incidence of LCH is approximately five per one million population per year. Most cases are diagnosed in the pediatric age group. LCH has a clear predilection for males (M/F = 3.7:1) and chiefly occurs in whites of northern European descent, being rare in blacks. LCH can be clustered within families, with high concordance in monozygotic twins, but there is no evidence for vertical transmission. LCD occurs in the neonatal period, where it is associated with a poor prognosis (Gee et al. 2013). In very rare instances, LCH can present as congenital disorder, sometimes with placental involvement (Terry et al. 2013).

Clinical Features

The clinical presentation and biology of LCH are highly heterogeneous and range from unifocal manifestations with an apparently self-limited course to multifocal and chronic, complex organ manifestations to rapidly progressing and fatal,

disseminated leukemia-like forms. LCH can be localized to a single site, multiple sites within a single system, or more disseminated and multisystemic. The solitary or unifocal form mainly involves bones and adjacent soft tissues and less commonly the skin, lung, lymph nodes, and other organs. Multifocal LCH is typically a bone disease, with involvement of the periosseous tissue. Preferential involvement sites in multisystemic LCH comprise the bone marrow, spleen, bone, skin, and liver. Interestingly, kidneys and gonads are very uncommonly involved. Clinically, solitary/unifocal lesions prevail in older children and adults and typically present as lytic bone defects. In skull base involvement, diabetes insipidus is common. Multisystem involvement predominantly occurs in infants and small children and is characterized by a febrile illness with skin, bone, and visceral lesions and cytopenia.

Classifications of LCH

What renders histopathologic diagnosis and classification difficult is the fact that the clinical heterogeneity is reflected in a broad spectrum of morphological lesions, heterogeneous themselves in regard to a given patient and her or his age and genetic background, the organ localization, the time point of examination, and the stage of disease, lesions that histologically sometimes do not appear to have something to do with a proliferative LC disorder. The criteria for a definitive diagnosis of LCH have been worked out and published in 1987 (Writing Group of the Histiocyte Society 1987); they are not further discussed here. Differential organ and tissue involvement has led to the definition of several subtypes, e.g., *unifocal LCH* (formerly, eosinophilic granuloma), *single-system LCH* (almost a third in one large study; Arico et al. 2003), and *multisystem/multiorgan/disseminated disease*. Pulmonary LCH (PLCH) is an important member of single-system LCH, being clearly distinct from systemic multiorgan LCH (Yousem et al. 2001; Sundar et al. 2003). A further variant of single-system LCH seems to be soft tissue solitary LCH (al-Abbadi et al. 1997).

Table 1 Working classification of Langerhans cell histiocytosis

Unifocal LCH (with or without marked eosinophilia, in the latter case corresponding to the former "eosinophilic granuloma")
Single-system LCH
Multifocal LCH (including manifestations corresponding to the former Hand-Schüller-Christian disease)
Multiorgan/disseminated LCH (acute, subacute; including manifestations corresponding to the former Letterer-Siwe disease)
Langerhans cell sarcoma
Langerhans cell tumors

Multisystem LCH covers syndromes originally denoted as Hand-Schüller-Christian disease and Letterer-Siwe disease, distinct by the rapidity of disease progression and by the involved organ/tissue spectrum, but an individual patient with multisystem LCH may present with signs intermediate between these apparent entities (Kato et al. 1981; Iupati and Chander 2006; Cugati et al. 2011). In the present chapter, the *working classification of LCH* summarized in Table 1 is used.

Langerhans cell tumors and Langerhans cell sarcomas are discussed in a separate paragraph.

General Morphologic Features of Langerhans Cell Histiocytosis

In principle, LCH is a progressive and apparently monoclonal proliferation of CD1a-positive cells, at least part of them containing Birbeck granules. "Langerhans cell granules" have already been reported for LCH then termed "subacute disseminated histiocytosis of Letterer-Siwe" in 1968 (Gianotti et al. 1968). The cells are medium sized (10–15 μm) of oval shape, lacking dendritic processes, with a slightly eosinophilic cytoplasm and grooved, folded, lobulated, or indented nuclei with fine chromatin and inconspicuous nucleoli. These cells are embedded in a cellular background with variable numbers of macrophages (in part multinucleated forms), eosinophils, neutrophils, and lymphocytes. Plasma cells are sparse. Eosinophils are sometimes very numerous, especially in solitary/unifocal bone lesions (the former

"eosinophilic granuloma"). Such lesions may contain eosinophilic abscesses with Charcot-Leyden crystals. Ultrastructurally, cells of LCH contain Birbeck granules, zipper-like structures with a tennis racquet shape, measuring 200–400 nm in length and 33 nm in width. Birbeck granules originate from subdomains of endosomal recycling compartments that consist of disks of two limiting membranes separated by leaflets with periodic zipper-like striations. Immunohistochemically, cells in LCH are strongly reactive for CD1a, langerin, and S100 protein. Langerin (CD207) is a trimeric C-type lectin that functions as a antigen receptor and in pathogen capture via the recognition of glycan motifs by three carbohydrate recognition domains (CRDs) (Muñoz-Garcia et al. 2015). Langerin recognizes hyaluronic acid on dendritic cells and is involved in the morphogenesis of Langerhans cell Birbeck granules (Chabrol et al. 2015). In addition, the tumor cells are positive for CD68, HLA-DR, and vimentin. LCs in LCH can express matrix metalloproteinase-9 (MMP-9), mostly co-expressed in cells that are also CD68+ and associated with recurrence of lesions (Zyada 2009).

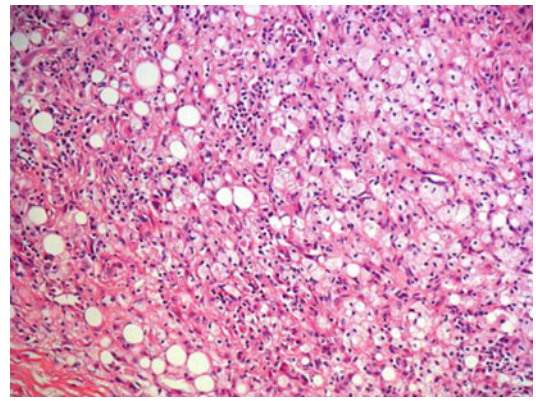

Fig. 1 Langerhans cell histiocytosis of the liver. Medium-sized to large cells have infiltrated the steatotic liver tissue (hematoxylin and eosin stain)

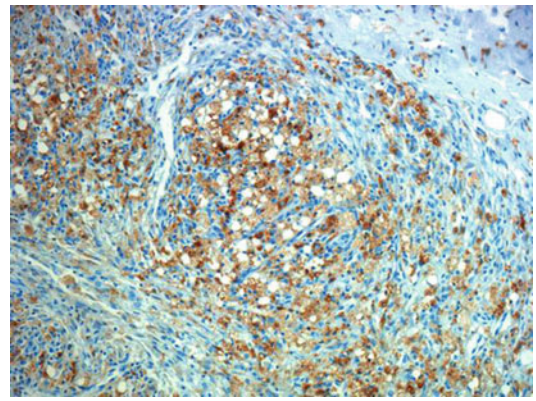

Fig. 2 Langerhans cell histiocytosis of the liver. Most of the neoplastic cells are reactive for CD1a (CD1a immunostain)

Liver Involvement in Langerhans Cell Histiocytosis

Introduction

In LCH, the liver is commonly involved, albeit with a rather broad spectrum of manifestations reflecting the different biologic phenotypes of LCH, including those with marked contribution of eosinophils (Figs. 1, 2, 3, 4, 5, and 6 and Table 2). Liver infiltration can sometimes cause massive hepatomegaly (Trochtenberg and Dessypris 1990). In multisystemic LCH, liver dysfunction may be the first clinical presentation (Liu et al. 2012). The morphology and immunophenotypes of LC in LCH of the liver are, in principle, similar to that of normal LC. For example, cells of LCH contain, albeit to variable degrees, Birbeck granules, a finding known since 1973 (Nezelof et al. 1973). However, LC in LCH expresses a phenotype of an LC apparently "fixed" at an earlier stage of activation, the cells being functionally defective in antigen capture and presentation and being very different in regard to tissue distribution and homing features (Chu and Jaffe 1994).

Selected References Avery et al. (1957), Parker and Lichtenstein (1963), Grosfeld et al. (1976), Leblanc et al. (1981), Jones et al. (1981), Favara (1981, 1996), Favara et al. (1983), Thompson et al. (1984), Sisto et al. (1987), Pirovino et al. (1988), Iwai et al. (1988), Heyn et al. (1990), Stieber et al. (1990), Concepcion et al. (1991), Squires et al. (1993), Granot et al. (1994), Debray et al. (1994), Finn and Jaffe

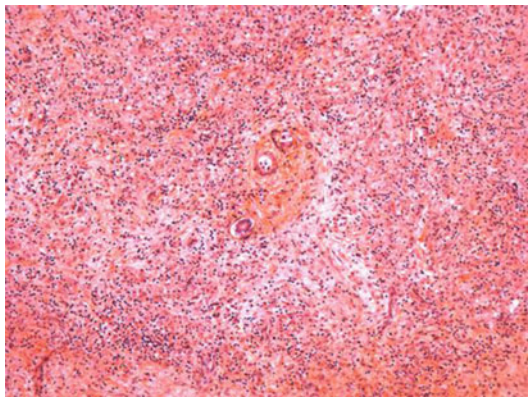

Fig. 3 Variant of Langerhans cell histiocytosis of the liver with xanthomatous cells and significant fibrosis. Variants with this phenotype were termed Hand-Schüller-Christian disease (hematoxylin and eosin stain)

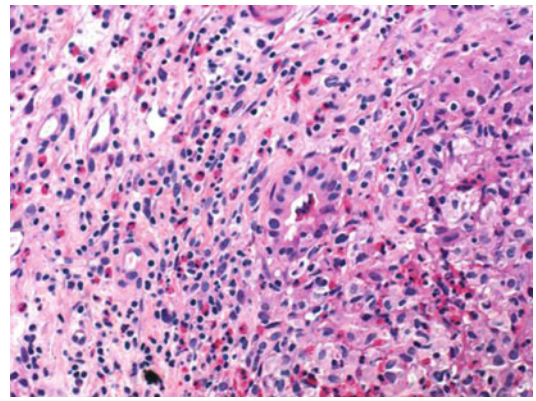

Fig. 5 Eosinophilic granuloma of the liver at higher magnification. The infiltrate is dominated by eosinophils, Langerhans cells, and lymphocytes. Eosinophils have invaded an interlobular bile duct, which is injured (eosinophilic cholangiopathy, hematoxylin and eosin stain)

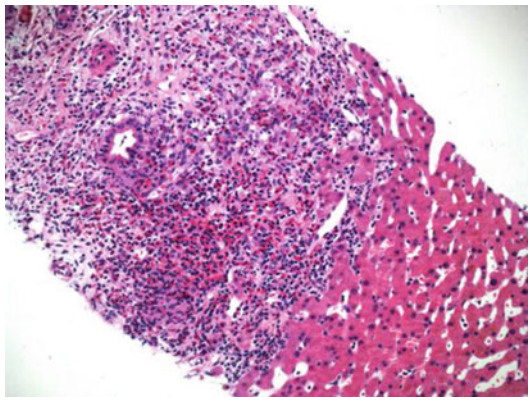

Fig. 4 Eosinophilic granuloma of the liver as a variant of Langerhans cell histiocytosis. In this biopsy, dense infiltrates of eosinophils, atypical round cells, and lymphocytes occupy an enlarged portal tract (hematoxylin and eosin stain)

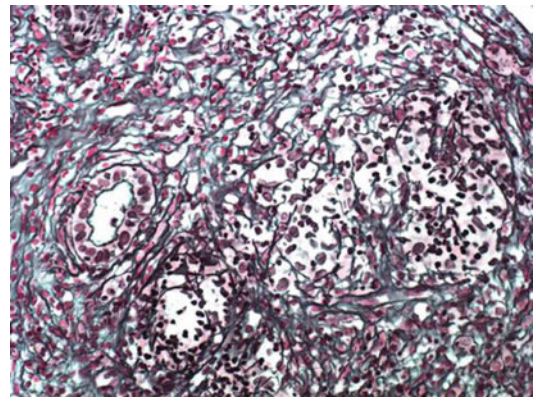

Fig. 6 Eosinophilic granuloma of the liver. The infiltrate is associated with increased reticulin fiber density. A small damaged bile duct is seen to the left (Gomori silver stain)

(1997), Kaplan et al. (1999), Guthery and Heubi (2001), Jaffe (2004), Chaudhary et al. (2006), Konno et al. (2007), Savva-Bordalo and Freitas-Silva (2008), Abdallah et al. (2011), and Ma et al. (2012).

Classifications of Hepatic LCH

There are several propositions to classify hepatic LCH, based on various criteria (Table 2).

Portal Tract/Bile Duct Involvement

Pretreatment liver biopsies show several lesions, a considerable part of the changes being nonspecific. In a study on 20 patients with LCH, pretreatment evaluation of liver tissues revealed various abnormalities of the portal tracts in 19/20 specimens, including "triaditis," small bile duct proliferation, variable fibrosis with infiltration of "histiocytes," and liver cirrhosis. One patient showed a granulomatous lesion (Heyn et al. 1990). In this study, patients with larger livers and hepatic dysfunction tended to exhibit

Table 2 Classifications of hepatic Langerhans cell histiocytosis

Clinicopathologic classification
I. Disseminated form (with or without sinusoidal spread)
II. Focal forms
1. Focal LC infiltration, microscopic pattern
2. Nodular LCH of the liver
3. Granulomatous hepatopathy
III. LCH cholangiopathy (in particular, sclerosing cholangitis)
IV. Posttransplant manifestations and associations of LCH
V. Paraneoplastic manifestations of LCH
Pathologic/pathogenic classification (Kaplan et al. 1999, modified)
A. Portal area/bile duct infiltration by LC causing:
Cholangionecrosis
Periductal sclerosis with or without LC ("PSC-like")
Ductopenia
Chronic cholestasis
Fibrosis/secondary biliary cirrhosis/atrophy-hypertrophy complex (AHC)
B. Sinusoidal infiltration
C. Disseminated infiltration
D. Multifocal infiltration with tumor-like lesions
E. Focal granulomatoid lesions (including "eosinophilic granuloma")
F. Secondary sclerosing cholangitis
G. Other liver manifestations

more marked histologic anomalies in the portal tracts, however, with considerable overlap. It turned out that patients showing fibrohistiocytic changes or cirrhosis initially were more likely to have continuing or progressive liver disease, although the liver histology was not diagnostic for LCH (Heyn et al. 1990). Triaditis was also observed in the majority of cases in another study (Favara 1996). In case of more advanced involvement of the liver, focal aggregates of LC (microscopic pattern) are observed in a polymorphous background of mature eosinophils, lymphocytes, neutrophils, and plasma cells (Kaplan et al. 1999). Specific LC infiltrates may be cholangiocentric, forming dense collections of cells surrounding damaged bile ducts (Favara 1996), or in the form of apparently random acinar "histiocytic" lesions (Favara 1996). Ductocentric LCH can result in progressive portal tract fibrosis or septal fibrosis (Arakawa et al. 1994). Involvement of the bile ducts with LCH may result in biliary wall calcification (Caruso et al. 2008). LCH may be associated with cholelithiasis and bile duct dilatation (Caruso et al. 2009).

Sinusoidal Infiltration

In part of cases of hepatic LCH, the CD1a-reactive tumor cells are found within the sinusoidal lumina, either as single cells or small clusters or groups of cells. This infiltration pattern can be associated with atrophy of hepatocyte plates.

Disseminated Infiltration

Relatively few data are available on the liver pathology in multisystemic/disseminated LCH, and in some of the published observations, it is difficult to judge as to what form of LCH one really deals with. In contrast to the chronic disseminated form of LCH (the former Hand-Schüller-Christian disease; Fig. 3), disseminated LCH is known to show an acute or subacute course. In the pediatric age group, the most impressive manifestation of disseminated LCH is the disorder characterized by a severe illness, a distinctive and frequently hemorrhagic skin rash, a low-grade fever, a leukemia-like blood change, and a massive hepatosplenomegaly with or without ascites, jaundice, lymphadenomegaly, soft tissue edema, and gingival necrosis, i.e., what has previously been termed Letterer-Siwe disease or "acute nonlipid disseminated reticuloendotheliosis" (see below; Batson et al. 1955; Komp 1987). Liver manifestations have been reported in the literature (Childers and Price 1954; Batson et al. 1955). In an autopsy case (two-and-a-half-year-old child with "classical" presentation of Letterer-Siwe disease), the enlarged liver showed numerous nodular projections on the capsular surface, a greenish-yellow color, and a firm consistency. Microscopy revealed an increased amount of connective tissue in the portal tracts associated with ductular proliferations, portal tract infiltrates of mononuclear

cells and small lymphocytes, and signs of cholestasis (Childers and Price 1954). The disease manifestations depend on the stage of disease, i.e., florid lesions with tissue damage together with highly cellular infiltrates being more prominent in early phase disease, while the portal tract lesions described in the case of Childers and Price reflect longer-standing disease.

Multifocal Infiltration with Tumor-like Lesions

LCH can produce focal infiltrations growing in the form of nodules, termed nodular LCH of the liver, but this type of manifestation is much rarer than the disseminated form (Foschini et al. 1995; Levy et al. 1998; Cavazza et al. 1999; Rice and Wyatt 2000; Yagita et al. 2001). In this situation, the liver substance is partially replaced by a hypercellular tissue forming lobulated, poorly demarcated nodules surrounded by fibrous tissue . The nodular lesions can clinically and radiologically resemble a primary hepatic malignancy and thus be misdiagnosed as liver cancer (Ma et al. 2014). The diameter of the nodules ranges from 1 mm to a few centimeters. In very few instances, only one hepatic nodule had been detected (Rice and Wyatt 2000). The infiltrate nodules may encroach upon small intrahepatic bile ducts (Parker and Lichtenstein 1963), but focal LCH confined to a bile duct has also been found (Finn and Jaffe 1997). Multifocal or disseminated hepatic LCH is mainly seen in patients who also show significant involvement of other organs and tissues and can present similar to multiple hepatic metastases (Hara et al. 1988; Guilarte Lopez-Manas et al. 1997). On the other hand, multiple tumor-like lesions at imaging may also be caused by marked periportal fibrosis in hepatic LCH (Arakawa et al. 1994).

Focal Granulomatoid Lesions (Including "Eosinophilic Granuloma")

Rarely, hepatic lesions in the context of LCH may contain numerous eosinophils, thus reflecting what previously has been termed eosinophilic granuloma, either unifocal or multifocal (the former Hand-Schüller-Christian disease; Parker and Lichtenstein 1963). Hepatic eosinophilic granuloma and other solitary liver lesions in LCH may radiologically be confounded with metastatic cancer (Saito et al. 2008). Hepatic lesions representing unifocal LCH may contain numerous lipid-laden macrophages in addition to eosinophils ("xanthomatous eosinophilic granuloma"; Fione and Rizzo 1959), leading to differential diagnostic problems with respect to other xanthomatous hepatic lesions such as those occurring in some lipidoses and in obstructive cholestasis. In an autopsy of a patient with multifocal LCH of the former Hand-Schüller-Christian type (chronic disseminated form of LCH), the liver was enlarged (1,900 g) and showed yellow flecks scattered about the parenchyma (Parker and Lichtenstein 1963). Histologically, the liver displayed marked cholestasis with formation of bile lakes, rounded portal tracts with fibrosis and ductular proliferations, and histiocyte-containing nodules (sometimes impinging upon bile ducts and producing florid duct lesions), containing in addition to histiocyte-like cells lipid-laden macrophages, but only few eosinophils, whereas a previous biopsy had shown eosinophil-rich nodules. This observation illustrates the transitional or overlapping features of LCH, lesions at one time point looking like the eosinophil-rich variant of focal LCH (eosinophilic granuloma) and showing at a later time point the features of xanthomatous lesions. Hence, an initial histologic diagnosis of eosinophil focal LCH or eosinophilic granuloma may result in the erroneous judgment that one deals with a benign process, what may then not be the case.

Langerhans Cell-Induced Secondary Sclerosing Cholangitis

A distinctive situation is obstructive cholestasis caused by secondary sclerosing cholangitis (SSC) in hepatic LCH (Leblanc et al. 1981; Thompson et al. 1984; Squires et al. 1993; Kaplan et al. 1999; Hadzic et al. 2000; Romao et al. 2002;

Lee et al. 2011). As in other forms of SSC, SSC due to LCH can result in secondary biliary cirrhosis. In a study of nine cases of LCH of the liver, four of the patients had SSC with visible infiltration of the ductal compartment with LC, but in two other patients, SSC was not associated with directly visible involvement of the ducts with LC (Kaplan et al. 1999). In children, LCH is probably a cause of SSC almost as frequent as SSC related to inflammatory bowel disease (Mieli-Vergani and Vergani 2001; Sabib et al. 2011). The pathogenesis of SSC in hepatic manifestations of LCH has not been clarified. In particular, infiltration of the bile ducts walls or the periductal tissues by LCH cells may be sparse. In five explanted livers with marked destructive cholangitis, CD1a staining revealed a small number of LCs in the choledochal wall in only one specimen (Braier et al. 2002). Conversely, there are highly unusual situations where marked infiltration of a hepatic duct in LCH has caused features clinically suggesting biliary atresia (Heitner et al. 1978). Furthermore, LCH of the eosinophilic granuloma type can produce highly cellular and micronodular lesions impinging upon the bile ducts, associated with florid duct lesions and focal-sectorial bile duct destruction (Parker and Lichtenstein 1963). The fibrotic response centered around the bile ducts results in a sonographic pattern characterized by hypoechoic or hyperechoic lesions, the hypoechoic changes probably corresponding to periportal inflammation (Chan et al. 1997).

Histologically, intrahepatic bile ducts show ductocentric fibrosis of varying cellularity, most of the infiltrate cells found in this periductal compartment consisting of lymphocytes, with variable contributions of macrophages (including epithelioid forms), plasma cells, and eosinophil granulocytes. Similar to SSC of other etiologies, lymphocytes and macrophages can reveal an intimate relation to bile ducts (Parker and Lichtenstein 1963), invade the normal-looking or already damaged biliary epithelium, with sectorial bile duct destruction, or infiltrate form micronodules impinging upon small bile ducts. The abnormal infiltration can be associated with portal tract fibrosis, sometimes with ductular proliferation (Parker and Lichtenstein 1963). In most situations, LC is only detectable when using immunohistochemistry (in particular CD1a), LC being recognized as single cells or small groups of cells intermingled with other cell types within the fibrotic areas. Usually, LC is not seen to invade the epithelial duct lining, even though this may occur. The array of these lesions has been put together to form two lesion groups, i.e., (a) small bile duct infiltration and destruction, producing clinicopathologic features of chronic cholestasis reminiscent of primary sclerosing cholangitis, and (b) destructive cholangitis of larger bile ducts, producing cystic dilatation and/or bile extravasation (Kaplan et al. 1999).

Biology of Disease

The clinical course strongly depends on stage of disease at presentation. Patients with solitary/unifocal disease have a 99 % or greater survival, while infants with multisystemic disease have a mortality of more than 60 %. Treatment strategies in LCH are based on the distribution pattern of disease and unifocality versus multifocality versus multisystemic disease. Low-risk organs include the skin, bone, lymph nodes, pituitary gland, and CNS. High-risk organs for unfavorable outcome are the bone marrow, lung, spleen, and liver involvement. The involution of lesions in some forms of LCH is well known, albeit multisystem variants can take a rapidly fatal course (Mosterd et al. 2008). In multisystem LCH (MS-LCH), reactivation is a frequent and early event, but involvement of risk organs at reactivation is rare and mortality is minimal. But reactivations have been shown to increase the risk for permanent consequences by about twofold (Minkow et al. 2008). The incidence of reactivation correlates with the stage of disease at diagnosis (Pollono et al. 2007). The spontaneous regression of lesions in single-system disease (and eventually in infantile self-healing forms) may be caused by apoptosis through the Fas/Fas-L pathway (Peng et al. 1999; Petersen et al. 2003).

On the other hand, LCH occurs in conjunction with, or is sometimes followed by, malignant

neoplasias involving a cell lineage different from LC. Examples of synchronous or metachronous neoplastic disorders comprise B-cell lymphoma (Almanaseer et al. 1986), T-cell lymphoblastic lymphoma (Li and Borowitz 2001; Rodig et al. 2008), splenic lymphomas (Llamas-Velasco et al. 2012), and Hodgkin's disease (Karadeniz et al. 1991; Ibarrola de Andres et al. 1999; Park et al. 2012). LCH has also been observed in conjunction with Erdheim-Chester disease (Pineles et al. 2011).

Cytogenetic and Molecular Features

Monoclonality and, hence, neoplastic features seem to be present in many, but not all, forms of LCH, clonality, i.e., having been identified in solitary lytic bone lesions, in multisystem disease of infancy, and in the intermediate form of the disease that usually has multisystem involvement and chronic course (Willman 1994; Willman et al. 1994; Yu et al. 1994; Badalian-Very et al. 2013), whereas the majority of cases with PLCH have been shown to be nonclonal lesions (Yousem et al. 2001). It has also been proposed that LCH may represent a reactive condition, possibly induced by immune stimulation (Bank et al. 2003). The clonal features of Langerhans cells may be related to elevated expression of p53, c-myc, and H-ras, the p53-p21 pathway and the p16-Rb pathway being activated (Schouten et al. 2002), and distinct deleted chromosomal segments, the highest frequency of LOH being found in chromosomes 1p and 7 (Murakami et al. 2002). As the abnormal dendritic histiocytes in LCH express elevated levels of tumor necrosis factor-alpha (TNF-alpha), IFN-gamma, GM-CSF, IL-1, and leukemia inhibitory factor (LIF), increased cytokine levels may contribute to the expansion of the cells, and polymorphisms of the TNF-alpha promoter in LCH could increase the production of that particular cytokine (Wu and McClain 1997), even though polymorphisms of the TNF-alpha promoter have not been detected in a more recent study (McClain et al. 2003). Tumor cells in LCH differ from normal epidermal LC in their transcription profile, in that they selectively express the Notch ligand Jagged 2, and are the only dendritic cells that express both Notch ligand and its receptor, suggesting the presence of a unique Notch signaling pathway in LCH cells (Hutter et al. 2012).

There is recent evidence that variably differentiated cells in LCH carry the BRAFV600E and BRAF600DLAT gene mutations (Badalian-Very et al. 2010; Sahm et al. 2012; Satoh et al. 2012; reviews: Badalian-Very et al. 2012, 2013), indicating that these mutations are somatic mutants enriched in LCH CD1a + cells. In BRAF V600E-negative LCH, a high prevalence of recurrent, mutually exclusive somatic MAP2K1 mutations was detected (Brown et al. 2014), supporting an important role for ERK (extracellular signal-regulated kinase) activation in pathogenic pathways involved in LCH (Chakraborty et al. 2014). There is evidence that MAPK activation in self-renewing hematopoietic progenitors cells can induce disseminated and high-risk disease, while MAPK activation in a more differentiated committed myeloid lineage promotes low-risk disease, shedding more light on the cells of origin of LCH (Collin et al. 2015).

Liver Manifestations of Eosinophilic Granuloma, Hand-Schüller-Christian Disease, and Abt-Letterer-Siwe Disease: What Is the Relationship with Modern LCH?

As specified above, these terms and the entities behind them are today obsolete; the disorders have been identified as related manifestations of a single nosologic entity, i.e., LCH (Lichtenstein 1953; Lieberman et al. 1969). In the context of the improvement of classification, based on increased knowledge regarding the cell involved, this is on the one hand a progress. On the other hand, the price that had to be paid is a certain loss of valuable information, mainly in regard to the understanding of excellent clinical and pathologic observations found in the older literature, specifically relating to liver involvement. In this paragraph, some informations pertinent to the liver and extractable from "historical" reports are

briefly summarized (historical reviews: Komp 1987; Coppes-Zantinga and Egeler 2002).

Originally, some of the "entities" discussed in this paragraph made part of what was called "nonlipid reticuloendothelioses" and defined to include Hand-Schüller-Christian disease (HSCD), eosinophilic granuloma of the bone, and acute disseminated reticuloendotheliosis (Letterer-Siwe disease, LSD). HSCD is characterized by the triad, diabetes insipidus, exophthalmos, and defects in membranous bones (Smith 1864; Hand 1893; Kay 1905; Schüller 1915; Christian 1919). Later reports put emphasis on the intriguing finding that the cells found in HSCD frequently accumulated considerable amounts of lipid ("lipoid histiocytosis," "lipoid granulomatosis"), resulting in the concept that the disorder might have something to do with a genuine lipid storage disease (Weidman and Freeman 1924). In contrast, acute forms of pediatric LCH do not usually show these features and thus were initially called "acute *nonlipid* disseminated reticuloendotheliosis" (Batson et al. 1955). Schüller, who appears in the eponym HSCD, described peculiar skull defects related to LCH and coined them "geographic skull defects (i.e., 'Landkartenschädel' in German)" (Schüller 1915). Later, he further discussed the lesions employing the term "dysostosis hypophysaria" (Schüller 1926). Henry Asbury Christian (1876–1951) had read the article of Schüller and, based on his own observations, thought that the disease in question was hypophyseal in origin, but apparently failed to recognize Dr. Hand's case of polyuria as being part of the same syndrome (Komp 1987). The cell type involved in these disorders, i.e., the LC, was detected during the same time period by the then 21-year-old medical student, Paul Langerhans (1847–1888), who studied medicine under Haeckel and Virchow and described in his 1869 thesis in the rabbit pancreas the structures that later became the islets of Langerhans, an eponymic term created by Edouard Laguesse (Coppes-Zantinga and Egeler 2002). The identification of skin dendritic cells (LC) was based on Cohnheim's gold chloride staining technique (Langerhans 1868).

The pathway to the concept of "eosinophilic granuloma" is rather complex as well. Two early reports independently documented, in the same year and in the same volume of the American Journal of Pathology patients with solitary bone lesions rich in both histiocytes and eosinophils (Lichtenstein and Jaffe 1940; Otani and Ehrlich 1940). "Unifocal" eosinophilic granuloma (UFEG), which is now classified as unifocal LCH, not only develops in bones but also in visceral organs including the liver. UFEG is its original description denotes the most benign disorder in the spectrum of LCH (review: Duncan et al. 1988). "Multifocal eosinophilic granuloma (MFEG)," proposed as a replacement for the designation formerly known as Hand-Schüller-Christian disease (HSCD) (Krutchkoff and Jones 1984), may also manifest in the liver. In contrast to UFEG/unifocal LCH, MFEG/HSCD is a chronic disorder with a complex manifestation pattern and a highly variable histology, including the participation of eosinophils, markedly depending on the manifestation site (Kaufman et al. 1976). In the liver, MFEG/HSCD presents in the form of multifocal lesions and displays a multifaceted infiltrate with or without numerous eosinophils, with or without easily detectable LC, and with or without lipid-laden macrophages or giant cells (Parker and Lichtenstein 1963). As the terms imply, a dense infiltrate of eosinophils should characterize these lesions. However, there are instances where unifocal LCH (the "new" entity) is poor in eosinophils, suggesting that unifocal LCH is heterogeneous (Papasozomenos 1999). This not only confers difficulties in histopathologic diagnosis but also has an impact on the pathogenesis of the lesion patterns associated with LCH.

The study of older reports on acute or subacute, rapidly progressive or even fulminant forms of LCH is fruitful insofar as one may obtain carefully collected clinical informations and pathology data from a pre-chemotherapy era. What has previously been termed Letter-Siwe disease (Abt-Letterer-Siwe disease; aleukemic reticulosis; Letterer 1924) is a highly impressive and catastrophic disorder mainly occurring in infants and children, fetal and congenital presentations also

being known (Shuangshoti and Seksarn 1987; Yu et al. 1990; Valde et al. 1993). Letterer reported an acute fulminant non-leukemic disorder of the Aschoffian reticuloendothelial system in a 6-month-old child (Letterer 1924). Nine years later, Siwe reported a further case (Siwe 1933) and formulated the diagnostic criteria of the disease. The eponymic term, Letterer-Siwe disease, goes back to Arthur Frederick Abt, an American physician. Together with Denenholz, he discussed the issue of so-called reticuloendothelioses by proposing the term Letterer-Siwe disease (Abt and Denenholz 1936). Hence, the disorder was sometimes called "Abt-Letterer-Siwe disease." A disseminated visceral involvement, including the liver, is a striking feature in many patients ("disseminated visceral histiocytosis X"; Landing 1987). The involvement of bona fide LC has been documented in at least part of the cases (Ruco et al. 1988). Lipid-laden histiocytes can also occur in the Letterer-Siwe type of LCD (Kawai et al. 1978), similar to MFEG/HSCD.

Langerhans Cell Tumors and Langerhans Cell Sarcoma

Introduction

A small subset of Langerhans cell neoplasms present as isolated mass lesions rather than a diffusely growing process. These Langerhans cell tumors (LCTs) have been proposed to be classified into two distinctive groups: (a) typical LCT consisting of cells found in classical Langerhans cell histiocytosis and (b) a sarcomatous form (Langerhans cell sarcoma, LCS) (Warnke et al. 1995; Lieberman et al. 1996; Pileri et al. 2002). The diagnosis of both lesions requires the detection of expression of both CD1a and S-100 protein, but there is frequently also expression of some histiocyte markers, such as CD68 and some focal, weak expression of lysozyme, the latter staining being clearly less than in histiocytic sarcoma and eventually being due to background staining or staining by infiltrating normal histiocytes/macrophages. Staining for CD35 or CNA.42 (Pileri et al. 2002); the transcription factor PU.1 (Muirhead et al. 2009); the phosphatidylserine receptors T-cell immunoglobulin mucin proteins 3 and 4 (Dorfman et al. 2010); langerin, fascin, DEC-205, and DC-SIGN (Orii et al. 2010); and CD163 (hemoglobin scavenger receptor) (Nguyen et al. 2005) has been described.

Langerhans Cell Tumors (LCTs)

Solitary or multiple circumscribed tumors consisting of Langerhans cells have seldom been observed in several organs and tissues, including the skin (Ricciardo et al. 2011) and the hepatobiliary tract. Multiple LCTs of the liver have been observed (Guilarte Lopez-Manas et al. 1997; Cavazza et al. 1999; Yagita et al. 2001) and in part suggested the existence of hepatic metastases of colorectal cancer. LCT has been found as a mass causing extrahepatic biliary obstruction in children, probably originating from periductal lymph nodes or lymph nodes situated near the porta hepatis (Chen et al. 1989). In rare instances, massive periportal fibrosis of the liver caused by hepatic Langerhans cell histiocytosis mimicked multiple liver tumors on CT and MR images (Arakawa et al. 1994).

Langerhans Cell Sarcoma (LCS)

ICD-O code 9756/3

Introduction

Langerhans cell sarcoma (LCS, synonyms: dendritic/histiocytic sarcoma, Langerhans cell type; malignant Langerhans cell tumor, MLCT; true histiocytic neoplasm of Langerhans cell type; malignant histiocytosis X) is a rare malignant dendritic cell neoplasm with a Langerhans cell phenotype and a highly aggressive biology (high grade), tending to disseminate throughout the body and leading to death usually within 1 year. This tumor has to be distinguished from LCH (Imamura et al. 1971; Henderson and Sage 1973; Wood et al. 1984; Delabie et al. 1991;

Tani et al. 1992; Favara et al. 1997; Itoh et al. 2001; Misery et al. 2003). It seems that at least part of the cases of LCS correspond to what has been reported in the literature "Letterer-Siwe disease of the adult" (Vollum 1979; Wells 1979). A particularly aggressive subset of LCS is positive for CD56/N-CAM (Kawase et al. 2005).

Morphology

LCS is composed of pleomorphic neoplastic cells, with nuclei having clumped chromatin and large nucleoli. Part of the cells display the diagnostically important complex grooves of LCH cells. The mitotic rate is usually high, with more than 50 mitotic figures per 10 HPFs. Ultrastructurally, Birbeck granules are present. Typical LCS has an immunohistochemical profile being CD1a/langerin/S100 +. Exceptionally, T-cell markers are expressed, e.g., CD3 (Xu et al. 2012b). LCS cells can express some members of the B7 superfamily, including B7-H1, B7-H3, and B7-H4, co-expressed with signals from the T-cell immunoglobulin and mucin-domain (TIM)-containing molecules, i.e., TIM-1, TIM-3, and TIM-4 (Li et al. 2013).

Epidemiology

LCS is a very uncommon neoplasm that almost exclusively occurs in adults, with a female predominance. The median age at diagnosis is 39 years (range 10–72 years). The most common sites of LCS are the skin and soft tissues, often with multiorgan involvement (lung, lymph nodes, spleen, bone, and liver). Rarely, LCS initially presents as a single-organ disorder, e.g., in the lung (Langfort et al. 2009) or in the thyroid (Kitahama et al. 1996).

Liver Involvement

As LCS may involve the liver, this lesion is discussed here in some more detail. In the patients described so far, the disease usually started in the skin in the form of erythematous nodules of up to a few centimeter diameter, followed by diffuse or nodular spread within the body. LCS exhibits overtly malignant cytologic features and marked, sometimes, extreme cellular pleomorphism (similar to histiocytic sarcoma), but cells with grooved nuclei are generally detected (Pileri et al. 2002). The cell involved exhibits immunohistochemical features typical for abnormal LC (CD1a and S-100 protein), and Birbeck granules have been detected (Wood et al. 1984). The cells of LCS express B7, a member of a group of proteins involved in the immunoescape of cancer cells (Li et al. 2012).

Multisystem involvement in LCS, including jaundice and infiltration of the liver, has been reported (Wood et al. 1984; Itoh et al. 2001; Kawase et al. 2005). In the patient described by Wood and coworkers (1984), autopsy of a patient with rapidly fatal MLCT revealed massive tumor infiltration of the liver; the neoplastic cells were identical to those detected in the earlier skin biopsies, many showing extremely large, multilobulated nuclei, looking like "bunches of grapes." Numerous mitoses were seen, and the eosinophilic cytoplasm was rather scanty. The neoplastic cells in this case exhibited typical Birbeck granules (Wood et al. 1984). LCS can arise in the gallbladder and involve locoregional lymph nodes (Zhao et al. 2009).

Biology of Disease

LCS is a high-grade tumor with rapid progression, still bearing a mortality of more than 50 %. LCS can undergo leukemic transformation (Sumida et al. 2008). The neoplasm may develop in the setting of other neoplasms. It can arise from Langerhans cell histiocytosis (Lee et al. 2006) and sometimes occurs on a background of other hematologic malignancies. LCS has been observed following ALL (Castro et al. 2010). A common clonal origin of an acute B-lymphoblastic leukemia and an LCS has been observed, suggesting evidence for hematopoietic plasticity (Ratei et al. 2010). LCS and dendritic cell tumors can occur in conjunction with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), suggesting a transdifferentiation of CLL/SLL B cells to a dendritic or

Langerhans tumor cell lineage (Shao et al. 2011). LCS was found to arise from hairy cell leukemia (Muslimani et al. 2012).

Spontaneously Regressing/Involuting "Histiocytic" Disorders (So-Called Autoinvolutive Disorders)

Introduction

Several regressing or self-healing disorders involving an expansion of Langerhans cells or still ill-defined "histiocytic" cells have been identified, mainly in infants and children (Jang et al. 2000). Based on the data in the literature, a classification of these disorders is emerging, but not yet settled (Jang et al. 2000). The reason for the difficulties arising in the attempt at creating reliable categories is based on the fact that older investigations did not yet have access to modern cell typing and that terms such as "histiocytosis X" have been used to identify disorders with some clinical resemblance but quite different cells involved (Ferrando et al. 1982; Coldiron et al. 1988; Oranje et al. 1988; Contreras et al. 1990; Kolde and Bonsmann 1992; Gianotti et al. 1993; Hernandez-Martin et al. 1997; Campourcy et al. 1997; Hashimoto et al. 1999; Wee et al. 2000).

Classification

A preliminary classification is presented in Table 3. What seems to be established is that self-healing, and most frequently congenital or infantile, "histiocytoses" can involve Langerhans cells or cells with a histiocyte phenotype, the latter lacking Birbeck granules (Oranje et al. 1988).

Table 3 Working classification of self-healing Langerhans cell and non-Langerhans cell "histiocytic" disorders

Langerhans cell* "*histiocytic*" *disorders
Congenital self-healing Langerhans cell histiocytosis (CSHLCH), Hashimoto-Pritzker type (including variants with epidermotropism, pagetoid variants)
Solitary congenital self-healing Langerhans cell histiocytosis (SCSHLCH)
Self-healing childhood histiocytosis X of the Illig-Fanconi type (Illig-Fanconi disease)
Benign regressing histiocytosis of the Langerhans cell type
Non-Langerhans cell* "*histiocytic*" *disorders (*non-X histiocytoses*, *non-X histiocytic syndromes*)
Congenital self-healing non-Langerhans cell histiocytosis
Acquired regressive cutaneous non-Langerhans cell histiocytosis of infancy
Generalized eruptive histiocytosis (GEH, possible variants with regressive course: generalized lichenoid juvenile xanthogranuloma, benign cephalic histiocytosis)
Juvenile xanthogranuloma
Xanthoma disseminatum
Scalloped cell xanthogranuloma

Self-Healing Langerhans Cell Histiocytosis: A Complex Spectrum of Diseases

Self-healing Hashimoto-Pritzker LCH (Hashimoto-Pritzker disease; congenital self-healing histiocytosis/reticulohistiocytosis, CSHH/CSHR; congenital self-healing Langerhans cell histiocytosis, CSHLCH) is a rare variant of LCH originally described in 1973 (Hashimoto and Pritzker 1973). Since, several terms have been employed to denote this disorder, including reticulohistiocytosis of benign evolution, autoinvolutive congenital reticulosis, congenital self-healing reticulohistiocytosis, childhood self-healing histiocytosis X, congenital self-healing histiocytosis, and Hashimoto-Pritzker disease (Laugier et al. 1975; Mascaro et al. 1978; Bonifazi et al. 1982; Berger et al. 1986; Hashimoto et al. 1986; Pujol et al. 1988; Cambazard et al. 1988; Larralde et al. 1999). CSHLCH is characterized by neonatal onset, with purple or necrotic nodular lesions, rare visceral manifestations, spontaneous regression within the first 3 months of life, and an overall histology similar or identical to that of LCH, albeit with less Birbeck granules. Apart from multiple lesions, solitary variants have also been observed (Masouye et al. 1990; Shy et al. 1996; Tay et al. 1998; Walia et al. 2004; Kapur et al. 2007; Belhadjali et al. 2008; Sankilampi et al. 2008;

Hatakeyama et al. 2009). Unusual cases showed involvement of monozygotic twins (Ersoy-Evans et al. 2006) or late-onset disease, e.g., in an 8-year-old girl (Nakahigashi et al. 2007). Rarely, CSHLCH presents as a blistering eruption (Higgins et al. 1994), with hemorrhagic bullae (Inuzuka et al. 2003) or with papulovesicular, herpes-like lesions (Morgan and Callen 2001), and a variant with marked epidermotropism of the abnormal Langerhans cells, with a pagetoid growth pattern, has been reported (Hashimoto et al. 1999). As skin lesions of CSHLCH may contain large numbers of mast cells, Darier's sign typical for mastocytosis can ensue (Butler et al. 2001). The infiltrating cells show, at electron microscopic examination, a complex cytoplasmic structure, with myelinoid inclusions, laminated profiles, and so-called vermiform bodies but only few Birbeck granules (Laugier et al. 1975; Bonifazi et al. 1982; Kanitakis et al. 1988; Larralde et al. 1999). It has to be emphasized that not all patients clinically presenting with CSHLCH will follow a favorable course. The disorder may, in its early phases, mimic congenital LCH, and the outcome may then be dismal (Longakter et al. 1994; Larralde et al. 2003).

Solitary Congenital Self-Healing Langerhans Cell Histiocytosis

SCSHLCH is a very rare congenital disorder characterized by single (solitary) cutaneous Langerhans cell lesions that show self-healing (Chun and Song 1992; Dorjsuren et al. 2011; Wheller et al. 2013; Yurkovich et al. 2013). One variant of SCSHLCH revealed a combine immunohistochemical phenotype, cells being both CD1a+ and S100+ (Tardio et al. 2013).

Self-Healing Childhood Histiocytosis X (Illig-Fanconi Disease)

Illig-Fanconi disease is a rare cutaneous self-healing Langerhans cell histiocytosis restricted to the pediatric age group. Clinically, the skin lesions are characterized by few, small, translucent, and confluent papules, sometimes purpuric. This histology is that of LCH, ultrastructurally with the presence of Birbeck granules (Ferrando et al. 1982; Calero et al. 1986).

Self-Healing Non-Langerhans Cell "Histiocytic" Disorders

Self-healing non-Langerhans cell, or non-X, histiocytoses constitute a group of disorders that share clinical manifestations and are characterized by proliferations of histiocyte-like cells or macrophages in the absence of evidence for Langerhans cell histiocytosis (Zelger et al. 1996). The diseases present as in part nodular cutaneous infiltrates consisting of cells with a histiocytic phenotype, being reactive for Leu M3 and HLA-DR, but CD1 – and Leu-6 – negative and lacking Birbeck granules (Oranje et al. 1988; Kodet et al. 1991). The cutaneous forms can occur as congenital lesions or as acquired regressive skin lesions.

Generalized eruptive histiocytosis/histiocytoma (GEH) is a rare and self-healing non-Langerhans cell histiocytosis, clinically characterized by recurrent crops of papules that appear in a symmetrical fashion on the face, trunk, and arms. The disorder occurs both in children and adults. GEH may represent an early undifferentiated stage of various histiocytic disorders (Winkelmann and Müller 1963; Stables and Mackie 1992; Wee et al. 2000; Seward et al. 2004). Benign cephalic histiocytosis is histologically similar to juvenile xanthogranuloma and generalized eruptive histiocytosis (Gianotti et al. 1993), but chiefly involves the head and the neck (Jih et al. 2002).

Liver Involvement in Self-Healing Histiocytosis Syndromes (Except Juvenile Xanthogranuloma and Xanthoma Disseminatum)

Congenital Self-Healing Langerhans Cell Histiocytosis (Hashimoto-Pritzker Disease)

CSHLCH may rarely involve inner organs, e.g., involvement of the lung (Chunharas et al. 2002) or infiltration of the eye (Zaenglein et al. 2001). Hepatomegaly has been encountered in CSHLCH

(Chunharas et al. 2002). In a female newborn with CSHLCH, liver ultrasonography revealed hypoechoic lesions with blurred borders, suggested to represent liver involvement with this form of histiocytosis (Parentin et al. 2011). In one patient with Hashimoto-Pritzker disease and marked cutaneous involvement, multisystem disease with involvement of the liver, bone marrow, lymph nodes, and lung was noted (Mandel et al. 2014).

Benign Regressing Histiocytosis

Benign regressing histiocytosis of the Langerhans cell type has been reported to manifest in the liver. In an adult patient, the disease presented in the form of multiple hepatic nodules varying in size from 0.5 to 1 cm, histologically composed of clusters of polygonal to roundish, S100-protein-positive cells with granular, eosinophilic cytoplasm and vesicular nuclei with central folding, admixed with an infiltrate of eosinophils and lymphocytes. At EM examination, no Birbeck granules were detectable. The liver nodules spontaneously disappeared within a relatively short time period (Foschini et al. 1995).

Juvenile Xanthogranuloma

In normolipemic juvenile xanthogranuloma (JXG, synonym: naevoxantho-endothelioma) and its variants, cutaneous accumulations of histiocytes lacking Birbeck granules and without the immunohistochemical features of Langerhans cells occur. JXG was first described as a clinicopathological entity, in 1905 (Adamson 1905) and 1912 (McDonagh 1912), but Virchow had already described a child with cutaneous xanthomas in 1871. JXG is the only more common non-Langerhans cell histiocytosis (Burgdorf and Zelger 1996; Hernandez-Martin et al. 1997; Dehner 2003; Janssen and Harms 2005; Sivapirabu et al. 2011) and is, in most instances, a benign disorder of infancy and early childhood characterized by yellowish cutaneous nodules that spontaneously regress over months to years.

Very few cases of typical JXG have been observed in the adult age group (Jain et al. 2011; Narvaez-Moreno et al. 2013). The most common skin lesions are classified as either solitary versus multiple or a "small nodular form" versus a "large nodular form," but other manifestations comprise keratotic, lichenoid, pedunculated, subcutaneous, clustered, plaque-like, giant, eruptive, disseminated, or disseminated clustered lesions (Sidwell et al. 2005; Aparicio et al. 2008; Kaur et al. 2008). In the vast majority of children, JXG is usually limited to the skin, but systemic forms occur (Chang 1999; Jain et al. 2011). JXG is currently thought to be a proliferative disorder of dendrocytes, possibly dermal dendrocytes (Kraus et al. 2001), i.e., a "dendritic cell-related histiocytosis." However, the cellular infiltrate is mixed, consisting of monocytoid and macrophage-like forms, epithelioid and foamy macrophages, Touton giant cells, lymphocytes, plasma cells, eosinophils, and spindle cells of two forms (dendritic and fusiform) (Tahan et al. 1989). Although JXG is classified as a non-Langerhans cell histiocytosis, very rare "overlap disorders" have been observed, e.g., LCH preceding the development of JXG, possibly caused by therapy-induced modulation of cell differentiation (Bains and Parham 2011), or LCH accompanying JXG as a deep-seated process (Tran et al. 2008).

Histologically, JXG is characterized by lipid-laden, foamy macrophages (foamy histiocytes) in upper parts of the dermis. These cells have centrally placed, bland nuclei of the macrophage type, usually without visible mitotic activity. These cells are intermingled with Touton giant cells, lymphocytes, and eosinophils. Touton cells ("xanthelasmic giant cells") were described in 1885 by Karl Touton, who was active as a specialist in dermatology and venereal diseases in Wiesbaden, Germany, where he also had duties as physician in a spa ("Badearzt") (Touton 1885; review: Aterman et al. 1988). Apart from this "classical" form, a hypolipidized or nonlipidized form also exists, showing a more diffuse pattern of infiltration, with or without rare Touton cells, and a mitotic activity that is somewhat higher than in the "classic" form. This phenotype has been termed mitotically active xanthogranuloma

(Batista et al. 2012; Ngendahayo and de Sant Aubain 2012).

The etiology and pathogenesis of JXG are not known. As the lesions can regress, a reactive process has been suggested, but at least one study showed a clonal bone marrow proliferation with a distinct abnormal karyotype, in the absence of leukemia (Maly et al. 2012). Clonality in another case has been demonstrated via the HUMARA technique (Janssen et al. 2007). JXG can be associated with certain other disease entities. An association between JXG and juvenile myelomonocytic leukemia, with or without neurofibromatosis type 1, has been recognized in more than 20 cases (Cooper et al. 1984; Shin et al. 2004; Cham et al. 2010; Al Ghamdi and Al Suwaidan 2010; Arachchillage et al. 2010; Raygada et al. 2010). JXG has been found in association with Wiskott-Aldrich syndrome (Jesenak et al. 2013).

JXG rarely presents with systemic involvement (systemic juvenile xanthogranuloma, "deep juvenile xanthogranuloma"), with involvement of diverse inner organs, including the central nervous system (sometimes with multiple cerebral lesions), heart, lung, kidney, bone marrow, and liver (Fig. 7). Involvement of the liver has been reported several times, also in the setting of neonatal systemic xanthogranulomatosis (Diard et al. 1982; de Graaf et al. 1992; Di Blasi et al. 1993; Guthrie and Arthur 1994; Freyer et al. 1996; Favara 1996; Dehner 2003; Chantranuwat 2004; Nakatani et al. 2004; Cabrera et al. 2005; Janssen and Harms 2005; Unuvar et al. 2007; Yeh et al. 2007; Azorin et al. 2009; Patel et al. 2010; Fan and Sun 2011). Among 34 children with various forms of systemic JXG, the median age was 0.3 years; 8/34 had involvement of the liver/spleen (Freyer et al. 1996). In a large study on 174 patients, visceral manifestations were identified in 5 % of the patients (Dehner 2003). Neonates with systemic JXG can develop severe and sometimes fatal liver disease associated with fever, jaundice, hepatomegaly, ascites, and giant cell neonatal hepatitis in addition to xanthogranulomas in the liver and other visceral sites (Hu et al. 2004; Chantorn et al. 2008; Azorin et al. 2009; Papadakis et al. 2012). Severe congenital systemic JXG with liver failure has been observed in monozygotic twins (Chantorn et al. 2008). Massive liver involvement in neonatal disseminated JXG with progressive cholestasis, marked hepatic infiltration, and portal hypertension may require liver transplantation (Haughton et al. 2008). Hepatic manifestation of JXG may be associated with hypergammaglobulinemia (de Graaf et al. 1992). Indirect liver changes consist of obstructive jaundice, e.g., in case the manifestations of JXG develop in the pancreatic head (Prasil et al. 1999).

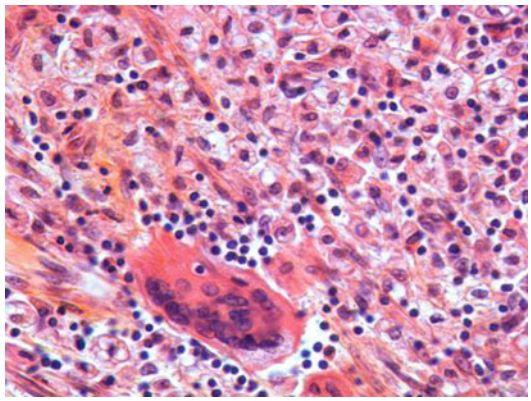

Fig. 7 Juvenile xanthoma in the liver. The lesion is characterized by foamy xanthomatous cells, but can also contain Touton-type giant cells (hematoxylin and eosin stain)

In severe liver involvement, hepatomegaly develops, and yellow nodules are seen on the liver surface at laparoscopy (Di Blasi et al. 1993). The cell types prevailing in extracutaneous sites consist of mononuclear (monocytoid) cells and spindle cells (arranged in fascicles or in a storiform pattern), whereas Touton giant cells are less common or even lacking. The portal tracts may be crowded with lipid-laden foamy macrophage-like cells or spindled nonlipidized cells (Dehner 2003; Haughton et al. 2008), and focal granulomatous lesions may be present (Favara 1996). The immunophenotype of these cells is characterized by uniform positivity for vimentin, CD68, and factor XIIIa, while S-100 protein and CD1a are consistently negative (Dehner 2003; Janssen and Harms 2005). The hepatic manifestations of JXG may be accompanied by syncytial giant cell hepatitis in neonates

and infants (Dehner 2003). In case of JXG-induced fulminant infantile hepatic failure, autopsy showed marked hepatomegaly, the organ containing extensive irregular nodular tumor infiltrates centered around blood vessels and portal tracts. Histologically, interlobular bile ducts were encircled by JXG tissue, but biliary epithelium was not infiltrated. The tumor cells consisted of a population of plump histiocytoid and spindle-shaped forms. Touton cells were present but rare. The process had infiltrated the lumen of hepatic vein, the veins sometimes being nearly completely occluded by tumor. There were signs of infantile syncytial giant cell hepatitis (Hu et al. 2004).

Xanthoma Disseminatum

Xanthoma disseminatum (XD, disseminated xanthoma, Montgomery syndrome) is a rare benign non-Langerhans cell histiocytic disorder in older children and adults of unknown etiology and pathogenesis. In 60 % of cases of XD, the age of onset has been between 5 and 25 years, men being affected twice as common as females (Altman and Winkelmann 1962). XD was first described in 1938 (Montgomery and Osterberg 1938), is characterized by the development of cutaneous xanthomas, and typically involves the skin of the flexor skinfolds and eyelids or a mucocutaneous disorder but may also affect inner organs, including the eye, CNS, pituitary gland, peripheral nerves, skeletal system, respiratory tract, kidney, pancreas, uterus, and gastrointestinal tract.

Involvement of the respiratory tract, complicated by dyspnea, life-threatening obstruction, and eventually asphyxiation, is the most recognized cause of morbidity in XD (Altman and Winkelmann 1962; Caputo et al. 1995; Ferrando et al. 1998; Davies et al. 2000). XD is usually not associated with hyperlipidemia. The biology of disease of XD is commonly benign, but visceral manifestations can cause morbidity and mortality (reviews: Ringel and Moschella 1962; Weiss and Keller 1993; Alexander et al. 2005). Caputo and coworkers (1995) identified three clinical patterns of XD. In the first pattern, skin lesions are persistent and continue unabated in patients who are otherwise in good health. The second form is characterized by spontaneous regression of lesions after many years (self-healing form). The third form, the rarest variant, exhibits systemic involvement, including the CNS and other organs. Involvement of the hypothalamo-pituitary region often causes diabetes insipidus. In a minority of patients with XD, malignant lymphoma has developed as a late complication (Battaglini and Olsen 1984; Shoo et al. 2008). Histologically, the foamy histiocytes/macrophages (xanthoma cells) form clusters and then develop into plaques or nodular lesions, the infiltrate being mostly situated in the upper and mid dermis. These cells are CD68+, but are negative for S-100 protein and CD1a, and lack Birbeck granules (Zelger et al. 1992; Weiss and Keller 1993; Ferrando et al. 1998; Caputo et al. 2003). The histiocytic infiltrate may contain Touton giant cells. Non-foamy histiocytes and lymphocytes may also occur (Caputo et al. 2003).

In a minority of patients, XD can involve the liver, with formation of nodular lesions of fatlike low density on CT images, consisting of xanthoma cells (Woollons and Darley 1998). A 32-year-old female patient with XD associated with diabetes insipidus and progressive CNS and ocular involvement revealed an echo-dense liver and gallbladder polyposis. A liver biopsy showed steatosis and foamy histiocytes in portal tracts (Knobler et al. 1990). Liver involvement was suspected in a child having XD with systemic manifestations in the skeleton and marrow cavities (Calverly et al. 1995). Hepatic steatosis has been observed in XD (Celic et al. 2004).

References

Abdallah M, Général T, Donadieu J, Emile JF, Chazouillères O, Gaujoux-Viala C et al (2011) Langerhans' cell histiocytosis of the liver in adults. Clin Res Hepatol Gastroenterol 35:475–481

Abla O, Egeler RM, Weitzman S (2010) Langerhans cell histiocytosis: current concepts and treatments. Cancer Treat Rev 36:354–359

Abt AF, Denenholz EJ (1936) Letterer-Siwe disease: splenomegaly associated with widespread hyperplasia of nonlipoid-storing macrophages; discussion of the

so-called reticulo-endothelioses. Am J Dis Child 51:499–522
Adamson HG (1905) Society intelligence: the Dermatological Society of London. Br J Dermatol 17:222
Al Ghamdi KM, Al Suwaidan SN (2010) Penile juvenile xanthogranuloma and neurofibromatosis type-1: risk association with juvenile myelomonocytic leukaemia? East Mediterr Health 16:451–454
Al-Abbadi M, Masih A, Braylan RC, Almasri NM (1997) Soft tissue Langerhans' cell histiocytosis in an adult. A case presentation with flow cytometric analysis and literature review. Arch Pathol Lab Med 121:169–172
Alexander AS, Turner R, Uniate L, Pearcy RG (2005) Xanthoma disseminatum: a case report and literature review. Br J Radiol 78:153–157
Allen CE, McClain KL (2007) Langerhans cell histiocytosis: a review of past, current and future therapies. Drugs Today (Barc) 43:627–643
Almanaseer IY, Kosova L, Pellettiere EV (1986) Composite lymphoma with immunoblastic features and Langerhans' cell granulomatosis (histiocytosis X). Am J Clin Pathol 85:111–114
Altman J, Winkelmann RK (1962) Xanthoma disseminatum. Arch Dermatol 86:582–596
Aparicio G, Mollet J, Batralot R, Bodet D, Heras C, Bassas P, Viros A, Garcia-Patos V (2008) Eruptive xanthogranuloma associated with relapsing acute lymphoblastic leukemia. Pediatr Dermatol 25:487–488
Arachchillage DR, Carr TF, Kerr B, Hawkins K, Kelsey A, Judge M, Wynn RF (2010) Juvenile myelomonocytic leukemia presenting with features of neonatal hemophagocytic lymphohistiocytosis and cutaneous juvenile xanthogranulomata and successfully treated with allogeneic hemopoietic stem cell transplant. J Pediatr Hematol Oncol 32:152–155
Arakawa A, Matsukawa T, Yamashita Y, Yoshimatsu S, Ohtsuka N, Miyazaki T, Yamamoto H, Harada M, Ishimaru Y, Takahashi M (1994) Periportal fibrosis in Langerhans' cell histiocytosis mimicking multiple liver tumors: US, CT, and MR findings. J Comput Assist Tomogr 18:157–159
Arico M, Egeler RM (1998) Clinical aspects of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 12:247–257
Arico M, Girschikofsky M, Genereau T, Klersy C, McClain K, Grois N, Emile JF, Lukina E, De Juli E, Danesino C (2003) Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. Eur J Cancer 39:2341–2348
Aterman K, Remmele W, Smith M (1988) Karl Touton and his "xanthelasmic giant cell." A selective review of multinucleated giant cells. Am J Dermatopathol 10:257–269
Avery ME, McAfee JG, Guld HG (1957) The course and prognosis of reticuloendotheliosis (eosinophilic granuloma, Schüller-Christian disease and Letterer-Siwe disease): a study of forty cases. Am J Med 22:636–652
Azorin D, Torrelo A, Lassaletta A, de Prada I, Colmenero I, Contra T, Gonzalez-Mediero I (2009) Systemic juvenile xanthogranuloma with fatal outcome. Pediatr Dermatol 26:709–712
Badalian-Very G, Vergilio JA, Degar BA, MacConail LE, Brandner B, Calicchio ML et al (2010) Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 116:1919–1923
Badalian-Very G, Vergilio JA, Degar BA, Rodriguez-Galindo C, Rollins BJ (2012) Recent advances in the understanding of Langerhans cell histiocytosis. Br J Haematol 156:163–172
Badalian-Very G, Vergilio JA, Fleming M, Rollins BJ (2013) Pathogenesis of Langerhans cell histiocytosis. Annu Rev Pathol 8:1–20
Bains A, Parham DM (2011) Langerhans cell histiocytosis preceding the development of juvenile xanthogranuloma: a case and review of recent developments. Pediatr Dev Pathol 14:480–484
Bank MI, Rengtved P, Carstensen H, Petersen BL (2003) Langerhans cell histiocytosis: an evaluation of histopathological parameters, demonstration of proliferation by Ki-67 and mitotic bodies. APMIS 111:300–308
Batista AC, Mendonça EF, Arantes Elias LS, Andrade BA, Almeida OP, Leon JE (2012) Nonlipidized juvenile xanthogranuloma: an unusual variant with a potential diagnostic pitfall. Int J Pediatr Otorhinolaryngol 76:295–299
Batson R, Shapiro JL, Christie A, Riley HD (1955) Acute nonlipid disseminated reticuloendotheliosis. AMA J Dis Child 90:323–343
Battaglini J, Olsen TG (1984) Disseminated xanthosiderohistiocytosis, a variant of xanthoma disseminatum, in a patient with a plasma cell dyscrasia. J Am Acad Dermatol 11:750–755
Belhadjali H, Mohamed M, Mahmoudi H, Youssef M, Moussa A, Chouchane S, Chouchane A et al (2008) Self-healing Langerhans cell histiocytosis (Hashimoto-Pritzker disease): two Tunisian cases. Acta Dermatovenerol Alp Panonica Adriat 17:188–192
Berger TG, Lane AT, Headington JT, Hartmann K, Burrish G, Levin MW, Disantagnese PA, Schwartz JL, Lambert JS (1986) A solitary variant of congenital self-healing reticulohistiocytosis: solitary Hashimoto-Pritzker disease. Pediatr Dermatol 3:230–236
Bonifazi E, Caputo R, Ceci A, Meneghini C (1982) Congenital self-healing histiocytosis. Arch Dermatol 118:267–272
Braier J, Ciocca M, Latella A, de Davila MG, Drajer M, Imventarza O (2002) Cholestasis, sclerosing cholangitis, and liver transplantation in Langerhans cell histiocytosis. Med Pediatr Oncol 38:178–182
Broadbent V, Egeler RM, Nesbit ME (1994) Langerhans cell histiocytosis – clinical and epidemiological aspects. Br J Cancer Suppl 23:S11–S16
Brown NA, Furtado LV, Betz BL, Kiel MJ, Weigelin HC, Lim MS, Elenitoba-Johnson KS (2014) High

prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. Blood 124:1655–1658

Burgdorf WH, Zelger B (1996) The non-Langerhans' cell histiocytoses in childhood. Cutis 58:201–207

Butler DF, Ranatunge BD, Rapini RP (2001) Urticating Hashimoto-Pritzker Langerhans cell histiocytosis. Pediatr Dermatol 18:41–44

Cabrera RA, Lacerda A, Lemos MM, Nunes JM, Mendonça ME (2005) Multiple visceral and subcutaneous nodules in a 4-month infant. Cytopathology 16:309–311

Calero G, Vallarino J, Centeno J (1986) Illig-Fanconi disease. First case described in Ecuador (in Spanish). Med Cutan Ibero Lat Am 14:1–4

Calverly DC, Wismer J, Rosenthal D, deSa D, Barr RD (1995) Xanthoma disseminatum in an infant with skeletal and marrow involvement. J Pediatr Hematol Oncol 17:61–65

Cambazard F, Kanitakis J, Zambruno G, Barre P, Jacquemier D, Thivolet J (1988) Hashimoto-Pritzker congenital self-healing histiocytosis (in French). Pediatrie 43:213–217

Campourcy M, Moreau-Cabarrot A, Gorguet B, Samalens G, Daste B, Eclache F, Bazex J (1997) Acquired regressive cutaneous non-Langerhans-cell histiocytosis in an infant (in French). Ann Dermatol Venereol 124:167–170

Caputo R, Veraldi S, Grimalt R, Gianotti R, Tosti A, Varotti C, de Kaminsky AR (1995) The various clinical patterns of xanthoma disseminatum. Considerations on seven patients and review of the literature. Dermatology 190:19–24

Caputo R, Passoni E, Cavicchini S (2003) Papular xanthoma associated with angiokeratoma of Fordyce: considerations on the nosography of this rare non-Langerhans cell histiocytoxanthomatosis. Dermatology 206:165–168

Caruso S, Miraglia R, Maruzzelli L, Luca A, Gridelli B (2008) Biliary wall calcification in Langerhans cell histiocytosis: report of two cases. Pediatr Radiol 38:791–794

Caruso S, Miraglia R, Spada M, Luca A, Gridelli B (2009) Biliary dilatation secondary to lithiasis in a child affected by Langerhans' cell histiocytosis. J Clin Ultrasound 37:366–368

Castro EC, Blazquez C, Boyd J, Correa H, de Chadarevian JP, Felgar RE, Graf N et al (2010) Clinicopathologic features of histiocytic lesions following ALL, with a review of the literature. Pediatr Dev Pathol 13:225–237

Cavazza A, Pasquinelli G, Carlinfante G, Cenini E, Bonvicini U, Gardini G (1999) Nodular Langerhans cell histiocytosis of the liver in an adult with colonic adenocarcinoma. Histopathology 34:273–275

Celic D, Rados J, Lipozencic J, Dobric I (2004) Xanthoma disseminatum: case report. Acta Dermatovenerol Croat 12:282–288

Chabrol E, Thépaut M, Dezutter-Dambuyant C, Vivès C, Marcoux J, Kahn R, Valladeau-Guillemond J, Vachettet P et al (2015) Alteration of the langerin oligomerization state affects Birbeck granule formation. Biophys J 108:666–677

Chakraborty R, Hampton OA, Shen X, Sinko S, Shih A, Abhyankar H, Lim KP, Covington K, Trevino L et al (2014) Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood 124:3007–3015

Cham E, Siegel D, Ruben BS (2010) Cutaneous xanthogranulomas, hepatosplenomegaly, anemia, and thrombocytopenia as presenting signs of juvenile myelomonocytic leukemia. Am J Clin Dermatol 11:67–71

Chan YL, Li CK, Lee CY (1997) Sonographic appearance of hepatic Langerhans cell histiocytosis. Clin Radiol 52:761–763

Chang MW (1999) Update on juvenile xanthogranuloma: unusual cutaneous and systemic variants. Semin Cutan Med Surg 18:195–205

Chantorn R, Wisuthsarewong W, Aanpreung P, Sanpakit K, Manonukul J (2008) Severe congenital systemic juvenile xanthogranuloma in monozygotic twins. Pediatr Dermatol 25:470–473

Chantranuwat C (2004) Systemic form of juvenile xanthogranuloma: report of a case with liver and bone marrow involvement. Pediatr Dev Pathol 7:646–648

Chaudhary A, Debnath J, Thulkar S, Seth T, Sinha A (2006) Imaging findings in hepatic Langerhans' cell histiocytosis. Indian J Pediatr 73:1036–1038

Chen BW, Chang MH, Lin DT, Lin KH, Chuu WM, Lin KS (1989) Extrahepatic biliary obstruction caused by cancer of non-liver origin in children: report of 5 cases. Taiwan Yi Xue Hui Za Zhi 88:819–823

Childers JH, Price PC (1954) Letterer-Siwe's disease; report of case. AMA Arch Pathol 58:142–150

Christian HA (1919) Defects in membranous bone, exophthalmos and diabetes insipidus. In: Contributions to medical and biological research: dedicated to Sir William Osler, Bart., M.D., F.R.S., in honor of his seventieth birthday, July 12, by his pupils and c-workers. New York, Paul B. Hoeber, vol. 1, pp 390–401

Chu, Jaffe (1994) PMID 7521202

Chun SI, Song MS (1992) Congenital self-healing reticulohistiocytosis – report of a case of the solitary type and review of the literature. Yonsei Med J 33:194–198

Chunharas A, Pabunruang W, Hongeng S (2002) Congenital self-healing Langerhans cell histiocytosis with pulmonary involvement: spontaneous regression. J Med Assoc Thai 85(Suppl 4):S1309–S1313

Coldiron BM, Cruz PD, Freeman RG, Sontheimer RD (1988) Benign non-X histiocytosis: a unique case bridging several of the non-X histiocytic syndromes. J Am Acad Dermatol 18:1282–1289

Collin M, Bigley V, McClain KL, Allen CE (2015) Cells (s) of origin of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 29:825–838

Concepcion W, Esquival CO, Terry A, Nakazato P, Garcia-Kennedy R, Houssin D et al (1991) Liver transplantation in Langerhans' cell histiocytosis (histiocytosis X). Semin Oncol 18:24–28

Contreras F, Fonseca E, Gamallo C, Burgos E (1990) Multiple self-healing indeterminate cell lesions of the skin in an adult. Am J Dermatopathol 12:396–401

Cooper PH, Frierson HF, Kayne AL, Sabio H (1984) Association of juvenile xanthogranuloma with juvenile myeloid leukemia. Arch Dermatol 120:371–375

Coppes-Zantinga A, Egeler RM (2002) Historical. review. The Langerhans cell histiocytosis X files revealed. Br J Haematol 116:3–9

Cugati G, Singh M, Pande A, Ramamurthi R, Vasudevan MC (2011) Hand Schuller Christian disease. Indian J Med Paediatr Oncol 32:183–184

Davies CWH, Marren P, Juniper MC, Gray W, Wojnorowska F, Benson MK (2000) Xanthoma disseminatum with respiratory tract involvement and fatal outcome. Thorax 55:170–172

De Graaf JH, Timens W, Tamminga RY, Molenaar WM (1992) Deep juvenile xanthogranuloma: a lesion related to dermal indeterminate cells. Hum Pathol 23:905–910

Debray D, Pariente D, Urvoas E, Hadchouel M, Bernard O (1994) Sclerosing cholangitis in children. J Pediatr 124:49–56

Dehner LP (2003) Juvenile xanthogranulomas in the first two decades of life: a clinicopathologic study of 174 cases with cutaneous and extracutaneous manifestations. Am J Surg Pathol 27:579–593

Delabie J, De Wolf-Peeters C, De Vos R, Vandenberghe E, Kennes K, De Jonge I, Desmet V (1991) True histiocytic neoplasm of Langerhans' cell type. J Pathol 163:217–223

Di Blasi A, de Seta L, Marsilia GM, Coletta S, Siani P, de Rosa I (1993) Juvenile xanthogranuloma. Description of a case with liver involvement (in Italian). Pathologica 85:85–90

Diard F, Cadier L, Billaud C, Trojani M (1982) Neonatal juvenile xanthogranulomatosis with pulmonary, extrapleural and hepatic involvement. One case report (in French). Ann Radiol (Paris) 25:113–118

Dorfman DM, Hornick JL, Shahsafaei A, Freeman GJ (2010) The phosphatidylserine receptors, T cell immunoglobulin mucin proteins 3 and 4, are markers of histiocytic sarcoma and other histiocytic and dendritic cell neoplasms. Hum Pathol 41:1486–1494

Dorjsuren G, Kim HJ, Jung JY, Bae BG, Lee JH (2011) Solitary type of congenital self-healing reticulohistiocytosis. Ann Dermatol 23(Suppl 1):S4–S7

Duncan WK, Post AC, McCoy BP (1988) Eosinophilic granuloma. Oral Surg Oral Med Oral Pathol 65:736–741

El Demellawy D, Young JL, de Nanassy J, Chernetsova E, Nasr A (2015) Langerhans cell histiocytosis: a comprehensive review. Pathology 47:294–301

Ersoy-Evans S, Gursoy T, Yigit S, Akcoren Z, Sahin S (2006) Solitary congenital self-healing reticulohistiocytosis in monozygotic twins. Pediatr Dermatol 23:273–275

Fan R, Sun J (2011) Neonatal systemic juvenile xanthogranuloma with an ominous presentation and successful treatment. Clin Med Insights Oncol 5:157–161

Favara BE (1981) The pathology of "histiocytosis". Am J Pediatr Hematol Oncol 3:45–56

Favara BE (1996) Histopathology of the liver in histiocytosis syndromes. Pediatr Pathol Lab Med 16:413–433

Favara BE, McCarthy RC, Meirau GW (1983) Histiocytosis X. Hum Pathol 14:663–676

Favara et al. (1997) PMID 9212839

Ferrando J, Estrach T, Bombi JA, Bassas S, Navarra E, Simon A (1982) Self-healing childhood histiocytosis X (Illig-Fanconi disease). Comments on ultrastructural aspects and etiopathogenic classification of histiocytosis (in Spanish). Med Cutan Ibero Lat Am 10:323–338

Ferrando J, Campo-Voegeli A, Soler-Carrillo J, Munoz E, Sole M, Palou J, Conill C et al (1998) Systemic xanthohistiocytoma: a variant of xanthoma disseminatum? Br J Dermatol 138:155–160

Finn LS, Jaffe R (1997) Langerhans cell granuloma confined to bile duct. Pediatr Pathol Lab Med 17:461–468

Fione and Rizzo (1959) PMID 13656855

Foschini MP, Milandri GL, Dina RE, Usellini L, Macchia S, Spongano P (1995) Benign regressing histiocytosis of the liver. Histopathology 26:363–366

Freyer DR, Kennedy R, Bostrom BC, Kohut G, Dehner LP (1996) Juvenile xanthogranuloma: forms of systemic disease and their clinical implications. J Pediatr 129:227–237

Gadner H, Minkov M, Grois N, Pötschger U, Thiem E, Arico M, Astigarraga I, Braier J et al (2013) Therapy prolongation improves outcome in multi-system Langerhans cell histiocytosis. Blood 121:5006–5014

Gee SN, Huang JT, Schmidt BA, Gellis SE (2013) Rapidly fatal multiorgan Langerhans cell histiocytosis in a neonate. Pediatr Dermatol 30:e85–e86

Gianotti F, Caputo R, Ranzi T (1968) Ultrastructural study of giant cells and "Langerhans cell granules" in cutaneous lesions and lymph-node and liver biopsies from four cases of subacute disseminated histiocytosis of Letterer-Siwe. Arch Klin Exp Dermatol 233:238–252

Gianotti R, Alessi E, Caputo R (1993) Benign cephalic histiocytosis: a distinct entity or a part of a wide spectrum of histiocytic proliferative disorders of children? A histopathologic study. Am J Dermatopathol 15:315–319

Granot E, Cohen P, Asli Y, Bar-Ziv J (1994) Histiocytosis X presenting as prolonged cholestatic jaundice in childhood. Eur J Gastroenterol Hepatol 6:275–279

Grosfeld JL, Fitzgerald JF, Wagner VM, Newton WA, Baehner RL (1976) Portal hypertension in infants and children with histiocytosis X. Am J Surg 131:108–113

Guilarte Lopez-Manas J, Bellot Garcia V, Fernandez Perez R, Caballero Morales T, Ardoy Ibanez FM, Gallego Rojo FJ (1997) Multifocal Langerhans-cell granulomatosis with hepatic lesions simulating tumors (in Spanish). Gastroenterol Hepatol 20:407–411

Guthery SL, Heubi JE (2001) Liver involvement in childhood histiocytic syndromes. Curr Opin Gastroenterol 17:474–478

Guthrie JA, Arthur RJ (1994) Case report: juvenile xanthogranuloma with pulmonary, subcutaneous and hepatic involvement. Clin Radiol 49:498–500

Hadzic et al (2000) PMID 11003364

Hand A (1893) Polyuria and tuberculosis. Arch Pediatr 10:673

Hand A (1921) Defects of membranous bones, exophthalmos and polyuria in childhood: is it dyspituitarism? Am J Med Sci 162:509

Hara T, Mizuno Y, Ishii E, Ueda K, Hirata T, Daimaru Y, Nakagawara A (1988) Histiocytosis X presenting as multiple intrahepatic nodules. Nippon Ketsueki Gakkai Zasshi 51:1059–1062

Hashimoto K, Pritzker MS (1973) Electron microscopic study of reticulohistiocytoma. Arch Dermatol 107:263–270

Hashimoto K, Bale GF, Hawkins HK, Langston C, Pritzker MS (1986) Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker type). Int J Dermatol 25:516–523

Hashimoto K, Schachner LA, Huneiti A, Tanaka K (1999) Pagetoid self-healing Langerhans cell histiocytosis in an infant. Pediatr Dermatol 16:121–127

Hatakeyama N, Hori T, Yamamoto M, Sogawa I, Inazawa N, Tsutsumi H, Suzuki N (2009) An infant with self-healing cutaneous Langerhans cell histiocytosis followed by isolated thymic relapse. Pediatr Blood Cancer 53:229–231

Haughton AM, Horii KA, Shao L, Daniel J, Nopper AJ (2008) Disseminated juvenile xanthogranulomatosis in a newborn resulting in liver transplantation. J Am Acad Dermatol 58(2 Suppl):S12–S15

Haupt R, Monkov M, Astigarraga I, Schäfer E, Nanduri V, Jubran R, Egeler RM, Janka G et al (2013) Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer 60:175–184

Heitner R, Mouton S, Rabinowitz L, Rosen EU (1978) Type I histiocytosis X presenting as biliary atresia. A case report. S Afr Med J 53:768–770

Henderson DW, Sage RE (1973) Malignant histiocytosis with eosinophils. Cancer 32:1421–1428

Hernandez-Martin A, Baselga E, Drolet BA, Esterly NB (1997) Juvenile xanthogranuloma. J Am Acad Dermatol 36:355–367

Herzog KM, Tubbs RR (1998) Langerhans cell histiocytosis. Adv Anat Pathol 5:347–358

Heyn RM, Hamoudi A, Newton WA (1990) Pretreatment liver biopsy in 20 children with histiocytosis X: a clinicopathological correlation. Med Pediatr Oncol 18:110–118

Higgins CR, Tatnall FM, Leigh IM (1994) Vesicular Langerhans cell histiocytosis – an uncommon variant. Clin Exp Dermatol 19:350–352

Hu WK, Gilliam AC, Wiersma SR, Dahms BB (2004) Fatal congenital systemic juvenile xanthogranuloma with liver failure. Pediatr Dev Pathol 7:71–76

Hutter C, Kauer M, Simonitsch-Klupp I, Jug G, Schwentner R, Leitner J, Bock P, Steinberger P et al (2012) Notch is active in Langerhans cell histiocytosis and confers pathognomonic features on dendritic cells. Blood 120:5199–5208

Ibarrola de Andres C, Toscano R, Lahuerta JJ, Martinez-Gonzalez MA (1999) Simultaneous occurrence of Hodgkin's disease, nodal Langerhans' cell histiocytosis and multiple myeloma IgA(kappa). Virchows Arch 434:259–262

Imamura M, Sakamoto S, Hanazono H (1971) Malignant histiocytosis: a case of generalized histiocytosis with infiltration of Langerhans' granule containing histiocytes. Cancer 28:267–275

Inuzuka M, Tomita K, Tokura Y, Takigawa M (2003) Congenital self-healing reticulohistiocytosis presenting with hemorrhagic bullae. J Am Acad Dermatol 48(Suppl 5):S75–S77

Itoh H, Miyaguni H, Kataoka H, Akiyama Y, Tateyama S, Marutsuka K, Asada Y, Ogata K, Koono M (2001) Primary cutaneous Langerhans cell histiocytosis showing malignant phenotype in an elderly woman: report of a fatal case. J Cutan Pathol 28:371–378

Iupati D, Chander S (2006) A case report of Langerhans histiocytosis presenting sequentially over a 21-year-period with Letterer-Siwe disease, Hand-Schuller-Christian disease and eosinophilic granuloma of bone. J Pediatr Hematol Oncol 28:746–749

Iwai M, Kashiwadani M, Okuno T, Takino T, Koshokawa T (1988) Cholestatic liver disease in a 20-year-old woman with histiocytosis X. Am J Gastroenterol 83:164–168

Jaffe R (2004) Liver involvement in the histiocytic disorder of childhood. Pediatr Dev Pathol 7:214–225

Jain A, Mathur K, Khatri S, Kasana S, Jain SK (2011) Rare presentation of juvenile xanthogranuloma in the thoracic spine of an adult patient: case report of literature review. Acta Neurochir (Wien) 153:1813–1818

Jang KA, Ahn SJ, Choi JH, Sung KJ, Moon KC, Koh JK (2000) Histiocytic disorders with spontaneous regression in infancy. Pediatr Dermatol 17:364–368

Janssen D, Harms D (2005) Juvenile xanthogranuloma in childhood and adolescence: a clinicopathologic study of 129 patients from the Kiel pediatric tumor registry. Am J Surg Pathol 29:21–28

Janssen D, Fölster-Holst R, Harms D, Klapper W (2007) Clonality in juvenile xanthogranuloma. Am J Surg Pathol 31:812–813

Jesenak M, Plamenova I, Plank L, Banovcin P (2013) Wiskott-Aldrich syndrome caused by a new mutation associated with multifocal dermal juvenile xanthogranulomas. Pediatr Dermatol 30:e91–e93

Jih DM, Salcedo SL, Jaworsky C (2002) Benign cephalic histiocytosis: a case report and review. J Am Acad Dermatol 47:908–913

Jones MB, Voet R, Pagani J, Lotysch M, O'Connell T, Koretz RL (1981) Multifocal eosinophilic granuloma involving the common bile duct: histologic and cholangiographic findings. Gastroenterology 80:384–389

Kanitakis J, Zambruno G, Schmitt D, Cambazard F, Jacquemier D, Thivolet J (1988) Congenital self-healing histiocytosis (Hashimoto-Pritzker). An ultrastructural and immunohistochemical study. Cancer 61:508–516

Kaplan KJ, Goodman ZD, Ishak KG (1999) Liver involvement in Langerhans' cell histiocytosis: a study of nine cases. Mod Pathol 12:370–378

Kapur P, Erickson C, Rakheja D, Carder KR, Hoang MP (2007) Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease): ten-year experience at Dallas Children's Medical Center. J Am Acad Dermatol 56:290–294

Karadeniz C, Sarialioglu F, Gogus S, Akyuz C, Kucukali T, Kutluk T, Buyukpamukcu M (1991) Multiple primary malignancy: a report on Langerhans cell histiocytosis associated with Hodgkin's disease. Turk J Pediatr 33:185–190

Kato T, Matsuda M, Ando H, Sasaki H (1981) A case of multifocal proliferations of histiocytic cells containing Langerhans' cell granules. Am J Clin Pathol 76:480–485

Kaufman A, Bukberg PR, Werlin S, Young IS (1976) Multifocal eosinophilic granuloma ("Hand-Schüller-Christian disease"). Report illustrating H-S-C chronicity and diagnostic challenge. Am J Med 60:541–548

Kaur MR, Brundler MA, Stevenson O, Moss C (2008) Disseminated clustered juvenile xanthogranuloma: an unusual morphological variant of a common condition. Clin Exp Dermatol 33:575–577

Kawai K, Harada T, Matsukuma H, Nakashita Y (1978) Letterer-Siwe disease with lipid-containing vacuolated cells – an autopsy case. Acta Pathol Jpn 28:787–796

Kawase T, Hamazaki M, Ogura M, Kawase Y, Murayama T, Mori Y, Nagai H, Tateno M et al (2005) CD56/NCAM-positive Langerhans cell sarcoma: a clinicopathologic study of 4 cases. Int J Hematol 81:323–329

Kay TW (1905) Acquired hydrocephalus with atrophic bone changes, exophthalmos and polyuria. Penn Med J 9:520

Kitahama S, Iitaka M, Shimizu T, Serizawa N, Fukasawa N, Miura S, Kawasaki S, Yamanaka K, Kawakami Y et al (1996) Thyroid involvement by malignant histiocytosis of Langerhans' cell type. Clin Endocrinol (Oxford) 45:357–363

Knobler RM, Neumann RA, Gebhart W, Radaskiewicz T, Ferenci P, Widhalm K (1990) Xanthoma disseminatum with progressive involvement of the central nervous and hepatobiliary systems. J Am Acad Dermatol 23:341–346

Kodet R, Elleder M, De Wolf-Peeters C, Mottl H (1991) Congenital histiocytosis. A heterogeneous group of diseases, one presenting as so-called congenital self-healing histiocytosis. Pathol Res Pract 187:458–466

Kolde G, Bonsmann G (1992) Generalized lichenoid juvenile xanthogranuloma. Br J Dermatol 126:66–70

Komp DM (1987) Historical perspectives of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1:9–21

Konno S, Hizawa N, Betsuyaku T, Yasuo M, Yamamoto H, Koizumi T, Nishimura M (2007) Adult Langerhans cell histiocytosis with independently relapsing lung and liver lesions that was successfully treated with etoposide. Intern Med 46:1231–1235

Kraus et al (2001) PMID 11285404

Krutchkoff DJ, Jones CR (1984) Multifocal eosinophilic granuloma: a clinical pathologic conference. J Oral Pathol 13:472–488

Ladisch S (1998) Langerhans cell histiocytosis. Curr Opin Hematol 5:54–58

Landing BH (1987) Lymphohistiocytosis in childhood. Pathologic comparison with fatal Letterer-Siwe disease (disseminated visceral histiocytosis X). Perspect Pediatr Pathol 9:48–74

Langerhans p (1868) Ueber die nerven der menschlichen haut. Arch Pathol Anat Physiol Klin Med 44:325–337

Langfort R, Radzikowska E, Czarnowska E, Wiatr E, Grajkowska W, Blasinska-Przerwa K et al (2009) Langerhans cell sarcoma with pulmonary manifestation, mediastinum involvement and bronchoesophageal fistula. A rare location and difficulties in histopathological diagnosis. Pneumol Allergol Pol 77:327–334

Larralde M, Rositto A, Giardelli M, Gatti CF, Santos Munoz A (1999) Congenital self-healing histiocytosis (Hashimoto-Pritzker). Int J Dermatol 38:693–696

Larralde et al (2003) PMID 12653927

Laugier P, Hunziker N, Laut J, Orusco M, Osmos L (1975) Reticulohistiocytosis of benign evolution (Hashimoto-Pritzker type). Electron microscopic study (in French). Ann Dermatol Syphiligr (Paris) 102:21–31

Leblanc A, Hadchouel M, Jehan P, Odievre M, Alagille D (1981) Obstructive jaundice in children with histiocytosis X. Gastroenterology 80:134–139

Lee JS, Ko GH, Kim HC, Jang IS, Jeon KN, Lee JH (2006) Langerhans cell sarcoma arising from Langerhans cell histiocytosis: a case report. J Korean Med Sci 21:577–580

Lee RJ, Leung C, Lim EJ, Angus PW, Bhathal PS, Crowley P, Gonzales M, Stella D et al (2011) Liver transplantation in an adult with sclerosing cholangitis due to multisystem Langerhans cell histiocytosis. Am J Transplant 11:1755–1756

Letterer E (1924) Aleukämische Retikulose (ein Beitrag zu den proliferativen Erkrankungen des Retikuloendothelialapparates). Frankfurt Ztschr Path 30:377

Levy S, Capron D, Joly JP, Cordonnier C, Sevestre H, Delamarre J, Tribout B, Capron JP (1998) Hepatic nodules as single organ involvement in an adult with Langerhans cell granulomatosis. A case report. J Clin Gastroenterol 26:69–73

Li S, Borowitz MJ (2001) CD79a(+) T-cell lymphoblastic lymphoma with coexisting Langerhans cell histiocytosis. Arch Pathol Lab Med 125:958–960

Li H, Wang C, Guo G, Gao C, Wu Y, Chen Y (2012) The characteristic expression of B7-associated proteins in Langerhans cell sarcoma. Acta Histochem 114:733–743

Li J, Cao D, Guo G, Wu Y, Chen Y (2013) Expression and anatomical distribution of TIM-containing molecules in Langerhans cell sarcoma. J Mol Histol 44:213–220

Lichtenstein L (1953) Histiocytosis X; integration of eosinophilic granuloma of bone, Letterer-Siwe disease, and Schüller-Christian disease as related manifestations of a single nosologic entity. AMA Arch Pathol 56:84–102

Lichtenstein L, Jaffe HL (1940) Eosinophilic granuloma of bone. Am J Pathol 16:595–604

Lieberman PH, Jones CR, Dargeon HW, Begg CF (1969) A reappraisal of eosinophilic granuloma of bone. Hand-Schüller-Christian syndrome and Letterer-Siwe syndrome. Medicine (Baltimore) 48:375–400

Lieberman PH, Jones CR, Steinman RM, Erlandson RA, Smith J, Gee T, Huvos A, Garin-Chesa P et al (1996) Langerhans cell (eosinophilic) granulomatosis. A clinicopathologic study encompassing 50 years. Am J Surg Pathol 20:519–552

Liu DG, Zhang YX, Li F (2012) Multisystem Langerhans cell histiocytosis with liver dysfunction as the first presentation: a case report. Oncol Lett 3:391–394

Llamas-Velasco M, Cannata J, Dominguez I, Garcia-Noblejas A, Aragues M, Fraga J et al (2012) Coexistence of Langerhans cell histiocytosis, Rosai-Dorfman disease and splenic lymphoma with fatal outcome after rapid development of histiocytic sarcoma of the liver. J Cutan Pathol 39:1125–1130

Longakter M, Frieden I, Leboit P, Sherertz E (1994) Congenital "self-healing" Langerhans cell histiocytosis: the need for long term follow-up. J Am Acad Dermatol 31:910–916

Ma XL, Shen KL, Wang B (2012) A child with pulmonary and liver Langerhans'-cell histiocytosis. Chin Med J (Engl) 125:1675–1676

Ma J, Jiang Y, Chen X, Gong G (2014) Langerhans cell histiocytosis misdiagnosed as liver cancer and pituitary tumor in an adult: a case report and brief review of the literature. Oncol Lett 7:1602–1604

Maly E, Przyborska M, Rybczynska A, Konatkowska B, Nowak J, Januszkiewicz D (2012) Juvenile xanthogranuloma with clonal proliferation in the bone marrow. J Pediatr Hematol Oncol 34:222–225

Mandel VD, Ferrari C, Cesinaro AM, Pellacani G, Del Forno C (2014) Congenital "self-healing" Langerhans cell histiocytosis (Hashimoto-Pritzker disease): a report of two cases with same cutaneous manifestations but different clinical course. J Dermatol. doi:10.1111/1346-8138

Mascaro JM, Aliaga A, Mascaro-Galy C (1978) Autoinvolutive congenital reticulosis (Hashimoto-Pritzker type) (in French). Ann Dermatol Venereol 105:223–227

Masouye I, Chavaz P, Salomon D, Balderer J, Carraux P, Saurat JH (1990) Solitary Langerhans cell histiocytoma: an unusual form of Hashimoto-Pritzker histiocytosis? Pediatr Dermatol 7:299–302

McClain KL, Laud P, Wu WS, Pollack MS (2003) Langerhans cell histiocytosis patients have HLA Cw7 and DR4 types associated with specific clinical presentations and no increased frequency in polymorphisms of the tumor necrosis factor alpha promoter. Med Pediatr Oncol 41:502–507

McDonagh JER (1912) A contribution to our knowledge of the naevo-xantho-endotheliomata. Br J Dermatol 24:85–99

Mieli-Vergani G, Vergani D (2001) Sclerosing cholangitis in the paediatric patient. Best Pract Res Clin Gastroenterol 15:681–690

Minkow M (2011) Multisystem Langerhans cell histiocytosis in children: current treatment and future directions. Paediatr Drugs 13:75–86

Minkow M, Steiner M, Pötschger U, Arico M, Braier J, Donadieu J, Grois N, Henter JI et al (2008) Reactivation in multisystem Langerhans cell histiocytosis: data of the international LCH registry. J Pediatr 153:700–705

Misery L, Godard W, Hamzeh H, Levigne V, Vinvent C, Perrot JL, Gentil-Perret A, Schmitt D, Cambazard F (2003) Malignant Langerhans cell tumor: a case with favorable outcome associated with the absence of blood dendritic cell proliferation. J Am Acad Dermatol 49:527–529

Montgomery H, Osterberg A (1938) Xanthomatous correlation of clinical, histopathological, and chemical studies of cutaneous xanthoma. Arch Dermatol Syphilol 37:373–402

Morgan KW, Callen JP (2001) Self-healing congenital Langerhans cell histiocytosis presenting as neonatal papulovesicular eruption. J Cutan Med Surg 5:486–489

Mosterd K, van Marion A, van Steensel MA (2008) Neonatal Langerhans' cell histiocytosis: a rare and potentially life-threatening disease. Int J Dermatol 47(Suppl 1):10–12

Muirhead D, Stone MS, Syrbu SI (2009) The utility of PU.1 as an immunohistochemical marker for histiocytic and dendritic lesions of the skin. Am J Dermatopathol 31:432–435

Munir A, Leech N, Windebank KP, McLelland J, Jones GL, Mitra D, Jenkins A, Qionton R (2012) Langerhans cell histiocytosis: a multisystem disorder. JR Coll Physicians Edinb 42:311–313

Muñoz-Garcia JC, Chabrol E, Vivès RR, Thomas A, de Paz JL, Rojo J, Imberty A, Fieschi F, Nieto PM, Angulo J (2015) Langerin-heparin interaction: two binding sites for small and large ligands as revealed by a combination of NMR spectroscopy and cross-linking mapping experiments. J Am Chem Soc 137:4100–4110

Murakami I, Gogusev J, Fournet JC, Glorion C, Jaubert F (2002) Detection of molecular cytogenetic aberrations in Langerhans cell histiocytosis of bone. Hum Pathol 33:555–560

Muslimani A, Chisti MM, Blenc AM, Boxwala I, Micale MA, Jaiyesimi I (2012) Langerhans/dendritic cell sarcoma arising from hairy cell leukemia: a rare phenomenon. Ann Hematol 91:1485–1487

Nakahigashi K, Ohta M, Sakai R, Sugimoto Y, Ikoma Y, Horiguchi Y (2007) Late-onset self-healing reticulohistiocytosis: pediatric case of Hashimoto-Pritzker type Langerhans cell histiocytosis. J Dermatol 34:205–209

Nakatani T, Morimoto A, Kato R, Tokuda S, Sugimoto T, Tokiwa K, Tsuchihashi Y, Imashuku S (2004) Successful treatment of congenital systemic juvenile xanthogranuloma with Langerhans cell histiocytosis-based chemotherapy. J Pediatr Hematol Oncol 26:371–374

Narvaez-Moreno B, Pulpillo-Ruiz A, De Zulueta-Dorado-T, Conjero-Mir J (2013) Disseminated juvenile xanthogranuloma associated with follicular lymphoma in a adult: successful treatment with chemotherapy and rituximab. A review of the literature. Actas Dermosifiliogr 104:242–246

Nezelof C, Basset F, Rousseau MF (1973) Histiocytosis X histogenetic arguments for a Langerhans cell origin. Biomedicine 18:365–371

Ngendahayo P, de Sant Aubain N (2012) Mitotically active xanthogranuloma: a case report with review of the literature. Am J Dermatopathol 34:e27–e30

Nguyen TT, Schwartz EJ, West RB, Warnke RA, Arber DA, Natkunam Y (2005) Expression of CD163 (hemoglobin scavenger receptor) in normal tissues, lymphomas, carcinomas, and sarcomas is largely restricted to the monocyte/macrophage lineage. Am J Surg Pathol 29:617–624

Oranje AP, Vuzevski VD, de Groot R, Prins ME (1988) Congenital self-healing non-Langerhans cell histiocytosis. Eur J Pediatr 148:29–31

Orii T, Takeda H, Kawata S, Maeda K, Yamakawa M (2010) Differential immunophenotypic analysis of dendritic cell tumours. J Clin Pathol 63:497–503

Otani S, Ehrlich JC (1940) Solitary granuloma of bone simulating primary neoplasm. Am J Pathol 16:479–490

Papadakis V, Volonaki E, Katsibardi K, Stefanaki K, Valari M, Anagnostakou M, Polychronopoulou S (2012) A rare case of neonatal systemic xanthogranulomatosis with severe hepatic disease and metachronous skin involvement. J Pediatr Hematol Oncol 34:226–228

Papasozomenos SC (1999) Hypothalamic Langerhans cell histiocytosis with no eosinophils. Clin Neuropathol 18:260–264

Parentin F, Ventura G, Pastore S, Kiren V, Bibalo C, Pensiero S, Lepore L (2011) A singular case of congenital self-healing histiocytosis with skin, liver and atypical eye involvement. Ocul Immunol Inflamm 19:337–339

Park IS, Park IK, Kim EK, Kim S, Jon SR, Huh JR, Suh CW (2012) Langerhans cell histiocytosis followed by Hodgkin's lymphoma. Korean J Intern Med 27:459–462

Parker JW, Lichtenstein L (1963) Severe hepatic involvement in chronic disseminated histiocytosis X. Report of a case with necropsy. Am J Clin Pathol 40:624–632

Patel P, Vyas R, Blickman J, Katzman P (2010) Multimodality imaging findings of disseminated juvenile xanthogranuloma with renal involvement in an infant. Pediatr Radiol 40(Suppl 1):S6–S10

Peng CT, Chow KC, Chang WC, Tsai CH, Lin TY, Lin SS, Chiu CF (1999) Expression of Fas ligand in Langerhans' cell histiocytosis: a case report of a boy with multisystem involvement. Am J Hematol 61:256–261

Petersen BL, Rengtved P, Bank MI, Carstensen H (2003) High expression of markers of apoptosis in Langerhans cell histiocytosis. Histopathology 42:186–193

Pileri SA, Grogan TM, Harris NL, Banks P, Campo E, Chan JK, Favera RD, Delsol G, De Wolf-Peeters C, Falini B, Gascoyne RD et al (2002) Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. Histopathology 41:1–29

Pineles SL, Liu GT, Acebes X, Arruga J, Nasta S, Glaser R, Pramick M, Fogt F, Roux PL et al (2011) Presence of Erdheim-Chester disease and Langerhans cell histiocytosis in the same patient: a report of 2 cases. J Neuroophthalmol 31:217–223

Pirovino et al (1988) PMID 3264377

Pollono D, Rey G, Latella A, Rosso D, Chantada G, Braier J (2007) Reactivation and risk of sequelae in Langerhans cell histiocytosis. Pediatr Blood Cancer 48:696–699

Prasil P, Cayer S, Lemay M, Pelletier L, Cloutier R, Leclerc S (1999) Juvenile xanthogranuloma presenting as obstructive jaundice. J Pediatr Surg 34:1072–1073

Pujol RM, Moreno A, Lopez D, Alomar A, de Moragas JM (1988) Childhood self-healing histiocytosis X. Pediatr Dermatol 5:97–102

Ratei R, Hummel M, Anagnostopoulos I, Jähne D, Arnold R, Dörken B, Mathas S, Benter T et al (2010) Common clonal origin of an acute B-lymphoblastic leukemia and a Langerhans' cell sarcoma: evidence for hematopoietic plasticity. Haematologica 95:1461–1466

Raygada M, Arthur DC, Wayne AS, Rennert OM, Toretsky JA, Stratakis CA (2010) Juvenile xanthogranuloma in a child with previously unsuspected neurofibromatosis type 1 and juvenile myelomonocytic leukemia. Pediatr Blood Cancer 54:173–175

Ricciardo B, Irvine A, McDermott M, Ryan J, Collins S (2011) A case of congenital solitary Langerhans cell histiocytoma. Australas J Dermatol 52:e1–e3

Rice AJ, Wyatt JI (2000) Solitary Langerhans cell histiocytosis in association with primary biliary cirrhosis. Histopathology 36:569–571

Ringel E, Moschella S (1962) Primary histiocytic dermatoses. Arch Dermatol 86:582–596

Rodig SJ, Payne EG, Degar BA, Rollins B, Feldman AL, Jaffe ES, Androkites A et al (2008) Aggressive Langerhans cell histiocytosis following T-ALL: clonally related neoplasms with persistent expression of constitutively active NOTCH1. Am J Hematol 83:116–121

Romao Z, Pontes J, Andrade P, Leitao MC, Donato A, Freitas D (2002) Secondary biliary cirrhosis in a patient with histiocytosis X (in Portuguese). Acta Med Port 15:55–59

Ruco LP, Remotti D, Monardo F, Uccini S, Cristiani ML, Modesti A, Baroni CD (1988) Letterer-Siwe disease: immunohistochemical evidence for a proliferative disorder involving immature cells of Langerhans lineage. Virchows Arch A Pathol Anat Histopathol 413:239–247

Sabib M, Ettair S, Erreimi N, Mouane N (2011) Sclerosing cholangitis revealing Langerhans cell histiocytosis in a 15-mont-old child (in French). Arch Pediatr 18:974–978

Sahm F, Capper D, Preusser M, Meyer J, Stenzinger A, Lasitschka F, Berghoff AS et al (2012) BRAFV600E mutant protein is expressed in cells of variable maturation in Langerhans cell histiocytosis. Blood 120: e28–e34

Saito F, Okabe Y, Suga H, Watanabe T, Arinaga T, Naito Y, Uchida S, Hisaka T, Toyonaga A et al (2008) A case of hepatic eosinophilic granuloma, which needs distinction with metastatic liver cancer (in Japanese). Nippon Shokakibyo Gakkai Zasshi 105:1509–1514

Sankilampi U, Huikko-Tarvainen S, Kärjä V, Pirinen E, Naukharinen A, Hollmén A (2008) Congenital Langerhans cell histiocytosis mimicking a "blueberry muffin baby". J Pediatr Hematol Oncol 30:245–248

Satoh T, Smith A, Sarde A, Lu HC, Mian S, Trouillet C, Mufti G, Emile JF, Fraternali F et al (2012) B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. PLoS One 7:e33891

Savva-Bordalo J, Freitas-Silva M (2008) Langerhans cell histiocytosis involving the liver of a male smoker: a case report. J Med Case Reports 2:376

Schouten B, Egeler RM, Leenen PJ, Taminiau AH, van den Broek LJ, Hogendoorn PC (2002) Expression of cell cycle-related gene products in Langerhans cell histiocytosis. J Pediatr Hematol Oncol 24:727–732

Schüller A (1915) Ueber eigenartige Schädeldefekte im Jugendalter ("Landkartenschädel"). Fortschr Geb Röntgenstrahlen 23:12–18

Schüller A (1926) Dysostosis hypophysaria. Br J Radiol 31:156–158

Seward JL, Malone JC, Callen JP (2004) Generalized eruptive histiocytosis. J Am Acad Dermatol 50:116–120

Shao H, Xi L, Raffeld M, Feldman AL, Ketterling RP, Knudson R, Rodriguez-Canales J et al (2011) Clonally related histiocytic/dendritic cell sarcoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: a study of seven cases. Mod Pathol 24:1421–1432

Shin HT, Harris MB, Orlow SJ (2004) Juvenile myelomonocytic leukemia presenting with features of hemophagocytic lymphohistiocytosis in association with neurofibromatosis and juvenile xanthogranulomas. J Pediatr Hematol Oncol 26:591–595

Shoo BA, Shinkai K, McCalmont TH, Fox LP (2008) Xanthogranulomas associated with hematologic malignancy in adulthood. J Am Acad Dermatol 59: 488–493

Shuangshoti S, Seksarn P (1987) Histiocytosis X: overlapping form between Letterer-Siwe disease and Hand-Schüller-Christian disease with advanced thymic involvement and obstructive jaundice. J Med Assoc Thai 70:344–350

Shy SW, Lee WH, Chang YC, Wu W (1996) A solitary congenital self-healing histiocytosis. Report of a case and review of the literature. Pathol Res Pract 192:869–874

Sidwell RU, Francis N, Slater DN, Mayou SC (2005) Is disseminated juvenile xanthogranulomatosis benign cephalic histiocytosis? Pediatr Dermatol 22:40–43

Sisto A, Feldman P, Garel L, Seidman E, Brochu P, Morin CL et al (1987) Primary sclerosing cholangitis in children: study of five cases and review of the literature. Pediatrics 80:918–923

Sivapirabu G, Sugo E, Wargon O (2011) Juvenile xanthogranuloma: challenges in complicated cases. Australas J Dermatol 52:284–287

Siwe S (1933) Die Reticuloendotheliose – ein neues Krankheitsbild unter den Hepatosplenomegalien. Z Kinderheilk 55:212–247

Smith T (1864) Skull-cap showing congenital deficiencies of bone. Trans Path Soc Lond 16:224

Squires RH, Weinberg AG, Zwiener RJ, Winick N (1993) Langerhans' cell histiocytosis presenting with hepatic dysfunction. J Pediatr Gastroenterol Nutr 16:190–193

Stables GI, Mackie RM (1992) Generalized eruptive histiocytoma. Br J Dermatol 126:196–199

Stieber AC, Sever C, Starzl TE (1990) Liver transplantation in patients with Langerhans' cell histiocytosis. Transplantation 50:330–340

Sumida K, Yoshidomi Y, Koga H, Kuwahara N, Matsuishi E, Karube K, Oshima K, Gondo H (2008) Leukemic transformation of Langerhans cell sarcoma. Int J Hematol 87:527–531

Sundar KM, Gosselin MV, Chung HL, Cahill BC (2003) Pulmonary Langerhans cell histiocytosis: emerging concepts in pathobiology, radiology, and clinical evolution of disease. Chest 123:1673–1683

Tahan SR, Pastel-Levy C, Bhan AK, Mihm MC (1989) Juvenile xanthogranuloma. Clinical and pathologic characterization. Arch Pathol Lab Med 113:1057–1061

Tani M, Ishii N, Kumagai M, Ban M, Sasase A, Mishima Y (1992) Malignant Langerhans cell tumour. Br J Dermatol 126:398–403

Tardio JC, Aguado M, Borbujo J (2013) Self-regressing S100-negative CD1a-positive cutaneous histiocytosis. Am J Dermatopathol 35:e57–e59

Tay YK, Friednash MM, Weston WL, Aeling JL (1998) Solitary congenital nodule in an infant. Solitary congenital self-healing reticulohistiocytosis. Arch Dermatol 134:627

Terry J, Luchinotta F, Sanders S, Vergilio JA, Hyde S, Boyd TK (2013) Congenital Langerhans cell histiocytosis with placental involvement. Pediatr Dev Pathol 16:224–228

Thompson HH, Pitt HA, Lewin KJ, Longmire WP (1984) Sclerosing cholangitis and histiocytosis X. Gut 25:526–530

Touton K (1885) Über das Xanthom, insbesondere dessen Histiologie und Histiogenese. Vierteljahrsschr Dermatol Syphil 12:3–53

Tran DT, Wolgamot GM, Olerud J, Hurst S, Argenyi Z (2008) An 'eruptive' variant of juvenile xanthogranuloma associated with Langerhans cell histiocytosis. J Cutan Pathol 35(Suppl 1):50–54

Trochtenberg DS, Dessypris EN (1990) Reversible hepatomegaly and diabetes mellitus in an adult with disseminated histiocytosis X. Am J Med Sci 299:179–184

Unuvar E, Devecioglu O, Akcay A, Gulluoglu M, Uysal V, Oguz F, Sidal M (2007) Successful therapy of systemic xanthogranuloma in a child. J Pediatr Hematol Oncol 29:425–427

Vade A, Hayani A, Pierce KL (1993) Congenital histiocytosis X. Pediatr Radiol 23:181–182

Vollum DI (1979) Letterer-Siwe disease in the adult. Clin Exp Dermatol 4:395–406

Walia M, Paul P, Mishra S, Mehta R (2004) Congenital Langerhans cell histiocytosis: the self-healing variety. J Pediatr Hematol Oncol 26:398–402

Warnke RA, Weiss LM, Chan JKC, Cleary ML, Dorfman RF (1995) Tumors of the lymph nodes and spleen. Atlas of tumor pathology, 3rd series, fascicle 14. Armed Forces Institute of Pathology, Washington, DC

Wee SH, Kim HS, Chang SN, Kim DK, Park WH (2000) Generalized eruptive histiocytoma: a pediatric case. Pediatr Dermatol 17:453–455

Weidman FD, Freeman W (1924) Xanthoma tuberosum: two necropsies disclosing lesions of central nervous system and other tissues. Arch Dermatol Syphilol 9:149

Weiss N, Keller C (1993) Xanthoma disseminatum: a rare normolipemic xanthomatosis. Clin Investig 71:233–238

Wells GC (1979) The pathology of adult type Letterer-Siwe disease. Clin Exp Dermatol 4:407–412

Wheller L, Carman N, Butler G (2013) Unilesional self-limited Langerhans cell histiocytosis: a case report and review of the literature. J Cutan Pathol 40:595–599

Willman CL (1994) Detection of clonal histiocytes in Langerhans cell histiocytosis: biology and clinical significance. Br J Cancer Suppl 23:S29–S33

Willman CL, Busque L, Griffith BB et al (1994) Langerhans cell histiocytosis (histiocytosis X): a clonal proliferative disease. N Engl J Med 331:154–160

Windebank KP, Nanduri V (2009) Langerhans cell histiocytosis. Arch Dis Child 94:904–908

Winkelmann RK, Müller SA (1963) Generalized eruptive histiocytoma: a benign papular histiocytic reticulosis. Arch Dermatol 88:154–164

Wood C, Wood GS, Deneau DG, Oseroff A, Beckstead JH, Malin J (1984) Malignant histiocytosis X. Report of a rapidly fatal case in an elderly man. Cancer 54:347–352

Woollons A, Darley CR (1998) Xanthoma disseminatum: a case with hepatic involvement, diabetes insipidus and type IIb hyperlipidaemia. Clin Exp Dermatol 23:277–280

Writing Group of the Histiocyte Society (1987) Histiocytosis syndromes in children. Lancet 1:208–209

Wu WS, McClain KL (1997) DNA polymorphisms and mutations of the tumor necrosis factor-alpha (TNF-alpha) promoter in Langerhans cell histiocytosis (LCH). J Interferon Cytokine Res 17:631–635

Xu X, Liu WP, Yang QP, Wang WY, Liao DY, Zhao S, Bi CF, Lin L, Min M (2012a) Langerhans cell histiocytosis: a clinicopathologic and immunohistochemical analysis of 258 cases (in Chinese). Zhonghua Bing Li Xue Za Zhi 41:91–96

Xu Z, Padmore R, Faught C, Duffet L, Burns BF (2012b) Langerhans cell sarcoma with an aberrant cytoplasmic CD3 expression. Diagn Pathol 7:128

Yagita K, Iwai M, Yagita-Toguri M, Kimura H, Taniwaki M, Misawa S, Okanoue T, Kashima K, Tsuchihashi Y (2001) Langerhans cell histiocytosis of an adult with tumors in liver and spleen. Hepatogastroenterology 48:581–584

Yeh BM, Nobrega KT, Reddy GP, Qayyum A (2007) Juvenile xanthogranuloma of the heart and liver: MRI, sonographic, and CT appearance. AJR Am J Roentgenol 189:W202–W204

Yousem SA, Colby TV, Chen YY, Chen WG, Weiss LM (2001) Pulmonary Langerhans' cell histiocytosis: molecular analysis of clonality. Am J Surg Pathol 25:630–636

Yu CP, Tseng HH, Tu YC (1990) Congenital Letterer-Siwe disease with intrauterine fetal death: a case report and review of the literature. J Formos Med Assoc 89:806–810

Yu RC, Chu C, Buluwela L, Chu AC (1994) Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet 343:767–768

Yurkovich M, Wong A, Lam JM (2013) Solitary congenital self-healing Langerhans cell histiocytosis: a benign variant of Langerhans cell histiocytosis? Dermatol Online J 19:3

Zaenglein AL, Stelle MA, Kamino H, Chang MW (2001) Congenital self-healing reticulohistiocytosis with eye involvement. Pediatr Dermatol 18:135–137

Zelger B, Cerio R, Orchard G, Fritsch P, Wilson-Jones E (1992) Histologic and immunohistochemical study comparing xanthoma disseminatum and histiocytosis X. Arch Dermatol 128:1207–1212

Zelger BW, Sidoroff A, Orchard G, Cerio R (1996) Non-Langerhans cell histiocytoses. A new unifying concept. Am J Dermatopathol 18:490–504

Zhao G, Luo M, Wu ZY, Liu Q, Zhang B, Gao RL, Zhang ZQ (2009) Langerhans cell sarcoma involving gallbladder and peritoneal lymph nodes: a case report. Int J Surg Pathol 17:347–353

Zyada MM (2009) Expression of matrix metalloproteinase-9 and significance of a macrophage assay in eosinophilic granuloma. Ann Diagn Pathol 13:367–372

Neoplasms of Histiocyte/Macrophage Lineage: Histiocytic Sarcoma and Similar Neoplasms

101

Contents

Abstract

Malignant neoplasms of the histiocyte/macrophage lineage can develop as primary lesions in the hepatobiliary tract, but more frequently involve the liver as metastatic lesions. Histiocytic sarcoma is a very rare and highly malignant neoplasm of cells with features of mature tissue histiocytes. The diagnosis of histiocytic sarcoma was previously more frequently formulated, but many of the former so-called malignant histiocytic neoplasms have later turned out to be poorly differentiated tumors of B and T lymphocytes and dendritic cells. True histiocytic sarcomas amount to less than 1 % of all lymphomas that occur in lymph nodes. Extranodal histiocytic sarcoma can very rarely involve the liver and/or biliary tract. Here the cancer presents in the form of a nodular or diffuse proliferation of oval to spindle-shaped abnormal histiocytes. Apart from mononuclear tumor cells, multinucleated giant cells also develop. The cells are immunoreactive for histiocyte-associated markers, specifically CD68 and CD163, but are consistently negative for CD1a and markers of the B- and T-cell lineages.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_101

Histiocytic Sarcoma

ICD-O code: **9755/3**

Introduction

According to the WHO classification of tumors, histiocytic sarcoma is a very rare, highly malignant neoplasm of cells with the features of mature tissue histiocytes. Neoplasms associated with acute monocytic leukemia are excluded (review: Grogan et al. 2008).

Terminology, Cell of Origin, and Classification

Most of malignancies formerly classified as so-called malignant "histiocytic" neoplasms have later turned out to be poorly differentiated B-cell, T-cell, or anaplastic lymphomas, and only a very small fraction of the lesions are histiocytic lymphomas of monocyte/macrophage or dendritic cell origin. Conditions previously termed "histiocytic medullary reticulosis" are now regarded as a heterogeneous group of lesions, but often belonging to the hemophagocytic syndromes. Histiocytic sarcoma is derived from macrophages/histiocytes, which in turn originate from bone marrow-derived monocytes. Macrophages and the phagocyte concept in general go back to Metchnikoff (review: Tauber 2003). Neoplasms with a histiocytic lineage are closely related to monocytic tumors, but are separated from tumors that arise in the setting of monoblastic/monocytic leukemias (review: Jaffe et al. 2008).

In order to separate lymphomas with a clear histiocyte lineage from other lymphomas that may morphologically resemble them, the term "true histiocytic lymphoma" has previously been proposed and employed (Isaacson et al. 1983; Pileri et al. 1985; Hsu et al. 1991; Levine et al. 1991; Kamel et al. 1995; Elghetany 1997; Copie-Bergman et al. 1998). Also the designation, monocytic sarcoma, was in use (Soria et al. 1992). These terms have now been replaced by histiocytic sarcoma as used in the most recent WHO classification. Histiocytic sarcoma was already employed as a term in the older literature (van der Valk et al. 1981; Lauritzen et al. 1994). In the 2001 WHO definition of histiocytic sarcoma, the absence of clonal immunoglobulin heavy chain (IgH) or TCR gene rearrangements were required for diagnosis. The 2008 version of the WHO classification no longer strictly requires the absence of these rearrangements, as histiocytic sarcomas that have developed concurrent with or subsequent to B- or T-cell non-Hodgkin's lymphomas, or mature B-cell neoplasms, can show IgH or TCR rearrangements (review: Takahashi and Nakamura 2013).

Epidemiology

Malignant neoplasms of the histiocyte lineage represent very rare lymphoid tissue tumors and amount to less than 1 % of all lymphomas occurring in lymph nodes. Most histiocytic sarcomas are diagnosed in adult patients (median age: 52 years), but the neoplasm also occurs in the pediatric age group (Brito et al. 2014). Whether a sex predilection is present is still a matter of controversy, but probably the neoplasm occurs equally between men and women.

Clinical and Imaging Features

Most histiocytic sarcomas were detected in extranodal compartments, specifically the skin, soft tissues, and the gastrointestinal tract. Less common organs include the CNS, mediastinum, kidney, breast, salivary glands, liver, and biliary tract. Apart from signs and symptoms related to tumor-induced alterations at the primary site (mass effects, pain, hemorrhage), many patients experience systemic signs and symptoms, such as fever, weight loss, fatigue, and anemia. Hepatosplenomegaly is a common finding. In

the GI tract, histiocytic sarcoma can cause hollow organ obstruction and bleeding. In a minority of patients, the neoplasm manifests as a systemic disorder with multiple nodules in many organs and tissues, a condition termed, "malignant histiocytosis." In advanced disease, the bone marrow can be extensively infiltrated, followed by pancytopenia and lytic bone lesions (Pileri et al. 1985; Ralfkiaer et al. 1990; Kamel et al. 1995; Copie-Bergman et al. 1998; Sun et al. 2003; Hornick et al. 2004; Gill-Samra et al. 2012; Guan et al. 2012; Sundersingh et al. 2012; Wang et al. 2012; Shen et al. 2013; Wu et al. 2013). In most patients, histiocytic sarcoma is a high-grade, aggressive lymphoma with a poor response to therapy. Many patients present with clinically high stage at diagnosis, associated with progressive disease, while patients with low stage and small tumors at diagnosis have a more favorable course.

Histiocytic Sarcoma of the Hepatobiliary Tract

Extranodal histiocytic sarcoma can rarely involve the liver and/or the biliary tract. Infiltration of the liver is rare and is present as a focal to diffuse infiltration causing hepatomegaly or in the form of tumor nodules/masses (Hornick et al. 2004; Hayase et al. 2010). In case of an ill-defined-non-nodular infiltrate, the histiocytoid or epithelioid cells form a non-cohesive monomorphous infiltrate that can efface the portal tracts and replace the parenchyma. Within lobules, the neoplastic cells can grow within hepatic sinusoids, forming a distinct intravascular infiltrate. Hepatic infiltrates show a cellular morphology similar to that in other organs and tissues, containing oval, polygonal, spindled, and multinuclear giant cells with an abundant eosinophilic and often vacuolated cytoplasm and round to ovoid or reniform nuclei with a mostly open chromatin structure. Histiocytic sarcoma can show evenly distributed multinucleated CD68(+)CD163(+) giant cells scattered among polygonal mononuclear cells

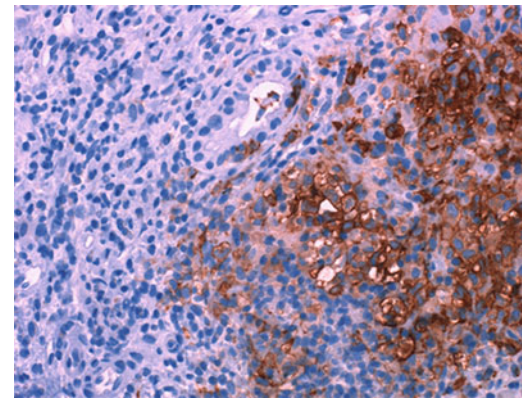

Fig. 1 Histiocytic sarcoma of the liver. The medium-sized to large neoplastic cells form a diffuse growth and are positive for CD68 (CD68 immunostain)

with epithelioid features (Copie-Bergman et al. 1998; Miliauskas 2003; Huang et al. 2007). The neoplasms show small numbers of background lymphocytes and reactive histiocytes/macrophages (Miliauskas 2003). The cells are immunoreactive for histiocyte-associated markers, i.e., CD68, CD163, lysozyme, and alpha-1-antitrypsin (Fig. 1), and for CD45 or CD45RO, but are consistently negative for CD1a/langerin, CD21, CD35, CD13, CD33, and markers of B-cell and T-cell lineages. Both CD68 and lysozyme show a markedly granular immunostaining, while CD163 shows a membrane and/or cytoplasmic staining (Hanson et al. 1989; Copie-Bergman et al. 1998; Sato et al. 2002; Vos et al. 2005). Part of the cells may express S100 protein (Copie-Bergman et al. 1998). The proliferation fraction varied considerably in published observations but may exceed 80 %. In one analysis, two distinct populations of cells were recognized. Oval cells were CD68(+)lysozyme(+) CD163(−), while spindle-shaped cells with abundant cytoplasm were CD68(+)lysozyme(−)CD163(−) (Wakahashi et al. 2010).

Nodular involvement of the liver is characterized by grayish white, solid, and soft tumors (Hayase et al. 2010). Involvement of the liver can result in hepatic dysfunction and peliosis hepatis (Fine et al. 1995). In an old male patient,

this type of neoplasm was found in the extrahepatic bile duct, causing stenosis and obstructive jaundice (Miyabe et al. 2014).

Differential Diagnosis

Cytomorphologically, histiocytic sarcoma can be confounded with malignant lymphoid neoplasms that have previously been classified as "true histiocytic," i.e., mainly high-grade B-cell, T-cell, and anaplastic non-Hodgkin's lymphomas. Immunohistochemistry, in particular CD68, CD163, and lysozyme immunostains, is mandatory for diagnosis.

Pathogenic Pathways

Etiology and pathogenesis of histiocytic sarcoma are still largely unknown. Histiocytic sarcoma or "true histiocytic lymphoma" was found to develop following other lymphoid or myeloid malignancies (so-called lineage conversion), including acute lymphoblastic neoplasms (Soslow et al. 1996; Bouabdallah et al. 2001; Dictor et al. 2009; Castro et al. 2010), hairy cell leukemia (Michonneau et al. 2014), low-grade follicular lymphoma (Stoecker and Wang 2013), chronic lymphocytic leukemia (Wang et al. 2010; Stoecker and Wang 2013), chronic myelomonocytic leukemia (Mori et al. 2010), or autoimmune lymphoproliferative syndrome and associated Rosai-Dorfman disease (Venkataraman et al. 2010). Interestingly, part of the tumors occurred in association with non-seminomatous germ cell tumors, mostly of the mediastinum and less often gonadal germ cell tumors, and usually malignant teratoma with or without yolk sac differentiation and embryonal carcinoma (Pileri et al. 1985; Ladanyi and Roy 1988; Koo et al. 1992; Margolin and Traweek 1992; Sasou et al. 1996; Suenaga et al. 2006). Histiocytic sarcoma often occurs within 1 year of germ cell tumor diagnosis. In addition to this sarcoma, other lymphoid malignancies are associated with germ cell tumors of the mediastinum and gonads. It has been suggested that embryonal progenitor cells occurring in certain germ cell tumors, such as teratocarcinoma, and capable to differentiate along a hematopoietic lineage may be involved in the emergence of histiocytic sarcoma.

Histiocytic sarcoma cells may show various cytogenetic abnormalities of several chromosomes, including chromosomes 3, 4, and 8 (Alonso-Dominguez et al. 2012). Recent investigations uncovered frequent BRAFV600E mutations in histiocytic sarcoma. In one study, these mutations were detectable in 62.5 % of the neoplasms and were more common than in Langerhans cell tumors and dendritic cell neoplasms (Go et al. 2014). A BRAFV600E mutation was also found in a histiocytic sarcoma arising from hairy cell leukemia (Michonneau et al. 2014). Human histiocytic sarcoma showed, similar to its murine counterpart, genetic or epigenetic inactivation of PTEN, p16(INK4A), and p14(ARF) (Carrasco et al. 2006).

"Reticulum Cell Sarcoma" of the Liver

Introduction

Reticulum cell sarcoma ("reticulosarcoma"; "retothelial sarcoma") is a now almost obsolete term. It denoted a mesenchymal malignant neoplasm that was formerly often diagnosed as a neoplastic lesion derived from reticulum cells and also appears in old references on hepatic sarcomas. It was described as a highly cellular sarcoma composed of small- to medium-sized spindle cells with pale cytoplasm and ovoid to slightly elongated nuclei and characterized by a high content of reticulin fibers as shown in silver stains. As a function of the redefinition of mesenchymal cells and tumors derived thereof, many if not most of the tumors previously diagnosed as "reticulum cell sarcoma" are now classified as other mesenchymal malignancies, in particular true malignant histiocytomas, and what the relatively few remaining cases really are remains to be clarified in more detail. However, for reasons of history and comparison, cases formerly diagnosed and reported as hepatic reticulum cell sarcoma are briefly discussed in this chapter. Based on the

description (although often very detailed) and the published figures, it is in many cases very difficult, or impossible, to transform the original diagnosis of reticulum cell sarcoma into a modern tumor category. However, at least part of the neoplasms may now represent dendritic cell neoplasms, neoplasms of the histiocyte lineage, or fibroblastic reticulum cell tumors.

Liver Involvement

Relatively few older reports described primary reticulum cell sarcoma or reticulosarcoma of the liver (Gasser 1955; Jozsa and Lusztig 1961; Leite 1963; Mastella and Paduano 1960; Ata and Kamel 1965; Markiewicz and Brzezinska 1965; Torres and Bollozos,1971; Portmann et al. 1976).

Macroscopy

The necropsy case reported by Gasser (1955) showed multiple tumor nodules that involved the entire organ. The white and firm nodules were isolated or clustered, and the largest nodule had the size of a fist.

Histopathology

Reticulum cell sarcomas were described as neoplasms composed of medium-sized to large, elongated, or polygonal cells with pale, ill-defined cytoplasm and pleomorphic nuclei. Part of the cells formed syncytia, and some cells were reported as histiocyte-like. There was a striking abundance of argentophilic reticulin fibers, forming a dense network, single tumor cells being surrounded by these fibers (Gasser 1955).

Differential Diagnosis

Some of the previous reticulum cell sarcomas of the liver may now be classified as metastatic fibroblastic reticulum cell sarcomas (Yaman et al. 2009) or as neoplasms of the dendritic cell and histiocytoid cell systems.

"Kupffer Cell Sarcoma" of the Liver

Several older reports describe so-called Kupffer cell sarcoma of the liver (Baker et al. 1956; Burston 1958; Pizzolato and Kistler 1959; Linquette et al. 1960; Matturi and Rossi 1963; Miller et al. 1964; Galup et al. 1965; Kwittken and Tartow 1966; Blackwell and Joske 1970; Mölleken 1973; Gentili et al. 1974; Greenberg 1977; Evans and Grasso 1978). In part of the cases, the tumors may have been angiosarcomas, because the authors employed the terms hemangioendothelioma ("reticulosarcoma angioplasticum"), hemangioendotheliosarcoma, or angioblastic reticuloendotheliomas as synonyms for Kupffer cell sarcoma (Matturi and Rossi 1963; Miller et al. 1964; Gentili et al. 1974). The macroscopy of a multinodular liver malignancy depicted by Baker et al. (1956) is that of a typical multinodular angiosarcoma. The figure shown in the report of Mölleken (1973) shows a neoplasm strongly resembling angiosarcoma, and the author diagnosed it as a special form of hemangioendothelioma classified as Kupffer cell sarcoma. Hepatic sarcomas thought to derive from Kupffer cells have also been observed in rats, in part following exposure to chemical carcinogens (Kendrey and Németh 1967; Chopra et al. 1979). In humans, Kupffer cell sarcoma is now an obsolete entity, part of the cases probably representing neoplasms of the macrophage/histiocyte and dendritic cell lineages.

"Histiocytoid Cell" Proliferations of Uncertain Cell Lineage

Introduction

There are several non-Langerhans cell proliferative "histiocytoid" disorders with an uncertain cell lineage and still unknown etiology. In regard to their biology, the lesions range from self-limited to progressive behavior. Part of these disorders

show multiple nodular or eruptive skin lesions but may also involve mucosal surfaces, inner organs, and the articuloskeletal system. Cutaneous forms can show a progressive course but may also exhibit regression.

ALK+ Histiocytosis

General Remarks

Histiocytic disorders in the pediatric age group mainly comprise Langerhans cell histiocytosis, several types of self-healing Langerhans cell and non-Langerhans cell disorders, EBV-associated hemophagocytic syndrome, and hemophagocytic lymphohistiocytosis. ALK+ histiocytosis is a novel systemic disorder that has been added to this list. The disease, characterized by a proliferation of morphologically distinctive histiocytes with unique expression of ALK, was described in three female infants who presented with pallor and prominent hepatosplenomegaly, but without fever. There was marked anemia and thrombocytopenia, but no leukopenia. Bone marrow showed no hemophagocytosis, but scanty ALK-positive cells or solitary or in tiny aggregates. The histiocytic process mainly involved the liver, but one patient developed a cutaneous infiltration morphologically resembling juvenile xanthogranuloma. In one patient, a TPM3-ALK fusion was detected. The disease in these three patients (two with chemotherapy) resolved slowly over many months (Chan et al. 2008).

Liver Involvement

Liver biopsies showed sinusoidal infiltration by single or small aggregates of very large histiocytes with and eosinophilic, vacuolated cytoplasm and irregularly folded or lobulated nuclei, a fine chromatin structure, and small nucleoli. Few cells contained two to four nuclei. Part of the cells revealed phagocytosis of lymphocytes, granulocytes, normoblasts, erythrocytes, or hemosiderin granules. In one patient, the histiocytes also infiltrated portal tracts. Ultrastructurally, Birbeck granules were not detectable. Immunohistochemically, the cells were strongly reactive for CD68, CD163, and lysozyme and heterogeneously for S100 protein. The cells were uniformly reactive for ALK in a membranous and weak cytoplasmic staining pattern. Immunostaining with anti-phospho-ALK antibody displayed granular cytoplasmic staining suggesting ALK fusion protein phosphorylated on tyrosine 664. There was no reactivity for CD1a and langerin (Chan et al. 2008).

Multicentric Reticulohistiocytosis

Multicentric reticulohistiocytosis (MRH; synonyms: generalized giant cell histiocytosis; lipoid dermatoarthritis; lipoid rheumatism; reticulohistiocytic granuloma; reticulomatosis with histiocytic giant cells; histiocytosis giganto-cellularis) is a rare condition characterized by widespread papulonodular skin and mucosal lesions, periungual coralliform nodules, periarticular nodules, severe symmetrical erosive to destructive and sometimes mutilating arthritis, and eventual involvement of inner organs, including bronchopulmonary system and the liver. MRH was described in the late nineteenth century (Targett 1897) and then in 1936 (Weber and Freudenthal). The disease starts with polyarthritis in at least half of patients, followed by skin lesions months to years later. Males and females are equally involved, and the disorder manifests between 40 and 45 years in most cases. Very rare pediatric cases are known. The skin lesions, which may grow to several cm of size, consist of proliferating histiocyte-like cells and multinucleated giant cells with an eosinophilic "ground-glass" cytoplasm (reviews: Holobar and Mach 1966; Rooney et al. 1975; Bach 1983; Liu and Fang 2004; Sroa et al. 2010; Islam et al. 2013). Liver involvement presented in the form of scattered nodules histologically showing the typical infiltrate including giant cells (Yang et al. 2009).

Progressive Nodular Histiocytosis

Introduction

Progressive nodular histiocytosis (PNH; synonyms: progressive nodular histiocytoma) is a rare form of non-Langerhans cell histiocytosis characterized by a progressive multinodular proliferation of dermal dendrocytoid cells of the macrophage/histiocyte lineage. The disorder had first been described in 1978 (Taunton et al. 1978), with relatively few cases having been described later (Burgdorf et al. 1981; Glavin et al. 2009; Lloyd et al. 2010; Nofal et al. 2011). The main cell lineage involved in PNH is a spindle-shaped histiocyte which also characterizes spindle cell xanthogranuloma (Zelger et al. 1996). The skin lesions in PNH are clinically characterized by multiple brown-yellowish papules or nodules. Superficial nodules are usually up to 5 mm in diameter, while deep nodules and tumors may reach a diameter of 3 cm. The disorder occurs in older patients (aged 40–20 years), in contrast to solitary spindle cell xanthogranuloma, which shows solitary lesions with a very similar morphology, but occurs in a younger age group (20–40 years; Zelger et al. 1995). PNH rarely involves inner organs, including the pharynx, larynx, lung, and liver (Lloyd et al. 2010). Patients with PNH usually follow a serious clinical course with progressive disfiguring skin lesions.

Vacuolated, lipidized/xanthomatized, scalloped, or oncocytic cells are often seen, as are multinucleated macrophages of the Touton type (Zelger et al. 1995). The cells are immunoreactive for a macrophage/dendritic cell lineage, mostly positive for CD68 and HAM56 but negative for S100 protein. At electron microscopic examination, no Birbeck granules are found. Pathogenetically, the neoplastic lineage that consists of dendritic-like spindled histiocytes that preferentially home to the dermis may in some patients also home to mucosal structures or even to deep-seated organs, the latter probably populated via hematogenous spread of macrophages or their precursors.

Liver Involvement

Liver involvement in patients with PNH is very uncommon (Gonzalez Ruiz et al. 2000; Lloyd et al. 2010). The development of hepatic lesions may follow a course similar to that observed in patients with multicentric reticulohistiocytosis (see above). In one male patient with multiple and in part confluent skin lesions, abdominal ultrasound examination revealed hepatosplenomegaly, with the spleen measuring 16 cm, suggesting marked visceral involvement, but a liver biopsy was not performed (Gonzalez-Ruiz et al. 2000).

References

Alonso-Dominguez JM, Calbacho M, Talavera M, Villalon C, Abalo L, Garcia-Gutierrez JV et al (2012) Cytogenetic findings in a histiocytic sarcoma case. Case Rep Hematol 2012:428279

Ata AA, Kamel IA (1965) Primary reticulum cell sarcoma of the liver. A case report. J Egypt Med Assoc 48:514–521

Bach GL (1983) VI. Die multizentrische Retikulohistiozytose. In: Aufdermaur M et al (eds) Handbuch der Inneren Medizin, vol 6, 2/C. Springer, Heidelberg, pp 852–857

Backwell, Joske RA (1970) Kupffer-cell sarcoma. Am J Dig Dis 15:133–138

Baker HD, Davson J, Paget GE (1956) Haemangioendothelioma (Kupffer-cell sarcoma) of the liver. J Pathol Bacteriol 72:173–182

Bouabdallah R, Abéna P, Chetaille B, Aurran-Schleinitz T, Sainty D, Dubus P, Arnoulet C et al (2001) True histiocytic lymphoma following B-acute lymphoblastic leukaemia: case report with evidence for a common clonal origin in both neoplasms. Br J Haematol 113:1047–1050

Brito MD, Silva C, Costa V, Sousa T (2014) Childhood histiocytic sarcoma – rare presentation with peripheral blood involvement. Eur J Haematol 93:265–266

Burgdorf WHC, Kusch SL, Nix TE, Pitha J (1981) Progressive nodular histiocytoma. Arch Dermatol 117:644–649

Burston J (1958) Kupffer cell sarcoma. Cancer 11:798–802

Carrasco DR, Fenton T, Sukhdeo K, Protopopova M, Enos M, You MJ, Di Vizio D et al (2006) The PTEN and INK4A/ARF tumor suppressors maintain myelolymphoid homeostasis and cooperate to constrain histiocytic sarcoma development in humans. Cancer Cell 9:379–390

Castro EC, Blazquez C, Boyd J, Correa H, de Chadarevian JP, Felgar RE, Graf N et al (2010) Clinicopathologic features of histiocyte lesions following ALL, with a review of the literature. Pediatr Dev Pathol 13:225–237

Chan JK, Lamant L, Algar E, Delsol G, Tsang WY, Lee KC, Tiedemann K, Chow CW (2008) ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy. Blood 112:2965–2968

Chopra P, Manga A, Nayak NC (1979) Kupffer cell sarcoma in rats after exposure to small doses of dimethylnitrosamine and *N*-2-acetylaminofluorene during hepatic regeneration. J Natl Cancer Inst 62:1089–1095

Copie-Bergman C, Wotherspoon AC, Norton AJ, Diss TC, Isaacson PG (1998) True histiocytic lymphoma: a morphologic, immunohistochemical, and molecular genetic study of 13 cases. Am J Surg Pathol 22:1386–1392

Dictor M, Warenholt J, György C, Mansson I, Larsson G (2009) Clonal evolution to histiocytic sarcoma with the BCR/ABL rearrangement 14 years after acute lymphoblastic leukemia. Leuk Lymphoma 50:1892–1895

Elghetany MT (1997) True histiocytic lymphoma: is it an entity? Leukemia 11:762–764

Evans JG, Grasso P (1978) Kupffer cell sarcoma of the liver. S Afr Med J 53:273

Fine KD, Solano M, Polkter DE, Tillery GW (1995) Malignant histiocytosis in a patient presenting with hepatic dysfunction and peliosis hepatis. Am J Gastroenterol 90:485–488

Galup LN, Hawkins RA, Manalo-Estrella P (1965) Kupffer cell sarcoma of the liver. Aerosp Med 36:988–989

Gasser H (1955) Primary retothelial sarcoma of the liver (in German). Virchows Arch 326:296–311

Gentili V, Vales O, San Roman A (1974) Kupfferian hemangioendothelio sarcoma of the liver (Kupffer cells sarcoma). Apropos of 2 observations (in Spanish). Rev Esp Enferm Apar Dig 44:811–816

Gill-Samra S, Ng T, Dexter M, Wong M, Nahar N, Allsopp K, Broadle RA, Varikatt W (2012) Histiocytic sarcoma of the brain. J Clin Neurosci 19:1456–1458

Glavin FL, Chhatwall H, Karimi K (2009) Progressive nodular histiocytosis: a case report with literature review, and discussion of differential diagnosis and classification. J Cutan Pathol 36:1286–1292

Go H, Jeon YK, Huh J, Choi SJ, Choi YD, Cha HJ, Kim HJ, Park G, Min S, Kim JE (2014) Frequent detection of BRAFV 600E mutations in histiocytic and dendritic cell neoplasms. Histopathology 65:261–272

Gonzalez Ruiz A, Bernal Ruiz AI, Aragoneses Fraile H, Peral Martinez I, Garcia Munoz M (2000) Progressive nodular histiocytosis accompanied by systemic disorders. Br J Dermatol 143:628–631

Greenberg M (1977) Kupffer cell sarcoma of the liver: report of 2 cases in South African blacks. S Afr Med J 52:244–246

Grogan TM, Pileri SA, Chan JKC, Weiss LM, Fletcher CDM (2008) In: Swerdlow SH et al (eds) WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edn. IARC, Lyon, pp 356–357

Guan ZY, Feng YF, Hou YY (2012) Primary signet-ring cell-like histiocytic sarcoma arising in stomach: report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 41:772–773

Hanson CA, Jaszcz W, Kersey JH, Astorga MG, Peterson BA, Gajl-Pcezalska KJ et al (1989) True histiocytic lymphoma: histopathologic, immunophenotypic and genotypic analysis. Br J Haematol 73:187–198

Hayase E, Kurosawa M, Yonezumi M, Suziki S, Suzuki H (2010) Aggressive sporadic histiocytic sarcoma with immunoglobulin heavy chain gene rearrangement and t(14;18). Int J Hematol 92:659–663

Holobar K, Mach L (1966) Histiocytosis gigantocellularis: Ein Beitrag zur Klinik und Histologie. Hautarzt 17:440–445

Hornick JL, Jaffe ES, Fletcher CD (2004) Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. Am J Surg Pathol 28:1133–1144

Hsu SM, Ho YS, Hsu PL (1991) Lymphomas of true histiocytic origin. Expression of different phenotypes in so-called true histiocytic lymphoma and malignant histiocytosis. Am J Pathol 138:1389–1404

Huang SC, Chang CL, Huang CH, Chang CC (2007) Histiocytic sarcoma – a case with evenly distributed multinucleated giant cells. Pathol Res Pract 203:683–689

Isaacson P, Wright DH, Jones DB (1983) Malignant lymphoma of true histiocytic (monocyte-macrophage) origin. Cancer 51:80–91

Islam AD, Naguwa SM, Cheema GS, Hunter JC, Gershwin ME (2013) Multicentric reticulohistiocytosis: a rare yet challenging disease. Clin Rev Allergy Immunol 45:281–289

Jaffe R, Pileri SA, Facchetti F, Jones DM, Jaffe ES (2008) Histiocytic and dendritic cell neoplasms, Introduction. In: Swerdlow SH et al (eds) WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edn. IARC, Lyon, pp 354–355

Jozsa L, Lusztig G (1961) On primary reticulosarcoma of the liver (in German). Zentralbl Allg Pathol 102:492–496

Kamel OW, Gocke CD, Kell DL, Cleary ML, Warnke RA (1995) True histiocytic lymphoma: a study of 12 cases based on current definition. Leuk Lymphoma 18:81–86

Kendrey G, Németh K (1967) Transplantable rat Kupffer-cell sarcoma; a new experimental tumour strain. Neoplasma 14:273–278

Koo CH, Reifel J, Kogut N, Cove JK, Rappaport H (1992) True histiocytic malignancy associated with a malignant teratoma in a patient with 46XY gonadal dysgenesis. Am J Surg Pathol 16:175–183

Kwittken J, Tartow LR (1966) Haemochromatosis and Kupffer-cell sarcoma with unusual localization of iron. J Pathol Bacteriol 92:571–573

Ladanyi M, Roy I (1988) Mediastinal germ cell tumors and histiocytosis. Hum Pathol 19:586–590

Lauritzen AF, Delsol G, Hansen NE, Horn T, Ersboll J, Hou-Jensen K, Ralfkiaer E (1994) Histiocytic sarcomas and monoblastic leukemias. A clinical, histologic, and immunophenotypical study. Am J Clin Pathol 102:45–54

Leite OC (1963) Primary cancer of the liver. Considerations on a case of reticulosarcoma (in Portuguese). Arg Cir Clin Exp 26:262–267

Levine EG, Hanson CA, Jaszcz W, Peterson BA (1991) True histiocytic lymphoma. Semin Oncol 18:39–49

Linquette M, Clay A, Dupont A, Fossati P, Demaille A, Mizon P (1960) Malignant Kupffer-cell tumor (anatomoclinical case) (in French). Lille Med 5:698–701

Liu YH, Fang K (2004) Multicentric reticulohistiocytosis with generalized systemic involvement. Clin Exp Dermatol 29:373–376

Lloyd CR, Nicholson AG, Wells AU, Hansell DM (2010) Non-Langerhans histiocytosis mimicking sarcoidosis on high-resolution computed tomography. J Thorac Imaging 25:W133–W135

Margolin K, Traweek T (1992) The unique association of malignant histiocytosis and a primary gonadal germ cell tumor. Med Pediatr Oncol 20:162–164

Markiewicz K, Brzezinska B (1965) Primary reticulosarcoma of the liver (in Polish). Pol Tyg Lek 20:186–187

Mastella G, Paduano AR (1960) Primary reticulosarcoma of the liver in an 8-year-old-boy (in Italian). Pharm Ind 68:722–736

Matturi L, Rossi L (1963) Angioblastic reticuloendotheliomatosis (Kupffer cell sarcomas). Presentation of 2 cases and review of the literature (in Italian). Fegato 9:127–148

Michonneau D, Kaltenbach S, Derrieux C, Triquand A, Brouzes C, Gibault L, North MO et al (2014) BRAFV600E in a histiocytic sarcoma arising from hairy cell leukemia. J Clin Oncol 32:e117–e121.

Miliauskas JR (2003) Fine-needle aspiration cytology: true histiocytic lymphoma/histiocytic sarcoma. Diagn Cytopathol 29:233–235

Miller EA, Eichards WG, Reed WH (1964) Hemangioendothelial sarcoma of the liver (Kupffer cell sarcoma). Case Rep Wis Med Soc 63:471–475

Miyabe K, Masaki A, Nakazawa T, Ando T, Hayashi K, Naitoh I, Okumura F, Shimizu S et al (2014) Histiocytic sarcoma of the bile duct. Intern Med 53:707–712

Mölleken K (1973) Zur Kenntnis des Kupfferzell-Sarkoms der Leber (About a Kupffer cell sarcoma of the liver). Zbl Allg Pathol 117:368–371

Mori M, Matsushita A, Takiuchi Y, Arima H, Nagano S, Shimoji S, Kimura T, Inoue D et al (2010) Histiocytic sarcoma and underlying chronic myelomonocytic leukemia: a proposal for the developmental classification of histiocytic sarcoma. Int J Hematol 92:168–173

Nofal A, Assaf M, Tawfik A, Elsayed N, Nofal E, Elnakib N, Elmosalamy K (2011) Progressive nodular histiocytosis: a case report and literature review. Int J Dermatol 50:1546–1551

Pileri S, Mazza P, Rivano MT, Martinelli G, Cavazzini G, Gobbi M, Taruscio D, Lauria F et al (1985) Malignant histiocytosis (true histiocytic lymphoma) clinicopathologic study of 25 cases. Histopathology 9:905–920

Pizzolato P, Kistler JJ (1959) Primary carcinoma of the liver with a report of a Kupffer cell sarcoma. South Med J 52:1423–1426

Portmann B, Schindler AM, Murray-Lyon IM, Williams R (1976) Histological sexing of a reticulum cell sarcoma arising after liver transplantation. Gastroenterology 70:82–84

Ralfkiaer E, Delsol G, O'Connor NTJ, Brandtktzaeg P, Brousset P, Vejlsgaard GL et al (1990) Malignant lymphomas of true histiocytic origin. A clinical, histological, immunophenotypic and genotypic study. J Pathol 160:9–17

Rooney PJ, Ballantyne D, Buchanan WW (1975) Disorders of the locomotor system associated with abnormalities of lipid metabolism and the lipidoses. Clin Rheum Dis 1:163

Sasou S, Nakamura SI, Habano W, Takano T (1996) True malignant histiocytosis developed during chemotherapy for mediastinal immature teratoma. Hum Pathol 27:1099–1103

Sato T, Terui T, Kogawa K, Nagaoka Y, Sato Y, Iyama S, Takada K, Hagiwara S et al (2002) A case of true malignant histiocytosis: identification of histiocytic origin with use of immunohistochemical and immunocytogenetic methods. Ann Hematol 81:285–288

Shen XZ, Liu F, Ni RJ, Wang BY (2013) Primary histiocytic sarcoma of the stomach: a case report with imaging findings. World J Gastroenterol 19:422–425

Soria C, Orradre JL, Garcia-Almagro D, Martinez B, Algara P, Piris MA (1992) True histiocytic lymphoma (monocytic sarcoma). Am J Dermatopathol 14:511–517

Soslow RA, Davis RE, Warnke RA, Cleary ML, Kamel OW (1996) True histiocytic lymphoma following therapy for lymphoblastic neoplasms. Blood 87:5207–5212

Sroa N, Zirwas MJ, Bechtel M (2010) Multicentric reticulohistiocytosis: a case report and review of the literature. Cutis 85:153–155

Stoecker MM, Wang E (2013) Histiocytic/dendritic cell transformation of B-cell neoplasms: pathologic evidence of lineage conversion in differentiated hematolymphoid malignancies. Arch Pathol Lab Med 137:865–870

Suenaga M, Matsushita K, Kawamata N, Kukita T, Hamakawa Y, Gejima K, Onodera R et al (2006) True malignant histiocytosis with trisomy 9 following primary mediastinal germ cell tumor. Acta Haematol 116:62–66

Sun W, Nordberg ML, Fowler MR (2003) Histiocytic sarcoma involving the central nervous system: clinical, immunohistochemical, and molecular genetic studies of a case with review of the literature. Am J Surg Pathol 27:258–265

Sundersingh S, Majhi U, Seshadhri RA, Tenali GS (2012) Multifocal histiocytic sarcoma of the gastrointestinal tract. Indian J Pathol Microbiol 55:233–235

Takahashi E, Nakamura S (2013) Histiocytic sarcoma – an updated literature review based on the 2008 WHO classification. J Clin Exp Hematop 53:1–8

Targett JH (1897) Giant cell tumors of the integuments. Arch Dermatol 113:330

Tauber AI (2003) Metchnikoff and the phagocytosis theory. Nat Rev 4:897–901

Taunton OD, Yeshurun D, Jarratt M (1978) Progressive nodular histiocytoma. Arch Dermatol 114:1505–1508

Torres A, Bollozos GD (1971) Primary reticulum cell sarcoma of liver. Cancer 27:1489–1492

van der Valk P, te Velde J, Jansen J, Ruiter DJ, Spaander PJ, Cornelisse CJ, Meijer CJLM (1981) Malignant lymphoma of true histiocytic origin: histiocytic sarcoma. Virchows Arch Pathol Anat 391:249–265

Venkataraman G, McClain KL, Pittaluga S, Rao VK, Jaffe ES (2010) Development of disseminated histiocyte sarcoma in a patient with autoimmune lymphoproliferative syndrome and associated Rosai-Dorfman disease. Am J Surg Pathol 34:589–594

Vos JA, Abbondanzo SL, Barekman CL, Andriko JW, Miettinen M, Aguilera NS (2005) Histiocytic sarcoma: a study of five cases including the histiocyte marker CD163. Mod Pathol 18:693–704

Wakahashi K, Shimoyama M, Katayama Y, Minagawa K, Yoshida K, Sasaki R, Nakayama S et al (2010) Histiocytic sarcoma with two immunohistopathologically distinct populations. Int J Hematol 92:642–646

Wang E, Hutchinson CB, Huang Q, Sebastian S, Rehder C, Kanaly A, Moore J, Datto M (2010) Histiocytic sarcoma arising in indolent small B-cell lymphoma: report of two cases with molecular/genetic evidence suggestive of a 'transdifferentiation' during the clonal evolution. Leuk Lymphoma 51:802–812

Wang J, Li T, Chen H, Liu Q (2012) A case of primary central nervous system histiocytic sarcoma. Clin Neurol Neurosurg 114:1074–1076

Wu W, Tanrivermis Sayit A, Vinters HV, Pope W, Mirsadraei L, Said J (2013) Primary central nervous system histiocytic sarcoma presenting as a postradiation sarcoma: case report and literature review. Hum Pathol 44:1177–1183

Yaman E, Gonul II, Buyukberber S, Ozturk B, Akyrek N, Coskun U, Kaya AO, Yildiz R et al (2009) Metastatic fibroblastic reticulum sarcoma of the liver: pathological and PET-CT evaluation. Pathology 41:289–292

Yang HJ, Ding YQ, Deng YJ (2009) Multicentric reticulohistiocytosis with lungs and liver involved. Clin Exp Dermatol 34:183–185

Zelger BW, Staudacher C, Orchard G, Wilson-Jones E, Burgdorf WH (1995) Solitary and generalized variants of spindle cell xanthogranuloma (progressive nodular histiocytosis). Histopathology 27:11–19

Zelger BW, Sidoroff A, Orchard G, Cerio R (1996) Non-Langerhans cell histiocytoses. A new unifying concept. Am J Dermatopathol 18:490–504

Tumors of the Dendritic Cell System 102

Contents

Abstract

The hepatobiliary tract can be involved by members of the dendritic cell tumor group. Follicular dendritic cell tumor/sarcoma is a rare neoplasm of young and middle-aged individuals, presenting with nodal and extranodal manifestations. The term follicular dendritic cell sarcoma (FDCS) is now proposed by the WHO classification. The main feature of FDCS is a proliferation of rather large fusiform or spindled cells arranged in the form of fascicular, storiform, or whorled patterns. These cells consistently express CD21, CD35, CAN-42, and variably S-100 protein and epithelial membrane antigen. FDCS develops in the liver as sometimes large mass lesions that can express EBV markers. A variant of FDCS displays inflammatory pseudotumor-like features. A second neoplasm of dendritic cells that can occur in the hepatobiliary tract is interdigitating dendritic cell sarcoma, a tumor that usually develops in lymph nodes of elderly subjects. It is characterized by a proliferation of CD1a-negative histiocyte-like cells with nuclear pleomorphism and expression of CD68 and S-100 protein. The liver may be the site of reticulum cell-related tumors (fibroblastic reticular cells tumors).

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_102

Follicular Dendritic Cell Tumor/ Follicular Dendritic Cell Sarcoma of the Liver

ICD-O code 9758/3

Introduction

Follicular dendritic cell tumor (FDCT) is an uncommon neoplastic lesion usually developing in young to middle-aged individuals. According to the WHO classification of tumors, the former follicular dendritic cell tumor (FDCT) is now classified as follicular dendritic cell sarcoma (FDCS) and is defined as a neoplastic proliferation of spindled to ovoid cells showing morphologic and immunophenotypic features of follicular dendritic cells. FDCS exhibits both, lymphonodal and extranodal, manifestation patterns (review: Kairouz et al. 2007). After the initial description (Monda et al. 1986), only about 50 cases of extranodal FDCT/FDCS have been reported so far (Perez-Ordonez and Rosai 1998; Tu et al. 2007; Zhang et al. 2008). The proliferating target cell is an ovoid to spindle cell sharing an immunophenotype with follicular dendritic cells/ FDC (Chan 1997; Perez-Ordonez and Rosai 1998; Tu et al. 2007). CD21 (C3d receptor; positive in 93 % of cases) and CD35 (C3b receptor; positive in 89 % of cases) are the most commonly used FDC tumor markers. Based on literature data, other markers employed comprise R4/23 (63 %), Ki-M4, CAN.42, CD68, EMA (41 %), desmoplakin, CD45 (21 %), S-100 protein (31 %), and clusterin. The cells of FDCS are consistently negative for CD1a and cytokeratins (reviewed by Martins et al. 2011). Some novel FDC markers have recently been identified and may be useful for the diagnosis of FDCS, including podoplanin/ D2-40 (Yu et al. 2007; Xie et al. 2008; Marsee et al. 2009), Glut-1 and claudin-1 (Jorge-Buys et al. 2008), gamma-synuclein (Zhang et al. 2011), and CXCL13 (Vermi et al. 2008).

FDCT makes part of the so-called accessory cell tumors. The accessory or dendritic cell (DC) compartment comprises (1) the follicular dendritic cells (FDC) of the germinal centers; (2) the Langerhans cells (LC) of the skin and certain mucosas; (3) the interstitial dendritic cells (IDC), LC-like cells of parenchymal organs; (4) veiled or indeterminate cells, derived from IDC or LC and migrating to lymphoid tissues subsequent to antigen contact; and (5) interdigitating dendritic cells (IDC) located in the T-cell zone of lymph nodes. Tumors derived from these cells types (accessory cell tumors) have recently been discussed together with tumors of histiocytes. These neoplasms comprise histiocytic sarcoma, tumors, and sarcoma of Langerhans cell type, interdigitating dendritic cell tumor/sarcoma, follicular dendritic cell tumor/sarcoma, and eventually further lesions (Pileri et al. 2002). The characteristic features of FDCT include a growth of rather large neoplastic cells of mostly fusiform or spindle shape, arranged in the form of fascicular, storiform, or whorled patterns, exhibiting indistinct borders and an abundant and markedly eosinophilic cytoplasm, nuclei being ovoid, with a finely dispersed chromatin, but a prominent nucleolus. Binucleate or even multinuclear cells occur. Ultrastructurally, the cells lack Birbeck granules, but show desmosomes. At electron microscopy, the indistinct cell borders manifest as villosities at the cell surface, the convoluted interdigitating cell processes being joined by desmosomes. The target cells consistently express FDC markers, most frequently CD21, CD35, and CAN-42, whereas S-100 protein and CD68 were more variably expressed. Positivity for EMA was observed in slightly less than 50 % (Pileri et al. 2002).

Hepatobiliary Follicular Dendritic Cell Tumor/Follicular Dendritic Cell Sarcoma

FDCSs have been reported to occur in the liver, and part of these cases were initially classified as FDCTs of the previous nomenclature or as inflammatory pseudotumors. In one patient, a recurrent tumor after resection of an "inflammatory pseudotumor" revealed the morphologic, ultrastructural, and immunohistochemical features of FDCS. Interestingly, ISH for EBV-encoded RNA was positive in the tumor cells, and the cells

showed identical episomal clonal EBV on Southern blot analysis, indicating a clonal proliferation of EBV-positive neoplastic FDC, a cell type known to express the EBV receptor CD21 (Shek et al. 1996). Few similar cases of EBV-related intra-abdominal/hepatic FDCT were reported (Selves et al. 1996; Shek et al. 1998; Arber et al. 1998; Chan et al. 2001; Cheuk et al. 2001; Bai et al. 2006). PCR studies on two liver tumors revealed a characteristic 30-bp deletion of the EBV latent membrane protein-1 (LMP-1) gene, corresponding to the B95-8 sequence (Chen et al. 2001). Apart from hepatic EBV-FDCS, few FDCS primary to the liver did not show EBV expression or were not tested (Torres et al. 2005; Wang et al. 2006; Tu et al. 2007; Zhang et al. 2008; Liu et al. 2009; Xu et al. 2009; Tsunemine et al. 2010; Wang et al. 2010; Martins et al. 2011; Shrinagare et al. 2011). Other such cases include intra-abdominal FDCS with liver metastases (Li et al. 2005). Hepatic FDCS are usually single neoplasms not associated with other neoplastic disorders. In one patient, however, FDCS of the liver was preceded by a history of hyaline-vascular type of Castleman's disease (Fritzsche et al. 2010).

Epidemiology

The number of FDCT primary to the liver is small and amounts to about 20 cases. Both FDCT and follicular dendritic cell sarcoma have been employed to denote these neoplasms (Khalid and Folman 2005; Torres et al. 2005; Wang et al. 2006, 2010; Yuan et al. 2007; De Pas et al. 2008; Granados et al. 2008; Zhang et al. 2008, 2010; Liu et al. 2009; Xu et al. 2009; Fritzsche et al. 2010; Li et al. 2010; Tsunemine et al. 2010; Yin et al. 2010; Martins et al. 2011; Shinagare et al. 2011). In a series of 13 published cases reported in 2011 (Martins et al. 2011), the majority of patients were female (11 F, 2 M), with an age range at diagnosis of 19–82 years. However, this review also contained nine cases of tumors that are now classified as EBV-related FDCT (see above). In the group of EBV-associated inflammatory pseudotumor-like lesions, female predominance is known (see the respective chapter).

Clinical Features

Hepatic FDCS presents as a mass lesion causing abdominal pain and distension, malaise, fever, weight loss, and eventually anemia and jaundice. Serum AFP, carcinoembryonic antigen, and CA19-9 levels are within normal limits (Martins et al. 2011). Hepatic EBV-FDCS may be associated with polyclonal gammopathy and cutaneous leukocytoclastic vasculitis with purpura (Chen et al. 2001). The tumors develop in a previously normal liver. In one patient, hepatic FDCS developed in a 76-year-old woman with a history of hyaline-vascular type of Castleman's disease (Fritzsche et al. 2010).

Biology of Disease

FDCT are regarded as variably aggressive lesions considered as intermediate-grade malignancy. Extrahepatic tumors revealed overall rates of recurrence, metastasis, and mortality of 43 %, 24 %, and 17 %, respectively (Chan et al. 1997). A 78-year-old female patient treated with transcatheter arterial chemoembolization/TACE was alive 27 months after diagnosis with residual hepatic tumors favorably controlled by repeated TACE (Tsunemine et al. 2010).

Pathology

Macroscopy

Macroscopically, the tumors were usually solitary, circumscribed, and fleshy to rubbery lesions with a pushing border, ranging from 3.5 to 22 cm in diameter, with hemorrhage and necrosis.

Histopathology

In typical cases, histology revealed FDC-like spindle cells (sometimes in a fascicular pattern) in a tissue background with abundant

lymphocytes and plasma cells, the tumor cells sometimes forming syncytia-like structures between spindle cells and plump cells (Shek et al. 1998; Cheuk et al. 2001). Large and atypical, pleomorphic cells of polygonal shape can occur as well. Individual cells have a slightly eosinophilic and often fibrillary cytoplasm. The nuclei of these cells are ovoid to irregular shaped, with either small or prominent amphophilic or eosinophilic nucleoli and "empty" nucleoplasm and a delicate violaceous nuclear membrane, but usually with low or minimal mitotic activity. Part of the tumor cells are binucleated, the nuclei usually having enlarged nucleoli. The tumors also contain few multinucleated cells. These cells may resemble Reed-Sternberg cells. The spindled cells form diffuse sheets, fascicles, whorls, and sometimes a vaguely storiform pattern. The tumor tissue may be traversed by dense fibrous and in part sclerotic septa with areas of calcification (Martins et al. 2011). Focal coagulative necroses and small hemorrhages are noted. Characteristically, many tumors show sprinkling across the entire tissue of small lymphocytes, sometimes with perivascular cuffing and rarely dense and mimicking lymphoma.

Immunohistochemistry

Immunohistochemically, FDCT express FDC markers, including CD21 (C3d receptor; positive in 93 % of cases), CD35 (C3b receptor; positive in 89 %), Ki-M4, and CAN.42. The complement receptors CD21 and CD35, which recognize activated products of complements C3 and C4, are predominantly expressed on B lymphocytes and FDCs (review: Roozendaal and Carroll 2007). Other well-known markers expressed in variable rates comprise EMA (around 40 %), vimentin (around 60 %), HLA-DR, desmoplakin, and podoplanin. Podoplanin (D2-40) is a highly effective marker for FDC and FDCT (Xie et al. 2008; Marsee et al. 2009; Zhang et al. 2010). A comparative study revealed that podoplanin/D2-40 highlighted more FDC meshworks than CD21 in Castleman's disease, follicular lymphoma, nodular lymphocyte predominance Hodgkin's lymphoma, and residual reactive germinal centers in a variety of conditions (Xie et al. 2008). The homeostatic chemokine CXCL13, which is preferentially produced in B-follicles and attracts B lymphocytes that express the receptor CXCR5, is a marker for FDC and FDCT (Vermi et al. 2008). Expression of clusterin distinguishes FDCT from other dendritic cell neoplasms (Grogg et al. 2004). Gamma-synuclein is a novel marker for reactive FDC and cells of FDCT (Zhang et al. 2011). FDCT nuclei are reactive for p53 protein (Li et al. 2010). In one study all cases were EBV-RNA positive in ISH, whereas EBV-LMP (latent membrane protein-1) expression was more variable (Cheuk et al. 2001).

Inflammatory Pseudotumor-Like FDCT

Some authors proposed that inflammatory pseudotumor-like FDCT(IP-FDCT) is a variant of FDCT differing from conventional FDCT in several respects, including marked female preponderance, frequent presence of systemic symptoms, indolent behavior, prominent lymphocyte infiltration, and consistent association with EBV (Cheuk et al. 2001; Kiryu et al. 2009). In contrast to some inflammatory myofibroblastic tumors and part of inflammatory pseudotumors, these distinct lesions do not appear to express anaplastic lymphoma kinase/ALK (Chan et al. 2001). IP-FDCT has also been detected in the liver (Granados et al. 2008). In a study on 11 patients with inflammatory pseudotumor-like FDCT observed in 10 female and 1 male patients (age range: 19–61 years), seven lesions were documented in the liver (Cheuk et al. 2001). Hepatic IP-FDCS has been documented in another report (An et al. 2009). Pathologically, IP-FDCTs are characterized by loosely aggregated or dispersed spindle cells or ovoid cells intimately admixed with abundant lymphocytes (sometimes with lymphoid follicles) and plasma cells. The spindle cells have a pale to faintly eosinophilic cytoplasm with instinct cell borders. Nuclei are elongated or oval, with a vesicular chromatin and only minor atypia. The larger cells usually have an ovoid shape or are stellate shaped. Mitotic figures are rare. Some

tumors may contain Reed-Sternberg cell-like cells. All tumors show positive staining for at least one of the FDC markers, CD21/CD35, CD23, and CAN.42, and all tumor cells showed strong nuclear in situ labeling for EBER (Cheuk et al. 2001).

What Are Follicular Dendritic Cells (FDC)?

The development, proliferation, activation, and survival of B lymphocytes critically depend on the interaction with specific mesenchymal cells which are generally termed stromal cells and are operational in primary lymphoid organs already (Kincade 1991). In this network, dendritic cells are the highly specialized antigen-presenting cells of the immune system that play a central role in the regulation of innate and adaptive immune responses. The FDC is a unique stromal cell type operational in the complex cell interaction network in secondary lymphoid organs, and specifically in the lymph follicle (follicular stromal cells), and exhibits a distinct morphology with cell processes joined by desmosomes. Dendritic cells with a lymphocyte-stimulating activity differentiate from a lineage of CD133 precursor cells, i.e., primitive myeloid progenitor cells (Bonetti et al. 2011). During the differentiation process, dendritic cells express dendritic cell-specific transmembrane protein (DC-STAMP). During dendritic cell maturation, DC-STAMP relocalizes toward the Golgi apparatus, and DC-STAMP interacts with a partner in the endoplasmic reticulum, LUMAN (CREB3 or LZIP), and endoplasmic reticulum-resident transcription factor. LUMAN is activated in a process called regulated intramembrane proteolysis (RIP), which involves translocation to the Golgi apparatus and subsequent proteolytic cleavage. This proteolytically activated form of LUMAN is then translocated to the nucleus. The LUMAN/DC-STAMP is a regulatory circuit of dendritic cells (Eleveld-Trancikova et al. 2010). FDCs mostly occur in nodal and extranodal lymph follicles, but they can develop ectopically, e.g., in autoimmune reactions, even though their precursor cell has not yet been identified (Imai and Yamakawa 1996; Kasajima et al. 1997; Van Nierop and de Groot 2002).

Dendritic cell shaves the distinct ability to cross-present exogenous antigens in association with major histocompatibility complex (MHC) class I to CD8+ T cells, whereby an immune-related GTPase called Igtp (Irgh3), located to the membranes of endoplasmic reticulum and lipid bodies, plays a significant role (Bougnères et al. 2009). Generally, dendritic antigen-presenting cells possess distinctive mechanisms to sense pathogen-derived and other foreign molecules such as lipopolysaccharides, non-self nucleic acids, and an enormous host of environmental antigens to trigger defense reactions. These sensors include the RIG-l-like helicase (RLH) family that specifically recognizes viral RNA, as well as the cytoplasmic, nucleotide-binding oligomerization domain (NOD)-like receptors and Toll-like receptors (TLR) pathways. Plasmacytoid dendritic cells utilize TLR9 to detect pathogen-associated DNA and trigger cytokines to stimulate immune cells. This response involves AIM2 (absent in melanoma 2) and an endoplasmic reticulum-associated protein, STING (stimulator of interferon genes (review: Barber 2011). Functionally, FDC are non-phagocytic but have the ability to trap and retain antigens for longer time periods in the form of immune complexes, thus acting as antigen depots during germinal center response. They express molecules involved in the proliferation and differentiation of lymphocytes, especially B cells, and in cell adhesion. FDCs appear to play a pivotal role in the germinal center response associated with the cellular events of anamnestic humoral immune responses, in particular the selection of memory B lymphocytes: FDC presents native antigens to potential memory cells, of which only B lymphocytes with high-affinity B-cell receptors can bind. In this context, the primary function of FDC seems to prevent apoptosis and support proliferation of germinal center B cells (via two newly identified FDC-signaling molecules; Li and Choi 2002), hence playing a central role in the organization of the follicle structure and supporting survival of long-lived

memory B cells (Cyster et al. 2000), whereas activated T cells induce the differentiation of germinal center B cells (Liu and Arpin 1997). The function of dendritic cells critically depends on Ca2+ signaling, which directs the dendritic cell responses to diverse antigens, including Toll-like receptor ligands, intact bacteria and their products, and microbial toxins. Calcium signaling is involved in dendritic cell activation, differentiation, migration, and the construction of immunological synapses with T lymphocytes. The dendritic cell instrumentarium for Ca2+ handling consists of calcium trafficking in the endoplasmic reticulum, the plasma membrane, and the inner mitochondrial membrane, where Ca2+ pumps, Ca2+/Na1+ antiports, and Ca2+-permeable channels or uniporters are expressed (review: Shumilina et al. 2011).

The molecular basis for the FDC-B cell interaction remains poorly characterized, but several FDC products have recently been identified, including a splicing isoform of the complement receptor CD21 (Liu et al. 1997); a transmembrane protein involved in FDC-B cell interaction (8D6; Zhang et al. 2001); chemokine B lymphocyte chemoattractant (BLC; CXCL13; Gunn et al. 1998), which is a strong FDC chemoattractant for B cells; a distinct serpin which may protect essential proteins from degradation (Mueller et al. 1997); and the secreted protein, FDC-SP, suggested to act upon B cells (Marshall et al. 2002).

Interdigitating Dendritic Cell Sarcoma

ICD-O code 9757/3

Introduction

Interdigitating dendritic cell sarcoma (IDCS; interdigitating reticulum cell (IRC) tumor, IRCT) is a rare neoplasm arising from the antigen-presenting interdigitating dendritic cell (Nakamura et al. 1988; review: Fonseca et al. 1998). IDTS or interdigitating dendritic cell tumors have been classified as group IV, interdigitating dendritic cell tumor/sarcoma in the approach from the International Lymphoma Study Group (Pileri et al. 2002). In exceptional cases, IDCS may overlap with true histiocytic sarcoma (Porter et al. 2004).

IDCS usually develops in peripheral lymph nodes of patients in the sixth to eighth decades. Extranodal presentations, including the skin, soft tissues, parotid gland, tonsil, lung, duodenum, small intestine, spleen, testis, and liver, have been reported. Clinically, patients usually present with an asymptomatic mass, but systemic symptoms and signs, such as fever, fatigue, and night sweats, may occur. IDCS is an aggressive neoplasm. According to a SEER analysis, only 55 % of IDCS presented with localized disease at diagnosis. Overall survival time was significantly worse than those for follicular dendritic cell sarcoma, with a median survival time of 35 months (Perkins and Shinohara 2013).

Distinctive histologic features are proliferation of histiocyte-like cells with nuclear polymorphism and occasionally multinucleated elements, in lymph nodes involving the paracortical area sparing the B lymphocyte compartments. The neoplastic proliferations commonly form fascicles, storiform patterns, or whorls of spindled to ovoid cells, and some tumors show nests or sheets of round cells. The cytoplasm of the neoplastic cells is pale or slightly eosinophilic and the nuclei are ovoid or spindle shaped, with no or only minor atypias. The mitotic rate is usually low or very low, less than 5/10 HPF (Liu et al. 1998). Sinusal infiltration, fibrosis, and dense infiltrates of eosinophils and plasma cells are frequently noted. The neoplastic cells lack Birbeck granules (Nakamura et al. 1988, 1994). At EM examination, distinct intracytoplasmic membrane complexes have been detected, representing profiles related to microtubuloreticular complexes (Nakamura et al. 1989). In series of IDCS, all were immunoreactive for S-100 protein, CD68, lysozyme, and vimentin; three-fourths were positive for CD45. The tumor cells are usually positive for fascin. Negative results were obtained for CD1a, langerin, CD3, CD20, CD21, CD30, actin, and cytokeratin (Nakamura et al. 1988; Gaertner et al. 2001).

Interdigitating Dendritic Cell Sarcoma of the Liver

IDCS is a very rare neoplasm in the liver (Figs. 1 and 2). IDCS has been observed as primary tumors in the liver and lung in the same patient (Radovic et al. 2012). Apart from primary hepatic IDCS, extensive liver infiltration can occur in the setting of intra-abdominal and/or lymphonodal IDCS (Turner et al. 1984; Chan and Zaatari 1986; Weiss et al. 1990; Miettinen et al. 1993; Olnes et al. 2002).

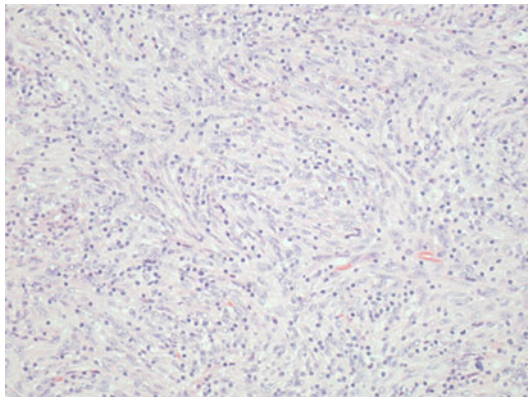

Fig. 1 Interdigitating dendritic cell sarcoma of the liver. The neoplasm is characterized by fascicles of spindle cells with a sparse lymphocytic infiltration (hematoxylin and eosin stain)

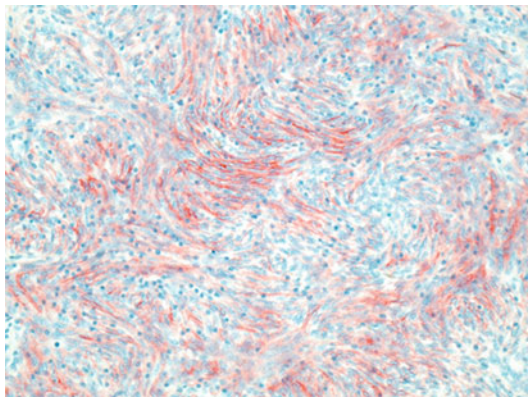

Fig. 2 Interdigitating dendritic cell sarcoma of the liver with reactivity of neoplastic spindle cells for S100 protein (S100 protein immunostain)

Overlap IDCS

Histiocytic sarcoma can show signs of interdigitating cell differentiation, representing an overlap lesion or a hybrid sarcoma (Yang et al. 2010). True histiocytic sarcoma with interdigitating cell differentiation was found in the liver and spleen of a 3-month-old boy presenting with hepatosplenomegaly and abdominal distention. In a liver biopsy, liver involvement was predominantly sinusoidal with some cellular nodules in portal tracts and invasion of terminal/central veins. The ovoid to elongated and in part large neoplastic cells showed large vesicular nuclei. Some of the nuclei were bean shaped, while others were indented. Many nuclei exhibited a large basophilic nucleolus. In EM pictures, no Birbeck granules were detectable. Immunohistochemically, the tumor cells were reactive for CD68, S100 protein, lysozyme, CD45, CD43, and vimentin. No reactivity for CD1a or CD21 was found (Porter et al. 2004).

Fibroblastic Reticular Cell Tumors (Reticulum Cell-Related Tumor, Including Fibroblastic Reticulum Cell (FBRC)-Related Neoplasms and Cytokeratin-Positive Interstitial Cell (CIRC) Neoplasms)

ICD-O code 9759/3

Introduction

Together with follicular dendritic cells and interdigitating reticulum cells, fibroblastic reticulum cells (FBRC) form a group of accessory cells of peripheral lymphoid tissues. FBRC are located in the parafollicular areas and the deep cortex of lymph nodes, where they are associated with the network ensheathing the postcapillary venules and nodal architectural structures, such as cords, channels, corridors, and conduits (Tykocinski et al. 1983; Gloghini and Carbone 1993; Gretz et al. 1997). FBRC are immunoreactive for vimentin, SMA, and desmin, suggesting a

myofibroblastic cell lineage (Tykocinski et al. 1983; Toccanier-Pelte et al. 1987). FBRC are thought to produce reticular/reticulin fibers and build a reticular framework in their biologic niche.

In contrast to paracortical dendritic cells that are in close contact with FBRC within the cellular framework of T-cell nodal areas, FBRC are negative for the 55 kDa actin-bundling protein, fascin (Hiroi et al. 2004). FBRC contain bundle filaments and dense bodies (Hiroi et al. 2004). Later, a subpopulation of cells was identified in the extrafollicular regions of the lymph nodes, spleen, and tonsils, showing immunoreactivity for cytokeratins 8 and 18 (cytokeratin-positive reticulum cells, CIRC; Franke and Moll 1987). CIRC already occur in fetal lymphoid organs (Doglioni et al. 1990). These cells can co-express smooth muscle actin (SMA) and desmin (more frequently SMA; Doglioni et al. 1990; Gould et al. 1995). CIRC are observed in both the outer and inner cortex of lymph nodes, as well as along the blood vessels in the node medulla (Gould et al. 1995). They have cytoplasmic processes connected by desmosome-like junctions and contain intermediate filaments, tonofilaments, and light bundles (Franke and Moll 1987; Doglioni et al. 1990). The cellular origin and the exact functions of FBRC and CIRC are not yet known; a mesenchymal stem cell has been taken into consideration. Apart from FBRC and follicular dendritic cells, secondary lymphoid organs show a third stromal cell that has recently been identified, the marginal reticular cell (Katakai 2012).

FBRC and CIRC Tumors

Neoplasms derived from FBRC or CIRC are very rare lesions. Reticulum cell neoplasms of the FBRC type have been characterized, and these tumors in fact share many features with FBRC (Andriko et al. 1998; Martel et al. 2003; Suarez-Vilela et al. 2012). The neoplasms may occur admixed with follicular dendritic cells (Jones et al. 2001). Cytokeratin-positive interstitial cell neoplasms (CIRC tumors) have also been characterized, mainly occurring in lymph nodes (Gould et al. 1990; Chan et al. 2000; Schuerfeld et al. 2003; Dong et al. 2008), but do not yet make part of the current classifications for histiocytic tumors, such as the ILSG classification. The tumors consist of spindle cells with elongated to round nuclei and prominent nucleoli, and these cells are arranged in a diffuse fascicular and vaguely whorled growth pattern. The mitotic activity is rather low, but necrosis may be seen. The neoplastic cells are immunoreactive for vimentin, desmin, S100 (inconstant), and lysozyme and focally for CD68 (inconstant); cytokeratins 7, 8, and 18; and AE1 and CK-pool. Ultrastructurally, the cells share the features known for normal CIRC (Chan et al. 2000; Schuerfeld et al. 2003). A progression of a FBRC tumor to cytokeratin-positive interstitial reticulum cell (CIRC) sarcoma has been reported (Lucioni et al. 2003), suggesting a common lineage of these two cell types.

FBRC Tumors of the Liver

Fibroblastic reticulum cell sarcoma metastatic to the liver has been reported (Yaman et al. 2009). In the older literature, several reports described so-called reticulum cell sarcoma of the liver (Torres and Bollozos 1971). Reticulum cells as they were classified in these times were slender and fusiform cells that were in close association with reticulum fibers and thought to be the producers of these fibers. Based on these reports, it is very difficult or even impossible to judge to which cell lineage the "reticulum cells" making up the neoplasms belonged.

References

An XJ, Zhang ZX, Shi QL, Wu B, Ma J, Zhou HB, Ma HH (2009) Hepatic inflammatory pseudotumor like follicular dendritic cell tumor. Report of one case and review of literature (in Chinese). J Diagn Concepts Pract 8:63–66

Andriko JAW, Kaldjian EP, Tsokos M, Abbondanzo SL, Jaffe ES (1998) Reticulum cell neoplasms of lymph

nodes: a clinicopathologic study of 111 cases with recognition of a new subtype derived from fibroblastic reticular cells. Am J Surg Pathol 22:1048–1058
Arber DA, Weiss LM, Chang KL (1998) Detection of Epstein-Barr virus in inflammatory pseudotumor. Semin Diagn Pathol 15:155–160
Bai LY, Kwang WK, Chiang IP, Chen PM (2006) Follicular dendritic cell tumor of the liver associated with Epstein-Barr virus. Jpn J Clin Oncol 36:249–253
Barber GN (2011) Innate immune DNA sensing pathways: STING, AIMII and the regulation of interferon production and inflammatory responses. Curr Opin Immunol 23:10–20
Bonetti MI, Pieri L, Domenici L, Urbani S, Romano G, Aldinucci A, Ballerini C, Monici M, Saccardi R et al (2011) Dendritic cells with lymphocyte-stimulating activity differentiate from human CD133 positive precursors. Blood 117:3983–3995
Bougnères L, Helft J, Tiwari S, Vargas P, Chang BH, Chan L, Campisi L, Lauvau G, Hugues S et al (2009) A role for lipid bodies in the cross-presentation of phagocytosed antigens by MHC class II in dendritic cells. Immunity 31:232–244
Chan JK (1997) Proliferative lesions of follicular dendritic cells: an overview, including a detailed account of follicular cell sarcoma, a neoplasm with many faces and uncommon etiologic associations. Adv Anat Pathol 4:387–411
Chan WC, Zaatari G (1986) Lymph node interdigitating reticulum cell sarcoma. Am J Clin Pathol 85:739–744
Chan et al. (1997) http://www.ncbi.nlm.nih.gov/pubmed/9010103
Chan AC, Serrano-Olmo J, Erlandson RA, Rosai J (2000) Cytokeratin-positive malignant tumors with reticulum cell morphology: a subtype of fibroblastic reticulum cell neoplasm? Am J Surg Pathol 24:107–116
Chan JK, Cheuk W, Shimizu M (2001) Anaplastic lymphoma kinase expression in inflammatory pseudotumors. Am J Surg Pathol 25:761–768
Chen TC, Kuo TT, Ng KF (2001) Follicular dendritic cell tumor of the liver: a clinicopathologic and Epstein-Barr virus study of two cases. Mod Pathol 14:354–360
Cheuk W, Chan JK, Shek TW, Chang JH, Tsou MH, Yuen NW, Ng WF, Chan AC, Prat J (2001) Inflammatory pseudotumor-like follicular dendritic cell tumor: a distinctive low-grade malignant intra-abdominal neoplasm with consistent Epstein-Barr virus association. Am J Surg Pathol 25:721–731
Cyster JG, Ansel KM, Reif K, Ekland EH, Hyman PL, Tang HL, Luther SA, Ngo VN (2000) Follicular stromal cells and lymphocyte homing to follicles. Immunol Rev 176:181–193
De Pas T, Spitaleri G, Pruneri G, Curigliano G, Noberasco C, Luini A, Andreoni B, Testori A et al (2008) Dendritic cell sarcoma: an analytic overview of the literature and presentation of original five cases. Crit Rev Oncol Hematol 65:1–7
Doglioni C, Dell'Orto P, Zanetti G, Iuzzolino P, Coggi G, Viale G (1990) Cytokeratin-immunoreactive cells of human lymph nodes and spleen in normal and pathological conditions. An immunohistochemical study. Virchows Arch A 416:479–490
Dong YC, Wu B, Sheng Z, Wang JD, Zhou HB, Zhou XJ (2008) Cytokeratin-positive interstitial reticulum cell tumors of lymph nodes: a case report and review of the literature. Chin Med J (Engl) 121:658–663
Eleveld-Trancikova D, Sanecka A, van Hout-Kuijer MA, Looman MW, Hendricks IA, Jansen BJ, Adema GJ (2010) DC-STAMP interacts with ER-resident transcription factor LUMAN which becomes activated during DC maturation. Mol Immunol 47:1963–1973
Fonseca R, Yamakawa M, Nakamura S, van Heerde P, Miettinen M, Shek TW, Myrhe Jensen O et al (1998) Follicular dendritic cell sarcoma and interdigitating reticulum cell sarcoma: a review. Am J Hematol 59:161–167
Franke WW, Moll R (1987) Cytoskeletal components of lymphoid organs. I. Synthesis of cytokeratin 8 and 18 and desmin in subpopulations of extrafollicular reticulum cells of human lymph nodes, tonsils, and spleen. Differentiation 36:145–163
Fritzsche FR, Bode B, Thies S, Donati OF, Schiesser M, Clavien PA, Jochum W (2010) Intrahepatic sarcoma of the follicular dendritic cells (in German). Pathologe 31:153–156
Gaertner EM, Tsokos M, Derringer GA, Neuhauser TS, Arciero C, Andriko JA (2001) Interdigitating dendritic cell sarcoma. A report of our cases and review of the literature. Am J Clin Pathol 115:589–597
Gloghini A, Carbone A (1993) The nonlymphoid microenvironment of reactive follicles and lymphomas of follicular origin as defined by immunohistology on paraffin-embedded tissues. Hum Pathol 24:67–76
Gould VE, Warren WH, Faber LP, Kuhn C, Franke WW (1990) Malignant cells of epithelial phenotype limited to thoracic lymph nodes. Eur J Cancer 26:1121–1126
Gould VE, Bloom KJ, Franke WW, Warren WH, Moll R (1995) Increased numbers of cytokeratin-positive interstitial reticulum cells (CIRC) in reactive, inflammatory and neoplastic lymphadenopathies: hyperplasia or induced expression. Virchows Arch 425:617–629
Granados R, Aramburu JA, Rodriguez JM, Nieto MA (2008) Cytopathology of a primary follicular dendritic cell sarcoma of the liver of the inflammatory pseudotumor-like type. Diagn Cytopathol 36:42–46
Gretz JE, Anderson AO, Shaw S (1997) Cords, channels, corridors and conduits: critical architectural elements facilitating cell interactions in the lymph node cortex. Immunol Rev 156:11–24
Grogg KL, Lae ME, Kurtin PJ, Macon WR (2004) Clusterin expression distinguishes follicular dendritic cell tumors from other dendritic cell neoplasms: report of a novel follicular dendritic cell marker and clinicopathologic data on 12 additional follicular dendritic cell tumors and 6 additional interdigitating dendritic cell tumors. Am J Surg Pathol 28:988–998

Gunn MD, Ngo VN, Ansel KM, Ekland EH, Cyster JG, Williams LT (1998) A B-cell-homing chemokine made in lymphoid follicles activates Burkitt's lymphoma receptor-1. Nature 391:799

Hiroi M, Kuroda N, Toi M, Hayashi Y, Miyazaki E, Naruse K, Enzan H (2004) Fascin-positive dendritic cells and fibroblastic reticulum cells build a framework of T-cell areas in lymph nodes. Virchows Arch 444:158–163

Imai Y, Yamakawa M (1996) Morphology, function and pathology of follicular dendritic cells. Pathol Int 46:807–833

Jones D, Amin M, Ordonez NG, Glassman AB, Hayes KJ, Medeiros LJ (2001) Reticulum cell sarcoma of lymph node with mixed dendritic and fibroblastic features. Mod Pathol 14:1059–1067

Jorge-Buys DL, Torres JE, Ortiz-Hidalgo C (2008) Expression of Glut-1 and claudin-1 in follicular dendritic cell sarcoma. Appl Immunohistochem Mol Morphol 16:204–205

Kairouz et al. (2007) http://www.ncbi.nlm.nih.gov/pubmed/17636477

Kasajima N, Maeda K, Liu D, Matsuda M, Fuyama S, Ito S, Arai S et al (1997) Origin and maturation of follicular dendritic cells (FDCs) – literature review and our preliminary observations on the ontogenesis of human FDCs. Dendritic Cells 7:53–58

Katakai T (2012) Marginal reticular cells: a stromal subset directly descended from the lymphoid tissue organizer. Front Immunol 3:200

Khalid T, Folman R (2005) Symptoms in cancer patients and an unusual tumor. Case 3. Follicular dendritic cell sarcoma. J Clin Oncol 23:9425–9426

Kincade PW (1991) Molecular interactions between stromal cells and B lymphocyte precursors. Semin Immunol 3:379–390

Kiryu S, Takeuchi K, Shibahara J, Uozaki H, Fukayama M, Tanaka H, Maeda E, Akahane M et al (2009) Epstein-Barr virus-positive inflammatory pseudotumour and inflammatory pseudotumour-like follicular dendritic cell tumour. Br J Radiol 82:e67–e71

Li L, Choi YS (2002) Follicular dendritic cell-signaling molecules required for proliferation and differentiation of GC-B cells. Semin Immunol 14:259–266

Li CF, Chuang SS, Lin CN (2005) A 70-year-old man with multiple intra-abdominal masses and liver and spleen metastases. Intra-abdominal follicular dendritic cell sarcoma with liver and spleen metastases. Arch Pathol Lab Med 129:e130–e131

Li L, Shi YH, Guo ZJ, Qiu T, Guo L, Yang HY, Zhang X, Zhao XM, Su Q (2010) Clinicopathological features and prognosis assessment of extranodal follicular dendritic cell sarcoma. World J Gastroenterol 16:2504–2519

Liu YJ, Arpin C (1997) Germinal center development. Immunol Rev 156:111–126

Liu YJ, Xu J, de Bouteiller O, Parham C, Grourd G, Djossou O, de Saint-Vis B, Lebecque S, Banchereau J, Moore K (1997) Follicular dendritic cells specifically express the long CR2/CD21 isoform. J Exp Med 185:165–170

Liu SM, Huang PH, Liu JM (1998) Interdigitating reticulum cell tumor of lymph node: a case report and literature review. Pathol Int 48:974–980

Liu J, Zhang ZT, Li JS, Wang Y (2009) Hepatic follicular dendritic cell sarcoma: a case report and review of the literature (in Chinese). Chin J Pract Surg 29:421–424

Lucioni M, Boveri E, Rosso R, Benazzo M, Necchi V, Danova M, Incardona P, Franco C, Viglio A, Riboni R et al (2003) Lymph node reticulum cell neoplasm with progression into cytokeratin-positive interstitial reticulum cell (CIRC) sarcoma: a case study. Histopathology 43:583–591

Marsee DK, Pinkus GS, Hornick JL (2009) Podoplanin (D2–40) is a highly effective marker of follicular dendritic cells. Appl Immunohistochem Mol Morphol 17:102–107

Marshall AJ, Du Q, Draves KE, Shikishima Y, HayGlass KT, Clark EA (2002) FDC-SP, a novel secreted protein expressed by follicular dendritic cells. J Immunol 169:2381–2389

Martel M, Sarli D, Colecchia M, Coppa J, Romito R, Schiavo M, Mazzaferro V, Rosai J (2003) Fibroblastic reticular cell tumor of the spleen: report of a case and review of the entity. Hum Pathol 34:954–957

Martins PN, Reddy S, Martins AB, Facciuto M (2011) Follicular dendritic cell sarcoma of the liver: unusual presentation of a rare tumor and literature review. Hepatobiliary Pancreat Dis Int 10:443–445

Miettinen M, Fletcher CD, Lasota J (1993) True histiocytic lymphoma of small intestine. Analysis of two S-100 protein-positive cases with features of interdigitating reticulum cell sarcoma. Am J Clin Pathol 100:285–292

Monda L, Warnke R, Rosai J (1986) A primary lymph node malignancy with features suggestive of dendritic reticulum cell differentiation. A report of 4 cases. Am J Pathol 122:562–572

Mueller CG, Ho S, Massacrier C, Lebecque S, Liu YJ (1997) Polymerase chain reaction-based identification of a novel serpin from human dendritic cells. Eur J Immunol 27:3130–3134

Nakamura S, Hara K, Suchi T, Ito M, Ikeda H, Nagahama M, Nakayama A, Nakagawa A, Kaneshima H, Asai J (1988) Interdigitating cell sarcoma. A morphologic, immunohistologic, and enzyme-histochemical study. Cancer 61:562–568

Nakamura S, Suzuki R, Asai J, Suchi T (1989) Observations on the fine structure of interdigitating cell sarcoma. Virchows Arch A Pathol Anat Histopathol 414:121–128

Nakamura S, Koshikawa T, Kitoh K, Nakayama A, Yamakawa M, Imai Y, Ishii K, Fujita M, Suchi T (1994) Interdigitating cell sarcoma: a morphologic and immunologic study of lymph node lesions in four cases. Pathol Int 44:374–386

Olnes MJ, Nicol T, Duncan M, Bohlman M, Erlich R (2002) Interdigitating dendritic cell sarcoma: a rare

malignancy responsive to ABVD chemotherapy. Leuk Lymphoma 43:817–821
Perez-Ordonez B, Rosai J (1998) Follicular dendritic cell tumor: review of the entity. Semin Diagn Pathol 15:144–154
Perkins SM, Shinohara ET (2013) Interdigitating and follicular dendritic cell sarcomas: a SEER analysis. Am J Clin Pathol 36:395–398
Pileri SS, Grogan TM, Harris NL, Banks P, Campo E, Chan JKC, Favera RD et al (2002) Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. Histopathology 41:1–29
Porter DW, Gupte GL, Brown RM, Spray C, English MW, deVille deGoyet J, McKiernan PJ (2004) Histiocytic sarcoma with interdigitating dendritic cell differentiation. J Pediatr Hematol Oncol 26:827–830
Radovic et al. (2012) http://www.ncbi.nlm.nih.gov/pubmed/2298549
Roozendaal R, Carroll MC (2007) Complement receptors CD21 and CD35 in humoral immunity. Immunol Rev 219:157–166
Schuerfeld K, Lazzi S, de Santi MM, Gozzetti A, Leoncini L, Pileri SA (2003) Cytokeratin-positive interstitial cell neoplasm: a case report and classification issues. Histopathology 43:491–494
Selves J, Meggetto F, Brousset P, Voigt JJ, Pradere B, Grasset D, Icart J, Mariame B, Knecht H, Delsol G (1996) Inflammatory pseudotumor of the liver. Evidence for follicular dendritic reticulum cell proliferation associated with clonal Epstein-Barr virus. Am J Surg Pathol 20:747–753
Shek TW, Ho FC, Ng IO, Chan AC, Ma L, Srivastava G (1996) Follicular dendritic cell tumor of the liver. Evidence for an Epstein-Barr virus-related clonal proliferation of follicular dendritic cells. Am J Surg Pathol 20:313–324
Shek TW, Liu CL, Peh WC, Fan ST, Ng IO (1998) Intra-abdominal follicular dendritic cell tumour: a rare tumor in need of recognition. Histopathology 33:465–470
Shrinagare AB, Ramaiya NH, Jagannathan JP, Hornick JL, Swanson RS (2011) Primary follicular dendritic cell sarcoma of liver treated with cyclophosphamide, doxorubicin, vincristine, and prednisone regimen and surgery. J Clin Oncol 29:e849–e851
Shumilina E, Huber SM, Lange F (2011) Ca2+ signaling in the regulation of dendritic cell functions. Am J Physiol Cell Physiol 300:C1205–C1214
Suarez-Vilela D, Izquierdo FM, Mendez-Alvarez JR, Escobar-Stein J (2012) Neoplasms of dendritic cells: related cell origins and diagnostic markers. Fibroblastic reticulum cells and fibroblastic reticulum cell tumors show several immunophenotypic profiles. Hum Pathol 43:1530–1531
Toccanier-Pelte MF, Skalli O, Kapanci Y, Gabbiani G (1987) Characterization of stromal cells with myoid features in lymph nodes and spleen in normal and pathologic conditions. Am J Pathol 129:109–118
Torres A, Bollozos GD (1971) Primary reticulum cell sarcoma of liver. Cancer 27:1489–1492
Torres U, Hawkins WG, Antonescu CR, DeMatteo RP (2005) Hepatic follicular dendritic cell sarcoma without Epstein-Barr virus association. Arch Pathol Lab Med 129:1480–1483
Tsunemine H, Akasawa H, Kusama T, Fujimoto K, Motoyama A, Aozasa K, Kodaka T (2010) Hepatic follicular dendritic cell sarcoma favourably controlled by transcatheter arterial chemoembolization. Intern Med 49:2703–2707
Tu XY, Sheng WQ, Lu HF, Wang J (2007) Clinicopathologic study of intraabdominal extranodal follicular dendritic cell sarcoma (in Chinese). Zhonghua Bing Li Xue Za Zhi 36:660–665
Turner RR, Wood GS, Beckstead JH, Colby TV, Horning SJ, Warnke RA (1984) Histiocytic malignancies. Morphologic, immunologic, and enzymatic heterogeneity. Am J Surg Pathol 8:485–500
Tykocinski M, Schinella RA, Greco A (1983) Fibroblastic reticulum cells in human lymph nodes. An ultrastructural study. Arch Pathol Lab Med 107:418–422
Van Nierop K, de Groot C (2002) Human follicular dendritic cells: function, origin and development. Semin Immunol 14:251–257
Vermi W, Lonardi S, Bosisio D, Uguccioni M, Danelon G, Pileri S, Fletcher C, Sozzani S, Zorzi F et al (2008) Identification of CXCL13 as a new marker for follicular dendritic cell sarcoma. J Pathol 216:356–364
Wang HM, Zhao JM, Li YW, Sun YL, Zhang XD, Gao L, Zhang JH (2006) Hepatic follicular dendritic cell sarcoma: case report and literature review (in Chinese). Chin J Misdiagn 6:4718–4720
Wang H, Su Z, Hu Z, Wen J, Liu B (2010) Follicular dendritic cell sarcoma. a report of six cases and a review of the Chinese literature. Diagn Pathol 5:67–72
Weiss LM, Berry GJ, Dorfman RF, Banks P, Kaiserling E, Curtis J, Rosai J, Warnke RA (1990) Spindle cell neoplasms of lymph nodes of probable reticulum cell lineage. True reticulum cell sarcoma ? Am J Surg Pathol 14:405–414
Xie Q, Chen L, Fu K, Harter J, Young KH, Sunkara J, Novak D, Villanueva-Siles E, Ratech H (2008) Podoplanin (d2–40): a new immunohistochemical marker for reactive follicular dendritic cells and follicular dendritic cell sarcomas. Int J Clin Exp Pathol 1:276–284
Xu YQ, Dai CL, Jia CJ, Yi YF, Shu H, Peng SL, Li XJ, Zhao L (2009) Hepatic follicular dendritic cell sarcoma (in Chinese). Chin Arch Gen Surg 3:151–154
Yaman E, Gonul II, Buyukberber S, Ozturk B, Kyurek N, Coskun U, Kaya AO, Yildiz R et al (2009) Metastatic fibroblastic reticulum cell sarcoma of the liver: pathological and PET-CT evaluation. Pathology 41:289–292
Yang GC, Besancenev CE, Tam W (2010) Histiocytic sarcoma with interdigitating dendritic cell differentiation: a case report with fine needle aspiration cytology and review of the literature. Diagn Cytopathol 38:351–356

Yin WH, Yu GY, Ma Y, Rao HL, Lin SX, Shao CK, Liang Q, Guo N, Chen GQ, Zhou W et al (2010) Follicular dendritic cell sarcoma: a clinicopathologic analysis of ten cases (in Chinese). Zhonghua Bing Li Xue Za Zhi 39:522–527

Yu H, Gibson JA, Pinkus GS, Hornick JL (2007) Podoplanin (D2–40) is a novel marker for follicular dendritic cell tumors. Am J Clin Pathol 128:776–782

Yuan J, Li XH, Lu YL, Song X (2007) Pathologic diagnosis of hepatic inflammatory pseudotumor and inflammatory pseudotumor-like follicular dendritic cell tumor (in Chinese). Linchuang Yu Shiyan Binglixue Zazhi 23:39–42

Zhang X, Li L, Jung J, Xiang S, Hollmann C, Choi YS (2001) The distinct roles of T cell-derived cytokines and a novel follicular dendritic cell-signaling molecule 8D6 in germinal center-B cell differentiation. J Immunol 167:49–56

Zhang ZX, Cheng J, Shi QL, Ma J, Zhou XJ, Zhou HB, Ma HH (2008) Follicular dendritic cell sarcoma: a clinicopathologic study of 8 cases (in Chinese). Zhonghua Bing Li Xue Za Zhi 37:395–399

Zhang SH, Zhou XG, Zheng YY, Zhang YN, Wang P, Xie JL, Jin Y, Zheng XD (2010) Clinicopathological study on the follicular dendritic cell sarcoma (in Chinese). Zhonghua Zhong Liu Za Zhi 32:123–127

Zhang H, Maitta RW, Bhattacharyya PK, Florea AD, Sen F, Wang Q, Ratech H (2011) γ-Synuclein is a promising new marker for staining reactive follicular dendritic cells, follicular dendritic cell sarcoma, Kaposi sarcoma, and benign and malignant vascular tumors. Am J Surg Pathol 35:1857–1865

Histiocytic Syndromes 103

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_103

Abstract

In addition to Langerhans cell histiocytosis and its variants, and histiocytic sarcoma, the hepatobiliary tract can be involved by a wide spectrum of other histiocytic neoplastic and nonneoplastic disorders. Rosai-Dorfman syndrome (sinus histiocytosis with massive lymphadenopathy), a polyclonal monocyte/macrophage/histiocyte disorder which involves various organs and tissue systems, can also present in the liver in the form of an atypical histiocytic infiltration, but hepatobiliary involvement is a rare event. Involvement of the liver, sometimes severe, is known for adult xanthogranulomatous disease, of which Erdheim-Chester disease is a prominent member. The liver frequently participates in various forms of hemophagocytic syndromes, including macrophage activation syndromes. Hemophagocytic lymphohistiocytosis is a heterogeneous group of inherited and acquired disorders of monocyte/macrophage function. The disorders include hereditary forms (familial hemophagocytic histiocytosis) and a broad array of histiocyte/macrophage disorders associated with or induced by autoimmune processes, collagen vascular diseases, tumors, and infections. In the liver, these disorders produce important macrophage accumulation associated with hemophagocytosis and sometimes destruction of small bile ducts, similar to biliary autoimmune diseases. A reactive histiocytosis associated with immunoglobulin-producing lymphomas is crystal-storing histiocytosis.

Introduction

In addition to Langerhans cell histiocytosis and its variants, and histiocytic sarcoma, there are several neoplastic and reactive histiocytic disorders of various etiology and pathogenesis that may involve the hepatobiliary tract (Table 1). Part of the novel immune-dysregulatory disorders, in particular those that are associated with macrophage activation syndromes, have recently been reviewed (Kaufman et al. 2014; Schulert and Grom 2014; Zhang et al. 2014b; de Jesus and Goldbach-Mansdky 2015; Put et al. 2015; Schulert and Grom 2015). These monogenic disorders result in dysregulated cytokine signaling and are therefore termed cytokinopathies (Moghaddas and Masters 2015).

Table 1 Neoplastic and reactive histiocytic disorders not related to Langerhans cell histiocytosis or histiocytic sarcomas

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy)
Adult xanthogranulomatous disease and Erdheim-Chester disease
Weber-Christian disease
Cytophagic histiocytic panniculitis
Hemophagocytic lymphohistiocytosis
Familial hemophagocytic lymphohistiocytosis (Farquhar-Claireaux disease)
Secondary forms of hemophagocytic lymphohistiocytosis
Monogenic immune-dysregulatory disorders associated with macrophage activation syndrome/MAS (hereditary autoimmune disorders associated with MAS)
Monogenic systemic-onset juvenile idiopathic arthritis caused by mutations in LACC1
Inflammasome disorder caused by NLRP3 mutations
Inflammasome disorder caused by NLRC4 mutations
Immune-dysregulatory syndromes with chronic type I interferon signature caused by mutations in TMEM173/STING IFIH1/MDA5 and DDX58/RIG-I
Immune-dysregulatory syndromes caused by mutations in ADA2, TRNT1 and COPA, AP1S3, and TFNRSF11A
Immune-dysregulatory syndromes caused by mutations in PRKDC, STAT3, CTLA4, and PIK3R1
Crystal-storing histiocytosis

Rosai-Dorfman Disease (Sinus Histiocytosis with Massive Lymphadenopathy)

Introduction

Sinus histiocytosis with massive lymphadenopathy (SHML) has first been described in 1965 (Destombes 1965), later established as a distinctive entity (Rosai and Dorfman 1969), and then termed Rosai-Dorfman disease (RDD) or Destombes-Rosai-Dorfman disease. The typical

clinical features of SHML include painless lymphadenopathy with considerable lymph node enlargement, fever, leukocytosis, and polyclonal hyperglobulinemia/gammopathy. The manifestation time of SHML ranges from congenital SHML to very old age, with a mean age of onset of 20.6 years; males outnumber females (Foucar et al. 1990). The disorder most probably represents a reactive rather than a neoplastic process, usually resolving spontaneously, with involvement of a polyclonal monocyte/macrophage/histiocyte proliferation. A familial form of SHML (Faisalabad histiocytosis, H disease) is caused by germline mutations in the SLC29A3 gene (Morgan et al. 2010; Melki et al. 2013).

The condition may present with extranodal manifestations in up to more than 40 % of the patients (reviews: Veinot et al. 1998; Esquivel et al. 1999; Gaitonde 2007; Haroche and Abla 2015). A detailed list of extranodal manifestations is found in the review of Foucar and coworkers (Foucar et al. 1990). In more detail, lymph node involvement alone is found in 57 % of patients, 15 % present with extranodal disease only, and in 28 % of patients, both nodal and extranodal sites are involved. The most common extranodal sites are the skin and the upper respiratory tract, each involved in approximately 11 % of the cases (Foucar et al. 1990). In a study of 423 examples of SHML, the most common sites of extranodal manifestations were the skin, upper respiratory tract, and bone. In general, prognosis had been found to correlate both with the number of nodal groups and with the number of extranodal systems involved by SHML, the prognosis being worse in case of extranodal disease (Foucar et al. 1990). The histologic features of SHML in extranodal sites are, at least in principle, similar to those seen in involved lymph nodes. But extranodal SHML tends to exhibit more fibrosis, fewer typical histiocytes, more angiocentric plasma cells, and less lymphocytophagocytosis (Foucar et al. 1990).

Liver Involvement in SHML

The digestive system, including the liver, is not often affected in SHML, about 15 cases having been reported (Buchino et al. 1982; Foucar et al. 1990; Antonius et al. 1996; Lauwers et al. 2000; Anders et al. 2003; Iwabuchi et al. 2003; Krok et al. 2007; Chow et al. 2009; Maheshwari et al. 2009; Di Tommaso et al. 2010). In a study of 423 cases of the Rosai-Dorfman disease registry, hepatic involvement was only seen in 1 % (Foucar et al. 1990). Among 11 patients with GIT manifestation, this involved the liver in 5 patients, and most patients also had evidence of disease in other extranodal sites as well as in one or more lymph node groups (Lauwers et al. 2000).

SHML involving the GIT system does not seem to spontaneously resolve the patients for which follow-up was available (eight patients; reviewed by Anders et al. 2003) beyond 1 year were either alive with continuing disease (five cases) or dead of disease. Involvement of the liver is rare; among 423 examples, the liver was considered to be abnormal in 27 patients (Foucar et al. 1990), in most cases manifested as mild hepatomegaly; only 4 patients had biopsy evidence of hepatic involvement by SHML. All of these four patients had lymph node disease and had a mean age lower than that of the remainder of registry patients, and the combination of manifestations was found to be a poor prognostic sign. In a 68-year-old man with lymphadenopathy and elevated liver function tests, liver biopsy showed a nodular portal tract infiltration typical for SHML (Krok et al. 2007). A case of congenital SHML showed anemia, thrombocytopenia, and hepatomegaly. Liver biopsy revealed essentially preserved normal architecture of the liver tissue including the portal tracts. The sinusoids and portal tracts were infiltrated by atypical histiocytic cells that showed abundant granular and pale eosinophilic cytoplasm and medium- to large-sized vesicular nuclei. These cells were reactive for CD68 and S100 protein, but were CD1a negative. Some of the histiocytoid cells displayed emperipolesis or lymphocytophagocytosis (Chow et al. 2009). In one report, a patient with hepatic involvement in SHML had coincidental follicular non-Hodgkin's lymphoma (Di Tommaso et al. 2010). SHML of the pancreatic head has been shown to cause obstructive jaundice (Zivin et al. 2009). SHML has been found in association with giant cell hepatitis (Suarez-Vilela et al. 2004).

Macroscopy

Macroscopically, SHML of the liver in these four patients was characterized by the following features: a 1.5 cm well-circumscribed white nodule (depicted in Figs. 1, 2, and 3a of the work of Lauwers et al. 2000); several areas of decreased radioactivity in a liver scan; a congested liver at autopsy without focal lesions; a hepatomegaly; and multiple pinpoint-sized yellow foci, respectively; thus illustrating the gross presentation may be highly variable (Foucar et al. 1990). In a more recent study, a 3-year-old female child revealed cervical, mediastinal, retroperitoneal, and perihepatic lymph node enlargement, and liver imaging showed a hypodense lesion 1.9 × 1.0 cm in the right liver lobe (Maheshwari et al. 2009). In another study, liver involvement was observed in at least one pediatric patient claimed to have died from SHML (Buchino et al. 1982).

Histopathology

The accumulation of the histiocytic elements mainly takes place within the lobular parenchyma, in sinusoids, and in the portal tracts, which are expanded and form nodular infiltrate-rich structures (Figs. 1 and 2). Histiocytoid cell-rich interface lesions may develop. Lymphophagocytosis/emperipolesis is a characteristic feature. In the stable phase of the disease, the hepatic infiltrate consists of a mixture of histiocytes (in part with foamy cytoplasm), lymphocytes, and plasma cells located in the sinusoidal spaces (Buchino et al. 1982). A granuloma-like morphology may also occur. The parenchymal infiltration may be accompanied by hepatic steatosis, hypertrophy, and hyperplasia of Kupffer cells, erythrophagocytosis, and siderosis (Brown and D'Cruz 1987). Apart from red blood cells, histiocytes engulf lymphocytes and plasma cells, i.e., emperipolesis (Buchino et al. 1982). The infiltrates may be accompanied by considerable fibrosis. Eosinophilia of the liver has been observed in a patient with SHML, but was associated with concurrent hypereosinophilic syndrome (Hernandez et al. 1987).

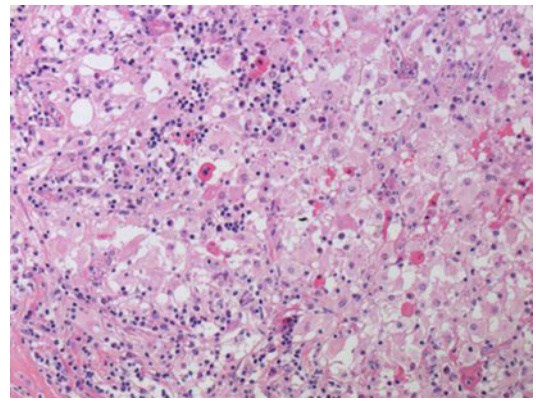

Fig. 1 Rosai-Dorfman disease of the liver. There is a diffuse growth of large histiocytoid and in part foamy cells, intermingled with lymphocytes. The eosinophilic cells are abnormal cells undergoing apoptosis (hematoxylin and eosin stain)

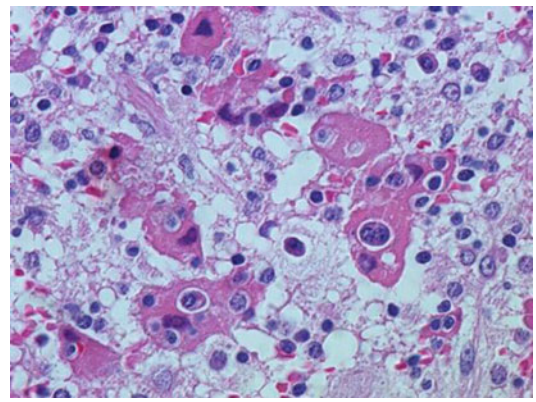

Fig. 2 Rosai-Dorfman disease in the liver. Large eosinophilic histiocytes display emperipolesis of lymphocytes (lymphocytophagocytosis; hematoxylin and eosin stain)

Morphology

General Morphology of Rosai-Dorfman Disease

In typical lymph node disease, the nodal sinuses are expanded by numerous histiocytes that occasionally can efface the nodal architecture. The involvement of a given node can be focal or diffuse, homogeneous, or multinodular. The cells have round to ovoid, vesicular nuclei, usually containing a single prominent nucleolus. Few nuclei are multilobulated, and rather slight nuclear atypia may be seen. Mitotic figures are usually

sparse. The cytoplasm of the histiocytes is predominantly abundant and slightly eosinophilic, but cells with glassy eosinophilic cytoplasm and distinct cellular margins can occur. A variable amount of foamy cells is in evidence. Electron microscopically, three types of histocytoid cells are recognized: (a) type I cells, with smooth cytoplasmic borders and moderate cytoplasmic lipids; (b) type II cells, cells with numerous interdigitating filopodia; and (c) type III cells, large cells with abundant lipid and formation of myelin figures. Emperipolesis of lymphocytes and plasma cells may be observed. This is the phenomenon of lymphophagocytosis (or better lymphocytophagocytosis), defined as lymphocyte penetration of an movement within another cell (review: Rastogi et al. 2014). In histiocytoid cells of SHML, the lymphocytes are often situated within vacuoles and thus seem to escape cell death and degradation (Colmenero et al. 2012). Sometimes, several lymphocytes are present in the cytoplasmic body of large histiocytoid cells. Emperipolesis may also involve neutrophils, plasma cells, and erythrocytes. Emperipolesis of neutrophils can be followed by neutrophil apoptosis in cutaneous SHML (Kusutani et al. 2011). The histiocytoid cell population is often accompanied by numerous, mature plasma cells which are arranged around postcapillary venules. The involved lymph nodes may, in addition to histiocytes, be infiltrated by neutrophils, sometimes with formation of microabscesses. Eosinophils are rare in SHML, in contrast to Langerhans cell histiocytosis.

Histogenesis of SHML

Currently, SHML is classified among the histiocytoses, one reason being the morphologic and clinical overlap between SHML and the prototypic idiopathic histiocytosis, i.e., LCH (Foucar et al. 1990), although the two respective cell types involved are clearly different with respect to their origin, lineage, immunophenotype, and function. Generally, results from immunohistochemical studies indicate that SHML cells belong to activated members of the monocyte/macrophage cell family. SHML cells consistently express S-100 protein; the monocyte/macrophage-associated antigens CD14, HAM 56, EBM11, CD33, CD64, and CD68; and the cellular adhesion molecule CD31/PECAM-1 (Eisen et al. 1990; Paulli et al. 1992; Slone et al. 2003). The SHML histiocytes express a pattern of further adhesion molecules that characterize circulating monocytes, i.e., CD11b, CD11c, CD18, CD62L, and CD103. A fraction of the cells are medium-sized mononuclear cells expressing an antigen pattern typical for recently immigrated monocytes, suggesting this cell as the main cell of origin of SHML cells (Paulli et al. 1992). Like Langerhans cells, SHML cells express aspartic proteinases, including cathepsin D (normally present in antigen-presenting cells) and cathepsin E, a macrophage marker. It has been suggested that stimulation of monocytes/macrophages via macrophage colony-stimulating factor (M-CSF) leading to immune suppressive macrophages represents a mechanism in the pathogenesis of SHML (Middel et al. 1999), hence the target cells of SHML making part of a polyclonal cell population. Polyclonality in SHML is supported by findings from the analysis of X-linked polymorphic loci by use of the HUMARA assay (Paulli et al. 1995).

Differential Diagnosis

In immune stimulated locoregional lymph nodes, marked accumulation of macrophages in sinus can be induced by primary and metastatic liver tumors. In a patient with hepatocellular carcinoma, this macrophage reaction in portal hepatic lymph nodes closely mimicked Rosai-Dorfman disease (Takagi et al. 2012).

Adult Xanthogranulomatous Disease (Including Erdheim-Chester Disease)

Introduction

Adult xanthogranulomatous disease (AXGD) is a group of four syndromes of non-Langerhans cell histiocytosis (type II) characterized by the development of inflammatory lesions

containing numerous lipid-laden foamy histiocytes/macrophages. AXGD includes adult-onset xanthogranuloma (AOX), adult-onset asthma, and periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma (NBX), and Erdheim-Chester disease (ECD).

Erdheim-Chester Disease

Erdheim-Chester disease (ECD; synonyms: Erdheim-Chester syndrome; polyostotic sclerosing histiocytosis; lipid/cholesterol granulomatosis) is a multisystemic form of non-Langerhans cell histiocytosis that has been described in 1930 (Chester 1930). ECD is characterized by a proliferation of histiocytes/macrophages, sometimes lipid-laden, in the marrow cavities of tubular bones, adipose tissues, and less commonly visceral organs (reviews: Abdelfattah et al. 2014; Haroche et al. 2014; Cives et al. 2015; Haroche and Abla 2015). ECD can develop in any age, but is mostly diagnosed in patients between 40 and 60 years of age. ECD clinically presents with fever, weight loss, malaise, asthenia, and permanent juxtaarticular bone pain, and sometimes with signs of retroperitoneal disease. In case of specific organ infiltration, alterations such as exophthalmos, diabetes insipidus, and signs of pachymeningosis may occur. Symmetrical involvement of long bones, mainly of the lower extremities, is an almost universal alteration. Bone marrow infiltration leads to an osseous reaction characterized by a bilateral, metaphyseal, and diaphyseal, symmetric cortical osteosclerosis of long bones. In flat bones, the infiltrate can induce osteolytic foci. Extraosseous organ involvement mainly includes the lungs (in 20 % of cases), kidneys and/or perirenal fat, skin (often eyelid xanthomas), retroorbital adipose tissue (sometimes with exophthalmos), retroperitoneal adipose tissue, heart and pericardium, large arteries ("coated aorta"), adrenal glands, dura mater, and pituitary gland/sellar region. ECD can be a life-threatening condition, with a reported global 5-year mortality of 30–40 %.

In regard to the question as to whether ECD is a reactive or a neoplastic process, results of mutational studies are important. More than 50 % of patients with ECD show the BRAFV600E mutation (see below; Blombery et al. 2012; Haroche et al. 2012; Hervier et al. 2014). It has recently been suggested that the histiocytosis ECD is an inflammatory myeloid neoplasm (Allen and Parsons 2015; Haroche et al. 2015).

Liver Involvement in Erdheim-Chester Disease

So far, only few studies have documented severe liver involvement in ECD (Ivan et al. 2003; Gupta et al. 2007; Dickson et al. 2008; Pan et al. 2011; Arabadzhieva et al. 2015; Shu et al. 2015). In the young male patient with ECD-related vertebral osteolytic lesions reported by Ivan et al. (2003), a mild cholestatic syndrome and signs of hepatic cytolysis were detected. Liver biopsies revealed an extensive infiltration and replacement of the hepatic tissue by foamy, lipid-laden histiocytes/macrophages, and a diffuse lymphocyte infiltration, fibrosis, and scattered Touton-like giant cells without a granulomatous reaction were also present. Electron microscopy disclosed numerous secondary lysosomes and phagolysosomes, but no Birbeck granules, in the target cells, supporting the macrophage lineage of the cells involved (Ivan et al. 2003). The necropsy of a further patient with ECD showed a white-yellow fibrous tissues that had bilaterally encased kidneys and adrenals and had extended along vessels and portal tracts into the liver (Dickson et al. 2008). The patient described by Pan et al. (2011) revealed xanthogranulomatous foci within the liver parenchyma, characterized by foamy, CD68+/CD1a- macrophages, multinucleated giant cells, and inflammatory cells. ECD can involve the large intrahepatic and extrahepatic bile ducts, causing biliary obstruction that may mimic Klatskin tumor (Gundling et al. 2007).

Pathology of Erdheim-Chester Disease

At autopsy, soft and fat-like yellow masses have been described in organs, measuring up to several

cm in diameter (Sheu et al. 2004). Histologically, the often extensive infiltrate in ECD is dominated by macrophages rich in finely granular cytoplasm, often with lipid storage and formation of foam cells. The macrophages can be accumulated in the form of small nodular structures, sometimes with formation of conglomerate nodules or small tumor-like masses. The infiltrate also contains multinucleated giant cells of the Touton type, lymphocytes, and rarely other leukocytes. The infiltrate is often surrounded by a sheath of fibrosis ("fibroxanthomatous granulomas"). The leading cells, the ECD histiocytes, are immunoreactive for CD68, but, in contrast to Langerhans cell histiocytosis, do not stain for CD1a or S-100 protein (the CD68+/CD1a- phenotype; Ono et al. 1996; Ota et al. 2012). Birbeck granules are absent (Ono et al. 1996).

Differential Diagnosis

Clinically, ECD can mimic Langerhans cell histiocytosis or collagen vascular diseases. In some patients, autoimmune disorders with arthritis and polyserositis may be difficult to distinguish from ECD. Isolated involvement of the pituitary gland with ECD has to be distinguished from other forms of xanthomatous or xanthogranulomatous hypophysitis (Folkerth et al. 1998; Yokoyama et al. 2004).

Pathogenic Pathways

Etiology and pathogenesis of ECD have only partially been clarified so far. Morphologically and on a molecular level, ECD is related to Langerhans cell histiocytosis (LCH), but the relationship between these two disorders is complex. In a recent investigation, ECD followed or was diagnosed simultaneously with, but never preceded, LCH (Hervier et al. 2014). It seems that the progressive infiltration by a macrophage-dominated cell population is caused by an abnormal, persistent immune response with defective termination mechanisms rather than by a true neoplastic process. The distinctive composition of the infiltrate in ECD suggests that there will be an intricate and complex interaction between macrophages and lymphocytes. In fact it was shown that tumor necrosis factor alpha is a master regulator of inflammation in ECD (Dagna et al. 2012). The disease is linked to a network of pro-inflammatory cytokines and chemokines involved in the recruitment of macrophages/histiocytes into ECD lesions (Cavalli et al. 2014). Novel findings have shown that ECD is associated with the BRAF V600E mutation, similar to Langerhans cell histiocytosis (Blombery et al. 2012; Haroche et al. 2012; Emile et al. 2013; Hervier et al. 2014; Bosco et al. 2015; Haroche and Abla 2015). In one study 13/24 patients with ECD (54 %) harbored the BRAF V600E mutation, in comparison with 11/29 patients (38 %) with Langerhans cell histiocytosis (Haroche et al. 2012). BRAF oncogene-induced senescence may represent the link between oncogenic mutation and the pathologic inflammatory response (Cavalli et al. 2014). In BRAF wild-type patients with ECD recurrent RAS and PIK3CA mutations were observed (Emile et al. 2014).

Necrobiotic Xanthogranuloma: Liver Involvement

Necrobiotic xanthogranuloma (NBX; synonym: necrobiotic xanthogranuloma with paraproteinemia) is a rare, destructive non-Langerhans cell histiocytic disorder with formation of lipid-rich granulomas, a distinct type of collagen degradation/necrosis, and a usually indolent progressive course. In rare cases, the liver is involved by NBX, associated with formation of tumor-like nodular transformation with non-cirrhotic portal hypertension (Hunter and Burry 1985; Novak et al. 1992). One NBX patient showed syncytial giant cell hepatitis (Amer et al. 2005).

The condition was first distinguished from normo- or hyperlipemic plane xanthomas in 1980 (Kossard and Winkelmann 1980). NBX is strongly associated with monoclonal gammopathy (paraproteinemia) with or without concomitant B-cell neoplasms, including plasmacytoma/

multiple myeloma. The latter develop before the skin lesions or later in the course of disease (Ugurlu et al. 2000). Monoclonal gammopathy, usually of the IgG type and much less commonly of the IgA type, is found in 80 % of patients. Clinically, NBX most often manifests as yellowish skin plaques and nodules, most commonly in the periorbital region and sometimes defigurating. Large plaques may ulcerate (Ugurlu et al. 2000). Inner/visceral organs may be affected, including the lung, pericardium, myocardium, salivary glands, larynx, kidney, and liver (Hunter and Burry 1985; Fortson and Schroeter 1990; Bara et al. 2003; Zainal et al. 2010). Amyloidosis may develop as a late complication. Histologically, the granulomatous reaction is characterized by hyaline band-like necrobiosis of collagen, emergence of collagen fiber bundle fragments acting as foreign bodies associated with bizarre angulated giant cells, a macrophage-rich infiltrate with numerous lipid-laden foam cells, Touton giant cells (sometimes with so-called Touton cell panniculitis), cholesterol clefts, and infiltrates of lymphocytes and plasma cells, sometimes with lymphoid follicles (Finan and Winkelmann 1987).

Panniculitis-Associated Histiocytic Disorders: Weber-Christian Disease

Introduction

Weber-Christian disease (WCD; synonyms: Pfeifer-Weber-Christian disease; idiopathic relapsing febrile lobular non-suppurative panniculitis; relapsing nodular non-suppurative panniculitis; Weber-Christian syndrome) is a form of acute to chronic, relapsing inflammation of subcutaneous adipose tissue, characterized by a distinct phenotype of lobular and later nodular panniculitis. The disorder was first described by Pfeifer in 1892 (Pfeifer 1892), and a second patient was documented in 1916 (Gilchrist and Ketron 1916). In 1925, Weber referred to these two patients in his publication on "Relapsing non-suppurative nodular panniculitis" (Weber 1925), and in 1928, Christian added the word "febrile" (Christian 1928). In 1936, Brill coined the term "Weber-Christian disease" (Brill 1936; reviews: Oram and Cochrane 1958; Steffen 2002). WCD prevails in females 30–60 years of age, but it also occurs in infants (Hendricks et al. 1978) and children (Wu and Zou 2007).

Clinical and Morphologic Features

Clinically, WCD is characterized by recurrent subcutaneous inflammatory tender to painful nodules, erythematous skin lesions, fever, arthralgia, weight loss, and malaise due to systemic inflammatory reactions. The process can result in fibrosis/scarring and atrophy of the adipose tissue (lipoatrophy). Part of patients revealed hyperlipidemia, anemia, or leukemoid reactions. Inner organs and tissues may be involved, including the pancreas (pancreatitis), lung (pleuritis and lipogranulomatous pneumonitis), mediastinum (mediastinitis/periaortitis), mesenterium (mesenteritis), and liver. The clinical course of WCD is variable, cases with skin involvement only having a good prognosis, while systemic variants often result in complications and eventually fatal outcome.

In the subcutaneous lesions of WCD, three histopathological stages can be identified. In stage 1, adipose lobules are infiltrated by neutrophils, macrophages, and lymphocytes, associated with adipocyte damage and death. Stage 2 is characterized by a strong phagocytic reaction, with macrophages phagocytosing damaged and dead adipocytes, leukocytes, red blood cells, and debris, with formation of so-called bean-bag cells. In this stage, foamy macrophages develop. In stage 3, the macrophage accumulations are progressively replaced by a fibroblastic reaction followed by fibrosis and lipoatrophy.

Liver Involvement

Suspected liver involvement with WCD, manifest as hepatomegaly and elevated serum transaminases, has been documented in several reports

(Friedman 1945; Kinmont 1952; Schwartz et al. 1952; Steinberg 1953; Oram and Cochrane 1958; Stanoeva and Miovski 1972; Edge et al. 1986; Amarapurkar et al. 2005; Wu and Zou 2007). In patients with verified liver involvement, the histology is characterized by several patterns. Similar to other histiocytoid disorder with lipid storage, foamy macrophages can accumulate in the liver (Miyazaki et al. 1977). In one case with fatal outcome, the liver macroscopically showed numerous rice grain-sized yellow nodules (Bjornstad 1951). Some patients have shown hepatic steatosis and/or steatohepatitis (Hanrahan et al. 1951; Oram and Cochrane 1958; Miyazaki et al. 1977; Wasserman et al. 2001). Steatotic hepatocytes may show Mallory-Denk bodies (Kimura et al. 1980), thus mimicking alcoholic or nonalcoholic steatohepatitis (ASH/NASH). In one patient with WCD who died of hepatic failure, necropsy revealed acute focal necrosis of the liver (Miller and Kritzler 1943). Steatonecrosis of the liver in WCD was described in another patients (Jones et al. 1950). In a pediatric patient with WCD, chronic active hepatitis associated with an LKM variant autoantibody was found, suggesting that autoimmune mechanisms are involved in pathogenic pathways of WCD (Edge et al. 1986).

Differential Diagnosis

In patients with WCD-associated steatohepatitis, ASH and NASH due to other causes have to be considered. Hepatic foamy macrophages in portal tracts occur in other histiocytic disorders, including xanthoma disseminatum. Various forms of panniculitis resembling WCD occur in the setting of autoimmune disorders (in particular systemic lupus erythematodes), pancreatic diseases, lymphoproliferative disorders, infections, and trauma. WCD can be mimicked by cytophagic histiocytic panniculitis, discussed in the following paragraph. A panniculitis resembling WCD has been detected in patients with rare mutations in the tumor necrosis factor receptor superfamily (TNFRSF) 1A gene (Lamprecht et al. 2004). TNFRSF 1A gene mutations are known to cause TNFR-associated periodic syndrome/TRAPS.

Panniculitis-Associated Histiocytic Disorders: Cytophagic Histiocytic Panniculitis

Introduction

Cytophagic histiocytic panniculitis (CHP; panniculitis associated with hemophagocytic syndrome) was described in 1980 as a form of severe lobular and nodular panniculitis, characterized by a strong phagocytic activity of histiocytes/macrophages (cytophagy of leukocytes and erythrocytes) in the lesions, a high rate of systemic manifestations, and a high mortality (Winkelmann 1980; Winkelmann and Bowie 1980). Some authors employ the term CHP to describe two different processes, one being a variant of lobular panniculitis ("classical" CHP), the other neoplastic, i.e., subcutaneous panniculitis-like T-cell lymphoma (reviews: Requena and Sanchez Yus 2001; Aronson and Worobec 2010). CHP is often associated with an underlying infectious (in particular viral), autoimmune, or neoplastic disease, but in some patients, no such predisposing condition can be identified. CHP has also been observed following bone marrow transplantation or interferon-alpha therapy. In some patients, an overlap between Weber-Christian disease and CHP was found (Steininger and Missmahl 1988).

Clinical and Morphologic Features

The cutaneous manifestations of CHP are characterized by plaques and nodules that occasionally are ecchymotic and ulcerated. Histologically the lesions are dominated by a dense infiltrate of large histiocytes/macrophages with marked cytophagic features. The cells are engaged in vigorous phagocytosis of dead adipocytes and fragments thereof, leukocytes, erythrocytes, and debris, with formation of "bean-bag cells" (Alegre and Winkelmann 1989). In systemic CHP, fever, pancytopenia,

jaundice, mucosal ulcers, coagulation disorders, and serositis are common signs. Classic CHP not associated with lymphoma is not associated with EBV infection and often has a first phase with a benign course, unless terminal hemophagocytic syndrome develops, leading to disease acceleration and often fatal outcome associated with terminal hemorrhagic diathesis. Hemorrhagic diathesis is caused by thrombocytopenia and massive coagulation disturbances due to liver failure (Crotty and Winkelmann 1981). Many cases of hemophagocytic syndrome in the setting of CHP are considered a natural disease progression of subcutaneous panniculitis T-cell lymphoma (Craig et al. 1998), such patients being prone to have a fatal outcome (Huilgol et al. 1998). Pediatric CHP has been found in a patient with fatal hemophagocytic lymphohistiocytosis caused by a perforin gene mutation (Chen et al. 2007).

Liver Involvement

Many patients with CHP exhibit signs of liver dysfunction mimicking hepatitis (Winkelmann and Bowie 1980; March et al. 1986; White and Winkelmann 1989; Pettersson et al. 1992; Tsukahara et al. 1995), often associated with hepatomegaly or hepatosplenomegaly (Guitart et al. 1998). Hepatomegaly and hepatopathy, sometimes severe, is mainly seen in patients with CHP complicated by hemophagocytic syndrome (Huilgol et al. 1998). In liver biopsies, the dominant features consist of histiocyte infiltrations in portal tracts (Winkelmann and Bowie 1980; Willis et al. 1985) and signs of hemophagocytosis (Hilton et al. 1990). In fatal systemic CHP, infiltration of the liver with numerous histiocytes together with T lymphocytes was found (Perniciaro et al. 1994). CHP can lead to liver failure (Crotty and Winkelmann 1981).

Differential Diagnosis

The main differential diagnoses include other forms of hemophagocytic syndromes and atypical or aggressive variants of Weber-Christian disease.

Hemophagocytic Syndromes

Hemophagocytic lymphohistiocytosis (HLH): A heterogeneous group of inherited and acquired disorders of monocyte/macrophage function

HLH comprises two different conditions, i.e., (a) *primary hemophagocytic lymphohistiocytosis* (*familial or sporadic*) and (b) *secondary hemophagocytic lymphohistiocytosis* (Henter et al. 1997). Although the primary form is usually termed familial HLH (FHLH), it often appears sporadic with a negative family history, since the disorder is autosomal recessive. Familial HLH may be elicited by, or associated with, infections. Secondary HLH is an exaggerated, reactive proliferation and activation of the lymphocytic and histiocytic/macrophage cell systems induced by several factors, including severe infection (*infection-associated hemophagocytic syndrome*, *IAHS*); viral infection in immunocompromised hosts (*virus-associated hemophagocytic syndrome*, *VAHS*; *distinct variant*: *EBVHS or EBV-HLH*); immune system activation during malignancies (*malignancy-associated hemophagocytic syndrome*, *MAHS*, *and lymphoma-associated hemophagocytic syndrome*, *LAHS*); and prolonged intravenous nutrition with administration of soluble lipids (fat overload syndrome) (Henter et al. 1991c). Secondary HLH with its several variants is also termed *macrophage activation syndrome* (*MAS*), or *reactive macrophage activation syndrome* (*rMAS*). However, it is still questioned whether reactive hemophagocytic lymphohistiocytosis and macrophage activation syndrome are the same or different entities (Grom 2003). What appears settled is that, as discussed below, MAS has strong clinical similarities with FHLH and reactive VAHS. In addition, similar pathogenic pathways seem to involved, in that abnormal NK cell function and depressed perforin expression are not only crucial features of FHLH but also of MAS, especially MAS developing in systemic-onset juvenile arthritis.

Secondary hemophagocytic syndromes: Sporadic hemophagocytic lymphohistiocytosis and macrophage activation syndrome

Introduction

Hemophagocytic lymphohistiocytosis is a syndrome characterized by extreme immune system activation causing massive inflammatory reactions, related to an exaggerated reaction to antigenic stimulation (review: Allen and McClain 2015). Most patients with a secondary hemophagocytic disorder have in fact what is now more frequently termed *macrophage activation syndrome* (MAS; reactive macrophage activation syndrome, rMAS; secondary hemophagocytic lymphohistiocytosis, HLH; hemophagocytic syndrome; histiocytic medullary reticulosis). MAS was first described in 1939 under the term histiocytic medullary reticulosis (Scott and Robb-Smith 1939). MAS is a serious complication of systemic inflammatory reactions, occurring in children and adults, probably caused by excessive activation of T lymphocytes, natural killer cells, and macrophages (review: Ravelli 2002). In principle, MAS is a secondary or reactive hemophagocytic syndrome (hence, the alternative term rMAS). MAS has to be considered in patients with a systemic inflammatory response syndrome (SIRS) – or Still's disease-like clinical presentation (Emmenegger et al. 2002). According to the Histiocyte Society, the diagnosis of MAS/HLH requires the fulfillment of five criteria: (1) fever; (2) cytopenia (two of three lineages); (3) splenomegaly; (4) hypertriglyceridemia and/or hypofibrinogenemia; and (5) hemophagocytosis (Henter et al. 1991a), but there are also patients with atypical presentations. It is recognized that the main features of MAS are in part those also observed in familial hemophagocytic lymphohistiocytosis (see above).

MAS: Causes and Associations

MAS is associated with a number of underlying diseases such as viral, rickettsial, bacterial, or fungal infections, parasitic infestations, hematological and other malignancies (in particular lymphomas), autoimmune conditions, inflammatory bowel disease, Kikuchi's disease, metabolic disorders, liver transplantation, Kawasaki disease (Cummings et al. 2008), and rarely after viral vaccinations (Kumakura et al. 1997; Tsuda 1997; Janka et al. 1998; Corbeel 1998; Mahadeva et al. 2000; Otagiri et al. 2002; Ohno et al. 2003; Bhatia et al. 2003; Dhote et al. 2003; Karasu et al. 2003). In a systematic review based on a PubMed search, most cases of MAS associated with bacterial infections were brucellosis, rickettsial diseases, and Q fever. For viral infections, most of the cases were reported in patients with avian influenza A subtype H5N1, while the most common protozoal disease was visceral leishmaniasis (Cascio et al. 2012). Viral infections associated with rapidly progressive and life-threatening MAS, e.g., include human herpesvirus 8 reactivation in HIV-infected patients (Fardet et al. 2003). Among noninfectious disorders, active systemic disease associated with systemic lupus erythematodes, rheumatoid arthritis, and adult Still's disease are predominant causes of MAS (Dhote et al. 2003; Félix et al. 2009; Atteritano et al. 2012). MAS is also a well-known complication of systemic juvenile idiopathic arthritis (Davi et al. 2011; Minoia et al. 2014).

Particularly impressive secondary hemophagocytic syndromes occur in patients with viral infections, and specifically EBV infections (Maakaroun et al. 2010), similar to what has been discussed for XLP (virus-associated hemophagocytic syndrome, VAHS; Daum et al. 1987; Dharancy et al. 2008). In fatal cases of H1N+ influenza, MAS is suggested to be a secondary event and is in fact related to mutations in hemophagocytic lymphohistiocytosis genes (Schulert et al. 2015). Per definition, VAHS is a nonneoplastic, generalized histiocyte/macrophage proliferation with prominent hemophagocytosis associated with a systemic viral infection. Even though a benign lesion per se, VAHS in the context of EBV infection may follow a malignant and fatal

course (Kikuta et al. 1993), with a relatively high mortality, not only in those patients having XLP. The majority of EBV-VAHS cases develop in apparently immunocompetent children and adolescents (Imashuku 2002). The severe disease manifestations seem to be related to unrestricted release of cytokines produced by EBV-infected lymphocytes (reviews: Favara 1992; Fisman 2000; Kikuta 1995). The reason why some, but not all, patients with EBV infection develop VAHS is not clear. However, recent investigations have shown that there may be distinct EBV-infected cell populations in EBV-related VAHS that exhibit different patterns of EBV latent gene expression and a different EBNA promoter methylation status (Yoshioka et al. 2003).

Pathogenic Pathways

Pathogenetically, an non-controlled T lymphocyte or natural killer cell activation with induction of a "cytokine storm" is thought to give rise to potentially life-threatening macrophage activation, the final common pathway of rMAS, and associated with the infiltration of many tissues by T lymphocytes and activated macrophages. A central role is played by granule-dependent cytotoxic activity following cell activation, polarization of cytotoxic granules toward the conjugated target cell, and fusion of granules with target cell membranes, with release of granule contents (reviews: Janka 2007a,b; Filipovich 2008; de Saint Basile et al. 2011; Usmani et al. 2013). The macrophage populations in MAS in fact show an activated phenotype, and they express major histocompatibility complex class I and II molecules and macrophage colony-stimulating factor receptors (Arico et al. 2001b). Several cytokines are markedly elevated in serum of patients with MAS, including INF-gamma, TNF-alpha, IL-10, IL-12, and the IL-2 receptor (Henter et al. 1991b). This is accompanied by a profoundly decreased cytotoxic T-lymphocyte function and hampered or even absent NK cell function, being a hallmark of the immune dysregulation characterizing MAS, in some way similar to FHLH (Egeler et al. 1996). It has been shown that soluble Fas/CD95 (sFas) and Fas ligand (sFasL) were significantly elevated in the serum of patients with MAS episodes, decreasing again during convalescence, suggesting that sFas and sFasL, via interfering with activation-induced cell death (AICD), might contribute to the pathogenesis of MAS (Emmenegger et al. 2000). In patients with EBV-associated MAS, infection of T lymphocytes with EBV appears to be a typical feature, irrespective of the clinical course (Beutel et al. 2009).

Hemophagocytosis in MAS

Activation of macrophages/histiocytes in MAS is typically associated with hemophagocytosis that involves the pathologic finding of activated macrophages engulfing erythrocytes, leukocytes, platelets, and their precursor cells (Favara 1992). The organs and tissues most frequently showing hemophagocytosis are the spleen, liver, lymph nodes, and bone marrow, but the CNS and the skin may also be affected.

Clinical Features

Patients with MAS/rMAS present with persistent fever unresponsive to antibiotics, malaise, arthralgia, fatigue, rash, cytopenia, hepatosplenomegaly, and signs of multiorgan dysfunction (reviews: Pradalier et al. 2004; Gupta et al. 2009; Larroche 2012). In addition, part of patients exhibit signs and symptoms of the underlying disease that has caused MAS, resulting in complex diagnostic situations. The serum ferritin is typically elevated in rMAS (Esumi et al. 1987). The combination of a high serum ferritin concentration and a low glycosylated ferritin concentration is a particularly potent marker of rMAS (Lambotte et al. 2003). Particularly in children, HLH can cause multiorgan failure as a presenting syndrome or early in the disease course (Nahum et al. 2000).

Pathology of the Liver in Macrophage Activation Syndrome

Hepatic effects of MAS are both structural and functional, and in some patients, various forms of histopathologic alterations have been observed. In infants and children, liver involvement with MAS is common and was found in up to 91.7 % of patients (Karapinar et al. 2009; Amin et al. 2014). In adults, hepatomegaly was present in 50 %, and serum aminotransferases, ferritin, alkaline phosphatase, and triglycerides were elevated in all (De Kerguenec et al. 2001; Larroche et al. 2007). MAS may closely mimic acute or chronic hepatitis (Favara 1992; King et al. 1994) and may end up with acute hepatic failure (Parizhskaya et al. 1999). Histologically, acute lobular hepatitis with an infiltrate rich in T lymphocytes and macrophages is a typical feature (Bihl et al. 2006). Large and activated Kupffer cells are found within sinusoids (Figs. 3 and 4). Kupffer cells are often increased in number, interpreted as diffuse Kupffer cell hyperplasia. Part of these activated macrophages contain red blood cells in their cytoplasm as sign of hemophagocytosis (Andreopoulos et al. 2007). The liver sinusoids may be dilated, sometimes markedly so. The portal tracts contain a usually minor cellular infiltrate composed of lymphocytes (mainly T cells) and CD68-positive macrophages, but cases with marked portal tract histiocytosis have also been reported (Terada et al. 1999). The lymphocytes accumulating in the liver in MAS are mostly CD8+ cells that produce interferon gamma, while macrophages were shown to produce IL-6 and TNF-alpha (Billiau et al. 2005). Canalicular and/or intracellular cholestasis is found in part of cases (Tsui et al. 1991). In part of the patients, cholestasis is caused by a severe injury of small bile ducts, similar to vanishing bile duct syndrome and sometimes resulting in secondary biliary cirrhosis (Fig. 5). It has been suggested that the hepatocyte and cholangiocyte

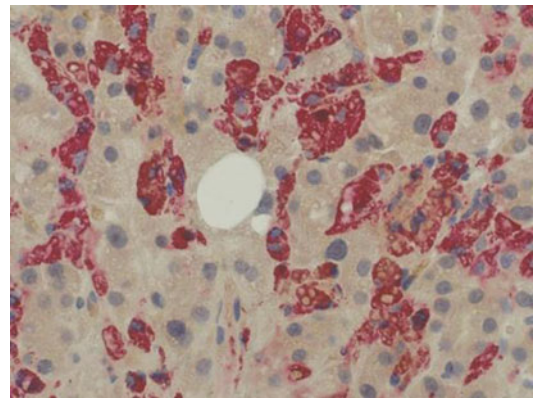

Fig. 4 Reactive macrophage activation syndrome of the liver. The sinusoids contain accumulations of activated macrophages (CD68 immunostain)

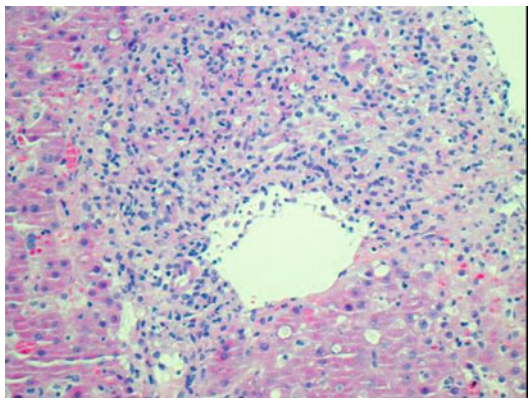

Fig. 3 Reactive macrophage activation syndrome of the liver. An enlarged portal tract is infiltrated with histiocytoid cells/macrophages and lymphocytes. The portal vein branch reveals signs of florid endotheliitis (hematoxylin and eosin stain)

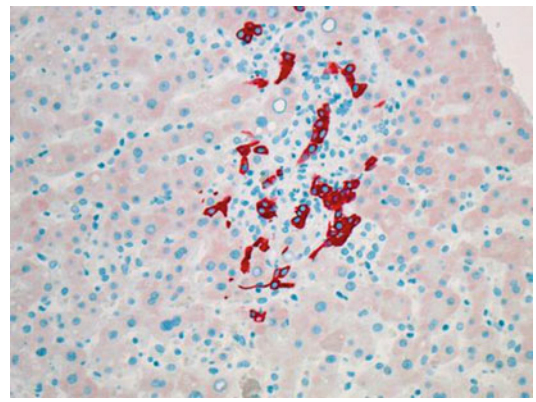

Fig. 5 Reactive macrophage activation syndrome of the liver. This disorder may be associated with injury and eventual destruction of small intrahepatic bile ducts, lymphohistiocytic cells invading and damaging the cholangiocyte lining (cytokeratin 19 immunostain)

injury are caused by a macrophage-lymphocyte-NK cell network attacking hepatic cells (Bihl et al. 2006). In the course of hemophagocytosis, marked siderosis of the liver can develop, an alteration which is also visualized in MR images (Zilkha et al. 1998).

Familial Hemophagocytic Lymphohistiocytosis (FHL; Farquhar Disease; Familial Erythrophagocytic Lymphohistiocytosis; Familial Hemophagocytic Reticulosis)

Introduction

Familial hemophagocytic lymphohistiocytosis (FHL; OMIM 267700) is a rare, autosomal recessive disease of infancy and early childhood. FHL was originally described in 1952 under the term "familial hemophagocytic reticulosis" (Farquhar and Claireaux 1952), and the specific hereditary features were outlined in 1984 (Gencik et al. 1984; review: Henter 1990). The estimated incidence is about 1 in 50,000 live births. In a large study on HLH in children (122 patients), a positive family history was detected 49 % of cases including two pairs of affected male twins; the median age at disease onset was 2.9 months, with the majority of patients being less than 1-year-old at onset, with no difference between familial and sporadic cases, and an associated infection (usually by common viral pathogens) was reported in 41 % of cases (Arico et al. 1996). Rarely, there are families with late onset of disease, i.e., between 9 and 17 years (Allen et al. 2001).

Clinical and Diagnostic Features

The presentation of the disorder is the same for bona fide familial HLH and the sporadic form, except the identification of distinct gene mutations in affected families, as briefly discussed below. The main features comprise malaise, intermittent fever, a rash, hemocytopenia (anemia and thrombocytopenia), lymphadenopathy, hepatosplenomegaly, signs of liver dysfunction, and a multivisceral accumulation of T lymphocytes and macrophages (Henter et al. 1991, 1993). Patients with FHL typically show hyperlipidemia. Hypofibrinogenemia in FHLH has been suggested to be caused by a direct action of activated histiocytes/macrophages on factor X via Mac-1 receptors, subsequent activation of the common pathway of the coagulation protease cascade, and uptake of fibrin/fibrinogen by these cells (Ooe 1991). More than half of the patients suffer from CNS involvement ranging from confusion to seizures and severe neurologic impairment (Horn et al. 2002). The involved organs and tissues are infiltrated by a reactive population of lymphoid cells and histiocytes/macrophages, with signs of hemophagocytosis. The latter is particularly evident in bone marrow biopsies (Cho et al. 1997). Rarely, the infiltrates involve the lung, causing a disorder resembling interstitial pneumonia and resulting in respiratory failure (Popper et al. 1994).

Etiology and Pathogenesis

In regard to the etiology of FHL, genetic studies have uncovered several altered gene functions in at least part of the patients with FHL indicating genetic heterogeneity of FHL (Dufourcq-Lagelouse et al. 1999a,b; Ohadi et al. 1999; Graham et al. 2000; Cicocki et al. 2014; Zhang et al. 2014a). The five types of FHL (FHL1 to FHL5) comprise alterations of perforin, Munc13-4/Unc13, syntaxin11, and SH2D1A genes.

The pathogenic pathways operational in all types of FHL are complex and only partially known. They are thought to involve an impaired lymphocyte- and NK-mediated cytotoxicity and defective triggering of apoptosis (Fadeel et al. 1999, 2001). This is thought to be related to lack of perforin expression in cytotoxic cell types in patients having a perforin gene mutation (Kogawa et al. 2002), while the mechanism is unclear in those patients disclosing a normal perforin phenotype. Effects of a systemic

hypercytokinemia, including IFN-gamma, TNF, and IL-6, have been proposed to be a common final pathway (Henter et al. 1991). The natural killer cell (NK) cytotoxic activity is markedly decreased in children with primary HLH (Kataoka et al. 1990), what may play a role in the disordered activity of the lymphohistiocytic network. Whole-exome sequencing revealed an overlap between MAS in systemic juvenile idiopathic arthritis and familial hemophagocytic lymphohistiocytosis (Kaufman et al. 2014).

In FHL patients with perforin mutations, the pathogenic pathways involve an altered function of cytotoxic T lymphocytes and natural killer (NK) cells. These two cell systems share a common cytotoxic pathway that is required for defense against virus-infected or transformed cells. Specifically, cytotoxic cells eliminate their target cells primarily via the secretion of granules containing perforin and granzymes (Shresta et al. 1998), and this multistep process involves target cell recognition, adhesion, formation of an immunologic synapse, reorientation of the Golgi complex and the microtubule-organizing center (MTOC), and the polarization of the lytic granule compartment toward the target cell contact site (Kupfer and Singer 1989). After establishing a synapse with the target cell, perforin-containing lytic granules are rapidly transferred to the target cell interface, followed by their docking and fusion with the respective plasma membrane, and release, whereupon the cell is destroyed. This interaction process requires the local concentration of talin and adhesion molecules (including LFA-1) at the contact site, forming a ring-like structure to which the polarized MTOC anchors. This ring surrounds a central supramolecular activation complex (cSMAC) containing the signal molecules, Lck and PKC delta. Polarized lytic granules then insert into the cSMAC before being secreted (Vyas et al. 2002). Which factors control the secretion process? Late in the exocytic pathway, the small GTPase, Rab27a, is an essential compound, as seen in respective human and animal mutation states (human Griscelli syndrome and the ashen mutant mouse; see below), but other factors remain to be identified.

Liver Involvement in Familial Hemophagocytic Lymphohistiocytosis

At autopsy, the enlarged liver shows hypertrophy of the Kupffer cells which exhibit erythrophagocytosis and a lymphocytic infiltration of portal tracts and the hepatic parenchyma, these cells predominantly expressing T-lymphocyte markers (Cho et al. 1997). In an autopsy study on 27 cases, infiltration of hepatic portal tracts of lymphocytes and histiocytes was present in 81 %, and the infiltrates were dense in 13/27 patients, sometimes resembling chronic hepatitis of low activity. This mixed infiltrates was also noted within liver lobules, albeit to a lesser degree. The number of Kupffer cells was moderately increased (Ost et al. 1998). In this study, hemophagocytic activity was only occasionally seen in the liver (3/27 patients; 11 %). The chronic hepatitis-like presentation was interpreted to probably represent the sequelae of a general lymphocyte activation in FHLH (Ost et al. 1998). Similar changes have been reported in other studies (Henter 1990; Favara 1992, 1996), and the pattern is very similar to that observed in sporadic hemophagocytic lymphohistiocytosis, with the apparently only distinguishing feature is the expression of CD21, CD30, and CD35 antigens by histiocytes (Boissy et al. 1997). Similar to reactive MAS, patients with FHLH can show severe loss of intrahepatic bile ducts (Kapelari et al. 2005).

Liver Pathology in Hemophagocytotic Forms of Griscelli Syndrome/GS (GS2; Rab27a Mutations)

A hemophagocytic syndrome has been described for GS several times, but chiefly in GS2 (Baumeister et al. 2000; Kumar et al. 2001; Sanal et al. 2002). Similar to FHLH, this disorder may be associated with decreased NK activity and hypertriglyceridemia (Baumeister et al. 2000). Recurrent hemophagocytosis can be severe and cause pancytopenia, already in neonates (Kumar et al. 2001). In GS associated with such reactions,

specifically in the so-called accelerated phase of GS, hepatomegaly with or without jaundice can occur (Sanal et al. 1993; Mancini et al. 1998; Baumeister et al. 2000). In one patient, hepatosplenomegaly was associated with hepatitis (Mancini et al. 1998). In pediatric patients with hepatomegaly, autopsy revealed lymphohistiocytosis and erythrophagocytosis of the liver (Sanal et al. 1993; Gögüs et al. 1995). In more detail, the liver is densely infiltrated by small lymphocytes and histiocytoid cells/macrophages, some of the engulfing erythrocytes (Gögüs et al. 1995), but in an autopsy study, erythrophagocytosis was particularly prominent in bone marrow and the spleen (Gögüs et al. 1995).

Liver Involvement in Chediak-Higashi Syndrome

In the accelerated phase of CHS, a syndrome develops that may be very similar to FHLH or to virus-induced hemophagocytic syndromes, including multivisceral lymphohistiocytosis, hemophagocytosis causing pancytopenia, hypertriglyceridemia, and eventual fatal outcome (Bejaoui et al. 1989; Shome et al. 2002). The lymphoid cell infiltrates are sometimes both very dense and atypical, leading to the differential diagnosis of malignant non-Hodgkin's lymphoma. The infiltrates may contain large histiocytoid cells and bona fide macrophages. Hemophagocytosis in lymph nodes, bone marrow, and visceral organs has consistently been reported (Donohue and Bain 1957; Efrati and Jonas 1958; Padgett et al. 1967; Bedoya et al. 1969; Krüger et al. 1971; Ito et al. 1972; Valenzuela et al. 1976). The presence of massive lymphohistiocytic infiltrates cannot only induce generalized lymphadenopathy but also hepatomegaly and splenomegaly (Krüger et al. 1971; Ahluwalia et al. 2003). In one study, the liver of each of four autopsied patients weighed 1.5–2 times normal (Rubin et al. 1985). Histologically, the typical hepatic changes consist of lymphohistiocytic infiltrates chiefly localized to the portal tracts (Valenzuela et al. 1976), but accumulation of lymphocytes and histiocytoid cells is also seen, albeit to a lesser degree, in the hepatic sinusoids. In some instances, the infiltrate extends between the hepatic lobules bridging the portal tracts (Rubin et al. 1985). Both the infiltrating histiocytoid cells and the resident Kupffer cells reveal prominent hemophagocytosis and nucleophagocytosis (Valenzuela et al. 1976). Among the phagocytosed elements, erythrocytes are by far the most numerous, but usually without significant phagocyte iron overload. At electron microscopic examination, giant lysosomal structures are also detectable in hepatocytes (Valenzuela et al. 1976). The hepatic infiltration may be associated with portal fibrosis (Krüger et al. 1971).

Hemophagocytic Lymphohistiocytosis and Liver Involvement in Wiskott-Aldrich Syndrome

Patients with WAS can develop EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH; Pasic et al. 2003) that induces liver alterations similar to those found in reactive MAS (see above).

Liver Changes in X-Linked Lymphoproliferative Disease

Liver pathology in XLP is dominated by infiltration by lymphoid cells, massive hemophagocytosis (Arico et al. 2001a), and other changes related to EBV infection. In the SAP-deficiency mouse model, hemophagocytosis has been documented (Yin et al. 2003). The marked hemophagocytosis observed in patients with XLP is strongly linked to massive EBV infection (predominantly fulminant infectious mononucleosis FIM) with virus-associated hemophagocytic syndrome (VAHS). EBV is a major triggering factor producing hemophagocytic syndromes, probably via hypercytokinemia caused by mono- or oligoclonal lymphocyte proliferation induced by EBV (Imashuku 2002). In a postmortem study of a boy with XLP-related FIM, the liver showed prominent polymorphous infiltrates (small and large, blast-like lymphocytes; plasma cells; macrophages; Reed-Sternberg-like cells) associated

with confluent zone 1 necrosis in the liver and hemophagocytosis (Maia and Garwacki 1999). The complex cellular infiltrate mainly involves the expanded portal tracts, but extends beyond the limiting plate to reach the periportal zone 1. Erythrophagocytosis is mainly accomplished by Kupffer cells (the hepatic macrophage system), but also by histiocytoid cells infiltrating the liver.

Localized and Generalized Crystal-Storing Histiocytosis

Introduction

Crystal-storing histiocytosis (CSH) occurs in conjunction with disorders associated with the production of monoclonal/monotypic immunoglobulins (paraproteins, Apitz 1940; multiple myeloma; extramedullary plasmacytoma; lymphoplasmacytic lymphoma; monoclonal gammopathy of undetermined significance, MGUS), but sometimes also in the context of other lymphoproliferative diseases (e.g., MALT lymphoma, low-grade B-cell NHL, extranodal marginal B-cell NHL, or large cell NHL) and even polyclonal disorders (e.g., in rheumatoid arthritis or in association with plasma cell granuloma). The hallmark of CSH is the accumulation of pinocytosed paraproteins (immunoglobulin light-chain proteins) in macrophages/histiocytes (the so-called "pseudo-pseudo-Gaucher cells," PPGC; Schaefer 1996) with subsequent formation of numerous intracytoplasmic crystals within lysosomes/pinosomes (Glaus 1917; Hamperl and Kalkhoff 1953; Ito et al. 1970; Jenkins et al. 1994; Papla et al. 2004; Keane and Gill 2008; Yang et al. 2010). The crystal-storing phenomenon in myeloma with associated amyloidosis has already been recognized in 1917 (Glaus 1917).

Immunoglobulins of light-chain-type kappa have been almost exclusively involved (lambda chain reported only about five times) without a consistent association with a particular Ig heavy chain. Crystal formation in CSH appears to be chiefly related to the type of light chain (kappa>>>lambda); kappa light chains are also involved in light-chain deposition disease and adult Fanconi syndrome with only rare exceptions (Maldonado et al. 1975; Ganeval et al. 1984).

Epidemiology

About 80 cases have been reported as of 2012, and most situations were detected together with myeloma or lymphoplasmacytic lymphoma. In a review of the literature, the mean age at presentation was 59 years for men and 61 years for women. Fifty-eight percent had localized CSH and 42 % had generalized CSH (Dogan et al. 2012). The latter mainly involved the bone marrow, liver, lymph nodes spleen, and/or kidney. The vast majority of the patients (90 %) had an underlying lymphoproliferative or plasma cell disorder, in particular myeloma, lymphoplasmacytic lymphoma, or MGUS. Tumor-like localized forms of CSH (crystal-storing histiocytoma) are rare and involved, e.g., the lung, heart, stomach, kidney, breast, central nervous system, and tongue (Dogan et al. 2012). In a more recent study, generalized involvement was detected in only 8 % (Kanagal-Shamanna et al. 2015).

Pathology of CSH

Morphologically, the inclusions present as eosinophilic needle-like structures in the cytoplasm of macrophages/histiocytes, frequently in a proportion of 30–50 % of the total cell volume (Lebeau et al. 2002). The crystals stain pink in hematoxylin-eosin preparations, reddish brown in Elastica van Gieson, and dark blue in Giemsa preparations (Lebeau et al. 2002). Ultrastructurally, rectangular and rhomboid crystal shapes predominate; the crystals do not reveal a periodic organization and have been shown to be located within lysosomes (Terashima et al. 1978). Immunohistochemistry may detect the Ig light-chain (kappa) character of the crystalline protein, although the staining may be weak and restricted to the crystals' periphery, owing to coverage of epitopes in the densely packed structures. Light-chain

crystal deposition can be confirmed by use of immunoelectron microscopy (immunogold labeling). The technique lacks the drawbacks of immunohistochemistry for crystalline deposits and seems to detect the disorders earlier; therefore, this method has been advocated to be employed in the diagnostic workup (Gu et al. 2003). The density of storing cells may sometimes exceedingly high, to the point that the underlying neoplastic disease may be camouflaged and the crystal-storing macrophages may adopt the appearance of Gaucher cells, suggesting the erroneous diagnosis of Gaucher's disease/glucocerebrosidosis (Ito et al. 1970).

CSH in the Hepatobiliary Tract

Liver manifestations of generalized CSH can be caused by the underlying lymphoproliferative disorder and its sequelae (Figs. 6 and 7). In one patient with multiple myeloma associated with CSH and amyloidosis, nodular myeloma cell infiltrates were scattered in the liver, spleen, and kidneys, accompanied by crystal-storing macrophages Takahashi et al. 1987). In generalized CSH involving the liver, crystals are mainly seen in the hepatic macrophage system, but in one case, crystals were also observed within hepatocytes (Papla et al. 2004). In a minority of cases of CSH, crystal-storing macrophages/histiocytes may represent the main pathologic liver finding. In one study, swollen Kupffer cells (hepatic macrophages) were found to contain crystalline inclusions, apparently obstructing the sinusoidal spaces. The cells involved were predominantly observed in central areas of the lobules, but crystal-storing macrophages are also located in the portal tracts (Terashima et al. 1978; Lebeau et al. 2002; Zioni et al. 2004). These macrophages exhibit positive immunoreactivity of kappa or lambda chains, IgA, IgG, or IgM, depending on the type of underlying lymphoproliferative disorder (Papla et al. 2004). At electron microscopic examination, the Kupffer cells may harbor an enormous amount of crystalline structures, sometimes displacing the nucleus to the periphery. Interestingly, these examinations also revealed intracytoplasmic crystals in hepatocytes, intermingled with mitochondria (Lebeau et al. 2002). Crystalline inclusions were also detected in hepatocytes in a case of multiple myeloma associated with generalized CSH (Kjeldsberg et al. 1977).

Differential Diagnosis

CSH should morphologically not be confounded with other disorders resulting in generalized

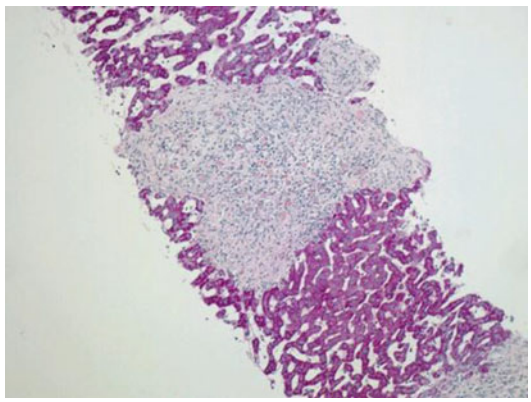

Fig. 6 Localized crystal-storing histiocytosis of the liver. The enlarged portal tracts are transformed into micronodular structures with a dense infiltrate containing PAS-positive cells (PAS stain)

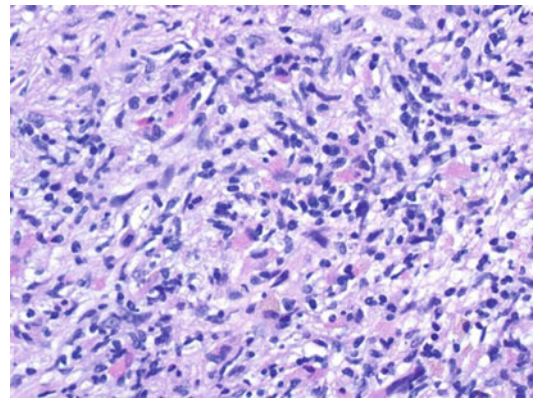

Fig. 7 Localized crystal-storing histiocytosis of the liver. The mixed cellular infiltrate contains large histiocytes/macrophages with bundles of immunoglobulin crystalloids (*pink structures*; Giemsa stain)

crystal deposition in the macrophage system, e.g., clofazimine-induced crystal-storing histiocytosis; clofazimine crystals are red in the frozen section and are brightly-red birefringent, but dissolve upon preparation of paraffin sections, leaving empty spaces, in contrast to the crystals of CSH (Sukpanichnant et al. 2000). Furthermore, Ig-containing crystals may accumulate in lymphoid cells of NHL, e.g., in follicular lymphoma, without involvement of the macrophage/histiocyte system (Wada et al. 2002).

Pathogenic Pathways

What are the pathogenic mechanisms of crystal formation in CSH? Overproduction of Ig light chains does not seem to be the key mechanism, because CSH has been observed in situations of minimal or no paraproteinemia or of low numbers of monoclonal Ig-producing cells. It has therefore been proposed that the stored paraproteins/light chains have sequence anomalies at specific sites promoting crystallization within target cells or adversely affect the cellular light-chain degradation pathway (Lebeau et al. 2002). Possible explanations surfaced from studies on the proximal renal tubular disorder, adult Fanconi syndrome, occurring in plasma cell dyscrasias, and caused by nephrotoxic Ig light chains. Diseases with production of abnormal immunoglobulin light chains (LC) can cause cast nephropathy or an accumulation of intracellular crystals in proximal tubular cells, a disorder termed myeloma-associated Fanconi syndrome with LC crystallization (Lajoie et al. 2000; Messiaen et al. 2000). In the latter disorder, proximal renal tubular cells carry numerous phagolysosomal inclusions with occasional crystalline periodic striation (Decourt et al. 2003).

Several studies have investigated molecular changes of LC in adult Fanconi syndrome (Rocca et al. 1995; Leboulleux et al. 1995; Deret et al. 1999; Decourt et al. 2003). In one study analyzing the molecular characteristics of LC, all three kappa chains responsible for crystal storage were encoded by the LCO2/O12 germline gene and had an unusual nonpolar residue in the CDR-L1 loop (Deret et al. 1999). A further study on patients with adult Fanconi syndrome showed that the variable domains of kappa chains were resistant to proteolytic cleavage in vitro, suggesting that crystal accumulation in lysosomes may result from resistance to degradation (Leboulleux et al. 1995). Unusual features restricted to the variable region of the kappa1 sequence were identified by another group, likely resulting from somatic hypermutation and probably altering the catabolism of the internalized proteins (Decourt et al. 2003). In murine models for LC-associated Fanconi syndrome, limited molecular changes introduced through site-directed mutagenesis in the variable domain may suppress formation of intracellular crystals within renal tubular cells (Decourt et al. 1999). In the light of these findings, it is of particular interest to note that, recently, an abnormal kappa LC has been characterized in CSH, showing unusual amino acid substitutions in the variable region of the stored LC and thought to be involved in pathogenesis of crystal storage (Lebeau et al. 2002).

References

Abdelfattah AM, Arnaout K, Tabbara IA (2014) Erdheim-Chester disease: a comprehensive review. Anticancer Res 34:3257–3261

Ahluwalia J, Pattari S, Trehan A, Marwaha RK, Garewal G (2003) Accelerated phase at initial presentation: an uncommon occurrence in Chediak-Higashi syndrome. Pediatr Hematol Oncol 20:563–567

Alegre VA, Winkelmann RK (1989) Histiocyte cytophagic panniculitis. J Am Acad Dermatol 20:177–185

Allen CE, McCain KL (2015) Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. Hematol Am Soc Hematol Educ Program 2015:177–1982

Allen CE, Parsons DW (2015) Biological and clinical significance of somatic mutations in Langerhans cell histiocytosis and related histiocytic neoplastic disorders. Hematol Am Soc Hematol Educ Program 2015:559–564

Allen M, De Fusco C, Legrand F, Clementi R, Conter V, Danesino C, Janka G, Arico M (2001) Familial hemophagocytic lymphohistiocytosis: how late can the onset be? Haematologica 86:499–503

Amarapurkar DN, Patel ND, Amarapurkar AD (2005) Panniculitis and liver disease (hepatic Weber Christian disease). J Hepatol 42:149–150

Amer R, Pe'er J, Pappo O, Dotan S (2005) Necrobiotic xanthogranuloma associated with choroidal infiltration

and syncytial giant cell hepatitis. J Neuroophthalmol 25:189–192
Amin N, Shah I, Bhatnagar S (2014) Hemophagocytic lymphohistiocytosis (HLH) in children presenting as liver disease. J Clin Hepatol 4:175–177
Anders RA, Keith JN, Hart J (2003) Rosai-Dorfman disease presenting in the gastrointestinal tract. Arch Pathol Lab Med 127:E74–E75
Andreopoulos A, Yiakoumis X, Antoniou TC, Andreopoulos G, Konstantopoulos K, Pangalis GA et al (2007) Primary adult-onset macrophage activation syndrome with multisystemic tissue phagocytosis. Int J Hematol 86:394–396
Antonius JI, Farid SM, Baez-Giangreco A (1996) Steroid-responsive Rosai-Dorfman disease. Pediatr Hematol Oncol 13:563–570
Apitz K (1940) Paraproteinosen. Ueber die Störungen des Eiweissstoffwechsels bei Plasmozytomen. Virchows Arch Pathol Anat 306:630–699
Arabadzhieva E, Yonkov A, Bonev S, Bulanov D, Taneva I, Pirdopska T, Terziev I, Dimitrova V (2015) Rosai-Dorfman disease involving gallbladder and liver – report of a case. Int J Surg Case Rep 12:140–142
Arico M, Janka G, Fischer A, Henter JL, Blanche S, Elinder G, Martinetti M, Rusca MP (1996) Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. Leukemia 10:197–203
Arico M, Imashuku S, Clementi R, Hibi S, Teramura T, Danesino C, Haber DA, Nichols KE (2001a) Hemophagocytic lymphohistiocytosis due to germline mutations in SH2D1A, the X-linked lymphoproliferative disease gene. Blood 97:1131–1133
Arico M, Danesino C, Pende D, Moretta L (2001b) Pathogenesis of haemophagocytic lymphohistiocytosis. Br J Haematol 114:761
Aronson IK, Worobec SM (2010) Cytophagic histiocytic panniculitis and hemophagocytic lymphohistiocytosis: an overview. Dermatol Ther 23:389–402
Atteritano M, David A, Bagnato G, Beninati C, Frisina A, Iaria C, Bagnato G, Cascio A (2012) Haemophagocytic syndrome in rheumatic patients. A systematic review. Eur Rev Med Pharmacol Sci 16:1414–1424
Bara C, Barbarot S, Hamidou M, Cassagnau E, Renaut JJ, Triau S, Roubeix Y, Stalder JF (2003) Systemic necrobiotic xanthogranuloma with initial pericardial and pulmonary involvement (in French). Ann Dermatol Venereol 130:341–344
Baumeister FA, Stachel D, Schuster F, Schmid I, Schaller M, Wolff H, Weiss M, Belohradsky BH (2000) Accelerated phase in partial albinism with immunodeficiency (Griscelli syndrome): genetics and stem cell transplantation in a 2-month-old girl. Eur J Pediatr 159:74–78
Bedoya V, Grimley PM, Duque O (1969) Chediak-Higashi syndrome. Arch Pathol 88:340–349
Bejaoui M, Veber F, Girault D, Gaud C, Blanche S, Griscelli C, Fischer A (1989) The accelerated phase of Chediak-Higashi syndrome (in French). Arch Fr Pediatr 46:733–736
Beutel et al (2009) http://www.ncbi.nlm.nih.gov/pubmed/19353621
Bhatia S, Bauer F, Bilgrami SA (2003) Candidiasis-associated hemophagocytic lymphohistiocytosis in a patient with human immunodeficiency virus. Clin Infect Dis 37:e61–e66
Bihl F, Emmenegger U, Reichen J, Neftel KA, Zimmermann A, Cerny A (2006) Macrophage activation syndrome is associated with lobular hepatitis and sever bile duct injury with cholestasis. J Hepatol 44:1208–1212
Billiau AD, Roskams T, Van Damme-Lombaerts R, Matthys P, Wouters C (2005) Macrophage activation syndrome: characteristic findings on liver biopsy illustrating the key role of activated, IFN-gamma-producing lymphocytes and IL-6- and TNF-alpha-producing macrophages. Blood 105:1648–1651
Bjornstad RT (1951) A fatal case of Weber-Christian disease (relapsing, febrile, nodular non-suppurative panniculitis). Acta Derm-Venereol (Stockh) 31:313–321
Blombery P, Wong SQ, Lade S, Prince HM (2012) Erdheim-Chester disease harboring the BRAF V600E mutation. J Clin Oncol 30:e331–e332
Boissy C, Velin P, Michiels JF, Diebold J, Hofman P (1997) Familial hemophagocytic lymphohistiocytosis. Differential diagnosis with secondary hemophagocytic syndromes (in French). Arch Anat Cytol Pathol 45:208–213
Bosco J, Allende A, Varikatt W, Lee R, Sewart GJ (2015) Does the BRAF(V600E)mutation herald a new treatment era for Erdheim-Chester disease? A case-based review of a rare and difficult to diagnose disorder. Intern Med J 45:348–351
Brill IC (1936) Medical papers dedicated to H.A Christian. Waverly Press, Baltimore
Brown RE, D'Cruz CA (1987) Sinus histiocytosis massive lymphadenopathy syndrome: histogenesis of the hepatic lesions. Ann Clin Lab Sci 17:162–170
Buchino JJ, Byrd RP, Kmetz DR (1982) Disseminated sinus histiocytosis with massive lymphadenopathy: its pathologic aspects. Arch Pathol Lab Med 106:13–16
Cascio A, Pernice LM, Barberi G, Delfino D, Biondo C, Beninati C, Mancuso G, Rodriguez-Morales AJ et al (2012) Secondary hemophagocytic lymphohistiocytosis in zoonoses. A systematic review. Eur Rev Med Pharmacol Sci 16:1324–1337
Cavalli G, Biavsco R, Borgiani B, Dagna L (2014) Oncogene-induced senescence as a new mechanism of disease: the paradigm of Erdheim-Chester disease. Front Immunol 5:281
Chen RL, Hsu YH, Ueda I, Imashuku S, Takeuchi K, Tu BP, Chuang SS (2007) Cytophagic histiocytic panniculitis with fatal haemophagocytic lymphohistiocytosis in a paediatric patient with perforin gene mutation. J Clin Pathol 60:1168–1169

Chester W (1930) Über Lipoidgranulomatose. Virchows Arch Pathol Anat 279:561–602

Cho HS, Park YN, Lyu CJ, Park SM, Oh SH, Yang CH, Yang WI, Kim KY (1997) EBV-elicited familial hemophagocytic lymphohistiocytosis. Yonsei Med J 38:245–248

Chow CP, Ho HK, Chan GC, Cheung AN, Ha SY (2009) Congenital Rosai-Dorfman disease presenting with anemia, thrombocytopenia, and hepatomegaly. Pediatr Blood Cancer 52:415–417

Christian HA (1928) Relapsing febrile nodular nonsuppurative panniculitis. Arch Intern Med (Chicago) 42:338–351

Cicocki F, Schlums H, Li H, Stache V, Holmes T, Lenvik TR, Chiang SC, Miller JS et al (2014) Transcriptional regulation of Munc13-4 expression in cytotoxic lymphocytes is disrupted by an intronic mutation associated with a primary immunodeficiency. J Exp Med 211:1079–1091

Cives M, Simone V, Rizzo FM, Dicuonzo F, Cristallo Lacalamita M, Ingravallo G, Silvestris F, Dammacco F (2015) Erdheim-Chester disease: a systematic review. Crit Rev Oncol Hematol 95:1–11

Colmenero I, Molho-Pessach V, Torrelo A, Zlotogorski A, Requena L (2012) Emperipolesis: an additional common histopathologic finding in H syndrome and Rosai-Dorfman disease. Am J Dermatopathol 34:315–320

Corbeel LM (1998) Non hereditary hemophagocytic (hps) syndrome. Eur J Pediatr 157:523

Craig AJ, Cualing H, Thomas G, Lamerson C, Smith R (1998) Cytophagic histiocytic panniculitis – a syndrome associated with benign and malignant panniculitis: case comparison and review of the literature. J Am Acad Dermatol 39:721–736

Crotty CP, Winkelmann RK (1981) Cytophagic histiocytic panniculitis with fever, cytopenia, liver failure, and terminal hemorrhagic diathesis. J Am Acad Dermatol 4:181–194

Cummings C, McCarthy P, van Hoff J, Porter G (2008) Kawasaki disease associated with reactive hemophagocytic lymphohistiocytosis. Pediatr Infect Dis J 27:1116–1118

Dagna L, Corti A, Langheim S, Guglielmi B, De Cobelli F, Doglioni C, Fragasso G et al (2012) Tumor necrosis factor a as a master regulator of inflammation in Erdheim-Chester disease: rationale for the treatment of patients with infliximab. J Clin Oncol 30:e286–e290

Daum GS, Sullivan JL, Ansell J, Mulder C, Woda BA (1987) Virus-associated hemophagocytic syndrome: identification of an immunoproliferative precursor lesion. Hum Pathol 18:1071–1074

Davi S, Consolaro A, Guseinova D, Pistorio A, Ruperto N, Martini A, Cron RQ, Ravelli A et al (2011) An international consensus survey of diagnostic criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis. J Rheumatol 38:764–768

De Jesus AA, Goldbach-Mansky R (2015) Newly recognized Mendelian disorders with rheumatic manifestations. Curr Opin Rheumatol 27:511–519

De Kerguenec C, Hillaire S, Molinié V, Gardin C, Degott C, Erlinger S, Valla D (2001) Hepatic manifestations of hemophagocytic syndrome: a study of 30 cases. Am J Gastroenterol 96:852–857

de Saint Basile G, Ménasché G, Latour S (2011) Inherited defects causing hemophagocytic lymphohistiocytic syndrome. Ann NY Acad Sci 1246:64–76

Decourt C, Rocca A, Bridoux F, Vrtovsnik F, Preud'homme JL, Cogne M, Touchard G (1999) Mutational analysis in murine models for myeloma-associated Fanconi's syndrome or cast myeloma nephropathy. Blood 94:3559–3566

Decourt C, Bridoux F, Touchard G, Cogne M (2003) A monoclonal V kappa I light chain responsible for incomplete proximal tubulopathy. Am J Kidney Dis 41:497–504

Deret S, Denoroy L, Lamarine M, Vidal R, Mougenot B, Frangione B, Stevens FJ, Ronco PM, Aucouturier P (1999) Kappa light chain-associated Fanconi's syndrome: molecular analysis of monoclonal immunoglobulin light chains from patients with and without intracellular crystals. Protein Eng 12:363–369

Destombes P (1965) Adénites avec surcharge lipidique de l'enfant ou de l'adulte jeune, observées aux Antilles et au Mali: quatre observations. Bull Soc Pathol Exot Fil 58:1169–1175

Dharancy S, Crombe V, Copin MC, Boleslawski E, Bocket L, Declerck N, Canva V et al (2008) Fatal hemophagocytic syndrome related to human herpesvirus-6 reinfection following liver transplantation: a case report. Transplant Proc 40:3791–3793

Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, Dupond JL, Larroche C, Piette AM, Mechenstock D et al (2003) Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. Arthritis Rheum 49:633–639

Di Tommaso L, Rahal D, Bossi P, Roncalli M (2010) Hepatic Rosai-Dorfman disease with coincidental lymphoma: report of a case. Int J Surg Pathol 18:540–543

Dickson BC, Pethe V, Chung CT, Howarth DJC, Bilbao JM, Fornasier VL, Streutker CJ et al (2008) Systemic Erdheim-Chester disease. Virchows Arch 452:221–227

Dogan S, Barnes L, Cruz-Vetrano WP (2012) Crystal-storing histiocytosis: report of a case, review odf the literature (80 cases) and a proposed classification. Head Neck Pathol 6:111–120

Donohue WL, Bain HW (1957) Chediak-Higashi syndrome. A lethal familial disease with anomalous inclusions in the leukocytes and constitutional stigmata: report of a case with necropsy. Pediatrics 20:416–430

Dufourcq-Lagelouse R, Pastural E, Barrat FJ, Feldmann J, Le Deist F, Fischer A, De Saint Basile G (1999a) Genetic basis of hemophagocytic lymphohistiocytosis syndrome (review). Int J Mol Med 4:127–133

Dufourcq-Lagelouse R, Jabado N, Le Deist F, Stephan JL, Souillet G, Bruin M, Vilmer E, Schneider M, Janka G, Fischer A, de Saint Basile G (1999b) Linkage of

familial hemophagocytic lymphohistiocytosis to 10q21-22 and evidence for heterogeneity. Am J Hum Genet 64:172–179
Edge J, Dunger DB, Dillon MJ (1986) Weber-Christian panniculitis and chronic active hepatitis. Eur J Pediatr 145:227–229
Efrati P, Jonas W (1958) Chediak's anomaly of leukocytes in malignant lymphoma associated with leukemic manifestations: case report with necropsy. Blood 13:1063–1073
Egeler RM, Shapiro R, Loechelt B, Filipovich A (1996) Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol 18:340
Eisen RN, Buckley PJ, Rosai J (1990) Immunophenotypic characterization of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Semin Diagn Pathol 7:74–82
Emile JF, Charlotte F, Amoura Z, Haroche J (2013) BRAF mutations in Erdheim-Chester disease. J Clin Oncol 31:398
Emile JF, Diamond EL, Hélias-Rodzewicz Z, Cohen-Aubart F, Charlotte F, Hyman DM et al (2014) Recurrent RAS and PIK3CA mutations in Erdheim-Chester disease. Blood 124:3016–3019
Emmenegger U, Zehnder R, Frey U, Reimers A, Spaeth PJ, Neftel KA (2000) Elevation of soluble Fas and soluble Fas ligand in reactive macrophage activation syndrome. Am J Hematol 64:116–119
Emmenegger U, Reimers A, Frey U, Fux C, Bihl F, Semela D, Cottagnoud P, Cerny A, Spaeth PJ, Neftel KA (2002) Reactive macrophage activation syndrome: a simple screening strategy and its potential in early treatment initiation. Swiss Med Wkly 132:230–236
Esquivel J, Krishnan J, Jundi M, Sugarbaker PH (1999) Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) of the pancreas: first case report. Hepatogastroenterology 46:1202–1205
Esumi N, Ikushima S, Todo S, Imashuku S (1987) Hyperferritinemia in malignant histiocytosis and virus-associated hemophagocytic syndrome. N Engl J Med 316:346–347
Fadeel B, Orrenius S, Henter JI (1999) Induction of apoptosis and caspase activation in cells obtained from familial hemophagocytic lymphohistiocytosis patients. Br J Haematol 106:406–415
Fadeel B, Orrenius S, Henter JI (2001) Familial hemophagocytic lymphohistiocytosis: too little cell death can seriously damage your health. Leuk Lymphoma 42:13–20
Fardet L, Blum L, Kerob D, Agbalika F, Galicier L, Dupuy A, Lafaurie M, Meignin V, Morel P, Lebbe C (2003) Human herpesvirus 8-associated hemophagocytic lymphohistiocytosis in human immunodeficiency virus-infected patients. Clin Infect Dis 37:285–291
Farquhar JW, Claireaux AF (1952) Familial hemophagocytic reticulosis. Arch Dis Child 27:519–525
Favara B (1992) Hemophagocytic lymphohistiocytosis: a hemophagocytic syndrome. Semin Diagn Pathol 9:63–74
Favara B (1996) Histopathology of the liver in histiocytosis syndromes. Pediatr Pathol Lab Med 16:413–433
Félix FH, Leal LK, Fontenele JB (2009) Cloak and dagger: the case for adult Still disease and hemophagocytic lymphohistiocytosis. Rheumatol Int 29:973–974
Filipovich AH (2008) Hemophagocytic lymphohistiocytosis and other hemophagocytic disorders. Immunol Allergy Clin North Am 28:293–313
Finan MC, Winkelmann RK (1987) Histopathology of necrobiotic xanthogranuloma with paraproteinemia. J Cutan Pathol 14:92–99
Fisman DN (2000) Hemophagocytic syndromes and infection. Emerg Infect Dis 6:601–608
Folkerth RD, Price DL, Schwartz M, Black PM, De Girolami U (1998) Xanthomatous hypophysitis. Am J Surg Pathol 22:736–741
Fortson JS, Schroeter AL (1990) Necrobiotic xanthogranuloma with IgA paraproteinemia and extracutaneous involvement. Am J Dermatopathol 12:579–584
Foucar E, Rosai J, Dorfman R (1990) Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. Semin Diagn Pathol 7:19–73
Friedman NB (1945) Fatal panniculitis. Arch Pathol (Chicago) 39:42–46
Gaitonde S (2007) Multifocal, extranodal sinus histiocytosis with massive lymphadenopathy: an overview. Arch Pathol Lab Med 131:1117–1121
Ganeval et al (1984) http://www.ncbi.nlm.nih.gov/pubmed/6434789
Gencik A, Signer E, Müller H (1984) Genetic analysis of familial erythrophagocytic lymphohistiocytosis. Eur J Pediatr 142:248–252
Gilchrist TC, Ketron LW (1916) A unique case of atrophy of the fatty layer of the skin preceded by the ingestion of the fat by large phagocytic cells-macrophages. Johns Hopkins Hosp Bull 27:291
Glaus A (1917) Ueber ein multiples Myelozytom mit eigenartigen, zum Teil kristallähnlichen Zelleinlagerungen, kombiniert mit Elastolyse und ausgedehnter Amyloidose und verkalkung. Virchows Arch Pathol Anat 223:301–339
Gögüs S, Topcu M, Kucukali T, Akcoren Z, Berkel I, Ersoy F, Günay M, Saatci I (1995) Griscelli syndrome: report of three cases. Pediatr Pathol Lab Med 15:309–319
Graham et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/10926299
Grom AA (2003) Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities? Curr Opin Rheumatol 15:587–590
Gu X, Barrios R, Cartwright J, Font RL, Truong L, Herrera GA (2003) Light chain crystal deposition as a manifestation of plasma cell dyscrasias: the role of immunoelectron microscopy. Hum Pathol 34:270–277

Guitart J, Sethi R, Gordon K (1998) Fatal cytophagic histiocytic panniculitis after a short response to cyclosporine. J Eur Acad Dermatol Venereol 10:267–268

Gundling F, Nerlich A, Heiltland WU, Schepp W (2007) Biliary manifestation of Erdheim-Chester disease mimicking Klatskin's carcinoma. Am J Gastroenterol 102:452–454

Gupta A, Aman K, Al-Babtain M, Al-Wazzan H, Morouf R (2007) Multisystem Erdheim-Chester disease; a unique presentation with liver and axial skeletal involvement. Br J Haematol 138:280

Gupta AA, Tyrrell P, Valani R, Benseler S, Abdelhaleem M, Weitzman S (2009) Experience with hemophagocytic lymphohistiocytosis/macrophage activation syndrome at a single institution. J Pediatr Hematol Oncol 31:81–84

Hamperl H, Kalkhoff KW (1953) Knotenbildungen in der Haut mit intracellulären Ablagerungen von Eiweisskristallen. Hautarzt 4:418–423

Hanrahan FR, Ippolito VD, Goldman L (1951) Weber-Christian disease. Report of two cases, one with autopsy. Ohio St Med J 47:427–429

Haroche J, Abla O (2015) Uncommon histiocytic disorders: Rosai-Dorfman, juvenile xanthogranuloma, and Erdheim-Chester disease. Hematol Am Soc Hematol Educ Program 2015:571–578

Haroche J, Charlotte F, Arnaud L, von Deimling A, Helias-Rodzewicz Z, Hervier B et al (2012) High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood 120:2700–2703

Haroche J, Arnaud L, Cohen-Aubart F, Hervier B, Charlotte F, Emile JF, Amoura Z (2014) Erdheim-Chester disease. Curr Rheumatol Rep 16:412

Haroche J, Cohen-Aubart F, Charlotte F, Maksud P, Grenier PA, Cluzel P, Mathian A, Emile JF, Amoura Z (2015) The histiocytosis Erdheim-Chester disease is an inflammatory myeloid neoplasm. Expert Rev Clin Immunol 11:1033–1042

Hendricks WM, Ahmad M, Gratz E (1978) Weber-Christian syndrome in infancy. Br J Dermatol 98:175–186

Henter JI (1990). Familial hemophagocytic lymphohistiocytosis. A clinical, metabolic and immunological study of a lymphohistiocytic inflammatory disorder. PhD thesis, Karolinska Institute, Stockholm, pp. 35–38

Henter JI, Elinder G, Ost A, FHL Study Group of the Histiocyte Society (1991a) Diagnostic guidelines for hemophagocytic lymphohistiocytosis. Semin Oncol 18:29–33

Henter JI, Elinder G, Soder O, Hansson M, Andersson B, Andersson U (1991b) Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. Blood 78:2918–2922

Henter JI, Carlson LA, Soder O, Nilsson-Ehle P, Elinder G (1991c) Lipoprotein alterations and plasma lipoprotein lipase reduction in familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand 80:675–681

Henter JI, Ehrnst A, Andersson J, Elinder G (1993) Familial hemophagocytic lymphohistiocytosis and viral infections. Acta Pediatr 82:369–372

Henter et al (1997) http://www.ncbi.nlm.nih.gov/pubmed/9121398

Hernandez D, Gutierrez L, Duque H, Olavarria R, Muci R, Wunaii H (1987) Association of sinus histiocytosis with massive lymphadenopathy and idiopathic hypereosinophilic syndrome. Histol Histopathol 2:239–242

Hervier B, Haroche J, Arnaud L, Charlotte F, Donadieu J, Néel A, Lifermann F, Villabona C et al (2014) Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the BRAFV600E mutation. Blood 124:1119–1126

Hilton DA, O'Malley BP, Durrant ST (1990) Histiocytic cytophagic panniculitis. Postgrad Med J 66:958–961

Horn M, Stutte HJ, Schlote W (2002) Familial erythrophagocytic lymphohistiocytosis (Farquhar's disease): involvement of the central nervous system. Clin Neuropathol 21:139–144

Huilgol SC, Fenton D, Pambakian H, Cerio R, McGibbon DM, Black MM (1998) Fatal cytophagic panniculitis and haemophagocytic syndrome. Clin Exp Dermatol 23:51–55

Hunter L, Burry AF (1985) Necrobiotic xanthogranuloma: a systemic disease with paraproteinemia. Pathology 17:533–536

Imashuku S (2002) Clinical features and treatment strategies of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Crit Rev Oncol Hematol 44:259–272

Ito S, Goshima K, Ninomi M, Horikoshi N, Nomura S (1970) Electron microscopic studies of the crystalline inclusions in the myeloma cells and kidney of K-bence-Jones protein type myeloma. Nippon Ketsueki Gakkai Zasshi 33:598–617

Ito J, Tokumaru M, Okazaki T (1972) Chediak-Higashi syndrome: report of a case with autopsy and electron microscopic studies. Acta Pathol Jpn 22:755–777

Ivan D, Neto A, Lemos L, Gupta A (2003) Erdheim-Chester disease: a unique presentation with liver involvement and vertebral osteolytic lesions. Arch Pathol Lab Med 127:e337–e339

Iwabuchi H, Kakihara T, Tanaka A, Uchiyama M, Shibuya H, Umezu H (2003) Congenital Rosai-Dorfman disease without lymphadenopathy. Pediatr Pathol Mol Med 22:399–403

Janka GE (2007a) Hemophagocytic syndromes. Blood Rev 21:245–253

Janka GE (2007b) Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr 166:95–109

Janka G, Imashuku S, Elinder G, Schneider M, Henter JI (1998) Infection-and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 12:435–444

Jenkins RE, Calonje E, Fawcett H, Greaves MW, Wilson-Jones E (1994) Cutaneous crystalline deposits in myeloma. Arch Dermatol 130:484–488

Jones PE, Lamb JH, Goldman L (1950) Panniculitis. Report of cases. South Med J 43:792–799

Kanagal-Shamanna R, Xu-Monette ZY, Miranda RN, Dogan A, Zou D, Luthra R, Weber DM, O'Malley DP, Jorgensen JL et al (2015) Crystal-storing histiocytosis: a clinicopathological study of 13 cases. Histopathology. doi:10.1111/his.12768

Kapelari K, Fruehwirth M, Heitger A, Konigsrainer A, Margreiter R, Simma B, Offner FA (2005) Loss of intrahepatic bile ducts: an important feature of familial hemophagocytic lymphohistiocytosis. Virchows Arch 446:619–625

Karapinar B, Yilmaz D, Balkan C, Akin M, Ay Y, Kvakli K (2009) An unusual cause of multiple organ dysfunction syndrome in the pediatric intensive care unit: hemophagocytic lymphohistiocytosis. Pediatr Crit Care Med 10:285–290

Karasu Z, Kilic M, Cagirgan S, Lebe E, Yilmaz F, Demirbas T, Tokat Y (2003) Hemophagocytic syndrome after living-related liver transplantation. Transplant Proc 35:1482–1484

Kataoka Y, Todo S, Morioka Y, Sugie K, Nakamura Y, Yidoi J, Imashuku S (1990) Impaired natural killer activity and expression of interleukin-2 receptor antigen in familial erythrophagocytic lymphohistiocytosis. Cancer 65:1937–1941

Kaufman KM, Linghu B, Szustakowski JD, Husami A, Yang F, Zhang K, Filipovich AH, Fall N, Harley JB, Nirmala NR et al (2014) Whole-exome sequencing reveals overlap between macrophage activation syndrome in systemic juvenile idiopathic arthritis and familial hemophagocytic lymphohistiocytosis. Arthritis Rheumatol 66:3486–3495

Keane C, Gill D (2008) Multi-organ involvement with crystal-storing histiocytosis. Br J Haematol 141:750

Kikuta H (1995) Epstein-Barr virus-associated hemophagocytic syndrome. Leuk Lymphoma 16:425–429

Kikuta H, Sakiyama Y, Matsumoto S, Oh-Ishi T, Nakano T, Nagashima T, Oka T, Hironaka T, Hirai K (1993) Fatal Epstein-Barr virus-associated hemophago-cytic syndrome. Blood 82:3259–3264

Kimura H, Kako M, Yo K, Oda T (1980) Alcoholic hyalins (Mallory bodies) in a case of Weber-Christian disease: electron microscopic observations of liver involvement. Gastroenterology 78:807–812

King PD, Diaz-Arias AA, Birkby WF, Loy TS (1994) Reactive hemophagocytic syndrome simulating acute hepatitis. A case due to hepatic peripheral T-cell lymphoma. J Clin Gastroenterol 19:234–237

Kinmont PDC (1952) Non-suppurative panniculitis. Br J Dermatol 64:108–109

Kjeldsberg CR, Eyre HJ, Totzke H (1977) Evidence for intracellular amyloid formation in myeloma. Blood 50:493–504

Kogawa K, Lee SM, Villanueva J, Marmer D, Sumegi J, Filipovich AH (2002) Perforin expression in cytotoxic lymphocytes from patients with hemophagocytic lymphohistiocytosis and their family members. Blood 99:61–66

Kossard S, Winkelmann RK (1980) Necrobiotic xanthogranuloma with paraproteinemia. J Am Acad Dermatol 3:257–270

Krok KL, Torbenson MS, Schulick RD, Thuluvath PJ (2007) Lymphadenopathy, elevated liver function tests and weight loss in a 68-year-old man. J Dig Dis 8:103–106

Krüger GRF, Bedoya V, Grimley PM (1971) Lymphoreticular tissue lesions in Steinbrinck-Chediak-Higashi syndrome. Virchows Arch A Pathol Anat 353:273–288

Kumakura S, Ishikura H, Umegae N, Yamagata S, Kobayashi S (1997) Autoimmune-associated hemophagocytic syndrome. Am J Med 102:113–115

Kumar M, Sackey K, Schmalstieg F, Trizna Z, Elghetany MT, Alter BP (2001) Griscelli syndrome: rare neonatal syndrome of recurrent hemophagocytosis. J Pediatr Hematol Oncol 23:464–468

Kupfer A, Singer SJ (1989) Cell biology of cytotoxic and helper T cell functions: immunofluorescence microscopic studies of single cells and cell couples. Annu Rev Immunol 7:309–337

Kusutani N, Tamiya H, Tsuruta D, Mizuno N, Sowa J, Kaida M, Ishii M, Yamamoto O, Kobayashi H (2011) Apoptosis of neutrophils resulting after emperipolesis in cutaneous Rosai-Dorfman disease: a new ultrastructural finding. J Cutan Pathol 38:529–531

Lajoie G, Leung R, Bargman JM (2000) Clinical, biochemical, and pathological features in a patient with plasma cell dyscrasia and Fanconi syndrome. Ultrastruct Pathol 24:221–226

Lambotte O, Cacoub P, Costedoat N, Le Moel G, Amoura Z, Piette JC (2003) High ferritin and low glycosylated ferritin may also be a marker of excessive macrophage activation. J Rheumatol 30:1027–1028

Lamprecht P, Moosig F, Adam-Klages S, Mrowietz U, Csernok E, Kirrstetter M, Ahmadi-Simab K et al (2004) Small vessel vasculitis and relapsing panniculitis in tumour necrosis factor receptor associated periodic syndrome (TRAPS). Ann Rheum Dis 63:1518–1520

Larroche C (2012) Hemophagocytic lymphohistiocytosis in adults: diagnosis and treatment. Joint Bone Spine 79:356–361

Larroche C, Ziol M, Zidi S, Dhote R, Roulot D (2007) Liver involvement in hemophagocytic syndrome (in French). Gastroenterol Clin Biol 31:959–966

Lauwers GY, Perez-Atayde A, Dorfman RF, Rosai J (2000) The digestive system manifestations of Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy): review of 11 cases. Hum Pathol 31:380–385

Lebeau A, Zeindl-Eberhart E, Muller EC, Muller-Hocker J, Jungblut PR, Emmerich B, Lohrs U (2002) Generalized crystal-storing histiocytosis associated with monoclonal gammopathy: molecular analysis of a disorder with rapid clinical course and review of the literature. Blood 100:1817–1827

Leboulleux M, Lelongt B, Mougenot B, Touchard G, Makdassi R, Rocca A, Noel LH, Ronco PM,

Aucouturier P (1995) Protease resistance and binding of Ig light chains in myeloma-associated tubulopathies. Kidney Int 48:72–79

Maakaroun NR, Moanna A, Jacob JT, Albrecht H (2010) Viral infections associated with hemophagocytic syndrome. Rev Med Virol 20:93–105

Mahadeva U, Allport T, Bain B, Chan WK (2000) Haemophagocytic syndrome and histiocytic necrotising lymphadenitis (Kikuchi's disease). J Clin Pathol 53:636–638

Maheshwari A, Seth A, Choudhury M, Aggarwal V, Patra B, Aggarwal S, Mukherjee SB, Aneja S (2009) Rosai-Dorfman disease: a case with lymphadenopathy and liver involvement. J Pediatr Hematol Oncol 31:200–202

Maia DM, Garwacki CP (1999) X-linked lymphoproliferative disease: pathology and diagnosis. Pediatr Dev Pathol 2:72–77

Maldonado et al (1975) http://www.ncbi.nlm.nih.gov/pubmed/163583

Mancini AJ, Chan LS, Paller AS (1998) Partial albinism with immunodeficiency: Griscelli syndrome: report of a case and review of the literature. J Am Acad Dermatol 38:295–300

March LM, Webb J, Eckstein RP (1986) Cytophagic panniculitis. Aust NZ J Med 16:397–401

Melki I, Lambot K, Jonard L, Couloigner V, Quartier P, Neven B, Bader-Meunier B (2013) Mutation in the SLC29A3 gene: a new cause of a monogenic, autoinflammatory condition. Pediatrics 131:1308–131

Messiaen T, Deret S, Mougenot B, Bridoux F, Dequiedt P, Dion JJ, Makdassi R, Meeus F, Pourrat J, Touchard G et al (2000) Adult Fanconi syndrome secondary to light chain gammopathy. Clinicopathologic heterogeneity and unusual features in 11 patients. Medicine (Baltimore) 79:135–154

Middel P, Hemmerlein B, Fayazi A, Kaboth U, Radzun HJ (1999) Sinus histiocytosis with massive lymphadenopathy: evidence for its relationship to macrophages and for a cytokine-related disorder. Histopathology 35:525–533

Miller JL, Kritzler RA (1943) Nodular nonsuppurative panniculitis. Arch Derm Syph (Chicago) 47:82–96

Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, Lehmberg K, Weitzman S, Insalaco A, Wouters C, Shenoi S et al (2014) Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol 66:3160–3169

Miyazaki K, Ooiso Y, Nakamura I, Oimomi M, Tai T, Saito K (1977) An unusual case which began with subcutaneous panniculitis followed by fever, severe hepatic involvement and hyperlipidemia. Acta Pathol Jpn 27:213–224

Moghaddas F, Masters SL (2015) Monogenic autoinflammatory diseases: cytokinopathies. Cytokine 74:237–246

Morgan NV, Morris MR, Cangul H, Gleeson D, Straatman-Iwanowska A, Davies N et al (2010) Mutations in SLC29A3, encoding an equilibrative nucleoside transporter ENT3, cause a familial histiocytosis syndrome (Faisalabad histiocytosis) and familial Rosai-Dorfman disease. PLoS Genet 6:e1000833

Nahum E, Ben-Ari J, Stain J, Schonfeld T (2000) Hemophagocytic lymphohistiocytic syndrome: unrecognized cause of multiple organ failure. Pediatr Crit Care Med 1:51–54

Novak PM, Robbins TO, Winkelmann RK (1992) Necrobiotic xanthogranuloma with myocardial lesions and nodular transformation of the liver. Hum Pathol 23:195–196

Ohadi M, Lalloz MR, Sham P, Zhao J, Dearlove AM, Shiach C, Kinsey S, Rhodes M, Layton DM (1999) Localization of a gene for familial hemophagocytic lymphohistiocytosis at chromosome 9q21.3-22 by homozygosity mapping. Am J Hum Genet 64:165–171

Ohno T, Ueda Y, Nagai K, Takahashi T, Konaka Y, Takamatsu T, Suzuki T, Sasada M, Uchiyama T, Kyoto University Hematology/oncology Study Group (2003) The serum cytokine profiles of lymphoma-associated hemophagocytic syndrome: a comparative analysis of B-cell and T-cell/natural killer cell lymphomas. Int J Hematol 77:286–294

Ono K, Oshiro M, Uemura K, Ota H, Matsushita Y, Ijima S, Iwase T, Uchida M, Katsuyama T (1996) Erdheim-Chester disease: a case report with immunohistochemical and biochemical examination. Hum Pathol 27:91–95

Ooe K (1991) Pathogenesis of hypofibrinogenemia in familial hemophagocytic lymphohistiocytosis. Pediatr Pathol 11:657–661

Oram S, Cochrane GM (1958) Weber-Christian disease with visceral involvement; an example with hepatic enlargement. Br Med J 34:281–284

Ost A, Nilsson-Ardnor S, Henter JI (1998) Autopsy findings in 27 children with haemophagocytic lymphohistiocytosis. Histopathology 32:310–316

Ota M, Sakamoto M, Sato K, Yoshida Y, Funakubo Asanuma Y, Akiyama Y, Yamakawa M et al (2012) Immunopathological analysis of Erdheim-Chester disease with massive ascites. Intern Med 51:2825–2830

Otagiri T, Mitsui T, Kawakami T, Katsuura M, Maeda K, Ikegami T, Sendo D, Hayasaka K (2002) Haemophagocytic lymphohistiocytosis following measles vaccination. Eur J Pediatr 161:494–496

Padgett et al (1967) http://www.ncbi.nlm.nih.gov/pubmed/6057596

Pan A, Doyle T, Schlup M, Lubcke R, Schultz M (2011) Unusual manifestaion of Erdheim-Chester disease. BMC Gastroenterol 11:77

Papla B, Spolnik P, Rzenno E, Zdunczyk A, Rudzki Z, Okon K, Szczepanski W, Dabros W et al (2004) Generalized crystal-storage histiocytosis as a presentation of multiple myeloma: a case with a possible pro-aggregation defect in the immunoglobulin heavy chain. Virchows Arch 445:83–89

Parizhskaya M, Reyes J, Jaffe R (1999) Hemophagocytic syndrome presenting as acute hepatic failure in two

infants: clinical overlap with neonatal hemochromatosis. Pediatr Dev Pathol 2:360–366
Pasic S, Micic D, Kuzmanovic M (2003) Epstein-Barr virus-associated haemophagocytic lymphohistiocytosisin Wiskott-Aldrich syndrome. Acta Paediatr 92:859–861
Paulli M, Rosso R, Kindl S, Boveri E, Marocolo D, Chioda C, Agostini C, Magrini U, Facchetti F (1992) Immunophenotypic characterization of the cell infiltrate in five cases of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Hum Pathol 23:647–654
Paulli M, Bergamaschi G, Tonon L, Viglio A, Rosso R, Facchetti F, Geerts ML, Magrini U, Cazzola M (1995) Evidence for a polyclonal nature of the cell infiltrate in sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Br J Haematol 91:415–418
Perniciaro C, Winkelmann RK, Ehrhardt DR (1994) Fatal systemic cytophagic histiocytic panniculitis: a histopathologic and immunohistochemical study of multiple organ sites. J Am Acad Dermatol 31:901–905
Petterson T, Kariniemi AL, Tervonen S, Franssila K (1992) Cytophagic histiocytic panniculitis: a report of four cases. Br J Dermatol 127:635–640
Pfeifer V (1892) Über einen Fall von herdweiser Atrophie des subkutanen Fettgewebes. Dtsch Arch Klin Med 50:438–449
Popper HH, Zenz W, Mache C, Ohlinger W (1994) Familial haemophagocytic lymphohistiocytosis. A report of three cases with unusual lung involvement. Histopathology 25:439–445
Pradalier A, Teillet F, Molitor JL, Drappier JC (2004) Macrophage activation syndrome, hemophagocytic syndrome (in French). Pathol Biol (Paris) 52:407–414
Put K, Avau A, Brisse E, Mitera T, Put S, Proost P, Bader-Meunier B, Westhovens R, Van den Eynde BJ, Orabona C et al (2015) Cytokines in systemic juvenile idiopathic arthritis and haemophagocytic lymphohistiocytosis: tipping the balance between interleukin-18 and interferon-γ. Rheumatology (Oxford) 54:1507–1517
Rastogi V, Sharma R, Misra SR, Yadav L, Sharma V (2014) Emperipolesis – a review. J Clin Diagn Res 8: ZM01–ZM02
Ravelli A (2002) Macrophage activation syndrome. Curr Opin Rheumatol 14:548–552
Requena L, Sanchez Yus E (2001) Panniculitis. Part II. Mostly lobular panniculitis. J Am Acad Dermatol 45:325–361
Rocca A, Khamlichi AA, Touchard G, Mougenot B, Ronco P, Denoroy L, Deret S, Preud'homme JL, Aucouturier P, Cogne M (1995) Sequences of V kappa L subgroup light chains in Fanconi's syndrome. Light chain V region gene usage restriction and peculiarities in myeloma-associated Fanconi's syndrome. J Immunol 155:3245–3252
Rosai J, Dorfman F (1969) Sinus histiocytosis with massive lymphadenopathy: a newly recognized benign clinicopathology entity. Arch Pathol 87:63–70
Rubin et al (1985) http://www.ncbi.nlm.nih.gov/pubmed/2988747
Sanal O, Kucukali T, Ersoy F, Tinaztepe K, Gogus S (1993) Griscelli's syndrome: clinical features of three siblings. Turk J Pediatr 35:115–119
Sanal O, Ersoy F, Tezcan I, Metin A, Yel L, Menasche G, Gurgey A, Berkel I, De Saint Basile G (2002) Griscelli disease: genotype-phenotype correlation in an array of clinical heterogeneity. J Clin Immunol 22:237–243
Schaefer (1996) http://www.ncbi.nlm.nih.gov/pubmed/9122036
Schulert GS, Grom AA (2014) Macrophage activation syndrome and cytokine-directed therapies. Best Pract Res Clin Rheumatol 28:277–292
Schulert GS, Grom AA (2015) Pathogenesis of macrophage activation syndrome and potential for cytokine-directed therapies. Annu Rev Med 66:145–159
Schulert GS, Zhang M, Fall N, Husami A, Kissell D, Hanosh A, Zhang K, Davis K, Jentzen JM, Napolitano L, Siddiqui J et al (2015) Whole exome sequencing reveals mutations in hemophagocytic lymphohistiocytosis and macrophage activation syndrome linked genes in fatal cases of H1N1 influenza. J Infect Dis pii: jiv550
Schwartz NH, Loftus ER, Fishler JS (1952) Relapsing nodular panniculitis. NY State J Med 52:241–243
Scott R, Robb-Smith A (1939) Histiocytic medullary reticulosis. Lancet 2:194–198
Sheu SY, Wenzel RR, Kersting C, Merten R, Otterbach F, Schmid KW (2004) Erdheim-Chester disease: case report with multisystemic manifestations including testes, thyroid, and lymph nodes, and a review of literature. J Clin Pathol 57:1225–1228
Shome DK, Al-Mukharraq H, Mahdi N, Ameen G, Farid E (2002) Clinicopathological aspects of Chediak-Higashi syndrome in the accelerated phase. Saudi Med J 23:464–466
Shresta S, Pham CT, Thomas DA, Graubert DA, Ley TJ (1998) How do cytotoxic lymphocytes kill their targets? Curr Opin Immunol 10:581–587
Shu D, Peng C, Zhu H, Mei Y, Li W, Li X (2015) A case report of overlapping Rosai-Dorfman disease of the liver and gallbladder combined with hepatocellular adenoma (in Chinese). Zhonghua Gan Zang Bing Za Zhi 23:387–388
Slone (2003) http://www.ncbi.nlm.nih.gov/pubmed/12653580
Stanoeva K, Miovski D (1972) Systemic form of Weber-Christian disease with hepatic enlargement. Dermatologica 145:48–55
Steffen C (2002) The men behind the eponym: Frederick Parkes Weber and henry A. Christian: Weber-Christian disease. Am J Dermatopathol 24:514–517
Steinberg B (1953) Systemic nodular panniculitis. Am J Pathol 29:1059–1081
Steininger H, Missmahl M (1988) Weber-Christian panniculitis with systemic cytophagic histiocytosis. Klin Wochenschr 66:365–372

Suarez-Vilela D, Izquierdo-Garcia FM, Olcoz-Goni JL (2004) Sinus histiocytosis with massive lymphadenopathy and giant cell hepatitis. An unreported association. Virchows Arch 444:90–91

Sukpanichnant S, Hargrove NS, Kachintorn U, Manatsathit S, Chancharujira T, Siritanaratkul N, Akaraviputh T, Thakerngpol K (2000) Clofazimine-induced crystal-storing histiocytosis producing chronic abdominal pain in a leprosy patient. Am J Surg Pathol 24:129–135

Takagi H, Nishio H, Goto T, Morita K, Uchizawa M, Mizuo H, Murakami Y, Sasaki Y et al (2012) Portal hepatic lymphadenopathy involved by Rosai-Dorfman disease-like changes in a patient with hepatocellular carcinoma. Nihon Skokakibyo Gakkai Zasshi 109:1213–1222

Takahashi K, Naito M, Takatsuki K, Kono F, Chitose M, Ooshima S, Mori N, Sakuma H, Uchino F (1987) Multiple myeloma, IgA kappa type, accompanying crystal-storing histiocytosis and amyloidosis. Acta Pathol Jpn 37:141–154

Terada T, Maeta H, Endo K, Horie S, Matsunaga Y, Ohta T (1999) Marked histiocytosis in the portal tract in a patient with reactive hemophagocytic syndrome: an autopsy case. Pathol Int 49:672–675

Terashima K, Takahashi K, Kojima M, Imai Y, Tsuchida S, Migita S, Ebina S, Itoh C (1978) Kappa-type light chain crystal storage histiocytosis. Acta Pathol Jpn 28:111–138

Tsuda H (1997) Hemophagocytic syndrome (HPS) in children and adults. Int J Hematol 65:215–226

Tsui MS, Wong KF, Tse CC (1991) Liver pathology in reactive hemophagocytic syndrome. Surg Pathol 4:356–357

Tsukahara T, Horiuchi Y, Iidaka K (1995) Cytophagic histiocytic panniculitis in systemic lupus erythematosus. Hiroshima J Med Sci 44:13–16

Ugurlu S, Bartley GB, Gibson LE (2000) Necrobiotic xanthogranuloma: long-term outcome of ocular and systemic involvement. Am J Ophthalmol 129:651–657

Usmani GN, Woda BA, Newburger PE (2013) Advances in understanding the pathogenesis of HLH. Br J Haematol 161:609–622

Valenzuela R, Aikawa M, O'Regan S, Makker S (1976) Chediak-Higashi syndrome in a black infant. A light and electron microscopic study with special emphasis on erythrophagocytosis. Am J Clin Pathol 65:483–494

Veinot JP, Eidus L, Jabi M (1998) Soft tissue Rosai Dorfman disease mimicking inflammatory pseudotumor: a diagnostic pitfall. Pathology 30:14–16

Vyas YM, Maniar H, Dupont B (2002) Visualization of signaling pathways and cortical cytoskeleton in cytolytic and noncytolytic natural killer cell immune synapses. Immunol Rev 189:161–178

Wada R, Ebina Y, Kurotaki H, Yagihashi S (2002) Intracytoplasmic immunoglobulin crystals in follicular lymphoma. Hum Pathol 33:1141–1144

Wasserman JM, Thung SN, Berman R, Bodenheimer HC, Sigal SH (2001) Hepatic Weber-Christian disease. Semin Liver Dis 21:115–118

Weber FP (1925) A case of relapsing non-suppurative nodular panniculitis, showing phagocytosis of subcutaneous fat-cells by macrophages. Br J Dermatol Syph 37:301–311

White JW, Winkelmann RK (1989) Cytophagic histiocytic panniculitis is not always fatal. J Cutan Pathol 16:137–144

Willis SM, Opal SM, Fitzpatrick JE (1985) Cytophagic histiocytic panniculitis. Systemic histiocytosis presenting as chronic, nonhealing, ulcerative skin lesions. Arch Dermatol 121:910–913

Winkelmann RK (1980) Panniculitis with cellular phagocytosis. Chronic form of histiocytic panniculitis with fever, pancytopenia, polyserositis and lethal hemorrhagic diathesis (in German). Hautarzt 31:588–594

Winkelmann RK, Bowie EJ (1980) Hemorrhagic diathesis associated with benign histiocytic, cytophagic panniculitis and systemic histiocytosis. Arch Intern Med 140:1460–1463

Wu F, Zou CC (2007) Childhood Weber-Christian disease: clinical investigation and virus detection. Acra Paediatr 96:1665–1669

Yang Y, Bekeris LG, Vohl DT, Bagg A (2010) Crystal-storing histiocytosis in plasma cell myeloma. Am J Hematol 85:444–445

Yin L, Al-Alem U, Liang J, Tong WM, Li C, Badiali M, Medard JJ, Sumgei J, Wang ZQ, Romeo G (2003) Mice deficient in the X-linked lymphoproliferative disease gene sap exhibit increased susceptibility to murine gammaherpesvirus-68 and hypo-gammaglobulinemia. J Med Virol 71:446–455

Yokoyama S, Sano T, Tajitsu K, Kusumoto K (2004) Xanthogranulomatous hypophysitis mimicking a pituitary neoplasm. Endocr Pathol 15:351–357

Yoshioka M, Kikuta H, Ishiguro N, Endo R, Kobayashi K (2003) Latency pattern of Epstein-Barr virus and methylation status in Epstein-Barr virus-associated hemophagocytic syndrome. J Med Virol 70:410–419

Zainal A, Razif MY, Makhashen M, Swaminathan M, Mazita A (2010) Necrobiotic xanthogranuloma of the parotid gland. J Laryngol Otol 124:569–571

Zhang K, Chandrakasan S, Chapman H, Valencia CA, Husami A, Kissell D, Johnson JA et al (2014a) Synergistic effects of different molecules in the cytotoxic pathway lead to clinical familial hemophagocytic lymphohistiocytosis. Blood 124:1331–1334

Zhang M, Behrens EM, Atkinson TP, Shakoory B, Grom AA, Cron RQ (2014b) Genetic defects in cytolysis in macrophage activation syndrome. Curr Rheumatol Rep 16:439

Zilkha A, Madan V, Leonidas JC, Valderrama E (1998) Liver and spleen MRI findings in virus-associated hemophagocytic syndrome in a patient with acute lymphocytic leukemia. Pediatr Radiol 28:920–922

Zioni et al (2004) http://www.ncbi.nlm.nih.gov/pubmed/15315320

Zivin SP, Atieh M, Mosier M, Paner GP, Aranha GV (2009) Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) of the pancreas: second case report. J Gastrointest Surg 13:806–809

Part XIX

Mesenchymal Hamartoma and Related Neoplasms

Mesenchymal Hamartoma of the Liver

104

Contents

Abstract

Mesenchymal hamartoma of the liver (MHL) is a rare primary hepatic tumor composed of a complex mixture of immature mesenchyme interspersed with small abnormal bile ducts, aberrant blood vessels, small hepatocyte islands, formation of stromal nodules, and frequently extramedullary hematopoiesis. MHL is usually a solitary tumor that typically develops in the pediatric age group, mainly in the first year of life. Fewer than 5 % present after the age of 5 years. Large tumors with numerous arteriovenous shunts can induce heart failure. MHL is associated with placental mesenchymal dysplasia. Apart from solid lesions, which may be associated with elevated serum alpha-fetoprotein levels, many tumors show extensive cystic change.

Large cysts (macrocysts) can undergo hemorrhage or purulent inflammation. Rare tumors exhibit satellite lesions or daughter nodules, but this does not indicate metastatic disease. MHL rarely occurs in older children or even in adult individuals.

The lesion is associated with distinct chromosomal translocations, mainly t(11;19).

Introduction

Mesenchymal hamartoma of the liver (MHL, hepatic mesenchymal hamartoma) is defined as hepatic tumor composed of a hamartomatous

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_104

mixture of immature mesenchyme interspersed with small abnormal bile ducts, aberrant blood vessels, and small hepatocyte islands (reviews: Siddiqui and Mckenna 2006; Baboiu et al. 2008; Rosado et al. 2013).

The first case was apparently reported in 1903 by Maresch under the term, lymphangioma of the liver, and this case has subsequently been cited several times as being MHL (Maresch 1903). However, when reading this report (in German) and studying the figures (which are drawings), there remains some doubt whether the lesion was in fact MHL. Maresch described a large hepatic tumor observed in a 5-year-old female patient (an unusual age group for MHL) with marked and progressive upper abdominal distension. The lesion was clinically suspected to be a huge ovarian cyst, and the mass had caused lumbar lordosis. At surgery, the tumor was pedunculated, being connected to the right liver lobe via an about 5 cm thick pedicle containing liver substance. Upon puncture of the tumor, a clear and yellowish fluid was oozing from the interior of the lesion. The tumor was completely removed, with an uncomplicated and recurrence-free follow-up. Grossly, the well-delimited mass measured up to 20 cm and contained numerous larger and smaller cystic cavities with a usually smooth inner surface. Histologically, the larger cavities had no cellular lining, while the microscopic cysts exhibited a lining with flat cells. No marked ductular proliferations were found in the tumor, but the lesion showed marked perilesional liver atrophy. It remains, therefore, unclear whether this mass did in fact represent lymphangioma, as the author concluded, or whether this represents the first case of MHL. Few reports described similar lesions between the 1940s and 1960s of the twentieth century (Benson and Penberthy 1942; Kay and Talbert 1950; Symmers and Ward-McQuaid 1950; Christopherson and Collier 1953; Packhard and Palmer 1955; Edmondson 1956; Grime et al. 1959; Nixon 1965; Stephens and Jenevein 1965; Ishida et al. 1966; Sutton and Eller 1968).

Hamartoma was used to designate such lesions in 1942 already (Benson and Penberthy 1942), but the currently employed term, MHL, was coined in 1956 by Edmondson, who reviewed the then available literature (Edmondson 1956). Previously, the term hamartoma had been applied to both focal nodular hyperplasia (FNH) and mesenchymal hamartoma. Edmondson pointed out that these two lesions had no similarity in structure and should be clearly distinguished. Other terms which have been employed to denote these lesions include lymphangioma, large solitary bile-cell fibroadenoma (Lee 1942/1943), and large cavernous lymphangiomatoid lesion.

Epidemiology

Overall, MHL is a rare hepatic tumor, and even large centers usually do not encounter more than one new case every 2 years (Raffensperger et al. 1983; Kwok et al. 1989; DeMaioribus et al. 1990; Murray and Ricketts 1998). However, after hemangiomas, MHL is the second most common benign hepatic tumor in childhood. In a review of more than 1,200 pediatric liver tumors, MHL accounted for 6 % of all specimens (Weinberg and Finegold 1983). MHL is more common in the first year of life (around 55 % of all cases; de Maioribus et al. 1990), and about 15 % have been observed in the neonatal period (Mulrooney et al. 2001). In fact, over 90 % are manifest in infancy and fewer than 5 % present after the age of 5 years. In a study of 18 cases, the mean age at presentation was 16 months (DeMaioribus et al. 1990). Roughly 75 % of MHL involve the right liver lobe. There is one report of ectopic MHL (Sarihan et al. 1994). It is estimated that approximately 25 % of benign hepatic tumors in infants are MHL (Kwok et al. 1989). The lesion is usually reported as a sometimes large or very large circumscribed solid mass with a propensity to cystic or pseudocystic change.

Clinical Features

MHL typically presents with abdominal distension and an upper abdominal mass, although some cases are found incidentally on physical examination or imaging. In contrast to undifferentiated (embryonal) sarcoma (see below), pain is

rarely a dominant feature. Few patients show anorexia, vomiting, or failure to thrive. Among 18 patients retrospectively studied, 13 patients were symptomatic, presenting with increasing abdominal distention (DeMaioribus et al. 1990). Abdominal distention may rapidly progress owing to increasing fluid accumulation in the stroma and in cysts (Srouji et al. 1978; Chandramouleeswari et al. 2012). Large MHL in neonates and young infants may compromise circulation and may evolve into life-threatening lesions (Silber et al. 1970; Smith et al. 1978). Intraabdominal pressure exerted by large tumors may cause engorged veins in the abdominal wall or edema of the lower limbs. Specifically, tumoral arteriovenous shunts may induce heart failure (Smith et al. 1978). In a neonate, a huge mass was shown to induce vascular steal with subsequent renal insufficiency (Mulrooney et al. 2001). MHL has also been reported to be associated with disseminated intravascular coagulation (Rao et al. 1984; Wan et al. 2009). An exceptional complication of macrocystic MHL is cyst rupture, with production of neonatal ascites (George et al. 1994).

In the neonatal period, MHL can result in respiratory distress or apnea (Srouji et al. 1978; Raffensperger et al. 1983; Lennington et al. 1993; Balmer et al. 1996; Kitano et al. 2000). Massive abdominal distension owing to rapid expansion of the tumor has been reported (Silber et al. 1970). High-output heart failure was observed in several infants, also in the presence of relatively small tumors (Smith et al. 1978; Lanuza et al. 1980; Ehren et al. 1983; Alkalay et al. 1985). There are few reports documenting pulmonary hypertension, vascular steal, and thrombocytopenia (Mulrooney et al. 2001). Rare complications in neonatal MHL comprise perinatal tumor rupture (George et al. 1994), compression of bile ducts with obstructive jaundice (Ehren et al. 1983), torsion of pedunculated MHL (Vazquez-Lima et al. 2009), and fatal hemorrhage in the tumor following birth trauma (Singh et al. 1996). MHL in infants and older children presents with a similar clinical configuration. Complications in the age group include obstructive jaundice (Heller et al. 1992), hemorrhage, anemia (Salisbury et al. 1986), abscess formation (Salisbury et al. 1986), pyrexia (Salisbury et al. 1986), constipation (Wholey and Wojno 1994), and disseminated intravascular coagulation (Rao et al. 1984).

In MHL, liver function tests are usually normal. Maternal serum AFP and/or betaHCG may be elevated (Foucar et al. 1983; Dickinson et al. 1999; Kitano et al. 2000). However, MHL may also be associated with slightly to moderately elevated alpha-fetoprotein (AFP) concentrations in the serum of the patient (Justrabo et al. 1998; Murray and Ricketts 1998; Boman et al. 2004; Cajaiba et al. 2007; Gunes et al. 2008; Unal et al. 2008; Fretzayas et al. 2009), but this may take up to a year because of ongoing hepatocyte regeneration (Justrabo et al. 1998). This elevation of serum AFP is thought to be caused by proliferating hepatocytes immunoreactive for AFP within the loose myxoid stroma of the tumor (Ito et al. 1984) or be caused by AFP overexpression of peritumoral hepatocytes (Boman et al. 2004). AFP levels in serum drop following tumor resection (Fretzayas et al. 2009). In a patient in whom MHL mimicked hepatoblastoma, serum AFP levels decreased after preoperative chemotherapy (Unal et al. 2008).

A fraction of MHL is already detectable prenatally (fetal MHL), usually diagnosed in the last trimester of pregnancy by fetal ultrasonography and/or CT owing to the multicystic aspect of the liver mass. So far, less than 20 reported cases of MHL diagnosed or detected prenatally by ultrasound examination are known (Foucar et al. 1983; Hirata et al. 1990; Bartho et al. 1992; Hansen and Ragavendra 1992; Ruiz et al. 1995; Bessho et al. 1996; Bejvan et al. 1997; Tovbin et al. 1997; Littlewood Teele et al. 1998; Dickinson et al. 1999; Kitano et al. 2000; Kamata et al. 2003; Ramirez-Garrido et al. 2003; Laberge et al. 2005; Heyer et al. 2007; Ruhland et al. 2011). The antenatal appearance of the tumor may be either solid (echogenic) or multiloculated cystic (Stanley et al. 1986). In a review of 13 reported cases (Kamata et al. 2003), two were solid, eight were cystic, and three were mixed, and the size of the masses varied from 5 to 14 cm. As a characteristic feature of this tumor, rapid tumor growth was observed in five cases,

four of them with a cystic morphology (Bessho et al. 1996; Bejvan et al. 1997; Tovbin et al. 1997; Dickinson et al. 1999), but signs of spontaneous regression were also seen in two cases (Littlewood Teele et al. 1998). Among 13 cases, perinatal complications were encountered in five. MHL manifest in the fetal liver can cause nonimmune hydrops (Alkalay et al. 1985; Bessho et al. 1996; Dickinson et al. 1999), sometimes followed by stillbirth or early postnatal death. Rapid tumor growth of fetal MHL seems to more frequently cause hydrops. Based on the sometimes impressive size, also MHL manifest in newborns (Balmer et al. 1996) has begone their growth in the fetal period already.

MHL is sometimes associated with malformations, including common mesentery with cecocolonic malposition (Sanchez Blanco et al. 1989), malrotation of the bowel (Ramareddy and Alladi 2012), Bochdalek diaphragmatic hernia (Ortiz Otero et al. 2012), and mesenchymation defects, such as protrusion through the chest wall and thus producing an extrathoracic lesion (Yesildag et al. 2004), or gastroschisis (Bulhak-Guz et al. 2005). MHL has also found to arise in an intrathoracic heterotopic liver (Antoniou et al. 2012).

Imaging Features

Ultrasound and computed tomography appearances reflect the main gross components of the tumors, ranging from a predominantly cystic or multicystic mass to a complex solid mass. Sonographically, round hyperechoic parietal nodules within the cystic spaces of MHL have been described. CT and MR of cystic forms reveal a multicystic, septated mass within the liver or on a pedicle.

Selected References Razek et al. 1973; Gilbert et al. 1978; Donovan et al. 1981; Rosenbaum and Mindell 1981; Egawa et al. 1983; Raffensperger et al. 1983; Schumacher and Westfechtel 1983; Giyanani et al. 1986; Stanley et al. 1986; Faleski and Ghiatas 1987; Roberts et al. 1989; Bovis et al. 1990; Federici et al. 1992; Kaufman 1992; Megremis et al. 1994; Wholey and Wojno 1994; Lai et al. 1996; Motiwale et al. 1996; Vandendriessche et al. 1996; Alwaidh et al. 1997; Meinders et al. 1998; Murray and Ricketts 1998; Koumanidou et al. 1999; Locham et al. 1999; Sato et al. 2000; Konez et al. 2001; Cetin et al. 2002; Arfa et al. 2003; Jaswal et al. 2003; Kamata et al. 2003; Yen et al. 2003; ye et al 2000; Millard et al. 2006; Gosset et al. 2008; Zhang et al. 2008; Ammor et al. 2009; Gow et al. 2009; Moore et al. 2009; Nakajo et al. 2009; Anil et al. 2011; Salihoglu et al. 2013.

Multicystic MHL can clinically and radiologically mimic lymphangioma (Arfa et al. 2003). A heterogeneous imaging pattern with varying signal intensities on MR is thought to correspond to different concentrations of proteinaceous material within the cysts (Wholey and Wojno 1994; Helmberger et al. 1999). Rarely, septal calcification visualized by imaging has been reported in cystic lesions (Kenney et al. 1986; Konez et al. 2001), and multifocal calcification has also been noted in the solid variant (Chung et al. 1999). Calcification may be detectable as a peripheral alteration (Steiner and Giles 2008). Large solitary cysts in MHL can grow to giant dimensions (Dooley et al. 1983) and may mimic hepatic hydatid disease (Smith et al. 2001). After contrast medium administration, solid components of MHL are enhanced, but there is no significant change in the density of cystic portions (Ros et al. 1986; Wholey and Wojno 1994; Alwaidh et al. 1997). Angiographically, abnormal blood vessels (Grases et al. 1979; Alanen et al. 1987) and multiple focal avascular areas are recognized, representing the cystic components (Wendth et al. 1976). The abnormal vasculature of MHL may mimic hemangioma in MRI (Andronikou et al. 2006). In addition to cystic tumors, solid or mixed morphologies are also recognized. In a study on 13 children with MHL, 31 % had a multiseptated cystic tumor, 38 % had a mixed solid and cystic tumor, and 31 % had a solid tumor (Kim et al. 2007).

Pathology

Macroscopy

The right lobe is preferentially involved (about 75 %); the remaining tumors occur in the left lobe or involve both lobes (Martinez-Mier et al. 2012). MHL is frequently large tumors, resected specimens weighing between 400 and in excess of 1,800 g, and tumors showing a diameter sometimes exceeding 30 cm and weighing 3 kg or more (Silber et al. 1970; Dehner et al. 1975; Weinberg and Finegold 1983; DeMaioribus et al. 1990; Shuto et al. 1993; Chau et al. 1994; Otal et al. 1994; Bove et al. 1998; Murray and Ricketts 1998; Orlowski and Breborowicz 2011). Some of the very large lesions occupy almost the entire liver (Shuto et al. 1993; Alwaidh et al. 1997). Similar to cavernous hemangiomas and FNH, MHL may grow in the form of pedunculated masses, up to 20 % and usually arising from the inferior surface of the liver (Raffensperger et al. 1983; Stocker and Ishak 1983; Bejvan et al. 1997; Rakheja et al. 2004). Exceedingly large lesions have been termed giant MHL (Narasimharao et al. 1988; Shuto et al. 1993; Narasimhan et al. 2004; Vargas-Vallejo et al. 2005). In a series of eight cases, the mean weight was 651 g, although the weights for three of the largest lesions were not recorded (Otal et al. 1994). MHL is usually solitary, spherical, dark red or reddish-brown tumors with smooth surfaces. On cut section, the outstanding feature in most cases is their irregular cystic appearance. Macroscopically, solid and macrocystic forms are recognized. In a series of 17 cases, seven (41 %) were solid and ten (59 %) cystic, and the solid variants showed a higher serum level of AFP (Chang et al. 2006). The tumor cysts, which do not communicate with the biliary tree, vary in size from few millimeters to more than 15 cm. In one case, almost 700 ml of fluid could be aspirated from the lesion (Stephens and Jenevein 1965), and in a neonate, MHL presented as giant intraabdominal cyst (Ramareddy and Alladi 2012). The macrocysts mostly contain clear or pale yellowish serous fluid or, less commonly, a mucoid fluid. The composition of the cyst fluid is similar to blood plasma except that the concentrations of protein, glucose, and cholesterol are lower (Dooley et al. 1983; Yandza and Valayer 1986; Mascarello and Krous 1992). Large cysts may show secondary changes, such as bleeding or empyema formation in case of infection, but intracystic bleeding is, overall, a rare event in MHL (Salisbury et al. 1986; Kwok et al. 1989; DeMaioribus et al. 1990; Lennington et al. 1993). In the stromal-predominant variant, the solid component with small cysts produces a Swiss-cheese pattern (Ros et al. 1986; Helmberger et al. 1999). Numerous small to tiny, in part confluent and bulging, whitish nodules of ovoid to irregular shape may be recognized to be interspersed with liver parenchyma (Bove et al. 1998). Gross examinations commonly reveal the presence of a gray white to red purple and usually edematous connective tissue between the cysts.

MHL is predominantly a solitary lesion, but there are several reports describing multifocality (review: Stringer and Alizai 2005). Small satellite lesions at the margin of the main tumor have been described (Stocker and Ishak 1983; Lack 1986; Stocker 2001). These lesions have also been termed daughter nodule (Fukahori et al. 2007). Such satellites may cause recurrence after apparent complete resection (Bejarano et al. 2003). In addition to satellites immediately related to the tumor periphery, more remote nodules have also been noted. In two adult patients with MHL, satellite nodules were found separate from the main lesion. In one of these cases, multiple small and cystic lesions with the histology of the principal tumor and measuring less than 1 cm were seen throughout the liver (Cook et al. 2002). In a neonate who died soon after birth showed at autopsy to have a large discrete MHL in the right and left lobes of the liver (Stringer and Alizai 2005).

Histopathology

The histopathology of MHL has been specified in detail (Dehner et al. 1975; Cooper et al. 1989; Figs. 1, 2, 3, 4, and 5). Depending on the

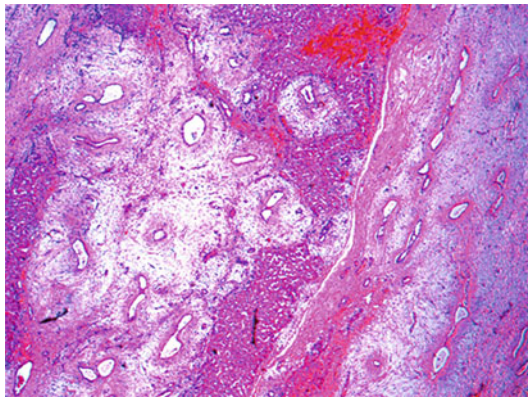

Fig. 1 Mesenchymal hamartoma of the liver. The tumor consists of nodular mesenchymal structures that contain abnormal bile duct-like profiles (hematoxylin and eosin stain)

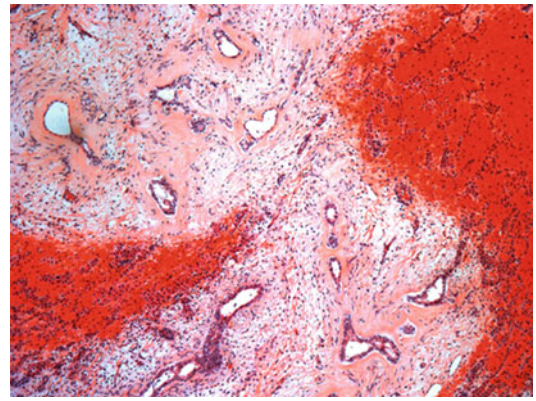

Fig. 3 Mesenchymal hamartoma of the liver. In part of mesenchymal nodules, bile duct equivalents are surrounded by hyaline connective tissue (hematoxylin and eosin stain)

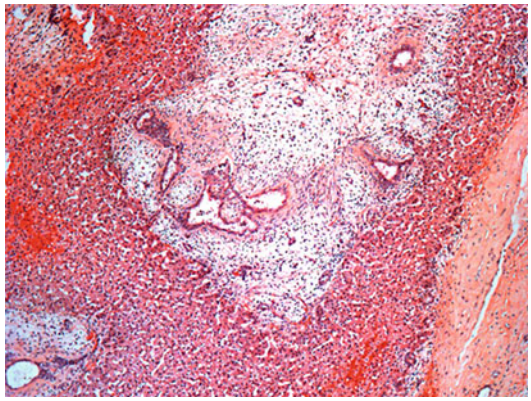

Fig. 2 Mesenchymal hamartoma of the liver. At higher magnification, the tissue surrounding bile duct equivalents is composed of immature, partly myxoid mesenchyme with spindle cells and stellate cells (hematoxylin and eosin stain)

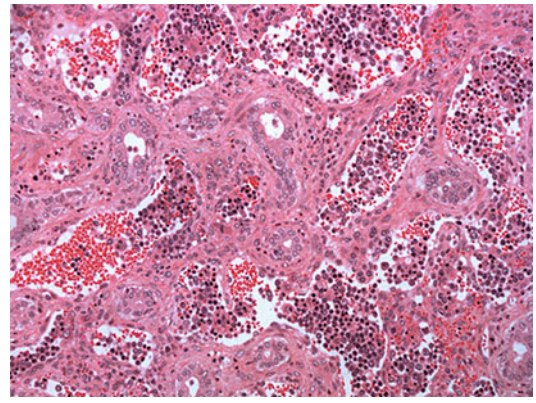

Fig. 4 Mesenchymal hamartoma of the liver with vigorous extramedullary hematopoiesis. The blood-forming cells are situated within vascular channels between mesenchymal septa with embedded bile ducts (hematoxylin and eosin stain)

contribution of tissue components, is has been proposed to histologically divide MHL into two forms, i.e., cystic predominant and stromal predominant (Cetin et al. 2002). The stromal component presents in the form of a paucicellular fibromyxoid tissue that appears to expand within the liver substance, sometimes having structures that mimic portal tracts, but without the normal portal vein architecture. Within this tissue bile duct-like profiles surrounded by a dense connective tissue are seen. This ductal/ductular compartment is usually more dense at the periphery of the tumors. It has been suggested that these small bile duct-like structures derive from dysplastic bile ducts (Ishida et al. 1966; Stocker an Ishak 1983; Lack 1986; DeMaioribus et al. 1990; de Chadarevian et al. 1994). The matrix is typically more condensed around the ducts and becomes more loose or even myxoid toward the neighboring liver substance. Within this myxoid stroma, macrocystic, microcystic, or cystoid change may develop. Large cysts are commonly devoid of an epithelial lining and may thus represent fluid-filled cystic spaces within a matrix rich in

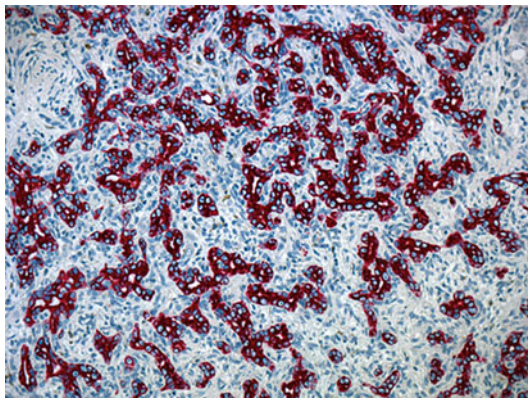

Fig. 5 Mesenchymal hamartoma of the liver. The tumor can contain areas with a high density of ductular structures (cytokeratin 7 immunostain)

interstitial fluid containing glycosaminoglycans (Stocker and Ishak 1983; Drachenberg et al. 1991). Some cysts exhibit a flat cellular lining that has, based on ultrastructure, been proposed to be mesothelium (O'Sullivan et al. 2001). In addition to bile ducts, the myxoid stroma contains small clusters of in part proliferating hepatocytes (Dehner et al. 1975). These hepatocytes are commonly smaller than normal, and they may be vacuolated (Stocker and Ishak 1983; Boman et al. 2004). At the interface between the portal tract-like compartments and the adjacent liver parenchyma, ductules in an arrangement resembling ductal plate malformation are sometimes in evidence. The epithelium of the ducts is irregular and may show signs of atrophy or at least flattening. The stroma frequently contains hemopoietic foci (Lack 1986; DeMaioribus et al. 1990; Otal et al. 1994), considered to be part of the fetal hepatic hemopoiesis that occurs in the hamartoma (Chau et al. 1994). There seems to exist a relationship between the gross presentation of MHL and the histology. The solid variant showed smaller bile ducts and more frequent proliferation of vessels, and in some solid tumors, larger amounts of evenly distributed hepatocytes were found, probably associated with a higher level of serum AFP in solid lesions (Chang et al. 2006). The vascular supply of MHL is only partially known. In one dissecting microscopic examination, analysis revealed a single vascular supply in one case, and this phenomenon was suggested to be the cause of early ischemic changes leading to cystic change (Lennington et al. 1993). There seem to be biliary connections between MHL and the adjacent liver (Senyuz et al. 1988). The liver parenchyma surrounding the tumor may show compression atrophy with ductular reaction (Chau et al. 1994), but there may also be interdigitation of MHL tissue with parenchyma, without signs of invasive growth. Specifically, small nodules of residual hepatic parenchyma may be found at the periphery of cystic spaces (Lennington et al. 1993).

Histologic Variants

Some MHL shows histologic features different from what is seen in "standard" MHL. One variant is termed stromal-predominant MHL (Mansour et al. 2005; Gunes et al. 2008). Few MHl show angiomatous elements, first described by Edmondson (Edmondson 1956). An uncommon but highly interesting phenotype is MHL combined with hemangioendothelioma, first reported by Lack (1986) and subsequently noted by other authors (Smith et al. 1978; Lanuza et al. 1980; Singh et al. 1996; Mulrooney et al. 2001). Such combinations suggest a fundamental disorder in mesenchymation and angiogenesis, also supported by the occurrence of placental mesenchymal dysplasia in some patients with MHL (see below).

Cytology

Relatively few MHL have been examined by fine-needle aspiration. Aspiration cytology of MHL revealed the presence of small groups and isolated benign-appearing spindle cells admixed with scarce amounts of myxoid stroma and normal ductal cells and hepatocytes. Although nonspecific, such findings are helpful to preoperatively exclude other liver tumors occurring in this age group (Al-Rikabi et al. 2000; Jimenez-Hefferman et al. 2000).

Ultrastructure

At electron microscopy, the tumor cells are stellate, oval to spindle shaped, with interconnected cytoplasmic processes encircling small and sometimes slit-like intercellular cystic spaces, which appeared to be the precursors of larger cysts (Dehner et al. 1975; Drachenberg et al. 1991). Tumor cells may reveal pinocytotic vesicles, a well-developed Golgi apparatus, and a moderately developed rough endoplasmic reticulum (Chau et al. 1994).

Immunohistochemistry

MHL exhibits a complex immunohistochemical phenotype, due to the various cellular components present (Table 1). In some respects, the phenotype is similar to that of undifferentiated embryonal sarcoma (see below).

Immunohistochemically, the mesenchymal tumor cells are consistently reactive for vimentin and, in a subset, for smooth muscle actin, suggesting a contribution of myofibroblastoid cells. Reactivities for desmin and alpha-1-antitrypsin were also detected in the mesenchymal cells (Von Schweinitz et al. 1999; Stocker 2001; Cook et al. 2002; Abdulkader et al. 2004). The mesenchymal cells also express fibroblast growth factor receptor, which may play a role in growth of the tumors (Von Schweinitz et al. 1999). Expectedly, the cells of the bile duct-like profiles and of epithelium-lined cysts are reactive for cytokeratins 7 and 19 (Chau et al. 1994; Justrabo et al. 1998; Cook et al. 2002; Yesim et al. 2005). Glypican-3 is expressed in a subset of MHL, what may cause differential diagnostic difficulties (Levy et al. 2012). One group detected Ki-67-positive proliferating mesenchymal cells in liver tissue at the margin of MHL but not within the tumor (Von Schweinitz et al. 1999), while another group found a low proliferative activity within the lesions, but with a prominent bcl-2 reactivity in the mesenchymal and epithelial components of the tumor, associated with a low apoptotic index (Abdulkader et al. 2004).

Table 1 Immunohistochemical phenotype of mesenchymal hamartoma of the liver

Mesenchymal cells positive for:
Vimentin
Smooth muscle actin (in part)
Desmin (in part)
Alpha-1-antitrypsin
Glypican-3 (in part)
Fibroblast growth factor receptor
Bcl-2
Cells of bile duct-like structures positive for:
Cytokeratin 7
Cytokeratin 19

Mesenchymal Hamartoma and Placental Mesenchymal Dysplasia

In some cases of prenatally diagnosed MHL, the liver tumor was associated with mesenchymal stem villous hyperplasia of the placenta (Alwaidh et al. 1997; Kitano et al. 2000; Carta et al. 2005; Laberge et al. 2005; Francis et al. 2007; Reed et al. 2008; Mack-Detlefsen et al. 2011; Harris et al. 2013). In one patient, the placenta was noticed to have multiple cysts at 16 weeks' gestation, and elevated maternal serum AFP was present (Kitano et al. 2000). In an infant with MHL associated with placental mesenchymal dysplasia, androgenetic/biparental mosaicism was detected, suggested to play a pathogenetic role in MHL (Reed et al. 2008). Mesenchymal stem villous hyperplasia of the placenta (MSVHP, mesenchymal dysplasia of the placenta) is an uncommon anomaly characterized by edema and stromal extension of the placental stem villi with relatively normal terminal villi, secondary to vascular malformations of the fetal plate (Takayama et al. 1986; Moscoso et al. 1991; Gibson et al. 2004). It has been described in phenotypically normal fetuses, illustrating that this disorder can coexist with normal fetal development, but may be occasionally associated with fetus anomalies (Lage 1991; Chen et al. 1997; Jauniaux et al. 1997), in particular intrauterine growth restriction and fetal demise (Pham et al. 2006).

MSVHP can coexist with chorangioma (Hojberg et al. 1994; Chen et al. 1997; Matsui et al. 2003). MSVHP is sometimes accompanied by omphalocele (Lage 1991; Pridmore et al. 1994), and an association of MSVHP and Beckwith-Wiedemann syndrome (BWS) has been observed several times (Lage 1991; McCowan and Becroft 1994; Hillstrom et al. 1995; Paradinas et al. 2001).

Mesenchymal Hamartoma of the Liver in Older Children

As outlined above, MHL typically occurs in children younger than 2 years of age or in the adult population. Only 5 % of MHL are diagnosed in children older than 5 years or in adults. Recently, a variant of MHL has been reported in an 11-year-old boy. This variant of MHL was characterized by a solid phenotype, i.e., without cystic structures, a predominantly myxoid stroma, and a minimal bile ductular component. It was suggested that this phenotype occurring in an older child might be reflected by a different biology of disease (Virgone et al. 2015).

Mesenchymal Hamartoma of the Liver in Adults

In addition to the classical MHL developing in the pediatric age group, MHL forms a group of tumors occurring in adults. They are more frequent in females, with an age range 21–69 and a reported size range 5–24 cm.

Selected References Grases et al. 1979; Dooley et al. 1983; Jennings et al. 1987; Gramlich et al. 1988; Gutierrez and Burgener 1988; Ito et al. 1989; Drachenberg et al. 1991; Wada et al. 1992; Megremis et al. 1994; Yamamoto et al. 1994; Bilge et al. 1996; Turlin et al. 1996; Fashir et al. 1998; Murray and Ricketts 1998; Chung et al. 1999; Papastratis et al. 2000; Cook et al. 2002; Brkic et al. 2003; Kim et al. 2003; Yesim et al. 2005; Ayadi-Kaddour et al. 2006; Hernandez et al. 2006; Mori et al. 2008; Klaassen et al. 2010.

In one patient, MHL was associated with pancreas divisum (Ito et al. 1989). Is the pathomorphology of adult-type MHl similar or the same as pediatric MHL? In a study of only three cases, it was found that, in contrast to childhood cases, the stromal component consisting of fibroblastoid cells and myofibroblasts was fibrotic with areas of dense hyalinization and only focal myxoid areas (Cook et al. 2002). It has also been described that adult-type MHL shows a series of histologic modifications, including progressive loss of hepatocytes, degeneration of bile duct epithelium, and cystic change of the mesenchymal component. In the infantile cases of MHL, bile duct-like structures and hepatocytes are abundant, while in adult-type tumors, hepatocytes were encountered preferentially at the periphery of the tumors and may be absent in the interior (Gramlich et al. 1988; Drachenberg et al. 1991; Chau et al. 1994). Some of these differences between pediatric and adult MHL may be caused by progression of the lesion toward a mesenchymal-predominant phenotype associated with progressive loss of epithelial lineages. In fact, sequential CT scans in childhood MHL have shown initial expansion of the lesion with subsequent involution (Barnhart et al. 1997).

Biology of Disease

As a rule, MHL has a benign course with good prognosis if the tumor is resected (Yen et al. 2003; Pandey et al. 2011). It has, therefore, been suggested that asymptomatic MHL can be managed by observation alone (Gottschalk et al. 1988; Roebuck 1998). In the perinatal period, however, the course may be complicated by hemodynamic instability and respiratory distress (Cornette et al. 2009), and complications may develop, in part caused by wrong diagnosis (Karpelowsky et al. 2008). Only a few cases with local relapse or metastatic spread have been reported, and such lesions are difficult to judge in regard to their hamartomatous nature.

Malignant Neoplasms Developing from Mesenchymal Hamartoma

As discussed in the respective chapter, undifferentiated (embryonal) sarcoma of the liver can develop from MLH (Begueret et al. 2001; O'Sullivan et al. 2001). In a 20-year-old male patient, hepatic angiosarcoma arose in MHL. The patient had a well-circumscribed mass on the undersurface of the right liver lobe, and histology revealed angiosarcoma with areas of MHL (Kulkarni et al. 2010). A second case of angiosarcoma arising in adult MHL was reported (Li et al. 2007).

Associated Hepatic Lesions

MHL can synchronously occur with other space-occupying lesions of the liver. In a cohort of 112 children with liver hemangioma, three of them (0.027 %) had concurrent MHL (Behr et al. 2012). MHL can occur in combination with infantile hepatic hemangioendothelioma (Hsiao et al. 2007; Behr et al. 2012) and congenital solitary nonparasitic liver cyst (Azar et al. 2003). The potential connection between MHL, MSVHP, and BWS is of interest in the light of hepatic tumors and tumor-like lesions occurring in BWS, including hepatoblastoma (Fukuzawa et al. 2003; Hamada et al. 2003; Rump et al. 2005), hepatic hemangioendothelioma (Drut et al. 1992), mixed hamartoma of the liver (which is different from FNH; Rhodes et al. 1978; Fukuzawa et al. 2001), focal nodular hyperplasia (FNH) of the liver (Bordeianou et al. 2005), liver cysts (Takano et al. 1997), and biliary dysgenesis (Steigman et al. 1990; Coppin et al. 1997).

Differential Diagnosis

Entirely intrahepatic MHL with prominent cystic changes should be distinguished from simple hepatic cysts (George et al. 1994), undifferentiated (embryonal) sarcoma of the liver, cystic alterations in hepatoblastoma (Ros et al. 1986), abscesses (Ros et al. 1986; Stanley et al. 1986), and echinococcosis, while pedunculated tumors with an important extrahepatically growing component may be confounded with cystic duplication (Ros et al. 1986), choledochal cyst (Stanley et al. 1986), lymphatic malformations or lymphangioma (Tzen et al. 1998), or loculated ascites (Ros et al. 1986; George et al. 1994).

Cytogenetic Alterations, Molecular Features, and Pathogenesis

So far, few reports have documented chromosomal aberrations in MHL (Table 2), including a balanced translocation between chromosomes 15 and 19 (Speleman et al. 1989); a balanced translocation between chromosomes 11 and 19 with a breakpoint at 19q13.4 as the most frequent recurrent anomaly (Mascarello and Krous 1992; Bove et al. 1998; Rakheja et al. 2004; Sugito et al. 2010); a complex translocation between chromosomes 11,17 and, 19 at bands q12, p11, and q13.3 (Murthi et al. 2003); and an inversion of chromosome 197. The involvement of chromosomes 11 and 19, Shetty et al. 2011; being a recurrent anomaly, with the breakpoint at 19q13.4 a common clonal abnormality potentially serving as a diagnostic feature of MHL (Bove et al. 1998; Sharif et al. 2006). A role of chromosome 19q is furthermore suggested by the finding of an interstitial deletion involving band 19q13.4 in MHL (Talmon and Cohen 2006). However, part of the MHL has been demonstrated, through flow cytometry, to be hyperdiploid (Otal et al. 1994), a feature that suggests the possibility of the involvement of a neoplastic cell lineage and that has also been found in undifferentiated (embryonal) sarcoma (UES) of the liver (see below; Chou et al. 1990).

Table 2 Cytogenetic aberrations in mesenchymal hamartoma of the liver

Balanced translocation t(11,19)
t(11,19)(q13;q13.4)
t(2;19)(q31.1;q13.42)
Inversion of chromosome 19
inv(19;19)(q13.42;q13;43)

By use of capture-based next-generation sequencing targeted to loci, chromosome rearrangements involving the MHLB1 (mesenchymal hamartoma of the liver B1) locus were identified in MHL, including the translocation 1 (11;19)(q13.1.; q14.42) involving the MALAT gene1 gene; the translocation t(2;19)(q31.1; q13.42) involving AK023515, an uncharacterized noncoding gene; and the inversion inv(19;19)(q13.42;q13.43) involving the PEG3 gene encoding a Kruppel-type zinc-finger protein (Mathews et al. 2013). The first translocation type is shared with undifferentiated embryonal sarcoma of the liver. A histogenetic relationship between MHL and UES has first been suggested by Stocker and Ishak (1978), subsequently challenged (Gallivan et al. 1983; Finegold 1986; Lack 1986; Chou et al. 1990; Aoyama et al. 1991), and later revived (de Chadarevian et al. 1994; Lauwers et al. 1997; Bove et al. 1998; Ramanujam et al. 1999; Begueret et al. 2001; O'Sullivan et al. 2001; Rajaram et al. 2007; Lahmar-Boufaroua et al. 2008). UES was also found to arise from MHL in adult patients (Tucker et al. 2012). There is histologic evidence that UES might evolve from preexisting MHL (malignant transformation of MHL; Ramanujam et al. 1999). In a more recent investigation, a single example of a UES arising in MHL with a complex karyotype including add (19q)(13) was reported (Lauwers et al. 1997), all these findings suggesting a pathogenetic link between MHL and UES. Similar to few instances of MHL, flow cytometry in UES revealed hyperdiploid cell lines (Chou et al. 1990). Among 14 structural chromosomal anomalies found in one study of UES, one case exhibited a breakpoint at 19q11, as in MHL (Sawyer et al. 1996). The breakpoint of the critical 11q13 region has been cloned and the sequence determined. The breakpoint at 11q13 occurred in the MALAT1 gene, and the breakpoint at 10q13.4 occurs at a locus termed, MHLB1, for mesenchymal hamartoma of the liver breakpoint 1 (Rajaram et al. 2007). MALAT1 (metastasis-associated lung adenocarcinoma transcript 1, synonym, NEAT2) is a conserved long noncoding RNA which is highly expressed in nuclei. Long noncoding RNAs (lncRNAs), with a size larger than 200 nt, are a group of RNA species that have no protein coding ability, but not only act as the intermediary between DNA and proteins but also regulate gene expression in many ways, including chromosome remodeling. lncRNAs, in particular MALAT1, HOTAIR, and ANRIL, contribute to cancer development and progression through their action on several critical carcinogenic pathways, including the expression of metastasis-associated genes (Tano and Akimitsu 2012; Li and Chen 2013; Qiu et al. 2013; Shi et al. 2013). MALAT1 is an important lncRNA, of which two alternative modes of action have been proposed, i.e., regulation of gene expression or alternative splicing (Gutschner et al. 2013). MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation (Long et al. 2009; Tripathi et al. 2010). MALAT1 cooperates with MALAT1-associated small cytoplasmic RNAs (mascRNAs). mascRNA is processed from the much longer nuclear MALAT1 by the action of RNAse P. However, under normal condition, knockout of MALAT1 in mice is compatible with cell viability and normal development (Eissmann et al. 2012). MALAT1 controls cell cycle progression by regulating the expression of the oncogenic transcription factor B-MYB (Tripathi et al. 2013). It positively regulates cell motility through transcriptional regulation of motility-associated genes.

The pathogenesis of MHL is unknown. Based on a low proliferative activity in the lesions, it has been suggested that most of the growth in MHL takes place before or just after birth, while cyst expansion is later responsible for postnatal tumor growth (Stocker and Ishak 1983). The lesion is conventionally classified as a tumor-like, nonneoplastic process, hence the name, hamartoma. Therefore, one hypothesis of pathogenesis refers to a developmental disorder. According to this hypothesis, MHL may be related to a ductal plate malformation and reflects features known from congenital hepatic fibrosis and Caroli's disease (Dehner 1975; Von Schweinitz et al. 1999; Stocker et al. 2002). A pathway characterized by aberrant development of hepatic tissues is further suggested by the

observation of MHL developing in an arrested liver in conjunction with infantile hemangioendothelioma (Bejarano et al. 2003).

A second hypothesis considers ischemia as a cause of MHL. That ischemia which can induce abnormal hepatic growth patterns is known from regenerative nodular hyperplasia and from FNH-like lesions that may develop in hepatic venous outflow disorders. Based on the comparison of the histology of MHL with that of a torsioned accessory liver lobe, it was suggested that MHL may be a consequence of reactive changes to regional ischemia within a sequestered hepatic lobe (Lennington et al. 1993). However, the distinct vascular supply pattern of MHL, characterized by the presence of commonly multiple feeding vessels, renders this hypothesis unlikely. Biliary maldevelopment and cystic changes in MHL have also been suggested to be caused by a fetal vascular insult (Okeda 1976).

The third hypothesis holds it that a neoplastic process is involved, albeit with a so far unknown cellular origin. The presence of cells sharing features with hepatic stellate cells (HSC) led to the hypothesis that MHL might be an HSC-derived tumor (Shintaku and Watanabe 2010). Is there evidence that MHL may in fact not be a hamartoma, but rather a true neoplasm? Theoretically, this would not be expected, owing to the involvement of several and apparently unrelated cell lineages. On the other hand, the often dominant mesenchymal component might be neoplastic, in some way inducing the biliary and, eventually, hepatocytic component (Bove et al. 1998), in the sense of a neoplastic disorder of mesenchymal to epithelial transition. Based on cytogenetic and DNA analysis findings, there is some evidence that a neoplastic process may be involved, and the possibility of MHL being a disorder of imprinting has been discussed (Reed and Kapur 2008).

References

Abdulkader I, Fraga M, Perez-Becerra E, Reyes-Santias RM, Bautista A, Chaves E, Forteza J (2004) Mesenchymal hamartoma of the liver; clinicopathological, immunohistochemical and flow cytometric study of two cases. Hepatol Res 28:216–219

Alanen A, Katevuo T, Toikkanen S (1987) A non-cystic mesenchymal hamartoma of the liver – an unusual case of an unusual entity. Case report and review of the literature. Bildgebung 56:181–184

Alkalay AL, Puri AR, Pomerance JJ, Kallus M, Gans SL, Hurvitz CH, Farber SJ, Sloninsky L (1985) Mesenchymal hamartoma of the liver responsive to cyclophosphamide therapy: therapeutic approach. J Pediatr Surg 20:125–128

Al-Rikabi AC, Buckai A, al-Sumayer S, al-Damegh S, al-Bassam AR (2000) Fine needle aspiration cytology of mesenchymal hamartoma of the liver. A case report. Acta Cytol 44:449–453

Alwaidh MH, Woodhall CR, Carty HT (1997) Mesenchymal hamartoma of the liver: a case report. Pediatr Radiol 27:247–249

Ammor A, Margi M, Lamalmi N, Oulahyane R, Malihy A, Cherkaoui A, Bouhafs A, Kaddouri N et al (2009) Mesenchymal hamartoma of the liver: a case report (in French). Arch Pediatr 16:1033–1036

Andronikou S, Soin S, Nafoos O, Platt K, Lakhoo K (2006) Hepatic mesenchymal hamartoma mimicking hemangioma on multiple-phase gadolinium-enhanced MRI. J Pediatr Hematol Oncol 28:322–324

Anil G, Fortier M, Low Y (2011) Cystic hepatic mesenchymal hamartoma: the role of radiology in diagnosis and perioperative management. Br J Radiol 84: e91–e94

Antoniou D, Soutis M, Karentzou O (2012) Cystic mesenchymal hamartoma arising in intrathoracic heterotopic liver: a case report. J Pediatr Surg 47:e49–e51

Aoyama C, Hachitanda Y, Sato JK, Said JW, Shimada H (1991) Undifferentiated (embryonal) sarcoma of the liver. A tumor of uncertain histogenesis showing divergent differentiation. Am J Surg Pathol 15:615–624

Arfa MN, Gharbi L, Zaafrani MR, Mbazaa M, Goutellier ben fadhel C, Mestiri H, Ben Ammar MS, Khalfallah MT (2003) Cystic mesenchymal hamartoma of the liver. Report of a case and review of literature. Hepatogastroenterology 50(suppl 2):ccxlix–ccli

Ayadi-Kaddour A, Saiji E, Ben Slama S, Chelly-Ennaiffer-I, Lahmar-Boufaroua A, Goutallier-Ben Fadhel C et al (2006) Hepatic mesenchymal hamartoma in adulthood: a case report with literature review (in French). Tunis Med 84:263–265

Azar GM, Kutin N, Kahn F (2003) Unusual hepatic tumor with features of mesenchymal hamartoma and congenital solitary nonparasitic cyst. Pediatr Dev Pathol 6:265–269

Baboiu OE, Saal H, Collins M (2008) Hepatic mesenchymal hamartoma: cytogenetic analysis of a case and review of the literature. Pediatr Dev Pathol 11:295–299

Balmer B, Le Coultre C, Feldges A, Hanimann B (1996) Mesenchymal liver hamartoma in a newborn; case report. Eur J Pediatr Surg 6:303–305

Barnhart DC, Hirschi RB, Garver KA, Geiger JD, Harmon CM, Coran AG (1997) Conservative management of mesenchymal hamartoma of the liver. J Pediatr Surg 32:1495–1498

Bartho S, Schulz HJ, Bollmann R, Specht U (1992) Prenatally diagnosed mesenchymal hamartoma of the liver (in German). Zentralbl Pathol 138:141–144

Begueret H, Trouette H, Vielh P, Laurent C, MacGrogan G, Delsol M, Belleannee G, Masson B, De Mascarel A (2001) Hepatic undifferentiated embryonal sarcoma: malignant evolution of mesenchymal hamartoma? Study of one case with immunohistochemical and flow cytometric emphasis. J Hepatol 34:178–179

Behr GG, Fishman SJ, Caty MG, Kulungowski AM, Paltiel HJ, Alomari AI (2012) Hepatic mesenchymal hamartoma and infantile hemangioma: a rare association. J Pediatr Surg 47:448–452

Bejarano PA, Serrano MF, Casillas J, Dehner LP, Kato T, Mitral N, Rodriguez MM, Tzakis A (2003) Concurrent infantile hemangioendothelioma and mesenchymal hamartoma in a developmentally arrested liver of an infant requiring hepatic transplantation. Pediatr Dev Pathol 6:552–557

Bejvan SM, Winter TC, Shields LE, Brock BV, Nghiem HV, Schmiedl UP, Waldhausen JH (1997) Prenatal evaluation of mesenchymal hamartoma of the liver: gray scale and power Doppler sonographic imaging. J Ultrasound Med 16:227–229

Benson CD, Penberthy GC (1942) Surgical excision of primary tumor of liver (hamartoma) in an infant seven month old with recovery. Surgery (St Louis) 12:881

Bessho T, Kubota K, Komori S, Ohtsuka Y, Uneo Y, Uematsu K, Koyama K (1996) Prenatally detected hepatic hamartoma: another cause of non-immune hydrops. Prenat Diagn 16:337–341

Bilge O, Emre A, Cevikbas U, Acarli K, Alper A, Ariogul O (1996) Liver hamartoma in an adult: report of a rare case. Surg Today 26:513–516

Boman F, Bossard C, Fabre M, Diab N, Bonnevalle M, Boccon-Gibod L (2004) Mesenchymal hamartoma of the liver may be associated with increased serum alpha foetoprotein concentrations and mimic hepatoblastomas. Eur J Pediatr Surg 14:63–66

Bordeianou L, Ryan DP, Goldstein AM (2005) Focal nodular hyperplasia in a child with Beckwith-Wiedemann syndrome. Pediatr Surg Int 21:742–744

Bove KE, Blough RI, Soukup S (1998) Third report of t (19q)(13.4) in mesenchymal hamartoma of liver with comments on link to embryonal sarcoma. Pediatr Dev Pathol 1:438–442

Bovis F, Kaemmerlen P, Thiesse P, Jonas P, Tran Minh VA (1990) Mesenchymal solid hamartoma of the liver (in French). Pediatrie 45:383–386

Brkic T, Hrstic I, Vucelic B, Jakic-Razumovic J, Skegro M, Romic B, Cukovic-Cavka S, Pulanic R, Ostojic R (2003) Benign mesenchymal liver hamartoma in an adult male: a case report and review of the literature. Acta Med Austriaca 30:134–137

Bulhak-Guz H, Lukaszek S, Samolewicz E (2005) Gastroschisis combined with mesenchymal hamartoma of the liver – case report. Case Rep Clin Pract Rev 6:247–250

Cajaiba MM, Sarita-Reyes C, Zambrano E, Reyes-Mugica M (2007) Mesenchymal hamartoma of the liver associated with features of Beckwith-Wiedemann syndrome and high serum alpha-fetoprotein. Pediatr Dev Pathol 10:233–238

Carta M, Maresi E, Giuffre M, Catalano G, Piro E, Siracusa F, Corsello G (2005) Congenital hepatic mesenchymal hamartoma associated with mesenchymal stem villous hyperplasia of the placenta: case report. J Pediatr Surg 40:e37–e39

Cetin M, Demirpolat G, Elmas N, Yuce G, Cetingul N, Balik E (2002) Stromal predominant type mesenchymal hamartoma of liver: CT and MR features. Comput Med Imaging Graph 26:167–169

Chandramouleeswari K, Anita S, Shivali B (2012) Mesenchymal hamartoma of the liver: a case report. J Clin Diagn Res 6:1552–1554

Chang HJ, Jin SY, Park C, Park YN, Jang JJ, Park CK, Suh YL, Yu E, Kang DY, Bae HI (2006) Mesenchymal hamartomas of the liver: comparison of clinicopathologic features between cystic and solid forms. J Korean Med Sci 21:63–68

Chau KY, Ho JW, Wu PC, Yuen WK (1994) Mesenchymal hamartoma of liver in man: comparison with cases in infants. J Clin Pathol 47:864–866

Chen CP, Chern SR, Wang TY, Huang ZD, Huang MC, Chuang CY (1997) Pregnancy with concomitant chorangioma and placental vascular malformation with mesenchymal hyperplasia. Hum Reprod 12:2553–2556

Chou P, Mangkornkanok M, Gonzalez-Crussi F (1990) Undifferentiated (embryonal) sarcoma of the liver: ultrastructure, immunohistochemistry, and DNA ploidy analysis of two cases. Pediatr Pathol 10:549–562

Christopherson WM, Collier HS (1953) Primary benign liver-cell tumors in infancy and childhood. Cancer 6:853

Chung JH, Cho KJ, Choi DW, Lee BH, Chi JG (1999) Solid mesenchymal hamartoma of the liver in adult. J Korean Med Sci 14:335–337

Cook JR, Pfeifer JD, Dehner LP (2002) Mesenchymal hamartoma of the liver in the adult: association with distinct clinical features and histological changes. Hum Pathol 33:893–898

Cooper K, Hadley G, Moodley P (1989) Mesenchymal hamartoma of the liver. A report of 5 cases. S Afr Med J 75:295–298

Coppin B, Moore I, Hatchwell E (1997) Extending the overlap of three congenital overgrowth syndromes. Clin Genet 51:375–378

Cornette J, Festen S, van den Hoonaard TL, Steegers EA (2009) Mesenchymal hamartoma of the liver: a benign tumor with deceptive prognosis in the perinatal period. Case report and review of the literature. Fetal Diagn Ther 25:196–202

De Chadarevian JP, Pawel BR, Faerber EN, Weintraub WH (1994) Undifferentiated (embryonal) sarcoma arising in conjunction with mesenchymal hamartoma of the liver. Mod Pathol 7:490–493

Dehner LP, Ewing SL, Sumner HW (1975) Infantile mesenchymal hamartoma of the liver. Histologic and ultrastructural observations. Arch Pathol 99:379–382

deMaioribus CA, Lally KP, Sim K, Isaacs H, Mamour GH (1990) Mesenchymal hamartoma of the liver. A 35-year review. Arch Surg 125:598–600

Dickinson JE, Knowles S, Phillips JM (1999) Prenatal diagnosis of hepatic mesenchymal hamartoma. Prenat Diagn 19:81–84

Donovan AT, Wolverson MK, deMello D, Craddock T, Silberstein M (1981) Multicystic hepatic mesenchymal hamartoma of childhood. Computerized tomography and ultrasound characteristics. Pediatr Radiol 11:163–165

Dooley JS, Li AK, Scheuer PJ, Hobbs KE, Sherlock S (1983) A giant cystic mesenchymal hamartoma of the liver: diagnosis, management, and study of cyst fluid. Gastroenterology 85:958–961

Drachenberg CB, Papadimitriou JC, Rivero MA, Wood C (1991) Distinctive case. Adult mesenchymal hamartoma of the liver: report of a case with light microscopic, FNA cytology, immunohistochemistry, and ultrastructural studies and review of the literature. Mod Pathol 4:392–395

Drut R, Drut RM, Toulouse JC (1992) Hepatic hemangiotheliomas, placental chorangiomas, and dysmorphic kidneys in Beckwith-Wiedemann syndrome. Pediatr Pathol 12:197–203

Edmondson H (1956) Differential diagnosis of tumors and tumorlike lesions of liver in infancy and childhood. Am J Dis Child 91:168–186

Egawa T, Kuroda C, Yoshioka H, Hori S, Tokunaga K, Fukui Y, Ikeda Y, Okada A, Sakurai M (1983) Mesenchymal hamartoma of the liver in infant: its roentgen diagnosis. Eur J Radiol 3:348–351

Ehren H, Mahour GH, Isaacs H (1983) Benign liver tumors in infancy and childhood: report of 48 cases. Am J Surg 145:325–329

Eissmann M, Gutschner T, Hämmerle M, Günther S, Caudron-Herger M, Gross M et al (2012) Loss of the abundant nuclear non-coding RNA MALAT1 is compatible with life and development. RNA Biol 9:1076–1087

Faleski EJ, Ghiatas AA (1987) Mesenchymal hamartoma of the liver. N J Med 84:885–888

Fashir BM, Gawdet S, Al Momen S, Hamid F (1998) Mesenchymal hamartoma in a 21-year-old man. Pediatr Radiol 28:514

Federici S, Galli G, Sciutti R, Cuoghi D (1992) Cystic mesenchymal hamartoma of the liver. Pediatr Radiol 22:307–308

Finegold M (1986) Pathology of neoplasia in children and adolescents. W.B. Saunders, Philadelphia

Foucar E, Williamson RA, Yiu-Chiu V, Varner MW, Kay BR (1983) Mesenchymal hamartoma of the liver identified by fetal sonography. AJR Am J Roentgenol 140:970–972

Francis B, Hallam L, Kecskes Z, Ellwood D, Craoker D, Kent A (2007) Placental mesenchymal dysplasia associated with hepatic mesenchymal hamartoma in the newborn. Pediatr Dev Pathol 10:50–54

Fretzayas A, Oustaki M, Kitsiou S, Nychtari G, Alexopoulou E (2009) Long-term follow-up of a multifocal hepatic mesenchymal hamartoma producing a-fetoprotein. Pediatr Surg Int 25:381–384

Fukahori S, Tsuru T, Tanikawa K, Akiyoshi K, Asagiri K, Tanaka Y, Kage M, Kojiro M et al (2007) Mesenchymal hamartoma of the liver accompanied by a daughter nodule: report of a case. Surg Today 37:811–816

Fukuzawa R, Umezawa A, Morikawa Y, Kim KC, Nagai T, Hata J (2001) Nesidioblastosis and mixed hamartoma of the liver in Beckwith-Wiedemann syndrome: case study including analysis of H19 methylation and insulin-like growth factor 2 genotyping and imprinting. Pediatr Dev Pathol 4:381–390

Fukuzawa R, Hata J, Hayashi Y, Ikeda H, Reeve AE (2003) Beckwith-Wiedemann syndrome-associated hepatoblastoma: wnt signal activation occurs later in tumorigenesis in patients with 11p15.5 uniparental disomy. Pediatr Dev Pathol 6:299–306

Gallivan MVE, Lack EE, Chun B, Ishak KG (1983) Undifferentiated ("embryonal") sarcoma of the liver: ultrastructure of a case presenting as a primary intracardiac tumor. Pediatr Pathol 1:291–300

George JC, Cohen MD, Tarver RD, Rosales RN (1994) Ruptured cystic mesenchymal hamartoma: an unusual cause of neonatal ascites. Pediatr Radiol 24:304–305

Gibson BR, Muir-Padilla J, Champeaux A, Suarez ES (2004) Mesenchymal dysplasia of the placenta. Placenta 25:671–672

Gilbert RF, Waugh DE, Clarke JS (1978) Mesenchymal hamartoma of the liver. South Med J 71:530–532

Giyanani VL, Myers PC, Wolfson JJ (1986) Mesenchymal hamartoma of the liver: computed tomography and ultrasonography. J Comput Assist Tomogr 10:51–54

Gosset N, Christophe C, Damry N, Delaet MH (2008) Predominantly cystic hepatic mesenchymal hamartoma. JBR-BTR 91:63

Gottschalk E, Schreiber D, Vetter R (1988) Hamartoma of the liver in childhood (in German). Zentralbl Chir 113:1564–1570

Gow KW, Lee L, Pruthi S, Patterson K, Healey PJ (2009) Mesenchymal hamartoma of the liver. J Pediatr Surg 44:468–470

Gramlich TL, Killough BW, Garvin AJ (1988) Mesenchymal hamartoma of the liver: report of a case in a 28-year-old. Hum Pathol 19:991–992

Grases PJ, Matos-Villalobos M, Arcia-Romero F, Lecuna-Torres V (1979) Mesenchymal hamartoma of the liver. Gastroenterology 76:1466–1469

Grime RT, Moore T, Nicholson A, Whitehead R (1959) Cystic hamartomas and polycystic disease of liver. Br J Surg 47:307

Gunes D, Uysal KM, Cecen E, Cakmakci H, Ozer E, Akgur FM, Olgun N (2008) Stromal-predominant mesenchymal hamartoma of the liver with elevated serum alpha-fetoprotein level. Pediatr Hematol Oncol 25:685–692

Gutierrez OH, Burgener FA (1988) Mesenchymal hamartoma of the liver in an adult: radiologic diagnosis. Gastrointest Radiol 13:341–344

Gutschner T, Hämmerle M, Diederichs S (2013) MALAT1 – a paradigm for long noncoding RNA function in cancer. J Mol Med (Berl) 91:791–801

Hamada Y, Takada K, Fukunaga S, Hioki K (2003) Hepatoblastoma associated with Beckwith-Wiedemann syndrome and hemihypertrophy. Pediatr Surg Int 19:112–114

Hansen GC, Ragavendra N (1992) Atypical mesenchymal hamartoma of the liver: prenatal sonographic diagnosis. AJR Am J Roentgenol 158:921–922

Harris K, Carreon CK, Vohra N, Williamson A, Dolgin S, Rochelson B (2013) Placental mesenchymal dysplasia with hepatic mesenchymal hamartoma: a case report and literature review. Fetal Pediatr Pathol 32:448–453

Heller K, Markus BH, Waag KL (1992) Central hamartoma of the liver in a child. Eur J Pediatr Surg 2:108–109

Helmberger TK, Ros PR, Mergo PJ, Tomczak R, Reiser MF (1999) Pediatric liver neoplasma: a radiologic-pathologic correlation. Pediatr Radiol 9:1339–1347

Hernandez JC, Alfonso C, Gonzalez L, Samada M, Ramos L, Cepero-Valdez M, Antonio Abdo A et al (2006) Solid mesenchymal hamartoma in an adult: a case report. J Clin Pathol 59:542–545

Heyer C, Weitkaemper A, Teig N, Mueller A, Rieger C, Nicolas V (2007) Hepatic mesenchymal hamartoma in a preterm newborn: demonstration by low-dose multidetector CT. Acta Paediatr 96:1538–1542

Hillstrom MM, Brown DL, Wilkins-Haug L, Genest DR (1995) Sonographic appearance of placental villous hydrops associated with Beckwith-Wiedemann syndrome. J Ultrasound Med 14:61–64

Hirata GI, Matsunaga ML, Medearis AL, Dixon P, Platt LD (1990) Ultrasonographic diagnosis of a fetal abdominal mass: a case of a mesenchymal liver hamartoma and a review of the literature. Prenat Diagn 10:507–512

Hojberg KE, Aagaard J, Henriques U, Sunde L (1994) Placental vascular malformation with mesenchymal hyperplasia and a localized chorangioma. A rarity simulating partial mole. Pathol Res Pract 190:808–813

Hsiao KH, Lin LH, Chen DF, Huang SH (2007) Hepatic mesenchymal hamartoma with infantile hepatic hemangioendothelioma in an infant. J Formos Med Assoc 106:S1–S4

Ishida M, Tsuchida Y, Saito S, Sawaguchi S (1966) Mesenchymal hamartoma of the liver – case report and literature review. Ann Surg 164:175–182

Ito H, Kishikawa T, Toda T, Arai M, Muro H (1984) Hepatic mesenchymal hamartoma of an infant. J Pediatr Surg 19:315–317

Ito Y, Seto Y, Okano H, Ueda T, Imanishi H, Nakamura K, Nakajima T, Okanoue T (1989) A case of mesenchymal hamartoma of the liver in adult woman with pancreas divisum and marked delay in ICG plasma clearance (in Japanese). Nippon Shokakibyo Gakkai Zasshi 86:1534–1539

Jaswal TS, Singh S, Purwar P, Sen R, Marwah N, Sharma LK (2003) Mesenchymal hamartoma of the liver – a case report. Indian J Pathol Microbiol 46:226–228

Jauniaux E, Nicolaides KH, Hustin J (1997) Perinatal features associated with placental mesenchymal dysplasia. Placenta 18:701–706

Jennings CM, Merrill CR, Slater DN (1987) The computed tomographic appearances of benign hepatic hamartoma. Clin Radiol 38:103–104

Jimenez-Hefferman JA, Vicandi B, Lopez-Ferrer P, Lamas M, Viguer JM (2000) Fine-needle aspiration cytology of mesenchymal hamartoma of the liver. Diagn Cytopathol 22:250–253

Justrabo E, Martin L, Yaziji N, Couillault JP, Gounot E, Olsson NO, Piard F (1998) Hepatic mesenchymal hamartoma in children. Immunohistochemical, ultrastructural and flow cytometric case study (in French). Gastroenterol Clin Biol 22:964–968

Kamata S, Nose K, Sawai T, Hasegawa T, Kuroda S, Sasaki T, Okada A, Tawara M (2003) Fetal mesenchymal hamartoma of the liver: report of a case. J Pediatr Surg 38:639–641

Karpelowsky JS, Pansini A, Lazarus C, Rode H, Millar AJ (2008) Difficulties in the management of mesenchymal hamartomas. Pediatr Surg Int 24:1171–1175

Kaufman RA (1992) Is cystic mesenchymal hamartoma of the liver similar to infantile hemangioendothelioma and cavernous hemangioma on dynamic computed tomography? Pediatr Radiol 22:582–583

Kay S, Talbert PC (1950) Adenoma of the liver, mixed type (hamartoma): report of two cases. Cancer 3:307

Kenney IJ, Hendry GMA, Mackinlay GA (1986) Spontaneous regression of mesenchymal hamartoma: observations using ultrasound. J Clin Ultrasound 14:72–76

Kim MH, Choi MS, Lee JH, Koh KC, Paik SW, Yoo BC, Jung JH, Choi SC, Kim DH et al (2003) Mesenchymal hamartoma of the liver in adults (in Korean). Taehan Kann Hakhoe Chi 9:31–34

Kim SH, Kim WS, Cheon JE, Yoon HK, Kang GH, Kim IO, Yeon KM (2007) Radiological spectrum of hepatic mesenchymal hamartoma in children. Korean J Radiol 8:498–505

Kitano Y, Ruchelli E, Weiner S, Adzick NS (2000) Hepatic mesenchymal hamartoma associated with mesenchymal stem villous hyperplasia of the placenta. Fetal Diagn Ther 15:134–138

Klaassen Z, Paragi PR, Chamberlain RS (2010) Adult mesenchymal hamartoma of the liver: case report and literature review. Case Rep Gastroenterol 4:84–92

Konez O, Goyal M, Vyas PK, Boinapally SB (2001) Mesenchymal hamartoma of the liver. Comput Med Imaging Graph 25:61–65

Koumanidou C, Vakaki M, Papadaki M, Pitsoulakis G, Savvidou D, Kakavakis K (1999) New sonographic appearance of hepatic mesenchymal hamartoma in childhood. J Clin Ultrasound 27:164–167

Kulkarni MP, Agashe SR, Singh RV, Sulhyan KR (2010) Hepatic angiosarcoma arising in an adult mesenchymal hamartoma. Indian J Pathol Microbiol 53:322–324

Kwok WK, Spitz L, Brereton RJ et al (1989) Mesenchymal hamartoma of the liver. Pediatr Surg Int 4:296–299

Laberge JM, Patenaude Y, Desilets V, Cartier L, Khalife S, Jutras L, Chen MF (2005) Large hepatic mesenchymal hamartoma leading to mid-trimester fetal demise. Fetal Diagn Ther 20:141–145

Lack EE (1986) Mesenchymal hamartoma of the liver. A clinical and pathologic study of nine cases. Am J Pediatr Hematol Oncol 8:91–98

Lage JM (1991) Placentomegaly with massive hydrops of placental stem villi, diploid DNA content, and fetal omphaloceles: possible association with Beckwith-Wiedemann syndrome. Hum Pathol 22:591–597

Lahmar-Boufaroua A, Goutallier C, Yacoubi MT, Manai S, Mestiri H, Mzabi Regaya S (2008) Hepatic un differentiated (embryonal) sarcoma arising in a mesenchymal hamartoma: association or malignant transformation (in French). Tunis Med 86:628–629

Lai FM, Jayakumar CR, Saw L, Kumar G (1996) Hepatic mesenchymal hamartoma: a case report and radiological findings. Singapore Med J 37:226–228

Lanuza A, Perez-Candela V, Ceres L, Cortina H, Mari A, Villanueva A (1980) Hepatic hamartoma in a newborn. Pediatr Radiol 9:111–112

Lauwers GY, Grant LD, Donnelly WH, Meloni AM, Foss RM, Sanberg AA, Langham MR (1997) Hepatic undifferentiated (embryonal) sarcoma arising in a mesenchymal hamartoma. Am J Surg Pathol 21:1248–1254

Lee ES (1942/1943) Large solitary bile-cell fibroadenoma of the liver. Proc R Soc Med 36:33–34

Lennington WJ, Gray GF, Page DL (1993) Mesenchymal hamartoma of liver. A regional ischemic lesion of a sequestered lobe. Am J Dis Child 147:193–196

Levy M, Trivedi A, Zhang J, Miles L, Mattis AN, Kim GE, Lassman C, Anders RA et al (2012) Expression of glypican-3 in undifferentiated embryonal sarcoma and mesenchymal hamartoma of the liver. Hum Pathol 43:695–701

Li CH, Chen Y (2013) Targeting long non-coding RNAs in cancers: progress and prospects. Int J Biochem Cell Biol 45:1895–1910

Li Q, Wang J, Sun Y, Cui Y, Hao X (2007) Hepatic angiosarcoma arising in an adult mesenchymal hamartoma. Int Semin Surg Oncol 4:3

Littlewood Teele R, Pease PW, Rowley RS (1998) Malrotation in newborns following antenatal diagnosis of intra-abdominal cyst. Pediatr Radiol 28:717–721

Locham KK, Bal MS, Kapila AK, Singh M (1999) Cystic mesenchymal hamartoma of liver. Indian Pediatr 36:931–935

Mack-Detlefsen B, Boemers TM, Groneck P, Bald R (2011) Multiple hepatic mesenchymal hamartomas in a premature associated with placental mesenchymal dysplasia. J Pediatr Surg 46:e23–e25

Mansour A, Qandeel M, Sughayer M, Kamona A, Sweidan M, Khawajah M (2005) Solid (stromal predominance) hepatic mesenchymal hamartoma. Pediatr Radiol 35:349–350

Maresch R (1903) Ueber ein Lymphangiom der Leber. Z Heilk 4:39–40

Martinez-Mier G, Cañas-Acar J, Gomez-Dorantes S, Santos-Aguilar U, Alderete-Vazquez G et al (2012) Left lobe mesenchymal hamartoma of liver. Uncommon location (in Spanish). Cir Cir 80:466–469

Mascarello JT, Krous HF (1992) Second report of a translocation involving 19q13.4 in a mesenchymal hamartoma of the liver. Cancer Genet Cytogenet 58:141–142

Mathews J, Duncavage EJ, Pfeifer JD (2013) Characterization of translocations in mesenchymal hamartoma and undifferentiated embryonal sarcoma of the liver. Exp Mol Pathol 95:319–324

Matsui H, Iitsuka Y, Yamazawa K, Tanaka N, Mitsuhashi A, Seki K, Sekiya S (2003) Placental mesenchymal dysplasia initially diagnosed as partial mole. Pathol Int 53:810–813

McCowan LM, Becroft DM (1994) Beckwith-Wiedemann syndrome, placental abnormalities, and gestational proteinuric hypertension. Obstet Gynecol 83:813–817

Megremis S, Sfakianaki E, Voludaki A, Chroniaris N (1994) The ultrasonographic appearance of a cystic mesenchymal hamartoma of the liver observed in middle-aged woman. J Clin Ultrasound 22:338–341

Meinders AJ, Simons MP, Heij HA, Aronson DC (1998) Mesenchymal hamartoma of the liver: failed management by marsupialization. J Pediatr Gastroenterol Nutr 26:353–355

Millard J, Fraser N, Stewart RJ (2006) Mesenchymal hamartoma of the liver: is biopsy always necessary? Pediatr Surg Int 22:622–625

Moore M, Anupindi SA, Mattei P, Sengupta A, Darge K (2009) mesenchymal cystic hamartoma of the liver: MR imaging with pathologic correlation. J Radiol Case Rep 3:22–26

Mori R, Morioka D, Morioka K, Ueda M, Sugita M, Takeda K, Matsuo K, Tanaka K et al (2008) Giant mesenchymal hamartoma of the liver in an adult. J Hepatobiliary Pancreat Surg 15:667–669

Moscoso G, Jauniaux E, Hustin J (1991) Placental vascular anomaly with diffuse mesenchymal stem villous hyperplasia. A new clinico-pathological entity? Pathol Res Pract 187:324–328

Motiwale SS, Karmarkar SJ, Oak SN, Kalgutkar AD, Deshmukh SS (1996) Cystic mesenchymal hamartoma of the liver – a rare condition. Indian J Cancer 33:157–160

Mulrooney DA, Carpenter B, Georgieff M, Angel C, Hunter D, Foker J, Steiner M (2001) Hepatic mesenchymal hamartoma in a neonate: case report and review of the literature. J Pediatr Hematol Oncol 23:316–317

Murray JD, Ricketts RR (1998) Mesenchymal hamartoma of the liver. Am Surg 64:1097–1103

Murthi GV, Paterson L, Azmy A (2003) Chromosomal translocation in mesenchymal hamartoma of liver: what is its significance? J Pediatr Surg 38:1543–1545

Nakajo M, Jinnouchi S, Hamada N, Suevoshi K, Matukita S, Tanabe H, Tateno R, Nakajo M (2009)

FDG PET/CT findings of mesenchymal hamartoma of the liver in an adult. Clin Nucl Med 34:327–329
Narasimhan KL, Radotra BD, Harish J, Rao KL (2004) Conservative management of giant hepatic mesenchymal hamartoma. Indian J Gastroenterol 23:26
Narasimharao KL, Narasimhan KL, Katariya S, Suri S, Kaushik S, Mitra SK (1988) Giant hamartoma of liver mimicking malignancy. Postgrad Med J 64:398–400
Nixon HH (1965) Hepatic tumors in childhood and their treatment by major hepatic resection. Arch Dis Child 40:169–172
Okeda R (1976) Mesenchymal hamartoma of the liver – an autopsy case with serial sections and some comments on its pathogenesis. Acta Pathol Jpn 26:229–236
Orlowski A, Breborowicz D (2011) Mesenchymal hamartoma of the liver – case report and short literature overview. Pol J Pathol 62:108–112
Ortiz Otero A, de Prada Vicente I, Gutierrez Herrera J, Azorin Cuadrilleros D (2012) Hepatic mesenchymal hamartoma in a neonate with a Bochdalek diaphragmatic hernia: a case report. J Pediatr Surg 47:e45–e48
O'Sullivan MJ, Swanson PE, Knoll J, Taboada EM, Dehner LP (2001) Undifferentiated embryonal sarcoma with unusual features arising within mesenchymal hamartoma of the liver: report of a case and review of the literature. Pediatr Dev Pathol 4:482–489
Otal TM, Hendricks JB, Pharis P, Donnelly WH (1994) Mesenchymal hamartoma of the liver. DNA flow cytometric analysis of eight cases. Cancer 74:1237–1242
Packhard GB, Palmer HD (1955) Primary neoplasms of the liver in infants and children. Ann Surg 142:214
Pandey A, Gangopadhyay AN, Sharma SP, Kumar V, Gupta DK, Gopal SC, Patne SC (2011) Long-term follow up of mesenchymal hamartoma of liver – single center study. Saudi J Gastroenterol 17:20–22
Papastratis G, Margaris H, Zografos GN, Korkolis D, Mannika Z (2000) Mesenchymal hamartoma of the liver in an adult: a review of the literature. Int J Clin Pract 54:552–554
Paradinas FJ, Sebire NJ, Fisher RA, Rees HC, Foskett M, Seckl MJ, Newlands ES (2001) Pseudo-partial moles: placental stem vessel hydrops and the association with Beckwith-Wiedemann syndrome and complete moles. Histopathology 39:447–454
Pham T, Steele J, Stayboldt C, Chan L, Benirschke K (2006) Placental mesenchymal dysplasia is associated with high rates of intrauterine growth restriction and fetal demise. Am J Clin Pathol 126:67–78
Pridmore BR, Khong TY, Wells WA (1994) Ultrasound placental cysts associated with massive placental stem villous hydrops, diploid DNA content, and exomphalos. Am J Perinatol 11:14–18
Qiu MT, Hu JW, Yin R, Xu L (2013) Long noncoding RNA: an emerging paradigm of cancer research. Tumour Biol 34:613–620
Raffensperger JG, Gonzalez-Crussi F, Skeehan T (1983) Mesenchymal hamartoma of the liver. J Pediatr Surg 18:585–587
Rajaram V, Knezevich S, Bove KE, Perry A, Pfeifer JD (2007) DNA sequence of the translocation breakpoints in undifferentiated embryonal sarcoma arising in mesenchymal hamartoma of the liver harboring the t(11;19) (q11;q13.4) translocation. Genes Chromosomes Cancer 46:508–513
Rakheja D, Margraf LR, Tomlinson GE, Schnieder NR (2004) Hepatic mesenchymal hamartoma with translocation involving chromosome band 19q13.4: a recurrent abnormality. Cancer Genet Cytogenet 153:60–63
Ramanujam TM, Ramesh JC, Goh DW, Wong KT, Ariffin WA, Kumar G, Taib NA (1999) Malignant transformation of mesenchymal hamartoma of the liver: case report and review of the literature. J Pediatr Surg 34:1684–1686
Ramareddy RS, Alladi A (2012) Neonatal mesenchymal hamartoma of liver: an unusual presentation. J Clin Neonatol 1:211–213
Rodnoguez-Fernandez A (2003) Prennatal and post-natal imaging of an heptice mesenchymal hamartoma, Eur j Pediatr, 62:57–58
Ramirez-Garrido F, LopezGonzalez-Garrido JD, Ruiz-Lopez MJ, Sabatell-Lopez RM, Miras-Baldo MJ and
Rao SP, Bhagavath S, Chen CK, Tolete-Velcek F (1984) Mesenchymal hamartoma of the liver in an older child: association with disseminated intravascular coagulation. Med Pediatr Oncol 12:112–115
Razek MS, Marroum MC, Nassar VH, Slim MS (1973) Cystic mesenchymal hamartoma of the liver in infants and children (a case report and review of the literature). J Med Liban 26:673–682
Reed R, Beischel L, Schoof J, Johnson J, Raff M, Kapur R (2008) Androgenetic/biparental mosaicism in an infant with hepatic mesenchymal hamartoma and placental mesenchymal dysplasia. Pediatr Dev Pathol 11:377–383
Rhodes RH, Marchildon MB, Luebke DC, Edmondson HA, Mikity VG (1978) A mixed hamartoma of the liver: light and electron microscopy. Hum Pathol 9:211–221
Roberts EA, Liu P, Stringer D, Superina RA, Mancer K (1989) Mesenchymal hamartoma in a 10-month-old infant: appearance by magnetic resonance imaging. Can Assoc Radiol J 40:219–221
Roebuck D (1998) Asymptomatic mesenchymal hamartoma of the liver can be treated by observation alone. J Pediatr Surg 33:1587
Ros PR, Goodman ZD, Ishak KG, Dachman AH, Olnsted WW, Hartman DS, Lichtenstein JE (1986) Mesenchymal hamartoma of the liver: radiologic-pathologic correlation. Radiology 158:619–624
Rosado E, Cabral P, Campo M, Tavares A (2013) Mesenchymal hamartoma of the liver – a case report and literature review. J Radiol Case Rep 7:35–43
Rosenbaum DM, Mindell HJ (1981) Ultrasonographic findings in mesenchymal hamartoma of the liver. Radiology 138:425–427
Ruhland B, Schröer A, Gembruch U, Noack F, Weichert J (2011) Prenatal imaging and postnatal pathologic

work-up in a case of fetal hepatic hamartoma and placental mesenchymal dysplasia. Ultrasound Obstet Gynecol 38:360–362

Ruiz MF, Vera P, de La Fuenta G, Linderman C, Echeverria P, Figueroa J, Ocaranza M et al (1995) Cystic hamartoma: prenatal diagnosis and follow-up of newborn infants (in Spanish). Rev Chil Obstet Ginecol 60:211–216

Rump P, Zeegers MP, van Essen AJ (2005) Tumor risk in Beckwith-Wiedemann syndrome: a review and meta-analysis. Am J Med Genet A 136:95–104

Salihoglu Q, Can E, Can S, Hatipoglu S (2013) 'Watchful waiting'may be an appropriate treatment for ELBW infant with hepatic mesenchymal hamartoma. Iran J Pediatr 23:366–368

Salisbury JR, Darby AJ, Portmann BC (1986) Mesenchymal hamartoma of the liver – report of an unusual case. Postgrad Med J 62:757–760

Sanchez Blanco JM, Miralles Sanchiz J, Galnares Barro R, Escribano Negueruela L (1989) Hepatic mesenchymal hamartoma (in Spanish). Rev Esp Enferm Apar Dig 75:73–77

Sarihan H, Yildiz K, Ozoran Y (1994) An unusual case of ectopic mesenchymal hamartoma of the liver. S Afr J Surg 32:152–153

Sato M, Ishida H, Konno K, Naganuma H, Hamashima Y, Komatsuda T, Ishida J, Watanabe S (2000) Liver tumors in children and young patients: sonographic and color Doppler findings. Abdom Imaging 25:596–601

Sawyer JR, Roloson GJ, Bett JM, Thomas JR, Teo C, Chadduck WM (1996) Telomeric associations in the progression of chromosome aberrations in pediatric solid tumors. Cancer Genet Cytogenet 90:1–13

Schumacher R, Westfechtel A (1983) Complex multicystic hamartoma of the liver in childhood – sonographic, roentgenologic and scintigraphic aspects (in German). Klein Pädiatr 195:60–63

Senyuz OF, Bozbora N, Girisken G (1988) Mesenchymal hamartoma of the liver of an infant – case report. Z Kinderchir 43:422–423

Sharif K, Ramani P, Lochbuhler H, Grundy R, de Ville de Goyet J (2006) Recurrent mesenchymal hamartoma associated with 19q translocation. A call for more radical surgical resection. Eur J Pediatr Surg 16:64–67

Shetty S, Pinto A, Roland B (2011) Mesenchymal hamartoma of the liver with inversion of chromosome 19. Pediatr Dev Pathol 14:407–410

Shi X, Sun M, Liu H, Yao Y, Song Y (2013) Long non-coding RNAs: a new frontier in the study of human diseases. Cancer Lett 339:159–166

Shintaku M, Watanabe K (2010) Mesenchymal hamartoma of the liver: a proliferative lesion of possible hepatic stellate cell (Ito cell) origin. Pathol Res Pract 206:532–536

Shuto T, Kinoshita H, Yamada C, Hirohashi K, Shiokawa C, Kubo S, Fujio N, Kobayashi Y (1993) Bilateral lobectomy excluding the caudate lobe for giant mesenchymal hamartoma of the liver. Surgery 113:215–222

Siddiqui MA, McKenna BJ (2006) Hepatic mesenchymal hamartoma: a short review. Arch Pathol Lab Med 130:1567–1569

Silber DL, Soper RT, Kent TH (1970) Life-threatening mesenchymal hamartoma of the liver. J Pediatr Surg 5:471–472

Singh ZN, Ray R, Sarode VR, Narang A (1996) Congenital mesenchymal hamartoma of liver. Indian Pediatr 33:415–417

Smith WL, Ballantine TV, Gonzalez-Crussi F (1978) Hepatic mesenchymal hamartoma causing heart failure in the neonate. J Pediatr Surg 13:183–185

Smith SL, Ramli NM, Somers JM (2001) Cystic mesenchymal hamartoma mimicking hepatic hydatid disease. Clin Radiol 56:599–601

Speleman F, De Telder V, De Potter KR, Dal CP, Van Daele S, Benoit Y, Leroy JG, van den Berghe H (1989) Cytogenetic analysis of a mesenchymal hamartoma of the liver. Cancer Genet Cytogenet 40:29–32

Srouji MN, Chatten J, Schulman WM, Ziegler MM, Koop CE (1978) Mesenchymal hamartoma of the liver in infants. Cancer 42:2483–2489

Stanley P, Hall TR, Wolley MM, Diament MJ, Gilsanz V, Miller JH (1986) Mesenchymal hamartoma of the liver in childhood: sonographic and CT findings. AJR Am J Roentgenol 147:1035–1039

Steigman CK, Uri AK, Chatten J, Peckham GJ (1990) Beckwith-Wiedemann syndrome with unusual hepatic and pancreatic features: a case expanding the phenotype. Pediatr Pathol 10:593–600

Steiner MA, Giles HW (2008) Mesenchymal hamartoma of the liver demonstrating peripheral calcification in a 12-year-old boy. Pediatr Radiol 38:1232–1234

Stephens CL, Jenevein EP (1965) Mesenchymal hamartoma of liver. Arch Pathol 80:413

Stocker JT (2001) Hepatic tumors in children. Clin Liver Dis 5:259–281

Stocker JT, Ishak KG (1978) Undifferentiated (embryonal) sarcoma of the liver. Report of 31 cases. Cancer 42:336–348

Stocker JT, Ishak KG (1983) Mesenchymal hamartoma of the liver: report of 30 cases and review of the literature. Pediatr Pathol 1:245–267

Stocker JT, Husain AN, Dehner LP et al (2002) The liver, gallbladder, and biliary tract. In: Stocker JT, Dehner LP (eds) Pediatric pathology, 2nd edn. Williams and Wilkins, Philadelphia, pp 757–760

Stringer MD, Alizai NK (2005) Mesenchymal hamartoma of the liver: a systematic review. J Pediatr Surg 40:1681–1690

Sugito K, Kawashima H, Uekusa S, Inoue M, Ikeda T, Kusafuka T (2010) Mesenchymal hamartoma of the liver originating in the caudate lobe with t(11;19)(q13;q13.4): report of a case. Surg Today 40:83–87

Sutton CA, Eller JL (1968) Mesenchymal hamartoma of the liver. Cancer 22:29

Symmers WSC, Ward-McQuaid JN (1950) Successful resection of a large cavernous lymphangiomatoid

lesion of the liver of a child aged nineteen months. Br J Surg 38:12
Takano H, Sato Y, Kao SC, D'Alessandro MP (1997) Enlarging giant liver cyst in Beckwith-Wiedemann syndrome. Pediatr Radiol 27:619–620
Takayama M, Soma H, Yaguchi S, Funayama H, Fujiwara K, Irie H, Yamabe S (1986) Abnormally large placenta associated with Beckwith-Wiedemann syndrome. Gynecol Obstet Invest 22:165–168
Talmon GA, Cohen SM (2006) Mesenchymal hamartoma of the liver with an interstitial deletion involving chromosome band 19q13.4: a theory as to pathogenesis? Arch Pathol Lab Med 130:1216–1218
Tano K, Akimitsu N (2012) Long non-coding RNAs in cancer progression. Front Genet 3:219
Tovbin J, Segal M, Tavori I, Lotan G, Maymon R (1997) Hepatic mesenchymal hamartoma: a pediatric tumor that may be diagnosed prenatally. Ultrasound Obstet Gynecol 10:63–65
Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, Freier SM, Bennett CF et al (2010) The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell 39:925–938
Tripathi V, Shen Z, Chakraborty A, Giri S, Freier SM, Wu X, Zhang Y, Gorospe M et al (2013) Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB. PLoS Genet 9:e1003368
Tucker SM, Cooper K, Brownschidle S, Wilcox R (2012) Embryonal (undifferentiated) sarcoma of the liver with peripheral angiosarcoma differentiation arising in a mesenchymal hamartoma in an adult patient. Int J Surg Pathol 20:297–300
Turlin B, Deugnier Y, Kerneis J, Campion JP, Verger P, Ramee MP (1996) Liver mesenchymal hamartoma in adulthood. Report of a new case (in French). Ann Pathol 16:192–195
Tzen CY, Chen BF, Chang PY, Wang NL (1998) Mesenchymal hamartoma of the liver: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 61:427–431
Unal E, Koksal Y, Akcoren Z, Tavl L, Gunel E, Kerimoglu U (2008) Mesenchymal hamartoma of the liver mimicking hepatoblastoma. J Pediatr Hematol Oncol 30:458–460
Vandendriessche L, Bonhomme A, Breysem L, Smet MH, Uyttebroeck A, Brock P, Baert AL (1996) Mesenchymal hamartoma: radiological differentiation from other possible liver tumors in childhood. J Belge Radiol 79:74–75
Vargas-Vallejo M, Alvarez-Solis R, Cabrera-Aguirre J, Bulnes Mendizabal D, Ulloa-Patino P (2005) Giant hepatic mesenchymal hamartoma in a 2-year-old girl (in Spanish). An Pediatr (Barc) 63:564–565
Vazquez-Lima I, Vazquez JL, Gallego M, Fernandez R, Fernandez P (2009) Torsed pedunculated hepatic hamartoma. Pediatr Radiol 39:62–65
Virgone C, Cecchetto G, Dall'igna P, Zanon GF, Cillo U, Alaggio R (2015) Mesenchymal hamartoma of the liver in older children: an adult variant or a different entity? Report of a case with review of the literature. Appl Immunohistochem Mol Morphol 23:667–673
Von Schweinitz D, Dammeier BG, Gluer S (1999) Mesenchymal hamartoma of the liver – new insights into histogenesis. J Pediatr Surg 34:1269–1271
Wada M, Ohashi E, Jin H, Nishikawa M, Shintani S, Yamashita M, Kano M, Yamanaka N et al (1992) Mesenchymal hamartoma of the liver: report of an adult case and review of the literature. Intern Med 31:1370–1375
Wan P, Susman J, Kandel J, Jan D, Jerome EH, Parravicini E (2009) Neonatal hepatic mesenchymal hamartoma causing cardiac failure and disseminated intravascular coagulopathy. Am J Perinatol 26:601–604
Weinberg AG, Finegold MJ (1983) Primary hepatic tumors of childhood. Hum Pathol 14:512–537
Wendth AJ, Shamoun J, Pantoja E, Luther P, Frede T (1976) Cystic hamartoma of the liver in a pediatric patient. Angiographic findings. Radiology 121:440
Wholey MH, Wojno KJ (1994) Pediatric hepatic mesenchymal hamartoma demonstrated on plain film, ultrasound and MRI, and correlated with pathology. Pediatr Radiol 24:143–144
Yamamoto M, Hagihara H, Mogaki M, Iimuro Y, Fujii H, Ainota T, Akahane Y, Matsumoto Y (1994) Adult mesenchymal hamartoma of the liver mimicking bile duct cystadenoma. J Gastroenterol 29:518–524
Yandza T, Valayer J (1986) Benign tumors of the liver in children: analysis of a series of 20 cases. J Pediatr Surg 21:419–423
Ye BB, Hu B, Wang LJ, Liu HS, Zou Y, Zhou YB, Kang Z (2005) Mesenchymal hamartoma of liver: magnetic resonance imaging and histopathologic correlation. World J Gastroenterol 11:5807–5810
Yen JB, Kong MS, Lin JN (2003) Hepatic mesenchymal hamartoma. J Paediatr Child Health 39:632–634
Yesildag E, Yeker Y, Erdogan E, Yeker D (2004) Extrathoracic liver hamartoma. Indian J Pediatr 71:265–267
Yesim G, Gupse T, Zafer U, Ahmet A (2005) Mesenchymal hamartoma of the liver in adulthood: immunohistochemical profiles, clinical and histopathological features in two patients. J Hepatobiliary Pancreat Surg 12:502–507
Zhang ZZ, Wang L, Wang Y, Tang LJ, Yao HX (2008) Mesenchymal hamartoma of the liver: a report of 2 cases (in Chinese). Zhongguo Dang Dai Er Ke Za Zhi 10:89–90

Undifferentiated (Embryonal) Sarcoma (UES)

105

ICD-O code 8991/3

Contents

Abstract

Undifferentiated embryonal sarcoma (UES) is defined as a highly malignant mesenchymal neoplasm of the liver. UES mainly occurs in the pediatric age group and is characterized by the presence of an immature and myxoid mesenchyme that contains numerous pleomorphic and giant cells with distinct eosinophilic globular cytoplasmic inclusions. UES is the third most common malignant hepatic tumor in children, whereby about 50 % of patients are 6–10 years old at diagnosis. In contrast to hepatoblastoma, only a minority of UES is diagnosed in children younger than 5 years. UES is a highly aggressive neoplasm that forms large liver tumors mainly in the right liver lobe, typically undergoing cystic change, sometimes mimicking hydatid disease. Spontaneous hemorrhage and tumor rupture may occur. Apart from a basic histologic pattern, several variants are known, including small cell, anaplastic and rhabdoid phenotypes, and tumors with various heterologous components. The abnormal mesenchyme of UES may surround abnormal and dilated intratumoral bile

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_105

duct-like structures. There is a pathogenetic relationship between UES and mesenchymal hamartoma of the liver.

Introduction

Undifferentiated (embryonal) sarcoma (UES) is defined as a highly malignant mesenchymal neoplasm of the liver, predominantly in children, characterized by the presence of an immature and myxoid mesenchyme containing pleomorphic and giant cells with globular eosinophilic cytoplasmic inclusions.

UES was first described in 1978 as a separate pathologic entity, based on 31 observations (Stocker and Ishak 1978). This tumor type may have first been reported in 1946, under the term, mesenchymoma, based on an observation in a 6-year-old boy, but the fact that this patient survived well for 13 months in a pre-chemotherapy era and based on the two histologic figures in the article leaves some doubt whether this tumor was not rather mesenchymal hamartoma (Donovan and Santulli 1946). Several terms had been employed to denote this neoplasm, including primary sarcoma of the liver (Willeford and Stembridge 1950), malignant mesenchymoma, embryonal sarcoma (Lagacé et al. 1974; Blattner et al. 1977; Forster and Berman 1977; Cornut-Sipido 1979; Cozzutto et al. 1981), primary mesenchymoma (Lorimer 1955), fibromyxosarcoma, primary malignant mesenchymal tumors, or simply sarcoma (Anderson 1951; Keeling 1971; Stanley et al. 1973). Prior to the 31 cases described by Stocker and Ishak (1978), the largest series of this lesion was that by Foster and Berman (1977) with 12 cases. The term, undifferentiated sarcomas of the liver, had however previously been employed to denote a primary hepatic sarcoma in an adult patient (Esposito et al. 1977). Within few years after the first description, several further cases have been reported (Abramowsky et al. 1980; Kinjo et al. 1980; Gallivan et al. 1983; Gonzalez-Crussi 1983; Weinberg and Finegold 1983; Parichatikanond and Parichatikanond 1985).

Epidemiology

UES is the third most common malignant tumor of the liver in the pediatric age group, accounting for about 9–15 % of childhood hepatic malignant neoplasms (Stocker and Ishak 1978; Weinberg and Finegold 1983). Among the 31 patients reported by Stocker and Ishak (1978), 51.6 % of the children were 6–10 years of age, followed by the groups 11–15 years (19.4 %), 0–5 years (16.1 %), 16–20 years (6.5 %), and >20 years (6.5 %). Four patients of this series were not in the pediatric age group and were 19, 20, 22, and 28 years old at diagnosis. In some reports, there was a male preponderance, but in a larger study of 20 patients, the male to female ratio was 1:1 (Nicol et al. 2007). As already specified in a report of 31 cases (Stocker and Ishak 1978), the majority of patients present between 6 and 10 years of age, i.e., clearly later than patients with hepatoblastoma. The neoplasm is not related to preexisting liver disease (literature reviews: Aghajanzadeh et al. 2003; Sakellaridis et al. 2006; Iqbal et al. 2008; Pachera et al. 2008; Mohapatra and Krisnanand 2007; Boybeyi et al. 2009; Pathirana et al. 2010).

Albeit typically a tumor of older children, there are numerous reports documenting UES in adult patients. Adult primary UES is a rare disease that, similar to cases in the pediatric age group, develops in livers without preexisting disease, in particular without liver cirrhosis.

Selected References Stocker and Ishak 1978; Chang et al. 1983; Miettinen and Kahlos 1989; Kanamaru et al. 1991; Kchir et al. 1991; Martins et al. 1992; McFadden et al. 1992; Reichel et al. 1994; Zaheer et al. 1994; Johnson et al. 1995; Mistry et al. 1995; Grazi et al. 1996; Houry et al. 1998; Tokunaga et al. 2000; Yedibela et al. 2000; Diedhiou et al. 2002; Shufaro et al. 2002; Nishio et al. 2003; Psatha et al. 2004; Alagiozian-Angelova et al. 2005; Dai et al. 2005; Agaram et al. 2006; Scudiere and Jakate 2006; McCarthy et al. 2007; Gourgiotis et al. 2008; Lenze et al. 2008;

Faraj et al. 2010; Jiménez-Fuertes et al. 2008; Ma et al. 2008; Pachera et al. 2008; Kullar et al. 2009; Yang et al. 2009; Kaur et al. 2010; Lee et al. 2010; Li et al. 2010; Massani et al. 2010; Yoon et al. 2010; Xu et al. 2010; Gasljevic et al. 2011; Kalra et al. 2011; Lightfoot and Nikfarjam 2012; Varol et al. 2012; Chen et al. 2013; Lin et al. 2013

Clinical Features

The patients commonly present with an abdominal mass and upper abdominal pain. Among 31 patients, 12 had an abdominal mass only, 10 abdominal pain only, and 6 abdominal mass and pain (Stocker and Ishak 1978; Wei et al. 2008). Abdominal discomfort and pain were experienced for periods of 3 days–1 month. Asymptomatic abdominal masses had been noted for periods of 2 weeks–6 months. Jaundice and systemic signs such as fever, malaise, lethargy, and weight loss may occur, and sometimes the patient is referred to the hospital in a severely ill state, e.g., owing to tumor rupture with abdominal crisis (Weinberg and Finegold 1983; Lack et al. 1991). In UES, serum AFP is in the normal range (Stocker and Ishak 1978; Kanamaru et al. 1991; Lack et al. 1991; Wei et al. 2008), but lectin-reactive AFP (AFP-L3) may be elevated in a minority of patients (Okuda et al. 2005). UES tends to invasion and tissue destruction, including extension of the neoplasm along the inferior vena cava to the heart (Gallivan et al. 1983; Bassly et al. 2008). Bronchobiliary fistula has been observed in a child suffering from UES (Corapçioglu et al. 2004). In adult patients, the frequently cystic tumor may mimic hepatic hydatid disease (Faraj et al. 2010; Yoon et al. 2010; Kalra et al. 2011). In one 46-year-old female patient, UES was associated with systemic lupus erythematosus (Jia et al. 2013). In one adult case, UES radiologically mimicked Klatskin tumor (Lee et al. 2010). Complications of UES comprise hemorrhage (Suarez et al. 2000; Küpeli et al. 2008),spontaneous rupture followed by hematoperitoneum and eventually hemorrhagic shock (Stocker and Ishak 1978; Lack et al. 1991; Yedibela et al. 2000; Uchiyama et al. 2001; Hung et al. 2007; Yu et al. 2009), or rupture following abdominal trauma (Ida et al. 2009). Exceptionally, UES is associated with paraneoplastic syndromes or disorders. In a single reported patient, UES was associated with peripheral eosinophilia (Zaheer et al. 1994), and another adult patient revealed an erythropoietin-secreting tumor (Lin et al. 2013). One patient experienced fever of unknown origin, secretory diarrhea, refractory long QT syndrome, and torsades de pointes, resolved following surgical resection (Fricchione et al. 2013).

Imaging Features

The imaging features of UES have been studied in detail, also with respect to radiologic-pathologic correlations and treatment response. Ultrasonography reveals large masses which are hyperechoic or isoechoic. Predominantly solid variants with many small anechoic spaces may be seen (Ros et al. 1986). On the other hand, a true cystic change of the tumor has already been described for one patient in the original series of 31 cases as of 1978, whereas in more than half of the cases of this series, there were multiple cystic areas containing necrotic debris, clotted blood, or gelatinous material (Stocker and Ishak 1978). Overall, CT usually shows large solid low-attenuating masses with cystic areas, with varying degrees of enhancement of the solid component and formation of hyperdense septa of variable thickness and a dense peripheral rim. Irregular high-density lesions exhibiting hemorrhage may occur. Cystic UES may show multiple internal septations (Ros et al. 1986; Joshi et al. 1997). The cystic changes may vary considerably both in size and shape and may cause a pitfall diagnosis in endemic hydatidosis areas (Joshi et al. 1997; Aggarwal et al. 2001; Charfi et al. 2008; Faraj et al. 2010). Large cysts in UES may also mimic complicated hepatic cysts at imaging (Tsukada et al. 2010). The cystic changes in UES may be the result of liquefied hemorrhage and/or necrosis, because hemorrhagic fluid in the cyst cavities suggested

that cystic "degeneration" was related to hemorrhage. However, the finding that the inner wall of the cysts in UES may be rather smooth led to the view that the cysts develop spontaneously (Dai et al. 2005). At MRI, T1-weighted images reveal well-defined hypointense masses, sometimes with scattered high signal intensities, while T2-weighted images show high signal intensity in most of the tumor volumes. MRI clearly displays the cystic space of the tumors, the septations, and often substantial central necrosis (Marti-Bonmati et al. 1993; Buetow et al. 1997; Woong et al. 1997; Yoon et al. 1997; Psatha et al. 2004). Angiographically, UESs are usually hypovascular tumors, although hypervascular areas may also occur (Stocker and Ishak 1978; Ros et al. 1986).

Selected References Ros et al. 1986; Marti-Bonmati et al. 1993; Urban et al. 1993; Moon et al. 1994, 1995; Sano et al. 1995; Buetow et al. 1997; Yoon et al. 1997; Helmberger et al. 1999; Chuang et al. 2002; Psatha et al. 2004; Goncalves-Matoso et al. 2005; Kim et al. 2008; Iqbal et al. 2008; Yu et al. 2008; Zhao et al. 2008; Crider et al. 2009; Lashkari et al. 2009; Yang et al. 2009; Kowalczyk and Carr 2010; Sodhi et al. 2010

Pathology

Macroscopy

Similar to other malignant hepatic tumors, UES develops more frequently in the right liver lobe (right lobe localization in 11/16 patients in one study, with contiguous involvement of the left lobe in three; Lack et al. 1991). UESs are usually large or even huge tumors that present as solitary and mostly well-delineated masses with variable areas of hemorrhage, confluent necrosis and sometimes macrocytic changes, resulting in a highly variegated cut surface. UES often grows to a very impressive size. In the series of Stocker and Ishak, tumor size was assessed in 20 cases, among which four were less than 10 cm in diameter, 10 were between 10 and 20 cm, and 6 exceeded 20 cm in diameter, the largest measuring 30 cm. The weight of the tumors varied from 90 to 3,375 g (average of 16 tumors, 1,310 g). In a study of 28 cases, the mean transverse diameter of the tumors was 14 cm (range, 10–25 cm). In a study of 16 patients, the average tumor diameter was 21 cm (range, 10–35 cm; Lack et al. 1991). The masses were predominantly solid (83 % of tumor volume), and pathologic and sonography findings were concordant (Buetow et al. 1997). The solid variants are globular in shape and are usually well demarcated from the rest of the liver. Typically, the tumors are nonencapsulated. Some tumors may show a pseudocapsule, but this impression is usually produced by compression and atrophy of adjacent liver substance.

The neoplasms are soft or fluctuant, with a glistening or variegated cut surface, colors ranging from gray-reddish to yellowish or even tan. Hemorrhage and necrosis may comprise up to 80 % of the tumor (Stocker and Ishak 1978; Ros et al. 1986; Leuschner et al. 1990; Lack et al. 1991; Parham et al. 1991; Kadomatsu et al. 1992; Walker et al. 1992; Buetow et al. 1997). The issue of macrocytic changes in UES has already been addressed above. In a minority of cases, "true" cystic cavities containing a mucoid fluid are in fact encountered. Mucoid or gelatinous areas are also observed. Together with necrosis cavities and spaces containing liquid or clotted blood, these can produce multiple cyst-like areas, seen in more than half of the cases in the series of 31 cases described by Stocker and Ishak (1978), but such lesions should not be confounded with the much rarer "true" cysts. Smaller cysts often contain a brownish mucoid fluid. UES may present as a single (solitary, unilocular) cyst of the liver (Chowdhary et al. 2004; Kim et al. 2009; Massani et al. 2010). Intravascularly growing tumors show a glistening, transparent quality with bosselations. Pedunculated tumors are very uncommon lesions, in contrast to mesenchymal hamartoma (Stanley et al. 1973; Stocker and Ishak 1978). In the case of Stanley and coworkers (1973), a 10-year-old boy had a partially cystic and solid pedunculated mass (17 cm diameter)

that was attached to the posterior inferior surface of the left liver lobe.

Histopathology

The histologic features of UES have been described in detail (Stocker and Ishak 1978; O'Sullivan et al. 2001; Bliuznikov et al. 2007). The tumors are often surrounded by a compressed fibrous pseudocapsule of varying thickness, with atrophy of the adjacent liver parenchyma. The interior of the masses is composed by various types of tissue components (Table 1).

The bulk of the tumor consists of a loose but cellular tissue consisting of immature-looking or undifferentiated mesenchymal cells. These appear in several types, dominated by stellate and spindle cells, and followed in frequency by giant and polymorphic cells and by round cells. Most of these cells display very indistinct cell borders, sometimes suggesting the formation of syncytia. These types of cell seem to reflect various pathways of differentiation (Aoyama et al. 1991). Most of the stellate and spindle cells are scattered loosely in a matrix rich in Alcian blue-positive mucopolysaccharides, but part of these cells may also form fascicles or whorls or are packed in sheets. Such cases resemble malignant fibrous histiocytoma or fibrosarcoma (Keating and Taylor 1985), or hemangiopericytoma/solitary fibrous tumor. Spindle cells with myoid differentiation occur (Walker et al. 1992) (Figs. 1, 2, 3, 4, 5, 6, 7, and 8).

Table 1 Histologic phenotypes of undifferentiated (embryonal) sarcoma (UES)

Standard morphology
Bimodal type with prominent cholangiocellular differentiation
Fibrous histiocytoma-like variant
Hemangiopericytoma-like variant
Anaplastic variant
Small cell variant
Rhabdoid features
Marked myoid differentiation
Marked lipomatous differentiation
Angiosarcomatous differentiation
Chondroid or osteoid differentiation

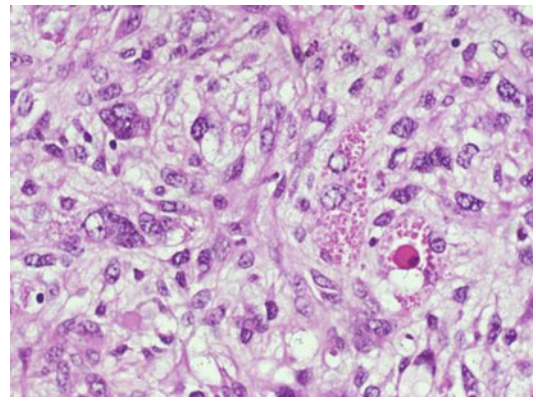

Fig. 1 Undifferentiated (embryonal) sarcoma of the liver. The hypercellular tumor consists of spindle cells and stellate cells with marked nuclear pleomorphism. Note the intracellular eosinophilic inclusions (hematoxylin and eosin stain)

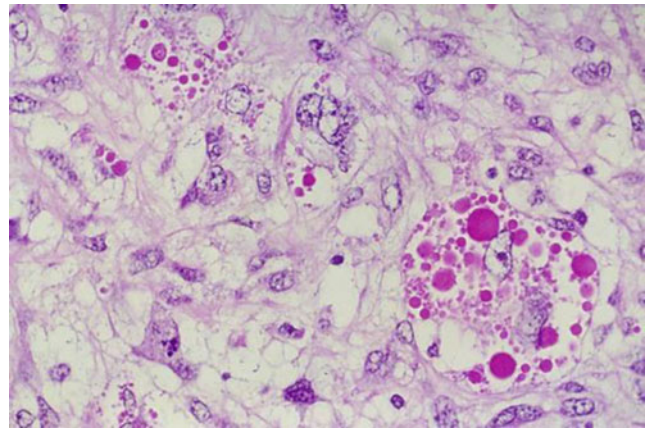

Fig. 2 Undifferentiated (embryonal) sarcoma of the liver. Tumor giant cells contain dense eosinophilic globular inclusions with a heterogeneous size distribution (PAS stain)

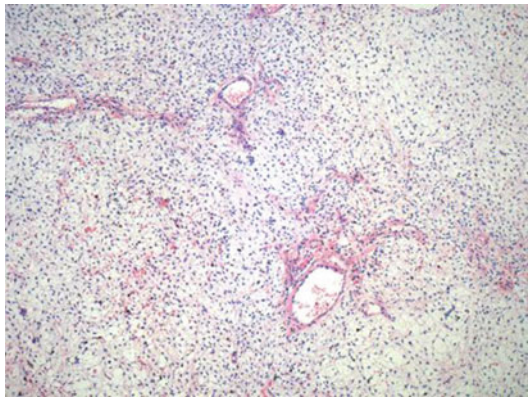

Fig. 3 Undifferentiated (embryonal) sarcoma of the liver with a markedly myxoid aspect and predominance of stellate tumor cells (hematoxylin and eosin stain)

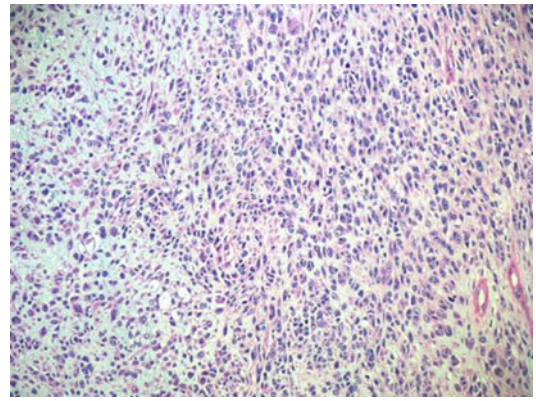

Fig. 5 Undifferentiated (embryonal) sarcoma of the liver with predominance of spindle cells and polygonal cells (hematoxylin and eosin stain)

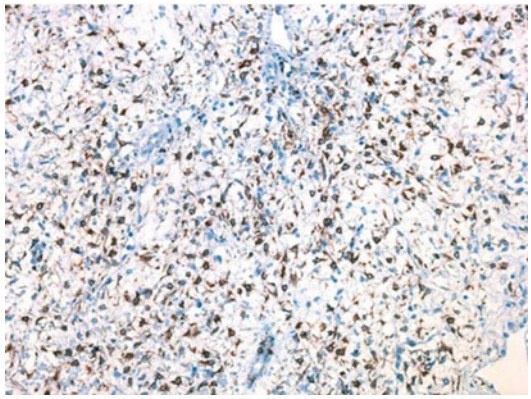

Fig. 4 Undifferentiated (embryonal) sarcoma, myxoid variant. The stellate aspect of tumor cells is well recognizable in a stain showing vimentin expression (vimentin immunostain)

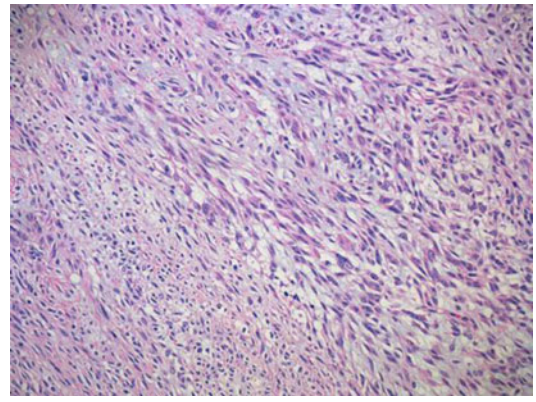

Fig. 6 Undifferentiated (embryonal) sarcoma of the liver. In this tumor, fascicles or interlacing bundles of spindle cells with an eosinophilic cytoplasm are present (myoid variant; hematoxylin and eosin stain)

In a minority of cases, a contribution of anaplastic or small cells is seen (Walker et al. 1992). It was suggested that an anaplastic component is more commonly encountered in UES arising in adults (Nishio et al. 2003). Osteoid formation in UES has been described (Lack et al. 1991). This abnormal mesenchyme of UES often surrounds abnormal and dilated intratumoral, CK 19-positive bile duct-like profiles, and the cellularity of the tissue may be higher close to the epithelial lining, forming a "cambium." This predominant component of UES shows high mitotic activity. The giant cells are either multinucleated or contain highly polyploidy and in part bizarre nuclei, with segregation of micronuclei, formation of nuclear bridges, and complex lobulations. Part of the large cells or giant cells contain few to numerous intracytoplasmic eosinophilic globules, measuring 2–40 μm in diameter, and sometimes hiding the nucleus. These globules are variably PAS-positive, but resistant to diastase digestion. In the Masson trichrome stain, they are blue to red, purple with PTAH, and positive with the Danielli staining method (Stocker and Ishak 1978). Globule-containing cells release the globules into the extracellular space upon cell death. The tumor tissue contains a fine network of reticulin fibers. Focally, dense bundles of partly hyalinized

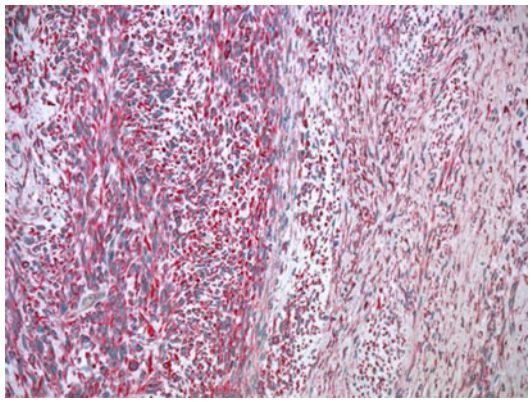

Fig. 7 Undifferentiated (embryonal) sarcoma of the liver, myoid variant. Numerous spindle cells are reactive for smooth muscle actin (alpha-SMA immunostain)

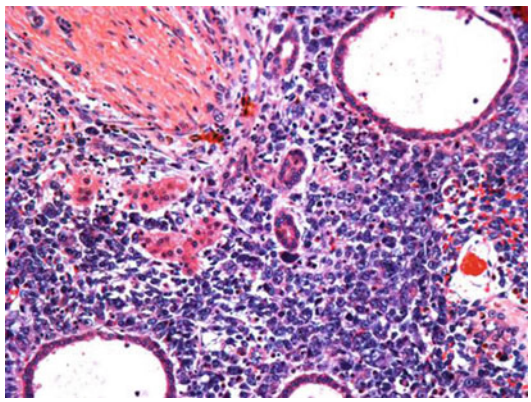

Fig. 8 Undifferentiated (embryonal) sarcoma of the liver, anaplastic variant. Small- to medium-sized cells with poor cytoplasm result in a "blue cellular tumor." Note the dilated bile duct within the tumor tissue (hematoxylin and eosin stain)

collagen are in evidence. Mainly in regions of necrosis, an infiltrate composed of lymphocytes, macrophages, and plasma cells is often present. UES has been diagnosed by the use of fine-needle aspiration cytology (Pieterse et al. 1985; Sola-Pérez et al. 1995; Krishnamurthy et al. 1996; Garcia-Bonafé et al. 1997; Allen et al. 1998; Pollono and Drut 1998; Sharifah et al. 1999; Anavi et al. 2001; Gupta et al. 2010; Kaur et al. 2010). Metastases of UES usually show the same histopathologic presentation as the primary lesion, but there are deviations from this presentation. Peritoneal metastases of UES in an adult patient were found to present as leiomyosarcomatous nodules (Fievez et al. 1983). This phenomenon may be linked to the fact that UES has been shown to undergo smooth muscle cell differentiation (Nishio et al. 2003), and such a cell lineage may then also evolve in metastatic disease.

A distinct feature of some UES is the focal differentiation along myoid (leiomyoid and/or rhabdomyoid) lineages or along an adipocyte-like lineage. Ultrastructural studies suggested a leiomyoblastic differentiation (Gonzalez-Crussi 1983), and features suggesting a leiomyoid cell lineage have been observed by previous investigators as well (Lagacé et al. 1974; Cozzutto et al. 1981 9) and supported by more recent findings (Walker et al. 1992; Nishio et al. 2003). A differentiation along a lipoblastoid lineage has chiefly been suggested based on the presence of oil red O staining (Stocker and Ishak 1978) and ultrastructural presence of lipid droplets in subsets of tumor cells (Cozzutto et al. 1981; Chang et al. 1983; Ellis and Cotton 1983; Gallivan et al. 1983; Parham et al. 1991). Lipid droplets in UES cells were detected in six out of seven neoplasms in one analysis (Parham et al. 1991). Morphologically, typical lipoblasts in UES have also been described (Lagacé et al. 1974). Whether this phenotype reflects liposarcomatous features of some, UES is not ascertained. In rare instances, aberrant differentiation patterns can occur, e.g., chondroid differentiation with formation of chondrosarcoma-like lesions (Kinjo et al. 2010), production of tumor osteoid (Chen et al. 2013), or lesions resembling telangiectatic hepatic adenoma (Tanaka et al. 2012). In one adult patient, UES arising from mesenchymal hamartoma exhibited peripheral angiosarcomatous differentiation (Tucker et al. 2012).

At the interface between the tumor and the liver, trapped and damaged hepatocytes, and abnormal and in part cystic bile ducts are seen (Figs. 9, 10, 11, and 12; Stanley et al. 1973; Stocker and Ishak 1978; Walker et al. 1992). The duct-like structures are sometimes markedly dilated and deformed; they may contain an eosinophilic material, but bile is consistently lacking. Only rarely were parenchymal cells seen deeper

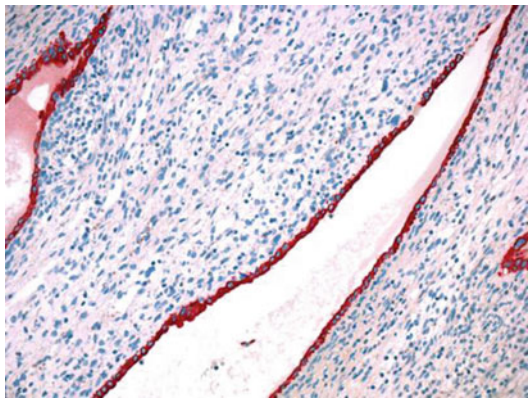

Fig. 9 Undifferentiated (embryonal) sarcoma of the liver. Dilated bile ducts embedded in the tumor tissue (cytokeratin 19 immunostain)

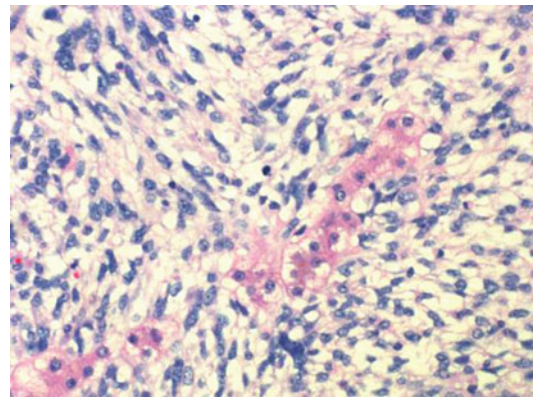

Fig. 11 Undifferentiated (embryonal) sarcoma of the liver with intratumoral clusters of hepatocytes. Note that the hepatocytes are in direct contact with mesenchymal tumor cells (hematoxylin and eosin stain)

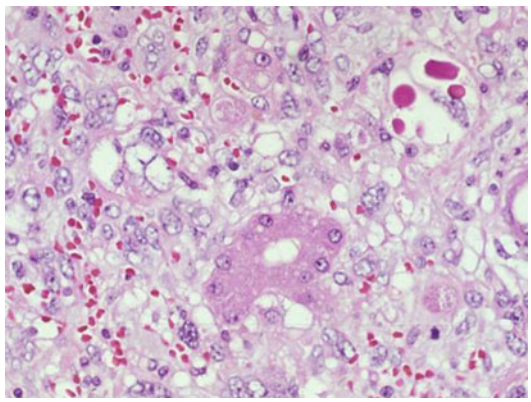

Fig. 10 Small bile ducts embedded in pleomorphic tissue of undifferentiated (embryonal) sarcoma. Cholangiocyte cytoplasm shows eosinophilia (hematoxylin and eosin stain)

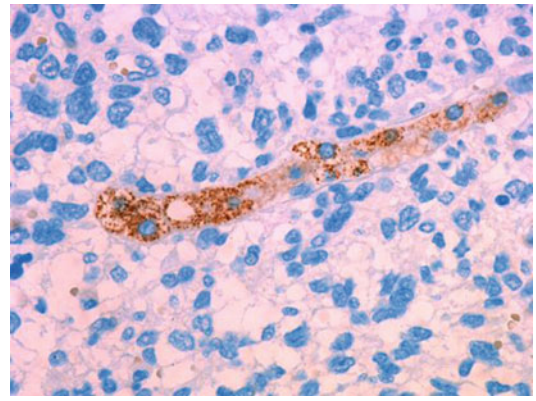

Fig. 12 Undifferentiated (embryonal) sarcoma with embedded intratumoral hepatocytes and no intervening cells. Hepatocytes are strongly positive for Hep Par1 (Hep Par1 immunostain)

than 0.5–1.0 cm from the edge of the tumor (Stocker and Ishak 1978). The dilated bile duct-like structures are separated from the tumor tissue by a thin, PAS-positive lamella which may represent a basement membrane, but focally this lamella is broached by sarcoma cells. The cholangiocyte lining is typically not atrophic, the cells being cuboid instead of flat, but some cells show signs of damage, with irregular arrangement of the cell within the single layer and hyperchromatic nuclei as a frequent feature (Stanley et al. 1973). As the sarcoma tissue directly encroaches upon these ducts, the absence of atrophy is striking. The marked cystic dilatation also requires the production of more cholangiocytes to cover this large surface. In a thin zone immediately surrounding the ducts, round tumor cells are sometimes more frequent, a phenomenon also depicted in Figs. 11 and 12 of the Stanley et al. publication (1973). Stocker and Ishak (1978) noted that there are tumor areas where the epithelial cells seem to be separated from one another and blended with the sarcomatous cells. This phenomenon may be striking and may either represent and transient contact between malignant mesenchymal and

nonneoplastic epithelial cells or eventually epithelial-mesenchymal transition. Whether these bile duct-like profiles are really entrapped bile ducts, as suggested by several authors (Stanley et al. 1973; Stocker and Ishak 1978), or represent neoplastic elements themselves has not been clarified (see below). An argument for entrapped bile ducts is their concentration in the area of the tumor closest to the interface between the involved liver and the tumor mass. Sections from central parts revealed only an occasional duct (Stanley et al. 1973).

Hepatocytes located within the tumor occur as single cells, small clusters, or even cell plates resembling those in the normal liver. The cells can show signs of damage or regeneration, and sometimes the hepatocytes are in direct contact with bile duct cells, suggesting differentiation of cholangiocytes from hepatocytes or their precursors.

The gelatinous center of the tumor may contain thrombosed vessels, sometimes with organization of the thrombi. Autopsy observations specifying the histology of metastases are available from the study of Stocker and Ishak (1978). All extrahepatic tumor manifestations contained sarcomatous cells, some of which had the typical PAS-positive globules. In one case, epithelial elements (bile duct-like structures) were found in the tumor adjacent to the stomach and bowel but in continuity with the hepatic lesion. But another case showed epithelium-lined structures in metastatic lesions in the lung. Stocker and Ishak (1978) argued that the epithelium-lined structures found in a tumor adjacent to the stomach and diaphragm, though still in continuity with the primary liver tumor, represent entrapped bile ducts carried along with the tumor mass as it extended beyond the boundaries of the liver. Furthermore, the epithelial structures these authors found in pulmonary metastases were interpreted as entrapped bronchioles. Hepatocytes (solitary cells, clusters, or even cords/plates) are sometimes found in UES. Stocker and Ishak (1978) observed parenchymal cells within the tumor's pseudocapsule and at the periphery of the neoplasm, but only rarely were hepatocytes found deeper than 0.5–1.0 cm from the edge of the tumor. Such intratumoral hepatocytes have been interpreted as entrapped parenchymal cells, because of their position near the tumor margin (Walker et al. 1992; their patient 2). However, we have found that morphologically abnormal hepatoid cells also occur in central parts of large tumors, these cells not showing signs of damage or atrophy caused by entrapment.

Electron Microscopy Findings

Relatively few UESs have been examined ultrastructurally (Lagacé et al. 1974; Cozzutto et al. 1981; Chang et al. 1983; Keating and Taylor 1985; Pieterse et al. 1985; Chou et al. 1990; Parham et al. 1991; Agaram et al. 2006). At electron microscopy, spindle and stellate cells including both single and multinucleated forms are embedded in a loose collagenous stroma. Neighboring cells may be connected by poorly formed desmosome-like junctions. The cytoplasm of the tumor cells contains relatively few mitochondria, but is rich in free ribosomes and RER profiles. The lumens of the RER may be dilated and contain an amorphous material. Golgi apparatus is rare and not prominent. The presence of tonofilament-like bundles of intermediate filaments and cell junctions in some cases has suggested epithelial differentiation of a subset of tumor cells (Miettinen and Kahlos 1989). Some of the cells contain lipid droplets. In some cases, a myoid differentiation ("leiomyoblastic" cells) has been detected (Gallivan et al. 1983; Gonzalez-Crussi 1983), rarely with signs of rhabdomyoblastic differentiation (Vetter et al. 1989).

Immunohistochemistry

UES usually displays a complex immunohistochemical pattern, with many markers being positive in a variable pattern (Parham et al. 1991; Table 2).

The mesenchymal tumor cells are consistently reactive for vimentin (Lack et al. 1991; Diedhiou et al. 2002; Kiani et al. 2006; Zheng et al. 2007; Wei et al. 2008; Shehata et al. 2011). In one study, all tumors were vimentin positive, and part of the

Table 2 Immunohistochemical profile of undifferentiated embryonal sarcoma

Positivity of tumor cells for:
Vimentin (consistently)
Smooth muscle actin (in part)
Desmin (in part)
Cytokeratins (in part)
CD56 (membranous staining)
Alpha-1-antitrypsin
Glypican-3 (in part)
Adipophilin (in part)

cases were reactive for Bcl-2 (Kiani et al. 2006), cytokeratin AE1/AE3, CD10, calponin, p53, and exceptionally desmin (Kiani et al. 2006), illustrating the polyantigenic features of this immature neoplasm. Focal cytokeratin expression has been documented in some reports (Chou et al. 1990; Lack et al. 1991), sometimes with formation of a paranuclear dot-like staining pattern (Pérez-Gomez et al. 2010). Part of the tumor cells is reactive for alpha-1-antitrypsin (Abramowsky et al. 1980; Miettinen and Kahlos 1989; Shehata et al. 2011). In particular, the typical PAS-positive intracellular globules were shown to contain alpha-1-antitrypsin, but these structures are ultrastructurally different from the inclusions found in hepatocytes of some forms of alpha-1-antitrypsin deficiency (Abramowsky et al. 1980). Diffuse membranous immunostaining of tumor cells for CD56 has been found (Pérez-Gomez et al. 2010). Rarely, clusters of spindle cells are positive for smooth muscle actin and desmin, suggesting muscle cell differentiation (Diedhiou et al. 2002; Nishio et al. 2003). In contrast, myogenin and myogenic regulatory protein D1 (MyoD1) were uniformly negative in UES (Nicol et al. 2007). The tumor cells do not express epithelial membrane antigen (EMA; Miettinen and Kahlos 1989), and nuclear accumulation of beta-catenin was not detected in UES (Yamaoka et al. 2006). UES, similar to mesenchymal hamartoma, shows cytoplasmic expression of glypican-3 (Levy et al. 2012). A part of the cells appear to share features with hepatic stellate cells, e.g., positivity for alpha-SMA and adipophilin-positive vesicles (Tanaka et al. 2012).

Cytogenetic Features

DNA ploidy studies revealed highly aneuploidy patterns as a sign of marked genomic instability (Chou et al. 1990; Leuschner et al. 1990). A DNA ploidy study demonstrated a single G0/G1 peak indicating a diploid DNA content, and only one tumor showed a hypodiploid DNA content (Leuschner et al. 1990). Another investigation found an aneuploidy cellular component (Chou et al. 1990). UES exhibits complex cytogenetic alterations. Both gains and losses of components of several chromosomes were detected, indicating extensive chromosomal rearrangements in UES (Iliszko et al. 1998). In one case, near-triploid and near-hexaploid clones with several chromosomal rearrangements were detected (Iliszko et al. 1998); this polyploidization probably reflected in the bizarre giant nuclei typically seen in this tumor. Aneuploidy of the cell population, usually with high S phase, is a typical feature of UES (Chou et al. 1990). Comparative genomic hybridization revealed multiple chromosomal amplifications and deletions in UES, including gains of 1q, 5p, 6q, 8p, and 12q and losses of 9p, 11p, and 14 (Sowery et al. 2001). UES is associated with a recurrent translocation t(11;19)(q11; q13.3–q13.4) or add(19)(q13.4) (see below).

Differential Diagnosis

As the clinical, radiological, and histologic presentations are highly characteristic and the tumor predominantly occurs in children beyond the hepatoblastoma age, this neoplasm can hardly be confounded with other tumors.

Biology of UES

UESs are aggressive tumors that so far implied a dismal outcome. However, new combined surgical and chemotherapy treatments have improved prognosis (Harris et al. 1984; Horowitz et al. 1987; Perilongo et al. 1987; Ware et al. 1988; Steiner et al. 1989; Orozco

et al. 1991; Walker et al. 1992; Urban et al. 1993; Douglass 1997; Webber et al. 1999; Bisogno et al. 2002; Kim et al. 2002; Almogy et al. 2004, 2005; Baron et al. 2007; Kim et al. 2007; McCarthy et al. 2007; Pachera et al. 2008; May et al. 2012; Gao et al. 2013; Geel et al. 2013; Ismail et al. 2013; Plant et al. 2013). In a study of 17 patients enrolled by the Italian and German Soft Tissue Sarcoma Cooperative Groups and treated by surgery at diagnosis followed by multi-agent chemotherapy and second-look surgery in case of residual disease, 12 patients were alive with follow-up ranging from 2.4 to 20 years (Bisogno et al. 2002). Liver transplantation has been successfully performed in pediatric patients with UES (Kelly et al. 2009; Okajima et al. 2009; Plant et al. 2013; Walther et al. 2013).

Relation to Mesenchymal Hamartoma of the Liver and to Other Tumors

In few cases, UES seems to have arisen from preexisting hepatic mesenchymal hamartoma (see below; de Chadarévian et al. 1994; Lauwers et al. 1997; Begueret et al. 2001; O'Sullivan et al. 2001; Rajaram et al. 2007; Lahmar-Boufaroua et al. 2008; Shehata et al. 2011). In the case of a 15-year-old girl, mapping of the tumor demonstrated a typical mesenchymal hamartoma transforming gradually into UES. Cytometrically, the hamartoma component was diploid, while the UES component showed a prominent aneuploid peak. Karyotypic analysis revealed structural alterations of chromosome 19 (Lauwers et al. 1997). More than ten cases have been reviewed from the literature, and in part of them, transition zones between mesenchymal hamartoma and UES have been identified (Shehata et al. 2011). UES has been found to be associated with tumors other than hepatic mesenchymal hamartoma. A teenage girl with UES developed metachronous vaginal rhabdomyosarcoma, and a middle-aged woman developed metachronous B-acute lymphoblastic leukemia (Gasljevic et al. 2011).

Pathogenesis

A pathogenic or histogenetic link between UES and mesenchymal hamartoma of the liver has been suggested as early as 1978 (Stocker and Ishak 1978), but has been challenged previously or later (Stanley et al. 1973; Dehner et al. 1975; Donnelly et al. 1978; Cozzutto et al. 1981; Gallivan et al. 1983; Finegold 1986; Lack 1986; Chou et al. 1990; Aoyama et al. 1991). However, there are in fact few observations suggesting that UES may develop within mesenchymal hamartoma of the liver (de Chadarévian et al. 1994; Lauwers et al. 1997; Ramanujam et al. 1999; Begueret et al. 2001). In a 15-year-old female patient, mapping of the hepatic tumor demonstrated an atypical mesenchymal hamartoma transforming gradually into UES composed on anaplastic stromal cells. Flow cytometry revealed that the cells of the mesenchymal hamartoma were diploid, while UES cells showed a prominent aneuploidy peak, and cytogenetic analysis of UES exhibited structural alterations (translocation) of chromosome 19q13.4 (Lauwers et al. 1997), implicated as a potential marker of mesenchymal hamartoma (Speleman et al. 1989; Mascarello and Krous 1992; Bove et al. 1998; Rakheja et al. 2004). Based on these constellations, a pathogenetic link between these two tumors was suggested (Lauwers et al. 1997). Mesenchymal hamartoma of the liver is associated with a distinct chromosomal translocation, i.e., t(11;19q)(q11;q13.4) (Mascarello and Krous 1992; Bove et al. 1998; Hu et al. 2012), and this abnormality is thought to play a role in the pathogenesis of both this benign tumor and UES which may develop from it. Analysis of the translocation breakpoints showed that, in one case, the breakpoint occurred in the MALAT1 gene, and the breakpoint was termed MHLB1, for mesenchymal hamartoma of the liver breakpoint 1 (Rajaram et al. 2007).

MALAT1 (metastasis-associated lung adenocarcinoma transcript 1; NEAT2, noncoding nuclear-enriched abundant transcript 2; gene located on chromosome 11q13.1) is a long noncoding RNA species which is highly expressed in

nuclei (Hutchinson et al. 2007) and whose expression correlates with the development and invasive behavior of several tumors (Ji et al. 2003; Diederichs 2010; Tani et al. 2010; Tano et al. 2010; Lin et al. 2011; Xu et al. 2011). In hepatocellular carcinoma, MALAT1 overexpression predicts tumor recurrence (Lai et al. 2012). MALAT1-associated small cytoplasmic RNA (also termed mascRNA) is roughly 53–61 nucleotides in length and is processed from the much longer noncoding (nc) RNA, MALAT1, by the enzyme RNAase P. MALAT1 regulates alternative splicing by controlling the activity of the SR protein family or splicing factors via phosphorylation (Tripathi et al. 2010; Ankö and Neugebauer 2010). Alternative splicing of pre-mRNA is employed to achieve increased transcriptome and proteome complexity. Alternative splicing utilizes specific serine/arginine (SR) splicing factors, which act in a cell-specific phosphorylation-dependent manner. SRs and several SR-related proteins interact with and process mRNA precursors and thus are master regulators of gene expression (reviews: Blencowe et al. 1999; Long and Caceres 2009). MALAT1 is localized to nuclear speckles and does not shuttle between the nucleus and cytoplasm, the localization to speckles being regulated by RNPS1, SRm160, and IBP160 (Miyagawa et al. 2012).

There is evidence that changes in p53 are involved in UES (Chuang et al. 2002; Lepreux et al. 2005; Sangkhathat et al. 2006). At least part of UES shows nuclear immunohistochemical reactivity for p53 protein (Chuang et al. 2002). Mutation analysis of UES revealed missense mutations of TP53 (Kusafuka et al. 1997; Hu et al. 2012). In one study of UES in adults, immunohistochemistry showed overexpression of p53 protein in more than 80 % of tumor cells, and mutations of the TP53 gene were observed in two cases, involving the sequence-specific DNA-binding domain (Lepreux et al. 2005). Missense mutations of TP53 were found in three tumors of another study, and the mutations were found specifically in tumor tissue and not detected in the surrounding normal hepatic tissue and were associated with strong p53 immunoreactivity. Mutation points were localized in exon 7 (Gly245Ser), exon 6 (Arg196Pro), and exon 8 (Arg273Pro) (Sangkhathat et al. 2006).

References

Abramowsky CR, Cebelin M, Choudhury A, Izant RJ (1980) Undifferentiated (embryonal) sarcoma of the liver with alpha-1-antitrypsin deposits: immunohistochemical and ultrastructural studies. Cancer 45:3108–3113

Agaram NP, Baren A, Antonescu CR (2006) Pediatric and adult hepatic embryonal sarcoma: a comparative ultrastructural study with morphologic correlations. Ultrastruct Pathol 30:403–408

Aggarwal S, Gularia S, Dinda AK, Kumar L, Tarique S (2001) Embryonal sarcoma of the liver mimicking a hydatid cyst in an adult. Trop Gastroenterol 22:141–142

Aghajanzadeh M, Riazi H, Kohsari MR, Jafroodi M, Hoda S, Ashtiani MN (2003) Undifferentiated (embryonal) sarcoma of the liver: case report and review of the literature. Saudi J Gastroenterol 9:139–141

Alagiozian-Angelova V, Jennings L, Jani J, Weisenberg E (2005) Arch Pathol Lab Med 129:947–949

Allen EA, Clark DP, Ali SZ (1998) Primary hepatic undifferentiated embryonal sarcoma: cytopathologic findings in peritoneal washings. Acta Cytol 42:449–451

Almogy G, Lieberman S, Gips M, Pappo O, Edden Y, Jurim O, Simon SB, Uzieli B, Eid A (2004) Clinical outcomes of surgical resections for primary liver sarcoma in adults: results from a single centre. Eur J Surg Oncol 30:421–427

Almogy G, Pappo O, Gips M, Lieberman S, Edden Y, Eid A (2005) Improved survival with surgery and systemic chemotherapy for undifferentiated embryonal sarcoma of the liver. Isr Med Assoc J 7:672–673

Anavi BL, Moumdjiev IN, Stoyanova AA, Sapunarova KG, Tashev PV, Dureva-Popova MK (2001) A case of undifferentiated (embryonal) sarcoma of the liver: fine needle aspiration cytology diagnosis by one cell type. Folia Med (Plovdiv) 43:53–58

Anderson DH (1951) Tumors of infancy and childhood: I. A survey of those seen in the pathology laboratory of the babies hospital during the years 1935–1950. Cancer 4:890–906

Ankö ML, Neugebauer KM (2010) Long noncoding RNAs add another layer to pre-mRNA splicing regulation. Mol Cell 39:833–834

Aoyama C, Hachitanda Y, Sato JK, Said JW, Shimada H (1991) Undifferentiated (embryonal) sarcoma of the liver. A tumor of uncertain histogenesis showing divergent differentiation. Am J Surg Pathol 15:615–624

Baron PW, Majlessipour F, Bedros AA, Zuppan CW, Ben-Youssef R, Yanni G, Ojogho ON, Concepcion W (2007) Undifferentiated embryonal sarcoma of the liver

successfully treated with chemotherapy and liver resection. J Gastrointest Surg 11:73–75
Bassly S, Wang L, Han B, Jubinsky PT (2008) Undifferentiated hepatic sarcoma with cardiac extension. Pediatr Blood Cancer 50:732
Begueret H, Trouette H, Vielh P, Laurent C, MacGrogan G, Delsol M, Belleannee G, Masson B, De Mascarel A (2001) Hepatic undifferentiated embryonal sarcoma: malignant evolution of mesenchymal hamartoma? Study of one case with immunohistochemical and flow cytometric emphasis. J Hepatol 34:178–179
Bisogno G, Pilz T, Perilongo G, Ferrari A, Harms D, Ninfo V, Treuner J, Carli M (2002) Undifferentiated sarcoma of the liver in childhood: a curable disease. Cancer 94:252–257
Blattner WA, Henson DE, Young RC, Fraumeni JF (1977) Malignant mesenchymoma and birth defects. Prenatal exposure to phenytoin. JAMA 238:334–335
Blencowe BJ, Bowman JA, McCracken S, Rosonina E (1999) SR-related proteins and the processing of messenger RNA precursors. Biochem Cell Biol 77:277–291
Bliuznikov OP, Shabanov MA, Perevozchikov AG (2007) Embryonic hepatic sarcoma in children: aspects of morphological diagnosis (in Russian). Arkh Patol 69:40–47
Bove KE, Blough TI, Soukup S (1998) Third report of t (19q)(13.4) in mesenchymal hamartoma of liver with comments on link to embryonal sarcoma. Pediatr Dev Pathol 1:438–442
Boybeyi O, Karnak I, Orhan D, Akçören Z, Tanyel FC (2009) Undifferentiated embryonal sarcoma of the liver: an intriguing diagnosis in a child. Eur J Pediatr Surg 19:328–330
Buetow PC, Buck JL, Pantongrag-Brown L, Marshall WH, Ros PR, Levine MS, Goodman ZD (1997) Undifferentiated (embryonal) sarcoma of the liver: pathologic basis of imaging findings in 28 cases. Radiology 203:779–783
Chang WWL, Farooq PA, Winfield SM (1983) Primary sarcoma of the liver in the adult. Cancer 51:1510–1517
Charfi S, Ayadi L, Toumi N, Frikha F, Daoud E, Makni S, Frikha M, Beyrouti MI, Sellami-Boudawara T (2008) Cystic undifferentiated sarcoma of the liver in children: a pitfall diagnosis in endemic hydatidosis areas. J Pediatr Surg 43:E1–E4
Chen et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/17033524
Chen JH, Lee CH, Wei CK, Chang SM, Yin WY (2013) Undifferentiated embryonal sarcoma of the liver with focal osteoid picture – a case report. Asian J Surg 36:174–178
Chou P, Mangkornkanok M, Gonzalez-Crussi F (1990) Undifferentiated (embryonal) sarcoma of the liver: ultrastructure, immunohistochemistry, and DNA ploidy analysis of two cases. Pediatr Pathol 10:549–562
Chowdhary SK, Trehan A, Das A, Marwaha RK, Rao KL (2004) Undifferentiated embryonal sarcoma in children: beware of the solitary liver cyst. J Pediatr Surg 39:E9–E12
Chuang WY, Lin JN, Hung IJ, Hsueh C (2002) Undifferentiated sarcoma of the liver. Chang Gung Med J 25:399–404
Corapçioglu F, Sarper N, Demir H, Güvenç BH, Sözübir S, Akansel G, Berk FS (2004) A child with undifferentiated sarcoma of the liver complicated with bronchobiliary fistula and detected by hepatobiliary scintigraphy. Pediatr Hematol Oncol 21:427–433
Cornut-Sipido P (1979) Généralisation d'un mesenchymome hépatique à predominance liposarcomateuse chez un jeune enfant. Ann Anat Pathol 24:65–72
Cozzutto C, De Bernardi B, Comelli A et al (1981) Malignant mesenchymoma of the liver in children: a clinicopathologic and ultrastructural study. Hum Pathol 12:481–485
Crider MH, Hoggard E, Manivel JC (2009) Undifferentiated (embryonal) sarcoma of the liver. Radiographics 29:1665–1668
Dai CL, Xu F, Shu H, Xu YQ, Huang Y (2005) Undifferentiated (embryonal) sarcoma of the liver in adult: a case report. World J Gastroenterol 11:926–929
de Chadarévian JP, Pawel BR, Faerber EN, Weintraub WH (1994) Undifferentiated (embryonal) sarcoma arising in conjunction with mesenchymal hamartoma of the liver. Mod Pathol 7:490–493
Dehner LP, Ewing SL, Sumner HW (1975) Infantile mesenchymal hamartoma of the liver. Arch Pathol 99:379–382
Diederichs S (2010) Non-coding RNA in malignant tumors. A new world of tumor biomarkers and target structures in cancer cells (in German). Pathologe 31(suppl 2):258–262
Diedhiou A, Genin P, Terris B, Sauvanet A, Belghiti J, Degott C (2002) Undifferentiated embryonal sarcoma of the liver in an adult: a case report (in French). Ann Pathol 22:134–136
Donnelly WH, Talbert JL, Miale T (1978) Malignant undifferentiated stromal tumor of the liver (mesenchymoma): an ultrastructural study. Lab Invest 38:385–386
Donovan EJ, Santulli TV (1946) Resection of the left lobe of the liver for mesenchymoma. Report of a case. Ann Surg 124:90–93
Douglass EC (1997) Hepatic malignancies in childhood and adolescence (hepatoblastoma, hepatocellular carcinoma, and embryonal sarcoma). Cancer Treat Res 92:201–212
Ellis IO, Cotton RE (1983) Primary malignant mesenchymal tumor of the liver in an elderly female. Histopathology 7:113–121
Esposito R, Pollavini G, de Lalla F (1977) A case of primary undifferentiated sarcoma of the liver. Endoscopy 8:108–110
Faraj W, Mukherji D, El Majzoub N, Shamseddine A, Shamseddine A, Khalife M (2010) Primary undifferentiated embryonal sarcoma of the liver

mistaken for hydatid disease. World J Surg Oncol 8:58
Fievez M, Jacques P, Guiot P, Golaire MC (1983) Malignant mesenchymatous hamartoma of the liver in adults. Apropos of a case (in French). Sem Hop 59:1625–1629
Finegold M (1986) Pathology of neoplasia in children and adolescents. W.B. Saunders, Philadelphia
Forster JH, Berman MM (1977) Solid liver tumors. W.B. Saunders, Philadelphia
Fricchione MJ, Glenn N, Follmer R, Kent PM (2013) Life-threatening paraneoplastic syndrome in a child with sarcoma of the liver cured by emergency resection. J Pediatr Hematol Oncol 35:153–155
Gallivan MV, Lack EE, Chun B, Ishak KG (1983) Undifferentiated ("embryonal") sarcoma of the liver: ultrastructure of a case presenting as a primary intracardiac tumor. Pediatr Pathol 1:291–300
Gao J, Fei L, Li S, Cui K, Zhang J, Yu F, Zhang B (2013) Undifferentiated embryonal sarcoma of the liver in a child: a case report and review of the literature. Oncol Lett 5:739–742
Garcia-Bonafé M, Allende H, Fantova MJ, Tarragona J (1997) Fine needle aspiration cytology of undifferentiated (embryonal) sarcoma of the liver. A case report. Acta Cytol 41(suppl):1273–1278
Gasljevic G, Lamovec J, Jancar J (2011) Undifferentiated (embryonal) liver sarcoma: synchronous and metachronous occurrence with neoplasms other than mesenchymal liver hamartoma. Ann Diagn Pathol 15:250–256
Geel JA, Loveland JA, Pitcher GJ, Beale P, Kotzen J, Poole JE (2013) Management of undifferentiated embryonal sarcoma of the liver in children: a case series and management review. S Afr Med J 103:728–731
Goncalves-Matoso et al (2005) http://www.ncbi.nlm.nih.gov/pubmed/16198096
Gonzalez-Crussi F (1983) Undifferentiated (embryonal) liver sarcoma of childhood: evidence of leiomyoblastic differentiation. Pediatr Pathol 1:281–290
Gourgiotis S, Moustafellos P, Germanos S (2008) Undifferentiated embryonal sarcoma of the liver in adult. Surgery 143:568–569
Grazi GL, Gallucci A, Masetti M, Jovine E, Fiorentino M, Mazziotti A, Gozzetti G (1996) Surgical therapy for undifferentiated (embryonal) sarcomas of the liver in adults. Am Surg 62:901–906
Gupta C, Iyer VK, Kaushal S, Agarwala S, Mathur SR (2010) Fine needle aspiration cytology of undifferentiated embryonal sarcoma of the liver. Cytopathology 21:414–416
Harris MB, Shen S, Weiner MA, Bruckner H, Dasgupta I, Bleicher M, Fortner JG, Leleiko NS et al (1984) Treatment of primary undifferentiated sarcoma of the liver with surgery and chemotherapy. Cancer 54:2859–2862
Helmberger TK, Ros PR, Mergo PJ, Tomczak R, Reiser MF (1999) Pediatric liver neoplasms: a radiologic-pathologic correlation. Eur Radiol 9:1339–1347
Horowitz ME, Etcubanas E, Webber BL, Kun LE, Rao BN, Vogel RJ, Pratt CB (1987) Hepatic undifferentiated (embryonal) sarcoma and rhabdomyosarcoma in children. Results of therapy. Cancer 59:396–402
Houry S, Gharbi L, Huguier M, Callard P, André T (1998) Undifferentiated embryonal sarcoma in the liver of adults (in French). Presse Med 27:518–520
Hu X, Chen H, Jin M, Wang X, Lee J, Xu W, Zhang R, Li S, Niu J (2012) Molecular cytogenetic characterization of undifferentiated embryonal sarcoma of the liver: a case report and literature review. Mol Cytogenet 5:26
Hung TY, Lu D, Liu MC (2007) Undifferentiated (embryonal) sarcoma of the liver complicated with rupture in a child. J Pediatr Hematol Oncol 29:63–65
Hutchinson JN, Ensminger AW, Clemson CM, Lynch CR, Lawrence JB, Chess A (2007) A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains. BMC Genomics 8:39
Ida S, Okajima H, Hayashida S, Takeichi T, Asonuma K, Baba H, Inomata Y (2009) Undifferentiated sarcoma of the liver. Am J Surg 198:e7–e9
Iliszko M, Czauderna P, Babinska M, Stoba C, Roszkiewicz A, Limon J (1998) Cytogenetic findings in an embryonal sarcoma of the liver. Cancer Genet Cytogenet 102:142–144
Iqbal K, Xian ZM, Yuan C (2008) Undifferentiated liver sarcoma – rare entity: a case report and review of the literature. J Med 2:20, Case Reports
Ismail H, Dembrowska-Baginska B, Broniszczak D, Kalicinski P, Maruszewski P, Kluge P, Dwieszkowska E et al (2013) Treatment of undifferentiated embryonal sarcoma of the liver in children – single center experience. J Pediatr Surg 48:2202–2206
Ji P, Diedrichs S, Wang W, Böing S, Metzger R, Schneider PM, Tidow N, Brandt B, Buerger H et al (2003) MALAT-1, a novel non-coding RNA, and thymosin beta4 predict metastasis an survival in early-stage non-small cell lung cancer. Oncogene 22:8031–8041
Jia C, Zhao W, Dai C, Wang X, Bu X, Peng S, Xu F, Xu Y, Zhao Y (2013) Undifferentiated embryonal sarcoma of the liver in a middle-aged adult with systemic lupus erythematosus. World J Surg Oncol 11:244
Jiménez-Fuertes M, Lopez AR, de Juan Burgueño M, Moya HA, Sanjuan RF et al (2008) Hepatic undifferentiated (embryonal) sarcoma in an adult: a case report and literature review (in Spanish). Gastroenterol Hepatol 31:12–17
Johnson JA, White JG, Thompson AR (1995) Undifferentiated (embryonal) sarcoma of the liver in adults. Am Surg 61:285–287
Joshi SW, Merchant NH, Jambhekar NA (1997) Primary multilocular cystic undifferentiated (embryonal) sarcoma of the liver in childhood resembling hydatid cyst of the liver. Br J Radiol 70:314–316
Kadomatsu K, Nakagawara A, Zaizen Y, Nagoshi M, Tsuneyoshi M, Fukushige T, Haigou A, Suita S

(1992) Undifferentiated (embryonal) sarcoma of the liver: report of three cases. Surg Today 22:451–455

Kalra N, Vyas S, Jyoti DP, Kochhar R, Srinivasan R, Khandelwal N (2011) Undifferentiated embryonal sarcoma of the liver in an adult masquerading as complicated hydatid cyst. Ann Hepatol 10:81–83

Kanamaru R, Wakui A, Kambe M, Ouchi K, Kobari M, Matsuno S, Kimura N, Takahashi T et al (1991) Undifferentiated sarcoma of the liver in a 21-year-old woman: case report. Jpn J Clin Oncol 21:227–232

Kaur J, Dey P, Das A (2010) Fine needle aspiration cytology of undifferentiated (embryonal) sarcoma of liver in an adult male. Diagn Cytopathol 38:547–548

Kchir N, Chatti S, Limam R, Kacem M, Haouet S, Cherif R, Boubaker S, Zitouna MM (1991) Undifferentiated "embryonal" sarcoma of the liver. Apropos of a case with immunohistochemical study (in French). Arch Anat Cytol Pathol 39:162–165

Keating S, Taylor GP (1985) Undifferentiated (embryonal) sarcoma of the liver: ultrastructural and immunohistochemical similarities with malignant fibrous histiocytoma. Hum Pathol 16:693–699

Keeling JW (1971) Liver tumours in infancy and childhood. J Pathol 103:69–85

Kelly MJ, Martin L, Alonso M, Altura RA (2009) Liver transplant for relapsed undifferentiated embryonal sarcoma in a young child. J Pediatr Surg 44:e1–e3

Kiani B, Ferrell LD, Qualman S, Frankel WL (2006) Immunohistochemical analysis of embryonal sarcoma of the liver. Appl Immunohistochem Mol Morphol 14:193–197

Kim DY, Kim KH, Jung SE, Lee SC, Park KW, Kim WK (2002) Undifferentiated (embryonal) sarcoma of the liver: combination treatment by surgery and chemotherapy. J Pediatr Surg 37:1419–1423

Kim KT, Han SY, Park EH, Jang JS, Roh MH, Lee SW, Jeong JS (2007) A case of the treatment in an adult with hepatic undifferentiated (embryonal) sarcoma (in Korean). Korean J Hepatol 13:96–102

Kim M, Tireno B, Slanetz PJ (2008) Undifferentiated embryonal sarcoma of the liver. AJR Am J Roentgenol 190:W261–W262

Kim HS, Kim GY, Lim SJ, Lee SM, Kim YW (2009) Undifferentiated pleomorphic sarcoma of the liver presenting as a unilocular cyst. Hepatobiliary Pancreat Dis Int 8:541–543

Kinjo M, Shimokama T, Tanaka K, Enjoji M, Arima T, Ikeda K (1980) Undifferentiated (embryonal) sarcoma of the liver. Acta Pathol Jpn 30:459–464

Kinjo S, Sakaurai S, Hirato J, Sunose Y (2010) Embryonal sarcoma of the liver with chondroid differentiation. World J Gastrointest Oncol 2:247–250

Kowalczyk N, Carr Z (2010) Undifferentiated embryonal sarcoma: a case report. Radiol Technol 81:329–334

Krishnamurthy SC, Datta S, Jambhekar NA (1996) Fine needle aspiration cytology of undifferentiated (embryonal) sarcoma of the liver: a case report. Acta Cytol 40:567–570

Kullar P, Stonard C, Jamieson N, Huguet E, Praseedom R, Jah A (2009) Primary hepatic embryonal sarcoma masquerading as metastatic ovarian cancer. World J Surg Oncol 7:55

Küpeli S, Yalçin B, Cil BE, Akçören Z, Büyükpamukçu M (2008) Undifferentiated embryonal sarcoma of the liver in a child complicated by haemorrhage. Pediatr Radiol 38:1259–1261

Kusafuka T, Fukuzawa M, Oue T, Komoto Y, Yoneda A, Okada A (1997) Mutation analysis of p53 gene in childhood malignant solid tumors. J Pediatr Surg 32:1175–1180

Lack EE (1986) Mesenchymal hamartoma of the liver. A clinical and pathologic study of nine cases. Am J Pediatr Hematol Oncol 8:91–98

Lack EE, Schloo BL, Azumi N, Travis WD, Grier HE, Kozakewich HP (1991) Undifferentiated (embryonal) sarcoma of the liver. Clinical and pathologic study of 16 cases with emphasis on immunohistochemical features. Am J Surg Pathol 15:1–16

Lagacé R, Delage C, Robert J (1974) Le mésenchymome primitif du foie. Etude ultrastructurale. Ann Anat Pathol 19:275–286

Lahmar-Boufaroua A, Giutallier C, Yacoubi MT, Mania S, Mestiri H, Mzabi Regaya S (2008) Hepatic undifferentiated (embryonal) sarcoma arising in a mesenchymal hamartoma: association or malignant transformation (in French). Tunis Med 86:628–629

Lai MC, Yang Z, Zhou L, Zhu QQ, Xie HY, Zhang F, Wu LM, Chen LM, Zheng SS (2012) Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. Med Oncol 29:1810–1816

Lashkari HP, Khan SU, Ali K, Sashikumar P, Mukherjee S (2009) Diagnosis of undifferentiated embryonal sarcoma of the liver – importance of combined studies of ultrasound and CT scan. J Pediatr Hematol Oncol 31:797–798

Lauwers GY, Grant LD, Donnelly WH, Meloni AM, Foss RM, Sanberg AA, Langham MR (1997) Hepatic undifferentiated sarcoma arising in a mesenchymal hamartoma. Am J Surg Pathol 21:1248–1254

Lee JA, Kim TW, Min JH, Byon SJ, Jang SH, Choi SY, Kim HJ (2010) A case of undifferentiated (embryonal) liver sarcoma mimicking Klatskin tumor in an adult (in Korean). Korean J Gastroenterol 55:144–148

Lenze F, Birkfellner T, Lenz P, Hussein K, Länger F, Kreipe H, Domschke W (2008) Undifferentiated embryonal sarcoma of the liver in adults. Cancer 112:2274–2282

Lepreux S, Rebouissou S, Le Bail B, Saric J, Balabaud C, Bloch B, Martin-Négrier ML, Zucman-Rossi J, Bioulac-Sage P (2005) Mutation of TP53 gene is involved in carcinogenesis of hepatic undifferentiated (embryonal) sarcoma of the adult, in contrast to Wnt or telomerase pathways: an immunohistochemical study of three cases with genomic relation in two cases. J Hepatol 42:424–429

Leuschner I, Schmidt D, Harms D (1990) Undifferentiated sarcoma of the liver in childhood: morphology, flow cytometry, and literature review. Hum Pathol 21:68–76

Levy M, Trivedi A, Zhang J, Miles L, Mattis AN, Kim GE, Lassman C, Anders RA, Misdraji J et al (2012) Expression of glypican-3 in undifferentiated embryonal sarcoma and mesenchymal hamartoma of the liver. Hum Pathol 43:695–701

Li XW, Gong SJ, Song WH, Zhu JJ, Pan CH, Wu MC, Xu AM (2010) Undifferentiated liver embryonal sarcoma in adults: a report of four cases and literature review. World J Gastroenterol 16:4725–4732

Lightfoot N, Nikfarjam M (2012) Embryonal sarcoma of the liver in an adult patient. Case Rep Surg 2012:382723

Lin R, Roychowdhury-Saha M, Black C, Watt AT, Marcusson EG, Freier SM, Edgington TS (2011) Control of RNA processing by a large non-coding RNA over-expressed in carcinomas. FEBS Lett 585:671–676

Lin JM, Heath JE, Twadell WS, Castellanti RJ (2013) Undifferentiated sarcoma of the liver: a case study of an erythropoietin-secreting tumor. Int J Surg Pathol

Long JC, Caceres JF (2009) The SR protein family of splicing factors: master regulators of gene expression. Biochem J 417:15–27

Lorimer WS (1955) Right hepatolobectomy for primary mesenchymoma of the liver. Ann Surg 151:246–250

Ma L, Geng CZ, Liu YP, Wu GX, Wang XL, Tian ZH (2008) Undifferentiated embryonal sarcoma of liver in an old female: case report and review of the literature. World J Gastroenterol 14:7267–7270

Marti-Bonmati L, Ferrer D, Menor F, Galant J (1993) Hepatic mesenchymal sarcoma: MRI findings. Abdom Imaging 18:176–179

Martins CC, Marcao I, Belo AI, Rolo J, Cabrita F, Partidario A, Castano J (1992) Undifferentiated sarcoma of the liver in the adult (in Portuguese). Acta Med Port 5:31–34

Mascarello JT, Krous HF (1992) Second report of a translocation involving 19q13.4 in a mesenchymal hamartoma of the liver. Cancer Genet Cytogenet 58:141–142

Massani M, Caratozzolo E, Baldessin M, Bonariol L, Bassi N (2010) Hepatic cystic lesion in adult: a challenging diagnosis of undifferentiated primary embryonal sarcoma. G Chir 31:225–228

May LT, Wang M, Albano E, Garrington T, Dishop M, Macy ME (2012) Undifferentiated sarcoma of the liver: a single institution experience using a uniform treatment approach. J Pediatr Hematol Oncol 34:e114–e116

McCarthy FP, Harris M, Kornman L (2007) Management of undifferentiated embryonal sarcoma of the liver in pregnancy. Obstet Gynecol 109:558–560

McFadden DW, Kelley DJ, Sigmund DA, Barrett WL, Dickson B, Aron BS (1992) Embryonal sarcoma of the liver in an adult treated with preoperative chemotherapy, radiation therapy, and hepatic lobectomy. Cancer 69:39–44

Miettinen M, Kahlos T (1989) Undifferentiated (embryonal) sarcoma of the liver. Epithelial features as shown by immunohistochemical analysis and electron microscopic examination. Cancer 64:2096–2103

Mistry RC, Deshpande RK, Chinoy R, Sampat M, Desai PB (1995) Undifferentiated embryonal sarcoma of the liver in childhood. Indian J Cancer 32:175–178

Miyagawa R, Tano K, Mizuno R, Nakamura Y, Ijiri K, Rakwal R, Shibato J, Masuo Y, Mayeda A et al (2012) Identification of cis- and trans-acting factors involved in the localization of MALAT-1 noncoding RNA to nuclear speckles. RNA 18:738–751

Mohapatra N, Krisnanand BR (2007) Embryonal sarcoma of liver: an undifferentiated rare primary solid and mucoid to cystic tumour. Indian J Pathol Microbiol 50:811–813

Moon WK, Kim WS, Kim IO, Yeon KM, Yu IK, Choi BI, Han MC (1994) Undifferentiated embryonal sarcoma of the liver. US and CT findings. Pediatr Radiol 24:500–503

Moon WK, Kim WS, Choi BI, Kim IO, Yeon KM, Han MC (1995) Undifferentiated embryonal sarcoma of the liver treated with chemotherapy: CT imaging in four patients. Abdom Imaging 20:133–137

Nicol K, Savell V, Moore J, Teot L, Spunt SL, Qualman S, Children's Oncology Group, Soft Tissue Sarcoma Committee (2007) Distinguishing undifferentiated embryonal sarcoma of the liver from biliary tract rhabdomyosarcoma: a Children's Oncology Group study. Pediatr Dev Pathol 10:89–97

Nishio J, Iwasaki H, Sakashita N, Haraoka S, Isayama T, Naito M, Miyayama H, Yamashita Y, Kikuchi M (2003) Undifferentiated (embryonal) sarcoma of the liver in middle-aged adults: smooth muscle differentiation determined by immunohistochemistry and electron microscopy. Hum Pathol 34:246–252

O'Sullivan MJ, Swanson PE, Knoll J, Taboada EM, Dehner LP (2001) Undifferentiated embryonal sarcoma with unusual features arising within mesenchymal hamartoma of the liver: report of a case and review of the literature. Pediatr Dev Pathol 4:482–489

Okajima H, Ohya Y, Lee KJ, Yamamoto H, Asonuma K, Nagaoki Y, Ohama K, Korogi M et al (2009) Management of undifferentiated sarcoma of the liver including living donor liver transplantation as a backup procedure. J Pediatr Surg 44:e33–e38

Okuda H, Saito A, Shiratori K, Yamamoto M, Takasaki K, Nakano M (2005) Clinicopathologic features of patients with primary malignant hepatic tumors seropositive for alpha-fetoprotein-L3 alone in comparison with other patients seropositive for alpha-fetoprotein-L3. J Gastroenterol Hepatol 20:759–764

Orozco H, Mercado MA, Takahashi T, Chan C, Quintanilla L, Jiménez M, Sosa R, Esquivel E (1991) Undifferentiated (embryonal) sarcoma of the liver. Report of a case (in Spanish). Rev Invest Clin 43:255–258

Pachera S, Nishio H, Takahashi Y, Yokoyama Y, Oda K, Ebata T, Igami T, Nagino M (2008) Undifferentiated

embryonal sarcoma of the liver: case report and literature survey. J Hepatobiliary Pancreat Surg 15:536–544
Parham DM, Kelly DR, Donnelly WH, Douglass EC (1991) Immunohistochemical and ultrastructural spectrum of hepatic sarcomas of childhood: evidence for a common histogenesis. Mod Pathol 4:648–653
Parichatikanond P, Parichatikanond P (1985) Undifferentiated (embryonal) sarcoma of the liver in childhood: report of two cases. J Med Assoc Thai 68:99–105
Pathirana A, Siriwardana RC, Deen KI, Rupasinghe Y (2010) A case of embryonal sarcoma of the liver. Ceylon Med J 55:90
Pérez-Gomez RM, Soria-Céspedes D, de Leon-Bojorge B, Ortiz-Hidalgo C (2010) Diffuse membranous immunoreactivity of CD56 and paranuclear dot-like staining pattern of cytokeratins AE1/3, CAM5.2, and OSCAR in undifferentiated (embryonal) sarcoma of the liver. Appl Immunohistochem Mol Morphol 18:195–198
Perilongo G, Carli M, Sainati L, Cecchetto G, Mancini A, Cordero di Montezemolo L, Cornelli A et al (1987) Undifferentiated (embryonal) sarcoma of the liver in childhood: results of a retrospective Italian study. Tumori 73:213–217
Pieterse AS, Smith M, Smith LA, Smith P (1985) Embryonal (undifferentiated) sarcoma of the liver. Fine-needle aspiration cytology and ultrastructural findings. Arch Pathol Lab Med 109:677–680
Plant AS, Busuttil RW, Rana A, Nelson SD, Auerbach M, Federman NC (2013) A single-institution retrospective cases series of childhood undifferentiated embryonal liver sarcoma (UELS): success of combined therapy and the use of orthotopic liver transplant. J Pediatr Hematol Oncol 35:451–455
Pollono DG, Drut R (1998) Undifferentiated (embryonal) sarcoma of the liver: fine-needle aspiration cytology and preoperative chemotherapy as an approach to diagnosis and initial treatment. A case report. Diagn Cytopathol 19:102–106
Psatha EA, Semelka RC, Fordham L, Firat Z, Woosley JT (2004) Undifferentiated (embryonal) sarcoma of the liver (USL): MRI findings including dynamic gadolinium enhancement. Magn Reson Imaging 22:897–900
Rajaram V, Knezevich S, Bove KE, Perry A, Pfeifer JD (2007) DNA sequence of the translocation breakpoints in undifferentiated embryonal sarcoma arising in mesenchymal hamartoma of the liver harboring the t(11;19)(q11;q13.4) translocation. Genes Chromosomes Cancer 46:508–513
Rakheja D, Margraf LR, Tomlinson GE, Schneider NR (2004) Hepatic mesenchymal hamartoma with translocation involving chromosome band 19q13.4: a recurrent abnormality. Cancer Genet Cytogenet 153:60–63
Ramanujam TM, Ramesh JC, Goh DW, Wong KT, Ariffin WA, Kumar G, Taib NA (1999) Malignant transformation of mesenchymal hamartoma of the liver: case report and report of the literature. J Pediatr Surg 34:1684–1686
Reichel C, Fehske W, Fishcer HP, Hartlapp JH (1994) Undifferentiated (embryonal) sarcoma of the liver in an adult patient with metastasis in the heart and brain. Clin Investig 72:209–212
Ros PR, Olmsted WW, Dachman AH, Goodman ZD, Ishak KG, Hartman DS (1986) Undifferentiated (embryonal) sarcoma of the liver: radiologic-pathologic correlation. Radiology 161:141–145
Sakellaridis T, Panagiotou I, Georgantas T, Micros G, Rontogianni D, Antiochos C (2006) Undifferentiated embryonal sarcoma of the liver mimicking acute appendicitis: case report and review of the literature. World J Surg Oncol 4:9
Sangkhathat S, Kusafuka T, Nara K, Yoneda A, Fukuzawa M (2006) Non-random p53 mutations in pediatric undifferentiated (embryonal) sarcoma of the liver. Hepatol Res 35:229–234
Sano N, Takehara H, Udaka H, Izumi K (1995) Undifferentiated sarcoma of the liver. Tokushima J Exp Med 42:37–40
Scudiere JR, Jakate S (2006) A 51-year-old woman with a liver mass. Undifferentiated embryonal sarcoma of the liver. Arch Pathol Lab Med 130:e24–e26
Sharifah NA, Muhaizan WM, Rahman J, Zulfikar A, Zahari Z (1999) Fine needle aspiration cytology of undifferentiated embryonal sarcoma of the liver: a case report. Malays J Pathol 21:105–109
Shehata B, Gupta NA, Katzenstein H, Steelman CK, Wulkan ML, Gow KW, Bridge JA et al (2011) Undifferentiated embryonal sarcoma of the liver is associated with mesenchymal hamartoma and multiple chromosomal abnormalities: a review of eleven cases. Pediatr Dev Pathol 14:111–116
Shufaro Y, Uzieli B, Pappo O, Abramov Y (2002) Pregnancy and delivery in a patient with metastatic embryonal sarcoma of the liver. Obstet Gynecol 99:951–953
Sodhi KS, Bekhitt E, Rickert C (2010) Paradoxical hepatic tumor: undifferentiated embryonal sarcoma of the liver. Indian J Radiol Imaging 20:69–71
Sola-Pérez J, Pérez-Guillermo M, Giménez-Bascunana A, Garre-Sanchez C (1995) Cytopathology of undifferentiated (embryonal) sarcoma of the liver. Diagn Cytopathol 13:44–51
Sowery RD, Jensen C, Morrison KB, Horsman DE, Sorensen PH, Webber EM (2001) Comparative genomic hybridization detects multiple chromosomal amplifications and deletions in undifferentiated embryonal sarcoma of the liver. Cancer Genet Cytogenet 126:128–133
Speleman F, De Telder V, De Potter KR, Dal CP, Van Daele S, Benoit Y, Leroy JG et al (1989) Cytogenetic analysis of a mesenchymal hamartoma of the liver. Cancer Genet Cytogenet 40:29–32
Stanley RJ, Dehner LP, Hesker AE (1973) Primary malignant mesenchymal tumors (mesenchymoma) of the liver in childhood. Cancer 32:973–984
Steiner M, Bostrum B, Leonard AS, Dehner LP (1989) Undifferentiated (embryonal) sarcoma of the liver.

A clinicopathologic study of a survivor treated with combined technique therapy. Cancer 64:1318–1322
Stocker JT, Ishak KG (1978) Undifferentiated (embryonal) sarcoma of the liver: report of 31 cases. Cancer 42:336–348
Suarez Y, De Lacy AM, Llovet JM (2000) Images in hepatology. Intrahepatic bleeding due to undifferentiated (embryonal) hepatic sarcoma. J Hepatol 32:361
Tanaka S, Takasawa A, Fukasawa Y, Hasegawa T, Sawada N (2012) An undifferentiated embryonal sarcoma of the liver containing adipophilin-positive vesicles in an adult with massive sinusoidal invasion. Int J Clin Exp Pathol 5:824–829
Tani H, Nakamura Y, Ijiri K, Akimitsu N (2010) Stability of MALAT-1, a nuclear long non-coding RNA in mammalian cells, varies in various cancer cells. Drug Discov Ther 4:235–239
Tano K, Mizuno R, Okada T et al (2010) MALAT-1 enhances cell motility of lung adenocarcinoma cells by influencing the expression of motility-related genes. FEBS Lett 584:4575–4580
Tokunaga Y, Ryo J, Hoppou T, Kitaoka A, Tokuka A, Osumi K, Tanaka T (2000) Hepatic undifferentiated (embryonal) sarcoma in an adult: a case report and review of the literature. Eur J Gastroenterol Hepatol 12:1247–1251
Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, Freier SM, Bennett CF, Sharma A et al (2010) The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell
Tsukada A, Ishizaki Y, Nobukawa B, Kawasaki S (2010) Embryonal sarcoma of the liver in an adult mimicking complicated hepatic cyst: MRI findings. J Magn Reson Imaging 31:1477–1480
Tucker SM, Cooper K, Brownschidle S, Wilcox R (2012) Embryonal (undifferentiated) sarcoma of the liver with peripheral angiosarcoma differentiation arising in a mesenchymal hamartoma in an adult patient. Int J Surg Pathol 20:297–300
Uchiyama M, Iwafuchi M, Yagi M, Iinuma Y, Kanada S, Yamazaki S, Ohtaki M, Shirai Y (2001) Treatment of ruptured undifferentiated sarcoma of the liver in children: a report of two cases and review of the literature. J Hepatobiliary Pancreat Surg 8:87–91
Urban CE, Mache CJ, Schwinger W, Pakisch B, Ranner G, Riccabona M, Schimpl G, Brandesky G et al (1993) Undifferentiated (embryonal) sarcoma of the liver in childhood. Successful combined-modality therapy in four patients. Cancer 72:2511–2516
Varol U, Karaca B, Muslu U, Degirmenci M, Uslu R, Göker E (2012) Undifferentiated embryonal sarcoma of the liver in an adult patient: case report. Turk J Gastroenterol 23:279–283
Vetter D, Bellocq JP, Amaral D, Boilletot A, Bockel PY, Paris F, Jaeck D, Batzenschlager A et al (1989) Hepatic undifferentiated (or embryonal) sarcoma. Diagnostic and therapeutic problems apropos of botryoid rhabdomyosarcoma (in French). Gastroenterol Clin Biol 13:98–103
Walker NI, Horn MJ, Strong RW, Lynch SV, Cohen J, Ong TH, Harris OD (1992) Undifferentiated (embryonal) sarcoma of the liver. Pathologic findings and long-term survival after complete surgical resection. Cancer 69:52–59
Walther A, Geller J, Coots A, Towbin A, Nathan J, Alonso M, Sheridan R, Tiao G (2013) Multimodal therapy including liver transplantation for hepatic undifferentiated embryonal sarcoma. Liver Transplant
Ware R, Friedman HS, Filston HC, Chaffee S, Kurtzberg J, Kinney TR, Falletta JM (1988) Childhood hepatic mesenchymoma: successful treatment with surgery and multiple-agent chemotherapy. Med Pediatr Oncol 16:62–65
Webber EM, Morrison KB, Pritchard SL, Sorenson PH (1999) Undifferentiated embryonal sarcoma of the liver: results of clinical management in one center. J Pediatr Surg 34:1641–1644
Wei ZG, Tang LF, Chen ZM, Tang HF, Li MJ (2008) Childhood undifferentiated embryonal liver sarcoma: clinical features and immunohistochemistry analysis. J Pediatr Surg 43:1912–1919
Weinberg AG, Finegold MJ (1983) Primary hepatic tumors of childhood. Hum Pathol 14:512–537
Willeford G, Stembridge VA (1950) Primary sarcoma of liver. Report of a case. AMA Am J Dis Child 80:404–407
Woong Y, Jae KK, Heoung KK (1997) Hepatic undifferentiated embryonal sarcoma: MR findings. J Cent Adv Telev 21:100–102
Xu HF, Mao YL, Du SD, Chi TY, Lu X, Yang ZY, Sang XT, Zhong SX, Huang JF (2010) Adult primary undifferentiated embryonal sarcoma of the liver: a case report. Chin Med J (Engl) 123:250–252
Xu C, Yang M, Tian J, Wang X, Li Z (2011) MALAT-1: a long non-coding RNA and its important 3′ end functional motif in colorectal cancer metastasis. Int J Oncol 39:169–175
Yamaoka H, Ohtsu K, Sueda T, Yokoyama T, Hiyama E (2006) Diagnostic and prognostic impact of beta-catenin alterations in pediatric liver tumors. Oncol Rep 15:551–556
Yang L, Chen LB, Xiao J, Han P (2009) Clinical feature and spiral computed tomography analysis of undifferentiated embryonic liver sarcoma in adults. J Dig Dis 10:305–309
Yedibela S, Reck T, Ott R, Müller V, Papadopoulos T, Hohenberger W (2000) Undifferentiated, embryonal sarcoma as a rare cause of spontaneous liver rupture in adults (in German). Chirurg 71:101–105
Yoon W, Kim JK, Kang HK (1997) Hepatic undifferentiated embryonal sarcoma. MR findings. J Comput Assist Tomogr 21:100–102
Yoon JY, Lee JM, Kim do Y, Choi GH, Park YN, Chung JW, Kim EY, Park JY, Ahn SH et al (2010) A case of embryonal sarcoma of the liver mimicking a hydatid cyst in an adult. Gut Liver 4:245–249

Yu RS, Chen Y, Jiang B, Wang LH, Xu XF (2008) Primary hepatic sarcomas: CT findings. Eur Radiol 18:2196–2205

Yu DC, Tandon R, Bohlke AK, Steiner RB, Haque S, Florman SS (2009) Resection of a large, ruptured undifferentiated embryonal sarcoma of the liver in a child: a case report and review of the literature. J La State Med Soc 161:41–44

Zaheer W, Allen SL, Ali SZ, Kahn E, Teichberg S (1994) Primary multicystic undifferentiated embryonal sarcoma of the liver in an adult presenting with peripheral eosinophilia. Ann Clin Lab Sci 24:495–500

Zhao H, Cai JQ, Bi XY, Zhao JJ, Huang Z, Lu HZ, Zhou HT (2008) Diagnosis, treatment, and prognostic of liver sarcoma: analysis of 16 cases (in Chinese). Zhonghua Yi Xue Za Zhi 88:1537–1539

Zheng JM, Tao X, Xu AM, Chen XF, Wu MC, Zhang SH (2007) Primary and recurrent embryonal sarcoma of the liver: clinicopathological and immunohistochemical analysis. Histopathology 51:195–203

Part XX

Metastatic Liver Disease

Metastatic Liver Disease: Pathological Aspects

106

Contents

Abstract

Liver metastases represent a highly important issue in hepatobiliary oncology. In Europe and North America, metastases of various cancers to the liver predominate over primary hepatic neoplasms in a ratio of over 40:1. the majority of liver metastases in adult patients are carcinomas and malignant melanoma, followed by non-Hodgkin's lymphomas, other hematological neoplasms, germ cell tumors, and sarcomas. In the pediatric age-group, neuroblastoma and other small cellular blue tumors, PNETs, and hematological neoplasms metastasize to the liver. Hepatic metastases present in the form of several characteristic macroscopic growth patterns, including macronodular patterns, micrometastases, diffuse intrasinusidal metastasis, inductal growth metastasis, intraportal metastasis and other intravascular manifestations, and the rarer neoplastic lymphangiosis. Liver metastases occur as solitary or multiple lesions. In part of cases, a large solitary metastasis can be the source of secondary lesions through intrahepatic spread. Metastases in the subcapsular area of the liver cause umbilicated nodules and tumors that may involve adjacent structures, such as the diaphragm. Distinct metastatic growth patterns occur in cirrhotic livers.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_106

Introduction

Metastatic liver disease is a very important issue in liver oncology, as in Europe and North America, metastases to the liver predominate over primary hepatic neoplasms in a ratio of over 40:1 (reviews: Pack and Brasfield 1955; Willis 1973; Schulz and Hort 1981; Weiss and Gilbert 1982; Kumar and Weaver 2009; Iacobuzio-Donahue and Ferrelll 2010). Conversely, there are regions where primary hepatic malignancies are more common than liver metastases, e.g., Southeast Asian and sub-Saharan African areas, mainly due to the high incidence of hepatocellular carcinoma, the rarity of certain cancers that are common Western countries, and a short life span that renders certain extrahepatic malignancies less frequent.

Epidemiology

The majority of liver metastases in adult patients are carcinomas and malignant melanomas, followed by malignant non-Hodgkin's lymphomas and other hematologic disorders, germ cell tumors, and sarcomas (Olubuyide and Odunfa 1989; Engels et al. 2002; Iacobuzio-Donahue and Ferrelll 2010). Based on clinical and surgical data, the most common liver metastases in adults are from carcinomas of the breast, colorectum, and stomach, whereas autopsy studies which more often include older patients more frequently listed testicular, pancreatic, gallbladder, and uveal tumors (DiSibio and French 2008). In certain western countries, metastatic liver disease is dominated by colorectal cancer metastasis (Faivre et al. 2003; Manfredi et al. 2006). Non-Hodgkin's lymphomas and Hodgkin's lymphoma involve the liver in up to 20 % of patients (Jaffe 1987). In the pediatric age-group, neuroblastoma and other small cellular "blue" tumors, PNETs, and hematologic malignancies often metastasize to the liver, whereas important liver malignancies producing intrahepatic metastatic disease comprise hepatoblastomas and pediatric hepatocellular carcinoma.

General Features of Hepatic Metastases

Based on the particular microenvironment, the distinct vascular system, and specific pro-metastatic features of the liver, hepatic metastases present with complex macroscopic and histopathological patterns, which are summarized in this paragraph before describing a selection of specific tumor metastases (Table 1).

Table 1 Growth patterns, secondary alterations, and effects of hepatic metastases

Growth patterns
Macronodular patterns
Micrometastases, including miliary metastases
Diffuse intrasinusoidal metastatic tumors
Intraductal growth of metastases
Intraportal metastasis
Metastasis in the hepatic vein system
Hepatic lymphangiosis carcinomatosa
Tumor-in-tumor metastasis
Secondary alterations of hepatic metastases
Necrosis, hemorrhage and infarction of liver metastasis
Calcifications
Metastasis infection and abscess formation
Tumor fibrosis
Cyst formation
Hepatic alterations caused by liver metastases
Hepatomegaly
Liver atrophy
Atrophy hypertrophy complex (AHC)
Perifocal changes
Perifocal fatty change
Perifocal clear cell change
Perifocal microvascular changes
Perifocal ischemia
Perifocal parenchymal atrophy
Perifocal bile duct changes
Perifocal immune reactions
Perifocal fibrosis
Metastasis-induced pseudocirrhosis
Hepar lobatum carcinomatosum
Chemotherapy-induced alterations

Growth Patterns of Hepatic Metastases

Hepatic Macrometastases

Hepatic macrometastases are those that can be detected macroscopically (Figs. 1, 2, 3, 4, 5, 6, and 7). In advanced tumor disease, most hepatic metastases are multiple lesions, although certain and frequent neoplasms can produce solitary, sometimes huge or massive metastases, e.g., colorectal carcinoma, renal cell carcinoma, and certain sarcomas. As discussed in more detail below, peripherally located hepatic metastases can show umbilication ("cancer navel") caused by tumor necrosis, tissue collapse, and capsular retraction. Several growth patterns occur, the most important being an expanding pattern with pushing borders, an infiltrative pattern with highly irregular borders, and metastases surrounded by satellite nodules. Less common patterns comprise intraductal growth and production of a tumor pseudocapsule. On sections, a majority of metastases appear as whitish or creamy-white masses of variable consistency, friable tumors found in lesions of high cellularity and poor stroma formation, and firm tumors in case of marked desmoplasia. Mucin-rich cancers display glistening or gelatinous masses of increased tissue transparency. Apart from this whitish color, certain metastases exhibit colors that can direct the observed to the type of neoplasm involved. The most evident example is of course malignant melanoma with its black metastases. Yellowish or tan metastases suggest neuroendocrine tumors, but a yellow color is also found in metastases undergoing fatty change. Intrahepatic metastases of hepatocellular carcinoma can be greenish due to bile deposition. A dark red color caused by marked hemorrhage mainly characterizes angiosarcoma, certain other sarcomas, choriocarcinoma, and renal cell carcinoma. Lymphomas, highly cellular carcinomas, and part of sarcomas may show an opaque, "fish flesh" appearance. Calcifications present as white to yellow speckles, grains, or irregularly shaped areas of gritty consistency (reviews: Engels et al. 2002; Centeno 2006).

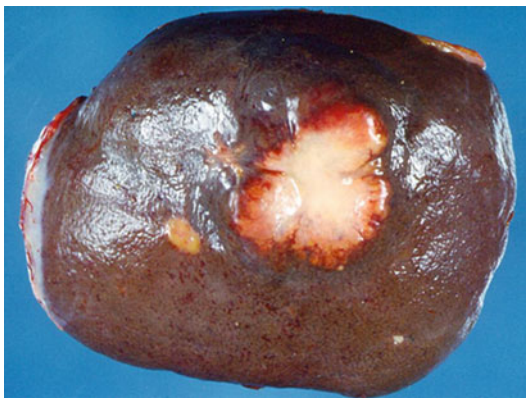

Fig. 1 Colorectal carcinoma metastasis of the liver. The metastatic nodule (*center*) is situated in the subcapsular area and has a central depression, the "cancer navel" (umbilication). The periphery of the nodule shows hyperemia. A small, *yellow* pseudolipoma of Glisson's capsule is seen to the left of the metastasis

Miliary Hepatic Metastases and Other Micrometastases

Introduction

In the course of metastatic spread to the liver it can be expected that metastases starting from distributed single cells are first small clusters of cells gradually growing to lesions that will become visible to the naked eye. Usually, the diameter limit of small metastases visualized, e.g., on the hepatic capsular surface in the course of laparoscopy, is in the region of larger granulomas, i.e., 1–2 mm in diameter. Such metastatic lesions are called miliary metastases, a form of micrometastases. A milium is a millet seed which has a diameter in the 1 or 2 mm range and has been used in the classical medical literature to denote several lesion types of this size, the best known being the milium (pl. milia) in miliary tuberculosis.

As outlined in more detail in the chapter on tumor staging, micrometastases are, according

Fig. 2 Liver metastasis of pancreatic ductal carcinoma. The cut surface of this large mass reveals a nodular texture and numerous hemorrhages (fixed resection specimen)

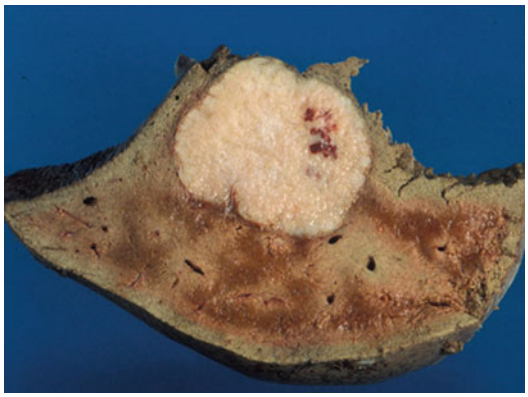

Fig. 3 Colorectal carcinoma metastasis of the liver. This metastasis has a finely granular structure and is close to the resection margin (fixed resection specimen)

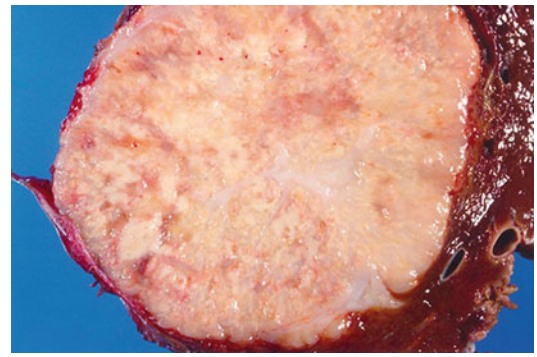

Fig. 4 Colorectal carcinoma metastasis of the liver. The mottled appearance of the cut surface, with *yellow* areas, is caused by multifocal necrosis associated with hemorrhage (non-fixed resection specimen)

to UICC 1992 and the guidelines of the 6th TNM classification, metastatic lesions with a diameter of 2 mm or less, indicated by the addition of the label "mi" in staging protocols (Hermanek 1999; Hermanek et al. 1999; Gusterson 2003; Sobin 2003). A main difference between micrometastases and miliary metastases is the type of distribution in involved organs. In miliary metastases, the small lesions are numerous and diffusely scattered throughout the organ, whereas micrometastases may show a discrete distribution, e.g., involving only part of an organ or being distributed perifocally around a macroscopic "mother" metastasis. It is assumed that, in most instances, miliary metastases represent a certain stage in the growth of metastases from small to larger lesions (the "miliary window"). However, there may be metastases that are as such characterized to grow with this pattern and metastases remaining small, owing to inherent growth limitations of the tumor or factors of the stromal-vascular bed. On the other hand, development and growth of micrometastases are modulated by neoadjuvant chemotherapy (NAC). In patients with CRC, NAC reduced the incidence of intrahepatic micrometastases but did not affect their distribution when such micrometastases were present (Wakai et al. 2012). The presence of micrometastases in resection specimens, which may only be detectable by immunohistochemistry, affects biology of disease and predicts

high risk for intrahepatic tumor recurrence after metastasectomy (Yokoyama et al. 2002).

Miliary Hepatic Metastases, Micrometastases, and the Problem of Early Detection of Metastatic Liver Disease

The interest in miliary metastases is based, apart from theoretical questions regarding tumor growth, on the clinically important aspect of hepatic lesions being too small to be identified as metastases at CT and other imaging methods (the "missed metastases" problem). Specifically, what is the risk that very small lesions seen on CT images will develop into miliary or micrometastases? Tumors metastasizing to the liver may produce micrometastases, and these lesions are thought to be responsible for at least part of recurrences post hepatectomy, because they may be located close to the resection margin (Schimanski et al. 2010). But initial staging CT scans in patients with colorectal carcinoma (CRC) may also show small, "indeterminate" hepatic lesions. In a study on 419 patients with CRC, 16.7 % of the patients had small liver lesions on their initial liver CT that could be definitely characterized. Among the 65.7 % of patients who underwent follow-up imaging, 10.9 % showed progression of the lesions suggestive of early metastases (Lim et al. 2009). In breast cancer patients, tiny hepatic lesions of indeterminate significance are termed TSTC (deemed too small to characterize). In a study on 7692 women with breast cancer, 1012 (13.2 %) underwent contrast-enhanced CT including liver assessment. The presence of at least one hepatic lesion deemed TSTC was detected in 277 of 941 women (29.4 %) in whom no definite hepatic metastasis was reported. At a median follow-up time of 54 weeks, the lesions were unchanged in 91.6 %, no longer visible in 4.2 %, and larger in 3.1 %. The enlarging hepatic lesions deemed TSTC were metastatic breast cancer in three, metastatic pancreatic cancer in one, and cysts in one patient (Khalil et al. 2005).

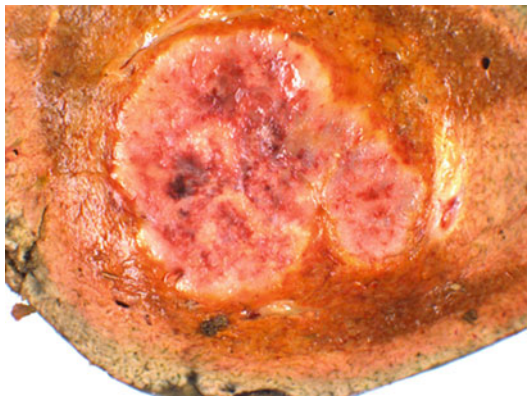

Fig. 5 Liver metastasis of bronchial carcinoma. In this non-fixed specimen, the *pink* tumor tissue contains fresh hemorrhage and the *center* is altered by gross necrosis. Note that a second nodule has grown out of the metastasis

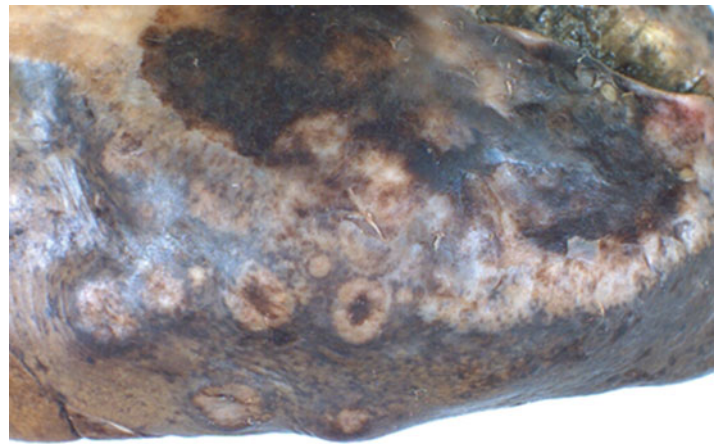

Fig. 6 Carcinoma metastasis of the liver. Even small subcapsular metastatic nodules can undergo tumor umbilication

Fig. 7 Liver metastasis of colorectal carcinoma metastasis. The tumor has invaded the diaphragm (*left* of the *middle*), causing adherence of the liver surface to the diaphragm

Epidemiology

Miliary hepatic metastases and micrometastases in general have been described for several types of tumors, including colorectal carcinoma (Hosch et al. 2002; Yokoyama et al. 2002; Votrubova et al. 2006), breast carcinoma (Khalil et al. 2005), pancreatic carcinoma (Suwa et al. 1999; Yokoyama et al. 2012), malignant melanoma (Pichon et al. 2004), including uveal melanoma (Servois et al. 2010; Borthwick et al. 2011), neuroendocrine carcinoma (Fazio et al. 2008), carcinoid tumors (Rixen et al. 1998), medullary carcinoma of the thyroid (Yanardag et al. 2003), and certain sarcomas (Probst-Cousin et al. 1997). In a study on liver metastases of endocrine tumors, the median size of depicted metastases was 12 mm for CT and 10.5 mm for MRI. A miliary pattern with numerous small hepatic lesions scattered throughout the liver was present in nine patients (22.5 %; Dromain et al. 2005). Micrometastases may dominate the metastatic pattern or occur in close vicinity of large hepatic metastases. The frequency of the latter phenomenon varies considerably among different cancer types, and was rather common in gastric cancer metastases (Nomura et al. 2009), but uncommon in CRC metastases (Kokudo et al. 2002).

Clinical Features

The clinical presentation of diffuse hepatic miliary metastatic spread differs from that of the much more frequent "classical" metastatic liver. Patients with miliary liver spread may show hepatomegaly associated with jaundice and signs of hepatocellular insufficiency, owing to the multifocal destruction of parenchyma by the innumerable small tumor nodules (Pichon et al. 2004). The presence of micrometastases and their detectetion has an important impact on the definition of the minimal distance to the resection margin in case of metastasectomy (Zhou et al. 2007).

General Histopathology

Micrometastases are also found in the vicinity of macroscopic metastases, e.g., of gastrointestinal primary tumors. Such lesions were, e.g., observed around 48 % of liver metastases of gastric carcinoma (Nomura et al. 2009). They may be found in relation to portal vein branches up to 29 mm distant from the macroscopic metastasis, what has an impact on the distance of the resection margin in hepatectomy (Isono et al. 1990). In CRCs metastasizing to the liver, micrometastases around macrometastases were not common and most were confined to the immediate vicinity of the tumor border. This observation has an impact on the selection of minimal resection margin distances (Kokudo et al. 2002). In some situations, growth of very small metastatic lesions is localized to the sinusoids. Such patients, e.g., those with breast cancer, may then present with occult micronodular pseudocirrhosis (Fournier et al. 2010; see also the respective paragraph).

Pathogenesis

In a murine tissue explant model, two-photon microscopy revealed that injected mammary tumor cells showed a greater extravasation tendency in liver than in lung, with 56 % of tumor cells in the liver having extravasated by 24 h, compared with only 22 % of tumor cells in the lung that had extravasated. In the liver, imaged tumor cells continually transitioned from an intravascular location to an extravascular site, while extravasation in lung slowed down after 6 h. Interestingly, micrometastases growing out from extravasated cells were heterogeneous in composition, containing tumor cells and endothelial cells (Martin et al. 2010).

Diffuse Intrasinusoidal Metastatic Tumors of the Liver

Introduction

A subset of carcinomas metastasizing to the liver show a distinct intrahepatic growth pattern characterized by diffuse growth of cancer cells within the sinusoidal channels, accompanied by an often discrete stromal reaction (Watson 1955). This chapter exclusively focuses on intrasinusoidal metastases caused by solid tumors, albeit the most common cause of acute hepatic failure secondary to malignant infiltration are lymphohematologic malignancies, treated in other chapters. Diffuse intrasinusoidal metastatic growth is mostly known from metastasizing carcinoma of the breast, including the lobular variant (Allison et al. 2004; Rajvanshi et al. 2005), and may occur in case of radiologically occult primary tumors (Allison et al. 2004).

Clinical and Imaging Features

Diffuse neoplastic infiltration of the liver can cause acute liver failure (ALF) but overall is an uncommon complication. In some patients with hepatic metastatic disease, tumors may replace up to 90 % of the liver without any manifestation of jaundice or other signs of hepatic malfunction. Among 4020 cases of acute liver failure over an 18-year period, only 0.44 % were attributed to malignant hepatic infiltration (Rowbotham et al. 1998). In another investigation, 7.2 % of 292 patients with metastatic liver disease developed hepatic coma (Bernuau et al. 1986), such large differences in prevalences likely to be caused by the type of hepatic metastases. In fact, diffuse and massive colonization in the hepatic microvascular bed by cancer cells may cause failure of perfusion resulting in ALF, including breast carcinoma, small cell carcinoma of the lung, nasopharyngeal carcinoma, gastric carcinoma, colorectal carcinoma, malignant melanoma, prostatic carcinoma, and urothelial carcinoma (Rajvanshi et al. 2005). It is proposed that ALF in this infiltration pattern is caused by a combination of hepatic microcirculation failure mainly compromising portal venous blood inflow, followed by ischemia of hepatocyte parenchyma and hepatocyte loss. However, as only a rather small fraction of patients develop ALF, other and more complex pathogenic pathways may be involved, including a direct effect of homing, adhering, and growing cancer cells on liver cell function. Dense accumulation of carcinoma cells in the sinusoidal bed may induce portal hypertension due to a sinusoidal block. Helical CT scanning of liver with intrasinusoidal metastases revealed marked hepatomegaly without any visible nodular lesions in the liver (Miyaaki et al. 2010). Owing to the development of ischemic areas, a mottled liver scan can result (Lin and Donati 1981). Diffuse sinusoidal cancer infiltration can also cause a contracted liver mimicking liver cirrhosis.

Pathology

In an autopsy study of three breast carcinomas having diffusely and intrasinusoidally metastasized to the liver, all livers were homogeneously firm, tan-yellow, without metastatic nodules (Allison et al. 2004). However, also grossly normal livers have been found at necropsy (Schneider and Cohen 1984).

Liver biopsies and necropsy specimens show a diffuse accumulation of carcinoma cells within

the sinusoids. The carcinoma cells often stick together, form intravascular Indian files, or small aggregates, associated with focal or diffuse dilatation of the vascular channels. The tumor cells may be surrounded by a thin fibrin layer and granular thrombotic material containing altered thrombocyte indicating local tumor cell-induced thrombosis. These tumor thrombi may extend into small portal venous branches, into sublobular veins, and even into larger veins of the vascular exit tract. The endothelial lining of the sinusoids may lack or no longer be visible owing to atrophy and encroaching tumor cells. But the sinusoidal architecture may in fact be destroyed, associated with decay of liver cell plates, apoptosis, and hepatocyte necrosis. Liver cell necrosis was related to the degree of sinusoidal involvement by tumor cells (Henrion et al. 1996). Following destruction of the sinusoidal wall, carcinoma cells may overrun hepatic cell plates, somewhat analogous to piecemeal necrosis (Krauss et al. 1979). A fine stromal reaction may follow the infiltrating tumor cells, this phenotype forming the transition to cases with more pronounced stromal formation and termed cancerous pseudocirrhosis, discussed in another chapter.

Immunohistochemistry

In case of diffuse accumulation of cancer cells in the lumina of sinusoidal vascular channels, lineage determination may be very difficult and hence requires immunohistochemistry. Cytokeratin markers will in most cases allow the diagnosis of carcinoma, even in case of poorly differentiated neoplasms. In metastatic breast carcinoma, which is well known to show a sinusoidal spreading pattern, gross cystic disease fluid protein-15 (GCDFP-15) was the most reliable marker, while BCA-25 is also positive in part of cholangiocarcinomas and metastatic carcinomas other than breast tumors (Akasofu et al. 1993). Histologically and cytologically, diffusely growing hepatic metastases of lobular breast carcinoma and signet ring cell carcinoma of the gastrointestinal tract may be difficult to distinguish. Immunohistochemically, all metastatic GIT signet ring cell carcinomas proved to be CK20 positive, while only 5 % of metastatic lobular breast carcinomas were CK20 positive. None of GIT signet ring cell carcinomas but the majority of lobular breast carcinomas were estrogen receptor positive (Tot 2000).

Pathogenesis

The mechanisms of a preferential growth within the sinusoidal vascular compartment are not known, but it is assumed that distinct homing mechanisms mediated by differential expression of adhesion molecules and their receptors are involved. Within sinusoids, circulating carcinoma cells are in close contact with endothelial cells, Kupffer cells/macrophages, perisinusoidal stellate cells, and Pit cells. Intrasinusoidal growth also requires that carcinoma cells engage in contact among themselves to form cellular aggregates. Local pericellular activation of the coagulation system may play an important role. The fine stromal reaction accompanying intrasinusoidal carcinoma growth, particularly in case of breast cancers, seems to be a condition necessary for cancer growth, as in other locations. Stromal cells may either derive from circulating mesenchymal stem cells or locally recruited from activated stellate cells and hepatic myofibroblasts.

Intraductal Growth of Metastases

Jaundice developing in patients with colorectal and other carcinoma and sarcoma metastases to the liver is usually caused by diffuse or multifocal parenchymal lesions that interfere with hepatocyte function. In part of the patients, however, jaundice is caused by obstructive lesions of the biliary tract, predominantly due to extrahepatic duct compression or stenosis, a situation first described in 1946 based on two cases (Herbut and Watson 1946). In the latter case, duct obstruction is either caused by duct wall invasion, intraluminal growth, or compression by enlarged lymph nodes harboring metastases, situated behind the duodenum, along the common bile duct, or at the liver hilus. But part of carcinomas metastasizing to the liver can invade the intrahepatic biliary tree and form intraductal growths that may cause duct stenosis or duct obliteration. This phenomenon has most commonly been observed with colorectal carcinoma

(CRC) metastases and several reports have documented this distinct clinical-pathological entity, but intraductal growth also occurs with metastases from other primary tumors.

It seems that CRC metastases have a distinct propensity or are predisposed to intraepithelial/intramucosal spread along intrahepatic bile ducts and their intact basement membranes, replacing the preexisting normal epithelial lining. But CRC also has a tendency to metastasize to the extrahepatic bile ducts (Nagler and Rochwarger 1977; Warshaw and Welch 1978; Gray et al. 1982; Morelli et al. 2007). Overall, intrahepatic intraductal growth of colorectal metastases is a phenomenon of variably frequency as based on the literature (Riopel et al. 1997; Nakanuma et al. 2011). One study reported a prevalence of 12 % of gross extension of colorectal metastasis into bile ducts (Okano et al. 1999), while a later study found that 3.7 % of resected colorectal liver metastases extended predominantly along the intrahepatic bile duct system without forming a relevant extraductal mass (Kubo et al. 2002). One investigation showed that more cases were recognized at exploration for hepatic resection than clinical or radiographic recognition (Povoski et al. 2000). It seems that the prognosis of disease with macroscopic bile duct invasion is better than that in patients with microscopic intraductal invasion, which tends to aggressively involve portal tracts (Okano et al. 1999; Kubo et al. 2002). Less often, other types of carcinomas metastatic to the liver show intraductal growth, the most frequent cancer being renal cell carcinoma (Ueda et al. 2002; Masuda et al. 2009; Simunek et al. 2011). Renal cell carcinoma is also well known to form polypoid and stenosing intraluminal metastases in the extrahepatic bile ducts (Kauffmann et al. 1992; Letessier et al. 1994; Miyagishima et al. 1996) and in the lumen of the gallbladder (Satoh et al. 1991; Nojima et al. 2008). Rarer examples of malignancies that cause intraductal growths include malignant melanoma (however mostly at the level of extrahepatic ducts; Kohler and Riemann 1987; Parquier et al. 1991) and pancreatic acinar cell carcinoma (Nagata et al. 2012). Melanoma metastatic to the common bile duct can clinically present as obstructive jaundice (England and Sarr 1990; Colovic et al. 2007).

Intraportal Metastasis of Solid Tumors

Introduction

Tumor thrombi are well-known and prognostically relevant complications of hepatocellular carcinoma, but metastatic deposits with or without thrombus formation in the portal vein and its branches also occur in extrahepatic tumors metastasizing to the liver, although portal vein thrombus as a complication of metastatic liver disease is much less common than HCC-induced portal vein thrombosis (Marn and Francis 1992; Ito et al. 1997). In a prospective study of 100 patients with liver metastasis using real-time ultrasound, 8 % of the patients were found to have portal vein thrombosis (Atri et al. 1990). However, the true incidence of portal vein metastasis remains unknown, because the mere fact that portal vein thrombosis is detected at imaging will not mean that this thrombus contains malignancy. The intraportal manifestations of tumors can result from direct metastatic translocation along the portal venous system (direct origin from the primary tumor) or indirectly via local transmural ingrowth from hepatic metastases followed by formation of an intravascular metastasis. Tumor thrombus in the portal vein system may be associated with tumor manifestations in the splenic vein and other veins communicating with the portal vein.

Metastatic Tumor Masses in the Portal Vein Trunk and Its Major Branches

Tumors metastasizing to the liver may produce intraportal metastases with formation of macroscopically visible tumor thrombi (Figs. 8 and 9). This phenomenon has been observed for several neoplasms, including colorectal carcinoma, gastric carcinoma, renal cell carcinoma, non-small cell carcinoma of the lung, ductal tumors of the pancreas, neuroendocrine tumors of the pancreas, malignant melanoma, and cholangiocarcinoma. The formation of a metastatic portal vein tumor thrombus can destroy even a large vein branch or the main PV trunk, sometimes resulting in a

cord-like portal vein remnant embedded in the tumor mass (Senda et al. 1995).

Macroscopic tumor thrombus in the portal vein (PV) from colorectal cancer is an uncommon event. In a retrospective review of the charts of 142 consecutive patients who underwent hepatic resection for colorectal liver metastasis it turned out that 2.8 % had macroscopic PV invasion (Tada et al. 2003). In a literature review of 15 cases of colorectal cancers inducing PV tumor thrombus, the main PV was involved in three cases, the left PV in six, the right PV in three, the posterior PV in two, and the anterior PV in one case. No specific clinical features typified patients with colorectal liver metastasis of PV tumor thrombus with respect to age, gender, or the primary tumor site. The interval from colorectal resection to diagnosis of PV tumor thrombus ranged from 4 to 141 months. In 12/15 cases (80 %), liver metastasis was accompanied by PV tumor thrombus, and 12/15 cases were metachronic metastases (Tomimaru et al. 2010). In a compilation of 15 published cases, PV tumor thrombosis was synchronous in 3 and metachronous in 12 patients (Tomimaru et al. 2010).

PV thrombus from colorectal carcinoma can rarely occur in the absence of a hepatic parenchymal metastasis (Matsumoto et al. 2009; Yamamoto et al. 2011), and the same phenomenon has been found with gastric carcinoma (Ishikawa et al. 1995). The pathways from an extrahepatic primary tumor to an intraportal metastasis are sometimes complex and involve more than one localization step. In case of renal cell carcinoma, PV tumor thrombus may be the second metastatic manifestation after a pancreatic metastasis (Kawakami et al. 2008). Radiologically, PV tumor thrombosis is generally characterized by enlargement of the involved vein segment, decreased density mass without intraluminal enhancement of the involved part, and nonvisualization of the portal venous branch in the involved lobe (Ishikawa et al. 1995). In cases with indirect metastatic involvement of the PV, tumor encasement of the vein may be seen on CT and MR images. Tumor-induced thrombosis of the PV can be followed by cavernous transformation of this vein (Ishikawa et al. 1995). Relevant stenosis or obstruction of the PV and its large branches cause ischemia of liver parenchyma and can result in hepatic infarctions seen as more or less extended well-defined homogeneous

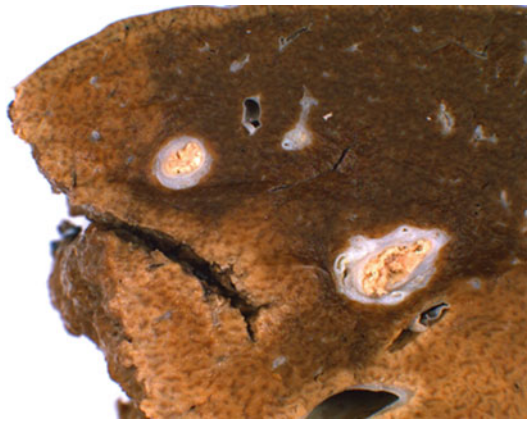

Fig. 8 In this liver with carcinoma metastases (not shown), cancer tissue has invaded portal venous branches in the vicinity of metastasis

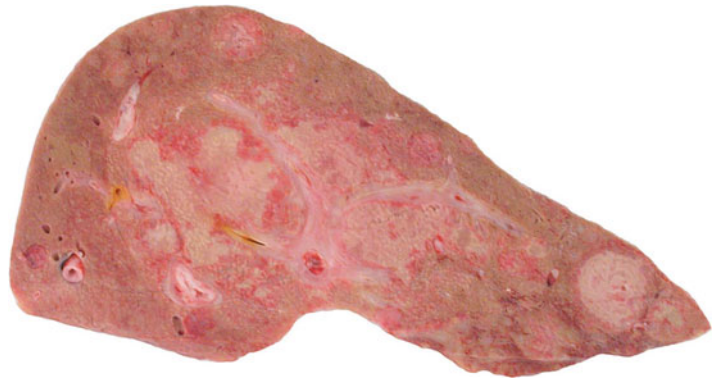

Fig. 9 Hepatic metastases with portal vein involvement (non-fixed specimen)

low-density areas on CT scans (Ogawa et al. 2009).

Metastatic Tumors in Small Portal Venous Branches

Microscopic tumor invasion into the small intrahepatic portal vein branches is detectable in about 20 % of cases with liver metastases from colorectal cancer (Yamamoto et al. 1995). In contrast, intravascular metastatic carcinomatous spread to small portal venous branches with formation of multiple tumor emboli is a rare event that may result in acute and sometimes fatal liver failure. In one study, tumor emboli were present within portal vein branches ranging from 0.12 to 2.9 mm in diameter and were freely floating or attached to the vascular walls, with or without varying degrees of superimposed organization (Bégin et al. 2001). Extensive metastatic deposits in small portal vein branches can massively compromise portal venous flow followed by parenchymal ischemia, hepatocyte necrosis, or even parenchymal infarction (Harrison et al. 1981; Fig. 10).

Macroscopy

Development of metastasis in the PV trunk and in the large PV branches is macroscopically visible as tumor thrombi. This alteration has most commonly been seen in metastasizing colorectal cancer. Tumor thrombi are friable or firm structures that may occlude the PV lumen and contain a significant proportion of coagulated blood, even with the striation typical for recent appositional thrombosis. Gray to whitish and in part necrotic tumor components are seen already from the surface of the thrombus or are then visualized when cutting through the thrombus. Tumor thrombi may adhere to the portal vein wall, and sometimes the tumor tissue itself mediates adhesion or has already invaded the venous wall. Segments of the PV containing tumor thrombi are usually dilated. In the majority of cases of colorectal cancer, PV thrombosis is associated with metastases in the liver parenchyma. These metastases may be situated close to the thrombosed PV or may be distant from it. In case the parenchymal metasdtatic nodule is closely associated with the PV tumor thrombus, outgrowth of cancer from the tumor thrombus through the PV wall has to be considered. With time, part of the thrombus organizes, and in case of slow-growing tumors, cavernous transformation of the PV may ensue. Marked stromal reaction taking place when the tumor has engaged with the venous wall may induce obliteration of the involved part of the PV, leaving a firm string.

Obstruction of the PV and its large branches can cause marked ischemia of the liver substance, ending up with Zahn's infarcts. Zahn's infarcts present as sharply demarcated pale to yellowish areas that may, in early stages, slightly bulge from the cut surface and exhibit a lobular texture that is coarser than normal, while in later stages the lobular architecture is effaced owing to confluent necrosis, edema, and exsudation.

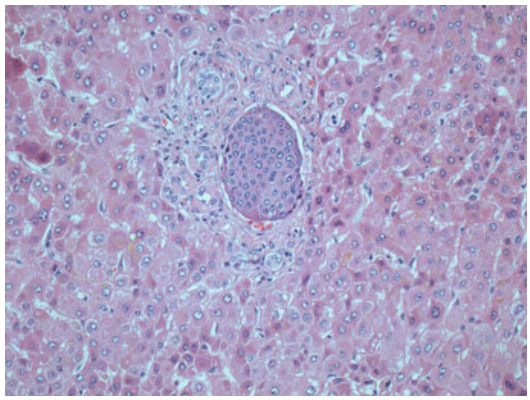

Fig. 10 Liver metastasis of neuroendocrine carcinoma. The tumor has invaded a small portal vein branch (hematoxylin and eosin stain)

Histopathology

Histologically, PV tumor thrombi show a mixture of fresh and older thrombotic material and cancer tissue embedded in the thrombus masses. Tumor cells are suspended as small clusters or even single cells in the thrombotic background, or form cohesive masses. Even in the latter, thin trabecula of fibrin often traverse the tumor tissue. With time, the thrombus will organize, with normal blood vessels sprouting from the venous wall, accompanied by fibroblasts/myofibroblasts and leukocytes, including macrophages. The interaction

between this non-neoplastic organizing granulation tissue and the tumor tissue is complex and not yet well studied. It may be assumed that the tumor recruits blood vessels and stromal cells from this organizing tissue, facilitating its further growth and invasion.

Invasion of the Sinusoidal Vascular System

Apart from primary intrasinusoidal metastasis (see above), cancer cells released from the periphery of a metastatic nodule can invade adjacent sinusoidal vascular channels (Fig. 11). In part of cases, intrasinusoidal invasion is extensive and causes marked obstruction of the sinusoidal bed, followed by parenchymal atrophy. In addition to direct tissue invasion of cancer cells, spread along the microvascular system is one mechanism causing involved resection margins (Fig. 12).

Metastases/Tumor Invasion of the Hepatic Vein System

In contrast to the portal vein system, which can be reached by tumor cells through a metastatic hematogenous pathway, involvement of the hepatic vein system by tumor much more results from direct intravascular growth of tumor following macrovascular invasion in the primary tumor. The typical model of this pathway are renal cancers, invading the inferior vena cava and then producing a cohesive tumor plug that may grow upward to the ostial region of hepatic veins and to the right atrium. This intravascular growth mode is a variant of metastatic spread that does not completely meet the definition of true metastasis. In a patient with a small hepatic colorectal metastasis, a microscopic tumor embolism was detected in the hepatic vein around the metastatic tumor nodule (Nakayama et al. 2005).

Budd-Chiari Syndrome Induced by Invasive-Metastatic Tumors

Malignant neoplasms growing into and within the hepatic veins can induce tumor thrombi analogous to those in the portal vein. Similar to hepatocellular carcinoma, metastatic tumor thrombi can cause Budd-Chiari syndrome, sometimes with a fulminant course. This complication has most often been observed in patients with renal carcinoma, which is well known to invade the inferior vena cava and to involve the hepatic veins and their ostia (Yanagizawa et al. 1983; Nakajima et al. 1989; Kume et al. 1999; Ciancio and Soloway 2001; Zisman et al. 2003; Sarwar and Khan 2008; Shih et al. 2009; Marangoni et al. 2010). Other metastatic tumors that have been found to be associated with Budd-Chiari syndrome include malignant melanoma, uterine carcinoma, PNET of the kidney, and sarcomas originating from the inferior vena cava, including leiomyosarcoma and rhabdomyosarcoma. As in other forms of Budd-Chiari syndrome, tumor-

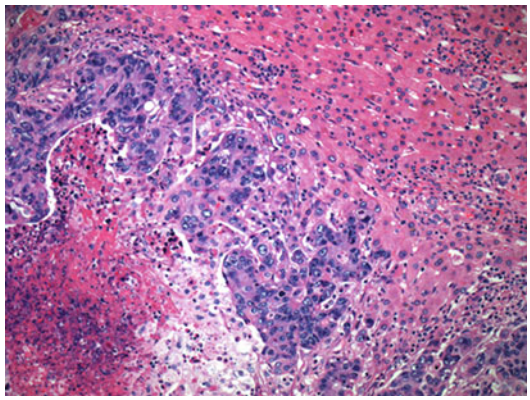

Fig. 11 Liver metastasis of poorly differentiated adenocarcinoma. At the periphery of the nodule, intrasinusoidal invasion is present. Note the central necrosis of the nodule (*left lower corner*; hematoxylin and eosin stain)

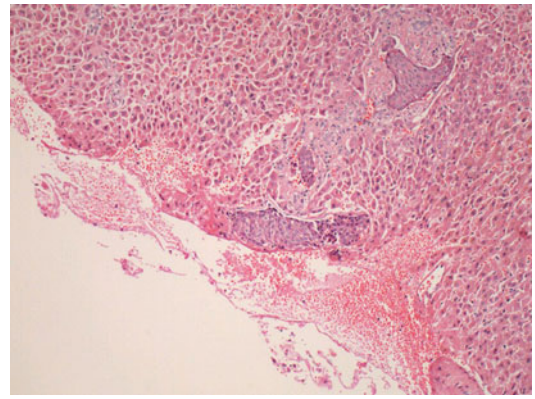

Fig. 12 Liver metastasis of squamous cell carcinoma. The neoplasm reaches the resection margin (hematoxylin and eosin stain)

induced Budd-Chiari syndrome can cause Zahn's infarct of the liver.

Hepatic Lymphangiosis Carcinomatosa

Lymphangiosis Carcinomatosa of the Liver: A Rarely Examined Lesion

Lymphangiosis carcinomatosa (LC) or lymphatic invasion, which has been studied in detail in other organs involved by cancer, has been much less investigated in the liver, although the lymphatic system of the liver has been analyzed in detail (Fig. 13; Szabo et al. 1975; Yamamoto and Phillips 1986). Pathways leading to lymphangiogenesis have also been investigated for several tumor systems (Achen and Stacker 2006; Achen and Stacker 2008). Among a total of 762 cases of malignancies, LC of the liver was found in 10 cases out of 250 cases with liver metastases. In eight cases, the primary tumor was gastric carcinoma (Itoh et al. 1988). The result of LC can be so-called lymphangitic liver metastasis. The intravascular cancer cell depositions located within low-flow lymphatics can undergo necrosis; this may be followed by dystrophic calcifications with a distinct branching pattern (Matsumoto et al. 2004). Carcinomatous thrombi located in portal tract lymph vessels can exert pressure on intrahepatic bile ducts and cause progressive jaundice (Tada et al. 1996; Ishizaki et al. 2001). The presence of intrahepatic lymphatic invasion by CRC cells predicted poor survival and recurrence after hepatectomy (Sasaki et al. 2002; Korita et al. 2007).

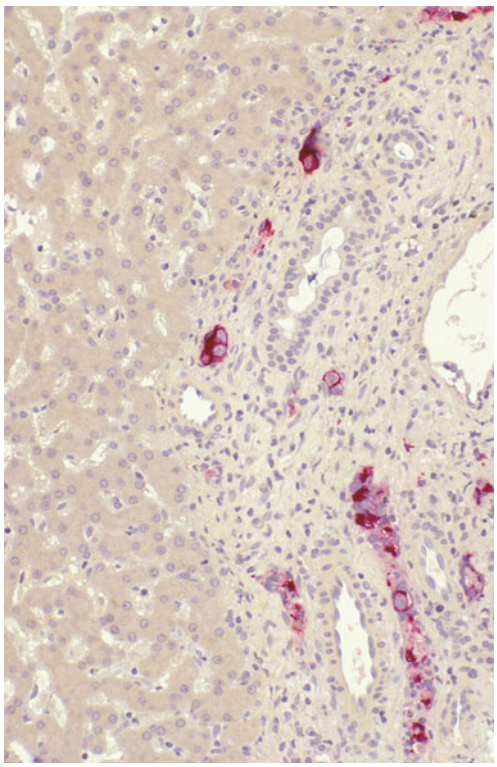

Fig. 13 Liver metastasis of poorly differentiated adenocarcinoma. The cancer cells are located in lymphatic vessels of a portal tract (lymphangiosis carcinomatosa; cytokeratin immunostain)

Lymphangitic Hepatic Metastasis

Lymphangiosis carcinomatosa, which is mostly located in the compartment of portal tracts of the liver, can give rise to a distinct variant of hepatic metastases (lymphangitic liver metastasis). On sonography and CT images, enlargement of the portal tracts with maginal obscurity was found, while cholangiograms revealed narrowing and dilatation of the intrahepatic bile ducts, and angiograms distortion, displacement, and occlusion of the hepatic artery and portal vein (Itoh et al. 1991).

Veno-Occlusive Lesions Associated with Lymphangiosis Carcinomatosa of Hepatic Veins

LC can involve the lymphatic vessels located to the wall of sublobular and hepatic veins. The subsequent lymph vessel obstruction may be associated with intimal proliferative lesions of terminal hepatic venules to larger hepatic veins, possibly induced by intimal lymph stasis and causing focal veno-occlusive disease (Shibayama et al. 1991).

Tumor-in-Tumor Metastasis

Tumors metastasizing into other tumors is a rare phenomenon that has, however, been described for a wide variety of cancers, with examples of carcinomas metastasizing to both other carcinomas or benign tumors (Elmaci et al. 2001; Sakai et al. 2010). Hepatocellular carcinoma has been found to metastasize into a medullary carcinoma of the thyroid (Sung et al. 2011).

Hepatic Metastasis in Fatty Liver

Whereas the prevalence of metastases of extrahepatic tumors to the liver in chronic hepatic disease, and in particular cirrhosis, has been studied in detail, relatively few data are available concerning other liver disorders and their potential impact on the hepatic metastasizing process. There is evidence that liver metastases are rare in patients with fatty liver (Murono et al. 2013). Among 839 patients with colorectal carcinoma who underwent resection, 121 patients were designed to have fatty liver based on ultrasonography, and 718 had no fatty liver. There were only 2 patients who had liver metastases in the fatty liver group in comparison with 115 patients with liver metastasis in the nonfatty liver group (Hayashi et al. 1997). In an investigation of 747 patients undergoing surgical treatment for colorectal cancer, synchronous hepatic metastases were present in 32 % of patients with normal liver, but only 15 % of patients with fatty liver (Iascone et al. 2005). These findings are also of interest on the background of liver changes caused by neoadjuvant chemotherapy. It has been found that this therapy administered prior to liver surgery for CRC metastases can cause marked steatosis and nonalcoholic steatohepatitis (Kampfenkel et al. 2011; Urdzik et al. 2012). On the other, there is more recent evidence that fatty liver in a rat model produces a pro-metastatic microenvironment for hepatocellular carcinoma via activation of heatic stellate cells whch secrete VEGF, interleukin-1alpha, and TGF-beta (Mikuriya et al. 2015).

The pathogenesis of a potential protective effect of hepatic steatosis against part of liver metastases is not clarified. The effect has been reproduced in a rat model. Rats with fatty liver seldom had experimental liver metastases (injection of a rat colon cancer cell line) compared to normal rats (Tamura et al. 1999). In rats, fatty liver suppresses angiogenesis in metastatic lesions, and this effect may play a role in the suppression of metastatic growth in fatty livers (Karube et al. 2000).

Metastases in Chronic and Cirrhotic Liver Disease

Introduction

Old observation and a series of studies suggest that metastatic carcinoma is rarely encountered in patients with liver cirrhosis, leading to the concept that the chronically damaged livers with remodeling and fibrosis are partially protected from metastasizing malignancies. Recent investigations confirmed that patients with chronic liver injury, including chronic viral hepatitis, have a significantly lower occurrence of hepatic CRC metastasis than patients with a healthy liver (Zeng et al. 2012; Augustin et al. 2013).

Epidemiological Considerations

The finding of the rarity of metastases in cirrhotic livers had led to the publication of cases with metastases in a cirrhotic liver, probably to document the uniqueness of such an event, either as single case reports or as small series. These reports might also have been stimulated to be published on the background of the marked contrast between the high frequency of primary liver cancer in cirrhosis in comparison with the uncommon metastases of extrahepatic primary malignancies. The first case of cancer metastasis in a cirrhotic liver was published in 1888 (Hanot and

Gilbert 1888), followed by numerous later reports. On the other hand, several reports have described the rarity of even absence of carcinoma metastases in cirrhotic livers, e.g., colorectal carcinoma/CRC (Uetsuji et al. 1992).

Selected References Poulain 1899; White 1897; Achard and Laubry 1902; Colwell 1905; Rolleston and McNee 1929; Lisa et al. 1942; Wallach et al. 1953; Lieber 1957; Gall 1960; Ruebner et al. 1961; Wegener 1961; Goldstein et al. 1966; Berge and Saldeen 1968; Goldstein 1969; Peichl et al. 1978; Mirouze and Michel 1982; Pérez Flores et al. 1987; Melato et al. 1989; Siu et al. 1999; Gervaz et al. 2003.

In the study of Ruebner and coworkers (1961), 399 patients with liver cirrhosis were selected from autopsies. Among these cirrhosis patients, only 20 % of malignancies had metastasized to the liver, in comparison with 36 % in the noncirrhotic control group. The distribution of types of cancer metastases to the liver in cirrhotic patients was very similar to that in the control group. It was concluded that the relative rarity of hepatic metastases could therefore not be attributed to a greater proportion of tumors a small propensity for metastatic spread to the liver. In a Japanese autopsy study, 8798 cases of liver cirrhosis were identified among 240′377 patients (3.66 %). Of these, 737 (8.4 % of the cirrhotics) had coexistent extrahepatic malignancy; 26.3 % of these had metastases in the cirrhotic liver, in comaprison with 38.3 % and 43.2 % in control groups of the time periods 1958–1959 and 1967–1968, respectively (Hamaya et al. 1975). In a study of consecutive autopsies comparing Italian (5241 autopsies; 500 cases of cirrhosis) and Japanese (6511 autopsies; 529 cases of cirrhosis) cases matched for sex and age, the results were similar in both areas and confirmed the opinion that metastases in the cirrhotic liver are rare (Melato et al. 1989). In the CRC study of Uetsuji and coworkers (1992), analyzing 250 patients with CRC, liver cirrhosis was not found among the 40 patients with metastases, but was present in 46 (21.9 %) of the 210 nonmetastatic patients. An investigation of 2162 consecutive autopsies performed during a 12.5-year period showed that the cirrhotic liver was less often affected by metastases than the noncirrhotic liver (33.3 % vs. 46.4 %). In cirrhotic livers, metastases from neuroendocrine tumors were predominantly localized within the parenchymatous nodules, whereas nonendocrine carcinomas had metastasized more often to the fibrous septa of cirrhotic livers (Van Boekrijck and Klöppel 1992). A later autopsy study confirmed that liver metastases of extrahepatic cancers are less frequent in cirrhotic patients (Pereira-Lima et al. 2003). Among 747 patients undergoing surgical treatment for colorectal cancer, synchronous hepatic metastases at the time of surgery amounted to 32 % of patients with a normal liver, 15 % of patients with fatty liver, and 4.7 % of patients with cirrhotic livers (Iascone et al. 2005).

Some authors questioned the concept of rarity of metastases in cirrhotic liver (Fisher et al. 1960; Norkin et al. 1962; Zotti et al. 1986). Fisher and coworkers (1960) analyzed 2865 autopsy cases, including 213 cases of liver cirrhosis, and did not find a difference in the frequency of hepatic metastases of extrahepatic cancers between cirrhotics and noncirrhotics, but detected a significant difference in the frequency of extrahepatic malignancies between these two groups. According to Ruebner and coworkers (1961), the rarity of hepatic metastases in patients with cirrhosis of the liver was, at least in part, due to a significant decrease in extrahepatic cancer in this group of patients compared with matched controls. In fact, extrahepatic malignant tumors in cirrhosis patients were found to be rare by all previous authors who had studied this problem (Hall and Sun 1951; Lieber 1957; Gall 1960; Fisher et al. 1960). If confirmed, the lesser prevalence of extrahepatic cancer in cirrhotics may be due to the reduced life span of cirrhotic patients, hence leaving less time for the development of extrahepatic malignancies. Such a mechanism has been proposed for other situations, e.g., the diminished prevalence of cancer in patients with tuberculosis or diabetes

mellitus (Pearl 1929; Cornfield 1959; Rockstroh and Schröter 1960). Some of the differences that have been published in several reports may be biased by the difficulties arising in the interpretation of autopsy data, eventually leading to fallacious conclusions (Mainland 1953). It has been pointed out that "even if two fatal diseases had no relationship in a living population, there would nevertheless be a negative association between them in an autopsy population. The autopsy incidence of one lethal disease (e.g., cancer) among patients affected by a second fatal disease (e.g., cirrhosis) would therefore, always be reduced in comparison with the rest of the necropsy material. The higher the mortality of the second disease, the smaller would the proportion of patients who, at autopsy, were affected by both diseases" (Cornfield 1959; quoted from Ruebner et al. 1961).

Pathogenetic Hypotheses

Liver cirrhosis is characterized by massive remodeling of the hepatic architecture, associated with a deranged microcirculation and arteriovenous shunting. The change in the structure and function of microvessels in cirrhosis may affect the homing and adhesion of circulating carcinoma cells. Also the capillarization that takes place in hepatic sinusoids in cirrhosis (Schaffner and Poper 1963; Neubauer et al. 2001) may affect the metastatic process, as tumor cells homing to sinusoids may face greater difficulties to egress from vessels due to the new basement membrane barrier characterizing sinusoidal capillarization. Fibroblast and myofibroblast functions are altered in the fibrotic process of cirrhosis, and this may have an impact on stromagenesis of metastasizing carcinomas, because myofibroblasts have a central role in tumor stroma remodeling (Otranto et al. 2012). There are differences between the findings obtained with studies on humans in comparison with findings in laboratory animals. In an experimental rat model of liver cirrhosis (induction of cirrhosis by the administration of carbon tetrachloride), an increased proportion of animals producing liver metastases following injection of Walker carcinosarcoma cells was observed, suggesting that, in this model, the cirrhotic liver is a "fertile soil" for hepatic metastases (Fisher and Fisher 1960).

Biopsy of Hepatic Metastases

For histological diagnosis, fine-needle aspiration (FNA)/fine-needle aspiration cytology (FNAC) and needle core biopsy (NCB) employing either transabdominal ultrasound or computed tomography scanning guidance are frequently used techniques to provide diagnostic samples with a high yield, particularly when FNA and NCB are combined (Jacobsen et al. 1983; Bell et al. 1986; Kern and Haber 1986; Cochand Priollet et al. 1987; Sautereau et al. 1987; Seitz et al. 1990; Lin et al. 1991; Tsai et al. 2002; Sanz and del Valle 2004; Larsen et al. 2007). In one study using FNA, 90 % of cases were positive on rinse, 78 % on smear, and 69.6 % on both rinse and smear (Axe et al. 1986). In a comparative study of 141 consecutive cases, FNA cytology was more sensitive and accurate than NCB, but the combination of these sampling techniques increased diagnostic sensitivity (Stewart et al. 2002).

In situations of increased risk of bleeding and/or the presence of small hepatic tumors, endoscopic ultrasound-guided fine-needle aspiration biopsy (by the transgastric route) may be performed and is a powerful, reliable, and safe procedure (Hollerbach et al. 2003). Use of FNA/FNAC in abdominal tumors has been reported to be fatal in 0.006–0.031 % of cases (Fornari et al. 1989; Smith 1991). The majority of biopsy-associated deaths occured with liver tumors and were due to fatal hemorrhage. A further complication which is well established for several types of liver malignancies is biopsy track seeding, including the skin. Metastatic disease can emerge subsequent to both FNA and NCB (Smith 1984; Denton et al. 1990; Roussel et al. 1989; Roussel 1990; McGrath et al. 1991) and has an overall estimated frequency of 0.005–0.009 % quoted for large series of fine-needle abdominal biopsies (Livraghi et al. 1983;

Smith 1991). For the liver, most cases have been reported after biopsy of hepatocellular carcinoma (review and meta-analysis: Silva et al. 2008). The complication has been reported to be less common in CRC metastases than in hepatocelular carcinoma (Glaser et al. 1989; Gayral et al. 1990; Scheele and Altendorf-Hofmann 1990; McGrath et al. 1991; Goletti et al. 1992; John and Garden 1993; Vergara et al. 1993; Abdelli et al. 1994; Herszenyi et al. 1995; Jourdan and Stubbs 1996; Ohlsson et al. 2002; Metcalfe et al. 2004), but a more recent study described needle track deposits as common and with an adverse effect on long-term survival (Jones et al. 2005). But the issue has raised critical voices in regard to indications versus contraindications of hepatic FNA and/or NCB in case of CRC metastases.

Neoplastic needle track seeding has, albeit very seldom, been observed following percutaneous radiofrequency ablation of hepatocellular carcinoma (with an estimated risk of 0.6–0.9 %; Livraghi et al. 2005; Stigliano et al 2007), and after percutaneous ablation of CRC liver metastases, sometimes with growth of cutaneous ulcerated cancer nodules (Bonatti et al. 2003; Charalampopoulos et al. 2007; Liu et al. 2009).

Prognostic Factors for the Outcome of Patients with Liver Metastases

Numerous studies comparing prognostic factors involved in primary tumor biology versus metastases have been performed and the results compiled (Gayowski et al. 1994; Shirabe et al. 1997; Bakalakos et al. 1998; Ohlsson et al. 1998; Ambiru et al. 1999; Iwatsuki et al. 1999; Nagashima et al. 1999; Minagawa et al. 2000; Seifert et al. 2000; Heslin et al. 2001; Imamura et al. 2001; Yamada et al. 2001; Aldrighetti et al. 2005; Schindl et al. 2005). Prognostic scoring systems have been developed (Iwatsuki et al. 1999; Schindl et al. 2005).

The disease-free interval (time interval between resection of primary tumor and metastatic disease) has been associated with an increased risk of liver recurrence (Logan et al. 1982; Registry of Hepatic Metastases 1988). Stage and site of CRCs are important prognosticators (Nordlinger et al. 2005). A prognostic effect of initial CRC stage has been reported several times (Butler et al. 1986; Iwatsuki et al. 1986; Doci et al. 1991; Scheele et al. 1995; Nordlinger et al. 1996; Jaeck et al. 1997; Minagawa et al. 2000). The presence of synchronous liver metastases is a high-risk factor in CRC (Scheele et al. 1995; Beckurts et al. 1997; Jenkins et al. 1997), as is tumor size (Registry of Hepatic Metastases 1988; Doci et al. 1991; Pedersen et al. 1994; Scheele et al. 1995; Nordlinger et al. 1996), number of metastases. Prognosis becomes worse as a function of the number of hepatic metastatic foci (Registry of Hepatic Metastases 1988; Gayowski et al. 1994; Elias et al. 2005; Onodera et al. 2005). The presence or absence of four or more hepatic metastases was a predominant prognostic determinant with a 5-year survival rate of 20 % in patients with less than four liver metastases, and no 3-year survivor among patients with four or more metastases (Ekberg et al. 1986). Unilateral lesions do better than bilateral lesions (Gayowski et al. 1994; Wanebo et al. 1996; Bakalakos et al. 1998). Tumor satellitosis affects outcome (Gibbs et al. 1998). In a study of 127 patients treated at a single center, the 3- and 5-year survival for patients with concomitant EHD were 47 % and 26 %, respectively, compared with 67 % and 49 % for those without EDH (a significant difference; Carpizo et al. 2009). In resected patients, the status of the resection margin has an impact on tumor biology (Ekberg et al. 1986; Iwatsuki et al. 1986; Nordlinger et al. 1996; Scheele et al. 1996; Jaeck et al. 1997; Shirabe et al. 1997; Bakalakos et al. 1998). A resection margin of less than 10 mm has an adverse effect (Ekberg et al. 1986). In CRC liver metastases, a positive hepatic resection margin was associated with a higher incidence of postoperative recurrence and lower survival rate. In a study of 293 consecutive CRC patients undergoing hepatic resection, the width of the resection margin did, however, not influence the postoperative recurrence rate or pattern of recurrence, suggesting that the "1 cm rule" should be abandoned (Hamady et al. 2006). Pushing invasion margins

are prognostically more favorable than infiltrating invasion margins (Cianchi et al. 1997). Incomplete resection is clearly associated with an elevated recurrence rate (Gayowski et al. 1994; Pedersen et al. 1994; Beckurts et al. 1997; Jenkins et al. 1997; Bakalakos et al. 1998). The prognosis of liver metastases is also markedly influenced by certain parameters of metastasis morphology and biology. Similar to hepatocellular carcinoma, the presence of a fibrous pseudocapsule around coloractal metastases is a favorable prognostic factor (Yamamoto et al. 1999). In a clinicopathological study conducted in 152 patients who underwent initial hepatic resection for metastatic colorectal cancer, presence of fibrous tissue between the tumor and the surrounding parenchyma was detected in 61 %. Presence of a microscopic fibrous pseudocapsule was identified in 28 % of metastases in another study (Ambiru et al. 1999). Pathologically, the presence and thickness (thin vs. thick, according to the number of collagen fiber bundles) of a pseudocapsule were related closely to less invasiveness into adjacent vessels. The postresection survival was significantly better in patients with thick or thin pseudocapsules than in those without a pseudocapsule (Okano et al. 2000). In an univariate survival analysis (N: 221), the presence of a fibrous pseudocapsule around metastatic nodules was found to a significant positive prognostic factor (Weber et al. 2001). An aggressive biology of CRC metastases may be reflected by the invasion mode and in particular by the incorpation of preexisting liver tissue and cells in the metastatic growth. In was shown that a high frequency of hepatocyte entrapment in metastasis is associated with lower 5-year survival rates (Koike et al. 2000). Angioinvasion in metastases is a high-risk facor (Gayowski et al. 1994).

In regard to the risk of extrahepatic metastasis in CRC, lymphatic permeation of the primary tumor has been shown to be a predicting factor (Sasaki et al. 2005a). The metastatic tumor doubling time was an important prehepatectomy predictor of survival and nonrecurrence of hepatic colorectal cancer metastases (Tanaka et al. 2004). The proliferative index of CRC metastases determined by Ki-67 immunohistochemistry was the most reliable prognostic factor of survival in one retrospective study (Weber et al. 2001). Concerning the significance of apoptosis of metastatic cells, the Fas/CD95 index determined in resected CRC liver metastases correlated with postoperative CEADT, number of metastases, and survival (Onodera et al. 2005). Nuclear p53 protein expression in resected hepatic CRC metastases is an independent prognostic factor for survival (Nitti et al. 1998; Heisterkamp et al. 1999) and is, together with DCC (deleted in colonic cancer), a positive prognosticator of survival after resection of hepatic CRC metastases (Saw et al. 2002). There is a higher expression of the oncoproteins, c-myc, c-erbB-2/neu, PCNA, and p53 in metastasizing colorectal cancer than in nonmetastasizing tumors (Yang et al. 1996). However, a later study on several genetic markers revealed that the DNA content and expression of c-myc, c-erbB-2, EGFR, H-ras, p53, PCNA, and nm23 do not predict survival after potentially curative resection of hepatic metastases, but that immunoreactivity for p53 protein may be an important marker of local recurrence in the liver (Crowe et al. 2001). By multivariate analysis, p53 and EGFR expression of colorectal liver metastases were the best predictors of disease-free survival after partial liver resection (De Jong et al. 1998).

Relatively few markers are available for CRC and its metastases. Serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9) are often elevated in patients with CRC. CEA, a complex glycopotein, is produced by about 90 % of CRC and is known to contribute to the malignant phenotype of this tumor. Serum levels of CEA are used as a marker of disease, and failure of serum CEA to return to normal levels after surgical resection is indicative of inadequate resection or occult systemic disease. Furthermore, CEA levels after salvage surgery appear to predict survival in patients undergoing resection of liver or lung metastases (review: Goldstein and Mitchell 2005). Patients with colorectal liver metastases and a preoperative CEA $<$ or $=$

30 ng/mL are more likely to be resectable, and they have the longest survival (Bakalakos et al. 1999). A multivariate analysis of 90 patients revealed that, in patients with CRC liver metastases, elevation of serum CA19-9 is a risk factor for extrahepatic metastasis, whereas elevated CEA could not predict extrahepatic metastatic disease (Sasaki et al. 2005b). In contrast, CA19-9 serum levels did not predict the prognosis and did not allow for detecting recurrence of CRC (Morita et al. 2004). Expression analysis of CEA (assessed via immunohistochemistry and PCR) revealed that patients with a lesser CEA expression score in the livermetastasis margin appeared to have a longer disease-free survival period than did those with a greater CEA expression score (Kim et al. 2003).

References

Abdelli N, Bouche O, Thiefin G, Renard P, Flament JB, Zeitoun P (1994) Subcutaneous seeding of the tract of percutaneous cytologic puncture with a fine needle of a hepatic metastasis from colonic adenocarc. Gastroenterol Clin Biol 18:652–656

Achard C, Laubry C (1902) Ascite latescente. Cancer du colon et cancer secondaire du foie attaint de cirrhose alcoolique hypertrophique. Bull Mem Soc Med Hop Paris 19:335–340

Achen MG, Stacker SA (2006) Tumor lymphangiogenesis and metastatic spread – new players begin to emerge. Int J Cancer 199:1755–1760

Achen MG, Stacker SA (2008) Molecular control of lymphatic metastasis. Ann N Y Acad Sci 1131:225–234

Akasofu M, Kawahara E, Kurumaya H, Nakanishi I (1993) Immunohistochemicsl detection of breast specific antigens and cytokeratins in metastatic breast carcinoma in the liver. Acta Pathol Jpn 43:736–744

Aldrighetti L, Castoldi R, Di Palo S, Arru M, Stella M, Orsenigo E, Gavazzi F, Ferla G et al (2005) Prognostic factors for long-term outcome of hepatic resection for colorectal liver metastases (in Italian). Chir Ital 57:55–570

Allison KH, Fligner CL, Parks WT (2004) Radiographically occult, diffuse intrasinusoidal hepatic metastases from primary breast carcinomas: a clinicopathologic study of 3 autopsy cases. Arch Pathol Lab Med 128:1418–1423

Ambiru S, Miyazaki M, Isono T, Ito H, Nakagawa K, Shimizu H, Kusashio K, Furuya S, Nakajima N (1999) Hepatic resection for colorectal metastases: analysis of prognostic factors. Dis Colon Rectum 42:632–639

Atri M, de Stempel J, Bret PM, Illescas FF (1990) Incidence of portal vein thrombosis complicating liver metastasis as detected by duplex ultrasound. J Ultrasound Med 9:285–289

Augustin G, Bruketa T, Korolija D, Milosevic M (2013) Lower incidence of hepatic metastases of colorectal cancer in patients with chronic liver diseases: meta-analysis. Hepatogastroenterology 60:1164–1168

Axe SR, Erozan YS, Ermatinger SV (1986) Fine-needle aspiration of the liver. A comparison of smear and rinse preparations in the detection of cancer. Am J Clin Pathol 86:281–285

Bakalakos EA, Kim JA, Young DC, Martin EW (1998) Determinants of survival following hepatic resection for metastatic colorectal cancer. World J Surg 22:399–404

Bakalakos EA, Burak WE, Young DC, Martin EW (1999) Is carcino-embryonic antigen useful in the follow-up managment of patients with colorectal liver metastases? Am J Surg 177:2–6

Beckurts KT, Hölscher AH, Thorban S et al (1997) Significance of lymph node involvement at the hepatic hilum in the resection of colorectal liver metastases. Br J Surg 84:1081–1084

Bégin LR, Boucher D, Lamoureux E (2001) Diffuse hepatic intravascular carcinomatous embolization resulting in fatal liver failure: a clinicopathologic study of 4 cases. Pathol Res Pract 197:433–440

Bell DA, Carr CP, Szyfelbein WM (1986) Fine needle aspiration cytology of focal liver lesions: results obtained with examination of both cytologic and histologic preparations. Acta Cytol 30:397–402

Berge T, Saldeen T (1968) Cancer metastasis to the cirrhotic liver. A study of experimental and autopsy material. Acta Pathol Microbiol Scand 74:340–352

Bernuau J, Rueff B, Benhamou JP (1986) Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis 16:97–106

Bonatti H, Bodner G, Obrist P, Bechter O, Wetscher G, Oefner D (2003) Skin implant metastasis after percutaneous radio-frequency therapy of liver metastasis of a colorectal carcinoma. Am Surg 69:763–765

Borthwick NJ, Thombs J, Polak M, Gabriel FG, Hungerford JL, Damato B et al (2011) The biology of micrometastases from uveal melanoma. J Clin Pathol 64:666–671

Butler J, Attiyeh FF, Daly JM (1986) Hepatic resection for metastasis of the colon and rectum. Surg Gynecol Obstet 162:109–113

Carpizo DR, Are C, Jarnagin W, Dematteo R, Fong Y, Gönen M, Blumgart L, D'Angelica M (2009) Liver resection for metastatic clorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. Ann Surg Oncol 16:2138

Centeno BA (2006) Pathology of liver metastases. Cancer Control 13:13–26

Charalampopoulos A, Macheras A, Misiakos E, Batistatou A, Peschos D, Fotiadis K, Charalabopoulos K (2007) Thoracoabdominal wall tumour seeding after percutaneous radiofrequency ablation for recurrent colorectal liver matastatic lesion: a case report with a brief literature review. Acta Gastroenterol Belg 70:239–242

Cianchi F, Messerini L, Palomba A, Boddi V, Perigli G, Pucciani F, Bechi P, Cortesini C (1997) Character of the invasive margin in colorectal cancer: does it improve prognostic information of Dukes staging? Dis Colon Rectum 40:1170–1175

Ciancio G, Soloway M (2001) Renal cell carcinoma invading the hepatic veins. Cancer 92:1836–1842

Cochand Priollet B, Chagnon S, Ferrand J, Blery M, Hoang C, Galian A (1987) Comparison of cytologic examination of smears and histologic examination of tissue cores obtained by fine needle aspiration biopsy of the liver. Acta Cytol 31:476–480

Colovic RB, Grubor NM, Jovanovic MD, Micev MT, Colovic NR (2007) Metastatic melanoma to the common bile duct causing obstructive jaundice: a case report. World J Gastroenterol 13:813–815

Colwell H (1905) Malignant disease of the liver and bile passages. Arch Middlesex Hosp Lond 5:123–141

Cornfield J (1959) Principles of research. Am J Ment Defic 64:240–252

Crowe PJ, Yang JL, Berney CR, Erskine C, Ham JC, Fisher R, Russell PJ (2001) Genetic markers of survival and liver recurrence after resection of liver metastases from colorectal cancer. World J Surg 25:996–1001

De Jong KP, Stellema R, Karrenbeld A, Koudstaal J, Gouw AS, Sluiter WJ, Peeters PM et al (1998) Clinical relevance of transforming growth factor alpha, epidermal growth factor receptor, p53, and Ki67 in colorectal liver metastases and corresponding primary tumors. Hepatology 28:971–979

Denton KJ, Cotton DWK, Nakielny RA, Goepel JR (1990) Secondary tumour deposits in needle biopsy tracks: an underestimated risk? J Clin Pathol 43:83

DiSibio G, French SW (2008) Metastatic patterns of cancers: results from a large autopsy study. Arch Pathol Lab Med 132:931–939

Doci R, Gennari L, Bignami P et al (1991) One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. Br J Surg 78:797–801

Dromain C, de Baere T, Lumbroso J, Caillet H, Laplanche A, Boige V, Ducreux M et al (2005) Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. J Clin Oncol 23:70–78

Ekberg H, Tranberg KG, Andersson R, Lundstedt C, Hägerstrand I, Ranstam J, Bengmark S (1986) Determinants of survival in liver resection for colorectal secondaries. Br J Surg 73:727–731

Elias D, Liberale G, Vernerey D, Pocard M, Ducreux M, Boige V, Malka D, Pignon JP, Lasser P (2005) Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. Ann Surg Oncol 12:900–909

Elmaci L, Ekinci G, Kurtkaya O, Sav A, Pamir MN (2001) Tumor in tumor metastasis of breast carcinoma to intracranial meningioma. Tumori 87:423–427

Engels K, Kriener S, Hansmann ML (2002) Epidemiology and pathology of liver metastases (in German). In: Vogt T, Mack MG, Balzer JO (eds) Lebermetastase – diagnose, intervention, therapie, vol 3. Springer, Berlin, pp 1–10

England MD, Sarr MG (1990) Metastatic melanoma: an unusual cause of obstructive jaundice. Surgery 107:595–596

Faivre J, Manfredi S, Bouvier AM (2003) Epidemiology of colorectal cancer liver metastases (in French). Bull Acad Natl Med 187:815–822

Fazio N, Di Meglio G, Lorizzo K, de Brand F (2008) Miliary hepatic metastases from neuroendocrine carcinoma. Dig Surg 25:330

Fisher E, Fisher B (1960) Experimental studies of factors influencing hepatic metastases: effect of cirrhosis. Cancer 13:860–864

Fisher E, Hellstrom H, Fisher B (1960) Rarity of hepatic metastasis in cirrhosis: a misconception. JAMA 174:366–369

Fornari F, Civardi G, Cavanna L, Di Stasi M, Rossi S, Sbolli G et al (1989) Complications of ultrasonically guided fine-needle abdominal biopsy. Results of a multicenter Italian study and review of the literature The Cooperative Italian Study Group Scand. J Gastroenterol 24:949–955

Fournier C, Tisman G, Kleinman R, Park Y, Macdonald WD (2010) Clinical evidence for overcoming capecitabine resistance in a woman with breast cancer terminating in radiologically occult micronodular pseudo-cirrhosis with portal hypertension: a case report. J Med Case Reports 4:112

Gall EA (1960) Primary and metastatic carcinoma of the liver. Relationship to hepatic cirrhosis. Arch Pathol 70:226–232

Gayowski TJ, Iwatsuki S, Madariaga JR, Selby R, Todo S, Irish W, Starzl TE (1994) Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 116:703–710

Gayral F, Dervanian P, Larrieu H (1990) Tumoral seeding after percutaneous liver biopsy of colonic metastasis (in French). Gastroenterol Clin Biol 14:685–686

Gervaz P, Pak-art R, Nivatvongs S, Wolff BG, Larson D, Ringel S (2003) Colorectal adenocarcinoma in cirrhotic patients. J Am Coll Surg 196:874–879

Gibbs JF, Weber TK, Rodriguez-Bigas MA, Driscoll DL, Petrelli NJ (1998) Intraoperative determinants of

unresectability for patients with colorectal hepatic metastases. Cancer 82:1244–1249
Glaser KS, Weger AR, Schmid KW, Bodner E (1989) Is fine-needle aspiration of tumours harmless? Lancet 1:620
Goldstein MJ (1969) Metastases in the cirrhotic liver. N Engl J Med 281:221
Goldstein MJ, Mitchell EP (2005) Carcinoembryonic antigen in the staging and follow-up of patients with colorectal cancer. Cancer Invest 23:338–351
Goldstein MJ, Frable WJ, Sherlock P (1966) Hepatic metastases and portal cirrhosis. Am J Med Sci 252:26–30
Goletti O, Chiarugi M, Buccianti P, Macchiarini P (1992) Subcutaneous implantation of liver metastasis after fine needle biopsy. Eur J Surg Oncol 18:636–637
Gray et al (1982) http://www.ncbi.nlm.nih.gov/pubmed/7060880
Gusterson BA (2003) The new TNM classification and micrometastases. Breast 12:387–390
Hall JW, Sun SC (1951) The effect of portal cirrhosis on the development of carcinomas. Cancer 4:131–135
Hamady ZZ, Cameron IC, Wyatt J, Prasad RK, Toogood GJ, Lodge JP (2006) Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: a critical appraisal of the 1 cm rule. Eur J Surg Oncol 32:557–563
Hamaya K, Hashimoto H, Maeda Y (1975) Metastatic carcinoma in cirrhotic liver – statistical survey of autopsies in Japan. Acta Pathol Jpn 25:153–159
Hanot V, Gilbert A (1888) Etudes sur les maladies du foie. Asselin & Houzeau, Paris
Harrison HB, Middleton HM, Crosby JH, Dasher MN (1981) Fulminant hepatic failure: an unusual presentation of metastatic liver disease. Gastroenterology 80:820–825
Hayashi S, Masuda H, Shigematsu M (1997) Liver metastasis rare in colorectal cancer patients with fatty liver. Hepatogastroenterology 44:1069–1075
Heisterkamp J, van Bommel J, Hop WC, Tilanus HW, Zondervan PE, Ijzermans JN (1999) P53 overexpression in colorectal metastases confined to the liver and outcome of liver resection. Hepatogastroenterology 46:3109–3114
Henrion J, Hautekeete M, Brenard R, Schapira M, Somers G, Geubel A, Schmitz A et al (1996) Fulminant and sub-fulminant hepatocellular failure caused by metastatic invasiveness of the liver: another cause of hypoxic hepatitis? (in French). Gastroenterol Clin Biol 20:535–543
Herbut and Watson (1946) http://www.ncbi.nlm.nih.gov/pubmed/20993481
Hermanek P (1999) Disseminated tumor cells versus micrometastasis: definitions and problems. Anticancer Res 19:2771–2774
Hermanek P, Hutter RVP, Sobin LH, Wittekind C (1999) Classification of isolated tumor cells and micrometastasis. Cancer 86:2668–2673
Herszenyi L, Farinati F, Cecchetto A, Marafin C, de Maria N, Cardin R et al (1995) Fine-needle biopsy in focal liver lesions: the usefulness of a screening programme and the role of cytology and microhistology. Ital J Gastroenterol 27:473–478
Heslin MJ, Medina-Franco H, Parker M, Vickers SM, Aldrete J, Urist MM (2001) Colorectal hepatic metastases: resection, local ablation, and hepatic artery infusion pump are associated with prolonged survival. Arch Surg 136:318–323
Hollerbach S, Willert J, Topalidis T, Reiser M, Schmiegel W (2003) Endoscopic ultrasound-guided fine-needle aspiration biopsy of liver lesions: histological and cytological assessment. Endoscopy 35:743–749
Hosch SB, Steffani KD, Scheunemann P, Izbicki JR (2002) Micrometastases from HBP malignancies and metastatic cancer. J Hepatobiliary Pancreat Surg 9:583–591
Iacobuzio-Donahue C, Ferrelll L (2010) Secondary tumours of the liver. In: Bosman F, Carneiro F, Hruban RH, Theise ND (eds) WHO classification of tumours of the digestive system. International Agency for Research of Cancer, Lyon
Iascone C, Rupero M, Barillari P (2005) Occurrence of synchronous colorectal cancemetastasis in the cirrhotic or fatty liver (in Italian). Minerva Chir 60:185–190
Imamura H, Matsuyama Y, Shimada R, Kubota M, Nakayama A, Kobayashi A, Kitamura H et al (2001) A study of factors influencing prognosis after resection of hepatic metastases from colorectal and gastric carcinoma. Am J Gastroenterol 96:3178–3184
Ishikawa et al (1995) http://www.ncbi.nlm.nih.gov/pubmed/7550867
Ishizaki N, Hamada N, Kadono J, Nakamura N, Taira A (2001) Obstructive jaundice caused by lymphatic remetastasis from the hepatic metastasis of rectosigmoid cancer. J Hepatobiliary Pancreat Surg 8:469–472
Isono T, Miyazaki M, Nakajima T, Okui K, Kondo Y (1990) Clinicopathological significance of intrahepatic micrometastases in hepatic metastatic carcinomas (in Japanese). Nihon Geka Gakkai Zasshi 91:1778–1783
Ito K, Higuchi M, Kada T, Mitchell DG, Nomura S, Honjo K, Fujita T, Awaya H, Matsumoto T et al (1997) CT of acquired abnormalities of the portal venous system. Radiographics 17:897–917
Itoh T, Kanaoka M, Obara A, Furuta M, Itoh H (1988) Lymphangiosis carcinomatosa of the liver. Acta Pathol Jpn 38:751–758
Itoh T, Itoh H, Konishi J (1991) Lymphangitic liver metastasis: radiologic-pathologic correlations. J Comput Assist Tomogr 15:401–404
Iwatsuki S, Esquivel CO, Gordon RD, Starkl TE (1986) Liver resection for metastatic colorectal cancer. Surgery 100:804–809
Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, Geller DA et al (1999) Hepatic resection for metastatic colorectal adenocarcinoam: a

proposal of a prognostic scoring system. J Am Coll Surg 189:291–299
Jacobsen GK, Gammelgaard J, Fugio M (1983) Coarse needle biopsy versus fine needle aspiration biopsy in the diagnosis of focal lesions of the liver: ultrasonically guided needle biopsy in suspected hepatic malignancy. Acta Cytol 27:152–156
Jaeck D, Bachellier P, Guiguet M et al (1997) Long-term survival following resection of colorectal hepatic metastases. Association Française de Chirurgie. Br J Surg 84:1081–1084
Jaffe ES (1987) Malignant lymphomas: pathology of hepatic involvement. Semin Liver Dis 7:257–268
Jenkins et al (1997) http://www.ncbi.nlm.nih.gov/pubmed/9202534
John TG, Garden OJ (1993) Needle track seeding of primary and secondary liver carcinoma after percutaneous liver biopsy. HPB Surg 6:199–203
Jones OM, Rees M, John TG, Bygrave S, Plant G (2005) Biopsy of resectable colorectal liver metastases causes tumour dissemination and adversely affects survival after liver resection. Br J Surg 92:1165–1168
Jourdan JL, Stubbs RS (1996) Percutaneous biopsy of operable liver lesions: is it necessary or advisable? N Z Med J 109:469–470
Kampfenkel et al (2011) http://www.ncbi.nlm.nih.gov/pubmed/21964894
Karube H, Masuda H, Hayashi S, Ishii Y, Nemoto N (2000) Fatty liver suppressed the angiogenesis in liver metastatic lesions. Hepatogasroenterology 47:1541–1545
Kauffmann et al (1992) http://www.ncbi.nlm.nih.gov/pubmed/1527194
Kawakami et al (2008) http://www.ncbi.nlm.nih.gov/pubmed/19015609
Kern WH, Haber H (1986) Fine needle aspiration minibiopsies. Acta Cytol 30:403–408
Khalil HI, Patterson SA, Panicek DM (2005) Hepatic lesions deemed too small to characterized at CT: prevalence and importance in women with breast cancer. Radiology 235:872–878
Kim JC, Roh SA, Kim HC, Koo KH, Cho YK, Yu CS, Kwon YM, Kim JS (2003) Coexpression of carcinoembryonic antigen and E-cadherin in colorectal adenocarcinoma with liver metastasis. J Gastrointest Surg 7:931–938
Kohler B, Riemann JF (1987) Obstructive jaundice due to an intraductal melanoma metastasis. Endoscopy 19:79–80
Koike M, Yasui K, Torii A, Kodama S (2000) Prognostic significance of entrapped liver cells in hepatic metastases from colorectal cancer. Ann Surg 232:653–657
Kokudo N, Miki Y, Sugai S, Yanagisawa A, Kato Y, Sakamoto Y, Yamamoto J, Yamaguchi T, Muto T, Makuuchi M (2002) Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. Arch Surg 137:833–840
Korita PV, Wakai T, Shirai Y, Sakata J, Takizawa K, Cruz PV, Ajioka Y, Hatakeyama K (2007) Intrahepatic lymphatic invasion independently predicts poor survival and recurrences after hepatectomy in patients with colorectal carcinoma liver metastases. Ann Surg Oncol 14:3472–3480
Krauss EA, Ludwig PW, Sumner HW (1979) Metastatic carcinoma presenting as fulminant hepatic failure. Am J Gastroenterol 72:651–654
Kubo et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/12366810
Kumar S, Weaver VM (2009) Mechanics, malignancy, and metastasis: the force journey of a tumor cell. Cancer Metastasis Rev 28:113–127
Kume H, Kameyama S, Kasuya Y, Taijima A, Kawabe K (1999) Surgical treatment of renal cell carcinoma associated with Budd-Chiari syndrome: report of four cases and review of the literature. Eur J Surg Oncol 25:71–75
Larsen LP, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T, Laurberg S (2007) The value of contrast enhanced ultrasonography in detection of liver metastases from colorectal cancer: a prospective double-blinded study. Eur J Radiol 62:302–307
Letessier E, Gibaud H, Hamy A, Cuillière P, Paineau J, Visset J (1994) Intraluminal polyp of the common bile duct corresponding to a metastasis of cancer of the kidney (in French). Ann Chir 48:201–205
Lieber (1957) http://www.ncbi.nlm.nih.gov/pubmed/13394591
Lim GH, Koh DC, Cheong WK, Wong KS, Tsang CB (2009) Natural history of small, "indeterminate" hepatic lesions in patients with colorectal cancer. Dis Colon Rectum 52:1487–1491
Lin and Donati (1981) http://www.ncbi.nlm.nih.gov/pubmed/6271440
Lin BP, Chu JM, Rose RA (1991) Ultrasound guided fine needle biopsy of the liver for cytology and histology. Australas Radiol 35:33–37
Lisa JR, Solomon C, Gordon EJ (1942) Secondary carcinoma in cirrhosis of the liver. Am J Pathol 18:137–140
Liu SY, Lee KF, Lai PB (2009) Needle track seeding: a real hazard after percutaneous radiofrequency ablation for colorectal liver metastasis. World J Gastroenterol 15:1653–1655
Livraghi T, Damascelli B, Lombardi C, Spagnoli I (1983) Risk in fine-needle abdominal biopsy. J Clin Ultrasound 11:77–81
Livraghi T, Lazzaroni S, Meloni F, Solbiati L (2005) Risk of tumour seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. Br J Surg 92:856–858
Logan SE, Meier SJ, Ramming K, Morton DL, Longmire WP (1982) Hepatic resection of metastatic colorectal carcinoma. A ten year experience. Arch Surg 117:25–28
Mainland D (1953) The risk of fallacious conclusions from autopsy data on the incidence of diseases with applications to heart disease. Am Heart J 45:644–654

Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM (2006) Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 244:254–259

Marangoni G, O'Sullivan A, Ali A, Faraj W, Heaton N (2010) Budd-Chiari syndrome secondary to caval recurrence of renal cell carcinoma. Hepatobiliary Pancreat Dis Int 9:321–324

Marn CS, Francis IR (1992) CT of portal venous occlusion. AJR Am J Roentgenol 159:717–726

Martin MD, Kremers GJ, Short KW, Rocheleau JV, Xu L, Piston DW, Matrisian LM et al (2010) Rapid extravsation and establishment of breast cancer micrometastases in the liver microenvironment. Mol Cancer Res 8:1319–1327

Masuda N, Shiraishi Y, Okubo K, Okada T, Segawa T, Takada M, Kawakita M (2009) A case report of renal cell carcinoma with metastatic intraductal tumor thrombus of the common bile duct (in Japanese). Hinyokika Kiyo 55:99–102

Matsumoto S, Mori H, Ando Y, Miyake H (2004) Lymphangiosis carcinomatosa of the liver deriving from gastric carcinoma with a unique branching calcification. Eur Radiol 14:1519–1520

Matsumoto et al (2009) http://www.ncbi.nlm.nih.gov/pubmed/19290461

McGrath FP, Gibney RG, Rowley VA, Scudamore CH (1991) Cutaneous seeding following fine needle biopsy of colonic liver metastases. Clin Radiol 43:130–131

Melato M, Laurino L, Mucli E, Valente M, Okuda K (1989) Relationship between cirrhosis, liver cancer, and hepatic metastases. An autopsy study. Cancer 64:455–459

Metcalfe MS, Bridgewater FHG, Mullin EJ, Maddern GJ (2004) Useless and dangerous – fine needle aspiration of hepatic colorectal metastases. Br Med J 328: 507–508

Mikuriya Y, Tashiro H, Kuroda S, Nambu J, Kobayashi T, Amano H, Tanaka Y, Ohdan H (2015) Fatty liver creates a pro-metastatic microenvironment for hepatocellular carcinoma through activation of hepatic stellate cells. Int J Cancer 136:E3–E13

Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J et al (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 231:487–499

Mirouze D, Michel H (1982) Non-hepatic cancer in cirrhotic patients. Apropos of 19 patients (in French). Acta Gastroenterol Belg 45:379–385

Miyaaki H, Ichikawa T, Taura N, Yamashima M, Arai H, Obata Y, Furusu A, Hayashi H et al (2010) Diffuse liver metastasis of small cell lung cancer causing marked hepatomegaly and fulminant hepatic failure. Intern Med 49:1383–1386

Miyagishima T, Ohnishi S, Chuma M, Kishimoto A, Kumagai K, Ishizuka J, Kobayashi T et al (1996) Intraluminal tumor of the common bile duct as a metastasis of renal cell carcinoma. Intern Med 35:720–723

Morelli L, Faraci R, Piscioli I, Pusiol T, Del Nonno F, Licci S (2007) Colon carcinoma metastasis to the intrapancreatic tract of the common biliary duct: a first case report. Scand J Gastroenterol 42: 777–778

Morita S, Nomura T, Fukushima Y, Hiraoka N, Shibata N (2004) Does serum CA19-9 play a practical role in the management of patients wirth colorectal cancer? Dis Colon Rectum 47:227–232

Murono K, Kitayama J, Tsuno NH, Nozawa H, Kawai K, Sunami E, Akahane M, Watanabe T (2013) Hepatic steatosis is associated with lower incidence of liver metastasis from colorectal cancer. Int J Colorectal Dis 28:1065–1072

Nagashima I, Oka T, Hamada C, Naruse K, Osada T, Muto T (1999) Histopathological prognostic factors influencing long-term prognosis after surgical resection for hepatic metastases from colorectal cancer. Am J Gastroenterol 94:739–743

Nagata S, Tomoeda M, Kubo C, Yoshizawa H, Yuki M, Kitamura M, Takenaka A, Uehara H et al (2012) Intraductal polypoid growth variant of pancreatic acinar cell carcinoma metastasizing to the intrahepatic bile duct 6 years after surgery: a case report and literature review. Pancreatology 12:23–26

Nagler and Rochwarger (1977) http://www.ncbi.nlm.nih.gov/pubmed/615806

Nakanuma Y et al (2011) Intraductal papillary growth of liver metastasis originating from colon carcinoma in the bile duct: report of a case. Surg Today 41:276–280

Nakajima et al (1989) http://www.ncbi.nlm.nih.gov/pubmed/2749933

Nakayama H, Takayama T, Hemmi A (2005) Small necrotic liver metastasis with microscopic tumor embolism in hepatic vein: a case report and review of the literature. Int Surg 90:293–296

Neubauer K, Saile B, Ramadori G (2001) Liver fibrosis and altered matrix synthesis. Can J Gastroenterol 15:187–193

Nitti D, Belluco C, Montesco MC, Bertorelle R, Da Pian PP, Fassina A, Ninfo V, Chieco-Bianchi L, Lise M (1998) Nuclear p53 protein expression in resected hepatic metastases from colorectal cancer: an independent prognostic factor of survival. Eur J Cancer 34:851–855

Nojima H, Cho A, Yamamoto H, Nagata M, Takiguchi N, Kainuma O, Souda H, Gunji H et al (2008) Renal cell carcinoma with unusual metastasis to the gallbladder. J Hepatobiliary Pancreat Surg 15:209–212

Nomura T, Kamio Y, Takasu N, Moriya T, Takeshita A, Mizutani M, Hachiya O, Hirai I et al (2009) Intrahepatic micrometastases around liver metastases from gastric cancer. J Hepatobiliary Pancreat Surg 16:493–501

Nordlinger B, Guigeut M, Vaillant JC et al (1996) Surgical resection of colorectal carcinoma metastases of the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Cancer 77: 1254–1262

Nordlinger et al (2005) http://www.ncbi.nlm.nih.gov/pubmed/15992694
Norkin S, Heimann R, Fahimi H (1962) Neoplasm, cirrhosis and hepatic metastases. Cancer 15:1004–1008
Ogawa et al (2009) http://www.ncbi.nlm.nih.gov/pubmed/20369711
Ohlsson B, Stenram U, Tranberg KG (1998) Resection of colorectal liver metastases: 25-year experience. World J Surg 22:268–276
Ohlsson B, Nilsson J, Stenram U, Akerman M, Tranberg KG (2002) Percutaneous fine-needle aspiration cytology in the diagnosis and management of liver tumours. Br J Surg 89:757–762
Okano et al (1999) http://www.ncbi.nlm.nih.gov/pubmed/10568181
Okano K, Yamamoto J, Kosuge T, Yamamoto S, Sakamoto M, Nakanishi Y, Hirohashi S (2000) Fibrous pseudocapsule of metastatic liver tumors from colorectal carcinoma. Clinicopathologic study of 152 first resection cases. Cancer 89:267–275
Onodera H, Mori A, Nagayama S, Fujimoto A, Tachibana T, Yonenaga Y, Tsuruyama T (2005) Fas/CD95 signaling rather than angiogenesis or proliferative activity is a useful prognostic factor in patients with resected liver metastases from colorectal cancer. Int J Colorectal Dis 20:477–484
Otranto M, Sarrazy V, Bonté F, Hinz B, Gabbiani G, Desmouliere A (2012) The role of the myofibroblast in tumor stroma remodeling. Cell Adh Migr 6:203–219
Pack and Brasfield (1955) http://www.ncbi.nlm.nih.gov/pubmed/13258972
Parquier JN, Peetrons P, Liénard D, Maisonnier H, Jeamart L (1991) Jaundice secondary to a metastasis of a malignant melanoma at the level of the common bile duct (in French). J Belge Radiol 74:201–204
Pearl R (1929) Cancer and tuberculosis. Am J Hyg 9:97–159
Pedersen IK, Burcharth F, Roikjaer O, Baden H (1994) Resection of liver metastases from colorectal cancer. Indications and results. Dis Colon Rectum 37:1078–1082
Peichl S, Chaloupka F, Krivohlavy A (1978) Problem of tumor metastasizing into cirrhotic liver (in Czech). Vnitr Lek 24:338–343
Pereira-Lima JE, Lichtenfels E, Barbosa FS, Zettler CG, Kulczynski JM (2003) Prevalence study of metastases in cirrhotic livers. Hepatogastroenterology 50:1490–1495
Pérez Flores R, Cortés Cansino J, Oliva Aldamiz H, Hernandez Quoi C (1987) Hepatic cirrhosis with and without implanted carcinoma. Apropos of 100 cases with necropsy (in Spanish). Rev Clin Esp 181:356–360
Pichon N, Delage-Corre M, Paraf F (2004) Hepatic metastatic miliaria from a malignant melanoma: 2 case reports (in French). Gastroenterol Clin Biol 28:593–595
Poulain A (1899) Cancer de l'estomac. Noyaux secondaires développés dans un foie cirrhotique. Bull Soc Anat Paris 1:1089–1093
Povoski et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/1097717
Probst-Cousin S, Schaus M, Feldt B, Al-Dandashi N, Gullotta F (1997) Malignant peripheral nerve sheath tumor with extensive miliary metastases: a case report. Gen Diagn Pathol 142:357–360
Rajvanshi P, Kowdley KV, Hirota WK, Meyers JB, Keeffe EB (2005) Fulminant hepatic failure secondary to neoplastic infiltration of the liver. J Clin Gastroenterol 39:339–343
Registry of Hepatic Metastases (1988) Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. Surgery 103:278–288
Riopel MA, Klimstra DS, Godellas CV, Blumgart LH, Westra WH (1997) Intrabiliary growth of metastatic colonic adenocarcinoma: a pattern of intrahepatic spread easily confused with primary neoplasia of the biliary tract. Am J Surg Pathol 21:1030–1036
Rixen D, Köhler L, Troidl H (1998) Coincidental finding of hepatic carcinoid micrometastases during routine laparoscopic cholecystectomy. Surg Endosc 12:281–282
Rockstroh H, Schröter H (1960) Die Häufigkeit des Krebses beim diabetes mellitus (The frequency of cancer in diabetes mellitus). Munch Med Wochenschr 102:897–901
Rolleston HD, McNee JW (1929) Diseases of the liver, gall-bladder and bile ducts, 3rd edn. Macmillan & Co., Ltd., London
Roussel F (1990) Risk of metastasis during fine needle aspiration. J Clin Pathol 43:878–879
Roussel F, Dalion J, Benozio M (1989) The risk of tumoral seeding in needle biopsies. Acta Cytol 6:936–939
Rowbotham D, Wendon J, Williams R (1998) Acute liver failure in hepatic infiltration: a single centre experience of 18 cases. Gut 42:576–580
Ruebner BH, Green R, Miyai K, Caranasos G, Abbey H (1961) The rarity of intrahepatic metastasis in cirrhosis of the liver. A statistical explanation with some comments on the interpretation of necropsy data. Am J Pathol 39:739–746
Sakai Y, Kanomata N, Itami H, Kajimoto K, Sakuma T, Ohbayashi C (2010) Signet-ring cell carcinoma of the stomach metastasizing to renal cell carcinoma: a case report and review of the literature. Kobe J Med Sci 55: E122–E131
Sanz A, del Valle ML (2004) Fine needle aspiration of hepatic colorectal metastases: fine needle aspiration has its place. Br Med J 329:290
Sarwar S, Khan AA (2008) Budd Chiari syndrome: a rare complication of renal cancer. J Coll Physicians Surg Pak 18:726–727
Sasaki A, Aramaki M, Kawano K, Yasuda K, Inomata M, Kitano S (2002) prognostic significance of intrahepatic lymphatic invasion in patients with hepatic resection due to metastases from colorecral carcinoma. Cancer 95:105–111
Sasaki A, Iwashita Y, Shibata K, Matsumoto T, Ohta M, Inomata M, Kitano S (2005a) Risk factors for early

extrahepatic metastasis in patients with liver metastasis from colorectal carcinoma. Hepatogastroenterology 52:1840–1844

Sasaki A, Kawano K, Inomata M, Shibata K, Matsumoto T, Kitano S (2005b) Value of serum carbohydrate antigen 19–9 for predicting extrahepatic metastasis in patients with liver metastasis from clorectal carcinoma. Hepatogastroenterology 52:1814–1819

Satoh H, Iyama A, Hidaka K, Nakashiro H, Harada S, Hisatsugu T (1991) Metastatic carcinoma of the gallbladder from renal cancer presenting as intraluminal polypoid mass. Dig Dis Sci 36:520–523

Sautereau D, Vire O, Cazes PY, Cazals JB, Catanzano G, Claude R, Pillegand B (1987) Value of sonographically guided fine needle aspiration biopsy in evaluating the liver with sonographic abnormalities. Gastroenterology 93:715–718

Saw RP, Koorey D, Painter D, Gallagher PJ, Solomon MJ (2002) P53, DCC and thymidylate synthase as predictors of survival after resection of hepatic metastases from colorectal cancer. Br J Surg 89:1409–1415

Schaffner F, Poper H (1963) Capillarization of hepatic sinusoids in man. Gastroenterology 44:239–242

Scheele J, Altendorf-Hofmann A (1990) Tumour implantation from needle biopsy of hepatic metastases. Hepatogastroenterology 37:335–337

Scheele J, Stang R, Altendorf-Hofmann A, Paul M (1995) Resection of colorectal liver metastases. World J Surg 19:59–71

Scheele J, Altendorf-Hofmann A, Stangl R, Schmidt K (1996) Surgical resection of colorectal liver metastases:gold standard for solitary and radically resectable lesions (in German). Swiss Surg (Suppl 4):4–17

Schimanski CC, Möhler M, Zimmermann T, Gockel I, Lang H, Arbogast R, Jäger D et al (2010) Detection of hepatic micrometastases in the context of adjuvant chemotherapy and surgery for hepatic metastases (in German). Dtsch Med Wochenschr 135:1078–1082

Schindl M, Wigmore SJ, Currie EJ, Laengle F, Garden OJ (2005) Prognostic scoring in colorectal cancer liver metastases: development and validation. Arch Surg 140:183–189

Schneider and Cohen (1984) http://www.ncbi.nlm.nih.gov/pubmed/6695227

Schulz W, Hort W (1981) The distribution of metastases in the liver. A quantitative postmortem study. Virchows Arch Pathol Anat 394:89–96

Seifert JK, Böttger TC, Weigel TF, Gönner U, Junginger T (2000) Prognostic factors following liver resection for hepatic metastases from colorectal cancer. Hepatogastroenterology 47:239–246

Seitz JF, Giovannini M, Monges G, Rosello R, Hassoun J, Mazel C, Gauthier A (1990) Comparative study of fine needle aspiration and large caliber needle biopsy under echographic control fort he diagnosis of abdominal tumors (in French). Gastroenterol Clin Biol 14:529–533

Senda T, Sawada S, Okuda Y, Kobayashi M, Tanigawa N (1995) CT demonstration of portal vein remnant within metastatic liver tumor. J Comput Assist Tomogr 19:135–137

Servois V, Mariani P, Malhaire C, Petras S, Piperno-Neumann S, Plancher C, Levy-Gabriel C et al (2010) Preoperative stahing of liver metastases from uveal melanoma by magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET). Eur J Surg Oncol 36:189–194

Shibayama Y, Hashimoto K, Nakata K (1991) Focal veno-occlusive lesions following metastasis of cancer in the liver with special reference to obstruction of lymphatics in hepatic veins. Virchows Arch A Pathol Anat Histopathol 418:169–174

Shih KL, Yen HH, Su WW, Soon MS, Hsia CH, Lin YM (2009) Fulminant Budd-Chiari syndrome caused by renal cell carcinomawith hepatic vein invasion: report of a case. Eur J Gastroenterol Hepatol 21:222–224

Shirabe K, Takenaka K, Gion T, Fujiwara Y, Shimada M, Yanaga K, Maeda T, Kajiyama K, Sugimachi K (1997) Analaysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin. Br J Surg 84:1077–1080

Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF (2008) Neddle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut 57:1592–1596

Simunek R, Sirotek L, Sefr R (2011) Renal cancer metastasis into common bile duct (in Czech). Rozhl Chir 90:190–193

Siu DC, Lam CM, Yuen ST, Fan ST (1999) Carcinoma of the colon with synchronous hepatic metastasis in a cirrhotic liver harboring a hepatocellular carcinoma. Hepatogastroenterology 46:2355–2357

Smith EH (1984) The hazards of fine needle aspiration biopsy. Ultrasound Med Biol 10:629–634

Smith EH (1991) Complications of percutaneous abdominal fine-needle biopsy. Review. Radiology 178:253–258

Sobin LH (2003) TNM, sixth edition: new developments in general concepts and rules. Semin Surg Oncol 21:19–22

Stewart CJ, Coldewey J, Stewart IS (2002) Comparison of fine needle aspiration cytology and needle core biopsy in the diagnosis of radiologically detected abdominal lesions. J Clin Pathol 55:93–97

Stigliano R, Marelli L, Yu D, Davies N, Patch D, Burroughs AK (2007) Sedding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What ist he risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev 33:437–447

Sung et al (2011) http://www.ncbi.nlm.nih.gov/pubmed/21757828

Suwa H, Hosotani R, Okino T, Monden K, Arii S, Inoue K, Kogire M, Ohshio G, Fukumoto M et al (1999)

Detection of multiple hepatic micrometastases in pancreatic adenocarcinoma with a solitary liver metastasis by direct sequencing of the K-ras gene: a case report. Surgery 125:113–116
Szabo et al (1975) http://www.ncbi.nlm.nih.gov/pubmed/1202595
Tada H, Morimoto M, Shima T, Hirana H, Nakagawa Y, Shimamoto K, Nagano N (1996) Progressive jaundice due to lymphangiosis carcinomatosa of the liver: CT appearance. J Comput Assist Tomogr 20:650–652
Tada et al (2003) http://www.ncbi.nlm.nih.gov/pubmed/12607055
Tamura R, Masuda H, Ishii Y, Nemoto N (1999) Relationship between fatty liver and liver metastasis in rats given injection of rat colon cancer cell line. Hepatogastroenterology 46:167–171
Tanaka K, Shimada H, Miura M, Fujii Y, Yamaguchi S, Endo I, Sekido H, Togo S, Ike H (2004) Metastatic tumor doubling time: most important prehepatectomy predictor of survival and nonrecurrence of hepatic colorectal cancer metastasis. World J Surg 28:263–270
Timar J, Csuka O, Orosz Z, Jeney A, Kopper L (2001) Molecular pathology of tumor metastasis. I. Predictive pathology. Pathol Oncol Res 7:217–230
Tomimaru et al (2010) http://www.ncbi.nlm.nih.gov/pubmed/21110841
Tot T (2000) The role of cytokeratins 20 and 7 and estrogen receptor analysis in separation of metastatic lobular carcinoma of the breast and metastatic signet ring cell carcinoma of the gastrointestinal tract. APMIS 108:467–472
Tsai YY, Lu SN, Changchien CS, Wang JH, Lee CM, Eng HL, Chang WC (2002) Combined cytologic and histologic diagnosis of liver tumors via one-shot aspiration. Hepatogastroenterology 49:644–647
Ueda K, Ohori M, Taka J, Kusano M (2002) Metastatic biliary polypoid thrombus from renal cell carcinoma: report of a case. Surg Today 32:458–461
Uetsuji S, Yamamura M, Yamamichi K, Okuda Y, Takada H, Hioki K (1992) Absence of colorectal cancer metastatic to the cirrhotic liver. Am J Surg 164:176–177
Urdzik et al (2012) http://www.ncbi.nlm.nih.gov/pubmed/22027576
Van Boeckrijck M, Klöppel G (1992) Incidence and morphology of liver metastasis from extrahepatic malignancies to cirrhotic livers. Zentralbl Pathol 138:91–96
Vergara V, Garripoli A, Marucci MM, Bonino F, Capussotti L (1993) Colon cancer seeding after percutaneous fine needle aspiration of liver metastasis. J Hepatol 18:276–278
Votrubova et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/16565845
Wakai et al (2012) http://www.ncbi.nlm.nih.gov/pubmed/22670174
Wallach JB, Hyman W, Angrist AA (1953) Metastasis to liver in portal cirrhosis. Am J Clin Pathol 23:989–993
Wanebo HJ, Chu QD, Vezeridis MP, Soderberg C (1996) Patient selection for hepatic resection of colorectal metastases. Arch Surg 131:322–329
Warshaw and Walch (1978) http://www.ncbi.nlm.nih.gov/pubmed/82427
Watson (1955) http://www.ncbi.nlm.nih.gov/pubmed/13243188
Weber JC, Nakano H, Bachellier P, Oussoultzoglou E, Inoue K, Shimura H, Wolf P, Chenard-Neu MP, Jaeck D (2001) Is a proliferation index of cancer cells a reliable prognostic factor after hepatectomy in patients with colorectal liver metastases? Am J Surg 182:81–88
Wegener F (1961) Metastatic-carcinomatous liver cirrhosis (in German). Acta Hepatosplenol 8:14–24
Weiss L, Gilbert HA (1982) Liver metastases. G.K. Hall Medical Publsihers, Boston
White WH (1897) Tumours of the liver. In: Albutt TC (ed) A system of medicine, vol 4. The Macmillan Co, New York, p 208
Willis RA (1973) Spread of tumors in the human body. Butterworth and Co., London
Yamada H, Kondo S, Okushiba S, Morikawa T, Katoh H (2001) Analysis of predictive factors for recurrence after hepatectomy for colorectal liver metastases. World J Surg 25:1129–1133
Yamamoto K, Phillips MJ (1986) Three-dimensional observation of the intrahepatic lymphatics by scanning electron microscopy of corrosion casts. Anat Rec 214:67–70
Yamamoto et al (1995) http://www.ncbi.nlm.nih.gov/pubmed/7826164
Yamamoto et al (1999) http://www.ncbi.nlm.nih.gov/pubmed/10201774
Yamamoto N, Sugano N, Morinaga S, Kanazawa A, Inagaki D, Shiozawa M, Rino Y et al (2011) Massive portal vein tumor thrombus colorectal cancer without any metastatic nodules in the liver parenchyma. Rare Tumors 3:e47
Yanagizawa R, Karasawa E, Iiizumi T, Tominaga T, Asano M (1983) Case of renal cell carcinoma causing Budd-Chiari syndrome by tumor thrombus of inferior vena cava (in Japanese). Nihon Hinyokika Gakkai Zasshi 74:1692–1699
Yanardag et al (2003) http://www.ncbi.nlm.nih.gov/pubmed/12624620
Yang JL, Ow KT, Russell PJ, Ham JM, Crowe PJ (1996) Higher expression of oncoproteins c-myc, c-erbB-2/neu, PCNA, and p53 in metastasizing colorectal cancer than in nonmetastasizing tumors. Ann Surg Oncol 3:574–579
Yokoyama N, Shirai Y, Ajioka Y, Nagakura S, Suda T, Hatakeyama K (2002) Immunohistochemically detected hepatic micrometastases predict a high risk of intrahepatic recurrence after resection of colorectal carcinoma liver metastases. Cancer 94:1642–1647
Yokoyama N, Otani T, Hashidate H, Maeda C, Katada T, Sudo N, Manabe S, Ikeno Y et al (2012) Real-time detection of hepatic micrometastases from pancreatic

cancer by intraoperative fluorescence imaging: preliminary results of a prospective study. Cancer 118:2813–2819

Zeng Y, He XW, He XS, Wu XJ, Ma JP, Wang JP, Lan P (2013) Chronic hepatic viral infection could be a protective factor for colorectal cancer liver metastases: analysis in a single institute. Hepatogastroenterology 60:37–41

Zhou XP, Quan ZW, Cong WM, Yang N, Zhang HB, Zhang SH, Yang GS (2007) Micrometastasis in surrounding liver and the minimal length of resection margin of primary liver cancer. World J Gastroenterol 13:4498–4503

Zisman A, Wieder JA, Pantuck AJ, Chao DH, Dorey F, Said JW, Gitlitz BJ, deKernion JB et al (2003) Renal cell carcinoma with tumor thrombus extension: biology, role of nephrectomy and response to immunotherapy. J Urol 169:909–916

Zotti S, Piccigallo E, Rampinelli L, Romagnoli G, Tufano A, Dagnini G (1986) Primary and metastatic tumors of the liver associated with cirrhosis: a study based on laparoscopy and autopsy. Gastrointest Endosc 32:91–95

Metastatic Liver Disease: Colorectal Carcinomas

107

Contents

Abstract

Among tumors causing hepatic metastatic disease, colorectal carcinoma (CRC) plays a very important and distinct role, both clinically and pathologically. The liver is the first and most common of CRC metastasis. CRC metastases to the liver occur in synchronous or metachronous manner, whereby synchronicity of CRC hepatic metastasis is a risk factor associated with poorer outcome. CRC metastatic to the liver has a complex molecular signature that will be employed for risk stratification and new treatment modalities. CRC metastasis to the liver presents a solitary or multiple lesions. The metastases involve the liver lobes with different frequencies, the right being involved more frequently. Typical solitary CRC metastases are bulky masses with a usually expanding growth pattern. The pattern of nodularity and growth patterns have resulted in classification systems for metastases. Large CRC nodules often reveal secondary changes, central necrosis being a very common feature. The tumors can invade the liver capsule and extend into adjacent structures, mainly the diaphragm, resulting in characteristic imaging findings. The metastatic nodules are associated with a distinct peritumoral immune reaction and may elicit formation of a pseudocapsule.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_107

Introduction

The liver is the first and most common site of colorectal cancer (CRC) metastasis; at autopsy, more than 50 % of patients dying with CRC will have hepatic metastases (Dionne 1965; Willis 1973; Bengmark and Hafstrom 1969; Pickren et al. 1982; Bird et al. 2006). About 25 % of patients who underwent CRC resection have liver metastases diagnosed presurgery or during surgery (synchronous liver metastases). CRC metastases are confined to the liver in 30–40 % of the patients at the time of their detection (Oxley and Ellis 1969; Ruers and Bleichroth 2002; Simmonds et al. 2006; Ong and Leen 2007). CRC metastases to the liver occur in a synchronous or metachronous manner, two groups which differ in their biology of disease (Slesser et al. 2013). Synchronicity of CRC hepatic metastases is a risk factor associated with poorer outcome (Adam 2007). Synchronous hepatic CRC metastasis can occur in the absence of regional lymph node metastasis (Fujii et al. 2013). CRC metastatic to the liver has a complex molecular signature (Jin et al. 2012; Murakami et al. 2013) that will result in distinct molecular signatures usable for tumor and therapy stratifications.

Clinical Features and Biology of Disease

The clinical presentation of colorectal liver metastases is highly variable, depending on the number and size of metastases, the growth patterns, the modes of vascular and/or bile duct invasion, and complications. The clinical features therefore range from an asymptomatic situation to nonspecific abdominal pain and discomfort and to fulminant hepatic failure. The clinical picture is also modified by the presence or absence of local colorectal recurrence and remote extrahepatic metastatic disease.

Hepatic resection is generally accepted as the best treatment for hepatic colorectal cancer metastases, although the resectability rate is reported to be only 25 % (Scheele et al. 1995; systematic review of published studies: Simmonds et al. 2006). Five-year survival rates achieved by this technique approach 50 %. But about 60 % of the patients undergoing this treatment develop tumor recurrence, up to more than 40 % in the liver (Hughes et al. 1986; Doci et al. 1991; Rees et al. 1997; Ohlsson et al. 1998; Minagawa et al. 2000; Carpizo et al. 2009). Recurrence at the level of the surgical margin was found in around one quarter of these patients with recurrent disease (Wang et al. 1996). Among extrahepatic recurrences after liver resection, pelvic recurrence amounted to 16.3 % in one study, and most patients with pelvic recurrence also developed recurrence in the liver (Assumpcao et al. 2008).

Principal Macroscopic Growth Patterns

The number of CRC metastases of the liver (solitary vs. few vs. numerous) varies markedly as a function of the material examined. Autopsy investigations have shown solitary lesions in 16 %, most livers having several to numerous nodules (Schulz et al. 1985). This paucity in solitary lesions is probably related to the far advanced disease encountered in autopsies of patients with treatment failure. Conversely, surgical resection specimens are expected to have more solitary lesions due to earlier intervention. CRC metastases involve the liver lobes with different frequencies. In a study of 26 metastasis-containing autopsy livers from patients with CRC, the overall incidence of metastases located in the right lobe was 61.2 % compared to 38.8 % on the left side (Schulz et al. 1985).

Most hepatic metastases of CRCs show a nodular growth pattern, with presence of either a solitary, often large nodule, or several to numerous nodules (Fig. 1). CRC metastases of the liver can, however, also present with one of the non-nodular growth patterns that have been described above. Typical solitary CRC metastases present as bulky, rather well-circumscribed masses with most often an expanding growth pattern, but lesions with a highly irregular

Fig. 1 Hepatic colorectal carcinoma metastasis with satellite nodules (fixed specimen)

contour and an invasive phenotype with few to numerous satellite nodules are also encountered. On cut surfaces, the tumors appear as cream-white to gray-white lesions that are often soft and friable in the center, due to marked necrosis, and more firm in peripheral parts, the high consistency mainly depending of the viability state of cancer cells and the amount of stroma present. In part of the cases, spotty to large hemorrhages are seen. The nodules may also show other secondary changes as discussed above. Based on macroscopic presentation, several gross classifications of CRC metastases have been proposed. In the Yasui classification (Yasui et al. 1997), a simple nodular (SN) type and a confluent nodular (CN) type are distinguished. The SN type has a smooth distinctive border and medullary structure with or without necrotic foci. The CN type is, in contrast, a multinodular tumor with an irregular border. The applicability and significance of this classification system was critically reassessed (Nanashima et al. 2002). Hepatic CRC metastases are also classified as pushing (expanding) vs. invading (infiltrative) lesions, whereby the pushing mode is associated with superior disease-free survival (Pinheiro et al. 2014). The peritumoral liver substance often shows a rim of atrophy, visualized as a slightly depressed zone of parenchyma having a reddish discoloration. A yellow rim surrounding the metastatic nodule indicates perifocal hepatic fatty change.

Penetration of the Liver Capsule and the Diaphragm

Large metastatic tumors and those located in the organ's periphery will frequently contact the liver capsule and grow beyond the organs' contour, with a dome-shaped tumor covered by thinned capsule and showing dilated and engorged blood vessels surrounding the lesion. In an autopsy study, CRC metastases reached to the liver surface in 49 % (Schulz et al. 1985). In case of large central necrosis within the nodule, a typical umbilication occurs, with a central or excentric dimple of sometimes several cm diameter (the so-called cancer navel). Contact of several types of metastatic carcinomas with the capsule can cause capsular retraction (Fennessy et al. 2004). On CT images, two types of capsular retraction can be found. In the first type, the retracted capsule is smooth and regular, while in the second type, the retracted capsular part is eroded or even ulcerated. Both lesion types were specific for malignant hepatic tumors (Soyer et al. 1994).

These growth modes can be associated with penetration of the liver capsule (Josephson and Wallace 1978). In early phases of this process, the liver capsule overlying the metastasis loses its glistening aspect and becomes dull, turbid, or opaque, due to loss of the mesothelial covering and deposition of an exudate rich in fibrin. In the superior part of the liver, this early inflammatory reaction can cause adhesion between the organ surface and the inferior aspect of the diaphragm, but this adhesion is easily removed, as it is only due to a fibrin "glue" and not fibrous tissue. In later phases, metastatic tissue invades the falciform ligament, or infiltrates the diaphragm, first by growing through adhesions into the adjacent subserosal space of the diaphragm and then into its muscle tissue (Figs. 2, 3, 4, and 5). Radiologically it may be difficult to distinguish between mere adhesion between the liver surface and the diaphragm and true invasion. Although metastatic CRC often reach to the liver capsule, invasion and penetration of this organ limit do not seem to be very frequent. The phenomenon was studied in 163 human autopsies showing metastatic

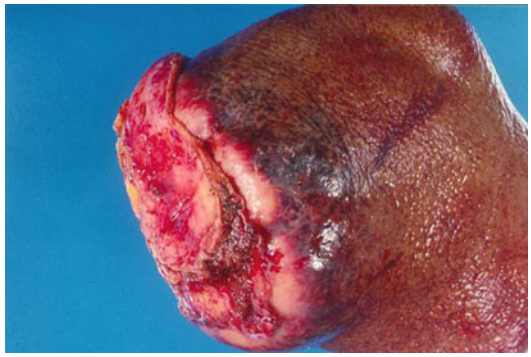

Fig. 2 Hepatic colorectal carcinoma metastasis with invasion of the diaphragm. A part of the muscular diaphragm (to the *left*) adheres to an umbilicated peripherally located metastasis. Note the growing tumor nodules forming a collar around the depressed tumor area

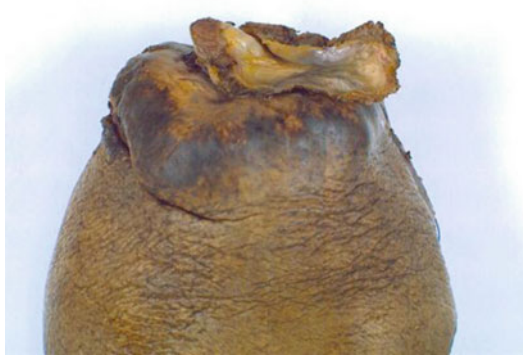

Fig. 3 Hepatic colorectal carcinoma metastasis with invasion of the diaphragm. This distinct mode of invasion is associated with typical imaging features (fixed resection specimen)

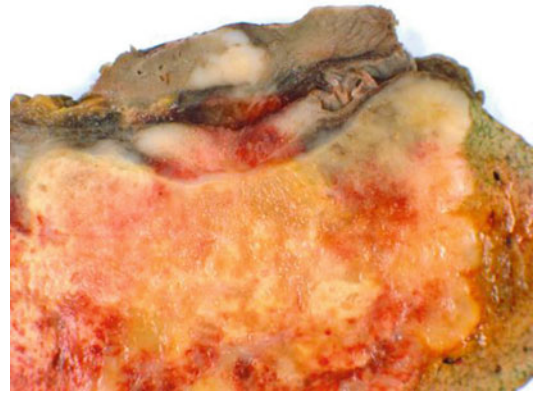

Fig. 4 Hepatic colorectal carcinoma metastasis with invasion of the diaphragm. On this cut surface, an epicapsular tumor mass is seen above the umbilicated part. A cancer nodule is located within the diaphragmatic muscle

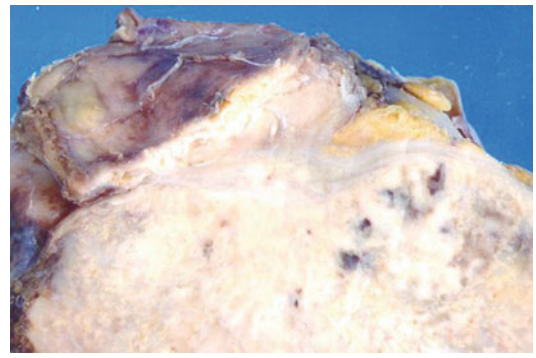

Fig. 5 Hepatic colorectal carcinoma metastasis with invasion of the diaphragm. In this case, the adherent part of the diaphragm is extensively infiltrated by tumor (fixed resection specimen)

subcapsular tumor nodules in the liver. In the majority (153/163 cases), there was some stretching and distortion of the hepatic capsule but no evidence of capsular infiltration by the tumor. Only ten cases showed small foci of tumor within the capsule proper, and in two cases only were tumor cells seen to have breached the capsule and overlying mesothelium and to be on the peritoneal surface. The rarity of penetration was also observed in scanning electron microscope, where subcapsular/capsular tumor nodules (sometimes umbilicated) bulge from the surface, however, mostly covered by mesothelium (Josephson and Wallace 1974, 1978).

The phenomenon of capsular invasion has been studied in detail by use of animal experimentation. In experimental hepatic metastases in rats (injection of Walker 256 carcinosarcoma cells into the mesenteric vein), it was found that hepatic subcapsular nodules penetrated the liver capsule in all animals and the tumor cells lodged on the peritoneal surface (Josephson and Wallace 1978). Scanning electron microscopy revealed that the mesothelial cell layer of the capsular peritoneum was distorted over the penetrating tumor nodules. This was followed by a local fibrinous reaction, loss of mesothelial cells, and lodging of tumor cells (single or clusters/clumps) in these gaps (Josephson and Wallace 1978).

Histopathology

Colorectal adenocarcinoma is somewhat unique because it has a highly characteristic morphology among adenocarcinomas, rendering it diagnosable in biopsies with high reliability (Figs. 6 and 7). In fact, most instances of metastatic colorectal cancer disease in the liver may be correctly diagnosed in biopsies using standard morphology (Centeno 2006; Van den Eynden et al. 2014). Most cases show the "classical" cylindrocellular adenocarcinoma pattern with variable expression of tubular, papillary, cribriform, and solid components, the cells having ovoid or elongated nuclei either placed basally or higher up in the cell body.

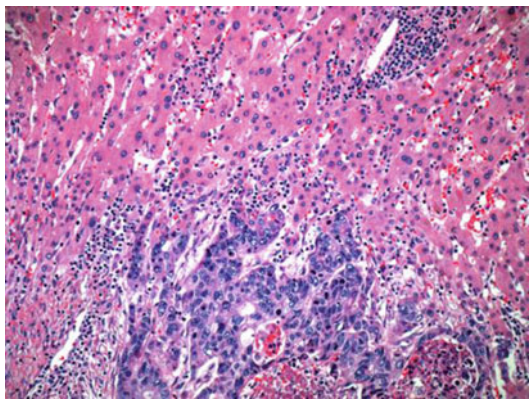

Fig. 6 Peripheral invasion pattern of hepatic colorectal carcinoma metastasis (hematoxylin and eosin stain)

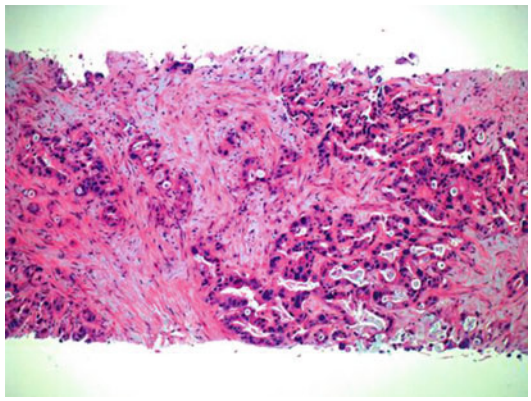

Fig. 7 Liver metastasis of colorectal carcinoma, needle biopsy. Note the abundant desmoplastic stroma (hematoxylin and eosin stain)

It is typical that the histologic differentiation (grade) of hepatic colorectal metastases is practically the same as that of the primary tumor. In case of the rarer mucinous, colloid, signet ring-cell, or poorly differentiated CRCs, the assignment of a metastasis to the colorectal origin is much more difficult or impossible, as the histologic presentation is the same as in other primaries having these features. Distinct histologic growth patterns have been defined for metastatic carcinomas of the liver. Small metastases with a size less than 1 mm show a replacement growth pattern in about two thirds of CRC cases, while metastatic nodules exceeding a diameter of 20 mm predominantly exhibit an expansive growth pattern. In contrast to other primary tumors, a sinusoidal growth pattern is less common in small CRC metastases (Terayama et al. 1996a). Macronodular CRC metastases typically display necrosis, sometimes extensive and involving most of the tumor mass. A type of necrosis that occurs in CRC metastasis and is highly characteristic for these neoplasms is so-called "dirty" or intraacinar necrosis/IAN, characterized by a focus of coagulation necrosis containing nuclear debris and a peripheral rim of preserved cylindrical tumor cells (Bizjak-Schwarzbartl 1987; Lash and Hart 1987). Necrosis can be followed by dystrophic calcification (Sanchez-Pérez et al. 1995). In a systematic comparative analysis, IAN was much more frequently encountered in CRC metastases than in metastases of other carcinomas (Wong and Neville 2007).

Immunohistochemistry

Immunohistochemically, expression patterns of certain antigens may be useful in typing of established or suspected liver metastases of carcinomas (Tot and Samii 2003), although the histomorphological presentation of CRC is so typical that the tumor can often be diagnosed with ease in H&E-stained preparations with high reproducibility. Hepatocellular carcinoma and cholangiocarcinoma can be distinguished from CRC metastasis by differences in staining patterns of HepPar1, pCEA, and of MOC31, the latter

labeling a cell surface glycoprotein (Niemann et al. 1999; Porcell et al. 2000; Proca et al. 2000; Morrison et al. 2002; Siddiqui et al. 2002; Lamps and Folpe 2003; Shiran et al. 2006). It has been shown that intrahepatic cholangiocarcinomas can more reliably be distinguished from colorectal cancer metastases by use of cytokeratin 7, 19, and 20 immunostaining (Maeda et al. 1996; Rullier et al. 1999, 2000; Shimonishi et al. 2000). CK20 seems to be a very useful marker for distinguishing gastrointestinal adenocarcinomas from adenocarcinomas of other primary sites (Moll et al. 1992; Chu et al. 2000; Rullier et al. 2000; Park et al. 2002; Tot 2004); in particular, the CK20[+] CK7[−] phenotype is characteristic for CRC metastasis (in more than 75 % of cases; Wauters et al. 1995; Tot 1999, 2002, Tot and Samii 2003). Reactivity for CK19 was not useful in differentiating cholangiocarcinoma from CRC metastasis (Lau et al. 2002). Das-1 immunostaining can discriminate between CRC metastasis and hepatocarcinoma (Zimmerman et al. 2002). Certain molecules expressed in CRC metastases affect outcome. For example, expression of folate receptor-alpha is present in a subset of resected hepatic CRC metastases, and this marker was independently associated with survival after resection (D'Angelica et al. 2011). Expression of the E-cadherin-catenin complex was also associated with tumor progression (Nanashima et al. 1999; Ikeguchi et al. 2001). Presence of certain cytokeratins has also been documented in CRC liver metastases at the RNA level, e.g., cytokeratin 20. It has been suggested that a high incidence of clinically inconspicuous lymph node and liver samples tested positive for cytokeratin 20, together with guanylyl cyclase, emphasizes the function of these two organs as primary filters for epithelial cells possibly shed from colorectal carcinomas (Conzelmann et al. 2003, 2005).

Fibrous Pseudocapsule of CRC Metastases

Parts of hepatic colorectal metastasis show a lamina of stromal tissue interposed between the tumor's periphery and adjacent liver parenchyma, termed a pseudocapsule (Yamamoto et al. 1995). Macroscopically, this pseudocapsule is sometimes visualized as a gray-white band or line, completely or incompletely surrounding the tumor nodule. Formation of a fibrous pseudocapsule is well known in various forms of hepatocellular carcinoma (HCC) and is a typical feature of one subset of small HCC. The incidence of a pseudocapsule in this tumor type varies considerably (in the literature ranging from less than 5–86 %), probably related to definitions used and subtypes of tumors studied. In non-small HCC, encapsulation has been reported to be associated with a less aggressive tumor biology and less frequent vascular invasion and tumor microsatellites (Ng et al. 1992). A fibrous pseudocapsule (FPC) has been noted in other epithelial and mesenchymal liver tumors, including various metastases. In liver metastases of CRC, an FPC can be observed in both small and large tumors (Yamamoto et al. 1995). At gross examination of fresh (unfixed) resection specimens, the FPC may be visualized as a whitish band of variable thickness, separating the tumor from the liver substance, and sometimes with retraction of liver parenchyma immediately outside the FPC. The retraction effect becomes more pronounced after fixation of the specimen and is probably caused by a rim of perifocal parenchymal atrophy, also recognized by flattening of the liver lobules in this area, associated with effacement of the terminal vein lumina and an elliptical shape of the lobules. In cases where the metastasis is located underneath the liver capsule, the FPC blends into the capsule, resulting in a thick encapsulation of the tumor where it may bulge from the surface (with or without umbilication). In deep-seated metastases, the FPC may either surround the entire lesion (complete FPC) or may only be present in certain sectors of the lesion (incomplete FPC). It has not been defined so far how much of a tumor circumference must show a fibrous interface to call this an FPC, but fibrous tissue between tumors and the liver substance was found in 67 % of surgically resected CRC liver metastases (Okano et al. 2000).

Histologically, the FPC varies markedly in relation to its thickness, geometry of separation from either the tumor or the adjacent liver, degree

of completeness, cellular composition, and amount of collagen layers. The FPC may present, on one end of the spectrum, as a thin layer of collagen, blending with the tumor's stroma, but usually distinguishable from stroma by the presence of delineated collagen bundles and the lower (myo)fibroblastic cellularity and lower content of glycosaminoglycans of the FPC in comparison with stroma. On the other end of the spectrum are thick pseudocapsules having ten or more layers of collagen bundles, rendering the FPC visible at naked eye examination. Based on the number of collagen bundles, a grading system has been proposed (none, no fibrous tissue observed; thin, tumor separated by several layers of collagen bundles; thick, tumor separated by ten or more layers of collagen bundles; Yamamoto et al. 1995; Okano et al. 2000). The cellularity of a given FPC is determined, on the one hand, by the amount of resident connective tissue cells (higher cellularity in "young" or active FPC vs. "old" and inactive, collagenized FPC) and on the other on the amount of infiltrate cells. Some FPC may contain lymphocytes, macrophages, and plasma cells in high densities, and the macrophage population may contain lipid-laden foam cells subsequent to phagocytosis of necrotic tumor cells and granulocytes. Often the peripheral half of the FPC, facing the adjacent liver parenchyma, exhibits a higher infiltrate density, with spillover of lymphocytes in the hepatocyte parenchyma, and collagenization seems to advance from the stromal compartment of the tumor toward the liver. Owing to the expansive growth of the metastasis, the FPC may be pushed to portal tracts, and these may then be integrated into the FPC, sometimes associated with ductular proliferations. Immunohistochemically, the (myo)fibroblastic cells located in the FPC are reactive for both vimentin and alpha-smooth muscle actin, supporting a myofibroblastic lineage.

Similar to HCCs, the presence of well-developed FPC in CRC liver metastases is a predictor of the post-resection outcome (Yamamoto et al. 1999). By a univariate analysis, the positive prognostic effect of a FPC was thickness dependent: a thicker (grade 3) pseudocapsule was associated with less frequent recurrence of disease and better patient survival. Interestingly, 63 % of patients with intra-bile ductal growth had a thick (grade 3) FPC, indicating that these features were common to a special subgroup with an excellent prognosis (Okano et al. 2000). The desmoplastic reaction surrounding CRC metastases was shown to favor tumor growth via alphaV integrin ligation (Conti et al. 2008).

Angiogenesis in CRC Metastases

Hepatic metastases are predominantly supplied by arterial blood, a finding having a strong impact on therapeutic measure such as arterial chemotherapy and chemoembolization (Breedis and Young 1954; Healey 1965; Ackerman 1974; Ridge et al. 1987; Archer and Gray 1989; Lin et al. 1984; Casillas et al. 1997; Liu and Matsui 2007). On the other hand, it has been emphasized numerous times that the portal vein contributes to the process of vascularization of metastases, either directly or through the sinusoids (Lin et al. 1984; Ackerman 1986; Haugeberg et al. 1988; Paku and Lapis 1993; Terayama et al. 1996; Kuruppu et al. 1997; Nikfarjam et al. 2003; Paku et al. 2005).

Similar to other malignancies, CRC metastases elicit a more or less vigorous angiogenic response in the tissue surrounding the tumor nodules. Histologically, angiogenesis is visualized as a dense network of small and in part sinusoid-like vessels in close spatial relationship with the stroma embedding the invasive cancer cells. Many newly formed blood vessels in and around CRC metastasis of the liver are lined with sinusoidal endothelial cells that differ from endothelia of larger vessels (Gervaz et al. 2000). These sinusoid-like channels can undergo capillarization (Terayama et al. 1996a). These endothelial cells may originate from endothelial progenitor cells located in the highly angiogenic tissue surrounding hepatic tumors (Yu et al. 2010). In and around metastases, angiogenesis is promoted by vascular endothelial growth factor/VEGF and E-selectin, but is suppressed by Netrin-4 and LK-68 (Xu et al. 2013). Angiogenesis driven by angiogenic factors may progress stepwise as a function

of enlarging metastatic nodules (Terayama et al. 1996b). An increase in number and density of microvessels is required for providing oxygen and nutrients to the growing tumor and is expected to exert an influence on progression and biology of disease. In human CRC liver metastases, a higher microvessel count was associated with decreased disease-free and overall survival (Nanashima et al. 2009).

In the rat, the liver lobule as homing area of circulating cancer cells shows arterioportal anastomoses and arterial terminations at the base of the lobule. These terminations supply one hepatic microcirculatory subunit per lobule, the so-called arterial hepatic microcirculatory subunit (aHMS). The sequence of ongoing arterialization of experimental metastasis includes the distortion of the aHMS by the growing metastatic nodule; the initial fusion of the sinusoids of the aHMS at the tumor-parenchyma interface; the fusion of sinusoids located at the base of the aHMS, leading to disruption of the vascular sphincter (burst pipe); the incorporation of the dilated artery and the fused sinusoids into the growing tumor; and the further development of the tumor vasculature (arterial tree) of metastasis larger than 2,000 μm by proliferation, remodeling, and continuous incorporation of fused sinusoids at the tumor-parenchyma interface. In this rat model, only half of the metastases of colon carcinoma were arterialized at the size of about 1,500 μm, but the arterialization process accelerates with increasing metastasis size (Dezsö et al. 2009). The size has also an impact on the number of arteries supplying a given nodule, in that smaller nodules were supplied by one artery branch, but acquired more branches as they became larger nodules (Ackerman 1974; Dezsö et al. 2009).

Immune Reactions in Primary CRCs and Their Liver Metastases

A relationship between local immune reactions, visualized as lymphocyte-rich intra- and peritumoral infiltrates, and survival advantage in primary CRC is well documented (Fig. 8). Patients with dense lymphocytic infiltration

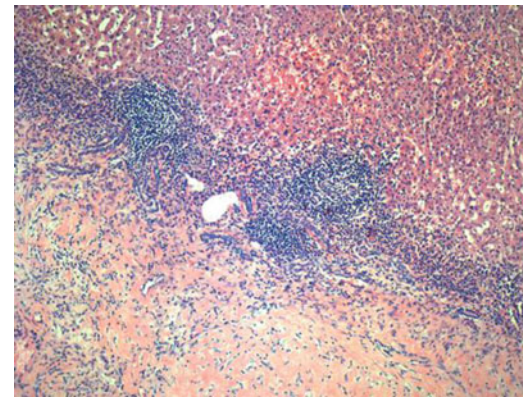

Fig. 8 Hepatic colorectal carcinoma metastasis with immune reaction. The metastatic nodule (*lower part of figure*) has undergone regression and fibrosis. At the tumor-liver interface, dense lymphocytic infiltrates with lymph follicles are found (hematoxylin and eosin stain)

(tumor-infiltrating lymphocytes) at the advancing margin of CRC have a favorable prognosis (Svennevig et al. 1984; Jass 1986; Ropponen et al. 1997).

In primary CRC, several pattern of lymphocyte-rich infiltrates can be distinguished. A rather common phenomenon is the presence of a discontinuous or, less often, a continuous band of lymphocytes located in the region of the advancing margin. Sometimes, this infiltration band is found between the epithelial front of the carcinoma and the adjacent liver, i.e., within the interposed stromal lamella. Here, the lymphocyte infiltrate may be admixed with plasma cells, macrophages, and granulocytes. In other cases, the lymphocytes predominate in the compartment of the invading carcinoma proper, i.e., intermingled with cancer cells and their intratumoral stroma. This phenomenon is only seen in viable-looking (chiefly peripheral) parts of the metastasis, whereas more deeply seated and often necrotic parts of the metastasis show few or no lymphocytes. Small lymphocytes are seen to infiltrate the epithelial formations themselves, whereby the lymphocytes are located between adjacent tumor cells and sometimes also in the lumina of tubular or cribriform structures. Foci of intraepithelial lymphocytes may be associated with tumor cell apoptosis, with formation of cell debris and typical, eosinophilic apoptotic bodies. Emperipolesis

of leukocytes may occur. In areas of dense intratumoral infiltrates, lymphocytes are observed within small tumor vessels, sometimes directly attached to the endothelium, probably representing effector cell homing. This phenomenon may also be noted within tumor stroma (particularly in the stroma interposed between the tumor front and the liver) and in hepatic sinusoids close to the invading tumor. Increased peritumoral lymphocytes and tumor-infiltrating lymphocytes are associated with tumor cell budding in primary CRC (Zlobec et al. 2007). Tumor-infiltrating lymphocytes are mainly T lymphocytes with cytotoxic activity directed against autologous tumor cells (Hom et al. 1993; Fossum et al. 1994). A further important class of T lymphocytes engaged in antitumor activity are regulatory T cells (Tregs) which accumulate within metastases. In CRC metastases, Tregs suppress the development and progression of these metastases through overcoming IL-17-producing T cells (Wang et al. 2014). Immunohistochemically, CD3+ and CD8+ small lymphocytes clearly prevail, and the intra-cancer and specifically intraepithelial infiltration is well demonstrable with these immunostains. The tumor-infiltrating T cells secrete cytokines in response to tumor stimulation in CRC (Diederichsen et al. 1999), and their antitumor effects may be mediated by this cytokine secretion. It has been shown that secretion of interleukin-4 and tumor necrosis factor-alpha by tumor-infiltrating lymphocytes in CRC confers improved survival (Barth et al. 1996). There are, however, also local factors that may blunt the antitumor T cell response. Reduced CD3-zeta chain, an important signaling component of the T cell receptor, is involved in incomplete cellular activation and antitumoral cytotoxicity of tumor-associated lymphocytes in CRC metastases (Yoong and Adams 1998). Another pathway for inhibiting lymphocyte-mediated antitumor immune responses is the induction of lymphocyte apoptosis and subsequent local lymphocyte depletion by tumor cells. Various cancer cell types have been shown to express Fas ligand (FasL) and to kill lymphoid cells by Fas-mediated apoptosis, thus causing apoptotic lymphocyte depletion within the Fas ligand-expressing tumors (Bennett et al. 1998). In CRC, expression of FasL was detected on the surface and within the cytoplasm of carcinoma cells in 61 % of the cases and was associated with apoptosis of tumor-infiltrating lymphocytes (Okada et al. 2000). Immunohistochemically, marked apoptotic death of T cells within the tumor is sometimes visualized in the form of CD3+ tiny apoptotic bodies or cellular debris or, in case of dense decaying infiltrates, a CD3+ granular material.

Apart from lymphocytes of several classes, macrophages are also present in hepatic CRC metastases, often located in the peripheral invasion front and/or in the stromal tissue surrounding the metastasis. Morphometric studies revealed that the macrophages are accumulated and activated in peritumoral regions of CRC metastases (Miyagawa et al. 2002). Parts of these macrophages home to the tumors as circulating monocytes and monocytoid cells. Hepatic macrophages mediate the adhesion of CRC cells to sinusoidal endothelial cells by cytokines (Gangopadhyay et al. 1998). A second population of CRC metastasis-associated macrophages is recruited from hepatic Kupffer cells (Meterissian et al. 1994; Paschos et al. 2010; Dent 2013; Wen et al. 2013). Kupffer cells are detectable in close spatial association as vimentin-positive spider-shaped cells (Wu et al. 1996) and play a role in arresting circulating tumor cells in hepatic sinusoids (Bayon et al. 1996). In an orthotopic murine model of CRC liver metastasis, it turned out that Kupffer cells have a bimodal role in determining tumor growth, in that these macrophages had an early inhibitory and late stimulating effect (Wen et al. 2013).

The survival advantage of pronounced lymphocytic infiltration in primary CRC is known for many years and has already been commented in 1931 (McCarthy 1931), and the phenomenon has since been reported several times (Zamcheck et al. 1975; Watt and House 1978; Thynne et al. 1980; Carlon et al. 1984; Svennevig et al. 1984; Jass 1986). In primary CRC, multivariate analysis showed that tumor-infiltrating lymphocytes were an independent prognostic factor of overall and recurrence-free survival in all cases ($N = 276$), as well as in patients with

T1-4N0-3M0 and T1-4N1-3M1 (Ropponen et al. 1997). Absence of CD8+ tumor-infiltrating lymphocytes was predictive of an adverse prognosis in patients with lymph node-negative, mismatch repair-proficient CRC (Zlobec et al. 2008). Similarly, CRC liver metastasis-associated lymphocytic infiltration is a significant prognostic factor for cancer-related survival after hepatectomy (Nagashima et al. 1999). Among 41 patients who underwent initial hepatic resection for hepatic CRC metastases, 44 % of the tumors showed a dense lymphocytic infiltration between the metastases and adjacent liver. Histologically, tumor invasion of the portal vein was rare in patients with dense infiltrates (12 %) compared with patients with weak infiltrates (36 %). Patients with dense lymphocytic infiltration phenotype exhibited a longer survival (Okano et al. 2003). There are, however, also studies failing to show a significant difference in survival between patients with conspicuous peritumoral infiltrate and those without it (Cianchi et al. 1997). An important role played by immune reactions is supported by the observation of rapid metastatic spread of CRCs following immunosuppression, e.g., due to solid organ transplantation (Lin et al. 2010). Although there is strong evidence that immune reactions located to CRC metastases have a protective effect, there are also findings that show a metastasis-promoting effect. For example, a host inflammatory response promotes liver metastasis through increasing intravascular tumor cell arrest and extravasation (Auguste et al. 2007).

Intraductal Growth of CRC Metastasis

Introduction

In primary liver cancers, intrabiliary invasion and growth are well-known growth patterns and have been documented for both hepatocellular carcinoma and cholangiocarcinoma (Lin et al. 1975; Kojiro et al. 1982; Yamamoto et al. 1997; Iyomasa et al. 1999; Suh et al. 2000; Nishio et al. 2002). The frequency of gross biliary tract invasion of hepatic colorectal cancer metastases is less frequently described in the literature, but the reported data depend on the demonstration of macroscopic vs. microscopic bile duct invasion. The phenomenon has been shown in one report to occur in about 10 % of surgically resected specimens (Okano et al. 1999), while other authors regard this pattern as rare (Tomizawa et al. 2003). In another investigation, 6 of 103 patients undergoing hepatectomy for colorectal liver metastases had macroscopic intrabiliary tumor growth (Sugiura et al. 2006). However, massive bile duct invasion by colorectal cancer metastases is much rarer. Intrabiliary cancer thrombi associated with biliary tract dilation is visualized by imaging techniques, including CT imaging (Okano et al. 2002). In one study, macroscopic intrabiliary tumors were detected pre- or intraoperatively by use of CT, ultrasonography, and intraoperative ultrasonography (Sugiura et al. 2006). Percutaneous transhepatic cholangiography reveled typical and circumscribed filling defects with the morphology of bulging masses (Sugiura et al. 2006). In case of involvement of the common bile duct or the confluence region by cancers, obstructive jaundice can be the leading sign (Thompson et al. 1993).

Selected References Herbut and Watson 1946; Nagler and Rochwarger 1977; Warshaw and Welch 1978; Gray et al. 1982; Sung et al. 1988; Riopel et al. 1997; Okano et al. 1999; Rullier et al. 1999; Povoski et al. 2000; Kubo et al. 2002; Tomizawa et al. 2003; Takamatsu et al. 2004; Uehara et al. 2004; Sugiura et al. 2006; Tokai et al. 2006; Estrella et al. 2013; Coppola et al. 2014; Peungjesada et al. 2013.

It has been proposed that intrabiliary extension of hepatic colorectal cancer metastases is associated with better prognosis (Okano et al. 1999; Kubo et al. 2002), but whether this is in fact a reproducible effect has to be investigated in systematic studies in more detail. For example, intraductal growth may be associated with an increased rate

of portal vein invasion (Sugiura et al. 2006), what will have an impact of prognosis.

Pathology

Macroscopy

The main features of the lesions have been compiled in a landmark article (Riopel et al. 1997). The intraductal component presents in one of several gross growth patterns, i.e., polypoid, papillary, and nodular patterns. The intraductal tumor is sometimes in direct contact with a mass of extraductal metastasis, but in part of the cases, only an intraductal tumor is seen macroscopically, closely resembling intraductal cholangiocarcinoma. In a study of 149 patients with first colorectal liver metastases, the 18 patients with gross intraductal extensions showed intraductal tumors measuring 4–42 mm in diameter (median: 17 mm; Okano et al. 1999). The duct stenosis caused by intraductal metastases can induce marked intrahepatic bile duct dilatation (Jhaveri et al. 2009). The wedge-shaped area seen on CT images in part of the cases was visualized as a well-demarcated dark red-brown region in the cut surface of resected specimens (Okano et al. 2002).

Grossly, intrabiliary manifestations of metastasis were described as prominent and soft papillary masses that extend into the intrahepatic ducts (Takamatsu et al. 2004). These lesions are usually more friable than intraparenchymal metastases and may show the morphology of a sessile polyp. They are usually more circumscribed than intraductal cholangiocarcinoma and commonly are not adhesive to the bile duct wall (Takamatsu et al. 2004). The cut surface of a fresh resection specimen may also show a whitish nodule of metastatic carcinoma within a large portal triad, bulging from the surface, sometimes misinterpreted as a satellite nodule (Riopel et al. 1997). In such a situation, intraductal growth is easily demonstratable by use of the points as small forceps that can be introduced between the tumor and the mucosal surface of the bile duct. Some metastases with intrabiliary growth show only a minimal invasion of adjacent liver parenchyma (Uehara et al. 2004).

Histopathology

Histopathological detection of intraductal growth of colorectal liver metastasis is much more frequent than the gross detection of this type of lesion. In one analysis, bile duct invasion was histologically observed in 42 % of 149 patients (Okano et al. 1999). A second study documented histological bile duct involvement of colorectal metastases even in 81 % of 151 patients, mostly intraepithelial ductal spread of CRC cells confirmed with CK7/CK20 immunohistochemistry (Wakai et al. 2011). Metastatic adenocarcinomas with intraductal growth may present both extraductal and intraductal manifestations, or be restricted to the intraductal space without evidence of extraductal disease. As in other intraluminally growing carcinomas, a papillary structure is common. Colorectal carcinoma invading intrahepatic bile ducts can show an exophytic, papillary growth resembling that of cholangiocarcinomas, but the cytologic features of the metastatic tumor differs from cholangiocarcinoma cells (Colagrande et al. 2004). Histologically, these villous growths may involve larger parts of the intrahepatic biliary tree, extending into peripheral branches distal to a bifurcation. The metastatic carcinoma may replace the epithelial lining of the invaded duct and extends along the epithelium (Tokai et al. 2006). In part of these cases, the intramucosal growth pattern closely resembled high-grade dysplasia or carcinoma in situ (Riopel et al. 1997). Intraductal metastases sometimes exhibit only minimal invasion of liver parenchyma (Uehara et al. 2004). In intramucosal or intraepithelial extension, carcinoma cells advance along the intact-looking basement membrane and replace the nonneoplastic biliary ductal epithelium. Interestingly, no intraepithelial extension advanced beyond the intraluminal extension, whereas in the proximal direction, the distance between the end of the macroscopical intraluminal extensions and intraepithelial extensions ranged

from 4 to 10 mm (Sugiura et al. 2006). The macroscopic friability of intraductal lesions of metastases is caused by poor stroma formation in contrast to intraparenchymatous metastatic foci. In contrast to intraductal cholangiocarcinoma, the transition between tumor cells and the nonneoplastic bile duct epithelium is abrupt (Takamatsu et al. 2004). Whereas extraductal metastatic tumor tissue usually reveals a marked stromal reaction, desmoplasia is mostly poor in the intraductal tumor part, but vascular stalks accompanied by stromal cells are sometimes noted.

Immunohistochemistry

CRC metastases to the liver generally reflect the immunophenotype of the primary colorectal lesions. In one patient with an intraductal colorectal metastasis, the tumor cells were CK7 negative but CK20 positive, supporting the immunophenotype of colorectal adenocarcinoma (Uehara et al. 2004; Kayashima et al. 2008; Seshadri and Majhi 2009; Wakai et al. 2011) and rendering cholangiocarcinoma much less likely (Tot 1999; Rullier et al. 2000). There are, however, certain differences in expression pattern between primary and secondary tumors. Claudin-1 and E-cadherin expressions were elevated in CRC metastatic lesions (Kinugasa et al. 2012).

Differential Diagnosis

Adenocarcinoma metastasis with intraductal growth closely mimics intrahepatic cholangiocarcinoma radiologically, macroscopically, and histologically (Riopel et al. 1997; Wenzel et al. 2003; Colagrande et al. 2004; Seshadri and Majhi 2009). Part of intraductally growing CRC metastases showed marked mucin production (Tokai et al. 2006), a feature that may suggest primary intraductal mucinous tumors. However, cholangiocarcinomas have cytological and nuclear features clearly different from those of metastatic adenocarcinomas, in particular colorectal tumors. On the other hand, intraductal papillary cholangiocarcinoma may be misinterpreted to be intraductal colorectal metastasis (Itatsu et al. 2007). In cases of doubt, immunohistochemistry will be helpful to distinguish the tumors in question, specifically cytokeratins 7 and 20.

Colorectal Liver Metastases in the Pediatric Age Group

Introduction

Colorectal carcinoma (CRC) is rare in children with an estimated incidence of one child per one million/year. CRC has been observed in children younger than 1 year of age (adenocarcinoma in a 9-month-old infant; Kern and White 1958). The first case was probably reported by Clar in 1885, who recorded a case of carcinoma of the colon in a 3-year-old boy (Clar 1885). The literature documents several series and case reports, amounting to more than 300 reported cases. Hoerner (1958) was able to collect 73 cases of carcinomas of the colon and 189 of carcinoma of the rectum occurring in individuals under 20 years of age and published between 1865 and 1958. A Japanese review published 1991 listed 41 Japanese cases reported in this country so far (Taguchi et al. 1991). In a study of 21 patients with CRC younger than 30 years of age, only 4 patients (19 %) were less than 20 years old (Shahrudin and Noori 1997). In a large series of patients (77 patients covering ages 7–19 years), 76 patients had one or more signs or symptoms of CRC, such as abdominal pain, altered bowel habits, weight loss, and anemia. However, pediatric CRCs seem to more often present with signs of obstruction. Johnston (1947) estimated that at least 70 % of cases in children present with intestinal obstruction. The reason for this clinical manifestation is thought to be the more rapid progression of CRC in children (Salem and Postlethwait 1960) and the higher risk that diagnosis is missed in comparison with adults, owing to the rarity of the lesion in the pediatric age group. The tumors were evenly distributed between the right and left colon. At presentation, 86 % of patients had advanced-stage

disease, and more than half had distant metastases (Hill et al. 2007). Pediatric CRC can also develop in the setting of ulcerative colitis (Wilcox and Beattie 1956).

Selected References Saner 1946; Scholefield 1946; Johnston 1947; Buchman and Calhoun 1958; Hoerner 1958; Salem and Postlethwait 1960; Donaldson et al. 1971; Rao et al. 1985; Koh and Johnson 1986; Lamego and Torloni 1989; Brown et al. 1992; Ameh and Nmadu 2000; Kravarusic et al. 2007; and Ferrari et al. 2008.

The histopathology of pediatric CRC differs from that in adults. Parts of the tumors are classical adenocarcinomas of the colorectal type, but mucinous or colloid carcinoma (Buchman and Calhoun 1958; Tandon et al. 1985; Brown et al. 1992; Redkar et al. 1993; Malik and Kamath 2011) and signet ring-cell carcinoma (Takai et al. 1988; Pandey et al. 2008) also occur, the mucinous variant being particularly common in several studies, amounting to 50 % (Hoerner 1958; Ladd and Grosfeld 2006). In adolescents, the tumor was a poorly differentiated adenocarcinoma in the majority of cases (Odone et al. 1982). In a study of 110 CRC patients from Japan younger than 20 years of age, there was a high incidence of poorly differentiated carcinoma (51.5 % for poorly differentiated adenocarcinoma, signet-ring-cell carcinoma, and undifferentiated carcinoma) and a high proportion of advanced stage at diagnosis (67.1 % for clinical stages IIIb and IV) (Yamamoto et al. 1996).

Liver Metastases in Pediatric Colorectal Carcinoma

CRC in younger individuals is an aggressive disease that often presents with high stage at diagnosis and has a poor survival. This distinct feature has already been documented in the old literature (Scholefield 1946; Hoerner 1958). Several cases of liver metastases in pediatric colorectal carcinoma have been reported (Ko et al. 1995; Karnak et al. 1999; Ameh and Nmadu 2000; Kam et al. 2004; Hill et al. 2007; Pandey et al. 2008). Due to the small number of cases observed in children, it is currently not known whether the propensity to metastasize to the liver is similar to or different from CRCs of the adult age group, but CRC in young individuals is rapidly progressive, with a high rate of recurrence, both local and remote. In adolescents, the natural history of CRC was found to be characterized with extensive disease at diagnosis and unresponsiveness to medical management. In a study of 24 adolescent patients, this was reflected in an 8-month median survival from diagnosis (Odone et al. 1982). In a Turkish study on 20 patients, all presented with advanced stages of disease. Peritoneum was the most common site of extensive intraabdominal disease, followed by omentum majus and liver (Karnak et al. 1999). An investigation from Taiwan (28 patients 20 years old or less) demonstrated that proportion of mucinous adenocarcinoma was higher than that in the older population and that most cases were advanced at diagnosis (Dukes stages C or D), with an overall survival rate of only 21 % (Chen et al. 2001). In a study of Argentina, patients with CRC of the group covering 0–20 years of age revealed a high-risk group in comparison with older patients, in that this group had significantly more advanced disease and poorer prognosis (Chantada et al. 2005). In a subset of patients with CRC younger than 18 years, six out of seven had tumor progression or relapse, and five died of their tumor (Ferrari et al. 2008).

References

Ackerman NB (1974) The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. Surgery 75:589–596

Ackerman NB (1986) Experimental studies on the role of the portal circulation in hepatic tumor vascularity. Cancer 58:1653–1657

Adam R (2007) Colorectal cancer with synchronous liver metastases. Br J Surg 94:129–131. Resection for colorectal metastases: analysis of prognostic factors. Dis Colon Rectum 42:632–639

Ameh EA, Nmadu PT (2000) Colorectal adenocarcinoma in children and adolescents: a report of 8 patients from Zaria, Nigeria. West Afr J Med 19:273–276

Archer SG, Gray BN (1989) Vascularization of small liver metastases. Br J Surg 76:545–548

Assumpcao L, Choti MA, Gleisner AL, Schulick RD, Swartz M, Herman J, Gearhart SL, Pawlik TM (2008) Patterns of recurrence following liver resection for colorectal metastases: effect of primary rectal tumor site. Arch Surg 143:743–749

Auguste P, Fallavollita L, Wang N, Burnier J, Bikfalvi A, Brodt P (2007) The host inflammatory response promotes liver metastasis by increasing tumor cell arrest and extravasation. Am J Pathol 170:1781–1792

Barth R, Camp B, Martuscello T, Dain BJ, Memoli VA (1996) The cytokine microenvironment of human colon carcinoma. Cancer 6:1168–1178

Bayon LG, Izquierdo MA, Sirovich I, van Rooijen N, Beelen RH, Meijer S (1996) Role of Kupffer cells in arresting circulating tumor cells and controlling metastatic growth in the liver. Hepatology 23:1224–1231

Bengmark S, Hafstrom L (1969) The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma at laparotomy. Cancer 23:198–202

Bennett MW, O'Connell J, O'Sullivan GC, Brady C, Roche D, Collins JK, Shanahan F (1998) The Fas counterattack in vivo: apoptotic depletion of tumor-infiltrating lymphocytes associated with Fas ligand expression by human esophageal carcinoma. J Immunol 160:5669–5675

Bird NC, Mangnall D, Majeed AW (2006) Biology of colorectal liver metastases: a review. J Surg Oncol 94:68–80

Bizjak-Schwarzbartl M (1987) Fine-needle aspiration biopsy in the diagnosis of metastases in the liver. Diagn Cytopathol 3:278–283

Breedis C, Young G (1954) The blood supply of neoplasms in the liver. Am J Pathol 30:969–977

Brown RA, Rode H, Millar AJ, Sinclair-Smith C, Cywes S (1992) Colorectal carcinoma in children. J Pediatr Surg 27:919–921

Buchman JA, Calhoun JD (1958) Colloid carcinoma of the colon in children. Am Surg 24:280–286

Carlon CA, Fabris G, Arslan-Pagnini C, Pluchinotta AM, Chinelli K, Carniato S (1984) Prognostic correlations of operable carcinoma of the rectum. Dis Colon Rectum 28:47–50

Carpizo DR, Are C, Jarnagin W, Dematteo R, Fong Y, Gönen M, Blumgart L, D'Angelica M (2009) Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. Ann Surg Oncol 16:2138–2146

Casillas S, Dietz DW, Brand MI, Jones SC, Vladisavljevic A, Milsom JW (1997) Perfusion to colorectal cancer liver metastases is not uniform and depends on tumor location and feeding vessel. J Surg Res 67:179–185

Centeno BA (2006) Pathology of liver metastases. Cancer Control 13:13–26

Chantada GL, Perelli VB, Lombardi MG, Amaral D, Cascallar D, Scopinaro M et al (2005) Colorectal carcinoma in children, adolescents, and young adults. J Pediatr Hematol Oncol 27:39–41

Chen LK, Hwang SJ, Li AF, Lin JK, Wu TC (2001) Colorectal cancer in patients 20 years old or less in Taiwan. South Med J 94:1202–1205

Chu P, Wu EBS, Weiss LM (2000) Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. Mod Pathol 13:962–972

Cianchi F, Messerini L, Palomba A, Boddi V, Perigli G, Pucciani F, Bechi P, Cortesini C (1997) Character of the invasive margin in colorectal cancer: does it improve prognostic information of Dukes staging? Dis Colon Rectum 40:1170–1175

Clar F. (1885/1904). Quoted by H. Nothnagel, Diseases of the intestines and peritoneum. Saunders, Philadelphia

Colagrande S, Batignani G, Messerini L, Pinzani M (2004) Intrabiliary metastasis from rectal cancer mimicking peripheral papillary-type cholangiocarcinoma. J Hepatol 41:172–174

Conti JA, Kendall TJ, Bateman A, Armstrong TA, Papa-Adams A, Xu Q, Packham G et al (2008) The desmoplastic reaction surrounding hepatic colorectal adenocarcinoma metastases aids tumor growth and survival via alphav integrin ligation. Clin Cancer Res 14:6405–6413

Conzelmann M, Dieterle CP, Linnemann U, Berger MR (2003) Cytokeratin 20 and guanylyl cyclase C mRNA is largely present in lymph node and liver specimens of colorectal cancer patients. Int J Cancer 107:617–628

Conzelmann M, Linnemann U, Berger MR (2005) Molecular detection of clinical colorectal cancer metastasis: how should multiple markers be put to use? Int J Colorectal Dis 20:137–146

Coppola S, Zucchini N, Romano F, Bovo G, Gilardoni E, Nespoli L, Gianotti L (2014) Colorectal liver metastasis with intrabiliary growth: case report and review of the literature. Int J Surg Pathol 22:272–279

D'Angelica M, Ammori J, Gonen M, Klimstra DS, Low PS, Murphy L, Weiser MR et al (2011) Folate receptor-α expression in resectable hepatic colorectal cancer metastases: patterns and significance. Mod Pathol 24:1221–1228

Dent P (2013) Janus-faced Kupffer cells in tumor metastasis. Cancer Biol Ther 14:875–876

Dezsö K, Bugyik E, Papp V, Laszlo V, Döme B, Tovari J, Timar J, Nagy P, Paku S (2009) Development of arterial blood supply in experimental liver metastasis. Am J Pathol 175:835–843

Diederichsen AC, Zeuthen J, Christensen PB, Kristensen T (1999) Characterisation of tumor infiltrating lymphocytes and correlations with immunological surface molecules in colorectal cancer. Eur J Cancer 35:721–726

Dionne L (1965) The pattern of blood-borne metastasis from carcinoma of rectum. Cancer 18:775–781

Doci R, Gennari L, Bignami P et al (1991) One hundred patients with hepatic metastases from colorectal cancer

treated by resection: analysis of prognostic determinants. Br J Surg 78:797–801
Donaldson MH, Taylor P, Rawitscher R, Sewell JB (1971) Colon carcinoma in childhood. Pediatrics 48:307–312
Estrella JS, Othman ML, Taggart MW, Hamilton SR, Curley SA, Rashid A, Abraham SC (2013) Intrabiliary growth of liver metastases: clinicopathologic features, prevalence, and outcome. Am J Surg Pathol 37:1571–1579
Fennessy FM, Mortele KJ, Kluckert T, Gogate A, Ondategui-Parra S, Ros P, Silverman SG (2004) Hepatic capsular retraction in metastatic carcinoma of the breast occurring with increase or decrease in size of subjacent metastasis. AJR Am J Roentgenol 182:651–655
Ferrari A, Rognone A, Casanova M, Zaffignani E, Piva L, Collini P, Bertario L, Sala P et al (2008) Colorectal carcinoma in children and adolescents: the experience of the Istituto Nazionale Tumori of Milan, Italy. Pediatr Blood Cancer 50:588–593
Fossum B, Gedde-Dahl T, Breivik J, Eriksen JA, Spurkland A, Thorsby E, Gaudernack G (1994) p21-ras-peptide-specific T-cell responses in a patient with colorectal cancer. CD4+ T cells recognize a peptide corresponding to a common mutation. Int J Cancer 56:40–45
Fujii et al (2013) http://www.ncbi.nlm.nih.gov/pubmed/23933928
Gangopadhyay A, Lazure DA, Thomas P (1998) Adhesion of colorectal carcinoma cells to the endothelium is mediated by cytokines from CEA stimulated Kupffer cells. Clin Exp Metastasis 16:703–712
Gervaz P, Scholl B, Mainquene C, Poitry S, Gillet M, Wexner S (2000) Angiogenesis of liver metastases: role of sinusoidal endothelial cells. Dis Colon Rectum 43:980–986
Gray RR, Mackenzie RL, Alan KP (1982) Cholangiographic demonstration of carcinoma of the colon metastatic to the lumen of the common bile duct. Gastrointest Radiol 7:71–72
Haugeberg G, Strohmeyer T, Lierse W, Böcker W (1988) The vascularization of liver metastases. Histological investigation of gelatine-injected liver specimens with special regard to the vascularization of micrometastases. J Cancer Res Clin Oncol 114:415–419
Healey JE (1965) Vascular patterns in human metastatic liver tumors. Surg Gynecol Obstet 120:1187–1193
Herbut PA, Watson JS (1946) Metastatic cancer of the extrahepatic bile ducts producing jaundice. Am J Clin Pathol 16:365–372
Hill DA, Furman WL, Billups CA, Riedley SE, Cain AM, Rao BN, Pratt CB, Spunt SL (2007) Colorectal carcinoma in childhood and adolescence: a clinicopathologic review. J Clin Oncol 25:5808–5814
Hoerner MT (1958) Carcinoma of the colon and rectum in persons under twenty years of age. Am J Surg 96:47–53
Hom S, Rosenberg S, Topalian S (1993) Specific immune recognition of autologous tumor by lymphocytes infiltrating colon carcinomas: analysis by cytokine secretion. Cancer Immunol Immunother 36:1–8
Hughes KS, Simon R, Songhorabodi S et al (1986) Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns and recurrences. Surgery 100:278–284
Ikeguchi M, Makino M, Kaibara N (2001) Clinical significance of E-cadherin-catenin complex expression in metastatic foci of colorectal carcinoma. J Surg Oncol 77:201–207
Itatsu K, Fujii T, Sasaki M, Zen Y, Nakanuma Y (2007) Intraductal papillary cholangiocarcinoma and atypical biliary epithelial lesions confused with intrabiliary extension of metastatic colorectal carcinoma. Hepatogastroenterology 54:677–680
Iyomasa S, Nimura Y, Kamiya J, Maeda S, Kondo S, Yasui A, Yamamoto H, Anami Y et al (1999) Cholangiocellular carcinoma in the caudate lobe with intraluminal growth in the extrahepatic bile duct. Hepatogastroenterology 39:570–573
Jass JR (1986) Lymphocytic infiltration and survival in rectal cancer. J Clin Pathol 39:585–589
Jhaveri KS, Halankar J, Aguirre D, Haider M, Lockwood G, Guindi M, Fischer S (2009) Intrahepatic bile duct dilatation due to liver metastases from colorectal carcinoma. AJR Am J Roentgenol 193:752–756
Jin K, Gao W, Lu Y, Lan H, Teng L, Cao F (2012) Mechanisms regulating colorectal cancer cell metastasis into liver (review). Oncol Lett 3:11–15
Johnston JH (1947) Carcinoma of the colon in childhood and adolescence. Am J Surg 73:703–712
Josephson RL, Wallace AC (1974) Invasion of Glisson's capsule by metastatic tumour: transmission and scanning electron microscopic observations. Proc Am Assoc Cancer Res 15:82–87
Josephson RL, Wallace AC (1978) Invasion of the hepatic capsule by tumour metastases to the liver. Pathology 10:95–102
Kam MH, Eu KW, Barben CP, Seow-Choen F (2004) Colorectal cancer in the young: a 12-year review of patients 30 years or less. Colorectal Dis 6:191–194
Karnak I, Ciftci AO, Senocak ME, Büyükpamukçu N (1999) Colorectal carcinoma in children. J Pediatr Surg 34:1499–1504
Kayashima H, Taketomi A, Yamashita Y, Kuroda Y, Kitagawa D, Harimoto N, Tsujita E, Maehara Y (2008) Liver metastasis with intraductal invasion originating from rectal cancer: report of a case. Surg Today 38:765–768
Kern WH, White WC (1958) Adenocarcinoma of the colon in a 9-month-old infant. Cancer 11:855–857
Kinugasa T, Akagi Y, Ochi T, Tanaka N, Kawahara A, Ishibashi Y, Gotanda Y, Yamaguchi K et al (2012) Increased claudin-1 protein expression in hepatic metastatic lesions of colorectal cancer. Anticancer Res 32:2309–2314
Ko et al (1995) http://www.ncbi.nlm.nih.gov/pubmed/7618477

Koh SJ, Johnson WW (1986) Cancer of the large bowel in children. South Med J 79:931–935
Kojiro M, Kawabata K, Kawano Y, Shirai F, Takemoto N, Nakashima T (1982) Hepatocellular carcinoma presenting as intrabile duct tumor growth: a clinicopathologic study of 24 cases. Cancer 49:2144–2147
Kravarusic D, Feigin E, Dlugy E, Steinberg R, Baazov A, Erez I, Lazar L, Kapuller V et al (2007) Colorectal carcinoma in childhood: a retrospective multicenter study. J Pediatr Gastroenterol Nutr 44:209–211
Kubo M, Sakamoto M, Fukushima N, Yachida S, Nakanishi Y, Shimoda T, Yamamoto J, Moriya Y, Hirohashi S (2002) Less aggressive features of colorectal cancer with liver metastases showing macroscopic intrabiliary extension. Pathol Int 52:514–518
Kuruppu D, Christophi C, O'Brien PE (1997) Microvascular architecture of hepatic metastases in a mouse model. HPB Surg 10:149–157
Ladd AP, Grosfeld JL (2006) Gastrointestinal tumours in children and adolescents. Semin Pediatr Surg 15:37–47
Lamego CM, Torloni H (1989) Colorectal adenocarcinoma in childhood and adolescent. Report of 11 cases and review of the literature. Pediatr Radiol 19:504–508
Lamps LW, Folpe AL (2003) The diagnostic value of hepatocyte paraffin antibody 1 in differentiating hepatocellular neoplasms form nonhepatic tumors: a review. Adv Anat Pathol 10:39–43
Lash RH, Hart WR (1987) Intestinal adenocarcinomas metastatic to the ovaries. A clinicopathologic evaluation of 22 cases. Am J Surg Pathol 11:114–121
Lau SK, Prakash S, Geller SA, Alsabeh R (2002) Comparative immunohistochemical profile of hepatocellular carcinoma, cholangiocarcinoma, and metastatic adenocarcinoma. Hum Pathol 33:1175–1181
Lin TY, Chen KM, Chen YR, Lin WS, Wang TH, Sung JL (1975) Icteric type hepatoma. Med Chir Dig 4:267–270
Lin G, Lunderquist A, Hägerstrand I, Boijsen E (1984) Postmortem examination of the blood supply and vascular pattern of small liver metastases in man. Surgery 96:517–526
Lin CT, Cha TL, Wu ST, Chuang FP (2010) Acute fulminant colon cancer metastasis after renal transplantation. Rev Esp Enferm Dig 102:447–448
Liu Y, Matsui O (2007) Changes of intratumoral microvessels and blood perfusion during establishment of hepatic metastases in mice. Radiology 243:386–395
Maeda T, Kajiyama K, Adachi E, Takenaka K, Sugimachi K, Tsuneyoshi M (1996) The expression of cytokeratins 7, 19, and 20 in primary and metastatic carcinomas of the liver. Mod Pathol 9:901–909
Malik R, Kamath N (2011) Anorectal mucinous adenocarcinoma in child: a case report. Eur J Pediatr 170:1461–1463
McCarthy WG (1931) Principles of prognosis in cancer. J Am Med Assoc 96:30–33
Meterissian SH, Toth CA, Steele GD, Thomas P (1994) Kupffer cell/tumor cell interactions and hepatic metastasis in colorectal cancer. Cancer Lett 81:5–12
Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J et al (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 231:487–499
Miyagawa S, Miwa S, Soeda J, Kobayashi A, Kawasaki S (2002) Morphometric analysis of liver macrophages in patients with colorectal liver metastasis. Clin Exp Metastasis 19:119–125
Moll R, Löwe A, Laufer J, Franke WW (1992) Cytokeratin 20 in human carcinomas. Am J Pathol 140:427–447
Morrison C, Marsh W, Frankel WL (2002) A comparison of CD10 to pCEA, MOC-31, and hepatocyte for the distinction of malignant tumors of the liver. Mod Pathol 15:1279–1287
Murakami T, Kawada K, Iwamoto M, Akagami M, Hida K, Nakanishi Y, Kanda K, Kawada M et al (2013) The role of CXCR3 and CXCR4 in colorectal cancer metastasis. Int J Cancer 132:276–287
Nagashima et al (1999) http://www.ncbi.nlm.nih.gov/pubmed/10086660
Nagler J, Rochwarger AM (1977) Metastatic colon carcinoma simulating primary bile duct carcinoma via endoscopic cholangiography. Gastrointest Radiol 2:75–76
Nanashima A, Yamaguchi H, Sawai T, Yasutake T, Tsuji T, Jibiki M, Yamaguchi E et al (1999) Expression of adhesion molecules in hepatic metastases of colorectal carcinoma: relationship to primary tumours and prognosis after hepatic resection. J Gastroenterol Hepatol 14:1004–1009
Nanashima A, Yamaguchi H, Sawai T, Shibasaki S, Yasutake T, Tsuji T, Hidaka S et al (2002) Analysis of tumor morphology in metastatic colorectal cancer: does this classification have any clinical significance? J Gastroenterol 37:791–797
Nanashima A, Shibata K, Nakayama T, Tobinaga S, Araki M, Kunizaki M, Takeshita H et al (2009) Clinical significance of microvessel count in patients with metastatic liver cancer originating from colorectal carcinoma. Ann Surg Oncol 16:2130–2137
Ng IOL, Path MRC, Lai ECS, Ng MMT, Fan ST (1992) Tumor encapsulation in hepatocellular carcinoma: a pathologic study of 189 cases. Cancer 70:45–49
Niemann TH, Hughes JH, De Young BR (1999) MOC-31 aids in the differentiation of metastatic adenocarcinoma from hepatocellular carcinoma. Cancer 87:295–298
Nikfarjam N, Muralidharan V, Malcontenti-Wilson C, Christophi C (2003) Scanning electron microscopy study of the blood supply of human colorectal liver metastases. EJSO 29:856–861
Nishio H, Miyata K, Hanai M, Kato M, Yoneyama F, Kobayashi Y (2002) Resection of an icteric type hepatoma with tumor thrombi filling the right posterior bile duct. Hepatogastroenterology 49:1682–1685
Odone V, Chang L, Caces J, George SL, Pratt CB (1982) The natural history of colorectal carcinoma in adolescents. Cancer 49:1716–1720

Ohlsson B, Stenram U, Tranberg KG (1998) Resection of colorectal liver metastases: 25-year experience. World J Surg 22:268–276

Okada K, Komuta K, Hashimoto S, Matsuzaki S, Kanematsu T, Koji T (2000) Frequency of apoptosis of tumor-infiltrating lymphocytes induced by fas counterattack in human colorectal carcinoma and its correlation with prognosis. Clin Cancer Res 6:3560–3564

Okano K, Yamamoto J, Moriya Y, Akasu T, Kosuge T, Sakamoto M, Hirohashi S (1999) Macroscopic intrabiliary growth of liver metastases from colorectal cancer. Surgery 126:829–834

Okano K, Yamamoto J, Kosuge T, Yamamoto S, Sakamoto M, Nakanishi Y, Hirohashi S (2000) Fibrous pseudocapsule of metastatic liver tumors from colorectal carcinoma. Clinicopathologic study of 152 first resection cases. Cancer 89:267–275

Okano K, Yamamoto J, Okabayashi T, Sugawara Y, Shimada K, Kosuge T, Yamasaki S, Furukawa H, Muramatsu Y (2002) CT imaging of intrabiliary growth of colorectal liver metastases: a comparison of pathological findings of resected specimens. Br J Radiol 75:497–501

Okano K, Maeba T, Moroguchi A, Ishimura K, Karasawa Y, Tzuishi K, Goda F, Usuki H et al (2003) Lymphocytic infiltration surrounding liver metastases from colorectal cancer. J Surg Oncol 82:28–33

Ong and Lean (2007) http://www.ncbi.nlm.nih.gov/pubmed/17499498

Oxley EM, Ellis H (1969) Prognosis of carcinoma of the large bowel in the presence of liver metastases. Br J Surg 56:149–152

Paku S, Lapis K (1993) Morphological aspects of angiogenesis in experimental liver metastases. Am J Pathol 143:926–936

Paku S, Kopper L, Nagy P (2005) Development of the vasculature in "pushing-type" liver metastases of an experimental colorectal cancer. Int J Cancer 115:893–902

Pandey A, Gangopadhyay A, Sharma S, Kumar V, Gupta D, Gopal S, Singh R (2008) Pediatric carcinoma of rectum – Varanasi experience. Indian J Cancer 45:119–122

Park SY, Kim HS, Hong EK, Kim WH (2002) Expression of cytokeratins 7 and 20 in primary carcinomas odf the stomach and colorectum and their value in the differential diagnosis of metastatic carcinomas to the ovary. Hum Pathol 33: 1078–1085

Paschos KA, Majeed AW, Bird NC (2010) Role of Kupffer cells in the outgrowth of colorectal cancer liver metastases. Hepatol Res 40:83–94

Peungjesada S, Aloja TA, Kaur H, Marcal L, Choi H, Vauthey JN, Loyer EM (2013) Intrabiliary growth of colorectal liver metastasis: spectrum of imaging findings and implications for surgical management. AJR Am J Roentgenol 201:W582–W589

Pickren JW, Tsukada Y, Lane WW (1982) Liver metastases: analysis of autopsy data. In: Weiss L, Gilbert MA (eds) Liver metastasis. G.K. Hall, Boston

Pinheiro RS, Herman P, Luipinacci RM, Lai Q, Mello ES, Coelho FF, Perini MV et al (2014) Tumor growth pattern as predictor of colorectal liver metastasis. Am J Surg 207:493–498

Porcell AI, De Young BR, Proca DM, Frankel WL (2000) Immunohistochemical analysis of hepatocellular and adenocarcinoma in the liver: MOC31 compares favorably with other putative markers. Mod Pathol 13:773–778

Povoski SP, Klimstra DS, Brown KT, Schwartz LH, Kurtz RC, Jarnagin WR, Fong Y, Blumgart LH (2000) Recognition of intrabiliary hepatic metastases from colorectal adenocarcinoma. HPB Surg 11:383–390

Proca DM, Niemann TH, Porcell AI, DeYoung BR (2000) MOC13 immunoreactivity in primary and metastatic carcinoma of the liver. Report of findings and review of other utilized markers. Appl Immunohistochem Mol Morphol 8:120–125

Rao BN, Pratt CB, Fleming ID, Dilawari RA, Green AA, Austin BA (1985) Colon carcinoma in children and adolescents. A review of 30 cases. Cancer 55:1322–1326

Redkar RG, Kulkarni BK, Naik A, Borweankar SS (1993) Colloid carcinoma of rectum in a 11 year old child. J Postgrad Med 39:218–219

Rees M, Plant G, Bygrave S (1997) Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg 84:1136–1140

Ridge JA, Bading JR, Gelbard AS, Benua RS, Daly JM (1987) Perfusion of colorectal hepatic metastases. Relative distribution of flow form the hepatic artery and portal vein. Cancer 59:1547–1553

Riopel MA, Klimstra DS, Godellas CV, Blumgart LH, Westra WH (1997) Intrabiliary growth of metastatic colonic adenocarcinoma: a pattern of intrahepatic spread easily confused with primary neoplasia of the biliary tract. Am J Surg Pathol 21:1030–1036

Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM (1997) Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 182:318–324

Ruers T, Bleichroth PR (2002) Treatment of liver metastases, and update on the possibilities and results. Eur J Cancer 38:1023–1033

Rullier A, Le Bail B, Rullier E, Lamouliatte H, Saric J, Bioulac-Sage P (1999) Three deceptive cases of intrahepatic metastases of colorectal origin with endobiliary growth, simulating cholangiocarcinoma. Importance of immunostaining of cytokeratin 7 and 20. Ann Pathol 19:33–36

Rullier A, Le Bail B, Fawaz R, Blanc JF, Saric J, Bioulac-Sage P (2000) Cytokeratin 7 and 20 expression in cholangiocarcinomas varies along the biliary tract but still differs from that in colorectal carcinoma metastasis. Am J Surg Pathol 24:870–876

Salem M, Postlethwait RW (1960) Malignancy of colon and rectum in patients under 20 years of age. Ann Surg 151:335–337

Sanchez Pérez MA, Rodriguez Pérez A, Geijo Martinez F, Gonzalez San Martin F, Rodriguez Rincon M et al (1995) Calcified hepatic metastases as the first manifestation of colonic cancer (in Spanish). Rev Esp Enferm Dig 87:268–269

Saner FD (1946) A case of carcinoma coli in a child. Br J Surg 34:398–400

Scheele J, Stang R, Altendorf-Hofmann A, Paul M (1995) Resection of colorectal liver metastases. World J Surg 19:59–71

Scholefield J (1946) Carcinoma of colon in youth of 17 causing acute intestinal obstruction. Br Med J 2:461

Schulz W, Hagen C, Hort W (1985) The distribution of liver metastases from colonic cancer. A quantitative postmortem study. Virchows Arch Pathol Anat 406:279–284

Seshadri RA, Majhi U (2009) Endobiliary metastasis from rectal cancer mimicking intrahepatic cholangiocarcinoma: a case report and review of literature. J Gastrointest Cancer 40:123–127

Shahrudin MD, Noori SM (1997) Cancer of the colon and rectum in the first three decades of life. Hepatogastroenterology 44:441–444

Shimonishi T, Miyazaki K, Nakanuma Y (2000) Cytokeratin profile relates to histological subtypes and intrahepatic location of intrahepatic cholangiocarcinoma and primary sites of metastatic adenocarcinoma of liver. Histopathology 37:55–63

Shiran MS, Isa MR, Sherina MS, Rampal L, Hairuszah I, Sabariah AR (2006) The utility of hepatocyte paraffin 1 antibody in the immunohistochemical distinction of hepatocellular carcinoma from cholangiocarcinoma and metastatic carcinoma. Malays J Pathol 28:87–92

Siddiqui MT, Saboorian MH, Gokaslan ST, Ashfaq R (2002) Diagnostic utility of the Hep Par1 antibody to differentiate hepatocellular carcinoma from metastatic carcinoma in fine-needle aspiration samples. Cancer 96:49–52

Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M (2006) Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 94:982–999

Slesser AA, Georgiou P, Brown G, Mudan S, Goldin R, Tekkis P (2013) The tumour biology of synchronous and metachronous colorectal liver metastases: a systematic review. Clin Exp Metastasis 30:457–470

Soyer P, Bluemke DA, Vissuzaine C, Beers BV, Barge J, Levesque M (1994) CT of hepatic tumors: prevalence and specificity of retraction of the adjacent liver capsule. AJR Am J Roentgenol 162:1119–1122

Sugiura T, Nagino M, Oda K, Ebata T, Nishio H, Arai T, Nimura Y (2006) Hepatectomy for colorectal liver metastases with macroscopic intrabiliary tumor growth. World J Surg 30:1902–1908

Suh KS, Roh HR, Koh YT, Lee KU, Park YH, Kim SW (2000) Clinicopathologic features of the intraductal growth type of peripheral cholangiocarcinoma. Hepatology 31:12–17

Sung MW, Bruckner HW, Szabo S, Mitty HA (1988) Extrahepatic obstructive jaundice due to colorectal cancer. Am J Gastroenterol 83:267–270

Svennevig JL, Lunde OC, Holter J, Bjorksvik D (1984) Lymphoid infiltration and prognosis in colorectal carcinoma. Br J Cancer 49:375–377

Taguchi T, Suita S, Hirata Y, Ishii E, Ueda K (1991) Carcinoma of the colon in children: a case report and review of 41 Japanese cases. J Pediatr Gastroenterol Nutr 12:394–399

Takai S, Yamamura M, Sakaguchi M, Uetsuji S, Yamamoto M (1988) Carcinoma of the colon in children: report of a case and review of the literature. Jpn J Surg 18:341–345

Takamatsu S, Teramoto K, Kawamura T, Kudo A, Noguchi N, Irie T, Ochiai T, Kumagau J, Koike M, Arii S (2004) Liver metastasis from rectal cancer with prominent intrabile duct growth. Pathol Int 54:440–445

Tandon R, Sharma U, Gupta S, Mathur K (1985) Mucinous adenocarcinoma of the colon in a child. J Indian Med Assoc 83:379–381

Terayama N, Terada T, Nakanuma Y (1996a) Histologic growth patterns of metastatic carcinomas of the liver. Jpn J Clin Oncol 26:24–29

Terayama N, Terada T, Nakanuma Y (1996b) A morphometric and immunohistochemical study on angiogenesis of human metastatic carcinomas of the liver. Hepatology 24:816–819

Thompson JF, Mathur MN, Coates AS (1993) Common bile duct obstruction due to intraluminal metastatic melanoma. Aust N Z J Surg 63:502–504

Thynne GS, Weiland LH, Moertel CG, Silvers A (1980) Correlation of histopathologic characteristics of primary tumor and uninvolved regional nodes in Dukes' C colonic carcinoma with prognosis. Mayo Clin Proc 55:243–245

Tokai H, Kawashita Y, Eguchi S, Kamohara Y, Takatsuki M, Okudaira S, Tajima Y, Hayashi T, Kanematsu T (2006) A case of mucin producing liver metastases with intrabiliary extension. World J Gastroenterol 12:4918–4921

Tomizawa N, Ohwada S, Tanahashi Y, Ikeya T, Ito H, Takeyoshi I, Morishita Y (2003) Liver metastasis of rectal cancer with intraluminal growth in the extrahepatic bile duct. Hepatogastroenterology 50:1625–1627

Tot T (1999) Adenocarcinomas metastatic to the liver: the value of cytokeratins 20 and 7 in the search for unknown primary tumors. Cancer 85:171–177

Tot T (2002) Cytokeratins 20 and 7 as biomarkers: usefulness in discriminating primary from metastatic adenocarcinoma. Eur J Cancer 38:758–763

Tot T (2004) Identifying colorectal metastases in liver biopsies: the novel CDX2 antibody is less specific than the cytokeratin 20+/CK7- phenotype. Med Sci Monit 10:BR139–BR143

Tot T, Samii S (2003) The clinical relevance of cytokeratin phenotyping in needle biopsy of liver metastasis. APMIS 111:1075–1082

Uehara K, Hasegawa H, Ogiso S, Sakamoto E, Igami T, Ohira S, Mori T (2004) Intrabiliary polypoid growth of liver metastasis from colonic adenocarcinoma with minimal invasion of the liver parenchyma. J Gastroenterol 39:72–75

Van den Eynden GG, van Dam PJ, Stroobants S, Dirix L, Vermeulen P, Liver Metastasis Research Network (2014) Histopathological evaluation of resected colorectal cancer liver metastasis: what should be done? Histopathology 64:315–316

Wakai T, Korita PV, Ajioka Y, Inoue M, Takamura M, Akazawa K, Shirai Y, Hatakeyama K (2011) Intraepithelial ductal spread in colorectal carcinoma liver metastasis. Hepatogastroenterology 58:583–588

Wang JY, Chiang JM, Jeng LB et al (1996) Resection of liver metastases from colorectal cancer: are there any truly significant clinical prognosticators? Dis Colon Rectum 39:847–851

Wang XF, Wang HS, Zhang F, Guo Q, Wang H, Wang KF, Zhang G, Bu XZ, Cai SH et al (2014) Nodal promotes the generation of M2-like macrophages and downregulates the expression of IL-12. Eur J Immunol 44:173–183

Warshaw AL, Welch JP (1978) Extrahepatic biliary obstruction by metastatic colon carcinoma. Ann Surg 188:593–597

Watt AG, House AK (1978) Colonic carcinoma. A quantitative assessment of lymphocyte infiltration at the periphery of colonic tumors related to prognosis. Cancer 41:279–282

Wauters CCAP, Smedts F, Gerrits LGM, Bosman MT, Ramaekers FC (1995) Keratin 7 and 20 as diagnostic markers of carcinomas metastatic to the ovary. Hum Pathol 26:852–855

Wen SW, Ager EI, Christophi C (2013) Bimodal role of Kupffer cells during colorectal cancer liver metastasis. Cancer Biol Ther 14:606–613

Wenzel DJ, Gaede JT, Wenzel LR (2003) Case report. Intrabiliary colonic metastasis mimicking primary biliary neoplasia. AJR Am J Roentgenol 180:1029–1032

Wilcox and Beattia (1956) http://www.ncbi.nlm.nih.gov/pubmed/13339742

Willis RA (1973) Spread of tumors in the human body. Butterworth and Co., London

Wong NACS, Neville LP (2007) Specificity of intra-acinar necrosis as a marker of colorectal liver metastasis. Histopathology 51:709–731

Wu HH, Tao LC, Cramer HM (1996) Vimentin-positive spider-shaped Kupffer cells. A new clue to cytologic diagnosis of primary and metastatic hepatocellular carcinoma by fine-needle aspiration biopsy. Am J Clin Pathol 106:517–521

Xu B, Shen F, Cao J, Jia L (2013) Angiogenesis in liver metastasis of colorectal carcinoma. Front Biosci (landmark Ed) 18:1435–1443

Yamamoto J, Sugihara K, Kosuge T, Takayama T, Shimada K, Yamasaki S, Sakamoto M et al (1995) Pathologic support for limited hepatectomy in the treatment of liver metastases from colorectal cancer. Ann Surg 221:74–78

Yamamoto T, Matsumoto K, Itiyama K (1996) Colorectal cancer in a patient younger than 20 years of age: report of a case and a review of the Japanese literature. Surg Today 26:810–813

Yamamoto J, Kosuge T, Takayama T, Shimada K, Yamasaki S, Sakamoto M, Hirohashi S, Makuuchi M (1997) Intrahepatic cholangiocarcinoma presenting intrabile duct extension: clinicopathologic study of five resected cases. Jpn J Clin Oncol 27:18–21

Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Sakamoto M, Fukuda H (1999) Factors influencing survival of patients undergoing hepatectomy for colorectal metastases. Br J Surg 86:332–337

Yasui K, Hirai T, Kato T, Torii A, Uesaka K, Morimoto T et al (1997) A new macroscopic classification predicts prognosis for patients with liver metastases from colorectal cancer. Ann Surg 226:582–586

Yoong KF, Adams DH (1998) Interleukin 2 restores CD3-zeta chain expression but fails to generate tumor-specific lytic activity in tumor-infiltrating lymphocytes derived from human colorectal hepatic metastases. Br J Cancer 77:1072–1081

Yu DC, Chen J, Ding YT (2010) Hypoxic and highly angiogenic non-tumor tissues surrounding hepatocellular carcinoma: the 'niche' of endothelial progenitor cells. Int J Mol Sci 11:2901–2909

Zamcheck N, Doos WG, Prudente R, Lurie BB, Gottlieb LS (1975) Prognostic factors in colon carcinoma. Correlation of serum carcinoembryonic antigen level and tumor histopathology. Hum Pathol 6:31–45

Zimmerman RL, Das KM, Fogt F, Burke M, Murakata LA (2002) The Das-1 immunostain is useful for discriminating metastatic colon adenocarcinoma from cholangiocarcinoma and hepatocellular carcinoma. Oncol Rep 9:1369–1372

Zlobec I, Lugli A, Baker K, Roth S, Minoo P, Hayashi S, Terracciano L, Jass JR (2007) Role of APAF-1, E-cadherin and peritumoral lymphocytic infiltration in tumour budding in colorectal cancer. J Pathol 212:260–268

Zlobec I, Minoo P, Baumhoer D, Baker K, Terracciano L, Jass JR, Lugli A (2008) Multimarker phenotype predicts adverse survival in patients with lymph node-negative colorectal cancer. Cancer 112:495–502

Metastatic Liver Disease: Tumors Other Than Colorectal Carcinoma

108

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_108

Abstract

Apart from the common colorectal carcinoma (CRC) metastases, malignancies that relatively often metastasize to the liver include small cell carcinoma of the lung, breast cancers, thyroid carcinoma of various types, gastric cancer, malignant melanoma of the skin and eye, and cancers of the genitourinary tract. In addition to the type, anatomic location, and local stage of a malignancy, its differentiation grade markedly influences propensity to metastasize to the liver. As in CRC, molecular and in particular genomic features will in the future be important means to predict metastatic disease. There is a large group of malignancies that metastasize to the liver less commonly than CRC and the cancers listed above. They mainly comprise squamous cell carcinoma of the skin and mucous membranes, ovarian carcinomas, and salivary gland tumors. Almost any type of sarcoma can metastasize to the liver, but hepatic sarcoma metastasis is generally less common than that of carcinomas. Very rarely, meningeal tumors and neoplasms of the central nervous system (CNS) produce liver metastases, sometimes via a shunt. A challenging group of hepatic metastases are those without, or not yet, identifiable primary tumor (cancer of unknown primary location, CUPL).

Common Hepatic Metastases of Non-sarcomatous Malignancies other than CRC

Non-CRC carcinomas that typically metastasize to the liver, sometimes in a massive manner, include small cell carcinoma of the lung, breast cancer, thyroid cancer of various types, gastric cancer, malignant melanoma of the skin, uveal melanoma, and cancers of the genitourinary tract (Figs. 1 and 2). Carcinoma of the prostate can metastasize more often than previously thought (Pouessel et al. 2007). It is still very difficult to estimate which primary tumors will be prone to produce metastases. For example, analysis of a series of recurrent breast cancers uncovered that

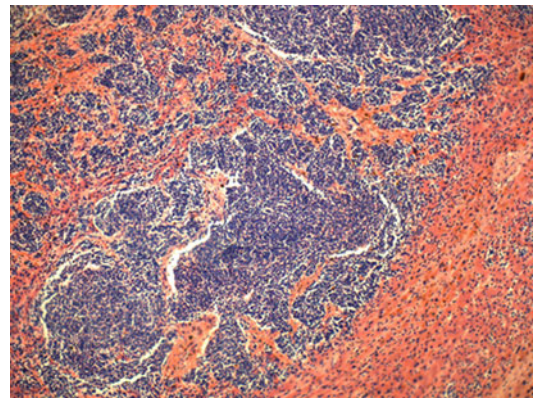

Fig. 1 Liver metastasis of bronchial small cell carcinoma (hematoxylin and eosin stain)

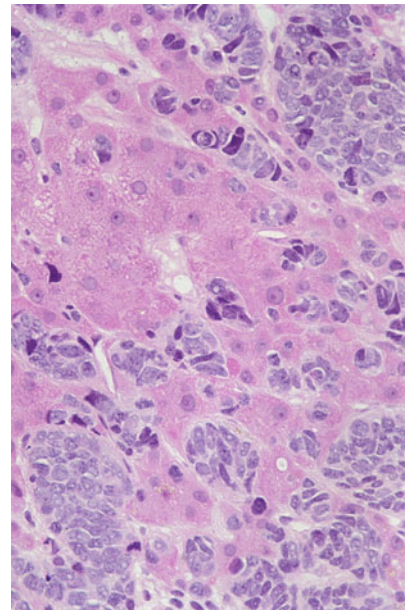

Fig. 2 Intrasinusoidal metastatic spread of bronchial small cell carcinoma (hematoxylin and eosin stain)

the presence of liver metastases was not associated with patient age, menopausal status, size of primary tumor, regional lymph node status, or the length of the recurrence-free interval, but patients with liver metastases were significantly closer to menopause than those without (Kamby et al. 1987). The propensity to metastasize to the liver is often dependent on the differentiation grade of the neoplasms in question. For example, anaplastic thyroid carcinomas were found to have

metastasized in 20 % of patients, whereas hepatic metastases of differentiated carcinomas of the thyroid are an uncommon event. A well known of malignancies metastasizing to the liver is neuroendocrine tumors, mainly originating from the gastrointestinal tract and the pancreas, whereby midgut carcinoid tumors are a particularly important example of metastasizing neoplasms. Although the appendix is an important location of carcinoids, it only rarely gives rise to hepatic metastases. Similarly, rectal carcinoids less than 2 cm in diameter rarely metastasize to the liver (Que et al. 1995; Chamberlain et al. 2000). Hepatic metastases of carcinoids and islet cell tumors are usually multiple, of varying size, and bilobar in the majority of cases (Chamberlain et al. 2000; Ihse et al. 2001). It is of interest to note that not only established types of cancers have different propensities to metastasize to the liver but that also subtypes differ in their hepatotropism. For example, ductal carcinoma of the breast more frequently metastasizes to the liver than its lobular counterpart (Fondrinier et al. 1997).

Similar to CRC metastases, several types of hepatic metastases can elicit intrahepatic complications, such as biliary obstruction due to extrinsic compression or direct invasion of bile ducts (Papo et al. 1996; Enomoto et al. 2006). Metastases other than CRC can also invade large hepatic venous branches, including multifocal intraportal invasion (Nakajima et al. 2005).

Epithelial Tumors that Less Often or Rarely Metastasize to the Liver

Skin Carcinomas

Basal cell carcinoma of the skin (basalioma) is a very common invasive neoplasm that however rarely metastasizes, with a metastasis rate of 1 in 1,000–35,000 patients (von Domarus and Stevens 1984). The most common sites of metastasis are the lungs, followed by the bone, lymph nodes, liver, and spleen (Farmer and Helwig 1980; Di Lernia et al. 2013). Hepatic metastasis can develop more than 20 years after primary therapy of the skin tumor (Postlethwaite et al. 1990). Squamous cell carcinomas primary to the skin or mucous membranes have a low metastatic potential, but can give rise to hepatic metastases (Warren and Hoerr 1939; Swanbeck and Hillstrom 1969; Lazarus et al. 1980; Chaux et al. 2011). Merkel cell carcinoma of the skin metastasizes to the liver (Sharma et al. 1991; Gollub et al. 1996).

Salivary Gland Tumors

Certain types of salivary gland tumors are well recognized to metastasize to distant organs. The likelihood of remote metastases is associated with high-grade neoplasms, including adenoid cystic carcinoma, salivary duct carcinoma, high-grade mucoepidermoid carcinoma, and tumors located in the submandibular gland, posterior tongue, and pharynx (Schwentner et al. 2006). Adenoid cystic carcinoma is the most common type of salivary gland tumors that gives rise to liver metastasis, and hepatic metastatic disease may be the initial presentation of this tumor (Spolverato et al. 2014). Exceptionally, also low-grade salivary gland mucoepidermoid carcinoma metastasized to the liver (Herd et al. 2012). Rarely, pleomorphic salivary gland adenoma, mostly of the parotid gland, can metastasize to the liver, even in the absence of histologic signs of malignancy, sometimes with a delay of many years (Youngs and Scheuer 1973; Olsha and Gottschalk-Sabag 1995; Singhal et al. 2010; Abou-Foul et al. 2014).

Ovarian Carcinomas

Parenchymal liver metastases of epithelial ovarian malignancies are relatively rare, ranging in frequency from 4 % to 9.4 % of patients (Dauplat et al. 1987; Loizzi et al. 2005; Lim et al. 2009; Alvarado-Cabrero et al. 2013). More often, subcapsular liver metastases of ovarian carcinomas are found (Triller et al. 1985). In contrast to liver parenchyma, the biliary tract was involved with metastases in 15 % of patients (Alvarado-Cabrero et al. 2013).

Carcinomas of Endocrine Glands

Carcinomas of the pituitary gland are rare, but well-known causes of liver metastasis, whereby ACTH-and prolactin-producing neoplasms prevail (Lormeau et al. 1997; Arias et al. 2000; Suzuki et al. 2002; van der Klaauw et al. 2009). Relatively rarely, adrenocortical carcinomas metastasize to the liver (Gaujoux et al. 2012), sometimes with a delay of more than 10 years after primary diagnosis and therapy (Maywardi et al. 2012). The uncommon parathyroid carcinomas are also known to produce hepatic metastases (Albertini et al. 1953).

Hepatic Metastases in the Pediatric Age Group

As outlined above, certain cancers occurring in adults, such as CRC, can also produce liver metastases in children. In addition, several types of malignancies that preferentially develop in infants and children frequently produce hepatic metastatic disease. These neoplasms mainly include neuroblastoma, Primitive neuroectodermal tumors (PNETs) nephroblastoma, cellular blue tumors of various types, pediatric soft tissue and bone sarcomas, and lymphomas. Also malignancies originating in the pediatric liver can cause intrahepatic metastases, including hepatoblastoma, pediatric hepatocellular carcinoma, and undifferentiated embryonal sarcoma. The prevalence of the diverse tumor types varies somewhat from one investigation to the other. In a study of 15 patients undergoing hepatic metastasectomy, seven patients had neuroblastoma, three Wilms' tumor, two osteogenic sarcoma, one GIT carcinoma, and two desmoplastic small round cell tumor (Su et al. 2007).

Hepatic Metastases of Sarcomas and Other Mesenchymal Tumors

Almost any type of sarcoma has been found to metastasize to the liver, but generally, sarcoma metastases are less common than those of carcinomas. The most common primary sites for hepatic sarcoma metastases are soft tissues and the gastrointestinal tract (GIT) (Hafner et al. 1995; Jaques et al. 1995; Lang et al. 2000; Rehders et al. 2009; Chua et al. 2011; Zacherl et al. 2011). Sarcomas with a relatively high incidence of hepatic metastases include malignant gastrointestinal stromal tumor and leiomyosarcoma of the gastrointestinal and genital tracts and of soft tissues (Merimsky et al. 1999; Lang et al. 2000), liposarcomas (Pisters and Sondack 2002; Estourgie et al. 2002), and angiosarcoma (Tateishi et al. 2003). In a series of 331 patients with sarcoma metastatic to the liver, 68 % had intra-abdominal sarcoma; 14 % retroperitoneal, 9 % extremity/trunk, and 9 % head/neck lesions; and 61 % gastrointestinal stromal tumor or GIT leiomyosarcoma (DeMatteo et al. 2001). Among 981 patients with soft tissue sarcoma, 65 patients showed hepatic metastases, and 61 of them had an intra-abdominal primary site, 85 % of the neoplasms being high-grade leiomyosarcomas (Jaques et al. 1995). The gross metastatic patterns vary markedly, in part depending on the type of sarcoma involved. In a study of 45 patients with soft tissue sarcoma metastasis to the liver, 59 % had a solitary metastasis, 22 % had two metastases, and 18 % had three or more metastatic nodules (Rehders et al. 2009).

Granulosa cell tumors of the ovaries have a certain tendency to metastasize to the liver, sometimes with cystic changes of the lesions (Margolin et al. 1985; Neste et al. 1996; Ali 1998; Madhuri et al. 2010). Metastases of malignant melanoma are discussed in a separate chapter.

Rare and Unusual Hepatic Metastases Produced by Intracranial and Intraspinal Tumors

Introduction

Apart from diverse types of carcinomas and sarcomas known or expected to metastasize to the liver, there are diagnostically difficult situations of neoplasms of the intracranial and intraspinal

compartments sometimes giving rise to liver metastases. Interestingly, part of these neoplasms is regarded as benign or low-grade malignant in their primary site, to later behave as highly malignant cancers as soon as they have produced metastatic disease. As such neoplasms are not extensively treated in many texts, and give rise to differential diagnostic problems, pertinent examples of these lesions are therefore discussed in more detail in the following paragraphs.

Meningioma Metastatic to the Liver

Meningiomas account for about 15–20 % of all primary CNS tumors and present with a complex spectrum of histologic phenotypes that have been defined in the WHO tumor classification (Louis et al. 2007a, b). Meningiomas usually grow in an expansive, space-occupying manner, but invasive growth is also known for certain types of this tumor. The prevalence of a malignant histology of meningiomas ranges from 2 % to 10 %. Invasive meningiomas can invade the bone, venous sinuses, brain, soft tissues of the scalp, and paranasal sinuses. In contrast, metastatic spread to remote organs is a rare event in meningiomas and is estimated to be less than 1 in 1,000 patients with meningioma (Enam et al. 1996). The most common metastatic site is the lung (60 % of cases), followed by the abdomen and liver (34 %), cervical lymph nodes (18 %), skeletal long bones, pelvis and skull (11 %), pleura (9 %), vertebrae (7 %), CNS (7 %), and mediastinum (5 %) (Kepes 1982; Bondy and Ligon 1996).

Only relatively few cases of meningiomas metastatic to the liver have been reported. The range of histologies includes meningothelial meningioma (Ku et al. 2005), fibroplastic meningioma (Ishibashi et al. 1983; Cerda-Nicolas et al. 2003; Rampurwala et al. 2011), atypical meningioma (Asqhar et al. 2009), transitional meningioma (Figueroa et al. 1999), rhabdoid meningioma (Wang et al. 2011), or anaplastic meningioma (Garcia-Conde et al. 2009; Lambertz et al. 2011). Rhabdoid meningioma (Perry et al. 1998; Matyia et al. 2010) and anaplastic meningioma are highly aggressive malignant neoplasms with a prominent tendency for invasion and metastatic spread. In histologically benign variants, liver metastasis may occur after a long delay, e.g., 31 years in a case of fibroplastic meningioma (Rampurwala et al. 2011).

A variety of factors have been associated with metastatic spread of meningioma. The estimation of factors favoring extracranial metastasis is complicated by the fact that metastasis is rare, with usually single cases being reported, and that histologic types and meningioma grading have been revised several times in recent years (review: Figueroa et al. 1999). What are the potential pathways of spread for an intracranial meningioma to reach the liver? Tumor may spread through the venous system of the sinuses or tumor veins. Penetration of the dura mater of venous sinuses favors the invasion of neoplastic cells into the jugular venous system and then the pulmonary venous system, the system of the vena azygos and hemiazygos, and vertebral venous plexuses (Shimanskii et al. 2011). A very rare pathway involves the spread of meningioma cells via a ventriculoperitoneal shunt, with seeding to the liver and subsequent growth of implantation metastases. In one case, a 61-year-old woman was diagnosed with intracranial atypical meningioma which twice recurred 2 and 4 years after the first resection. The recurrent tumors were resected and a ventriculoperitoneal shunt was installed. At age 68 years, the patient had developed a liver metastasis of meningioma, situated in segments 4 and 5 and measuring 8.3 cm in diameter (Moir et al. 2010).

Meningeal Hemangiopericytoma Metastatic to the Liver

Meningeal hemangiopericytoma (MHPC; hemangiopericytomatous meningioma) was formerly regarded as a form of angioplastic meningioma, but has been shown to be a neoplasm that clearly differs from meningiomas in both its histologic phenotype and its biology. The neoplasm accounts for about 1 % of all primary intracranial tumors. In a series of 44 cases, the average age of the patients

at diagnosis was 42 years, and 55 % of these tumors occurred in men (Guthrie et al. 1989).

MHPC is an aggressive tumor which, in its biological behavior, is clearly different from true meningiomas. In the study of Guthrie et al. (1989), the average time before the first recurrence was 47 months, with the recurrence rates at 1, 5, and 10 years after primary surgery being 15 %, 65 %, and 76 %, respectively. The 10- and 15-year rates of metastasis were 33 % and 64 %, respectively. MHPC has a marked tendency for local invasion, including skull bones, and for multiple metastatic progressions. Distant metastases may occur several years after initial treatment (Chang et al. 2004; Shi et al. 2009). Similar to other hemangiopericytomas, MHPC may be associated with paraneoplastic hypoglycemia. Histologically, the tumor is characterized by marked cellularity, vascularity, and dense net of reticulin fibers. Cells are medium-sized or large, in part spindled cells with large nuclei and often rather sparse cytoplasm. These cells form nests and fascicles, but also may be arranged as proliferating elements around endothelium-lined vascular channels with a staghorn pattern (Fabiani et al. 1980; Kochanek et al. 1986). MHPC is either grade II or grade III lesion. Immunohistochemically, MHPC lacks strong expression of cytokeratins, while vimentin is at least focally positive (Moss 1987; Chang et al. 2004). In one study, focal CAM 5.2 expression was noted in 26 % of MHPC (Rajaram et al. 2004). MHPC is strongly positive for CD99 and Bcl-2, and all cases showed individual cell factor XIIIa reactivity (Rajaram et al. 2004). Typically – and in contrast to meningothelial meningioma – MHPCs are negative for diffuse epithelial membrane antigen (EMA) expression, and also expression of S100 protein is not detectable (Chang et al. 2004; Sundaram et al. 2010). However, MHPC cells can show focal EMA positivity, and a minor EMA reactivity does therefore not preclude a diagnosis of this tumor (Rajaram et al. 2004).

Several reports have documented the occurrence of liver metastases of MHPC. Liver metastases can develop with a long delay after primary diagnosis, e.g., 9 years (Soares et al. 2003). Also MHPC metastasizing to the liver can be associated with hypoglycemia (Ferguson and Flinn 1995; Nabeya et al. 1998; Miyamoto et al. 2004), in one case with high blood levels of an abnormal form of insulin-like growth factor type 2/IGFII (Grunenberger et al. 1999).

Selected References Chakravarty et al. 1991; Kaneko et al. 1993; Ferguson and Flinn 1995; Nabeya et al. 1998; Davies et al. 1999; Grunenberger et al. 1999; Soares et al. 2003; Chang et al. 2004; Miyamoto et al. 2004; Spatola and Privitera 2004.

Glioblastoma

Extracranial metastases of glioblastoma are very rare, with a reported frequency of only 0.44 %. The predominant metastatic sites are the locoregional lymph nodes, lungs and pleura, and skeletal system (review: Pasquier et al. 1980). Glioblastoma can invade blood vessels and is capable to produce extracranial hematogenous metastases, also to the liver (Leifer et al. 1989; Shuto et al. 1995; Widjaja et al. 2000; Saad et al. 2007; Piccirilli et al. 2008; Robert and Wastie 2008; Schönsteiner et al. 2011). Liver metastases may be multiple and sometimes very large (Robert and Wastie 2008). It has been proposed that metastasis to the liver may occur via vascular anastomoses between the vertebral and portal venous systems (Shuto et al. 1995).

Several reports have demonstrated the spread of intracranial glioblastoma to the peritoneal cavity through a ventriculoperitoneal shunt. Shunt-mediated tumor seeding can result in multiple, sometimes coalescent implants or large proliferating tumor masses that compromise adjacent abdominal organs and the omentum (Newton et al. 1992a; Fecteau et al. 1998; Kumar et al. 1999). Peritoneal glioblastoma implants can involve the liver and induce hepatic metastases (Kayama et al. 1981).

The transmission of donor-related malignancies by solid organ transplantation is a well-known, albeit rare, event. In a study of 342 donor hepatectomies, 13 cases had primary cerebral neoplasia. Among these, four were glioblastoma. Recurrent malignancy related to CNS neoplasia was observed once. The donor of the liver had undergone surgical resection of an intracerebral multiform glioblastoma and died from tumor relapse. The female recipient of the liver developed, 4 months after transplantation, intraperitoneal and intrahepatic masses identified as glioblastoma metastases (Jonas et al. 1996). In a retrospective review of 1,173 liver transplants performed between 1992 and 2006, 42 donors with a CNS tumor were identified. Thirty-two CNS tumors were malignant (20 of them had glioblastoma multiforme) and 10 tumors were benign. The rate of recurrence for the entire group was 2.4 % (all CNS tumors; Kashyap et al. 2009).

Malignant Astrocytoma

High-grade astrocytoma is known to sometimes metastasize to extracranial remote sites (LoRusso et al. 1988). Very few examples of malignant (non-glioblastomatous) astrocytomas metastatic to the liver in the absence of a shunt have been published (Schuster et al. 1976; Pasquier et al. 1980).

Similar to glioblastoma, grade III astrocytoma can spread via ventriculoperitoneal shunts, producing peritoneal seeding (Declercq et al. 1992). The intraperitoneal implants may form a tumor ascites with numerous suspended, GFAP-positive tumor cells (Wakabayashi et al. 1985).

Pilomyxoid Astrocytoma

Pilomyxoid astrocytoma of the spinal cord was found to spread to the peritoneal cavity through a ventriculoperitoneal shunt, producing widespread peritoneal gliomatosis and confirming the sometimes aggressive biology of this neoplasm (Arulrajah and Huisman 2008).

Oligodendroglioma and Oligoastrocytoma

According to the WHO classification of brain tumors, oligodendroglial tumors are separated into oligodendrogliomas WHO grade II, anaplastic oligodendrogliomas WHO grade II, oligoastrocytomas WHO grade II, anaplastic oligoastrocytomas WHO grade II, and glioblastomas with an oligodendroglioma component WHO grade IV. These neoplasms have distinct molecular features (review: Hartmann and von Deimling 2009). Oligodendroglial tumors of higher grade rarely cause metastatic disease (James and Pagel 1951; Jellinger et al. 1969; review: Zustovich et al. 2008). Few cases of oligodendroglioma liver metastases have been observed (Spataro and Sacks 1968; Macdonald et al. 1989; Uzuka et al. 2007; Yokosuka et al. 2007; Han et al. 2008), mostly with an anaplastic histology. Massive peritoneal metastasis of pediatric oligodendroglioma was noted in one patient after ventriculoperitoneal shunting (Becker et al. 1978).

Ependymoma

Ependymomas rarely metastasize outside the central nervous system. Among 81 ependymomas evaluated in the Memorial Sloan-Kettering Cancer Center between 1956 and 1989, five (6.2 %) had extraneural metastases. Two of the tumors were anaplastic and three histologically benign. Metastatic sites included the lung, thoracic lymph nodes, pleura, peritoneum, and liver (Newton et al. 1992b). Metastasis of ependymoma may occur with impressive timely delay. In one case, liver and lung metastases were diagnosed 40 years after primary diagnosis of cerebral ependymoma (Graf et al. 1999). Peritoneal seeding of high-grade ependymoma (ependymoblastoma) via ventriculoperitoneal shunt has been described (Shibasaki et al. 1977) and may result in liver metastasis (Kayama et al. 1981).

Ependymoma can also occur in the ovaries and metastasize to the liver (Fan et al. 2006). There are few anecdotal reports of primary extraneural "ectopic" ependymomas. These lesions were

mostly localized close to the neural axis, i.e., sacrococcygeal region, posterior mediastinum, or ovaries. One single case of apparently primary hepatic ependymoma has been reported, a tumor detected in 41-year-old female without any evidence of a CNS primary tumor (Wiendl et al. 2003).

Gliosarcoma

Gliosarcoma is a rare primary CNS neoplasm characterized by a biphasic pattern consisting of glioblastoma and fibrosarcomatous and/or MFH-like components. Gliosarcomas have a temporal lobe predilection and infrequently show EGFR mutations (Sreenan and Prayson 1997; Han et al. 2010). Gliosarcoma may arise in oligodendroglial tumors (oligosarcoma; Rodriguez et al. 2007). Gliosarcoma has a strong propensity for hematogenous metastasis, sometimes with intravascular gliomatosis. Metastasis to the liver has been demonstrated (Smith et al. 1969; Yokoyama et al. 1985; Matsuyama et al. 1989; Beaumont et al. 2007).

Intracranial Germinoma

Intracranial germ cell tumors form a distinct group of neoplasms that predominantly develop in the suprasellar and pineal regions. The major types comprise germinoma, teratomas, yolk sac tumor, embyronal carcinoma, and choriocarcinoma (Matsutani et al. 1997). The rarest type in these locations is pure embryonal carcinoma (Maruki et al. 2000). The histologic typing of intracranial germ cell tumors is sometimes difficult owing to the fact of internal heterogeneity of the neoplasms. For example, suprasellar embryonal carcinoma was found to undergo differentiation into yolk sac tumor and choriocarcinoma (Wang et al. 1995), and embryonal carcinoma of the pineal gland can undergo yolk sac differentiation (Iwanowski et al. 1997).

Intracranial germinomas are usually located to the pineal gland region. These neoplasms often carry a good prognosis owing to their radiosensitivity. Recurrence is rare, but few patients may develop neural and extraneural metastases, including arachnoid, dural and extradural spaces, spines, skin, lymph nodes, heart, lungs, adrenal, kidneys, pancreas, and liver (Motomochi et al. 1980; Adachi et al. 1991). In one young male patient, suprasellar germinoma metastasizing to the liver contained syncytiotrophoblastic giant cells and was associated with elevated serum chorionic gonadotropin levels (Adachi et al. 1991). Metastasis in the sense of peritoneal implants can occur via ventriculoperitoneal shunt, in part of the cases showing infiltration of the omentum and displacement of the liver (Triolo and Schulz 1980; Haimovic et al. 1981; Kun et al. 1981; Devkota et al. 1984; Talamo and Mendelow 1985; Pallini et al. 1991; Blasco et al. 1993; Ung et al. 1993; Wong et al. 1996; Uchino et al. 1999; Altundag et al. 2002). In the intraperitoneal implant metastases, differentiation of the tumor may change, reflecting the differentiation plasticity of germ cell tumors. In a male patient who had pineal germinoma, the tumor spreads to the peritoneal cavity via shunt where it changed into yolk sac tumor, with formation of a large liver tumor (Uchino et al. 1999). Transformation of germinoma into yolk sac tumor in intraperitoneal implants was detected in another patient (Back et al. 1997). In another case, pineal germinoma transformed into a mixed germ cell tumor with teratoma components in the large intraperitoneal tumor that was located close to the shunt tip (Saibara et al. 1991). In a 10-year-old patient, teratocarcinoma of the pineal gland region which had spread to the abdominal cavity through a ventriculoperitoneal shunt had transformed into pure germinoma (Iwamuro et al. 2002).

Intracranial Yolk Sac Tumor

Intracranial yolk sac tumors typically occupy either the suprasellar region or the pineal gland. These malignancies can spread to the peritoneal cavity through ventriculoperitoneal shunts (Wilson et al. 1979; Bamberg et al. 1984; Kimura et al. 1984).

Intracranial Choriocarcinoma

Parts of germinomas have been shown to contain syncytiotrophoblastic cells (Adachi et al. 1991), but choriocarcinoma sensu stricto is a very uncommon intracranial malignancy. Suprasellar choriocarcinoma was described in a 19-year-old male patient, causing the patient's death. Autopsy revealed remote metastases in the skin, lungs, kidney, intestine, and liver (Shinmura et al. 1983).

Intracranial Teratocarcinoma

Cerebral teratocarcinoma of a young adult patient metastasized to the abdominal cavity via a ventriculoperitoneal shunt, resulting in a massive abdominal tumor (Rickert et al. 1998).

Pineoblastoma (Pinealoblastoma)

Pineoblastoma is the main member of the pineal parenchymal tumor group, which comprises a spectrum of lesions ranging from pineocytoma of intermediate differentiation pineal parenchymal tumor to the less-differentiated pineoblastoma (Lutterbach et al. 2002; Han et al. 2011). Pineoblastomas, which represent the most aggressive of pineal parenchymal tumors (Tate et al. 2011), occur in the pediatric age group, but also form a distinct group of adult tumors. In adults, the median age at diagnosis was 36 years, and in one series all patients presented with hydrocephalus (Chang et al. 1995). Osseous metastases from primary central nervous system tumors are rather rare, except for medulloblastoma and glioblastoma, and also pineoblastoma is well known to metastasize to the skeletal system (Jacobs and Rosenberg 1989; Fraser et al. 2000; Charafe-Jauffret et al. 2001; Constantine et al. 2005). Peritoneal seeding can occur via ventriculoperitoneal shunt, characterized by peritoneal implants and sometimes large intra-abdominal tumor masses (Pfletschinger et al. 1986; Cranston et al. 1992; Gururangan et al. 1994). Tumor-induced ascites may develop (Cranston et al. 1992).

Choroid Plexus Carcinoma

Peritoneal dissemination via a ventriculoperitoneal shunt has been observed in pediatric choroid plexus carcinoma, causing death with widespread metastasis (Donovan and Prauner 2005).

Medulloblastoma

Medulloblastoma is an aggressive and mostly infratentorial tumor that is known to produce extracranial metastases, mostly to the skeletal system (in particular pelvis, femur, and vertebrae; Kleinman et al. 1981; Rickert 2003). Also in adult with medulloblastoma, bones are the predominant metastatic site (Rochkind et al. 1991). Systemic metastases occurred earlier in patients with ventriculoperitoneal shunts (Kleinman et al. 1981). In a series of 103 patients, eight developed extra-CNS metastases (7.7 %). In one of these eight patients, metastasis was located to the liver (Kochbati et al. 2006). But in an autopsy study, liver metastases hold the third place in frequency (28 %) after bone metastases (82 %) and lymph node metastases (65 %) (Kleinman et al. 1981). In a comparison of pediatric and adult cases of medulloblastoma, liver metastases were more frequent in children (15 %), while adults had more often lung metastases (Rochkind et al. 1991). Medulloblastoma can spread to the abdominal cavity via ventriculoperitoneal shunts (Makeever and King 1966; Hoffman et al. 1976; Oemus et al. 1992; Jamjoom et al. 1993; Carrasco Torrents et al. 2001; Magtibay et al. 2003; Loiacono et al. 2006).

Atypical Teratoid/Rhabdoid Tumor

Atypical teratoid/rhabdoid tumors (AT/RT) of the CNS are rare and extremely aggressive malignancies. These tumors usually occur in early childhood, but adult cases are also known (Lutterbach et al. 2001). AT/RT can spread to the peritoneal cavity through ventriculoperitoneal shunts (Ingold et al. 2009).

Chordoma

Chordoma, a tumor derived from notochordal remnants, occurs mostly in patients in the fifth to seventh decade and is an aggressively growing tumor causing metastatic disease in up to 30 % of cases. Liver metastases of intracranial chordoma are, however, rare (Ashwood et al. 1994; Chopra et al. 2010). The same holds true for liver metastasis of sacrococcygeal chordoma of adults (Raguin et al. 1987; Tavernaraki et al. 2003). Also sacrococcygeal chordoma of childhood has been shown to sometimes have an aggressive course with generalized metastases, including the liver, and histologically with predominance of "pink" cells over physaliform cells (Shinmura et al. 2003). In childhood, subsets of sacrococcygeal chordomas are highly proliferative lesions with nuclear atypia, classified as either dedifferentiated chordoma with anaplastic histology or atypical chordoma with sarcomatoid appearance (Iwasa et al. 1998). It has been reported that also adult cases of sacrococcygeal chordomas can undergo an aggressive course, associated with a change in differentiation to sarcomas with variable cell lineages, including fibrosarcoma or osteosarcoma (dedifferentiated chordoma).

Apparently Locally Growing Neoplastic Lesions Metastasizing to the Liver

There are few examples of apparently reactive, or locally growing, lesions that metastasize to the liver. One of these unusual lesions is aneurysmal bone cyst. Aneurysmal bone cysts (ABCs) account for 1–2 % of all primary bone tumors and are predominantly diagnosed in the first two decades of life. Histologically, ABCs consist of blood-filled spaces lined by a cellular tissue composed of densely packed spindle cells and numerous multinucleated giant cells. Giant cells in ABCs express an osteoclast-like phenotype and are formed from CD14+ macrophage precursors, while CD14- mononuclear stromal cells express osteoclastogenic factors and interact with CD14+ cells to form osteoclast-like giant cells by a RANKL-dependent mechanism (Taylor et al. 2012). ABCs are rapidly growing and locally aggressive/recurrent lesions that have been regarded as reactive processes. However, subsequent cytogenetic and molecular studies revealed a neoplastic basis of at least part of ABCs by the demonstration of clonal chromosome band 17p13/16q22 translocations that place the USP6 (TRE2 or TRE17) oncogene under the regulatory influence of the active CDH11/osteoblast cadherin 11 gene promoter (Oliveira et al. 2004). Metastasizing ABC was detected in a 48-year-old woman with a giant ABC of the left ilium. The patient died 2 years after diagnosis, and at autopsy, metastases of ABC were found in both lungs, both kidneys, and the liver. There was no evidence for telangiectatic osteosarcoma having developed from ABC (van de Luijtgaarden et al. 2009).

Liver Metastases from Cancer of Unknown Primary Site/Location (CUPL)

Introduction

In part of patients with liver metastasis, even detailed clinical investigations will not elucidate their origin. This situation is termed liver metastases from cancer of unknown primary site or location (CUPL; synonyms, hepatic metastases from an unknown primary neoplasm, UPN). CUPL is the hepatic manifestation of CUP (cancer of unknown primary origin). CUP is usually defined as histologically proven malignancy for which the primary site could not be found after anamnesis, complete physical examination, imaging, and routine chemistries. CUPL is a diagnostic challenge in clinical practice even in the face of the advanced diagnostic technologies currently available (Mousseau et al. 1991; Hogan et al. 2002; Pouessel et al. 2005; Shaw

et al. 2007). This also generally holds true for CUP as a group (reviews: Gaber et al. 1983; Perchalski et al. 1992).

Epidemiology

Cancer of unknown primary origin (CUP; synonyms, neoplasms of an unknown primary site (NUPS); metastasis of unknown origin (MUO); metastases of undetermined source) is estimated to account for 2–10 % of all malignant neoplasms at presentation (Fizazi 2006). About 2 % of more than one million cases of cancer diagnosed in residents of SEER areas for the 15-year period 1973–1987 were designated as being CUP (Muir 1995). By reviewing 1,656 autopsies performed on adults, 43 cases of NUPS were found (Mayordomo et al. 1993). In a review of 9,436 consecutive autopsies performed between 1984 and 1999 at the Mayo Clinic and matched with 177,167 cancer patients treated in the same time period, there were 64 patients who died of CUP. Autopsy located the primary site in 35 patients (55 %; Blaszyk et al. 2003). Also another study showed that primary sites could be identified by autopsy in 51 % of cases (Al-Brahim et al. 2005), but it is seen that roughly half of the cases remain MUO even after necropsy. In a large retrospective study, 3.7 % of all referrals to the cancer center were CUP. The three most common CUP subgroups were CUPL (25 %), CUP-bone (21 %), and CUP-brain (16 %). The remaining subgroups occurred at frequencies of less than 10 % each (Shaw et al. 2007). Generally, patients with CUP show an unfavorable biology of disease, however, with markedly variable data concerning survival time (Pimiento et al. 2007). The median survival for all 1,000 consecutive CUP patients analyzed at the Anderson Cancer Center in Houston was 11 months (Hess et al. 1999), while for 1,285 patients from the Netherlands, the median survival was only 11 weeks, and only 15 % of the CUP patients were still alive 1 year after diagnosis (van der Wouw et al. 2002). There may be subsets of "unfavorable" CUP that may profit from targeted treatments based on molecular profiling (Amela et al. 2012).

CUPL Histology at the Time Point of Diagnosis

Clinicopathologic and morphologic approaches to classify metastatic neoplasms in regard to the primary site have been worked out and reviewed (Marchevsky et al. 2010). In a group of 100 CUPL patients from a single French center, 66 had adenocarcinoma, 19 undifferentiated carcinoma, and 11 squamous cell carcinoma in their hepatic metastases (Culine et al. 1998). Another study of 88 patients included adenocarcinoma in 70, neuroendocrine in 4, squamous cell carcinoma in 4, small cell carcinoma in 4, and some rarer types (Hogan et al. 2002). Among 118 patients with CUPL, the most frequent histologic types observed were adenocarcinoma, undifferentiated, neuroendocrine, and squamous cell carcinomas. In a retrospective study of 49 CUPL patients, the commonest histologic types encountered were adenocarcinoma ($N = 34$) and undifferentiated carcinoma ($N = 12$). In 38 % of cases, the liver was the only metastatic site (Lazaridis et al. 2008). Adenocarcinomas were the most frequent type of carcinoma in a series of 1539 CUP (Altman and Cadman 1986), and poorly differentiated carcinomas and poorly differentiated adenocarcinomas may account for roughly a third of all CUP cancers (Lenzi et al. 1997). These results illustrate what is generally known from liver metastases, i.e., that adenocarcinomas are the most common metastatic tumors, mainly caused by the high incidence of metastasizing tumors of the gastrointestinal tract and the breast. This has led to the concept of adenocarcinoma of unknown primary site (ACUPS; Moertel 1979; Markman 1982; Hamilton and Langlands 1987). A synonym of this term is unknown primary adenocarcinoma or UPA (Speel et al. 2008). In the group of CUP, ACUPS is a dominant histology, accounting to 42.8 % of all cases in one investigation (Pimiento et al. 2007). Among patients with ACUPS, the

most common sites of metastases were the lymph nodes, liver, lung, and bone in order. In 60.5 % of patients, the dominant tumor location was below the diaphragm (Song et al. 2002). Patients having their major sites of disease above the diaphragm experienced a significantly longer survival than patients whose disease was below the diaphragm (Markman 1982).

Clinical Features and Biology of Disease of CUPL

For patients with CUP, strategies to be followed in order to arrive at diagnosis and identification of the primary site have been standardized in sets of guidelines (Bugat et al. 2003; Lesimple et al. 2003). According to general views, CUPL are not expected to present in a manner different from that of other hepatic metastases. Liver metastases from unknown primary site are often multiple and often hypervascular on MRI images, whereas solitary metastases are more often hypovascular (Braga et al. 2003). However, novel concepts suggest that at least part of tumors that present as CUP or CUPL differs in their biology and molecular features from other malignancies with a similar or the same histologic type. Overall, patients with CUPL have a dismal prognosis (Ayoub et al. 1998). Among 47 patients who had received first-line chemotherapy (42 platinum-based), only six showed an objective response, and median survival was 10 months (Lazaridis et al. 2008). In a study on 107 patients who had received at least a front-line of chemotherapy (74 platinum-based), the overall response rate was 19.4 %, and the overall median survival was 6.6 months (Pouessel et al. 2005). CUPL patients with adenocarcinoma seem to carry a particularly dismal prognosis (Hogan et al. 2002).

Assignment of Primary Tumors: The Significance of Histopathology and Immunohistochemistry

As at least a subset of patients with CUPL may profit from chemotherapies, attempts should be undertaken to identify the primary site by the use of optimal histological classification and immunohistochemistry (review: Krishna 2010). In the course of histologic evaluation, it is good practice to first allocate the CUPL case in question to one of the major tumor categories, as in any diagnostic approach, i.e., carcinoma vs. sarcoma vs. melanoma vs. neuroendocrine vs. hemolymphatic vs. others (Oien 2009). For carcinomas, and in particular adenocarcinomas, experience will often allow to suspect or even reliably identify colorectal carcinoma or breast carcinomas. Conversely, the presence of squamous cell carcinoma will not permit the identification of the primary site, owing to the similarity of all squamous cell tumors in any locations they occur. In case of undifferentiated tumors, distinct marker panels applied to biopsies may identify small cell carcinoma vs. poorly differentiated adenocarcinoma, PNET, and other anaplastic tumors (van der Gaast et al. 1996). For fine-needle aspiration cytology approaches, a panel including CK5/6, CK7, CK20, CA125, thyroid transcription factor 1/TTF-1, and CDX2 was proposed (Onofre et al. 2007). For colorectal carcinoma metastases, the CK20+/CK7- pattern showed a specificity of 98.7 % in predicting colorectal primary localization, superior to that of CDX2 expression (Tot and Samii 2003; Tot 2004). In contrast, the CK7+/CK20- phenotype favors a lung primary adenocarcinoma (Rubin et al. 2001). In addition to immunohistochemical analysis, molecular approaches for the identification of tissue of origin can successfully be employed (review: Monzon and Koen 2010). Established methods include gene expression profiling and several commercially available molecular test systems, e.g., including Theros CancerTYPE ID, Pathwork tissue-of-origin test, miRview mets, CupPrint, and CUP assay.

Molecular Assignment of Origin in CUPL

Gene expression profiling methods (multiple expression signatures) were shown to accurately assign CUP to a primary tissue of origin (Bloom

et al. 2004; Ismael et al. 2006; Staub et al. 2010). cDNA- and oligonucleotide-based classifiers accurately predicted the known primary site of origin for an independent set of metastatic lesions (Bloom et al. 2004). Classifiers trained on combined expression data from both normal tissue data sets were able to predict the site of origin in a cohort of 652 primary tumors with approximately 90 % accuracy (Staub et al. 2010). In a systematic literature review, it was found that molecular assignment may not predict response to therapy and outcome, suggesting that CUP may harbor molecular traits distinct from tumors of known primary sites (Pentheroudakis et al. 2009).

Pathogenesis

Apart from CUP cases where the primary tumor could not be identified due to diagnostic difficulties or limitations, CUP tumors may tend to present in this distinct manner owing to inherent biologic characteristics (review: van de Wouw et al. 2003). It was suggested that CUP tumors may show a clonal relationship between multiple tumors within individual CUP patients. A molecular resemblance would argue for an early clonal outgrowth of tumor cells from the primary neoplasm, a mutual feature observed within this group of neoplasms (Speel et al. 2008). By the use of genomic hybridization, it was found that primary tumors and multiple metastases sampled at autopsy of CUP patients are clonally related, independent of the anatomical origin of the cancer. The findings suggest that tumor progression is particularly rapid in CUP patients, limiting the chance of clonal divergence (Speel et al. 2008).

References

Abou –Foul AK, Madi M, Bury D, Merritt A (2014) Metastasising pleomorphic salivary gland adenoma presenting as synchronous pulmonary and hepatic metastases. BMJ Cases Rep. doi:10.1136/bcr-2014-204351

Adachi J, Ono N, Misumi S, Tamura M, Ohye C (1991) Multiple liver metastases of a suprasellar germ cell tumor treated with combined chemotherapy of cisplatin and etoposide (in Japanese). No Shinkei Geka 19:671–675

Albertini AV, Koller F, Gaiser H (1953) Functioning parathyroid tumor with liver metastasis. Acta Endocrinol (Copenh) 12:289–302

Al-Brahim N, Ross C, Carter B, Chorneyko K (2005) The value of postmortem examination in cases of metastasis of unknown origin- 20-year retrospective data form a tertiary care center. Ann Diagn Pathol 9:77–80

Ali SZ (1998) Metastatic granulosa-cell tumor in the liver: cytopathologic findings and staining with inhibin. Diagn Cytopathol 19:293–297

Altman E, Cadman E (1986) An analysis of 1539 patients with cancer of unknown primary site. Cancer 57:120–124

Altundag OO, Celik I, Kars A (2002) Pineal germ cell tumor metastasis via ventriculoperitoneal shunt. Am J Clin Oncol 25:104–105

Alvarado-Cabrero I, Rodriguez-Gomez A, Castelan-Pedraza J, Valencia-Cedillo R (2013) Metastatic ovarian tumors: a clinicopathologic study of 150 cases. Anal Quant Cytopathol Histopathol 35:241–248

Amela EY, Lauridant-Philippin G, Cousin S, Ryckewaert T, Adenis A, Penel N (2012) Management of "unfavorable" carcinoma of unknown primary site: synthesis of recent literature. Crit Rev Oncol Hematol 84:213–223

Arias M, Pereiro I, Requena I, Ventura M, Iglesias C, Lema C (2000) Malignant prolactinoma with intra-and extracranial metastasis: clinico-radiologic study (in Spanish). An Med Interna 17:192–194

Arulrajah S, Huisman TA (2008) Pilomyxoid astrocytoma of the spinal cord with cerebrospinal fluid and peritoneal metastasis. Neuropediatrics 39:243–245

Ashwood N, Hoskin PJ, Saunders MI (1994) Metastatic chordoma: pattern of spread and response to chemotherapy. Clin Oncol (R Coll Radiol) 6:341–342

Asqhar AH, Mahmood H, Faheem M, Rizvi S, Irfan J (2009) Hepatic and skeletal metastases from primary intracranial atypical meningioma. J Coll Phys Surg Pak 19:316–317

Ayoub et al. (1998) http://www.ncbi.nlm.nih.gov/pubmed/9626210

Back MR, Hu B, Rutgers J, French S, Moore TC (1997) Metastasis of an intracranial germinoma through a ventriculoperitoneal shunt: recurrence as a yolk-sac tumor. Pediatr Surg Int 12:24–27

Bamberg M, Metz K, Alberti W, Heckemann R, Schulz U (1984) Endodermal sinus tumor of the pineal region. Metastases through a ventriculoperitoneal shunt. Cancer 54:903–906

Beaumont TL, Kupsky WJ, Barger GR, Sloan AE (2007) Gliosarcoma with multiple extracranial metastases: case report and review of the literature. J Neurooncol 83:39–46

Becker H, Walter GF, Tritthart H, Oberbauer RW (1978) Extraneural metastasis of an oligodendroglioma in ventriculo-peritoneal shunt (in German). Onkologie 1:216–220

Blasco A, Dominguez P, Ballestin C, Arguelles M, de Agustin P (1993) Peritoneal implantation of pineal germinoma via a ventriculoperitoneal shunt. Acta Cytol 37:637–638

Blaszyk H, Hartmann A, Bjornsson J (2003) Cancer of unknown primary: clinicopathologic correlations. APMIS 111:1089–1094

Bloom G, Yang IV, Boulware D, Kwong KY, Coppola D, Eschrich S, Quackenbush J et al (2004) Multi-platform, multi-site, microarray-based human tumor classification. Am J Pathol 164:9–16

Bondy M, Ligon BL (1996) Epidemiology and etiology of intracranial meningiomas: a review. J Neurooncol 29:197–205

Braga et al. (2003) http://www.ncbi.nlm.nih.gov/pubmed/14599537

Bugat et al. (2003) http://www.ncbi.nlm.nih.gov/pubmed/12915904

Carrasco Torrents R, Sancho MA, Julia V, Montaner A, Costa JM, Morales L (2001) Intraabdominal metastasis of cerebellar medulloblastoma through ventriculoperitoneal shunt (in Spanish). An Esp Pediatr 54:83–85

Cerda-Nicolas M, Lopez-Gines C, Perez-Bacete M, Roldan P, Talamantes E, Barbera J (2003) Histologically benign metastatic meningioma: morphological and cytogenetic study. Case Rep J Neurosurg 98:194–198

Chakravarty BJ, Munn S, Lane MR (1991) Hepatic metastasis from a meningeal haemangiopericytoma. Aust NZ J Med 21:884–885

Chamberlain RS, Canes D, Brown KT, Saltz L, Jarnagin W, Fong Y, Blumgart LH (2000) Hepatic neuroendocrine metastases: does intervention alter outcomes ? J Am Coll Surg 190:432–445

Chang SM, Lillis-Hearne PK, Larson DA, Wara WM, Bollen AW, Prados MD (1995) Pineoblastoma in adults. Neurosurgery 37:383–390

Chang CC, Chang YY, Lui CC, Huang CC, Liu JS (2004) Meningeal hemangiopericytoma with delayed multiple distant metastases. J Chin Med Assoc 67:527–532

Charafe-Jauffret E, Lehmann G, Fauchon F, Michiels JF, Paquis P, Maraninchi D (2001) Vertebral metastases from pineoblastoma. Arch Pathol Lab Med 125:939–943

Chaux A, Reuter V, Lezcano C, Velazquez E, Codas R, Cubilla AL (2011) Autopsy findings in 14 patients with penile squamous cell carcinoma. Int J Surg Pathol 19:164–169

Chopra S, Frank SJ, Gu M (2010) Cytologic diagnosis of chordoma in a peritoneal effusion: a case report. Acta Cytol 54:341–344

Chua TC, Chu F, Morris DL (2011) Outcomes of single-centre experience of hepatic resection and cryoablation of sarcoma liver metastases. Am J Clin Oncol 34:317–320

Constantine C, Miller DC, Gardner S, Balmaceda C, Finlay J (2005) Osseous metastasis of pineoblastoma: a case report and review of the literature. J Neurooncol 74:53–57

Cranston PE, Hatten MT, Smith EE (1992) Metastatic pineoblastoma via a ventriculoperitoneal shunt: CT demonstration. Comput Med Imaging Graph 16:349–351

Culine S, Gazagne L, Ychou M, Romieu G, Fabbro M, Cupissol D, Dubois JB (1998) Carcinoma of unknown primary site. Apropos of 100 patients treated at the Montpellier regional center of cancer prevention (in French). Rev Med Interne 19:713–719

Dauplat J, Hacker NF, Nieberg RK, Berek JS, Rose TP, Sagae S (1987) Distant metastases in epithelial ovarian carcinoma. Cancer 60:1561–1566

Davies C, Schick B, Kronsbein H, Hendus J (1999) Meningeal hemangiopericytoma with liver metastasis (in German). HNO 47:183–187

Declercq H, De Man R, Vanderperre H, De Praetere P, Wilms G (1992) Peritoneal seeding of a cerebral malignant astrocytoma via a ventriculo-peritoneal shunt. J Belge Radiol 75:191–193

DeMatteo RP, Shah A, Fong Y, Jarnagin WR, Blumgart LH, Brennan MF (2001) Results of hepatic resection for sarcoma metastatic to liver. Ann Surg 234:540–547

Devkota J, Brooks BS, el Gammal T (1984) Ventriculoperitoneal shunt metastasis of a pineal germinoma. Comput Radiol 8:141–145

Di Lernia V, Ricci C, Zalaudek I, Argenziano G (2013) Metastasizing basal cell carcinoma. Cutis 92:244–246

Donovan DJ, Prauner RD (2005) Shunt-related abdominal metastases in a child with choroid plexus carcinoma: case report. Neurosurgery 56, E412

Enam SA, Abdulrauf S, Mehta B, Malik GM, Mahmood A (1996) Metastasis in meningioma. Acta Neurochir (Wien) 138:11172–11177

Enomoto K, Amano S, Sakurai K (2006) Two cases of obstructive jaundice that developed with breast cancer hepatic metastasis – a treatment by a bile duct stent obtaining high efficacy (in Japanese). Gan To Kagaku Ryoho 33:1907–1909

Estourgie et al. (2002) http://www.ncbi.nlm.nih.gov/pubmed/12173385

Fabiani et al. (1980) http://www.ncbi.nlm.nih.gov/pubmed/7195128

Fan F, Hernandez-Rios P, Damjanov I, Dusing RW (2006) Metastasis of ovarian ependymoma to the liver diagnosed by fine needle aspiration cytology. Acta Cytol 50:709–710

Farmer ER, Helwig EB (1980) Metastatic basal cell carcinoma: a clinicopathologic study of seventeen cases. Cancer 46:748–757

Fecteau AH, Penn I, Hanto DW (1998) Peritoneal metastasis of intracranial glioblastoma via a ventriculoperitoneal shunt preventing organ retrieval: case report and review of the literature. Clin Transplant 12:348–350

Ferguson JM, Finn J (1995) Intracranial meningioma with hepatic metastases and hypoglycaemia treated by

selective hepatic arterial chemo-embolization. Australas Radiol 39:97–99
Figueroa BE, Quint DJ, McKeever PE, Chandler WF (1999) Extracranial metastatic meningioma. Br J Radiol 72:513–516
Fizazi K (2006) Carcinoma of unknown primary site. Taylor & Francis, New York
Fondrinier E, Guérin O, Lorimier G (1997) A comparative study of metastatic patterns of ductal and lobular carcinoma of the breast from two matched series (376 patients) (in French). Bull Cancer 84:1101–1107
Fraser G, Rampling R, Smith C, Nicoll J, Stephen M (2000) Long-term survival following extra-neural metastasis from a pineoblastoma. J Neurooncol 48:141–144
Gaber AO, Rice P, Eaton C, Pietrafitta JJ, Spatz E, Deckers PJ (1983) Metastatic malignant disease of unknown origin. Am J Surg 145:493–497
Garcia-Conde M, Roldan-Delgado H, Martel-Barth-Hansen D, Manzano-Sanz C (2009) Anaplastic transformation of an atypical intraventricular meningioma with metastases to the liver: case report. Neurocirurgia (Astur) 20:541–549
Gaujoux S, Al-Ahmadie H, Allen PJ, Gonen M, Shia J, D'Angelica M, Dematteo R, Fong Y, Blumgart L et al (2012) Resection of adrenocortical carcinoma liver metastasis: is it justified? Ann Surg Oncol 19:2643–2651
Gollub MJ, Gruen DR, Dershaw DD (1996) Merkel cell carcinoma: CT findings in 12 patients. AJR Am J Roentgenol 167:617–620
Graf M, Blaeker H, Otto HF (1999) Extraneural metastasizing ependymoma of the spinal cord. Pathol Oncol Res 5:56–60
Grunenberger F, Bachellier P, Chenard MP, Massard F, Caraman PL, Perrin E, Zapf J et al (1999) Hepatic and pulmonary metastases from a meningeal hemangiopericytoma and severe hypoglycemia due to abnormal secretion of insulin-like growth factor: a case report. Cancer 85:2245–2248
Gururangan S, Heideman RL, Kovnar EH, Sanford RA, Kun LE (1994) Peritoneal metastases in two patients with pineoblastoma and ventriculo-peritoneal shunts. Med Pediatr Oncol 22:417–420
Guthrie BL, Eberesold MJ, Scheithauer BW, Shaw EG (1989) meningeal hemangiopericytoma: histopathological features, treatment, and long-term follow-up of 44 cases. Neurosurgery 25:514–522
Hafner GH, Rao U, Karakousis CP (1995) Liver metastases from soft tissue sarcomas. J Surg Oncol 58:12–16
Haimovic IC, Sharer L, Hyman RA, Beresford HR (1981) Metastasis of intracranial germinoma through a ventriculoperitoneal shunt. Cancer 48:1033–1036
Hamilton and Langlands (1987) http://www.ncbi.nlm.nih.gov/pubmed/3114181
Han SR, Yoon SW, Yee GT, Choi CY, Lee DJ, Sohn MJ, Chang CH, Whang CJ (2008) Extraneural metastases of anaplastic oligodendroglioma. J Clin Neurosci 15:946–949
Han SJ, Yang I, Tihan T, Prados MD, Parsa AT (2010) Primary gliosarcoma: key clinical and pathologic distinctions from glioblastoma with implications as a unique oncologic entity. J Neurooncol 96:313–320
Han SJ, Clark AJ, Ivan ME, Parsa AT, Perry A (2011) Pathology of pineal parenchymal tumors. Neurosurg Clin N Am 22:335–340
Hartmann C, von Deimling A (2009) Molecular pathology of oligodendroglial tumors. Recent Results Cancer Res 171:25–49
Herd MK, Murugaraj V, Ghataura SS, Brennan PA, Anand R (2012) Low-grade mucoepidermoid carcinoma of the palate – a previously unreported case of metastasis to the liver. J Oral Maxillofac Surg 70:2343–2346
Hess KR, Abbruzzese MC, Lenzi R, Raber MN, Abbruzzese JL (1999) Classification and regression tree analysis of 1000 consecutive patients with unknown primary carcinoma. Clin Cancer Res 5:3403–3410
Hoffman HJ, Hendrick EB, Humphreys RP (1976) Metastasis via ventriculoperitoneal shunt in patients with medulloblastoma. J Neurosurg 44:562–566
Hogan BA, Thornton FJ, Brannigan M, Browne TJ, Pender S, O'Kelly P, Lyon SM et al (2002) Hepatic metastases from an unknown primary neoplasm (UPN): survival, prognostic indicators and value of extensive investigations. Clin Radiol 57:1073–1077
Ihse I, Lindell G, Tibblin S (2001) Neuroendocrine tumors metastatic to the liver. In: Holzheimer RG, Mannick JA (eds) Surgical treatment: evidence-based and problem-oriented. Zuckschwerdt Publishers, Munich
Ingold B, Schulz S, Budczies J, Neumann U, Ebert MP, Weichert W, Röcken C (2009) The role of vascular CXCR4 expression in colorectal carcinoma. Histopathology 55:576–586
Ishibashi Y, Okada H, Mori T, Suzuki J (1983) Meningioma with extracranial multiple metastases – a case report (in Japanese). No Shinkei Geka 11:203–208
Ismael G, de Azambuja E, Awada A (2006) Molecular profiling of a tumor of unknown origin. N Engl J Med 355:1071–1072
Iwamuro Y, Seo S, Hirose Y, Jito J, Shirahata M, Tokime T, Hosotani K, Tokuriki Y (2002) Intrathecal and intraperitoneal germinomas occurring 20 years after total removal of a pineal teratoma. Case Rep J Neurosurg 96:364–367
Iwanowski L, Kupryjanczyk J, Kuchna I, Matyia E, Wierzba-Bobrowicz T, Zabek M (1997) Embryonal carcinoma of the pineal gland with yolk sac tumor differentiation. A case report. Folia Neuropathol 35:128–132
Iwasa Y, Nakashima Y, Okajima H, Morishita S (1998) Sacral chordoma in early childhood: clinicopathological and immunohistochemical study. Pediatr Dev Pathol 1:420–426
Jacobs JJ, Rosenberg AE (1989) Extracranial skeletal metastasis from a pineoloblastoma. A case report and review of the literature. Clin Orthop Relat Res 247:256–260

James TGI, Pagel W (1951) Oligodendroglioma with extracranial metastases. Br J Surg 39:56–65
Jamjoom ZA, Jamjoom AB, Sulaiman AH, Naim-Ur-Rahman, al Rabiaa A (1993) Systemic metastasis of medulloblastoma through ventriculoperitoneal shunt: report of a case and critical analysis of the literature. Surg Neurol 40:403–410
Jaques DP, Coit DG, Casper ES, Brennan MF (1995) Hepatic metastases from soft-tissue sarcoma. Ann Surg 221:392–397
Jellinger K, Minauf M, Salzer-Kuntschik M (1969) Oligodendroglioma with extraneural metastases. J Neurol Neurosurg Psychiatr 32:249–253
Jonas S, Bechstein WO, Lemmens HP, Neuhaus R, Thalmann U, Neuhaus P (1996) Liver graft-transmitted glioblastoma multiforme. A case report and experience with 13 multiorgan donors suffering from primary cerebral neoplasia. Transpl Int 9:426–429
Kamby C, Dirksen H, Vejborg I, Daugaard S, Guldhammer B, Rossing N, Mouridsen HT (1987) Incidence and methodoligic aspects of the occurrence of liver metastases in recurrent breast cancer. Cancer 59:1524–1539
Kaneko T, Harada A, Isshiki K, Murakami H, Nakao A, Nonami T, Yano M, Kakumu S et al (1993) Hemangiopericytomatous meningioma metastasized to the liver: report of a case and review of the literature. Surg Today 23:644–648
Kashyap R, Ryan C, Sharma R, Maloo MK, Safadjou S, Graham M, Tretheway D et al (2009) Liver grafts from donors with central nervous system tumors: a single-center perspective. Liver Transpl 15:1204–1208
Kayama T, Mori T, Wada T (1981) Systemic metastasis of brain tumors via ventriculoperitoneal shunt. Report of two cases. Neurol Med Chir (Tokyo) 21:1177–1182
Kepes JJ (1982) Meningiomas: biology, pathology, and differential diagnosis. Masson monographs in diagnostic pathology, vol 4. Masson, New York
Kimura N, Namiki T, Wada T, Sasano N (1984) Peritoneal implantation of endodermal sinus tumor of the pineal region via a ventriculoperitoneal shunt. Cytodiagnosis with immunocytochemical demonstration of alpha-fetoprotein. Acta Cytol 28:143–147
Kleinman GM, Hochberg FH, Richardson EP (1981) Systemic metastases from medulloblastoma: report of two cases and review of the literature. Cancer 48:2296–2309
Kochanek S, Schröder R, Firsching R (1986) Hemangiopericytoma of meninges. I. Histopathological variability and differential diagnosis. Zentralbl Neurochir 47:183–190
Kochbati L, Bouaouina N, Hentati D, Nasr C, Besbes M, Benna F, Boussen H, Maalej M (2006) Medulloblastoma with extracentral nervous system metastases: clinical presentation and risk factors (in French). Cancer Radiother 10:107–111
Krishna M (2010) Diagnosis of metastatic neoplasms. An immunohistochemical approach. Arch Pathol Lab Med 134:207–215
Ku JK, Vasquez JC, Hoyt DB, Coimbra R (2005) Metastatic meningioma to the liver successfully treated with a wedge resection and radiation therapy: report of a case. Surg Today 35:82–85
Kumar R, Jain R, Tandon V (1999) Thalamic glioblastoma with cerebrospinal fluid dissemination in the peritoneal cavity. Pediatr Neurosurg 31:242–245
Kun LE, Tang TT, Sty JR, Camitta BM (1981) Primary cerebral germinoma and ventriculoperitoneal shunt metastasis. Cancer 48:213–216
Lambertz N, Koehler J, Schulte DM, Kuehl H, Wohlschlaeger J, Hense J, Schuler M, Mueller OM (2011) Multivisceral systemic metastases from an intracranial anaplastic meningioma: a case report and review of literature. Clin Neurol Neurosurg 113:592–595
Lang H, Nussbaum KT, Kaudel P, Frühauf N, Flemming P, Raab R (2000) Hepatic metastases from leiomyosarcoma: a single-center experience with 34 liver resections during a 15-year period. Ann Surg 231:500–505
Lazaridis G, Pentheroudakis G, Fountzilas G, Pavlidis N (2008) Liver metastases from cancer of unknown primary (CUPL): a retrospective analysis of presentation, management and prognosis in 49 patients and systematic review of the literature. Cancer Treat Rev 34:693–700
Lazarus HM, Herzig RH, Bornstein R, Laipply TC (1980) Metastatic squamous cell carcinoma of the skin. J Natl Med Assoc 72:1196–1199
Leifer D, Moore T, Ukena T, Wilner D, Thor A, Hedley-Whyte ET (1989) Multifocal glioblastoma with liver metastases in the absence of surgery. Case Rep J Neurosurg 71:772–776
Lesimple et al. (2003) http://www.ncbi.nlm.nih.gov/pubmed/14715428
Lenzi et al. (1997) http://www.ncbi.nlm.nih.gov/pubmed/9164218
Lim MC, Kang S, Lee KS, Han SS, Park SJ, Seo SS, Park SY (2009) The clinical significance of hepatic parenchymal metastasis in patients with primary epithelial ovarian cancer. Gynecol Oncol 112:28–34
Loiacono F, Morra A, Venturini S, Balestreri L (2006) Abdominal metastases of medulloblastoma related to a ventriculoperitoneal shunt. AJR Am J Roentgenol 186:1548–1550
Loizzi V, Rossi C, Cormio G, Cazzolla A, Altomare D, Selvaggi L (2005) Clinical features of hepatic metastasis in patients with ovarian cancer. Int J Gynecol Cancer 15:26–31
Lormeau B, Miossec P, Sibony M, Valensi P, Attali JR (1997) Adrenocorticotropin-producing pituitary carcinoma with liver metastasis. J Endocrinol Invest 20:230–236
LoRusso PM, Tapazoglou E, Zarbo RJ, Cullis PA, Austin D, Al-Sarraf M (1988) Intracranial astrocytoma with diffuse bone marrow metastasis: a case report and review of the literature. J Neurooncol 6:53–59

Louis DN, Ohgaki H, Wiestler OD, Cavanee WK (2007a) Who classification of tumours of the central nervous system. IARC, Lyon

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007b) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109

Lutterbach J, Liegibel J, Koch D, Madlinger A, Frommhold H, Pagenstecher A (2001) Atypical teratoid/rhabdoid tumors in adult patients: case report and review of the literature. J Neurooncol 52:49–56

Lutterbach J, Fauchon F, Schild SE, Chang SM, Pagenstecher A, Volk B, Ostertag C et al (2002) Malignant pineal parenchymal tumors in adult patients: patterns of care and prognostic factors. Neurosurgery 51:44–55

Macdonald DR, O'Brien RA, Gilbert JJ, Cairncross JG (1989) Metastatic anaplastic oligodendroglioma. Neurology 39:1593–1596

Madhuri TK, Butler-Manuel S, Karanjia N, Tailor A (2010) Liver resection for metastases arising from recurrent granulosa cell tumor of the ovary – a case series. Eur J Gynaecol Oncol 31:342–344

Magtibay PM, Friedman JA, Rao RD, Buckner JC, Cliby WA (2003) Unusual presentation of adult metastatic peritoneal medulloblastoma associated with a ventriculoperitoneal shunt: a case study and review of the literature. Neuro Oncol 5:217–220

Makeever LC, King JD (1966) Medulloblastoma with extracranial metastasis through a ventriculovenous shunt. Report of a case and review of the literature. Am J Clin Pathol 46:245–249

Marchevsky AM, Gupta R, Balzer B (2010) Diagnosis of metastatic neoplasms. A clinicopathologic and morphologic approach. Arch Pathol Lab Med 134:194–206

Margolin KA, Pak HY, Esensten ML, Doroshow JH (1985) Hepatic metastasis in granulosa cell tumor of the ovary. Cancer 56:691–695

Markman (1982) http://www.ncbi.nlm.nih.gov/pubmed/7177043

Maruki C, Takara K, Abe K, Tsunoda A, Ebato M, Ikeya F (2000) Primary pineal embryonal carcinoma occurring in a middle aged man (in Japanese). No Shinkei Geka 28:909–912

Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O, Funata N, Seto T (1997) Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. J Neurosurg 86:446–455

Matsuyama J, Mori T, Hori S, Nakano T, Yamada A (1989) Gliosarcoma with multiple extracranial metastases. Case report (in Japanese). Neurol Med Chir (Tokyo) 29:938–943

Matyia E, Grajkowska W, Nauman P, Bonicki W, Bojarski P, Marchel A (2010) Necrotic rhabdoid meningiomas with aggressive clinical behavior. Clin Neuropathol 29:307–316

Mayordomo JI, Guerra JM, Guijarro C, Garcia-Prats MD, Gomez A, Lopez-Brea M et al (1993) Neoplasms of unknown primary site: a clinicopathological study of autopsied patients. Tumori 79:321–324

Maywardi et al. (2012) http://www.ncbi.nlm.nih.gov/pubmed/22421721

Merimsky O, Terrier P, Stanca A, Le Chevalier T, Spielmann M, Tursz T, Le Cesne A (1999) Liver metastases from extremity soft tissue sarcoma. Am J Clin Oncol 22:70–72

Miyamoto S, Matsuda W, Tsunoda T, Sasaki M, Itabashi M (2004) Multiple extracranial metastases from a meningeal hemangiopericytoma and severe hypoglycemia: a case report (in Japanese). No Shinkei Geka 32:367–372

Moertel (1979) http://www.ncbi.nlm.nih.gov/pubmed/484971

Moir JA, Haugk B, French JJ (2010) Hepatic metastasis via a ventriculo-peritoneal shunt from an intracranial meningioma: case report and review of the literature. Case Rep Gastroenterol 4:267–272

Monzon FA, Koen TJ (2010) Diagnosis of metastatic neoplasms. Molecular approaches for identification of tissue of origin. Arch Pathol Lab Med 134:216–224

Moss TH (1987) Immunohistochemical characteristics of haemangiopericytic meningiomas: comparison with typical meningiomas, haemangioblastomas and haemangiopericytomas from extracranial sites. Neuropathol Appl Neurobiol 13:467–480

Motomochi M, Makita Y, Nabeshima S, Aoyama I, Ichijima K, Yamabe H, Kobashi Y (1980) A case of intracranial germinoma with multiple remote metastases (in Japanese). No Shinkei Geka 8:563–570

Mousseau M, Scharer R, Lutz JM, Ménégoz F, Faure H, Swiercz P (1991) Hepatic metastasis of unknown primary site (in French). Bull Cancer 78:725–736

Muir C (1995) Cancer of unknown primary site. Cancer 75(1 suppl):353–356

Nabeya Y, Okazaki Y, Watanabe Y, Tohnosu N, Yamazaki M, Matsuda M, Iizuka H et al (1998) Metastatic malignant meningioma of the liver with hypoglycemia: report of a case. Surg Today 28:953–958

Nakajima T, Sekoguchi S, Nishikawa T, Takashima H, Watanabe T, Minami M, Itoh Y et al (2005) Multifocal intraportal invasion of breast carcinoma diagnosed by laparoscopy-assisted liver biopsy. World J Gastroenterol 11:2360–2363

Neste MG, Francis IR, Bude RO (1996) Hepatic metastases from granulosa cell tumor of the ovary: CT and sonographic findings. AJR Am J Roentgenol 166:1122–1124

Newton HB, Rosenblum MK, Walker RW (1992a) Extraneural metastases of infratentorial glioblastoma multiforme to the peritoneal cavity. Cancer 69:2149–2153

Newton HB, Henson J, Walker RW (1992b) Extraneural metastases in ependymoma. J Neurooncol 14:135–142

Oemus K, Gerlach H, Rath FW (1992) A rare complication of shunt therapy. Metastasis of brain tumors by cerebrospinal fluid drainage (in German). Zentralbl Neurochir 53:25–32

Oien KA (2009) Pathologic evaluation of unknown primary cancer. Semin Oncol 36:8–37

Oliveira AM, His BL, Weremovicz S, Rosenberg AE, Dal CP, Joseph N, Bridge JA et al (2004) USP6 (Tre2) fusion oncogenes in aneurysmal bone cyst. Cancer Res 64:1920–1923

Olsha O, Gottschalk-Sabag S (1995) Metastatic pleomorphic adenoma. Invasion Metastasis 15:163–166

Onofre AS, Pomjanski N, Buckstegge B, Böcking A (2007) Immunocytochemical diagnosis of hepatocellular carcinoma and identification of carcinomas of unknown primary metastatic to the liver on fine-needle aspiration cytologies. Cancer 111:259–268

Pallini R, Bozzini V, Scerrati M, Zuppi C, Zappacosta B, Rossi GF (1991) Bone metastasis associated with shunt-related peritoneal deposits from a pineal germinoma. Case report and review of the literature. Acta Neurochir (Wien) 109:78–83

Papo M, Fernandez J, Quer JC, Sirvent JJ, Richart C (1996) Metastatic breast carcinoma presenting as obstructive jaundice. Am J Gastroenterol 91:2240–2241

Pasquier B, Pasquier D, N'Golet A, Panh MH, Couderc P (1980) Extraneural metastases of astrocytomas and glioblastomas: clinicopathological study of two cases and review of literature. Cancer 45:112–125

Pentheroudakis G, Greco FA, Pavlidis N (2009) Molecular assignment of tissue of origin in cancer of unknown primary may not predict response to therapy or outcome: a systematic literature review. Cancer Treat Rev 35:221–227

Perchalski JE, Hall KL, Dewar MA (1992) Metastasis of unknown origin. Prim Care 19:747–757

Perry A, Scheithauer BW, Stafford SL, Abell-Aleff PC, Meyer FB (1998) "Rhabdoid" meningioma: an aggressive variant. Am J Surg Pathol 22:1482–1490

Pfletschinger J, Olive D, Czorny A, Marchal AL, Hoeffel JC, Schmitt M, Brasse F (1986) Peritoneal metastasis of a pineoblastoma in a patient with a ventriculoperitoneal shunt (in French). Pediatrie 41:231–236

Piccirilli M, Brunetto GM, Rocchi G, Giangaspero F, Salvati M (2008) Extra central nervous system metastases from cerebral glioblastoma multiforme in elderly patients. Clinico-pathological remarks on our series of seven cases and critical review of the literature. Tumori 94:40–51

Pimiento JM, Teso D, Malkan A, Dudrick SJ, Palesty JA (2007) Cancer of unknown primary origin: a decade of experience in a community-based hospital. Am J Surg 194:833–837

Pisters PW, Sondack VK (2002) Metastatic patterns of extremity liposarcoma and their outcome. J Surg Oncol 80:94–95

Postlethwaite KR, Courtney DJ, Gosney JR (1990) Basal cell carcinoma with hepatic metastases. Br J Oral Maxillofac Surg 28:111–113

Pouessel D, Thezenas S, Culine S, Becht C, Senesse P, Ychou M (2005) Hepatic metastases from carcinomas of unknown primary site. Gastroenterol Clin Biol 29:1224–1232

Pouessel D, Gallet B, Bibeau F, Avancès C, Iborra F, Sénesse P, Culine S (2007) Liver metastases in prostate carcinoma: clinical characteristics and outcome. BJU Int 99:807–811

Que FG, Nagorney DM, Batts KP, Linz LJ, Kvols LK (1995) Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 169:36–42

Raguin JM, Wendling D, Montcuquet P, Guidet M (1987) Metastatic chordoma. General review apropos of 2 cases (in French). Rev Rhum Mal Osteoartic 54:575–582

Rajaram V, Brat DJ, Perry A (2004) Anaplastic meningioma versus meningeal hemangiopericytoma: immunohistochemical and genetic markers. Hum Pathol 35:1413–1418

Rampurwala M, Pazooki M, Schauer P (2011) delayed hepatic metastasis from a benign fibroblastic meningioma thirty-one years after surgical resection of the intracranial tumor. J Clin Oncol 29:e214–e215

Rehders A, Peiper M, Stoecklein NH, Alexander A, Boelke E, Knoefel WT, Rogiers X (2009) Hepatic metastasectomy for soft-tissue sarcomas: is it justified ? World J Surg 33:111–117

Rickert CH (2003) Extraneural metastases of paediatric brain tumors. Acta Neuropathol 105:309–327

Rickert CH, Reznik M, Lenelle J, Rinaldi P (1998) Shunt-related abdominal metastasis of cerebral teratocarcinoma: report of an unusual case and review of the literature. Neurosurgery 42:1378–1382

Robert M, Wastie M (2008) Glioblastoma multiforme: a rare manifestation of extensive liver and bone metastases. Biomed Imag Interv J 4, e3

Rochkind S, Blatt I, Sadeh M, Goldhammer Y (1991) Extracranial metastases of medulloblastoma in adults: literature review. J Neurol Neurosurg Psychiatry 54:80–86, extensive liver and bone metastases. Biomed.Imaging Interv. J. 4, e3

Rodriguez FJ, Scheithauer BW, Jenkins R, Burger PC, Rudzinskiy P, Vlodavsky E et al (2007) Gliosarcoma arising in oligodendroglial tumors ("oligosarcoma"): a clinicopathologic study. Am J Surg Pathol 31:351–362

Rubin BP, Skarin AT, Pisick E, Rizk M, Salgia R (2001) Use of cytokeratins 7 and 20 in determining the origin of metastatic carcinoma of unknown primary, with special emphasis on lung cancer. Eur J Cancer Prev 10:77–82

Saad AG, Sachs J, Turner CD, Proctor M, Marcus KJ, Wang L, Lidov H, Ullrich NJ (2007) Extracranial metastases of glioblastoma in a child: case report and review of the literature. J Pediatr Hematol Oncol 29:190–194

Saibara T, Hashimoto T, Takahashi M, Horie S, Fukami T, Nakagawa Y (1991) Abdominal metastasis of a pineal region tumor through ventriculoperitoneal shunt. Case report (in Japanese). Neurol Med Chir (Tokyo) 31:1012–1017

Schönsteiner SS, Bommer M, Haenle MM, Klaus B, Scheuerle A, Schmid M, Mayer-Steinacker R (2011)

Rare phenomenon: liver metastases from glioblastoma multiforme. J Clin Oncol 29:e668–e671
Schuster H, Jellinger K, Gund A, Regele H (1976) Extracranial metastases of anaplastic cerebral gliomas. Acta Neurochir (Wien) 35:247–259
Schwentner I, Obrist P, Thumfart W, Sprinzl G (2006) Distant metastasis of parotid gland tumors. Acta Otolaryngol 126:340–345
Sharma D, Flora G, Grunberg SM (1991) Chemotherapy of metastatic Merkel cell carcinoma: case report and review of the literature. Am J Clin Oncol 14:166–169
Shaw PH, Adams R, Jordan C, Crosby TD (2007) A clinical review of the investigation and management of carcinoma of unknown primary in a single cancer network. Clin Oncol (R Coll Radiol) 19:87–95
Shi ZP, Lin YS, Lin CK, Chen HC, Wang CH (2009) Multiple metastatic progression of meningeal hemangiopericytoma initially diagnosed as atypical meningioma with temporal bone invasion. Otolaryngol Head Neck Surg 140:278–280
Shibasaki T, Takeda F, Kawafuchi J (1977) Extraneural metastases of malignant brain tumors through ventriculoperitoneal shunt – report of two autopsy cases and a review of the literature (in Japanese). No Shinkei Geka 5:71–79
Shimanskii VN, Rotin DL, Shishkina LV, Otarashvili IA, Kobiakov GL (2011) Meningioma with extracranial metastases (in Russian). Zh Vopr Neirokhir Im N N Burdenko 75:62–67
Shinmura F, Takayasu K, Sakata R, Ariwa R, Takagi S (1983) Autopsy case of extra-neural metastasis of suprasellar pineal germinoma (in Japanese). Gan No Rinsho 29:832–837
Shinmura Y, Miura K, Yajima S, Tsutsui Y (2003) Sacrococcygeal chordoma in infancy showing an aggressive clinical course: an autopsy case report. Pathol Int 53:473–477
Shuto T, Fujino H, Inomori S, Nakayama S, Satoh H, Ideguchi H, Tashiro Y (1995) Glioblastoma multiforme with liver metastasis – case report (in Japanese). No To Shinkei 47:772–777
Singhal A, Shrago SS, Li SF, Huang Y, Kohli V (2010) A hepatic metastasis from pleomorphic adenoma of salivary gland: an unusual presentation. Hepato-Gastroenterol 57:330–333
Smith DR, Hardman JM, Earle KM (1969) Contiguous glioblastoma multiforme and fibrosarcoma with extracranial metastasis. Cancer 24:270–276
Soares P, Ferlicot S, Laasou K, Castaing D, Benoit G (2003) Renal and hepatic metastasis from meningeal hemangiopericytoma (in French). Prog Urol 13:498–501
Song et al. (2002) http://www.ncbi.nlm.nih.gov/pubmed/12647637
Spataro J, Sacks O (1968) Oligodendroglioma with remote metastases: case report. J Neurosurg 28:373–379
Spatola C, Privitera G (2004) Recurrent intracranial hemangiopericytoma with extracranial and unusual multiple metastases: case report and review of the literature. Tumori 90:265–268
Speel EJ, van de Wouw AJ, Claessen SM, Haesevoets A, Hopman AH, van der Wurff AA et al (2008) Molecular evidence for a clonal relationship between multiple lesions in patients with unknown primary adenocarcinoma. Int J Cancer 123:1292–1300
Spolverato G, Fite J, Bishop J, Argani P, Pawlik TM (2014) Liver metastasis as the initial presentation of adenoid cystic carcinoma. Dig Dis Sci 59:2004–2006
Sreenan JJ, Prayson RA (1997) Gliosarcoma. A study of 13 tumors, including p53 and CD34 immunohistochemistry. Arch Pathol Lab Med 121:129–133
Staub E, Buhr HJ, Gröne J (2010) Predicting the site of origin of tumors by a gene expression signature derived from normal tissues. Oncogene 29:4485–4492
Su WT, Rutigliano DN, Gholizadeh M, Jarnagin WR, Blumgart LH, La Quaglia MP (2007) Hepatic metastasectomy in children. Cancer 109:2089–2092
Sundaram C, Uppin SG, Uppin MS, Rekha JS, Panigrahi MK, Purohit AK, Rammurti S (2010) A clinicopathological and immunohistochemical study of central nervous system hemangiopericytomas. J Clin Neurosci 17:469–472
Suzuki K, Morii K, Nakamura J, Kaneko S, Ukisu J, Hanyu O, Nakagawa O, Aizawa Y (2002) Adrenocorticotropin-producing pituitary carcinoma with metastasis to the liver in a patient with Cushing's disease. Endocr J 49:153–158
Swanbeck G, Hillstrom L (1969) Analysis of etiological factors of squamous cell skin cancer of different locations: part 1: the lower limbs. Acta Derm Venereol (Stockh) 49:427–435
Talamo TS, Mendelow H (1985) Primary intracranial germinoma with massive ventriculoperitoneal shunt metastases. J Surg Oncol 28:39–41
Tate MC, Rutkowski MJ, Parsa AT (2011) Contemporary management of pineoblastoma. Neurosurg Clin N Am 22:409–412
Tateishi U, Hasegawa T, Muramatsu Y, Moriyama N (2003) Hepatic metastases of soft tissue angiosarcoma: CT and MR imaging findings. Abdom Imaging 28:660–664
Tavernaraki A, Andriotis E, Moutaftsis E, Attard A, Liodantonaki P, Stasinopoulou M (2003) Isolated liver metastasis from sacral chordoma. Case report and review of the literature. J BUON 8:381–383
Taylor RM, Kashima TG, Hemingway FK, Dongre A, Knowles HJ, Athanasou NA (2012) CD14- mononuclear stromal cells support (CD14+) monocyte-osteoclast differentiation in aneurysmal bone cyst. Lab Invest 92:600–605
Tot T (2004) Identifying colorectal metastases in liver biopsies: the novel CDX2 antibody is less specific than the cytokeratin 20+/CK7- phenotype. Med Sci Monit 10:BR139–BR143
Tot T, Samii S (2003) The clinical relevance of cytokeratin phenotyping in needle biopsy of liver metastasis. APMIS 111:1075–1082

Triller J, Goldhirsch A, Reinhard JP (1985) Subcapsular liver metastasis in ovarian cancer. Computed tomography and surgical staging. Eur J Radiol 5:261–266

Triolo PJ, Schulz EE (1980) Metastatic germinoma (pinealoma) via a ventriculoperitoneal shunt. AJR Am J Roentgenol 135:854–855

Uchino M, Nemoto M, Ohtsuka T, Seiki Y, Shibata I (1999) Extraneural metastasis of pineal germinoma through a ventriculoperitoneal shunt, following histological change (in Japanese). No Shinkei Geka 27:269–274

Ung AO, Triscott JA, Leditschke JF, Smith JA (1993) Metastasis of pineal germinoma via ventriculoperitoneal shunt. Aust NZ J Surg 63:409–412

Uzuka T, Kakita A, Inenaga C, Takahashi H, Tanaka R, Takahashi H (2007) Frontal anaplastic oligodendroglioma showing multi-organ metastases after a long clinical course. Case report. Neurol Med Chir (Tokyo) 47:174–177

van de Luijtgaarden AC, Veth RP, Slootweg PJ, Wijers-Koster PM, Schultze Kool LJ et al (2009) Metastatic potential of an aneurysmal bone cyst. Virchows Arch 455:455–459

Van der Gaast A, Verwij J, Planting AS, Stoter G, Henzen-Logmans SC (1996) The value of immunohistochemistry in patients with poorly differentiated adenocarcinomas and undifferentiated carcinomas of unknown primary. J Cancer Res Clin Oncol 122:181–185

Van der Klaauw AA, Kienitz T, Strasburger CJ, Smit JW, Romijn JA (2009) Malignant pituitary corticotroph adenomas: report of two cases and a comprehensive review of the literature. Pituitary 12:57–66

van der Wouw AJ, Janssen-Heijnen ML, Coebergh JW, Hillen HF (2002) Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984–1992. Eur J Cancer 38:409–413

van der Wouw AJ, Jansen RL, Speel EJ, Hillen HF (2003) The unknown biology of the unknown primary tumour: a literature review. Ann Oncol 14:191–196

Von Domarus H, Stevens PJ (1984) Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. J Am Acad Dermatol 10:1043–1060

Wakabayashi T, Yoshida J, Kageyama N, Mutsuga N, Takeuchi Y (1985) Extraneural metastasis of malignant glioma through a ventriculo-peritoneal shunt: growth in peritoneal cavity as ascetic form (in Japanese). No Shinkei Geka 13:547–552

Wang JN, Lin SJ, Chio CC, Liu HM (1995) Suprasellar embryonal carcinoma: report of one case. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 36:438–441

Wang Z, Kong M, Li J, Xiao W, Zheng S (2011) Intraspinal rhabdoid meningioma metastasis to the liver. J Clin Neurosci 18:714–716

Warren S, Hoerr SO (1939) A study of pathologically verified epidermoid carcinoma of the skin. Surg Gynecol Obstet 69:726–737

Widjaja A, Mix H, Gölkel C, Flemming P, Egensperger R, Holstein A, Rademaker J, Becker H et al (2000) Uncommon metastasis of a glioblastoma multiforme in liver and spleen. Digestion 61:219–222

Wiendl H, Feiden W, Scherieble H, Renz T, Dichgans J, Weller M (2003) March 2003: a 41-year-old female with a solitary lesion in the liver. Brain Pathol 13:421–423

Wilson ER, Takei Y, Bikoff WT, O'Brien MS, Tindall GT, Boehm WM (1979) Abdominal metastases of primary intracranial yolk sac tumors through ventriculoperitoneal shunts: report of three cases. Neurosurgery 5:356–364

Wong KT, Koh KB, Lee SH, Chee CP (1996) Intracranial germinoma metastasizing via a ventriculo-peritoneal shunt. Singap Med J 37:441–442

Yokosuka K, Ishii R, Suzuki Y, Hirano K, Ishii N, Sekihara Y, Hamazaki S, Nishimura H (2007) Extraneural metastasis of high grade glioma without simultaneous central nervous system recurrence. Case Rep Neurol Med Chir (Tokyo) 47:273–277

Yokoyama H, Ono H, Mori K, Ishikawa M, Kihara M (1985) Extracranial metastasis of glioblastoma with sarcomatous component. Surg Neurol 24:641–645

Youngs GR, Scheuer PJ (1973) Histologically benign mixed parotid tumour with hepatic metastasis. J Pathol 109:171–172

Zacherl M, Bernhardt GA, Zacherl J, Gruber G, Komprat P, Bacher H, Mischinger HJ et al (2011) Surgery for liver metastases originating from sarcoma-case series. Langenbecks Arch Surg 396:1083–1091

Zustovich F, Della Puppa A, Scienza R, Anselmi P, Furlan C, Cartei G (2008) Metastatic oligodendrogliomas: a review of the literature and case report. Acta Neurochir (Wien) 150:699–702

Metastatic Liver Disease: Secondary Alterations of Hepatic Metastases

109

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_109

Abstract

Hepatic metastases undergo several types of secondary changes. Part of these alterations is mainly observed in tumor progression, when neoplasms increase in size and are subject to decreasing vascular supply and oxygenation. Large and rapidly growing hepatic metastases typically show necrosis. This necrosis is commonly of the coagulation type and is, in the absence of chemotherapy, caused by tumor hypoxia. Hypoxic necrosis mainly involves central parts of a metastatic nodule, while blood circulation in peripheral parts is preserved. Usual necrosis can also be induced by chemotherapy, which in addition can elicit infarct-like necrosis. Necrotic tumor tissue often undergoes dystrophic calcification. Rupture of tumor blood vessels in necrotic areas may result in massive hemorrhage, and involvement of adjacent bile ducts induces bile impregnation of necrotic areas. Large necrosis may undergo sequestration, can burst, or become infected by circulating or ascending bacteria. Infection of necrotic tissue may result in large collections of pus and, in case of infection with gas-producing microorganisms, show pneumatic lesions. In necrotic metastases, anaerobic bacteria can elicit hepatic necrobacillosis. A rare secondary alteration of metastases is spontaneous regression, known for several types of tumors.

Necrosis and Infarction of Hepatic Metastases

Introduction

Large and rapidly growing hepatic metastases typically undergo necrosis, sometimes extensive, causing characteristic secondary phenomena with an impact on clinic-radiological diagnosis and changing the biology of the metastasis. In diagnostic surgical pathology, necrosis of metastases is a difficult challenge, because it may be very demanding to answer the question as to whether viable tumor still exists in a given metastatic nodule. Approaches to solve this question are discussed in a separate chapter.

Necrosis of hepatic metastases, and specifically of carcinoma metastases, presents as one of several patterns, which reflect the dynamics of necrosis and secondary phenomena modifying the necrosis' morphology.

Coagulation Necrosis (So-Called Usual Necrosis or Dirty Necrosis)

Coagulation necrosis of a carcinoma metastasis is the most common phenotype. In the absence of chemotherapy, it is caused by hypoxia and thus reflects the morphology of other ischemic necroses (Figs. 1, 2, 3, and 4). Macroscopically, the center of a metastatic nodule is occupied by a whitish to "dirty-looking" mass with a finely granular texture on cut surfaces. When cutting through this mass, artifacts may occur, e.g., slit-like spaces caused by shearing forces in a tissue with a markedly reduced coherence or the falling off of entire

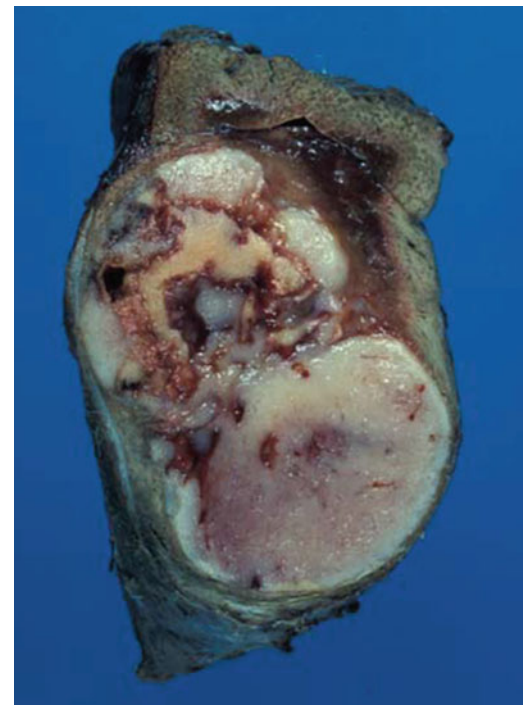

Fig. 1 Focal necrosis and hemorrhage of hepatic metastasis

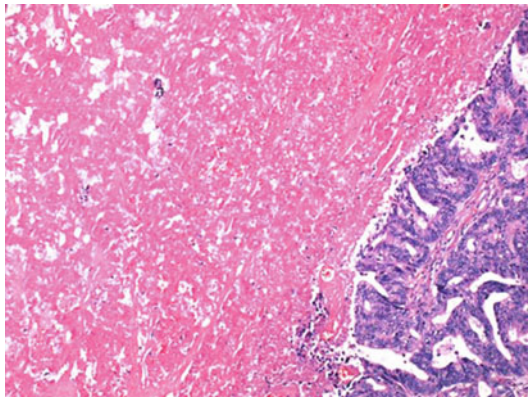

Fig. 2 Massive necrosis of colorectal carcinoma metastasis of the liver. The original structure of adenocarcinoma is still seen in the form of shadow tumor cells (hematoxylin and eosin stain)

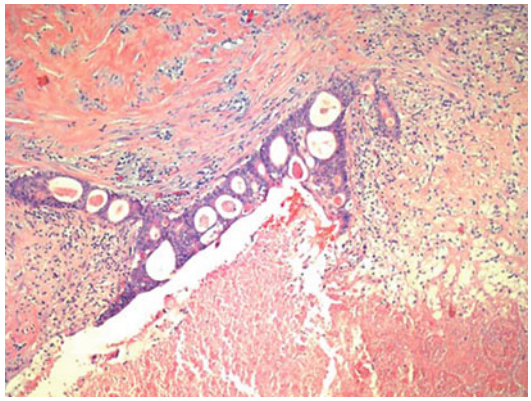

Fig. 3 Extensive necrosis of hepatic colorectal carcinoma metastasis. Note that the tumor stroma remains intact (left upper corner; hematoxylin and eosin stain)

tumor fragments following cutting. Greasy masses are typically left on the knife's blade. The transition between the necrosis and viable tumor tissue at the nodules periphery is often abrupt. In some tumors, the color of the necrotic area deviates from the common whitish tinge, e.g., being yellowish or pink or blackish in the case of malignant melanoma. Coagulation necrosis causes a reduction in tissue mass. This is best seen in necrotic nodules situated in the subcapsular area of the liver. Necrosis in such nodules typically causes the development of depressed central zone or dimple, called umbilication. The center of this tumor umbilicus is often pale or

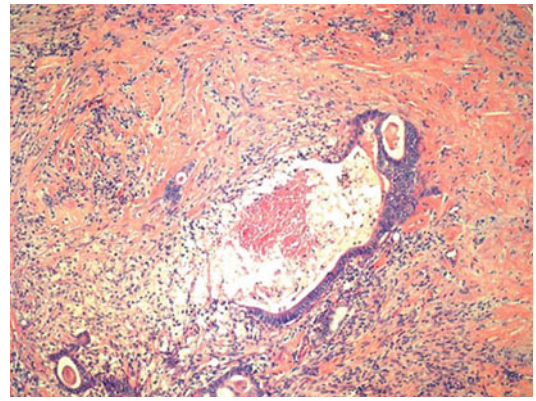

Fig. 4 Liver metastasis of colorectal carcinoma metastasis with focal loss of tumor cells through necrosis and apoptosis. Defects in continuity of tubule lining can result in mucin leakage, followed by an inflammatory reaction (to the left and left lower corner; hematoxylin and eosin stain)

yellowish, caused by the necrotic area which is here very close to the capsular surface.

Histologically, coagulation necrosis is characterized by an eosinophilic acellular mass with densely packed granular structures representing ghost cells and cytoplasmic debris. Nuclear debris are often seen in the form of basophilic dots clearly smaller than nuclei. As reticulin fibers resist decay within a necrotic tissue for longer time periods, a reticulin stain will be of great diagnostic help, because it usually depicts the original reticulin network and often still shows the shape and size of the necrotic tumor cells and their characteristic arrangement and relation to stroma. In case of doubt, it is therefore strongly recommended to perform such stains.

Liquefactive Necrosis

In a minority of necrotic metastases, the necrotic tissue mass undergoes liquefaction, causing the accumulation of a turbid fluid with suspended necrotic fragments in the core of metastasis. The pathogenesis of liquefactive necrosis is not yet fully known, but the action of proteolytic enzymes generated by tumor cells and/or leukocytes was suggested.

Necrosis of Metastases Following Chemotherapy

There are two general patterns of necrosis present in hepatectomy specimens with colorectal metastases preceded by perioperative chemotherapy – one type representing the so-called "dirty" or usual necrosis and the other type consisting of larger zonal areas of necrosis with surrounding fibrosis, designated infarct-like necrosis. In the latter, a rim of fibrotic tissue with numerous foamy macrophages is present. In a systematic study, infarct-like necrosis was significantly associated with perioperative chemotherapy and was associated with improved disease-free survival compared with metastases having usual or coagulative necrosis (Chang et al. 2012). Colorectal liver metastases may contract centripetally as a response to chemotherapy. Central necrosis was prominent in untreated metastases but disappeared after chemotherapy, where discrete islands of viable tumor cells outside of the main tumor mass can be seen. The shrinkage of central necrosis subsequent to chemotherapy can be followed by central tumor fibrosis (Ng et al. 2008).

Hemorrhage of Necrosis

The rupture of necrotic blood vessels within the metastasis can cause extensive bleeding (La Fianza et al. 1999). Several patterns of intrametastatic and intranecrotic hemorrhage can be distinguished. In part of the tumors, several foci of hemorrhage develop, causing roundish bloody spots on the cut surface. Histologically, these hemorrhages are situated around intranecrotic blood vessels having undergone rupture and identified in connective tissue stains. A second pattern is characterized by larger hemorrhages that may dissect the necrotic tissue, with isolation of individual necrotic areas. In a third situation, the entire necrotic area is imbibed with blood, causing a morphology mimicking a hematoma. After lysis, a central blood clot may remain. A fourth pattern shows liquefaction and lysis of hemorrhage, with accumulation of a reddish liquid in the center of the necrosis.

Calcification of Necrosis

In part of necrotic metastases, calcifications are found within the necrotic masses. This alteration is discussed in more detail below.

Mummification of Necrosis ("Putty Necrosis")

In rare cases of complete necrosis of a metastasis with no remaining viable tumor cells, the necrotic tissue may undergo marked shrinking with progressive loss of tissue fluid. This process, which may be associated with calcification, results in roundish mass of sticky material grossly resembling putty used for windows ("putty necrosis"). This phenomenon is better known from the caseiform coagulation necrosis occurring in tuberculosis.

Mucin-Rich Necroses

In hepatic metastases of colloid carcinomas characterized by a very high amount of mucin, mucin will remain within necrotic areas following decay of viable tumor tissue (Fig. 5). These mucin masses of "mucin lakes" are situated within the extracellular space of necrosis and present as amphophilic or slightly basophilic, thready or

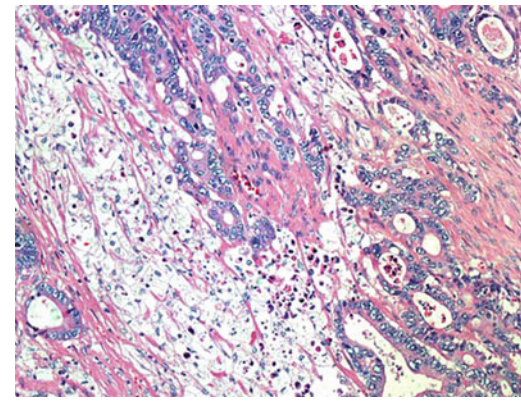

Fig. 5 Hepatic colorectal carcinoma metastasis with necrosis and release of mucinous matter (hematoxylin and eosin stain)

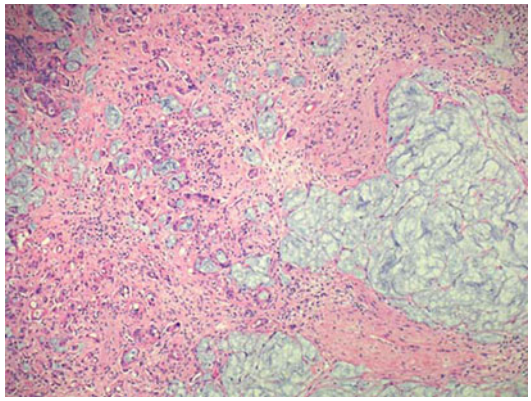

Fig. 6 Hepatic metastasis of mucin-rich adenocarcinoma. Leakage of tumor mucus has caused so-called mucin lakes, characterized by large amounts of extracellular mucin accumulating in stroma and liver tissue (right half of figure; hematoxylin and eosin stain)

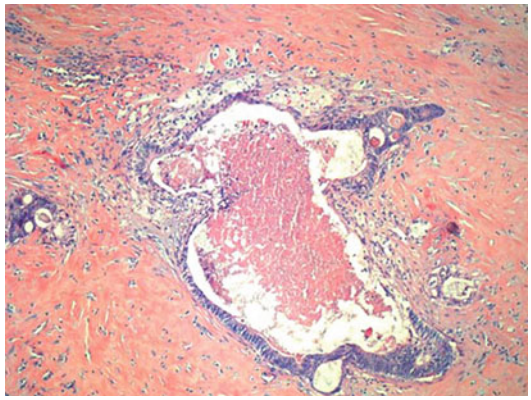

Fig. 7 Liver metastasis of colorectal carcinoma. The dilated tubular structure is focally surrounded by clear cells (upper aspect of tubule) representing mucophage nests (hematoxylin and eosin stain)

clumpy, striated masses in an eosinophilic and granular background. Mucin stains (PAS, alkaline acian blue) will clearly show the mucin material, which is often intermingled with dead tumor cells and connective tissue fiber fragments of the preexisting stroma. In bursting necrotic metastases, the mucin masses may spill over into adjacent liver tissue and cause mucinous tissue dissection associated with the accumulation of mucophages and even mucus granulomas with foreign body-type giant cells (Figs. 6, 7, and 8).

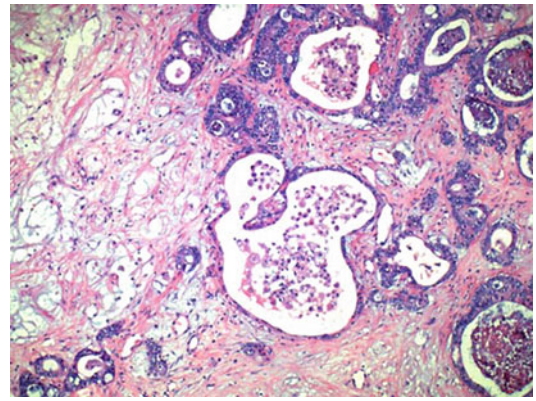

Fig. 8 Liver metastasis of mucin-producing carcinoma with intratubular accumulation of mucophages (hematoxylin and eosin stain)

Bile Impregnation of Necrotic Metastases

In case a necrotic metastasis encroaches upon intrahepatic bile ducts or invades such a duct, bile leaks may ensue, causing bile to infiltrate the necrotic mass. Histology shows small deposits of brightly yellow bile admixed with the necrotic tissue, sometimes with bile accumulations situated within slit-like spaces probably represented original perivascular spaces.

Mural Nodules and Other Signs of Cancer Regrowth After Necrosis

In some markedly necrotic liver metastases, marginal nodules of viable tumor tissue are noted. These nodules are situated at the border of metastases and, like satellite nodules, seem to grow from the original peripheral part of the metastasis into the adjacent liver substance. It is suggested that this pattern of apparent regrowth may be related to the emergence of favorably neovascularized zones, where angiogenesis at the tumor border has taken place as a response to tumor damage. In some metastases with necrosis, regrowth can be found deep within the necrotic area itself. In these instances, careful search will almost always reveal the presence of new blood vessels that have sprouted into the area concerned,

and among which surviving, dormant cancer cells have started to proliferate again. In cases where granulation tissue is interposed between the periphery of a necrotic metastasis and the liver, a similar phenomenon may be encountered, characterized by growth of carcinoma in close relationship with the granulation tissue's vascular compartment.

Bursting Metastasis and Liver Rupture

Hepatic metastases with rapid growth and extensive necrosis may burst, associated with laceration of the liver capsule, organ rupture, and sometimes massive bleeding. Postnecrotic rupture of liver metastasis can develop with several types of metastasizing cancers, but it predominantly occurs in tumors known to have a tendency for necrosis and rupture, including small cell carcinomas, colorectal carcinoma, renal cell carcinoma, choriocarcinoma, and squamous cell carcinoma (Mittleman 1987; Murakami et al. 2000; Tung et al. 2002; Gulati et al. 2009; Duan et al. 2014). Delayed hepatic rupture after radiofrequency ablation for colorectal hepatic metastasis was observed (Chang et al. 2014).

Sequestration of Necrotic Metastasis

In older and large necroses of metastases of long duration and poor vascularization, the necrotic tissue mass may undergo contraction, with detachment of the necrotic core from a peripheral rim of variable thickness, resulting in a more or less spherical sequester of necrotic tissue separated from the remaining nodule by a circular slit-like space. At macroscopic examination, this sequester may easily be removed from the nodule following cutting through the metastasis.

Infection of Tumor Necrosis

The necrotic tissue of tumors, including hepatic metastases, is a favorable substratum for the growth of diverse bacteria and fungi, due to the availability of low-molecular-weight energy sources and large amounts of proteins. Thus, necrotic metastases may become infected, the type of infection being strongly influenced by the oxygenation and the iron resources of the tissue. Expectedly, large necroses with poor oxygenation will favor the replication of anaerobes. Growth of bacteria within necroses is easily detectable in H&E-stained sections already, due to the characteristic regular and invariant morphology of bacteria and fungi in comparison with the irregular nuclear debris. Gram and fungus stains will help to identify the microorganisms involved. In case bacterial growth takes place in peripheral parts of the necrosis, i.e., closer to still perfused tumor vessels, the chemotactic and chemokinetic activity of bacteria will cause granulocyte immigration. This may lead to suppuration of the necrotic metastasis, typically starting in the mantle zone of metastasis, eventually followed by liquefaction of necrotic tissue through granulocyte proteases (the "suppurative liquefaction" or in German "puriforme Erweichung" of older pathology texts). Histolysis caused by bacterial or fungal infection may cause bursting of metastasis, invasion into adjacent structures, or even fistulation.

Immune Reactions Directed Against Necrotic Tumor Tissue

In the devascularized tissue composing the center of necrosis, no cellular infiltrate suggesting a cellular reaction of the host is found, except nuclear debris of neutrophil granulocytes. In contrast, variable degrees of leukocytic infiltrations are regularly found around necrotic metastases. These infiltrates consist mostly of T lymphocytes, both of the CD4+ and CD8+ classes, usually, however, with a predominance of the latter. Relatively few B lymphocytes are noted, while plasma cells may be encountered in larger numbers. These immune cells either form small collections of cells in the liver tissue surrounding the metastasis, with some of the cells scattered within the tumor tissue itself, or form a band-like infiltrate following to peripheral contour of the tumor. Macrophages and

eosinophil granulocytes are often seen in these infiltrates. There is no obvious difference in the type and density of these infiltrates between metastases with extensive vs. minor necrosis. However, for some colorectal metastases with extensive necroses and particularly those where the necrotic tumor tissue reaches near the intact adjacent liver tissue, a macrophage reaction may be more prominent, sometimes with an epithelioid cell component, suggesting a cell-bound immune reaction directed against tumor-associated antigens released in the course of necrosis. In few hepatic carcinoma metastases, the formation of granulation tissue starting to organize the necrotic mass is seen.

Calcification of Hepatic Metastases

Introduction

Hepatic metastases of carcinomas (mainly adenocarcinomas), neuroendocrine tumors, and some other epithelial neoplasms are known to undergo calcification (mineralization). This type of calcification in metastases is of the dystrophic type and has to be distinguished from calcium salts making part of osteoid, representing apatite and found in the liver, e.g., in metastasizing osteosarcoma. These calcifications are often visualized on radiographic images (Green and Stephens 1971; Easson et al. 1996; Hale et al. 1998) and are apparently not clearly related to the type of underlying histology. However, calcified hepatic metastases are most often found in colorectal carcinoma (CRC), especially the mucinous variety (Stoupis et al. 1998). It is estimated that calcification occurs in 12–28 % of hepatic CRC metastases (Wells 1956; Appleby and Hacking 1958; Karras and Cannon 1960; Green and Stephens 1971; Takahashi et al. 1971; Franca et al. 1978; Bernardino 1979; Rubaltelli et al. 1983; Ferrozzi and Rossi 1991; Easson et al. 1996; Hale et al. 1998). In a retrospective analysis of patients with CRC, 11 % had calcified liver metastases at presentation and 4 % developed calcification during chemotherapy (Hale et al. 1998). Other malignancies that have been reported to show calcifications in their liver metastases comprise lung carcinoma, breast cancer, stomach carcinoma, renal cell carcinoma, carcinoma of the prostate, medullary thyroid carcinoma, and neuroblastoma. In medullary carcinoma of the thyroid, calcifications are typically seen in primary tumors and are often encountered in lymph node and liver metastases (McDonnell et al. 1986). In a retrospective study of 230, CT analyses of hepatic masses yielded 28 cases (12.2 %) which contained calcifications. Calcifications were found in 15.3 % with hepatocellular carcinoma, 18.3 % with CRC metastases, 2.8 % with non-colonic liver metastases, and 11 % with a benign liver mass (Scatarige et al. 1983). Calcifications of hepatic CRC metastases sometimes occur in the course of systemic chemotherapy or hepatic infusion chemotherapy (Rubaltelli et al. 1983; Aoki et al. 1987; Hale et al. 1998).

Pathology

In most cases where calcifications are seen at histologic examination, this change is not visible at gross examination. In case of marked calcification, cut surfaces of tumors, and in particular CRC metastases, show single or clustered, gray-white to cream-colored speckles within necrotic areas of the tumor. In fixed specimens, the necrosis sometimes displays fissures or slits as artifacts where macroscopic deposits of calcifications are seen. Rarely, the amount of granular calcium salt deposits is such that the cut surface of the tumor is gritty, and the deposits are felt when cutting through the metastasis. In part of the lesions, coalescent calcium-containing deposits develop, with the formation of firm or even "stony" conglomerates. However, dry calcified necroses ("chalky necroses") as seen in tuberculomas do not develop in calcified metastases. Exceptionally, the entire metastasis appears as a stone-hard lesion. Calcifications may follow the branches of tumor vessels. In some CRC metastases, calcifications are predominantly localized at the interface between central necrotic tumor tissue and the peripheral viable parts of the tumor.

Histologically, calcifications of metastases present with several patterns. The most frequent morphology is that of multiple to numerous basophilic calcium salt deposits localized within necrotic tumor areas. These deposits may show an internal gradient of basophilia, depending on the age of the lesions and the local concentration of calcium salts. The deposits stain black in the von Kossa stain. In some of the lesion, a faint PAS positivity is seen in the deposits, caused by the accumulation of glycoproteins serving as the calcification matrix or the deposition of remnant mucin components of the tumor. A second type of calcification is characterized by sickle-shaped basophilic calcifications seen in peripheral parts of the tumor. In a third type, large conglomerates of dense calcium-containing deposits are present, without necrosis or tumor. This is an end stage of extensive dystrophic calcification, and the tissue samples may require decalcification prior to sectioning and staining. Within these larger deposits, ossification with osteoid and mature lamellar bone may develop (osseous metaplasia; metaplastic ossification; orthoplastic calcification), sometimes even with hematopoietic bone marrow. A fourth type of calcification is characterized by calcium salt deposits along the tumor vascular tree, mainly along the adventitia of tumor arteries.

In some reports it was claimed that the mucinous type of CRC was more often associated with calcification of hepatic metastases. This view was not confirmed in other investigations. In a group of 31 patients with calcified metastases, calcification occurred independent of the degree of tumor differentiation, the presence of mucinous adenocarcinoma, or the hepatic tumor burden (Easson et al. 1996). In a study of 22 cases of calcified hepatic CRC metastases, there was no correlation between calcification and the pathologic subtype of primary CRCs (Xu et al. 2010).

Differential Diagnosis

The main differential diagnoses comprise primary hepatic tumors that are well known to mineralize, including hepatocellular carcinoma, fibrolamellar carcinoma, cholangiocarcinoma, and liver cell adenoma. In liver cell adenomas, calcifications may be solitary or multiple and are commonly located eccentrically. Calcifications in cholangiocarcinomas are seen in around 18 % of CT images and are typically associated with a marked desmoplastic reaction. In fibrolamellar carcinomas, calcifications are detectable in 15–25 % of cases (Stoupis et al. 1998). Less common situations comprise calcified mixed tumors and primary osteosarcomas of the liver. Hepatic hemangiomas, especially large ones (giant hemangiomas) may contain large and coarse calcifications that are usually centrally placed, within the tumor's fibrotic core. These calcifications are seen on CT images in about 20 % of cases. Multifocal hepatic calcifications have been reported in epithelioid hemangioendothelioma (den Bakker et al. 1998).

Biological Significance of Calcifications in Hepatic Metastases

There are few data regarding the eventual impact of metastasis calcification on tumor biology and prognosis. In a retrospective study, the survival of patients with calcified hepatic CRC metastases was compared with those without calcification. The two groups were comparable with respect to sex, age, time to calcification, time to metastasis, and treatment type. The presence of calcification had a statistically significant improvement in survival, independent of other variables (Easson et al. 1996).

Pathogenesis

It has been proposed that calcification in metastases arises through a double mechanism: primary, characterized by calcified osteoid formation (orthoplastic calcification), and secondary as a result of necrosis and other regressive changes (dystrophic calcification) or through calcification of mucoid material or tumor amyloid. Mucins produced by adenocarcinomas appear to trap calcium salts (Habighorst 1963). Part of cases

showing calcification in metastases has been observed during local or systemic chemotherapy (Rubaltelli et al. 1983; Hale et al. 1998). As the extent of calcifications in metastases of colorectal cancer changes under chemotherapy (Hale et al. 1998), it may be assumed that the increasing mass of necrotic tissue acting as a calcium salt sink is involved in this phenomenon. On the other hand, calcification of tumor metastases may represent inherent features related to distinct metabolic characteristics of the neoplastic cell lineage. For example, it was found that recurrent tumors following lumpectomy of hepatic CRC metastases develop calcification and that calcification in newly developing tumor masses was similar to that of their primary counterparts (Xu et al. 2010).

Hepatic Metastases Complicated by Liver Abscesses, Puriform Liquefaction, and Pneumatic Tumors

Abscess Formation

Hepatic metastases can undergo necrosis followed by suppuration and abscess formation. Abscess formation within or around tumors has also been seen in primary hepatic tumors (Yu et al. 2007). Pure abscesses, i.e., lesions not associated with gas-forming bacteria (see below), are rare alterations that are either solitary or multiple (Josef 1979; Pisano et al. 2007). As in liver abscesses not associated with hepatic metastases, infection with a broad array of microorganisms is pathogenically involved (Brook and Frazier 1998). Liver metastasis undergoing abscess formation may rupture due to the puriform destruction of the tissue (Josef 1979). More common are liver abscesses that are indicators of silent or manifest colorectal cancer, a tumor that is well known to be associated with solitary or more often multiple pyogenic liver abscesses (Cohen et al. 1989; Lonardo et al. 1992; Pierrugues et al. 1994; Teitz et al. 1995; Tzur et al. 2003; Alvarez et al. 2004; Yokota et al. 2005; Giuliani et al. 2007; Hiraoka et al. 2007; Lee et al. 2008). This type of abscess can be caused by several bacterial species, including *Streptococcus milleri* (Tzur et al. 2003) and anaerobic germs such as *Bacteroides* and *Peptostreptococcus* (Lonardo et al. 1992; Alvarez et al. 2004; Lieuw-a-Fa et al. 2008). Abscesses caused by anaerobic bacteria including *Bacteroides* tend to have a liquid consistency in contrast to necrotic liver metastases (Lieuw-a-Fa et al. 2008). The pathogenic pathways involved in liver abscess formation in patients with CRC and other gastrointestinal cancers not having liver metastasis are not elucidated, but transfer of intestinal bacteria from ulcerated tumor surfaces to the liver via the portal circulation, with or without pylephlebitis, is considered. In fact, portal pyemia secondary to carcinoma of the rectum has been described (Ritchie, 1975). Multiple sterile liver abscesses may as such mimic metastatic disease during imaging workup (Acharya 2012).

Abscess-Like Lesions in Hepatic Metastases Caused by Anaerobic Bacteria ("Hepatic Necrobacillosis")

"Hepatic necrobacillosis" is a condition characterized by solitary or multiple liver abscesses caused by anaerobic bacteria. In part of the cases, necrotic metastases, mostly of CRC, have been identified as a background alteration favoring infection with anaerobic germs. Bacteria cultivated from such lesions comprise *Bacteroides* species, *Fusobacterium nucleatum*, and *Peptostreptococcus* species (Young et al. 1977; Trump et al. 1978; Tweedy and White 1987; Hagelskjaer and Pedersen 1993; Katzenstein et al. 1994; Athavale et al. 2002; Sarmiento and Sarr 2002; Le Roux et al. 2006; Kim et al. 2011). Pathologically, the centers of the lesions exhibit extensive coagulation necrosis, while peripheral parts display a purulent exudate sometimes demarcated by granulation tissue. The latter may develop wedge-shaped necroses due to microvascular/capillary damage induced by toxic products of the anaerobic bacteria. The necrosis may later undergo liquefaction caused by enzymes of bacteria and leukocytes ("puriform liquefaction"). Due to their destructive features, abscesses developing in the context of "hepatic necrobacillosis" may

mimic primary hepatic malignancy (Athavale et al. 2002).

What Are the Essential Features of Bacteria Causing "Hepatic Necrobacillosis"?

Bacteroides is an obligately anaerobic, Gram-negative, saccharolytic bacterium which comprises at least ten valid species. Bacteroides species organisms are the predominant commensal bacteria in the human gut and are now considered to be reservoirs of antibiotic resistance genes due to their capacity to harbor and disseminate these genes in the course of homologous and heterologous conjugation through mobile transmissible elements occurring in great variety (Nguyen and Vedantam 2011). The original *Bacteroides* genus described in 1898 was later partitioned into three genera, i.e., *Bacteroides sensu stricto*, *Prevotella*, and *Porphyromonas*. The species of the latter two genera generally are associated with the oral cavity and rumen. *B. fragilis* and other intestinal *Bacteroides* species play an important role in the enterohepatic circulation of bile acids. Primary bile acids entering the GIT via bile are deconjugated and transformed into 15–20 secondary bile acids by these bacteria. As very well-adapted gut symbionts, *Bacteroides* species possess membrane-spanning sensor histidine kinases to sense complex carbohydrates which the bacteria degrade (Lowe et al. 2012). The *Bacteroides fragilis* species group is one of the most important pathogens in polymicrobial infections, linked to a complex and variegated spectrum of virulence factors (Brook 1989; Wexler 2007). In patients with *B. fragilis* bacteremia, malignancy was the most common comorbidity, and intra-abdominal infections accounted for approximately half of the infection sources (Cheng et al. 2009). Patients with colorectal cancer reveal changes in the composition of the gut flora, a condition termed microbial dysbiosis. *Bacteroides* species are associated with colorectal carcinoma (Sobhani et al. 2011). In a study of ten patients, *B. vulgatus* and *B. fragilis* and B. ovatus were the least frequently isolated *Bacteroides* species in the feces (Namavar et al. 1989). In contrast to CRC, patients with colorectal adenomas show, among mucosal adherent bacteria, more often species of the genera *Dorea* and *Faecalibacterium* and less often *Bacteroides* and *Coprococcus* (Shen et al. 2010). *Fusobacterium* species (*F. necrophorum*, *nucleatum*, *mortiferum*, and *varium*) are associated with several clinical conditions. In a review of 52 consecutive patients with *Fusobacterium bacteremia*, 10 % showed Lemierre's syndrome, 27 % were previously healthy patients who had *F. necrophorum* sepsis without vascular thrombosis, 12 % were women who had puerperal infections, and 52 % were older patients who had cardiovascular, pulmonary, or neoplastic diseases (Nohrström et al. 2011). Lemierre's syndrome is a disorder chiefly affecting young healthy adults. This syndrome usually develops after bacterial purulent tonsillitis and peritonsillitis. Purulent peritonsillar pockets and abscesses are then the niches where anaerobic *Fusobacteria* can survive and proliferate. These bacteria can invade the soft tissues of the neck and penetrate the jugular vein system to induce infected thrombosis, the source of subsequent bacteremia, sepsis, and all its complications. Sepsis following a throat infection was first reported in 1918 by Scottmuller, but it was Lemierre in 1936 who described the condition in detail based on 20 cases. Overall, *Fusobacterium bacteremia* is a rare disorder, accounting for approximately 0.9 % of patients with bacteremia, with *F. nucleatum* being the most common species accounting for 41.5 % in one study (Su et al. 2009). *Fusobacterium bacteremia* is encountered in patients with neutropenia, e.g., associated with leukemia and lymphoma (Candoni et al. 2003). In the course of F. *nucleatum bacteremia*, portal vein thrombosis (Bultink et al. 1999; Verna et al. 2004), pylephlebitis with liver abscess (Etienne et al. 2001), and multiple infected liver abscesses can develop (Scoular et al. 1992; Le Roux et al. 2006). This constellation has been proposed to be termed "digestive variant" of Lemierre's syndrome (Le Roux et al. 2006). *Peptostreptococcus* is a genus of Gram-positive

anaerobic non-spore-forming bacteria. The species of *Peptostreptococcus* (*P.*) identified in the setting of clinical infections were formerly part of the genus known as *Peptococcus*. Several *Peptostreptococcus* species (most commonly *P. magnus*, *asaccharolyticus*, *anaerobius*, *prevotii*, and *micros*) are commensal organisms in humans and predominantly colonize the oral cavity, skin, and the gastrointestinal and genitourinary tracts. Another clinically relevant bacterium, *Gaffkya anaerobia*, was renamed *P. tetradius. Peptostreptococcus* species become pathogenic in immunocompromised hosts and in situations where anaerobic niches are created in the body, e.g., necrotic tumors. In the course of septicemic *Peptostreptococcus* infections, abscesses can develop in several organs, including the liver. A recently identified member of the *Bacteroidetes* group that is associated with CRC is *Alistipes finegoldii*, a bacterium clustered with *Alistipes putredinis*, a member of the human gut flora (Fenner et al. 2007).

Infection of Hepatic Metastases with Gas-Forming Bacteria

The infection of hepatic and at least partially necrotic metastases with gas-forming bacteria, chiefly *Clostridium* species, has predominantly been found with metastases of CRC (Kahn et al. 1972; Kolbeinsson et al. 1991; Urban et al. 2000; Kurtz et al. 2005), but other tumors such as carcinoma of the breast (Thel et al. 1994), pancreatic carcinoma (Fondran and Williams 2005), and choriocarcinoma can also be involved (Lee and Hsieh 1999). This complication is typically found in hepatic CRC metastases that have outgrown their blood supply and hence provide an anaerobic microenvironment ideal for bacterial growth. In case of marked local gas production, the necrotic metastases can accumulate gas that is visible at imaging (intrahepatic pneumatic tumor; "pneumometastasis"; Tokita et al. 1988; Urban et al. 2000). Gas formation in hepatic metastases can develop in short time, e.g., within 3 days as seen in follow-up CTs (Urban et al. 2000). The accumulated gas can remain limited to metastases on CT and not extend into the healthy adjacent liver (Urban et al. 2000), but *Clostridium*-induced intrametastatic gas formation can also cause rupture of the lesion followed by pneumoperitoneum (Raghavendra et al. 2013).

Clostridium (*C.*) *septicum* was detected in most cases (Thel et al. 1994; Lee and Hsieh 1999; Kurtz et al. 2005), but *C. perfringens* was also isolated (Fondran and Williams 2005). *C. septicum* is as anaerobic Gram-positive bacillus that can cause infections which rapidly progress to sepsis. This bacterium is strongly associated with malignancy, especially of the gastrointestinal tract and in particular CRC (Alpern and Dowell 1969; Koransky et al. 1979; Kolbeinsson et al. 1991). Although widely spread in the environment, *C. septicum* germinates and proliferates predominantly in devitalized and necrotic tissues with failing blood supply and low oxygen tension, including tumors and their metastases.

Anaerobic Necrosis and Abscesses of Hepatic Metastases Following Nonsurgical Therapies

Extensive liver necrosis with inflammatory reactions has been observed after radiofrequency ablation of liver metastases (Kvitting et al. 2006). Marked necrosis and inflammation were found following intra-arterial chemotherapy for metastatic CRC (D'Orsi et al. 1979).

Cyst Formation in Hepatic Metastases

Introduction

Hepatic metastases of diverse types of extrahepatic malignant neoplasms can undergo secondary cystic change, sometimes resulting in large single cysts or multiple cysts distributed in both liver lobes. These alterations may cause significant differential diagnostic problems, some of the cystic metastases resembling simple benign cysts or parasitic cysts.

Epidemiology

Numerous types of extrahepatic malignancies have been reported to cause cystic hepatic metastases. Similar to metastases in other organs, squamous cell carcinomas seem to have a higher tendency to show cystic hepatic metastases than other carcinoma types. In malignant melanoma, cystic metastases may develop more than 10 years after surgical excision of the primary lesion (Takauji et al. 2005). Massive cystic change of hepatic metastases of malignant melanoma may occur following transarterial chemoembolization (Ataergin et al. 2009). In the pediatric age group, PNETs (Shah and McHugh 2000) and neuroblastomas are well known to cause cystic liver metastases, sometimes with the formation of numerous cysts (Lee et al. 1998; Chacko et al. 2007). Cystic liver metastases in neuroblastoma can be associated with a distinct clinical entity, i.e., bilateral cystic adrenal neuroblastoma, a rare condition (Cassady and Winters 1997). Among neoplasms metastasizing to the liver and forming cystic metastases, neuroendocrine tumors, including carcinoid tumors of the GIT, have been reported more often than other tumors, suggesting that these lesions have a pronounced tendency to undergo cystic change in their metastases (Saubier et al. 1970; Dent and Feldman 1984; Bremer et al. 1986; McDermott 1987; Isomura et al. 1980; Salamone et al. 2010; Wijesuriya et al. 2010). The cysts may become large and eventually mimic *Echinococcus* cysts (Krohn et al. 2011). The reason why neuroendocrine tumors more often undergo cystic changes is not known.

Pathology

Macroscopically, cysts in liver metastasis are more prominent in large tumor masses. They produce a broad spectrum of changes ranging from small and ill-defined centrally placed cysts to large cysts that occupy most of the tumor mass, leaving only a thin rim of usually necrotic tissue. The cyst fluid is frequently turbid, with floating necrotic tissue fragments, and may show a hemorrhagic or yellowish color. In rare instances, the cyst lining is smooth and the lesion then mimics a benign nonparasitic cyst or a cystadenoma. Following cyst hemorrhage, masses of coagulated blood are found in the cyst lumen.

Cystic Changes in Treated Gastrointestinal Stromal Tumor Metastases

A distinct situation is the development of cysts in metastatic gastrointestinal stromal tumors (GIST) following treatment with imatinib mesylate/IM (Joensuu et al. 2001; Chen et al. 2002; Bechtold et al. 2003; Reichardt et al. 2004; Vanel et al. 2005; Linton et al. 2006; Phongkitkarun et al. 2008; Ulusan et al. 2008). IM is a specifically designed tyrosine kinase receptor inhibitor, which targets, among others, the KIT receptor and interrupts neoplastic growth messages to the cell. Liver metastases from GIST are often hypervascular prior to treatment and therefore not easily visualized on conventional portal venous phase CT images (Sandrasegaran et al. 2005). The development of cystic metastases was a consistent finding in several studies. In an investigation of four GIST patients who had received IM, follow-up CT showed that all hepatic metastases resembled cystic lesions after 8 weeks of treatment (Chen et al. 2002). In the review of seven patients with unresectable metastases from GIST who were treated with IM, hepatic metastases showed significant decreased attenuation in the first 2 months and continued decreasing attenuation at the 12-month follow-up. These metastases resembled simple cysts (Bechtold et al. 2003). In a retrospective, another study investigated the serial histological changes in GIST treated with IM and showed that therapy-induced cystic change of tumors is associated with tumor response and that cystic metastases had a lower mitotic count and lower proliferation indices and shrinkage of tumor tissue (Reichardt et al. 2004). In 13/39 patients with GIST who developed hepatic metastases, a cyst-like appearance was noted (Vanel et al. 2005). However, cystic liver metastases from GISTs have also been noted before any

treatment (Zonios et al. 2003; Jain et al. 2009). The pathogenesis of cyst formation in metastases following IM therapy is still uncertain, because such imaging changes are not typical cancer response patterns to conventional cytotoxic chemotherapy. Tumor shrinkage may follow cystic change; in one case report, hepatic metastases of GIST became cystic in MR appearance after 4 weeks of IM and became smaller after 8 weeks of treatment (Joensuu et al. 2001). GISTs showed myxoid changes and pycnotic nuclei in an eosinophilic myxoid background (Berman and O'Leary 2001), suggesting apoptotic cell decay. In a c-KIT-dependent GIST cell line, inhibition of c-KIT with IM triggers the upregulation of the proapoptotic protein BIM via both transcriptional and posttranslational mechanisms, suggesting a mechanism for IM-induced apoptosis (Gordon and Fisher 2010).

Tumor Fibrosis

Part of slowly growing hepatic tumor metastases undergoes progressive fibrosis that can rarely result in advanced scarring. As a spontaneous process, advanced fibrosis is an uncommon phenomenon and may be induced by marked immune reactions of the host, organization of necrotic tumor tissue, or a late change of tumor stroma. The fibrosis can rarely be associated with reactive ossification. A marked fibrosis overgrowth of CRC liver metastasis occurs in tumors that regress after chemotherapy (Rubbia-Brandt et al. 2007).

Spontaneous Regression of Hepatic Metastases

Introduction

Exceptionally, apparently spontaneous regression of hepatic metastases has been reported for renal cell carcinoma (Deweerd et al. 1977), colorectal carcinoma (Serpick 1976), malignant melanoma (Kalialis et al. 2008), and gastric carcinoma (Rosenberg et al. 1972). Renal cell carcinoma has shown metastasis regression following surgical removal of the primary lesion (Deweerd et al. 1977; Ritchie et al. 1988).

In an exemplary historical case report, a 44-year-old patient with familial polyposis, reported by Rankin and coworkers (1965), underwent resection of a rectal adenocarcinoma (poorly differentiated), and four metastatic liver nodules of 1 cm diameter each were detected, colorectal metastases confirmed through biopsy. Without further treatment, the patient was found to be well 7 years after rectal surgery. Three years later, a second carcinoma was found in the ascending colon, which was resected. During this operation, there was no evidence of the previously observed liver metastases.

Pathology

The histopathology of regressing metastases is characterized by the decay of preexisting carcinoma structures, such as disintegration of trabecules and acini, tumor cell necrosis and apoptosis, detachment of tumor cells from stromal elements, hemorrhage, and variable amounts of infiltrating leukocytes, mainly lymphocytes. Metastasis shrinkage may be associated with fibrosis, stellate scars, and finally a fibrosclerosed stroma (Figs. 9, 10, 11, 12, and 13). Spontaneous development of host immunity directed against

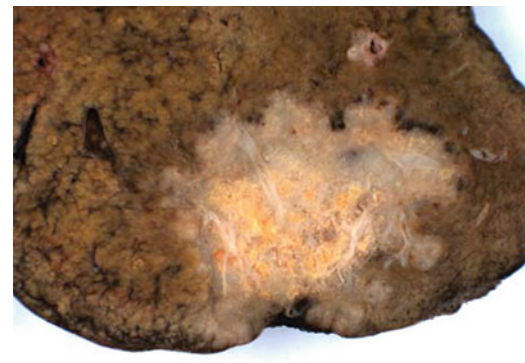

Fig. 9 Hepatic colorectal carcinoma metastasis with marked necrosis and shrinkage. The center of the metastasis consists of yellowish necrotic tissue. Shrinkage of the tumor has caused a stellate aspect of the nodule, in part reflecting tumor vessel patterns

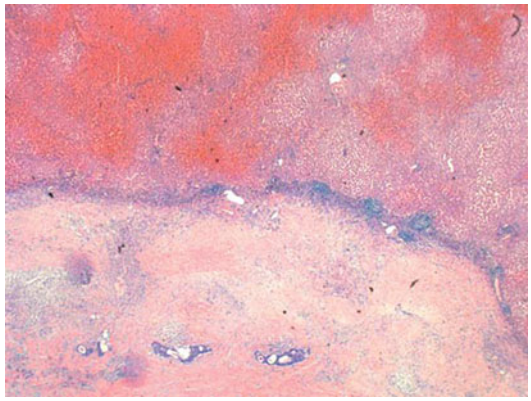

Fig. 10 Marked regression of hepatic colorectal carcinoma metastasis. Most of the tumor nodule consists of fibrosed stroma, with few remnant carcinoma tubules. At the interface between tumor and adjacent liver, an immune reaction is seen (hematoxylin and eosin stain)

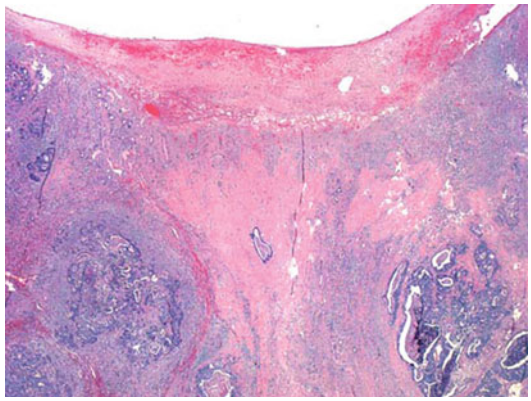

Fig. 11 Shrinkage and retraction of hepatic colorectal carcinoma metastasis at a site of capsular invasion and umbilication (hematoxylin and eosin stain)

tumor-associated antigens has been suggested as a regression-inducing mechanism (Bulkley et al. 1975). In regression induced by chemoembolization, a foreign body reaction can be observed (Fig. 14).

Tumor Alterations Caused by Bioptic Procedures

The trauma induced within metastatic and other tumor manifestations by biopsy needles can result in hemorrhage and necrosis. This alteration

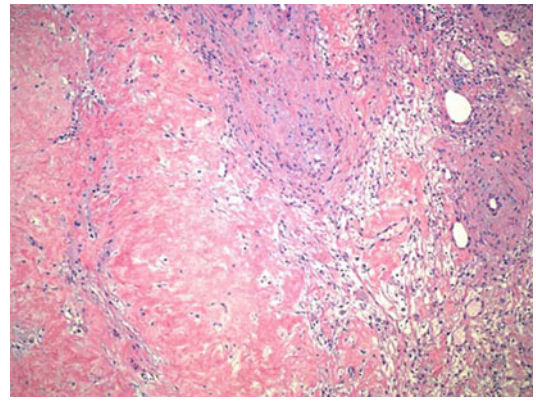

Fig. 12 In regression of hepatic metastases, tumor stroma can undergo sclerosis and hyalinization (hematoxylin and eosin stain)

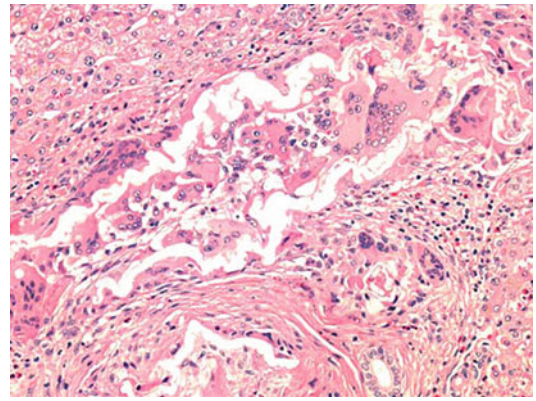

Fig. 13 Chemoembolization of hepatic carcinoma metastasis. This therapy can induce a vigorous foreign body reaction with multinucleated giant cells derived from fused macrophages (hematoxylin and eosin stain)

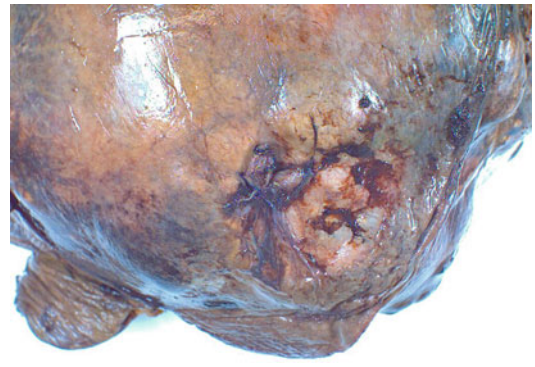

Fig. 14 Liver metastasis. Morphology of an excisional biopsy site

typically reflects the dimension of the biopsy needle that had been used (Fig. 14).

References

Acharya MN (2012) Multiple sterile liver abscesses: an unusual presentation mimicking metastatic disease. Dig Liver Dis 44, e5

Alpern RJ, Dowell VR (1969) Clostridium septicum infections and malignancy. JAMA 209:385–388

Alvarez JA, Baldonedo RF, Bear IG, Alvarez P, Jorge JL (2004) Anaerobic liver abscesses as initial presentation of silent colonic cancer. HPB (Oxford) 6:41–42

Aoki T, Arai Y, Kido C, Endo T, Sato Y, Ozawa H (1987) The effect and CT imaging of FAM hepatic infusion chemotherapy in patients with liver metastasis from colorectal carcinoma (in Japanese). Gan To Kagaku Ryoho 14:2744–2748

Appleby A, Hacking PM (1958) Calcification in hepatic metastases. Br J Radiol 31:449–450

Ataergin S, Tasar M, Solchaga L, Ozet A, Arpaci F (2009) Unusual severe complication following transarterial chemoembolization for metastatic malignant melanoma giant intrahepatic cyst and fatal hepatic failure. Cardiovasc Intervent Radiol 32:361–364

Athavale NV, Leitch DG, Cowling P (2002) Liver abscesses due to Fusobacterium spp. that mimick malignant metastatic liver disease. Eur J Clin Microbiol Infect Dis 21:884–886

Bechtold RE, Chen MY, Stanton CA, Savage PD, Levine EA (2003) Cystic changes in hepatic and peritoneal metastases from gastrointestinal stromal tumors treated with Gleevec. Abdom Imaging 28:808–814

Berman J, O'Leary TJ (2001) Gastrointestinal stromal tumor workshop. Hum Pathol 32:578–582

Bernardino ME (1979) Computed tomography of calcified liver metastases. J Comput Assist Tomogr 3:32–35

Bremer A, De Graef J, Duret R, Heimann R, Chaikh A, Rutsaert J (1986) A voluminous hepatic pseudocyst: metastasis of a carcinoid tumor of the ileum (in French). Acta Gastroenterol Belg 49:517–524

Brook I (1989) Pathogenicity of the Bacteroides fragilis group. Ann Clin Lab Sci 19:360–376

Brook I, Frazier EH (1998) Microbiology of liver and spleen abscesses. J Med Microbiol 47:1075–1080

Bulkley GB, Cohen MH, Banks PM, Char DH, Ketcham AS (1975) Long-term spontaneous regression of malignant melanoma with visceral metastases. Report of a case with immunologic profile. Cancer 36:485–494

Bultink IE, Dorigo-Zetsma JW, Koopman MG, Kuijper EJ (1999) Fusobacterium nucleatum septicemia and portal vein thrombosis. Clin Infect Dis 28:1325–1326

Candoni A, Fili C, Trevisan R, Silvestri F, Fanin R (2003) Fusobacterium nucleatum: a rare cause of bacteremia in neutropenic patients with leukemia and lymphoma. Clin Microbiol Infect 9:1112–1115

Cassady C, Winters WD (1997) Bilateral cystic neuroblastoma: imaging features and differential diagnoses. Pediatr Radiol 27:758–759

Chacko J, Karl S, Sen S, Eapen A, Mathai J (2007) Bilateral cystic adrenal neuroblastoma with cystic metastasis in the liver. J Pediatr Surg 42:E11–E13

Chang HH, Leeper R, Chan G, Quan D, Driman DK (2012) Infarct-like necrosis: a distinct form of necrosis seen in colorectal carcinoma liver metastases treated with perioperative chemotherapy. Am J Surg Pathol 36:570–576

Chang et al (2014) http://www.ncbi.nlm.nih.gov/pubmed/2502506

Chen MY, Bechtold RE, Savage PD (2002) Cystic changes in hepatic metastases from gastrointestinal stromal tumors (GISTs) treated with Gleevec (imatinib mesylate). AJR Am J Roentgenol 179:1059–1062

Cheng CW, Lin HS, Ye JJ, Yang CC, Chiang PC, Wu TS, Lee MH (2009) Clinical significance of and outcomes for Bacteroides fragilis bacteremia. J Microbiol Immunol Infect 42:243–250

Cohen JL, Martin FM, Schoetz DJ (1989) Liver abscess: the need for complete gastrointestinal evaluation. Arch Surg 124:461–464

D'Orsi CJ, Ensminger W, Smith EH, Lew M (1979) Gas-forming intrahepatic abscess: a possible complication of arterial infusion chemotherapy. Gastrointest Radiol 4:157–161

den Bakker MA, den Bakker AJ, Beenen R, Mulder AH, Eulderink F (1998) Subtotal liver calcification due to epithelioid hemangioendothelioma. Pathol Res Pract 194:189–194

Dent GA, Feldman JM (1984) Pseudocystic liver metastases in patients with carcinoid tumors: report of three cases. Am J Clin Pathol 82:275–279

Deweerd JH, Hawthorne NJ, Adson MA (1977) Regression of renal cell hepatic metastasis following removal of primary lesions. J Urol 117:790–792

Duan YF, Tan Y, Yuan B, Zhu F (2014) Spontaneous rupture of hepatic metastasis from small cell neuroendocrine carcinoma of maxillary sinus. World J Surg Oncol 12:126

Easson AM, Barron PT, Cripps C, Hill G, Guindi M, Michaud C (1996) Calcification in colorectal hepatic metastases correlates with longer survival. J Surg Oncol 63:221–225

Etienne M, Gueit I, Abboud P, Pons JL, Jacquot S, Caron F (2001) Fusobacterium nucleatum hepatic abscess with pylephlebitis associated with idiopathic CD4(+) T lymphocytopenia. Clin Infect Dis 32:326–328

Fenner L, Roux V, Ananian P, Raoult D (2007) Alistipes finegoldii in blood cultures from colon cancer patients. Emerg Infect Dis 13:1260–1262

Ferrozzi F, Rossi A (1991) X-ray computed tomographic aspects of calcifying metastases. Apropos of 40 cases (in French). J Radiol 72:305–312

Fondran J, Williams GB (2005) Liver metastasis presenting as pneumoperitoneum. South Med J 98:248–249

Franca F, Stanta G, Bianchi C (1978) Calcification of hepatic metastases of carcinoma of the large intestine (in Italian). G Clin Med 59:51–57

Giuliani A, Caporale A, Demoro M, Scimo M, Galati F, Galati G (2007) Silent colon carcinoma presenting as a hepatic abscess. Tumori 93:616–618

Gordon PM, Fisher DE (2010) Role for the proapoptotic factor BIM in mediating imatinib-induced apoptosis in a c-KIT-dependent gastrointestinal stromal tumor cell line. J Biol Chem 285:14109–14114

Green PA, Stephens DH (1971) Hepatic calcification in cancer of the large bowel. Am J Gastroenterol 55:466–470

Gulati A, Vyas S, Lal A, Harsha TS, Gupta V, Nijhawan R, Khandelwal N (2009) Spontaneous rupture of hepatic metastasis from choriocarcinoma: a review of imaging and management. Ann Hepatol 8:384–387

Habighorst (1963) http://www.ncbi.nlm.nih.gov/pubmed/14043436

Hagelskjaer L, Pedersen G (1993) Fusobacterium necrophorum septicemia complicated by liver abscess. A case report. APMIS 101:904–906

Hale et al (1998) http://www.ncbi.nlm.nih.gov/pubmed/9817090

Hiraoka A, Yamashita Y, Uesugi K, Koizumi Y, Yamamoto Y, Doi H, Hasebe A, Ichikawa S et al (2007) Three cases of liver abscesses complicated with colon cancer without liver metastasis: importance of screening for digestive disease. Intern Med 46:2013–2017

Jain P, Jha AK, Rai RR (2009) Cystic hepatic metastasis from gastrointestinal stromal tumor prior to imatinib mimicking a liver abscess. J Gastrointestin Liver Dis 18:121–122

Joensuu H, Robert PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D et al (2001) Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl Med 344:1052–1056

Josef A (1979) Multiple ruptured abscessed liver metastases (in German). Chirurg 50:181–182

Kahn SP, Lindenauer SM, Wojtalik RS, Hildreth D (1972) Clostridia hepatic abscess. An unusual manifestation of metastatic colon carcinoma. Arch Surg 104:209–212

Kalialis LV, Drzewiecki KT, Mohammadi M, Mehlsen AB, Klyver H (2008) Spontaneous regression of metastases from malignant melanoma: a case report. Melanoma Res 18:279–283

Karras BG, Cannon AH (1960) Calcified hepatic metastases from colonic carcinoma. Q Bull Northwest Univ Med Sch 34:163–166

Katzenstein TL, Jensen T, Arpi M (1994) Multiple liver abscesses caused by Fusobacterium necrophorum infection (in Danish). Ugeskr Laeger 156:6706–6707

Kim YH, Yoon HJ, Park CW, Kim JH, Lee MK, Kim KB, Na DJ, Kim JM (2011) A case of liver abscess caused by Fusobacterium nucleatum in a patient with recurrent periodontal diseases (in Korean). Korean J Gastroenterol 57:42–46

Kolbeinsson ME, Holder WD, Aziz S (1991) Recognition, management, and prevention of Clostridium septicum abscess in immunosuppressed patients. Arch Surg 126:642–645

Koransky JR, Stargel MD, Dowell VR (1979) Clostridium septicum bacteremia: its clinical significance. Am J Med 66:63–66

Krohn M, Grieser C, Weichert W, Pascher A, Denecke T (2011) Well-differentiated neuroendocrine carcinoma mimicking an echinococcus cyst of the liver in CT-MRI findings with hepatocyte specific contrast material. J Gastrointest Liver Dis 20:439–442

Kurtz JE, Claudel L, Collard O, Limacher JM, Bergerat JP, Dufour P (2005) Liver abscess due to Clostridium septicum. A case report and review of the literature. Hepatogastroenterology 52:1557–1558

Kvitting JP, Sandström P, Thorelius L, Kullman E, Borch K, Svanik J (2006) Radiofrequency ablation of a liver metastasis complicated by extensive liver necrosis and sepsis caused by gas gangrene. Surgery 139:123–125

La Fianza A, Alberici E, Biasina AM, Preda L, Tateo S, Campani R (1999) Spontaneous hemorrhage of a liver metastasis from squamous cell cervical carcinoma: case report and review of the literature. Tumori 85:290–293

Le Roux K, Sève P, Gornard E, Boibieux A, Beziat C, Stankovic K, Brousolle C (2006) Lemierre syndrome variant: hepatic abscesses and hepatic venous thrombosis due to Fusobacterium nucleatum septicemia (in French). Rev Med Interne 27:482–486

Lee CH, Hsieh SY (1999) Case report: clostridium septicum infection presenting as liver abscess in a case of choriocarcinoma with liver metastasis. J Gastroenterol Hepatol 14:1227–1229

Lee SY, Chuang JH, Huang CB, Hsiao CC, Wan YL, Ng SH, Lee TY, Ko SF (1998) Congenital bilateral cystic neuroblastoma with liver metastases and massive intracystic haemorrhage. Br J Radiol 71:1205–1207

Lee JK, Kum J, Ghosh P (2008) Nonmetastatic cancer of the colon associated with pyogenic liver abscess. Am J Gastroenterol 103:798–799

Lieuw-a-Fa M, Peringa J, Leeksma O, Terpstra W (2008) Sepsis from liver abscesses in metastatic colorectal carcinoma after chemoimmunotherapy. J Clin Oncol 26:1381–1382

Linton KM, Taylor MB, Radford JA (2006) Response evaluation in gastrointestinal stromal tumours treated with imatinib: misdiagnosis of disease progression on CT due to cystic change in liver metastases. Br J Radiol 79:e40–e44

Lonardo A, Grisendi A, Pulvirenti M, Della Casa G, Melini L, Di Gregorio C, Nasi G et al (1992) Right colon adenocarcinoma presenting as Bacteroides fragilis liver abscesses. J Clin Gastroenterol 14:335–338

Lowe EC, Baslé A, Czjzek M, Firbank SJ, Bolam DN (2012) A scissor blade-like closing mechanism implicated in transmembrane signaling in a Bacteroides

hybrid two-component system. Proc Natl Acad Sci U S A 109:7298–7303
McDermott EW (1987) Metastatic carcinoid tumor presenting as a hepatic pseudocyst. Ir J Med Sci 156:149–150
McDonnell CH, Fishman EK, Zerhouni EA (1986) CT demonstration of calcified liver metastases in medullary thyroid carcinoma. J Comput Assist Tomogr 10:976–978
Mittleman RE (1987) Hepatic rupture due to metastatic lung carcinoma. Am J Clin Pathol 88:506–509
Murakami R, Taniai N, Kumazaki T, Kobayashi Y, Ogura J, Ichikawa T (2000) Rupture of a hepatic metastasis from renal cell carcinoma. Clin Imaging 24:72–74
Namavar F, Theunissen EB, Verweij-Van Vught AM, Peerbooms PG, Bal M, Hoitsma HF et al (1989) Epidemiology of the Bacteroides fragilis group in the colonic flora in 10 patients with colonic cancer. J Med Microbiol 29:171–176
Ng JK, Urbanski SJ, Mangat N, Mckay A, Sutherland FR, Dixon E, Dowden S, Ernst S et al (2008) Colorectal liver metastases contract centripetally with a response to chemotherapy: a histomorphologic study. Cancer 112:363–371
Nguyen M, Vedantam G (2011) Mobile genetic elements in the genus Bacteroides, and their mechanism(s) of dissemination. Mob Genet Elements 1:187–196
Nohrström E, Mattila T, Pettilä V, Kuusela P, Carlson P, Kentala E, Mattila PS (2011) Clinical spectrum of bacteraemic Fusobacterium infections: from septic shock to nosocomial bacteraemia. Scand J Infect Dis 43:463–470
Pérez Flores R, Cortés Cansino J, Oliva Aldamiz H, Hernandez Quoi C (1987) Hepatic cirrhosis with and without implanted carcinoma. Apropos of 100 cases with necropsy (in Spanish). Rev Clin Esp 181:356–360
Phongkitkarun S, Phaisanphrukkun C, Jatchavala J, Sirachainan E (2008) Assessment of gastrointestinal stromal tumors with computed tomography following treatment with imatinib mesylate. World J Gastroenterol 14:892–898
Pierrugues R, Taourel P, Avril P (1994) Liver abscess revealing adenocarcinoma of the right colon (in French). J Chir (Paris) 131:521–522
Pisano M, Cogoni GF, Meloni A, Gromo C, Piga S, Saliu A, Ottonello R (2007) Pyogenic abscess in hepatic metastasis: unusual first manifestation of colorectal cancer. A case report (in Italian). Chir Ital 59:423–427
Raghavendra GK, Carr M, Dharmadhikari R (2013) Colorectal cancer liver metastasis presenting as pneumoperitoneum: case report and literature review. Indian J Surg 75(suppl 1):266–268
Rankin GB, Brown CH, Crile G (1965) Spontaneous regression of hepatic metastases from a carcinoma of the colon: 10-year follow up of a patient with familial polyposis. Ann Surg 162:156–159
Reichardt P, Schneider U, Stroszczynski C, Pink D, Hohenberger P (2004) Molecular response of gastrointestinal stromal tumour after treatment with tyrosine kinase inhibitor imatinib mesylate. J Clin Pathol 57:215–217
Ritchie AW, Layfield LJ, deKernion JB (1988) Spontaneous regression of liver metastasis from renal carcinoma. J Urol 140:596–597
Ritchie (1975) http://www.ncbi.nlm.nih.gov/pubmed/1058689
Rosenberg SA, Fox E, Churchill WH (1972) Spontaneous regression of hepatic metastases from gastric carcinoma. Cancer 29:472–474
Rubaltelli L, Zacchi C, Angelini F, Bulzacchi A (1983) Liver metastases with posterior acoustic shadow in echography: causes and differential diagnosis (in Italian). Radiol Med 69:316–319
Rubbia-Brandt L, Giostra E, Brezault C, Roth AD, Andres A, Audard V, Sartoretti P et al (2007) Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. Ann Oncol 18:299–304
Salamone L, McCarthy S, Salem RR (2010) Atypical cystic carcinoid tumors of the liver. J Clin Gastroenterol 44:e256–e259
Sandrasegaran K, Rajesh A, Rushing DA, Rydberg J, Akisik FM, Henley JD (2005) Gastrointestinal stromal tumors: CT and MRI findings. Eur Radiol 15:1407–1414
Sarmiento JM, Sarr MG (2002) Necrotic infected liver metastasis from colon cancer. Surgery 132:110–111
Saubier EC, Brault JA, Gaillard P, Moulay A, Lesbros F (1970) Carcinoid tumor of the small intestine with voluminous cystic metastasis of the liver. Excision at both sites (in French). Lyon Chir 66:445–448
Scatarige JC, Fishman EK, Sahsouk FA, Siegelman SS (1983) Computed tomography of calcified liver masses. J Comput Assist Tomogr 7:83–89
Scoular A, Corcoran GD, Malin A, Evans BA, Davies A, Miller RF (1992) Fusobacterium nucleatum bacteraemia with multiple liver abscesses in an HIV-I antibody positive man with IgG2 deficiency. J Infect 24:321–325
Serpick A (1976) Spontaneous regression of colon carcinoma. Natl Cancer Inst Monogr 44:21
Shah BK, McHugh K (2000) Cystic liver metastases from extracranial primitive neuroectodermal tumour: a case report. Pediatr Radiol 30:834–836
Shen XJ, Rawls JF, Randall T, Burcal L, Mpande CN, Jenkins N, Jovov B, Abdo Z et al (2010) Molecular characterization of mucosal adherent bacteria and associations with colorectal adenomas. Gut Microbes 1:138–147
Sobhani I, Tap J, Roudot-Thoraval F, Roperch JP, Letulle S, Langella P, Corthier G et al (2011) Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One 6, e16393
Stoupis C, Taylor HM, Paley MR, Buetow PC, Marre S, Baer HU, Vock P, Ros PR (1998) The rocky liver:

radiologic-pathologic correlation of calcified hepatic masses. Radiographics 18:675–685

Su CP, Huang PY, Yang CC, Lee MH (2009) Fusobacterium bacteremia: clinical significance and outcomes. J Microbiol Immunol Infect 42:336–342

Takahashi T, Yamada S, Fukami A, Kin M (1971) Case of calcified hepatic metastasis of rectal cancer (in Japanese). Gan No Rinsho 17:711–715

Takauji S, Matsumoto A, Shibata N, Yoshida A, Orii F, Fujii T, Taruishi M, Miyokawa N (2005) Case report: cystic metastasis in liver fifteen years after surgical operation of malignant melanoma (in Japanese). Nihon Shokakibyo Gakkai Zasshi 102:1321–1326

Teitz S, Guidetti-Sharon A, Manor H, Halevy A (1995) Pyogenic liver abscess: warning indicator of silent colonic cancer. Report of a case and review of the literature. Dis Colon Rectum 38:1220–1223

Thel MC, Ciaccia D, Vredenburgh JJ, Peters W, Corey GR (1994) Clostridium septicum abscess in hepatic metastases: successful medical management. Bone Marrow Transpl 13:495–496

Tokita H, Shimizu M, Ohshima K, Kobayashi S, Nishikawa Y, Takai T, Takahashi Y et al (1988) A case of nontraumatic Clostridium septicum infection with intrahepatic pneumatic tumor and adenocarcinoma of the transverse colon (in Japanese). Nippon Naika Gakkai Zasshi 77:1873–1878

Trump DL, Fahnestock R, Cloutier CT, Dickman MD (1978) Anaerobic liver abscess and intrahepatic metastases: a case report and review of the literature. Cancer 41:682–686

Tung CF, Chang CS, Chow WK, Peng YC, Hwang JI, Wen MC (2002) Hemoperitoneum secondary to spontaneous rupture of metastatic epidermoid carcinoma of liver: case report and review of the literature. Hepatogastroenterology 49:1415–1417

Tweedy CR, White WB (1987) Multiple Fusobacterium nucleatum liver abscesses. Association with a persistent abnormality in humoral immune function. J Clin Gastroenterol 9:194–197

Tzur T, Liberman S, Felzenstein I, Cohen R, Rivkind AI, Almogy G (2003) Liver abscesses caused by Streptococcus milleri: an uncommon presenting sign of silent colonic cancer. Isr Med Assoc J 5:206–207

Ulusan S, Koç Z, Kayaselçuk F (2008) Imaging characteristics of liver metastasis from gastrointestinal stromal tumor before and after imatinib mesylate treatment. Turk J Gastroenterol 19:129–132

Urban BA, McCormick R, Fishman EK, Lillemoe KD, Petty BG (2000) Fulminant Clostridium septicum infection of hepatic metastases presenting as pneumoperitoneum. AJR Am J Roetgenol 174:962–964

Vanel D, Albiter M, Shapeero L, Le Cesne A, Bonvalot S, Le Pechoux C, Terrier P et al (2005) Role of computed tomography in the follow-up of hepatic and peritoneal metastases of GIST under imatinib mesylate treatment: a prospective study of 54 patients. Eur J Radiol 54:118–123

Verna EC, Larghi A, Faddoul SG, Stein JA, Worman HJ (2004) Portal vein thrombosis associated with Fusobacterium nucleatum septicemia in a patient with ulcerative colitis. J Clin Gastroenterol 38:611–612

Wells J (1956) Calcified liver metastases. N Engl J Med 255:639–640

Wexler HM (2007) Bacteroides: the good, the bad, and the nitty-gritty. Clin Microbiol Rev 20:593–621

Wijesuriya SR, Siriwardana R, Deen K (2010) Education and imaging. Hepatobiliary and pancreatic: carcinoid tumor with cystic liver metastases. J Gastroenterol Hepatol 25:647

Xu L, Zhou Y, Qiu D (2010) Correlation between calcified liver metastases and histopathology of primary colorectal carcinoma in Chinese. J Huazhong Sci Technol Med Sci 30:815–818

Yokota T, Iwamoto K, Watanabe Y, Yamauchi H, Kikuchi S, Hatori M (2005) Pyogenic liver abscesses secondary to carcinoma of the sigmoid colon: a case report and clinical features of 20 cases in Japan. Ups J Med Sci 110:241–244

Young EJ, Harper WK, Taylor RL (1977) Hepatic necrobacillosis. Report of a case resembling metastatic tumor. Arch Intern Med 137:804–807

Yu JS, Park C, Yoon DS, Lwee KS, Park MS, Kim KW (2007) Case report: biliary papillary neoplasm engulfed by an hepatic abscess. Clin Radiol 62:387–390

Zonios D, Soula M, Archimandritis AJ, Revenas K (2003) Cyst-like hepatic metastases from gastrointestinal stromal tumors could be seen before any treatment. AJR Am J Roentgenol 181:282

Metastatic Liver Disease: Hepatic Lymph Node Involvement

110

Contents

Abstract

Metastatic cancers of the liver can undergo further spread via the liver lymph drainage system, reaching lymph nodes close to the liver and the retroperitoneal space. Hepatic lymph is drained to a rather large group of locoregional lymph nodes. A first lymph node station is located very close to the liver, in the transverse fissure, associated with the left hepatic artery. Liver-associated lymph nodes are less common and smaller on the right side. The main lymphatic drainage route for hepatic cancer cells, including cells released from metastases, is along the hepatic artery to hepatic nodes at the hilum, from here to the celiac group; along the falciform ligament to right phrenic nodes and then to mediastinal nodes; through the esophageal hiatus and the caval foramen and transdiaphragmatically to right phrenic and mediastinal nodes; to paracardial upper gastric lymph nodes; and along the phrenic arteries directly to celiac nodes. Overall, the prevalence of hepatic pedicle lymph node metastases in diverse liver malignancies ranges from 10 % to 20 %, but the rate of macroscopically visible hepatic locoregional lymph node metastases is less, around 7 %. Involvement of liver-associated lymph nodes in hepatic metastatic disease has an impact on outcome. For hepatic colorectal

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_110

carcinoma metastasis, intrahepatic lymphatic vascular dissemination is associated with increased risk of recurrence and poor survival, and involvement of liver-associated nodes confers a poorer result following metastasis resection.

General Remarks and Anatomy

The lymphatic drainage of the liver is notable for its volume and flow to a rather large number of lymph node groups. Within the liver, the lymph vessel system is arborized and forms a network with unhindered communication from one area to another (Huth 1974; Wolodjko 1967; Szabo et al. 1975; Sapin and Usovich 1983; August et al. 1985). A first lymph node system is located close to the liver, i.e., in the transverse fissure (very small nodes, about 2 mm diameter), posterior to the portal vein, posterior to the pars transversa of the left portal vein, and associated with the left hepatic artery. Generally, lymph nodes are less common and smaller on the right side, and lymph nodes are not found or are seldom found between the portal vein, hepatic artery, and bile ducts in the fissures (Hardy et al. 1976). The main drainage routes from the liver comprise (August et al. 1985):

1. Along the hepatic artery to the hepatic nodes at the hilum and from here to the celiac node group
2. Along the falciform ligament to supradiaphragmatic right phrenic lymph nodes and then to mediastinal or internal mammary lymph node chains
3. Through the esophageal hiatus and the caval foramen and transdiaphragmatically to supradiaphragmatic right phrenic and mediastinal lymph nodes
4. Along the superior border of the lesser omentum to the paracardial upper gastric lymph nodes
5. Along the phrenic arteries directly to the celiac lymph nodes

The common hepatic node group is connected with the nodes on the anterior surface of the pancreatic head, and this pathway terminates in the node situated to the right of the origins of the celiac trunk and the superior mesenteric artery (Deki and Sato 1988). The convergence system of lymphatics is also connected with the lymphatic drainage of the gallbladder. The first node is the cystic node or pericholedochal node. The further drainage comprises at least three pathways: (1) the cholecysto-retropancreatic (main) pathway (This pathway has two routes, one running spirally and posteriorly from the anterior surface of the common bile duct to the right and the other running almost straight down from the posterior surface of the common bile duct. At the retroportal segment, these routes converge at a large lymph node being the terminal node of this pathway.), (2) the cholecysto-celiac pathway terminating in the celiac nodes, and (3) the cholecysto-mesenteric pathway, by which some lymphatics run to the left in front of the portal vein and connected with the nodes at the superior mesenteric root (Ito et al. 1991; Uesaka et al. 1996). The spread of CRC to hepatic locoregional lymph nodes is well documented and, as outlined below, has a marked impact on disease progression and survival (Gayowski et al. 1994; Beckurts et al. 1997; Ohlsson et al. 1998; Kokudo et al. 1999; Rodgers and McCall 2000; Ishibashi et al. 2006). The phenomenon is biologically interesting, because it is an example of cancer spread from metastasis to metastasis, described long ago (Vines 1949; Viadana and Au 1975; Viadana et al. 1978).

Frequency and Distribution of Hepatic Lymph Node Involvement

Overall, the prevalence of hepatic pedicle lymph node metastases ranges from 10 % to 20 % (August et al. 1985; Jaeck 2003; Viana et al. 2009). The rate of macroscopic hepatic lymph node metastasis has been reported to be 7 % and the incidence of macroscopic and

microscopic node metastasis 19 % (Elias and Ouellet 2003). As periportal/hilar and celiac lymph nodes are rather commonly involved, routine periportal/celiac lymph node biopsies have been advocated (Gibbs et al. 1998). Among 100 consecutive patients undergoing curative hepatectomy for CRC metastases with extensive lymph dissection of the hepatic pedicale in the absence of macroscopic node involvement, microscopic lymph node involvement was found in 14 patients. Node metastases involved very different lymph node sites and was related only to the number of metastases, extent of liver involvement, and carcinoembryonic antigen level (Elias et al. 1996). In one series, hepatic lymph node sampling was done in 78/182 cases of hepatic resections for colorectal metastases. Twelve percent showed secondary lymph node metastases in the hepatoduodenal ligament. There was a tendency for liver metastases in the right liver lobe to metastasize to lymph node No. 12b (or node of the foramen of Winslow, lymph nodes along the common bile duct) and liver metastases in the left liver lobe to metastasize to No. 8a (anterosuperior group of the lymph nodes along the common hepatic artery). In another study, a total of 111 hepatic lymph nodes were removed from 33 patients with synchronous CRC liver metastases during the resection of the primary tumor. Hepatic lymph node metastasis was found in nine patients (27 %). The node sites involved were three along the hepatic artery, three in the hepatoduodenal ligament, and three in both (Ishibashi et al. 2006). Among 156 patients undergoing curative liver resection for RCR metastases, microscopic hepatic lymph node involvement occurred in 15 % of the patients and was associated with a poor 5-year survival (Laurent et al. 2004). In a retrospective series of 62 patients who were deemed not resectable at laparotomy, 11 % were found to have positive portal or celiac nodes as the only site of extrahepatic disease (Gibbs et al. 1998). It was reported that, based on CT and PET scans, routine sampling of perihepatic lymph nodes will have a low yield in patients without some evidence of disease on preoperative CT or PET scans or at the time of exploration (Grobmyer et al. 2006).

Impact on Disease Progression and Outcome

For hepatic colorectal metastasis, intrahepatic lymphatic vascular dissemination was associated with increased risk of intrahepatic recurrence and poorer overall survival (review: Lupinacci et al. 2014). In the presence of hepatic lymph node involvement, it has previously been suggested that liver resection for metastasis is not contraindicated (Nims 1984; Yasui et al. 1995; Beckurts et al. 1997). Specifically, it has been proposed that positive nodes located near the hilum and along the hepatic pedicle (area 1) should not be considered an absolute contraindication to resection of hepatic metastasis (Jaeck 2003). One study has reported a survival benefit of hepatic lymph node dissection for some patients, provided a potentially curative (R0) resection is feasible (Wakai et al. 2009). On the other hand, the involvement of the hepatic lymph nodes has been a contraindication for resection for other authors, because it is considered as tertiary metastasis (Ohlsson et al. 1998; Minagawa et al. 2000). The outcome of patients with positive nodes is or was generally regarded as poor in comparison with node-negative patients and one of the most significant prognostic indicators (Nakamura et al. 1992; Scheele et al. 1996; Elias and Ouellet 2003; Pandey 2008; Ishida et al. 2011; Cardona et al. 2013). However, the unfavorable progression of disease depends on the node group involved in the era of new chemotherapy strategies. Formerly, when the positive nodes reach the celiac trunk (area 2), there was no survival benefit after metastasis resection (Jaeck 2003), whereas with new therapies, node involvement of area 1 or 2 does not anymore affect survival after CRC metastasis resection (Oussoultzoglou et al. 2009). Even the presence of microscopic lymph node metastases may have an impact on outcome in patients submitted to

curative hepatectomy (Lupinacci et al. 2013). Currently, there seems to be no convincing evidence of a survival benefit for routine or selective lymphadenectomy, and survival rates are low in patients with positive lymph nodes draining the liver irrespective of whether they are detected by routine lymphadenectomy or by macroscopic involvement (Gurusamy et al. 2008, with review). So far, there are a few 5-year survivors after liver resection for hepatic CRC metastases involving the hepatic lymph nodes, with or without lymph node dissection (Nakamura et al. 1992, 1999; Yasui et al. 1995; Ambiru et al. 1999; Rodgers and McCall 2000). The most common sites of tumor recurrence in the node-positive patients are the remnant liver and again the hepatic lymph nodes (Kokudo et al. 1999). The cell subpopulations giving rise to lymph node metastases of cancers also spreading to the liver are not yet well defined. From genetic and epigenetic studies, it surfaced that lymph node and liver metastasis appear to originate in clonally different processes. Specifically, remote organ metastases harbor more molecular abnormalities than those located in lymph nodes (Miranda et al. 2013).

Immune Reactions in Metastasis-Draining Lymph Nodes: Tumor-Draining Lymph Nodes (TDNLs), Metastasis-Draining Lymph Nodes (MDLNs), and the Concept of Metinel Nodes

As in lymph nodes draining primary tumors, metastatic tumors can elicit distinct patterns of immune reactions in locoregional lymph nodes. For the liver, tumor-draining lymph nodes (TDLNs) can undergo reactive enlargement mimicking metastatic disease. Lymphadenomegaly is in these situations caused by expansion of the follicular cortex and/or the paracortical area; the accumulation of other immunologic effector cells, including plasma cells and macrophages; and the recruitment of myeloid and other dendritic cells and of granulocytes, mainly eosinophils, all these alterations representing a concerted immune response directed against tumor-associated antigens. With time, locoregional immune reactions lead to an important change in the nodal microarchitecture (Heys and Eremin 1992; Chandrasekaran and King 2014). Markedly activated TAMs in TDLNs can result in the development of epithelioid macrophages which form a granulomatous reaction (review: Bhatia et al. 2009), which may sometimes mimic sarcoidosis. In addition to humoral and cell-bound immune reactions, lymph nodes under changes are linked to secondary alterations of primary tumors of their metastases. In case of tumor hemorrhage, lymph nodes contain fresh blood translocated by lymphatics, macrophages with erythrophagocytosis, and hemosiderin deposition, while tumor necrosis can induce the accumulation of numerous macrophages and lipid-rich foamy cells in dependent nodes.

Immune reactions in TDLNs as a main element of tumor surveillance are both of the innate and adaptive type. Adaptive immune responses to cancers are mainly directed against tumor-associated antigens (TAAs) that are shed from neoplastic cells to be presented by antigen-presenting dendritic cells. Adenocarcinomas (primary tumors and metastases) promote a vigorous B lymphocyte reaction in TDLNs. An increased number of B cells in locoregional lymph nodes suggest antitumor immune responses characterized by interactions between activated T lymphocytes and B cells, whereby nodes draining adenocarcinomas often show B lymphocytes with expression of CD80 (Lores et al. 1998; Contassot et al. 2009). The CD8(+) T-cell response is regulated not only by antigen presentation by dendritic cells and interaction with B cells but also by the expression of regulatory factors. The T-box transcription factor eomesodermin controls CD(8+) cells activity and lymph node metastasis in CRCs (Atreya et al. 2007). TDLNs also contain specific populations of immunologic effector cells that exert an important effect on tumor growth and progression. TDLNs draining colorectal cancer contain variable number of regulatory T cells (TREGS) with a FOXP3-positive phenotype, and it is expected that also metastasis-draining lymph nodes (MDLNs) exhibit this distinct cell

population. FOXPs(+)TREG infiltration was associated with more advanced colorectal cancer disease and lymph node metastasis (Gai et al. 2013). These TREGs potentially influence CD8(+) T-cell functions in that FOXP3(+) TREGs can impair CD8(+) cell function (Deng et al. 2010). An important role in immune defense directed against spreading cancer cells is played by the first nodes that drain a metastasis. These nodes were termed metinel nodes, and they contain interferon-gamma-producing lymphocytes that show clonal expansion, suggesting the presence of tumor-reactive lymphocytes (Dahl et al. 2008). Apart from cellular reactions, TDLNs and MDLNs express several proteins that are associated with nodal metastasis. In sentinel lymph nodes of colorectal cancers, upregulation of four metastasis-associated proteins was found, including hnRNP A1, ezrin, tubulin beta-2C, and annexin A1 (He et al. 2010).

Adenocarcinoma cells metastasizing to lymph nodes induce intranodular epithelial-mesenchymal transition (EMT) and recruit mesenchymal cells to become stromal cells, induced nodal stroma providing a critical microenvironment (niche) for metastatic tumor growth. In a first phase, the nodal pro-metastatic niche is characterized by a predominance of monocytes and macrophages (tumor-associated macrophages (TAMs)), associated with T and B cells, TREGs, myeloid dendritic cells, natural killer cells, and eosinophils. The complex interactome of these niche cells can induce the transformation of local mesenchymal cells or homing mesenchymal stem cells into cancer-associated fibroblasts (CAFs) and myofibroblasts as most important cell populations of stroma (review: Horst and Horny 1988). After the homing of cancer cells to the lymph node niche, a complex cross talk between CAFs of the stroma and carcinoma cells takes place, a process markedly modulated by STAT1 signaling (Kaler et al. 2014). There is evidence that carcinoma cells and CAFs are cooperative in the metastatic spread, in that, e.g., they show co-migration induced by TGF-beta1, a process enhancing metastasis (Gonzalez-Zubeldia et al. 2015). Cells making part of the premetastatic nodal niche also operate in the induction of angiogenesis and lymphangiogenesis that facilitate metastatic growth. Nodal lymphangiogenesis induced by tumor cells increases lymph flow and tumor metastasis (Harrell et al. 2007). TAMs and CAFs are engaged in a cellular prolymphangiogenic cross talk that is important for the initiation of a distinct vascular bed within the metastatic site (Schlereth et al. 2014).

References

Ambiru S, Miyazaki M, Isono T, Ito H, Nakagawa K, Shimizu H, Kusashio K, Furuya S, Nakajima N (1999) Hepatic resection for colorectal metastases: analysis of prognostic factors. Dis Colon Rectum 42:632–639

Atreya I, Schimanski CC, Becker C, Wirtz S, Dornhoff H, Schnürer E, Berger MR, Galle PR, Herr W et al (2007) The T-box transcription factor eomesodermin controls CD8 T cell activity and lymph node metastasis in human colorectal cancer. Gut 56:1572–1578

August DA, Sugarbaker PH, Schneider PD (1985) Lymphatic dissemination of hepatic metastases. Implications for the follow-up and treatment of patients with colorectal cancer. Cancer 55:1490–1494

Beckurts KT, Hölscher AH, Thorban S et al (1997) Significance of lymph node involvement at the hepatic hilum in the resection of colorectal liver metastases. Br J Surg 84:1081–1084

Bhatia A, Kumar Y, Kathpalia AS (2009) Granulomatous inflammation in lymph nodes draining cancer: a coincidence or a significant association! Int J Med Med Sci 1:13–16

Cardona K, Mastrodomenico P, D'Amico F, Shia J, Gönen M, Weiser MR, Paty PB et al (2013) Detailed pathologic characteristics of the primary colorectal tumor independently predict outcome after hepatectomy for metastases. Ann Surg Oncol 20:148–154

Chandrasekaran S, King MR (2014) Microenvironment of tumor-draining lymph nodes: opportunities for liposome-based targeted therapy. Int J Mol Sci 15:20209–20239

Contassot E, Preynat-Seauve O, French L, Uard B (2009) Lymph node tumor metastases: more susceptible than primary tumors to CD8+ T-cell immune destruction. Trends Immunol 30:569–573

Dahl K, Karlsson M, Marits P, Hoffstedt A, Winqvist O, Thörn M (2008) Metinel node – the first lymph node draining a metastasis – contains tumor-reactive lymphocytes. Ann Surg Oncol 15:1454–1463

Deki H, Sato T (1988) An anatomic study of the peripancreatic lymphatics. Surg Radiol Anat 10:121–135

Deng L, Zhang H, Luan Y, Zhang J, Xing Q, Dong S, Wu X, Liu M, Wang S (2010) Accumulation of foxp3 + T regulatory cells in draining lymph nodes correlates

with disease progression and immune suppression in colorectal cancer patients. Clin Cancer Res 16:4105–4112
Elias DM, Ouellet JF (2003) Incidence, distribution, and significance of hilar lymph node metastases in hepatic colorectal metastases. Surg Oncol Clin N Am 12:221–229
Elias D, Saric J, Jaeck D, Arnaud JP, Gayet B, Rivoire M, Lorimier G, Carles J, Lasser P et al (1996) Prospective study of microscopic lymph node involvement of the hepatic pedicle during curative hepatectomy for colorectal metastases. Br J Surg 83:942–945
Gai XD, Song Y, Li C, Lei YM, Yang B (2013) Potential role of plasmacytoid dendritic cells for FOXP3+ regulatory T cell development in human colorectal cancer and tumor draining lymph node. Pathol Res Pract 209:774–778
Gayowski TJ, Iwatsuki S, Madariaga JR, Selby R, Todo S, Irish W, Starzl TE (1994) Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 116:703–710
Gibbs JF, Weber TK, Rodriguez-Bigas MA, Driscoll DL, Petrelli NJ (1998) Intraoperative determinants of unresectability for patients with colorectal hepatic metastases. Cancer 82:1244–1249
Gonzalez-Zubeldia I, Dotor J, Redrado M, Bleau A, Manrique I, de Aberasturi AL, Villable M, Calvo A (2015) Co-migration of colon cancer cells and CAFs induced by TGFβ1 enhances liver metastasis. Cell Tissue Res 359:829–839
Grobmyer SR, Wang L, Gonen M, Fong Y, Klimstra D, D'Angelica M, DeMatteo RP, Schwartz L, Blumgart LH, Jarnagin WR (2006) Perihepatic lymph node assessment in patients undergoing partial hepatectomy for malignancy. Ann Surg 244:260–264
Gurusamy KS, Imber C, Davidson BR (2008) Management of the hepatic lymph nodes during resection of liver metastases from colorectal cancer: a systematic review. HPB Surg 2008:684150
Hardy KJ, Wheatley IC, Anderson AI, Bond RJ (1976) The lymph nodes of the porta hepatis. Surg Gynecol Obstet 143:225–228
Harrell MI, Iritani BM, Ruddell A (2007) Tumor-induced sentinel lymph node lymphangiogenesis and increased lymph flow precede melanoma metastasis. Am J Pathol 170:774–786
He ZY, Wen H, Shi CB, Wang J (2010) Up-regulation of hnRNP A1, ezrin, tubulin β-2C and annexin A1 in sentinel lymph nodes of colorectal cancer. World J Gastroenterol 16:4670–4676
Heys SD, Eremin O (1992) The relevance of tumor draining lymph nodes in cancer. Sur Gynecol Obstet 174:533–540
Horst HA, Horny HP (1988) Cellular stromal reaction in lymph node metastases of human colorectal carcinomas. Hepatogastroenterology 35:140–143
Huth F (1974) Morphological aspects of the lymph vessel system of the liver (in German). Leber Magen Darm 4:262–273
Ishibashi K, Ohsawa T, Yokoyama M, Ishizuka N, Miyazaki T, Nakada H, Gonda T, Ishida H (2006) Hepatic lymph node involvement in patients with synchronous multiple liver metastases of colorectal cancer (in Japanese). Gan To Kagaku Ryoho 33:1834–1837
Ishida H, Ishibashi K, Ohsawa T, Okada N, Kumamoto K, Haga N (2011) Significance of hepatic lymph node metastasis in patients with unresectable synchronous liver metastasis of colorectal cancer. Int Surg 96:291–299
Ito M, Mishima Y, Sato T (1991) An anatomical study of the lymphatic drainage of the gallbladder. Surg Radiol Anat 13:89–104
Jaeck D (2003) The significance of hepatic pedicle lymph nodes metastases in surgical management of colorectal liver metastases of other liver malignancies. Ann Surg Oncol 10:1007–1011
Kaler P, Owusu BY, Augenlicht L, Klampfer L (2014) The role of STAT1 for crosstalk between fibroblasts and colon cancer cells. Front Oncol 4:88
Kokudo et al (1999) http://www.ncbi.nlm.nih.gov/pubmed/1058765
Laurent C, Sa Cunha A, Rullier E, Smith D, Rullier A, Saric J (2004) Impact of microscopic hepatic lymph node involvement on survival after resection of colorectal liver metastasis. J Am Coll Surg 198:884–891
Lores et al (1998) http://www.ncbi.nlm.nih.gov/pubmed/9852289
Lupinacci RM, Herman P, Coelho FC, Viana EF, D'Albuquerque LA, Cecconello I (2013) Diagnosis and impact of hilar lymph node micrometastases on the outcome of resected colorectal liver metastasis. Hepatogastroenterology 60:333–336
Lupinacci RM, Paye F, Coelho FF, Kruger JA, Herman P (2014) Lymphatic drainage of the liver and its implications in the management of colorectal cancer liver metastases. Updates Sur 66:239–245
Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, Yamamoto J et al (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 231:487–499
Miranda E, Bianchi P, Destroy A, Morenghi E, Malesci A, Santoro A, Laghi L, Roncalli M (2013) Genetic and epigenetic alterations in primary colorectal cancers and related lymph node and liver metastases. Cancer 119:266–276
Nakamura S, Yokoi Y, Suzuki S, Baba S, Muro H (1992) Results of extensive surgery for liver metastases in colorectal carcinoma. Br J Surg 79:35–38
Nakamura S, Suzuki S, Konno H (1999) Resection of hepatic metastases of colorectal carcinoma: 20 years' experience. J Hepato-Biliary-Pancreatic Surg 6:16–22
Nims TA (1984) Resection of the liver for metastatic cancer. Surg Gynecol Obstet 158:46–48
Ohlsson B, Stenram U, Tranberg KG (1998) Resection of colorectal liver metastases: 25-year experience. World J Surg 22:268–276
Oussoultzoglou E, Romain B, Panaro F, Rosso E, Pessaux P, Bachellier P, Jaeck D (2009) Long-term

survival after liver resection for colorectal liver metastases in patients with hepatic pedicle lymph nodes involvement in the era of new chemotherapy regimens. Ann Surg 249:879–886

Pandey D (2008) Biological behavior of perihepatic lymph node metastasis and its impact on prognosis following liver resection for colorectal metastases. Ann Surg Oncol 15:2620

Rodgers MS, McCall JL (2000) Surgery for colorectal liver metastases with hepatic lymph node involvement: a systematic review. Br J Surg 87:1142–1155

Sapin MR, Usovich AK (1983) Anatomy and topography of the regional lymph nodes of the liver and gallbladder (in Russian). Vopr Onkol 29:45–52

Scheele J, Altendorf-Hofmann A, Stangl R, Schmidt K (1996) Surgical resection of colorectal liver metastases: gold standard for solitary and radically resectable lesions (in German). Swiss Surg (Suppl 4): 4–17.

Schlereth SL, Refaian N, Iden S, Cursiefen C, Heindle LM (2014) Impact of the lymphangiogenic crosstalk in the tumor microenvironment on lymphatic cancer metastasis. Biomed Res Int 2014:639058

Szabo G, Magyar Z, Jakab F (1975) The lymphatic drainage of the liver capsule and hepatic parenchyma. Res Exp Med (Berlin) 166:193–200

Uesaka K, Yasui K, Morimoto T, Torii A, Yamamura Y, Kodera Y, Hirai T, Kato T, Kito T (1996) Visualization of routes of lymphatic drainage of the gallbladder with a carbon particle suspension. J Am Coll Surg 183:345–350

Viadana E, Au KL (1975) Patterns of metastases in adenocarcinomas of man. J Med 6:1–14

Viadana E, Bross IDJ, Pickren JW (1978) Cascade spread of blood-borne metastases in solid and nonsolid cancers of humans. In: Weiss L, Gilbert HA (eds) Pulmonary metastases. G.K. Hall, London

Viana EF, Herman P, Siqueira SC, Taka T, Carvalho P, Coelho FF, Pugliese V, Saad WA, D'Albuquerque LA (2009) Lymphadenectomy in colorectal cancer liver metastases resection: incidence of hilar lymph nodes micrometastasis. J Surg Oncol 100:534–537

Vines HWC (1949) Green's manual of pathology, 17th edn. Bailiere, Tindall and Cox, London

Wakai T, Shirai Y, Sakata J, Nagahashi M, Kaneko K, Hatakeyama K (2009) Hepatic lymph node dissection provides a survival benefit for patients with nodal disease of colorectal carcinoma liver metastases. Hepatogastroenterology 56:186–190

Wolodjko WP (1967) The lymphatic system of the human liver in relation to its segmentation (in German). Z Anat Entwicklungsgesch 126:154–171

Yasui K, Hirai T, Kato T, Morimoto T, Tori T, Uesata K (1995) Major anatomical hepatic resection with regional lymph node dissection for liver metastases from colorectal cancer. J Hepato-Biliary-Pancreatic Surg 2:103–107

Metastatic Liver Disease: Associated Liver Lesions

111

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_111

Abstract

The presence and progression of hepatic metastases elicit a spectrum of secondary changes in the liver. Many metastases induce, due to their progressive growth, hepatomegaly, which often involves both liver lobes. However, in cases where metastatic disease compromises the portal venous system and/or bile duct system of one lobe, enlargement can involve only one liver lobe, the other undergoing shrinkage, the so-called atrophy/hypertrophy complex. Metastases in the liver induce various perifocal alterations in the parenchyma. Perifocal fatty change of hepatocytes is a common change and may be caused by tumor-induced microvascular obstruction and hypoxia. In the case of severely compromised microcirculation, perifocal ischemia with necrosis or perifocal atrophy ensues. Hepatocytes situated around metastatic nodules sometimes exhibit clear cell change. Cancer cells of metastases can induce activation of adjacent hepatic stellate cells, followed by matrix production and stroma induction. This may, in certain cancers such as metastasizing breast cancer, result in metastasis-related liver remodeling and pseudocirrhosis. Sinusoids in liver harboring metastases undergo a complex spectrum of alterations, including peliosis-like changes and microthrombangiopathy.

Hepatomegaly, Liver Atrophy, and the Atrophy/Hypertrophy Complex (AHC) in Metastatic Liver Disease

Gross hepatic metastases, a particular multiple metastases, cause hepatomegaly, sometimes to a very impressive degree, with liver weights exceeding 8 kg in some patients. On the other hand, a compromised hepatic circulation caused by even discrete metastatic liver disease can induce changes in liver mass and volume. It has been shown that the reduction of portal blood flow in patients with occult hepatic metastases may cause a decrease in liver volume (Ishizawa et al. 2005). This is related to the pathophysiological effect that any reduction in portal venous flow will compromise liver maintenance and cause atrophy due to lack of hepatotropic effects (Rous and Larimore 1920; Bax et al. 1956; Rozga et al. 1986; Takayasu et al. 1986). The pathogenesis of portal venous flow changes in the presence of metastases is unknown, but they do not seem to only depend on effects of mechanical vessel obstruction but also on the effects of humoral mediators.

In a study of 63 consecutive patients undergoing curative resection of hepatic CRC metastases, the CT-estimated liver volume (Kawasaki et al. 1993) was 841 ml in 8 patients who subsequently developed overt hepatic metastases during a 2-year follow-up and 1,145 ml in 55 patients without (occult) metastases. The results suggested that the liver with occult metastases decreases in size before overt metastatic tumors develop to be detectable (Ishizawa et al. 2007). It is known that even small hepatic metastases may lead to subtle changes in liver blood flow detected by hepatic flow scintigraphy (Leveson et al. 1985; Huguier et al. 1993; Kopljar et al. 2004), a phenomenon also detectable in experimental metastasis models in animals (Hemingway et al. 1991, 1993; Nott et al. 1989, 1991). Using Doppler ultrasonography, the Doppler perfusion index (DPI) was defined as the ratio of hepatic arterial flow to total liver blood flow and found to be useful in assessing tumor effects on liver circulation (Leen et al. 1993; Oktar et al. 2006). Changes in DPI are sensitive indicators for occult hepatic metastases (Leen et al. 1995; review: Leen 1999). In the context of such measurements, it has been taken into account that patient age has an effect on liver volume and liver blood flow. There is a significant negative correlation between age and both liver volume and apparent liver blood flow, whether expressed in absolute terms or per unit body weight. Similarly, a significant negative correlation is observed between apparent liver blood flow per unit of liver volume (i.e., liver perfusion) and age (Wynne et al. 1989). What is not clarified is the question as to why metastasis/portal hypoperfusion-induced atrophy in deprived parts is not compensated by reactive hypertrophy of the

uninvolved parts, because this a well-known response to atrophy in other situations, in the form of a so-called atrophy/hypertrophy complex (Bax et al. 1956; Lambotte et al. 2000; Ueda et al. 2004).

In some patients having massive and diffuse hepatic metastatic disease, and particularly those with breast cancer, the process can end up with liver atrophy. This alteration may represent the end stage of pseudocirrhosis or be an early response circumventing the pseudocirrhotic stage. Progressive liver atrophy can cause liver failure (Shitara et al. 2008). Mainly in cases where the metastatic tumor encroaches upon large bile ducts, causing stenosis or even obstruction, atrophy/hypertrophy complex (AHC) of the involved area may develop. As described in more detail in chapters of cholangiocarcinoma, AHC is characterized by the combination of parenchymal atrophy, hypertrophic changes with formation of nodular structures, and biliary-type fibrosis (review: Lory et al. 1994).

Perifocal Liver Changes in Hepatic Metastatic Disease

Introduction

Hepatic metastases can be associated with, or induce, a wide spectrum of changes in adjacent liver tissue, mostly in close vicinity to metastases. These alterations may, in the case of numerous metastases, compromise the function of the normal liver. On the other hand, the changes may exert an influence on the further growth of metastases within the hepatic environment or may affect the development of new metastatic nodules or satellite nodules. In what follows, the most important perifocal changes are briefly discussed.

Perifocal Fatty Change

Perifocal fatty change of hepatocytes located close to the periphery of metastases is a rather common alteration. It mostly presents as macrovesicular fatty change and less often as microvesicular fatty change. Macrovesicular fatty change is most commonly observed in liver parenchyma surrounding metastases of carcinomas and particularly those of colorectal cancer. In part of the cases, this change is macroscopically visualized as a brightly yellow of whitish-yellow rim of variable width directly adjacent to the metastatic nodules. The peripheral border of the rim facing the parenchyma is sharply demarcated in most cases, but may display an interdigitating interface. Histologically, hepatocytes in this rum show the typical large cytoplasmic vacuoles as seen in other forms of triglyceride fatty change. In a minority of cases, infiltrates of leukocytes, including neutrophils, lymphocytes, and macrophages, are present, causing a histology sometimes resembling that of nonalcoholic steatohepatitis/NASH, but fibrotic changes are not observed. Few apoptotic bodies (apoptosis of damaged hepatocytes) may be encountered. Accumulation of stainable iron is lacking. In the rare instances of microvesicular perimetastatic fatty change of hepatocytes, the alteration is only detectable histologically and is characterized by slightly enlarged liver cells showing a foamy cytoplasm. Inflammatory changes are not seen in this type of fatty change. The pathogenesis of perifocal fatty change has not been elucidated. It may be assumed that a deranged energy supply to hepatocytes localized just outside the growing tumor, e.g., due to poor oxygenation of tissue, causes accumulation of neutral fat and lipids in hepatocytes.

Perifocal Clear Cell Change

This rare alteration presents either as clusters or larger areas of clear hepatocytes rich in glycogen or as a ballooning (so-called hydropic degeneration) of liver cells without formation of Mallory-Denk bodies. Clear cell change may be associated with macrovesicular fatty change. Similar to pericentral ballooning found in toxic or other types of hepatocyte damage, peritumoral clear cell change is sometimes associated with cholestasis of the tissue concerned.

Perifocal Ischemic Change

The vascular bed of the liver and blood flow can be markedly compromised by tumor metastasis and particularly those of large size and with an invasive growth front. Due to pressure effects, microvascular/sinusoidal damage, and induction of intravascular coagulation, perifocal hepatic parenchyma may suffer severe ischemia resulting in perifocal necrosis of the coagulative type. These necrosis are commonly focal and form small patches reflecting the vascular architecture, but larger and rim-like zones of necrosis are also encountered. Within the eosinophilic necrosis, nuclear shadows of former liver cell plates and hepatocytes are seen. The necroses may be demarcated by a leukocyte reaction on the sides facing liver parenchyma. In very rare instances, infarctoid necroses resembling Rattone-Zahn infarct are detectable, probably caused by obstruction of larger portal venous branches by the invasive metastasis. Apart from frank ischemic necrosis, apoptosis of hepatocytes, necroptosis, and other ischemic cellular changes (including the so-called cloudy swelling; "trübe Schwellung" or "tropfige Entmischung" in German; Schilling 1894; Albrecht 1903; Findlay 1927) are encountered. Similar to ballooning, cloudy swelling is caused by an energy supply disorder (Shibayama et al. 1991), including deranged phosphorylation steps (Fonnesu and Severi 1954), and is thought to mainly involve defective functions of cellular membranes and mitochondrial membranes in toxic stress and hypoxia (Abdelhalim and Jarrar 2011). The membrane changes are associated with macromolecular crowing which contributes to hepatocyte swelling (Del Monte 2005).

Perifocal Atrophy

Atrophy of liver parenchyma surrounding tumors including metastases is a well-known phenomenon (Figs. 1, 2, and 3). It is, however, more commonly found in expanding tumors with low growth than in markedly invasive and rapidly growing tumors, because the latter destroy the tissue before it can undergo visible atrophy. Perifocal atrophy seen at gross examination is the form of a rim-like area surrounding the tumor, characterized by a pale color and a crowding of terminal veins. In fresh non-fixed specimens, the atrophic zone may exhibit a slightly higher consistency in comparison with normal liver substance. On cut surfaces of formalin-fixed specimens, the atrophic zone may display as a sunken area clearly contrasting with the usually bulging tumor. Histologically, liver lobules in the atrophic zone are undersized and elliptically deformed, the longer axis of the ellipse being oriented more or less parallel to the peripheral contour of the pushing tumor. Liver cell plates are thinned, associated with sinusoidal dilatation. Increased lipofuscin deposition in hepatocytes is usually not observed.

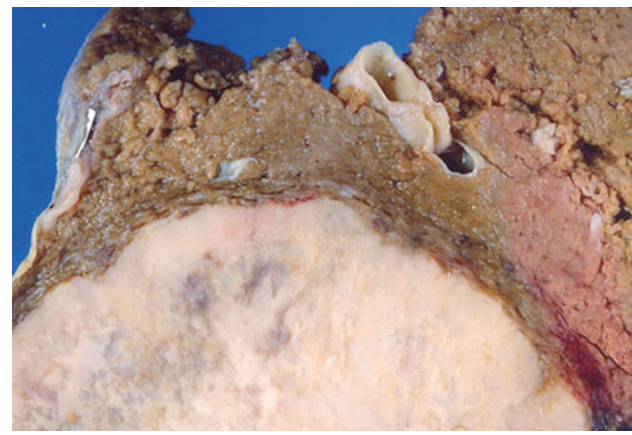

Fig. 1 Hepatic metastasis with perifocal atrophy of the liver substance

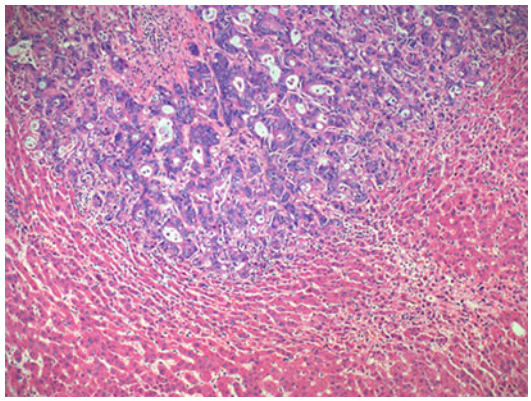

Fig. 2 Hepatic colorectal carcinoma metastasis with perifocal atrophy of liver parenchyma (hematoxylin and eosin stain)

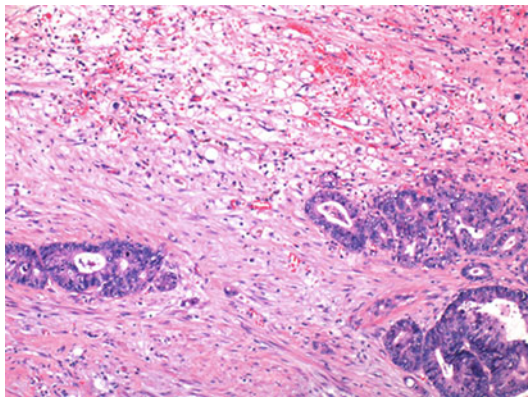

Fig. 3 Liver metastasis of colorectal carcinoma. Peritumoral hepatocytes exhibit dissociation, atrophy, and ballooning (hematoxylin and eosin stain)

Perifocal Alterations of Bile Ducts

Hepatic tumors, including metastases, are known to induce complex alterations of intermediate and small bile ducts and ductules in parenchyma surrounding the tumors and in adjacent portal tracts. The changes include bile duct compression and obliteration, acute cholangitis and cholangiohepatitis, secondary sclerosing cholangitis, bile duct erosion and fistulas, induction of biliary leaks, and ductular proliferations. Ductular proliferations with or without associated fibrosis may be marked and can involve both tissues directly surrounding the metastases and/or adjacent portal tracts. CK7- and CK19-positive ductules or ductular cells may be integrated in the growing, invasive metastases. Apart from cholangiocytes of the ductules, hepatocytes located to perimetastatic parenchyma may also show CK7 positivity. The pathogenic pathways leading to ductular proliferations in association with hepatic metastases are not fully known, but biliary obstruction caused by tumor has been implicated.

Perifocal Hepatic Stellate Cell Activation, Stroma Induction, and Fibrosis

Metastatic tumor can induce activation of perifocal hepatic stellate cells (HSCs), with differentiation into alpha-SMA-positive myofibroblasts. This alteration may be associated with circumscribed capillarization of the sinusoids, with formation of a basement membrane in the Disse space between the sinusoidal endothelium and the hepatocytes plates, visualized as a type IV collagen- and laminin-positive membrane.

Interactions between metastatic tumor cells and HSCs play a role in the generation of tumor stroma required for further growth and invasion of metastases. In a nude mouse model, it was found that intrasplenically injected human CRC cells migrated into the spaces of Disse and underwent proliferation, in close associated with hepatocytes and HSCs. In this model, HSCs were accumulated at 14 days after injection around the tumor mass and started to express alpha-SMA. Conditioned medium of activated HSCs contained PDGF-AB, hepatocyte growth factor, and TGF-beta, augmenting proliferation and migration of the CRC cells (Shimizu et al. 2000). Myofibroblasts as the differentiated offspring of hepatic stellate cells affect the biological behavior of cancer cells. It is, e.g., known that human hepatic myofibroblasts increase the invasiveness of HCC cells, mediated by motogenic hepatocyte growth factor secreted by the myofibroblasts (Neaud et al. 1997). Tumor cells themselves produce factors that induce hepatocyte growth factor in

fibroblasts of stroma (Nakamura et al. 1997). The activation process of fibrogenic cells is also thought to be involved in the development of perimetastatic fibrosis and formation of myofibroblast-containing tumor pseudocapsules, which are however seen only in the minority of metastatic nodules and which are usually less pronounced than those of primary liver tumors.

Perifocal Sinusoidal Changes

Liver tissue surrounding metastatic nodules reveals a variety of alterations of the microvascular system and in particular of sinusoids. The latter show collapse or obliteration, dilatations (focal segmental, diffuse, saccular), peliosis-like changes, and microthrombangiopathy. Peliosis-like changes may be difficult to distinguish from hemorrhages in perimetastatic liver tissue. Microthrombi in perifocal sinusoids, both hyaline and granular, may be caused by the procoagulative effects of some tumors.

Perifocal Obliterative Changes of Veins

Hepatic metastases may be associated with thrombosis and fibrous obliteration of small- to medium-sized portal vein branches ("perifocal portal phlebopathy"). Around metastases, sublobular and terminal veins/venules can rarely develop endophlebitis followed by fibrous obliteration, resulting in a complex of alterations resembling veno-occlusive disease/VOD. Classical VOD can develop following chemotherapy, but is then not restricted to perimetastatic liver tissue.

Tumor Cell Scattering and Perifocal Invasion

In the liver tissue surrounding metastases, scattering of tumor cells as an early step in the invasion cascade can be noted. It is seen as single tumor cells or tumor cell clusters in small vessels, in particular sinusoids. It is likely that these cells form the origin of satellite nodules developing in the vicinity of larger metastatic nodules. The current concept in fact is that the process of hepatic invasion by carcinoma cells originates in the sinusoids, where intrasinusoidal cells (Kupffer cells/macrophages), perisinusoidal cells (HSCs/myofibroblasts), and hepatocytes interact with metastasizing cells, through the expression of numerous cell adhesion molecules (CAMs) (Paschos et al. 2009). The differential and dynamic expression of CAMs in this distinct microenvironment of early invasion and spread is crucial for cancer cell homing mechanisms. The scattered intravascular tumor cells may be associated with microthrombi.

Some of the scattered cells are situated within hepatic lymph vessels, but these cells are less easily recognizable owing to the difficulty of identifying lymph vessels. Podoplanin immunostaining should be used to detect lymph vessels, mainly in portal tracts adjacent to metastatic nodules, and to test whether cancer cells are really located in the lumen of podoplanin-positive vascular profiles. Starting from the periphery of an established hepatic metastasis, extravascular invasion of tumor into the perimetastatic parenchyma can occur. Cohesive carcinoma cells grow into adjacent liver cell plates, replace and eventually destroy the hepatocyte population of the plates, and apparently employ the plate matrix as a scaffold. In a nude mouse model of metastasizing human CRC cells, injected tumor cells adhered to the endothelial layer of terminal portal venules and periportal sinusoids, followed by deep invasion of hepatocyte plates. The tumor cells were linked with each other or with adjacent hepatocytes by desmosomes, these desmosomes being maintained during mitosis. When invading tumor cells were exposed to bile canaliculi, they generated microvilli on the surface. After adhesion of tumor cells to endothelial cells, the latter retract rapidly and cancer cells bind to hepatocytes. In carcinoma cell-hepatocyte cocultures, CRC cells formed long cytoplasmic protrusions toward hepatocytes in their close vicinity and these protrusions attached to microvilli of hepatocytes. Then, adhering membrane areas were formed by both

cell types, and a distinct set of integrin subunits was expressed in carcinoma cells (Mook et al. 2008). In a rat model, occlusion of sinusoids by metastasizing CRC tumor cells was not sufficient to establish stable tumor cell arrest, suggesting that adhesion molecules and homing receptors play an important role (Gassmann et al. 2009).

Immune and Other Defense Reactions Around Liver Metastases

The parenchymal liver zone surrounding metastases harbors distinct sets of cells that are involved in antitumor defense, including Kupffer cells, various classes of lymphocytes, plasma cells, dendritic cells, and granulocytes, in particular eosinophils (Phillips 1989; Roh et al. 1990; Zhang et al. 1993; Van der Bij et al. 2005; Gulubova et al. 2008; Paschos et al. 2010). More details on the morphology and function of these cell systems around metastases are treated in a separate paragraph.

Metastasis-Related Pseudocirrhosis and Related Alterations of the Liver

Introduction

A variety of structural and contour changes can develop in patients with metastases to the liver, mainly after chemotherapy of metastasizing breast cancer, characterized by fine, diffusely nodularity that resembles liver cirrhosis and the development of non-cirrhotic portal hypertension. This spectrum of alterations is called pseudocirrhosis (synonyms: metastatic carcinomatous liver cirrhosis, diffuse desmoplastic metastatic cancer of the liver; Amtrup 1971). Pseudocirrhosis in metastatic liver disease is almost exclusively seen in treated carcinoma of the breast (Amtrup 1971; Sonnenblick et al. 2011), but is also observed in metastatic liver disease in the absence of breast cancer chemotherapy. It has also been found in occult breast cancer. Relatively few other cancers have been found to cause pseudocirrhosis including medullary thyroid cancer (Harry et al. 2012), esophageal cancer (Kobashigawa et al. 2010), carcinoma of the pancreas (Kang et al. 2008), and colorectal carcinoma (Theophilidou et al. 2012). In metastasizing breast cancer, pseudocirrhosis has been found subsequent to treatment with various agents, including Adriamycin, cyclophosphamide, cisplatin, 5-fluorouracil, vinblastine, vincristine, ifosfamide, navelbine, paclitaxel, and tamoxifen.

Epidemiology

Depending on the imaging criteria used, metastasis-associated pseudocirrhosis is a relatively frequent change of the liver. Hepatic capsular retraction as an indicator of pseudocirrhosis was observed in 29/58 patients with hepatic breast cancer metastases (50 %; Fennessy et al. 2004). Among 91 women with breast cancer metastatic to the liver who received chemotherapy, hepatic contour abnormalities were seen in 75 %, and portal hypertension was detected in 6 out of 16 patients with diffuse nodularity (Qayyum et al. 2007).

Clinical Features

The marked remodeling of liver substance and the vascular system of the liver often causes portal hypertension based due to blood shunting through abnormal vascular communications between liver and tumor nodules and angiogenesis (Viguier et al. 2006; Sass et al. 2007). Non-cirrhotic portal hypertension in pseudocirrhosis is associated with splenomegaly and ascites (Viguier et al. 2006). In one study, ascites was noted in 52 % and splenomegaly in 27 % of the patients (Young et al. 1994). Less commonly, hepatic encephalopathy and/or variceal bleeding has been found (Qayyum et al. 2007). In the case of massive metastasis and advanced remodeling of the liver parenchyma by multiple metastatic nodules, liver failure can ensue (Sonnenblick et al. 2011). Liver failure has also been observed in massive diffuse liver metastasis of occult breast carcinoma

(Morrison and Pennington 1984). Pseudocirrhosis due to metastasizing pancreatic cancer was found to be reversible with early recognition and management (Kang et al. 2008).

Pathology

Macroscopically, livers with pseudocirrhosis are either of normal weight or may have lost substance. The contour is irregular, and the organ has a nodular aspect both from the capsular surface and on cut surfaces, but the consistency is not increased to the degree found in cirrhosis. The condition sometimes resembles macronodular cirrhosis (Wallace et al. 2003), with large regenerative nodules embedded in a fibrous tissue background. Histologically the vascular relationships are preserved, in contrast to true cirrhosis. Specifically, true cirrhotic nodules are consistently lacking. The fibrosis is often associated with capsular retraction causing a lobular deformation, which is sometimes massive and will be further discussed in a subsequent paragraph. In some cases, mainly those with incomplete treatment response, preserved carcinoma nodules are closely intermingled with regenerating liver parenchyma. The fibrous tissue reaction in the liver may blend into preserved stromal areas of the carcinoma, resulting in a very complex picture of hepatic remodeling. In cases with remaining cancer, carcinoma cells may grow within sinusoids or abnormal vascular communications, also within stroma-containing septa.

Differential Diagnosis

The main differential diagnosis is liver cirrhosis, characterized by cirrhotic nodules (pseudoacini) and deranged vascular relationships, both lacking in pseudocirrhosis.

Pathogenic Pathways

Pathogenically it is assumed that chemotherapy induces inflammatory changes directed against damaged or necrotic cancer cells followed by a fibrogenic response that, together with desmoplasia of the tumor, leads to fibrous remodeling of the liver. Alternatively, nodular regenerative hyperplasia (NRH) as a well-known reaction to chemotherapy has been proposed to contribute to the pathogenesis of pseudocirrhosis (Key et al. 1987; Rosen et al. 1991; Young et al. 1994). Definite NRH was seen in 3 out of 22 patients with breast cancer-induced pseudocirrhosis (Young et al. 1994). It is assumed that the sometimes large nodules of NRH compress parenchyma and the sinusoidal network, followed by atrophy. A vascular factor promoting NRH is suggested by the observation that marked pseudocirrhosis was observed in patients who had received either intra-arterial infusions of chemotherapeutic agents or hepatic arterial embolizations, causing parenchymal damage and/or bile duct injury (Shirkhoda and Baird 1994).

Hepar Lobatum Carcinomatosum

Introduction

Hepar lobatum carcinomatosum (HLC) is a very rare acquired structural alteration of the liver characterized by the secondary development of deep fissures and retractions of the liver surface causing coarse lobulations of the liver substance. There are multiple cancer-bearing scar-like alterations and compensatory nodular hyperplastic changes of the spared parenchyma. The picture closely resembles that seen in end-stage tertiary syphilis of the liver (Honma 1987). HLC may represent an uncommon, excessive variant of metastasis-associated pseudocirrhosis ("forme majeure").

Epidemiology

HLC has predominantly been observed in patients with metastasizing breast cancer after chemotherapy, i.e., in the same context as pseudocirrhosis (Chin et al. 1987; Honma 1987; Graber et al. 2010). In fact, there seems to be a continuum from capsular retraction seen in breast cancer-

induced pseudocirrhosis, with incipient lobulation, to the fully developed HLC. Among 22 breast cancer patients showing retraction of the capsular surface of the liver causing a lobular margin, marked retraction with coarse lobule formation developed over 1–3 months on serial CT images (Young et al. 1994). In part of the cases, HLC may result from a general shrinkage process of the tumor and fibrosed liver, because HLC has been seen after complete chemotherapeutic regression of hepatic metastases (Chin et al. 1987). Apart from treated breast cancer, HLC has rarely been noted in other cancers metastasizing to the liver, including colorectal carcinoma (Teke et al. 2011).

Pathology

At gross examination, the liver may be underweight or looking shrunken and shows a coarsely lobulated contour associated with multiple capsular indentations, crevices, and fissures, from which scar-like fibrous septa extend deeply into the parenchyma. These septa divide the liver substance into several macronodules of variable size, whereby a predominant centrifugal distribution of the lesional areas is seen. Many of the septa abut on the centers of regressed tumor nodules (Gravel et al. 1996) and extend to the roots of fissures or crevices. The portal venous system does usually not contain tumor, but old organized thrombi or signs of phlebosclerosis may be noted.

Histologically, the macronodular areas causing the coarse lobulation of the liver consist of hepatic parenchyma with signs of regeneration (liver cell plates exceeding three cells in width) and deformation of liver lobules. However, lobules and vascular relationships are preserved in the nodules and nodes, and cirrhotic nodules are consistently lacking. Partially or completely necrotic tumor tissue is found interspersed between parenchymal nodules and scar-like septa. A macrophage reaction, foam cells, iron pigment deposition, and a lymphocytic infiltrate may be present in close association with regressed tumor tissue. The septa themselves consist of two components. First, part of the septa show collagenous fibrous tissue of variable fibroblastic/myofibroblastic cellularity. This component of septa results from tissue collapse associated with a fibrogenic response. Second, scar-like septa may contain stroma from infiltrating carcinoma, and in these stromal areas, regrowth of carcinoma and tumor-induced angiogenesis can take place.

Pathogenesis

The pathogenesis of HLC seems to be related to chemotherapy-induced regression of tumor nodules, followed by tissue collapse, inflammation, fibrosis, coalescence of fibrotic areas with remaining tumor stroma, and eventual regrowth of tumor in the stromal areas making part of scars. HLC is often associated with multifocal carcinomatous obstruction of portal venous branches and the hepatic venous tract (Honma 1987). These changes will cause ischemic injury to parenchyma and result in infarctoid changes. Part of the fibrous retractions may in fact be postnecrotic scars.

Chemotherapy-Associated Steatosis and Steatohepatitis (CASH) in Patients with Liver Metastases

Introduction

Chemotherapy of liver metastases, in particular of colorectal carcinoma, has proved to be an efficient therapy. It can reduce the size of metastases that are unresectable rendering them resectable (downstaging) and decreases the postoperative recurrence rates in patients with initially resectable tumors. However, chemotherapy of hepatic metastasis bears the risk of hepatotoxicity.

Selected references: Fong and Bentrem 2006; Abdalla and Vauthey 2008; Tannapfel and Reinacher-Schick 2008; Choti 2009; Chun et al. 2009; Cleary et al. 2009; Aloia and Fahy 2010; Baumgaertner et al. 2010; Tannapfel et al. 2011; Pilgrim et al. 2012.

An emerging chemotherapy-associated hepatotoxic entity is hepatic steatosis/steatohepatitis. Nonalcoholic fatty liver disease (NAFLD) may develop after therapy with 5-fluorouracil (Norum

1995; Sorensen et al. 1995) or chemotherapy of breast cancers (Shirkhoda and Baird 1994), while nonalcoholic steatohepatitis (NASH; chemotherapy-associated steatohepatitis, CASH), a serious complication of NAFLD, is known to occur after irinotecan treatment, specifically in obese patients (Fernandez et al. 2005; Pawlik et al. 2007; Morris-Stiff et al. 2008; Benoist and Nordlinger 2009; Khan et al. 2009). BMI correlates with the frequency of hepatic steatosis after chemotherapy (Kampfenkel et al. 2011; Makowiec et al. 2011).

5-FU-induced steatosis can be diagnosed by the use of CT imaging (Peppercorn et al. 1998; Miyake et al. 2005). Irinotecan-induced CASH affects hepatic functional reserve and increases both morbidity and mortality after hepatectomy for metastasis (Callery 2005; Fernandez et al. 2005; Fong and Bentrem 2005; Zorzi et al. 2007; Sotiropoulos et al. 2009; Pessaux et al. 2010; Kneuertz et al. 2011; Vigano et al. 2012). Steatohepatitis as such, but not simple steatosis, increases morbidity after liver resection. In a series of 248 patients having received preoperative chemotherapy (fluorouracil [FU] alone, irinotecan plus FU, and oxaliplatin plus FU), 36 patients (8.9 %) had NAFLD, and 22 (5.4 %) had NASH. In this study, irinotecan was significantly associated with CASH compared with no chemotherapy, and patients with CASH had an increased 90-day mortality compared with patients who did not have steatohepatitis (Vauthey et al. 2006; comment: Gentilucci et al. 2006). In patients treated with irinotecan alone, steatosis >30 % was found in 27.3 % of patients (Pawlik et al. 2007). Among 146 patients who had post-chemotherapy liver resection for CRC metastases, 32 patients developed NAFLD (steatosis > or = 30 %) and 15 had CASH. In multivariate analysis, a BMI >27 was the only risk factor for steatosis or NASH (Brouquet et al. 2009). A high prevalence of steatosis was also detected in combination chemotherapies. Of 54 patients having neoadjuvant chemotherapy with FOLFOX-4 (folinic acid/5-FU/oxaliplatin), 68 % showed steatosis of the liver surrounding the metastases even in the absence of obesity (Aloysius et al. 2007). However, the main hepatic lesion induced by preoperative 5-FU/oxaliplatin chemotherapy in patients with colorectal liver metastases was vascular and not steatosis in an analysis investigating 92 randomly selected patients, of whom 75 had received preoperative chemotherapy (Aloia et al. 2006). Steatosis and steatohepatitis as complications of preoperative chemotherapy were not detected in other studies (Kandutsch et al. 2008; Ryan et al. 2010). In the study of Ryan and coworkers (2010), moderate to severe fatty injury was uncommon among 334 patients with CRC hepatic metastases, CASH being detectable in only eight cases/2.4 %, 7 of whom did not receive chemotherapy. The prosteatotic effects of 5-FU and irinotecan were reproduced in C57BL/6 mouse model, but steatosis had no adverse effect on liver regeneration after partial hepatectomy (Rickenbacher et al. 2011). In the same mouse strain, oxaliplatin was found to induce CASH (Keizman et al. 2010).

Pathology

Steatosis and CASH are histologically not different from the respective alterations occurring in other settings. As in alcoholic steatohepatitis and NASH, liver tissue in CASH can show hepatocyte ballooning, liver cell apoptosis, and eventually Mallory-Denk bodies. Quantification of steatosis in NAFLD and NASH associated with chemotherapy may be supported by modern digital techniques and imaging methods. In the assessment of steatosis in chemotherapy-treated patients with CRC hepatic metastases, classical histopathology was less reliable than digital quantification of steatosis (DQS), and proton MR spectroscopy ([1] H MRS) showed very similar steatosis levels and high reliability compared with DQS. [1] H MRS was able to predict steatohepatitis with 100 % sensitivity and 89 % specificity (Urdzik et al. 2012).

Differential Diagnosis

Steatosis occurring in chemotherapy of liver metastases is usually a diffuse alteration, but it may also present as a lesion with focal predominance. In such situation, focal steatosis/

steatohepatitis may radiologically mimic metastasis (Yates and Streight 1986; Choi and Kim 2011).

Portal Venous Gas Following Metastasis Chemotherapy

Introduction

Patients with synchronous colorectal liver metastases are at risk for septic complications following chemotherapy. Necrotic metastasis tissue can be superinfected by various bacterial taxa, including gas-forming germs. The latter infection can result in gas accumulation in the necrotic tumor tissue itself and/or the transit of gas into the portal venous system. Gas in metastatic liver lesions is as such not an uncommon finding.

Not all situations of gas within metastases are caused by gas-forming bacteria. Apart from gas produced by complicating anaerobic bacterial infection, external air may be entrapped in the lesions during a surgical procedure. Furthermore, a hepatic and partially necrotic metastasis can be superimposed with a pyogenic infection, resulting in a pyogenic abscess with an air-fluid level rather than central gas accumulations. In the absence of bacterial infections causing gas formation, gas accumulation is typically restricted to the metastatic lesions, while in the former situation, gas accumulation is often also seen outside the metastatic lesion (review: Bozkurt et al. 2012). Pneumatosis cystoides intestinalis and portal venous gas have also been observed secondary to CRC chemotherapy (Clemente et al. 2010), neoadjuvant radiochemotherapy (Duchon et al. 2011), and targeted molecular cancer therapies (Lee et al. 2012).

Pathology

In the case of gas-producing bacterial infections of hepatic metastasis, the tumors usually show extensive necrosis and/or suppuration, the necrotic tissue crackling upon palpation and eventually showing a foamy cut surface, with gas bubbles of various sizes, some of them collapsing following incision. Gas bubbles may also be seen in the parenchyma surrounding the lesion, but usually not in more remote parts of the liver, this phenomenon being important in the differential diagnosis of diffuse clostridial gangrene of the liver. Conversely, hepatic abscesses with an air-fluid level are more difficult to diagnose macroscopically, because the central air-containing space immediately undergoes collapse following incision. Free gas in large portal venous branches are mostly recognizable during necropsy and less easily in resection specimens. Following incision of the portal vein during dissection, gas bubbles and blood mixed with gas foam may be found, a foul smell being characteristic for gas-forming infections in contrast to the non-smelling artificially entering ambient air. The only histological landmark of gas in the portal venous system is the presence of "empty holes" within the properly fixed blood masses seen in the venous lumina.

Pathogenic Pathways

In patients with colorectal carcinoma with or without hepatic metastatic disease, gas can enter the portal venous system through various mechanisms. A rapid response to chemotherapy may cause extensive necrosis of the primary tumor, followed by necrotizing enterocolitis with dissecting gas in the bowel wall, gas then entering the portal circulation. Gastrointestinal perforation following cancer therapy can also result in portal venous gas (Ortega et al. 2009). Following chemotherapy of metastasis, almost complete or complete necrosis of the tumor can subsequently turn into a liver abscess, which may then fistulize into the portal vein system (Zalinski et al. 2009). The process may progress into fulminant abdominal gas gangrene, with gas-containing liver metastases and involvement of locoregional lymph nodes (lymphonodal gas gangrene) and portal vein branches (Bozkurt et al. 2012).

References

Abdalla EK, Vauthey JN (2008) Chemotherapy prior to hepatic resection for colorectal liver metastases: helpful until harmful? Dig Surg 25:421–429

Abdelhalim MA, Jarrar BM (2011) Gold nanoparticles induced cloudy swelling to hydropic degeneration, cytoplasmic hyaline vacuolation, polymorphism, binucleation, karyopyknosis, karyolysis, karyorrhexis and necrosis in the liver. Lipids Health Dis 10:166

Albrecht E (1903) Ueber trübe Schwellung und Fettdegeneration. Verh Deut Pathol Ges XIV:63

Aloia TA, Fahy BN (2010) Chemotherapy-associated hepatotoxicity: how concerned should we be? Expert Rev Anticancer Ther 10:521–527

Aloia T, Sebagh M, Plasse M, Karam V, Lévi F, Giacchetti S, Azoulay D, Bismuth H, Castaing D, Adam R (2006) Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 24:4983–4990

Aloysius MM, Zaitoun AM, Beckingham IJ, Neal KR, Aithal GP, Bessell EM, Lobo DN (2007) The pathological response to neoadjuvant chemotherapy with FOLFOX-4 for colorectal liver metastases: a comparative study. Virchows Arch 451:943–948

Amtrup F (1971) Metastatic carcinomatous liver cirrhosis. Dan Med Bull 18:46–48

Baumgaertner I, Ratziu V, Vaillant JC, Hannoun L, Poynard T, André T (2010) Hepatotoxicity of metastatic colorectal cancer chemotherapy: systematic review (in French). Bull Cancer 97:559–569

Bax HR, Mansens BJ, Schalm L (1956) Atrophy of the liver after occlusion of the bile ducts or portal vein and compensatory hypertrophy of the unoccluded portion and its clinical importance. Gastroenterology 31:131–155

Benoist S, Nordlinger B (2009) The role of preoperative chemotherapy in patients with resectable colorectal liver metastases. Ann Surg Oncol 16:2385–2390

Bozkurt M, Okutur K, Aydin K, Namal E, Oztürk A, Balci C, Demir G (2012) Fulminant abdominal gas gangrene in metastatic colon cancer. Oncol Lett 3:469–471

Brouquet A, Benoist S, Julie C, Penna C, Beauchet A, Rougier P, Nordlinger B (2009) Risk factors for chemotherapy-associated liver injuries: a multivariate analysis of a group of 146 patients with colorectal metastases. Surgery 145:362–371

Callery MP (2005) Chemotherapy-related steatohepatitis: proceed with caution. Gastroenterology 129:2114–2115

Chin NW, Chapman I, Jimenez FA (1987) Complete chemotherapeutic regression of hepatic metastases with resultant hepar lobatum. Am J Gastroenterol 82:149–151

Choi JS, Kim MJ (2011) Education and imaging: hepatobiliary and pancreatic: focal steatohepatitis mimicking a metastasis. J Gastroenterol Hepatol 26:415

Choti MA (2009) Chemotherapy-associated hepatotoxicity: do we need to be concerned? Ann Surg Oncol 16:2391–2394

Chun YS, Laurent A, Maru D, Vauthey JN (2009) Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. Lancet Oncol 10:278–286

Cleary JM, Tanabe KT, Lauwers GY, Zhu AX (2009) Hepatic toxicities associated with the use of preoperative systemic therapy in patients with metastatic colorectal adenocarcinoma to the liver. Oncologist 14:1095–1105

Clemente G, Chiarla C, Giovannini I, De Rose AM, Astone A, Barone C, Nuzzo G (2010) Gas in portal circulation and pneumatosis cystoides intestinalis during chemotherapy for advanced rectal cancer. Curr Med Res Opin 26:707–711

Del Monte U (2005) Swelling of hepatocytes injured by oxidative stress suggests pathological changes related to macromolecular crowding. Med Hypotheses 64:818–825

Duchon R, Pindak D, Sucha R, Bernadic M, Dolnik J, Pechan J (2011) Portomesenteric vein gas and pneumatosis intestinalis – a rare complication after neoadjuvant radiochemotherapy in oesophageal cancer. Bratisl Lek Listy 112:463–465

Fennessy FM, Mortele KJ, Kluckert T, Gogate A, Ondategui-Parra S, Ros P, Silverman SG (2004) Hepatic capsular retraction in metastatic carcinoma of the breast occurring with increase or decrease in size of subjacent metastasis. AJR Am J Roentgenol 182:651–655

Fernandez FG, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM (2005) Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg 200:845–853

Findlay GM (1927) Mitochondria and cell injury. J R Microsc Soc 47:258–265

Fong Y, Bentrem DJ (2005) CASH (chemotherapy-associated steatohepatitis) costs. Ann Surg 243:8–9

Fong Y, Bentrem DJ (2006) CASH (chemotherapy-associated steatohepatitis) costs. Ann Surg 243:8–9

Fonnesu A, Severi C (1954) Phosphorylation mechanisms in cloudy swelling. Experientia 10:28–30

Gassmann P, Hemping-Boyenkerk A, Mees ST, Haier J (2009) Metastatic tumor cell arrest in the liver-lumen occlusion and specific adhesion are not exclusive. Int J Colorectal Dis 24:851–858

Gentilucci UV, Santini D, Vincenzi B, Fiori E, Picardi A, Tonini G (2006) Chemotherapy-induced steatohepatitis in colorectal cancer patients. J Clin Oncol 24:5467

Graber I, Dumortier J, Poncet G, Queneau PE, Mathevet P, Scoazec JY (2010) Hepar lobatum carcinomatosum revealing an occult metastatic lobular carcinoma of the breast. Ann Diagn Pathol 14:438–442

Gravel DH, Bégin LR, Brisson ML, Lamoureux E (1996) Metastatic carcinoma resulting in hepar lobatum. Am J Clin Pathol 105:621–627

Gulubova M, Manolova I, Cirovski G, Sivrev D (2008) Recruitment of dendritic cells in human liver with metastases. Clin Exp Metastasis 25:777–785

Harry BL, Smith ML, Burton JR, Dasari A, Eckhardt SG, Diamond JR (2012) Medullary thyroid cancer and pseudocirrhosis: case report and literature review. Curr Oncol 19:e36–e41

Hemingway DM, Cooke TG, Grime SJ, Nott DM, Jenkins SA (1991) Changes in hepatic haemodynamics and hepatic perfusion index during the growth and development of hypovascular HSN sarcoma in rats. Br J Surg 78:326–330

Hemingway DM, Cooke TG, Grime SJ, Jenkins SA (1993) Changes in liver blood flow associated with the growth of hepatic LV10 and MC28 sarcomas in rats. Br J Surg 80:495–498

Honma K (1987) Hepar lobatum carcinomatosum due to metastatic breast carcinoma. Virchows Arch A Pathol Anat Histopathol 410:465–469

Huguier M, Maheshwari S, Toussaint P, Houry S, Mauban S, Mensch B (1993) Hepatic flow scintigraphy in evaluation of hepatic metastases in patients with gastrointestinal malignancy. Arch Surg 128:1057–1059

Ishizawa T, Yamamoto T, Nishida K, Tsukui H, Sekikawa T (2005) Diagnostic value of measuring liver volume for detecting occult hepatic metastases from colorectal or gastric cancer. World J Surg 29:719–722

Ishizawa T, Yamamoto T, Sekikawa T (2007) The diagnostic value of measuring the liver volume in detecting occult hepatic metastases from colorectal cancer. Hepato-Gastroenterology 54:514–517

Kampfenkel T, Tischoff I, Bonhag H, Eckardt M, Schmiegel W, Tannapfel A, Reinacher-Schick A (2011) Chemotherapy-associated steatohepatitis in patients with colorectal cancer and surgery on hepatic metastases: clinical validation of a histopathological scoring system and preoperative risk assessment (in German). Z Gastroenterol 49:1707–1411

Kandutsch S, Klinger M, Hacker S, Wrba F, Gruenberger B, Gruenberger T (2008) Patterns of hepatotoxicity after chemotherapy for colorectal cancer liver metastases. Eur J Surg Oncol 34:1231–1236

Kang SP, Taddei T, Mclennan B, Lacy J (2008) Pseudocirrhosis in a pancreatic cancer patient with liver metastases: a case report of complete resolution of pseudocirrhosis with an early recognition and management. World J Gastroenterol 14:1622–1624

Kawasaki S, Makuuchi M, Matsunami H, Hashikura Y, Ikegami T, Chisuwa H, Ikeno T et al (1993) Preoperative measurement of segmental liver volume of donors for living related liver transplantation. Hepatology 18:1115–1120

Keizman D, Maimon N, Ish-Shalom M, Buchbut D, Inbar M, Klein B, Bernheim J, Goldiner I et al (2010) An animal model for chemotherapy-associated steatohepatitis and its prevention by the oral administration of fatty acid bile acid conjugate. Cancer 116:251–255

Key NS, Kelly PM, Emerson PM, Chapman RW, Allan NC, McGee JO (1987) Oesophageal varices associated with busulphan-thioguanine combination therapy for chronic myeloid leukemia. Lancet 2:1050–1052

Khan AZ, Morris-Stiff G, Makuuchi M (2009) Patterns of chemotherapy-induced hepatic injury and their implications for patients undergoing liver resection for colorectal liver metastases. J Hepato-Biliary Pancreat Surg 16:137–144

Kneuertz PJ, Maithel SK, Staley CA, Kooby DA (2011) Chemotherapy-associated liver injury: impact on surgical management of colorectal cancer liver metastases. Ann Surg Oncol 18:181–190

Kobashigawa C, Nakamoto M, Hokama A, Hirata T, Kinjo F, Fujita J (2010) Pseudocirrhosis in metastatic esophageal cancer. South Med J 103:488–489

Kopljar M, Brkljacic B, Doko M, Horzic M (2004) Nature of Doppler perfusion index changes in patients with colorectal cancer liver metastases. J Ultrasound Med 23:1295–1300

Lambotte L, Li B, Leclercq I, Sempoux C, Saliez A, Horsmans Y (2000) The compensatory hyperplasia (liver regeneration) following ligation of a portal branch is initiated before the atrophy of the deprived lobes. J Hepatol 32:940–945

Lee JY, Han HS, Lim SN, Shim YK, Choi YH, Lee OJ, Lee KH, Kim ST (2012) Pneumatosis intestinalis and portal venous gas secondary to Gefitinib therapy for lung adenocarcinoma. BMC Cancer 12:87

Leen E (1999) The detection of occult liver metastases of colorectal carcinoma. J Hepato-Biliary Pancreat Surg 6:7–15

Leen E, Goldberg JA, Robertson J, Angerson WJ, Sutherland GR, Cooke TG, McArdle CS et al (1993) Early detection of occult colorectal hepatic metastases using duplex colour Doppler sonography. Br J Surg 80:1249–1251

Leen E, Angerson WJ, Wotherspoon H, Moule B, Cook TG, McArdle CS (1995) Detection of colorectal liver metastases: comparison of laparotomy, CT, US, and Doppler perfusion index and evaluation of postoperative follow-up results. Radiology 195:113–116

Leveson SH, Wiggins PA, Giles GR, Parkin A, Robinson PJ (1985) Deranged liver blood flow patterns in the detection of liver metastases. Br J Surg 72:128–130

Lory J, Schweizer W, Blumgart LH, Zimmermann A (1994) The pathology of the atrophy/hypertrophy complex (AHC) of the liver. A light microscopic and immunohistochemical study. Histol Histopathol 9:541–554

Makowiec F, Möhrle S, Neeff H, Drognitz O, Illerhaus G, Opitz OG, Hopt UT, Zur Hausen A (2011) Chemotherapy, liver injury, and postoperative complications in colorectal liver metastases. J Gastrointest Surg 15:153–164

Miyake K, Hayakawa K, Nishino M, Morimoto T, Mukaihara S (2005) Effects of oral 5-fluorouracil drugs on hepatic fat content in patients with colon cancer. Acad Radiol 12:722–727

Mook OR, van Marle J, Jonges R, Vreeling-Sindelarova H, Frederiks WM, Van Noorden CJ (2008) Interactions between colon cancer cells and hepatocytes in rats in relation to metastasis. J Cell Mol Med 12:2052–2061

Morrison WL, Pennington CR (1984) Liver metastases from an occult breast carcinoma presenting as acute fulminant hepatic failure. Br J Clin Pract 38:273–274

Morris-Stiff G, Tan YM, Vauthey JN (2008) Hepatic complications following preoperative chemotherapy with oxaliplatin or irinotecan for hepatic colorectal metastases. Eur J Surg Oncol 34:609–614

Nakamura T, Mastusmoto K, Kiritoshi A, Tano Y, Nakamura T (1997) Induction of hepatocyte growth factor in fibroblasts by tumor-derived factors affects invasive growth of tumor cells: in vitro analysis of tumor-stromal interactions. Cancer Res 57:3305–3313

Neaud V, Faouzi S, Guirouilh J, Le Bail B, Balabaud C, Bioulac-Sage P, Rosenbaum J (1997) Human hepatic myofibroblasts increase invasiveness of hepatocellular carcinoma cells: evidence for a role of hepatocyte growth factor. Hepatology 26:1458–1466

Norum J (1995) 5-Fluorouracil/levamisole induced intrahepatic fat infiltration imitating liver metastasis. Acta Oncol 34:971–972

Nott DM, Grime SJ, Yates J, Day DW, Baxter JN, Jenkins SA, Cooke TG (1989) Changes in the hepatic perfusion index during the development of experimental hepatic tumours. Br J Surg 76:259–263

Nott DM, Grime SJ, Yates J, Baxter JN, Cooke TG, Jenkins SA (1991) Changes in hepatic haemodynamics in rats with overt liver tumour. Br J Cancer 64:1088–1092

Oktar SO, Yücel C, Demirogullari T, Uner A, Benekli M, Erbas G, Özdemir H (2006) Doppler sonographic evaluation of hemodynamic changes in colorectal liver metastases relative to liver size. J Ultrasound Med 25:575–582

Ortega J, Hayes JM, Antonia S (2009) Hepatic portal venous gas in a patient with metastatic non-small cell lung cancer on bevacizumab therapy: a case report and review of the literature. Cancer Chemother Pharmacol 65:187–190

Paschos KA, Canovas D, Bird NC (2009) The role of cell adhesion molecules in the progression of colorectal cancer and the development of liver metastasis. Cell Signal 21:665–674

Paschos KA, Majeed AW, Bird NC (2010) Role of Kupffer cells in the outgrowth of colorectal cancer liver metastases. Hepatol Res 40:83–94

Pawlik TM, Olino K, Gleisner AL, Torbenson M, Schulick R, Chori MA (2007) Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 11:860–868

Peppercorn PD, Reznek RH, Wilson P, Slevin ML, Gupta RK (1998) Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. Br J Cancer 77:2008–2011

Pessaux P, Chenard MP, Bachellier P, Jaeck D (2010) Consequences of chemotherapy on resection of colorectal liver metastases. J Vasc Surg 147:e193–e201

Phillips NC (1989) Kupffer cells and liver metastasis. Optimization and limitation of activation of tumoricidal activity. Cancer Metastasis Rev 8:231–252

Pilgrim CH, Thomson BN, Banting S, Phillips WA, Michael M (2012) The developing clinical problem of chemotherapy-induced hepatic injury. ANZ J Surg 82:23–29

Qayyum A, Lee GK, Yeh BM, Allen JN, Venook AP, Coakley FV (2007) Frequency of hepatic contour abnormalities and signs of portal hypertension at CT in patients receiving chemotherapy for breast cancer metastatic to the liver. Clin Imaging 31:6–10

Rickenbacher A, DeOliveira ML, Tian Y, Jang JH, Riener MO, Graf R, Moritz W, Clavien PA (2011) Arguments against toxic effects of chemotherapy on liver injury and regeneration in an experimental model of partial hepatectomy. Liver Int 31:313–321

Roh MS, Wang L, Oyedeji C, LeRoux ME, Curley SA, Pollock RE, Klostergaard J (1990) Human Kupffer cells are cytotoxic against human colon adenocarcinoma. Surgery 108:400–404

Rosen AA, Iseri O, Fishhbein G, Knodell RG (1991) Nodular regenerative hyperplasia: a cause of ascites and hepatomegaly after chemotherapy for leukemia. Am J Gastroenterol 86:86–88

Rous P, Larimore LD (1920) Relation of the portal blood to liver maintenance: a demonstration of liver atrophy conditional on compensation. J Exp Med 31:609–632

Rozga J, Jeppsson B, Bengmark S (1986) Hepatotrophic effect of portal blood during hepatic arterial recirculation. Eur Surg Res 18:302–311

Ryan P, Nanji S, Pollett A, Moore M, Moulton CA, Gallinger S, Guindi M (2010) Chemotherapy-induced liver injury in metastatic colorectal cancer: semiquantative histologic analysis of 334 resected liver specimens shows that vascular injury but not steatohepatitis is associated with preoperative chemotherapy. Am J Surg Pathol 34:784–791

Sass DA, Clark K, Grzybicki D, Rabinovitz M, Shaw-Stiffel TA (2007) Diffuse desmoplastic metastatic breast cancer simulating cirrhosis with severe portal hypertension: a case of "pseudocirrhosis". Dig Dis Sci 52:749–752

Schilling C (1894) Das Verhalten der Altmann'schen Granula bei der trüben Schwellung. Virchows Arch CXXXV:470

Shibayama Y, Asaka S, Nishijima A (1991) Mechanism of liver injury following ischemia. Exp Mol Pathol 55:251–260

Shimizu S, Yamada N, Sawada T, Ikeda K, Kawada N, Seki S, Kaneda K, Hirakawa K (2000) In vivo and in vitro interactions between human colon carcinoma cells and hepatic stellate cells. Jpn J Cancer Res 91:1285–1295

Shirkhoda and Baird (1994) http://www.ncbi.nlm.nih.gov/pubmed/8161901

Shitara K, Nakamura K, Kasai M, Munakata M, Muto O, Kazaana K, Sakata Y (2008) A case of advanced breast cancer associated with development of liver atrophy with progressive liver failure during treatment. Gan To Kagaku Ryoho 35:983–986

Sonnenblick A, Appelbaum L, Peretz T (2011) Liver failure on the background of pseudocirrhosis in patients with liver metastasis from breast cancer, who responded to therapy. Onkologie 34:199–201

Sorensen P, Edal A, Madsen E (1995) Reversible hepatic steatosis in patients treated with interferon alfa-2a and 5-fluorouracil. Cancer 75:2592–2596

Sotiropoulos GC, Saner FH, Molmenti EP, Radtke A, Timm S, Baba HA, Paul A, Lang H (2009) Unexpected liver failure after right hemihepatectomy for colorectal liver metastasis due to chemotherapy-associated steatohepatitis: time for routine preoperative liver biopsy? Int J Colorectal Dis 24:241

Takayasu K, Muramatsu Y, Shima Y, Moriyama N, Yamada T, Makuuchi M (1986) Hepatic lobar atrophy following obstruction of the ipsilateral portal vein from hilar cholangiocarcinoma. Radiology 160:389–393

Tannapfel A, Reinacher-Schick A (2008) Chemotherapy associated hepatotoxicity in the treatment of advanced colorectal cancer (CRC) (in German). Z Gastroenterol 46:435–440

Tannapfel A, Reinacher-Schick A, Flott-Rahmel B (2011) Steatohepatitis after chemotherapy for colorectal liver metastases (CASH) (in German). Pathologe 32:330–335

Teke Z, Nessar G, Kiremitci S, Aksoy E, Elbir OH (2011) Hepar lobatum carcinomatosum associated with metastatic rectal carcinoma: an unusual cause of liver dysmorphy. Med Pric Pract 20:93–96

Theophilidou E, Waraich N, Raza T, Agarwal PK (2012) Liver metastases, a rare cause of portal hypertension and stoma bleeding. Brief review of literature. Int J Surg Case Rep 3:173–176

Ueda J, Chijiiwa K, Nakano K (2004) Cyclin expression in the atrophying and proliferating lobes of the liver after portal vein branch ligation and hepatectomy in rats. J Surg Res 120:89–96

Urdzik J, Bjerner T, Wanders A, Weis J, Duraj F, Haglund U, Norén A (2012) The value of pre-operative magnetic resonance spectroscopy in the assessment of steatohepatitis in patients with colorectal liver metastasis. J Hepatol 56:640–646

Van der Bij GJ, Oosterling SJ, Meijer S, Beelen RH, van Egmond M (2005) Therapeutic potential of Kupffer cells in prevention of liver metastases outgrowth. Immunobiology 210:259–265

Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C et al (2006) Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 24:2065–2072

Vigano L, Ravarino N, Ferrero A, Motta M, Torchio B, Caoussotti L (2012) Prospective evaluation of accuracy of liver biopsy findings in the identification of chemotherapy-associated liver injuries. Arch Surg 147:1085–1091

Viguier et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/16885877

Wallace G, Conologue TL, Murphy TJ (2003) Metastatic breast carcinoma mimicking macronodular cirrhosis. Mayo Clin Proc 78:1431

Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, James OF (1989) The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology 9:297–301

Yates CK, Streight RA (1986) Focal fatty infiltration of the liver simulating metastatic disease. Radiology 159:83–84

Young ST, Paulson EK, Washington K, Gulliver DJ, Vredenburgh JJ, Baker ME (1994) CT of the liver in patients with metastatic breast carcinoma treated by chemotherapy: findings simulating cirrhosis. AJR Am J Roentgenol 163:1385–1388

Zalinski S, Scatton O, Jacqmin S, Tacher V, Brézault C, Soubrane O (2009) Portal venous gas following chemotherapy for colorectal cancer liver metastasis. Eur J Surg Oncol 35:557–560

Zhang W, Arii S, Sasaoki T, Adachi Y, Funaki N, Higashitsuji H, Fujita S, Furutani M et al (1993) The role of Kupffer cells in the surveillance of tumor growth in the liver. J Surg Res 55:140–146

Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK (2007) Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 94:274–286

Pathogenic Features of Liver Metastasis: Growth, Regrowth, Stem Cells, and Circulating Tumor Cells

112

Contents

Abstract

Growth and regrowth of hepatic cancer metastases depend on distinct cell kinetic features of the various tumors involved, on tumor stem cell characteristics, and on the biology of circulating tumor cells. Hepatic metastases display distinct growth patterns, the most common being expanding, replacement, desmoplastic (stroma-rich), and frankly invasive patterns. There is a relationship between these patterns and proliferative, invasive, and angiogenic features of tumors involved. The progressive growth of hepatic metastases not only depends on the proliferative and invasive capacities of the tumor cells but also on the biology of the so-called metastatic niche in the liver, involving complex interactions between tumor cells and cells of the microenvironment, including stromal cells, cancer-associated fibroblasts, stellate cells, and several cell types of the immune system. Metastatic cancer cells can, in turn, modulate the function of cells in the hepatic metastatic niche. Metastases in the liver can release tumor-initiating cells, in part with stem cell features, that enter circulation and give rise to further intrahepatic and extrahepatic metastases. These circulating cells and their remote metastatic offspring are capable to re-home to the liver and to induce new metastatic foci in programmed pre-metastatic niches.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_112

Growth of Liver Metastases

Growth Patterns

Hepatic metastases show various growth patterns, the most common being expanding ("pushing"), desmoplastic, replacement, or frankly invasive patterns. There is a relation between these growth patterns and angiogenesis, in that CRC liver metastases with a replacement pattern were non-angiogenic, while those with a using pattern were most angiogenic, the latter situation associated with poor survival (Van den Eynden et al. 2012). In contrast to other malignant neoplasms, biologically more aggressive CRCs do not seem to have a higher proliferative capacity (Anjomshoaa et al. 2008). There is evidence that hepatic CRC metastases are sometimes slow growing (Agui et al. 2002; Kitabatake et al. 2002; Seong et al. 2004). Based on a study of 73 primary CRCs and 27 CRC hepatic metastases, it was found that, compared with the primary tumors, metastases had a significantly lower expression of multigene proliferation signature and a lower Ki-67 proliferative activity, whereas the M30 apoptotic index was similar in primaries and metastases. It was suggested in this study that a low relative proliferation appears to be a biological feature of CRCs with a high metastatic potential (Anjomshoaa et al. 2009). The CDX-2 gene product is a transcription factor that is involved in the proliferation and differentiation of intestinal epithelial cells and is a marker for gastrointestinal adenocarcinomas (Werling et al. 2003; Li and Folpe 2004), in particular also for colorectal adenocarcinoma (Barbareschi et al. 2003). In metastatic gastrointestinal adenocarcinoma, CDX-2 demonstrated nuclear staining in 86 % of the cases (Saad et al. 2004).

Effects of Tumor Size at Metastasis

There is a relation between the size of a primary malignancy and the probability of metastatic spread. Although large tumors contain much more cells than small ones, there is generally a tendency that large lesions produce less metastases than smaller ones (Martinez et al. 1956; Kimmel and Flehinger 1991; Xu and Prorok 1998), probably due to a lesser content in metastasis-producing tumor cells. On the other hand, a critical tumor size must be achieved in order to produce micrometastases (Liotta et al. 1977; Withers and Lee 2006).

Growth of Colorectal Carcinoma Metastases Following Hepatic Resection (Growth in the Regenerating Liver) and Regrowth After Chemotherapy

Liver resection for hepatic metastasis is sometimes followed by a significant surge of tumor recurrence. There is evidence that the regenerating liver exerts stimulatory effects on tumor growth (reviews: Christophi et al. 2008; Krause et al. 2013). In colorectal carcinoma metastases, macrophage inflammatory protein-2 contributes to liver resection-induced acceleration of growth (Kollmar et al. 2006). Liver resection for hepatic metastases is sometimes followed by a significant surgery of tumor recurrence. There is evidence that the regenerating liver exerts stimulatory effects on metastatic tumor growth (review: Christophi et al. 2008).

Tumor Stem Cells, Tumor-Initiating Cells, and Circulating Tumor Cells

Introduction

The evolution of cancer is now considered to be driven by cells with stem-like features. These cells are commonly termed tumor stem cells (TSCs) or cancer stem cells (CSCs), but most studies now utilize the term tumor-initiating cells (TICs; synonym: cancer-initiating cells, CICs; Zhou et al. 2009; Garvalov and Acker 2011). Some authors used the term tumor-propagating cells. TICs form a fraction of the circulating cells identified as circulating tumor cells (CTCs), whereby CTCs form a heterogeneous population of cells consisting of TICs and other stem cells, and post-

stem cell-differentiated tumor cells that have escaped from the primary tumor. It is important to note that the concept of a "cancer stem cell" or now TIC does not imply that these cells are derived from normal, i.e., non-transformed stem cells. Cancers can originate from transformed stem cells characterizing the tissue of origin, but such cells must not necessarily be the cells that are later identified as TICs, although both cell types share the important features of low proliferation activity, unlimited self-renewal, and longevity. It is currently unknown whether part of the original transformed stem cells become TICs ("sneaking-through TICs") or whether all TICs evolve in a post-initiation phase of cancer. According to a current model, TICs emerge through mutations either from stem cells, multipotent progenitor cells, or even primed progenitor cells (Zhou et al. 2009). TICs were identified as cells capable of initiating and sustaining growth of tumors in immunodeficient mice (Lapidot et al. 1994; Singh et al. 2004) and are characterized by apparently unlimited self-renewal, stress resistance (in particular resistance to chemotherapy), special homing features, and the capability for the establishment of distant metastases. TICs/CICs represent a subset of rare, hierarchically organized cancer cells that cannot only accomplish tumor onset but also progressive accumulation of mutations followed by tumor cell maintenance and metastatic spread. The identification of TICs/CICs uncovered that cancers show a previously unknown hierarchical structure, involving several sets of neoplastic cells acting in an ordered interaction and interdependence pattern. The concept of TICs has rendered to original and too simplicistic view of tumors releasing more or less differentiated cancer cells into an "invasion and metastasis cascade" obsolete. There is evidence that in order to assume a self-renewal state, cells to become TICs acquire expression of a stem cell gene map that possesses an embryonal stem cell-like transcriptional program (Wong et al. 2008). TICs can stay dormant for certain and sometimes long time periods (so-called dormant cancer cells), to be activated and mobilized in a later phase (McCubrey et al. 2011, 2012). The mechanisms that shift dormant TICs to an active state characterized by "moving" the cancer process ahead are critical for cancer progression but are not yet well known. An important role in the control of TICs and their activation state is the immune system of the host. A competent immune system of the host may recognize TICs and destroy them as soon as they shift from the dormant state (Maccalli et al. 2014).

Tumor-Initiating Cells (TICs): Important Mediators of Cancer Metastasis and Progression

Progression of cancer and in particular metastatic spread involve distinct populations of TICs. Part of TICs can, in the setting of their circulation in the body, home to distinct sites, probably the pre-metastatic niches discussed above. According to this concept, TICs coerce host tissue to cancer spread (Malanchi 2013). TICs engaged in metastatic spread are sometimes termed metastatic cancer stem cells or tumor-propagating cells/TPCs (Lau et al. 2014). Metastatic TICs derived from CRC primary tumors express a stem cell marker present in CRC stem cells, Musashi-1, regulated by Notch3 signaling (Pasto et al. 2014). After having settled at the future metastasis sites, TICs can undergo epithelial-to-mesenchymal transition (EMT) induced by the transcription factor Snail1. EMT is an important step for TICs to initiate metastatic growth (Sun and Qiu 2013), and EMT itself enriches for TICs to again release these cells into circulation. Therefore, TICs and EMT form a potent engine that employs TICs to undergo EMT, to produce TICs via a complex to-and-fro mechanism, and to prime TICs to develop metastatic tumor cells. EMT involving TICs results in two populations of cells, i.e., TICs with epithelial features (E-TICs) and those with mesenchymal features (M-TICs). It was shown that E-TICs derived from carcinoma can elicit metastasis, while M-TIC cells were nonmetastatic. These two cell populations cooperated, in that M-TICs enhanced the invasiveness of M-TICs and promoted the escape of E-TICs from primary implantation sites to accelerate their metastatic colonization (Celia-Terrassa et al. 2012). EMT

involving TICs and their differentiated offspring induces complex rearrangements of the cytoskeleton, including upregulation of vimentin in epithelial lineage cells, detyrosination of alpha-tubulin, and the production of cell projections important for niche attachment, such as microtentacles (Charpentier and Martin 2013).

Role of Stem Cells in the Development of Metastases

Migrating cancer stem cells (MCSCs) are now considered to play a significant role in the pathogenesis of metastases (Dalerba and Clarke 2007; Li et al. 2007). In the case of CRC, MCSCs can be isolated from primary tumors. Among these cells, a CD110+ and CDCP11 subpopulation was shown to mediate organ-specific metastasis, specifically to the liver and lung (Gao et al. 2013). Primary CRCs and their metastases contain a subset of colony-forming CD133+ cells, where a higher percentage of these cells was detected in metastases in comparison with primary tumors. CD133+ in CRCs are considered to be cancer stem cells (Puglisi et al. 2009).

Circulating Tumors Cells

The liver is a major metastasis-susceptible site (review: Vidal-Vanaclocha 2008). CRC reach the liver via the venous splanchnic circulation and chiefly through the portal vein. There is a relation between venous invasion in the primary tumor and the emergence of hepatic metastases. The average number of foci of venous invasion by CRC with metachronous liver metastasis did not differ significantly from that with synchronous ones, and invasion into extramural large veins appeared to be associated with liver metastases (Mori et al. 2009). In rat experiments, in vivo microscopy has revealed that the numbers of intracardially injected cells arrested in the hepatic sinusoidal circulation did not depend on the sinusoidal diameter, whereas more lumen-occluding arrested cells were seen in a rat strain with a narrower sinusoidal bed. Cell arrest was partly impaired by inhibition of beta-1 or beta-4 integrins (Gassmann et al. 2009).

Apart from cancer stem cells and TICs that can circulate in blood and lymph, more differentiated tumor cells also circulate in blood and lymph and are the "classical" cells that mediate spread and metastasis (circulating tumor cells, CTCs; review: Mavroudis 2010). CTCs have also been termed the "leukemic phase" of solid cancers (Mocellin et al. 2006). As outlined above, settling and growth of CTCs are more complex than previously thought and depend on distinct tissues niches that are also programmed and prepared by cells other than established tumor cells, including TICs. The presence and the levels of CTCs are strongly associated with tumor disease relapse and metastatic rates. CTCs therefore form a non-invasive window to screen disease progression and outcome for various cancer types (Paterlini-Bréchot and Benali 2007; Cohen et al. 2009; Allen and El-deiry 2010). CTCs express organ-specific markers (Paterlini-Bréchot 2011) and share with their parent tumor genomic and microRNA profiles (Smirnov et al. 2005; Sieuwerts et al. 2011), allowing the determination of their origin and possible fate. Long after their discovery is, however, still not clarified as to how many of CTCs are capable to survive, proliferate, and give rise to metastases. Viable CTCs have invasive features (Friedlander et al. 2014). The fate of CTCs is strongly influenced by their interaction with endothelium and other cells of pre-metastatic niches, immune responses of the host, mechanisms of epithelial-mesenchymal transition (EMT), factors inducing apoptosis, and their intrinsic survival engine modulated by genomic instability. Similar to cancer stem cells, more mature CTCs are subject to EMT, a factor that exerts a strong influence on the development of metastasis (Kallergi et al. 2011; Lecharpentier et al. 2011; Gorges et al. 2012). Circulating breast cancer cells simultaneously expressed epithelial and mesenchymal markers, but cells with mesenchymal features were highly enriched in CTCs, these mesenchymal cells occurring as both single cells and multicellular clusters expressing known EMT regulators (Yu et al. 2013). Subsets of CTCs are in an apoptotic status (apoptotic circulating

tumor cells, apoCTCs). In breast cancer patients, apoCTCs could be detected irrespective of the clinical status, although these cells are more frequent in patients with early disease compared with those having metastatic disease (Kallergi et al. 2013). apoCTCs correlated with the total number of CTCs in patients with small-cell lung cancer (Hou et al. 2012). In patients with CRC, apoCTCs were associated with liver metastasis (Allen et al. 2014).

Circulating Tumor Cell Clusters, Circulating Tumor Fragments, and Tumor Emboli

Part of CTCs can form multicellular aggregates in circulation, termed circulating tumor cell clusters (CTC clusters; Molnar et al. 2001). CTC clusters may form through intercellular adhesion, adhesion mediated by platelets, or EMT (see above), or represent original tiny tissue fragments released from the primary tumors. That CTC clusters may escape as such from primary tumors is supported by the observation that CTC clusters found in the blood of prostate cancer patients can contain circulating fibroblast-like cells. The presence of circulating fibroblast-like cells correlated with a more aggressive course of tumors (Jones et al. 2013). The exact biology of CTC clusters is, however, not yet known in more detail.

In addition to CTC clusters, larger multicellular tumor cell aggregates associated with activated and aggregated platelets and clotted plasma occur, the tumor microthrombi and tumor microemboli. Tumor microemboli can circulate in blood and correlate with the total CTC number (Hou et al. 2012). Clusters and tumor microemboli can be arrested in microvessels and eventually obturate these vascular channels. Even larger circulating structures are circulating tumor tissue fragments containing stromal cells and vascular cells and resulting from invasion of entire tumor tissue parts into the vascular bed (Kats-Ugurlu et al. 2009). Tumor embolism mediated by such fragments is a source of metastatic disease (Hart 2009) but is less well documented than that occurring with CTCs and TICs. A distinct mode of metastasis is the invasion-independent entry or intravasation of tumor cell nests through gaps in sinusoid-like vascular channels of certain tumors, resulting in the release of small nests enveloped by endothelial cells (Sugino et al. 2004).

References

Agui et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/12168867

Allen JE, El-deiry WS (2010) Circulating tumor cells and colorectal cancer. Curr Colorectal Cancer Rep 6:212–220

Allen JE, Saroya BS, Kunkel M, Dicker DT, Das A, Peters KL, Joudeh J, Zhu J et al (2014) Apoptotic circulating tumor cells (CTCs) in the peripheral blood of metastatic colorectal cancer patients are associated with liver metastasis but not CTCs. Oncotarget 5:1753–1760

Anjomshoaa A, Lin YH, Black MA, McCall JL, Humar B, Song S, Fukuzawa R, Yoon HS et al (2008) Reduced expression of a gene proliferation signature is associated with enhanced malignancy in colon cancer. Br J Cancer 99:966–973

Anjomshoaa A, Nasri S, Humar B, McCall JL, Chatterjee A, Yoon HS, McNoe L, Black MA, Reeve AE (2009) Slow proliferation as biological feature of colorectal cancer metastasis. Br J Cancer 101:822–828

Barbareschi M, Murer B, Colby TV, Chilosi M, Macri E, Loda M, Doglioni C (2003) CDX-2 homeobox gene expression is a reliable marker of colorectal adenocarcinoma metastases to the lungs. Am J Surg Pathol 27:141–149

Celia-Terrassa T, Meca-Cortes O, Mateo F, de Paz AM, Rubic N, Arnal-Estapé A, Ell BJ et al (2012) Epithelial-mesenchymal transition can suppress major attributes of human epithelial tumor-initiating cells. J Clin Invest 122:1849–1868

Charpentier M, Martin S (2013) Interplay of stem cell characteristics, EMT, and microtentacles in circulating breast tumor cells. Cancers (Basel) 5:1545–1565

Christophi C, Harun N, Fifis T (2008) Liver regeneration and tumor stimulation – a review of cytokine and angiogenic factors. J Gastrointest Surg 12:966–980

Cohen SJ, Punt CJA, Iannotti N, Saidman BH, Sabbath KD, Gabrail NY, Picus J et al (2009) Prognostic significance of circulating tumor cells in patients with metastatic colorectal cancer. Ann Oncol 20:1223–1229

Dalerba P, Clarke MF (2007) Cancer stem cells and tumor metastasis: first steps into uncharted territory. Cell Stem Cell 1:241–242

Friedlander TW, Ngo VT, Dong H, Premasekharan G, Weinberg V, Doty S, Zhao Q et al (2014) Detection and characterization of invasive circulating tumor cells derived for men with metastatic castration-resistant prostate cancer. Int J Cancer 134:2284–2293

Gao W, Chen L, Ma Z, Du Z, Zhao Z, Hu Z, Li Q (2013) Isolation and phenotypic characterization of colorectal cancer stem cells with organ-specific metastatic potential. Gastroenterology 145:636–646

Garvalov and Acker (2011) http://www.ncbi.nlm.nih.gov/pubmed/20890588

Gassmann P, Hemping-Boyenkerk A, Mees ST, Haier J (2009) Metastatic tumor cell arrest in the liver-lumen occlusion and specific adhesion are not exclusive. Int J Colorectal Dis 24:851–858

Gorges TM, Tinhofer I, Drosch M, Röse L, Zollner TM, Krahn T, von Ahsen O (2012) Circulating tumour cells escape from EpCAM-based detection due to epithelial-to-mesenchymal transition. BMC Cancer 12:178

Hart IR (2009) New evidence for tumour embolism as a mode of metastasis. J Pathol 219:275–276

Hou JM, Krebs MG, Lancashire L, Sloane R, Backen A, Swain RK, Priest LJ, Greystoke A et al (2012) Clinical significance and molecular characteristics of circulating tumor cells and circulating tumor microemboli in patients with small-cell lung cancer. J Clin Oncol 30:525–532

Jones ML, Siddiqui J, Pienta KJ, Getzenberg RH (2013) Circulating fibroblast-like in men with metastatic prostate cancer. Prostate 73:176–181

Kallergi G, Papadaki MA, Politaki E, Mavroudis D, Georgoulias V, Agelaki S (2011) Epithelial to mesenchymal transition markers expressed in circulating tumour cells of early and metastatic breast cancer patients. Breast Cancer Res 13:R59

Kallergi G, Konstantinidis G, Markomanolaki H, Papadaki MA, Mavroudis D, Stournaras C et al (2013) Apoptotic circulating tumor cells in early and metastatic breast cancer patients. Mol Cancer Ther 12:1886–1895

Kats-Ugurlu G, Roodink I, de Weijert M, Tiemessen D, Maass C, Verrijp K, van der Laak J et al (2009) Circulating tumour tissue fragments in patients with pulmonary metastasis of clear cell renal carcinoma. J Pathol 219:287–293

Kimmel M, Flehinger BJ (1991) Nonparametric estimation of the size-metastasis relationship in solid cancers. Biometrics 47:987–1004

Kitabatake et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/12027197

Kollmar O, Menger MD, Schilling MK (2006) Macrophage inflammatory protein-2 contributes to liver resection-induced acceleration of hepatic metastatic tumor growth. World J Gastroenterol 12:858–867

Krause P, Flikweert H, Monon M, Seif Amir Hosseini A, Helms G, Cantanhede G, Ghadimi BM, Koenig S (2013) Increased growth of colorectal liver metastasis following partial hepatectomy. Clin Exp Metastasis 30:681–693

Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, Minden M et al (1994) A cell initiating human acute myeloid leukemia after transplantation into SCID mice. Nature 367:645–648

Lau AN, Curtis SJ, Fillmore CM, Rowbotham SP, Mohseni M, Wagner DE, Beede AM et al (2014) Tumor-propagating cells and Yap/Taz activity contribute to lung tumor progression and metastasis. EMBO J 33:468–481

Lecharpentier A, Vielh P, Perez-Moreno P, Planchard D, Soria JC, Farace F (2011) Detection of circulating tumour cells with a hybrid (epithelial/mesenchymal) phenotype in patients with metastatic non-small cell lung cancer. Br J Cancer 105:1338–1341

Li MK, Folpe AL (2004) CDX-2, a new marker for adenocarcinoma of gastrointestinal origin. Adv Anat Pathol 11:101–105

Li F, Tiede B, Massagué J, Kang Y (2007) Beyond tumorigenesis: cancer stem cells in metastasis. Cell Res 17:3–14

Liotta LA, Delisi C, Saidel G, Kleineman J (1977) Micrometastases formation: a probabilistic model. Cancer Lett 3:203–208

Maccalli C, Volonté A, Cimminiello C, Parmiani G (2014) Immunology of cancer stem cells in solid tumours. A review. Eur J Cancer 50:649–655

Malanchi I (2013) Tumour cells coerce host tissue to cancer spread. Bonekey Rep 2:371

Martinez C, Miroff G, Bittner JJ (1956) Effect of size and/or rate of growth of a transplantable mouse adenocarcinoma on lung; metastasis production. Cancer Res 16:313–315

Mavroudis D (2010) Circulating cancer cells. Ann Oncol 21(suppl 7):vii95–vii100

McCubrey JA, Chappell WH, Abrams SL, Franklin RA, Long JM, Sattler JA, Kempf CR et al (2011) Targeting the cancer initiating cell: the Achilles' heel of cancer. Adv Enzym Regul 51:152–162

McCubrey JA, Steelman LS, Abrams SL, Misaghian N, Chappell WH, Basecke J et al (2012) Targeting the cancer initiating cell: the ultimate target for cancer therapy. Curr Pharm Des 18:1784–1795

Mocellin et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/16488189

Molnar B, Ladanyi A, Tanko L, Sreter L, Tulassay Z (2001) Circulating tumor cell clusters in the peripheral blood of colorectal cancer patients. Clin Cancer Res 7:4080–4085

Mori D, Shibaki M, Masuda M, Yamasaki F (2009) Quantitative measurement of venous invasion of colorectal cancer with metachronous liver metastasis. Histopathology 55:654–659

Pasto A, Serafin V, Pilotto G, Lago C, Bellio C, Trusolino L, Bertotti A, Hoey T, Plateroti M et al (2014). NOTCH3 signaling regulates Musashi-1 expression in metastatic colorectal cancer cells. Cancer Res 74:2106–2118

Paterlini-Bréchot P (2011) Organ-specific markers in circulating tumor cell screening: an early indicator of metastasis-capable malignancy. Future Oncol 7:849–871

Paterlini-Bréchot P, Benali NL (2007) Circulating tumor cells (CTC) detection: clinical impact and future directions. Cancer Lett 253:180–204

Puglisi MA, Sgambato A, Saulnier N, Rafanelli F, Barba M, Boninsegna A, Piscaglia AC et al (2009) Isolation and characterization of $CD133^{+}$ cell population within human primary and metastatic colon cancer. Eur Rev Med Pharm Sci 13(suppl 1):55–62

Saad RS, Essig DL, Silverman JF, Liu Y (2004) Diagnostic utility of CDX-2 expression in separating metastatic

gastrointestinal adenocarcinoma from other metastatic adenocarcinoma in fine-needle aspiration cytology using cell blocks. Cancer 102:168–173

Seong et al (2004) http://www.ncbi.nlm.nih.gov/pubmed/15118987

Sieuwerts AM, Mostert B, Bolt-de Vries J, Peeters D, de Jongh FE, Stouthard JM et al (2011) mRNA and microRNA expression profiles in circulating tumor cells and primary tumors of metastatic breast cancer patients. Clin Cancer Res 17:3600–3618

Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD et al (2004) Identification of human brain tumour initiating cells. Nature 432:396–401

Smirnov DA, Zweitzig DR, Foulk BW, Miller MC, Doyle GV, Pienta KJ, Meropol NJ et al (2005) Global gene expression profiling of circulating tumor cells. Cancer Res 65:4993–4997

Sugino T, Yamaguchi T, Ogura G, Saito A, Hashimoto T, Hoshi N, Yoshida S, Goodison S et al (2004) Morphological evidence for an invasion-independent metastasis pathway exists in multiple human cancers. BMC Med 2:9

Sun S, Qiu XS (2013) Cancer stem cells and tumor metastasis. J cancer Res Ther 9(suppl):S150–S152

Van den Eynden GG, Bird NC, Majeed AW, Van Laere S, Dirix LY, Vermeulen PB (2012) The histological growth pattern of colorectal cancer liver metastases has prognostic value. Clin Exp Metastasis 29:541–549

Vidal-Vanaclocha F (2008) The prometastatic microenvironment of the liver. Cancer Microenviron 1:113–129

Werling RW, Yaziji H, Bacchi CE, Gown AM (2003) CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. Am J Surg Pathol 27:303–310

Withers HR, Lee SP (2006) Modeling growth kinetics and probability of presenting with metastasis at detection. Biometrics 53:579–591

Wong DJ, Liu H, Ridky TW, Cassarino D, Segal E, Chang HY (2008) Module map of stem cell genes guides creation of epithelial cancer stem cells. Cell Stem Cell 2:333–344

Xu JL, Prorok PC (1998) Nonparametric estimation of solid cancer size at metastasis. Biometrics 54:859–864

Xu JL, Prorok PC (1998) Estimating a distribution function of the tumor size at metastasis. Biometrics 54:859–864

Yu M, Bardia A, Wittner BS, Stott SL, Smas ME, Ting DT, Isakoff SJ, Ciciliano JC et al (2013) Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition. Science 339:580–584

Zhou BBS, Zhang H, Damelin M, Geles KG, Grindley JC, Dirks PB (2009) Tumour-initiating cells: challenges and opportunities for anticancer drug discovery. Nat Rev Drugs Discov 8:806–823

Pathogenic Features of Liver Metastasis: Mechanisms Involving Platelets, Tumor Stroma, Epithelial-Mesenchymal Transition, and the Premetastatic Niche

113

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_113

Abstract

Homing of circulating cells to pre-metastatic niches of the liver and their subsequent growth to a metastasis requires a complex interaction between tumor cells and various normal cellular and matrix components of the future metastatic site. In the course of homing to endothelial surfaces of hepatic blood vessels and vascular invasion, tumor cells interact with platelets and induce platelet adhesion and aggregation. Tumor cell-induced thrombocyte aggregation facilitates early steps of metastasis through increased tumor cell arrest and formation of tumor cell emboli. Platelets participating in tumor cell aggregates promote cell adhesion and invasion and release growth factors for cancer cells. Following their exit from blood vessels, tumor cells engage in complex interactions with stromal cells. The stromal microenvironment profoundly influences growth and invasion of tumor cells in the metastatic site. Stromal cells interacting with tumor cells include cancer-associated fibroblasts and myofibroblasts, vascular cells, tumor-associated macrophages/TAMs, myeloid suppressor cells, and other cells of local immune responses. Cancer cells in turn constantly modulate the cellular composition of stroma, promote angiogenesis, and are subject to epithelial-mesenchymal transition.

Platelet Interactions, Platelet Aggregation, and the Formation of Tumor Metastasis

Introduction

In the course of vascular invasion and the associated endothelial cell damage, cancer cells having contact to streaming blood can induce platelet homing and thrombocyte aggregation. These thrombocyte aggregates, being in contact with the subendothelial space following endothelial cell loss, form a distinct niche for tumor cells that promotes growth and the formation of metastases. Tumor cell-induced platelet aggregation facilitates hematogenous metastatic spread by increasing the arrest of tumor cell clusters and tumor cell emboli in the microcirculation and is also involved in differential homing of platelet-tumor cell aggregates to distinct vascular beds (reviews: Honn et al. 1992; Tsuruo and Fujita 2008; Sharma et al. 2014). Generally, platelets can exert pro-metastatic effects. Platelet-tumor cell interactions are sufficient to prime tumor cells for subsequent metastasis, involving TGF-beta/Smad and NF-kB pathways via platelet-derived TGF-beta (Labelle et al. 2011). Platelets possess a complex granule proteome (Koseoglu and Flaumenhaft 2013) that contains numerous factors that can affect neoplastic cells. Through secretion of granule proteins, platelets modulate growth of tumor cells and the associated angiogenesis (Dovizio et al. 2014; Riedl et al. 2014). Thrombocyte alpha-granules of platelets also contain chemokines that can affect tumor cell behavior (Karshovska et al. 2013). In addition, platelets store laminins 411/421 and 511/521 in non-alpha- or dense-granule compartments and secrete these proteins via microvesicles (Pook et al. 2014).

Thrombocyte-Tumor Cell Interactions

It is known for long that patients with solid cancers can show elevated platelet blood counts in the absence of a paraneoplastic thrombocythemia. This thrombocytosis varies widely in its severity but may be associated with shorter patient survival (review: Buergy et al. 2012) and is associated with a higher metastatic load, e.g., in hepatocellular carcinoma. Elevated circulating thrombocytes enhance cancer cell migration and promote hematogenous metastasis in patients with lung cancer (Li et al. 2014). Neoplastic cells of solid cancers can undergo complex interactions with thrombocytes, whereby these interactions are capable to induce platelet aggregation favoring homing of cancer cells after intravascular spread (see below; Chang et al. 2009) or to affect the biological behavior of neoplastic cells, e.g., promoting their proliferation, cell-matrix adhesion, and/or invasive features. Cancer cells, also those of metastases, can internalize thrombocytes

or thrombocyte fragments (Panasci et al. 1980; Bhatia and Dey 2013), a process probably inducing complex signaling pathways mediated by platelet granule factors.

Platelets and Platelet Aggregates as Pacemakers of Metastatic Spread

In the setting of metastatic spread, thrombocytes play a pro-metastatic role involving several steps of the invasion and metastatic cascade (Karpatkin and Pearlstein 1981; Gasic 1984; Mehta 1984; Falanga et al. 2003; Borsig 2008; Erpenbeck and Schön 2010; Jain et al. 2010; Bambace and Holmes 2011; Gay and Felding-Habermann 2011). Interactions between platelets and tumor cells are important for metastatic spread and are mediated by adhesive receptors expressed by both partners of the interaction (Oleksowicz and Dutcher 1995). Thrombocytes promote the adhesion of spreading tumor cells to endothelial cell surfaces (Nierodzik et al. 1995), form aggregates that can store growth factors to be delivered to tumor cells, mediate access to the subendothelial space via collagen-induced viscous metamorphosis, slow down the streaming blood through induction of coagulation, induce a focal angiogenic response, and shield tumor cells from attack of host cells, in particular natural killer cells (Table 1; Yahalom et al. 1985; Eldor et al. 1987; Honn et al. 1992; Tsuruo and Fujita 2008; Gil-Bernabé et al. 2013; Reymond et al. 2013). Promotion of tumor angiogenesis by platelet products is an important mechanism that is not only dependent on VEGF and is the result of a combined action of several molecules that form the angiogenic payload of platelets (Battinelli et al. 2011; Sabrkhany et al. 2011; Radziwon-Balicka et al. 2012; Etulain et al. 2013). Platelet extracts induced growth, migration, and invasion in human hepatocellular carcinoma in vitro (Carr et al. 2014). Direct signaling between thrombocytes and tumor cells also induces epithelial-mesenchymal transition/EMT, an alteration that is critically involved in tumor metastasis (Labelle et al. 2011). Important steps in the process of platelet-induced tumor cell adhesion, homing, and transendothelial migration are mediated by P-selectin. P-selectin plays an important role in liver metastasis even in the absence of natural killer cell function (Coupland et al. 2012).

Table 1 Effects of platelets on malignant neoplastic cells

Induction of platelet aggregation (via Aggrus/podoplanin-CLEC-2 pathway)
Promotion of adhesion to endothelial cells
Induction of tumor cell motility and migration
Vessel wall transmigration
Stimulation of tumor cell growth
Induction of epithelial-mesenchymal transition
Signaling of platelet-tumor cell interactions (in part through platelet internalization)
Induction of angiogenesis

Tumor Cells Can Promote Platelet Aggregation and Release of Microvesicles and Exosomes

Several tumor types have been shown to produce and secrete the platelet aggregation-inducing factor Aggrus, a protein also termed podoplanin. Aggrus is secreted by various tumors, including CRC (Kato et al. 2003). Aggrus released by tumor cells interacts with a platelet receptor termed CLEC-2, and the ligand-receptor binding induced thrombocyte aggregation (Takagi et al. 2013). Aggrus-induced aggregate formation plays an important role for the changes in blood rheology required for tumor cell homing in the microvascular bed (Jurasz et al. 2004). Platelet aggregates and thrombocyte-induced local blood coagulation cause slowdown of streaming blood in microvessels, enabling tumor cells to engage with endothelia and adhere to the inner vessel wall. In fact, platelet-derived Aggrus/podoplanin was shown to promote metastasis (Kunita et al. 2007; Suzuki-Inoue 2011; Fujita and Takagi 2012; Lowe et al. 2012). One mechanism of metastasis promotion by podoplanin involves an induction of tumor cell migration (Shen et al. 2010; Kunita et al. 2011), whereby serine moieties in the intracellular tail of podoplanin regulate cell motility (Krishnan et al. 2013). In addition, contacts between platelet aggregates

induced by tumor cells permit the transfer of granule and nongranule proteins of platelets and of exosomes to adjacent endothelial cells and tumor cells. Platelet-derived microvesicles or microparticles are important participants in intercellular communication and play a role in cancer progression (Varon and Shai 2009; Aatonen et al. 2012). Activated platelets secrete granule proteins and parallel release two types of membrane microvesicles, namely, simple microvesicles by surface shedding and more complex exosomes derived from multivesicular bodies and alpha-granules (Heijnen et al. 1999). Platelet-derived microvesicles (microparticles) possess membrane domains that contain adhesion molecules and diverse receptors and contain signal substances that can stimulate angiogenesis (Varon and Shai 2009) and tissue regeneration (Varon et al. 2012).

Platelet Mimicry of Cancer Cells

Certain cancer cell types acquire a geno-phenotype the closely resembles that of thrombocytes/platelets. Such tumor cells express megakaryocyte genes, including adhesion receptors alpha IIb beta 3, thrombin receptor and PECAM/Cd31, and/or platelet-type 12-LOX. These acquired expression patterns enable the cancer cells to activate the coagulation cascade. It is currently considered that these platelet-like features of cancer cells affect their capability to spread and metastasize (Timar et al. 2005).

The Metastatic Stromal and Vascular Environment of the Liver

Introduction

The liver is known to provide a tissual microenvironment that favors the establishment of metastases of various malignancies, but specifically carcinomas. Part of the tumor cells transported into the liver via the vascular system resists antitumor defense mechanisms and can adhere as viable cells to endothelium of blood vessels, chiefly endothelia of hepatic sinusoids. Here, they start to respond to growth factors produced and secreted by neighboring hepatocytes, perisinusoidal cells, and vascular cells. In the first step, this results in avascular micrometastases in periportal areas of liver lobules. The next step is characterized by stroma formation, a prerequisite for angiogenesis, because newly formed blood vessels depend on being embedded within a mesenchymal matrix with its specific extracellular matrix (ECM) proteins. Fibroblasts from portal tracts become cancer-associated fibroblasts (CAFs) as an important component of stroma, and stromal myofibroblasts are recruited from activated hepatic stellate cells and portal tracts. Together, these cells generate a "private" tumor microenvironment that has a pro-metastatic effect (Vidal-Vanaclocha 2008, 2011).

The Pro-metastatic Effect of Stromal Interactions

The stromal microenvironment profoundly influences many steps of cancer progression, including the ability of cancer cells to metastasize (the 'stromal factor'; Wernicke et al. 2011). Within stroma, influences of this distinct and complex microenvironment are mediated by bidirectional interactions between epithelial tumor cells and the neighboring stromal cells, these interactions referring to adhesion, migration, proteolysis, angiogenesis, homing strategies, epithelial-mesenchymal transition, immune escape mechanisms, and survival (reviews: Bogenrieder and Herlyn 2003; Orimo and Weinberg 2006).

What are the pathways leading to stromal formation in metastases? Early in the outgrowth phase of murine colorectal carcinoma micrometastases, hepatic Kupffer cells and fibroblasts are recruited and start to invade the metastatic nodules. These transitional metastases are connected by protrusions of fibroblast-rich tissues co-localized with collagen-rich matrix and CD31-positive cells. The latter step is characterized by the generation of a pro-angiogenic niche and the switch of a transitional metastasis to an established, vascularized metastasis (Higashi et al. 2002). Stromal components, including

fibroblasts, myofibroblasts, endothelial and other vascular cells, mesenchymal stem cells, granulocytes, and cells of the immune system, interact with carcinoma cells to promote growth, invasion, and metastasis (reviews: Li et al. 2007; Aharinejad et al. 2009; Finger and Giaccia 2010; Pietras and Ostman 2010; Udagawa and Wood 2010). Stroma-derived growth factors and cytokines produced by stromal-resident lymphoid cells and macrophages activate autocrine and paracrine oncogenic signaling pathways, which in turn promote proliferation or spread of epithelial cancer cells. Stromal cell can produce matrix metalloproteinases (MMPs) which are known to operate within the invasion cascade. However, whereas MMP-9 is upregulated in primary CRCs, it is expressed mainly by macrophages in the invasion zone of hepatic metastases and there generally less expressed than in primary tumors (Illemann et al. 2006). Both mesenchymal cells and macrophages are active in the procoagulative environment of tumors, coagulation factors such as fibrinogen and thrombin affecting tumor cell growth and differentiation. Components of stromal cells may also promote the locomotor and migratory activity of carcinoma cells. The intermediate filament protein, vimentin, a constituent of mesenchymal cells, is an AKT1 target mediating motility and invasion (Zhu et al. 2011a). Factors regulating epithelial-mesenchymal transition (EMT) affect the metastatic process. The developmental transcription factor, Six1, induces EMT in dependence of TGF-beta signaling. Six1 is a critical mediator of the switch in TGF-beta signaling from tumor-suppressive to tumor-promotional activity, the TGF-beta type I receptor being the target of Six1 and a critical effector of Six1-induced TGF-beta signaling and EMT (Micalizzi et al. 2010).

Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) seem to regulate many aspects of tumorigenesis and cancer spread (reviews: Orimo and Weinberg 2006; Cirri and Chiarugi 2012). Stromal fibroblasts in CRC metastases originate from resident fibroblasts and create an inflammatory microenvironment characterized by TNF-alpha-mediated upregulation of IL-8 via nuclear factor kappaB (Mueller et al. 2007). Colorectal cancer-associated fibroblasts represent a genetically distinct population of stromal cells (Mrazek et al. 2014). Activated CAFs residing in tumor stroma are a source of growth factors for carcinoma cells, factors promoting angiogenesis and lymphangiogenesis, cytokines mediating tumor immunity, and factors involved in epithelial-mesenchymal transition (Räsänen and Vaheri 2010). Primary CAFs from colorectal liver metastases express several inflammatory, tumor-enhancing factors, including IL6 and monocyte-chemoattractant protein (MCP)-1. Both factors are induced by TNF-alpha, which also upregulates ICAM-1. A similar reaction pattern was found for liver-resident, non-tumor-associated fibroblasts (Mueller et al. 2010), which may therefore constitute a cell type playing a role in the generation of a pro-metastatic stroma. The stroma of carcinomas exerts an influence on angiogenesis and antiangiogenesis and by this affects the development of metastases. The growth of metastases is dependent on the growth of blood vessels into the tumor mass. The extracellular matrix of the stroma and its specific proteins, including basement membrane laminin, fibronectin, and tenascin, is a source of both pro-angiogenic factor activation and endogenous angiogenesis inhibitors, such as endostatin (review: Nyberg et al. 2008). Multicellular spheroids of murine colorectal cancer cells mimic micrometastases and their growth pattern activates the pro-angiogenic phenotype of the carcinoma cells (Valcarcel et al. 2008). Antiangiogenic effects and hypoxia-dependent signaling pathways are counteracted by semaphorin 3A produced by cancer cells in metastases (Maione et al. 2012).

Lymphangiogenesis in Hepatic Metastasis: Does It Play a Role?

For the metastatic spread of cancer cells, generation of a lymph vessel network (lymphangiogenesis) plays a crucial role. A dynamic lymph vessel system has an active role

in metastatic dissemination, and metastasizing tumor cells are capable to synthesize and secrete factors that promote lymphangiogenesis. In a mouse model of breast cancer, tumor cells produced the homeodomain-containing transcription factor SIX1, which induces lymphangiogenesis and metastasis via upregulation of VEGF-C (Wang et al. 2012a).

Interactions of Metastatic Carcinoma Cells with Hepatic Stellate Cells (HSC)

As stroma plays a significant role in homing and growth of carcinoma metastasis, cells potentially producing stroma in the liver are of specific interest. Apart from fibroblasts and myofibroblasts in portal tracts and vessel walls, the only cell type of the liver capable of producing extracellular matrix is the hepatic stellate cell (HSC). We have shown that HSCs can interact and form tight adhesions with hepatocytes during the early regeneration phase of the normal rat liver (Mabuchi et al. 2004a, b), suggesting that HSCs can form a epithelial-mesenchymal interactome in the liver. By the use of a nude mouse model, it was demonstrated that intrasplenically injected colon carcinoma cells migrated into the space of Disse and underwent proliferation, in close association with hepatocytes and HSCs. At 14 days, HSCs were accumulated around the emerging small tumor mass and showed transformation into alpha-SMA-positive myofibroblasts. The growing colon carcinoma cells produced PDGF-AB, enhancing proliferation and migration of HSCs, while HSCs produced PDGF-AB, HGF, and TGF-beta and could augment proliferation of carcinoma cells, suggesting complex bidirectional interactions between metastasizing carcinoma cells and activated HSCs (Shimizu et al. 2000). This interaction may result in an "amplification loop" to further metastatic growth in the liver (review: Kang et al. 2011). The transition from HSCs to myofibroblasts in pro-metastatic hepatic stroma is regulated by the fibrillar collagen receptor discoidin domain receptor 2 (DDR2). Downregulation of DDR2 promotes myofibroblast transition and predisposes hepatic tissue to colorectal carcinoma metastasis in mice (Badiola et al. 2011).

Stroma-Associated Inflammatory and Immunologic Effector Cells Control Metastasis Formation: TANs, TAMs, Myeloid-Derived Suppressor Cells (MDSCs), Myeloid Angiogenic Cells (MACs), and Lymphocytes

The stroma of many tumors contains leukocytic infiltrates/inflammatory cells which are instrumental in immune reactions that either inhibit tumors or produce factors that stimulate growth and metastasis. An inflammatory microenvironment induced by myeloid cells is key alteration for promoting tumor invasion and metastatic spread (Grugan et al. 2012; Capece et al. 2013; Smith and Kang 2013; Keskinov and Shurin 2014). A specific role is attributed to tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), and myeloid-derived suppressor cells/MDSCs. The presence of TAMs and TANs has been linked to poor clinical outcomes in solid tumors, as these cells can switch from a tumor-suppressing to a tumor-promoting phenotype (review: Alphonso and Alahari 2009). TANs can play a role in tumor cell detachment (tumor cell individualization as a prerequisite for motility and migration), have a pro-angiogenic activity, and secrete MMP-9 playing a role in tumor invasion (Benson et al. 2012).

TAMs form a major component of tumor stroma, consist of several functionally different subsets, and originate from distinct circulating monocytes that home to the tumor microenvironment (Movahedi et al. 2010). But accumulation of TAMs in stroma is also accomplished by in situ proliferations of TAMs in tumors (Tymoszuk et al. 2014). Local accumulation of monocytes differentiating into TAMs is promoted by the TGF-beta superfamily member, Nodal, which is an embryonal morphogen that is upregulated in numerous tumors (Wang et al. 2014a). The interaction of stromal cells with TMAs results in differential macrophage programming in the tumor microenvironment (Ruffell et al. 2012). TAMs are

major players in the tumor microenvironment and exert a strong influence on progression and metastatic spread of cancer (Hao et al. 2012; Galdiero et al. 2013). In the course of tumor progression, TAMs and their hematogenous precursors, the monocytes, are actively recruited into tumor tissue, and particularly its stroma. In their interaction with tumor and stromal cells, TAMs can undergo several functional changes. Whereas classical M1 macrophages are engaged in inflammatory responses, antitumor immunity, and antigen clearance, alternative M2 macrophages are active in anti-inflammatory reactions, wound healing, stroma formation, and tumor progression (reviews: Chanmee et al. 2014; Van Overmeire et al. 2014). TAMs most closely resemble polarized class two macrophages/M2 and are cells that markedly modulate the composition and function of tumor microenvironments (Mantovani et al. 2002). TAMs have upregulated expression of CD206 and CD163 markers of alternative activation but do not have increased expression of classically activated macrophage markers, CCR2 and CCR5. Monocytes as precursors of M2 TAMs are recruited to metastatic sites by distinct homing mechanisms. A major ligand facilitating monocyte accumulation is P-selectin glycoprotein ligand-1/PSGL-1 (Hoos et al. 2014).

The interaction of TAMs with tumor cells is mediated by adhesion molecules and glycosaminoglycans. Hyaluronan synthase HAS2 stimulates the interaction between cancer cells and TAMs and promotes tumor progression and metastasis (Okuda et al. 2012). The interactome of TAMs, lymphoid cells (mainly T cells), and myeloid-derived suppressor cells is active in pro-angiogenic reactions and the preparation of homing vascular surface facilitating tumor cell and platelet adherence and cancer cell transmigration (reviews: Labelle and Hynes 2012; Smith and Kang 2013).

M2 TAMs exhibit a distinct functional profile characterized by the (stimulated) production of a wide array of factors. Activated TAMs can produce a host of cytokines that can modulate tumor cell behavior and affect stromal cell production function. TAMs strongly express interleukin receptor-associated kinase (IRAK)-M, a serine/threonine kinase that is a potent negative regulator of Toll-like receptor signaling (Kobayashi et al. 2002). In tumors, IRAK-M is induced by TGF-beta1 from stromal cells and regulates tumor growth (Standiford et al. 2011). TGF-beta1 plays a central role in myeloid cell regulation (Pang et al. 2013). TAMS can secrete matrix metalloproteinases (MMPs), including MMP-9, whereby differentiation-related expression of MMP depends on an interaction of the ECM component, laminin.-5, with monocytes (Kamoshida et al. 2014). TAMs produce oncostatin M and VEGF (Benson et al. 2012). Tumor-infiltrating monocytes/macrophages produce and secrete the innate immune response mediator, human beta-defensin-3, a factor that inhibits cancer cell migration through downregulation of metastasis-associated 1 family, member 2 (MTA2 9 expression (Uraki et al. 2014)). TAMs are involved in the progression of HCC, as M2 type macrophages can modulate the composition of HCC stroma and modify immunosuppressive functions of immune effector cells (Shirabe et al. 2012). In HCCs, TAMs can promote a stem cell-like property of cancer cells through TGF-beta1-induced epithelial-mesenchymal transition (Fan et al. 2014), a mechanism that favors a metastatic phenotype. TAMs can also induce the expression of the macrophage receptor, CD163, in malignant cells, thus resulting in some sort of "induced receptor sistership". CD163 expression in a subpopulation of cancer cells may constitute a phenotypic shift associated with epithelial-mesenchymal transition, increased invasion, and a metastatic phenotype (Maniecki et al. 2012). Part of TMAs are involved in the promotion of angiogenesis (Owen and Mohamadzadeh 2013). These specialized cells are termed myeloid angiogenic cells (MACs). MACs are in part Tie-2 expressing monocytes and significantly contribute to angiogenesis and vascular repair through paracrine mechanisms as they lack the capacity to differentiate into endothelial cells (Chambers et al. 2013). Experimental selective ablation of TAMs with MAC features suppresses angiogenesis and metastatic tumor spread (Lin et al. 2013). MAC-induced angiogenesis depends on the expression of the myeloid cell receptor LRP1/

CD91 that regulates monocyte recruitment and VEGF availability in tumors (Staudt et al. 2013).

In addition to TAN and TAM, myeloid-derived suppressor cells (MDSCs) play a significant role in the function of tumor microenvironment, tumor progression, and metastasis (reviews: Schmid and Varner 2012; Brandau et al. 2013; Diaz-Montero et al. 2014). MDSCs are bone marrow-derived myeloid cells that are recruited to tumors, where they are transformed to potent immunosuppressive cells, which, however, also have functions other than blunting immune reactions (reviews: Mantovani et al. 2009; Dumitru et al. 2012; Schmid et al. 2012; Diaz-Montero et al. 2014). Apart from their role in mediating immunosuppression via strong inhibition of antitumor immune reactions produced by T cells, MDSCs strongly stimulate tumorigenesis, tumor growth, and metastasis (Umansky and Sevko 2013), probably by modulating the cellular composition of stroma in pro-metastatic niches. MDSCs enhance the stemness of cancer cells by inducing micron-101 and suppressing the corepressor CtBP2 (C-terminal binding protein-2, a protein that directly targets stem cell core genes resulting in cancer cell stemness and an invasive and metastatic phenotype (Cui et al. 2013)). The function of MDSCs is regulated by microRNA-155. Downregulation of the miR enhances the recruitment and function of MDSCs in the tumor microenvironment (Wang et al. 2014d).

Interactions of Carcinoma Cells with Hepatic Blood Vessel Cells and Vascularization of Metastases

Successful growth of metastases requires the generation of a stroma harboring blood vessels produced in the setting of tumor-induced angiogenesis. The mode of neovascularization of metastases originating from various tumors varies itself considerably, suggesting an "individualized" mode of angiogenesis. A corrosion case study of 22 livers with multiple metastases from different primary neoplasms showed the development of an individual pattern of vascularization in all metastases. The majority of metastase displayed a distinct blood supply by branches of the hepatic artery and portal vein branches, whereby all metastases of the same liver showed an identical vascularization pattern (Strohmeyer et al. 1986). Intra- and peritumoral connections between vessels fed by the arteries and portal vein branches are mediated by sinusoidal connections (Nikfarjam et al. 2003). Also a Microfil injection study in human autopsies with liver metastases showed both an arterial and portal mode of vascularization, although the hepatic artery mode was more important (Lin et al. 1984). Injection studies of human liver metastases exhibited a highly abnormal mode of vascularization, never imitating the normal angioarchitecture of the liver (Strohmeyer et al. 1987). Gelatine-injected specimens of human hepatic metastases also revealed that vascularized micrometastases in the vicinity of macrometastases are more common than anticipated from routine preparations (Haugeberg et al. 1988). A gamma camera imaging study of colorectal hepatic metastases revealed that more than twice as much of test substrate was delivered per volume of tumor relative to liver by the hepatic artery as by the portal vein (Ridge et al. 1987). Portal vein blood played a minor role in a rat model of liver metastases (Archer and Gray 1989). In a murine model, blood feeding metastases was distributed from arteries to capillaries of the metastasis center, from where it flowed to a superficial venous network and then further to hepatic veins (Voboril 2005).

In a murine hepatic metastasis model, sinusoidal endothelial cells are activated by interaction with colon carcinoma cells. These activated endothelial cells display an increased expression of mannose receptor (ManR) and ManR-mediated endocytosis. This effect depends on a two-step mechanism: (1) release of COX-2-dependent IL-1 stimulating factors by LFA1-expressing C26 cells in response to ICAM1, which is expressed by activated sinusoidal endothelial cells and (2) widespread upregulation of ManR in endothelia through tumor cell-induced IL-1. ICAM-1-induced tumor COX-2 decreases antitumor activity during hepatic metastasis through Il-1-induced ManR in endothelial cells, ManR therefore constituting a common mediator

for the pro-metastatic effect of Il-1, COX-2, and ICAM-1 (Arteta et al. 2010).

Features of Hepatic Parenchyma That Can Promote Metastatic Growth

Ischemia/reperfusion injury to liver parenchyma can accelerate the outgrowth of preestablished colorectal micrometastases (van der Bilt et al. 2005). With increasing ischemia times, tissue necrosis, and ischemia/reperfusion injury-accelerated tumor growth in mice increased, and in this murine model, outgrowth of micrometastases was further increased by increasing the age of the mice and steatosis of the livers (van der Bilt et al. 2008).

Actions of miRNAs in the Tumor Stroma

In breast cancer metastases, it has been found that miRNA-31 inhibits metastatic growth through the pleiotropic suppression of pro-metastatic target genes that include integrin alpha(5), radixin, and RhoA (Valastyan et al. 2010). Heparanase, a potent protumorigenic and pro-metastatic enzyme which is produced by stromal cells, is targeted and suppressed by miRNA-1258 (Zhang et al. 2011). Epigenetic alterations of miRNA deregulation are common in various tumors. Enhancer of zeste homolog 2 (histone H3 lysine 27 trimethylating enzyme), frequently upregulated in malignancies, epigenetically silences multiple tumor suppressor miRNAs to promote liver cancer metastasis (Au et al. 2012).

Pathogenic Features of Liver Metastases: Epithelial-Mesenchymal Transition (EMT)

Introduction

Epithelial-mesenchymal transition (EMT) is a major process involved in the construction of tissues in early stages of ontogenesis. There, EMT is characterized by the internalization of epithelial cells to give rise to mesodermal/mesenchymal tissues. To arrive at this result, epithelial cells must undergo dramatic changes, including the disconnection of junctions, undergoing polarization and shape change to become migrating cells, and altering cell surface adhesion molecule complements (the "adhesome"). Specifically, distinct expression patterns of integrins are involved in EMT, described as an integrin adhesome (Zaidel-Bar et al. 2007; Zaidel-Bar and Geiger 2010; Winograd-Katz et al. 2014). Other adhesion platforms involved in EMT generation comprise the cadherin adhesome (Zaidel-Bar 2013) and dystroglycan adhesome (Bello et al. 2014). EMT in cancer is characterized by dysregulation of several molecules that comprise, apart from adhesion molecules, intermediate filament proteins, calcium-binding proteins, and transcription factors. Tumor cells in EMT show loss of E-cadherin expression, upregulation of vimentin, induction of alpha-SMA, and expression of Snail1 and Snail2/Slug (Maeng et al. 2014). Typically, cells engaged in EMT fail to express E-cadherin, an important adhesin. The dissolution of the E-cadherin-mediated adherens junction is an important early step in EMT in epithelial malignancies. Downregulation of E-cadherin is accomplished by the action of several transcription factors forming a hierarchical system. Initial transcriptional inducers of EMT are Snail1 and Snail2/Slug, which lead to the activation of ZEB family members, TCF3, TCF4, Twist, Goosecoid, FOXC1, FOXC2, H-Ras, CD44, claudin-1, TGF-beta1, and TNF-alpha. Upregulation of Snail2/Slug and FOXC2 by either Snail1 or Twist does not depend in TGF-beta1 signaling (Taube et al. 2010; Hugo et al. 2011; Qin et al. 2012; Xu et al. 2012; Suh et al. 2013; Caja and Vannucci 2014; Liu et al. 2014b; Okabe et al. 2014). Slug (or now Snail2) is a transcriptional repressor of E-cadherin and is a downstream target of SPARC/osteonectin (Fenouille et al. 2012). Twist1, a basic helix-loop-helix protein transcription factor involved in EMT both in ontogenesis and cancer, is regulated by phosphoregulation (Firulli and Conway 2008) and stabilized by autophagy deficiency via

binding of SQSTM1 to Twist1 in order to prevent autophagosomal Twist1 degradation (Qiang and He 2014). A negative regulator in EMT-related TGF-beta signaling is Smurf2, a protein that interacts with the HCV viral protease NS3-4A (Verga-Gérard et al. 2013). The factors activated by the master EMT inducers Snail1 and Slug have themselves distinct targets that mediate their effects in the EMT molecular pathway. For example, ZEB1 has the collagen receptor tyrosine kinase, discoidin domain receptor 1/DDR1 as its transcriptional target, whereby ZEP1 downregulates DDR1 and contributes to an invasive cancer cell phenotype (Koh et al. 2014). Twist1, having a central role as an effector for EMT induction, can also induce endothelial transdifferentiation of cancer cells through a Jagged1-Krüppel-like factor/KLF-4 signaling axis (Chen et al. 2014a). A further transcription factor involved in EMT and metastasis I a cytotoxic T-lymphocyte agonist epitope of brachyury. EMT is also regulated by the Wnt/beta-catenin signaling cascade, which is activated in the setting of EMT by stromal cell-derived factor 1/SDF-1 and its receptor, CXCR4 (Hu et al. 2014). EMT induced by TNF-alpha requires stabilization of Snail1 mediated by Akt/GSK-3beta signaling, GSK-3beta being a Wnt signaling component (Wang et al. 2013a). EMT can be induced by extravasated platelet aggregation, one critical molecular being CD42b coexpressed with Snail1 (Miyashita et al. 2014).

In addition to factors promoting EMT, there are pathways counteracting EMT generation, and it may be anticipated that failure of such inhibitory pathways in tumors might be involved in metastasis. Protocadherin 9, frequently lost in HCC, inhibits EMT and cell migration through activation of the Wnt signaling component, GSK-3beta (Zhu et al. 2014). EMT can be repressed expression of SMAR1 which represses Snail2/Slug transcription and inhibits E-cadherin degradation in cancer cells (Adhikary et al. 2014). SMAR1 is a nuclear protein involved in chromatin homeostasis that binds to nuclear matrix attachment regions/MARs, regions crucial for proper periodic chromatin arrangement.

Epithelial-Mesenchymal Transition as a Metastasis-Promoting Alteration in Cancer

EMT plays a central role in the generation of a proinvasive tumor microenvironment and metastatic spread of cancer (reviews: Chaffer and Weinberg 2011; Jing et al. 2011; Meng and Wu 2012; Jung et al. 2015). EMT provides cancer cells with migratory, invasive, stroma interactive, and stem cell properties that enable them to disseminate and settle at remote sites. Advanced cancer stage and metastatic spread in HCC are associated with a typical EMT-related cellular alteration, i.e., downregulation of E-cadherin (Zhai et al. 2014). Abnormal expression of EMT-related proteins in HCC, i.e., loss of E-cadherin and overexpression of vimentin and S100 proteins, is correlated with an aggressive metastatic phenotype of this tumor (Zhai et al. 2014). EMT in HCC is related to hepatitis virus infection, viral proteins promoting EMT pathways by various mechanisms (Wang et al. 2014d). For example, HCV-induced expression of osteopontin, a pro-metastatic phosphoprotein overexpressed in HCC, is associated with EMT via the activation of the GSK-3beta signaling pathway (Iqbal et al. 2013).

EMT promoting invasion and metastatic spread in cancers, including liver cancer, is induced by aberrant expression of various pro-EMT factors. Metastasis in HCC is strongly promoted by overexpression of the pro-EMT transcription factor, Snail2/Slug (Sun et al. 2014). TGF-beta1 plays a central role in EMT induction and metastasis in HCC (Reichl et al. 2012). TGF-beta1, which induces EMT in HCC, is induced in these tumors by tumor-associated macrophages/TAMS which also promote cancer stem cell-like features in HCC cells (Fan et al. 2014). Tumor-derived secretory clusterin, a protein involved in the regulation of TGF-beta1-Smad3 signaling, facilitates HCC metastasis via induction of EMT (Wang et al. 2012b). Another member of the TGF-beta family of proteins, bone morphogenetic protein-9/BMP-9, also induces EMT in HCC (Li et al. 2013). Upregulation of hepatocyte growth factor/HGF promotes

carcinogenesis and EMT in HCC through Akt and COX-2 pathways, whereby HGF causes loss of cell surface E-cadherin (Ogunwobi and Liu 2011). Expression of the Hedgehog signaling effector, Gli1, in HCC promotes EMT, invasion, and metastasis (Chen et al. 2014b). ZEB1, a second rank effector of EMT-inducing factors, reduces E-cadherin expression in HCC cells and increased expression of N-cadherin and vimentin, promoting EMT and metastasis in HCC (Zhou et al. 2012). Forkhead box Q1/FOXQ1, a master regulator of tumor metastasis, promotes HCC metastasis by transactivating the EMT inducer ZEB2 (Xia et al. 2014). Loss of expression of functional p53 in HCC is correlated with EMT via regulation of the beta-catenin signaling pathway (Wang et al. 2013b). Downregulation of lipocalin-22 by TGF-beta1 is associated with Tist1 expression and EMT in HCC (Wang et al. 2013b). Stress-activated protein kinase (SAPK)-interacting protein1 or SIN1 which is a key regulator of Akt is overexpressed in HCC and promotes metastasis via induction of EMT (Xu et al. 2013). Activated Wnt/beta-catenin signaling enhances hypoxia-induced EMT in HCC via crosstalk with hypoxia inducing factor-1alpha signaling (Zhang et al. 2013b). Hypoxia and hypoxia-inducible factor-1alpha as such induce EMT in HCCs through activation of Snail1 (Zhang et al. 2013c). EMT-related upregulation of hypoxia-inducible factor-1alpha induces the transcription factor PROX1, resulting in HCC metastasis (Liu et al. 2013). Sirtuin 1/SIRT1, a protein implicated I telomere maintenance and growth in HCC, can mediate EMT in these neoplasms by GSK-3beta/beta-catenin signaling (Chen et al. 2013). Metastasis of HCC induced by EMT is promoted by elevated expression of myeloid differentiation factor 88/MyD88, a protein interacting with p85, a regulatory subunit of phosphoinositide 3-kinase/PI3-K, causing Akt activation, subsequent GSK-3beta phosphorylation, and stabilization of the pro-EMT factor Snail1 (Jia et al. 2014). HCC expresses mortalin, a member of the HSP70 heat shock protein family involved in stress response regulation. Overexpression of mortalin is associated with EMT, angiogenesis metastasis in HCC (Yi et al. 2008; Chen et al. 2014c). In HCC, EMT is induced metadherin, a protein known to increase metastasis in these tumors (Zhu et al. 2011b). In various cancer types, including HCC, EMT as a mechanism involved in metastasis is modulated through the expression of members of a calcium-binding family, the S100 proteins. S100 proteins are critically involved in tumor cell-stromal cell interactions, promotion of EMT, and the generation of a proinflammatory tumor microenvironment promoting invasion and spread (Lukanidin and Sleeman 2012). Induction of EMT by S100A4 is regulated by the Sonic Hedgehog-Gli1 signaling pathway, whereby the Hedgehog effector Gli1 modulates S100A4 expression via cis-acting elements (Xu et al. 2014). S100A4 induces migration and invasion in HCC cells through the induction of an NF-kappaB-dependent MMP-9 signal (Zhang et al. 2013d). In HCC, abnormal expression of EMT-related S100A4 is correlated with an aggressive tumor biology (Zhai et al. 2014). The metastasis-associated protein S100A4 induces a network of inflammatory cytokines that activate stromal cells to have protumorigenic features (Bettum et al. 2014). In addition to S100A4, a second S100 protein can induce EMT, i.e., S100A2, acting through functional interaction with Smad3 which is enhanced in the presence of high calcium and TGF-beta activity (Naz et al. 2014). In HCC, ectopic expression of metastasin, a further calcium-binding protein, induces typical EMT with decreased E-cadherin and upregulation of vimentin via upregulation of SNAI1 (Zheng et al. 2013). Several EMT-associated proteins are regulated by BTB/POZ domain-containing protein 7/BTBD7 in HCC (Tao et al. 2013). In cancers, EMT is connected with the induction of an inflammatory microenvironment that plays a role both in favoring invasion and spread and tumor control by immune mechanisms. TGF-beta1 contributes to an inflammatory niche through promotion of immune cell homing and switching the phenotypes of tumor-infiltrating immune cells (Fuxe and Karlsson 2012).

Regulation of Epithelial-Mesenchymal Transition

EMT as a motor of the metastatic pathway is regulated by several mechanisms that control expression of pro- and anti-EMT factors. Numerous factors are regulated by epigenetic promoter methylation, with a complex EMT-related or even EMT-specific DNA methylome. EMT factors are controlled by microRNAs. MiR-29c mediates EMT in human CRC metastases via modulation of beta-catenin signaling (Zhang et al. 2014a). MiR-424-5p can reverse EMT in HCC by targeting the beta-catenin inhibitor, ICAT (Zhang et al. 2014b). MiR-122 triggers EMT and suppresses HCC cell motility, migration, and invasion via targeting RhoA (Wang et al. 2014b). Downregulation of microRNA-30a in HCC facilitates migration and invasion through promotion of EMT (Liu et al. 2014a). This miR can, however, also inhibit EMT via targeting the pro-EMT factor Snail1/Snai1, an effect circumvented by its downregulation in cancers (Kumarswamy et al. 2012). MicroRNA-26b inhibits EMT by targeting USP9X, a protein which in turn affects EMT through Smad4 and the TGF-beta signaling pathway (Shen et al. 2014). MicroRNA-148a suppresses EMT and metastasis of HCC by targeting Snail signaling (Zhang et al. 2014c). MiR-491 is involved in the regulation of HCC metastasis by blocking EMT via increase of surface E-cadherin expression (Zhou et al. 2013). Overexpression of microRNA-106b promotes cell migration and metastasis in HCC via promoting EMT via overexpression of the RhoGTPases, RhoA, and RhoC (Yau et al. 2013). Micro-RNA-490-3p modulates HCC cell growth and EMT by targeting endoplasmic reticulum-Golgi intermediate compartment protein 3/ERGIC3 (Zhang et al. 2013). The invasive and metastatic behavior of HCC is suppressed by microRNA-612 which inhibits EMT (Tao et al. 2013). Metastasis regulated by EMT is also subject to modulation by long noncoding RNAs that affect transcriptional and posttranscriptional steps in synthesis of critical factors (Serviss et al. 2014). A long noncoding RNA activated by TGF-beta promotes the invasion-metastatic cascade in HCC (Yuan et al. 2014).

The Concept of the Pre-metastatic Niche

Introduction

The establishment of a microenvironment that favors homing and growth of cancer cells is a critical condition for the generation of metastasis. The biogenesis of metastases requires a distinct tumor cell-host organ interface in early phases of the metastatic process (Gassmann and Haier 2008). The cellular basis for this pathway of metastasis has been reviewed (Oppenheimer 2006) and has resulted in the concept of the pre-metastatic niche (pre-MN). A pre-MN is defined as a distinct variant of microenvironment that is induced in target organs of metastasis and facilitates homing, adhesion, growth, invasion, and survival of metastatic tumor cells (Kaplan et al. 2006; Perelmuter and Manskikh 2012; Zoccoli et al. 2012). In this sense, the pre-MN is a structure that precedes, and eventually anticipates, the generation of a metastasis, a novel concept for the understanding of a metastasis cascade. Also for the liver, which is a major metastasis-susceptible organ, a pre-or pro-metastatic microenvironment has been discussed (review: Vidal-Vanaclocha 2008).

The Cellular Preparation of the Pre-metastatic Niche

It was demonstrated that bone marrow-derived cells/BMDC home to the pre-MN via the action of adhesion molecule and chemokine signaling, and there establish clusters that precede the arrival of even single metastasizing cancer cells. Interaction of these BMDC with local cells promotes the upregulation of several factors that will be important for cancer cell growth, including signaling chemokines, stromal differentiation factors, and angiogenic factors (review: Kaplan et al. 2006). Bone marrow-derived myeloid progenitor cells can induce mesenchymal-epithelial transition/MET in remote tissues (Gao et al. 2012b).

Cancer Progenitor/Stem Cells in a Pre-metastatic Niche

Cancer stem cells are thought to possess distinct tissue and cell selection capabilities allowing them to home to a pre-MN (Malanchi et al. 2011). In their interaction with microenvironmental structures, cancer stem cells are not a fixed set of cells but rather a flexible population of cells that can differentiate to typical tumor cells and revert to a stemlike state. There is strong evidence that this switching is regulated by interactions with mesenchymal cells of the niche (Fessler et al. 2013), these cells themselves being programmed to later become true stromal cells, including cancer-associated fibroblasts and myofibroblasts. Within a pre-MN, cancer stem cells dwell in some sort of a "CSC niche" which controls their self-renewal, differentiation, and departure for other niches (Borovski et al. 2011).

Cross-Talk Between Tumor Cells and Elements of the Pre-metastatic Niche

In addition to several classes of stem cells that can prepare the pre-MN, differentiated tumor cells themselves interact in a complex manner with elements of the pre-MN. The interaction with cells of the pre-MN can induce genetic and epigenetic alterations in the homing tumor cells, changes that can themselves promote a metastatic phenotype of the cancer cells (Carlini et al. 2011). The offspring of tumor cells that have undergone such pre-MN-induced changes may be primed to transfer these acquired changes to other potential metastatic sites, eventually to induce novel pre-MNs. On the other hand, tumor cells that have settled in the niche can prime the further development of cells active in the niche (Deng et al. 2012) and induce the evolution of the pre-MN to a complete and active, vascularized stroma (the concept of induced stromal progression).

Programming of the Pre-metastatic Niche by Exosomes

The mechanisms as to how homing cells induce resident cells to become a pre-metastatic microenvironment and then a tumor stroma and an angiogenic field are still not well known. It is assumed that direct contact of homing bone marrow-derived cells and cancer stem cells and differentiated tumor cells with tissue can elicit a differentiation switch of mesenchymal and vascular cells in situ. On the other hand, exosomes delivered by tumor cells and harboring genetic information or signaling molecules can drive pre-MN formation (Alderton 2012). Exosomes contain membrane anchors that allow them to attach to target cells in a niche, to deliver their information cargo (Pant et al. 2012). Exosomes released from melanoma cells and transported to sentinel lymph nodes prepare these nodes for metastasis through remodeling of the lymphonodular microenvironment (Hood et al. 2011). Exosomes released from malignant cells, e.g., melanoma cells, can also educate noncancer progenitor cells toward a pre-metastatic phenotype through the action of the receptor tyrosine kinase Met (Peinado et al. 2012). For this pathway to work, certain conditions must be present in resident cells to interact with exosomes, such as expression of the CD44v6 isoform of CD44, this factor assembling a soluble matrix for exosomes to allow cell embedding and growth (Jung et al. 2009).

Programming the Pre-metastatic Niche by Soluble Factors from Progenitor Cells and Tumor Cells

Apart from direct interaction with future stromal cells and release of exosomes, tumor cells can also secrete various factors that "prepare" the future niche, and in particular its endothelial cells, for cancer cell homing. Such secreted factors include vascular endothelial growth factors, TGF-beta and TNF-alpha. These molecules can elicit the release of secondary signal substances from the

niche, e.g., the chemokines S100A8 and S100A9 (Rafii and Lyden 2006). The latter two chemokines are also produced by macrophages, including those located in pre-MNs (Maru 2007). Proteins of the S100A family, including S100A4, are metastasis-associated proteins (Hemandas et al. 2006). Myeloid progenitor cells from the bone marrow can secrete the proteoglycan, which is capable to regulate remote microenvironments to become of pre-MN (Gao et al. 2012a). Carcinoma cells secreting vascular endothelial growth factor C into lymph, draining the cancer, can induce characteristic changes in locoregional lymph nodes, including an increase in lymphatic vessels and the induction of high endothelial venules, before the arrival of tumor cells (Chung et al. 2012).

Counteracting the Function of the Pre-metastatic Niche

There are several mechanisms that may abolish the generation and functions of pre-MN. Mesenchymal cells and endothelial cells in certain tissues and organs may be refractory to pre-MN-inducing cells and factors, being one explanation why certain tissues are only seldom involved by metastases, e.g., skeletal muscle. Tumor cells having settled and grown in the area of the pre-MN can later destroy this microenvironment (Bidard et al. 2008), rendering it non-functional. A third mechanism depends on the formation of tumor-entrained neutrophils (TENs), cells that circulate in the blood as a response to malignancies but are absent in healthy subjects. TENs inhibit metastatic seeding by blunting the function of pre-MNs via secretion of hydrogen peroxide (Granot et al. 2011).

References

Aatonen M, Grönholm M, Siljander PR (2012) Platelet-derived microvesicles: multitalented participants in intercellular communication. Semin Thromb Hemost 38:102–113

Adhikary A, Chakraborty S, Mazumdar M, Ghosh S, Mukherjee S, Manna A, Mohanty S et al (2014) Inhibition of epithelial to mesenchymal transition by E-cadherin up-regulation via repression of slug transcription and inhibition of E-cadherin degradation: dual role of SMAR1 in breast cancer cells. J Biol Chem 289:25431–25444

Aharinejad S, Sioud M, Lucas T, Abraham D (2009) Targeting stromal-cancer cell interactions with siRNAs. Methods Mol Biol 487:243–266

Alderton GK (2012) Metastasis. Exosomes drive premetastatic niche formation. Nat Rev Cancer 12:447

Alphonso A, Alahari SK (2009) Stromal cells and integrins: conforming to the needs of the tumor microenvironment. Neoplasia 11:1264–1271

Archer SG, Gray BN (1989) Vascularization of small liver metastases. Br J Surg 76:545–548

Arteta B, Lasuen N, Lopategi A, Sveinbjörnsson B, Smedsrod B, Vidal-Vanaclocha F (2010) Colon carcinoma cell interaction with liver sinusoidal endothelium inhibits organ-specific antitumor immunity through interleukin-1-induced mannose receptor in mice. Hepatology 51:2172–2182

Au SL, Wong CC, Lee JM, Fan DN, Tsang FH, Ng IO, Wong CM (2012) Enhancer of zeste homolog 2 epigenetically silences multiple tumor suppressor microRNAs to promote liver cancer metastasis. Hepatology 56(2):622–631

Badiola I, Olaso E, Crende O, Friedman SL, Vidal-Vanaclocha F (2011) Discoidin domain receptor 2 deficiency predisposes hepatic tissue to colon carcinoma metastasis. Gut 26:971–978

Bambace NM, Holmes CE (2011) The platelet contribution to cancer progression. J Thromb Haemost 9:237–249

Battinelli EM, Markens BA, Italiano JE (2011) Release of angiogenesis regulatory proteins from platelet alpha granules: modulation of physiologic and pathologic angiogenesis. Blood 118:1359–1369

Bello V, Moreau N, Sirour C, Hidalgo M, Buisson N, Darribère T (2014) The dystroglycan: nestled in an adhesome during embryonic development. Dev Biol. doi:10.1016/j.ydbio.2014.07.006

Benson DD, Meng X, Fullerton DA, Moore EE, Lee JH, Ao L, Silliman CC, Barnett CC (2012) Activation state of stromal inflammatory cells in murine metastatic pancreatic adenocarcinoma. Am J Physiol Regul Integr Comp Physiol 302:R1067–R1075

Bettum IJ, Vasiliauskaine K, Nygaard V, Clancy T, Pettersen SJ, Tenstad E, Maelandsmo GM et al (2014) Metastasis-associated protein S100A4 induces a network of inflammatory cytokines that activate stromal cells to acquire pro-tumorigenic properties. Cancer Lett 344:28–39

Bhatia A, Dey P (2013) Platelet internalization within the cancer cells: what is the significance? Diagn Cytopathol 41:659–660

Bidard FC, Pierga JY, Vincent-Salomon A, Poupon MF (2008) A "class action" against the microenvironment: do cancer cells cooperate in metastasis? Cancer Metastasis Rev 27:5–10

Bogenrieder T, Herlyn M (2003) Axis of evil: molecular mechanisms of cancer metastasis. Oncogene 22:6524–6536

Borovski T, De Sousa E, Melo F, Vermeulen L, Medema JP (2011) Cancer stem cell niche: the place to be. Cancer Res 71:634–639

Borsig L (2008) The role of platelet activation in tumor metastasis. Expert Rev Anticancer Ther 8:1247–1255

Brandau S, Moses K, Lang S (2013) The kinship of neutrophils and granulocytic myeloid-derived suppressor cells in cancer: cousins, siblings or twins? Semin Cancer Biol 23:171–182

Buergy D, Wenz F, Groden C, Brockmann MA (2012) Tumor-platelet interaction in solid tumors. Int J Cancer 130:2747–2760

Caja F, Vannucci L (2014) TGFβ: a player on multiple fronts in the tumor microenvironment. J Immunotoxicol 20:1–8

Capece D, Fischietti M, Verzella D, Gaggiano A, Cicciarelli G, Tessitore A, Zazzeroni F et al (2013) The inflammatory microenvironment in hepatocellular carcinoma: a pivotal role for tumor-associated macrophages. Biomed Res Int 2013:187204

Carlini MJ, De Lorenzo MS, Puricelli L (2011) Cross-talk between tumor cells and the microenvironment at the metastatic niche. Curr Pharm Biotechnol 12:1900–1908

Carr BI, Cavallini A, D Allessandro R, Refolo MG, Lippolis C, Mazzocca A, Messa C (2014) Platelet extracts induced growth, migration and invasion in human hepatocellular carcinoma in vitro. BMC Cancer 14:43

Chaffer CL, Weinberg RA (2011) A perspective on cancer cell metastasis. Science 331:1559–1564

Chambers SE, O'Neill CL, O'Doherty TM, Medina RJ, Stitt AW (2013) The role of immune-related myeloid cells in angiogenesis. Immunobiology 218:1370–1375

Chang MC, Chan CP, Ho YS, Lee JJ, Lin PS, Lin BR, Huang YL, Hahn LJ, Yeh HW et al (2009) Signaling pathways for induction of platelet aggregation by SAS tongue cancer cells – a mechanism of hematogenous metastasis. J Oral Pathol Med 38:434–440

Chanmee T, Ontong P, Konno K, Itano N (2014) Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel) 6:1670–1690

Chen J, Chan AW, To KF, Chen W, Zhang Z, Ren J, Song C, Cheung YS, Lai PB et al (2013) SIRT2 overexpression in hepatocellular carcinoma mediates epithelial to mesenchymal transition by protein kinase B/glycogen synthase kinase-3β/β-catenin signaling. Hepatology 57:2287–2298

Chen HF, Huang CH, Liu CJ, Hung JJ, Hsu CC, Teng SC, Wu KJ (2014a) Twist1 induces endothelial differentiation of tumour cells through the Jagged1-KLF4 axis. Nat Commun 5:4697

Chen JS, Li HS, Huang JQ, Zhang LJ, Chen XL, Wang Q, Lei J, Feng JT, Liu Q et al (2014b) Down-regulation of Gli-1 inhibits hepatocellular carcinoma cell migration and invasion. Mol Cell Biochem 393:283–291

Chen J, Liu WB, Jia WD, Xu GL, Ma JL, Huang M, Deng YR, Li JS (2014c) Overexpression of Mortalin in hepatocellular carcinoma and its relationship with angiogenesis and epithelial to mesenchymal transition. Int J Oncol 44:247–255

Chung MK, Do IG, Jung E, Son YI, Jeong HS, Baek CH (2012) Lymphatic vessels and high endothelial venules are increased in the sentinel lymph nodes of patients with oral squamous cell carcinoma before the arrival of tumor cells. Ann Surg Oncol 19:1595–1601

Cirri P, Chiarugi P (2012) Cancer-associated fibroblasts and tumour cells: a diabolic liaison driving cancer progression. Cancer Metastasis Rev 31:195–208

Coupland LA, Chong BH, Parish CR (2012) Platelets and P-selectin control tumor cell metastasis in an organ-specific manner and independently of NK cells. Cancer Res 72:4662–4671

Cui TX, Kryczek I, Zhao L, Zhao E, Kuick R, Roh MH, Vatan L, Szeliga W, Mao Y et al (2013) Myeloid-derived suppressor cells enhance stemness of cancer cells by inducing microRNA101 and suppressing the corepressor CtBP2. Immunity 39:611–621

Deng J, Liu Y, Lee H, Herrmann A, Zhang W, Zhang C, Shen S, Priceman SJ, Kujawski M et al (2012) S1PR1-STAT3 signaling is crucial for myeloid cell colonization at future metastatic sites. Cancer Cell 21:642–654

Diaz-Montero CM, Finke J, Montero AJ (2014) Myeloid-derived suppressor cells in cancer: therapeutic, predictive, and prognostic implications. Semin Oncol 41:174–184

Dovizio M, Alberti S, Guillem-Llobat P, Patrignani P (2014) Role of platelets in inflammation and cancer: novel therapeutic strategies. Basic Clin Pharmacol Toxicol 114:118–127

Dumitru CA, Moses K, Trellakis S, Lang S, Brabdau S (2012) Neutrophils and granulocytic myeloid-derived suppressor cells: immunophenotyping, cell biology and clinical relevance in human oncology. Cancer Immunol Immunother 61:1155–1167

Eldor A, Bar-Ner M, Yahalom J, Fuks Z, Vlodavsky I (1987) Role of heparanase in platelet and tumor cell interactions with the subendothelial extracellular matrix. Semin Thromb Hemost 13:475–488

Erpenbeck L, Schön MP (2010) Deadly allies: the fatal interplay between platelets and metastasizing cancer cells. Blood 115:3427–3436

Etulain J, Fondevila C, Negrotto S, Schattner M (2013) Platelet-mediated angiogenesis is independent of VEGF and fully inhibited by aspirin. Br J Pharmacol 170:255–265

Falanga A, Marchetti M, Vignoli A, Balducci D (2003) Clotting mechanisms and cancer: implications in thrombus formation and tumor progression. Clin Adv Hematol Oncol 1:673–678

Fan QM, Jing YY, Yu GF, Kou XR, Ye F, Gao L, Li R, Zhao QD, Yang Y, Lu ZH et al (2014) Tumor-associated macrophages promote cancer stem cell-like properties via transforming growth factor-beta1-induced epithelial-mesenchymal transition in hepatocellular carcinoma. Cancer Lett 352:160–168

Fenouille N, Tichet M, Dufies M, Pottier A, Mogha A, Soo JK, Rocchi S, Mallavialle A et al (2012) The epithelial-

mesenchymal transition (EMT) regulatory factor SLUG (SNAI2) is a downstream target of SPARC and AKT in promoting melanoma cell invasion. PLoS One 7:e40378

Fessler E, Dijgraaf FE, Melo FD, Medema JP (2013) Cancer stem cell dynamics in tumor progression and metastasis: is the microenvironment to blame? Cancer Lett 341:97–104

Finger EC, Giaccia AJ (2010) Hypoxia, inflammation, and the tumor microenvironment in metastatic disease. Cancer Metastasis Rev 29:285–293

Firulli AB, Conway SJ (2008) Phosphoregulation of Twist1 provides a mechanism of cell fate control. Curr Med Chem 15:2641–2647

Fujita and Takagi (2012) http://www.ncbi.nlm.nih.gov/pubmed/22992842

Fuxe J, Karlsson MC (2012) TGF-β-induced epithelial-mesenchymal transition: a link between cancer and inflammation. Semin Cancer Biol 22:455–461

Galdiero MR, Garlanda C, Jaillon S, Marone G, Mantovani A (2013) Tumor associated macrophages and neutrophils in tumor progression. J Cell Physiol 228:1404–1412

Gao D, Vahdat LT, Wong S, Chang JC, Mittal V (2012a) Microenvironment regulation of epithelial-mesenchymal transitions in cancer. Cancer Res 72:4883–4889

Gao D, Joshi N, Choi H, Ryu S, Hahn M, Catena R, Sadik H, Argani P, Wagner P et al (2012b) Myeloid progenitor cells in the premetastatic lung promote metastasis by inducing mesenchymal to epithelial transition. Cancer Res 72:1384–1394

Gasic GJ (1984) Role of plasma, platelets, and endothelial cells in tumor metastasis. Cancer Metastasis Rev 3:99–114

Gassmann P, Haier J (2008) The tumor cell-host organ interface in the early onset of metastatic organ colonisation. Clin Exp Metastasis 25:171–181

Gay LJ, Felding-Habermann B (2011) Contribution of platelets to tumour metastasis. Nat Rev Cancer 11:123–134

Gil-Bernabé AM, Lucotti S, Muschel RJ (2013) Coagulation and metastasis: what does the experimental literature tell us? Br J Haematol 162:433–441

Granot Z, Henke E, Comen EA, King TA, Norton L, Benezra R (2011) Tumor entrained neutrophils inhibit seeding in the premetastatic lung. Cancer Cell 20:300–314

Grugan KD, McCabe FL, Kinder M, Greenplate AR, Harman BC, Ekert JE, van Rooijen N et al (2012) Tumor-associated macrophages promote invasion while retaining Fc-dependent anti-tumor function. J Immunol 189:5457–5466

Hao NB, Lü MH, Fan YH, Cao YL, Zhang ZR, Yang SM (2012) Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol 2012:948098

Haugeberg G, Strohmeyer T, Lierse W, Böcker W (1988) The vascularization of liver metastases. Histological investigation of gelatine-injected liver specimens with special regard to the vascularization of micrometastases. J Cancer Res Clin Oncol 114:415–419

Heijnen et al (1999) http://www.ncbi.nlm.nih.gov/pubmed/10572093

Hemandas AK, Salto-Tellez M, Maricar SH, Leong AF, Leow CK (2006) metastasis-associated protein S100A4 – a potential prognostic marker for colorectal cancer. J Surg Oncol 93:498–503

Higashi N, Ishii H, Fujiwara T, Morimoto-Tomita M, Irimura T (2002) Redistribution of fibroblasts and macrophages as micrometastases develop into established liver metastases. Clin Exp Metastasis 19:631–638

Honn KV, Tang DG, Crissman JD (1992) Platelets and cancer metastasis: a causal relationship? Cancer Metastasis Rev 11:325–351

Hood JL, San RS, Wickline SA (2011) Exosomes released by melanoma cells prepare sentinel lymph nodes for tumor metastasis. Cancer Res 71:3792–3801

Hoos A, Protsyuk D, Borsig L (2014) Metastatic growth progression caused by PSGL-1-mediated recruitment of monocytes to metastatic sites. Cancer Res 74:695–704

Hu et al (2014) http://www.ncbi.nlm.nih.gov/pubmed/25150783

Hugo HJ, Kokkinos MI, Blick T, Ackland ML, Thompson EW, Newgreen DF (2011) Defining the E-cadherin repressor interactome in epithelial-mesenchymal transition: the PMC42 model as a case study. Cells Tissues Organs 193:23–40

Illemann M, Bird, Majeed A, Sehested M, Laerum OD, Lund LR, Dano K, Nielsen BS (2006) MMP-9 is differentially expressed in primary human colorectal adenocarcinomas and their metastases. Mol Cancer Res 4:293–302

Iqbal J, McRae S, Banaudha K, Mai T, Waris G (2013) Mechanism of hepatitis C virus (HCV)-induced osteopontin and its role in epithelial to mesenchymal transition of hepatocytes. J Biol Chem 288:36994–37009

Jain S, Harris J, Ware J (2010) Platelets: linking hemostasis and cancer. Arterioscler Thromb Vasc Biol 30:2362–2367

Jia RJ, Cao L, Zhang L, Jing W, Chen R, Zhu MH, Guo SW, Wu GB, Fan XY, Wang H et al (2014) Enhanced myeloid differentiation factor 88 promotes tumor metastasis via induction of epithelial-mesenchymal transition in human hepatocellular carcinoma. Cell Death Dis 5:e1103

Jing Y, Han Z, Zhang S, Liu Y, Wei L (2011) Epithelial-mesenchymal transition in tumor microenvironment. Cell Biosci 1:29

Jung T, Castellana D, Klingbeil P, Cuesta Hernandez I, Vitacolonna M, Orlicky DJ et al (2009) CD44v6 dependence of premetastatic niche preparation by exosomes. Neoplasia 11:1093–1105

Jung HY, Fattet L, Yang J (2015) Molecular pathways: linking tumor microenvironment to epithelial-mesenchymal transition in metastasis. Clin Cancer Res 21:962–968

Jurasz et al (2004) http://www.ncbi.nlm.nih.gov/pubmed/15492016

Kamoshida G, Ogawa T, Oyanagi J, Sato H, Komiya E, Higashi S, Miyazaki K, Tsuji T (2014) Modulation of matrix metalloproteinase-9 secretion from tumor-associated macrophage-like cells by proteolytically processed laminin-322 (laminin-5). Clin Exp Metastasis 31:285–291

Kang N, Gores GJ, Shah VH (2011) Hepatic stellate cells: partners in crime for liver metastases? Hepatology 54:707–713

Kaplan RN, Rafii S, Lyden D (2006) Preparing the "soil": the premetastatic niche. Cancer Res 66:11089–11093

Karpatkin S, Pearlstein E (1981) Role of platelets in tumor cell metastases. Ann Intern Med 95:636–641

Karshovska E, Weber C, von Hundelshausen P (2013) Platelet chemokines in health and disease. Thromb Haemost 110:894–902

Kato et al (2003) http://www.ncbi.nlm.nih.gov/pubmed/14588983

Keskinov AA, Shurin MR (2014) Myeloid regulatory cells in tumor spreading and metastasis. Immunobiology. doi:10.1016/j.imbio.2014.07.017

Kobayashi K, Hernandez LD, Galan JE, Janeway CA, Medzhitov R, Flavell RA (2002) IRAK-M is a negative regulator of Toll-like receptor signaling. Cell 110:191–202

Koh M, Woo Y, Valiathan RR, Jung HY, Park SY, Kim YN, Kim HR, Fridman R, Moon A (2014) Discoidin domain receptor 1 is a novel transcriptional target of ZEB1 in breast epithelial cells undergoing H-Ras-induced epithelial to mesenchymal transition. Int J Cancer. doi:10.1002/ijc.29154

Koseoglu S, Flaumenhaft R (2013) Advances in platelet granule biology. Curr Opin Hematol 20:464–471

Krishnan et al (2013) http://www.ncbi.nlm.nih.gov/pubmed/23530051

Kumarswamy R, Mudduluru G, Ceppi P, Muppala S, Kozlowski M, Niklinski J, Papotti M et al (2012) MicroRNA-30a inhibits epithelial-to-mesenchymal transition by targeting Snail1 and is downregulated in non-small cell lung cancer. Int J Cancer 130:2044–2053

Kunita et al (2007) http://www.ncbi.nlm.nih.gov/pubmed/17392172

Kunita et al (2011) http://www.ncbi.nlm.nih.gov/pubmed/21801875

Labelle M, Hynes RO (2012) The initial hours of metastasis: the importance of cooperative host-tumor cell interactions during hematogenous dissemination. Cancer Discov 2:1091–1099

Labelle M, Begum S, Hynes RO (2011) Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 20:576–590

Li H, Fan X, Houghton J (2007) Tumor microenvironment: the role of the tumor stroma in cancer. J Cell Biochem 101:805–815

Li Q, Gu X, Weng H, Ghafoory S, Liu Y, Feng T, Dzieran J, Li L, Ilkavets I, Kruithof-de Julio M et al (2013) Bone morphogenetic protein-9 induces epithelial to mesenchymal transition in hepatocellular carcinoma cells. Cancer Sci 104:398–408

Li Y, Miso LY, Xiao YL, Cai HR, Zhang DP (2014) Elevated platelets enhance cancer cell migration, promote hematogenous metastasis and associated with a poor prognosis in advanced non-small cell lung cancer cases. Asian Pac J Cancer Prev 15:139–143

Lin G, Hägerstrand I, Lunderquist A (1984) Portal blood supply of liver metastases. AJR Am J Roentgenol 143:53–55

Lin Y, Wei C, Liu Y, Qiu Y, Liu C, Guo F (2013) Selective ablation of tumor-associated macrophages suppresses metastasis and angiogenesis. Cancer Sci 104:1217–1225

Liu Y, Zhang JB, Qin Y, Wang W, Wie L, Teng Y, Guo L, Zhang B, Lin Z, Liu J, Ren ZG et al (2013) PROX1 promotes hepatocellular carcinoma metastasis by way of up-regulating hypoxia-inducible factor 1α expression and protein stability. Hepatology 58:692–705

Liu Z, Tu K, Liu Q (2014a) Effects of microRNA-30a on migration, invasion and prognosis of hepatocellular carcinoma. FEBS Lett 588:3089–3097

Liu L, Dai Y, Chen J, Zeng T, Li Y, Chen L, Zhu YH, Li J, Li Y, Ma S, Xie D, Yuan YF et al (2014b) Maelstrom promotes hepatocellular carcinoma metastases by inducing epithelial-mesenchymal transition by way of Akt/GSK-3β/Snail signaling. Hepatology 59:531–543

Lowe et al (2012) http://www.ncbi.nlm.nih.gov/pubmed/22682130

Lukanidin E, Sleeman JP (2012) Building the niche: the role of the S100 proteins in metastatic growth. Semin Cancer Biol 22:216–225

Mabuchi A, Mullaney I, Sheard PW, Hessian PA, Mallard BL, Tawadrous MN, Zimmermann A et al (2004a) Role of hepatic stellate cell/hepatocyte interaction and activation of hepatic stellate cells in the early phase of liver regeneration in the rat. J Hepatol 40:910–916

Mabuchi A, Mullaney I, Sheard P, Hessian P, Zimmermann A, Wheatley AM (2004b) Role of hepatic stellate cells in the early phase of liver regeneration in rat: formation of tight adhesion to parenchymal cells. Comp Hepatol 3(Suppl 1):S29

Maeng YI, Kim KH, Kim JY, Lee SJ, Sung WJ, Lee CK, Park JB, Park KK (2014) Transcription factors related to epithelial mesenchymal transition in tumor center and margin in invasive lung adenocarcinoma. Int J Clin Exp Pathol 7:4095–4103

Maione F, Capano S, Regano D, Zentilin L, Giacca M, Casanovas O, Bussolino F et al (2012) Semaphorin 3A overcomes cancer hypoxia and metastatic dissemination induced by antiangiogenic treatment in mice. J Clin Invest 122:1832–1848

Malanchi I, Santamaria-Martinez A, Susanto E, Peng H, Lehr HA, Delaloye JF, Huelsken J (2011) Interactions between cancer stem cells and their niche govern metastatic colonization. Nature 481:85–89

Maniecki MB, Etzeroth A, Ulhoi BP, Steiniche T, Borre M, Dyrskjot L, Ornoft TF, Moestrup SK et al (2012) Tumor-promoting macrophages induce the expression of the macrophage-specific receptor CD163 in malignant cells. Int J Cancer 131:2320–2331

Mantovani A, Sozzani S, Locati M, Allavena P, Sica A (2002) Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol 23:549–555

Mantovani A, Sica A, Allavena P, Garlanda C, Locati M (2009) Tumor-associated macrophages and the related myeloid-derived suppressor cells as a paradigm of the diversity of macrophage activation. Hum Immunol 70:325–330

Maru Y (2007) Which came first, tumor cells or macrophages? Cell Adh Migr 1:107–109

Mehta P (1984) Potential role of platelets in the pathogenesis of tumor metastasis. Blood 63:55–63

Meng F, Wu G (2012) The rejuvenated scenario of epithelial-mesenchymal transition (EMT) and cancer metastasis. Cancer Metast Rev 31:455–467

Micalizzi DS, Wang CA, Farabaugh SM, Schiemann WP, Ford HL (2010) Homeoprotein Six1 increases TGF-beta type I receptor and converts TGF-beta signaling from suppressive to supportive for tumor growth. Cancer Res 70:10371–10380

Miyashita T, Tajima H, Makino I, Nakagawara H, Kitagawa H, Fushida S, Harmon JW et al (2014) Metastasis-promoting role of extravasated platelet activation in tumor. J Surg Res. doi:10.1016/j.jss.2014.07.037

Movahedi K, Laoui D, Gysemans C, Baeten M, Stangé G, Van den Bossche J, Mack M et al (2010) Different tumor microenvironments contain functionally distinct subsets of macrophages derived from Ly6C(high) monocytes. Cancer Res 70:5728–5739

Mrazek AA, Carmical JR, Wood TG, Hellmich MR, Eltorky M, Bohanon FJ, Chao C (2014) Colorectal cancer-associated fibroblasts are genotypically distinct. Curr Cancer Ther Rev 10:197–218

Mueller L, Goumas FA, Affeldt M, Sandtner S, Gehling UM, Brilloff S, Walter J, Karnatz N et al (2007) Stromal fibroblasts in colorectal liver metastases originate from resident fibroblasts and generate an inflammatory microenvironment. Am J Pathol 171:1608–1618

Mueller L, von Seggern L, Schumacher J, Goumas F, Wilms C, Braun F, Broering DC (2010) TNF-alpha similarly induces IL-6 and MCP-1 in fibroblasts from colorectal liver metastases and normal liver fibroblasts. Biochem Biophys Res Commun 397:586–591

Naz S, Bashir M, Ranganathan P, Bodapati P, Santosh V, Kondaiah P (2014) Protumorigenic actions of S100A2 involve regulation of PI3/Akt signaling and functional interaction with Smad3. Carcinogenesis 35:14–23

Nierodzik ML, Klepfish A, Karpatkin S (1995) Role of platelets, thrombin, integrin IIb-IIa, fibronectin and von Willebrand factor on tumor adhesion in vitro and metastasis in vivo. Thromb Haemost 74:282–290

Nikfarjam N, Muralidharan V, Malcontenti-Wilson C, Christophi C (2003) Scanning electron microscopy study of the blood supply of human colorectal liver metastases. EJSO 29:856–861

Nyberg P, Salo T, Kalluri R (2008) Tumor microenvironment and angiogenesis. Front Biosci 13:6537–6553

Ogunwobi OO, Liu C (2011) Hepatocyte growth factor upregulation promotes carcinogenesis and epithelial-mesenchymal transition in hepatocellular carcinoma via Akt and COX-2 pathways. Clin Exp Metastasis 28:721–731

Okabe H, Ishimoto T, Mima K, Nakagawa S, Hayashi H, Kuroki H, Imai K, Nitta H et al (2014) CD44s signals the acquisition of the mesenchymal phenotype required for anchorage-independent cell survival in hepatocellular carcinoma. Br J Cancer 110:958–966

Okuda H, Kobayashi A, Xia B, Watabe M, Pai SK, Hirota S, Xing F, Liu W, Pandey PR et al (2012) Hyaluronan synthase HAS2 promotes tumor progression in bone by stimulating the interaction of breast cancer stem-like cells with macrophages and stromal cells. Cancer Res 72:537–547

Oleksowicz L, Dutcher JP (1995) Adhesive receptors expressed by tumor cells and platelets: novel targets for therapeutic anti-metastatic strategies. Med Oncol 12:95–102

Oppenheimer SB (2006) Cellular basis of cancer metastasis: a review of fundamentals and new advances. Acta Histochem 108:327–334

Orimo A, Weinberg RA (2006) Stromal fibroblasts in cancer: a novel tumor-promoting cell type. Cell Cycle 5:1597–1601

Owen JL, Mohamadzadeh M (2013) Macrophages and chemokines as mediators of angiogenesis. Front Physiol 4:159

Panasci LC, Comis R, Ginsberg S, Rudolph A, Theodorakis M, Klag M, Fitzpatrick A et al (1980) Pharmacokinetics of vinblastine-loaded platelets utilized in the treatment of platelet-phagocytizing tumors. Cancer Treat Rep 64:1227–1233

Pang Y, Gara SK, Achyut BR, Li Z, Yan HH, Day CP, Weiss JM, Trinchieri G, Morris JC et al (2013) TGF-β signaling in myeloid cells is required for tumor metastasis. Cancer Discov 3:936–951

Pant S, Hilton H, Burczynski ME (2012) The multifaceted exosome: biogenesis, role in normal and aberrant cellular function, and frontiers for pharmacological and biomarker opportunities. Biochem Pharmacol 83:1484–1494

Peinado H, Aleckovic M, Lavotshkin S, Matei I, Costa-Silva B, Moreno-Bueno G, Hergueta-Redondo M et al (2012) Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nat Med 18:883–891

Perelmuter VM, Manskikh VN (2012) Preniche as missing link of the metastatic niche concept explaining organ-preferential metastasis of malignant tumors and the type of metastatic disease. Biochemistry (Mosc) 77:111–118

Pietras K, Ostman A (2010) Hallmarks of cancer: interactions with the tumor stroma. Exp Cell Res 316:1324–1331

Pook M, Tamming L, Padarai K, Tiido T, Maimets T, Patarroyo M, Juronen E, Jaks V, Ingerpuu S (2014) Platelets store laminins 411/421 and 511/521 in compartments distinct from α- or dense granules and secrete these proteins via microvesicles. J Thomb Haemost 12:519–527

Qiang L, He YY (2014) Autophagy deficiency stabilizes TWIST1 to promote epithelial-mesenchymal transition. Autophagy 10:1864–1865

Qin Q, Xu Y, He T, Qin C, Xu J (2012) Normal and disease-related biological functions of Twist1 and underlying molecular mechanisms. Cell Res 22:90–106

Radziwon-Balicka A, Moncada de la Rosa C, Jurasz P (2012) Platelet-associated angiogenesis regulating factors: a pharmacological perspective. Can J Physiol Pharmacol 90:679–688

Rafii S, Lyden D (2006) S100 chemokines mediate bookmarking of premetastatic niches. Nat Cell Biol 8:1321–1323

Räsänen K, Vaheri A (2010) Activation of fibroblasts in cancer stroma. Exp Cell Res 316:2713–2722

Reichl P, Haider C, Grubinger M, Mikulits W (2012) TGF-β in epithelial to mesenchymal transition and metastasis of liver carcinoma. Curr Pharm Des 18:4135–4147

Reymond N, d'Agua BB, Ridley AJ (2013) Crossing the endothelial barrier during metastasis. Nat Rev Cancer 13:858–870

Ridge JA, Bading JR, Gelbard AS, Benua RS, Daly JM (1987) Perfusion of colorectal hepatic metastases. Relative distribution of flow form the hepatic artery and portal vein. Cancer 59:1547–1553

Riedl J, Pabinger I, Ay C (2014) Platelets in cancer and thrombosis. Hamostaseologie 34:54–62

Ruffell B, Affara NI, Coussens LM (2012) Differential macrophage programming in the tumor microenvironment. Trends Immunol 33:119–126

Sabrkhany S, Griffioen AW, Oude Egrbrink MG (2011) The role of blood platelets in tumor angiogenesis. Biochim Biophys Acta 1815:189–196

Schmid MC, Varner JA (2012) Myeloid cells in tumor inflammation. Vasc Cell 4:14

Serviss JT, Johnsson P, Grandér D (2014) An emerging role for long non-coding RNAs in cancer metastasis. Front Genet 5:234

Sharma D, Brummel-Ziedins KE, Bouchard BA, Holmes CE (2014) Platelets in tumor progression: a host factor that offers multiple potential targets in the treatment of cancer. J Cell Physiol 229:1005–1015

Shen et al (2010) http://www.ncbi.nlm.nih.gov/pubmed/20123990

Shen G, Lin Y, Yang X, Zhang J, Xu Z, Jia H (2014) MicroRNA-26b inhibits epithelial-mesenchymal transition in hepatocellular carcinoma by targeting USP9X. BMC Cancer 14:393

Shimizu S, Yamada N, Swada T, Ikeda K, Nakatani K, Seki S, Kaneda K, Hirakawa K (2000) Ultrastructure of early phase hepatic metastasis of human colon carcinoma cells with special reference to desmosomal junctions with hepatocytes. Pathol Int 50:953–959

Shirabe K, Mano Y, Muto J, Matono R, Motomura T, Toshima T, Takeishi K, Ichiyama H et al (2012) Role of tumor-associated macrophages in the progression of hepatocellular carcinoma. Surg Today 42:1–7

Smith HA, Kang Y (2013) The metastasis-promoting roles of tumor-associated immune cells. J Mol Med (Berl) 91:411–429

Standiford TJ, Kuick R, Bhan U, Chen J, Newstead M, Keshamouni VG (2011) TGF-β-induced IRAK-M expression in tumor-associated macrophages regulates lung tumor growth. Oncogene 30:2475–2484

Staudt ND, Jo M, Hu J, Bristow JM, Pizzo DP, Gaultier A, VandenBerg SR, Gonias SL (2013) Myeloid cell receptor LRP1/CD91 regulates monocyte recruitment and angiogenesis in tumors. Cancer Res 73:3902–3912

Strohmeyer T, Haugeberg G, Lierse W (1986) Vascularization of liver metastases: a corrosion cast study (in German). Acta Anat (Basel) 126:172–176

Strohmeyer T, Haugeberg G, Lierse W (1987) Angioarchitecture and blood supply of micro-and macrometastases in human livers. An anatomic-pathological investigation using injection-techniques. J Hepatol 4:181–189

Suh Y, Yoon CH, Kim RK, Lim EJ, Oh YS, Hwang SG, An S, Yoon G, Gye MC et al (2013) Claudin-1 induces epithelial-mesenchymal transition through activation of the c-Abl-ERK signaling pathway in human liver cells. Oncogene 32:4873–4882

Sun Y, Song GD, Sun N, Chen JQ, Yang SS (2014) Slug overexpression induces stemness and promotes hepatocellular carcinoma cell invasion and metastasis. Oncol Lett 7:1936–1940

Suzuki-Inoue (2011) http://www.ncbi.nlm.nih.gov/pubmed/21693546

Takagi et al (2013) http://www.ncbi.nlm.nih.gov/pubmed/23991201

Tao YM, Huang JL, Zeng S, Zhang S, Fan XG, Wang ZM, Yang XH, Yuan XH et al (2013) BTB/POZ domain-containing protein 7: epithelial-mesenchymal transition promoter and prognostic biomarker of hepatocellular carcinoma. Hepatology 57:2326–2337

Taube JH, Herschkowitz JI, Komurov K, Zhou AY, Gupta S, Yang J, Hartwell K, Onder TT et al (2010) Core epithelial-to-mesenchymal transition interactome gene-expression signature is associated with claudin-low and metaplastic breast cancer subtypes. Proc Natl Acad Sci U S A 107:15449–15454

Timar et al (2005) http://www.ncbi.nlm.nih.gov/pubmed/16138000

Tsuruo T, Fujita N (2008) Platelet aggregation in the formation of tumor metastasis. Proc Jpn Acad Ser B Phys Biol Sci 84:189–198

Tymoszuk P, Evens H, Marzola V, Wachowicz K, Wasmer MH, Datta S, Müller-Holzner E et al (2014) In situ proliferation contributes to accumulation of tumor-associated macrophages in spontaneous mammary tumors. Eur J Immunol 44:2247–2262

Udagawa T, Wood M (2010) Tumor-stromal cell interactions and opportunities for therapeutic intervention. Curr Opin Pharmacol 10:369–374

Umansky V, Sevko A (2013) Tumor microenvironment and myeloid-derived suppressor cells. Cancer Microenviron 6:169–177

Uraki S, Sugimoto K, Shiraki K, Tameda M, Inagaki Y, Ogura S, Kasai C, Nojiri K et al (2014) Human β-defensin-3 inhibits migration of colon cancer cells via downregulation of metastasis-associated 1 family, member 2 expression. Int J Oncol 45: 1059–1064

Valastyan S, Chang A, Benaich N, Reinhardt F, Weinberg RA (2010) Concurrent suppression of integrin alpha5, radixin, and RhoA phenocopies the effects of miR-31 on metastasis. Cancer Res 70:5147–5154

Valcarcel M, Arteta B, Jaureguibeitia A, Lopatregi A, Martinez I, Mendoza L, Muruzabal FJ et al (2008) Three-dimensional growth as multicellular spheroid activates the proangiogenic phenotype of colorectal carcinoma cells via LFA-1-dependent VEGF: implications on hepatic micrometastasis. J Transl Med 6:57

van der Bilt JD, Kranenburg O, Nijkamp MW, Smakman N, Veenendaal LM, Te Velde EA et al (2005) Ischemia/reperfusion accelerates the outgrowth of hepatic micrometastases in a highly standardized murine model. Hepatology 42:165–175

van der Bilt JD, Kranenburg O, Borren A, van Hillegersberg R, Borel Rinkes IH (2008) Ageing and hepatic steatosis exacerbate ischemia/reperfusion-accelerated outgrowth of colorectal micrometastases. Ann Surg Oncol 15:1392–1398

Van Overmeire E, Laoui D, Keirsse J, Bonelli S, Lahmar Q, Van Ginderachter JA (2014) STAT of the union: dynamics of distinct tumor-associated macrophage subsets governed by STAT1. Eur J Immunol 44:2238–2242

Varon and Shai (2009) http://www.ncbi.nlm.nih.gov/pubmed/20040277

Varon et al (2012) http://www.ncbi.nlm.nih.gov/pubmed/23026678

Verga-Gérard A, Porcherot M, Meyniel-Schicklin L, André P, Lotteau V, Perrin-Cocon L (2013) Hepatitis C virus/human interactome identifies SMURF2 and the viral protease as critical elements for the control of TGF-β signaling. FASEB J 27:4027–4040

Vidal-Vanaclocha F (2008) The prometastatic microenvironment of the liver. Cancer Microenviron 1:113–129

Vidal-Vanaclocha F (2011) The liver prometastatic reaction of cancer patients: implications for microenvironment-dependent colon cancer gene regulation. Cancer Microenviron 4:163–180

Voboril R (2005) Blood supply of metastatic liver tumors: an experimental study. Int Surg 90:71–77

Wang CA, Jedlicka P, Patrick AN, Micalizzi DS, Lemmer KC, Deitsch E, Casas-Selves M et al (2012a) SIX1 induces lymphangiogenesis and metastasis via upregulation of VEGF-C in mouse models of breast cancer. J Clin Invest 122:1895–1906

Wang C, Jiang K, Kang X, Gao D, Sun C, Li Y, Sun L, Zhang S, Liu X, Wu W, Yang P et al (2012b) Tumor-derived secretory clusterin induces epithelial-mesenchymal transition and facilitates hepatocellular carcinoma metastasis. Int J Biochem Cell Biol 44:2308–2320

Wang H, Wang HS, Zhou BH, Li CL, Zhang F, Wang XF, Zhang G, Bu XZ, Cai SH et al (2013a) Epithelial-mesenchymal transition (EMT) induced by TNF-α requires AKT/GSK-3β-mediated stabilization of snail in colorectal cancer. PLoS 8:e56664

Wang Z, Jiang Y, Guan D, Li J, Yin H, Pan Y, Xie D, Chen Y (2013b) Critical roles of p53 in epithelial-mesenchymal transition and metastasis of hepatocellular carcinoma cells. PLoS One 8, e72846

Wang XF, Wang HS, Zhang F, Guo Q, Wang H, Wang KF, Zhang G, Bu XZ, Cai SH, Du J (2014a) Nodal promotes the generation of M2-like macrophages and downregulates the expression of IL-12. Eur J Immunol 44:173–183

Wang SC, Lin XL, Li J, Zhang TT, Wang HY, Shi JW, Yang S, Zhao WT, Xie RY et al (2014b) MicroRNA-122 triggers mesenchymal-epithelial transition and suppresses hepatocellular carcinoma cell motility and invasion by targeting RhoA. PLoS One 9:e101330

Wang T, Jin Y, Zhao R, Wu Y, Zhang Y, Wu D, Kong D, Jin X, Zhang F (2014c) High load hepatitis B virus replication inhibits hepatocellular carcinoma cell metastasis through regulation of epithelial-mesenchymal transition. Int J Infect Dis 20:37–41

Wang J, Yu F, Jia X, Iwanowycz S, Wang Y, Huang S, Ai W, Fan D (2014d) MicroRNA-155 deficiency enhances the recruitment and functions of myeloid-derived suppressor cells in tumor microenvironment and promotes solid tumor growth. Int J Cancer. doi:10.1002/ijc.29151

Wernicke M, Roitman P, Manfre D, Stern R (2011) Breast cancer and the stromal factor. The "prometastatic healing process" hypothesis. Medicina (B Aires) 71:15–21

Winograd-Katz SE, Fässler R, Geiger B, Legate KR (2014) The integrin adhesome: from genes and proteins to human disease. Nat Rev Mol Cell Biol 15:273–288

Xia L, Huang W, Tian D, Zhang L, Qi X, Chen Z, Shang X, Nie Y, Wu K (2014) Forkhead box Q1 promotes hepatocellular carcinoma metastasis by transactivating ZEB2 and VersicanV1 expression. Hepatology 59:958–973

Xu ZY, Ding SM, Zhou L, Xie HY, Chen KJ, Zhang W, Xing CY, Guo HJ, Zheng SS (2012) FOXC1 contributes to microvascular invasion in primary

hepatocellular carcinoma via regulating epithelial-mesenchymal transition. Int J Biol Sci 8:1130–1141
Xu J, Li X, Yang H, Chang R, Kong C, Yang L (2013) SIN1 promotes invasion and metastasis of hepatocellular carcinoma by facilitating epithelial-mesenchymal transition. Cancer 119:2247–2257
Xu et al (2014) http://www.ncbi.nlm.nih.gov/pubmed/25072505
Yahalom J, Eldor A, Biran S, Fuks Z, Vlodavsky I (1985) Platelet-tumor cell interaction with the subendothelial extracellular matrix: relationship to cancer metastasis. Radiother Oncol 3:211–225
Yau WL, Lam CS, Ng L, Chow AK, Chan ST, Chan JY, Wo JY, Ng KT, Man K et al (2013) Over-expression of miR-106b promotes cell migration and metastasis in hepatocellular carcinoma by activating epithelial-mesenchymal transition process. PLoS One 8: e57882
Yi X, Luk JM, Lee NP, Peng J, Leng X, Guan XY, Lau GK, Beretta L, Fan ST (2008) Association of mortalin (HSPA9) with liver cancer metastasis and prediction for early tumor recurrence. Mol Cell Proteomics 7:315–325
Yuan JH, Yang F, Wang F, Ma JZ, Guo YJ, Tao QF, Liu F, Pan W, Wang TT et al (2014) A long noncoding RNA activated by TGF-β promotes the invasion-metastasis cascade in hepatocellular carcinoma. Cancer Cell 25:666–681
Zaidel-Bar R (2013) Cadherin adhesome at a glance. J Cell Sci 126:373–378
Zaidel-Bar R, Geiger B (2010) The switchable integrin adhesome. J Cell Sci 123:1385–1388
Zaidel-Bar R, Itzkovitz S, Ma'ayan A, Iyengar R, Geiger B (2007) Functional atlas of the integrin adhesome. Nat Cell Biol 9:858–867
Zhai X, Zhu H, Wang W, Zhang S, Zhang Y, Mao G (2014) Abnormal expression of EMT-related proteins, S100A4, vimentin and E-cadherin, is correlated with clinicopathological features and prognosis in HCC. Med Oncol 31:970
Zhang L, Sullivan PS, Goodman JC, Gunaratne PH, Marchetti D (2011) MicroRNA-1258 suppresses breast cancer brain metastasis by targeting heparanase. Cancer Res 71:645–654
Zhang LY, Liu M, Tang H (2013a) miR-490-3p modulates cell growth and epithelial to mesenchymal transition of hepatocellular carcinoma cells by targeting endoplasmic reticulum-Golgi intermediate compartment protein 3 (ERGIC3). J Biol Chem 288:4035–4047
Zhang Q, Bai X, Chen W, Ma T, Hu Q, Liang C, Xie S, Chen C, Hu L, Xu S, Liang T (2013b) Wnt/β-catenin signaling enhances hypoxia-induced epithelial-mesenchymal transition in hepatocellular carcinoma via crosstalk with hif-1α signaling. Carcinogenesis 34:962–973
Zhang L, Huang G, Li X, Zhang Y, Jiang Y, Shen J, Liu J, Wang Q, Zhu J, Feng X et al (2013c) Hypoxia induces epithelial-mesenchymal transition via activation of SNAI1 by hypoxia-inducible factor-1α in hepatocellular carcinoma. BMC Cancer 13:108
Zhang J, Zhang DL, Jiao XL, Dong Q (2013d) S100A4 regulates migration and invasion in hepatocellular carcinoma HepG2 cells via NF-kB-dependent MMP-9 signal. Eur Rev Med Pharmacol Sci 17:2372–2382
Zhang JX, Mai SJ, Huang XX, Wang FW, Liao YJ, Lin MC, Kung HF, Zeng YX et al (2014a) MiR-29c mediates epithelial-to-mesenchymal transition in human colorectal carcinoma metastasis via PTP4A and GNA13 regulation of β-catenin signaling. Ann Oncol 25:2196–2204
Zhang Y, Li T, Guo P, Kang J, Wie Q, Jia X, Zhao W, Huai W, Qiu Y, Sun L, Han L (2014b) MiR-424-5p reversed epithelial-mesenchymal transition of anchorage-independent HCC cells by directly targeting ICAT and suppressed HCC progression. Sci Rep 4:6248
Zhang JP, Zeng C, Xu L, Gong J, Fang JH, Zhuang SM (2014c) MicroRNA-148a suppresses the epithelial-mesenchymal transition and metastasis of hepatoma cells by targeting Met/Snail signaling. Oncogene 33:4069–4076
Zheng X, Gai X, Wu Z, Liu Q, Yao Y (2013) Metastasin leads to poor prognosis of hepatocellular carcinoma through partly inducing EMT. Oncol Rep 29:1811–1818
Zhou YM, Cao L, Li B, Zhang RX, Sui CJ, Yin ZF, Yang JM (2012) Clinicopathological significance of ZEB1 protein in patients with hepatocellular carcinoma. Ann Surg Oncol 19:1700–1706
Zhou Y, Li Y, Ye J, Jiang R, Yan H, Yang X, Liu Q, Zhang J (2013) MicroRNA-491 is involved in metastasis of hepatocellular carcinoma by inhibitions of matrix metalloproteinase and epithelial to mesenchymal transition. Liver Int 33:1271–1280
Zhu QS, Rosenblatt K, Huang KL, Lahat G, Brobey R, Bolshakov S, Nguyen T, Ding Z et al (2011a) Vimentin is a novel AKT1 target mediating motility and invasion. Oncogene 30:457–470
Zhu K, Dai Z, Pan Q, Wang Z, Yang GH, Yu L, Ding ZB, Shi GM, Ke AW, Yang XR et al (2011b) Metadherin promotes hepatocellular carcinoma metastasis through induction of epithelial-mesenchymal transition. Clin Cancer Res 17:7294–7302
Zhu P, Lv J, Yang Z, Guo L, Zhang L, Li M, Han W, Chen X, Zhuang H, Lu F (2014) Protocadherin 9 inhibits epithelial-mesenchymal transition and cell migration through activating GSK-3β in hepatocellular carcinoma. Biochem Biophys Res Commun 452:567–574
Zoccoli A, Iuliani M, Pantano F, Imperatori M, Intagliata S, Vincenzi B, Marchetti P et al (2012) Premetastatic niche: ready for new therapeutic interventions? Expert Opin Ther Targets 16(Suppl 2):S119–S129

Pathogenic Features of Liver Metastasis: The Complex Cancer Cell–Cancer Cell, and Cancer Cell–Microenvironment Interactomes

114

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_114

Abstract

In order to enter an invasive and metastatic cascade, cancer cells must be released and individualized. Cell budding is a process characterized by single cells or small clusters of cancer cells that leave the invasion front. These individualized cells are capable to invade blood vessels and lymph vessels, a process which requires cell motility, differential cell-matrix adhesion, production of invadopodia, and the secretion of lytic enzymes, including metalloproteinases. The invasion armamentarium of cancer cells is not only an inborn feature of these cells but is also modulated by nonneoplastic cells encountered by cancer cells on their invasive track. For example, stromal cell-derived factor 1/CXCL12 stimulates motility and migration of cancer cells that express the respective receptor, CXCR4. Apart from budding cells that are prone to become invasive cells, malignant neoplasms can release, already in early phases, cells that will evolve independent from the primary tumor. These so-called premalignant cells or circulating tumor cells (CTCs) have a fate of their own and possess a high degree of plasticity. There is evidence that such cells are capable to induce premetastatic niches in target organs and to generate a cancer field within the body. Along their metastatic spread and within the premetastatic niche, cancer cells can fuse with normal cell partners of the microenvironment, forming chimeras that play a role in the regulation of growth and epithelial-mesenchymal transition (EMT).

Tumor Cell Budding, Motility, and Invasion as Driving Forces for Liver Metastases

Tumor Cell Budding as a Mode of Tumor Cell Individualization

Colorectal Carcinoma (CRC) cells exert distinct growth patterns that affect disease progression and prognosis, in particular tumor cell budding at the invasive margin. Budding (or sprouting) is defined as small clusters of individualized and poorly differentiated carcinoma cells in or outside the invasion front. The presence of such dissociated, dedifferentiated tumor cells at the tumor-host interface is predictive of lymphatic involvement of CRC (Ogawa et al. 2009), lymphovascular invasion (also in early stage N0 CRC; Wang et al. 2009), predicts local and distant metastases (Nakamura et al. 2005; Zlobec et al. 2008; Suzuki et al. 2009), including lymph node metastasis (Yamauchi et al. 2008), and is correlated with an enhanced malignant potential in CRC (Okuyama et al. 2002; Prall 2007; Kanazawa et al. 2008). These budding cells have undergone epithelial-mesenchymal transition (EMT) and are growth-arrested due to increased expression of p16 and other mechanisms (Jung et al. 2001). Low cellular proliferation at the invasion front, the niche of budding cells, has been associated with poor prognosis in CRC (Palmqvist et al. 1999). Loss of expression of the adhesion molecule, E-cadherin, and APAF-1 were independent predictors of budding, and the loss was associated with more frequent peritumoral lymphocytes and tumor-infiltrating lymphocytes (Zlobec et al. 2007).

Motility, Migration, and Invasion of Tumor Cells: The Role of Invadopodia

The dissociation process of budding cells at the invasion front requires distinct modes of motility/cell locomotion linked to the tumor cells' cytoskeleton. Individualized cancer cells are capable to migrate through the extracellular matrix (ECM) and can form ECM-degrading, actin-rich ventral membrane protrusions called invadopodia, similar to the podosomes of macrophages. These dynamic organelle-like structures adhere to, and proteolytically digest, collagens, laminin, and fibronectin located in the ECM (Yamaguchi et al. 2006; Stylli et al. 2008).

The formation of invadopodia requires WAVE2 expression but seems to be independent of the tubulin system (Kikuchi and Takahashi

2008). In the regulation pathways programming the conversion between rounded and elongated modes of cancer cell movement, DOCK3, NEDD9, WAVE2, and ARHGAP22 are key factors regulating Rac and Rho signaling (Croft and Olson 2008). The formation of diverse types of lamellipode with actin reassembly at the leading edge requires the membrane transport of WAVE2. The membrane transport of WAVE2 requires the association between the constitutive complex of betaPIX and GIT1 with WAVE2 (Morimura et al. 2009) and a small GTPase, Rac1, the motor protein kinesin, and microtubules (the latter not of importance in invadopodia). The p21-activated kinase Pak1 is a downstream effector of Rac1 and binds to WAVE2 and is transported with WAVE2 to the leading edge by stimulation with hepatocyte growth factor. Concomitantly, phosphorylation of tubulin-bound stathmin/Op18 at serine 25 and serine 38, microtubule growth, and stathmin/Op18 binding to the kinesin-WAVE2 complex are induced (Takahashi and Suzuki 2009). The human ortholog of mammalian enabled (hMena), an actin regulatory phosphoprotein involved in the control of cell motility, is expressed at the invasion margin of CRC and here particularly in budding cells (Toyoda et al. 2009).

Immunohistochemical staining for the cytoskeletal component, beta(III)-tubulin, was evident in budding CRC cells, suggesting that changes in tubulin isotypes could modulate the invading activity of these cells (Portyanko et al. 2009). 14-3-3 sigma is frequently expressed in budding tumor cells in the invasive area, and overexpression of the protein modulates cell migration in the presence of the ECM protein, tenascin-C (Ide et al. 2007). As motile dissociated cancer cells (including budding/sprouting cells) with a decreased level of differentiation play a crucial role in carcinoma invasion, the actin remodeling system critically participating in the locomotion machinery is studied in cancer, including CRC. At the leading edge of migrating cells (lamellipodia and invadopodia), protrusive forces are developed by the assembly of F-actin filaments organized in dendritic array at the front and a more distal lamellar linear array. Production and remodeling of F-actin depends on several proteins acting in a highly orchestrated fashion. Tropomyosin markedly inhibits lamellipodium formation and facilitates the distal lamellar linear array, in that it competes with the actin nucleator, actin-related protein 2/3 (Arp2/3) during filament branching, and counteracts the effects of the neural Wiskott-Aldrich syndrome protein, N-WASP (Bugyi et al. 2010). Cortactin is an F-actin-binding protein that stabilizes F-actin networks and promotes actin polymerization by activating the Arp 2/3 complex. Overexpression of cortactin stimulates cell migration in cancer cells, and in CRC cells, cortactin interacts with the zona occludens-1(ZO-1) protein, and expression of this complex favors an invasive and spreading/metastasizing phenotype (Hirakawa et al. 2009). Actin-related protein 2 (Arp2) colocalizes with WAVE2 in CRC cells and this is correlated with liver metastasis (Iwaya et al. 2007). Two CARMIL (capping protein, Arp2/3, and myosin-I linker) family proteins exert important regulatory functions. CARMIL1 localizes to lamellipodia and macropinosomes, and loss of its function causes loss of lamellipodial actin, along with defects in protrusion, ruffling, and macropinocytosis. CARMIL2 colocalizes with vimentin, and loss of its function causes a distinct multipolar phenotype, associated with decreased levels of myosin-IIB (Liang et al. 2009). An important group of regulating factors are members of the TOCA family of F-BAR-containing proteins. These proteins bind to and remodel lipid bilayers in a clathrin-dependent manner via their conserved F-BAR domains and regulate actin dynamics via their N-WASP binding SH3 domains. In mammalian cells, TOCA1 is associated with N-WASP and WPS-1 directly or WAVE2 indirectly via ABI-1 (Giuliani et al. 2009). Generally, BAR (Bin-Amphiphysin-Rvs) domain proteins can sense membrane curvature and recruit actin to membranes. They are also critically involved in clathrin-mediated endocytosis, in which actin polymerization mediated by the Arp2/3 complex is essential for membrane tubulation and vesicle formation and fission. The tubulated membrane between the future endocytic vesicle and the plasma membrane seems to form

an arc upon scission of the endocytic vesicle, and the formation of this structure depends on arc sensing mediated by the RFC/F-BAR domain protein, FBP17 (Suetsugu 2009). In endocytosis, BAR proteins also interact with other components of the endocytic and cytoskeletal machinery, including the GTPase dynamin (which mediates vesicle fission), N-WASP (an Arp2/3 complex regulator), and synaptojanin (a phosphoinositide phosphatase). Three classes of BAR proteins have been defined, i.e., BAR, N-BAR, and F-Bar (Dawson et al. 2006).

Stromal Factors Exerting an Influence on Tumor Cell Migration and Invasion

CXCL12 (stromal cell-derived factor 1) is an important factor for the stimulation of cancer cell motility and migration. CXCL12 promotes motility in neoplastic cells that express the receptor, CXCR4 (Do Carmo et al. 2010). CXCL12+ tumor budding in CRC is a significant prognostic factor (Akishima-Fukasawa et al. 2009). CXCR4 is also known to enhance the proliferation of certain cancer cells via AKT and ERK-dependent pathways (Shen et al. 2010). The liver has high concentrations of CXCL12 (Kim et al. 2005) that could provide a specific homing target and promoting factor for CXCR4-expressing CRC cells. CXCL12 is a constitutively expressed chemokine which orchestrates a large array of functions. Six different isoforms exist in humans (α, β, γ, δ, ε, and ϕ), all differing in their C-terminal domain (Yu et al. 2006). CXCL12 binds to the receptor, CXCR4, which is transcriptionally regulated by HIF-1alpha and a constitutively activated EGFR variant, EGFRvIII (Rahimi et al. 2010). Angiogenesis is promoted by attraction of motile endothelial cells by CXCL12. The axis markedly affects the migration of tumor cells to metastatic sites, allowing cancer cells to access cellular niches expressing the CXCR4 receptor favoring cell survival and growth ("metastatic homing" of cancer cells; Murphy 2001; Burger and Kipps 2006; Dewan et al. 2006). In CRC, CXCR4 expression was found to increase the risk for recurrence, liver metastasis, and poor survival (Kim et al. 2005). The role of the microvascular bed in mechanisms of tumor cell spread surfaced in the observation that concomitant overexpression of CXCR4 and vascular endothelial growth factor (VEGF) in the tumors predicts early distant relapse in stage II-III CRC patients (Ottaiano et al. 2006).

Pathogenic Features of Liver Metastases: Dissemination and Evolution of Premalignant Cells (Circulating Tumor Cells, CTCs) and the "Wandering Field"/"Cancer Field" Hypotheses

In the previous paragraph, it was outlined that the settling of tumor cells and their progenitors at future metastatic sites requires the establishment of a premetastatic niche that permits circulating cells to home to tissues and to interact with the host organ (Sleeman 2012). On the other hand, the early metastatic process also requires that subpopulations of cells are released that are capable to home to a niche and to produce a metastatic growth. The capacity of tumor cells to escape from the primary tumor, individualize, migrate, invade, and spread to remote tissues was described as a phenomenon resembling Darwinian selection (Klein 2013). However, this may represent a simplistic view, as the so-called invasion and metastasis cascade does not seem to exactly work that way. Rather, there is recent evidence that tumor cells and particularly their progenitors (cancer stem cells) individualize and disseminate in very early and primordial malignant neoplasms already, having a still not well-studied status of "premalignant" cells (PMCs), single disseminated tumor cells (DTCs), or circulating tumor cells (CTCs) (Klein 2000; Diamond et al. 2012) that will evolve almost or completely independent from the primary tumor (Ansieau et al. 2008). These individualized cells have a fate of their own and possess a high degree of plasticity (Bednarz-Knoll et al. 2012). It is these PMCs that will acquire, by progressive genomic instability and

selection pressures, distinct genomic signatures, and these alterations will render PMCs capable to induce, and interact with, future premetastatic niches. In this setting, spread of cancer may be described by the features of a "wandering field hypothesis," meaning that PMCs and their induced premetastatic niches form a cancer field that is distributed within the host. The generation and distribution of tumor cells that can finally give rise to metastases in "field-like" body structure has been addressed by methods of systems biology, discussing selection-driven independence, invasion, and so-called swarm intelligence (Tarabichi et al. 2013).

Pathogenic Features of Liver Metastases: Parallel and Nonparallel Progression of Tumor and Metastases

Introduction

An older view of metastatic spread identified the primary tumor as the single important engine determining metastasis through the production and release of fully metastasis-capable cells. A second hypothesis, termed the parallel progression model (Klein 2009), proposes parallel, independent progression of metastases arising from early disseminated cells (single disseminated tumor cells (DTCs); see above). Clonal expansion mechanisms and a marked genetic disparity between primary tumors and disseminated tumor cells (Stoecklein and Klein 2010) support this hypothesis. Other findings were not compatible with the parallel progression model, but the linear progression model in this hypothesis works when it is assumed that tumors harbor two types of cells, i.e., metastasis-forming cells (MFCs), likely to derive from tumor stem cells, and a second set that is not capable to produce metastases. There is evidence that the proportion of MFCs decreases as a function of increasing tumor size, one possible explanation for the observation that at least part of large tumors have a lesser probability to produce metastases (review: Koscielny and Tubiana 2010).

Do Primary Tumors and Their Metastases Share a Parallel Evolution?

Animal experimentation had already shown that removal of a primary malignancy can be followed by rapid outgrowth of metastases. This observation illustrates that primary tumors might exert an effect on growth of their metastases and that primary tumor and metastases may not have parallel growth patterns. In human CRCs, resection of the primary tumor was associated with a modest increase in cancer cell proliferation of synchronous hepatic metastases and a significant decrease in metastatic tumor cell apoptosis. These findings suggest that primary tumors can inhibit growth of their metastases (Peeters et al. 2006).

Pathogenic Features of Liver Metastases: Tumor Self-seeding and Cross-seeding in Metastasis

Introduction

According to classical concepts, metastasis has been considered to be a unidirectional process, whereby cancer cells are released by, or actively emigrate from, the primary tumor and seed cells into lymph nodes and to remote organs. This pathogenetic view, oriented on a mode "as the river flows," has not been questioned for a long time. There is now evidence that metastasis is a multidirectional process, whereby cancer cells can not only seed to distant sites but also back to the primary tumor. The process of recolonizing of the primary tumor and its premetastatic niche is termed, tumor self-seeding. This hypothesis is based on the presence of tumor cell-supporting noncancerous cells not only in remote tissues but also in the primary tumor. The self-seeding model may answer many open questions regarding the complexity of the metastatic process (Norton and Massagué 2006; Norton 2008; Kim et al. 2009; reviews: Leung and Brugge 2009; Aguirre-Ghiso 2010; Hahnfeldt 2010; Norton 2011; Comen et al. 2011; Sleeman et al. 2011; Comen 2012; Comen and Norton 2012). In mice tumor models, it was shown that the self-seeding process can

select more aggressive cells involved in cancer progression (Kim et al. 2009). Circulating tumor cells were found to enhance primary tumor growth, probably through stromal paracrine effects (Hahnfeldt 2010).

Homing Mechanisms in Tumor Self-seeding

How are tumor cells attracted to reinfiltrate primary tumors? Circulating tumors studied in mice secrete factors ("seed-derived factors") that favor stromal recruitment and angiogenesis also in the primary lesion, including the chemokine CXCL1 (Kim et al. 2009). It has been shown that the protein chromogranin A inhibits the shedding of cancer cells into circulation from primary tumors, as well as the reinfiltration of primary tumors, via decreased vascular leakage in tumors and inhibition of transendothelial migration of cancer cells (Dondossola et al. 2012).

Pathogenic Features in Liver Metastases: Cell Clone Ecology Hypothesis

In the cell clone ecology hypothesis, it is assumed that the survival and fate of cell clones that behave like "parasites" in the organism and result in cancer are governed by the principles of ecology. The hypothesis is based on the concept that mutated and aneuploid cell clones undergoing progressive genomic instability are prone to degradation rather than becoming "successfully progressing clones," with an inherent risk to become extinct or enfeebled to become a benign condition. In order to establish a "fit" clone, the cells of a so-called transient clone must undergo cell-cell fusion (the cell fusion model of cancer progression and metastasis). Cell-cell fusion provides, according to this hypothesis, a sex-like mode of reproduction essential for an ecologically fit parasite organism, provides the opportunity required by tumors to rejuvenate cell lines containing abnormal and instable genomes, and serves to overcome erosion of telomeres during clone expansion (Parris 2006a, b).

Pathogenic Features in Liver Metastases: Cancer Cell-Normal Cell Fusion Theory of Metastasis

Introduction

Invasion and spread of cancer cells require an intricate interaction between the tumor cells and normal cells of their invaded tissue environment, involving complex patterns or mutual cross talk between tumor cells, stromal cells, and leukocytes (the so-called seed and soil theory; review : Mareel and Madani 2006). In this complex interplay, cells involved create close contacts through cell-to-cell adhesion and enter a complex interactomics (van der Bij et al. 2005). This may potentially lead to the secretion of factors involved in tumor-stromal interactions (e.g. the matricellular protein SPARC; Podhajcer et al. 2008) and mutual signaling via exchange of signaling substances between normal cells and tumor cells. For example, secreted activated leukocyte adhesion molecule (sALCAM) attenuates melanoma cell invasion (van Kilsdonk et al. 2008). Leukocytes infiltrating tumors facilitate dissemination in that they disrupt intercellular junctions and cell surface adhesion molecules (Man et al. 2011). Leukocytes in contact with tumor cells can create a premetastatic niche (Oppenheimer 2006), but they may also act as myeloid-derived suppressor cells (review: Nardin and Abastado 2008). Furthermore, information may be exchanged between stem cells and cancer cells via horizontal genomic transfer (large-scale transfer of DNA and chromatin; Glinsky 2005). This has been suggested for cancer cells expressing antigen of tumor-associated macrophages (TAMs) (Shabo and Svanvik 2011). However, there is evidence of a more intimate interaction between normal cells and cancer cells (Lagarde 1986). It has been found that macrophages and other bone marrow-derived cells can fuse with cancer cells forming heterologous

chimeras (Vignery 2005; Vignery 2008). Cell-to-cell fusion results in a complex sharing of several cellular features by the chimeras and the eventual emergence of novel types of behavior, including a metastatic phenotype (Lagarde and Kerbel 1985; Parris 2008). Somatic cell fusion is a potent source of genetic rearrangement leading to potentially metastatic cell variants (Larizza and Schirrmacher 1984; Carter 2008). In vitro fusion of a nonmetastatic tumor cell type with a bone marrow-derived macrophage results in the tumor cell's high metastatic capacity (Larizza et al. 1984a). In animal tumor xenograft models, this phenomenon was associated with tumor metastasis (review : Pawelek and Chakraborty 2008).

Macrophage-Tumor Cell Chimeras

It is known that diverse types of malignant neoplastic cells acquire distinct sets of macrophage properties, including morphological appearance, surface adhesion, phagocytosis, motile behavior, and membrane lipid composition (Huysentruyt et al. 2008). This phenomenon has led to the concept of "cancer as a macrophage-mediated autoaggressive disease" (Muntarova and Kovarik 1987). It has been observed that such features may be acquired through heterologous cell-to-cell hybridization (Kerbel et al. 1983; Lagarde and Kerbel 1985). Tumor cell fusion with leukocytes is a source of myeloid traits in cancer, including the acquisition of typical motile behaviors (Rachkovsky et al. 1998; Pawelek 2005). Also the distinct features of tumor-associated macrophages (TAMs) may be acquired by tumor cells via cell fusion (review: Pawelek et al. 2006). Fusion of melanoma cells with macrophages results in acquired melanocyte stimulating hormone-inducible chemotaxis in the tumor cells (Rachkovsky and Pawelek 1999). Macrophage-melanoma cell fusion-induced hybrids upregulate N-acetylglucosaminyltransferase V (beta 1,6-branching; Gnt-V) (Chakraborty et al. 2001), acquire specific motility patterns, are highly metastatic in vivo, and express macrophage-associated traits of increased Gnt-V (Chakraborty and Pawelek 2003; Chakraborty and Pawelek 2007). Gnt-V forms beta 1,6 branching on the trimannosyl terminus of N-glycans, causing the production of beta 1,6 Glc-NAc-bearing oligosaccharide, important for the adhesion and motile behavior of both normal granulocytes and tumor cells. In macrophage-melanoma cell hybrids, these oligosaccharides colocalize with coarse melanin granules (Rupani et al. 2004). It has been proposed that mechanisms allowing escape from the extracellular matrix are important for migration and invasion, and such escape strategies may be acquired through cell fusion (review: Parris 2006b). Macrophages are capable to fuse with epithelial cells of murine intestinal tumors, resulting in nuclear reprogramming with the expression of unique subsets of transcripts (Powell et al. 2011). There is suggestive evidence that the highly metastatic variant ESb of the T cell lymphoma Eb is derived from spontaneous fusion with a host macrophage (Larizza et al., 1984b). Leukocyte-cancer cell fusion might act as the initiator for the use of aerobic glycolysis as a metabolic energy source of cancer cells, the Warburg effect (Lazova et al. 2011).

Tumor Cell-Normal Cell Chimeras

Native or damaged tumor cells can fuse with nonneoplastic host cells, e.g., following irradiation (Wiener et al. 1974a; Ber et al. 1978). Heterospecifc chimeras are a mechanism for horizontal transmission of malignancy (Goldenberg 2012). Normal diploid cells fused to malignant neoplastic cells can suppress the malignant phenotype in the chimeras (Harris et al. 1969; Wiener et al. 1974b). On the other hand, murine melanoma–macrophage hybrids showed enhanced metastatic behavior (Rachkovsky et al. 1998). A fusion-induced alteration in the cell surface structure, involving N-glycosylation of membrane proteins mediated by N-acetylglucosaminyltransferase V, is involved in this mechanism (Sodi et al. 1998; Chakraborty et al. 2001).

Tumor Cell-Tumor Cell Chimeras

There is strong evidence that tumor cells can form hybrids/chimeras among each other by cell fusion. The capability to fuse is not restricted by the type of cell origin or cell lineages involved, in that epithelial cells can form somatic hybrids with mesenchymal cells or germ cell tumor cells (Peterson and Weiss 1972; Litwack and Croce 1979; Fortuna et al. 1989). Fusion of tumor cells, also in vivo, can alter the biological behavior of the cells and effect invasion and spread. Spontaneous fusion of two mouse tumor cell subpopulations resulted in a more aggressive tumor cell variant (Miller et al. 1989), in part with enhanced metastatic potential (Mi et al. 2012), but loss of malignancy of hybrids derived from two murine malignant cell lines has also been observed (Jami and Ritz 1975). A predominance of a metastatic phenotype has been observed in hybrids formed by fusion of mouse and human melanoma cells (van Golen et al. 1996). Certain oncogenic features expressed in tumor cell chimeras can behave in a switchable dominant manner (Zimmermann et al. 1981).

Fusion of Intact Cancer Cells with Cancer Cell Components

Cells can not only fuse with intact partner cells but also with parts of the partner cell body, e.g., organelles and plasma membrane vesicles. Fusion of plasma membrane vesicles from highly metastatic cancer cells affect arrest and metastasis of blood-borne tumor cells (Poste and Nicolson 1980). Fusion of plasma membrane vesicles from highly metastatic cancer cells with blood-borne tumor cells can modify the arrest and mestatatic behavior of the recipient cells (Poste and Nicolson 1980).

Stem Cell-Tumor Cell Chimeras

As a mechanism of pathogenesis of cancer it has long been hypothesized that cancer cells might arise from a hybrid cell which derives from normal somatic cell fusion but obtains a proliferative advantage (Qian 1993). On the other hand, it has been suggested that distinct features of stem cells can be transferred to tumor cells through cell fusion. According to this concept, cancer can result from a fusion between an "altered" premalignant cell and a bone marrow-derived stem cell, aneuploidy as a typical feature of tumor cells being the direct result of this fusion process. This model might explain striking similarities between stem cells and cancer cells (He et al. 2005).

Organelle Chimeras of Normal Cells

Through cell fusion, cells can uptake organelles from partner cells. The resulting organelle chimera is heteroplasmic (heteroplasmy). On a genomic level, heteroplasmy denotes a situation characterized by the presence of a mixture of more than one type of organelle genomes, mainly mitochondrial DNA and plastid DNA, within a cell or individual. However, the term heteroplasmy is most often employed to describe a distinct state of the mitochondrial genome. Mitochondrial heteroplasmy results from mutations in the mitochondrial genome, whereby microheteroplasmy with numerous independent mutations is normally found in organisms. There is evidence that the most dramatic effects of heteroplasmy on the fate of the chimeric cells are obtained in case of mitochondrial chimeras, which contain two or more sets of mitochondrial DNA (Hua et al. 2012). Very low-level heteroplasmy mitochondrial DNA variations are an inherited trait in humans (Guo et al. 2013). Normal mammalian cells can even be propagated after integration of organelles as foreign as those of plants, e.g., chloroplasts (Nass 1969).

Heterosis

Heterosis or hybrid vigor (synonym: outbreeding enhancement) denotes the phenomenon that hybrids of two genetically pure cell lines grow more rapidly or give rise to more cells than the

parental pure lines. The phenomenon of heterosis results in increased yield of cellular offspring and therefore increased biomass (Shull 1948; McDaniel and Sarkissian 1966; Baranwal et al. 2012; Groszmann et al. 2013). Effects of gene dosage imbalances play a significant role in heterosis. The underlying mechanisms seem to involve cumulative positive effects in the differential expression of sets of genes on yield-producing metabolic pathways (reviews: Kamb 2003; Baranwal et al. 2012). For a heterotic phenotype to occur, genetic and genomic studies have shown that gene expression in hybrids is regulated by the interactions of the two parental epigenetic systems and their genomes (review: Groszmann et al. 2013).

Cell Chimeras and Nuclear Alterations

Fusion of two contiguous tumor cells will increase the chromosome content of the resultant chimera, and this increase of ploidy could facilitate and heighten the inherent genomic instability of the lineage. This phenomenon has been observed as spontaneous fusion between metastatic mammary tumor subpopulations (Miller et al. 1988; review: Hart 1983). Murine fusion-derived hepatocytes showed ploidy reductions (Duncan et al. 2009).

Cancer Cell Chimeras and Cell Differentiation

Progression of cancer, including the establishment of a metastatic phenotype, depends on the proliferative status and the differentiation of the neoplastic cells. It is known that hybrid formation between cells affects differentiation of the fusion partners. In hybridization experiments using cells of defined and different histotypes, it turned out that both parental determinations are retained by hybrid cells and that parental differentiation modes are repressed only in a mutually exclusive fashion (Fougère and Weiss 1978). On the other hand, fusion of interspecific cells (rat and mouse) demonstrated that one specific function of one of the fusion partners can be expressed in the hybrid cells (Peterson and Weiss 1972). In hybrids between murine melanoma and teratocarcinoma cells, the formation of "supermelanotic chimeras" depends on the activation of genes involved in differentiation (Watanabe 1984).

Fusion of Human Cells with Cells of Nonhuman Organisms

It has been theorized that normal cells might acquire "dangerous" genetic information by integration of genetic information other than that of viruses. One hypothesis suggests that tumorigenic cells in part originate from fusions between normal human cells and bacteria, the fusion product termed "bactocytes" (Shaw 2003).

Pathogenic Features of Liver Metastases: Transfer of Cell-Free Genomic and Signaling Components Between Metastatic Cells and Between Normal Cells and Tumor Cells. An Extended Concept of Metastasis

Introduction

There is evidence that genetic and signaling information can spread from cancer cells to other cancer cells or normal, nontransformed cells (review: Garcia-Olmo et al. 2012). Through such mechanisms, metastasis of cancer has lived a conceptual extension from spread of malignant cells to spread and intracorporeal distribution of subcellular elements and components.

Exosomes

Exosomes are defined as small membrane-bound vesicles which cells can release into their microenvironment and from there to blood and lymph. The morphogenesis and biogenesis of exosomes involve a process of inward budding of membrane compartments into the lumen of late endosomes, followed by the fusion of the proto-multivesicular bodies

with the plasma membrane. The cargo of exosomes consists of noncoding RNAs (including microRNAs and onco-miRs), signaling substances, adhesion molecules, and lipids (Rak 2010; Ludwig and Giebel 2012). As exosomes carry and transport bioactive lipids, and are enriched in cholesterol and sphingolipids in comparison with their parental cells, exosomes can serve as structures mediating intercellular communication dependent on lipid signaling (Record et al. 2014). The transfer of this exosomal cargo may induce pathologic alterations at the exosomal terminals (so-called exosomopathies; Korc 2015). Circulating exosomes and their cargo can successfully be employed as molecular biomarkers for diagnosis, classification, and monitoring of various malignant neoplasms.

Circulating Nuclear DNA (fcDNA)

In cancers, release of intact nuclear DNA or of DNA fragments from cancer cells is a common phenomenon, due to ongoing decay of neoplastic cells and their nuclei caused by apoptosis and necrosis. This DNA enters circulation in the form of free circulating DNA (fcDNA; circulating nucleic acids in plasma and serum, CNAPS; Schwarzenbach et al. 2011; Garcia-Olmo and Garcia-Olmo 2012; Garcia-Olmo et al. 2012; Gonzalez-Masia et al. 2013). In addition to cancer cells, also normal cells and cells of benign tumor release fcDNA. Assessments of fcDNA can be used as diagnostic markers, molecular characterization of primary and metastatic tumors, and design of personalized therapies (Goessl 2003; Fleischhacker and Schidt 2010; Vlassov et al. 2010; Ulivi and Silvestrini 2013).

Circulating Nucleosomes (cNUCs)

Nucleosomes as complexes of nuclear DNA and histone proteins can be released as intact particles from stressed, dying, or dead cells, including cancer cells. In patients with various malignancies, plasma and serum concentrations of nucleosomes are frequently elevated (Gezer et al. 2013). This "nucleosomics" can serve as a biomarker, e.g., for the detection of colorectal cancer (Holdenrieder et al. 2014) and the prognostication in cancer patients undergoing chemotherapy (Stoetzer et al. 2012). Nucleosomes are released from cells stimulated intrinsically or extrinsically to undergo apoptotic cell death, but in certain cells, e.g., neutrophils, nucleosomes can also be released by an active secretion process (Holdenrieder et al. 2012). Increased circulating nucleosomes (cNUCs) are also detected in autoimmune diseases, psoriasis, sepsis, trauma, and situations of large tissue necrosis. As a vehicle for DNA, circulating nucleosomes in cancer patients can be employed similar to fcDNA for diagnostic and monitoring purposes (Holdenrieder et al. 2001; Holdenrieder et al. 2008, Holdenrieder and Stieber 2009; Stoetzer et al. 2012; Wittwer et al. 2013). Nucleosomes and in particular their histones can also form the cargo of exosomes. Interestingly, cancer patients show distinct posttranslational modifications, including trimethylated histone tails, of histones carried by exosomes (Gezer et al. 2012; Leszinski et al. 2012; Gezer and Holdenrieder 2014).

Circulating Mitochondrial DNA (ccfmtDNA)

Similar to nuclear DNA, also mtDNA can escape from damaged normal and cancer cells and enter circulation, either as free mtDNA or in the setting of mitochondria. Circulating mtDNA (circulating cell-free mtDNA, ccfmtDNA) increases with age and can act as so-called damage-associated molecular pattern (DAMP) agents and are considered to be a pathogenic component for a low-grade chronic inflammatory status occurring in elderly subjects, a condition termed "inflamm-aging" (review : Pinti et al. 2014). mtDNA can undergo characteristic mutational changes in various tumors. Circulating cancer-derived mutant mtDNA can therefore be used as a predictive biomarker in several neoplasms

(Ellinger et al. 2012; Uzawa et al. 2012; Yu 2012).

microRNAs (miRNAs) and Other Noncoding RNAs

Micro-RNAs play an important role in the pathogenesis of metastases, as they control the expression of stem cell molecules and molecules involved in invasion and spread (Nicoloso et al. 2009). All examined biological fluids in the body contain extracellular miRNAs that are nuclease resistant. In patients with cancer, neoplastic cells can release miRNA and via this mechanism transfer part of their molecular signature into the organism. In addition to represent a cancer marker, extracellular miRNA are considered molecules with an important cell-to-cell communication function (Turchinovich et al. 2013). Part of miRNAs released into the extracellular space enter blood and lymph circulation and thus become circulating miRNAs. As these miRNAs are highly stable, they are suitable as diagnostic cancer markers that can easily be detected and measured. Circulating miRNAs have now been utilized as markers for several solid neoplasms and hematologic malignancies (Zheng et al. 2013). In particular, plasma miRNA have been identified and evaluated for the early detection, monitoring, and outcome prediction of CRCs and their metastases (Giraldez et al. 2013; Luo et al. 2013; Kjersem et al. 2014). Certain species of miRNA are characteristic for CRCs, such as circulating miRNA-106a, −130b, −378, and −484 (Kjersem et al. 2014; Zanutto et al. 2014). MicroRNA signatures can discriminate between colorectal cancer recurrences to lymph nodes and liver and between CRC metastases and primary hepatic tumors (Drusco et al. 2014). Lymph node metastases of colorectal cancer express distinct patterns of long noncoding RNAs (lncRNAs) (Han et al. 2014), a phenomenon that might, similar to microRNAs, be transferred to remote areas in the body. Apart from microRNAs, other types of noncoding RNAs can be released into circulation, including small interfering RNA (Valiunas et al. 2015).

Exosome-Derived MicroRNAs (miRNAs)

Apart from miRNAs freely circulating in blood and lymph following their release from normal and cancer cells, miRNA can also travel in circulation as cargo located within exosomes (Camacho et al. 2013; Kosaka et al. 2013). Exosomal miRNAs (exomiRNAs) are thought to have a significant role in intercellular communication and transfer of specific signals, as circulating exomiRNA can be taken up by recipient cells to alter gene expression in these cells via RNA interference. This mechanism can induce several functional changes in recipient cells, including induction of pro-inflammatory cytokine expression (Mobergslien and Sioud 2014); exomiRNAs are increasingly employed as noninvasive biomarkers for diagnosing and screening of malignancies (Cazzoli et al. 2013).

References

Aguirre-Ghiso JA (2010) On the theory of tumor self-seeding: implications for metastasis progression in humans. Breast Cancer Res 12:304

Akishima-Fukasawa Y, Nakanishi Y, Ino Y, Moriya Y, Kanai Y, Hirohashi S (2009) Prognostic significance of CXCL12 expression in patients wirh colorectal carcinoma. Am J Clin Pathol 132:202–210

Ansieau S, Hinkal G, Thomas C, Bastid J, Puisieux A (2008) Early origin of cancer metastases. Dissemination and evolution of premalignant cells. Cell Cycle 7:3659–3663

Baranwal VK, Mikkilineni V, Zehr UB, Tyagi AK, Kapoor S (2012) Heterosis: emerging ideas about hybrid vigour. J Exp Bot 63:6309–6314

Bednarz-Knoll N, Alix-Panabières C, Pantel K (2012) Plasticity of disseminating cancer cells in patients with epithelial malignancies. Cancer Metastasis Rev 31:673–687

Ber R, Wiener F, Fenyö EM (1978) Proof of in vivo fusion of murine tumor cells with host cells by universal fusers. J Natl Cancer Inst 60:931–933

Bugyi B, Didry D, Carlier MF (2010) How tropomyosin regulates lamellipodial actin-based motility: a combined biochemical and reconstituted motility approach. EMBO J 29:14–26

Burger JA, Kipps TJ (2006) CXCR4: a key receptor in the crosstalk between tumor cells and the microenvironment. Blood 107:1761–1767

Camacho L, Guerrero P, Marchetti D (2013) MicroRNA and protein profiling of brain metastasis competent cell-derived exosomes. PLoS One 8, e73790

Carter A (2008) Cell fusion theory: can it explain what triggers metastasis? J Natl Cancer Inst 100:1279–1281

Cazzoli R, Buttitta F, Di Nicola M, Malatesta S, Marchetti A, Rom WN, Pass HI (2013) microRNAs derived from circulating exosomes as noninvasive biomarkers for screening and diagnosing lung cancer. J Thorac Oncol 8:1156–1162

Chakraborty AK, Pawelek JM (2003) GnT-V, macrophage and cancer metastasis: a common link. Clin Exp Metastasis 20:365–373

Chakraborty AK, Pawlek J (2007) Beta 1,6-branched oligosaccharides regulate melanin content and motility in macrophage-melanoma fusion hybrids. Melanoma Res 17:9–16

Chakraborty AK, Pawelek J, Ikeda Y, Miyoshi E, Kolesnikova N, Funasaka Y, Ichichhashi M et al (2001) Fusion hybrids with macrophage and melanoma cells up-regulate N-acetylglucosaminyltransferase V, beta1-6 branching, and metastasis. Cell Growth Differ 12:623–630

Comen EA (2012) Tracking the seed and tending the soil: evolving concepts in metastatic breast cancer. Discov Med 14:97–104

Comen E, Norton L (2012) Self-seeding in cancer. Recent Results Cancer Res 195:13–23

Comen E, Norton L, Massagué J (2011) Clinical implications of cancer self-seeding. Nat Rev Clin Oncol 8:369–377

Croft DR, Olson MF (2008) Regulating the conversion between rounded and elongated modes of cancer cell movement. Cancer Cell 14:349–351

Dawson JC, Legg JA, Machesky LM (2006) Bar domain proteins: a role in tubulation, scission and actin assembly in clathrin-mediated endocytosis. Trends Cell Biol 16:493–498

Dewan MZ, Ahmed S, Iwasaki Y, Ohba K, Toi M, Yamamoto N (2006) Stromal cell-derived factor-1 and CXCR4 receptor interaction in tumor growth and metastasis of breast cancer. Biomed Pharmacother 60:273–276

Diamond E, Lee GY, Akhtar NH, Kirby BJ, Giannakakou P, Tagawa ST, Nanus DM (2012) isolation and characterization of circulating tumor cells in prostate cancer. Front Oncol 2:131

Do Carmo A, Patricio I, Cruz MT, Cavalheiro H, Oliveira CR, Lopes MC (2010) CXCL12/CXCR4 promotes motility and proliferation of glioma cells. Cancer Biol Ther 9:56–65

Dondossola E, Crippa L, Colombo B, Ferrero E, Corti A (2012) Chromogranin A regulates tumor self-seeding and dissemination. Cancer Res 72:449–459

Drusco A, Nuovo GJ, Zanesi N, Di leva G, Pichiorri F, Volinia S, Fernandez C, Antenucci A, Costinean S et al (2014) MicroRNA profiles discriminate among colon cancer metastasis. PLoS One 9:e96670

Duncan AW, Hickey RD, Paulk NK, Culberson AJ, Olson SB, Finegold MJ, Grompe M (2009) Ploidy reductions in murine fusion-derived hepatocytes. PLoS Genet 5, e1000385

Ellinger J, Müller DC, Müller DC, Hauser S, Heukamp LC, von Ruecker A, Bastian PJ et al (2012) Circulating mitpchondrial DNA in serum: a universal diagnostic biomarker for patients with urological malignanices. Urol Oncol 30:509–515

Fleischhacker M, Schmidt B (2010) Free circulating nucleic acids in plasma and serum (CNAPS) – useful fort he detection of lung cancer patients? Cancer Biomark 6:211–219

Fortuna MB, Dewey MJ, Furmanski P (1989) Cell fusion in tumor development and progression: occurrence of cell fusion in primary methycholanthrene-induced tumorigenesis. Int J Cancer 44:731–737

Fougère C, Weiss MC (1978) Phenotypic exclusion in mouse melanoma-rat hepatoma hybrid cells: pigment and albumin production are not reexpressed simultaneously. Cell 15:843–854

Garcia-Olmo DC, Garcia-Olmo D (2012) Circulating nucleic acids in plasma and serum: an intriguing phenomenon. Expert Opin Biol Ther 12(suppl 1):S1–S2

Garcia-Olmo DC, Picazo MG, Garcia-Olmo D (2012) Transformation of non-tumor host cells during tumor progression: theories and evidence. Expert Opin Biol Ther 12(suppl 1):S199–S207

Gezer U, Holdenrieder S (2014) Post-translational histone modifications in circulating nucleosomes as new biomarkers in colorectal cancer. In Vivo 28:287–292

Gezer U, Mert U, Ozgür E, Yörüker EE, Holdenrieder S, Dalay N (2012) Correlation of histone methyl marks with circulating nucleosomes in blood plasma of cancer patients. Oncol Lett 3:1095–1098

Gezer U, Ustek D, Yörüker EE, Cakiris A, Abaci N, Leszinski G, Dalay N, Holderieder S (2013) Characterization of H3K9me3- and H4K20me3-associated circulating nucleosomal DNA by high-throughput sequencing in colorectal cancer. Tumour Biol 34:329–336

Giraldez MD, Lozano JJ, Ramirez G, Hijona E, Bujanda L, Castells A, Gironella M (2013) Circulating microRNAs as biomarkers of colorectal cancer: results from a genome-wide profiling and validation study. Clin Gastroenterol Hepatol 11:681–688

Giuliani C, Troglio F, Bai Z, Patel FB, Zucconi A, Malabarba MG, Disanza A, Stradal TB et al (2009) Requirements for F-BAR proteins TOCA-1 and TOCA-2 in actin dynamics and membrane trafficking during caenorhabditis elegans oocyte growth and embryonic epidermal morphogenesis. PLoS Genet 5(10):E1000675

Glinsky GV (2005) Death-from-cancer signatures and stem cell contribution to metastatic cancer. Cell Cycle 4:1171–1175

Goessl C (2003) Diagnostic potential of circulating nucleic acids for oncology. Expert Rev Mol Diagn 3:431–442

Goldenberg DM (2012) Horizontal transmission of malignancy by cell-cell fusion. Expert Opin Biol Ther 12(suppl 1):S133–S139

Gonzalez-Masia JA, Garcia-Olmo D, Garcia-Olmo DC (2013) Circulating nucleic acids in plasma and serum

(CNAPS): applications in oncology. Onco Targets Ther 6:819–832
Groszmann M, Greaves IK, Fujimoto R, Peacock WJ, Denis ES (2013) The role of epigenetics in hybrid vigour. Trends Genet 29:684–690
Guo Y, Li CI, Sheng Q, Winther JF, Cai Q, Boice JD, Shyr Y (2013) Very low-level heteroplasmy mtDNA variations are inherited in humans. J Genet Genomics 40:607–615
Hahnfeldt P (2010) Significance of tumor self-seeding as an augmentation to the classic metastasis paradigm. Future Oncol 6:681–685
Han J, Rong LF, Shi CB, Dong XG, Wang J, Wang BL, Wen H, He ZY (2014) Screening of lymph nodes metastasis associated lncRNAs in colorectal cancer patients. World J Gastroenterol 20:8139–8150
Harris H, Miller OJ, Klein G, Worst P, Tachibana T (1969) Suppression of malignancy by cell fusion. Nature 223:363–368
Hart IR (1983) Tumor cell hybridization and neoplastic progression. Symp Fundam Cancer Res 36:133–143
He X, Tsang TC, Pipes BL, Ablin RJ, Harris DT (2005) A stem cell fusion model of carcinogenesis. J Exp Ther Oncol 5:101–109
Hirakawa H, Shibata K, Nakayama T (2009) Localization of cortactin is associated with colorectal cancer development. Int J Oncol 35:1271–1276
Holdenrieder S, Stieber P (2009) Clinical use of circulating nucleosomes. Crit Rev Clin Lab Sci 46:1–24
Holdenrieder S, Stieber P, Bodenmüller H, Busch M, Fertig G, Fürst H, Schalhorn A et al (2001) Nucleosomes in serum of patients with benign and malignant diseases. Int J Cancer 95:114–120
Holdenrieder S, Nagel D, Schalhorn A, Heinemann V, Wilkowski R, von Pawel J, Raith H et al (2008) Clinical relevance of circulating nucleosomes in cancer. Ann NY, Acad Sci 1137:180–189
Holdenrieder S, Kolligs FT, Braess J, Manukyan D, Stieber P (2012) Nature and dynamics of nucleosome release from neoplastic and non-neoplastic cells. Anticancer Res 32:2179–2183
Holdenrieder S, Dharuman Y, Standop J, Trimpop N, Herzog M, Hettwer K, Simon K, Uhlig S, Micallef J (2014) Novel serum nucleosomics biomarkers for the detection of colorectal cancer. Anticancer Res 34:2357–2362
Hua S, Lu C, Song Y, Li R, Liu X, Quan F, Wang Y, Liu J, Su F, Zhang Y (2012) High levels of mitochondrial heteroplasmy modify the development of ovine-bovine interspecies nuclear transferred embryos. Reprod Fertil Dev 24:501–509
Huysentruyt LC, Mukherjee P, Banerjee D, Shelton LM, Seyfried TN (2008) Metastatic cancer cells with macrophage properties: evidence from a new murine tumor model. Int J Cancer 123:73–84
Ide M, Saito K, Tsutsumi S, Tsuboi K, Yamaguchi S, Asao T, Kuwano H, Nakajima T (2007) Overexpression of 14-3-3sigma in budding colorectal cancer cells modulates cell migration in the presence of tenascin-C. Oncol Rep 18:1451–1456
Iwaya K, Oikawa K, Semba S, Tsuchiya B, Mukai Y, Otsubo T, Nagao T, Izumi M, Kuroda M et al (2007) Correlation between liver metastasis of the cololocalization of actin-related protein 2 and 3 complex and WAVE2 in colorectal carcinoma. Cancer Sci 98:992–999
Jami J, Ritz E (1975) Nonmalignancy of hybrids derived from two mouse malignant cells. II. Analysis of malignancy of LM (TK-) CI 1D parental cells. J Natl Cancer Inst 54:117–122
Jung A, Schrauder M, Oswald U, Knoll C, Sellberg P, Palmqvist R, Niedobitek G, Brabletz T, Kirchner T (2001) The invasion front of human colorectal adenocarcinomas shows co-localization of nuclear β-catenin, cyclin D1, and p16INK4A and is a region of low proliferation. Am J Pathol 159:1613–1617
Kamb A (2003) Consequences of nonadaptive alterations in cancer. Mol Biol Cell 14:2201–2205
Kanazawa H, Mitomi H, Nishiyama Y, Kishimoto I, Fukui N, Nakamura T, Watanabe M (2008) Tumour budding at invasive margins and outcome in colorectal cancer. Colorectal Dis 10:41–47
Kerbel RS, Lagarde AE, Dennis JW, Donaghue TP (1983) Spontaneous fusion in vivo between normal host and tumor cells: possible contribution to tumor progression and metastasis studied with a lectin-resistant mutant tumor. Mol Cell Biol 3:523–538
Kikuchi K, Takahashi K (2008) WAVE2-and microtubule-dependent formation of long protrusions and invasion of cancer cells cultured on three-dimensional extracellular matrices. Cancer Sci 99:2252–2259
Kim J, Takeuchi H, Lam ST, Turner RR, Wang HJ, Kuo C, Foshag L, Bilchik AJ, Hoon DS (2005) Chemokine receptor CXCR4 expression in colorectal cancer patients increases the risk for recurrence and for poor survival. J Clin Oncol 23:2744–2753
Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, Massagué J (2009) Tumor self-seeding by circulating cancer cells. Cell 139:1315–1326
Kjersem JB, Ikdahl T, Lingiaerde OC, Guren T, Tveit KM, Kure EH (2014) Plasma microRNAs predicting clinical outcome in metastatic colorectal cancer patients receiving first-line oxaliplatin-based treatment. Mol Oncol 8:56–67
Klein CA (2000) The biology and analysis of single disseminated tumour cells. Trends Cell Biol 10:489–493
Klein CA (2009) Parallel progression of primary tumours and metastases. Nat Rev Cacner 9:302–312
Klein CA (2013) Selection and adaptation during metastatic cancer progression. Nature 501:365–372
Korc M (2015) Pancreatic cancer-associated diabetes is an "exosomopathy". Clin. Cancer Res pii: clincanres.2990.2014
Kosaka N, Yoshioka Y, Hagiwara K, Tominaga N, Katsuga T, Ochiya T (2013) Trash and treasure: extracellular microRNAs and cell-to-cell communication. Front Genet 4:173

Koscielny S, Tubiana M (2010) Parallel progression of tumour and metastases. Nat Rev Cancer 10:156

Lagarde AE (1986) Sporadic somatic fusion between MDAY-D2 murine tumor cells and DBA/2 host cells: role in metastasis. Int J Cancer 37:905–910

Lagarde AE, Kerbel RS (1985) Somatic cell hybridization in vivo and in vitro in relation to the metastatic phenotype. Biochim Biophys Acta 823:81–110

Larizza L, Schirrmacher V (1984) Somatic cell fusion as a source of genetic rearrangement leading to metastatic variants. Cancer Metastasis Rev 3:193–222

Larizza L, Schirrmacher V, Pflüger E (1984a) Acquisition of high metastatic capacity after in vitro fusion of a nonmetastatic tumor line with a bone marrow-derived macrophage. J Exp Med 160:1579–1584

Larizza L, Schirrmacher V, Graf L, Pflüger E, Peres-Martinez M, Stöhr M (1984b) Suggestive evidence that the highly metastatic variant ESb of the T-cell lymphoma Eb is derived from spontaneous fusion with a host macrophage. Int J Cancer 34:699–707

Lazova R, Chakraborty A, Pawelek JM (2011) Leukocyte-cancer cell fusion: initiator of the Warburg effect in malignancy? Adv Exp Med Biol 714:151–172

Leszinski G, Gezer U, Siegele B, Stoetzer O, Holdenrieder S (2012) Relevance of histone marks H3K9me3 and H4K20me3 in cancer. Anticancer Res 32:2199–2205

Leung CT, Brugge JS (2009) Tumor self-seeding: bidirectional flow of tumor cells. Cell 139:1226–128

Liang Y, Niederstrasser H, Edwards M, Jackson CE, Cooper JA (2009) Distinct roles for CARMIL isoforms in cell migration. Mol Biol Cell 20:5290–5305

Litwack G, Croce CM (1979) Somatic cell hybrids between totipotent mouse teratocarcinoma and rat hepatoma cells. J Cell Physiol 101:1–8

Ludwig AK, Giebel B (2012) Exosomes: small vesicles participating in intercellular communication. Int J Biochem Cell Biol 44:11–15

Luo X, Stock C, Burwinkel B, Brenner H (2013) Identification and evaluation of plasma microRNAs for early detection of colorectal cancer. PLoS One 8, e62880

Man YG, Mason J, Harley R, Kim YH, Zhu K, Gardner WA (2011) Leukocyte-mediated cell dissemination and metastasis: findings from multiple types of human tumors. J Cell Biochem 112:1154–1167

Mareel M, Madani I (2006) Tumour-associated host cells participating at invasion and metastasis: targets for therapy ? Acta Chir Belg 106:635–640

McDaniel RG, Sarkissian IV (1966) Heterosis: complementation by mitochondria. Science 152:1640–1642

Mi R, Pan C, Bian X, Song L, Tian W, Cao F, Yin J, Peng H, Ma J (2012) Fusion between tumor cells enhances melanoma metastatic potential. J Cancer Res Clin Oncol 138:1651–1658

Miller FR, McInerney D, Rogers C, Miller BE (1988) Spontaneous fusion between metastatic mammary tumor subpopulations. J Cell Biochem 36:129–136

Miller FR, Mohamed AN, McEachern D (1989) Production of a more aggressive tumor cell variant by spontaneous fusion of two mouse tumor subpopulations. Cancer Res 49:4316–4321

Mobergslien A, Sioud M (2014) Exosome-derived miRNAs and cellular miRNAs activate innate immunity. J Innate Immun 6:105–110

Morimura S, Suzuki K, Takahashi K (2009) BetaPIX and GIT1 regulate HGF-induced lamellipodia formation and WAVE2 transport. Biochem Biophys Res Commun 382:614–619

Muntarova M, Kovalik J (1987) Is cancer a macrophage-mediated autoaggressive disease? Lancet 1:952–954

Murphy PM (2001) Chemokines and the molecular basis of cancer metastasis. N Engl J Med 345:833–835

Nakamura T, Mitomi H, Kikuchi S, Ohtani Y, Sato K (2005) Evaluation of the usefulness of tumor budding on the prediction of metastasis to the lung and liver after curative excision of colorectal cancer. Hepatogastroenterology 52:1432–1435

Nardin A, Abastado JP (2008) Macrophages and cancer. Front Biosci 13:3494–3505

Nass MM (1969) Uptake of isolated chloroplasts by mammalian cells. Science 165:1128–1131

Nicoloso MS, Spizzo R, Shimizu M, Rossi S, Calin GA (2009) MicroRNAs – the micro steering wheel of tumour metastases. Nat Rev Cancer 9:293–302

Norton L (2008) Cancer stem cells, self-seeding, and decremented exponential growth: theoretical and clinical implications. Breast Dis 29:27–36

Norton L (2011) Tumor self-seeding in breast cancer. Clin Adv Hematol Oncol 9:541–542

Norton L, Massagué J (2006) Is cancer a disease of self-seeding? Nat Med 12:875–878

Ogawa T, Yoshida T, Tsuruta T, Tokuyama W, Adachi S, Kikuchi M, Mikami T, Saigenji K, Okayasu I (2009) Tumor budding is predicitive of lymphatic involvement and lymph node metastases in submucosal invasive colorectal adenocarcinomas and in non-polypoid compared with polypoid growths. Scand J Gastroenterol 44:605–614

Okuyama T, Oya M, Yamaguchi M (2002) Budding (sprouting) as a useful prognostic marker in colorectal mucinous carcinoma. Jpn J Clin Oncol 32:412–416

Oppenheimer SB (2006) Cellular basis of cancer metastasis: a review of fundamentals and new advances. Acta Histochem 108:327–334

Ottaiano A, Franco R, Aiello Talamanca A, Liguori G, Tatangelo F, Delrio P, Nasti G et al (2006) Overexpression of both CXC chemokine receptor 4 and vascular endothelial growth factor proteins predicts early distant relapse in stage II-III colorectal cancer patients. Clin Cancer Res 12:2795–2803

Palmqvist R, Sellberg P, Oberg A, Tavelin B, Rutegard JN, Stenling R (1999) Low tumour cell proliferation at the invasive margin is associated with a poor prognosis in Dukes' stage B colorectal cancers. Br J Cancer 79:577–581

Parris G (2006a) The cell clone hypothesis and the cell fusion model of cancer progression and metastasis: history and experimental support. Med Hypotheses 66:76–83

Parris G (2006b) The cell clone ecology hypothesis and the cell fusion model of cancer progression and metastasis (II): three pathways for spontaneous cell-cell fusion and escape from the intercellular matrix. Med Hypotheses 67:172–176

Parris GE (2008) Cell-cell fusion is the rate-limiting step in causation and progression of clinically significant cancers. Cancer Genet Cytogenet 185:113

Pawelek JM (2005) Tumour-cell fusion as a source of myeloid traits in cancer. Lancet Oncol 6:988–993

Pawelek JM, Chakraborty AK (2008) The cancer cell-leukocyte fusion theory of metastasis. Adv Cancer Res 101:397–444

Pawelek J, Chakraborty A, Lazova R, Yilmaz Y, Cooper D, Brash D, Handerson T (2006) Co-opting macrophage traits in cancer progression: a consequence of tumor cell fusion? Contrib Microbiol 13:138–155

Peeters CF, de Waal RM, Wobbes T, Westphal JR, Ruers TJ (2006) Outgrowth of human liver metastases after resection of the primary colorectal tumor: a shift in the balance between apoptosis and proliferation. Int J Cancer 119:1249–1253

Peterson JA, Weiss MC (1972) Expression of differentiated functions in hepatoma cell hybrids: induction of mouse albumin production in rat hepatoma-mouse fibroblasts hybrids. Proc Natl Acad Sci U S A 69:571–575

Pinti M, Cevenini E, Nasi M, De Biasi S, Salvioli S, Monti D, Benatti S, Gibellini L, Cotichini R et al (2014) Circulating mitochondrial DNA increases with age and is a familiar trait: implications for "inflamm-aging". Eur J Immunol 44:1552–1562

Podhajcer OL, Benedetti L, Girotti MR, Prada F, Salvatierra E, Llera AS (2008) The role of the matricellular protein SPARC in the dynamic interaction between the tumor and the host. Cancer Metastasis Rev 27:523–537

Portyanko A, Kovalev P, Gorgun J, Cherstvoy E (2009) Beta(III)-tubulin at the invasive margin of colorectal cancer: possible link to invasion. Vorchows Arch 454:541–548

Poste G, Nicolson GL (1980) Arrest and metastasis of blood-borne tumor cells are modified by fusion of plasma membrane vesicles from highly metastatic cells. Proc Natl Acad Sci U S A 77:399–403

Powell AA, Anderson EC, Davies PS, Silk AD, Pelz C, Impey S, Wong MH (2011) Fusion between intestinal epithelial cells and macrophages in a cancer context results in nuclear reprogramming. Cancer Res 71:1497–1505

Prall F (2007) Tumour budding in colorectal carcinoma. Histopathology 50:151–162

Qian LW (1993) A hypothesis on the pathogenesis of cancer: cancer might arise following an event of normal somatic cell fusing. Med Hypotheses 41:521–524

Rachkovsky M, Pawelek J (1999) Acquired melanocyte stimulating hormone-inducible chemotaxis following macrophage fusion with Cloudman S91 melanoma cells. Cell Growth Differ 10:517–524

Rachkovsky M, Sodi S, Chakraborty A, Avissar Y, Bolognia J, McNiff JM, Platt J, Bermudes D et al (1998) Melanoma x macrophage hybrids with enhanced metastatic potential. Clin Exp Metastasis 16:299–312

Rahimi M, George J, Tang C (2010) EGFR variant-mediated invasion by enhanced CXCR4 expression through transcriptional and post-transcriptional mechanisms. Int J Cancer 126:1850–1860

Rak J (2010) Microparticles in cancer. Semin Thromb Hemost 36:888–906

Record et al. (2014). http://www.ncbi.nlm.nih.gov/pubmed/24140720

Rupani R, Handerson T, Pawelek J (2004) Co-localization of beta 1,6-branched oligosaccharides and coarse melanin in macrophage-melanoma fusion hybrids and human melanoma cells in vitro. Pigment Cell Res 17:281–288

Schwarzenbach H, Hoon DS, Pantel K (2011) Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer 11:426–437

Shabo I, Svanvik J (2011) Expression of macrophage antigens by tumor cells. Adv Exp Med Biol 714:141–150

Shaw A (2003) Bactocytes: a new cancer hypothesis. Med Hypotheses 60:739–741

Shen X, Arunyan A, Jackson D, Thomas RM, Lowy AM, Kim J (2010) Chemokine receptor CXCR4 enhances proliferation in pancreatic cancer cells through AKT and ERK dependent pathways. Pancreas 39:81–87

Shull GH (1948) What is "heterosis"? Genetics 33:439–446

Sleeman JP (2012) The metastatic niche and stromal progression. Cancer Metastasis Rev 31:429–440

Sleeman JP, Nazarenko I, Thiele W (2011) Do all roads lead to Rome? Routes to metastasis development. Int J Cancer 128:2511–2526

Sodi SA, Chakraborty AK, Platt JT, Kolesnikova N, Rosemblat S, Keh-Yen A, Bolognia JL et al (1998) Melanoma x macrophage fusion hybrids acquire increased melanogenesis and metastatic potential: altered N-glycosylation as an underlying mechanism. Pigment Cell Res 11:299–309

Stoecklein NH, Klein CA (2010) Genetic disparity between primary tumours, disseminated tumour cells, and manifest metastasis. Int J Cancer 126:589–598

Stoetzer OJ, Wittwer C, Lehner J, Fahmueller YN, Kohles N, Fersching DM, Leszinski G et al (2012) Circulating nucleosomes and biomarkers of immunogenic cell death as predictive and prognostic markers in cancer patients undergoing cytotoxic therapy. Expert Opin Biol Ther 12(suppl 1):S217–S224

Stylli et al. (2008). http://www.ncbi.nlm.nih.gov/pubmed/1118468901

Suetsugu S (2009) The direction of actin polymerization for vesicle fission suggested from membranes tubulated by the EFC/F-BAR domain protein FBP17. FEBS Lett 583:3401–3404

Suzuki A, Togasht K, Nokubi M, Koinuma K, Miyakura Y, Horie H, Lefor AT, Yasuda Y (2009) Evaluation of venous invasion by Elastica van Gieson stain and tumor budding predicts local and distant metastases in patients with T1 stage colorectal cancer. Am J Surg Pathol 33:1601–1607

Takahashi K, Suzuki K (2009) Membrane transport of WAVE2 and lamellipodia formation require Pak1 that mediates phosphorylation and recruitment of stathmin/Op18 to Pak1-WAVE2-kinesin complex. Cell Signal 21:695–703

Tarabichi M, Antoniou A, Saiselet M, Pita JM, Andry G, Dumont JE, Detours V, Maenhaut C (2013) Systems biology of cancer: entropy, disorder, and selection-drive evolution to independence, invasion and "swarm intelligence". Cancer Metastasis Rev 32:403–421

Toyoda A, Kawana H, Azuhata K, Yu J, Omata A, Kishi H, Higashi M, Harigaya K (2009) Aberrant expression of human ortholog of mammalian enabled (hMena) in human colorectal carcinomas: implications for its role in tumor progression. Int J Oncol 34:53–60

Turchinovich A, Samatov TR, Tonevitsky AG, Burwinkel B (2013) Circulating miRNAs: cell-cell communication function ? Front Genet 4:119

Ulivi P, Silvestrini R (2013) Role of quantitative and qualitative characteristics of free circulating DNA in the management of patients with non-small cell lung cancer. Cell Oncol (Dordr) 36:439–448

Uzawa K, Baba T, Uchida F, Yamatoji M, Kasamatsu A, Sakamoto Y, Ogawara K et al (2012) Circulating tumor-derived mutant mitochondrial DNA: a predictive biomarker of clinical prognosis in human squamous cell carcinoma. Oncotarget 3:670–677

Valiunas V, Wang HZ, Li L, Gordon C, Valiuniene L, Cohen IS, Brink PR (2015) A comparison of two cellular delivery mechanisms for small interfering RNA. Physiol Rep 3, pii:e12286

van der Bij GJ, Oosterling SJ, Meijer S, Beelen RH, van Egmond M (2005) The role of macrophages in tumor development. Cell Oncol 27:203–213

Van Golen KL, Rison S, Staroselsky A, Berger D, Tainsky MA, Pathak S, Price JE (1996) Predominance of the metastatic phenotype in hybrids formed by fusion of mouse and human melanoma clones. Clin Exp Metastasis 14:95–106

van Kilsdonk JW, Wilting RH, Bergers M, van Muijen GN, Schalkwijk J, van Kempen LC et al (2008) Attenuation of melanoma invasion by a secreted variant of activated leukocyte cell adhesion molecule. Cancer Res 68:3671–3679

Vignery A (2005) Macrophage fusion: are somatic and cancer cells possible partners? Trends Cell Biol 15:188–193

Vignery A (2008) Macrophage fusion: molecular mechanisms. Methods Mol Biol 475:149–161

Vlassov VV, Laktionov PP, Rykova EY (2010) Circulating nucleic acids as a potential source for cancer biomarkers. Curr Mol Med 10:142–165

Wang LM, Kevans D, Mulcahy H, O'Sullivan J, Fennelly D, Hyland J, O'Donoghue D, Sheahan K (2009) Tumor budding is a strong and reproducible prognostic marker in T3N0 colorectal cancer. Am J Surg Pathol 33:134–141

Watanabe T (1984) Supermelanotic hybrids between mouse teratocarcinoma and mouse melanoma cells. Exp Cell Res 154:625–631

Wiener F, Fenyö EM, Klein G (1974a) Tumor-host cell hybrids in radio-chimeras. Proc Natl Acad Sci U S A 71:148–152

Wiener F, Klein G, Harris H (1974b) The analysis of maligancy by cell fusion. V Further evidence of the ability of normal diploid cells to suppress malignancy. J Cell Sci 15:177–183

Wittwer C, Boeck S, Heinemann V, Haas M, Stieber P, Nagel D, Holdenrieder S (2013) Circulating nucleosomes and immunigenic cell death markers HMGB1, sRAGE and DNAse in patients with advance pancreatic cancer undergoing chemotherapy. Int J Cancer 133:2619–2630

Yamaguchi H, Pixley F, Condeelis J (2006) Invadopodia and podosomes in tumor invasion. Eur J Cell Biol 85:213–218

Yamauchi H, Tigashi K, Kawamura YJ, Horie H, Sasaki J, Tsujinaka S, Yasuda Y, Konishi F (2008) Pathological predictors for lymph node metastasis in T1 colorectal cancer. Surg Today 38:905–910

Yu M (2012) Circulating cell-free mitochondrial DNA as a novel cancer biomarker: opportunities and challenges. Mitochondrial DNA 23:329–332

Yu L, Cecil J, Peng SB, Schrementi J, Kovacevic S, Paul D, Su EW, Wang J (2006) Identification and expression of novel isoforms of human stromal cell-derived factor 1. Gene 374:174–179

Zanutto S, Pizzamiglio S, Ghilotti M, Ravagnani F, Perrone F, Leo E, Pilotti S, Verderio P et al (2014) Circulating miR-378 in plasma: a reliable, haemolysis-independent biomarker for colorectal cancer. Br J Cancer 110:1001–1007

Zheng H, Liu JY, Song FJ, Chen KX (2013) Advances in circulating microRNAs as diagnostic and prognostic markers for ovarian cancer. Cancer Biol Med 10:123–130

Zimmermann A, Schaer JC, Schneider J, Molo P, Schindler R (1981) Dominant versus recessive behavior of a cold-and a heat-sensitive mammalian cell cycle variant in heterokaryons. Somatic Cell Genet 7:591–601

Zlobec I, Lugli A, Baker K, Roth S, Minoo P, Hayashi S, Terracciano L, Jass JR (2007) Role of APAF-1, E-cadherin and peritumoral lymphocytic infiltration in tumour budding in colorectal cancer. J Pathol 212:260–268

Zlobec I, Minoo P, Baumhoer D, Baker K, Terracciano L, Jass JR, Lugli A (2008) Multimarker phenotype predicts adverse survival in patients with lymph node-negative colorectal cancer. Cancer 112:495–502

Pathogenic Features of Colorectal Liver Metastasis: Prometastatic and Antimetastatic Genes

115

Contents

Abstract

The metastatic spread of various malignancies is regulated by prometastatic genes and antimetastatic genes and their products. In addition to the function of these metastasis-associated genes, numerous epigenetic mechanisms affecting the metastatic cascade have been observed. By this approach, a molecular portrait or molecular signatures of cancers prone to metastasis are identified. In metastasizing hepatocellular carcinoma (HCC) and liver metastases of extrahepatic cancers, alterations of several metastasis suppressor genes have been found. In HCC, well-known members comprise KAI1(CD82) and nm23. Both in HCC and metastasizing colorectal carcinoma, downregulation of KAI1 occurs, thus abolishing the antimetastatic function of this gene. The expression patterns of KAI1 are modulated by various factors, including hepatitis B virus-mediated epigenetic silencing. Nm23, a second antimetastatic protein, acts through its function as a protein that removes prometastatic proteins from the cytosol. In several malignancies, both upregulation and downregulation of this protein were observed.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_115

Metastasis Promoting and Suppressing Genes

Genetic and Epigenetic Mechanisms Controlling Metastatic Spread: Identification of a Molecular Metastasis Portrait

There is increasing evidence that a tumor's proclivity for distinct remote metastatic sites may be encoded in genetic, epigenetic, and transcriptional programs that are expressed in early phases of tumor evolution already and which might allow predictions as to patterns of metastatic sites (reviews: Ramaswamy 2006; Nadal et al. 2007; Chiang and Massagué 2008). DNA microarray-based gene expression profiling has identified specific transcriptional signatures in primary tumors that destine involved cells to perform a metastatic spread (Hunter et al. 2003; Ramaswamy et al. 2003; Minn et al. 2005; Eltarhouny et al. 2008; Kroon et al. 2008; Molloy et al. 2012). These analyses identify what is called a "molecular portrait" of cancers prone to produce metastases. In breast cancer, e.g., a 70-gene prognosis signature has been found, which represents a classifier for the metastatic process and prognosis (Weigelt et al. 2005).

Prometastatic Genes and Gene Products

The search for metastasis-related genes is accomplished by primary-secondary tumor comparisons from large-scale databases (Kim and Lee 2009). By use of expression profiling experiments, a signature of 115 genes was established that differentiated metastatic from nonmetastatic primary CRC. Among these, the TGFbeta inhibitor BAMBI (bone morphogenetic protein and activin membrane-bound inhibitor) was highly expressed in about half of metastatic primary tumors and metastases but not in nonmetastatic tumors. BAMBI is a transmembrane TGFR1/BMPR1-related pseudoreceptor which antagonizes TGF-beta/BMP signaling by inhibiting the formation of functional authentic receptor complexes. BAMBI is a target of canonical Wnt signaling in colorectal tumor cells (Sekiya et al. 2004). This involves the beta-catenin coactivator BCL9-2, and it is suggested that BAMBI regulates CRC metastasis by connecting the Wnt/beta-catenin and TGFbeta signaling pathways (Fritzmann et al. 2009; comment: Carethers 2009). BCL9, the mammalian ortholog of Drosophila Legless, and its homolog BCL9-2 are essential components of canonical Wnt signaling (Brack et al. 2009). BAMBI also undergoes epigenetic regulatory changes, including silencing via hypermethylation of its gene, a mechanism thought to play a role in cancer invasiveness (Khin et al. 2009). Detection of DNA mutations has been accomplished by PCR restriction fragment length polymorphism or mutant-specific amplification K-ras and p53 genes (Hayashi et al. 1995) and has augmented the diagnosis rate of colorectal liver metastases (Schimanski et al. 1999). K-ras codon 12 and 13 mutations are correlated with differential patterns of tumor cell dissemination in CRC patients, in that CRC with codon 12 mutation showed the same pattern of tumor cell dissemination as their K-ras wild-type counterparts, while codon 13 mutants had higher rates of circulating epithelial cells (Conzelmann et al. 2004). Overexpression of fibrinogen-like protein 2 in cancer cells promotes metastatic tumor progression via induction of EMT (Qin et al. 2014).

Metastasis Suppressors: KAI1 (CD82)

Both in metastasizing HCC and metastases of extrahepatic primary tumors, a group of potent metastasis suppressor genes has been identified (reviews: Cook et al. 2011; Hurst and Welch 2011). In HCC, well-known members are KAI1 and nm23. The gene KAI1 (also termed CD82) is a general suppressor of metastasis in numerous types of cancer. The expression of KAI1, encoding a membrane scaffold protein, is reduced in advanced colon cancer and its liver metastasis (Maurer et al. 1999; Zheng et al. 2007), similar to hepatocellular carcinoma metastases (Guo et al. 1998). The antimetastatic actions of KAI1 are as yet

incompletely known. As a membrane scaffold, KAI1 regulates cell adhesion by altering alpha4 integrin stability and regulating spatial integrin arrangement (Termini et al. 2014). KAI1 expression is greater in HCC without intrahepatic metastases (Sun et al. 1998). The expression of KAI1 is modulated by several factors involved in hepatocarcinogenesis. Hepatitis B virus inhibits KAI1 expression via epigenetic hypermethylation of its promoter in HCC cells (Yu et al. 2014). KAI1 expression is downregulated by microRNA-197 which directly targets CD82 (Dai et al. 2014).

Metastasis Suppressors: Nm23

Another protein involved in the metastatic pathway is the nm23 protein group (NDPK-A; Sarris and Lee 2001; Marino et al. 2012). Nm23 (Nm23-H1) was established as the first metastasis suppressor gene (An et al. 2010), while the closely related isoform, Nm23-H2, has antimetastatic functions (Boissan and Lacombe 2006). The gene encodes a protein with multiple functions of which only part are implicated in metastasis suppression. Nm23-H1 is a multifunctional enzyme with nucleoside diphosphate kinase, histidine protein kinase, and exonuclease activities. Owing to the latter function, it was assumed that Nm23 reduces the acquisition of mutations that may promote a transition to a metastatic phenotype. Through protein-protein interactions, Nm23 may remove prometastatic proteins from the cytosol (Marino et al. 2011). In fact, Nm23 can bind numerous proteins that are involved in cancer cell invasion and metastasis, including proteins of Rho, Ras, TGF-beta and ERK-signaling pathways, cytoskeletal components (tubulin, vimentin), cell adhesion proteins, and proteins involved in transcription regulation (Marino et al. 2012). Nm23-H1 suppresses HCC cell adhesion and motility/migration by modulating glycosylation of integrin beta1 (She et al. 2010). Nm23 is expressed in part of HCCs and affects metastasis and prognosis (Nakayama et al. 1992; Yamaguchi et al. 1994; Huang et al. 1998; Guo et al. 2010). In contrast to Nm23-H1, Nm23-H2 can exert a prooncogenic potential in hepatocarcinogenesis and is positively associated with telomerase activity (Iizuka et al. 2003). Low expression of the homeobox gene Barx2 in HCC correlates with metastasis (Zhang et al. 2014), suggesting that Barx2 may act as a HCC tumor suppressor.

Colorectal Carcinoma Metastasis as an Example for Molecular Pathways

Introduction

Investigations regarding distinct gene expression patterns (transcriptomics) characterizing metastasizing colorectal cancers aim at defining predictive models of metastatic spread and personalized treatment strategies (reviews: Ki et al. 2007; Welsh et al. 2008; Jin et al. 2012). In a study on colorectal cancers using array comparative genomic hybridization (aCGH) to assess DNA copy number changes in primary tumors, it turned out that primary tumors which subsequently produced liver metastases had genomic aberrations on chromosome 20q (Bruin et al. 2010). Most colorectal liver metastases harbor the genetic abnormalities also observed in the primary tumors. But liver metastases from many cases showed, in addition, acquisition of genetic aberrations not found in the primary. These aberrations included genetic lesions associated with metastatic colorectal carcinoma, and the acquisition of new chromosomal abnormalities, e.g., losses of chromosomes 4 and 10q and gains of chromosomes 5p and 6p (Munoz-Bellvis et al. 2012). Chromosome 20p11 gains were associated with liver-specific metastasis in patients with CRC (Mekenkamp et al. 2013). The molecular characterization of circulating colorectal carcinoma cells resulted in the identification of 410 genes that formed a signature for these cells (Barbazan et al. 2012).

The Wnt/Beta-Catenin Signaling Pathway in Metastasis

In the initiation phase of colorectal carcinogenesis, dysregulation of the Wnt/beta-catenin

pathway linked to progressive genomic instability plays a significant role (Grady 2008). In early colorectal carcinogenic steps, Wnt signaling is often deregulated by acquired mutations and loss of heterozygosity (LOH) of the adenomatous polyposis coli (APC) tumor suppressor gene, the protein product of which regulates cellular beta-catenin via control of the respective degradation pathway. APC mutation abrogates the colonocyte's capability to regulate intracellular compartmental beta-catenin concentration and causes transport of beta-catenin in the nucleus. In fact, both sporadic and familial APC-associated adenomas show high nuclear concentrations of beta-catenin (Grady 2008). The function of beta-catenin is closely linked with the cell surface adhesion molecule, E-cadherin. In colorectal carcinomas, changes in E-cadherin expression have been correlated with tumor size, histopathology, and differentiation, but the results are still inconsistent (review: Tsanou et al. 2008).

Notch Signaling

A second signaling branch involved in the pathogenesis of metastases is Notch signaling (review: Ishii and Saito 2008). Notch signaling pathways are implicated in the maintenance of self-renewal potential in stem cells, binary cell fate determination in progenitor cells, and induction of terminal cell differentiation (Artavanis-Tsakonas et al. 1999). The Notch receptor is also linked to Wnt/beta-catenin-mediated tumorigenesis (Radtke and Raj 2003). Ligands for the several Notch receptors (NOTCH1, NOTCH2, NOTCH3, and NOTCH4) comprise Delta homologs (DLL1, DLL3, DLL4) and Serrate homologs (JAG1, JAG2).

Ligand binding induces the cleavage of Notch receptors by metalloproteinase and gamma secretase to induce nuclear translocation of the Notch intracellular domain (NICD). Notch signaling inhibitors, NUMB and NUMB-like (NUMBL), are docking proteins that modify distinct pathways of cellular differentiation (Katoh and Katoh 2006a). Gamma secretase is an intramembrane aspartyl protease complex that mediates Notch cleavage and the production of amyloid beta-proteins (reviews: Iwatsubo 2004; Li et al. 2009). The metalloproteinases active in Notch cleavage are a disintegrin and metalloproteases, ADAMs. ADAM proteases have complex functions that include shedding of proteins from cells and matrix contact sites, including matrix proteins (matrix protein sheddases; Franzke et al. 2009) and cytokines such as TNF (TNF sheddases; ADAM17 as a TNF convertase; Black et al. 1997; Moss et al. 1997; ADAM10, Mezyk-Kopec et al. 2009). ADAM10 and ADAM17 are involved in Notch receptor cleavage (Bozkulak and Weinmaster 2009), and ADAM10 is the rate-limiting protease of regulated intramembrane proteolysis, its ectodomain itself processed by ADAM9, ADAMS5, and gamma secretase (Tousseyn et al. 2009). The ectodomain of bound Jagged1 itself is cleaved by an ADAM17-like activity, similar to the cleavage of Drosophila Delta by Kuzbanian. The ectodomain shedding of ligand can be stimulated by Notch and yields membrane-tethered C-terminal fragments of Jagged and Delta accumulating in cells. Presenilin (PS) forms stable complexes with Jagged and Delta and their C-terminal fragments. PS/gamma secretase then mediates the cleavage of the latter to release the Jagged and Delta intracellular domains, a portion of which can enter the nucleus to act as signaling fragments (LaVoie and Selkoe 2003). Intranuclear NICD forms a nuclear complex with CSL (RBPSUH), Mastermind (MAML), p300, and histone acetyltransferase, and this complex induces transcriptional activation of Notch target genes, including HES1, HES5, HES7, HEY1, m HEY2, and HEYL. Overexpression of hes 1 and other Notch targets have been associated with sporadic CRCs. In colorectal cancer cells, the Notch effector is downstream of Wnt/beta-catenin, and it has been shown that Jagged1 is the pathological link between Wnt and Notch pathways (Rodilla et al. 2009). This is of specific interest because it has been shown that Jagged1 is expressed on several progenitor cell systems due to canonical Wnt signaling activation, and this induces self-

renewal of stem cells due to activated Notch signaling (Katoh and Katoh 2006b).

TGF-Beta Signaling in Metastatic Pathways

A third pathway involved in colorectal carcinogenesis is the TGF-beta system, which is now known to be linked to Wnt/beta-catenin signaling. TGF-beta belongs to a ligand-receptor family which also includes several members of the bone morphogenetic protein (BMP) family, and BMPs are involved in carcinogenesis of the colon (Jung et al. 2004). Advanced malignancies often exhibit increased concentrations of TGF-beta, which has been suggested to promote invasion, spread, and metastasis of tumor cells. Inhibition of cell proliferation by TGF-beta is mainly mediated by the Smad pathway; epithelial focal complex formation is independent of Smad. In contrast, focal complex formation of epithelial cells in response to TGF-beta is mediated by two mitogen-activated protein kinases (MAP kinases), extracellular signal-regulated kinase (ERK), and Jun N-terminal kinase (JNK), thus mediating cell migration of epithelial cells in an Smad4-independent manner (Imamichi et al. 2005; Giehl et al. 2007). The TGF-beta pathway is linked to the activin/activin receptor signaling system. The activin type II receptor (ACVR2) gene is a member of the TGF-beta type II receptor (TGFBR2) family and is a putative tumor suppressor gene which is frequently mutated in microsatellite-unstable colorectal cancers (MSI-H colorectal cancers). TGFBR2- and ACVR2-signaling pathways share distinct cellular effectors, the SMAD proteins. ACVR2 transmits the growth effects of activin via phosphorylation of SMAD proteins to affect gene transcription.

References

An R, Meng J, Shi Q, Dai XX, Chen JH, Lei YJ, Shan B, Gao C, Chu YL, Dong XP (2010) Expressions of nucleoside diphosphate kinase (nm23) in tumor tissues are related with metastasis and length of survival of patients with hepatocellular carcinoma. Biomed Environ Sci 23:267–272

Artavanis-Tsakonas S, Rand MD, Lake RJ (1999) Notch signaling: cell fate control and signal integration in development. Science 284:770–776

Barbazan J, Alonso-Alconada L, Muinelo-Romay L, Vieito M, Abalo A, Alonso-Nocelo M et al (2012) Molecular characterization of circulating tumor cells in human metastatic colorectal cancer. PLoS One 7:e40476

Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, Wolfson MF et al (1997) A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells. Nature 385:729–733

Boissan M, Lacombe ML (2006) Nm23/NDP kinases in hepatocellular carcinoma. J Bioenerg Biomembr 38:169–175

Bozkulak E, Weinmaster G (2009) Selective use of ADAM10 and ADAM17 in activation of Notch1 signaling. Mol Cell Biol 29:5679–5695

Brack AS, Murphy-Seiler F, Hanifi J, Deka J, Eyckerman S, Keller C, Aguet M, Rando TA (2009) BCL9 is an essential component of canonical Wnt signaling that mediates the differentiation of myogenic progenitors during muscle regeneration. Dev Biol 335:193–205

Bruin SC, Klijn C, Liefers GJ, Braaf LM, Joosse SA, van Beers EH, Verwaal VJ et al (2010) Specific genomic aberrations in primary colorectal cancer are associated with liver metastases. BMC Cancer 10:662

Carethers JM (2009) Intersection of transforming growth factor-beta and Wnt signaling pathways in colorectal cancer and metastasis. Gastroenterology 137:33–36

Chiang AC, Massagué J (2008) Molecular basis of metastasis. N Engl J Med 359:2814–2823

Conzelmann M, Linnemann U, Berger MR (2004) K-ras codon 12 and codon 13 mutations are correlated with differential patterns of tumor cell dissemination in colorectal cancer patients. Int J Oncol 24:1537–1544

Cook LM, Hurst DR, Welch DR (2011) Metastasis suppressors and the tumor microenvironment. Semin Cancer Biol 21:113–122

Dai W, Wang C, Wang F, Wang Y, Shen M, Chen K, Cheng P, Zhang Y, Yang J et al (2014) Anti-miR-197 inhibits migration in HCC cells by targeting KAI 1/CD82. Biochem Biophys Res Commun 446:541–548

Eltarhouny SA, Elsawy WH, Radpour R, Hahn S, Holzgreve W, Zhong XY (2008) Genes controlling spread of breast cancer to lung “gang of 4”. Exp Oncol 30:91–95

Franzke CW, Bruckner-Tuderman L, Blobel CP (2009) Shedding of collagen XVII/BP180 in skin depends on both ADAM10 and ADAM9. J Biol Chem 284:23386–23396

Fritzmann J, Morkel M, Besser D, Budczies J, Kosel F, Brembeck FH, Stein U, Fichtner I et al (2009) A colorectal cancer expression profile that includes

transforming growth factor beta inhibitor BAMBI predicts metastatic potential. Gastroenterology 137:165–175
Giehl K, Imamichi Y, Menke A (2007) Smad4-independent TGF-beta signaling in tumor cell migration. Cells Tissues Organs 185:123–130
Grady WM (2008) Genomic and epigenetic instability in colorectal cancer pathogenesis. Gastroenterology 135:1079–1099
Guo XZ, Friess H, Di Mola FF, Heinicke JM, Abou-Shady M, Graber HU, Baer HU, Zimmermann A et al (1998) KAI1, a new metastasis suppressor gene, is reduced in metastatic hepatocellular carcinoma. Hepatology 28:1481–1488
Guo H, Nan K, Hu T, Meng J, Hui W, Zhang X, Qin H, Sui C (2010) Prognostic significance of co-expression of nm23 and p57 protein in hepatocellular carcinoma. Hepatol Res 40:1107–1116
Hayashi N, Iti I, Yamagisawa A, Kato Y, Nakamori S, Imaoka S, Watanabe H, Ogawa M et al (1995) Genetic diagnosis of lymph-node metastasis in colorectal cancer. Lancet 345:1257–1259
Huang B, Wu ZB, Ruan YB (1998) Expression of nm23 gene in hepatocellular carcinoma tissue and its relation with metastasis. World J Gastroenterol 4:266–267
Hunter K, Welch DR, Liu ET (2003) Genetic background is an important determinant of metastatic potential. Nat Genet 34:23–24
Hurst DR, Welch DR (2011) Metastasis suppressor genes: at the interface between the environment and tumor cell growth. Int Rev Cell Mol Biol 286:107–180
Iizuka N, Mori N, Tamesa T, Tangoku A, Oka M (2003) Telomerase activity and Nm23-H2 protein expression in hepatocellular carcinoma. Anticancer Res 23:43–47
Imamichi Y, Waldmann O, Hein R, Eleftheriou P, Giehl K, Menke A (2005) TGF beta-induced focal complex formation in epithelial cells is mediated by activated ERK and JNK MAP kinases and is independent of Smad4. Biol Chem 386:225–236
Ishii H, Saito T (2008) Cancer metastasis as disrupted developmental phenotype. Curr Genomics 9:25–28
Iwatsubo T (2004) The gamma-secretase complex: machinery for intramembrane proteolysis. Curr Opin Neurobiol 14:379–383
Jin K, Gao W, Lu Y, Lan H, Teng L, Cao F (2012) Mechanisms regulating colorectal cancer cell metastasis into liver (review). Oncol Lett 3:11–15
Jung B, Doctolero RT, Tajima A, Nguyen AK, Keku T, Sandler RS, Carethers JM (2004) Loss of activin receptor type 2 protein expression in microsatellite unstable colon cancers. Gastroenterology 126:654–659
Katoh M, Katoh M (2006a) NUMB is a break of WNT-Notch signaling cycle. Int J Mol Med 18:517–521
Katoh M, Katoh M (2006b) Notch ligand, JAG1, is evolutionarily conserved target of canonical WNT signaling pathway in progenitor cells. Int J Mol Med 17:681–685
Khin SS, Kitazawa R, Win N, Aye TT, Mori K, Kondo T, Kitazawa S (2009) BAMBI gene is epigenetically silenced in subset of high-grade bladder cancer. Int J Cancer 125:328–338
Ki DH, Jeung HC, Park CH, Kang SH, Lee GY, Lee WS, Kim NK, Chung HC et al (2007) Whole genome analysis for liver metastasis gene signatures in colorectal cancer. Int J Cancer 121:2005–2012
Kim S, Lee D (2009) Mining metastases related genes by primary-secondary tumor comparisons from large-scale databases. BMC Bioinformatics 10(suppl 3):52
Kroon BK, Leijte JA, van Boven H, Wessels LF, Velds A, Horenblas S, van't Veer LJ (2008) Microarray gene-expression profiling to predict lymph node metastasis in penile carcinoma. BJU Int 102:510–515
LaVoie MJ, Selkoe DJ (2003) The Notch ligands, Jagged and Delta, are sequentially processed by alpha-secretase and presenilin/gamma-secretase and release signaling fragments. J Biol Chem 278:34427–34437
Li H, Wolfe MS, Selkoe DJ (2009) Toward structural elucidation of the gamma-secretase complex. Structure 17:326–334
Marino N, Marshall JC, Steeg PS (2011) Protein-protein interactions: a mechanism regulating the anti-metastatic properties of Nm23-H1. Naunyn Schmiedebergs Arch Pharmacol 384:351–362
Marino N, Nakayama J, Collins JW, Steeg PS (2012) Insights into the biology and prevention of tumor metastasis provided by the Nm23 metastasis suppressor gene. Cancer Metastasis Rev 31:593–603
Maurer CA, Graber HU, Friess H, Beyermann B, Willi D, Netzer P, Zimmermann A, Büchler MW (1999) Reduced expression of the metastasis suppressor gene KAI1 in advanced colon cancer and its metastases. Surgery 126:869–880
Mekenkamp LJ, Haan JC, Koopman M, Vink-Börger ME, Israeli D, Teerenstra S et al (2013) Chromosome 2op11 gains are associated with liver-specific metastasis in patients with colorectal cancer. Gut 62:94–101
Mezyk-Kopec R, Bzowska M, Stalinska K, Chemicki T, Podkalicki M, Jucha J, Kowalczyk K et al (2009) Identification of ADAM10 as a major TNF sheddase in ADAM17-deficient fibroblasts. Cytokine 46:309–315
Minn AJ, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, Viale A, Olshen AB et al (2005) Genes that mediate breast cancer metastasis to lung. Nature 436:518–524
Molloy TJ, Roepman P, Naume B, van't Veer LJ (2012) A prognostic gene expression profile that predicts circulating tumor cell presence in breast cancer patients. PLoS One 7:e32426
Moss ML, Jin SL, Milla ME, Bickett DM, Burkhart W, Carter HL et al (1997) Cloning of a disintegrin metalloproteinase that processes precursor tumour-necrosis factor-alpha. Nature 385:733–736
Munoz-Bellvis L, Fontanillo C, Gonzalez-Gonzalez M, Garcia E, Iglesias M, Esteban C et al (2012) Unique genetic profile of sporadic colorectal cancer liver metastasis versus primary tumors as defined by high-density single-nucleotide polymorphism arrays. Mod Pathol 25:590–601

Nadal C, Maurel J, Gascon P (2007) Is there a genetic signature for liver metastasis in colorectal cancer? World J Gastroenterol 13:5832–5844

Nakayama T, Ohtsuru A, Nakao K, Shima M, Nakata K, Watanabe K, Ishii N, Kimura N et al (1992) Expression in human hepatocellular carcinoma of nucleoside diphosphate kinase, a homologue of the nm23 gene product. J Natl Cancer Inst 84:1349–1354

Qin WZ, Li QL, Chen WF, Xu MD, Zhang YQ, Zhong YS, Ma LL, Hu JW, Cai MY et al (2014) Overexpression of fibrinogen-like protein 2 induces epithelial-to-mesenchymal transition and promotes tumor progression in colorectal carcinoma. Med Oncol 51:181

Radtke F, Raj K (2003) The role of Notch in tumorigenesis: oncogene or tumor suppressor? Nat Rev Cancer 3:765–767

Ramaswamy S (2006) Cancer transcriptomics: modeling metastasis. Eur J Hum Genet 14:1–2

Ramaswamy S, Ross KN, Lander ES, Golub TR (2003) A molecular signature of metastasis in primary solid tumors. Nat Genet 33:49–54

Rodilla V, Villanueva A, Obrador-Hevia A, Robert-Moreno A, Fernandez-Majada V, Grilli A et al (2009) Jagged1 is the pathological link between Wnt and Notch pathways in colorectal cancer. Proc Natl Acad Sci U S A 106:6315–6320

Sarris M, Lee CC (2001) nm23 protein expression in colorectal carcinoma metastasis in regional lymph nodes and the liver. Eur J Surg Oncol 27:170–174

Schimanski CC, Linnemann U, Berger MR (1999) Sensitive detection of k-ras mutations augments diagnosis of colorectal cancer metastases in the liver. Cancer Res 59:5169–5175

Sekiya T, Adachi S, Kohu K, Yamada T, Higuchi O, Furukawa Y, Nakamura Y, Nakamura T et al (2004) Identification of BMP and activin membrane-bound inhibitor (BAMBI), an inhibitor of transforming growth factor-beta signaling, as a target of the beta-catenin pathway in colorectal tumor cells. J Biol Chem 279:6840–6846

She S, Xu B, He M, Lan X, Wang Q (2010) Nm23-H1 suppresses hepatocarcinoma cell adhesion and migration on fibronectin by modulating glycosylation of integrin beta1. J Exp Clin Cancer Res 29:93

Sun HC, Tang ZY, Zhou G, Li XM (1998) KAI1 gene expression in hepatocellular carcinoma and its relationship with intrahepatic metastases. J Exp Clin Cancer Res 17:307–311

Termini CM, Cotter ML, Marjon KD, Buranda T, Lidke KA, Gillette JM (2014) The membrane scaffold CD82 regulates cell adhesion by altering α4 integarin stability and molecular density. Mol Biol Cell 25:1560–1573

Tousseyn T, Thathiah A, Jorissen E, Raemaekers T, Konietzko U, Reiss K, Maes E, Snellinx A et al (2009) ADAM10, the rate-limiting protease of regulated intramembrane proteolysis of Notch and other proteins, is processed by ADAMs-9, ADAMS-15, and the gamma-secretase. J Biol Chem 284:11738–11747

Tsanou E, Peschos D, Batistatou A, Charalabopoulos A, Charalabopoulos K (2008) The E-cadherin adhesion molecule and colorectal cancer. A global literature approach. Anticancer Res 28:3815–3826

Weigelt B, Hu Z, He X, Livasy C, Carey LA, Ewend MG, Glas AM, Perou CM, van't Veer LJ (2005) Molecular portraits and 70-gene prognosis signature are preserved throughout the metastatic process of breast cancer. Cancer Res 65:9155–9158

Welsh FK, Tekkis PP, John TG, Rees M (2008) Predictive models in colorectal liver metastases – can we personalize treatment and outcome? Dig Surg 25:406–412

Yamaguchi A, Urano T, Goi T, Takeuchi K, Niimoto S, Nakagawara G, Furukawa K et al (1994) Expression of human nm23-H1 and nm23-H2 proteins in hepatocellular carcinoma. Cancer 73:2280–2284

Yu G, Bing Y, Li W, Xia L, Liu Z (2014) Hepatitis B virus inhibits the expression of CD82 through hypermethylation of its promoter in hepatoma cells. Mol Med Rep. doi:10.3892/mmr.2014.2495

Zhang Y, Zhang JX, Huang LL, He LJ, Liao YJ, Lai YR, Deng HX, Tian XP, Kung HF et al (2014) Low expression of BARX2 in human primary hepatocellular carcinoma correlates with metastasis and predicts poor prognosis. Hepatol Res. doi:10.1111/hepr.12340

Zheng H, Tsuneyama K, Cheng C, Takahashi H, Cui Z, Murai Y, Takano Y (2007) Expression of KAI1 and tenascin, microvessel density were closely correlated with liver metastasis of gastrointestinal adenocarcinoma. J Clin Pathol 60:50–56

Part XXI

Tumors and Tumor-Like Lesions of the Hepatic Ligaments

Tumors and Tumor-Like Lesions of the Hepatic Ligaments

116

Contents

Abstract

Several types of tumors, tumor-like lesions, and cysts can develop in the hepatic ligaments, mainly in the falciform and round ligament. Among mesenchymal tumors, lipoma is a well-known, albeit rare primary neoplasm of hepatic ligaments. These neoplasms take their origin from adipocytes localized between the peritoneal folds of ligaments. Lipomas have to be distinguished from the properitoneal fat pad associated with the falciform ligament. Other rare benign tumors of ligaments include perivascular epithelioid cell tumors, fibroma, lymphangioma, gastrointestinal stromal tumor, paraganglioma, and mature teratoma. There are very rare malignant neoplasms primary to hepatic ligaments, e.g., malignant mesothelioma, leiomyosarcoma, and several other types of sarcoma. Hepatic malignancies can extend into the ligaments and thus mimic primary tumors of these structures. In addition, the hepatic ligaments can be the site of metastatic tumor spread. Cysts located to ligaments include congenital mesothelial or epithelial cysts and hydatid cysts. Mass-forming lesions of ligaments that may be confounded with neoplasms comprise hematomas, abscesses, bilomas, and soft tissue necrosis in pancreatitis.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_116

Introduction

Various types of benign and malignant neoplasms, cysts, and tumor-like lesions can develop in hepatic ligaments, mainly in the falciform and round ligament (ligamentum falciforme hepatis and ligamentum teres hepatis, respectively). Due to their topographic relationship with the liver, tumors of the ligaments can be confounded with neoplasms originating from the liver substance proper. The anatomy and ontogenesis of hepatic ligaments are discussed in a paragraph at the end of this chapter.

Lipoma of the Hepatic Ligaments

Overall, the hepatic ligaments are considered to be a low potential source of intraabdominal tumors, and in fact, only few bona fide neoplastic lesions originating from these structures have been reported so far, adipose tissue tumors being the most frequently described. The knowledge of such lesions is, however, of interest insofar as several mass-producing lesions of the liver may develop close to the hepatic ligaments and hence result in differential diagnostic difficulties. This question in principle arises in any situation of masses or cystic lesions detected in the left hepatic intersegmental fissure.

Several reports have documented lipomas in the falciform (Honda et al. 1983; Bruneton et al. 1987; Kakitsubata et al. 1993;) or round (Adamsen 1983; Budarin 1988; Farkas et al. 1991) hepatic ligaments. These neoplasms may take their origin from the adipocyte population localized between the peritoneal folds of these structures, and being richly developed mainly in the round ligament, here being in continuity with the adipose tissue of the perihilar hepatic area. Ligamentary lipomas may grow to a large size, in one report resulting in a mass of 20 cm diameter (giant lipoma; Farkas et al. 1991). Similar to lipomas in other locations, regressive changes or even infarction can occur (Adamsen 1983). On imaging, adipose tumorous lesions of the falciform ligament have to be distinguished from focal fatty change of the liver, which frequently occurs close to this ligament, and may result in a diagnostic pitfall on CT, MR, and sonography (Yoshikawa et al. 1987; Ohashi et al. 1995; Soyer et al. 1996; Spelle et al. 1997). Fatty pseudolesions in segment IV adjacent to the falciform ligament have been observed to be caused by drainage of the paraumbilical vein, related to the vascular connections discussed above (Kobayashi et al. 2001). The properitoneal fat pad associated with the falciform ligament (see above; Feldberg and van Leeuwen 1990) may radiologically be confounded with a ligamentary lipoma. Finally, extraperitoneal lipomatous appendages of the falciform ligament can undergo twisting and thus result in differential diagnostic problems on US and CT (Coulier et al. 2001).

Other Rare Benign or Semimalignant Tumors of the Hepatic Ligaments

Only very few other rare benign tumors have been reported as primary ligamentary neoplasms, including angiofibroma (Spay et al. 1973), cystic lymphangioma (Zaev 1989; Morgan and Ricketts 2004), mature cystic teratoma (Abe et al. 1976; Ayyappan et al. 2007; Gangopadhyay et al. 2009; Srivastava et al. 2011), perivascular epithelioid cell tumor (Choi et al. 2009), gastrointestinal stromal tumor (Abedalthagafi 2012), and paraganglioma (Delbridge and Connolly 1982).

Primary Malignant Tumors of the Hepatic Ligaments

The very rare malignant tumors primary to the hepatic ligaments described so far include leiomyosarcoma (Yamagiwa et al. 1967; Mital and Bazaz-Malik 1971; Adachi et al. 1979; Tomaszewski et al. 1986; Morita et al. 1987; Yamaguchi et al. 1996), malignant mesothelioma (Marubayashi et al. 1998), malignant fibrous histiocytoma (Toughrai et al. 2007), fibromyxoid sarcoma (Harish et al. 2003), solitary fibrous tumor with malignant change (Gidwani

et al. 2004), stromal tumor (Poilblanc et al. 2006), and hemangiopericytoma (Majnarich and Stout 1960). These tumors may grow to impressive size; the hemangiopericytoma reported by Majnarich and Stout (1960) had a weight of 3 kg at surgery. The single report of malignant mesothelioma in the falciform ligament (Marubayashi et al. 1998) is of some theoretical interest, because approximately 30 % of mesotheliomas involve the peritoneal cavity, either solely or in combination with a pleural neoplasm. The patient described by Marubayashi and coworkers had a 10 cm-sized, encapsulated mass with no evidence of diffuse mesenteric thickening or multiple nodules, suggesting that the falciform ligament tumor either originated from cells of the mesothelial peritoneal covering of the ligament or from a precursor cell system located within the ligamentary tissue itself.

Malignant neoplasms of the hepatic ligaments also develop in the pediatric age group. Leiomyosarcoma of the ligamentum teres has been found in a 10-year-old girl (Tomaszewski et al. 1986). In a 14-month-old boy, an endodermal sinus (yolk sac) tumor was observed in the falciform ligament (Atkinson et al. 1992). Clear cell myomelanocytic tumors of the falciform and round ligaments are discussed in the chapter on pediatric liver tumors.

Extension of Primary Hepatic Malignancies into the Hepatic Ligaments

The hepatic ligaments are sometimes involved by primary hepatic neoplasms extending into these structures, e.g., hepatocellular carcinoma (Miyazaki et al. 1989), the spreading pathways probably employing the vascular network connecting the liver with its ligaments (Solomon and Rubinstein 1984). Owing to its distinct angioarchitecture and the vascular connections, the round ligament may offer a particularly efficient spreading pathway for hepatic cancer cells; it has, e.g., been demonstrated that HCC can extend along the round ligament to finally reach the umbilical area (Kim and Lim 1985).

Metastases to the Hepatic Ligaments

Malignant neoplasms of the abdominal cavity can metastasize to the hepatic ligaments, mostly in the setting of peritoneal carcinosis (Missalek 1993; Saida et al. 1994).

Cystic Lesions of the Hepatic Ligaments

Apart from solid neoplastic lesions, cystic space-occupying lesions rarely evolve in the ligaments of the liver and can result in focal porta hepatis scintiscan defects (Karabin 1951; McClelland 1975). Congenital or acquired ligamentary cysts (mesothelial or rarely epithelial), which may produce upper abdominal pain, occur in both ligaments (Motolese Lazzaro 1966; Krylov and Shurkalin 1968; Tessari 1970; Seniutovich et al. 1976; Enterline et al. 1984; Smirnov and Pravdin 1989; Bryan and Pillarisetty 1992; Lagoudianakis et al. 2008; Patel et al. 2009). These cysts probably have a malformative cause, although this has so far not been investigated in a conclusive manner. The hepatic ligaments can be involved by echinococcosis resulting in cystic lesions of variable size (Vadala et al. 1985). Cystic lesions originating in the falciform ligament may radiologically be mimicked by internal herniation of small intestine through a primary or iatrogenic defect ("window") of this ligament (Kobayashi et al. 1999; Vorburger et al. 2000; Sourtzis et al. 2002; Charles et al. 2005). A cyst-like phenomenon may also result from fluid collections in hepatic fissures caused by normal anatomic variations or pathologic furrows (e.g., in cirrhosis and liver atrophy) and recesses (Auh et al. 1994).

Tumor-Like Lesions of the Hepatic Ligaments

Tumorous lesions of the hepatic ligaments may also be suspected in case of other reactive changes occurring in these structures. Rarely, primary abscesses develop in the falciform ligament (Doscher et al. 1980; Sones et al. 1981; Lipinski

et al. 1985; Laucks et al. 1986; Kaneko et al. 1990; Pratap et al. 2006). In acute pancreatitis, diffusion of blood into the falciform ligament, and from here to the subcutaneous umbilical tissues (Cullen's sign; Bem and Bradley 1998), or causing necrosis of the round ligament (Lange and Rozentale 1995) can develop and induce a ligamentary mass effect. Tumor-like expansion by edema and hemorrhage of the round and falciform ligaments has been demonstrated to occur in isolated gangrene of the ligaments, a rare cause of peritonitis (Charuzi and Freund 1976; Watson et al. 1988; Pans et al. 1999; Losanoff and Kjossev 2002; Tison et al. 2005), and similar alterations may result from strangulation of the round hepatic ligament (Turkina et al. 1990) and in the so-called idiopathic segmental fatty tissue necrosis of the round ligament (Goti et al. 2000). Furthermore, abscesses, biliomas, and hemorrhages of the liver and the pericholecystic area can spread along the hepatic ligaments and cause a mass effect (Mori et al. 1989; Pratap et al. 2006). The falciform ligament can undergo torsion and induce a local peritonitis with edema and exudation (Llyod 2006). Falciform ligament hernia after cholecystectomy, fundoplication, or blunt abdominal trauma has been reported (Charles et al. 2005; Lakdawala et al. 2009; Sykes et al. 2010). A neoplastic mass may be suspected in certain malformations of the liver (Parke et al. 1996). Owing to abnormal hepatic fixation, the liver moves to an unusual site ("wandering liver," "hepatic vagrancy"). In persistence of the primitive ventral mesogastrium and congenital absence of the coronary and triangular ligaments, the liver and spleen may freely be mobile (Susani et al. 1983; Siddins and Cade 1990). In the congenital absence of the falciform and the triangular hepatic ligaments, hepatic torsion with complete dislocation of the liver into the left upper quadrant can ensue, resulting in an unusual mass effect (Tate 1993). Congenital defects of the falciform ligament may cause small bowel herniation through this gap (falciform ligament window) followed by obstruction of the bowel and falciform ligament deformation through traction (Gaster 1948; Miller 1981; Vorburger et al. 2000; Bedioui et al. 2008; Gingalewski and Lalikos 2008; Coulier et al. 2009; Shiozaki et al. 2012). The gallbladder may be situated within the coronary ligament, and thus produce a retrohepatic mass (Principe et al. 1979).

Ontogenesis and Anatomy of the Hepatic Ligaments

The hepatic ligaments serve to connect the liver with the abdominal wall and the diaphragm. The falciform ligament (ligamentum falciforme hepatis) and the round hepatic ligament (ligamentum teres hepatis) are the so-called ventral mesohepaticum. Peritoneal attachments of the liver to the diaphragm include the falciform ligament, the left triangular ligament, and the coronary ligament with the right triangular ligament. The latter is the lateral unification of the layers of the coronary ligament. The liver is posteriorly connected to the diaphragm, and thus the coronary ligament has superior and inferior layers rather than anterior and posterior layers (Umidon 1967; Mirilas and Skandalakis 2002). These authors proposed to employ the term "peritoneal attachment," instead of "ligament," but the established term is used throughout the present text. These ligaments are the ontogenetic remnants of the development of the liver within the septum transversum.

The anatomy of the hepatic ligaments has been investigated to considerable detail (Li et al. 2004), chiefly also in the light to better understand the pathogenesis of the abnormal venous flow occurring in portal hypertension, including the mechanisms operational in the development of caput medusae (Krahn 1974). The imaging anatomy of the falciform ligament is important in the echocardiographic diagnosis of ascites, as this structure helps to distinguish ascites from pericardial effusions, pleural effusions, and pericardial cysts (Cardello et al. 2006). The falciform ligament is characterized by a duplication of the peritoneum connecting the upper abdominal wall and the inferior surface of the diaphragm with the anterior surface of the liver. This structure is visualized also in ultrasonic examinations (Hillman et al. 1979). At its inferior end, the ligament is in

continuation with the round hepatic ligament, where also vascular connections are present (see below).

The presence of a hepatic falciform artery (HFA) may clinically manifest in situations where, following hepatic artery infusion chemotherapy, a supraumbilical skin rash developed (Williams et al. 1985). The HFA is a rather small vessel usually arising as a terminal branch of the middle or left hepatic artery. It had first been described by Albrecht von Haller in 1753 as Ramulus ad appendicem ensiformem et lineam albam to denote the arterial vessels located within the anterior abdominal adipose tissue body in the midline between the posterior layer of the rectus sheath and the peritoneum, and extending to the falciform ligament (Merklin 1971; Feldberg and van Leeuwen 1990). The artery provides partial blood supply around the umbilicus and communicates with branches of the internal thoracic and superior epigastric arteries, and its terminal branches end in the midline rectus sheath and the peritoneum, extending into the base of the falciform ligament. The HFA is usually single, but may branch early and course along the falciform ligament as two vessels side by side, but the falciform ligament itself may be supplied by multiple vessels rather than one or two larger vessels (Williams et al. 1985). In a systematic angiographic study on 53 patients, this artery was detected in 24.5 % of the patients by use of celiac or common hepatic angiograms, with no difference in the incidence between patients with normal livers and patients with chronic liver disease (Gibo et al. 2001). In this study, the blood flow of the HFA was slower than that of the peripheral hepatic arteries. Conversely, only 25 among 1,250 patients (2 %) who underwent celiac or hepatic arteriography showed an HFA. Among these patients, the HFA arose as a terminal branch of the middle hepatic artery in 56 % and of the left hepatic artery in 44 %. The vessel was single in 72 % and double in 28 %. The HFA ran within the falciform ligament and the branches were connected with the liver around the falciform ligament (Baba et al. 2000). In another investigation, the origin of the HFA was analyzed in more detail. In a total of 340 liver cirrhosis patients undergoing hepatic artery chemoembolization for HCC, the angiographic incidence of an HFA was 7.6 % (26/340). The origin was the middle hepatic artery (A4) in 16, the superior branch of the middle hepatic artery in 3, the inferior branch of the middle hepatic artery in 2, the inferior branch of the left hepatic artery (A3) in 3, and the confluence of A3 and A4 in 3 cases. Anastomoses between the HFA and the subcutaneous artery were either direct or via the ensiform branch of the internal thoracic artery, located at the lower and upper part of the falciform ligament, respectively (Ibukuro et al. 1998). In contrast to angiographic findings, the anatomic incidence of an HFA was clearly higher, amounting to 38/55 (68 %) anatomic dissections (Michels 1955). By use of computed tomography hepatic arteriography (CTHA), the detection rate of the HFA was 77 % (Tajima et al. 2009).

The ligamentum teres hepatis (round hepatic ligament) has an average length of 17.6 $\pm$ 5.5 cm and a mean diameter of 1.8 $\pm$ 0.4 cm (Ying et al. 1997). The round ligament consists of three parts: (a) the distal part, situated in a subperitoneal niche of the abdominal wall and reaching from the navel to the root of the falciform ligament; (b) the part situated within the peritoneal duplication of the caudal area of the falciform ligament; and (c) the part located under the liver in the sagittal fissure between the left liver lobe and the quadrate lobe, frequently covered by connective tissue or by a bridge of liver substance. Portions of the round ligament are situated within the properitoneal fat pad which is also associated with the falciform ligament and contains the ensiform vessels (Merklin 1971; Feldberg and van Leeuwen 1990). The adipose tissue within this fad pad, which had a mean thickness of 1.2 cm in a CT study in 103 patients (Feldberg and van Leeuwen 1990), is in direct continuation with the variably developed fatty tissue of the round ligament. The distal insertion of the round ligament varies considerably: in a study on 220 patients submitted to laparoscopy, 50 % of the patients showed a round ligament not directly running from the porta hepatis to the umbilicus, but to a point of insertion cranial to the umbilicus in the median

line of the anterior abdominal wall, resulting in the potentially significant situation that, in case of portal hypertension with Cruveilhier-Baumgarten syndrome, large-caliber porto-femoral "umbilical" vessels might in fact be running a course to the left of the umbilicus and thus be prone to injury at laparoscopy (Friedrich et al. 1988). The central venous rudiment in the round ligament derives from the umbilical vein keeping its potential to be recanalized (Gonzales-Carbalhaes 1959; Chevrel et al. 1982; Ying et al. 1992). Under normal conditions, the round ligament proper is characterized by a connective tissue string being round to ovoid on cross sections. The central vein (zone 1 of Krahn) is enveloped by a sheath of fibrillar tissue containing small blood vessels and few myocytes, followed by a rim of myocyte fascicles and more loose connective tissue (zone 2 of Krahn) The periphery of the bundle consists of connective tissue with longitudinally oriented muscle cells, the adventitia (zone 3 of Krahn). Between the bundle or string itself and the peritoneal covering is a sheath of adipose tissue of variable thickness, traversed by blood and lymph vessels and nerves (zone 4 of Krahn). It has to be emphasized that this ordered construction may vary considerably, some of the three zones being poorly distinguishable or even lacking (Krahn 1974). The small central vein of the bundle takes its origin at the pars umbilicalis of the left portal vein branch. The diameter of its lumen varies markedly, the diameter sometimes decreasing from proximal parts to distal parts of the round ligament, whereas in other situations the residual lumen in the cranial and middle segments is larger (Ying et al. 1997). Distally, the vein branches into several small veins or venules. The vein exhibits, already after its origin from the left portal vein and in the hepatic part of the round ligament, numerous venous anastomoses with neighboring veins, resulting in loose or dense venous networks connecting intraligamentous and extraligamentous veins (Krahn 1974). The intraligamentous veins form two groups, one located within the muscle layer and another with an extramuscular location. The extraligamentous veins correspond to Sappey's paraumbilical veins (Sappey 1893), and a second connecting system links the round ligament veins to the veins of the falciform ligament. The latter form a connection between the convexity of the liver and the abdominal wall or the diaphragm (the upper venous group of Sappey). The largest of these veins is thought to represent the persistence of the so-called Burow's vein in adults (Burow 1838). Most of the veins accompanying the round ligament and connecting the liver with the abdominal wall follow the ligament in a more or less parallel fashion (Sappey 1893). Sometimes, the distal veins spread in a delta-like manner to form a fan-like network in the abdominal wall ("Schaltvenen"; Baumgarten 1881). Small arteries are usually found in peripheral parts of the round ligament and along the paraumbilical veins, whereas the central parts of the ligament are poor in arteries. Stereologic measurements have shown that the overall vessel number is higher and the vessel transverse sectional area is larger in the cranial and middle segments of the round ligament than in the caudal segment (Ying et al. 1997).

The lymphatic system of the hepatic ligaments has been studied in detail (Borisov 1968; Golab 1972; Mielke 1972). Both large hepatic ligaments contain a dense network of lymphatic channels/vessels. Similar to the peritoneal covering of the diaphragm (Bettendorf 1978; Li and Jiang 1993), the mesothelial surface of the ligaments contains so-called stomata, i.e., holes which are considered to be connections between the peritoneal cavity and the subperitoneal lymphatic vessels and capable to allow the transperitoneal traffic of both fluid and particulate matter (Tesch et al. 1990). Whether these openings also permit the migration of malignant neoplastic cells and are therefore involved in local tumor spread has to our knowledge not yet been studied so far.

References

Abe H, Ikeda K, Watanabe I (1976) Teratoma of the ligamentum teres of the liver – a case report. Fukushima J Med Sci 23:1–10

Abedalthagafi M (2012) Gastrointestinal stromal tumour originating from the hepatic falciform ligament. BMJ Case Rep. 2012. pii: bcr0320126136

Adachi M, Sugita T, Maehara M, Sugaya H, Ihori M, Hisauchi T, Harada T, Kogure H, Tajima Y (1979) A case report of leiomyosarcoma originating in the ligamentum teres of the liver. Gastroenterol Jpn 14:238–242

Adamsen S (1983) Infarction of a lipoma in the round ligament of the liver causing acute abdomen (in Danish). Ugeskr Laeger 145:3259

Atkinson JB, Foster CE, Lally KP, Isaacs H, Siegel SE (1992) Primary endodermal sinus (yolk sac) tumor of the falciform ligament. J Pediatr Surg 27:105–107

Auh YH, Lim JH, Kim KW, Lee DH, Lee MG, Cho KS (1994) Loculated fluid collections in hepatic fissures and recesses: CT appearance and potential pitfalls. Radiographics 14:529–540

Ayyappan AP, Singh SE, Shah A (2007) Mature cystic teratoma in the falciform ligament of the liver. J Postgrad Med 53:48–49

Baba Y, Miyazono N, Ueno K, Kanetsuki I, Nishi H, Inoue H, Nakajo M (2000) Hepatic falciform artery. Angiographic findings in 25 patients. Acta Radiol 41:329–333

Baumgarten P (1881) Ueber die Nabelvene des Menschen. Arbeiten auf dem Gebiet der pathol. Anatomie und Bakteriologie aus dem Patholog.-Anatom. Institut zu Tübingen, I, Braunschweig

Bedioui H, Daghfous A, Daghfous A, Ksantini R, Nouira K, Chebbi F, Fteriche F, Rebai W et al (2008) Internal herniation through the falciform ligament revealed by acute intestinal obstruction (in French). Presse Med 37:44–47

Bem J, Bradley EL (1998) Subcutaneous manifestations of severe acute pancreatitis. Pancreas 16:551–555

Bettendorf U (1978) Lymph flow mechanism of the subperitoneal diaphragmatic lymphatics. Lymphology 11:111–116

Borisov AV (1968) Architectonics and histotopography of lymphatic capillary networks in the hepatic ligaments in man (in Russian). Arkh Anat Gistol Embriol 55:15–19

Bruneton JN, Kerboul P, Drouillard J, Menu Y, Normand F, Santini N (1987) Hepatic lipomas: ultrasound and computed tomographic findings. Gastrointest Radiol 12:299–303

Bryan DH, Pillarisetty S (1992) Cyst of the falciform ligament of the liver: a rare cause of right upper quadrant pain. Am Surg 58:779–781

Budarin VN (1988) Large lipoma of the round ligament of the liver (in Russian). Klin Khir 9:61

Burow KA (1838) Beiträge zur Gefässlehre des Fötus. Arch Anat Physiol 5:44–45

Cardello FP, Yoon DH, Halligan RE, Richter H (2006) The falciform ligament in the echocarcdiographic diagnosis of ascites. J Am Soc Echocardiogr 19:1047.e3–1047.e4

Charles A, Shaikh AA, Domingo S, Kreske E (2005) Falciform ligament hernia after laparoscopic cholecystectomy: a rare case and review of the literature. Am Surg 71:359–361

Charuzi I, Freund H (1976) Gangrene of the hepatic round ligament causing diffuse peritonitis: a case report. Am Surg 42:925–926

Chevrel JP, Salama J, Kemeny JL (1982) Anatomical and surgical study of the permeability of the round ligament of the liver (based on 197 cases). Anat Clin 4:285–287

Choi CW, Kim TO, Kim KY, Lee SM, Kim GH, Kang DH, Song GA, Kim S, Kim DH (2009) Perivascular epithelioid cell tumor (PEComa) of abdominal cavity from falciform ligament: a case report. J Korean Med Sci 24:346–349

Coulier B, Cloots V, Ramboux A (2001) US and CT diagnosis of a twisted lipomatous appendage of the facliform ligament. Eur Radiol 11:213–215

Coulier B, Broze B, Mailleux P, Maldague P (2009) Small-bowel herniation through the falciform ligament: 64-row MDCT. Emerg Radiol 17:73–78

Delbridge L, Connolly J (1982) Paraganglioma of the falciform ligament: a case report. Aust N Z J Surg 52:315–317

Doscher W, Chgardavoyne R, Teicher I (1980) Abscess of falciform ligament. N Y State J Med 80:1131–1133

Enterline DS, Rauch RE, Silverman PM, Korobkin M, Akwari OE (1984) Cyst of the falciform ligament of the liver. AJR Am J Roentgenol 142:327–328

Farkas E, Besznyak I, Koves I (1991) Giant lipoma of the ligamentum teres hepatis (in Hungarian). Orv Hetil 132:637–638

Feldberg MA, van Leeuwen MS (1990) The properitoneal fat pad associated with the falciform ligament. Imaging of extent and clinical relevance. Surg Radiol Anat 12:193–202

Friedrich K, Vogel HM, Henning H (1988) The importance of variant insertions of the ligamentum teres hepatis in the Cruveilhier-Baumgarten syndrome. Endoscopy 20:254–259

Gangopadhyay AN, Srivastava P, Upadhyaya VD, Hasan Z, Vijayendra KR, Sharma SP (2009) Mature cystic teratoma in falciform ligament of the liver in an infant. Afr J Paediatr Surg 6:132–133

Gaster J (1948) Internal hernia with strangulation of bowel due to a defect in the falciform ligament. Ann Surg 128:248–252

Gibo M, Hasuo K, Inoue A, Miura N, Murata S (2001) Hepatic falciform artery: angiographic observations and significance. Abdom Imaging 26:515–519

Gidwani AL, Mullan FJ, Kenny B (2004) Solitary fibrous tumour of the falciform ligament containing multiple foci of malignant transformation. J Clin Pathol 57:546–547

Gingalewski C, Lalikos J (2008) An unusual cause of small bowel obstruction: herniation through a defect in the falciform ligament. J Pediatr Surg 43:398–400

Golab B (1972) Lymphatic vessels of the hepatic ligaments in humans (in Polish). Folia Morphol 31:283–286

Gonzales-Carbalhaes O (1959) Portography. A preliminary report of new technique via the umbilical v. Clin Proc Child Itop 15:120–122

Goti F, Reinhart M, Decurtins M (2000) Idiopathic segmental fatty tissue necrosis of the ligamentum teres hepatis. Variation of a theme (in German). Chirurg 71:225–227

Harish K, Ashok AC, Alva NK (2003) Low grade fibromyxoid sarcoma of the falciform ligament: a case report. BMC Surg 3:7

Hillman BJ, D'Orsi CJ, Smith EH, Bartrum RJ (1979) Ultrasonic appearance of the falciform ligament. AJR Am J Roentgenol 132:205–206

Honda H, Watanabe K, Mihara K, Hoshi H, Sakihama M (1983) Lipoma of the hepatic falciform ligament. J Comput Assist Tomogr 7:170

Ibukuro K, Tsukiyama T, Mori K, Inoue Y (1998) Hepatic falciform ligament artery: angiographic anatomy and clinical importance. Surg Radiol Anat 20:367–371

Kakitsubata Y, Nakamura R, Shiba T, Sugimura H, Suzuki Y, Kakitsubata S, Watanabe K, Kawana T, Iwamura T (1993) Lipoma of the falciform ligament: US, CT, and MRI appearances. Clin Imaging 17:27–29

Kaneko K, Hara H, Ando H, Takagi A, Ema Y (1990) A case of adult falciform ligament hepatic abscess (in Japanese). Nippon Shokakibyo Gakkai Zasshi 87:268–272

Karabin JE (1951) Cyst in the ligamentum teres of the liver, remnant of the umbilical vein. Am J Surg 82:531–532

Kim SY, Lim JH (1985) Extension of hepatoma to the rectus abdominis muscle via ligamentum teres hepatis. Gastrointest Radiol 10:119–121

Kobayashi S, Terasaki M, Kuno T, Okamoto Y, Sakamoto E, Kamiya S, Shinohara T, Asaba Y (1999) A case of internal hernia through a defect in the falciform ligament treated with laparoscopic surgery (in Japanese). Nippon Geka Gakkai Zasshi 100:513–516

Kobayashi S, Matsui O, Gabata T (2001) Pseudolesion in segment IV of the liver adjacent to the falciform ligament caused by drainage of the paraumbilical vein: demonstration by power Doppler ultrasound. Br J Radiol 74:273–276

Krahn V (1974) Position of blood vessels in ligamentum teres hepatis and description of structure pecularities of the chorda venae umbilicalis (in German). Anat Anz 136:378–393

Krylov LB, Shurkalin BK (1968) A solitary cyst of the round ligament of the liver (in Russian). Khirurgiia 44:140–141

Lagoudianakis EE, Michalopoulos N, Markogiannakis H, Papdima A, Filis K, Kekis P, Katergiannakis V et al (2008) A symptomatic cyst of the ligamentum teres of the liver: a case report. World J Gastroenterol 14:3266–3268

Lakdawala M, Chaube SR, Kazi Y, Bhasker A, Kanchwala A (2009) Internal hernia through an iatrogenic defect in the falciform ligament: a case report. Hernia 13:217–219

Lange H, Rozentale I (1995) Necrosis of the ligamentum teres hepatis and the anterior abdominal wall in acute pancreatitis (in German). Zentralbl Chir 120:328–330

Laucks SS, Ballantine TV, Boal DK (1986) Abscess in the falciform ligament in a child with ventriculoperitoneal shunt. J Pediatr Surg 21:979–980

Li J, Jiang B (1993) A scanning electron microscopic study on three-dimensional organization of human diaphragmatic lymphatics. Funct Dev Morphol 3:129–132

Li XP, Xu DC, Tan HY, Li CL (2004) Anatomical study on the morphology and blood supply of the falcifoem ligament and its clinical significance. Surg Radiol Anat 26:106–109

Lipinski JK, Vega JM, Cywes S, Cremin BJ (1985) Falciform ligament abscess in an infant. J Pediatr Surg 20:556–558

Llyod T (2006) Primary torsion of the falciform ligament: computed tomography and ultrasound findings. Australas Radiol 50:252–254

Losanoff JE, Kjossev KT (2002) Isolated gangrene of the round and falciform liver ligaments: a rare cause of peritonitis: case report and review of the world literature. Am Surg 68:751–755

Majnarich G, Stout AP (1960) Hemangiopericytoma of the ligamentum teres of the liver; report of a case. Am J Surg 100:740–743

Marubayashi et al. (1998). http://www.ncbi.nlm.nih.gov/pubmed/9744402

McClelland RR (1975) Focal porta hepatis scintiscan defects: what is their significance? J Nucl Med 16:1007–1012

Merklin RJ (1971) The anterior abdominal fat body. Am J Anat 132:33–44

Michels NA (1955) Blood supply and anatomy of the upper abdominal organs. Lippincott, Philadelphia, pp 416–511

Mielke F (1972) Pathologische-anatomische Untersuchungen des Lymphgefässsystems im Lig. falciforme hepatis bei Leberzirrhosen. Acta Hepatogastroenterol 19:38–47

Miller BJ (1981) Falciform ligament aperture causing intestinal strangulation. Can J Surg 24:401–402

Mirilas P, Skandalakis JE (2002) Benign anatomical mistakes: right and left coronary ligaments. Am Surg 68:832–835

Missalek W (1993) Identification of the ligamentum teres hepatis by ultrasound and the clinical importance of its thickening. Trop Geogr Med 45:131–134

Mital RN, Bazaz-Malik G (1971) Leiomyosarcoma of ligamentum teres of the liver. Am J Gastroenterol 56:48–51

Miyazaki H, Takagi I, Toshima K, Onizawa N, Zeniya M, Kameda H, Yamaguchi H (1989) An autopsy case of hepatocellular carcinoma invaded into the ligamentum teres hepatis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 86:2464–2468

Morgan K, Ricketts RR (2004) Lymphangioma of the falciform ligament – a case report. J Pediatr Surg 39:1276–1279

Mori H, Aikawa H, Hirao K, Futagawa S, Fukuda T, Maeda H, Hayashi K (1989) Exophytic spread of

hepatobiliary disease via perihepatic ligaments: demonstration with CT and US. Radiology 172:41–46
Morita Y, Saito H, Okushiba S, Shinohara M, Satoh N, Uchino J (1987) A case report of leiomyosarcoma of the hepatic falciform ligament – clinical significance of the hepatic falciform artery (in Japanese). Rinsho Hoshasen 32:1613–1616
Motolese Lazzaro O (1966) On a case of a cyst of the falciform ligament of the liver (in Italian). Acta Chir Ital 22(Suppl 2):197–206
Ohashi I, Ina H, Gomi N, Himeno Y, Okada Y, Hanafusa K, Suzuki S, Shibuya H (1995) Hepatic pseudolesion in the left lobe around the falciform ligament at helical CT. Radiology 196:245–249
Pans A, Burnel M, Gillard R (1999) Gangrene of the round liver ligament: an unrecognized pathology (in French). Chirurgie 124:551–554
Parke WW, Settles HE, Bunger PC, Van Demark RE (1996) Malformations of the liver: some prenatal and postnatal developmental aspects. Clin Anat 9:309–316
Patel A, Lefemine V, Ramanand BS (2009) A rare case of peritoneal cyst arising in the falciform ligament. Cases J 2:134
Poilblanc M, Coquaz S, Welschbillig K, Arnaud JP, Hamy A (2006) A case report of stromal tumor in the ligamentum teres hepatis (in French). Gastroenterol Clin Biol 30:469–470
Pratap A, Tiwari A, Anachal N, Agrawal CS, Shreshta P, Shakya VC (2006) Falciform ligament abscess with portal pyemia in a newborn. J Pediatr Surg 41:1473–1475
Principe A, Spangaro M, Lapilli A, Vecchi R, Volta L, De Lorenzi P (1979) Congenital anomalies of the gallbladder. A case of retrohepatic gallbladder contained in the coronary ligament (in Italian). Minerva Chir 34:879–884
Saida Y, Tsunoda HS, Itai Y, Matsueda K (1994) Peritoneal implants without ascites: preoperative CT diagnosis in colon carcinoma patients. Radiat Med 12:221–224
Sappey MC (1893) Mémoire sur les veines portes accessoires. J Anat 19:517–524
Seniutovich VF, Genyk SN, Krysa VM (1976) Serous cyst of the round ligament of the liver (in Russian). Khirurgiia 1:128
Shiozaki H, Sakurai S, Sudo K, Shimada G, Inoue H, Ohigashi S, Deshpande GA, Takahashi O et al (2012) Pre-operative diagnosis and successful surgery of a strangulated internal hernia through a defect in the falciform ligament: a case report. J Med Case Reports 6:206
Siddins MT, Cade RJ (1990) Hepatocolonic vagrancy: wandering liver with colonic abnormalities. Aust N Z J Surg 60:400–403
Smirnov VE, Pravdin IS (1989) Serous cysts of the round ligament of the liver (in Russian). Vestn Khir Im I I Grek 143:60–61
Solomon A, Rubinstein Z (1984) Importance of the falciform ligament, ligamentum teres and splenic hilus in the spread of malignancy as demonstrated by computed tomography. Gastrointest Radiol 9:53–56
Sones PJ, Thomas BM, Masand PP (1981) Falciform ligament abscess: appearance on computed tomography and sonography. AJR Am J Roentgenol 137: 161–162
Sourtzis S, Canizares C, Thibeau JF, Philippart P, Damry N (2002) An unusual case of herniation of small bowel through an iatrogenic defect of the falciform ligament. Eur Radiol 12:531–533
Soyer P, Devine N, Somveille E, Rebibo G, Rambert C, Scherrer A (1996) Hepatic pseudolesion around the falciform ligament: prevelance on CT examination. Abdom Imaging 21:324–328
Spay G, Toure P, Diouf AB (1973) Angiofibroma of the hepatic round ligament (in French). Bull Soc Med Afr Noire Lang Fr 18:201–203
Spelle L, Soyer P, Rondeau Y, Giuhiri M, Scherrer A, Rymer R (1997) Nontumorous hepatic pseudolesion around falciform ligament: prevalence on gadolinium chelate-enhanced MR examination. AJR Am J Roentgenol 137:161–162
Srivastava PK, Gangopadhyay AN, Gupta DK, Sharma SP, Kumar V (2011) Unusual content of omphalocele: a congenital mature cystic teratoma of falciform ligament of the liver. Pediatr Surg Int 27:1355–1356
Susani M, Asboth F, Brinskele N (1983) A rare malformation of the liver in adults (in German). Morphol Med 3:81–88
Sykes JA, Norton KI, Bhattacharya N, Stombaugh L (2010) Small bowel obstruction secondary to strangulation through a defect in the falciform ligament after blunt abdominal trauma in a pediatric patient. Pediatr Emerg Care 26:436–438
Tajima T, Yoshimitsu K, Irie H, Nishie A, Hirakawa M, Ishigami K, Ushijima Y, Okamoto D, Honda H (2009) Hepatic falciform ligament artery in patients with chronic liver diseases: detection on computed tomography hepatic arteriography. Acta Radiol 50:743–751
Tate PS (1993) Hepatic torsion and dislocation with hypotension and colonic obstruction. Am Surg 59:455–458
Tesch C, Henne-Bruns D, Holstein AF (1990) Open lymph vessels of the ligamentum falciforme hepatis in the human (in German). Langenbecks Arch Chir 375:130–134
Tessari R (1970) Congenital cysts of the falciform ligament of the liver (in Italian). Minerva Med 61:625–632
Tison C, Regenet N, Frampas E, Masliah C, Le Borgne J (2005) Gangrene of the ligamentum teres hepatis (in French). Gastroenterol Clin Biol 29:204–205
Tomaszewski MM, Kuenster JT, Hartman K (1986) Leiomyosarcoma of ligamentum teres of liver: case report. Pediatr Pathol 5:147–156
Toughrai I, Errougani A, Elabssi M, M'bida R, Amraoui M, Chkoff R (2007) Malignant fibrous histiocytoma of the falciform ligament (in French). J Chir 144:173–175
Turkina NV, Pudiakov SM, Babkov AA, Semenov AB (1990) Strangulation of the round hepatic ligament in

white-line abdominal hernia (in Russian). Vestn Khir Im I I Grek 145:50–51

Umidon M (1967) Architectonic and topography of the left triangular ligament of the liver, the plica ligamenti triangularis sinistri and the phrenico-hepatic fossa in man (in Italian). Arch Ital Chir 93:661–672

Vadala G, Buffone A, Giarlotta R, Vadala V, Patti P, Falanga R (1985) A case of echinococcal cyst in the round ligament of the liver. Preliminary note (in Italian). Minerva Med 76:647–649

Vorburger S, Zuber M, Renggli JC, Schnabel K (2000) The window in the falciform ligament. A rare cause of hernia of the small intestine through the falciform ligament (in German). Chirurg 71:466–468

Watson SD, McComas B, Rannick GA, Stanton PE (1988) Gangrenous ligamentum teres hepatic causing acute abdominal symptoms. South Med J 81:267–279

Williams DM, Cho KJ, Ensminger WD, Ziessman HA, Gyves JW (1985) Hepatic falciform artery: anatomy, angiographic appearance and clinical significance. Radiology 156:339–340

Yamagiwa H, Onishi C, Kobayashi M (1967) Leiomyosarcoma of the suspensory ligament of the liver. Mie Med J 16:229–233

Yamaguchi J, Azuma T, Fujioka H, Tanaka K, Furui J, Tomioka T, Kanematsu T (1996) Leiomyosarcoma occurring in the ligamentum teres of the liver: a case report and a review of seven reported cases. Hepatogastroenterology 43:1051–1056

Ying DJ, Ho GT, Zhang ZZ (1992) Biomechanical study of revascularization of ligamentum teres hepatis. Proc Biomech Eng 1:119–121

Ying DJ, Ho GT, Cai JX (1997) Anatomic bases of the vascularized hepatic teres ligament flap. Surg Radiol Anat 19:293–294

Yoshikawa J, Matsui O, Takashima T, Sugiura H, Katayama K, Nishida Y, Tsuji M (1987) Focal fatty change of the livert adjacent to the falciform ligament: CT and sonographic findings in five surgically confirmed cases. AJR Am J Roentgenol 149:491–494

Zaev KN (1989) Multi-chamber cyst-like lymphangioma of the round ligament of the liver in a child (in Russian). Vestn Khir Im I I Grek 142:81–82

Part XXII

Nodular Hyperplastic Lesions of the Liver

Focal Nodular Hyperplasia (FNH) of the Liver

117

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_117

Abstract

Focal nodular hyperplasia (FNH) of the liver is a reactive mass-forming regenerative hyperplastic response of hepatocytes, secondary to localized vascular and circulatory abnormalities. FNH has a predilection for young females and represents, after hemangioma, the second most common benign hepatic tumorous lesion of the liver in adults. Many FNH are asymptomatic and detected by chance, but a minority of FNH are associated with various symptoms mainly related to large size or atypical location. Most FNH are solitary lesions that are predominantly located in the right liver lobe. In a minority of patients, multiple lesions, sometimes exceeding 30, are present. Macroscopically, FNH are well-circumscribed nodular, yellowish to tan masses with a characteristic nodular texture, radiating septa, and a central stellate scar-like fibrotic structure. Part of the lesions protrude from the liver and can become pedunculated masses. The diameter of FNH may exceed 20 cm. Histologically, FNH is characterized by nodules that consist of normal-looking hepatocytes forming thin plates. These nodules are separated from each other by fibrous septa and interspersed portal tract-like structures. The latter lack interlobular bile ducts but contain ductular proliferations. The fibrous tissue areas contain abnormal thick-walled blood vessels.

Introduction

According to the 2010 WHO classification, focal nodular hyperplasia (FNH; synonyms: hamartoma of the liver; hepatic pseudotumor; solitary hyperplastic nodule; lobar cirrhosis) is a regenerative hyperplastic response of hepatocytes, secondary to localized vascular abnormalities. The process is not neoplastic.

Ewing mentioned that typical cases of FNH were already described by Rokitansky, Salter, Engelhardt, and Wegelin (Ewing 1940). One of the first detailed descriptions emphasizing the septal architecture and the lack of bile ducts is that by Wegelin. In his thesis as of 1905 (in German, under the tutorship of Professor Theodor Langhans, Berne, the discoverer of the Langhans giant cell), Karl Wegelin described a solitary, well-circumscribed liver tumor, histologically characterized by a solid growth of hepatocyte plates with intervening sinusoids. Beginning at the periphery of the lesion, thin septa entered the nodule, dividing the tumor into irregular subunits of variable size. In the nodes of the septa, large vessels, including arteries and veins, were seen, but no bile ducts (Wegelin 1905; Walthard 1968). In later studies, the lesions were called "adenoma" (Branch et al. 1945), or "benign hepatoma" (Hoffman 1942). In the following years, the criteria of the entity and issues of nomenclature and classification and of pathology and pathogenesis have been developed step by step, ending up with a standardized diagnosis of FNH (Patton 1948; Greinacher 1950; Kay and Talbert 1950; Bartlett and Shellito 1951; Benz and Baggenstoss 1953; Wilson and Macgregor 1969; Knowles and Wolff 1976; Kerlin et al. 1983; Shortell and Schwartz 1991; Bartlett et al. 1996; Kondo 2000; Bioulac-Sage et al. 2001b, 2007)

Epidemiology

FNH occurs in both men and women, but shows a predilection for young women, with a ratio F:M of up to 8:1 (Reddy et al. 2001). After hemangioma, FNH is the second most common benign hepatic tumorous lesion in adults, with an incidence in adult autopsies of about 0.8 %. However, the diagnosis of FNH in the general population is now more frequently done, mainly due to improved imaging techniques, and the reported incidence is up to 3 %. FNH is diagnosed in wide age range, from small children to old age. In a study of 305 cases, median age at diagnosis was 38 years (Nguyen et al. 1999). Male patients may show multiple FNH in the absence of associated liver disease or medications (Cadranel et al. 2003).

FNH is an unusual hepatic lesion in children (Schmelling 1934; Benson and Pemberthy 1942; Maier 1955; Rhodes et al. 1978; Lack and

Ornvold 1986; Feng et al. 2000; Hung et al. 2001; Al-Attar et al. 2004; Chen et al. 2010; Towbin et al. 2011; Franchi-Abella and Branchereau 2013; Valentino et al. 2014). In a retrospective study examining 14 cases of FNH in children who previously had been treated for a malignancy, it turned out that FNH appears to be a late complication of a iatrogenic vascular disease, alkylating agents, veno-occlusive disease, and hepatic radiotherapy possibly playing a role in the generation of endothelial/vascular damage (Bouyn et al. 2003). Pediatric FNH has also been observed in an infant antenatally exposed to steroids (Prasad et al. 1995) and has been found in identical twins (Mindikoglu et al. 2005), suggesting a genetic background of an underlying vascular hepatic anomaly.

Clinical and Imaging Features

Many FNH are asymptomatic lesions that are detected by chance, but a minority of FNH are associated with various symptoms that are mainly related to large or huge size, atypical location, or unusual growth such as pedunculation (Chun Hsee et al. 2005). In a study of 305 lesions, 35.4 % were discovered incidentally (Nguyen et al. 1999). 57.7 % of patients with symptomatic FNH experienced abdominal pain, while an abdominal mass was detected in only 3.8 % and hepatomegaly in 0.8 % (Nguyen et al. 1999). FNH can undergo a variety of complications. In contrast to liver cell adenoma, spontaneous hemorrhage and rupture of FNH are a rare event (Becker et al. 1995; Li et al. 2007), but may result in life-threatening acute intraabdominal bleeding (Ishak and Rabin 1975; Knowles et al. 1978; Koch et al. 2006). As unusual as hemorrhage is central necrosis of FNH that results in sudden upper abdominal pain and fever (Cimmino and Scott 1978). Necrosis of FNH can result from infarction (Bathe et al. 2003), and the mechanisms may be similar to infarction of cirrhotic nodules (Kim et al. 2000). FNH can cause hepatic vein obstruction in case of large and centrally placed lesions (Arrive et al. 1999; Rangheard et al. 2002). In very rare instances, FNH was associated with elevated serum alpha-fetoprotein/AFP levels (Mneimneh et al. 2011), probably caused by regenerating hepatocytes in the lesion.

Numerous imaging features characterizing FNH have been described on CT and MR images. FNH are well-delineated mass lesions with a typical internal structure revealing an epithelial mass having the features of hepatic parenchyma, a radiant array of septa, and a central stellate scar-like fibrosis (Shamsi et al. 1993). An important diagnostic radiological feature is the so-called central scar (review: Elsayes et al. 2007), an alteration that is, however, not really a "true scar", but rather a complex fibrovascular structure resulting from remodeling during FNH growth and having a distinct pathophysiology. The central scar (the "scar sign"; Wenzel and Winters 1983) that is in evidence particularly in larger lesions, and is frequently seen in both CT and MRI pictures, can even more efficiently be visualized by more specific techniques, e.g., as the "star sign" on gadolinium-enhanced MR angiography (Ko et al. 2002). An enhancing scar has, overall, been reported to occur in 14–43 % of cases (Vilgrain et al. 1992). There are rare examples of FNH lacking a central scar (Matsushita et al. 1995). Part of FNH shows a spoke-wheel arterial pattern related to the architecture of septa originating from the central scar (Ungermann et al. 2007). FNH is viewed as a hyperplastic reaction by the liver parenchyma to a preexisting abnormal hypertrophic artery system without significant blood supply from the portal vein (Wanless et al. 1985a; Reddy and Schiff 1993; Namasivayam et al. 2007).

Macroscopic Pathology

Most FNH are solitary lesions (about 75 %) that predominantly develop in the right liver lobe. In approximately 30 %, three to five nodules are found, whereas more than five nodules (multiple FNH) occur in a minority of patients, however sometimes exceeding 30 nodules, either in one lobe or with a diffuse distribution (Knowles and Wolff 1976; Vilgrain et al. 1992; Colle et al. 1998; Kim et al. 2004; Finley et al. 2005;

Shen et al. 2007; Cordeiro et al. 2009). The size varies from few mm to more than 20 cm in diameter. In a study of 305 lesions, the median diameter of lesions was 3 cm; 26.3 % were 2 cm in diameter or less, 38 % measured 2–5 cm, and 35.7 % had a diameter of more than 5 cm (Nguyen et al. 1999). Macroscopically, most FNH are well-circumscribed, expanding intrahepatic lesions with a typically lobulated contour (Figs. 1, 2, 3, 4, 5, 6, 7, and 8). Pedunculated lesions with a defined vascular stalk occur, but are rare (Maier 1955; Brouquet et al. 1985; Sawhney et al. 1992; Nguyen et al. 1999; Wasif et al. 2008). In the study of Nguyen and coworkers, pedunculated lesions were found in 7/305 cases (Nguyen et al. 1999). "Classical" FNH are mostly of yellowish to tan color, rarely red congested areas are seen. On cut section, several patterns of nodularity are in evidence. The most common pattern is that of elongated or oval nodules arranged along septa in a more or less radiated fashion. In a second pattern, more elongated and sometimes bent or hook-shaped nodules form a "cerebriform" pattern or a pattern resembling the cut surface of a truffle. In a third pattern, the nodules are arranged in a haphazard fashion. The mass is usually composed of subunits each measuring 2–3 mm, causing the multinodular aspect on cut surfaces. Especially in large lesions, one dominant nodule is sometimes seen, associated with a rim of smaller nodules at the periphery or a cluster of small nodules at one place, suggesting that one nodule started earlier with growth or was subject to a stronger growth stimulation. Subcapsular lesions may bulge and often exhibit a geographical pattern or a regular checkerboard-like or

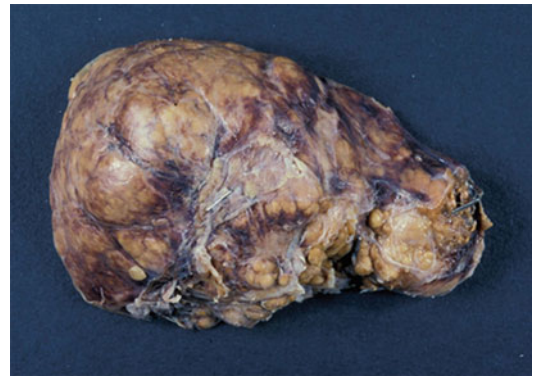

Fig. 1 Large focal nodular hyperplasia of the liver, resection surface

Fig. 2 Focal nodular hyperplasia of the liver, cut surface of a fresh, nonfixed resection specimen

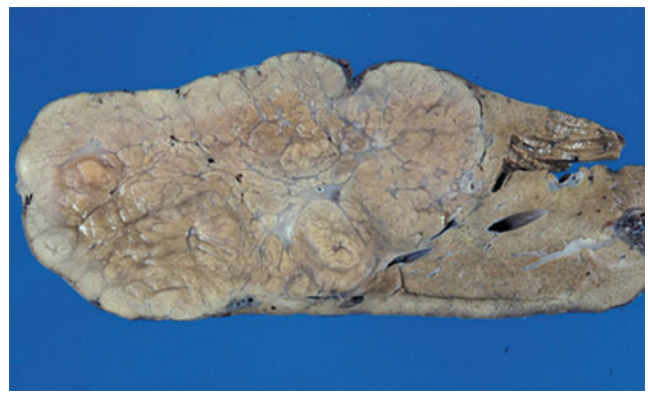

Fig. 3 Focal nodular hyperplasia of the liver, macronodular pattern

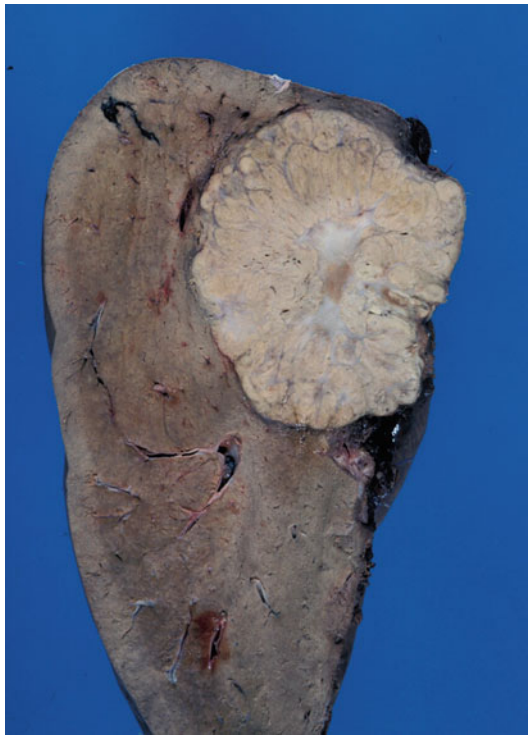

Fig. 4 Focal nodular hyperplasia of the liver reaching to the resection margin

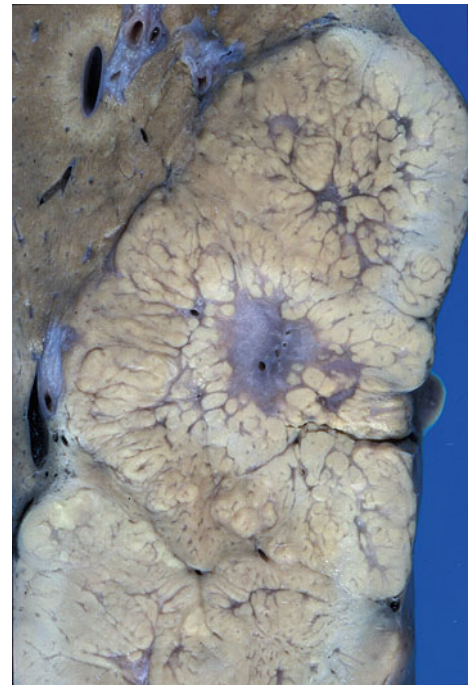

Fig. 5 Focal nodular hyperplasia of the liver with stellate scars (cut surface of a fixed resection specimen)

cobble-stone pattern, caused by the network of fibrous septa anchored to the capsule. On cut sections, the central stellate scar as a leading alteration in FNH can often be visualized with naked eye. It was found in 45.4 % among 305 lesions, and 3.6 % of lesions revealed more than one scar (Nguyen et al. 1999). Rarely, the central scar can extend, via fibrous septa, to the liver capsule, causing capsular retraction (Ko et al. 2003).

FNH can undergo several secondary changes, including central necrosis, infarction, hemorrhage, and calcification. Central necrosis of FNH can produce sudden onset of abdominal pain. Necrosis may be large and mimic parenchymal infarction (Bathe et al. 2003). Bleeding can produce blood-filled cysts that may later show fibrous obliteration (Langman and Hall 2001). Apart from necrosis or even infarction, FNH can rarely develop other changes, such as cluster-like internal cysts due to fibrinoid necrosis (Kottke et al. 2007).

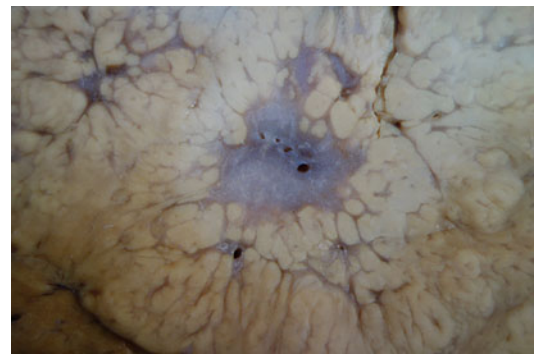

Fig. 6 Focal nodular hyperplasia of the liver. The *center* shows a stellate scar with prominent vessels at high magnification (cut surface)

Histopathology

The histopathologic presentation has been described and reviewed in detail in numerous reports (Orda et al. 1973; Lepreux et al. 2002;

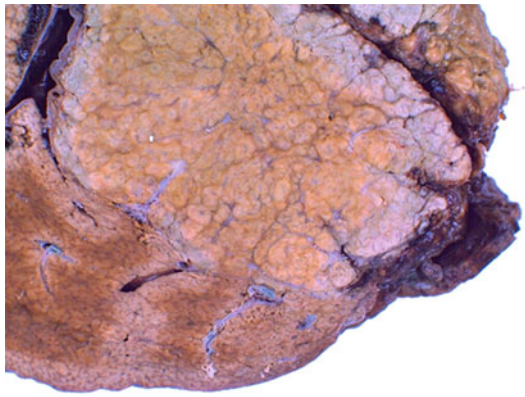

Fig. 7 Focal nodular hyperplasia of the liver with a micronodular pattern

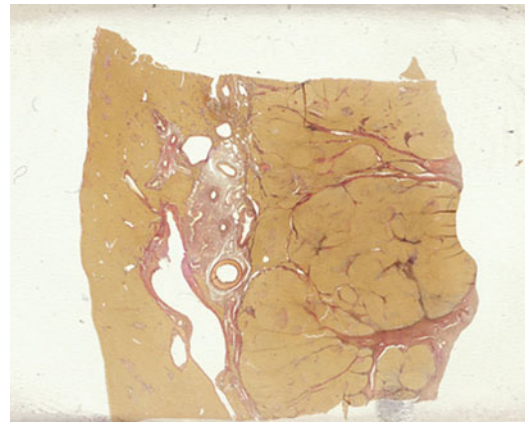

Fig. 9 Focal nodular hyperplasia of the liver. Nodular subunits are separated from each other by fibrous septa (Elastica van Gieson stain)

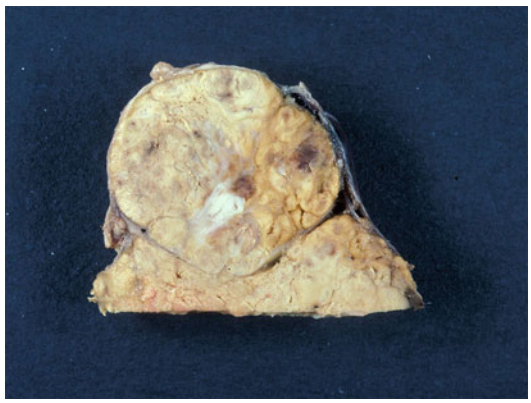

Fig. 8 Focal nodular hyperplasia of the liver, exophytically growing variant

Pan et al. 2004; Bioulac-Sage et al. 2007), including precursor lesions of FNH or "pre-FNH" (see below; Bioulac-Sage et al. 2008).

Parenchymal Nodules

Generally, typical and fully established FNH is characterized by a conglomerate of hepatocyte nodules separated by fibrous bands or septa (Fig. 9). The hepatocytes forming the nodules are arranged in a pattern reflecting normal hepatic parenchyma, i.e., liver cell plates that are two cells thick (couplets), although plates seemingly being one cell thick only may be seen. The hepatocytes forming the parenchyma of FNH do not differ morphologically from normal hepatocytes. Hepatocytes of FNH can undergo fatty change/steatosis, thought to be an extension of fatty liver to fatty FNH (Mitchell et al. 1991; Mortelé et al. 2000). Steatosis or granulocytic steatohepatitis has also been found in FNH-like lesions developing in the setting of alcoholic liver disease (Kim et al. 2008). In a subset of lesions, Mallory-Denk body formation has been reported (Wetzel and Alexander 1979). The nodules are separated by atrophic parenchyma and abnormal, portal tract-like structures. These abnormal portal tract-like structures almost always exhibit a marked ductular reaction, and this reaction is also found at the interface between nodular parenchyma and the periphery of the septa (Butron Vila et al. 1984). Typically, an interlobular bile duct is not found in the portal tract-like areas, which, therefore, per definition are not true portal tracts, as a triad (bile duct, artery, portal venous branch) is not present. In variable densities, lymphocytic infiltrates occupy these spaces. A fibrous capsule is lacking (Knowles and Wolff 1976). The characteristic deficiency of bile ducts has led to the term, "nodular hyperplasia with ductopenia" (Wanless; cited in Kageyama et al. 1998).

Central Scar and Abnormal Blood Vessels

Most lesions show a central fibrous scar (stellate or star-shaped scar), or several of these, the largest scar usually being situated close to the central part of the mass, and the other stellate scars being situated at variable distances from the center, and sometimes being connected to the major scar by fibrous septa (Figs. 10, 11, 12, and 13). These scars, and chiefly the central one, disclose malformed vascular structures, in particular large arteries and arterialized veins, but a bona fide portal venous branch is lacking. Large vessels have an irregular, markedly thickened intima with focal medial attenuation. Typically, the internal elastic lamina is poorly developed or duplicated. In the area of the central scar-like fibrosis, activated hepatic stellate cells are present, thought to contribute to fibrosis and being activated due to oxidative stress caused by arterial hyperperfusion in central parts of the lesion (Sato et al. 2009). The centers of FNH typically exhibit an abnormal compartment of arterial vessels. Most lesions are supplied by one or more anomalous arteries larger than expected for the target area. These arteries tend to branch and to form a spider-like structures or a complex network (Wanless 1987), seem

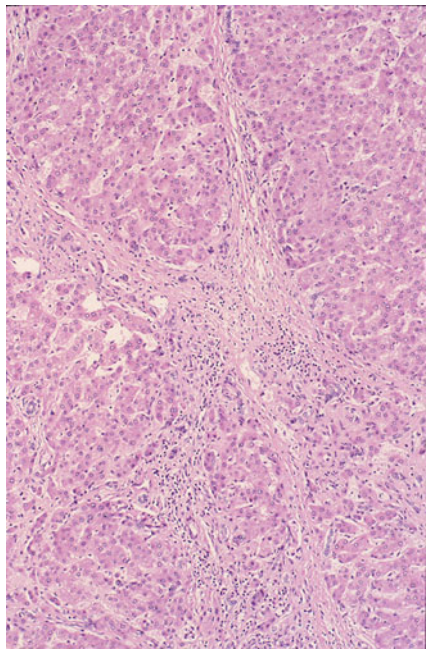

Fig. 10 Focal nodular hyperplasia of the liver, stellate scar. Note the absence of intralobular bile ducts (hematoxylin and eosin stain)

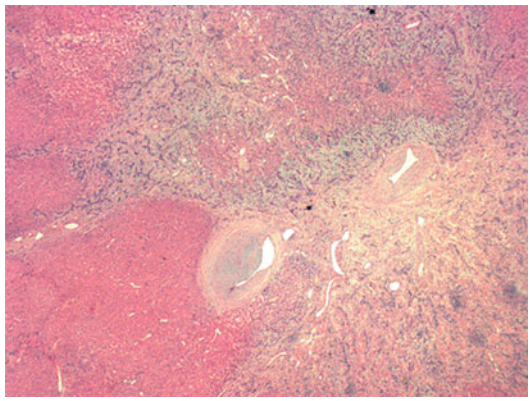

Fig. 11 Focal nodular hyperplasia of the liver, stellate scar with abnormal blood vessels. Part of the vessels show a marked excentrical intimal thickening of the wall (hematoxylin and eosin stain)

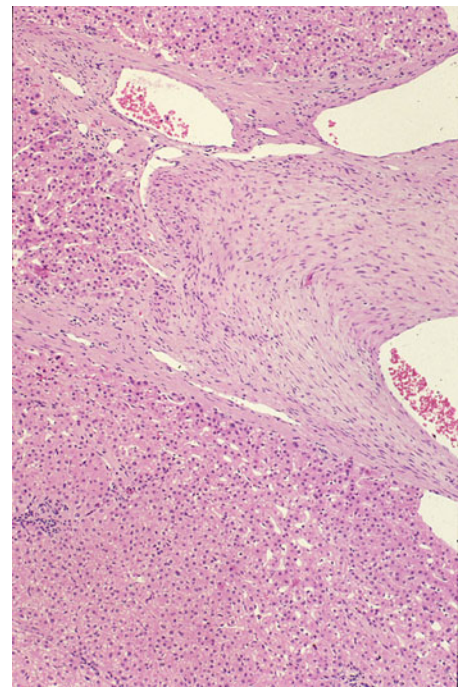

Fig. 12 Focal nodular hyperplasia of the liver. Abnormal blood vessels with thickened walls are situated within a stellate scar (hematoxylin and eosin stain)

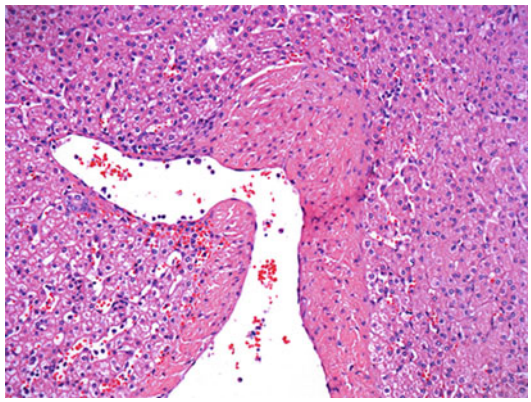

Fig. 13 Abnormal blood vessel in focal nodular hyperplasia at higher magnification (hematoxylin and eosin stain)

to take their origin in the central fibrous scar (Fechner and Roehm 1977), and are not accompanied by an interlobular bile duct and a portal venous branch.

It has been described that each artery branch feeds a separate nodule of about 1 mm diameter (Wanless et al. 1985a), and adjacent nodules then coalesce to form a compound nodular lesion. The arterial blood drains directly into sinusoids and into hepatic veins. In a study on 29 resected FNH, the vascular pattern of the masses was investigated by use of colored gelatin injection. No orientation with respect to portal tracts and central/terminal veins was evident in any of these lesions. Anomalous arteries were in connection with capillaries located to the fibrous septa, and the latter drained into CD34-and vWF-positive sinusoids adjacent to the septa. venous vessels were connected to central or hepatic veins surrounding the nodular lesions, and intranodular sinusoids were connected to the sinusoids in the adjacent normal liver. Gelatin injected at autopsy into the hepatic artery appeared not only in the anomalous arteries, but also in capillaries and in sinusoids adjacent to the fibrous septa, and CT during arterial portography disclosed no portal flow in the lesions. It was concluded that arterial blood in FNH flows from the anomalous arteries via the capillary bed into sinusoids adjacent to the fibrous septa (Fukukura et al. 1998). In rare situations, the abnormal vascular network in the center of FNH reveals angioma-like features (Saito et al. 2005; Glas et al. 2008). FNH can be diagnosed by needle biopsy, especially in the knowledge that the sample comes from a mass, and when the tissue shows the characteristic interface between abnormal portal tract-like structures with ductular profiles, abnormal arteries and lack of a bile duct, and the normal-looking parenchyma (Fabre et al. 2002; Makhlouf et al. 2005). These hallmarks are not usually found in fine needle aspiration preparations. In cytological preparations of histologically verified FNH, spindle cell fragments have been observed, potentially leading to misinterpretation as a mesenchymal tumor (Krishnamurthy and Nerurkar 2002).

Other Histologic Features

Calcifications have been noted in FNH (Langman and Hall 2001) and may be related to postnecrotic calcium salt deposition (so-called dystrophic calcification). They are in evidence by use of imaging in 1.4 % (5/357; Caseiro-Alves et al. 1996), in another study in 1/78 cases (Brancatelli et al. 2001), and they are visualized histologically. They were evident in the form of small, solitary spots located centrally or peripherally within the lesions and resemble calcified lesions seen in fibrolamellar carcinoma. Sometimes, the abnormal, thick-walled vessels of FNH exhibit tiny calcifications. Apart from calcifications, focal ossification of FNH has been described (Langman and Hall 2001). Whereas the number of Kupffer cells is reduced in HCCs, specifically in large tumors and those of low differentiation, Kupffer cell numbers are increased in FNH in comparison with extranodular liver in up to 46.2 % of cases (Tanaka et al. 1996), this phenomenon being one reason for the selective uptake of superparamagnetic iron oxide by these lesions. Iron-poor FNH can occur in iron-storing livers in hemochromatosis. In a patient with peripheral portal vein tumor thrombosis, segmental hepatic iron deposition of the parenchyma peripheral to the occluded portal venous branch was noted, and it was suggested that the absence of portal blood flow may cause this focal change (Kawamori

et al. 1991). On the other hand, it has been proposed that FNH can accumulate iron in situation of intralesional hemolysis (Mahfouz et al. 1999).

Immunohistochemistry

The pertinent immunohistochemical features of FNH and their position in the differential diagnosis of hepatocellular adenoma have been reviewed (Bioulac-Sage et al. 2012, 2014; Balabaud et al. 2013; Sempoux et al. 2013, 2014). In cytokeratin immunostains, hepatocytes in the periphery of lobules of FNH may show a mild CK7 immunostaining, while, expectedly, the proliferated ductular profiles in portal tract-like structures are strongly reactive for both CK7 and CK19 (Fig. 14; Iyer et al. 2008; Ahmad et al. 2009). The ductular cells are also reactive for Bcl-2, as ductules in normal liver (Charlotte et al. 1994).

Upregulation of hypophosphorylated activated beta-catenin is present in FNH in the absence of activating mutations and regulates the overexpression of six perivenous genes, including glutamine synthetase. Hepatocytes in FNH are immunoreactive for glutamine synthetase/GS, a beta-catenin target (Rebouissou et al. 2008a; Bioulac-Sage et al. 2008, 2009; review: Bioulac-Sage et al. 2011). The expression of GS is a sensitive and specific marker for diagnosing FNH (Tsai et al. 2012) and is helpful specifically in needle biopsies, where diagnosis of FNH is sometimes difficult as the typical architecture of FNH is not easily seen, but after GS immunostaining the diagnosis was certain in 86.7 % of cases (Bioulac-Sage et al. 2012). Positive cytoplasmic staining formed large areas, anastomosed in a map-like pattern, often surrounding hepatic veins, but GS was not expressed in hepatocytes close to fibrotic bands containing arteries and ductules (Bioulac-Sage et al. 2009; Sempoux et al. 2014). There are forms of FNH that lack a map-like staining pattern for GS, but rather display a patchy GS pattern along with expression of serum amyloid-associated protein (Joseph et al. 2014). A further maker of mature hepatocytes that stains all FNH cases is arginase-1 (McKnight et al. 2012). The expression of E-cadherin, N-cadherin, and alpha-catenin of normal hepatocytes is preserved in liver cells of FNH (Kozyraki et al. 1996). FNH can be reactive for fatty acid-binding protein and serum amyloid A protein.

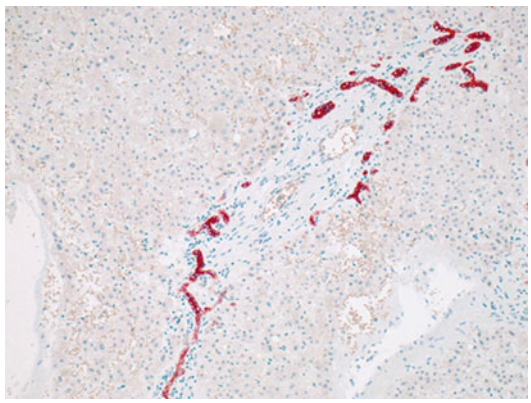

Fig. 14 Ductular proliferations in focal nodular hyperplasia. No interlobular bile ducts are seen (cytokeratin 19 immunostain)

In CD34 immunostains, FNH revealed various patterns of endothelial cell staining, ranging from CD34 inflow staining to mixed inflow-diffuse, to diffuse staining patterns (Kong et al. 2000; Iyer et al. 2008; Ahmad et al. 2009). FNH show a downregulation of CD143, in that the number of CD143+ sinusoidal endothelial cells was significantly reduced in FNH in comparison with extralesional liver and hepatocellular adenoma, suggesting that CD143 immunostaining might be of diagnostic use (Grantzdorffer et al. 2004). The capillarized sinusoidal channels in FNH express podocalyxin-like protein 1, a CD34-related sialomucin that is also expressed in tumor-associated microvasculature endothelial cells in HCCs (Heukamp et al. 2006). Fibrillin-1 and elastin as components of the microfibrillar system show a distribution and expression in FNH that is different from normal extralesional liver. Fibrillin-1 was more strongly expressed in the perisinusoidal space of FNH than normal liver, but showed a similar continuous expression along the perisinusoidal space, while expression was discontinuous in liver cell adenomas (Lepreux et al. 2004). We showed that, in contrast to hepatocellular carcinoma, liver cells in FNH are not reactive

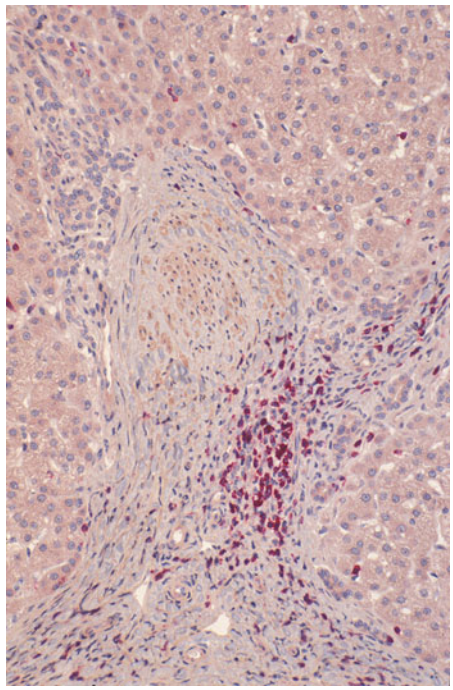

Fig. 15 Focal nodular hyperplasia of the liver with focal T-cell infiltrates in a stellate scar (CD3 immunostain)

for glypican-3 (Zhu et al. 2001), a finding confirmed by several subsequent studies (Libbrecht et al. 2006a; Ligato et al. 2008; Wang et al 2008; Nassar et al. 2009). FNH do no express agrin (Tatrai et al. 2009). In contrast to HCC, nuclei of FNH do not express p53 protein (Ojanguren et al. 1995; Schaff et al. 1995). FNH possess a distinct extracellular matrix produced by fibroblastoid cells, myofibroblasts, and activated stellate cells. Immunohistochemically, the matrix of central scars resembled that of portal tracts, but contained more vitronectin. The fibrous zone surrounding the scar itself was rich in laminin and thrombospondin, suggesting a strong fibrogenic response. The matrix lining the sinusoid-like vessels in the FNH parenchyma retained the features of hepatic perisinusoidal space, including the presence of tenascin. The perisinusoidal fibrosis developing in FNH is accompanied by the induction of integrin receptors on hepatocytes and sinusoidal endothelial cells (Scoazec et al. 1995). In contrast to hepatocellular carcinoma, FNH is not immunoreactive for the marker aldo-ketoreductase family 1B10/AKR1B10 (Matkowskyj et al. 2014).

In the tissue forming portal tract-like structures and fibrous septa, lymphoid cell infiltrates may be found, usually of low density and mostly consisting of CD3-positive T-cells (Fig. 15).

FNH Variants and Possible Precursor Lesions of FNH

Introduction

Apart from classical FNH, several variants of this lesion have been described and classified over the years under various, not yet standardized or generally accepted names. Future consensus studies will clarify and standardize these lesions further.

FNH with Microvascular Abnormalities and So-called Telangiectatic FNH

There are variants of FNH showing marked dilatations of the sinusoidal vascular bed. This change may involve large sectors of the nodule and is already visualized at low magnification. It was proposed to denote such lesions, FNH with major sinusoidal dilatation, whereby the regions with sinusoidal ectasia may not stain for GS (Sempoux et al. 2014). Currently, telangiectatic FNH (TFNH) is defined as a lesion different from classical FNH and to represent a variant of liver cell adenoma rather than FNH (Paradis et al. 2004; Bioulac-Sage et al. 2005). Telangiectatic nodular liver lesions previously termed TFNH are, therefore, treated in a separate chapter. Previously, TFNH was described as an uncommon lesion that has been defined as FNH with one cell-thick hepatic plates separated by markedly dilated sinusoids, lacking a central scar, few fibrous bands/septa, few reactive ductules, and with subtle or even no architectural distortion. Occasional hemorrhagic and necrotic centers are noted (Wanless et al. 1989; Nguyen et al. 1999; Fabre et al. 2002; Lepreux et al. 2003b). TFNH frequently presents with multiple lesions (MTFNH), described under the term multiple FNH syndrome (Wanless et al. 1989).

Steatotic FNH

Part of FNH shows marked steatosis of hepatocytes, whereby small to large triglyceride droplets are visualized in the target cells (steatotic FNH). Accumulation of fat in lesional hepatocytes is also known for true liver cell neoplasms, including hepatocellular adenoma and HCC. Steatotic FNH has characteristic imaging features, specifically MR (Ronot et al. 2013).

Pre-FNH

Bioulac-Sage and coworkers described a "pre-FNH" by use of glutamine synthetase/GS (Bioulac-Sage et al. 2008). In this early lesion, GS-reactive hepatocytes occupied a wider area than in the surrounding perilesional liver and tended to extend outwards. Portal tracts bordering the nodule were more fibrotic, lacked portal vein branches and interlobular bile ducts, but with arterial proliferation often in proximity with large draining veins. There were rare isolated arteries and hepatic veins were rare. The findings of this early lesions confirmed that, according to the "Wanless hypothesis," there is an initial portal tract injury in FNH morphogenesis leading to local portal vein damage, resulting in abnormal circulation, arteriovenous shunts, scar formation, ductular reaction, and compensatory liver cell hyperplasia.

Small FNH and "Subtle" FNH

Owing to the more refined imaging techniques, more and more small hepatic nodules are detected where the diagnosis may be difficult to achieve, also with respect to histologic examination. By "small" one usually refers to nodular lesions not exceeding a diameter of 2 cm. Such small nodules, due to their probably early stage of development, may lack the key features of FNH as defined in larger lesions (Schilling et al. 2000; Bioulac-Sage and Balabaud 2001), and differentiation from small liver cell adenoma becomes a demanding task (Bioulac-Sage et al. 2001a). It seems to be safe to assume that nodules larger than 3 cm in most instances show the features described as typical for *bona fide* FNH in daily practice. Small lesions with a somewhat ambiguous morphology have, in the sense of a working formulation, arbitrarily been classified into four types, a fifth type representing fully developed FNH (Lepreux et al. 2003a), as follows: (1) Type 1 lesion: Tiny nodules, steatotic or not, with mildly disorganized liver architecture and dilatation of thin-walled vessels in the immediate vicinity of portal tracts; (2) Type 2 lesion: Nodules with mildly disorganized liver architecture and enlarged or tortuous arteries (with tortuosity identified by finding multiple cross-sections of the same vessel) in portal tracts or in septa. Portal tracts sometimes lack a bile duct or portal vein; (3) Type 3 lesion: Nodules like those of type 2 that also include hyperplastic foci; (4) Type 4 lesions: Minor or "subtle" forms of FNH with incomplete or very small fibrous scar, inconstant ductular reaction, and incomplete nodular organization; and (5) Type 5 lesion: Full-blown FNH. Macroscopically, small FNH-like lesions are distinguished from the surrounding normal liver tissue by a slight change in color, in that these nodules are usually paler (Lepreux et al. 2003a). In the latter study, nonclassified nodules detected by imaging techniques corresponded to type 1 and 2 lesions, and subtle FNH (type 4 lesions) occasionally had type 2 or 3 lesions at their periphery. On the other hand, small FNH showing in the center cirrhotic-like nodules may be surrounded with type 1 and type 2 lesions. The hyperplastic foci seen in type 3 (hyperplasia required for this type) were fed by arterioles accompanied by slight cytokeratin 7-positive ductular reaction (poor or no staining for cytokeratin 19). Via formation of thin fibrous bands tending to approximate neighboring hepatic veins, the morphology of type 4 lesions emerges (minor form of FNH, subtle FNH). It is reasonable to assume that at least part of these lesions represent changes along the pathway leading from simple nodules to established FNH, although the four types described reflect single steps within a pathogenic continuum (Lepreux et al. 2003a). Lepreux and coworkers theorized that communications of arterioles with

various blood vessels (terminal portal vein branches, inlet venules, and even sinusoids) may lead to dilatation of the latter and to an abnormal local circulation.

Histopathology of the Extralesional Liver

In at least part of livers harboring FNH, several types of abnormalities have been detected. In one investigation, abnormal small arteries not accompanied by portal tracts were found more often in FNH livers, as were CD34-positive sinusoids around portal tracts. In addition, small uniform nodule formations with ring-like siderosis were noted (Motosugi et al. 2009). In a further study, the extranodular liver area in 73 % of FNH cases revealed alterations that were similar to but milder than those in the FNH nodule (Kondo et al. 1998).

FNH in Livers with Preexistent Chronic Liver Disease

FNH usually occurs in normal or, at least, noncirrhotic livers. In fact, the International Working Party formulation of nodular hepatic lesions defines FNH as "a nodule composed of benign-appearing hepatocytes occurring in a liver that is otherwise histologically normal or nearly normal" (International Working Party 1995). This observation as such suggests that FNH is not a simple, exaggerated regenerative response. However, there are situations where FNH, either solitary or multiple, or FNH-like lesions, develop in abnormal livers, including livers with chronic fibrosing hepatopathy/cirrhosis, livers with sequelae of hepatic venous outflow disorders, and associations of FNH with other synchronous liver tumors (see below). Relatively few studies have reported the occurrence of FNH in chronic liver disease. Adenomatous hyperplasia, as it was previously termed, resembling FNH (Terada et al. 1993), and FNH-like hyperplastic nodular lesions (Sugihara et al. 1990; Nakashima et al. 1996; Kageyama et al. 1998; Libbrecht et al. 2001, 2006b) were described in cirrhotic livers. The lesions described by Terada and coworkers were small (approximately 1 cm) and contained portal tracts, but a large number of arteries were present in central star-like fibrotic areas (Terada et al. 1993). It has been suggested that FNH-like lesions in cirrhosis can be histologically distinguished from bona fide FNH by the finding that FNH-like lesions containing a central stellate fibrosis exhibit, in contrast to FNH, a fibrous capsule, and they lack signs of hepatocyte hyperplasia and may show iron deposition (Sugihara et al. 1990). Typically, FNH lacks a fibrous capsule (Knowles and Wolff 1976). Among the published cases with available histologic figures, the case of Kageyama and coworkers reveals a marked resemblance to "true" FNH, with a diameter of 4.5 cm, a central stellate-like scar and radiating septa, and lacking portal tracts, but again with a fibrous capsule (Kageyama et al. 1998; their Fig. 3). In a retrospective study on 146 liver transplants with cirrhosis, five patients showed a total of 12 nodules (size range: 4–23 mm; median: 10.5 mm; 1.2 % of a total of 240 nodular lesions) with histologic features suggestive of FNH (FNH-like nodules; Quaglia et al. 2003). All these small lesions showed a nodular architecture with mildly inflamed vascular fibrous septa and fibrous scar-like areas containing a predominantly lymphocytic infiltrate with ductular proliferations, as seen in FNH. Unpaired small arteries were found in the liver parenchyma of three lesions. The majority of the nodules exhibited a predominantly marginal sinusoidal pattern of CD34 expression, as seen in cirrhotic livers; all lesions revealed canalicular cholestasis, and large-sized arteries adjacent to the lesion were detected in the majority of the cases (Quaglia et al. 2003). Together, these observations suggest that nodular lesions with many features of FNH can, albeit rarely, occur in the context of hepatic cirrhosis. These small nodular lesions should not be confounded with macroregenerative nodules developing in cirrhosis (Theise et al. 1992; Ferrell et al. 1992

FNH: Association with Other Hepatic Tumors or Disease States

FNH and Hepatocellular Adenoma

A synchronous/simultaneous presentation of FNH and hepatocellular adenoma in the same liver has been documented several times (Casarella et al. 1978; Reichlin et al. 1980; Grange et al. 1987; Nguyen et al. 1999; Di Carlo et al. 2003; Laurent et al. 2003). In a series of 168 patients with 305 FNH lesions, the association of FNH with liver cell adenoma was observed in 3.6 % of the cases (Nguyen et al. 1999). In another study, liver cell adenoma together with FNH was found in 5 out of 30 cases of "multiple benign hepatocytic nodules," and all five patients were women on oral contraceptives (Laurent et al. 2003). Three patients exhibited additional small nodules that could not be classified with certainty. In most situations, the two lesions have developed sequentially (metachronically), but in some of these it is difficult to judge whether one of the lesions was in fact FNH (Antoniades et al. 1975; Goldfarb 1976). In one instance with apparently bona fide FNH, an adenoma was resected; 23 months later three new 2-cm lesions were detected via angiography, and two of them fulfilled the criteria of FNH (McLoughlin et al. 1973). Data on the occurrence of this combination may be controversial due to the difficult assessment of small lesions, the features of FNH versus adenoma sometimes being overlapping; for example, a liver cell adenoma may be modified be recurrent hemorrhage with subsequent scarring, thus grossly resembling FNH. On the other hand, a small sample of an FNH may look like an adenoma histologically. The association of liver cell adenoma and FNH could be coincidental or then related to a common cause, such as contraceptive-induced angiogenic abnormalities, tumor-induced growth factors, or thrombosis and local arteriovenous shunting (Laurent et al. 2003). A common pathway may be considered in those rare situations where hepatocellular adenoma develop within FNH (Guntz et al. 1983). There is few reports describing mixed adenoma-focal nodular hyperplasia of the liver (Handra-Luca et al. 2006; Chen et al. 2011).

FNH and Hepatocellular Carcinoma

Several reports have described the synchronous occurrence of hepatocellular carcinoma (HCC) and FNH (Kobayashi et al. 1993; Chen et al. 2001; Coopersmith et al. 2002; Cucchetti et al. 2003; Kellner et al. 2003; Zhang et al. 2004). In a carefully performed autopsy study on 11 patients having HCC in noncirrhotic and nonfibrotic livers, four exhibited FNH (Kobayashi et al. 1993). In one study, the two masses were closely associated within one tumorous lesion, and clonal analysis (based on HUMARA) suggested that FNH and HCC derived from the clonal expansion of two different clones (Chen et al. 2001). In another patient, the two synchronously detectable tumors were not spatially related, and no chromosomal aberrations (based on comparative genomic hybridization) were found in the FNH occurring synchronously with the HCC (Kellner et al. 2003). Lesions fulfilling the criteria of FNH may be difficult to discern from larger regenerative nodules in cirrhotic livers with HCC, because such hyperplastic foci can aggregate to form larger units of hyperplastic parenchyma with a rearrangement of fibrous tissue septa (Kato et al. 2001).

FNH and Nodular Regenerative Hyperplasia

A complex relationship between HCC and nonneoplastic hyperplastic hepatocyte reactions is further illustrated by the observation that HCC may be associated with nodular regenerative hyperplasia (NRH). Among 342 noncirrhotic livers with HCC, 23 showed NRH (Nzeako et al. 1996). In an autopsy study on 11 patients with HCC without cirrhosis, NRH occurred in one

instance (Kobayashi et al. 1993). Apart from ordinary HCC, FNH has also been found to be associated with fibrolamellar carcinoma in the same liver (Saul et al. 1987; Davidson et al. 1990). In one reported patient, nodular hyperplasia resembling FNH surrounded fibrolamellar carcinoma (Saxena et al. 1994). In this patient, there was an apparently direct transition between the two lesions, whereas in another report, FNH was adjacent to but distinct from FL-HCC (Saul et al. 1987). The nodules may represent a hyperplastic response to the high vascularity of FL-HCC.

FNH and Hepatic Vascular Tumors

Further published associations comprise FNH with hemangioma (Mathieu et al. 1989; Wanless 2000; Vilgrain et al. 2003), hemangioma and multiple liver cysts (Toshikuni et al. 2001), hepatic adenoma and hemangioma (Di Carlo et al. 2003), and angiomyolipoma, bile duct adenoma, and hemangioma (Langner et al. 2001). FNH occurring with hemangioma of the liver is of particular practical and theoretical interest. In the older literature, hepatic hemangiomas in association with FNH were observed in 7 of 34 patients (20 %; Benz and Baggenstoss 1953), 6 of 23 patients (26 %; Mathieu et al. 1989), and 4 of 23 autopsied patients (17 %; Wanless et al. 1989). In a more recent and larger study, among 148 patients with FNH, 29 (20 %) had FNH with one or more associated hepatic hemangiomas, in comparison with 9 % in a control group without FNH, indicating that patients with FNH are in fact more likely to have an associated liver hemangioma in a significant and nonrandom manner (Vilgrain et al. 2003). The association of FNH with hemangioma has been suggested to be related to a common vascular-mediated pathogenic pathway, because hemangiomas have also been observed together with other regenerative nodules of the liver (Ndimbie et al. 1990). Furthermore, it has been noted that FNH and liver cell adenomas occur more often patients who have coexisting vascular tumors, portal venous absence or occlusion, or portohepatic venous shunts (Ishak and Rabin 1975; Grazioli et al. 2000). Multiple FNH have been observed together with two different types of hepatic vascular tumors: cavernous hemangioma and epithelioid hemangioendothelioma (EHE) (Bralet et al. 1999; comment: Wanless 2000). In this young woman taking oral contraceptives, EHE affected both liver and lung. The authors suggested that, as EHE typically infiltrates liver sinusoids and intrahepatic veins with polypoid projections, this tufted intravascular growth pattern may have caused decreased perfusion of the liver in EHE areas, with consequent increased blood flow to other hepatic areas; this nonuniformity of blood flow eventually favors the emergence of FNH (Bralet et al. 1999). This hypothesis is supported by the observation that epithelioid hemangioendothelioma of the liver occurred together with hepatic nodular regenerative hyperplasia (Malamut et al. 2001).

Other Associations

Multiple FNH have been observed to occur in conjunction with hepatic leiomyosarcoma with epithelioid features (Iordanidis et al. 2002), the FNH lesions proposed to have been emerged owing to abnormal hepatic blood supply. The coexistence of FNH and hepatic focal fatty change producing so-called pseudotumor has been reported (Wu et al. 2003). FNH has been observed in association with familial glioblastoma (Everson and Fraumeni 1976).

Differential Diagnosis

The main differential diagnoses comprise liver cell adenoma, macroregenerative nodules, and other hepatocellular nodular lesions (review: Hytiroglou and Theise 1998). Furthermore, other liver cell masses with a central scar-like structure have to be distinguished, e.g., hepatocellular carcinoma with a central scar (Yamamoto et al. 2006). Nodules resembling FNH occur in alcoholic liver cirrhosis (Lee et al. 2007) and are discussed in another paragraph.

The Natural History of FNH and Biology of Disease

Growing FNH

FNH may develop rapidly, mainly in cases with vascular disorders, but after their initial phase, growth may vary considerably among the lesions. By use of an MRI follow-up, interval growth was seen in 15 % of lesions over 7–48 months, with increase in size of 2–1.7 cm and percentage change of 105–340 % (mean: 64 %; Halankar et al. 2012). A significant proportion of FNH exhibit slow growth or seemingly remain stable in size. Rarely, FNH show accelerated or rapidly expanding growth, due to unknown reasons ("progressive type of FNH"; Sadowski et al. 1995). There are also situations where the number of lesions will suddenly increase (Sato et al. 2006). Progression of multiple lesions of FNH has been observed, associated with an angiographically documented increase in artery diameter, suggesting a role of arterial hyperperfusion of the target area (Kaji et al. 1998). Relatively few observations have so far suggested that there is no direct relationship of FNH growth and oral contraceptive intake (Kubota et al. 2001). In case of progressive growth, FNH may compromise large intrahepatic vessels, such as the hepatic veins, and hence produce a clinically dangerous behavior (Papanikolaou et al. 2009).

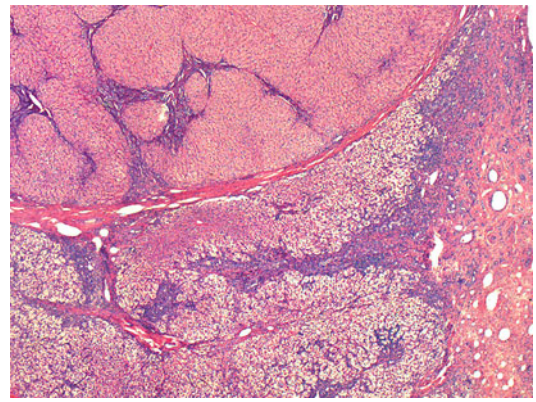

Fig. 16 Focal nodular hyperplasia with circumscribed regressive changes (lower half of figure; hematoxylin and eosin stain)

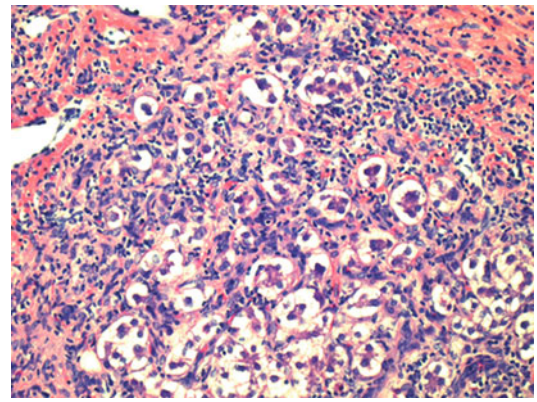

Fig. 17 Focal nodular hyperplasia with regressive changes. Part of the cells exhibit marked ballooning (hematoxylin and eosin stain)

Regressing FNH

FNH can undergo regressive changes, characterized by a distortion of the nodular arrays, generation of dense fibrotic tissue in a focal distribution, crowing of blood vessels, and collapse of GS-positive areas (regressing FNH; Sempoux et al. 2014; Figs. 16 and 17). FNH can regress partially or completely (Ohmoto et al. 2002; Kuo et al. 2009; Laumonier et al. 2010). One case of regressing FNH was histologically studied based on a resection specimen. Part of the 4-cm-sized nodule was still recognizable FMH, with glutamine synthetase-positive hepatocyte nodules surrounded by fibrous bands, inflammatory infiltrates, and mild ductular reaction. A second part of the nodule was more fibrotic, with numerous arteries showing extremely thick walls and a very narrow lumen. This part was devoid of GS-positive hepatocytes and of ductular reaction (Laumonier et al. 2010). In an ultrasound study of 16 cases with a mean follow-up of 33 months, the size was reduced in 7/16 at the end of the follow-up, and in 1/16 the lesion had disappeared (Di Stasi et al. 1996). The process of regression may extend over long time periods, e.g., 10 years (Aufort et al. 2003). In the investigation of Kuo et al. (2009), the significant factors associated with regression or even disappearance of FNH were older age, nodule diameter less than 2 cm,

and longer follow-up time. Multiple regression analysis showed that older age and longer follow-up time were the independent factors associated with regression/disappearance of FNH. In a retrospective MRI study of 120 consecutive patients with FNH, interval regression was noted in 8 % of nodules over a period of 7–63 months, with decrease in size of 0.2–0.9 cm (mean: 0.5 cm; Halankar et al. 2012). There few observations suggest that regression of FNH may ensue subsequent to discontinuation of oral contraceptives (Ross et al. 1976; Aldinger et al. 1977; Scott et al. 1984; Cote 1997), but a role of sex steroids is still disputed.

Pathogenesis of FNH

Abnormal Vascularization in FNH

Distinct patterns of vascular abnormalities, and a disordered local blood flow caused by them, are in the center of pathogenetic pathways leading to FNH. The frequent presence of obstructive vascular lesions not only in established FNH, but also in early FNH and putative FNH precursor lesions, and the finding of abnormally structured and abnormally large vessels in FNH has led to the hypothesis that FNH is a parenchymal response to focally increased blood flow (Kondo 2001, 2003; Kondo et al. 2004). There is increasing evidence that an abnormal blood circulation in the liver is a major etiologic factor for the development of FNH, but the mechanisms leading from an early focal regenerative or hyperplastic response to a sometimes large lesion with a distinctive architecture are far from clear. Theories relating to a "vascular factor" in the pathogenic pathway focused both at the inflow tract and the outflow tract of the liver. Wanless and his group suggested that a local portal vein injury, e.g., caused by thrombotic occlusion or pylephlebitis/portal vein endophlebitis, is an initial step in a pathogenetic cascade of events (Wanless et al. 1985a; the "Wanless hypothesis"). This initial PV lesion leads to secondary large arteriovenous shunts, followed by arterialization of the local PV system associated with irregular thickening of the vascular intima, resulting in highly abnormal thick-walled vessels resembling dystrophic arteries. The authors also proposed that the loss of interlobular bile ducts as a typical feature of FNH and followed by reactive ductular proliferation is related to portal tract changes, but this has to be studied in more detail, as bile ducts are not fed by the portal vein, but by branches of the hepatic artery. Another hypothesis has it that the primary lesion is situated in the outflow tract, outflow obstruction (e.g., hepatic vein thrombosis) causing congestion with fibrosis, parenchymal collapse, arteriovenous shunting, and subsequent portal vein and bile duct loss. In both the "primary inflow variant" and the "outflow variant" of mechanisms, the end result is a local rearrangement of vascular structure and an abnormally increased local flow of partially arterialized blood.

Based on the finding of abnormal and supernumerary arteries and arterioles in FNH, it has been proposed that an increased arterial flow might cause hyperperfusion of the target parenchyma, thus leading to subsequent hepatocellular hyperplasia (Wanless et al. 1985a). In fact, in addition to the typical centrifugal flow, a centripetal shift of arterial blood from hepatic arteries directly to sinusoids and hepatic veins has been demonstrated with single-level dynamic CT during hepatic arteriography (Miyayama et al. 2000). However, the risk of FNH and other hyperplastic liver lesions is obviously also increased in hepatic circulation disorders not primarily related to changes in arterial perfusion, including venous malformations, and disorders of the hepatic venous outflow tract. The idea has therefore emerged that FNH, similar to NRH, might be a rather nonspecific reaction to any type of focal ischemia induced by various mechanisms. If so, this hypothesis would however require an explanation as to why FNH and its putative precursors are single lesions in some, and multiple lesions in other patients, and why FNH lesions never occur to such an amount and in such a distribution as, e.g., the lesions in NRH. A distinctive situation with formation of a pathologic vascular "field effect" favoring multiple and synchronous FNH lesions might be represented by FNH occurring in oral contraceptive users, because these livers show an

abnormal hepatic vascular bed also outside the nodules themselves (Lepreux et al. 2003b). In what follows, several entities causing abnormal hepatic blood flow and known to be associated with FNH and FNH-like lesions are discussed.

Hepatocyte Hyperplasia in Hepatic Inflow Disorders

Portal Vein Thrombosis

There are several situations supporting a pathogenic role of venous inflow disorders of the liver for the development of hepatic nodular hyperplastic changes. FNH is a complication of long-standing portal vein thrombosis (Chiti et al. 1992; Bureau et al. 2004), and FNH can develop around a portal vein cavernoma (Ribera Cano et al. 2007; Marin et al. 2011).

Congenital Absence of the Portal Vein

Congenital absence of the portal vein (CAPV; for classification, see Morgan and Superina 1994; Badler et al. 2002), with visceral venous return to the suprahepatic inferior vena cava, is sometimes associated with hyperplastic hepatocyte nodules, including FNH (Okuda et al. 1988; Matsuoka et al. 1992; Guariso et al. 1998; Altavilla and Guariso 1999; Kinjo et al. 2001; De Gaetano et al. 2004; Koizumi et al. 2006; Schmidt et al. 2006; Chandler et al. 2011; Scheuermann et al. 2012) or nodular regenerative hyperplasia (Motoori et al. 1997; Arana et al. 1997; Grazioli et al. 2000; Tanaka et al. 2003; Kudo 2003). The hyperplastic nodular lesions can grow to impressive size (e.g., 10 cm diameter; Tanaka et al. 2003). Similarly, a hypoplasia of the intrahepatic portal venous system in congenital extrahepatic portocaval shunt can cause hepatic hyperplastic nodules (Yonemitsu et al. 2000). In other situations, intrahepatic portal venous obstruction due to failure of communication between the embryonic vitelline veins has caused abnormal gross hepatic lobulation already in utero, suggesting that pathologic venous flow can induce an early abnormal liver growth response (Johnson et al. 1979). The effects of portal vein agenesis can be mimicked by portal vein thrombosis that has been shown to be associated with nodular regenerative hyperplasia of the liver (Fukai et al. 1992) or with partial nodular transformation/PNT (Terayama et al. 1995). PNT has also been found around intrahepatic portal venous emboli of hepatocellular carcinoma (Hoso et al. 1996).

Congenital and Acquired Portocaval Shunts

First described by Abernethy in 1793, congenital vascular shunts between the main portal vein or its main central branches and the inferior vena cava (the "Abernethy malformation") are rare defects (Park et al. 1990; Howard and Davenport 1997; Lane et al. 2000) classified into Abernethy type 1 (usually in girls with other congenital anomalies; includes congenital absence of the portal vein with redirection of portal blood directly into the inferior caval vein) and type 2 (includes a side-to-side primarily extrahepatic connection between the inferior vena cava and an otherwise normal portal vein (Howard and Davenport 1997; Badler et al. 2002). The drainage sites of the splanchnic veins are the inferior vena cava, the left renal vein, the right atrium, and the azygos veins.

Congenital extrahepatic portocaval shunts can be associated with hepatic hyperplastic nodules (Yonemitsu et al. 2000), including large FNH nodules (Kitzing et al. 2011; Lisovsky et al. 2011; Pupulim et al. 2013). Sometimes, these lesions are of remarkable size; a large hyperplastic liver nodule has been noted in congenital portocaval shunt of Abernethy type 2 (Kanamori et al. 2003). In an animal model, congenital portacaval-shunt rats display focal hyperplastic changes of hepatocytes and even hyperplastic foci nodules, the latter mainly in the periportal zone (Vonnahme et al. 1984; Bioulac-Sage et al. 1985). Portocaval anastomosis in the rat can cause the emergence of hyperplastic foci in the otherwise atrophic liver (Dubuisson et al. 1985). Hyperplastic liver nodules after portacaval anastomosis have been described (Weinbren and Washington 1976). On the other hand, there are investigators who failed to produce hepatic hyperplastic nodules in rats by portacaval anastomosis and testosterone (Wanless and

Gledhill 1979). Multiple FNH have been observed after portocaval shunting (Scheuermann et al. 2013), and hyperplastic nodular hepatic lesions have been found following end-to-side portocaval shunting in childhood (Fukushima et al. 2007).

Spontaneous intrahepatic portosystemic shunts (SIPSS) are very rare, and less than 50 cases have been reported. SIPSS may be acquired, and they are then associated with liver cirrhosis and portal hypertension, taking the form of a large tubular vessel that connects the right portal vein to the retrohepatic vena cava (Masatoshi et al. 1993; Landen and Delugeau 2003). Congenital SIPSS usually result from patent ductus venosus (Arantii) or vitelline veins. Spontaneous intrahepatic portosystemic shunts (Lalonde et al. 1992; Landen and Delugeau 2003), spontaneous intrahepatic portohepatic shunts (Materne and Van Beers 1998), mesocaval shunts (Sakatoku et al. 1996), and intrahepatic porto-portal communications in the absence of the horizontal segment of the right portal vein and the umbilical portion of the left portal vein (Mignon et al. 1996) were associated with FNH.

Abnormal Branching of the Portal Vein

That an anomalous venous supply of the liver can provoke a circumscribed expansion of the hepatocyte population is shown by giant caudate lobe hyperplasia in case of anomalous caudate portal vein branching (Gabata et al. 1999; Kwak et al. 2000).

Hyperplastic Hepatocyte Reactions in Acquired Portal Vein Obstruction

In case of invasion of portal vein branches by malignancies, obstructive portal venopathy can induce a peritumoral hyperplasia of the liver. However, such hyperplasias lack the nodular aspect, the ductular reaction, and the central scar of FNH (Arnason et al. 2013).

Hepatoportal Sclerosis

Hepatocytic hyperplastic lesions also emerge in hepatoportal sclerosis, characterized by distal portal vein phlebosclerosis with the formation of portocaval shunts (Blanc et al. 2000), but FNH has apparently not yet been observed in this phlebopathy.

Hepatocyte Hyperplasia in Persistence of the Ductus Venosus and in Association with Umbilical Vein Anomalies

The ductus venosus connects the umbilical vein to the inferior vena cava in fetal life and subsequently closes rapidly after birth. About 50 % of umbilical venous blood passes through the ductus venosus, while the remainder is distributed to both lobes of the liver, the fetal liver exerting a major role in influencing venous return to the heart and in regulating oxygen distribution (Rudolph 1983). Predicted blood flows in humans through the ductus venosus and umbilical vein increase throughout gestation (from about 25 to 75 ml/min and from about 45 to 370 ml/min, respectively), while the flow fraction shunted via the ductus venosus diminishes (Edelstone 1980; Pennati et al. 2003). Persistence of a patent ductus venosus, which occurs sporadically or as a familial trait, results in an intrahepatic portosystemic venous communication from the portal venous system to the inferior vena cava (Barsky et al. 1989). A patent ductus venosus has been detected in infants with and without cardiac defects. In adults, the diagnosis is made as an incidental finding or in subjects presenting with hypoglycemia or portosystemic encephalopathy. Nodular hepatic lesions occur as a complication of a persistent ductus venosus, e.g., partial nodular transformation (PNT) of the liver (Wanless et al. 1985b), and other hepatocytic tumor-like lesions of the liver (Matsubara et al. 1996). PNT is a rare condition of unknown pathogenesis in which nodules composed of hepatocytes replace portions of the liver substance. PNT has also been observed in connection with portal vein thrombosis (Terayama et al. 1995). In familial patent ductus venosus, notable attenuation of the main portal vein with diminished intrahepatic branches was observed, and large hyperplastic liver lesions compatible with FNH were detected in one study (see below; Jacob et al. 1999).

Variations and malformations of the umbilical veins are extremely rare (Prust and Eskandari 1967; Theander and Karlsson 1978; Ricklan

et al. 1988). In the normal situation, the umbilical cord initially has two umbilical veins. Toward the end of the 4th gestational week, blood from the two vitelline and two umbilical veins passes directly into the sinus venosus. Subsequently, the growing hepatocyte cords interrupt the course of the vitelline veins, thus forming the sinusoidal network. After approximately 6 weeks, the umbilical vein system becomes connected to the hepatic sinusoids, the right umbilical vein obliterates and disappears by days 33–34, either by complete atrophy or by fusion with the left umbilical vein, whereas the part of the left umbilical vein between the body wall and the liver persists throughout fetal life, as does the ductus venosus. With the increase in blood flow from the placental circulation, a direct connection is established between the remaining left umbilical vein and the right hepatocardiac channel, which is the ductus venosus. Congenital anomalies of the umbilical veins can cause disorders of parenchymal development and hyperplastic reactions in the liver. They have been categorized into three groups (Ricklan et al. 1988). In the first group, the veins show normal attachment point to the abdominal wall and to the liver, but their intraabdominal course is abnormal, sometimes causing intestinal obstruction. The second group is characterized by anomalies of the umbilical vein itself. The neonatal umbilical cord can contain two veins instead of one; this accessory vein represents the persistent right umbilical vein. A persistent right umbilical vein compromises the placental blood flow achieved by the ductus venosus, with excessive placental blood returning to the fetal heart. The third group comprises abnormalities of the umbilical vein within the body and includes an umbilical vein bypassing the liver to enter the right atrium, the coronary sinus, the inferior vena cava, the iliac vein, or the right branch of the portal vein.

FNH or FNH-Like Lesions Developing in Hepatic Venous Outflow Disorders

In Budd-Chiari syndrome, several types of nodular hyperplastic lesion have been observed,

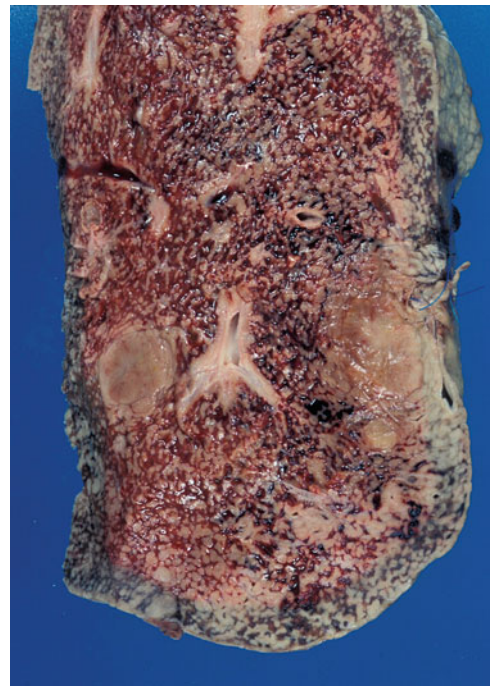

Fig. 18 Focal nodular hyperplasia (FNH) and FNH-like lesions in Budd-Chiari syndrome

including large regenerative nodules, lesions resembling FNH, and nodules that can histologically not be distinguished from bona fide FNH (Fig. 18; Ibarrola et al. 2004). In 23 patients followed up for Budd-Chiari syndrome, 19 patients developed multiple benign nodules, most of which were smaller than 4 cm in diameter (Vilgrain et al. 1999). Multiple macroregenerative nodules of the liver have been found to be caused by failure of hepatic venous drainage in Budd-Chiari syndrome (Zhou et al. 2000; Ibarrola et al. 2004). In a study of multiple nodular hepatic lesions occurring in the livers of four patients with Budd-Chiari syndrome, 15 of 32 nodules examined histologically displayed a central scar, and some nodules had other alterations typical for FNH (Maetani et al. 2002). FNH-like lesions subsequent to hepatic venous thrombosis have been reported (Schilling et al. 2000; Cazals-Hatem et al. 2003). However, not every nodular hepatic lesion developing in the setting of Budd-Chiari syndrome is a hepatocytic nodular lesion, but may also represent focal hemorrhage (Shapiro et al. 1993).

Nodular hyperplastic changes of the liver, mainly nodular regenerative hyperplasia, occur in stenosing lesions of small hepatic veins, in particular VOD/veno-occlusive disease (Russmann et al. 2001).

Hepatocyte Hyperplasia in Arterial and Other Vascular Malformations

Hereditary hemorrhagic telangiectasia (HHT; see the ▶ Chap. 58, "Tumor-Like Vascular Malformations") is sometimes associated with nodular transformation of the liver, the nodules being related to abnormally developed arteries and arteriovenous shunts (Wanless and Gryfe 1986; Ravard et al. 2004; Gincul et al. 2008; Khalid and Garcia-Tsao 2008). The prevalence of hyperplastic nodular lesions varies, however, considerably among different investigations. Among 52 HHT families who underwent a screening program for the detection of hepatic vascular malformations, FNH was found in 5 out of 274 subjects, with tumor diameters ranging from 2 to 9 cm (1.8 %; Buscarini et al. 2004). Thirty patients (19 women) with HHT studied in the setting of the Belgian Registry showed more nodular lesions: the authors observed a high prevalence (47 %) of asymptomatic hepatic tumors with radiologic and histologic characteristics of FNH for the majority of these tumors (Brenard et al. 2010). Among 171 consecutive HHT patients, hepatic nodular lesions were found in 6 (3.5 %; Scardapane et al. 2013). Pathogenetically, the complex intrahepatic arteriovenous shunts are likely to cause focal hyperperfusion with arterialized blood, causing a hyperplastic liver cell response. It has to be emphasized that hepatic arterioportal shunts themselves can radiologically mimic hepatic tumors (Matsuo et al. 2002).

Vascular malformations of the celiac axis and the hepatic artery branch in Klippel-Trenaunay syndrome can be associated with multiple FNH (Haber et al. 1995; Bathgate et al. 1999). There is a rare syndrome of FNH, neoplasia of the brain, and intracranial vascular malformations (Wanless et al. 1989; Goldin and Rose 1990).

Hepatocyte Hyperplasia in Disorders of Sinusoidal Perfusion

Sinusoidal obstruction is well established to cause nodular regenerative hyperplasia (Rubbia-Brandt et al. 2010), but can also be associated with larger hyperplastic lesions. FNH has been observed in patients with sinusoidal obstruction syndrome due to hematopoietic stem cell transplantation (Sudour et al. 2009). Two reports document children with sickle cell anemia (sickle cell disease, SCD) who developed FNH, possibly caused by the impairment of blood flow by sickling erythrocytes (erythrostasis) and the tendency for small vessel occlusion (Markowitz et al. 1980; Heaton et al. 1991). In fact, sickling in the sinusoidal vascular bed, making part of sickle cell hepatopathy, causes a nonuniform blood distribution. However, the effects of sickling on the microvascular bed are more complex. In SCD, microvascular flow is episodic, even in asymptomatic patients, so the effect of sickling is also modulated by factors other than mere sickling. The present concept is that SCD is also an inflammatory state associated with the activation of several cell types. Conduit vessels in SCD exhibit impaired vasodilation to endogenous and exogenous nitric oxide (Eberhardt et al. 2003). In SCD, blood microparticles derived from erythrocytes, thrombocytes, monocytes, and endothelial cells circulate, expressing tissue factor promoting blood coagulation (Shet et al. 2003).

Hepatocyte Hyperplasia in Portal Hypertension

FNH can develop in the context of idiopathic portal hypertension (IPH; Kondo et al. 1998). In some patients, multiple FNH emerged (Eda et al. 1999). Ten FNH were detected in a female patient with IPH, CREST syndrome, and protein S deficiency (Sanchez Manuel et al. 1997).

FNH Developing in Conjunction with Liver Hemangiomas

As outlined above, FNH can be combined with hemangioma in the same liver, but the relationship between these two lesions is not clarified. In one small child with a spontaneously shrinking liver hemangioma, follow-up showed that a nodule of FNH had emerged exactly at the site where previously the involuting hemangioma was situated, suggesting a causal relation between the two lesions (Turowski et al. 2009).

FNH and FNH-Like Nodules Associated with Steroid Hormones

Up to three quarters of females with FNH were found to be long-term users of oral contraceptives (OC). Therefore, prolonged OC intake and pregnancy have been suggested to be related to FNH pathogenesis (Davis et al. 1975; Bartok et al. 1980; Tajada et al. 2001). Low levels of estrogen receptors have been detected in FNH (Bojar et al. 1984), whereas expression of progesterone receptors was not demonstrated in FNH (Kubota et al. 2001). However, in a large study on 216 women, neither the size nor number of FNH lesions were influenced by OC use, and pregnancy was not associated with FNH changes or complications (Mathieu et al. 2000). A lack of effect of pregnancy on growth progression or complications of large FNH was confirmed in a recent study (Rifai et al. 2013). The question as to the pathogenetic significance of OC and other sex steroids has, therefore, to be tested in further studies. In the light of the important role played by vascular, and particularly portal venous alterations in FNH, thrombotic events induced by OC and related substances may theoretically be considered as pathogenetic elements. Few cases of FNH have also been found in association with androgenic substances (Cap et al. 1983; Serke et al. 1986; Helsing and Nielsen 2006) and intraconazole (Wolf et al. 2001).

FNH Developing Post-chemotherapy and/or Post-radiotherapy

FNH of the liver is increasingly diagnosed in children that had treatments for hematooncologic diseases, including leukemias and solid tumors, among the latter specifically neuroblastoma (Joyner et al. 2005; Marabelle et al. 2008; Benz-Bohm et al. 2010). The pathogenesis of these FNH is not known, but damage of hepatic vasculature by chemotherapeutic agents or ionizing radiation has been considered; for example, a role of endothelial damage by alkylating agents or radiotherapy has been suggested (Bouyn et al. 2003). Multiple FNH was found in association with oxaliplatin-based chemotherapy (Donadon et al. 2013).

Other and Rare Associations

FNH was found in grafted livers, possibly as a consequence of an altered hepatic circulation in the posttransplant liver (Ra et al. 2010). In children, FNH was detected following hematopoietic stem cell transplantation (Masetti et al. 2013). Interesting observations are also those where FNH was found within tumors showing hypervascularity; for example, FNH almost completely surrounded by metastatic renal cell carcinoma has been described, and the observers suggested that tumor-associated hyperemia may have played a pathogenic role (Nisar et al. 2002). FNH developed within 1 year after blunt abdominal trauma (Savoye-Collet et al. 2002). The pathogenic relationship is not clear, but traumatic injury to the liver can cause vascular lesions that might induce a hyperplastic response, such as hepatic artery pseudoaneurysms or arteriovenous fistulas (Schmidt et al. 1980). Rarely, FNH has been detected in the context of thorotrast liver disease (Sano et al. 1985). It has to be added that other reactive hepatocytic nodular changes, i.e., nodular regenerative hyperplasia of the liver (Dachman et al. 1987; Beer et al. 1998), and an ill-defined nodularity of the liver (Velasquez et al. 1985) have also been observed in association with thorotrastosis.

FNH was found in association with biliary atresia after Kasai hepatic portoenterostomy (Okugawa et al. 2008), Fanconi anemia (Nuamah et al. 2006), glycogenosis type I (Takamura et al. 1995), and glycogenosis type VI (Ogawa et al. 2010). Similar to liver cell adenoma (Beuers et al. 1991), FNH has been reported in association with Klinefelter syndrome (47, XXY), suggested to be related to the hormone imbalance present in this disorder (Santarelli et al. 2003) and in Turner syndrome (Roulot 2013).

Clonality of FNH, FNH Dysplasia, and Hepatic Malignancy

By use of several methods, it turned out in most studies that FNH are polyclonal lesions in 50–100 % of cases (Paradis et al. 1997; Nakayama et al. 2006; Cai et al. 2009; Gong et al. 2009), although results of monoclonality have also been published (Gaffey et al. 1996).

In a minority of cases, hyperplasic hepatocytes of FNH may undergo dysplastic changes (Fig. 19). Rarely, marked hepatocellular atypia interpreted as so-called large cell change has been found in FNH (Agaimy et al. 2003; Pai et al. 2009). In a 73-year-old male patient, this change was associated with formation of Mallory bodies in the atypical target cells, and it was suggested that these alterations characterize a distinct rare variant of FNH (Agaimy et al. 2003).

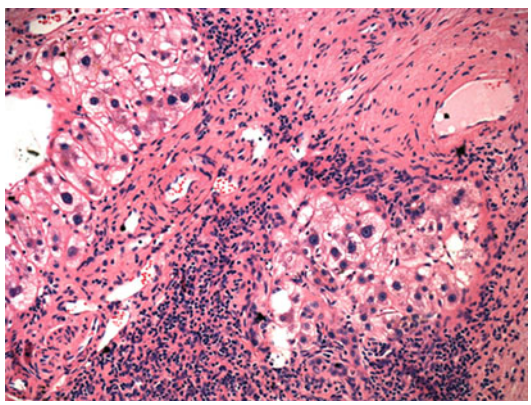

Fig. 19 Focal nodular hyperplasia with cellular/nuclear atypia (hematoxylin and eosin stain)

Dysplastic changes that develop in FNH are thought to be a first step in a carcinogenic pathway. In fact, there are relatively uncommon instances where hepatocellular carcinoma developed within preexisting FNH (Davis et al. 1975; Langrehr et al. 2006; Petsas et al. 2006; Haubert et al. 2010). Fibrolamellar carcinoma has also been reported to arise in FNH (Imkie et al. 2005). This has led some authors to assume that fibrolamellar carcinoma might be the malignant counterpart of FNH.

Cytogenetic and Molecular Features

Most FNH have no or relatively few genetic abnormalities. Chromosomal gains found in FNH mainly included 11q, 9q, 17q, and 22q (Chen et al. 2002). Trisomies of chromosomes 1 and 8 found in HCC were not found in FNH (Nasarek et al. 1995). In one child with FNH, a dup(8p)/(del(8q) recombinant chromosome had been found (Tokutomi et al. 2007). As outlined above, they show upregulation of activated beta-catenin in the absence of activating beta-catenin gene mutations (review: Rebouissou et al. 2008a).

Liver cell adenomas and FNH have been studied in detail in regard to molecular features (Rebouissou et al. 2008b). Based on the assessment of 209 selected genes in 14 FNH samples by use of RT-PCR, it was found that seven genes were significantly upregulated or downregulated in these lesions. Among these, the most informative were angiopoietin-1 and angiopoietin-2 (Paradis et al. 2003). In FNH, angiopoietin-1 was upregulated, and angiopoietin-2 was downregulated, and the Ang-1/Ang-2 ratio was highly and specifically increased in FNH compared with normal liver or other groups of lesions. Tie-2 mRNA, the receptor of Ang-1 and Ang-2, was detected at the same level in FNH as in normal liver. The specific increase of the Ang-1/Ang-2 ratio in the presence of a functional angiopoietin receptor may thus be involved in the pathogenesis of abnormal blood vessels in FNH (Paradis et al. 2003). In a recent study of nine FNH, a significant increase of angiopoietin-1 was found, whereas no significant changes in

angiopoietin-2, receptor tyrosine kinase with immunoglobulin-like and EGF-like domains 2, VEGF-A, or VEGFR-2 were observed. Based on a frequent history of vascular injury in FNH, it was concluded that angiopoietin-1 might exert different effects in FNH, such as stimulating the recruitment of myofibroblasts to result in dystrophic vessels (Gouw et al. 2010).

References

Agaimy A, Kaiser A, Wuensch PH (2003) Severe cytological atypia (large cell change) in focal nodular hyperplasia with numerous Mallory bodies. A benign (adaptive) change? Pathol Res Pract 199:509–511

Ahmad I, Iyer A, Marginean CE, Yeh MM, Ferrell L, Qin L, Bifulco CB, Jain D (2009) Diagnostic use of cytokeratins, CD34, and neuronal cell adhesion molecule staining in focal nodular hyperplasia and hepatic adenoma. Hum Pathol 40:726–734

Al-Attar M, Verma R, Shannon RS, McKeever PA, Rickett A (2004) Focal nodular hyperplasia in a child with hemihypertrophy and multiple cutaneous vascular malformations. Australas Radiol 48:77–79

Aldinger K, Ben-Menachem Y, Whalen G (1977) Focal nodular hyperplasia of the liver associated with high dose estrogens. Arch Intern Med 137:357–359

Altavilla G, Guariso G (1999) Focal nodular hyperplasia of the liver associated with portal vein agenesis: a morphological and immunohistochemical study of one case and review of the literature. Adv Clin Path 3:139–145

Antoniades K, Campbell WN, Hecksher RH, Kessler WB, McCarthy GE (1975) Liver cell adenoma and oral contraceptives. Double tumor development. JAMA 234:628–629

Arana E, Marti-Bonmati L, Martinez V, Hoyos M, Montes H (1997) Portal vein absence and nodular regenerative hyperplasia of the liver with giant inferior mesenteric vein. Abdom Imaging 22:506–508

Arnason T, Fleming KE, Wanless IR (2013) Peritumoral hyperplasia of the liver: a response to portal vein invasion by hypervascular neoplasms. Histopathology 62:458–464

Arrive L, Dahan H, Tubiana JM (1999) Hepatic vein obstruction in a case of focal nodular hyperplasia. AJR Am J Roentgenol 173:857

Aufort S, Gallix BP, Perney P, Achard C, Blanc F, Bruel JM (2003) Spontaneous regression of a focal nodular hyperplasia (in French). J Radiol 84:705–708

Badler R, Price AP, Moy L, Katz DS (2002) Congenital portacaval shunt: CT demonstration. Pediatr Radiol 32:28–30

Balabaud C, Al-Rabih WR, Chen PJ, Evason K, Ferrell L, Hernandez-Prera JC, Huang SF et al (2013) Focal nodular hyperplasia and hepatocellular adenoma around the world viewed through the scope of the immunopathological classification. Int J Hepatol 2013:268625

Barsky MF, Rankin RN, Wall WJ et al (1989) Patent ductus venosus: problems in assessment and management. Can J Surg 32:271–275

Bartlett WC, Shellito JG (1951) Hamartoma of the liver. Surgery 29:593–595

Bartlett DL, Schwartz LH, Klimstra D, Blumgart LH (1996) Diagnosis and treatment of focal nodular hyperplasia. J Hepatobiliary Pancreat Surg 3:111–121

Bartok I, Decastello A, Csikos F, Nagy I (1980) Focal nodular hyperplasia of the liver and hepatic cell adenoma in women on oral contraceptives. Hepatogastroenterology 27:435–440

Bathe O, Mies C, Franceschi D, Casillas J, Livingstone A (2003) Massive hemorrhage and infarction complicating focal nodular hyperplasia of the liver. HPB (Oxford) 5:123–126

Bathgate A, MacGilchrist A, Piris J, Garden J (1999) Multiple focal nodular hyperplasia in Klippel-Trenaunay syndrome. Gastroenterology 117:284–285

Becker YT, Raiford DS, Webb L, Wright JK, Chapman WC, Pinson CW (1995) Rupture and hemorrhage of hepatic focal nodular hyperplasia. Am Surg 61:210–214

Beer TW, Carr NJ, Buxton PJ (1998) Thorotrast associated nodular regenerative hyperplasia of the liver. J Clin Pathol 51:941–942

Benson CD, Pemberthy GC (1942) Surgical excision of primary tumor of liver (hamartoma) in infant seven months old with recovery. Surgery 12:881–886

Benz EJ, Baggenstoss AH (1953) Focal cirrhosis of the liver: its relation to the so-called hamartoma (adenoma, benign hepatoma). Cancer 6:743–755

Benz-Bohm G, Hero B, Grossmann A, Simon T, Körber F, Berthold F (2010) Focal nodular hyperplasia of the liver in longterm survivors of neuroblastoma: how much diagnostic imaging is necessary ? Eur J Radiol 74:e1–e5

Beuers U, Richter WO, Ritter MM, Wiebecke B, Schwandt P (1991) Klinefelter's syndrome and liver adenoma. J Clin Gastroenterol 13:214–216

Bioulac-Sage P, Saric J, Boussarie L, Balabaud C (1985) Congenital portacaval shunt in rats: liver adaptation to lack of portal vein – a light and electron microscopic study. Hepatology 5:1183–1189

Bioulac-Sage P, Balabaud C (2001) Liver nodules resembling focal nodular hyperplasia. J Hepatol 34:781–782

Bioulac-Sage P, Lépreux S, Laurent C, Balabaud C (2001a) Adenoma or focal nodular hyperplasia of the liver? A difficult pathological diagnosis (in French). Gastroenterol Clin Biol 25:866–868

Bioulac-Sage P, Balabaud C, Wanless IR (2001b) Diagnosis of focal nodular hyperplasia. Not so easy. Am J Surg Pathol 25:1322–1325

Bioulac-Sage P, Rebouissou S, Sa Cunha A, Jeanot E, Lepreux S, Blanc JF, Blanche H et al (2005) Clinical, morphologic, and molecular features defining so-called

telangiectatic focal nodular hyperplasias of the liver. Gastroenterology 128:1211–1218
Bioulac-Sage P, Balabaud C, Bedossa P, Scoazec JY, Chiche L, Dhillon AP, Ferrell L et al (2007) Pathological diagnosis of liver cell adenoma and focal nodular hyperplasia: Bordeaux update. J Hepatol 46:521–527
Bioulac-Sage P, Laumonier H, Cubel G, Saric J, Balabaud C (2008) Over-expression of glutamine synthase in focal nodular hyperplasia (part 1): early stages in the formation support the hypothesis of a focal hyperarterialisation with venous (portal and hepatic) and biliary drainage. Comp Hepatol 7:2
Bioulac-Sage P, Laumonier H, Rullier A, Cubel G, Laurent C, Zucman-Rossi J, Balabaud C (2009) Overexpression of glutamine synthetase in focal nodular hyperplasia: a novel easy diagnostic tool, in surgical pathology. Liver Int 29:459–465
Bioulac-Sage P, Cubel G, Balabaud C, Zucman-Rossi J (2011) Revisiting the pathology of resected benign hepatocellular nodules using new immunohistochemical markers. Semin Liver Dis 31:91–103
Bioulac-Sage P, Cubel G, Taouji S, Scoazec JY, Leteurtre E, Paradis V, Sturm N et al (2012) Immunohistochemical markers on needle biopsies are helpful for the diagnosis of focal nodular hyperplasia and hepatocellular adenoma subtypes. Am J Surg Pathol 36:1691–1699
Bioulac-Sage P, Sempoux C, Balabaud C (2014) Immunohistochemical pitfalls in the diagnosis of focal nodular hyperplasia and inflammatory hepatocellular adenoma. Clin Res Hepatol Gastroenterol 38:245–249
Blanc JF, Bernard PH, Le Bail B, De Ledinghen V, Saric J, Balabaud C, Bioulac-Sage P (2000) Vascular pathology in the portal vein distal branches: a rare cause of liver transplantation and a protean clinical presentation (in French). Gastroenterol Clin Biol 24:667–670
Bojar H, Petzinna D, Brölsch C, Staib W (1984) Steroid receptor status of focal-nodular hyperplasia of the human liver. Klin Wochenschr 62:446–450
Bouyn CI, Leclere J, Raimondo G, Le Pointe HD, Couanet D, Valteau-Couanet D, Hartmann O (2003) Hepatic focal nodular hyperplasia in children previously treated for a solid tumor. Incidence, risk factors, and outcome. Cancer 97:3107–3113
Bralet MP, Terris B, Vilgrain V, Brégeaud L, Molas G, Corbic M, Belghiti J, Fléjou JF, Degott C (1999) Epithelioid hemangioendothelioma, multiple focal nodular hyperplasias, and cavernous hemangiomas of the liver. An unusual association. Arch Pathol Lab Med 123:846–849
Brancatelli G, Federle MP, Grazioli L, Blachar A, Peterson MS, Thaete L (2001) Focal nodular hyperplasia: CT findings with emphasis on multiphasic helical CT in 78 patients. Radiology 219:61–68
Branch A, Tonning D, Skinner GF (1945) Adenoma of the liver. Can Med Assoc J 53:53–54
Brenard R, Chapaux X, Deltenre P, Henrion J, De Maeght S, Horsmans Y, Borbath I et al (2010) Large spectrum of liver vascular lesions including high prevalence of focal nodular hyperplasia in patients with hereditary haemorrhagic telangiectasia: the Belgian Registry based on 30 patients. Eur J Gastroenterol Hepatol 22:1253–1259
Brouquet et al. (1985). http://www.ncbi.nlm.nih.gov/pubmed/2997901
Bureau C, Peron JM, Sirach E, Selves J, Otal P, Vinel JP (2004) Liver nodules resembling focal nodular hyperplasia after portal vein thrombosis. J Hepatol 41:499–500
Buscarini E, Danesino C, Plauchu H, de Fazio C, Olivieri C, Brambilla G, Menozzi F et al (2004) High prevalence of hepatic focal nodular hyperplasia in subjects with hereditary hemorrhagic telangiectasia. Ultrasound Med Biol 30:1089–1097
Butron Vila MM, Haot J, Desmet VJ (1984) Cholestatic features in focal nodular hyperplasia of the liver. Liver 4:387–395
Cadranel JF, Hadj-Nacer K, Kikassa JC, Cazier A (2003) Multiple focal nodular hyperplasia of the liver in a patient with prostatic cancer. Gut 52:1071
Cai YR, Gong L, Teng XY, Zhang HT, Wang CF, Wei GL, Guo L, Ding F, Liu ZH et al (2009) Clonality and allelotype analyses of focal nodular hyperplasia compared with hepatocellular adenoma and carcinoma. World J Gastroenterol 15:4695–4708
Cap et al. (1983). http://www.ncbi.nlm.nih.gov/pubmed/6297692
Casarella WJ, Knowles DM, Wolff M, Johnson PM (1978) Focal nodular hyperplasia and liver cell adenoma: radiologic and pathologic differentiation. AJR Am J Roentgenol 131:393–402
Caseiro-Alves F, Zins M, Mahfouz AE, Rahmouni A, Vilgrain V, Menu Y, Mathieu D (1996) Calcification in focal nodular hyperplasia: a new problem for differentiation from fibrolamellar hepatocellular carcinoma. Radiology 198:889–892
Cazals-Hatem D, Vilgrain V, Genin P, Denninger MH, Durand F, Belghiti J, Valla D et al (2003) Arterial and portal circulation and parenchymal changes in Budd-Chiari syndrome: a study in 17 explanted livers. Hepatology 37:510–519
Chandler TM, Heran MK, Chang SD, Parvez A, Harris AC (2011) Multiple focal nodular hyperplasia lesions of the liver associated with congenital absence of the portal vein. Magn Reson Imaging 29:881–886
Charlotte F, L'Herminé A, Martin N, Geleyn Y, Nollet M, Gaulard P, Zafrani ES (1994) Immunohistochemical detection of bcl-2 protein in normal and pathological human liver. Am J Pathol 144:460–465
Chen TC, Chou TB, Ng KF, Hsieh LL, Chou YHW (2001) Hepatocellular carcinoma associated with focal nodular hyerplasia. Report of a case with clonal analysis. Virchows Arch 438:408–411
Chen YJ, Chen PJ, Lee MC, Yeh SH, Hsu MT, Lin CH (2002) Chromosomal analysis of hepatic adenoma and focal nodular hyperplasia by comparative genomic hybridization. Genes Chromosomes Cancer 35:138–143

Chen LL, Ji Y, Xu JF, Lu SH, Hou YY, Hou J, Sujie A, Zeng HY, Tan YS (2011) Focal nodular hyperplasia of liver: a clinicopathologic study of 238 patients (in Chinese). Zhonhua Bing Li Xue Za Zhi 40:17–22

Chen WH, Peng CM, Chou CM, Chen HC, Jan YJ (2010) Focal nodular hyperplasia of the liver in a 5-year-old girl. J Chin Med Assoc 73:611–614

Chiti A, Giovanella LC, Bestetti A, Castellani M, Gattoni F, Bossi MC, Tarolo GL (1992) Final scintigraphic diagnosis with [[99mTc] HIDA in a case of focal nodular hyperplasia with essential thrombocythemia and portal thrombosis (in Italian). Radiol Med 84:491–493

Chun Hsee L, McCall JL, Koea JB (2005) Focal nodular hyperplasia: what are the indications for resection? HPB (Oxford) 7:298–302

Colle I, de Beeck BO, Hoorens A, Hautekeete M (1998) Multiple focal nodular hyperplasia. J Gastroenterol 33:904–908

Coopersmith CM, Lowell JA, Hassan A, Howard TK (2002) Hepatocellular carcinoma in a patient with focal nodular hyperplasia. HPB (Oxford) 4:135–138

Cordeiro MN, Cunha GN, Freitas PM, Alves FC (2009) Multiple focal nodular hyperplasia of the liver associated with spinal and pulmonary arteriovenous malformations. J Neuroradiol 36:290–293

Cote C (1997) Regression of focal nodular hyperplasia of the liver after oral contraceptive discontinuation. Clin Nucl Med 22:587–590

Cucchetti A, Vivarelli M, De Ruvo N, Bellusci R, Cavallari A (2003) Simultaneous presence of focal nodular hyperplasia and hepatocellular carcinoma: case report and review of the literature. Tumori 89:434–436

Dachman AH, Ros PR, Goodman ZD et al (1987) Nodular regenerative hyperplasia of the liver: clinical and radiologic observations. Am J Roentgenol 148:717–722

Davidson BR, Vaisamidakis N, Scheuer P, Hobbs K (1990) Fibrolamellar carcinoma arising in an abnormal liver (letter). J Hepatol 11:388

Davis M, Portmann B, Searle M, Wright R, Williams R (1975) Histological evidence of carcinoma in a hepatic tumour associated with oral contraceptives. Br Med J 4:496–498

De Gaetano AM, Gui B, Macis G, Mafredi R, Di Stasi C (2004) Congenital absence of the portal vein associated with focal nodular hyperplasia in the liver in an adult woman. Abdom Imaging 29:455–459

Di Carlo I, Urrico GS, Ursino V, Russello D, Puleo S, Latteri F (2003) Simultaneous occurrence of adenoma, focal nodular hyperplasia, and hemangioma of the liver: are they derived from a common origin? J Gastroenterol Hepatol 18:227–230

Di Stasi et al. (1996). http://www.ncbi.nlm.nih.gov/pubmed/8873856

Donadon M, Di Tommaso L, Roncalli M, Torzilli G (2013) Multiple focal nodular hyperplasia induced by oxaliplatin-based chemotherapy. World J Hepatol 5:340–344

Dubuisson L, Vonnahme FJ, Stzark F, Bioulac-Sage P, Balabaud C (1985) Hyperplastic foci in the atrophic liver of rats after portacaval anastomosis. Liver 5:21–28

Eberhardt RT, McMahon L, Duffy SJ, Steinberg MH, Perrine SP, Loscalzo J, Coffman JD, Vita JA (2003) Sickle cell anemia is associated with reduced nitric oxide bioactivity in peripheral conduit and resistance vessels. Am J Hematol 74:104–111

Eda Y, Yajima Y, Shibuya D, Kitagawa Y, Abe Y, Miyazaki A, Oohira S, Matsuhashi T, Naganuma H (1999) A case of idiopathic portal hypertension complicated with multiple focal nodular hyperplasia (FNH) like lesions (in Japanese). Nippon Shokakibyo Gakkai Zasshi 96:431–436

Edelstone DI (1980) Regulation of blood flow through the ductus venosus. J Dev Physiol 2:219–238

Elsayes KM, Peterson CM, Menias CO (2007) The central scar: pathophysiology and imaging features. Curr Probl Diagn Radiol 36:247–257

Everson RB, Fraumeni JF (1976) Familial glioblastoma with hepatic focal nodular hyperplasia. Cancer 38:310–313

Ewing J (1940) Neoplastic diseases: a treatise on tumors, 4th edn. W.B. Saunders Company, Philadelphia, p 735

Fabre A, Audet P, Vilgrain V, Nguyen BN, Valla D, Belghiti J, Degott C (2002) Histologic scoring of liver biopsy in focal nodular hyperplasia with atypical presentation. Hepatology 35:414–420

Fechner RE, Roehm JO (1977) Angiographic and pathologic correlations of hepatic focal nodular hyperplasia. Am J Surg Pathol 1:217–224

Feng CY, Lai HS, Huang SF (2000) Focal nodular hyperplasia of the liver in a child. J Formos Med Assoc 99:870–872

Ferrell L, Wright T, Lake J, Roberts J, Ascher N (1992) Incidence and diagnostic features of macroregenerative nodules vs. small hepatocellular carcinoma in cirrhotic livers. Hepatology 16:1372–1381

Finley AC, Hosey JR, Noone TC, Shackelford DM, Varadarajulu S (2005) Multiple focal nodular hyperplasia syndrome: diagnosis with dynamic, gadolinium-enhanced MRI. Magn Res Imaging 23:511–513

Franchi-Abella S, Branchereau S (2013) Benign hepatocellular tumors in children: focal nodular hyperplasia and hepatocellular adenoma. Int J Hepatol 2013:215064

Fukai T, Ishibashi H, Noda T, Dohmen K, Kudo J, Nagafuchi S, Sueshi K, Yamasaki T, Sameshima H (1992) Nodular regenerative hyperplasia of the liver with portal vein thrombosis and hyperplasia of the adrenal gland. Gastroenterol Jpn 27:108–114

Fukukura Y, Nakashima O, Kusaba A, Kage M, Kojiro M (1998) Angioarchitecture and blood circulation in focal nodular hyperplasia of the liver. J Hepatol 29:470–475

Fukushima N, Kuromatsu R, Uchiyama D, Itano S, Takata A, Ando E, Sumie S, Torimura T et al (2007) Hyperplastic nodular hepatic lesions following end-to-

side portacaval shunting in childhood. Intern Med 46:1203–1208
Gabata T, Matsui O, Kadoya M, Yoshikawa J, Mitchell DG, Ueda K, Kawamori Y, Takashima T (1999) Giant hyperplasia of the caudate lobe of the cirrhotic liver: correlation with an anomaly of the caudate portal branch. Abdom Imaging 24:153–156
Gaffey MJ, Iezzoni JC, Weiss LM (1996) Clonal analysis of focal nodular hyperplasia of the liver. Am J Pathol 148:1089–1096
Gincul R, Lesca G, Gelas-Dore B, Rollin N, Barthelet M, Dupuis-Girod S, Pilleul F et al (2008) Evaluation of previously nonscreened hereditary hemorrhagic telangiectasia patients shows frequent liver involvement and early cardiac consequences. Hepatology 48:1570–1576
Glas L, Scoazec JY, Adham M, Pilleul F (2008) Focal nodular hyperplasia of the liver with pseudo-angiomatous appearance of the central area: MRI findings and physiopathological insights. J Radiol Case Rep 2:8–12
Goldfarb (1976). http://www.ncbi.nlm.nih.gov/pubmed/179705
Goldin RD, Rose DS (1990) Focal nodular hyperplasia of the liver associated with intracranial vascular malformations. Gut 31:554–555
Gong L, Li YH, Su Q, Li G, Zhang WD, Zhang W (2009) Use of X-chromosome inactivation pattern and laser microdissecrion to determine the clonal origin of focal nodular hyperplasia of the liver. Pathology 41:348–355
Gouw AS, Zeng W, Buiskool M, Platteel I, van den Heuvel MC, Poppema S, de Jong KP et al (2010) Molecular characterization of the vascular features of focal nodular hyperplasia and hepatocellular adenoma: a role for angiopoietin-1. Hepatology 52:540–549
Grange JD, Guechot J, Legendre C, Giboudeau J, Darnis F, Poupon R (1987) Liver adenoma and focal nodular hyperplasia in a man with high endogenous sex steroids. Gastroenterology 93:1409–1413
Gräntzdorffer I, Lendeckel U, Carl-McGrath S, Roessner A, Rocken C (2004) Angiotensin I-converting enzyme (CD143) is down-regulated in focal nodular hyperplasia of the liver. Am J Surg Pathol 28:84–88
Grazioli L, Alberti D, Olivetti L, Rigamonti W, Codazzi F, Matricardi L, Fugazzola C, Chiesa A (2000) Congenital absence of portal vein with nodular regenerative hyperplasia of the liver. Eur Radiol 10:820–825
Greinacher I (1950) Zur Kenntnis der Leber-Hamartome. Beitr Pathol Anat Allgem Pathol 111:1–12
Guariso G, Fiorio S, Altavilla G, Gamba PG, Toffolutti T, Chiesura-Corona M, Tedeschi U, Zancan L (1998) Congenital absence of the portal vein associated with focal nodular hyperplasia of the liver and cystic dysplasia of the kidney. Eur J Pediatr 157:287–290
Guntz et al. (1983). http://www.ncbi.nlm.nih.gov/pubmed/6313462
Haber M, Reuben A, Oliveiro P, Salem RR, West B (1995) Multiple focal nodular hyperplasia of the liver associated with hemihypetrophy and vascular malformations. Gastroenterology 108:1256–1262
Halankar JA, Kim TK, Jang HJ, Khalili K, Masoom HA (2012) Understanding the natural history of focal nodular hyperplasia in the liver with MRI. Indian J Radiol Imaging 22:116–120
Handra-Luca A, Paradis V, Vigrain V, Dubois S, Durand F, Belghiti J, Valla D, Degott C (2006) Multiple mixed adenoma-focal nodular hyperplasia of the liver associated with spontaneous intrahepatic porto-systemic shunt: a new type of vascular malformation associated with the multiple focal nodular hyperplasia syndrome ? Histopathology 48:309–311
Haubert L, Yearsley M, Bloomston M (2010) Hepatocellular carcinoma arising within focal nodular hyperplasia. Am Surg 76:335–336
Heaton ND, Pain J, Cowan NC, Salisbury J, Howard ER (1991) Focal nodular hyperplasia of the liver: a link with sickle cell disease ? Arch Dis Child 66:1073–1074
Helsing P, Nielsen EW (2006) Hepatocellular focal nodular hyperplasia after Danazol treament for hereditary angio-oedema. Acta Derm Venereol 86:272–273
Heukamp LC, Fischer HP, Schirmacher P, Chen X, Breuhahn K, Nicolay C, Buttner R et al (2006) Podocalyxin-like protein 1 expression in primary hepatic tumours and tumour-like lesions. Histopathology 49:242–247
Hoffman HS (1942) Benign hepatoma. Review of literature and report of a case. Ann Intern Med 17:130–139
Hoso M, Terada T, Nakanuma Y (1996) Partial nodular transformation of liver developing around intrahepatic portal venous emboli of hepatocellular carcinoma. Histopathology 29:580–582
Howard ER, Davenport M (1997) Congenital extrahepatic portocaval shunts-the Abernethy malformation. J Pediatr Surg 32:494–497
Hung PL, Huang SC, Kuo HW, Shieh CS, Tiao MM (2001) Hepatic focal nodular hyperplasia in children: report of three cases. Chang Gung Med J 24:657–662
Hytiroglou P, Theise ND (1998) Differential diagnosis of hepatocellular nodular lesions. Semin Diagn Pathol 15:285–299
Ibarrola C, Catsellano VM, Colina F (2004) Focal hyperplastic hepatocellular nodules in hepatic venous outflow obstruction: a clinicopathological study of four patients and 24 nodules. Histopathology 44:172–179
Imkie M, Myers SA, Li Y, Fan F, Bennett TL, Forster J, Tawfik O (2005) Fibrolamellar hepatocellular-carcinoma arising in a background of focal nodular hyperplasia: a report of 2 cases. J Reprod Med 50:633–637
International Working Party (1995) Terminology of nodular hepatocellular lesions. Hepatology 22:983–993
Iordanidis F, Hytiroglou P, Drevelegas A, Kodonas F, Ioannidis I, Nenopoulou H, Papadimitriou CS (2002) A 25-year-old man with a large hepatic tumor and multiple nodular lesions. Semin Liver Dis 22:97–102
Ishak KG, Rabin L (1975) Benign tumors of the liver. Med Clin N Am 59:995–1013
Iyer A, Robert ME, Bifulco CB, Salem RR, Jain D (2008) Different cytokeratin and neuronal cell adhesion

molecule staining patterns in focal nodular hyperplasia and hepatic adenoma and their significance. Hum Pathol 39:1370–1377

Jacob S, Farr G, De Vun D, Takiff H, Mason A (1999) Hepatic manifestations of familial patent ductus venosus in adults. Gut 45:442–445

Johnson AO, Obisesan AO, Williams AO (1979) Extrahepatic portal hypertension due to congenital obstruction of the portal vein and associated gross hepatic lobulation. Clin Pediatr (Phila) 18:619–621

Joseph NM, Ferrell LD, Jain D, Torbenson MS, Wu TT, Yeh MM, Kakar S (2014) Diagnostic utility and limitations of glutamine synthetase and serum amyloid-associated protein immunohistochemistry in the distinction of focal nodular hyperplasia and inflammatory hepatocellular adenoma. Mod Pathol 27:62–72

Joyner BL, Levin TL, Goyal RK, Newman B (2005) Focal nodular hyperplasia of the liver: a sequela of tumor therapy. Pediatr Radiol 35:1234–1239

Kageyama F, Kobayashi Y, Kawasaki T, Nakamura H, Baba S, Nakamura S, Nakashima O, Kojiro M (1998) An unusual hyperplastic hepatocellular nodule in a patient with hepatitis C virus-related liver cirrhosis. Am J Gastroenterol 93:2588–2593

Kaji K, Kaneko S, Matsushita E, Kobayashi K, Matsui O, Nakanuma Y (1998) A case of progressive multiple focal nodular hyperplasia with alteration in imaging studies. Am J Gastroenterol 93:2568–2572

Kanamori Y, Hashizume K, Kitano Y, Sugiyama M, Motoi T, Tange T (2003) Congenital extrahepatic portocaval shunt (abernethy type 2), huge liver mass, and patent ductus arteriosus – a case report of its rare clinical presentation in a young girl. J Pediatr Surg 38, E15

Kato K, Ozaki D, Zheng K, Kondo F, Urashima T, Asano T, Ochiai T, Suzuki Y, Ebara M, Saisho H, Kondo Y (2001) Characterization of hyperplastic foci observed in surgical specimens of hepatocellular carcinoma. Pathol Int 51:20–25

Kawamori Y, Matsui O, Kitagawa K, Kadoya M, Yamahana T, Takashima T, Kidani H, Masuda S, Nakanuma Y (1991) Segmental hepatic iron deposition due to peripheral portal vein tumor thrombus: MR features. J Comput Assist Tomogr 15:1042–1044

Kay S, Talbert PC (1950) Adenoma of the liver, mixed type (hamartoma); report of two cases. Cancer 3:307–315

Kellner U, Jacobsen A, Kellner A, Mantke R, Roessner A, Rocken C (2003) Comparative genomic hybridization. Synchronous occurrence of focal nodular hyperplasia and hepatocellular carcinoma in the same liver is not based on common chromosomal aberrations. Am J Clin Pathol 119:265–271

Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PF (1983) Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. Gastroenterology 84:994–1002

Khalid SK, Garcia-Tsao G (2008) hepatic vascular malformations in hereditary hemorrhagic telangiectasia. Semin Liver Dis 28:247–258

Kim T, Baron RL, Ma N (2000) Infarcted regenerative nodules in cirrhosis: CT and MR imaging findings with pathologic correlation. AJR Am J Roentgenol 175:1121–1125

Kim J, Nikiforov YE, Moulton JS, Lowy AM (2004) Multiple focal nodular hyperplasia of the liver in a 21-year-old woman. J Gastrointest Surg 8:591–595

Kim SR, Imoto S, Ikawa H, Ando K, Mita K, Shimizu K, Taniguchi M, Sasase N, Matsuoka T (2008) Focal nodular hyperplasia-like lesion with venous washout in alcoholic liver cirrhosis. Intern Med 47:1899–1903

Kinjo T, Aoki H, Sunagawa H, Kinjo S, Muto Y (2001) Congenital absence of the portal vein associated with focal nodular hyperplasia of the liver and congenital choledochal cyst: a case report. J Pediatr Surg 36:622–625

Kitzing YX, Gallagher J, Waugh R (2011) Large focal nodular hyperplasia and extrahepatic portosystemic shunt in a male patient: multi-modality imaging findings. J Med Imaging Radiat Oncol 55:502–505

Knowles DM, Wolff M (1976) Focal nodular hyperplasia of the liver: a clinicopathologic study and review of the literature. Hum Pathol 7:533–545

Knowles DM, Casarella WJ, Johnson PM, Wolff M (1978) The clinical, radiological, and pathological characterization of benign hepatic neoplasms. Medicine 57:223–237

Ko SF, Ng SH, Lee TY, Wan YL, Lin JW, Chen CL (2002) Hepatic focal nodular hyperplasia: the "star sign" on gadolinium-enhanced magnetic resonance angiography. Hepatogastroenterology 49:1377–1381

Ko KR, Lee DH, Park JS, Yi BH, Lim JW, Ko YT, Kim YW (2003) Focal nodular hyperplasia with retraction of liver capsule: a case report. Korean J Radiol 4:66–69

Kobayashi S, Saito K, Nakanuma Y (1993) Nodular regenerative hyperplasia of the liver in hepatocellular carcinoma. An autopsy study. J Clin Gastroenterol 16:155–159

Koch N, Gitzburger D, Seelentag W, Denys A, Gillet M, Halkic N (2006) Rupture of hepatic focal nodular hyperplasia. About two cases (in French). Ann Chir 131:279–282

Koizumi J, Yamashita T, Dowaki S, Tobita K, Shimamura K, Hirabayashi K, Inai Y, Imaizumi T (2006) Hepatobiliary and pancreatic: hepatic adenoma, focal nodular hyperplasia and congenital absence of the portal vein. J Gastroenterol Hepatol 21:619

Kondo F, Nagao T, Sato T, Tomizawa M, Kondo Y, Matsuzaki O, Wada K, Wakatsuki S et al (1998) Etiological analysis of focal nodular hyperplasia of the liver, with emphasis on similar abnormal vasculatures to nodular regenerative hyperplasia and idiopathic portal hypertension. Pathol Res Pract 194:487–495

Kondo F (2000) Focal nodular hyperplasia of the liver: controversy over etiology. J Gastroenterol Hepatol 15:1229–1231

Kondo F (2001) Benign nodular hepatocellular lesions caused by abnormal hepatic circulation: etiological analysis and introduction of a new concept. J Gastroenterol Hepatol 16:1319–1328

Kondo F, Koshima Y, Ebara M (2004) Nodular lesions associated with abnormal liver circulation. Intervirology 47:277–287

Kong CS, Appenzeller M, Ferrell LD (2000) Utility of CD34 reactivity in evaluating focal nodular hepatocellular lesions samples by fine needle aspiration biopsy. Acta Cytol 44:218–222

Kottke R, Horger M, Schimmel H, Wehrmann M (2007) Atypical focal nodular hyperplasia with cluster-like internal cysts due to fibrinoid necrosis. AJR Am J Roentgenol 189:W247–W250

Kozyraki R, Scoazec JY, Fléjou JF, D'Errico A, Bedossa P, Terris B, Fiorentino M et al (1996) Expression of cadherins and alpha-catenin in primary epithelial tumors of the liver. Gastroenterology 110:1137–1149

Krishnamurthy S, Nerurkar AY (2002) Spindle cell fragments in focal nodular hyperplasia of the liver. A case report. Acta Cytol 46:582–584

Kubota T, Shimizu K, Sonoyama T, Ikeda E, Kurioka H, Ouchi T, Suyama Y, Hosokawa Y, Yamagishi H (2001) Enlarged focal nodular hyperplasia of the liver under the influence of oral contraceptives. Hepatogastroenterology 48:1736–1739

Kudo M (2003) Hepatic nodular lesions caused by abnormal hepatic circulation: etiological and clinical aspects. J Gastroenterol 38:308–310

Kuo YH, Wang JH, Lu SN, Hung CH, Wie YC, Hu TH, Chen CH, Yen YH, Lee CM et al (2009) Natural course of hepatic focal nodular hyperplasia: a long-term follow-up study with sonography. J Clin Ultrasound 37:132–137

Kwak HS, Lee JM, Lee SY, Han YM, Kim CS, Moon WS, Yu HC (2000) Pseudotumorous hyperplasia of the caudate lobe in the non-cirrhotic liver: MR and CT arterial portography appearance. Hepatogastroenterology 47:909–911

Lack EE, Ornvold K (1986) Focal nodular hyperplasia and hepatic adenoma: a review of eight cases in the pediatric age group. J Surg Oncol 33:129–135

Lalonde L, Van Beers B, Trigaux JP, Delos M, Melange M, Pringot J (1992) Focal nodular hyperplasia in association with spontaneous intrahepatic portosystemic shunt. Gastrointest Radiol 17:154–156

Landen S, Delugeau V (2003) Spontaneous portal-venous shunts of the liver. Dig Surg 20:165–166

Lane MJ, Jeffrey RB, Katz DS (2000) Spontaneous intrahepatic vascular shunts. AJR Am J Roentgenol 174:125–131

Langman G, Hall PD (2001) Focal nodular hyperplasia with calcification and ossification. Pathology 33:396–398

Langner C, Homayounfar K, Ruten B, Fass J, Ruschoff J (2001) Concomitant occurrence of angiomyolipoma, focal nodular hyperplasia, bile duct adenoma, and cavernous hemangioma of the liver (in German). Pathologe 22:417–423

Langrehr JM, Pfitzmann R, Hermann M, Radke C, Neuhaus P, Pech M, Denecke T et al (2006) Hepatocellular carcinoma in association with hepatic focal nodular hyperplasia. Acta Radiol 47:340–344

Laumonier H, Leblanc F, Balabaud C, Bioulac-Sage P (2010) Spontaneous regression of focal nodular hyperplasia: a pathological report. BMJ Case Rep. doi: 10.1136/bcr.02.2020.2704

Laurent C, Trillaud H, Lepreux S, Balabaud C, Bioulac-Sage P (2003) Association of adenoma and focal nodular hyperplasia: experience of a single French academic center. Comp Hepatol 2:6–8

Lee YH, Kim SH, Cho MY, Shim KY, Kim MS (2007) Focal nodular hyperplasia-like nodules in alcoholic liver cirrhosis: radiologic-pathologic correlation. AJR Am J Roentgenol 188:W459–W463

Lepreux S, Lautent C, Balabaud C, Bioulac-Sage P (2002) Focal nodular hyperplasia lacking some key histopathological features making the diagnosis difficult. Virchows Arch 440:445–446

Lepreux S, Laurent C, Balabaud C, Bioulac-Sage P (2003a) FNH-like nodules: possible precursor lesions in patients with focal nodular hyperplasia. Comp Hepatol 26:7

Lepreux S, Lauent C, Le Bail B, Saric J, Balabaud C, Bioulac-Sage P (2003b) Multiple telangiectatic focal nodular hyperplasia: vascular abnormalities. Virchows Arch 442:226–230

Lepreux S, Desmouliere A, Rosenbaum J, Balabaud C, Bioulac-Sage P (2004) Expression of fibrillin-1 in focal nodular hyperplasia of the liver: a role in microcirculation adaptability. Comp Hepatol 3(Suppl 1): S57

Li T, Qin LX, Ji Y, Sun HC, Ye QH, Wang L, Pan Q, Fan J, Tang ZY (2007) Atypical hepatic focal nodular hyperplasia presenting as acute abdomen and misdiagnosed as hepatocellular carcinoma. Hepatol Res 37:1100–1105

Libbrecht L, Desmet V, Van Damme B et al (2001) Nodular lesions in cirrhotic livers resembling focal nodular hyperplasia. J Hepatol 34(Abstr, Suppl 1):96

Libbrecht L, Severi T, Cassiman D, Borght SV, Pirenne J, Nevens F, Verslype C, Pelt JV et al (2006a) Glypican-3 expression distinguishes small hepatocellular carcinomas from cirrhosis, dysplastic nodules, and focal nodular hyperplasia-like nodules. Am J Surg Pathol 30:1405–1411

Libbrecht L, Cassiman D, Verslype C, Maleux G, Van Hees D, Pirenne J, Nevens F, Roskams T (2006b) Clinicopathological features of focal nodular hyperplasia-like nodules in 130 cirrhotic explant livers. Am J Gastroenterol 101:2341–2346

Ligato S, Mandich D, Cartun RW (2008) Utility of glypican-3 in differentiating hepatocellular carcinoma from other primary and metastatic lesions in FNA of the liver: an immunocytochemical study. Mod Pathol 21:626–631

Lisovsky M, Konstas AA, Misdraji J (2011) Congenital extrahepatic portosystemic shunts (Abernathy malformation): a histopathologic evaluation. Am J Surg Pathol 35:1381–1390

Maetani Y, Itoh K, Egawa H, Haga H, Sakurai T, Nishida N, Ametani F, Shibata T et al (2002) Benign hepatic nodules in Budd-Chiari syndrome: radiologic-pathologic correlation with emphasis on the central scar. AJR Am J Roentgenol 178:869–875

Mahfouz AE, Rahmouni A, Terem C, Cherqui D, Mathieu D, Chariot P, Nhieu JT, Vasile N (1999) MRI of intralesional hemolysis in focal nodular hyperplasia of the liver. J Comput Assist Tomogr 23:684–686

Maier W (1955) Das gestielte Hamartom der Leber. Ein Beitrag zur Diagnostik, Morphologie und Behandlung von Lebertumoren im Kindesalter. Zschr Kinderheilkde 77:422–432

Makhlouf HR, Abdul-Al HM, Goodman ZD (2005) Diagnosis of focal nodular hyperplasia of the liver by needle biopsy. Hum Pathol 36:1210–1216

Malamut G, Perlemuter G, Buffet C, Bedossa P, Joly JP, Colombat M, Kuoch V, Pelletier G (2001) Epithelioid hemangioendothelioma associated with nodular regenerative hyperplasia (in French). Gastroenterol Clin Biol 25:1105–1107

Marabelle A, Campagne D, Déchelotte P, Chipponi J, Deméoq F, Kanold J (2008) Focal nodular hyperplasia of the liver in patients previously treated for pediatric neoplastic diseases. J Pediatr Hematol Oncol 30:546–549

Marin D, Galluzzo A, Plessier A, Brancatelli G, Valla D, Vilgrain V (2011) Focal nodular hyperplasia-like lesions in patients with cavernous transformation of the portal vein: prevalence, MR findings and natural history. Eur Radiol 21:2074–2082

Markowitz RI, Harcke HT, Ritchie WG, Huff DS (1980) Focal nodular hyperplasia of the liver in a child with sickle cell anemia. AJR Am J Roentgenol 134:594–597

Masatoshi K, Shusuke T, Hitoshi T, Kazushi M, Akio T (1993) Intrahepatic portosystemic venous shunt: diagnosis by color Doppler imaging. Am J Gastroenterol 88:723–729

Masetti R, Zama D, Gasperini P, Morello W, Prete A, Colecchia A, Festi D, Pession A (2013) Focal nodular hyperplasia of the liver in children after hematopoietic stem cell transplantation. Pediatr Transplant 17:479–486

Materne R, Van Beers BE (1998) Images in clinical radiology spontaneous intrahepatic portohepatic shunt and focal nodular hyperplasia. J Belge Radiol 81:180

Mathieu D, Zafrani ES, Anglade MC, Dhumeaux D (1989) Association of focal nodular hyperplasia and hepatic hemangioma. Gastroenterology 97:154–157

Mathieu D, Kobeiter H, Maison P, Rahmouni A, Cherqui D, Zafrani ES, Dhumeaux D (2000) Oral contraceptives use and focal nodular hyperplasia of the liver. Gastroenterology 118:560–564

Matkowskyj KA, Bai H, Liao J, Zhang W, Li H, Rao S, Omary R, Yang GY (2014) Aldoketoreductase family 1B10 (AKR1B10) as a biomarker to distinguish hepatocellular carcinoma from benign liver lesions. Hum Pathol 45:834–843

Matsubara T, Sumazaki R, Saitoh H, Imai H, Nakayama J, Takita H (1996) Patient ductus venosus associated with tumor-like lesions of the liver in a young girl. J Pediatr Gastroenterol Nutr 22:107–111

Matsuo M, Kanematsu M, Kondo H, Maeda S, Goshima S, Suenaga I, Hoshi H (2002) Arterioportal shunts mimicking hepatic tumors with hyperintensity on T2-weighted MR images. J Magn Reson Imaging 15:330–333

Matsuoka Y, Ohtomo K, Okubo T, Nishikawa J, Mine T, Ohno S (1992) Congenital absence of the portal vein. Gastrointest Radiol 17:31–33

Matsushita M, Hajiro K, Suzaki T, Takakuwa H, Sawami H, Kusumi F, Konishi Y, Maruo M et al (1995) Focal nodular hyperplasia of the liver without central scar. Dig Dis Sci 40:2407–2410

McKnight R, Nassar A, Cohen C, Siddiqui MT (2012) Arginase-1: a novel immunohistochemical marker of hepatocellular differentiation in fine needle aspiration cytology. Cancer Cytopathol 120:223–229

McLoughlin MJ, Colapinto RF, Gilday DL, Hobbs BB, Korobkin MT, McDonald P, Phillips MJ (1973) Focal nodular hyperplasia of the liver: angiography and radioisotope scanning. Radiology 107:257–263

Mignon F, Mesurolle B, Cazaban A, Lemesle J (1996) Focal nodular hyperplasia and spontaneous intrahepatic porto-portal communication (in French). J Radiol 77:1233–1236

Mindikoglu AL, Regev A, Levi JU, Casillas J, Schiff ER (2005) Focal nodular hyperplasia in identical twins. Am J Gastroenterol 100:1616–1619

Mitchell DG, Palazzo J, Hann HW, Rifkin MD, Burk DL, Rubin R (1991) Hepatocellular tumors with high signal on T1-weighted MR images: chemical shift MR imaging and histologic correlation. J Comput Assist Tomogr 15:762–769

Miyayama S, Matsui O, Ueda K, Kifune K, Yamashiro M, Yamamoto T, Komatsu T, Kumano T (2000) Hemodynamics of small hepatic focal nodular hyperplasia: evaluation with single-level dynamic CT during hepatic arteriography. AJR Am J Roentgenol 174:1567–1579

Mneimneh W, Farges O, Bedossa P, Belghiti J, Paradis V (2011) High serum level of alpha-fetoprotein in focal nodular hyperplasia of the liver. Pathol Int 61:491–494

Morgan G, Superina R (1994) Congenital absence of the portal vein: two cases and a proposed classification system for portasystemic vascular anomalies. J Pediatr Surg 29:1239–1241

Mortelé KJ, Stubbe J, Praet M, Van Langenhove P, De Bock G, Kunnen M (2000) Intratumoral steatosis in focal nodular hyperplasia coinciding with diffuse hepatic steatosis: CT and MRI findings with histologic correlation. Abdom Imaging 25:179–181

Motoori S, Shinozaki M, Goto N, Kondo F (1997) Case report: congenital absence of the portal vein associated with nodular hyperplasia in the liver. J Gastroenterol Hepatol 12:639–643

Motosugi U, Murata S, Shimizu M, Yasuda M, Sakurai T, Shimizu Y, Ban S, Nagata K et al (2009) Extranodular background liver parenchyma of focal nodular hyperplasia: histopathological characteristics. Virchows Arch 454:557–562

Nakashima O, Watanabe J, Tanaka M et al (1996) Clinicopathologic study of hyperplastic nodules in patient with chronic alcoholic liver disease. Acta Hepatol Jpn 37:704–713

Nakayama S, Kanbara Y, Nishimura T, Nishida N, Hanioka K, Morita M, Fujita M, Sakurai K et al (2006) Genome-wide microsatellite analysis of focal nodular hyperplasia: a strong tool for the differential diagnosis of non-neoplastic liver nodule from hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 13:416–420

Namasivayam S, Salman K, Mittal PK, Martin D, Small WC (2007) Hypervascular hepatic focal lesions: spectrum of imaging features. Curr Probl Diagn Radiol 36:107–123

Nasarek A, Werner M, Nolte M, Klempnauer J, Georgii A (1995) trisomy 1 and 8 occur frequently in hepatocellular carcinoma but not in liver cell adenoma and focal nodular hyperplasia. A fluorescence in situ hybridization study. Virchows Arch 427:373–378

Nassar A, Cohen C, Siddiqui MT (2009) Utility of glypican-3 and surviving in differentiating hepatocellular carcinoma from benign and preneoplastic hepatic lesions and metastatic carcinomas in liver fine-needle aspiration biopsies. Diagn Cytopathol 37:629–635

Ndimbie OK, Goodman ZD, Chase RL, Ma CK, Lee MW (1990) Hemangiomas with localized nodular proliferation of the liver. A suggestion on the pathogenesis of focal nodular hyperplasia. Am J Surg Pathol 14:142–150

Nguyen BN, Fléjou JF, Terris B, Belghiti J, Degott C (1999) Focal nodular hyperplasia of the liver: a comprehensive pathologic study of 305 lesions and recognition of new histologic forms. Am J Surg Pathol 23:1441–1454

Nisar PJ, Zaitoun AM, Damera A, Hodi Z, Tierney GM, Beckingham IJ (2002) Metastatic renal adenocarcinoma to the liver associated with focal nodular hyperplasia. J Clin Pathol 55:967–969

Nuamah NM, Hamaloglu E, Ozdemir A, Ozenc A, Sozseker C, Sokmensuer C (2006) Hepatic focal nodular hyperplasia developing in a Fanconi anemia patient: a case report and literature review. Haematologica 91(8 Suppl):ECR39

Nzeako UC, Goodman ZD, Ishak KG (1996) Hepatocellular carcinoma and nodular regenerative hyperplasia: possible pathogenetic relationship. Am J Gastroenterol 91:879–884

Ogawa A, Ogawa E, Yamamoto S, Fukuda T, Sugie H, Kohno Y (2010) Case of glycogen storage disease type VI (phosphorylase deficiency) complicated by focal nodular hyperplasia. Pediatr Int 52:e150–e153

Ohmoto K, Honda T, Hirokawa M, Mitsui Y, Iguchi Y, Kuboki M, Yamamoto S (2002) Spontaneous regression of focal nodular hyperplasia of the liver. J Gastroenterol 37:849–853

Ojanguren I, Ariza A, Castella EM, Fernandez-Vasalo A, Mate JL, Navas-Palacios J (1995) p53 immunoreactivity in hepatocecllular adenoma, focal nodular hyperplasia, cirrhosis and hepatocellular carcinoma. Histopathology 26:63–68

Okuda Y, Ono M, Kato N et al (1988) Congenital absence of the portal vein in a 17-year-old woman (in Japanese). Nippon Igaku Hoshasen Gakkai Zasshi 48:86

Okugawa Y, Uchida K, Inoue M, Kawamoto A, Ohtake K, Sakurai H, Uchida K, Isaji S et al (2008) Focal nodular hyperplasia in biliary atresia patient after Kasai hepatic portoenterostomy. Pediatr Surg Int 24:609–612

Orda R, Wiznitzer T, Griffel B, Bawnik JB (1973) Large solitary hepatic hamartoma. Ann Surg 39:592–595

Pai R, Khadilkar UN, Diaz E, Prabhu S, Gupta S (2009) Nonclassical focal nodular hyperplasia of the liver in a chronic alcoholic: a diagnostic dilemma on FNAC. Kathmandu Univ Med J 7:76–78

Pan Y, Wang ZM, Mou LJ, Teng XD, Zheng ZJ, Ying LX (2004) Focal nodular hyperplasia of the liver: pathological analysis of 11 cases. Hepatobiliary Pancreat Dis Int 3:199–203

Papanikolaou V, Vrochides D, Margari P, Giakoustidis D, Antoniadis N, Tsinoglou K et al (2009) Hepatic focal nodular hyperplasia: when a benign lesion becomes “malignant”. Report of a case. Hippokratia 13:114–115

Paradis V, Laurent A, Flejou JF, Vidaud M, Bedossa P (1997) Evidence for the polyclonal nature of focal nodular hyperplasia of the liver by the study of X-chromosome inactivation. Hepatology 26:891–895

Paradis V, Bieche I, Dargere D, Laurendeau I, Nectoux J, Degott C, Belghiti J, Vidaud M, Bedossa P (2003) A quantitative gene expression study suggests a role for angiopoietins in focal nodular hyperplasia. Gastroenterology 14:651–659

Paradis V, Benzekri A, Dargere D, Bieche I, Laurendeau I, Vilgrain V, Belghiti J, Vidaud M et al (2004) Telangiectatic focal nodular hyperplasia: a variant of hepatocellular adenoma. Gastroenterology 126:1323–1329

Park JH, Cha SH, Han JK et al (1990) Intrahepatic portosystemic venous shunt. AJR Am J Roentgenol 155:527–528

Patton RJ (1948) Hamartoma of the liver. Ann Surg 127:180–186

Pennati G, Corno C, Costantino ML, Bellotti M (2003) Umbilical flow distribution to the liver and the ductus venosus in human fetuses during gestation: an anatomy-based mathematical modeling. Med Eng Phys 25:229–238

Petsas T, Tsamandas A, Tsota I, Karavias D, Karatza C, Vassiliou V, Kardamakis D (2006) A case of hepatocellular carcinoma arising within large focal nodular hyperplasia with review of the literature. World J Gastroenterol 12:6567–6571

Prust FW, Eskandari F (1967) Intestinal obstruction due to an aberrant umbilical vein. Am Surg 165:464–465

Pupulim LF, Vullierme MP, Paradis V, Valla D, Terraz S, Vilgrain V (2013) Congenital portosystemic shunts associated with liver tumors. Clin Radiol 68: e362–e369

Quaglia A, Tibballs J, Grasso A, Prasad N, Nozza P, Davies SE, Burroughs AK, Watkinson A, Dhillon AP (2003) Focal nodular hyperplasia-like areas in cirrhosis. Histopathology 42:14–21

Ra SH, Kaplan JB, Lassman CR (2010) Focal nodular hyperplasia after orthotopic liver transplantation. Liver Transpl 16:98–103

Rangheard et al. (2002). http://www.ncbi.nlm.nih.gov/pubmed/12185058

Ravard G, Soyer P, Boudiaf M, Terem C, Abitbol M, Yeh JF, Brouard R, Hamzi L et al (2004) Hepatic involvement in hereditary hemorrhagic telangiectasia: helical computed tomography features in 24 consecutive patients. J Comput Assist Tomogr 28:488–495

Rebouissou S, Couchy G, Libbrecht L, Balabaud C, Imbeaud S, Auffray C, Roskams T et al (2008a) The beta-catenin pathway is activated in focal nodular hyperplasia but not in cirrhotic FNH-like nodules. J Hepatol 49:61–71

Rebouissou S, Bioulac-Sage P, Zucman-Rossi J (2008b) Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma. J Hepatol 48:163–170

Reddy KR, Schiff ER (1993) Approach to a liver mass. Semin Liver Dis 13:423–435

Reddy KR, Kligerman S, Levi J, Livingstone A, Molina E, Franceschi D, Badalamenti S et al (2001) Benign and solid tumors of the liver: relationship to sex, age, size of tumors, and outcome. Am Surg 67:173–178

Reichlin B, Stalder GA, Rüedi T, Bianchi L (1980) Co-occurring liver cell adenoma and focal nodular hyperplasia due to contraceptives. Case report (in German). Schweiz Med Wochenschr 110:873–874

Rhodes RH, Marchildon MB, Luebke DC, Edmondson HA, Mikity VG (1978) A mixed hamartoma of the liver: light and electron microscopy. Hum Pathol 9:211–220

Ribera Cano A, Debette-Gratien M, Descottes B, Languepin J (2007) Focal nodular hyperplasia involving portal cavernoma (in French). Arch Pediatr 14:1315–1317

Ricklan DE, Collett TA, Lyness SK (1988) Umbilical vein variations: review of the literature and a case report of a persistent right umbilical vein. Teratology 37:95–100

Rifai K, Mix H, Krusche S, Potthoff A, Manns MP, Gebel MJ (2013) No evidence of substantial growth progression or complications of large focal nodular hyperplasia during pregnancy. Scand J Gastroenterol 48:88–92

Ronot M, Paradis V, Duran R, Kerbaol A, Vuillerme MP, Belghiti J, Valla DC, Vilgrain V (2013) MR findings of steatotic focal nodular hyperplasia and comparison with other fatty tumors. Eur Radiol 23:914–923

Ross D, Pena J, Mirza M, Galvan A, Ponce L (1976) Regression of focal nodular hyperplasia after discontinuation of oral contraceptives. Ann Intern Med 85:203–204

Roulot D (2013) Liver involvement in turner syndrome. Liver Int 33:24–30

Rubbia-Brandt L, Lauwers GY, Wang H, Majino PE, Tanabe K, Zhu AX, Brezault C et al (2010) Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxiplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology 56:430–439

Rudolph AM (1983) Hepatic and ductus venosus blood flows during fetal life. Hepatology 3:254–258

Russmann S, Zimmermann A, Krähenbühl S, Kern B, Reichen J (2001) Veno-occlusive disease, nodular regenerative hyperplasia and hepatocelular carcinoma after azathioprine treatment in a patient with ulcerative colitis. Eur J Gastroenterol Hepatol 13:287–290

Sadowski DC, Lee SS, Wanless IR, Kelly JK, Heathcote EJ (1995) Progressive type of coal nodular hyperplasia characterized by multiple tumors and recurrence. Hepatology 21:970–975

Saito M, Nagashima K, Horita S (2005) Focal nodular hyperplasia of the liver with angioma-like features in the center. Intern Med 44:503–504

Sakatoku H, Hirokawa Y, Inoue M, Kojima M, Yabana T, Sakurai M (1996) Focal nodular hyperplsia in an adolescent with glycogen storage disease type I with mesocaval shunt operation in childhood: a case report and review of the literature. Acta Paediatr Jpn 38:172–175

Sanchez Manuel J, Seco Gil JL, Saez-Royuela F, Llanos Chavarri MC, Perez Alvarez JC, Garcia Plata E, Lopez Morante A (1997) Idiopathic portal hypertension, multiple focal nodular hepatic hyperplasia, the CREST syndrome and protein S deficiency (in Spanish). Rev Esp Enferm Dig 89:55–59

Sano Y, Nakamura S, Kitazawa T, Sakaguchi S, Kitanaka H, Kaneko M, Maeda M, Muro H, Shirasawa H (1985) Focal nodular hyperplasia-like lesions of the liver associated with thorotrast liver disease – report of a case (in Japanese). Gan No Rinsho 31:1445–1450

Santarelli L, Gabrielli M, Orefice R, Nista EC, Serricchio M, Nestola M, Rapaccini G, De Ninno M, Pola P, Gasbarrini M et al (2003) Association between Klinefelter syndrome and focal nodular hyperplasia. J Clin Gastroenterol 37:189–191

Sato A, Rai T, Takahashi A, Saito H, Takagi T, Shibukawa G, Wakatsuk T, Takahashi Y et al (2006) A case od rapidly expanding and increasing focal nodular hyperplasia. Fukushima J Med Sci 52:149–155

Sato Y, Harada K, Ikeda H, Fijii T, Sasaki M, Zen Y, Nakanuma Y (2009) Hepatic stellate cells are activated around central scars of focal nodular hyperplasia of the liver – a potential mechanism of central scar formation. Hum Pathol 40:181–188

Saul SH, Titelbaum DS, Gansler TS, Varello M, Burke DR, Atkinson BF, Rosato EF (1987) The fibrolamellar variant of hepatocellular carcinoma. Its association with focal nodular hyperplasia. Cancer 60:3049–3055

Sawhney S, Jain R, Safaya R, Berry M (1992) Pedunculated focal nodular hyperplasia. Pediatr Radiol 22:231–232

Saxena R, Humphreys S, Williams R, Portmann B (1994) Nodular hyperplasia surrounding fibrolamellar carcinoma: a zone of arterialized liver parenchyma. Histopathology 25:275–278

Savoye-Collet C, Herve S, Koning E, Scotte M, Dacher JN (2002) Focal nodular hyperplasia occurring after blunt abdominal trauma. Eur J Gastroenterol Hepatol 14:329–330

Scardapane A, Ficco M, Sabba C, Lorusso F, Moschetta M, Maggialetti N, Suppressa P et al (2013) hepatic nodular regenerative lesions in patients with hereditary haemorhagic telangiectasia: computed tomography and magnetic resonance findings. Radiol Med 118:1–13

Schaff Z, Darosi I, Hsia CC, Kiss A, Tabor E (1995) p53 in malignant and benign liver lesions. Eur J Cancer 31A:1847–1850

Scheuermann U, Foltys D, Otto G (2012) Focal nodular hyperplasia precedes hepatocellular carcinoma in an adult with congenital absence of the portal vein. Transpl Int 25:e67–e68

Scheuermann U, Strempel M, Emrich T, Foltys D, Otto G (2013) Development of multiple focal nodular hyperplasia lesions after portocaval shunting. A case report. J Gastrointestin Liver Dis 22:451–453

Schilling MK, Zimmermann A, Redaelli C, Seiler CA, Büchler MW (2000) Liver nodules resembling focal nodular hyperplasia after hepatic venous thrombosis. J Hepatol 33:673–676

Schmelling JW (1934) Rare case of congenital multiple tumors of liver (hamartomas) in infant 4 months old. Ned Tydschr Geneeskd 78:3566

Schmidt B, Bhatt GM, Abo MN (1980) Management of post-traumatic vascular malformations of the liver by catheter embolization. Am J Surg 140:332–335

Schmidt S, Saint-Paul MC, Anty R, Bruneton JN, Gugenheim J, Chevalier P (2006) Multiple focal nodular hyperplasia oft he liver associated with congenital absence of the portal vein (in French). Gastroenterol Clin Biol 30:310–313

Scoazec JY, Flejou JF, D'Errico A, Couvelard A, Kozyraki R, Fiorentino M, Grigioni WF, Feldmann G (1995) Focal nodular hyperplasia of the liver: composition of the extracellular matrix and expression of cell-cell and cell-matrix adhesion molecules. Hum Pathol 26:1114–1125

Scott LD, Katz AR, Duke JH, Cowan DF, Maklad NF (1984) Oral contraceptives, pregnancy, and focal nodular hyperplasia of the liver. JAMA 251:1461–1463

Sempoux C, Chang C, Gouw A, Chiche L, Zucman-Rossi J, Balabaud C, Bioulac-Sage P (2013) Benign hepatocellular nodules: what we have learned using the pathomolecular classification. Clin Res Hepatol Gastroenterol 37:322–327

Sempoux C, Balabaud C, Bioulac-Sage P (2014) Pictures of focal nodular hyperplasia and hepatocellular adenomas. World J Hepatol 6:580–595

Serke S, Dienemann D, Speck B, Zimmerman R, Baer V, Huhn D (1986) Hepatocellular carcinoma and focal nodular hyperplasia associated with norethandrolone therapy: a case report. Blut 52:111–116

Shamsi K, De Schepper A, Degryse H, Deckers F (1993) Focal nodular hyperplasia of the liver: radiologic findings. Abdom Imaging 18:32–38

Shapiro RS, Maldjian JA, Stancato-Pasik A, Ramos R (1993) Hepatic mass in Budd-Chiari syndrome: CT and MRI findings. Comput Med Imaging Graph 17:457–460

Shen YH, Fan J, Wu ZQ, Ma ZC, Zhou XD, Zhou J, Qiu SJ, Qin LX, Ye QH, Sun HC et al (2007) Focal nodular hyperplasia of the liver in 86 patients. Hepatobiliary Pancreat Dis Int 6:52–57

Shet AS, Aras O, Gupta K, Hass MJ, Rausch DJ, Saba N, Koopmeiners L, Key NS, Hebbel RP (2003) Sickle blood contains tissue factor-positive microparticles derived from endothelial cells and monocytes. Blood 102:2678–2683

Shortell CK, Schwartz SI (1991) Hepatic adenoma and focal nodular hyperplasia. Surg Gynecol Onstet 173:426–431

Sudour H, Mainard L, Baumann C, Clement L, Salmon A, Bordigoni P (2009) Focal nodular hyperplasia of the liver following hematopoietic SCT. Bone Marrow Transplant 43:127–132

Sugihara S, Nakashima O, Kiyomatsu K, Ijiri M, Edamitsu O, Kojiro M (1990) A case of liver cirrhosis with a hyperplastic nodular lesions. Acta Pathol Jpn 40:699–703

Tajada M, Nerin J, Ruiz MM, Sanchez-Dehesa M, Fabre E (2001) Liver adenoma and focal nodular hyperplasia associated with oral contraceptives. Eur J Contracept Reprod Health Care 6:227–230

Takamura M, Mugishima H, Oowada M, Harada K, Uchida T (1995) Type Ia glycogen storage disease with focal nodular hyperplasia in siblings. Acta Paediatr Jpn 37:510–513

Tanaka M, Nakashima O, Wada Y, Kage M, Kojiro M (1996) Pathomorphological study of Kupffer cells in hepatocellular carcinoma and hyperplastic nodular lesions in the liver. Hepatology 24:807–812

Tanaka Y, Takayanagi M, Shiratori Y, Imai Y, Obi S, Tateishi R, Kanda M, Fujishima T, Akamatsu M et al (2003) Congenital absence of portal vein with multiple hyperplastic nodular lesions of the liver. J Gastroenterol 38:288–294

Tatrai P, Somoracz A, Batmunkh E, Schirmacher P, Kiss A, Schaff Z, Nagy P, Kovalszky I (2009) Agrin and CD34 immunohistochemistry for the discrimination of benign versus malignant hepatocellular lesions. Am J Surg Pathol 33:874–885

Terada T, Kitani S, Ueda K, Nakanuma Y, Kitagawa K, Masuda S (1993) Adenomatous hyperplasia of the liver resembling focal nodular hyperplasia in patients with chronic liver disease. Virchows Arch A Pathol Anat Histopathol 422:247–252

Terayama N, Terada T, Hoso M, Nakanuma Y (1995) Partial nodular transformation of the liver with portal vein thrombosis. A report of two autopsy cases. J Clin Gastroenterol 20:71–76

Theander and Karlsson (1978). http://www.ncbi.nlm.nih.gov/pubmed/654952

Theise ND, Schwartz M, Miller C, Thung SN (1992) Macroregenerative nodules and hepatocellular carcinoma in forty-four sequential adult liver explants with cirrhosis. Hepatology 16:949–955

Tokutomi T, Hayashi S, Imai K, Chida A, Ishiwata T, Asano Y, Inazawa J, Nonoyama S (2007) dup(8p)/del (8q) recombinant chromosome in a girl with hepatic focal nodular hyperplasia. Am J Med Genet A 143A:1334–1337

Toshikuni N, Kawaguchi K, Miki H, Kihara Y, Sawayama T, Yamasaki S, Takano S, Minato T (2001) Focal nodular hyperplasia coexistent with hemangioma and multiple cysts of the liver. J Gastroenterol 36:206–211

Towbin AJ, Luo GG, Yin H, Mo JQ (2011) Focal nodular hyperplasia in children, adolescents, and young adults. Pediatr Radiol 41:341–349

Tsai JH, Jeng YM, Pan CC, Lu SW, Kuo YJ (2012) Immunostaining of glutamine synthetase is a sensitive and specific marker for diagnosing focal nodular hyperplasia in needle biopsy. Pathology 44:605–610

Turowski C, Feist H, Alzen G, Glüer S, Petersen C (2009) Conversion of a neonatal hepatic hemangioma to focal nodular hyperplasia. Pathol Int 59:251–254

Ungermann L, Elias P, Zizka J, Ryska P, Klzo L (2007) Focal nodular hyperplasia: spoke-wheel arterial pattern and other signs on dynamic contrast-enhanced ultrasonography. Eur J Radiol 63:290–294

Valentino PL, Ling SC, Ng VL, John P, Bonasoni P, Castro DA, Taylor G, Chavhan GB et al (2014) The role of diagnostic imaging and liver biopsy in the diagnosis of ocal nodular hyperplasia in children. Liver Int 34:227–234

Velasquez G, Ward CF, Bohrer SP (1985) Thorium dioxide: still around. South Med J 78:743–745

Vilgrain V, Fléjou JF, Arrive L, Belghiti J, Najmark D, Menu Y, Zins M, Vullierme MP, Nahum H (1992) Focal nodular hyperplasia of the liver: MR imaging and pathologic correlation in 37 patients. Radiology 184:699–703

Vilgrain V, Lewin M, Vons C, Denys A, Valla D, Fléjou JF, Belghiti J, Menu Y (1999) Hepatic nodules in Budd-Chiari syndrome: imaging features. Radiology 210:443–450

Vilgrain V, Uzan F, Brancatelli G, Federle MP, Zappa M, Menu Y (2003) Prevalence of hepatic hemangioma in patients with focal nodular hyperplasia: MR imaging analysis. Radiology 229:75–79

Vonnahme FJ, Dubuisson L, Kubale R, Klempnauer R, Grun M (1984) Ultrastructural characteristics of hyperplastic alterations in the liver of congenital portacaval-shunt rats. Br J Exp Pathol 65:585–596

Walthard B (1968) Carl Wegelin. 1879–1968 (in German). Schweiz Med Wschr 98:1016–1018

Wang HL, Anatelli F, Zhai QJ, Adley B, Chuang ST, Yang XJ (2008) Glypican-3 as a useful diagnostic marker that distinguishes hepatocellular carcinoma from benign hepatocellular mass lesions. Arch Pathol Lab Med 132:1723–1728

Wanless IR, Gledhill RW (1979) Failure to produce hepatic hyperplastic nodules in rats by portacaval anastomosis and testosterone. Nature 277:327–328

Wanless IR, Mawdsley C, Adams R (1985a) On the pathogenesis of FNH of the liver. Hepatology 5:1194–1200

Wanless IR, Lentz JS, Roberts EE (1985b) Partial nodular transformation of the liver in an adult with persistent ductus venosus. Review with hypothesis on pathogenesis. Arch Pathol Lab Med 109:427–432

Wanless IR, Gryfe A (1986) Nodular transformation of the liver in hereditary hemorrhagic teleangiectasia. Arch Pathol Lab Med 110:331–335

Wanless IR (1987) The use of morphometry in the study of nodular and vascular lesions of the liver. Anal Quant Cytol Histol 9:39–41

Wanless IR, Albrecht S, Bilbao J et al (1989) Multiple focal nodular hyperplasia of the liver associated with vascular malformations of various organs and neoplasia of the brain: a new syndrome. Mod Pathol 2:456–462

Wanless IR (2000) Epithelioid hemangioendothelioma, multiple focal nodular hyperplasias, and cavernous hemangiomas of the the liver (comment). Arch Pathol Lab Med 124:1105–1107

Wasif N, Sasu S, Conway WC, Bilchik A (2008) Focal nodular hyperplasia: report of an unusual case and review of the literature. Am Surg 74:1100–1103

Wegelin K (1905) Über das Adenokarzinom und Adenom der Leber. Thesis, accepted by Prof. Theodor Langhans, Bern

Weinbren K, Washington SL (1976) Hyperplastic nodules after portacaval anastomosis in rats. Nature 264:440–442

Wenzel D, Winters C (1983) The scar sign in hepatic neoplasia. J Ultrasound Med 2:160–168

Wetzel WJ, Alexander RW (1979) Focal nodular hyperplasia of the liver with alcoholic hyaline bodies and cytologic atypia. Cancer 44:1322–1326

Wilson TS, Macgregor JW (1969) Focal nodular hyperplasia of the liver: the solitary cirrhotic liver nodule. Can Med Assoc J 100:567–572

Wolf R, Wolf D, Kuperman S (2001) Focal nodular hyperplasia of the liver after intraconazole treatment. J Clin Gastroenterol 33:418–420

Wu WC, Chen SC, Dia CY, Yu ML, Hsieh MY, Lin ZY, Wang LY, Tsia JF, Chang WY, Chuang WL (2003) Coexistence of focal nodular hyperplasia and pseudotumor caused by focal spared lesion in the liver of a young man. J Gastroenterol Hepatol 18:1320–1322

Yamamoto M, Ariizumi S, Yoshitoshi K, Saito A, Nakano M, Takasaki K (2006) Hepatocellular

carcinoma with a central scar and a scalloped tumor margin resembling focal nodular hyperplasia in mascroscopic appearance. J Surg Oncol 94:587–591

Yonemitsu H, Mori H, Kimura T, Kagawa K, Tsuda T, Yamada Y, Kiyosue H, Matsumoto S (2000) Congenital extrahepatic portocaval shunt associated with hepatic hyperplastic nodules in a patient with Dubin-Johnson syndrome. Abdom Imaging 25:572–575

Zhang SH, Cong WM, Wu MC (2004) Focal nodular hyperplasia with concomitant hepatocellular carcinoma: a case report and clonal analysis. J Clin Pathol 57:556–559

Zhou H, Wolff M, Pauleit D, Fischer HP, Pfeifer U (2000) Multiple macroregenerative nodules in liver cirrhosis due to Budd-Chiari syndrome. Case report and review of the literature. Hepatogastroenterology 47:522–527

Zhu ZW, Friess H, Wang L, Abou-Shady M, Zimmermann A, Lander AD, Korc M et al (2001) Enhanced glypican-3 expression differentiates the majority of hepatocellular carcinomas from benign hepatic disorders. Gut 48:558–564

Nodular Regenerative Hyperplasia and Other Noncirrhotic Nodular Hyperplastic Lesions of the Liver

118

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_118

Abstract

Nodular regenerative hyperplasia (NRH) of the liver is a multilobular regenerative nodular lesion that develops in a noncirrhotic liver. NRH is characterized by the presence of nodules composed of normal-looking hepatocytes that form enlarged cell plates. These nodules are not surrounded by collagenous tissue, but a compressed reticulin network is present between the nodules and adjacent parenchyma. Cells within the nodules exhibit an increased proliferative activity. NRH is a major cause of noncirrhotic portal hypertension and develops in association with several systemic and local disorders, including autoimmune and related diseases, vascular disorders of the liver, myeloid neoplasms and various lymphoproliferative disorders, various drugs (mainly immunosuppressive agents), immunodeficiency syndromes, infections, and numerous other but rare conditions. There is evidence that, as a major pathogenic pathway, obliteration of small portal venous branches that causes atrophy of downstream liver lobules is followed by compensatory hyperplasia of adjacent lobules. There are other, less common forms of noncirrhotic nodular hyperplastic lesions of the liver, including partial nodular transformation.

Nodular Regenerative Hyperplasia (NRH) of the Liver

Introduction

Nodular regenerative hyperplasia (NRH) of the liver (synonyms: micronodular transformation; nodular transformation; nodular noncirrhotic liver; noncirrhotic nodulation of the liver) is multilobular regenerative nodular lesion developing in a noncirrhotic liver. NRH is morphologically characterized by the presence of nodules of regenerating, normal-looking hepatocytes, without fibrous septa, usually distributed diffusely across the liver parenchyma (Stromeyer and Ishak 1981). NRH is a major cause of noncirrhotic portal hypertension (review: Nakanuma et al. 2001). An important pathogenic mechanism, outlined in more detail below, is that obliteration of small portal venous branches causes atrophy of downstream liver lobules followed by compensatory hyperplasia of adjacent lobules with a still intact portal blood supply (reviews: Connolly 1977; Rougier et al. 1978; Smith 1978; Alperstein et al. 1981; Stromeyer and Ishak 1981; Mones and Saldana 1984; Moran et al. 1991; Tsui and So 1993; Pettei et al. 1995; Dall'Igna et al. 1996; Trenschel et al. 2000; Kondo et al. 2004).

Epidemiology

In several reports, Rauström is credited with being the first to describe a case of NRH of the liver in 1953, however by using the term *miliary hepatocellular adenomatosis* (Rauström 1953). In 1959, Steiner coined the term *nodular regenerative hyperplasia of the liver* (Steiner 1959). The prevalence of NRH may be as high as 0.6 % on the basis of autopsy series (Wanless et al. 1980). NRH is predominantly a disease of adult subjects but is also well recognized in the pediatric age-group (). In children, NRH may follow completion of solid tumor chemotherapy and may mimic hepatic metastases (Chu and Roebuck 2003; Citak et al. 2007). There are very rare instances of familial occurrence of NRH (Dumortier et al. 1999). A trimorphic syndrome with familial idiopathic pulmonary fibrosis, bone marrow hypoplasia, and hepatic NRH has been described (Talbot-Smith et al. 2009). The causes and pathogenic pathways of NRH are discussed in more detail at the end of this chapter.

Clinical and Imaging Features

NRH may be asymptomatic (Reshamwala et al. 2006), but in autopsy studies, NRH is associated with noncirrhotic portal hypertension in part of patients with this disorder (Wanless 1990). Noncirrhotic portal hypertension has been observed in at least half of patients with NRH (Sherlock et al. 1966; Classen et al. 1970; Rougier

et al. 1978; Stromeyer and Ishak 1981; Naber et al. 1991; Arvanitaki and Adler 2001; Gentilucci et al. 2011; review: Hartleb et al. 2011). Noncirrhotic portal hypertension is also caused by NRH in the pediatric age-group (Alperstein et al. 1981). Hemodynamic studies have suggested that portal hypertension in NRH is primarily sinusoidal, similar to that seen in liver cirrhosis (Ueno et al. 1996). In a more recent study of 24 NRH patients with symptomatic portal hypertension analyzing wedged hepatic vein, inferior vena cava, and portal vein pressures, findings were those of a presinusoidal component to portal hypertension, probably related to compression of portal venules by the regenerative nodules (Bissonnette et al. 2012). Rarely, NRH was associated with pulmonary arterial hypertension (Yutani et al. 1988; Bedossa et al. 1990). NRH may be associated with elevated serum AFP levels, caused by the regenerative hepatocyte response (Mneimneh et al. 2011). The prognosis of NRH is thought to be related more to the severity of underlying disease or systemic disorder than to the hepatic involvement itself (Colina et al. 1989).

The nodules of NRH have variable echogenicity on sonography, with hyperechoic or hypoechoic lesions (Casillas et al. 1997). In many cases, the reflexion pattern of the nodules is similar to that produced by cirrhotic liver, but in contrast to cirrhosis, the liver surface is smooth and free from the typical nodularity found in cirrhosis, and the coarsening or thickening of the lower edge of the liver is absent (Classen et al. 1970). By use of contrast-enhanced ultrasound (CEUS), distinct coral atoll-like lesions were detected in predisposed patients (Caturelli et al. 2011). Multiple small echogenic masses with occasional anechoic centers corresponding to hemorrhagic foci within the nodules may be encountered (Dachman et al. 1987). Radiologically, multiple small to medium-sized nodules and larger masses caused by conglomerate nodules on a background of a noncirrhotic liver are visible (Reynolds and Wanless 1984). The imaging features of multiple NRH lesions may mimic hepatic metastases (Clouet et al. 1999). These findings may be associated with splenomegaly and/or ascites on plain films or upper gastrointestinal series, and esophageal varices in barium studies, features of portal hypertension (Dachman et al. 1987). On CT images, the nodules are often hypodense without significant enhancement. The lack of enhancement is an important finding to distinguish NRH from large regenerative liver nodules which exhibit enhancement in a large proportion of cases (Ames et al. 2009). In a larger series, masses seen on CT images measured 0.2–10 cm in diameter, the latter representing conglomerate nodules (Dachman et al. 1987). Conglomerate lesions may produce a pseudotumoral aspect (Patriarche et al. 1988; Casillas et al. 1997). T1-weighted MR images of the liver show high-signal nodular lesions with central hypointense foci, while T2-weighted images reveal that the nodular lesions are isointense with central hyperintense foci (Siegelman et al. 1995; Horita et al. 2002; Wang et al. 2008; Leung et al. 2009). The nodules may take up technetium sulfur colloid (reviews: Dachman et al. 1987; Kobayashi et al. 2009). Angiographically, the findings were strikingly similar to what has been reported in cases of idiopathic portal hypertension (Shedlofsky et al. 1980). In splenoportography, an abrupt reduction in the contrast density of the smallest hepatic branches was seen, typical for a block at the level of hepatic microcirculation (Classen et al. 1970). Detection in intranodular Kupffer cells with superparamagnetic iron oxide enhanced MR imaging is an important indicator that a nodule is regenerative rather than neoplastic (Kobayashi et al. 2009).

Pathology

Macroscopy

At autopsy, livers with NRH often show a smooth capsule, in contrast to cirrhosis. However, in cases with advanced disease and formation of conglomerate nodules, the macroscopic features may resemble liver cirrhosis, also on small biopsy samples (Fig. 1; Qizilbash and Castelli 1980). On cut surfaces the picture varies considerably, ranging from an apparently preserved lobular

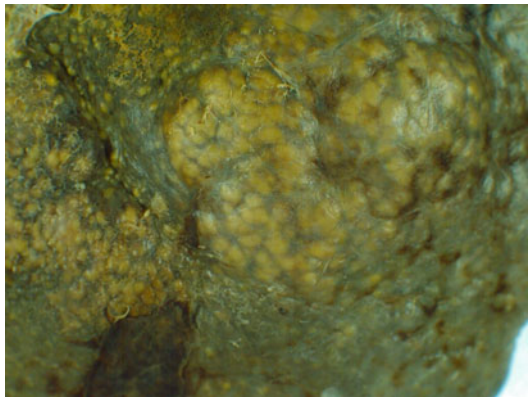

Fig. 1 Marked nodular regenerative hyperplasia of the liver

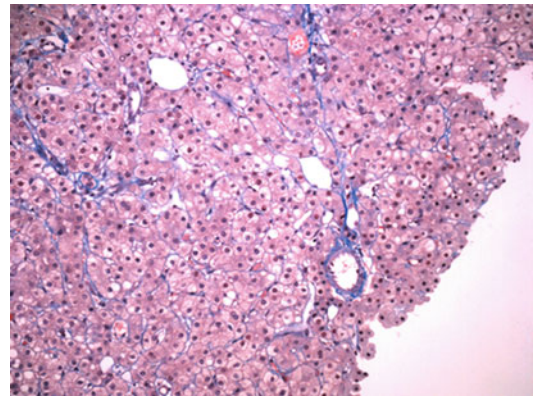

Fig. 3 Nodular regenerative hyperplasia of the liver. As seen in this collagen stain, the nodular lesion is not surrounded by fibrosis (CAB stain)

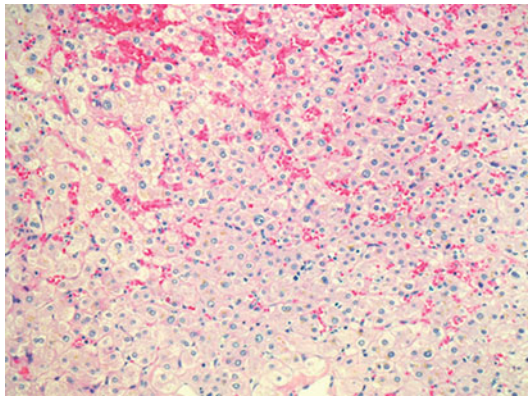

Fig. 2 Nodular regenerative hyperplasia of the liver. Hyperplastic areas show enlarged liver cell plates, darker cells and nuclear unrest (*center* of figure, hematoxylin and eosin stain)

architecture without visible nodular structures to multiple round to polygonal nodules, sometimes resulting in a picture resembling liver cirrhosis. The nodules typically measure 1–3 mm in diameter, but a macronodular aspect of the liver may also be found. In most instances, the nodules are more or less spherical, have a color identical or similar to the background parenchyma, and do not bulge from the cut surface. In contrast to cirrhotic nodules, the borders of the nodular structures are blurred or ill defined, because they are not delimitated by a fibrous shell (Stromeyer and Ishak 1981; Solis Herruzo et al. 1985; Wanless 1990; Forbes et al. 1991). Rarely, conglomerate nodules may be formed, resulting in lesions approaching 10 cm in diameter or even pseudotumoral presentation (Casillas et al. 1997). At abdominal surgery, granularity of the liver surface has been described (Blendis et al. 1970). Laparoscopically, histologically proven NRH grossly presented as a non-nodular undulated liver surface, a recognizable lobular pattern, and a hepatic consistency softer than normal to palpation (Cano-Ruiz et al. 1985).

Histopathology

The pertinent histological features of NRH have been described in detail (Weinbren and Mutum 1984). The salient presentation is that of well-circumscribed or vague hepatocyte nodules without associated fibrosis, whereby the nodularity is finer than the macroscopic appearance of granularity in cases of diffuse NRH (Figs. 2 and 3). NRH can develop in a focal pattern or may exist as diffuse NRH occupying the entire liver (diffuse regenerative hyperplasia, DNRH; Colina et al. 1989), depending on the underlying causes. The diameter of the nodules ranges from minute spherical hepatocyte clusters that may not be seen easily without a reticulin stain to macronodules that can be seen with naked eye (Trenschel et al. 2000). The hepatocyte plates within the nodules exhibit a characteristic thickening, the plates having three or four rows instead of two.

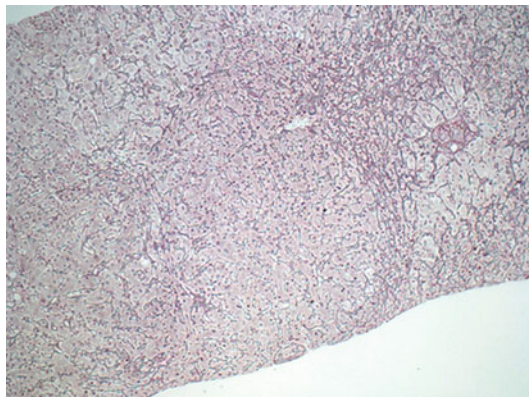

Fig. 4 Nodular regenerative hyperplasia of the liver. The nodular lesion is best visualized in reticulin stains (*middle* of figure; Gomori silver stain)

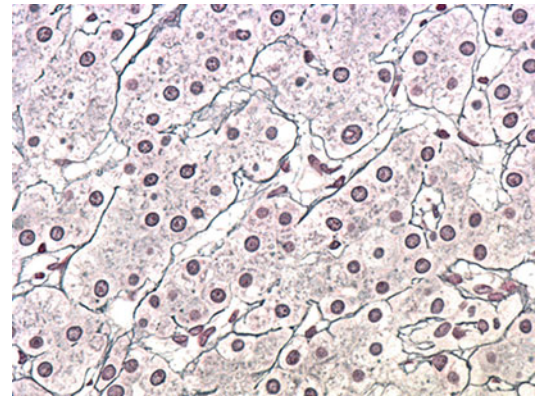

Fig. 6 Nodular regenerative hyperplasia of the liver. In this reticulin stain, an enlargement of hepatocyte plates (more than two cells in width) is seen (Gomori silver stain)

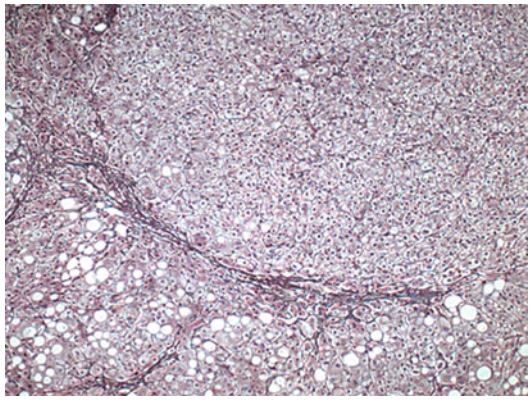

Fig. 5 Nodular regenerative hyperplasia of the liver may induce compression of adjacent liver tissue and condensation of reticulin fibers (Gomori silver stain)

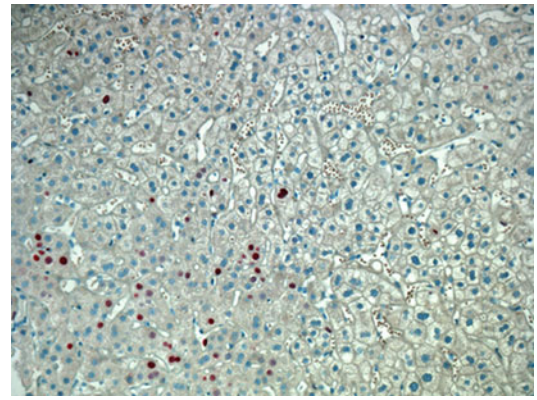

Fig. 7 Nodular regenerative hyperplasia of the liver. In areas with hyperplasia, hepatocytes exhibit an increased proliferative activity (*left half* of figure; MIB1 immunostain)

This feature is particularly well visualized in a reticulin stain (Figs. 4, 5 and 6). Thick hepatocyte plates are a constant and striking feature and represent the result of regenerative cell proliferation (Fig. 7; Weinbren and Mutum 1984). Within the nodules and their conglomerates, sinusoids are commonly narrow and the number of branches of the hepatic vein are reduced. Portal tracts may be trapped within nodules, producing a pattern of reversed lobulation, but this a rather rare finding. Portal tracts entrapped within regenerative nodules may show a mild lymphocytic infiltration and some fibrosis, even with incomplete septa. Obliterative portal phlebopathy may be in evidence (Nakanuma et al. 1996). Typically, the parenchyma adjacent to the nodules reveals a preserved lobular architecture, i.e., without any cirrhotic remodeling, but it manifests varying degrees of atrophy, with compression and thinning of hepatocyte plates, best seen in reticulin stains. Due to the expansion of nodules, the reticulin network is compressed and therefore more dense, a feature that has not to be confounded with true fibrosis. In and around the nodules of NRH, sinusoids may be significantly dilated in the absence of a hepatic venous outflow disorder (Kakar et al. 2004). Sinusoids of livers with NRH may contain increased

numbers of lymphocyte. CD8+ cytotoxic T lymphocytes were detected in 14 of 44 NRH patients. The cells were located near atrophic liver cell plates. Significantly more granzyme B+ and CD57+ lymphocytes were observed in NRH than chronic hepatitis C samples with quantitatively similar CD8+ lymphocyte infiltrates. It was suggested that CD8+ cytotoxic cells may damage sinusoidal endothelial cells and participate in the pathogenesis of NRH (Ziol et al. 2004). NRH may be associated with other histological liver alterations, depending on the type of underlying disease. In certain hematologic disorders, including myeloproliferative syndromes, obliterative portal venopathy is found in association with NRH (Wanless et al. 1980). NRH occurring in the setting of primary hypogammaglobulinemia was often associated with accumulation of lymphocytes in hepatic sinusoids (Malamut et al. 2008).

Immunohistochemistry

In one report, periportal immunostaining of hepatocytes for alpha-1-antitrypsin was more frequent in biopsies showing NRH than in non-NRH samples, suggesting that this staining may be useful in confirming the needle biopsy diagnosis of NRH (Nakhleh and Snover 1988).

Causes of Nodular Regenerative Hyperplasia

The causes of NRH cover a broad spectrum. Many if not most causative factors operate through a pathway involving vascular damage. The mode of progression or the reversibility of NRH are currently unknown. Known causes and associations of NRH are compiled in Table 1.

Drugs

Drug-induced NRH is common form of this disorder, probably amounting to more than 60 % of cases (Colina et al. 1989; Ghabril and Vuppalanchi 2014), but the underlying cause is

Table 1 Known causes and associations of nodular regenerative hyperplasia

Autoimmune and related disorders
Rheumatoid arthritis
Felty's syndrome
Systemic lupus erythematodes (SLE)
Sclerderma
Sjögren's syndrome
Polyarteritis nodosa
Immune complex-induced microvasculitis
Mixed cryoglobulinemia
Inflammatory bowel disease (IBD)
Celiac disease
Primary biliary cirrhosis (with or without CREST)
Antiphospholipid syndrome
Membranous and membranoproliferative glomerulonephritis
Drugs (mostly used as immunosuppressants)
Vascular disorders of the liver
Portal vein agenesis
Portal vein thrombosis and other obliterative lesions (portal obliterative venopathy)
Patent ductus venosus
Congenital extrahepatic portosystemic shunts
Veno-occlusive disease
Budd-Chiari syndrome
Hepatic arteritis/vasculitis
Hereditary hemorrhagic telangiectasia
Hematologic disorders
Acute leukemias
Myeloproliferative disorders
Non-Hodgkin's lymphomas
Hodgkin lymphoma
Castleman's disease
Hypereosinophilic syndromes
Aplastic anemia
Immunodeficiency syndromes
Hypogammaglobulinemia
Solid organ and cell transplantation (post-transplant NRH)
Liver transplantation
Renal transplantation
Bone marrow transplantation
Infections
HIV infection
Tuberculosis
Hepatic granulomatous disorders
Sarcoidosis
Microcirculatory disorders caused by hepatic tumors or metastases
Thorotrastosis

(*continued*)

Table 1 (continued)

Inborn errors of metabolism
Cystinosis
Hyperhomocysteinemia
Krabbe's disease
Other congenital disorders
Turner syndrome
Multiple malformations
Familial pulmonary fibrosis
Familial nodular regenerative hyperplasia

often the disorder treated with the implicated drugs. In fact, the drugs involved are mostly immunosuppressive agents used in the treatment of autoimmune disorders, inflammatory bowel disease and transplantation, and agents employed in cancer chemotherapy.

Classical thiopurines (azathioprine and 6-mercaptopurine) are commonly used as immunosuppressants in transplanted patients and patients with inflammatory bowel disease (IBD), in both Crohn's disease and ulcerative colitis. Hepatotoxicity is considered to be a relatively rare adverse event and is generally characterized by an increase in routine liver test parameters without clinical symptoms and signs. However, azathioprine (AZA) is well documented to cause NRH as a hepatic side effect (Duvoux et al. 1991; Mion et al. 1991; Russmann et al. 2001; Daniel et al. 2005; Seiderer et al. 2006; Schumann et al. 2008; Blogowski et al. 2011; Seksik et al. 2011; review: Musumba 2013). Male gender seems to be a major risk factor by providing a predisposing pharmacogenetic profile of purine analogue metabolism (Daniel et al. 2005). Several studies have shown NRH in IBD patients treated with AZA (Ehmsen et al. 2008), but has also been found in other disorders treated with this agent, including multiple sclerosis (Mion et al. 1991). In patients with inflammatory bowel disease treated with AZA, NRH is however an uncommon complication. In a study of 1888 consecutive IBD patients treated with AZA, the cumulative incidence of NRH was 1.28 % at 10 years (Seksik et al. 2011). A vascular effect may be involved in AZA-induced NRH, as NRH has been found in association with veno-occlusive disease in one patient with AZA-treated ulcerative colitis (Russmann et al. 2001).

NRH has been reported as a complication of 6-thioguanine therapy, both when used as a cancer therapy agent and as an immunosuppressive agent. In IBD patients, NRH has been increasingly found in azathioprine- or 6-mercaptopurine-intolerant patients using 6-thioguanine as a rescue drug (Shepherd et al. 1991; Dubinsky et al. 2003; Geller et al. 2004; Shastri et al. 2004; de Boer et al. 2005; Seiderer et al. 2005; De Bruyne et al. 2006; Ravikumara et al. 2006; Ferlitsch et al. 2007; Teml et al. 2007). 6-thioguanine is closely related to 6-mercaptopurine and azathioprine and has principally been used in the treatment of hematological malignancies. It has been reported to cause hepatocyte damage and necrosis and veno-occlusive disease, the latter being the most characteristic hepatic side effect caused by 6-thioguanine. The prevalence of NRH in patients treated with 6-thioguanine varies considerably, being 27.1 % (Teml et al. 2007), 39 % (Zech et al. 2007), and 76 % of patients undergoing liver biopsy in a group of IBD patients with hepatic laboratory abnormalities (Dubinsky et al. 2003). Among patients with inflammatory bowel disease treated with 6-thioguanine, 53 % of those who had a liver biopsy showed NRH in the reticulin stain, whereas only 11 % of the NRH cases were identified in H&E sections (Geller et al. 2004). It was proposed that NRH in the setting of 6-thioguanine therapy may well be dose or level dependent, NRH being less common under low-dose therapy. In a prospective multicenter study of inflammatory bowel disease patients using low-dose 6-thioguanine for at least 30 consecutive months, 28 liver biopsies were analyzed. In 93 % of biopsies, no signs of NRH were found, and in 2 patients the findings were not conclusive (de Boer et al. 2008a). On the other, NRH also develops in thiopurine-naïve patients with inflammatory bowel disease. In one study having analyzed 83 liver specimens (61 % of them from Crohn's disease patients), NRH was observed in 6 % of the samples, suggesting that NRH is occurring in IBD without specific therapy (de Boer et al. 2008b).

NRH occurs in patients with colorectal carcinoma liver metastases treated with cycles of neoadjuvant 5-fluorouracil and oxaliplatin before major liver surgery (Hubert et al. 2007; van den Broek et al. 2009; Wicherts et al. 2011; Morris-Stiff et al. 2014). Pathogenetically, a disturbance of hepatic microvascular circulation caused by chemotherapeutic agents may be considered. It was found that patients treated by oxiplatin more often had NRH compared with oxiplatin-naïve patients with metastatic colorectal cancer (Wicherts et al. 2011). Oxaliplatin-based chemotherapy has been shown to cause severe hepatic sinusoidal obstruction (the so-called sinusoidal obstruction syndrome; Arotçarena et al. 2006; Rubbia-Brandt et al. 2006; Rubbia-Brandt et al. 2010), and microvascular hepatic changes were found to be significantly associated with oxiplatin therapy in patients with metastatic colorectal cancer (Ryan et al. 2010).

Cytosine arabinoside and daunorubicine used for leukemia treatment has caused NRH (Rosen et al. 1991). Transcatheter arterial embolization therapy of hepatocellular carcinoma can be followed by NRH due to disturbance of vascular supply (Kobayashi et al. 1993).

NRH is observed in HIV-infected patients (Fernandez-Miranda et al. 1993; Arey et al. 2007; Tateo et al. 2008; Bihl et al. 2010; Kochin et al. 2010) and is thought to be related to antiretroviral drugs, e.g., ART therapy and IL-2 therapy, probably caused by the known capillary toxicity of high-dose IL-2 leading to decreased hepatic sinusoidal blood flow in murine models (Podevin et al. 2006; Arey et al. 2007; Sandrine et al. 2007; Maida et al. 2008). Didanosine therapy is implicated in HIV-associated NRH (Sood et al. 2014). NRH in HIV-infected patients seem to be related to age and the cumulative exposure to nucleoside and nucleotide analogues (Cotte et al. 2011).

Autoimmune and Related Disorders

NRH develops in several collagen vascular disorders and has been found in rheumatoid arthritis (Rauström 1953; Harris et al. 1974; Reynolds and Wanless 1984; Goritsas et al. 2001; Ebert and Hagspiel 2011) and in patients with Felty's syndrome (Ellman et al. 1955; Blendis et al. 1974, 1978; Reisman et al. 1977; Belaiche et al. 1978; Guarda and Hales 1981; Thorne et al. 1982; Young et al. 1992; Moots et al. 1994). Rheumatoid vasculitis accompanying these disorders seems to play a significant role in pathogenesis (Young et al. 1992). Several reports document the development of NRH in patients with systemic lupus erythematosus /SLE (Kuramochi et al. 1982; Klemp et al. 1986; Perez Ruiz et al. 1990; van Hoek 1996; Matsumoto et al. 2000; Horita et al. 2002; Park et al. 2006; Leung et al. 2009; Vaiphei et al. 2011; Grover et al. 2014). In an older study of 33 histologically proven cases of SLE, the spectrum of liver diseases included cirrhosis, but not NRH (Runyon et al. 1980). Pathogenetically, vasculitic changes induced by SLE may be considered. Some reports document NRG in the setting of systemic sclerosis (Friguet et al. 1984; Matsumoto et al. 2000) and Sjögren's syndrome (Gonzalez-Alvaro et al. 1994). Also the rare instance of NRH associated with mixed cryoglobulinemia, cryoglobulin-induced obliterative vasculitis may be pathogenetically involved (Garcia Buey et al. 1987).

NRH was observed in association with hepatobiliary autoimmune disorders. Numerous observations document the association between NRH and primary biliary cirrhosis, a disorder rather often associated with portal hypertension already in early-stage disease (Kew et al. 1971; Lebrec et al. 1976; Nakanuma and Ohta 1987; Nakanuma et al. 1989; Castellano et al. 1992; Sasaki et al. 2006). In part of the patients, CREST syndrome was found in association with NRH and primary biliary cirrhosis, suggesting an overlap syndrome (McMahon et al. 1989; Riviere et al. 2010). Patients with autoimmune disorders and other diseases of the bile duct system undergoing liver transplantation may present with portal hypertension already in the precirrhotic stage of liver disease. A study of 306 liver explants of such cases has shown that NRH is a major cause of this form of portal hypertension; in patients in whom portal hypertension was the major indication for OLT, NRH was detected in 73 % and

obliterative portal venopathy in 55 % of explants (Abraham et al. 2006).

NRH has been found in association with mesangiocapillary glomerulonephritis and idiopathic membranous glomerulonephritis (McCulloch et al. 1981; Haratake et al. 1987; Haboubi et al. 1991).

Antiphospholipid Syndromes

IgG and IgA antiphospholipid syndromes (APS) are systemic autoimmune disorders characterized by the combination of arterial and/or venous thrombosis, thrombocytopenia, and presence of antiphospholipid antibodies in serum. Antiphospholipid antibodies (aPL) form a heterogeneous group of circulating autoantibodies found in the sera of healthy individuals and patients with autoimmune and infectious diseases. aPL are directed against anionic phospholipids or protein/phospholipid complexes, usually containing beta2-glycoprotein I or prothrombin, but also other proteins involved in coagulation, including protein C, protein S, and annexin V. Several reports document the association of APS and NRH (Keegan et al. 1994; Cadranel et al. 1996; Perez-Ruiz and Zea-Mendoza 1998; Klein et al. 2003; Gaya et al. 2005). An association between NRH and circulating aPL was also observed in patients with systemic lupus erythematosus and suggested to play a role in the pathogenesis of NRH of the liver, probably via thrombotic obliterative changes taking place in small portal vein branches (Perez Ruiz et al. 1990). Part of HIV-infected patients show acquired autoimmune protein S paucity and secondary thrombophilia, associated with obliterative portal venopathy and NRH (Mallet et al. 2009).

Vascular Disorders of the Liver

NRH can develop in several types of portal venopathies. It has been found in portal vein thrombosis (Fukai et al. 1992; Terayama et al. 1995) and portal obliterative venopathy associated with myeloproliferative syndromes (Wanless et al. 1980; Wanless 1987). In a study of 64 NRH cases detected among 2500 autopsies, obliteration of many small portal veins was seen in all cases, but only 4.7 % of these had evidence of portal hypertension (Wanless 1990). Several studies reported on the development of NRH in congenital absence of the portal vein (Arana et al. 1997; Tanaka et al. 2003; Tsuji et al. 2005; Peker et al. 2009). Congenital absence of portal vein occurs in association with other hyperplastic hepatic lesions, specifically focal nodular hyperplasia/FNH (De Gaetano et al. 2004; Schmidt et al. 2006). Hepatic nodular lesions corresponding to NRH were seen in patients with patent ductus venosus (Kim et al., 2004a) and congenital extrahepatic portosystemic shunts (Abernethy type 2 malformation; Lisovsky et al. 2011). Congenital portosystemic shunts can be associated with NRH (Pupulim et al. 2013). NRH was also observed in obliterative portal phlebopathy, e.g., induced by macroglobulinemia (Wanless et al. 1981). Extensive obliteration of portal vein branches by cancer cell emboli can cause NRH (Turk et al. 2013). NRH can develop in Budd-Chiari syndrome (Castellano et al. 1989; de Sousa et al. 1991; Rha et al. 2000). In a systematic study of Budd-Chiari syndrome based on 17 explanted livers, obstructive portal venopathy associated with NRH was a constant finding, supporting the view that Budd-Chiari syndrome is associated with complex disturbances of hepatic arterial and portal circulation and their sequelae (Cazals-Hatem et al. 2003). However, large nodular hyperplastic lesions, FNH-like nodules, and FNH are more common complications of Budd-Chiari syndrome than NRH. A well-established cause of NRH is veno-occlusive disease involving the small and terminal hepatic veins (Snover et al. 1989). NRH can occur in the setting of hereditary hemorrhagic telangiectasia (Wanless and Gryfe 1986; Scardapane et al. 2013).

Hepatic vasculitis may cause NRH, including polyarteriitis nodosa (Nakanuma et al. 1984; Matsumoto et al. 2000; Tanaka et al. 2012), vasculitis in collagen vascular disorders, in particular SLE, but also vasculitis/hepatic arteritis in

rheumatoid arthritis (Reynolds and Wanless 1984), Felty's syndrome (Reisman et al. 1977), and microvasculitis in idiopathic hypereosinophilic syndrome (Baker et al. 1991). Similar to other vascular disorders, blood vessel stenosis or obliteration in vasculitis is thought to promote a hepatocyte regenerative response.

Granulomatous Hepatitis

NRH is known to develop in the setting of sarcoidosis of the liver (Devaney et al. 1993), likely due to obliterative (granulomatous) microvascular alterations.

Hypogammaglobulinemia

NRH can occur in the setting of primary hypogammaglobulinemia, e.g., caused by common variable immunodeficiency (Ravindran et al. 1995; Smith et al. 1995; Arenillas Rocha et al. 2003; Carbone et al. 2005; Ward et al. 2008; Fuss et al. 2013), and has been described as the main liver disease in these disorders (Malamut et al. 2008). In a systematic study, NRH in primary hypogammaglobulinemia was histologically associated with lymphocytic intrasinusoidal infiltrate and was found in 87 % of the patients with a liver biopsy. As other patients without liver biopsy often showed cholestasis (52 %) and splenomegaly (46.5 %) it was expected that the prevalence of NRH in hypogammaglobulinemia is high throughout. An association with intrasinusoidal T cells, portal vein endophlebitis, autoimmune diseases, and peripheral lymphocytic abnormalities suggest an autoimmune mechanism for NRH in this setting (Malamut et al. 2008).

NRH in the Setting of Cell and Organ Transplantations

NRH can develop de novo in liver grafts (Gane et al. 1994; Devarbhavi et al. 2007). The development of NRH after orthotopic liver transplantation (OLT) has usually been ascribed to the use of azathioprine. However, there are also reports showing that NRH can emerge in OLT patients in the absence of azathioprine therapy. Fourteen patients of one study developed NRH 3 months to 11 years after OLT; a total of ten patients developed NRH within 4 years (early onset), and four other patients showed the alteration beyond 4 years of OLT (late onset). These patients may later develop portal hypertension. A total of seven symptomatic patients, all in the early-onset group, had features of portal hypertension with vascular abnormalities on Doppler ultrasonography that were preceded by the diagnosis of NRH (Devarbhavi et al. 2007). At a certain stage, NRH occurring in the context of liver grafts becomes an irreversible lesion (gane et al. 1994). NRH has been observed in the setting of bone marrow transplantation (Pezzullo et al. 2000) and following renal transplantation, whereby azathioprine may play a role in at least part of the patients (Bredfeldt and Havey 1981; Morales et al. 1987; Buffet et al. 1988).

Hematologic Disorders

NRH occurs in the setting of various hematologic disorders (review: Al-Mukhaizeem et al. 2004). It can occur in reactive disorders such as aplastic anemia (Gonzalez-Huezo et al. 2006), but more commonly it develops in the setting of hematologic malignancies, including acute lymphoblastic leukemia (Mesa Latorre et al. 1990), myelofibrosis, polycythemia rubra vera, and other myeloproliferative syndromes (Shorey et al. 1979; Wanless et al. 1990; Al-Mukhaizeem et al. 2004). NRH occurring in myeloproliferative disorders may be caused by obliterative portal venopathy following venous thrombosis (Wanless et al. 1980). In myelofibrosis with hepatic extramedullary hematopoiesis, obstruction of small hepatic vascular channels by hematopoietic cells is thought to the pathogenic mechanism of NRH. A vascular pathogenic role is suggested by the observation of NRH in the setting of light

chain deposition in the liver in a patient with Waldenström's macroglobulinemia (Voinchet et al. 1988). NRH is a known complication of mastocytosis and is thought to be related to portal venopathy and veno-occlusive disease occurring in this disorder (Mican et al. 1995). NRH was also observed in patients with several types of Non-Hodgkin lymphomas, including macroglobinemia Waldenström and T-cell lymphomas, or with Hodgkin's disease (Wanless et al. 1981; Zuber et al. 1989; Gonzalez-Alegre et al. 2004; Kataoka et al. 2006; Ciria-Bru et al. 2014; Lopez et al. 2014). NRH was also found in association with Castleman's disease, with a possible pathogenic role of IL-6 (Kiyuna et al. 2005).

Gastrointestinal Disorders

NRH has been observed in children and adult patients with celiac disease and portal hypertension (Riestra et al. 2001; Biecker et al. 2006). IgA anticardiolipin antibodies were reported in celiac patients with NRH, suggesting a pathogenic role of these antibodies in celiac disease (Cancado et al. 2006). NRH can occur in the setting of Crohn's disease (Petrovic et al. 2011).

Hepatic Microcirculatory Disorders Caused by Tumors

Multiple hepatic metastases can compromise the microcirculation of the liver and induced NRH (Minato and Nakanuma 1992). NRH has been observed in a patient with an advanced carcinoid tumor, thought to be caused by vasoactive hormones secreted by the tumor followed by intrahepatic microcirculatory disturbances (Al-Hamoudi et al. 2009). In other situations, NRH associated with liver tumors, including hepatocellular carcinoma, may be caused by tumor treatment, in particular hepatic arterial infusion chemotherapy followed by vascular damage (Kobayashi et al. 1993).

Thorotrastosis

Thorotrast, following injection as contrast medium can damage portal vein radicles (Isner et al. 1978) and induce NRH (Dachman et al. 1987; Beer et al. 1998).

Infections

NRH was observed in association with subacute infectious endocarditis (Knowles et al. 1975) and following liver tuberculosis (Rougier et al. 1978; Boursier et al. 2005).

Congenital Metabolic Disorders

NRH can develop in patients with chronic granulomatous disease. In a study of 194 patients, NRH was seen in nine patients, including 6 of 12 autopsy specimens (Hussain et al. 2007). As venopathy of the portal vein was found in 80 % and venopathy of the central veins in 63 %, a vascular etiology of NRH has to be considered. Patients with cystinosis can develop noncirrhotic portal hypertension, mainly due to a sinusoidal block caused by accumulation of crystal-laden Kupffer cells in the sinusoids and deposition of collagens in Disse space (Klenn and Rubin 1994; DiDomenico et al. 2004; Rossi et al. 2005). But also NRH is a are late complication of cystinosis, with an undefined mechanism (O'Brien et al. 2006). NRH has been found in hyperhomocysteinemia associated with portal vein thrombosis and pronounced vascular lesions both in portal venules and in arterioles (Buchel et al. 2005).

Other Congenital Disorders

There are rare observations of NRH in the fetal liver, associated with severe malformations (Galdeano and Drut 1991). NRH can occur in patients with Turner syndrome, the pathogenesis being unknown (de Lédighen et al. 1994; Thevenot et al. 1998; Roulot 2013). There are

very rare instances of familial NRH (Albuquerque et al. 2013).

Pathogenic Pathways

Why Nodules

The pathogenesis of nodules in NRH has been discussed in detail (Reshamwala et al. 2006). For many cases of NRH, a common pathogenic pathway seems to involve hepatic obliterative vascular damage inducing a post-ischemic regenerative response of hepatocytes, although such vascular changes are lacking in other cases (Ibarrola and Colina 2003), rendering the definition of a common pathogenic pathway difficult. A blood vessel-based mechanism is rather well established for the microvascular vasculitis which often accompanies rheumatoid arthritis, Felty's syndrome, SLE, and other collagen vascular/immune-complex-mediated autoimmune diseases. But why should stenosing arterial lesions promote hepatocyte regeneration, as the hepatocyte parenchyma depends on portal blood flow, and not on hepatic arterial blood flow? Based on a morphometric study of the liver of a patient with rheumatoid vasculitis it was proposed that the arterial lesions caused secondary portal venous obliteration and portal hypertension followed by NRH (Reynolds and Wanless 1984).

Partial Nodular Transformation of the Liver

Introduction

Partial nodular transformation of the liver (PNTL) is a rare hepatic condition of still unknown pathogenesis, characterized by hepatocyte nodules that replace certain regions of the otherwise noncirrhotic liver. The perihilar region of the liver is predominantly affected, a but a subcapsular localization or a restriction to certain liver segments are also known. Many patients with PNTL have noncirrhotic portal hypertension and portal vein thrombosis.

Epidemiology and Clinical Features

In 1966, Sherlock and colleagues described four cases of a liver disease showing multiple hepatocyte nodules in the perihilar area of the liver associated with bleeding from oesophageal varices, the latter being caused by portal hypertension. The authors termed this constellation, partial nodular transformation of the liver/PNTL (Sherlock et al. 1966). In the following years, several other cases were reported (Maillard et al. 1967; Classen et al. 1970; Dick and Gresham 1972; Variend 1978; Donoso 1980; Fletcher and Wight 1980; Shedlofsky et al. 1980; Sansonno et al. 1981; Pedinelli et al. 1983; Terayama et al. 1995; Hoso et al. 1996; Takahata et al. 1997; Hytiroglou and Theise 1998; Simizu et al. 2006). PNTL is a rare disorder and an uncommon cause of noncirrhotic portal hypertension. In a study of 107 livers of patients with noncirrhotic, long-standing portal hypertension (92 wedge biopsies and 15 autopsy specimens), PNTL was found in only two cases and was much less common than NRH (Nakanuma et al. 1996). PNTL is often diagnosed at an early age and seem to be more common in females of childbearing age. In one review of the literature, the mean age at presentation was 35 years (Pedinelli et al. 1983), i.e., later then many types of liver cirrhosis. PNTL also develops in the pediatric liver (Tsui and So 1993). PNTL has been found in a patient with persistent ductus venosus and hypoplasia of the major intrahepatic portal veins (Wanless et al. 1985).

Pathology

Macroscopy

Patients with PNTL often show a grossly nodular region occupying the perihilar area, while more peripheral parts do not show nodular change. The diameter of the nodules ranges from a few millimeters to 4 cm. On cut surfaces of the liver, dilated vessels in the center of polygonal nodules may be seen, the adjacent parenchyma protruding above the periphery of the nodules (Classen et al. 1970). Typically, the parenchyma outside the nodular area does not show any nodular changes. Larger

nodules of the perihilar liver area may compress portal vein branches (Dick and Gresham 1972). However, other hepatic regions may also be involved, often with marked enlargement of the affected area, e.g., the caudate lobe (Fletcher and Wight 1980), and in some patients, nodules are mainly found in otherwise atrophic subcapsular parts of the liver. In PNTL, the extrahepatic portal vein usually exhibits evidence of old thrombosis, and distortions and stenosis of intrahepatic portal vein branches are often found. The extrahepatic portal vein can show wall thickening and calcifications, residual changes after organized thrombosis.

Histopathology

The regenerative nodules are composed of in part enlarged hepatocytes with irregular nuclei, liver cell plates often being thicker than two liver cells. Similar to NRH, the reticulin network may be compressed or condensed between nodules. The nodularity of the parenchyma causes an irregular arrangement of portal tracts, with abnormal portal tract spacing. Portal vein branches in nodular areas or in the vicinity of nodules may show intimal fibro-elastic thickening (Dick and Gresham 1972). Portal tracts with some fibrous extensions and abnormal vessels are often located in the centers of nodules, with a radiating arrangement of hepatocyte plates. Within the nodules, the number of branches of the hepatic vein are considerably reduced (Classen et al. 1970). Portal tracts situated in the perinodular tissue show minor degrees of ductular proliferation, caused either by compression of intrahepatic bile ducts by nodules, or by a progenitor cell reaction. In part of the cases, perihilar nodule formation is associated with portal tract fibrosis and septal fibrosis, causing interlaced "calloused" strands associated with some lymphocytic infiltration (Classen et al. 1970).

Differential Diagnosis

PNTL may histologically resemble nodular regenerative hyperplasia with a focal expression pattern, but nodules in PNTL are often larger than those in NRH and show a distinct spatial distribution pattern in the liver, e.g., with a perihilar predominance, or involvement of a segment or a lobe. Patients with noncirrhotic portal hypertension may, in the absence of clear-cut NRH or PNTL, show a vague nodular hyperplasia of hepatocytes not surrounded by fibrous septa, mainly in stages with subcapsular parenchymal atrophy (Nakanuma et al. 2001).

Is PNTL the Same Alteration as Incomplete Septal Cirrhosis of the Liver?

Incomplete septal cirrhosis (ISC) is an enigmatic disorder characterized by macronodular liver change and the development of fine, thin and incomplete septa taking their origin in portal tracts (review: Schinoni et al. 2004). Definition of ISC and the elucidation of its pathogenesis pose difficulties, because (1) ISC may be associated with other nodular liver lesions, including NRH, PNTL and some forms of true cirrhosis; (2) at least some ISCs may represent nonactive macronodular cirrhosis with signs of reversion of the cirrhotic process and vanishing of complete septa; and (3) different criteria and interpretations as to what ISC is have been formulated. In fact, it has been proposed that ICS is not a disease as such, but rather a stage of progression and regression of liver fibrosis (Schinoni et al. 2004).

In livers with ICS, abnormal spacing between portal tracts and veins, crowding of reticulin fibers between adjacent zones of hyperplastic parenchyma, and hepatocyte hyperplasia have been noted (Sciot et al. 1988), alterations known for nodular regenerative hyperplasia/NRH. Noncirrhotic nodular change with increased fibrosis of portal areas with the penetration of a few thin strands of connective tissue into the parenchyma and isolation of single nodules just under the liver capsule has been described in idiopathic portal hypertension (see below; Ziarkiewicz-Wroblewska et al. 2004). Such a nodular pattern resembles that of PNTL, which may also be associated with minor degrees of portal tract fibrosis. One may therefore consider that ICS, PNTL and

NRH share common pathogenic pathways, in particular hepatic vascular damage, and represent different manifestations of the same pathologic process.

Pathogenic Pathways

PNTL as a Disorder Caused by Vascular Abnormalities

It has been suggested that the pathogenesis of PNTL is similar to that of nodular regenerative hyperplasia (NRH) and focal nodular hyperplasia (FNH), i.e., a regenerative hepatocyte response in the vicinity of hypoperfused atrophic parenchyma (Wanless et al. 1985; Kondo 2001; Kondo et al. 2004). This suggestion is supported by the observation of portal vein thrombosis in the immediate vicinity of coalescent nodules at the liver hilus (Terayama et al. 1995) and by rare situations where PNTL and NRH synchronously develop in the same liver (Shedlofsky et al. 1980). Kondo (2001) developed the concept that congenital vascular anomalies are the origin of benign nodular hepatic lesions (the anomalous portal tract syndrome, APTS). It has later been proposed that the concept of APTS may be helpful in understanding the clinicopathological and radiological features of various hyperplastic liver lesions (Ueda et al. 2011). Irrespective of the concept of APTS, which implies a congenital base of vascular change, several acquired forms of obstructive vascular alterations, mainly of the portal vein system, have been implicated as a cause of nodular hyperplastic lesions of the liver. Slowly developing parenchymal ischemia not leading to acute mass necrosis or liver infarction is thought to be the driving force for the regenerative hepatocyte response. This is typically expected for obliterative portal venopathy. A postischemic pathogenic pathway may also be assumed for cases where PNTL emerges around intrahepatic portal venous emboli of tumors, e.g., hepatocellular carcinoma (Hoso et al. 1996). PNTL has also been observed in the setting of extrahepatic portal obstruction (Simizu et al. 2006). Why differ nodules in nodular regenerative hyperplasia/NRH from those in PNTL? It has been proposed that in NRH obliteration of small portal vein branches leads to uniform small hepatocyte nodules, whereas in most cases of PNTL portal vein thrombosis with irregular recanalization causes larger nodules often near large portal vein branches (Wanless et al. 1985).

One unresolved question is to explain why this hyperplasic response is nodular instead of diffuse or other patterns. As, in contrast to liver cirrhosis, the nodules developing in NRH, PNTL and FNH are not surrounded by fibrotic tissue, a scaffold effect exerted by extracellular matrix does not seem to be a likely pathway. A nodular hyperplastic response may, therefore, have several causes or combinations thereof, e.g., an effect reflecting the geometry of the damaged vascular network and its finest ramifications; the creation of an abortive, not well regulated liver lobule; or the outgrowth of clonal cells in the form of a nodular hepatocyte colony.

PNTL and Related Hepatic Hyperplastic Lesions as a Cause of Noncirrhotic Portal Hypertension

Banti, in 1889, published his research on splenomegaly and anemia, probably including a variety of disorders that we now classify as forms of cirrhosis with portal hypertension, and noncirrhotic portal hypertension (Banti 1889). Guido Banti (born 1852 in Montebicchieri; deceased 1925 in Florence, Italy) is considered to be the most eminent Italian pathologist of the early twentieth century who, in addition to histological works, published the first Italian textbook of bacteriological technique. From 1882 to 1904, Banti studied various forms of spleen enlargement, then called primitive splenomegalies (noninfectious splenomegalies). During these investigations, he found the intricate relationship between splenomegaly, anemia, and chronic liver disease, a constellation later termed Banti's disease or Banti's syndrome. These findings paved the way for the later understanding of portal hypertension, congestive splenic disease, and splenogenic hematological disorders, although Banti thought that this constellation was a primary splenic disorder, a view refuted by William Osler already in 1900 (Ravenna 1940; Costa 1958; Grannis 1975). In the sixties of the last century,

Indian investigators described a distinct group of adult patients having portal hypertension in the absence of liver cirrhosis (Ramalingaswami et al. 1962; Wig et al. 1966). In the same time period it was reported that patients with portal hypertension without cirrhosis can show concentric thickening or sclerosis of the portal vein and its radicles, a condition termed "hepatoportal sclerosis" (Mikkelsen et al. 1965). Boyer and coworkers identified patients having portal hypertension in the absence of liver cirrhosis and proposed the term "idiopathic portal hypertension" (Boyer et al. 1967). The authors compared patients with "idopathic portal hypertension" with those having cirrhosis or extrahepatic portal vein obstruction and found that patients with portal hypertension associated with hepatoportal sclerosis had a better prognosis. As suggested by the term "hepatoportal sclerosis," many cases of noncirrhotic portal hypertension were attributed to stenosing lesions of the portal vein and its large branches, but it later emerged that stenosing lesions in the hepatic microcirculation can cause, or be associated with, the same type of blood flow disorder, including the entire spectrum of hyperplastic lesions of the liver.

Serum Amyloid A-positive Hepatocellular Neoplasms/Nodules

Introduction

In patients with alcoholic liver cirrhosis, distinct hypervascular hepatocellular nodules or neoplasms resembling inflammatory hepatocellular adenoma (IHCA) were detected. These atypical nodules occurred more often in males than females, were multiple (more than 3 lesions) in all patients, and were serum amyloid A positive and in part CRP positive, thus resembling the phenotype of IHCA, but with certain differences (Sasaki et al. 2012, 2013, 2014). These nodules may coexist with focal nodular hyperplasia-like nodules in alcoholic cirrhosis, but these FNH-like lesions showed focal or no immunoreactivity for serum amyloid A (Sasaki et al. 2013). In small fraction (11.8 %) of serum amyloid A-positive nodules, STAT3 mutations were identified (Sasaki et al. 2014). These nodules developing in livers with alcoholic cirrhosis may represent a novel form of inflammatory hepatocellular neoplasm.

Pathology

Histologically, the nodules displayed a hepatocellular cell lineage, increased cellular density, inflammatory infiltrates, sinusoidal dilatation, arteries with abnormally thickened walls, variable ductular reaction, and positivity for serum amyloid A. In contrast to other hepatocellular neoplasms these nodules were negative for glutamine synthetase and glypican-3 (Sasaki et al. 2012). One serum amyloid A-positive abnormal nodule was CRP positive (Kim et al. 2004b).

Hypervascular FNH-Like Nodules in Alcoholic Liver Disease (ALD)

In patients with chronic alcoholic liver disease (ALD) and subsequent liver cirrhosis, distinct hypervascular nodules may develop, lesions that may be confounded with small hepatocellular carcinomas. In one type of such nodules, randomly distributed lesions measuring 9–21 mm in diameter were detected by ultrasonography during follow-up of cirrhosis as hypoechoic or isoechoic nodules, were high attenuated in early phase CT and iso attenuated in delayed phase (without wash-out in the venous phase), showed hypervascularity on angiography, and histologically shared features with focal nodular hyperplasia (Nakashima et al. 2004). Other types of hypervascular hepatic lesions occurring in ALD ("type 2") were described by Kim and coworkers (2004b). The authors found hypoechoic nodules measuring 2–4 cm in diameter that were isodense in early CT images, hypointense in T1-and T2-weighted MR images, and markedly hypervascular in angiograms. The differential diagnosis included HCC, FNH, and angiomatous tumors.

The nodular lesions described by Nakashima et al. (2004) were macroscopically encapsulated in part of the cases and showed scar-like fibrosis in

more than half of cases (one nodule with central stellate fibrosis). Histologically, the nodules were devoid of portal tracts but contained scar-like fibrotic tracts containing artery-like and vein-like anomalous vessels, and inflammatory cell infiltrate, and a ductular reaction along the interface of fibrotic tracts. Hepatocytes in the nodules showed iron overload, mainly in encapsulated nodules. Fatty change of Mallory-Denk bodies were not found. The lesions were interpreted as FNH-like nodules which are found in several types of liver cirrhosis (Nakashima et al. 2004). The lesions described by Kim and coworkers (2004b) either showed the histology of large hyperplastic hepatocyte nodules with hypercellularity and a trabecular pattern, or nodules showing fibrosis in the absence of hepatocyte hyperplasia, in part with stellate scar-like fibrosis, i.e., resembling FNH. It follows that larger hypervascular liver nodules developing in chronic ALD cover a spectrum of lesions ranging from hyperplastic nodules with increased vascularity to FNH-like lesions.

Regenerative Nodules in Alagille Syndrome

Introduction

Alagille syndrome (synonyms: arteriohepatic syndrome, arteriohepatic dysplasia, syndromatic hepatic ductular hypoplasia, Alagille-Watson syndrome) is a congenital mostly autosomal dominant disorder that manifests as cholestasis in infancy, related to progressive intrahepatic bile duct paucity. The syndrome is also characterized by a characteristic facies, vertebral malformations (butterfly vertebra), eye abnormalities (posterior embryotoxon), retarded physical, mental, and sexual development, and a mesosystolic murmur caused by pulmonary stenosis (Alagille et al. 1975). About 39 % of patients also have renal involvement, mainly renal dysplasia. Histologically, intrahepatic bile duct paucity and associated fibrosis increase with age and may result in secondary biliary cirrhosis (Emerick et al. 1999). Alagille syndrome is known to complicated by hepatocellular carcinoma (Rabinovitz et al. 1989; Le Bail et al. 1990; Perez Becerra et al. 1991), but also benign hyperplastic nodular lesions develop in this condition.

Alagille syndrome type 1 (ALGS1; OMIM 118450) is caused by mutations (haploinsufficiency) of the Jagged1/JAG1 gene located on chromosome 20p12.2. The JAG1 gene product is the ligand for the Notch receptor. Mutations in JAG1 can be found in more than 90 % of Alagille syndrome patients. ALGS2 (OMIM 600275) is caused by mutations in the NOTCH2 gene. Notch2 receptor mutations account for less than 1 % of Alagille syndrome patients. A very rare autosomal recessive variant of Alagille-like syndrome not related to a mutation of the JAG1 has also been reported (Dyack et al. 2007).

Regenerative Liver Nodules in Alagille Syndrome

A patient with Alagille syndrome died at age 17 years, autopsy showed liver cirrhosis and large hyperplastic liver nodule interpreted as a hamartoma resembling focal nodular hyperplasia/FNH (Nishikawa et al. 1987). A 6-year-old boy with liver cirrhosis caused by Alagille syndrome showed, on CT images, a high-density nodular lesion in the right liver lobe. In the liver explant of OLT, the nodular region was large and lobulated, clearly distinguished from the surrounding hepatic tissue. Histologically, the lesion consisted of hyperplastic hepatocytes (Torizuka et al. 1996). In a boy with ALGS1, pre-transplantation CT and MRI examinations revealed a large hepatic lesion associated with multiple small nodular lesions, representing hepatic nodular hyperplasia (Tajima et al. 2001). Hepatic hyperplastic changes were also observed in adults with ALGS1. Pseudotumorous hyperplasia of the caudate lobe has been found in an 31-year-old female patient with Alagille syndrome. The caudate lobe was increased in size (Tuset et al. 1995). Syed and coworkers (2008) reported the multimodality imaging features of two patients with Alagille syndrome and hepatic regenerative nodules. One patient had a lesion

with a diameter of 3.8 cm, while the second patient showed a mass of 10.5 cm diameter, illustrating that nodular regenerative lesions in Alagille syndrome can grow to large size and may be confounded with HCC.

References

Abraham SC, Kamath PS, Eghtesad B, Demetris AJ, Krasinskas AM (2006) Liver transplantation in precirrhotic biliary tract disease: portal hypertension is frequently associated with nodular regenerative hyperplasia and obliterative portal venopathy. Am J Surg Pathol 30:1454–1461

Alagille D, Odièvre M, Gautier M, Dommergues JP (1975) Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. J Pediatr 86:63–71

Albuquerque A, Cardoso H, Lopes J, Cipriano A, Carneiro F, Macedo G (2013) Familial occurrence of nodular regenerative hyperplasia of the liver. Am J Gastroenterol 108:150–151

Al-Hamoudi WK, Pasieka JL, Urbanski SJ, Lee SS (2009) Hepatic nodular regenerative hyperplasia in a patient with advanced carcinoid tumor. Eur J Gastroenterol Hepatol 21:1083–1085

Al-Mukhaizeem KA, Rosenberg A, Sherker AH (2004) Nodular regenerative hyperplasia of the liver: an under-recognized cause of portal hypertension in hematological disorders. Am J Hematol 75:225–230

Alperstein G, Kahn E, Aiges H, Daum F (1981) Nodular regenerative hyperplasia of the liver: an unusual cause of portal hypertension in childhood. Am J Dis Child 135:572–574

Ames JT, Federle MP, Chopra K (2009) Distinguishing clinical and imaging features of nodular regenerative hyperplasia and large regenerative nodules of the liver. Clin Radiol 64:1190–1195

Arana E, Marti-Bonmati L, Martinez V, Hoyos M, Montes H (1997) Portal vein absence and nodular regenerative hyperplasia of the liver with giant inferior mesenteric vein. Abdom Imaging 22:506–508

Arenillas Rocha L, Soriano Viladomiu A, Smithson Amat A (2003) Nodular regenerative hyperplasia and common variable immunodeficiency. Gastroenterol Hepatol 26:524

Arey B, Markov M, Ravi J, Prevette E, Batts K, Nadir A (2007) Nodular regenerative hyperplasia of liver as a consequence of ART. AIDS 21:1066–1068

Arotçarena R, Calès V, Berthelémy P, Parent Y, Malet M, Etcharry F, Ferrari S, Pariente A (2006) Severe sinusoidal lesions: a serious and overlooked complication of oxaliplatin-containing chemotherapy? Gastroenterol Clin Biol 30:1313–1316

Arvanitaki M, Adler M (2001) Nodular regenerative hyperplasia of the liver. A review of 14 cases. Hepatogastroenterology 48:1425–1429

Baker BL, Axiotis C, Hurwitz ES, Leavitt R, Di Bisceglie AM (1991) Nodular regenerative hyperplasia of the liver in idiopathic hypereosinophilic syndrome. J Clin Gastroenterol 13:452–456

Banti G (1889) Splenomegalie mit Leberzirrhose. Beitr Pathol Anat Allgem Pathol 24:21–33

Bedossa P, Ngendayo L, Hervé P, Rain B, Poynard T, Simonneau G (1990) Nodular regenerative hyperplasia and pulmonary arterial hypertension (in French). Gastroenterol Clin Biol 14:881–884

Beer TW, Carr NJ, Buxton PJ (1998) Thorotrast associated nodular regenerative hyperplasia of the liver. J Clin Pathol 51:941–942

Belaiche J, Vesin P, Fischer D, Wechsler J, Franco D, Bismuth H, Cattan D (1978) Nodular regenerative hyperplasia of the liver with portal hypertension associated with Felty's syndrome. Report of a case (in French). Gastroenterol Clin Biol 2:63–70

Biecker E, Trebicka J, Fischer HP, Sauerbruch T, Lammert F (2006) Portal hypertension and nodular regenerative hyperplasia in a patient with celiac disease. Z Gastroenterol 44:395–398

Bihl F, Jansens F, Boehlen F, Rubbia-Brandt L, Hadengue A, Spahr L (2010) Anticoagulant therapy for nodular regenerative hyperplasia in a HIV-infected patient. BMC Gastroenterol 10:6

Bissonnette J, Généreux A, Côté J, Nguyen B, Perreault P, Bouchard L, Pomier-Layargues G (2012) Hepatic hemodynamics in 24 patients with nodular regenerative hyperplasia and symptomatic portal hypertension. J Gastroenterol Hepatol 27:1336–1340

Blendis et al. (1970). http://www.ncbi.nlm.nih.gov/pubmed/5411618

Blendis LM, Parkinson MC, Skilkin KB, Williams R (1974) Nodular regenerative hyperplasia of the liver in Felty's syndrome. Q J Med 43:25–32

Blendis LM, Lovell D, Barnes CG, Ritland S, Cattan D, Vesin P (1978) Oesophageal variceal bleeding in Felty's syndrome associated with nodular regenerative hyperplasia. Ann Rheum Dis 37:183–186

Blogowski W, Marlicz W, Smereczynski A, Lawniczak M, Lewosuik A, Starzynska T (2011) Nodular regenerative liver hyperplasia as a complication of azathioprine-containing immunosuppressive treatment for Crohn's disease. Immunopharmacol Immunotoxicol 33:398–402

Boursier J, Foulet A, Pilette C (2005) Nodular regenerative hyperplasia following liver tuberculosis (in French). Gastroenterol Clin Biol 29:1051–1053

Boyer JL, Sen Gupta KP, Biswas SK, Pal NC, Basu Mallick KC, Iber FL, Basu AK (1967) Idiopathic portal hypertension. Comparison with the portal hypertension of cirrhosis and extrahepatic portal vein obstruction. Ann Intern Med 66:41–68

Bredfeldt JE, Havey AL (1981) Nodular regenerative hyperplasia of the liver following renal transplantation. Dig Dis Sci 26:271–274

Buchel O, Roskams T, Van Damme B, Nevens F, Pirenne J, Fevery J (2005) Nodular regenerative hyperplasia, portal vein thrombosis, and avascular hip necrosis due to hyperhomocysteinemia. Gut 54:1021–1023

Buffet C, Cantarovitch M, Pelletier G, Fabre M, Martin E, Charpentier B, Etienne JP, Fries D (1988) Three cases of nodular regenerative hyperplasia of the liver following renal transplantation. Nephrol Dial Transplant 3:327–330

Cadranel JF, Demontis R, Guettier C, Bouraya D, Dautreaux M, Ghazali A, Poux JM et al (1996) Nodular regenerative hyperplasia associated with primary antiphospholipid syndrome (in French). Gastroenterol Clin Biol 20:901–904

Cancado EL, Medeiros DM, Deguti MM, Dos Santos MS, de Mello ES, Vendramini MB et al (2006) Celiac disease associated with nodular regenerative hyperplasia, pulmonary abnormalities, and IgA anticardiolipin antibodies. J Clin Gastroenterol 40:135–139

Cano-Ruiz A, Martin-Scapa MA, Larraona JL, Gonzalez-Martin JA, Moreno-Caparros A et al (1985) Laparoscopic findings in seven patients with nodular regenerative hyperplasia of the liver. Am J Gastroenterol 80:796–800

Carbone J, Escudero A, Mayayo M, Ballesteros M, Perez-Corral A, Sanchez-Ramon S et al (2005) Partial response to anti-CD20 monoclonal antibody treatment of severe immune thrombocytopenic purpura in a patient with common variable immunodeficiency. Ann N Y Acad Sci 1051:666–671

Casillas C, Marti-Bonmati L, Galant J (1997) Pseudotumoral presentation of nodular regenerative hyperplasia of the liver: imaging in five patients including MR imaging. Eur Radiol 7:654–658

Castellano G, Cang F, Solis-Herruzo JA, Colina F, Martinez-Montiel MP, Morillas JD (1989) Budd-Chiari syndrome associated with nodular regenerative hyperplasia of the liver. J Clin Gastroenterol 11:698–702

Castellano G, Colina F, Moreno D, Pinedo F, Canga F, Solis Herruzo JA (1992) Nodular regenerative hepatic hyperplasia associated with primary biliary cirrhosis (in Spanish). Rev Clin Esp 191:433–434

Caturelli E, Ghittoni G, Ranalli TV, Gomes VV (2011) Nodular regenerative hyperplasia of the liver: coral atoll-like lesions on ultrasound are characteristic in predisposed patients. Br J Radiol 84:e129–e134

Cazals-Hatem D, Vilgrain V, Genin P, Denninger MH, Durand F, Belghiti J, Valla D et al (2003) Arterial and portal circulation and parenchymal changes in Budd-Chirai syndrome: a study in 17 explanted livers. Hepatology 37:510–519

Chu WC, Roebuck DJ (2003) Nodular regenerative hyperplasia of the liver simulating metastases following treatment for bilateral Wilms tumor. Med Pediatr Oncol 41:85–87

Ciria-Bru V, Giraldez-Gallego A, Pascual-Vaca-Gomez D, Zulueta-Dorado T, Nacarino-Meijas V (2014) Nodular regenerative hyperplasia of the liver and cutaneous T-cell lymphoma: an unreported association. Rev Esp Enferm Dig 106:289–292

Citak EC, Karadeniz C, Oguz A, Boyunaga O, Ekinci O, Okur V (2007) Nodular regenerative hyperplasia and focal nodular hyperplasia of the liver mimicking hepatic metastasis in children with solid tumors and a review of literature. Pediatr Hematol Oncol 24:281–289

Classen M, Elster K, Pesch HJ, Demling L (1970) Portal hypertension caused by partial nodular transformation of the liver. Gut 11:245–249

Clouet M, Boulay I, Boudiaf M, Soyer P, Nemeth J, Kiselman R, Rymer R (1999) Imaging features of nodular regenerative hyperplasia of the liver mimicking hepatic metastases. Abdom Imaging 24:258–261

Colina F, Alberti N, Solis JA, Martinez-Tello FJ (1989) Diffuse nodular regenerative hyperplasia of the liver (DNRH). A clinicopathologic study of 24 cases. Liver 9:253–265

Connolly CE (1977) Nodular transformation of the liver: report of a case. Hum Pathol 8:350–352

Costa A (1958) Guido Banti. Sci Med Ital 6:377–411

Cotte L, Bénet T, Billioud C, Miailhes P, Scoazec JY, Ferry T, Brochier C, Boibieux A et al (2011) The role of nucleoside and nucleotide analogues in nodular regenerative hyperplasia in HIV-infected patients: a case control study. J Hepatol 54:489–496

Dachman AH, Ros PR, Goodman ZD, Olmsted WW, Ishak KG (1987) Nodular regenerative hyperplasia of the liver: clinical and radiologic observations. AJR Am J Roentgenol 148:717–722

Dall'Igna P, Cecchetto G, Perilongo G, Scapinello A, Talenti E, Gamba PG, Zancan L et al (1996) Nodular regenerative hyperplasia of the liver: description of two cases. Med Pedaitr Oncol 26:190–195

Daniel F, Cadranel JF, Seksik P, Cazier A, Duong Van Huyen JP, Ziol M, Coutarel P et al (2005) Azathioprine induced nodular regenerative hyperplasia in IBD patients. Gastroenterol Clin Biol 29:600–603

de Boer NK, Mulder CJ, van Bodegraven AA (2005) Nodular regenerative hyperplasia and thiopurines: the case for level-dependent toxicity. Liver Transpl 11:1300–1301

de Boer NK, Zondervan PE, Gilissen LP, den Hartog G, Westerveld BD, Derijks LJ et al (2008a) Absence of nodular regenerative hyperplasia after low-dose 6-thioguanine maintenance therapy in inflammatory bowel disease patients. Dig Liver Dis 40:108–113

de Boer NK, Tuynman H, Bloemena E, Westerga J, Van Der Peet DL, Mulder CJ et al (2008b) Histopathology of liver biopsies from a thiopurine-naïve inflammatory bowel disease cohort: prevalence of nodular regenerative hyperplasia. Scand J Gastroenterol 43:604–608

De Bruyne R, Portmann B, Samyn M, Bansal S, Knisely A, Mieli-Vergani G, Dhawan A (2006) Chronic liver disease related to 6-thioguanine in children with acute lymphoblastic leukaemia. J Hepatol 44:407–410

De Gaetano AM, Gui B, Macis G, Manfredi R, Di Stasi C (2004) Congenital absence of the portal vein associated with focal nodular hyperplasia in the liver in an adult woman: imaging and review of the literature. Abdom Imaging 29:455–459

de Lédighen V, Levillain P, Besson I, Palazzo L, Fabre M, Silvain C, Morichau-Beauchant M (1994) Nodular regenerative hyperplasia of the liver and Tunrer syndrome (in French). Gastroenterol Clin Biol 18:898–899

de Sousa JM, Portmann B, Williams R (1991) Nodular regenerative hyperplasia of the liver and the Budd-Chirai syndrome. Case report, review of the literature and reappraisal of pathogenesis. J Hepatol 12:28–35

Devaney K, Goodman ZD, Epstein MS, Zimmerman HJ, Ishak KG (1993) Hepatic sarcoidosis. Clinicopathologic features in 100 patients. Am J Surg Pathol 17:1272–1280

Devarbhavi H, Abraham S, Kamath PS (2007) Significance of nodular regenerative hyperplasia occurring de novo following liver transplantation. Liver Transpl 13:1552–1556

Dick AP, Gresham GA (1972) Partial nodular transformation of the liver presenting with ascites. Gut 13:289–292

DiDomenico P, Berry G, Bass D, Fridge J, Sarwal M (2004) Noncirrhotic portal hypertension in association with juvenile nephropathic cystinosis: case presentation and review of the literature. J Inherit Metab Dis 27:693–699

Donoso S (1980) Partial nodular transformation of the liver (in Spanish). Rev Med Chil 108:625–628

Dubinsky MC, Vasiliauskas EA, Singh H, Abreu MT, Papadakis KA, Tran T, Martin P et al (2003) 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. Gastroenterology 125:298–303

Dumortier J, Boillot O, Chevallier M, Berger F, Potier P, Valette PJ, Paliard P, Scoazec JY (1999) Familia occurrence of nodular regenerative hyperplasia of the liver: a report on three families. Gut 45:289–294

Duvoux C, Kracht M, Lang P, Vernant JP, Zafrani ES, Dhumeaux D (1991) Nodular regenerative hyperplasia of the liver associated with azathioprine therapy (in French). Gastroenterol Clin Biol 15:968–973

Dyack S, Cameron M, Otley A, Greer W (2007) An autosomal recessive form of Alagille-like syndrome that is not linked to JAG1. Genet Med 9:544–550

Ebert EC, Hagspiel KD (2011) Gastrointestinal and hepatic manifestations of rheumatoid arthritis. Dig Dis Sci 56:295–302

Ehmsen L, Marko C, Breidert M (2008) Portal vein hypertension during azathioprine therapy in patients with Crohn's disease – a frequent phenomenon? (in German). Dtsch Med Wochenschr 133:950–953

Ellman P, Cudkowicz L, Elwood JS (1955) Therapy of Felty's syndrome. Ann Rheum Dis 14:84–89

Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA (1999) Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. Hepatology 29:822–829

Ferlitsch A, Teml A, Reinisch W, Ulbrich G, Wrba F, Homoncik M, Gangl A, Peck-Radosavljevic M et al (2007) 6-thioguanine associated nodular regenerative hyperplasia in patients with inflammatory bowel disease may induce portal hypertension. Am J Gastroenterol 102:2495–2503

Fernandez-Miranda C, Colina F, Delgado JM, Lopez-Carreira M (1993) Diffuse nodular regenerative hyperplasia of the liver associated with human immunodeficiency virus and visceral leishmaniasis. Am J Gastroenterol 88:433–435

Fletcher MS, Wight DG (1980) Partial nodular transformation of the caudate lobe of the liver presenting with ascites. Postgrad Med J 56:276–279

Forbes GM, Shilkin KB, Reed WD (1991) Nodular regenerative hyperplasia of the liver: the importance of combined macroscopic and microscopic findings. Med J Aust 154:415–417

Friguet JL, Deugnier Y, Messner M, Lauvin R, Launois B, Brissot P, Ferrand B, Bourel M (1984) Regenerative nodular hyperplasia in scleroderma: a new case (in French). Gastroenterol Clin Biol 8:979

Fukai T, Ishibashi H, Noda T, Dohmen K, Kudo J, Nagafuchi S, Sueishi K, Yamasaki T et al (1992) Nodular regenerative hyperplasia of the liver with portal vein thrombosis and hyperplasia of the adrenal gland. Gastroenterol Jpn 27:108–114

Fuss IJ, Friedn J, Yang Z, He JP, Hooda L, Boyer J, Xi L, Raffeld M, Kleiner DE et al (2013) Nodular regenerative hyperplasia in common variable immunodeficiency. J Clin Immunol 33:748–758

Galdeano S, Drut R (1991) Nodular regenerative hyperplasia of fetal liver: a report of two cases. Pediatr Pathol 11:479–485

Gane E, Portmann B, Saxena R, Wong P, Ramage J, Williams R (1994) Nodular regenerative hyperplasia of the liver graft after liver transplantation. Hepatology 20:88–94

Garcia Buey L, Garcia Sanchez A, Moreno Otero R, Gonzalez Estecha A, Pozo A, Pajares JM (1987) Hepatic nodular regenerative hyperplasia associated with essential mixed cryoglobulinemia (in Spanish). Rev Clin Esp 181:285–287

Gaya DR, Oien KA, Stanley AJ, Morris AJ (2005) Bleeding gastric varices and antiphospholipid syndrome. Nat Clin Pract Gastroenterol Hepatol 2:156–159

Geller SA, Dubinsky MC, Poordad FF, Vasiliauskas EA, Cohen AH, Abreu MT, Tran T et al (2004) Early hepatic nodular hyperplasia and submicroscopic fibrosis associated with 6-thioguanine therapy in inflammatory bowel disease. Am J Surg Pathol 28:1204–1211

Gentilucci UV, Gallo P, Perrone G, Del Vescovo R, Galati G, Spataro S, Mazzarelli C et al (2011) Non-cirrhotic portal hypertension with large regenerative nodules: a diagnostic challenge. World J Gastroenterol 17:2580–2584

Ghabril M, Vuppalanchi R (2014) Drug-induced nodular regenerative hyperplasia. Semin Liver Dis 34:240–245

Gonzalez Huezo MS, Villela LM, Zepeda-Florencio MC, Carrillo-Ponce CS, Mondragon-Sanchez RJ (2006) Nodular regenerative hyperplasia associated to aplastic anemia: a case report and literature review. Ann Hepatol 5:166–169

Gonzalez-Alegre MT, Guerra-Vales JM, Martinez G, Gutierrez A, Guillen V (2004) Nodular regenerative hyperplasia of the liver and Hodgkin's disease: a case report. Acta Gastroenterol Belg 67:358–360

Gonzalez-Alvaro I, Carmona-Ortell L, Amigo-Etxenagusia A, Castaneda Sanz S (1994) Nodular regenerative hyperplasia of the liver and primary Sjögren's syndrome. J Rheumatol 21:168–169

Goritsas C, Roussos A, Ferti A, Trigidou R (2001) Nodular regenerative hyperplasia in a rheumatoid arthritis patient without Felty's syndrome. J Clin Gastroenterol 35:363–364

Grannis FW (1975) Guido Banti's hypothesis and its impact on the understanding and treatment of portal hypertension. Mayo Clin Proc 50:41–48

Grover S, Rastogi A, Singh J, Rajbongshi A, Bihari C (2014) Spectrum of histomorphologic findings in liver in patients with SLE: a review. Hepat Res Treat 2014:562979

Guarda LA, Hales MR (1981) Nodular regenerative hyperplasia of the liver: report of two cases and review of the literature. J Clin Gastroenterol 3:157–164

Haboubi NY, Smith VJ, Coyne JD, Ackrill P (1991) Nodular regenerative hyperplasia of the liver in a non-treated patient with mesangiocapillary glomerulonephritis. Histopathology 18:367–368

Haratake J, Horie A, Takasugi M, Hiroshige K (1987) Nodular regenerative hyperplasia of the liver associated with idiopathic membranous glomerulonephritis. Am J Gastroenterol 82:677–680

Harris M, Rash RM, Dymock IW (1974) Nodular, noncirrhotic liver associated with portal hypertension in a patient with rheumatoid arthritis. J Clin Pathol 27:963–966

Hartleb M, Gutkowski K, Milkiewicz P (2011) Nodular regenerative hyperplasia: evolving concepts on underdiagnosed cause of portal hypertension. World J Gastroenterol 17:1400–1409

Horita T, Tsutsumi A, Takeda T, Yasuda S, Takeuchi R, Amasaki Y, Ichikawa K, Atsumi T et al (2002) Significance of magnetic resonance imaging in the diagnosis of nodular regenerative hyperplasia of the liver complicated with systemic lupus erythematosus: a case report and review of the literature. Lupus 11:193–196

Hoso M, Terada T, Nakanuma Y (1996) Partial nodular transformation of liver developing around intrahepatic portal venous emboli of hepatocellular carcinoma. Histopathology 29:580–582

Hubert C, Sempoux C, Horsmans Y, Rahier J, Humblet Y, Machiels JP, Ceratti A et al (2007) Nodular regenerative hyperplasia: a deleterious consequence of chemotherapy for colorectal liver metastases? Liver Int 27:938–943

Hussain N, Feld JJ, Kleiner DE, Hoofnagle JH, Garcia-Eulate R, Ahlawat S, Koziel DE et al (2007) Hepatic abnormalities in patients with chronic granulomatous disease. Hepatology 45:675–683

Hytiroglou P, Theise ND (1998) Differential diagnosis of hepatocellular nodular lesions. Semin Diagn Pathol 15:285–299

Ibarrola C, Colina F (2003) Clinicopatholical features of nine cases of non-cirrhotic portal hypertension: current definitions and criteria are inadequate. Histopathology 42:251–264

Isner JM, Sazama KJ, Roberts WC (1978) Vascular complications of thorium dioxide. Am J Med 64:1069–1074

Kakar S, Kamath PS, Burgart LJ (2004) Sinusoidal dilatation and congestion in liver biopsy: is it always due to venous outflow impairment? Arch Pathol Lab Med 128:901–904

Kataoka TR, Tsukamoto Y, Kanazawa N, Izumi T, Awata N, Nishizawa Y, Ohsawa M et al (2006) Concomitant hepatocellular carcinoma and non-Hodgkin's lymphoma in a patient with nodular regenerative hyperplasia. Pathol Int 56:279–282

Keegan AD, Brooks LT, Painter DM (1994) Hepatic infarction and nodular regenerative hyperplasia of the liver with associated anticardiolipin antibodies in a young woman. J Clin Gastroenterol 18:309–313

Kew MC, Varma RR, Dos Santos HA, Schuer PJ, Sherlock S (1971) Portal hypertension in primary biliary cirrhosis. Gut 12:830–834

Kim T, Murakami T, Sugihara E, Hori M, Wakasa K, Nakamura H (2004a) Hepatic nodular lesions associated with abnormal development of the portal vein. AJR Am J Roentgenol 183:1333–1338

Kim SR, Maekawa Y, Imoto S, Sugano M, Kudo M (2004b) Hypervascular liver nodules in heavy drinkers of alcohol. Alcohol Clin Exp Res 28:174S–180S

Kim SR, Kondo F, Otono Y, Ando K, Hirakawa M, Fukuda K, Sasaki M, Kim SK, Komaki T et al (2014) Serum amyloid A and C-reactive protein positive nodule in alcoholic liver cirrhosis, hard to make definite diagnosis. Hepatol Res 44:584–590

Kiyuna A, Sunagawa T, Hokama A, Touyama M, Tomiyama R, Sakugawa H, Kinj F, Saito A (2005) Nodular regenerative hyperplasia of the liver and Castleman's disease: potential role of interleukin-6. Dig Dis Sci 50:314–316

Klein R, Goller S, Bianchi L (2003) Nodular regenerative hyperplasia (NRH) of the liver – a manifestation of organ-specific antiphospholipid syndrome? Immunobiology 207:51–57

Klemp P, Timme AH, Sayers GM (1986) Systemic lupus erythematosus and nodular regenerative hyperplasia of the liver. Ann Rheum Dis 45:167–170

Klenn PJ, Rubin R (1994) Hepatic fibrosis associated with hereditary cystinosis: a novel form of noncirrhotic portal hypertension. Mod Pathol 7:879–882

Knowles D, Kaye GI, Godman GC (1975) Nodular regenerative hyperplasia of the liver. Gastroenterology 69:746

Kobayashi S, Saito K, Nakanuma Y (1993) Nodular regenerative hyperplasia of the liver in hepatocellular

carcinoma. An autopsy study. J Clin Gastroenterol 16:155–159
Kobayashi S, Matsui O, Gabata T, Sanada J, Koda W, Minami T, Ryu Y (2009) Radiological and histopathological manifestations of hepatocellular nodular lesions concomitant with various congenital and acquired hepatic hemodynamic abnormalities. Jpn J Radiol 27:53–68
Kochin I, Magid M, Arnon R, Glascock A, Kerkar N, Miloh T (2010) Variceal bleeding in an adolescent with HIV diagnosed with hepatoportal sclerosis and nodular regenerative hyperplasia. J Pediatr Gastroenterol Nutr 50:340–343
Kondo F (2001) Benign nodular hepatocellular lesions caused by abnormal hepatic circulation: etiological analysis and introduction of a new concept. J Gastroenterol Hepatol 16:1319–1328
Kondo F, Koshima Y, Ebara M (2004) Nodular lesions associated with abnormal liver circulation. Intervirology 47:277–287
Kuramochi S, Tashiro Y, Torikata C, Watanabe Y (1982) Systemic lupus erythematosus associated with multiple nodular hyperplasia of the liver. Acta Pathol Jpn 32:547–560
Le Bail B, Bioulac-Sage P, Arnoux R, Perissat J, Saric J, Balabaud C (1990) Late recurrence of a hepatocellular carcinoma in a patient with incomplete Alagille syndrome. Gastroenterology 99:1514–1516
Lebrec D, Sicot C, Degott C, Benhamou JP (1976) Portal hypertension and primary biliary cirrhosis. Digestion 14:220–226
Leung VK, Loke TK, Luk IS, Ng WL, Chau TN, Law ST, Chan JC (2009) Nodular regenerative hyperplasia of the liver associated with systemic lupus erythematosus: three cases. Hong Kong Med J 15:139–142
Lisovsky M, Konstas AA, Misdraji J (2011) Congenital extrahepatic portosystemic shunts (Abernethy malformation): a histopathologic evaluation. Am J Surg Pathol 35:1381–1390
Lopez R, Barrera L, Vera A, Andrade R (2014) Concurrent liver Hodgkin lymphoma and nodular regenerative hyperplasia on an explanted liver with clinical diagnosis of alcoholic cirrhosis at University Hospital fundacion santa fe de Bogota. Case Rep Pathol 2014:193802
Maida I, Garcia-Gasco P, Sotgiu G, Rios MJ, Vispo ME, Martin-Carbonero L, Barreiro P et al (2008) Antiretroviral-associated portal hypertension: a new clinical condition? Prevalence, predictors and outcome. Antivir Ther 13:103–107
Maillard JN, Potet F, Benhamou JP (1967) Partial nodular transformation of the liver with portal hypertension (in French). Presse Med 75:2799–2802
Malamut G, Ziol M, Suarez F, Beaugrand M, Viallard JF, Lascaux AS, Verkarre V et al (2008) Nodular regenerative hyperplasia: the main liver disease in patients with primary hypogammaglobulinemia and hepatic abnormalities. J Hepatol 48:74–82
Mallet VO, Varthaman A, Lasne D, Viard JP, Gouya H, Borgel D, Lacroix-Desmazes S et al (2009) Acquired protein S deficiency leads to obliterative portal venopathy and to compensatory nodular regenerative hyperplasia in HIV-infected patients. AIDS 23:1511–1518
Matsumoto T, Kobayashi S, Shimizu H, Nakajima M, Watanabe S, Kitami N, Sato N et al (2000) The liver in collagen diseases: pathologic study of 160 cases with particular reference to hepatic arteritis, primary biliary cirrhosis, autoimmune hepatitis and nodular regenerative hyperplasia of the liver. Liver 20:366–373
McCulloch AJ, Morley AR, Wilkinson R, Lesna M (1981) Nodular regenerative hyperplasia of the liver with membranous glomerulonephritis. Postgrad Med J 57:402–403
McMahon RF, Babbs C, Warnes TW (1989) Nodular regenerative hyperplasia of the liver, CREST syndrome and primary biliary cirrhosis: an overlap syndrome? Gut 30:1430–1433
Mesa Latorre J, de Dios Garcia Diaz J, Larregla Garraus S, Ortiz Conde MC (1990) Nodular regenerative hyperplasia of the liver and acute lymphoblastic leukemia (in Spanish). Rev Clin Esp 186:192–193
Mican JM, Di Bisceglie AM, Fong TL, Travis WD, Kleiner DE, Baker B, Metcalfe DD (1995) Hepatic involvement in mastocytosis: clinicopathologic correlations in 41 cases. Hepatology 22:1163–1170
Mikkelsen WP, Edmondson HA, Peters RL, Redeker AG, Reynolds TB (1965) Extra- and intra-heppatic portal hypertension without cirrhosis (hepatoportal sclerosis). Ann Surg 162:602–620
Minato H, Nakanuma Y (1992) Nodular regenerative hyperplasia of the liver associated with metastases of pancreatic endocrine tumour: report of two autopsy cases. Virchows Arch A Pathol Anat Histopathol 421:171–174
Mion F, Napoleon B, Berger F, Chevallier M, Bonvoisin S, Descos L (1991) Azathioprine induced liver disease: nodular regenerative hyperplasia of the liver and perivenous fibrosis in a patient treated for multiple sclerosis. Gut 32:715–717
Mneimneh W, Farges O, Bedossa P, Belghiti J, Paradis V (2011) High serum level of alpha-fetoprotein in focal nodular hyperplasia of the liver. Pathol Int 61:491–494
Mones JM, Saldana MJ (1984) Nodular regenerative hyperplasia of the liver in a 4-month-old infant. Am J Dis Child 138:79–81
Moots RJ, Elias E, Hübscher S, Salmon M, Emery P (1994) Liver disease in twins with Felty's syndrome. Ann Rheum Dis 53:202–205
Morales JM, Prieto C, Colina F, Mestre MJ, Lopez I, Perez-Sola A, Solis Herruzo JA et al (1987) Nodular regenerative hyperplasia of the liver in renal transplantation. Transplant Proc 19:3694–3696
Moran CA, Mullick FG, Ishak KG (1991) Nodular regenerative hyperplasia of the liver in children. Am J Surg Pathol 15:449–454

Morris-Stiff G, White AD, Gomez D, Cameron IC, Farid S, Toogood GJ, Lodge JP et al (2014) Nodular regenerative hyperplasia (NRH) complicating oxaliplatin chemotherapy in patients undergoing resection of colorectal liver metastases. Eur J Surg Oncol 40:1016–1020

Musumba CO (2013) Review article: the association between nodular regenerative hyperplasia, inflammatory bowel disease and thiopurine therapy. Aliment Pharmacol Ther 38:1025–1037

Naber AH, Van Haelst U, Yap SH (1991) Nodular regenerative hyperplasia of the liver: an important cause of portal hypertension in non-cirrhotic patients. J Hepatol 12:94–99

Nakanuma Y, Ohta G (1987) Nodular hyperplasia of the liver in primary biliary cirrhosis of early histological stages. Am J Gastroenterol 82:8–10

Nakanuma Y, Ohta G, Sasaki K (1984) Nodular regenerative hyperplasia of the liver associated with polyarteritis nodosa. Arch Pathol Lab Med 108:133–135

Nakanuma Y, Nonomura A, Hayashi M, Doishita K, Takayanagi N, Uchida T, Obata Y et al (1989) Pathology of the liver in "idiopathic portal hypertension" associated with autoimmune disease. The Ministry of Health and Welfare Disorders of Portal Circulation Research Committee. Acta Pathol Jpn 39:586–592

Nakanuma Y, Hoso M, Sasaki M, Terada T, Katayanagi K, Nonomura A, Kurumaya H et al (1996) Histopathology of the liver in non-cirrhotic portal hypertension of unknown aetiology. Histopathology 28:195–204

Nakanuma Y, Tsuneyama K, Ohbu M, Katayanagi K (2001) Pathology and pathogenesis of idiopathic portal hypertension with an emphasis on the liver. Pathol Res Pract 197:65–76

Nakashima O, Kurogi M, Yamaguchi R, Miyaaki H, Fujimoto M, Yano H, Kumabe T et al (2004) Unique hypervascular nodules in alcoholic liver cirrhosis: identical to focal nodular hyperplasia-like nodules? J Hepatol 41:992–998

Nakhleh RE, Snover DC (1988) Use of alpha-1-antitrypsin staining in the diagnosis of nodular regenerative hyperplasia of the liver. Hum Pathol 19:1048–1052

Nishikawa A, Mori H, Takahashi M, Ojima A, Shimokawa K, Furuta T (1987) Alagille's syndrome. A case with a hamartomatous nodule of the liver. Acta Pathol Jpn 37:1319–1326

O'Brien K, Hussain N, Warady BA, Kleiner DE, Kleta R, Bernardini I, Heller T, Gahl WA (2006) Nodular regenerative hyperplasia and severe portal hypertension in cystinosis. Clin Gastroenterol Hepatol 4:387–394

Park YW, Woo H, Jeong YY, Lee JH, Park JJ, Lee SS (2006) Association of nodular regenerative hyperplasia of the liver with porto-pulmonary hypertension in a patient with systemic lupus erythematosus. Lupus 15:686–688

Patriarche C, Pelletier G, Attali P, Ladouch-Badre A, Fabre M, Roche A, Etienne JP (1988) Ultrasonography, angiography, computed tomography and magnetic resonance in nodular regenerative hyperplasia of the liver: report of a pseudo-tumoral case. Radiat Med 6:111–114

Pedinelli L, Quilichini R, Lebreuil G (1983) Partial nodular transformation of the liver with portal hypertension. A new case. Review of the literature (in French). J Chir 120:717–720

Peker A, Ucar T, Kuloglu Z, Ceyhan K, Tutar E, Fitoz S (2009) Congenital absence of portal vein associated with nodular regenerative hyperplasia of the liver and pulmonary hypertension. Clin Imaging 33:322–325

Perez Becerra E, Fuster M, Fraga M, Antunez J, Pintos E, Pavon P, Forteza J (1991) Alagille's s syndrome: a family case and its association with hepatocellular carcinoma (in Spanish). Rev Clin Esp 188:459–462

Perez Ruiz F, Zea Mendoza AC, Orte Martinez FJ (1990) Antiphospholipid antibodies may play a role in pathogenesis of nodular regenerative hyperplasia of the liver. Br J Rheumatol 29(suppl 2):107

Perez-Ruiz F, Zea-Mendoza AC (1998) Nodular regenerative hyperplasia of the liver and antiphospholipid antibodies. J Clin Gastroenterol 27:90–91

Petrovic LM, Palmer SL, Fong TL (2011) A patient with Crohn's disease and portal hypertension. Nodular regenerative hyperplasia. Gastroenterology 140:e3–e4

Pettei MJ, Valderamma E, Levine JJ, Ilowite NT (1995) Childhood nodular regenerative hyperplasia of the liver complicated by severe hypoxemia. J Pediatr Gastroenterol Nutr 20:343–346

Pezzullo L, Muretto P, De Rosa G, Picardi M, Lucania A, Rotoli B (2000) Liver nodular regenerative hyperplasia after bone marrow transplant. Haematologica 85:669–670

Podevin P, Spiridon G, Terris B, Chauvelot-Moachon L, Guillevin L, Chaussade S et al (2006) Nodular regenerative hyperplasia of the liver after IL-2 therapy in an HIV-infected patient. AIDS 20:313–315

Pupulim LF, Vuillerme MP, Paradis V, Valla D, Terraz S, Vilgrain V (2013) Congenital portosystemic shunts associated with liver tumours. Clin Radiol 68: e362–e369

Qizilbash AH, Castelli M (1980) Nodular regenerative hyperplasia of the liver. diagnosis by liver biopsy. Can Med Assoc J 122:1151–1154

Rabinovitz M, Imperial JC, Schade RR, Van Thiel DH (1989) Hepatocellular carcinoma in Alagille's syndrome: a family study. J Pediatr Gastroenterol Nutr 8:26–30

Ramalingaswami V, Wig KL, Sama SK (1962) Cirrhosis of the liver in northern India. A clinicopathological study. Arch Intern Med 110:350–358

Rauström S (1953) Miliary hepatocellular adenomatosis. Acta Pathol Microbiol Scand 33:225

Ravenna P (1940) Banti syndrome (fibrocongestive splenomegaly). Definition, classification and pathogenesis. Arch Intern Med 66:879–892

Ravikumara M, Hill FG, Wilson DC, Gillett PM, Thomas A, Brown R, Darbyshire PJ et al (2006)

6-thioguanine-related chronic hepatotoxicity and variceal haemorrhage in children treated for acute lymphoblastic leukaemia – a dual-centre experience. J Pediatr Gastroenterol Nutr 42:535–538

Ravindran J, Gillis D, Rowland R, Heddle R (1995) Common variable immunodeficiency associated with nodular regenerative hyperplasia of the liver. Aust N Z J Med 25:741

Reisman T, Levi JU, Zeppa R, Clark R, Morton R, Schiff ER (1977) Noncirrhotic portal hypertension in Felty's syndrome. Am J Dig Dis 22:145–148

Reshamwala PA, Kleiner DE, Heller T (2006) Nodular regenerative hyperplasia: not all nodules are created equal. Hepatology 44:7–14

Reynolds WJ, Wanless IR (1984) Nodular regenerative hyperplasia of the liver in a patient with rheumatoid vasculitis: a morphometric study suggesting a role for hepatic arteritis in the pathogenesis. J Rheumatol 11:838–842

Rha SE, Lee MG, Lee YS, Kang GH, Ha HK, Kim PN, Auh YH (2000) Nodular regenerative hyperplasia of the liver in Budd-Chiari syndrome: CT and MR features. Abdom Imaging 25:255–258

Riestra S, Dominguez F, Rodrigo L (2001) Nodular regenerative hyperplasia of the liver in a patient with celiac disease. J Clin Gastroenterol 33:323–326

Riviere E, Vergniol J, Reffet A, Lippa N, Le Bail B, de Ledinghen V (2010) Gastric variceal bleeding uncovering a rare association of CREST syndrome, primary biliary cirrhosis, nodular regenerative hyperplasia and pulmonary hypertension. Eur J Gastroenterol Hepatol 22:1145–1148

Rosen AA, Iseri O, Fishbein G, Knodell RG (1991) Nodular regenerative hyperplasia: a cause of ascites and hepatomegaly after chemotherapy for leukemia. Am J Gastroenterol 86:86–88

Rossi S, Herrine SK, Navarro VJ (2005) Cystinosis as a cause of noncirrhotic portal hypertension. Dig Dis Sci 50:1372–1375

Rougier P, Degott C, Rueff B, Benhamou JP (1978) Nodular regenerative hyperplasia of the liver: report of six cases and review of the literature. Gastroenterology 75:169–172

Roulot D (2013) Liver involvement in Turner syndrome. Liver Int 33:24–30

Rubbia-Brandt L, Mentha G, Terris B (2006) Sinusoidal obstruction syndrome is a major feature of hepatic lesions associated with Oxaliplatin neoadjuvant chemotherapy for liver colorectal metastases. J Am Coll Surg 202:199–200

Rubbia-Brandt L, Lauwers GY, Wang H, Maino PE, Tanabe K, Zhu AX, Brezault C et al (2010) Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology 56:430–439

Runyon BA, La Brecque DR, Anuras S (1980) The spectrum of liver disease in systemic lupus erythematosus. report of 33 histologically-proved cases and review of the literature. Am J Med 69:187–194

Russmann S, Zimmermann A, Krähenbühl S, Kern B, Reichen J (2001) Veno-occlusive disease, nodular regenerative hyperplasia and hepatocellular carcinoma after azathioprine treatment in a patient with ulcerative colitis. Eur J Gastroenterol Hepatol 13:287–290

Ryan P, Nanji S, Pollett A, Moore M, Moulton CA, Gallinger S, Guindi M (2010) Chemotherapy-induced liver injury in metastatic colorectal cancer: semiquantitative histologic analysis of 334 resected liver specimens shows that vascular injury but not steatohepatitis is associated with preoperative chemotherapy. Am J Surg Pathol 34:784–791

Sandrine PF, Sylvie A, André E, Abdoulaye D, Bernard L, André C (2007) Nodular regenerative hyperplasia: a new serious antiretroviral drugs side effect? AIDS 21:1498–1499

Sansonno DE, Giustino V, Buongiorno GP, Demundo T, Leone G, Loiodice L (1981) Partial nodular transformation of the liver. Apropos of a case (in Italian). Minerva Med 72:1543–1548

Sasaki M, Hodo Y, Nakanuma Y (2006) Hepatocellular carcinoma arising in primary biliary cirrhosis presenting with nodular regenerative hyperplasia: report of an autopsy case. J Gastroenterol Hepatol 21:1866–1868

Sasaki M, Yoneda N, Kitamura S, Sato Y, Nakanuma Y (2012) A serum amyloid A-positive hepatocellular neoplasm arising in alcoholic cirrhosis: a previously unrecognized type of inflammatory hepatocellular tumor. Mod Pathol 25:1584–1593

Sasaki M, Kondo F, Sawai Y, Imai Y, Kadowaki S, Sano K, Fukusato T, Matsui O, Nakanuma Y (2013) Serum amyloid A-positive hepatocellular neoplasms in the resected liver from 3 patients with alcoholic cirrhosis. Histol Histopathol 28:1499–1505

Sasaki M, Yoneda N, Sawai Y, Imai Y, Kondo F, Fukusato T, Yoshikawa S, Kobayashi S et al (2014) Clinicopathological characteristics of serum amyloid A-positive hepatocellular neoplasms/nodules arising in alcoholic cirrhosis. Histopathology. doi:10.1111/his.12588

Scardapane A, Ficco M, Sabba C, Lorusso F, Moschetta M, Maggialetti N, Suppressa P et al (2013) Hepatic nodular regenerative lesions in patients with hereditary haemorrhagic telangiectasia: computed tomography and magnetic resonance findings. Radiol Med 118:1–13

Schinoni MI, Andrade Z, de Freitas LA, Oliveira R, Parana R (2004) Incomplete septal cirrhosis: an enigmatic disease. Liver Int 24:452–456

Schmidt S, Saint-Paul MC, Anty R, Bruneton JN, Gugenheim J, Chevalier P (2006) Multiple focal nodular hyperplasia of the liver associated with congenital absence of the portal vein (in French). Gastroenterol Clin Biol 30:310–313

Schumann M, Preiss JC, Loddenkemper C, Günther C, Somasundaram R, Siegmund B et al (2008) Nodular

regenerative hyperplasia as a side effect of azathioprine in a patient with Crohn's disease (in German). Dtsch Med Wochenschr 133:1897–1900

Sciot R, Staessen D, Van Damme B, Van Steenbergen W, Fevery J, De Groote J, Desmet VJ (1988) Incomplete septal cirrhosis: histopathological aspects. Histopathology 13:593–603

Seiderer J, Zech CJ, Reinisch W, Lukas M, Diebold J, Wrba F, Teml A, Chalupna P et al (2005) A multicenter assessment of liver toxicity by MRI and biopsy in IBD patients on 6-thioguanine. J Hepatol 43:303–309

Seiderer J, Zech CJ, Diebold J, Schoenberg SO, Brand S, Tillack C, Göke B, Ochsenkühn T (2006) Nodular regenerative hyperplasia: a reversible entity associated with azathioprine therapy. Eur J Gastroenterol Hepatol 18:553–555

Seksik P, Mary JY, Beaugerie L, Lémann M, Colombel JF, Vernier-Massouille G, Cosnes J (2011) Incidence of nodular regenerative hyperplasia in inflammatory bowel disease patients treated with azathioprine. Inflamm Bowel Dis 17:565–572

Shastri S, Dubinsky MC, Fred Poordad F, Vasiliauskas EA, Geller SA (2004) Early nodular hyperplasia of the liver occurring with inflammatory bowel diseases in association with thioguanine therapy. Arch Pathol Lab Med 128:49–53

Shedlofsky S, Koehler RE, DeSchryver-Kecskemeti K, Alpers DH (1980) Noncirrhotic nodular transformation of the liver with portal hypertension: clinical, angiographic, and pathological correlation. Gastroenterology 79:938–943

Shepherd PC, Fooks J, Gray R, Allan NC (1991) Thioguanine used in maintenance therapy of chronic myeloid leukaemia causes non-cirrhotic portal hypertension. Results from MRC CML.II.Trial comparing busulphan and thioguanine. Br J Haematol 79:185–192

Sherlock S, Feldmann CA, Moran B, Scheuer PJ (1966) Partial nodular transformation of the liver with portal hypertension. Am J Med 40:195–203

Shorey J, Weinberg MN, Frenkel EP, Fallis BD (1979) Nodular regenerative hyperplasia of the liver in a case of myelofibrosis with extramedullary hematopoiesis and secondary portal venous hypertension. Am J Clin Pathol 72:122–125

Siegelman ES, Outwater EK, Furth EE, Rubin R (1995) MR imaging of hepatic nodular regenerative hyperplasia. J Magn Reson Imaging 5:730–732

Simizu C, Ro T, Kawamura N, Nakayama T, Eguchi T, Aishima S (2006) A case of partial nodular transformation of the liver associated with extrahepatic portal obstruction. Jpn J Clin Radiol 51:1231–1236

Smith JC (1978) Non-cirrhotic nodulation of the liver. Arch Pathol Lab Med 102:398–401

Smith MS, Webster AD, Dhillon AP, Dusheiko G, Boulton R, Savage K et al (1995) Orthotopic liver transplantation for chronic hepatitis in two patients with common variable immunodeficiency. Gastroenterology 108:879–884

Snover DC, Weisdorf S, Bloomer J, McGlave P, Weisdorf D (1989) Nodular regenerative hyperplasia of the liver following bone marrow transplantation. Hepatology 9:443–448

Solis Herruzo JA, Duran A, Colina F, Santalla F, Garcia-Cabezudo J, Muñoz-Yague MT et al (1985) Laparoscopic and histological problems in the diagnosis of nodular regenerative hyperplasia of the liver. Endoscopy 17:105–108

Sood A, Castrejon M, Saab S (2014) Human immunodeficiency virus and nodular regenerative hyperplasia of liver: a systematic review. World J Hepatol 6:55–63

Steiner PE (1959) Nodular regenerative hyperplasia of the liver. Am J Pathol 35:943–953

Stromeyer FW, Ishak KG (1981) Nodular transformation (nodular "regenerative" hyperplasia) of the liver. A clinicopathologic study of 30 cases. Hum Pathol 12:60–71

Syed MA, Khalili K, Guindi M (2008) Regenerating nodules in arteriohepatic syndrome: a case report. Br J Radiol 81:e79–e83

Tajima T, Honda H, Yanaga K, Kuroiwa T, Yoshimitsu K, Irie H, Kuwabara Y, Taguchi K et al (2001) Hepatic nodular hyperplasia in a boy with Alagille syndrome: CT and MR appearances. Pediatr Radiol 31:584–588

Takahata T, Sasaki Y, Hirano K, Ishiguro Y, Takahashi T, Suto K, Suto T, Munakata A et al (1997) A case of nodular transformation of the liver with idiopathic portal hypertension (in Japanese). Nippon Shokakibyo Gakkai Zasshi 94:615–621

Talbot-Smith A, Syn WK, MacQuillan G, Neil D, Elias E, Ryan P (2009) Familia idiopathic pulmonary fibrosis in association with bone marrow hypoplasia and hepatic nodular regenerative hyperplasia: a new "trimorphic" syndrome. Thorax 64:440–443

Tanaka Y, Takayanagi M, Shiratori Y, Imai Y, Obi S, Tateishi R, Kanda M, Fujishima T et al (2003) Congenital absence of portal vein with multiple hyperplastic nodular lesions in the liver. J Gastroenterol 38:288–294

Tanaka I, Imaizumi K, Hashimoto I, Asai N, Yokoi T, Matsuno T, Hasegawa Y (2012) Interstitial pneumonia and nodular regenerative hyperplasia of the liver as initial manifestations of polyarteritis nodosa. Intern Med 51:635–638

Tateo M, Sebagh M, Bralet MP, Teicher E, Azoulay D, Mallet V, Pol S, Castaing D et al (2008) A new indication for liver transplantation: nodular regenerative hyperplasia in human immunodeficiency virus-infected patients. Liver Transpl 14:1194–1198

Teml A, Schwab M, Hommes DW, Almer S, Lukas M, Feichtenschlager T, Florin T et al (2007) A systematic survey evaluating 6-thioguanen-related hepatotoxicity in patients with inflammatory bowel disease. Wien Klin Wochenschr 119:519–526

Terayama N, Terada T, Hoso M, Nakanuma Y (1995) Partial nodular transformation of the liver with portal vein thrombosis. A report of two autopsy cases. J Clin Gastroenterol 20:71–76

Thevenot T, Dhote R, Tulliez M, Baverel F, Permal S, Rabineau D, Christoforov B (1998) Turner syndrome and nodular regenerative hyperplasia of the liver (in French). Ann Med Interne 149:295–296

Thorne C, Urowitz MB, Wanless I, Roberts E, Blendis LM (1982) Liver disease in Felty's syndrome. Am J Med 73:35–40

Torizuka T, Tamaki N, Fujita T, Yonekura Y, Uemoto S, Tanaka K, Yamaoka Y, Konishi J (1996) Focal liver hyperplasia in Alagille syndrome: assessment with hepatoreceptor and hepatobiliary imaging. J Nucl Med 37:1365–1367

Trenschel GM, Schubert A, Dries V, Benz-Bohm G (2000) Nodular regenerative hyperplasia of the liver: case of a 13-year-old girl and review of the literature. Pediatr Radiol 30:64–68

Tsui WM, So KT (1993) Partial nodular transformation of liver I a child. Histopathology 22:594–596

Tsuji K, Naoki K, Tachiyama Y, Fukumoto A, Ishida Y, Kuwabara T, Sumida T, Tatsugami M et al (2005) A case of congenital absence of the portal vein. Hepatol Res 31:43–47

Turk AT, Szabolcs MJ, Lefkowitch JH (2013) Portal hypertension, nodular regenerative hyperplasia of the liver, and obstructive portal venopathy due to metastatic breast cancer. Case Rep Pathol 2013:826284

Tuset E, Ribera JM, Doménech E, Vaquero M, Oller B, Armengol M, Planas R, Navarro JT et al (1995) Pseudotumorous hyperplasia of the caudate lobe of the liver in a patient with Alagille syndrome (in Spanish). Med Clin 104:420–422

Ueda T, Starkey J, Mori K, Fukunaga K, Shimofusa R, Motooti K, Minami M, Kondo F (2011) A pictorial review of benign hepatocellular nodular lesions: comprehensive radiological assessment incorporating the concept of anomalous portal tract syndrome. J Hepatobiliary Pancreat Sci 18:386–396

Ueno S, Tanabe G, Sueyoshi K, Yoshinaka H, Yamamoto S, Kurita K, Yoshidome S et al (1996) Hepatic hemodynamics in a patient with nodular regenerative hyperplasia. Am J Gastroenterol 91:1012–1015

Vaiphei K, Bhatia A, Sinha SK (2011) Liver pathology in collagen vascular discorders highlighting the vascular changes within portal tracts. Indian J Pathol Microbiol 54:25–31

van den Broek MAJ, Olde Damink SWM, Driessen A, Dejong CHC, Bemelmans MHA (2009) Nodular regenerative hyperplasia secondary to neoadjuvant chemotherapy for colorectal liver metastases. Case Rep Med 2009:457975

Van Hoek B (1996) The spectrum of liver disease in systemic lupus erythematosus. Neth J Med 48:244–253

Variend S (1978) An unusual nodular lesion of the liver: probably partial nodular transformation. Histopathology 2:363–373

Voinchet O, Degott C, Scoazec JY, Feldmann G, Benhamou JP (1988) Pleiosis hepatic, nodular regenerative hyperplasia of the liver, and light-chain deposition in a patient with Waldenström's macroglobulinemia. Gastroenterology 95:482–486

Wang HM, Lo GH, Hsu PI, Lin CK, Chan HH, Chen WC, Lai KH, Wang BW, Lin SL (2008) Nodular regenerative hyperplasia of the liver. J Chin Med Assoc 71:523–527

Wanless IR (1987) The use of morphometry in the study of nodular and vascular lesions of the liver. Anal Quant Cytol Histol 9:39–41

Wanless IR (1990) Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 11:787–797

Wanless IR, Gryfe A (1986) Nodular transformation of the liver in hereditary hemorrhagic telangiectasia. Arch Pathol Lab Med 110:331–335

Wanless IR, Godwin TA, Allen F, Feder A (1980) Nodular regenerative hyperplasia of the liver in hematologic disorders, a possible response to obliterative portal venopathy: a morphometric study of nine cases with an hypothesis on the pathogenesis. Medicine 59:367–379

Wanless IR, Solt LC, Kortan P, Deck JH, Gardiner GW, Prokipchuk EJ (1981) Nodular regenerative hyperplasia of the liver associated with macroglobulinemia. A clue to the pathogenesis. Am J Med 70:1203–1209

Wanless IR, Lentz JS, Roberts EA (1985) Partial nodular transformation of liver in an adult with persistent ductus venosus. Review with hypothesis on pathogenesis. Arch Pathol Lab Med 109:427–432

Wanless IR, Peterson P, Das A, Boitnott JK, Moore GW, Bernier V (1990) Hepatic vascular disease and portal hypertension in polycythemia vera and agnogeneic myeloid metaplasia: a clinicopathological study of 145 patients examined at autopsy. Hepatology 12:1166–1174

Ward C, Lucas M, Piris J, Collier J, Chapel H (2008) Abnormal liver function in common variable immunodeficiency disorders due to nodular regenerative hyperplasia. Clin Exp Immunol 153:331–337

Weinbren K, Mutum SS (1984) Pathological aspects of diffuse nodular hyperplasia of the liver. J Pathol 143:81–92

Wicherts DA, de Haas RJ, Sebagh M, Ciacio O, Lévi F, Paule B, Giacchetti S, Guettier C et al (2011) Regenerative nodular hyperplasia of the liver related to chemotherapy: impact on outcome of liver surgery for colorectal metastases. Ann Surg Oncol 18:659–669

Wig KL, Ramasingaswami V, Sama SK (1966) Clinicopathological classification of intrahepatic portal hypertension (cirrhosis and non-cirrhotic). J Assoc Physicians India 14:411–415

Young ID, Segura J, Ford PM, Ford SE (1992) The pathogenesis of nodular regenerative hyperplasia of the liver associated with rheumatoid vasculitis. J Clin Gastroenterol 14:127–131

Yutani C, Imakita M, Ishibashi-Ueda H, Okubo S, Naito M, Kunieda T (1988) Nodular regenerative hyperplasia of the liver associated with primary pulmonary hypertension. Hum Pathol 19:726–731

Zech CJ, Seiderer J, Reinisch W, Ochsenkuhn T, Schima W, Diebold J, Wrba F, Reiser MF et al (2007) Thioguanin-induced nodular regenerative hyperplasia of the liver – ROC analysis of different MR techniques. Eur Radiol 17:1898–1905

Ziarkiewicz-Wroblewska et al. (2004). http://www.ncbi.nlm.nih.gov/pubmed/15507857

Ziol M, Poirel H, Kountchou GN, Boyer O, Mohand D, Mouthon L, Tepper M, Guillet JG et al (2004) Intrasinusoidal cytotoxic CD8+ T cells in nodular regenerative hyperplasia of the liver. Hum Pathol 35:1241–1251

Zuber M, Gherardi R, Defer G, Gaulard P, Divine M, Zafrani ES (1989) Peripheral neuropathy, coagulopathy, and nodular regenerative hyperplasia of the liver in a patient with multiple serologic auto-antibody activities abd IgM B-cell lymphoma. J Intern Med 226:291–295

Part XXIII

Hepatobiliary Pseudotumors

Pseudotumors and Related Lesions of the Hepatobiliary Tract

119

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_119

Abstract

Pseudotumors and inflammatory pseudotumors form a heterogeneous group of lesions characterized by the presence of an inflammatory infiltrate and proliferations of fibroblasts and myofibroblasts. Pseudotumors are mass-forming lesions, also in the hepatobiliary tract, that may mimic diverse malignancies. Specifically, pseudotumors can grow in the walls of extrahepatic bile ducts, with formation of stenosing and obstructive lesions clinically similar to cholangiocarcinoma. The term inflammatory myofibroblastic tumor (IMT) has been proposed as synonym for pseudotumor, with a generally benign behavior. However, a subset of these lesions show an aggressive growth pattern and even malignant behavior, suggesting a neoplastic character of some pseudotumors. Furthermore, about half of recently analyzed cases of IMT carry rearrangements of the anaplastic lymphoma kinase (ALK) locus on chromosome 2p23, causing aberrant ALK expression. Based on these findings, the classification of so-called pseudotumors, mainly the identification of reactive versus neoplastic forms, requires revision. A variant lesion that is sometimes classified together with IMT is Epstein-Barr virus-positive inflammatory pseudotumor (inflammatory pseudotumor-like follicular dendritic cell tumor).

Hepatobiliary Pseudotumors: A Heterogeneous Group of Intriguing Lesions

Introduction

Hepatic lesions resembling or being identical with inflammatory pseudotumors observed in other organs and in particular the lung of young male patients are now well recognized. The first reports on primary hepatic inflammatory pseudotumor (HIP; synonyms: pseudolymphoma, fibroinflammatory tumor, inflammatory myofibroblastic tumor, plasma-cell granuloma, inflammatory pseudotumor-like granuloma) date back to the 1950s–1970s (Pack and Baker 1953; Hertzer et al. 1971; Someren 1978), the case of Pack and Baker representing a 40-year-old man. Since that time, many cases have been described, albeit mostly as single reports or small series hepatic inflammatory pseudotumors (HIP; review: Craig 1997) now become increasingly recognized because of the more frequent use of advanced abdominal imaging methods, in particular ultrasonography and CT. But what is a "pseudotumor" ?

Pseudotumors: A General Overview

The term pseudotumor is, as such, rather a misnomer and may in fact be a very inaccurate term: a tumor, in its original meaning, is a mass lesion of whatever cause and composition, although now being more and more reserved for a bona fide neoplasm; so, what is a "pseudo-mass," and what is an adequate definition of it ? "The term is typically employed to connote the presence of a mass lesion (which, by definition, is a tumor)" that on clinical or pathologic grounds, or both, is thought to represent a neoplasm. Thus, the name "pseudoneoplasm" would be more à propos under such circumstances (Wick and Ritter 1997). The two authors just cited employ the term, "pseudoneoplastic lesions," but they will be right in their introductory statement that, even though the term is utterly unsatisfactory, it will remain in the active medical literature, because of the difficulty that is generally encountered in challenging an established clinicopathologic rubric. First employed to denote orbital masses producing exophthalmos (Birch-Hirschfeld 1930), pseudotumors have later been subdivided in accordance with predominant histologic features, including "inflammatory," "granulomatous," "xanthomatous," " plasmacellular," and "fibrous" variants. It has to be emphasized that, even though such adjectives may offer some (primary or first line) help in classification, they unfortunately surmise that the lesions so denoted may represent "entities." This approach operates such as general pathology or pathophysiology would not exist: it is obvious that a reactive process driven by an

exuberant inflammatory response may later develop fibrosis, or may accumulate numerous lipid-laden macrophages subsequent to hemorrhage or necrosis, classifying adjectives and therefore identifying a type of response within a timely sequence rather than an inherent feature. More interesting (and probably also more important) is the phenomenon as to why such apparently nonneoplastic lesions exhibit excessive growth, may show invasive characteristics, and may or may not spontaneously regress, in some way reflecting the behavior of an abnormally healing wound.

Inflammatory Pseudotumor Versus Inflammatory Myofibroblastic Tumor

The term inflammatory myofibroblastic tumor (IMT) has been proposed as a synonym of inflammatory pseudotumor and characterized as lesions containing myofibroblastic spindle cells and a mixed pattern of leukocytic infiltrates, including plasma cells, and exhibiting a generally benign behavior. The majority of lesions previously described as inflammatory pseudotumors meet this definition, but cases reported in past decades were described as having "spindle cells" often interpreted as fibroblasts, because the myofibroblast concept and the immunohistochemistry to identify myofibroblasts were not yet developed. However, the spectrum of IMT and related lesions has recently evolved along several lines, causing some misconceptions or even confusion regarding classification. First, a subset of IMT show an aggressive growth pattern and a malignant behavior rather than a benign phenotype, sometimes with formation of metastases ("aggressive form of IMT"). Based on this behavior, some IMTs were classified as neoplastic lesions, or reactive lesions, that have undergone malignant transformation. Secondly, about half of recently analyzed cases of IMT carry rearrangements of the anaplastic lymphoma kinase (ALK) locus on chromosome 2p23, causing aberrant ALK expression. As these lesions markedly deviate from the "purely" inflammatory and mixed-cellular forms of inflammatory tumors, mainly due to their neoplastic nature, these lesions are treated in a separate chapter.

Pseudotumors as Neoplastic Versus Reactive Processes

Is HIP a reactive or a neoplastic process? Some features have been quoted that seemingly contradict the purely reactive/inflammatory nature of these lesions, including a progressive growth; a local recurrence; the development of noncontiguous, multifocal masses; an infiltrative border; the destruction of liver substance and bile ducts; and the vascular (portal-venous) invasion (Coffin et al. 1998). However, the histologic pattern of the majority of the lesions, lacking one typical target cell, their usually benign course, and the tendency for spontaneous regression do, on the other hand, not favor a bona fide neoplastic process. We therefore propose that the majority of HIPs are in fact reactive lesions, i.e., pseudotumors, but that a subset of hepatic lesions with a similar morphology have a neoplastic phenotype, in particular those with a proliferation of follicular dendritic reticulum cells. These lesions are discussed in the following chapter. In addition, there might be instances where part of a mass exhibits the histologic features of HIP, but this component may represent a reaction to a hidden and later overt malignant neoplasm, e.g., a sarcoma, thus initially causing the false impression of malignant HIP.

Inflammatory Pseudotumor of the Liver (Hepatic Inflammatory Pseudotumor, HIP; Hepatic Inflammatory Myofibroblastic Tumor, HIMT), Probably Reactive Forms (Excluding IgG4-Related Disease)

Introduction

The lesions described in this section comprise reactive phenotypes that, on the one hand, correspond to what has been described as inflammatory pseudotumors in the "pre-myofibroblast era" and

to lesions now termed inflammatory myofibroblastic tumors, however with the exception of those which have documented ALK gene rearrangements, expression of EBV, and/or signs of a bona fide neoplastic cell lineage. Also inflammatory pseudotumors developing in the setting of systemic IgG4 sclerosing disease are excluded from this section and are discussed in a separate chapter. As specified above, "type A" as a working formulation denotes a heterogeneous group of reactive and probably nonneoplastic lesions that awaits further classification. For this purpose, the older term, inflammatory pseudotumor, is employed in this section, also for comparative lesions in regard to the older literature.

Epidemiology

HIP has been first described in 1953 (Pack and Baker 1953) and has since been documented numerous times in the literature, mostly under the term inflammatory pseudotumor, notwithstanding the fact that the term inflammatory myofibroblastic tumor was already coined in 1995. HIP occurs at all ages. The age of the patients at presentation of the lesion ranges from infancy (3 months; Lee and DuBois 2001; 9 months; Lacaille et al. 1999) or early childhood up to more than 80 years, with a male to female ratio varying considerably from one series to other, from about 1:1 up to 8:1 (Horiuchi et al. 1990; Shek et al. 1993). HIP occurring in the pediatric age group has been reported several times (Someren 1978; Newbould et al. 1992; Passalides et al. 1996; Bankole-Sinni et al. 1997; Ueda et al. 2003; Swinney et al. 2006). The overall prevalence of HIP is not known, but in a study on 403 consecutive patients carrying a total of 717 focal liver lesions and undergoing liver resection, three patients proved to have HIP accounting for 0.7 % of all patients and 0.4 % of all focal liver lesions (Torzilli et al. 2001). The features of the lesions have been described in numerous reports.

Selected References Pack and Baker 1953; Hertzer et al. 1971; Someren 1978; Heneghan et al. 1984; Anthony and Telesinghe 1986; Grouls 1987; Lee et al. 1987; Morita et al. 1987; Collina et al. 1987; Kessler et al. 1988; Joh et al. 1988; Levitt et al. 1988; Hirasawa et al. 1988; Standiford et al. 1989; Jimenez-Mejias et al. 1989; Irie et al. 1989; Li et al. 1989; Lupovitch et al. 1989; Andreola et al. 1990; Horiuchi et al. 1990; Imafuku et al. 1990; Jakab et al. 1990; Imazato et al. 1990; Tsao et al. 1990; Lopez et al. 1990; Feng 1991; Alonso et al. 1991; Isobe et al. 1991; Jackson and Gatling 1991; Pokorny et al. 1991; Gollapudi et al. 1992; Hata et al. 1992; Lopez 1992; Ozeki et al. 1993; Shek et al. 1993; Fukuya et al. 1994; Maeng et al. 1994; Noi et al. 1994; Jais et al. 1995; Schmid et al. 1996; Uetsuji et al. 1996; Gosavi et al. 1997; Kafeel and Telesinghe 1997; Nonomura et al. 1997; Ogawa et al. 1998; Tajima et al. 1998; Gluszek et al. 1999; Kim et al. 1999; Lacaille et al. 1999; Voss et al. 1999; Yoon et al. 1999; Ishida et al. 2000; Toda et al. 2000; Kaneko et al. 2001; Lee and DuBois 2001; Levy et al. 2001; Sakai et al. 2001; Torzilli et al. 2001; Yan et al. 2001; Casassus-Builhe et al. 2002; Sakai et al. 2002; Saito et al. 2002; Wang et al. 2002; Biecker et al. 2003; Inaba et al. 2003; Koea et al. 2003; Maiga et al. 2003; Rai et al. 2003; Schneider et al. 2003; Aguirre-Garcia 2004; Del Fabbro et al. 2004; Fritzsch et al. 2004; Lo et al. 2004; Papachristou et al. 2004; Seki et al. 2004; Tamsel et al. 2004; Alimoglu et al. 2005; Bernard et al. 2005; Cohen et al. 2005; Colakoglu et al. 2005; Druez et al. 2005; Locke et al. 2005; Nishimura et al. 2005; Sandilla et al. 2005; Sasahira et al. 2005; Teranishi et al. 2005; Akatsu et al. 2006; Kawamura et al. 2006; Kim et al. 2006; Koide et al. 2006; Park et al. 2006; Schuessler et al. 2006; Swinney et al. 2006; Diaz-Torné et al. 2007; Gohy et al. 2007; Hoosein et al. 2007; Kai et al. 2007, Perera et al. 2007; Schnelldorfer et al. 2007; Sturm et al. 2007; Tsou et al. 2007; Vassiliadis et al. 2007; Weiss et al. 2007; Yamaguchi et al. 2007; Alfieri et al. 2008; Chen et al. 2008; Peddu et al. 2008; Singh et al. 2008; Ashcroft et al. 2009; Chong et al. 2009; Ganesan et al. 2009; Geramizadeh et al. 2009; Goldsmith et al. 2009; Jover Diaz et al. 2009; Lee et al. 2009; Manolaki et al. 2009, Milias et al. 2009; Mouelhi

et al. 2009; Ueda et al. 2009; Al-Jabri et al. 2010; Brage-Varela et al. 2010; Bruyeer and Ramboer 2010; Deng et al. 2010; Sari et al. 2010; Tang et al. 2010; Terada 2010; Faraj et al. 2011; Hasan et al. 2011; Herek and Karabulut 2011; Jerraya et al. 2011; Ntinas et al. 2011; Renzing et al. 2011; Kawaguchi et al. 2012; Patnana et al. 2012.

Clinical Features

The lesions are mostly solitary (multiple in about 20 %), more frequently right sided (about 60 %), and located within the liver substance or extended into the hilar/perihilar area. However, multiple nodules of HIP occur and may mimic liver abscesses, primary hepatic malignancy, or hepatic metastases. The size of the lesions is variable but may reach a diameter of up to 25 cm. HIP may clinically present as fever of unknown origin (FUO; mainly low-grade intermittent fever), malaise, vague abdominal symptoms and pain, an epigastric mass, a history of weight loss, jaundice, and/or laboratory data suggesting an inflammatory process (leukocytosis, raised erythrocyte sedimentation rate, polyclonal hyperglobulinemia). In part of the patients, HIP was asymptomatic and was detected as an "incidentaloma" or liver metastasis. In case the masses develop close to large bile ducts or within the bile duct wall, HIP may cause stenosis of intrahepatic bile ducts and sometimes obstructive jaundice, either due to involvement of the hilar compartment of the liver and/or large extrahepatic bile ducts, sometimes mimicking perihilar bile duct carcinoma, or as a disease centered around the intrahepatic biliary tree, or involving both the hepatobiliary and pancreatic system. HIP evolving with a ductocentric pattern can develop a hamartoma-like growth associated with fibrosclerosis, a lesion proposed to be termed "fibroductal variant" of HIP (Terada et al. 1992). HIP can develop in extrahepatic bile ducts, including the mid-portion, and closely mimic cholangiocarcinoma (Vasiliadis et al. 2014). HIP also occurs in the distal part of the common bile duct, i.e., close to the pancreatic head (Haith et al. 1964). A further distinct feature of HIP is endophlebitis, sometimes obliterative, involving medium-sized to large branches of the portal vein and eventually resulting in portal hypertension (Kaneko et al. 1984; Chen 1984; Heneghan et al. 1984; Horiuchi et al. 1990; Tsao et al. 1990), and also developing in young children (Someren 1978), sometimes with the angiographic demonstration of the portal vein draining into the lesion to be occluded (Hata et al. 1992).

In a minority of cases, HIP may undergo spontaneous regression. This regression process may take several months and can occur in the absence of any treatment, owing to unknown reasons, but it may be assumed that HIP regress when the causative factors, in particular infection, have disappeared (Gollapudi et al. 1992; Levy et al. 2001; Biecker et al. 2003; Druez et al. 2005; Koide et al. 2006; Tsou et al. 2007; Yamaguchi et al. 2007; Peddu et al. 2008; Chong et al. 2009; Brage-Varela et al. 2010; Jerraya et al. 2011). Regression of HIP has been achieved by treatment with nonsteroidal anti-inflammatory drugs (Colakoglu et al. 2005; Vassiliadis et al. 2007).

Imaging Features

Ultrasonography usually reveals hypoechoic and well-circumscribed masses (Abehsera et al. 1995; Nam et al. 1996; Sakai et al. 2002). As sonography sometimes reveals enlarged locoregional lymph nodes, a primary hepatic malignancy may be suspected (Fukuya et al. 1994; Schuessler et al. 2006). At non-enhanced CT, HIPs appear as an irregularly shaped, inhomogeneous mass with an internal low-density area in the delayed phase (Noi et al. 1994; Lim and Lee 1995; Lee and DuBois 2001; Nishimura et al. 2005; Goldsmith et al. 2009; Herek and Karabulut 2011) or ill-defined, hypoattenuating lesions, whereas at contrast-enhanced CT, the masses exhibit central hypoattenuating areas with an iso- or hyperattenuating and thickened periphery or a multiseptate appearance (Yoon et al. 1999). HIP may show calcifications (Lacaille et al. 1999). Changes in tumor size during relatively short

time periods are often observed in HIP, in contrast to most other hepatic mass lesions. An enhancement of the peripheral regions of HIP was often observed in the early phase of contrast medium dynamic CT, thought to be due to abnormal vessels located in peripheral parts of the lesions and to result from obliteration of preexisting vessels in portal tracts within the inflamed tissue (Seki et al. 2004). HIP may present capsular retraction as an uncommon imaging fining (Ganesan et al. 2009).

Findings at MRI have been reported several times (Flisak et al. 1994; Kelekis et al. 1995; Borgonovo et al. 1998; Yan et al. 2001; Sakai et al. 2002; Hasan et al. 2011), showing no early arterial enhancement (a key difference to hypervascular HCC), peripheral enhancement, septum and small nodular enhancement occurring in portal venous, and delayed phases. MRI with mangafodipir trisodium might help distinguish HIP from HCC (Materne et al. 1998; Mortele et al. 2002). On post-gadolinium gradient-echo (GE) images, an early, intense, and peripheral enhancement was followed by a homogeneous, complete, and persistent enhancement, and during follow-up, a peripheral intense rim appeared on precontrast T1-weighted images (Mortele et al. 2002). Due to the high content in metabolically active cells of diverse leukocyte lineages, HIP can be diagnosed by PET based on its markedly increased 18 F-FDG uptake (Kawamura et al. 2006; Chong et al. 2009). The high macrophage content of most HIP allows the detection of these lesions by use of ferumoxide-enhanced MR imaging (Kato et al. 2004).

Pathology

Macroscopy

At gross examination, HIPs are rather firm or even hard masses (depending on the collagenization) with usually sharp margins. The cut surface is variegated, gray to whitish or yellow, and sometimes with signs of hemorrhage and/or necrosis (Figs. 1 and 2).

Histopathology

Histologically, the "background" tissue consists of fibroblasts/fibroblastoid cells and myofibroblasts. The cellularity of the spindle cell component may be so abundant that these areas may be misdiagnosed as sarcoma. The spindle cell areas are frequently heavily collagenized, producing a hyaline or sclerosed aspect of the tissue. The vascularity may be high, reflected by the imaging presentation as a vascular tumor (Shek et al. 1993). The tissue is densely infiltrated by a mixed population of leukocytes, usually with a predominance of small lymphocytes. In some instances, the lymphocytic infiltration exhibits a density and a monomorphic presentation

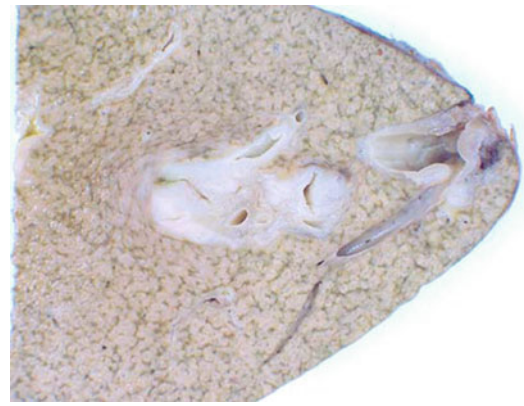

Fig. 1 Inflammatory pseudotumor of the hepatobiliary tract. A whitish tissue has developed around intrahepatic bile ducts, causing duct stenosis

Fig. 2 Stenosing inflammatory pseudotumor of the extrahepatic bifurcation. The lesion macroscopically mimics stenosing cholangiocarcinoma

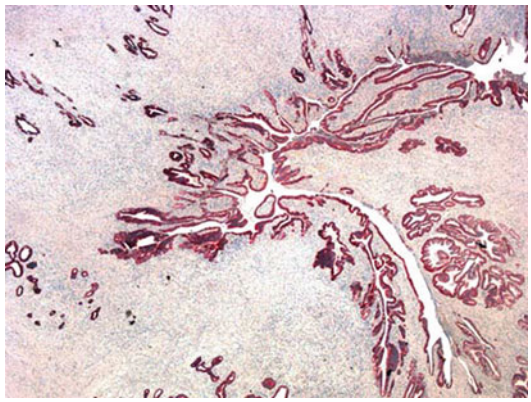

Fig. 3 The extrahepatic bile ducts are markedly stenosed by an inflammatory tissue (cytokeratin 7 immunostain)

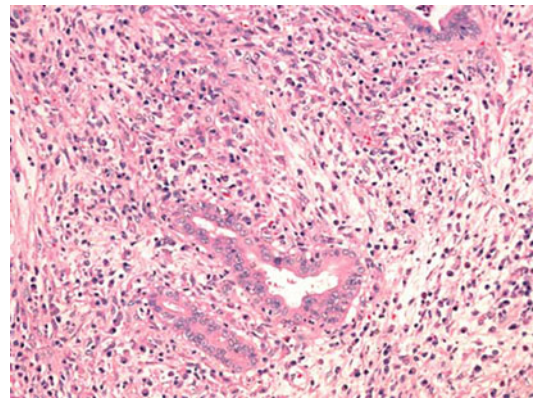

Fig. 4 Hepatobiliary inflammatory pseudotumor. The tissue surrounding bile ducts is infiltrated with lymphocytes, plasma cells, and macrophages, and there is an increase in fibroblastoid cells (hematoxylin and eosin stain)

reminiscent of malignant non-Hodgkin's lymphoma, one reason why such lesions have also been termed pseudolymphoma of the liver (Grouls 1987). Lymphocytes may be arranged as aggregates or lymph follicles, even with formation of germinal centers. In addition to lymphocytes, various amounts of mature plasma cells and plasmacytoid elements are regularly noted and may sometimes form dense clusters or aggregates mainly around blood vessels, previously having led to the term plasma-cell granuloma (Anthony 1993). Neutrophil and eosinophil granulocytes are mostly sparse, with the exception of cases with development of microabscesses or with cholangitic features. As a reaction to tissue breakdown, numerous foamy macrophages may be in evidence, sometimes resulting in a so-called pseudoxanthomatous reaction (Figs. 3, 4, 5, 6, and 7). Some of the tumors contain increased numbers of dendritic cells, including giant atypical reactive dendritic cell forms (Sturm et al. 2007).

Histopathologic diagnosis by needle biopsy is possible and has been reported (Irie et al. 1989; Nakama et al. 2000; Hosler et al. 2004; Sari et al. 2010; Kawaguchi et al. 2012). Fine-needle aspiration shows hypocellular smears with an admixture of various cell types including plasma cells, macrophages, lymphocytes, fibroblasts, and granulation tissue fragments. Foamy macrophages are a striking feature in some cases (Lupovitch et al. 1989; Yoshida et al. 2003; Hosler et al. 2004; Kawaguchi et al. 2012).

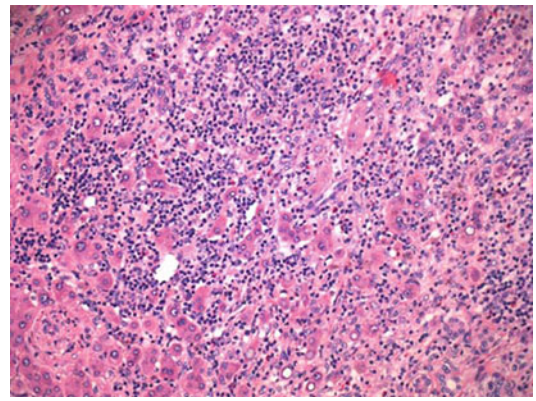

Fig. 5 Hepatobiliary inflammatory pseudotumor. An infiltrate rich in lymphohistiocytic cells has caused dissociation of hepatic parenchyma (hematoxylin and eosin stain)

Immunohistochemistry

The spindle cells found in HIP are vimentin positive, and at least part of them express alpha-smooth muscle actin (alpha-SMA), classifying these cells as myofibroblasts. In contrast to smooth muscle cells found in the muscle layer cells (Montani et al. 2010) and in leiomyomas and leiomyosarcomas of the gastrointestinal tract, the spindle cells of inflammatory pseudotumors are negative for the smooth muscle-specific cytoskeletal protein, smoothelin (Coco et al. 2009). Myofibroblasts do not seem

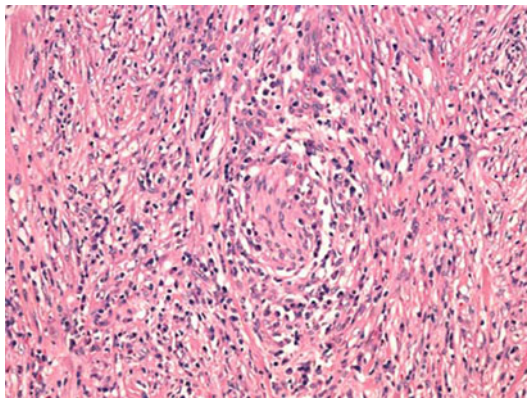

Fig. 6 Inflammatory pseudotumor of the liver. Lymphocytes, plasma cells, and macrophages infiltrate a tissue with abundant fibroblastoid cells and are present around a small nerve (center; hematoxylin and eosin stain)

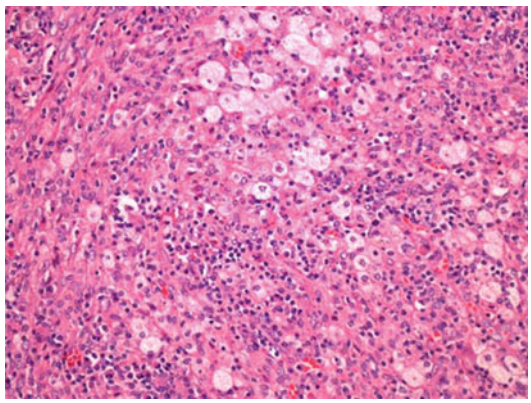

Fig. 7 Inflammatory pseudotumor of the liver. This lesion contains numerous lipid-rich, foamy macrophages (pseudoxanthoma cells; hematoxylin and eosin stain)

to express smoothelin (Nam et al. 2012). Immunohistochemically, the lymphocyte population is typically a mixture of T and B lymphocytes (Kim et al. 1999), even though T (in particular CD8-reactive) cells may predominate, also in portal tracts of the liver adjacent to the tumor, and the plasma cells are polytypic (Uccheddu et al. 1995; Sakai et al. 2001), showing a mixture of IgA-, IgM-, and IgG-producing cells and the expression of both lambda and kappa light chains (Tsao et al. 1990). However, in one reported case, most of the lymphocytes and plasma cells produced IgA and predominantly lambda light chains (Grouls 1987). Macrophages in the infiltrate are frequently activated and CD68-positive.

Attempts for a Histologic Classification of HIP

Referring to the predominant histologic patterns, attempts have been undertaken to classify the lesions in more detail. Someren categorized HIP into three morphotypes, i.e., hyalinized sclerosing, xanthogranuloma, and plasma-cell granuloma types (Someren 1978). As in other lesions with heterogeneity owing to an internal gradient of cellular responses, such a classification is prone to considerable sampling variation and therefore of doubtful significance. Based on 74 previously reported cases and an own pediatric patient, Lee and DuBois have recently proposed a novel classification (Lee and DuBois 2001). In contrast to histopathologic categories, they put emphasis on the clinical/radiologic presentation, i.e., solitary or multiple lesions. Their type 1 or solitary HIPs were typically large and centrally located lesions, exhibited a mean diameter of 7 cm, showed a low-density central core on CT representing necrosis, have a hypovascular or even avascular angiographic appearance, and were a predominant variant of HIP in children (16/18). The more central location of type 1 lesions may result in bile duct stenosis and portal venous and obliterative endophlebitis, as discussed below. Owing to these complications, type 1 according to Lee and DuBois may require surgery more frequently than other manifestations of HIP. Type 2 or multiple HIPs are typically smaller lesions (2–6 cm diameter) in a bilobar distribution, occur in adults and children, and are less likely to involve bile ducts and/or portal vein branches (Lee and DuBois 2001). In CT, the nodules are solid and exhibit a low but uniform density, similar to metastases, so that exclusion of malignancy is a major concern in case of type 2 lesions.

Differential Diagnosis

The differential diagnosis of HIP mainly includes chronic liver abscess, malignancy (sarcoma; malignant fibrous histiocytoma; lymphoma; desmoplastic carcinoma), benign mesenchymal tumors, and (sclerosed) vascular tumors.

Biology of Disease

In situations without biliary or vascular involvement and complications, or large lesions, the clinical course is usually benign and self-limiting; it sometimes even undergoes spontaneous regression (Gollapudi et al. 1992; Zamir et al. 1998; Young et al. 1998; Soudack et al. 2000; Nakama et al. 2000; Levy et al. 2001), but in patients with large and non-resolving lesions, hepatectomy is now advocated to be the treatment of choice in comparison with conservative therapy (Mangiante et al. 1997), even though selected patients may profit from conservative treatment, including antibiotics (Jais et al. 1995; Casassus-Builhe et al. 2002). The question as to whether HIP may undergo malignant evolution is not settled so far. A patient with HIP has been described where a subsequent evolution into malignant non-Hodgkin's lymphoma occurred (Pecorella et al. 1999).

Etiology and Pathogenesis

HIP is often associated with diverse conditions that may deliver clues as to pathogenic pathways involved (Lyons et al. 1993). In regard to pathogenic considerations, the apparently reproducible association of HIP and chronic cholangitis (Gough and Chakrabarti 1993; Nakanuma et al. 1994) or with recurrent pyogenic cholangitis (Yoon et al. 1999) merits particular attention. Yoon and coworkers investigated on 13 inflammatory hepatic pseudotumors evolving in 10 patients. All these patients had CT features of recurrent pyogenic cholangitis, such as hepatolithiasis, intrahepatic bile duct stricture and dilatation, common bile duct calculi, pneumobilia, or signs of atrophy/hypertrophy complex of the liver. The presence of chronically infected extrahepatic and/or intrahepatic bile ducts may, therefore, represent a risk factor for the development of IPTL, and a marked local host response to bacterial infection may in fact be the driving force for the establishment of a tumor-like, exuberant repair reaction, also involving strong immune reactions of both the cellular and humoral type. A causal relationship to local bacterial infection is further indicated by the observation of a spatial connection between HIP and adjacent abscesses (Jimenez-Mejias et al. 1989). Furthermore, situations with dilatation of bile ducts and frequently complicated by bacterial infection may later be accompanied by HIP (Terada et al. 1992; Kuhara et al. 1994). A possible significance of more remote visceral infections is indicated by the finding of HIP occurring together with diverticulitis (Coleman and Rees 1999) and with chronic abdominal abscesses followed by sepsis (White et al. 1997). In one case, fine-needle aspirate yielded a growth of *Klebsiella* organisms (Kafeel and Telesinghe 1997) and, in another, *Escherichia* and *Actinomyces* species (Schmid et al. 1996). In a patient with multiple HIP, *Enterococcus durans* bacteremia was detected (Jover Diaz et al. 2009). A further argument for the pathogenetic significance of infections is offered by the observation that HIP can regress under antibiotic therapy (Casassus-Builhe et al. 2002). HIP was also found in association with primary hepatic actinomycosis (Tamsel et al. 2004) and amebic infections (Alfieri et al. 2008) and with *Mycobacterium* tuberculosis infection in an immunocompetent child (Manolaki et al. 2009). The observation of HIP in association with HIV infection (Tai et al. 1998) might, if not a fortuitous coincidence, suggest a role of deranged immune responses to the more frequent bacterial infections in this disorder.

That immune or autoimmune mechanisms may play a role in the pathogenesis of HIP is suggested by the observation of such lesions in patients with primary biliary cirrhosis (Rai et al. 2003; Koide et al. 2006), primary sclerosing cholangitis (Toda et al. 2000), and after liver transplantation (Lykavieris et al. 2000); in patients with Crohn's disease (Papachristou et al. 2004; Mouelhi et al. 2009; Renzing et al. 2011) and rheumatoid arthritis (Diaz-Torné et al. 2007); and in the setting of Sjögren's syndrome (Hosokawa et al. 1998). HIP has been observed as the first manifestation of Crohn's disease (Amankonah et al. 2001), and it was speculated that the lesion may be related to underlying inflammatory bowel disease. Furthermore, inflammatory reactions

located elsewhere may be modified by the presence of HIP; e.g., both fever and recurrent arthritis related to gout completely resolved after surgery of HIP (Takahashi et al. 2001). HIP has been observed to complicate severe congenital neutropenia (Kostmann's disease; Hsiao et al. 1999; Schneider et al. 2003) and to occur in a hereditary disorder associated with the development of hepatic abscesses, Papillon-Lefevre syndrome (Czauderna et al. 1999).

Some pseudotumors seem to develop in association with collapsed liver cysts or form a residuum of biliary cystadenoma (Hoosein et al. 2007). HIP has been observed in association with gallstones (Al-Jabri et al. 2010), including hepatolithiasis (Ueda et al. 2009; Terada 2010); biliary atresia (Wang et al. 2002); intra-abdominal foreign bodies, e.g., intrahepatic wooden toothpicks or migrated fishbone (Del Fabbro et al. 2004; Perera et al. 2007); abdominal malignancy (Nishimura et al. 2005), GISTs (Lo et al. 2004); and leukemias (Isobe et al. 1991; Tajima et al. 1998). It has developed as a possible complication of percutaneous radiofrequency ablation of hepatocellular carcinoma (Lee et al. 2009). HIP was found during pregnancy (Maze et al. 1999).

Inflammatory Myofibroblastic Tumors of the Liver and Related Lesions

Introduction

Inflammatory myofibroblastic tumor (IMT) is a distinctive mesenchymal tumor that has emerged from within the heterogeneous group of inflammatory pseudotumors as an entity characterized by neoplastic features, a proliferation of myxoid spindle cells, an inflammatory infiltrate, and a rearrangement of anaplastic lymphoma kinase (ALK) in at least 50 % of the cases (reviews: Dehner 2004; Gleason and Hornick 2008). ALK rearrangement of the respective locus on chromosome 2p23 causes aberrant ALK expression in the neoplastic cells (Griffin et al. 1999). The term, IMT, implies that the neoplastic cell lineage characterizing IMT is a myofibroblast or a myofibroblast-like cell. However, alternative views regarding the cell of origin have been formulated, e.g., a proliferation of fibroblastic reticulum cells, a subtype of cell of the accessory immune system (Nonaka et al. 2005).

IMTs occur primarily during the first two decades of life (Coffin et al. 2007) and chiefly arise in the lung, retroperitoneum, and abdominopelvic region (Coffin et al. 1995). IMTs also occur in the pediatric age group (Mergan et al. 2005; Ernst et al. 2011). Less common localizations comprise the central nervous system, salivary glands, thyroid, larynx, breast, spleen, urinary bladder, and skin.

Inflammatory Myofibroblastic Tumors of the Hepatobiliary Tract

IMT of the liver is a rather common intra-abdominal manifestation of IMTs (Beauchamp et al. 2011). In a fine-needle aspiration cytologic study of 20 cases, nine were localized to the liver (Stoll and Li 2011). IMT of the liver was also found in children (Mergan et al. 2005). IMT very rarely develops in the bile duct system. The lesions developing in the distal part of the common bile duct usually make part of the syndrome IgG4-associated sclerosing disease (Yamamoto et al. 2009). IMTs not associated with IgG4 disease have very rarely been reported (Stamatakis et al. 1979; Bolla et al. 1988; Ikeda et al. 1990; Imafuku et al. 1990; Fukushima et al. 1997; Saint-Paul et al. 1999; Worley et al. 2001; Ashcroft et al. 2009) and also develop in the ampullary/periampullary region (Leese et al. 1986; Price et al. 1993). IMTs can develop in the hilar region, producing extending structures and mimicking a Klatskin tumor (Worley et al. 2001). Bile duct IMTs are usually lesions with a benign behavior, but aggressive forms have also been reported. In a 63-year-old female patient with aggressive hilar IMT, pulmonary metastasis developed (Kim et al. 2011).

Pathology

The typical feature is a growth of slightly eosinophilic spindle cells resembling fibroblasts, with bland-looking nuclei and absent mitoses or a low mitotic count. The spindle cells, which are immunohistochemically myofibroblasts, may be embedded in a myxoid or hypocellular fibrosclerotic matrix (Fig. 8). In a minority of cases, a round cell transformation of IMT was observed (Chen and Lee 2008). Cellular atypia is more frequent in aggressive variants of IMT. Cellular atypia was found in 69 % of tumors that recurred and in all cases showing malignant transformation (Hussong et al. 1999).

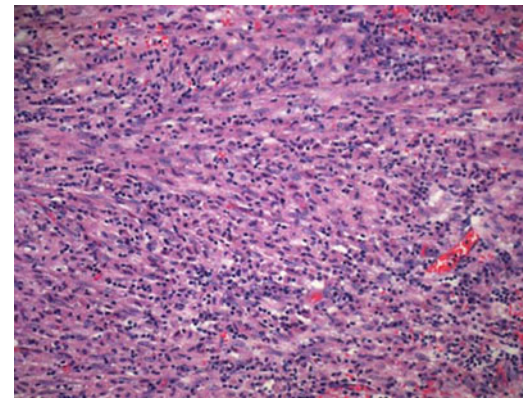

Fig. 8 Myofibroblastic pseudotumor of the liver. A dense collection of myofibroblasts and other spindle cells is infiltrated with lymphocytes (hematoxylin and eosin stain)

Immunohistochemistry

Apart from aberrant ALK expression (see below), hepatic IMT cells have been shown to be positive for alpha-SMA (Qiu et al. 2008) and actin (100 %; Stoll and Li 2011), supporting the myofibroblastic character of these cells (Fig. 9). Aggressive IMT may show nuclear p53 expression (Hussong et al. 1999).

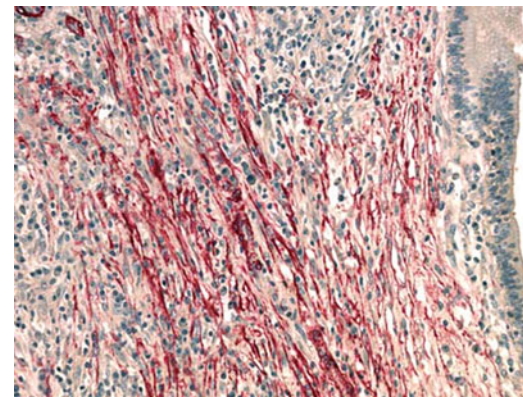

Fig. 9 Myofibroblastic pseudotumor of a bile duct. The inflamed tissue contains numerous spindle cells with reactivity for smooth muscle actin. The inflammatory infiltrate contains numerous plasma cells (alpha-SMA immunostain)

Biology of Disease

IMTs usually show a rather indolent course, but may exhibit invasive growth and spread. Currently, IMT is considered to be an intermediate-grade neoplasm that can recur in up to 25 % of cases (Hussong et al. 1999). However, in the subset of abdominal and pelvic IMTs, the recurrence rate was 85 % in one investigation (Coffin et al. 2007), suggesting an important role for the site of origin. Rarely, IMT can undergo malignant transformation, with locoregional and/or distant metastases (Hussong et al. 1999; Ernst et al. 2011). In a study of 24 cases, 8 % underwent malignant transformation (Hussong et al. 1999). Low-grade myofibroblastic sarcoma, which may be confounded with IMT, is currently not regarded as a member of the family of ALK-positive tumors (Qiu et al. 2008).

ALK Rearrangements in Hepatic IMT

IMTs primary to the liver may show ALK gene rearrangements with variable fusion partners. An unusual rearrangement is that between the Ran-binding protein 2 and ALK, associated with nuclear membrane expression of ALK (Chen and Lee 2008). Aberrant anaplastic lymphoma kinase (ALK) expression caused by ALK gene rearrangements is a frequent alteration in IMTs. ALK plays a significant role in the regulation of cell proliferation in several cell lineages and is the

partner of several fusion proteins in distinct chromosomal translocations (reviews: Ladanyi 2000; Palmer et al. 2009; Schonherr et al. 2012). ALK is a receptor tyrosine kinase that is highly related to leukocyte tyrosine kinase (Morris et al. 1997). ALK was expressed in 47.1 % of cases analyzed by fine-needle aspiration cytology (Stoll and Li 2011). In a study of 73 IMTs, immunohistochemical ALK positivity was detected in 60 % of cases. In contrast, all cases of nodular fasciitis, desmoid fibromatosis, and gastrointestinal stromal tumors were ALK negative (Cook et al. 2001). Among sixteen children (age range 1–15 years), aberrant ALK expression was detected in only 18.8 % of patients (Mergan et al. 2005). In one study, ALK-negative IMTs occurred in older patients and had a greater nuclear pleomorphism, atypia, and atypical mitoses, and all metastatic IMTs were ALK-negative, suggesting that ALK negativity is an indicator of an aggressive course and metastasizing disease (Coffin et al. 2007). The significance of ALK in the biology of IMT is highlighted by the observation that the ALK inhibitor, crizotinib, has led to a sustained partial response of IMT (Butrynski et al. 2010). Another myofibroblastic neoplasm that expresses ALK with a nuclear membrane or perinuclear expression pattern is epithelioid inflammatory myofibroblastic sarcoma, a predominantly intra-abdominal variant of IMT (Mariño-Enriquez et al. 2011).

Molecular characterizations have identified ALK fusions involving tropomyosins 3 and 4 (TPM-3 and TPM-4; Lawrence et al. 2000), clathrin heavy chain (CLTC; Bridge et al. 2001), cysteinyl-tRNA synthase (CARS), and Ran-binding protein 2 genes as fusion partners. IMTs with Ran-binding protein 2 (RANBP2/Nup358) fused with ALK are rare. The N-terminal 867 residues of RANBP2 are fused to the cytoplasmic segment of ALK in the RANBP2-ALK chimeric protein, and this chimerization causes ALK to be localized to the nuclear membrane (Ma et al. 2003). RANBP2 is a large (358 kDa) nucleopore protein (nucleoporin) localized at the cytoplasmic side of the nuclear pore complex. It is mutated in familial or recurrent acute necrotizing encephalopathy (Neilson et al. 2010; Loh and Appleton 2010), and the major component of the cytoplasmic filaments of the nuclear pore complex has a critical function in capturing recycling RanGTP-importin-beta complexes at cytoplasmic fibrils to allow for adequate classical nuclear localization signal-mediated cargo import (Hamada et al. 2011). The mediation of cargo processes is also related to the association of RANBP2, through its kinesin-binding domain, with kinesin-1, and RANBP2 is a positive allosteric activator of the kin2718esin-1 system (Cho et al. 2009). The protein is involved in the distribution of SR splicing factors enriched in nuclear speckles or interchromatin granule clusters and plays a role in the speckled distribution of phosphorylated pre-mRNA processing factors (Saitoh et al. 2012). RanBP2 contains a domain that catalyzes E3 ligase activity and forms a stable complex with SUMO-modified RanGAP1 and UBC9 at the nuclear pore complex (Gareau et al. 2012).

Epstein-Barr Virus-Positive Inflammatory Pseudotumor/ Inflammatory Pseudotumor-Like Follicular Dendritic Cell Tumor

Introduction

Lesions histologically resembling inflammatory pseudotumors have been found to be infected with Epstein-Barr virus (EBV), which is thought to play a role in the pathogenesis of these lesions. 18 inflammatory pseudotumor specimens (from lymph nodes, spleen, and liver) from 17 patients were studied by in situ hybridization for EBV RNA, and EBV virus RNA expression was detected in 41.2 % of cases, including one from the liver. Two morphologically different EBV-positive cell types, spindled and round cells, were evident, whereby the EBV-positive spindled cells were present exclusively in the extranodal lesions. Part of the EBV-positive spindled cells co-expressed smooth muscle actin, while others had immunohistochemical features of follicular dendritic cells (Arber et al. 1995). The presence of EBV virus in inflammatory

pseudotumors is an interesting finding regarding the pathogenesis of these lesions and has also been found in rare smooth muscle tumors in immunosuppressed individuals (reviews: Arber et al. 1998; Deyrup 2008). Since 1995, several examples of this distinct lesion have been reported for several organs, including the spleen (Yamaguchi et al. 2000; Kutok et al. 2001; Neuhauser et al. 2001; Lewis et al. 2003; Horigichi et al. 2004; Oz Puyan et al. 2004; Kiryu et al. 2009; Rosenbaum et al. 2009). In splenic lesions, two growth patterns have been noted, viz., a cellular spindle cell pattern and a hypocellular fibrous pattern, and immunohistochemistry revealed the myofibroblastic nature of the spindle cells (Neuhauser et al. 2001). Few examples in intracranial EBV-positive inflammatory pseudotumors are reported, one originating from the trigeminal nerve (Jung et al. 2006) and another showing an intraventricular site (Nishioka et al. 2009). A second splenic lesion that has been shown to express EBV RNA is sclerosing angiomatoid nodular transformation (SANT), a lesion which is thought by some authors to represent a final stage of splenic inflammatory pseudotumor (Weinreb et al. 2007, Kashiwagi et al. 2008).

Recently, the term inflammatory pseudotumor-like follicular dendritic cell tumor (IPL-FDCT) has been proposed to denote such lesions (Cheuk et al. 2001). The authors characterized a distinctive variant of FDCT morphologically mimicking inflammatory pseudotumor based on 11 patients (10 women, 1 man). All tumors occurred in intra-abdominal sites, i.e., liver (seven cases), spleen, and peripancreatic region, and were biologically classified as a low-grade malignant neoplasm. Of the nine patients with follow-up data, six were alive and well, one developed recurrence at 9 years, and two had repeated recurrences over many years. The term has recently been employed to denote splenic lesions formerly termed inflammatory pseudotumor (Horiguchi et al. 2004; Gong et al. 2008; Kiryu et al. 2009). Another term to denote such lesions was follicular dendritic reticulum cell tumor mimicking inflammatory pseudotumor, e.g., of the spleen (Brittig et al. 2004).

Hepatobiliary EBV-Positive Inflammatory Pseudotumors

In about the same frequency as the spleen, EBV-associated inflammatory tumors/IPL-FDCTs develop in the liver. In contrast to FDCTs in extrahepatic and extrasplenic areas, hepatic FDCTs have a strong association with EBV and a stronger inflammatory component and are more prevalent in females. FDCT not associated with EBV also occurs in the liver and is discussed in a separate chapter. The first EBV-positive hepatic inflammatory pseudotumor was described in 1995 (Arber et al. 1995). In the following year, an EBV-related clonal proliferation of follicular dendritic cells was described as follicular dendritic cell tumor of the liver (Shek et al. 1996). This tumor was initially reported as a hepatic inflammatory pseudotumor, but the lesion recurred as two separate tumor masses 30 months after complete resection. Histologically, the tumor contained bland-looking spindle cells amidst a background of lymphocytes and highly pleomorphic tumor cells reactive for CD21, CD35, R4/23, and Ki-M4. Both cell populations were positive for EBV-encoded RNA by in situ hybridization. The tumor cells expressed EBV latent membrane protein (LMP1), but not EBV-encoded nuclear antigen 2/EBNA2 (Shek et al. 1996). In this case, IPL-FDCT may have developed as a neoplastic lineage from an EBV-positive inflammatory pseudotumor. Again in 1996, Selves and coworkers described an "inflammatory pseudotumor" of the liver with a spindle cell component that was shown to be derived from follicular dendritic reticulum cells (FDRC). This cell population expressed the EBV receptor CD21 and contained clonal EBV genomes and EBV RNA transcripts (EBER) and expressed EBV latent membrane protein (Selves et al. 1996). In one young male patient with a large inflammatory pseudotumor of the liver (75 mm diameter) clinically associated with high fever and malaise, only EBV LMP1 was demonstrated within the lesion (Fritzsch et al. 2004). In a 30-year-old female patient, the 6 cm-sized hepatic tumor consisted of an admixture of spindle cells, lymphocytes, plasma cells, and macrophages. The spindle cells

were arranged in a wavy pattern, were immunoreactive for CD21 and CD68, and expressed EBV-encoded nuclear RNAs, leading to the diagnosis of FDCT (Bai et al. 2006). Further reported cases from the liver were identified as IPL-FDCT (Cheuk et al. 2001).

Pathology

Macroscopically, the neoplasms have been described as solitary and fleshy lesions with areas of hemorrhage and necrosis. Histologically, spindle cells are the predominant lineage, embedded in a tissue containing an inflammatory infiltrate consisting of lymphocytes, plasma cells, and macrophages. The proportion of spindle cells to lymphoid and plasma cells is variable in different areas, a typical finding in inflammatory pseudotumors. Parts of the spindle cells are bland looking, with a slightly eosinophilic cytoplasm and inconspicuous nuclei. These cells may be confounded with fibroblasts. A significant number of spindle cells show two nuclei, suggesting features of follicular dendritic cells. Sometimes, these large binucleated cells resemble Reed-Sternberg cells. Other spindle cells are atypical, with vesicular nuclei and distinct nucleoli. The spindle cells may be arranged in the form of fascicles, and a storiform pattern may be found. Atypical large ovoid cells are also noted. Immunohistochemically, the neoplastic cells are reactive for follicular dendritic cell markers, i.e., CD21 (C3d receptor), CD35 (C3b receptor), Ki-M4P, CD23, and CNA42, but only a fraction of cells are positive for DRC1 (Selves et al. 1996; Cheuk et al. 2001). The binucleated cells with large vesicular nuclei are consistently negative for CD15 and CD30. Normal-looking and atypical spindle cells express EBV markers, including immunoreactivity for LMP1 and EBNA2, and EBV-encoded RNA is detectable with in situ hybridization. Cells bearing EBV signals were CD21-positive by double immunostaining (Selves et al. 1996). Expression of EBV markers is also seen in those lesions that do not show clear-cut follicular dendritic cell features. Oval cells were negative for CD15, CD20, CD30, ALK protein, Bcl-2, S-100 protein, EMA, CD34, and HHV-8 (Rosenbaum et al. 2009). A small population of binucleated cells show an increased proliferative activity in Ki-67 immunostains. The lymphocytes are predominantly T cells, more CD8+ than CD4+ cells, while B cells are relatively scarce. The plasma-cell population is polytypic. Numerous CD68+ macrophages are commonly present (Selves et al. 1996).

Pathogenic Pathways

There is evidence that IPL-FDCT can develop from EBV-infected cells located in a primary inflammatory pseudotumor without clear frank signs of neoplasia (Shek et al. 1996).

Calcifying Fibrous Tumor (Calcifying Fibrous Pseudotumor) of the Hepatobiliary Tract

Introduction

Calcifying fibrous tumor/pseudotumor (CFT) is a unique, benign tumor or pseudotumor that was described as a childhood lesion in 1988 (Rosenthal and Abdul-Karim 1988) and later again in 1993 by Fetsch and coworkers, who first used the term calcifying fibrous pseudotumor (Fetsch et al. 1993). CFT most commonly occurs in soft tissues of the extremities and in the pleura, with a predilection for young individuals. According to the WHO classification, the lesion is now termed calcifying fibrous tumor. It is histologically characterized by the presence of hyalinized collagen with dystrophic calcifications (sometimes with psammoma bodies) and a mixed lymphocytic and plasmacytic infiltrate, with some contribution of IgG4-positive plasma cells (Kuo et al. 2009; Agaimy et al. 2010). About 10 % of the lesions showed recurrence (Fetsch et al. 1993), and about 10 % of the patients had multiple lesions (Pinkard et al. 1996). It has been discussed whether CFT might represent a late stage of

inflammatory myofibroblastic tumor (Van Dorpe et al. 1999; Sigel et al. 2001). In addition to soft tissues, CFT can also occur in visceral organs and tissues, including lung, heart, esophagus, stomach, omentum, mesentery, small intestine, rectum, fallopian tube, and adrenal gland. CFT also occurs in the gallbladder (Mourra et al. 2004). Calcifying fibrous tumor has been observed as multiple lesions of the peritoneum (Kocova et al. 1997; Farah et al. 2007), in one situation with familial occurrence (Chen 2003). Interestingly, abdominal CFT may be associated with sclerosing angiomatoid nodular transformation of the spleen (SANT). In a study of ten cases of SANT, five cases were associated with disseminated abdominal CFT, and IgG4-positive plasma cells were found in all SANT and CTF (Kuo et al. 2009), suggesting a possible relationship with sclerosing IgG4-related systemic disease.

Whether CFT is a pseudotumor or rather a neoplastic lesion is not yet settled. Based on 15 cases, it was proposed that CFT might represent a benign mesenchymal neoplasm with a low risk of recurrence (Nascimento et al. 2002).

Calcifying Fibrous Tumor of the Liver

CFT has rarely been observed in the liver substance (Jo et al. 2011; Nobili et al. 2011). Liver involvement has been observed in a patient with multiple nodules in several organs (Azam et al. 2014). On CT images, multiple laminated and amorphous calcifications are seen. Macroscopically, the masses are well circumscribed and exhibit a hard consistence due to multiple calcifications. The nodules reveal a fibrous texture and gray-white color and can reach a diameter exceeding 10 cm. The tumor may show a hardness that does not allow insertion of a biopsy needle (Jo et al. 2011). Histologically, the tumors are usually hypocellular and mainly consist of a vascularized collagenous mass with embedded spindle cells. The multiple calcifications are either amorphous or present as psammoma-like bodies. Lymphocytes and plasma cells are predominantly found in peripheral parts of the mass and in the peritumoral tissue.

References

Abehsera M, Vilgrain V, Belghiti J, Flejou JF, Nahum H (1995) Inflammatory pseudotumor of the liver: radiologic-pathologic correlation. J Comput Assist Tomogr 19:80–83

Agaimy A, Bihl MP, Tornillo L, Wünsch PH, Hartmann A, Michal M (2010) Calcifying fibrous tumor of the stomach: clinicopathologic and molecular study of seven cases with literature review and reappraisal of histogenesis. Am J Surg Pathol 34:271–278

Aguirre-Garcia J (2004) Inflammatory pseudotumor of the liver. Ann Hepatol 3:34

Akatsu T, Wakabayashi G, Tanimoto A, Kaneyama K, Kitajima M (2006) Inflammatory pseudotumor of the liver masquerading as hepatocellular carcinoma after a hepatitis B virus infection: report of a case. Surg Today 36:1028–1031

Alfieri R, Alaggio R, Ruol A, Castoro C, Cagol M, Michieletto S, Pomerri F, Acquaviva A, Ancona E (2008) Hepatogastric inflammatory pseudotumor presumably deriving from prior amebic infection. Tumori 94:585–588

Alimoglu O, Sahin M, Eryilmaz R, Turgut H, Kurtulmus N, Igci A (2005) Inflammatory pseudotumour of the liver presenting with obstructive jaundice. Acta Chir Belg 105:309–312

Al-Jabri T, Sanjay P, Shaikh I, Woodward A (2010) Inflammatory myofibroblastic pseudotumor of the liver in association with gall stones – a rare case report and brief review. Diagn Pathol 5:53

Alonso EM, Zdunek TM, Brown MR, Yousefzadeh DK, Whitington PF (1991) Fibroinflammatory tumor of the liver causing biliary cirrhosis in an infant. J Pediatr Gastroenterol Nutr 12:283–287

Amankonah TD, Strom CB, Vierling JM, Petrovic LM (2001) Inflammatory pseudotumor of the liver as the first manifestation of Crohn's disease. Am J Gastroenterol 96:2520–2522

Andreola S, Cattoretti G, Lombardi L, Audisio RA, Regalia E, Bosch JP, Mazzaferro V, Doci R (1990) Inflammatory pseudotumor of the liver: report of two cases. Tumori 76:517–523

Anthony PP (1993) Inflammatory pseudotumor (plasma cell granuloma) of lung, liver and other organs. Histopathology 23:501–503

Anthony PP, Telesinghe PU (1986) Inflammatory pseudotumor of the liver. J Clin Pathol 39:761–768

Arber DA, Kamel OW, van de Rijn M, Davis RE, Medeiros LJ, Jaffe ES, Weiss LM (1995) Frequent presence of the Epstein-Barr virus in inflammatory pseudotumor. Hum Pathol 26:1093–1098

Arber DA, Weiss LM, Chang KL (1998) Detection of Epstein-Barr virus in inflammatory pseudotumor. Semin Diagn Pathol 15:155–160

Ashcroft MW, Ng CS, Frost RA, Freeman AH (2009) Biliary inflammatory pseudotumor: report of two cases and review of the literature. Clin Radiol 64:449–455

Azam F, Chatterjee M, Kelly S, Pinto M, Aurangabadkar A, Latif MF, Marshall E (2014) Multifocal calcifying fibrous tumor at six sites in one patient: a case report. World J Surg Oncol 12:235

Bai LY, Kwang WK, Chiang IP, Chen PM (2006) Follicular dendritic cell tumor of the liver associated with Epstein-Barr virus. Jpn J Clin Oncol 36:249–253

Bankole-Sinni R, Coulibaly B, Denoulet D, Nandiolo R, Mobiot L et al (1997) Inflammatory pseudotumor of the liver in a child: case report. Med trop (Mars) 57:269–272

Beauchamp A, Villanueva A, Feliciano W, Reymunde A (2011) Inflammatory myofibroblastic tumor of the liver in an elderly woman following a second liver biopsy: a case report. Bol Asoc Med P R 103:60–64

Bernard M, Marie I, Riachi G, Goria O, Lerebours E, François A, Levesque H, Michel P (2005) Inflammatory pseudotumor of the liver revealing gynecological Corynebacterium infection. Scand J Gastroenterol 40:875–877

Biecker E, Zimmermann A, Dufour JF (2003) Spontaneous regression of an inflammatory pseudotumor of the liver. Z Gastroenterol 41:991–994

Birch-Hirschfeld A (1930) Die Krankheiten der Orbita, part 1. In: Graefe A, Saemisch T (eds) Handbuch der gesamten Augenheilkunde, vol 9. Springer, Berlin, pp 111–130

Bolla G, Stracca Pansa V, Cimaglia ML, Spata F, Guarise P (1988) Inflammatory pseudotumor as a cause of obstructive jaundice. Report of a case in a child (in Italian). Pediatr Med Chir 10:523–525

Borgonovo G, Razzetta F, Varaldo E, Cittadini G, Ceppa P, Torre GC, Mattioli F (1998) Pseudotumor of the liver: a challenging diagnosis. Hepatogastroenterology 45:1770–1773

Brage-Varela A, Estévez-Boullosa P, Pombo-Otero J, Blanco-Rodriguez M, Lago-Novoa M et al (2010) Multifocal hepatic inflammatory pseudotumor: spontaneous regression in a diabetic patient. Rev Esp Enferm Dig 102:507–509

Bridge JA, Kanamori M, Ma Z, Pickering D, Hill DA, Lydiatt W, Lui MY, Colleoni GW et al (2001) Fusion of the ALK gene to the clathrin heavy chain gene, CLTC, in inflammatory myofibroblastic tumor. Am J Pathol 159:411–415

Brittig F, Aitay E, Jakso P, Kelényi G (2004) Follicular dendritic reticulum cell tumor mimicking inflammatory pseudotumor of the spleen. Pathol Oncol Res 10:57–60

Bruyeer E, Ramboer K (2010) Multiple inflammatory pseudotumors of the liver and spleen. JBR-BTR 93:122–123

Butrynski JE, D'Adamo DR, Hornick JL, Dal CP, Antonescu CR, Jhanwar SC et al (2010) Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med 363:1727–1733

Casassus-Builhe D, Le Bougeant P, Carmois T, Terrier F, Chauveau E, Armand JP, Oddes B (2002) Hepatic inflammatory pseudotumor regressing with antibiotic therapy (in French). Presse Med 31:838–840

Chen KT (1984) Inflammatory pseudotumor of the liver. Hum Pathol 15:694–696

Chen KT (2003) Familial peritoneal multifocal calcifying fibrous tumor. Am J Clin Pathol 119:811–815

Chen ST, Lee JC (2008) An inflammatory myofibroblastic tumor in liver with ALK and RNABP2 gene rearrangement: combination of distinct morphologic, immunohistochemical, and genetic features. Hum Pathol 39:1854–1858

Chen HW, Lai EC, Huang XJ, Chen FN, Lu RL, Pan AZ, Lau WY (2008) Inflammatory myofibroblastic tumours of the spleen and liver. Asian J Surg 31:25–28

Cheuk W, Chan JK, Shek TW, Chang JH, Tsou MH, Yuen NW, Ng WF, Chan AC et al (2001) Inflammatory pseudotumor-like follicular dendritic cell tumor: a distinctive low-grade malignant intra-abdominal neoplasm with consistent Epstein-Barr virus association. Am J Surg Pathol 25:721–731

Cho KI, Yi H, Desai R, Hand AR, Haas AL, Ferreira PA (2009) RANBP2 is an allosteric activator of the conventional kinesin-1 motor protein, KIF5B, in a minimal cell-free system. EMBO Rep 10:480–486

Chong A, Jeong SY, Min JJ (2009) Inflammatory pseudotumours resembling multiple hepatic metastases and their complete regression, as revealed by 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging 36:1199–1200

Coco DP, Hirsch MS, Hornick JL (2009) Smoothelin is a specific marker for smooth muscle neoplasms of the gastrointestinal tract. Am J Surg Pathol 33:1795–1801

Coffin CM, Watterson J, Priest JR, Dehner LP (1995) Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor): a clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol 19:859–872

Coffin CM, Humphrey PA, Dehner LP (1998) Extrapulmonary inflammatory myofibroblastic tumor: a clinical and pathological survey. Semin Diagn Pathol 15:85–101

Coffin CM, Hornick JL, Fletcher CD (2007) Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J Surg Pathol 31:509–520

Cohen M, Huminer D, Salamon F, Cohen M, Tur-Kaspa R (2005) Inflammatory pseudotumor of the liver: a therapeutic dilemma. Isr Med Assoc J 7:472–473

Colakoglu O, Unsal B, Haciyanli M, Tunakan M, Buyrac Z, Yorukoglu G, Yazicioglu N, Genc H (2005) A successfully managed inflammatory pseudotumor of liver without surgery: report of a case. Acta Gastroenterol Belg 68:382–384

Coleman M, Rees M (1999) Inflammatory pseudotumort of the liver: a rare complication of diverticulitis? Hosp Med 60:606

Collina G, Baruzzi G, Eusebi V (1987) Inflammatory pseudotumor of the liver: report of two cases. Tumori 73:407–412

Cook JR, Dehner LP, Collins MH, Ma Z, Morris SW, Coffin CM, Hill DA (2001) Anaplastic lymphoma

kinase (ALK) expression in the inflammatory myofibroblastic tumor: a comparative immunohistochemical study. Am J Surg Pathol 25:1364–1371

Craig JR (1997) Pseudoneoplastic lesions of the liver and the biliary tree. In: Wick MR, Humphrey PA, Ritter JH (eds) Pathology of pseudoneoplastic lesions. Lippincott-Raven, Philadelphia, pp 157–182

Czauderna P, Sznurkowska K, Korzon M, Roszkiewicz A, Stoba C (1999) Association of inflammatory pseudotumor of the liver and Papillon-Lefevre syndrome – a case report. Eur J Pediatr Surg 9:343–346

Dehner LP (2004) Inflammatory myofibroblastic tumor: the continued definition of one type of so-called inflammatory pseudotumor. Am J Surg Pathol 28:1652–1654

Del Fabbro D, Torzilli G, Gambetti A, Leoni P, Gendarini A, Olivari N (2004) Liver inflammatory pseudotumor due to an intrahepatic wooden toothpick. J Hepatol 41:498

Deng FT, Li YX, Ye L, Tong L, Yang XP, Chai XQ (2010) Hilar inflammatory pseudotumor mimicking hilar cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 9:219–221

Deyrup AT (2008) Epstein-Barr virus-associated epithelial and mesenchymal neoplasms. Hum Pathol 39:473–483

Diaz-Torné C, Narvaez J, De Lama E, Diez-Garcia M, Narvaez JA, Bernad B, Llatios R, Nolla JM et al (2007) Inflammatory pseudotumor of the liver associated with rheumatoid arthritis. Arthritis Rheum 57:1102–1106

Druez P, Cornet P, Rahier J, Horsmans Y (2005) Spontaneous regression of inflammatory pseudotumor of the liver: a case report. Acta Gastroenterol Belg 68:101–103

Ernst CW, Van Der Werff Ten Bosch J, Desprechins B, de Mey J, De Maesener M (2011) Malignant transformation of an abdominal inflammatory myofibroblastic tumor with distant metastases in a child. JBR-BTR 94:78–80

Farah RB, Dimet S, Bidault AT, benbraheim C, Ndiaye N, Lazure T, Gayral F, Buffet C et al (2007) Multiple peritoneal calcifying fibrous tumors revealed by ischemic colitis. Ann Diagn Pathol 11:460–463

Faraj W, Ajouz H, Mukherji D, Kealy G, Shamseddine A, Khalife M (2011) Inflammatory pseudo-tumor of the liver: a rare pathological entity. World J Surg Oncol 9:5

Feng YQ (1991) Hepatic inflammatory pseudotumor. A report of 5 cases (in Chinese). Zhonghua Wai Ke Za Zhi 29:101–103

Fetsch JF, Montgomery EA, Meis JM (1993) Calcifying fibrous pseudotumor. Am J Surg Pathol 17:502–508

Flisak ME, Budris DM, Olson MC, Zarling EJ (1994) Inflammatory pseudotumor of the liver: appearance on MRI. Clin Imaging 18:1–3

Fritzsch J, Richter M, Edelmann C, Lange R, Tannapfel A (2004) 35-year-old male with fever and round mass of the liver (in German). Internist (Berl) 45:713–716

Fukushima N, Suzuki M, Abe T, Fukayama M (1997) A case of inflammatory pseudotumour of the common bile duct. Virchows Arch 431:219–224

Fukuya T, Honda H, Matsumata T, Kawanami T, Shimada Y, Muranaka Y, Hayashi T, Maeda T et al (1994) Diagnosis of inflammatory pseudotumor of the liver: value of CT. AJR Am J Roentgenol 163:1087–1091

Ganesan K, Viamonte B, Peterson M, Kono Y, Santillan C, Middleton M, Sirlin C (2009) Capsular retraction: an uncommon imaging finding in hepatic inflammatory pseudotumour. Br J Radiol 82:e256–e260

Gareau JR, Reverter D, Lima CD (2012) Determinants of small ubiquitin-like modifier 1 (SUMO1) protein specificity, E3 ligase, and SUMO-RanGAP1 binding activities of nucleoporin RanBP2. J Biol Chem 287:4740–4751

Geramizadeh B, Tahamtan MR, Bahador A, Sefidbakht S, Modjalai M, Nabai S, Hosseini SA (2009) Inflammatory pseudotumor of the liver: two case reports and a review of the literature. Indian J Pathol Microbiol 52:210–212

Gleason BC, Hornick JL (2008) Inflammatory myofibroblastic tumours: where are we now? J Clin Pathol 61:428–437

Gluszek S, Kot M, Czerwaty M (1999) Inflammatory pseudotumor of the liver treated surgically. Hepatogastroenterology 46:2959–2960

Gohy S, Hubert C, Deprez P, Van beers BE, Annet L, Lhommel R, Sempoux C, Jean-François G (2007) Benign biliary inflammatory pseudotumor mimicking a Klatskin tumor. Hepatogastroenterology 54:1348–1352

Goldsmith PJ, Loganathan A, Jacob M, Ahmad N, Toogood GJ, Lodge JP, Prasad KR (2009) Inflammatory pseudotumours of the liver: a spectrum of presentation and management options. Eur J Surg Oncol 35:1295–1298

Gollapudi P, Chejfec G, Zarling EJ (1992) Spontaneous regression of hepatic pseudotumor. Am J Gastroenterol 87:214–217

Gong QX, Fan QH, Zhou ZH, Yu MN, Wang Z, Wang C, Zhang WM (2008) Inflammatory pseudotumor-like follicular dendritic cell tumor of spleen (in Chinese). Zhonghua Bing Li Xue Za Zhi 37:40–44

Gosavi A, Agashe S, Phansopkar M, Jadhav SS, Agrawal BR (1997) Inflammatory pseudotumor of liver: a case report. Indian J Pathol Microbiol 40:81–83

Gough J, Chakrabarti S (1993) Inflammatory pseudotumor of the liver in a patient with chronic sclerosing cholangitis. Am J Gastroenterol 88:1452–1453

Griffin CA, Hawkins AL, Dvorak C, Henkle C, Ellingham T, Perlman EJ (1999) Recurrent involvement of 2p23 in inflammatory myofibroblastic tumors. Cancer Res 59:2776–2780

Grouls V (1987) Pseudolymphoma (inflammatory pseudotumor) of the liver. Zentralbl Allg Pathol 133:565–568

Haith EE, Kepes JJ, Holder TM (1964) Inflammatory pseudotumor involving the common bile duct of a six-year old boy: successful pancreaticoduodenectomy. Surgery 56:436–441

Hamada M, Haeger A, Jeganathan KB, van Ree JH, Malureanu L, Wälde S, Joseph J et al (2011) Ran-dependent docking of importin-beta to RanBP2/Nup358 filaments is essential for protein import and cell viability. J Cell Biol 194:597–612

Hasan W, Sheehan KM, Ridgway PF, Traynor O (2011) Inflammatory pseudotumors of the liver – role of dynamic MRI scan and surgical exploration. Ir Med J 104:58

Hata Y, Sasaki F, Matuoka S, Hamada H, Taguchi K, Hasumi T, Manabe K, Uchino J, Nojima T, Hujioka Y et al (1992) Inflammatory pseudotumor of the liver in children: report of cases and review of the literature. J Pediatr Surg 27:1549–1552

Heneghan MA, Kaplan CG, Priebe CJ, Partin JS (1984) Inflammatory pseudotumor of the liver: a rare cause of obstructive jaundice and portal hypertension in a child. Pediatr Radiol 14:433–435

Herek D, Karabulut N (2011) Education and imaging Hepatobiliary and pancreatic: inflammatory pseudotumors of the liver. J Gastroenterol Hepatol 26:1217

Hertzer NR, Hawk WA, Hermann RE (1971) Inflammatory lesions of the liver which simulate tumor: report of two cases in children. Surgery 69:839–846

Hirasawa R, Shimohara Y, Yabe H, Tobita A, Kataoka H, Okada K, Ito H, Miyake M (1988) A case of inflammatory pseudotumor of the liver (in Japanese). Nippon Naika Gakkai Zasshi 77:1710–1714

Hoosein MM, Tapuria N, Standish RA, Koti RS, Webster GJ, Millar AD, Davidson BR (2007) Inflammatory pseudotumor of the liver: the residuum of biliary cystadenoma? Eur J Gastroenterol Hepatol 19:333–336

Horiguchi H, Matsui-Horiguchi M, Sakata H, Ichinose M, Yamamoto T, Fujiwara M et al (2004) Inflammatory pseudotumor-like follicular dendritic cell tumor of the spleen. Pathol Int 54:124–131

Horiuchi R, Uchida T, Kojima T, Shikata T (1990) Inflammatory pseudotumor of the liver. Clinicopathologic study and review of the literature. Cancer 65:1583–1590

Hosler GA, Steinberg DM, Sheth S, Hamper UM, Erozan YS, Ali SZ (2004) Inflammatory pseudotumor: a diagnostic dilemma in cytopathology. Diagn Cytopathol 31:267–270

Hosokawa A, Takahashi H, Akaike J, Okuda H, Murakami R, Kawahito Y, Tokuno T, Makiguchi Y, Sakamoto H, Hinoda Y, Imai K (1998) A case of Sjogren's syndrome associated with inflammatory pseudotumor of the liver (in Japanese). Nihon Rinsho Meneki Gakkai Kaishi 21:226–233

Hsiao CC, Chen CL, Eng HL (1999) Inflammatory pseudotumor of the liver in Kostmann's disease. Pediatr Surg Int 15:266–269

Hussong JW, Brown M, Perkins SL, Dehner LP, Coffin CM (1999) Comparison of DNA ploidy, histologic, and immunohistochemical findings with clinical outcome in inflammatory myofibroblastic tumors. Mod Pathol 12:279–286

Ikeda H, Oka T, Imafuku I, Yamada S, Yamada H, Fujiwara K, Hirata M, Idezuki Y et al (1990) A case of inflammatory pseudotumour of the gallbladder and bile duct. Am J Gastroenterol 85:203–206

Imafuku K, Ikeda H, Yamada M, Yamada H, Aizawa C, Fujiwara K, Oka H, Oka T (1990) A case of obstructive jaundice due to inflammatory pseudotumor-like granuloma (in Japanese). Nippon Naika Gakkai Zasshi 79:533–534

Imazato M, Isobe Y, Ueno E (1990) Inflammatory pseudotumor of the liver. AJR Am J Roentgenol 154:201

Inaba K, Suzuki S, Yokoi Y, Ota S, Nakamura T, Konno H, Baba S, Takehara Y, Nakamura S (2003) Hepatic inflammatory pseudotumor mimicking intrahepatic cholangiocarcinoma: report of a case. Surg Today 33:714–717

Irie H, Muranaka T, Nanjo T, Hanada K, Oshiumi Y (1989) Inflammatory pseudotumor of the liver. Radiat Med 7:217–219

Ishida H, Tatsuta M, Furukawa H, Ohta H, Hashimoto K, Hayashi N, Morimoto O, Ikeda M, Miya A, Masutani S, Kawasaki T, Satomi T, Yoshioka H, Hanai J (2000) Multiple inflammatory pseudotumors mimicking liver metastasis from colon cancer: report of a case. Surg Today 30:530–533

Isobe H, Nishi Y, Fukutomi T, Iwamoto H, Nakamuta M, Sakai H, Andoh B, Sakamoto S, Nawata H (1991) Inflammatory pseudotumor of the liver associated with acute myelomonocytic leukemia. Am J Gastroenterol 86:238–240

Jackson RB, Gatling RR (1991) Inflammatory pseudotumor of the liver. Surgery 109:329–332

Jais P, Berger JF, Vissuzaine C, Paramelle O, Clays-Schouman E, Potet F, Mignon M (1995) Regression of inflammatory pseudotumor of the liver under conservative therapy. Dig Dis Sci 40:752–756

Jakab F, Sugar I, Sagi S, Mezei L, Horvath G, Faller J (1990) Inflammatory pseudotumor of the liver. Acta Chir Hung 31:239–245

Jerraya H, Jarboui S, Daghmoura H, Zaouche A (2011) A new case of spontaneous regression of inflammatory hepatic pseudotumor. Case Rep Med 2011: 139125

Jimenez-Mejias ME, Ferrer T, Fernandez-Alonso J, Bernardo A, leon J, Alarcon A (1989) Inflammatory pseudotumor of the liver (in Spanish). Rev Esp Enferm Apar Dig 76:177–180

Jo BJ, Yoon SW, Ahn HJ, Kwon SW (2011) Imaging finding of calcifying fibrous tumour of the liver. Br J Radiol 84:e31–e34

Joh S, Nishimura H, Matsumoto S, Koganemaru M, Ohtake H, Kenmochi K, Nakayama K (1988) A case of inflammatory pseudotumor of the liver (in Japanese). Rinsho Hoshasen 33:1039–1042

Jover Diaz F, Martin Gonzalez C, Mayol belda MJ, Cuadrado Pastor JM (2009) Multiple inflammatory pseudotumors and *Enterococcus durans* bacteraemia (in Spanish). Gastroenterol Hepatol 32:97–100

Jung TY, Jung S, Lee MC, Moon KS, Kim IY, Kang SS, Kim SH (2006) Hemorrhagic intracranial inflammatory pseudotumor originating from the trigeminal nerve: a case report. J Neurooncol 76:139–142

Kafeel G, Telesinghe PU (1997) Inflammatory pseudotumor of the liver. J Clin Pathol 50:352–353

Kai K, Matsuyama S, Ohtsuka T, Kitahara K, Mori D, Miyazaki K (2007) Multiple inflammatory pseudotumor of the liver, mimicking cholangiocarcinoma with tumor embolus in the hepatic vein: report of a case. Surg Today 37:530–533

Kaneko T, Mitari Y, Watasugi K et al (1984) A case of inflammatory pseudotumor of the liver. Jpn Soc Pediatr Surg 20:167–171

Kaneko K, Ando H, Watanabe Y, Seo T, Nagino M, Kamiya J, Nimura Y (2001) Aggressive preoperative management and extended surgery for inflammatory pseudotumor involving the hepatic hilum in a child. Surgery 129:757–760

Kashiwagi S, Kumasaka T, Bunsei N, Fukumura Y, Yamasaki S, Abe K, Mitani K et al (2008) Detection of Epstein-Barr virus-encoded small RNA-expressed myofibroblasts and IgG4-producing plasma cells in sclerosing angiomatoid nodular transformation of the spleen. Virchows Arch 453:275–282

Kato H, Kanematsu M, Kondo H, Osada S, Goshima S, Yamada T, Yamada Y, Yokoyama R et al (2004) Inflammatory pseudotumor of the liver: ferumoxide-enhanced MR imaging as a tiebreaker. J Magn Reson Imaging 20:501–505

Kawaguchi T, Mochizuki K, Kizu T, Miyazaki M, Yakushijin T, Tsutsui S, Morii E, Takehara T (2012) Inflammatory pseudotumor of the liver and spleen diagnosed by percutaneous needle biopsy. World J Gastroenterol 18:90–95

Kawamura E, Habu D, Tsushima H, Torii K, Kawabe J, Ohsawa M, Shiomi S (2006) A case of hepatic inflammatory pseudotumor identified by FDG-PET. Ann Nucl Med 20:321–323

Kelekis NL, Warshauer DM, Semelka RC, Eisenberg LB, Woosley JT (1995) Inflammatory pseudotumor of the liver: appearance on contrast enhanced helical CT and dynamic MR images. J Magn Reson Imaging 5:551–553

Kessler E, Turani H, Kayser S, Bar-Ziv J, Chaimoff C (1988) Inflammatory pseudotumor of the liver. Liver 8:17–23

Kim SR, Hayashi Y, Kudo M, Matsuoka T, Imoto S, Sasaki K, Shintani S, Song KB, Park SY, Kim JH, Ando K, Koterazawa T, Kim KI, Ninomiya T (1999) Inflammatory pseudotumor of the liver in a patient with chronic hepatitis C: difficulty in differentiating it from hepatocellular carcinoma. Pathol Int 49:726–730

Kim YW, Lee JG, Kim KS, Yoon DS, Lee WJ, Kim BR, Shin EA, Park YN, Choi JS (2006) Inflammatory pseudotumor of the liver treated by hepatic resection: a case report. Yonsei Med J 47:140–143

Kim BS, Joo SH, Kim GY, Joo KR (2011) Aggressive hilar inflammatory myofibroblastic tumor with hilar bile duct carcinoma in situ. J Korean Surg Soc 81(Suppl 1):S59–S63

Kiryu S, Takeuchi K, Shibahara J, Uozaki H, Fukayama M, Maeda E, Akahane M, Ohtomo K (2009) Epstein-Barr virus-positive inflammatory pseudotumour and inflammatory pseudotumour-like follicular dendritic cell tumor. Br J Radiol 82:e67–e71

Kocova L, Michal M, Sulc M, Zamecnik M (1997) Calcifying fibrous pseudotumour of visceral peritoneum. Histopathology 31:182–184

Koea JB, Broadhusrt GW, Rodgers MS, McCall SL (2003) Inflammatory pseudotumor of the liver: demographic, diagnosis and the case for nonoperative management. J Am Coll Surg 196:226–235

Koide H, Sato K, Fukusato T, Kashiwabara K, Sunaga N, Tsuchiya T, Morino S, Sohara N et al (2006) Spontaneous regression of hepatic inflammatory pseudotumor with primary biliary cirrhosis: case report and literature review. World J Gastroenterol 12:1645–1648

Kuhara N, Yokogawa Y, Dohmen K, Arase K, Nakamura H, Asayama R, Kato M, Nakagaki M, Nojiri I, Takahashi M et al (1994) Occurrence of inflammatory pseudotumor of the liver after the operation for congenital common bile duct dilatation complicated with gallbladder cancer (in Japanese). Nippon Shokakibyo Gakkai Zasshi 91:2009–2015

Kuo TT, Chen TC, Lee LY (2009) Sclerosing angiomatoid nodular transformation of the spleen (SANT): clinicopathological study of 10 cases with or without abdominal disseminated calcifying fibrous tumors, and the presence of a significant number of IgG4+ plasma cells. Pathol Int 59:844–850

Kutok JL, Pinkus GS, Dorfman DM, Fletcher CD (2001) Inflammatory pseudotumor of lymph node and spleen: an entity biologically distinct from inflammatory myofibroblastic tumor. Hum Pathol 32:1382–1387

Lacaille F, Fournet JC, Sayegh N, Jaubert F, Revillon Y (1999) Inflammatory pseudotumor of the liver: a rare benign tumor mimicking a malignancy. Liver Transpl Surg 5:83–85

Ladanyi M (2000) Aberrant ALK tyrosine kinase signaling. Different cellular lineages, common oncogenic mechanisms. Am J Pathol 157:341–345

Lawrence B, Perez-Atayde A, Hibbard MK, Rubin BP, Dal CP, Pinkus JL, Pinkus GS et al (2000) TPM3-ALK and TMP4-ALK oncogenes in inflammatory myofibroblastic tumors. Am J Pathol 157:377–384

Lee SL, DuBois JJ (2001) Hepatic inflammatory pseudotumor: case report, review of the literature, and a proposal for morphologic classification. Pediatr Surg Int 17:555–559

Lee SC, Lee CS, Lee CY (1987) Inflammatory pseudotumor of the liver: a case report. Korean J Gastrointest Endosc 7:87–89

Lee SH, Kim SH, Lee JY, Kim SJ, Kim MA, Han JK, Choi BI (2009) Inflammatory myofibroblastic tumor: a possible complication of percutaneous radiofrequency ablation for hepatocellular carcinoma. Korean J Radiol 10:635–640

Leese T, Neoptolemos JP, West KP, Talbot IC, Carr-Locke DL (1986) Tumours and pseudotumours of the region of the ampulla of Vater: an endoscopic, clinical and pathological study. Gut 27:1186–1192

Levitt MD, Rode J, Russell RC (1988) Inflammatory pseudotumor of the liver. Aust NZ J Surg 58:743–745

Levy S, Sauvanet A, Diebold MD, Marcus C, Da Costa N, Thiefin G (2001) Spontaneous regression of an inflammatory pseudotumor of the liver presenting as an obstructing malignant biliary tumor. Gastrointest Endosc 53:371–374

Lewis JT, Gaffney RL, Casey MB, Farrell MA, Morice WG, Macon WR (2003) Inflammatory pseudotumor of the spleen associated with a clonal Epstein-Barr virus genome. Case report and review of the literature. Am J Clin Pathol 120:56–61

Li GH, Li JQ, Lin YZ (1989) Inflammatory pseudotumor of the liver. J Surg Oncol 42:244–248

Lim JH, Lee JH (1995) Inflammatory pseudotumor of the liver: ultrasound and CT features. Clin Imaging 19:43–46

Lo OS, Poon RT, Lam CM, Fan ST (2004) Inflammatory pseudotumor of the liver in association with a gastrointestinal stromal tumor: a case report. World J Gastroenterol 10:1841–1843

Locke JE, Choti MA, Torbenson MS, Horton KM, Molmenti EP (2005) Inflammatory pseudotumor of the liver. J Hepatobiliary Pancreat Surg 12:314–316

Loh NR, Appleton DB (2010) Untreated recurrent acute necrotising encephalopathy associated with RANBP2 mutation, and normal outcome in a Caucasian boy. Eur J Pediatr 169:1299–1302

Lopez JI (1992) Inflammatory pseudotumor of the liver. J Clin Gastroenterol 14:274

Lopez JI, Eizaguirre B, Nevado M, Ruiz-Jaureguizuria JC (1990) Inflammatory pseudotumor of the liver. Report of a case and literature review. APMIS 98:1022–1026

Lupovitch A, Chen R, Mishra S (1989) Inflammatory pseudotumor of the liver. Report of the fine needle aspiration cytologic findings in a case of initially misdiagnosed as malignant. Acta Cytol 33:259–262

Lykavieris P, Fabre M, Waguet J, Bernard O (2000) Inflammatory pseudotumor after liver transplantation. J Pediatr Gastroenterol Nutr 31:309–312

Lyons TJ, Benbow EW, Taylor PM, McCloy RF (1993) Inflammatory pseudotumor of the liver: antecedent causes and clinical experience. J Hepatol 19:273–278

Ma Z, Hill DA, Collins MH, Morris SW, Sumegi J, Zhou M, Zuppan C, Bridge JA (2003) Fusion of ALK to the Ran-binding protein 2 (RANBP2) gene in inflammatory myofibroblastic tumor. Genes Chromosomes Cancer 37:98–105

Maeng YH, Park JH, Kim YW, Park YK, Lee JH, Yang MH (1994) Inflammatory pseudotumor of the liver: a case report. Korean J Pathol 28:90–92

Maiga MY, Dembele M, Sissoko F, Sidine S, Kane M, Trarore HA, Koumare AK (2003) Inflammatory pseudotumor of the liver (in French). Ann Chir 128:273–274

Mangiante GL, Colombari R, Portuese A, Bortolasi L, Marinello P, Colucci G, Montresor E, Serio GE (1997) Inflammatory pseudotumor of the liver: case report and review of the literature. G Chir 18:417–420

Manolaki N, Vaos G, Zavras N, Sbokou D, Michael C, Syriooulou V (2009) Inflammatory myofibroblastic tumor of the liver due to *Mycobacterium tuberculosis* in an immunocompetent girl. Pediatr Surg Int 25:451–454

Mariño-Enriquez A, Wang WL, Roy A, Lopez-Terrada D, Lazar AJ, Fletcher CD, Coffin CM, Hornick JL (2011) Epithelioid inflammatory myofibroblastic sarcoma: an aggressive intra-abdominal variant of inflammatory myofibroblastic tumor with nuclear membrane or perinuclear ALK. Am J Surg Pathol 35:135–144

Materne R, Van Beers BE, Gigot JF, Horsmans Y, Lacrosse M, Pringot J (1998) Inflammatory pseudotumor of the liver: MRI with mangafodipir trisodium. J Comput Assist Tomogr 22:82–84

Maze GL, Lee M, Schenker S (1999) Inflammatory pseudotumor of the liver and pregnancy. Am J Gastroenterol 94:529–530

Mergan F, Jaubert F, Sauvat F, Hartmann O, Lortat-Jacob S, Révillon Y, Nihoul-Fékété C et al (2005) Inflammatory myofibroblastic tumor in children: clinical review with anaplastic lymphoma kinase, Epstein-Barr virus, and human herpes virus 8 detection analysis. J Pediatr Surg 40:1581–1586

Milias K, Madhavan KK, Bellamy C, Garden OJ, Parks RW (2009) Inflammatory pseudotumors of the liver: experience of a specialist surgical unit. J Gastroenterol Hepatol 24:1562–1566

Montani M, Thiesler T, Kristiansen G (2010) Smoothelin is a specific and robust marker for distinction of muscularis propria and muscularis mucosae in the gastrointestinal tract. Histopathology 57:244–249

Morita Y, Choji K, Fujita N, Uchino J, Nojima T, Manabe K (1987) A case of inflammatory pseudotumor of the liver (in Japanese). Rinsho Hoshasen 32:537–540

Morris SW, Naeve C, Mathew P, James PL, Kirstein MN, Cui X, Witte DP (1997) ALK, the chromosome 2 gene locus altered by the t(2;5) in non-Hodgkin's lymphoma, encodes a novel neural receptor tyrosine kinase that is highly related to leukocyte tyrosine kinase (LTK). Oncogene 14:2175–2188

Mortele KJ, Wiesner W, de Hemptinne B, Elewaut A, Preat M, Ros PR (2002) Multifocal inflammatory pseudotumor of the liver: dynamic gadolinium-enhanced, ferumoxides-enhanced, and mangafodipir trisodium – enhanced MR imaging findings. Eur Radiol 12:304–308

Mouelhi L, Abbes L, Houissa F, Debbeche R, Mekki H, Rejeb MB, Trabelsi S, Salem M, Najjar T (2009) Inflammatory pseudotumor of the liver associated with Crohn's disease. J Crohns Colitis 3:305–308

Mourra N, Bell S, Parc R, Fléjou JF (2004) Calcifying fibrous pseudotumour: first case report in the gallbladder. Histopathology 44:84–86

Nakama T, Hayashi K, Komada N, Ochiai T, Hori T, Shioiri S, Tsubouchi H (2000) Inflammatory pseudotumor of the liver diagnosed by needle liver biopsy under ultrasonographic tomography guidance. J Gastroenterol 35:641–645

Nakanuma Y, Tsuneyama K, Masuda S, Tomioka T (1994) Hepatic inflammatory pseudotumor associated with chronic cholangitis: report of three cases. Hum Pathol 25:86–91

Nam KJ, Kang HK, Lim JH (1996) Inflammatory pseudotumor of the liver: CT and sonographic findings. AJR Am J Roentgenol 167:485–487

Nam YH, Lee SK, Sammut D, Davies DE, Howarth PH (2012) Preliminary study of the cellular characteristics of primary bronchial fibroblasts in patients with asthma: expression of alpha-smooth muscle actin, fibronectin containing extra type III domain A, and smoothelin. J Investig Allergol Clin Immunol 22:20–27

Nascimento AF, Ruiz R, Hornick JL, Fletcher CDM (2002) Calcifying fibrous "pseudotumor": clinicopathologic study of 15 cases and analysis of its relationship to inflammatory myofibroblastic tumor. Int J Surg Pathol 10:189–196

Neilson DE, Adams MD, Orr CM, Schelling DK, Eiben RM, Kerr DS, Anderson J et al (2010) Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. Am J Hum Genet 84:44–51

Neuhauser TS, Derringer GA, Thompson LD, Fanburg-Smith JC, Aguilera NS, Andriko J et al (2001) Splenic inflammatory myofibroblastic tumor (inflammatory pseudotumor): a clinicopathologic and immunophenotypic study of 12 cases. Arch Pathol Lab Med 125:379–385

Newbould MJ, Kelsey A, Lendon M, Gururangan S (1992) Inflammatory pseudotumor of the liver masquerading as a metastasis in a child treated for nephroblastoma. Med Pediatr Oncol 20:172–175

Nishimura R, Mogami H, Teramoto N, Tanada M, Kurita A (2005) Inflammatory pseudotumor of the liver in a patient with early gastric cancer: CT-histopathological correlation. Jpn J Clin Oncol 35:218–220

Nishioka H, Shibuya M, Nakajima S, Ohno S, Ikeda Y (2009) A case of an intraventricular inflammatory pseudotumor presumably caused by Epstein-Barr virus infection. Surg Neurol 71:685–688

Nobili C, Rosso E, Oussoultzoglou E, Casnedi S, Jaeck D, Bachellier P (2011) Image of the month. hepatic calcifying fibrous pseudotumor. Arch Surg 146:237–238

Noi I, Loberant N, Cohen I (1994) Inflammatory pseudotumor of the liver. Clin Imaging 18:283–285

Nonaka D, Birbe R, Rosai J (2005) So-called inflammatory myofibroblastic tumour: a proliferative lesion of fibroblastic reticulum cells? Histopathology 46:604–613

Nonomura A, Minato H, Shimizu K, Kadoya M, Matsui O (1997) Hepatic hilar inflammatory pseudotumor mimicking cholangiocarcinoma with cholangitis and phlebitis – a variant of primary sclerosing cholangitis? Pathol Res Pract 193:519–525

Ntinas A, Kardassis D, Miliaras D, Tsinoglou K, Dimitriades A, Vrochides D (2011) Inflammatory pseudotumor of the liver: a case report and review of the literature. J Med Case Reports 5:196

Ogawa T, Yokoi H, Kawarada Y (1998) A case of inflammatory pseudotumor of the liver causing elevated serum CA19–9 levels. Am J Gastroenterol 93:2551–2555

Oz Puyan F, Bilgi S, Unlu E, Yalcin O, Altaner S, Demir M, Cakir B (2004) Inflammatory pseudotumor of the spleen with EBV positivity: report of a case. Eur J Haematol 72:285–291

Ozeki Y, Matsubara N, Saiga T, Ishida H, Kimura T, Yasumura M, Fujita S (1993) Inflammatory tumor of the hepatic hilus mimicking bile duct cancer-report of a case (in Japanese). Nippon Geka Gakkai Zasshi 94:1064–1067

Pack GT, Baker HW (1953) Total right hepatic lobectomy, report of a case. Ann Surg 138:253

Palmer RH, Vernersson E, Grabbe C, Hallberg B (2009) Anaplastic lymphoma kinase: signalling in development and disease. Biochem J 420:345–361

Papachristou GI, Wu T, Marsh W, Plevy SE (2004) Inflammatory pseudotumor of the liver associated with Crohn's disease. J Clin Gastroenterol 38:818–822

Park KS, Jang BK, Chung WJ, Cho KB, Hwang JS, Kang YN et al (2006) Inflammatory pseudotumor of the liver: a clinical review of 15 cases. Korean J Hepatol 12:429–438

Passalides A, Keramidas D, Mavrides G (1996) Inflammatory pseudotumor of the liver in children. A case report and review of the literature. Eur J Pediatr Surg 6:35–37

Patnana M, Sevrukov AB, Elsayes KM, Viswanathan C, Lubmer M, Menias CO (2012) Inflammatory pseudotumor: the great mimicker. AJR Am J Roentgenol 198:W217–W227

Pecorella I, Ciardi A, Memeo L, Trombetta G, de Quarto A, de Simone P, di Tondo U (1999) Inflammatory pseudotumor of the liver – evidence for malignant transformation. Pathol Res Pract 195:115–120

Peddu P, Huang D, Kane PA, Karani JB, Knisely AS (2008) Vanishing liver tumours. Clin Radiol 63:329–339

Perera MT, Wijesuriya SR, Kumarage SK, Ariyaratne MH, Deen KI (2007) Inflammatory pseudotumor of the liver caused by a migrated fish bone. Ceylon Med J 52:141–142

Pinkard NB, Wilson RW, Lawless N et al (1996) Calcifying fibrous pseudotumor of pleura: a report of three cases of a newly described entity involving the pleura. Am J Clin Pathol 105:189–194

Pokorny CS, Painter DM, Waugh RC, McCaughan GW, Gallagher ND, Tattersall MH (1991) Inflammatory pseudotumor of the liver causing biliary obstruction. Treatment by biliary stenting with 5-year follow-up. J Clin Gastroenterol 13:338–341

Price J, Clarke A, Tait N (1993) The mucosal rosette: a peri-ampullary pseudotumour within a duodenal diverticulum. Clin Radiol 48:145–146

Qiu X, Montgomery E, Sun B (2008) Inflammatory myofibroblastic tumor and low-grade myofibroblastic sarcoma: a comparative study of clinicopathologic features and further observations on the immunohistochemical profile of myofibroblasts. Hum Pathol 39:846–856

Rai T, Ohira H, Tojo J, Takiguchi J, Shishido S, Sato Y, Nozawa Y, Masuda T (2003) A case of hepatic inflammatory pseudotumor with primary biliary cirrhosis. Hepatol Res 26:249–253

Renzing N, Ebsen M, Schwerk W (2011) Inflammatory pseudotumors of the liver associated with Crohn's disease: a possible pitfall in contrast-enhanced ultrasound (in German). Z Gastroenterol 49:827–831

Rosenbaum L, Fekrazad MH, Raninowitz I, Vasef MA (2009) Epstein-Barr virus-associated inflammatory pseudotumor of the spleen: report of two cases and review of the literature. J Hematol 2:127–131

Rosenthal NS, Abdul-Karim FW (1988) Childhood fibrous tumor with psammoma bodies. Clinicopathologic features in two cases. Arch Pathol Lab Med 112:798–800

Saint-Paul MC, Hastier P, Baldini E, Chevallier A, Chevallier P, Gigante M, Gugenheim J, Michiels JF (1999) Inflammatory pseudotumor of the intrahepatic biliary tract (in French). Gastroenterol Clin Biol 23:581–584

Saito K, Kotake F, Ito N, Tabuchi T, Goto Y, Katano M, Hashimoto T, Abe K (2002) Inflammatory pseudotumor of the liver in a patient with rectal cancer: a case report. Eur Radiol 12:2484–2487

Saitoh N, Sakamoto C, Hagiwara M, Agredano-Moreno LT, Jimenez-Garcia LF, Nakao M (2012) The distribution of phosphorylated SR proteins and alternative splicing are regulated by RANBP2. Mol Biol Cell 23:1115–1128

Sakai M, Ikeda H, Suzuki N, Takahashi A, Kuroiwa M, Hirato J, Hatakeyama S, Tsuchida Y (2001) Inflammatory pseudotumor of the liver: case report and review of the literature. J Pediatr Surg 36:663–666

Sakai T, Shiraki K, Yamamoto N, Kawakita T, Ohmori S, Itoh I, Nakano T, Yasuda M, Yamakado K, Takeda K, Yagi S, Yamagiwa K, Yokoi H, Noguchi T, Uemoto S (2002) Diagnosis of inflammatory pseudotumor of the liver. Int J Mol Med 10:281–285

Sandilla J, Gallagher PJ, Koorey D, Magnussen J, McLeod D, Young G (2005) Hepatobiliary and pancreatic: pseudotumor of the liver. J Gastroenterol Hepatol 20:953

Sari A, Tunakan M, Ünsal B, Ekinci N, Rezanko T, Elçin F, Aydogdu Z (2010) Inflammatory pseudotumor of the liver diagnosed by needle biopsy: report of three cases (one with neuroendocrine tumor of the rectum and lung). Turk J Gastroenterol 21:308–312

Sasahira N, Kawabe T, Nakamura A, Shimura K, Shimura H, Itobayashi E, Asada M, Shiratori Y et al (2005) Inflammatory pseudotumor of the liver and peripheral eosinophilia in autoimmune pancreatitis. World J Gastroenterol 11:922–925

Schmid A, Janig D, Bohuszlavizki A, Henne-Bruns D (1996) Inflammatory pseudotumor of the liver presenting as incidentaloma: report of a case and review of the literature. Hepatogastroenterology 43:1009–1014

Schneider G, Fries P, Samaras P, Remberger K, Uder M, Kramann B (2003) Inflammatory pseudotumor of the liver in a patient with congenital granulocytopenia and HCV infection. Eur J Radiol 48:293–298

Schnelldorfer T, Chavin KD, Lin A, Lewin DN, Baliga PK (2007) Inflammatory myofibroblastic tumor of the liver. J Hepatobiliary Pancreat Surg 14:421–423

Schonherr C, Hallberg B, Palmer R (2012) Anaplastic lymphoma kinase in human cancer. Crit Rev Oncog 17:123–143

Schuessler G, Fellbaum C, Fauth F, Jacobi V, Schmidt-Matthiesen A, Ignee A, Dietrich CF (2006) The inflammatory pseudotumour – an unusual liver tumour (in German). Ultraschall Med 27:273–279

Seki S, Kitada T, Sakaguchi H, Iwai S, Hirohashi K, Higaki I, Nakamura K, Wakasa K, Kinoshita H (2004) A clinicopathological study of inflammatory pseudotumor of the liver with special reference to vessels. Hepatogastroenterology 51:1140–1143

Selves J, Meggetto F, Brousset P, Voigt JJ, Pradère B, Grasset D, Icart J, Mariamé B et al (1996) Inflammatory pseudotumor of the liver. Evidence for follicular dendritic reticulum cell proliferation associated with clonal Epstein-Barr virus. Am J Surg Pathol 20:747–753

Shek TWH, Ng IOL, Chan KW (1993) Inflammatory pseudotumor of the liver. Am J Surg Pathol 17:231–238

Shek TW, Ho FC, Ng IO, Chan AC, Ma L, Srivastava G (1996) Follicular dendritic cell tumor of the liver. Evidence for an Epstein-Barr virus-related clonal proliferation of follicular dendritic cells. Am J Surg Pathol 20:313–324

Sigel JE, Smith TA, Reith JD, Goldblum JR (2001) Immunohistochemical analysis of anaplastic lymphoma kinase expression in deep soft tissue calcifying fibrous pseudotumor: evidence of a late sclerosing stage of inflammatory myofibroblastic tumor ? Ann Diagn Pathol 5:10–14

Singh P, Singla M, Gupta N, Muzaffar J, Babu R, Sakhuja P, Agarwal A, Kar P (2008) Inflammatory pseudotumor of the liver: a diagnostic dilemma. Trop Gastroenterol 29:40–43

Someren A (1978) "Inflammatory pseudotumor" of liver with occlusive phlebitis: report of a case in a child and review of the literature. Am J Clin Pathol 69:176–181

Soudack M, Shechter A, Malkin L, Hayek T, Gaitini D (2000) Inflammatory pseudotumor of the liver: sonographic and computed tomographic features with complete regression. J Ultrasound Med 19:501–514

Stamatakis JD, Howard ER, Williams R (1979) Benign inflammatory tumour of the common bile duct. Br J Surg 66:203–206

Standiford SB, Sobel H, Dasmahapatra KS (1989) Inflammatory pseudotumor of the liver. J Surg Oncol 40:283–287

Stoll LM, Li QK (2011) Cytology of fine-needle aspiration of inflammatory myofibroblastic tumor. Diagn Cytopathol 39:663–672

Sturm N, Guillou L, Laverrière MH, Pinel N, Bosseray A, Létoublon C, Brambilla E (2007) Inflammatory pseudotumor of the liver: a variant rich in giant atypical reactive dendritic cells. Histopathology 50:400–403

Swinney R, Sadri R, Muenchow S (2006) Nonresectable inflammatory pseudotumor of the porta hepatis. J Pediatr Surg 41:e21–e23

Tai YS, Lin PW, Chen SG, Chang KC (1998) Inflammatory pseudotumor of the liver in a patient with human immunodeficiency virus infection. Hepatogastroenterology 45:1760–1763

Tajima K, Kosugi S, Fuyama S, Maeda K, Hayashi T, Yahagi A, Akiba J, Suzuki K, Satoh S et al (1998) Multiple inflammatory pseudotumors of the liver associated with acute myeloblastic leukemia. Intern Med 37:542–545

Takahashi T, Haneda T, Nagano T, Kawahito Y, Mori Y, Senga K, Nakamura K, Ishiguro T, Imai K (2001) Inflammatory pseudotumor of the liver complicated with recurrent gouty arthritis. Intern Med 40:493–498

Tamsel S, Demirpolat G, Killi R, Elmas N (2004) Primary hepatic actinomycosis: a case of inflammatory pseudotumor (case report) (in Turkish). Tani Girisim Radyol 10:154–157

Tang L, Lai EC, Cong WM, Li AJ, Fu SY, Pan ZY, Zhou WP, Lau WY, Wu MC (2010) Inflammatory myofibroblastic tumor of the liver: a cohort study. World J Surg 34:309–313

Terada T (2010) Hepatic multiple minute inflammatory pseudotumors containing many biliary elements and hepatolithiasis: a suggestion of biliary origin. Scand J Gastroenterol 45:633–634

Terada T, Nakanuma Y, Nonomura A (1992) Hamartomatous lesion of the liver in an adult patient with biliary dilatations: a variant of inflammatory pseudotumor of the liver? Gastroenterol Jpn 27:258–263

Teranishi N, Yoshida H, Mamada Y, Taniai N, Mizuguchi Y, Shimizu T, Takahashi T, Akimaru K et al (2005) Inflammatory pseudotumor in the Spiegel lobe of the liver of an elderly woman. J Nippon Med Sch 72:121–126

Toda K, Yasuda I, Nishigaki Y, Enya M, Yamada T, Nagura K, Sugihara J, Wakahara T, Tomita E, Moriwaki H (2000) Inflammatory pseudotumor of the liver with primary sclerosing cholangitis. J Gastroenterol 35:304–309

Torzilli G, Inoue K, Midorikawa Y, Hui AM, Takayama T, Makuuchi M (2001) Inflammatory pseudotumors of the liver: prevalence and clinical impact in surgical patients. Hepatogastroenterology 48:1118–1123

Tsao TY, Nieh S, Tseng HH, Tu YC, Yu CY, Liu YC, Chen VT (1990) Inflammatory pseudotumor of the liver with occlusive endophlebitis: report of a case. J Formos Med Assoc 89:818–822

Tsou YK, Lin CJ, Liu NJ, Lin CH, Lin SM (2007) Inflammatory pseudotumor of the liver: report of eight cases, including three unusual cases and a literature review. J Gastroenterol Hepatol 22:2143–2147

Uccheddu A, Faa G, Cois A, Ambu R (1995) Inflammatory pseudotumor of the liver. A report of two cases with unusual histologic picture. Tumori 81:151–156

Ueda M, Yukihide Y, Ogawa K, Haga H, Ogura Y, Ito T, Tanaka K (2003) A case of inflammatory pseudotumor of the liver hilum successfully treated with aggressive hepatectomy. J Pediatr Surg 38:E9–E11

Ueda J, Yoshida H, Taniai N, Onda M, Hayashi H, Tajiri T (2009) Inflammatory pseudotumor in the liver associated with intrahepatic bile duct stones mimicking malignancy. J Nippon Med Sch 76:154–159

Uetsuji S, Nakagawa A, Kwon AH, Komada H, Imamura A, Kamiyama Y (1996) Inflammatory pseudotumor of the liver: report of a case and review of the literature. Surg Today 26:517–521

Van Dorpe J, Ectors N, Geboes K, D'Hoore A, Sciot R (1999) Is calcifying fibrous pseudotumor a late sclerosing stage of inflammatory myofibroblastic tumor ? Am J Surg Pathol 23:329–335

Vasiliadis K, Fortounis K, Papavasiliou C, Kokarhidas A, Al Nimer A, Fachiridis D, Pervana S, Makridis C (2014) Mid common bile duct inflammatory pseudotumor mimicking cholangiocarcinoma. A case report and literature review. Int J Surg Case Rep 5:12–15

Vassiliadis T, Vougiouklis N, Patsiaoura K, Mpoumponaris A, Nikolaidis N, Giouleme O, Evgenidis N (2007) Inflammatory pseudotumor of the liver successfully treated with nonsteroidal anti-inflammatory drugs: a challenge diagnosis for one not so rare entity. Eur J Gastroenterol Hepatol 19:1016–1020

Voss SD, Kruskal JB, Kane RA (1999) Chronic inflammatory pseudotumor arising in the hepatobiliary-pancreatic system: progressive multisystemic organ involvement in four patients. AJR Am J Roentgenol 173:1049–1054

Wang ZJ, Coakley FV, Ferrell LD, Rosenthal P (2002) CT and MRI of hepatic pseudotumor in long-standing biliary atresia. J Comput Assist Tomogr 26:444–447

Weinreb I, Bailey D, Battaglia D, Kennedy M, Perez-Ordoñez B (2007) CD30 and Epstein-Barr virus RNA expression in sclerosing angiomatoid nodular transformation of spleen. Virchows Arch 451:73–79

Weiss GA, Shor DB, Schachter P (2007) Inflammatory pseudotumor of the liver: an unlikely cause of multiple hepatic lesions. Isr Med Assoc J 9:894–895

White JE, Chase CW, Kelley JE, Brock WB, Clark MO (1997) Inflammatory pseudotumor of the liver associated with extrahepatic infection. South Med J 90:23–29

Wick MR, Ritter JH (1997) Pseudoneoplastic lesions: an overview. In: Wick MR, Humphrey PA, Ritter JH (eds)

Pathology of pseudoneoplastic lesions. Lippincott-Raven, Philadelphia

Worley PJ, Roberts-Thomson IC, Dymock RB, Maddern GJ (2001) Benign inflammatory pseudotumour of the biliary tract masquerading as a Klatskin tumour. HPB (Oxford) 3:179–181

Yamaguchi M, Yamamoto T, Tate G, Matsumoto T, Matsumiya A, Kuzume M, Sanada Y et al (2000) Specific detection of Epstein-Barr virus in inflammatory pseudotumor of the spleen in a patient with a high serum level of soluble IL-2 receptor. J Gastroenterol 35:563–566

Yamaguchi J, Sakamoto Y, Sano T, Shimada K, Kosuge T (2007) Spontaneous regression of inflammatory pseudotumor of the liver: report of three cases. Surg Today 37:525–529

Yamamoto H, Yamaguchi H, Aishima S, Oda Y, Kohashi K, Oshiro Y, Tsuneyoshi M (2009) Inflammatory myofibroblastic tumor versus IgG4-related sclerosing disease and inflammatory pseudotumor: a comparative clinicopathologic study. Am J Surg Pathol 33:1330–1340

Yan FH, Zhou KR, Jiang YP, Shi WB (2001) Inflammatory pseudotumor of the liver: 13 cases of MRI findings. World J Gastroenterol 7:422–424

Yoon KH, Ha HK, Lee JS, Suh JH, Kim MH, Kim PN, Lee MG, Yun KJ, Choi SC, Nah YH, Kim CG, Won JJ, Auh YH (1999) Inflammatory pseudotumor of the liver in patients with recurrent pyogenic cholangitis: CT-histopathologic correlation. Radiology 211:373–379

Yoshida T, Nishimori I, Kumon M, Kohsaki T, Taniuchi K, Ohtsuki Y, Onishi S (2003) Inflammatory pseudotumor of the liver: report of a case diagnosed by needle biopsy. Hepatol Res 27:83–86

Young TH, Chao YC, Tang HS (1998) Spontaneous regression of hepatic pseudotumor demonstrated by Ga-67 imaging. Clin Nucl Med 23:624

Zamir D, Jarchowsky J, Singer C, Abumoch S, Groisman G, Ammar M, Weiner P (1998) Inflammatory pseudotumor of the liver – a rare entity and a diagnostic challenge. Am J Gastroenterol 93:1538–1540

Part XXIV

Nonneoplastic Mass Lesions of the Hepatobiliary Tract

Ectopias and Heterotopies as Tumor-Like Lesions of the Hepatobiliary Tract

120

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_120

Abstract

Numerous types of ectopias and heterotopias located to the liver can result in tumor-like lesions. The presence of ectopic splenic tissue in various abdominal organs, including the liver, is termed splenosis. The liver can also contain various types of ectopic pancreatic tissue, ranging from exocrine lobules to small clusters of intrahepatic acinar cells. Adrenal cortex can ectopically adhere to the inferior-posterior capsule of the liver, a condition called adrenohepatic fusion. Other rare ectopic tissue components include thyroid gland ectopia, hepatogonadal fusion, hepatic endometriosis and endometrioma, and hepatic pregnancy.

Splenosis of the Liver

Introduction

Splenosis denotes the presence of splenic tissue in a more or less remote tissue compartment, most commonly occurring after traumatic splenic rupture and splenectomy, or due to overgrowth of congenitally ectopic splenic tissue. The histologic features of splenosis have been described in detail (Carr and Turk 1992), and splenosis is known to occur in the liver. Instead of splenosis, the term hepatic spleen nodules (HSN) has also been proposed (Mescoli et al. 2010).

The term splenosis was coined in 1939 (Buchbinder and Lipkoff 1939); however, autotransplantation of splenic tissue after trauma has been described much earlier, i.e., in 1910 (cited in Garamella and Hay 1954). It is now thought that, subsequent to splenic trauma, fragments of splenic pulp are seeded throughout the peritoneal cavity (Fleming et al. 1976; review: Fremont and Rice 2007). This view is supported by observations of splenosis occurring after laparoscopic splenectomy (Losanoff and Jones 2001), including growth of splenic tissue in a port site (Kumar and Borzi 2001). By use of an experimental rat model, it has been shown that the pneumoperitoneum may facilitate abdominal splenosis after laparoscopy if the splenic capsule is ruptured or if splenic tissue spills compared with surgery without gas (Espert et al. 2001). After trauma, splenic tissue embolization via the splenic vein or through other blood vessel routes may then result in remote manifestations, including the liver. Splenosis can, therefore, occur at numerous sites, intraabdominal and thoracic localizations being the most frequent (Kutzen and Levy 1978; Bizekis et al. 2003; Mavi et al. 2003). In the peritoneal cavity, the number of splenic nodules ranges from a few to hundreds, and their sizes range from a few millimeters to several centimeters. The implants can increase in mass and size, owing to stimulations that also produce splenomegaly in the original organ, and splenotic lesions can also induce recurrence of diseases related to splenomegaly having resulted in therapeutic splenectomy, including Felty's syndrome and idiopathic thrombocytopenic purpura. Rare locations of splenosis comprise the skin (subcutis; Velitchkov et al. 2000), the lung (Sarda et al. 2001), the brain (Rickert et al. 1998), and the liver. Splenotic lesions are not identical to accessory spleens, known as "splenculi," "splenunculi," "lienculi," and "splenules."

Ectopic splenic tissue was observed in 47 out of 250 (19 %) consecutive necropsies (Wadham et al. 1981). In a follow-up study, the incidence of splenosis was 66 % after splenic removal due to severe traumatic rupture (Ludtke et al. 1989). Improved detection methods include Tc-99 m sulfur colloid scintigraphy (Castellani et al. 2001), heat-denaturated Tc-99 m red blood cell scintigraphy (Laflamme and Boucher 2003), and combined transmission-emission tomography (TET, fusion of SPET and CT data; Horger et al. 2003). Splenosis post splenectomy may be suggested due to the absence of Howell-Jolly bodies in erythrocytes.

Splenosis of the Liver

A supernumerary spleen enclosed in the liver was reported already in 1914 (De Teyssieu 1914). The authors described an alteration that is still typical for many later cases of hepatic splenosis: the right

liver lobe showed, on its inferior surface, a cup-shaped depression of 4 cm diameter containing a well-delineated, egg-shaped focus of splenic tissue, in the presence of a normal-looking orthotopic spleen. Although rare, hepatic splenosis has since been reported several times.

Selected References Cavallini (1958), Yoshimitsu et al. (1993), Davidson and Reid (1997), Gruen and Gollub (1997), D'Angelica et al. (1998), Wekerle et al. (1998), Foroudi et al. (1999), De Vuysere et al. (2000), Hierholzer et al. (2001), Lee et al. (2002), Gamulin et al. (2002), Pekkafali et al. (2002), Yang et al. 2002b; Galloro et al. (2003), Nakata et al. (2003), Kim et al. (2003), Zhao and Xu (2004), Izzo et al. (2004), Di Costanzo et al. (2004), Kondo et al. (2004), Martinez Del Valle Torres et al. (2005), Ishikawa et al. (2007), Yang et al. (2007), Choi et al. 2008; Grande et al. (2008), Labat-Debelleix et al. (2008), Lu et al. (2008), Kashgari et al. (2009), Menth et al. (2009), Mescoli et al. (2010), Li et al. (2011), Liu et al. (2012a), Casella et al. (2013), Incedayi et al. (2013), Inchingolo et al. (2013), Röther et al. (2013), Chung (2014), Levi Sandri et al. (2014), and Sato et al. (2014).

Apart from hepatic splenosis, the term hepatic spleen nodules (HSN) has also been proposed (Mescoli et al. 2010). The timely delay between splenic trauma and the manifestation of hepatic splenosis may be considerable, reports indicating 20 years (Davidson and Reid 1997; Lee et al. 2002), 23 years (Yoshimitsu et al. 1993), 27 years (Gamulin et al. 2002), or even 34 years (De Vuysere et al. 2000).

Hepatic splenosis presents with two forms, namely, intrahepatic splenosis and perihepatic splenosis. In perihepatic splenosis, the splenic tissue foci are located to Glisson's capsule (Incedayi et al. 2013). Hepatic splenosis can occur as an isolated form of splenosis or occur in conjunction with splenosis synchronously situated elsewhere, e.g., the colon (Liu et al. 2012b). Intrahepatic lesions may present as an incidental finding, being somewhat similar to hemangiomas or other hepatic tumors on CT and MRI images, owing to hypervascularization/arterialization (Yoshimitsu et al. 1993; Izzo et al. 2004; Inchingolo et al. 2013), and remaining slightly hyperintensive relative to the hypointensive liver on T2WI after injection of superparamagnetic iron oxide (De Vuysere et al. 2000; Nakata et al. 2003). The lesions can be identified and diagnosed by means of selective Tc-99 m-labeled heat-denatured autologous red blood cells scintigraphy (Menth et al. 2009). However, hepatic splenosis may simulate an intrahepatic mass and can thus evoke differential diagnostic difficulties, including lesions mimicking hepatocellular carcinoma, especially in patients with viral hepatitis and cirrhosis (Yoshimitsu et al. 1993; Lee et al. 2002; Kim et al. 2003; Galloro et al. 2003; Zhao and Xu 2004; Di Costanzo et al. 2004; Abu Hilal et al. 2009; Kashgari et al. 2009; Menth et al. 2009; Chung 2014; Levi Sandri et al. 2014; Sato et al. 2014; Li et al. 2015; Liu et al. 2015) or liver cell adenoma (Gruen and Gollub 1997). Also perihepatic forms of splenosis can mimic a focal liver lesion (Casella et al. 2013). Apart from solitary lesions, instances of multiple hepatic splenotic nodules have been recognized (Di Costanzo et al. 2004). Such multiple splenotic foci may mimic hepatic metastatic disease (Foroudi et al. 1999; Kang et al. 2011; Li et al. 2012). In some situations of multiple intraabdominal splenosis, splenotic foci are distributed over the liver surface (Imbriaco et al. 2008).

At gross examination, intrahepatic splenosis presents as solitary or multiple nodules, sometimes presenting as a dark-red and angioma-like lesion (Cavallini 1958), and rarely a bilobed mass has been detected, in part projecting outward from the liver (Davidson and Reid 1997). The lesions are sharply delineated an exhibit a dark-red cut surface, i.e., the features of splenic pulp. The diameter of the lesions varies considerably, larger lesions having been reported as 3.5 cm (Lee et al. 2002; Kondo et al. 2004), the size of a "walnut" (Cavallini 1958), 4.8 cm (Galloro et al. 2003), 6 cm (De Vuysere et al. 2000), and 6.6 cm (Gamulin et al. 2002).

Histologically, intrahepatic splenosis has the characteristics previously described for splenosis

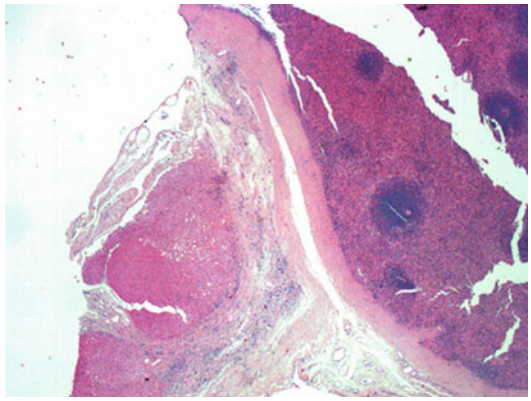

Fig. 1 Splenosis of the liver. Ectopic splenic tissue adheres to the liver tissue, whereby the capsule of the splenic tissue is interposed (hematoxylin and eosin stain)

at other sites (Carr and Turk 1992; Fig. 1). The ectopic splenic tissue is usually in direct contact with the adjacent liver substance, i.e., without intervening fibrous capsule (Davidson and Reid 1997), but a fibrous interface has also been described (Cavallini 1958). Typically, splenosis has no hilar structure, and the vascular supply is achieved from the periphery of the lesion. The splenotic tissue itself displays a texture with both red and white pulp, although sometimes the white pulp (including central arterioles) may be less prominent than usually known for the spleen. Germinal centers may occur in the white pulp. In one case, Gamna-Gandy bodies have been detected in the ectopic splenic tissue (Cavallini 1958). These bodies are well known from the orthotopic spleen and exhibit characteristic radiologic and histologic features. The first to describe Gamna-Gandy bodies was Marini in 1902 (Marini 1902). The authors giving the eponym reported on them only later; in 1905 for Gandy, in a patient with biliary cirrhosis (Gandy 1905), and in 1921 for Gamna, who used the term "siderotic splenogranulomatosis" (Gamna 1921). Hepatic splenosis may show marked iron overload, causing atypical MRI imaging (Nakajima et al. 2008). Immunohistochemically, splenosis has been shown to have a distribution of B- vs. T-lymphocytes not different from that of the normal spleen (Carr and Turk 1992). In case of splenosis growing out of the liver contour (abortive pedunculation), a common capsule enclosed the liver and the splenic tissue (Davidson and Reid 1997). Apart from a slight perifocal atrophy of parenchyma, the adjacent liver tissue does not show any relevant changes.

Ectopic Liver in the Spleen

Splenic hepatic ectopy is a much more uncommon event than splenosis. In one case, in a 69-year-old man, a large splenic tumor was detected and shown to be intrasplenic hepatocellular carcinoma, associated with heterotopic liver remnants (hepatocytes and biliary ductules) in the splenic capsule (Matsuyama et al. 2011). Foci of mature ectopic liver have been noted in the wall of an epithelial cyst of the spleen (Del Sordo et al. 2011).

Pancreatic Tissue Heterotopia of the Hepatobiliary Tract (Pancreas Aberrans; Pancreas Accessorium)

Introduction

Pancreatic heterotopia (heterotopic pancreas; pancreatic choristoma; pancreas aberrans; pancreas accessorium) is defined as the presence of any pancreatic tissue components in an abnormal location without parenchymal, stromal, or vascular connection with the main pancreas (Horgan 1921; Mobini et al. 1974). As cited by Hsia et al. (1999), Jean Schultz was the first to describe, in 1727, heterotopic pancreas in an intestinal diverticulum. This author found at the autopsy of a newborn child "wart similar to a gland" in the apex of a cone-shaped diverticulum of the ileum; no histologic confirmation was possible at this time (Schultz 1727). More than hundred years later, Klob (1859) reported the histologic proof of pancreatic heterotopia in two cases, using the term pancreas accessorium. This issue was further outlined in 1905 by Merkel (1905), Von Heinrich (1909), and, based on gastric pancreatic heterotopia, by Delhougne (1924). Instead of

heterotopic pancreas, the terms adenomyoma or myoepithelial hamartoma have been used to denote these lesions (Mitchell and Augrist 1943; Bill et al. 1982), but this might generate confusion, because adenomyoma of the ampullary region exists in the absence of pancreatic tissue elements.

Epidemiology

The lesion appears in 0.5–13 % of autopsies (Pearson 1951); this review also presented the first case with common bile duct obstruction caused by this type of heterotopia. Clinically, pancreatic heterotopia is identified with an estimated frequency of one in every 500 upper abdominal operations (Barbosa de Castro et al. 1946; Dolan et al. 1974; Lai and Tompkins 1986; Pang 1988; Tanaka et al. 1993; Zinkiewicz et al. 2003). Involved sites include the oesophagus, stomach (25.5 %), duodenum (27.7 %), ampulla of Vater, the main pancreatic duct, proximal jejunum (15.9 %), ileum, Meckel's diverticulum, and the hepatobiliary tract. Unusual sites are the umbilical region, Fallopian tube, mediastinum, salivary glands, tongue, and lymph nodes. The liver and the bile ducts are very rarely involved (Ballinger 1941; Barbosa de Castro et al. 1946; Gadrat et al. 1965; Mobini et al. 1974; Pujari and Deodhare 1979; Armstrong et al. 1981; Hsia et al. 1999; Fukueda et al. 2000). Stomach and duodenum together account for more than 50 % of heterotopic pancreatic tissue, also in the pediatric age group (Delhougne 1924; Ogata et al. 2008; Gokhale et al. 2010).

Classification and General Histologic Features

Depending on the pancreatic tissue components represented in the heterotopia, *classifications* have been proposed (Von Heinrich 1909; Gaspar-Fuentes et al. 1973; Table 1).

Histological features of pancreatic heterotopia show varying combinations of excretory ducts, glands of the exocrine apparatus (with a lobular or ill-defined architecture), and islets of Langerhans (Pang 1988). Pancreatic heterotopia can undergo secondary changes, including acute and chronic inflammation, fibrosis, duct obstruction with duct dilatation, and tumor development. Mucostasis in dilated ducts of heterotopic pancreatic tissue followed by mucus leakage and formation of mucus lakes may mimic colloid carcinoma (Teke et al. 2010). In the duodenal wall, heterotopic pancreas can undergo a complex change to so-called cystic dystrophy of the duodenal wall (Galloro et al. 2008).

Table 1 Classifications of pancreatic heterotopia

Von Heinrich classification (Von Heinrich 1909)	
Type I	Presence of all epithelial components of the normal pancreas
Type II	Pancreatic tissue without islets
Type III	The tissue only consist of (proliferated) ductules
Gaspar-Fuentes classification (Gaspar-Fuentes et al. 1973)	
Type I	Total heterotopia with all pancreatic components
Type II	Ductular proliferations only ("canalicular variety")
Type III	Acinar structures only ("exocrine pancreas")
Type IV	Islet tissue only ("endocrine pancreas")

Heterotopic Pancreas in the Liver

In the liver, pancreatic heterotopia usually manifests in the form of a solitary nodule. Gadrat and coworkers described two patients with liver cirrhosis in whom a hepatic needle biopsy revealed exocrine pancreatic tissue, one biopsy additionally with an islet of Langerhans. Hepatic pancreatic heterotopia may present as an abdominal mass (Mobini et al. 1974), because such tissue in the liver has been shown to rarely form a cystic mass of up to 7 cm diameter, almost completely covered by a smooth and transparent serosa and connected to the liver through a pedicle (Mobini et al. 1974). However, most lesions are much smaller, e.g., in the range of 2–3 cm (Pujari and Deodhare 1979). Intrahepatic pancreatic tissue

can consist of acini, ducts, and islets, but some authors specify that only acinar cells, but not islet tissue, were present (Mobini et al. 1974; Suzuki et al. 1999). In one early reported case, islet cell carcinoma causing hypoglycemia apparently developed from hepatic pancreatic heterotopia, implying a preexisting islet-containing lesion (Ballinger 1941). Rarely, ectopic pancreatic tissue in the liver undergoes secondary changes, e.g., resulting in large pseudocysts (Kralik and Pesula 1993). The heterotopic lesions are usually circumscribed, but, in some instances, small foci of pancreatic tissue are scattered in the adjacent liver substance, in addition to the main heterotopia (Mobini et al. 1974). The heterotopic pancreatic tissue may undergo atrophy, with remaining duct and ductule profiles.

Pancreatic Metaplasia in the Liver

A distinctive situation is the presence of numerous microscopic foci of exocrine pancreatic tissue in the liver, instead of one grossly visualized mass (Terada et al. 1990; Wolf et al. 1990; Kuo et al. 2009; Fig. 2). Terada and coworkers (1990) identified foci of exocrine pancreas in 41 of 1,000 consecutive autopsy livers (4.1 %) and regarded these foci as heterotopic pancreas, but the morphology of the lesions they described together with their localization in large portal tracts and the lack of islet cells rather suggest acinar metaplasia. In the patient reported by Wolf and coworkers (Wolf et al. 1990), a nodular liver with septal fibrosis contained acinar cell and ductule containing pancreatic structures embedded in fibrous tissue (but not encapsulated). The foci measured 0.1–1.0 mm (average: 0.4 mm), clearly separated from hepatocytes and with an estimated frequency of one focus per 4.3 cm^2. Some of the pancreatic foci displayed a lobular construction. Alpha-amylase-reactive acinar cells were detectable, while islet cells or endocrine cells were lacking. In a study analyzing 382 liver explants from 1995 to 2000, 16 livers (4.2 %) contained pancreatic acini-like tissue. Fifteen of these liver were cirrhotic. The pancreas tissue foci appeared as small clusters of

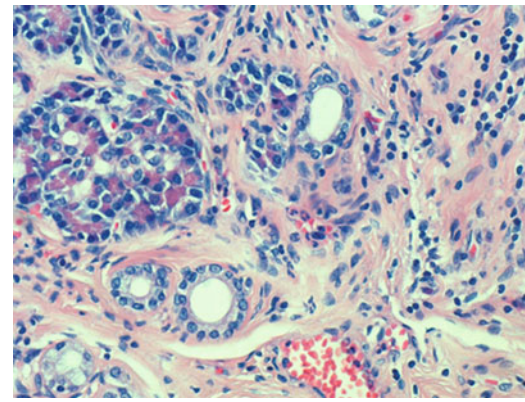

Fig. 2 Intrahepatic ectopic pancreatic acini (hematoxylin and eosin stain)

compactly packed cells that either blended imperceptibly with or were in close proximity to adjacent bile ducts or ductules. The acinar tissue was positive for pancreatic alpha-amylase and weakly positive for cytokeratin 8, but negative for cytokeratins 7 and 19, in contrast to the adjacent biliary-type epithelium, but the close spatial relationship with small bile ducts and ductules suggested a metaplastic process in the pathogenesis of these lesions, derived from a hepatic progenitor cell lineage (Kuo et al. 2009). On the other hand, acinar cells may be derived from the remodeling ductal plate (Terada 2012).

Heterotopic Pancreas in the Biliary Tract

Apart from ectopia within the liver substance itself, ectopic pancreatic tissue has been observed in intra-or/and extrahepatic bile ducts. According to a distributional analysis on 471 cases of pancreatic ectopia/heterotopia of Barbosa de Castro and coworkers (Barbosa de Castro et al. 1946), 0.4 % were located to the common bile duct, where it can induce stenosis or even obstruction (Pearson 1951; Weber et al. 1968; Sabini et al. 1970; Lehur et al. 1983; Pang 1988; Schu et al. 1988; Thognon et al. 1998; Molinari et al. 2000; Maisonnette et al. 2004; Karahan et al. 2006; Yan et al. 2012), in case of a localization in the distal common bile duct associated

with marked bile duct dilatation (Tsunoda et al. 1990; Molinari et al. 2000). In MR cholangiopancreatography, a hypointense nodular filling defect was detected in one patient, associated with dilatation of the intrahepatic biliary tree (Karahan et al. 2006). When the heterotopic pancreatic tissue is located in the extrahepatic bile duct bifurcation, a filiform stenosis mimicking Klatskin tumor has been described (Heer et al. 2010). Obstruction of the common hepatic duct by ectopic pancreas has been reported (Schu et al. 1988). Involvement of intra- and extrahepatic ducts was detected in patients with choledochal cysts (Suzuki et al. 1999; Prasad et al. 2001; Bahadir et al. 2006) and with congenital biliary dilatation (Kattepura et al. 2010). Heterotopic pancreas has also been observed in the cystic duct wall, causing duct stenosis and gallbladder hydrops (Inceoglu et al. 1993; Bhana and Chetty 1999; Weppner et al. 2009). The heterotopic tissue is situated deep in the submucosa or may occupy a larger part of the duct wall (Mrak et al. 2010). In a 45-year-old female patient with a 3 cm-sized mass in the bile duct of the left liver lobe near the hepatic hilum, histology showed that an adenocarcinoma had arisen from heterotopic pancreas, with perineural invasion in the hilar region (Yan et al. 2012).

Heterotopic Pancreas of the Gallbladder

Misplaced pancreatic tissue also occurs in the wall of the gallbladder, first described by Poppi in 1916 (Fig. 3). Since this report, numerous descriptions of this clinic-pathologic entity have appeared (Cerullo et al. 2011; Gucer et al. 2011). This issue is discussed in detail in the chapter on pseudotumors of the gallbladder.

Heterotopic Pancreas Associated with Choledochal Cysts

In a 36-year-old female patient with intra- and extrahepatic bile duct cysts and abnormal arrangement of the pancreatobiliary junction region, pancreatic tissue with acinar cells, centroacinar cells, and ductal elements but without Langerhans islets was scattered along the abnormal biliary tract. The pancreatic foci ranged from 200 to 800 μm in size (Suzuki et al. 1999).

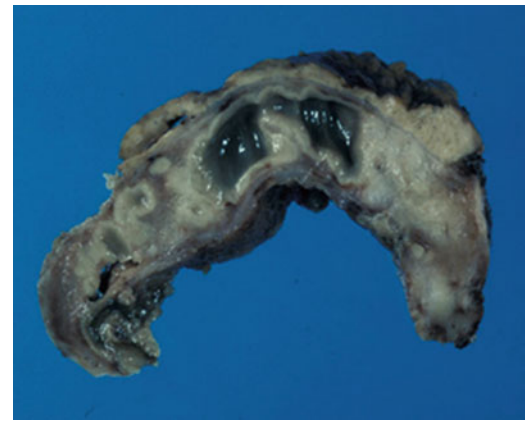

Fig. 3 Ectopic pancreas of the gallbladder

Pancreatic Metaplasia of the Biliary Tract

Pancreatic metaplasia with formation of acinar and/or ductal cells in a glandular mucosa is well known to occur in the stomach and in Barrett's mucosa, but less often also develops in the biliary tract. Pancreatic acinar metaplasia has been observed in up to 10 % of cases of end-stage primary sclerosing cholangitis (Lewis et al. 2010).

Selected References Hoelzer (1940), Mitchell and Augrist (1943), Barbosa de Castro et al. (1946), Varay (1946), Pearson (1951), Barber and Barber (1952), Falco Raucci (1960), Weber et al. (1968), Paraf et al. (1970), Sabini et al. (1970), Berenguer et al. (1972), Laughlin et al. (1983), O'Reilly et al. (1983), Coupland et al. (1987), Hammarström and Nordgren (1999), Molinari et al. (2000), Chen et al. (2001), Contini et al. (2003), Maisonnette et al. (2004), Wagle et al. (2005), Chou et al. (2006), and Filippou et al. (2006).

Differential Diagnosis

Radiologically, hepatobiliary ectopic pancreas should not be confounded with heterotopic pancreas located to the retroperitoneal space, where it may eventually produce lipoma-like tumors owing to massive pancreatic lipoatrophy (Moriki et al. 2004). Remnants of pancreatic tissue located to the retroperitoneal space vary considerably in size and may, e.g., present as small nests in the periaortic space (Heller et al. 2010).

Heterotopic Liver in the Pancreas

Pathogenetically interesting is the reverse situation, i.e., heterotopic liver in the pancreas, sometimes giving rise to hepatocellular carcinoma in the pancreas (Cardona et al. 2007; Kubota et al. 2007).

Pathogenic Pathways

Proposals reported so far include (a) incomplete regression of the ventral anlage; (b) regression to more primitive distribution pattern of pancreatic tissue, resembling the pattern in lower vertebrates, with a diffuse distribution of pancreatic tissue foci in the liver, intestinal wall, and peritoneum; (c) aberrant differentiation of a displaced pluripotent cell system; (d) separation of pancreatic anlage from the orthotopic pancreas by the rapidly growing intestine; (e) metaplasia; and (f) transdifferentiation.

The liver and pancreas develop in close proximity, and very early developmental defects in humans can therefore involve both systems together, e.g., combined absence of bile ducts and pancreatic ducts (Nakamura et al. 2003). The pancreas develops from the dorsal and ventral pancreatic buds of endodermal cells arising from the caudal part of the foregut, the bulk of the pancreas deriving from the dorsal bud, while the ventral bud gives rise to the uncinate process. Recent studies show that the pancreatic progenitor cells first give rise at the ventral endoderm prior to the formation of dorsal and ventral pancreatic buds (Yoshida et al. 2009). Early progenitors seem to be bipotential, i.e., pancreatobiliary progenitor cells which coexpress the transcription factors PDX1 and SOX17 (concept of hepatic and pancreatic stem cells; Burke and Tosh 2012; Arndtfield and van der Kooy 2013). The subsequent lineage segregation of these cells produces a PDX1+ ventral pancreas and a SOX17+ biliary primordium, and this pathway is SOX17-dependent (Spence et al. 2009). It has been postulated that prior to fusion of the pancreatic buds, small branches of the anterior and posterior pancreatic buds may become attached to the gut wall at various locations, these branches eventually remaining grafted to the gut wall and thus giving origin to heterotopic tissue (Derbyshire 1940). That displacement of bud components may occur is illustrated by a bifid ventral bud resulting in annular pancreas, and the frequent location of pancreatic heterotopia in the duodenal wall, probably via fragmentation of the ventral bud. It may be surmised that such cellular fragments may be integrated into the hepatic primordium and then be translocated to the definitive liver.

Is hepatic pancreatic heterotopia caused by metaplasia and/or transdifferentiation?

Metaplasia has been suggested in the rare situation where hundreds of pancreatic foci have been found to be distributed within the liver (Wolf et al. 1990). A metaplastic change of hepatocytes into pancreatic cells is known from animal observations, in particular liver tumors induced by carcinogens (Kimbrough 1973; Rao et al. 1986; Lee et al. 1989). Another concept refers to transdifferentiation, i.e., a change in the cell lineage program. The plasticity of both liver and pancreas in regard to mutual transdifferentiation has been studied in several models, demonstrating a biochemical shift of liver to pancreas, but so far not a structurally identifiable transdifferentiation. Recombinant-adenovirus-mediated gene transfer of PDX-1 to the livers of mice activated expression of the endogenous, otherwise silent genes for mouse insulin 1 and 2 and prohormone convertase one third, indicating the capacity of a major pancreatic developmental regulator to reprogram extrapancreatic tissue toward a beta cell

phenotype (Ferber et al. 2000). In subsequent experiments in mice, it surfaced that PDX-1 triggers a long-lasting process of liver to pancreas developmental shift, chiefly in perivenous hepatocytes, demonstrating that PDX-1 possesses an instructive role in pancreas differentiation also when ectopically expressed in mature fully differentiated tissue such as the liver (Ber et al. 2003). In transgenic Xenopus tadpoles carrying a modified Pdx-1 homolog (Xlhbox8), part or all of the liver was converted to pancreas, containing both exocrine and endocrine cells, and this same construct also brought about transdifferentiation of human hepatocytes in culture, with formation of exocrine and endocrine pancreatic cells (Horb et al. 2003). Adult hepatic stem cells can transdifferentiate in vitro into pancreatic endocrine hormone-producing cells, forming self-assembled 3D islet cell-like clusters expressing islet cell differentiation-related transcripts, e.g., PDX-1, PAX-4, PAX-6, and Nkx2.2 (Yang et al. 2002a). The "mirror situation" is transdifferentiation of pancreas into the liver, early been detected by the observation that the pancreas can almost completely convert to the liver in the adult rat (Rao et al. 1988) and recently reviewed with respect to the mechanisms involved (Shen et al. 2003a). The temporal and hierarchical control of transdifferentiation of liver to pancreas is regulated by distinct transcription factors, including Pdx1, Pax4, and Mafa/3pTs (Berneman-Zeitouni et al. 2014). The glucagon-like peptide-1 antagonist, exendin-4, promotes liver cell proliferation and enhances the Pdx-1-induced liver to pancreas transdifferentiation process (Aviv et al. 2009). What are the cellular sources of hepatic metaplasia in the pancreas? Rat and human pancreatic islets and ducts contain a distinct population of cytokeratin-19 and peptide hormone-negative cells expressing the neural stem cell-specific marker, nestin. These nestin-positive islet-derived progenitor (NIP) cells seem to be multipotential and are able to differentiate into cells that express liver and exocrine pancreas markers (Zulewski et al. 2001). More recently, it has been shown that glucocorticoids induce the appearance of hepatocyte-like cells of islet origin in organ cultures of embryonal rat pancreas based on the expression of liver markers, albumin, alpha-1-antitrypsin, and transthyretin, associated with a downregulation of Pdx-1 and an upregulation of the transcription factor, C/EBPbeta (Shen et al. 2003b). It remains to be shown whether transdifferentiation mechanisms are involved in the pathogenesis of nodular or multifocal hepatic pancreas heterotopias in humans.

Thyroid Gland Ectopia in the Hepatobiliary Tract

Introduction

Thyroid tissue ectopias chiefly occur along the developmental axis of this organ, i.e., in the posterior part of the tongue (area of the foramen caecum; lingual thyroid) and in salivary glands, and in association of the descending pathway of the thyroid anlage. However, thyroid primordia may also be displaced together with other organs undergoing a physiologic descent during ontogenesis, resulting in intrathoracic thyroid ectopia, e.g., the lung, the oesophagus, and the heart (struma cordis). Thyroid ectopia may even extend to compartments below the diaphragm, e.g., in the duodenal wall, pancreas, hilum of the spleen, small intestinal mesentery, adrenal gland, vagina, and liver and gallbladder. Even thyroid ectopias outside the thorax and abdomen have been observed, e.g., in the axilla. Malignant transformation of thyroidal ectopias (papillary carcinoma of thyroid) is extremely rare (Michigishi et al. 1991; Zink et al. 1991; Hari et al. 1999; Matsumoto et al. 1999).

Thyroid Ectopia in the Liver

Ectopic thyroid tissue in the liver is a very unusual alteration, and most patients displayed the tissue in or near the porta hepatis. In one instance, where the thyroid features of the tissue were confirmed by immunohistochemistry, displaced thyroid tissue was detected in a fetus with trisomy 18, who showed a eutopic thyroid gland without changes,

and a focus (2 mm) follicular, thyroglobulin-reactive thyroid tissue (immunohistochemically without calcitonin-reactive cells) at the porta hepatis, close to a bile duct (Sekine et al. 2000). Five additional published observations on thyroid ectopia at the hepatic porta are available (Schubert 1957; Rahn 1959; Strohschneider et al. 1993; Jamshidi et al. 1998; Ghanem et al. 2003).

In the case of Strohschneider and coworkers, the thyroid ectopia produced a mass of 4.5 cm diameter, and the tissue was identical to normal thyroid gland tissue. In contrast, another case was characterized by the presence of nodular goitrous tissue at the porta hepatis, producing a mass (Jamshidi et al. 1998). The case of Ghanem and coworkers (Ghanem et al. 2003) refers to a 24-year-old female patient who was admitted to the hospital to explore an incidentally detected subhepatic tumorous lesion in the porta hepatis via routine abdominal ultrasonography. CT revealed an inhomogeneous, slightly attenuated, lobulated lesion measuring up to 10 cm, with some calcifications. Fine needle aspiration yielded typical thyrocytes and thyroid follicles. A subsequent 123-I-scintigraphy confirmed the diagnosis of thyroid ectopia. The lesion was resected, weighed 580 g, and exhibited a nodular structure as seen in nodular goiter, further exemplifying that strumigenic factors may also act in ectopic thyroid tissue. Hepatic thyroid ectopia may be mimicked by metastasis of well-differentiated follicular carcinoma of the thyroid (Kondo et al. 2000).

Thyroid Ectopia in the Biliary Tract

Few reports have described thyroid ectopia in the gallbladder (Curtis and Sheahan 1969; Harach 1998; Ihtiyar et al. 2003; Cassol et al. 2010; Liang et al. 2010). In all but one case, thyroid ectopia was an incidental finding. In the case of Harach (1998), a spheroid nodule up to 7 mm was found lying within the fibrofatty tissue adjacent to the neck of the gallbladder, containing thyroid follicles of various sizes filled with colloid and lined by typical thyrocytes. The follicular cells and the colloid showed patchy thyroglobulin immunoreactivity but were negative for calcitonin. In one reported patient, the ectopia presented as a gallbladder mass (Liang et al. 2010).

Endometriosis of the Liver

Introduction

Endometriosis, first described by Rokitansky in 1860, is a condition in which endometrial tissue becomes implanted on extrauterine sites (reviews: Giudice and Kao 2004; Clement 2007; Baldi et al. 2008), most commonly within the pelvis, but rarely also in foregut derivatives, i.e., the pancreas and the liver. Albeit as such a benign lesion, endometriosis is a condition that predisposes to cancer.

Epidemiology

As endometriosis is strongly associated with abdominal trauma and abdominal-pelvic surgery, reliable informations concerning its incidence are difficult to obtain. The literature shows around 25 published cases of hepatic endometriosis. Hepatic endometriosis predominates in the right liver lobe and was mostly detected in patients younger than 60 years of age. In more than 50 % of patients, hepatic endometriosis was detected before menopause (Fluegen et al. 2013).

Clinical and Imaging Features

Hepatic endometriosis is clinically silent in most of cases, but some of the patients reported so far had several symptoms and signs, including chronic epigastric (right) pain or upper abdominal tenderness, and nausea. The disorder can also cause cyclic right subcostal pain (Cravello et al. 1996; Verbeke et al. 1996; Watari et al. 2012) or, rarely, obstructive jaundice (Jeanes et al. 2002; Khan et al. 2002). In one patient, hepatic endometriosis progressed to the hepatic hilar region, causing obstructive jaundice and portal vein thrombosis (Khan et al. 2002). Hepatic

endometriosis is rarely associated with involvement of the falciform ligament (Weinfeld et al. 1998). The majority of published cases of hepatic endometriosis had no past history of pelvic endometriosis. As a complication, hepatic endometriosis can give rise to bronchobiliary fistula (Schuld et al. 2011). Apart from the liver substance, endometriosis occurs in a perihepatic distribution (Weinfeld et al. 1998), including the diaphragm (Kalkur et al. 2013). Endometriosis also occurs in the gallbladder and can cause occult bleeding (Saadat-Gilani et al. 2007).

The ultrasonographic and imaging features have been specified (Grabb et al. 1986; Nakanishi et al. 1994; Inal et al. 2000). Apart from solid liver manifestations (hepatic endometrioma; Groves et al. 2003), hepatic endometriosis presents in the form of cystic hepatic lesions, sometimes with (punctate) calcifications of the cyst wall and with or without septation (Finkel et al. 1986; Cravello et al. 1996; Verbeke et al. 1996; Chung et al. 1998; Inal et al. 2000; Huang et al. 2002; Reid et al. 2003; Tuech et al. 2003; Kouto Fichet et al. 2004; Nezhat et al. 2005; Goldsmith et al. 2009; Roesch-Dietlen et al. 2011; Bouras et al. 2013; Fluegen et al. 2013). Radiologically, the intrahepatic lesion can closely mimic hepatobiliary cystadenoma (Rivkine et al. 2013). The size of hepatic endometriotic cysts ranges from 50 to 240 mm in diameter, and the cysts are either solitary or multilocular. On contrast-enhanced CT images, a heterogeneous mass with both solid and cystic parts is typical, while on MR images, hemorrhagic parts are low-signal intense on T1-weighted and high-signal intense on T2-weighted images (Zawin et al. 1989; Inal et al. 2000). The differential diagnosis of endometriotic hepatic cysts chiefly comprises hemorrhagic simple cysts (Vilgrain et al. 1993; Hanazaki et al. 1997; Hagiwara et al. 2001). Multiple foci of hepatic endometriosis can mimic metastatic liver disease (Asran et al. 2010).

Pathology

At gross examination, hepatic endometriosis occurs in the left or right liver lobe, and bilobar manifestation is exceptional (Khan et al. 2002) and is mostly manifest as a cystic lesion (see above) with fresh or altered blood in the cavity or the features of a so-called chocolate cyst, as known for genital endometriosis, and may produce a liver mass ("endometrioma"; Grabb et al. 1986; Rovati et al. 1990; Inal et al. 2000; Bohra and Diamond 2001). The cystic structures are sometimes multiloculated. The diameter of endometriotic foci in the liver can exceed 20 cm in diameter (30 cm: Tuech et al. 2003). Solid variants of hepatic endometriosis present as an expanding, well-delineated and sometimes multilobated mass of dark-red to red-brown color. A spongy texture may occur, and on cutting, fresh and old blood or a brownish fluid with suspended cholesterol crystals may ooze from the cut surface. The perifocal liver substance is atrophic. Histologically, a typical bimodal morphology with both endometrium-type epithelium and cellular stroma is in evidence, sometimes with secondary changes such as hemorrhage and deposition of stainable iron. The lesions are well delineated and may develop a capsule-like structure with variable inflammatory changes. In old cysts, much of the epithelium may have decayed, and the stroma may be atrophic and/or fibrosed, rendering the histologic diagnosis more difficult. Subsequent to necrosis and/or hemorrhage, nodules containing numerous lipid-laden macrophages ensue in part of the cases (necrotic pseudoxanthomatous nodules in endometriosis; Clement et al. 1988).

In endometriosis, acellular, laminated, ring-like, eosinophilic, and in part PAS-positive structures called Liesegang rings can develop (Schwartz and Bellin 1991; Perrotta et al. 1998), occurring also in other situations of tissue damage, and thought to result from a periodic deposition of proteins within a colloid-like matrix (Cartwright et al. 1999; Henisch 2002). Liesegang rings are named after the German scientist Raphael Eduard Liesegang (1869–1947), an extraordinary and multi-interested personality who translated a Malay grammar when still in school, was formed as a painter, published in 1891 the probably first

article on "the question of electric television" (the "Phototel"), was active in the photographic factory of his father, became an outstanding colloid scientist, visualized neuronal ramifications by use of the Golgi impregnation technique, reported in 1896 periodic phenomena occurring in colloids (later called "Liesegang rings" by Wilhelm Ostwald), and became director of the colloid science branch of the Kaiser-Wilhelm Institute of Biophysics in Frankfurt in 1937.

Immunohistochemically, the glandular epithelium is reactive for Ca19-9 and the stromal cells for CD10 (Carbone et al. 2004). CD10 is known to be a marker for normal and neoplastic endometrial stromal cells (Toki et al. 2002) and may be used in detecting occult or inconspicuous endometrial stromal cells in presumptive endometriosis (Groisman and Meir 2003). The stromal cells of hepatic endometriosis show strong nuclear reactivity for estrogen receptor protein (Carbone et al. 2004).

Hepatic Endometriosis and Malignancy

Both gonadal and extragonadal endometriosis can be complicated by malignancy (ovary 80 %, extragonadal sites 20 %; Heaps et al. 1990; Leiserowitz et al. 2003). Endometrioid adenocarcinomas account for 69 % of the lesions, clear cell carcinomas 13 %, and adenosarcomas 12 % (Clement and Scully 1990). Adenocarcinoma in situ has been found in cystic liver endometriosis (Sanchez-Perez et al. 2006). One report documents squamous carcinoma in hepatic endometriosis (Weinfeld et al. 1998). Adenosarcoma arising in liver endometriosis has also been reported (N'Senda et al. 2000; Jelovsek et al. 2004). There is also one reported observation of low-grade endometrial stromal sarcoma arising in hepatic endometriosis, manifest in the form of a large mass lesion occupying the entire right liver lobe (Khan et al. 2002). Primary extrauterine endometrial stromal sarcoma is known to occur at several sites, in part related to endometriosis (Chang et al. 1993).

Differential Diagnosis

Differential diagnostically, endometriosis of the liver has to distinguish from endometriosis and endometriomas developing in the perihepatic compartment. Endometriosis occurs in the diaphragm (Vercellini et al. 2007), where it can mimic Fitz-Hugh and Curtis syndrome (Takeuchi et al. 2005), and endometrioma has been observed in the subhepatic retroperitoneal space (Lolis et al. 2007). Hepatic endometriosis may histologically be confounded with endometrial stromal sarcoma which can metastasize to the liver (Ramia et al. 2012).

Adrenal Ectopia, Adrenohepatic Fusion (AHF), and Adrenohepatic Adhesion (AHA)

Introduction

Whereas ectopic adrenal tissue is widely recognized in many sites of the body, and in particular the urogenital system, ectopic adrenocortical tissue in the liver is exceedingly rare. In the context of hepatic tumors, ectopic or fused adrenal tissue is of certain significance insofar as these misplaced tissues can give rise to intrahepatic adrenocortical tumors. The complex issue of adrenal rest tumor of the liver is discussed in a separate chapter.

Adrenal Ectopia

In a neonate, a small nodule of adrenal cortical tissue situated deep within the liver has been observed, the cortex consisting of both fetal and adult types (Vestfrid 1980). In another pediatric patient with undifferentiated embryonal sarcoma of the liver, ectopic adrenal cortical tissue was detected under the Glisson's capsule (O'Sullivan et al. 2001). Ectopic adrenal tissue has also been identified in the gallbladder wall (Busuttil 1974). Conversely, heterotopic liver has been observed within the adrenal gland (Honoré 1985; Buck and Koss 1988).

Ectopic adrenocortical neoplastic lesions have been observed in the liver. In a small boy with signs of virilism and Cushing's syndrome, a calcified tumor was detected in the liver, in the absence of the right adrenal gland. The large tumor (8 cm) was embedded within the liver substance and in fact occupied much of the right liver lobe. Histologically, the tumor was composed of large cells typical for an adrenocortical neoplasm (Wilkins and Ravitch 1952).

Adrenohepatic Adhesion

Adrenohepatic adhesion (synonyms employed in the literature: adrenohepatic fusion; adrenohepatic union; hepatic adrenal dystopia) denotes tissual continuity between an entire or a part of the adrenal gland (or glands) with the liver's surface (Schmorl 1891; Oberndorfer 1900; Miloslavich 1914; Weller 1925; Cullen 1925; Hamperl 1970; Dolan and Janovski 1968; Honoré and O'Hara 1976; Honma 1991; O'Sullivan et al. 2001; Figs. 4 and 5). The several terms sometimes used as synonyms may in fact represent different changes caused by different mechanisms. In a first critical review of the issue, adrenal heterotopia was defined as partial or complete fusion of the adrenal with the kidney or liver, the amount of adrenal medulla present being roughly inversely proportional to the degree of fusion (Weller 1925). Later, true adrenorenal heterotopia and accessory or aberrant adrenal rests were clearly distinguished (Culp 1939). Three reports in the literature refer to the incidence of this phenomenon; in one study, 4 among 510 necropsy cases (08 %) were observed (Schmorl 1891), while another study documented 2 among 115 cases (1.7 %; Dolan and Janovski 1968), and a third 63 among 636 nonselected autopsies (9.9 %; Honma 1991). It therefore appears that adrenohepatic adhesion is a rather common incidental finding in autopsy material. In one autopsy series, the incidence of AHF was much higher in older age group, interpreted to suggest that AHF may be an ageing phenomenon (Honma 1991).

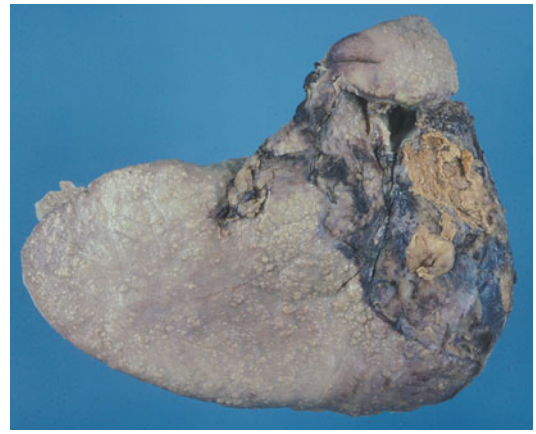

Fig. 4 Adrenohepatic fusion. Yellow adrenocortical tissue (*right half of figure*) adheres to the the liver capsule

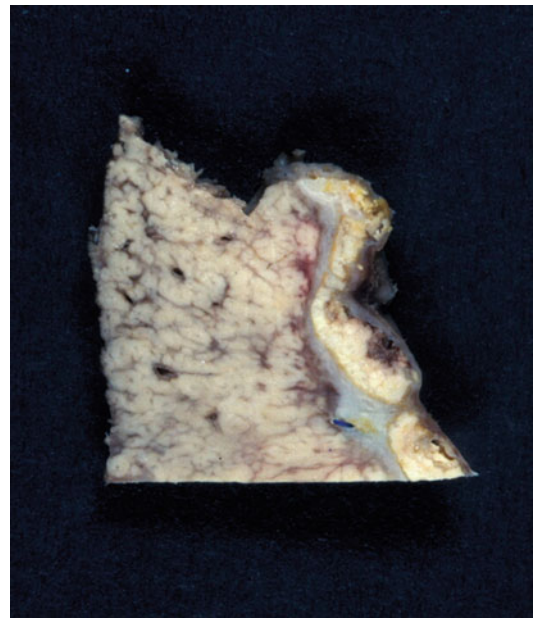

Fig. 5 Adrenohepatic fusion. A *yellow* rim of adrenal tissue is in direct contact to liver tissue

Pathology

At gross examination, heterotopic adrenal tissue may be in evidence in form of clearly identifiable yellow adrenal cortical tissue adherent to the inferior surface of the liver, more frequently on the right side, but rarely also in a bilateral position. Histologically, a broad spectrum of spatial

relationships between the two tissues in question can be observed, having resulted in a more specific nomenclature and views regarding pathogenic pathways. The heterotopic adrenal tissue consists of lipid-rich, typical cortical cells, mostly of the spongiocytic type. The adjacent liver tissue shows only minor changes, compatible with perifocal atrophy, and sometimes ectatic blood vessels. In one systematic study, adrenohepatic fusion (AHF) was distinguished from adrenohepatic adhesion (AHA), AHF being characterized by parenchymal intermingling, whereas AHA was defined as firm attachment of both organs without evidence of parenchymal intermingling (Honma 1991). In more detail, AHF was defined as union of the liver and the right adrenal with close intermingling of the respective parenchymal cells, with or without partial absence of a fibrous organ capsule (Honma 1991; Fig. 5). This author also identified three types of AHF: (a) adrenocortical cells within the liver, (b) hepatocytes and/or bile duct epithelium within the adrenal, and (c) bidirectional intermingling showing features of both (a) and (b). Extrahepatoparenchymal adrenocortical nodules may occur (Honma 1991). In 71 % of AHF cases, adrenocortical hyperplasia was detected, but the significance of hyperplasia for the genesis of AHF is not known (Honma 1991). The histologic separation between AFH and AHA depends on the number of sections performed to identify parenchymal intermingling. AHA and adrenorenal fusion may occur as combined alterations (Miloslavich 1914).

Adrenal Tumors Arising in the Setting of Adrenohepatic Fusion

AHF may be associated with neoplastic processes. In few patients, AHF harbored adrenal cortical adenoma (Woo et al. 2007; Park et al. 2009). In one patient, CT revealed a nodule in the posterior section of the right liver, and the surgeon found that the right adrenal was adherent to a subcapsular nodule of 1.5 cm diameter, which was a lipid-rich adrenocortical adenoma (Woo et al. 2007). In a second patient, a solid hepatic tumor was incidentally detected at ultrasound examination for an unrelated lesion. At surgery, the neoplasm was a lipid-rich cortical adenoma deeply situated within adrenohepatic fusion tissue (Park et al. 2009). In a 69-year-old female patient with a diagnosis of primary aldosteronism, enhanced CT scan before surgery revealed a right adrenal tumor (aldosteronoma) located to an adrenohepatic fusion (Takeuchi et al. 2013).

Adrenal Metastases Developing Through an Adrenohepatic Fusion

Metastasizing hepatocellular carcinoma may use the vascular connections situated within an adrenohepatic adhesion to form metastases in the adrenal gland (Okano et al. 2004). In one patient with a right-sided periadrenal metastasis of hepatocellular carcinoma, this metastasis was supplied by the hepatic artery. It was suggested that cancer cell invasion through an adrenohepatic fusion was the most likely mode of periadrenal metastasis in this case (Iwamoto et al. 1997).

Hepatogonadal Fusion

Introduction

Fusion of the gonadal anlagen with other embryonal organs is a rare but well-described condition. Clinically important is splenogonadal fusion, first described by Pommer in 1889 and characterized by the presence of heterotopic masses of aberrant splenic tissue adherent to the gonads (Putschar and Manion 1956; Kocher et al. 2014). Classical splenogonadal fusion clinically manifests as a palpable, painless left scrotal swelling. Three types of splenogonadal fusion have been described: continuous, discontinuous, and combined, what is of some importance for the understanding of hepatogonadal fusion. In the continuous variety, the main spleen remains connected to the left gonadal mesonephric structures by a continuous cord, which may be completely splenic, fibrous, or beaded with

multiple nodules of splenic tissue. In the discontinuous variety, discrete masses of aberrant heterotopic splenic tissue are found fused to the same structures (Putschar and Manion 1956). In the combined variety, there is an extension of functional splenic tissue from the orthotopic spleen into the abdomen, but there is no connection to the ectopic spleen near the gonad.

Hepatogonadal Fusion

Fusion of a liver component with testis is highly unusual and has only reported few times. It is a form of ectopic liver tissue (Ferro et al. 1996; Fan et al. 2012). A 4-month-old boy operated for right inguinal hernia with completely patent processus vaginalis showed a reddish nodule adherent to the upper pole of the right testicle. This nodule continued upward in a thin fibrous pedicle found to enter the porta hepatis. Histology revealed a small lobe of hepatic tissue that contained several portal tracts of different sizes. The hepatic parenchyma consisted of liver cell plates and intervening sinusoids, and the portal tracts contained interlobular bile ducts. In a second patient, a 3-month-old boy showed an unusual spermatic cord-like structure connecting the liver and right testis. Liver tissue was found along the entire length of this structure (Fan et al. 2012).

Pathogenic Pathways

Gonadal fusion events may be better understood owing to increasing knowledge of gonadal development and gonadal descent (Byskov 1986; Werdelin and Nilsonne 1999). The testis begins its descent at about the eighth week, when the liver, spleen, and adrenal anlagen are already formed. In regard to splenogonadal fusion, it has been suggested that, owing to the close spatial relation between the developing spleen and the left gonad during rotation of the dorsal mesogastrium, adhesion between the splenic peritoneum and the gonadal ridge may occur and result in fusion (Gouw et al. 1985; Carragher 1990).

Hepatic Pregnancy

Hepatic pregnancy is briefly discussed here because of the focal hepatic or perihepatic changes and potential mass effects induced by this disorder, resulting in a complex differential diagnosis. Primary peritoneal pregnancy is rare, and implantation may occur anywhere but most commonly on the surface of the pelvic peritoneum. The four chief criteria to be fulfilled in order to diagnose primary peritoneal pregnancy comprise (a) normal tubes and ovaries without evidence of injury, (b) no evidence of utero-peritoneal fistula, (c) pregnancy-related exclusively to the peritoneal surface, and (d) pregnancy at an early enough stage of gestation to exclude the possibility of a secondary implantation following initial eliminated primary tubal nidation (Studdiford 1942). The liver, respectively, its visceral peritoneum, is an exceptional site of implantation (Mear et al. 1965; Kirby 1969; Luwuliza-Kirunda 1978; Gordeev 1980; Hietala et al. 1983; Mitchell and Teare 1984; Shukla et al. 1985; Paulino-Netto and Roselli 1986; Veress and Wallmander 1987; Borlum and Blom 1988; Schlatter et al. 1988; Harris et al. 1989; De Almeida Barbosa et al. 1991; Leshchenko et al. 1994; Kato 1995; Nichols et al. 1995; Delabrousse et al. 1999; Chui et al. 2001; Jané et al. 2008). Hepatic pregnancy may present as a bleeding mass of several centimeters diameter, with angiographic features similar to those in tubal pregnancy (Hietala et al. 1983), but hepatic implantation may also be compatible with a living infant (Mear et al. 1965; Shukla et al. 1985). Exceptionally, hepatic pregnancy is diagnosed after long delay, i.e., in a state of lithopedion (Luwuliza-Kirunda 1978). Lithopedion (Greek: lithos, stone; paidion, child) designates a fetus that has become bony or calcified after death (Fagan et al. 1980) and has apparently first been described in the tenth century by an Arab surgeon named Albucasis (cited in Lachman et al. 2001). In the late nineteenth century, lithopedion has been classified based on the kyemal components involved by calcification/ossification (Küchenmeister 1881; Hemley and Schwinger

1951), i.e., lithokelyphos (stone sheath or egg shell; Kelyphos, Greek, = husk, shell; calcified membranes forming a hard shell surrounding the fetus), lithokelyphopedion (stone sheath child; both membranes and fetus are calcified), and true lithopedion (stone child; fetus, but not membranes, is calcified). The clinical and radiologic differential diagnosis of hepatic pregnancy comprises, apart from other heterogeneously structured masses, hepatic hemorrhage occurring during pregnancy.

Fetus in Fetu

An extraordinary cause of an abdominal mass in infancy is fetus in fetu (FIF), FIF being "applied to any structure in which the fetal form is in a very high development of organogenesis and to the presence of a vertebral axis" (Gonzales-Crussi 1982). FIF was first described by Meckel in 1800 and defined by Willis (1953). FIF is thought to arise from inclusion of a monozygotic diamniotic twin where the parasitic twin installs and grows in the body of its partner (Gürses et al. 1990; Hoeffel et al. 2000; review: Brand et al. 2004), although it has been proposed that FIF may represent a fetiform, highly organized teratoma (a "pseudofetus"; de Lagausie et al. 1997). FIF is distinguished from bona fide benign teratoma by the presence of an amniotic or at least amnion-coated cavity and of a vertebral axis with limb buds (present in 91 % and 82.5 %, respectively; Hoeffel et al. 2000) or other appropriately situated bones or organs. FIF is extremely rare; the estimated incidence is 1 per 500,000 births (Grant and Pearn 1969). In almost 90 %, there was a single parasitic fetus apart from five reports in which the number of the fetus ranged from 2 to 5 (Hoeffel et al. 2000). Most of the FIF reported were cases of pedunculated masses within a capsule containing fluid and with an umbilical cord containing only two vessels. The typical site of FIF is the upper retroperitoneal space, but very rare other sites include the pelvic area, the ileal mesentery, the cranial cavity, the scrotum, and the liver. FIF may undergo postnatal growth (Kim and Shinn 1993).

FIF in the right liver lobe presented as a sac containing the fetus (Al-Baghdadi 1992). In one patient, a fetal liver abnormality was detected during routine ultrasound examination, and postnatal examinations allowed the diagnosis of three lesions of intrahepatic fetus in fetu, associated with multiple small subcapsular and perimass vascular hamartomas. The surgically removed specimen (hemihepatectomy) revealed two lesions with an amnion-lined cavity and one lesion with the features of benign teratoma (Magnus et al. 1999).

Ectopic Cartilage of the Hepatobiliary Tract

Foci of hyaline and mature cartilage at the porta hepatis have been described in patients with extrahepatic biliary atresia (EHBA) (Hassab et al. 1996; Mirkin and Knisely 1997; Kashiwagi et al. 2007; Stahlschmidt et al. 2008). Several band-like portions of hyaline cartilage were present in the adventitia of the nearly obliterated bile duct, while other patients revealed small nodules of hyaline cartilage adjoining residual peribiliary glands. The chondroid tissue exhibited a rich development of cartilage matrix, and the foci were demarcated by perichondrium. Respiratory-type epithelium was not detected, although the cartilaginous structures were sometimes reminiscent of the bars and plates seen in bronchi. In one case, the cartilage islands closely followed the lumens of small bile ducts (Hassab et al. 1996). In a 3-month-old infant with biliary atresia, islets of hyaline cartilage were found in the wall of a stringlike gallbladder, whereas the porta hepatis did not show cartilage in this case (Altamirano and Drut 2008).

Heterotopias that contain hyaline cartilage may occur as a result of developmental malformation or as a result of connective tissue metaplasia. It has been suggested that chondroid heterotopia in EHBA may result from long-standing inflammation inducing a metaplastic response, similar to the cartilage observed in renal cystic dysplasia (Bernstein 1971; Mirkin and Knisely 1997).

References

Abu Hilal M, Harb A, Zeidan B, Steadman B, Primrose JN, Pearce NW (2009) Hepatic splenosis mimicking HCC in a patient with hepatitis C liver cirrhosis and mildly raised alpha feto protein; the important role of explorative laparoscopy. World J Surg Oncol 7:1

Al-Baghdadi R (1992) Fetus in fetu of the liver: case report and review of the literature. J Pediatr Surg 27:1491–1492

Altamirano E, Drut R (2008) Extrahepatic biliary atresia with cartilaginous metaplasia in the gallbladder remnants. J Clin Pathol 61:965–966

Armstrong CP, King PM, Dixon JM, McLeod IB (1981) The clinical significance of heterotopic pancreas in the gastrointestinal tract. Br J Surg 68:384–387

Arndtfield M, van der Kooy D (2013) The adult mammalian pancreas contains separate precursors of pancreatic and neural crest development origins. Stem Cells Dev 22:2145–2157

Asran M, Rashid A, Szklaruk J (2010) Hepatic endometriosis mimicking metastatic disease: a case report and review of the literature. J Radiol Case Rep 4:26–31

Aviv V, Meivar-Levy I, Rachmut IH, Rubinek T, Mor E, Ferber S (2009) Exendin-4 promotes liver cell proliferation and enhances the PDX-1-induced liver to pancreas transdifferentiation process. J Biol Chem 284:33509–33520

Bahadir B, Ozdamar SO, Gun BD, Bektas S, Numanoglu KV, Kuzey GM (2006) Ectopic pancreas associated with choledochal cyst and multiseptate gallbladder. Pediatr Dev Pathol 9:312–315

Baldi et al. (2008). http://www.ncbi.nlm.nih.gov/pubmed/18357365

Ballinger J (1941) Hypoglycemia from metastasizing insular carcinoma of aberrant pancreatic tissue in the liver. Arch Pathol 32:227–285

Barber H, Barber H (1952) Pancreatic heterotopia causing post-cholecystectomy symptoms and obstructive jaundice. Ann Surg 138:124–126

Barbosa de Castro JC, Dockerty M, Waugh JM (1946) Pancreatic heterotopia. Review of the literature an report of 41 authenticated surgical cases of which 25 were clinically significant. Surg Gynecol Obstet 82:527–542

Ber I, Shternhall K, Perl S, Ohanuna Z, Goldberg I, Barshack I, Benvenisti-Zarum L, Meivar-Levy I, Ferber S (2003) Functional, persistent and extended liver to pancreas transdifferentiation. J Biol Chem 278:32950–32957

Berenguer J, Sala T, Carrasquer J, Rodrigo M, Garrido G, Pertejo V (1972) Duodenal aberrant pancreas, uncommon cause of obstructive jaundice. Apropos of a case (in Spanish). Rev Esp Enferm Apar Dig 36:567–574

Berneman-Zeitouni D, Molekandov K, Elgart M, Mor E, Fornoni A, Dminguez MR, Kerr-Conte J et al (2014) The temporal and hierarchical control of transcription factors-induced liver to pancreas transdifferentiation. PLoS One 9:e87812

Bernstein J (1971) The morphogenesis of renal parenchymal maldevelopment (renal dysplasia). Pediatr Clin North Am 18:395–407

Bhana BD, Chetty R (1999) Heterotopic pancreas – an unusual cause of cholecystitis. S Afr J Surg 37:105–107

Bill K, Belber JP, Carson JW (1982) Adenomyoma (pancreatic heterotopia) of the duodenum producing common bile duct obstruction. Gastrointest Endosc 28:182–184

Bizekis CS, Pua B, Glassman LR (2003) Thoracic splenosis: mimickry of a neurogenic tumor. J Thorac Cardiovasc Surg 125:1155–1156

Bohra AK, Diamond T (2001) Endometrioma of the liver. Int J Clin Pract 55:286–287

Borlum KG, Blom R (1988) Primary hepatic pregnancy. Int J Gynaecol Obstet 27:427–429

Bouras AF, Vincentelli A, Boleslawski E, Truant S, Liddo G, Prat A, Pruvot FR, Zerbib P (2013) Liver endometriosis presenting as a liver mass associated with high blood levels of tumoral biomarkers. Clin Res Hepatol Gastroenterol 37:e85–e88

Brand A, Alves MC, Saraiva C, Loio P, Goulao J, Malta J, Palminha JM, Martina M (2004) Fetus in fetu – diagnostic criteria and differential – a case report and literature review. J Pediatr Surg 39:616–618

Buchbinder JH, Lipkoff CJ (1939) Splenosis: multiple peritoneal splenic implants following abdominal injury. Surgery 6:927–934

Buck FS, Koss MN (1988) Heterotopic liver in an adrenal gland. Pediatr Pathol 8:535–540

Burke ZD, Tosh D (2012) Ontogenesis of hepatic and pancreatic stem cells. Stem Cell Rev 8:586–596

Busuttil A (1974) Ectopic adrenal within the gall-bladder wall. J Pathol 113:231–233

Byskov AG (1986) Differentiation of mammalian embryonic gonad. Physiol Rev 66:71–117

Carbone A, Prete FP, Sofo L, Alfieri S, Rotondi F, Zannoni GF, Doglietto GB (2004) Morphological and immunohistochemical characterization of an endometriotic cyst of the liver: diagnostic approach to endometriosis. Histopathology 45:420–422

Cardona D, Grobmyer S, Crawford JM, Liu C (2007) Hepatocellular carcinoma arising from ectopic liver tissue in the pancreas. Virchows Arch 450:225–229

Carr NJ, Turk EP (1992) The histological features of splenosis. Histopathology 21:549–553

Carragher AM (1990) One hundred years of splenogonadal fusion. Urology 35:471–475

Cartwright JHE, Garcia-Ruiz JM, Villacampa AI (1999) Pattern formation in crystal growth: liesegang rings. Comput Phys Commun 121:411–413

Casella G, Villanacci V, Yarygina M, Bassotti G (2013) Perihepatic splenosis simulating a focal liver lesion in a patient with chronic hepatitis C. Rev Esp Enferm Dig 105:435–436

Cassol CA, Noria D, Asa SL (2010) Ectopic thyroid tissue within the gall bladder: case report and brief review of the literature. Endocr Pathol 21:263–265

Castellani M, Cappellini MD, Cappelletti M, Fedriga E, Reschini E, Cerino M, Gerundini P (2001) Tc-99m sulphur colloid scintigraphy in the assessment of residual splenic tissue after splenectomy. Clin Radiol 56:596–598

Cavallini A (1958) Unusual case of accessory spleen in the liver with sclerosiderotic area of Gandy-Gamna (in Italian). Minerva Med 49:687–690

Cerullo G, Marrelli D, Di Mare G, Onorati M, Tripodi S, Neri A, Roviello F (2011) Heterotopic pancreatic tissue in the gallbladder. Two case reports and brief review of the literature. G Chir 32:259–262

Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR (1993) Primary extrauterine endometrial stromal neoplasms: a clinicopathologic study of 20 cases and a review of the literature. Int J Gynecol Pathol 12:282–296

Chen CH, Yang CC, Yeh YH, Chou DA, Kuo CL (2001) Ectopic pancreas located to the major duodenal papilla: case report an d review. Gastrointest Endosc 53:121–123

Choi GH, Ju MK, Kim JY, Kang CM, Kim KS, Choi JS, Han KH, Park MS, Park YN et al (2008) Hepatic splenosis preoperatively diagnosed as hepatocellular carcinoma in a patient with chronic hepatitis B: a case report. J Korean Med Sci 23:336–341

Chou SJ, Chou YW, Jan HC, Chen VT, Chen TH (2006) Ectopic pancreas in the ampulla of vater with obstructive jaundice. A case report and review of literature. Dig Surg 23:262–264

Chui AKK, Lo KWK, Choi PCL, Sung MCC, Lau JWY (2001) Primary hepatic pregnancy. Aust N Z J Surg 71:260–261

Chung WJ (2014) Splenosis mimicking hepatocellular carcinoma. Korean J Gastroenterol 64:173–175

Chung CC, Liew CT, Hewitt PM, Leung KL, Lau WY (1998) Endometriosis of the liver. Surgery 123:106–108

Clement PB (2007) The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. Adv Pathol Anat 14:241–260

Clement PB, Scully RE (1990) Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of literature. Hum Pathol 21:363–381

Clement PB, Young RH, Scully RE (1988) Necrotic pseudoxanthomatous nodules of ovary and peritoneum in endometriosis. Am J Surg Pathol 12:390–397

Contini S, Zinicola R, Bonati L, Caruana P (2003) Heterotopic pancreas in the ampulla of vater. Minerva Chir 58:404–408

Coupland RM, Aukland P, Harrison DA (1987) Heterotopic pancreas: a rare cause of obstructive jaundice. J R Coll Surg Edinb 32:168–170

Cravello L, D'Ercole C, Le Treut YP, Blanc B (1996) Hepatic endometriosis: a case report. Fertil Steril 66:657–659

Cullen TS (1925) Accessory lobes of the liver. Arch Surg 11:718–764

Culp OS (1939) Adrenal heterotopia. A survey of the literature and report of a case. J Urol 41:303

Curtis LE, Sheahan DG (1969) Heterotopic tissues in gallbladder. Arch Pathol 88:677–683

D'Angelica M, Fong Y, Blumgart LH (1998) Isolated hepatic splenosis: first reported case. HBP Surg 11:39–42

Davidson LA, Reid IN (1997) Intrahepatic splenic tissue. J Clin Pathol 50:532–533

De Almeida Barbosa A, Rodrigues de Freitas LA, Andrade Mota M (1991) Primary pregnancy in the liver. A case report. Pathol Res Pract 187:329–331

De Lagausie P, de Napoli Cocci S, Stempfle N, Truong QD, Vuillard E, Ferkadji L, Aigrain Y (1997) Highly differentiated teratoma and fetus-in-fetu: a single pathology? J Pediatr Surg 32:115–116

De Teyssieu M (1914) Rate surnuméraire incluse dans le foie. J Med Bordeaux 44:99

De Vuysere S, Van Steenbergen W, Aerts R, Van Hauwaert H, Van Beckevoort D, Van Hoe L (2000) Intrahepatic splenosis: imaging features. Abdom Imaging 25:187–189

Del Sordo R, Bellezza G, Colella R, Mameli MG, Giansanti M, Cavaliere A (2011) Epithelial cyst of the spleen with foci of ectopic liver. J Pediatr Surg 46: e21–e23

Delabrousse E, Site O, Le Mouel A, Riethmuller D, Kastler B (1999) Intrahepatic pregnancy: sonography and CT findings. AJR Am J Roentgenol 173:1377–1378

Delhougne F (1924) Ueber Pancreaskeime im Magen (On pancreatic primordia in the stomach). Arch Klin Chir 129:116–123

Derbyshire RC (1940) Studies of accessory pancreas. Thesis. Mayo Graduate School of Medicine, University of Minnesota, Rochester

Di Costanzo GG, Picciotto FP, Marsilia GM, Ascione A (2004) Hepatic splenosis misinterpreted as hepatocellular carcinoma in cirrhotic patients referred for liver transplantation: report of two cases. Liver Transpl 10:706–709

Dolan MF, Janovski NA (1968) Adreno-hepatic union (adrenal dystopia). Arch Pathol 86:22–24

Dolan RV, Remine WH, Dockery MB (1974) The fate of heterotopic pancreatic tissue. Arch Surg 109:762–765

Espert JJ, Targarona EM, Bombuy E, Setoain J, Visa J, Trias M (2001) Evaluation of risk of splenosis during laparoscopic splenectomy in rat model. World J Surg 25:882–885

Fagan et al. (1980). http://www.ncbi.nlm.nih.gov/pubmed/7387366

Falco Raucci F (1960) On a case of aberrant pancreas in the duodenal wall with concomitant duodenal ulcer (in Italian). G Ital Chir 16:451–462

Fan R, Faught PR, Sun J, Meldrum KK (2012) Hepatogonadal fusion. J Pediatr Surg 47:e5–e6

Ferber S, Halkin A, Cohen H, Ber I, Einav Y, Goldberg I, Barshack I, Seijffers R, Kopolovic J, Kaiser N, Karasik A (2000) Pancreatic and duodenal homeobox gene

1 induces expression of insulin genes in liver and ameliorates streptozotocin-induced hyperglycemia. Nat Med 6:568–572
Ferro F, Lais A, Boldrini R, De Peppo F, Federici G, Bosman C (1996) Hepatogonadal fusion. J Pediatr Surg 31:435–436
Filippou DK, Vezakis A, Filippou G, Condilis N, Rizos S, Skandalakis P (2006) A rare of ectopic pancreas in the ampulla of vater presented with obstructive jaundice. Ann Ital Chir 77:517–519
Finkel L, Marchevsky A, Cohen B (1986) Endometrial cyst of the liver. Am J Gastroenterol 81:576–578
Fleming CR, Dickson ER, Harrison EG (1976) Splenosis: autotransplantation of splenic tissue. Am J Med 61:414–419
Fluegen G, Jankowiak F, Zacarias Foehrding L, Kroepil F, Knoefel WT, Topp SA (2013) Intrahepatic endometriosis as differential diagnosis: case report and literature review. World J Gastroenterol 19:4818–4822
Foroudi F, Ahern V, Peduto A (1999) Splenosis mimicking metastases from breast carcinoma. Clin Oncol (R Coll Radiol) 11:190–192
Fremont RD, Rice TW (2007) Splenosis: a review. South Med J 100:589–593
Fukueda M, Hamada N, Kaieda M, Kadono J, Nakamura N, Ishizaki N (2000) A case of heterotopic pancreas in the liver with primary cholesterol hepatolithiasis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 97:1057–1061
Gadrat J, Ribet A, Suduca P, Bertrand J (1965) Intrahepatic aberrant pancreas. Two cases diagnosed by needle biopsy controlled by laparoscopy in two cirrhotics (in French). Arch Mal Appar Dig Malnutr 54:1143–1148
Galloro P, Marsilia GM, Nappi O (2003) Hepatic splenosis diagnosed by fine-needle cytology (in Italian). Pathologica 95:57–59
Galloro G, Napolitano V, Magno L, Diamantis G, Nardone G, Bruno M, Mollica C, Persico G (2008) Diagnosis and therapeutic management of cystic dystrophy of the duodenal wall in heterotopic pancreas. A case report and revision of the literature. JOP 9:725–732
Gamna C (1921) Sopra alcune lesioni die vasi nella siderosi emolitica delle milza. Giornale R Accad Med Torino 84:291
Gamulin A, Oberholzer J, Rubbia-Brandt L, Mentha G (2002) An unusual, presumable hepatic mass. Lancet 360:2066
Gandy C (1905) Lésions particulières de la rate dans un cas de cirrhose biliaire. Bull Soc Anat Paris 80:872–879
Garamella JJ, Hay L (1954) Autotransplantation of spleen: splenosis. Ann Surg 140:107–112
Gaspar-Fuentes A, Campos Tarrech JM, Fernandez Burgui JL et al (1973) Ectopias pancreaticas. Rev Esp Enferm Apar Dig 39:255–268
Ghanem N, Bley T, Altehoefer C, Hogerle S, Langer M (2003) Ectopic thyroid gland in the porta hepatis and lingua. Thyroid 13:503–507
Giudice LC, Kao LC (2004) Endometriosis. Lancet 364:1789–1799
Gokhale UA, Nanda A, Pillai R, Al-Layla D (2010) Heterotopic pancreas in the stomach: a case report and a brief review of the literature. JOP 11:255–257
Goldsmith PJ, Ahmad N, Dasgupta D, Campbell J, Guthrie JA, Lodge JP (2009) Case hepatic endometriosis: an continuing diagnostic dilemma. HPB Surg 2009:407206
Gonzales-Crussi F (1982) Extragonadal teratomas, vol 2, Atlas of Tumor Pathology. Armed Forces Institute of Pathology, Washington, DC, fasc. 18
Gordeev VI (1980) Extrauterine pregnancy with fetal implantation in the liver (in Russian). Klin Khir 4:67–68
Gouw ASH, Elema JD, Bink-Boelkens MTE, de Jongh HJ, ten Kate LP (1985) The spectrum of splenogonadal fusion: case report and review of 84 reported cases. Eur J Pediatr 144:316–323
Grabb A, Carr L, Goodman JD, Mendelson DS, Cohen B, Finkel L (1986) Hepatic endometrioma. J Clin Ultrasound 14:478–480
Grande M, Lapecorella M, Ianora AA, Longo S, Rubini G (2008) Intrahepatic and widely distributed intraabdominal splenosis: multidetector CT, US and scintigraphic findings. Intern Emerg Med 3:265–267
Grant P, Pearn JH (1969) Foetus-in-foetu. Med J Aust 1:1016–1020
Groisman GM, Meir A (2003) CD10 is helpful in detecting occult or inconspicuous endometrial stromal cells in cases of presumptive endometriosis. Arch Pathol Lab Med 127:1003–1006
Groves AM, Whitfield R, Lomas DJ, Gibbs P (2003) Imaging of hepatic endometrioma in a patient with multiple haemangiomas. J Hepatol 38:547
Gruen DR, Gollub MJ (1997) Intrahepatic splenosis mimicking hepatic adenoma. AJR Am J Roentgenol 168:725–726
Gucer H, Bagci P, Coskunoglu EZ, Karadag C (2011) Heterotopic pancreatic tissue located in the gallbladder wall. A case report. JOP 12:152–154
Gürses N, Gürses N, Bernay F (1990) Twin fetuses in fetu and a review of the literature. Z Kinderchir 45:319–322
Hagiwara A, Inoue Y, Shutoh T, Kinoshita H, Wakasa K (2001) Haemorrhagic hepatic cyst: a differential diagnosis of cystic tumour. Br J Radiol 74:270–272
Hammarström LE, Nordgren H (1999) Ectopic pancreas of the ampulla of vater. Endoscopy 31:S67
Hamperl H (1970) On the 'adrenal rest- tumors' (hypernephromas) of the liver. Z Krebsforsch 74:310–317
Hanazaki K, Wakabayashi M, Mori H, Sodeyama H, Yoshizawa K, Yokoyama S, Sode Y, Kawamura N, Miyazaki T (1997) Hemorrhage into a simple liver cyst: diagnostic implications of a recent case. J Gastroenterol 32:848–851
Harach HR (1998) Ectopic thyroid tissue adjacent to the gallbladder. Histopathology 32:90–91

Hari CK, Brown MJ, Thompson I (1999) Tall cell variant of papillary carcinoma arising from ectopic thyroid tissue in the trachea. J Laryngol Otol 113:183–185
Harris GJ, Al-Jurf AS, Yuh WT, Abu-Yousef MM (1989) Intrahepatic pregnancy. A unique opportunity for evaluation with sonography, computed tomography, and magnetic resonance imaging. JAMA 261:902–904
Hassab MH, Baez-Giangreco A, Afzal M, Shadi SM, Al Olayet YF (1996) Extrahepatic biliary atresia with hyaline cartilage and multiple congenital anomalies: a case report. Saudi J Gastroenterol 2:156–159
Heaps JM, Nieberg RK, Berek JS (1990) Malignant neoplasms arising in endometriosis. Obstet Gynecol 75:1023–1028
Heer C, Pförtner M, Hamberger U, Raute-Kreisen U, Hanraths M, Bartsch DK (2010) Heterotopic pancreatic tissue in the bifurcation of the bile duct. Rare diagnosis mimicking a Klatskin tumour (in German). Chirurg 81:151–154
Heller DS, Harrison LE, Peters S (2010) Periaortic pancreatic rests: a case report. J Reprod Med 55:430–432
Hemley SD, Schwinger A (1951) Lithopedion: case report and survey. Radiology 58:235–238
Henisch HK (2002) Crystals in gels and Liesegang rings. Cambridge University Press, Cambridge
Hierholzer J, Fuchs H, Menzel B (2001) Intrahepatic splenosis (in German). Rofo Fortschr Geb Röntgenstr Neuen Bildgeb Verfahr 173:769–771
Hietala SO, Andersson M, Emdin SO (1983) Ectopic pregnancy in the liver. Report of a case and angiographic findings. Acta Chir Scand 149:633–635
Hoeffel CC, Nguyen KQ, Phan HT, Truong NH, Nguyen TS, Tran TT, Fornes P (2000) Fetus in fetu: a case report and literature review. Pediatrics 105:1335–1344
Hoelzer H (1940) An occlusion of vater's papilla by accessory pancreas. Zentralbl Chir 67:1715–1717
Honma K (1991) Adreno-hepatic fusion. An autopsy study. Zentralbl Pathol 137:117–122
Honoré LH (1985) Intra-adrenal hepatic heterotopia. J Urol 133:652–654
Honoré and O'Hara (1976). http://www.ncbi.nlm.nih.gov/pubmed/1255896
Horb ME, Shen CN, Tosh D, Slack JM (2003) Experimental conversion of liver to pancreas. Curr Biol 13:105–115
Horgan EJ (1921) Accessory pancreatic tissue. Arch Surg 2:521–534
Horger M, Eschmann SM, Lengerke C, Claussen D, Pfannenberg C, Bares R (2003) Improved detection of splenosis in patients with haematological disorders: the role of combined transmission-emission tomography. Eur J Nucl Med Mol Imaging 30:316–319
Hsia CY, Wa CW, Lai WY (1999) Heterotopic pancreas: a difficult diagnosis. J Clin Gastroenterol 28:144–147
Huang WT, Chen WJ, Chen CL, Cheng YF, Wang JH, Eng HL (2002) Endometrial cyst of the liver: a case report and rview of the literature. J Clin Pathol 55:715–717
Ihtiyar E, Isiksoy S, Algin C, Sahin A, Erkasap S, Yasar B (2003) Ectopic thyroid in the gallbladder: report of a case. Surg Today 33:777–780
Imbriaco M, Camera L, Manciuria A, Salvatora M (2008) A case of multiple intra-abdominal splenosis with computed tomography and magnetic resonance imaging correlative findings. World J Gastroenterol 14:1453–1455
Inal M, Bicakci K, Soyupak S, Oguz M, Ozer C, Demirbas O, Akgul E (2000) Hepatic endometrioma: a case report and review of the literature. Eur Radiol 10:431–434
Incedayi M, Saglam M, Sonmez G, Sivrioglu AK (2013) Medical image. Splenosis of Glisson's capsule. N Z Med J 126:72–74
Inceoglu R, Dosluoglu HH, Kullu S, Ahiskali R, Doslu FA (1993) An unusual cause of hydropic gallbladder and biliary colic – heterotopic pancreatic tissue in the cystic duct: report of a case and review of the literature. Surg Today 23:532–534
Inchingolo R, Peddu P, Karani J (2013) Hepatic splenosis presenting as arterialized liver lesion in a patient with NASH. Eur Rev Med Pharmacol Sci 17:2853–2856
Ishikawa M, Tsujimoto T, Uemura M, Kawaratani H, Fujimoto M, Hirai T, Kuriyama S, Fkui H (2007) A case of intrahepatic splenosis (in Japanese). Nippon Shokakibyo Gakkai Zasshi 104:1758–1765
Iwamoto S, Okuda K, Takeda N, Sonoda K, Sanefuji H (1997) Case report: right-sided periadrenal metastasis supplied by the hepatic artery. Clue to the genesis of pedunculated hepatocellular carcinoma. J Gastroenterol Hepatol 12:392–397
Izzo L, Caputo M, Galati G (2004) Intrahepatic accessory spleen: imaging features. Liver Int 24:216–217
Jamshidi M, Kasirye O, Smith DJ (1998) Ectopic thyroid nodular goiter presenting as a porta hepatis mass. Am Surg 64:305–306
Jané Z, Farkasdi J, Jager L, Kneffel P, Koupany C, Markus B, Puskas T (2008) A rare localisation of ectopic pregnancy – a case of hepatic pregnancy (in Hungarian). Magy Seb 61:270–272
Jeanes AC, Murray D, Davidson B, Hamilton M, Watkinson AF (2002) Case report: hepatic and retroperitoneal endometriosis presenting as obstructive jaundice with ascites: a case report and review of the literature. Clin Radiol 57:226–229
Jelovsek JE, Winans C, Brainard J, Falcone T (2004) Endometriosis of the liver containing mullerian adenosarcoma: case report. Am J Obstet Gynecol 191:1725–1727
Kalkur S, Raza A, Richardson RE (2013) Right upper quadrant pain? Think outside the liver: a case of diaphragmatic perihepatic endometriosis. J Obstet Gynaecol 33:743–744
Kang KC, Cho GS, Chung GA, Kang GH, Kim YJ, Lee MS, Kim HK, Park SJ (2011) Intrahepatic splenosis mimicking liver metastasis in a patient with gastric cancer. J Gastric Cancer 11:64–68

Karahan OI, Kahriman G, Soyuer I, Artis T, Comu NB (2006) MR cholangiopancreatography findings of heterotopic pancreatic tissue in the distal common bile duct. Diagn Interv Radiol 12:180–182

Kashgari AA, Al-mana HM, Al-Kadhi YA (2009) Intrahepatic splenosis mimicking hepatocellular carcinoma in a cirrhotic liver. Saudi Med J 30:429–432

Kashiwagi Y, Kawashima H, Ioi H, Amaha M, Nishimata S, Takekuma K, Hoshika A et al (2007) Biliary atresia with cartilage formation. Pediatr Int 49:683–685

Kato K (1995) Primary hepatic pregnancy (in Japanese). Ryoikibetsu Shokogun Shirizu 8:523–525

Kattepura S, Nanjegowda NB, Babu MK, Das K (2010) Macroscopic pancreatic heterotopia on a congenital biliary dilatation. Pediatr Surg 26:847–849

Khan A, Craig M, Jarmulowicz M, Davidson B (2002) Liver tumours due to endometriosis and endometrial stromal sarcoma. HPB (Oxford) 4:43–45

Kim OH, Shinn KS (1993) Postnatal growth of fetus-in-fetu. Pediatr Radiol 23:411–412

Kim KA, Park CM, Kim CH, Choi SY, Park SW, Kang EY, Seol HY, Cha IH (2003) An interesting hepatic mass: splenosis mimicking a hepatocellular carcinoma. Eur Radiol 13:2713–2715

Kimbrough RD (1973) Pancreatic-type tissue in livers of rats fed polychlorinated biphenyls. J Natl Cancer Inst 51:679–681

Kirby NG (1969) Primary hepatic pregnancy. Br Med J 1:269

Klob J (1859) Pancreas accessorium. Ztschr Kaiserl Königl Gesellsch Aerzte Wien 15:732

Kocher NJ, Tomaszewski JJ, Parsons RB, Cronson BR, Altman H, Kutikov A (2014) Splenogonadal fusion: a rare etiology of solid testicular mass. Urology 83:e1–e2

Kondo T, Katoh R, Omata K, Oyama T, Yagawa A, Kawaoi A (2000) Incidentally detected liver metastasis of well-differentiated follicular carcinoma of the thyroid mimicking ectopic thyroid. Pathol Int 50:509–513

Kondo M, Okazaki H, Takai K, Nishikawa J, Ohta H, Uekusa T, Yoshida H, Tanaka K (2004) Intrahepatic splenosis in a patient with chronic hepatitis C. J Gastroenterol 39:1013–1015

Kouto Fichet G, Aubé C, Lebigot J, Pessaux P, Rousselet MC, Caron C (2004) Hepatic endometriotic cyst (in French). J Radiol 85:124–127

Kralik J, Pesula E (1993) A pancreatic pseudocyst in the liver (in Czech). Rozhl Chir 72:91–93, 151

Kubota K, Kita J, Rokkaku K, Iawsaki Y, Sawada T, Imura J, Fujimori T (2007) Ectopic hepatocellular carcinoma arising from pancreas: a case report and review of the literature. World J Gastroenterol 13:4270–4273

Küchenmeister F (1881) Ueber Lithopädion. Arch Gynäk 17:153–259

Kumar RJ, Borzi PA (2001) Splenosis in a port site after laparoscopic splenectomy. Surg Endosc 15:413–414

Kuo FY, Swanson PE, Yeh MM (2009) Pancreatic acinar tissue in liver explants: a morphologic and immunohistochemical study. Am J Surg Pathol 33:66–71

Kutzen BM, Levy N (1978) Splenosis simulating an intramural gastric mass. Radiology 126:45–46

Labat-Debelleix V, Carpentier E, Causse X, Kerdraon R, Bonneua C, Michenet P (2008) Hepatic splenosis: a rare etiology of hepatic nodules (in French). Gastroenterol Clin Biol 32:83–87

Lachman N, Satyapal KS, Kalideen JM, Moodley TR (2001) Lithopedion: a case report. Clin Anat 14:52–54

Laflamme L, Boucher L (2003) Splenosis detected by heat-denaturated Tc-99m red blood cell scintigraphy. Clin Nucl Med 28:39–42

Lai EC, Tompkins RK (1986) Heterotopic pancreas. Review of a 26 year experience. Am J Surg 151:697–700

Laughlin EH, Keown ME, Jackson JE (1983) Heterotopic pancreas obstructing the ampulla of vater. Arch Surg 118:979–980

Lee BC, Hendricks JD, Bailey GS (1989) Metaplastic pancreatic cells in liver tumors induced by diethylnitrosamine. Exp Mol Pathol 50:104–113

Lee JB, Ryu KW, Song TJ, Suh SO, Kim YC, Koo BH, Choi SY (2002) Hepatic splenosis diagnosed as hepatocellular carcinoma: report of a case. Surg Today 32:180–182

Lehur PA, Potiron L, Moyen J, Hingrat JY, Paineau J (1983) Pancreatic heterotopy in the choledochus. Apropos of a case (in French). Ann Chir 37:31–33

Leiserowitz GS, Gumbs JL, Oi R, Dalrymple JL, Smith LH, Ryu J, Scudder S, Russell AH (2003) Endometriosis-related malignancies. Int J Gynecol Cancer 13:466–471

Leshchenko AP, Saplina OI, Timoshenko LD, Kolechko VV (1994) Abdominal pregnancy with implantation of the ovum in the liver (in Russian). Vestn Khir Im I I Grek 152:47–48

Levi Sandri GB, Lai Q, Bosco S, Berloco PB (2014) Liver splenosis mimicking hepatocellular carcinoma in cirrhotic liver. Liver Int 34:162

Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC (2010) Precancerous bile duct pathology in end-stage primary sclerosing cholangitis, with and without cholangiocarcinoma. Am J Surg Pathol 34:27–34

Li et al. (2011). http://www.ncbi.nlm.nih.gov/pubmed/22119260

Li H, Snow-Lisy D, Klein EA (2012) Hepatic splenosis diagnosed after inappropriate metastatic evaluation in patient with low-risk prostate cancer. Urology 79: e73–e74

Li T, Yang XY, Tang ZY (2015) Intrahepatic and intraperotineal splenosis mimicking hepatocellular carcinoma with abdominal wall metastasis in a patient with hepatitis C cirrhotic liver. Surgery 157:954–956

Liang K, Liu JF, Wang YH, Tang GC, Teng LH, Li F (2010) Ectopic thyroid presenting as a gallbladder mass. Ann R Coll Surg Engl 92:W4–W6

Liu Y, Ji B, Wang G, Wang Y (2012a) Abdominal multiple splenosis mimicking liver and colon tumors: a case report and review of the literature. Int J Med Sci 9:174–177

Liu K, Liang Y, Liang X, Yu H, Wang Y, Cai X (2012b) Laparoscopic resection of isolated hepatic splenosis mimicking liver tumors: case report with a literature review. Surg Laparosc Endosc Percutan Tech 22:e307–e311

Liu C, Liu J, Wang F (2015) Intrahepatic splenosis mimicking liver cancer: report of a case and review of literature. Int J Clin Exp Pathol 8:1031–1035

Lolis ED, Carvounis EE, Vasilikostas G, Voros D (2007) Subhepatic retroperitoneal endometrioma: report of a case. Gynecol Endocrinol 3:1–3

Losanoff JE, Jones JW (2001) Splenosis after laparoscopic splenectomy. Surg Endosc 15:1497

Lu et al. (2008). http://www.ncbi.nlm.nih.gov/pubmed/18691204

Ludtke FE, Mack SC, Schuff-Werner P, Voth E (1989) Splenic function after splenectomy for trauma. Role of autotransplantation and splenosis. Acta Chir Scand 155:533–539

Luwuliza-Kirunda JM (1978) Primary hepatic pregnancy. Case report. Br J Obstet Gynaecol 85:311–313

Magnus KG, Millar AJ, Sinclair-Smith CC, Rode H (1999) Intrahepatic fetus-in-fetu: a case report and review of the literature. J Pediatr Surg 34:1861–1864

Maisonnette F, Abita T, Lachachi F, Pichon N, Durand-Fontanier S, Valleix D, Descottes B (2004) Aberrant pancreas: report of five cases (in French). Ann Chir 129:241–243

Marini G (1902) Sopra un caso di splenomegalia con cirrosi epatica. Arch Sci Med 26:105–116

Martinez Del Valle Torres MD, Ortega Lozano SJ, Jimenez-Hoyuela Garcia JM, Delgado Garcia A, Gavilan Carrasco JC, Bermudez Recio FJ (2005) Utility of Tc-99m labeled heat-denaturated red blood cell scintigraphy in a case of hepatic splenosis (in Spanish). Gastroenterol Hepatol 28:279–282

Matsumoto K, Watanabe Y, Asano G (1999) Thyroid papillary carcinoma arising in ectopic thyroid tissue within a branchial cleft cyst. Pathol Int 49:444–446

Matsuyama M, Sugiura S, Kakita A, Sato Y, Kuroda M (2011) Hepatocellular carcinoma arising from ectopic liver tissue in the spleen producing insulin-like growth factor II. Pathol Res Pract 207:124–126

Mavi A, Degirmenci B, Bekis R, Durak H (2003) Intra-abdominal splenosis mimicking massive gastrointestinal bleeding. Clin Nucl Med 28:226–227

Mear Y, Ekra JB, Raoelison S (1965) A case of hepatic implantation pregnancy with a living infant (in French). Sem Hop 41:1430–1433

Menth M, Herrmann K, Haug A, Raziorrouh B, Zachoval R, Jung CM, Otto C (2009) Intra-hepatic splenosis as an unexpected cause of a focal liver lesion in a patient with hepatitis C and liver cirrhosis: a case report. Cases J 2:8335

Merkel H (1905) Über abgesprengte Pankreasanlagen (On detached pancreatic buds). Münch Med Wschr 52:337

Mescoli C, Castoro C, Sergio A, Ruol A, Farinati F, Rugge M (2010) Hepatic spleen nodules (HSN). Scand J Gastroenterol 45:628–632

Michigishi T, Mizukami Y, Mura T, Nomura T, Watanabe K, Tonami N, Hisada K (1991) Papillary carcinoma in ectopic thyroid detected by TJ 201 scintigraphy. Clin Nucl Med 16:337–339

Miloslavich E (1914) Ueber Bildungsanomalien der Nebeniere. Virchows Arch Path Anat 218:131

Mirkin LD, Knisely AS (1997) Hyaline cartilage at porta hepatis in extrahepatic biliary atresia. Pediatr Pathol Lab Med 17:587–591

Mitchell N, Augrist A (1943) Myoepithelial hamartoma of the gastrointestinal tract. Ann Intern Med 19:952–964

Mitchell RW, Teare AJ (1984) Primary hepatic pregnancy. A case report and review. S Afr Med J 65:220

Mobini J, Krouse TB, Cooper DR (1974) Intrahepatic pancreatic heterotopia: review and report of a case presenting as an abdominal mass. Am J Dig Dis 19:64–70

Molinari M, Ong A, Farolan MJ, Helton WS, Espat NJ (2000) Pancreatic heterotopia and other uncommon causes of non-malignant biliary obstruction. Surg Oncol 9:135–142

Moriki T, Ohtsuki Y, Takahashi T, Ueta S, Mitani M, Ichien M, Fukata S, Murata Y (2004) Lipoma-like tumor mass probably arising in the retroperitoneal heterotopic pancreas: a previously undescribed lesion. Pathol Int 54:527–531

Mrak K, Eberl T, Tschmelitsch J, Langner C (2010) Heterotopic pancreatic tissue in the cystic duct: complicating factor or coexisting pathology. South Med J 103:471–473

N'Senda P, Wendum D, Balladur P, Dahan H, Tubiana JM, Arrive L (2000) Adenosarcoma arising in hepatic endometriosis. Eur Radiol 10:1287–1289

Nakajima T, Fujiwara A, Yamaguchi M, Makiyama A, Wakae T, Fujita K, Yoshikawa K et al (2008) Intrahepatic splenosis with severe iron deposition presenting with atypical magnetic resonance images. Intern Med 47:743–746

Nakamura K, Mitsubuchi H, Miyayama H, Yatsunami K, Ishimatsu J, Yamamoto T, Endo F (2003) Complete absence of bile and pancreatic ducts in a newborn: a new entity of congenital anomaly in hepato-pancreatic development. J Hum Genet 48:380–384

Nakanishi K, Bohndorf K, Lindemann F, Leipprand E (1994) Endometriosis of the liver: findings of imaging diagnosis (in German). Rofo Fortschr Geb Röntgenstr Bildgeb Verfahr 161:379–381

Nakata Y, Yoshida H, Shiono T, Asai S, Araki T (2003) Intrahepatic splenosis: a case report (in Japanese). Nippon Igaku Hoshasen Gakkai Zasshi 63:11–113

Nezhat C, Kazerooni T, Berker B, Lashay N, Fenandez S, Marziali M (2005) Laparoscopic management of hepatic endometriosis: report of two cases and review of the literature. J Minim Invasive Gynecol 12:196–200

Nichols C, Koong D, Faulkner K, Thompson G (1995) A hepatic ectopic pregnancy treated with direct methotrexate injection. Aust N Z J Obstet Gynaecol 35:221–223

O'Reilly DJ, Craig RM, Korenzo G, Yokoo H (1983) Heterotopic pancreas mimicking carcinoma of the head of the pancreas: a rare cause of obstructive jaundice. J Clin Gastroenterol 5:165–168

O'Sullivan MJ, Swanson PE, Knoll J, Taboada EM, Dehner LP (2001) Undifferentiated embryonal sarcoma with unusual features arising within mesenchymal hamartoma of the liver: report of a case and review of the literature. Pediatr Dev Pathol 4:482–489

Oberndorfer S (1900) Beitrag zur Kasuistik der Lebersyphilis. Nebst einem Anhang: Keimversprengung von Nebenieren in die Leber. Centralbl Allg Pathol Pathol Anat 11:145–151

Ogata H, Oshio T, Ishibashi H, Takano S, Yagi M (2008) Heterotopic pancreas in children: review of the literature and report of 12 cases. Pediatr Surg Int 24:271–275

Okano K, Usuki H, Maeta H (2004) Adrenal metastasis from hepatocellular carcinoma through an adrenohepatic fusion. J Clin Gastroenterol 38:912

Pang LC (1988) Pancreatic heterotopia: a reappraisal and clinicopathologic analysis of 32 cases. South Med J 81:1264–1275

Paraf A, Potet F, Menager C, Rautureau J (1970) Aberrant pancreas affecting the duodenal wall, unusual cause of common bile duct obstruction (in French). Rev Med Chir Mal Foie 45:165–170

Park BK, Kim CK, Jung BC, Suh YL (2009) Cortical adenoma in adrenohepatic fusion tissue: clue to making a correct diagnosis at preoperative computed tomography examination. Eur Urol 56:1082–1085

Paulino-Netto A, Roselli A (1986) Hepatic ectopic pregnancy: successful surgical treatment of a patient with hepatic pregnancy and acute hemorrhage. Mt Sinai J Med 53:514–517

Pearson S (1951) Aberrant pancreas. Review of the literature and report of three cases, one of which produced common and pancreatic duct obstruction. Arch Surg 63:168–184

Pekkafali Z, Karsli AF, Silit E, Basekim CC, Narin Y, Mutlu H, Kizilkaya E (2002) Intrahepatic splenosis: a case report. Eur Radiol 12(Suppl 3):S62–S65

Perrotta PL, Ginsburg FW, Siderides CI, Parkash V (1998) Liesegang rings and endometriosis. Int J Gynecol Pathol 17:358–362

Prasad TR, Gupta SD, Bhatnagar V (2001) Ectopic pancreas associated with a choledochal cyst and extrahepatic biliary atresia. Pediatr Surg Int 17:552–554

Pujari BD, Deodhare SG (1979) Intrahepatic ectopic pancreas (report of a case). Indian J Med Sci 33:157–159

Putschar WGJ, Manion WC (1956) Splenic-gonadal fusion. Am J Pathol 32:15–33

Rahn J (1959) Ueber eine eigenartige Heterotopie von Schilddrüsengewebe. Zentralbl Allg Pathol 99:80

Ramia JM, De la Plaza R, Garcia I, Perna C, Veguillas P, Garcia-Parreño J (2012) Liver metastasis of endometrial stromal sarcoma. World J Hepatol 4:415–418

Rao MS, Bendayan M, Kimbrough RD, Reddy JK (1986) Characterization of pancreatic-type tissue in the liver of rat induced by polychlorinated biphenyls. J Histochem Cytochem 34:197–201

Rao MS, Dwivedi RS, Subbaro V et al (1988) Almost total conversion of pancreas to liver in the adult rat: a reliable model to study transdifferentiation. Biochem Biophys Res Commun 156:131–136

Reid GD, Kowalski D, Cooper MJ, Kaloo P (2003) Hepatic endometriosis: a case report and review of the literature. Aust N Z J Obstet Gynaecol 43:87–89

Rickert et al. (1998). http://www.ncbi.nlm.nih.gov/pubmed/9669351

Rivkine E, Jakubowicz D, Marciano L, Polliand C, Poncelet C, Ziol M, Barrat C (2013) Hepatic endometrioma: a case report and review of the literature: report of a case. Surg Today 43:1188–1193

Roesch-Dietlen F, Jimenez-Garcia A, Pérez-Morales A, Grube-Pagola P, Ramirez-Cervantes KL et al (2011) Hepatic endometriosis. Ann Hepatol 10:347–348

Röther M, Dufour JF, Schnüriger B (2013) An uncommon cause of a focal liver lesion. Post-traumatic splenosis. Gastroenterology 144:510

Rovati V, Faleschini E, Vercellini P, Nervetti G, Tagliabue G, Benzi G (1990) Endometrioma of the liver. Am J Obstet Gynecol 163:1490–1492

Saadat-Gilani K, Bechmann L, Frilling A, Gerken G, Canbay A (2007) Gallbladder endometriosis as a cause of occult bleeding. World J Gastroenterol 13:4517–4519

Sabini AM, Baden JP, Norman JD, Martin JR (1970) Heterotopic pancreatic tissue in the common bile duct or ampulla of vater. Am Surg 36:662–666

Sanchez-Perez B, Santoyo-Santoyo J, Suarez-Munoz MA, Fernandez-guilar JL, Aranda-Narvaez JM, Gonzalez-Sanchez A, de la Fuente-Perucho A (2006) Hepatic cystic endometriosis with malignant transformation (in Spanish). Cir Esp 79:310–312

Sarda R, Sproat I, Kurtycz DF, Hafez R (2001) Pulmonary parenchymal splenosis. Diagn Cytopathol 24:352–355

Sato N, Abe T, Suzuki N, Waragai M, Teranishi Y, Takano Y, Sato A, Azami A, Gotoh M (2014) Intrahepatic splenosis in a chronic hepatitis C patient with no history of splenic trauma mimicking hepatocellular carcinoma. Am J Case Rep 15:416–420

Schlatter MG, DePree B, Van der Kolk KJ (1988) Hepatic abdominal pregnancy: a case report. J Reprod Med 33:921–924

Schmorl G (1891) Zur Kenntnis der accessorischen Nebennieren. Beitr Pathol Anat 9:523–529

Schu W, Copeland R, Fromm D, Elbadawi A (1988) Obstruction of the common hepatic duct by ectopic pancreas. N Y State J Med 88:197–198

Schubert W (1957) Ueber eine akzessorische Schilddrüse an der Leberpforte. Zentralbl Allg Pathol 96:339–341

Schuld J, Justinger C, Wagner M, Bohle RM, Kollmar O, Schilling MK, Richter S (2011) Bronchobiliary fistula: a rare complication of hepatic endometriosis. Fertil Steril 804:e15–e18

Schultz J (1727) Acta naturalium curiosorum (interesting natural facts). vol 1. Amsterdam, p. 504, obs. 226

Schwartz DA, Bellin HJ (1991) Liesegang rings developing within intraperitoneal endometriotic implants. A case report. J Reprod Med 36:403–406
Sekine S, Nagata M, Hamada H, Watanabe T (2000) Heterotopic thyroid tissue at the porta hepatis in a fetus with trisomy 18. Virchows Arch 436:498–501
Shen CN, Horb ME, Slack JM, Tosh D (2003a) Transdifferentiation of pancreas to liver. Mech Dev 120:107–116
Shen CN, Seckl JR, Slack JM, Tosh D (2003b) Glucocorticoids suppress beta cell development and induce hepatic metaplasia in embryonic pancreas. Biochem J 375:41–50
Shukla VK, Pandey S, Pandey LK, Roy SK, Vaidya MP (1985) Primary hepatic pregnancy. Postgrad Med J 61:831–832
Spence JR, Lange AW, Lin SC, Kaestner KH, Lowy AM, Kim I, Whitsett JA, Wells JM (2009) Sox17 regulates organ lineage segregation of ventral foregut progenitor cells. Dev Cell 17:62–74
Stahlschmidt J, Stringer MD, Wyatt J, Davison S, Rajwal S, McClean P (2008) Histologic oddities at the porta hepatis in biliary atresia. J Pediatr Surg 43:1328–1332
Strohschneider T, Timm D, Worbes C (1993) Ectopic thyroid gland tissue in the liver (in German). Chirurg 64:751–753
Studdiford WE (1942) Primary peritoneal pregnancy. Am J Obstet Gynecol 44:487–491
Suzuki K, Uchida T, Nakayama H, Ugajin W, Inaniwa Y, Sugitani M, Mori Y (1999) Heterotopic pancreatic tissue associated with intra-and extrahepatic choledochal cysts. Pathol Int 49:759–762
Takeuchi H, Kitade M, Sakurai A, Kikuchi I, Kumakiri J, Kinoshita K (2005) Fitz-Hugh and Curtis syndrome-like diaphragmatic endometriosis. Fertil Steril 83:1039–1040
Takeuchi T, Inoue T, Kanemoto K, Hagiwara K, Mikami K, Hattori M, Zaitsu M, Tonooka A et al (2013) Possible origin of aldosteronoma from adrenohepatic fusion resulting in intrahepatic tumor. Open J Urol 3:223–226
Tanaka K, Tsunoda T, Eto T, Yamada M, Tajima Y, Shimogama H, Yamaguchi T, Matsuo S et al (1993) Diagnosis and management of heterotopic pancreas. Int Surg 78:32–35
Teke Z, Zengin NI, Atalay F, Karaman K, Demirbag AE, Akdogan M (2010) A tumor-like lesion mimicking mucinous (colloid) carcinoma in heterotpic pancreas of the prepyloric antrum: a formidable challenge for frozen examination. JOP 11:237–243
Terada et al. (1990). http://www.ncbi.nlm.nih.gov/pubmed/2182371
Terada T (2012) Differentiation of intrahepatic peribiliary glands and pancreatic acinar cells from the remodelling ductal plate in human foetuses. Hepatology 56:2004–2005
Thognon P, Descottes B, Valleix D (1998) Heterotopic pancreas. Three cases (in French). Ann Chir 52:491–494
Toki T, Shimizu M, Takagi Y, Ashida T, Konishi I (2002) CD10 is a marker for normal and neoplastic endometrial stromal cells. Int J Gynecol Pathol 21:41–47
Tsunoda T, Eto T, Yamada M, Oshibuchi H, Fujioka H, Tajima Y, Tsuchiya R (1990) Heterotopic pancreas: a rare cause of bile duct dilatation – report of a case and review of the literature. Jpn J Surg 20:217–220
Tuech JJ, Rousselet MC, Boyer J, Descamps P, Arnaud JP, Ronceray J (2003) Endometrial cyst of the liver: case report and review. Fertil Steril 79:1234–1236
Varay A (1946) Microscopic epithelioma of vater's papilla. Paris Med 1:183
Velitchkov NG, Kjossev KT, Losanoff JE, Kavardjikova VA (2000) Subcutaneous splenosis: a clue to diagnosis of thoracic splenosis. J R Coll Surg Edinb 45:66
Verbeke C, Harle M, Sturm J (1996) Cystic endometriosis of the upper abdominal organs: report on three cases and review of the literature. Pathol Res Pract 192:300–304
Vercellini P, Abbiati A, Vigano P, Somigliana ED, Daguati R, Meroni F, Crosignani PG (2007) Asymmetry in distribution of diaphragmatic endometriotic lesions: evidence in favour of the menstrual reflux theory. Hum Reprod 22:2359–2367
Veress B, Wallmander T (1987) Primary hepatic pregnancy. Acta Obstet Gynecol Scand 66:563–564
Vestfrid MA (1980) Ectopic adrenal cortex in neonatal liver. Histopathology 4:669–672
Vilgrain V, Silbermann O, Benhamou JP, Nahum H (1993) MR imaging in intracystic hemorrhage of simple hepatic cysts. Abdom Imaging 18:164–167
Von Heinrich H (1909) Ein Beitrag zur Histologie des sog. Akzessorischen Pankreas. Virchows Arch A Pathol Anat Histopathol 198:392–440
Wadham BM, Adams PB, Johnson MA (1981) Incidence and location of accessory spleens. N Engl J Med 304:1111
Wagle PK, Shetty GS, Sampat M, Patel K (2005) Ectopic pancreatic tissue mimicking ampullary tumor. Indian J Gastroenterol 24:265–266
Watari H, Shibahara N, Ebisawa S, Nogami T, Fujimoto M, Hikiami H, Shimada Y (2012) Case report; a case of hepatic endometriosis with periodic upper quadrant pain (in Japanese). Nippon Naika Gakkai Zasshi 101:3233–3235
Weber CM, Zito PF, Becker SM (1968) Heterotopic pancreas: an unusual cause of obstruction of the common bile duct. Report of a case and review of the literature. Am J Gastroenterol 49:153–159
Weinfeld RM, Johnson SC, Lucas CE, Saksouk FA (1998) CT diagnosis of perihepatic endometriosis complicated by malignant transformation. Abdom Imaging 23:183–184
Wekerle T, Eichinger S, Maier A, Wrba F, Moschl P (1998) Intrahepatic splenic tissue in a patient with recurrent idiopathic thrombocytopenic purpura. Surgery 123:596–599
Weller CV (1925) Heterotopia of adrenal in liver and kidney. Am J Med Sci 169:696–712

Weppner JL, Wilson MR, Ricca R, Lucha PA (2009) Heterotopic pancreatic tissue obstructing the gallbladder neck: a case report. JOP 10:532–534

Werdelin L, Nilsonne A (1999) The evolution of the scrotum and testicular descent in mammals: a phylogenetic review. J Theor Biol 196:61–72

Wilkins L, Ravitch MM (1952) Adrenocortical tumor arising in the liver of a three year old boy with signs of virilism and Cushing's syndrome. Pediatrics 9:671–681

Willis RA (1953) The structure of teratomata. J Pathol Bacteriol 40:1–36

Wolf HK, Burchette JL, Garcia JA, Michalopoulos G (1990) Exocrine pancreatic tissue in human liver: a metaplastic process? Am J Surg Pathol 14:590–595

Woo HS, Lee KH, Park SY, Han HS, Yoon CJ, Kim YH (2007) Adrenal cortical adenoma in adrenohepatic fusion tissue: a mimic of malignant hepatic tumor at CT. AJR Am J Roentgenol 188:W246–W248

Yan ML, Wang YD, Tian YF, Lin Y (2012) Adenocarcinoma arising from intrahepatic heterotopic pancreas: a case report and literature review. World J Gastroenterol 18:2881–2884

Yang L, Li S, Hatch H, Ahrens K, Cornelius JG, Petersen BE, Peck AB (2002a) In vitro trans-differentiation of adult hepatic stem cells into pancreatic endocrine hormone-producing cells. Proc Natl Acad Sci U S A 99:8078–8083

Yang XY, Heller DS, Baergen RN (2002b) Splenopancreatic field abnormality in trisomy. 13. Pediatr Dev Pathol 5:414–415

Yang B, Yang GZ, Shi PZ, Zhou HS, Zhu DR, Li X, Xu RJ (2007) Abdominal splenosis: CT and MRI features of 2 cases. Chin J Traumatol 10:381–384

Yoshida T, Murata K, Shiraki N, Kume K, Kume S (2009) Analysis of gene expressions of embryonic stem-derived Pdx1-expressing cells: implications of genes involved in pancreas differentiation. Dev Growth Differ 51:463–472

Yoshimitsu K, Aibe H, Nobe T, Ezaki T, Tomoda H, Hayashi I, Koga M (1993) Intrahepatic splenosis mimicking a liver tumor. Abdom Imaging 18:156–158

Zawin M, McCarthy S, Scout L, Comite F (1989) Endometriosis: appearance and detection at MR imaging. Radiology 171:693–696

Zhao M, Xu HW (2004) Splenosis simulating an intrahepatic mass. Chin J Traumatol 7:62–64

Zink A, Raue F, Hoffmann R, Ziegler R (1991) Papillary carcinoma in an ectopic thyroid. Horm Res 35:86–88

Zinkiewicz K, Justkiewicz W, Zgodinski W, Szumilo J, Cwik G, Furtak J, Maciejewski R et al (2003) Ectopic pancreas: endoscopic, ultrasound and radiological features. Folia Morphol (Warsz) 62:205–209

Zulewski et al. (2001). http://www.ncbi.nlm.nih.gov/pubmed/11246871

Tumor-Like Lesions of the Hepatobiliary Tract: Anatomical Variations and Malformations Resulting in Hepatic Mass Effects or Focal Defects

121

Contents

Abstract

Gross malformations of the liver can result in mass effects or focal defects that can resemble tumors or hepatic changes induced by tumors. Accessory liver lobes characterized by solitary or multiple parts of liver substance connected to the main liver by a bridge or stalk can mimic a pedunculated liver tumor. One well-known example is Riedel's lobe, an inferior, tongue-like projection of the anterior border of the right liver lobe. Several anomalies of the caudate lobe of the liver can also resemble tumorous growths. A similar effect can be produced by subdiaphragmatic and supradiaphragmatic ectopias of the liver.

Anatomic Variations of the Liver Mimicking a Hepatic Tumor

Albeit rare events, gross malformations of the liver may pose considerable differential diagnostic problems, even in the present time with its sophisticated imaging techniques; hence, misinterpretations of anatomic anomalies as neoplastic lesions have occurred and still occur. It therefore seems appropriate to summarize important aspects of liver substance abnormalities and to give an overview on the spectrum of the lesions in question.

How to classify hepatic malformations? In what follows we summarize what is, according to our view, the still best classification system

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_121

Table 1 The Jacquemet classification of malformations (listed in Cullen 1925)

1. Liver modified in form and in dimensions but retaining its place in abdomen
1.1. Anomalies by reduction
1.1.1. Diminution of the left lobe
1.1.2. Diminution of the right lobe
1.2. Anomalies through increase in size of the liver
1.2.1. Increase involving right lobe
1.2.2. Increase involving right lobe
1.2.3. Increase of Spiegel's lobe
1.2.4. Increase involving quadrate lobe
1.3. Modifications in form of the liver without any sensible augmentation in volume
1.3.1. Incised liver (furrowing of parenchyma; one or more fissures)
1.3.2. Liver with multiple lobes (accessory lobes)
1.3.2.1. Accessory lobe attached to the liver by a pedicle of liver tissue
1.3.2.2. Accessory lobe connected with the liver by a mesohepaticum ("mesentery" in the original text, this being a misnomer)
1.3.3. Isolated accessory livers
1.3.4. Isolated nodules of liver tissue in the suspensory ligament
1.4. Liver modified in form and in dimensions and out of place
1.4.1. Liver misplaced and rotated to a vertical axis
1.4.2. Liver almost free in the abdominal cavity owing to loss of the greater portion of its ligamentous attachment
1.5. Elongated right lobe of the liver (Riedel's lobe)
2. Liver not modified in form but displaced
2.1. Anomalies of the liver in abnormal subjects
2.1.1. Thoracic displacement of the liver
2.1.2. Portion of the liver in amniotic hernia
2.1.3. Accessory lobe of the liver springing from the surface of the gallbladder

(Jacquemet 1896; Cullen 1925), which is based on a purely phenotypic approach to the question. In the future, modern embryological aspects of hepatic morphogenesis will certainly alter, expand, and refine such an attempt at classifying these lesions.

Selected References Meckel 1822a; Wagner 1861; Vegandt 1876; Toldt and Zuckerkandl 1876; Calori 1880; Gruber 1880; Broca 1880; Duchesne 1881; Tarenetzki 1883; Musser 1888; Grenet 1895; Thomson 1898; Moser 1898; Chiari 1899; Tarozzi 1904; Barclay-Smith 1908; Inglis 1911.

The Jacquemet system (listed in Cullen 1925) is shown in Table 1.

It is important to note that hepatic anatomic variations are not stable features, but rather represent changes submitted to a dynamic evolution. In a study on 52 perinatal livers, remarkable discrepancies between the adult and perinatal incidences of various anomalous manifestations were noted (Parke et al. 1996). In particular, ectopic accessory lobes were very rare in the adults analyzed in this study and in other groups reported in the literature. They were, in contrast, a relatively common finding in the perinatal group as were gallbladder bridges of hepatic tissue, hypertrophic papillary lobes, and marked accessory fissures, but marginal accessory lobes were not observed in perinatal livers. This may be due to postnatal gross liver remodeling, with most of the ectopic lobes, bridges of liver substance, hypertrophic caudate lobe extensions, and accessory fissures disappearing after birth (Parke et al. 1996).

Accessory Lobes of the Liver

Accessory lobes of the liver are developmental anomalies of the liver characterized by solitary or multiple parts of liver substance, of variable size, usually covered by a liver capsule, and connected to the main, orthotopic liver by a bridge or a stalk (Meckel 1822b; Gruber 1849; Wagner 1861). Most of the cases reported in the nineteenth century and before have been compiled in 1915 (Forni 1915). The cases described in the literature are, based on the descriptions, not always attributable to accessory lobes sensu stricto or to liver ectopia; this mainly holds true for hepatic masses situated in hepatic ligaments, where the descriptions sometimes do not allow to reconstruct the type of connections to the main liver. Accessory lobes are, with one exception (Riedel's lobe), rare alterations (Cullen 1925; Chouke 1932; Watson and Lee 1964); in a series of 5500 autopsies, 13 children with

supernumerary lobes have been identified (Eiserth 1962). It has to be emphasized that liver furrowing is rather frequent in the newborn and infancy periods, and mostly involves superficial parts of the right liver lobe (Jacquemet 1896), but part of these changes seem to be reversible (Parke et al. 1996). The issue of accessory liver lobes has been discussed in a comprehensive review (Cullen 1925). Cullen described all degrees of hepatic lobation, from multiple deep furrowing to complete separation of parts of hepatic tissue from the main, orthotopic liver. Some supernumerary lobes (or rather lobe equivalents) were attached to the main liver mass by a pedicle of hepatic tissue, while others were attached by some sort of a meso (a "mesohepaticum") containing blood vessels and bile ducts only. Pathogenetically related may be the situation where the right and left liver lobes are completely separated, with a fibrovascular plate separating the two parts (Kschischo 1912). Multiple accessory lobes result in congenital hepar lobatum, and the liver may then consist of more than ten lobar units. Cullen (1925) cites the remarkable case of Moser who had found the liver to be partitioned into no less than 16 lobes, in some way reflecting the situation frequently found in some mammals, such as the pig and the dog.

Riedel's lobe (RL) is an inferior, tongue-like projection of the anterior border of the right liver lobe, to the right of the gallbladder, termed after the author of the first description (Riedel 1888). Already in 1903, the term, Riedel's lobe, was employed (Lockwood 1903). Riedel observed this change in seven females who had palpable masses in the right hypochondrium, and the abnormal "lobe" was subsequently confirmed at surgery. Probably, two other authors have described and reported this change in the same year, in one patient as a hepatic lesion simulating movable kidney (Pichevin 1888; Musser 1888). In the early nineteenth century, some surgeons had surmised that RL was due to tight corseting (Finney 1925), and already Riedel himself thought of this possibility (Riedel 1888). RL has since been documented and discussed several times.

Selected References Lockwood 1903; Wilhelmi 1923; Reitemeier et al. 1958; James et al. 1963; Lane 1966; Keyloun and Pinkernell 1967; Couinaud et al. 1968; Baum et al. 1982; Kudo 2000.

What is the incidence of RL in the adult population? In a review of 2604 patients, RL as identified by technetium scintigraphy was present in 86 (3.3 %). In a second study of 564 patients, the prevalence of RL was 14.5 %, however, defined by liver scintigraphy only (Baum et al. 1982). The reasons for such differences in prevalence are, on the one hand, related to definition of what RL is and, on the other hand, linked to age-related changes of the liver and its anatomy (see below; Gillard et al. 1998). In a larger series, no significant differences in the prevalence of RL between the sexes were found (Gillard et al. 1998). RL is usually an asymptomatic lesion presenting as a palpable mass in the right hypochrondrium, but it may lead to possible confusion with a hepatic or renal tumor or with right-sided nephroptosis (Wilhelmi 1923; James et al. 1963; Kudo 2000). RL can exert compression effects on neighboring organs, e.g., gastric outlet obstruction (Akbulut et al. 2011). In a study on 31 patients with RL (age at diagnosis ranging from 31 to 77 years), a palpable mass in the right side of the abdomen was present in 18 patients, and the existence of a mass was known before the diagnosis of RL in seven. In contrast with the series described by Riedel, no gallbladder was palpable in these 31 patients (Reitemeier et al. 1958). Clinically significant lesions originating within RL are extremely rare but include cirrhosis and metastatic lesions (Soo and Adatepe 1990). In 30 of the 86 individuals analyzed by Sham and co-workers, RL was found to be hypertrophic, more frequently in females (Sham et al. 1978). Therefore, particularly RL hypertrophy makes part of the differential diagnosis of a right-sided abdominal mass. RL is readily diagnosed by ultrasonography (Chaulieu et al. 1982), CT, and MRI (Yano et al. 2000) and has distinctive angiographic features (Lipchik and Schwartz 1967). Radiologically, RL necessitates an extended sequence of sectional imaging in order

not to miss lesions in its most distal parts (Gillard et al. 1998). The morphological presentation of RL has been studied in detail (Gillard et al. 1998). As a secondary phenomenon, the apex of RL can be attached to the right (hepatic) colonic flexure, but these adhesions may be much more extended, involving almost the entire undersurface of RL, connecting RL with both the right colon and the duodenum and causing kinking of the colon (Figs. 11, 12, and 13 in the work of Cullen 1925). Similar to other anatomic anomalies of liver lobes, RL seems to be a lesion subject to a dynamic evolution. For example, the proportion of individuals in whom the most caudal margin of the liver was inferior to the most caudal costal margin was age dependent and increased to 65 % in the 50–59-year age group; moreover, the craniocaudal dimension of the liver decreased with age, overall suggesting that the prevalence of RL is dependent on age-related changes in liver size and skeletal shape (Gillard et al. 1998).

What is the possible fate of RL? Riedel reported that there was an apparent regression of the abnormal lobe after cholecystectomy (Riedel 1888). RL can be complicated by torsion, with necrosis and signs of acute abdomen (Lefaucher et al. 1978). It has also been theorized that RL, or at least parts of this lobe, may undergo atrophy, resulting in a hanging spheroid lobe of liver tissue connected with the lower end of the right liver lobe by a fibrovascular band. Such a hanging lobe, with two associated satellite nodules, has already been described in 1880 (Taruffi 1880).

It is still debated whether RL is a congenital change (Reitemeier et al. 1958; Farmer et al. 1969; Sham et al. 1978) or an acquired change (Riedel 1888; Reitemeier et al. 1958). It has been proposed that RL is, in fact, not a bona fide malformation but rather a simple variant of clinical anatomy (Lane 1966), all the more so as the change can be subject to regression. Very rarely, two inferior accessory lobes, each one somewhat resembling a RL, have been found, right and left to the round ligament, a "double RL" (Giacomini 1884). Moreover, tongue-like projections with a configuration similar to RL occur in the left liver lobe (Chiba et al. 1991). Rarely, RL is the site of cancerogenesis, e.g., hepatocellular carcinoma (Zamfir et al. 2008).

Anomalies of the Caudate Lobe of the Liver

The caudate lobe (CL) of the liver has a complex anatomy with five surfaces that is clarified by embyrologic and anatomic analysis (Van Minh et al. 1992; Couinaud 1998; Abdalla et al. 2002; Murakami and Hata 2002). In some contrast to the concept of Couinaud (see below; Couinaud 1998), some authors state that the CL consists of three parts, i.e., (a) the Spiegel's lobe (the caudate lobe plus papillary process of the anatomists), (b) the caudate process, and (c) the paracaval portion corresponding to the dorsally located parenchyma in front of the inferior vena cava. All three parts are supplied by primary branches originating from the left and right portal veins, including the hilar bifurcation area. The hilar bifurcation branch often (50 %) supplies the paracaval portion, and it sometimes (29 %) extends its territory to Spiegel's lobe (Murakami and Hata 2002). The CL belongs, according to Couinaud (1998), to the so-called posterior sector of the liver which is, in its development and anatomy, independent of the right and left liver and the main portal fissure. In particular, the CL is the midportion of the posterior liver and the only part of the liver that is in contact with the caval vein, except at the entrance of the main hepatic veins into the vena cava. This dorsal sector extends in front and to the sides of the inferior vena cava, separating the caval axis from the main liver, resulting in a single unit composed of the dorsal sector itself and the retrohepatic portion of the caval vein (Couinaud 1998). In contrast to the three-part concept of the CL as outlined above, Couinaud's view is that the dorsal sector is made of two segments: left (segment I) larger than the Spiegel lobe and right (segment IX) incorporated in the posterior surface of the right liver, where the caudate process is not regarded as a peculiar element but rather the inferior margin of segment IX. The vascular and bile duct anatomy related to CL has been studied in detail.

Selected References Couinaud 1998; Filipponi et al. 2000; Kanamura et al. 2001; Kwon et al. 2002; Sato et al. 2002; Bargallo et al. 2003;

Kitami et al. 2004; Lee et al. 2004; Ortale and Borges Keiralla 2004; Takamatsu et al. 2004; Tohma et al. 2005.

Alterations of the CL may mimic a mass or space-occupying lesion in the portocaval space. Specifically, the variable anatomy of the papillary process may cause misinterpretations of the gross morphology of the posterior sector. In an ultrasound study of 400 patients, the papillary process appeared to be separate from the liver in 15.5 % and had an egg shape with a maximum transverse diameter of 8–39 mm. In this subfraction of patients, the papillary process appeared above and in front of the common hepatic artery close to the portal vein and pancreatic isthmus, and enlarged papillary processes were more frequently seen in patients with chronic liver disease (Donoso et al. 1989). Hypertrophy of the papillary process of CL can mimic a liver mass (Reuther 1992). The papillary process may also be separated from the caudate lobe as such by a fissure, thus leading to erroneous sonography interpretation as a space-occupying lesion (Korn et al. 1991). But also the caudate process of the caudate lobe can undergo pseudotumorous hyperplasia (Kwak et al. 2000). Other mass-inducing changes of the CL is, e.g., a pseudotumorous hyperplasia of this lobe that has been seen in Alagille syndrome (Tuset et al. 1995).

Other hepatic malformations of the liver are characterized by additional lobes or lobe-like formations.

Very rare malformations include small ectopic livers (Marquand et al. 1980), a pendulated accessory liver lobe (Fogh et al. 1989), anomalous lobes displacing stomach and duodenum (Meyers and Jacobson 1958), and juxtacholecystic hepatic nodules (Perez Ara and Silva Ruiz 1954).

Atrophy, Hypoplasia, and Aplasia/Agenesis of Liver Lobes

This issue of gross disorders of lobar or segmental development of the liver has been reviewed (Champetier et al. 1985). Congenital hypoplasia of the right hepatic lobe with compensatory hypertrophy of the left lobe and of the left liver lobe has been described (Heller 1870; Krauspe 1923; Morgenstern and Mazur 1959); it is sometimes associated with a so-called floating gallbladder (Kabaroudis et al. 2003). In some cases, atrophy subsequent to ischemia or birth trauma may be more likely than hypoplasia, a question already raised in an early report on liver hypoplasia (*Vitium primae formationis* vs. acquired alteration; Heller 1870; Lancereaux 1899). Hepatic lobar agenesis is exceedingly rare (Reddy 1954; Auguste et al. 1955; Bertrand 1963) but can cause portal hypertension (Negre et al. 1962; Bertrand et al. 1962).

Subdiaphragmatic and Supradiaphragmatic Ectopias of the Liver

Subdiaphragmatic Ectopias

Liver ectopias are, in contrast to accessory lobes, usually not in connection via liver substance with the main liver, but may be supplied by liver vessels and drained by bile ducts. Subdiaphragmatic locations include the left triangular ligament, supraumbilical part of the round ligament, hepatoumbilical ligament, omentum majus, pancreas, spleen, retroperitoneal space, and gallbladder (Eiserth 1940; McCreadie and Burkhardt 1965; Cardona et al. 2007; Kanzaki et al. 2010; Matsuyama et al. 2011; Zonca et al. 2013). In connection with the transient omphalic cleft during ontogeny, ectopic liver has been observed in the umbilicus, in the absence of an umbilical hernia (Shaw and Pierog 1969; Park et al. 1991), in one instance in the form of a separate hepatic lobe (D'Agostino et al. 1989), as ectopic liver in the umbilical cord (Preminger et al. 2001; Wax et al. 2007; Lara-Diaz et al. 2011; Vaideeswar et al. 2011), and as a supernumerary liver lobe within omphalocele (Fock 1963; Louda and Baumelt 1981; Charbonnet et al. 1988; Festen et al. 1988).

In Fock's two cases, the liver tissue within the omphalocele was completely separated from the

intra-abdominal liver. In the case described by Shaw and Pierog (1969), a 2 cm reddish-purple, pedunculated mass was present, attached to the depths of the umbilicus of a baby. A dark-red drainage was noted to be coming from this umbilical tissue mass. Histology revealed a polypoid fragment of liver covered by capsule, with diffuse hepatic fibrosis and ductular proliferation (Shaw and Pierog 1969). A different situation was described in a newborn infant with a 7.5 cm sized ectopic mass of liver tissue connected to the orthotopic liver by blood vessels traversing an otherwise normal umbilicus (Nora and Carr 1946). These authors cite a similar case (a "duplicated liver") that had already been described in the eighteenth century by Morgagni (De sedibus et causis morborum 1767). In the case of omphalocele, an accessory liver displaced into the cell may be connected to the right liver lobe by a vascular stalk (Kleinhaus et al. 1968). Aberrant ectopic liver tissue has been detected as a nodule attached to the edge of the gastrohepatic omentum along the anterior border of Winslow's foramen (reported by H.N. Costello, Hartford Hospital; cited by Cullen 1925). A small ectopic liver nodule had been found in the greater omentum, with cirrhotic change (Brühl 1926), an early observation of a phenomenon that has been discussed again in the recent years. Foci of ectopic liver were found in an epithelial cyst of the spleen (Del Sordo et al. 2011).

Similar to cholecystic pancreatic heterotopia (Jarde et al. 1989; El Mezni et al. 1993), varying amounts of liver substance are known to occur as ectopic tissue (hepar succenturiatum) close to the gallbladder, within the wall of this organ, or in the tissue surrounding the cystic duct.

Selected References Henle 1866; Moore 1882; Tarenetzki 1883; Corsy 1922; Walzel and Gold 1925; Cullen 1925; Eiserth 1940; Ashby 1969; Torchio and Maconi 1978; Natori et al. 1986; Fellbaum et al. 1987; Tejada and Danielson 1989; Watanabe et al. 1989; Castro Viera et al. 1990; Hamdani and Baron 1994; Acar et al. 2002; Sakarya et al. 2002.

Liver Ectopia of the Gallbladder

Liver ectopia of the gallbladder presents as variably sized and encapsulated nodules at the serosal surface (Fig. 1), with (Ashby 1969) or without a mesohepatic ligament, may be situated within the wall itself, protruding into the lumen or forming a spur-like structure adjacent to the gallbladder wall. In case of a mesohepatic ligament (first described for such an ectopia by Henle in 1866, based on a museum specimen), this may contain a branch of the cystic artery and a small bile duct (Ashby 1969). The ectopic tissue can form a pedunculated mass covered by serosa (Corsy 1922). The ectopic tissue has a lobular architecture and bile ducts, but may undergo cirrhotic change similar to that of the main organ. These lesions may, in dependence to their size, lead to

Fig. 1 Liver ectopia in the gallbladder. A pedunculated elliptic, encapsulated nodule of liver tissue is connected with external structures of the gallbladder through a thin vascular stalk

differential diagnostic problems in a clinical workup of a mass lesion in this area.

Supradiaphragmatic Ectopias

Supradiaphragmatic ectopic liver tissue has been found in the extrapulmonary and mediastinal spaces (Naganuma et al. 1993; Han and Soylu 2009), within the lungs (Iber and Rintala 1999; Babu and Van der Avoirt 2001; Mehta et al. 2010; Bannon et al. 2013), within the pleura (Rodriguez-Perez 1955), and in the chest wall (Chalak and Parham 2007). Intrathoracic livers may be connected with the main liver via a vascular and biliary pedicle traversing the diaphragm (Rendina et al. 1989). Ectopic liver in the lungs can form a mass resembling a primary pulmonary tumor (Wang et al. 2010), and pulmonary and pleural liver ectopia can present as multiple nodules mimicking metastatic disease (Song et al. 2011). In very rare instances, ectopic liver was found in the heart cavities, mainly in the atria (Trocciola et al. 2011; Xu et al. 2012).

Intravascular Liver Ectopia

In very rare situations, ectopic liver tissue is present within the lumen of large veins. Ectopic intracaval liver, sometimes presenting as a floating intracaval mass, has been described (Chapman-Fredricks et al. 2010; Morris et al. 2012; Rafiei et al. 2012). The intravenous liver tissue can be attached to the vein wall by a thin stalk (Morris et al. 2012) and may extend to the right atrium, producing a pedunculated intracardiac mass (Chapman-Fredricks et al. 2010). Pathogenetically, a deranged morphogenesis of the caudate lobe of the liver with aberrant migration of hepatocyte precursors into the developing retrocaudate vena cava was proposed (Chapman-Fredricks et al. 2010). Intracaval ectopic liver may be confounded with retrohepatic invasion of the inferior vena cava by well-differentiated hepatocellular carcinoma (Ohwada et al. 1994; Kaneko et al. 1996; Uemura et al. 2004). A further differential diagnosis of intravenous liver ectopia is traumatic dislocation of liver tissue into the vena cava.

Gallbladder Ectopia

Gallbladder ectopia can occur in an intrahepatic location (Galli and Donati 1968; Zhuravlev 1968; Mincsev 1968; Maekawa et al. 1978; Lloyd 1979; Schmahmann et al. 1982; Lusink and Sali 1985; Matsuzaki et al. 1995; Guiteau et al. 2009), also as an accessory organ (Wolnicki et al. 1974), and results in an area of decreased tracer concentration in liver scans (Wysong and Gorten 1980; Dumont and Danais 1984; Velchik and Noel 1987; Soudry et al. 1995) with a characteristic focal defect in 99mTc-sulfur colloid imaging (Schulz et al. 1975), eventually leading to the suspicion of an intrahepatic neoplasm. Intrahepatic gallbladders may undergo inflammatory and fibrous changes resulting in intrahepatic porcelain gallbladder (Smith et al. 2012).

There are several other situations of congenital or acquired gallbladder disease which may produce differential diagnostic problems at imaging. A suprahepatic or retrohepatic gallbladder is usually combined with hypoplasia or even agenesis of the right liver lobe (Faintuch et al. 1980; Youngwirth et al. 1983; D'Araujo and Coelho 1992; Sheu et al. 1995; Hsu et al. 1997), but rarely both parts are found in a supradiaphragmatic position without hepatic hypoplasia (Organ and Hayes 1980). The gallbladder is rarely situated to the left side (sinistroposition; Large 1963; Siebermair 1986; Banzo et al. 1990; Idu et al 1996; Fujita et al. 1998), sometimes associated with hypoplasia of the right liver lobe (Stankovic et al. 1998) or with duplication of the common bile duct (Bender et al. 2007). A hepatic tumor may be suspected in case of gallbladder duplication (McDonald and Lwin 1986; Nursal et al. 2007; Pitiakoudis et al. 2008). In case of missed double gallbladder, perforation can occur after laparoscopic cholecystectomy (Borghi et al. 2008). False-positive hepatobiliary imaging can be caused by congenital absence of the gallbladder (Dickinson et al. 1984). The Phrygian cap anomaly of the

gallbladder can simulate a hepatic mass lesion (Smergel and Maurer 1984).

Apart from congenital malformations, the gallbladder can also be displaced in patients with liver cirrhosis (Owshalimpur and Karimeddini 1982). An enlarged gallbladder filled with blood has been shown to result in nonvisualization, with a rounded photon-deficient area (Davis et al. 1993). Gallbladder perforation has been shown to rarely result in tumor-like, large pseudocyst (Fernandez et al. 2000).

References

Abdalla EK, Vauthey JN, Couinaud C (2002) The caudate lobe of the liver: implications of embryology and anatomy for surgery. Surg Oncol Clin N Am 11:835–848

Acar T, Tacyildiz R, Karakayali S (2002) Ectopic liver tissue attached to the gallbladder. Acta Chir Belg 102:210–211

Akbulut S, Cakabay B, Sevinc MM, Basak F (2011) Gastric outlet obstruction caused by Riedel's lobe of the liver: a diagnostic and therapeutic challenge for surgeons. Hepatogastroenterology 58:589–592

Ashby EC (1969) Accessory liver attached to the gallbladder. Br J Surg 56:311–331

Auguste C, Lagache G, Delecourt M (1955) Radiological syndrome of absence of left lobe of liver (in French). Arch Mal Appar Dig Mal Nutr 44:105–110

Babu R, Van der Avoirt A (2001) Ectopic intrathoracic liver. Pediatr Surg Int 17:461–462

Bannon K, Hraemic J, Mittal V (2013) Ectopic liver tissue sequestered in the lung. Am Surg 79:E104–E105

Banzo I, Carril JM, Arnal C, Quirce R (1990) Left-sided gallbladder. An incidental finding on hepatobiliary scintigraphy. Clin Nucl Med 15:358–359

Barclay-Smith E (1908) A liver exhibiting multiple anomalies. J Anat Physiol 43:346

Bargallo X, Gilabert R, Nicolau C, Garcia-Pagan JC, Bosch J, Bru C (2003) Sonography of the caudate vein: values in diagnosing Budd-Chiari syndrome. AJR Am J Roentgenol 181:1641–1645

Baum S, Locko RC, d'Avignon MB (1982) Functional anatomy and radionuclide imaging: Riedel's lobe of the liver. Anat Clin 4:121–123

Bender EA, Springhetti S, Shemisa K, Wittenauer J (2007) Left-sided gallbladder (sinistroposition) with duplication of the common bile duct. JSLS 11:148–150

Bertrand L (1963) On congenital abnormalities of the left lobe of the liver (agenesis, hypoplasia, atrophy or angiomatosis) (in French). Rev Med Chir Mal Foie 38:233–248

Bertrand L, Janbon M, Negre E, Bertrand A (1962) Agenesia of the right lobe of the liver. Hemorrhages caused by manifesting portal hypertension. 2 observations (in French). Lyon Med 94:419–434

Borghi F, Giraudo G, Geretto P, Ghezzo L (2008) Perforation of missed double gallbladder after primary laparoscopic cholecystectomy: endoscopic and laparoscopic management. J Laparoendosc Adv Surg Tech A 18:429–431

Broca P (1880) Sur une microcéphalie agé de deux ans et demi, anomalies viscérales régressives. Bull Soc Anthropol Paris 3:387

Brühl R (1926) Ueber eine Nebenleber mit zirrhotischen Veränderungen. Zbl Path 37:245

Calori L (1880) Sulla coesistenza di un eccessiva divisione del fegato e di qualche dito soprannumerario nelle mani o nei piedi. Mem Accad Sci Ist Bologna 2:335

Cardona D, Grobmyer S, Crawford JM, Liu C (2007) Hepatocellular carcinoma arising from ectopic liver tissue in the pancreas. Virchows Arch 450:225–229

Castro Viera GA, Sanuy ME, Camara HA, Cordoba OC (1990) Accessory liver in gallbladder. Apropos of a case report (in Spanish). Rev Esp Enferm Dig 77:295–296

Chalak LF, Parham DM (2007) A newborn with Poland anomaly and liver ectopy: an unusual association with important prognostic implications. Pediatr Dev Pathol 10:134–137

Champetier J, Yver R, Letoublon C, Vigneau B (1985) A general review of anomalies of hepatic morphology and their clinical implication. Anat Clin 7:285–299

Chapman-Fredricks J, Birusingh R, Ricci M, Rodriguez M (2010) Intracaval liver with cardiac extension. A new developmental anomaly? Fetal Pediatr Pathol 29:401–406

Charbonnet E, Van Kote G, Godeffroy Y, Dreux-Boucard-H, Menguy M, Leconte D (1988) Supernumerary liver. A case with a particular location in an omphalocele (in French). Chir Pediatr 29:330–335

Chaulieu C, Claudon M, Regent D, Treheux A (1982) Riedel's lobe. Echotomographic aspects (in French). J Radiol 63:637–641

Chiari H (1899) Ueber die Genese der "Zwerchfellfurchen" der Leber. Verh Ges Dtsch Naturf Aerzte 71:7

Chiba S, Suzuki T, Kasai T, Chiba S, Suzuki T, Kasai T (1991) A tongue-like projection of the left lobe in human liver, accompanied with lienorenal venous shunt and intrahepatic arterial anastomosis. Okajimas Folia Anat Jpn 68:51–66

Chouke KS (1932) A note on an anomalous lobe of the liver. Anat Rec 53:177–179

Corsy F (1922) Lobe surnuméraire du foie implanté sur la face inférieure de la vésicule biliaire. C R Soc Biol (Marseille) 86:695

Couinaud C (1998) Dorsal sector of the liver (in French). Chirurgie 123:8–15

Couinaud C, Perez R, Manouvrier J (1968) Riedel's lobe and the diaphragmatic fissures. Source of error in the interpretation of hepatic radiography and radioisotope scanning (in French). Presse Med 76:2143–2144

Cullen T (1925) Accessory lobes of the liver. Arch Surg 11:718
D'Agostino S, Musi L, Dante S, Belloli G (1989) Supernumerary liver localized in the navel. Description of a case (in Italian). Pediatr Med Chir 11:451–453
D'Araujo JM, Coelho PS (1992) Agenesis of the right lobe of the liver with supra-hepatic gallbladder. Acta Radiol 33:81
Davis RB, Shih WJ, Stigers K, Fried A (1993) An abnormal gallbladder presenting as a huge, rounded photon-deficient area in radionuclide hepatobiliary imaging. J Natl Med Assoc 85:222–224
Del Sordo R, Bellezza G, Colella R, Mameli MG, Giansanti M, Cavaliere A (2011) Epithelial cyst of the spleen with foci of ectopic liver. J Pediatr Surg 46:e21–e23
Dickinson CZ, Powers TA, Sandler MP, Partain CL (1984) Congenital absence of the gallbladder: another cause of false-positive hepatobiliary image. J Nucl Med 25:70–72
Donoso L, Martinez-Noguera A, Zidan A, Lora F (1989) Papillary process of the caudate lobe of the liver: sonographic appearance. Radiology 173:631–633
Duchesne E (1881) Notes sur quelques anomalies régressives observées sur les viscères d'un nègre mozambique. Bull Soc Anthropol Paris 4:329
Dumont M, Danais S (1984) Intrahepatic gallbladder simulating choledochal cyst on DISIDA scintigraphy. Clin Nucl Med 9:657–658
Eiserth P (1940) Beiträge zur Kenntnis der Nebenlebern. Virchows Arch 307:307–313
Eiserth P (1962) Cited by Willis RA: The borderland of embryology and pathology, 2nd edn. Butterworth, Washington, DC, p 330
El Mezni F, Jebali A, Najeh N, Ben Jilani S (1993) Pancreatic heterotopia in the gallbladder. Report of a case (in French). Ann Pathol 13:271–272
Faintuch J, Machado MC, Raia AA (1980) Suprahepatic gallbladder with hypoplasia of the right lobe of the liver. Arch Surg 115:658–659
Farmer RG, Hermann RE, Sullivan BH (1969) Congenital hepatic fibrosis of Riedel's lobe causing portal hypertension. Cleve Clin Q 36:143–148
Fellbaum C, Beham A, Schmid C (1987) Isolated accessory liver (hepar succenturiatum) at the neck of the gallbladder. Case report with review of the literature (in German). Wien Klin Wochenschr 99:825–827
Fernandez V, Tons C, Schumpelick V (2000) Large flank tumor after covered gallbladder perforation (in German). Chirurg 71:222–224
Festen C, Severijnen RS, van der Staak FH (1988) Gallbladder embedded in an accessory liver lobe in umbilical cord hernia. J Pediatr Surg 23:978–979
Filipponi F, Romagnoli P, Mosca F, Couinaud C (2000) The dorsal sector of human liver: embryological, anatomical and clinical relevance. Hepatogastroenterology 47:1726–1731
Finney GMT (1925) Reported by Cullen T (1925) Accessory lobes of the liver. Arch Surg 11:743
Fock G (1963) Ectopic liver in omphalocele. Acta Paediatr 52:288
Fogh J, Tromholt N, Jorgensen F (1989) Persistent impairment of liver function caused by a pendulated accessory liver lobe. Eur J Nucl Med 15:326–327
Forni G (1915) Contributo allo studio del cosidetto fegato accessorio. Bull Sci Med Bologna 3:106
Fujita N, Shirai Y, Kawaguchi H, Tsukada K, Hatakeyama H (1998) Left-sided gallbladder on the basis of a right-sided round ligament. Hepatogastroenterology 45:1482–1484
Galli R, Donati G (1968) Case of an 'intrahepatic gallbladder'. With bibliographic review (in Italian). Osp Ital Chir 19:9–16
Giacomini C (1884) Annotazioni sopra l'anatomia del negro. G Accad Med Torino 32:563
Gillard JH, Patel MC, Abrahams PH, Dixon AK (1998) Riedel's lobe of the liver: fact or fiction? Clin Anat 11:47–49
Grenet A (1895) Foie multilobulé. Bull Soc Anat Paris 70:44
Gruber W (1849) Neue Anomalien als Beiträge zur physiologischen, chirurgischen und pathologiscehn Anatomie. Verlag Albert Förstner, Berlin
Gruber W (1880) Doppelte Nebenleber. Virchows Arch Pathol Anat Physiol Klin Med 82:476–477
Guiteau JJ, Fisher M, Cotton RT, Goss JA (2009) Intrahepatic gallbladder. J Am Coll Surg 209:672
Hamdani SD, Baron RL (1994) Ectopic liver simulating a mass in the gallbladder wall: imaging findings. AJR Am J Roentgenol 162:647–648
Han S, Soylu L (2009) Accessory liver lobe in the left thoracic cavity. Ann Thorac Surg 87:1933–1934
Heller A (1870) Mangelhafte Entwicklung des rechten Leberlappens. Virchows Arch 51:355
Henle J (1866) Anatomie des Menschen. Braunschweig 2:191
Hsu KL, Cheng YF, Ko SF (1997) Hypoplastic right hepatic lobe with retrohepatic gallbladder complicated by hepatolithiasis and liver abscess: a case report. Hepatogastroenterology 44:803–807
Iber T, Rintala R (1999) Intrapulmonary ectopic liver. J Pediatr Surg 34:1425–1426
Idu M, Jakimowicz J, luppa A, Cuschieri A (1996) Hepatobiliary anatomy in patients with transposition of the gallbladder: implications for safe laparoscopic cholecystectomy. Br J Surg 83:1442
Inglis JPP (1911) Extra intrinsic hepatic lobe. Polyclinic 15:9
Jacquemet M (1896) Considérations sur les anomalies du foie et des voies biliaires. Thèse (thesis) de Lyon, number 1231
James PM, Howard JM, Wolferth CC (1963) Riedel's lobe of the liver. Am J Surg 105:812–815
Jarde O, Barrat JP, Degardin P, Maingueux P, Tardif B (1989) Aberrant pancreas in the gallbladder (in French). J Chir (Paris) 126:476–477
Kabaroudis A, Papaziogas B, Atmatzidis K, Argiriadou E, Paraskevas A, Galanis I, Papziogas T

(2003) Hypoplasia of the right hepatic lobe combined with a floating gallbladder. Acta Chir Belg 103: 425–427
Kanamura T, Murakami G, Hirai I, Hata F, Sato TJ, Kumon M, Nakajima Y (2001) High dorsal drainage routes of Spiegel's lobe. J Hepatobiliary Pancreat Surg 8:549–556
Kaneko T, Nakao A, Nomoto S, Endo T, Itoh S, Takagi H (1996) Intracaval endovascular ultrasonography for preoperative assessment of retrohepatic inferior vena cava infiltration by malignant hepatic tumors. Hepatology 24:1121–1127
Kanzaki R, Yamada T, Gotoh K, Takahashi H, Ohigashi H, Ishikawa O (2010) Ectopic hepatocellular carcinoma arising in the left triangular ligament of the liver. Case Rep Gastroenterol 4:138–142
Keyloun VE, Pinkernell B (1967) Riedel's lobe and cirrhosis. Report of a case. Am J Dig Dis 12:1174–1177
Kitami M, Murakami G, Ko S, Takase K, Tuboi M, Saito H, Nakajima Y, Takahashi S (2004) Spiegel's lobe bile ducts often drain into the right hepatic duct or its branches: study using drip-infusion cholangiography – computed tomography in 179 consecutive patients. World J Surg 28:1001–1006
Kleinhaus et al. (1968). http://www.ncbi.nlm.nih.gov/pubmed/5673064
Korn MA, Mostbeck GH, Tscholakoff D (1991) Papillary process of the caudate lobe – erroneous sonography interpretation as a space-occupying lesion (in German). Ultraschall Med 12:197–200
Krauspe K (1923) Ueber Hypoplasie des rechten Leberlappens. Virchows Arch 247:180
Kschischo P (1912) Ueber eine Missbildung der Leber. Zbl Path 23:293
Kudo M (2000) Riedel's lobe of the liver and its clinical implication. Intern Med 39:87–88
Kwak HS, Lee JM, Lee SY, Han YM, Kim CS, Moon WS, Yu HC (2000) Pseudotumorous hyperplasia of the caudate lobe in the non-cirrhotic liver: MR and CT arterial portography appearance. Hepatogastroenterology 47:909–911
Kwon D, Murakami G, Hata F, Wang HJ, Chung MS, Hirata K (2002) Location of the ventral margin of the paracaval portion of the caudate lobe of the human liver with special reference to the configuration of hepatic portal vein branches. Clin Anat 15:387–401
Lancereaux P (1899) Traité des maladies du foie et du pancréas. Doin, Paris
Lane D (1966) Masses in the right hypochondrium and Riedel's lobe. Med J Aust 1:896–899
Lara-Diaz VJ, Garza-Bulnes R, Garza-Garza R, Durand M (2011) Ectopic liver within the umbilical cord in a very preterm infant from a multiple gestation. Pediatr Dev Pathol 14:422–425
Large AM (1963) Left-sided gallbladder and liver without situs inversus. Arch Surg 87:982–985
Lee UY, Murakami G, Han SH (2004) Arterial supply and biliary drainage of the dorsal liver: a dissection study using controlled specimens. Anat Sci Int 79:158–166
Lefaucher C, Dupuis E, Muller J, Laham A (1978) Torsion of Riedel's lobe. Two cases (in French). J Chir (Paris) 115:25–28
Lipchik EO, Schwartz SI (1967) Angiographic and scintillographic identification of Riedel's lobe of the liver. Radiology 88:48–50
Lloyd TV (1979) Empyema of an intrahepatic gallbladder. Clin Nucl Med 4:341
Lockwood CB (1903) Hepatectomy for the removal of Riedel's lobe. Lancet 162:223–224
Louda V, Baumelt V (1981) Liver tissue in omphalocele (in Czech). Cas Lek Cesk 120:289–290
Lusink C, Sali A (1985) Intrahepatic gallbladder and obstructive jaundice. Med J Aust 142:53–54
Maekawa N, Uehara H, Honda Y, Nishino I, Kyoi M, Kawakami K, Inoue T, Yamamoto M, Ueno T, Mibayashi Y, Takeda R (1978) A case of intrahepatic gallbladder detected by liver scintigram (in Japanese). Nippon Shokakibyo Gakkai Zasshi 75:1295–1298
Marquand J, Lemaitre F, Houssin D (1980) Aberrant liver lobes, ectopic, and accessory livers. Two cases of small ectopic livers (in French). Chirurgie 106:114–117
Matsuyama M, Sugiura S, Kakita A, Sato Y, Kuroda M (2011) Hepatocellular carcinoma arising from ectopic liver tissue in the spleen producing insulin-like growth factor II. Pathol Res Pract 207:124–126
Matsuzaki M, Suda K, Akaza K, Sakuma H (1995) Intrahepatic gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 8:154–155
McCreadie SR, Burkhardt TB (1965) Ectopic left lobe of the liver. Marquette Med Rev 31:15–17
McDonald KL, Lwin T (1986) Sonographic and scintigraphic evaluation of gallbladder duplication. Clin Nucl Med 11:692–693
Meckel JF (1822a) Tabulae anatomico-pathologicae. Lipsiae; fasc. tertius, p 14, Tabula XXIV
Meckel JF (1822b) Beschreibung zweier durch sehr ähnliche Bildungsabweichung entstellter Geschwister. Dtsch Arch Physiol 7:99–172
Mehta RI, Lai CK, Kee S, Fishbein MC (2010) Intrapulmonary ectopic liver after orthotopic heart transplantation. Arch Pathol Lab Med 134:1060–1062
Meyers HI, Jacobson G (1958) Displacements of stomach and duodenum by anomalous lobes of the liver. Am J Roentgenol Radium Ther Nucl Med 79:789–792
Mincsev M (1968) Intrahepatic gallbladder (vesica fellea intrahepatica seu parenchymatosa seu occulta) (in Hungarian). Orv Hetil 109:1637–1640
Moore N (1882) A rare variety in lobulation of the liver. Trans Path Soc Lond 33:192
Morgagni GB (1767) De sedibus et causis morborum. Epistolas II 48:55
Morgenstern L, Mazur M (1959) Hypoplasia of the right hepatic lobe. Am J Surg 98:628–630
Morris MW, Helling TS, Creswell LL, Jordan B, Mitchell ME (2012) Ectopic liver masquerading as a floating intracaval mass. J Vasc Surg 55:1759–1761

Moser W (1898) Anomalous lobulations of the liver. Med Rec 54:88
Murakami G, Hata F (2002) Human liver caudate lobe and liver segment. Anat Sci Int 77:211–224
Musser JH (1888) Deformity of liver simulating movable kidney. Trans Path Soc Phila 14:82
Naganuma H, Ishida H, Niizawa M, Morikawa P, Masamune O, Kato T (1993) Intrathoracic accessory lobe of the liver. J Clin Ultrasound 21:143–146
Natori T, Hawkin S, Aizawa M, Asai T, Kameda Y, Ikuyohashi K (1986) Intra-cholecystic ectopic liver. Acta Pathol Jpn 36:1213–1216
Negre E, Pujol H, Thevenet A (1962) Portal hypertension in agenesis of the right lobe of the liver (in French). Presse Med 70:2501–2504
Nora E, Carr EE (1946) Umbilical accessory liver. Am J Obstet Gynecol 52:330
Nursal TZ, Ulusan S, Tercan F, Yildirim S, Tarim A, Noyan T, Bilgin N (2007) Laparoscopic management of gallbladder duplication. Int Surg 92:195–197
Ohwada S, Tanahashi Y, Kawashima Y, Satoh Y, Nakamura S, Kobayashi I, Ohya T et al (1994) Surgery for tumor thrombi in the right atrium and inferior vena cava of patients with recurrent hepatocellular carcinoma. Hepatogastroenterology 41:154–157
Organ CH, Hayes DF (1980) Supradiaphragmatic right liver lobe and gallbladder. Arch Surg 115:989–990
Ortale JR, Borges Keiralla LC (2004) Anatomy of the portal branches and the hepatic veins in the caudate lobe of the liver. Surg Radiol Anat 26:384–391
Owshalimpur D, Karimeddini MK (1982) Gallbladder displacement in a cirrhotic patient simulating ectopia. Clin Nucl Med 7:284–286
Park et al. (1991). http://www.ncbi.nlm.nih.gov/pubmed/2023091
Parke WW, Settles HE, Bunger PC, Van Demark RE (1996) Malformations of the liver: some prenatal and postnatal developmental aspects. Clin Anat 9: 309–316
Perez Ara A, Silva Ruiz F (1954) Considerations on accessory livers and report of a case of juxtacholecystic hepatic nodule (in Spanish). Rev Kuba Med Trop Parasitol 10:73–77
Pichevin R (1888) Coincidence d'un lobe du foie flottant et d'un rein mobile. Prog Méd 8:253
Pitiakoudis M, Papanas N, Polychronidis A, Maltezos E, Prassopoulos P, Simopoulos C (2008) Double gallbladder – two pathologies: a case report. Acta Chir Belg 108:261–263
Preminger A, Udassin R, Pappo O, Arad I (2001) Ectopic liver tissue within the umbilical cord. J Pediatr Surg 36:1085–1086
Rafiei P, Sebastian S, Patel RB, Roda MS (2012) Ectopic intracaval liver. Clin Imaging 36:869–872
Reddy DJ (1954) Complete absence of the left lobe of the liver. J Indiana State Med Assoc 23:405–406
Reitemeier RJ, Butt HR, Baggenstoss AH (1958) Riedel's lobe of the liver. Gastroenterology 34:1090–1095
Rendina EA, Venuta F, Pescarmona EO, Martelli M, Ricci C (1989) Intrathoracic lobe of the liver. Case report and review of the literature. Eur J Cardiothorac Surg 3:75–78
Reuther G (1992) An unclear space-occupying lesion in the portocaval space. A hypertrophied papillary process in the caudate lobe of the liver (in German). Radiologe 32:407–408
Riedel I (1888) Ueber den zungenförmigen Fortsatz des rechten Leberlappens und seine pathognostische Bedeutung für die Erkrankung der Gallenblase nebst Bemerkungen über Gallensteinoperationen. Berl Klein Wochenschr 29:577–881
Rodriguez-Perez D (1955) Accessory intrapleural ectopic liver lobe. Bol Asoc Med P R 47:353–356
Sakarya A, Erhan Y, Ayede H, Kara E, Ilkgul O, Ciftdogan C (2002) Ectopic liver (choristoma) associated with the gallbladder encountered during laparoscopic cholecystectomy: a case report. Surg Endosc 16:1106
Sato TJ, Hirai I, Murakami G, Kanamura T, Hata F, Hirata K (2002) An anatomical study of short hepatic veins, with special reference to delineation of the caudate lobe for hanging maneuver of the liver without the usual mobilization. J Hepatobiliary Pancreat Surg 9:55–60
Schmahmann JD, Dent DM, Mervis B, Kottler RE (1982) Cholecystitis in an intrahepatic gallbladder. A case report. S Afr Med J 62:1042–1043
Schulz RC, Shields JB, Fletcher JW, Donati RM (1975) Liver scanning and the intrahepatic gallbladder: case report. J Nucl Med 16:1029–1030
Sham R, Sain A, Silver L (1978) Hypertrophic Riedel's lobe of the liver. Clin Nucl Med 3:79–81
Shaw A, Pierog S (1969) "Ectopic" liver in the umbilicus: an unusual focus of infection in a newborn infant. Pediatrics 44:448–450
Sheu BS, Lin XZ, Chen CY, Chow NH, Lin PW, Tsai HM (1995) Suprahepatic gallbladder and right lobe anomaly of the liver in patients with biliary cancers. Dig Dis Sci 40:2411–2416
Siebermair J (1986) Left-sided gallbladder-a rare anatomic variant (in German). Chirurg 57:653–654
Smergel EM, Maurer AH (1984) Phrygian cap simulating mass lesion in hepatobiliary scintigraphy. Clin Nucl Med 9:131–133
Smith PW, Farrar RA, Evangelista RS (2012) Intrahepatic porcelain gallbladder: coexistence of pathologies. Am Surg 78:E414–E415
Song Z, Chen G, Xu X, Chen J, Zhou Q (2011) Pleural ectopic hepatic tissues mimicking intrapleural dissemination of tumour. ANZ J Surg 81:756–757
Soo MS, Adatepe MH (1990) Metastatic lesions arising in a Riedel's lobe. Findings from a sulfur colloid liver-spleen scan. Clin Nucl Med 15:814–815
Soudry G, Ahn CS, Tow DE (1995) Focal defect in liver scans due to intrahepatic gallbladder. Clin Nucl Med 20:460–461
Stankovic N, Petrovic M, Kostic Z (1998) Left-sided gallbladder and hypoplasia of the right hepatic lobe – a rare

congenital anomaly (in Serbo-Croatian). Vojnosanit Pregl 55:215–218
Takamatsu S, Goseki N, Nakajima K, Teramoto K, Iwai T, Arii S (2004) Distributing pattern of the bile duct of the caudate lobe on computed tomography with drip infusion cholangiography and its surgical significance. Hepatogastroenterology 51:29–32
Tarenetzki A (1883) Abnorme Form einer Leber nebst Nebenlebern. St Petersburg Med Wochenschr 8:251
Tarozzi G (1904) Osservazioni e ricerche sopra le inclusioni epatiche nel legamento triangulare sinistro del fegato. Sper Arch Biol 58:499
Taruffi C (1880) Due rare alterazioni di fegato. Mem Accad Sci Ist Bologna Serie 4 1:167
Tejada E, Danielson C (1989) Ectopic or heterotopic liver (choristoma) associated with the gallbladder. Arch Pathol Lab Med 113:950–952
Thomson A (1898) The morphological significance of certain fissures in the human liver. J Anat Physiol 33:546
Tohma T, Cho A, Okazumi S, Makino H, Shuto K, Mochiduki R, Matsubara K, Gunji H, Ochiai T (2005) Communicating arcade between the right and left hepatic arteries: evaluation with CT and angiography during temporary balloon occlusion of the right or left hepatic artery. Radiology 237:361–365
Toldt, Zuckerkandl (1876) Ueber die Form-und Texturveränderungen der menschlichen Leber während des Wachsthums. Sitzungsber Wien Akad Wiss 72:241
Torchio B, Maconi G (1978) Nodule of ectopic hepatic parenchyma in the wall of the gallbladder (in Italian). Minerva Chir 33:39–44
Trocciola SM, Balsam LB, Yee H, Gianos E, Srichai MB, DeAnda A (2011) Ectopic liver: an unexpected finding in a right atrial mass. Ann Thorac Surg 92:715–718
Tuset E, Ribera JM, Domenech E, Vaquero M, Oller B, Armengol M, Planas R, Navarro JT, Feliu E (1995) Pseudotumorous hyperplasia of the caudate lobe of the liver in a patient with Alagille syndrome (in Spanish). Med Clin (Barc) 104:420–422
Uemura M, Sasaki Y, Yamada T, Eguchi H, Ohigashi H, Doki Y, Murata K, Miyashiro I et al (2004) Surgery for hepatocellular carcinoma with tumor thrombus extending into the right atrium: report of a successful resection without the use of cardiopulmonary bypass. Hepatogastroenterology 51:1259–1262
Vaideeswar P, Yewatkar D, Nanavati R, Bhuiyan P (2011) Ectopic liver tissue in umbilical cord. J Postgrad Med 57:229–230
Van Minh T, Galizia G, Lieto E (1992) Anatomy of the caudate lobe of the liver. New aspects and surgical applications (in French). Ann Chir 46:309–317
Vegandt (1876) Hepar accessorium. Voyenno Med J (St Petersburg) 127:145–147
Velchik MG, Noel AW (1987) False-positive liver scan due to an intrahepatic gallbladder detected by cholescintigraphy. Clin Nucl Med 12:50–52
Wagner E (1861) Zwei Fälle von Neubildung von Lebersubstanz im Ligamentum suspensorium hepatis. Arch Heilkd 2:471
Walzel P, Gold E (1925) Zur Anatomie der sog. Nebenleber (Hepar succenturiatum). Arch Klin Chir 135:1388
Wang Y, Junlin L, Zhang WG, Chen JH, He Y, Chen JM (2010) Accessory lobe of right liver mimicking a pulmonary tumor in an adult male. Ann Thorac Surg 89:e9–e10
Watanabe M, Matsura T, Takatori Y, Ueki K, Kobatake T, Hidaka M, Hirakawa H, Fukukmoto S, Shimada Y (1989) Five cases of ectopic liver and a case of accessory lobe of the liver. Endoscopy 21:39–42
Watson JR, Lee RE (1964) Accessory lobe of the liver with infarction. Arch Surg 88:490–493
Wax JR, Pinette MG, Cartin A, Blackstone J (2007) Ectopic liver: a unique prenatally diagnosed solid umbilical cord mass. J Ultrasound Med 26:377–379
Wilhelmi OJ (1923) Riedel's lobe simulating nephroptosis. JAMA 80:1755–1757
Wolnicki S, Swadzba S, Borgiel W (1974) Accessory intrahepatic gallbladder (in Polish). Pol Przegl Radiol Med Nukl 38:629–633
Wysong CB, Gorten RJ (1980) Intrahepatic gallbladder. South Med J 73:825–826
Xu L, Jeudy J, Burke AP (2012) Ectopic hepatic tissue presenting as right atrial mass. Hum Pathol 43:958–960
Yano K, Ohtsubo M, Mizota T, Kato H, Hayashida Y, Morita S, Furukawa R, Hayakawa A (2000) Riedel's lobe of the liver evaluated by multiple imaging modalities. Intern Med 39:136–138
Youngwirth LD, Peters JC, Perry MC (1983) The suprahepatic gallbladder. An unusual anatomical variant. Radiology 149:57–58
Zamfir R, Brasoveanu V, Boros M, Herlea V, Popescu I (2008) Hepatocellular carcinoma in Riedel's lobe. Chirurgia (Bucur) 103:121–123
Zhuravlev SP (1968) Dystopia of the gallbladder in the liver (in Russian). Klin Khir 6:79
Zonca P, Martinek L, Ihnat P, Fleege J (2013) Ectopic liver: different manifestations, one solution. World J Gastroenterol 19:6485–6489

Solitary Necrotic Nodule of the Liver 122

Contents

Abstract

Solitary necrotic nodule of the liver (SNNL) is a rare benign lesion defined as a reactive circumscribed nodule characterized by a central coagulative necrosis and a fibrous demarcation. Most cases of SNNL are clinically silent and are incidental findings in the setting of liver resections or autopsies. SNNL can grow to important size, but can also undergo spontaneous regression. Macroscopically, SNNL are round to ovoid well-delineated lesion showing a whitish to yellowish central part and a capsule-like fibrous peripheral sheath. Most cases are solitary, but multiple lesions have also been reported. SNNL may contain calcifications and cholesterol crystals. Rarely, a foreign body-type reaction with giant cells is noted. Accumulation of lipid-rich foamy macrophages is a common finding. Etiology and pathogenesis of SNNL are still not clarified.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_122

Introduction

Solitary necrotic nodule of the liver (SNNL) is a rare benign lesion, initially reported in 1983 (Shepherd and Lee 1983). SNNL is defined as a reactive and benign, circumscribed nodular liver lesion characterized by a central coagulative necrosis and a fibrous demarcation. Since 1983, several other reports have confirmed the existence of this lesion (about 50 cases reported) and have further characterized it, including its radiologic features. Most SNNL are clinically silent or are incidental findings. However, SNNL can mimic a primary liver neoplasm, as it can grow to important size, but it can also undergo spontaneous regression.

Selected References Berry 1985a, b; Shepherd 1990; Berry and Shepherd 1990; Sundaresan et al. 1991; Tsui et al. 1992; Carella et al. 1993; Clouston et al. 1993; Di Stasi et al. 1993; Desai et al. 1995; Nakanuma 1995; Alfieri et al. 1997; Grazi et al. 1998; Yoon et al. 2000; De Luca et al. 2000; Iwase et al. 2002; Colagrande et al. 2003; Koea et al. 2003; Marongiu et al. 2004; Glas et al. 2006; Kondi-Pafiti et al. 2006; Zuo et al. 2006; Chen et al. 2007, 2010; Shonaka et al. 2007; Wang et al. 2007; Koea and Smith 2008; Zhou et al. 2008; Delis et al. 2009; Choi et al. 2010; Deniz and Coban 2010; Deniz et al. 2011).

Epidemiology

The prevalence of SNNL is difficult to estimate; in one study, seven nodules were retrieved from 4000 necropsy and surgical liver specimens coming to light over 5 years (Tsui et al. 1992). All these lesions were incidentally detected, the patient ages ranging from 48 to 79 years (mean: 63.7 years), without gender predilection. SNNL occur as solitary lesions or are multiple nodules. They may occur more frequently in anterior portions of the liver (Shepherd and Lee 1983; Berry 1985a; Sundaresan et al. 1991) and are more common in the right liver lobe (Kondi-Pafiti et al. 2006). In a recent Chinese retrospective study of 51 patients with histologically confirmed SNNL, the mean age at presentation was lower (45.3 years; the youngest patient 5 years old), with a clear male preponderance (68.6 %; Zhou et al. 2008).

Imaging Features

As the lesions range in size from few mm to more than 8 cm, many can be detected by modern imaging methods. Hepatobiliary ultrasonography reveals a hypoechogenic, target-appearing nodular formation, which appears as a perfusion defect in contrast-enhanced ultrasonography (CEUS) (Wang et al. 2007). Doppler examinations display a lack of flux within the lesion (De Luca et al. 2000; Yoon et al. 2000; Colagrande et al. 2003; Koea et al. 2003). Lesions thought to have undergone dehydration of the coagulative necrosis may show central hyperechogenicity on US, with a rough patchy core (Colagrande et al. 2003). CT scans usually show a hypodense nodular lesion without enhancement after contrast media injection, whereas MR exhibits low signal in the weighted T1 images, hyperintensity on T2WI, and isointense in the later echoes of the SE sequences. In a study of 33 pathologically proved lesions, MR revealed hypointense nodules on T1-weighted images in 93.9 % and isointense lesions in 6.1 % only, while the nodules were hyperintense on T2-weighted images in 36.4 %, isointense or invisible in 45.4 %, and hypointense in 18.2 %. After injection of gadopentetate, all lesions were hypointense and none of them showed enhancement (Geng et al. 2012). Calcifications are frequent and were noted in more than half of the cases (Kondi-Pafiti et al. 2006). On F-18 FDG PET, SNNLs are hypermetabolic lesions (Chen et al. 2010). At imaging, SNNL may mimic liver metastasis (Shepherd and Lee 1983; Carella et al. 1993; Yoon et al. 2000; Colagrande et al. 2003). Primary malignancy may be suspected, including hepatocellular carcinoma (Kondi-Pafiti et al. 2006; Shonaka et al. 2007; Delis et al. 2009), in particular because in some instances SNNL may show rapid growth

(Imura et al. 2006). Imaging differential diagnosis chiefly comprises inflammatory pseudotumor, regressing angiomas, rare infections producing masses in the liver (tuberculosis; mycoses; pneumocystosis), and the rare rheumatoid hepatic nodules.

Macroscopic Pathology

At gross examination, SNNL are spheroid to ovoid, well-delineated lesions that display a whitish to yellowish central part, representing coagulation necrosis, and a capsule-like fibrous demarcation zone at the periphery (Fig. 1). The average diameter of the lesions was 23 mm (range: 10–55 mm) (Zhou et al. 2008). Although the term, SNNL, expectedly indicates that we deal with single lesions, there are few instances where the lesion was not solitary but multiple (less than 10 % of the cases; Kondi-Pafiti et al. 2006). The lesions tend to more commonly occupy the subcapsular area of the liver than deeper parts of the liver substance (almost 87 % in one study; Kondi-Pafiti et al. 2006), but large masses (8.5 cm; Imura et al. 2006) grossly mimicking malignancy are also encountered. Subcapsular SNNL causes a typical, flat retraction of the capsule, the adjacent lesion then assuming a roughly triangular shape. SNNL may be hard and gritty, owing to extensive mineralization/calcification. In large masses, the calcification pattern may be reticular and chiefly localized to central parts of the lesion. Such lesions grossly mimic metastasis of colorectal cancer. Rarely, a small cystic space may be found in the center of the lesion (Iwase et al. 2002).

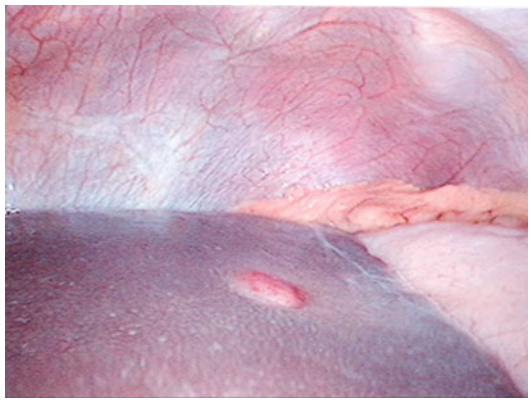

Fig. 1 Solitary necrotic nodule of the liver

Histopathology

Histologically, the inner part of SNNL is occupied by a necrotic mass consisting of an eosinophilic, partly granular material of widely variable necrotic cellularity ("ghost cells"), depending on the cause of the lesion. Descriptively, the central mass histologically represents the nonspecific features of coagulation necrosis, but not of caseification, nuclear debris usually not being prominent. SNNL sometimes contain calcifications and cholesterol crystals. In rare instances, almost the entire nodule may be calcified. Accumulations of foamy macrophages are a relatively frequent finding, and cholesterol granulomas may be observed, also at the interface between the necrosis and the peripheral fibrous tissue. Multinuclear giant cells of the foreign-body type have been observed (Iwase et al. 2002). Typically, the necrotic eosinophilic core is surrounded by a hyalinized fibrotic tissue of variable thickness, with or without a cellular infiltrate (Figs. 2 and 3). This strip of fibrous tissue is visualized at ultrasonography (De Luca et al. 2000, their Fig. 1). SNNL may show varying numbers of small mural vessels with intimal fibrosis and

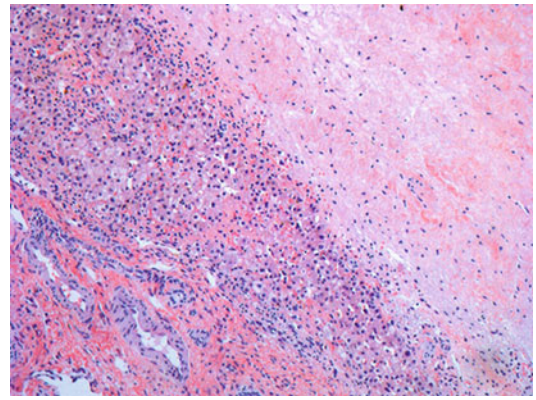

Fig. 2 Solitary necrotic nodule of the liver. The nonencapsulated nodule (right half of figure) consists of hypocellular fibrous tissue with focal necrosis (hematoxylin and eosin stain)

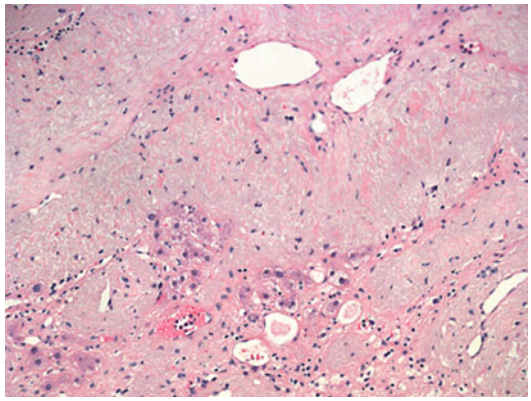

Fig. 3 Solitary necrotic nodule of the liver. In this case, fibrous tissue of the nodule displays elastosis, a secondary change of collagenous matrix. Note three enclosed nests of hepatic parenchyma (hematoxylin and eosin stain)

obliteration. In case of doubt about the nature of a given nodule, a reticulin stain showing a characteristic fiber network in case of SNNL is helpful. In particular, this stain will in most cases allow the distinction between a benign SNNL and a necrotic malignant tumor, the most important differential diagnosis. In a minority of cases, remnants of metastatic carcinoma or fragments of echinococcal membranes were found within a lesion otherwise fulfilling the criteria of SNNL (Deniz and Coban 2010), suggesting that copious sampling for histology should be performed. In one case, remnants of not further specified larval infestation were detected (Chen et al. 2010).

Differential Diagnosis

Several other benign nodular liver lesions are known that may mimic SNNL at imaging and in part also histologically (nonneoplastic nodular lesions of the liver, NNNLL; Nakanuma 1995). A particularly important group includes nodular lesions characterized by a granulomatous reaction and scarring, because such changes occur in SNNL. Rarely, the liver is involved in rheumatoid arthritis, with formation of hepatic rheumatoid nodules (rheumatoid nodulosis) showing a central fibrinoid necrosis and peripheral palisading histiocytes/epithelioid macrophages (Smits and Kooijman 1986; Fitz et al. 1987). Manifestations of sarcoidosis in the liver can produce confluent and sometimes rather large granulomatous lesions that typically produce scarring, but no significant necrosis (nodular hepatic sarcoidosis; Bilir et al. 2000; Thanos et al. 2002; Sartori et al. 2002). Tuberculosis, morphologically characterized by a granulomatous reaction and a distinctive type of coagulative necrosis (caseification), occurs in the liver in the form of several phenotypes according to Levine: (1) miliary tuberculosis, (2) pulmonary tuberculosis with liver involvement, (3) primary liver tuberculosis, (4) tuberculoma, and (5) tuberculous cholangitis (Levine 1990). Hepatic tuberculosis rarely results in large hepatic lesions, termed tuberculomas, nodular, or pseudotumoral tuberculosis (Belloir et al. 1988; Oliva et al. 1990). Macronodular hepatic tuberculomas (Levine 1990; Moskovic 1990; Kawamori et al. 1992; Murata et al. 1996; Ohta et al. 1996; Amaris et al. 1997; Tan et al. 1997; Fan et al. 1998) or giant tuberculomas of the liver (Chan and Pang 1989) may resemble SNNL at imaging. In particular, tuberculomas are hypodense on CT, as SNNL usually are. Contrast enhancement occurs in the peripheral granulomatous tissue while the central low density caseation necrosis shows less enhancement (Levine 1990; Mercusot et al. 1995). As in some SNNL, tuberculomas exhibit calcifications visualized at imaging; they may increase in number, enlarge, or remain unchanged at different stages of healing (Belloir et al. 1988; Chan and Pang 1989; Moskovic 1990), so that the features of calcifications as such will not help in the differential diagnostic judgments. Nodular lesions in the liver with necrosis, and with or without purulent inflammation, can occur in hepatic nocardiosis (Nocardia brasiliensis, N. asteroides, and Rhodococcus equi; Pretet et al. 1979; Akan et al. 1998), aspergillosis (Aspergillus (A.) israelii, A. viscosus, A. naeslundii, A. odontolyticus, A. meyeri, A. gerencseriae, A. terreus; Roesler and Wills 1986; Kazmi and Rab 1989; Ow et al. 1991; Vargas et al. 1992; Miyamoto and Fang 1993; Nazarian et al. 1994; Trachana et al. 2001), brucellosis (brucelloma; Colmenero et al. 2002), cat scratch disease (Danon et al. 2000), and amebiasis (Yeoh et al. 1997).

Etiology and Pathogenesis

What are the causes of SNNL ? The possible origins of these lesions are still debated and theoretically include hematomas, necrotic parasites (e.g., liver flukes, or Armillifer armillatus/pentastomiasis), trauma (owing to the frequently anterior position of the lesions), old hepatic infarctions, and regressing benign tumors. Already in 1985, Berry hypothesized that SNNL might represent an evolution of hepatic hemangioma, based on the observation of a sclerotic and calcified hemangioma, and the detection of a "feeding vessel" (Berry 1985a, b). In a larger histologic study, an origin in hemangiomas of the liver has been confirmed for most of the lesions studied (Sundaresan et al. 1991). Arguments to propose an origin from hemangiomas comprised that SNNL had, in the latter study, a feeding vessel consisting of a muscular artery and that reticulin stains revealed traces of preexisting hemangioma components. However, it was later concluded that the etiology is in fact multifactorial, several lesions having a similar endpoint with the features of SNNL, including regressing hemangiomas, infected abscesses, parasitic granulomas, hematomas, and benign tumors (i.e., not preferentially hemangiomas). In one case, *Clonorchis sinensis* was identified within a lesion (Tsui et al. 1992), and in another patient, a central coiled nematode was detected (Clouston et al. 1993). The presence of *Capillaria hepatica* in SNNL was histologically confirmed in one case (Koea and Smith 2008). Fragments of echinococcal membranes were identified in two cases (Deniz and Coban 2010). An ischemic origin of SNNL was suggested based on the observation of subtotal stenosis of the celiac tripod in one case, followed by progressive reduction of the lesion's diameter upon surgical correction (De Luca et al. 2000).

References

Akan H, Akova M, Ataoglu H, Aksu G, Arslan O, Koc H (1998) Rhodococcus equi and Nocardia brasiliensis infection of the brain and liver in a patient with acute nonlymphoblastic leukemia. Eur J Microbiol Infect Dis 17:737–739

Alfieri S, Carriero C, Doglietto GB, Pacelli F, Crucitti F (1997) Solitary necrotic nodule of the liver: diagnosis and treatment. Hepatogastroenterology 44:1210–1211

Amaris J, Kardache M, Soyer P, Lalande F, Boudiaf M, Scherrer A, Rymer R (1997) Radiological aspects of hepatic tuberculoma. 3 cases (in French). Gastroenterol Clin Biol 21:888–892

Belloir A, Guiry P, Guiry M, Maubon A, Rouanet JP, Bruel JM, Lamarque JL (1988) Pseudotumoral hepatic tuberculosis: Ultrasonics and X-ray computed tomography: apropos of a case. J Radiol 69:21–23

Berry CL (1985a) Solitary "necrotic nodule" of the liver: a probable pathogenesis. J Clin Pathol 38:1278–1280

Berry CL (1985b) Solitary necrotic nodule of liver: a non-existent lesion. J Pathol 146:263A

Berry CL, Shepherd NA (1990) Solitary necrotic nodule of the liver. J Clin Pathol 43:348–349

Bilir M, Mert A, Ozaras R, Yanardag H, Karayel T, Senturk H, Tahan V, Ozbay G, Sonsuz A (2000) Hepatic sarcoidosis: clinicopathologic features in thirty-seven patients. J Clin Gastroenterol 31:337–338

Carella R, Fortunato C, Gubinelli M, D'Errico A, Mancini AM (1993) Solitary necrotic nodule of the liver simulating a metastasis (in Italian). Pathologica 85:573–577

Chan HS, Pang J (1989) Isolated giant tuberculomata of the liver detected by computed tomography. Gastrointest Radiol 14:305–307

Chen Z, Ni JL, Liu LY, Yan JJ, Huang L, Yan YQ (2007) Diagnosis and treatment for solitary necrotic nodule of the liver: report of 15 patients (in Chinese). Zonghua Wai Ke Za Zhi 45:1328–1330

Chen CJ, Chou SC, Chen HJ, Chen HY (2010) Solitary necrotic nodule with larval infestation in the liver on F-18 FDG PET/CT. Clin Nucl Med 35:724–725

Choi CS, Cho EY, Jeong JS, Im CJ, Yang BJ, Kim HC (2010) Spontaneous regression of a solitary necrotic nodule of the liver. Hepatol Int 4:649–652

Clouston AD, Walker NI, Prociv P (1993) Parasitic origin of a solitary necrotic nodule of the liver. J Clin Pathol 46:578

Colagrande S, Politi LS, Messerini L, Mascalchi M, Villari N (2003) Solitary necrotic nodule of the liver: imaging and correlation with pathologic features. Abdom Imaging 28:41–44

Colmenero JD, Queipo-Ortuno MI, Maria Reguera J, Angel Suarez-Munoz M, Martin-Carballino S, Morata P (2002) Chronic hepatosplenic abscesses in brucellosis. Clinico-therapeutic features and molecular diagnostic approach. Diagn Microbiol Infect Dis 42:159–167

Danon O, Duval-Arnould M, Osman Z, Boukobza B, Kazerouni F, Cadranel JF, Neuenschwander S, Nocton F (2000) Hepatic and splenic involvement in cat-scratch disease: imaging features. Abdom Imaging 25:182–183

De Luca M, Luigi B, Formisano C, Formato A, De Werra C, Cappuccio M, Loffredo A, Forestieri P

(2000) Solitary necrotic nodule of the liver misinterpreted as malignant lesion: considerations on two cases. J Surg Oncol 74:219–222
Delis SG, Kelgiorgi DA, Sofianidis AA, Triantopoulou CC, Papailiou IA, Dervenis CG (2009) Solitary necrotic nodule of the liver mimicking hepatocellular carcinoma: a case report. Cases J 2:85
Deniz K, Coban G (2010) Solitary necrotic nodule of the liver: always benign? J Gastrointest Surg 14:536–540
Deniz K, Tank A, Tekelioglu F, Özcan S (2011) Solitary necrotic nodule of the liver. J Gastrointestin Liver Dis 20:346
Desai S, Prabhu SR, Shrividya S (1995) Fibrosing necrotic nodule of the liver. Indian J Gastroenterol 14:23–24
Di Stasi M, Zangrandi A, Buscarini E (1993) Imaging of solitary necrotic nodule of the liver. Report of one case. JEMU 14:187–195
Fan ZM, Zeng QY, Huo JW, Bai L, Liu ZS, Luo LF, Yang JC, Zhou XH (1998) Macronodular multi-organ tuberculoma: CT and MR appearances. J Gastroenterol 33:285–288
Fitz JG, Petri M, Hellmann D (1987) Chronic active hepatitis presenting with rheumatoid nodules and arthritis. J Rheumatol 14:595–598
Geng L, Lin C, Huang B, Long XA, Dai BH, Cong WM, Yang JM (2012) Solitary necrotic nodule of the liver: MR findings in 33 pathologically proved lesions. Eur J Radiol 81:623–629
Glas L, Guyennon A, Chomel S, Coulon A, Chevallier M, Berthezène Y, Rode A (2006) What is your diagnosis ? Solitary necrotic nodule of the liver (in French). J Radiol 87:676–679
Grazi GL, Mazziotti A, Gruttadauria S, Jovine E, Principe A, Cavallari A (1998) Solitary necrotic nodules of the liver. Am Surg 64:764–767
Imura S, Miyake K, Ikemoto T, Morine Y, Fujii M, Sano N, Shimada M (2006) Rapid-growing solitary necrotic nodule of the liver. J Med Invest 53:325–329
Iwase K, Higaki J, Yoon HE, Mikata S, Miyazaki M, Torikai K, Shirai Y, Awai K, Imakita M, Kamiike W (2002) Solitary necrotic nodule of the liver. J Hepatobiliary Pancreat Surg 9:120–124
Kawamori Y, Matsui O, Kitagawa K, Kadoya M, Takashima T, Yamahana T (1992) Macronodular tuberculoma of the liver: CT and MR findings. AJR Am J Roentgenol 158:311–313
Kazmi KA, Rab SM (1989) Primary hepatic actinomycosis: a diagnostic problem. Am J Trop Med Hyg 40:310–311
Koea J, Smith D (2008) Solitary necrotic nodule revisited. ANZ J Surg 78:109–111
Koea J, Taylor G, Miller M, Rodgers M, McCall J (2003) Solitary necrotic nodule of the liver: a riddle that is difficult to answer. J Gastrointest Surg 7:627–630
Kondi-Pafiti AI, Grapsa DS, Kairi-Vasilatou ED, Voros DK, Smyrniotis VE (2006) "Solitary" necrotic nodule of the liver: an enigmatic entity mimicking malignancy. Int J Gastrointest Cancer 37:74–78
Levine C (1990) Primary macronodular hepatic tuberculosis: US and CT appearances. Gastrointest Radiol 15:307–309
Marongiu L, Capra F, Cautero N, Pinna AD (2004) Solitary necrotic nodule of the liver: diagnostic and therapeutic considerations regarding a case. Chir Ital 56:567–570
Mercusot B, Arrive L, Rotenberg L, Bouras T, de Sigalony JP, Hannoun L, Tubiana JM (1995) Imaging of hepatic tuberculoma. J Radiol 76:277–279
Miyamoto MI, Fang FC (1993) Pyogenic liver abscess involving Actinomyces: case report and review. Clin Infect Dis 16:303–309
Moskovic E (1990) Macronodular hepatic tuberculosis in a child: computed tomographic appearances. Br J Radiol 63:656–658
Murata Y, Yamada I, Sumiya Y, Shichijo Y, Suzuki Y (1996) Abdominal macronodular tuberculomas: MR findings. J Comput Assist Tomogr 20:643–646
Nakanuma Y (1995) Non-neoplastic nodular lesions in the liver. Pathol Int 45:703–714
Nazarian LN, Spencer JA, Mitchell DG (1994) Multiple actinomycotic liver abscesses: MRI appearances with etiology suggested by abdominal radiography. Case report. Clin Imaging 18:119–122
Ohta H, Fukuyama T, Sakamoto M, Komibuchi T, Shintaku M (1996) Liver tuberculoma detected by Ga-67 imaging. Clin Nucl Med 21:577
Oliva A, Duarte B, Jonasson O, Nadimpalli V (1990) The nodular form of local hepatic tuberculosis. A review. J Clin Gastroenterol 12:166–173
Ow C, Maldjian C, Shires GT, Markisz J, kazam E (1991) CT, US, and MR imaging of hepatic aspergilloma. J Comput Assist Tomogr 15:852–854
Pretet S, Paul G, Claret Y, Marin I, Bagot M, Dyan A (1979) Hepato-pulmonary Nocardia infections (report of one case) (in French). J Chir (Paris) 116:637–640
Roesler PJ, Wills JS (1986) Hepatic actinomycosis: CT feature. J Comput Assist Tomogr 10:335–337
Sartori S, Galeotti R, Calia N, Gualandi M, Nielsen I, Trevisani L, Ceccotti P, Abbasciano V (2002) Sonographically guided biopsy and sonographic monitoring in the diagnosis and follow-up of 2 cases of sarcoidosis with hepatic nodules and inconclusive thoracic findings. J Ultrasound Med 21:1035–1039
Shepherd NA (1990) Solitary necrotic nodule. J Clin Pathol 43:348–349
Shepherd NA, Lee G (1983) Solitary necrotic nodules of the liver simulating hepatic meatstases. J Clin Pathol 36:1181–1183
Shonaka T, Kurauchi N, Okawa Y, Misawa K, Sano H (2007) Case of solitary necrotic nodule of the liver difficult to distinguish from malignant hepatoma (in Japanese). Nippon Shokakibyo Gakkai Zasshi 104:47–51
Smits JG, Kooijman CD (1986) Rheumatoid nodules in liver. Histopathology 10:1211–1213
Sundaresan M, Lyons B, Akosa AB (1991) "Solitary" necrotic nodules of the liver: an aetiology reaffirmed. Gut 32:1378–1380

Tan TC, Cheung AY, Wan WY, Chen TC (1997) Tuberculoma of the liver presenting as a hyperechoic mass on ultrasound. Br J Radiol 70:1293–1295

Thanos L, Zormpala A, Brountzos E, Nikita A, Kelekis D (2002) Nodular hepatic and splenic sarcoidosis in a patient with normal chest radiograph. Eur J Radiol 41:10–11

Trachana M, Roilides E, Gompakis N, Kanellopoulou K, Mpantouraki M, Kanakoudi-Tsakalidou F (2001) Case report. Hepatic abscesses due to Aspergillus terreus in an immunodeficient child. Mycoses 44:415–418

Tsui WM, Yuen RW, Chow LT, Tse CC (1992) Solitary necrotic nodule of the liver: parasitic origin? J Clin Pathol 45:975–978

Vargas C, Gonzales C, Pagani W, Torres E, Fas N (1992) Hepatic actinomycosis presenting as liver mass: case report and review of the literature. P R Health Sci J 11:19–21

Wang Y, Yu X, Tang J, Li H, Liu L, Gao Y (2007) Solitary necrotic nodule of the liver: contrast-enhanced sonography. J Clin Ultrasound 35:177–181

Yeoh KG, Yap I, Wong ST, Wee A, Guan R, Kang JY (1997) Tropical liver abscess. Postgrad Med J 73:89–92

Yoon KH, Yun KJ, Lee JM, Kim CG (2000) Solitary necrotic nodules of the liver mimicking hepatic metastasis: report of two cases. Korean J Radiol 1:165–168

Zhou YM, Li B, Xu F, Wang B, Li DQ, Liu P, Yang YM (2008) Clinical features of solitary necrotic nodule of the liver. Hepatobiliary Pancreat Dis Int 7:485–489

Zuo Z, Zhang JF, Tang FX, Feng L (2006) Solitary necrotic nodule of the liver (in Chinese). Zhonghua Bing Li Xue Za Zhi 35:317

Hepatic and Perihepatic Involvement in Pneumokonioses and Other Mineral-Induced Diseases

123

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_123

Abstract

Various types of mineral dust can induce tumor-like lesions in the liver. A nowadays rare form is hepatic silicosis or anthracosilicosis, a condition usually combined with splenic silicosis. Silicium dioxide crystals are probably transported to the liver by macrophages and induce, within parenchyma and portal tracts, a vigorous inflammatory reaction similar to that found in the bronchopulmonary tract. Asbestosis is rarely associated with a circumscribed fibroinflammatory reaction in the liver. Similar changes may be observed in talcosis. Thorotrastosis, caused by deposition of highly radioactive thorium dioxide particles in tissues following radiographic examinations, was an important cause of morbidity in former times but is now no longer observed. Thorotrastosis caused a vigorous and sometimes tumor-like fibrotic reaction in the hepatobiliary tract and is a well-known example of radiation-induced carcinogenesis.

Hepatic Anthracosis, Anthracotic Liver Nodules, and Cirrhosis Hepatis Anthracotica

Hepatic anthracosis has not well been studied, although coal pigment can sometimes been found in hepatic macrophages, usually in conjunction with marked pulmonary anthracosis (Weigert 1883; Welch 1891; Chiari 1907; Orth 1917; Hanser 1930; Heggie 1946; Anderson 1971; Beckert 1972; Pounder 1983; Cabarcos and Gomez Dorronsoro 1984; Sampedro Nuño et al. 1985).

The earliest recorded instance of so-called blood anthracosis is that of Soyka in 1878 (cited by Weigert 1883), in which carbon pigment was found in the spleen, liver, and kidneys of a man of 70 years, suffering from anthracosis of the lungs. Soyka formed the hypothesis that the coal particles had passed through the lymph nodes and thoracic duct into the blood stream. Anthracotic pigment may be found in hepatic macrophages in patients with silicosis, a pneumokoniosis which is known to favor spread of coal particles owing to a markedly altered lymphatic drainage. Among 100 liver biopsies from patients with pulmonary silikotuberculosis, 35 biopsies showed coal dust particles, in 24 of them with pigment deposits in portal tract macrophages. Coal particles were also found in intrasinusoidal macrophages (Kupffer cells; sometimes with formation of black nodules in lobular zone 3) and in endothelial cells of central/terminal veins (Beckert 1972). Some of the macrophages contain hemosiderin together with coal particles. Apart from Welch's patient (1891; discussed below), only one report described the gross features of hepatic anthracosis. The autopsy of an 81-year-old male patient with severe anthracosilicosis showed the liver to have a general grayish color due to marked pigment accumulation. On section the lobular pattern was rendered unusually distinct by the black deposits of carbon in the portal tracts, while the intervening parenchyma was yellowish gray (Heggie 1946). It is thought that hepatic anthracosis results from the systemic dissemination of carbon pigment following rupture of a thoracic anthracotic lymph node into a pulmonary vessel, the transmigration of coal-laden macrophages through pulmonary venous wall, or the transport of pigmented macrophages via the lymph stream into the blood circulation (the Soyka hypothesis). Arnold has pointed out the frequent association of emphysema of the lungs with the presence of coal pigment in the spleen, liver, and elsewhere. Weigert has shown that adhesions and destructive inflammations may open the way for the passage of coal pigments from bronchial lymph nodes into the circulation and from there to remote organs and tissues (Weigert 1883). Cirrhosis hepatic anthracotica is a term coined in 1891, based on the observation of a peculiar form of liver cirrhosis associated with the massive deposition of coal pigment in the liver (Welch 1891). The patient was a 70-year-old German who had lived for many years as a farmer in the neighborhood of Mercersburg, Pa, and had formerly been a weaver in Germany. After having been in good health, he began to suffer from vomiting, loss of appetite, and severe abdominal pain. He developed ascites, became emaciated,

and expired. An autopsy was performed. The peritoneal surface, the omentum, the mesentery, and superficial parts of the liver were massively involved by nodular growths of a carcinoma of unknown origin (the necropsy was incomplete). The liver cut surface showed numerous black specks and small streaks. These little black dots and lines were present everywhere throughout the liver scattered irregularly at intervals not more than 0.5–1 mm apart. The black structure was not present in the cancer nodules and was not more abundant in the neighborhood of cancer than elsewhere. Around many of the black specks, the tissue had a grayish color. Histologically, the black structures were accumulations of black granular pigment identical with the coal pigment found in the lungs. The pigment resisted treatment of tissue with concentrated sulphuric acid, nitric acid, and hypochloric acid. The black granules occurred both free and enclosed in cells. Dense accumulations of black pigment separated unchanged hepatocytes, and the pigment was in part accumulated within Kupffer cells and other macrophages, the latter situated within fibrous bands, but was never found in hepatocytes. Hepatocyte nodules as in cirrhotic remodeling were in evidence. The fibrous areas differed in distribution and in appearance from the fibrous tissue in ordinary liver cirrhosis, in that the bands never completely surrounded a lobule, but were also present within lobules and around the central veins, producing a peculiar type of micronodular ("monocellular") cirrhosis. A ductular reaction was almost lacking. Overall, the picture resembled that of indurative anthracosis of the lungs (Naeye 1971). It is assumed that in such situations, anthracotic pigment may harbor another toxic substance transported together with the coal into target organs.

Hepatic Silicosis and Anthracosilicosis

Introduction

Involvement of the liver in silicosis (chalicosis) is not uncommon and is usually associated with splenic involvement (hepatosplenic silicosis). In the two largest published series, the prevalence of hepatic involvement in pulmonary silicosis was 6/60 (Ambrosi 1965) and 13/93 (Cisno et al. 1971).

Selected References Uchiyama 1928; Giese 1931; Lynch 1942; Cioni 1943; Polachek and Pijanowski 1960; Argento et al. 1962; Ambrosi 1965; Cisno et al. 1971; Ortuno Pacheco and Sampedro Nuno 1974, 1975; Langlois et al. 1977; Pimental and Menezes 1978; Gong and Tashkin 1979; Carmichael et al. 1980; Slavin et al. 1985; Liu et al. 1991; Oswald et al. 1995.

Liver Lesions: Silicotic Hepatic Nodules

Macroscopically, hepatic silicosis manifests as nodular and firm lesions consisting of sclerotic tissue, sometimes with black pigmentation. There is no evidence that these lesions may undergo so-called callosity liquefaction (called phthisis atra in pulmonary silicosis). In the lung, callosity liquefaction is caused by loss of silicotic and necrotic tissue via the bronchial tree (Breining 2003), and a similar mechanism may be expected to occur in case the invasive and destructive hepatic silicotic lesions obtain access to the biliary draining system. Histologically, the lesions correspond to typical silicosis nodules at various stages of development. The spectrum ranges from granulomas to nodules of almost acellular hyaline collagenous nodules with central densely calcified cores that contain no or little quartz crystals (Uchiyama 1928; Arai 1931; Giese 1931; Ritterhoff 1941). In a patient with fatal silicosis and hepatic involvement, liver biopsy showed numerous noncaseating granulomas scattered throughout the hepatic lobules. These granulomas were associated with various amounts of fibrous tissue. Smaller nodules were composed of epithelioid macrophages and lymphocytes, while larger nodules were hyalinized, with a fibrous core surrounded by lymphocytes and macrophages, without giant cells. Polarizing microscopy revealed rare needle-shaped birefringent particles within the hyalinized nodules (Carmichael et al. 1980).

In an autopsy study of 21 patients with hepatic silicosis, liver granulomas with various amounts of fibrosis were present in 20 cases, and portal tract fibrosis was seen in ten. Intralobular silicotic nodules tended to be more frequent close to the terminal vein (Ortuno Pacheco and Sampedro Nuno 1975). Intermediate lesions in the liver usually are surrounded with an outer rim of fibroblasts and quartz-containing macrophages (Langlois et al. 1977). In a detailed study of extrapulmonary manifestations of silicosis, silicotic nodules in the liver were coniotic and fibroconiotic lesions recognized in portal tracts and within parenchyma. Sclerohyaline nodules were, in contrast, only found in portal tracts. The fibrosed portal tracts were sometimes associated with incomplete and complete, portal-to-portal septa. Silicotic nodules enlarged as they progressed, ranging from 0.1 mm (coniotic nodules) to 1.7 mm (silicosclerohyalinized nodules). Nodules containing silica and other dusts (mixed dust coniotic nodules) were also encountered (Slavin et al. 1985). Macrophages with coal particles are sometimes seen. Silicotic nodules have experimentally been produced in rodents by intraperitoneal injection of silica (Mosinger et al. 1957), and a hepatic granulomatous reaction to silica has been observed in an experimental rat model (Kanta et al. 1986). In patients with hepatic silicosis, lymph nodes located to the hepatic hilar/perihilar area may be markedly enlarged, being extensively replaced by conglomerated silicotic nodules (Slavin et al. 1985). Generally, reports of autopsies in patients with hepatic silicosis also mention silicotic lesions in portal and abdominal lymph nodes (Giese 1931; Polachek and Pijanowski 1960; Langlois et al. 1977). The demonstration of typical eggshell calcifications of silicosis in perihilar/portal lymph nodes by abdominal radiographs in patients with pulmonary silicosis (Polachek and Pijanowski 1960; Langlois et al. 1977; Gong and Tashkin 1979) might indicate concomitant silicotic lesions in the liver (Slavin et al. 1985). Anthracosilicosis of the liver may also present in the form of mainly subcapsular, partly calcified nodular lesions, similar to what can develop in the spleen (Vanhoenacker et al. 2001). Such macroscopically black nodules can also develop on the hepatic visceral peritoneum (Miranda et al. 1996). In a study of 21 patients, three patients showed numerous, lead gray to black nodules measuring 0.1–0.3 mm on the hepatic capsular surface, and one patient exhibited larger capsular nodules, up to 8 mm diameter, with a gray center and a black peripheral rim. At some places, these nodules coalesced to form conglomerate, plaque-like lesions (Ortuno Pacheco and Sampedro Nuno 1975). Experimentally, hepatic silicosis associated with cirrhosis, liver cell adenoma, and carcinoma develops in nude mice given silicon dioxide (quartz) by the subcutaneous and intraperitoneal routes (Williams and Knapton 1996).

Pathogenically, it is thought that quartz crystals enter the liver via circulating monocytes/macrophages that change into Kupffer cells or deliver their phagocytosed crystals to already resident Kupffer cells. The uptake of silica particles by macrophages is receptor mediated (Kolb-Bachofen 1992). Specifically, the binding of crystalline silica particles is mediated by the macrophage scavenger receptors (SR; review: Murphy et al. 2005). SR are cell surface receptors that bind a wide variety of ligands, including bacteria, nonopsonized particles, modified lipoproteins, and inorganic substances. There are eight known classes of SR designated A through H, which are dissimilar in structure, but related in ligands recognized. Known class A SR comprise three splice variants SR-AI (CD204), SR-AII, and SR-AIII, MARCO (macrophage receptor with collagenous structure), SRCL, and SCARA5. The SR most associated with macrophage silica binding are SR-AI, SR-AII, and MARCO (Hamilton et al. 2006, 2008). MARCO is a critical binding receptor for nonopsonized inhaled environmental particles and bacteria (Palecanda et al. 1999; Arredouani et al. 2004), and MARCO-null mice are unable to clear silica particles from lung alveoles (Thakur et al. 2009). Macrophages having engulfed silica become activated and secrete cytokines, including fibrokines (TNF-alpha, IL-1, and TGF-beta; Schmidt et al. 1984; Piguet et al. 1990; Williams and Knapton 1996; Hamilton et al. 2008), thus

mediating the fibrogenic reaction in silicosis. Exposure to silica particles induces activation of NF kappaB and AP-1 (activator protein-1) and the associated signaling pathways in macrophages. Activation of AP-1 causes a decrease in cyclin-dependent kinase 4/CDK4, mediated by the ERK and JNK pathway (Shen et al. 2008). In addition, silica is involved in the cellular production of reactive oxygen/nitrogen species (review: Castranova 2004).

Asbestosis

Introduction

In asbestosis, asbestos fibers are known to be transported to numerous organs and tissues in addition to the bronchopulmonary compartment, including the liver (Pollice et al. 1997). Fibers can be dragged from the lung interstitium by pulmonary lymph flow (primary translocation), wherefrom they can reach the blood stream and subsequently distribute to the whole body (secondary translocation). Fiber concentration in organs correlates with specific conditions of interstitial fluid dynamics, in line with the notion that in all organs microvascular filtration occurs from capillaries to the extravascular spaces. Concentration of fibers is high in the kidney (high perfusion pressure and flow) and in the liver (high microvascular permeability). Ultrafine fibers (length <5 μm, diameter <0.25 μm) can travel larger distances due to low steric hindrance. For example, in mesotheliomas, 90 % of the fibers are ultrafine (review: Miserocchi et al. 2008). In contrast, it has long been uncertain whether asbestos *bodies* found in extrapulmonary sites have been transported as mature structures from the lung or formed de novo at the extrapulmonary site. One study has, however, shown that asbestos bodies can in fact be formed in extrapulmonary sites, but that the coating efficiency (coating of asbestos fibers by a cellular iron- and protein-rich matrix) in the lung is much greater than that within the liver or spleen (Williams et al. 2001).

Asbestosis of the Liver

In most cases, deposition of fibers in the liver will not cause visible hepatic lesions, but a fibroinflammatory reaction may rarely ensue to even produce nodular lesions. Asbestosis can seldom cause calcified fibro-hyaline plaques on the liver (Fondimare et al. 1974; Andrion et al. 1983) that may be confounded with other circumscribed sclerotic lesions in the liver's periphery.

An autopsy study has revealed that there is a correlation between peritoneal and liver plaques and asbestos exposure (Mollo et al. 1993). Pulmonary asbestos can also be associated with a generalized fibrotic tissue reaction, and this fibrosis, including liver fibrosis, is accompanied by the accumulation of asbestos bodies in the fibrotic tissue (Kobayashi et al. 1983). Asbestosis can involve locoregional lymph nodes of the liver, as these nodes are connected with intrathoracic nodes. Silicosis of retropancreatic lymph nodes has been found to block the common bile duct and to cause obstructive jaundice (Chassagnon and Silie 1966). Asbestos is known to induce mesotheliomas and other cancers. In an autopsy study of 525 cases of asbestosis in Japan, there were 174 lung cancers (33.1 %), 73 malignant mesotheliomas (13.9 %), 29 stomach cancers (5.5 %), but also 14 liver cancers (2.7 %) (Murai and Kitagawa 2000). Primary malignant biphasic mesothelioma of the liver has been observed in a patient with asbestosis (Sasaki et al. 2009). Asbestos bodies have been found in a cholangiocarcinoma of a patient with asbestosis (Szendröi et al. 1983).

Talcosis

Introduction

The mineral talc is a soft, hydrous magnesium silicate known to have the physical characteristic of birefringence. Generally, talc in the liver is highly suggestive of intravenous drug abuse (Min et al. 1974; Molos et al. 1987; Sherman

et al. 1995) but may also occur in the absence of an abuse history (Klatskin 1977). When drugs containing talc (e.g., "Blue Velvet") are injected intravenously, they pass to the pulmonary vascular bed that retains most of the crystalline particles, but part of the crystals escape this filter via pulmonary arteriovenous shunts caused by lung disease, or via cardiac shunts, to be spread to parenchymatous organs.

Hepatic Talcosis

In an autopsy study of 273 drug addicts, 38 % of the patients had talc in their liver. Those with hepatic talc were older and had a longer history of i.v. drug abuse, and the presence of birefringent particles in the liver was always associated with a nonspecific portal tract lymphocytic infiltration (Kringsholm and Christoffersen 1982). Among 70 patients with chronic hepatitis and a history of active or past i.v. drug abuse, birefringent crystalline particles consistent with talc were found in liver tissue in 63 % (Allaire et al. 1989). Histologically, talc microcrystals are situated predominantly in activated portal tract macrophages. The crystals observed in the liver are birefringent and unevenly green, needle or rod shaped, and arranged singly or in clusters, with a mean length of 3 mm (Liu et al. 1991). Electron microscopy of involved macrophages reveals the characteristic "flake-pastry" appearance of this ingested mineral (Allaire et al. 1989). Ultrastructurally, the crystals are 5–12 mm, elongated with sharp edges, electron-dense, laminated, and located in phagosomes of macrophages (Buschmann and Mir 1979). Liver biopsies show birefringent crystals also in Kupffer cells within lobules (Molos et al. 1987). Deposition of talc in the liver can induce a granulomatous reaction, with formation of talc granulomas (Groth et al. 1972; Min et al. 1974; Szanto 1975; Mariani-Costantini et al. 1982; Kringsholm and Christoffersen 1982; Lewis et al. 1985; Molos et al. 1987; Racela et al. 1988; da Cunha et al. 1999).

Thorotrastosis

Introduction

Thorotrast is or was the trade name of a 25 % colloidal aqueous solution of thorium (Th232) dioxide. Thorium-containing contrast media, first called Umbrathor and Thordiol, were introduced 1927 in Japan and 1928 in Germany (Frik and Blühbaum 1928; Kalbrenner 1928; review: Oka 1930). Then, in 1930, Thorotrast, developed by the German firm Heyden, was preferentially used. Thorotrast was an excellent contrast agent that could be administered intravenously and intraarterially and was first thought to have no side effects. Th(232) only exists as a radioactive substance (predominantly an alpha particle emitter, 90 %; beta and gamma, 10 %) with a physical half-life of $1.4 \times 10(10)$ years. The biologic half-life is about 400 years. It is estimated that up to 100,000 patients worldwide were exposed to Thorotrast from 1930 to 1964. The carcinogenic action of colloidal thorium dioxide was recognized in 1934 in rat experiments (Roussy et al. 1934, 1936), and the risk of employing this contrast medium was already recognized in 1933 by the FDA, and in the years to come, a broad array of Th232-induced late effects were identified (Boyd et al. 1968; Horta et al. 1972).

The first case of angiosarcoma of the liver in a Thorotrast patient was published in 1947, and the first report concerning Thorotrast-induced late effects in Japan dealt with a case of liver cirrhosis in observed in 1945 (Shimauchi et al. 1949). The use of intravascularly administered Thorotrast was discontinued when it was recognized that its radioactivity caused long-term deleterious effects, most notably hepatic and hematologic malignancies and hepatic fibrosis (da Silva Horta 1967; Abbatt 1979; Bo et al. 2001; Lipshutz et al. 2002). A German study of 2326 originally exposed subjects revealed that median life expectancy was shortened by 14 years (German Thorotrast Study; Becker et al. 2008). But, for instance, in Japan, the use of Thorotrast continued until about 1954 (Mori et al. 1999a,b). The history

of Thorotrast use and toxicity has been reviewed (Abbatt 1979).

Thorotrast-Induced Liver Malignancy

The Thorotrast-induced changes cause a rise in overall mortality, essentially due to malignant neoplasms and specifically those of the liver. Thorium dioxide-induced hepatic carcinogenesis has also been studied in experimental animal models (Grampa 1967; Okamoto 1974; Wesch et al. 1985; Taylor et al. 1993).

Selected References Bauer 1943; Matthes 1956; Baserga et al. 1960; Dahlgren 1961; Nettleship and Fink 1961; Suchow et al. 1961; Batzenschlager et al. 1963; Möbius and Lembke 1963; Leitner 1965; Mori et al. 1967; Tsukamoto 1968; Visfeldt and Poulsen 1972; Faber 1978; Farid 1982; Yamada et al. 1983; Kato and Kido 1987; Andersson et al. 1994; Lee et al. 1996; Mori et al. 1999a; dos Santos Silva et al. 1999; Travis et al. 2001; Lipshutz et al. 2002; Nyberg et al. 2002; Sharp 2002; Becker et al. 2008.

In the liver, Thorotrast has been found to induce three major types of neoplasms, namely, angiosarcoma, cholangiocarcinoma, and hepatocellular carcinoma (reviews: Ito et al. 1988; Sitarik et al. 1999; Lipshutz et al. 2002). There is a latency period of 16 to >45 years for the development of hepatic malignancy after Th232 administration. In the German Thorotrast Study, 899 patients and 662 controls had follow-up every 2 years, beginning in 1969. Results in 1991 showed a high rate of liver cancer (410 in the Thorotrast group, 2 in the control group) observed after the 15th year of Thorotrast exposure. The frequency of tumor development was correlated with the cumulative dose, not the age at injection (Van Kaick et al. 1991). In a Swedish study of patients exposed to Thorotrast, the relative cancer risk at any site was 3.0, and the relative risk for primary liver and gallbladder cancer was 39.2 (Nyberg et al. 2002). In the Danish National Study of 1003 patients, 584 were alive 15 years later, and 40 remained alive at the end of the follow-up period. Among these 584 patients, 127 liver cancers were detected (45 HCCs, 41 cholangiocarcinomas, and 33 hepatic angiosarcomas). The median time from injection to diagnosis of liver cancer was 35 years, with a range of 18–48 years (Andersson et al. 1994). In a Japanese study, the risk of death from any cause was threefold greater, and the risk of liver cancer was 47-fold greater than in unexposed individuals (Kato and Kido 1987; Mori et al. 1999a). In regard to liver malignancies, the updated (1998) Japanese Thorotrast study revealed, in the autopsy analysis, that Th (232)-induced liver malignancies showed remarkable differences in the proportions of histologic types of tumors from those of non-Thorotrast liver malignancies since 1975, and the results showed 523 liver malignancies per 10(4) person Gy for Japanese male Thorotrast carriers (wasted dose 10 years; Mori et al. 1999b). From the studies of Travis et al. (1992) and Andersson et al. (1994), it was estimated that the excess lifetime risk of developing liver cancer is 260–712 patients/10,000 persons/Gy. Among 157 Japanese autopsy cases of thorotrastosis, there were 102 cases of thorium dioxide-associated hepatic malignancies: 43.1 % cholangiocarcinomas, 38.3 % angiosarcomas, 15.7 % HCCs, and 2.9 % double cancers. The average age for thorium-associated cholangiocarcinoma patients was significantly lower than that for cholangiocarcinomas in the non-thorium series. Peripheral intrahepatic cholangiocarcinomas were much more frequent than hilar carcinomas in comparison with non-Thorotrast cases (Ito 1988).

The development of Thorotrast-induced malignant tumors requires a long incubation period. Exceptions are known, e.g., one of the first reported Thorotrast-related hepatic angiosarcomas was detected 3 years and 2 months after Thorotrast injection (Da Silva Horta 1953). Reasons for the phenomenon of delayed hepatic cancer seem to include an uneven distribution of radionuclide, the limited range of radiation, and the movement of tumor precursor cells. Target

cells susceptible to malignant transformation may undergo one event and may then migrate outside of the range of alpha particles, thereby avoiding immediate induction of successive additional events that would lead to cell death or neoplastic change (Yamamoto et al. 2009). In the liver, Th (232) induces foci of altered hepatocytes that may represent early lesions in a carcinogenic pathway (Kopp-Schneider et al. 2006).

Angiosarcoma of the Liver

Hepatic angiosarcoma is one of the most important malignancies caused by Thorotrast and is, in some way, a "marker tumor" for thorium dioxide-induced late effects. 7–10 % of hepatic angiosarcomas were Thorotrast-related in the time period when Th(232)-exposed individuals were alive. Epidemiologic data showed that previously thorium 232 dioxide was the most iatrogenic cause of hepatic angiosarcoma (MacMahon et al. 1947; Falk et al. 1979; van Kampen et al. 2007). Thorotrast-related hepatic angiosarcoma was found in conjunction with combined HCC and cholangiocarcinoma in a single patient (Masamichi et al. 1982).

Selected References MacMahon et al. 1947; Da Silva Horta 1953; Lüdin 1953; Tesluk and Nordin 1955; Caroli et al. 1956; Grampa and Tomamasini-Degna 1958; Rosenbaum 1959; Vallenga 1962; Rakov et al. 1963; Heger and Bayindir 1970; Howard et al. 1971; Futh and Pietzke 1974; Quinlan and Scopa 1976; Jennings and Priestley 1978; Popper et al. 1978; Underwood and Huck 1978; Telles et al. 1979; Baxter et al. 1980; Hiraoka et al. 1981; Benjamin and Albukerk 1982; Silverman et al. 1983; Mohr et al. 1984; Kojiro et al. 1985; Abe and Wakasa 1987; Schmid and Beham 1987; Hardt and Geisthövel 1988; Ito et al. 1988; Azodo et al. 1993; Arteche et al. 2007.

Hepatocellular Carcinoma

Hepatocellular carcinoma related to hepatic Thorotrast deposition is a well-known complication and was in some studies observed more often than cholangiocarcinoma and angiosarcoma (Morgan et al. 1958; MacKay and Ross 1964; Person and Isaac 1964; Akagi et al. 1966; Kuisk et al. 1967; Forbes et al. 1968; Smoron and Battifora 1972; Kiely et al. 1973; Espasa et al. 1981; Lageron et al. 1984; Lally 1993; Andersson et al. 1994). There are no data as to whether the types and grades of Thorotrast-associated HCCs are the same as or different from those of nonirradiated individuals.

Other Liver Tumors

In addition to these three major malignancies induced by Thorotrast, several other hepatic malignant neoplasms occur in association with hepatic Thorotrast deposits. Cholangiocarcinoma has been reported several times (Heitmann 1954; Roberts and Carlson 1956; Stemmermann 1960; Batzenschlager et al. 1961; Ellis 1964; Yuda et al. 1969; Rota et al. 1971; Johnson and Babb 1975; Vanhaecke et al. 1979; Rubel and Ishak 1982; Sakai et al. 1984; Ito 1988; Masbou et al. 1995; Sahani et al. 2003; Zhu et al. 2004). Less common hepatobiliary cancers apparently induced by Thorotrast comprise gallbladder carcinoma (Hashizume et al. 1980), primary squamous cell carcinoma of the liver (Larson 1963), and mucoepidermoid carcinoma of the liver (Lambrianides et al. 1986).

Nonneoplastic Liver Changes

Apart from overt malignancies, Thorotrast induces focal and sometimes nodular reactive lesions in the liver ("Thorotrast-related hepatosis"). In Thorotrast patients, abdominal radiography shows typical depositions of thorium dioxide in liver, spleen, and locoregional lymph nodes. The hepatic distribution patterns markedly depend on the amount of injected Thorotrast. Type 1 has agglomerates of thorium dioxide in periportal lymph nodes; type 2 shows, in addition, dot-like deposits in the spleen; type 3 additionally reveals shell-like deposits beneath the liver capsule; types 4–6 exhibit a progressive deposition in the liver, ranging from a fine network to coarse

and conglomerate lesions (Van Kaick et al. 1999). These hepatic changes are associated with a shrinkage of the organ, with a mean atrophy of 260 g in one study (Bast et al. 1995). In hilar/perihilar lymph nodes, Thorotrast-induced fibrotic lesions may cause sclerosed conglomerate lesions (Poti et al. 1980) that mimick perihilar malignancy, in particular Klatskin tumor.

Thorotrast Deposition and Turnover in the Liver

Histologically, deposition of Thorotrast in the liver presents in the from of dark pigmented granules that are situated either within macrophages or in the extracellular space (Figs. 1 and 2). The strong ionizing radiation emitted by these particles is clearly demonstrable by use of autoradiography preparations (Fig. 3). In cases with induced malignancy, Thorotrast particles may be present adjacent to tumor tissue (Fig. 4).

The liver is particularly involved in thorotrastosis owing to its position as an important

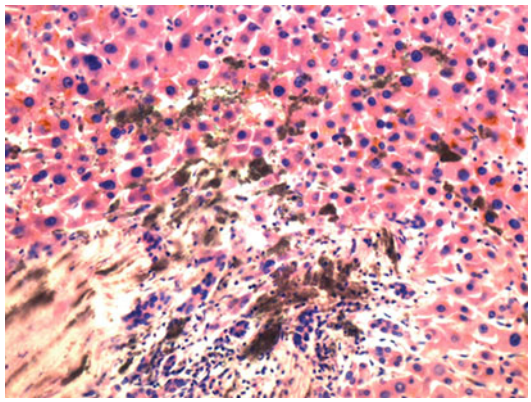

Fig. 1 Thorotrastosis. Accumulation of dark pigment in liver tissue, in part within phagocytes (hematoxylin and eosin stain)

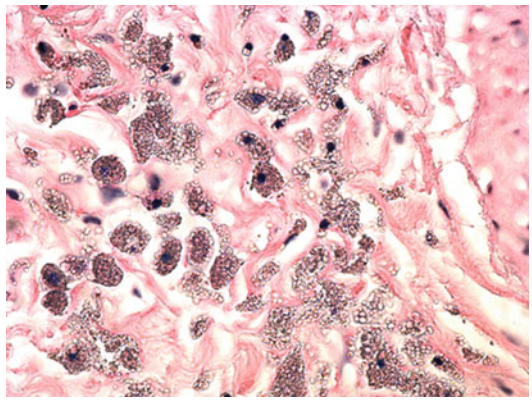

Fig. 2 Thorotrastosis of the liver. In this area, thorium dioxide particles are stored within macrophages (hematoxylin and eosin stain)

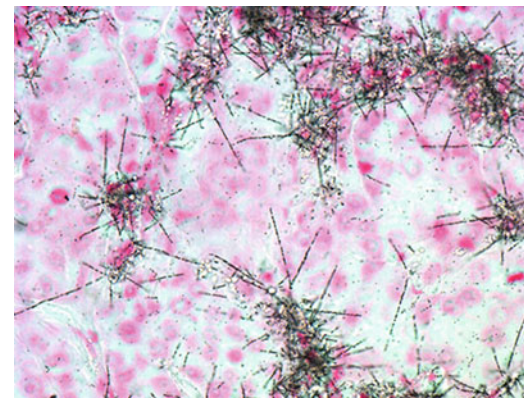

Fig. 3 Thorotrastosis. In this autoradiograph, silver grain tracts of high-LET radiation emerge from thorium dioxide particles. Note that the tract length does not exceed 5–8 cell diameters (photoemulsion autoradiography)

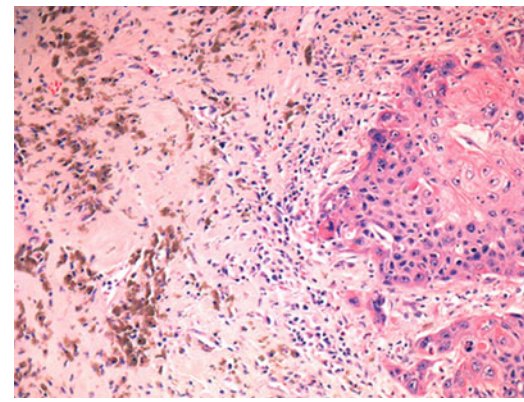

Fig. 4 Thorotrastosis of the liver. Long-lasting ionizing radiation from Thorotrast depositions is associated with biliary squamous cell carcinoma in this case (hematoxylin and eosin stain)

target of Th(232) (review: Tavares et al. 1979). Thorium dioxide depositions in the liver have first been reported in 1944 (Lüdin and Scheidegger 1944). In 1946, von Meyenburg reported on liver cirrhosis diagnosed 5 years following Thorotrast angiography (von Meyenburg 1946). It is estimated that the annual dose to the liver from a typical 25 ml of Thorotrast injection is 0.0025 Gy (Travis et al. 1992). This is mainly due to the liver's high content in macrophages (Kupffer cells) capable of phagocytosing Thorotrast particles (Tessmer and Chang 1967; Wegener et al. 1976; Kaul et al. 1979; Irie and Mori 1987), where Thorotrast particles can also be detected by autoradiography (Yasumizu et al. 1999) and by X-ray microanalysis (Terzaksi et al. 1974; Odegaard et al. 1978). In an assessment of the whole-body distribution of thorium and its daughters in a patient injected with Thorotrast 36 years prior to her death, approximately 45 % of all the activity was retained in the liver, and 3.5 % in a thorotrastoma (McInroy et al. 1992). In a later study, organ partition of Th(232) revealed a revised estimate of the relative partition of (232) Th in the liver, spleen, bone marrow, and other tissues of 53:14:25:8, respectively (Ishikawa et al. 1999). That Thorotrast phagocytosed by macrophages can locate from extrahepatic compartments to the liver has also been demonstrated in a patient with a liver allograft who had received intraarticular Thorotrast 36 years prior to transplantation. A liver graft biopsy performed 10 years posttransplant showed typical Thorotrast particles in macrophages in portal tracts and around central veins (Krasinskas et al. 2004).

CT findings of thorium dioxide deposition are pathognomonic. High-density deposits are seen in the liver, spleen, and lymph nodes, often associated with fibrosis-induced atrophy of the tissues involved. CT and MRI of the liver provide, therefore, an excellent method of early detection of thorium-related tumors (Brecht et al. 1980; Dunky and Klumair 1980; Silverman et al. 1983; Rao et al. 1986; Findley and Childress 1987). Also scintigraphy reveals characteristic findings of liver thorotrastosis (Oliveira et al. 1979).

Fibrotic Changes Induced by Thorotrast and "Thorotrastomas"

The morphology and the pathogenesis of these reactive alterations have been studied in detail (Dahlgren 1967; Visfeldt and Poulsen 1972; Helpap and Tschubel 1980). In the liver, Thorotrast particles concentrate, via phagocytosis, in Kupffer cells/hepatic macrophages, first within the sinusoids, where the particle-containing macrophages can form plug-like structures (Irie et al. 1986). A focal or diffuse proliferation of hepatic macrophages seems to be an typical phenomenon and has been described in early reports of Thorotrast liver damage (Lüdin and Scheidegger 1944; Schmidt et al. 1950; Obiditsch and Obiditsch-Mayer 1954; Hackenthal 1956; Selmair and John 1970). This phenomenon may cause sinusoidal obstruction and eventually nodular regenerative hyperplasia (Beer et al. 1998). A first report regarded granuloma-like lesions caused by Thorotrast in the liver as a foreign body-type reaction ("foyers granulomateux"; Lanari et al. 1937). The production of granuloma-like liver lesions caused by Thorotrast irradiation and containing epithelioid macrophages plus thorium dioxide granules was then reported in 1950 (Rotter 1950). The macrophages then congregate in the parenchyma and later in the portal tracts, forming aggregates of Thorotrast-laden cells (Kaul et al. 1979; Irie et al. 1986). Some of these aggregates have the features of so-called Thorotrast granuloma, a feature already published in 1950 (Rotter 1950; Polacarz et al. 1992; Srinavasan and Dean 1997). Thorotrast granulomas have also been found in locoregional lymph nodes, caused by translocation of Thorotrast particles by migrating and transported phagocytes (Danese and Mollura 1974; Wegener and Wesch 1979). Conglomerates of such confluent lesions may cause a mass effect, a lesion pattern called "thorotrastoma." The stable deposition of macrophages with Thorotrast particles will lead to high-LET irradiation of the tissue compartment for long time periods. Alpha particles have a range of only up to 100 mm, resulting in local doses as much as 100 Gy/year at points 20 mm from a deposit of Thorotrast 5 mm in

diameter (Kaul et al. 1979; Dagle et al. 1992). The radiation tracks can histologically be visualized by use of slide autoradiography and imaging plate autoradiography (Hassler et al. 1964; da Silva Horta and Nunes 1973; Polacarz et al. 1992; Goto et al. 2002). Pathogenetically, and owing to the laden macrophages' preferential localization around blood vessels and bile ducts in the liver, the highest concentration of thorium dioxide is found in paravascular deposits (van Kaick et al. 1999). The mean dose rate in these areas was calculated to be 5 Gy/year (van Kaick et al. 1999). This irradiation will induce a fibrosis reaction which, together with the macrophage accumulation, may result in macroscopic nodular lesions termed thorotrastoma (Duriez et al. 1973). Larger lesions of this type may form "fibroadenomatoid" growths (Krücke 1950). In addition to tumor-like lesions, node-shaped histiocytic proliferations with characteristic eosinophilic substance around Thorotrast deposits have also been described (Levy 1960). On the other hand, septal fibrosis and cirrhosis of the liver may ensue (Aizawa et al. 1960; Momose et al. 1966; Ueda et al. 1966; Takagi and Hasebe 1972; Vanhaecke et al. 1979; Mori et al. 1983; Morant and Rüttner 1987; Marti Vicente et al. 1993; Sharp 2002), with an often coarsely nodular pattern (Krasinskas et al. 2004). In regard to cirrhosis, a 20-fold increase in risk has been calculated (Kato and Kido 1987). The Thorotrast-induced fibrosis can induce biliary obstruction and cholangitis (Malamud and Berra 1964; da Silva Horta 1967) which may, in its turn, cause secondary hepatic changes.

Thorotrast-Induced Vascular Lesions

Fibrosclerotic reactions caused by Thorotrast induce vascular obstructive lesions, including veno-occlusive disease (Dejgaard et al. 1984) and hepatoportal sclerosis. Nodular regenerative hyperplasia (Dachman et al. 1987) and focal nodular hyperplasia (FNH)-like lesions of the liver associated with thorotrastosis (Sano et al. 1985) may be caused by such vascular anomalies. Pronounced changes can be found in sinusoidal endothelial cells in hepatic thorotrastosis (Helpap and Tschubel 1980), and this injury to sinusoidal endothelia is thought to cause peliosis that has been observed after Thorotrast exposure (Okuda et al. 1981; Dejgaard et al. 1984). It has been suggested that advanced so-called micropeliosis might be a precursor lesion for hepatic angiosarcoma in thorotrastosis (Tateno et al. 1984). Veno-occlusive disease has been found in association with Thorotrast administration and was found in conjunction with peliosis hepatis (Dejgaard et al. 1984).

Thorotrast Deposits in Thorotrast-Induced Tumors

Thorotrast deposits can also be detected in Th232-induced tumors. Thorotrast particles, in part within macrophages, have been observed in the tissue surrounding the tumor and also in regions of tumor necrosis, where macrophages harboring particles accumulate. Also free Thorotrast particles can be seen in tumors, and some tumor cells seem to take up the particles (Visfeldt and Poulsen 1972).

Pathogenic Pathways

There is a relationship between the tissue compartments loaded with Thorotrast particles and carcinogenesis. Autoradiographic studies have shown that cancer was rarely in the center of fibrotic and macrophage-rich regions with heavy Thorotrast deposition, but rather at a distance from the deposits, suggesting mechanisms more complex than a mere local effect of alpha particles (Yamasaki et al. 2004; Yamamoto et al. 2009). The mechanisms causing the marked delay between thorium dioxide injection and manifestation of liver cancer have not been fully elucidated. One model proposed that target cells susceptible to malignant transformation may undergo one event by alpha particles and may then migrate outside of the range of alpha particles, thereby avoiding immediate induction of successive additional events for neoplastic change (Yamamoto et al. 2010). Thorium dioxide is also transported within organs via migration of macrophages that have ingested the Thorotrast particles

(Goto et al. 2002), microdistribution therefore being markedly influenced by the migration dynamics of phagocytosing cells. The distribution of colloidal thorium dioxide within the liver has been studied in a rat model of hepatic carcinogenesis (Grampa 1967).

Thorium dioxide induces chromosomal anomalies (Kemmer et al. 1973), and Th232-induced cholangiocarcinomas exhibit microsatellite instability (Liu et al. 2002). Genetic changes induced by Thorium dioxide have been detected in several hepatic tumors induced by this agent (Kamikawa et al. 1999; Liu et al. 2004; review: Ishikawa et al. 2001; Andersson 1997). LOH analysis revealed Thorotrast-induced intrahepatic cholangiocarcinomas (ICC) share some LOH features with ICC and HCC that were not induced by Thorotrast (Liu et al. 2004). Frequent and multiple point mutations in K-ras-2 were found in Thorotrast-induced hepatic angiosarcomas (Przygodski et al. 1997). Alpha particles such as thorium dioxide cause p53 gene mutations (Hollstein et al. 1997; Iwamoto et al. 1999).

Tumor-like Mineralizations/ Calcifications of the Liver

Introduction

Rarely, calcification (or mineralizations, as it is also termed) of the liver can result in mass-forming pseudotumoral lesions that can be confounded with calcified benign or malignant neoplasms (Fig. 5; early reports on liver calcification: Kaufman 1951; Bruce 1957; Schröder 1959; Reeder 1975; Darlak et al. 1980; Pounder 1985; reviews: Paley and Ros 1998; Stoupis et al. 1998). In what follows, the most important situations of hepatic calcifications are summarized.

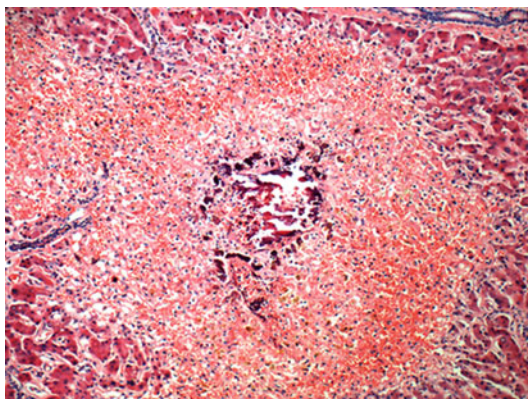

Fig. 5 Calcium granuloma in a necrotic area of the liver (hematoxylin and eosin stain)

Hepatic Calcification in Ischemia of the Liver

Diffuse dystrophic parenchymal calcification of the liver has been observed subsequent to ischemic hepatic necrosis (Nguyen and Leonard 1986), including shock (Shibuya et al. 1985b). Yet, there are also more complex situations with a mixed pathogenesis, such as combined hepatic ischemic injury and hypercalcemia due to chronic renal failure (Milstein and Moulton 1993).

Hepatic Calcification in Uremia

Uremia can cause extraosseous calcification, sometimes massive (Floege 2004). The pathogenesis may, at least to a good part, involve hypercalcemia, i.e., causing metastatic calcification (Ibels 1980). Calcification of liver tissue in uremia has rarely been reported (Shibuya et al. 1985a; Ladefoged and Frifelt 1987; Milstein and Moulton 1993; Kinjo et al. 2007), also in patients treated with peritoneal dialysis (Abbas et al. 1996). Calcifications were found in damaged parenchyma in the centrilobular to midzonal areas of liver lobules, but uremia-induced hepatic calcifications involving the epithelia of proliferated bile ductules have also been described (Kurumaya et al. 1989). Centri- and midzonal hepatic necrosis with intracellular and extracellular calcifications of round or rod-like shape was seen in uremic patients who had received hemodialysis, necrotic hepatocytes sometimes being almost completely replaced by calcium salt deposits (Sugiura et al. 1987; Kinjo et al. 2007).

Postinflammatory/Postnecrotic Hepatic Calcification

Several types of hepatic infection causing inflammation and necrosis are known to be accompanied, or followed, by hepatic calcification. They include placental infections spreading through the venous system to the liver (Arda et al. 2000), tuberculosis (Stoupis et al. 1998), calcified granulomas in hepatic brucellosis (Pons et al. 1981), and in cat-scratch disease (Talenti et al. 1994). Tuberculoma (macronodular tuberculosis) of the liver produces large and sometimes round hypointense nodules that may show calcifications at imaging (Chan and Pang 1989; Levine 1990; Fan et al. 1998). Amoebic liver abscesses older than 7 years have been found to undergo calcification (Blessmann et al. 2006). Liver calcification was also noted in neonates after transplacental infection (Shackelford and Kirks 1977).

Calcified Parasites

Parasites can, following their death, accumulate calcium salts in their necrotic tissue and cause circumscribed calcified masses. This phenomenon is known for hepatic schistosomiasis (Radhakrishnan et al. 1988) but has also been observed in liver fluke disease (fascioliasis, infestations with *Clonorchis* and *Opisthorchis*).

Calcified Necrosis, Infarcts, and Hematomas

Small and large hepatic necroses and infarcts can undergo dystrophic calcification, as insoluble calcium salts tend to accumulate in necrotic tissues. Also hematomas, as soon as they dehydrate and leave a mass of blood cell proteins, can calcify (Krivokhizh et al. 1983).

Hepatic Calcification After Liver Transplantation

Postoperative ectopic calcification located to several tissues seems to be rather subsequent to liver transplantation and appears to be caused by intraoperative manipulations of serum calcium levels, renal failure, ischemia, and other factors (Wachtel et al. 1992). An important mechanism of liver calcification posttransplantation is mediated by ischemia-reperfusion injury (Kalantari et al. 2007). Masses of posttransplantation lymphoproliferative disorder in a liver graft may primarily calcify (Lecouvet et al. 1996).

Hepatic Calcification Due To Amyloidosis

Marked hepatic calcification can develop in conjunction with amyloidosis of the liver, amyloid being known to have an affinity for calcium salts (Kennan and Evans 1991; Gibson et al. 1992; Jacobs et al. 1997).

Metastatic Calcification of the Liver

Liver cell calcification has been observed both in primary hyperparathyroidism (parathyroid adenoma; Monma et al. 1987) and in secondary hyperparathyroidism caused by renal failure (Ladefoged and Frifelt 1987). In the case published by Ladefoged and Frifelt (1987), the necropsy of a 20-year-old female who had had renal, cardiac failure and secondary hyperparathyroidism showed chronic passive congestion of the liver, associated with severe centrilobular necrosis and calcification. The calcium phosphate deposits stained black with the von Kossa stain (which stains phosphates) and orange red with the Alizarin-Red S method for calcium. The hepatocytes near the central vein were totally replaced by calcium phosphate, forming a black von Kossa-positive ring around the vein, while hepatocytes in the peripheral zone of the lobule showed calcium-containing granules in their cytoplasm. On the other hand, there are primary hepatic tumors inducing hypercalcemia (Oldenburg et al. 1982), for example, cholangiocarcinoma (Naide et al. 1968; Hirano et al. 1978; Davis et al. 1994) and hepatocellular carcinoma (with parathyroid hormone activity; Knill-Jones et al. 1970), including the sclerosing variant (Omata et al. 1981).

Hepatic Calcification in Other Metabolic Disorders

Hepatic calcification develops in the autosomal recessive connective tissue disorder, pseudoxanthoma elasticum (OMIM 264800) (Vanakker et al. 2006). This disorder has the phenotype triad of popular lesions and increased skin laxity in the flexural areas of the body, angioid streaks in the ocular fundus, and accelerated atherosclerosis leading to cardiovascular complications. Alterations of the elastic fibers in several tissues cause progressive fiber fragmentation and mineralization, which is the histologic hallmark of the disease. Aberrant mineralization of connective tissues has also been detected in a mouse model of pseudoxanthoma elasticum (Jiang et al. 2007). The responsible gene (termed ABCC6, multidrug resistance protein 6) is located on chromosome 16p13.1, encodes an ATP-dependent transmembrane transporter of substrate, is mainly expressed in the liver, and reveals numerous mutations in pseudoxanthoma elasticum (Ringpfeil et al. 2001; Li et al. 2009; Ratajewski et al. 2009; Costrop et al. 2010; Uitto et al. 2010). In murine hepatic Abcc6 expression, HNF4alpha and NF-E2 are the key transcriptional regulators (Douet et al. 2006), and in cultured human hepatocytes, the ERK1/ERK2-HNF4alpha axis regulates ABCC6 expression (De Boussac et al. 2010). In the liver, vitamin K precursor is secreted by ABCC6 as a glutathione or glucuronide conjugate, and the lack of ABCC6 may prevent the liver from providing sufficient amounts of vitamin K to the periphery (Borst et al. 2008). Low serum vitamin K in pseudoxanthoma elasticum results in defective carboxylation of mineralization inhibitors, and this is thought to play a role in the pathogenesis of ectopic calcifications (Vanakker et al. 2010).

Hepatic Calcification in Cystic Lesions of the Liver

Calcification, sometimes ring-like, in cyst walls of hepatic hydatid disease is well established and occurs in 10–20 % of cases (Scherer et al. 1978; Darlak et al. 1980; de Diego Choliz et al. 1982; Beggs 1983; Pandolfo et al. 1984; Kalovidouris et al. 1986; Stoupis et al. 1998). Hereditary polycystic liver disease is a very rare cause of intrahepatic calcification (Travers et al. 1983).

Hepatic Arterial Calcification

In contrast to the mesenteric and splenic arteries, the hepatic artery is seldom calcified. Calcification of this artery has been noted in a liver transplant recipient 13 years after transplantation (Eisele et al. 2009). It may sonographically mimic intrahepatic biliary calculi (White and Wilson 1994) or pneumobilia (Pai and Bude 2002). Calcifications have also been found to involve the ductus arteriosus and the ligamentum botalli (Currarino and Jackson 1970).

Calcification of Venous Vessels of the Liver

Most venous calcifications occurring in the liver are based on mineralization of venous thrombi or thromboemboli, well documented for the portal vein (Friedman et al. 1981; de Filippi and betta 1988). Calcifications can occur in the ductus venosus and veins of the ligamentum teres hepatis (Beluffi et al. 1998). The radiologic localization of calcifications to the structures of this compartment may be difficult (Lafortune 1990; Abu-Yousef 1990). A calcified ductus venosus associated with "tram-track" calcifications have been seen in neonates and suggested to be caused by catheterism (Rizzo et al. 1989).

Calcifications of the Bile Ducts

Biliary wall calcification has been found in Langerhans cell histiocytosis (Caruso et al. 2008).

Peritoneal Calcification

Peritoneal calcification (progressive calcifying peritonitis) can develop in patients with uremia

on continuous ambulatory peritoneal dialysis/CAPD (Dejima et al. 2008) and may involve the hepatic peritoneum.

Tumor-Like Calcification of the Liver

Solitary necrotic nodules of the liver are typically calcified (Colagrande et al. 2008). Mineralized conglomerates of hepatic granulomas may present as a calcified pseudotumor of the liver (Yuan et al. 1988; Fig. 6). Large calcifying granulomatous and necrotic masses are characteristic for hepatic brucelloma (Ruiz Carazo et al. 2005).

Calcified Tumors in the Liver

Focal nodular hyperplasia (FNH) is rarely associated with calcific deposits within the nodular lesion (Caseiro-Alves et al. 1996). In FNH, calcifications were found in the form of small, solitary spots located centrally or peripherally within the lesions, and the calcified foci were similar to those encountered in fibrolamellar carcinoma (Caseiro-Alves et al. 1996). Calcifications are rarely encountered in liver cell adenoma. Calcifications may be solitary or multiple and are usually located excentrically within a complex heterogeneous mass (Stoupis et al. 1998). In a multiphase CT study of 25 patients, calcifications were uncommon in liver cell adenoma (5 %; Ichikawa et al. 2000). Calcification has also been noted in liver adenomatosis (Khan et al. 1992). Tumor calcification also occurs in bile duct adenoma (Maeda et al. 2006). A distinct type of peripheral calcification occurs in mesenchymal hamartoma of the liver (Steiner and Giles 2008). Tumor calcification, often punctate, is regarded as rather typical for fibrolamellar hepatocellular carcinoma and occurs more frequently than calcification in ordinary hepatocellular carcinoma. The prevalence in published observations is given as 38 % (Friedman et al. 1985), 40 % (Soyer et al. 1991), 55 % (Brandt et al. 1988), and 68 % (Ichikawa et al. 1999). Calcification in untreated hepatocellular carcinoma has been reported to be rare, with most patterns fine granular, single, or multiple punctate and coarse and conglomerate (Weiss et al. 1972; Itai et al. 1979; Kunstilger et al. 1980; Scatarige et al. 1983; Teefev et al. 1987;) In part of the tumors, calcification involves the neoplasm's stroma (Moenandar 1974). In a CT study, calcific deposits were noted in 15.3 % of patients with hepatocellular carcinoma (Scatarige et al. 1983). Few HCCs show a rim or ring calcification that may mimic parasitic hydatid disease (Mitchell et al. 1994; Fukuya et al. 1999). Calcified cholangiocarcinomas seem to be rarer than calcified hepatocellular carcinomas (Hall et al. 1970; Yamasaki et al. 1977; Nagakura et al. 1999; Kitade et al. 2005), but in the intrahepatic variants, calcifications have been noted in up to 18 % (Stoupis et al. 1998). There are exceptional situations where psammoma body formation is a feature of cholangiocarcinoma (Yamada et al. 2000). Secondary calcification is well known in carcinoma metastases, in particular colorectal carcinoma (CRC) metastases (Miele and Edmonds 1963; Green and Stephens 1971; Kutzner and Wagner 1973; Sanchez Perez et al. 1995; Easson et al. 1996). Calcified hepatic metastases may be the first manifestation of CRC (Sanchez Perez et al. 1995), and they have characteristic CT features. By use of CT examination, 18.3 % of patients with CRC hepatic metastases showed calcific deposits (Scatarige et al. 1983). Among

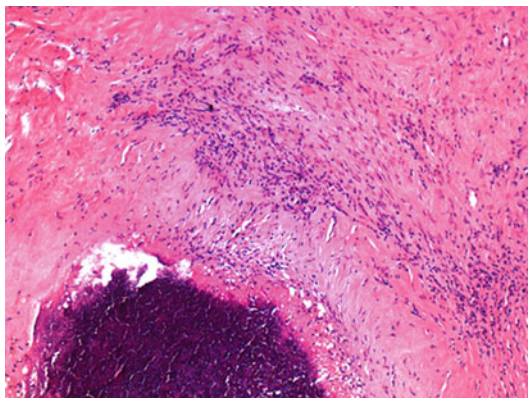

Fig. 6 Tumor-like calcification of the liver. The large accumulation of calcium salts (*bottom*) is associated with a fibrosed epithelioid cell reaction (hematoxylin and eosin stain)

265 patients with hepatic CRC metastases, 11 % had calcified metastases at presentation and 4 % developed calcification during chemotherapy (Hale et al. 1998). Calcification in colorectal hepatic metastases has been found to correlate with longer patient survival (Easson et al. 1996). Calcifications are also rather typical for certain vascular tumors. Cavernous hemangiomas, especially giant hemangiomas, may contain large, coarse calcifications that are centrally located in areas of fibrosis (Aspray 1945) and may be seen at CT (20 % of cases) or radiography (10 % of cases; Stoupis et al. 1998). Calcification is known for epithelioid hemangioendothelioma (Den Bakker et al. 1998),

Pathogenic Pathways

A crucial component of mineralization (both *loco classico* and ectopic) is the collagen fibril. During mineralization the fibril is formed first and then water within the fibril is replaced with mineral. The collagen fibril therefore provides the aqueous compartment in which mineral grows. Size exclusion experiments have shown that molecules smaller than a 6-kDa protein diffuse into all of the water within the collagen fibril, whereas molecules larger than a 40-kDa protein are excluded from this water phase. Large nondiffusible molecules can, however, initiate mineralization by forming small apatite crystal nuclei that diffuse into the fibril (Toroian et al. 2007). Other molecules inhibit the extra-fibril formation of apatite crystal, especially the serum inhibitor of apatite growth, fetuin-A, a protein synthesized in the liver (Toroian and Price 2008; mineralization by inhibitor exclusion, Price et al. 2009).

Cells involved in the initiation of mineralization in newly formed bone and in areas with ectopic mineralization/calcification release a distinct microstructure called matrix vesicles (MVs). MVs are extracellular, lipid bilayer-enclosed microstructures that are enriched in several phospholipids, especially phosphatidylserine (PS), a lipid with high affinity for Ca^{2+}. PS/Ca^{2+}.inorganic phosphate complexes (CPLXs) have been found in calcifying tissues, including bone, cartilage, and tumors. Critical components of MVs are the annexins II, V, and VI, and types II and X collagen are associated with MVs, and these interactions mediated by annexin V stimulate Ca^{2+} uptake and mineralization of MVs. The formation of annexin II, V, and VI Ca^{2+} channels in MVs together with stimulation of annexin V channel activity by collagens II and X binding provide the MVs with the ability to rapidly uptake calcium and to initiate the formation of the first crystal phase (Kirsch et al. 2000; Genge et al. 2007). Annexin V (A5) has the ability to bind in a calcium-dependent manner to phosphatidylserine, which is located in the inner leaflet of the plasma membrane. By this binding, A5 can form a membrane-bound two-dimensional crystal lattice (van Genderen et al. 2008). In calcification developing in and around hepatic necrosis, myofibroblasts play a pathogenic role. They have been shown to express bone-specific proteins, such as osteopontin, type I collagen, and bone sialoprotein. In addition, TGFbeta-1 and BMP2, two growth factors implicated in osteoblast differentiation, and Runx2 and Msx2, two transcription factor targets of TGFbeta-1 and BMP2, were also expressed in these cells (Kalantari et al. 2007).

References

Abbas MA, Petersen J, Eller DJ, Katz DS (1996) Hepatic calcification associated with continuous ambulatory peritoneal dialysis. AJR Am J Roentgenol 167:1592–1593

Abbatt JD (1979) History of the use and toxicity of Thorotrast. Environ Res 18:6–12

Abe M, Wakasa H (1987) Thorotrast-induced hepatic angiosarcoma with 39 years latency. A pathological and immunohistochemical study. Acta Pathol Jpn 37:1653–1660

Abu-Yousef MM (1990) Is it calcification of the ductus venosus or calcification of the ligamentum teres? Radiology 176:291

Aizawa M, Kobayashi H, Maruyama K, Hagihara K (1960) Two cases of cirrhotic liver associated with Thorotrast deposit. Acta Pathol Jpn 10(Suppl):615–620

Akagi G, Hizawa K, Kitamuro T, Fukuda F, Yamashita S (1966) Primary hepatoma 31 years after injection of Thorotrast. Tokushima J Exp Med 13:111–119

Allaire GS, Goodman ZD, Ishak KG, Rabin L (1989) Talc in liver tissue of intravenous drug abusers with chronic

hepatitis. A comparative study. Am J Clin Pathol 92:583–588
Ambrosi L (1965) Aspetti istologici del fegato nei silicotici. Med Lav 56:795
Anderson WAD (1971) Pathology, vol 2, 6th edn. C.V. Mosby, St. Louis
Andersson M (1997) Long-term effects of internally deposited alpha-particle emitting radionuclides. Epidemiological, pathological and molecular-biological studies of Danish Thorotrast-administered patients and their offspring. Dan Med Bull 44:169–190
Andersson M, Vyberg M, Visfeldt J, Carstensen B, Storm HH (1994) Primary liver tumors among Danish patients exposed to Thorotrast. Radiat Res 137:262–273
Andrion A, Pira E, Mollo F (1983) Peritoneal plaques and asbestos exposure. Arch Pathol Lab Med 107:609–610
Arai T (1931) Ueber Chalicosis pulmonum. Virchows Arch Pathol Anat 228:510
Arda K, Ozdemirel D, Tosun, Olcer T (2000) Postpartum follow-up of hepatic calcification detected by prenatal ultrasound. JBR-BTR 83:231–233
Argento A, Durante E, Gazzerro F (1962) La funzionalità epatica nella silicosi polmonare. Fol med 42:149
Arredouani M, Yang Z, Ning Y, Qin G, Soininen R, Tryggvason K, Kobzik L (2004) The scavenger receptor MARCO is required for lung defense against pneumococcal pneumonia and inhaled particles. J Exp Med 200:267–272
Arteche E, Ostiz S, de Miguel CL (2007) Case 2. Diffuse hepatic angiosarcoma secondary to Thorotrast deposit (in Spanish). Radiologia 49:28
Aspray M (1945) Calcified haemangiomas of the liver. Am J Roentgenol 53:446
Azodo MV, Gutierrez OH, Greer T (1993) Thorotrast-induced ruptured hepatic angiosarcoma. Abdom Imaging 18:78–81
Baserga R, Yokoo H, Henegar G (1960) Thorotrast-induced cancer in man. Cancer 13:1021–1031
Bast T, Zuna I, Layer G, van Kaick G (1995) CT-measurements of liver and spleen in Thorotrast patients and their influence to dose rate calculations. In: van Kaick G (ed) Health effects of internally deposited radionuclides: emphasis on radium and thorium. World Scientific, Singapore, pp 235–239
Batzenschlager A, Keiling R, Kuntzmann F (1961) Cancers of the bile ducts on thorotrastosis of the liver (in French). Ann Anat Pathol (Paris) 6:457–478
Batzenschlager A, Dorner A, Weil-Bousson M (1963) The tumoral pathology of Thorotrast in man. Review of the literature – personal statistical data (in French). Oncologia 16:28–63
Bauer KH (1943) Thorotrast und Krebsgefahr. Chirurg 15:204
Baxter PJ, Langlands AO, Anthony PP, MacSween RN, Scheuer PJ (1980) Angiosarcoma of the liver: a marker tumour for the late effects of Thorotrast in Great Britain. Br J Cancer 41:446–453
Becker N, Liebermann D, Wesch H, Van Kaick G (2008) Mortality among Thorotrast-exposed patients and an unexposed comparison group in the German Thorotrast study. Eur J Cancer 44:1259–1268
Beckert W (1972) Anthracotic pigment in the liver punctuate (in German). Zentralbl Allg Pathol 115:284–288
Beer TW, Carr NJ, Buxton PJ (1998) Thorotrast associated nodular regenerative hyperplasia of the liver. J Clin Pathol 51:941–942
Beggs I (1983) The radiological appearances of hydatid disease of the liver. Clin Radiol 34:555–563
Beluffi G, Rotoli P, Calo L, Tinelli C, Fiori P (1998) Botallo's duct calcification in children: radiologic findings (in Italian). Radiol Med (Torino) 96:204–208
Benjamin AG, Albukerk JN (1982) Thorotrast-induced angiosarcoma of liver. N Y State J Med 82:751–753
Blessmann J, Khoa ND, Van An L, Tannich E (2006) Ultrasound patterns and frequency of focal liver lesions after successful treatment of amoebic liver abscess. Trop Med Int Health 11:504–508
Bo M, Grassone D, Fabris F (2001) Unexpected diagnosis of Thorotrast-induced cirrhosis (in Italian). Recenti Prog Med 92:667–669
Borst P, van de Wetering K, Schlingemann R (2008) Does the absence of ABCC6 (multidrug resistance protein 6) in patients with Pseudoxanthoma elasticum prevent the liver from providing sufficient vitamin K to the periphery? Cell Cycle 7:1575–1579
Boyd JT, Langlands AO, Maccabe JJ (1968) Long term hazards of Thorotrast. Br Med J 2:517–521
Brandt DJ, Johnson CD, Stephens DH, Weiland LH (1988) Imaging of fibrolamellar hepatocellular carcinoma. AJR Am J Roentgenol 151:295–299
Brecht G, Helpap B, Lackner K (1980) Thorotrastosis: survey and CT pattern (in German). Rontgenblatter 33:232–238
Breining H (2003) Frequency, morphology, pathogenesis and complications of silicotic callosities (phthisis atra). A disappearing disease (in German). Pathologe 24:98–102
Bruce R (1957) Intrahepatic calcification. Br Med J (5031):1343–1344
Buschmann RJ, Mir J (1979) Electron microscopic identity of talc in the liver of a narcotic addict. Hum Pathol 10:736–739
Cabarcos A, Gomez Dorronsoro M (1984) Extrathoracic anthracosis (in Spanish). Med Clin (Barcelona) 83:469
Carmichael GP, Targoff C, Pintar K, Lewin KJ (1980) Hepatic silicosis. Am J Clin Pathol 73:720–722
Caroli J, Eteve J, Platteborse R (1956) Thorotrast and malignant hemangioendothelioma of liver (in French). Rev Med Chir Mal Foie 31:53–65
Caruso S, Miraglia R, Maruzzelli L, Luca A, Gridelli B (2008) Biliary wall calcification in Langerhans cell histiocytosis: report of two cases. Pediatr Radiol 38:791–794
Caseiro-Alves F, Zins M, Mahfouz A-E, Rahmouni A, Vilgrain V, Menu Y, Mathieu D (1996) Calcification in focal nodular hyperplasia: a new problem for differentiation from fibrolamellar hepatocellular carcinoma. Radiology 198:889–892

Castranova V (2004) Signaling pathways controlling the production of inflammatory mediators in response to crystalline silica exposure: role of reactive oxygen/nitrogen species. Free Radic Biol Med 37:916–925

Chan HS, Pang J (1989) Isolated giant tuberculomata of the liver detected by computed tomography. Gastrointest Radiol 14:305–307

Chassagnon C, Silie M (1966) A cse of silico-tuberculosis complicated by obstructive jaundice. Retro-pancreatic silicotic lymph nodes blocking the bile ducts (in French). Arch Mal Prof 27:718–719

Chiari H (1907) Ueber die Intravasation des anthrakotischen Pigments in die Blutgefässe der Lungen (On the intravasation of anthracotic pigment into blood vessels of the lung). Münch Med Wschr 54:1309

Cioni C (1943) Sopra un caso di grave coniosi ad estesa diffusione. I. Lesioni pulmonari, linfoghiandolari, spleniche ed epatiche. Arch Ital Anat Istol Pathol 17:86

Cisno F, Azzalini M, Camagna MT (1971) Considerazioni su 16 casi di silicosi del fegato e della milza. Med Lav 62:378

Colagrande S, Paolucci ML, Messerini L, Schima W, Stadler A, Bartolotta TV, Vanzulli A, Brancatelli G (2008) Solitary necrotic nodules of the liver: cross-sectional imaging findings and follow-up in nine patients. AJR Am J Roentgenol 191:1122–1128

Costrop LM, Vanakker OO, Van Laer L, le Saux O, Martin L, Chassaing N, Guerra D et al (2010) Novel deletions causing pseudoxanthoma elasticum underscore the genomic instability of the ABCC6 region. J Hum Genet 55:112–117

Currarino G, Jackson JH (1970) Calcification of the ductus arteriosus and ligamentum botalli. Radiology 94:139–142

Da Cunha DF, dos Santos VM, da Cunha SF, Santana JH, Fatureto MC, dos Reis MA, Teixeira Vde P (1999) Systemic talc granulomatosis in a HIV-negative intravenous drug addict (in Portuguese). Rev Assoc Med Bras 45:285–288

Da Silva Horta J (1953) Lebersarkom einer Frau 3 Jahre und 2 Monate nach Thorotrastinjektion. Chirurg 24:218–223

Da Silva Horta JS (1967) Late effects of Thorotrast on the liver and spleen, and their efferent lymph nodes. Ann N Y Acad Sci 145:676–699

da Silva Horta J, Nunes JM (1973) Historadiographies and autoradiographies from pieces of organs of people injected systemically with Thorotrast. RISO Rep 294:259–266

Dachman AH, Ros PR, Goodman ZD, Olmsted WW, Ishak KG (1987) Nodular regenerative hyperplasia of the liver: clinical and radiologic observations. AJR Am J Roentgenol 148:717–722

Dagle GE, Moen EP, Adee RR, Hui TE, James AC, Filipy RE, Kathren RL (1992) Microdistribution and microdensity of thorium deposited in the liver. Health Phys 63:41–45

Dahlgren S (1961) Thorotrast tumors: a review of the literature and report of two cases. Acta Pathol Microbiol Scand 53:147–161

Dahlgren S (1967) Late effects of thorium dioxide on the liver of patients in Sweden. Ann N Y Acad Sci 145:718–723

Danese CA, Mollura J (1974) Thorotrast granuloma of periaortic nodes. Lymphology 7:85–89

Darlak JJ, Moskowitz M, Kattan KR (1980) Calcifications in the liver. Radiol Clin North Am 18:209–219

Davis JM, Sadasivan R, Dwyer T, van Veldhuizen P (1994) Case report: cholangiocarcinoma and hypercalcemia. Am J Med Sci 307:350–352

De Boussac H, Ratajewski M, Sachrajda I, Köblös G, Tordai A, Pulaski L, Buday L et al (2010) The ERK1/2-hepatocyte nuclear factor 4alpha axis regulates human ABCC6 gene expression in hepatocytes. J Biol Chem 285:22800–22808

De Diego Choliz J, Lecumberri Olaverri FJ, Franquet Casas T, Ostiz Zubieta S (1982) Computed tomography of hepatic echinococcosis. AJR Am J Roentgenol 139:699–702

De Filippi G, Betta PG (1988) Vascular liver calcification in infants. A case report with some pathogenetic considerations. Pediatr Radiol 18:413–415

Dejgaard A, Krogsgaard K, Jacobsen M (1984) Veno-occlusive disease and peliosis of the liver after Thorotrast administration. Virchows Arch A Pathol Anat Histopathol 403:87–94

Dejima K, Mitsuhashi H, Yasuda G, Hirawa N, Ikeda Y, Umemura S (2008) Localization and extent of peritoneal calcification in three uremic patients on continuous ambulatory peritoneal dialysis. Ther Apher Dial 12:413–416

Den Bakker MA, den Bakker AJ, Beenen R, Mulder AH, Eulderink F (1998) Subtotal liver calcification due to epithelioid hemangioendothelioma. Pathol Res Pract 194:189–194

Dos Santos Silva I, Jones M, Malveiro F, Swerdlow A (1999) Mortality in the Portuguese Thorotrast study. Radiat Res 152(Suppl 6):S88–S92

Douet V, Van Wart CM, Heller MB, Reinhard S, Le Saux O (2006) HNFalpha4 and NF-E2 are key transcriptional regulators of the murine Abcc6 gene expression. Biochem Biophys Acta 1759:426–436

Dunky A, Klumair J (1980) Computertomographic diagnosis of thorotrastosis (in German). Röfo 133:219–220

Duriez et al. 1973. http://www.ncbi.nlm.nih.gov/pubmed/4767267

Easson AM, Barron PT, Cripps C, Hill G, Guindi M, Michaud C (1996) Calcification in colorectal hepatic metastases correlates with longer survival. J Surg Oncol 63:221–225

Eisele RM, Schumacher G, Podrabsky P, Stange B, Glanemann M (2009) Hepatic artery calcification in a liver transplant recipient. Transplant Proc 41:777–779

Ellis PA (1964) A case of thorium-induced cholangioma. Br J Surg 51:74–76

Espasa R, Puig Costa M, Salva JA, Broggi MA, Sala Patau E (1981) Hepatocarcinoma caused by Thorotrast (in Spanish). Rev Clin Esp 161:261–264
Faber M (1978) Malignancies in Danish Thorotrast patients. Health Phys 35:153–158
Falk H, Telles NC, Ishak KG, Thomas LB, Popper H (1979) Epidemiology of Thorotrast-induced hepatic angiosarcoma in the United States. Environ Res 18:65–73
Fan ZM, Zeng QY, Huo JW, Bai L, Liu ZS, Luo LF, Yang JC, Zhou XH (1998) Macronodular multi-organs tuberculoma: CT and MR appearances. J Gastroenterol 33:285–288
Farid I (1982) Thorium dioxide and liver cancer. JAMA 248:550
Findley A, Childress MH (1987) Computed tomography of thorotrastosis. J Comput Tomogr 11:188–189
Floege J (2004) When man turns to stone: extraosseous calcification in uremic patients. Kidney Int 65:2447–2462
Fondimare A, Duwoos H, Desbordes J, Perrotey J, Tayot J (1974) Letter: calcified fibro-hyaline plaques in the liver in asbestosis (in French). Nouv Presse Med 3:893
Forbes IJ, Geddes RA, Wood NM (1968) Thorotrast-induced hepatoma with dysgammaglobulinaemia. Med J Aust 55:762–765
Friedman AP, Haller JO, Boyer B, Cooper R (1981) Calcified portal vein thromboemboli in infants: radiography and ultrasonography. Radiology 140:381–382
Friedman AC, Lichtenstein JE, Goodman Z, Fishman EK, Siegelman SS, Dachman AH (1985) Fibrolamellar hepatocellular carcinoma. Radiology 157:583–587
Frik K, Blühbaum T (1928) Eine neue Anwendungsart der Kolloide in der Röntgendiagnostik. Fortschr Röntgenstr 38:1111–1119
Fukuya T, Yabuuchi H, Seo Y, Fukuda T, Koga M (1999) Hepatocellular carcinoma with ring calcification: report of two cases. Radiat Med 17:379–382
Futh U, Pietzke HU (1974) Hemangioendothelioma of the liver following Thorotrast administration 30 years ago (in German). Fortschr Geb Rontgenstr Nuklearmed 121:398–399
Genge BR, Wu LN, Wuthier RE (2007) Kinetic analysis of mineral formation during in vitro modeling of matrix vesicle mineralization: effect of annexin A5, phosphatidylserine, and type II collagen. Anal Biochem 367:159–166
Gibson JM, Baillod R, Platts AD (1992) Hepatic and splenic calcifications due to amyloidosis. Clin Radiol 45:68
Giese W (1931) Quartzstaub, Schwielenlunge und Lungentuberculose. In: Aschoff L et al (eds) Veröffentlichungen aus der Gewerbe-und Konstitutionspathologie. Gustav Fischer, Jena
Gong H, Tashkin DP (1979) Silicosis due to intentional inhalation of abrasive scouring powder. Am J Med 67:358
Goto A, Takebayashi Y, Liu D, Li L, Saiga T, Mori T, Yamadera A, Fukumoto M (2002) Microdistribution of alpha particles in pathological sections of tissues from Thorotrast patients detected by imaging plate autoradiography. Radiat Res 158:54–60
Grampa G (1967) Liver distribution of colloidal thorium dioxide and development of liver epithelial tumors in rats. Ann N Y Acad Sci 145:738–747
Grampa G, Tomamasini-Degna G (1958) Hemangioendothelioma of the liver following intravenous injection of Thorotrast. Acta Genet Stat Med 8:65–78
Green PA, Stephens DH (1971) Hepatic calcification in cancer of the large bowel. Am J Gastroenterol 55:466–470
Groth NH, Mackay GR, Crable JV, Cochran TH (1972) Intravenous injection of talc in a narcotics addict. Arch Pathol 94:171–178
Hackenthal P (1956) Beitrag zu den morphologischen Veränderungen durch Thorotrastablagerungen. Zbl Allg Path Path Anat 94:352
Hale HL, Husband JE, Gossios K, Norman AR, Cunningham D (1998) CT of calcified liver metastases in colorectal carcinoma. Clin Radiol 53:735–741
Hall PM, Winkelman EI, Hawk WA, Hermann RE (1970) Calcification in the liver, an unusual feature of ductal cell hepatic carcinoma. Report of a case. Cleve Clin Q 37:93–105
Hamilton RF, Thakur SA, Mayfair JK, Holian A (2006) MARCO mediates silica uptake and toxicity in alveolar macrophages from C57BL/6 mice. J Biol Chem 281:34218–34226
Hamilton RF, Thakur SA, Holian A (2008) Silica binding and toxicity in alveolar macrophages. Free Radic Biol Med 44:1246–1258
Hanser R (1930) Atrophie, Nekrose, Ablagerungen und Speicherungen (sog. Degenerationen). In: Henke F, Lubarsch O (eds) Handb. d. speziellen pathologischen Anatomie u. Histologie, vol 1. Springer, Berlin, p 132
Hardt M, Geisthövel W (1988) Malignant hemangioendothelioma of the liver 39 years following one-time Thorotrast administration (in German). Med Klin (Munich) 83:151–153
Hashizume Y, Shinohara K, Koide O, Takei R (1980) Carcinoma of the gallbladder in thorotrastosis – case report (in Japanese). Rinsho Hoshasen 25:951–954
Hassler O, Bostroem K, Dahlback LO (1964) Thorotrast tumors. Report of 3 cases and microradiological study of the deposits of Thorotrast in man. Acta Pathol Microbiol Scand 61:13–20
Heger N, Bayindir MD (1970) Thorotrast: primary liver sarcoma 22 years after the administration. Minn Med 53:1137–1139
Heggie JF (1946) Anthracosis of the liver. J Pathol Bacteriol 58:575–578
Heitmann W (1954) Carcinoma of the biliary tract and the liver following injection of Thorotrast. Chirurg 25:223–225

Helpap B, Tschubel K (1980) Morphology of late hepatic lesions after Thorotrast (in German). Leber Magen Darm 10:65–72

Hirano T, Tsuchiyama H, Yanagawa M (1978) An autopsy case of cholangiocarcinoma with hypercalcemia. Acta Pathol Jpn 28:465–469

Hiraoka T, Kambara T, Morinaga T, Nakagawa S (1981) Hemangioendothelial sarcoma of the liver after Thorotrast injection. Acta Pathol Jpn 31:853–861

Hollstein M, Bartsch H, Wesch H, Kure EH, Mustonen R, Mühlbauer KR, Spiethoff A et al (1997) p53 gene mutation analysis in tumors of patients exposed to alpha-particles. Carcinogenesis 18:511–516

Horta J, Abbatt JD, Motta LC, Tavares MH (1972) Leukaemia, malignancies and other late effects following administration of Thorotrast. Z Krebsforsch Klin Onkol Cancer Res Clin Oncol 77:202–216

Howard RJ, Todd EP, Dietzman RH, Filleher RC (1971) Thorotrast-induced endothelial cell sarcoma of liver. Minn Med 54:685–688

Ibels LS (1980) The pathogenesis of metastatic calcification in uraemia. Prog Biochem Pharmacol 17:242–250

Ichikawa T, Federle MP, Grazioli L, Madariaga J, Nalesnik M, Marsh W (1999) Fibrolamellar hepatocellular carcinoma: imaging and pathologic findings in 31 recent cases. Radiology 213:352–361

Ichikawa T, Federle MP, Grazioli L, Nlesnik M (2000) Hepatocellular adenoma: multiphase CT and histopathologic findings in 25 patients. Radiology 214:861–868

Irie, Mori 1987. http://www.ncbi.nlm.nih.gov/pubmed/6741545

Irie H, Mori W, Mori T, Ohami H, Saito T, Suzuki K (1986) Ultrastructural localization of Thorotrast (thorium dioxide) in human liver by analytical scanning electron microscope. Acta Pathol Jpn 36:1871–1878

Ishikawa Y, Humphreys JA, Collier CG, Priest ND, Kato Y, Mori T, Machinami R (1999) Revised organ partition of thorium-232 in Thorotrast patients. Radiat Res 152(Suppl 6):S102–S106

Ishikawa Y, Wada I, Fukumoto M (2001) Alpha-particle carcinogenesis in Thorotrast patients: epidemiology, dosimetry, pathology, and molecular analysis. J Environ Pathol Toxicol Oncol 20:311–315

Itai Y, Nishikawa J, Tasaka A (1979) Computed tomography in the evaluation of hepatocellular carcinoma. Radiology 131:165–170

Ito Y (1988) Pathomorphological characteristics of Thorotrast-related cholangiocarcinoma. Kurume Med J 35:63–69

Ito Y, Kojiro M, Nakashima T, Mori T (1988) Pathomorphologic characteristics of 102 cases of Thorotrast-related hepatocellular carcinoma, cholangiocarcinoma, and hepatic angiosarcoma. Cancer 62:1153–1162

Iwamoto KS, Fujii S, Kurata A, Suzuki M, Hayashi T, Ohtsuki Y, Okata Y, Narita M et al (1999) p53 mutations in tumor and non-tumor tissues of Thorotrast recipients: a model for cellular selection during radiation carcinogenesis in the liver. Carcinogenesis 20:1283–1291

Jacobs JE, Birnbaum BA, Furth EE (1997) Abdominal visceral calcification in primary amyloidosis: CT findings. Abdom Imaging 22:519–521

Jennings RC, Priestley SE (1978) Haemangioendothelioma (Kupffer cell angiosarcoma), myelofibrosis, splenic atrophy, and myeloma paraproteinaemia after parenteral Thorotrast administration. J Clin Pathol 31:1125–1132

Jiang Q, Li Q, Uitto J (2007) Aberrant mineralization of connective tissues in a mouse model of pseudoxanthoma elasticum: systemic and local regulatory factors. J Invest Dermatol 127:1392–1402

Johnson PK, Babb RR (1975) Cholangiocarcinoma in a patient previously given Thorotrast. Am J Dig Dis 20:384–390

Kalantari F, Miao D, Emadali A, Tzimas GN, Goltzman D, Vali H, Chevet E, Auguste P (2007) Cellular and molecular mechanisms of abnormal calcification following ischemia-reperfusion injury in human liver transplantation. Mod Pathol 20:357–366

Kalbrenner H (1928) Über eine neue röntgenologische Untersuchungsmethode des Dickdarms: die Darstellung des Schleimhautreliefs mit Umbrathor. Fortschr Rontgenstr 38:325–332

Kalovidouris A, Pissiotis C, Pontifex G, Gouliamos A, Pentea S, Papavassiliou C (1986) CT characterization of multivesicular hydatic cysts. J Comput Assist Tomogr 10:428–431

Kamikawa T, Amenomori M, Itoh T, Momoi H, Hiai H, Machinami R, Ishikawa Y, Mori T et al (1999) Analysis of genetic changes in intrahepatic cholangiocarcinoma induced by Thorotrast. Radiat Res 152(Suppl): S118–S124

Kanta J, Horsky J, Kovarova H, Tilser I, Korolenko TA, Bartos F (1986) Formation of granulomas in liver of silica-treated rats. Br J Exp Pathol 67:889–899

Kato I, Kido C (1987) Increased risk of death in Thorotrast-exposed patients during the late follow-up period. Jpn J Cancer Res 78:1187–1192

Kaufman SA (1951) Intrahepatic calcification. US Armed Forces Med J 2:1863–1866

Kaul A, Foll U, Haase VA, Palme G, Riedel W, Stolpmann HJ (1979) Microdistribution of Thorotrast and dose to cellular structures. Environ Res 18:13–22

Kemmer W, Muth H, Tranekjer F, Borkenhagen U (1973) Chromosome aberrations caused by Thorotrast. RISO Rep 294:104–113

Kennan NM, Evans C (1991) Case report: hepatic and splenic calcification due to amyloid. Clin Radiol 44:60–61

Khan SS, Fink M, King S (1992) Case report: liver adenomatosis presenting as multiple calcified masses. Clin Radiol 45:206–207

Kiely JM, Titus JL, Orvis AL (1973) Thorotrast-induced hepatoma presenting as hyperparathyroidism. Cancer 31:1312–1314

Kinjo K, Yamashiro M, Akamine K, Kinjo M, Oshiro M (2007) Diffuse hepatocellular calcification developing in a patient on chronic hemodialysis after ischemic hepatitis. Intern Med 46:1729–1733

Kirsch T, Harrison G, Golub EE, Nah HD (2000) The roles of annexin and types II and X collagen in matrix vesicle-mediated mineralization of growth plate cartilage. J Biol Chem 275:35577–35583

Kitade M, Yoshiji H, Yamao J, Fujimoto M, Kojima H, Mitoro A, Yoshida M, Naisaki T et al (2005) Intrahepatic cholangiocarcinoma associated with central calcification and arterioportal shunt. Intern Med 44:825–828

Klatskin G (1977) Hepatic granulomata: problems in interpretation. Mt Sinai Med J 44:798–812

Knill-Jones RP, Buckle RM, Parsons V, Calne RY, Williams R (1970) Hypercalcemia and increased parathyroid-hormone activity in a primary hepatoma. N Engl J Med 282:704–708

Kobayashi H, Okamura A, Ohnishi Y, Kondo A, Yamamoto T, Ozawa H, Morita T (1983) Generalized fibrosis associated with pulmonary asbestosis. Acta Pathol Jpn 33:1223–1231

Kojiro M, Nakashima T, Ito Y, Ikezaki H, Mori T, Kido C (1985) Thorium dioxide-related angiosarcoma of the liver. Pathomorphologic study of 29 autopsy cases. Arch Pathol Lab Med 109:853–857

Kolb-Bachofen V (1992) Uptake of toxic silica particles by isolated rat liver macrophages (Kupffer cells) is receptor mediated and can be blocked by competition. J Clin Invest 90:1819–1824

Kopp-Schneider A, Haertel T, Burkholder I, Bannasch P, Wesch H, Groos J, Heeger S (2006) Investigating the formation and growth of alpha-article radiation-induced foci of altered hepatocytes: a model-based approach. Radiat Res 166:422–430

Krasinskas AM, Minda J, Saul SH, Shaked A, Furth EE (2004) Redistribution of Thorotrast into a liver allograft several years following transplantation: a case report. Mod Pathol 17:117–120

Kringsholm B, Christoffersen P (1982) Liver pathology in fatal drug addiction. Forensic Sci Int 20:141–151

Krivokhizh VN, Odintsov AI, Kasaev AA, Sokurov VP, Balashova VF (1983) Calcified hematoma of the liver simulating a pulmonary tuberculoma (in Russian). Pediatriia 6:71

Krücke W (1950) Histopathologische Befunde an den Körperorganen nach Arteriographie des Gehirns mit Thorotrast. Zbl Neurochir 10:189

Kuisk H, Sanchez JS, Mizuno NS (1967) Colloidal thorium dioxide (Thorotrast) in radiology with emphasis on hepatic cancerogenesis. A case report of occluded carotid and jugular vessels with nerve injuries and a case of hepatoma, 27 and 33 years after its administration. Am J Roentgenol Radium Ther Nucl Med 99:463–475

Kunstilger FK, Federle MP, Moss AA, Marks W (1980) Computed tomography of hepatocellular carcinoma. AJR Am J Roentgenol 134:431–437

Kurumaya H, Yoshida K, Kono N, Nakanuma Y, Takeda S, Oiko Y (1989) Hepatic calcification in proliferated bile ductules in an uremic patient. Arch Pathol Lab Med 113:411–413

Kutzner J, Wagner R (1973) Calcified liver metastases from islet cell carcinoma (in German). Fortschr Geb Rontgenstr Nuklearmed 118:255–258

Ladefoged C, Frifelt JJ (1987) Hepatocellular calcification. Virchows Arch A Pathol Anat Histopathol 410:461–463

Lafortune M (1990) Is it calcification of the ductus venosus or calcification of the umbilical vein? Radiology 176:290–291

Lageron A, Paraf A, Lévy VG (1984) Hepatoma after Thorotrast. Morphological and autoradiographic data. Acta Histochem 74:5–10

Lally JF (1993) Radiograph of the month. Thorotrast-induced hepatocellular carcinoma. Del Med J 65:93–94

Lambrianides AL, Askew AR, Lefevre I (1986) Thorotrast-associated mucoepidermoid carcinoma of the liver. Br J Radiol 59:791–792

Lanari EL, Jorg ME, Aguirre JA (1937) Résultats des recherches effectuées sur les blocages viscéraux en vue d'une exploration radiologique. Presse Med 89:1562

Langlois SL, Sterrett GF, Henderson DW (1977) Hepatosplenic silicosis. Australas Radiol 21:143–149

Larson B (1963) A case of postangiographic Thorotrast deposition and primary squamous cell carcinoma of the liver. Acta Pathol Microbiol Scand 58:389

Lecouvet F, Clapuyt P, Van Nieuwenhuyse JP, Everarts P, Baudrez V, Reding R, de Ville de Goyet J, Sokal E, Otte JB (1996) Primary calcification in post-transplantation lymphoproliferative disorder involving the hepatic graft: an exceptional finding. Pediatr Radiol 26:152–154

Lee FI, Tharakan J, Vasudev KS, Isaacs PE (1996) Malignant hepatic tumours associated with previous exposure to Thorotrast: four cases. Eur J Gastroenterol Hepatol 8:1121–1124

Leitner ZA (1965) Sequelae of Thorotrast. Br Med J 2:1062–1063

Levine C (1990) Primary macronodular hepatic tuberculosis: US and CT appearances. Gastrointest Radiol 15:307–309

Levy H (1960) Histiocytic, node-shaped, nontumor-like proliferations of the liver, spleen and lymph nodes after thorotrast injection. A case with characteristic eosinophil substance around the Thorotrast deposits in the spleen (in German). Frankf Z Pathol 70: 423–446

Lewis JH, Sundeen JT, Simon GL, Schulof RS, Wand GS, Gelfand RL, Miller H, Garrett CT et al (1985) Disseminated talc granulomatosis. An unusual finding in a patient with acquired immunodeficiency syndrome and fatal cytomegalovirus infection. Arch Pathol Lab Med 109:147–150

Li Q, Jiang Q, Pfender E, Varadi A, Uitto J (2009) Pseudoxanthoma elasticum: clinical phenotypes, molecular genetics and putative pathomechanisms. Exp Dermatol 18:1–11

Lipshutz GS, Brennau TV, Warren RS (2002) Thorotrast-induced liver neoplasia: a collective review. J Am Coll Surg 195:713–718

Liu YC, Tomashefski J, McMahon JT, Petrelli M (1991) Mineral-associated hepatic injury: a report of seven cases with X-ray microanalysis. Hum Pathol 22:1120–1127

Liu D, Momoi H, Li L, Ishikawa Y, Fukumoto M (2002) Microsatellite instability in Thorotrast-induced human intrahepatic cholangiocarcinoma. Int J Cancer 102:366–371

Liu D, Wada I, Tateno H, Ogino D, Suzuki M, Lu W, Kojiro M, Fukuyama M, Okabe H, Fukumoto M (2004) Allelotypic characteristics of Thorotrast-induced intrahepatic cholangiocarcinoma: comparison to liver cancers not associated with Thorotrast. Radiat Res 161:235–243

Lüdin M (1953) Hemangioendotheliomatosis of liver and spleen after administration of thorium dioxide sol (Thorotrast) (in German). Schweiz Z Allg Pathol 16:987–994

Lüdin M, Scheidegger S (1944) Thorotrast-Dépot in der Milz nach Gehirn-Arteriographie. Radiol Clin (Basel) 13:73–75

Lynch KM (1942) Silicosis of systemic distribution. Am J Pathol 18:313

MacKay JS, Ross RC (1964) Hepatoma induced by thorium dioxide (Thorotrast). Can Med Assoc J 94:1298–1303

MacMahon E, Murphy AS, Bates MI (1947) Endothelial cell sarcoma of the liver following Thorotrast injection. Am J Pathol 23:585–613

Maeda E, Uozumi K, Kato N, Akahane M, Inoh S, Inoue Y, Beck Y, Goto A, Mahuuchi M, Ohtomo K (2006) Magnetic resonance findings of bile duct adenoma with calcification. Radiol Med 24:459–462

Malamud SW, Berra JL (1964) Chronic cholangiohepatitis (Role of Thorotrast) (in Spanish). Dia Med 36:378

Mariani-Costantini R, Jannotta FS, Johnson FB (1982) Systemic visceral talc granulomatosis with miliary tuberculosis in a drug addict. Am J Clin Pathol 78:785–789

Marti Vicente A, Gonzalez Carro P, Enriquez J, Vilardell F (1993) Thorotrast-related hepatosis (in Spanish). Rev Esp Enferm Dig 83:16–19

Masamichi K, Yoshiro K, Hiroshi K, Toshiro N, Hidefumi I (1982) Thorotrast-induced hepatic angiosarcoma, and combined hepatocellular carcinoma and cholangiocarcinoma in a single patient. Cancer 49:2161–2164

Masbou J, Valmary J, Bili H, Coutant G, Algayres JP, Arborio M, Sarrazin JL, Vicq P et al (1995) Simultaneous hepatic cholangiocarcinoma and bone fibrosarcoma 45 years after ingestion of Thorotrast (in French). Gastroenterol Clin Biol 19:120–122

Matthes TH (1956) Development of a carcinoma in a Thorotrast-fibrotic liver. Strahlentherapie 99:94–106

McInroy JF, Gonzales ER, Miglio JJ (1992) Measurement of Thorium isotopes and 228Ra in soft tissue and bones of a deceased Thorotrast patient. Health Phys 63:54–71

Miele AJ, Edmonds HW (1963) Calcified liver metastases: a specific roentgen diagnostic sign. Radiology 80:779–785

Milstein MJ, Moulton JS (1993) Diffuse hepatic calcification after ischemic liver injury in a patient with chronic renal failure. AJR Am J Roentgenol 161:75–76

Min KW, Gyorkey F, Cain GD (1974) Talc granulomata in liver disease in narcotic addicts. Arch Pathol 98:331–335

Miranda RN, McMillan PN, Pricolo VE, Finkelstein SD (1996) Peritoneal silicosis. Arch Pathol Lab Med 120:300–302

Miserocchi G, Sancini G, Mantegazza F, Chiappino G (2008) Translocation pathways for inhaled asbestos fibers. Environ Health 7:4

Mitchell AW, Higgins JN, Tate J, Dick R (1994) Rim calcification in primary liver cell carcinoma mimicking hydatid disease. Gut 35:567–568

Möbius G, Lembke K (1963) Thorotrast tumours of the liver. Zentralbl Allg Pathol 105:41–56

Moenandar IM (1974) Extensive calcification in the stroma of primary hepatic carcinoma. J Pathol 114:53–54

Mohr CP, Kaup FG, Gossmann HH, Teschke R (1984) Hemangioendothelioma of the liver 38 years after administration of thorium dioxide (in German). Z Gastroenterol 22:153–157

Mollo F, Bellis D, Magnani C, Delsedime L, Andrion A (1993) Hyaline splenic and hepatic plaques. Correlation with cirrhosis, pulmonary tuberculosis, and asbestos exposure. Arch Pathol Lab Med 117:1017–1021

Molos MA, Litton N, Schubert TT (1987) Talc liver. J Clin Gastroenterol 9:198–203

Momose T, Masuda S, Kiyose H, Tabata N (1966) Adverse effect of Thorotrast causing hepatic cirrhosis-like symptoms (in Japanese). Naika 18:965–972

Monma N, Iwasaki T, Masuda T, Satodate R (1987) Light an electron microscopic observation on the process of tissue calcification in a case of parathyroid adenoma. Acta Pathol Jpn 37:1621–1635

Morant R, Rüttner JR (1987) Late complications of Thorotrast. Experiences from Zurich (in German). Schweiz Med Wochenschr 117:952–957

Morgan A, Jayne W, Marrack D (1958) Primary liver cell carcinoma 24 years after intravenous injection of Thorotrast. J Clin Pathol 11:7–18

Mori T, Sakai T, Nozue Y, Okamoto T, Wada T, Tanaka T, Tsuya A (1967) Malignancy and other injuries following Thorotrast administration. Follow-up study of 147 patients in Japan. Strahlentherapie 134:229–254

Mori T, Kato Y, Aoki N, Hatakeyama S (1983) Statistical analysis of Japanese Thorotrast-administered autopsy cases – 1980. Health Phys 44(Suppl 1):281–292

Mori T, Kido C, Fukutomi K, Kato Y, Hatakeyama S, Machinami R, Ishikawa Y, Kumatori T et al (1999a) Summary of entire Japanese Thorotrast follow-up study: updated 1998. Radiat Res 152(Suppl 6): S84–S87

Mori T, Fukutomi K, Kato Y, Hatakeyama S, Machinami R, Tanooka H, Ishikawa Y, Kumatori T

(1999b) 1998 results of the first series of follow-up studies on Japanese Thorotrast patients and their relationships to an autopsy series. Radiat Res 152(Suppl 6): S72–S80

Mosinger M, Fiorentini H, El Feki M, Cartouzou G (1957) Sur les réactions locales et générales consécutives à l'administration intrapéritoneale de fortes quantitésde silice. Arch Mal Prof 18:781

Murai Y, Kitagawa M (2000) Autopsy cases of asbestosis in Japan: a statistical analysis on registered cases. Arch Environ Health 55:447–452

Murphy JE, Tedbury PR, Homer-Vanniasinkam S, Walker JH, Ponnambalam S (2005) Biochemistry and cell biology of mammalian scavenger receptors. Atherosclerosis 182:1–15

Naeye RL (1971) The anthracotic pneumoconioses. Curr Top Pathol 55:37–68

Nagakura S, Shirai Y, Yamai K, Hatakeyama K (1999) Calcification in mucinous cholangiocellular carcinoma. Hepatogastroenterology 46:465–466

Naide W, Matz R, Spear PW (1968) Cholangiocarcinoma causing hypercalcemia and hypophosphatemia without skeletal metastases (pseudohyperparathyroidism). Am J Dig Dis 13:705–708

Nettleship A, Fink WJ (1961) Neoplasms of the liver following injection of Thorotrast. Am J Clin Pathol 35:422–426

Nguyen DL, Leonard JC (1986) Ischemic hepatic necrosis: a cause of fetal liver calcification. AJR Am J Roentgenol 147:596–597

Nyberg U, Nilsson B, Travis LB, Holm LE, Hall P (2002) Cancer incidence among Swedish patients exposed to radioactive Thorotrast: a forty year follow-up survey. Radiat Res 157:419–425

Obiditsch R, Obiditsch-Mayer J (1954) Morphologische und funktionelle Veränderungen des retikulohistiozytären Systens bei Thorotrastschäden. Verh Dtsch Path ges 37:244

Odegaard A, Ophus EM, Larsen AM (1978) Identification of thorium dioxide in human liver cells by electron microscopic X-ray microanalysis. J Clin Pathol 31:893–896

Oka M (1930) Klinische Anwendung der "Lienographie", einer neuen Methode zur roentgenologischen Darstellung von Milz und Leber. Fortschr Roentenstr 41:892–898

Okamoto T (1974) Hepatic cholangiocarcinoma in Syrian hamster induced by Thorotrast administration (in Japanese). Nippon Igaku Hoshasen Gakkai Zasshi 34:254–266

Okuda K, Omata M, Itoh Y, Ikezaki H, Nakashima T (1981) Peliosis hepatis as a late and fatal complication of Thorotrast liver disease. Report of five cases. Liver 1:110–122

Oldenburg WA, van Heerden JA, Sizemore GW, Abboud CF, Sheedy PF (1982) Hypercalcemia and primary hepatic tumors. Arch Surg 117:1363–1366

Oliveira EA, Saragoça A, Oliveira MP, Tavares MH, Horta JS (1979) Thorium dioxide and the liver – scintigraphic aspects. Environ Res 18:216–217

Omata M, Peters RL, Tatter D (1981) Sclerosing hepatic carcinoma: relationship to hypercalcemia. Liver 1:33–49

Orth J (1917) Pathologisch-anatomische Diagnostik, 8th edn. Verlag von August Hirschwald, Berlin

Ortuno G, Sampedro A (1974) Hepatosplenic silicosis (in Spanish). Rev Clin Esp 135:161–169

Ortuno Pacheco G, Sampedro Nuno A (1975) Hepatic silicosis. Analysis of 21 cases (in Spanish). Rev Esp Enferm Apar Dig 46:107–130

Oswald P, Filippi de la Palavesa MM, Uhl G, Ghnassia JP, Doffoel M, Dietemann JL (1995) Hepatosplenic silicosis (in French). J Radiol 76:513–516

Pai SS, Bude RO (2002) Sonographic appearance of extensive hepatic arterial calcification mimicking pneumobilia. J Clin Ultrasound 30:38–41

Palecanda A, Paulauskis J, Al-Mutairi E, Imrich A, Qin G, Suzuki H, Kodama T, Tryggvason K et al (1999) Role of the scavenger receptor MARCO in alveolar macrophage binding of unopsonized environmental particles. J Exp Med 189:1497–1506

Paley MR, Ros PR (1998) Hepatic calcification. Radiol Clin North Am 36:391–398

Pandolfo I, Blandino G, Scribano E, Longo M, Certo A, Chirico G (1984) CT findings in hepatic involvement by *Echinococcus granulosus*. J Comput Assist Tomogr 8:839–845

Person DA, Isaac E (1964) Thorotrast induced carcinoma of the liver. Arch Surg 88:503–510

Piguet PF, Collart MA, Grau GE, Sappino AP, Vassalli P (1990) Requirement of tumor necrosis factor for development of silica-induced pulmonary fibrosis. Nature 344:245–247

Pimental JC, Menezes AP (1978) Pulmonary and hepatic granulomatous disorders due to the inhalation of cement and mica dusts. Thorax 33:219–227

Polacarz SV, Laing RW, Loomes R (1992) Thorotrast granuloma: an unexpected diagnosis. J Clin Pathol 45:259–261

Polachek AA, Pijanowski WJ (1960) Extrathoracic egg-shell calcification in silicosis. Am Rev Respir Dis 82:714–720

Pollice L, Molinini R, Paoletti L, Batisti D, Caruso G, Di Nunno C, Gentile A (1997) Asbestos fiber count in extra-pulmonary tissues (in Italian). G Ital Med Lav Ergon 19:39–41

Pons JC, Teyssau H, Bureau M, Ruiz R, Surzur J, Tessier JP (1981) Hepatic calcifications in isolated necrotizing, granulomatous hepatitis due to Brucella. A case report and review of the literature (in French). J Radiol 62:521–525

Popper H, Thomas LB, Telles NC, Falk H, Selikoff IJ (1978) Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast, and arsenic: comparison with cases of unknown etiology. Am J Pathol 92:349–376

Poti A, Genovese MG, Benincasa A, Bosio C, Torchio B, Nobile D, Garberoglio R (1980) Radiological signs of a disease that is dying out: hepato-splenic atrophy and

cholangiocarcinoma after administration of thorium dioxide (Thorotrast) (in Italian). Minerva Med 71:3229–3234
Pounder DJ (1983) Malarial pigment and hepatic anthracosis. Am J Surg Pathol 7:501–502
Pounder DJ (1985) Hepatocellular calcification. Pathology 17:115–118
Price PA, Toroian D, Lim JE (2009) Mineralization by inhibitor exclusion: the calcification of collagen with fetuin. J Biol Chem 284:17092–17101
Przygodski RM, Finkelstein SD, Keohavong P, Zhu D, Bakker A, Swalsky PA, Soini Y et al (1997) Sporadic and Thorotrast-induced angiosarcomas of the liver manifest frequent and multiple point mutations of K-ras-2. Lab Invest 76:153–159
Quinlan MF, Scopa J (1976) Thorotrast-induced haemangioendothelial sarcoma – a lesson from the past. Aust N Z J Med 6:329–335
Racela LS, Papasian CJ, Watanabe I, McGregor DH, Lee SH, Talley R (1988) Systemic talc granulomatosis associated with disseminated histoplasmosis in a drug abuser. Arch Pathol Lab Med 112:557–560
Radhakrishnan S, Al Nakib B, Sivanandan R, Menon NK (1988) Hepatosplenic and small bowel calcification due to *Schistosoma mansoni* infection. Dig Dis Sci 33:1637–1640
Rakov HL, Smalldon TR, Derman H (1963) Hepatic hemangioendo-theliosarcoma. Report of a case due to thorium. Arch Intern Med 112:173–178
Rao BK, Brodell GK, Haaga JR, Whitlatch S, Chiu LC (1986) Visceral CT findings associated with Thorotrast. J Comput Assist Tomogr 10:57–61
Ratajewski M, Boussac H, Pulaski L (2009) Liver-specific enhancer in ABCC6 promoter – functional evidence from natural polymorphisms. Biochem Biophys Res Commun 383:73–77
Reeder MM (1975) Liver calcification. Semin Roentgenol 10:171
Ringpfeil F, Pulkkinen L, Uitto J (2001) Molecular genetics of pseudoxanthoma elasticum. Exp Dermatol 10:221–228
Ritterhoff RJ (1941) Acute silicosis occurring in employees of abrasive soap powder industries. Am Rev Respir Dis 42:117
Rizzo AJ, Haller JO, Mulvihill DM, Cohen HL, Da Silva MG (1989) Calcification of the ductus venosus: a case of right upper quadrant calcification in the newborn. Radiology 173:89–90
Roberts J, Carlson K (1956) Hepatic duct carcinoma seventeen years after injection of thorium dioxide. AMA Arch Pathol 62:1–7
Rosenbaum FJ (1959) Hepatic sarcoma after Thorotrast. Dtsch Med Wochenschr 84:428–433
Rota AN, Weindling HK, Goodman PG (1971) Cholangiocarcinoma associated with thorium dioxide (Thorotrast): report of a case. Mich Med 70:911–915
Rotter W (1950) Ueber Gewebeschäden durch Thorotrast unter besonderer Berücksichtigung der Gefässveränderungen und aplastischer Knochenmarkreaktionen. Beitr Pathol Anat 111:144
Roussy G, Oberling C, Guerin M (1934) Action cancerigène du dioxide du thorium chez le rat blanc. Bull Acad Med 112:809
Roussy G, Oberling C, Guerin M (1936) Über Sarkomerzeugung durch kolloidales Thoriumdioxid bei der weissen Ratte. Strahlentherapie 56:160–167
Rubel LR, Ishak KG (1982) Thorotrast-associated cholangiocarcinoma: an epidemiologic and clinicopathologic study. Cancer 50:1408–1415
Ruiz Carazo E, Munoz Parra F, Jimenez Villares MP, del Mar Catellano Garcia M, Moyano Calvente SL, Medina Benitez A (2005) Hepatosplenic brucelloma: clinical presentation and imaging features in six cases. Abdom Imaging 30:291–296
Sahani D, Prasad SR, Tannabe KK, Hahn PF, Mueller PR, Saini S (2003) Thorotrast-induced cholangiocarcinoma: case report. Abdom Imaging 28:72–74
Sakai K, Shiina M, Ishihara N, Kato Y (1984) Thorotrast-induced multiple primary malignant tumors of the liver – cholangiocarcinoma and malignant hemangioendothelioma. Jpn J Clin Oncol 14:411–416
Sampedro Nuño A, Pérez-Guillermo Garcia M, Ortuño Pacheco G (1985) Extrathoracic anthracosis (in Spanish). Med Clin (Barcelona) 85:168–169
Sanchez Perez MA, Rodriguez Perez A, Geijo Martinez F, Gonzalez San Martin F, Rodriguez Rincon M, Rodrigo Rodriguez M (1995) Calcified hepatic metastases as the first manifestation of colonic cancer (in Spanish). Rev Esp Enferm Dig 87:268–269
Sano Y, Nakamura S, Kitazawa T et al (1985) Focal nodular hyperplasia-like lesion of the liver associated with Thorotrast liver disease – report of a case. Gan To Kagaku Ryoho 31:1445–1450
Sasaki et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19195066
Scatarige JC, Fishman EK, Saksouk FA, Siegelman SS (1983) Computed tomography of calcified liver masses. J Comput Assist Tomogr 7:83–89
Scherer U, Weinzierl M, Sturm R, Schildberg FW, Zrenner M, Lissner J (1978) Computed tomography in hydatid disease of the liver: a report on 13 cases. J Comput Assist Tomogr 2:612–617
Schmid C, Beham A (1987) Angiosarcoma of the liver and renal cell carcinoma with panmyelopathy following Thorotrast administration 40 and 41 years ago. Case reports with immunohistochemical studies (in German). Pathologe 8:177–182
Schmidt W, Schulte AS, Lapp H (1950) Klinischer und anatomisch-pathologischer Beitrag zur Frage der Schädigung durch Thorotrast (Panmyelopathie nach Thorotrastinjektion vor 10 Jahren). Strahlentherapie 81:93
Schmidt JA, Oliver CN, Lepe-Zuniga JL, Green I, Grey I (1984) Silica-stimulated monocytes release fibroblast proliferation factors identical to interleukin-1. A

potential role for interleukin-1 in the pathogenesis of silicosis. J Clin Invest 73:1462–1472
Schröder JS (1959) Calcification in the liver. J Med Assoc Ga 48:398
Selmair H, John HD (1970) Clinical aspects and pathology of Thorotrast-damaged liver (in German). Med Welt 26:1203–1208
Shackelford GD, Kirks DR (1977) Neonatal hepatic calcification secondary to transplacental infection. Radiology 122:753–757
Sharp GB (2002) The relationship between internally deposited alpha-particle radiation and subsite-specific liver cancer and liver cirrhosis: an analysis of published data. J Radiat Res (Tokyo) 43:371–380
Shen F, Fan X, Liu B, Jia X, Gao A, Du H, Ye M, You B, Huang C, Shi X (2008) Downregulation of cyclin D1-CDK4 protein in human embryonic lung fibroblasts (HELF) induced by silica is mediated through the ERK and JNK pathway. Cell Biol Int 32:1284–1292
Sherman KE, Lewey SM, Goodman ZD (1995) Talc in the liver of patients with chronic hepatitis C infection. Am J Gastroenterol 90:2164–2166
Shibuya A, Sugimoto T, Yamakado M, Tagawa H, Unuma T, Yamaguchi T, Machii K, Tanaka S (1985a) A case of chronic renal failure with diffuse hepatic and myocardial calcification (in Japanese). Nippon Naika Gakkai Zasshi 74:1257–1264
Shibuya A, Unuma T, Sugimoto T, Yamakado M, Tagawa H, Tagawa K, Tanaka S, Takanashi R (1985b) Diffuse hepatic calcification as a sequela to shock liver. Gastroenterology 89:196–201
Shimauchi T, Shioya S, Suwa N, Yokoyama Y (1949) An autopsy case of the cerebellum tumor who was administered thorium colloid for hepatolienography 18 years before (in Japanese). Nisshin Igaku 35:506–511
Silverman PM, Ram PC, Korobkin M (1983) CT appearance of abdominal Thorotrast deposition and Thorotrast-induced angiosarcoma of the liver. J Comput Assist Tomogr 7:655–658
Sitarik K, Freed KS, Sheafor DH (1999) Thorotrast revisited: contrast-induced hepatic neoplasm. Am J Roentgenol 172:842–843
Slavin RE, Swedo JL, Brandes D, Gonzalez-Vitale JC, Osornio-Vargas A (1985) Extrapulmonary silicosis: a clinical, morphologic, and ultrastructural study. Hum Pathol 16:393–412
Smoron GI, Battifora HA (1972) Thorotrast-induced hepatoma. Cancer 30:1252–1259
Soyer P, Roche A, Levesque M, Legmann P (1991) CT of fibrolamellar hepatocellular carcinoma. J Comput Assist Tomogr 15:533–538
Srinavasan R, Dean HA (1997) Thorotrast and the liver – revisited. J Toxicol Clin Toxicol 35:199–202
Steiner MA, Giles HW (2008) Mesenchymal hamartoma of the liver demonstrating peripheral calcification in a 12-year-old boy. Pediatr Radiol 38:1232–1234
Stemmermann G (1960) Adenocarcinoma of the intrahepatic biliary tree following Thorotrast. Am J Clin Pathol 32:446–454
Stoupis C, Taylor HM, Paley MR, Buetow PC, Marre S, Baer HU, Vock P, Ros PR (1998) The rocky liver: radiologic-pathologic correlation of calcified hepatic masses. Radiographics 18:675–685
Suchow E, Henegar GC, Baserga R (1961) Tumors of the liver following administration of Thorotrast. Am J Pathol 38:663–677
Sugiura H, Yoshida K, Nakanuma Y, Ohta G, Izumino K, Takazakura H (1987) Hepatic calcifications in the course of hemodialysis. Am J Gastroenterol 82:786–789
Szanto PB (1975) Morphologic findings in the narcotic addict. Int Surg 60:331–334
Szendröi M, Németh L, Vajta G (1983) Asbestos bodies in a bile duct cancer after occupational exposure. Environ Res 30:270–280
Takagi H, Hasebe M (1972) Case of hepatic fibrosis caused by Thorotrast and statistical observation on occurrence of late Thorotrast complication (in Japanese). Naika 29:185–191
Talenti E, Cesaro S, Scapinello A, Perale R, Zanesco L (1994) Disseminated hepatic and splenic calcifications following cat-scratch disease. Pediatr Radiol 24:342–343
Tateno H, Hosoda S, Yamada S, Kido C (1984) Proliferative lesions in Thorotrast-deposited livers pertaining to the development of primary cancers (in Japanese). Gan No Rinsho 30:23–34
Tavares MH, Saragoça A, Oliveira EA, Oliveira MP, Horta JS (1979) Thorium dioxide and the liver. up-dated clinical and biochemical findings. Environ Res 18:173–177
Taylor GN, Lloyd RD, Mays CW (1993) Liver cancer induction by 239Pu, 241Am, and Thorotrast in the grasshopper mouse, Onychomys leukogaster. Health Phys 64:141–146
Teefev SA, Stephens DH, Weiland LH (1987) Calcification in hepatocellular carcinoma: not always an indication of fibrolamellar histology. AJR Am J Roentgenol 149:1173–1174
Telles NC, Thomas LB, Popper H, Ishak KG, Falk H (1979) Evolution of Thorotrast-induced hepatic angiosarcomas. Environ Res 18:74–87
Terzaksi JA, Sommers SC, Snyder RW et al (1974) X-ray microanalysis of hepatic thorium depositions. Arch Pathol 98:241–242
Tesluk H, Nordin W (1955) Hemangioendothelioma of liver following thorium dioxide administration. AMA Arch Pathol 60:493–501
Tessmer CF, Chang JP (1967) Thorotrast localization by light and electron microscopy. Ann N Y Acad Sci 145:545–575
Thakur SA, Beamer CA, Miliaccio CT, Holian A (2009) Critical role of MARCO in crystalline silica-induced pulmonary inflammation. Toxicol Sci 108:462–471

Toroian D, Price PA (2008) The essential role of fetuin in the serum-induced calcification of collagen. Calcif Tissue Int 82:116–126

Toroian D, Lim JE, Price PA (2007) The size exclusion characteristics of type I collagen: implication for the role of noncollagenous bone constituents in mineralization. J Biol Chem 282:22437–22447

Travers B, Marie C, Belaiche J, Kalifat R, Cattan D (1983) A very rare cause of intrahepatic calcification: polycystic liver (in French). Gastroenterol Clin Biol 7:1039–1040

Travis et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1522013

Travis LB, Land CE, Andersson M et al (2001) Mortality after cerebral angiography with or without radioactive Thorotrast: an international cohort of 3143 two-year survivors. Radiat Res 156:136–150

Tsukamoto K (1968) Epidemiological study of Thorotrast induced malignancies in Japan. In: The Dosimetry and Toxicity of Thorotrast. IAEA, Vienna, pp 152–156

Uchiyama T (1928) Ueber die Chalicosis pulmonum in Japan. Beitr Path Anat Allg Path 80:218

Ueda H, Sasaki Y, Mori M, Yamamoto M, Saito S (1966) Case of hepatic cirrhosis due to Thorotrast and a review of the literature (in Japanese). Naika 17:960–968

Uitto J, Li Q, Jiang Q (2010) Pseudoxanthoma elasticum: molecular genetics and putative pathomechanisms. J Invest Dermatol 130:661–670

Underwood JC, Huck P (1978) Thorotrast associated hepatic angiosarcoma with 36 years latency. Cancer 42:2610–2612

Vallenga IR (1962) A case of hemangiosarcoma of the liver 25 years after Thorotrast injection for cerebral angiography. J Belg Radiol 45:682–688

Van Genderen HO, Kenis H, Hofstra L, Narula J, Reutelingsperger CP (2008) Extracellular annexin A5: functions of phosphatidylserine-binding and two-dimensional crystallization. Biocheim Biophys Acta 1783:953–963

Van Kaick G, Wetsch H, Lührs H, Liebermann D, Kaul A (1991) Neoplastic diseases induced by chronic alpha-irradiation – epidemiological, biophysical and clinical results of the German Thorotrast Study. J Radiat Res 32:20–33

Van Kaick G, Bahner ML, Liebermann D, Lührs H, Wesch H (1999) Thorotrast-induced liver cancer: results of the German Thorotrast study (in German). Radiologe 39:643–651

Van Kampen RJW, Erdkamp FLC, Peters FPJ (2007) Thorium dioxide-related haemangiosarcoma of the liver. J Med 65:279–282

Vanakker OM, Voet D, Petrovic M, van Robaeys F, Leroy BP, Coucke P, de Paepe A (2006) Visceral and testicular calcifications as part of the phenotype in pseudoxanthoma elasticum: ultrasound findings in Belgian patients and healthy carriers. Br J Radiol 79:221–225

Vanakker OM, Martin L, Schurgers LJ, Quaglino D, Costrop L, Vermeer C, Pasquali-Ronchetti I et al (2010) Low serum vitamin K in PXE results in defective carboxylation of mineralization inhibitors similar to the GGCX mutations in the PXE-like syndrome. Lab Invest 90:895–905

Vanhaecke J, Hendrickx H, Fevery J, Baert A, Vandenbroucke J, de Wolf-Peeters C, Desmet V, de Groote J (1979) Liver cirrhosis and cholangiocarcinoma following Thorotrast administration (in Dutch). Ned Tijdschr Geneeskd 123:2218–2223

Vanhoenacker FM, Van den Brande P, De Schepper AM (2001) Hepatosplenic anthracosilicosis: a rare cause of splenic calcifications. Eur Radiol 11:1184–1186

Visfeldt J, Poulsen H (1972) On the histopathology of liver and liver tumours in thorium-dioxide patients. Acta Pathol Microbiol Scand A 80:97–108

Von Meyenburg H (1946) Pathologisch-anatomische Demonstrationen z.T. in Verbindung mit den behandelnden Ärzten. Schweiz Med Wochenschr 76:41

Wachtel MS, Khettry U, Arkin CF (1992) Tissue calcification after orthotopic liver transplantation. An autopsy study. Pathol Lab Med 116:930–933

Wegener K, Wesch H (1979) Pathological changes of lymph nodes in Thorotrast patients: pathoanatomical, autoradiographical, and quantitative investigations. Environ Res 18:245–255

Wegener K, Wesch H, Kampmann H (1976) Investigations into human thorotrastosis. Tissue concentrations of 232-Th and late effects in 13 autopsy cases. Virchows Arch A Pathol Anat Histol 371:131–143

Weigert C (1883) Ueber den Eintritt des Kohlepigments aus den Atmungsorganen in den Blutkreislauf (On the entry of coal pigment of respiratory organs into the blood circulation). Fortschr Med 1:441

Weiss B, Horstkotte W, Lindemann B, Kohler H (1972) Highly calcified liver carcinoma. Contribution to the differential diagnosis of liver calcification (in German). Munch Med Wochenschr 114:538–542

Welch WH (1891) Cirrhosis hepatis anthracotica. Johns Hopkins Hosp Bull 2:32–33

Wesch H, Riedel W, Hasenöhrl K, Wegener K, Kaul A, Muth H, van Kaick G (1985) German Thorotrast study: results of the long-term animal studies on the effect of incorporated radioactive and nonradioactive particles. Strahlentherapie Sonderb 80:186–188

White LM, Wilson SR (1994) Hepatic arterial calcification: a potential pitfall in the sonographic diagnosis of intrahepatic biliary calculi. J Ultrasound Med 13:141–144

Williams AO, Knapton AD (1996) Hepatic silicosis, cirrhosis, and liver tumors in mice and hamsters: studies of transforming growth factor beta expression. Hepatology 23:1268–1275

Williams MG, Dodson RF, Dickson EW, Fraire AE (2001) An assessment of asbestos body formation in extrapulmonary sites: liver and spleen. Toxicol Ind Health 17:1–6

Yamada S, Hosoda S, Tateno H et al (1983) Survey of Thorotrast-associated liver cancers in Japan. J Natl Cancer Inst 70:31–35

Yamada S, Sanefuji H, Morimoto H, Harada Y, Mine S, Morimoto I, Eto S (2000) Parathyroid hormone-related peptide producing cholangiocellular carcinoma with a marked psammoma formation. J Gastroenterol Hepatol 15:1442–1446

Yamamoto Y, Usuda N, Takatsuji T, Kuwahara Y, Fukumoto M (2009) Long incubation period for the induction of cancer by Thorotrast is attributed to the uneven irradiation of liver cells at the microscopic level. Radiat Res 171:494–503

Yamamoto Y, Usuda N, Oghiso Y, Kuwahara Y, Fukumoto M (2010) The uneven irradiation of a target cell and its dynamic movement can mathematically explain incubation period for the induction of cancer by internally deposited radionuclides. Health Phys 99:388–393

Yamasaki I, Tagata K, Hamamoto Y, Goto S, Teshima M, Eguchi S, Ishitobi S (1977) An autopsy case of calcifying cholangiocellular carcinoma. Yonago Acta Med 21:127–131

Yamasaki K, Yamasaki A, Tosaki M, Isozumi Y, Hiai H (2004) Tissue distribution of Thorotrast and role of internal irradiation in carcinogenesis. Oncol Rep 12:733–738

Yasumizu R, Amoh Y, Ikehara S (1999) Identification of Thorotrast by gamma-spectrometry and simplified autoradiography in pathological specimens. Pathol Int 49:737–741

Yuan CY, Yuan CC, Shieh JC, Chen DY (1988) Hepatic granuloma manifested as a pseudotumor with calcification: report of a case. Taiwan Yi Xue Hui Za Zhi 87:1121–1124

Yuda K, Nagashima T, Yamazaki N, Kutsukata A, Kawakami H (1969) Autopsy case of cancer of the bile duct presumably caused by Thorotrast accumulation (in Japanese). Iryo 23:241–246

Zhu AX, Lauwers GY, Tanabe KK (2004) Cholangiocarcinoma in association with Thorotrast exposure. J Hepatobiliary Pancreat Surg 11:430–433

Tumor-Like Lesions of the Hepatobiliary Tract Caused by Gallstones, Foreign Bodies, and Bile

124

Contents

Abstract

Gallstones, foreign bodies, and bile can induce tumor-like lesions in the hepatobiliary tract. Dropped or impacted gallstones can induce a vigorous inflammatory reaction followed by fibrosis and scarring, and eventually production of a pseudotumor. Medical material can elicit a foreign body reaction in the hepatic area, sometimes imitating a neoplastic process. Materials known to be involved include cotton pledgets, cloth, cottonoids, and several textiles, giving rise to "textilomas" and "gossypibomas." Similarly, ingested foreign bodies that migrate to the hepatic area can induce mass-forming foreign body reactions. Other materials that elicit such reactions comprise embolized particulate materials and bile accumulations (bilomas).

Gallstones and Gallstone Fragments

Some authors reported that as many as a third of all laparoscopic cholecystectomies are complicated by dropped gallstones (Sathesh-Kumar et al. 2004; Lohan et al. 2005; Tumer et al. 2005). Gallstones may also be dropped in the course of open cholecystectomy, but they are easier to retrieve due to larger operating field (Sathesh-Kumar et al. 2004). The main complications of dropped gallstones include localized or systemic infections, abscess formation, adhesions, fibrosis, ileus, and formation of fistulas

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_124

(Zamir et al. 1999). It was estimated that dropped gallstones cause an intra-abdominal abscess in 0.6–2.9 % of cases of dropped gallstones and bile spillage (Rice et al. 1997; Morrin et al. 2000; Lohan et al. 2005). The abscesses can obstruct the digestive tract or drain into the digestive tract to cause a communicating abscess. Abscesses may open into the peritoneal cavity and hence cause an empyema (Roberts and Chun 2005). Dropped gallstones can favor the development of actinomycosis (Ramia et al. 2004). Draining abscesses and their fistulas can cause communications of abdominal hollow organs with each other or create communications between bowel and skin (enterocutaneous fistula) and rarely between the abdominal cavity and the bronchial tree with formation of broncholithiasis (Noda et al. 1998). Gallstone-associated abscesses may develop with considerable delay, e.g., 5 years after laparoscopic cholecystectomy (Awwad et al. 2010). Due to inflammatory infiltrates with foreign body reaction and subsequent fibrosis, dropped gallstones can produce mass lesions that may mimic tumors, e.g., colon cancer (Perl et al. 2009). Intraperitoneal gallstone granulomas can be formed (Warren and Wyatt 1996; Tham and Ng 2001). Intraperitoneal abscesses developing around gallstones can invade the liver substance (Mahmood et al. 2008). In the liver, late abscesses after spilled gallstones can induce a liver mass mimicking malignancy (Casillas and Kittur 2003). Gallstone-induced abscesses rarely encircle the extrahepatic bile ducts, causing stenosis and obstructive jaundice (Stevens et al. 2003).

Hepatic Foreign Body Reactions Caused by Medical Material

Among surgical hemostatic agents, some are nonresorbable and are removed (various types of cotton pledgets; cloth such as muslin; synthetic rayon hemostats, such as cottonoids and kites). Muslin is a cotton fabric used to provide reinforcement, e.g., of vessel walls, and is composed of transparent fibers that are apparent under polarized light. Cottonoids and kites are synthetic strips and pledgets composed of rayon fibers containing a filament or strip impregnated with radiopaque barium sulfate. Conversely, bioabsorbable hemostats are often left in the surgical bed. They mainly include gelatin foam (Gelfoam), oxidized cellulose (Oxycel), and microfibrillar collagen. Nonresorbable material left in the body will produce a marked foreign body reaction, and this inflammation together with subsequent fibrosis can induce a pseudotumor. Several terms have been coined to denote these lesions, depending on the material involved. A textiloma is a mass ("oma") developing around a retained textile. The term, gossypiboma, is more complex and somewhat exotic; it derives from a genus of cotton plants, *Gossypium*, and a Kiswahili term, "borna," meaning "a place of concealment." A gauzoma contains surgical gauze, and a muslinoma is a pseudotumor induced by retained muslin (Ezaki et al. 1994; Farina et al. 1995; Zbar et al. 1998; Rajagopal and Martin 2002; Tacyildiz and Aldemir 2004). Pseudotumorous subhepatic gauzomas have been observed postcholecystectomy (Sok et al. 1989). Retained surgical swabs prodding a gossypiboma can produce a distinct CT features characterized by a calcified reticulate rind sign (Cerwenka et al. 2005; Lu et al. 2005). In case gossypibomas or gauzomas are located to the liver's surface, they may mimic a hepatic tumor, and intrahepatic foreign body granulomas may be confounded with liver metastasis (Poyanli et al. 2005). Oxidized cellulose ("Oxycel") can induce a granulomatous reaction in the liver, with formation of a pseudotumor (Bradley and Singh 1991). Thick gelfoam slurry used to embolize a hepatic needle biopsy tract was found to migrate to the common bile duct and the gallbladder (Riddle et al. 2008). Subcapsular hepatic abscess has been described as a rare complication of ventriculoperitoneal shunt (Reddy 1987). Also embolized foreign material particles can produce masses (see below; Murakata et al. 2006). Hepatic seed implant embolization was observed after prostate brachytherapy (Nguyen 2006).

Hepatic Inflammatory Masses, Abscesses, and Pseudotumors Caused by Ingested Foreign Bodies

Rarely, sharp objects may penetrate the intestinal tract and subsequently involve the liver, a complication already described in 1955 (Griffiths 1955). About 80–90 % of ingested foreign bodies pass through the gastrointestinal tract within 1 week, and perforation has been observed in less than 1 % of the patients. In the majority of cases, the left liver lobe is involved (Horii et al. 1999). Most foreign bodies migrating to the liver take their origin from the stomach and the duodenum, but the gut (Harjai 2000; Kumar and Gupta 2000) and colon (specifically the transverse colon) are also known as a source (Houli et al. 2003). A small set of foreign bodies clearly dominate the situation. Toothpicks can penetrate the upper GI tract and migrate into the liver, often causing a marked inflammatory reaction or even a liver abscess (Rafizadeh et al. 1981; Tsuboi et al. 1981; Bloch 1984; Pedersen et al. 1986; Cheung et al. 2000; Kanazawa et al. 2003; Chiang et al. 2006; Serwe et al. 2007; Stoica et al. 2007; Ammari et al. 2009; Liu et al. 2009; Glick et al. 2012). Migrating toothpicks can, in case of marked inflammatory response with fibroplasia, induce a hepatic pseudotumor (Del Fabbro et al. 2004). Hepatic complications with abscess formations are well known after migration of entire bones and bone fragments (particularly, fishbone) migrating from the stomach or the duodenum to the liver (Gower et al. 1961; Aron et al. 1966; Berk and Reit 1971; Gonzalez et al. 1988; Iwasa et al. 1988; Masunaga et al. 1991; Chan et al. 1999; Horii et al. 1999; De la Vega et al. 2001; Kessler and Kourtis 2001; Theodoropoulou et al. 2002; Goh et al. 2005; Starakis et al. 2005; Santos et al. 2007; Clarençon et al. 2008). Migrated fishbones are the most frequent cause of liver abscess (Gundara and Harrison 2010; Chen et al. 2011; Ng et al. 2011), sometimes with rupture (Kadowaki et al. 2007). Migrated fishbone was shown to induce a hepatic pseudotumor (Perera et al. 2007).

Ingested intact or broken needles can migrate from the stomach or the duodenum into the liver and cause an inflammatory response, sometimes with abscess formation (Abel et al. 1971; Acosta and Lantz 1996; Omejc 2002; Chintamani et al. 2003; Rahalkar et al. 2003; Azili et al. 2007; Akçam et al. 2009; Feng et al. 2009; Saitua et al. 2009; Jutte and Cense 2010; Senol et al. 2010). In few instances, intrahepatic sewing needles were found to remain for years without harm (Saitua et al. 2009; Senol et al. 2010). Exceptionally, ingested plant twigs such as rosemary can dislocate to the liver (Karamarkovic et al. 2007). Sometimes, unusual swallowed objects have caused colonohepatic penetration, e.g., a toothbrush (Lee et al. 2006). There are unusual types and origins of ingested foreign material. Systemic and particularly liver granulomatosis with noncaseating, giant cell-containing granulomas has been observed in a patient with malocclusion, bruxism, and worn dental prostheses, the foreign material in the granulomas being feldspars as a principal component of porcelain (Ballestri et al. 2001).

Metallic and Other Foreign Bodies Migrating From Places Other than the Digestive Tract

Apart from ingestion, needles may locate to the liver via penetration through the skin (Nishimoto et al. 2003; Azili et al. 2007). Hypodermic needles have been observed in peripheral parts of the liver, without marked foreign body reaction (Muddaiah and Varghese 2008). Dropped clips at laparoscopic interventions can cause infection, inflammation, intra-abdominal abscesses, and eventually sepsis (Labuski and Wise 1999; Hussain 2001). Ventriculoperitoneal shunts can show intrahepatic dislocation (Berkmann et al. 2011). They can also pass through the liver and diaphragm and migrate to the lung (Nazaroglu et al. 2009). Penetration of a fractured Bird's Nest filter strut into the liver substance has been described (Maleux et al. 2011). Dissemination of wear particles of the liver has been found in patients with hip or knee replacement (Urban et al. 2000).

Inflammatory Hepatic Mass Lesions Subsequent to Embolization of Particulate Matter

Embolotherapy of liver tumors has gained a role in the treatment of several neoplastic hepatic lesions. The embolization of particulate matter induces a foreign body reaction which is thought to contribute to the so-called postembolization syndrome (Siskin et al. 2003). Histologically, particles are found within the vascular lumina (sometimes with stretching of the vessels) and are in contact either with an intact endothelial layer, a denudated inner vascular surface, or with cells of the foreign body reaction. In situations of inflammation, the outer contour of the spherical particle may be irregular and in direct contact mainly with lymphocytes, monocytes/macrophages, and multinucleated giant cells. The thickness of the cellular rim encircling the particle is highly variable. At the periphery, the leukocytic and giant cell reaction is followed by a zone of fibroblast and myofibroblast proliferation, sometimes forming small nodular masses. In marked fibroplastic reactions, the contained vessels are deformed, causing a cobblestone shape or even a threadlike appearance of the remaining embolized particles (Stampfl et al. 2009). In rare situations, embolized material causes an inflammatory pseudotumor, e.g., cyanoacrylate hepatic pseudotumor (Velasco et al. 2005).

Biloma and Other Bile Accumulations

Introduction

Biloma is defined as an extraductal collection of bile within a newly formed intrahepatic or extrahepatic space. It is thought that biloma starts with bile leakage forming first a bile lake, which then increases in size to become a space-occupying lesion, viz., a biloma. Due to their presentation as a cystic mass, bilomas can mimic a hepatobiliary neoplastic process.

Causes and Clinic-Radiologic Features of Bilomas

A common basic mechanism and cause of bilomas is a defect in the biliary tract, induced by trauma, necrosis, and inflammatory changes. Bilomas have been observed in the setting of postoperative bile leakage after surgery (Vazquez et al. 1985), postcholecystectomy (Antonopoulos et al. 2009; Kannan et al. 2009), liver trauma (Esensten et al. 1983; Cañete Gomez et al. 2009), acute cholecystitis with gallbladder perforation (Tsai et al. 2009), bile duct necrosis secondary to transcatheter arterial chemoembolization for hepatocellular carcinoma or liver metastases (TACE; Kobayashi et al. 1993; Komatsu et al. 1998; Sakamoto et al. 2003; Chen et al. 2005), microsphere usage (Huang et al. 2007), radiofrequency ablation of hepatocellular carcinoma (Chang et al. 2010), endoscopic retrograde cholangiopancreatography (ERCP; Dupas et al. 1988), metastatic liver disease (Hiraki et al. 1998), hepatocellular carcinoma (Fritz et al. 1989), and bile leak from the duct of Luschka (Neumann et al. 2010). Liver infarction can rarely be associated with biloma. Sickle cell disease is known to produce several complications in the liver, such as cholelithiasis, intrahepatic cholestasis, hepatic crisis, cirrhosis, and infarction (Schubert 1986). An expanding intrahepatic bile-filled cyst representing a biloma has been reported, suggested to a consequence of liver infarction (Middleton and Wolper 1984; Lebensburger et al. 2008).

Ultrasound of bilomas shows cystic and well-circumscribed lesions with the echogenicity of protein-containing fluid (Gould and Patel 1979; Esensten et al. 1983; Kuligowska et al. 1983; Mueller et al. 1983). On CT, intrahepatic biloma appears as a more or less spherical, solitary, or multiple cystic area. But there are also cases which present as a branching appearance of hypoattenuating areas along Glisson's sheaths (Mueller et al. 1983; Sakamoto et al. 2003). Subcapsular hepatic cysts are also a known manifestation of biloma. Radiologically, a subcapsular

fluid collection is defined as fluid deep in the liver capsule and superficial to the liver parenchyma without rupture into the peritoneal cavity (Chen et al. 2009).

Pathology

Macroscopically, biloma is round or irregularly shaped collections of thin or sometimes viscous bile, resembling a bile-containing cyst. The color of the biloma fluid varies markedly, depending on the concentration of bile pigments and the contribution of exudate, blood, pus, and mucus, hence ranging from deep green yellow to brownish or reddish. Sometimes, intrahepatic bilomas are visualized as circumscribed bile accumulation with a bile duct in the center, i.e., bile collection within a Glisson tract.

Bile can flow from the biloma to adjacent tissue compartment, such as Glisson's sheaths and the subcapsular hepatic space. In bilomas developing secondary to bile duct and liver necrosis, e.g., post-chemoembolization, bile accumulates within the coagulative parenchymal necrosis (bile-stained or "yellow" necrosis). In case of neutrophil reaction, the histologic picture may resemble Charcot infarction. Bile accumulation is later demarcated by a fibrosing granulation tissue of variable thickness, with perifocal infiltration of lymphocytes and macrophages. The latter may pinocytose bile and eventually form bile granulomas. In case of biloma infection, there is a fibrin-containing exudative reaction with variable amounts of neutrophils and, later in the process, plasma cells as a local humoral immune response.

References

Abel RM, Fischer JE, Hendren WH (1971) Penetration of the alimentary tract by a foreign body with migration to the liver. Arch Surg 102:227–228

Acosta S, Lantz L (1996) A case report. A pin in the appendix caused hepatic abscess. Lakartidningen 93:4278

Akçam M, Koçkar C, Tola HT, Duman L, Gündüz M (2009) Endoscopic removal of an ingested pin migrated into the liver and affixed by its head to the duodenum. Gastrointest Endosc 69:382–384

Ammari I, Longueira Suarez R, Lamas Ferreiro JL, Iribarren Diaz M, Toscano Novella A, Martinez Vazquez C (2009) Foreign body: an uncommon cause of liver abscess (in Spanish). Gastroenterol Hepatol 32:179–180

Antonopoulos C, Voulimeneas I, loannides P, Kotsifas T, Kavallieratos N, vagianos C (2009) Bile leaks after cholecystectomy: the significance of patient selection. Surg Laparosc Endosc Percutan Tech 19:379–383

Aron E, Roy B, Groussin P (1966) Abscess of the liver caused by fish bone. Presse Med 74:1957–1958

Awwad A, Mulholland K, Clements B (2010) Abdominal abscess due to retained gallstones 5 years after laparoscopic cholecystectomy. BMJ Case Rep. bcr07. 2009.2126

Azili MN, Karaman A, Karaman I, Erdogan D, Cavusoglu YH, Aslan MK, Cakmak O (2007) A sewing needle migrating into the liver in a child: case report and review of the literature. Pediatr Surg Int 23:1135–1137

Ballestri M, Baraldi A, Gatti AM, Furci L, Bagni A, Loria P, Rapana RM, Carulli N, Albertazzi A (2001) Liver and kidney foreign bodies granulomatosis in a patient with malocclusion, bruxism, and worn dental prostheses. Gastroenterology 121:1234–1238

Berk RN, Reit RJ (1971) Intra-abdominal chicken-bone abscess. Diagn Radiol 101:311–313

Berkmann S, Schreiber V, Khamis A (2011) Recurrent intrahepatic dislocation of ventriculoperitoneal shunt. Minim Invasive Neurosurg 54:83–86

Bloch DB (1984) Venturesome toothpick. A continuing source of pyogenic hepatic abscess. JAMA 252:797–798

Bradley M, Singh G (1991) Case report: an oxidized cellulose granuloma – another hepatic pseudotumor? Clin Radiol 44:206–207

Cañete Gomez J, Alamo Martinez JM, Martin Jimenez C, Muñoz Ortega A, Valera Sanchez Z (2009) Biloma secondary to liver trauma (in Spanish). Cir Esp 85:379–380

Casillas S, Kittur DS (2003) Late abscess formation after spilled gallstones masquerading as a liver mass. Surg Endosc 17:833

Cerwenka H, Bacher H, Komprat P, Mischinger HJ (2005) Gossypiboma of the liver: CT, MRI and intraoperative ultrasonography findings. Dig Surg 22:311–312

Chan SC, Chen HY, Ng SH, Lee CM, Tsai CH (1999) Hepatic abscess due to gastric perforation by ingested fish bone demonstrated by computed tomography. J Formos Med Assoc 98:145–147

Chang IS, Rhim H, Kim SH, Kim YS, Choi D, Park Y, Lim HK (2010) Biloma formation after radiofrequency ablation of hepatocellular carcinoma: incidence,

imaging features, and clinical significance. AJR Am J Roentgenol 195:1131–1136
Chen MJ, Lin CC, Chang WH, Yang FS (2005) Biloma following repeated transcatheter arterial embolization and complicated by intrahepatic duct stones: a case report. World J Gastroenterol 11:4764–4765
Chen CJ, Chang WH, Shih SC, Wang TE, Chang CW, Chen MJ (2009) Clinical presentation and outcome of hepatic subcapsular fluid collections. J Formos Med Assoc 108:61–68
Chen HK, Kuo JR, Uen YH, Sun DP (2011) Liver abscess secondary to fish bone migration from the duodenum. ANZ J Surg 81:206
Cheung YC, Ng SH, Tan CF, Ng KK, Wan YL (2000) Hepatic inflammatory mass secondary to toothpick perforation of the stomach: triphasic CT appearances. Clin Imaging 24:93–95
Chiang TH, Liu KL, Lee YC, Chiu HM, Lin JT, Wang HP (2006) Sonographic diagnosis of a toothpick traversing the duodenum and penetrating into the liver. J Clin Ultrasound 34:237–240
Chintamani SV, Lubhana P, Durkhere R, Bhandari S (2003) Liver abscess secondary to a broken needle migration – a case report. BMC Surg 3:8
Clarençon F, Scatton O, Brzgière E, Silvera S, Afanou G, Soubrane O, Vignaux O, Legmann P (2008) Recurrent liver abscess secondary to ingested fish bone migration: report of a case. Surg Today 38:572–575
De la Vega M, Rivero JC, Ruiz L, Suarez S (2001) A fish bone in the liver. Lancet 358:982
Del Fabbro D, Torzilli G, Gambetti A, Leoni P, Gendarini A, Olivari N (2004) Liver inflammatory pseudotumor due to an intrahepatic wooden toothpick. J Hepatol 41:498
Dupas JL, Mancheron H, Sevent F, Delamarre J, Delcenserie R, Capron JP (1988) Hepatic subcapsular biloma. An unusual complication of endoscopic retrograde cholangiopancreatography. Gastroenterology 94:1225–1227
Esensten M, Ralls PW, Colletti P, Halls J (1983) Posttraumatic intrahepatic biloma: sonographic diagnosis. AJR Am J Roentgenol 140:303–305
Ezaki T, Okamura T, Yoshida Y, Shirakusa T, Tanimoto A, Hiratsuka R (1994) Foreign-body granuloma mimicking an extrahepatically growing liver tumor: report of a case. Surg Today 24:829–832
Farina LA, Villavicencio H, Chechile G (1995) Preoperatively recognized chronically retained pararenal gauzoma. Int Urol Nephrol 27:33–35
Feng QZ, Wang J, Sun H (2009) A sewing needle in liver: a case report and review of the literature. Cases J 2:6520
Fritz HP, Polio J, Hewitt JK (1989) Biloma secondary to hepatocellular carcinoma in an HIV-seropositive patient. Am J Gastroenterol 84:1560–1563
Glick WA, Simo KA, Swan RZ, Sindram D, Iannitti DA, Martinie JB (2012) Pyogenic hepatic abscess secondary to endolumenal perforation of an ingested foreign body. J Gastrointest Surg 16:885–887
Goh BK, Yong WS, Yeo AW (2005) Pancreatic and hepatic abscess secondary to fish bone perforation of the duodenum. Dig Dis Sci 50:1103–1106
Gonzalez JG, Gonzalez RR, Patino JV (1988) CT finding in gastrointestinal perforation by ingested fish bones. J Comput Assist Tomogr 12:88–90
Gould L, Patel A (1979) Ultrasound detection of extrahepatic encapsulated bile: "biloma". AJR Am J Roentgenol 132:1014–1015
Gower ND, Mond NC, Owen D (1961) Liver abscess after perforation of liver by a fish bone. Br Med J 1:475–476
Griffiths FE (1955) Liver abscess due to foreign-body migration from the alimentary tract; a report of two cases. Br J Surg 42:667–668
Gundara JS, Harrison R (2010) An unusual zoonosis: liver abscess secondary to asymptomatic colonic foreign body. HPB Surg 2010:794271
Harjai MM (2000) Foreign bodies migrating from gut to liver. Indian J Gastroenterol 19:41–42
Hiraki A, Ueoka H, Tabata M, Kiura K, Bessho A, Yamane H, Nogami N, Harada M (1998) Spontaneous biloma as a complication of small cell lung cancer. Lung Cancer 19:127–130
Horii K, Yamazaki O, Matsuyama M, Higaki I, Kawai S, Sakaue Y (1999) Successful treatment of a hepatic abscess that formed secondary to fish bone penetration by percutaneous transhepatic removal of the foreign body: report of a case. Surg Today 29:922–926
Houli N, MacGowan K, Hosking P (2003) Hepatic abscess complicating foreign body perforation of the transverse colon. ANZ J Surg 73:255–259
Huang CK, Chen SC, Shih PM, Chuang WL (2007) Biloma following transcatheter arterial chemoembolization with microspheres: a case report. Kaohsiung J Med Sci 23:470–474
Hussain S (2001) Sepsis from dropped clips at laparoscopic cholecystectomy. Eur J Radiol 40:244–247
Iwasa M, Sekoguti T, Wada K (1988) Granulomatous abscess of the liver – a case and review of the Japanese literature (in Japanese). Nippon Rinshou Geka Gakkaisi 49:2382–2387
Jutte E, Cense H (2010) Liver abscess due to sewing needle perforation. Scientific World Journal 10:1532–1534
Kadowaki Y, Tamura R, Okamoto T, Mori T, Mori T (2007) Ruptured hepatic abscess caused by fish bone penetration of the duodenal wall: report of a case. Surg Today 37:1018–1021
Kanazawa S, Ishigaki K, Miyake T, Ishida A, Tabuchi A, Tanemoto K, Tsunoda T (2003) A granulomatous liver abscess which developed after a toothpick penetrated the gastrointestinal tract: report of a case. Surg Today 33:312–314
Kannan U, Parshad R, Regmi SK (2009) An unusual presentation of biloma five years following cholecystectomy: a case report. Cases J 2:8048
Karamarkovic AR, Djuranovic SP, Popovic NP, Bumbasirevic VD, Sijacki AD, Blazic IV (2007) Hepatic abscess secondary to a rosemary twig

migrating from the stomach into the liver. World J Gastroenterol 13:5530–5532
Kessler AT, Kourtis AP (2001) Images in clinical medicine. Liver abscess due to *Eikenella corrodens* from a fishbone. N Engl J Med 345:e5
Kobayashi S, Nakanuma Y, Terada T, Matsui O (1993) Postmortem survey of bile duct necrosis and biloma in hepatocellular carcinoma after transcatheter arterial chemoembolization therapy: relevance to microvascular damages of peribiliary capillary plexus. Am J Gastroenterol 88:1410–1415
Komatsu M, Fuji T, Goto T, Ohshima S, Nakane K, Yoneyama K, Ando H, Tanaka J, Hashimoto M (1998) Giant hepatic biloma following transcatheter oily chemoembolization in a patient with hepatic metastases from malignant pheochromocytoma. Intern Med 37:1034–1038
Kuligowska E, Schlesinger A, Miller KB, Lee VW, Grosso D (1983) Bilomas: a new approach to the diagnosis and treatment. Gastrointest Radiol 8:237–243
Kumar S, Gupta NM (2000) Foreign bodies migrating from gut to liver. Indian J Gastroenterol 19:42
Labuski MR, Wise SW (1999) Recurrent abdominal abscess secondary to a dropped laparoscopic clip: CT images. Abdom Imaging 24:191–192
Lebensburger J, Esbenshade A, Blakely M, Hankins J, Wang W (2008) Biloma and pneumobilia in sickle cell disease. Pediatr Blood Cancer 51:288–305
Lee MR, Hwang Y, Kim JH (2006) A case of colohepatic penetration by a swallowed toothbrush. World J Gastroenterol 12:2464–2465
Liu HJ, Liang CH, Huang B, Xie SF, Wang GY (2009) Migration of a swallowed toothpick into the liver: the value of multiplanar CT. Br J Radiol 82:e79–e81
Lohan D, Walsh S, McLoughlin R, Murphy J (2005) Imaging of the complications of laparoscopic cholecystectomy. Eur Radiol 15:904–912
Lu YY, Chenung YC, Ko SF, Ng SH (2005) Calcified reticulate rind sign: a characteristic feature of gossypiboma on computed tomography. World J Gastroenterol 11:4927–4929
Mahmood SK, Tomford JW, Rosenblatt S, Gordon S (2008) The clinical picture. Dropped gallstones disguised as a liver abscess. Cleve Clin J Med 75:316–318
Maleux G, Heye S, Verhamme P, Vaninbroukx J, Delcroix M (2011) Penetration of a fractured Bird's Nest filter strut into the liver parenchyma: report of two cases. Acta Radiol 52:643–645
Masunaga S, Abe M, Imura T, Asano M, Minami S, Fujisawa I (1991) Hepatic abscess secondary to a fishbone penetrating the gastric wall: CT demonstration. Comput Med Imaging Graph 15:113–116
Middleton JP, Wolper JC (1984) Hepatic biloma complicating sickle cell disease. A case report and review of the literature. Gastroenterology 86:743–744
Morrin MM, Kruskal JB, Hochman MG, Saldinger PF, Kane RA (2000) Radiologic features of complications arising from dropped gallstones in laparoscopic cholecystectomy patients. AJR Am J Roentgenol 174:1441–1445
Muddaiah M, Varghese GK (2008) Hypodermic needles in the liver. J Postgrad Med 54:324–325
Mueller PR, Ferrucci JT, Simeone JF, Cronan JJ, Wittenberg J, Neff CC, vanSonnenberg E (1983) Detection and drainage of bilomas: special considerations. AJR Am J Roentgenol 140:715–720
Murakata et al. (2006). http://www.ncbi.nlm.nih.gov/pubmed/16619001
Nazaroglu H, Ozkan U, Ozmen CA, Akay HO (2009) Migration of ventriculoperitoneal shunt into the lung by passing through the liver and diaphragm. Diagn Interv Radiol 15:19–21
Neumann H, Fry LC, Malfertheiner P, Mönkemüller K (2010) Bile leak from the duct of Luschka. Z Gastroenterol 48:256–257
Ng CT, Htoo A, Tan SY (2011) Fish bone-induced hepatic abscess: medical treatment. Singapore Med J 52: e56–e58
Nguyen BD (2006) Cardiac and hepatic seed implant embolization after prostate brachytherapy. Urology 68:e17–e19
Nishimoto Y, Suita S, Taguchi T, Noguchi S, Ieiri S (2003) Hepatic foreign body – a sewing needle – in a child. Asian J Surg 26:231–233
Noda et al. (1998). http://www.ncbi.nlm.nih.gov/pubmed/9594896
Omejc M (2002) Laparoscopic removal of an ingested pin migrating into the liver. Surg Endosc 16:537
Pedersen VM, Geerdsen JP, Bartholdy J (1986) Foreign body perforation of the gastrointestinal tract with formation of liver abscess. Ann Chir Gynaecol 75:245–246
Perera MT, Wijesuriya SR, Kumarage SK, Ariyaratne MH, Deen KI (2007) Inflammatory pseudotumor of the liver caused by a migrated fish bone. Ceylon Med J 52:141–142
Perl L, Mekori YA, Mor A (2009) Dropped gallstones mimicking colon cancer. Isr Med Assoc J 11:697–698
Poyanli A, Bilge O, Kapran Y, Guyen K (2005) Foreign body granuloma mimicking liver metastasis. Br J Radiol 78:752–754
Rafizadeh F, Silver H, Fieber S (1981) Pyogenic liver abscess secondary to a toothpick penetrating the gastrointestinal tract. J Med Soc N J 78:377–378
Rahalkar MD, Pai B, Kukade G, Al Busaldi SS (2003) Sewing needles as foreign bodies in the liver and pancreas. Clin Radiol 58:84–86
Rajagopal A, Martin J (2002) Gossypiboma – "a surgeon's legacy": report of a case and review of the literature. Dis Colon Rectum 45:119–120
Ramia JM, Mansilla A, Villar J, Muffak K, Garrote D, Ferron JA (2004) Retroperitoneal actinomycosis due to dropped gallstones. Surg Endosc 18:345–349
Reddy SC (1987) Subcapsular hepatic abscess: a rare complication of ventriculo-peritoneal shunt. South Med J 80:1309–1311

Rice DC, Memon MA, Jamison RL, Agnessi T, Ilstrup D, Bannon MB, Farnell MB, Grant CS et al (1997) Long-term consequences of intraoperative spillage of bile and gallstones during laparoscopic cholecystectomy. J Gastrointest Surg 1:85–91

Riddle C, Ahmed B, Doyle J, Connolly BL (2008) Migration of Gelfoam to the gallbladder after liver biopsy. Pediatr Radiol 38:806–809

Roberts DJ, Chun HM (2005) Dropped gallstones as a nidus of intra-abdominal abscess complicated by empyema. Clin Infect Dis 41:e64–e66

Saitua F, Acosta S, Soto G, Herrera P, Tapia D (2009) To remove or not remove . . .asymptomatic sewing needle within hepatic right lobe in an infant. Pediatr Emerg Care 25:463–464

Sakamoto I, Iwanaga S, Nagaoki K, Matsuoka Y, Ashizawa K, Uetani M, Fukuda T et al (2003) Intrahepatic biloma formation (bile duct necrosis) after transcatheter arterial chemoembolization. AJR Am J Roentgenol 181:79–87

Santos SA, Alberto SC, Cruz E, Pires E, Figueira T, Coimbra E, Estevez J, Oliveira M, Novais L, Deus JR (2007) Hepatic abscess induced by foreign body: case report and literature review. World J Gastroenterol 13:1466–1470

Sathesh-Kumar T, Saklani AP, Vinayagam R, Blackett RL (2004) Spilled gall stones during laparoscopic cholecystectomy: a review of the literature. Postgrad Med J 80:77–79

Schubert TT (1986) Hepatobiliary system in sickle cell disease. Gastroenterology 90:2013–2021

Senol A, Isler M, Minkar T, Oyar O (2010) A sewing needle in the liver: 6 years later. Am J Med Sci 339:390–391

Serwe S, Weber J, Strock P, Lens V (2007) Liver abscess caused by an unnoticed swallowed toothpick perforating the colonic wall. Z Gastroenterol 45:1060–1062

Siskin et al. (2003). http://www.ncbi.nlm.nih.gov/pubmed/12525592

Sok D, Boerma EJ, Tan PB (1989) A remarkable subhepatic tumour. Neth J Surg 41:114–116

Stampfl et al. (2009). http://www.ncbi.nlm.nih.gov/pubmed/19139955

Starakis I, Karavlas D, Marangos M, Psoni E, Bassaris H (2005) A rooster's revenge: hepatic abscess caused by a chicken bone. Eur J Emerg Med 12:41–42

Stevens S, Rivas H, Cacchione RN, O'Rourke NA, Allen JW (2003) Jaundice due to extrabiliary gallstones. JSLS 7:277–279

Stoica M, Saftoiu A, Gheonea DI, Dumitrescu D, Surlin V (2007) Pyogenic liver abscess caused by accidental ingestion of a wooden toothpick: role of preoperative imaging. J Gastrointestin Liver Dis 16:221–222

Tacyildiz I, Aldemir M (2004) The mistakes of surgeons: "gossypiboma". Acta Chir Belg 104:71–75

Tham CH, Ng BK (2001) Gallstone granuloma: a rare complication of laparoscopic cholecystectomy. Singapore Med J 42:174–175

Theodoropoulou A, Roussomoustakaki M, Michalodimitrakis MN, Kanaki C, Kouroumalis EA (2002) Fatal hepatic abscess caused by a fish bone. Lancet 359:977

Tsai MJ, Chen JD, Tiu CM, Chou YH, Hu SC, Chang CY (2009) Cab acute cholecystitis with gallbladder perforation be detected preoperatively by computed tomography in ED? Correlation with clinical data and computed tomography features. Am J Emerg Med 27:574–581

Tsuboi K, Nakajima Y, Yamamoto S, Nagao M, Nishimura K, Yoshii M (1981) A case of an intrahepatic fish bone penetration – possibility of the preoperative diagnosis by CT (in Japanese). Nippon Geka Hokan 50:899–903

Tumer AR, Yubsek YN, Yasti AC, Gozalan U, Kama NA (2005) Dropped gallstones during laparoscopic cholecystectomy: the consequences. World J Surg 29:437–440

Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M (2000) Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. J Bone Joint Surg Am 82:457–476

Vazquez JL, Thorsen MK, Dodds WJ, Quiroz FA, Martinez ML, Lawson TL, Stewart ET, Foley WD (1985) Evaluation and treatment of intraabdominal bilomas. AJR Am J Roentgenol 144:933–938

Velasco J, Menéndez CL, Alonso de la Campa J, Pinto J, Crespo M (2005) Cyanoacrylate hepatic pseudotumor: role of fine needle aspiration. Acta Cytol 49:585–586

Warren CW, Wyatt JI (1996) Gallstones split at laparoscopic cholecystectomy: a new cause of intraperitoneal granulomas. J Clin Pathol 49:84–85

Zamir G, Lyass S, Pertsemlidis D, Katz B (1999) The fate of the dropped gallstones during laparoscopic cholecystectomy. Surg Endosc 13:68–70

Zbar AP, Agrawal A, Saeed IT, Utidjian MR (1998) Gossypiboma revisited: a case report and review of the literature. J R Coll Surg Edinb 43:417–418

Hepatobiliary Pseudotumors Consisting of Nonneoplastic Hematopoietic Cells and Cells of the Macrophage Lineage

125

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_125

Abstract

The hepatobiliary tract can develop tumor-like lesions or pseudotumors that consist of hematopoietic tissue or macrophage accumulations. Extramedullary hematopoiesis can occur in the liver and may result in macroscopically visible nodular lesions (nodular extramedullary hematopoiesis). Macroscopically, the lesions may have several cm in diameter and usually show a red-brown or tan color. One variant is characterized by the production of an abundant fibrous stroma (sclerosing extramedullary hematopoietic tumor). The liver can be the site of various eosinophilic pseudotumors and eosinophilic necrosis. Macrophage-rich lesions of the liver that can result in tumor-like nodular lesions comprise lipogranulomas, xanthomatous lesions, rheumatoid nodules, malakoplakia, and accumulations of Gaucher cells in Gaucher's disease.

Hematopoietomas and other Nodular Manifestations of Extramedullary Hematopoiesis in the Liver

Introduction

Extramedullary hematopoiesis (EMH) refers to the production of blood cells outside the bone marrow and is often a compensatory response to cope with marrow infiltration, marrow depletion, or marrow hyperactivity seen in certain chronic anemias (review: O'Malley 2007). Moreover, EMH is a typical feature of several myeloproliferative disorders. Mostly, EMH is a diffuse or "microfocal" process. However, there are situations where EMH presents in the form of gross nodular lesions or tumorous masses. Tumor-like extramedullary hematopoiesis (nodular EMH) was originally described in 1945 (Ask-Upmark 1945) and occurs at several sites, including the spleen, the kidney (Moskovitz et al. 1991; Tamiolakis et al. 2003), the intrathoracic compartment (Malamos et al. 1962), the adrenal gland (Ask-Upmark 1945), and the liver. Based on the cases reported so far, an intrathoracic paravertebral location seems to prevail (Verani et al. 1980). Nodular EMH has been observed in several hematologic and bone marrow disorders, including sickle cell disease (Verani et al. 1980; Lemos et al. 1997), congenital dyserythropoietic anemia (Heimpel et al. 2009), thalassemia major (Papavisiliou and Sfikakis 1964; Kumar et al. 1995), beta-thalassemia intermedia (Wong et al. 1999), beta-thalassemia trait (Ma and Au 1999), hemoglobin E-thalassemia disease (Da Costa et al. 1974), myelofibrosis (Navarro et al. 2000) as a manifestation of thymoma (Hervé et al. 2001), and medullary tuberculosis (Ben Rejeb et al. 1992).

Nodular Extramedullary Hematopoiesis of the Liver

Since the liver is a site for early hematopoiesis, it is not surprising that it is a relatively frequent site of extramedullary hematopoiesis. In pediatric patients, EMH is considered normal up to about 5 weeks of age. Nodular extramedullary hematopoiesis of the liver (NEMH-L) occurs in the form of solitary or multiple lesions of highly variable size, involving one or both liver lobes (Kopecky et al. 1986; Wiener et al. 1987; Abbitt and Teates 1989; Dewar et al. 1990; Bradley and Metreweli 1990; Warshauer and Schiebler 1991; Kumar et al. 1995; Tamm et al. 1995; Lemos et al. 1997; Aytac et al. 1999; Wong et al. 1999; Kwak and Lee 2000; Navarro et al. 2000; Hervé et al. 2001; Gil-Fernandez et al. 2001; Parwani and Ali 2003; Tamiolakis et al. 2004; Gupta et al. 2004; Jelali et al. 2006; Lee et al. 2008). Among eight cases with sufficient data compiled from the literature, five were multiple and three solitary lesions (Wong et al. 1999). NEMH-L can present as a solitary space-occupying lesion mimicking a primary liver neoplasm, mainly HCC, metastatic disease, FNH, or an atypical hemangioma (Wiener et al. 1987; Bradley and Metreweli 1990; Gil-Fernandez et al. 2001; Tamiolakis et al. 2004), thus promoting diagnostic fine needle aspiration (Dardi et al. 1990; Raab et al. 1993; Lemos et al. 1997). Metastatic disease may in particular be suspected in case NEMH-L produces

several lesions with nodular hepatomegaly (Hervé et al. 2001). Sizes of the nodules have been reported to range from tiny lesions mimicking microabscesses (Kopecky et al. 1986) to 1.5 cm (Hervé et al. 2001), 3 cm (Wong et al. 1999), 7 cm (Parwani and Ali 2003), and 8 cm (Ma and Au 1999). Massive solitary NEMH-L has been observed in thalassemia (Dewar et al. 1990) and in myelofibrosis (Navarro et al. 2000). The masses may grow rather rapidly; particularly post-splenectomy; in one observation, the first hepatic manifestation was a 3 cm lesion, growing to 6 cm within 3 months (Wong et al. 1999). On the other hand, even very large lesions have been reported to remain unchanged for 4 years (Ma and Au 1999).

At ultrasound examination, the lesions are usually hypoechoic (Bradley and Metreweli 1990; Dardi et al. 1990; Dewar et al. 1990; Aytac et al. 1999; review: Wong et al. 1999). CT shows fairly well-defined, homogeneously low attenuated masses. On contrast-enhanced portal venous phase CT, most of the lesions show intense enhancement (Wong et al. 1999; Kwak and Lee 2000; Lee et al. 2008). The appearance of the lesions on MR consists of slightly increased signal on T2-weighted images with heterogeneous enhancement of some of the lesions during bolus infusion of gadolinium, while the T1-weighted images post-gadolinium showed no delayed enhancement (Warshauer and Schiebler 1991; Jelali et al. 2006). The imaging features for Doppler US (Aytac et al. 1999) and for Technetium-99 m red blood cell SPECT (Tamm et al. 1995) have been reported. When using the latter method, NEMH-L may mimic hepatic hemangioma (Tamm et al. 1995). Radiologically, NEMH-L can present as a fatty lesions, thus causing differential diagnostic difficulties (Gupta et al. 2004).

Macroscopically, NEMH are generally described as nodular and sometimes bulky, rather well-defined lesions, that are of medium consistency and show a cut surface that varies from red-brown or tan (in case of high vascularity and/or iron deposition) to grayish-white. Histologically, NEMH-L is composed of normal-looking hematopoietic tissue consisting of all three lineages (Figs. 1, 2, and 3). Few small cells

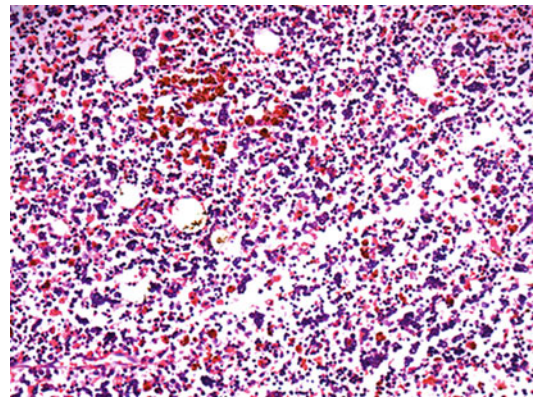

Fig. 1 Hematopoietoma of the liver, a mass-forming variant of extramedullary hematopoiesis. There is focal hemosiderosis (hematoxylin and eosin stain)

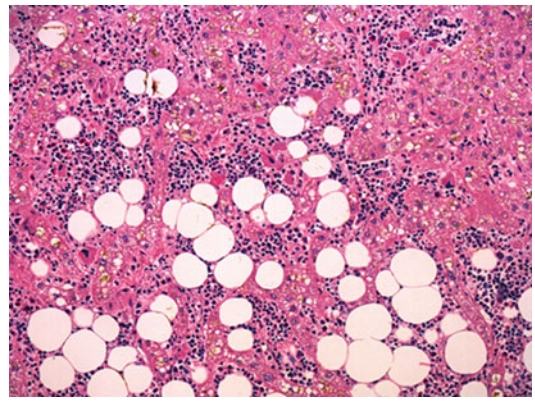

Fig. 2 Hematopoietoma of the liver. This lesion is associated with formation of adipose tissue (hematoxylin and eosin stain)

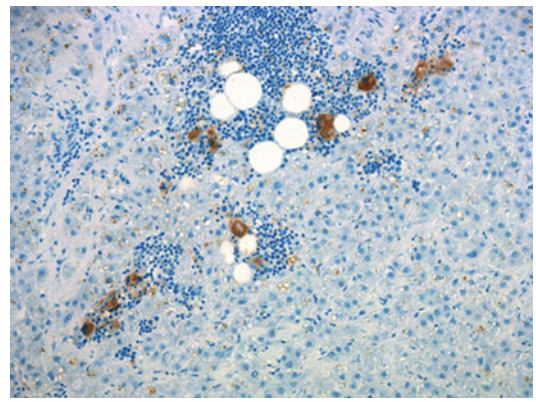

Fig. 3 Extramedullary hematopoiesis of the liver with production of megakaryocytes (CD61 immunostain)

with a lymphoid morphology may be present. It is not yet known whether such cells may, in addition to a lymphocyte population, represent hematopoietic stem cells. Similar to bone marrow, the hemopoietic tissue contains scattered macrophages with or without stainable iron. In addition, cells with a spindle-shaped morphology are detectable in small numbers (an analogue to marrow stromal cells?). In larger lesions, extracellular matrix may be increased, sometimes with focal fibrosis or sclerosis. In fact, NEMH-L can produce stellate scars visible in MRI and CT (Wong et al. 1999). The adjacent liver substance is compressed in large lesions, and perifocal hepatocytes may show iron overload (Ma and Au 1999). The morphologic differential diagnosis of NEMH-L chiefly includes hepatic myelolipoma and malignant tumors of the hemopoietic lineage.

Sclerosing Extramedullary Hematopoietic Tumor of the Liver

Sclerosing extramedullary hematopoietic tumor (SEMHT) is a rare lesion that typically arises in patients with chronic myeloproliferative disorders (Remstein et al. 2000; Yang et al. 2002; Sukov et al. 2009). Multiple intra-abdominal nodules of SEMHT can develop after splenectomy in patients with chronic myeloproliferative syndrome (Gualco et al. 2010). Macroscopically, these lesions are soft to firm, gray-white to yellow-tan nodular masses. Histology reveals extramedullary hepatopoiesis with atypical megakaryocytes, granulocytic precursors, and erythroid precursors set in a background of dense collagenous sclerosis. SEMHT has been observed in the ligamentum teres of the liver, in one patient in association with chronic idiopathic myelofibrosis (Kwon et al. 2004).

Benign Extramedullary Hematopoietic Proliferations of the Biliary Tract

In very rare instances, benign extramedullary hematopoiesis develops in and around the walls of large bile ducts. These foci of hematopoiesis occur in myeloid neoplasms destroying the bone marrow and in certain other situations of marked secondary extramedullary hematopoiesis. In massive forms, the intrahepatic biliary tract may be encased by the hematopoietic tissue, causing hepatic failure (La Fianza et al. 2010).

Hepatic Myeloid Hyperplasia in Caffey's Disease

Infantile cortical hyperostosis (ICH; Caffey's disease; OMIM 114000) was described in 1945 (Caffey and Silverman 1945). The disorder is characterized by cortical thickening of affected bones (mainly diaphysis of long bones) and inflammatory swelling of the contiguous soft tissues (reviews: Glorieux 2005; Kamoun-Goldrat and le Merrer 2008). The acute manifestations are usually inflammatory in nature, with fever and hot swelling of involved bones, clinically suggesting osteomyelitis. ICH usually manifests in young infants (the classical infantile form), but is sometimes also seen in neonates and in fetuses as early as 20 weeks of gestation (Herman 1996; Schweiger et al. 2003). A distinct variant is early-onset prenatal ICH (Lecolier et al. 1992). The classical form reveals autosomal-dominant inheritance (Fried et al. 1981), whereas autosomal recessive inheritance has been suggested for the early-onset prenatal variant. The disorder is assigned to chromosome 17q21-31-q22. Patients with classical ICH have been shown to have a 3040C>>>T mutation in the COL 1A1 gene (Gensure et al. 2005; Cho et al. 2008; Kamoun-Goldrat et al. 2008). Early-onset prenatal ICH, the form which shows liver alterations, is divided into two forms, a severe form with onset before 35 weeks of gestation, associated with polyhydramnios, lung disease, hydrops fetalis, anasarca, hepatomegaly, prematurity, and high lethality, and a mild form, with onset after 35 weeks of gestation and lack of complications (Schweiger et al. 2003). In a detailed autopsy analysis of a patient with early-onset prenatal ICH, hepatomegaly was found to be

caused by marked myeloid hyperplasia. Myeloid hyperplasia was most prominent in the tissue surrounding the portal tracts, and myeloid precursors were located within hepatic sinusoids. In contrast, an increase in erythropoiesis was not noted. This extramedullary myeloid hyperplasia was suggested to be caused by the generalized skeletal inflammatory process characterized by ICH, with microabscess formation and widespread granulation tissue at the interface between bone and periosteum (Wright et al. 2005).

Focal Eosinophilic Infiltration of the Liver

Introduction

Hypereosinophilia is associated with several conditions, comprising allergic reactions, parasite infestations, connective tissue diseases, and neoplastic processes, but idiopathic forms are also recognized. Idiopathic hypereosinophilic syndrome (HES) is a heterogeneous group of disorders that has been defined as peripheral eosinophilia $>1500/mm^3$ for at least 6 months and evidence of end-organ involvement in the absence of an identifiable cause (Leiferman and Gleich 2004). A subset of patients with a myeloproliferative variant of hypereosinophilic syndrome (MHES) is characterized by elevated serum tryptase levels, increased atypical mast cells in the bone marrow, tissue fibrosis, and the presence of the fusion tyrosine kinase, Fip1-like 1 (FIP1L1) – PDGFRalpha (generated by a cryptic interstitial deletion on chromosome 4q12; del (4)(q12q112)), a therapeutic target of imatinib mesylate (Griffin et al. 2003; Klion et al. 2003; Cools et al. 2003; Pardanani et al. 2003; Klion et al. 2004a). This novel fusion kinase is detectable in chronic eosinophilic leukemia (CEL), MHES, and systemic mast cell disease (Coutre and Gotlib 2004; Cools et al. 2004; Gotlib et al. 2004). Recently, familial eosinophilia (FE; OMIM 131400) has been characterized, a disorder that can also cause end-organ damage (Klion et al. 2004b).

Liver Alterations in Hypereosinophilic Syndromes

Hypereosinophilic syndrome may cause eosinophil-related tissue alterations in various organs, including the gastrointestinal tract (eosinophilic gastrointestinal disorders, EGID; Rothenberg 2004) and the liver (Table 1).

In a study on 13 patients, mild to moderate hepatomegaly was found in all cases, and seven patients exhibited multiple round or oval hypoechoic or variably echogenic lesions measuring 1–2 cm with poorly defined margins in both lobes of the liver, but four patients showed lesions of up to 4 cm diameter. The number of lesions and the extent of diffuse lesions seemed to be proportional to the degree of eosinophilia (Nam et al. 1999). The lesions may mimic multiple liver metastases or hepatocellular carcinoma (Won et al. 1999; Jang et al. 2002; Kwak et al. 2004). CT demonstrates well-defined, homogeneous, or heterogeneous low attenuation with a straight margin limited to a hepatic lobe, segments, or subsegments, in the latter situation with multiple, ovoid, or wedge-shaped lesions (Lim et al. 2000; Yoo et al. 2003).

Pathologically, hypereosinophilia causes several groups of hepatobiliary lesions. In cases of low to moderate eosinophilia, an infiltrate dominated by eosinophils is chiefly identifiable in portal tracts, but the number of these cells is also increased within sinusoids and around the central veins (Fig. 4; Lim et al. 2000). The liver involvement in marked peripheral eosinophilia can present as cholestatic liver disease (Valente et al. 1997). In case of direct hepatic involvement

Table 1 Hepatobiliary tissue changes in hypereosinophilia

Eosinophilic infiltration (mainly of portal tracts)
Focal eosinophilic infiltration
Eosinophilic abscess (mainly in parasite infestation)
Eosinophilic pseudotumor of the liver
Focal eosinophilic necrosis (FEN)
Eosinophil-induced chronic active hepatitis
Eosinophil-induced cholestatic liver disease
Eosinophilic cholangitis/eosinophilic sclerosing cholangitis

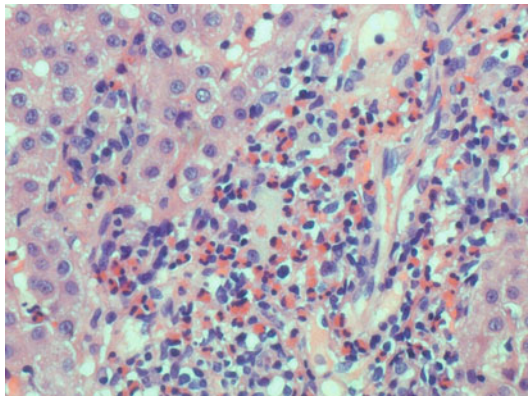

Fig. 4 Focal eosinophilia of the liver (hematoxylin and eosin stain)

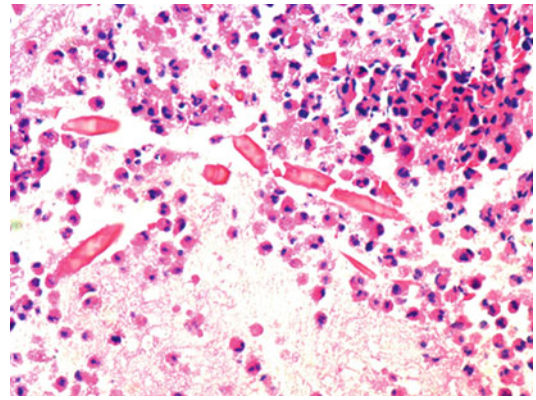

Fig. 5 Charcot-Leyden crystalloids in focal eosinophilia of the liver (hematoxylin and eosin stain)

by parasites (fasciola, clonorchis, and other liver flukes; visceral larva migrans, e.g., *Toxocara* or *Ascaris suum*; *Capillaria*; echinococcosis), the dense eosinophilic infiltrate is found in close association with the parasite, sometimes to a degree to form a focal eosinophilic infiltration, an eosinophilic abscess, or an eosinophilic pseudotumor (Pulpeiro et al. 1991; Han et al. 1993, 1996, 1999; Bhatia and Sarin 1994; Murrell et al. 1997; Kim et al. 1999, 2002; Hayashi et al. 1999; Andresen et al. 2000; Azuma et al. 2002; Sakakibara et al. 2002). These lesions are further discussed in another chapter.

The hypereosinophilic lesions may contain accumulations of Charcot-Leyden crystals (CLC; Fig. 5). These crystals accumulate in any situation where numerous eosinophils are present in tissues, including eosinophilic abscess (Fig. 6). The crystal constituents show indirect lysophospholipase activity (galectin-10, CLC protein; chromosome 19; Mastrianni et al. 1992; Zhou et al. 1992; Leonidas et al. 1995). The galectins form a family of proteins playing a role in myeloid differentiation (Dyer et al. 1997; Abedin et al. 2003) and include, apart from the CLC galectin-10, the placental protein 13 (galectin-13) that also has lysophospholipase activity. The CLC protein, galectin-10, is not a lysophospholipase as such, as has been sometimes reported, but a protein that binds a lysophospholipase inhibitor in a distinct structural fashion (Ackerman et al. 2002). CLC are not only

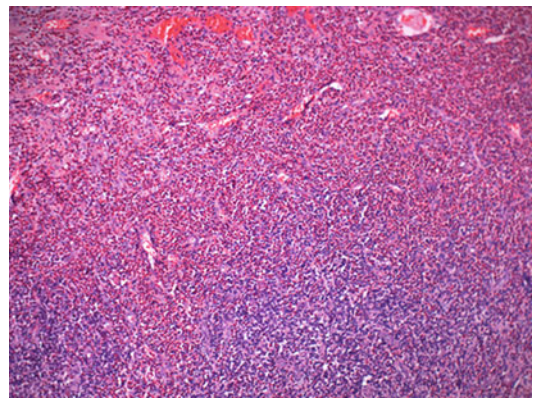

Fig. 6 Eosinophilic abscess of the liver. The abscess mainly consists of eosinophil granulocytes, with cell decay and nuclear debris in the center (hematoxylin and eosin stain)

formed by eosinophils but also by basophil granulocytes (Ackerman et al. 1982).

Focal Eosinophilic Necrosis of the Liver (FEN)

A second and distinct situation occurs when eosinophil infiltration of the liver is associated with tissue necrosis, a condition termed focal of eosinophil-related necrosis, eosinophilic hepatic necrosis (Figs. 7, 8, and 9; Ung et al. 2000; Hur et al. 2005; Laghi et al. 2010), focal eosinophilic necrosis (FEN; Jang et al. 2002), or focal eosinophilic liver disease (FELD; Kim et al. 2010). FEN

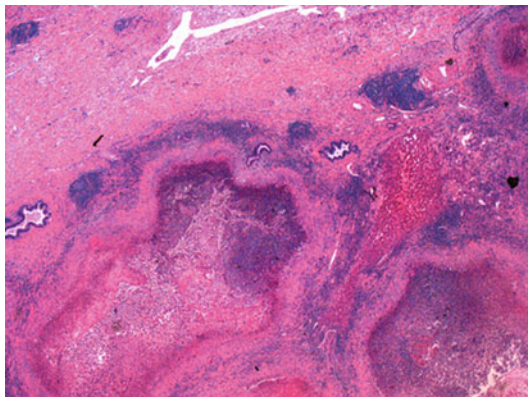

Fig. 7 Focal eosinophilic necrosis of the liver. Collapsed areas of necrosis with eosinophilia and nuclear debris are important features (hematoxylin and eosin stain)

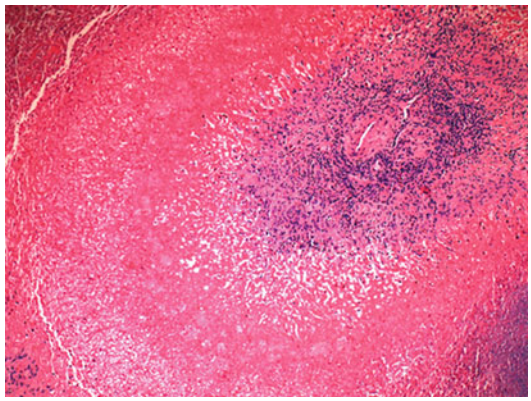

Fig. 8 Focal eosinophilic necrosis of the liver. The necrotic aspect of the lesion is more prominent in this case (hematoxylin and eosin stain)

is a descriptive term based on pathologic features and has not yet been clearly defined (Jang et al. 2002). In principle, FEN is a distinct type of parenchymal necrosis (mostly periportal), associated with eosinophilic infiltration. The main difference to focal eosinophilic infiltration and eosinophilic abscess is the presence of necrosis, thought to be caused by cytotoxic proteins released from eosinophils, but necrosis also occurs in abscesses and the separation of the entities is therefore somewhat arbitrary. FEN seems to almost always be accompanied by peripheral eosinophilia, and it occurs in several conditions causing eosinophilia, including lymphoma, leukemia, and carcinomas (Lee et al. 1999, 2011); Jang

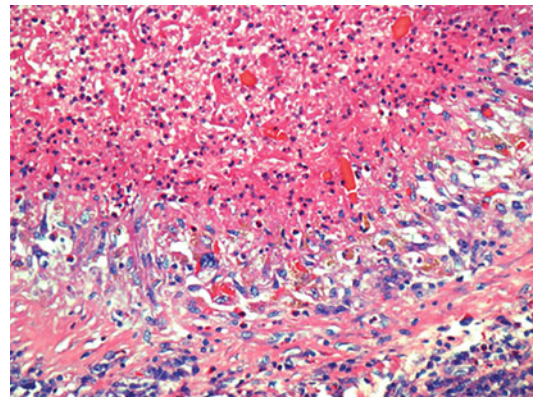

Fig. 9 Focal eosinophilic necrosis of the liver. The area of eosinophilic necrosis is demarcated by activated, epithelioid macrophages. Note few Charcot-Leyden crystalloids within the necrosis (hematoxylin and eosin stain)

et al. 2002; Yu et al. 2005; Choi et al. 2009, 2010. In these instances, eosinophil-recruiting facts such as tumor-associated eosinophil-chemotactic factor are thought to be involved (Wasserman et al. 1974).

Pathologically, FEN is characterized by focal coagulative necrosis of hepatic parenchyma associated with an infiltration of eosinophils. The necrosis is, due to high protein content, markedly eosinophilic, but this oxyphilic staining features may also be caused by the high content of the necrosis of eosinophil granules and debris. In the adjacent tissue and particularly in portal tracts, an eosinophilic infiltration is noted.

Xanthomatous Lesions of the Liver

Introduction

Xanthomas are solitary or multiple lesions characterized by grossly yellowish to frankly yellow plaques (Greek: xanthos, yellow) histologically consisting of an accumulation of lipid-rich macrophages/histiocytes. Xanthomas chiefly occur in several types of hyperlipidemia/hyperlipoproteinemia and mainly involve the skin and the soft tissues, but may also involve deep-seated tissues. In periocular areas, the term xanthelasma is employed (Greek: elasma, plaque; yellow

plaque). Xanthomas were first described by Rayer under the term "plaques jaunatres des paupières" (what exactly means, "yellowish plaques," i.e., xanthelasmas; Rayer 1835). In 1851, the same type of lesions was described under the term "vitiligoidea," with a "plana" and a "tuberosa" variant (Addison and Gull 1851). The term, xanthelasma, was coined in 1863 by Wilson, while the tumor-like appearance of some of the yellow nodules led to the name xanthoma by Smith in 1869.

Liver Xanthomas

Xanthomas and xanthogranulomas of the liver are rare lesions, but may produce multiple nodular changes suggesting manifestations of a neoplastic process (Figs. 10, 11, and 12; Tanino and Ohta 1981). Probably the first description of hepatic xanthoma is the report by Chvostek in 1911, who also used the term *xanthoma of the liver* (Chvostek 1911). Before, other terms had been used, such as "xanthomatous tubercles" (Hardaway 1884). A similar case has been described in 1938, based on a partial autopsy (performed by Ludwig Aschoff) of a patient with liver cirrhosis and partially eruptive skin xanthomas (Thannhauser and Magendantz 1938). In part of the cases, the hepatic xanthomatous reaction was suggested to be caused by hyperlipidemia. For example, multiple liver xanthomas have been found in multiple myeloma associated with hyperlipidemia (Yim et al. 1995). In proliferative plasmacytic disorders, xanthomas are known to occur in other locations, and lipid deposits may, apart from hyperlipidemia, be caused by paraprotein Ig-mediated complexing of lipoproteins (Moschella 1970; Roberts-Thomson et al. 1975; Taylor et al. 1978). A xanthomatous mass at the liver hilum has been described in a 9-year-old boy with generalized xanthomatosis and xanthoma tuberosum (Weidman and Freeman 1924). Xanthomas may also involve the liver capsule (Weidman and Boston 1937). In

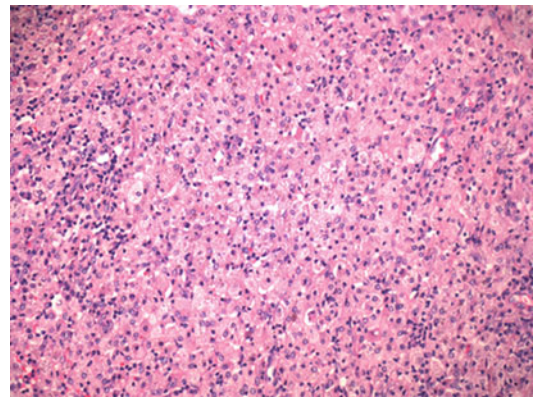

Fig. 11 Xanthoma of the liver. Numerous lipid-rich foamy macrophages occupy the tissue, associated with focal lymphocytic infiltration (hematoxylin and eosin stain)

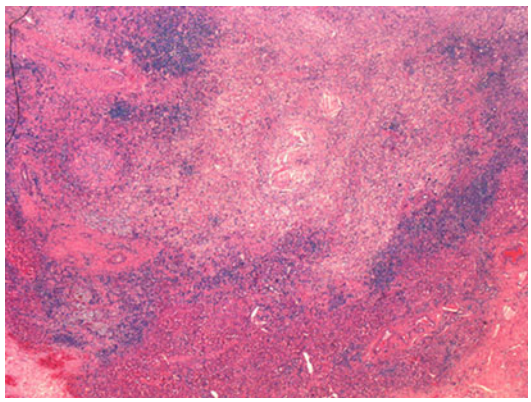

Fig. 10 Tumor-like hepatic xanthoma (hematoxylin and eosin stain)

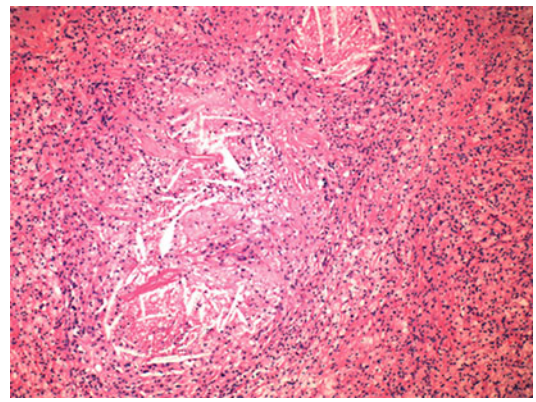

Fig. 12 Hepatic xanthoma. In this lesion, numerous cholesterol clefts are noted (hematoxylin and eosin stain)

hyperlipoproteinemia associated with extensive xanthoma tuberosum, hepatocytes in addition to macrophages may take part in lipid storage, sometimes resulting in parenchymal changes reminiscent of adrenocortical tissue (Weidman and Stokes 1937). Xanthomatous lesions of the liver parenchyma itself also occur in obstructive cholestasis; the lesions are characterized by the accumulation of foamy macrophages chiefly in the periportal zone ("xanthomatosis of the liver," Thannhauser and Magendantz 1938; Desmet 1995; Woollons and Darley 1998). Multiple xanthomatous foci have been reported to occur in the liver in the systemic form of juvenile xanthogranuloma (Chantranuwat 2004), a disorder further discussed in the chapter of Langerhans cell histiocytosis.

Xanthomatous Cholangitis (Xanthomatous Cholangiopathy)

An interesting group of lesions has been termed *xanthomatous cholangitis,* now rarely found in the current literature. The lesion spectrum has been summarized under the term "xanthomatosis of the bile ducts" (Thannhauser and Magendantz 1938). Early reports go back to the end of the nineteenth century (Moxon 1873) and the beginning of the twentieth century (Futcher 1905). We propose the term *xanthomatous cholangiopathy*, to denote these lesions, as this alteration is not primarily an inflammatory disorder, but rather a lesion characterized by the focal accumulation of lipid-laden macrophages within the inner parts of medium-sized and large bile ducts, albeit usually with some lymphocytic infiltration. This lesion has mainly been seen in patients with biliary cirrhosis or diabetes mellitus and usually eruptive, sometimes papulopustular, skin xanthomas. At gross examination, the lesions are spheroid to oblong, elevated, rather sharply delineated spots or patches, sometimes showing a dimple in the center (molluscum-like lesions). In some patients, the involved bile ducts were dilated, had thickened walls, and were lined by bright yellow granular incrustive material (Weidman and Boston 1937). In an another patient, the walls of the bile ducts were of a deep yellow color, and there were minute yellow flecks in the mucosa of the bile ducts (Futcher 1905). Histology is characterized by a patchy accumulation of foam cells involving the mucosa and, in larger lesions, inner parts of the bile duct muscularis. The lesions may be accompanied by impressive hyperplasia of the peribiliary glands (Weidman and Boston 1937) and by scarring causing stenosis or even obstruction (Weidman and Boston 1937; Thannhauser and Magendantz 1938). The pathology has already been described in early reports. It is difficult to judge of what these patients had suffered, but reading the original works suggests that most of them may have had primary or secondary biliary cirrhosis, or diabetes mellitus. In one patient with xanthomata diabeticorum, the postmortem examination showed dilated bile ducts with white to yellowish, opaque, xanthelasma-looking patches on the mucosal surface of the ducts (Moxon 1873). In another patient, the xanthomatous lesion was located to the bifurcation of the hepatic duct (Thannhauser and Magendantz 1938). The striking resemblance of bile duct xanthomas to the respective skin lesions, or to atheromas, has been acknowledged in an early report ("Patches precisely like those in the eyelids and hands were found on the surface of the spleen and in the mucous membrane of the dilated hepatic ducts." "The patches in the ducts looked just like atheroma in the artery with which condition, indeed, they correspond histologically"; Pye Smith 1873). The xanthomatous patches may cause stenosis or occlusion of bile ducts involved (Futcher 1905; Weidman and Stokes 1937).

Hepatic Xanthomatous Reactions in Xanthomatous Cholecystitis

In severe xanthogranulomatous cholecystitis, the massive macrophage reaction with production of foamy cells can extend into the gallbladder bed and from there into the liver substance of the right lobe, mimicking cancer (Pinocy et al. 2003; Yang et al. 2007). Xanthogranulomatous cholecystitis, treated in more detail in a separate chapter, was first described in 1970

under the term fibroxanthogranulomatous cholecystitis (Christensen and Ishak 1970), while the term xanthogranulomatous cholecystitis was coined in 1976 (McCoy et al. 1976). Alternative terms include biliary granulomatous cholecystitis, ceroid-like histiocytic granuloma, and ceroid granuloma. The change is found in 1.2 % of cholecystectomy specimens. It is not yet clear whether the incidence of carcinoma is increased in the presence of this distinct type of inflammation (Benbow 1990; Franco et al. 1990; Reed et al. 1994; Parra et al. 2000). Histologically, three different types of xanthogranulomatous cholecystitis are distinguished, i.e., multinodular, focal, and diffuse, the latter being the least common (Franco et al. 1990). Apart from an extension of the xanthomatous (or better pseudo-xanthomatous) reaction into the liver, this type of cholecystitis has been reported to be associated with liver abscess (Eriguchi et al. 2002).

Xanthomatous Inflammatory Pseudotumors

A further group of masses located to the liver and sometimes containing large numbers of lipid-laden, foamy macrophages are the several variants of inflammatory pseudotumor, discussed in more detail in a separate chapter. The accumulation of fatty macrophages can result in xanthomatous features; therefore, these lesions have also been termed xanthogranuloma of the liver. In some situations, the masses are large and present as lobulated, yellowish tumors measuring up to 7 cm in diameter, with septate fibrotic bands, or are manifest as multiple yellow nodules of few cm size, with or without abscesses in the vicinity (Noi et al. 1994; Tai et al. 1998; Yoon et al. 1999; Yoshida et al. 2003). Histology is characterized by a complex mixture of foamy macrophages, plasma cells, lymphocytes, and granulation tissue. A high lipid content of pseudotumors are in part due to accompanying purulent changes with massive decay of lipid-rich granulocytes, such as pyogenic cholangitis (Yoon et al. 1999).

Hepatic Lipogranulomatosis (Farber's Disease)

Disseminated lipogranulomatosis Farber or Farber disease is a rare inherited autosomal recessive disorder of lipid metabolism in the childhood population due to a genetically determined defect in ceramide degradation (acid ceramidase deficiency), with ceramide accumulation in the lung, liver, bowel, skeletal muscle, cartilage, and bone. Ceramidase splits ceramide into free fatty acids and sphingosine. The storage cells show lysosomal inclusions containing lamellar and curvilinear membrane profiles, zebra structures, and banana bodies (Farber bodies). This storage process is followed by a sometimes massive lipogranulomatous reaction associated with the presence of macrophages, lymphocytes, and fibroblasts. Liver involvement is clinically manifest as hepatomegaly and histologically in the form of dense focal infiltrations of ceramide-containing storage cells (histiocytes/macrophages). Lipid-containing foam cells can form hepatic granuloma-like lesions (Koga et al. 1992). The multiple, up to pinhead-sized lesions in the liver, may already be evident in the newborn period (Schäfer et al. 1996). Type 4 disease (see below) is particularly prone to develop marked lipogranulomatous changes in the liver, sometimes forming tumor-like masses. Liver involvement in type 4 Farber's disease can cause neonatal liver failure (Willis et al. 2008). Lipid-laden foam cells in Farber's disease may develop in suture foreign body granulomas of the liver (Koga et al. 1992).

Farber's lipogranulomatosis (Farber disease; ceramidase deficiency; OMIM 228000) is a rare genetic, autosomal recessive lysosomal storage disease caused by acid ceramidase (E.C. 3.5.1.23) deficiency, which leads to ceramide accumulation in several organs (Koch et al. 1996; review: Ehlert et al. 2007). Farber's disease presents with six phenotypes. Type 1 is the classic variant with early subcutaneous nodules and joint involvement, and often progressive neurologic involvement and lung disease. Type 2 and 3 patients show only slight alterations of the central nervous system, but severe manifestations in the soft tissues. Type 4 patients show severe

neurologic deterioration and marked hepatosplenomegaly already in the neonatal period. Type 5 is characterized by progressive CNS dysfunction, beginning already at 1–2 ½ years of life. Finally, type 6 is a combination of Farber's disease and Sandhoff's disease. Ceramide is an important cellular lipid involved in signal transduction, the synthesis of complex sphingolipids, and in apoptosis pathways (el Bawab et al. 2002; Pettus et al. 2002). The Farber phenotype has been divided into seven different subgroups that differ in the age of onset, severity of symptoms and signs, and tissue involvement of ceramide storage. The acid ceramidase gene has 14 exons and 13 introns, and mutations so far described in humans have recently been reviewed (Zhang et al. 2000; Bar et al. 2001; Muramatsu et al. 2002). In the mouse, insertional mutagenesis of the acid ceramidase gene cause early embryonic lethality in homozygotes and progressive lipid storage disease in heterozygotes (Li et al. 2002).

Differential Diagnosis

Hepatic xanthomas have to be distinguished from situations where visible depositions of cholesterol-rich lipids involve liver cell systems in a diffuse distribution pattern (e.g., "hepatic cholesterolosis" in hepatic cholesterol storage disease; a minor variant of Wolman's disease; Verola et al. 1983). This distinct type of lipid accumulation in several hepatic cell systems has also been observed in the respective animal model, the Wolman's disease rat or Yoshida rat (Kuriwaki and Yoshida 1999).

Lipogranulomas, Lipogranulomatosis, and Mineral Oil Granulomas of the Liver

Hepatic Lipogranuloma

Hepatic lipogranulomas in a wider sense of the term are focal accumulations of macrophages that have pinocytosed neutral fat and other lipids. Lipogranulomas are well known to occur in adipose tissue following adipocyte damage with release of neutral fat from injured or dead cells, but they also occur in fatty livers subsequent to steatotic hepatocyte injury and death. In case of numerous such lesions, the term lipogranulomatosis is sometimes used. Clusters of hepatic lipogranulomas can be identified in vivo by means of modern imaging techniques and may present as small tumor-like lesions.

The morphologic definition of lipogranulomas led to the inclusion, apart from those caused by neutral fat, also of reactions to exogenous substances inducing a similar or the same histology, e.g., mineral oil. Lipogranulomas sensu stricto represent a macrophage- and lymphocyte-driven reaction to triglycerides (neutral fat) (Iversen et al. 1970; Christoffersen et al. 1971). They mainly occur in the setting of hepatic steatosis of any cause (Christoffersen et al. 1971; Andersen et al. 1984; Ferrell et al. 1995). In a study of 61 morbidly obese patients, patients showing lipogranulomas in liver biopsies were significantly more obese than patients without this change (Andersen et al. 1984). In a study comparing patients with nonalcoholic steatohepatitis (NASH) and alcoholic steatohepatitis (ASH), lipogranulomas were more remarkable in the ASH group (Morita et al. 2005). The etiology of hepatic lipogranulomas depends, however, markedly on epidemiological factors. Lipogranulomas are also a features of some types of chronic HCV infection. Among 376 sequential, archival liver biopsy specimens examined in New York, 58 (15.4 %) had hepatic lipogranulomas, including 46 patients with hepatitis C and 14 patients with fatty liver disease. Hepatic lipogranulomas were more often seen in patients with hepatitis C (21 %) and fatty liver disease (18 %). Therefore, hepatitis C, which can be associated with hepatic steatosis, is an additional important cause of lipogranulomas (Zhu et al. 2010).

The prevalence of hepatic lipogranulomas is only partially known, and the data are markedly related to the sampling used (biopsies vs. autopsies) and to the histologic methods employed (paraffin sections vs. lipid staining). Part of the investigations include lesions that may have been caused by exogenous oily

substances, such as mineral oil, hence not representing true lipogranulomas. In liver biopsies, lipogranulomas have an estimated frequency of 2.4–5 % (Delladetsima et al. 1987; Scheuer and Lefkowitch 2006). Portal tract lipogranulomas were recognized in 2.4 % of biopsies and were consistently associated with hepatic steatosis (Delladetsima et al. 1987). In an autopsy study (465 autopsies), they were found in 48 %, which is a very high figure that may markedly depend on the autopsy material and the criteria used (Wanless and Geddie 1985). In this study, hepatic lipogranulomas were more common in portal tracts than adjacent to the terminal hepatic venules and more frequent in older subjects (especially men). These two findings suggest that, in addition to neutral fat, mineral oil exposure (see below) may have played a significant role in the etiology of the lipogranulomas found in this investigation (what also the authors took into consideration).

Pathology

In case of larger lipogranulomas, the yellowish cut surface of steatotic livers may show discrete spots of a darker yellow, usually of the size of 1–2 mm. Numerous lipogranulomas forming dense clusters appear as yellow granular collections of coalescing lesions. As in other organs and tissues, lipogranulomas of the liver are histologically defined as roughly spheroid accumulations of activated macrophages and lymphocytes. In early lesions, the macrophages (Kupffer cells) surround extracellular lipid droplets (vacuoles in paraffin sections). The macrophages may show discrete epithelioid changes in some cases. The periphery of lipogranulomas mostly exhibits only few lymphocytes. Older lesions reveal less vacuoles, but the macrophages have pinocytosed the lipid and have become lipophages (foamy cells). Some lipogranulomas may contain multinucleated giant foam cells of the Touton type (Touton giant cells; see below), although Touton cells are more frequently encountered in xanthomatous lesions described in the previous chapter. Hepatic lipogranulomas are usually microscopic, but they may grow to macroscopically recognizable size and, in case they form conglomerate lesions, may be seen radiologically. Rarely, lipogranulomas result in a generalized process in the liver, progressively replacing the liver parenchyma and portal tracts.

Where are lipogranulomas typically located within the liver? Many authors noted that hepatic lipogranulomas are usually located in portal tracts (Stryker 1941; Goldberg and Saphir 1960; Boitnott and Margolis 1970; Nochomovitz et al. 1975; Blewitt et al. 1977), which may more often represent mineral oil granulomas, while other authors found most lipogranulomas in the pericentral lobule zone 3 (Christoffersen et al. 1971; Klatskin 1977; Dincsoy et al. 1982). True neutral fat lipogranulomas will probably develop at sites where most steatotic hepatocytes are damaged or are decaying. Ultrastructurally, fat droplets in severely fatty livers are encircled by lymphoid cells and histiocytoid cells. There was evidence that fat droplets protruded through the cell membranes of hepatocytes, followed by settling of macrophages/histiocytes and lymphocytes around such fat protrusions. Remnants of liver cells may be seen between the fat droplets and the macrophages (Petersen and Christoffersen 1979). Lipogranulomas consist of lipid-storing macrophages that are CD68-immunoreactive. It is not yet known whether cells of the hepatic macrophage system, i.e., Kupffer cells, are recruited to form granulomas, or whether blood-borne monocytes attracted to lipid accumulations are involved. However, prominently enlarged and aggregated Kupffer cells were observed in steatohepatitis, with a predominantly perivenular distribution, suggesting a potential direct Kupffer cell role in hepatic lipid processing (Lefkowitch et al. 2002).

Hepatic Phlebocentric Lipogranulomatosis

This is a very rare disorder of unknown cause that has first been described based on autopsy findings in two patients with no history of liver disease (Keen et al. 1985). The livers showed congestive alterations caused by a process mimicking veno-occlusive disease. In both patients, central veins

were occluded by an inflammatory and fibrosing process, with a striking accumulation of lipid-containing macrophages showing large fat vacuoles (Oil Red O-positive and osmiophilic). Giant cells were also noted. In one of the patients, the process had extended into the sublobular venous radicles, where intimal proliferation and sclerosis were present. The etiology of these lesions remained unknown, but an environmental insult such as a drug or toxin were suspected.

Other Types of Granulomas Containing Neutral Fat

An increased prevalence of hepatic lipogranulomas (56 %) was observed in patients with rheumatoid arthritis who had been routinely biopsied to evaluate side effects of methotrexate therapy. The lipogranulomas contained a dark pigment shown, in few cases, to represent gold-containing particles (chrysiasis). It was, therefore, assumed that lipogranulomas were caused by the frequent administration of gold in an oily vehicle (Landas et al. 1992).

Mineral Oil Granulomas

Lipogranulomas in the liver can be induced by exogenous lipoid-like substances or substances histologically mimicking lipid accumulation, such as mineral oil (Stryker 1941; Boitnott and Margolis 1970; Nochomovitz et al. 1975; Dincsoy et al. 1982; Fleming et al. 1998) or paraffin oil (Trivalle et al. 1991). This issue has already been discussed briefly above. Mineral oil has been used or is still used for the treatment of constipation and enters the food chain owing to its use as a lubricant for machines, e.g., in bakeries.

What Are Touton Giant Cells?

Touton giant cells are large and multinucleated cells resembling foreign body-type giant cells, but usually with a ringlike arrangement of the nuclei and a central vacuolated area containing numerous lipid droplets. Although not investigated so far, it is assumed that these giant cells, similar to other multinuclear giant cells, develop via fusion of macrophages mediated by several cytokines/lymphokines (McNally and Anderson 1995; Anderson 2000). The eponymic designation goes back to Karl Touton (1858–1934), a German dermatologist. Student of Ernst Ziegler, Moriz Kaposi, Albert Neisser, and Isidor Neumann, and after studies in Augsburg and Breslaw, he settled in Wiesbaden as a dermatologist and built up an international reputation (Herxheimer 1935; Gougerot 1935; Gans 1964; Holubar 1990). In this function, he published several articles on phytodermatosis and described his "xanthelasmic giant cell" (Touton 1885; Aterman et al. 1988). Touton wrote his survey on xanthomas when he was only 25 years of age. Touton described the characteristic features of multinucleated giant cells occurring in xanthomatous lesions, but the presence of such cells in lesions, then called "endothelioma adiposo," had been noted earlier already by an Italian author, who noted large cells showing numerous nuclei "da impartire loro la forma de celluli giganti" ("rendering them the feature of giant cells"; De Vincentiis 1883; reviewed in Aterman et al. 1988). Apart from Touton's activities as a physician and professor of medicine, he was an outstanding botanist specialized mainly in the composite genus, *Hieracium*. He published numerous botanical works and left a *Hieracium* herbarium consisting of about 20,000 specimens, now kept in the Botanical Museum Berlin-Dahlem, Germany (Vogt 1998). Among this genus of hawkweed, one species has his name (*Hieracium toutoni*).

Necrobiotic Granulomas of the Liver (Rheumatoid Nodules, Rheumatoid Nodulosis, Rheumatismus Nodosus Hepatis)

Introduction

Patients with seropositive rheumatoid arthritis develop rheumatoid nodules (RN; Hart 1994). RN have already been recognized as a soft tissue

manifestation of rheumatoid arthritis in the nineteenth century (Hilliers in 1868 and Jacoud in 1874), but the first detailed description is by Meynet (1875). The pathology of rheumatism was studied in detail by the pathologists Aschoff, Klinge, and Gräff (review: Keitel 2008). The term, rheumatismus nodosus, had been coined by Rehn. Classic RN occur in approximately 20–25 % of patients with seropositive rheumatoid arthritis and are the most common extra-articular manifestation of this disease (Kaye et al. 1984; Ziff 1990). A much greater incidence (75 %) is observed in patients with rheumatoid arthritis-associated Felty syndrome. The HLA-DR4 haplotype is predictive of the risk of subcutaneous RN in rheumatoid arthritis. Homozygosity for HLA-DRB1 *0401 makes rheumatoid arthritis patients susceptible to major organ involvement. These nodules may evolve very rapidly, within few hours to days, and grow up to few cm in diameter, may form conglomerate lesions, and are known to also develop in visceral organs and tissues. The nodules can undergo accelerated growth (subsequent to therapy, e.g., with methotrexate), but can also regress spontaneously (McCarty 1991; Garcia-Patos 2007; Highton et al. 2007).

Rheumatoid Nodules of the Hepatobiliary Tract ("Rheumatismus Nodosus Hepatis")

RNs (nodulosis) in the liver are very rare (Fig. 13). An autopsy report referring to a patient with chronic rheumatoid polyarthritis documented, apart from widespread amyloidosis, numerous grayish-white nodules with a peripheral zone scattered throughout the liver, their maximum diameter being 5 mm. Histologic analysis of these nodules disclosed a central necrosis surrounded by histiocytes/macrophages in a palisade arrangement, and peripheral fibrosis associated with chronic inflammation. This morphology closely resembled that of typical rheumatoid nodules in observed in the subcutis (Smits and Kooijman 1986). RN rarely also develop in the mesentery and may mimic an intra-abdominal malignancy (Thinda and Tomlinson 2009).

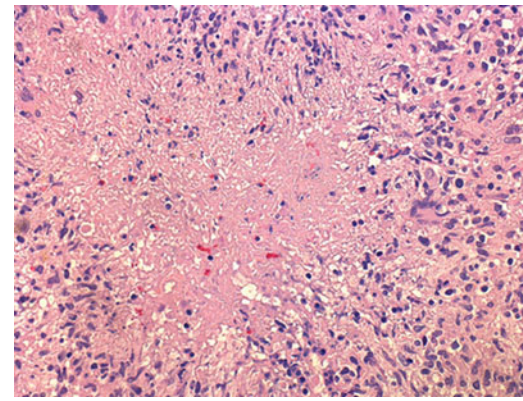

Fig. 13 Rheumatoid nodule of the liver. A focus of fibrinoid necrosis (*center*) is surrounded by a palisading granuloma (hematoxylin and eosin stain)

What Are Rheumatoid Nodules?

Rheumatoid nodules (RN, tumefactive necrobiotic granulomas; nodulosis) are histologically characterized by a central, so-called fibrinoid, necrosis showing a typical, "geographic" shape, a demarcation zone consisting of epithelioid macrophages (sometimes arranged in a typical palisading, radial, or corona-like pattern), and a peripheral rim of fibrosclerotic tissue (Ziff 1990). The histopathologic progression of RN occurs in three stages: an acute inflammatory stage, a granulomatous stage, and finally a necrotic stage. In the acute inflammatory stage, a nonspecific granulation tissue develops as a reparation response. The second or granulomatous stage is the stage of massive macrophage reaction with palisading. Fibrinoid necrosis develops in the preexisting collagenous tissue, but also involves the macrophages of the granulomas. The most prominent cells of the rheumatoid nodule belong to the monocyte/macrophage lineage. These cells migrate from the vascular periphery of the nodule toward the central palisade layer (Palmer et al. 1987a). The migrating cells undergo differentiation to epithelioid macrophages (so-called maturation) and release cytokines and the

MRP-8/MRP-14 heterodimer, labeling them as newly arrived activated macrophages (Palmer et al. 1987b; De Rycke et al. 2005). The immigrating macrophages and their epithelioid offspring accumulate in the palisade interspersed with myofibroblasts and fibroblasts. In addition to monocytes /macrophages, lymphocytes are present in and around the RN. Both CD4 and CD8 subtypes are detectable in the nodules, and these cells tend to accumulate around blood vessels and in the area immediately outside the palisade (Highton et al. 2007). Lymphoid cells in this tissue space are attracted by chemokines produced by the nodules, including CCL21, CXCL12, and CXCL13. The peri-palisade compartment also contains dendritic cells (Highton et al. 2000). In contrast to T cells, B lymphocyte density around RN is more variable, and B cells in RN are mostly sparse and sometimes almost undetectable, but B cell signaling and the formation of germinal centers has been reported. The markedly eosinophilic necrosis was initially interpreted to contain large amounts of fibrin (Fahr 1918), finally resulting in the term fibrinoid necrosis to denote the fibrin-like staining of the central necrosis. The name "fibrinoid" goes back 1880, when Neumann described a new picrocarmine staining to demonstrate the features of "fibrinoid degeneration" (Neumann 1880; reviewed in Bajema and Bruijn 2000). A change from "degeneration" to "necrosis" appeared in 1932 (Klinger 1932), and still later, several morphologic variants of fibrinoid necrosis were distinguished (Zeek 1952). In regard to the composition of fibrinoid necrosis, it was first assumed that precipitation of fibrin and/or other coagulation factors, necrosis of collagen, and coagulation of the intercellular ground substance, or a combination of these, were involved (Altshuler and Angevine 1949). In fact, fibrin is one component that is detectable in this type of lesions (Gitlin et al. 1957). But later it was found that the eosinophilic material of fibrinoid at least in part consists of fibronectin isoforms indicating that the lesion is actually part of a wound-healing process (Bajema et al. 1998). RN are also termed tumefactive necrobiotic granulomas, or nodulosis (Riedlinger et al. 2005), and rheumatoid nodulosis employed for variants of rheumatoid arthritis with numerous soft tissue nodules and an unusual, rather benign course (Ginsberg et al. 1975; Wisnieski and Askari 1981; Couret et al. 1988; Goni et al. 1992).

Malakoplakia of the Hepatobiliary Tract

Introduction

Malakoplakia (Greek: soft plaque; frequently used term: malacoplakia, von Hansemann's disease) is an unusual inflammatory process that was first described in the early 1900s (Michaelis and Gutmann 1902), although the discovery of the lesion as such goes back to Michaelis and Gutmann's senior colleague, von Hansemann (reviews: Damjanov and Moriber Katz 1981; Stanton and Maxted 1981; Dasgupta et al. 1999). Malakoplakia is mostly known from the urinary tract, but it may also involve extra-urinary sites (Yousef and Naghibi 2007), including the appendix, colon, spleen, skin, frontal and ethmoidal sinuses, tongue, lungs, lymph nodes, and brain.

The eponymic designations go back to Carl Gutmann (born 1872), a German physician, and Leonor Michaelis (1875–1947). Leonor Michaelis, an assistant of Paul Ehrlich, is particularly known for his role in the formulation of the Michaelis-Menten law, equation, and constant in enzymology (1913). Maud Leonora Menten (1879–1960), one of the first Canadian women to become a doctor, came to Berlin in 1912 to work together with Michaelis on invertase enzyme activity, and together they developed their now famous equation. Michaelis also discovered Janus green as a supravital stain for mitochondria. Together with Sam Granick, he furthermore characterized ferritin and apoferritin. However, the first human case of malakoplakia was in fact seen by von Hansemann in 1901, who had read about a similar disease described by Olt in a veterinary magazine in 1900. von Hansemann provided his assistant, Dr. Gutmann, with the details of his case, as Dr. Michaelis had agreed to investigate the disease in a collaborative approach. von Hansemann himself published

this index case 1 year after Michaelis and Gutmann (Von Hansemann 1903; review: Dasgupta et al. 1999). Malakoplakia may, hence, be called von Hansemann's disease.

Malakoplakia of the Hepatobiliary Tract

Malakoplakia of the liver is a rare condition (Moldavskii and Rustamov 1984; De Saint-Maur and Gallot 1990; Robertson et al. 1991; Boucher et al. 1994; Chen et al. 1994; Hartman et al. 2002; Botros et al. 2014). Hepatic malakoplakia may be detected as an incidental alteration at autopsy (Botros et al. 2014). Reported cases of liver malakoplakia were associated with immunosuppression and liver abscess (Robertson et al. 1991), perforated colonic diverticulum (Boucher et al. 1994), small bowel ileus in conjunction with *Klebsiella* sepsis (Hartman et al. 2002), hepatic invasion by renal parenchymal malakoplakia (Chen et al. 1994), hepatic multichamber pseudocyst in miliary tuberculosis (Moldavskii and Rustamov 1984), infected polycystosis (De Saint-Maur and Gallot 1990), and systemic lupus erythematodes (Botros et al. 2014). It is seen that in part of cases, bacterial infection seems to have been involved. Malakoplakia also occurs in the bile duct system and in the gallbladder (Sahel et al. 1976; Charpentier et al. 1983; Hide et al. 2001; Regragui et al. 2003; Agnarsdottir et al. 2004; Di Tommaso et al. 2005). Interestingly, renal and intestinal malakoplakia has been repeatedly observed in patients after liver transplantation (Rull et al. 1995; Kamishima et al. 2000; Weinrach et al. 2004), but this association is likely to be based on immunosuppression, because a similar association has been seen in renal graft recipients (Ourahma et al. 1996; Berney et al. 1999).

Lesions of malakoplakia are variably sized yellow to brownish plaques or nodules that are usually soft (malakos, soft) and friable, sometimes with central liquefaction and frequently with a peripheral rim of inflammatory hyperemia. Malakoplakia in the liver appears to follow a sequence of changes also seen in other locations of this disorder. There are three phases in the histopathologic evolution, originally defined for urinary tract malakoplakia (Smith 1965). In the early phase, plasma cells and the distinct macrophages (the so-called von Hansemann cells) prevail, and classic Michaelis-Gutmann bodies are not usually seen. In the second or classic (granulomatous) phase, large macrophages with Michaelis-Gutmann bodies, lymphocytes, and occasional giant cells are found. The third phase is the "healing" phase, which consists of fibroblasts and collagen deposits around macrophages, along with rather few and sometimes extracellular Michaelis-Gutmann bodies. In the liver, the fully developed lesion shows a rather circumscribed accumulation of histiocytes/macrophages with an admixture of plasma cells and lymphocytes. Already in the H&E preparation, targetoid cytoplasmic inclusions are seen in the macrophages, which represent the Michaelis-Gutmann bodies which have distinct histochemical and ultrastructural features (McClure et al. 1981; Robertson et al. 1991). In a liver biopsy specimen, portal and periportal regions showed scattered small, round to oval targetoid structures consistent with Michaelis-Gutmann bodies that stained with PAS (with and without diastase treatment), von Kossa calcium stain, and colloidal iron stain. CD 68 immunohistochemistry identified the bodies to be situated within macrophages (Hartman et al. 2002). In late stage, fibrosed lesions of malakoplakia and Michaelis-Gutmann bodies tend to accumulate in the extracellular space, both in hepatic malakoplakia (Robertson et al. 1991) and in extrahepatic malakoplakia (Esparza et al. 1981). In malakoplakia of the gallbladder wall, yellowish plaques or nodules are noted, with a histology as outlined above, whereby the targetoid Michaelis-Gutmann bodies may be crowed just beneath the mucosal epithelium (Di Tommaso et al. 2005).

Etiology and Pathogenesis

Malakoplakia is usually associated with bacterial or fungal infections, in particular infections with *Klebsiella* and *Escherichia coli*, suggesting a

pathogenetic relationship between bacterial antigen and a functional disorder of the macrophage system. Apart from *Klebsiella* and *Escherichia coli*, germs found in conjuncture with malakoplakia include mycobacterium tuberculosis, *Rhodococcus equi* (mainly pleuropulmonary lesions in AIDS patients), *Shigella boydii*, and paracoccidioidomycosis (Yuoh et al. 1996; Rocha et al. 1997; Raguin et al. 1999; Altwegg and Hinrickson 1999; Guerrero et al. 1999; Caterino-de-Araujo et al. 2000). The reason why macrophages react in a particular way in infected patients developing malakoplakia is not known, but functional and structural monocyte abnormalities are suspected to play a role (van Crevel et al. 1998). The morphogenesis of Michaelis-Gutmann bodies has been studied (Ho 1979; Yuoh et al. 1996). Immature or early Michaelis-Gutmann bodies consist of a circular, electron-dense core containing bacteria and parts thereof, whereas mature Michaelis-Gutmann bodies have a concentric, trilaminated structure with a central mineralized core and usually no remnants of bacterial cell walls. These findings suggested that the bodies are formed around undigested or incompletely digested bacteria as a seemingly alternative pathway for bacterial destruction (Yuoh et al. 1996).

Hepatic Gaucher Cell Pseudotumors ("Gaucheroma")

Introduction

Gaucher disease is autosomal recessive glucocerebrosidosis and is the most common lysosomal storage disease (reviews: Rosenbloom and Weinreb 2013). It is caused by deficiency of the lysosomal enzyme, beta-glucocerebrosidase, leading to the accumulation of the substrate, glucocerebroside, in the monocyte/macrophage system of many tissues and organs. Glucocerebrosidase normally splits the glycolipid, glucocerebroside, into ceramide and glucose (Chen and Wang 2008). Based on the age of manifestation and clinical presentation, three types of Gaucher disease are recognized, all localized to the same chromosomal region and involving the same gene. Type 1 (the non-neuropathic type; OMIM 230800) is the most frequent form of the disease. Type 2 (acute infantile neuropathic Gaucher disease; OMIM 230900) typically begins within 6 months of birth and has a rapidly progressive course with unfavorable outcome. Type 3 (chronic neuropathic Gaucher disease; OMIM 231000) begins at any time in childhood or even adulthood. It has a milder phenotype than type 2 and shows a slow progression. Type 3 predominates in the northeastern part of Sweden, Norrbotten (Norrbottnian type; Erikson 1986). Around 300 unique mutations have been reported in the glucocerebrosidase gene (GBA), with a distribution that spans the entire gene.

More than 200 of these mutations are missense mutations, while nonsense mutations and splice junction mutations each account for less than 20 mutation types. Thirty-six small insertions or deletions that lead to either frameshifts or in-frame alterations have been found. Recombination events with a highly homologous pseudogene downstream of the GBA locus have been identified, resulting from gene conversion, fusion, or duplication (Hruska et al. 2008). Mutant glucocerebrosidase variants present variable degrees of endoplasmic reticulum (ER) retention and undergo ER-associated degradation (ERAD) in the proteasome (Bendikov-Bar and Horowitz 2012). The degree of ERAD of the mutant enzyme correlates with and is one of the factors that determine Gaucher disease severity (Ron et al. 2010). Gaucher cells typically accumulate in the bone marrow, causing severe bone complications (Poll et al. 2010).

Liver Manifestations of Gaucher's Disease

Among 500 patients with Gaucher disease, 7.8 % had sonographic evidence of hepatic disease. Hepatomegaly is a well-known feature and is sometimes marked with rounded or blunt liver margins (Gruber 1930). The color of the involved liver is variable, in children sometimes pink yellow in case of marked. In long-standing cases, the

liver is grayish yellow, tan, or, rarely, chocolate brown.

Gaucher Cell Infiltration

Pick noted a characteristic whitish network in the parenchyma resulting in a geographic lesion pattern. Focal accumulations of Gaucher cells can produce nodules of variable diameter. These lesions are usually hyperechoic and slowly evolving (Hadas-Halpem et al. 2010).

Accumulation of cerebroside-laden macrophages (the Gaucher cells) in hepatic sinusoids and portal tracts are a typical feature of this storage disorder. In the course of the disease, chiefly in patients without adequate therapy, inflammation, septal fibrosis, and cholestatic liver cirrhosis may develop (Bothe et al. 2013; Debnath et al. 2013). Under enzyme replacement therapy, the number of Gaucher cells is markedly decreased (Hulkova et al. 2009). Large accumulations of Gaucher cells with nodules formation may develop central necrosis (Gruber 1930).

Patients with Gaucher disease type 1 show a frequent iron overload of both hepatocytes and Kupffer cells (Bohte et al. 2013). This alteration is associated with hyperferritinemia (with a mean 3.7-elevation of serum ferritin), and prior splenectomy is associated with most severe hyperferritinemia. This iron overload is not related to HFE mutations (Stein et al. 2010).

Gaucher Cell Pseudotumors (So-Called Gaucheromas)

Gaucher cell pseudotumor is defined as a mass-like accumulation of Gaucher cells (cerebroside-containing macrophages). This lesion occurs in the liver, where pseudotumors of this type within or adjacent to parenchymal tissue are a common finding (Poll et al. 2000). Sometimes, gaucheromas grow to important size. In a 23-year-old male patient with Gaucher disease presented with hepatomegaly, an ultrasound of the abdomen showed a hyperechoic mass of up to 9 cm in diameter. Liver MRI demonstrated a well-delineated mass, which appeared hyperintense in comparison to adjacent liver substance on T2-weighted images. A central hypointense scar was detected, suggestive of focal nodular hyperplasia. Biopsy of the lesion revealed accumulation of typical Gaucher cells (Poll and vom Dahl 2009).

Differential Diagnosis

Storing macrophages resembling Gaucher cells can occur in the bone marrow and probably also in visceral organs of some patients with hematologic malignancy or anemia. These cells are termed pseudo-Gaucher cells. The cells have also been found in large numbers in the liver following chemotherapy and bone marrow transplantation (Stenzel and Weeks 2013). In case of large Gaucher cell nodules, hepatocellular carcinoma (HCC) should be excluded in this situation, because HCC without preexisting cirrhosis is increased in Gaucher disease (Breiden-Langen et al. 1991; Xu et al. 2005; De Fost et al. 2006). Cholangiocarcinoma has also been reported (Hulkova et al. 2009).

Neutrophilic Dermatoses/Systemic Neutrophilic Diseases: Manifestations in the Liver

Introduction

Neutrophilic dermatoses (systemic neutrophilic diseases) constitute a group of related and in part hereditary disorders which comprise pyoderma gangrenosum, Sweet's syndrome, erythema elevatum diutinum, subcorneal pustular dermatosis, acute generalized exanthematous pustulosis (AGEP), pustular vasculitis, and CANDLE syndrome. There are phenotypical overlaps between part of these diseases (review: Cohen 2009). The most important members of this group of disorders are pyoderma gangrenosum and Sweet's syndrome, both characterized by dense dermal inflammatory infiltrates composed of neutrophils, usually with little evidence of a primary vasculitis

(review: Lear et al. 1997). Part of these disorders are associated with visceral aseptic abscesses, including the liver. Such abscesses are deep, sterile, round lesions consisting of neutrophils that do not respond to antibiotics but improve rapidly with corticosteroids.

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis of unknown etiology (review: Wollina and Haroske 2011). In its classical clinical presentation, the main feature of PG are pustules or plaques that rapidly progress painful skin ulcers with a necrotic center and red to violaceous undermined margins. PG is typically associated with systemic inflammatory disease, but particularly with inflammatory bowel disease and arthritis, including juvenile rheumatoid arthritis. It has been reported that PG develops in 30–60 % of patients with inflammatory bowel disease (Powell et al. 1996). PG can be associated with visceral manifestations, including cavitating nodular pulmonary inflammation (the lung being the most frequent internal organ site of PG), aseptic splenic abscess, pancreatitis, and focal liver inflammation.

Involvement of the Liver and the Biliary Tract

In PG, focal and sometimes multiple liver lesions representing aseptic abscesses can develop (Urano et al. 1995; Ferrazzi et al. 1996; Hastier et al. 1996; Rodot et al. 1996; Vadillo et al. 1999; Delbrel et al. 2001; Matsumura et al. 2011). At imaging the nodular liver lesions show up as cystic, well-circumscribed foci with cystic change (Vadillo et al. 1999). Aseptic abscesses of the liver in PG are often associated with analogous lesions in the spleen (hepatosplenic abscesses; Vadillo et al. 1999). Fine needle aspiration of the liver lesions yielded purulent, neutrophil-rich fluid, Gram and Ziehl-Neelsen stains being negative (Vadillo et al. 1999).

PG is sometimes associated with other hepatic disorders, including chronic active hepatitis (Byrne et al. 1976; Marshall et al. 1978; Burns and Sarkany 1979; Sampson et al. 1982; Banerjee 1990) and chronic persistent hepatitis (Green et al. 1985).

References

Abbitt PL, Teates CD (1989) The sonographic appearance of extramedullary hematopoiesis in the liver. J Clin Ultrasound 17:280–282

Abedin et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12714580

Ackerman et al. 1982. http://www.ncbi.nlm.nih.gov/pubmed/7042896

Ackerman et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/11834744

Addison T, Gull W (1851) On a certain affection of the skin, Vitiligoidea – A. plana, B. tuberosa, with remarks. Guys Hosp Rev 7:265

Agnarsdottir M, Willen R, El Hag IA (2004) Three cases of malacoplakia of the gallbladder. Ups J Med Sci 109:255–259

Altshuler CH, Angevine DM (1949) Histochemical studies on the pathogenesis of fibrinoid. Am J Pathol 25:1061–1077

Altwegg M, Hinrickson HP (1999) *Shigella boydii* as cause of malakoplakia in a human immunodeficiency virus-infected patient. Clin Infect Dis 29:1602

Andersen T, Christoffersen P, Gluud C (1984) The liver in consecutive patients with morbid obesity: a clinical, morphological, and biochemical study. Int J Obes 8:107–115

Anderson JM (2000) Multinucleated giant cells. Curr Opin Hematol 7:40–47

Andresen B, Blum J, von Weymarn A, Burge M, Steinbrich W, Duewell S (2000) Hepatic fascioliasis: report of two cases. Eur Radiol 10:1713–1715

Ask-Upmark E (1945) Tumours simulating intrathoracic heterotopia of bone marrow. Acta Radiol 26:425–440

Aterman K, Remmele W, Smith M (1988) Karl Touton and his "xanthelamatic giant cell". A selective review of multinucleated giant cells. Am J Dermatopathol 10:257–269

Aytac S, Fitoz S, Akyar S, Atasoy C, Erekul S (1999) Focal intrahepatic extramedullary hematopoiesis: color Doppler US and CT findings. Abdom Imaging 24:366–368

Azuma et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12041704

Bajema IM, Bruijn JA (2000) What stuff is this! A historical perspective on fibrinoid necrosis. J Pathol 191:235–238

Bajema IM, Hagen EC, de Heer E, Bruijn JA (1998) The PAF-Halmi staining distinguishes two types of glomerular fibrinoid necrosis in systemic vasculitis. J Am Soc Nephrol 9:532A

Banerjee 1990. http://www.ncbi.nlm.nih.gov/pubmed/2317437

Bar J, Linke T, Ferlinz K, Neumann U, Schuchman EH, Sandhoff K (2001) Molecular analysis of acid ceramidase deficiency in patients with Farber disease. Hum Mutat 17:199–209

Ben Rejeb A, Haouala H, Ben Hammadi F, Ben Othman M, Khelil A, Gueddiche M, Ben Cheikh M, Rokbani L (1992) Pseudotumor extramedullary hematopoiesis. Report of 3 cases and review of literature (in French). Ann Pathol 12:183–187

Benbow EW (1990) Xanthogranulomatous cholecystitis. Br J Surg 77:255–256

Bendikov-Bar I, Horowitz M (2012) Gaucher disease paradigm: from ERAD to comorbidity. Hum Mutat 33:1398–1407

Berney T, Chautems R, Ciccarelli O, Latinne D, Pirson Y, Squifflet JP (1999) Malakoplakia of the caecum in a kidney-transplant recipient: presentation as acute tumoral perforation and fatal outcome. Transpl Int 12:293–296

Bhatia and Sarin 1994. http://www.ncbi.nlm.nih.gov/pubmed/8147371

Blewitt RW, Bradbury K, Greenall MJ et al (1977) Hepatic damage associated with mineral oil deposits. Gut 18:476–479

Bohte et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23554863

Burns and Sarkany 1979. http://www.ncbi.nlm.nih.gov/pubmed/535175

Byrne et al. 1976. http://www.ncbi.nlm.nih.gov/pubmed/999311

Boitnott JK, Margolis S (1970) Saturated hydrocarbons in human tissues: III. Oil droplets in the liver and spleen. Johns Hopkins Med J 127:65–78

Bothe AE, van Dussen L, Akkerman EM, Nederveen AJ, Sinkus R, Jansen PL, Stoker J et al (2013) Liver fibrosis in type I Gaucher disease: magnetic resonance imaging, transient elastography and parameters of iron storage. PLoS One 8:e57507

Botros N, Yan SR, Wanless IR (2014) Malakoplakia of liver: report of two cases. Pathol Res Pract 210:459–462

Boucher LD, Aoki M, Lee EY, Cibull ML (1994) Malakoplakia of liver associated with a perforated colonic diverticulum. A case report and review of the literature. J Clin Gastroenterol 19:318–320

Bradley MJ, Metreweli C (1990) Sonography of extramedullary hematopoiesis of the liver. AJR Am J Roentgenol 154:900–901

Breiden-Langen et al. 1991. http://www.ncbi.nlm.nih.gov/pubmed/16511436

Caffey J, Silverman WA (1945) Infantile cortical hyperostosis: preliminary report on a new syndrome. AJR Am J Roentgenol 54:1–16

Caterino-de-Araujo A, de los Santos-Fortuna E, Zandona-Meleiro MC, Calore EE, Perez Calore NM (2000) Detection of the 20-kDA virulence-associated antigen of *Rhodococcus equi* in malakoplakia-like lesion in pleural tissue obtained from an AIDS patient. Pathol Res Pract 196:321–327

Chantranuwat C (2004) Systemic form of juvenile xanthogranuloma: report of a case with liver and bone marrow involvement. Pediatr Dev Pathol 7:646–648

Charpentier P, Prade M, Bognel C, Gadenne C, Duvillard P (1983) Malacoplakia of the gallbladder. Hum Pathol 14:827–828

Chen M, Wang J (2008) Gaucher disease: review of the literature. Arch Pathol Lab Med 132:851–853

Chen CS, Lai MK, Hsueh S, Hwang TL, Chuang CK (1994) Renal malacoplakia with secondary hepatoduodenal involvement. J Urol 151:982–985

Cho TJ, Moon HJ, Cho DY, Park MS, Lee DY, Yoo WJ, Chung CY, Choi IH (2008) The c.3040C > T mutation in COL1A1 is recurrent in Korean patients with infantile cortical hyperostosis (Caffey disease). J Hum Genet 53:947–949

Cho ES, Yu JS, Kim MJ, Kim JH, Chung JJ, Kim KW (2010) Focal eosinophilic necrosis on superparamagnetic iron oxide-enhanced MRI. AJR Am J Roentgenol 194:1296–1302

Choi JI, Lee JM, Kim SH, Lee JY, Lee MW, Han CK, Choi BI (2009) Differentiating focal eosinophilic necrosis of the liver from hepatic metastases using unenhanced and portal venous phase computed tomographic imagings: results of univariate and multivariate statistical analyses. J Comput Assist Tomogr 33:705–709

Christensen AH, Ishak KG (1970) Benign tumors and pseudotumors of the gallbladder. Report of 180 cases. Arch Pathol 90:423–432

Christoffersen P, Braendstrup O, Juhl E, Poulsen H (1971) Lipogranulomas in human liver biopsies with fatty change. A morphological, biochemical and clinical investigation. Acta Pathol Microbiol Scand A 79:150–158

Chvostek F (1911) Xanthelasma und Ikterus. Ztschr f Klein Med 73:476

Cohen PR (2009) Neutrophilic dermatoses: a review of current treatment options. Am J Clin Dermatol 10:301–312

Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, Kutok J, Clark J, Galinsky I, Griffin JD, Cross NC et al (2003) A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med 348:1201–1214

Cools J, Stover EH, Wlodarska I, Marynen P, Gilliland DG (2004) The FIP1L1-PDGFRalpha kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia. Curr Opin Hematol 11:51–57

Couret M, Combe B, Chuong VT, Leroux JL, Blotman F, Sany J (1988) Rheumatoid nodulosis: report of two cases and discussion of diagnostic criteria. J Rheumatol 15:1427–1430

Coutre S, Gotlib J (2004) Targeted treatment of hypereosinophilic syndromes and chronic eosinophilic

leukemias with imatinib mesylate. Semin Cancer Biol 14:23–31
Da Costa JL, Loh YS, Hanam E (1974) Extramedullary hemopoiesis with multiple tumor-simulating mediastinal masses in hemoglobin E-thalassemia disease. Chest 65:210–212
Damjanov I, Moriber Katz S (1981) Malakoplakia. Pathol Annu 16:103–126
Dardi LE, Marzano M, Froula E (1990) Fine needle aspiration cytologic diagnosis of focal intrahepatic extramedullary hematopoiesis. Acta Cytol 34:567–569
Dasgupta P, Womack C, Turner AG, Blackford HN (1999) Malacoplakia: von Hansemann's disease. BJU Int 84:464–469
De Fost M, vom Dahl S, Weverling GJ, Brill N, Brett S, Häussinger D et al (2006) Increased incidence of cancer in adult Gaucher disease in Western Europe. Blood Cells Mol Dis 36:53–58
De Rycke L, Baeten D, Foell D et al (2005) Differential expression and response to anti-TNF alpha treatment by infiltrating versus resident tissue macrophage subsets in autoimmune arthritis. J Pathol 206:17–27
De Saint-Maur P, Gallot D (1990) Hepatic malacoplakia as a complication of polycystosis (in French). Ann Pathol 10:50–51
De Vincentiis C (1883) Endothelioma adiposo. Riv Clin 35:481–501
Debnath CR, Debnath MR, Nabi N, Khan NA, Chakraborty S (2013) A case of Gaucher's disease progressing to liver cirrhosis. Mymensingh Med J 22:394–396
Delbrel X, Germain P, Fach J, Etienne G, Beylot C, Parrens M, De Mascarel A, Le Bras M et al (2001) Cutaneous pyoderma gangrenosum with hepatosplenic localization and monoclonal gammopathy. A case report (in French). Ann Med Interne (Paris) 152:65–67
Delladetsima JK, Horn T, Poulsen H (1987) Portal tract lipogranulomas in liver biopsies. Liver 7:9–17
Desmet VJ (1995) Histopathology of cholestasis. Verh Dtsch Ges Pathol 79:233–240
Dewar G, Leung NWY, Ng HK, Bradley M, Li AKC (1990) Massive, solitary, intrahepatic, extramedullary hematopoietic tumor in thalassemia. Surgery 107:704–707
Di Tommaso L, Arizzi C, Roncalli M (2005) Malacoplakia of the gallbladder. Histopathology 46:474–475
Dincsoy HP, Weesner RE, MacGee J (1982) Lipogranulomas in non-fatty human livers. A mineral oil induced environmental disease. Am J Clin Pathol 78:35–41
Dyer et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9119387
Ehlert K, Frosch M, Fehse N, Zander A, Roth J, Vormoor J (2007) Farber disease: clinical presentation, pathogenesis and a new approach to treatment. Pediatr Rheumatol 5:15
el Bawab S, Mao C, Obeid LM, Hannun YA (2002) Ceramidases in the regulation of ceramide levels and function. Subcell Biochem 36:187–205
Eriguchi N, Aoyagi S, Horiuchi H, Tamae T, Uchida S, Hiraki M, Nishimura K, Kawabata M, Hamada S (2002) Xanthogranulomatous cholecystitis with a liver abscess and metastatic endophthalmitis: report of a case. Surg Today 32:285–288
Erikson A (1986) Gaucher disease – Norrbottnian type (III). Neuropaediatric and neurobiological aspects of clinical patterns and treatment. Acta Paediatr Scand Suppl 326:1–42
Esparza AR, Mckay DB, Cronan JJ et al (1981) Renal parenchymal malakoplakia. Histologic spectrum and its relationship to megalocytic interstitial nephritis and xanthogranulomatous pyelonephritis. Am J Surg Pathol 13:225–236
Fahr Th (1918) Zur Frage des Rheumatismus nodosus. Zbl Path 29:625
Ferrazzi V, Rivière S, Sany J (1996) Association of pyoderma gangrenosum with hepato-pancreatic involvement in rheumatoid polyarthritis (in French). Rev Med Interne 17:266–267
Ferrell LD, Lee R, Brixko C, Bass NM, Lake JR, Roberts JP, Ascher N, Rabkin J (1995) Hepatic granulomas following liver transplantation. Clinicopathologic features in 42 patients. Transplantation 60:926–933
Fleming KA, Zimmerman H, Shubnik P (1998) Granulomas in the livers of humans and Fischer rats associated with the ingestion of mineral hydrocarbons: a comparison. Regul Toxicol Pharmacol 27:75–81
Franco V, Aragona F, Genova G, Florena AM, Stella M, Campesi G (1990) Xanthogranulomatous cholecystitis. Histopathological study and classification. Pathol Res Pract 186:383–390
Fried K, Manor A, Pajewski M, Starinsky R, Vure E (1981) Autosomal dominant inheritance with incomplete penetrance in Caffey disease (infantile cortical hyperostosis). Clin Genet 19:271–274
Futcher TB (1905) Xanthelasma and chronic jaundice. Am J Med Sci 130:939–951
Gans O (1964) Zur Geschichte der Vereinigung südwestdeutscher Dermatologen. Hautarzt 15:623–625
Garcia-Patos V (2007) Rheumatoid nodule. Semin Cutan Med Surg 26:100–107
Gensure RC, Mäkitie O, Barcklay C, Chan C, DePalma SR, Bastepe M, Abuzahra H et al (2005) A novel COL1A1 mutation in infantile cortical hyperostosis (Caffey disease) expands the spectrum of collagen-related disorders. J Clin Invest 115:1250–1257
Gil-Fernandez JJ, Martinez-Chamorro C, Tomas JF (2001) The irreplaceable image: a giant hepatic mass of myeloid metaplasia in a patient without myelofibrosis. Haematologica 86:445
Ginsberg MH, Genant HK, Yu TF, McCarty DJ (1975) Rheumatoid nodulosis: an unusual variant of rheumatoid disease. Arthritis Rheum 18:49–58
Gitlin D, Craig JM, Janeway CA (1957) Studies on the nature of fibrinoid in the collagen diseases. Am J Pathol 33:55–77
Glorieux FH (2005) Caffey disease: an unlikely collagenopathy. J Clin Invest 115:1142–1144

Goldberg GM, Saphir O (1960) Lipidosis of the liver portal spaces: I. A study of its relationship to the lymphatics of the liver. Arch Pathol Lab Med 69:586–593

Goni MA, Scheines EJ, Paira SO, Barcelo HA, Maldonado Cocco JA (1992) Rheumatoid nodulosis: a puzzling variant of rheumatoid arthritis. Clin Rheumatol 11:396–401

Gotlib J, Cools J, Malone JM, Schrier SL, Gilliland DG, Coutre SE (2004) The FIP1L1-PDGFR(alpha) fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and managment. Blood 104:2879–2891

Gougerot M (1935) Karl Touton. Bull Soc Fr Dermatol Syphiligr 42:413–415

Green et al. 1985. http://www.ncbi.nlm.nih.gov/pubmed/4067029

Griffin JH, Leung J, Bruner RJ, Caligiuri MA, Briesewitz R (2003) Discovery of a fusion kinase in EOL-1 cells and idiopathic hypereosinophilic syndrome. Proc Natl Acad Sci U S A 100:7830–7835

Gruber GB (1930) 6. Die Leber bei Erkrankungen des blut- und lymphbildenden Gewebs-Apparates. In: Henke F, Lubarsch O (eds) Handbuch der speziellen pathologischen Anatomie und Histologie, Vol. 5, Verdauungsdrüsen, Erster Teil, Leber. Julius Springer, Berlin, pp 669–672

Gualco G, Ojopi EB, Chioato L, Cordeiro DL, Negretti F, Bacchi CE (2010) Postsplenectomy sclerosing extramedullary hematopoietic tumor with unexpected good clinical evolution: morphologic, immunohistochemical, and molecular analysis of one case and review of the literature. Appl Immunohistochem Mol Morphol 18:291–295

Guerrero MF, Ramos JM, Renedo G, Gadea I, Alix A (1999) Pulmonary malacoplakia associated with *Rhodococcus equi* infection in patients with AIDS: case report and review. Clin Infect Dis 28:1334–1336

Gupta P, Naran A, Auh YH, Chung JS (2004) Focal intrahepatic extramedullary hematopoiesis presenting as fatty lesions. AJR Am J Roentgenol 182:1031–1032

Hadas-Halpem I, Deeb M, Abrahamov A, Zimran A, Elstein D (2010) Gaucher disease: spectrum of sonographic findings in the liver. J Ultrasound Med 29:727–733

Han JK, Choi BI, Cho JM, Chung KB, Han MC, Kim CW (1993) Radiological findings of human fascioliasis. Abdom Imaging 18:261–264

Han JK, Han D, Choi BI, Han MC (1996) MR findings in human fascioliasis. Trop Med Int Health 1:367–372

Han JK, Jang HJ, Choi BI, Kim SH, Kim TK, Won HJ, Kim YI, Cho SY (1999) Experimental hepatobiliary fascioliasis in rabbits: a radiology-pathology correlation. Invest Radiol 34:99–108

Hardaway W (1884) Xanthoma multiplex. J Cutan Vener Dis 354:20

Hart FD (1994) Rheumatoid nodules. Ann Rheum Dis 53:83

Hartman G, Yong SL, Chejfec G (2002) Malakoplakia of liver diagnosed by a needle core biopsy: a case report and review of the literature. Arch Pathol Lab Med 126:372–374

Hastier P, Caroli-Bosc FX, Bartel HR, Harris AG, Maes B, Arpurt JP, Taillan B, Bodock I et al (1996) Pyoderma gangrenosum with hepatopancreatic manifestations in a patient with rheumatoid arthritis. Dig Dis Sci 41:594–597

Hayashi et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10475929

Heimpel H, Dührsen U, Hofbauer P, Rigamonti-Wermlinger V, Kreuser ED, Schwarz K et al (2009) Bulky extramedullary hematopoiesis is not a rare complication of congenital dyserythropoietic anemia. Ann Hematol 88:937–941

Herman TE (1996) Antenatal-onset cortical hyperostosis and nonimmune hydrops. J Perinatol 16:137–139

Hervé S, Savoye G, Savoye-Collet C, Behbahani A, Auliac JB, Bota S, François A, Lerebours E (2001) Intrahepatic extramedullary hematopoiesis as a manifestation of a malignant thymoma: an unusual cause of nodular hepatomegaly (in French). Gastroenterol Clin Biol 25:711–713

Herxheimer K (1935) Karl Touton. Dermatol Zschr 70:247–248

Hide G, Desai S, Bloxham CA (2001) Malakoplakia of the gallbladder: imaging and histological features. Clin Radiol 56:326–328

Highton J, Kean A, hessian P, Wilsher M (2000) Cells expressing dendritic cell markers are present in the rheumatic nodule. J Rheumatol 27:339–346

Highton J, Hessian PA, Stamp L (2007) The rheumatoid nodule: peripheral or central to rheumatoid arthritis? Rheumatology (Oxford) 46:1385–1387

Ho KJ (1979) Michaelis-Gutmann bodies. Arch Pathol Lab Med 103:488–489

Holubar K (1990) Looking back. . .Paul Langerhans, Theodor Langhans, and Carl Touton – contemporary histopathologists. Am J Dermatopathol 12:534–535

Hruska KS, LaMarca ME, Scott CR, Sidransky E (2008) Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat 29:567–583

Hulkova H, Ledvinova J, Poupetova H, Kohout A, Malinova V, Elleder M (2009) Autopsy case of Gaucher disease type I in a patient on enzyme replacement therapy. Comments on the dynamics of persistent storage process. J Inherit Metab Dis 32:551–559

Hur J, Park MS, Yu JS, Lim JS, Hong SW, Kim KW (2005) Focal eosinophilic necrosis versus metastasis in the liver: the usefulness of two-phase dynamic CT. AJR Am J Roentgenol 184:1085–1090

Iversen K, Christoffersen P, Poulsen H (1970) Epithelioid cell granulomas in liver biopsies. Scand J Gastroenterol Suppl 7:61–67

Jang HJ, Lee WJ, Lee SJ, Kim SH, Lim HK, Lim JH (2002) Focal eosinophilic necrosis of the liver in patients with

underlying gastric or colorectal cancer: CT differentiation from metastasis. Korean J Radiol 3:240–244
Jelali MA, Luciani A, Kobeiter H, Zafrani S, Anglade MC, Zegai B et al (2006) MRI features of intrahepatic extramedullary haematopoiesis in sickle cell anaemia. Cancer Imaging 6:182–185
Kamishima T, ito K, Awaya H, Mitchell DG (2000) MR imaging of bilateral renal malakoplakia after liver transplantation. AJR Am J Roentgenol 175:919–920
Kamoun-Goldrat A, le Merrer M (2008) Infantile cortical hyperostosis (Caffey disease). A review. J Oral Maxillofac Surg 66:2145–2150
Kamoun-Golsdrat A, Martinovic J, Saada J, Sonigo-Cohen P, Razavi F, Munnich A, Le Mercier M (2008) Prenatal cortical hyperostosis with COL 1A1 gene mutation. Am J Med Genet A 146A:1820–1824
Kaye BR, Kaye RL, Bobrove A (1984) Rheumatoid nodules. Review of the spectrum of associated conditions and proposal of a new classification, with a report of four seronegative cases. Am J Med 76:279–292
Keen ME, Engstrand DA, Hafez GR (1985) Hepatic lipogranulomatosis simulating veno-occlusive disease of the liver. Arch Pathol Lab Med 109:70–72
Keitel W (2008) The pathologists: Aschoff, Klinge and Gräff (in German). Z Rheumatol 67:165–171
Kim KA, Lim HK, Kim SH, Lee WJ, Lim JH (1999) Necrotic granuloma of the liver by human fascioliasis: imaging findings. Abdom Imaging 24:462–464
Kim et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12191679
Kim WH, Kim SH, Kim YH, Youn SH, Kang WJ, Kim MA, Han JK, Choi BI (2010) Fluorine-18-FDG PET findings of focal eosinophilic liver disease: correlation with CT and/or MRI, laboratory, and pathologic findings. Abdom Imaging 35:437–446
Klatskin G (1977) Hepatic granulomata: problems in interpretation. Mt Sinai J Med 44:798–812
Klinger H (1932) Grenzformen der Periarteriitis nodosa. Frankf Z Pathol 42:455–480
Klion AD, Noel P, Akin C, Law MA, Gilliland DG, Cools J, Metcalfe DD, Nutman TB (2003) Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. Blood 101:4660–4666
Klion AD, Robyn J, Akin C, Noel P, Brown M, Law M, Metcalfe DD, Dunbar C, Nutman TB (2004a) Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. Blood 103:473–478
Klion AD, Law MA, Riemenschneider W, McMaster ML, Brown MR, Horne M, Karp B, Robinson M, Sachdev V et al (2004b) Familial eosinophilia: a benign disorder? Blood 103:4050–4055
Koch J, Gartner S, Li CM, Quintern LE, Bernardo K, Levran O, Schnabel D, Desnick RJ, Schuchman EH, Sandhoff K (1996) Molecular cloning and characterization of a full-length complementary DNA encoding human acid ceramidase. Identification of the first molecular lesion causing Farber disease. J Biol Chem 271:33110–33115
Koga M, Ishihara T, Uchino F, Fujiwaki T (1992) An autopsy case of Farber's lipogranulomatosis in a Japanese boy with gastrointestinal involvement. Acta Pathol Jpn 42:42–48
Kopecky KK, Moriarty AT, Antony AC, Baker MK (1986) Extramedullary hematopoiesis in acute lymphocytic leukemia masquerading as hepatic, renal, and splenic microabscesses. AJR Am J Roentgenol 147:846–847
Kumar A, Aggarwal S, de Tilly LN (1995) Case of the season: thalassemia major with extramedullary hematopoiesis in the liver. Semin Roentgenol 2:99–101
Kuriwaki K, Yoshida H (1999) Morphological characteristics of lipid accumulation in liver-constituting cells of acid lipase deficiency rats (Wolman's disease model rats). Pathol Int 49:291–297
Kwak HS, Lee JM (2000) CT findings of extramedullary hematopoiesis in the thorax, liver and kidneys, in a patient with idiopathic myelofibrosis. J Korean Med Sci 15:460–462
Kwak HS, Han YM, Lee JM (2004) Focal eosinophilic infiltration of the liver mimicking hepatocellular carcinoma; case reports. Clin Imaging 28:36–39
Kwon Y, Yu E, Huh J, Lee SK, Ro JY (2004) Sclerosing extramedullary hematopoietic tumor involving the lesser omentum and ligamentum teres in liver explant. Ann Diagn Pathol 8:227–232
La Fianza A, van der Byl G, Maccabelli G, Torretta L, Calliada F (2010) CT and MR findings in extramedullary haematopoiesis with biliary system encasement: a case report. J Radiol Case Rep 4:1–8
Laghi F, Catalano O, Maresca M, Sandomenico F, Siani A (2010) Indeterminate, subcentimetric focal liver lesions in cancer patients: additional role of contrast-enhanced ultrasound. Ultraschall Med 31:283–288
Landas SK, Mitros FA, Furst DE, LaBrecque DR (1992) Lipogranulomas and gold in the liver in rheumatoid arthritis. Am J Surg Pathol 16:171–174
Lear JT, Atherton MT, Byrne JP (1997) Neutrophilic dermatosis: pyoderma gangrenosum and Sweet's syndrome. Postgrad Med J 73:65–68
Lecolier B, Bercau G, Gonzalez M, Afriat R, Rambaud D, Mulliez N, de Kermadec S (1992) Radiographic, haematological, and biochemical findings in a fetus with Caffey disease. Prenat Diagn 12:637–641
Lee WJ, Lim HK, Lim JH, Kim SH, Choi SH, Lee SJ (1999) Foci of eosinophil-related necrosis in the liver: imaging findings and correlation with eosinophilia. AJR Am J Roentgenol 172:1255–1261
Lee IJ, Kim SH, Kim DS, Lee JM, Han JK, Choi BI (2008) Intrahepatic extramedullary hematopoiesis mimicking a hypervascular hepatic neoplasm on dynamic – and SPIO-enhanced MRI. Korean J Radiol 9(Suppl): S34–S38
Lee MH, Kim SH, Kim H, Lee MW, Lee WJ (2011) Differentiating focal eosinophilic infiltration from

metastasis in the liver with gadoxetic acid-enhanced magnetic resonance imaging. Korean J Radiol 12:439–449
Lefkowitch JH, Haythe JH, Regent N (2002) Kupffer cell aggregation and perivenular distribution in steatohepatitis. Mod Pathol 15:699–704
Leiferman KM, Gleich GJ (2004) Hypereosinophilic syndrome: case presentation and update. J Allergy Clin Immunol 113:50–58
Lemos LB, Baliga M, Benghuzzi HA, Cason Z (1997) Nodular hematopoiesis of the liver diagnosed by fine-needle aspiration cytology. Diagn Cytopathol 16:51–54
Leonidas DD, Elbert BL, Zhou Z, Leffler H, Ackerman SJ, Acharya KR (1995) Crystal structure of human Charcot-Leyden crystal protein, an eosinophil lysophospholipase, identifies it as a new member of the carbohydrate-binding family of galectins. Structure 3:1379–1393
Li CM, Park JH, Simonaro CM, He X, Gordon RE, Friedman AH, Ehleiter D, Paris F, Manova K, Hepbildikler S et al (2002) Insertional mutagenesis of the mouse acid ceramidase gene leads to early embryonic lethality in homozygotes and progressive lipid storage disease in heterozygotes. Genomics 79:218–224
Lim JH, Lee WJ, Lee DH, Nam KJ (2000) Hypereosinophilic syndrome: CT findings in patients with hepatic lobar or segmental involvement. Korean J Radiol 1:98–103
Ma SK, Au WY (1999) Images in haematology. Hepatic haemopoiesis in beta-thalassemia trait. Br J Haematol 107:1
Malamos B, Papavisiliou C, Avramidis A (1962) Tumor-simulating intrathoracic extramedullary hemopoiesis. Acta Radiol 57:227–231
Marshall et al. 1978. http://www.ncbi.nlm.nih.gov/pubmed/285688
Mastrianni DM, Eddy RL, Rosenberg HF, Corrette SE, Shows TB, Tenen DG, Ackerman SJ (1992) Localization of the human eosinophil Charcot-Leyden crystal protein (lysophospholipase) gene (CLC) to chromosome 19 and the human ribonuclease 2 (eosinophil-derived neurotoxin) and ribonuclease 3 (eosinophil cationic protein) genes (RNS2 and RNS3) to chromosome 1. Genomics 13:240–242
Matsumura Y, Nishiwaki F, Morita N, Kore-Eda S, Miyachi Y (2011) Pyoderma gangrenosum in a patient with myelodysplastic syndrome followed by possible extracutaneous manifestations in the gallbladder, liver, bone and lung. J Dermatol 38:1102–1105
McCarty DJ (1991) Complete reversal of rheumatoid nodulosis. J Rheumatol 18:736–737
McClure J, Cameron CHS, Garrett R (1981) The ultrastructural features of malakoplakia. J Pathol 134:13–25
McCoy JJ, Vila R, Petrossian G, McCall RA, Reddy KS (1976) Xanthogranulomatous cholecystitis. Report of two cases. J S C Med Assoc 72:78–79
McNally AK, Anderson JM (1995) Interleukin-4 induces foreign body giant cells from human monocytes/macrophages. Differential lymphokine regulation of macrophage fusion leads to morphological variants of multinucleated giant cells. Am J Pathol 147:1487–1499
Meynet C (1875) Rhumatisme articulaire subaigu avec productions de tumeures multiples dans les tissus fibreux périarticulaires et sur le périoste d'un grand nombre d'os. Lyon Med 20:495
Michaelis L, Gutmann C (1902) Ueber Einschlüsse in Blasentumoren. Z Klin Med 47:208–215
Moldavskii MI, Rustamov IR (1984) Multichamber pseudocyts of the liver with malacoplakia (in Russian). Klin Khir 9:64–65
Morita Y, Ueno T, Sasaki N, Kuhara K, Yoshioka S, Tateishi Y, Nagata E, Kage M, Sata M (2005) Comparison of liver histology between patients with non-alcoholic steatohepatitis and patients with alcoholic steatohepatitis in Japan. Alcohol Clin Exp Res 29(12 Suppl):277S–281S
Moschella SL (1970) Xanthomatosis, associated with multiple myeloma. Arch Dermatol 102:121–123
Moskovitz B, Malberger E, Brenner B, Gaitini D, Vardi Y, Bolkier M (1991) Renal extramedullary hematopoiesis simulating hypernephroma. Eur Urol 19:343–345
Moxon W (1873) Simple stricture of hepatic duct, causing chronic jaundice and xanthelasma. Trans Path Soc Lond 129:129–134
Muramatsu T, Sakai N, Yanagihara I, Yamada M, Nishigaki T, Kokubu C, Tsukamoto H, Ito M, Inui K (2002) Mutation analysis of the acid ceramidase gene in Japanese patients with Farber disease. J Inherit Metab Dis 25:585–592
Murrell et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9105307
Nam KJ, Jung WJ, Choi JC, Koo BS, Park BH, Lee KN, Han SY, Shin WW, Han SS (1999) Hepatic involvement in hypereosinophilia: sonographic findings. J Ultrasound Med 18:475–479
Navarro M, Crespo C, Perez L, Martinez C, Galant J, Gonzalez I (2000) Massive intrahepatic extramedullary hematopoiesis in myelofibrosis. Abdom Imaging 25:184–186
Neumann E (1880) Die Picrocarminfärbung und ihre Anwendung auf die Entzündungslehre. Arch Mikrosk Anat 18:130–150
Nochomovitz LE, Uys CJ, Epstein S (1975) Massive deposition of mineral oil after prolonged ingestion. S Afr Med J 49:2187–2190
Noi I, Loberant N, Cohen I (1994) Inflammatory pseudotumor of the liver. Clin Imaging 18:283–285
O'Malley DP (2007) Benign extramedullary myeloid proliferations. Mod Pathol 20:405–415
Ourahma S, Barrou B, Bitker MO, Sylla C, Mouquet C, Chatelain C (1996) Rectal malakoplakia in a renal transplant recipient. Transplant Proc 28:2824
Palmer DG, Hogg N, Highton J, Hessian PA, Denholm I (1987a) Macrophage migration and maturation within rheumatoid nodules. Arthritis Rheum 30:729–736
Palmer DG, Hogg N, Allen CA, Highton J, Hessian PA (1987b) A mononuclear phagocyte subset associated with cell necrosis in rheumatoid nodules: identification

with monoclonal antibody 5.5. Clin Immunol Immunopathol 45:17–28
Papavisiliou C, Sfikakis P (1964) Tumour-simulating intrathoracic marrow heterotopia in thalassaemia major. Thorax 19:121–124
Pardanani A, Ketterling RP, Brockman SR, Flynn HC, Paternoster SF, Shearer BM et al (2003) CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. Blood 102:3093–3096
Parra JA, Acinas O, Bueno J, Guezmes A, Fernandez MA, Farinas MC (2000) Xanthogranulomatous cholecystitis: clinical, sonographic, and CT findings in 26 patients. AJR Am J Roentgenol 174:979–983
Parwani AV, Ali SZ (2003) Pathologic quiz case. A 52-year-old woman with a liver mass. Arch Pathol Lab Med 127:631–632
Petersen P, Christoffersen P (1979) Ultrastructure of lipogranulomas in human fatty liver. Acta Pathol Microbiol Scand A 87:45–49
Pettus BJ, Chalfant CE, Hannun YA (2002) Ceramide in apoptosis: an overview and current perspectives. Biochim Biophys Acta 1585:114–125
Pinocy J, Lange A, Konig C, Kaiserling E, Becker HD, Krober SM (2003) Xanthogranulomatous cholecystitis resembling carcinoma with extensive tumorous infiltration of the liver and colon. Langenbecks Arch Surg 388:48–51
Poll LW, vom Dahl S (2009) Image of the month. Hepatic gaucheroma mimicking focal nodular hyperplasia. Hepatology 50:985–986
Poll LW, Koch JA, vom Dahl S, Loxtermann E, Sarbia M, Niederau C et al (2000) Extraosseous manifestation of Gaucher's disease type I: MR and histological appearance. Eur Radiol 10:1660–1663
Poll LW, Willers R, Häussinger D, Mödder U, vom Dahl S (2010) MRI bone marrow findings in 63 patients with type I Gaucher disease. Rofo 182:979–985
Powell FC, Su WP, Pemy HO (1996) Pyoderma gangrenosum: classification and management. J Am Acad Dermatol 34:395–409
Pulpeiro JR, Armesto V, Varela J, Corredoira J (1991) Fascioliasis: findings in 15 patients. Br J Radiol 64:798–801
Pye Smith PH (1873) Xanthelasma (Vitiligoidea plana) of skin, peritoneum and mucous membrane, associated with jaundice: autopsy. Trans Path Soc Lond 24:250–253
Raab SS, Silverman JF, McLeod DL, Geisinger KR (1993) Fine-needle aspiration cytology of extramedullary hematopoiesis (myeloid metaplasia). Diagn Cytopathol 9:522–526
Raguin G, nemeth J, Wassef M et al (1999) Identification of *Shigella boydii* in colonic malakoplakia by universal bacterial 16S ribosomal DNA-based amplification in a human immunodeficiency virus-infected patient. Clin Infect Dis 28:142–143
Rayer PFO (1835) Traité théorique et pratique des maladies de la peau. Baillière, Paris
Reed A, Ryan C, Schwartz SI (1994) Xanthogranulomatous cholecystitis. J Am Coll Surg 179:249–252
Regragui A, Amrani M, Gamra L, Alaoui Belabbas M (2003) Malacoplakia of the biliary tract and duodenum. Case report (in French). Gastroenterol Clin Biol 27:655–656
Remstein ED, Kurtin PJ, Nascimento AG (2000) Sclerosing extramedullary hematopoietic tumor in chronic myeloproliferative disorders. Am J Surg Pathol 24:51–55
Riedlinger WF, Lairmore TC, Balfe DM, Dehner LP (2005) Tumefactive necrobiotic granulomas (nodulosis) of the pancreas in an adult with long-standing rheumatoid arthritis. Int J Surg Pathol 13:207–210
Robertson SJ, Higgins RB, Powell C (1991) Malacoplakia of liver: a case report. Hum Pathol 22:1294–1295
Roberts-Thomson PJ, Venables GS, Onitiri AC, Lewis B (1975) Polymeric IgA myeloma, hyperlipidemia and xanthomatosis: a further case and review. Postgrad Med J 51:44–51
Rocha N, Suguiama EH, Maia D, Costa H, Coelho KI, Franco M (1997) Intestinal malakoplakia associated with paracoccidiodomycosis: a new association. Histopathology 30:79–83
Rodot S, Lacour JP, Van Elslande L, Cognard C, Castanet J, Ortonne JP (1996) Extracutaneius manifestations of neutrophilic dermatosis (in French). Ann Dermatol Venereol 123:129–134
Ron et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20643691
Rosenbloom BE, Weinreb NJ (2013) Gaucher disease: a comprehensive review. Crit Rev Oncog 18:163–1975
Rothenberg ME (2004) Eosinophilic gastrointestinal disorders (EGID). J Allergy Clin Immunol 113:11–28
Rull R, Grande L, Garcia-Valdecasas JC, Bombi JA, Alos LL, Fuster J, Lacy AM, Cugat E et al (1995) Malakoplakia in the gastrointestinal tract of a liver transplant recipient. Transplantation 59:1492–1494
Sahel J, Scheiner C, Lebreuil G, Sarles H (1976) Malacoplasia of the cystic duct (in French). Arch Fr Mal App Dig 65:585–590
Sakakibara et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12132528
Sampson et al. 1982. http://www.ncbi.nlm.nih.gov/pubmed/7183305
Schäfer A, Harzer K, Kattner E, Schafer HJ, Stoltenburg G, Lietz H (1996) Disseminated lipogranulomatosis (Farber disease) with hydrops fetalis (in German). Pathologe 17:145–149
Scheuer PJ, Lefkowitch JH (2006) Liver biopsy interpretation, 7th edn. Elsevier Sanders, Philadelphia
Schweiger S, Chaoui R, Tennstedt K, Mudlos S, Tinschert S (2003) Antenatal onset of cortical hyperostosis (Caffey disease): case report and review. Am J Med Genet 120A:547–552

Smith B (1965) Malakoplakia of the urinary tract: a study of twenty-four cases. Am J Clin Pathol 43:409–417

Smits JG, Kooijman CD (1986) Rheumatoid nodules in liver. Histopathology 10:1211–1213

Stanton JM, Maxted W (1981) Malacoplakia: a study of the literature and current concepts of pathogenesis, diagnosis and treatment. J Urol 125:139–146

Stein P, Yu H, Jain D, Mistry PK (2010) Hyperferritinemia and iron overload in type 1 Gaucher disease. Am J Hematol 85:472–476

Stenzel P, Weeks DA (2013) Abundant hepatic Gaucher-like cells following chemotherapy and bone marrow transplantation for hematologic malignancy: report of two cases. Int J Surg Pathol 21:89–92

Stryker WA (1941) Absorption of liquid petrolatum (mineral oil) from the intestine: a histologic and chemical study. Arch Pathol Lab Med 29:691–699

Sukov WR, Remstein ED, Nascimento AG, Sethi S, Lewin M (2009) Sclerosing extramedullary hematopoietic tumor: emphasis on diagnosis by renal biopsy. Ann Diagn Pathol 13:127–131

Tai YS, Lin PW, Chen SG, Chang KC (1998) Inflammatory pseudotumor of the liver in a patient with human immunodeficiency virus infection. Hepatogastroenterology 45:1760–1763

Tamiolakis D, Ptassolopoulos P, Simopoulos C, Kotini A, Venizelos J, Alexiadis G, Manavis J, Papadopoulos N (2003) Renal extramedullary hematopoietic tumor diagnosed by fine needle aspiration: a case report. Acta Clin Belg 58:299–301

Tamiolakis D, Venizelos J, Prassopoulos P, Simopoulos S, Bolioti S, Tsiapali M, Papadopoulos N (2004) Intrahepatic extramedullary hematopoietic tumor mimicking metastatic carcinoma from a colonic primary. Onkologie 27:65–67

Tamm EP, Rabushka LS, Fishman EK, Hruban RH, Diehl AM, Klein A (1995) Intrahepatic, extramedullary hematopoiesis mimicking hemangioma on technetium-99m red blood cell SPECT examination. Clin Imaging 19:88–91

Tanino M, Ohta G (1981) An autopsy case of xanthogranuloma in the liver (in Japanese). Nippon Shokakibyo Zasshi 78:1803–1806

Taylor JS, Lewis LA, Battle JD, Butkus A, Robertson AL, Deodhar S, Roenigk HH (1978) Plane xanthoma and multiple myeloma with lipoprotein-paraprotein complexing. Arch Dermatol 114:425–431

Thannhauser SJ, Magendantz H (1938) The different clinical groups of xanthomatous diseases: a clinical physiological study of 22 cases. Ann Intern Med 11:1662–1746

Thinda S, Tomlinson JS (2009) Mesenteric rheumatoid nodules masquerading as an intraabdominal malignancy: a case report and review of the literature. World J Surg Oncol 7:59

Touton K (1885) Ueber das Xanthom, insbesondere dessen Histiologie und Histiogenese. Vierteljahrschr Dermatol Syph 12:3.53

Trivalle C, Profit P, Bonnet B, Manchon ND, Ducastelle T, Hemet J, Bercoff E, Bourreille J (1991) Liver lipogranulomas with long-term fever caused by paraffin oil (in French). Gastroenterol Clin Biol 15:551–553

Ung KA, Remotti H, Olsson R (2000) Eosinophilic hepatic necrosis in hypereosinophilic syndrome. J Clin Gastroenterol 31:323–327

Urano S, Kodama H, Kato K, Nogura K (1995) Pyoderma gangrenosum with systemic involvement. J Dermatol 22:515–519

Vadillo M, Jucgla A, Podzamczer D, Rufi G, Domingo A (1999) Pyoderma gangrenosum with liver, spleen and bone involvement in a patient with chronic myelomonocytic leukaemia. Br J Dermatol 141:541–543

Valente AI, Pinto HC, Ramalho F, Cabrita PF, Catarino C, Serejo F, Baptista A, Saragoca A, Bordalo O, Moura MC (1997) Idiopathic hypereosinophilic syndrome presenting as cholestatic liver disease. Eur J Gastroenterol Hepatol 9:815–817

Van Crevel R, Curfs J, van der Ven AJ, Assmann K, Meis JF, van der Meer JW (1998) Functional and morphological monocyte abnormalities in a patient with malakoplakia. Am J Med 105:74–77

Verani R, Olson J, Moak JL (1980) Intrathoracic extramedullary hematopoiesis: report of a case in a patient with sickle-cell disease-beta-thalassemia. Am J Clin Pathol 73:133–137

Verola O, de Roquancourt A, Chanu B, Rouffy J, Brocheriou C (1983) Hepatic cholesterolosis. Histological, histochemical and ultrastructural study of 2 cases (in French). Sem Hop 59:1753–1759

Vogt R (1998) Das Hieracium-Herbar von Karl Touton. Willdenowia 28:253–261

Von Hansemann D (1903) Ueber Malakoplakie der Harnblase. Virchows Arch Pathol Anat 173:302–308

Wanless IR, Geddie WR (1985) Mineral oil lipogranulomata in liver and spleen. A study of 465 autopsies. Arch Pathol Lab Med 109:283–286

Warshauer DM, Schiebler ML (1991) Intrahepatic extramedullary hematopoiesis: MR, CT and sonographic appearance. J Comput Assist Tomogr 15:683–685

Wasserman SI, Goetzl EJ, Ellman L, Austen KF (1974) Tumor-associated eosinophilotactic factor. N Engl J Med 21:420–424

Weidman FD, Boston LN (1937) Generalized xanthoma tuberosum with xanthomatous changes in fresh scars of an intercurrent zoster. Arch Intern Med 59:793–822

Weidman FD, Freeman W (1924) Xanthoma tuberosum. Two necropsies disclosing lesions of the central nervous system and other tissues. Arch Derm Syphilol 9:149–175

Weidman FD, Stokes J (1937) Extensive xanthoma tuberosum in childhood due to infectious cirrhosis of the liver. Am J Dis Child 53:1230–1244

Weinrach DM, Wang KL, Cisler JJ, Diaz LK (2004) Pathologic quiz case: a 54-year-old liver transplant recipient with diffuse thickening of the sigmoid colon.

Malakoplakia of the colon associated with liver transplant. Arch Pathol Lab Med 128:e133–e134
Wiener MD, Halvorsen RA, Vollmer RT, Foster WL, Roberts L (1987) Focal intrahepatic extramedullary hematopoiesis mimicking neoplasm. AJR Am J Roentgenol 149:1171–1172
Willis A, Vanhuse C, Newton KP, Wasserstein M, Morotti RA (2008) Farber's disease type IV presenting with cholestasis and neonatal liver failure: report of two cases. Pediatr Dev Pathol 11:305–308
Wisnieski JJ, Askari AD (1981) Rheumatoid nodulosis. A relatively benign rheumatoid variant. Arch Intern Med 141:615–619
Wollina U, Haroske G (2011) Pyoderma gangraenosum. Curr Opin Rheumatol 23:50–56
Won JH, Kim BM, Ji H, Chung JJ, Yoo HS, Lee JT, Park YN, Hong SW (1999) Focal eosinophilic infiltration of the liver: a mimic of hepatic metastasis. Abdom Imaging 24:369–372
Wong Y, Chen F, Tai KS, Yip LK, Tsang KW, Chan FL, Ooi GC (1999) Imaging features of focal intrahepatic extramedullary haematopoiesis. Br J Radiol 72:906–910
Woollons A, Darley CR (1998) Xanthoma disseminatum: a case with hepatic involvement, diabetes insipidus and type IIb hyperlipidemia. Clin Exp Dermatol 23:277–280
Wright JR, Van den Hof MC, Macken MB (2005) Prenatal infantile cortical hyperostosis (Caffey's disease): a 'hepatic myeloid hyperplasia-pulmonary hypoplasia sequence' can explain the lethality of early onset cases. Prenat Diagn 25:939–944
Xu R, Mistry P, McKenna G, Emre S, Schiano T, Bu-Ghanim M, Levi G, Fiel MI (2005) Hepatocellular carcinoma in type 1 Gaucher disease: a case report with review of the literature. Semin Liver Dis 25:226–229
Yang X, Bhuiya T, Esposito M (2002) Sclerosing extramedullary hematopoietic tumor. Ann Diagn Pathol 6:183–187
Yang T, Zhang BH, Zhang J, Zhang YJ, Jiang XQ, Wu MC (2007) Surgical treatment of xanthogranulomatous cholecystitis: experience in 33 cases. Hepatobiliary Pancreat Dis Int 6:504–508
Yim H, Ahn HJ, Park C, Cheon JY (1995) Xanthoma of the liver in a patient with multiple myeloma associated with hyperlipidemia. A case report. J Korean Med Sci 10:453–456
Yoo SY, Han JK, Kim YH, Kim TK, Choi BI, Han MC (2003) Focal eosinophilic infiltration in the liver: radiologic findings and clinical course. Abdom Imaging 28:326–332
Yoon KH, Ha HK, Lee JS, Suh JH, Kim MH, Kim PN, Lee MG, Yun KJ, Choi SC, Nah YH, Kim CG, Won JJ, Auh YH (1999) Inflammatory pseudotumor of the liver in patients with recurrent pyogenic cholangitis: CT-histopathologic correlation. Radiology 211:373–379
Yoshida T, Nishimori I, Kumon M, Kohsaki T, Taniuchi K, Ohtsuki Y, Onishi S (2003) Inflammatory pseudotumor of the liver: report of a case diagnosed by needle biopsy. Hepatol Res 27:83–86
Yousef GM, Naghibi B (2007) Malakoplakia outside the urinary tract. Arch Pathol Lab Med 131:297–300
Yu JS, Yoon SW, Park MS, Lee JH, Kim KW (2005) Eosinophilic hepatic necrosis: magnetic resonance imaging and computed tomography comparison. J Comput Assist Tomogr 29:765–771
Yuoh G, Hove MG, Wen J, Haque AK (1996) Pulmonary malakoplakia in acquired immunodeficiency syndrome: an ultrastructural study of morphogenesis of Michaelis-Gutmann bodies. Mod Pathol 9:476–483
Zeek PM (1952) Periarteritis nodosa: a critical review. Am J Clin Pathol 22:777–790
Zhang Z, Mandal AK, Mital A, Popescu N, Zimonjic D, Moser A, Moser H, Mukherjee AB (2000) Human acid ceramidase gene: novel mutations in Farber disease. Mol Genet Metab 70:301–309
Zhou et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1464731
Zhu H, Bodenheimer HC, Clain DJ, Min AD, Theise ND (2010) Hepatic lipogranulomas in patients with chronic liver disease: association with hepatitis C and fatty liver disease. World J Gastroenterol 16:5065–5069
Ziff M (1990) The rheumatoid nodule. Arthritis Rheum 33:761–767

Liver Abscesses as Pseudotumoral Lesions

126

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_126

Abstract

An important hepatic lesion that produces masses that may mimic cancer is pyogenic liver abscess. Liver abscesses are caused by diverse bacterial organisms, but certain bacteria are prominent inducers of liver abscesses, such as *Klebsiella* and *Staphylococcus*. The spread of bacteria to the liver follows hematogenous or ascending routes, sometimes associated with infectious pylephlebitis. Pyogenic liver abscesses exhibit a characteristic macroscopic presentation, with a purulent center followed to the periphery by a belt of granulation tissue and a hyperemic demarcation zone. In the curse of fibrous repair, pyogenic abscesses can collapse and leave a scar-like lesion. Distinct variants of bacterial liver abscesses and related lesions are caused by *Salmonella* species. In case of infection with anaerobic germs, and in particular *Clostridium* species, complex morphologies ensue, in part with prominent gas formation.

Classical Pyogenic Liver Abscess

Introduction

Pyogenic liver abscess (PLA) is a potentially life-threatening disorder that may, owing to the invasive and destructive mode of presentation in the liver, be confounded with malignancy. PLA develops in a wide variety of patients (Branum et al. 1990; Huang et al. 1996; Seeto and Rockey 1996; Johannsen et al. 2000; Alvarez Perez et al. 2001).

Epidemiology

PLA is usually found in elderly patients with biliary tract disease, and males predominate in all major studies (Frey et al. 1989; Kurland and Brann 2004; Chan et al. 2005). There are marked differences in epidemiology and etiology between western countries and tropical countries, in particular what regards the contribution of amebic infections. A study performed in India has shown that 51.2 % of all abscesses were amebic, 23.2 % were PLA, and 25.6 % had unknown causes (Mohan et al. 2006). In contrast, most liver abscesses in the West are in fact PLA. The epidemiology of PLA has markedly changed in recent years, in that the incidence of PLA is rising in numerous countries and that the etiology is changing (Land et al. 1985; Seeto and Rockey 1996). This is also specifically due to the emergence of *Klebsiella*-associated PLA, a distinct syndrome (Lederman and Crum 2005). Whereas PLA formerly was mainly associated with preexisting hepatobiliary disease and polymicrobial infections, dominated by *Escherichia coli*, more and more patients with PLA have no preexisting hepatobiliary disease, but suffer, e.g., from diabetes mellitus and have PLA caused by *Klebsiella*. A nationwide analysis of PLA in Taiwan from 1996 through 2004 showed that the annual incidence of PLA increased steadily from 11.15/100,000 population in 1996 to 17.59/100,000 in 2004. Diabetes mellitus, malignancy, renal disease, and pneumonia were associated with a higher risk for PLA (Tsai et al. 2008).

Clinical Features

Malaise, anorexia, abdominal pain (mainly focal abdominal tenderness), and night sweats are the leading symptoms in patients with PLA. Up to 60 % of patients present with these nonspecific features, which have been specified in numerous reports, while fever was noted in up to 80 % (less often chills), and a variable number of patients show hepatomegaly and weight loss. Jaundice is usually only present in case of simultaneous biliary obstruction (Warren and Hardy 1968; Young 1976; Perera et al. 1980; Rubin et al. 1981; Kandel and Marcon 1984; Beaumont and Davis 1985; Gyorffy et al. 1987; Hau and Hartmann 1987; Bansal and Prabhakar 1988; Frey et al. 1989).

In PLA not caused by *Klebsiella* (see below), the most common coexisting diseases are diabetes mellitus, followed by biliary stone disorders and other types of biliary tract disease (Rockey 2001),

and intra-abdominal infectious and neoplastic disease (Lin et al. 2011a; Law and Li 2012), in particular colonic disease (McDonald et al. 1984), including colorectal cancer (Lonardo et al. 1992; Yokota et al. 2005; Pisano et al. 2007, Lee et al. 2008). Silent colorectal cancer (CRC) can manifest as PLA in the absence of metastasis (Teitz et al. 1995; Fernandez Ruiz et al. 2007; Giuliani et al. 2007; Hiraoka et al. 2007; Chen et al. 2012; Jeong et al. 2012; Qu et al. 2012), a constellation which is an important cancer-inflammation syndrome (the CRC-PLA syndrome, as I tend to call it). PLA has also found to be the initial manifestation of hepatocellular carcinoma (Yeh et al. 1998; Lin et al. 2011a). Diabetes mellitus is a very important risk factor for PLA, as poorly controlled diabetic patients are immunocompromised and are susceptible to bacterial infections. In a large study, persons with diabetes mellitus had a 3.6-fold increased risk of experiencing PLA in comparison with a control population, and patients with PLA who had diabetes mellitus had a higher 30-day post-discharge mortality rate, compared with patients with PLA who did not have diabetes (Thomsen et al. 2007; Tian et al. 2012). On one study, 10–16 % of patients with PLA had diabetes mellitus (McDonald et al. 1984). There are less common predisposing conditions for PLA, such as pylephlebitis in pancreatitis (Rustagi et al. 2012) and Crohn's disease (McGreal et al. 2012). In case no infectious cause is identified, the term cryptogenic liver abscess is used (Stokes 1960).

PLA are usually more often solitary than multiple lesions; among 483 patients with PLA, 343 PLA were single lesions, 140 multiple abscesses. In this study, single abscesses were usually larger than 5 cm, whereas multiple abscesses were usually smaller than 5 cm. Solitary abscesses were predominantly located to the right liver lobe. Multiple PLA were more often associated with preexistent biliary tract disease (Chou et al. 1997). Abdominal pain was more frequent in case of single PLA than with multiple PLA, but jaundice was more often found in multiple PLA. However, there are also series where solitary and multiple PLA had about the same prevalence (Strong et al. 2003).

Complications

Portal and/or hepatic vein thrombosis can be caused by PLA (Syed et al. 2007). Sometimes, the classical Budd-Chiari develops (Karadag et al. 2005). Such thrombotic events can extend into the inferior vena cava and/or the right atrium (Bagri et al. 2013). Abscess rupture causes subdiaphragmatic abscess (specifically, this is an empyema per definition), and such a process can penetrate through the diaphragm and pericardial wall to induce pyopericardium (Chong et al. 2010). PLA can cause septic pulmonary embolism (Lin and Chang 2008). This complication is more common in patients with diabetes mellitus (Yang et al. 2008). A subset of PLA is characterized by gas formation (gas-containing PLA; Hayashi et al. 1989; Ukikusa et al. 2001; Chen et al. 2008a; Chong et al. 2008; Huang et al. 2009; Oh et al. 2011; Safe et al. 2013). In part of these PLA, the bacteria causing the infection express formic hydrogen lyase, leading to mixed acid fermentation and gas formation. Etiologically, classical gas-forming bacteria may be involved (such as Clostridia; Kahn et al. 1972; Ogah et al. 2012), but at least 75 % of all gas-containing PLA have been found to be caused by *Escherichia coli* and *Klebsiella* (Zhang et al. 2013). Other germs inducing gas-forming PLA are *Salmonella enteritidis* (Tee Yu et al. 2013) and diverse anaerobic bacteria. Gas-forming PLA, which are rare variants of liver abscesses, most often occur in patients with diabetes mellitus (Yang et al. 1993) and are associated with a high mortality rate. In case a gas-forming PLA ruptures, pneumoperitoneum ensues (Matsuyama et al. 1994; Ukikusa et al. 2001).

There is evidence that patients with PLA have a higher rate of primary liver cancer than matched controls, suggesting that PLA is a warning sign for liver cancer (Huang et al. 2013). In a study of 1257 PLA patients from Taiwan, 186 were diagnosed with cancer after a median follow-up of 3.33 years, including 56 liver cancer, 22 biliary tract cancer, and 40 colorectal cancer patients: The highest standard incidence ratio/SIR of all cancers, hepatocellular carcinoma, biliary tract

cancer, and colorectal cancer, occurred within 90 days of follow-up (Kao et al. 2012).

Pathology

Macroscopy

Non-gas-containing PLA are usually spherically, wedge-shaped or irregular mass-producing lesions varying in diameter from few millimeter to more than 20 cm (Figs. 1, 2, 3, and 4). PLA can present as solitary or multiple lesions, sometimes involving both liver lobes. In case the PLA extends to the liver capsule, the capsule may be thinned, a yellowish or hemorrhagic mass being visible through the transparent capsule, and the capsular surface can be eroded or covered by an exudate (fibrinous or fibrinopurulent), or coagulated blood. On cut surfaces, the center of PLA is occupied by thick, viscous, or liquefied pus that flows off the cut surface and sticks to the knife. In contrast to tuberculosis, the purulent material is never cream white, but has several shades of yellow to yellow green, a greenish tinge being caused by neutrophil myeloperoxidase, a green enzyme, or by pyocyanin in case of *Pseudomonas*

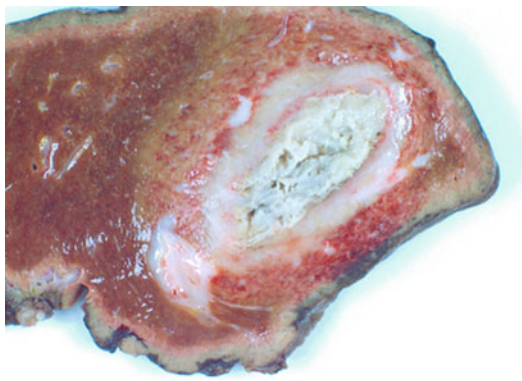

Fig. 1 Pyogenic liver abscess. On cut surfaces, hepatic abscesses frequently show a distinct concentric structure, as in this case. The innermost part is occupied by pus (whitish-yellow mass), followed by a zone of granulation tissue and scar tissues (white rim) and a peripheral hyperemic zone

Fig. 2 Pylephlebitic liver abscess. The pyogenic abscess in this case displays the distribution of portal veins with infectious pylephlebitis, through which the pyogenic infection has spread to the liver substance

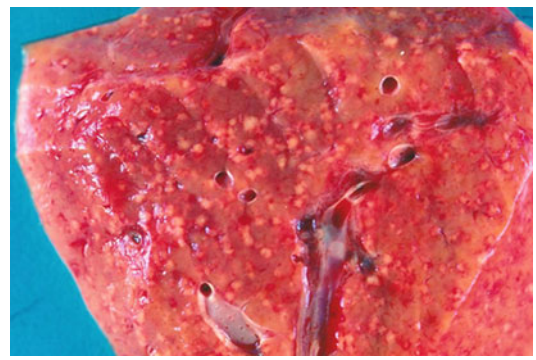

Fig. 3 Multiple miliary abscesses of the liver in a patient with septicemia. The lesions are evenly distributed

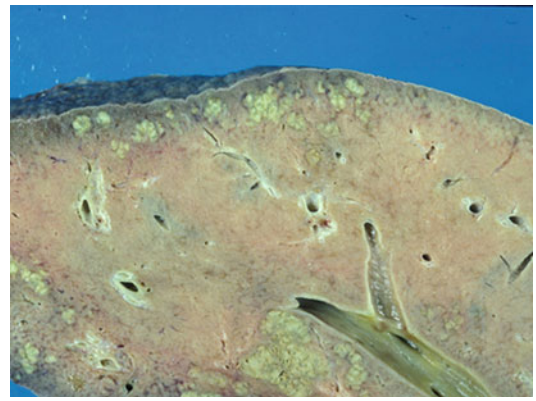

Fig. 4 In this case, small or miliary abscesses accumulated in terminal ramifications of the intrahepatic portal venous system

aeruginosa infection. In some cases, the central part of the abscess exhibits a fluid-filled cyst in which purulent exudate flakes may float. Part of PLA contain hemorrhagic pus. In acute PLA, the purulent material directly contacts the adjacent liver substance, while older lesions show a dark-red demarcation zone mainly consisting of a wall of granulation tissue. In PLA undergoing contraction, this vessel-rich zone collapses and shows a wavy contour. The parenchyma surrounding a PLA may contain spotty hemorrhage and sometimes a perifocal steatosis. PLA may destroy the walls of intrahepatic bile ducts and discharge the pus into the ductal lumina. Bile may flow back into the abscess cavity, greenishly discoloring the purulent exudate. PLA can break through the organ's limits and give rise to fistulae entering diverse tissues and organs in the vicinity of the liver. In PLA caused by gas-forming bacteria, the tissue may produce a blistering or crackling sound on palpation, and the cut surface shows a foamy or spongy appearance due to the presence of gas bubbles. Sometimes, gas bubbles float within the pus, an effect difficult to distinguish from artificial air entering upon cutting the tissue.

Macroscopically, the etiology of PLA is difficult to assess. A foul and feculent odor indicates *E. coli* infection, while in case of *Pseudomonas aeruginosa* infection, the pus may have a bluish-green tinge due to accumulation of pyocyanin. Gas production suggests anaerobic infections.

Histopathology

Histologically, the purulent exudate reveals the classical composition of neutrophils and macrophages in all stages of decreasing viability. Many of the phagocytes remain only as shadow cells or nuclear debris, specifically in the central, older parts of the abscess. Bacteria are shown by use of bacterial stains and are either present as free organisms or bacteria located within phagocytic cells. Viable phagocytic cells are usually seen at the periphery of the lesion, where active leukodiapedesis from blood vessels of the granulation tissue takes place. The granulation tissue itself is nonspecific and lacks an epithelioid cell reaction of granulomas. At the parenchymal face of granulation tissue, dilated blood vessels entering the parenchyma are seen. The sinusoidal vascular bed is usually hyperemic in the area surrounding the PLA. The suppurative process may cause damage of adjacent intrahepatic bile ducts, followed by bile leakage (Fig. 5). Abscesses may be associated with peliosis hepatis (Van Schil et al. 1988). In healing PLA, the purulent exudate becomes more viscid and histologically dense, with less and less phagocytes being visible. The wall of granulation tissue transforms into a less vascular scar tissue, associated with focal hemosiderosis. Through organization, the exudate may completely vanish at the end, but in large PLA, a cyst may remain, as the granulation tissue is unable to form a bridge through large exudate masses.

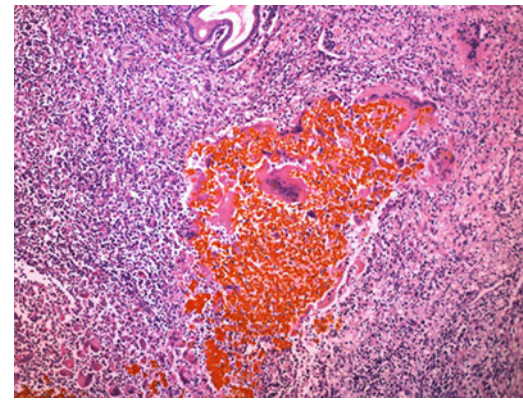

Fig. 5 Intrahepatic bile duct damage due to purulent inflammation. There is marked bile leakage with induction of a foreign body reaction (multinucleated giant cells; hematoxylin and eosin stain)

Differential Diagnosis

Radiologically, PLA can mimic massively necrotic primary liver cancer or necrotic metastases (Klotz and Penn 1987), in particularly those of tumors with a high tendency of necrosis, such as colorectal, pancreas, and bronchopulmonary primaries. It is important to note that PLA may hide a primary malignant liver tumor, in particular necrotic HCC (Yeh et al. 1998).

Biology of Disease

The Acute Physiology and Chronic Health Evaluation II (APACHE II) classification system (Knaus et al. 1985; Knaus 2002) has been evaluated in patients with PLA and found to be useful in predicting in-hospital mortality of PLA (Levison and Zeigler 1991; Hsieh et al. 2006). In a multivariate analysis, it turned out that the mortality from PLA was associated with gas-forming abscess, multidrug-resistant isolates, anaerobic infection, APACHE II score > or = 15, and blood urea nitrogen level > 7.86 mmol/l (Chen et al. 2008b). The cumulative recurrence rates of PLA were lower in both the cryptogenic and diabetic groups than in the underlying biliary tract disease group (Cheng et al. 2008).

Pathogens Causing PLA

Worldwide, causative agents of PLA mostly include *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae*, *Enterococcus* species, *Staphylococcus* species, *Streptococcus* species, *Bacteroides* species, and a large group of other organisms (Gyorffy et al. 1987; Chou et al. 1997), but *E. coli* and *Klebsiella* are by far the most common pathogens, with *Klebsiella* having a specific role in that it causes as distinct syndrome of invasive infection.

Over the past years, a new type of invasive *Klebsiella pneumoniae* disease (*Klebsiella* liver abscess syndrome, KLAS; invasive *Klebsiella pneumoniae* liver abscess syndrome), which typically manifests as a community-acquired primary liver abscess associated with bacteremia, has been identified, first in Taiwan (Wang et al. 1998; Rahimian et al. 2004; Lee et al. 2010), but then also in other countries (Saccente 1999; Lederman and Crum 2005; Gomez et al. 2007; Keynan and Rubinstein 2007; Casella et al. 2009; Frazee et al. 2009; Pope et al. 2011; Fung et al. 2012; Moore et al. 2013). KLAS is caused by the *Klebsiella* capsular phenotype K1, magA KP, which confers a unique hypermucoviscous phenotype to the bacterium (see below). Community-acquired primary liver abscess caused by *K. pneumoniae* or KLAS mainly occurs in diabetic patients without previous hepatobiliary or intra-abdominal infection. Patients with this type of infectious syndrome can present with or without hepatic metastatic complications, but the development of metastatic infections is a typical feature in part of the patients, and 10–20 % of reported cases developed metastatic meningitis, endophthalmitis, endocarditis, and metastatic manifestations in other organs (Wang et al. 1998; Fung et al. 2002; Chan et al. 2007, Cheng et al. 2007; Chen et al. 2008a). There are certain clinical differences between KLAS patients from Eastern Asia, South Africa, and western countries (Ko et al. 2002). *Klebsiella pneumoniae* causing this syndrome has several distinct microbiologic features and a distinct genomic signature based on complete genome sequencing (Wu et al. 2009a). The main feature is the HMVKp (hypermucoviscous *Klebsiella pneumoniae*) phenotype, caused by the capsular serotype K1, magA + Kp. The mucoviscous phenotype is seen when contacting a bacterial colony in culture with a probe, resulting in the production of a viscous thread between the probe and the colony. The mucoviscosity-associated gene A, magA (wzy_K1), is the K1 polymerase gene, which encodes a 43 kDa outer membrane protein involved in the synthesis of exopolysaccharides (Fang et al. 2010; Yeh et al. 2010). *Klebsiella pneumoniae* isolates causing KLAS carry three rmpA/A2 genes, two large-plasmid-carried genes (p-rempA and p-rampA2), and one chromosomal gene (c-rmpA) (Hsu et al. 2011). Hyperviscosity, an extremely sticky phenotype of K. pneumonia, is associated with this destructive abscess syndrome (Kawai 2006; Lee et al. 2006; Yu et al. 2006; Pan et al. 2008). The K antigen, a capsular polysaccharide, is a very important virulence factor for *K. pneumoniae*. Expression of the rmpA and magA genes is associated with the hypermucoviscous phenotype and is linked to *Klebsiella* virulence and an aggressive clinical presentation (Yu et al. 2006). Capsular polysaccharide production leading to the hypermucoviscous phenotype is linked to the expression of genes regulating *Klebsiella* biofilm formation, treC (encoding trehalose-6-phosphate

hydrolase) and sugE (Wu et al. 2011). The pathogenic mechanism by which this distinct *Klebsiella* phenotype is related to the unique clinical presentation is only partially known. Expression of K1 antigen hampers complement- and neutrophil-mediated killing of *Klebsiella*, a mechanism thought to promote an invasive phenotype (Lin et al. 2010; Fung et al. 2011). In fact, capsular serotypes K 1 and K2 impair *Klebsiella* phagocytosis in type 2 diabetic patients (Lin et al. 2006), and phagocytosis-resistant *Klebsiella* serotypes are highly prevalent in PLA (Lin et al. 2004). Antibodies directed against capsule polysaccharide protect the host from magA+ *Klebsiella pneumoniae*-induced lethal disease by evading Toll-like receptor 4 signaling (Wu et al. 2009b). Other virulence factors that markedly influence the aggressiveness of *Klebsiella* include the expression of FimH as an adhesive subunit of type 1 enterobacterial fimbriae (Stahlhut et al. 2009). Fimbriae play an important role in target cell adhesion and invasion of the host. The expression of *Klebsiella* fimbriae is highly associated with K1 serotype isolates. The genome of *Klebsiella pneumoniae* contains nine fimbrial gene clusters, comprising type 1 and type 3 fimbriae and a group of fimbriae termed Kpa, Kpb, Kpc, Kpd, Kpe, Kpf, and Kpg. The Kpc fimbriae are regulated by the site-specific recombinase Kpcl (Wu et al. 2010). *Klebsiella pneumoniae* must acquire iron for replication; for this, it utilizes iron-scavenging siderophores, such as enterobactin, glycosylated enterobactin (salmochelin), and yersiniabactin. Siderophore-dependent iron acquisition systems are implicated in *Klebsiella* virulence, and three are upregulated in *Klebsiella* strains causing KLAS, *Yersinia* high-pathogenicity island, lucABCDiutA, and iroA(iroNDCB) (Hsieh et al. 2008). Yersiniabactin is a virulence factor that is prevalent among *K. pneumoniae* carbapenemase (KPC)-producing strains (Bachman et al. 2011). Hypervirulent *K. pneumoniae* secretes more and more active iron-acquisition molecules than classical *K. pneumoniae*, and this enhances virulence (Russo et al. 2011). The uptake of iron from extrabacterial compartments is regulated by the ferric uptake regulator Fur, which also modulates *Klebsiella* capsular polysaccharide biosynthesis via repression of the expression of rmpA, rmapA2, and rcsA (Lin et al. 2011b). Another *Klebsiella* species that much less commonly causes PLA is *K. ozaenae*, which is generally considered an opportunist of low virulence and colonizer of the respiratory tract implicated in atrophic rhinitis/ozaena (Chowdhury and Stein 1992).

PLA Caused by *Escherichia coli*

In an investigation of 72 patients with *E. coli* PLA, the majority of the abscesses were solitary, involved the right lobe of the liver, and comprised polymicrobial infections. The local cause of PLA involved the biliary tract in 66.7 % of the patients, and the most concomitant diseases were diabetes mellitus (30.6 %) and underlying malignancy (30.6 %) (Chen et al. 2005). Among 202 patient with PLA, there was no significant difference in mortality between patients with *E. coli* and those with *Klebsiella pneumoniae* infections, although for patients with PLA caused by *E. coli*, the APACHE II score at admission, malignancy, and right lobe abscess were significant predictors of death (Chen et al. 2007).

PLA Caused by Other Bacteria

Less common bacteria causing or having been isolated from PLA comprise *Staphylococcus aureus* (Smith et al. 2007), *Pseudomonas aeruginosa* (Goldani et al. 2005), *Enterococcus* species (Thomas et al. 1983), *Bacteroides fragilis* (Lonardo et al. 1992), *Streptococcus mitis* (Sarthe and DiBardino 2013), *Streptococcus anginosus* (Giuliano et al. 2012), *Aeromonas sobria* (Kamano et al. 2003), *Citrobacter koseri* (Gupta et al. 2013), *Aggregatibacter aphrophilus* (Tsui et al. 2012), *Yersinia enterocolitica* (Pulvirenti et al. 2007), *Fusobacterium necrophorum* (Hagelskjaer and Pedersen 1993; Athavale et al. 2002; Thatcher 2003), periodontal bacteria (*Fusobacterium nucleatum*, *Treponema denticola*, *Prevotella intermedia*, *Porphyromonas*

gingivalis; Ohyama et al. 2009), several anaerobic bacteria (Sabbai et al. 1972; Ogah et al. 2012), and a large number of other germs, which have in part been observed in immunocompromised patients.

Staphylococcus aureus is a well-known cause of solitary or multiple pyogenic liver abscesses and is estimated to account for 7 % of infectious liver abscess in case of non-mixed infection. Also other *Staphylococcus* species, e.g., *S. epidermidis*, were identified as causative agents, but much less often. Pyogenic liver abscess may be caused by mixed bacterial infections, a frequent partner of *S. aureus* being *Escherichia coli*. Staphylococcal liver abscesses are commonly medium-sized to large solitary lesions with indistinct ("invasive") borders, but multiple smaller abscesses or even a miliary abscess pattern (so-called microabscesses) has also been encountered. Multiple hepatic microabscesses caused by *S. aureus* can radiologically mimic *Candida* abscesses. An increasing number of hepatic abscesses is caused by the highly virulent methicillin-resistant *Staphylococci*/CA-MRSA, which can cause liver abscesses also in previously healthy adult individuals and in children. PLA caused by *Staphylococcus aureus* seems to be more common in patients with schistosomiasis (Teixeira et al. 2001). An association between schistosomiasis and *Salmonella* infection is also well documented (Lambertucci et al. 2001). In rare instances, PLA contained *Ascaris lumbricoides* (Hamid et al. 2013), a parasite which either induces PLA or moved into an abscess cavity.

Liver Abscesses in Crohn's Disease

Perforating Crohn's disease is characterized by the formation of intra-abdominal abscesses which develop in 20–24 % of patients. However, liver abscess represents a rare complication of Crohn's disease (Fagge 1870; Taylor 1949; Lerman et al. 1962; Watts 1978; Macpherson and Scott 1985; Mir-Madjlessi et al. 1986; Vakil et al. 1994; Kreuzpaintner et al. 2000). In a review of 59 cases (Kreuzpaintner et al. 2000), 72.9 % were men. 62.2 % of the patients suffered from active and 37.8 % from inactive Crohn's disease. In 52.9 % of the patients with active disease, the liver abscess presented as the initial manifestation of Crohn's disease. 47.2 % had a solitary abscess, 9.4 % double abscesses, and 43.4 % multiple abscesses. Microbiological analyses revealed that *Streptococcus milleri* was the dominating pathogen, followed by other streptococci, anaerobes, and enterobacteriaceae.

Pyogenic Abscesses and Necroses Caused by Gas-Forming Bacteria: *Clostridium* Liver Abscess

Introduction

Clostridium infections cover a broad spectrum of illnesses ranging from tetanus and severe and highly dangerous food intoxications to diarrheal disorders and highly aggressive organ and tissue lesions characterized by necrosis and gas-forming lesions (reviews: Maclennan 1962). Certain *Clostridium* species can cause large hepatic abscesses or abscess-like lesions that may mimic hepatic malignancy.

Liver Abscess

Clostridium species are a known cause of liver abscesses, in part with gas formation (Fiese 1950; Kivel et al. 1958; Sarmiento and Sarr 2002; Kurtz et al. 2005; Tabarelli et al. 2009; Ng et al. 2010; Rajendran et al. 2010; Huang et al. 2012; Ogah et al. 2012). Clostridial species causing liver abscess include *C. perfringens*, *C. clostridioforme*, *C. baratii*, *C. septicum*, and *C. welchii*. Among 83 patients with gas-forming pyogenic liver abscesses, 85.5 % of the patients had diabetes mellitus (Chou et al. 1995). The development of a clostridial liver abscess may be favored by the development of a hypoxic/anoxic hepatic area. For example, an abscess caused by *Clostridium perfringens* together with *Hafnia* and *Enterobacter cloacae* infection developed after obliteration of the portal vein by pancreatic cancer tissue (Tabarelli et al. 2009). Gas-forming hepatic abscess can develop as a complication of arterial

infusion chemotherapy (D'Orsi et al. 1979). Clostridial hepatic abscess may show a highly aggressive course, with extension of the abscess into adjacent organs (including the right kidney and the intestinal tract) and induction of portal vein thrombosis (Ogah et al. 2012). Liver abscess caused by C. perfringens can be followed by massive intravascular hemolysis (Kreidl et al. 2002; Au and Lau 2005; Ng et al. 2010), or intravascular hemolysis and septicemia (Rajendran et al. 2010).

Hepatic Gas Gangrene

Hepatic gas gangrene (gangrenous clostridial hepatitis) is an uncommon condition mainly caused by bacterial infection by *C. perfringens* (Fig. 6). It is a life-threatening disorder associated with a mortality rate (Ashley 1965; Birnbaum et al. 2012). The pathologic features of this rare disorder are characteristic. At autopsy, the liver is enlarged, pale, and fatty and feels crepitant. When this liver is put into water, it floats. On sections through the organ, multiple gas-filled spaces or cysts of variable sizes are noted, and sometimes the entire organ has a foamy aspect ("foamy liver"). Histologically, the liver exhibits separation of the hepatocyte plates, similar to far advanced autolysis. The gas-filled spaces are lined by flattened liver cells, and a leukocyte-mediated inflammatory reaction is lacking. Pressure exerted by the gas bubbles may cause crowding of the hepatocyte remnants, with formation of highly cellular areas without any lobular architecture. Gram-positive rods are present in this severely damaged tissue, sometimes in enormous numbers (Ashley 1965).

Clostridial Infection of Liver Metastasis

Colorectal liver metastases undergoing necrosis and forming an anaerobic niche can undergo infection with *Clostridium* followed by tumor abscess and eventually gas formation (Kahn et al. 1972; Saleh et al. 2009; Sucandy et al. 2012). Gas accumulating in the abscess may enter the peritoneal cavity and produce pneumoperitoneum (Urban et al. 2000; Fondran and Williams 2005; Sucandy et al. 2012). In one patient, infection of a hepatic CRC metastasis by *C. septicum* took place following alcohol injection into the liver lesion (Saleh et al. 2009). *C. septicum* infection presenting as a liver abscess has also been observed in a case of choriocarcinoma with liver metastasis (Lee and Hsieh 1999) and in metastases of breast carcinoma (Thel et al. 1994).

Microbiology

Clostridium is a genus of Gram-positive, rod-shaped bacteria belonging to the family *Clostridiaceae*, order *Clostridiales*. The genome of *C. perfringens* has been sequenced, and its genome analyzed in regard to toxin expression

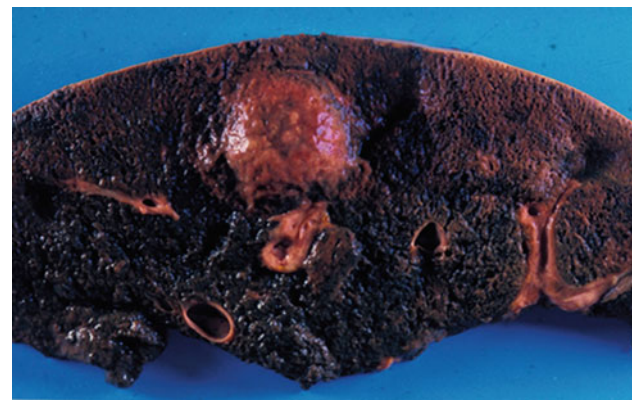

Fig. 6 Tumor-like, bulging, and hemorrhagic liver abscess associated with gas-forming *Clostridium* infection causing numerous gas bubbles in hepatic parenchyma

patterns (Myers et al. 2006). It is an obligate anaerobic group of microorganisms capable of developing endospores. There are about 100 clostridial species, of which a subset is pathogenic to humans, including *C. botulinum* (the cause of botulism), *C. tetani* (the causative agent of tetanus), *C. difficile* (bacterial diarrhea and antibiotic-induced enterocolitis), *C. perfringens/welchii* (gas gangrene), and *C. sordellii*. An increasing number of other *Clostridium* species have recently been isolated from humans, both with clinical manifestations and as isolates from apparently healthy individuals (*C. aldanense*, *C. amygdalinum*, *C. asparagiforme*, *C. baratii*, *C. celerecrescens*, *C. clostridioforme*, *C. fallax*, *C. glycolyticum*, *C. glycyrrhizinilyticum*, *C. hathewayi*, *C. intestinale*, *C. leptum*, *C. scindens*, *C. sphenoides*, and *C. symbiosum*. The clinically important taxon, *C. clostridioforme*, is now a mixture of three species that are different in terms of 16S rRNA sequences, phenotypic characteristics, and antimicrobial susceptibility (Finegold et al. 2005).

Pathogenic Pathways

Clostridium species are commonly found in soil, leaf litter, animal feces, and freshwater sediments, from where they can enter the human organism, either as complete viable bacteria or as spores. In the human host, they most commonly inhabit the intestinal tract.

Virulence Factors

C. perfringens has a variegated system of virulence factors, regulated at the transcriptional level by the products of the virR and virS genes that mainly comprise numerous extracellular toxins including alpha-toxin (phospholipase C), beta-toxin, theta-toxin (perfringolysin), kappa-toxin (a collagenase), and a sporulation-associated enterotoxin (reviews: Smith 1979; Rood and Cole 1991; Rood 1998). The global VirRS two-component signal transduction pathway regulates gene expression of alpha-toxin and perfringolysin O. In this regulatory pathway, the response regulator VirR regulates directly the expression of the theta-toxin/perfringolysin O gene and ccp, encoding the cysteine protease alpha-clostripain (which is not essential for *C. perfringens*-induced tissue necrosis), and indirectly regulates the expression of plce gene encoding the alpha-toxin, the colA gene (kappa-toxin of collagenase), and other genes. Alpha-toxin is a zinc-metallophospholipase C toxin mainly produced by *C. perfringens* and is responsible for necrosis and gas gangrene. It also possesses hemolytic activity and is the key virulence factor of *C. perfringens* infections. It induces the release of IL-8 from host cells through a dual pathway via tyrosine kinase A/TrkA acting on the ERK1/2/NF-kappaB and p38 MAPK pathways (Oda et al. 2012).

C. perfringens toxins affect the function of blood platelets and neutrophils and cause a reduction in blood supply to affected tissues (Hickey et al. 2008), a mechanism that may be important in the pathogenesis of *Clostridium*-induced tissue necrosis. *C. perfringens* beta-toxin is a necrotizing agent and is capable to release catecholamines from the host. The toxin forms potential-dependent, cation-selective channels in lipid bilayers and is a pore-forming agent with cytopathic effects. The *C. perfringens* iota toxin, only produced by type E strains, is an ADP-ribosyltransferase that induces ion-permeable channels in cells. The theta toxin of *C. perfringens* is also termed perfringolysin O. Perfringolysin O is a member of the cholesterol-dependent cytolysin family and a pore-forming agent that requires high concentrations of cholesterol to insert into host cell membranes. After binding to membrane cholesterol and transmembrane protein rafts, it oligomerizes into a prepore structure containing around 50 monomers followed by structural changes to create a rigid transmembrane beta-barrel (review: Nelson et al. 2010). *C. perfringens* epsilon-toxin is produced by type B and D strains and belongs to the aerolysin-like family of pore-forming toxins and is one of the most potent bacterial toxins that can cause fatal toxinemia in animals and eventually humans. Its expression is regulated by the agr operon (Chen et al. 2011). *C. perfringens* produces an

enterotoxin (CPE) which is responsible for the diarrheal signs and symptoms of *C. perfringens* type A food poisoning and antibiotic-associated diarrhea. CPE is 35 kDa polypeptide with an N-terminal toxicity domain that binds to tight junctions and damages their structure and function (McClane 2001). In tight junctions, CPE interacts with occludin, forming a complex that causes the internalization of occludin into the cytoplasm, followed by disruption of the normal paracellular permeability barrier (McClane and Chakrabarti 2004). CPE is a potent cytolytic agent and has been shown to rapidly and specifically destroy cancer cells expressing the CPE receptors, the tight junction proteins claudin-3 and claudin-4 (Kominsky et al. 2004, 2007; Kominsky 2006). *Clostridium* species produce several pore-forming toxins involved in the induction of host cell death and necrosis. The pore-forming alpha-toxin of *C. septicum* can induce programmed cellular necrosis, a distinct form of cell death described also in ischemia/perfusion injury and mediated by a disordered Ca^{2+} flux in target cells (Kennedy et al. 2009). Enterotoxic *C. perfringens* causing disease in birds and particularly in poultry produces a necrotic enteritis B-like toxin or NetB, a member of the beta-barrel pore-forming toxin family (Keyburn et al. 2010). *C. perfringens* strains also express up to three different sialidases which affect the host cell adherence and epsilon-toxin-induced cytotoxicity (Li et al. 2011), but as such are not decisive virulence factors (Chiarezza et al. 2009). Apart from the VirRS virulence factor system briefly discussed above, *C. perfringens* has a second important virulence effector and response regulator termed RevR, which affects cell morphology and regulates the expression of alpha-clostripain, hyaluronidase, and sialidase (Hiscox et al. 2011).

Liver Abscesses and Other Hepatobiliary Lesions in Salmonellosis

Introduction

Salmonella (S.) species cause both acute and chronic infections, depending on bacterial species, strains, virulence, and the host's immune defense system. Salmonellosis is the main cause of bacterial enteritis in humans and animals, and it is estimated that 1.4 million cases of salmonellosis occur among humans in the USA. Chronic infections increase the risk of inflammatory bowel disease and cancer. Typhoid (enteric) fever or *Typhus abdominalis* ("Typhus" in German, not to be confounded with the English term, typhus, which denotes a rickettsial disease) is a severe acute septicemic infectious illness caused by *S. typhi* (typhosa) and *S. paratyphi* A, less often by *S. paratyphi* B and C, and uncommonly by other S. species (review: Bhan et al. 2005). In typhoid fever, involvement of the liver can result in the development of focal lesions that may mimic hepatic malignancy.

Hepatobiliary Involvement

Pathologically, typhoid fever is characterized by a severe and diffuse enterocolitis, associated first with hyperplasia/hypertrophy of the intestinal (Peyer's patches) and lymphonodal lymphatic tissue (during the invasion phase) and then with necrosis and ulcerations of the Peyer's patches toward the end of the fastigium phase. In the course of typhoid septicemia, marked splenomegaly develops.

Salmonellosis and in particular typhoid fever can be associated with several forms of hepatobiliary disease (Table 1). These liver alterations were described in detail in the older literature, but have become uncommon due to the potent treatment modalities now available. The lesions can, however, be still encountered in

Table 1 Hepatobiliary involvement in salmonellosis

Miliary/submiliary typhoid nodules (so-called typhomas) and *Salmonella*-associated granulomatous hepatitis
Miliary hepatic necroses
Microabscesses
Macroabscesses
Typhoid hepatitis
Cholestatic typhoid hepatitis
Cholangitis typhosa (typhoid cholangitis)
Cholecystitis typhosa

regions with poor medical care and/or high exposition to *Salmonellae*.

Miliary Typhoid Granulomas and Salmonellotic Granulomatous Hepatitis

In the course of typhoid fever (*Typhus abdominalis*), submiliary or miliary nodules of whitish to gray-white color (so-called typhomas or typhoid pseudotubercles; Fig. 7) can develop in the liver, often in association with similar nodules in the subperitoneal tissue and the kidneys. In the original observation, these nodules were compared to "lymph follicles" owing to similarities in size, color, and shape (Friedreich 1857; Wagner 1860, as cited in Mallory 1898) and have been related to lymphomas ("miliary lymphomas"; Gruber 1916), but were later found to be specific nodular lesions not exclusively composed of lymphocytes (Fraenkel and Simmonds 1886), but histologically presenting two patterns, i.e., liver necroses surrounded by a neutrophil reaction (Reed 1895) or lesions resembling granulomas as seen in tuberculosis (Joest's "pseudotubercles"; Joest 1914).

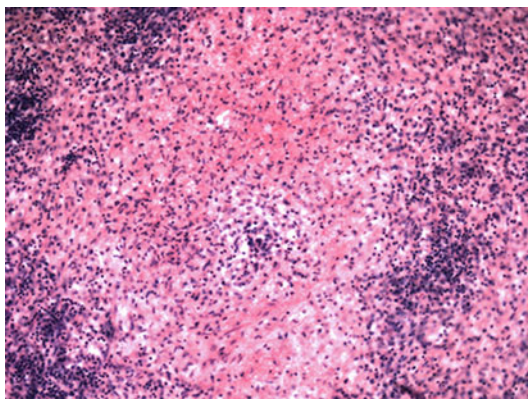

Fig. 7 Hepatic typhoid nodule (typhoid pseudotubercle; "typhoma") in *Salmonella typhi* infection. The granulomatous lesion shows central necrosis and exudation and a peripheral lymphocytic reaction (hematoxylin and eosin stain)

Histologically, these lesions chiefly consist of activated macrophages similar to those found in other tissues in the invasion and fastigium phases of disease (Mallory 1898). These macrophages are sometimes highly activated and enlarged. These are the so-called Rindfleisch cells which may phagocytose *Salmonellae* and/or erythrocytes. These large macrophages were originally described by Georg Eduard von Rindfleisch (1836–1908), a scholar of Virchow who was active in the then Breslau (now Wroclaw), Zurich, and Bonn and intensely worked on typhoid fever (Rindfleisch 1867). Stimulated macrophages may be associated with multinucleated giant cells (derived from macrophages), elements that occur in Peyer's patches, mesenteric lymph nodes, and liver, and detected by Billroth and Grohe in 1861 and Hoffmann in 1869 (cited in Mallory 1898). In the fastigium phase, and similar to Peyer's patches and mesenteric lymph nodes, the macrophage nodules undergo necrosis, sometimes with a central focus of coagulation necrosis, however without caseification, in contrast to tuberculosis. The necroses may a contain a filamentous, slightly eosinophilic network of fibrin-containing filaments, and the granulomas often show a peripheral infiltrate of lymphocytes in a rim of atrophic or decaying hepatocytes (Fraenkel and Simmonds 1886; McCrae and Klotz 1908; Büchner 1956). In case of septicemia and reduced monocyte activated, necrosis of the lesion can increase, associated with epithelioid cell loss, resulting in miliary hepatic necroses that may or may not contain bacteria (Kaiserling et al. 1972). In patients with an intact cell-mediated immunity, and in later stage disease, activated macrophages can form epithelioid cells and granulomas, usually without multinucleated giant cells or only very few giant cells. The granulomas may have direct contact with the lining of terminal vein ("nodular endophlebitis typhosa circumscripta"). These phlebocentric lesions can cause thrombosis of terminal veins and terminal vein obliteration.

Miliary Hepatic Necroses

In some patients with typhoid fever, small and round intra-acinar foci of coagulation necrosis are present in the absence of a significant macrophage reaction. These lesions may have pathogenesis similar to other so-called areactive necroses occurring in the setting of infections, e.g., peracute forms of tuberculosis, and are probably related to a distinct immune status of the host.

Hepatic Macroabscesses and Microabscesses in Typhoid Fever

Liver abscess is a rare, but well-known complication of both enteric typhoid fever and non-enteric *Salmonella* infections. In salmonellosis, liver abscesses are caused by *S. typhi* (Rodriguez and Undurraga 1955; Penaloza et al. 1974; Chogle et al. 1981; Rovito and Bonanno 1982; Petersen 1984; Matar et al. 1990; Soni et al. 1994; Ciraj et al. 2001; Rogers and Wadula 2001; Chaudhry et al. 2003; Chou et al. 2006; Kabra and Wadhwa 2006), *S. paratyphi* A (Rajagopal et al. 2002; Chaudhry et al. 2003; Jeans and McKendrick 2007), *S. enteritidis* (Hirschowitz 1952; Collazos et al. 1991; Elias et al. 1996; Vidal et al. 2003; Sheikh et al. 2011), *S. infantis* (Simmers et al. 1997), *Salmonella* group D non-typhi (Choi et al. 2006), *S. choleraesuis* (Luong and Fournier 1960), and *S. bareilly* (Allegra and Niutta 1957).

Salmonella abscess of the liver may develop within necrotic hepatic tumor metastases (Modol et al. 2006) or hepatocellular carcinoma (Elias et al. 1996; Lee et al. 2002), in intrahepatic hematoma (Cerwenka et al. 1997), via secondary infection of an amoebic liver abscess (Essien et al. 1965; Mansharamani et al. 1971; Marr and Haff 1971; Jeans and McKendrick 2007), and as a late complication of simple liver cyst infection (Gömceli et al. 2006; Sangwaiya et al. 2009). Hepatic *Salmonella* abscess can follow *Salmonella cholangitis* (Holler and Starlinger 1954) and may be combined with splenic abscesses (Chaudhry et al. 2003).

Typhoid Hepatitis

In the course of typhoid fever, a form of acute hepatitis may develop, mimicking viral hepatitis or leptospirosis and rarely ending up with fulminant hepatitis, liver failure, and encephalopathy (Ramachandran et al. 1974; Pais 1984; Ramanathan 1991; Husain 2011; Karoli et al. 2012).

Cholestatic Typhoid Hepatitis

A minority of patients with typhoid fever can develop cholestatic hepatitis, the pathogenic mechanism being unknown (Arabaci et al. 2003; Albayrak et al. 2011; Ratnayake et al. 2011).

Cholangitis Typhosa (Typhoid Cholangitis)

Cholangitis associated with hepatic microabscesses was observed in infections with *Salmonella enteritidis* serovar Choleraesuis (Vogel et al. 2007).

Cholecystitis Typhosa (Typhoid Cholecystitis)

Cholecystitis caused by *Salmonella* is a rare but clinically important complication of *Salmonella typhi* infection (Bender 1946; Avalos et al. 1992; Lai et al. 2006; Ruiz-Rebollo et al. 2008; Ali et al. 2013).

Differential Diagnosis

The main differential diagnosis of hepatic *Salmonella* abscess is abscess formation caused by other bacterial species. In most cases, salmonellosis is nowadays promptly diagnosed, but there are rare situations where liver abscess caused by *Salmonella* may be attributed to other types of hepatic

mass-forming lesions. In patients with septic salmonellosis, hepatic malignancies may mimic (expected) liver abscesses, as the necroses that develop in malignant tumors may resemble cavitated *Salmonella* abscesses on CT images (Hagiwara et al. 2009). Conversely, liver abscesses in septic salmonellosis may be confounded with multiple hepatocellular carcinomas (Simmers et al. 1997).

Microbiology

Salmonella is a genus of rod-shaped, Gram-negative, chemoorganotrophic, predominantly motile bacteria of the family *Enterobacteriaceae*. The bacteria are peritrich, i.e., they have flagella all around their body. *Salmonella* is very closely related to *Escherichia* and occurs worldwide in the environment and in cold- and warm-blooded animals. Most species are facultative intracellular pathogens. There are about 2500 serotypes (serovars) of *Salmonella*, which are allocated to few species. The taxonomy and nomenclature of *Salmonella* species have evolved from an initial one serotype-one species concept, and each serotype was previously considered a separate species, but taxonomy has undergone several revisions. *Salmonella* species formerly included five species, namely, *S. arizonae*, *S. choleraesuis* (the type species of the genus), *S. enteritidis*, *S. typhi*, and *S. typhimurium*. According to the Centers for Disease Control and Prevention (CDC), the genus *Salmonella* contains only two species, each of which contains multiple serotypes. The two species are termed *S. enterica* and *S. bongeri*. *S. enterica* contains the subspecies referred to by a Roman numeral and a name: I, *S. enterica* subsp. *enterica*; II, *S. enterica* subsp. *salamae*; IIIa, *S. enterica* subsp. *arizonae*; IIIb, *S. enterica* subsp. *diarizonae*; IV, *S. enterica* subsp. *houtenae*; and VI, *S. enterica* subsp. *indica* (review: Brenner et al. 2000). Clinically well-known "species" are in part distinct serovars, e.g., the former *S. typhi* is now *S. enterica* subsp. *enterica* ser. Typhi.

What Is Typhoid Fever?

Typhoid fever may present as diarrhea followed by sustained fever, anorexia, vomiting, abdominal distention, headache, and apathy. The illness usually starts after an incubation of 10–14 days, but it ranges from 5 to 30 days, chiefly depending on the size of the infectious dose and the strain's virulence. In the classical medical literature, the first week of clinically manifest infection was termed *Stadium incrementi* ("stage of increase"), characterized by step-wise increase of fever, while the severe *Stadium fastigii* was defined as the stage with continuous high fever (typically 39–40 C). The *Stadium amphibolicum* (third week) was defined as disease with end of continuous fever, with high evening fever and low temperature in the morning. The *Stadium decrementi* ("stage of decrease") was typically in the fourth week of illness and was characterized by lytic fall of fever and decrease of splenomegaly. Today, untreated typhoid fever is usually classified to progress through five stages, i.e., incubation, invasion, fastigium, lysis, and convalescence. In the course of active invasion, patients experience a stepwise elevation in body temperature from day to day, and part of the patients develop rose-colored skin spots grossly resembling petechiae, the roseoles of typhoid fever which have a histologic substrate of perivascular cellular infiltrates, but only rarely minor bleedings. Symptoms and signs are maximum in the fastigium stage, which is also characterized by a continuous fever with only minor daily fluctuations (the well-known "febris continua" or briefly, "continua" of typhoid fever). In the lysis stage, the symptoms start to wane and the fever slowly falls, however still with sometimes extreme daily fever fluctuations. In the convalescence stage, the condition of the patient improves, but fatigue and weakness can continue for a long time period.

Typhoid fever can show several complications, including septic metastases in several organs, osteomyelitis typhosa, nephritis, meningitis, parotitis, orchitis, pneumonia, and hepatobiliary disease. About 3 % of patients develop chronic

typhoid cholecystitis after 1 year, the infected gallbladder forming a reservoir for viable *Salmonellae* (the carrier state).

Pathways of Infection

Salmonella species adhere to host cells through fimbrial adhesins. In the course of cellular invasion, *Salmonella* species interact in a complex manner with the actin cytoskeleton of host cells. Rearrangements of the actin cytoskeleton are brought about by elements of the bacterial type III protein secretion system, a virulence complex which activates the regulatory proteins, Cdc42 and Rac, to produce membrane ruffles that engulf the bacteria, while the pathogenicity island 2/SPI2 translocates effectors that promote intracellular survival and growth, associated with focal actin polymerization around the *Salmonella*-containing vacuole of the host cell (Guiney and Lesnick 2005). *Salmonellae* can also be taken up by host cells through macropinocytosis and phagocytosis, e.g., by luminal neutrophils in the inflamed gut during early infection (Loetscher et al. 2012). Replicating bacteria within host cells can counteract the autophagy pathway and evade elimination via the induction of aggresome-like induced structures through the action of a translocated virulence protein, deubiquitinase (Thomas et al. 2012).

The *Salmonella* type II secretion effector protein AvrA is a multifunctional enzyme having important roles in inhibiting inflammation, regulating apoptosis, and increasing proliferation. In a mouse model of salmonellosis, AvrA expression suppressed intestinal inflammation and inhibited the secretion of the cytokines, IL-12, IFN-gamma, and TNF-alpha. On the other hand, AvrA promoted the bacterium's invasion and was associated with *Salmonella* translocation to the gallbladder and liver abscess formation (Lu et al. 2010).

Host cell death plays a significant role in *Salmonella* infections (review: Guiney 2005). *Salmonella* species can induce cell death through apoptosis, a process dependent of the type III secretion system of the bacterium (Boise and Collins 2001). In particular, intestinal epithelial cells/enterocytes are killed by caspase-dependent apoptosis in salmonellosis, while macrophages undergo a caspase-1-dependent proinflammatory programmed cell death called pyroptosis (Monack et al. 2001; Fink and Cookson 2007).

References

Albayrak A, Gunbey SS, Aktas F (2011) Cholestatic hepatitis due to *Salmonella typhi*. Clin Pract 1:e13

Ali R, Ahmed S, Qadir M, Atiq H, Hamid M (2013) Salmonella cholecystitis: atypical presentation of a typical condition. J Coll Physicians Surg Pak 23:826–827

Allegra G, Niutta R (1957) Solitary abscess of the liver caused by *Salmonella Bareilly* (in Italian). Policlinico Prat 64:1879–1882

Alvarez Perez JA, Gonzalez JJ, Baldonedo RF, Sanz L, Carreno G, Junco A et al (2001) Clinical course, treatment, and multivariate analysis of risk factors for pyogenic liver abscess. Am J Surg 181:177–186

Arabaci F, Irmak H, Akdeniz H, Demiröz AP (2003) Jaundice with cholestasis: a case of typhoid hepatitis. Turk J Infect 17:99–102

Ashley DJB (1965) Two cases of clostridial hepatitis. J Clin Pathol 18:170–174

Athavale NV, Leitch DG, Cowling P (2002) Liver abscesses due to *Fusobacterium* ssp. that mimick malignant metastatic liver disease. Eur J Clin Microbiol Infect Dis 21:884–886

Au WY, Lau LS (2005) Massive haemolysis because of *Clostridium perfringens* liver abscess in a patient on peritoneal dialysis. Br J Haematol 131:2

Avalos ME, Cerulli MA, Lee RS (1992) Acalculous acute cholecystitis due to *Salmonella typhi*. Dig Dis Sci 37:1772–1775

Bachman MA, Oyler JE, Burns SH, Caza M, Lépine F, Dozois CM, Weiser JN (2011) *Klebsiella pneumoniae* yersiniabactin promotes respiratory infection through evasion of lipocalin 2. Infect Immun 79:3309–3316

Bagri N, Yadav D, Hemal A (2013) Inferior vena caval and right atrial thrombosis: complicating pyogenic liver abscess. Indian Pediatr 50:701–703

Bansal AS, Prabhakar P (1988) Clinical aspects of pyogenic liver abscess: the University Hospital of the West Indies experience. J Trop Med Hyg 91:87–93

Beaumont DM, Davis M (1985) Clinical presentation of pyogenic liver abscess in the elderly. Age Ageing 14:339–344

Bender CE (1946) Salmonella fever; report of five cases, one complicated by cholecystitis, perforation and

peritonitis with autopsy findings. Northwest Med 45:660–665
Bhan MK, Bahl R, Bhatnagar S (2005) Typhoid and paratyphoid fever. Lancet 366:749–762
Birnbaum DJ, Grégoire E, Hardwigsen J, Le Treut YP (2012) Salvage liver transplantation for hepatic gas gangrene. J Gastrointest Surg 16:1802–1804
Boise LH, Collins CM (2001) Salmonella-induced cell death: apoptosis, necrosis or programmed cell death? Trends Microbiol 9:64–67
Branum GD, Tyson GS, Branum MA, Meyers WC (1990) Hepatic abscess. Changes in etiology, diagnosis, and management. Ann Surg 212:655–662
Brenner FW, Villar RG, Angulo FJ, Tauxe R, Swaminathan B (2000) Salmonella nomenclature. J Clin Microbiol 38:2465–2467
Büchner F (1956) Allgemeine Pathologie. Pathologie als Biologie und als Beitrag zur Lehre vom Menschen. Urban & Schwarzenberg, München/Berlin, figure 72a on page 105
Casella F, Manenti MG, Conca C, Repetti V, Longhi P, Lazzaroni S, Mercieri A, Furlan R (2009) Liver abscess caused by *Klebsiella pneumoniae*. Dig Liver Dis 41:838
Cerwenka H, Werkgartner G, Bacher H, el-Shabrawi A, Mischinger HJ (1997) Intrahepatic hematoma with secondary *Salmonella* infection via biliary fistula. Hepatogastroenterology 44:529–532
Chan KS, Chen CM, Cheng KC, Hou CC, Lin HJ, Yu WL (2005) Pyogenic liver abscess: a retrospective analysis of 107 patients during a 3-year period. Jpn J Infect Dis 58:366–368
Chan KS, Yu WL, Tsai CL, Cheng KC, Hou CC, Lee MC, Tan CK (2007) Pyogenic liver abscess caused by *Klebsiella pneumoniae*: analysis of the clinical characteristics and outcomes in 84 patients. Chin Med J (Engl) 120:136–139
Chaudhry R, Mahajan RK, Diwan A, Khan S, Singhal R, Chandel DS, Hans C (2003) Unusual presentation of enteric fever: three cases of splenic and liver abscesses due to *Salmonella typhi* and *Salmonella paratyphi* A. Trop Gastroenterol 24:198–199
Chen SC, Yen CH, Lai KC, Tsao SM, Cheng KS, Chen CC, Lee MC, Chou MC (2005) Pyogenic liver abscesses with *Escherichia coli*: etiology, clinical course, outcome, and prognostic factors. Wien Klin Wochenschr 117:809–815
Chen SC, Wu WY, Yeh CH, Lai KC, Cheng KS, Jeng LB, Wang PH, Lin DB, Chen CC et al (2007) Comparison of *Escherichia coli* and *Klebsiella pneumoniae* liver abscesses. Am J Med Sci 334:97–105
Chen HW, Wang CC, Su WC, Wang PC (2008a) Education and imaging hepatobiliary and pancreatic: gas-forming abscess after radiofrequency ablation for hepatocellular carcinoma. J Gastroenterol Hepatol 23:990
Chen SC, Tsai SJ, Chen CH, Huang CC, Lin DB, Wang PH, Chen CC, Lee MC (2008b) Predictors of mortality in patients with pyogenic liver abscess. Neth J Med 66:196–203
Chen J, Rood JI, McClane BA (2011) Epsilon-toxin production by *Clostridium perfringens* type D strain CN3718 is dependent upon the agr operon but not the VirS/VirR two-component regulatory system. MBio 2. pii: e00275–11
Chen YY, Lee JC, Yen HH, Wu SS, Soon MS (2012) Pyogenic liver abscess and colorectal neoplasia: a case series. Scand J Infect Dis 44:848–851
Cheng KS, Tang HL, Hsu CH, Lai HC, Yu CJ, Chou FT (2007) A clinical survey of *Klebsiella pneumoniae* virulence and genotype in pyogenic liver abscess. Adv Ther 24:589–593
Cheng HC, Chang WL, Chen WY, Kao AW, Chuang CH, Sheu BS (2008) Long-term outcome of pyogenic liver abscess: factors related with abscess recurrence. J Clin Gastroenterol 42:1110–1115
Chiarezza M, Lyras D, Pidot SJ, Flores-Diaz M, Awad MM, Kennedy CL, Cordner LM et al (2009) The Nanl and NanJ sialidases of *Clostridium perfringens* are not essential for virulence. Infect Immun 77:4421–4428
Chogle AR, Sawant BN, Sequeira RD, Pai-Dhunghat JV, Joshi VR (1981) Salmonella liver abscess (a case report). J Assoc Physicians India 29:73–75
Choi JW, Choi SJ, Kwon HC, Cheong JY, Lee KM, Yoo BM, Hahm KB et al (2006) A case of *Salmonella* liver abscess (in Korean). Korean J Gastroenterol 47:316–319
Chong VH, Yong AM, Wahab AY (2008) Gas-forming pyogenic liver abscess. Singapore Med J 49:e123–e125
Chong VH, Zainal-Abidin Z, Hassan H, Chong CF (2010) Rare complications of pyogenic liver abscess. Singapore Med J 51:e169–e172
Chou FF, Sheen-Chen SM, Chen YS, Lee TY (1995) The comparison of clinical course and results of treatment between gas-forming and non-gas-forming pyogenic liver abscess. Arch Surg 130:401–405
Chou FF, Sheen-Chen SM, Chen YS, Chen MC (1997) Single and multiple pyogenic liver abscesses: clinical course, etiology, and results of treatment. World J Surg 21:384–388
Chou YP, Changchien CS, Chiu KW, Kuo CM, Kuo FY, Kuo CH (2006) Salmonellosis with liver abscess mimicking hepatocellular carcinoma in a diabetic and cirrhotic patient: a case report and review of the literature. Liver Int 26:498–501
Chowdhury P, Stein DS (1992) Pyogenic hepatic abscess and septic pulmonary emboli associated with *Klebsiella ozanae* bacteremia. South Med J 85:638–641
Ciraj AM, Reetika D, Bhat GK, Pai CG, Shivananda PG (2001) Hepatic abscess caused by *Salmonella typhi*. J Assoc Physicians India 49:1021–1022
Collazos J, Egutbide V, de Migual J, Echeverria J, Usera MA (1991) Liver abscess due to *Salmonella enteritidis* 19 months after an episode of gastroenteritis in a man who underwent a cholecystectomy. Rev Infect Dis 13:1027–1028
D'Orsi CJ, Ensminger W, Smith EH, Lew M (1979) Gas-forming intrahepatic abscess: a possible

complication of arterial infusion chemotherapy. Gastrointest Radiol 4:157–161
Elias N, Naschitz JE, Dubin Z, Yeshurun D (1996) *Salmonella enteritidis* liver abscess within hepatocellular carcinoma. AJR Am J Roentgenol 166:993
Essien EM, Ahimie HS, Laja AO (1965) *Salmonella typhi* in amoebic liver abscess. Report of a case. West Afr Med J 14:121–124
Fagge GH (1870) Hepatic abscesses, following ulceration of the large intestine. Trans Pathol Soc Lond 21:235–236
Fang CT, Lai SY, Yi WC, Hsueh PR, Liu KL (2010) The function of wzy_K1 (magA), the serotype K1 polymerase gene in *Klebsiella pneumoniae* cps gene cluster. J Infect Dis 201:1268–1269
Fernandez Ruiz M, Guerra Vales JM, Castelbon Fernandez FJ, Llenas Garcia J (2007) Pyogenic liver abscess as presenting manifestation of silent colon adenocarcinoma (in Spanish). Rev Esp Enferm Dog 99:303–305
Fiese MJ (1950) Tympany over the liver in hepatic abscess caused by *Clostridium welchii*. Report of a case. Calif Med 73:505–506
Finegold SM, Song Y, Liu C, Hecht DW, Summanan P, Könönen E, Allen SD (2005) *Clostridium clostridioforme*: a mixture of three clinically important species. Eur J Microbiol Infect Dis 24:319–324
Fink SL, Cookson BT (2007) Pyroptosis and host cell death responses during *Salmonella* infection. Cell Microbiol 9:2562–2570
Fondran J, Williams GB (2005) Liver metastasis presenting as pneumoperitoneum. South Med J 98:248–249
Fraenkel E, Simmonds M (1886) Die ätiologische Bedeutung des Typhus-Bacillus. Voss, Hamburg/Leipzig
Frazee BW, Hansen S, Lambert L (2009) Invasive infection with hypermucoviscous *Klebsiella pneumoniae*: multiple cases presenting to a single emergency department in the United States. Ann Emerg Med 53:639–642
Frey CF, Zhu Y, Suzuki M, Isaji S (1989) Liver abscesses. Surg Clin North Am 69:259–271
Friedreich A (1857) Ein neuer Fall von Leukämie. Virchows Arch Pathol Anat Physiol 12:53
Fung CP, Chang FY, Lee SC, Hu BS, Kuo BI, Liu CY, Ho M, Siu LK (2002) A global emerging disease of *Klebsiella pneumoniae* liver abscess: is serotype K1 an important factor for complicated endophthalmitis? Gut 50:420–424
Fung CP, Chang FY, Lin JC, Ho DM, Chen CT, Chen JH, Yeh KM, Chen TL et al (2011) Immune response and pathophysiological features of *Klebsiella pneumoniae* liver abscesses in an animal model. Lab Invest 91:1029–1039
Fung CP, Lin YT, Lin JC, Chen TL, Yeh KM, Chang FY, Chuang HC, Wu HS et al (2012) *Klebsiella pneumoniae* in gastrointestinal tract and pyogenic liver abscess. Emerg Infect Dis 18:1322–1325
Giuliani A, Caporale A, Demoro M, Scimo M, Galati F, Galati G (2007) Silent colon carcinoma presenting as a hepatic abscess. Tumori 93:616–618
Giuliano S, Rubini G, Conte A, Goldoni P, Falcone M, Vena A, Venditti M, Morelli S (2012) *Streptococcus anginosus* group disseminated infection: case report and review of literature. Infez Med 20:145–154
Goldani LZ, dos Santos RP, Sugar AM (2005) Pyogenic liver abscess in patients with schistosomiasis mansoni. Trans R Soc Trop Med Hyg 99:932–936
Gömceli I, Gürer A, Ozdogan M, Ozlem N, Aydin R (2006) *Salmonella typhi* abscess as a late complication of simple cyst of the liver: a case report. Turk J Gastroenterol 17:151–152
Gomez C, Broseta A, Otero JR, Chaves F (2007) Primary pyogenic liver abscess caused by magA+ *Klebsiella pneumoniae* in Spain. Clin Microbiol Newsl 29:100–102
Gruber G (1916) Ueber die durch Infektion mit Bakterien der Typhusgruppe in der Leber bedingten knötchenförmigen Nekroseherde (sog. "miliare Lymphome"). Zbl Bakteriol. Parasitenkunde Infektionskrankh 77:301
Guiney DG (2005) The role of host cell death in *Salmonella* infections. Curr Top Microbiol Immunol 289:131–150
Guiney DG, Lesnick M (2005) Targeting of the actin cytoskeleton during infection by *Salmonella* strains. Clin Immunol 114:248–255
Gupta M, Sharma A, Singh R, Lehl SS (2013) Citrobacter koseri: an unusual cause of pyogenic liver abscess. BMJ Case Rep. pii: bcr2013008974
Gyorffy EJ, Frey CF, Silva J, McGahan J (1987) Pyogenic liver abscess. Diagnostic and therapeutic strategies. Ann Surg 206:699–705
Hagelskjaer L, Pedersen G (1993) *Fusobacterium necrophorum* septicemia complicated by liver abscess. A case report. APMIS 101:904–906
Hagiwara S, Ogino T, Takahashi Y, Yamada T, Ishihara K, Matsumura N, Miyanaga T, Iino Y (2009) Hepatocellular carcinoma mimicking liver abscesses in a cirrhotic patient with severe septic shock as a result of *Salmonella* O9 HG infection. Case Rep Gastroenterol 3:56–60
Hamid R, Wani S, Ahmad N, Akhter A (2013) Post-partum pyogenic abscess containing *Ascaris lumbricoides*. Trop Parasitol 3:79–81
Hau T, Hartmann E (1987) Pathology, diagnosis and therapy of liver abscess (in German). Zentralbl Chir 112:529–547
Hayashi Y, Uchiyama M, Inokuma T, Torisu M (1989) Gas-containing pyogenic liver abscess – a case report and review of the literature. Jpn J Surg 19:74–77
Hickey MJ, Rain Y, Kwan Q, Awad MM, Kennedy CL, Young LF, Hall P, Cordner LM (2008) Molecular and cellular basis of microvascular perfusion deficits induced by *Clostridium perfringens* and *Clostridium septicum*. PLoS Pathog 4:e1000045
Hiraoka A, Yamashita Y, Uesugi K, Koizumi Y, Yamamoto Y, Doi H, Hasebe A, Ichikawa S

et al (2007) Three cases of liver abscesses complicated with colon cancer without liver metastasis: importance of screening for digestive disease. Intern Med 46:2013–2017

Hirschowitz BI (1952) Pyogenic liver abscess: a review with a case report on a solitary abscess caused by *Salmonella enteritidis*. Gastroenterology 21:291–299

Hiscox TJ, Chakravorty A, Choo JM, Ohtani K, Shimizu T, Cheung JK, Rood JI (2011) Regulation of virulence by the RevR response regulator in *Clostridium perfringens*. Infect Immun 79:2145–2153

Holler G, Starlinger F (1954) Infection of the biliary passages with typhoid and paratyphoid bacteria and its consequences, especially liver abscess (in German). Med Klin (Munich) 49:429–434

Hsieh CB, Tzao C, Yu CY, Chen CJ, Chang WK, Chu CH, Chou SJ, Tung HJ, Yu JC (2006) APACHE II score and primary liver cancer history had risk of hospital mortality in patients with pyogenic liver abscess. Dig Liver Dis 38:498–502

Hsieh PF, Lin TL, Lee CZ, Tsai SF, Wang JT (2008) Serum-induced iron-acquisition systems and TonB contribute to virulence in *Klebsiella pneumoniae* causing primary pyogenic liver abscess. J Infect Dis 197:1717–1727

Hsu CR, Lin TL, Chen YC, Chou HC, Wang JT (2011) The role of *Klebsiella pneumoniae* rmpA in capsular polysaccharide synthesis and virulence revisited. Microbiology 157:3446–3457

Huang CJ, Pitt HA, Lipsett PA, Osterman FA, Lillemoe KD, Cameron JL et al (1996) Pyogenic hepatic abscess. Changing trends over 42 years. Ann Surg 223:600–609

Huang CY, Chou WK, Lin MS, Tsai KC, Sun JT (2009) Gas-forming pyogenic liver abscess. QJM 102:885–886

Huang et al. (2012). http://www.ncbi.nlm.nih.gov/pubmed/22561510

Huang WK, Lin YC, Chiou MJ, Yang TS, Chang JW, Yu KH, Kuo CF, See LC (2013) Pyogenic liver abscess as a warning sign for primary liver cancer: a nationwide population-based study. Asian Pac J Cancer Prev 14:4727–4731

Husain EH (2011) Fulminant hepatitis in typhoid fever. J Infect Public Health 4:154–165

Jeans AR, McKendrick MW (2007) Salmonella paratyphi A liver abscess – secondary infection of an amoebic liver abscess? Travel Med Infect Dis 5:144–146

Jeong SW, Jang JY, Lee TH, Kim HG, Hong SW, Park SH, Kim SG, Cheon YK et al (2012) Cryptogenic pyogenic liver abscess as the herald of colon cancer. J Gastroenterol Hepatol 27:248–255

Joest K (1914) Vergleichende Untersuchungen über die durch Bakterien der Gärtnergruppe in der Leber des Kalbes und die durch Typhusbazillen in der Leber des Menschen bedingten Pseudotuberkel. Verh Dtsch Pathol Ges 17:238

Johannsen EC, Sifri CD, Madoff LC (2000) Pyogenic liver abscesses. Infect Dis Clin North Am 14:547–563

Kabra S, Wadhwa V (2006) Hepatic abscess caused by *Salmonella typhi*. Indian Pediatr 43:81–82

Kahn SP, Lindenauer SM, Wojtalik RS, Hildreth D (1972) Clostridia hepatic abscess. Arch Surg 104:209–212

Kaiserling E, Racz P, Tenner K, Lennert K (1972) Vorkommen intrazellulärer Bakterien in Makrophagen beim Typhus abdominalis des Menschen. Zur Feinstruktur, Herkunft und Funktion der Rindfleisch-Zellen. Virchows Arch. Abt B Zellpath 11:343–357

Kamano Y, Ohashi H, Kikuchi T, Watanabe K, Kitahara M (2003) Liver abscess and *Aeromonas* bacteremia with septic pulmonary embolism. Intern Med 42:1047–1049

Kandel G, Marcon NE (1984) Pyogenic liver abscess: new concepts of an old disease. Am J Gastroenterol 79:65–71

Kao WY, Hwang CY, Chang YT, Su CW, Hou MC, Lin HC, Lee FY, Lee SD, Wu JC (2012) cancer risk in patients with pyogenic liver abscess: a nationwide cohort study. Aliment Pharmacol Ther 36:467–476

Karadag O, Akinci D, Aksov DY, Bayraktar Y (2005) Acute Budd-Chiari syndrome resulting from a pyogenic liver abscess. Hepatogastroenterology 52:1554–1556

Karoli R, Fatima J, Chandra A, Singh G (2012) *Salmonella* hepatitis: an uncommon complication of a common disease. J Family Med Prim Care 1:160–162

Kawai T (2006) Hypermucoviscosity: an extremely sticky phenotype of *Klebsiella pneumoniae* associated with emerging destructive tissue abscess syndrome. Clin Infect Dis 42:1359–1361

Kennedy CL, Smith DJ, Lyras D, Chakravorty A, Rood JI (2009) Programmed cellular necrosis mediated by pore-forming a-toxin from *Clostridium septicum*. PLoS Pathog 5:e1000516

Keyburn AL, Bannam TL, Moore RJ, Rood JI (2010) NetB, a pore-forming toxin from necrotic enteritis strains of *Clostridium perfringens*. Toxins (Basel) 2:1913–1927

Keynan Y, Rubinstein E (2007) The changing face of *Klebsiella pneumoniae* infections in the community. Int J Antimicrob Agents 30:385–389

Kivel RM, Kessler A, Cameron DJ (1958) Liver abscess due to *Clostridium perfringens*. Ann Intern Med 49:672–679

Klotz SA, Penn RL (1987) Clinical differentiation of abscess from neoplasm in newly diagnosed space-occupying lesions of the liver. South Med J 80:1537–1541

Knaus WA (2002) APACHE 1978–2001: the development of a quality assurance system based on prognosis: milestones and personal reflections. Arch Surg 137:37–41

Knaus WA, Draper EE, Wagner DP, Zimmermann JE (1985) APACHE II: a severity of disease classification. Crit Care Med 13:818–829

Ko WC, Paterson DL, Sagnimeni AJ, Hasne DS, Von Gottberg A, Mohapatra S, Casellas JM et al (2002) Community-acquired *Klebsiella pneumoniae* bacteremia: global differences in clinical patterns. Emerg Infect Dis 8:160–166

Kominsky SL (2006) Claudins: emerging targets for cancer therapy. Expert Rev Mol Med 8:1–11

Kominsky SL, Vali M, Korz D, Gabig TG, Weitzman SA, Argani P, Sukumar S (2004) *Clostridium perfringens* enterotoxin elicits rapid and specific cytolysis of breast carcinoma cells mediated through tight junction proteins claudin 3 and 4. Am J Pathol 164:1627–1633

Kominsky SL, Tyler B, Sosnowski J, Brady K, Doucet M, Nell D, Smedley JG, McClane B et al (2007) *Clostridium perfringens* enterotoxin as a novel-targeted therapeutic for brain metastasis. Cancer Res 67:7977–7982

Kreidl KO, Green GR, Wren SM (2002) Intravascular hemolysis from a *Clostridium perfringens* liver abscess. J Am Coll Surg 194:387

Kreuzpaintner G, Schmidt WU, West TB, Tischendorf FW (2000) Two large liver abscesses complicating Crohn's disease. Z Gastroenterol 38:837–840

Kurland JE, Brann OS (2004) Pyogenic and amoebic liver abscesses. Curr Gastroenterol Rep 6:273–279

Kurtz JE, Claudel L, Collard O, Limacher JM, Bergerat JP, Dufour P (2005) Liver abscess due to *Clostridium septicum*. A case report and review of the literature. Hepatogastroenterology 52:1557–1558

Lai CH, Huang CK, Chin C, Lin HH, Chi CY, Chen HP (2006) Acute acalculous cholecystitis: a rare presentation of typhoid fever in adults. Scand J Infect Dis 38:196–200

Lambertucci JR, Rayes AA, Serufo JC, Nobre V (2001) Pyogenic abscesses and parasitic diseases. Rev Inst Med Trop Sao Paulo 43:67–74

Land MA, Moinuddin M, Bisno AL (1985) Pyogenic liver abscess: changing epidemiology and prognosis. South Med J 8:1426–1430

Law and Li (2012). http://www.ncbi.nlm.nih.gov/pubmed/22416187

Lederman ER, Crum NF (2005) Pyogenic liver abscess with a focus on *Klebsiella pneumoniae* as a primary pathogen: an emerging disease with unique clinical characteristics. Am J Gastroenterol 100:322–331

Lee CH, Hsieh SY (1999) Case report: *Clostridium septicum* infection presenting as liver abscess in a case of choriocarcinoma with liver metastasis. J Gastroenterol Hepatol 14:1227–1229

Lee CC, Poon SK, Chen GH (2002) Spontaneous gas-forming liver abscess caused by *Salmonella* within hepatocellular carcinoma: a case report and review of the literature. Dig Dis Sci 47:586–589

Lee HC, Chuang YC, Yu WL, Lee NY, Chang CM, Ko NY, Wang LR, Ko WC (2006) Clinical implications of hypermucoviscosity phenotype in *Klebsiella pneumoniae* isolates: association with invasive syndrome in patients with community-acquired bacteraemia. J Intern Med 259:606–614

Lee JK, Kum J, Ghosh P (2008) Nonmetastatic cancer of the colon associated with pyogenic liver abscess. Am J Gastroenterol 103:798–799

Lee CH, Liu JW, Su LH, Chien CC, Li CC, Yang KD (2010) Hypermucoviscosity associated with *Klebsiella pneumoniae*-mediated invasive syndrome: a prospective cross-sectional study in Taiwan. Int J Infect Dis 14:e688–e692

Lerman B, Garlock JH, Janowitz HD (1962) Suppurative pylephlebitis with multiple liver abscesses complicating regional ileitis: review of literature – 1940–1960. Ann Surg 155:441–448

Levison MA, Zeigler D (1991) Correlation of APACHE II score, drainage technique and outcome in postoperative intra-abdominal abscess. Surg Gynecol Obstet 172:89–94

Li J, Sayeed S, Robertson S, Chen J, McClane BA (2011) Sialidases affect the host cell adherence and epsilon toxin-induced cytotoxicity of *Clostridium perfringens* type D strain CN3718. PLoS Pathog 7:e1002429

Lin JC, Chang FY (2008) Pyogenic liver abscess associated with septic pulmonary embolism. J Chin Med Assoc 71:603–604

Lin JC, Chang FY, Fung CP, Xu JZ, Cheng HP, Wang JJ, Huang LY, Siu LK (2004) High prevalence of phagocytic-resistant capsular serotypes of *Klebsiella pneumoniae* in liver abscess. Microbes Infect 6:1191–1198

Lin JC, Siu LK, Fung CP, Tsou HH, Wang JJ, Chen CT, Wang SC, Chang FY (2006) Impaired phagocytosis of capsular serotypes K1 or K2 *Klebsiella pneumoniae* in type 2 diabetes mellitus patients with poor glycemic control. J Clin Endocrinol Metab 91:3084–3087

Lin JC, Chang FY, Fung CP, Yeh KM, Chen CT, Tsai YK, Siu LK (2010) Do neutrophils play a role in establishing liver abscesses and distant metastases caused by *Klebsiella pneumoniae*? PLoS One 5:e15005

Lin YT, Liu CJ, Chen TJ, Chen TL, Yeh YC, Wu HS, Tseng CP, Wang FD, Tzeng CH et al (2011a) Pyogenic liver abscess as the initial manifestation of underlying hepatocellular carcinoma. Am J Med 124:1158–1164

Lin CT, Wu CC, Chen YS, Lai YC, Chi C, Lin JC, Chen Y, Peng HL (2011b) Fur regulation of the capsular polysaccharide synthesis and iron-acquisition systems of *Klebsiella pneumoniae* CG43. Microbiology 157:419–429

Loetscher Y, Wieser A, Lengefeld J, Kaiser P, Schubert S, Heikenwalder M, Hardt WD et al (2012) *Salmonella* transiently reside in luminal neutrophils in the inflamed gut. PLoS One 7:e34812

Lonardo A, Grisendi A, Pulvirenti M, Della Casa G, Melini L, Di Gregorio C, Nasi G, Sarti M et al (1992) Right colon adenocarcinoma presenting as *Bacteroides fragilis* liver abscesses. J Clin Gastroenterol 14:335–338

Lu R, Wu S, Liu X, Xia Y, Zhang YG, Sun J (2010) Chronic effects of a *Salmonella* type III secretion effector protein AvrA in vivo. PLoS One 5:e10505

Luong NH, Fournier J (1960) Abscess of the liver and septicemia due to Salmonella cholerae suis in a mountain-dweller of Lang-Bian. The question of bacterial abscesses of the liver in Vietnam (in French). Bull Soc Pathol Exot Filiales 53:256–264

Maclennan JD (1962) The histotoxic clostridial infections of man. Bacteriol Rev 26:177–276

Macpherson DS, Scott DJA (1985) Liver abscess and Crohn's disease. Am J Gastroenterol 80:399
Mallory FB (1898) A histological study of typhoid fever. J Exp Med 3:611–638
Mansharamani GG, Madhavan HN, Madhavan M, Krishnamurthy K (1971) Isolation of *Salmonella typhi* from an amebic liver abscess. Report of a case. Indian J Med Sci 25:98–99
Marr JJ, Haff RC (1971) Superinfection of an amoebic abscess by *Salmonella enteritidis*. Arch Intern Med 128:291–294
Matar IM, Rashed AH, Nyman UR (1990) Salmonella liver abscess. Trans R Soc Trop Med Hyg 84:431–432
Matsuyama S, Satoh H, Yunotani S, Mashima H, Haraoka S, Harada S, Hisatsugu T (1994) An unusual presentation of spontaneous pneumoperitoneum secondary of the rupture of a gas-containing pyogenic liver abscess: report of a case. Surg Today 24:63–66
McClane BA (2001) The complex interactions between *Clostridium perfringens* enterotoxin and epithelial tight junctions. Toxicon 39:1781–1791
McClane BA, Chakrabarti G (2004) New insights into the cytotoxic mechanisms of *Clostridium perfringens* enterotoxin. Anaerobe 10:107–114
McCrae J, Klotz O (1908) Necroses of the liver. J Pathol Bacteriol 12:279–286
McDonald MI, Corey GR, Gallis HA, Durack DT (1984) Single and multiple pyogenic liver abscesses. Natural history, diagnosis and treatment, with emphasis on percutaneous drainage. Medicine (Baltimore) 63:291–302
McGreal S, Sayers R, Wurm P, West K (2012) Crohn's disease presenting with pyogenic liver abscess: a case report. Case Rep Gastrointest Med 2012:762480
Mir-Madjlessi SH, McHenry MC, Farmer RG (1986) Liver abscess in Crohn's disease. Report of four cases and review of the literature. Gastroenterology 91:987–993
Modol JM, Santaeugenia S, Tudela P, Barlueng E (2006) Liver abscess by *Salmonella* within a metastases of Müllerian uterine cancer (in Spanish). Med Clin (Barcelona) 127:518–519
Mohan S, Talwar N, Chaudhary A, Andley M, Ravi B, Kumar A (2006) Liver abscess: a clinicopathological analysis of 82 cases. Int Surg 91:228–233
Monack DM, Navarre WW, Falkow S (2001) Salmonella-induced macrophage death: the role of caspase-1 in death and inflammation. Microbes Infect 3:1201–1212
Moore R, O'Shea D, Geoghegan T, Mallon PW, Sheehan G (2013) Community-acquired *Klebsiella pneumoniae* liver abscess: an emerging infection in Ireland and Europe. Infection 41:681–686
Myers GSA, Rasko DA, Cheung JK, Ravel J, Seshadri R, DeBoy RT, Ren Q, Varga J et al (2006) Skewed genomic variability in strains of the toxigenic bacterial pathogen, *Clostridium perfringens*. Genome Res 16:1031–1040
Nelson LD, Chiantia S, London E (2010) Perfringolysin O association with ordered lipid domains: implications for transmembrane protein raft affinity. Biophys J 99:3255–3263
Ng H, Lam SM, Shum HP, Yan WW (2010) *Clostridium perfringens* liver abscess with massive haemolysis. Hong Kong Med J 16:310–312
Oda M, Shiihara R, Ohmae Y, Kabura M, Takagishi T, Kobayashi K, Nagahama M et al (2012) *Clostridium perfringens* alpha-toxin induces the release of IL-8 through a dual pathway via TrkA in A549 cells. Biochim Biophys Acta 1822:1581–1589
Ogah K, Sethi K, Karthik V (2012) *Clostridium clostridioforme* liver abscess complicated by portal vein thrombosis in childhood. J Med Microbiol 16:297–299
Oh JH, Jung SH, Jeon EJ (2011) Gas-forming pyogenic liver abscess suspected on a plain chest X-ray. Korean J Intern Med 26:364
Ohyama H, Nakasho K, Yamanegi K, Noiri Y, Kuhara A, Kato-Kogoe N, Yamada N et al (2009) An unusual autopsy case of pyogenic liver abscess caused by periodontal bacteria. Jpn J Infect Dis 62:381–383
Pais P (1984) A hepatitis-like picture in typhoid fever. Br Med J 289:225–226
Pan YJ, Fang HC, Yang HC, Lin TL, Hsieh PF, Tsai FC, Keynan Y, Wang JT (2008) Capsular polysaccharide synthesis regions in *Klebsiella pneumoniae* serotype K57 and a new capsular serotype. J Clin Microbiol 46:2231–2240
Penaloza JL, llausas A, Kumate J (1974) Pyogenic liver abscess caused by *Salmonella typhi* (in Spanish). Bol Med Hosp Infant Mex 31:917–924
Perera MR, Kirk A, Noone P (1980) Presentation, diagnosis and management of liver abscess. Lancet 1:134–136
Petersen JM (1984) Salmonella liver abscess: report of a case with successful computerized tomography guided percutaneous drainage and treatment. J Am Osteopath Assoc 83:496–501
Pisano M, Cogoni GF, Meloni A, Gromo C, Piga S, Saliu A, Ottonello R (2007) Pyogenic abscess in hepatic metastasis: unusual first manifestation of colorectal cancer. A case report (in Italian). Chir Ital 59:423–427
Pope JV, Teich DL, Clardy P, McGillicuddy DC (2011) *Klebsiella pneumoniae* liver abscess: an emerging problem in North America. J Emerg Med 41:e103–e105
Pulvirenti D, Aikaterini T, Neri S (2007) Septicemia, hepatic abscess, and encephalitis due to Yersinia enterocolitica. J Clin Gastroenterol 41:333–334
Qu K, Liu C, Wang ZX, Tian F, Wie JC, Tai MH, Zhou L, Meng FD, Wang RT et al (2012) Pyogenic liver abscesses associated with nonmetastatic colorectal cancers: an increasing problem in Eastern Asia. World J Gastroenterol 18:2948–2955
Rahimian J, Wilson T, Oram V, Holzman RS (2004) Pyogenic liver abscess: recent trends in etiology and mortality. Clin Infect Dis 39:1654–1659

Rajagopal A, Ramasamy R, Mahendran G, Thomas M (2002) Hepatic abscess complicating paratyphoid infection. Trop Gastroenterol 23:181–182

Rajendran G, Bothma P, Brodbeck A (2010) Intravascular haemolysis and septicaemia due to *Clostridium perfringens* liver abscess. Anaesth Intensive Care 38:942–945

Ramachandran S, Godfrey JJ, Perera MVF (1974) Typhoid hepatitis. JAMA 230:236–240

Ramanathan M (1991) Unusual hepatic manifestations in typhoid fever. Singapore Med J 32:335–337

Ratnayake EC, Shivanthan C, Wijesiriwardena BC (2011) Cholestatic hepatitis in a patient with typhoid fever – a case report. Ann Clin Microbiol Antimicrob 10:35–37

Reed W (1895) An investigation into the so-called lymphoid nodules of the liver in abdominal typhus. Am J Med Sci 110:543–559

Rindfleisch GE (1867) Lehrbuch der pathologischen Gewebelehre (Textbook of pathologic histology). Engelmann, Leipzig

Rockey DC (2001) Hepatobiliary infections. Curr Opin Gastroenterol 17:257–261

Rodriguez M, Undurraga O (1955) Multiple hepatic abscesses caused by *Salmonella typhosa* (in Spanish). Rev Chil Pediatr 26:63–64

Rogers T, Wadula J (2001) *Salmonella typhi* liver abscess. S Afr J Surg 39:137–138

Rood J (1998) Virulence genes of *Clostridium perfringens*. Annu Rev Microbiol 52:333–360

Rood JI, Cole ST (1991) Molecular genetics and pathogenesis of *Clostridium perfringens*. Microbiol Rev 55:621–648

Rovito V, Bonanno CA (1982) Salmonella hepatic abscess: an unusual complication of the *Salmonella* carrier state? Am J Gastroenterol 77:338–339

Rubin RH, Swartz MN, Malt R (1981) Hepatic abscess: changes in clinical, bacteriologic and therapeutic aspects. Am J Med 57:601–610

Ruiz-Rebollo ML, Sanchez-Antolin G, Garcia-Pajares F, Vallecillo-Sande MA, Fernandez-Orcajo P et al (2008) Acalculous cholecystitis due to *Salmonella enteritidis*. World J Gastroenterol 14:6408–6409

Russo TA, Shon AS, Beanan JM, Olson R, MacDonald U, Pomakov AO, Visitacion MP (2011) Hypervirulent *K. pneumoniae* secretes more and more active iron-acquisition molecules than "classical" *K. pneumoniae* thereby enhancing its virulence. PLoS One 6:e26734

Rustagi T, Uy EM, Rai M (2012) Pyogenic liver abscesses secondary to pylephlebitis complicating acute or chronic pancreatitis. J Dig Dis 13:439–443

Sabbai J, Sutter VL, Finegold SM (1972) Anaerobic pyogenic liver abscess. Ann Intern Med 77:627–638

Saccente M (1999) *Klebsiella pneumoniae* liver abscess, endophthalmitis, and meningitis in a man with newly recognized Diabetes mellitus. Clin Infect Dis 29:1570–1571

Safe IP, Couceiro KN, Martins AG (2013) Gas-forming pyogenic liver abscess. Rev Soc Bras Med Trop 46:528

Saleh N, Sohail MR, Hashmey RH, Al Kaabi M (2009) *Clostridium septicum* infection of hepatic metastases following alcohol injection: a case report. Cases J 2:9408

Sangwaiya A, Patel A, Chan J, Arnold J (2009) Simple liver cyst as a focus of Salmonella paratyphi abscess: a case report. J Trop Med 2009:456810

Sarmiento JM, Sarr MG (2002) Necrotic infected liver metastasis from colon cancer. Surgery 132:110–111

Sarthe J, DiBardino D (2013) Pyogenic liver abscess caused by *Streptococcus mitis*. Lancet Infect Dis 13:822

Seeto RK, Rockey DC (1996) Pyogenic liver abscess. Changes in etiology, management, and outcome. Medicine (Baltimore) 75:99–113

Sheikh I, Sievers C, Mullen K (2011) Salmonella enteritidis liver abscess. Ann Hepatol 10:370–371

Simmers TA, Mijnhout GS, Van Meyel JJ (1997) Salmonellosis: an unusual complication of hepatocellular carcinoma. Scand J Gastroenterol 32:1180–1182

Smith LD (1979) Virulence factors of *Clostridium perfringens*. Rev Infect Dis 1:254–262

Smith BM, Zyromski NJ, Allison DC (2007) Community-acquired methicillin-resistant *Staphylococcus aureus* liver abscess requiring resection. Surgery 141:110–111

Soni PN, Hoosen AA, Pillay DG (1994) Hepatic abscess caused by *Salmonella typhi*. A case report and review of the literature. Dig Dis Sci 39:1694–1696

Stahlhut SG, Chattopadhyay S, Struye C, Weissman SJ, Aprikian P, Libby SJ, Fang FC et al (2009) Population variability of the FimHtype 1 fimbrial adhesin in *Klebsiella pneumoniae*. J Bacteriol 191:1941–1950

Stokes JF (1960) Cryptogenic liver abscess. Lancet 1:355–358

Strong R, Fawcett J, Lynch S, Wall D (2003) Hepatectomy for pyogenic liver abscess. HPB (Oxford) 5:86–90

Sucandy I, Gallagher S, Josloff RK, Nussbaum ML (2012) Severe clostridium infection of liver metastases presenting as pneumoperitoneum. Am Surg 78:E338–E339

Syed MA, Kim TK, Jang HJ (2007) Portal and hepatic vein thrombosis in liver abscess: CT findings. Eur J Radiol 61:513–519

Tabarelli W, Bonatti H, Cejna M, Hartmann G, Stelzmüller I, Wenzl E (2009) *Clostridium perfringens* liver abscess after pancreatic resection. Surg Infect (Larchmt) 10:159–162

Taylor FW (1949) Regional enteritis complicated by pylephlebitis and multiple liver abscesses. Am J Med 7:838–840

Tee Yu HH, Tsang S, Cheung TT (2013) An unusual cause of acute abdomen – gas-forming liver abscess due to *Salmonella enteritidis*. Asian J Surg Aug 23 Pii: S1015 (13)00071-7

Teitz S, Guidetti-Sharon A, Manor H, Halevy A (1995) Pyogenic liver abscess: warning indicator of silent colonic cancer. Report of a case and review of the literature. Dis Colon Rectum 38:1220–1223

Teixeira R, Pfeilsticker FJ, Santa Cecilia GD, Nobre V, Fonseca LP, Serufo JC, Coelho PM, Lambertucci JR (2001) *Schistosomiasis mansoni* is associated with pyogenic liver abscesses in the state of Minas Gerais, Brazil. Mem Inst Oswaldo Cruz 96(suppl):143–146

Thatcher P (2003) Hepatic abscesses caused by *Fusobacterium necrophorum* as part of the Lemierre syndrome. J Clin Gastroenterol 37:196–197

Thel MC, Ciaccia D, Vredenburgh JJ, Peters W, Corey GR (1994) *Clostridium septicum* abscess in hepatic metastases: successful medical management. Bone Marrow Transplant 13:495–496

Thomas CT, Berk SL, Thomas E (1983) Enterococcal liver abscess associated with moxalactam therapy. Review of literature on enterococcal superinfections in association with moxalactam therapy. Arch Intern Med 143:1780–1781

Thomas M, Mesquita FS, Holden DW (2012) The DUB-ious lack of ALIS in Salmonella infection: a *Salmonella* deubiquitinase regulates the autophagy of protein aggregates. Autophagy 8:1824–1826

Thomsen RW, Jepsen P, Sorensen HT (2007) Diabetes mellitus and pyogenic liver abscess: risk and prognosis. Clin Infect Dis 44:1194–1201

Tian LT, Yao K, Zhang XY, Zhang ZD, Liang YJ, Yin DL, Lee L, Jiang HC, Liu LX (2012) Liver abscesses in adult patients with and without diabetes mellitus: an analysis of the clinical characteristics, features of the causative pathogens, outcomes and predictors of fatality: a report based on a large population, retrospective study in China. Clin Microbiol Infect 18:E314–E330

Tsai FC, Huang YT, Chang LY, Wang JT (2008) Pyogenic liver abscess as endemic disease, Taiwan. Emerg Infect Dis 14:1592–1600

Tsui K, Tsai CR, Lin LC, Yang CC, Huang CH (2012) Aggregatibacter aphrophilus pyogenic liver abscess in an immunocompetent young woman. J Microbiol Immunol Infect 45:385–389

Ukikusa M, Inomoto T, Kitai T, Ino K, Hgashiyama H, Arimoto A, Nakajima Y, Hanafusa T, Awane H (2001) Pneumoperitoneum following the spontaneous rupture of a gas-containing pyogenic liver abscess: report of a case. Surg Today 31:76–79

Urban BA, McCormick R, Fishman EK, Lillemoe KD, Petty BG (2000) Fulminant *Clostridium septicum* infection of hepatic metastases presenting as pneumoperitoneum. AJR Am J Roentgenol 174:962–964

Vakil N, Hayne G, Sharma A, Hardy DJ, Slutsky A (1994) Liver abscess in Crohn's disease. Am J Gastroenterol 89:1090–1095

Van Schil P, Mortelmans L, Schoofs E, Bourgeois N, Van Hee R, Vaneerdeweg W, Vereycken H, Heytens L (1988) Peliosis hepatis associated with liver and retroperitoneal abscesses. Digestion 41:55–60

Vidal JE, da Silva PR, Schiavon Nugueria R, Bonasser Filho F, Hernandez AV (2003) Liver abscess due to *Salmonella enteritidis* in a returned traveler with HIV infection: case report and review of the literature. Rev Inst Med Trop Sao Paulo 45:115–117

Vogel Y, Tannapfel A, Rabsch W, Henning B (2007) Cholangitis with hepatic microabscesses caused by *Salmonella enterica* serovar choleraesuis (in German). Dtsch Med Wochenschr 132:1214–1218

Wang JH, Liu YC, Lee SS, Yen MY, Chen YS, Wang JH, Wann SR, Lin HH (1998) Primary liver abscess due to *Klebsiella pneumoniae* in Taiwan. Clin Infect Dis 26:1434–1438

Warren KW, Hardy KJ (1968) Pyogenic hepatic abscess. Arch Surg 97:40–45

Watts HD (1978) Multiple hepatic abscesses complicating regional enteritis. The importance of prior surgery or corticosteroid therapy. Dig Dis 23:41S–47S

Wu KM, Li LH, Yan JJ, Tsao N, Liao TL, Tsai HC, Fung CP, Chen HJ, Liu YM et al (2009a) Genome sequencing and comparative analysis of *Klebsiella pneumoniae* NTUH-K2044, a strain causing liver abscess and meningitis. J Bacteriol 191:4492–4501

Wu MF, Yang CY, Lin TL, Wang JT, Yang FL, Wu SH, Hu BS, Chou TY, Tsai MD et al (2009b) Humoral immunity against capsule polysaccharide protects the host from magA+ *Klebsiella pneumoniae*-induced lethal disease by evading Toll-like receptor 4 signaling. Infect Immun 77:615–621

Wu CC, Huang YJ, Fung CP, Peng HL (2010) Regulation of *Klebsiella pneumoniae* Kpc fimbriae by the site-specific recombinase Kpcl. Microbiology 156:1983–1992

Wu MC, Lin TL, Hsieh PF, Yang HC, Wang JT (2011) Isolation of genes involved in biofilm formation of a *Klebsiella pneumoniae* strain causing pyogenic liver abscess. PLoS One 6:e23500

Yang CC, Chen CY, Lin XZ, Chang TT, Shin JS, Lin CY (1993) Pyogenic liver abscess in Taiwan: emphasis on gas-forming liver abscess in diabetics. Am J Gastroenterol 88:1911–1915

Yang PW, Lin HD, Wang LM (2008) Pyogenic liver abscess associated with septic pulmonary embolism. J Chin Med Assoc 71:442–447

Yeh TS, Jan YY, Jeng LB, Chen TC, Hwang TL, Chen MF (1998) Hepatocellular carcinoma presenting as pyogenic liver abscess: characteristics, diagnosis, and management. Clin Infect Dis 26:1224–1226

Yeh KM, Lin JC, Yin FY, Fung CP, Hung HC, Siu LK, Chang FY (2010) Revisiting the importance of virulence determinant magA and its surrounding genes in *Klebsiella pneumoniae* causing pyogenic liver abscesses: exact role in serotype K1 capsule formation. J Infect Dis 201:1259–1267

Yokota T, Iwamoto K, Watanabe Y, Yamauchi H, Kikuchi S, Hatori M (2005) Pyogenic liver abscesses secondary to carcinoma of the sigmoid colon: a case report and clinical features of 20 cases in japan. Ups J Med Sci 110:241–244

Young A (1976) The clinical presentation of pyogenic liver abscess. Br J Surg 63:216–219

Yu WL, Ko WC, Cheng KC, Lee HC, Ke DS, Lee CC, Fung CP, Chuang YC (2006) Association between rmpA and magA genes and clinical syndromes caused by *Klebsiella pneumoniae* in Taiwan. Clin Infect Dis 42:1351–1358

Zhang Y, Zang GQ, Tang ZH, Yu YS (2013) Fatal gas-forming pyogenic liver abscess due to *Klebsiella pneumoniae*. Rev Inst Med Trop Sao Paulo 55:144

Tumor-Like Lesions of the Hepatobiliary Tract Caused by Mycobacterial Infections: Tuberculosis and Lepra

127

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_127

Abstract

Primary and secondary tuberculosis of the liver can result in several types of tumor-like lesions. A common manifestation of hepatic tuberculosis is miliary hepatic tuberculosis and granulomatous hepatitis. Tumor-like lesions mainly include local forms of hepatic tuberculosis, with conglomerate tubercles, tuberculomas (macronodular tuberculosis), and nodular tuberculous pseudotumors. Hepatobiliary tuberculosis can also involve the biliary tract proper, with ulcerating and granulomatous cholangitis resulting in significant strictures. The infection also causes distinct vascular changes, such as granulomatous vasculitis and tuberculous pylephlebitis. A second mycobacterial infection that may involve the liver is leprosy, causing granulomatous hepatitis and the formation of so-called lepromas.

Tuberculosis and Tuberculomas

Introduction

Tuberculosis is a still widespread mycobacterial infectious disease that belongs to the most intensively studied pathologies, numerous detailed studies already being available from the nineteenth to early twentieth centuries (Louis 1825; Lorentz 1913; Liebermeister 1921; Saphir 1929; Morris 1930; reviews: Yew and Leung 2008). Abdominal forms of tuberculosis can cause impressive tumor-like lesions in the liver that may closely mimic hepatic primary malignancy or metastatic disease of the liver. The basics of microbiology are briefly summarized at the end of the chapter.

Epidemiology

About one-third of the world's population is infected with *M. tuberculosis*, and the WHO estimates of 1.6 million deaths were caused in 2005 by *M. tuberculosis*. Hepatic tuberculosis is also known in the pediatric age group (Praharaj et al. 1979; Moskovic 1990). A very large number of individuals in the world have latent tuberculosis, caused by a complex interaction between viable bacteria and a host with a potent immune system. These numerous persons with latent tuberculosis represent an enormous reservoir of potential tuberculosis cases, because any transient or persisting failure of controlling immune reactions can lead to outbreak of clinically manifest disease (reviews: Tufariello et al. 2003; Cardona 2007). On the other hand, *M. tuberculosis* itself can become a latent *bacillus*, meaning that it can adapt to the stressful conditions generated by the immunocompetent host.

Latent mycobacteria can downregulate their metabolism, alter their antigenic profile, transiently lose their invasive features, and hence appear "silent" to the immune system. This dormant state can persist for many years, but may not be longer than 10 years. When the properties of the niche harboring silent or dormant mycobacteria alter in favor of a "resuscitation" of the bacteria (e.g., in case of poor immune response), silent bacteria can resume their fully virulent state, but this readaptation requires longer time periods (Cardona and Ruiz-Manzano 2004; Zhang 2004; Sridhar et al. 2011).

Classifications of Hepatic Tuberculosis

During the long period of investigations on tuberculosis of the liver, both primary and secondary resulted in several variants of classification. These classifications are in part a mixture between clinical and radiological findings, and of pathologic-anatomic changes observed at surgery or autopsy, rendering some of the classifications complicated and difficult to reproduce. The diagnostic elements that enter a given classification have been worked out in detail, but as such cannot deliver the skeleton usable for classification. An often-used system of criteria is that of Maharaj et al. (1987), which consists of detection of acid-fast bacilli in liver tissue; tubercle bacilli elsewhere, plus hepatic granulomas with or without Langhans-type giant cells, and/or caseation; typical

Table 1 Forms of hepatic tuberculosis

Miliary hepatic tuberculosis and granulomatous hepatitis (lesions/tubercles 0.6–2 mm in diameter)
Liver involvement in Landouzy's sepsis (sepsis tuberculosa acutissima)
Local hepatic tuberculosis (lesions larger than 2 mm in diameter)
Conglomerate tubercles
Tuberculomas (macronodular hepatic tuberculosis)
So-called tuberculous abscesses
Nodular tuberculosis pseudotumors
Tuberculous caverns of the liver (cavernous hepatic tuberculosis)
Bile duct tuberculosis
Tuberculous vascular lesions of the liver
Granulomatous vasculitis
Tuberculous pylephlebitis
Portal vein thrombosis
So-called tuberculous cirrhosis

macroscopic appearance on laparotomy or peritoneoscopy; and response to antituberculous therapy. A novel classification of secondary hepatic tuberculosis is proposed in Table 1.

An old classification as of 1929 divided hepatic tuberculosis into miliary and local forms (Rolleston and McNee 1929). A later approach as of 1984 separated miliary hepatic tuberculosis associated with generalized miliary tuberculosis, primary miliary tuberculosis of the liver without involvement of other organs, and a primary nodular hepatic lesion termed tuberculoma or frank tuberculous abscess (Spiegel and Tuazon 1984). The nomenclature of these lesions has not been employed in a consistent way, some definitions lacking for a long time period. For example, the so-called tuberculous abscess has been used to denote tuberculoma, but these lesions are clearly different. What has probably been meant with "abscess" are large nodular tuberculous lesions with partial colliquation of the necrosis, rendering the lesion similar to pyogenic abscess at imaging. However, and in contrast to other bacterial infections, tuberculosis does not induce suppuration which characterized abscess, but a distinct type of coagulation necrosis (caseiform necrosis). In rare instances, superinfection of a tuberculous necrosis with pyogenic bacteria may add a suppurative component, but this is always a secondary phenomenon.

Clinical Presentation of Hepatic Tuberculosis

Apart from hepatomegaly, many patients usually do not show symptoms or signs of their liver disease (Gold et al. 1957). Common symptoms and signs are weight loss, loss of appetite, abdominal pain, fever, abdominal distension, and jaundice (Cruice 1914; Pariente et al. 1963; Saluja et al. 2007; Chong 2008; Hwang et al. 2009). In a study of 200 patients with hepatic tuberculosis, hepatomegaly was the most striking and constant physical sign and was present in 71 % of patients with miliary tuberculosis and 95 % of those with focal tuberculosis (Hersch 1964). On the other hand, some authors found that patients complain of upper abdominal tenderness in addition to liver enlargement (Lichtman 1949; Maharaj et al. 1987). In the study of Hersch (1964), clinical jaundice was noted in 15.4 % of patients.

Patients with hepatic tuberculosis often show elevated serum alkaline phosphatase (Klatskin and Yesner 1950; Korn et al. 1959). Among 96 patients with tuberculous hepatitis, the characteristic serum profile included hyponatremia (64 %), raised alkaline phosphatase (83 %) and gamma-glutamyl transferase (77 %), hypoalbuminemia (63 %), and hypergammaglobulinemia (83 %). In 78 %, serum aminotransferases were moderately elevated (Essop et al. 1984). In few cases, hepatic tuberculosis was associated with marked hyperferritinemia masquerading adult-onset Still's disease (Manoj et al. 2012). In generalized miliary tuberculosis with bone marrow involvement, miliary liver tuberculosis with jaundice can be accompanied by pancytopenia (Evans et al. 1998). There are several causes of obstructive jaundice in hepatobiliary tuberculosis, discussed in more detail in later paragraphs. In case of extensive liver involvement, tuberculosis can cause portal hypertension (Bruguera et al. 1968; Mojtahedzadeh et al. 2012). Rare manifestations of tuberculosis involving the liver include hepatic failure in extensive miliary liver

tuberculosis (Asada et al. 1991; Godwin et al. 1991) and hemophagocytic syndrome (Balasubramanian et al. 2008; Lee et al. 2008).

Primary (Isolated) Hepatic Tuberculosis

In comparison with secondary hepatic tuberculosis, primary tuberculosis of the liver is nowadays less common, but has been reported many times in the preantibiotic era. More recent reports described the principal morphology of primary hepatic lesions and in part emphasize the tumor-like presentation of primary hepatic tuberculosis (Fig. 1; Essop et al. 1983a,b; Nagai et al. 1989; Oliva et al. 1990; Errougani et al. 1991; Emre et al. 1992; Kok and Yapp 1999b; Sheen-Chen et al. 2001; Chen et al. 2003; Varela et al. 2003). Primary hepatic tuberculosis radiologically manifests as echogenic masses in ultrasonography and hypodense, tumor-like masses on CT images (Kok and Yapp 1999b; Chen et al. 2003). Focal hepatic tuberculosis forming a mass or tuberculoma (pseudotumor) can closely mimic primary hepatic malignancy at imaging (Sheen-Chen et al. 2001; Varela et al. 2003) or may resemble hepatic metastatic disease (Zipser et al. 1976; Achem et al. 1992). Mixed attenuation lesions in primary hepatic tuberculosis can grow to impressive size, e.g., occupying a good part of a liver lobe and sometimes confounded with hepatocellular carcinoma (Brookes et al. 2006). Primary hepatic tuberculosis can also present as miliary tuberculosis, i.e., in the form of a specific granulomatous hepatitis (Cinque et al. 1964; Terry and Gunnar 1957). In case of bona fide primary hepatic tuberculosis, the spread of disease to locoregional lymph nodes situated in the perihilar area and the hepatoduodenal ligament has been observed (the "tuberculous primary complex" of the liver; Nordmann 1927).

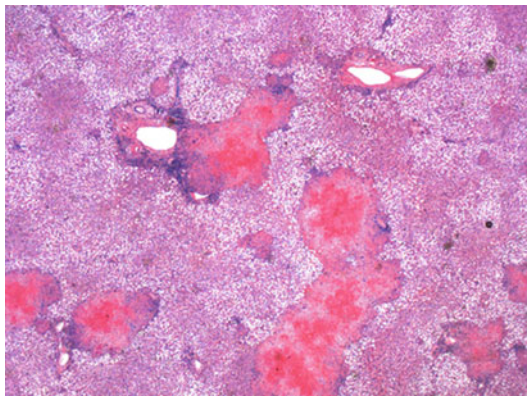

Fig. 1 Hepatic tuberculosis. Several and in part confluent caseous necroses (strongly eosinophilic areas) with a peripheral granulomatous reaction are present. The lesions are in contact with portal tracts. Hepatocyte steatosis surrounds the lesions (hematoxylins and eosin stain)

Secondary Hepatic Tuberculosis

Most cases of hepatic tuberculosis are secondary forms (Amarapurkar and Agrawal 2006). Formerly, this was a rather common complication of tuberculosis. In the time period before efficient antituberculosis treatment, hepatic involvement was found clinically in 50–80 % of all patients dying of pulmonary tuberculosis and in up to 91 % at autopsy (Gelb et al. 1973; Leder and Low 1995). It has been proposed to differentiated secondary hepatic tuberculosis into several forms (Hersch 1964).

Granulomatous Hepatitis

Miliary tuberculosis is a severe and often generalized manifestation of tuberculosis, characterized by the development of multiple necrotizing granulomas in diverse organs and tissue, the lesions usually containing visible mycobacteria (Auerbach 1944; Proudfoot et al. 1969; Kim et al. 1990; Siemann et al. 1999; Mert and Ozaras 2005; Tajiri et al. 2011). In generalized tuberculosis, tuberculous granulomatous hepatitis was one of the most common manifestations of the infection in the preantibiotic era (Arnold 1880). The liver substance is either reached by bacteria circulating in the blood or by the hepatic homing of infected monocytes to become macrophages. In many instances, pulmonary tuberculosis with tuberculous phlebitis of pulmonary veins with subsequent invasion of the bloodstream was a significant pathogenic mechanism (Silbergleit 1905).

Based on detailed autopsy studies, Silbergleit (1905) could detect yellowish, elongated, and prominent lesion on the intima of pulmonary veins, sometimes associated with smaller and gray, milium-sized nodules in the venous intima. These lesions are regarded as the source of mycobacterial spread through the bloodstream in miliary tuberculosis. Miliary hepatic tubercles have been observed in various forms of tuberculosis, including acute disseminated miliary tuberculosis and extrapulmonary tuberculosis, and in fatal cases of pulmonary tuberculosis. It is estimated that the liver as part of generalized miliary tuberculosis is involved in 50–80 % of all patients dying from pulmonary tuberculosis (Morris 1930). Similar figures have later been found (Glaus 1919; Terry and Gunnar 1957; Korn et al. 1959; Bottiger et al. 1962; Cinque et al. 1964; Steniu-Aarniala and Tukiainen 1979; Sharma et al. 2005; Amarapurkar et al. 2008; Kumar and Pandey 2008; review: Alvarez and Carpio 1983). Among 200 cases of hepatic tuberculosis studied in the time period 1955–1961, only miliary tuberculosis of the liver was found in the pediatric cases, whereas in adults miliary hepatic tuberculosis was present in 86 % and focal hepatic tuberculosis in 14 % of the cases (Hersch 1964). In a series of 38 patients with generalized miliary tuberculosis, hepatomegaly was found in 37 % (Mert et al. 2001). Severe forms of hepatic miliary tuberculosis can cause jaundice (Curry and Alcott 1955) or hepatic failure (Sharma et al. 1981; Hussain et al. 1995). Miliary liver tuberculosis is rarely a primary form of tuberculosis, in the absence of active pulmonary disease (Terry and Gunnar 1957; Pitzus and Verme 1960; Traissac et al. 1961; Cinque et al. 1964; Tritou et al. 2000). Hepatic miliary tuberculosis has also been described in congenital tuberculosis with multiorgan involvement (Chou 2002). Apart from *M. tuberculosis*, hepatic granulomas can also be induced by *M. scrofulaceum* (Patel 1981).

Ultrasonographically, multiple granulomas result in a "bright liver," although one may note hypoechoic or hyperechoic lesions. In CT images, miliary granulomas are visualized as multiple low-density lesions with small calcifications, usually with attenuation values in the range of +35 to +45 Holmstrom units with peripheral contrast uptake (Kohli et al. 1996; Yu et al. 2004). Angiographically, miliary liver tuberculosis displayed abnormalities of the distal arterioles, with small, nodular, and irregular formations, while the portal and hepatic veins were normal (Rémond et al. 1976; Dwek et al. 1981). Most cases of tuberculous granulomatous hepatitis are caused by *M. tuberculosis*, but other species have also caused a granulomatous reaction in livers, mostly in immunosuppressed hosts, including *M. avium* complex (MAC) bacteria (Farhi et al. 1986; Ruiz et al. 2002; Akhtar and Shaheen 2007; Todd et al. 2007; Laramore et al. 2009), *M. gordonae* (Kurnik et al. 1983; den Broeder et al. 2003), *M. mucogenicum* (Goldblatt and Ribes 2002), and *M. chelonae* (Fernandez-Rodriguez et al. 2004). Hepatomegaly associated with deranged liver function tests suggesting hepatitis was observed in *M. fortuitum* infection (Zainal Muttakin and Tan 2006).

The gross visualization of miliary liver tuberculosis depends on the number of granulomas and their size. It is generally agreed that submiliary, i.e., also very early, lesions may not be visible with the naked eye. Miliary lesions are best recognized when, in the setting of generalized miliary tuberculosis, they are situated as numerous lesions just beneath the liver capsule, where they are seen in the form as whitish or opaque nodules of 1–2 mm diameter. The granulomas are less easily recognized on cut surfaces, particularly in case of liver steatosis. By use of a magnifying glass, granulomas are often seen to be situated close to blood vessels in Glisson's sheaths. Extensive miliary liver tuberculosis can be associated with enlarged, caseous lymph nodes at the porta hepatis (Arends 1950; Leggat et al. 1953).

Histopathologically, tuberculoid granulomas have been recognized as a key element in miliary tuberculosis. Early lesions are characterized by small accumulations of macrophages/Kupffer cells (the "Retothelknötchen/retothel nodules" of older nomenclature; Hamperl 1953; Ringleb 1953). The lesions consist of nodular accumulations of epithelioid macrophages with a central caseiform coagulation necrosis. The earliest

lesions are characterized by tiny accumulations of lymphocytes and a central group of three to five larger and pale cells representing macrophages. In fully developed granulomas, lymphocytes form a layer of variable width surrounding the macrophage nodule. The granulomas are situated within the hepatocyte parenchyma, portal tract spaces, or in the adventitia of blood vessels. In some cases, granulomas are present in the intima of hepatic veins (endophlebitis granulomatosa tuberculosa). Many tuberculoid granulomas contain Langhans-type giant cells which develop via macrophage fusion. The morphology of the Langhans giant cell has been studied in detail (Herxheimer 1914; Haythorn 1929). Typically, the nuclei which have more or less the same structure as those found in epithelioid macrophages are arranged at the cell body periphery, often with an anuclear gap which shows up as a "horseshoe-like" arrangement in tissue sections. The central part of the cytoplasm may contain a foamy structure with tiny dots representing the numerous centrosome/centriole stacks ("centrosome swarm"; sometimes with a central astrosphere) arranged in the center of the cell body. The tissue occupied by granulomas is usually necrotic or shows signs of hepatocyte atrophy and disintegration of hepatocyte plates. By use of special stains, acid-fast bacilli are present in the granulomas, often in the border zone between necrosis and preserved macrophages. Tuberculoid granulomas in tuberculosis are readily diagnosed in liver biopsies (Schinnerling 1966), but in order to obtain a reasonable chance to find the lesion, a large amount of granulomas must be present in the liver. It is estimated that, for having around three granulomas in the section of biopsy cylinder of 2.5 cm length, approximately 100,000 randomly distributed granulomas must have developed in the entire liver.

Liver Involvement in Landouzy's Sepsis (Sepsis Tuberculosa Acutissima)

Landouzy's sepsis (LS; generalized nonreactive tuberculosis, sepsis tuberculosa acutissima, Landouzy's typhobacillosis) is severe, acute, or peracute (fulminant) systemic disease caused by widespread infection with *M. tuberculosis* in the absence of an adequate macrophage-mediated defense reaction of the host (Landouzy 1891; Eckel 1929; Arends 1950; Von Knorre 1950; Jenss et al. 1981). LS as the most devastating form of areactive tuberculosis has also been called acute caseating tuberculosis by Rich (1944), the Yersin type of tuberculosis, and generalized nonreactive tuberculosis, a term coined by Siegmund (1939). Rennen called the disorder sepsis tuberculosa gravissima (Rennen 1922).

LS is named after Louis Théophile Joseph Landouzy (1845–1917), a French physician who was influenced by Jean-Martin Charcot and was a coworker of Déjérine's studies on the muscular disorder having the latter's eponym. Landouzy was the first to suggest the infectious nature of herpes. Landouzy published his work on LS 1891, under the title "Bacterial pretuberculous fevers with a typhoid presentation: typhobacillosis" (Landouzy 1891). LS is mostly caused by *M. tuberculosis* but has also been encountered with other mycobacterial species. The clinical course of LS is usually that of an acute, overwhelming infectious disease. Less commonly, patients with LS present with subacute pyrexia of unknown origin (FUO). The main pathogenic feature is the virtual absence of a monocyte/macrophage response to mycobacteria spread to tissues. Histologically, the hallmark is a multifocal coagulative, caseous necrosis without associated macrophage reaction, i.e., without tuberculoid granulomas. This areactive state is caused by failure of monocyte stimulation by primed T lymphocytes or by secondary deficiency of immunocompetent effector cells. LS can, therefore, develop in immunosuppressed individuals (Jenss et al. 1981). As LS is a generalized disorder, liver involvement is to be expected in most patients and has in fact been documented at autopsy (Arends 1950; Moriwaki 1959; Rodin and Hnatko 1963).

At autopsy, only splenomegaly may be seen, as the whitish-gray miliary lesions found in miliary tuberculosis are lacking. Some patients showed hepatomegaly, up to 2600 g (Arends 1950). The liver showed some fibrinous epicapsular exudates in one case (Arends 1950). By use of magnifying

glass, the tiny necroses may be visualizing as white pinhead-sized spots less than 1 mm diameter. Less commonly, larger yellowish necroses of 1 cm diameter may be observed, probably resulting from coalescence of numerous and densely packed small lesions. Draining lymph nodes are either normal or show multiple necroses, but no granular aspect of the cut surface, because granulomas are absent (Pagel and Woolf 1949). Histologically, the leading feature is that of a focus of coagulative necrosis, often with "ghost cells" reflecting the original parenchyma. The necrosis may contain nuclear debris (karyorrhexis), similar to caseous necrosis found in miliary tuberculosis, and may be rich in fibrin and blood (Arends 1950). Typically, the lesions contain large amounts of acid-fast bacilli packed together (Rodin and Hnatko 1963), resulting in what has been called "felt-like masses" (O'Brien 1954). The tissue around these lesions is mostly normal and either completely lacks any lymphoid cell or monocyte infiltrates or shows a few scattered lymphocytes surrounding the necrosis (Gibson 1946; Arends 1950), reflecting a certain variation in immune reaction failure, ranging from complete to partial areactivity. In one autopsy, few Langerhans-type giant cells were found around the necroses (Arends 1950), again suggesting a certain monocyte-mediated reaction.

Hepatic Tuberculoma (Macronodular Hepatic Tuberculosis)

Hepatic tuberculomas or macronodular hepatic tuberculosis (MNHT) is a rare form of liver tuberculosis in Western countries, but may be more commonly seen in tropical areas with a high prevalence of tuberculosis (Figs. 2, 3, and 4). Even in Europe of the nineteenth and early twentieth centuries, when tuberculosis was a common disease, macronodular liver tuberculosis was rarely reported; in 1912, Lotheissen could only extract 34 observations from the literature (cited in Culp 1921). It is characterized by the presence of solitary or multiple, macroscopically visible nodules consisting of a caseous necrosis and surrounding tuberculoid granulomas. MNHT is chiefly a

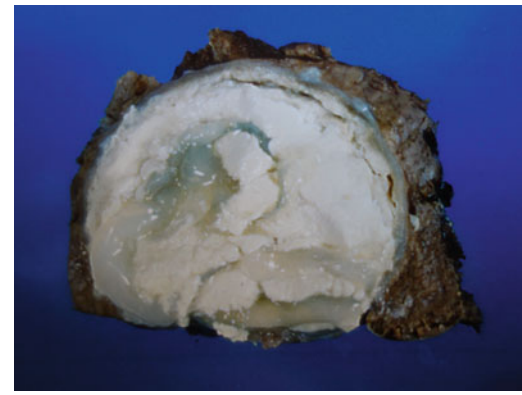

Fig. 2 Tuberculoma of the liver. The tumor-like mass mainly consists of caseous necrosis, which is macroscopically *whitish* in contrast to *yellow* pus. The cream-like mass typically shows cracks and fragmentation

disease of adults, but has also been diagnosed in children (Daynes 1971; Moskovic 1990; Kohli et al. 1996). MNHT uncommonly develops in the absence of abdominal tuberculosis (Desai et al. 2006). On plain radiographs, hepatic tuberculosis often shows calcifications, in the form of large "chalky" and confluent calcifications, nodal-type calcifications along the course of bile ducts, or smaller mineralizations of flecks and speckles (Maglinte et al. 1988). Ultrasonography showed hypo- or hyperechoic, ill-defined masses in the liver (Brauner et al. 1989; Tan et al. 1997). CT images show variably sized tumor-like lesions of low density, sometimes with multiple flecked calcifications (Small 1974; Brauner et al. 1989; Levine 1990; Buxi et al. 1992; Kawamori et al. 1992; Denton and Hossain 1993; Mercusot et al. 1995; Yu et al. 2004). Rarely, a honeycomb appearance has been found on CT. MR images showed low signal intensity on both T1-and T2-weighted images (Murata et al. 1996; Fan et al. 1998). Large mass lesions, sometimes exceeding 10 cm in diameter, mimic primary hepatic cancer (giant tuberculoma; Chan and Pang 1989; Achem et al. 1992; Brookes et al. 2006; Malik et al. 2011) or gallbladder cancer (Bikhchandani et al. 2005). Tuberculoma located to the porta hepatis can clinically and radiologically resemble Klatskin tumor (Arora et al. 2008). Multiple MNHT is also known and may present as calcified lesions (Chan and Pang

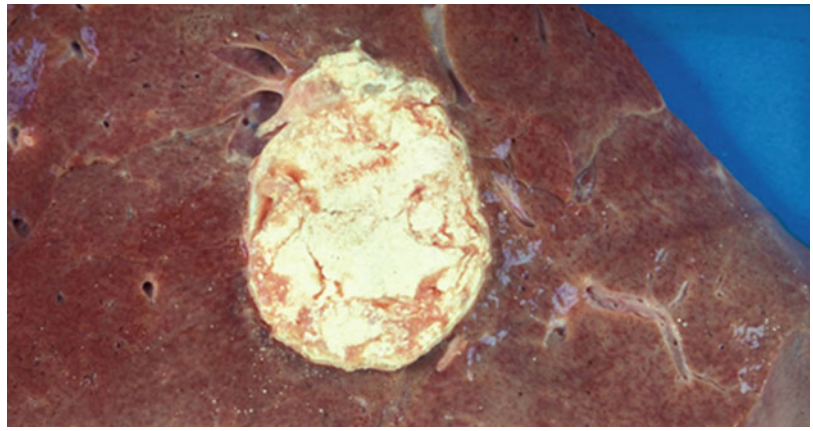

Fig. 3 Tuberculoma of the liver. Old lesions become sticky masses with a chalk-like aspect

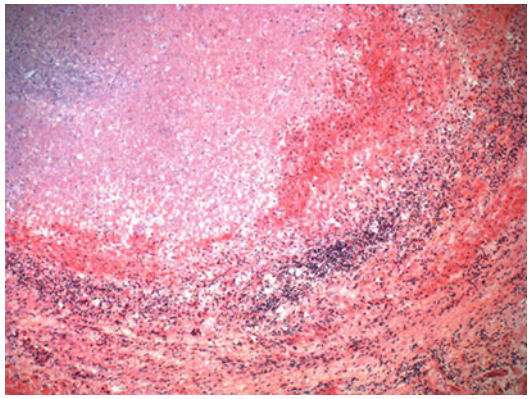

Fig. 4 Tuberculoma of the liver. The center of the lesion exhibits typical coagulation necrosis with nuclear debris. At the periphery of the lesion, a rim of epithelioid cells is observed. The *crescent-shaped* strongly eosinophilic structure is a zone of freshly necrotic epithelioid macrophages. The interface between the granulomatous belt and adjacent liver shows a lymphocytic infiltration and fibrosis (hematoxylin and eosin stain)

1989). These multiple nodules can closely resemble metastatic cancer foci at imaging (Fernandes et al. 1984; Wei et al. 2012). In case the tuberculoma is situated close to the gallbladder fossa, gallbladder cancer may be mimicked (Ben et al. 1995; Bikhchandani et al. 2005). MNHT is sometimes centered around intrahepatic bile ducts (Rosenkranz and Howard 1936).

In active hepatic tuberculosis, the histiodestructive process of a tuberculoma can extend beyond the anatomical limits of the liver, e.g., invading the pericardium (Mutreja et al. 2010). Tuberculomas can undergo or cause complications. MNHT can undergo secondary hemorrhage, similar to tumors (Prochazka et al. 1986), and was associated with portal vein thrombosis and portal hypertension (Ka et al. 2004; Venkatesh et al. 2005). Hepatic tuberculoma has also been detected after orthotopic liver transplantation (Berzigotti et al. 2006). In the past literature, part of hepatic tuberculous mass necroses now called tuberculomas have also been termed tuberculous liver abscesses. This designation is to be understood in a clinical-radiological setting, because necrotic lesions occurring in tuberculosis are, by definition, not true (pyogenic) abscesses, because an abscess is defined as a necrotic lesion with a dense granulocyte/neutrophil exudate, what is not the case in tuberculosis (Kanagaraj et al. 2008).

Apart from *M. tuberculosis*, tuberculomas, sometimes mimicking liver cancer or hepatic metastatic disease, have also been found in infections with other mycobacteria, including *M. kansasii* (Kaur et al. 2011) and *M. avium* (Hurley et al. 2011).

Selected References (Orth 1876; Zehden 1897; Elliesen 1900; Ernst 1901; Rome 1904; Fischer 1907; Dodel 1908; Ullom 1909; Fellerbaum 1912; Jenny 1913; Fraenkel 1917; Brütt 1919; Culp 1921; Gerlach 1923; Rosenkranz and Howard 1936; Leader 1952; Bloodworth 1954; Sandberg et al. 1957; Joseph et al. 1959; Korn

et al. 1959; Chimene et al. 1965; Gracey 1965; Grave 1972; Gattegno et al. 1973; Rab and Beg 1977; Rosin 1978; Siwach and Srivastava 1978; Jain et al. 1981; Purhoit and Verma 1982; Bhargava et al. 1983; Spiegel and Tuazon 1984; Gallinger et al. 1986; Mustard et al. 1986; Goh et al. 1987; Stevens and Little 1987; Chan and Pang 1989; Levine 1990; Oliva et al. 1990; Reed et al. 1990; Asada et al. 1991; Wilde and Kueh 1991; Achem et al. 1992; Emre et al. 1992; Purl et al. 1994; Ben et al. 1995; Chien et al. 1995; Herman et al. 1995; Nampoory et al. 1995; Amaris et al. 1997; Tan et al. 1997; Hickey et al. 1999; Jain et al. 1999; Agrawal et al. 2001; Rahmatulla et al. 2001; Huang et al. 2003; Mert et al. 2003; Ardiles et al. 2004; Hayashi et al. 2004; Köksal et al. 2006; Hassani et al. 2010; Abe et al. 2011; Singh et al. 2011).

Macroscopically, tuberculomas (hepatic tubercles) are pea-sized to walnut- or apple-sized solitary or multiple masses that may present as tumor-like lesions (Figs. 2, 3, and 4). In several investigations, multiple lesions were more common than solitary lesions. The nodules are usually well delineated and have a whitish-dull to gray-green color. Large and solitary masses are often bile stained ("green tubercles"), due to erosion of intrahepatic bile ducts and extravasation of bile into the necrotic areas. It is this type of greenish nodule that might macroscopically be confounded with a bile-storing liver cancer. Histologically, most of the mass of hepatic tubercles or tuberculomas consists of caseiform necrotic masses. These are pale eosinophilic and finely granular masses that may contain shadow cells and nuclear debris. Typically, these necrotic areas show fissures as an artifact occurring during tissue processing. Calcification is often seen, either in the form of tiny basophilic depositions or dense accumulations of calcified matter. The periphery of these areas is occupied by an epithelioid cell wall of variable thickness, without palisading. In smaller lesions, the micronodular aspect of this wall which results from fused granulomas is still seen, while large lesions often only show a very thin rim of epithelioid cells.

Nodular Tuberculous Pseudotumors

Large and in particular conglomerate focal lesions may give rise to tumor-like nodular masses (giant solitary liver tubercles, conglomerated tubercles, nodular tuberculous pseudotumors; NTPT). Almost all of these usually solitary tumor-like lesions seem to develop through coalescence of several preexisting tubercles. This pathway is likely because there are transition forms between several discrete nodules and a solitary pseudotumor, in which a coalescence of spherical necrosis with visible overlaps is easily seen, with the remaining epithelioid cell wall forming a peripheral structure resembling a fortification structure. Large tuberculous pseudotumors can progress to multilobulated masses strikingly resembling hepatic malignancy at gross examination. In rare instances, large areas of caseification may undergo condensation to thick and viscous homogeneous, grayish masses similar to those seen in renal tuberculosis ("putty tubercles of the liver"). The epidemiology of tuberculous pseudotumors is not well known. Among 682 patients from China who had undergone liver resection, eight were confirmed pathologically as having hepatic tuberculous pseudotumors (Xing et al. 2005). In some cases, NTPT are manifest as so-called hepatic pseudometastases, lesions that cause diagnostic difficulties, in particular, as they may coexist with true hepatic carcinoma metastases (Sen et al. 2004). NTPT may cause compression of bile ducts and lead to biliary obstruction (Wee et al. 1995).

Selected References (Sigg 1901; Debray et al. 1972; Zipser et al. 1976; Eichenlaub 1983; Forward et al. 1985; Gallinger et al. 1986; Dhekne et al. 1987; Mitlehner and Dibmann 1987; Belloir et al. 1988; Blangy et al. 1988; Errougani et al. 1991; Benelbarhdadi et al. 1995; Wee et al. 1995; Martin-Vivaldi Martinez et al. 1996; Xing et al. 2005; Ba et al. 2010; Landen et al. 2010).

Tuberculous Caverns of the Liver (Cavernous Hepatic Tuberculosis)

In pulmonary cavernous tuberculosis, the morphogenesis of caverns requires that the bronchus system is connected with large necrotic lesions in order air can get access to the lesions that may afterwards drain, with formation with a fluid-air interface. Cystic tuberculous lesions of the liver have been described as intrahepatic tuberculous biliary caverns (Sergent 1895; Jacobson 1897; Fletcher 1899; Rauber et al. 1956; Kemeny et al. 1981), In one patient, necropsy showed multiple biliary caverns of the liver, measuring 1–2 cm in diameter, with a grayish-greenish content (Kemenyi et al. 1981). Pathologenetically, the cavernous aspect, in contrast to tuberculous lung caverns, was probably caused by biliary drainage of necroses, leaving a fluid-filled cystic space.

In rare cases, tuberculosis restricted to intrahepatic bile ducts can mimic, due to wall destruction and dilation of ducts, alterations previously observed in bronchial tuberculosis and termed "Röhrentuberkulose" (tube-type tuberculosis; Hall 1911). Macroscopically, dilated intrahepatic bile duct protrudes from the liver's cut surface due to their markedly inflamed walls and the accumulation of caseiform necrosis in the walls. Histologically, the picture is dominated by a severe ulcerating granulomatous cholangitis with increase in duct wall thickness and sometimes sickle-shaped caseiform necrosis occupying sectors of the duct walls (Orth 1876; Gruber 1930). The necrotic bile duct may contain concrements, resulting in the effacement of the bile duct structure.

Tuberculous Vascular Alterations of the Liver

Invasive tuberculomas can involve the wall of the portal vein and induce so-called tuberculous thrombosis (pylephlebitis tuberculosa; Fig. 5). Tuberculous pylephlebitis is a very rare complication, sometimes also associated with tuberculous lymphadenitis of the hepatic hilum (Caroli and Paraf 1956; Savioz et al. 1993). In situations of pylephlebitis associated with hilar tuberculous lymphadenitis, it is assumed that inflamed nodes with granulomatous perilymphadenitis adhere to the adventitia of the portal vein, followed by transmural inflammation of the vein and thrombogenic endothelial damage. Another potential thrombogenic mechanism is endophlebitis tuberculosa of the portal vein, with formation of subendothelial tuberculoid and caseating granulomas. Perihilar tuberculous lymphadenitis can also cause bland, i.e., noninfected portal vein thrombosis and portal hypertension (Caroli-Bosc et al. 1997). In rare instances, tuberculosis manifests in the wall of the hepatic artery and its branches, sometimes causing hepatic artery aneurysm and associated hemobilia (Klepetko et al. 1986).

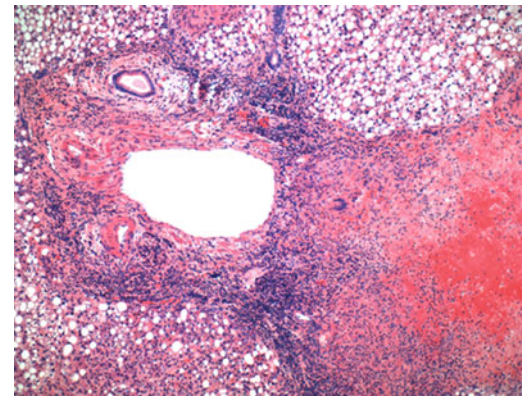

Fig. 5 Pylephlebitis tuberculosa. A sector of the portal vein is involved with tuberculosis. A granuloma with a typical Langhans giant cell has destroyed the venous wall (*right of the middle*). This lesion is in continuation with a large necrosis (hematoxylin and eosin stain)

Hepatic Tuberculosis in the Absence of Disseminated Abdominal Tuberculosis

In a series of seven patients, all presented with fever and hepatomegaly, five complained of pain in the upper abdomen and vomiting, and two patients were jaundiced. On ultrasonography,

two had multiple hypodense lesions, one showed a coarse echotexture of the liver, and one had a hypoechoic pattern (Desai et al. 2006). The lesions may mimic hepatic metastases (Kok and Yapp 1999b).

Associated Liver Alterations

Patients with tuberculosis often show, apart from specific hepatic lesions, a broad array of other liver alterations, in part related to the infections itself, in part caused by antituberculosis therapies (side effects of tuberculostatic drugs). In an autopsy study of 150 adult patients with tuberculosis, the liver showed granulomas in 42 %, fatty change in 32.6 %, portal tract inflammation in 40 %, sinusoidal congestion in 32 %, and fibrotic changes in 16 % (Amarapurkar and Agrawal 2006). In disseminated tuberculosis, small punctiform hemorrhages can develop in the liver, of unknown pathogenesis (Mittasch 1920; Peltason 1921). Tuberculous lesions of the liver can induce parenchymal atrophy and vascular alterations followed by nodular hypatocyte hyperplasia (Wegerle 1913). The liver capsule might be involved in encapsulating peritoneal sclerosis that has been found in *M. fortuitum* infection in peritoneal dialysis patient (Simbli et al. 2012).

Tuberculous Cholangitis, Biliary Stenosis, and Strictures

In abdominal tuberculosis, four mechanisms have been described to cause obstructive jaundice: (1) mass-producing tuberculosis of the pancreatic/peripancreatic region, (2) periductal/peripanceatic or retroperitoneal tuberculous lymphadenitis, (3) tuberculosis of the bile ducts, and (4) retroperitoneal tuberculosis with mass formation. Tuberculosis of the bile ducts causing ulcerations (Fig. 6), biliary stenosis, or strictures is a rare form of hepatobiliary tuberculosis that may mimic biliary tract malignancy. In a review of 17 cases (Iwai et al. 2006), six involved the common hepatic duct, six the common bile duct, one both the common hepatic and common bile duct,

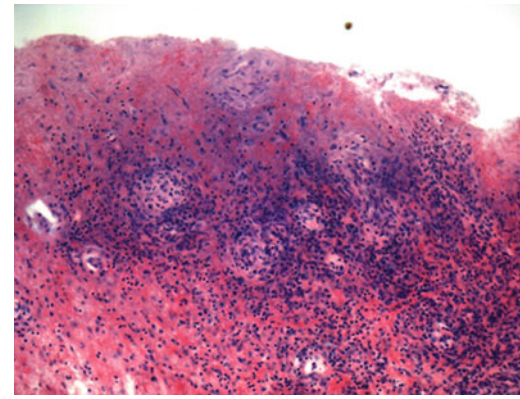

Fig. 6 Cholangitis tuberculosa ulcerosa. The wall of this bile duct is destroyed by tuberculous inflammation, leaving an ulcer covered with a necrotic matter. Deeper parts of the ulcer show several granulomas (hematoxylin and eosin stain)

one both the right hepatic duct and the common bile duct, one the hepatic duct, and two multiple strictures. Tuberculosis of the bile ducts can radiologically present with multiple flecked calcifications (Yu et al. 2004). The diagnosis can be confirmed by the finding of *M. tuberculosis* in bile duct by the use of PCR (Iwai et al. 2006) and by the histologic visualization of bile duct granulomas (Kotlar 1894). In one patient, stenosing biliary tuberculosis was associated with ampullary carcinoma (Chong et al. 2009), and tuberculosis can also involve the ampulla as an isolated lesion causing bile duct stenosis (Ricci et al. 2000). The coexistence of cancer and tuberculosis is not unexpected and occurs in several organs, probably owing to the fact that patients with tuberculosis are immunocompromised. Periampullary carcinoma has also been observed in coexistence with peripancreatic tuberculous lymphadenitis (Desai et al. 2004). The pathogenesis of bile duct tuberculosis has not been clarified in detail. Several pathogenic mechanisms have been proposed, including an infection of the duct mucosa from intraluminal bacteria eliminated from the liver ("Ausscheidungstuberkulose/excretory tuberculosis"; Lichtenstein 1912). Tuberculosis can also affect the gallbladder (Goyal et al. 1998; Gupta et al. 1998; Abu-Zidan and Zayat 1999; Banerjee and Sen 2003; Ruhl et al. 2003; Leong et al. 2011), an issue discussed

in another chapter. Macroscopically, the granulomatous and later fibrosing inflammation of the bile ducts is characterized by stenosis, strictures, and saccular dilatations (Abascal et al. 1988).

Selected References (Stemmerman 1941; Autio et al. 1963; Bergdahl and Boquist 1972; Gupta et al. 1985; Abascal et al. 1988; Bonnel et al. 1988; Fan et al. 1989; Ratanaparee and Pausawadi 1991; Bearer et al. 1996; Behera et al. 1997; Hickey et al. 1999; Kenneth et al. 1999; Kok and Yapp 1999a; Valeja et al. 1999; Yeh et al. 1999; Inal et al. 2000; Prasad and Pandey 2001; Alsawat and Aljebreen 2006; Iwai et al. 2006; Chong et al. 2009).

Bile Duct Perforation Due to Tuberculosis

Common bile duct perforations and fistula formation due to tuberculosis has mainly been observed in HIV-infected patients (Desta et al. 1998; Patino et al. 2003; Jarmin et al. 2004). Tuberculous fistulas may connect the bile duct with the duodenum (Patino et al. 2003) or with the small intestine (Desta et al. 1998).

Biliary Obstruction Due to Tuberculosis of Adjacent Organs

Tuberculous lymphadenitis, e.g., involving retropancreatic or periportal lymph nodes, can cause compression of the common bile duct and obstructive jaundice. The tuberculous lymph nodes may coalesce to form a multinodular mass that can mimic cancer of the pancreatic head. Sometimes, a single and markedly enlarged tuberculous lymph node situated posterior to the pancreatic head can result in perilymphadenitis, fistulation, and stenosis of the distal bile duct (Colovic et al. 2008). The resemblance to malignancy is furthered by the trend of these inflamed lymph nodes to adhere to adjacent structures, mimicking cancer invasion. Tuberculous lymph nodes, in the form of a coalesced mass, can compress the entire hepatic pedicle (Francillon et al. 1970). In tuberculous hepatic parenchymal disease, lymph nodes draining the liver and situated in the periportal area or the hepatoduodenal ligament may show enlargement due to granulomatous lymphadenitis and cause duct stenosis (Schmid 1957; Stanley et al. 1984; Mathieu et al. 1986; Pombo et al. 1990; Iglesias Castañon et al. 1995; Inal et al. 2000; Peyré et al. 2004; Kimura et al. 2005; Liew et al. 2011). The first case of periportal tuberculous lymphadenitis, causing obstructive jaundice in a child, had been reported in 1895 (Knight 1895). Tuberculous lymphadenitis has also been found to involve the cystic duct node (de Melo et al. 2004; Sidhu et al. 2007). Peritoneal tuberculosis may cause choledochal and duodenal stenosis (Paris et al. 1966).

Selected References (Päzolt 1968; Kohen and Altman 1973; Landa and Kravetskaia 1973; Jakab and Gönci 1974; Martinon and Aurousseau 1976; Murphy and Gray 1980; Alvarez and Carpio 1983; Lafay and Fouet 1983; Stanley et al. 1984; Mathieu et al. 1986; Arlandis Félix et al. 1990; Queralt et al. 1992; Arrese et al. 1997; Poon et al. 2001; Obama et al. 2003; Patino et al. 2003; Xia et al. 2003; Peyré et al. 2004; Saluja et al. 2007; Colovic et al. 2008).

The pancreas itself and/or the peripancreatic region can be involved by tuberculosis and lead to obstruction of the distal-most part of the common bile duct, mimicking malignancy of the pancreatic head (Queralt et al. 1992; Weiss et al. 2005; Foo et al. 2007). Tuberculosis can rarely involve the pancreatic substance itself and exert pressure on the traversing bile duct followed by obstructive jaundice (Crowson et al. 1984; Leborgne et al. 1989; Chen et al. 1999; Shan et al. 2000; Singh et al. 2002; Kumar et al. 2003). Pancreatic tuberculosis may spread to pancreas-associated lymph nodes and induce peripancreatic tuberculous lymphadenitis (Xia et al. 2003). Tuberculosis of the duodenum has been found to cause obstructive jaundice (Shah et al. 1991). Tuberculosis of the duodenum causes choledochoduodenal fistula and obstructive jaundice (Caudhary et al. 1989; Miyamoto et al. 2001).

Hepatic Fibrosis in Tuberculosis

The granulomatous response and associated portal tract inflammation can elicit diverse grades of liver fibrosis, ranging from simple portal tract fibrosis to incomplete and complete septal fibrosis, and eventual extensive fibrosis associated with hepatic remodeling/cirrhosis. Periportal fibrosis in hepatic tuberculosis is an observation already found in early literature (Lavenson and Karsner 1909). The advanced type of liver fibrosis with formation of nodular regenerative changes has either been termed cirrhosis or pseudocirrhosis (Egeli 1953). A peculiar type of liver fibrosis has been described in patients with *M. kansasii* infection (Listwan et al. 1975).

Silicotuberculosis of the Liver

Retropancreatic tuberculous lymphadenitis associated with lymph node silicosis has been shown to cause obstructive jaundice (Chassagnon and Silie 1966).

Liver Involvement in Generalized *Bacillus* Calmette-Guérin (BCG) Infection

Involvement of the liver in generalized BCG infection is a very rare disorder sometimes associated with so-called "BCGitis," mainly in children (Göttke et al. 2000; Karpelowsky et al. 2008; Li et al. 2010). An analysis of 830 pediatric autopsies in Canada revealed that 26 of the 36 infants given BCG vaccine shortly after birth exhibited tuberculoid granulomas in various organs, including the liver. In part of the cases, *M. bovis* BCG type could be isolated (Trevenen and Pagtakhan 1982). BCG as such is an invasive organism in immunocompromised organisms. In SCID mice having a severe T-cell defect, BCG bacteria caused hepatic parenchymal cell destruction in the absence of a protecting macrophage reaction (Mills et al. 2001).

Liver Involvement Following Intravesical *Bacillus* Calmette-Guérin Instillation

Intravesical instillation of BCG has been used as a therapy for superficial bladder cancer. Severe adverse reactions are uncommon in this treatment modality, but in rare instances, this treatment was complicated by disseminated BCG infection associated with sepsis, pancytopenia, abscess formation, mycotic aneurysms, hemolytic uremic syndrome, and multiorgan failure (Lamm et al. 1986). Clinical liver involvement with hepatomegaly and jaundice was sometimes found (Korac et al. 2009), and in some patients with this complication, granulomatous hepatitis was identified (Dederke et al. 1998; Hristea et al. 2007; Kaklamanos et al. 2011).

Microbiology of Tuberculosis

The genus *Mycobacterium* (M.) comprises more than 100 species and belongs to the family Mycobacteriaceae, suborder Corynebacterineae, and order Actinomycetales. One clinically relevant classification of mycobacterial species is based on the growth features of the bacteria. The *slowly growing group* (*generation time 6–24 h*) contains the *M. tuberculosis* complex (MTBC; *M. tuberculosis*, *M. bovis*, *M. bovis* BCG, *M. microti*, *M. africanum*, and others); the *M. avium* complex (MAC; *M. avium*, *M. paratuberculosis*, and others); the *M. gordonae* clade (*M. gordonae*, *M. asiaticum*); the *M. kansasii* clade (*M. kansasii*, *M. gastri*); and several other clades. The *group with intermediate growth rate* comprises *M. intermedium*. The *group of rapidly growing mycobacteria* (*generation time about 1–4 h*) contains numerous species grouped into several clades, of which some are human pathogens, e.g., *M. fortuitum*. Many mycobacterial species are currently ungrouped. Another classification of mycobacteria is based on the capability to synthesize carotenoid pigments in the presence or

absence of light. Photochromogens (group I; e.g., *M. kansasii*) have nonpigmented colonies in the dark and pigmented ones after light exposure. Scotochromogens (group II; e.g., *M. gordonae*, *M. scrofulaceum*) produce brisk yellow to orange colonies both in the dark and in the presence of light. Non-chromogens (groups III and IV; e.g., *M. tuberculosis*, *M. bovis*, *M. avium* intracellulare, *M. ulcerans*) only have a pale yellow or tan pigment that does not intensify following light exposure.

M. tuberculosis is a nonmotile aeorobic bacterium requiring high oxygen levels and is a member of a mycobacterial species group with a complex phylogeny (Hartmans et al. 2006). The bacterium, which had been detected by Robert Koch in 1882 (the reason why the agent is sometimes called, Koch's *bacillus*), possesses a wax-like coat containing mycolic acid, this coat rendering it impervious to Gram staining. The bacterium is therefore neither Gram-positive nor Gram-negative, i.e., the germ does not retain crystal violet or only to a very minor degree ("ghost bacteria"). The germ can be identified due to its acid-fast features in stains. The most commonly used stain is the Ziehl-Neelsen stain, other stains being Chen's modification of Ziehl-Neelsen stain (2012), modified Schaeffer and Fulton stain, Fite's stain, Kinyoun stain (1915; the "cold staining method," because it omits the heating step of the Ziehl-Neelsen stain), and the auramine O fluorescence method. Morphologically, *M. tuberculosis* is a fairly large thin rod 2–4 μm in length, often with a slightly curved and twisted shape. Following division, the two daughter bacteria may stick together for a short time at one end, resulting in a V-shaped structure. Smears from old in vitro colonies often reveal serpentine cords, caused by the expression of cord factor, a virulence factor already found by Robert Koch. Ultrastructurally, the bacterium contains and has a slightly irregular contour, sometimes rendering it finely "granular" or "beaded" in the Ziehl-Neelsen stain.

Leprosy: A Rare Cause of Large Hepatic Mass Lesions (Lepromas)

Introduction

Leprosy is an infectious disease caused by *Mycobacterium leprae* (review: Eichelmann et al. 2013). This multifaceted disorder is known since antiquity; Egyptian papyri dating back to 4000 BC make reference of the disease. Millions of persons with leprosy, and pejoratively called lepers, suffered a terrible destiny during thousands of years, being disfigured by skin nodules, loss of facial structures, deformation of limbs, and autoamputation caused by neuropathic sensory loss. It is well known that lepers were separated from society, had to announce themselves, e.g., by bells when underway, and were forced to live in specific buildings well outside cities and villages. It is estimated that, in the middle ages, 190,000 such leper hospitals and sanctuaries had been constructed in Europe. A review on some historical aspects is presented at the end of this chapter.

In the environment, *M. leprae* is present in certain mammals (e.g., the nine-banded armadillo), but the bacterium can also been taken up and stored in viable condition by free-living pathogenic amebas. Although the transmission mode has not been clarified, it is assumed that *M.leprae* is spread from person to person in respiratory droplets and by close contact. The probability of an infectious hit upon close contact varies considerably and seems to also depend on the infection dose, genetic background of hosts, and possibly on virulence. Incidence studies have shown that infection rates from contacts of lepromatous leprosy range from 6.2 per 1000 in Cebu (the Philippines) to 55.8 per 1000 per year in Southern India. The incubation period may be as short as few weeks and exceed 30 years. The entry rout of *M. leprae* is thought to be the skin and upper respiratory mucosae. Interaction of *M. leprae* with respiratory epithelial cells is mediated by a cell surface proteome of at least 11 potential adhesins. An important biological niche for *M. leprae* is the macrophage, where acid-fast bacilli can survive and proliferate, depending on the

host's immune defense. *M.leprae* can also invade other cell systems, whereby Schwann cells play a central role in lepric lesions of the peripheral nerve system (review: Polycarpou et al. 2013). *M. leprae* has a unique predilection for Schwann cells and employs distinct entry pathways to parasitize these cells. There is evidence that invasion of Schwann cells by *M. leprae* reprograms these cells to stem-like cells for promoting the dissemination of infection (Masaki et al. 2013). Invasion of Schwann cells is the main mechanism for the pathogenesis of the characteristic, mutilating neuropathy of leprosy (review: Rambukkana 2001).

Clinical Features

Clinically, leprosy is divided into two major forms of presentation, viz., the tuberculoid leprosy and the more malignant lepromatous (Virchowian) leprosy (Rabello 1937), a classification which reflects the host's defense reactions and illustrates opposite poles of the patient's response, i.e., efficient defense versus anergy (Ridley and Jopling 1966). An intermediate form, called borderline (dimorphous), develops in patients whose immune response is situated between the two major types. When leprosy is too early in stage or too mild for classification, it is called "indeterminate leprosy." Based on the Ridley-Jopling proposition, the principal groups employed now include tuberculoid, borderline tuberculoid, borderline, borderline lepromatous, and lepromatous leprosy. In tuberculoid leprosy, host defense is maximal, while in the polar form, lepromatous leprosy, it is minimal.

Another classification divides leprosy into multibacillary and paucibacillary groups, this classification determining the duration of treatment. Paucibacillary leprosy is characterized by one to five lesions and includes the tuberculoid and borderline tuberculoid forms (ICD-10 A30.1. A30.2). Multibacillary leprosy has usually more than five lesions and includes two Ridley-Jopling groups, i.e., midborderline or borderline (ICD-10 A30.3) and borderline lepromatous and lepromatous (ICD-10 A30.4, A30.5). These clinical presentation patterns are highly reflective of a Th1 (cell-mediated) or Th2 (humoral) immune response, respectively (Parkash 2009). There is also a humoral immune response in leprosy that leads to distinct inflammatory skin nodules, a condition termed erythema nodosum leprosum, a lesion that may result in nerve and organ damage (Voorend and Post 2013).

General Pathology of Leprosy

The first detailed descriptions of the pathology of leprosy were published in 1848 and 1895 (Danielssen and Boeck 1848; Hansen and Looft 1895). The histopathologic patterns in leprosy reflect the type and magnitude of the host's immune reactions directed against *M.leprae* and its antigens (Ridley and Jopling 1966; Turk and Waters 1969). Activation of the monocyte/macrophage system with formation of granulomas is, similar to tuberculosis, a hallmark of certain evolution stages of leprosy (Adams and Krahenbuhl 1996). In tuberculoid leprosy, the host displays near maximum resistance to the leprosy *bacillus*, and this is histologically seen in the presence of activated, epithelioid macrophages forming granulomas and a varying amount of lymphocytes, mainly of the T class. In these lesions, bacilli are typically not found, owing to the successful elimination of the germ. In the other polar form of leprosy, lepromatous (Virchowian) leprosy, cell-mediated immune reactions are deficient, allowing marked proliferation of *M.leprae* within the macrophage system. This results in the accumulation of enlarged and usually foamy (vacuolated) macrophages in involved tissues. Numerous acid-fast bacilli are detected in lepromatous leprosy, in contrast to the tuberculoid form (Mahlberg and Levis 2008). For the intermediate stages of leprosy, the bacterial load, lymphocyte responses, and recruitment and activation of the macrophage system correlate with the progression of disease. Apart from the skin and neural lesions, leprosy can involve mucosal surfaces and visceral organs, including the oral cavity/tongue (Bétourné et al. 1964) and the liver. In the liver,

lesions in general correspond in morphology to the skin infiltrates in lepromatous leprosy.

Hepatobiliary Manifestations

The spectrum of hepatic alterations caused by, or associated with, leprosy comprises nonspecific hepatomegaly, acute reactive (immune-mediated) hepatitis, granulomatous hepatitis, mass lesions (lepromas), fibrosis, cirrhosis, amyloidosis, fatty liver (mainly in patients with poor general health caused by leprosy), and drug-induced liver disease. Apart from the type of immune reaction and defense, and therefore the type of leprosy present, the probability of lepric liver lesions strongly depends on the efficiency and duration of treatment (Chen et al. 1976). The hepatic lesions occurring in leprosy have been reviewed (Browne 1964).

Granulomas

In tuberculoid leprosy, epithelioid cell granulomas have been detected in the liver in 1936 (Arning 1936). This visceral tuberculoid leprosy was first put in doubt, but the findings were subsequently confirmed (Campos and Molina 1950; Okada 1954; Verghese and Job 1965), also in puncture biopsy specimens of the liver (Okada 1954; Verghese and Job 1965). Among ten biopsied cases of tuberculoid leprosy, four showed paraportal granulomas, but only about 30 % of all the portal tracts were involved. The granulomas consisted of epithelioid cells and lymphocytes, but not of foamy cells, and no acid-fast bacilli were found. Rarely, granulomas were also observed in other areas of the liver. In addition to granulomas, small accumulations of non-epithelioid macrophages associated with lymphocytes and few neutrophils, but only very occasional plasma cells were noted in parenchyma (Sood and Grueber 1969). The latter lesions correspond to the so-called "retothel" nodules of older reports on tuberculosis and are focal immune reactions involving the macrophage-lymphocyte lineages (Hamperl 1953; Ringleb 1953). However, in a an autopsy study of 37 cases, no liver lesions were found in non-lepromatous cases (Desikan and Job 1968), and in an investigation of 21 more recent autopsies of tuberculoid leprosy, no leprous lesions were found in the liver, while biphasic leprous lesions may be found in borderline leprosy in several organs (Liu and Qiu 1984).

Lepromatous Lesions (Foamy Cells, Virchow Cells, Leprosy Cells)

It seems that most findings of significant liver lesions observed in leprosy are in patients with the lepromatous (Virchowian) form. In a study of 19 patients (11 lepromatous, five borderline, and three tuberculoid types) where puncture biopsies of the liver were performed and which is presented as an example well reflecting the situation, eight of 11 lepromatous patients showed numerous granulomas; in the borderline group, four out of five patients showed multiple hepatic granulomas, and also the tuberculoid cases showed granulomas (Verghese and Job 1965). There were histological differences as a function of the leprosy types. In lepromatous leprosy, the granulomas were usually in a paraportal position consisted of collections of foamy macrophages and lymphocytes. In fact, when one focuses on studies where lepromatous cases have been investigated, liver involvement is a rather frequent event in leprosy (Riecke 1928; Black and Denny 1936; Mitsuda and Ogawa 1937; Kean and Childress 1942; Fite et al. 1947; Ferrand 1954; Powell and Swan 1955; Battaglia 1960; Dogliotti and Fazio 1960; Bétourné et al. 1964; Garcia Perez et al. 1966; Desikan and Job 1968; Contreras and Val Bernal 1969; Sood and Grueber 1969; Agarwal et al. 1970; Bernard and Vazquez 1973; Chen et al. 1976; Kumar and Corder 1979; Liu and Qiu 1984; Azulay 1987; Ferrari et al. 2002; Singh et al. 2006). In 13 patients with lepromatous leprosy where liver biopsies had been performed, all 13 showed granulomatous involvement with accumulation of foamy cells and/or epithelioid cells.

Foamy cell lesions of the liver in lepromatous leprosy may be seen macroscopically as small yellowish foci that may render the liver surface spotty (von Bergmann1897). Histologically, the macrophages have a markedly vacuolated cytoplasm and small nuclei pushed to the periphery. Numerous acid-fast bacilli are found in the macrophages, where they are often arranged parallel in bundles. Bloated macrophages (foamy macrophages) are termed Virchow lepra cells. Older and markedly enlarged cells may contain so-called globi ("Keimkugeln"; "Zoogloea-Massen"; Wynne 1890; Storch 1897; Gurd 1911; Cowdry 1940), spherical fatty structures up to 100 μm in diameter containing masses of bacilli that replace most of the cytoplasm. Gurd (1911) was the first to recognize that the spherical spaces called globi were situated within the so-called lepra cells. The ballooned and often damaged macrophages contain a paranuclear clear space that contains compacted acid-fast bacilli (the globus), whereby the dark and compact inner part may be lobulated or show spikes ("cactus globi," Cowdry 1940). Between the bacterial accumulation and the peripheral border of the body, a halo may be present. After decay of the cell, the bacterial masses enter the extracellular space and form large acid-fast masses that may be phagocytosed by multinuclear giant cells.

In the borderline and tuberculoid cases, granulomas are small and composed of epithelioid cells, Langhans-type giant cells, and lymphocytes. In these two situations, no acid-fast bacilli were detected. In no case caseification was found. The granulomas occurring in lepromatous leprosy, characterized by foamy cells, were called "miliary lepromas" or foam cell granulomas (Bernard and Vazquez 1973; Chen et al. 1976). The very small hepatic granulomas arising in tuberculoid leprosy were almost always formed during exacerbation of the disease following a generalized spread, suggesting a macrophage-driven immune reaction, while in lepromatous leprosy, infected granulomas are the leading lesions. The diameter of lepromatous granulomas in portal tracts varied from 45 to 180 μm, and the granulomas were eccentrically placed in the portal tracts or involved the entire portal tract space. Eight of the 13 cases showed acid-fast bacilli in the granulomatous lesions and/or foamy cells (Sood and Grueber 1969). Among 75 autopsy cases, 64 cases (85.3 %) had leprous liver lesions, dominated by miliary lepromas consisting of bacilli-positive foamy macrophages and hyperplastic Kupffer cells with a foamy appearance and some bacilli in their cytoplasm. The miliary lepromas were mainly located in portal tracts or near the central veins (Liu and Qiu 1984). Leprosy can undergo so-called reactions (or acute exacerbation), caused by a change in the host's immune responses. In tuberculoid leprosy, reactions reveal reddening and elevation of skin lesions, new lesions, painful neuritis, and eventually the emergence of bacilli in lesions that were previously abacillary. In lepromatous leprosy, reactions are clinically characterized by bouts of high fever, enlargement and reddening of all lesions, an enormous increase in bacteria with bacillemia, and the emergence of new lesions. Liver histology in reaction states of lepromatous leprosy shows lepromatous lesions with foam cells, sometimes infiltrated by neutrophils, epithelioid granulomas, exudative lesions, and portal vasculitis in some cases (Patnaik et al. 1989). In a study of 30 patients of lepromatous leprosy in a state of reaction, hepatic involvement in the form of foam cell granulomas was observed in all, and 93.3 % of the cases exhibited the presence of acid-fast bacilli in the lesions (Zawar et al. 1983). Instead of fully developed granulomas, small hepatic accumulations of macrophages/Kupffer cells (sometimes only a few grouped cells) with a clear and vacuolated cytoplasm and numerous mycobacteria can be noted (Bétourné et al. 1964). Lepromatous patients who had the infection for shorter duration showed acid-fast bacilli in their Kupffer cells but lacked hepatic granulomas (review: Verghese and Job 1965). There may be transition forms that are difficult to classify in regard to bacterial load, because there are few reports of tuberculoid leprosy showing acid-fast bacilli in hepatic granulomas (Bru and Rollier 1957; Garcia Perez et al. 1966). In a study of 21 patients, it was shown that the prevalence of hepatic granulomas correlated with the cutaneous reactions in lepromatous leprosy, but the association was poor for

other stages of disease. Hepatic involvement varied with the severity of cutaneous infection and with the frequency and intensity of bacteremia. An estimated 1000–10,000 acid-fast bacilli/ml blood was required to induce the hepatic infiltrate (Chen et al. 1976).

Lepromatous Hepatic Mass Lesions (Lepromas; Leprosy Tumors)

Lepromas are large nodular lesions that occur in several organs in conjunction with lepromatous or histoid leprosy (Figs. 7 and 8). Apart from the skin, lepromas have been observed in the soft tissue, bone, tongue, and breast, where they can mimic primary malignancy or metastatic disease. Histologically, these masses chiefly consist of bacteria-containing macrophage accumulations with or without necrosis. There are relatively rare situations where lepromatous liver lesions coalesce to larger nodules or grow to tumor-like lesions, called leprosy pseudotumors or lepromas. Larger nodular lesions may be visualized by ultrasonography (Taneja et al. 1990). Abscess-like cavitations with numerous leprosy cells in the wall have been described (Arning 1884).

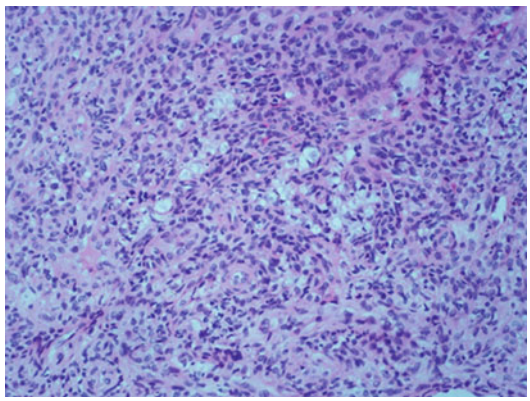

Fig. 7 Lepromatous lesion of the liver with a granulomatous reaction and several ballooned Hansen cells (hematoxylin and eosin stain)

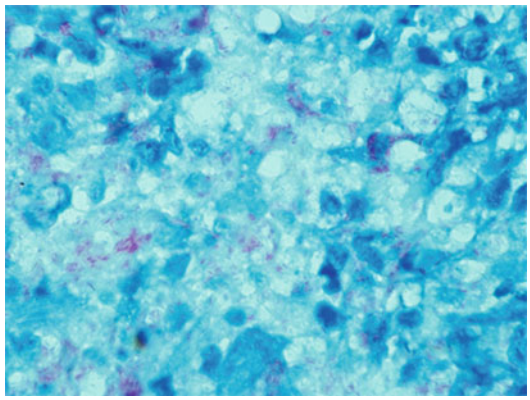

Fig. 8 Hepatic lepromatous lesion with numerous mycobacterial organisms (*red rods*). The large pale cells are Hansen cells (Ziehl-Neelsen stain for acid-fast organisms)

Liver Involvement in Lucio's Leprosy (Lazarine Leprosy)

Lucio's leprosy (diffuse leprosy of Lucio-Latapi, Lucio-Alvarado-Latapi form of leprosy, Mal de San Lazaro, diffuse lepromatous leprosy with erythema necroticans/Lucio's phenomenon, lepra manchada, "pretty leprosy," spotted or Lazarine leprosy) is an unusual manifestation of lepromatous leprosy that is or was mainly observed in Latin America, in particular Mexico (reviews: Wade 1949; Saul and Novales 1983; Diogenes et al. 2001; Kaur et al. 2005). It is a diffuse necrotizing or spotted type of leprosy originally reported in 1852 (Lucio and Alvarado 1852) and subsequently in 1948 (Latapi and Zamora 1948). Lucio's leprosy is often unmasked by a specific reactional state, the Lucio phenomenon, characterized by well-shaped erythematous spots which later become necrotic with ulcerations and later scars (Donner and Shively 1967; Moshella 1968), akin to type II lepra reaction. It is currently thought that Lucio's phenomenon, the hallmark of Lucio's leprosy, is caused by deposition of immune complexes (IC) in vessel walls, followed by IC-mediated vasculitis. In Lucio's leprosy, the skin histologically shows ulceration and necrosis of the upper layers, and beneath the necrotic area, there is an extensive inflammation of the dermis and the underlying subcutis, associated with proliferation of small blood vessels (angiogenesis), angiectasia, thrombosis of small vessels, and necrotizing vasculitis. Numerous vacuolated

macrophages containing large numbers of acid-fast bacilli are seen, and these bacilli may also be found in endothelial cells of damaged blood vessels (Vargas-Ocampo 2007). The distinct form of panvasculitis chiefly involves medium-sized arteries which histologically show necrosis, a granulomatous reaction, and clusters of intramural macrophages with large numbers of bacilli (Magaña et al. 2008). In one patient, liver biopsy disclosed multiple scattered granulomas distributed along portal tracts and within the lobules. Small epithelioid cell granulomas were in part located to dilated sinusoids, while larger granulomas appeared as coalescent lesions with Virchow-type foamy cells and numerous acid-fast bacilli (Kramarsky et al. 1968).

Liver Involvement in Histoid Leprosy (Wade's Histoid Variety of Lepromatous Leprosy)

Histoid leprosy is a rare variant of lepromatous leprosy with specific clinical, pathological, and bacteriological features. The disorder has been described in 1963 (Wade 1963) and is characterized by firm, reddish, skin-colored, dome-shaped, or oval papules and/or nodules (lepromas), with a translucent shiny and stretched overlying skin. Sometimes, sharply demarcated plaques are noted. Few to numerous (6–50) lesions may be found over the lower back, buttocks, face, and extremities. As these lesions protrude from the skin, a tumor-like appearance may result (Sehgal et al. 2009). Several reports have confirmed this entity (Mansfield 1969; Rodriguez 1969; Sehgal et al. 1987; Seghal and Srivastava 1988; Kalla et al. 2000; Pereyra et al. 2007; Kaur et al. 2009). Histoid leprosy is uncommon. Among 962 leprosy patients having attended the Hansen Clinic in New Delhi from June 2000 to June 2009, 11 cases were diagnosed as histoid leprosy (prevalence of 1.1.4 %; Mediratta et al. 2011). The disorder prevails in females, and most patients were between 16 and 35 years of age. Macroscopically, histoid lepromas are expansively growing, tumor-like lesions, in contrast to the infiltrative lesions in lepromatous leprosy (Wade 1963; Seghal and Srivastava 1987; Sehgal et al. 1987; Seghal and Srivastava 1988; Bakry and Attia 2012). Histologically, the lesions show numerous spindle-shaped histiocytes/macrophages forming interlacing bundles and bands or whorls. The cells show a vacuolated cytoplasm (Mansfield 1969), but much less than the foamy macrophages of lepromatous leprosy. The lesions contain numerous bacilli, which are detectable as needle-shaped negative images within macrophages/histiocytes in H&E-stained sections and are acid-fast in the Ziehl-Neelsen stain. Interestingly, many of these bacilli are longer than the usual leprosy bacilli seen in other lesions. These abnormally sized bacilli have been interpreted to be mutant forms resulting from the development of drug resistance (review: Seghal et al. 2009). Histoid leprosy may be the expression of an enhanced immune response to multibacillary disease, with an increase in both cell-mediated and humoral responses (Sehgal and Srivastava 1987).

Amyloidosis

Similar to other long-lasting infections and inflammatory disorders, leprosy can often be complicated by amyloidosis (Shuttleworth and Ross 1956; Garcia Perez et al. 1966). As in other forms of hepatic amyloidosis, the amyloid is localized to the spaces of Disse, associated with marked atrophy or destruction of hepatocyte plates (Garcia Perez et al. 1966). Amyloidosis is a frequent secondary change in chronic untreated or incompletely treated leprosy and is in fact the most common hepatic alteration in some studies. Among necropsies of leprosy patients, amyloidosis was detected in 38/89 cases (Hansen and Looft 1894), 17/50 cases (Powell and Swan 1955), 12/109 cases (Inaba 1940), 9/16 cases (Tilden 1945), and 14/60 cases (Bernard and Vazquez 1973).

Other Liver Alterations in Patients with Leprosy

Steatosis of the liver is seen in part of patients with leprosy. As in other individuals, the causes and morphology of liver steatosis are highly variable,

but small-droplet fatty change (microvesicular steatosis) seems to be a feature more common in leprosy (Singh et al. 2006). Significant hepatic steatosis was found in 4/12 biopsied cases, usually multifocal and in part of the microvesicular type (Garcia Perez et al. 1966). In an necropsy study of 60 leprosy patients, steatosis of the liver was noted in ten cases, three being massive (Bernard and Vazquez 1973). Peliosis hepatis has been observed in a patient with lepromatous leprosy (Furuta et al. 1982). Leprosy can elicit a form of immune-type (interstitial) hepatitis, which was detected in 9/12 biopsied patients in one series (Garcia Perez et al. 1966). In the quiescent stage of lepromatous leprosy of the liver, periportal and septal fibrosis as a fibrogenic end result of immune reactions (immune-mediated hepatitis) can develop, sometimes with hepatic remodeling or even cirrhosis. Among 75 autopsy cases with examination of the liver, formation of pseudolobules was found in three cases (Liu and Qiu 1984).

Locoregional Lymph Nodes of the Liver

Involvement of hepatic lymph nodes was always associated with lepromatous lesions of the liver (Liu and Qiu 1984). Whereas lymph nodes in tuberculoid leprosy may not show any alterations or then signs of immune stimulations, lymph nodes in lepromatous leprosy show epithelioid cell accumulations (also in the paracortex), epithelioid foam cells (sudanophilic Virchow cells), and microgranulomas, and acid-fast bacilli are detectable.

Historical Aspects of Leprosy

In the eighteenth century, a leading figure in leprosy research was the Norwegian Daniel Danielssen, the head of the Bergen leprosy hospital. Together with Carl Boeck, he published the work, On Leprosy, containing the hypothesis that leprosy was inherited rather than transmitted. In 1866, another Norwegian from Bergen (born 1841), Gerhard Henrik Armauer Hansen (1841–1912; Grzybowski et al. 2013), became the collaborator of Danielssen and worked in the Bergen Lundegaard Leper Hospital. Here he started to analyze the pathologic features of leprosy. In 1874, he published findings that completely changed the views one had on leprosy so far; he described ". . .in every leprous tubercle extirpated from a living individual. . .small staff-like bodies, much resembling bacteria, lying within cells; not in all, but in many of them." These organisms were *M. leprae*, and leprosy is often termed Hansen's disease in honor of Hansen's discovery. Hansen could not isolate the germ and fulfill Koch's postulates and failed to grow the bacterium on artificial media or in live rabbits. After autoinoculation experiments had not caused the disease in him and Danielssen, Hansen performed human experimentation in 1879 by cutting the eye of a female patient, without consent, with a cataract knife which just previously had been used to cut a nodule from a patient with lepromatous leprosy. Hansen was accused and found guilty for failure to obtain consent and lost his position (cited from Tan and Graham 2008). Leprosy in all its aspects was the issue of many reviews (Arnold and Fasal 1973; Scollard et al. 2006; Hussain 2007; Misch et al. 2010; Piris et al. 2010; Walsh et al. 2010; Rodrigues and Lockwood 2011).

References

Abascal J, Martin F, Pereira F, Herrera J, Ratia T, Menendez J (1988) Atypical hepatic tuberculosis presenting as obstructive jaundice. Am J Gastroenterol 83:1183–1186

Abe K, Aizawa T, Maebayashi T, Nakayama H, Sugitani M, Sakaguchi M, Shizukuishi T et al (2011) Isolated tuberculous liver abscess invading the abdominal wall: report of a case. Surg Today 41:741–744

Abu-Zidan FM, Zavat I (1999) Gallbladder tuberculosis (case report and review of the literature). Hepatogastroenterology 46:2804–2806

Achem SR, Kolts BE, Grisnik J, MacMath T, Monteiro CB, Goldstein J (1992) Pseudotumoral hepatic tuberculosis. Atypical presentation and comprehensive review of the literature. J Clin Gastroenterol 14:72–77

Adams LB, Krahenbuhl JL (1996) Granulomas induced by *Mycobacterium* leprae. Methods 9:220–232

Agarwal V, Agarwal RL, Gaur KJ, Saxena BP (1970) Liver changes in leprosy. J Assoc Physicians India 18:667–669

Agrawal CS, Jain BK, Das DN, Singh NP (2001) Solitary tuberculous abscess of liver. J Indian Med Assoc 99:591–592

Akhtar AJ, Shaheen M (2007) Jaundice in African-American and Hispanic patients with AIDS. J Natl Med Assoc 99:1381–1385

Alsawat KE, Aljebreen AM (2006) Resolution of tuberculous biliary stricture after medical therapy. World J Gastroenterol 12:1153–1156

Alvarez SZ, Carpio R (1983) Hepatobiliary tuberculosis. Dig Dis Sci 28:193–200

Amarapurkar A, Agrawal V (2006) Liver involvement in tuberculosis – an autopsy study. Trop Gastroenterol 27:69–74

Amarapurkar DN, Patel ND, Amarapurkar AD (2008) Hepatobiliary tuberculosis in western India. Indian J Pathol Microbiol 51:175–181

Amaris J, Kardache M, Soyer P, Lalande F, Boudiaf M, Scherrer A, Rymer R (1997) Radiological aspects of hepatic tuberculoma. 3 cases (in French). Gastroenterol Clin Biol 21:888–892

Ardiles V, Rossi G, Acuna Barrios J, Romero Vecce R, Mullen E, Lepoez MM, de Santibanes E (2004) Hepatic tuberculoma: presentation of cases and review of the literature (In Spanish). Acta Gastroenterol Latinoam 34:21–26

Arends A (1950) Blood disease and the so-called generalized non-reactive tuberculosis; typhobacillosis of Landouzy, sepsis tuberculosa acutissima. Acta Med Scand 136:417–429

Arlandis Félix FJ, Villalobos Talero J, Mazure Lenhoff RA, Cabrerizo Comitre E, Polo Camacho M et al (1990) Tuberculosis of the biliary system: presentation of a case and review of the literature (in Spanish). Rev Esp Enferm Dig 78:43–45

Arning E (1884) Zur Frage der viszeralen Lepra. Arch Dermatol Syph 29:147

Arning E (1936) Tuberculoid changes in the viscera. Int J Lepr 4:102–103

Arnold J (1880) Beiträge zur Anatomie des miliaren Tuberkels. I. Über Lebertuberkulose. Virchows Arch Pathol Anat Physiol 82:377

Arnold HL, Fasal P (1973) Leprosy. Diagnosis and management, 2nd edn. Charles C. Thomas, Springfield

Arora R, Sharma A, Bhowate P, Bansal VK, Guleria S, Dinda AK (2008) Hepatic tuberculosis mimicking Klatskin tumor: a diagnostic dilemma. Indian J Pathol Microbiol 51:382–385

Arrese M, Lopez F, Rossi R, Traipe E, Cruz F (1997) Extrahepatic cholestasis attributable to tuberculous adenitis. Am J Gastroenterol 92:912–913

Asada Y, Hayashi T, Sumiyoshi A, Aburaya M, Shishime E (1991) Miliary tuberculosis presenting as fever and jaundice with hepatic failure. Hum Pathol 22:92–94

Auerbach O (1944) Acute generalized miliary tuberculosis. Am J Pathol 20:121

Autio V, Virtanen S, Antila L (1963) Biliary tract tuberculosis. A case report with bacteriological consideration. Ann Chir Gynaecol Fenn 52:50–57

Azulay RD (1987) Primary visceral Virchowian (lepromatous) hanseniasis. Int J Lepr Other Mycobact Dis 55:450–453

Ba TT, Cambier E, Tinton N, Lam HD, Navez B (2010) Pseudo-tumoral hepatic tuberculosis: a report of two cases. Acta Chir Belg 110:83–86

Bakry OA, Attia AM (2012) Histoid leprosy: case report. Acta Dermatovenerol Croat 20:256–259

Balasubramanian S, Kaarthigeyan K, Aparna V, Srinivas S (2008) Tuberculosis associated hemophagocytic syndrome in infancy. Indian Pediatr 45:593–595

Banerjee S, Sen S (2003) Tuberculosis of the gall bladder. J Indian Med Assoc 101:556–557

Battaglia F (1960) On the hepatic localization of leprosy (in Italian). Arch Vecchi Anat Pathol 32:85–92

Bearer EA, Savides TJ, McCutchan JA (1996) Endoscopic diagnosis and management of hepatobiliary tuberculosis. Am J Gastroenterol 91:2602–2604

Behera A, Kochhar R, Dhavan S, Aggarwal S, Singh K (1997) Isolated common bile duct tuberculosis mimicking malignant obstruction. Am J Gastroenterol 92:2122–2123

Belloir A, Guiry P, Guiry M, Maubon A, Rouanat JP, Bruel JM, Lamarque JL (1988) Pseudotumoral hepatic tuberculosis. Ultrasonics and x-ray computed tomography – apropos of a case (in French). J Radiol 69:21–23

Ben RJ, Young T, Lee HS (1995) Hepatobiliary tuberculosis presenting as a gall bladder tumor. Scand J Infect Dis 27:415–417

Benelbarhdadi I, Benazzouz M, Ajana FZ, Ibrahimi A, Sassenou I, Afifi R, Belkhayat S et al (1995) The pseudo-tumoral form of hepatic tuberculosis. Five case reports (in French). Ann Gastroenterol Hepatol (Paris) 31:277–280

Bergdahl L, Boquist L (1972) Tuberculosis of the gallbladder. Br J Surg 59:289–292

Bernard JC, Vazquez CAJ (1973) Visceral lesions in lepromatous leprosy. Study of sixty necropsies. Int J Lepr 41:94–101

Berzigotti A, Bianchi G, Dapporto S, Pinna AD, Zoli M (2006) Isolated hepatic tuberculoma after orthotopic liver transplantation: a case report. Intern Emerg Med 1:314–316

Bétourné C, Vallin J, Gentilini M, Hayem F (1964) Lepromatous leprosy with hepatic localization (in French). Bull Mem Soc Med Soc Paris 115:535–540

Bhargava DK, Verma K, Malaviya AN (1983) Solitary tuberculoma of liver: laparoscopic, histologic, and cytologic diagnosis. Gastrointest Endosc 29:329–330

Bikhchandani J, Malik VK, Kumar V, Sharma S (2005) Hepatic tuberculosis mimicking carcinoma gall bladder. Indian J Gastroenterol 24:25

Black SH, Denny OE (1936) Comment on tuberculoid changes in the viscera. Int J Lepr 4:104–105

Blangy S, Cornud F, Sibert A, Vissuzaine C, Saraux JL, Benacerraf R (1988) Hepatitis tuberculosa presenting

as tumoral diseases on ultrasonography. Gastrointest Radiol 13:52–54
Bloodworth AF (1954) Tuberculous abscess of the liver. South Med J 47:901–902
Bonnel D, Dumont JL, Liguory C, Langlois P, Ziza JM, Cornud F, Lefèbvre JF, Canard JM (1988) Jaundice caused by tuberculous biliary stenosis. Percutaneous treatment (in French). Presse Med 17:1586
Bottiger LE, Nordenstam HH, Wester PO (1962) Disseminated tuberculosis as a cause of fever of obscure origin. Lancet 1:19–20
Brauner M, Buffard MD, Jeantils V, Legrand I, Gotheil C (1989) Sonography and computed tomography of macroscopic tuberculosis of the liver. J Clin Ultrasound 17:563–568
Brookes MJ, Field M, Dawkins DM, Gearty J, Wilson P (2006) Massive primary hepatic tuberculoma mimicking hepatocellular carcinoma in an immunocompetent host. Med GenMed 8:11
Browne SG (1964) The liver in leprosy: a review. W Afr Med J 13:35–41
Bru P, Rollier R (1957) La ponction-biopsie du foie dans la lèpre. Maroc Med 36:1194
Bruguera M, Rodes J, Vilardell E, Gibert-Queralto J (1968) Portal hypertension associated with autonomous hepatic tuberculosis (in French). Rev Int Hepatol 18:895–903
Brütt H (1919) Zur Kenntnis der Behandlung der geschwulstartigen Lebertuberkulose. Beitr Klin Chir 118:125
Buxi TB, Vohra RB, Sujatha Y, Chawla D, Byotra SP, Gupta PS, Dewan VK, Kanwar CK (1992) CT appearances in macronodular hepatosplenic tuberculosis: a review with five additional new cases. Comput Med Imaging Graph 16:381–387
Cardona PJ (2007) New insights on the nature of latent tuberculosis infection and its treatment. Inflamm Allergy Drug Targets 6:27–39
Cardona PJ, Ruiz-Manzano J (2004) On the nature of *Mycobacterium* tuberculosis-latent bacilli. Eur Respir J 24:1044–1051
Caroli J, Paraf A (1956) Tuberculous pylephlebitis (in French). Rev Med Chir Mal Foie 31:73–77
Caroli-Bosc FX, Conio M, Maes B, Chevallier P, Hastier P, Delmont JP (1997) Abdominal tuberculosis involving hepatic lymph nodes. A cause of portal vein thrombosis and portal hypertension. J Clin Gastroenterol 25:541–543
Chan HS, Pang J (1989) Isolated giant tuberculomata of the liver detected by computed tomography. Gastrointest Radiol 14:305–307
Chassagnon C, Silie M (1966) A case of silico-tuberculosis complicated by obstructive jaundice. Retro-pancreatic silicotic lymph nodes blocking the bile ducts (in French). Arch Mal Prof 27:718–719
Chaudhary A, Bhan A, Malik N, Dilawari JB, Khanna SK (1989) Choledocho-duodenal fistula due to tuberculosis. Indian J Gastroenterol 8:293–294
Chen TS, Drutz DJ, Whelan GE (1976) Hepatic granulomas in leprosy. Their relation to bacteremia. Arch Pathol Lab Med 100:182–185
Chen CH, Yang CC, Yeh YH, Yang JC, Chou DA (1999) Pancreatic tuberculosis with obstructive jaundice – a case report. Am J Gastroenterol 94:2534–2536
Chen HC, Chao YC, Shyu RY, Hsieh TY (2003) Isolated tuberculous liver abscesses with multiple hyperechoic masses on ultrasound: a case report and review of the literature. Liver Int 23:346–350
Chien RN, Lin PY, Liaw YF (1995) Hepatic tuberculosis: comparison of miliary and local form. Infection 23:5–8
Chimene DR, Roberts TW, Rohman M (1965) Solitary tuberculoma of the liver. NY State J Med 65:2479–2481
Chong VH (2008) Hepatobiliary tuberculosis: a review of presentations and outcomes. South Med J 101:356–361
Chong VH, Telisinghe PU, Yapp SK, Jalihal A (2009) Biliary strictures secondary to tuberculosis and early ampullary carcinoma. Singapore Med J 50:e94–e96
Chou YH (2002) Congenital tuberculosis proven by percutaneous liver biopsy: report of a case. J Perinat Med 30:423–425
Cinque TJ, Gary NE, Palladino VS (1964) "Primary" miliary tuberculosis of the liver. Am J Gastroenterol 42:611–619
Colovic R, Grubor N, jesic R, Micev M, Jovanovic T, Colovic N, Atkinson HD (2008) Tuberculous lymphadenitis as a cause of obstructive jaundice: a case report and literature review. World J Gastroenterol 14:3098–3100
Contreras F, Val Bernal F (1969) Liver diseases in lepromatous leprosy (in Spanish). Rev Clin Esp 115:91–96
Cowdry EV (1940) Cytological studies on globi in leprosy. Am J Pathol 16:103–142
Crowson MC, Perry M, Burden E (1984) Tuberculosis of the pancreas: a rare cause of obstructive jaundice. Br J Surg 71:239
Cruice JM (1914) Jaundice in tuberculosis. Am J Med Sci 147:720
Culp W (1921) Über grossknotige Lebertubwerkulose kombiniert mit Leberzirrhose unter dem Bilde einer Lebervergrösserung. Beitr Klein Tuberkulos Spezif Tuberkulose-Forsch 46:219–226
Curry FJ, Alcott D (1955) Tuberculous hepatitis with jaundice – report of 2 cases. Gastroenterology 28:1037–1041
Danielssen DC, Boeck CW (1848) Traité de la Spedalskhed ou Elephantiasis des Grecs. J.N. Baillière, Paris
Daynes G (1971) Tuberculoma of the liver in a child. S Afr Med J 45:48
de C. Campos R, Molina SM (1950) Visceral tuberculoid leprosy. Int J Lepr 18:351–359
De Melo VA, de Melo GB, Silva RL, Piya N, Almeida ML (2004) Tuberculosis of the cystic duct lymph node. Braz J Infect Dis 8:112–114

Debray J, Krulik M, Bernar JF (1972) La tuberculose pseudotumorale du foie. Sem Hôp Paris 48:3165–3173

Dederke B, Riecken EO, Weinke T (1998) A case of BCG sepsis with bone marrow and liver involvement after intravesical BCG instillation. Infection 26:54–57

Den Broeder AA, Vervoort G, van Assen S, Verduyn Lunal F, de Lange WC, de Sévaux RG (2003) Disseminated *Mycobacterium gordonae* infection in a renal transplant recipient. Transpl Infect Dis 5:151–155

Denton T, Hossain J (1993) A radiological study of abdominal tuberculosis in a Saudi population, with special reference to ultrasound and computed tomography. Clin Radiol 47:409–414

Desai CS, lala M, Joshi A, Abraham P, Desai D, Deshpande RB, Shah SR (2004) Co-existence of periampullary carcinoma with peripancreatic tuberculous lymphadenopathy. JOP 5:145–147

Desai CS, Josh AG, Abraham P, Desai DC, Deshpande RB, Bhaduri A, Shah SR (2006) Hepatic tuberculosis in absence of disseminated abdominal tuberculosis. Ann Hepatol 5:41–43

Desikan and Job (1968) http://www.ncbi.nlm.nih.gov/pubmed/5689648

Desikan KV, Job CK (1970) Visceral lesions caused by M. leprae – a histopathological study. Indian J Pathol Bacteriol 13:100–108

Desta TT, Man KM, Bouvier D, Leung JW (1998) Choledocho-enteric fistula due to *Mycobacterium* tuberculosis in a patient with acquired immunodeficiency syndrome. Gastrointest Endosc 48:623–626

Dhekne RD, Moore WH, Long SE, Barron BJ (1987) Tuberculous pseudotumor of the liver. Clin Nucl Med 12:816–819

Diogenes MJN, De Morals RM, De S. Tomé G, Da Cunha MB, Da C.B. Neto C (2001) The Lucio-Alvarado-Latapi form of leprosy. Lepr Rev 72:360–362

Dodel FX (1908) Ein Fall von Konglomerattuberkulose der Leber. Thesis, Munich

Dogliotti M, Fazio M (1960) Biopsy of the liver in lepromatous leprosy. Acta Hepatosplenol 7:7–24

Donner RS, Shively JA (1967) The 'Lucio phenomenon' in diffuse leprosy. Ann Intern Med 67:831–836

Dwek JH, Schechter LS, Grinberg ME (1981) Hepatic angiography in a patient with tuberculosis of the liver. Am J Gastroenterol 75:307–308

Eckel F (1929) Ein Fall von Typhobacillose Landouzy unter dem Bilde der aleukämischen Mikromyeloblastenleukämie. Med Klein 223:50

Egeli ES (1953) Über die Cirrhose und Pseudocirrhose tuberculösen Ursprungs. Dtsch Arch Klin Med 200:358

Eichelmann K, Gonzalez Gonzalez SE, Salas-Alanis JC, Ocampo-Candiani J (2013) Leprosy. An update: definition, pathogenesis, classification, diagnosis, and treatment. Actas Dermosifilogr 104:554–563

Eichenlaub D (1983) Large nodular pseudotumorous liver tuberculosis (in German). MMW Munch Med Wochenschr 125:509–510

Elliesen T (1900) Über multiple solitäre Tuberkulose in der Leber. Thesis, Erlangen

Emre A, Akpinar E, Acarli K, Alper A, Cevikbas U, Ariogul O (1992) Primary solitary tuberculosis of the liver. HPB Surg 5:261–264

Ernst P (1901) Isolierte Konglomerattuberkulose der Leber. Verh Dtsch Ges Pathol 4:235

Errougani A, Chkoff C, Mkinsi O, Mansouri F, Assem M, Amraoui M, Balafrei S (1991) Pseudotumor form of hepatic tuberculosis. Apropos of a case (in French). J Chir (Paris) 128:251–253

Essop AR, Moosa MR, Segal I (1983a) Primary tuberculosis of the liver. A case report. Tuber Lung Dis 64:291–293

Essop AR, Hodkinson JH, Posen J, Segal I, Macerollo P (1983b) Simultaneous hepatic tuberculosis, cirrhosis and hepatoma. A case report. S Afr Med J 64:1102–1104

Essop AR, Posen JA, Hodkinson JH, Segal I (1984) Tuberculosis hepatis: a clinical review of 96 cases. QJM 53:465–477

Evans RH, Evans M, Harrison NK, Price DE, Freedman AR (1998) Massive hepatosplenomegaly, jaundice and pancytopenia in miliary tuberculosis. J Infect 36:236–239

Fan ST, Ng IO, Choi TK, Lai EC (1989) Tuberculosis of the bile duct: a rare cause of biliary stricture. Am J Gastroenterol 84:413–414

Fan ZM, Zeng QY, Huo JW, Bai L, Liu ZS, Luo LF, Yang JC, Zhou XH (1998) Macronodular multi-organ tuberculoma: CT and MR appearances. J Gastroenterol 33:285–288

Farhi DC, Mason UG, Horsburgh CR (1986) Pathologic findings in disseminated *Mycobacterium avium*-intracellulare infection. A report of 11 cases. Am J Clin Pathol 85:67–72

Fellerbaum A (1912) Massive tuberculosis of the liver. NY Med J 96:481

Fernandes JD, Nebesar RA, Wall SG, Minihan PT (1984) Report of tuberculous hepatitis presenting as metastatic disease. Clin Nucl Med 9:345–347

Fernandez-Rodriguez et al. (2004) http://www.ncbi.nlm.nih.gov/pubmed/15622550

Ferrand B (1954) Puncture biopsy of the liver in leprosy (in French). Bull Soc Pathol Exot Fil 47:203–207

Ferrari TC, Araujo MG, Ribeiro MM (2002) Hepatic involvement in lepromatous leprosy. Lepr Rev 73:72–75

Fischer W (1907) Über grossknotige tumorähnliche Tuberkulose der Leber, wahrscheinlich kombiniert mit Syphilis. Virchows Arch Pathol Anat Physiol 188:21

Fite GL, Cambre PJ, Turner MH (1947) Procedure for demonstrating lepra bacilli in paraffin sections. Arch Pathol 43:624–625

Fletcher HM (1899) Tuberculous cavities in the liver. J Pathol Bacteriol 6:146

Foo FJ, Verbeke CS, Guthrie JA, Ala A, Menon KV (2007) Pancreatic and peripancreatic tuberculosis mimicking malignancy. JOP 8:201–205

Forward KR, Tong AY, Campbell RO, Nolan RL (1985) Tuberculous pseudotumor of the liver developing during antituberculous chemotherapy. Can Med Assoc J 132:45–47

Fraenkel E (1917) Über geschwulstartige Lebertuberkulose. Z Tuberk 27:52

Francillon J, Fischer L, Braconnot P, Peschaud R, Mouret P, Vignal J (1970) Tuberculous lymph node compression of the hepatic pedicle (in French). Ann Gastroenterol Hepatol (Paris) 6:27–33

Furuta M, Asamoto H, Kitaichi M, Harada N, Obara A, Matsumoto S (1982) A case of peliosis hepatis appearing in a patient with lepromatous leprosy (in Japanese). Nippon Rai Gakkai Zasshi 51:22–27

Gallinger S, Strasberg SM, Marcus HI, Brunton J (1986) Local hepatic tuberculosis, the cause of a painful hepatic mass: case report and review of the literature. Can J Surg 29:451–452

Garcia Perez A, Aguirre Jaca M, Hernandez Guio C, Oliva H, Navarro V (1966) Hepatic leprosy (in French). Rev Int Hepatol 16:1353–1367

Gattegno B, Cedisier G, Huguier M, Croisier JC (1973) Abcès tuberculeux du foie. Arch Fr Mal Appar Dig 62:241–244

Gelb AF, Leffler C, Brewin A, Mascatello V, Lyons HA (1973) Miliary tuberculosis. Am Rev Resp Dis 108:1327–1332

Gerlach W (1923) Über den tuberkulösen Abszess der Leber. Z Tuberkul 38:110

Gibson A (1946) Monocytoid leukaemoid reaction associated with tuberculosis and a mediastinal teratoma. J Pathol Bacteriol 58:469–475

Glaus A (1919) Isolierte Miliartuberkulose der Leber bei Tuberkulose des Pankreas und der Vena lienalis. Berl Klein Wochenschr 23:22

Godwin JE, Coleman AA, Sahn SA (1991) Miliary tuberculosis presenting as hepatic and renal failure. Chest 99:752–754

Goh KL, Pathmanathan R, Chang KW, Wong NW (1987) Tuberculous liver abscess. J Trop Med Hyg 90:255–257

Gold J, Wigderson A, Lehman E, Schwartz IR (1957) Tuberculous hepatitis; report of a case with review of the literature. Gastroenterology 33:113–120

Goldblatt MR, Ribes JA (2002) *Mycobacterium mucogenicum* isolated from a patient with granulomatous hepatitis. Arch Pathol Lab Med 126:73–75

Göttke MU, Wong P, Muhn C, Jabbari M, Morin S (2000) Hepatitis in disseminated *bacillus* Calmette-Guérin infection. Can J Gastroenterol 14:333–336

Goyal SC, Goyal R, Malhotra V, Kaushik K (1998) Tuberculosis of the gall bladder. Indian J Gastroenterol 17:108

Gracey L (1965) Tuberculosis abscess of the liver. Br J Surg 52:442–443

Grave GF (1972) Tuberculoma of the liver. Cent Afr J Med 18:148–149

Gruber GB (1930) Spezielle Infektionsfolgen der Leber. Handb Speziellen Pathologischen Anat Histol 5:559–578

Grzybowski A, Sak J, Pawlikowski J, Iwanowicz-Palus G (2013) Gerhard Henrik Armauer Hansen (1841–1912) – the 100th anniversary of the death of the discoverer of *Mycobacterium* leprae. Clin Dermatol 31:653–655

Gupta NM, Chaudary A, Talwar BL (1985) Isolated biliary tuberculosis. Asian Med J 28:636–640

Gupta NM, Khaitan A, Singh V, Radotra B (1998) Isolated gallbladder tuberculosis with postoperative biliary fistula. Endoscopy 30:S73–S74

Gurd FB (1911) A contribution to the cytology of the leprous lesion. J Pathol Bacteriol 16:1–15

Hall HC (1911) Ein Fall von "Röhrentuberkulose" der Leber, wahrscheinlich mit Syphilis kombiniert. Virchows Arch Pathol Anat Physiol 206:167

Hamperl H (1953) Über Retothelknötchen in Leberpunktaten von Tuberkulose-kranken. Klin Wochenschr 31:681

Hansen GA, Looft C (1894) Die Lepra von klinischem und pathologischem Standpunkt. Bibliotheca Med D II, vol 2

Hansen GA, Looft C (1895) Leprosy in its clinicopathologic aspects. John Wright & sons, Bristol

Hart PD, Rees RJ (1967) Lepromin and Kveim antigen reactivity in man, and their relation to tuberculin reactivity. Br Med Bull 23:80–85

Hartmans S, De Bont JAM, Stackebrandt E (2006) The genus *Mycobacterium* – nonmedical. Prokaryotes 3:889–918

Hassani KIM, Ousadden A, Ankouz A, Mazaz K, Taleb KA (2010) Isolated liver tuberculosis abscess in a patient without immunodeficiency: a case report. World J Hepatol 2:354–357

Hayashi M, Yamawaki I, Okajima K, Tomimatsu M, Ohkawa S (2004) Tuberculous liver abscess not associated with lung involvement. Intern Med 43:521–523

Haythorn SR (1929) Multinucleated giant cells. With particular reference to the foreign body giant cell. Arch Pathol 7:651–699

Herman P, Pugliese V, Laurino Neto R, Machado MC, Pinotti HW (1995) Nodular form of local hepatic tuberculosis: case report. J Trop Med Hyg 98:141–142

Hersch C (1964) Tuberculosis of the liver. A study of 200 cases. S Afr Med J 38:857–863

Herxheimer G (1914) Zur feineren Struktur der tuberkulösen Riesenzellen. Verh Dtsch Ges Pathol (Jena) 25(Suppl):128–135

Hickey N, McNulty JG, Osborne H, Finucane J (1999) Acute hepatobiliary tuberculosis: a report of two cases and a review of the literature. Eur Radiol 9:886–889

Hristea A, Neascu A, Ion DA, Streinu-cercel A, Staniceanu F (2007) BCG-related granulomatous hepatitis. Pneumologia 56:32–34

Huang WT, Wang CC, Chen WJ, Cheng YF, Eng HL (2003) The nodular form of hepatic tuberculosis: a review with five additional cases. J Clin Pathol 56:835–839

Hurley JJ, Turner J, Campbell IA, Dolwani S (2011) An opportune finding in suspected liver metastases. BMJ Case Rep. (2011). pii:bcr0520103013

Hussain T (2007) Leprosy and tuberculosis: an insight-review. Crit Rev Microbiol 33:15–66
Hussain W, Mutimer D, Harrison R, Hubscher S, Neuberger J (1995) Fulminant hepatic failure caused by tuberculosis. Gut 36:792–794
Hwang SW, Kim YJ, Cho EJ, Choi JK, Kim SH, Yoon JH, Kim CY, Lee HS (2009) Clinical features of hepatic tuberculosis in biopsy-proven cases (in Korean). Korean J Hepatol 15:159–167
Iglesias Castanon A, Lecumberri Olaverri FJ, Arias Gonzalez M, Bilbao Jaurequizar JI, Idoate Saralegui F (1995) Periportal adenitis secondary to abdominal tuberculosis. A CT study (in Spanish). Rev Esp Enferm Dig 87:259–261
Inaba T (1940) Amiloidosis general en lepra. La Lepra 11 (Suppl):89
Inal M, Aksungur E, Akgül E, Demirbas O, Oguz M, Erkocak E (2000) Biliary tuberculosis mimicking cholangiocarcinoma: treatment with metallic biliary endoprothesis. Am J Gastroenterol 95:1069–1071
Iwai T, Kida M, Kida Y, Shikama N, Shibuya A, Saigenji K (2006) Biliary tuberculosis causing cicatricial stenosis after oral anti-tuberculosis therapy. World J Gastroenterol 12:4914–4917
Jacobson G (1897) Sur les tubercles et caverns biliaires chez l'enfant. Rev Mens Mal Enfant 16:42
Jain VK, Mathur KC, Chadda VS, Lodha SK (1981) Tuberculous liver abscess. Indian J Chest Dis Allied Sci 23:97–99
Jain R, Sawhney S, Gupta RG, Acharya SK (1999) Sonographic appearances and percutaneous management of primary tuberculous liver abscess. J Clin Ultrasound 27:159–163
Jakab F, Gönci L (1974) Compression of the choledochus due to specific and unspecific lymph node enlargement (in German). Bruns Beitr Klein Chir 221:599–604
Jarmin R, Alwi RI, Shaharuddin S, Salleh KM, Gunn A (2004) Common bile duct perforation due to tuberculosis: a case report. Asian J Surg 27:342–344
Jenny H (1913) Über die Abkapselung von tuberkulösen Herden in der Leber des Menschen. Virchows Arch Pathol Anat Physiol 213:1–8
Jenss H, Gärtner HV, Malchow H (1981) Areactive generalized tuberculosis ("Landouzy sepsis") in immunosuppressive therapy (in German). Internist (Berl) 22:518–522
Joseph R, Nezelof C, Job JC (1959) La tubérculose macronodulaire du foie. Une observation avec revue de la littérature. Ann Pediatr 6:342–345
Ka MM, Mbengue M, Dangou JM, Pouye A, Toure-Fall AO, Leye A, Diop BM, Diop PM (2004) Portal and splenic veins thrombosis revealing a miliary tuberculosis of the liver (in French). Dakar Med 49:150–152
Kaklamanos M, Hardavella G, Trigidou R, Dionellis G, Paissios N, Koulouris N, Goritsas C (2011) Multi-organ failure with atypical liver granulomas following intravesical *Bacillus* Calmette-Guérin instillation. World J Hepatol 3:79–82
Kalla G, Purohit S, Vyas MC (2000) Histoid, a clinical variant of multibacillary leprosy: report from so called endemic areas. Int J Lepr 68:267–271
Kanagaraj A, Marthandam LR, Sriramakrishnan V, Rajesh A, Meenakumari P (2008) Tuberculous liver abscess. J Assoc Physicians India 56:647–648
Karpelowsky JS, Alexander AG, Peek SD, Millar AJ, Rode H (2008) Surgical complications of bacilli Calmette-Guérin (BCG) infection in HIV-infected children: time for a change in policy. S Afr Med J 98:801–804
Kaur C, Thami GP, Mohan H (2005) Lucio phenomenon and Lucio leprosy. Clin Exp Dermatol 30:525–527
Kaur L, Dogra S, De D, Saikia UN (2009) Histoid leprosy: a retrospective study of 40 cases from India. Br J Dermatol 160:305–310
Kaur P, Fishman JA, Misdraji J, Varma MC, Kotton CN (2011) Disseminated *Mycobacterium kansasii* infection with hepatic abscesses in a renal transplant recipient. Transpl Infect Dis 13:531–535
Kawamori Y, Matsui O, Kitagawa K, Kadoya M, Takashima T, Yamahana T (1992) Macronodular tuberculoma of the liver: CT and MR findings. AJR Am J Roentgenol 158:311–313
Kean BE, Childress ME (1942) A summary of 103 autopsies on leprosy patients on the Isthmus of Panama. Int J Lepr 10:51–59
Kemeny F, Karsenti P, Kemeny JL, Amouroux J, Paraf A (1981) Intra-hepatic tuberculous biliary caverns. A case report (in French). Arch Anat Cytol Pathol 29:246–248
Kenneth YY, Kok KYY, Samuel KS (1999) Tuberculosis of bile duct: a rare cause of obstructive jaundice. J Clin Gastroenterol 29:161–164
Kim JH, Langston AA, Gallis HA (1990) Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. Rev Infect Dis 12:583–590
Kimura T, Yonemaru M, Kawasiro T (2005) Four cases of tuberculous adenitis (in Japanese). Kansenshogaku Zasshi 79:402–406
Klatskin G, Yesner R (1950) Hepatic manifestations of sarcoidosis and other granulomatous diseases. Yale J Biol Med 23:207
Klepetko W, Laufer G, Grabenwöger F, Schwarz C, Kreuzer W (1986) Tuberculous aneurysms of the hepatic artery – a rare cause of hemobilia (in German). Chirurg 57:522–524
Knight HE (1895) A case of fatal jaundice in a child. QJM 7:373
Kohen MD, Altman KA (1973) Jaundice due to a rare cause: tuberculous lymphadenitis. Am J Gastroenterol 59:48–53
Kohli V, Kumar L, Kataria S (1996) Multiple hepatosplenic tuberculous abscesses in an eight-year-old boy. Pediatr Infect Dis J 15:178–179
Kok KY, Yapp SK (1999a) Tuberculosis of the bile duct: a rare cause of obstructive jaundice. J Clin Gastroenterol 29:161–164
Kok KYY, Yapp SKS (1999b) Isolated hepatic tuberculosis: report of five cases and review of the literature. J Hepatobiliary Pancreat Surg 6:195–198

Köksal D, Köksal AS, Köklü S, Çiçek B, Altparmak E, Sahin B (2006) Primary tuberculous liver abscess: a case report and review of the literature. South Med J 99:393–395

Korac M, Milosevic B, Lavadinovic L, Janjic A, Brmbolic B (2009) Disseminated BCG infection in patients with urinary bladder carcinoma (in Serbian). Med Pregl 62:592–595

Korn RJ, Kellow WF, Heller P, Chomet B, Zimmerman HJ (1959) Hepatic involvement in extrapulmonary tuberculosis: histologic and functional characteristics. Am J Med 27:60–71

Kotlar A (1894) Über die Pathogenese der sog. Gallengangstuberkel in der Leber des Menschen. Z Heilkde 15:110

Kramarsky B, Edmondson HA, Peters RL, Reynolds TB (1968) Lepromatous leprosy in reaction. A study of the liver and skin lesions. Arch Pathol 85:516–531

Kumar A, Corder CN (1979) Case 10–1979: liver involvement in leprosy. N Engl J Med 300:1217

Kumar V, Pandey D (2008) Isolated hepatosplenic tuberculosis. Hepatobiliary Pancreat Dis Int 7:328–330

Kumar R, Kapoor D, Singh J, Kumar N (2003) Isolated tuberculosis of the pancreas: a report of two cases and review of the literature. Trop Gastroenterol 24:76–78

Kurnik et al. (1983) http://www.ncbi.nlm.nih.gov/pubmed/6824016

Lafay JP, Fouet P (1983) Compressive tuberculous lymphadenitis of the common bile duct: spontaneous recovery by fistulization in the choledochus (in French). Gastroenterol Clin Biol 7:915–918

Lamm DL, Stigdill VD, Stogdill BJ, Crispen RG (1986) Complications of *bacillus* Calmette-Guérin immunotherapy in 1278 patients with bladder cancer. J Urol 135:272–274

Landa IE, Kravetskaia RM (1973) Diagnosis of tuberculous pericholedochal lymphadenitis (in Russian). Probl Tuberk 51:90

Landen S, Ballet T, Bollars P, Badic B, Herman D, Delugeau V (2010) Liver tuberculosis mistaken for malignancy. The role of needle biopsy. Acta Gastroenterol Belg 73:278–279

Landouzy L (1891) Les fièvres bacillaires prétuberculeuses à forme typhoide: Typhobacillose. Sem Méd 11:225–238

Laramore AP, Rubinas TC, Varnholt H (2009) *Mycobacterium avium* complex in the liver. Ann Hepatol 8:241

Latapi F, Zamora AC (1948) La lepra manchada de Lucio. Estudio inicial clinico e histopatologico (The "spotted" leprosy of Lucio. An introduction to its clinical and histological study). Int J Lepr 16:421–429

Lavenson RS, Karsner HT (1909) Periportal fibrosis of the liver in tuberculosis. Univ Pennsylvania Med Bull 22:167

Leader SA (1952) Tuberculosis of the liver and gallbladder with abscess formation: a review and case report. Ann Intern Med 37:594–606

Leborge J, Bouvier S, Dupas B, Deret C, Guiberteau B (1989) Pseudotumoral lymph node tuberculosis of the hepatic pedicle complicated by a choledocho-lymph node fistula. Ultrasound and x-ray computed tomography study. Apropos of a case (in French). J Chir (Paris) 126:419–420

Leder RA, Low VH (1995) Tuberculosis of the abdomen. Radiol Clin N Am 33:691

Lee SW, Wang CY, Lee BJ, Kuo CY, Kuo CL (2008) Hemophagocytic syndrome in miliary tuberculosis presenting with noncaseating granulomas in bone marrow and liver. J Formos Med Assoc 107:495–499

Leggat PO, Jones GP, Taylor PJ (1953) Tuberculous portal pyaemia with splenomegaly. Br J Tuberc Dis Chest 47:221–224

Leong BD, Chan KW, Ramu P, Kumar VM, Chuah JA (2011) Tuberculosis of gallbladder with candidiasis, a rare entity. Med J Malaysia 66:146–147

Levine C (1990) Primary macronodular hepatic tuberculosis: US and CT appearances. Gastrointest Radiol 15:307–309

Li HM, Zhao SY, He JX, Jiang ZF (2010) Clinical analysis of 18 children with disseminated Bacille Calmette-Guérin infection (in Chinese). Zhonghua Er Ke Za Zhi 48:65–68

Lichtenstein M (1912) Sind die Gallengangstuberkel in der Leber das Resultat einer Ausscheidungstuberkulose? Beitr Klein Tuberkul Spezfi Tuberkulose-Forsch 25:53–59

Lichtman SS (1949) Diseases of the liver, 2nd edn. Lea and Febiger, Philadelphia

Liebermeister G (1921) Tuberkulose: Ihre verschiedenen Erscheinungsformen und Stadien sowie ihre Bekämpfung. Springer, Berlin

Liew E, Sutherland T, Slavin J, Darby J (2011) Isolated periportal tuberculosis causing portal vein thrombosis. J Ultrasound Med 30:1599–1601

Listwan WJ, Roth DA, Tsung SH, Rose HD (1975) Disseminated *Mycobacterium kansasii* infection with pancytopenia and interstitial nephritis. Ann Intern Med 83:70–73

Liu TC, Qiu JS (1984) Pathological findings on peripheral nerves, lymph nodes, and visceral organs of leprosy. Int J Lepr Other Mycobact Dis 52:377–383

Lorentz FH (1913) Die Leber in ihrem Verhalten zur Tuberculose and Cirrhose. Zschr Tuberkul 20:232

Louis PCA (1825) Recherches anatomico-pathologiques sur la phthisie. Gabon et Cie, Paris

Lucio R, Alvarado I (1852) Opusculo sobre el mal de San Lazaro o elefanciasis de los griegos. M Murguia y Cia, Mexico, p 53

Magaña M, Fernandez-Diez J, Magaña ML (2008) Lucio's phenomenon is a necrotizing panvasculitis: mostly a medium-sized granulomatous arteritis. Am J Dermatopathol 30:555–560

Maglinte DD, Alvarez SZ, Ng AC, Lapena JL (1988) Patterns of calcifications and cholangiographic findings in hepatobiliary tuberculosis. Gastrointest Radiol 13:331–335

Maharaj B, Leary WP, Pudifin DJ (1987) A prospective study of hepatic tuberculosis in 41 black patients. QJM 63:517–522

Mahlberg MJ, Levis WR (2008) Lepromatous leprosy. Dermatol Online J 14:27

Malik M, Kurban L, Murray GI, Alkari B (2011) Isolated tuberculosis of the liver: a diagnostic challenge. BMJ Case Rep 15:2011

Manoj EM, Srigrishna R, Ragunathan MK (2012) Hepatic tuberculosis presenting with extreme hyperferritinemia masquerading as adult-onset Still's disease: a case report. J Med Case Rep 6:195

Mansfield RE (1969) Histoid leprosy. Arch Pathol 87:580–585

Martinon F, Aurousseau R (1976) Compression of retropancreatic common bile duct by tuberculous lymph nodes causing obstructive icterus (in French). J Chir (Paris) 112:145–152

Martin-Vivaldi Martinez R, Espinosa Aguilar MD, Nogueras Lopez F, Quintero Fuentes D et al (1996) Pseudotumorous hepatic tuberculosis: laparoscopic appearance (in Spanish). Gastroenterol Hepatol 19:456–458

Masaki T, Qu J, Cholewa-Waclaw J, Burr K, Raaum R, Rambukkana A (2013) Reprogramming adult Schwann cells to stem cell-like cells by leprosy bacilli promotes dissemination of infection. Cell 152:51–67

Mathieu D, Ladeb MF, Guigui B, Rousseau M, Vasile N (1986) Periportal tuberculous adenitis: CT features. Radiology 161:713–715

Mendiratta V, Jain A, Chander R, Khan A, Barara M (2011) A nine-year clinico-epidemiological study of histoid Hansen in India. J Infect Dev Ctries 5:128–131

Mercusot B, Arrivé L, Rotenberg L, Bouras T, de Sigalony JP, Hannoun L, Tubiana JM (1995) Imaging of hepatic tuberculoma (in French). J Radiol 76:277–279

Mert A, Ozaras R (2005) A terminological controversy: do disseminated and miliary tuberculosis mean the same? Respiration 72:113

Mert A, Bilir M, Tabak F, Ozaras R, Ozturk R, Senturk H, Aki H, Seyhan N, Karayel T, Aktuglu Y (2001) Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. Respirology 6:217–224

Mert A, Ozaras R, Tabak F, Ozturk R, Bilir M (2003) Localized hepatic tuberculosis. Eur J Intern Med 14:511–512

Mills JW, Ryan L, LaCourse R, North RJ (2001) Extensive *Mycobacterium* bovis BCG infection of liver parenchymal cells in immunocompromised mice. Infect Immun 69:3175–3180

Misch EA, Berrington WR, Vary JC, Hawn TR (2010) Leprosy and the human genome. Microbiol Mol Biol Rev 74:589–620

Mitlehner W, Dibmann W (1987) Pseudotumoröse Lebertuberkulose mit multiple Organabszessen. Dtsch Med Wochenschr 112:760–763

Mitsuda K, Ogawa M (1937) A study of 150 autopsies on cases of leprosy. Int J Lepr 5:53–60

Mittasch G (1920) Über Leberblutungen bei Lungentuberkulose. Virchows Arch 228:476–482

Miyamoto S, Furuse J, Maru Y, Tajiri H, Muto M, Yoshino M (2001) Duodenal tuberculosis with a choledochoduodenal fistula. J Gastroenterol Hepatol 16:235–238

Mojtahedzadeh M, Otoukesh S, Shahsafi MR, Tahbaz MO, Rahvari SK, Poorabdollah M et al (2012) Case report: portal hypertension secondary to isolated liver tuberculosis. Am J Trop Med Hyg 87:162–164

Moriwaki S (1959) An autopsy case of typhobacillosis. Acta Pathol Jpn 9(Suppl):923–925

Morris E (1930) Tuberculosis of the liver. Am Rev Tuberc 22:585–592

Moshella SL (1968) Primary diffuse lepromatous leprosy with erythema necroticans (Lucio phenomenon). Arch Dermatol 97:593–594

Moskovic E (1990) Macronodular hepatic tuberculosis in a child: computed tomographic appearances. Br J Radiol 63:656–658

Murata Y, Yamada I, Simiya Y, Shichijo Y, Suzuki Y (1996) Abdominal macronodular tuberculomas: MR findings. J Comput Assist Tomogr 20:643–646

Murphy TF, Gray GF (1980) Biliary tract obstruction due to tuberculous adenitis. Am J Med 68:452–454

Mustard RA, Mackenzie RL, Gray RG (1986) Percutaneous drainage of a tuberculous liver abscess. Can J Surg 29:449–450

Mutreja D, Nangia R, Mishra P (2010) Pseudotumoral hepatic tuberculosis with pericardial abscess. Indian J Pathol Microbiol 53:763–766

Nagai H, Shimizu S, Kawamoto H, Yamanoue M, Tsuchiya T, Yamamoto M (1989) A case of solitary tuberculosis of the liver. Jpn J Med 28:251–255

Nampoory MR, Halim MM, Sreedharan R, al-Sweih NA, Gupta RK, Constandi JN, Johny KV (1995) Liver abscess and disseminated intravascular coagulation in tuberculosis. Postgrad Med J 71:490–492

Nordmann M (1927) Der tuberkulöse Primärkomplex in der Leber. Zschr Tbk 47:193

Obama K, Kanai M, Taki Y, Nakamoto Y, Takabayashi A (2003) Tuberculous lymphadenitis as a cause of obstructive jaundice: report of a case. Surg Today 33:229–231

O'Brien (1954) http://www.ncbi.nlm.nih.gov/pubmed/13192197

Okada S (1954) Studies on tuberculoid visceral leprosy. Tuberculoid granulomata in the liver revealed by puncture biopsy. Int J Lepr 22:41–45

Oliva A, Duarte B, Jonasson O, Nadimpalli V (1990) The nodular form of local hepatic tuberculosis. A review. J Clin Gastroenterol 12:166–173

Orth J (1876) Über lokalisierte Tuberkulose der Leber. Virchows Arch 66:113

Pagel W, Woolf AL (1949) On fulminant tuberculous septicemia with leukopenia. Am Rev Tuberc 59:311–316

Pariente R, Etienne JP, Chretien J (1963) Study of 22 cases of tuberculosis of the liver demonstrated anatomically (etiologic, clinical, laparoscopic and histologic aspects) (in French). Sem Hop 39:2563–2570

Paris J, Ribet M, Gérard A, Druart R (1966) Choledochal and duodenal stenosis due to peritoneal tuberculosis (in French). Lille Med 11:563–566

Parkash O (2009) Classification of leprosy into multibacillary and paucibacillary groups: an analysis. FEMS Immunol Med Microbiol 55:1–5

Patel KM (1981) Granulomatous hepatitis due to *Mycobacterium scrofulaceum*: report of a case. Gastroenterology 81:156–158

Patino C, Fontes B, Poggetti RS, Mitteldorf C, Alvarenga C, Birolini D (2003) Bile duct-duodenal fistula caused by AIDS/HIV-associated tuberculosis. Rev Hosp Clin Fac Med Sao Paulo 58:223–226

Patnaik JK, Saha PK, Satpathy SK, Das BS, Bose TK (1989) Hepatic morphology in reactional states of leprosy. Int J Lepr Other Mycobact Dis 57:499–505

Päzolt HJ (1968) Compression of extrahepatic bile ducts by tuberculous lymph nodes (in German). Zentralbl Chir 93:1000–1004

Peltason F (1921) Über multiple Leberblutungen bei Miliartuberkulose. Virchows Arch Pathol Anat Physiol 230:230–259

Pereyra SB, Danielo CA, Ponssa GJ, Consigli JE, Papa MB, Ghirardi G (2007) Wade's histoid leprosy: three clinical presentations. Int J Dermatol 46:944–946

Peyré CG, Wakim M, Mateo R, Genyk Y, Singh G, Selby RR, Jabbour N (2004) Unusual cases of jaundice secondary to non-neoplastic bile duct obstruction. Am Surg 70:620–624

Piris A, Lobo AZ, Moschella SL (2010) Global dermatopathology: Hansen's disease – current concepts and challenges. J Cutan Pathol 37(Suppl 1):125–136

Pitzus F, Verme G (1960) So-called "primary" miliary tuberculosis of the liver. Observations on a clinical case (in Italian). Arch Ital Mal Appar Dig 27:548–560

Polycarpou A, Walker SL, Lockwood DN (2013) New findings in the pathogenesis of leprosy and implications for the management of leprosy. Curr Opin Infect Dis 26:413–419

Pombo F, Soler R, Martin R, Castro JM (1990) Periportal-peripancreatic tuberculous adenitis. US and CT findings. Röfo 152:142–146

Poon RT, Lo CM, Fan ST (2001) Diagnosis and management of biliary obstruction due to periportal tuberculous adenitis. Hepatogastroenterology 48:1585–1587

Powell CS, Swan LL (1955) Pathologic changes observed in 50 consecutive necropsies. Am J Pathol 31:1131–1147

Praharaj KC, Praharaj SC, Nanda BK, Rao PG (1979) Hepatic involvement in childhood tuberculosis. Indian Pediatr 16:497–502

Prasad A, Pandey KK (2001) Tuberculous biliary strictures: uncommon cause of obstructive jaundice. Australas Radiol 45:365–368

Prochazka M, Vyhnanek F, Vorreith V, Jirasek M (1986) Bleeding into solitary hepatic tuberculoma. Report of a case treated by resection. Acta Chir Scand 152:73–75

Proudfoot AT, Akhtar AJ, Douglas AC, Horne NW (1969) Miliary tuberculosis in adults. Br Med J 2:273–276

Purhoit VP, Verma R (1982) Tuberculous liver abscess. J Postgrad Med 28:221–222

Purl AS, Nayyan AK, Vij JC (1994) Hepatic tuberculosis. Indian J Tub 41:131–133

Queralt CB, Cruz JM, Comet V, Almajano C, Val-Carreres C (1992) Obstructive jaundice due to peripancreatic tuberculous adenitis (in Spanish). Rev Esp Inferm Dig 82:201–202

Rab SM, Beg MZ (1977) Tuberculous liver abscess. Br J Clin Pract 31:157–158

Rabello FE (1937) A clinic-epidemiological classification of the forms of leprosy. Int J Lepr 5:343–356

Rahmatulla RH, al-Mofleh IA, al-Rashed RS, al-Hedaithy MA, Mayet IY (2001) Tuberculous liver abscess: a case report and review of literature. Eur J Gastroenterol Hepatol 13:437–440

Rambukkana A (2001) Molecular basis for the peripheral nerve predilection of *Mycobacterium* leprae. Curr Opin Microbiol 4:21–27

Ratanaparee S, Pausawadi A (1991) Tuberculosis of the common bile duct. HPB Surg 3:205–208

Rauber G, Sommelet J, Larcan A, Fourrie R (1956) Caverne hépatique géante. Difficultés d'un diagnostic et incidences medico-chirurgicales. Rev Int Hepatol 6:279–293

Reed DH, Nash AF, Valabhji P (1990) Radiological diagnosis and management of a solitary tuberculous hepatic abscess. Br J Radiol 63:902–904

Rémond A, Capron JP, Henry X, Piétri J, Trinez G (1976) Angiographic findings in primary miliary hepatic tuberculosis (in French). J Radiol Electrol Med Nucl 57:7–11

Rennen K (1922) Über Sepsis tuberculosa gravissima bei einem Fall von Polycythaemia. Beitr Klein Tuberk 53:197

Ricci PD, Guaiana G, Malfatti G, Mosaico A (2000) A rare case of cholostasis from tuberculotic infiltration of Vater's ampulla (in Italian). Minerva Gastroenterol Dietol 46:57–59

Rich AR (1944) The pathogenesis of tuberculosis Charles C Thomas, Springfield IL

Ridley DS, Jopling WH (1966) Classification of leprosy according to immunity. A five-group system. Int J Lepr Other Mycobact Dis 34:255–273

Riecke GH (1928) Über einen Fall von Lepra tuberosa. Beitr Pathol Anat Allg Pathol 80:201

Ringleb D (1953) Über Retothelknötechen der Leber bei Tuberkulösen. Arch Pathol Anat 324:357

Rodin and Hnatko (1963) http://www.ncbi.nlm.nih.gov/pubmed/14060176

Rodrigues LC, Lockwood DNJ (2011) Leprosy now: epidemiology, progress, challenges, and research gaps. Lancet Infect Dis 11:464–470

Rodriguez JN (1969) The histoid leproma: its clinical characteristics and significance. Int J Lepr 37:1–21

Rolleston HD, McNee JW (1929) Diseases of the liver, gall bladder and bile ducts. MacMillan and Co., London

Rome RR (1904) Excision of tuberculous mass from liver. Ann Surg 39:98–99

Rosenkranz K, Howard LD (1936) Tuberculosis of the liver. Arch Pathol 22:743–754
Rosin RD (1978) Tuberculoma of the liver. Tubercle 59:47–54
Ruhl KM, Krones CJ, Hermanns B, Schumpelick V (2003) Tuberculosis of the gall bladder (in German). Chirurg 74:478–481
Ruiz A, Mederos L, Capo V (2002) Isolation of *Mycobacterium avium*-intracellular from a hepatic biopsy (in Spanish). Rev Cubana Med Trop 54:161–163
Saluja SS, Ray S, Pal S, Kukeraja M, Srivastava DN, Sahni P, Chattopadhyay TK (2007) Hepatobiliary and pancreatic tuberculosis: a two decade experience. BMC Surg 7:10
Sandberg IR, Sundberg L, Warfvinge LE (1957) Tuberculoma hepatis. Nord Med 57:558–559
Saphir O (1929) Changes in the liver and in the pancreas in chronic pulmonary tuberculosis. With special reference to the islets of Langerhans. Arch Pathol 7:1026–1041
Saul A, Novales J (1983) Lucio-Latapi leprosy and the Lucio phenomenon (in French). Acta Leprol 1:115–132
Savioz D, Nicod L, Mentha G, Mirescu D, Morel P, Rohner A (1993) Resurgence of a forgotten pathology: pyelephlebitis caused by tuberculous adenopathies (in French). Gastroenterol Clin Biol 17:747–749
Schinnerling W (1966) On the diagnosis of miliary tuberculosis through liver puncture before and after tuberculostatic therapy (in German). Frankf Z Pathol 75:1–13
Schmid MA (1957) X-ray differential diagnosis of calculi of the common bile duct, with a study of isolated tuberculous lymph nodes of the Ligamentum hepatoduodenale (in German). Bruns Beitr Klein Chir 194:426–438
Scollard DM, Adams LB, Gillis TP, Krähenbuhl JL, Truman RW, Williams DL (2006) The continuing challenges of leprosy. Clin Microbiol Rev 19:338–381
Seghal VN, Srivastava G (1987) Status of histoid leprosy – a clinical, bacteriological, histopathological and immunological appraisal. J Dermatol (Tokyo) 14:38–42
Seghal VN, Srivastava G (1988) Histoid leprosy – a prospective diagnostic study in 38 patients. Dermatologica 177:212–217
Seghal VN, Srivastava G, Beohar PC (1987) Histoid leprosy – a histopathological reappraisal. Acta Leprol 105:125–131
Seghal VN, Srivastava G, Singh N (2009) Histoid leprosy: histopathological connotations' relevance in contemporary context. Am J Dermatopathol 31:268–271
Sen M, Turan M, Karadayi K, Ugurlu L, Elagoz S (2004) Isolated hepatic tuberculous pseudometastasis co-existent with adenocarcinoma of the stomach; report of a case. Acta Chir Belg 104:601–603
Sergent E (1895) Tubercules et cavernes biliaires. Thesis, Paris
Shah P, Ramakantan R, Deshmukh H (1991) Obstructive jaundice – an unusual complication of duodenal tuberculosis: treatment with transhepatic balloon dilatation. Indian J Gastroenterol 10:62–63
Shan YS, Sy ED, Lin PW (2000) Surgical resection of isolated pancreatic tuberculosis presenting as obstructive jaundice. Pancreas 21:100–101
Sharma SK, Shamim SQ, Bannerjee CK, Sharma BK (1981) Disseminated tuberculosis presenting as massive hepatosplenomegaly and hepatic failure. Am J Gastroenterol 76:153–156
Sharma SK, Mohan A, Sharma A, Mitra DK (2005) Miliary tuberculosis: new insights into an old disease. Lancet Infect Dis 5:415–430
Sheen-Chen SM, Chen MC, Hu TH, Eng HL, Chen WJ, Cheng YF, Lee TY (2001) Computed tomography and angiography in hepatic tuberculosis mimicking liver tumor. Int J Tuberc Lung Dis 5:876–878
Shuttleworth JS, Ross H (1956) Secondary amyloidosis in leprosy. Ann Intern Med 45:23–38
Sidhu DS, Singh M, Jindal RK, Gupta S, Simpy R (2007) Isolated cystic duct lymph node tuberculosis. J Indian Med Assoc 105:460
Siegmund H (1939) Areaktive generalisierte Tuberkulose. Beitr Pathol Anat Allg Pathol 5:431–450
Siemann M, Rabenhorst G, Bramann A, Renk C (1999) A case of cryptic miliary tuberculosis mimicking cholecystitis with sepsis. Infection 27:44–45
Sigg E (1901) Über Konglomerattuberkel in der Leber. Thesis, Zurich
Silbergleit H (1905) Beiträge zur Entstehung der akuten allgemeinen Miliartuberkulose. Virchows Arch Pathol Anat Physiol Klin Med 179:283–337
Simbli MA, Niaz FA, Al-Wakeel JS (2012) Encapsulating peritoneal sclerosis in a peritoneal dialysis patient presenting with complicated *Mycobacterium fortuitum* peritonitis. Saudi J Kidney Dis Transpl 23:635–641
Singh B, Moodley J, Baitang S, Chetty R (2002) Isolated pancreatic tuberculosis and obstructive jaundice. S Afr Med J 92:357–359
Singh N, Bhatia A, Lakra A, Arora VK, Bhattacharya SN (2006) Comparative cytomorphology of skin, lymph node, liver and bone marrow in patients with lepromatous leprosy. Cytopathology 17:257–261
Singh B, Saxena PD, Kumar V, Yadav D, Rajpoot P (2011) Tubercular liver abscess in immune-competent patients. J Assoc Physicians India 59:523–524
Siwach SB, Srivastava SC (1978) Tuberculous abscess of the liver. Indian J Chest Dis Allied Sci 20:145–147
Small MJ (1974) Tuberculosis of the liver: scan appearance before and after successful treatment. J Nucl Med 15:135–136
Sood VK, Grueber HLE (1969) Correlation of histopathologic changes in the liver and bone marrow of leprosy patients. Int J Lepr 37:28–39
Spiegel CT, Tuazon CU (1984) Tuberculous liver abscess. Tubercle 65:127–131
Sridhar S, Pollock K, Lalvani A (2011) Redefining latent tuberculosis. Future Microbiol 6:1021–1035
Stanley JH, Yantis PL, Marsh WH (1984) Periportal tuberculous adenitis: a rare cause of obstructive jaundice. Gastrointest Radiol 9:227–229

Stemmerman M (1941) Bile duct tuberculosis. Q Bull Sea View Hosp 6:316
Stenius-Aarniala B, Tukiainen P (1979) Miliary tuberculosis. Acta Med Scand 206:417–422
Stevens and Little (1987) http://www.ncbi.nlm.nih.gov/pubmed/3675397
Storch E (1897) Über den anatomischen Befund bei einem für Deutschland endogenen Fall von lepra tuberosa. Zugleich ein Beitrag zur Frage nach den Beziehungen zwischen Aussatz und Tuberkulose. Virchows Arch 148:389
Tajiri T, Tate G, Makino M, Akita H, Omatsu M, Enoswa T, Hamatani S, Masunaga A et al (2011) Autopsy cases of miliary tuberculosis: clinicopathologic features including background factors. J Nippon Med Sch 78:305–311
Tan SY, Graham C (2008) Armauer Hansen (1841–1912): discoverer of the cause of leprosy. Singapore Med J 49:520–521
Tan TC, Cheung AY, Wan WY, Chen TC (1997) Tuberculoma of the liver presenting as a hyperechoic mass on ultrasound. Br J Radiol 70:1293–1295
Taneja K, Khanna NV, Shiv VK, Pandhi RK, Bhargava SK (1990) Hepatic ultrasonography in patients with lepromatous leprosy. Indian J Lepr 62:443–447
Terry RB, Gunnar RM (1957) Primary miliary tuberculosis of the liver. J Am Med Assoc 164:150–157
Tilden IL (1945) Lepra lepromatosa como enfermedad reticuloendotelial. Aspectors histopatologicos. Am J Clin Pathol 15:165
Todd JL, Lakey J, Howell D, Reidy M, Zaas D (2007) Portal hypertension and granulomatous liver disease in a lung transplant recipient due to disseminated atypical mycobacterial infection. Am J Transplant 7:1300–1303
Traissac M, Martin C, Battin JJ (1961) A case of primary miliary tuberculosis of the liver (in French). Arch Fr Pediatr 18:1240–1244
Trevenen CL, Pagtakhan RD (1982) Disseminated tuberculoid lesions in infants following BCG vaccination. Can Med Assoc J 127:502–504
Tritou I, Prassopoulos P, Daskalogiannaki M, Charoulakis N, Papakonstantinou O, Gourtsoyiannis N (2000) Miliary hepatic tuberculosis not associated with splenic or lung involvement. A case report. Acta Radiol 41:479–481
Tufariello JM, Chan J, Flynn JL (2003) Latent tuberculosis: mechanisms of host and *bacillus* that contribute to persistent infection. Lancet Infect Dis 3:557–590
Turk JL, Waters MRF (1969) Cell-mediated immunity in patients with leprosy. Lancet 2:243–246
Ullom JT (1909) The liver in tuberculosis. Am J Med Sci 137:694–698
Valeja R, Pal S, Mann MS, Hadke NS, Bhardwai M (1999) Isolated common bile duct tuberculosis. Indian J Gastroenterol 18:125–126
Varela M, Fernandez J, Navasa M, Bruix J (2003) Pseudotumoral hepatic tuberculosis. J Hepatol 39:654
Vargas-Ocampo F (2007) Diffuse leprosy of Lucio and Latapi: a histologic study. Lepr Rev 78:248–260
Venkatesh SK, Tan LK, Siew EP, Putti TC (2005) Macronodular hepatic tuberculosis associated with portal vein thrombosis and portal hypertension. Australas Radiol 49:322–324
Verghese A, Job CK (1965) Correlation of liver function with the pathology of the liver in leprosy. Int J Lepr 33:342–348
Von Bergmann R (1897) Die Lepra. Dtsch Zschr Chir 106:55
Von Knorre G (1950) Miliary tuberculosis with clinical aspect of panmyelopathy, and its relation to Landouzy's typhobacillosis (in German). Beitr Klein Tuberk Spezif Tuberkuloseforsch 103:340–343
Voorend CG, Post EB (2013) A systematic review of the epidemiological data of erythema nodosum leprosum, a type 2 leprosy reaction. PLoS Negl Trop Dis 7:e2440
Wade HW (1949) The Lucio and lazarine forms of leprosy. Int J Lepr 17:95–102
Wade HW (1963) The histoid variety of lepromatous leprosy. Int J Lepr 31:129–143
Walsh DS, Portaels F, Meyers WM (2010) Recent advances in leprosy and Buruli ulcer (*Mycobacterium* ulcerans infection). Curr Opin Infect Dis 23:445–455
Wee A, Nilsson B, Wang TL, Yap I, Siew PY (1995) Tuberculous pseudotumor causing biliary obstruction. Report of a case with diagnosis by fine needle aspiration biopsy and bile cytology. Acta Cytol 39: 559–562
Wegerle O (1913) Subakute Leberatrophie mit knotiger Hyperplasia auf tuberkulöser Grundlage und über akute Leberatrophie im Kindesalter überhaupt. Bergmann Verlag, Wiesbaden
Wei YF, Chang CY, Chang SC (2012) Tuberculosis manifesting as an invasive pulmonary mass and liver nodules mimicking malignancy with metastases. QJM 105:203–204
Weiss ES, Klein WM, Yeo CJ (2005) Peripancreatic tuberculosis mimicking pancreatic neoplasia. J Gastrointest Surg 9:254–262
Wilde CC, Kueh YK (1991) Case report: tuberculous hepatic and splenic abscess. Clin Radiol 43:215–216
Wynne ET (1890) On the distribution of the leprosy *bacillus*. Lancet 135:14
Xia F, Poon RT, Wang SG, Bie P, Huang XQ, Dong JH (2003) Tuberculosis of pancreas and peripancreatic lymph nodes in immunocompetent patients: experience from China. World J Gastroenterol 9:1361–1364
Xing X, Li H, Liu WG (2005) Hepatic segmentectomy for treatment of hepatic tuberculous pseudotumor. Hepatobiliary Pancreat Dis Int 4:565–568
Yeh TS, Chen NH, Jan YY, Hwang TL, Jeng LB, Chen MF (1999) Obstructive jaundice caused by biliary tuberculosis: spectrum of the diagnosis and management. Gastrointest Endosc 50:105–108

Yew WW, Leung CC (2008) Update in tuberculosis 2007. Am J Respir Crit Care Med 177:479–485

Yu RS, Zhang SZ, Wu JJ, Li RF (2004) Imaging diagnosis of 12 patients with hepatic tuberculosis. World J Gastroenterol 10:1639–1642

Zainal Muttakin AR, Tan AM (2006) *Mycobacterium fortuitum* catheter-related sepsis in acute leukaemia. Singapore Med J 47:543–545

Zawar PB, Holla VV, Patil SM, Zawar MP, Chawhan RN (1983) Bacillaemia in lepra reaction: its correlation with liver pathology. Lepr India 55:570–575

Zehden G (1897) Über Tuberkulose der Leber. Zentralbl. f. allgem. Pathol Anat 8:468

Zhang Y (2004) Persistent and dormant tubercle bacilli and latent tuberculosis. Front Biosci 9:1136–1156

Zipser RD, Rau JE, Ricketts RR, Bevans LC (1976) Tuberculous pseudotumors of the liver. Am J Med 61:946–951

Tumor-Like Lesions of the Hepatobiliary Tract Caused by Actinomycosis, Nocardiosis, and Botryomycosis

128

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_128

Abstract

An invasive and aggressive hepatic infection of the hepatobiliary tract that can mimic malignancy is actinomycosis, caused by *Actinomyces* species. This severe bacterial infection can present in the form of several and distinct clinico-pathological phenotypes. The most common form is primary and secondary abscess-forming hepatic actinomycosis with solitary, multiple, or fistulating abscesses. Similar to other organs involved in this infection, hepatic abscesses may contain yellow bacterial colonies called "sulfur granules." *Actinomyces* infection of the liver can also cause mass-forming lesions and actinomycomas. The latter can resemble cholangiocarcinomas, because they sometimes occupy the hilar region of the liver. Chronic actinomycosis of the liver may result in a marked inflammatory reaction with granulation tissue and fibrosis, a lesion termed actinomycotic inflammatory pseudotumor.

Hepatobiliary Actinomycosis

Introduction

Actinomycosis (first described in 1878 by Israel) is an acute to chronic infectious disease characterized by abscess formation, invasiveness mimicking malignancy, draining sinuses, and subsequent fibrosis/scarring (review: Smego and Foglia 1998). It is caused by several species of the genus *Actinomyces*, encompassing a taxonomically heterogeneous collection of anaerobic and aerotolerant, nonspore-forming, nonacid-fast, Gram-positive rod-shaped organisms. Actinomycosis of the hepatobiliary tract is an important differential diagnostic issue in the setting of liver tumors, because this infection is known as the "great imitator" owing to its invasive features and its remarkably varied clinical presentation. Three main clinical types of actinomycosis are recognized, i.e., cervicofacial (the most common), thoracic, and abdominopelvic, hepatobiliary manifestations almost always occurring in conjunction with the abdominopelvic form. Actinomycosis causes a destructive inflammatory process with a sometimes impressive induration of the diffusely involved soft tissues (the so-called wood-like phlegmonous induration, the "ligneous phlegmon"). In chronic forms, the diagnosis may be difficult and thus delayed, sometimes with delays of months to years from onset of symptoms and signs to correct diagnosis. As specified in a later paragraph, the clinical entity of actinomycosis can be caused by other bacteria, specifically *Propionibacterium propionicum* (formerly, *Arachnia propionica*). In contrast, infections caused by *Nocardia* species do not closely mimic the typical presentation of actinomycosis.

Microbiology

Actinomyces is a bacterial genus of anaerobic to microaerophilic, Gram-positive non-motile microorganisms that do not form endospores. While individual *Actinomyces* bacteria are rod-shaped, their colonies form fungus-like branched networks of filaments that resemble fungal hyphae. Individual rods are straight or slightly bent, with a thickness of 0.2–0.3 μm. Taxonomically, *Actinomyces* belongs to the family *Actinomycetaceae*. This family also includes the genera *Actinobaculum*, *Arachnia*, *Arcanobacterium*, *Mobiluncus*, and *Varibaculum*. Recently, molecular taxonomy has added much to aid in the identification and classification of *Actinomyces*-like organisms, the recognition of novel species, and the elucidation of clinical phenotype-genospecies relationships (Goodfellow et al. 1999; Clarridge and Zhang 2002; Hall et al. 2003). Of all the known species and culture isolates not yet allocated to species, less than ten preferentially cause disease in humans, including *A. israelii*, *A. gerencseriae*, *A. naeslundii*, *A. odontolyticus*, *A. viscosus*, *A. massiliensis*, *A. meyeri*, and *A. gerencseriae* (Schaal and Lee 1992; Smego and Foglia 1998). However, *A. israelii* and *gerencseriae* remain the principal causative agents of actinomycosis (review: Hall 2008). *Actinomyces israelii* is an organism typically found in soil and in decaying organic matter including wet hay and straw, where a

microaerophilic environment prevails. The germ is also a commensal and normal inhabitant of the oropharynx. Apart from the oral cavity, this bacterium is also a member of the natural genital tract flora in mammals. *A. israelii* is common in women with intrauterine devices, and in fact 85 % of cases of pelvic actinomycosis, a rare infection, are in women with IUDs. A distinct partner of *Actinomyces*, *Actinobacillus actinomycetemcomitans* (the Latin adjective meaning "accompanying *Actinomyces*," the bacterium often accompanying *Actinomyces israelii*; Zambon 1985), now assigned to a novel genus name, *Aggregatibacter* (Norskov-Lauritsen and Kilian 2006), was first isolated from a cervicofacial actinomycotic lesion in 1912 and initially termed *Bacterium actinomycetemcomitans*. In 1921, the organism was referred to as *Bacterium comitans* by Lieske and finally named *Actinobacillus actinomycetemcomitans* in 1929. In a more recent study analyzing genotype diversity of *Actinomyces* species, *Actinomyces israelii* was in fact the only *Actinomyces* species co-isolated with *Aggregatibacter actinomycetemcomitans* (Clarridge and Zhang 2002). It is strongly associated with localized aggressive periodontitis (LAP) and adult periodontitis and is the causative agent for some severe systemic infections (Fives-Taylor et al. 2000). *Actinomyces* species associated with mucosal and dental surfaces are members of complex biofilms (Yeung 1999). Biofilms containing *Actinomyces* preferentially develop on surfaces with specific physical properties, such as teeth or, for *Actinomyces israelii*, intrauterine devices/IUDs. In the oral cavity, and specifically in dental plaques and the parodontal space, *Actinomyces* species exist in close association with other microorganisms, often in mutual dependence and as members of complex biofilms (review, Hall 2008). The oral biofilm is a complex microbial community comprising more than 700 bacterial species belonging to 11 divisions of phyla of which, however, about 50 % are known only by 16SrRNA gene sequences (so-called phylotypes; Siquera and Roças 2005). While *A. odontolyticus* dominates at the tongue surface, *A. naeslundii* genospecies 1 and 2 colonize plaque and buccal surfaces but with different patterns (Hallberg et al. 1998; Mager et al. 2003). In this biotope, they attach to tissue surfaces by means of fimbriae.

Actinomycosis of the Hepatobiliary Tract

Actinomycosis induces a whole spectrum of clinico-pathologic conditions in the liver and biliary tract (Table 1).

Actinomycosis of the Liver Proper

Several early reports have documented liver involvement in actinomycosis, which makes part of the abdominopelvic form out of four known clinical forms of actinomycosis. In fact, the liver was found to be involved in the first human cases of actinomycosis (Israel 1878). It is of interest to note that, only shortly after Israel's report, relatively numerous cases of hepatic actinomycosis were reported toward the end of the nineteenth century. Hepatic lesions are estimated to occur in about 15 % of cases of abdominal actinomycotic infections and in 5–20 % of all cases of actinomycosis. The liver is frequently reached via spread from abdominal infection, e.g., subsequent to appendiceal actinomycosis, colonic diverticular disease (Joshi et al. 2010), or uterine actinomycosis caused by long-standing intrauterine anticonceptive devices (Ramirez Sanchez et al. 1997; Tamsel et al. 2004), but apparently, primary hepatic actinomycosis in the absence of such an infection elsewhere has also been described (Meade 1980; Hisaoka et al. 1991; Lai et al. 2004). Hepatic actinomycosis has been

Table 1 Clinico-pathologic forms of hepatobiliary actinomycosis

Actinomycotic cholecystitis and pericholecystitis
Cystic stump actinomycosis
Common bile duct actinomycosis
Primary and secondary hepatic abscess-forming actinomycosis
Solid or tumorous/pseudotumorous actinomycosis
Actinomycotic inflammatory pseudotumor

suspected to have its starting point in periodontitis (Uehara et al. 2010). Hepatic actinomycosis very uncommonly occurs in the pediatric age group, where it may mimic a wide variety of diseases (Rabusin et al. 1996; Lin et al. 2001; Buyukavci et al. 2004). It was reported that only 4 out of 56 hepatic actinomycosis were pediatric cases (Sharma et al. 2002). Actinomycosis of the pediatric liver has been observed following other infections, e.g., varicella (Guven et al. 2008). Primary hepatic actinomycosis is caused by *A. israelii* and other common species causing actinomycosis, but unusual species such as *A. odontolyticus* have also been found to cause hepatic abscess (Chao et al. 2011).

Selected References Zemann 1883; Heller 1884; Grill 1895; Barth 1890; Baumgarten 1890; Taylor 1891; Koch 1894; Leith 1894; Grill 1895; Habel 1896; Abée 1897; Isemer 1878; Poncet and Bernard 1898; Litten 1900; Yamada et al. 1971; Mir et al. 1978; Chandarlapaty et al. 1975; Golematis et al. 1976; Mir et al. 1978; Miyamoto and Fang 1993; Tamsel et al. 2004; Schmeding et al. 2005; Chen et al. 2006; Braun et al. 2009; Cetinkaya et al. 2010; Kanellopoulou et al. 2010; Lall et al. 2010; Wang et al. 2012.

In the meta-analysis on 13 published cases of pseudotumoral hepatic actinomycosis by Lai and coworkers (Lai et al. 2004), the mean age of patients at presentation was 43 years, with a male preponderance. The most common presenting manifestations were fever, abdominal pain, and weight loss. Hepatomegaly was present in 38 %. Larger lesions may mimic liver tumors (Lange et al. 2009), and multiple lesions simulate hepatic metastatic disease (Kanellopoulou et al. 2010). The lesions were solitary in three and multiple in ten cases, with bilobar involvement in seven. Extension into the gallbladder or the common bile duct, and/or to surrounding organs, was a common finding. Due to the highly invasive features of actinomycosis, the process may fistulate through the abdominal wall (Saad and Moorman 2005), can be associated with, or cause, right-sided pleural empyema (Kocabay et al. 2006), and may penetrate through the diaphragm to invade the lung (Kasano et al. 1996; Islam et al. 2005). On CT images, hepatic actinomycosis presents as solitary or coalescing hypodense lesions (Boucenna and Arrivé 1999; Lakshmana Kumar et al. 2005), and MRI images revealed irregularly shaped, inhomogeneous, and hypointense lesions (Lange et al. 2009). The rather aggressive lesions may communicate among others and develop fistulation, also detectable in CT scans (Roesler and Wills 1986). Angioinvasive actinomycosis can induce portal vein occlusion (Cheng et al. 1989) and like this clinically resemble an aggressive cancer. Clinico-pathologically, actinomycosis of the liver proper can be divided into several phenotypes (Table 2).

Table 2 Clinico-pathologic phenotypes of actinomycosis occurring in the liver substance

Primary and secondary abscess-forming hepatic actinomycosis
Solitary abscess
Multiple abscesses
Fistulating abscesses
Solid/mass-forming hepatic actinomycosis (actinomycoma)
Actinomycotic inflammatory pseudotumor of the liver

Primary and Secondary Abscess-Forming Hepatic Actinomycosis

Actinomycosis of the liver substance proper can present as a solitary abscess or as multiple abscesses in up to half of the patients. Actinomycotic abscesses of the liver are found to be male predominant (70–97 %) with 30–50 years as the most common age group (Miyamoto and Fang 1993; Sugano et al. 1997; Sharma et al. 2002). The imaging presentation is that of space-occupying lesions (Meade 1980; Jacobs et al. 1981; Roesler and Wills 1986; Felekouras et al. 2004).

Selected References Brewer and Allen 1980; Ruutu et al. 1982; Jonas et al. 1987; Sheth et al. 1987; Bhatt et al. 1990; Hisaoka et al. 1991; Miyamoto and Fang 1993; Sugano et al. 1997; Al-Khuwaitir et al. 2000; Tambay et al. 2001; Christodoulou et al. 2004 (with review); Jermini

et al. 2004; Saad and Moorman 2005; Chen et al. 2006; Wong et al. 2006.

Solid/Mass-Forming Actinomycosis of the Liver (Hepatic Actinomycoma)

Hepatic actinomycosis can cause large hilar and/or intrahepatic tumor-like lesions mimicking cholangiocarcinoma and other liver malignancies and termed mass-forming actinomycosis, solid actinomycosis, actinomycoma, or actinomycosis with pseudocancerous features. One particularly detailed report summarized here as a typical example refers to a 42-year-old patient having a solid space-occupying lesion in the right liver lobe. Due to suspected cholangiocarcinoma, the mass was resected. The liver specimen showed a huge tumor-like mass with a nodularly structured periphery and a yellowish cut surface. The lesion had extended beyond the organ's limits and had infiltrated the diaphragm and the abdominal wall. The histology was typical for actinomycosis, most of the mass being necrotic tissue and abscesses. In another patient, isolated actinomycosis of the liver also involving large bile ducts was manifest at necropsy in the form of firm and yellowish tumoral nodes, of the size of duck's eggs. The cut surface disclosed several yellow foci. The process had invaded the liver substance and followed the intrahepatic periductal tissue, including here a nodular, firm sheath having caused biliary stenosis (Schmeding et al. 2005).

Selected References Zehle 1906; Diehl 1911; Fleischer and Kühn 1973; Lamoureux et al. 1984; Sondag et al. 1989; Vargas et al. 1992; Berthet et al. 1994; Kasano et al. 1996; Boucenna and Arrivé 1999; Lin et al. 2001; Campeanu et al. 2004; Lai et al. 2004; Schmeding et al. 2005; Yamashita et al. 2007; Ciria-Bru et al. 2008; Braun et al. 2009; Wayne et al. 2011.

Actinomycotic Inflammatory Pseudotumor of the Liver

Cases of hepatobiliary inflammatory pseudotumor caused by *Actinomyces* have been reported, sometimes presenting as a mass of more than 10 cm diameter and again mimicking liver malignancy (Kim et al. 2007). Histologically, there is an overlap between the tumor-like lesions described in the previous paragraph and actinomycotic inflammatory pseudotumors; hence, they might be lumped together. In a meta-analysis of 13 published cases of pseudotumoral hepatic actinomycosis (Lai et al. 2004), the average age of patients at diagnosis was 43 years, with a male preponderance. The most common presenting manifestations were fever, abdominal pain, and weight loss. Hepatomegaly was present in 38 %. The lesions were solitary in three and multiple in ten cases, with bilobar involvement in seven. Extension into the gallbladder or the common bile duct, and/or to surrounding organs, was a common finding. In one instance, a mixed infection was found in the lesion, i.e., *Actinomyces* associated with *Bacteroides caccae* (White et al. 1997).

Selected References Chandarlapaty et al. 1975; Cedermark et al. 1982; Meade 1980; Ruutu et al. 1982; Mongiardo et al. 1986; Jonas et al. 1987; Shurbaji et al. 1987; Detre et al. 1988; Cheng et al. 1989; Kazmi and Rab 1989; Logan et al. 1989; Bhatt et al. 1990; Berthet and Assadourian 1992; Nazarian et al. 1994; Shiau et al. 1995; Rabusin et al. 1996; White et al. 1997; Sugano et al. 1997; Harsch et al. 2001; Barajas Martinez et al. 2002; Sharma et al. 2002; Campeanu et al. 2004; Christodoulou et al. 2004; Lai et al. 2004; Tamsel et al. 2004.

Macroscopic Pathology

The morphology of hepatic actinomycosis is highly variable. Already Israel described multiple miliary-like foci in the liver substance (Israel 1878). But the solitary or multiple necroinflammatory lesions produced in hepatic actinomycosis may grow to impressive size, sometimes via formation of conglomerate masses, as outlined in the previous paragraph. Macroscopically, small to large nodular lesions induced by *Actinomyces* infection are yellowish-gray to

hemorrhagic and friable masses, which sometimes present as a typical abscess. The cut surface may bulge and reveal a variegated texture, with friable masses of necrotic and massively infiltrated tissue. Langhans noted the interesting finding that large actinomycomas may show, on their cut surface, a microalveolar-like texture in some way reminiscent of alveolar echinococcosis or of lung tissue, with numerous densely packed abscesses (Langhans 1888). This honeycomb-like structure of the cut surface has been confirmed in a subset of cases (Diehl 1911; Tiling 1912; Roth 1921). It was also noted that the abscess cavities may be arranged in a particular way, forming branching structures (Langhans 1888). When performing necropsies of patients with liver actinomycosis, Langhans noted that notwithstanding hot ambient temperature, autolysis was unusually delayed, what he suspected to be caused by an "antiseptic" action of *Actinomyces* (Langhans 1888). This suggestion is of some actuality insofar as members of *Actinomycetales* are now known to produce an array of antibiotic agents. Large actinomycomas may be associated with smaller lesions ("satellites") in their vicinity (Diehl 1911). In case of portal vein invasion, hematogenous spread starting from infected and puriform venous thrombi results in disseminated liver abscesses (Kramer 1911; Diehl 1911). Involvement of the portal had previously been documented at necropsy. One patient described by Israel (1878) showed actinomycotic pus flowing off the opened portal vein which also contained infectious thrombi. The shape of actinomycotic abscesses and large actinomycomas ranges from almost spherical lesions, usually in case of smaller abscesses, to irregularly delineated masses resembling a necrotic malignant tumor, and to ill-defined or ramified lesions, the ramification pattern thought to reflect the architecture of large intrahepatic veins (Israel 1878; Abée 1897; Diehl 1911). The abscesses may bulge from the organ's surface ("tuberous actinomycosis"). Peripheral masses may form umbilication of the hepatic capsular area, similar to tumor metastases (Tiling 1912). Macroscopically, the purulent material of actinomycotic abscesses was described as unusually thick and viscid, and more transparent than common pus, greenish in color, and with a foul odor (Langhans 1888). A striking green color of the actinomycotic pus was also noted by another author of an early documentation of actinomycosis, Habel (1896). The commonly aggressive lesions of actinomycosis may communicate among each other and develop fistulations, also detectable in CT scans (Roesler and Wills 1986).

In the purulent material, sulfur granules typical but not pathognomonic for actinomycosis can be identified. The color of these granules is in fact often brightly yellow or golden, as the term "sulfur" suggests (Diehl 1911), but the granules, which consist of bacterial radiating colonies admixed with debris, exudate proteins, and leukocytes, are sometimes dark or even greenish-blackish (Israel 1885; Askanazy 1913). In his later work on human actinomycosis, Israel described the granules as highly variable in color, ranging from colorless or sago-like to brightly yellow, green-yellow, dark green to sepia brown (Israel 1885). He noted that the granules were firmer than pus (he compares them to sebum particles) and could, therefore, easily be taken out from pus by use of a needle's tip. The granules were most numerous in the grayish-red and viscid pus that was obtained by applying pressure on the abscess (the so-called pus crudum of the historical medicine), i.e., the older and compact pus sticking to the abscess capsule, whereas the granules were rarer in the more liquid pus spontaneously flowing off the incised lesions. This finding of an outstanding clinical observer has a modern pathophysiological facet, as it is known that growth of *Actinomyces* can occur under microaerophilic conditions, which may prevail only in certain regions of an abscess, e.g., between central and peripheral parts rather than in the center with its toxic neutrophil products or the periphery, where oxygenation by the granulation tissue is stronger. Israel also observed that, when he let actinomycotic pus flow over a glass plate, the grains stuck to this surface (Israel 1878), suggesting distinct adhesion properties of the bacterium required for biofilm formation. By the use of low magnification, Israel recognized that, under gentle pressure under the cover slide, the

granules had a central brownish-yellow, slightly glistening core surrounded by a dark ring composed of leukocytes with fatty change suspended between long and tortuous bacterial filaments. In his later work on human actinomycosis, Israel described the granules as highly variable in color, ranging from colorless or sago-like to brightly yellow, green-yellow, dark green to sepia brown, yellow being more common with small grains and darker color with grains of increasing diameter (Israel 1878, 1885). Langhans described the granules as clearly black in one of his cases of hepatic actinomycosis but noted that the color faded in alcohol (Langhans 1888). The latter author observed that most of the small abscess cavities contained one granule, but purulent lesions with two or three granules were also encountered. He reported that, at higher magnification, the granules are speckled, with the blackish color being restricted to certain areas of the granules. Langhans, as an excellent observer, saw that subsequent to spreading of the pus with a knife, the granules were separated from the pus by a transparent zone. I presume that this zone corresponds to the macroscopic aspect of what has later been described as the Splendore-Hoeppli phenomenon (see below). The granules may better be visualized by running sterile water or saline over the gauze used to cover a lesion: the water washes away the purulent material leaving the granules on the gauze.

Why are sulfur granules pigmented? *Actinomyces* species are known to produce colored agents, including yellow substances (the yellow *Actinomyces* group), melanin-like or melanoid pigments, iron-containing green pigments, and colored antibiotics (flavofungins, flaveolins, flavacid), also rendering *Actinomyces* cultures pigmented, colors ranging from creamy pinkish, yellowish to gray-violet or even dark gray (Naidenova and Vladimirova 2000). The distinct microstructure of sulfur granules is caused, apart from the microbial growth pattern, by the distinct surface structure of *Actinomyces*, the cell surface showing a dense array of hair-like fimbriae protruding through a thick fuzzy surface coat (Figdor and Davies 1997). Noninfectious pseudoactinomycotic radiate granules (PAMRAGs) can mimic actinomycotic sulfur granules (Pritt et al. 2006).

Histopathology

Histologically, the abscesses consist of a purulent exudate which is peripherally demarcated by a rim of granulation tissue. The adjacent tissue commonly contains increased numbers of macrophages and plasma cells. Granules suspended in the pus contain the characteristic Gram-positive branched filaments that also form the interior part of the microbial drusen grossly seen as sulfur granules. The microbial core of the granules is visualized by Gram stains, modified Fite-Faraco stain, or Grocott's hexamine-silver stain. The Gram-positive filamentous branching rods show peripheral clubbing. The granules are sometimes associated with the Splendore-Hoeppli phenomenon (Fig. 1).

The Splendore-Hoeppli phenomenon denotes eosinophilic, pseudomycotic structures composed of necrotic debris, granulocyte proteins, and immunoglobulins forming a characteristic radiating structure, the "rays" consisting of eosinophilic or amphophilic rods of variable length (see above; Hamann et al. 1989; Rodig and Dorfman 2001). Some of the sulfur granules exhibit a corona of

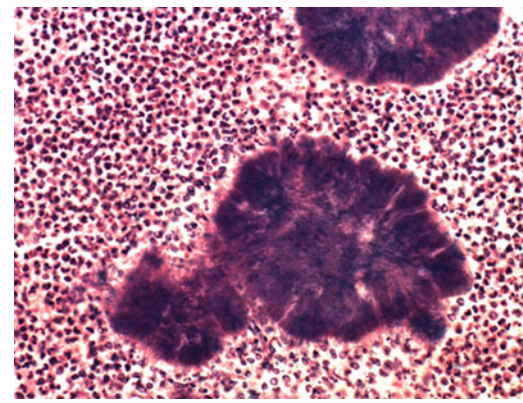

Fig. 1 Actinomycosis of the liver. Basophilic microbial drusen, macroscopically visible as sulfur granules, float within a purulent exudate. The periphery of the granules shows a thin rim of eosinophilic club-shaped bodies. This is the Splendore-Hoeppli phenomenon (hematoxylin and eosin stain)

neutrophil granulocytes, sometimes separated from the more compact pus of the abscess by a slit-like artifact. Fistulation of actinomycotic abscesses of the liver may result in destructive mine-like conduits which can reach the bile ducts or medium-sized to large hepatic veins, followed by mycotic thrombosis.

Auxiliary Methods for the Identification of *Actinomyces* in Tissues

The specific identification of bacteria with a filamentous morphology can be difficult, particularly for Gram-positive bacteria growing in the form of threads or long chains. In situ hybridization employing DNA probes directed against the variable regions of 16S ribosomal RNA genes of *Actinomyces* is a rapid and specific technique also suitable for culture-negative or clinically difficult cases of infection (Isotalo et al. 2009).

Actinomycosis of the Extrahepatic and Intrahepatic Bile Ducts

Relatively few cases of actinomycosis have been observed in the common bile duct (Kühn and Fleischer 1974; Hadley et al. 1981; Bledsoe et al. 2008; Thadani et al. 2010), intrahepatic ducts (Jung et al. 2005), and the cystic duct (Ormsby et al. 1998). Actinomycosis of the common bile duct ranging from the pancreatic head to the porta hepatis was diagnosed in one patient by the use of endoscopic ultrasound (EUS) fine-needle aspiration. EUS showed a heterogeneous isoechoic mass abutting the portal vein and the common bile duct (Thadani et al. 2010). Actinomycosis of the common bile duct can masquerade as cholecystitis. In a 56-year-old male patient with epigastric pain and fever, oral cholecystography failed to visualize the gallbladder, and intravenous cholangiography revealed a 10 mm common bile duct without visualization of the gallbladder. At cholecystectomy, operative cholangiography disclosed a persistent filling defect in the distal common bile duct. Choledochoscopy showed a firm, frond-like mass attached to the mucosal surface of the common bile duct, and histology exhibited actinomycosis, culturally confirmed to be caused by *Actinomyces israelii* (Hadley et al. 1981). Actinomycosis of the extrahepatic bile ducts can cause cholecystocholedochal fistulas (Bledsoe et al. 2008). Actinomycosis of intrahepatic bile ducts was found in association with hepatolithiasis (Jung et al. 2005).

Actinomycosis of the Gallbladder Bed, the Pericholecystic Space, and the Cystic Stump

Actinomyces naeslundii infection of the cystic stump has been reported (Ormsby et al. 1998). In this patient, stump actinomycosis emerged after a complicated history of fistulating cholecystitis. Abdominal and retroperitoneal actinomycotic abscesses can occur after laparoscopic cholecystectomy, again with infection with *A. naeslundii* (Vyas et al. 2007). Interestingly, such complications are sometimes related to retained/dropped gallstones (Ramia et al. 2004), raising the question whether gallstones might form an adhesive surface for *Actinomycetes*.

Hepatic Actinomycosis Caused by *Propionibacterium* (Arachnia) *propionicum*

Arachnia was originally identified as a propionic acid-producing *Actinomyces*-like microorganism (*Actinomyces propionicus*). Arachnia propionica was shown to be related to propionibacteria (Propionibacterium Orla-Jensen 1909) and has been renamed *Propionibacterium propionicum* (Summanen 1993). *P. propionicum* can cause an infection which clinically and morphologically resembles actinomycosis proper (Brock et al. 1973). The organism has been isolated from hepatic abscesses occurring in disseminated

Propionibacterium-type actinomycosis (Garcia-Martos et al. 1992).

Differential Diagnosis

Microbial drusen or granules can be produced by the growth of microorganisms other than *Actinomyces* species. In botryomycosis, *Staphylococcus aureus* has been shown to produce granules in the tissue, with an eosinophilic rim at the periphery and being Gram-positive (see the respective chapter). As this morphology resembles actinomycosis grains, these alterations have been proposed to be called granular bacteriosis on descriptive terms (Waisman 1962; Tomb et al. 2009). The Grocott stain is helpful in these settings, as actinomycotic colonies are Grocott-positive but not colonies seen in botryomycosis.

The Detection of *Actinomyces* and of the Distinct Sulfur Granules: A Historical Résumé

The index species of the known species, *A. israelii*, is named after James Adolf Israel (1848–1926, born in Berlin), one of the leading kidney surgeons of his time, who also made several important contributions to maxillofacial surgery (Bloch 1983; Knöner and Schultheiss 2003). After having studied medicine in Berlin, he went to Vienna, where he became a resident in the surgery division of the Jewish Community Hospital, a division headed by the famous surgeon, Bernhard von Langenbeck. Interested in antisepsis, he worked for a while with Joseph Lister in Edinburgh. In 1877, Israel detected yellowish grains in the pus of certain chronic abscesses, the later sulfur granules. In his work of 1878 (published in Virchows Archiv, Israel 1878), he personally illustrated the microscopic features of these unique grains, characterized by filamentous microorganisms (interpreted to be a mycosis by him), forming colonies which are called "drusen" in German (in mineralogy, a "druse" is an incrustation of small crystals on the surface of a rock or mineral; the term was used to denote the radial structure of the bacterial colonies owing to the resemblance with such crystalline formations). On Israel's published drawings, one microbial colony already clearly shows a distinct radial symmetrical corona with terminal club-shaped structures, a feature later described as Splendore-Hoeppli phenomenon (for details, see the chapter on botryomycosis). Based on their striking yellow color, the grains are termed sulfur granules. Sulfur granules have, however, already been documented about 30 years earlier, in fact not referred to in texts on actinomycosis. In the appendix to Israel's seminal publication of 1878, Israel mentions that the surgeon von Langenbeck had already seen in 1845 similar grains located in a vertebral abscess examined in Kiel. He cites von Langenbeck's report in its complete version, and it is remarkable to note that the surgeon's description of the objects clearly represents what has later been described by Israel (in the original German text: "Dem ziemlich dünnen, übelriechenden Eiter sind rundliche, gelblich aussehende Körperchen von der Grösse von Mohnsamenkörnern in grosser Menge beigemischt. Unter dem Deckgläschen leicht comprimiert zeigte sich jedes Klümpchen aus feinen, cylindrischen, radienartig aneinander geordneten Stäbchen von sehr regelmässiger Gestalt und ziemlich konstanter Grösse zusammengesetzt " [Admixed to the rather thin and foul-smelling pus are numerous spherical, yellowish-looking bodies of the size of poppy seeds. Gently compressed beneath a cover slid, each globule is seen to be composed of thin, cylindrical, ray-like arranged rodlets of very regular shape and rather constant size]). We owe to the recognition by von Langenbeck of these "ray-like rodlets" the terminological roots for *Actinomyces*, the "ray-like fungus." Are sulfur granules seen in all forms of actinomycosis ? In a detailed study, clear-cut sulfur granules were only detected in infections caused by *A. israelii* and *A. meyeri* (Clarridge and Zhang 2002), but it may be assumed that other species may produce similar microbial colonies.

Hepatobiliary Nocardiosis

Introduction

Nocardiosis is a mixed suppurative and granulomatous inflammatory disease caused by numerous species of the Gram-positive bacterium genus, *Nocardia*. The majority of infections are caused by the *N. asteroides* complex which includes *N. asteroides* sensu stricto, *N. farcinica*, and *N. nova*. The first human infection with *Nocardia* was reported in 1924.

Microbiology

Nocardia is an aerobic Gram-positive member of the family *Nocardiaceae* within the order *Actinomycetales*. There are currently more than 30 species of nocardiae of human clinical significance, and current molecular taxonomy approaches will augment this number in the future (Brown-Elliott et al. 2006). The optimal growth of *Nocardia* in tissues requires iron, which is accumulated by nocardial siderophores. *N. brasiliensis* produces the siderophore brasilibactin A, a membrane-bound siderophore with structural similarity to the mycobactin class of siderophores in mycobacteria.

Epidemiology and Main Clinical Phenotypes

Human *Nocardia* infections are rare, with an estimated incidence in the USA of 1,000 cases per year. Nocardiosis is in principle an opportunistic infection mainly described in immunocompromised individuals, although several cases have been described in immunocompetent hosts (Harris 1980; Beaman and Beaman 1994; Lederman and Crum 2004; Filice 2005). In a retrospective study covering the years 1997–2003, all patients had active comorbidities at the time of infection (Munoz et al. 2007). In organ transplant recipients, receipt of high-dose steroids, history of cytomegalovirus disease, and high levels of calcineurin inhibitors were found to be independent risk factors for *Nocardia* infection (Peleg et al. 2007). Nocardiosis is an infection complicating chronic granulomatous disease (Bassiri-Jahromi and Doostkam 2011). The respiratory tract is the most commonly involved system, followed by CNS and cutaneous infections and, less commonly, other sites. Skin infections are divided into three types, i.e., nocardial mycetoma/actinomycetoma, localized cutaneous nocardiosis, and a type typically associated with painful locoregional lymphadenopathy, the lymphocutaneous type of nocardiosis (reviews: Harris 1980; Kalb et al. 1985; Lerner 1996; Saubolle and Sussland 2003; Wilson 2012).

Hepatobiliary Nocardiosis

Nocardia species (e.g., *N. asteroides* and *N. brasiliensis*) have been reported to cause liver abscesses (Pretet et al. 1979; Salfield et al. 1983; Cockerill et al. 1984; Roman et al. 1991; Ramseyer and Nguyen 1993; Elliott et al. 1997; Benes et al. 2003; Nakahara et al. 2011). The hepatic lesions may radiologically resemble amebic abscess (Pretet et al. 1979). Liver abscess caused by *N. farcinica* has been observed in patient following multivisceral transplantation (Wiesmayr et al. 2005). In one patient with nocardiosis, multiple liver abscesses developed in association with Crohn's disease treated with infliximab (Nakahara et al. 2011). In addition to abscesses, focal collections of granulomas forming multiple small hypodense lesions on CT images may develop (Akan et al. 1998).

Pathology

Macroscopically, liver abscesses in nocardiosis do not show the features described for actinomycosis. The lesions rather resemble abscesses caused by bacterial infections than actinomycetomas (see the respective paragraph). Histologically, a fibrinopurulent exudate with a marked peripheral macrophage and plasma cell reaction prevails, encircled by a granulation tissue, but often without granuloma formation. In the Gram stain, the

organism is visualized as clusters of short, beaded, variably Gram-positive, sinuous non-branching rods within the suppurative areas. The organisms stain red purple in the Ziehl-Neelsen stain. Depending on the immune reaction of the host, hepatic nocardiosis can also present in the form of a granulomatous hepatitis (Akan et al. 1998), sometimes with conglomerates of granulomas that form multiple liver masses resembling metastatic disease.

Differential Diagnosis

The main differential diagnosis consists of other purulent focal lesions of the liver containing filamentous Gram-positive bacterial elements, in particular actinomycosis and infections with *Candida albicans*.

Botryomycosis and Botryomycomas

Introduction

Botryomycosis is characterized by a chronic, suppurative, more or less granulating (not granulomatous, as it is sometimes stated) bacterial-induced but not fungal inflammation in which the specific feature is the presence of fungus-like grains or granules (microbial drusen) which contain, unlike actinomycosis, non-branching bacteria (Winslow 1959; Greenblatt et al. 1964). These grains are called Bollinger grains (not to be confounded with Bollinger bodies, which are cellular inclusion bodies occurring in avian pox/fowl pox and containing fowl pox virus). Botryomycosis is named after the Greek word "botrys," meaning "bunch of grapes," and mycosis because of the initially supposed fungal origin of the disease. Synonyms of the disorder include bacterial pseudomycosis (Greenblatt et al. 1964), staphylococcic actinophytosis (Berger et al. 1936), granular bacteriosis (Waisman 1962; Tomb et al. 2009), and actinobacillosis (Beaver and Thompson 1933).

Botryomycosis was first described in 1870 in a horse with a pulmonary infection then thought to be a true mycosis (Bollinger 1870). Otto Bollinger (1843–1909) was a German pathologist considered to be one of the founders of comparative pathology. In 1876, he also discovered actinomycosis in cattle. The term, botryomycosis, was coined 14 years after Bollinger's description by Rivolta under the impression that it was caused by a true fungus, based on observations on botryomycotic lesions in stallions after castration (Rivolta 1884). Botryomycosis has formerly also been termed the "champignon de castration," because of original descriptions of this disease after castration in horses (Finegold et al. 1978). The first human case of botryomycosis was published in 1910 (Archibald 1910). In 1913, Opie published the first report of a human case of botryomycosis in the USA, which was also the first account of liver involvement (Opie 1913). Botryomycoma has to be separated from telangiectatic granuloma. Telangiectatic granuloma was previously described under the term human botryomycosis by Poncet and Dor in 1879, but in 1899, Sabrazès and Laubie denied a relation with botryomycosis and created the name telangiectatic granuloma (cited in Hagedoorn 1934). Botryomycosis was originally thought to be caused by fungus-like organisms, and several now obsolete terms were employed to denote putative causative agents, including Zoogloea pulmonis equi (Bollinger 1870) and Dyscomyces equi (Rivolta 1884).

Microbiology

Botryomycosis can be caused by a wide range of bacteria, but *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Neisseria mucosa*, and certain fungi are particularly important causes. Rarer etiologies include *Propionibacterium acnes*, *Serratia marcescens*, *Moraxella nonliquefaciens*, and fusobacteria. The pathogenesis of this unique tissue reaction is still unknown, but low-virulent strains of bacteria together with a distinct immune reaction of the host are discussed. In early animal experiments done in the French Pasteur Institute, it was shown that the number of microorganisms inoculated

into healthy test animals was critical to induce botryomycosis. Very high and very low concentrations of bacteria were not effective, whereas intermediate concentrations resulted in granules as seen in human botryomycosis (Magrou 1919).

Hepatobiliary Botryomycosis and Botryomycoma of the Liver

Botryomycosis is known to involve visceral organs and has been reported for the liver (Opie 1913; Beaver and Thompson 1933; Fink 1941; Schlossberg et al. 1980, 1988; Omar and Cooper 1995). In the liver, botryomycosis can present as a sometimes huge hepatic abscess, as described in the first report on hepatic botryomycosis (Opie 1913). Staphylococcus as the causative agent of hepatic botryomycosis was first reported in 1941 (Fink 1941). In one patient, abdominal CT showed multiple low-density nodular lesions ("botryomycomas") throughout the liver, measuring up to few cm in size (Schlossberg et al. 1998). Densely placed lesions may coalesce, and fistula formation may develop. The botryomycotic lesions can induce obstructive jaundice (Bagby and Gunning 1978) and have sometimes been misinterpreted as malignancy, including hepatocellular carcinoma (Omar and Cooper 1995). Histology shows purulent inflammation, sometimes presenting as an active abscess, demarcated by a granulation tissue of variable thickness, and in the exudate, different kinds of bacteria may be detectable by the use of special stains or microbial culture. Between the exudate rich in intact and decaying neutrophils and the granulation tissue, varying amounts of macrophages, including foamy cells, are in evidence, and even a pseudoxanthomatous reaction may ensue in disease of longer-standing duration. Bollinger bodies may be directly visualized in the purulent exudate, but they can more easily be recognized in wet mounts subsequent to clarification of the tissue by means of 10 % potassium hydroxide (KOH) treatment followed by examination with polarized light. Similar to botryomycosis in other locations, hepatic botryomycosis may show the Splendore-Hoeppli phenomenon associated with Bollinger granules (Schlossberg et al. 1998; case of streptococcal botryomycosis of the liver). The liver tissue adjacent to botryomycomas is atrophic, and scattered leukocytes are seen in the perifocal sinusoids and also in portal tracts situated in the vicinity of the lesions.

Pathology of Botryomycosis

Bollinger grains, an eponym linked to the discoverer of botryomycosis (see above), are small, yellowish to white granules in mulberry-like masses, usually with a diameter of 1–3 mm, hence visible with the naked eye. The granules consist of intact and decaying leukocytes (mostly granulocytes) and are rich in non-branching bacteria, which may form a radiate pattern and therefore representing so-called microbial drusen. Histologically, Bollinger granules resemble pseudoactinomycotic radiate granules (PAMRAGs) found in the lower female genital tract (Bhagavan et al. 1982). Instead of white to yellow Bollinger granules, botryomycosis may sometimes show granules that are red (so-called red grain botryomycosis), caused by *Actinomadura pelletieri* (Gerber 1971) and *Actinomadura vinacea* (Maiti et al. 2003). In *Actinomadura*-induced red grain botryomycosis, the red color of the bacterial drusen is caused by synthesis of prodigiosin, an antibiotically active red pyrrole alkaloid of the prodigiosin-roseophilin family (Gerber 1971; Bennett and Bentley 2000; Fürstner 2003). Red grain botryomycosis has also been observed in a *Staphylococcus aureus*-induced lesion (Katkar et al. 2009). Prodigiosins and roseophilins can also be synthesized by cocci, e.g., *Streptococcus* species (Kawasaki et al. 2008).

Splendore-Hoeppli Phenomenon

The bacterial colonies may be encircled by a distinct hyaline, eosinophilic corona with a radial symmetry, the Splendore-Hoeppli phenomenon. This phenomenon is named for the two scientists who described it in 1908 and 1932, respectively. In 1908, Splendore described in human tissues

what he regarded as a new species of *Sporotrichum*, and he named this structure "*Sporotrichum asteroides*" (aster, star) owing to the star-like configuration of the coating around it (Splendore 1908). In 1912, de Beurmann and Gougerot reexamined Splendore's material and listed the "germ" in their work on sporotrichosis under the name "*Sporotrichum beurmanni* variété asteroides" (De Beurmann and Gougerot 1912). Almost 25 years later, Hoeppli reported the same phenomenon seen around schistosomal ova in rabbit tissues but made no reference to Splendore's observations (Hoeppli 1932). The occurrence of clubs and knobby or smooth shells formed around microorganisms was reported by Meyer in 1934 (Meyer 1934). The Splendore-Hoeppli phenomenon is also termed pseudoactinomycotic radiate granules, radiate granules, actinophytosis, pseudo-sulfur granules, Splendore-Hoeppli radiate reaction, and pseudoactinomycotic sulfur granules, sulfur granules being reserved for actinomycosis proper (Padberg et al. 2002). Actinophytosis is a term that has to be rejected, because it signifies a lesion characterized by ray formation produced by any microorganism, and it may be confounded with actinomycosis (Winslow 1959). The latter author, in his seminal work on botryomycosis, has referred to the occurrence of "clubs" and knobby or smooth shells which form around microorganisms in certain cases of botryomycosis, with deposition of an eosinophilic and safranophilic material, without referring to the reports of Splendore and Hoeppli, but cites works describing clubbing in actinomycosis going back to 1925 (Winslow 1959). Histologically, the phenomenon is characterized by an eosinophilic to amphophilic material composed of hyaline rods of variable length (sometimes with slight peripheral clubbing) arranged in ray-like fashion around deposits of microbes, parasite/parasite eggs, or foreign material (Hussein 2008). The inner zone of the material contains diastase-resistant PAS-positive, safranophilic material and lipids and is acid-fast and autofluorescent. The outer zone is less reactive to stains and is not autofluorescent (Johnson 1976). Electron microscopically, the material shows signs of protein precipitation and exhibits a fibrillary material suggesting the presence of fibrin (Padberg et al. 2002). It is thought that Splendore-Hoeppli phenomenon represents a distinct type of antigen-antibody reaction with local activation of the complement cascade and of coagulation factors. The Splendore-Hoeppli phenomenon is not unique to botryomycosis but can be seen in actinomycosis, mycetoma, phycomycosis, coccidioidomycosis, sporotrichosis, and even around foreign bodies, including intrauterine devices and silk sutures.

It has been suggested that the granule-associated Splendore-Hoeppli phenomenon, with a hyaline matrix rich in IgG and complement C3, may be associated with maximum host reactivity through antigen-antibody interaction (Williams et al. 1969).

References

Abée J (1897) 3 Fälle tödlich verlaufender Aktinomykose. Beitr Pathol Anat Z Allg Path 22:132

Akan H, Akoya M, Ataoglu H, Aksu G, Arslan O, Koc H (1998) Rhodococcus equi and Nocardia brasiliensis infection of the brain and liver in a patient with acute nonlymphoblastic leukemia. Eur J Clin Microbiol Infect Dis 17:737–739

Al-Khuwaitir et al. 2000. http://www.ncbi.nlm.nih.gov/pubmed/11423894

Archibald RG (1910) Human botryomycosis. Br Med J 2:971

Askanazy M (1913) Aktinomyces. Aschoff's Lehrbuch der pathologischen Anatomie. Band 1, 3. Auflage. pp 198–202

Bagby GC, Gunning JJ (1978) Botryomycosis as an obstructive hepatic disease. Arch Intern Med 138:472–473

Barajas Martinez JM, Vicente Gutierrez M, Rivera Vaquerizo P, Garcia Garcia V, Herrero Quiros C, Loeches Prado N, Perez-Flores R (2002) Primary hepatic abscess caused by *Actinomyces meyeri* (in Spanish). Rev Esp Enferm Dig 94:108–109

Barth H (1890) Ueber Bauchaktinomykose. Dtsch Med Wochenschr 16:742

Bassiri-Jahromi S, Doostkam A (2011) Actinomyces and nocardia infections in chronic granulomatous disease. J Glob Infect Dis 3:348–352

Baumgarten K (1890) Aktinomyzes. Lehrbuch der pathologischen Mykologie. p 878

Beaman BL, Beaman L (1994) Nocardia species: host-parasite relationships. Clin Microbiol Rev 7:213–264

Beaver DC, Thompson L (1933) Actinobacillosis in man. Report of a fatal case. Am J Pathol 9:603–622

Benes J, Viechova J, Picha D, Horova B, Zatloukal P (2003) Disseminated Nocardia asteroides infection in an immunocompetent woman following an arm injury. Infection 31:112–114

Bennett JW, Bentley R (2000) Seeing red: the story of prodigiosin. Adv Appl Microbiol 47:1–32

Berger L, Vallée A, Vézina C (1936) Genital staphylococcic actinophytosis (botryomycosis) in human beings. Arch Pathol 21:273–283

Berthet B, Assadourian R (1992) Primary hepatic actinomycosis, a tumor of diagnostic difficulties (in French). Presse Med 21:1870

Berthet et al. 1994. http://www.ncbi.nlm.nih.gov/pubmed/7844181

Bhagavan BS, Ruffier J, Shinn B (1982) Pseudoactinomycotic radiate granules in the lower female genital tract: relationship to the Splendore-Hoeppli phenomenon. Hum Pathol 13:898–904

Bhatt BD, Zuckerman MJ, Ho H, Polly SM (1990) Multiple actinomycotic abscesses of the liver. Am J Gastroenterol 85:309–310

Bledsoe et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18306863

Bloch P (1983) Erinnerungen an James Israel. In: Winau R (ed) James Israel (1848–1926). Franz Steiner, Wiesbaden, pp 7–97

Bollinger O (1870) Mycosis der Lunge beim Pferde. Virchows Arch Pathol Anat 49:583–586

Boucenna M, Arrivé L (1999) Images in hepatology. Pseudotumoral hepatic actinomycosis. J Hepatol 31:928

Braun KP, Gastinger I, May M, Kaufmann O, Ernst H (2009) Diagnostic and therapeutic procedures in actinomycosis of the liver – a case report (in German). Zentralbl Chir 134:166–169

Brewer and Allen 1980. http://www.ncbi.nlm.nih.gov/pubmed/7403920

Brock DW, Georg LK, Brown JM, Hickoin MD (1973) Actinomycosis caused by Arachnia propionica: report of 11 cases. Am J Clin Pathol 59:66–77

Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ (2006) Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. Clin Microbiol Rev 19:259–283

Buyukavci M, Caner I, Eren S, Aktas O, Akdag R (2004) A childhood case of primary hepatic actinomycosis presenting with cutaneous fistula. Scand J Infect Dis 36:62–63

Campeanu I, Bogdan M, Mosoioa L, Lucescu I, Corneci D, Vasilescu F, Curea M (2004) Hepatic actinomycosis – pseudotumoral form (in Hungarian). Chirurgia (Bucur) 99:157–161

Cedermark B, Sundblad R, Willems JS (1982) Suspected neoplasm of the liver with pulmonary metastases cured by surgery and penicillin. Disseminated actinomycosis revisited. Am J Surg 141:384–386

Cetinkaya Z, Kocakoc E, Coskun S, Ozerkan IH (2010) Primary hepatic actinomycosis. Med Princ Pract 19:196–199

Chandarlapaty SK, Dusol M, Edwards R, Pereiras R, Clark R, Schiff ER (1975) 67Gallium accumulation in hepatic actinomycosis. Gastroenterology 69:752–755

Chao CT, Liao CH, Lai CC, Hsueh PR (2011) Liver abscess due to Actinomyces odontolyticus in an immunocompetent patient. Infection 39:77–79

Chen LW, Chang LC, Shie SS, Chien RN (2006) Solitary actinomycotic abscesses of liver: report of two cases. Int J Clin Pract 60:104–107

Cheng YF, Hung CF, Liu YH, Ng KK, Tsai CC (1989) Hepatic actinomycosis with portal vein occlusion. Gastrointest Radiol 14:268–270

Christodoulou N, Papadakis I, Velegrakis M (2004) Actinomycotic liver abscess. Case report and review of the literature. Chir Ital 56:141–146

Ciria-Bru et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18570851

Clarridge JE, Zhang Q (2002) Genotype diversity of clinical Actinomyces species: phenotype, source, and disease correlation among genospecies. J Clin Microbiol 40:3442–3448

Cockerill FR, Edson RS, Roberts GD, Waldorf JC (1984) Trimethoprim/sulfamethoxazole-resistant Nocardia asteroides causing multiple hepatic abscesses. Successful treatment with ampicillin, amikacin, and limited computed tomography-guided needle aspiration. Am J Med 77:558–560

De Beurmann CL, Gougerot H (1912) Les sporotrichoses. Felix Alcan, Paris, p 138

Detre Z, Guoth M, Fules P, Lehoczky D (1988) Actinomycosis of the liver in wearers of IUDs (in Hungarian). Morphol Igazsagugyi Orv Sz 28:59–66

Diehl K (1911) Ueber Aktinomykose der Leber. Mitt Grenzgeb Med Chir 22:135

Elliott MA, Tefferi A, Marshall WF, Lacy MQ (1997) Disseminated nocardiosis after allogeneic bone marrow transplantation. Bone Marrow Transplant 20:425–426

Felekouras E, Menenakos C, Griniatsos J, Deladetsima I, Kalaxanisi N, Nikiteas N et al (2004) Liver resection in cases of isolated hepatic actinomycosis: case report and review of the literature. Scand J Infect Dis 36:535–538

Figdor D, Davies J (1997) Cell surface structures of Actinomyces israelii. Aust Dent J 42:125–128

Filice GA (2005) Nocardiosis in persons with human immunodeficiency virus infection, transplant recipients, and large, geographically defined populations. J Lab Clin Med 145:156–162

Finegold SM, Martin WJ, Scott EG (1978) Bailey and Scott's diagnostic microbiology, 5th edn. C.V. Mosby, St. Louis

Fink AA (1941) Staphylococcus actinophytotic abscess of the liver with pulmonary involvement. Arch pathol 31:103–107

Fives-Taylor PM, Meyer DH, Mintz KP, Brissette C (2000) Virulence factors of Actinobacillus actinomycetemcomitans. Periodontol 20:136–167

Fleischer EM, Kühn H (1973) Liver actinomycosis with tumor aspects following cholecystectomy (in German). Zentralbl Chir 98:1213–1215

Fürstner A (2003) Chemistry and biology of roseophilin and the prodigiosin alkaloids: a survey of the last 2500 years. Angew Chem Int Ed Engl 42:3582–3603

Garcia-Martos P, Candau J, Benjumeda M, de la Rubia F, Soria MJ, Perez R (1992) Disseminated actinomycosis and hepatic abscess caused by *Arachnia propionica* (in Spanish). Enferm Infecc Microbiol Clin 10:123–124

Gerber NN (1971) Prodigiosin-like pigments from *Actinomadura* (*Nocardia*) *pelletieri*. J Antibiot 24:636

Golematis B, Hatzitheofilou C, Melissas J (1976) Liver actinomycosis: a case report. Am J Gastroenterol 65:148–151

Goodfellow M, Isik K, Yates E (1999) Actinomycete systematics: an unfinished synthesis. Nova Acta Leopold 80:47–82

Greenblatt M, Heredia R, Ruberstein L (1964) Bacterial pseudomycosis ("botryomycosis"). Am J Clin Pathol 41:188–193

Grill A (1895) Ueber Aktinomykose des Magens und Darmes beim Menschen. B Beitr Klein Chir 13:551

Guven A, Kesik V, Deveci MS, Ugurel MS, Ozturk H, Koseoglu V (2008) Post varicella hepatic actinomycosis in a 5-year-old girl mimicking acute abdomen. Eur J Pediatr 167:1199–1201

Habel A (1896) Ueber Aktinomykose. Virchows Arch Pathol Anat Physiol 164:1

Hadley DA, Porschen RK, Juler GL (1981) Actinomycosis of the common bile duct presenting as chronic cholecystitis. Surgery 90:117–119

Hagedoorn A (1934) Telangiectatic granuloma – botryomycosis. Br J Ophthalmol 18:561–570

Hall 2008. http://www.ncbi.nlm.nih.gov/pubmed/18222714

Hall V, Collins MD, Hutson RA, Inganäs E, Falsen E, Duerden BI (2003) *Actinomyces oricola* sp. nov., from a human dental abscess. Int J Syst Evol Microbiol 53:1515–1518

Hallberg K, Hammarström KJ, Felsen E, Dahlen G, Gibbons RJ, Hay DI, Strömberg N (1998) Actinomyces naeslundii genospecies 1 and 2 express different binding specificities to N-acetyl-b-D-galactosamine, whereas *Actinomyces odontolyticus* expresses a different binding specificity in colonizing the human mouth. Oral Microbiol Immunol 13:327–336

Hamann KJ, Kephart GM, Kazacos KR, Gleich GJ (1989) Immunofluorescent localization of eosinophil granule major basic protein in fatal human cases of *Baylisascaris procyonis* infection. Am J Trop Med Hyg 40:291–297

Harris GK (1980) Nocardiosis: a literature review and a case report of *Nocardia asteroides* infection. Am J Med Technol 46:44–48

Harsch IA, Benninger J, Niedobitek G, Schindler G, Schneider HT, Hahn EG, Nusko G (2001) Abdominal actinomycosis: complication of endoscopic stenting in chronic pancreatitis? Endoscopy 33:1065–1069

Heller C (1884) Ein Fall von Aktinomykose unter dem Bild einer akuten Infektionskrankheit verlaufend. Dtsch Arch Klin Med 37:372

Hisaoka M, Nakamura T, Haratake J, Horie A (1991) Primary actinomycosis in the liver. J UOEH 13:29–34

Hoeppli R (1932) Histological observations in experimental schistosomiasis japonica. Chin Med J 46:1179

Hussein MR (2008) Mucocutaneous Splendore-Hoeppli phenomenon. J Cutan Pathol 35:979–988

Isemer K (1878) Zwei Fälle von Blinddarmentzündung, hervorgerufen durch Aktinomyzes. Inaug. Dissertation, Greifswald

Islam T, Athar MN, Athar MK, Usman MH, Misbah B (2005) Hepatic actinomycosis with infiltration of the diaphragm and right lung: a case report. Can Respir J 12:336–337

Isotalo PA, Qian X, Hayden RT, Roberts GD, Lloyd RV (2009) In situ hybridization for the differentiation of *Actinomyces* and *Nocardia* in tissue sections. Diagn Mol Pathol 18:183–188

Israel J (1878) Neue Beobachtungen auf dem Gebiet der Mykosen des Menschen. Virchows Arch Pathol Anat Physiol 74:15–53

Israel J (1885) Klinische Beitiäge zur kenntnis der aktinomykose des menschen. Hirschwald A, Berlin.

Jacobs et al. 1981. http://www.ncbi.nlm.nih.gov/pubmed/7347067

Jermini et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15553899

Johnson FB (1976) Splendore-Hoeppli phenomenon. In: Binford CH, Connor DH (eds) Pathology of tropical and extraordinary diseases, vol 2. Armed Forces Institute of Pathology, Washington, DC, p 681

Jonas RB, Brasitus TA, Chowdhury L (1987) Actinomycotic liver abscess. Dig Dis Sci 32:1435–1437

Joshi V, Koulaouzidis A, McGoldrick S, Tighe M, Tan C (2010) Actinomycotic liver abscess: a rare complication of colonic diverticular disease. Ann Hepatol 9:96–98

Jung JH, Choi HJ, Yoo J, Kang SJ, Kang CS (2005) Actinomycosis of the intrahepatic bile duct, superimposed on hepatolithiasis: a case report. Kor J Pathol 39:140–144

Kalb RE, Kaplan MH, Grossman ME (1985) Cutaneous nocardiosis. Case reports and review. J Am Acad Dermatol 13:125–133

Kanellopoulou T, Alexopoulou A, Tiniakos D, Koskinas J, Archimandritis AJ (2010) Primary hepatic actinomycosis mimicking metastatic liver tumor. J Clin Gastroenterol 44:458–459

Kasano Y, Tanimura H, Yamaue H, Hayashido M, Umano Y (1996) Hepatic actinomycosis infiltrating the diaphragm and right lung. Am J Gastroenterol 91:2418–2420

Katkar V, Mohammad F, Raut S, Amir R (2009) Red grain botryomycosis due to *Staphylococcus aureus* – a novel case report. Indian J Med Microbiol 27:370–372

Kawasaki T, Sakurai F, Hayakawa Y (2008) A prodigiosin from the roseophilin producer *Streptomyces griseoviridis*. J Nat Prod 71:1265–1267

Kazmi KA, Rab SM (1989) Primary hepatic actinomycosis: a diagnostic problem. Am J Trop Med Hyg 40:310–311

Kim HS, Park NH, Park KA, Kang SB (2007) A case of pelvic actinomycosis with hepatic actinomycotic pseudotumor. Gynecol Obstet Invest 64:95–99

Knöner W, Schultheiss D (2003) James Israel (1848–1926). His contribution to oral and maxillofacial surgery (in German). Mund Kiefer Gesichts Chir 7:146–150

Kocabay G, Cagatay A, Eraksoy H, Tiryaki B, Alper A, Calangu S (2006) A case of isolated hepatic actinomycosis causing right pulmonary empyema. Chin Med J (Engl) 119:1133–1135

Koch C (1894) Weitere Fälle von Actinomycosis hominis. München Med Wochenschr 8:22

Kramer J (1911) Ueber fortgeleitete aktinomykotische Thrombose der Vena lienalis und der Pfortader. Inaug.-Diss, München

Kühn H, Fleischer EM (1974) Isolated actinomycosis of the liver and bile ducts following cholecystectomy (in German). Z Gesamten Inn Med 29:343–347

Lai AT, Lam CM, Ng KK, Yeung C, Ho WL, Poon LT, Ng IQ (2004) Hepatic actinomycosis presenting as a liver tumour: case report and literature review. Asian J Surg 27:345–347

Lakshmana Kumar YC, Javherani R, Malini A, Prasad SR (2005) Primary hepatic actinomycosis. Trans R Soc Trop Med Hyg 99:868–870

Lall T, Shehab TM, Valenstein P (2010) Isolated hepatic actinomycosis: a case report. J Med Case Rep 4:45

Lamoureux et al. 1984. http://www.ncbi.nlm.nih.gov/pubmed/6710689

Lange CM, Hofmann WP, Kriener S, Jacobi V, Welsch C, Just-Nuebling G, Zeuzem S (2009) Primary actinomycosis of the liver mimicking malignancy. Z Gastroenterol 47:1062–1064

Langhans T (1888) Drei Fälle von Aktinomykose. Korrespbl Schweiz Aerzte 18:1–11

Lederman ER, Crum NF (2004) A case series and focused review of nocardiosis: clinical and microbiologic aspects. Medicine (Baltimore) 83:300–313

Leith J (1894) Actinomycosis of the liver. Edinb Hosp Rep 2:121–191

Lerner PI (1996) Nocardiosis. Clin Infect Dis 22:891–903

Lin TP, Fu LS, Peng HC, Lee T, Chen JT, Chi CS (2001) Intra-abdominal actinomycosis with hepatic pseudotumor and xanthogranulomatous pyelonephritis in a 6-y-old boy. Scand J Infect Dis 33:551–553

Litten M (1900) Ein Fall von aktinomykotischem Leberabszess. Dtsch Med Wochenschr 40:3–8

Logan MN, Stanley PJ, Exley A, Gagg C, Farrell ID (1989) Actinomycetes in pyogenic liver abscess. Eur J Clin Microbiol Infect Dis 8:394–396

Mager DL, Ximenez-Fyvie LA, Haffajee AD, Socransky SS (2003) Distribution of selected bacterial species on intraoral surfaces. J Clin Periodontol 30:644–654

Magrou J (1919) Les formes actinomycotiques du staphylocoque. Ann Inst Pasteur 35:344–374

Maiti PK, Bandyopadhyay D, Dey JB, Majumdar M (2003) Mycetoma caused by a new red grain mycetoma agent in members of a family. J Postgrad Med 49:322–324

Meade RH (1980) Primary hepatic actinomycosis. Gastroenterology 78:355–359

Meyer K (1934) Sur la génèse des masses des Actinomycètes. Compt Rend Soc Biol 115:1684–1686

Mir AM, Mir MA, Ahrari H (1978) Hepatic actinomycosis: case report with review of the literature. Br J Clin Pract 32:238–242

Miyamoto MI, Fang FC (1993) Pyogenic liver abscess involving Actinomyces: case report and review. Clin Infect Dis 16:303–309

Mongiardo N, De Rienzo B, Zanchetta G, Lami G, Pellegrino F, Squadrini F (1986) Primary hepatic actinomycosis. J Infect 12:65–69

Munoz et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17374898

Naidenova M, Vladimirova D (2000–2002) Isolation and taxonomic investigation of actinomycetes from specific biotopes in Bulgaria. J Cult Collect 3:15–24

Nakahara T, Kan H, Nakahara H, Asamoto Y, Komatsu H, Tokumo H, Ishida K (2011) A case of liver nocardiosis associated with Crohn's disease while treating infliximab (in Japanese). Nihon Shokakibyo Gakkai Zasshi 108:619–626

Nazarian LN, Spencer JA, Mitchell DG (1994) Multiple actinomycotic liver abscesses: MRI appearances with etiology suggested by abdominal radiography. Case report. Clin Imaging 18:119–122

Norskov -Lauritsen N, Kilian M (2006) Reclassification of Actinobacillus actinomycetemcomitans, Haemophilus aphrophilus, Haemophilus paraphrophilus and Haemophilus segnis as *Aggregatibacter actinomycetemcomitans* gen.nov., comb.nov., *Aggregatibacter aphrophilus* comb. nov. and *Aggregatibacter segnis* comb.nov., and emended description of *Aggregatibacter aphrophilus* to include V factor-dependent and V factor-independent isolates. Int J Syst Evol Microbiol 56:2135–2146

Omar T, Cooper K (1995) Botryomycosis of the liver. Histopathology 27:71–73

Opie EL (1913) Human botryomycosis of the liver. Arch Intern Med 11:425–439

Ormsby AH, Bauer TW, Hall GS (1998) Actinomycosis of the cholecystic duct: case report and review. Pathology 30:65–67

Padberg BC, Kolb SA, August C, Schroder S (2002) IUD-associated pseudoactinomycotic radiate granules (Splendore-Hoeppli phenomenon) in uterine curettages (in German). Pathologe 23:135–139

Peleg AY, Husain S, Qureshi ZA, Silveira FP, Sarumi M, Shutt KA, Kwak EJ, Paterson DL (2007) Risk factors,

clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: a matched case-control study. Clin Infect Dis 44:1307–1314
Poncet C, Bernard C (1898) Traité clinique de l'actinomycose humaine. Masson, Paris
Pretet S, Paul G, Claret Y, Marin I, Bagot M, Dyan A (1979) Hepato-pulmonary Nocardia infections (report of one case) (in French). J Chir (Paris) 116:637–640
Pritt et al. 2006. http://www.ncbi.nlm.nih.gov/pubmed/16394276
Rabusin M, D'Andrea N, Brizzi F, Bussani R, Ventura A (1996) Primary hepatic actinomycosis. Pediatr Infect Dis J 15:382–384
Ramia et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15106577
Ramirez Sanchez C, Perez Marin MA, Ibanez Merino J, Ramirez Cruz HM (1997) Liver actinomycosis. Report of a case (in Spanish). Rev Gastroenterol Mex 42:36–40
Ramseyer LT, Nguyen DL (1993) Nocardia brasiliensis liver abscesses in an AIDS patient: imaging findings. AJR Am J Roentgenol 160:898–899
Rivolta S (1884) Del micelio e delle varietà e specie di discomiceti patogeni. G Anat Fisiol Patol Anim 16:181–198
Rodig SJ, Dorfman DM (2001) Splendore-Hoeppli phenomenon. Arch Pathol Lab Med 125:1515–1516
Roesler PJ, Wills JS (1986) Hepatic actinomycosis: CT features. J Comput Assist Tomogr 10:335–337
Roman HO, Vilar JH, Corrales JL, Lanari Zubiaur FJ (1991) Liver abscess caused by Nocardia. Report of a case (in Spanish). Rev Esp Enferm Dig 80:282–283
Roth H (1921) Ein Fall von aktinomykotischem Leberabszess nach Appendizitis. Zbl Allg Pathol Pathol Anat 31:341
Ruutu P, Pentikainen PJ, Larinkari U, Lempinen M (1982) Hepatic actinomycosis presenting as repeated cholestatic reactions. Scand J Infect Dis 14:235–238
Saad M, Moorman J (2005) Images in clinical medicine. Actinomyces hepatic abscess with cutaneous fistula. N Engl J Med 353:e16
Salfield SA, Duerden BI, Dickson JA, Milner RD (1983) Abdominal nocardiosis in a Sudanese girl. Eur J Pediatr 140:135–137
Saubolle MA, Sussland D (2003) Nocardiosis: review of clinical and laboratory experience. J Clin Microbiol 41:4497–4501
Schaal and Lee 1992. http://www.ncbi.nlm.nih.gov/pubmed/1612438
Schlossberg D, Keeney GE, Lifton LJ, Azizkhan RG (1980) Anaerobic botryomycosis. J Clin Microbiol 11:184–185
Schlossberg D, Pandey M, Reddy R (1998) The Splendore-Hoeppli phenomenon in hepatic botryomycosis. J Clin Pathol 51:399–400
Schmeding M, Neumann U, Neuhaus P (2005) Solid actinomycosis of the liver (in German). Dtsch Med Wochenschr 130:2705–2707
Sharma M, Briski LE, Khatib R (2002) Hepatic actinomycosis: an overview of salient features and outcome of therapy. Scand J Infect Dis 34:386–391
Sheth et al. 1987. http://www.ncbi.nlm.nih.gov/pubmed/3302299
Shiau YR, Lin SC, Wang TE, Shih SC, Yang TL, Chen BF (1995) Hepatic actinomycosis: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 56:62–65
Shurbaji MS, Gupta PK, Newman MM (1987) Hepatic actinomycosis diagnosed by fine needle aspiration. A case report. Acta Cytol 31:751–755
Siquera and Roças 2005. http://www.ncbi.nlm.nih.gov/pubmed/1600454
Smego and Foglia 1998. http://www.ncbi.nlm.nih.gov/pubmed/9636842
Sondag et al. 1989. http://www.ncbi.nlm.nih.gov/pubmed/2666241
Splendore A (1908) Sobre a cultura d'uma nova especie de cogumello pathogenico (Sporotrichose de Splendore). Revista Soc. Scientif. Sao Paulo II, ns. 3 and 7, 62
Sugano S, Matuda T, Suzuki T, Makino H, Iinuma M, Ishii K, Ohe K, Mogami K (1997) Hepatic actinomycosis: case report and review of the literature in Japan. J Gastroenterol 32:672–676
Summanen P (1993) Recent taxonomic changes for anaerobic gram-positive and selected gram-negative organisms. Clin Infect Dis 16(Suppl 4):S168–S174
Tambay et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11573105
Tamsel S, Demirpolat G, Killi R, Elmas N (2004) Primary hepatic actinomycosis: a case of inflammatory pseudotumor (in Turkish). Tani Girisim Radyol 10:154–157
Taylor A (1891) A case of actinomycosis of the liver and lungs. Guys Hosp Rep 33:311–323
Thadani A, Chick J, Gollogly H, Galandauer I, Pais S (2010) Actinomycosis of the common bile duct diagnosed by endoscopic ultrasound fine-needle aspiration. Gastroenterol Hepatol (N Y) 6:725–727
Tiling K (1912) Beitrag zur Aktinomykose des Bauchfells. Virchows Arch Pathol Anat Physiol 207:86
Tomb RR, Stephan F, Haddad A, Choucair J (2009) Cutaneous granular bacteriosis, a rarely diagnosed infection of the head and the neck. Clin Exp Dermatol 34:887–889
Uehara Y, Takahashi T, Yagoshi M, Shimoguchi K, Yanai M, Kumasaka K, Kikuchi K (2010) Liver abscess of Actinomyces israelii in a hemodialysis patient: case report and review of the literature. Intern Med 49:2017–2020
Vargas et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1603930
Vyas et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17173208
Waisman M (1962) Staphylococcic actinophytosis botryomycosis. Granular bacteriosis of the skin. Arch Dermatol 86:525–529
Wang HK, Sheng WH, Hung CC, Chen YC, Liew PL, Hsiao CH, Chang SC (2012) Hepatosplenic

actinomycosis in an immunocompetent patient. J Formos Med Assoc 111:228–231
Wayne MG, Narang R, Chaudhdry A, Stelle J (2011) Hepatic actinomycosis mimicking an isolated tumor recurrence. World J Surg Oncol 9:70
White et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9003818
Wiesmayr S, Stelzmueller I, Tabarelli W, Bargehr D, Graziadei I, Freund M, Ladurner R et al (2005) Nocardiosis following solid organ transplantation: a single-centre experience. Transpl Int 18:1048–1053
Williams AO, von Lichtenberg F, Smith JH, Martinson FD (1969) Ultrastructure of phycomycosis due Entomophthora, Basidiobolus, and associated, "Splendore-Hoeppli" phenomenon. Arch Pathol 87:459–468
Wilson JW (2012) Nocardiosis: updates and clinical overview. Mayo Clin Proc 87:403–407
Winslow DJ (1959) Botryomycosis. Am J Pathol 35:153–167
Wong JJ, Kinney TB, Miller FJ, Rivera-Sanfeliz G (2006) Hepatic actinomycotic abscesses: diagnosis and management. AJR Am J Roentgenol 186:174–176
Yamada T, Sakai A, Tonouchi S, Hawashima K (1971) Actinomycosis of the liver. Report of a case with special reference to liver function tests. Am J Surg 121:341–345
Yamashita et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17485951
Yeung MK (1999) Molecular and genetic analyses of *Actinomyces* spp. Crit Rev Oral Biol Med 10:120–138
Zambon IJ (1985) Actinobacillus actinomycetemcomitans in human periodontal disease. J Clin Periodontol 12:1–20
Zehle K (1906) Beitrag zur pathologischen Anatomie der Aktinomykose des Menschen. Inaug.-Diss, Leipzig
Zemann P (1883) Ueber die Aktinomykose des Bauchfells und der Baucheingeweide beim Menschen. Med Jahrb (Ges Aerzte Wien) 477

Tumor-Like Lesions of the Hepatobiliary Tract: Granulomatous Masses in Syphilis, Brucellosis, and Cat-Scratch Disease

129

Contents

Abstract

Venereal syphilis caused by *Treponema pallidum* induces a complex spectrum of lesions in the hepatobiliary tract, ranging from a distinct fibrosing disease in connatal syphilis to gummatous hepatitis in adult patients. Early syphilis of the liver is characterized by syphilitic hepatitis, a disorder well known in patients with HIV infection. In later stages of the infection, i.e., in tertiary syphilis, hepatic mass lesions can develop. These include syphilomas and gummas. The latter are macroscopic inflammatory lesions of a firm consistence, an irregular rather than spherical shape, and a geographic pattern on cut surfaces. Mass lesions of the liver can also occur in brucellosis. These lesions are spherical, may have a diameter of more than 5 cm, and are characterized by central necrosis, several layers of granulomatous inflammatory reaction, and a peripheral fibrous demarcation. Necrotic and inflammatory nodular lesions with a granulomatous reaction in the liver also occur in cat-scratch disease.

Syphilis and Hepatic Gummas

Introduction

Venereal syphilis (lues) is a complex infectious disease caused by the spirochete *Treponema pallidum* (reviews: Singh and Romanowski

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_129

1999; Antal et al. 2002; LaFond and Lukehart 2006; Lee and Kinghorn 2008).

Treponema is a helical spirochete that belongs to the family *Spirochaetaceae*, order *Spirochaetales*. *Primary syphilis* is the stage of infection when the bacterium penetrates surfaces of mucosae or microabrased skin, this first contact resulting in a lesion called chancre, a painless and later indurated ulcer at the inoculation site. As *T. pallidum* is a highly invasive organism, it spreads already at the primary stage of disease to numerous tissues and organs. Within 3 months of primary infection, manifestations of this spread in the form of a multisystem disorder are in evidence, the *secondary syphilis*. The manifestations of secondary syphilis appear in the form of a characteristic rash, initially roseolar or macular, long-standing lesions then becoming papular or even nodular. In rare situations, the skin lesions become necrotic, a condition termed lues maligna. After this stage of disease, patients enter latent syphilis. Latent syphilis is a form of the disorder that is diagnosed serologically, at least in the asymptomatic phases of this stage. Early latent syphilis, occurring within the first 2 years after infection, is asymptomatic. Late latent syphilis is either asymptomatic or symptomatic. In about one-third of patients having late latent syphilis, symptomatic disease develops. This is also called *tertiary syphilis*.

Epidemiology

Syphilis remains a very common infectious disease. Humans are the only source of *T. pallidum* infection; there are no known nonhuman reservoirs. The WHO estimates that there are 12 million new cases of syphilis per year worldwide. Social disruption, poverty, and changing sexual behaviors have contributed to the sometimes epidemical increase of infections. Also the incidence of congenital syphilis is increasing in many resource-restricted countries.

Liver Involvement in Syphilis

In the course of syphilitic infection, liver involvement occurs in three distinct periods, i.e., congenital (usually transplacental) infection, in the secondary period when treponemes reach the liver via the portal venous blood within a few weeks to a few months after the initial chancre, and in the tertiary (symptomatic latent) period, when after a variably latency interval, manifestations of late syphilis such as gummas develop. Syphilis can induce a broad array of hepatobiliary diseases including hepatitis. Visceral and specifically hepatic manifestations are variable and may mimic several other disorders; this is the reason why this infection has been termed by Sir William Osler, the great imitator (of other diseases; Witkowski and Parish 2002).

Syphilitic Hepatitis

Syphilitic hepatitis is a typical manifestation of early (secondary) syphilis, owing to the spread of numerous viable spirochetes during this stage of disease. Syphilitic hepatitis is common among HIV-infected individuals (Lynn and Lightman 2004; Crum-Cianflone et al. 2009). Among a total of 62 HIV-infected patients with early syphilis, 19.3 % demonstrated abnormal liver enzymes consistent with syphilitic hepatitis (Manavi et al. 2012). Another investigation on 100 HIV-infected patients with acute syphilis revealed 19 patients with laboratory parameters of liver involvement (Jung et al. 2012). Studies with higher incidences of hepatitis in HIV-infected patients with early syphilis have been reported, e.g., 38 % (Crum-Cianflone et al. 2009). Syphilitic hepatitis was also detected after liver transplantation (Camara et al. 2007).

Selected References Baker et al. 1971; Sherlock 1971; Sobel and Wolf 1972; Bhowmick et al. 1975; Feher et al. 1975; Hanchard et al. 1978; Campisi and Whitcomb 1979; Roge et al. 1979; Tiliakos et al. 1980; Agrawal et al. 1982; Echard et al. 1982; Keisler et al. 1982; Petersen et al. 1983; Perrin et al. 1985; Vas et al. 1985; Veerahu 1985; Fischer et al. 1986; Rampal et al. 1986; Archambeaud-Mouveroux et al. 1987; Bukharovich et al. 1989;

Granicki et al. 1990; Relvas et al. 1992; Young et al. 1992; Gschwantler et al. 1996.

Symptomatic syphilitic hepatitis with or without cholestasis is a well-recognized, albeit uncommon complication of early/secondary syphilis (Hahn 1943; Parker 1972; Morrison et al. 1980; Archambeaud-Mouveroux et al. 1987; Schossberg 1987; Young et al. 1992). Cholestatic forms of syphilitic hepatitis are well recognized (Kim et al. 2010), and the cholestasis is sometimes severe ("Icterus syphiliticus praecox"; Michael 1914; Fuhs and Weltmann 1922; Ridruejo et al. 2004) and jaundice marked (Icterus gravis syphiliticus; Wile and Karshner 1917). Already the famous clinician, F. Parkes Weber, described a severely jaundiced patient with secondary syphilis (disseminated lobular necrosis of the liver with jaundice/hepar necroticum cum ictero of Curschmann and Oertel; Weber 1909), relating his observations to a publication of Oertel (1906). Syphilitic hepatitis is usually characterized biochemically by a markedly increased ALP and a minor increase in the aminotransferases. However, syphilitic hepatitis can rarely also result in fulminant hepatic failure (Lo et al. 2007). Histologically, one notes a usually mild lymphohistiocytic portal tract inflammation, sometimes associated with vacuolization and regenerative changes in the interlobular bile duct epithelium. It has been reported that *Treponema* is detectable in the liver lesion in 70 % of the patients (Buschke and Fischer 1905; Jozsa et al. 1977).

Hepatic Mass Lesions in Syphilis: Gummas and Syphilomas

Tertiary syphilis is, in contrast to the preantibiotic era, a rather rare disease, although, e.g., more than 25,000 cases of primary or secondary syphilis are diagnosed annually in the United States. In the early- to mid-twentieth century, the liver was regarded as the commonest internal organ to harbor a syphilitic gumma (Rolleston and McNee 1929), although the clinical diagnosis of hepatic gumma was rarely made in this time period (Tucker and Dexter 1946; Neuner 1950; Nicol and Terry 1951; Viranuvatti and Kochaseni 1953; Ito et al. 1963). The frequency of tertiary liver involvement in syphilis (identified at necropsy as hepar lobatum) as based on necropsies is given in the literature as 0.45 % (66 cases among 14,561 autopsies performed between 1908 and 1941; Hahn 1943) and 0.42 % (102 cases among 23,792 autopsies; Symmers and Spain 1946) and was found to be 0.3–1.5 % of cases in a nonselected autopsy series (Kellock and Laird 1956). Due to the less efficient diagnostic techniques available those days, it is thought that many of the commonly silent gummatous liver lesions were not detected in living patients (Shapiro and Weiner 1951). The more potent treatment measures available have caused tertiary liver syphilis to be a rare disease, but the rapidly increasing frequency of syphilis in certain regions of the world is expected to cause more of these lesions in the future.

Gummatous Syphilis of the Liver

Gummatous syphilis of the liver (hepatitis gummosa), a visceral manifestation of tertiary syphilis, is characterized by the development of solitary or multiple luic gummas in the liver substance.

Selected References McRae and Caven 1926; Hahn 1943; Symmers and Spain 1946; Shapiro and Weiner 1951; Viranuvatti and Kochaseni 1953; Kellock and Laird 1956; de Gouveia et al. 1961; Gencsi 1962; Ito et al. 1963; Salembier 1967; Parnis 1975; Naveau et al. 1982; Shapiro and Gale 1987; Cronin et al. 1987; Fischbach et al. 1991; Dämmrich et al. 1992; Rossi et al. 1992; Maincent et al. 1997; Peeters et al. 2005; Chen et al. 2008.

Tertiary liver involvement was found at postmortem examinations in 4.9 % of 1,165 adults suffering from syphilis at any stage (Hahn 1943), in 16 % for another series of 314 patients with tertiary syphilis (Symmers and Spain 1946), and in 0.3–1.5 % of cases in a nonselected necropsy series (Kellock and Laird 1956). Hepatic gummas

have also been recognized in congenital syphilis (Whitehouse and Macfarlane 1958; Debré et al. 1962), a currently resurgent disorder (Dobson 2004; Walker and Walker 2007), although congenital gummatous hepatitis was identified to be an exceptional finding in an extensive compilation on congenital syphilis (Nabarro 1954), and was not found in a study on 22 children with this disease (Flegel 1951). In adult patients, these mass lesions may cause differential diagnostic difficulties in relation to suspected malignancy, in particular multinodular metastatic disease (Rampal et al. 1986; Fischbach et al. 1991; Maincent et al. 1997; Shim 2010). On CT, gummas have a low-density appearance with slight peripheral enhancement upon contrast (Fischbach et al. 1991; Dämmrich et al. 1992). In contrast to tuberculosis, calcifications are seldom seen (Alergant 1956; Rampal et al. 1986; Shapiro and Gale 1987). The presence of several or numerous luic/syphilitic lesions in tertiary syphilis can result in syphilitic multinodular liver that may mimic malignancy (Gruber 1930; Alergant 1956; Rampal et al. 1986). Sclerogummatous hepatitis in syphilis may be associated with amyloidosis (Naveau et al. 1982). Upon successful treatment, liver gummas leave a small scar on CT scans (Peeters et al. 2005).

The gummas are usually firm nodes of irregular rather than spherical shape that are situated within the liver substance, close to the hilar area, or in the subcapsular compartment. They can reach a diameter of 2.5 cm or more (Maincent et al. 1997). The cut surface is either homogeneous gray to gray reddish or with a geographic pattern (reviewed by Gruber 1930). Gummatous lesions may develop along the intrahepatic bile ducts (pericholangitis gummosa) or along the intrahepatic portal vein branches (peripylephlebitis gummosa). Sometimes, the process involves the inner parts of venous walls (Chiari's endophlebitis luica hepatica), causing venous obliteration (endophlebitis hepatica obliterans). In the portal venous system, an obliterative sclerosing process with vein atrophy may ensue (pylephlebosclerosis). Gummas located close to the liver surface may be associated with fibrosing perihepatitis, fibrosis of Glisson's capsule (Nicol and Terry 1951), and fibrous adhesions between the liver and adjacent organs. Gummas can also be associated with syphilitic artery disease (endarteritis and mesoarteritis luica hepatica). Liver shrinkage/atrophy caused by gummous lesions can elicit a marked compensatory hypertrophy/hyperplasia of the liver substance (Reinecke 1898; Schorr 1907).

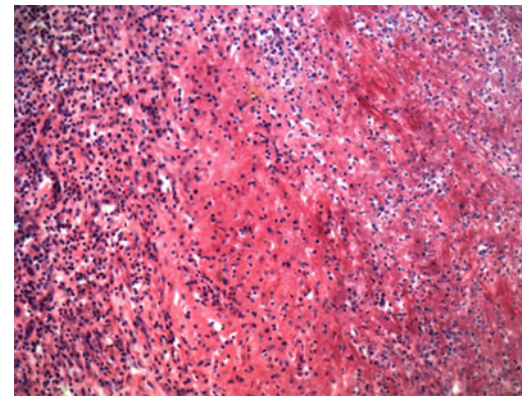

Fig. 1 Gumma in hepatic syphilis. The *right* of the figure shows necrosis with nuclear debris. In the *middle*, fresh eosinophilic necrosis is noted, however without associated granulomas. The *left* part shows fibrosing granulation tissue (hematoxylin and eosin stain)

Histologically, hepatic gummas show a central necrosis with a usually still preserved reticulin fiber network (Fig. 1). The necrosis is sometimes described in the literature as caseous, but close examination will uncover certain differences, mainly a lack of the numerous nuclear debris typically found in tuberculosis. At the border of the lesions, a granulomatous reaction is seen, commonly in the form of a band of loosely arranged epithelioid cells with confluent small and sometimes blurred granulomas. Langhans-type giant cells are rare (Binder 1904). A cellular infiltrate of variable density forms the interface to scarred zone surrounding the gumma. Around small vessels there is sometimes a lymphocytic and plasmacellular infiltration suggesting vasculitis. The adjacent liver tissue may show lymphocytic portal tract infiltration (accompanying portal hepatitis; similar to what is seen in secondary syphilis).

Typically, and in contrast to early syphilis, gummas contain morphologically detectable spirochetes in 0–5 % of cases only. Within the same liver, the entire spectrum of gummatous lesions may be found, ranging from cellular lesions (so-called active gumma or syphiloma) with poor fibrosis, to markedly fibrosclerosed nodules (sclerogummas). The centripetal sclerosis (or scarring) of gummas leads to retraction of the liver substance, the pathogenic mechanism leading to hepar lobatum (Nicol and Terry 1951; Cronin et al. 1987; Peeters et al. 2005). Grossly, hepar lobatum is characterized by a coarse nodular deformation of the organ with usually deep furrows between the lobe-like parts of the liver substance caused by the retracting scars. The resulting picture may mimic metastatic disease. On the other hand, metastatic carcinoma itself may cause hepar lobatum owing to stromal reactions of scarring necroses (Klinge and Ormann 1988; Gravel et al. 1996), also after chemotherapy (hepar lobatum carcinomatosum; Chin et al. 1987; Qizilbash et al. 1987; Uhlmann et al. 1996). In situations where only one liver lobe is involved, the contralateral liver lobe may undergo compensatory hypertrophy, resulting in the atrophy/hypertrophy complex. Scarring lesions close to the liver hilum can comprise the portal vein and cause portal hypertension (Berthelot et al. 1964), sometimes with formation of portal vein cavernoma (Hunt 1961).

Hepatic Syphilomas

The term, syphiloma, has been coined by Wagner in the nineteenth century (Wagner 1864) to denote focal lesions different from gummas. Miliary syphilomas have chiefly been observed in patients with congenital syphilis. These lesions are commonly associated with hepatomegaly, a firm liver, and sometimes with fibrous perihepatitis, this capsular fibrosis containing stainable spirochetes. Syphilomas are grossly ill defined and small yellowish to gray lesions which may seldom reach the size of a pea, but commonly show the size of a milium (hence the term, miliary syphilomas). The smallest lesions have been compared to semolina grains (grains de semoule; Gubler 1852). They are sometimes diffusely scattered through the liver. Superficial syphilomas may bulge through the liver capsule (Gruber 1930). Owing to their color, syphilomas are easily recognizable against the darker color of the parenchyma. Miliary syphilomas are histologically characterized by a central, non-caseous necrosis containing remnants of hepatocytes (with fatty change, causing the grossly yellowish color of the lesions; Fig. 2) and usually showing nests of stainable spirochetes, the bacteria being visibly damaged in the center of the lesion in comparison with microorganisms in the periphery (Gruber 1930). The necrotic foci are either surrounded by a dense granulocyte reaction (so-called abscess-like miliary syphilomas; Müller 1883; Aschoff 1903) or one notes an epithelioid cell reaction or even a granulomatous reaction around the necrosis (miliary granuloma or miliary gumma; Gruber 1930), this granulomatous form usually lacking multinucleated Langhans-type giant cells. Miliary syphilomas are commonly located within the lobules and are preferentially situated close to the terminal veins (Gruber 1930). Syphilomas may form confluent grapelike clusters surrounded by fibroblastoid granulation tissue. Hepatic syphilomas developing in congenital syphilis may contain numerous spirochetes (see below).

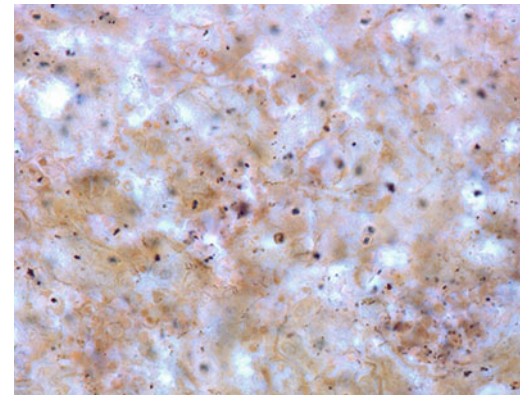

Fig. 2 Syphiloma of the liver. Within a background of necrosis, few *Treponema* organisms are seen (thin waved rods of dark color; Warthin-Starry stain)

Hepatic Pseudotumors in Syphilis of the Liver

Inflammatory pseudotumor of the liver has been observed in secondary syphilis (Mahto et al. 2006). Gummatous syphilis of the liver is seldom associated with peliosis hepatis and has been found to cause tumor-like lesions (peliosis hepatis pseudotumor) of several cm size (Chen et al. 2008).

Syphilis of the Bile Duct System

Rarely, syphilitic gummata may develop along the biliary tract and cause biliary obstruction (gummous cholangiopathy; Rolleston 1907; Edwards and Weir 1964). Syphilitic gumma of the pancreas may involve the most distal part of the common bile duct (Lelong et al. 1952). Gummous lesions can involve the gallbladder (cholecystitis luica gummosa). In early syphilis, *Treponemas* may colonize vascular structures in hepatic portal tracts and are thought to induce a vasculitis followed by epithelial damage of small bile ducts and ductules (Romeu et al. 1980). This process can end up with non-syndromic small duct ductopenia. Bile duct paucity has been found in a 2-week-old girl with congenital syphilis. She presented with jaundice and hepatosplenomegaly and has a high titer of IgM antibody to *Treponema pallidum*. The patient died of respiratory failure and autopsy showed syncytial giant cell hepatitis and paucity of small intrahepatic bile duct, associated with marked ductular proliferation (Sugiura et al. 1988).

Brucellosis and Brucelloma

Introduction

Brucellosis is a zoonotic disease caused by intracellular bacteria of the genus *Brucella* (reviews: Pappas et al. 2005; Ficht 2010). Regions where brucellosis is endemic are the Mediterranean basin, the Middle East, Russia, Mongolia, Latin America, the Caribbean, and Mexico. Brucellosis in humans is characterized by a greatly varied clinical image, and the course of the disease may be acute, subacute, or chronic. Patients often present with a febrile illness, in part of the patients associated with organ involvement, including severe liver disease. The infection in humans is mainly observed in specifically exposed persons, such as veterinarians, veterinary technicians, insemination service employees, zoo technicians, farmers working on multi-herd farms, slaughterhouse employees, and persons working in meat, milk, or fur processing enterprises (Galinska and Zagorski 2013).

The cause of Malta fever was identified by the Scottish military physician, bacteriologist, and pathologist, David Bruce (1855–1931), during his stay in the Valetta Hospital in Malta. Bruce was impressed by Robert Koch's discovery of the tubercle bacillus and decided to investigate Malta fever which affected many soldiers of the British garrison. Late in 1886 he found, by means of a purchased microscope, enormous numbers of single, gentian violet-positive and Gram-negative micrococci in the spleen of a fatally ill patient. Bruce inoculated three monkeys with the organisms cultured in peptone broth, and 16 days later one monkey's temperature rose to 41 centigrades and the animal died. From several inoculated monkeys, the organism could be cultivated in pure culture, hence fulfilling Koch's criteria (Bruce 1887; 1888). The genus *Brucella* belongs to the alpha2 subdivision of proteobacteria, together with *Ochrobactrum*, *Rhizobium*, *Rhodobacter*, *Agrobacterium*, *Bartonella*, and *Rickettsia*. Transmission of *Brucella* species to the human host occurs through the consumption of infected, unpasteurized milk products, through contact with infected animal parts and through the inhalation of *Brucella*-containing aerosolized particles. Brucellosis is also an occupational disease (shepherds, abattoir workers, dairy-industry professionals). *Brucellae* can enter the human host via the oral and respiratory tracts and can also penetrate the mucous membranes covering the conjunctiva and vagina as well as non-damaged skin, similar to *Leptospira* pathogens. On surfaces in the environment and in the host, *Brucella* produces complex populations, including biofilms,

subject to quorum sensing. After invasion of mucosal surfaces, phagocytes (mainly macrophages) ingest the organisms. Most of the ingested *Brucellae* are killed, but 15–30 % survived in gradually evolving *Brucella*-containing compartments. These surviving organisms proliferate within the macrophage system without affecting host cell integrity. In macrophages, *Brucella* dwells in a parasitophorous vacuole derived from membranes of the endoplasmic reticulum of the host cells via subversion of the host's cell secretory pathway.

Clinical Features

Brucellar infection is a disease of protean manifestations, but fever is invariably present (spiking, relapsing, or protracted). Malodorous perspiration is regarded as almost pathognomonic. Lymphadenopathy, hepatomegaly, and splenomegaly are frequently present. The most common complication of brucellosis is inflammatory osteoarticular disease (mainly peripheral arthritis, sacroiliitis, and spondylitis). The second most common site of focal brucellosis is the reproductive system (epididymoorchitis). Brucellosis during pregnancy is characterized by invasion of the trophoblast by *Brucella* and confers a significant risk of abortion. Hepatitis is common, but mass-producing lesions (see below) are rare. Involvement of the central nervous system (neurobrucellosis) occurs in 5–7 % of cases. Endocarditis (mainly of the aortic valve) is the main cause of mortality. As the organism tends to persist in the macrophage system, long-lasting infection is a well-recognized feature of brucellosis. *Brucella* DNA load persists for years after clinical cure (Vrioni et al. 2008). Relapses, at a rate of about 10 %, usually occur in the first year after infection and are often milder than the initial disease.

Tumor-like Liver Involvement in Brucellosis: Hepatic Brucelloma

Hepatic brucellar lesions (abscesses and necroses) are a manifestation of chronic hepatosplenic brucellosis (Ariza et al. 2001; Shouval 2010). No distinction is usually made in the literature between small multifocal hepatosplenic abscesses, detected rather in acute brucellosis, and larger lesions that are usually caseiform necroses with calcification. Small purulent lesions can develop in relatively early phases of brucellosis already, chiefly in severe infection with multiple visceral manifestations. However, mass-producing (pseudotumoral) caseiform necroses with calcification typical for brucellosis of the liver usually emerge in chronic infection. These pseudotumoral brucellar lesions are now termed brucelloma. The term, hepatic brucelloma, had been coined by Davion and coworkers in 1987 who reviewed 14 cases from the literature and added an own observation (Davion et al. 1987). Previously, brucelloma has been described under a wide range of terms (pseudotumoral brucellar caseous necrosis of the liver; chronic hepatosplenic suppurative brucellosis; caseiform necrotizing brucellar hepatitis; hepatic brucellar abscess; necrotizing hepatic granulomatosis; brucellar caseiform hepatic abscess), based on numerous old and recent published observations, the first report probably dating from 1957 (Spink 1957), followed by numerous other observations. Hepatic brucelloma is known to be caused by *Brucella melitensis*, but similar lesions have also been observed in conjunction with *Brucella* suis infection (Spink 1957; Paton et al. 2001). The delay between the primary infection and the diagnosis of brucellomas ranges between few months and more than 40 years (Davion et al. 1987). Clinically, liver brucellomas may be latent lesions, detected during laparotomy for other reasons or in context with abdominal imaging. It can also be the cause of fever, malaise and abdominal discomfort, and pain. In a review of 14 cases, abdominal pain was present in 8 cases (Davion et al. 1987). Hepatomegaly due to larger lesions has been reported. Imaging studies revealed that the lesions are single in about two-thirds and multiple in one-third of the cases. With ultrasonography, the lesions are iso- or hypoechoic with respect to the surrounding parenchyma and have poorly defined borders. Some lesions contain multiple, small anechoic areas (Meloni et al. 2008). In

Fig. 3 Tumor-like manifestation of hepatic brucellosis (brucelloma). The encapsulated lesion displays central laminated and partially calcified necrosis and concentric layers of inflammation

contrast-enhanced CT, brucellomas are predominantly solid with irregular borders, and the majority are hypodense with the liver. A constant finding is the presence of hypodense solid areas and/or tiny cystic areas separated by fine or thick enhancing trabeculations (Arcomano et al. 1977; Pons et al. 1981; Cosme et al. 2001; Sisteron et al. 2002; Ruiz Carazo et al. 2005; Chourmouzi et al. 2009). A unique type of calcification in the necrotic foci is typical for hepatic brucelloma and occurs in 80–100 % of reported cases (Williams and Hara 1967; Bastin et al. 1973; Arcomano et al. 1977; Pons et al. 1981; Ruiz Carazo et al. 2005; Ennibi et al. 2010). They may be single or multiple, sometimes exceeding 1 cm in size. Their shape varies from flocculant densities to crescent-like structures or a dense central calcification surrounded by one or several concentric halos.

Selected References Spink 1964; Bastin et al. 1973; Morera et al. 1975; VicDupont et al. 1976; Janbon and Bertrand 1978; Ladero Quesada et al. 1979; Pons et al. 1981; Cervantes et al. 1982; De Marliave et al. 1982; Williams and Crossley 1982; Naveau et al. 1983; Greiner et al. 1984; Davion et al. 1987; Di Palo et al. 1987; Vargas et al. 1991; Berthet et al. 1994; Débat-Zuguéreh et al. 1995; Colmenero et al. 1996; Vallejo et al. 1996; Banos Madrid et al. 1999; Halimi et al. 1999; Ariza et al. 2001; Paton et al. 2001; Sadia Pérez et al. 2001; Villar et al. 2001; Colmenero Jde et al. 2002; Sisteron et al. 2002; Ruiz Carazo et al. 2005; Akritidis et al. 2007; Ibis et al. 2007; Kilicaslan et al. 2008; Starakis et al. 2008; Ennibi et al. 2009; Barutta et al. 2013.

Small and early hepatic brucellar lesions are either single or multiple abscess-like foci, sometimes with a red rim reflecting active hyperemia or grossly resemble miliar lesions of tuberculosis. Brucelloma is circumscribed tumor-like lesion with a diameter of 1 cm to several cm (Fig. 3). In hepatic resection specimens, peripheral brucellomas situated close to the liver capsule may be associated with marked capsular thickening and fibrosing perihepatitis, eventually with formation of a whitish firm plaque resembling so-called pseudocartilaginous perihepatitis. The cut surface of large brucellomas has highly characteristic features. The center of the mass is commonly occupied by a white to yellowish-gray necrosis, with accumulation of a crumbling, "cloudy," and friable material that is rather sharply demarcated and tends to bulge. However, this type of necrosis is not creamy white and sticky as in tuberculous caseification necrosis. Surrounding this central necrosis, one notes a striking sequence of circular complete or incomplete lamellae of yellowish to reddish-brown color, likely to reflect the growing phases of the lesion, and also clearly seen at imaging. In some cases, the mass contains grossly visible hemorrhages. Flocculent or crescent-shaped calcifications are found, and sometimes calcification is extensive, not permitting to cut

the mass with a knife before decalcification. Large brucellomas may be surrounded by satellite nodules of variable size.

In brucelloma, a purulent inflammation (suppurative hepatic brucellosis) is usually only seen in early phases of the disease or in small lesions developing in the course of the infection. Therefore, the term "hepatic abscess," previously employed in several publications on large hepatic lesions, is misleading in a considerable number of cases. Necrosis in brucelloma is, at low magnification, characterized by an amphophilic or even slightly basophilic mass, this staining feature being caused by the accumulation of numerous nuclear debris. At the periphery of this caseiform coagulation necrosis, a red rim is regularly observed, caused by a protein-rich exudative reaction. Calcifications are noted within the necrosis and/or the fibrosed peripheral parts of it (Figs. 4, 5, and 6). The necrosis is surrounded by a rim of epithelioid macrophages, often without isolated granulomas. This zone is followed to the periphery by a cellular immune reaction, containing numerous lymphocytes and sometimes lymph follicles. Most of the lymphocytes are CD3-positive T cells, but CD79a- and CD20-positive B cells are also in evidence. A striking feature is the high content of plasma cells (CD38 positive), usually not seen in caseiform tuberculosis. A granulation tissue develops around the lesion, and the inflammatory process blends into the adjacent liver tissue, with formation of interface lesions. In large and older brucellomas, the necrosis is progressively replaced by a hypocellular collagenous tissue that still reflects the circular lamellar pattern and contains calcifications.

There is some controversy in the literature regarding granuloma formation in hepatic brucellosis (Nagalotimath et al. 1979; Young 1979; Ledro et al. 1983), but this may be due to differential epithelioid cell production as a function of

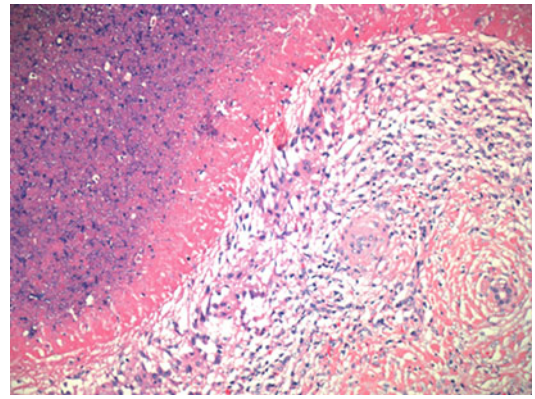

Fig. 5 Brucellosis of the liver. A zone of basophilic necrosis with high density of nuclear debris (*left upper* corner) blends into a zone of fresh eosinophilic necrosis showing shadow epithelioid cells. Note the well-developed granulomatous rim in contact with a portal tract (*right lower* corner; hematoxylin and eosin stain)

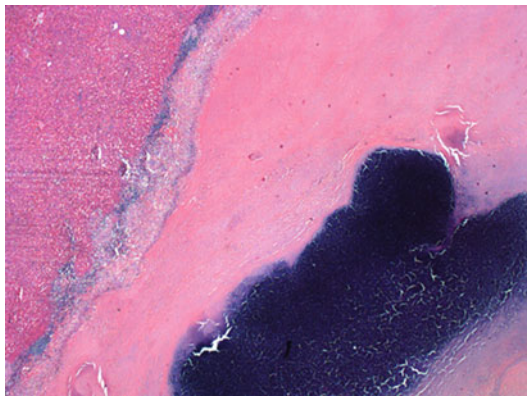

Fig. 4 Hepatic brucelloma. The strongly eosinophilic necrosis reveals marked central dystrophic calcification. Necrosis is peripherally demarcated from liver tissue by a granulomatous rim (to the *left*; hematoxylin and eosin stain)

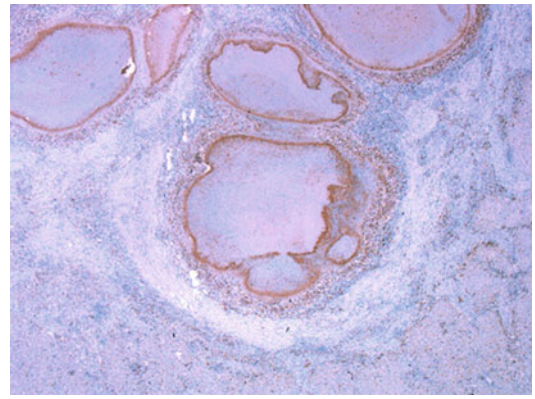

Fig. 6 Nodular lesions in hepatic brucellosis are surrounded by numerous activated macrophages (brown rims; CD68 immunostain)

the antigenic profile of *Brucella* strains, the immune status of the host, and the phase of the infectious disease at the time point of sampling. In forid caseiform necrosis, an epithelioid cell reaction with or without epithelioid cell micronodules (granulomas) at the peripheral interface of the necrosis is an almost constant feature.

Other Hepatic Manifestations of Brucellosis

Rarely, brucellosis is associated with febrile illness, hepatomegaly, cholestasis, and the presence of small hypodense rounded lesions in the liver and the spleen (Fernandez Fernandez et al. 2010; Schmid and Birkenfeld 2010). This damage pattern may in part be caused by liver cells themselves, as *Brucella*-infected hepatocytes mediate tissue-damaging immune responses, in that they secrete IL-8, express ICAM-1, attract neutrophils, and induce the expression of MMP-9 in neutrophils (Delpino et al. 2010).

Cat-Scratch Disease: Hepatobiliary Manifestations

Introduction

Cat-scratch disease (CSD; synonym: cat-scratch fever) is caused by *Bartonella* (*B.*) *henselae*, a worldwide distributed zoonotic pathogen (Zangwill 2013). CSD is therefore classified as a bartonellosis. The term, cat-scratch fever, is now obsolete, because not all patients with CSD show a febrile course, and the term might be confounded with cat-bite fever (rat bite fever; Sodoku). As a function of the immune status of the host, *B. henselae* can cause a broad spectrum of clinical manifestations, the most important being CSD usually occurring in immunocompetent hosts and bacillary angiomatosis, which is typically seen in immunocompromised hosts (Carithers 1985; Maguiña et al. 2009; Kaiser et al. 2011).

CSD was first described in 1950 (Debré et al. 1950; Keefer and Greer 1950), although Parinaud described similar symptoms in the context of oculoglandular syndrome in 1889 (Parinaud 1889). In the publication of Keefer and Greer (1950), it is noted that "cat-scratch fever" is a term that was first used by Dr. Lee Foshay of the University of Cincinnati College of Medicine to describe lymphadenitis of unknown etiology following cat scratches. Keffer and Greer obtained a vial from Lee Foshay containing "cat fever antigen" prepared from a former patients' bubo, heated to 60 centigrades on two subsequent days, and performed an intradermal injection to their patient, followed by itching, redness, and swelling at the injection site. This seems to be the first skin test performed for an agent that was unknown those days. CSD as a disease entity was then described in detail in 1951 (Greer and Keefer 1951).

Microbiology

In 1983, a report described a small, pleomorphic Gram-negative bacillus detected by the Warthin-Starry silver stain in infected lymph nodes of patients with cat-scratch disease (Wear et al. 1983). The organism was successfully isolated and cultured about 5 years later (English et al. 1988), and in 1991 Brenner and coworkers coined the taxon name *Afipia felis* to denote this bacterium, after the Armed Forces Institute of Pathology (Brenner et al. 1991). In 1992, *Rochalimaea henselae* was isolated from HIV-infected patients with bacillary angiomatosis, peliosis hepatis, and fever syndromes, and it was noted that the majority of the patients with clinically suspected cat-scratch disease studied had high serum titers to the *Rochalimaea henselae* antigen (Regnery et al. 1992). Later, *Afipia felis* was refuted and the genera *Bartonella* and *Rochalimaea* were united, the genus *Bartonella* having precedence (Brenner et al. 1993; Bowman 2011).

Clinical Presentation

B. henselae can cause two different pathologic reactions, depending on the immune status of the host: CSD and bacillary angiomatosis. The latter

condition, characterized by abnormal angiogenesis, is treated in a separate chapter. CSD typically starts as localized papule of the skin appearing 3–5 days after a cat scratch or bite and progresses into a pustule. Within 2 weeks, a tender locoregional lymphadenitis develops. In several reports it was stated that most patients remain afebrile and do not show systemic symptoms and signs. However, an analysis of 130 seropositive patients from Japan revealed that 77 % had general symptoms, such as fever, headache, and malaise. 20.8 % of the cases were classified as atypical CSD (Murakami et al. 2002). CSD is, in most cases, a self-limited illness resolving in 2–4 months, with locoregional unilateral lymphadenitis as its hallmark. However, some immunocompetent patients may show atypical CSD caused by systemic *B. henselae* infection, including prolonged fever or fever of unknown origin (FUO), malaise, headache, sore throat, myalgia, arthralgia, erythema nodosum-like skin eruptions, and parotid gland swelling, features that may lead into another diagnostic direction. Complications occur in about 2 % of the patients (Adal et al. 1994) and comprise Parinaud's oculoglandular syndrome, signs of encephalopathy, neuroretinitis with occlusive vasculitis, cat-scratch optic neuropathy (CSON), valvular endocarditis and myocarditis, osteolytic lesions, mesenteric lymphadenitis, and hepatosplenic involvement. Among 27 Japanese patients with atypical CSD, 37 % had FUO, 22.2 % neuroretinitis, 14.8 % encephalopathy, and 11.1. hepatic lesions (Murakami et al. 2002). The diagnosis is made in the appropriate clinical setting by finding an inoculation site, a positive skin test, positive serology and indirect immunofluorescence assay, and eventually a PCR-based typing. Real-time PCR assay targeting the groEL gene has been developed as a rapid and sensitive method for the detection of *Bartonella* species (Diederen et al. 2007).

Hepatic Manifestations of Cat-Scratch Disease

Hepatic and/or splenic involvement has more often been described in children, adolescents, and young adults than in older individuals. CSD of the liver is often associated with splenic lesions (hepatosplenic CSD; Belvisi et al. 2012), although involvement of the spleen is more common than that of the liver. In patients in whom the diagnosis was made by skin testing, splenomegaly was observed in 12 % (Margileth et al. 1987). Hepatic infection with *B. henselae* can present in several forms, including a distinct form of exudative granuloma-like masses, granulomatous hepatitis (Lenoir et al. 1988), focal inflammation (anicteric hepatitis; Korbitz 1973; Katner et al. 1986), peliosis hepatis, and bacillary angiomatosis, the latter two manifestations being seen in immunosuppressed patients. The first hepatic focal lesions were described in 1950 as "visceral granulomatous lesions" (Inglis and Tonge 1950). Since then, numerous cases of CSD-induced granulomatous hepatitis and tumor-like masses of the liver have been reported. These forms of CSD are mostly associated with CSD having systemic signs including a febrile course. Early reports identified hepatomegaly in association with classical CSD, in association with lymphadenopathy (Rocco et al. 1985), and as the sole focus of involvement in FUO (Malatack and Jaffe 1993). Typical CSD-associated liver masses have also been found in transplanted livers (Bonatti et al. 2006; Thudi et al. 2007). The mass lesions have in part been described as hepatic abscesses, but as outlined below, the histomorphology of the lesions is not exactly that of abscesses in the proper sense of the term.

Selected References Rocco et al. 1985; Rizkallah et al. 1988; Port and Leonidas 1991; Rappaport et al. 1991; Cataldi et al. 1995; Vanlemmens et al. 1995; Lamps et al. 1996; Siret and Hardy 1996; Danon et al. 2000; Le Tallec et al. 2003; Ishikawa et al. 2006; Liao et al. 2006; Marsilia et al. 2006; Renou et al. 2010; Vanderheyden et al. 2012.

In mass-forming hepatic CSD, ultrasonography revealed multiple round hypoechoic lesions of variable size, but up to 3 cm diameter and rarely more (Rocco et al. 1985; Port and Leonidas 1991; Rappaport et al. 1991; Stuart and Nowicki 1998), while CT examination both before and after IV

contrast administration has shown multiple, well-defined, low-attenuation lesions, ranging in diameter from 3 to 2 cm (Delbeke et al. 1988; Rappaport et al. 1991). Larger lesions can show peripheral enhancement after injection of contrast material (Rappaport et al. 1991). The nodules may form confluent masses (Kahr et al. 2000) and can form calcifications as a late change (Talenti et al. 1994). Hepatic masses in CSD may be associated with involvement of periportal, periaortic, and peripancreatic lymph nodes. Involvement of the gallbladder has been reported in one case (Marsilia et al. 2006).

Pathology

Laparoscopy in a pediatric patients with hepatosplenic manifestations of CSD revealed multiple soft, whitish-tan lesions (Liao et al. 2006). In the course of open liver biopsy, well-demarcated nodules of several mm diameter were seen, the lesions having slightly hyperemic margins (Rappaport et al. 1991). Yellowish stellate (collapsed) abscess-like alterations may be seen. In some cases, the abscess-containing granulomatous lesions grow to tumors of up to 3.5 cm diameter (Murano et al. 2001).

The histologic hallmark of CSD is a complex granuloma-like lesion termed necrotizing granuloma (Figs. 7 and 8; Rizkallah et al. 1988; Rappaport et al. 1991; Malatack and Jaffe 1993; Vanlemmens et al. 1995; Lamps et al. 1996; Liston and Koehler 1996; VanderHeyden et al. 2012), a lesion which may grow to large, tumor-like masses (Murano et al. 2001). This unique lesion patterns mainly occurring in lymph nodes of patients with pseudotuberculosis had previously been termed reticulocytic absceding lymphadenitis (Masshoff 1953). It is characterized by a central and often stellate (star-shaped) abscess-like exudate containing variable numbers of neutrophils and numerous nuclear and cellular debris, resulting in a basophilic area at low magnification and a stippled appearance at higher magnification. Apoptosis of leukocytes causes the large amounts of cell fragments and condensed nuclear remnants. In principle, this complex composition of the exudative reaction does correspond neither to typical abscess nor to necrosis. Parts of the lesion are not stellate shaped but rather exhibit a cerebriform or garland-like morphology. The inflammatory reaction around this focus typically shows three layers. Just outside this stellate exudate, one notes a rim of palisading epithelioid macrophages/histiocytes, sometimes with interspersed multinucleated giant cells of the Langhans type. This is followed by a zone rich in lymphocytes, non-epithelioid macrophages, and few plasma cells. The outermost layer has less infiltrate cells and shows fibrosis. It is assumed that the characteristic stellate morphology of the inner part of the lesion results from the

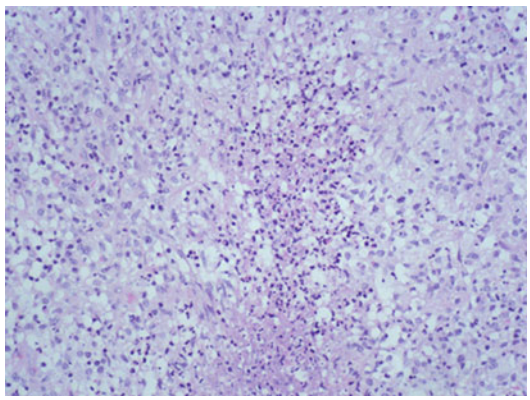

Fig. 7 Cat's scratch disease of the liver. Central slit-like (collapsed) abscesses are surrounded by a granulomatous reaction (hematoxylin and eosin stain)

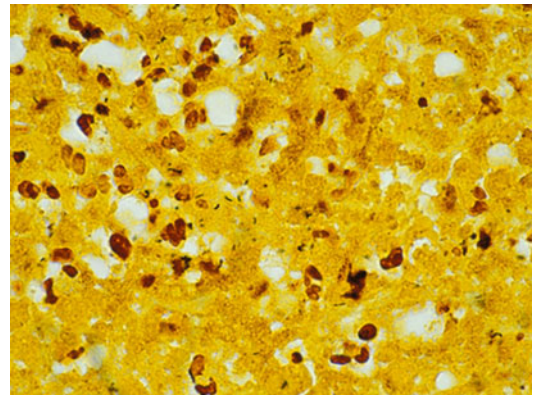

Fig. 8 Cat's scratch disease of the liver. *Bartonella* organisms are visible as short black rods (Warthin-Starry stain)

lesion's collapse. Within the lesions, but mainly in the transition zone between the central stellate focus and epithelioid cells, short rodlike bacteria can be found by use of the Warthin-Starry and Steiner silver stains. The Steiner silver stain seems to be the most sensitive test but is the least specific in comparison with immunofluorescence and PCR. It was found that granulomas in CSD consist of S100A8-, S100A9-, HLA-DR+, CD40+, and TNFalpha+ macrophages, while macrophages embracing the granulomas were S100A8+ and S100A9+. It was shown that the latter macrophages continuously migrate to granulomas, where part of the macrophages undergo apoptosis (Schweyer and Fayyazi 2002). By use of specific antibodies, *B. henselae* can immunohistochemically be detected in the lesions (Reed et al. 1992; Min et al. 1994; Caponetti et al. 2009). The bacteria can also be diagnosed in formalin-fixed tissue via PCR assays (Qian et al. 2005).

References

Adal KA, Cockerel CJ, Petri WA (1994) Cat scratch disease, bacillary angiomatosis, and other infections due to Rochalimaea. N Engl J Med 330:1509–1515

Agrawal NM, Sassaris M, Brooks B, Akdamar K, Hunter F (1982) The liver in secondary syphilis. South Med J 75:1136–1138

Akritidis N, Tzivras M, Delladetsima I, Stefanaki S, Moutsopoulos HM, Pappas G (2007) The liver in brucellosis. Clin Gastroenterol Hepatol 5:1109–1112

Alergant CD (1956) Gumma of liver with calcification. AMA Arch Intern Med 98:340–343

Antal et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/11825779

Archambeaud-Mouveroux F, Morand P, Bernard P, Sautereau D, Meloni B, Antoine E, Catanzano G (1987) Hepatic involvement in secondary syphilis (in French). Gastroenterol Clin Biol 11:93–95

Arcomano JP, Pizzolato NF, Singer R, Zucker SM (1977) A unique type of calcification in chronic brucellosis. AJR Am J Roentgenol 128:135–137

Ariza J, Pigrau C, Canas C, Marron A, Martinez F, Almirante B, Correidora JM et al (2001) Current understanding and management of chronic hepatosplenic suppurative brucellosis. Clin Infect Dis 32:1024–1033

Aschoff L (1903). Über akute entzündliche Erscheinungen an Leber und Nebennieren bei kongenitaler Syphilis. Verhandl. Deutsch. pathol. Ges. 6. Tagung Kassel, 205

Baker AL, Kaplan MM, Wolfe HJ, McGowan JA (1971) Liver disease associated with early syphilis. N Engl J Med 284:1422–1423

Banos Madrid R, Gomez J, Vicente Cantero M (1999) Hepatic abscess from Brucella (in Spanish). Gastroenterol Hepatol 22:162

Barutta L, Ferrigno D, Melchio R, Borretta V, Bracco C, Brignone C, Giraudo A, Serraino C et al (2013) Hepatic brucelloma. Lancet Infect Dis 13:987–993

Bastin R, Vilde JL, Lapresie C, Marsac C, Dupont B (1973) Hépatite brucelienne avec nécrose caséiforme. Med Chir Dig 2:199–201

Belvisi et al (2012) http://www.ncbi.nlm.nih.gov/pubmed/22801097

Berthelot P, Caroli J, Eteve J, Demirleau J (1964) Tertiary syphilis of the liver with portal hypertension and portacaval anastomosis (in French). Rev Med Chir Mal Foie 39:149–158

Berthet B, Moutardier V, Stein A, Raoult D, Le Trent YP, Assadourian R (1994) Hepatic tumoral form of bacterial infections. Diagnostic and therapeutic considerations. J Chir (Paris) 131:291–295

Bhowmick BK, Simpson B, Way SP (1975) Secondary syphilis presenting jaundice. Postgrad Med J 51:412–416

Binder A (1904) Über Riesenzellenbildung bei kongenitaler Lues (On the formation of giant cells in congenital syphilis). Virchows Arch Pathol Anat Physiol 177:44

Bonatti H, Mendez J, Guerrero I, Krishna M, Ananda-Michel J, Yao J, Steers JL, Hellinger W et al (2006) Disseminated *Bartonella* infection following liver transplantation. Transpl Int 19:683–687

Bowman DD (2011) Introduction to the alpha-proteobacteria: Wolbachia and Bartonella, Rickettsia, Brucella, Ehrlichia, and Anaplasma. Top Companion Anim Med 26:173–177

Brenner DJ, Hollis DG, Moss CW et al (1991) Proposal for *Afipia* gen.nov., with Afipia felis sp.nov. (formerly cat-scratch disease bacillus). *Afipia clevelandensis* sp. nov. (formerly the Cleveland Clinic Foundation strain), *Afipia broomeae* sp.nov., and three unnamed genospecies. J Clin Microbiol 29:2450–2460

Brenner DJ, O'Connor SP, Winkler HJ, Steigerwalt AG (1993) Proposals to unify the genera Bartonella and Rochalimaea, with description of *Bartonella quintana* comb.nov., *Bartonella vinsonii* comb.nov., *Bartonella henselae* comb.nov., and *Bartonella elizabethae* comb. nov; and to remove the family Bartonellaceae from the order Rickettsiales. Int J Syst Bacteriol 43:777–786

Bruce D (1887) Note on the discovery of a micro-organism in Malta fever. Practitioner 39:161–170

Bruce D (1888) The micrococcus of Malta fever. Practitioner 40:241–249

Bukharovich AM, Sokol AN, Knigovskii AM, Khil'ko IN (1989) Liver involvement in early secondary syphilis (in Russian). Vestn Dermatol Venerol (9):58–61

Buschke A, Fischer L (1905) Lues-Spirochäten. Dtsch Med Wochenschr 20:791

Camara B, Kamar N, Bonafe JL, Danioux M, Suc B, Rostaing L (2007) Syphilis-related hepatitis in a liver transplant patient. Exp Clin Transplant 5:724–726

Campisi D, Whitcomb C (1979) Liver disease in early syphilis. Arch Intern Med 139:365–366

Caponetti GC, Pantanowitz L, Marconi S, Havens JM, Lamps LW, Otis CN (2009) Evaluation of immunohistochemistry in identifying *Bartonella henselae* in cat-scratch disease. Am J Clin Pathol 131:250–256

Carithers HA (1985) Cat-scratch disease: an overview based on a study of 1200 patients. Am J Dis Child 139:1124–1133

Cataldi A, Lovato R, Aicardi C, Baldoni ME, Cimadamore N, Giaretto G (1995) Abdominal granulomatosis with disseminated hepato-splenic lesions from suspected cat scratch disease (in Italian). Radiol Med 90:153–155

Cervantes F, Bruguera M, Carbonell J, Force L, Webb S (1982) Liver disease in brucellosis. A clinical and pathological study of 40 cases. Postgrad Med J 58:346–350

Chen JF, Chen WX, Zhang HY, Zhang WY (2008) Peliosis and gummatous syphilis of the liver: case report. World J Gastroenterol 14:1961–1963

Chin NW, Chapman I, Jimenez FA (1987) Complete chemotherapeutic regression of hepatic metastases with resultant hepar lobatum. Am J Gastroenterol 82:149–151

Chourmouzi D, Boulogianni G, Kalomenopoulou M, Kanellos I, Drevelegas A (2009) Brucella liver abscess; imaging approach, differential diagnosis, and therapeutic management: a case report. Cases J 2:7143

Colmenero Jde D, Queipo-Ortuno MI, Maria Reguera J, Angel Suarez-Munoz M, Martin-Carballino S, Morata P (2002) Chronic hepatosplenic abscesses in Brucellosis. Clinico-therapeutic features and molecular diagnostic approach. Diagn Microbiol Infect Dis 42:159–167

Colmenero JD, Reguera JM, Martos F et al (1996) Complications associated with *Brucella melitensis* infection: a study of 530 cases. Medicine (Baltimore) 75:195–211

Cosme A, Barrio J, Ojeda E, Ortega J, Tejada A (2001) Sonographic findings in brucellar hepatic abscess. J Clin Ultrasound 29:109–111

Cronin EB, Williams WH, Tow DE (1987) Radionuclide imaging in a case of tertiary syphilis involving the liver and bones. J Nucl Med 28:1047–1051

Crum-Cianflone N, Weekes J, Bavaro M (2009) Syphilitic hepatitis among HIV-infected patients. Int J STD AIDS 20:278–284

Dämmrich J, Fischbach W, Mössner J, Altmann HW (1992) Tertiary gummatous syphilis of the liver – an unexpected disease today. Report of two cases. Leber Magen Darm 22:79–82

Danon O, Duval-Arnould M, Osman Z, Boukobza B, Kazerouni F, Cadranel JF, Neuenschwander S et al (2000) Hepatic and splenic involvement in cat-scratch disease: imaging features. Abdom Imaging 25:182–183

Davion T, Delamarre J, Sallebert S, Ducroix JP, Dusehu E, Capron JP (1987) Hepatic brucelloma (pseudotumoral brucellar caseous necrosis of the liver). Study of a case and review of the literature (in French). Clin Biol 11:424–428

De Gouveia O, Prata DJ, Dacorso Filho P (1961) Hepatic gumma and hepar lobatum (in Portuguese). Med Cir Farm 296:278–290

De Marliave H, Reboud JP, Dyon JF, Gaillat J, Bacle B (1982) A new case of pseudotumoral hepatic granuloma of brucellar origin (in French). Pediatrie 37:531–537

Débat-Zuguéreh D, Badiaga S, Uzan E, Le Treut YP, Lebreuil G, Bougeade A (1995) Necrotizing hepatic granuloma of brucellosis origin. Apropos of a case (in French). Rev. Med. Interne 16:63–66

Debré R, Lamy M, Jammet M, Costil L, Mozzicona P (1950) La maladie des griffes de chat. Bull Mem Soc Med Hop Paris 66:76–79

Debré R, Lemaire A, Hepp J, Aussannaire M, Etienne JP, Cabanes J, Wacjberg A, Brevart P (1962) Partial hepatectomy for unrecognized congenital sclerogummatous syphilis (in French). Presse Med 70:413–416

Delbeke et al (1988) http://www.ncbi.nlm.nih.gov/pubmed/3165442

Delpino MV, Barrionuevo P, Scian R, Fossati CA, Baldi PC (2010) Brucella-infected hepatocytes mediate potentially tissue-damaging immune responses. J Hepatol 53:145–154

Di Palo S, Marassi A, Staudacher C, Di Carlo V (1987) Hepatic resection on demand in a case of abscessed hepatic granuloma secondary to brucellosis focus (in Italian). Minerva Chir 42:869–871

Diederen BM, Vermeulen MJ, Verbakel H, van der Zee A, Bergmans A, Peeters MF (2007) Evaluation of an internally controlled real-time polymerase chain reaction assay targeting the groEL gene for the detection of Bartonella spp. DNA in patients with suspected cat-scratch disease. Eur J Clin Microbiol Infect Dis 26:629–633

Dobson S (2004) Congenital syphilis resurgent. Adv Exp Med Biol 549:35–40

Echard M, Penalba C, Saigot T, Develoux M, Chomette G, Gentilini M, Bousquet O (1982) Early syphilitic hepatitis. Two cases (in French). Ann Med Interne (Paris) 133:564–568

Edwards and Weir (1964) http://www.ncbi.nlm.nih.gov/pubmed/6018691

English CK, Wear DJ, Margileth AM, Lissner CR, Walsh GP (1988) Cat-scratch disease: isolation and culture of the bacterial agent. JAMA 259:1347–1352

Ennibi K, Rabhi M, Chemsi M, Elouennass M, Chaari J, Toloune F (2009) Nodular liver lesions with fever in a Moroccan man. Hepatic brucelloma (in French). Med Trop (Marseille) 69:509–511

Feher J, Somogyi T, Timmer M, Jozsa L (1975) Syphilitic hepatitis: clinical, immunological and morphological aspects. Acta Med Acad Sci Hung 32:155–161

Fernandez Fernandez MA, Garcia de Paso Mora MG, Mateos Checa RM, Croche B et al (2010) Brucellosis infection presenting with cholestasis. Int J Infect Dis 14(suppl 3):e322–e324

Ficht T (2010) Brucella taxonomy and evolution. Future Microbiol 5:859–866

Fischbach W, Mössner J, Dämmrich J, Jenett M (1991) Tertiary syphilis with liver gummata (in German). Dtsch Med Wochenschr 116:1013–1017

Fischer J, Baumgarten R, Fengler JD, Roschlau G (1986) Syphilitic hepatitis (in German). Z Aerztl Fortbild (Jena) 80:379–380

Flegel H (1951) Liver pathology in congenital syphilis (in German). Zentralbl Allg Pathol 87:302–314

Fuhs H, Weltmann O (1922) Über Ikterus bei Lues (On jaundice in syphilis). Arch Dermatol Syphil 140:247–270

Galinska EM, Zagorski J (2013) Brucellosis in humans – etiology, diagnostics, clinical forms. Ann Agric Environ Med 20:233–238

Gencsi G (1962) Tertiary syphilis of the liver (hepar lobatum) and portal hypertension (in Portuguese). J Med 47:409–420

Granicki O, Winogrodzka-Szaflik H, Chelmicka A, Wilczynska J (1990) Syphilitic hepatitis (in Polish). Wiad Lek 43:289–290

Gravel DH, Bégin LR, Brisson ML, Lamoureux E (1996) Metastatic carcinoma resulting in hepar lobatum. Am J Clin Pathol 105:621–627

Greer WE, Keefer CS (1951) Cat-scratch fever; a disease entity. N Engl J Med 244:545–548

Greiner L, Franken FH, Schubert GE, Haberich M, Usmiani J, Becker M (1984) Solitary liver abscesses in chronic brucellosis (in German). Z Gastroenterol 22:337–342

Gruber GB (1930) Spezielle Infektionsfolgen der Leber. In: Henke F, Lubarsch O (eds) Handbuch der Speziellen Pathologischen Anatomie und Histologie, Vo. 5 (Verdauungsdrüsen), Part 1 (Leber). Julius Springer, Berlin, pp 578–629

Gschwantler M, Gulz W, Schrutka-Kolbl C, Kogelbauer G, Schober G, Bibus B, Weiss W (1996) Acute hepatitis as the leading symptom of secondary syphilis (in German). Dtsch Med Wochenschr 121:1457–1461

Gubler J (1852) Mémoires sur une nouvelle affection du foie lié à la syphilis héréditaire. Gaz Med Paris 17–22.

Hahn RD (1943) Syphilis of the liver. Am J Syph Gonorrh Vener Dis 27:529–562

Halimi C, Bringard N, Boyer N, Vilgrain V, Panis Y, Degott C, Brouland JP, Boudiaf M et al (1999) Hepatic brucelloma: 2 cases abd a review of the literature (in French). Gastroenterol Clin Biol 23:513–517

Hanchard B, Brooks SE, Terry S (1978) Pathology of the liver in early syphilis. West Indian Med J 27:91–95

Hunt A (1961) Five cases of syphilitic hepar lobatum with portal obstruction. Proc R Soc Med 54:973–975

Ibis C, Sezer A, Batman AK, Baydar S, Eker A, Unlu E, Kuloglu F, Cakir B, Coskun I (2007) Acute abdomen caused by brucellar hepatic abscess. Asian J Surg 30:283–285

Inglis JA, Tonge JI (1950) A disease with visceral granulomatous lesions of unknown etiology. Med J Aust 1:433–436

Ishikawa T, Suzuku T, Shinoda M, Takashi H, Yamaguchi H, Suzuki T, Miyake N, Kamiya T (2006) A case of hepatosplenic cat scratch disease (in Japanese). Nihon Shokakibyo Gakkai Zasshi 103:1050–1054

Ito Y, Arai O, Ono T (1963) Autopsy case of hepatic gumma and bibliographic remarks (in Japanese). Naika 12:758–764

Janbon M, Bertrand A (1978) An unusual modality of brucellosis due to *B. melitensis*: chronic granulomatous foci of spleen and liver with caseification and calcification (in French). Bull Acad Natl Med (Paris) 162:380–384

Jozsa L, Timmer M, Somogyi T, Fehér J (1977) Hepatitis syphilitica. A clinico-pathologic study of 25 cases. Acta Hepatogastroenterol (Stuttg) 24:344–347

Jung N, Kümmerle T, Brengelmann SD, Gielen J, Lehmann C, Wyen C, Birtel A, Fischer J et al (2012) Liver involvement in HIV-infected patients diagnosed with syphilis. Infection 40:543–547

Kahr et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/10782400

Kaiser PO, Riess T, O'Rourke F, Linke D, Kempf VA (2011) Bartonella spp.: throwing light on uncommon human infections. Int J Med Microbiol 301:7–15

Katner HP, Treen B, Pankey GA, Glasgow S, Cortez LM, Dalovisio J (1986) Pleural effusion and anicteric hepatitis associated with cat-scratch disease. Chest 89:302–303

Keefer CS, Greer W (1950) Cat scratch fever. Trans Am Clin Climatol Assoc 62:151–164

Keisler DS, Starke W, Looney DJ, Mark WW (1982) Early syphilis with liver involvement. JAMA 247:1999–2000

Kellock IA, Laird SM (1956) Late hepatic syphilis. Br J Vener Dis 32:236–241

Kilicaslan B, Cengiz N, Pourbagher MA, Cemil T (2008) Hepatic abscess a rare manifestation of brucellosis in children. Eur J Pediatr 167:699–700

Kim GH, Kim BU, Lee JH, Choi YH, Chae HB, Park SM, Youn SJ, Lee JY, Yoon TY et al (2010) Cholestatic hepatitis and thrombocytosis in a secondary syphilis patient. J Korean Med Sci 25:1661–1664

Klinge O, Ormann W (1988) Hepar lobatum carcinomatosum (in German). Pathologe 9:97–102

Korbitz (1973) http://www.ncbi.nlm.nih.gov/pubmed/4100723

Ladero Quesada JM, Gilsanz G, Aboin Massieu FJ, Ispizua Uribarri I, Ladero Alvarez F (1979) Abscesos hepaticos caseificantes multiples por brucellas. Rev Clin Esp 152:311–314

LaFond and Lukehart (2006) http://www.ncbi.nlm.nih.gov/pubmed/16418521

Lamps LW, Gray GF, Scott MA (1996) The histologic spectrum of hepatic cat scratch disease. A series of six cases with confirmed *Bartonella henselae* infection. Am J Surg Pathol 20:1253–1259

Le Tallec V, Abgueguen P, Pichard E, Chennebault JM, Bellec V, Delbos V, Rousselet MC et al (2003) Hepatosplenic localization of cat scratch disease in immunocompetent adults. Two cases (in French). Gastroenterol Clin Biol 27:225–229

Ledro D, Llamas R, Herrerias JM, Domecq G, Justo E, Garrido M (1983) The presence of granulomas due to *Brucella melitensis* in hepatitis. J Infect Dis 147:606–607

Lee V, Kinghorn G (2008) Syphilis: an update. Clin Med 8:330–333

Lelong M, Alison F, Vinh LT, Blanguernon A (1952) Jaundice in newborn due to syphilitic gumma of the pancreas involving the bile duct (in French). Arch Fr Pediatr 9:1058–1061

Lenoir et al (1988) http://www.ncbi.nlm.nih.gov/pubmed/2896959

Liao HM, Huang FY, Chi H, Wang NL, Chen BF (2006) Systemic cat scratch disease. J Formos Med Assoc 105:674–679

Liston TE, Koehler JE (1996) Granulomatous hepatitis and necrotizing splenitis due to Bartonella henselae in a patient with cancer: case report and review of hepatosplenic manifestations of *Bartonella* infections. Clin Infect Dis 22:951–957

Lo JO, Harrison RA, Hunter AJ (2007) Syphilitic hepatitis resulting in fulminant hepatic failure requiring liver transplantation. J Infect 54:e115–e117

Lynn WA, Lightman S (2004) Syphilis and HIV: a dangerous combination. Lancet Infect Dis 4:456–466

Maguiña C, Guerra H, Ventosilla P (2009) Bartonellosis. Clin Dermatol 27:271–280

Mahto M, Mohammed F, Wilkins E, Mason J, Haboubi NY, Khan AN (2006) Pseudohepatic tumour associated with secondary syphilis in an HIV-positive male. Int. J. STD AIDS 17:139–141

Maincent G, Labadie H, Fabre M, Novello P, Derghal K, Patriarche C, Licht H (1997) Tertiary syphilis. A treatable cause of multinodular liver. Dig Dis Sci 42:447–450

Malatack JJ, Jaffe R (1993) Granulomatous hepatitis in three children due to cat-scratch disease without peripheral adenopathy: un unrecognized cause of fever of unknown origin. Am J Dis Child 147:949–953

Manavi K, Dhasmana K, Cramb R (2012) Prevalence of hepatitis in early syphilis among an HIV cohort. Int. J. STD AIDS 23:e4–e6

Margileth AM, Wear DJ, English CK (1987) Systemic cat scratch disease: report of 23 patients with prolonged or recurrent severe bacterial infection. J Infect Dis 155:390–402

Marsilia GM, La Mura A, Galdiero R, Galdiero E, Aloj G, Ragozzino A (2006) Isolated hepatic involvement of cat scratch disease in immunocompetent adults: Enhanced magnetic resonance imaging, pathological findings, and molecular analysis – two cases. Int J Surg Pathol 14:349–354

Masshoff W (1953) Eine neuartige Form der mesenterialen Lymphadenitis. Dtsch Med Wochenschr 78:532–535

McRae T, Caven WR (1926) Tertiary syphilis of the liver. Am J Med Sci 172:781–796

Meloni MF, Andreano A, Laeseke PF, Lee FT, Sironi S, Filice C, Ferraioli G (2008) Contrast-enhanced ultrasonographic findings in a brucellar hepatic abscess. J Ultrasound Med 27:1511–1515

Michael M (1914) Der Icterus syphiliticus praecox unter besonderer Berücksichtigung der dabei auftretenden akuten Leberatrophie. Arch Dermatol Syphil 120:694–718

Min KW, Reed JA, Welch DF, Slater LN (1994) Morphologically variable bacilli of cat scratch disease are identified by immunocytochemical labeling with antibodies to Rochalimaea. Am J Clin Pathol 101:607–610

Morera J, Pedro-Botet J, Martinez-Ballarin I, Rodriguez Sanchon B (1975) Una forma poco frecuente de brucellosis cronica: el absceso hepatico brucelar. Med Clin 65:407–411

Morrison EB, Norman DA, Wingo CS, Henrich WL (1980) Simultaneous hepatic and renal involvement in acute syphilis. Dig Dis Sci 25:875–878

Müller R (1883) Beitrag zur pathologischen Anatomie der Syphilis hereditaria der Neugeborenen. Virchows Arch pathol Anat Physiol 92:532

Murakami K, Tsukahara M, Tsuneoka H, Iino H, Ishida C, Tsujino K, Umeda A, Furuya T et al (2002) Cat scratch disease: analysis of 130 seropositive cases. J Infect Chemother 8:349–352

Murano I, Yoshii H, Kurashige H, Sugio Y, Tsukahara M (2001) Giant hepatic granuloma caused by *Bartonella henselae*. Pediatr Infect Dis J 20:319–320

Nabarro D (1954) Congenital syphilis. Edward Arnold, London

Nagalotimath SJ, Darbar RD, Jogalekar MD (1979) Granulomatous hepatitis in brucellosis. J Indian Med Assoc 72:1–4

Naveau S, Vilde F, Patri B, Dubrisay J, Beinis JY, Roswag D, Loison F, Arkwright S (1982) Hepatic syphilis with amyloidosis and chronic diarrhea. A discussion of etiologic mechanisms (in French). Sem Hop 58:988–990

Naveau S, Poitrine A, Delfraissy JF, Brivet F, Dormont J (1983) Brucellosis hepatic abscesses and pregnancy. Gastroenterology 84:1643

Neuner L (1950) Gumma of the liver (in German). Klin Med Osterr Z Wiss Prakt Med 5:554–558

Nicol CS, Terry RB (1951) Late syphilis of the liver treated with penicillin. Br J Vener Dis 27:20–22

Oertel H (1906) A further contribution to the knowledge of multiple non-inflammatory necrosis of the liver with jaundice (hepar necroticum cum ictero), and to the knowledge of cell degeneration and cytolysis in general. J Exp Med 8:103–119

Pappas G, Akritidis N, Bosilkovski M, Tsianos E (2005) Brucellosis. N Engl J Med 352:2325–2336

Parinaud H (1889) Conjonctivite infectieuse transmise par les animaux. Ann d'Oculistique 101:252–253
Parker JDJ (1972) Uncommon complications of early syphilis. Hepatitis, periostitis, iritis with papillitis, and meningitis. Br J Vener Dis 48:32–36
Parnis R (1975) Gumma of the liver. Br J Surg 62:236–238
Paton NI, Tee NW, Vu CK, Teo TP (2001) Visceral abscesses due to *Brucella suis* infection in a retired pig farmer. Clin Infect Dis 32:129–130
Peeters L, Van Vaerenbergh W, Van der Perre C, Lagrange W, Verbeke M (2005) Tertiary syphilis presenting as hepatic bull's eye lesions. Acta Gastroenterol Belg 68:435–439
Perrin P, Lang F, Parlier H et al (1985) Syphilitic hepatitis as the presenting feature of secondary syphilis. Sem Hop (Paris) 61:2377–2390
Petersen LR, Mead RH, Perlroth MG (1983) Unusual manifestations of secondary syphilis occurring after orthotopic liver transplantation. Am J Med 75:166–170
Pons JC, Teyssau H, Bureau M, Ruiz R, Surzur J, Tessier JP (1981) Hepatic calcifications in isolated necrotizing, granulomatous hepatitis due to *Brucella*. A case report and review of the literature (in French). J Radiol 62:521–525
Port J, Leonidas JC (1991) Granulomatous hepatitis in cat-scratch disease: ultrasound and CT observations. Pediatr Radiol 21:598–599
Qian X, Jin L, Hayden RT, Macon WR, Lloyd RV (2005) Diagnosis of cat scratch disease with *Bartonella henselae* infection in formalin-fixed paraffin-embedded tissues by two different PCR assays. Diagn Mol Pathol 14:146–151
Qizilbash A, Kontozoglou T, Sianos J, Scully K (1987) Hepar lobatum associated with chemotherapy and metastatic breast cancer. Arch Pathol Lab Med 111:58–61
Rampal P, Veyres B, Agrati D, Saint Paul MC, Rampal A, François E, Lafont J, Delmont J (1986) Les atteintes hépatiques de la syphilis (hepatic involvement in syphilis). Ann Gastroenterol Hepatol 22:77–81
Rappaport DC, Cumming WA, Ros PR (1991) Disseminated hepatic and splenic lesions in cat-scratch disease: imaging features. AJR Am J Roentgenol 156: 1227–1228
Reed JA, Brigati DJ, Flynn SD, McNutt NS, Min KW, Welch DF, Slater LN (1992) Immunocytochemical identification of Rochalimaea henselae in bacillary (epithelioid) angiomatosis, parenchymal bacillary peliosis, and persistent fever with bacteremia. Am J Surg Pathol 16:650–657
Regnery RL, Olson JG, Perkins BA, Bibb W (1992) Serological response to "Rochalimaea henselae" antigen in suspected cat-scratch disease. Lancet 339:1443–1445
Reinecke K (1898) Kompensatorische Leberhypertrophie bei Syphilis und bei Echinococcus der Leber. Zieglers Beitr 23:238
Relvas S, Carreira F, Castro B (1992) Liver involvement in secondary syphilis. Am J Gastroenterol 87:1528
Renou F, Raffray L, Gerber A, Moiton MP, Ferrandiz D, Yvin JL (2010) Hepatic localization of cat scratch disease in an immunocompetent patient (in French). Med Mal Infect 40:172–174
Ridruejo E, Mordoh A, Herrera F, Avagnina A, Mando OO (2004) Severe cholestatic hepatitis as the first symptom of secondary syphilis. Dig Dis Sci 49:1401–1404
Rizkallah MF, Meyer L, Ayoub EM (1988) Hepatic and splenic abscesses in cat scratch disease. Pediatr Infect Dis 7:191–195
Rocco VK, Roman RJ, Eigenbrodt EH (1985) Cat scratch disease. Report of a case with hepatic lesions and a brief review of the literature. Gastroenterology 89:1400–1406
Roge J, Husson JM, Biclet P, Camilleri JP, Amat D, Roge F, Bloch F, Husset E (1979) Does the hepatitis of secondary syphilis exist ? Two cases (in French). Nouv Presse Med 8:3335–3338
Rolleston HD (1907) Congenital syphilitic obstruction of the common bile duct. Br J Med 2:947–948
Rolleston H, McNee JW (1929) Diseases of the liver, gall bladder and bile ducts. Macmillan, London
Romeu J, Rybak B, Dave P, Coven R (1980) Spirochaetal vasculitis and bile ductular damage in early hepatic syphilis. Am J Gastroenterol 74:352–354
Rossi P, Bacaro D, Quintiliano D, Stolfi VM, Russo F, Federico F, Solivetti FM, Gentileschi P (1992) Tertiary syphilis as a cause of hypoechoic solid focal lesions of the liver parenchyma. A case report (in Italian). Radiol Med (Torino) 83:129–131
Ruiz Carazo E, Munoz Parra F, Jimenez Villares MP, de Mar Castellano Garcia M, Moyano Calvente SL, Medina Benitez A (2005) Hepatosplenic brucelloma: clinical presentation and imaging features in six cases. Abdom Imaging 30:291–296
Sadia Pérez D, Cea-Calvo L, Aguado Garcia JM, Ruiz Llundain G, Lopez Martin A, Gonzalez Gomez C (2001) Brucella hepatic abscess. report of a case and review of the literature (in Spanish). Rev Clin Esp 201:322–326
Salembier Y (1967) Case of hepatic syphilis (in French). Lille Med 12:1215–1216
Schmid SA, Birkenfeld G (2010) A 37-year-old patient with fever, dyspnea and elevated transaminases after a stay in Mexico (in German). Med Klin (Munich) 105:286–290
Schorr G (1907) Selten mächtige regeneratorische Hyperplasie des linken Leberlappens bei syphilitischer Verschrumpfung des rechten Leberlappens. Beitr Pathol Anat Allgem Pathol 42:179–191
Schossberg D (1987) Syphilitic hepatitis: a case report and review of the literature. Am J Gastroenterol 82:552–554
Schweyer S, Fayyazi A (2002) Activation and apoptosis of macrophages in cat scratch disease. J Pathol 198:534–540
Shapiro MP, Gale ME (1987) Tertiary syphilis of the liver: CT appearance. J Comput Assist Tomogr 11:546–547
Shapiro E, Weiner H (1951) The diagnosis of tertiary syphilis of the liver: 25 years after McRae. Am J Med 222:494–499
Sherlock S (1971) The liver in secondary (early) syphilis. N Engl J Med 284:1437–1438

Shim HJ (2010) Tertiary syphilis mimicking hepatic metastases of underlying primary peritoneal serous carcinoma. World J Hepatol 2:362–366
Shouval D (2010) New insight into the mechanism of hepatic involvement in brucellosis. J Hepatol 53:1–2
Singh AE, Romanowski B (1999) Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. Clin Microbiol Rev 12:187–209
Siret D, Hardy R (1996) Radiological case of the month. Hepatic and splenic nodules in cat-scratch disease (in French). Arch Pediatr 3:391–392
Sisteron O, Souci J, Chevallier P, Cua E, Bruneton JN (2002) Hepatic abscess caused by *Brucella*. US, CT and MRI findings. Case report and review of the literature. J Clin Imaging 26:414–417
Sobel HJ, Wolf EH (1972) Liver involvement in early syphilis. Arch Pathol 93:565–568
Spink WW (1957) Suppuration and calcification of the liver and spleen due to long standing infection with Brucella suis. N Engl J Med 257:209–210
Spink WW (1964) Host parasite relation-ship in human brucellosis with prolonged illness due to suppuration of the liver and spleen. Am J Med Sci 247:129–136
Starakis I, Polyzogopoulou E, Siagris D, Mazokopakis E, Gogos CA (2008) Unusual manifestation of brucellosis: liver abscess and pancytopenia caused by Brucella melitensis. Eur J Gastroenterol Hepatol 20:349–352
Stuart and Nowicki (1998) http://www.ncbi.nlm.nih.gov/pubmed/9701150
Sugiura H, Hayashi M, Koshida R, Watanabe R, Nakanuma Y, Ohta G (1988) Nonsyndromatic paucity of intrahepatic bile ducts in congenital syphilis. A case report. Acta Pathol Jpn 38:1061–1068
Symmers D, Spain DM (1946) Hepar lobatum: clinical significance of the anatomic changes. Arch Pathol 42:64–68
Talenti E, Cesaro S, Scapinello A, Perale R, Zanesco L (1994) Disseminated hepatic and splenic calcifications following cat-scratch disease. Pediatr Radiol 24:342–343
Thudi KR, Kreikemeier JT, Phillips NJ, Salvalaggio PR, Kennedy DJ, Hayashi PH (2007) Cat scratch disease causing hepatic masses after liver transplant. Liver Int 27:145–148
Tiliakos N, Shamma'a JM, Nasrallah SM (1980) Syphilitic hepatitis. Am J Gastroenterol 73:60–61
Tucker HA, Dexter DD (1946) Arch Intern Med 78:313
Uhlmann F, Martin H, Ringk H, Krocker J (1996) Hepar lobatum carcinomatosum due to chemotherapy of a metastatic breast carcinoma. Gen Diagn Pathol 141:279–284
Vallejo JG, Stevens AM, Dutton RV, Kaplan SL (1996) Hepatosplenic abscesses due to Brucella melitensis: report of a case involving a child and review of the literature. Clin Infect Dis 22:485–489
Vanderheyden TR, Fimmel CJ, Yong SL, Breitschwerdt EB, Parada JP, Mihalik AR et al (2012) Granulomatous hepatitis due to Bartonella henselae infection in an immunocompetent patient. BMC Infect Dis 12:17
Vanlemmens P, Leroy J, Eastavoyer JM, Destuynder O, Aubert D, Viennet G, Colin P (1995) A little known cause of persistent fever and granulomatous hepatitis in children: cat scratch disease (in French). Arch Pediatr 2:657–661
Vargas V, Comas P, Llatzer R, Esteban R, Guardia J, Gasser I (1991) Brucellar hepatic abscess. J Clin Gastroenterol 13:477–478
Vas W, Thomasson J, Tang-Barton P, Salimi Z, Catral B (1985) Computed tomography and ultrasound appearance of liver disease in secondary syphilis. Diagn Imaging Clin Med 54:1–6
Veerahu M (1985) Diagnosis of liver involvement in early syphilis. A critical review. Arch Intern Med 145:132–134
VicDupont M, Bismuth H, Vachon F, Lagarde P, Vernant D, Mignon E (1976) Un cas de granulomatose hépatique nécrosante isolée mélitotoccique: problèmes diagnostiques et place du traitement chriurgical. Ann Med Interne (Paris) 127:253–257
Villar JM, Garrote D, Villegas MT, Alvarez MJ, Mansilla A, Ferron JA (2001) Hepatic brucelloma. J Am Coll Surg 194:86
Viranuvatti V, Kochaseni S (1953) A case of gumma of liver diagnosed by liver biopsy. Rev Gastroenterol 20:118–121
Vrioni G, Pappas G, Priavali E, Gartzonika C, Levidiotou S (2008) An eternal microbe: Brucella DNA load persists for years after clinical cure. Clin Infect Dis 46:e131–e136
Wagner K (1864) Das Syphilom. Wagner's Arch. Heilkd. 4, 347 and 440; and 5, 121
Walker GJ, Walker DG (2007) Congenital syphilis: a continuing but neglected problem. Semin Fetal Neonatal Med 12:198–2006
Wear DJ, Margileth AM, Hadfield TL, Fischer GW, Schlagel CJ, King FM (1983) Cat-scratch disease: a bacterial infection. Science 221:1403–1405
Weber FP (1909) Disseminated lobular necrosis of the liver with jaundice (Hepar necroticum com ictero of Curschmann and H. Oertel), and a case of acute hepatic atrophy in secondary syphilis. Proc R Soc Med 2(Pathol. Sect):109–122
Whitehouse D, Macfarlane WV (1958) Gumma of the liver in congenital syphilis. Arch Dis Child 33:58–60
Wile UJ, Karshner RG (1917) Icterus gravis syphiliticus. JAMA 68:1311–1314
Williams and Hara (1967) http://www.ncbi.nlm.nih.gov/pubmed/6018691
Williams RK, Crossley K (1982) Acute and chronic hepatic involvement of brucellosis. Gastroenterology 83:455–458
Witkowski JA, Parish LC (2002) The great imitator: malignant syphilis with hepatitis. Clin Dermatol 20:156–163
Young EJ (1979) *Brucella melitensis* hepatitis: the absence of granulomas. Ann Intern Med 91:414–415
Young MF, Sanowski RA, Manne RA (1992) Syphilitic hepatitis. J Clin Gastroenterol 15:174–176
Zangwill KM (2013) Cat scratch disease and other *Bartonella* infections. Adv Exp Med Biol 764:159–166

Tumor-Like Lesions of the Hepatobiliary Tract: Specific Abscess-Forming Bacterial Infections

130

Contents

Abstract

Several types of specific abscess-forming bacterial infections induce mass lesions in the liver. Yersiniosis is associated with hepatic miliary necroses (necrotizing hepatitis), miliary abscesses, macroabscesses, pseudotuberculoma, and granulomatous hepatitis. In tularemia, caused by *Francisella tularensis*, mild hepatitis is a common feature. Less frequently, focal suppurative hepatitis with abscess formation develops, usually without granulomatous reaction. Large necrosis and abscess of the liver are caused by melioidosis, caused by *Burkholderia pseudomallei*. The multifocal hepatic necrotizing and suppurative inflammation often results in large abscesses. Abscesses that may resemble tumors are also induced in the liver by listeriosis and glanders.

Yersiniosis (Pseudotuberculosis)

Introduction

Yersinia (*Y.*) *enterocolitica* and *Y. pseudotuberculosis* are two species that are very similar to the causative agent of plague, *Y. pestis*. These two enterobacteriacean germs most often cause self-limiting enteritis and mesenteric lymphadenitis, subsequent to ingestion of contaminated food or water. *Y. enterocolitica* is a zoonotic agent that causes gastrointestinal disease in humans as well as reactive arthritis and erythema nodosum. However, systemic infections

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_130

with septicemia are observed in patients with diabetes mellitus, liver cirrhosis, and, in particular, iron overload (Ljungberg et al. 1995). In addition, sudden onset of pseudotuberculosis in humans, in the form of small epidemics, has been reported in Japan, Russia, and France, probably related to contaminated water and plants (review: Vincent et al. 2008). Enteric yersiniosis disseminating systemically may have a case fatality of up to 70 % (review: Barnes et al. 2006). As the clinical presentation and hepatobiliary manifestations of the two *Yersinia* species are very similar, their clinicopathologic features are described together, except where the histology is different under certain circumstances.

Microbiology

Y. enterocolitica and *Y. pseudotuberculosis* belong to the genus *Yersinia*, which also contains *Y. pestis* and more than 15 other species. *Yersinia* is a member of the family Enterobacteriaceae, order Enterobacteriales. The organisms are rod-shaped, nonmotile, Gram-negative, facultatively anaerobic bacteria. *Yersinia* is a microorganism living in various habitats of the environment, e.g., on diverse plants and their leaf litter, vegetables, and soil, where the bacteria can resist low temperatures. Upon entry into a warm-blooded organism, yersiniae have to adapt their biochemical machinery to the suddenly higher temperature. They can do this by using the *Yersinia* virulence regulator, RovA, which acts as a protein thermometer. Thermal shifts encountered in the host lead to reversible conformational changes of the autoactivator, which reduces its DNA-binding functions and renders it more susceptible for proteolysis.

Clinical Features

Infection with both organisms leads to a febrile enteritis associated with right-sided abdominal pain. Enteric infections with *Y. enterocolitica* are usually self-limiting (review: Fabrega and Vila 2012). In *Y. pseudotuberculosis* infection, however, the diarrheal component is often absent, and this infection may mimic acute appendicitis, predominantly in children and young adults, because mesenterial lymphadenitis located in the region of the terminal ileum and the periappendiceal space is a prominent feature of pseudotuberculosis. *Y. pseudotuberculosis* can cause septicemia and septic arthritis associated with high mortality. Reactive arthritis caused by *Yersinia* infections is a well-recognized complication, but septic arthritis is observed at a much lower frequency. Severe forms of *Yersinia* infections, in particular septicemia, are often associated with iron overload (Mischnik et al. 2012).

In 1959, an epidemic of *Y. pseudotuberculosis* infections on the Pacific coast of Russia was called Far East scarlet-like fever (FESLF) or scarlatinoid fever for its clinical similarity to scarlet fever caused by group A streptococci. This infectious disease is severe and may result in toxic shock syndrome. The *Y. pseudotuberculosis* strains causing FESLF have acquired an altered genomic composition via horizontal acquisition and incorporation of different genetic information into the chromosome, two plasmids (pVM82 and pIB), and the capability to produce the superantigenic exotoxin, *Y. pseudotuberculosis*-derived mitogen (Eppinger et al. 2007; Nörenberg et al. 2013).

Hepatobiliary Yersiniosis

In the hepatobiliary tract, *Yersinia* species can induce several types of lesions that exert a mass effect and can thus mimic neoplastic disease (Table 1). The size of the focal lesions ranges from tiny, miliary necroses and microabscesses to large purulent and granulomatous lesions. Most of these focal liver lesions developing in the setting of *Yersinia* infections are encountered in septicemic forms of yersiniosis.

Table 1 Hepatic lesions caused by *Yersinia* species

Miliary necroses (necrotizing hepatitis)
Microabscesses (miliary abscesses)
Macroabscesses
Pseudotuberculoma
Granulomatous hepatitis

Miliary Necrosis/Necrotizing Hepatitis

This form of liver disease found in septicemic yersiniosis is characterized by several to numerous foci of parenchymal necrosis. Macroscopically, the liver shows tiny to millet seed-sized nodules that are diffusely distributed in the hepatic parenchyma. These nodules are whitish-yellowish and show, on the cut surface, a slightly concave center. A hyperemic rim surrounding the lesions may be noted. Aschoff, in his handbook, described the nodules as very similar to small tuberculous lesions (miliary tuberculosis) with a perifocal macrophage reaction, sometimes with formation of epithelioid cells. In contrast to lymph node lesions in pseudotuberculosis, fully developed granulomas are not a feature of the hepatic lesions (Schneider 1915; Dubois et al. 1982; Collazos et al. 1995).

Hepatic Abscesses

Liver abscesses as a complication of septicemic yersiniosis mostly occur in adult patients, but pediatric cases are known as well, sometimes in association with hematologic disorders causing iron overload, including sideroblastic anemia or thalassemia (Leighton and MacSween 1987; Brunel et al. 1993; Grigull et al. 2005). Yersiniotic liver abscesses are mostly associated with systemic infection (i.e., septicemia and multiorgan involvement; Saebe and Lassen 1992), but rare instances of liver abscess subsequent to portal venous transfer of *Yersinia* in the absence of systemic manifestations are known (Viteri et al. 1981). Also in adults, the development of hepatic abscess in yersiniosis may be favored by iron overload, e.g., primary hemochromatosis (Olesen et al. 1989; Watson et al. 1989; Santoro et al. 1994; Vadillo et al. 1994; Abdelli et al. 1996; Zapata and Garcia 1997; Bergmann et al. 2001; Höpfner et al. 2001; Mennecier et al. 2001), hepatic hemosiderosis of unknown cause (Beeching et al. 1985), or subsequent to long-term blood transfusion (Schuchmann et al. 1997) or iron injections (Leighton et al. 1987). When reviewing the literature, one notes that both *Y. pseudotuberculosis* and *Y. enterocolitica* produce liver abscesses. Hepatic abscesses caused by *Y. pseudotuberculosis* seem to be less common than those caused by *Y. enterocolitica* and may occur after yersiniotic terminal ileitis.

The lesions are sometimes solitary lesions that can grow to large size, but multiple yersiniotic liver abscesses are more common (Beeching et al. 1985; Hopwood and Riddle 1986; Ismail et al. 1987; Leighton et al. 1987; Leyman et al. 1989; Nemoto et al. 1992; Vadillo et al. 1994; Schuchmann et al. 1997; Zapata and Garcia 1997; Grigull et al. 2005). Abdominal ultrasound reveals solitary or multiple fluid-filled lesions in which Doppler ultrasound fails to show flow (Schuchmann et al. 1997). Ultrasonographically, hypoechogenic liver abscesses may be accompanied by ascites and signs of pseudoappendicitis (Grigull et al. 2005). Liver CT scans show solitary or multiple low-density areas (Leyman et al. 1989; Nemoto et al. 1992).

Selected References Fraenkel 1914; Capron et al. 1981; Beeching et al. 1985; Farrer et al. 1988; Ljungberg et al. 1995; Mennecier et al. 2001; and Navascues et al. 2005. Liver abscess caused by *Y. enterocolitica* is predominantly found in association with septicemia (Viteri et al. 1981; Hopwood and Ridddle 1986; Ismail et al. 1987; Leyman et al. 1989; Olesen et al. 1989; Nemoto et al. 1992; Santoro et al. 1994; Vadillo et al. 1994; Collazos et al. 1995; Strungs et al. 1995; Abdelli et al. 1996; Schuchmann et al. 1997; Zapata and Garcia 1997; Bergmann et al. 2001; Mennecier et al. 2001; Benbrika et al. 2005; Grigull et al. 2005; Navascues et al. 2005; Pulvirenti et al. 2007).

Macroscopically, the smaller abscesses are grayish-white lesions with a soft, yellowish center (Fig. 1). The lesions are described to be pea sized or bean sized; they may be accompanied by miliary, i.e., smaller, lesions. Large abscess may grow to diameters of several centimeters; these abscesses are often wax yellow and have a softened, puriform center. In the case of multiple lesions, the abscesses may show confluence,

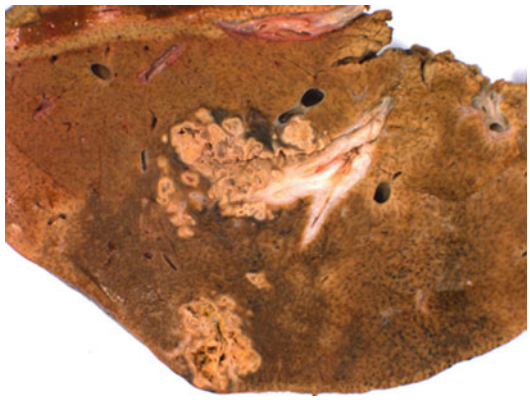

Fig. 1 Yersiniosis (pseudotuberculosis) of the liver. The distribution of the grape-like abscesses reflects bacterial spread through the portal venous system

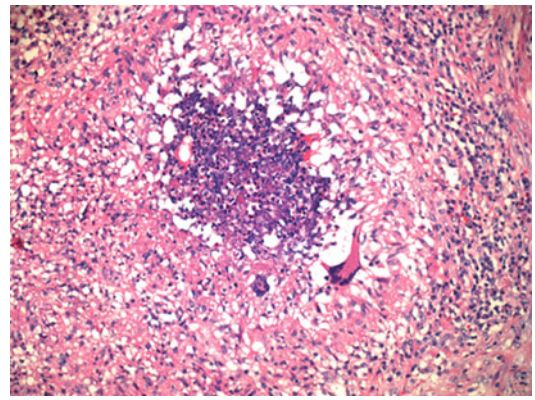

Fig. 2 Yersiniosis (pseudotuberculosis) of the liver. Typically, the lesions show a central abscess instead of coagulation necrosis. This abscess is surrounded by a granulomatous reaction with Langhans-type giant cells (hematoxylin and eosin stain)

resulting in large conglomerate lesions. Usually, abscesses located in peripheral parts of the liver are larger than centrally placed lesions, and sometimes large peripheral abscesses are accompanied by miliary lesions situated in the core of the liver (Roman 1916; Fraenkel 1924). Needle biopsy may reveal pus which grows *Yersinia* (Strungs et al. 1995). Histologically, the lesions have a central part consisting of coagulation necrosis (but without caseification), neutrophils, neutrophil debris with abundant nuclear fragments, and macrophages (Fig. 2). This part is demarcated by a rim of various thicknesses, showing an infiltrate of lymphocytes and macrophages, sometimes with epithelioid cell change. Plasma cells are rare of lacking. This presentation resembles the alteration seen in the appendix and ileum in cases of yersiniosis and the lymph node changes formerly termed "reticulocytic abscedent lymphadenitis."

Pseudotuberculomas

In analogy to large, tumor-like masses seen in caseating tuberculosis, conglomerate lesions formed by confluence of several large yersiniotic liver abscesses with extensive central necrosis and suppuration may form large masses, which mimic malignancy and may be termed "pseudotuberculomas."

Granulomatous Hepatitis

In part of patients, hepatic manifestations of yersiniosis are characterized by granulomatous hepatitis, sometimes with suppurative granulomas (Dubois et al. 1982; Piéron et al. 1983; Guarga et al. 1984; Stjernberg et al. 1987; Drebber et al. 2008).

Differential Diagnosis

Multiple liver abscesses in yersiniosis may radiologically mimic metastatic liver disease (Leighton et al. 1987).

Tularemia

Introduction

Tularemia is a zoonotic disease caused by the Gram-negative bacterium, *Francisella tularensis* (reviews: Oyston 2008; Splettstoesser et al. 2008; Harik 2013). Other names of this contagious disease include Ohara's disease, Francis disease, rabbit fever, deer fly fever, and marketmen's disease. Tularemia is a predominantly Northern Hemispheric disorder and is widely endemic throughout North America,

continental Europe, Russia, China, and Japan. The greatest numbers of human cases reported are from northern and central Europe (in particular Scandinavia), from Russia, and more recently also from certain Balkan regions. In these areas, tularemia sometimes presented as large-scale epidemic outbreaks. Increased concerns about the potential use of *Francisella tularensis* as a bioterrorism and bioweapon agent led, in 2000, to the reinstatement of tularemia on the list of notifiable disease in the USA after it had been removed in 1994. In the early twentieth century, a Japanese physician, Hachiro Ohara, described a disease affecting those who hunted or ate rabbits (yato-byo, meaning rabbit fever in Japanese), endemic to the Abukuma Mountains in Japan. There are certain clinical differences between the Japanese yato-byo and North American tularemia.

Microbiology

Deer fly fever was described in 1910 by the Utah physician R.A. Pearse, and in 1912, McCoy and Chapin isolated the causative agent of this plague-like disease from California ground squirrels and named it *Bacterium tularense*, after Tulare County where the work was performed. Dr. Edward Francis identified the cause of deer fly fever as *Bacterium tularense* in 1928. The genus was later changed into *Francisella*, in honor of Edward Francis. *F. tularensis* is a member of the family *Francisellaceae*, which in turn belongs, together with *Thiotrichaceae* and *Piscirickettsiaceae*, to the order *Thiotrichales* (bacterial class *Gammaproteobacteria*). The *Francisellaceae* family is composed of a group of closely related organisms that are widespread in nature. Apart from the few *Francisella* species (see below), the family also includes *Wolbachia* species and several *Francisella*-like endosymbionts (Kugeler et al. 2005; Escudero et al. 2008). The natural reservoir chiefly consists of small mammals (mice, water rats, voles, squirrels, rabbits, and hares; overall more than 250 species), and diverse arthropods are vectors transmitting the infection among susceptible mammals. The human host is infected in rural environments by infected arthropod bites, handling of infected animals or parts thereof (e.g., hunters and trappers), ingestion of contaminated water or soil, and inhalation of infective aerosols. Infection of the human host may occur after exposure to as few as ten bacteria. The incubation period is about 3–5 days but can take as long as 2 weeks for symptoms and signs to appear. Uptake of the bacterium into monocytes/macrophages occurs by so-called looping phagocytosis, in which the bacterium is engulfed in a spacious, asymmetric pseudopod loop. Contact with and trafficking in host cells critically depend on the features of the bacterium's surface membrane proteins, the membrane complexome (Dresler et al. 2011).

Clinical Presentation

The clinical presentation is variable and depends on the infection mode (Evans et al. 1985; Ellis et al. 2002); several presentation forms of tularemia are recognized (ulceroglandular, glandular, oculoglandular (Parinaud's oculoglandular syndrome), oropharyngeal, pneumonic, and typhoidal tularemia and visceral and septic forms). In humans, ulceroglandular tularemia is the most common form of the disease and is usually a consequence of a bite from an arthropod (tick) vector which has previously fed on an infected animal. An ulcer, which can persist for several months, forms at the site of infection (usually a tick bite site), soon associated with lymphangitis caused by local bacterial spread and locoregional lymphadenitis with lymph node enlargement (hence the term ulceroglandular form). Lymphadenomegaly may be impressive and resemble that in bubonic plague. Ulceroglandular tularemia may show a protracted course and recovery, but is seldom fatal. The oculoglandular form is rare and characterized by primary conjunctival infection followed by lymphadenitis. From the lymph node reservoirs, the infection may spread to internal organs and eventually produce sepsis. The dangerous pneumonic form of the disease occurs rarely but is the likely form of disease should the causative

bacterium be used as a category A bioterrorism agent (Ellis et al. 2002).

Hepatic Manifestations of Tularemia

Hepatitis, usually of a mild degree, is common (Evans et al. 1985). Hepatomegaly was found in two of three patients with pulmonary tularemia, and the results of liver function tests were abnormal in all three (Martone et al. 1979). It was suggested that dissemination to the liver in tularemia may be more frequent than has been recognized. In regard to focal liver lesions, the most frequently observed alteration is coagulative necrosis with associated sinusoidal dilatation and suppurative inflammation, the latter chiefly found in larger lesions (Francis 1928; Foulger et al. 1932; Foshay 1937; Pullen and Stuart 1945; Dienst 1963; Gourdeau et al. 1983; Zaidi and Singer 2002). Focal suppurative hepatitis with abscess formation has become uncommon under modern antibiotic treatment strategies, except in septicemic tularemia.

Liver abscesses in tularemia are histologically characterized by a central suppurative focus with necrosis and nuclear debris, followed at the periphery by a zone of better preserved leukocytes (neutrophils and macrophages). The lesions are separated from liver tissue by a rim of inflammatory infiltrate rich in macrophages, lymphocytes, and sometimes also plasma cells (Baskerville et al. 1978; Gourdeau et al. 1983; Zaidi and Singer 2002; Lamps et al. 2004). Epithelioid cell and giant cell granulomas are rare findings (Ortego et al. 1986). In a murine model of tularemia, lysis of infected hepatocytes was mediated by leukocytes (Conlan and North 1992).

Melioidosis

Introduction

Melioidosis (burkholderiosis) is caused by the Gram-negative bacterium *Burkholderia pseudomallei*, a germ which is found in damp soil, paddy water, and stream banks mainly in Southeast Asia (White 2003; Leelarasamee 2004; Wiersinga et al. 2006; Gilad 2007). This infection was first reported in 1912 based on the observation of a hitherto undescribed, glanders-like disease occurring among the population of Rangoon (Whitmore and Krishnaswami 1912). Clinically, melioidosis is most frequently recognized as a respiratory infection that varies in severity from a mild tracheobronchitis to an overwhelming and frequently fatal pneumonia. Due to its often very aggressive course, melioidosis is a potential biothreat.

Microbiology

B. pseudomallei belongs to the family *Burkholderiaceae*. The genus *Burkholderia* contains more than 30 species, many of them being environmentally adaptable plant-associated bacteria and some species being bacterial endosymbionts of plant-associated insects and of plant-pathogenic fungi, such as *Rhizopus microsporus*, the causal agent of rice seedling blight. Some *Burkholderia* species are nonphytopathogenic and beneficial microorganisms associated with the phytosphere and the rhizosphere, involved in the important mechanism of leguminous plant root nodulation. The most pathogenic members of this genus are *B. pseudomallei*, *B. mallei* (the cause of glanders), and, in certain conditions such as cystic fibrosis, *B. cepacia*. *B. pseudomallei* is a saprophyte and resilient microorganism that is capable of surviving hostile environmental conditions, including nutrient deficiency; antiseptic, acid, and detergent exposure; and dehydration, but the factors that determine whether an environment is suitable for the organism remain poorly understood. It has been discussed that *B. pseudomallei* may exist in a viable, non-cultivable state in the environment, that it probably forms biofilms, and that interactions with other organisms, particularly protozoa, might explain the adaptation of this bacterium to an intracellular niche. The transfer of *B. pseudomallei* from environmental reservoirs to attachment and invasion of phagocytic cells and epithelial cells is a complex sequence of events that is closely linked to the expression of

virulence factors (reviews: Inglis et al. 2001; Compant et al. 2008; Adler et al. 2009; Lazar Adler et al. 2009; Allwood et al. 2011).

Clinical Features

The lung is the most commonly involved organ, and lung imaging shows acute pulmonary consolidation, multiple nodules, and abscesses. The most dreaded form of melioidosis is a fulminant septicemic infection, striking as severe diarrhea, massive pneumonia, and sometimes visceral manifestations, including the liver (Sheehy et al. 1967; Brundage et al. 1968; Weber et al. 1969; Puthucheary et al. 1992; Dance 2002; White 2003; Cheng and Currie 2005; Inglis 2011; Limmathurotsakul and Peacock 2011; Torres and Steinmetz 2012). In this form, death may follow within few days. The clinical definitions of melioidosis have recently been reported (Cheng et al. 2013). Melioidosis also exists in an encephalomyelitic form.

In a study of ten patients with acute melioidosis, the average duration of illness was 14 days and ranged from 3 to 42 days (Piggott and Hocholzer 1970). Apart from these acute courses, chronic melioidosis may ensue, characterized by predominant involvement of the lung, lymph nodes, skin, or bone (Kingston 1971). Chronic cavitary pulmonary melioidosis mimics tuberculosis clinically and radiologically (Spotnitz et al. 1967). In endemic regions, apparently not all persons exposed to this bacterium develop clinical melioidosis, as, e.g., surveys in Malaysia and Thailand have found circulating antibodies to *B. pseudomallei* in as much as 30 % of the normal population (Nigg 1963). Melioidosis is known to often show recurrence caused by two different mechanisms, i.e., relapse and reinfection. A study on 140 patients with disease recurrence showed that similar patterns of organ involvement occurred during the first and second episode of infection, independent of whether this was caused by relapse or reinfection (Limmathurotsakul et al. 2009). An intriguing phenomenon in this infection is the long incubation period in recrudescent melioidosis, sometimes exceeding 10 or even 20 years (review: Gan 2005).

Liver Manifestations of Melioidosis

Liver involvement in *B. pseudomallei* infection is chiefly characterized by a multifocal necrotizing and suppurative inflammation, commonly leading to the formation of sometimes large abscesses (Greenawald et al. 1969; Atisook and Panyathanya 1988; Thurnheer et al. 1988; Puthucheary et al. 1992; Vatcharapreechasakul et al. 1992; Wong et al. 1995; Ben et al. 2004; Machado Braga and Carvalho de Almeida 2005; Apisarnthananarak et al. 2006; Cheng and Johnson 2006; Lee et al. 2006; Azali et al. 2007; Mukhopadhya et al. 2007; Laopaiboon et al. 2009; Lim and Chong 2010; Apisarnthanarak et al. 2011; Rajadhyaksha et al. 2012). In a study of 16 bacteriologically proven cases accessioned to the Armed Forces Institute of Pathology during a 25-year period (1944–1968), liver involvement was detected in seven patients (Piggott and Hochholzer 1970). The etiology of hepatic necroabscesses in melioidosis has been confirmed by the cultural identification of *B. pseudomallei* in aspiration material (Mukhopadhya et al. 2007). *B. pseudomallei* abscesses are significantly associated with the presence of poorly controlled diabetes mellitus (Chong 2006).

Imaging of *B. pseudomallei*-induced hepatic mass lesions shows the typical features of hypodense abscesses with variable peripheral enhancement at CT. The lesions may be multiloculated and multiseptated, with a so-called honeycomb appearance, and a "necklace sign" may be seen in lesions greater than 5 cm in diameter (Vachara-preechasakul et al. 1992; Wibulpolprasert and Dhiensiri 1999; Ben et al. 2004; Apisarnthananarak et al. 2006). In a comparative study, it was shown that liver abscesses in melioidosis can be distinguished from non-melioidosis abscesses based on distinct features of size, enhancement patterns, and organ distribution (Laopaiboon et al. 2009).

Pathology

Early hepatic melioidosis presents in the form of few to numerous small yellowish to tan lesions

resembling small pyogenic abscesses, usually measuring 0.1–0.5 cm (Greenawald et al. 1969). As the disease persists, these focal lesions increase in size and become large and in part coalescing necroses with a purulent center. Early lesions in acute melioidosis are characterized by a suppurative inflammation, with formation of small, well-circumscribed abscesses, 1–3 mm in diameter rand sharply delineated from the surrounding tissue. These abscesses may be found in many organs, but are most often seen in the lungs, liver, spleen, and lymph nodes. In a given organ, they are usually multiple (Piggott and Hochholzer 1970; Wong et al. 1995). In small and early hepatic lesions, a mixture of neutrophils and macrophages predominates, and necrosis is a feature almost from the beginning, while larger and older lesions chiefly contain neutrophils intermingled with nuclear debris and necrotic tissue (Fig. 3). A rim of necrosis surrounding the central pus is frequently noted. Within the purulent masses, bacteria can be demonstrated, often in large numbers, best visualized by the use of the Brown-Hopps tissue Gram stain, but also reliably detectable in the Warthin-Starry and Goodpasture stains. The bacteria are not well demonstrable in the Brown-Brenn and silver methenamine preparations (Piggott and Hochholzer 1970). In case the illness persists more than several days, the abscesses tend to enlarge and often coalesce, forming complex clusters or conglomerates of nodular lesions. Large lesions commonly contain a fibrinous exudate, whereas hemorrhage is not a prominent feature in liver lesions (Piggott and Hochholzer 1970).

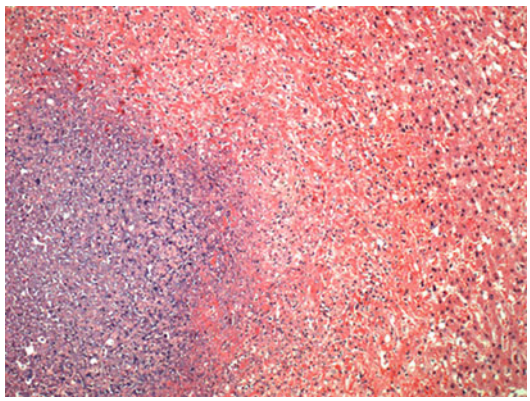

Fig. 3 Tumor-like melioidosis of the liver. The lesions are characterized by massive necrosis which rapidly extends into hepatic parenchyma, leaving shadow structures of hepatocyte plates. Central parts are basophilic due to numerous nuclear debris (karyorrhexis, hematoxylin and eosin stain) monocytogene organisms (hematoxylin and eosin stain)

In chronic melioidosis, visceral involvement is more seldom seen. The lesions present as a combination of necrosis and an epithelioid cell or granulomatous reaction, often with formation of Langhans-type giant cells. Perifocal fibrosis develops. The central necrosis of the nodules may contain pus, but a coagulation necrosis looking like tuberculous caseification may also develop, such lesions markedly resembling tuberculosis, tularemia, or brucelloma.

Glanders

Introduction

Glanders (glanders disease; Malleasmus; *Malleus humidus* of Vegetius; Latin, malleus (hammer, mallet); German (Rotz, Mürde); French (morde, farcin)) is an aggressive infection mainly of horses and other equids, caused by *Burkholderia mallei* (reviews: Strube 1900; Neubauer et al. 2005; Gilad 2007; Whitlock et al. 2007; Dvorak and Spickler 2008; Van Zandt et al. 2013).

Glanders is known since antiquity, and Aristotle (c. 350 BC) gave it the name melis (Greek melis later transformed into Latin malleus; citation from Aristotle's *Historia Animalium*: "The ass suffers chiefly from one particular disease which they call melis. It arrives first in the head, and a clammy humour runs down the nostrils, thick and red; if it stays in the head the animal may recover, but if it descends into the lungs the animal will die. . ."). This observation is still nowadays valid because it described the dismal outcome in case glanders spreads to internal organs. It has also been hypothesized that Achaean disease, a mortal illness described in the first book of Homer's Iliad, was glanders (Urso 1993). Until the beginning of the twentieth century, glanders was widespread among army horses, with a last

important peak during World War II, followed by a decline due to rigorous testing (Wilkinson 1981; Blancou 1994). However, glanders is again increasing since the 1990s, mainly among racing horses and army horses in the Middle East, South Asia, and South America. Owing to the highly aggressive course of the infection caused by *B. mallei*, this bacterium may serve as a means of bacterial warfare and terrorism (*B. mallei* is a category B biothreat agent).

In equids, acute glanders is characterized by high fever, a distinct form of ulcerating rhinitis (*Malleus humidus*), pharyngolaryngitis and tracheobronchitis, and locoregional lymphadenitis. The acute glanders syndrome is more common in mules and donkeys than in horses. Chronic glanders, which predominates in horses, is characterized by ulcerous skin manifestations (called farcy or glanders of the skin, *Malleus farciminosus*) and inner organ spread with development of pneumonia (glanders pneumonia, Lungenrotz in German). In humans, glanders manifestations can be variable. At least six forms of infection have been described, including nasal and pharyngolaryngeal, localized, pulmonary, septicemic, disseminated, and chronic infections. The variety of these forms is explained by various routes of infection, the virulence of the bacterial strain, the immune status of the host, and modes of spread within the body.

Clinical Features

An acute infection with *B. mallei* is characterized by an erysipelas-like inflammation of the nasal skin and adjacent regions of the face (sometimes followed by hemorrhagic necrosis, also involving the upper lip and the gingiva), a necrotizing inflammation of the tracheobronchial tree, multiple and sometimes numerous pustular skin lesions, and either a febrile pneumonia if the organism was inhaled or sepsis with multiple abscesses if the skin was the portal of entry (review: Srinivasan et al. 2001). The purulent nodular lesions in the skin form craterlike ulcers forming chains along the lymphatic vessels, the so-called farcy pipes. Chronic glanders in humans presents with lymphadenitis, ulcerating or necrotizing nodules in the alimentary and respiratory tracts (visceral glanders), weight loss, and numerous subcutaneous abscesses (Robins 1906). The chronic, sometimes nonclinical glanders in humans is also termed farcy.

Liver Lesions in Glanders

In generalized *B. mallei* infection, abscesses and leukocyte-rich necroses can develop in multiple organs, most notably the lungs, liver, and spleen. The pathologic features of liver involvement are mainly found in the older literature (Sommerbrodt 1864; Bollinger 1874, 1876; Strube 1897, 1900; Koch 1902; Helly 1907; Bernstein and Carling 1909; Jochmann 1914; Spinner 1926). Because untreated human glanders is almost uniformly fatal and imaging appearances of hepatic involvement may mimic echinococcal or amebic infection, a high index of suspicion is mandatory and requires knowledge of the imaging features (Georgiades and Fishman 2001). In contrast-enhanced CT, cystic and sometimes multiseptate, low-attenuation lesions of variable size have been observed (Georgiades and Fishman 2001; Srinivasan et al. 2001).

The liver is usually enlarged (Sommerbrodt 1864; Bollinger 1874; Jochmann 1914). The lesions range in size and shape from miliary foci without central liquefaction but with a red hyperemic rim to medium-sized nodules of gray-yellow color (sometimes coalesced to form clover leaf-shaped structures) or to large abscesses or necroses with perifocal atrophy of the liver substance (Sommerbrodt 1864). In the autopsy case of a 29-year-old farmer with septicemic glanders, reported by Spinner (1926), the liver was scattered with millet-sized purulent foci with a hyperemic rim. Helly (1907) reported on the necropsy of a patient who had attracted *B. mallei* infection in the laboratory. The liver showed an arborizing cavity containing pus, associated with thrombophlebitis of the portal vein. Large purulent hepatic lesions may communicate with intrahepatic bile ducts (Sommerbrodt 1864). Older necrotic lesions are

described to by dry on the cut surface and to resemble compact tuberculous caseification necrosis (Spinner 1926). In extended hepatic disease with multiple lesions, hepatomegaly may be a striking feature (Spinner 1926). In one case, a large abscess cavity of variegated or arborescent shape was spatially associated with portal vein thrombophlebitis (Helly 1907).

Histopathology

Postmortem examinations of livers involved with glanders showed several types of lesions, depending on the phase of infection and the severity of involvement. The early pattern is characterized by the formation of epithelioid cell granulomas, sometimes with a miliary pattern (Fig. 4). This is followed by enlargement of these lesions, resulting in numerous, small necrotizing and sometimes caseating nodules, similar to lesions that are well known in glanders pneumonia. The so-called glanders nodule (Rotzknötchen) was first described by Virchow in 1854. The centers of these nodules exhibit nuclear debris and decaying granulocytes, forming sometimes large basophilic foci surrounded by inflammatory cells (Spinner 1926). In the center of the nodules, numerous glanders bacteria are found. This pattern shows a striking similarity to both brucelloma and the lesions seen in melioidosis (see the respective chapters). Larger nodules show a central, caseiform necrosis containing numerous debris of granulocytes and their nuclei, surrounded at the periphery by a rim of epithelioid macrophages. Epithelioid macrophages in fact dominate the histologic picture in glanders (Strube 1897). Giant cells may be found, but are generally rare in glanders (Strube 1897). In the vicinity of the lesions, vascular damage and thrombophlebitis are common alterations. The lesions may contain necrotic liver cell plates, and in the parenchyma surrounding the lesions, fatty change of hepatocytes is noted. As a function of disease advancement, these nodules may coalesce into larger, confluent necroses with or without marked pus formation, but occasionally forming large abscesses.

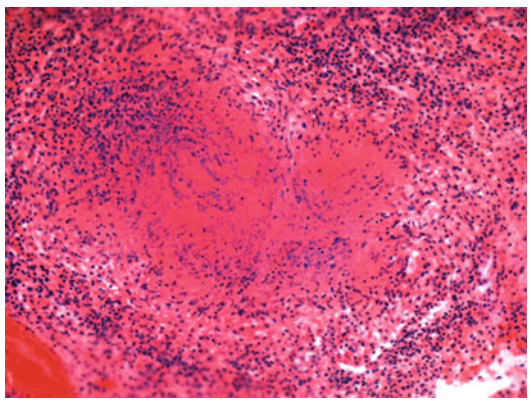

Fig. 4 Necrotic and granulomatous hepatic lesion in septicemic glanders (hematoxylin and eosin stain)

Glanders may also involve the bile ducts. A tubular-shaped intrahepatic cholangitis of larger ducts has been described, with ulcers and so-called diphtheroid lesions (Sommerbrodt 1864).

Listeriosis

Introduction

Listeria monocytogenes is an opportunistic bacterial pathogen that causes food-borne illnesses and is well known to cause neonatal and adult sepsis, recognized in 1929 already. The pathogenic spectrum in humans is rather broad and comprises meningitis, septicemia, abortion, and gastroenteritis. *L. monocytogenes* is widely distributed in the environment and also occurs in the intestinal tract of healthy animals and humans (Barbuddhe and Chakraborty 2009). *Listeria* can be isolated from sources as diverse as wild and domestic animals (including insects), soil, stale water supplies, waste water, vegetation (typically grazing areas), and food (particularly dairy products).

L. monocytogenes is a typical example of a bacterium that can switch from a saprophytic organism to a virulent mammalian pathogen. The microorganism is capable to live and survive in several environmental niches, is resistant to dry and cold environment, and can grow at temperatures as low as 3 C in high-salt or acid-stress environments, permitting replication in refrigerated processed

food. As a result, *Listeria* may be transmitted in ready-to-eat foods that have been kept properly refrigerated and heated before use. *L. monocytogenes* grows best at −18–10 C but is also able to grow and survive at relatively high temperatures.

Epidemiology

It has been suggested that up to 5 % or more of normal healthy people harbor *Listeria*, usually in the gut, where the germ can stay for long time periods without causing harm. Listerial infections occur most frequently in neonates and in adults with immunosuppression, in pregnancy, advanced age, HIV infection, alcoholism, kidney diseases, or diabetes mellitus, with an estimated incidence in adults of less than 1/100,000. In a French study, patients with chronic lymphocytic leukemia had a more than 1,000-fold increased risk of acquiring listeriosis, and a 100–1,000-fold increased risk of listeriosis was observed in patients with liver cancer, myeloproliferative disorders, multiple myeloma, acute leukemias, immune complex vasculitis, dialysis, several types of solid cancers, brain tumors, liver cirrhosis, and pregnancy (Goulet et al. 2012). *L. monocytogenes* causes a variety of diseases, including infection in pregnancy, the manifestations here ranging from mild chill to severe illness precipitating miscarriage or premature birth, and meningitis in the newborn. Meningoencephalitis and sepsis are particularly well-known manifestations of listerial infection in adult individuals.

Liver Involvement in Listeriosis

Liver involvement in listerial infections probably has its origins either in a primary bacteremia (septic listeriosis), the spreading to different organs, or through the portal venous system after enteric colonization. This is the reason for the development of several patterns of clinical presentation for listerial liver disease (review: Scholing et al. 2007). Transplacental transmission of *L. monocytogenes* causes a distinct prenatal/perinatal syndrome called granulomatosis infantiseptica (septic granulomatosis of the infant). This severe disorder is characterized by disseminated, *Listeria*-containing abscesses and/or granulomas mainly involving the fetal liver, lung, spleen, brain, and skin. In contrast, the predominant clinical manifestations in the adult patients comprise CNS involvement or a primary bacteremia. In adults, it is the latter presentation which will most commonly cause liver disease, which is however not common. One reason for the relative rarity of hepatic listerial infection in adults may be related to the distinct defense environment of the liver, complex interactions in this organ between resident cells and immigrating lymphocytes, and monocytes and neutrophils providing a strong innate defense and immunity to listerial infection (Cousens and Wing 2000; Gregory and Wing 2002).

Listerial Liver Abscesses

Purulent hepatitis with abscess formation is an uncommon manifestation of hepatic listeriosis. Solitary liver abscess, multiple liver abscesses, or supramiliary purulent hepatitis (microabscesses) are recognized.

Selected References Seeliger et al. 1961; Yu et al. 1982; Al Dajani and Khati 1983; Herreman et al. 1990; Ribière et al. 1990; Bugnon et al. 1991; Beaufigueau et al. 1993; Manian 1994; Marino et al. 1996; Brönnimann et al. 1998; and Lopez-Prieto et al. 2000.

Based on a literature review (Scholing et al. 2007), *solitary* listerial liver abscesses had an average patient age of onset of 59 years (range: 28–77 years) and were, among ten cases reviewed, exclusively found in patients with diabetes mellitus. The clinical signs are variable, but often mimic malignancy, with fever, epigastric pain, night sweats, and weight loss. Solitary listerial liver abscess is not associated with extrahepatic manifestations of listeriosis. In extended perifocal liver disease, jaundice and abnormal liver function tests may ensue, causing the presentation of acute icteric hepatitis (Yu et al. 1982). In a review, 11 patients (8 males and 3 females) with *multiple* listerial liver *abscesses* were

identified (Manian 1994; Marino et al. 1996; review: Scholing et al. 2007). The average age of onset in this group was also 59 years (range: 22–81 years), i.e., the same as in solitary listerial hepatic abscesses. The majority of the patients had underlying conditions such as diabetes mellitus, grafts with immunosuppression, or chronic steroid use. In 80 % of the patients, blood cultures were positive for *L. monocytogenes*, and slightly more than a third had concomitant meningitis. In contrast to solitary abscess, multiple abscesses carry a poor prognosis, with a mortality of about 70 %, causes of death including septic shock, meningitis, and multiorgan failure (Scholing et al. 2007). The abscesses were recognized as miliary lesions ("miliary abscesses") in two reports (Simpson et al. 1967; Yu et al. 1982).

Macroscopically, solitary listerial liver abscesses range in diameter from 1 to 20 cm, whereas multiple abscesses are usually smaller, most lesions not exceeding 2 cm in diameter (review: Scholing et al. 2007). The lesion in part resembles pyogenic liver abscess, but pus formation is often less prominent, and tissue necrosis dominated the presentation. Histologically, listerial abscesses commonly present as necrotic foci with shadow cells, nuclear debris, and variable numbers of viable or decayed phagocytes, both neutrophils and macrophages, but sometimes necrosis prevails, with few infiltrate cells (Fig. 5). By the use of bacterial stains, *Listeria* organisms may be detectable as thin, Gram-positive rods, either within phagocytes or situated in the necrotic masses.

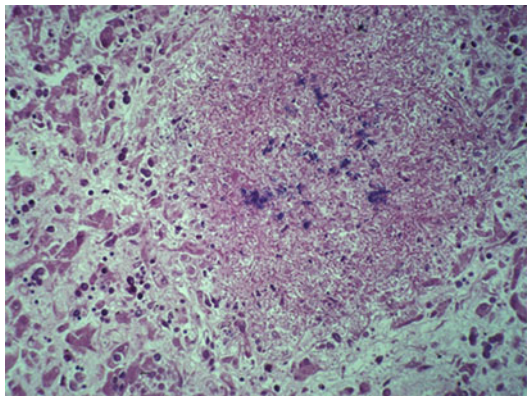

Fig. 5 Hepatic necrosis in listeriosis. The lesion is poor in leukocytic infiltrates and contains numerous *Listeria* organisms (hematoxylin and eosin stain)

Nodular Hepatic Listeriosis

Nodular hepatic lesions have been noted at necropsy of two adult patients dying from listeriosis (Seeliger et al. 1961). The lesions represent coalesced necroses and abscess with a demarcation zone of granulation and fibrous tissue.

Miliary Granulomatous Hepatitis

Listeriosis may induce a cell-mediated immune reaction with strong macrophage activation and formation of epithelioid cell granulomas (Seeliger et al. 1961; Henderson and Ramsey 1967). These granulomas may cause miliary lesions resembling those in tuberculosis (Henderson and Ramsey 1967). Necrosis can develop in the center of the granulomas, and *Listeria* organisms have been identified in macrophages surrounding the necrotic foci (Kumada et al. 1989).

Diffuse Listerial Hepatitis

Listerial diffuse hepatitis was observed in patients with alcohol abuse, underlying viral hepatitis, pregnancy, or steroid treatment, but not in patients with diabetes mellitus. Almost all of these patients had listerial bacteremia, and almost half suffered from meningitis (Yu et al. 1982; De et al. 1992; Teodor et al. 2012).

References

Abdelli N, Thiefin G, Chevalier P, Zeitoun P (1996) Spontaneously regressive liver abscess caused by *Yersinia enterocolitica* revealing genetic hemochromatosis: a second case (in French). Gastroenterol Clin Biol 20:212–213

Adler NR, Govan B, Cullinane M, Harper M, Adler B, Boyce JD (2009) The molecular and cellular basis of pathogenesis in melioidosis: how does *Burkholderia pseudomallei* cause disease? FEMS Microbiol Rev 33:1079–1099

Al Dajani O, Khati R (1983) Cryptogenic liver abscess due to *Listeria monocytogenes*. J Infect Dis 147:961

Allwood EM, Devenish RJ, Prescott M, Adler B, Boyce JD (2011) Strategies for intracellular survival of *Burkholderia pseudomallei*. Front Microbiol 2:170

Apisarnthananarak P, Apisarnthanark A, Mundy LM (2006) Computed tomography characteristics of *Burkholderia pseudomallei*-associated liver abscess. Clin Infect Dis 42:989–993

Apisarnthanarak P, Thairatananon A, Muangsomboon K, Lu DS, Mundy LM, Apisarnthanarak A (2011) Computed tomography characteristics of hepatic and splenic abscesses associated with melioidosis: a 7-year study. J Med Imag Radiat Oncol 55:176–182

Atisook K, Panyathanya R (1988) Acute systemic melioidosis: an autopsy study of six cases. Southeast Asian J Trop Med Public Health 19:637–642

Azali HY, Norly S, Wong LM, Tan KS, Safian NM (2007) Liver abscess caused by tuberculosis and melioidosis. Asian J Surg 30:138–140

Barnes et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/16754724

Barbuddhe SB, Chakraborty T (2009) Listeria as an enteroinvasive gastrointestinal pathogen. Curr Top Microbiol Immunol 337:173–195

Baskerville A, Hambleton P, Dowsett AB (1978) The pathology of untreated and antibiotic-treated experimental tularaemia in monkeys. Br J Exp Pathol 59:615–662

Beaufigueau M, Paris F, Bachellier P, Vanwymeersch S, Monteil H, Jaeck D (1993) Liver abscess revealing listeriosis (in French). Presse Med 22:492

Beeching NJ, Hart HH, Synek BJ, Bremner DA (1985) A patient with hemosiderosis and multiple liver abscesses due to *Yersinia enterocolitica*. Pathology 17:530–532

Ben RJ, Tsai YY, Chen JC, Feng NH (2004) Non-septicemic *Burkholderia pseudomallei* liver abscess in a young man. J Microbiol Immunol Infect 37:254–257

Benbrika S, Boukari L, Stirnemann J, Letellier E, Fain O, Thomas M, kettaneh A (2005) A case of yersiniosis with multiple liver abscesses (in French). Rev Med Interne 26:151–152

Bergmann TK, Vinding K, Hey H (2001) Multiple hepatic abscesses due to *Yersinia enterocolitica* infection secondary to primary haemochromatosis. Scand J Gastroenterol 36:891–895

Bernstein JM, Carling ER (1909) Observations on human glanders: with a study of six cases and a discussion of the methods of diagnosis. Br Med J 1:319–325

Blancou J (1994) Early methods for the surveillance and control of glanders in Europe. Rev Sci Tech 13:545–557

Bollinger O (1874) Infectionen durch thierische Gifte. Der Rotz des Menschen. In: Handbuch der chronischen Infektionskrankheiter. Baeumler C, Heller A, Bollinger O, (eds), F.C.W. Vogel, Leipzig, vol 3, pp 397–399

Bollinger O (1876) Zoonosen (Rotz, Malleus humidus). In: Ziemssen's Handbuch der Speziellen Pathologie. Ziemssen H, ed; Vogel F, Leipzig; 3, p 438

Brönnimann S, Baer HU, Malinverni R, Büchler MW (1998) Listeria monocytogenes causing solitary liver abscess. Case report an review of the literature. Dig Surg 15:364–368

Brundage WG, Thuss CJ, Walden DC (1968) Four fatal cases of melioidosis in U.S. soldiers in Vietnam. Bacteriologic and pathologic characteristics. Am J Trop Med Hyg 17:183–191

Brunel F, François P, Durand C, Croize J, Jeannoel P (1993) Hepatic abscess due to *Yersinia* in a child with thalassemia (in French). Pediatrie 48:159–162

Bugnon PY, Ruchard D, Gautier-Benoit C (1991) Isolated *Listeria monocytogenes* liver abscess: suspected diabetes mellitus (in French). J Chir (Paris) 128:499

Capron JP, Delamarre J, Delcenserie R, Gineston JL, Dupas JL, Lorriaux A (1981) Liver abscess complicating *Yersinia pseudotuberculosis* ileitis. Gastroenterology 81:150–152

Cheng AC, Johnson DF (2006) Multiloculated hepatosplenic abscesses. Clin Infect Dis 43:264–265

Cheng AC, Currie BJ, Dance DA, Funnell SG, Limmathurotsakul D, Simpson AJ, Peacock SJ (2013) Clinical definitions of melioidosis. Am J Trop Med Hyg 88:411–413

Chong VH (2006) Is a honeycomb appearance on computer tomography characteristic for *Burkholderia pseudomallei* liver abscess? Clin Infect Dis 43:265–266

Collazos J, Guerra E, Fernandez A, Mayo J, Martinez E (1995) Miliary liver abscesses and skin infection due to *Yersinia enterocolitica* in a patient with unsuspected hemochromatosis. Clin Infect Dis 21:223–224

Compant S, Nowak J, Coenye T, Clément C, Ait Barka E (2008) Diversity and occurrence of *Burkholderia* spp. in the natural environment. FEMS Microbiol Rev 32:607–626

Conlan JW, North RJ (1992) Early pathogenesis of infection in the liver with the facultative intracellular bacteria *Listeria monocytogenes*, *Francisella tularensis*, and *Salmonella typhimurium* involves lysis of infected hepatocytes by leukocytes. Infect Immun 60:5164–5171

Cousens LP, Wing EJ (2000) Innate defenses in the liver during *Listeria* infection. Immunol Rev 174:150–159

Dance (2002) http://www.ncbi.nlm.nih.gov/pubmed/11964912

De VT, Echevarria S, Crespo J, Artinano E, San MG, Pons RF (1992) Acute hepatitis by *Listeria monocytogenes* in an HIV patient with chronic HBV hepatitis. J Clin Gastroenterol 15:251–255

Dienst FT (1963) Tularemia: a perusal of three hundred thirty-nine cases. J La State Med Soc 115:114–124

Drebber U, Kasper HU, Ratering J, Wedemeyer I, Schirmacher P, Dienes HP, Odenthal M (2008) Hepatic

granulomas: histological and molecular pathological approach to differential diagnosis – a study of 442 cases. Liver Int 28:828–834
Dresler J, Klimentova J, Stulik J (2011) *Francisella tularensis* membrane complexome by blue native/SDS-PAGE. J Proteomics 75:257–269
Dubois A, Gervais C, Arich C, Gouby A, Pignodel C, Fabre S, Janbon C (1982) Liver diseases associated with *Yersinia* infections (in French). Nouv Presse Med 11:1619–1621
Dvorak GD, Spickler AR (2008) Glanders. J Am Vet Med Assoc 233:570–577
Ellis et al (2002) http://www.ncbi.nlm.nih.gov/pubmed/12364373
Epinger M, Rosovitz MJ, Fricke WF, Rasko DA, Kokorina G, Fayolle C, Lindler LE et al (2007) The complete genome sequence of *Yersinia pseudotuberculosis* IP31758, the causative agent of Far East scarlet-like fever. PLoS Genet 3, e142
Escudero R, Toledo A, Gil H, Kovacsova K, Rodriguez-Vargas M, Jado I, Garcia-Amil C et al (2008) Molecular method for discrimination between *Francisella tularensis* and Francisella-like endosymbionts. J Clin Microbiol 46:3139–3143
Evans et al (1985) http://www.ncbi.nlm.nih.gov/pubmed/3892222
Fabrega A, Vila J (2012) *Yersinia enterocolitica*: pathogenesis, virulence and antimicrobial resistance. Enferm Infecc Microbiol Clin 30:24–32
Farrer W, Kloser P, Ketyer S (1988) Yersinia pseudotuberculosis sepsis presenting as multiple liver abscesses. Am J Med Sci 295:129–132
Foshay L (1937) Cause of death in tularemia. Arch Intern Med 60:22–38
Foulger M, Glazer A, Foshay L (1932) Tularemia: report of a case with post-mortem observations and a note on the staining of Bacterium tularense in tissue section. JAMA 98:951–954
Fraenkel E (1914) Über Pseudotuberkulose des Menschen. Zeitschr Hyg Inf Krankh 101:406
Francis E (1928) A summary of present knowledge of tularemia. Medicine (Baltimore) 7:411–432
Gan (2005) http://www.ncbi.nlm.nih.gov/pubmed/16235187
Georgiades C, Fishman EK (2001) Clinical image. Glanders disease of the liver and spleen: CT evaluation. J Comput Assist Tomogr 25:91–93
Gilad J (2007) *Burkholderia mallei* and *Burkholderia pseudomallei*: the causative micro-organisms of glanders and melioidosis. Recent Pat Antiinfect Drug Discov 2:233–241
Goulet V, Hebert M, Hedberg C, Lauent E, Vaillant V, De Valk H, Desenclos JC (2012) Incidence of listeriosis and related mortality among groups at risk of acquiring listeriosis. Clin Infect Dis 54:652–660
Gourdeau M, Lamothe F, Ishak M, Côté J, Breton G, Villeneuve JP, D'Amico P (1983) Hepatic abscess complicating ulceroglandular tularemia. Can Med Assoc J 129:1286–1288
Greenawald KA, Nash G, Foley FD (1969) Acute systemic melioidosis. Autopsy findings in four patients. Am J Clin Pathol 52:188–198
Gregory SH, Wing EJ (2002) Neutrophil-Kupffer cell interaction: a critical component of host defenses to systemic bacterial infections. J Leukoc Biol 72:239–248
Grigull L, Linderkamp C, Sander A, Schmid H, Mutschler U, Welte K, Beilken A (2005) Multiple spleen and liver abscesses due to *Yersinia enterocilitica* septicemia in a child with congenital sideroblastic anemia. J Pediatr Hematol Oncol 27:624–626
Guarga A, Urrutia A, Tor J, Muga R, Vidal MT, Rey-Joly C (1984) *Yersinia enterocolitica* hepatic granulomatosis (in Spanish). Med Clin (Barc) 82:362–363
Harik NS (2013) Tularemia: epidemiology, diagnosis, and treatment. Pediatr Ann 42:288–292
Helly D (1907) Demonstration der Präparate eines Falles von Rotzinfektion. Prag Med Wochenschr 32:424
Henderson JR, Ramsey CA (1967) Miliary granulomata in fatal adult case of listerial meningitis. Postgrad Med J 43:794–796
Herreman G, Jaisson B, Quignodon JF, Mundler B, De La Fontaine P (1990) Abscès du foie à Listeria monocytogenes chez une malade diabétique. Presse Med 20:479
Höpfner M, Nitsche R, Rohr A, Harms D, Schubert S, Fölsch UR (2001) Yersinia enterocolitica infection with multiple liver abscesses uncovering a primary hemochromatosis. Scand J Gastroenterol 36:220–224
Hopwood AH, Riddle BW (1986) Yersinia enterocolitica hepatic abscesses. J Ky Med Assoc 84:13–15
Inglis T (2011) VIth World Melioidosis Congress report: celebrating a century of research. Future Microbiol 6:263–264
Inglis TJJ, Mee BJ, Chang BJ (2001) The environmental microbiology of melioidosis. Rev Med Microbiol 12:13–20
Ismail MH, Hodkinson HJ, Patel M, Koornhof HJ (1987) Multiple liver abscesses caused by *Yersinia enterocolitica*. A case report. S Afr Med J 72:291–292
Jochmann G (1914) Rotz. In: Lehrbuch der Infektionskrankheiten für Ärzte und Studierende. Verlag von Julius Springer, Berlin, p 919
Kingston CW (1971) Chronic or latent melioidosis. Med J Aust 2:618–621
Koch J (1902) Zur Diagnose des akuten Rotzes beim Menschen. Langenbeck's Arch Klin Chir 65:37–56
Kugeler KJ, Gurfield N, Creek JG, Mahoney KS, Versage JL, Petersen JM (2005) Discrimination between *Francisella tularensis* and Francisella-like endosymbionts when screening ticks by PCR. Appl Environ Microbiol 71:7594–7597
Kumada T, Enari T, Kobayashi S, Fukada T, Katahira J, Totsuka K, Shimizu K, Takahashi K (1989) Four cases of adult *Listeria monocytogenes* infection in the last 5 years – hepatic necrotic foci in the adult septic case (in Japanese). Kansenshogaku Zasshi 63:534–540

Lamps et al (2004) http://www.ncbi.nlm.nih.gov/pubmed/15001997

Laopaiboon V, Chamadol N, Buttham H, Sukeepaisarnjareon W (2009) CT findings of liver and splenic abscesses in melioidosis: comparison with those in non-melioidosis. J Med Assoc Thai 92:1476–1484

Lee YL, Lee SS, Tsai HC, Chen YS, Wann SR, Kao CH, Liu YC (2006) Pyogenic liver abscess caused by *Burkholderia pseudomallei* in Taiwan. J Formos Med Assoc 105:689–693

Leelarasamee A (2004) Recent development in melioidosis. Curr Opin Infect Dis 17:131–136

Leighton PM, MacSween HM (1987) Yersinia hepatic abscesses subsequent to long-term iron therapy. JAMA 257:964–965

Leyman P, Baert AL, Marchal G, Fevery J (1989) Ultrasound and CT of multifocal liver abscesses caused by *Yersinia enterocolitica*. J Comput Assist Tomogr 13:913–915

Lim KS, Chong VH (2010) Radiological manifestations of melioidosis. Clin Radiol 65:66–72

Limmathurotsakul D, Chaowagul W, Day NP, Peacock SJ (2009) Patterns of organ involvement in recurrent melioidosis. Am J Trop Med Hyg 81:335–337

Limmatthurotsakul D, Peacock SJ (2011) Melioidosis: a clinical overview. Br Med Bull 99:125–139

Ljungberg P, Valtonen M, Harjola VP, Kaukoranta-Tolvanen SS, Vaara M (1995) Report of four cases of *Yersinia pseudotuberculosis* septicemia and a literature review. Eur J Clin Microbiol Infect Dis 14:804–810

Lopez-Prieto MD, Aller Garciia AI, Alcaraz GS, Lopez Cepero J (2000) Liver abscess due to *Listeria monocytogenes*. Clin Microbiol Infect 6:226–227

Machado Braga MD, Carvalho de Almeida PR (2005) First description of an autopsied case of melioidosis in Ceara State (in Portuguese). Rev Soc Brasileira Med Trop 38:58–60

Manian FA (1994) Liver abscess due to *Listeria monocytogenes*. Clin Infect Dis 18:841–842

Marino P, Maggioni M, Preatoni A, Cantoni A, Invernizzi F (1996) Liver abscesses due to *Listeria monocytogenes*. Liver 16:67–69

Martone WJ, Marshall LW, Kaufmann AF, Hobbs JH, Levy ME (1979) Tularemia pneumonia in Washington DC. A report of three cases with possible common-source exposures. JAMA 242:2315–2317

Mennecier D, Lapprand M, Hernandez E, Minvielle F, Bredin C, Potier V, Thiolet C, Farret O (2001) Liver abscesses due to *Yersinia pseudotuberculosis* discloses a genetic hemochromatosis (in French). Gastroenterol Clin Biol 25:1113–1115

Mischnick A, Dahme T, Bekeredijan R, Zimmermann S (2012) Haemophilia-associated *Yersinia pseudotuberculosis* serotype O:1 septicaemia: the role of iron. J Med Microbiol 61:157–159

Mukhopadhya A, Balaji V, Jesudason MV, Amte A, Jeyamani R, Kurian G (2007) Isolated liver abscesses in melioidosis. Indian J Med Microbiol 25:150–151

Navascues A, Etxeberria D, Garcia-Irure JJ, Dorronsoro I (2005) Bacteriemia and hepatic abscess secondary to *Yersinia pseudotuberculosis* infection (in Spanish). Enferm Infecc Microbiol Clin 23:47–48

Nemoto H, Murabayashi K, Kawamura Y, Sasaki K, Wakata N, Kinoshita M, Furuba M (1992) Multiple liver abscesses secondary to *Yersinia enterocolitica*. Intern Med 31:1125–1127

Neubauer et al (2005) http://www.ncbi.nlm.nih.gov/pubmed/1615091

Nigg C (1963) Serologic studies on subclinical melioidosis. J Immunol 91:18–28

Nörenberg D, Wieser A, Magistro G, Hoffmann C, Meyer C, Messerer M, Schubert S (2013) Molecular analysis of a novel Toll/interleukin-1 receptor (TIR)-domain containing virulence protein of *Y. pseudotuberculosis* among Far East scarlet-like fever serotype I strains. Int J Med Microbiol 303:583–594

Olesen LL, Ejlertsen T, Paulsen SM, Knudsen PR (1989) Liver abscesses due to *Yersinia enterocolitica* in patients with hemochromatosis. J Intern Med 225:351–354

Ortego TJ, Hutchins LF, Rice J, Davis GR (1986) Tularemic hepatitis presenting as obstructive jaundice. Gastroenterology 91:461–463

Oyston (2008) http://www.ncbi.nlm.nih.gov/pubmed/18628490

Piéron R, Grivaux M, Mafart Y, Meyniel D, Chatelet F (1983) Hepatic granulomatosis and positive serodiagnosis of *Yersinia* infections (in French). Sem Hop 59:2447–2451

Piggott JA, Hochholzer L (1970) Human melioidosis. A histopathologic study of acute and chronic melioidosis. Arch Pathol 90:101–111

Pullen RL, Stuart BM (1945) Tularemia: analysis of 225 cases. JAMA 129:495–500

Pulvirenti D, Aikaterini T, Neri S (2007) Septicemia, hepatic abscess, and encephalitis due to *Yersinia enterocolitica*. J Clin Gastroenterol 41:333–334

Puthucheary SD, Parasakthi N, Lee MK (1992) Septicaemic melioidosis: a review of 50 cases from Malaysia. Trans R Soc Trop Med Hyg 86:683–685

Rajadhyaksha A, Sonawale A, Khare S, Kalal C, Jankar R (2012) Disseminated melioidosis presenting as septic arthritis. J Assoc Physicians India 60:44–45

Ribière O, Cotarel P, Jarlier V et al (1990) Abscès du foie à *Listeria monocytogenes* chez une malade diabétique. Presse Med 19:1538–1540

Robins GD (1906) A study of chronic glanders in man with report of a case: analysis of 156 cases collected from the literature. Stud R Vic Hosp Montr 2:1–98

Roman B (1916) Über einen Fall von bazillärer Pseudotuberkulose beim Menschen. Virchows Arch Pathol Anat Physiol 222:53

Saebe A, Lassen J (1992) Acute and chronic liver disease associated with *Yersinia enterocolitica* infection: a

Norwegian 10-year follow-up study of 458 hospitalized patients. J Intern Med 231:531–535
Santoro MJ, Chen YK, Seid NS, Abdulian JD, Collen MJ (1994) Yersinia enterocolitica liver abscesses unmasking idiopathic hemochromatosis. J Clin Gastroenterol 18:253–254
Schneider P (1915) Ueber disseminierte miliare, nicht syphilitische Lebernekrose bei Kindern mit eigenartigen argentophilen Bakterien. Virchows Arch Pathol Anat Physiol 219:74
Scholing et al (2007) http://www.ncbi.nlm.nih.gov/pubmed/17646920
Schuchmann M, Gerbes AL, Heesemann J, Sauter G (1997) Multiple liver abscesses caused by *Yersinia enterocolitica* in a patient receiving long-term transfusion therapy for osteomyelosclerosis. Dig Dis Sci 42:2501–2504
Seeliger HPR, Meyer VF, Eyer H (1961) Listeriosis. Hafner, New York
Sheehy TW, Deller JJ, Weber DR (1967) Melioidosis. Ann Intern Med 67:897–900
Simpson JF, Leddy JP, Hare JD (1967) Listeriosis complicating lymphoma. Report of four cases and interpretative review of pathogenetic factors. Am J Med 43:39–49
Sommerbrodt J (1864) Ein Fall von Rotzkrankheit beim Menschen. Virchows Arch Pathol Anat Physiol 31:463–483
Spinner H (1926) Zur Kenntnis der pathologischen Histologie des Rotzes an Hand von menschlichem und experimentellem Beobachtungsmaterial. Frankfurt Zeitschr Pathol 33:327–348
Splettstoesser WD, Piechotowski I, Buckendahl A, Frangoulidis D, Kaysser P, Kratzer W et al (2008) Tularemia in Germany: the tip of the iceberg? Epidemiol Infect 23:1–8
Spotnitz M, Rudnitzky JR, Rambaud JJ (1967) Melioidosis pneumonitis. JAMA 202:950–954
Srinivasan A, Kraus CN, DeShazer D, Becker PM, Dick JD, Spacek L, Bartlett JG et al (2001) Glanders in an military research microbiologist. N Engl J Med 345:256–258
Stjernberg U, Silseth C, Ritland S (1987) Granulomatous hepatitis in *Yersinia enterocolitica* infection. Hepatogastroenterology 34:56–57
Strube G (1897) Klinisches und Anatomisches über einen Fall von acutem Rotz beim Menschen. Charité-Annalen 22:213–221
Strube G (1900) Ueber die Rotzkrankheit beim Menschen, Arch Klin Chir 61:376–403
Strungs I, Farrell DJ, Matar LD, Dekker L, Franz RJ (1995) Multiple hepatic abscesses due to *Yersinia enterocolitica*. Pathology 27:374–377
Teodor A, Teodor D, Miftode E, Prisacaru D, Leca D, Petrovici C, Doneanu O, Dorobat CM (2012) Sever invasive listeriosis – case report. Rev Med Chir Soc Med Nat Iasi 116:808–811
Thurnheer U, Novak A, Michel M, Ruchti C, Jutzi H, Weiss M (1988) Septic melioidosis following a visit to India (in German). Schweiz Med Wschr 118:558–564
Torres AG, Steinmetz I (2012) Recent progress in melioidosis and glanders. Front Microbiol 3:149
Urso C (1993) Hypothesis on the Achaean disease (in Italian). Pathologica 85:441–443
Vadillo M, Corbella X, Pac V, Fernandez-Viladrich P, Pujol R (1994) Multiple liver abscesses due to *Yersinia enterocolitica* discloses primary hemochromatosis: three cases reports and review. Clin Infect Dis 18:938–941
Van Zandt KE, Greer MT, Gelhaus HC (2013) Glanders: an overview of infection in humans. Orphanet J Rare Dis 8:131
Vatcharapreechasakul T, Suputtamongkol Y, Dance DA, Chaowagul W, White NJ (1992) Pseudomonas pseudomallei liver abscesses: a clinical, laboratory, and ultrasonographic study. Clin Infect Dis 14:412–417
Vincent P, Leclercq A, Martin L, Yersinia Surveillance Network, Duez JM, Simonet M, Carniel E (2008) Sudden onset of pseudotuberculosis in humans, France, 2004–05. Emerg Infect Dis 14:1119–1122
Viteri AL, Howard PH, May JL, Ramesh GS, Roberts JW (1981) Hepatic abscess due to *Yersinia enterocolitica* without bacteriemia. Gastroenterology 81:592–593
Watson JA, Windsor JA, Wynne-Jones G (1989) Conservative management of a *Yersinia enterocolitica* hepatic abscess. Aust NZ J Surg 59:353–354
Weber DR, Douglass LE, Brundage WG, Stallkamp TC (1969) Acute varieties of melioidosis occurring in U.S. soldiers in Vietnam. Am J Med 46:234–244
White NJ (2003) Melioidosis. Lancet 361:1715–1722
Whitlock et al (2007) http://www.ncbi.nlm.nih.gov/pubmed/18031330
Whitmore A, Krishnaswami CS (1912) An account of the discovery of a hitherto undescribed infective disease occurring among the population of Rangoon. Indian Med Gaz 47:262–276
Wibulpolprasert B, Dhiensiri T (1999) Visceral abscesses in melioidosis: sonographic findings. J Clin Ultrasound 27:29–34
Wiersinga WJ, van der Poll T, White NJ, Day NP, Peacock SJ (2006) Melioidosis: insights into the pathogenicity of *Burkholderia pseudomallei*. Nat Rev Microbiol 4:272–282
Wilkinson L (1981) Glanders: medicine and veterinary medicine in common pursuit of a contagious disease. Med Hist 25:363–384
Wong KT, Puthucheary SD, Vadivelu J (1995) The histopathology of human melioidosis. Histopathology 26:51–55
Yu VL, Miller WP, Wing EJ, Romano JM, Ruiz CA, Bruns FJ (1982) Disseminated listeriosis presenting as acute hepatitis. Am J Med 73:773–777
Zaidi SA, Singer C (2002) Gastrointestinal and hepatic manifestations of tickborne diseases in the United States. Clin Infect Dis 34:1206–1212
Zapata R, Garcia P (1997) Multiple hepatosplenic abscesses caused by *Yersinia enterocolitica* in a patient with hemochromatosis (in Spanish). Rev Med Chil 125:917–921

Tumor-Like Lesions of the Hepatobiliary Tract Caused by Fungal Infections

131

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_131

Abstract

Systemic *Candida* infections (candidiasis), most commonly observed in immunosuppressed and/or neutropenic individuals, can induce several types of hepatic lesions. They comprise disseminated or miliary hepatic candidiasis, granulomatous hepatitis, candidal liver abscess, *Candida* pseudotumor ("candidoma"), and candidal cholangitis. Large nodular lesions show a complex histology with necrosis, purulent inflammation, and eventually a granulomatous reaction. A similar spectrum of lesions is induced by cryptococcosis, with formation of miliary lesions, abscesses, and hepatic cryptococcoma. Macroabscesses and pseudotumors of the liver are also induced in the setting of zygomycosis including mucormycosis and in systemic aspergillosis. In the latter, aspergillomas and hepatic pseudotumors are sometimes associated with angioinvasive mycosis.

Hepatobiliary Candidiasis

Introduction

Candida species are diploid fungi that cause the dominant fungal disease, invasive candidiasis (review: Rueping et al. 2009). Candidiasis is most commonly observed in immunosuppressed and/or neutropenic individuals and occurs as acute, smoldering, or chronic forms (Swerdloff et al. 1993). In the liver, *Candida* infections can produce mass lesions that may be confounded with hepatic neoplasias.

The genus *Candida* belongs to the family *Saccharomycetaceae* of the order *Saccharomycetales* and phylum *Ascomycota*. The main *Candida* species of clinical relevance includes *C. albicans*, but an increasing number of non-*albicans Candida* (NAC) have been reported (Krcmery and Barnes 2002; Chen et al. 2009).

Epidemiology

Candida albicans is a commensal yeast colonizing the gastrointestinal tract and being detectable in the oral cavity in about one-third to one-half of the healthy population. Apart from effects of the composition of the oral microbial community, salivary factors seem to be involved in oral *Candida* colonization. Saliva of *Candida*-free subjects inhibits the blastoconidial growth more than that of *Candida* carriers, suggesting that salivary components modulate persistent oral *Candida* carriage (Hibino et al. 2009). Invasive candidiasis as a condition of great medical importance has shown a dramatical increase in incidence over the last 50 years. *Candida* species are regularly reported to be the fourth commonest cause of bloodstream infection (fungemia), but the incidence of infections with *Candida albicans* is falling in recent years, while other *Candida* infections are on the rise (Hobson 2003). In fact, the epidemiology has recently changed with regard to *Candida* species involved. In a US study on 2019 patients with candidemia, the incidence of candidemia caused by non-*albicans Candida* species (54.4 %) was higher than the incidence of candidemia caused by *C. albicans* (45.6 %). Patients with *C. parapsilosis* candidemia had the lowest mortality rate and were less likely to be neutropenic compared with patients infected with other *Candida* species. *Candida krusei* candidemia was most commonly associated with prior use of antifungal agents, hematologic malignancy, stem cell transplantation, or neutropenia, and patients infected by this fungus showed the highest crude 12-week mortality (Horn et al. 2009).

Hepatobiliary Candidiasis

Hepatobiliary candidiasis is increasingly seen in recent years due to factors already briefly discussed above. It predominantly occurs in immunocompromised patients and cancer patients (Lewis et al. 1982; Haron et al. 1987; Thaler et al. 1988; Carstensen et al. 1990). It presents as

Table 1 Phenotypical classification of hepatobiliary candidiasis

Disseminated ("miliary") hepatic candidiasis
Granulomatous hepatitis
Candidal liver abscess
Focal hepatic candidiasis (candidoma of the liver, *Candida* pseudotumor)
Candidal hepatic thrombovasculitis
Candidal cholangitis
Candidal cholecystitis

several forms of hepatic tissue damage associated with inflammatory changes (Table 1). In an autopsy study, hepatic granulomas and microabscesses were the two most common histologic lesions attributable to *Candida* infection (Lewis et al. 1982). The emergence of a given phenotype of hepatic infection depends on *Candida* virulence, *Candida* species, the neutrophil and immune status of the host, duration of disease, and effects of treatment measures. Part of the inflammatory and necrobiotic alterations cause mass lesions that may mimic hepatic malignancy. Hepatic candidiasis is often associated with manifestations in the spleen (the hepatosplenic candidiasis syndrome), particularly in patients with acute leukemia and those with neutropenia (Miller et al. 1982; Fenaux et al. 1989; von Eiff et al. 1990; Loeliger et al. 1992; Anttila et al. 1994, 1997; Colovic et al. 1999; Sallah 1999; Rammaert et al. 2012). There are also patients showing a protracted from of hepatic/hepatosplenic candidiasis (chronic disseminated candidiasis; Blade et al. 1992; Pagano et al. 2002; Masood and Sallah 2005). In hepatic candidiasis, *C. albicans* is a dominant causing agent, but other *Candida* species are also involved, including *C. glabrata* (Pinès et al. 1994) and *C. tropicalis* (McGuire et al. 1992).

Disseminated ("Miliary") Hepatic Candidiasis

This phenotype of candidiasis is characterized by small abscesses spread throughout the organ. The

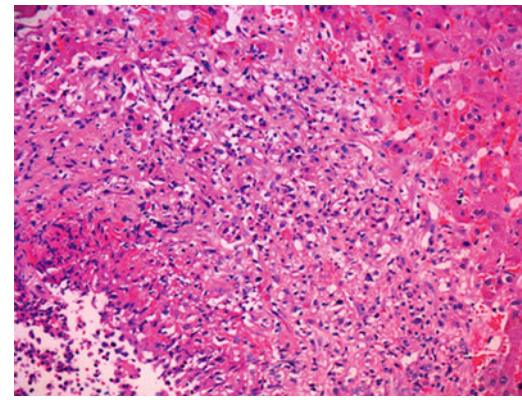

Fig. 1 Candidoma of the liver. A central necrosis with neutrophil reaction (*left lower corner*) is demarcated from the liver tissue by granulomas (hematoxylin and eosin stain)

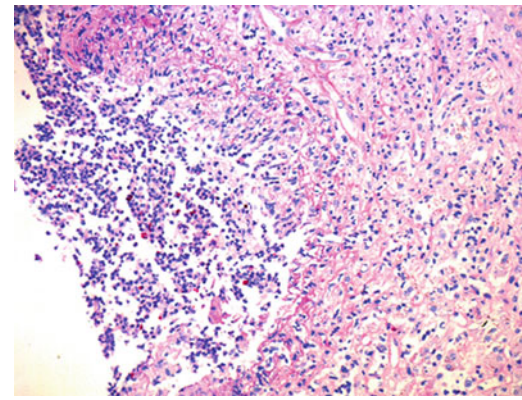

Fig. 2 The exudative center in hepatic candidoma contains PAS-positive *Candida* organisms (PAS stain)

lesions are characterized by small accumulations of neutrophils and macrophages, the latter being more frequent at the periphery of the lesions, where also a few lymphocytes and eosinophils may be seen. The center of lesions may show focal tissue necrosis, but not of the caseifying type. Within the lesions, typical *Candida* elements can be found (Figs. 1 and 2).

Granulomatous Hepatitis

Candida infection of the liver may induce the formation of epithelioid macrophages and the

generation of granulomas, depending on the immune status of the host and macrophage reactivity. *Candida*-induced granulomatous hepatitis was observed in patients with hematologic malignancies (Jones 1981), The granulomas may contain *Candida* elements or may not show any microorganisms.

Candidal Liver Abscesses

Most of liver abscesses caused by *Candida* species occur in patients with hematologic malignancies and are a manifestation of disseminated candidiasis (Lewis et al. 1982; Haron et al. 1987). The clinical features of these sometimes large lesions have been described in detail. Apart from disseminated candidiasis, candidal liver abscesses can also develop subsequent to fungemia from the portal vein or an ascending retrograde infection from the biliary tract (McGuire et al. 1992; Annunziata et al. 1997). Candidal liver abscess may rarely develop in immunocompetent and nondiabetic hosts, e.g., following severe calculous cholecystitis (Lima et al. 2010), in primary sclerosing cholangitis (Melero et al. 2008), and in neonates (Filippi et al. 2009). Candidal liver abscesses are solitary or multiple lesions, whereby the latter seem to be more common. These lesions produce a characteristic imaging picture. In the active phase of disease, hepatomegaly is found together with the "wheel-in-wheel" phenomenon, the "wagon wheel" appearance, and/or the "bull's eye" lesions, whereas later phases show hypoechoic parenchymal defects (Bartley et al. 1982; Ho et al. 1982; Schmidt et al. 1986; Grunebaum et al. 1991; Rudolph et al. 2004). Histopathologically, the morphologic presentation of candidal abscesses deviates somewhat from that of bacterial abscesses. Pus is present in the center of most lesions, but the delimitating wall of granulation tissue more often displays activated macrophages and epithelioid cells, sometimes with a granulomatous reaction. This feature can be recognized in needle or wedge liver biopsies (Johnson et al. 1988). The suppurative exudate that may contain significant components of necrotic debris is tissue sludge, and fungal elements are often visible in H&E-stained preparations already.

Selected References Finkelstein et al. (1985), Friedman et al. (1987), Maxwell and Mamtora (1988), Filice et al. (1989), Ishii et al. (1990), Singh et al. (1992), Miyata et al. (1995), Lipsett et al. (1997), Lai et al. (2005), Tsai et al. (2006), Melero et al. (2008), Lima et al. (2010), and Yellapu et al. (2010).

Focal Hepatic Candidiasis ("Candidomas")

Focal hepatic candidiasis is a distinct clinical variant of candidiasis occurring mainly in immunocompromised patients. Although affected patients may exhibit previous evidence of extrahepatic candidiasis, disease manifestations are localized to the liver at the time point of diagnosis (Tashjian et al. 1984; Abella et al. 1990; Tsui and Liang 1991). Clinically, patients with focal hepatic candidiasis have fever unresponsive to antibacterial therapy, marked abdominal symptoms, elevated serum alkaline phosphatase, and hepatic defects on abdominal CT. Peritoneoscopy may reveal studding of the liver surface with white plaques, which may later be followed by perihepatic adhesions (Gordon et al. 1990).

Histologically, the focal lesions consist of parenchymal necrosis colonized by variable numbers of *Candida* elements, mainly hyphal forms. Some of the focal lesions have an infarctoid aspect, so that vascular oburation (e.g., due to fungal vasculitis) may be assumed. The damaging effects of neutrophil granulocytes may play an important pathogenic role. This is underlined by the observation that focal hepatic lesions may become invisible during neutropenia (Pestalozzi et al. 1997). Some lesions contain large amounts of fibrin-rich exudate intermingled with necrotic debris. It has been suggested that this exudative reaction is responsible for the "sonographic snowstorm" seen in some cases of focal hepatic fungal infection (Keane et al. 1995).

Candidal Cholangitis (Mycotic Biliary Obstruction, *Candida* Bile Duct Obstruction, Biliary Fungus Balls)

Infections of the biliary tract with *Candida* species are rare disorders but have increasingly been seen in the past years. Symptomatic biliary tract candidiasis (candidal cholangitis) can involve the bile duct system as a component of a systemic infection or as an isolated affliction, the former being uncommon. In most cases, the presence of *Candida* in the lumina of bile ducts does not seem to be of clinical significance. In a series of 123 consecutive patients undergoing ERCP, 54 patients showed *Candida* species in bile samples. The yeasts were mainly *C. albicans* and *C. glabrata* and rarely *C. parapsilosis* (Lenz et al. 2009). *Candida* species have also been found as a biofilm on biliary stents, e.g., *C. glabrata* in microbial community with *Mycoplasma salivarium* (Henrich et al. 2010). However, in a subset of infected patients, and mainly those with immunosuppression, candidal cholangitis (symptomatic biliary tract candidiasis) develops, eventually associated with biliary obstruction (Uflacker et al. 1982; Gupta et al. 1985; Chen et al. 1986; Irani and Truong 1986; Morris et al. 1990; Radin and Johnson 1992; Potoczek and Kuliczkowski 1994; Diebel et al. 1996; Wig et al. 1998; Alvarez et al. 2000; Reeves et al. 2000; Domagk et al. 2001; Zhao et al. 2005; Kulaksiz et al. 2006; Rodriguez et al. 2007). In cholangitic patients, endoscopy can reveal the typical signs of inflammatory change with stenosis and mycelia in the bile duct system (Domagk et al. 2006). *Candida* may be the sole identified organism, but patients may also show mixed fungal and bacterial infections of the bile ducts (so-called polymicrobial cholangitis; Diebel et al. 1996; Alvarez et al. 2000). Candidiasis of the common bile duct may cause high-degree stenosis with prestenotic dilatation, followed by chronic secondary sclerosing cholangitis with a bead-like deformation of the bile ducts (Domagk et al. 2001). Cholangiography showed dominant or multiple stenosis and irregular contour of the bile duct mucosa, and one or more intraluminal filling defects represent fungus balls. In a subset of patients with biliary candidiasis, large amounts of *Candida* organisms proliferate in superficial parts of, and in exudate on, the mucosa. In case this layer of fungal mycelia intermingled with the exudate and the bile detaches from the bile duct surface, large fungal masses may develop, termed fungal balls. These structures may cause biliary obstruction (Marcucci et al. 1978; Magnussen et al. 1979; Uflacker et al. 1982; Carstensen et al. 1986; Irani and Truong 1986; Ho et al. 1988; Cheema 1995).

Pathologically, the bile duct in biliary candidiasis shows varying degrees of mucosal inflammation, sometimes with erosions and ulcerations. The inflamed mucosa and the mucosal defects are covered with bile-containing exudate, in which the typical *Candida* elements are seen, often forming a dense population of organisms. *Candida* fungi may invade the epithelium and cause necrosis and apoptosis. In one patient, a long tubular filamentous structure with several branches could be extracted from the common bile duct, representing a *Candida* conglomerate (Domagk et al. 2001).

Promotion of Liver Metastases by *Candida*

Systemic candidiasis favors the development of hepatic metastases. *Candida* contains peptide components that enhance melanoma cell adhesion to endothelial cells (Ramirez-Garcia et al. 2011).

Hepatobiliary Cryptococcosis

Introduction

Cryptococcosis or cryptococcal disease is a common and potentially fatal fungal infection caused by species of *Cryptococcus* (the name meaning "hidden sphere"), mainly *Cryptococcus neoformans*. This infectious disease is also termed the Buschke disease or Busse-Buschke disease (Buschke 1895; Busse 1894). *Cryptococcus* is a basidiomycete fungus genus that is found worldwide and causes disease (cryptococcosis) in humans and diverse vertebrate animal species

(review: Casadevall and Perfect 1998). The classification of one of the most important pathogenic yeast genera in medicine, *Cryptococcus*, is complex because *Cryptococcus* is not monophyletic and forms a species complex (Lin and Heitman 2006). Cryptococci belong to the class *Hymenomycetes*, but there are cryptococci in the orders *Cystofilobasidiales*, *Trichosporonales*, *Filobasidiales*, and *Tremellales*. The genus *Cryptococcus* includes more than 50 species, but *C. neoformans* (including its variant grubii), *C. gattii*, *C. albidus*, *C. uniguttulatus*, *C. laurentii*, and *C. uzbekistanensis* are the only species that are pathogenic for humans.

Clinical Features

Cryptococcosis presents with a distinct spectrum of manifestations (Lewis and Rabinovich 1972). Clinically, three principal types of infection are recognized, viz., wound or cutaneous cryptococcosis, pulmonary cryptococcosis, and cryptococcal meningitis/meningoencephalitis (CNS cryptococcosis). Less common clinical entities comprise bone cryptococcosis (chiefly osteolytic lesions), chorioretinitis, myocarditis, cellulitis, and focal cryptococcal lesions of internal organs. In part of the patients, cryptococcosis presents as an asymptomatic pulmonary infection followed by the development of meningitis/meningoencephalitis, while disseminated cryptococcosis is a rare disease occurring in immunocompromised patients, chiefly AIDS patients but also organ transplant recipients. This is due to the important role played by the T-lymphocyte system in anti-*Cryptococcus* defense (Lewis and Rabinovich 1972).

Liver Involvement in Cryptococcosis

Involvement of the liver is a recognized feature, however, with several presentation patterns. The overall prevalence of liver disease in cryptococcosis is only partially known. Among 171 liver specimens from patients with AIDS (155 autopsies and 16 biopsies), eight patients (5 %) showed hepatic cryptococcosis (Lanjewar et al. 2004).

Table 2 Forms of hepatobiliary cryptococcosis

Miliary cryptococcosis of the liver
Hepatic cryptococcal abscess
Hepatic cryptococcoma
Cryptococcal hepatitis
Cryptococcal cholangitis
Cryptococcal inflammatory pseudotumors
Fungal peritonitis

Overall, several studies report rates of hepatic cryptococcosis ranging from 1 % to 13 % of AIDS patients, as determined by biopsy or by autopsy. In contrast, cryptococcal liver infection is rare in non-HIV-infected patients. In review of 13 patients performed by Liu et al. (2009), two patients had hepatic failure, three had hepatitis, two showed miliary hepatic cryptococcosis, four had cholestatic jaundice, one suffered from cirrhosis, and one had acute abdominal pain.

Pathologically, hepatobiliary cryptococcosis can present in the form of several phenotypes (Table 2).

The essential histologic features of cryptococcosis in immunocompromised patients consist of fungal accumulations with a typical morphology, necrosis, and a macrophage response, but only minor lymphocytic and neutrophilic components (Staib 1986; Shibuya et al. 2001). The fungi present as globose to ovoid yeast cells (depending on the variety; see above) that have a capsule, producing neither well-developed pseudohyphae nor true hyphae. *Cryptococcus* differs from *Candida* by not forming pseudohyphae. Macrophages containing *Cryptococcus* may show a faint cytoplasmic PAS positivity. This phenomenon may be due to the fact that cryptococci located within macrophages are associated with permeabilization of phagosomes and the accumulation of polysaccharide-containing vesicles in the cytoplasm (Tucker and Casadevall 2002).

Miliary Cryptococcosis

In patients with laboratory signs of *Cryptococcus*-induced liver damage, the involvement may be microscopic only, with typical fungi located in dilated hepatic sinusoids (Fig. 3; Utili et al. 2004;

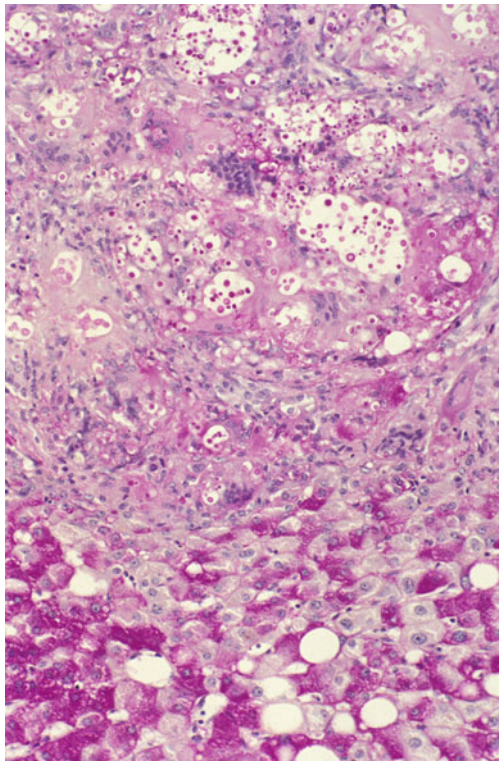

Fig. 3 Cryptococcosis of the liver. The numerous organisms present as clusters of encapsulated spherical fungi (PAS stain)

Lu et al. 2009). The spread of fungi to several organs may induce the formation of miliary lesions resembling tuberculosis (Pomar et al. 2005).

Hepatic Cryptococcal Abscess

Rarely, disseminated cryptococcosis is associated with hepatic abscesses visualized as low-attenuated liver lesions (Liu et al. 2009). These forms of abscesses deviate in their histologic presentation from bacterial abscesses, in that a macrophage component is prominent.

Cryptococcomas

Cryptococcomas are tumor-like lesions consisting of tissue necrosis, massive accumulation of fungi, and masses of phagocytes, in particular macrophages. Cryptococcomas are known from the central nervous system, but have also been observed in other tissues, including the breast (Collins et al. 1971) and the liver. In the liver, these lesions may grow to a size of several centimeters and present as low-attenuated lesions at CT, similar to abscesses. Due to their mass effect, cryptococcomas may stenose bile ducts and cause obstructive jaundice (Nara et al. 2008). Hepatobiliary cryptococcomas may develop within the lumen of bile ducts (Kim et al. 1994). Mass-forming cryptococcal lesions similar to cryptococcomas of humans have experimentally been induced in mice (Price and Bulmer 1972). Histologically, cryptococcomas are characterized by a focal parenchymal necrosis with a relatively minor cellular reactions and accumulation of numerous capsulated fungal organisms.

Cryptococcal Hepatitis

Cryptococcal hepatitis is a very uncommon manifestation of cryptococcosis (Procknow et al. 1965; Wright and Harman 1983). It may cause hepatic failure (Sabesin et al. 1963); in fact, severe hepatobiliary dysfunction may be the initial manifestation of disseminated cryptococcosis, parenchymal failure being caused by extensive hepatic necrosis (Lin et al. 1999). Necrotizing cryptococcal hepatitis can cause intrahepatic cholestasis (Mendez-Sanchez et al. 2006). Cryptococcal hepatitis can induce biliary obstruction and subsequent cirrhosis (Goenka et al. 1995).

Cryptococcal Cholangitis

A further form of hepatobiliary cryptococcosis is characterized by a distinct cholangitis resembling primary sclerosing cholangitis (Lefton et al. 1974; Bucuvalas et al. 1985).

Cryptococcal Inflammatory Pseudotumors

Cryptococcal infection may induce mass lesions that are rich in plump spindle cells arranged in a

storiform pattern. These lesions are termed cryptococcal inflammatory pseudotumors and may mimic malignancy (Sing and Ramdial 2007). Hepatobiliary cryptococcosis has been shown to sometimes have a presentation resembling Klatskin's tumor with obstructive jaundice (Kothari and Kothari 2004).

Fungal Infections in Tissue Adjacent to or Surrounding the Liver

Cryptococcosis may develop in structures adjacent to the liver. Spontaneous fungal peritonitis caused by *Cryptococcus* in immunosuppressed or non-immunosuppressed patients with liver cirrhosis is a rare disorder (Mabee et al. 1995; Stiefel et al. 1999; Sungkanuparph et al. 2002; Albert-Braun et al. 2005; Singh et al. 2010). Patients with liver cirrhosis and cryptococcosis may develop cryptococcal ascites (Franca et al. 2005; Sikorski and Marcinowska-Suchowierska 2007).

Hepatic Mucormycosis (Zygomycosis)

Introduction

Zygomycosis (formerly termed mucormycosis) is an important emerging fungal infection caused by several fungal taxa of the *Zygomycetes*. Zygomycosis in a debilitated patients is a highly aggressive and often fulminating disease with high morbidity and mortality. Zygomycosis typically involves the rhino-facial-cranial area, lungs, gastrointestinal tract, skin, and less often other organ systems (reviews: Ribes et al. 2000; Prabhu and Patel 2004; Brown 2005; Roden et al. 2005; Naggie and Perfect 2009; Skiada et al. 2011). The term, *Zygomycetes*, is an older designation of the group and traditionally existed in two orders of organisms that produce human disease, the *Mucorales* and the *Entomophthorales* (Kwon-Chung 2012). Most human zygomycoses are caused by members of the *Mucorales*; this is the main reason why many infections are termed mucormycosis, but this would require the proof (via culture or, now more commonly, molecular biology methods) that the genus *Mucor* is in fact involved. The *Mucorales* are commonly associated with angioinvasive fungal disease, often leading to thrombosis, necrosis, or infarction of the involved tissues and organs and tissue destruction mediated by a number of fungal proteases, lipases, and mycotoxins (review: Ribes et al. 2000).

Epidemiology and Clinical Features

Zygomycosis or, specifically, mucormycosis is a rare opportunistic fungal infection with increased frequency in immunosuppressed individuals (including graft recipients), patients with hematologic neoplastic disease, and during chemotherapy-induced neutropenia (Fisher et al. 1980; Singh et al. 1995; Pagano et al. 1997; Spellberg et al. 2005). *Zygomycetes* are known for their great ability to infect a broader, more heterogeneous population of human hosts than other opportunistic molds. *Mucor* infection provokes several clinical entities, namely, rhinocerebral, pulmonary (these two are the most common), cutaneous, gastrointestinal, and disseminated diseases (Mantadakis and Samonis 2009). The gastrointestinal form (including the liver) is uncommon, accounting for about 2 % of the cases only (Singh et al. 1995).

Liver Involvement in Zygomycosis

Liver involvement has been recognized under several circumstances, but mostly occurs in patients with disseminated zygomycosis (Chailly and Couturier 1976; McGinnis et al. 1982; ter Borg et al. 1990; Al-Asiri et al. 1996; Erdem et al. 1996; Oliver et al. 1996; Schipper et al. 1996; Suh et al. 2000; Tsaousis et al. 2000; Yamauchi et al. 2002; Mekeel et al. 2005; Padmanabhan et al. 2007; Skiada et al. 2009; Lüer et al. 2009; Busca et al. 2010; Itoh et al. 2012). The radiologic presentation of *Mucor*-induced lesions has been described. Abdominal CT demonstrates few to multiple hypodense lesions with distinct margins (Hagspiel et al. 1995; Suh et al. 2000; Singh 2002; Busca et al. 2010). Zygomycosis of the

Table 3 Hepatic lesions in zygomycosis

Miliary necroses/microabscesses
Mycotic macroabscess
Eumycetoma/mycotic pseudotumor
Hilar mycotic pseudotumor
Mycotic venous thrombosis
Mycotic arterial thrombosis
Mycotic hepatic artery rupture
Mycotic aneurysms

liver can result in hepatic failure (Erdem et al. 1996). In zygomycosis, several types of parenchymal lesions of the liver can develop (Table 3).

Macroscopically, the fungus-induced lesions are either small and ill-defined necroses or, less commonly, larger infarct-like lesions. These large lesions are called eumycetomas (Sedlacek et al. 2009). As zygomycosis is markedly angioinvasive, the formation of mural vascular thrombi that harbor masses of fungal hyphae is a hallmark. *Mucor*-induced thrombosis of the major hepatic veins associated with Budd-Chiari syndrome has been observed (Vallaeys et al. 1989). In grafted livers, *Mucor* infection can compromise the liver artery anastomosis via induction of thrombosis (Marco del Pont et al. 2000; Brandao et al. 2003). Infection of the hepatic artery can lead to artery rupture (Zhan et al. 2008).

Miliary Necroses/Microabscesses

Histologically, liver lesions are necrotic foci of variable size. Typically, the morphology of the necrosis is that of the so-called coagulative necrosis, with nuclear debris (karyorrhexis) and signs of karyopyknosis. The necroses may, at their periphery, be demarcated by an epithelioid macrophage reaction, and multinucleate giant cells with phagocytosed hyphae may be in evidence (McGinnis et al. 1982). The inflammatory response in zygomycosis is predominantly neutrophilic in about half of the cases, whereas less common presentations are pyogranulomatous or granulomatous. Fungal angioinvasion and perineural invasion are seen in practically all cases (Frater et al. 2001). In tissue sections, the hyphae in zygomycosis are irregularly shaped filaments with focal bulbous dilatations ("ballooning"), a "twisted ribbon" appearance, and infrequent septations (Fig. 4). In contrast to *Aspergillus*, branching is blunt, i.e., with angles more than 45°. The organisms are readily recognized in PAS, silver methenamine, and Grocott stains. As primitive coenocytic hyphae, the filaments are delicate and may be rapidly damaged by processing, rendering diagnosis difficult in some cases.

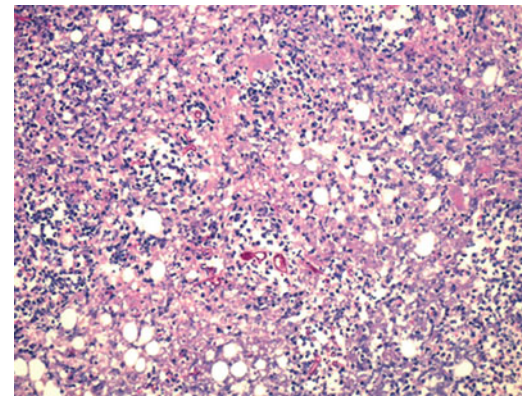

Fig. 4 Hepatic zygomycosis (mucormycosis). A densely infiltrated tissue area in a steatotic liver contains irregularly shaped fungal organisms (PAS stain)

Mycotic Macroabscess

Some zygomycotic infections can induce liver masses that correspond to classical pyogenic liver abscess, e.g., *Rhizopus oryzae* (Dalgic et al. 2011).

Hepatic Hilar Zygomycotic Pseudotumor

Zygomycosis caused by *Mucor* species can mimic hilar cholangiocarcinoma. In a 36-year-old man with jaundice, abdominal CT and MR revealed a mass lesion occupying the porta hepatis and partial left lateral liver lobe. MR cholangiopancreatography demonstrated an abrupt stenosis of the

bile duct confluence with symmetric upstream dilatation of the intrahepatic bile ducts. The resection specimen showed inflammatory tissue with fungal hyphae typical for *Mucor* (Li et al. 2010).

Mycotic Venous Thrombosis

Infection with *Mucor* can cause thrombosis of hepatic veins and Budd-Chiari syndrome (Chailly and Couturier 1976; Vallaeys et al. 1989).

Mycotic Arterial Thrombosis

Infection of the wall of the hepatic artery by *Mucor* species can cause thrombosis of this vessels. This severe complication has also been found in a liver graft (Marco de Pont et al. 2000).

Mycotic Aneurysms

Zygomycosis can result in the development of mycotic artery aneurysms and pseudoaneurysms, including the aorta, pulmonary arteries, and also visceral arteries, e.g., the splenic artery (Nevitt et al. 2001). The involved hepatic artery can undergo rupture (Zhan et al. 2008).

Hepatobiliary Aspergillosis

Introduction

Aspergillus species are opportunistic pathogens that cause the human infectious disease, aspergillosis (review: Latge 1999). Aspergillosis is the term employed to denote any animal or human disease caused by any member of the *Aspergillus* genus on a living host. *Aspergillus fumigatus* causes 90 % of invasive aspergillosis, a devastating disease with a still very high mortality rate. Besides this acute invasive aspergillosis, a chronic form of this infection may be encountered as chronic necrotizing pulmonary aspergillosis or chronic invasive sinusitis. The fungal genus *Aspergillus* already received its name in 1729. In viewing the conidia-bearing fungus in the microscope, Micheli was reminded of the sprinkling device used in Roman Catholic ritual, the asperges. The defining feature of the genus *Aspergillus* is the aspergillum-like conidia-bearing structure. End cells or foot cells of hyphae develop a specialized structure called conidiophore perpendicular to the long axis of the hyphal cell. The conidiophore enlarges at its apex and forms a club-shaped vesicle. The fertile domain of the vesicle procures a layer of cells called phialides (synonym: stigmata). The phialides generate long chains of mitotic spores called conidiospores or conidia. The conidia have distinct colors in different *Aspergillus* species (green in *A. fumigatus*, black in *A. niger*). *Aspergillus* has at least 250 defined species.

Epidemiology

The incidence of aspergillosis is increasing in parallel with the number of immunosuppressed individuals, but it is also a well-recognized disease in critically ill but non-immunocompromised patients. Among patients with solid organ transplantation, lung and liver transplant recipients are at the highest risk of developing acute invasive aspergillosis (Rubio et al. 2011). After liver transplantation, aspergillosis has been found in 19/408 (4.6 %) recipients by the use of routine and molecular methods (Badiee et al. 2010). Other associated conditions include influenza, nonfungal pneumonia, chronic obstructive lung disease, immaturity, sepsis, alcoholism, acute and chronic liver failure, and surgery (Falcone et al. 2011; Stevens and Melikian 2011).

Clinical Manifestations of Aspergillosis

Aspergillosis presents in the form of several disease phenotypes which differ between patients with or without immunosuppression, generalized infections being more common in the latter. The most important clinical form of this fungal infection is pulmonary aspergillosis. It manifests as noninvasive aspergillosis characterized by

aspergilloma (fungus balls, often in the setting of tuberculosis or silicosis), acute invasive pulmonary aspergillosis (mainly in neutropenic patients), chronic narcotizing aspergillosis (a slowly progressive, semi-invasive form mainly seen in mildly immunosuppressed individuals), and allergic aspergillosis (ranging from extrinsic asthma to hypersensitivity pneumonitis). Noninvasive aspergilloma may develop following repeated exposure to inhaled conidia and usually target preexisting lung cavities such as bronchiectases or healed tuberculous caverns. Allergic bronchopulmonary aspergillosis is found in individuals with altered lung function such as asthma and cystic fibrosis. A second important form is a group of localized aspergillosis, mainly of the paranasal sinuses and the skin. Thirdly, there is disseminated aspergillosis, caused by hematogenous dissemination to several visceral and other organs.

Hepatobiliary Aspergillosis

It has been found that 11 % of patients who die of or with aspergillosis have liver involvement (Young et al. 1970). The clinical pattern of hepatic aspergillosis varies and depends on the extent of invasion and the anatomic site of the liver involved. In few instances, primary hepatic aspergillosis has been observed in adult patients with no evident immunological impairment (Carosi et al. 1985). Preexisting liver disease can be followed by aspergillus infection, e.g., biloma (Ioannidis et al. 1995).

Aspergillosis of the liver presents in eight major forms (Table 4), i.e., septic foci with miliary to submiliary lesions, liver abscesses, aspergilloma, fungus-containing liver necroses, *Aspergillus* cholangitis, angioinvasive aspergillosis with invasion of large hepatic veins, hepatic artery aspergillosis, and disseminated aspergillosis with a presentation resembling veno-occlusive disease.

Table 4 Major forms of hepatobiliary aspergillosis

Submiliary/miliary aspergillosis of the liver
Aspergillotic liver abscess
Aspergilloma of the liver
Aspergillotic inflammatory pseudotumor of the liver
Aspergillus cholangitis
Angioinvasive aspergillosis with invasion of large hepatic veins
Hepatic artery aspergillosis
Disseminated aspergillosis mimicking veno-occlusive disease

Submiliary/Miliary Hepatic Aspergillosis

In part of the patients with disseminated aspergillosis, multiple liver lesions mimicking those seen in hepatosplenic candidiasis may develop, chiefly during neutropenic phases following an induction chemotherapy (Callister et al. 2004; Potenza et al. 2008). The lesions consist of small foci of parenchymal necrosis containing *Aspergillus*, but only a minor cellular infiltrate, owing to the neutropenic status of the patients (Figs. 5 and 6). In most situations, one notes a tiny focus of parenchymal necrosis, sometimes, with apoptotic bodies, admixed with a fibrinous exudate. Within this background of slightly eosinophilic granular debris, typical *Aspergillus* hyphae are in evidence. As the hyphae are sometimes pale, they may be overlooked in the necrosis background, but they are clearly visualized in PAS and silver methenamine stains. *Aspergillus* hyphae are septated and typically branched with a bifurcation angle of

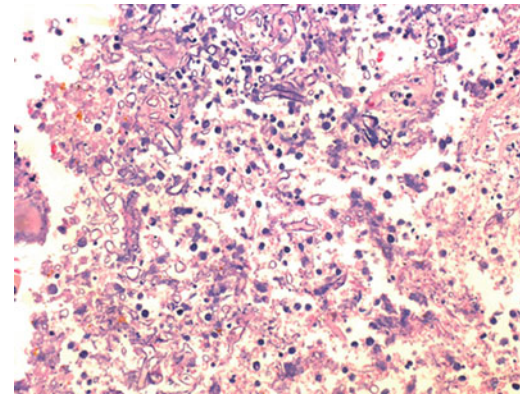

Fig. 5 Aspergillus abscess of the liver. The lesion contains numerous filamentous fungi that show bifurcation (hematoxylin and eosin stain)

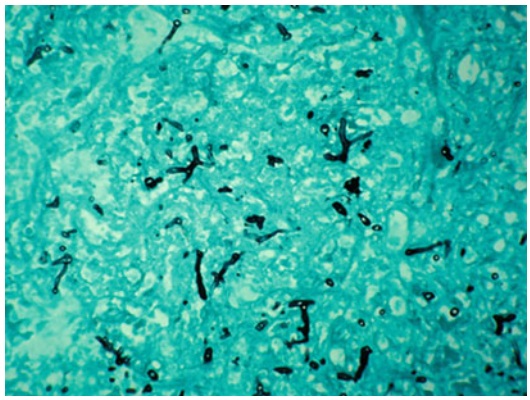

Fig. 6 Hepatic aspergillosis. The fungal filaments bifurcate with an angle smaller than 90° (silver methenamine stain)

about 45°. The reticulin network may still be preserved. At the periphery of the lesions, few neutrophils and lymphocytes are noted, and there may be signs of Kupffer cell activation in the vicinity. The fungal hyphae may invade small vascular channels, in particular sinusoids of adjacent liver parenchyma, with sinusoidal thrombosis.

Aspergillotic Liver Abscess

The development of true and large hepatic abscesses by *Aspergillus* infection is rare and has predominantly been found in patients with acute leukemia and other hematologic malignancies (Trachana et al. 2001; Lee et al. 2003; Marotta et al. 2005; Yamada et al. 2010, Yeon et al. 2010). *Aspergillus* liver abscesses are also found in immunodeficient children, e.g., caused by *Aspergillus terreus* in common variable immunodeficiency (Trachana et al. 2001). Hepatic aspergillus abscesses can be diagnosed by the use of fine needle aspiration cytology. It has been reported that puncture yielded a clear milky fluid that was positive for *Aspergillus* fungi (Vairani et al. 1990). Liver abscesses in aspergillosis may show a diameter of several centimeters and mimic neoplastic tumors. Histologically, the abscesses exhibit a central part which consists of necrotic tissues, a leukocyte accumulation, and a fibrinous exudative reaction. The leukocyte population varies markedly from one lesion to the other and is poor in neutrophils in neutropenic patients. In the latter, the abscess is atypical in that necrosis and exudate predominate over the classical pus expected in true abscesses. The periphery of the abscess shows an infiltrate that contains lymphocytes, macrophages, and few plasma cells. An epithelioid cell reaction may be encountered, but a true granulomatous response is usually not in evidence.

Aspergilloma of the Liver

It is, above all, hepatic aspergilloma which may clinically and radiologically mimic liver malignancy. The imaging features of aspergilloma in the liver have been outlined (Ow et al. 1991). Aspergillomas are large lesions that result from confluence of smaller abscesses and/or necroses caused by parenchymal *Aspergillus* infections. Most of the masses are usually accounted for by necrotic tissue admixed with exudate. The lesions are demarcated by a rim of granulation tissue.

Aspergillotic Inflammatory Pseudotumor of the Liver

In rare instances, a marked inflammatory response ensues, resulting in hepatic mass chiefly consisting of cellular infiltrates replacing necrosis, granulation tissue, and fibroblastic proliferations with deposition of extracellular matrix (Tamsei et al. 2004). It may be difficult to detect viable *Aspergillus* organisms within this tissue.

Aspergillus Cholangitis

The gallbladder and gallbladder stones form a niche where several species of fungi can exist, including *Aspergillus*, often without clinically manifest fungal infection (Gupta et al. 1993). Aspergillosis of the biliary tract with inflammatory changes in duct walls (cholangitis) is observed in

patients with relevant immunosuppression, e.g., after liver transplantation. In biliary duct biopsies, an exudative inflammation is seen, the exudate and the adjacent tissue being colonized by *Aspergillus* hyphae (Yuchong et al. 2010).

Angioinvasive Aspergillosis with Invasion of Hepatic Veins

Hepatic aspergillosis with invasion of hepatic veins causes a disorder resembling Budd-Chiari syndrome (Young 1969). Following liver transplantation, *Aspergillus* invasion of the portal vein system, associated with thrombosis of these vessels, has been observed (Gavilan et al. 1998).

Hepatic Artery Aspergillosis

Aspergillus invasion of the hepatic artery was observed following liver transplantation (Gavilan et al. 1998). Mixed *Aspergillus* and *Mucor* hepatic artery infection after liver transplantation led to artery rupture in one patient following combined liver and kidney transplantation (Zhan et al. 2008).

Disseminated Aspergillosis Mimicking Hepatic Veno-occlusive Disease

Disseminated aspergillosis mimicking hepatic veno-occlusive disease is very uncommon and is caused by invasion of hepatic sinusoids by fungal hyphae (Daikos et al. 2005).

Differential Diagnosis

In regard to etiology, aspergillosis may be confounded with other fungal infections characterized by growing hyphae, in particular *Mucor* infections. Both *Aspergillus* and *Mucor* have septated hyphae. In PAS- or silver methenamine-stained sections, the branching mode of the hyphae is a decisive diagnostic discriminator, as hyphae in *Aspergillus* consistently show acute branching angles, while branching angles in *Mucor* are blunt and exceed 90°.

Histoplasmosis

Introduction

Histoplasmosis is a fungal infection caused by the onygenalean fungi *Histoplasma* (*H.*) *capsulatum* and *H. duboisii* (reviews: Cano and Hajjeh 2001; Nosanchuk and Gacser 2008; Kauffman 2007, 2009). The fungal infection is also known under the terms Cave disease, Darling's disease (in honor of the scientist who found the fungus), Spelunker's lung, and Caver's disease. Infections with *H. capsulatum* reveal certain endemic features; e.g., histoplasmosis caused by this agent is endemic to the Midwestern and east central states in the United States near the Mississippi and the Ohio River valleys ("Ohio River valley fever"), Mexico, and Rio de Janeiro state in southeastern Brazil. Endemic areas in Europe have also been detected (Ashbee et al. 2008). One species of *Histoplasma*, *H. duboisii*, is common in caves of southern and East Africa. It is estimated that *H. capsulatum* is the most common cause of invasive fungal pulmonary disease worldwide and that about 500,000 infections occur in the United States each year.

Hepatobiliary Involvement in Histoplasmosis

Gastrointestinal and hepatic involvement are common in disseminated histoplasmosis caused by *H. capsulatum*, both in immunocompetent and immunosuppressed subjects (Goodwin et al. 1980; Escher et al. 2012). In African histoplasmosis caused by *H. duboisii*, gastrointestinal involvement has been estimated to be 26 % (Pichard et al. 1987). The liver has been estimated to be involved in up to 90 % of cases with disseminated *H. capsulatum* disease (Goodwin et al. 1980), but this figure may be too high. In HIV-infected patients having hepatobiliary disease and treated with non-highly active antiviral therapy, liver biopsies revealed *Histoplasma* infection in 20 % (Lizardi-Cervera et al. 2005).

Clinically, hepatomegaly was detected in about two-thirds of patients with disseminated histoplasmosis by the use of CT (Radin 1991).

In histoplasmosis, several types of liver lesions can develop (Table 5).

In the liver, the most common findings are hepatic granulomas (granulomatous hepatitis, both within the parenchyma and in portal tracts; Jariwalla et al. 1977; Lazo 1977; Lizardi-Cervera et al. 2005; Kibria et al. 2009) and portal tract lymphohistiocytic inflammation. Granulomatous hepatitis in histoplasmosis is less common than nonspecific hepatitis and seen in less than 20 % of involved livers in one study of 52 patients (Lamps et al. 2000). Rarely, hepatic histoplasmosis is manifest as acute granulomatous hepatitis (Lanza et al. 1970). In disseminated histoplasmosis, a diffuse accumulation of macrophages containing the fungi may occur (Escher et al. 2012). This is the diffuse hepatic macrophageal disease (DHMD). Increased numbers of fungus-containing macrophages are noted in the distended sinusoids, and these macrophages apparently cause sinusoidal congestion.

Large accumulations of parasitized macrophages may coalesce to form nodular lesions that are visualized at gross examination (the nodular form of hepatic histoplasmosis). Among 36 autopsied patients with liver involvement, grossly enlarged livers were found in 47 %, and 39 % had mottled or markedly congested livers. 17 % had discrete, grossly apparent hepatic lesions, forming nodules ranging from 0.2 cm to more than 1.0 cm in greatest dimension. These nodules were parenchymal and capsular in location (Lamps et al. 2000). In advanced disease, necrosis resembling caseous necrosis can develop (Darling 1909; Chen and Lin 1990). In the cases analyzed by Darling (1909), the areas of necrosis were grayish yellow in color, the larger ones often being arborescent in shape. These arborescent necroses involved the portal radicals which they followed, and these arborescent twigs had four to six limbs, reflecting to angioarchitecture and hence suggesting a vascular damage pathway. The necrobiotic changes associated with inflammation can resemble tuberculous lesions ("pseudotubercles"), all the more so as they can cause hepatic calcification (Okudaira et al. 1961). Histologically, the necroses resemble coagulation necrosis with shadow cells and nuclear debris. These areas often contain large cells, probably macrophages, that are distended by parasites (Fig. 7; Darling 1909). Few multinucleated giant cells of the Langhans type are noted. In smears of fresh lesions, the yeast form of *H. capsulatum* is round or oval in outline and measures 1–4 μm

Table 5 Types of liver involvement in histoplasmosis

Granulomatous hepatitis
Portal lymphohistiocytic hepatitis
Diffuse hepatic macrophageal disease (DHMD)
Nodular hepatic histoplasmosis
Giant cell-rich lesions in African histoplasmosis
Histoplasmotic pseudotumor

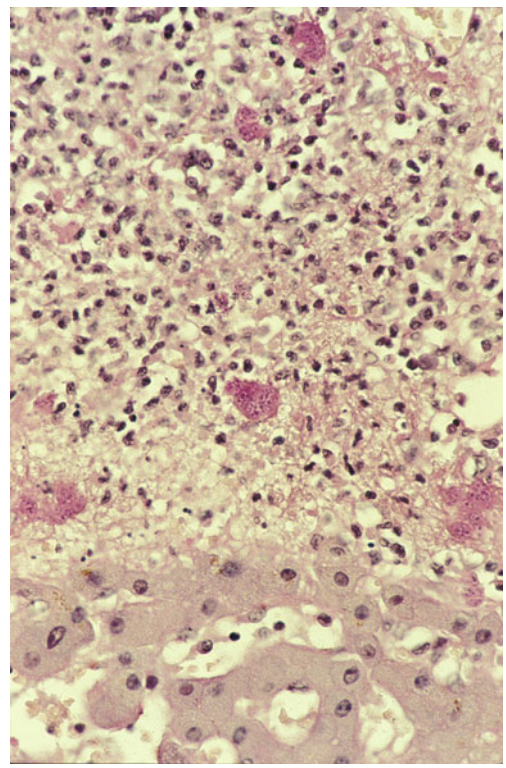

Fig. 7 Histoplasmosis of the liver. Enlarged macrophages contain numerous small spherical fungal organisms (PAS stain)

through its greatest diameter. In Leishman's or Hastings' stains, the inner part of the fungal cell contains variably shaped chromatoid bodies. The latter occupy the periphery of the fungal cell, while they are more centrally placed in yeasts located within macrophages. The yeast is typically surrounded by a refractile capsule, one-sixth of the diameter of the fungus in width, which does usually not stain. *Histoplasma* is seen within macrophages as numerous small and spheroid organisms, already visualized in H&E-stained sections, but more evident in PAS and Gomori methenamine stains.

The liver may be involved in African histoplasmosis (Williams et al. 1971; Valmary et al. 1984; Delclaux et al. 1992). The pathological presentation of African histoplasmosis is distinct from that of classical histoplasmosis caused by *H. capsulatum*. In a necropsy study of 45 cases of African histoplasmosis observed in Nigeria (Williams et al. 1971), the liver was usually enlarged to about 1.5 times its normal size. The capsule was studded with tiny yellowish discrete nodules, and miliary lesions of yellow to whitish color were also noted in the parenchyma. Most of these lesions did not exceed 3 mm in diameter; they may coalesce, the resultant confluent nodules then becoming much larger, causing a tumor-like space-occupying mass with satellite nodules (Williams et al. 1971). Similar miliary lesions were sometimes found on the peritoneal surface of the gallbladder. Histologically, a typical *H. duboisii* lesion is a granuloma that may be rich in multinucleated giant cells of the Langhans type. Some of the foci almost exclusively consist of these giant cells. The lesions contain numerous yeast cells that are larger (8–15 μm in diameter) and thicker walled than those of *H. capsulatum*. These yeast cells may occur in chains of four to five cells (review: Gugnani and Muotoe-Okafor 1997).

Involvement of Extrahepatic Bile Ducts

In disseminated histoplasmosis, involvement of the extrahepatic bile ducts may occur. It has been observed in pediatric patients in the absence of HIV infection, i.e., in one child with lymphoblastic leukemia and histoplasmotic cystic duct obstruction (Patrick et al. 1992) and in another child without any signs of immunosuppression and common bile duct obstruction (Rescorla et al. 1994). Extrahepatic bile duct involvement has also been found in adults with and without HIV infection, sometimes causing biliary obstruction (Kahi et al. 2005; Abu al Rub et al. 2009; Kapelusznik et al. 2011). In two of these cases, distal common bile duct obstruction was associated with duodenal and in part ulcerative inflammation (Abu al Rub et al. 2009; Kapelusznik et al. 2011).

Basidiobolomycosis

Introduction

Basidiobolomycosis is a newly emerging fungal infection of the zygomycosis type caused by *Basidiobolus ranarum* (Kian Joe et al. 1956; Symmers 1960; review: Gugnani 1999). It is chiefly a cutaneous and subcutaneous infection, but part of the patients have gastrointestinal disease (gastrointestinal basidiobolomycosis, GIB) that causes substantial morbidity and mortality (Khan et al. 2001; Lyon et al. 2001).

Epidemiology

Kian Joe and coworkers (1956) seem to be the first who have identified *B. ranarum* with certainty as the cause of human infection, based on extensive subcutaneous granulomas found in an Indonesian child (Kian Joe et al. 1956). These authors cited to other reports in which infection had been attributed to *B. ranarum*, one concerning a horse from the East Indies (van Overeem 1925) and the other concerning an infected gastric ulcer from a man of Istria (Casagrandi 1931). Basidiobolomycosis is mainly a disease of children and young adolescents, being less common in older adolescents and adults. Females are more often affected. Most

cases of basidiobolomycosis have been identified in warm or tropical countries.

Clinical Features

The cutaneous-subcutaneous form of basidiobolomycosis (subcutaneous zygomycosis) is clinically characterized fluctuant firm and non-tender swellings on trunk and extremities. Gastrointestinal basidiobolomycosis (gastrointestinal zygomycosis) has a nonspecific presentation and most often involves the colon (Khan et al. 2001; van den Berk et al. 2006; Hussein et al. 2007; El-Shabrawi and Kamal 2011; Vikram et al. 2012). It presents with fever, abdominal pain, signs of the so-called acute abdomen, abdominal mass, and high blood eosinophilia. In children, intestinal basidiobolomycosis can resemble fistulating Crohn's disease (Saadah et al. 2012). Colonic basidiobolomycosis can cause colonic masses closely mimicking malignancy. Basidiobolomycosis can also manifest as pulmonary disease, retroperitoneal infection, or a disseminated fungal disease, the latter form having a high mortality and developing in both immunocompetent and immunocompromised individuals.

Hepatobiliary Basidiobolomycosis

In part of the patients with gastrointestinal basidiobolomycosis, the infection involves the liver and produces pseudotumoral masses mimicking a hepatic malignancy (van den Berk et al. 2006). Among 44 patients with gastrointestinal basidiobolomycosis, liver or gallbladder involvement was detected in 13 patients (30 %) (Vikram et al. 2012). In a 61-year-old male with stenosing colonic basidiobolomycosis, abdominal CT revealed a hepatic mass of 6 cm diameter, first thought to be an amoebic abscess. Under therapy, the lesion grew to a diameter of 9 cm, and biopsy revealed basidiobolomycosis (van den Berk et al. 2006).

Histopathology is characterized by a marked granulomatous reaction with giant cells and formation of palisading granulomas around fungal elements. In tissue sections, the fungus is visualized as unusually large, thin-walled, aseptate or rarely septate broad hyphae or hyphal fragments with an eosinophilic sheath (Williams 1969). The latter can present as typical Splendore-Hoeppli phenomenon (Williams et al. 1969). The fungus is often localized within macrophages and multinucleated giant cells derived thereof. An eosinophilic infiltrate is a characteristic feature.

Pneumocystosis: An Unusual Fungal Infection of the Hepatobiliary Tract

Introduction

Pneumocystis as an opportunistic pathogen causes a severe and frequently fatal pneumonia when the host immune system fails, e.g., in AIDS and during cancer chemotherapy (review: Wazir and Ansari 2004). In individuals with HIV infection leading to AIDS, *P. carinii* pneumonia has been a major cause of death prior to the advent of HAART. Usually, *Pneumocystis* maintain an extracellular existence in pulmonary alveoli, but in severe infections, extrapulmonary manifestations can occur, including the hepatobiliary system.

The organism now termed *Pneumocystis carinii* was first reported in the early twentieth century (Chagas 1909; Carini 1910). Carlos Justiniano Ribeiro Chagas was born in 1878 and was the later director of the renowned Instituto Oswaldo Cruz in Brazil. Both authors thought that the organisms were novel species of *Trypanosoma*. Chagas discovered the organism in experimental animals and confused it with part of the life cycle of *Trypanosoma cruzi* (the causal agent of Chagas disease) and later called both organisms *Schizotrypanum cruzi*, a form of trypanosome infecting humans. The genus was again discovered in 1912 by Delanoe and Delanoe (Delanoe and Delanoe 1912) at the Pasteur Institute in Paris. These authors proposed the genus name and termed the species, *carinii*, in honor of Dr. Carini who had described the cysts in 1910 ("the cysts of Carini" in the title of the French publication). The fungus was redescribed as a human pathogen in 1942 (Van der Meer and

Brug 1942). Originally classified as a protozoan, members of the genus *Pneumocystis* are now allocated to the fungal kingdom, based on phylogenetic analyses of several parasite genes (Haase 1997).

Hepatobiliary *Pneumocystis carinii* Infection

Hepatobiliary pneumocystosis occurs in the setting of generalized extrapulmonary *Pneumocystis* infection associated or not associated with AIDS, and usually organs other than the liver are also involved, in particular the spleen, the bone marrow, lymph nodes, and the CNS (Jarnum et al. 1968; Rahimi 1974; Unger et al. 1988; Cote et al. 1990). Extrapulmonary infection with this agent in AIDS patients is regarded as uncommon. Hepatic pneumocystosis is an uncommon disease presenting in the form of various manifestations (Table 6).

Pneumocystis Hepatitis

Hepatic involvement can present in the form of hepatitis with or without cholestasis, sometimes with progressive elevation of liver enzymes in serum (Jarnum et al. 1968; Awen and Baltzan 1971; Rahimi 1974; Grimes et al. 1987; Pilon et al. 1987; Steigman et al. 1987; Hagopian and Huseby 1989; Poblete et al. 1989; Sachs et al. 1991; Wilkins et al. 1991; Merkel et al. 1992; Mendez-Sanchez et al. 2006; Levitt et al. 2012). In the case reported by Hagopian and Huseby, liver biopsy showed acellular nodules of necrosis with a foamy eosinophil appearance, in a periportal distribution. Methenamine silver stain revealed the presence of typical cup-shaped *Pneumocystis* structures within necrosis (Hagopian and Haseby 1989). In some situations, hepatic sinusoids were expanded by foamy eosinophilic material associated with diffuse Kupffer cell necrosis and focal hepatocellular necrosis, these lesions containing *P. carinii*. The organisms were mainly found in sinusoidal spaces, in intimate association with the location of Kupffer cells. Immunohistochemically, trophic forms were found lining the hepatocytes, similar to what is seen in pulmonary alveoli (Cote et al. 1990). *Pneumocystis* organisms in hepatitis lesions were described in a subsequent report (Levitt et al. 2012). Granulomatous hepatitis with presence of *Pneumocystis* within granulomas has been documented by the use of electron microscopy (Guan et al. 2001).

Table 6 Classification of hepatobiliary pneumocystosis

Pneumocystis hepatitis
Granulomatous *Pneumocystis* hepatitis
Multiple focal necroses
Pseudotumoral hepatobiliary pneumocystosis
Hepatic calcifications
Biliary obstruction by extrinsic compression

Multiple Focal Necroses

In other cases, infection of the liver by *P. carinii* presented in multiple focal necrotic liver lesions (Davey et al. 1989; Hardy et al. 1989; Dembinski et al. 1991; Trojan et al. 1998). In one patient with AIDS, autopsy revealed multiple well-circumscribed white nodules (1–5 mm diameter) in the liver, histologically composed of a foamy acellular eosinophilic material without an accompanying host inflammatory response. Central calcification was present in some of the lesions. In these foci, *P. carinii* was detectable in silver stains and immunohistochemically (Dembinski et al. 1991). In one patient of a necropsy series of 227 patients with HIV infection, the liver exhibited multiple lentil-sized whitish foci containing a granular material incrustated by calcium salts, these lesions being positive for *Pneumocystis* cysts (Trojan et al. 1998).

Pseudotumoral Hepatobiliary Pneumocystosis

Involvement of hepatic hilar structures can produce a mass and bile duct stenosis with intrahepatic duct

dilatation. In one patient with these changes, endoscopic biopsy of the common hepatic duct revealed cholangiocytes and associated foamy material containing *P. carinii* (Mustafa et al. 2002). *P. carinii infection* of the common bile duct has been found to rarely cause an intraluminal mass consisting of an exuberant vascular proliferation associated with a multinucleated giant cell reaction, the giant cells being attached to the branching blood vessels. This abnormal tissue contained numerous *Pneumocystis* cysts in the Grocott methenamine silver stain (Yang 2000).

Hepatic Calcifications

In some patients, hepatobiliary pneumocystosis presents in the form of calcifications in the liver substance. These calcifications may be multiple punctate lesions on imaging (Feuerstein et al. 1990; Fishman et al. 1990; Lubat et al. 1990; Radin et al. 1990; Dembinski et al. 1991; Valdè et al. 1994). In one patient with punctate lesions, fine needle aspiration of the liver was positive for *P. carinii* (Lubat et al. 1990), and *P. carinii* was detectable by immunohistochemistry in calcified liver lesions in another patient postmortem (Valdès et al. 1994). Calcifications may also involve extrapulmonary blood vessels (Wakabayashi et al. 1992). It is likely that vascular calcifications are causally related to hypercalcemia associated with *P. carinii* infections and in particular *P. carinii* pneumonia (Ahmed and Jaspan 1993; Mills et al. 1999; Aguirre et al. 2007). It is thought that the marked macrophage/epithelioid cell reaction in this infection may be involved in the pathogenesis of hypercalcemia, because monocyte-derived cells can convert vitamin D3 into its active metabolite via expression of D3 bioactivating CYP27A1 (Gottfried et al. 2006).

Biliary Obstruction by Extrinsic Compression

Biliary obstruction in pneumocystosis can emerge caused by lymphonodal involvement at the porta hepatis (Hassan et al. 1992).

Life Cycle

In regard to the organism's morphology, four morphotypes are identified, i.e., trophozoites, cysts, precysts, and sporozoites (review: Wazir and Ansari 2004). Trophozoites are pleomorphic and measure 2–4 mm. They are unicellular structures that may contain two or more nuclei. The cyst is the cytologically/histopathologically diagnostic form and steins with Giemsa, Papanicolaou, and Grocott methenamine silver nitrate stains and also immunohistochemically. In the light microscope, the cysts embedded in a characteristic foam-like background appear as a spherical, cup-shaped, or crescent-shaped object measuring 4–8 mm in diameter. Part of these cysts seem empty and collapsed, while others contain dark bodies or dots representing focal thickenings of the cyst wall. Cysts contain up to eight sporozoites. Sporozoite-containing cysts have a pellicle consisting of three layers, i.e., the inner plasmalemma, an electron-lucent middle layer, and an electron-dense outer layer. Referring to the life cycle of this organism (review: Cushion et al. 1997; Cushion 1998), the terminology so far follows zoological terms rather than mycological terms, reflecting the initial misinterpretation of *Pneumocystis* as a protozoan parasite. An asexual mode of replication through binary fission of the trophic form and a sexual mode mediated by mating of trophic forms and resulting in the formation of an ascus (cyst) containing eight ascospores have been distinguished. The cysts or asci often collapse forming crescent-shaped bodies clearly visible in stained sections. Apart from the ascus and the trophic forms, several intermediate forms have been identified that are thought to represent the progression from zygote through meiosis, the additional mitotic step to generate eight nuclei, and the subsequent separation into ascospores.

The natural reservoirs are not well known, because no environmental form or life cycle has so far been identified. Infection of the human host is initiated by attachment of inhaled *Pneumocystis* trophs to alveolar type I pneumocytes. Once in the alveolar space, clusters of organisms proliferate from the trophic forms anchored to pneumocytes and start to fill the alveolar space, ending up with

the characteristic "foamy" material that is seen in the microscope.

References

Abella E, Ribera JM, Humbert P, Escribano C (1990) Focal hepatosplenic candidiasis in a female patient with acute myeloblastic leukemia (in Spanish). Med Clin (Barc) 95:718

Abu Al Rub F, Whitt K, Tombazzi C (2009) Disseminated histoplasmosis presenting with biliary obstruction and duodenal ulcer. Tenn Med 102:45–46

Aguirre AR, Balbo BE, Ianhez LE, da Costa MC, Andrade L (2007) Hypercalcemia and suppressed PTH levels in a renal transplant patient infected with *Pneumocystis carinii*. Ren Fail 29:513–516

Ahmed B, Jaspan JB (1993) Case report: hypercalcemia in a patient with AIDS and *Pneumocystis carinii* pneumonia. Am J Med Sci 306:313–316

Al-Asiri RH, Van Dijken PJ, Mahmood MA, Al-Shahed MS, Rossi ML, Osoba AO (1996) Isolated hepatic mucormycosis in an immunocompetent child. Am J Gastroenterol 91:606–607

Albert-Braun S, Venema F, Bausch J, Hunfeld KP, Schäfer V (2005) *Cryptococcus neoformans* peritonitis in a patient with alcoholic cirrhosis: case report and review of the literature. Infection 33:282–288

Alvarez OA, Vanegas F, Maze GL, Gross GW, Lee M (2000) Polymicrobial cholangitis and liver abscess in a patient with the acquired immunodeficiency syndrome. South Med J 93:232–234

Annunziata GM, Blackstone M, Hart J, Piper J, Baker AL (1997) Candida (*Torulopsis glabrata*) liver abscesses eight years after orthotopic liver transplantation. J Clin Gastroenterol 24:176–179

Anttila VJ, Ruutu P, Bondestam S, Jansson SE, Nordling S, Färkkilä M, Sivonen A et al (1994) Hepatosplenic yeast infection in patients with acute leukemia: a diagnostic problem. Clin Infect Dis 18:979–981

Anttila VJ, Elonen E, Nordling S, Sivonen A, Ruutu T, Ruutu P (1997) Hepatosplenic candidiasis in patients with acute leukemia: incidence and prognostic implications. Clin Infect Dis 24:375–380

Ashbee HR, Evans EG, Viviani MA, Dupont B, Chryssanthou E, Surmont I, Tomsikova A et al (2008) Histoplasmosis in Europe: report on an epidemiological survey from the European Confederation of Medical Mycology Working Group. Med Mycol 46:57–65

Awen C, Baltzan M (1971) Systemic dissemination of *Pneumocystis carinii* pneumonia. Can Med Assoc J 104:809–812

Badiee P, Alborzi A, Malekhosseini SA, Nikeghbalian S, Shkiba E (2010) Determining the incidence of aspergillosis after liver transplant. Exp Clin Transplant 8:220–223

Bartley DL, Hughes WT, Parvey LS, Parham D (1982) Computed tomography of hepatic and splenic fungal abscesses in leukemic children. Pediatr Infect Dis 1:317–321

Blade J, Lopez-Guillermo A, Rozman C, Granena A, Bruguera M, Bordas J, Cervantes F et al (1992) Chronic systemic candidiasis in acute leukemia. Ann Hematol 64:240–244

Brandao A, Marroni CA, Cerski CT, Gleisner AL, Zanotelli ML, Cantisani G (2003) Zygomycosis following liver transplantation in adults: report of three cases (in Portuguese). Rev Soc Bras Med Trop 36:729–733

Brown J (2005) Zygomycosis: an emerging fungal infection. Am J Health Syst Pharm 62:2593–2596

Bucavalas JC, Bove KE, Kaufman RA, Gilchrist MJ, Oldham KT, Balistreri WF (1985) Cholangitis associated with *Cryptococcus neoformans*. Gastroenterology 88:1055–1059

Busca A, Marmont F, Locatelli F, Limerutti G, Sorrentino MT, Barbui A, Patrono D et al (2010) Combined antifungal therapy, iron chelation and surgical resection as treatment of hepatic zygomycosis in a patient with haematological malignancy. Mycoses 53:275–278

Buschke A (1895) Ueber eine durch Coccidien hervegerufene krankheit des Menschen. Dtsch Med Wschr 21:14

Busse O (1894) Ueber parasitäse zelleinschlüsse und ihre züchtung. Centralbl Bakt Parasiten Kole 16:175–180

Callister et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/1533665

Cano MV, Hajjeh RA (2001) The epidemiology of histoplasmosis: a review. Semin Respir Infect 16:109–118

Carini A (1910) Formas de eschizogonia de *Trypanosoma lewisii*. Soc Med Civ Sao Paulo 38:8

Carosi G, Maccabruni A, Michelone G, Viale P, Cavanna C (1985) Primary hepatic aspergillosis: report of case. Boll Ist Sieroter Milan 64:324–325

Carstensen H, Nilsson KO, Nettelblad SC, Cederlund CG, Hildell J (1986) Common bile duct obstruction due to an intraluminal mass of candidiasis in a previously healthy child. Pediatrics 77:858–861

Carstensen H, Widding E, Storm K, Ostergaard E, Herlin T (1990) Hepatosplenic candidiasis in children with cancer. Three cases in leukemic children and a literature review. Pediatr Hematol Oncol 7:3–12

Casadevall A, Perfect JR (1998) *Cryptococcus neoformans*. ASM Press, Washington, DC

Casagrandi C (1931) Sulla presenza di Basidiobolus nell'uom. Riv Biol 13:1–8

Chagas C (1909) Nova tripanozomiaze humana. Estudos sobre a morfolojia e ciclo evolutivo do Schizotrypanum cruzi n.gen.n.sp., ajente etiolojico de nova entidade morbida do homem. Mem Inst Oswaldo Cruz 1:159–218

Chailly P, Couturier E (1976) A case of mucormycosis with hepatic involvement (in French). Med Chir Dig 5:157–158

Cheema MA (1995) Candia fungal ball obstruction of the common bile duct. Ann Saudi Med 15:69–70

Chen GH, Lin LB (1990) Disseminated histoplasmosis capsulatum. A report of two autopsy cases. Chin Med J (Engl) 103:256–269

Chen CC, Chang PY, Chen CL (1986) Refractory cholangitis after Kasai's operation caused by candidiasis: a case report. J Pediatr Surg 21:736–737

Chen SC, Marriott D, Playford EG, Nguyen Q, Ellis D, Meyer W, Sorrell TC, Slavin M et al (2009) Candidemia with uncommon *Candida* species: predisposing factors, outcome, antifungal susceptibility, and implications for management. Clin Microbiol Infect 15:662–669

Collins DN, Oppenheim IA, Edwards MR (1971) Cryptococcosis associated with systemic lupus erythematosus. Arch Pathol 910:78–88

Colovic M, Lazarevic V, Colovic R, Jankovic G, Suvaydzic N, Bogdanovic A, Bila J (1999) Hepatosplenic candidiasis after neutropenic phase of acute leukaemia. Med Oncol 16:139–142

Cote RJ, Rosenblum M, Telzak EE, May M, Unger PD, Cartun RW (1990) Disseminated *Pneumocystis carinii* infection causing extrapulmonary organ failure: clinical, pathologic, and immunohistochemical analysis. Mod Pathol 3:25–30

Cushion MT (1998) Taxonomy, genetic organization, and life cycle of *Pneumocystis carinii*. Semin Respir Infect 13:304–312

Cushion MT, Walzer PD, Smulian AG, Linke MJ, Ruffolo JJ et al (1997) Terminology for the life cycle of *Pneumocystis carinii*. Infect Immun 65:4365

Daikos et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/16103483

Dalgic B, Bukulmez A, Sari S (2011) Pyogenic liver abscess and peritonitis due to Rhizopus oryzae in a child with Papillon-Lefevre syndrome. Eur J Pediatr 170:803–805

Darling ST (1909) The morphology of the parasite (*Histoplasma capsulatum*) and the lesions of histoplasmosis, a fatal disease of tropical America. J Exp Med 11:515–531

Davey RT, Margolis D, Kleiner D, Deyton L, Travis W (1989) Digital necrosis and disseminated *Pneumocystis carinii* infection after aerosolized pentamidine prophylaxis. Ann Intern Med 111:681–682

Delanoe P, Delanoe M (1912) Sur les rapports des kystes de Carini du poumon des rats avec le *Trypanosoma lewisi*. C R Acad Sci 155:658–661

Delclaux C, Schutz R, Calzolari M, Balloul E, Zango B (1992) Generalized histoplasmosis due to *Histoplasma duboisii* with mediastino-pulmonary infection. Cure after 15 months of treatment with ketoconazole (in French). Rev Mal Respir 9:559–560

Dembinski AS, Smith DM, Goldsmith JC, Woods GL (1991) Widespread dissemination of *Pneumocystis carinii* infection in a patient with acquired immune deficiency syndrome receiving long-term treatment with aerosolized pentamidine. Am J Clin Pathol 95:96–100

Diebel et al. 1996. http://www.ncbi.nlm.nih.gov/pubmed/8862389

Domagk D, Bisping G, Poremba C, Fegeler W, Domschke W, Menzel J (2001) Common bile duct obstruction due to candidiasis. Scand J Gastroenterol 36:444–446

Domagk D, Fegeler W, Conrad B, Menzel J, Domschke W, Kucharzik T (2006) Biliary tract candidiasis: diagnostic and therapeutic approaches in a case series. Am J Gastroenterol 101:2530–2536

El-Shabrawi MH, Kamal NM (2011) Gastrointestinal basidiobolomycosis in children: an overlooked emerging infection ? J Med Microbiol 60:871–880

Erdem G, Caglar M, Ceyhan M, Akcoren Z, Kanra G (1996) Hepatic mucormycosis in a child with fulminant hepatic failure. Turk J Pediatr 38:511–514

Escher M, Kainikkara TM, Grabner A, Ott G, Strange EF, Herrlinger KR (2012) Histoplasmosis: uncommon opportunistic infection in a patient with HIV infection (in German). Dtsch Med Wochenschr 137:260–264

Falcone M, Massetti AP, Russo A, Vullo V, Venditti M (2011) Invasive aspergillosis in patients with liver disease. Med Mycol 49:406–413

Fenaux P, Lemaitre L, Ajana F, Colcher-Plantier I, Jouet JP, Bauters F (1989) Hepatosplenic candidiasis: an overlooked cause of prolonged fever during recovery from an episode of neutropenia. Nouv Rev Fr Hematol 31:45–49

Feuerstein IM, Francis P, Raffeld M, Pluda J (1990) Widespread visceral calcifications in disseminated *Pneumocystis carinii* infection: CT characteristics. J Comput Assist Tomogr 14:149–151

Filice C, Brunetti E, Carnevale G, Dughetti S, Pirola F, Rondanelli EG (1989) Ultrasonographic and microbiological diagnosis of mycetic liver abscesses in patients with AIDS. Microbiologica 12:101–104

Filippi L, Poggi C, Gozzini E, Meleleo R, Mirabile L, Fiorini P (2009) Neonatal liver abscesses due to *Candida* infection effectively treated with caspofungin. Acta Paediatr 98:906–909

Finkelstein R, Wichtig C, Hashmonai M (1985) *Candida albicans* liver abscesses. Infection 13:243–244

Fisher J, Tuazon CU, Geelhoed GW (1980) Mucormycosis in transplant patients. Am Surg 46:315–322

Fishman EK, Magid D, Kuhlman JE (1990) *Pneumocystis carinii* involvement of the liver and spleen: CT demonstration. J Comput Assist Tomogr 14:146–148

Franca AV, Carneiro M, dal Sasso K, Souza Cda S, Martinelli A (2005) Cryptococcosis in cirrhotic patients. Mycoses 48:68–72

Frater JL, Hall GS, Procop GW (2001) Histologic features of zygomycosis: emphasis on perineural invasion and fungal morphology. Arch Pathol Lab Med 125:375–378

Friedman E, Blahut RJ, Bender MD (1987) Hepatic abscesses and fungemia from *Torulopsis glabrata*. Successful treatment with percutaneous drainage and amphotericin B. J Clin Gastroenterol 9:711–715

Gavilan et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9611874

Goenka MK, Mehta S, Yachha SK, Nagi B, Chakraborty A, Malik AK (1995) Hepatic involvement culminating in cirrhosis in a child with disseminated cryptococcosis. J Clin Gastroenterol 20:57–60

Goodwin RA, Shapiro JL, Thurman GH, Thurman SS, Des Prez RM (1980) Disseminated histoplasmosis: clinical and pathologic correlations. Medicine (Baltimore) 59:1–33

Gordon SC, Watts JC, Veneri RJ, Chandler FW (1990) Focal hepatic candidiasis with perihepatic adhesions: laparoscopic and immunohistologic diagnosis. Gastroenterology 98:214–217

Gottfried E, Rehli M, Hahn J, Holler E, Andreesen R, Kreutz M (2006) Monocyte-derived cells express CYP27A1 and convert vitamin D3 into its active metabolite. Biochem Biophys Res Commun 349:209–213

Grimes MM, LaPook JD, Bar MH, Wasserman HS, Dwork A (1987) Disseminated *Pneumocystis carinii* infection in a patient with acquired immunodeficiency syndrome. Hum Pathol 18:307–308

Grunebaum M, Ziv N, Kaplinsky C, Kornreich L, Horev G, Mor C (1991) Liver candidiasis. The various sonographic patterns in the immunocompromised child. Pediatr Radiol 21:497–500

Guan XQ, Zhou LC, Liao XG, Lin X, Li YY (2001) Pathological changes of diffuse *Pneumocystis carinii* infection in the liver of an AIDS patient (in Chinese). Zhongguo Ji Sheng Chong Xue Ji Sheng Chong Bing Za Zhi 19:236–238

Gugnani HC (1999) A review of zygomycosis due to *Basidiobolus ranarum*. Eur J Epidemiol 15:923–929

Gugnani HC, Muotoe-Okafor F (1997) African histoplasmosis: a review. Rev Iberoam Micol 14:155–159

Gupta NM, Chaudhary A, Talwar P (1985) Candidal obstruction of the common bile duct. Br J Surg 72:13

Gupta BK, Kumar R, Kaur S, Khurana S (1993) Incidence of fungal infection in extra hepatic biliary disease. Indian J Pathol Microbiol 36:110–112

Haase G (1997) *Pneumocystis carinii* Delanoe & Delanoe (1912) has been placed in the Archiascomycetales, a class of the Ascomycota. Infect Immun 65:4365–4366

Hagopian WA, Huseby JS (1989) Pneumocystis hepatitis and choroiditis despite successful aerosolized pentamidine pulmonary prophylaxis. Chest 96:949–951

Hagspiel KD, Kempf W, Hailemariam S, Marincek B (1995) Mucormycosis of the liver: CT findings. AJR Am J Roentgenol 165:340–342

Hardy WD, Northfelt DW, Drake TA (1989) Fatal, disseminated pneumocystosis in a patient with acquired immunodeficiency syndrome receiving prophylactic aerosolized pentamidine. Am J Med 87:329–331

Haron E, Feld R, Tuffnell P, Patterson B, Hasselback R, Matlow A (1987) Hepatic candidiasis: an increasing problem in immunocompromised patients. Am J Med 83:17–26

Hassan T, Mikhail N, Cappell MS (1992) Extrapulmonic *Pneumocystis carinii* infection at a porta hepatis lymph node. Am J Gastroenterol 87:403–404

Henrich B, Schmitt M, Bergmann N, Zanger K, Kubitz R, Häussinger D, Pfeffer K (2010) Mycoplasma salivarium detected in a microbial community with *Candida glabrata* in the biofilm of an occluded biliary stent. J Med Microbiol 59:239–241

Hibino K, Samaranayake LP, Hägg U, Wong RW, Lee W (2009) The role of salivary factors in persistent oral carriage of *Candida* in humans. Arch Oral Biol 54:678–683

Ho B, Cooperberg PL, Li DK, Mack L, Naiman SC, Grossman L (1982) Ultrasonography and computed tomography of hepatic candidiasis in immunosuppressed patients. J Ultrasound Med 1:157–159

Ho F, Snape WJ, Venegas R, Lechago J, Klein S (1988) Choledochal fungal ball. An unusual cause of biliary obstruction. Dig Dis Sci 33:1030–1034

Hobson RP (2003) The global epidemiology of invasive *Candida* infections – is the tide turning? J Hosp Infect 55:159–168

Horn DL, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, Marr KA et al (2009) Epidemiology and outcome of Candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis 48:1695–1703

Hussein MR, Musalam AO, Assiry MH, Eid RA, El Motawa AM, Gamel AM (2007) Histological and ultrastructural features of gastrointestinal basidiobolomycosis. Mycol Res 111:926–930

Ioannidis et al. 1995. http://www.ncbi.nlm.nih.gov/pubmed/7620038

Irani M, Truong LD (1986) Candidiasis of the extrahepatic biliary tract. Arch Pathol Lab Med 110:1087–1090

Ishii H, Hiruma K, Morio S, Hirasawa A, Wakita H, Endoh N, Oh H, Yoshida S, Aotsuka N et al (1990) Multiple liver abscesses due to *Candida albicans* in a patient with acute promyelocytic leukemia: percutaneous transhepatic intraportal administration of amphotericin B (in Japanese). Rinsho Ketsueki 31:330–334

Itoh M, Oki M, Yanagi H, Oka A, Tajiri S, Fukuda R, Ozawa H, Takagi A (2012) Disseminated mucormycosis infection after a first course of dose-modified R-EPOCH for advanced-stage lymphoma. J Infect Chemother 18:395–398

Jariwalla A, Tulloch BR, Fox H, Kelly J, Davies R (1977) Disseminated histoplasmosis in an English patient with diabetes mellitus. Br Med J 1:1002–1004

Jarnum S, Rasmussen EF, Ohlsen AS, Sorensen AW (1968) Generalized *Pneumocystis carinii* infection with severe idiopathic hypoproteinemia. Ann Intern Med 68:138–145

Johnson TL, Barnett JL, Appelman HD, Nostrant T (1988) Candida hepatitis. Histopathologic diagnosis. Am J Surg Pathol 12:716–720

Jones JM (1981) Granulomatous hepatitis due to *Candida albicans* in patients with acute leukemia. Ann Intern Med 94:475–477

Kahi CJ, Wheat LJ, Allen SD, Sarosi GA (2005) Gastrointestinal histoplasmosis. Am J Gastroenterol 100:220–231

Kapelusznik L, Arumugam V, Caplivski D, Bottone EJ (2011) Disseminated histoplasmosis presenting as AIDS cholangiopathy. Mycoses 54:262–264

Kauffman 2007. http://www.ncbi.nlm.nih.gov/pubmed/17223625

Kauffman 2009. http://www.ncbi.nlm.nih.gov/pubmed/19395629

Keane MA, Finlayson C, Joseph AE (1995) A histologic basis for the 'sonographic snowstorm' in opportunistic infection of the liver and spleen. Clin Radiol 50:220–222

Khan ZU, Khoursheed M, Makar R, Al-Waheeb S, Al-Bader I, Al-Muzaini A, Chandy R et al (2001) *Basidiobolus ranarum* as an etiologic agent of gastrointestinal zygomycosis. J Clin Microbiol 39:2360–2363

Kian JL, Pohan A, Ni TE, van der Meulen H (1956) *Basidiobolus ranarum* as a cause of subcutaneous mycosis in Indonesia. AMA Arch Derm 74:378–383

Kibria R, Bari K, Ali SA, Barde CJ (2009) "Ohio River valley fever" presenting as isolated granulomatous hepatitis: a case report. South Med J 102:656–658

Kim JS, Choi BI, Han MC (1994) Cryptococcal cholangiohepatitis with intraductal cryptococcoma. AJR Am J Roentgenol 163:995–996

Kothari AA, Kothari KA (2004) Hepatobiliary dysfunction as initial manifestation of disseminated cryptococcosis. Indian J Gastroenterol 23:145–146

Krcmery V, Barnes AJ (2002) Non-albicans *Candida* spp. causing fungemia: pathogenicity and antifungal resistance. J Hosp Infect 50:243–260

Kulaksiz H, Rudolph G, Kloeters-Plachky P, Sauer P, Geiss H, Stiehl A (2006) Biliary *Candida* infections in primary sclerosing cholangitis. J Hepatol 45:711–716

Kwon-Chung KJ (2012) Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: molecular mycologic perspectives. Clin Infect Dis 54(suppl 1):S8–S15

Lai et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/15786561

Lamps LW, Molina CP, West AB, Haggitt RC, Scott MA (2000) The pathologic spectrum of gastrointestinal and hepatic histoplasmosis. Am J Clin Pathol 113:64–72

Lanjewar DN, Rao RJ, Kulkarni SB, Hira SK (2004) Hepatic pathology in AIDS: a pathological study from Mumbai. India HIV Med 5:251–252

Lanza FL, Nelson RS, Somayaji BN (1970) Acute granulomatous hepatitis due to histoplasmosis. Gastroenterology 58:392–396

Latge JP (1999) Aspergillus fumigatus and aspergillosis. Clin Microbiol Rev 12:310–350

Lazo RF (1977) Hepatic histoplasmosis (in Spanish). Rev Ecuat Hig Med Trop 30:217–224

Lee TY, Yang SS, Chen GH, Hwang WL, Lin YH, hwang JI (2003) Hepatic abscess caused by *Aspergillus fumigatus* infection following splenectomy and immunosuppressive therapy. J Formos Med Assoc 102:501–505

Lefton HB, Farmer RG, Buchwald R, Haselby R (1974) Cryptococcal hepatitis mimicking primary sclerosing cholangitis. A case report. Gastroenterology 67:511–515

Lenz P, Conrad B, Kucharzik T, Hilker E, Fegeler W, Ullerich H, Heinecke A, Domschke W et al (2009) Prevalence, associations, and trends of biliary-tract candidiasis: a prospective observational study. Gastrointest Endosc 70:480–487

Levitt L, Messina A, Dumois J, Gonzalez-Gomez I, Berman DM (2012) Photo Quiz. A 12-month-old boy with pneumonia and hepatitis. Clin Infect Dis 54 (1784):1814–1815

Lewis JL, Rabinovich S (1972) The wide spectrum of cryptococcal infections. Am J Med 53:315–322

Lewis JH, Patel HR, Zimmerman HJ (1982) The spectrum of hepatic candidiasis. Hepatology 2:479–487

Li KW, Wen TF, Li GD (2010) Hepatic mucormycosis mimicking hilar cholangiocarcinoma: a case report and literature review. World J Gastroenterol 16:1039–1042

Lima R, Shams W, Kalra S, Borthwick T (2010) *Candida glabrata* liver abscess and fungemia complicating severe calculous cholecystitis in an immunocompetent nondiabetic host. South Med J 103:245–247

Lin X, Heitman J (2006) The biology of the *Cryptococcus neoformans* species complex. Annu Rev Microbiol 60:69–105

Lin JI, Kabir MA, Tseng HC, Hillman N, Moezzi J, Gopelswamy N (1999) Hepatobiliary dysfunction as the initial manifestation of disseminated cryptococcosis. J Clin Gastroenterol 28:273–275

Lipsett PA, Huang CJ, Lillemoe KD, Cameron JL, Pitt HA (1997) Fungal hepatic abscesses: characterization and management. J Gastrointest Surg 1:78–84

Liu PY, Yang Y, Shi ZY (2009) Cryptococcal liver abscess: a case report of successful treatment with amphotericin-B and literature review. Jpn J Infect Dis 62:59–60

Lizardi-Cervera J, Soto Ramirez LE, Poo JL, Uribe M (2005) Hepatobiliary diseases in patients with human immunodeficiency virus (HIV) treated with non highly active anti-retroviral therapy: frequency and clinical manifestations. Ann Hepatol 4:188–191

Loeliger A, van Leeuwen M, Rozenberg-Arska M, Dekker AW (1992) Hepatosplenic candidiasis, a fatal disease? Infection 20:336–338

Lu S, Furth EE, Blumberg EA, Bing Z (2009) Hepatic involvement in a liver transplant recipient with disseminated cryptococcosis. Transpl Infect Dis 11:1179–1182

Lubat E, Megibow AJ, Balthazar EJ, Goldenberg AS, Birnbaum BA, Bosniak MA (1990) Extrapulmonary *Pneumocystis carinii* infection in AIDS: CT findings. Radiology 174:157–160

Lüer S, Berger S, Diepold M, Duppenthaler A, von Gunten M, Mühletaler K, Wolf R, Aebi C (2009)

Treatment of intestinal and hepatic mucormycosis in an immunocompromized child. Pediatr Blood Cancer 52:872–874

Lyon GM, Smilack JD, Komatsu KK, Pasha TM, Leighton JA, Guarner J, Colby TV et al (2001) Gastrointestinal basidiobolomycosis in Arizona: clinical and epidemiological characteristics and a review of the literature. Clin Infect Dis 32:1448–1455

Mabee CL, Mabee SW, Kirkpatrick RB, Koletar SL (1995) Cirrhosis: a risk factor for cryptococcal peritonitis. Am J Gastroenterol 90:2042–2045

Magnussen CR, Olson JP, Ona FV, Graziani AJ (1979) Candida fungus balls in the common bile duct. Unusual manifestation of disseminated candidiasis. Arch Intern Med 139:821–822

Mantadakis E, Samonis G (2009) Clinical presentation of zygomycosis. Clin Microbiol Infect 15(suppl 5):15–20

Marco del Pont J, De Cicco L, Galo G, Ilera J, De Santibanez E, D'Agostino D (2000) Hepatic arterial thrombosis due to *Mucor* species in a child following orthotopic liver transplantation. Transpl Infect Dis 2:33–35

Marcucci RA, Whitely H, Armstrong D (1978) Common bile duct obstruction secondary to infection with *Candida*. J Clin Microbiol 7:490–492

Marotta G, Tozzi M, Sammassimo S, Defina M, Raspadori D, Gozzetti A, Lauria F (2005) Complete resolution of hepatic aspergillosis after non-myeloablative hematopoietic stem cell transplantation in a patient with acute myeloid leukemia. Hematology 10:383–386

Masood A, Sallah S (2005) Chronic disseminated candidiasis in patients with acute leukemia: emphasis on diagnostic definition and treatment. Leuk Res 29:493–501

Maxwell AJ, Mamtora H (1988) Fungal liver abscesses in acute leukemia – a report of two cases. Clin Radiol 39:197–201

McGinnis MR, Walker DH, Dominy IE, Kaplan W (1982) Zygomycosis caused by *Cunninghamella bertholletiae*: clinical and pathologic aspects. Arch Pathol Lab Med 106:282–286

McGuire et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1520371

Mekeel KL, Hemming AW, Reed AI, Matsumoto T, Fujita S, Schain DC, Nelson DR et al (2005) Hepatic mucormycosis in a renal transplant recipient. Transplantation 79:1636

Melero JL, Bastida G, Yago M, Nevarez A, Nos P, Ponce J (2008) Fungal liver abscesses in a patient with primary sclerosing cholangitis and Crohn's disease (in Spanish). Gastroenterol Hepatol 31:576–579

Mendez-Sanchez N, Pichardo-Bahena R, Castrejon HV, Berron-Pérez RD, Hernandez-Bautista VM et al (2006) Necrotizing hepatitis and intrahepatic cholestasis associated to *Cryptococcus* sp. and *Pneumocystis carinii*. Ann Hepatol 5:289–290

Merkel IS, Good CB, Nalesnik M, Roseman SR (1992) Chronic *Pneumocystis carinii* infection of the liver. A case report and review of the literature. J Clin Gastroenterol 15:55–58

Miller JH, Greenfield LD, Wald BR (1982) Candidiasis of the liver and spleen in childhood. Radiology 142:375–380

Mills AK, Wright SJ, Taylor KM, McCormack JG (1999) Hypercalcemia caused by *Pneumocystis carinii* pneumonia while in leukemic remission. Aust NZ J Med 29:102–103

Miyata A, Honda K, Fujita M, Kikuchi T (1995) Multiple candida liver abscesses successfully treated by continuous intrahepatic arterial infusion of amphotericin B using a reservoir in a case with acute myelocytic leukemia (M2) (in Japanese). Rinsho Ketsueki 36:1217–1222

Morris et al. 1990. http://www.ncbi.nlm.nih.gov/pubmed/2193353

Mustafa M, Sandhir S, Agarwal S (2002) Endoscopic diagnosis of biliary *Pneumocystis carinii*. Gastrointest Endosc 56:937–939

Naggie S, Perfect JR (2009) Molds: hyalohyphomycosis, phaeohyphomycosis, and zygomycosis. Clin Chest Med 30:337–353

Nara S, Sano T, Ojima H, Onaya H, Ikeda M, Morizane C, Esaki M, Sakamoto Y et al (2008) Liver cryptococcosis manifesting as obstructive jaundice in a young immunocompetent man: report of a case. Surg Today 38:271–274

Nevitt PC, Das NL, Hingsbergen EA (2001) Mucormycosis resulting in a pseudoaneurysm in the spleen. Pediatr Radiol 31:115–116

Nosanchuk JD, Gacser A (2008) *Histoplasma capsulatum* at the host-pathogen interface. Microbes Infect 10:973–977

Okudaira M, Straub M, Schwarz J (1961) The etiology of discrete splenic and hepatic calcifications in an endemic area of histoplasmosis. Am J Pathol 39:599–6111

Oliver MR, Van Voorhis WC, Boeckh M, Mattson D, Bowden RA (1996) Hepatic mucormycosis in a bone marrow transplant recipient who ingested naturopathic medicine. Clin Infect Dis 22:521–524

Ow C, Maldjian C, Shires GT, Markisz J, Kazam E (1991) CT, US, and MR imaging of hepatic aspergilloma. J Comput Assist Tomogr 15:852–854

Padmanabhan S, Battiwalla M, Hahn T, Ball D, Paplham P, Brown K, Segal BH et al (2007) Two cases of hepatic zygomycosis in allogeneic stem cell transplant recipients and review of the literature. Transpl Infect Dis 9:148–152

Pagano L, Ricci P, Tonso A, Nosari A, Cudillo L, Montillo M, Cenacchi A, Pacilli L et al (1997) Mucormycosis in patients with haematological malignancies: a retrospective clinical study of 37 cases. GIMEMA Infection Program (Gruppo Italiano malattie Ematologiche Maligne dell'Adulto). Br J Haematol 99:331–336

Pagano L, Mele L, Fianchi L, Melillo L, Martino B, D'Antonio D, Tosti ME, Posteraro B et al (2002)

Chronic disseminated candidiasis in patients with hematologic malignancies. Clinical features and outcome of 29 episodes. Haematologica 87:535–541

Patrick CC, Flynn PM, Henwick S, Pui CH (1992) Disseminated histoplasmosis presenting as a cystic duct obstruction. Pediatr Infect Dis J 11:593–594

Pestalozzi BC, Krestin GP, Schanz U, Jacky E, Gmür J (1997) Hepatic lesions of chronic disseminated candidiasis may become invisible during neutropenia. Blood 90:3858–3864

Pichard E, Dufio B, Sangare S, Naco A, Diallo AN (1987) African histoplasmosis in Mali. Ann Med Int 138:278–281

Pilon VA, Echols RM, Celo JS, Elmendorf SL (1987) Disseminated *Pneumocystis carinii* infection in AIDS. N Engl J Med 316:1410–1411

Pinès E, Malbec D, Lepennec MP, Hilpert F, Boudon P (1994) Hepatic candidiasis caused by *Candida glabrata* (in French). Ann Gastroenterol Hepatol (Paris) 30:208–211

Poblete RB, Rodriguez K, Foust RT, Reddy KR, Saldana MJ (1989) *Pneumocystis carinii* hepatitis in the acquired immunodeficiency syndrome (AIDS). Ann Intern Med 110:737–738

Pomar V, Carrera G, Paredes R, Domingo P (2005) Disseminated cryptococcosis resembling miliary tuberculosis in an HIV-1-infected patient. Lancet Infect Dis 5:189

Potenza L, Barozzi P, Rossi G, Palazzi G, Vallerini D, Riva G, Cellini M, Morselli M et al (2008) Assessment of *Aspergillus*-specific T cells for diagnosis of invasive aspergillosis in a leukemic child with liver lesions mimicking hepatosplenic candidiasis. Clin Vaccine Immunol 15:1625–1628

Potoczek S, Kuliczkowski K (1994) Candidiasis of the bile ducts and liver in the course of acute leukemia (in Polish). Pol Arch Med Wewn 91:479–482

Prabhu RM, Patel R (2004) Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect 10(suppl 1):31–47

Price JT, Bulmer GS (1972) Tumor induction by *Cryptococcus neoformans*. Infect Immun 6:199–205

Procknow JJ, Benfield JR, Rippon JW et al (1965) Cryptococcal hepatitis presenting as a surgical emergency. First isolation of *Cryptococcus neoformans* from point source in Chicago. JAMA 191:269–274

Radin DR (1991) Disseminated histoplasmosis: abdominal CT findings in 16 patients. AJR Am J Roentgenol 157:955–958

Radin DR, Johnson MB (1992) Candida cholangitis in a diabetic woman. AJR Am J Roentgenol 158:1029–1030

Radin DR, Baker EL, Klatt EC, Balthazar EJ, Jeffrey RB, Megibow AJ, Ralls PW (1990) Visceral and nodal calcification in patients with AIDS-related *Pneumocystis carinii* infection. AJR Am J Roentgenol 154:27–31

Rahimi SA (1974) Disseminated *Pneumocystis carinii* in thymic alymphoplasia. Arch Pathol 97:162–165

Ramirez-Garcia et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21858674

Rammaert B, Desjardins A, Lortholary O (2012) New insights into hepatosplenic candidiasis, a manifestation of chronic disseminated candidiasis. Mycoses 55: e74–e84

Reeves AR, Johnson MS, Stine S (2000) Percutaneous diagnosis and treatment of biliary candidiasis. J Vasc Interv Radiol 11:107–109

Rescorla FJ, Kleiman MB, Grosfeld JL (1994) Obstruction of the common bile duct in histoplasmosis. Pediatr Infect Dis J 13:1017–1019

Ribes JA, Vanover-Sams CL, Baker DJ (2000) Zygomycetes in human disease. Clin Microbiol Rev 13:236–301

Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL et al (2005) Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 41:634–653

Rodriguez et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17604436

Rubio E, Jimenez M, Alvira LG, Lucena JL, Arrieta FM, Chaparro MD, Cuervas-Mons V, Turrion VS (2011) Influence of infection by Aspergillus in arterial complications after liver transplantation: evolution and results in 670 transplants. Transplant Proc 43:751–752

Rudolph J, Rodenwaldt J, Ruhnke M, Hamm B, Kopka L (2004) Unusual enhancement pattern of liver lesions in hepatosplenic candidiasis. Acta Radiol 45:499–503

Rueping MJ, Vehreschild JJ, Cornely OA (2009) Invasive candidiasis and candidemia: from current opinions to future perspectives. Expert Opin Invest Drugs 18:735–748

Saadah OI, Farouq MF, Daajani NA, Kamal JS, Ghanem AT (2012) Gastrointestinal basidiobolomycosis in a child: an unusual fungal infection mimicking fistulasing Crohn's disease. J Crohn's Colitis 6:368–372

Sabesin SM, Fallon HJ, Bethesda VTA (1963) Hepatic failure as a manifestation of cryptococcosis. Arch Intern Med 111:661–669

Sachs JR, Greenfield SM, Sohn M, Turner JL (1991) Disseminated *Pneumocystis carinii* infection with hepatic involvement in a patient with the acquired immune deficiency syndrome. Am J Gastroenterol 86:82–85

Sallah S (1999) Hepatosplenic candidiasis in patients with acute leukemia: increasingly encountered complication. Anticancer Res 19:757–760

Schipper MA, Maslen MM, Hogg GG, Chow CW, Samson RA (1996) Human infection by *Rhizopus azygosporus* and the occurrence of azygospores in Zygomycetes. J Med Vet Mycol 34:199–203

Schmidt H, Fische dick AR, Peters PE, von Lengerke HJ (1986) Candida abscesses in the liver and spleen. The sonographic and computed tomographic morphology (in German). Dtsch Med Wochenschr 111:816–820

Sedlacek P, Vavra V, Masova I, Codl D, Laznickova T, Malaskova L, Nyc O, Stary J (2009) Successful therapy with ABLC, surgery and posaconazole for *Rhizopus*

microspores var. *rhizopodiformis* liver eumycetoma in a child with acute leukemia. Mycoses 52:276–279
Shibuya K, Coulson WF, Wollman JS, Wakayama M, Ando T, Oharaseki T, Takahashi K, Naoe S (2001) Histopathology of cryptococcosis and other fungal infections in patients with acquired immunodeficiency syndrome. Int J Infect Dis 5:78–85
Sikorski T, Marcinowska-Suchowierska E (2007) Cryptococcal ascites and ascitic lymphocytosis in cirrhotic patients. Am J Med 120:e23
Sing Y, Ramdial PK (2007) Cryptococcal inflammatory pseudotumors. Am J Surg Pathol 31:1521–1527
Singh S, Gupta S, Mirdha B, Hak S, Singh YN (1992) Large single candidal liver abscess treated with aspiration and antifungal drugs. Indian J Gastroenterol 11:176–177
Singh N, Gayowski T, Yu VL (1995) Invasive gastrointestinal zygomycosis in a liver transplant recipient: case report and review of zygomycosis in solid-organ transplant recipients. Clin Infect Dis 20:617–620
Singh DK, Tyagi I, Saran RK, Gonadal R (2010) Fatal spontaneous *Cryptococcal peritonitis* in a woman with decompensated liver cirrhosis. Acta Cytol 54 (suppl):1087–1089
Skiada A, Vrana L, Polychronopoulou H, Prodromou P, Chnatzis A, Tofas P, Daikos GL (2009) Disseminated zygomycosis with involvement of the central nervous system. Clin Microbiol 15(suppl 5):46–49
Skiada A, Pagano L, Groll A, Zimmerli S, Dupont B, Lagrou K, Lass-Flol C, Bouza E et al (2011) Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on zygomycosis between 2005 and 2007. Clin Microbiol Infect 17:1859–1867
Spellberg B, Edwards J, Ibrahim A (2005) Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 18:556–559
Staib F (1986) Detection of *Cryptococcus neoformans* in biopsy specimens from the spleen and liver of AIDS patients: critical comments. Mykosen 29:551–555
Steigman CK, Pastore L, Park CH, Fox CH, DeVinates ML, Connor DH et al (1987) AIDS case for diagnosis series. Mil Med 152:M1–M8
Stevens DA, Melikian GL (2011) Aspergillosis in the 'non-immunocompromised' host. Immunol Invest 40:751–766
Stiefel P, Pamies E, Miranda ML, Martin-Sanz MV, Fernandez-Moyano A, Villar J (1999) Cryptococcal peritonitis: report of a case and review of the literature. Hepatogastroenterology 46:1618–1622
Suh IW, Park CS, Lee MS, Lee JH, Chang MS, Woo JH, Lee IC, Ryu JS (2000) Hepatic and small bowel mucormycosis after chemotherapy in a patient with acute lymphocytic leukemia. J Korean Med Sci 15:351–354
Sungkanuparph S, Vibhagool A, Pracharktam R (2002) Spontaneous cryptococcal peritonitis in cirrhotic patients. J Postgrad Med 48:201–202
Swerdloff et al. 1993. http://www.ncbi.nlm.nih.gov/pubmed/8274612
Symmers WS (1960) Mucormycotic granuloma possibly due to *Basidiobolus ranarum*. Br Med J 1:1331–1333
Tamsei S, Demirpolat G, Killi R, Elmas N (2004) Primary hepatic aspergillosis: a case of inflammatory pseudotumor (case report) (in Turkish). Tani Girisim Radyol 10:154–157
Tashjian LS, Abramson JS, Peacock JE (1984) Focal hepatic candidiasis: a distinct clinical variant of candidiasis in immunocompromised patients. Rev Infect Dis 6:689–703
ter Borg F, Kuijper EJ, van der Lelie H (1990) Fatal mucormycosis presenting as an appendiceal mass with metastatic spread to the liver during chemotherapy-induced granulocytopenia. Scand J Infect Dis 22:499–501
Thaler M, Pastakia B, Shawker TH, O'Leary T, Pizzo PA (1988) Hepatic candidiasis in cancer patients: the evolving picture of the syndrome. Ann Intern Med 108:88–100
Trachana M, Roilides E, Gompakis N, Kanellopoulos u K, Mpantouraki M, Kanakoudi-Tsakalidou F (2001) Case report. Hepatic abscesses due to *Aspergillus terreus* in an immunodeficient child. Mycoses 44:415–418
Trojan A, Kreuzer KA, Flury R, Schmid M, Schneider J, Schröder S (1998) Liver changes in AIDS. Retrospective analysis of 227 autopsies of HIV-positive patients (in German). Pathologe 19:194–200
Tsai SH, Peng YJ, Wang NC (2006) Pyomyositis with hepatic and perinephric abscesses caused by *Candida albicans* in a diabetic nephropathy patient. Am J Med Sci 331:292–294
Tsaousis G, Koutsouri A, Gatsiou C, Paniara O, Peppas C, Chalevelakis G (2000) Liver and brain mucormycosis in a diabetic patient type II successfully treated with liposomial amphotericin B. Scand J Infect Dis 32:335–337
Tsui E, Liang R (1991) Successful treatment of focal hepatic candidiasis in a patient with acute myeloid leukaemia. Scand J Infect Dis 23:267–270
Tucker and Casadevall 2002. http://www.ncbi.nlm.nih.gov/pubmed/11880650
Uflacker R, Wholey MH, Amaral NM, Lima S (1982) Parasitic and mycotic causes of biliary obstruction. Gastrointest Radiol 7:173–179
Unger PD, Rosenblum M, Krown SE (1988) Disseminated *Pneumocystis carinii* infection in a patient with acquired immunodeficiency syndrome. Hum Pathol 19:113–116
Utili R, Tripodi MF, Ragone E, Casillo R, Pasquale G, De Santo L, Esposito S (2004) Hepatic cryptococcosis in a heart transplant recipient. Transpl Infect Dis 6:33–36
Vairani G, Rebeschini R, Barbazza R (1990) Hepatic and subcutaneous abscesses due to aspergillosis. Initial diagnosis of a case by intraoperative fine needle aspiration cytology. Acta Cytol 34:891–894
Valdès E, Borzoni F, Onnis D, Piras S, Vespa A, Varsi C (1994) Disseminated *Pneumocystis carinii* infection: clinico-pathologic findings in an AIDS patint (in Italian). Pathologica 86:659–664

Vallaeys JH, Praet MM, Roels HJ, Van Marck E, Kaufman L (1989) The Budd-Chiari syndrome caused by a zygomycete. A new pathogenesis of hepatic vein thrombosis. Arch Pathol Lab Med 113:1171–1174

Valmary J, Bauduceau B, Lartisien D, Flechaire A, Debord T, Daly JP, Laverdant C (1984) Disseminated *Histoplasma duboisii* histoplasmosis in a female inhabitant of the Ivory Coast (in French). Med Trop (Mars) 44:369–373

van den Berk GE, Noorduyn LA, van Ketel RJ, van Leeuwen J, Bemelman WA, Prins JM (2006) A fatal pseudo-tumour: disseminated basidiobolomycosis. BMC Infect Dis 6:140

van Overeem C (1925) Ueber ein merkwürdiges vorkommen von basidiobolus ranarum. Bull jardin Bot Buitenzorg 7:423–431

Vikram HR, Smilack JD, Leighton JA, Crowell MD, De Petris G (2012) Emergence of gastrointestinal basidiobolomycosis in the United States, with a review of worldwide cases. Clin Infect Dis 54:1685–1691

Von Eiff M, Essink M, Roos N, Hiddemann W, Büchner T, van de Loo J (1990) Hepatosplenic candidiasis, a late manifestation of *Candida septicemia* in neutropenic patients with haematologic malignancies. Blut 60:242–248

Wakabayashi T, Oka S, Shimada K, Nakano I, Iwatsubo T, Mori S (1992) Disseminated *Pneumocystis carinii* infection in a hemophiliac patient with acquired immunodeficiency syndrome. Acta Pathol Jpn 42:262–266

Wazir JF, Ansari NA (2004) *Pneumocystis carinii* infection. Update and review. Arch Pathol Lab Med 128:1023–1027

Wig JD, Singh K, Chawla YK, Vaiphei K (1998) Cholangitis due to candidiasis of the extra-hepatic biliary tract. HPB Surg 11:51–54

Wilkins MJ, Lindley R, Dourakis SP, Goldin RD (1991) Surgical pathology of the liver in HIV infection. Histopathology 18:459–464

Williams AO (1969) Pathology of phycomycosis due to *Entomophthora* and *Basidiobolus* species. Arch Pathol 87:13–20

Williams AO, Von Lichtenberg F, Smith JH, Martinson FD (1969) Ultrastructure of phycomycosis due to *Entomophthora*, *Basidiobolus*, and associated "Splendore-Hoeppli" phenomenon. Arch Pathol 87:459–468

Williams AO, Lawson EA, Lucas AO (1971) African histoplasmosis due to *Histoplasma duboisii*. Arch Pathol 92:306–318

Wright S, Harman RRM (1983) Primary hepatic cryptococcosis. Br Med J 287:464

Yamada R, Horikawa K, Ishihara S, Hoshino K, Kawaguchi T, Iyama K, Mitsuya H, Asou H (2010) Successful treatment of *Aspergillus* liver abscesses in a patient with acute monoblastic leukemia using combination antifungal therapy including micafungin as a key drug. Int J Hematol 91:711–715

Yamauchi T, Misaki H, Arai H, Iwasaki H, Naiki H, Ueda T (2002) An autopsy case of disseminated mucormycosis in a neutropenic patient receiving chemotherapy for the underlying solid malignancy. J Infect Chemother 8:103–105

Yang GC (2000) *Pneumocystis carinii* infection presents as common bile duct mass biopsied by fine-needle aspiration. Diagn Cytopathol 22:25–26

Yellapu RK, Mittal V, Grewal P (2010) Education and imaging. Hepatobiliary and pancreatic: Candida liver abscesses associated with endocarditis. J Gastroenterol Hepatol 25:1017

Yeom SK, Kim HJ, Byun JH, Kim AY, Lee MG, Ha HK (2010) Abdominal aspergillosis: CT findings. Eur J Radiol 77:478–482

Young RC (1969) The Budd-Chiari syndrome caused by *Aspergillus*; two patients with vascular invasion of the hepatic veins. Arch Intern Med 124:754–757

Young et al. 1970. http://www.ncbi.nlm.nih.gov/pubmed/4913991

Yuchong C, Dingheng Z, Zhizhong Y, Hongyu Y, Jing H, Jianghan C (2010) Aspergillosis of biliary tract after liver transplantation: a case report. Mycopathologia 170:117–121

Zhan HX, Zhang Y, Liu C, Wang B, Jiang YY, Liu XM (2008a) Hepatic and renal artery rupture due to *Aspergillus* and *Mucor* mixed infection after combined liver and kidney transplantation: a case report. Transplant Proc 40:1771–1773

Zhan HX, Lv Y, Zhang Y, Liu C, Wang B, Jiang YY, Liu XM (2008b) Hepatic and renal artery rupture due to *Aspergillus* and *Mucor* mixed infection after combined liver and kidney transplantation: a case report. Tranplant Proc 40:1771–1773

Zhao Q, Liao J, Qin H, Wang J (2005) Clinical evaluation of ERCP and nasobiliary drainage for biliary fungal infection – a report of five cases of severe combined and fungal infection of the biliary tract. J Huazhong Univ Sci Technol Med Sci 25:427–430

Tumor-Like Protozoal Infections of the Hepatobiliary Tract

132

Contents

Abstract

Amebiasis is a common infection worldwide and is still a major cause of death. Infections with *Entamoeba histololytica* induce a highly characteristic type of liver abscess or an abscess-like ass-forming lesion with an aggressive biology. This form of hepatic lesion is more prevalent in males and persons with suppressed cell-mediated immunity. The process is usually localized to the right liver lobe. Through coalescence of smaller parenchymal necroses, larger lesions develop that contain a thick liquid of reddish-brown color. Histologically, the term "abscess" is a misnomer, as a purulent reaction is not the feature of amoebic liver lesions. The process can involve the biliary tract and may extend beyond the organ boundaries. Invasive hepatic amebiasis can penetrate and perforate the diaphragm to produce hepatothoracic fistulas. Pathogenetically, *Entamoeba* trophozoites reach the liver through the portal venous system and are translocated to the sinusoidal channels. Within hepatic sinusoids, endothelial cells are induced by trophozoites to undergo apoptosis, allowing trophozoite contact with hepatocytes which are destroyed leading to an immune reaction and inflammation.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_132

Amebiasis

Introduction

Amebiasis belongs to the top three causes of death from parasitic disease worldwide. It is estimated that amebiasis is responsible for up to 100,000 deaths worldwide each year (Petri 1996, 2002; Stanley 2003; Ali et al. 2008; Raston and Petri 2011). Amoeba infections (but not disease) are caused by one of three species – *Entamoeba histolytica*, *E. dispar*, and *E. moshkovskii* – whereas classical invasive amebiasis is only caused by *E. histolytica*. *E. histolytica* colonizes the human intestine causing amoebic colitis and disseminates through the vascular route to form liver abscesses. Morbidity and mortality due to amebiasis have remained high, also owing to the hepatic and other complications caused by this parasite. The main hepatic manifestation of amebiasis is the amoebic liver abscess, which is different from pyogenic liver abscess in many respects. These sometime very large inflammatory lesions show an invasive phenotype and may mimic primary or secondary hepatic malignancy.

The classification of amoebae is a complex task due to the fact that many members of the group lack morphologically reliable features. A thorough understanding of the taxonomy of amoebae therefore requires genetic data such as rRNA and DNA sequencing (Stothard et al. 1998). Traditionally, amoebae have been classified as the protozoan taxon Sarcodina, with a taxonomic structure that separated species with supported pseudopodia from those with unsupported pseudopodia and those with skeletal elements from those without (Corliss 1984; Cavalier-Smith 1993; Patterson 1999; Tree of Life Web Project, http://tolweb.org). Three species of *Entamoeba* are capable to infect the human organism, i.e., *E. histolytica* (the only species that can cause invasive amebiasis), *E. dispar*, and *E. moshkovskii*. In the environment, amoeba exists in a distinct microhabitat. Hydrophobic organic matter accumulates at the water-air interface of all natural water bodies to establish the surface microlayers. These form a dynamic environment where bacteria, protists, and aquatic molds are enriched compared to their numbers in the bulk liquid phase; this is also the case for amoebae (Preston 2003). The recent sequencing of the *E. histolytica* genome has opened the way to large-scale approaches to the biology and biochemistry of this organism. *Entamoeba histolytica* is an amitochondriate protozoan with numerous bacterium-like fermentation enzymes. The development of disease following contact with *Entamoeba histolytica* involves a complex pathogenic cascade (review, Petri 2002). During colonization of the gut, transcriptome analysis has shown that diverse *Entamoeba histolytica* genes are activated.

Amoebic Liver Abscess

Amoebic liver abscess is more prevalent in persons with suppressed cell-mediated immunity, in men, and in younger people (Hughes and Petri 2000; Kurland and Brann 2004; Lodhi et al. 2004). A higher prevalence in young men is in contrast to pyogenic liver abscesses, which are more commonly found in persons older than 50 years and are typically associated with a history of diabetes and jaundice. In a retrospective study on 75 patients with confirmed disease, mean patient age at presentation was 35.5 years, and 80 % were male (Hoffner et al. 1999). The abscess usually develops in the right liver lobe; 10 % or less of the lesions are found in the left lobe and are usually a solitary lesion, at least initially. Liver abscesses caused by *E. histolytica* are invasive lesions that, similar to malignant neoplasms, tend to destroy the liver substance and to form pathological communications between the abscess and perihepatic organs and tissues. Patients present with fever, right-upper quadrant discomfort or pain, hepatomegaly, and sometimes jaundice (see below). Among 75 patients, the most common complaint was fever, (77 %), followed by abdominal pain (72 %), cough (16 %), and chest pain (19 %), and the majority of patients had symptoms for less than 13 days (Hoffner et al. 1999). Both in adults and in

children, these lesions can sometimes follow a fulminant course, with recurrence of multiple abscesses and pleuropulmonary complications (Genel et al. 2004). Mainly large abscess can extend beyond the limits of the liver and invade and perforate the diaphragm; communicate with pleural space, bronchi, and/or pericardial cavity (Salles et al. 2003); rupture into the peritoneal cavity (Bukhari 2003); form a hepatogastric fistula (Chang et al. 2002); open into the vena cava (Guevara-Gonzalez and Mendez-Sanchez 2002); or invade the hepatic artery, sometimes followed by formation of an aneurysm (Yanagisawa et al. 2002) or a pseudoaneurysm (Khan et al. 2011). Clinically, amoebic liver abscess may produce a mass effect similar to hepatic tumors. The lesion can imitate metastatic carcinoma (Ritchie et al. 2005).

Pathology of Amoebic Liver Abscess

Through coalescence of small parenchymal necroses, larger lesions result that contain a homogeneous thick liquid of reddish-brown to yellow or chocolate-like color, similar to "anchovy paste" (Figs. 1 and 2). Based on this morphology, the term "abscess" is a misnomer, because an abscess is per definition an accumulation of pus in non-preexisting tissue space, while amebiasis of the liver is characterized by a massive necrosis with accumulation of blood and blood products, in the absence of grossly visible pus. Through liquefaction of the necrosis, large cysts can develop which lead to massive hepatomegaly (Kaur et al. 2001). In case of intrahepatic bile duct invasion, bile enters the abscess fluid and causes a yellowish-greenish discoloration of the fluid. In the central fluid, fragments of necrotic tissue or coagulated blood are floating.

Histology mainly shows a massive necrosis of liver substance, with parts exhibiting coagulation necrosis with hepatic shadow cells and parts showing a hemorrhagic proteinaceous fluid containing intact or lysed erythrocytes and erythrocyte fragments. At the border of the lesion, a thick layer of granulation tissue is found, containing numerous macrophages. In the transition zone between necrosis and granulation tissue, amoebae can be found, especially by the use of a PAS stain (Fig. 3). In peripheral parts of the abscess, but particularly in the atrophic liver tissue surrounding the lesion, variable infiltrates of lymphocytes, macrophages, neutrophils, and plasma cells are found. It has been shown that abscess-associated lymphocytes exert a high amebicidal activity (Vohra et al. 2003).

Amoebic Involvement of the Biliary Tract

Bile duct involvement in amebiasis has mainly been observed in situations of amoebic liver

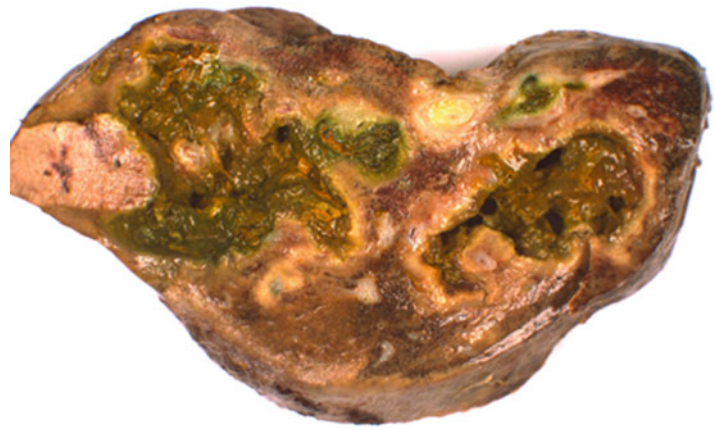

Fig. 1 Amebiasis of the liver (so-called amoebic abscess). Large cavities with necrotic walls are a salient feature

Fig. 2 Amoebic liver abscesses can contain a chocolate-brown mass derived from blood decay in long-standing hemorrhage

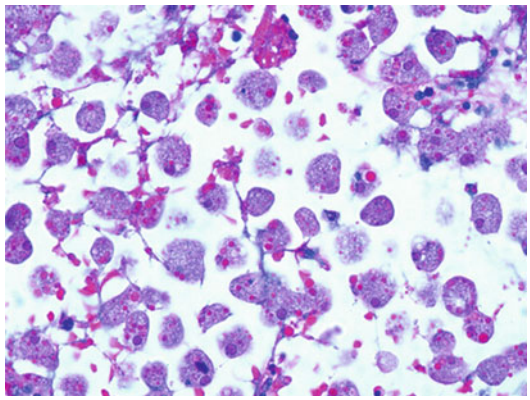

Fig. 3 Amebiasis of the liver. *Entamoeba histolytica* organisms with signs of erythrocytophagocytosis (PAS stain)

abscesses communicating with intrahepatic bile ducts (fistula) or with intrabiliary rupture (Boquien and Lenne 1962; Viana 1966; Shrimali and Choudhary 1969; Brondum Nielsen and Hegedüs 1975; Griffin et al. 1983; Ibrarullah et al. 1994; Agarwal et al. 1995; Kumar et al. 1995; Misra et al. 1997; Sonsuz et al. 1998). In comparison with other perforation sites, intraductal drainage of amoebic liver abscess is uncommon; among 100 patients with such an abscess, perforation into pleuropulmonary structures was found in 72 %, the subphrenic space in 14 %, and the peritoneal cavity in 10 %, while bile duct perforation was only seen in a few cases (Meng and Wu 1994). Fistulation of an amoebic abscess can cause hemobilia (Moine et al. 1965). In a systematic study on 525 patients from India with hepatic abscesses, there were 20 patients who developed a demonstrable communication between liver abscess and intrahepatic ducts (mainly the right hepatic dust), and out of these, 16 were amoebic abscesses (Sharma et al. 2006). In 33 consecutive patients with amoebic liver abscess, abscess-biliary communication was found in 27 %, and patients with such a communication presented more frequently with jaundice (67 % vs. 0 %) and with a longer duration of illness and had larger lesions (median 600 ml vs. 320 ml), requiring a longer period of drainage (Agarwal et al. 1995).

There are few informations relating to the occurrence of amoeba in the biliary tract in the absence of an amoebic liver abscess (Steinitz and Talis 1964). Amoebic liver abscess can cause obstructive jaundice. Although mild jaundice is not an infrequent finding in amoebic liver abscess, severe obstructive jaundice is, however, a rare complication (Haider et al. 1975; Ramachandran et al. 1976; Nigam et al. 1985; Sharma and Sarin 1987; Khan et al. 1990). In a review of 70 cases of amoebic liver abscess, clinical jaundice was present in up to 33 % of all cases, but moderate to severe jaundice was found in only 7 % (Sharma and Sarin 1987). In a another study analyzing 137 patients with amoebic liver abscess, clinical

jaundice was noted in 8 %, but only two patients had a serum bilirubin concentration exceeding 5 mg/100 ml (Ramachandran et al. 1976). The patients presenting with jaundice are usually reported to have an acute onset of the disease, occurring especially in males with a history of excessive alcohol intake. Moreover, jaundice is more common in patients with multiple abscesses (43 %) than in those with a solitary abscess (33 %) and seems to be proportional to the size of the abscess. This may suggest that a pressure effect in the biliary tract may be involved. In fact, exterior compression of bile ducts by a large amoebic liver abscess causing obstructive jaundice has been observed (Sarda et al. 1998).

Pathogenic Pathways of Hepatic Amebiasis

E. histolytica entering the liver interacts with several hepatic cell types. Trophozoites reach the liver through the portal venous system, the parasites being transported to the sinusoidal channel network. Within sinusoids, endothelial cells respond to interaction with *E. histolytica* by retraction and apoptotic cell death, through effects of the amoeba on cell cycle gene expression and integrin-mediated adhesion signaling (Faust et al. 2011). In the early phase of infection, trophozoites are found close to undamaged hepatocytes. As a consequence of these interactions, hepatocytes are destroyed, leading to host immune cell activation, characterized by an infiltrate containing CD8+ T lymphocytes, CD68+ macrophages, and neutrophils (Ventura-Juarez et al. 2003). In the pathway leading to hepatocyte destruction, Kupffer cells play an important role via their induced secretion of TNF-alpha (Helk et al. 2013).

Hepatobiliary Leishmaniasis

Introduction

Leishmaniasis is a widespread and serious infection prevalent in Europe, Africa, Asia, and the Americas, debilitating millions and killing thousands of people each year. An estimated two million new cases are reported annually, and it appears that around 350 million people are at risk worldwide. At least 20 *Leishmania* species infect humans. Leishmaniasis in the human host is classified as follows: (a) visceral leishmaniasis, the most dangerous form, characterized by the spread of the parasite from the entry site to several visceral organs and tissues, including the liver, spleen, and bone marrow; (b) cutaneous leishmaniasis, in which the parasites remain at the site of entry and cause a chronic ulcerating skin disease (review, Akilov et al. 2007); and (c) mucocutaneous leishmaniasis, a chronic inflammation of mucosal tissues that develops from cutaneous leishmaniasis in less than 5 % of affected persons.

Cutaneous leishmaniasis is caused by the *Leishmania* species, *L. major*, *L. tropica*, *L. aethiopica*, *L. infantum*, and *L. archibaldi* in Eurasia and Africa and by *L. mexicana*, *L. venezuelensis*, *L. amazonensis*, *L. braziliensis*, *L. panamensis*, *L. chagasi*, *L. guyanensis*, and *L. peruviana* in the Americas (review, Akilov et al. 2007). Visceral leishmaniasis is commonly caused by *L. donovani* (anthroponotic cycle) and by *L. infantum* (zoonotic cycle). Old World leishmaniasis is transmitted by sandflies of the genus *Phlebotomus*. There is a striking association between certain Old World species complexes of *Leishmania* and particular subgenera of *Phlebotomus*, suggesting features of coevolution (review, Ready 2000). In the Americas, leishmaniasis is transmitted by sandflies of the genus *Lutzomyia*.

Hepatobiliary Leishmaniasis

Liver disease in leishmaniasis is found in all forms of visceral leishmaniasis, the susceptibility to which is modulated by genetic factors of the host, virulence factors of the parasite, and environmental factors (El-Safi et al. 2006). Several types of manifestations are recognized (Table 1). These various types of manifestations are in part linked to the immune status of the host (reactivity or areactivity of the immune system). In a pediatric group of patients ($N = 367$) with kala-azar,

Table 1 Classification of hepatic leishmaniasis

Diffuse leishmaniasis of the hepatic macrophage system
Granulomatous form of hepatic leishmaniasis
Macronodular (pseudotumoral) form of hepatic leishmaniasis
Necrotizing hepatic leishmaniasis

liver function tests were deranged in two thirds of the patients (Rahim and Ashkan 2007), but hepatomegaly is commonly less pronounced than splenomegaly in this age group (Bhattacharya et al. 2006). Among nine autopsies of AIDS patients infected with *L. infantum*, liver involvement associated with generalized parasitic disease was observed in four patients (Hofman et al. 2000). Visceral leishmaniasis is rarely associated with the hemophagocytic syndrome (Marom et al. 2001; Pahwa et al. 2004; Agarwal et al. 2006) and may exceptionally result in acute liver failure (Sagnelli et al. 2012). Imaging findings in hepatic leishmanial involvement are variable but include multiple hypodense, nodular liver lesions (sometimes forming conglomerates several cm in diameter) that may pose diagnostic difficulties (Bütke et al. 2004).

Diffuse Leishmaniasis of the Hepatic Macrophage System

Hepatic involvement in visceral leishmaniasis is common and is mainly dominated by sometimes massive accumulation of amastigotes in hepatic macrophages and by parenchymal cell damage (Koshy et al. 2001; Artan et al. 2006; Gangneux et al. 2006). The intracellular amastigotes are usually clusters of round to ovoid intracytoplasmic bodies, 2–5 μm in diameter. They are amphophilic in the hematoxylin-eosin stain and slightly more basophilic in the H&E safran stain and dark blue in the Giemsa stain. Already in H&E stains, a tiny dot can be recognized in an eccentric location of the amastigotes, representing the kinetoplast (Fig. 4). In the Giemsa preparation, this structure is stained in purple or red. Extracellular parasites may rarely be seen, but it is difficult to judge whether they entered the extracellular space

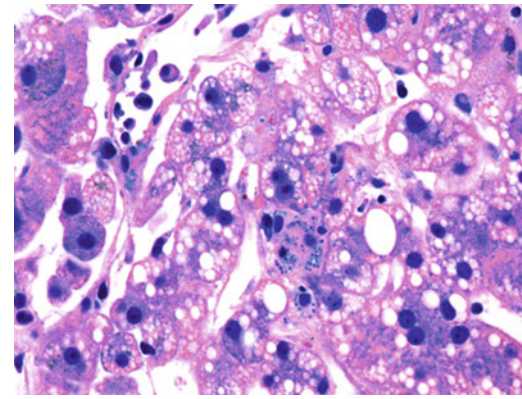

Fig. 4 Leishmaniasis of the liver. Hepatic macrophages (center of figure) contain very small and spherical, strongly basophilic microorganisms (Giemsa stain).

owing to cell decay. Macrophages containing amastigotes are found in portal tracts or in hepatic macrophages/Kupffer cells located to the sinusoidal space. A variable lymphocytic infiltration of portal tracts may be seen. In a series of 18 patients with visceral leishmaniasis, a specimen before treatment showed Kupffer cells/hepatic macrophages colonized by amastigotes in 40 % of the cases (El Hag et al. 1994). Large accumulations of parasite-laden macrophages, with or without a granulomatous reaction, may form large nodular lesions that are low-attenuated in CT (Bütke et al. 2004). Apart from macrophages, electron microscopic investigations have shown that also hepatocytes may harbor amastigotes, eventually entering this cell population by endocytosis (Duarte et al. 1989).

Granulomatous Form of Hepatic Leishmaniasis

A granulomatous hepatic reaction has been observed in liver leishmaniasis (El Hag et al. 1994; Geramizadeh et al. 2011), developing as a function of the immune response of the host. Granulomas are also recognized in experimental murine hepatic leishmaniasis (Gutierrez et al. 1984). The prevalence of *Leishmania*-induced granulomas in livers varies considerably. In a series of patients with visceral leishmaniasis

undergoing liver biopsy, no granulomas were detected (El Hag et al. 1994). Apart from epithelioid granulomas, fibrin-ring granulomas may occur in hepatic leishmaniasis (Moreno et al. 1988; Marazuela et al. 1991).

Macronodular (Pseudotumoral) Hepatic Leishmaniasis

These granulomas may grow to large size (macronodular hepatic granulomas, "leishmaniomas") and may thus be confounded with neoplastic lesions. In one reported observation, ultrasound examination of the liver showed two solid lesions with peripheral hypoechoic halo, 3 cm and 1.5 cm in diameter. Needle aspiration of the larger nodule revealed a granulomatous reaction associated with numerous amastigotes in macrophages (Canalias et al. 1997).

Necrotizing Hepatic Leishmaniasis (Areactive Leishmaniasis)

In immunodeficient individuals, viscerotropic *Leishmania infantum* infection of the liver can rarely induce scattered and in part large necroses of the liver substance, thought to depend on the immune reaction status of the host (Angarano et al. 1998).

Associated Alterations of the Liver

Associated parenchymal alterations include hepatocyte ballooning, hepatocyte apoptosis, lobular infiltrates, perisinusoidal fibrosis, portal tract infiltrates (sometimes with interface lesions), portal tract fibrosis, and fibrosis of the hepatic terminal venules (El Hag et al. 1994). In few cases, the lobular fibrosis is diffuse (Duarte and Corbett 1987). Fibrotic changes, in particular pericellular fibrosis and portal tract fibrosis, appear to increase in frequency after treatment of visceral leishmaniasis (El Hag et al. 1994), but regression of diffuse intralobular fibrosis has also been reported (Corbett et al. 1993). Diffuse fibrosis of the liver with signs of remodeling (interpreted as "cirrhosis") occurring in conjunction with leishmaniasis had already been described in India in 1908 (Rogers 1908), but the pathogenic relationships are difficult to judge based on such observations. Rare instances of hepatic leishmaniasis are characterized by marked cytolysis and cholestasis, eventually leading to liver failure (Khaldi et al. 1990) or to fulminant hepatitis (Singh et al. 1995). Diffuse nodular regenerative hyperplasia has been seen in an HIV-infected patient with visceral leishmaniasis and suggested to be caused by deranged sinusoidal blood flow caused by enlarged infected macrophages (Fernandez-Miranda et al. 1993).

References

Agarwal DK, Baijal SS, Roy S, Mittal BR, Gupta R, Choudhuri G (1995) Percutaneous catheter drainage of amebic liver abscesses with and without intrahepatic biliary communication: a comparative study. Eur J Radiol 20:61–64

Agarwal S, Narayan S, Sharma S, Kahkashan E, Patwari AK (2006) Hemophagocytic syndrome associated with visceral leishmaniasis. Indian J Pediatr 73:445–446

Akilov OE, Khachemoune A, Hasan T (2007) Clinical manifestations and classification of Old World cutaneous leishmaniasis. Int J Dermatol 46:132–142

Ali IK, Clark CG, Petri WA (2008) Molecular epidemiology of amebiasis. Infect Genet Evol 8:698–707

Angarano G, Maggi P, Rollo MA, Larocca AM, Quarto M, Scalone A, Gradoni L (1998) Diffuse necrotic hepatic lesions due to visceral leishmaniasis in AIDS. J Infect 36:167–169

Artan R, Yilmaz A, Akçam M, Aksoy NH (2006) Liver biopsy in the diagnosis of visceral leishmaniasis. J Gastroenterol Hepatol 21:299–302

Bhattacharya SK, Sur D, Karbwang J (2006) Childhood visceral leishmaniasis. Indian J Med Res 123:353–356

Boquien Y, Lenne C (1962) Fistulization of amebic abscesses of the liver into the bile ducts (in French). Cah Rmf Bull Med Guide Pract Rev 76:281–286

Brondum NK, Hegedüs V (1975) Amoebic liver abscess with biliary fistula. Röfo 123:486–488

Bukhari AJ (2003) Ruptured amebic liver abscess. J Coll Phys Surg Pak 13:159–160

Bütke Y, Nazaroglu H, Mete A, Yilmaz F (2004) Visceral leishmaniasis with multiple nodular lesions of the liver and spleen: CT and sonographic findings. Abdom Imaging 29:82–84

Canalias J, Falco J, Martin J, Jurado I (1997) Macronodular hepatic granulomas due to visceral leishmaniasis in an

AIDS patient: imaging findings. J Comput Assist Tomogr 21:677–679
Cavalier-Smith T (1993) Kingdom protozoa and its 18 phyla. Microbiol Rev 57:953–994
Chang YT, Wu MS, Hung CC, Lin JT (2002) Amebic liver abscess with a hepatogastric fistula. Gastrointest Endosc 56:906
Corbett CE, Duarte MI, Bustamante SE (1993) Regression of diffuse intralobular liver fibrosis associated with visceral leishmaniasis. Am J Trop Med Hyg 49:616–624
Corliss JO (1984) The kingdom Protista and its 45 phyla. Biosystems 17:87–126
Duarte MJ, Corbett CEP (1987) Histopathological patterns of the liver involvement in visceral leishmaniasis. Rev Inst Med Trop Sao Paulo 29:131–136
Duarte MI, Mariano ON, Corbett CE (1989) Liver parenchymal cell parasitism in human visceral leishmaniasis. Virchows Arch A Pathol Anat Histopathol 415:1–16
El Hag et al. (1994) http://www.ncbi.nlm.nih.gov/pubmed/8063939
El-Safi S, Kheir MM, Bucheton B, Argiro L, Abel L, Dereure J, Dedet JP, Dessein A (2006) Genes and environment in susceptibility to visceral leishmaniasis. C R Biol 329:863–870
Faust DM, Marquay Markiewicz J, Danckaert A, Soubigou G, Guillen N (2011) Human liver sinusoidal endothelial cells respond to interaction with *Entamoeba histolytica* by changes in morphology, integrin signalling and cell death. Cell Microbiol 13:1091–1106
Fernandez-Miranda C, Colina F, Delgado JM, Lopez-Carreira M (1993) Diffuse nodular regenerative hyperplasia of the liver associated with human immunodeficiency virus and visceral leishmaniasis. Am J Gastroenterol 88:433–435
Gangneux JP, Donaghy L, Marty P (2006) Liver involvement during visceral leishmaniasis (in French). Gastroenterol Clin Biol 30:1027–1032
Genel F, Atlihan F, Targan S, Gulez N, Hacikara S, Karaca I (2004) Fulminant amoebiasis in a child with recurrent multiple amoebic liver abscesses and pleuropulmonary complications. Ann Trop Paediatr 24:267–269
Geramizadeh B, Jahangiri R, Moradi E (2011) Causes of hepatic granuloma: a 12-year single center experience from southern Iran. Arch Iran Med 14:288–289
Griffin J, Jennings C, Owens A (1983) Hepatic amoebic abscess communicating with the biliary tree. Br J Radiol 56:887–890
Guevara-Gonzelz L, Mendez-Sanchez N (2002) Amebic liver abscess open to the inferior vena cava. Ann Hepatol 1:90
Gutierrez et al. (1984) http://www.ncbi.nlm.nih.gov/pubmed/6696043
Haider Z, Raul A, Ahmed I (1975) Amoebic liver abscess presenting as obstructive jaundice: a case report. J Trop Med Hyg 78:131–132
Helk E, Bernin H, Ernst T, Ittrich H, Jacobs T, Heeren J, Tacke F, Tannich E, Lotter H (2013) TNFa-mediated liver destruction by Kupffer cells and Ly6Chi monocytes during *Entamoeba histolytica* infection. PLoS Pathog 9:e1003096
Hoffner RJ, Kilaghbian T, Esekogwu VI, Henderson SO (1999) Common presentation of amebic liver abscess. Ann Emerg Med 34:351–355
Hofman V, Marty P, Perrin C, Saint-Paul MC, Le Fichoux Y, Michiels JF, Glaichenhaus N et al (2000) The histological spectrum of visceral leishmaniasis caused by *Leishmania infantum* MON-1 in acquired immune deficiency syndrome. Hum Pathol 31:75–84
Hughes MA, Petri WA (2000) Amebic liver abscess. Infect Dis Clin N Am 14:565–582
Ibrarullah M, Agarwal DK, Baijal SS, Mittal BR, Kapoor VK (1994) Amebic liver abscess with intra-biliary rupture. HPB Surg 7:305–310
Kaur N, Gupta S, Minocha VR, Singh UR (2001) Massive amebic liver abscess – an unusual presentation. Indian J Gastroenterol 20:157–158
Khaldi F, Bennaceur B, Ben Othman H, Achouri E, Ayachi R, Regaieg R (1990) Severe forms of liver involvement in visceral leishmaniasis. Apropos of 7 cases (in French). Arch Fr Pediatr 47:257–260
Khan JA, Jafri SMV, Khan MA (1990) Obstructive jaundice: an unusual presentation of amoebic liver abscess. J Trop Med Hyg 93:194–196
Khan A, Pal KM, Khan HI (2011) Hepatic artery pseudoaneurysm; a rare complication of amoebic liver abscess. J Pak Med Assoc 61:839–840
Koshy A, Al-Azmi WM, Narayanan S, Grover S et al (2001) Leishmaniasis diagnosed by liver biopsy: management of two atypical cases. J Clin Gastroenterol 32:266–267
Kumar N, Sreenivas DV, Chowdhury V, Puri AS (1995) Amoebic liver abscess communicating with intrahepatic bile duct. Trop Gastroenterol 16:47–49
Kurland JE, Brann OS (2004) Pyogenic and amebic liver abscesses. Curr Gastroenterol Rep 6:273–279
Lodhi S, Sarwari AR, Muzammil M, Salam A, Smego RA (2004) Features distinguishing amoebic from pyogenic liver abscess: a review of 577 adult cases. Trop Med Int Health 9:718–723
Marazuela M, Moreno A, Yebra M, Cerezeo E, Gomez-Gesto C, Vargas JA (1991) Hepatic fibrin-ring granulomas: a clinicopathologic study of 23 patients. Hum Pathol 22:607–613
Marom D, Offer I, Tamary H, Jaffe CL, Garty BZ (2001) Hemophagocytic lymphohistiocytosis associated with visceral leishmaniasis. Pediatr Hematol Oncol 18:65–70
Meng XY, Wu JX (1994) Perforated amebic liver abscess: clinical analysis of 110 cases. South Med J 87:985–990
Misra SP, Dwivedi M, Misra V, Keswani NK (1997) Amoebic liver abscess communicating with intrahepatic bile ducts. Trop Dr 27:181–182
Moine, Mine, Dumas, Forestier M (1965) A. A case of traumatic hemobilia. B. A case of hemobilia after an amebic abscess of the liver (in French). Mem Acad Chir (Paris) 91:839–845

Moreno A, Marazuela M, Yebra M, Hernandez MJ, Hellin T, Montalban C, Vargas JA (1988) Hepatic fibrin-ring granulomas in visceral leishmaniasis. Gastroenterology 95:1123–1126

Nigam P, Gupta AK, Kapur KK, Sharan GR, Goyal BM, Joshi LD (1985) Cholestasis in amoebic liver abscess. Gut 26:140–145

Pahwa R, Singh T, Khurana N (2004) Hemophagocytic syndrome in malaria and kala-azar. Indian J Pathol Microbiol 47:348–350

Patterson DJ (1999) The diversity of eukaryotes. Am Nat 154(suppl):S96–S124

Petri WA (1996) Recent advances in amebiasis. Crit Rev Clin Lab Sci 33:1–37

Petri WA (2002) Pathogenesis of amebiasis. Curr Opin Microbiol 5:443–447

Preston TM (2003) The water-air interface: a microhabitat for amoebae. Eur J Protistol 39:385–398

Rahim KM, Ashkan MM (2007) Epidemiological, clinical and therapeutic features of pediatric kala-azar. Southeast Asian J Trop Med Public Health 38:626–630

Ralston KS, Petri WA (2011) Tissue destruction and invasion by *Entamoeba histolytica*. Trends Parasitol 27:254–263

Ramachandran S, Goonatillake HD, Induruwa PAC (1976) Syndromes in amoebic liver abscess. Br J Surg 63:220–225

Ready PD (2000) Sand fly evolution and its relationship to leishmania transmission. Mem Inst Oswaldo Cruz 95:589–590

Ritchie J, Harper A, Malykh V, Rowland J (2005) Amoebic liver abscess imitating metastatic caecal carcinoma. Age Ageing 34:527–528

Rogers L (1908) A peculiar intralobular cirrhosis of the liver produced by the protozoal parasites of Kala-azar. Ann Trop Med Parasitol 2:147–152

Sagnelli C, Di Martino F, Coppola N, Crisci A, Sagnelli E (2012) Acute liver failure: a rare clinical presentation of visceral leishmaniasis. New Microbiol 35:93–95

Salles JM, Moraes LA, Salles MC (2003) Hepatic amebiasis. Braz J Infect Dis 7:96–110

Sarda AK, Kannan R, Gupta A, Mahajan V, Jain PK, Prasad S (1998) Amebic liver abscess with jaundice. Surg Today 28:305–307

Sharma MP, Sarin SK (1987) Amoebic liver abscess in a North Indian hospital – current trends. Br J Clin Pract 41:789–793

Sharma BC, Agarwal N, Garg S, Kumar R, Sarin SK (2006) Endoscopic management of liver abscesses and cysts that communicate with intrahepatic bile ducts. Endoscopy 38:249–253

Shrimali R, Choudhary S (1969) Amoebic liver abscess with radiological demonstration of rupture into biliary tract (A rare entity – case report and review of literature). J Assoc Physicians India 17:435–437

Singh UK, Sinha RK, Sharma VK (1995) Fulminant hepatitis in Kala-azar. Indian J Pediatr 62:571–574

Sonsuz A, Basaranoglu M, Sentürk H, Celik AF, Tanriover V (1998) Amebic liver abscess of the caudate lobe with spontaneous rupture into the biliary tract. J Clin Gastroenterol 26:355–356

Stanley SL (2003) Amoebiasis. Lancet 361:1015–1034

Steinitz H, Talis B (1964) The occurrence of amoebae in the biliary tract (in Swedish). Dapim Refuiim 23:349–352

Stothard DR, Schroeder-Diedrich JM, Awwad MH, Gast RJ, Ledee DR, Rodriguez-Zaragoza S et al (1998) The evolutionary history of the genus *Acanthamoeba* and the identification of eight new 18S rRNA gene sequence types. J Eukaryotic Microbiol 45:45–54

Ventura-Juarez J, Jarillo-Luna RA, Fuentes-Aguilar E, Pineda-Vazquez A, Munoz-Fernandez L et al (2003) Human amoebic hepatic abscess: in situ interactions between trophozoites, macrophages, neutrophils and T cells. Parasite Immunol 25:503–511

Viana RL (1966) Amoebic liver abscess, draining into bile ducts. Gut 7:285–287

Vohra H, Kaur U, Sharma AK, Bhalla V, Bhasin D (2003) Effective human defense against *E. histolytica*: high amoebicidal activity of lymphocytes and monocytes in amoebic liver abscess patients until 3 months follow-up. Parasitol Int 52:193–202

Yanagisawa M, Kaneko M, Aizawa T, Michimata T, Takagi H, Mori M (2002) A case of amebic liver abscess complicated by hemobilia due to rupture of hepatic artery aneurysm. Hepatogastroenterology 49:375–378

Tumor-Like Parasitic Lesions of the Hepatobiliary Tract: Liver Flukes and Other Trematodes

133

Contents

Abstract

Tumor-like parasitic lesions and hepatobiliary cancers can be induced by several species of liver flukes. Fascioliasis is an infestation of the biliary tract by the common liver fluke, *Fasciola hepatica*, and by *Fasciola gigantica*. Liver flukes are an important cause of ruminant disease in Europe, Africa, and Latin America. *Fasciola* has a complex life cycle involving a distinct developmental stage in aquatic snails. Metacercariae released from snails are ingested by ruminants and humans who eat uncooked aquatic food such as watercress. Infestation of the human biliary tract by *Fasciola* results in a chronic, often severe and fibrosing cholangitis, sometimes ending up in hepatic inflammatory pseudotumor. Rarely, fascioliasis results in the formation of huge and multilocular lesions, mimicking hydatid disease. Clonorchiasis denotes an infestation with the oriental liver fluke, *Clonorchis sinensis*. Infestation rate is high in certain regions of East Asia and is associated with increased risk for cholangiocarcinoma. Species of the trematode genus *Opisthorchis* cause the zoonotic parasitic disease, opisthorchiasis, mainly involving *O. viverrini* and *O. felineus*. Similar to clonorchiasis, this parasitosis causes chronic bile duct inflammation, abnormal hyperregeneration of epithelia, and association with cholangiocarcinoma.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_133

Fascioliasis

Introduction

Fascioliasis (fasciolosis) is the infestation of the biliary tract by the common liver fluke, *Fasciola hepatica* (Linnaeus 1758), and by *Fasciola gigantica* (reviews: Chen and Mott 1990; Saba et al. 2004; Lim et al. 2008; Marcos et al. 2008). *F. hepatica* is a parasitic digenean flatworm of the family Fasciolidae. Liver flukes are an important cause of ruminant (cattle and sheep) disease mainly in Europe, Africa, and Latin America. *F. hepatica* expanded from its European origin due to the exportation of European livestock to colonize five continents, where it has adapted to other indigenous mammal species, such as camelids in Africa, aukenids in South America, and marsupials in Australia. Strikingly, the parasite is capable to adapt to new host species rather rapidly and along wide taxonomic mammal ranges. A second factor of importance in worldwide spread dynamics is the expansion of the intermediate vector, i.e., pond snails of the genera *Galba* and *Pseudosuccinea*.

F. gigantica is the main fasciolid species in Egypt and is also widely distributed in other parts of Africa. Intermediate/hybrid/introgressed forms between *F. hepatica* and *F. gigantica* have been described (Periago et al. 2008). Sequence analysis of rDNA supports the existence of the intermediate *Fasciola* between *F. hepatica* and *F. gigantica* in mainland China (Lin et al. 2007). The wide distribution of *F. hepatica* is related to climatic factors such as the availability of humid habitats subject to flooding offering niches for the intermediate vector, pond snails. Successful spread of fascioliasis is also related to the capacity of the parasite to adapt to highly various environments, including high altitude.

Human fascioliasis is a very old disease and has been detected (via coprolith analysis) down to Stone and Bronze Ages. It is at present emerging and reemerging in many countries, and as a distinct vector-borne infestation, it presents the widest known latitudinal, longitudinal, and altitudinal distribution. The most important health problems caused by fascioliasis are found in western Europe, the Caspian area (Iran and neighboring countries), Andean South America, the Caribbean (specifically Cuba), and northern Africa. The highest prevalences and intensities have been found in the Northern Bolivian Altiplano. Similar hyperendemic areas are Peru and Egypt. Interestingly, a global analysis of the distribution of human cases has shown that the expected correlation between animal and human fascioliasis only appears at the basic level and that other epidemiological patterns, e.g., high infestation intensities in females and children, have to be taken into account (reviews: Mas-Coma et al. 1999; Mas-Coma 2005).

The Parasite

Fasciola species are highly specialized members of digenean flatworms that, during evolution, probably migrated from Africa to Eurasia, with secondary colonization of Africa (Lotfy et al. 2008). The living adult liver fluke is a flat, roughly lancet-shaped worm of brownish-gray color, 18–50 mm long and with a width of 7–14 mm. The cone-shaped head region (the apical conus) is separated from the body by a shoulder. The oral sucker is situated at the top of the apical cone and the abdominal sucker at the cone's base. The body of the fluke displays markedly arborizing inner organs, mainly gonads and the uterus.

Parasitic Life Cycle

Fasciola hepatica has a complex life cycle, as it requires a distinct developmental stage in an aquatic snail. Embryonated eggs produced by the parasite in the host's bile ducts are passed in the feces. A fluke can produce up to 20,000 eggs per day, and it is estimated that a sheep with numerous flukes will deposit half a million eggs onto pasture per day. Part of the eggs can be stored for 8–16 weeks in the gallbladder of the mammalian host. Upon contact with sufficiently oxygenated water in the environment, the egg's operculum opens at temperatures more than

10 centigrades, and a larva is liberated which will develop into a mature miracidium. A miracidium is a free-living multicellular and ciliated larva which can actively swim. This larva searches its first host in the cycle, aquatic snails (pond snails). During this search, the miracidium does not feed, and in case it does to reach its host, it will not survive much beyond 24 h. The first hosts are snails of the genus *Galba*, *Pseudosuccinea*, and *Lymnaea*, most commonly *Galba truncatula* and *Pseudosuccinea columella*, and in Latin America *Lymnaea cubensis*, *L. viatrix*, and *L. neotropica* (family Lymnaeidae, pond snails). The miracidium enters the snail by use of a pair of large penetration glands which open near the apical papilla. Within the snail host, the parasite undergoes a complex cycle comprising sporocysts and rediae. After penetration of the snail host, the miracidium reaches the snail's digestive gland and develops, within about 14 days, into the second larval stage, the sporocyst larva. Rediae are highly active and motile larvae which feed on the snail's body fluid and cells. Rediae migrate to the digestive glands of the snail. Important for the further propagation of the parasite is the production of another swimming larva termed cercaria, looking like a tiny tadpole. It is produces by germ balls of daughter rediae in the winter period. Cercariae leave the mother or rediae through their birth pores. From the germ balls of each redia, 14–20 cercariae are produced. From the digestive glands of the host snails, cercariae pass into the pulmonary sac and then escape into the surrounding water. They actively swim through water bodies in pasture, capable of swimming 5 min to 1 h in summer. They attach on nearby vegetation, e.g., water plants at the borders of ponds, the tail is cast off, and the cercaria encysts to become a metacercaria. Together with plants, metacercariae are ingested by ruminants or by humans who eat uncooked food such as infested watercress. The low pH in the stomach of the final host prepares excystment, which then takes place in the duodenum, where the liberated juvenile parasites burrow through the intestinal wall into the peritoneal cavity. The juvenile parasite then finds contact with the liver surface, where it starts feeding on hepatic parenchyma (the hepatic phase or hepatic stage). The juvenile parasites browse on liver tissue for up to 5–6 weeks and then find their way to the lumina of bile ducts, where final maturation to flukes takes place (the biliary phase or biliary stage). Cross-fertilization between two mature flukes takes place in the bile duct lumen. Embryonated eggs are released through the gonopores and are transported by the bile into the intestinal tract and from there into the environment.

Clinical Features

The clinical presentation of fascioliasis is characterized by abdominal pain, fever, chills, weakness, pruritus, weight loss, and eventually muscle pain (Aksoy et al. 2006). The definitive diagnosis of fascioliasis is based on the presence of *Fasciola* eggs in a stool or gallbladder sample or on a positive serological test plus imaging findings indicating this parasitosis. In accordance with the evolution of disease, human fascioliasis is classified as acute and chronic disease. Acute disease is present if the duration of symptoms is less than 4 months and there are no motile echogenic images on the gallbladder at admission. Chronic disease is present if signs and symptoms persist for more than 4 months or there are motile echogenic images in the gallbladder (Saba et al. 2004). *F. hepatica* can localize to the lumen of the common bile duct (Kim et al. 2006) and may cause common bile duct obstruction (Dobrucali et al. 2004; Gulsen et al. 2006; Caprino et al. 2007), sometimes mimicking cholangiocarcinoma (Yalay et al. 2012). Biliary fascioliasis rarely causes hemobilia (Wong et al. 1985; Bahcecioglu et al. 2007). This complication may be due to bleeding bile duct ulcers induced by the parasite (Acuna-Soto and Braun-Roth 1987). Exceptionally, fascioliasis is associated with generalizer vasculitis (Llanos et al. 2006).

Hepatobiliary Alterations

Imaging findings are different in the hepatic stage vs. the biliary tract stage. During the hepatic stage,

flukes migrate through the liver substance and digest and consume hepatocytes and other liver cells, and they thus dig tunnels and caves where they stay for months. These alterations are mainly seen in peripheral, subcapsular parts of the liver, because this is the region where metacercariae penetrate the organ (Kabaalioglu et al. 2000; Maeda et al. 2008). Clusters of microabscesses arranged in tract-like fashion develop (burrow tracts; Han et al. 1993). These lesions are nodular or tubular hypodense foci. In contrast to pyogenic abscesses, necrotic cavitated lesions caused by *F. hepatica* do not coalesce to form large abscesses; rather, small necrotic lesions (so-called microabscesses; they are not true abscesses with accumulation of pus) are arranged in a serpentine fashion, the lesions starting at or close to the liver surface (the entry site), reflecting the complex feeding tract of the parasite within the liver (Lim et al. 2008; Figs. 1, 2, 3, and 4).

The tract-like hepatic tissue necrosis elicits granulation tissue and scarring, the reason why at imaging these tracts are seen for months or even years. Following necrosis of infested and inflamed bile ducts, well-demarcated cystic masses mimicking a necrotic cystic tumor may develop, containing greenish-yellow, bile-containing necrotic material and surrounded by dense fibrous tissue. These lesions can contain mummified adult worms and eggs (Kim et al. 1999a). On CT images, the entire migration and necrosis path may be visualized, accompanied by clustered small necrotic cavities seen as caves (Kim et al. 1999a; Lim et al. 2008). In a study of ten patients, CT revealed tubular branching lesions in five patients and nodular lesions, suggesting small abscesses in four (Aksoy et al. 2006). On MR images, three types of lesions have been identified, arranged in a tract-like fashion. The outermost area presents as an iso-signal area in T1-weighted images, with slightly higher signal intensity in T2-weighted images and diffuse enhancement after i.v. contrast. The second type is a well-defined low signal area in T1WI, not enhanced, and also shows low signal intensity in T2WI. The third type has low signal intensity in T1WI, not enhanced, and has high signal intensity in T2WI, similar to a fluid-containing lesion such as an abscess (Han et al. 1996). Rarely, the necrotic lesions at the parasite entry site at the liver surface may induce fistulization, with subsequent formation of subcapsular or perihepatic abscess.

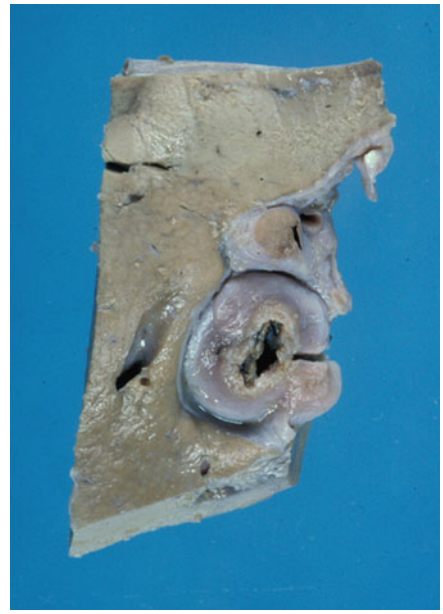

Fig. 1 Fascioliasis of the liver (*Fasciola hepatica* infestation). An inflamed bile duct with a thickened wall contains a thin and flat structure in the lumen, a liver fluke

Fig. 2 Cross-sectioned inflamed and fibrosed bile duct at higher magnification. The intraluminal leaflet-like parasite is well recognizable

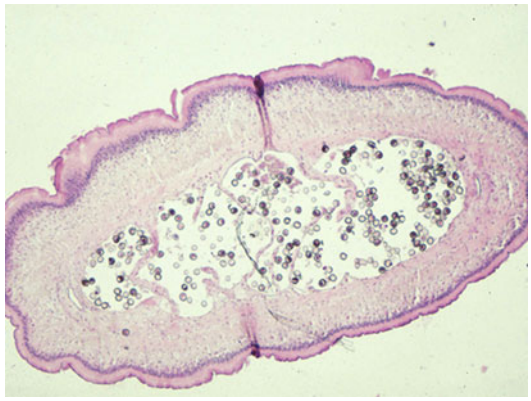

Fig. 3 Cross-sectioned *Fasciola hepatica*

Fig. 4 Hepatic fascioliasis. In this long-standing *Fasciola hepatica* infestation, the involved bile duct shows a marked ulcerating and fibrosing inflammation (fixed necropsy specimen)

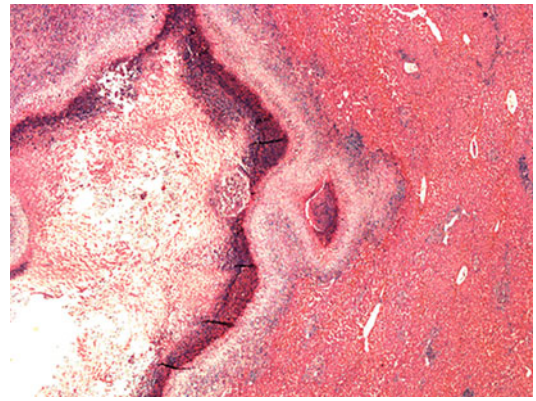

Fig. 5 Fascioliasis of the liver. *Fasciola* infestation can elicit bile duct destruction followed by abscess formation, often with a strong eosinophilic infiltration and epithelioid cell reaction (hematoxylin and eosin stain)

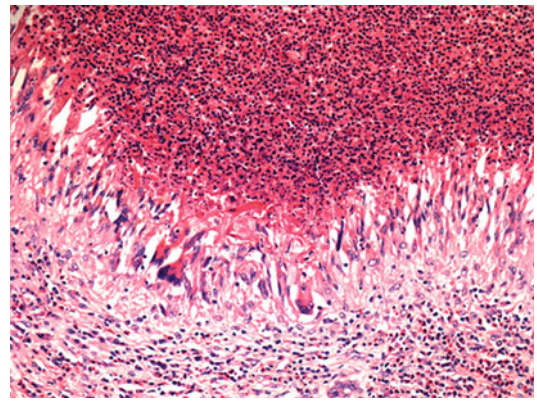

Fig. 6 Fascioliasis of the liver. The purulent exudate of this abscess is dominated by eosinophils ("eosinophil pus," eosinophilic abscess). The abscess is demarcated by epithelioid cells and giant cells. Increased numbers of eosinophils are also present in adjacent tissue (hematoxylin and eosin stain)

In the biliary stage, the parasites find their way to the lumina of the intrahepatic bile ducts, and later they may advance into the extrahepatic ducts and the gallbladder. Adult liver flukes are demonstrated on sonography, CT, or MR cholangiography as small intraductal profiles and sometimes as floating objects on sonography (Lim et al. 2007, 2008; Aminian et al. 2012). The parasites can be identified during ERCP (Dias et al. 1996), which also allows endoscopic extraction of living flukes (Ozer et al. 2003). Adult flukes promote hyperplastic and hypertrophic bile duct wall changes, resulting in a thickening of the walls detectable by sonography or CT (Bassily et al. 1989).

F. hepatica can induce an inflammatory reaction, ending up in hepatic pseudotumor and eosinophilic abscesses (Figs. 5 and 6; Cabanillas et al. 1989). Intrahepatic multiple ill-defined hypoattenuating lesions and filling defects of the lesion lumens may mimic intrahepatic cholangiocarcinoma (Adachi et al. 2005; Kim et al. 2005; Yalay et al. 2012). Rarely, *F. hepatica* infestation results in the formation of huge and multilocular lesions, mimicking hydatid disease (Maeda et al. 2008).

Clonorchiasis: A Parasitosis Highly Associated with Cholangiocarcinoma

Introduction

Clonorchiasis denotes infestation with the Chinese or oriental liver fluke, *Clonorchis sinensis*. Clonorchiasis is of major socioeconomic importance in parts of Asia, including China, Taiwan, Japan, Korea, and Vietnam (reviews: Lun et al. 2005; Rim 2005; Rana et al. 2007; Petney et al. 2013).

Epidemiology

Clonorchiasis is widely distributed in southern Korea, mainland China and Taiwan, Japan, northern Vietnam, and the easternmost part of Russia. Owing to increased migrations, clonorchiasis is also known in areas where Asian immigrants from endemic areas have settled. It has been estimated in a report of 1994 that about 17 million people were infested with oriental liver flukes, 9 million with *Opisthorchis viverrini*, 7 million with *Clonorchis sinensis*, and 1.5 million with *Opisthorchis felineus* (IARC 1994). In certain East Asian regions, the infestation rate with *C. sinensis* is still high. Among 3,080 consecutive Korean patients admitted with gastrointestinal disease, 12.9 % had clonorchiasis (Kim et al. 2009).

The Parasite

C. sinensis (Looss 1907) is a trematodan flatworm of the family Opisthorchiidae. The life cycle of *C. sinensis* has been well studied. Definitive hosts of this fluke comprise humans, dogs, cats, hogs, martens, badgers, weasels, mink, and rats. Egg discharge in the human feces is high in infested subjects, the average number of eggs per gram feces in one Chinese study being 3,055 (Liang et al. 2008). Embryonated eggs pass via feces into water bodies of the environment, where they are ingested by water snails of the genera *Parafossarulus* (China, Korea, Japan, eastern Russia), *Bithynia (*China), *Melanoides* (China), *Assiminea* (China), *Semisulcospira* (China), and *Tarebia* (China). Inside the snail, miracidia hatch from the ingested eggs. The miracidium develops into a sporocyst, inside which several asexual generations of rediae emerge. The rediae are the source of several rounds of cercariae, one miracidium therefore producing a large number of cercariae. The cercariae are free-swimming larvae which seek and penetrate the second intermediate host, freshwater fish of the cyprinid group, including the genera *Pseudorasbora*, *Gnathopogon*, *Pseudogobio*, *Pungtungia*, *Acheilognathus*, *Hemibarbus*, and *Sarcocheilichthys*. Inside fish muscle, the cercariae produce a protective metacercarial cyst, thus encapsulating the parasite body. When uncooked cyprinid fish are ingested by humans, acid-resistant metacercariae pass the stomach undigested to reach the small intestine. From here, metacercariae (or juveniles; "adolescariae") actively reach the orifice of the common bile duct and ascend the biliary tract. Experimental infestations in rodents have shown that the common bile duct is the only natural route taken by *C. sinensis* (Sun et al. 1968). Alternative ways seem to be possible, based on animal experiments with common bile duct ligation (Wykoff and Lepe 1957). In the bile duct lumina, the hermaphrodite worms mate and start producing eggs, eggs being delivered every 1–30 s.

Clinical Features

Clonorchiasis may be symptomatic or asymptomatic. Among 2,175 Chinese individuals having *C. sinensis* in their stools, 57.2 % showed symptomatic infestation (Liang et al. 2008). The spectrum of lesions induced by this fluke is complex and has been clinically summarized under the term oriental cholangiohepatitis, often with recurrent pyogenic cholangitis (Stunnell et al. 2006). The course of the disease often goes on for many years, owing to the longevity of the parasites, their lifetimes sometimes exceeding 20 years (Sun 1984). There is a clear relationship between parasite burden and the pattern of clinical

manifestations. Clinically, signs and symptoms may be mild and nonspecific, mainly in patients with small worm burdens (fewer than 100 flukes). Up to 40 % of the patients experience peripheral eosinophilia. Patients with greater parasite numbers (several hundred up to 1,000) often display malaise, diarrhea, fatigue, weight loss, fever, and chills. In contrast to Fascioliasis, *Clonorchis sinensis* is a fluke that chiefly inhabits the medium-sized and small intrahepatic bile ducts, often in a diffuse pattern and sometimes with formation of worm conglomerates. This constellation will determine the characteristic pattern of liver disease. The flukes induce bouts of intrahepatic cholangitis followed by typically multifocal periductal fibrosis and eventually liver atrophy. The inflammatory process induced by *C. sinensis* can induce reactive common bile duct masses (Oh and Kim 2010) or extend into the ampullary region and cause papillitis with obstructive jaundice (Lim et al. 2011). Patients with severe parasitosis may harbor up to 20,000 or more flukes and show attacks of severe cholangitis and obstructive jaundice. Cholangitis may end up with the formation of a hepatic parasitic abscess, mimicking intrahepatic cholangiocarcinoma (Jang et al. 2007). The flukes can also induce focal intrahepatic duct dilatation, mimicking intrahepatic cholangiocarcinoma (Kim et al. 2011). In the late stage, hepatosplenomegaly, portal hypertension, ascites, and biliary cancer may ensue. Clonorchis is also well known to cause pancreatitis (Balthazar and Lamb 1993; Kim 1999a) and cholecystitis/cholecystolithiasis (Qiao et al. 2012). *C. sinensis* has been shown to cause eosinophilic cholecystitis (Kim 1999b). Imaging is useful for diagnosis, but serology will be the decisive diagnostic step. Serodiagnosis is accomplished by assessing excretory-secretory antigen by ELISA (Choi et al. 2003) and a trematode-nematode pan-specific antigen expressed by *C. sinensis* (Chen et al. 2011). Other antigens which may serve in serodiagnosis comprise an excretory-secretory lysophosphatidic acid phosphatase homolog (Hu et al. 2007) and MYND-type tegumental zinc finger protein (Wang et al. 2010).

Pathology of Hepatobiliary Inflammatory and Hyperplastic Changes Associated with Clonorchiasis

C. sinensis causes, mostly at the level of small and intermediate intrahepatic bile ducts, chronic fibrosing inflammation associated with epithelial (cholangiocyte) hyperplasia, metaplastic changes, and epithelial dysplasia (Hou 1955; Sun 1984), also documented in experimental infestation in rodents (Lee et al. 1978; Hong et al. 1990) and the cat (Hou 1965). In the human host, macroscopic alterations in severe chronic infestation present as dilated intrahepatic bile ducts visible through the liver capsule already and being prominent on cut surface. Histology of these bile ducts reveals a lymphohistiocytic infiltration in the duct walls and surrounding the ducts, with or without prominent eosinophilia. Cholangiocyte epithelial hyperplasia is a hallmark of clonorchiasis, as is periductal fibrosis. Metaplasia of the cholangiocyte lining into mucin-producing cells occurs already early in infestation. These mucin-secreting cells may form glandular-like structures and may involve peribiliary glands, causing mucin-rich and sometimes viscid bile (Chou and Gibson 1970). Infestation of bile ducts may be associated with gallstone disease. Gallbladder stones in clonorchiasis can contain parasite eggs, this phenomenon being helpful in diagnostic procedures (Qiao et al. 2013).

Cholangiocarcinoma in Clonorchiasis

C. sinensis infestation is associated with cholangiocarcinoma, although the link is less strong than that for infestation with *Opisthorchis*. This relation has been recognized early in the literature, in fact as early as 1900 (Katsurada 1900; Watson-Wemyss 1919; Nauck and Liang 1928), and has since been confirmed in numerous observations and studies (Hou 1956; Belamaric 1973; Purtilo 1976; Chow and Allen 1978; Flavell 1981; Schwartz 1980, 1986; Chan and Lam 1987; IARC monograph 1994; Watanapa and Watanapa 2002). In 2009, infestation with *Clonorchis*

sinensis was classified as carcinogenic to humans (group 1 carcinogen) based on its involvement in the etiology of cholangiocarcinoma by the International Agency for Research on Cancer. Studies in Korea have shown that known areas of *C. sinensis* endemicity revealed high incidence rates of cholangiocarcinoma. From a meta-analysis, the summary odds ratio for cholangiocarcinoma due to *C. sinensis* infestation was 4.7, and overall about 10 % of cholangiocarcinomas in Korea were caused by chronic *C. sinensis* infestation (Shin et al. 2010). *C. sinensis* promotes the induction of cholangiocarcinoma during a two-step carcinogenesis (Lee et al. 1994). In carcinogenic pathways, products of the excretory-secretory system seem to cooperate with known environmental carcinogens such as dimethylnitrosamine (Pairojkul et al. 1991). For the elucidation of genes and gene products involved in carcinogenesis, the transcriptome of *C. sinensis* is currently studied in detail by the use of high-throughput sequencing (Young et al. 2010).

Infestation with *C. sinensis* induces characteristic alterations of the biliary tract mucosa, including cholangiocellular hyperplasia (Hou 1955; Sun 1984), sometimes of the papillary type (Kim et al. 1999b). Experimentally, it has been shown that cholangiocyte turnover is increased in clonorchiasis (Hong et al. 1993). It is thought that these hyperplastic alterations shift into dysplasia and from there to cholangiocarcinoma, which is significantly associated with clonorchiasis (Kim 1984a; Choi et al. 2004). Cholangiocarcinomas associated with clonorchiasis comprise almost the entire histological spectrum known for this tumor group, including mucinous cholangiocarcinoma (Shim et al. 2004), forms of intrahepatic/peripheral cholangiocarcinoma (Belamaric 1973; Ona and Dytoc 1991), hilar cholangiocarcinoma (Sher et al. 1989), and cholangiocarcinoma of the extrahepatic ducts (mostly located in the proximal third; Kim 2003a). Intraductal papillary neoplasms of the bile ducts have been found in clonorchiasis (Kim et al. 1989; Suh et al. 2000; Jang et al. 2008). These tumors of patients with clonorchiasis differ in their MUC expression from those of noninfested patients (Jang et al. 2008).

Gallbladder carcinoma has been observed in conjunction with clonorchiasis (Drinka and Sheeny 1985; Kim 2003b). Rarely, hepatocellular carcinoma has been detected in patients with clonorchiasis (Nakashima et al. 1977).

Pseudotumoral Hepatic Lesions Associated with *C. sinensis*

C. sinensis was found to be associated with solitary necrotic nodule of the liver (Tsui et al. 1992).

Opisthorchis viverrini

Introduction

Species of the trematode genus *Opisthorchis* cause the zoonotic parasitic disease, opisthorchiasis (reviews: Sripa 2003; Upatham and Vivanant 2003), one of the common forms of fish-borne zoonotic trematodiasis (review: Hung et al. 2013). The taxonomy of *Opisthorchis* species was first in state of some confusion (review: Kaewkes 2003). In 1908, Verdun and Bruyant noted that *Opisthorchis felineus* was found in Indochina. In 1911, worms were described, collected from the autopsy of two prisoners in Chiang Mai (Northern Thailand) as *O. viverrini* (Leiper 1911), whereas a later report (Kerr 1916) identified parasites in male Chiang Mai prisoners as *O. felineus*. In 1927, Prommas reported a single case of *O. felineus* from a human autopsy in Northern Thailand. In 1929, Bedier and Chesneau reported that *O. viverrini* was present in 23 % of 1,231 examinees in Thakhek and in 15 % of 523 persons in Vientiane, two Laotian cities. Today, it is settled that all cases of opisthorchiasis in Thailand, Laos, and Cambodia are caused by *O. viverrini*, while *O. felineus* is a parasite occurring in the more western parts of Asia and in Eastern Europe.

Epidemiology

O. viverrini infestation is predominantly found in Thailand, Laos, and Cambodia, whereas *O. felineus* is endemic in Western Siberia, Kazakhstan, Ukraine, parts of Eastern Europe, and Germany. *O. viverrini* exhibits a very heterogeneous distribution pattern in the target areas: it is, e.g., widely distributed in Northern Thailand, while it has a lower prevalence in Central Thailand, and opisthorchiasis as a disease does not seem to occur in Southern Thailand. It was estimated that 3.5 million persons in Thailand harbor *O. viverrini* (review: Smout et al. 2011a). The infestation begins at a very early age, with prevalence rapidly rising as a function of age, this rise being related to the increasing consumption of dishes prepared with raw fish. Owing to the longevity of the parasite (years to decades), infestation remains relatively constant through older host ages. Epidemiology of human infestation reveals marked seasonal differences. The largest number of human infestations occurs during the last portion of the rainy season and the first third of the dry season, when pond snails producing cercariae and cyprinids harboring the fluke metacercariae are very abundant. The construction of dams, ponds, irrigation systems, and roads has an impact on parasite-harboring water bodies (Sithithaworn et al. 2012b).

Opisthorchiasis shows a very high reinfection rate after successful therapy. In one study, 88.7 % of subjects having negative stools following praziquantel therapy were again positive within 1 year of treatment. Interestingly, moderate disease instead of low-level disease was more prevalent in reinfected subjects in comparison with the pretreatment situation (Upatham et al. 1988).

The Parasite

O. viverrini (synonym: *Distoma viverrini*) is a trematodan flatworm of the family Opisthorchiidae, which is paraphyletic to Heterophyidae. Recent molecular studies suggest that *O. viverrini* consists of two cryptic species with genetic microheterogeneity or even forms a species complex (Saijuntha et al. 2007; Sithithaworn et al. 2012a). Similar to *Fasciola* and *Clonorchis*, the adult worm has two main body parts, i.e., a headlike region and the body which is dominated by the genital organs. Overall, adult worms are flat and leaf shaped and almost transparent, however, with a slightly bile-like reddish color. The leaflike and flabby worms have a size range from 8.0 to 15.0 mm long by up to 4 mm wide. The size of worms collected from the human host is slightly larger than that from dogs or cats. The parasites have an impressive longevity, surviving up to 20 years or even more.

The life cycle of *O. viverrini* is similar to that of *Clonorchis sinensis*. It involves a snail as the first intermediate host, where asexual expansion of larval stages takes place, following by liberation of invasive cercariae which invade cyprinid fish as second intermediary hosts. For *O. viverrini*, 3 subspecies of *Bithynia siamensis* and 18 species of cyprinid fish are susceptible first and second intermediate hosts, respectively (Wykoff et al. 1965; Kaewkes 2003). *Bithynia siamensis* is only known snail species to be parasitized by *O. viverrini*. This snail ingests embryonated eggs released into water bodies, and within the snail, miracidia hatch which will then develop into a sporocyst, followed by asexual production of rediae and cercariae. Free-swimming and invasive cercariae infest cyprinid fish, where they locate in fins, skin, and muscles. Cyprinid genera known to act as second intermediary hosts comprise *Puntius*, *Puntioplites*, *Hampala*, *Labiobarbus*, *Cyclocheilichthys*, *Esomus*, *Mystacoleucus*, *Onychostoma*, *Osteochilus*, *Hypsibarbus*, and *Barbodes*. In Thailand, the most important intermediate fish hosts are *Puntius orphoides*, *Hampala dispar*, and *Cyclocheilichthys siaja*. These cyprinids inhabit numerous standing or flowing water bodies (including rice paddies, draining trenches, irrigation channels, and ponds) in Thailand and Laos and are caught in large quantities for food, dishes often prepared of raw or semi-fermented fish, vegetables, and spices, e.g., koi pla, a highly appreciated dish in rural parts of Thailand. The infested fish contain the encapsulated metacercariae of the

parasite, which upon ingestion are freed in the intestine of the definitive hosts. The natural definitive host for *O. viverrini* is *Prionailurus bengalensis* (a small fish-eating feline called leopard cat); other hosts include man, dogs, and domestic cats. Hatched metacercariae enter the papilla of Vater to ascend into the biliary tract. Adult worms live long (in the range of decades) and produce up to 200 eggs per day.

Clinical Features

The pattern of clinical presentation markedly resembles that of clonorchiasis (Wykoff et al. 1966; review: Mairiang and Mairiang 2003). It is estimated that about 80 % of infested individuals are asymptomatic, at least for extended time periods, but peripheral eosinophilia is commonly found. A typical acute stage as in *O. felineus* infestation does not occur with *O. viverrini*. Again, similar to clonorchiasis, the clinical features are linked to parasite burden. In asymptomatic weak infestation, 1,000 eggs or less are present in 1 g of feces. Heavy infestation is characterized by general malaise, epigastric and right upper quadrant pain, anorexia, diarrhea, weight loss, mild fever and eventually jaundice. In long-lasting infestations and with heavy parasite burdens, the gallbladder shows obstructive hydrops and is excluded (Sripa et al. 2003). As in clonorchiasis, flukes cause chronic and recurrent cholangitis followed by periductal fibrosis and biliary-type cirrhosis with ascites and eventually biliary tract cancer. In experimental hamster infestation, periductal fibrosis is correlated with TGF-beta activity and upregulation of matrix metalloproteinases and their inhibitor, TIMP (Prakobwong et al. 2009). Advanced periductal fibrosis correlates with elevated levels of interleukin-6 (Sripa et al. 2009). The source of interleukin-6 and interleukin-8 are the cholangiocytes, via upregulation of toll-like receptor 4 by excretory/secretory products of the fluke (Ninlawan et al. 2010). Apart from the clinical presentation and imaging findings, serology testing of antibodies directed against fluke or fluke larval-associated antigens is a decisive diagnostic procedure (reviews: Akai et al. 1994; Upatham and Vivanant 2003; Wongratanacheewin et al. 2003). *O. viverrini* also produces distinct metabolic products, the excretory-secretory antigens. One component (89 kDa) is copiously passed via feces, this antigen component being detectable by Mab-ELISA (Sirisinha et al. 1995).

Pathology

The pathology of hepatic *O. viverrini* infestation has been reviewed in detail (Sripa 2003). The livers of markedly infested livers are enlarged, sometimes more than double the normal. A dilatation of peripheral and in part subcapsular intrahepatic bile ducts is in evidence, these ducts usually showing a fibrotically thickened wall (Hitanant et al. 1987; Riganti et al. 1989). In early-stage intrahepatic bile duct disease, the histologic changes are discrete or even lacking. In significant chronic disease, epithelial hyperplasia ensues, often with formation of glandular/acinar structures (Riganti et al. 1989). There is a periductal infiltration of lymphocytes, macrophages, eosinophils, and some plasma cells. In this stage, progressive periductal fibrosis (PDF) develops, first with a loose and hypercellular connective tissue rich in glycosaminoglycans, followed by a dense and hypocellular fibrous tissue. Parasite-induced PDF can be identified by ultrasound examinations (Chamadol et al. 2014). In case parasite eggs are transferred to the hepatic parenchyma, a foreign body reaction is seen (Viranuvatti and Stitnimankarn 1972; Riganti et al. 1989). In addition to intrahepatic ducts, adult parasites may also be found in the gallbladder, extrahepatic ducts, and the pancreatic duct, the numbers of flukes found in the gallbladder ranging from few to more than 100 (Pungpak et al. 1985; Sithithaworn et al. 1991; Sripa et al. 2003). The gallbladder changes, characterized by hydrops, thickening of the wall owing to inflammation and fibrosis, and bile sludge are evident at imaging and sonography (Haswell-Elkins et al. 1991; Mairiang et al. 1992). Cholelithiasis is not frequent in *O. viverrini* infestation. In sludge and gallstones, parasite fragments and fluke eggs have been detected (Riganti et al. 1988).

Cholangiocarcinoma

O. viverrini is classified as a class I carcinogen due to the association between chronic *O. viverrini* infestation and cholangiocarcinoma (reviews: Kaewpitoon et al. 2008; Sripa et al. 2012), also analyzed in experimental animal models (Songserm et al. 2009). Numerous cases of cholangiocarcinoma associated with *O. viverrini* infestation have been reported (Elkins et al. 1990; Akai et al. 1994; Watanapa and Watanapa 2002). According to the 1994 report of the World Health Organization and the International Agency for Research on Cancer (IARC), an estimated 9 million persons were infested with *O. viverrini* and 1.7 million with *O. felineus*, and of these infested patients, a part will develop cholangiocarcinoma. These patients often present with jaundice (60 % in a Northeastern Thailand study), and this jaundice may be of the pure obstructive type, febrile obstructive jaundice, or jaundice associated with signs of acute cholangitis with fever. In one study from Thailand, more than two-thirds of the patients were male, and the mean age at diagnosis of cholangiocarcinoma was 48.8 years in males and 48.1 years in females (Bunyaratvej et al. 1981). A study published in 1988 showed that the incidence of cholangiocarcinoma was almost twice that of hepatocellular carcinoma in endemic areas of *O. viverrini* in Northeastern Thailand (Srivatanakul et al. 1988). As in clonorchiasis, several types of cholangiocarcinoma have been observed in opisthorchiasis, including peripheral cholangiocarcinoma, hilar/perihilar carcinomas, and carcinomas of the extrahepatic duct system. Genetic and environmental determinants of risk for *O. viverrini*-associated cholangiocarcinoma in Thailand have been analyzed (Honjo et al. 2005).

The molecular pathways leading from chronic fluke infestation of bile ducts to carcinogenic pathways are complex and involve mutagenic substances delivered from inflammatory cells (including reactive oxygen species), continuously augmented cholangiocyte regeneration associated with increased mutagenicity, and preneoplastic factors (parasite proteome) secreted by the parasite (Laha et al. 2007; Wongratanacheewin et al. 2003; Mulvenna et al. 2010). Exome sequencing of *O. viverrini*-associated cholangiocarcinoma revealed mutations of TP53 in 44.4 % of cases, KRAS in 16.7 %, SMAD4 in 16.7 %, and several newly implicated genes in 3.7–14.8 % of cases. The latter included inactivating mutations in MLL3, ROBO2, RNF4, and PEG3 and activating mutations in the GNAS oncogene (Ong et al. 2012). Exome sequencing identified distinct mutational patterns in liver fluke-related and fluke-non-related cholangiocarcinomas, indicating that different causative factors may induce distinct somatic changes (Chan-On et al. 2013). One of the proteases of *O. viverrini*, cathepsin F, has been suggested to be a factor for cholangiocarcinogenesis (Pinlaor et al. 2009). Ov-GRN-1, a granulin-like growth factor from *O. viverrini*, causes proliferation of mammalian host cells (Smout et al. 2009, 2011b). In vitro, components of the excretory-secretory product of *O. viverrini* increased cell proliferation of mouse fibroblasts (Thuwajit et al. 2004). Secreted *O. viverrini* glutathione S-transferase regulates cell proliferation through AKT and ERK pathways in cholangiocarcinoma cells (Daorueang et al. 2012). Several oxysterols have been identified in bile in the context of biliary tract infection, and there is evidence that these compounds play a role in biliary tract carcinogenesis (Kuver 2012). In extracts of *O. viverrini*, novel oxysterol derivatives have been detected, part of them having an estrogen core (Vale et al. 2013).

Opisthorchis felineus

Epidemiology

It is currently estimated that worldwide around 1.2 million persons are infested with *O. felineus* (WHO 1995). High prevalences are known in Belarus, Russia, and the Ukraine and in certain regions of Europe, specifically Germany and Greece (Bernhard 1985; Sänger et al. 1991; Hering-Hagenbeck and Schuster 1996; Tselepatiotis et al. 2003). Infestation with *O. felineus* has also been observed in Italy, from fish of two lakes, including the Lake Trasimeno

(Crotti et al. 2007), the patients having ingested raw tench filets (*Tinca tinca*) (Armignacco et al. 2008, 2013; Pozio et al. 2013).

The Parasite

O. felineus (Rivolta 1884) is a trematodan flatworm of the family Opisthorchiidae, discovered in 1884 by Sebastiano Rivolta in the liver of a cat. Five years later, the parasite was detected in the human host by Vongradov, who termed this parasite Siberian liver fluke. The life cycle of *O. felineus* was specified in 1934 (Vogel 1934). Embryonated eggs in water infest water snails of the genus *Bithynia* as first intermediate hosts (*Bithynia inflate*, *B. troschelii*, and *B. leachii*). Here, miracidia emerge which transform into sporocyst to produce rediae and cercariae, as specified in the paragraph on *O. viverrini*. It is estimated that 2 weeks are required between entry of the parasite into the human body and homing into the bile ducts.

Clinical Presentation

In contrast to *O. viverrini* infestation, *O. felineus* may cause an acute disease stage occurring 2–4 weeks after ingestion of raw fish, characterized by fever, malaise, arthralgia, lymphadenopathy, and skin rash (Brodov 1968; Belov 1971). Subacute and chronic disease is dominated by (recurrent) pyogenic cholangitis (Brazhnikova 1989) and liver abscesses (Kirilenko 1979). *O. felineus* can be identified by the use of PCR (Pauly et al. 2003).

Paragonimiasis of the Liver

Introduction

Paragonimiasis is an infestation caused by lung flukes of the genus *Paragonimus* (*P.*), mainly *P. westermani* which is endemic to Asia. Clinical manifestations of paragonimiasis, characterized by abdominal pain, fever, and diarrhea, are caused by the host's immune and inflammatory reactions toward the migrating parasites (Yokogawa 1969). Apart from the lung, other tissue and organ "terminals" are known, such as the CNS and the liver (extrapulmonary paragonimiasis).

The Parasite and Its Life Cycle

Paragonimus species belong to the platyhelminthic family, Troglotrematidae, and class Trematoda. The definitive hosts of *Paragonimus* species are mammals, and the life cycle requires two intermediate hosts, an aquatic snail and a crustacean. Humans attract the parasite by eating undercooked crustaceans containing infective metacercariae. Ingested metacercariae leave the intestine and move to the abdomen and then to lungs, where they transform into a cyst containing fertile adults. These are flukes with a size of 15 mm length and 8 mm width. In cysts, adult flukes cross-fertilize with one another. The cyst will rupture in the lung and liberated eggs are swallowed and transferred to the environment. In water bodies, eggs hatch and become ciliated miracidia which infect the first intermediate host, aquatic snails. The relevant gastropod taxa belong to the two superfamilies, Cerithoidea and Rissooidea (Davis et al. 1994). The second intermediate host, a crustacean, becomes infected by feeding on infected snails. *P. westermani* was the first human lung fluke described (in 1878 by Kerbert; Kim 1984b). Apart from *P. westermani*, several other species have been identified in the human host in Asia, including *P. skrjabini*, *P. heterotremus*, *P. compactus*, *P. hueit'ungensis*, *P. miyazakii*, *P. miyazakii manipurinus*, *P. cenocopiosis*, *siamensis*, and *P. pseudoheterotremus* (Wang et al. 2011; Intapan et al. 2012; Singh et al. 2012). In North America, *P. kellicotti* is an important species (North American paragonimiasis; Procop 2009; Lane et al. 2012).

Liver Involvement

Paragonimus larvae, starting their migration track in the intestinal wall, may get access to the liver and there produce parasitic mass lesions. These lesions, most of which consist of a marked inflammatory response, are macroscopic and spherical, mimicking malignancy at imaging (Lee et al. 1985, 1987; Singcharoen et al. 1988; Kim et al. 1991, 2002, 2004; Nabeshima et al. 1991; Takemasa et al. 2002; Cheng et al. 2010; Li et al. 2012). On CT images, the lesions usually present as clusters of small cysts with rim enhancement in peripheral parts of the liver (Kim et al. 2004). In one patient, a cystic lesion with internal septation and a peripheral thick capsule was found in the left liver lobe (Rha et al. 1999). Hepatic lesions are occasionally elongated form of tubular low-attenuated lesions of up to 2 cm in length. Laparoscopically, such lesions appear as a white, slightly elevated patch (Lee et al. 2005). In case of multifocal hepatic infestation, multiple low-density areas on CT can develop (Takemasa et al. 2002). In *P. skrjabini* infestation, large chronic eosinophilic liver abscesses with Charcot-Leyden crystalloids were found at autopsy (Hu et al. 1982). The parasite larvae sometimes stop their migration track on the liver surface, causing active hepatic capsulitis (Sasaki et al. 2002). In the setting of peritoneal parasite spread, multiple perihepatic adhesions can develop (Hu et al. 1982).

References

Acuna-Soto R, Braun-Roth G (1987) Bleeding ulcer in the common bile duct due to *Fasciola hepatica*. Am J Gastrenterol 82:560–562

Adachi S, Kotani K, Shimizu T, Tanaka K, Shimizu T, Okada K (2005) Asymptomatic fascioliasis. Intern Med 44:1013–1015

Akai PS, Pungpak S, Chaicumpa W, Viroj K, Bunnag D, Befus AD (1994) Serum antibody response to *Opisthorchis viverrini* antigen as a marker for opisthorchiasis-associated cholangiocarcinoma. Trans R Soc Trop Med Hyg 88:471–474

Aksoy DY, Kerimoglu U, Oto A, Ergüven S, Arslan S, Unal S, Batman F, Bayraktar Y (2006) *Fasciola hepatica* infection: clinical and computerized tomographic findings in ten patients. Turk J Gastroenterol 17:40–45

Aminian K, Rezayat KA, Shafaghi A, Tanhaeevash R (2012) Living *Fasciola hepatica* in biliary tree: a case report. Ann Hepatol 11:395–398

Armignacco O, Caterini L, Marucci G, Ferri F, Bernardini G, Natalini Raponi G, Ludovisi A et al (2008) Human illnesses caused by *Opisthorchis felineus* flukes. Italy Emer Infect Dis 14:1902–1905

Armignacco O, Ferri F, Gomez-Morales MA, Caterini L, Pozio E (2013) Cryptic and asymptomatic *Opisthorchis felineus* infections. Am J Trop Med Hyg 88:364–366

Bahcecioglu IH, Ataseven H, Aygen E, Coskun S, Kuzu N, Ilhan F (2007) *Fasciola hepatica* case with hemobilia. Acta Med (Hradec Kralove) 50:155–156

Balthazar EJ, Lamb T (1993) CT of *Clonorchis sinensis* pancreatitis. Int J Parasitol 14:189–194

Bassily et al. 1989. http://www.ncbi.nlm.nih.gov/pubmed/2566815

Belamaric J (1973) Intrahepatic bile duct carcinoma and *C. sinensis* infection in Hong Kong. Cancer 31:468–473

Belov GF (1971) Acute period in the clinical picture of opisthorchiasis. Clin Med 49:135–139

Bernhard K (1985) Detection of special kinds of helminths in East German citizens (in German). Angew Parasitol 26:223–224

Brazhnikova NA (1989) Opisthorchiasis-induced suppurative cholangitis. Klin Med 67:89–94

Brodov LE (1968) Acute period in the clinical picture of opisthorchiasis. Sov Med 31:91–94

Bunyaratvej S, Meenakanit V, Tantachamrun T, Srinawat P, Susilaworn P, Chongchitnan N (1981) Nationwide survey of major liver diseases in Thailand; analysis of 3305 biopsies as to year-end 1978. J Med Assoc Thai 64:432–439

Cabanillas A, Saenz P, Sanz A, Garcia G, Herraez J, Bénitez J (1989) *Fasciola hepatica*: hepatosplenic pseudotumor lesions. Report of 2 cases (in Spanish). Enferm Infecc Microbiol Clin 7:174–175

Caprino P, Ferranti F, Passa G, Quintiliani A (2007) A rare case of obstructive jaundice and cholecystitis in hepatic fascioliasis in Italy (in Italian). Chir Ital 59:891–894

Chamadol N, Pairojkul C, Khuntikeo N, Laopaiboon V, Loilome W, Sithihaworn P, Yongvanit P (2014) Histological confirmation of periductal fibrosis from ultrasound diagnosis in cholangiocarcinoma patients. J Hepatobiliary Pancreat Sci 21:316–322

Chan CW, Lam SK (1987) Diseases caused by liver flukes and cholangiocarcinoma. Baillieres Clin Gastroenterol 1:297–318

Chan-On W, Nairismägi ML, Ong CK, Lim WK, Dima S, Pairojkul C, Lim KH, McPherson JR et al (2013) Exome sequencing identifies distinct mutational

patterns in liver fluke-related and non-infection-related bile duct cancers. Nat Genet 45:1474–1478
Chen MG, Mott KE (1990) Progress in assessment of morbidity due to *Fasciola hepatica* infection. A review of recent literature. Trop Dis Bull 87:1–38
Chen et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/20865432
Cheng W, Li F, Zhuang H, Zhong D, Wu C, Zhu Z (2010) Hepatic paragonimiasis revealed by FDG PET/CT. Clin Nucl Med 35:726–728
Choi et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12666728
Choi D, Hong ST, Lim JH, Cho SY, Rim HJ, Ji Z, Yuan R, Wang S (2004) Sonographic findings of active *Clonorchis sinensis* infection. J Clin Ultrasound 32:17–23
Chou ST, Gibson JB (1970) The histochemistry of biliary mucins and the changes caused by infection with *Clonorchis sinensis*. J Pathol 101:185–197
Chow CW, Allen PW (1978) Test and teach number fourteen. Diagnosis: *Clonorchis sinensis* infestation of liver associated with cholangiocarcinoma. Pathology 130:174–175
Crotti D, D'Annibale ML, Crotti S (2007) Opistorchiasi autoctona del Lago Trasimeno (Perugia): descrizione di due episodi epidemic da *Opisthorichis felineus* e problematiche diagnostiche differenziali. Microbiol Med 42:36–41
Daorueang D, Thuwajit P, Roitrakul S, Laha T, Kaewkes S, Endo Y, Thuwajit C (2012) Secreted *Opisthorchis viverrini* glutathione S-transferase regulates cell proliferation through AKT and ERK pathways in cholangiocarcinoma. Parasitol Int 61:155–161
Davis GM, Chen CE, Kang ZB, Liu YY (1994) Snail hosts of *Paragonimus* in Asia and the Americas. Biomed Environ Sci 7:369–382
Dias LM, Silva R, Viana HL, Palhinhas M, Viana RL (1996) Biliary fascioliasis: diagnosis, treatment and follow-up by ERCP. Gastrointest Endosc 43:616–620
Dobrucali A, Yigitbasi R, Erzin Y, Sunamak O, Polat E, Yakar H (2004) *Fasciola hepatica* infestation as a very rare cause of extrahepatic cholestasis. World J Gastroenterol 10:3076–3077
Drinka P, Sheeny G (1985) *Clonorchis sinensis* infection associated with adenocarcinoma of the gallbladder and cystic duct. Wis Med J 84:16–18
Elkins DB, Haswell-Elkins MR, Mairiang E, Mairiang P, Sithithaworn P, Kaewkes S et al (1990) A high frequency of hepatobiliary disease and suspected cholangiocarcinoma associated with heavy *Opisthorchis viverrini* infection in a small community in Northeast Thailand. Trans R Soc Trop Med Hyg 84:715–719
Flavell DJ (1981) Liver-fluke infection as an aetiological factor in bile-duct carcinoma of man. Trans R Soc Trop Med Hyg 75:814–824
Gulsen MT, Savas MC, Koruk M, Kadayifci A, Demirci F (2006) Fascioliasis: a report of five cases presenting with common bile duct obstruction. Net J Med 64:17–19
Han JK, Choi BI, Cho JM et al (1993) Radiological findings of human fascioliasis. Abdom Imaging 18:261–264
Han JK, Han D, Choi BI, Han MC (1996) MR findings in human fascioliasis. Trop Med Int Health 1:367–372
Haswell-Elkins et al. 1991. http://www.ncbi.nlm.nih.gov/pubmed/1945529
Hering-Hagenbeck S, Schuster R (1996) A focus of opisthorchiidosis in Germany. Appl Parasitol 37:260–265
Hong ST, Huh S, Kho WG, Ryu JR, Chai JY, Lee SH, Kim EJ (1990) Changes of histopathological and serological findings of the liver after treatment in rabbit clonorchiasis. Seoul J Med 31:117–127
Hong ST, Kho WG, Kim WH, Chai JY, Lee SH (1993) Turnover of biliary epithelial cells in *Clonorchis sinensis* infected rats. Korean J Parasitol 31:83–89
Honjo S, Srivatanakul P, Sriplung H, Kikukawa H, Hanai S, Uchida K, Todoroki T et al (2005) Genetic and environmental determinants of risk for cholangiocarcinoma via *Opisthorchis viverrini* in a densely infested area in Nakhon Phanom, northeast Thailand. Int J Cancer 117:854–860
Hou PC (1955) The pathology of *Clonorchis sinensis* infestation of the liver. J Pathol Bacteriol 70:53–64
Hou PC (1956) The relationship between primary carcinoma of the liver and infestation with *Clonorchis sinensis*. J Pathol Bacteriol 72:239–246
Hou PC (1965) Pathological changes in the intrahepatic bile ducts of cats (*Felis catus*) infested with *Clonorchis sinensis*. J Pathol Bacteriol 89:357–364
Hu X, Feng R, Zheng Z, Liang J, Wang H, Lu J (1982) Hepatic damage in experimental and clinical paragonimiasis. Am J Trop Med Hyg 31:1148–1155
Hu F, Yu X, Ma C, Zhou Z, Li Y, Lu F, Xu J, Wu Z, Hu X (2007) *Clonorchis sinensis*: expression, characterization, immunolocalization and serological reactivity of one excretory/secretory antigen-LPAP homologue. Exp Parasitol 117:157–164
Hung NM, Madsen H, Fried B (2013) Global status of fishborne zoonotic trematodiasis in humans. Acta Parasitol 58:231–258
Intapan PM, Sanpool O, Thanchomnang T, Imtawil K, Pongchaiyakul C, Nawa Y, Maleewong W (2012) Molecular identification of a case of *Paragonimus pseudoheterotremus* infection in Thailand. Am J Trop Med Hyg 87:706–709
IARC (International Agency for Research on Cancer) (1994) Infection with liver flukes (*Opisthorchis viverrini*, *Opisthorchis felineus* and *Clonorchis sinensis*). IARC Monogr Eval Carcinog Risks Hum 61:21–175
Jang YJ, Byun JH, Yoon SE, Yu E (2007) Hepatic parasitic abscess caused by clonorchiasis: unusual CT findings of clonorchiasis. Korean J Radiol 8:70–73
Jang KT, Hong SM, Lee KT, Lee JG, Choi SH, Heo JS, Choi DW, Choi D, Lim JH (2008) Intraductal papillary

neoplasm of the bile duct associated with *Clonorchis sinensis* infection. Virchows Arch 453:589–598
Kabaalioglu A, Cubuk M, Senol U et al (2000) Fascioliasis: US, CT and MRI findings with new observations. Andom Imaging 25:400–404
Kaewkes 2003. http://www.ncbi.nlm.nih.gov/pubmed/14611872
Kaewpitoon N, Kaewpitoon SJ, Pengsaa P, Sripa B (2008) *Opisthorchis viverrini*: the carcinogenic human liver fluke. World J Gastroenterol 14:666–674
Katsurada F (1900) Beitrag zur Kenntnis des *Distomum spatulatum*. Beitr Pathol Anat Allg Path 28:479–505
Kerr AFG (1916) Intestinal parasites of northern Siam. Trans Soc Trop Med 9:82–89
Kim YI (1984a) Liver carcinoma and liver fluke infection. Arzneimittelforsch 34:1121–1126
Kim DC (1984b) *Paragonimus westermani*: life cycle, intermediate hosts, transmission to man and geographical distribution in Korea. Arzneimittelforschung 34:1180–1183
Kim YH (1999a) Pancreatitis in association with *Clonorchis sinensis* infestation: CT evaluation. AJR Am J Roentgenol 172:1293–1296
Kim YH (1999b) Eosinophilic cholecystitis in association with clonorchiasis sinensis infestation in the common bile duct. Clin Radiol 54:552–554
Kim YH (2003a) Extrahepatic cholangiocarcinoma associated with clonorchiasis: CT evaluation. Abdom Imaging 28:68–71
Kim YH (2003b) Carcinoma of the gallbladder associated with clonorchiasis: clinicopathologic and CT evaluation. Abdom Imaging 28:83–86
Kim YI, Yu ES, Kim ST (1989) Intraductal variant of peripheral cholangiocarcinoma of the liver with *Clonorchis sinensis* infection. Cancer 63:1562–1566
Kim SL, Kim SE, Lee KS, Cho JG, Jang MY, Kim JM (1991) A case of liver paragonimiasis. Korean J Intern Med 41:140–145
Kim KA, Lim HK, Kim SH, Lee WJ, Lim JH (1999a) Necrotic granuloma of the liver by human fascioliasis: imaging findings. Abdom Imaging 24:462–464
Kim KH, Kim CD, Lee HS, Lee SJ, Jeen YT, Chun HJ, Song CW, Lee SW, Um SH et al (1999b) Biliary papillary hyperplasia with clonorchiasis resembling cholangiocarcinoma. Am J Gastroenterol 94:514–517
Kim DM, Chung JP, Park WI, Park YN, Park SW, Lee SJ, Song SY, Lee KS, Chung JB et al (2002) A case of hepatic paragonimiasis combined with intrahepatic bile duct stones. Korean J Gastroenterol 39:133–136
Kim EA, Juhng SK, Kim HW, Kim GD, Lee YW, Cho HJ, Won JJ (2004) Imaging findings of hepatic paragonimiasis: a case report. J Korean Med Sci 19:759–762
Kim YH, Kang KJ, Kwon JH (2005) Four cases of hepatic fascioliasis mimicking cholangiocarcinoma (in Korean). Korean J Hepatol 11:169–175
Kim JC, Lee SK, Seo DW, Lee SS, Kim MH (2006) *Fasciola hepatica* in the common bile duct. Gastrointest Endosc 63:501
Kim et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19115472
Kim BG, Kang DH, Choi CW, Kim HW, Lee JH, Kim SH, Yeo HJ, Lee SY (2011) A case of clonorchiasis with focal intrahepatic duct dilatation mimicking an intrahepatic cholangiocarcinoma. Clin Endosc 44:55–58
Kirilenko MP (1979) Early complications after a gastric resection for peptic ulcer combined with late phase of opisthorchiasis. Vestn Klin Im II Grek 122:7–11
Kuver R (2012) Mechanisms of oxysterol-induced disease: insights from the biliary system. Clin Lipidol 7:537–548
Laha T, Pinlaor P, Mulvenna J, Sripa B, Sripa M, Smout MJ, Gasser RB, Brindley PJ et al (2007) Gene discovery for the carcinogenic human liver fluke, *Opisthorchis viverrini*. BMC Genomics 8:189
Lane MA, Marcos LA, Onen NF, Demertzis LM, Hayes EV, Davila SZ, Nurutdinova DR et al (2012) Paragonimus kellicotti flukes in Missouri, USA. Emerg Infect Dis 18:1263–1267
Lee SH, Shim TS, Lee SM, Chi JG (1978) Studies on pathological changes of the liver in albino rats infected with *Clonorchis sinensis*. Korean J Parasitol 16:148–155
Lee JS, Jung TJ, Cho SY, Huh SC, Chun HI, Um SJ (1985) A case of liver paragonimiasis. Korean J Intern Med 29:294–297
Lee HK, Kang MW, Kim JH, Yeo HS, Park HB (1987) A case of extrapulmonary paragonimiasis involving liver and cecum. Kor J Gastrointest Endosc 7:65–70
Lee JH, Yang HM, Bak UB, Rim HJ (1994) Promoting role of *Clonorchis sinensis* infection on induction of cholangiocarcinoma during two-step carcinogenesis. Korean J Parasitol 32:13–18
Lee HJ, Choi YW, Kim SM, Lee TH, Im EH, Huh KC, Na MJ, Kang YW (2005) Familial infestation of *Paragonimus westermani* with peritonitis and pleurisy. Kor J Gastreonterol 46:242–246
Leiper RT (1911) Notes on the occurrence of parasites presumably rare in man. J Lond Sch Trop Med 1:16–19
Li XM, Yu JQ, He D, Peng LQ, Chu ZG, Chen DD, Luo Y (2012) CT evaluation of hepatic paragonimiasis with simultaneous duodenal or splenic involvement. Clin Imaging 36:394–397
Liang SD, Wu YR, Pan YL (2008) Analysis on 2175 admitted cases of *clonorchis sinensis* in Guigang City (in Chinese). Zhongguo Ji Sheng Chong Xue Ji Sheng Chong Bing Za Zhi 26:374–375
Lim JH, Kim SY, Park CM (2007) Parasitic diseases of the biliary tract. AJR Am J Roentgenol 188:1596–1603
Lim et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/17934771
Lim JU, Joo KR, Shin HP, Cha JM, Lee JI, Lim SJ (2011) Obstructive jaundice caused by *Clonorchis*-associated duodenal papillitis: a case report. J Korean Med Sci 26:135–137
Lin RQ, Dong SJ, Nie K, Wang CR, Song HQ, Li AX, Huang WY, Zhu XQ (2007) Sequence analysis of the

first internal transcribed spacer of rDNA supports the existence of the intermediate *Fasciola* between *F. hepatica* and *F. gigantica* in mainland China. Parasitol Res 101:813–817

Llanos C, Soto L, Sabugo F, Gallegos I, Valenzuela O, Verdaguer J, Cuchacovich M (2006) Systemic vasculitis associated with *Fasciola hepatica* infection. Scand J Rheumatol 35:143–146

Lotfy WM, Brant SV, DeJong RJ, Le TH, Demiaszkiewicz A, Rajapakse RP, Perera VB et al (2008) Evolutionary origins, diversification, and biogeography of liver flukes (Digenea, Fasciolidae). Am J Trop Med Hyg 79:248–255

Lun ZR, Gasser RB, Lai DH, Li AX, Zhu XQ, Yu XB, Fang YY (2005) Clonorchiasis: a key foodborne zoonosis in China. Lancet Infect Dis 5:31–41

Maeda T, Yamada H, Akao N, Iga M, Endo T, Koibuchi T, Nakamura T, Odawara T et al (2008) Unusual radiological findings of *Fasciola hepatica* infection with huge cystic and multilocular lesions. Intern Med 47:449–452

Mairiang E, Mairiang P (2003) Clinical manifestation of opisthorchiasis and treatment. Acta Trop 88:221–227

Mairiang et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1311966

Marcos et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18725803

Mas-Coma S (2005) Epidemiology of fascioliasis in human endemic areas. J Helminthol 79:207–216

Mas-Coma MS, Esteban JG, Bargues MD (1999) Epidemiology of human fascioliasis: a review and proposed new classification. Bull World Health Organ 77:340–346

Mulvenna J, Sripa B, Brindley PJ, Gorman J, Jones MK, Colgrave ML, Jones A, Nawaratna S et al (2010) The secreted and surface proteomes of the adult stage of the carcinogenic human liver fluke *Opisthorchis viverrini*. Proteomics 10:1063–1078

Nabeshima K, Inoue T, Sekiya R et al (1991) Intrahepatic paragonimiasis – a case report. Jpn J Parasitol 40:296–300

Nakashima T, Sakamoto K, Okuda K (1977) A minute hepatocellular carcinoma found in a liver with *clonorchis sinensis* infection: report of two cases. Cancer 39:1306–1311

Nauck EG, Liang B (1928) Primärer Leberkrebs und *Clonorchis*-Infektion. Arch Schiffs Tropenhyg 32:109–112

Ninlawan K, O'Hara SP, Splinter PL, Yongvanit P, Kaewkes S, Surapaitoon A, LaRusso NF et al (2010) *Opisthorchis viverrini* excretory/secretory products induce toll-like receptor 4 upregulation and production of interleukin 6 and 8 in cholangiocyte. Parasitol Int 59:616–621

Oh JH, Kim HG (2010) A case of clonorchiasis presenting as common bile duct mass (in Korean). Korean J Gastroenterol 56:211–213

Ona FV, Dytoc JN (1991) *Clonorchis*-associated cholangiocarcinoma: a report of two cases with unusual manifestations. Gastroenterology 101:831–839

Ong CK, Subimerb C, Pairojkul C, Wongkham S, Cutcutache I, Yu W, McPherson JR et al (2012) Exome sequencing of liver fluke-associated cholangiocarcinoma. Nat Genet 44:690–693

Ozer B, Serin E, Gümürdülü Y, Gür G, Yilmaz U, Boyacioglu S (2003) Endoscopic extraction of living *Fasciola hepatica*: case report and literature review. Turk J Gastroenterol 14:74–77

Pairojkul C, Shirai T, Hirohashi S, Thamavit W, Bhudhisawat W, Uttaravicien T, Itoh M, Ito N (1991) Multistage carcinogenesis of the liver-fluke-associated cholangiocarcinoma in Thailand. Princess Takamatsu Symp 22:77–86

Pauly A, Schuster R, Steuber S (2003) Molecular characterization and differentiation of opisthorchiid trematodes of the species *Opisthorchis felineus* (Rivolta, 1884) and Metorchis bilis (Braun, 1790) using polymerase chain reaction. Parasitol Res 90:409–414

Periago MV, Valero MA, El Sayed M, Ashrafi K, El Wakeel A, Mohamed MY, Desquesnes M et al (2008) First phenotypic description of *Fasciola hepatica*/*Fasciola gigantica* intermediate forms from the human endemic area of the Nile Delta, Egypt. Infect Genet Evol 8:51–58

Petney TN, Andrews RH, Saijuntha W, Wenz-Mücke A, Sithithaworn P (2013) The zoonotic, fish-borne liver flukes *Clonorchis sinensis*, *Opisthorchis felineus* and *opisthorchis viverrini*. Int J Parasitol 43:1031–1046

Pinlaor P, Kaewpitoon N, Laha T, Sripa B, Kaewkes S, Morales ME, Mann VH, Parriott SK et al (2009) Cathepsin F cysteine protease of the human liver fluke. *Opisthorchis viverrini*. PLoS Negl Trop Dis 3, e398

Pozio E, Armignacco O, Ferri F, Morales MA (2013) *Opisthorchis felineus* an emerging infection in Italy and its implication for the European Union. Acta Trop 126:54–62

Prakobwong S, Pinlaor S, Yongvanit P, Sithithaworn P, Pairojkul C, Hiraku Y (2009) Time profiles of the expression of metalloproteinases, tissue inhibitors of metalloproteinases, cytokines and collagens in hamsters infected with *Opisthorchis viverrini* with special reference to peribiliary fibrosis and liver injury. Int J Parasitol 39:825–835

Procop GW (2009) North American paragonimiasis (caused by Paragonimus kellicotti) in the context of global paragonimiasis. Clin Microbiol Rev 22:415–446

Pungpak et al. 1985. http://www.ncbi.nlm.nih.gov/pubmed/4095605

Purtilo DT (1976) Clonorchiasis and hepatic neoplasms. Trop Geogr Med 28:21–27

Qiao T, Ma RH, Luo ZL, Zheng PM (2012) Cholecystolithiasis is associated with *Clonorchis sinensis* infection. PLoS One 7, e42471

Qiao T, Ma RH, Luo XB, Zheng PM, Luo ZL, Vang LQ (2013) Microscopic examination of gallbladder stones improves rate of detection of *Clonorchis sinensis* infection. J Clin Microbiol 51:2551–2555

Rana SS, Bhasin DK, Nanda M, Singh K (2007) Parasitic infestations of the biliary tract. Curr Gastroenterol Rep 9:156–164

Rha SE, Ha HK, Kim JG, Choi BI, Kim PN, Lee MG, Shim JC, Yu E, Auh YH (1999) CT features of intraperitoneal manifestations of parasitic infestation. AJR Am J Roentgenol 172:1289–1292

Riganti et al. 1989. http://www.ncbi.nlm.nih.gov/pubmed/2772709

Rim HJ (2005) Clonorchiasis: an update. J Helminthol 79:269–281

Saba R, Korkmaz M, Inan D, Mamikoglu L, Turhan O, Günseren F, Cervikol C, Kabaalioglu A (2004) Human fascioliasis. Clin Microbiol Infect 10:385–387

Saijuntha W, Sithihaworn P, Wongkham S, Laha T, Pipitgool V, Tesana S, Chilton NB et al (2007) Evidence of a species complex within the food-borne trematode *Opisthorchis viverrini* and possible co-evolution with their first intermediate hosts. Int J Parasitol 37:695–703

Sänger R, Möller FW, Lafrenz M, Ziegler K (1991) An endemic focus of *Opisthorchis felineus* in Mecklenburg-Pommerania/Germany. In: Proc. From the 1st German Congress for Infectious and Tropical medicine, Berlin

Sasaki M, Kamiyama T, Yano T, Nakamura-Uchiyama F, Nawa Y (2002) Active hepatic capsulitis caused by *Paragonimus westermani* infection. Intern Med 41:661–663

Schwartz DA (1980) Helminths in the induction of cancer: *Opisthorchis viverrini*, *Clonorchis sinensis* and cholangiocarcinoma. Trop Geogr Med 32:95–100

Schwartz DA (1986) Cholangiocarcinoma associated with liver fluke infection: a preventable source of morbidity in Asian immigrants. Am J Gastroenterol 81:76–79

Sher L, Iwatsuki S, Lebeau G, Zajko AB (1989) Hilar cholangiocarcinoma associated with clonorchiasis. Dig Dis Sci 34:1121–1123

Shim HS, Lim BJ, Kim MJ, Lee WJ, Park C, Park YN (2004) Mucinous cholangiocarcinoma associated with *Clonorchis sinensis* infestation: a case report (in Korean). Korean J Hepatol 10:223–227

Shin HR, Oh JK, Lim MK, Shin A, Kong HJ, Jung KW, Won YJ, Park S, Park SJ, Hong ST (2010) Descriptive epidemiology of cholangiocarcinoma and clonorchiasis in Korea. J Korean Med Sci 25:1011–1016

Singcharoen T, Rawd-Aree P, Baddeley H (1988) Computed tomography findings in disseminated paragonimiasis. Br J Radiol 61:83–86

Singh TS, Sugiyama H, Rangsiruji A (2012) Paragonimus & paragonimiasis in India. Indian J Med Res 136:192–204

Sirisinha S, Chawengkirttikul R, Haswell-Elkins MR, Elkins DB, Kaewkes S, Sithithaworn P (1995) Evaluation of a monoclonal antibody-based enzyme-linked immunosorbent assay for the diagnosis of *Opisthorchis viverrini* infection in endemic area. Am J Trop Med Hyg 52:521–524

Sithithaworn et al. 1991. http://www.ncbi.nlm.nih.gov/pubmed/1801350

Sithithaworn P, Andrews RH, Petney TN, Saijuntha W, Laoprom N (2012a) The systematics and population genetics of *Opisthorchis viverrini* sensu lato: implications in parasite epidemiology and bile duct cancer. Parasitol Int 61:32–37

Sithithaworn P, Ziegler AD, Grundy-Warr C, Andrews RH, Petney TN (2012b) Changes to the life cycle of liver flukes: dams, roads, and ponds. Lancet Infect Dis 12:588

Smout MJ, Laha T, Mulvenna J, Sripa B, Suttiprapa S, Jones A, Brindley PJ, Loukas A (2009) A granulin-like growth factor secreted by the carcinogenic liver fluke, *Opisthorchis viverrini*, promotes proliferation of host cells. PLoS Pathog 5, e1000611

Smout MJ, Sripa B, Laha T, Mulvenna J, Gasser RB, Young ND, Bethony JM, Loukas A (2011a) Infection with the carcinogenic human liver fluke, *Opisthorchis viverrini*. Mol Biosyst 7:1367–1375

Smout MJ, Mulvenna JP, Jones MK, Loukas A (2011b) Expression, refolding and purification of Ov-GRN-1, a granulin-like growth factor from the carcinogenic liver fluke, that causes proliferation of mammalian host cells. Protein Expr Purif 79:263–270

Songserm N, Prasongwattana J, Sithihaworn P, Sripa B, Pipitkool V (2009) Cholangiocarcinoma in experimental hamsters with long-standing *Opisthorchis viverrini* infection. Asian Pac J Cancer Prev 10:299–302

Sripa B (2003) Pathobiology of opisthorchiasis: an update. Acta Trop 88:209–220

Sripa B, Haswell-Elkins MR, Sinawat P (2003) Histological analysis of gallbladder diseases in relation to opisthorchiasis in endemic areas of Thailand. Acta Trop 88:239–246

Sripa B, Mairiang E, Thinkhamrop B, Laha T, Kaewkes S, Sithithaworn P, Tessana S et al (2009) Advanced periductal fibrosis from infection with the carcinogenic human liver fluke *Opisthorchis viverrini* correlates with elevated levels of interleukin-6. Hepatology 50:1273–1281

Sripa B, Brindley PJ, Mulvenna J, Laha T, Smout MJ, Mairiang E, Bethony JM, Loukas A (2012) The tumorigenic liver fluke *Opisthorchis viverrini* – multiple pathways to cancer. Trends Parasitol 28:395–407

Srivatanakul P, Sontipong S, Chotiwan P, Parkin DM (1988) Liver cancer in Thailand: temporal and geographic variations. J Gastroenterol Hepatol 3:413–420

Stunnell H, Buckley O, Geoghegan T, Torreggiani WC (2006) Recurrent pyogenic cholangitis due to chronic infestation with *Clonorchis sinensis*. Eur Radiol 16:2612–2614

Suh KS, Roh HR, Koh YT, Lee KU, Park YH, Kim SW (2000) Clinicopathologic features of the intraductal growth type of peripheral cholangiocarcinoma. Hepatology 31:12–17

Sun T (1984) Pathology and immunology of *Clonorchis sinensis* infection of the liver. Ann Clin Lab Sci 14:208–215

Sun T, Chou ST, Gibson JB (1968) Route of entry of *Clonorchis sinensis* to the mammalian liver. Exp Parasitol 22:346–351

Takemasa H, Saito K, Nakayamada S, Kanazawa T, Tanaka Y (2002) A case of Paragonimiasis westermani complicated with migrating subcutaneous induration and multiple involvement of the liver (in Japanese). Kansensho-gaku Zasshi 76:594–599

Thuwajit C, Thuwjit P, Kaewkes S, Sripa B, Uchida K, Miwa M, Wongkham S (2004) Increased cell proliferation of mouse fibroblast NIH-3T3 in vitro induced by excretory/secretory product(s) from *Opisthorchis viverrini*. Parasitology 129:455–464

Tselepatiotis et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/14735389

Tsui WM, Yuen RW, Chow LT, Tse CC (1992) Solitary necrotic nodule of the liver: parasitic origin? J Clin Pathol 45:975–978

Upatham ES, Vivanant V (2003) *Opisthorchis viverrini* and opisthorchiasis: a historical review and future perspective. Acta Trop 88:171–176

Upatham ES, Vivanant V, Brockelman WY, Kurathong S, Lee P, Kraengraeng R (1988) Rate of re-infection by *Opisthorchis viverrini* in an endemic northeast Thai community after chemotherapy. Int J Parasitol 18:643–649

Vale N, Gouveia MJ, Botelho M, Sripa B, Suttiprapa S, Rinaldi G, Gomes P, Brindley PJ et al (2013) Carcinogenic liver fluke *Opisthorchis viverrini* oxysterols detected by LC-MS/MS survey of soluble fraction parasite extract. Parasitol Int 62:535–542

Viranuvatti and Stitnimankarn 1972. http://www.ncbi.nlm.nih.gov/pubmed/4265700

Vogel H (1934) Der Entwicklungszyklus von *Opisthorchis felineus*. Far East Assoc Trop Med Nanking 1:619–624

Wang L, Yu X, Yang Y, Chen J, Hu D, Deng C, Yang X, Hu X, Xu J (2010) Molecular characterization and expression of the MYND-ZF gene from *Clonorchis sinensis*. Parasitol Res 107:1249–1255

Wang W, Blair D, Min T, Li F, Wang D (2011) Paragonimus worm from a New Guinea native in 1926. Asian Pac J Trop Med 4:76–78

Watanapa P, Watanapa WB (2002) Liver fluke-associated cholangiocarcinoma. Br J Surg 89:962–970

Watson-Wemyss HL (1919) Carcinoma of the liver associated with infection of *Clonorchis sinensis*. Edinb Med J 22:103

WHO Study Group (1995) Control of foodborne trematode infections. Report of a WHO study group. World Health Organ Tech Rep Ser 849:1–157

Wong RK, Peura DA, Mutter ML, Heit HA, Birns MT, Johnson LF (1985) Hemobilia and liver flukes in a patient from Thailand. Gastroenterology 88:1958–1963

Wongratanacheewin S, Sermswan RW, Sirisinha S (2003) Immunology and molecular biology of *Opisthorchis viverrini* infection. Acta Trop 88:195–207

Wykoff DE, Lepe TJ (1957) Studies on *Clonorchis sinensis* I. Observation on the route of migration in the definitive host. Am J Trop Med Hyg 6:1061–1065

Wykoff et al. 1965. http://www.ncbi.nlm.nih.gov/pubmed/14275209

Wykoff DE, Chittayasothorn K, Winn MM (1966) Clinical manifestations of *Opisthorchis viverrini* infections in Thailand. Am J Trop Med Hyg 15:914–918

Yalay O, Yagmur Ö, Ülkü A, Akcam AT, Sönmez H (2012) A rare cause of obstructive jaundice: *Fasciola hepatica* mimicking cholangiocarcinoma. Turk J Gastroenterol 23:604–607

Yokogawa M (1969) Paragonimus and paragonimiasis. Adv Parasitol 7:375–387

Young ND, Campbell BE, Hall RS, Jex AR, Cantacessi C, Laha T, Sohn WM, Scripa B et al (2010) Unlocking the transcriptomes of two carcinogenic parasites, *Clonorchis sinensis* and *Opisthorchis viverrini*. PLoS Negl Trop Dis 4, e719

Tumor-Like Parasitic Lesions of the Hepatobiliary Tract: Echinococcosis and Cysticercosis

134

Contents

Abstract

Echinococcosis is a widespread infestation with mainly two species of *Echinococcus* (*E.*), *E. alveolaris* (the cause of alveolar echinococcosis), and *E. hydatidosus*/*granulosus* (the cause of hydatid disease). Adult *E.* tapeworms inhabit the intestinal tract of various canids, including domesticated dogs and foxes. In both forms of echinococcosis, man is infested by the ingestion of embryonated eggs that hatch into larvae. These transmigrate from the intestinal tract into various tissues and form complex colonies of larvae. Alveolar echinococcosis of the liver is a severe and sometimes life-threatening condition characterized by invasively growing parasite colonies that produce large masses that may extend beyond the organ boundaries. The process can clinically mimic hepatic cancer. In contrast, cystic echinococcosis or hydatid disease is characterized by solitary or multiple cystic structures lined by chitin lamellae and a cambium of embryonal parasite cells that give rise to daughter organisms. In contrast to alveolar echinococcosis, the daughter cysts of hydatid disease contain larvae equipped with a scolex bearing hooklets, an important diagnostic feature. In rare instances, human livers are infested with larvae of the pork tapeworm, *Taenia solium*, a condition termed cysticercosis.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_134

Echinococcosis

Introduction

Echinococcosis, caused by several tapeworm species of the genus *Echinococcus*, is a dangerous and potentially fatal helminthic zoonosis in wildlife animals, livestock, and humans. Echinococcosis occurs in four forms, i.e., cystic echinococcosis (CE; hydatid disease) caused by *Echinococcus* (*E.*) *granulosus*, alveolar echinococcosis (AE) caused by *E. multilocularis*, and the uncommon polycystic echinococcosis (PCE) caused by *E. vogeli* and unicystic echinococcosis (UCE) caused by *E. oligarthra*. CE has a worldwide distribution, whereas hepatic AE is endemic in the Northern Hemisphere (Palearctic and Nearctic distribution), while PCE and UCE originated in the neotropics (reviews: Vuitton 1997; Eckert et al. 2001; McManus and Thompson 2003; Eckert and Deplazes 2004).

CE is a parasitosis that is known since antiquity (review: Cox 2002). Hippocrates, Galen, and Aretaeus mentioned large cysts of the liver filled with water. First and more exact descriptions of hydatids date from the sixteenth and seventeenth centuries (e.g., by Felix Plater). Well-described cases of CE are found in the work "Sepulchretum" (Bonetus/Bonet 1679), a text on anatomy and pathology based on numerous necropsies. Until the seventeenth century, the cysts were regarded as cystic enlargements of lymphatic vessels. It was Francesco Redi in the seventeenth century who first appreciated the parasitic nature of the cysts (Redi 1684). Redi, a physician and naturalist interested in entomology and parasitology, was struck by his observation that living macroorganisms can dwell inside another living organism. The German clinician and naturalist Pierre Simon Pallas demonstrated, in 1766, that cysts are the larval stages of tapeworms (Pallas 1766). The causative parasite of CE was first designated as *Hydatigera granulosa* by Batsch in 1786. The genus, *Echinococcus*, was coined in 1801 by Karl Asmund Rudolphi from Greifswald (1771–1832). The first detailed scientific descriptions of *Echinococcus* in the human body dates from 1819, by the physician and parasitologist Johann Gottfried Bremser (1767–1827), who had created a famous helminthologic collection in Vienna. He published excellent documentations on tapeworms in his book, entitled *Living Worms in the Living Human* (*Über lebende Würmer im lebenden Menschen*; Bremser 1819). In 1855, Virchow published his findings on *E. multilocularis* and hence was the first to recognize this disease as caused by a distinct *Echinococcus* species (Virchow 1855; review: Tappe and Frosch 2007). Frans Buhl had described the lesion before and had termed it "alveolar colloid," but he interpreted it as a form of gelatinous cancer (Buhl 1852, 1854). A third case was reported by Zeller (1854). By careful examination of his case, including necropsy findings, Virchow recognized vesicles suggesting *Echinococcus* elements, and he finally detected protoscolices, being very rare in human AE. Furthermore, he uncovered the infiltrative aspect of this parasite, a highly characteristic feature of AE. In the title of his work, he termed the disorder, "echinococcal tumor/Echinokokkengeschwulst" (Virchow 1855). Aspects of hepatic echinococcosis were summarized in 1856 by Luschka (1856). A detailed compilation of facts regarding several types of helminth parasites in man, including hydatid disease, appeared as a book (*On Human Entozoa*) in 1863 (Smith 1863), and hepatic echinococcosis was again summarized in book form in 1869 (Lindner 1869). The species *E. alveolaris*/*multilocularis* was described in 1863 by Leuckart. Experimental evidence for the complex life cycles was obtained by von Siebold (1853) who found that *Echinococcus* cysts from sheep produced adult tapeworms when ingested by dogs and by Naunyn (1863), who observed adult tapeworms in dogs fed with hydatid cysts from a human.

The Parasites

The tapeworm genus *Echinococcus* belongs to the Cestoda family Taeniidae and contains nine valid species (Nakao et al. 2013a,b; Table 1). In two of them (*E. granulosus* and *E. multilocularis*), the complete genomes have been analyzed (Tsai et al. 2013).

Table 1 Species of *Echinococcus* (*E.*)

Species	Disease
E. multilocularis (syn.: *E. alveolaris*)	Alveolar echinococcosis
E. granulosus sensu stricto (syn.: *E. hydatidosus*)	Cystic echinococcosis
E. equinus	
E. ortleppi	
E. canadensis	Cystic echinococcosis
E. shiquicus	
E. vogeli	Polycystic echinococcosis
E. oligarthrus (*E. oligarthra*)	Unicystic echinococcosis

Alveolar Echinococcosis: General Aspects

AE is the most serious form of echinococcosis, with a high morbidity and mortality rate (Clerc 1912; Weinberg 1947). In contrast to CE, AE has a distribution involving the Northern Hemisphere, including northern areas of Asia, Europe, and North America (Palearctic and Nearctic distribution). Regions with a high incidence of AE are Russia (including Siberia), China, northern Japan, southern Germany, Switzerland, France, and Alaska. Since the late 1980s, a number of hot spots were found in continental Asia, mostly in China and Central Asia, with discrete patches of endemicity. This phenomenon particularly relates to south Gansu, at the eastern border of the Tibetan plateau, south Ningxia, and the western Tian Shan. Within these hot spots, distinct transmission ecologies involving small mammal "flagship" species were found (Giraudoux et al. 2013). While CE seems to decrease in frequency, the prevalence and distribution of AE in red foxes in Europe increased significantly in the last 10–15 years, with a majority of cases identified in France, Germany, and Switzerland (Craig 2003).

Alveolar Echinococcosis: Macroscopic Pathology

The pathology of AE has been summarized in detail (Daujat 1912; Posselt 1931). At gross examination, AE lesions are characterized by ill-defined or polycyclic masses with a granulovesicular cut surface, from which usually no fluid emerges, in contrast to CE (Figs. 1 and 2). AE usually presents in the form of a solitary pseudotumor, while diffusely infiltrating variants are very rare. Most lesions occupy central or core parts of the liver, and the liver margins are usually spared. Similar to malignancies, the right liver lobe is more often affected. The size ranges from few cm to masses exceeding the size of a human head. The shape of the masses is ovoid, wedge-shaped, or irregular, sometimes with complex arborizations or tunnellike or mine-like extensions. Small satellite lesions may occur. The cut surface is whitish gray, but may also have reddish-

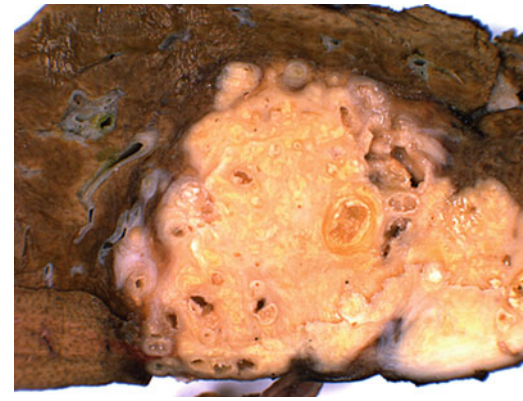

Fig. 1 Alveolar echinococcosis of the liver. An invasive tumor-like mass consisting of necrotic tissue and numerous small parasites has destroyed part of the liver substance

Fig. 2 Invasion of the hepatic pedicle in alveolar echinococcosis

brown areas or may be yellow (bile stained) in case of bile duct invasion. The masses can resemble a neoplastic process with invasive features. In fact, some patients show gross invasion of bile ducts and/or large hepatic veins, or the inferior vena cava. In contrast to primary liver cancer or metastases, AE lesions reaching the liver capsule do not result in umbilication or production of surface furrows. However, superficial masses may bulge from the surface and can even produce grape-like masses protruding from the liver surface. AE lesions can extend to the porta hepatis, or may primarily develop in this region. The masses may penetrate the liver capsule, or invade the gallbladder. The vesicles or alveolar structures typical of AE are small (2 mm diameter or less), but part of them may be visualized with the naked eye, the largest vesicles attaining pea size or even the size of a cherry (cited in Posselt 1931). There are AE lesions that almost exclusively consist of very small vesicles, not discernible at gross examinations. Such lesions may easily be confounded with a malignant neoplastic process.

AE lesions can undergo several secondary alterations. Large lesions can develop a central cavity caused by necrosis. There is evidence that bile, which can enter the parasite mass following bile duct invasion, promotes severe parasite damage and necrosis (bile infarction of parasite; Melnikow-Raswedenkow 1901). In large central necroses, putrefaction occurs, with discharge of a sanious, fetid, or ichorous fluid (in the German literature, "Verjauchung"; Posselt 1931). Cystic necroses may perforate the liver capsule and penetrate into the peritoneal cavity. Necrosis and/or infection of the parasite mass can elicit ulcerations of central cystic spaces (Mangold 1892). The fluid in cystically altered necrotic foci can contain blood, hemoglobin, and hematoidin (Posselt 1931). Cystic necrosis can result in sequestration of parts of the parasite and/or the involved liver substance (Kränzle 1880). The sequesters appear as ill-defined gray to whitish of bile-stained, friable tissue areas sometimes separated from the remaining liver and parasite by a slit-like space. In contrast to CE, gas formation almost never occurs in AE (Posselt 1931).

The liver areas harboring AE lesions can undergo atrophy with or without associated fibrosis and nodular hyperplasia, sometimes with a cirrhosis-like change in the liver substance surrounding the parasite (review: Posselt 1931).

Alveolar Echinococcosis: Histopathology

The histologic hallmark of AE is the presence of a complex, sievelike system of vesicular structures ("alveoles"; hence the name alveolar echinococcosis) surrounded by an eosinophilic, PAS-positive lamina, the parasite elements being embedded in a fibrous matrix with inflammatory infiltrates (Figs. 3 and 4). Three-dimensional digital reconstruction of *E. alveolaris* larval structures from hepatic tissues demonstrated a rootlike network of interconnected vesicles and tubules extending into the periphery of the lesion (Tappe et al. 2010). There is evidence that new vesicles and microcysts first devoid of a laminated covering arise from mother vesicles as bleb-like cellular sprouts and grow into tissue in the form of rootlets resembling those of plant-penetrating soil. Larger vesicles and growing cysts then start to add a laminated cover (Vogel 1978; Mehlhorn et al. 1983). In contrast to

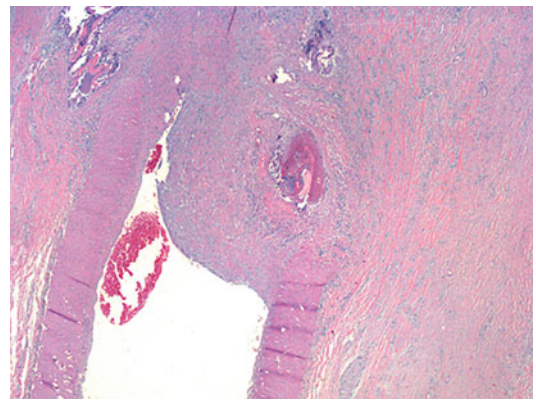

Fig. 3 Hepatic alveolar echinococcosis with arterial invasion. The wall of the artery is interrupted by an inflammatory lesion that contains a focus of parasite lamellae without cysts or hooklets (hematoxylin and eosin stain)

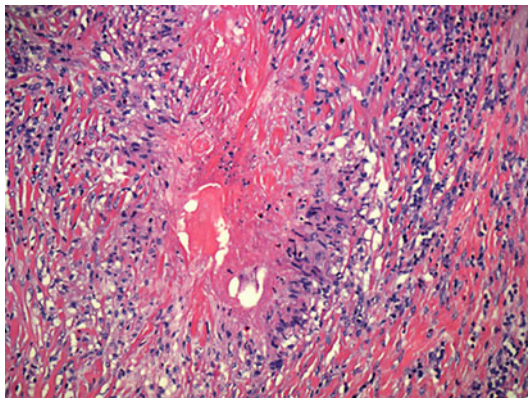

Fig. 4 Echinococcal granuloma in hepatic alveolar echinococcosis (hematoxylin and eosin stain)

CE, AE in the human host hardly ever shows fully developed protoscolices (Mehlhorn 2001), although Virchow detected them in his classical investigation leading to the recognition of AE as an echinococcal disease (Virchow 1855). In rodents harboring *E. multilocularis* metacestodes, protoscolices are regularly found, suggesting that the asexual production of protoscolices strongly depends on the intermediate host involved. Echinococcal differentiation processes directed toward the protoscolex stage involve an echinococcal gene encoding an epidermal growth factor receptor orthologue (Spiliotis et al. 2003) and a gene encoding a member of the insulin receptor family (Konrad et al. 2003), genes that may be differentially expressed in various hosts. Histologically, the invasive features of the parasite seen at macroscopy are confirmed. Clusters of vesicles accompanied by PAS-positive lamellae of varying thickness grow into the tissue of liver in an infiltrative fashion, similar to invasive cancer, and may penetrate into bile ducts and the walls of the portal vein, hepatic veins, and inferior vena cava. Similar to a carcinoma, the parasite is associated with a fibrous, stroma-like tissue.

Similar to cancers, the invasive cascade of AE involves several types of peptidases and proteases, including a cathepsin L-like peptidase (Sako et al. 2007) and a cathepsin B-like peptidase (Sako et al. 2011). A cysteine protease produced by *E. multilocularis* metacestodes digests eotaxin, a CC pro-inflammatory chemokine (Mejri and Gottstein 2009). On the other hand, the parasite also secretes proteins that inhibit proteases, such as a serpin active on trypsin, neutrophil elastase, and a trypsin-like plasmin (Merckelbach and Ruppel 2007).

Antigens of *E. multilocularis* elicit of vigorous local immune reaction mediated by lymphocytes and macrophages (Bresson-Hadni et al. 2008; Brehm 2010). The parasite contains and expresses several antigens, e.g., a laminated layer-associated protein (Ingold et al. 1998), a T24-like tetraspanin located to the germinal layer (Dang et al. 2009), and the B antigen complex (Mamuti et al. 2004). Metacestodes of *E. multilocularis* modulate cellular cytokine and chemokine release by mononuclear cells. This modulation leads to differential up- and downregulations of certain cytokines, in particular Th1 and Th2 cytokines and chemokines, thus generating a pro-inflammatory immune response (Hübner et al. 2006). Secretory products of *E. multilocularis* metacestodes induce tolerogenic properties and apoptosis in dendritic cells in vitro (Nono et al. 2012). Infestation with *E. multilocularis* results in a fibrotic reaction surrounding the parasite cysts. In the pericystic hepatic tissue, increased expression of the fibrokine, TGF-beta, and an activated TGF-beta/Smad signaling pathway have been identified (Wang et al. 2013). *E. multilocularis* can elicit a granulomatous reaction in the liver (Gaultier et al. 2009), sometimes with giant cells (Caesar 1901). The formation of epithelioid cells and macrophages is probably linked to specific interactions between components of the parasite, specifically its protoscolices, and Kupffer cells/macrophages (Walbaum et al. 1994). On the other hand, clustering of cases within families and a link to certain MHC polymorphisms suggest that *E. multilocularis* may modulate immune reactions to escape host defense (Vuitton et al. 2006; Gottstein and Hemphill 2008). The complex interaction between *E. multilocularis* and its hosts is regulated by the parasite's distinct proteome, which will also be used for diagnostic typing of strains (Cui et al. 2013).

Cystic Echinococcosis (CE; Hydatid Disease): General Aspects

Cystic echinococcosis (CE; hydatid disease) is in most instances caused by *E. granulosus* (hydatidosus), but infestations with *E. canadensis* strain G7 (pig strain) are increasing in Central Europe (Schneider et al. 2010). CE is known in human medicine for a long time and has, e.g., been described in 1840 under the name *Echinococcus hominis*, as a "rare species of hydatid" found in the human liver (Curling 1840). CE is a widespread parasitosis with a worldwide distribution and represents a global problem of increasing importance (Matossian et al. 1977; McManus and Thompson 2003). It was a rather common parasitosis in former times, but the worldwide incidence and prevalence of CE have fallen significantly over the past decades (Grosso et al. 2012). The impressive differences in incidence from one country or region to the other are, apart from control programs, mainly due to different distributions and numbers of intermediate hosts (goat flocks, seminomadic and nomadic sheep) and canines as final hosts, with the common sheep G1 strain being the predominant strain (Grosso et al. 2012). In most instances, hydatid involves adults, but pediatric cases of CE are also well known (Young 1923).

Hepatobiliary CE is characterized by the development of the larvae of *E. granulosus* causing liver cysts. Early hepatic hydatid disease is usually asymptomatic for long time periods, but as the parasitic cysts slowly grow and enlarge over years, they can exert a mass effect sometimes resembling a hepatic neoplasm (Barrier 1840; Frerichs 1860/1861; Duclaux 1875; Scherer et al. 1978; WHO Informal Working Group 2003; Nunnari et al. 2012). Solitary cysts or cysts with satellite lesions produce space-occupying masses that may, in slender individuals, seen as bulging tumors, or are palpable as fluctuant lesions. Hepatomegaly is sometimes important, with marked displacement of the liver by the parasite cysts.

These large cystic or multicystic lesions have distinct physical properties linked to the presence of fluid-filled spheres with a membrane and a pericyst which are under a certain tension. These cysts that are distended by fluid have remarkable elasticity, so that a shock is transmitted through the whole mass as a prolonged trembling motion (Smith 1863). This may rarely lead to a unique auscultatory and percussion phenomenon termed "son hydatique" (Piorry 1828) in French, translated as "hydatid sound" or "hydatid fremitus" (Markham 1856; Little 1857). Pierre Adolphe Piorry (1794–1879) was an outstanding clinician and pioneer of percussion and pleximetry. He was struck by the peculiar vibrations at auscultation and found that the vibrant feature may also be obtained through percussion. Markam (1856) described that a hydatid projecting from the liver, "when percussed, communicates to the finger which is struck a most peculiar sensation, resembling very exactly that which arises from the vibrations of a loosely hung steel spring." Apart from right upper abdominal discomfort or pain, the cysts may give rise to complications, such as cyst infection, cyst rupture, or compression of bile ducts. Rarely, CE was associated with, or caused, Budd-Chiari syndrome (Parker 1959; Raciti 1972; Agarwal and Kumar 2009). This complication is due to the fact that *E. granulosus* cysts can invade veins and the heart cavities and can even cause pulmonary embolism.

Cystic Echinococcosis: Macroscopic Pathology

In his 1840 article on liver hydatid associated with *Echinococcus hominis*, Curling gave a pertinent macroscopic description of the cystic parasite, which clearly illustrates the typical features of this disease. He noted, "a cyst of fibro-cartilaginous structure, lined by a soft loose albuminous membrane enclosing a large number of separate hydatid cysts of various sizes from that of a pea to that of a large cherry, surrounded by and floating in a transparent fluid. Upon opening a cyst, there escaped a large number of small white particles, some of which were found floating in the fluid within, while others were in contact with the inner surface of the membrane composing it. The latter appeared like grains of white sand thickly studded over the interior of the

cyst. On examination in the microscope, these little bodies were ascertained to be the vermiculi of the *Echinococcus*" (Curling 1840). These "vermiculi" ("small worms") represent the protoscolices of the present nomenclature, and the "sand" (in German, "Hydatidensand") is a mixture of viable and dead protoscolices and parasite debris. Curling (1840) identified the crown of hooklets and the suckers and also found that part of the hooklets had detached and were floating in the cyst fluid or were stuck within protein masses.

Solitary cysts or mother cysts in case of a conglomerate of cysts range in size from 5 mm to more than the size of an orange (Figs. 5 and 6).

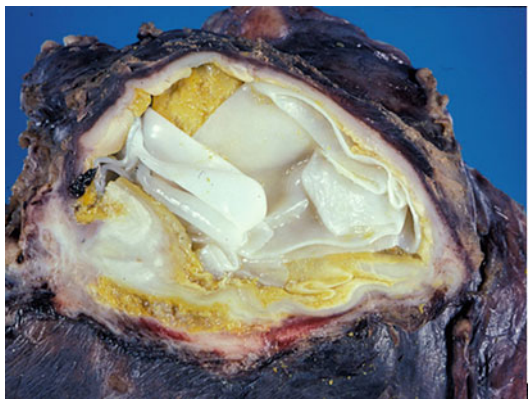

Fig. 5 Cystic echinococcosis (hydatid disease) of the liver. The large parasitic cyst contains a partially detached milky-white parasitic lamella lining the cyst. The yellow discoloration is due to leakage of bile from damaged bile ducts

The cyst walls are generally of uniform thickness, roughly proportional to the size of the cyst. The interior cyst wall surface is either colorless and transparent or of opaque tint in fresh specimens, while it turns to a milky or turbid color upon formalin fixation. In has been compared to the appearance of a boiled egg. In case of bile duct rupture or hemorrhage, the wall is yellow or reddish brown, respectively. The cavity of the cysts contains a more or less abundant liquid, which is serous or limpid, and sometimes viscid. Large hydatid cysts (the parent hydatid or mother cyst) may enclose several smaller daughter cysts, which are connected with the wall of the mother cyst or are freely floating. The internal surface of young cysts is smooth, while it becomes rough in older cysts, sometimes covered with a thick exsudation.

Part of hepatic cysts in CE display daughter cysts that are located exterior to the fibrous pericyst of the largest mother cyst ("extracapsular cysts"). In one study, this phenomenon was found in 16 % of cases (Kalovidouris et al. 1992), whereas the real incidence of these cysts in operative specimens was as high as 29.5 % (Voros et al. 1999). The germinal layer and recently produced material of the laminated layer may detach from the older cyst layer and float within the cyst. Old cysts often show internal septations and daughter cysts. As cysts become older, the intracystic fluid, which is usually limpid, diminishes in quantity and thickens, with a more viscid consistency, finally assuming the appearance of painter's putty or chalk (Smith 1863). In other

Fig. 6 Cystic echinococcosis (hydatid disease) of the liver. In this case, the cyst is filled with necrotic parasitic matter following therapy, mimicking a necrotic malignancy

cases, the cyst content assumes a color and consistency strikingly similar to that of tuberculous calcification or resembles that of an atheroma/epidermoid cyst. In large cysts, the pericyst frequently undergoes calcification, and in part of the lesions, the entire cyst wall may be replaced by a thick calcified shell with a bony consistence. In case of bile duct invasion or rupture into bile ducts, bile can flow into the parasite cysts, staining them yellow. Hydatid cyst may be infected, followed by supportive inflammation and eventually formation of a cyst empyema. In case of infection with anaerobic bacteria, gas formation can occur (Garnier 1907; Adnet 1910; Fiessinger 1924). In the presence of large cysts, the involved liver part can undergo atrophy.

Cystic Echinococcosis: Histopathology

Active, viable cysts are lined by a layer of small parasite cells, the germinal layer. This germinal layer is the site from where secondary larval colonies arise, first forming small bud-like structures that grow out into macroscopic, milky-white and coral-like and cauliflower-like structures containing numerous so-called brood capsules (Figs. 7, 8, and 9). These structures are lined with a germinal cell layer morphologically similar or identical to that in larger mother cysts. At many places, the metacestodic larval cell system of the brood capsule generates protoscolices having the complete set of hooks. The cell systems of the germinal layer are in contact with tegument cells which in turn line the multilayered, PAS-positive lamina, which is produced by tegument cells. Hooks (or hooklets) which either form a crown in protoscolices or are free structures embedded in parasite or host tissue, or are floating in the cyst fluid, are small in *E. granulosus* and *E. multilocularis* (17–49 μm in length) and have a much larger size in neotropical *Echinococcus* species (43–60 μm).

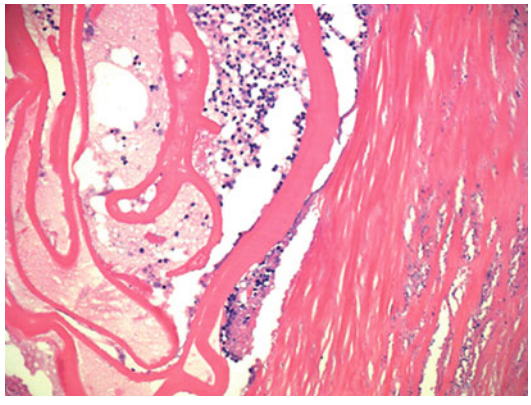

Fig. 7 Cystic echinococcosis (hydatid disease) of the liver. Parasitic cysts are lined by a layered eosinophilic lamella or membrane. Viable embryonal parasite cells which line these membranes are not seen in the present case (hematoxylin and eosin stain)

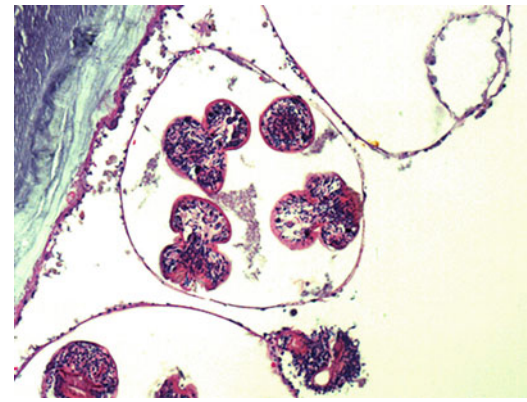

Fig. 8 In contrast to alveolar echinococcosis, cystic echinococcosis contains hydatid cysts with parasite embryos (Masson's trichrome stain)

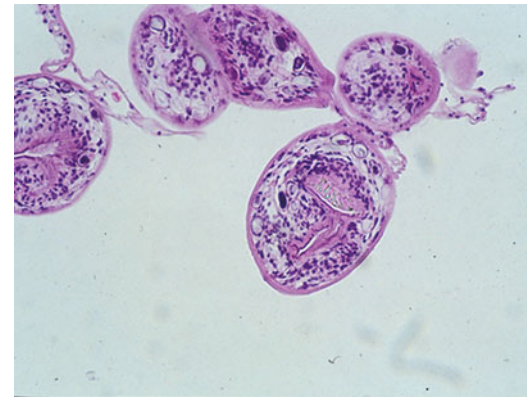

Fig. 9 Cystic echinococcosis of the liver. Parasite embryos show a ring or collar of hooklets that is also found in the adult parasite (hematoxylin and eosin stain)

Old cysts may undergo atrophy of the parasite, or the epithelial component of the parasite may completely vanish in dead *Echinococcus*, and the hooklets of the protoscolices will furnish the only indication of the previous existence of CE (Smith 1863). The hooklets are transparent objects and may this be missed, but they stain pink or red in the Ziehl-Neelsen stain. The laminated membrane of old or dead cysts shows accumulation of fat droplets, crystalloids, and signs of rupture of laminae seen in the PAS stain. The entire membrane may become ruffled and can finally collapse due to loss of stability and failure of fluid production by the dead parasite, with subsequent effacement of the cyst cavity. In PAS stains, collapsed cysts show contracted membranes folded together, with an appearance like "petals of a poppy enclosed within the calyx" (Smith 1863). Even after complete atrophy of a cyst, both the membrane and the hooklets resist degradation for long time periods, and even after years one my detect hooklets and/or membraneous shreds.

Infestation with *E. granulosus* elicits a vigorous immune reaction driven by parasite antigens (Delunardo et al. 2010). Immune reactions induced by *Echinococcus* are thought to serve as a protection of the host against the parasite, but the parasite itself may also profit from a complex immunologic interplay (review: Vuitton 2003). Antigen B (EgAgB) is a major metacestodic protein antigen belonging to a gene family composed of at least ten unique genes which are differentially expressed in different life cycle stages of *E. granulosus* and play a role in modulating immune responses of the host (Zhang et al. 2010). Expression and secretion of interleukin-17A by immunologic effector cells results in immunoprotection against the parasite (Mezioug and Touil-Boukoffa 2012). The local generation of cytokines and fibrokines results of the generation of a fibrous zone surrounding the parasite cyst (the so-called pericyst), associated with a cellular infiltrate.

The pericyst surrounding the parasite cyst consists of collagen fibers, fibroblasts/myofibroblasts, and a cellular infiltrate of variable density. This infiltrate contains eosinophilic granulocytes, lymphocytes (both T-and B-cells), macrophages, and plasma cells. The density of this infiltrate is usually greater in early hydatid disease, while it is often sparse in old fibrotic and/or calcified lesions. In case of rupture of a parasitic cyst into the bile duct system, entry of parasite material and in particular the cyst fluid containing brood capsules and necrotic parasite elicits a vigorous immune and inflammatory reaction, with formation of ductocentric epithelioid cell granulomas, granulomas protruding in the duct lumen, and a periductal inflammatory infiltrate with numerous eosinophils. Fragments of the PAS-positive lamella, entire viable or dead protoscolices, or hooklets may "heal" into these granulomatous areas, promoting the formation of foreign body-type giant cells. Following albendazole therapy, germinal layer cells and protoscolices revealed degenerative changes and a loss of viability (Stankovic et al. 2005).

Morphology of Echinococcal Parasites

Echinococcal parasites have a complex internal structure. In *E. multilocularis* (alveolaris), the small interconnecting cysts are surrounded by an acellular laminated layer containing glycoproteins and chitin, therefore being strongly PAS positive. The interconnecting cysts are filled with fluid, and the larval cell system forms a thin layer (germinal layer, germinal membrane) juxtaposed to the laminar layer. The germinal membrane consists of asexually proliferating cells. Several metacestodic cell types are identified including tegumental cells forming a syncytium underneath the laminated layer and synthesizing the layer substance, glycogen storage cells, muscle cells, calcareous corpuscle cells, excretory duct cells, and stem cells. Furthermore, *E. alveolaris*/*multilocularis* possesses a larval nervous system with nerve cells (Koziol et al. 2013). Within the labyrinth of PAS-positive interconnecting cysts, the metacestode larvae are not always easily detectable, because the parasite tissue is fragile and often damaged by tissue processing. Invaginations of the cyst walls result in so-called brood capsules which may contain protoscolices. The protoscolices, which have a structure similar to

that of the scolex of an adult tapeworm, is invaginated within a small posterior body (Koziol et al. 2013). The germinal layer cells of *E. multilocularis* have been cultured, and these cells can be used to produce metacestodes in experimental animal models (Yamashita et al. 1997; Brehm and Spiliotis 2008). As in other species of *Echinococcus*, germinal cells can give rise to small structures exhibiting a central body, a small number of concentric layers and calcified matter, the so-called calcareous corpuscles. These bodies can also arise from brood capsule cells (Ohnishi and Kutsumi 1991). The generation of new metacestodes is thought to mainly originate from germinal cells situated on the inner surfaces of brood capsules, but there are also cell accumulations on the outer brood capsule surface, suggesting that brood capsule itself may have the potential to produce new brood capsules (Ohnishi and Kutsumi 1995). A germinal cell layer lining the cyst wall is also found in *E. granulosus*, the parasite causing CE. Although cysts in CE tend to grow slowly, germinal cells in culture are capable for rapid proliferation, with an estimated population doubling time of 48 h (Albani et al. 2010, 2013). It has been shown that, in the course of scolicogenesis, the protoscolex surface displays five cellular territories, and three of these territories are surrounded by a basal lamina. These cellular territories correlate with the expression of specific genes and the regionalization of DNA synthesis in protoscolices (Galindo et al. 2008).

Life Cycles and Pathways of Infestation

The life cycles of *Echinococcus* species are closely linked with a predator-prey association involving two obligate mammalian hosts. Definitive hosts of the adult tapeworms are carnivores, mainly canids. Intermediate hosts harboring the metacestode larvae are herbivore preys, such as ungulates, lagomorphs, and rodents. Humans form an accidental host for metacestode infestation. In the human host, the metacestode larvae usually develop in the liver, but other parenteral sites can also be infested.

Infestations of *E. multilocularis* proceed along a sylvatic cycle, wild canids – in particular red fox and arctic fox – being the definitive hosts. A second life cycle in *E. multilocularis* infestation is the synanthropic cycle, in which domestic dogs and cats are definitive hosts. Intermediate hosts in AE are small microtine and arvicoline rodents. These infested rodents harbor metacestodes which, when ingested by predators, give rise to adult tapeworms which deliver embryonated eggs in the feces of definitive hosts. Humans are infested via contact with material contaminated with excrements of foxes, such as forest berries and mushrooms, on which embryonated eggs can survive for a while. It follows that infestation with eggs strongly depends on behavioral and occupational factors, berry and mushroom pickers, hunters, and trappers being at higher risk. Domestic dogs are well-known sources of human infestation, but the role of domestic cats is less clear. In humans, ingested embryonated eggs become oncospheres migrating to organs (specifically the liver), where they develop into metacestodes.

In CE, the definitive hosts are primarily dogs and other canids, mainly the domestic dog, while the intermediate hosts are primarily ungulates, marsupials, and primates. Gravid proglottids of the tapeworms pass in the feces and rupture, releasing eggs that are ingested by the intermediate hosts. These are many mammals, but sheep predominate. The ingested eggs hatch in the intestine of intermediate hosts, giving rise to oncospheres that penetrate the intestinal mucosa, enter the bloodstream, and develop into metacestodes and hydatid cysts in several organs and tissues. The life cycle is completed when the metacestode cyst is ingested by a definitive host.

E. vogeli has the bush dog (*Speothos venaticus*) as its final host. The bush dog (called cachorro-vinagre, "vinegar dog," in Brazil) is a canid inhabiting Central and South America. It is the closest living relative of the South American mane wolf. The main prey of bush is the large caviomorph rodent, the paca (*Cuniculus paca*), which is the intermediate host of *E. vogeli* and harbors the metacestodes (the cycle in neotropical forests; D'Alessandro and Rausch 2008). Humans are thought to be infested via ingestion of

embryonated eggs attracted from infested dogs that had fed on pacas (the domiciliary transmission). After ingestion of embryonated eggs, the oncospheres released in the intestine are transferred to the liver, where the oncosphere produces a primary lacuna, and then the development of the metacestode is initiated. In nonnatural intermediate host such as humans, an initial vesicle is formed, from which new vesicles sprout through asexual proliferation (D'Alessandro and Rausch 2008). *E. oligarthrus*/*oligarthra* metacestodes were identified in opossums, agoutis, spiny rats, pacas, and rabbits. The most common final host of *E. oligarthrus*/*oligarthra* is the cougar (*Puma concolor*), but it is expected that this parasite can also parasitize other felids.

Cysticercosis of the Liver

Introduction

Cysticercosis is the infestation of the human host with larvae (*Cysticercus cellulosae*) of the pork tapeworm, *Taenia solium*, following ingestion of embryonated *Taenia* eggs. Infestation takes place via intake of contaminated food or water, external feces, or, in case the human host itself harbors a pork tapeworm, the person's own feces being the source of the eggs. The infestation of humans with cysticerci is a "dead end" for the parasite, as no further transmission takes place. In contrast, intestinal infestation of humans by the pork tapeworm, *Taenia solium*, requires the ingestion of viable cysticercal larvae through ingestion of undercooked or uncooked pork and pork products.

After ingestion of *T. solium* eggs, these eggs hatch in the intestinal tract and give rise to migrating and invasive larvae, the *Cysticercus cellulosae*. These larvae are semitransparent, opalescent white organisms of an oval to elongated shape and have a body length of up to 1.8 cm. Cysticerci have a scolex with four large suckers and a rostellum armed with double row of large and small hooklets, numbering 22–32 (review: Sparks et al. 1976). The cysticerci penetrate the intestinal wall, enter the bloodstream, and start to spread in the human body, to settle at few predominant sites. At these sites, the larvae form a cystic space containing protoscolices. Typical sites are the brain and spinal cord (neurocysticercosis; including the development of cysts in the ventricles), ophthalmic cysticercosis, muscle cysticercosis, and cutaneous/subcutaneous cysticercosis. Neurocysticercosis and ophthalmic cysticercosis together account for more than 85 % of cases. In muscle and soft tissues, the cysticerci can encapsulate and may survive for many years. Rare localizations comprise the heart, peritoneum, lung, and other visceral organs, such as the liver.

Cysticercosis of the Liver

Hepatic cysticercosis is a rare disorder, of which only few cases have been reported. Hepatic involvement is usually diagnosed in the setting of disseminated cysticercosis (Cocchi 1953; Hrusovsky et al. 1989; Vianna et al. 1991; Sickel et al. 1995; Figurnov et al. 2002; Vijayaraghavan 2004; Sathyanarayanan et al. 2011; Singh et al. 2012; Chaudhary et al. 2014). Among 25 autopsies of patients with cysticercosis, liver involvement was detected in 4 % (Vianna et al. 1991). Solitary cystic or nodular hepatic lesions caused by cysticercosis usually remain asymptomatic, while multicystic lesions may cause signs and symptoms resembling hepatitis or a neoplastic process. The hepatic cysticercus reported by Sickel et al. (1995) was a symptomatic lesion found in a 62-year-old male patient. In the patient with cysticercosis described by Vijayaraghavan (2004), multiple elliptical millet seed-shaped calcifications were seen in the liver, mesentery, and retroperitoneal adipose tissue. Multiple small cysticercus foci are well known in intermediate animal hosts. The 25-year-old male patients described by Sathyanarayanan et al. (2011) presented with hepatomegaly and peripheral eosinophilia. Abdominal ultrasound revealed multiple cystic lesions in the liver with scolices inside the cysts. IgG of cysticercosis detected by ELISA was strongly positive.

The cysts consist of a wall that exhibits, away from scolices, a thickness of 100–200 μ. The

interior cyst surface often contains projections that are 10–25 μ in diameter (Sparks et al. 1976). The main constituent of the cyst wall is the tegument, which is a thin lamella of less than 5 μ of thickness, covered by microvilli at its outer surface. The tegument is surrounded by a layer containing two rows of smooth muscle cells and a layer of tegumental cells. In the region of the scolex, the tegument is thicker, up to 20 μ. The scolex has four suckers and a double row of hooklets on its rostellum. The entire cyst is embedded in a tissue infiltrated with lymphocytes, macrophages, plasma cells and eosinophils, and a fibrous zone surrounding the cyst develops in older lesions.

References

Adnet PL (1910) La suppuration gazeuse spontanée des kystes hydatiques du foie. Thèse, Université de Paris

Agarwal N, Kumar S (2009) Budd-Chiari syndrome owing to liver hydatid disease: case report and review of the literature. Ann Trop Paediatr 29:301–304

Albani CM, Elissondo MC, Cumino AC, Chisari A, Denegri GM (2010) Primary cell culture of *Echinococcus granulosus* developed from the cystic germinal layer: biological and functional characterization. Int J Parasitol 40:1269–1275

Albani CM, Cumino AC, Elissondo MC, Denegri GM (2013) Development of a cell line from *Echinococcus granulosus* germinal layer. Acta Trop

Barrier FM (1840) De la tumeur hydatique du foie: thèse pour le doctorat en mödecine présentée et soutenue le 24 juin 1840. Medical Faculty of the University of Paris, Imprimerie et Fonderie de Rignoux

Bonetus T (Bonet T) (1679) Sepulchretum sive anatomia practica ex cadaveribus morbo denatis, 2 vols. Chouet, Geneva

Brehm K (2010) The role of evolutionarily conserved signalling systems in *Echinococcus multilocularis* development and host-parasite interaction. Med Microbiol Immunol 199:247–259

Brehm K, Spiliotis M (2008) Recent advances in the in vitro cultivation and genetic manipulation of *Echinococcus multilocularis* metacestodes and germinal cells. Exp Parasitol 119:506–515

Bremser JG (1819) Über lebende Würmer im lebenden Menschen. Ein Buch für ausübende Aerzte. Carl Schaumburg and Company, Vienna

Bresson-Hadni S, Miguet JP, Mantion G, Giraudoux P, Vuitton DA (2008) Alveolar echinococcosis: a disease comparable to a slow growing cancer (in French). Bull Acad Natl Med 192:1131–1138

Buhl F (1852) 2 Fälle von Alveolarcolloid der Leber. Illustrirte Medicinische Zeitung München 1:102

Buhl F (1854) Mittheilungen aus der Pfeufer'schen Klinik. Zschr Ration Med NF 4:356

Caesar F (1901) Über Riesenzellenbildung bei *Echinococcus multilocularis* und über Kombination von Tuberkulose mit demselben Thesis, Tübingen

Chaudhary V, Bano S, Kumar P, Narula MK, Anand R (2014) Hepatic cysticercosis: a rare entity. Abdom Imaging 39:1182–1185

Clerc E (1912) Zur Kenntnis des *Echinococcus multilocularis*. Korrespond. Bl. Schweiz. Aerzte Nr. 32

Cocchi U (1953) A case of cysticercosis of the lung and of the liver (in Italian). Radiol Clin 22:54–57

Cox FEG (2002) History of human parasitology. Clin Microbiol Rev 15:595–612

Craig P (2003) *Echinococcus multilocularis*. Curr Opin Infect Dis 16:437–444

Cui SJ, Xu LL, Zhang T, Xu M, Yao J, Fang CY, Feng Z, Yang PY, Hu W, Liu F (2013) Proteomic characterization of larval and adult developmental stages in *Echinococcus granulosus* reveals novel insight into host-parasite interactions. J Proteomics 84:158–175

Curling TB (1840) Case of a rare species of hydatid, the *echinococcus hominis*, found in the human liver. Med Chir Trans 23:385–389

D'Alessandro and Rausch 2008. http://www.ncbi.nlm.nih.gov/pubmed/18400802

Dang Z, Watanabe J, Kajino K, Oku Y, Matsumoto J, Yagi K, Kouguchi H, Sugimoto C (2009) Molecular cloning and characterization of a T24-like protein in *Echinococcus multilocularis*. Mol Biochem Parasitol 168:117–119

Daujat C (1912) Echinococcose alvéolaire principale du foie. Thèse, Lyon

Delunardo F, Ortona E, Margutti P, Perdicchio M, Vacirca D, Teggi A, Sorica M, Siracusano A (2010) Identification of a novel 19 kDa *Echinococcus granulosus* antigen. Acta Trop 113:42–47

Duclaux A-P (1875) Des kystes hydatiques du foie. Considérés au point de vue de la marche et du traitement. Thesis, Medical Faculty of Paris

Eckert et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11314583

Eckert J, Deplazes P (2004) Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev 17:107–135

Fiessinger N (1924) Les kystes hydatiques gazeux primitifs du foie. Paris Med 19:461

Figurnov VA, Chruin AN, Lenshin AV, Grigorenko AA, Churina SA, Figurnova EV et al (2002) A case of isolated hepatic cysticercosis in a nine-year-old girl. Med Parazitol (Mosk) 1:56–57

Frerichs FT (1860–1861) A clinical treatise on disease of the liver. Translated by C. Murchison. New Sydenham Society, London

Galindo M, Schadebrodt G, Galanti N (2008) *Echinococcus granulosus*: cellular territories and morphological

regions in mature protoscoleces. Exp Parasitol 119:524–533
Garnier M (1907) Sur un microbe particulier trouvé dans un kyste hydatique suppuré et gazeux (Bacill. moniliformis). Arch Méd Expér Anat Path (Paris) 19:785
Gaultier JB, Hot A, Mauservey C, Dumortier J, Coppéré B, Ninet J (2009) Granulomatous liver disease as the presenting feature of alveolar echinococcosis in an hepatitis C infected cardiac transplant patient (in French). Rev Med Interne 30:812–815
Girodoux P, Raoul F, Afonso E, Ziadinov I, Yang Y, Li L, Li T, Quéré JP, Feng X et al (2013) Transmission ecosystems of *Echinococcus multilocularis* in China and Central Asia. Parasitology 5:1–12
Gottstein B, Hemphill A (2008) *Echinococcus multilocularis*: the parasite-host interplay. Exp Parasitol 119:447–452
Grosso G, Gruttadauria S, Biondi A, Marventano S, Mistretta A (2012) Worldwide epidemiology of liver hydatidosis including the Mediterranean area. World J Gastroenterol 18:1425–1437
Hrusovsky S, Krcméry V, Sobota K, Cermak P, André I, Sobotova O, Dubrava M, Kovac A, Gocar E (1989) Ultrasonography of echinococcosis, toxocariasis and cysticercosis of the liver (in Slovak). Cesk Radiol 43:318–324
Hübner MP, Manfras BJ, Margos MC, Eiffler D, Hoffmann WH, Schulz-Key H, Kern P et al (2006) *Echinococcus multilocularis* metacestodes modulate cellular cytokine and chemokine release by peripheral blood mononuclear cells in alveolar echinococcosis patients. Clin Exp Immunol 145:243–251
Ingold K, Gottstein B, Hemphill A (1998) Identification of a laminated layer-associated protein in *Echinococcus multilocularis* metacestodes. Parasitology 116:363–372
Kalovidouris A, Voros D, Gouliamos A, Vlachos L, Papavasiliou C (1992) Extracapsular (satellite) hydatid cysts. Gastrointest Radiol 17:353–356
Konrad C, Kroner A, Spiliotis M, Zavala-Gongora R, Brehm K (2003) Identification and molecular characterization of a gene encoding a member of the insulin receptor family in *Echinococcus multilocularis*. Int J Parasitol 33:301–312
Koziol U, Krohne G, Brehm K (2013) Anatomy and development of the larval nervous system in *Echinococcus multilocularis*. Front Zool 10:24
Kränzle L (1880) Fünf neue Fälle von *Echinococcus multilocularis* hepatis. Ein beitrag zur pathologischen Anatomie dieser Krankheit. Inaugural-Dissertation, H. Laupp Verlag
Lindner OE (1869) Über Echinococcus der Leber. Thesis, Naumann Verlag, Leipzig
Little WJ (1857) The "hydatid fremitus" of Piorry. Br Med J 1:189–190
Luschka H (1856) Zur Lehre von der Echinokokkenkrankheit der menschlichen Leber. Virchows Arch 10:206
Mamuti W, Yamasaki H, Sako Y, Nakao M, Xiao N, Nakaya K, Sato N, Vuitton DA et al (2004) Molecular cloning, expression, and serological evaluation of an 8-kilodalton subunit of antigen B from *Echinococcus multilocularis*. J Clin Microbiol 42:1082–1088
Mangold K (1892) Über den multiloculären Echinococcus und seine Taenie. Thesis, Schumacher Verlag, Tübingen
Markham WO (1856) Diagnostic value of the hydatid sound ("son hydatique" of Piorry). Assoc Med J 4:1072
Matossian RM, Rickard MD, Smyth JD (1977) Hydatodosis: a global problem of increasing importance. Bull World Health Organ 55:499–507
McManus DP, Thompson RC (2003) Molecular epidemiology of cystic echinococcosis. Parasitology 127 (suppl):S37–S51
Mehlhorn H (2001) Echinococcosis. In: Mehlhorn H (ed) Encyclopedic reference of parasitology, vol 2, 2nd edn. Springer, Berlin, p 199
Mehlhorn H, Eckert J, Thompson RC (1983) Proliferation and metastases formation of larval *Echinococcus multilocularis*. II. Ultrastructural investigations. Z Parasitenkd 69:749–763
Mejri N, Gottstein B (2009) *Echinococcus multilocularis* metacestode metabolites contain a cysteine protease that digests eotaxin, a CC pro-inflammatory chemokine. Parasitol Res 105:1253–1260
Melnikow-Raswedenkow N (1901) Studien über den *Echinococcus alveolaris* sive multilocularis. Histologische Untersuchungen. Gustav Fischer, Jena, Beitr. Pathol. Anat. Allgem. Pathol
Merckelbach A, Ruppel A (2007) Biochemical properties of an intracellular serpin from *Echinococcus multilocularis*. Mol Biochem Parasitol 156:84–88
Meziourg D, Touil-Boukoffa C (2012) Interleukin-17A correlates with interleukin-6 production in human cystic echinococcosis: a possible involvement of IL-17A in immunoprotection against *Echinococcus granulosus* infection. Eur Cytokine Netw 23:112–119
Nakao M, Lavikainen A, Yanagida T, Ito A (2013a) Phylogenetic systematics of the genus *Echinococcus* (Cestoda: Taeniidae). Int J Parasitol 43:1017–2
Nakao M, Yanagida T, Konyaev S, Lavikainen A, Odnokurtsev VA, Zaikov VA, Ito A (2013b) Mitochondrial phylogeny of the genus *Echinococcus* (Cestoda: Taeniidae) with emphasis on relationships among *Echinococcus canadensis* genotypes. Parasitology 140:1625–1636
Naunyn B (1863) Über die zu *Echinococcus hominis* gehörige Taenie. Arch Anat Physiol Wiss Med 4:412–416
Nono JK, Pletinckx K, Lutz MB, Brehm K (2012) Excretory/secretory-products of *Echinococcus multilocularis* larvae induce apoptosis and tolerogenic properties in dendritic cells in vitro. PLoS Negl Trop Dis 6:e1516
Nunnari G, Pinzone MR, Gruttadauria S, Celesia BM, Madeddu G, Malaguamera G et al (2012) Hepatic

echinococcosis: clinical and therapeutic aspects. World J Gastroenterol 18:1448–1458

Ohnishi K, Kutsumi H (1991) Possible formation of calcareous corpuscles by the brood capsule in secondary hepatic mertacestodes of *Echinococcus multilocularis*. Parasitol Res 77:600–601

Ohnishi K, Kutsumi H (1995) Possible formation of new brood capsule by the previously formed brood capsule in *Echinococcus multilocularis* metacestodes. Southeast Asian J Trop Med Public Health 26:319–321

Pallas PS (1766) Miscellanea zoologica: Quibus novae imprimus atque obscurae animalium species. Describuntur et observationibus iconibusque illustrantur. Petrum van Cleff, The Hague

Parker RG (1959) Occlusion of the hepatic vein in man. Medicine (Baltimore) 38:369–402

Piorry PA (1828) De la percussion mediate et des signes obtenus à l'aide de ce nouveau moyen d'exploration, dans les maladies des organes thoraciques et abdominaux. Chaudé and Baillière, Paris

Posselt A (1931) Die pathologische Anatomie der vielkammerigen Blasenwurmgeschwulst. Frankf & schr pathol 41:45–99

Raciti A (1972) La syndrome di Budd-Chiari secondaria a cisti d'Echinococco de fegato. Gazzetta Internat Med Chir 77:1297

Redi F (1684) Osservazioni di Francesco Redi intorno agli animali viventi che si trovano negli animali viventi. Piero Martini, Florence

Sako Y, Yamasaki H, Nakaya K, Nakao M, Ito A (2007) Cloning and characterization of cathepsin L-like peptidases of *Echinococcus multilocularis* metacestodes. Mol Biochem Parasitol 154:181–189

Sako Y, Nakaya K, Ito A (2011) *Echinococcus multilocularis*: identification and functional characterization of cathepsin B-like peptidases from metacestode. Exp Parasitol 127:693–701

Sathyanarayanan V, Sambhaji C, Saravu K, Razak A, Polnaya A, Rao SN (2011) A rare case of hepatic cysticercosis. Asian Pac J Trop Biomed 2011: S141–S142

Scherer U, Weinzierl M, Sturm R, Schildberg FW, Zrenner M, Lissner J (1978) Computed tomography in hydatid disease of the liver: a report on 13 cases. J Comput Assist Tomogr 2:612–617

Schneider R, Gollackner B, Schindl M, Tucek G, Auer H (2010) *Echinococcus canadensis* G7 (pig strain): an underestimated cause of cystic echinococcosis in Austria. Am J Trop Med Hyg 82:871–874

Sickel JZ, Fultz PJ, Penwarden B, Laczin J (1995) Hepatic cysticercosis. Report of an unusual case. J Clin Gastroenterol 20:160–163

Singh N, Singh DK, Parihar A, Singh R (2012) Disseminated cysticercosis: rare manifestation of a common disease. BMJ Case Rep. 2012 pii: bcr2012007876

Smith WA (1863) On human entozoan: comprising the description of the different species of worms found in the intestines and other parts of the human body, and the pathology and treatment of the various affections produced by their presence. H.K. Lewis, London, pp 125–132, 154–158

Sparks AK, Neafie RC, Connor DH (1976) Cystocercosis. In: Binford CH, Connor DH (eds) Pathology of tropical and extraordinary diseases, vol 2. Armed Forces Institute of Patholog, Washington, DC, pp 539–543

Spiliotis M, Kroner A, Brehm K (2003) Identification, molecular characterization and expression of the gene encoding the epidermal growth factor receptor orthologue from the fox-tapeworm *Echinococcus multilocularis*. Gene 323:57–65

Stankovic N, Ignjatovic M, Nozic D, Hajdukovic Z (2005) Liver hydatid disease: morphological changes of protoscoleces after albendazole therapy. Vojnosanit Pregl 62:175–179

Tappe D, Frosch M (2007) Rudolf Virchow and the recognition of alveolar Echinococcosis, 1850s. Emerg Infect Dis 13:732–735

Tappe D, Zidowitz S, Demmer P, Kern P, Barth TF, Frosch M (2010) Three-dimensional reconstruction of *Echinococcus multilocularis* larval growth in human hepatic tissue reveals complex growth patterns. Am J Trop Med Hyg 82:126–127

Tsai IJ, Zarowiecki M, Holroyd N, Garciarrubio A, Sanchez-Flores A, Brooks KL, Tracey A et al (2013) The genomes of four tapeworm species reveal adaptations to parasitism. Nature 496:57–63

Vianna LG, Macedo V, Costa JM (1991) Musculocutaneous and visceral cysticercosis: a rare disease? (in Portuguese). Rev Inst Med Trop Sao Paulo 33:129–136

Vijayaraghavan SB (2004) Sonographic appearances in cysticercosis. J Ultrasound Med 23:423–427

Virchow R (1855) Die multiloculäre, ulcerierende Echinokokkengeschulst der Leber. Verh Physicalisch-Med Ges 1855:84–95

Vogel H (1978) How does the alveolar echinococcus grow? (in German). Tropenmed Parasitol 29:1–11

Von Siebold CT (1853) Über die Verwandlung der Echinococcus-Brut in Taenien. Z Wiss Zool 4:409–425

Voros D, Kalovidouris A, Gouliamos A, Vlachos L, Danias N, Papadimitriou J (1999) The real incidence of extracapsular (satellite) cysts of liver echinococcus. HPB Surg 11:249–252

Vuitton DA (1997) The WHO informal working group on Echinococcosis. The coordinating board of the WHO-IWGE. Acta Trop 67:147–148

Vuitton DA (2003) The ambiguous role of immunity in echinococcosis: protection of the host or of the parasite? Acta Trop 85:119–232

Vuitton DA, Zhang SL, Yang Y, Godot V, Beurton I, Mantion G, Bresson-Hadni S (2006) Survival strategy of *Echinococcus multilocularis* in the human host. Parasitol Int 55(suppl):S51–S55

Walbaum S, al Nahhas S, Gabrion C, Mesnil M, Petavy AF (1994) *Echinococcus multilocularis*: in vitro interactions between protoscolices and Kupffer cells. Parasitol Res 80:381–387

Wang J, Zhang C, Wei X, Blagosklonov O, Lv G, Lu X, Mantion G, Vuitton DA, Wen H et al (2013) TGF-b and

TGF-b/Smad signaling in the interactions between *Echinococcus multilocularis* and its hosts. PLoS One 8:e55379

Weinberg T (1947) *Echinococcus alveolaris* infection of the human liver. J Mt Sinai Hosp NY 13:331–336

WHO Informal Working Group (2003) International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. Acta Trop 85:253–261

Yamashita K, Uchino J, Sato N, Furuya K, Namieno T (1997) Establishment of a primary culture of *Echinococcus multilocularis* germinal cells. J Gastroenterol 32:344–350

Young HM (1923) Echinococcus cysts of the liver in a girl ten years old. Can Med Assoc J 13:48–49

Zeller E (1854) Alveolarcolloid der Leber. Thesis, University of Tübingen, Germany

Zhang W, Li J, Jones MK, Zhang Z, Zhao L, Blair D, McManus DP (2010) The *Echinococcus granulosus* antigen B gene family comprises at least 10 unique genes in five subclasses which are differentially expressed. PLoS Negl Trop Dis 4:e784

Tumor-Like Parasitic Lesions of the Hepatobiliary Tract: Round Worm Infestations

135

Contents

Abstract

Several species of round worms (nematodes) can induce circumscribed and in part tumor-like lesions in the liver. Pinworms of the genus *Enterobius* can, during their oviposition at the anal outlet, migrate into the genitourinary tract to invade the peritoneal cavity. From here they may enter the liver and produce parasite granulomas. The liver can also be involved in capillariasis. This is an infestation syndrome caused by in humans by several species of the genera *Calodium*, *Capillaria*, *Eucoleus*, and *Pearsonema*. In the liver, capillarids can induce mass lesions consisting of necrosis, granulomas with eosinophils, granulation tissue, and finally fibrosis. Toxocariasis denotes an infestation with larvae of nematode parasites of the genus *Toxocara*. Men acquire toxocariasis through the ingestion of embryonated eggs attached to hair and soil contaminated by the natural hosts, cats, and dogs. In the human liver, *Toxocara* induces eosinophilic granulomas, eosinophilic abscesses, pseudotumors, and focal calcifications.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_135

Hepatic Enterobiasis (Hepatic Pinworm Granuloma)

Introduction

Pinworms (*Enterobius*; threadworms; seatworms) are common intestinal nematode parasites that chiefly infest children in a worldwide distribution. Pinworms belong to the genus *Enterobius* (family Oxyuridae of the phylum Nematoda). Humans are hosts only to one of two *Enterobius* species, *Enterobius vermicularis* (formerly *Oxyuris vermicularis*) and *E. anthropopitheci*, parasitizing the chimpanzee. The infestation is called enterobiasis or oxyuriasis, the latter term being now obsolete. In Western countries, the pinworm is the most common parasitic worm infestation. In United States, the Center for Disease Control reported an overall incidence of 11.4 % among people of all ages, and in England the infestation rate in the childhood age group was 50 %.

The Parasite

The pinworm is a small and thin nematode, with females having a length of 8–13 mm and males 2–5 mm. The entire parasite life cycle takes place within the intestinal tract of a single human host. Eggs contaminate a wide spectrum of objects, including the hands and fingernails, bed linen, cushions, night clothing, water, food, furniture, toys, bathroom and toilet objects, and house pets. After ingestion of embryonated eggs, the eggs hatch in the duodenal lumen. The hatched larvae rapidly grow and migrate through the intestine to the colon, with two molts underway to reach the mature stage. Pinworms mate in the ileum. Egg laying starts about 5 weeks post ingestion of eggs. In the course of egg laying, the female migrates through the colon (12–14 cm/h) to reach the rectum and the anal canal. The female emerges from the anus and stays on the anal skin in order to obtain oxygen required for egg maturation.

Hepatic Enterobiasis

During their oviposition at the anal outlet, pinworms can migrate into the genitourinary tract and may ascend the uterine cavity and the uterine tubes and enter the peritoneal cavity. In the abdominal cavity, *Enterobius* is known to cause parasite granulomas in several organs and tissues, including the liver. Few cases of hepatic enterobiasis (oxyuriasis) have been reported. Hepatic manifestations are of certain interest insofar as the liver nodules induced by the parasite can be misinterpreted as malignancies, in particular metastases. The first case may have been reported in 1973 (Little et al. 1973). In a later report, oxyural granuloma of the liver was observed in a 62-year-old female with a history of recurrent surgery for colorectal cancer (Daly and Baker 1984). So-called threadworm or pinworm granuloma was reported by other authors (Slais 1962/1963; Ng et al. 2004). In a 74-year-old male patient, a nodule was incidentally seen at the liver surface during left colectomy. Histology revealed a granuloma containing numerous *Enterobius* eggs and a cross section of a mature nematode (Mondou and Gnepp 1989). Several reports document the tumor-like presentations of hepatic oxyuriasis (Arkoulis et al. 2012; Roberts et al. 2012). In one patient, a solitary liver nodule was diagnosed as a liver metastasis following rectal cancer. The resection specimen showed a necrotic nodule containing *E. vermicularis* (Roberts et al. 2012).

Capillariasis

Introduction

Capillariasis is an infestation syndrome caused by several species of the nematode family Capillariidae, containing 17 genera and more than 300 species (Okulewicz and Zalesny 2005). Humans are infested by four species of capillarids, viz., *Calodium hepaticum*, *Capillaria philippinensis*, *Eucoleus aerophilus*, and

Pearsonema plica (formerly *Capillaria plica*) (-Moravec 2001). *Calodium hepaticum* (synonyms: *Capillaria hepatica*; *Hepaticola hepatica*, Bancroft 1893) is the main parasite causing the zoonosis, capillariasis, and is a nematode parasite of wild rodents and other mammals, including primates and humans. Human capillariasis (visceral larva migrans; Lee et al. 1976) is an infestation that was first reported in 1924 (McArthur 1924). The clinical presentation is variable, sometimes rather bland, with nonspecific upper abdominal discomfort. Hepatomegaly (sometimes persistent febrile hepatomegaly) and peripheral eosinophilia are well-known features.

Hepatic Capillariasis

Several reports have described hepatic capillariasis, which may produce mass lesions (McArthur 1924; Berger et al. 1990; Pannenbecker et al. 1990; Choe et al. 1993; Tesana et al. 2007; Fuehrer et al. 2011). In the liver, *C. hepaticum* induces necrosis, granulomas with variable eosinophil infiltration and Charcot-Leyden crystalloids, granulation tissue, and finally fibrosis. Multinucleated giant cells may be noted (Attah et al. 1983; Kaplan et al. 2001). Within this inflamed area, barrel-shaped bioperculated eggs are seen, showing polar plugs and a thick trilaminar capsule with striation of the outer layer. The parasite is a known cause of solitary necrotic nodule of the liver (Koea and Smith 2008). In part of the cases, the chronic inflammatory process can induce septal fibrosis of the liver (Ferreira and Andrade 1993), a phenomenon which has also been observed in hepatic capillariasis of the rat (Santos et al. 2001, 2007). Hepatic capillariasis may cause a hepatic mass associated with locoregional lymphadenopathy, suggesting a neoplastic process (Kohatsu et al. 1995; Klenzak et al. 2005). In a 54-year-old man with such a mass lesion, the segmental resection specimen showed a 2.5 cm, irregular serpiginous mass of necrotizing granulomatous inflammation with marked eosinophilia and several small degenerating roundworms exhibiting the banded esophageal stichosome typical for *Calodium hepaticum* (Klenzak et al. 2005).

Toxocariasis

Introduction

Toxocariasis denotes the infestation with larvae of nematode parasites of the genus *Toxocara*. In the human host, two *Toxocara* species are recognized as parasites, *T. canis* and less often *T. cati*. Wilder in 1950 was the first to described toxocariasis in humans, based on the observations of ocular granulomas in patients thought to have retinoblastoma, and disease was then described in more detail in 1952 (Beaver et al. 1952). It is currently assumed that toxocariasis is the most common human parasitic worm infestation in the United States, affecting millions of Americans living in poverty. Toxocariasis is also highly prevalent in many developing countries, owing to a very high infestation rate of dogs (Hotez and Wilkins 2009). In North America, the prevalence of *Toxocara* infestation is about 20 % for adult dogs and 80 % for puppies, while in Mexico the prevalence is 28–42 % for cats. The mature *T. canis* living in the intestine of canines is an ascariform roundworm.

In the human host, toxocariasis is acquired via ingestion of infective embryonated eggs from hair and soil contaminated with the feces of the natural hosts, dogs and cats, this mode of acquisition being typical for preschool children, but toxocariasis is also a food-borne disorder in societies where the consumption of raw meat is prevalent. Infestation by ingestion of raw meat, specifically uncooked liver from paratenic hosts (mainly pig and poultry viscera), is becoming more frequent. Also the ingestion of raw cow liver is a pathway of infestation. When humans ingest embryonated eggs, larvae hatch in the intestine, whereas in the case of ingestion of infested raw meat, arrested larvae are present. In both

situations, larvae invade the intestinal wall and get access to the portal venous blood stream. The larvae settle in the liver, lungs, and other organs, where their development is arrested in the human host. In the liver, the larvae are 0.5 mm in length. During their slow migration in hepatic parenchyma, they induce an immune reaction with epithelioid macrophages, giant cells, and eosinophilia, the lesions slowly growing to sizes exceeding 1 cm.

Hepatic Toxocariasis

Toxocara invading the liver produces distinct focal lesions that may closely mimic metastatic disease (Park et al. 2012). Densely packed lesions in severe hepatic infestation (Hartleb and Januszewski 2001) may coalesce to form tumor-like masses that may require hepatic resection (Takacs et al. 2004; Chang et al. 2006). As parasites are not easy to identify as such, serological tests are crucial for the establishment of diagnosis (rapid screening ELISA, quantitative ELISA, immunodiffusion tests) using *Toxocara* excretory-secretory antigens.

Toxocariasis of the liver is characterized by several types of focal lesions, part of which may mimic a neoplastic process (Table 1).

In the liver, the migrating *Toxocara* larvae induce a granulomatous reaction accompanied by variable and sometimes marked eosinophilia (parasitic eosinophilic granuloma and eosinophilic abscess; Rayes et al. 1999; Kaplan et al. 2001; Leone et al. 2006; Jung et al. 2007; Lee and Shin 2011; Treska et al. 2011; Mukund et al. 2013). This reaction is driven by excretory-secretory antigens produced by the larvae (Kayes 1997). The center of the lesions is often occupied by a granular eosinophilic material probably consisting of necrotic and apoptotic cells and parasitic proteins. This part is surrounded by a rim of epithelioid macrophages sometimes forming round granulomas with or without multinucleated giant cells. The granulomatous reaction is surrounded by an eosinophilic infiltrate of variable density, sometimes with typical Charcot-Leyden crystalloids. Eosinophilic parasite granulomas may coalesce to form large conglomerated masses, mimicking a neoplastic process (parasitic eosinophilic hepatic pseudotumors; Chang et al. 2006; Kantarcioglu et al. 2009; Jackson et al. 2010; Pilsczek 2010). Numerous large nodules can resemble hepatic metastatic disease (Ota et al. 2009). In the center of the lesions, more or less intact components of the PAS-positive larvae can be seen. Mainly in peripheral parts of the lesion, a lymphocytic infiltration is observed, the cells also being intermingled with the epithelioid macrophages. *T. canis* elicits both T helper (Th)1 and Th2 responses with Th2 predominance, the latter being important for eosinophilia and IgE production. A subset of lymphocytes belong to the $CD25^{+}CD4^{+}$ regulatory T cell population (Fehérvari and Sakaguchi 2004). The lymphocyte populations surrounding the lesions' cores have been shown to contain Foxp3-expressing regulatory cells (Othman et al. 2011; Fan et al. 2013), cells that have been shown to be important for the homeostasis of the immune system and to play a distinctive role in the regulation of parasite-induced immune reactions. In experimental toxocariasis, the density of these cells increased as a function of the lesions' evolution, and the cells were also detected in adjacent portal tracts (Othman et al. 2011). De novo Foxp3 expression in T cells is stimulated by parasitic antigens, in particular excretory-secretory antigens, through the TGF-beta pathway (Grainger et al. 2010).

Table 1 Liver manifestations of toxocariasis

Parasitic eosinophilic granuloma
Eosinophilic abscess
Parasitic eosinophilic hepatic pseudotumor
Focal calcifications

References

Arkoulis N, Zerbinis H, Simatos G, Nisiotis A (2012) Enterobius vermicularis (pinworm) infection of the liver mimicking malignancy: presentation of a new case and review of current literature. Int J Surg Case Rep 3:6–9

Attah et al. (1983). http://www.ncbi.nlm.nih.gov/pubmed/6849289
Bancroft TL (1893) On the whip-worm of the rats liver. J Proc Royal Soc New South Wales 27:86–90
Beaver PC, Synder CH, Carrera GM (1952) Chronic eosinophilia due to visceral larva migrans. Pediatrics 9:7–19
Berger T, Degrémont A, Gebbers JO, Tönz O (1990) Hepatic capillariasis in a 1-year-old child. Eur J Pediatr 149:333–336
Chang S, Lim JH, Choi D, Park CK, Kwon NH, Cho SY, Choi DC (2006) Hepatic visceral larva migrans of Toxocara canis: CT and sonographic findings. AJR Am J Roentgenol 187:W622–W629
Choe G, Lee HS, Seo JK, Chai JY, Lee SH, Eom KS, Chi JG (1993) Hepatic capillariasis: first case report in the Republic of Korea. Am J Trop Med Hyg 48:610–625
Daly JJ, Baker GF (1984) Pinworm granuloma of the liver. Am J Trop Med Hyg 33:62–64
Fan CK, Liao CW, Cheng YC (2013) Factors affecting disease manifestation of toxocarosis in humans: genetics and environment. Vet Parasitol 193:342–352
Fehérvari Z, Sakaguchi S (2004) Development and function of $CD25^{+}CD4^{+}$ regulatory T cells. Curr Opin Immunol 16:203–208
Ferreira LA, Andrade ZA (1993) Capillaria hepatica: a cause of septal fibrosis of the liver. Mem Inst Oswaldo Cruz 88:441–447
Fuehrer HP, Igel P, Auer H (2011) Capillaria hepatica in man – an overview of hepatic capillariosis and spurious infections. Parasitol Res 109:969–979
Grainger JR, Smith KA, Hewitson JP, McSorley HJ, Harcus Y, Filbey KJ, Finney CA, Greenwood EJ et al (2010) Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF-b pathway. J Exp Med 207:2331–2341
Hartleb M, Januszewski K (2001) Severe hepatic involvement in visceral larva migrans. Eur J Gastroenterol Hepatol 13:1245–1249
Hotez PJ, Wilkins PP (2009) Toxocariasis: America's most common neglected infection of poverty and ahelminthiasis of global importance?. http://www.ncbi.nlm.nih.gov/pubmed/19333373
Jackson G, Kathuria M, Abraham B, Schnadig VJ (2010) Fine needle aspiration diagnosis of necrotizing eosinophilic abscess clinically mimicking hepatic neoplasia: a case report. Acta Cytol 54:60–62
Jung JK, Jung JT, Lee CH, Kim EY, Kwon JG, Kim BS (2007) A case of hepatic abscess caused by toxocara (in Korean). Korean J Hepatol 13:409–413
Kantarcioglu M, Turan I, Karslioglu Y, Kilciler G (2009) An unusual cause of liver masses. Liver Int 29:1348–1349
Kaplan KJ, Goodman ZD, Ishak KG (2001) Eosinophilic granuloma of the liver: a characteristic lesion with relationship to visceral larva migrans. Am J Surg Pathol 25:1316–1321
Kayes SG (1997) Human toxocariasis and the visceral larva migrans syndrome: correlative immunopathology. Chem Immunol 66:99–124
Klenzak J, Mattia A, Valenti A, Goldberg J (2005) Hepatic capillariasis in Maine presenting as a hepatic mass. Am J Trop Med Hyg 72:651–653
Koea J, Smith D (2008) Solitary necrotic nodule revisited. ANZ J Surg 78:109–111
Kohatsu H, Zaha O, Shimada K, Chibana T, Yara I, Shimada A, Hasegawa H, Sato Y (1995) A space-occupying lesion in the liver due to Capillaria infection. Am J Trop Med Hyg 52:414–418
Lee, Shin (2011). http://www.ncbi.nlm.nih.gov/pubmed/22042425
Lee KT, Min HK, Chung PR, Chang JK (1976) Studies on the inducing possibility of human visceral larva migrans associated with eating habit of raw liver of domestic animals. Korean J Parasitol 14:51–60
Leone N, Baronio M, Tosdros L, David E, Brunello F, Artioli S, Rizzetto M (2006) Hepatic involvement in larva migrans of Toxocara canis: report of a case with pathological and radiological findings. Dig Liver Dis 38:511–514
Little MD, Cuello CJ, D'Alessandro A (1973) Granuloma of the liver due to Enterobius vermicularis. Report of a case. Am J Trop Med Hyg 22:567–569
McArthur WP (1924) A case of infestation of human liver with Hepaticola hepatica (Bancroft, q893) Hall, 1916; with sections from the liver. Proc RSoc Med 17:83–84
Mondou EN, Gnepp DR (1989) Hepatic granuloma resulting from *Enterobius vermicularis*. Am J Clin Pathol 91:97–100
Moravec (2001). http://www.ncbi.nlm.nih.gov/pubmed/11227884
Mukund A, Arora A, Patidar Y, Mangla V, Bihari C, Rastogi A, Sarin SK (2013) Eosinophilic abscesses: a new facet of hepatic visceral larva migrans. Abdom Imaging 38:774–777
Ng WS, Gallagher J, McCaughan G (2004) "Pinworm" infection of the liver: unusual CT appearance leading to hepatic resection. Dig Dis Sci 49:466–468
Okulewicz A, Zalesny G (2005) Biodiversity of Capillariinae (in Polish). Wiad Parazytol 51:9–14
Ota KV, Dimaras H, Héon E, Babyn PS, Yau YC, Read S, Budning A, Gallie BL, Chan HS (2009) Toxocariasis mimicking liver, lung, and spinal cord metastases from retinoblastoma. Pediatr Infect Dis 28:252–254
Othman AA, El-Shourbagy SH, Soliman RH (2011) Kinetics of Foxp3-expressing regulatory cells in experimental Toxocara canis infection. Exp Parasitol 127:454–459
Pannenbecker J, Miller TC, Miller J (1990) Capillaria hepatica. Monatschr Kinderheilk 138:767–777
Park S, Kim YS, Kim YJ, Kyung SY, Park JW, Jeong SH, Lee SP (2012) Toxocariasis masquerading as liver and lung metastatic nodules in patients with gastrointestinal cancer: clinicopathologic study of five cases. Dig Dis Sci 57:155–160
Pilsczek FH (2010) Helminthic infections mimicking malignancy: a review of published case reports. J Infect Dev Ctries 4:425–429

Rayes et al. (1999). http://www.ncbi.nlm.nih.gov/pubmed/10482069

Roberts KJ, Hübscher S, Mangat K, Sutcliffe R, Marudanayagam R (2012) Pinworm infection masquerading as colorectal liver metastasis. Ann R Coll Surg Engl 94:e195–e197

Santos AB, Tolentino M, Andrade ZA (2001) Pathogenesis of hepatic septal fibrosis associated with Capillaria hepatica infection of rats. Rev Soc Bras Med Trop 34:503–506

Santos CC, Onofre-Nunes Z, Andrade ZA (2007) Role of partial hepatectomy on Capillaria hepatica-induced hepatic fibrosis in rats. Rev Soc Bras Med Trop 40:495–498

Slais J (1962/63) A threadworm granuloma of the human liver. Helminthologia 4:479–483

Takacs I, Pakozdi A, Szekanecz Z, Vagvölgyi A, Dezso B, Dévényi K, Sapy P (2004) Liver resection for a rare parasitic infection – visceral larva migrans (in Hungarian). Orv Hetil 145:1333–1336

Tesana S, Puapairoi A, Saeseow O (2007) Granulomatous, hepatolithiasis and hepatomegaly caused by Capillaria hepatica infection: first case report of Thailand. Southeast Asian J Trop Med Public Health 38:636–640

Treska V, Sutnar A, Mukensnabl P, Manakova T, Sedlacek D, Mirka H, Ferda J (2011) Liver abscess in human toxocariasis. Bratisl Lek Listy 112:644–647

Tumor-Like Parasitic Lesions of the Hepatobiliary Tract: Pentastomiasis

136

Contents

Abstract

Pentastomiasis (so-called tongue worm infestation) is an infestation by members of the *Pentastomida*, a group of taxons related to crustacean arthropods. Species that infest humans belong to pentastomid families *Linguatulidae*, *Armilliferidae*, and *Porocephalidae*. More than 90 % of human cases are caused by larvae or nymphs of *Linguatula serrata* and *Armillifer armillatus*. Adult reproducing pentastomids inhabit the respiratory tract of reptiles and amphibians, in particular snakes. Man can become infested through contact with infested snakes and their food, i.e., rodents, or contaminated environment. The human host can only harbor larvae. In humans, visceral pentastomiasis, including the hepatic form, is caused by larval stages that migrate to the liver and form solitary or multiple, tumor-like nodules. These mainly consist of necrotic tissue, but may contain larval remnants.

Introduction

Human pentastomiasis (tongue worm infestation) is an infestation by members of the *Pentastomida Diesing*, 1836. This is an ancient parasitic zoonosis that has been described in the eighteenth and early nineteenth centuries (Frölich 1789; Rudolphi 1819; Diesing 1835) and in more detail by Pruner in 1847, the parasite (or one of them)

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_136

then being scientifically described by Wyman in 1848 (reviews Sambon 1922; Cannon 1942; Self and Kuntz 1967; Self 1969; Drabick 1987; Tappe and Büttner 2009).

Pentastomids or tongue worms form a group of parasitic invertebrates that are not "worms" but are phylogenetically related to arthropods (see below) and are composed of numerous taxons that have recently been revised (Poore 2012; Christoffersen and De Assis 2013). Many taxons of vertebrates are parasitized by pentastomids, including man. The human host is infested by the larval stages (nymphs) of only a few species of pentastomids (*Linguatula serrata*, *Armillifer armillatus*, *Armillifer moniliformis*, *Armillifer grandis*, *Porocephalus crotali*, and *Porocephalus taiwana*). Infestations with *Linguatula serrata* are termed linguatuliasis, those with *Porocephalus* species, porocephalosis. The phylogenetic positioning of pentastomids among metazoans has a complex history. Originally placed in a separate phylum of wormlike animals, the parasites are currently defined as arthropods (based on molecular studies) and assigned to a separate subclass of the crustacean class *Maxillopoda*, related to fish lice/*Branchiura*. The taxonomical term, *Ichthyostraca*, has been proposed for a clade comprising *Branchiura* + *Pentastomida*. The anterior end of the parasite is equipped with four clawed retractile leg-like structures and an armed mouth constructed for blood sucking. These five structures evoking the impression of five mouths have led to the organisms' name, pentastomids ("those with five mouths"). The life cycle includes a main host and an intermediate host. Pentastomids are bloodsucking endoparasites that normally inhabit the lung and other parts of the respiratory tract of reptiles and amphibians, especially snakes (Riley and Henderson 1999). It is estimated that around 70 % of the definitive hosts are snakes, followed by crocodiles, lizards, amphibians, and turtles. Few species occur in marine birds, and one (*Linguatula serrata*) occurs in the nasopharynx of canines. Embryonated eggs laid by the parasites are discharged by the nasal and fecal discharges of the animal hosts and contaminate soil, vegetation, and several types of water bodies. Intermediate hosts comprise mammals (mainly rodents and small herbivores such as goats and sheep), reptiles, amphibians, and insects. Rodents as important intermediate hosts acquire the embryonated eggs via ingestion of contaminated environmental components (mainly plants). The eggs hatch in the intestine, and the larvae burrow their way into the visceral cavity and into more remote organs, where they encyst within a variety of tissue sites (often abdominal fat bodies, liver, lymph nodes, and lungs), causing the development of granulomas with eosinophil infiltration and a mast cell reaction (McHardy et al. 1993). When snakes predate on these infested rodents, the life cycle is completed. Through contact with contaminated environmental components and infested snakes or rodents, carnivores, herbivores, and man can become infested, the pathway being thought to be same as in rodents (see above). Man can be infested by direct handling of infested snakes, utilizing snakes or other edible reptiles as food (Magnino et al. 2009), via contact with oral slime, or through contact with fecal droppings. A special situation occurs when raw or incompletely cooked offal of infested herbivores or carnivores harboring large numbers of parasites is consumed, causing infestation of the human or animal nasopharynx (a disorder called halzoun or halazoun, or Marrara syndrome; Kirk 1958; Khalil and Schacher 1965; Schacher et al. 1969; Yagi et al. 1996; Morsy et al. 1999). In halzoun, worm-shaped parasites are released in the nasal discharge, e.g., during coughing and sneezing.

Epidemiology

Species that infest humans belong to the pentastomid families *Linguatulidae*, *Armilliferidae*, and *Porocephalidae*. More than 90 % of human cases are caused by the larvae/nymphs of *Linguatula serrata* and *Armillifer armillatus*. Most human cases of pentastomiasis have been reported from Africa, Southeast Asia, and the Middle East, less often from East Asia and Latin America. The disorder is rare in North America and Europe (Tappe and Büttner 2009). The highest prevalences are known from necropsy records in Malaysia (45.4 %; with a large

proportion of aborigines; Prathap et al. 1969) and Central Africa (22.5 %; Meyers et al. 1976). In Europe and North America, most cases seem to refer to persons having emigrated from endemic areas.

Hepatic Pentastomiasis

Visceral pentastomiasis in humans is caused by larval stages (nymphs) of pentastomids. The liver is frequently involved (Gast-Galvis 1960; Gardiner et al. 1984; Baird et al. 1988; Guardia et al. 1991; Ma et al. 2002; Dakubo et al. 2008; Yao et al. 2008). Part of patients, specifically those having widespread liver involvement, become symptomatic, with abdominal pain, abdominal tension, fever, diarrhea, weight loss, and anemia (Lai et al. 2010; Wang et al. 2013). The parasite larvae elicit a distinct type of hepatic necrosis associated with an inflammatory response, forming usually spherical lesions. In patients with disseminated liver involvement, severe parenchymal damage and hepatic encephalopathy may develop. In one of these patients, the entire liver was studded with numerous calcified parasite nodules, which were also detected in the bowel, rectum, mesentery, and urinary bladder (Adeyekun et al. 2011).

Multifocal hepatic pentastomiasis presents as numerous small, pearly, cystic, and friable nodules 3–10 mm in diameter ("*Linguatula* nodules"; Symmers and Valteris 1950; Guardia et al. 1991; Ma et al. 2002; Latif et al. 2011). Larger lesions may resemble hepatic abscess (Latrive et al. 1980) or may cause infarct-like mass lesions mimicking a hepatic tumor (Machado et al. 2006). In the case reported by Machado and coworkers (2006), a liver mass had been detected during routine abdominal ultrasound examination, visualized as a 3 cm tumor in segment VI on CT images. The resection specimen revealed a white, soft, well-defined rounded lesion with peripheral endurance and a cystic central area. During the opening of the specimen, a white tubular wormlike organism measuring 2 cm in length was noted inside. In some cases of hepatic pentastomiasis, a miliary pattern of the lesions has also been described

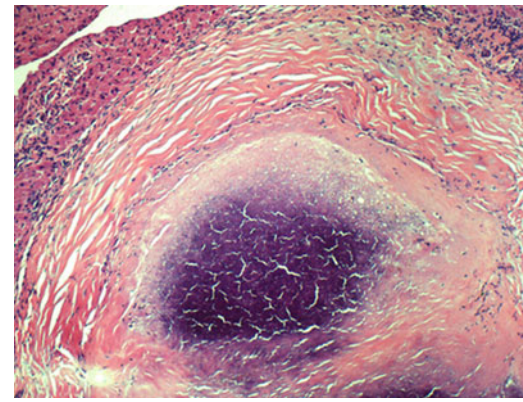

Fig. 1 Pentastomiasis (tongue worm infestation) of the liver. The spherical lesion is characterized by central necrosis with dystrophic calcifications, surrounded by a fibrous zone. Parasite remnants are often not detectable (hematoxylin and eosin stain)

(Yao et al. 2008), probably representing granuloma formation. The larva and the associated tissue reaction may be seen in the form of typically pearly and sometimes protruding foci on the surface of the liver (Ma et al. 2002; Dakubo et al. 2008). A free larva stuck in an intrahepatic portal vein radicle was observed (Dakubo et al. 2008). In some of the fresh resection specimens, coiled nymphs can be found and isolated.

Histologically, the lesions are characterized by three types of patterns. The first pattern is that with a preserved (viable) parasite, described below. The second and most common pattern is characterized by a focus of necrosis developing after death of the parasite, with or without detectable nymph, often surrounded by a thin rim of epithelioid macrophages and a collagenous capsule-like zone (Fig. 1). The necrotic foci resemble caseification and may show calcification (in particular, calcified parasite remnants), these changes tending to be concentric and targetoid in appearance (Ma et al. 2002). Outside the fibrous zone, one notes dense infiltrates of lymphocytes, macrophages, plasma cells, eosinophils, and sometimes multinucleated giant cells, as dead pentastomids release large amounts of parasite antigens (Tappe and Büttner 2009). Pentastomiasis of the liver can elicit a marked and florid granulomatous reaction surrounding the necrotic center of the lesions (Gardiner

et al. 1984; Baird et al. 1988), but in older lesions this reaction tends to be replaced by fibrosis/scarring. The third lesion pattern is seen after the dead parasite has been resolved and the immune reaction has been downregulated, leaving a central calcified necrosis within a hyalinized scar surrounded by minor round cell infiltrates.

In a considerable number of cases, no conclusive parasitic remnants are seen in the necrotic masses, except some cuticular fragments (Ali-Kahn and Bowner 1972; Self 1972; Self et al. 1972). In these situations, the parasitological diagnosis is difficult or impossible. However, some of the lesions may show better preserved parasites or parts thereof, in the form of a worm-like organism arranged in a flat C-shaped spiral and located in a cystic space. After several molts within the focus, the nymphs resemble adult pentastomes in shape, albeit they are smaller/shorter. The living parasite is surrounded by a thin rim of secreted eosinophilic material. Lesions harboring viable parasites usually show less inflammatory reaction, because less antigenic material is shedded (Tappe and Büttner 2009). Remnants of dead parasites are visualized as more or less complete necrotic shadows of the parasite with the oral and circumoral apparatus, as two pairs of circumoral hook-like structures, or scissors-like structures indicating a longitudinal section of a hook (Ma et al. 2002). Mouth parts with arciform fulcra may be found, with largest transverse diameter of 90–100 μm, consistent with the measurement of the mouth region of the *L. serrata* nymph (Ma et al. 2002).

References

Adeyekun AA, Ukadike I, Adetiloye VA (2011) Severe pentastomide Armillifer armillatus infestation complicated by hepatic encephalopathy. Ann Afr Med 10:59–62

Ali-Kahn Z, Bowner EJ (1972) Pentastomiasis in Western Canada: a case report. Am J Trop Med Hyg 21:58–61

Baird JK, Kassebaum LJ, Ludwig GK (1988) Hepatic granuloma in a man from North America caused by a nymph of Linguatula. Pathology 20:198–199

Cannon DA (1942) Linguatulid infestation of man. Ann Trop Med Parasitol 36:160–167

Christoffersen ML, De Assis JE (2013) A systematic monograph of the recent Pentastomida, with a compilation of their hosts. Zool Med Leiden 87:1–206

Dakubo et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/19452026

Diesing KM (1835) Versuch einer Monographie der Gattung Pentastoma. Ann Wien Mus Naturgesch 1:1–32

Drabick 1987. http://www.ncbi.nlm.nih.gov/pubmed/3321358

Frölich JA (1789) Beschreibung einiger neuer Eingeweidewürmer. Der Naturforscher 24:101–162

Gardiner CH, Dyke JW, Shirley SF (1984) Hepatic granuloma due to a nymph of Linguatula serrata in a woman from Michigan: a case report and review of the literature. Am J Trop Med Hyg 33:187–189

Gast-Galvis A (1960) Linguatula serrata in a human liver (in Spanish). Bol Chil Parasitol 15:15–16

Guardia SN, Sepp H, Scholten T, Morava-Protzner I (1991) Pentastomiasis in Canada. Arch Pathol Lab Med 115:515–517

Kirk R (1958) Notes on a form of parasitic pharyngitis in the Middle East Known as "halazoun". Al Hakeim Khartoum 4:6–11

Khalil and Schacher 1965. http://www.ncbi.nlm.nih.gov/pubmed/4953379

Lai et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20592934

Latif B, Omar E, Heo CC, Othman N, Tappe D (2011) Human pentastomiasis caused by *Armillifer moniliformis* in Malaysian Borneo. Am J Trop Med Hyg 85:878–881

Latrive JP, Trinh Dinh H, Ho Thi S, Huguier M, Le Quintrec Y (1980) Liver abscess and visceral linguatulosis with *Linguatula serrata*. A case report with radiologic and histologic studies (in French). Sem Hop 56:567–569

Ma KC, Qiu MH, Rong YL (2002) Pathological differentiation of suspected cases of pentastomiasis in China. Trop Med Int Health 7:166–177

Machado MA, Makdissi FF, Canedo LF, Martino R:B, Crescentini F, Chieffi PP, Bacchella T, Machado MC (2006) Unusual case of pentastomiasis mimicking liver tumor. J Gastroenterol Hepatol 21:1218–1220

Magnino S, Colin P, Dei-Cas E, Madsen M, McLaughlin J, Nöckler K, Maradona MP et al (2009) Biological risks associated with consumption of reptile products. Int J Food Microbiol 134:163–175

McHardy P, Riley J, Huntley JF (1993) The recruitment of mast cells, exclusively of the mucosal phenotype, into granulomatous lesions caused by the pentastomid parasite *Porocephalus crotali*: recruitment is irrespective of site. Parasitology 106:47–54

Meyers WM, Neafie RC, Connor DH (1976) Pentastomiasis. In: Binford CH, Connor DH (eds) Pathology of tropical and extraordinary diseases, vol 2. Armed Forces Institute of Pathology, Washington D. C, pp 546–550

Morsy et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/12561918
Poore GC (2012) The nomenclature of the recent Pentastomida (Crustacea), with a list of species and available names. Syst Parasitol 82:211–240
Prathap K, Lau KS, Bolton JM (1969) Pentastomiasis: a common finding at autopsy among Malaysian aborigines. Am J Trop Med Hyg 18:20–27
Riley J, Henderson RJ (1999) Pentastomids and the tetrapod lung. Parasitology 119(suppl):S89–S105
Rudolphi KA (1819) Entozoorum synopsis. Augustus Rücker, Berlin
Sambon LW (1922) A synopsis of the family Linguatulidae. J Trop Med Hyg 12:188–206
Schacher et al. 1969. http://www.ncbi.nlm.nih.gov/pubmed/5368014
Self JT (1969) Biological relationships of the Pentastomida: a bibliography on the Pentastomida. Exp Parasitol 21:63–119
Self JT (1972) Pentastomiasis: host responses to larval and nymphal infections. Trans Am Microsc Soc 91:2–8
Self JT, Kuntz RE (1967) Host-parasite relations in some Pentastomida. J Parasitol 32:117–126
Self JT, Hopps HC, Williams AO (1972) Porocephaliasis in man and experimental mice. Exp Parasitol 32:117–126
Symmers WS, Valteris K (1950) Two cases of human infestation by larvae of *Linguatula serrata*. J Clin Pathol 3:212–219
Tappe D, Büttner DW (2009) Diagnosis of human visceral pentastomiasis. PLoS Negl Trop Dis 5, e320
Wang HY, Zhu GH, Luo SS, Jiang KW (2013) Childhood pentastomiasis: a report of three cases with the following-up data. Parasitol Int 62:289–292
Yagi H, el Bahari S, Mohamed HA, Ahmed El-R S, Mustafa B, Mahmoud M, Saad MB et al (1996) The Marrara syndrome: a hypersensitivity reaction of the upper respiratory tract and buccopharyngeal mucosa to nymphs of *Linguatula serrata*. Acta Trop 62:127–134
Yao MH, Wu F, Tang LF (2008) Human pentastomiasis in China: case report and literature review. J Parasitol 94:1295–1298

Tumor-Like Necroses of the Liver: Liver Infarct and Hepatic Pseudo-infarct (Zahn's Infarct)

137

Contents

Abstract

Liver infarcts are macroscopic parenchymal alterations that may mimic, through their mass effect, neoplastic processes. An anemic infarct or infarction of the liver is defined as an ischemic necrosis that is usually caused by hepatic artery occlusion, thrombosis of the celiac artery, portal vein occlusion, or mixed hepatic vascular occlusions. Although hepatic artery circulation is crucial for the biliary tract, acute occlusion of this artery can also cause hepatic ischemic necrosis. Anemic liver infarcts are well-demarcated pale areas of sometimes more than 10 cm diameter, often wedge shaped and located both peripherally and deep in the liver substance. These lesions can undergo secondary changes, including abscess formation following infection, hemorrhage, liquefaction, calcification, bile accumulation, and fibrosis/scarring. Large infarcts may be separated from preserved liver parenchyma, a process termed sequestration. In contrast to true infarct, hepatic pseudo-infarct or Zahn's infarct is a well-demarcated zone of hepatic congestion leading to parenchymal atrophy.

Introduction

Infarct (anemic infarction) of the liver is defined as an ischemic necrosis that results in a macroscopically visible area or mass that may be confounded with a neoplastic process. In contrast,

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_137

pseudo-infarct of the liver (Zahn's infarct) represents a hepatic area of marked congestion associated with atrophy of the parenchyma, but without coagulation necrosis. True anemic liver infarct can, due to the altered features of tissue and tissue swelling, produce a mass that can closely mimic a hepatic tumor (Bohn et al. 2010).

Epidemiology

True anemic infarction of the liver is rare, but has already been described in the nineteenth century (Rattone 1888; Ogle 1895; Baldwin 1902; Rudczynski 1905; Kretz 1916; Wiessner 1917; Pass 1935; Woolling et al. 1953; Parker 1955; Kanter 1965; Seeley et al. 1972; Soni and Persaud 1972; Chen et al. 1976). The rarity of this lesion has been attributed to the protection of the liver from ischemic events and complications provided by the double arterial and portal venous blood supply. However, this proposed explanation does not hold true, because if the arterial blood supply alone is arrested, an intact portal venous blood supply cannot protect the liver from infarction in many cases (Nakata and Kanbe 1966; review: Carroll 1963). Winternitz (1911) did not encounter a single case among 3,500 autopsies performed at Johns Hopkins Hospital. In an investigation of 5,420 consecutive autopsy cases, 20 hepatic infarction cases could be selected in Japan (Saegusa et al. 1993). Anemic liver infarction is a disorder mainly occurring in adults, but it also exists in the pediatric age group (Kochin et al. 2011).

Etiology of True Hepatic Infarction

Numerous types of vascular lesions can cause anemic liver infarction, but most of the reported cases are due to occlusion of the hepatic artery related to various pathologies. The main vascular lesions causing, or associated with, liver infarction are listed in Table 1. It has once again to be emphasized that an intact portal vein blood flow cannot protect the liver substance from infarction when the hepatic arterial blood flow is arrested. In addition to distinct occlusive events of hepatic blood vessels, systemic circulation failure can significantly contribute to the development of hepatic infarction, even in the absence of complete vascular occlusion. In the autopsy study of Saegusa and coworkers (1993), 85 % of the infarct cases were clinically associated with systemic circulatory insufficiency. In fact, the pathogenesis of hepatic infarction often requires an association of several factors synchronously compromising compensatory blood flow mechanisms in the liver.

Table 1 Vascular lesions causing anemic infarction of the liver

Hepatic artery occlusion
Spontaneous thrombosis of the hepatic artery
Hepatic artery thrombosis in hepatic cancer
Hepatic artery thromboembolism
Embolized vegetations in bacterial endocarditis
Polyarteritis nodosa and other types of arteritis/vasculitis
Hepatic artery aneurysms and pseudoaneurysms
Dissecting aortic aneurysm
Coagulopathies
Accidental artery ligation
Thrombosis of the celiac artery
Portal vein (PV) occlusion
PV occlusion in liver cirrhosis
PV occlusion in hematologic diseases and coagulation disorders
PV occlusion in infectious disease/pylephlebitis
PV occlusion in malignant hepatic disease
Mixed hepatic vascular occlusions
Thrombosis of both the hepatic artery and portal vein
Thrombosis of the portal vein combined with hepatic arterial vasospasm
Mixed thrombosis of the hepatic artery and portal vein (e.g., in polycythemia vera)

Hepatic Artery Occlusion

Although hepatic parenchyma strongly depends on portal vein blood flow, the hepatic artery plays a critical role in blood supply of the liver and specifically for the biliary tract (review: Rappaport and Schneiderman 1976). There are documented events of spontaneous hepatic artery thrombosis followed by anemic liver infarction (Carroll 1963; OConnor et al. 1976).

Thrombosis of the hepatic artery causing infarction was found in patients with primary hepatic cancer or hepatic metastatic disease (Carroll 1963). A further cause of hepatic artery occlusion is an entire spectrum of abdominal interventional procedures, including angiography, therapeutic transcatheter arterial chemoembolization/TACE, radiofrequency ablation, and ethanol injection (Trojanowski et al. 1980; Holbert et al. 1996; Fujiwara et al. 2004; Akahane et al. 2005; Dai et al. 2007; Kim et al. 2007; Chiu et al. 2009; Guiu et al. 2012; Ladra Gonzalez et al. 2013; Dolak et al. 2014), and disorders leading to hemoconcentration, such as nephrotic syndrome (Vea et al. 1990). The hepatic artery can also be occluded by a thromboembolus originating from the left heart (e.g., subsequent to atrial fibrillation or mural ventricle thrombus after myocardial infarction) or from atherosclerotic plaques of the aorta or celiac trunk. Embolic occlusion of the hepatic artery can be followed by secondary thrombosis proximal to the embolus. A second source of embolism is detached vegetations in bacterial endocarditis (Henrich et al. 1975; Carroll 1963). Hepatic infarction caused by hepatic vascular accidents is a well-established complication of preeclampsia and eclampsia (Kronthal et al. 1990; Miyakoshi et al. 2004; Cholongitas and Burroughs 2008).

True liver infarction is a well-documented complication of polyarteritis nodosa involving the celiac plexus and the hepatic artery (Pass 1935; Price and Flanagan 1953; Haratake et al. 1988, Bohn et al. 2010). Other types of vasculitis causing hepatic artery stenosis or occlusion and hepatic infarction include Churg-Strauss syndrome (Otani et al. 2003), chronic periaortitis (Salvarani et al. 2011), vasculitis in systemic lupus erythematosus/SLE (Matsumoto et al. 1992a), vasculitis in the antiphospholipid syndrome (Millan-Mon et al. 1993), and radiation aortitis (Cox and Millar 1993). The hepatic artery can also undergo occlusion in the setting of artery aneurysms and pseudoaneurysm followed by liver infarction (Ross and Osler 1877–1878; Chuang et al. 2005) or dissecting aneurysm of the aorta (Myrtue et al. 1994). Anemic liver infarct was also observed following therapeutic or accidental hepatic artery ligation, e.g., in the setting of cholecystectomy (Kehr 1903; Kerr 1933; Graham and Cannell 1932–1933). Similar to thrombosis of the hepatic artery proper, thrombotic occlusion of the celiac trunk can also cause anemic hepatic infarction (MacDonald and Holt 1966).

Occlusion of the Portal Vein

In comparison with hepatic artery occlusion, thrombotic occlusion of the portal vein alone only rarely gives rise to hepatic anemic infarction, although most of the parenchyma is supplied by portal venous blood (Versé 1907; Yamashita et al. 1997). Hepatic infarction due to portal vein thrombosis was found in patients with liver cancer, cirrhosis, or chronic pancreatitis (Kim et al. 2002).

Mixed Hepatic Vascular Occlusions

Anemic liver infarction resulting from mixed hepatic and portal vein thrombosis was observed following blunt abdominal trauma (Francque et al. 2004), liver transplantation (Haque et al. 2009), transcatheter arterial embolization/TAE (Takakuwa et al. 1993), or polycythemia vera rubra (Ghandur-Mnaymneh 1976). Hepatic infarct can also develop in patients with HELLP syndrome and factor V Leiden having portal vein thrombosis plus arterial vasospasm (Seige et al. 1998).

Complex Mechanisms Affecting Several Vascular Systems

Very rarely, hepatic infarction was caused by torsion of an accessory liver lobe, inducing complex patterns of vascular occlusion and also primarily involving the microvascular system (Lotte and Madier 1960). Hepatic infarction was also observed in the setting of S-A hemoglobin (Mengel et al. 1963).

Hepatic Infarction in the Absence of Vascular Occlusion

Exceptionally, hepatic infarction was observed in the absence of radiologically detectable vascular occlusions (so-called nonocclusive hepatic infarction; Sundaram et al. 1978).

Clinical and Imaging Features

The clinical signs and symptoms of anemic hepatic infarction are largely nonspecific and include upper abdominal pain or discomfort, vomiting, and signs of acute abdomen or upper abdominal peritonitis. At imaging, hepatic infarcts appear as wedge-shaped, rounded or oval, or irregularly shaped low-attenuation lesions usually paralleling bile ducts, whereby wedge-shaped infarcts are peripherally located (Adler et al. 1984; Lev-Toaff et al. 1987; Holbert et al. 1996; Cook and Crofton 1997; Smith et al. 1998).

Macroscopic Pathology

Macroscopically, anemic liver infarcts are well-demarcated pale areas of sometimes more than 10 cm diameter that are wedge shaped and located either deep in the liver substance or to peripheral parts of the organ (Figs. 1 and 2).

Fig. 1 Peripheral anemic infarction in a cholestatic liver

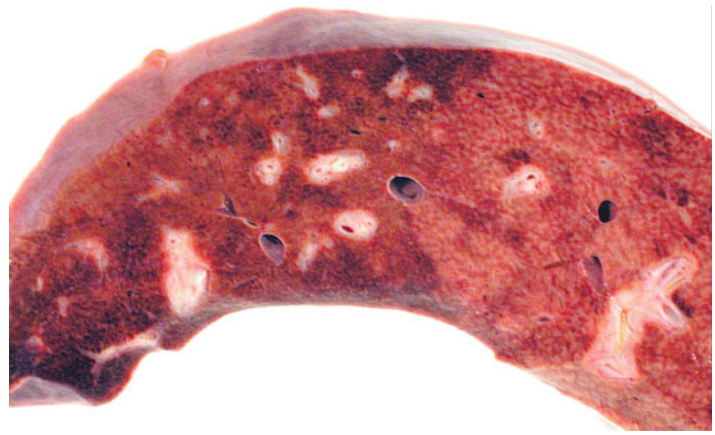

Fig. 2 Anemic infarction of the liver in hepatic arteritis

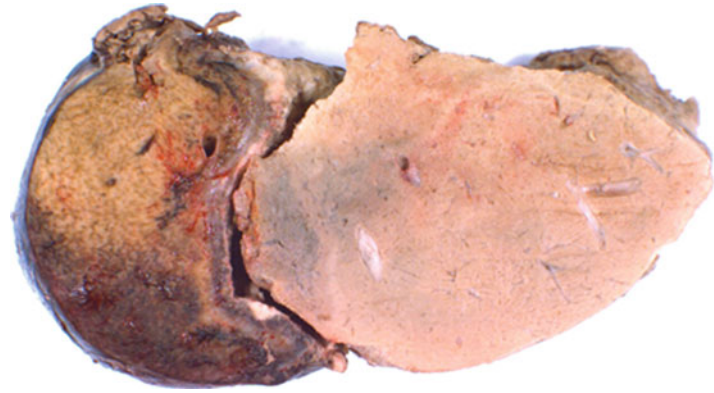

Fig. 3 Large sequestered infarct of the liver. The necrotic tissue has detached from the intact adjacent liver substance

Peripheral infarcts are typically separated from the liver capsule by a thin rim of preserved liver parenchyma, as this tissue is supplied by a different vascular system. Subcapsular infarcts were also observed following liver transplantation (Abecassis et al. 1991). In rare cases, an infarct can occupy almost an entire liver lobe (Carroll 1963). The pale area of ischemic necrosis can show a red rim at the edge caused by hyperemia (congestion) and hemorrhage from damaged microvessels. In infarcts caused by hepatic artery thrombosis, the arterial thrombus often or always extends up to the infarct in the liver substance (Carroll 1963).

Liver infarcts can undergo several types of secondary changes, including liver abscess due to superinfection, hemorrhage, liquefaction of necrotic tissue, calcification, and fibrosis/scarring. In case the infarction involves larger intrahepatic bile ducts, bile leakage ensues, resulting in bile accumulation in the infarcted tissue (bile lakes; Peterson and Neumann 1984). Large necrotic areas may become separated from preserved (vital) hepatic parenchyma, resulting in infarct sequestration (Fig. 3).

Pass (1935) reported that hepatic infarcts caused by polyarteritis nodosa of the hepatic artery frequently convert into large abscesses that may be difficult to distinguish from genuine pyogenic abscesses. Large postinfarction abscesses of the liver may be associated with collapse of the right lower lobe of the lung (Davson et al. 1948).

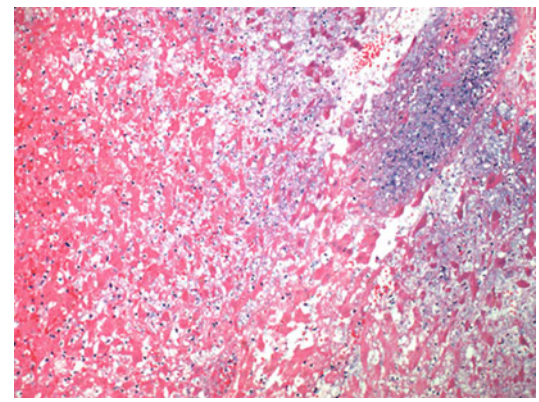

Fig. 4 Anemic infarction of the liver. The traces of the previous hepatic parenchyma are visible in the form of "shadow liver plates/trabecules." Note the numerous nuclear debris (hematoxylin and eosin stain)

Histopathology

Macroinfarcts typically show distinct zones, similar to those described in renal ischemia (Figs. 4, 5, and 6; Sheehan and Davis 1958) and animal experiments (Beresnegowski 1908). A central area of variable diameter shows eosinophilic cells with a granular cytoplasm, a vague circumference, and fading or faded nuclei (karyolysis). Nuclear debris are found (karyorrhexis). Remnants of sinusoids are noted, devoid of red cells and Kupffer cells, and usually without endothelial nuclei or then only nuclei with signs of karyopyknosis. Remnants of blood vessels can contain an affine web of fibrin (Carroll 1963), but no fresh thrombi and no fibrinoid thrombi. In

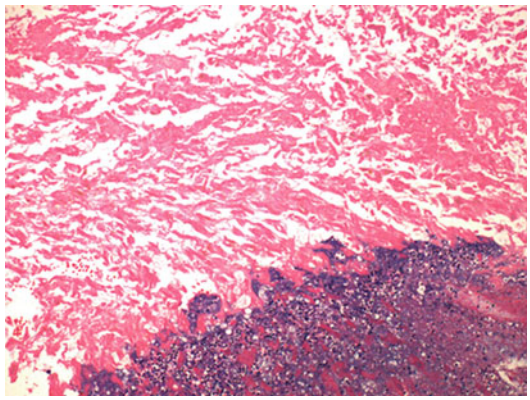

Fig. 5 In advanced hepatic infarction, compacted areas of coagulative necrosis, nuclear debris, chromatin fragments, and strongly basophilic "DNA powder" may ensue (hematoxylin and eosin stain)

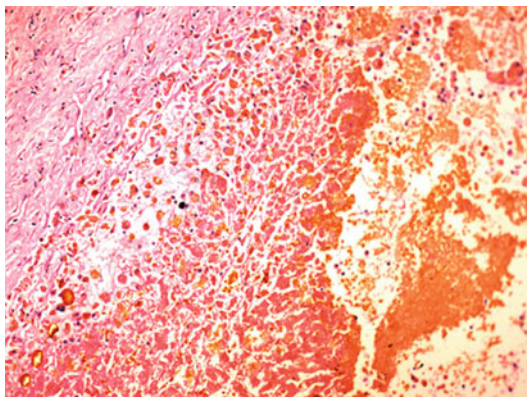

Fig. 6 Anemic infarction of the liver with bile duct destruction and leakage of bile (hematoxylin and eosin stain)

central parts, neutrophils are lacking, as they cannot be transported to this area excluded from circulation. In hepatic infarction caused by portal vein thrombosis, the borders between infarcted parenchymal areas and preserved parenchyma are usually located around central veins, corresponding to the periphery of the portal venous blood flow system (Saegusa et al. 1993). After few days, the centrally located area of coagulation necrosis is surrounded with a zone showing an infiltrate of neutrophils and few macrophages. Here, the hepatocytes appear shrunken, with a strongly eosinophilic cytoplasm and karyopyknotic nuclei. In this zone, sinusoids contain erythrocytes and Kupffer cells. After about 10 days, ductular proliferations containing progenitor cells start to appear. These proliferations originate from portal tracts and later invade the damaged lobular parenchyma. The tissue surrounding the infarct shows signs of hepatocyte regeneration, with an increase of hepatocyte mitotic figures. The necrotic process can also involve portal tracts, where interlobular bile ducts display severe ischemic damage or are absent, mainly in cases with hepatic artery occlusion (ischemic cholangiopathy). Involvement of larger bile ducts can result in bile leakage (Fig. 6) and the formation of bile duct cysts (Doppman et al. 1979). Infarcted liver parenchyma elicits an inflammatory reaction in the surrounding hepatic tissue, followed by granulation tissue, scarring, atrophy, and tissue contraction.

Differential Diagnosis

Anemic liver infarct clinically and radiologically resembles pyogenic liver abscess, in particular when infarcts undergo secondary suppurative changes, amebic liver abscess, and cancer. A difficult differential diagnostic situation may occur when ascending infection through the portal vein causes pylephlebitis followed by liver abscess (Brown et al. 2003). In patients with preeclampsia or eclampsia, hepatic hepatoma occurs (Sherbahn 1996) that may mimic infarction.

Hepatic Pseudo-infarct (Zahn's Infarct)

A rare differential diagnosis of liver infarct is the pseudo-infarct of the liver or Zahn's infarct (also termed infarct-like cyanotic atrophy). In contrast to true ischemic infarction, Zahn's infarct is a more or less, usually well-demarcated zone of hepatic congestion leading to parenchymal atrophy. Zahn's infarct is named after Friedrich Wilhelm Zahn (1845–1904), a German pathologist who studied under von Recklinghausen and received his M.D. in 1870 based on a work he performed in Bern, Switzerland, under Edwin

Klebs (review: Benaroyo 1991). After having served as a military physician during the war of 1870, he became professor of pathologic anatomy in Geneva, where he organized the new institute. Zahn is well known for contributions to the understanding and definition of thrombus. He was the first to put emphasis on the distinction of red and white thrombi and offered detailed descriptions of the process of thrombus corrugation (Zahn 1872, 1875, 1891: reviews: Bräunig and Doerr 1991, 1994). Zahn described the hepatic lesion named after him in 1897 under the term "atrophische rothe Leberinfarcte" (atrophic red hepatic infarcts), although he noted that there was no evidence of hepatocyte necrosis, but rather liver cell atrophy, "infarct" therefore being a misnomer. This has later led to the term "pseudo-infarction." As a pathogenic pathway, Zahn considered the combination of occlusion of a branch of the hepatic artery and an elevated pressure in the inferior vena cava and the hepatic veins caused by right-sided heart failure. However, part of these cases had portal vein thrombosis. Zahn's infarct has been observed in the setting of various vascular processes, including occlusive phlebitis in portal vein radicles (Matsumoto et al. 1992b), portal vein thrombosis (Funatsu et al. 1994), portal vein thromboembolism (Symmers 1951), and tumor-induced stenosis of intrahepatic vessels (Tsuuchi et al. 1990). Macroscopically, Zahn's pseudo-infarcts appear as more or less circumscribed dark red areas. Due to congestion and decrease of oxygenation, the lesions may turn bluish red, leading to the term "cyanotic atrophy." In contrast to true anemic infarction, Zahn's infarct mostly shows severe centrilobular congestion (passive hyperemia) associated with hepatocyte plate atrophy, but no coagulation necrosis, or then only a minor centrilobular hepatocyte necrosis. Sinusoids are usually dilated and packed with red cells, this change increasing in severity toward the center of lobules. In pericentral areas with incipient or established hepatocyte necrosis, neutrophils accumulate, reflecting that sinusoidal circulation is not interrupted, in contrast to true anemic infarction (Horrocks and Tapp 1966). The pathogenesis of centrilobular necrosis following congestion, including Zahn's pseudo-infarct, is complex and not yet fully understood (review: Shibayama et al. 1993).

References

Akahane M, Koga H, Kato N, Yamada H, Uozumi K, Tateishi R, Teratani T, Shiina S et al (2005) Complications of percutaneous radiofrequency ablation for hepatocellular carcinoma: imaging spectrum and management. Radiographics 25(suppl 1):S57–S68

Abecassis JP, Pariente D, Hazebroucq V, Houssin D, Chapuis Y, Bonnin A (1991) Subcapsular hepatic necrosis in liver transplantation: CT appearance. AJR Am J Roentgenol 156:981–983

Adler DD, Glazer GM, Silver TM (1984) Computed tomography of liver infarction. AJR Am J Roentgenol 142:315–318

Baldwin FA (1902) Multiple anemic infarcts of the liver. J Med Res 8:431–445

Benaroyo L (1991) Contribution of Friedrich Wilhelm Zahn (1845–1904) to the study of inflammation (in French). Gesnerus 49:395–408

Beresnegowski N (1908) Zur Frage der morphologischen Veränderungen der Leber nach Unterbindung der Leberarterie. Zentralbl Chir 35:151–152

Bohn J, Schippers E, Wagner S, Küsters W, Müller J, Meesmann M, Scheppach W (2010) Solitary liver tumor as a manifestation of polyarteritis nodosa (in German). Dtsch Med Wochenschr 135:236–239

Bräunig G, Doerr W (1991) 100 years ago: Friedrich Wilhelm Zahn defines once and for all the separated thrombus (in German). Pathologe 12:226–229

Bräunig G, Doerr W (1994) Die Pathologen der Rheinpfalz. Sitzungsberichte der Heidelberger Akademie der Wissenschaften, Mathematisch-naturwissenschaftliche Klasse. Springer, Berlin, pp 51–107

Brown KT, Gandhi RT, Covey AM, Brody LA, Getrajdman GI (2003) Pylephlebitis and liver abscess mimicking hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2:221–225

Carroll R (1963) Infarction of the human liver. J Clin Pathol 16:133–136

Chen V, Hamilton J, Qizilbash A (1976) Hepatic infarction. A clinicopathologic study of seven cases. Arch Pathol Lab Med 100:32–36

Chiu YC, Chuang CH, Tsai HM, Chen CY (2009) Massive hepatic infarction after pure ethanol injection and radiofrequency ablation therapy for hepatocellular carcinoma: a case report. Kaohsiung J Med Sci 25:156–159

Cholongitas E, Burroughs AK (2008) Liver diseases specific to pregnancy. Ann Gastroenterol 21:164–172

Chuang CH, Chen CY, Tsai HM (2005) Hepatic infarction and hepatic artery pseudoaneurysm with peritoneal bleeding after radiofrequency ablation for hepatoma. Clin Gastroenterol Hepatol 3:A23

Cook GJ, Crofton ME (1997) Hepatic artery thrombosis and infarction. Evolution of the ultrasound appearances in liver transplant recipients. Br J Radiol 70:248–251

Cox MR, Millar DM (1993) Gastric, hepatic and small bowel infarction due to radiation aortitis in a 42 year old woman. Aust NZ J Surg 63:499–501

Dai H, Ding H, Liu F, Yao Z, Li L, Li C, Tan Y, Wang J (2007) Complications of chemoembolization for hepatic neoplasms. Saudi Med J 28:1208–1212

Davson J, Ball J, Platt R (1948) Kidney in periarteritis nodosa. Quart J Med 17:175–180

Dolak W, Schreiber F, Schwaighofer H, Gschwantler M, Plieschnegger W, Ziachehabi A et al (2014) Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. Surg Endosc 28:854–860

Doppman JL, Dunnick NR, Girton M, Fauci AS, Popovsky M (1979) Bile duct cysts secondary to liver infarction. Radiology 130:1–5

Francque S, Condat B, Asselah T, Vilgrain V, Durand F, Moreau R, Valla D (2004) Multifactorial aetiology of hepatic infarction: a case report with literature review. Eur J Gastroenterol Hepatol 16:411–415

Fujiwara H, Kanazawa S, Hiraki T, Mimura H, Yasui K, Akaki S, Yagi T, Naomoto Y et al (2004) Hepatic infarction following abdominal interventional procedures. Acta Med Okayama 58:97–106

Funatsu K, Nishihara H, Tabuchi E, Nozaki Y, Takano K, Katsuragi M, Sugihara S et al (1994) A case of a primary hepatic tumor causing segmental changes on imaging and its relation to Zahn's infarct. Kurume Med J 41:109–116

Ghandur-Mnaymneh L (1976) Anemic infarction of the liver resulting from hepatic and portal vein thrombosis. Johns Hopkins Med J 139(Suppl):78–81

Graham RR, Cannell D (1932–1933) Accidental ligation of the hepatic artery. Br J Surg 20:566–579

Guiu B, Deschamps F, Aho S, Munck F, Dromain C, Boide V, Malka D, Leboulleux S et al (2012) Liver/biliary injuries following chemoembolisation of endocrine tumours and hepatocellular carcinoma: lipiodol vs. drug-eluting beads. J Hepatol 56:609–617

Haque M, Schumacher PA, Harris A, Scudamore CH, Steinbrecher UP, Chung SW et al (2009) Late acute celiac and hepatic artery thrombosis with portal vein thrombosis resulting in hepatic infarction 12 years post orthotopic liver transplantation. Ann Hepatol 8:396–399

Haratake J, Horie A, Furuta A, Yamato H (1988) Massive hepatic infarction associated with polyarteritis nodosa. Acta Pathol Jpn 38:89–93

Henrich WL, Huehnegarth RJ, Rösch J, Melnyk CS (1975) Gallbladder and liver infarction occurring as a complication of acute bacterial endocarditis. Gastroenterology 68:1602–1607

Holbert BL, Baron RL, Dodd GD (1996) Hepatic infarction caused by arterial insufficiency: spectrum and evolution of CT findings. AJR Am J Roentgenol 166:815–820

Horrocks P, Tapp E (1966) Zahn's 'infarcts' of the liver. J Clin Pathol 19:475–478

Kanter DM (1965) Hepatic infarction. Arch Intern Med 115:479–481

Kehr H (1903) Der erste Fall von erfolgreicher Unterbindung der Art. hepatica propria wegen Aneurysma. Münch Med Wschr 50:1861–1867

Kerr RW (1933) A case of infarction of the liver following cholecystectomy. J Kansas Med Soc 34:175–178

Kim BC, Joo KR, Lee HS, Jeong YK, Suh HS, Kim DH, Park NH, Park JH (2002) A case of chronic pancreatitis associated with liver infarction and acrodermatitis enteropathica. Korean J Intern Med 17:263–265

Kim YS, Rhim H, Lim HK, Choi D, Lee WJ, Kim SH (2007) Hepatic infarction after radiofrequency ablation of hepatocellular carcinoma with an internally cooled electrode. J Vasc Interv Radiol 18:1126–1133

Kochin IN, Miloh TA, Arnon R, Iyer KR, Suchy FJ, Kerkar N (2011) Benign liver masses and lesions in children: 53 cases over 12 years. Isr Med Assoc J 13:542–547

Kretz R (1916) Zur Kenntnis des Leberinfarktes. Virchows Arch Path Anat 222:30–34

Kronthal AJ, Fishman EK, Kuhlman JE, Bohlman ME (1990) Hepatic infarction in preeclampsia. Radiology 177:726–728

Ladra Gonzalez MJ, Echevarria Canoura M, Fernandez Castroagudin J, Bustamante Montalvo M (2013) A massive hepatic infarction after radiofrequency ablation (in Spanish). Cir Esp 91:122–124

Lev-Toaff AS, Friedman AC, Cohen LM, Radecki PD, Caroline DF (1987) Hepatic infarcts: new observations by CT and sonography. AJR Am J Roentgenol 149:87–90

Lotte J, Madier C (1960) Infarction caused by torsion of an accessory lobule of the liver. Surgery. Cure (in French). Presse Med 68:838

MacDonald CA, Holt PR (1966) Celiac artery thrombosis resulting in infarction of the liver and the small intestine. Ann Intern Med 64:1057–1062

Matsumoto T, Yoshimine T, Shimouchi K, Shiotu H, Kuwabara N, Fukuda Y, Hoshi T (1992a) The liver in systemic lupus erythematosus: pathologic analysis of 52 cases and review of the Japanese Autopsy Registry Data. Hum Pathol 23:1151–1158

Matsumoto T, Kuwabara N, Abe H, Fukuda Y, Suyama M, Fujii D, Kojima K, Futagawa S (1992b) Zahn infarct of the liver resulting from occlusive phlebitis in portal vein radicles. Am J Gastroenterol 87:365–368

Mengel CE, Schauble JF, Hammond CB (1963) Infarct-necrosis of the liver in a patient with S-A hemoglobin. Arch Intern Med 111:93–98

Millan-Mon A, Porto JL, Novo C, Garcia-Martin C, Guitian D (1993) Hepatic infarction in a pregnant patient with the 'primary' antiphospholipid syndrome. Lupus 2:275–279

Miyakoshi K, Tanaka M, Ono A, Ohno A, Serita R, Suzuki T, Shinmoto H, Morisaki H et al (2004) Massive hepatic infarction in preeclampsia: successful treatment

with continuous hemodiafiltration and corticosteroid therapy. J Perinat Med 32:453–455
Myrtue GS, Guul SJ, Gerlif C (1994) Liver infarction diagnosed by CT in a patient with dissecting thoracic aorta aneurysm (in Danish). Ugeskr Laeger 156:6040–6041
Nakata K, Kanbe A (1966) The terminal distribution of the hepatic artery and its relationship to the development of focal liver necrosis following interruption of the portal blood supply. Acta Pathol Jpn 16:313–321
Oconnor PJ, Buhac I, Balint JA (1976) Spontaneous hepatic artery thrombosis with infarction of the liver. Gastroenterology 70:599–601
Ogle C (1895) Infarcts of the liver. Trans Pathol Soc London 46:73–74
Otani Y, Anzai S, Shibuya H, Fujiwara S, Takayasu S, Asada Y, Terashi H, Takuma M et al (2003) Churg-Strauss syndrome (CSS) manifested as necrosis of fingers and toes and liver infarction. J Dermatol 30:810–815
Parker RG (1955) Arterial infarction of the liver in man. J Pathol Bacteriol 70:521–528
Pass IJ (1935) Infarction of the liver. Am J Pathol 111:503–526
Peterson IM, Neumann CH (1984) Focal hepatic infarction with bile lake formation. AJR Am J Roentgenol 142:1155–1156
Price HP, Flanagan CJ (1953) Infarction of the liver due to polyarteritis nodosa. J Med Soc NJ 50:500–502
Rappaport AM, Schneiderman JH (1976) The function of the hepatic artery. Rev Physiol Biochem Pharmacol 76:129–175
Rattone G (1888) Lugli infarti emorragici del fegato. Arch per le Sci Med (Torino) 12:224–241
Ross G, Osler W (1877–1878) Aneurism of hepatic artery; multiple abscesses of the liver. Can J Med Sci 6:1–12
Rudczynski B (1905) Zur Kenntnis der arteriellen Infarktbildungen in der Leber des Menschen. Ztschr Heilkde 26:147–162
Saegusa M, Takano Y, Okudaira M (1993) Human hepatic infarction: histopathological and postmortem angiological studies. Liver 13:239–245
Salvarani C, Calamia KT, Matteson EL, Hunder GG, Pipitone N, Miller DV, Warrington KJ (2011) Vasculitis of the gastrointestinal tract in chronic periaortitis. Medicine (Baltimore) 90:28–39
Seeley TT, Blumenfeld CM, Ikeda R, Knapp W, Ruebner BH (1972) Hepatic infarction. Hum Pathol 3:265–276
Seige M, Schweigart U, Moessmer G, Schneider KT, Classen M (1998) Extensive hepatic infarction caused by thrombosis of the right portal vein branches and arterial vasospasm in HELLP syndrome associated with homozygous factor V Leiden. Am J Gastroenterol 93:473–474
Sheehan HL, Davis JC (1958) Complete permanent renal ischemia. J Pathol Bacteriol 76:569–587
Sherbahn R (1996) Spontaneous ruptured subcapsular liver hematoma associated with pregnancy. A case report. J Reprod Med 41:125–128
Shibayama Y, Urano T, Asaka S, Hashimoto K, Nakata K (1993) Pathogenesis of centrilobular necrosis following congestion of the liver. J Gastroenterol Hepatol 8:530–534
Smith GS, Birnbaum BA, Jacobs JE (1998) Hepatic infarction secondary to arterial insufficiency in native livers: CT findings in 10 patients. Radiology 208:223–229
Soni SR, Persaud V (1972) Central rupture of the liver with massive liver-cell necrosis. A case report and review of the literature. Br J Surg 59:660–662
Sundaram M, Srivisal S, Lagos JA, Ho JE (1978) Angiographic demonstration of non-occlusive hepatic infarction with scintigraphic and microscopic correlation. Gastrointest Radiol 3:39–42
Symmers WSTC (1951) Portal embolism following thrombosis of splenic vein, and causing infarct-like cyanotic atrophy (‘Zahn’s infarcts ‘) of the liver. A complication of splenectomy performed in the course of total gastrectomy. Br J Surg 38:498–502
Takakuwa T, Yokota J, Sugimoto T (1993) Liver infarction produced by dual vessels occlusion due to trauma and TAE: long follow up using CT, US, and MRI. Med J Osaka Univ 41–42:23–27
Trojanowski JQ, Harrist TJ, Athanasoulis CA, Greenfield AJ (1980) Hepatic and splenic infarctions: complications of therapeutic transcatheter embolization. Am J Surg 139:272–277
Tsuuchi Y, Kojima K, Seo H, Ohkawa M, Tanabe M, Ikeda K, Satoh A, Hino I (1990) A case of pseudoinfarct of the liver (Zahn’s infarct) (in Japanese). Rinsho Hoshasen 35:975–978
Vea AM, Ruiz CG, Conejero AS, Artal EM, Rotellar JAO (1990) Hepatic infarction: an unusual complication of nephrotic syndrome in a patient with diabetes mellitus. Postgrad Med J 66:968–970
Versé M (1907) Über totale Pfortaderobliteration und anämische Infarkte der Leber. Verhandl d Deutsch Path Ges 13:314–315
Wiessner JMP (1917) Ein Fall von anämischen Leberinfarkten. Thesis, Junge & Sohn, Erlangen
Winternitz MC (1911) The effect of occlusion of the various hepatic vessels upon the liver. Bull Johns Hopkins Hosp 22:396–404
Woolling KR, Baggenstoss AH, Weir JF (1953) Infarction of the liver. Proc Staff Meet Mayo Clin 28:239–244
Yamashita K, Tsukuda H, Mizukami Y, Ito J, Kondo Y, Kinoshita H, Fujisawa Y, Imai K (1997) Hepatic infarction with portal thrombosis. J Gastroenterol 32:684–688
Zahn FW (1872) Untersuchungen über Thrombose. Centralbl Med Wiss 9:129–130
Zahn FW (1875) Untersuchungen über die Bildung von Thromben. Virchows Arch 62:81–124
Zahn FW (1891) Ueber die Rippenbildung an der freien Oberfläche der Thromben. In: Internationale Beiträge zur wissenschaftlichen Medizin. Festschrift für Rudolf Virchow, Bd. II, August Hirschwald, Berlin, pp. 201–215.35.14.Cystic disorders mimicking cystic tumors

Part XXV

Reactive Cystic Lesions of the Liver

Cystic Hepatobiliary Lesions Mimicking Cystic Neoplasms

138

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_138

Abstract

The liver can develop several types of reactive cystic lesions that can resemble cystic hepatobiliary neoplasms, in particular mucinous cystic neoplasms. A large cyst can exert a mass effect. The most common nonparasitic liver cysts are simple cysts related to congenital maldevelopment of certain parts of the biliary system. These cysts have an estimated incidence of 0.1–2.5 % in the general population and are usually asymptomatic lesions. The detection rate increases as a function of age. The cysts usually do not communicate with the biliary tract and are lined by a normal-looking biliary epithelium. A second, but less common type of hepatic cyst is ciliated foregut cyst, lined by a ciliated epithelium. This type of cysts also occurs in the gallbladder. Hepatic cysts can undergo secondary changes, including hemorrhage and infection.

Nonparasitic Liver Cysts: Simple Cysts and Ciliated Foregut Cyst

Introduction

Several types of nonparasitic cysts of the liver can grow to a large size and produce a mass effect, thus resulting in tumor-like lesions. The cysts may also mimic cystic hepatic neoplasms, in particular cystadenomas and related lesions. The main types of nonparasitic liver cysts comprise simple (biliary) cyst and ciliated foregut cyst.

Simple Hepatic Nonparasitic Cysts

Introduction

Simple liver cysts (non-hereditary developmental cysts) are common hepatic lesions that rarely cause significant morbidity or mortality. These cysts are related to congenital maldevelopment of certain parts of the biliary system, but are non-hereditary lesions. Large symptomatic cysts can have a mass effect and mimic malignant disease.

Nomenclature

Simple cysts are benign hepatic cystic lesions that can be classified by etiology into congenital and acquired cysts. To distinguish simple cysts from hydatid cysts, they are termed nonparasitic cysts. These cysts are congenital and are divided into parenchymal and biliary cysts, whereby parenchymal cysts can be isolated/solitary, multiple, or polycystic. As polycystic liver disease is a hereditary disorder with distinct mutations of critical proteins, liver polycystosis does not make part of the spectrum of simple nonparasitic liver cysts sensu stricto, although these cysts can be multiple. Complicated cysts are simple nonparasitic cysts that have undergone certain "complications," including hemorrhage and infection, or malignant transformation (see below).

Epidemiology

Simple cysts constitute the most common form of liver cysts in adults, with an estimated prevalence between 0.1 % and 2.5 % in the general population. In a study performed at the Mayo Clinic, it was estimated that the incidence of hepatic cystic disease is 17 per 10,000 abdominal explorations (Sanfelippo et al. 1974). However, the incidence is probably higher, as small cysts may be missed at conventional imaging. In autopsies, the incidence ranged from 14 to 53 per 10,000 (Eliason and Smith 1944). A study from Taiwan documents an overall prevalence of 3.6 %. An increasing prevalence with age was demonstrated, ranging from 0.83 % from below age of 40 up to 7.81 % of patients over 60 years old (Huang et al. 1995). Simple congenital cysts are also diagnosed in children and adolescents, where they rarely induce symptoms (Rogers et al. 2007; Bryce et al. 2008). Most antenatally detected liver cysts appear to be simple (Charlesworth et al. 2007). In a study testing patients with spiral CT in situations unrelated to hepatic pathology,

the prevalence of simple cysts was 18 % (Carrim and Murchison 2003). In an analysis of 78 patients with large (> or =4 cm) hepatic cysts, 57 of the lesions were simple cysts (Regev et al. 2001). These lesions were much more common in females (F:M, 49:8). Large cysts are preferentially found in women. Most of congenital cysts manifest in the fifth to seventh decades, with a mean patient age of 59 years (Sanfelippo et al. 1974).

Clinical Features

Most simple hepatic cysts are asymptomatic. Symptoms and signs arise when cysts become large (typically larger than 4 cm) and start to exert pressure on critical intrahepatic or extrahepatic structures (review: Tonolini et al. 2014). Large cysts can compress the biliary tree or, in very large lesions, adjacent organs such as the stomach. Cyst-induced compression of bile ducts can promote obstructive jaundice (Cappell 1988; Terada et al. 1993). Compression of the portal vein can promote gastric varices in the absence of liver cirrhosis (Kinjo et al. 2013). Rarely, simple liver cysts cause complications, such as bleeding, rupture, and cyst infection (Ishikawa et al. 2002; Agrawal et al. 2012; Macutkiewicz et al. 2012). As large hemorrhagic cysts can show an unevenly thickened wall and high-density strips at imaging, they sometimes resemble hepatobiliary cystadenoma (Zhang et al. 2009b). Upon cyst rupture, fluid can be retained under the liver capsule (Ueda et al. 2010). Infection can result in purulent change of cysts, cyst empyema, or abscess formation (Plenk 1910; Chatzipetrou et al. 2008). In infection, cysts can rapidly enlarge due to accumulation of intracystic exudate. Such growing cysts can compress the inferior vena cava and induce Budd-Chiari syndrome (Long et al. 2014). Large cysts can induce thrombosis of the inferior cava (Musielak et al. 2014). Cyst sclerosis may cause biliary stenosis mimicking malignancy (Muñoz-Bellvis et al. 2012). Huge cysts can encroach upon the atrium and eventually cause arrhythmia/atrial premature beats (Ker 2010).

Pathology

Macroscopy

Most simple hepatic cysts are small lesions. In a Taiwanese investigation, 53 % of cysts had a diameter of 1–3 cm, and only 7 % were larger than 5 cm (Huang et al. 1995). Cysts are classified as large when they have a diameter of =>4 cm. In rare instances, simple cysts become huge lesions that occupy a large part of the upper abdominal cavity and may reach down into the pelvis in case they show extrahepatic extension. Müller described a cyst containing 6 l of hemorrhagic fluid (Müller 1893). In the female patient reported by Plenk, the fluctuating and massively infected cyst (*Streptococcus* infection) filled with purulent exudate had a diameter of about 20 cm and had markedly displaced the stomach (Plenk 1910). With few exceptions (see below), simple cysts have no biliary communication (Harris et al. 1986). The cysts show a fibrous wall of usually uniform thickness and contain a watery, clear, and nonviscous (serous) fluid that is not bile stained, but may be yellowish following hemorrhage (Winckler 1891; Leppmann 1900; Figs. 1 and 2). In case of bleeding, the cyst content is reddish brown or may look like frank blood. The inner surface of uncomplicated cysts is smooth and glistening, in the majority of cases without trabecula or septa, while fibrous strands or plaques are found in complicated cysts after infection or following sclerotherapy. Subsequent to hemorrhage, the cyst wall shows a brownish or yellow, patchy discoloration due to deposition of hemosiderin and bilirubin (hematoidin). Part of the cysts are located beneath the hepatic capsule and

Fig. 1 Simple nonparasitic cyst in a cirrhotic liver

Fig. 2 Simple nonparasitic cyst of the liver. In this cyst deroofing specimen, secondary alterations of the cyst wall are present, including plaque-like fibrosis/scarring after bouts of inflammation

are visualized as slightly bulging cysts covered by a thinned capsule. Depending on the cyst content, the color of subcapsular cysts ranges from grayish greenish (serous fluid) to red blue (hemorrhagic fluid). Large subcapsular cysts may show a thickened fibrotic wall (the "cyst roof"), in case of recurrent inflammation with fibrous strands and/or adhesions. Some large simple cysts protrude from the liver as pedunculated cysts, relatively often close to the gallbladder, forming a sac with a thin fibrous wall containing macroscopical blood vessels. Pedunculated cysts can become huge and extend into the pelvic region, sometimes being confounded with cystic tumors of the ovaries. Some of these cysts exhibit a vascular pedicle and may undergo torsion followed by hemorrhage and necrosis/infarction. Extrahepatic cysts may adhere to the gallbladder. Rare forms of simple cysts show septal structures, a feature that may suggest cystadenoma (Sato et al. 2013). Liver lobes occupied by large cysts undergo perifocal atrophy, sometimes massive, with compensatory hypertrophy of the contralateral lobe (atrophy-hypertrophy complex).

Histopathology

The epithelial lining of simple cysts consists of a single layer of columnar, cuboidal, or flat epithelial cells with a biliary phenotype (Fig. 3). The cells typically lack cilia. Similar to epithelial cells

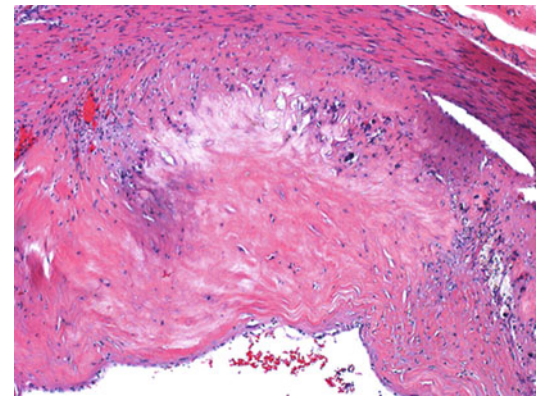

Fig. 3 Simple nonparasitic cyst of the liver. The epithelial lining of this cyst is lost, and the cyst wall is thickened due to fibrosis and scarring (hematoxylin and eosin stain)

of polycystic liver disease, the epithelial lining of simple cysts has little mucin (Terada et al. 1991). The cells express biliary-type cytokeratins, but with variable intensity. High epithelial cells are usually found in small or young cysts, while flat cells predominate in large cysts (epithelial atrophy). Large cysts or those with complications often show extended areas lacking any epithelial lining. This is also a finding frequently encountered in deroofing preparations. The subepithelial tissue consists of vascularized collagenous connective tissue with rare elastic fibers. With few exceptions, smooth muscle cells are uncommon. Hemorrhage into cysts is followed by granulation tissue formation, accumulation of macrophages, and hemosiderosis. Sclerotherapy is followed by

the formation of hypocellular fibrous tissue within the collapsed cyst wall.

Hepatic Cysts with a Biliary Communication

The large majority of simple hepatic cysts have no communication with the biliary tree, in contrast to cystic lesions in Caroli's disease. There is, however, a very small subset of cysts showing biliary communication (Ravindra et al. 1999; Yamada et al. 2009). The communication can be identified through cystography (Yamada et al. 2009). The communication may also be detected during deroofing as bile leakage from a small orifice in the cyst cavity (Chiba and Obata 2002; Masatsugu et al. 2003).

Hilar Cysts

A heterogeneous subset of cysts is located to the liver hilus and sometimes accompanies larger bile ducts (Ozeki and Miura 1994; Fujioka et al. 1997; Yuasa et al. 1997; Colina et al. 1998). Some of these cysts appear as multiple lesions closely following bile ducts (Yuasa et al. 1997). The spectrum of hilar cysts is complex, as part of these lesions are solitary or multiple peribiliary cysts and not congenital parenchymal cysts (Johnson et al. 2007).

Malignancy Arising in Simple Nonparasitic Liver Cysts

These cysts can be complicated by cholangiocarcinoma and squamous cell carcinoma (discussed in separate chapters). Very rarely, other malignancies develop in cysts, e.g., biliary carcinosarcoma (Terada et al. 1994).

Differential Diagnosis

Simple nonparasitic cysts have to be distinguished from hydatid cyst, ciliated foregut cyst, hepatobiliary cystadenoma, cystic malignant tumors (including cystic metastases), and cystic GIST metastasis following imatinib mesylate therapy. On the other hand, biliary cystadenoma with a thin wall can mimic a simple hepatic cyst (Matsumoto et al. 1997).

Pathogenic Pathways

Although thought to be congenital lesions, the cause of simple hepatic cysts is not yet known. A derangement of bile duct/ductal plate development or dilatation of biliary microhamartomas have been discussed. An origin from aberrant bile ducts has been proposed (Cesaris-Demel 1905; Plenk 1910).

Ciliated Foregut Cyst

Introduction

Ciliated hepatic foregut cyst (CHFC) is a rare, usually solitary and unilocular cyst in the liver. A solitary nonparasitic hepatic cyst with a ciliated epithelium has first been described by Friedreich in 1857 (Friedreich 1857), followed by a short report in 1866 (Eberth 1866). Few cases followed in the nineteenth century (von Recklinghausen 1881; Zahn 1896). Friedreich proposed that this type of cyst is a congenital lesion and compared the lining with that of the ciliated bile ducts occurring in some mammals. The cyst has later been termed ciliated hepatic foregut cyst, in 1984 (Wheeler and Edmondson 1984), and interpreted to derive from the embryonic foregut already then. The designation is based on the hypothesis that the epithelial phenotype of this cyst reflects the primitive foregut which is the origin of the tracheobronchial tree, the esophagus, and part of the liver, explaining the presence of ciliated columnar cells, mucin-producing cells, and stratified squamous epithelial cells. This pathogenic view is supported by the fact that there are other ciliated cysts in foregut derivatives, including the respiratory tract, mediastinum, stomach, pancreas, upper

intestinal tract, and ciliated cysts in Brunner gland hamartomas (Chatelain et al. 2002). Ciliated cells that may have derived from foregut endoderm are normally found in normal murine intrahepatic bile ducts (Grisham 1963). Less than 100 cases of CHFC have been reported.

Selected References Mukai et al. (1988), Nogami et al. (1990), Sasaki et al. (1990), Peltier et al. (1993), Shoenut et al. (1994), Kakita et al. (1995), Murakami et al. (1996), Vick et al. (1999a), Bogner and Hegedüs (2002), Balducci et al. (2003), Horii et al. (2003), Cai et al. (2004), Jakowski et al. (2004), Kang et al. (2006), Straus and Osipov (2006), Stringer et al. (2006), Sharma et al. (2008), Shaw et al. (2008), Goodman et al. (2009), and Oida et al. (2009), at least 24 in Japan until 2008 (Mannami et al. 2008).

Epidemiology

The mean age at diagnosis, based on 96 published cases, was 48 ± 12 years (Sharma et al. 2008), and there is a slight male predilection (Vick et al. 1999a). CHFC has also been diagnosed in the pediatric age group, including neonates and infants (Carnicer et al. 1996; Kim et al. 2005; Stringer et al. 2006; Rogers et al. 2007; Young et al. 2007; Betalli et al. 2008; Guérin et al. 2010; Zaydfudim et al. 2010).

Clinical Presentation

CHFC is thought to be small in children but will then slowly grow during life to reach a diameter that may cause symptoms. In a review of the published cases, the average cyst diameter was 3.6 cm at diagnosis (range: 1.1–13 cm). It is commonly a benign and asymptomatic cystic lesion incidentally found on imaging. In the review of Sharma et al. (2008), 62 % of the patients were asymptomatic at the time of diagnosis; others complained of upper abdominal pain. Pain occurring even in case of small cysts may be related to the cysts' location close to the liver capsule, causing stretching of the Glissonian, innervated capsule. Part of the patients have symptoms and signs, e.g., portal hypertension by hepatic vein compression (Harty et al. 1998) or obstructive jaundice by hepatic duct compression (Dardik et al. 1964). Rarely, stones can develop within a CHFC (Ozeki 1995). In exceptional situations, CHFC is not located to the liver substance proper, but to the subhepatic area (Idress et al. 2005).

Imaging Features

On ultrasonography, CHFC is characterized by a commonly unilocular hypoechoic cyst (Mukai et al. 1988; Shoenut et al. 1994). Among the numerous cases reviewed by Sharma et al. (2008), 71 % of the cysts were hypoechoic, 7 % hyperechoic, and 1.8 % anechoic. Complex cystic spaces with echogenic material in the lumen may also occur, overall found in 32 % of the cases (Kadoya et al. 1990; Vick et al. 1999a). Unenhanced CT usually shows hypodense lesions in most patients (Kadoya et al. 1990; Sato 1990; Kanzaki 1992; Shoenut et al. 1994; Benlolo et al. 1996). MRI using T1-weighted images showed a mixed picture with cysts presenting with variable densities. Conversely, T2-weighted images are commonly bright and hyperdense in nature (Fang et al. 2005). CHFC may have a solid tumor appearance on CT (Kimura et al. 1990; Sasaki et al. 1991; Abe et al. 1994) and mimic hepatic malignancy (Wu et al. 1998). CHFC may also be confounded with hydatid cyst (Geramizadeh et al. 2008).

Macroscopic Pathology

CHFC are usually unilocular lesions. Most cysts are unilocular, only 7/96 being multilocular in one report (Sharma et al. 2008). However, one of the first reports (Eberth 1866) already described a multilocular variant. In the review of Sharma et al. (2008), 7/96 cases were multilocular. CHFC is mostly located to the left liver lobe, with a strong predilection for segment IV (44/96

patients; Sharma et al. 2008), but it is also described for the right liver lobe (26/96 patients). In children, the cyst may be in communication with the intrahepatic bile ducts, a phenomenon which may cause rapid cyst growth owing to bile accumulation in the cyst lumen. In most cases, the cysts contain a viscous or mucoid fluid, while bile-stained fluid was detected in only very few patients (three in the study of Sharma et al. 2008), illustrating the fact that most cysts are not connected to the bile duct system. The three cases with bile-stained cyst fluid were those with such a communication, and all referred to pediatric patients (Stringer et al. 2006; Rogers et al. 2007; Young et al. 2007). The case of Eberth was described as a subcapsular cyst, the size of a hazelnut, with several chambers filled with gray-yellow, mucoid fluid, histologically lined by a ciliated epithelium. The inner surface of the cyst is usually smooth, but in situations of inflammation, patches of sticky exudate may be attached to the cyst wall. After cyst hemorrhage, coagulated fresh or old blood may adhere to the wall. The cyst content is either watery and clear or viscous/mucinous.

Histopathology

CHFC has a characteristic four-layered wall. The innermost layer consists of a single or pseudostratified cuboid to columnar epithelium with or without mucin production. At least part of cells possess typical cilia, and the ciliated phenotype may in some cases involve the entire cyst lining (Fig. 4). Goblet cells positive for PAS, alkaline alcian blue, mucicarmine, and high-iron diamine are found (Vick et al. 1999a). The second layer is the subepithelial connective tissue layer which shows arcades of thin-walled blood vessels and capillaries, followed by the third layer, smooth muscle bundles. There are very rare examples of CHFC lacking any smooth muscle cells in the wall (Sato et al. 2006; variant CHFC). The outermost layer consists of dense collagenous fibrous tissue (Wheeler and Edmondson 1984; Terada et al. 1990; Vick et al. 1999a; Chatelain et al. 2000; Bogner and Hegedüs 2002; Horii et al. 2003). In contrast to bronchogenic cysts, CHFC never contains hyaline cartilage. Owing to the presence of ciliated epithelial cells in the aspiration material, CHFC can be diagnosed by cytology (Zaman et al. 1995; De et al. 2006; Kaplan et al. 2007a; Young et al. 2007). This examination has a predictive value of 76 % (Sharma et al. 2008). The diagnostic feature is the presence of ciliated pseudostratified tall columnar cells suspended in a mucoid background. In case of inflammation, granulocytes and macrophages may be seen, admixed with erythrocytes. The only differential diagnosis of a cyst having ciliated cells would be bronchogenic cyst, but this type of cyst apparently does not exist within the liver. Ultrastructurally, the cilia display the characteristic 9 + 2 pattern of microtubules (Vick et al. 1999a).

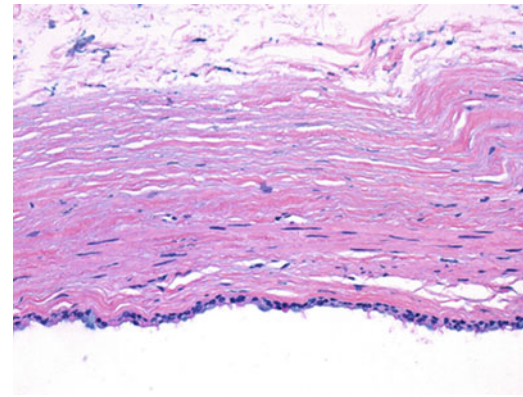

Fig. 4 Ciliated foregut cyst of the liver (hematoxylin and eosin stain)

Immunohistochemistry

The cells lining CHFC are immunoreactive for cytokeratins (AE1/AE3 and CAM5.2), epithelial membrane antigen (EMA), and CEA (Terada et al. 1990; Vick et al. 1999a). Some of the cells within the epithelial lining of CHFC are immunoreactive for CC10, where CC10 is a secretory protein which is specific for bronchiolar Clara cells (Chatelain et al. 2000). The lining

also contains relatively few endocrine cells reactive for chromogranin A, synaptophysin, calcitonin, and bombesin (Chatelain et al. 2000). The smooth muscle layer stains for alpha-SMA, and the epithelial basement membrane and outer connective tissue layer stain positively for type IV collagen and laminin (Vick et al. 1999a). The histologic and immunohistochemical features of CHFC are similar to those of bronchi (Terada et al. 1990), but also of bronchioles of the lower respiratory tract; this has led to the assumption that this hepatic cyst may represent an intrahepatic bronchiolar cyst (Chatelain et al. 2000).

Secondary Changes in CHFC

Hemorrhage and Inflammatory Changes

CHFC can undergo hemorrhage, sometimes with massive intracystic bleeding. Accumulation of blood in the cyst lumina is associated with atrophy or loss of cyst epithelium. Later, hemosiderin may be deposited in the cyst wall, and a loose infiltrate of lymphocytes and macrophages may develop, sometimes with a slight degree of fibrosis. Cholesterol crystals and cholesterol granulomas may be found in few cases. Few cysts underwent purulent or mucopurulent inflammation (Momin et al. 2004). Exceptionally, cyst empyema can develop, with or without a hemorrhagic component.

Metaplastic Changes

Similar to other epithelial surfaces having ciliated columnar cells, squamous cell metaplasia (sometimes extensive) is known to occur in CHFC, however much less commonly than, e.g., in the bronchial tree or in bronchogenic cysts (de Lajarte-Thirouard et al. 2002; Furlanetto and Paolo Dei Tos 2002; Ben Mena et al. 2006; Zhang et al. 2009a). The squamous epithelium can undergo keratinization. The squamous cell expresses cytokeratins 5 and 6, and the superficial squamous cell is CK7 positive (Ben Mena et al. 2006).

Malignant Neoplasms Arising in Ciliated Foregut Cyst of the Liver

CHFC can be complicated by secondary malignancy. Squamous cell carcinoma arising in bona fide CHFC has been observed at least three times (Vick et al. 1999b; de Lajarte-Thirouard et al. 2002; Furlanetto and Paolo Dei Tos 2002; Zhang et al. 2009a) and is associated with squamous metaplasia and high-grade dysplasia of the cyst epithelium (Furlanetto and Dei Tos. 2002; Zhang et al. 2009a). In the case of Zhang and coworkers (2009a), the hepatic resection specimen disclosed an irregular, smooth tumor mass measuring $7 \times 6 \times 5$ cm. The cut surface showed a partially encapsulated gray-white and solid tumor with multiple cystic areas. Histology revealed squamous cell carcinoma within a cyst that still showed a lining of ciliated cells. There were areas with squamous metaplasia and high-grade dysplasia, from which the bulky carcinoma had arisen. In a fourth report, squamous carcinoma had developed in a right-sided hepatic cyst classified as epidermoid intestinal cyst; however, a photomicrograph of this report depicted a cyst wall with ciliated epithelium in addition to squamous metaplasia (Caratozzolo et al. 2001).

Ciliated Foregut Cyst of the Gallbladder

CHFC is observed in the gallbladder (Kakitsubata et al. 1995; Benlolo et al. 1996; Vick et al. 1999a; Chatelain et al. 2000; Nam et al. 2000; Hirono et al. 2002; Muraoka et al. 2003). The case by Kakitsubata et al. (1995) referred to a 71-year-old man with a gallbladder cyst measuring 1.1 cm in diameter, with a thin wall composed of a fibromuscular layer and lining of ciliated columnar cells. These authors suggested that this cyst may have originated in Luschka's duct. However, Luschka's duct does not have a ciliated epithelium. Benlolo et al. (1996) described a ciliated gallbladder cyst they found in a 75-year-old female. The cyst measured 3 cm in diameter. In the case reported by Nam et al. (2000), the cyst measured 1.5 cm in diameter, was unilocular, without communication to the lumen. Similar to

the hepatic counterpart, the cyst showed an underlying smooth muscle cell layer. Where specified in the literature, the cysts were located in the gallbladder fundus (Kakitsubata et al. 1995; Benlolo et al. 1996; Nam et al. 2000). A rare case of a hepatic CHFC communicating with the gallbladder has been reported (Koletsa et al. 2005).

Hepatic Pseudocyst in Pancreatitis (Intrahepatic Pancreatic Pseudocysts)

Introduction

Pseudocysts are one of the best known sequelae and complications in patients suffering from pancreatitis. They are defined as a collection of pancreatic juice admixed with inflammatory exudate, enclosed by a wall of nonepithelialized granulation tissue or fibrous tissue. The incidence of pseudocysts is 5–16 % following acute pancreatitis and 20–40 % in chronic pancreatitis (Ahgdassi et al. 2008). Twenty percent of pancreatic pseudocysts are extrapancreatic, with the most common sites being the spleen, pelvis, pleura, and mediastinum and rarely other organs such as the kidney and liver. After acute or chronic pancreatitis, the development of a pseudocyst located to the liver is an exceptional event. A published literature search as of 2009 documented 22 reported cases, 17 men and 6 women, with a mean age at presentation of 51 years. 17/22 patients suffered from acute pancreatitis, and the pseudocyst(s) were in the left liver lobe in 12, in the right lobe in 6, and in both lobes in 5 cases (Guesmi et al. 2009). Intrahepatic pseudocysts mostly develop in the context of acute pancreatitis and are mainly located in the left liver lobe. Intrahepatic pseudocysts subsequent to chronic pancreatic are more seldom seen (Les et al. 2006).

Selected References Julien et al. (1965), Gautier-Benoit et al. (1974), Gould et al. (1979), Epstein et al. (1982), Hospitel et al. (1983), Atienza et al. (1987), Lantink et al. (1989), Okuda et al. (1991), Hamm and Franzen (1993), Wang et al. (1993), Scappaticci and Markowitz (1995), Lederman et al. (1997), Mehler et al. (1998), Mofredj et al. (2000), Shibasaki et al. (2002), Bhasin et al. (2005), Yi et al. (2008), Al-Ani et al. (2009), and Atia et al. (2009).

Clinical and Imaging Features

Clinically, patients with intrahepatic pancreatic pseudocysts can present with recurrent pain attacks following pancreatitis or suffer from continuous epigastric pain (Mofredj et al. 2000). Physical examination may reveal a palpable abdominal mass, hepatomegaly, or sometimes jaundice (Gautier-Benoit et al. 1974; Hospitel et al. 1983; Atienza et al. 1987; Aiza et al. 1993; Wang 1993; Lederman et al. 1997). Intrahepatic pseudocysts may be stable in size, slowly grow, or regress (with obliteration of the cavity and fibrosis/scarring) (Les et al. 2006).

CT scans of the abdomen characteristically reveal round to oval often well-delineated intrahepatic areas of decreased attenuation. In case of accumulation of blood and/debris, areas of high attenuation may develop (Epstein et al. 1982; Lantink et al. 1989; Hamm and Franzen 1993; Mehler et al. 1998). In the context of acute pancreatitis, contrast-enhanced CT of intrahepatic pseudocysts has shown dilated, low-attenuation tubular structures in the porta hepatis that branched into the liver substance following the geometry of the biliary tract (Scappaticci and Markowitz 1995). MRI with gadolinium for endovenous contrast showed well-delimitated cystic lesions without enhancement after gadolinium administration (Les et al. 2006).

Pathology

Macroscopy shows a rather broad spectrum of presentations, ranging from thin-walled cystic lesions containing a considerable amount of juice to lesions filled with debris and exudate and only a small collection of juice. Cysts filled with necrotic masses and viscous exudate also occur. The pancreatic origin of the pseudocysts

can be documented by the detection of amylase and/or lipase activity in the fluid collections (Balzan et al. 2005; Yi et al. 2008; Atia et al. 2009). An amylase level <479 U/L had a 73 % sensitivity and 98 % specificity for diagnosing pancreatic pseudocyst (Ryu et al. 2004). Pseudocysts in the right liver lobe are even much less common (Mofredj et al. 2000; Ancel et al. 2005; Balzan et al. 2005). Intrahepatic pseudocyst has also been identified in the caudate liver lobe (Wang et al. 1993) and may involve both liver lobes (Aiza et al. 1993; Atia et al. 2009). Pancreatic pseudocyst can also produce fistula to the common bile duct, but this complication is not associated with intrahepatic pseudocyst (Hauptmann et al. 1992). Puncture of intrahepatic pseudocysts may drain a fluid with a reddish-yellow or slightly green color, with floating exudate or debris particles; typically, this fluid does not grow bacteria. Most intrahepatic pseudocysts are solitary lesions, but multiple cysts have also been described (Slim et al. 1992; Casado et al. 2007). In the case reported by Casado et al. (2007), three soft cystic tumors were located in the left lobe of the liver with a very dense and necrotic content on exploration with intraoperative ultrasonography. The pseudocysts were full of debris with only a small amount of juice. Histologically, the cyst contains either an eosinophilic, protein-rich fluid with suspended debris and exudate cells or an accumulation of necrotic eosinophilic matter with shadow cells and more or less preserved leukocytes. The peripheral wall consists of granulation tissue rich in macrophages, followed at the periphery by fibrous tissue. An epithelial lining is typically lacking. The adjacent liver tissue shows some atrophy, ductular proliferations, and an inflammatory infiltrate of lymphocytes, macrophages, and few plasma cells.

Pathogenic Pathways

Hypothetically, the location of the "mother" pseudocyst in the pancreas may have an impact on the location of the intrahepatic pseudocyst, because it is thought that leaking pancreatic juice with active enzymes plays an important pathogenic role. A first pathway between the inflamed pancreas and the liver suggests the release of pancreatic juice from the posterior part or tail of the pancreas toward the lesser sac and from there toward the left liver lobe along the lesser omentum or the gastrohepatic ligament, where the juice will get into contact with the liver surface and invade the liver substance by its enzymes. A second pathway includes a propagation of pancreatic juice from the pancreatic head via the hepatoduodenal ligament to the porta hepatis; the latter mechanism would also explain the development of right-sided lesions or even bilobar lesions (Scappaticci and Markowitz 1995; Shibasaki et al. 2002; review: Casado et al. 2007). The presence of pancreatic enzymes in the intrahepatic pseudocyst fluid is an argument for the role of pancreatic juice invading the liver, although the production of amylase by cholangiocytes and effects of liver cell transdifferentiation have also been proposed (Atia et al. 2009).

Cerebrospinal Fluid Pseudocyst

Introduction

Intrahepatic collections of cerebrospinal fluid can occur as a complication of ventriculoperitoneal (VP) shunts. VP shunting of cerebrospinal fluid (CSF) is a standard therapy for the management of hydrocephalus. Even after the introduction of silastic catheters, abdominal complications still occur, including pseudocysts (review: Bryant et al. 1988). Intra-abdominal CSF pseudocysts are a rare but important complication of VP shunting; since 1954, more than 100 cases of pediatric CSF pseudocysts have been reported. In one study, the incidence of pseudocyst formation was 4.5 % (Rainov et al. 1994). A relation between pseudocyst formation and abdominal procedures after the initial insertion of the shunt has been suggested (Fischer and Schilito 1969; Gotierrez and Raimondi 1976; Goldfinc et al. 1978). Important predisposing factors comprise multiple shunt revisions and infections. The

most common presentation is with symptoms of elevated intracranial pressure and abdominal pain.

Hepatic CSF Pseudocysts

Intrahepatic CSF pseudocysts are among the rarest forms of CSF pseudocysts (Rana et al. 1985; Wang and Miller 1989; Banka et al. 2007; Kaplan et al. 2007b; Kolic et al. 2010; Faraj et al. 2011; Dabdoub et al. 2013). They have been classified as intra-and extra-axially growing cysts (Kaplan et al. 2007b). Intrahepatic CSF cysts can present as a tumor-like hepatic mass (Wang and Miller 1989), may mimic hydatid disease (Faraj et al. 2011), and can form large fluid collections reaching to the porta hepatis and causing elevated liver enzymes (Rana et al. 1985). Intrahepatic CSF pseudocyst can be caused by perforation of the intraperitoneal catheter through the liver capsule, followed by dissection of the liver substance by the CSF and a fluid accumulation that can induce hepatomegaly (Wang and Miller 1989). Misplaced ventriculoperitoneal shunt can also cause a pseudocyst of Glisson's capsule (Peltier et al. 2011).

Macroscopically, one notes thin-walled pseudocysts that contain a clear or only slightly turbid watery fluid, the cystic space having a smooth, glistening surface. Histologically, the pseudocyst cyst wall consists of compressed liver tissue with a proteinaceous layer with our without leukocytes or, in late stages, of a hypocellular fibrous tissue, with accumulation of macrophages and lymphocytes in the innermost part of the wall (Rainov et al. 1994).

Other Hepatobiliary Cysts That May Mimic Hepatic Cystic Neoplasms

Hepatic Epidermoid Cyst

Epidermoid cysts located within the liver substance or related to bile ducts are very rare alterations of unknown etiology. A developmental error has been considered, with endodermal cells fated to an aberrant cell lineage, or keratinocytes derived from an accessory foregut bud. On the other hand, squamous metaplasia of biliary cysts followed by epidermization may be another explanation (Fernandez-Castroagudin et al. 2001; Chiu et al. 2005). The lesions were also observed in children (Schullinger et al. 1983). Epidermoid cysts of the liver usually present as solitary cystic lesions, but multiloculated forms are also known (Sando et al. 1996). They can grow to a large size and eventually mimic hydatid disease (Fernandez-Castroagudin et al. 2001). Epidermoid cysts of the liver can be complicated by intrahepatic squamous cell carcinoma (Lombardo et al. 1995; Odemis et al. 2006).

Hepatic Bronchogenic Cyst

Bronchogenic cyst, which shares a ciliated epithelium with ciliated foregut cyst, can occur, apart from its well-known mediastinal sites, in the diaphragm but is the rarest hepatic nonparasitic cyst (Cerwenka et al. 2000).

Intramural Bile Duct Cysts

Intramural bile duct cysts are very rare lesions that may derive from dilated peribiliary glands, secondary obliterated diverticula, or may represent small choledochoceles or circumscribed, incomplete ductal duplications (Scotiniotis and Kochman 2001; Garcia-Cano et al. 2005).

References

Abe M, Kato H, Katafuchi S, Takano S, Ishimura Y, Ogawa M (1994) A case of ciliated hepatic foregut cyst simulating a solid tumor. Nippon Shokaki Geka Gakkai Zasshi 27:1080–1084

Agrawal S, Khurana J, Sahu M (2012) Hemorrhagic liver cyst. J Gastrointest Surg 16:1629–1631

Ahgdassi A, Mayerle J, Kraft M, Sielenkämper AW, Heidecke CD, Lerch MM (2008) Diagnosis and treatment of pancreatic pseudocysts in chronic pancreatitis. Pancreas 36:105–112

Aiza I, Barkin JS, Casillas VJ, Molina EG (1993) Pancreatic pseudocysts involving both hepatic lobes. Am J Gastroenterol 88:1450–1452

Al-Ani R, Ramadan K, Abu-Zidan FM (2009) Intrahepatic pancreatic pseudocyst. NZ Med J 122:75–77

Ancel D, Lefebvre M, Peyrin-Biroulet L, Chone L, Sido A, regent D, Bigard MA (2005) Pancreatic pseudocysts of the right hepatic lobe during acute biliary pancreatitis (in French). Gastroenterol Clin Biol 29:743–745

Atia A, Kaira S, Rogers M, Murthy R, Borthwick TR, Smalligan RD (2009) A wayward cyst. JOP 10:421–424

Atienza P, Couturier D, Grandjouan S, Guierre J, Bettan L, Chapuis Y, Vasile N (1987) Intrahepatic collections of fluid of pancreatic origin. A case (in French). Presse Med 16:1195–1198

Balducci G, Bellagamba R, De Siena T, Mercantini P, Rebonato A, Ziparo V (2003) Ciliated hepatic foregut cysts: a case report. G Chir 24:189–192

Balzan S, Kiamanesh R, Farges O, Sauvanet A, O'toole D, Levy P, Ruszniewski P et al (2005) Right intrahepatic pseudocyst following acute pancreatitis: an unusual location after acute pancreatitis. J Hepatobiliary Pancreat Surg 12:135–137

Banka S, Johnson K, Sgouros S (2007) Liver cyst caused by the peritoneal catheter of a cerebrospinal fluid shunt. Pediatr Neurosurg 43:343–344

Ben Mena N, Zalinski S, Svrcek M, Lewin M, Fléjou JF, Wendum D, Paye F (2006) Ciliated hepatic foregut cyst with extensive squamous metaplasia: report of a case. Virchows Arch 449:730–733

Benlolo D, Vilgrain V, Terris B, Zins M, Belghiti J, Menu Y (1996) Imaging of ciliated hepatic or biliary cysts. 4 cases. Gastroenterol Clin Biol 20:497–501

Betalli P, Gobbi D, Talenti E, Alaggio R, Gamba P, Zanon GF (2008) Ciliated hepatic foregut cyst: from antenatal diagnosis to surgery. Pediatr Radiol 38:230–232

Bhasin DK, Rana SS, Chandail VS, Nanda M, Nadkarni N, Sinha SK, Nagi B (2005) An intra-hepatic pancreatic pseudocyst successfully treated with endoscopic transpapillary drainage alone. JOP 6:593–597

Bogner B, Hegedüs G (2002) Ciliated hepatic foregut cyst. Pathol Oncol Res 8:278–279

Bryant MS, Bremer AM, Tepas JJ, Mollitt DL, Nguyan TQ, Talbert JL (1988) Abdominal complications of ventriculoperitoneal shunts. Case reports and review of the literature. Am Surg 54:50–55

Bryce Y, Wood B, Baron P, Gibbs L (2008) An unusual congenital hepatic cyst in an adolescent and review of differential diagnoses of complex liver cysts. J Radiol Case Rep 2:18–23

Cai XJ, Huang DY, Liang X, Yu H, Li W, Wang XF, Peng SY (2004) Ciliated hepatic foregut cyst: report of first case in China and review of literature. J Zhejiang Univ (Sci) 5:483–485

Cappell MS (1988) Obstructive jaundice from benign, nonparasitic hepatic cysts: identification of risk factors and percutaneous aspiration for diagnosis and treatment. Am J Gastroenterol 83:93–96

Caratozzolo E, Massani M, Recordare A, Ciardo L, Antoniutti M, Jelmoni A, Bassi N (2001) Squamous cell liver cancer arising from an epidermoid cyst. J Hepatobiliary Pancreat Surg 8:490–493

Carnicer J, Duran C, Donoso L, Saez A, Lopez A (1996) Ciliated hepatic foregut cyst. J Pediatr Gastroenterol Nutr 23:191–193

Carrim ZI, Murchison JT (2003) The prevalence of simple renal and hepatic cysts detected by spiral computed tomography. Clin Radiol 58:626–629

Casado D, Sabater L, Calvete J, Mayordomo E, Aparisi L, Sastre J, Ledo S (2007) Multiple intrahepatic pseudocysts in acute pancreatitis. World J Gastroenterol 13:4655–4657

Cerwenka H, Uggowitzer M, Bacher H, Werkgartner G, El-Shabrawi A, Mischinger HJ (2000) Bronchogenic cyst appearing as a hepatic mass. Abdom Imaging 25:86–88

Cesaris-Demel A (1905) Über die aberranten Gallengänge vom pathologisch-anatomischen Gesichtspunkte her. Zbl Pathol 16:674

Charlesworth P, Ade-Ajayi N, Davenport M (2007) Natural history and long-term follow-up of antenatally detected liver cysts. J Pediatr Surg 42:494–499

Chatelain D, Chailley-Heu B, Terris B, Molas G, Le Cae A, Vilgrain V, Belghiti J, Degott C, Fléjou JF (2000) The ciliated hepatic foregut cyst, an unusual bronchiolar foregut malformation: a histological, histochemical, and immunohistochemical study of 7 cases. Hum Pathol 31:241–246

Chatelain D, Maillet E, Boyer L, Checkouri C, Mourra N, Fléjou JF (2002) Brunner gland hamartoma with predominant adipose tissue and ciliated cysts. Arch Pathol Lab Med 126:734–735

Chatzipetrou M, Avgerinos E, Christianakis E, Barmparas G, Pashalidis N, Stathoulopoulos A et al (2008) Hepatic abscess in a pre-existed simple hepatic cyst as a late complication of sigmoid colon ruptured diverticula: a case report. J Med Case Rep 2:83

Chiba M, Obata H (2002) Cholangiography in a patient with hilar peribiliary cysts. J Hepatol 37:288

Chiu B, Melin-Aldana H, Superina RA (2005) Management of an epidermoid cyst of the intrahepatic bile ducts. J Pediatr Surg 40:e31–e33

Colina F, Castellano VM, Gonzalez-Pinto I, Garcia I, Novo O, Garcia-Hidalgo E, Garcia-Muñoz H et al (1998) Hilar biliary cysts in hepatic transplantation. Report of three symptomatic cases and occurrence in resected liver grafts. Transpl Int 11:110–116

Dabdoub CB, Fontoura EA, Santos EA, Romero PC, Diniz CA (2013) Hepatic cerebrospinal fluid pseudocyst: a rare complication of ventriculoperitoneal shunt. Surg Neurol Int 4:162

Dardik H, Glotzer P, Silver C (1964) Congenital hepatic cyst causing jaundice: report of a case and analogies with respiratory malformations. Ann Surg 159:585–592

de Lajarte-Thirouard AS, Rioux-Leclercq N, Boudjema K, Gandon Y, Ramee MP, Turlin B (2002) Squamous cell

carcinoma arising in a hepatic foregut cyst. Pathol Res Pract 198:697–700
De J, Rossman L, Kott MM, Deavers MT (2006) Cytologic diagnosis of ciliated hepatic foregut cyst. Diagn Cytopathol 34:846–849
Eberth (1866) Cyste mit Flimmerepithel der Leber. Arch Pathol Anat 35:478–480
Eliason EL, Smith DC (1944) Solitary nonparasitic cyst of the liver: case report. Clinics 3:607
Epstein BM, Rad FF, Conidaris C (1982) Pseudocysts involving the left lobe of the liver. CT demonstration. Br J Radiol 55:928–930
Fang SH, Dong DJ, Zhang SZ (2005) Imaging features of ciliated foregut cyst. World J Gastroenterol 11:4287–4289
Faraj W, Ahmad HH, Mukherji D, Khalife M (2011) Hepatic cerebrospinal fluid pseudocyst mimicking hydatid liver disease: a case report. J Med Case Rep 5:475
Fernandez-Castroagudin J, Bustamante Montalvo M, Delgado Blanco M, Gonzalez-Quintela A et al (2001) Epidermoid cyst: a rare cause of cystic liver disease (in Spanish). Gastroenterol Hepatol 24:247–249
Fischer EG, Schilito J (1969) Large abdominal cysts: a complication of peritoneal shunts. J Neurosurg 31:441–444
Friedreich N (1857) Cyste mit Flimmerepithel in der Leber. Arch Pathol Anat 11:466–469
Fujioka Y, Kawamura N, Tanaka S, Fujita M, Suzuki H, Nagashima K (1997) Multiple hilar cysts of the liver in patients with alcoholic cirrhosis: report of three cases. J Gastroenterol Hepatol 12:137–143
Furlanetto A, Paolo Dei Tos A (2002) Squamous cell carcinoma arising in a ciliated hepatic foregut cyst. Virchows Arch 441:296–298
Garcia-Cano J, Nieto J, Godoy MA, Gomez Ruiz CJ, Sanchez-Manjavacas N, Pérez Sola A (2005) Small size choledochocele as a cause of chronic epigastric pain: diagnosis and treatment by means of ERCP (in Spanish). An Med Interna 22:591–593
Gautier-Benoit C, Luez J, Cécile JP (1974) Pseudocyst of the pancreas with intrahepatic development. Sem Hop 50:1235–1237
Geramizadeh B, Salehzadeh A, Nikeghbalian S (2008) Ciliated hepatic foregut cyst mimicking a hydatid cyst: a case report and review of literature. Saudi J Gastroenterol 14:142–143
Goldfinc SL, Turetz F, Beck AR, Eiger M (1978) Cerebrospinal fluid intraperitoneal cyst: an unusual abdominal mass. AJR Am Roentgenol 130:568–569
Goodman MD, Mak GZ, Reynolds JP, Tevar AD, Pritts TA (2009) Laparoscopic excision of a ciliated hepatic foregut cyst. JSLS 13:96–100
Gotierrez FA, Raimondi AJ (1976) Peritoneal cysts: a complication of ventriculo-peritoneal shunts. Surgery 79:188–192
Gould L, Khademi M, Guarnaccia M, Patel NK (1979) Pancreatic pseudocyst simulating an intrahepatic mass. Am J Gastroenterol 72:75–78
Grisham JW (1963) Ciliated epithelial cells in normal murine intrahepatic bile ducts. Proc Soc Exp Biol Med 114:318–320
Guérin F, Hadhri R, Fabre M, Pariente D, Fouquet V, Martelli H, Gauthier F, Branchereau S (2010) Prenatal and postnatal ciliated hepatic foregut cysts in infants. J Pediatr Surg 45:E9–E14
Guesmi F, Zoghlami A, Saidi Y, Najeh N, Dziri C (2009) Pancreatic pseudocysts located in the liver: a systematic review of the literature. Tunis Med 87:801–804
Hamm VB, Franzen N (1993) Atypically located pancreatic pseudocyst in liver, spleen, stomach wall and mediastinum: their CT diagnosis. Röfo 159:522–527
Harris KM, Morris DL, Tudor R, Toghill P, Hardcastle JD (1986) Clinical and radiographic features of simple and hydatid cysts of the liver. Br J Surg 73:835–838
Harty MP, Hebra A, Ruchelli ED, Schnaufer L (1998) Ciliated hepatic foregut cyst causing portal hypertension in an adolescent. AJR Am J Roentgenol 170:688–690
Hauptmann EM, Wojtowycz M, Reichelderfer M, Dermott J, Crummy A (1992) Pancreatic pseudocyst with fistula to the common bile duct: radiological diagnosis and management. Gastrointest Radiol 17:151–153
Hirono S, Tanimura H, Yokoyama S, Uchiyama K, Tani M, Onishi H, Yamaue H (2002) Clinical features of ciliated foregut cyst of the gallbladder: a rare entity of cystic lesion in the gallbladder. Dig Dis Sci 47:1817–1820
Horii T, Ohta M, Mori T, Sakai M, Hori N, Yamaguchi K, Fujino H, Oishi T, Inada Y et al (2003) Ciliated hepatic foregut cyst. A report of one case and a review of the literature. Hepatol Res 26:243–248
Hospitel S, Guinot B, Teyssou H, Meyblum J, Tessier JP (1983) Intrahepatic localization of a pancreatic pseudocyst. J Radiol 64:355–358
Huang JF, Chen SC, Lu SN, Lin ZY, Chuang WL, Hsieh MY, Wang LY, Tasi JF et al (1995) Prevalence and size of simple hepatic cysts in Taiwan: community-and hospital-based sonographic surveys. Gaoxiong Yi Xue Ke Xue Za Zhi 11:564–567
Idress MT, Reid-Nicholson M, Unger P, Jaffer S (2005) Subhepatic ciliated foregut cyst. Ann Diagn Pathol 9:54–56
Ishikawa H, Uchida S, Yokokura Y, Iwasaki Y, Horiuchi H, Hiraki M, Kinoshita H, Shirouzu K (2002) Nonparasitic solitary huge liver cysts causing intracystic hemorrhage or obstructive jaundice. J Hepatobiliary Pancreat Surg 9:764–768
Jakowski JD, Lucas JG, Seth S, Frankel WL (2004) Ciliated hepatic foregut cyst: a rare but increasingly reported liver cyst. Ann Diagn Pathol 8:342–346
Johnson MA, Ravichandran P, Surendran R (2007) Solitary extra-hepatic hilar peribiliary cyst presenting with obstructive jaundice: a case report. Acta Chir Belg 107:716–719
Julien C, Chevrel B, Etévé J, Demirleau J, Sultan C, Caroli J (1965) Acute pancreatitis with

necroticohemorrhagic lesion of the spleen and the liver (in French). Rev Med Mal Foie 40:257–274
Kadoya M, Matsui O, Nakanuma Y, Yoshikawa J, Arai K, Takashima T, Amano M (1990) Ciliated hepatic foregut cyst: radiologic features. Radiology 175:475–477
Kakita A, Kimura T, Takahashi T (1995) Ciliated hepatic foregut cyst and hepatic foregut cyst. Ryoikibetsu Shokogun Shirizu 8:128–131
Kakitsubata Y, Kakitsubata S, Marutsuka K, Watanabe K (1995) Epithelial cyst of the gallbladder demonstrated by ultrasonography. Radiat Med 13:309–310
Kang CM, Ahn SG, Kim HK, Park YN, Kim KS, Choi JS, Lee WJ, Kim BR (2006) Laparoscopic excision of ciliated hepatic foregut cyst: a first report in Korea. Surg Laparosc Endosc Percutan Tech 16:255–258
Kanzaki S (1992) Imaging diagnosis of ciliated hepatic foregut cyst. Jpn J Med Imag 11:633
Kaplan KJ, Escobar M, Alonzo M, Berlin JW (2007a) Ciliated hepatic foregut cyst: report of a case on fine-needle aspiration. Diagn Cytopathol 35:245–249
Kaplan M, Ozel SK, Akgun B, Kazez A, Kaplan S (2007b) Hepatic pseudocyst as a result of ventriculoperitoneal shunts: case report and review of the literature. Pediatr Neurosurg 43:501–503
Ker J (2010) The liver and right atrium – hepatic cyst as a cause of arrhythmia. Clin Med Insights Cardiol 4:63–67
Kim S, White FV, McAlister W, Shepherd R, Mychaliska G (2005) Ciliated hepatic foregut cyst in a young child. J Pediatr Surg 40:e51–e53
Kimura A, Makuuchi M, Takayasu K, Sakamoto M, Hirohashi S (1990) Ciliated hepatic foregut cyst with solid tumor appearance on CT. J Comput Assist Tomogr 14:1016–1018
Kinjo N, Yano H, Sugimachi K, Tanaka J, Tanaka K, Saeki H, Tsukamoto S, Mimori K et al (2013) Large simple hepatic cysts leading to gastric fundal varices in a noncirrhotic patient. Fukuoka Igaky Zasshi 104:449–455
Koletsa T, Tzioufa V, Mcihalopoulos A, Apostolidis S, Papadopoulos B, Hytiroglou P (2005) Ciliated hepatic foregut cyst communicating with gallbladder. Virchows Arch 446:200–201
Kolic Z, Kukuljan M, Bonifacic D, Vukas D (2010) CSF liver pseudocyst as a complication of a ventriculo-peritoneal shunt. Wien Klin Wochenschr 122:641–644
Lantink JA, Heggelman BGF, Geerdink RA (1989) Intrahepatic rupture of a pancreatic pseudocyst: sonographic and CT demonstration (letter). AJR Am J Roentgenol 152:1129
Lederman E, Cajot O, Canva-Delcambre V, Ernst O, Notteghem B, Paris JC (1997) Pseudocysts of the left liver: uncommon complication of acute pancreatitis. Gastroenterol Clin Biol 2:340–341
Leppmann F (1900) Über die echten Zysten der Leber. Dtsch Zschr Chir 54:466
Les I, Cordoba J, Vragas V, Guamer L, Boyé R, Pineda V (2006) Pancreatic pseudocyst located in the liver. Rev Esp Enferm Dig 98:616–620
Lombardo FP, Hertford DE, Tan LK, Kazam E, Ramirez de Arellaro E (1995) Epidermoid cyst of the liver complicated by microscopic squamous cell carcinoma: CT, ultrasound, and pathology. J Comput Assist Tomogr 19:131–134
Long J, Vaughan-Williams H, Moorhouse J, Sethi H, Kumar N (2014) Acute Budd-Chiari syndrome due to a simple liver cyst. Ann R Coll Surg Engl 96:109E–111E
Macutkiewicz C, Plastow R, Chrispijn M, Filobbos R, Ammori BA, Sherlock DJ, Drenth JP et al (2012) Complications arising in simple and polycystic liver cysts. World J Hepatol 4:406–411
Mannami T, Ohfuji Y, Fujiwara K, Enomura K, Ohta T, Kunisue H, Nomura S, Eguchi K et al (2008) Ciliated hepatic foregut cyst: report of a case and a summary of the 24 cases reported in Japan (in Japanese). Nippon Shokakibyo Gakkai Zasshi 105:235–243
Masatsugu T, Shimizu S, Noshiro H, Mizumoto K, Yamaguchi K, Chijiiwa K, Tanaka M (2003) Liver cyst with biliary communication successfully treated with laparoscopic deroofing: a case report. JSLS 7:249–252
Matsumoto S, Miyake H, Mori H (1997) Case report: biliary cystadenoma with mucin-secretion mimicking simple hepatic cyst. Clin Radiol 52:316–318
Mehler CI, Soyer P, Kardache M, Pelage JP, Boudiaf M, Paris Y, Abitbol M, Hamzi L, Rymer R (1998) Computed tomography of intrahepatic pseudocysts (in French). J Radiol 79:751–755
Mofredj A, Cadranel JF, Dautreaux M, Kazerouni F, Hadj-Nacer K, Deplaix P, François G et al (2000) Pancreatic pseudocyst located in the liver: a case report and literature review. J Clin Gastroenterol 30:81–83
Momin TA, Milner R, Sarmiento JM (2004) Ciliated hepatic foregut cyst of the left hepatic vein. J Gastrointest Surg 8:601–603
Mukai T, Takahashi S, Ishii M et al (1988) A case report of congenital hepatic cyst consisting of respiratory epithelium containing mass-like internal echoes. Jpn J Med Ultrason 15:505–510
Müller W (1893) Über nicht parasitäre Leberzysten. Zbl Chir 20:66
Muñoz-Bellvis L, Esteban Velasco C, Pordomingo AF, Rodriguez Pérez A, Gomez Alonso A (2012) Biliary stenosis secondary to simple cyst sclerosis, mimicking a malignant tumor (in Spanish). Cir Esp 90:472–473
Murakami T, Imai A, Nakamura H, Tsuda K, Kanai T, Wakasa K (1996) Ciliated foregut cyst in cirrhotic liver. J Gastroenterol 31:446–449
Muraoka et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12928855
Musielak MC, Singh R, Hartman E, Bernstein J (2014) Simple hepatic cyst causing inferior vena cava thrombus. Int J Surg Case Rep 5:339–341
Nam ES, Lee HI, Kim DH, Choi CS, Kim YB, Kim JS, Shin HS (2000) Ciliated foregut cyst of the gallbladder: a case report and review of the literature. Pathol Int 50:427–430

Nogami A, Nomura Y, Yabuuchi I, Negoro H, Nishioka M, Matsuda Y, Kawano K (1990) A case of hepatic ciliated cyst. Acta Hepatol Jpn (Kanzo) 31:1458–1463

Odemis B, Köksal AS, Yüksel O, Kacar S, Turhan N (2006) Squamous cell cancer of the liver arising from an epidermoid cyst: case report and review of the literature. Dig Dis Sci 51:1278–1284

Oida T, Mimatsu K, Kawasaki A, Kuboi Y, Kanou H, Amano S (2009) Laparoscopic excision for an enlarged ciliated hepatic foregut cyst as a minimally invasive procedure. J Laparoendosc Adv Surg Tech A 19:203–206

Okuda K, Sugita S, Tsukada E, Sakuma Y, Ohkubo K (1991) Pancreatic pseudocyst in the left hepatic lobe: a report of two cases. Hepatology 13:359–363

Ozeki Y (1995) Ciliated hepatic foregut cyst with stone formation: report of a case. Acta Hepatol Jpn (Kanzo) 36:296–301

Ozeki Y, Miura J (1994) A case report of multiple hepatic hilar cyst associated with hepatocellular carcinoma (in Japanese). Nihon Shokakibyo Gakkai Zasshi 91:1052–1056

Peltier E, Leger-Ravet MB, Franco D, Lemaigre G, Bedossa P (1993) Kystes à revêtement cilié du foie. Gastroenterol Clin Biol 17:859–862

Peltier J, Demuynck F, Fichten A, Lefranc M, Toussaint P, Desenclos C, Nicot B, Pruvot AS et al (2011) Non-traumatic pseudocyst of Glisson capsule complicating a ventriculoperitoneal shunt. Neurochiurgie 57:31–33

Plenk L (1910) Zur Kenntnis der solitären Leberzysten. Virchows Arch 210:335–349

Rainov N, Schobess A, Heidecke V, Burkert W (1994) Abdominal CSF pseudocysts in patients with ventriculo-peritoneal shunts. Report of fourteen cases and review of the literature. Acta Neurochir (Wien) 127:73–78

Rana SR, Quivers ES, Haddy TB (1985) hepatic cyst associated with ventriculoperitoneal shunt in a child with brain tumor. Childs Nerv Syst 1:349–351

Ravindra KV, Rao BV, Rozario AP, Pais AV, Thomas PG (1999) Segment IV liver cyst with biliary communication following laparoscopic deroofing. Indian J Gastroenterol 18:39–40

Regev A, Reddy KR, Berho M, Sleeman D, Levi JU, Livingstone AS, Levi D, Ali U, Molina EG et al (2001) Large cystic lesions of the liver in adults: a 15-year experience in a tertiary center. J Am Coll Surg 193:36–45

Rogers TN, Woodley H, Ramsden W, Wyatt JI, Stringer MD (2007) Solitary liver cysts in children: not always so simple. J Pediatr Surg 42:333–339

Ryu JK, Woo SM, Hwang JH, Jeong JB, Yoon YB, Park IA et al (2004) Cyst fluid analysis for the differential diagnosis of pancreatic cysts. Diagn Cytopathol 31:100–105

Sando Z, Le Coultre C, Belli D, Bugmann P, Cox JN (1996) Multiloculated epidermoid cyst of the liver. Pediatr Surg Int 11:384–386

Sanfelippo PM, Beahrs OH, Weiland LH (1974) Cystic disease of the liver. Ann Surg 179:922–925

Sasaki M, Terada T, Nakanuma Y, Wakabayashi T, Sugioka G, Watanabe K (1990) A case of ciliated hepatic foregut cyst. Acta Hepatol Jpn (Kanzo) 31:1235–1239

Sasaki M, Yagi S, Suzuki M, Uozu K, Hasegawa H, Sekikawa H (1991) A case of congenital liver cyst showing solid mass (hepatic foregut cyst). Nippon Shokaki Geka Gakkai Zasshi 24:2579–2583

Sato T (1990) Imaging diagnosis of cystic disease: ciliated hepatic foregut cyst. Acta Hepatol Jpn (Kanzo) 31:137

Sato Y, Kitagawa S, Zen Y, Minato H, Nakanuma Y (2006) Ciliated hepatic cyst without smooth muscle layer: a variant of ciliated hepatic foregut cyst? Pathol Int 56:340–344

Sato T, Imai M, Hayashi K, isokawa O, Nomura T, Tsuchiya Y, Kawasaki T (2013) Giant hepatic cyst with septal structure: diagnosis and management. Int J Hepatol 2013:981975

Scappaticci F, Markowitz SK (1995) Intrahepatic pseudocyst complicating acute pancreatitis: imaging findings. AJR Am J Roentgenol 165:873–874

Schullinger JN, Wigger HJ, Price JB, Benson M, Harris RC (1983) Epidermoid cysts of the liver. J Pediatr Surg 18:240–242

Scotiniotis IA, Kochman ML (2001) Intramural cyst of the bile duct demonstrated by cholangiography and intraductal US. Gastrointest Endosc 54:260–262

Sharma S, Dean AG, Corn A, Kohli V, Wright HI (2008) Ciliated hepatic foregut cyst: an increasingly diagnosed condition. Hepatobiliary Pancreat Dis Int 7:581–589

Shaw JM, Krige JE, Beningfield SJ, Locketz ML (2008) Ciliated hepatic foregut cyst: a rare cystic liver lesion. J Gastrointest Surg 12:1304–1306

Shibasaki M, Bandai Y, Ukai T (2002) Pancreatic pseudocyst extending into the liver via hepatoduodenal ligament: a case report. Hepato-Gastroenterology 49:1719–1721

Shoenut JP, Semelka RC, Levi C, Greenberg H (1994) Ciliated hepatic foregut cysts: US, CT, and contrast-enhanced MR imaging. Abdom Imaging 19:150–152

Slim K, Hendaoui L, Larabi B (1992) Multiple intrahepatic pseudocysts in acute pancreatitis (in French). Gastroenterol Clin Biol 16:902

Straus T, Osipov V (2006) Ciliated hepatic foregut cyst in a patient with renal cell carcinoma. BMC Cancer 6:244

Stringer MD, Jones MO, Woodley H, Wyatt J (2006) Ciliated hepatic foregut cyst. J Pediatr Surg 41:1180–1183

Terada T, Nakanuma Y, Kono N, Ueda K, Kadoya M, Matsui O (1990) Ciliated hepatic foregut cyst. A mucus histochemical, immunohistochemical and ultrastructural study in three cases in comparison with normal bronchi and intrahepatic bile ducts. Am J Surg Pathol 14:356–363

Terada T, Nakanuma Y, Ohta T, Nagakawa T, Motoo Y, Harada A, Hamato N, Inaba T (1991) Mucin-histochemical and immunohistochemical profiles of

epithelial cells of several types of hepatic cysts. Virchows Arch A Pathol Anat Histopathol 419:499–504
Terada N, Shimizu T, Imai Y, Kobayashi T, Terashima M, Furukawa K, Kumazawa S, Kiyosawa K (1993) Benign, non-parasitic hepatic cyst causing obstructive jaundice. Intern Med 32:857–860
Terada T, Notsumata K, Nakanuma Y (1994) Biliary carcinosarcoma arising in nonparasitic simple cyst of the liver. Virchows Arch 424:331–335
Tonolini M, Rigiroli F, Binaco R (2014) Symptomatic and complicated nonhereditary developmental liver cysts: cross-sectional imaging findings. Emerg Radiol 21:301–308
Ueda J, Yoshida H, Taniai N, Kawano Y, Uchida E (2010) A case of spontaneous rupture of a simple hepatic cyst. J Nippon Med Sch 77:181–185
Vick DJ, Goodman ZD, Deavers MT, Cain J, Ishak KG (1999a) Ciliated hepatic foregut cyst: a study of six cases and review of the literature. Am J Surg Pathol 23:671–677
Vick DJ, Goodman ZD, Ishak KG (1999b) Squamous cell carcinoma arising in a ciliated hepatic foregut cyst. Arch Pathol Lab Med 123:1115–1117
Von Recklinghausen F (1881) Über die Ranula, die Cyste der Bartholin'schen Drüse und die Flimmercyste der Leber. Arch Pathol Anat 84:425–495
Wang F, Miller JH (1989) Cerebrospinal fluid pseudocyst as a hepatic mass: a complication of ventriculoperitoneal shunt. Pediatr Radiol 19:326–327
Wang SJ, Chen JJ, Changchien CS et al (1993) Sequential invasions of pancreatic pseudocysts in pancreatic tail., hepatic left lobe, caudate lobe, and spleen. Pancreas 8:133–136
Wheeler DA, Edmondson HA (1984) Ciliated hepatic foregut cyst. Am J Surg Pathol 8:467–470
Winckler C (1891) Zur Kasuistik der Leberzysten. Thesis, Marburg
Wu ML, Abecassis MM, Rao MS (1998) Ciliated hepatic foregut cyst mimicking neoplasm. Am J Gastroenterol 93:2212–2214
Yamada T, Furukawa K, Yokoi K, Mamada Y, Kanazawa Y, Tajiri T (2009) Liver cyst with biliary communication successfully treated with laparoscopic deroofing: a case report. J Nippon Med Sch 76:103–108
Yi CY, Na GJ, Baek HC, Kim JH, Bae SH, Kim DH, Je IS, Kwon BP (2008) A case of intrahepatic pseudocyst complicating acute pancreatitis (in Korean). Korean J Gastroenterol 51:56–59
Young AS, Nicol KK, Teich S, Ii WE (2007) Catheter-based drainage and agitation for definitive cytological diagnosis of ciliated hepatic foregut cyst n a child. Pediatr Dev Pathol 10:153–156
Yuasa N, Nimura Y, Hayakawa N, Kamiya J, Maeda S, Kondo S, Nagasaka T (1997) Multiple hepatic cysts along the intrahepatic bile duct – case report. Hepato-Gastroenterology 44:1262–1266
Zahn FW (1896) Über mit Flimmerepithelian ausgekleidete Cysten im Oesophagus, der Pleura und der Leber: beitrag zur lehre von den angeborenen Mucoidcysten. Arch Pathol Anat 143:170–187
Zaman SS, Langer JE, Gupta PK (1995) Ciliated hepatic foregut cyst: report of a case with findings on fine needle aspiration. Acta Cytol 39:781–784
Zaydfudim V, Rosen MJ, Gillis LA, Correa H, Lovvorn HN, Pinson CW, Kelly BS (2010) Ciliated hepatic foregut cysts in children. Pediatr Surg Int 26:753–757
Zhang X, Wang Z, Dong Y (2009a) Squamous cell carcinoma arising in a ciliated hepatic forgeut cyst: case report and literature review. Pathol Res Pract 205:498–501
Zhang YL, Yuan L, Shen F, Wang Y (2009b) Hemorrhagic hepatic cysts mimicking biliary cystadenoma. World J Gastroenterol 15:4601–4603

Part XXVI

Hepatobiliary Mass Lesions Caused by Noninfectious Granulomas

Tumor-Like Granulomatous Disorders of the Hepatobiliary Tract 139

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_139

Abstract

The granulomatous hepatobiliary reactions that characterized sarcoidosis (Morbus Boeck) induce a wide array of secondary alterations, part of which resemble neoplastic conditions. Liver involvement in sarcoidosis amounts to 10 % or more than 80 % of cases, depending on criteria used. The main features of hepatic sarcoidosis comprise granulomatous hepatitis, chronic cholestasis, portal hypertension, Budd-Chiari syndrome, and liver cirrhosis. Cholestasis in sarcoidosis can clinically mimic primary biliary cirrhosis or primary sclerosing cholangitis. Granulomatous hepatitis is a very common manifestation of hepatic sarcoidosis. Typically, sarcoid granulomas lack central necrosis but may contain Schaumann bodies and asteroid bodies. Hepatic granulomas can coalesce to form larger nodular and tumor-like lesions. Such masses may grow to large size to form pseudotumors or so-called sarcoidomas. The granulomatous inflammation can involve bile ducts and cause biliary obstruction with typical secondary liver changes. Also, small bile duct involvement is known, resulting in vanishing bile duct syndrome.

Sarcoidosis of the Liver

Introduction

Sarcoidosis (Boeck's disease; Morbus Boeck; Morbus Boeck-Besnier-Schaumann) is a chronic granulomatous disorder of unknown etiology and characterized by a highly variable presentation spectrum and course, although pulmonary and lymph node involvements are predominant features (review: Morgenthau and Iannuzzi 2011). Abdominal sarcoidosis is diagnosed by imaging modalities in 5–15 % of the patients (Warshauer et al. 1994a,b), and the most common CT findings in abdominal sarcoidosis are hepatosplenomegaly and lymphadenopathy (Britt et al. 1991; Foltz et al. 1995).

Epidemiology

How frequent are manifestations of sarcoidosis in the liver? Among a total of 736 sarcoidosis patients enrolled in the ACCESS study (A Case Control Etiologic Study of Sarcoidosis), 85 patients or 11.5 % had liver involvement (Baughman et al. 2001). In a study of 1,436 patients with presumed sarcoidosis, 340 patients had abnormalities in liver tests, and 40 with confirmed sarcoidosis underwent a liver biopsy. Among these, 50 % had bile duct depletion and 26 % had bridging fibrosis or cirrhosis. Male gender, hepatomegaly, splenomegaly, and normal chest radiograph were associated with hepatic sarcoidosis (Kahi et al. 2006). Exclusive liver involvement without lung disease in patients with systemic sarcoidosis is uncommon and only found in 13 % of patients (Kennedy et al. 2006). Severe chronic liver diseases, i.e., cirrhosis and/or portal hypertension, are only observed in 1 % of patients with sarcoidosis.

Clinical Features of Hepatic Sarcoidosis

The main features of hepatic sarcoidosis comprise granulomatous hepatitis, chronic cholestasis, portal hypertension, Budd-Chiari syndrome, and biliary cirrhosis. In part of patients, hepatic sarcoidosis is associated with splenic involvement (hepatosplenic sarcoidosis; Sekine et al. 2012). Chronic cholestasis is a typical albeit uncommon hepatic manifestation of sarcoidosis. Most cases are caused by progressive destruction of small intrahepatic bile ducts (vanishing bile duct syndrome), discussed in more detail below.

Selected References Shay et al. (1951), Branson and Park (1954), Cheitlin et al. (1960), Porter (1961), Maddrey et al. (1970), Rudzki et al. (1975), Thomas and Micci (1977), Hughes et al. (1983), Valla et al. (1987), Murphy et al. (1990), Panasci et al. (1992), Devaney et al. (1993), James and Sherlock (1994), Ishak (1998), Mueller et al. (2000), Baughman et al. (2001), Ganne-Carrié et al. (2001), Blich

and Edoute (2004), Ayyala and Padilla (2006), Kahi et al. (2006), Karagiannidis et al. (2006), Deniz et al. (2008), Ebert et al. (2008), Rose et al. (2008), Aravinthan et al. (2012), Bakker et al. (2012), Elloumi et al. (2012), Buxbaum et al. (2013), and Hashash et al. (2013).

Cholestasis in sarcoidosis can mimic primary biliary cirrhosis (PBC) (Rudzki et al. 1975; Thomas and Micci 1977; Bass et al. 1982; Hughes et al. 1983) or primary sclerosing cholangitis (PSC) (Alam et al. 1997; Maambo et al. 2007), two autoimmune disorders which are also characterized by a granulomatous reaction in the liver. On the other hand, there is evidence that sarcoidosis may in fact be combined with autoimmune disorders such as PBC and PSC. Cutaneous sarcoidosis has been observed to occur in conjunction with AMA-positive PBC (Karlish et al. 1969; Stanley et al. 1972; Byrne et al. 1977; Keefe 1987; Xerri et al. 1989; Leff et al. 1990; Hughes and McGavin 1997; Kishor et al. 2008). Late-onset sarcoidosis has been observed in a patient after liver transplantation for primary biliary cirrhosis (Gur et al. 2007). Sarcoidosis has been found in conjunction with PSC (Keller et al. 1997), and hepatic sarcoidosis can be associated with an elevated serum level of immunoglobulin IgG4 (Inoue et al. 2012). Cholestasis in sarcoidosis can also be caused by granulomatous and fibrosing cholangitis of the large bile ducts (Bloom et al. 1978; Kusielewicz et al. 1988; Albu et al. 1995; Rezeig and Fashir 1997) and compression of the extrahepatic bile ducts by enlarged lymph nodes showing granulomatous lymphadenitis (Bloom et al. 1978; Baughman 1988). Liver-associated lymph nodes may develop large sizes in sarcoidosis (Inoue et al. 1995). Sarcoid stenosis of bile ducts may mimic cholangiocarcinoma (Rezeig and Fashir 1997).

Hepatic sarcoidosis can seldom recur after liver transplantation, with biopsy-proven hepatic granulomas (Fidler et al. 1997; Cengiz et al. 2005), in one case manifesting with severe hypercalcemia (Cengiz et al. 2005). On the other hand, three post-transplant patients having died from non-sarcoidosis-related causes did not show liver granulomas at necropsy (Casavilla et al. 1993). Generalized sarcoidosis can be complicated by subsequent malignant non-Hodgkin's lymphoma, the sarcoidosis-lymphoma syndrome (Goljan-Geremek et al. 2013), which may be expected to potentially involve the hepatobiliary tract.

Macroscopic Pathology

Whitish and well-defined nodules of variable size without a hyperemic margin are noted (Giovinale et al. 2009). Many of these nodules are visualized by sonography (Sartori et al. 2002) and as low-density areas on CT and have bioptically been shown to represent conglomerated masses of non-caseating and fibrosing granulomas (Nakata et al. 1989; Kim et al. 1992; Hoeffel et al. 1996; Scott et al. 1997; Thanos et al. 2002), but there are also focal hepatic lesions that are not detectable by CT or MRI (Sakai et al. 1995). Nodular hepatic lesions may be isolated or occur together with similar lesions in the spleen. In a review of images of 20 cases, isolated splenic involvement was seen in seven, isolated hepatic involvement in four, and simultaneous hepatic and splenic involvement in nine patients (Scott et al. 1997). Large confluent sarcoid lesions may present as tumorous nodules and hence mimic disseminated hepatic malignancy (Oketani et al. 1992). In stage IV disease (biliary cirrhosis), the organ is coarsely nodular and shows irregularly or garland-shaped regenerative nodules on the cut surface, with dense and broad fibrous septa and with or without signs of cholestasis. In fibrosing sarcoidosis of the hilar region, hilar cholangiocarcinoma can be mimicked (Suzuki et al. 2011).

Histopathology

Granulomatous Hepatitis

Liver biopsies performed owing to clinical evidence of liver disease show sarcoid granulomas in

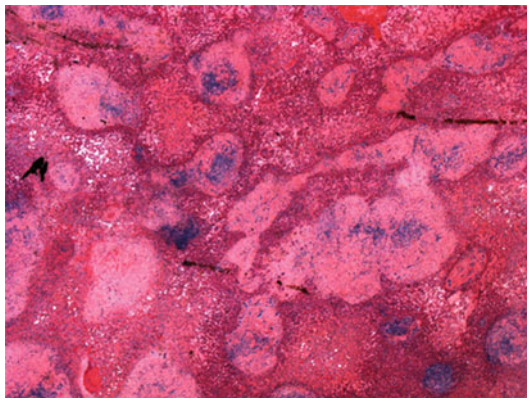

Fig. 1 Sarcoidosis of the liver. Numerous, in part confluent, non-caseating granulomas are seen (hematoxylin and eosin stain)

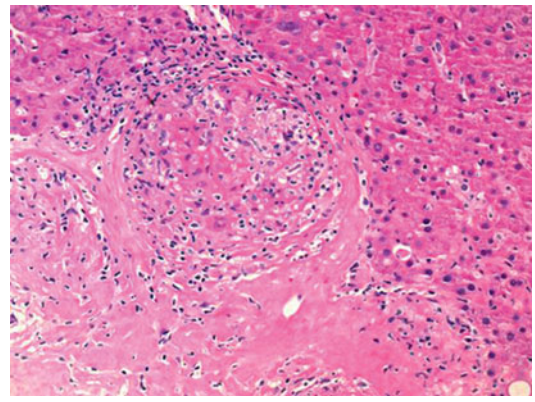

Fig. 3 Sarcoidosis of the liver. In sarcoidosis, granulomas tend to undergo fibrosclerosis which may compromise the structure of involved bile ducts and blood vessels (hematoxylin and eosin stain)

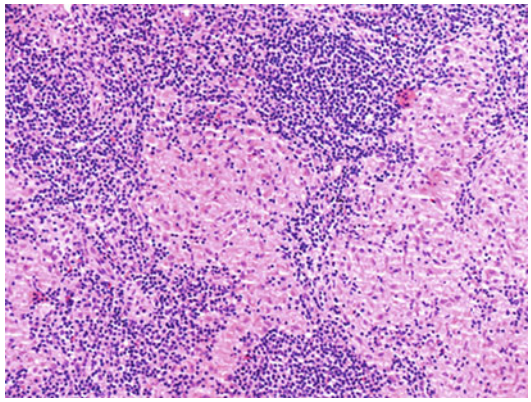

Fig. 2 Sarcoidosis of the liver. Epithelioid cell granulomas without necrosis (hematoxylin and eosin stain)

a large proportion of cases (Figs. 1, 2, and 3; Klatskin and Yesner 1950; Hercules and Bethlem 1984; Devaney et al. 1993; Trenn et al. 1999; Bilir et al. 2000; Aravinthan et al. 2012; Aga et al. 2013). Reported prevalences of hepatic granulomas in sarcoidosis range, however, from 11 % to more than 80 % (Branson and Park 1954; Maddrey et al. 1970; Bilir et al. 2000; Ayyala and Padilla 2006; Harder et al. 2007), these differences probably being related to varying immune reactions, individual interpretation of biopsies (small epithelioid cell clusters vs. giant cell-containing, well-developed granulomas), and sampling effects. How many cases of granulomatous hepatitis in general are caused by sarcoidosis ? In a retrospective study of 442 cases with biopsy-proven hepatic granulomas found in a series of 12,161 liver biopsies of a single center, 37 cases (8.37 %) were caused by sarcoidosis, while 215 cases or 48.64 % were caused by primary biliary cirrhosis (Drebber et al. 2008). In other studies with smaller number of cases, the prevalence of sarcoidosis among cases of granulomatous hepatitis was 7.5 % (Dourakis et al. 2007) and 11.1 % (Gaya et al. 2003). The granulomas are more often located to portal tracts than to the lobular parenchyma (Elloumi et al. 2012). In a minority of cases, granulomas in sarcoidosis may show central necrosis but not of the caseification type (Bilir et al. 2000). Giant cells of the Langhans type are often present in sarcoid granulomas and develop via cell fusion of epithelioid macrophages (van Maarsseveen et al. 2009). The characteristic inclusions of giant cells, i.e., Schaumann bodies and asteroid bodies, are regarded as typical for senescent granulomas in sarcoidosis and have been found in hepatic granulomatous lesions (Bilir et al. 2000) but are not seen in all cases (Ishak 1998). Schaumann bodies (Metchnikoff-Schaumann bodies) are strongly basophilic ("blue"), concentrically laminated ovoid structures. When fully developed, Schaumann bodies look like raspberries. The bodies contain calcium and iron, and calcium oxalate monohydrate is detectable

in them (Kirkpatrick et al. 1988; Reid and Andersen 1988; Symmans et al. 1995). Schaumann bodies are often found within giant cells, but in case they are very large or numerous, they can be extruded into the extracellular space. Small birefringent calcific particles and particles of dolomite found in epithelioid cells may be precursors of Schaumann bodies (Reid and Andersen 1988). Asteroid bodies are stellate inclusions of giant cells with numerous rays radiating from a central core. Asteroid bodies are thought to be derivatives of the cytosphere. The body and arms of the star-like structure consist of longitudinally oriented microfilaments with accompanying microtubules (Cain and Kraus 1977). Asteroid body morphogenesis seems to involve unusual microtubule dynamics in monocyte-derived epithelioid cells (Gadde and Moscovic 1994). Granulomas may heal without leaving a trace, but confluent granulomas often induce a fibrosing reaction, probably via production of fibrokines by the immunologic effector cells, causing scarring and the formation of supramiliary nodules.

Nodular Lesions

In part of the patients, coalescent clusters of granulomas with or without fibrosis/sclerosis can form tumor-like nodular lesions (Kim et al. 1992; Warshauer et al. 1995). The nodules are usually small (Warshauer et al. 1995) but may reach a diameter of up to 1.5 cm. Sarcoidosis with nodular lesions is associated with hepatomegaly and adenopathy (Warshauer et al. 1995). Large nodules consisting of scarred confluent granulomas may mimic cholangiocarcinoma (Menias et al. 2008).

Pseudotumoral Hepatic Sarcoidosis (Sarcoidomas)

Rare cases of nodular hepatic sarcoidosis characterized by large nodules having a diameter of 1.5 cm or more (Warshauer et al. 1994b), or conglomerates reaching several cm in diameter, have been called pseudotumoral hepatic sarcoidosis or "sarcoidomas" (Devaney et al. 1993). The lesions may reach a size of 6 cm or even more and may mimic malignancy (Stephan et al. 1965; Jung et al. 2004). In case such large lesions are located to the bile duct or hilar compartments, obstructive jaundice can develop (Albu et al. 1995). Healing conglomerated lesions may end up in rather large irregular scars that are sometimes difficult to interpret.

Granulomatous and Fibrosing Cholangitis

In a subset of patients with hepatobiliary sarcoidosis, a special form of granulomatous cholangitis develops, with a tendency for fibrosis (Bloom et al. 1978; Kusielewicz et al. 1988; Rezeig and Fashir 1997; Buxbaum et al. 2013). In the fibrosing/scarring phase, the bile duct changes may radiologically and histologically resemble primary sclerosing cholangitis (PSC) (Tombazzi et al. 2008). Specifically, the fibrosing process can cause multiple bile duct strictures that radiologically closely resemble those in PSC (Alam et al. 1997). The ductocentric fibrosclerosing process in certain patients with sarcoidosis may mimic cholangiocarcinoma (Nehls et al. 2006), in particular Klatskin's tumor (Pungpapong et al. 2006).

Small Bile Duct Disease

Hepatobiliary sarcoidosis can be associated with distinct patterns of small bile duct disease. The most important is vanishing bile duct syndrome, which has been documented in the literature several times (Nakanuma et al. 1979, 1983, 2001; Pereira-Lima and Schaffner 1987; Sherlock 1987; Ludwig et al. 1988; Desmet 1990; Murphy et al. 1990; Devaney et al. 1993; Reau and Jensen 2008; Farouj et al. 2011). In a study of 100 patients with sarcoidosis, 19 patients displayed bile duct lesions similar to primary biliary cirrhosis, and in 37 patients with chronic cholestasis, a decrease in the number of the small bile ducts (ductopenia) was noted (Devaney et al. 1993). Bile duct disease

in sarcoidosis is associated with hepatic cholestasis and histochemically detectable copper deposition in hepatocytes (Mounajjed et al. 2013).

Phlebitis

The inflammatory reaction of the small intrahepatic bile ducts is often accompanied by alterations of the small portal vein branches. These comprise florid phlebitis, adventitial granuloma formation, and phlebosclerosis with luminal narrowing (Moreno-Merlo et al. 1997; Nakanuma et al. 2001; Chawla and Dhiman 2008). This stenosing phlebopathy is probably causing parenchymal ischemia and may contribute to chronic fibrosing hepatopathy in sarcoidosis.

Fibrosis and Cirrhosis

The chronic granulomatous inflammation in the portal tract spaces causes fibrosis which may develop along extensions of portal tracts, ending up with septal fibrosis and cirrhosis, which is visualized on postcontrast CT images (Tsukada et al. 1993). Almost half of the cases are characterized by large central regenerative nodules associated with wedge-shaped areas of peripheral parenchymal atrophy (Ferreira et al. 2013). This progression has histologically been proven (Yoshiji et al. 2011). Histologically, portal tract and septal fibrosis are of the type seen in many forms of chronic biliary obstruction, with ductular proliferations and so-called biliary piecemeal necroses (Nakanuma et al. 2001). Mostly due to chronic biliary obstruction with bile duct loss but also in the course of progressive fibrosis of granulomatous inflammation, secondary biliary cirrhosis can develop (Thomas and Micci 1977; Hughes et al. 1983; Kitamura et al. 1998; Khan and Irfan 2001; Gavilan et al. 2003; Gupta et al. 2008). True liver cirrhosis in sarcoidosis has been observed in the setting of HFE-associated hemochromatosis (Barton et al. 2009). The fibrosing hepatic remodeling in sarcoidosis can cause portal hypertension (Mino et al. 1949; Cheitlin et al. 1960; Bruix et al. 1980; Windler et al. 1983; Tekeste et al. 1984; Yoshiji et al. 2011; Ivonye et al. 2012; Tan et al. 2012).

Budd-Chiari Syndrome

Hepatic venous thrombosis as a complication of hepatic sarcoidosis has been reported only few times. As in other situation of this syndrome, the main clinical manifestations were ascites, jaundice, and hepatomegaly (Natalino et al. 1978; Russi et al. 1986; Deniz et al. 2008; Delfosse et al. 2009; Maamouri et al. 2009; Van Brusselen et al. 2012).

Alterations in Liver-Associated Locoregional Lymph Nodes

Locoregional lymph nodes of the hepatobiliary tract can participate in sarcoidosis of the liver and show alterations known from other anatomical sites. The hallmark of lymph node sarcoidosis is the presence of non-caseating epithelioid cell granulomas with multinucleated giant cells of the Langhans type (granulomatous lymphadenitis). In early-stage disease, microgranulomas are mainly found in the subcapsular area of nodes, a phenomenon which rose suspicion of an infectious process reaching the lymph node by the lymph. Enlarging granulomas may then coalesce, ending up with an almost complete or complete effacement of the lymph node architecture. This progressive granulomatous reaction can be associated with fibrosis. In the centers of large granulomas, epithelioid macrophages may undergo atrophy or decay, and even small eosinophilic necroses may ensue, but the granular eosinophilic coagulation necrosis characterizing caseification in tuberculosis is absent. In and around granulomas, Schaumann bodies and/or asteroid bodies can be found. In sarcoidosis, Schaumann bodies are found in up to 88 % of lymph nodes, but asteroid bodies are much less common, occurring in 2–9 % of sarcoidotic

lymph nodes. Small yellow-brown, ovoid, or spindled bodies consisting of a ceroid-like substance and resembling budding fungal organisms may be observed. These structures are termed Hamazaki-Wesenberg bodies (synonyms: yellow-brown/Y-B bodies, Hamazaki corpuscles). The bodies stain with predigested PAS and are acid-fast in the long Ziehl-Neelsen acid fast stain but not in ordinary Ziehl-Neelsen stains. They are located in the cytoplasm of epithelioid cells and Langhans giant cells, sometimes in large numbers, but can also be extruded into the extracellular space and into sinusoids. The bodies were first described by Hamazaki in 1938 in mesenteric lymph nodes (Hamazaki 1938) and were later redescribed by Menne, again in mesenteric lymph nodes (Menne 1952). Apart from sarcoidosis, Hamazaki-Wesenberg bodies also occur in lymph nodes draining cirrhotic livers, appendicitis, colorectal cancer, and lymphoid neoplasms (Sieracki and Fisher 1973; Ro et al. 1987; Winters et al. 2007). The bodies are altered giant lysosomes, and the yellow-brown material may represent a distinct form of ceroid resulting from lipid oxidation in decaying macrophages/epithelioid cells.

Sarcoidosis of the Gallbladder

Granulomatous inflammation in sarcoidosis can rarely involve the gallbladder (Lloyd-Davies and Forbes 1965; Mert et al. 2004)

Hepatic Sarcoidosis and Malignancy

Sarcoidosis seems to be associated with an increased incidence of malignancy (Romer et al. 1998; Askling et al. 1999). Hepatic sarcoidosis was found to be complicated by hepatocellular carcinoma (Wong et al. 1999; Chalasani et al. 2005; Ogata et al. 2010). In a patient with ulcerative colitis, primary sclerosing cholangitis, and generalized sarcoidosis, bile duct carcinoma had developed (Van Steenbergen et al. 1987).

Differential Diagnosis

The key feature of hepatic pathology in sarcoidosis, i.e., granulomas, is typically also found in the portal tracts of primary biliary cirrhosis, overlap syndrome, and primary sclerosing cholangitis (Ludwig et al. 1995). Sarcoid-type granulomas have been found in locoregional lymph nodes draining hilar cholangiocarcinoma (Onitsuka et al. 2003). A disorder related to sarcoidosis is necrotizing sarcoid granulomatosis (NSG). NSG is predominantly a pulmonary disorder with features in between those of sarcoidosis and Wegener's granulomatosis (Popper et al. 2003; Lazzarini et al. 2008; Yeboah et al. 2012). NSG can rarely involve extrapulmonary organs and tissues, e.g., the central nervous system (Strickland-Marmol et al. 2000) and the gastrointestinal tract (Le Gall et al. 1996; Ahmed et al. 2010).

Etiology and Pathogenic Pathways

The etiology and pathogenesis of sarcoidosis have not been clarified (review: Müller-Quernheim et al. 2012). Sarcoidosis development has a genetic background (Rybicki et al. 2007; Smith et al. 2008). Genetic associations of American sarcoidosis susceptibility implicate MHC class II allele, DRB1*1101. Patients with sarcoidosis reveal oligoclonal populations of alphabeta CD4+ T cells, consistent with an MHC-restricted antigen-driven process (review: Oswald-Richter et al. 2010). Recent molecular, genetic, and immunologic studies suggest the association of sarcoidosis with infectious agent antigens (review: Saidha et al. 2012). Currently, strong candidates comprise antigens of *Propionibacterium* and *Mycobacterium* species (Song et al. 2005; Drake et al. 2007; Dubaniewicz et al. 2007). A Th-1 immune response to mycobacterial protein antigens has been detected within sarcoidosis samples, proteins that are actively secreted by the mycobacterial SecA 2 secretion system (review: Oswald-Richter and Drake 2010). In sarcoidosis, cellular responses directed against the mycobacterial virulence factors, ESAT-6 and katG, occur (Drake et al. 2007). Recognition of the

mycobacterial ESAT-6 peptide by CD4+ T cells presented by antigen-presenting cells depends on the expression of MHC class II DRB1*1101 (Oswald-Richter et al. 2010).

Pathogenetically, sarcoidosis is related to the function of inflammasomes and NOD proteins forming nodosomes (reviews: Tattoli et al. 2007; Dagenais et al. 2010; Khare et al. 2010). In the cytoplasm, NOD1 and NOD2 proteins are chiefly expressed by antigen-presenting cells (dendritic cells and macrophages) and epithelial cells (NOD1 in most epithelia, NOD2 in Paneth cells). NODs recognize distinctive muropeptide structures derived from bacterial cell wall peptidoglycans and released by growing bacteria. Specifically, NOD1 detects meso-diaminopimelic acid, a component which is mainly found in Gram-negative bacteria. NOD2 recognizes and senses muramyl dipeptide, a component present in both Gram-positive and Gram-negative bacteria. NOD1 is upregulated by interferon-gamma, NOD2 by both interferon-gamma and TNF-alpha. The signaling pathways of NOD sensors are further discussed in the paragraph on Blau syndrome.

Autoinflammatory Granulomatous Diseases: Blau Syndrome and Early-Onset Sarcoidosis

Introduction

Blau syndrome (juvenile sarcoidosis; OMIM 186580), described in 1985, and its counterpart, early-onset sarcoidosis (EOS), share a phenotype characterized by skin rash, arthritis, and uveitis, with a distinct granulomatous reaction (Raphael et al. 1993; Becker and Rose 2005; Shetty and Gedalia 2008; Sfriso et al. 2012). Blau syndrome makes part of a complex group of monogenic autoinflammatory syndromes (MAIS; Caso et al. 2013; Tripathi and Leslie 2013; Caso et al. 2014, 2015).

Blau Syndrome

Blau syndrome (OMIM 186580; familial juvenile systemic granulomatosis; Jabs syndrome) is caused by mutations in the NOD2/CARD15 gene (see below) and is clinically characterized by erythematous and papular skin rash, arthritis (in part polyarthritis), uveitis/iridocyclitis, often with a granulomatous inflammatory reaction, and granulomatous hepatitis. The symptoms and signs timely occur in this sequence, but the presentation is variable, mainly in regard of ocular manifestations, and part of the patients may have fever is the sole sign (Kurokawa et al. 2003; Arostegui et al. 2007; Rose et al. 2011). In comparison with sarcoidosis, patients with Blau syndrome have elevated serum angiotensin-converting enzyme, but they have a negative Kveim-Sitzbach test and lack pulmonary involvement (James 1994). The disorder is caused by mutations in the CARD15/NOD2 gene (Pillai and Sobrin 2013). Many mutations are detectable in the centrally located NOD region and are associated with ligand-independent NFkappaB activation (Priori et al. 2004; Okafuji et al. 2009). The phenotype of Blau syndrome is influenced by the type of NOD2 mutations involved, in that certain mutations are associated with arteritis of the Takayasu type (Khubchandani et al. 2012; Inoue et al. 2013). Recently, Blau syndrome has been associated with *Mycobacterium avium* subspecies paratuberculosis (MAP), the cause of an inflammatory enteric disease predominantly in ruminant animals and termed Johne's disease. It has been suggested that MAP induces autoimmune disorders in human through triggering of autoimmune antibodies via its heat shock proteins (Dow 2012).

Blau syndrome is histologically characterized by the presence of non-caseating granulomas in the involved tissue. The granulomas are in principle of the type found in adult sarcoidosis (De Chadarévian et al. 1993), however with certain special features. In contrast to granulomas found in sarcoidosis and NOD2-associated Crohn's disease, Blau syndrome biopsy specimens typically showed polycyclic granulomas with large lymphocyte coronas, extensive emperipolesis of lymphocytes within multinucleated giant cells, giant cell death, fibrinoid necrosis, and fibrosis (Janssen et al. 2012). Liver granulomas have

been observed in both Blau syndrome and the related disorder early-onset sarcoidosis (EOS) (Saini and Rose 1996).

Classification

Blau syndrome and related disorders belong to the monogenic autoinflammatory syndromes (MAIS; Table 1). MAIS are characterized by amplified danger sensing and cytokine dysregulation (Sanchez et al. 2013) involving numerous complex sensing and signaling platforms and interactomes (see below).

An especially important group of hereditary autoimmune disorders is the periodic fever syndromes. Familial Mediterranean fever (FMF; OMIM 249100; also termed recurrent polyserositis, periodic peritonitis, Reimann's syndrome, and Wolff periodic disease) is an autosomal-recessive condition characterized by recurrent and self-limited attacks of fever,

Table 1 Monogenic autoinflammatory syndromes (MAIS; review: Caso et al. 2013)

***Hereditary recurrent fevers* (*periodic fever syndromes*)**
Familial Mediterranean fever (FMF)
FMF-related neutrophilic lobular panniculitis
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
Mevalonate kinase deficiency (hyperimmunoglobulinemia D syndrome)
Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome (PAPA)
PAPA-hidradenitis suppurativa (PAPASH)
***Cryopyrin-associated periodic syndromes* (*CAPS*; *inflammasomopathies*)**
Cryopyrin-associated periodic syndrome
Neonatal-onset multisystem inflammatory disease (NOMID)
Muckle-Wells syndrome
Familial cold autoinflammatory syndrome (FCAS)
Pyogenic disorders
CRMO syndrome
Majeed syndrome
Deficiency of the interleukin-1 receptor antagonist
Immune-mediated granulomatous diseases
Blau syndrome
Early-onset sarcoidosis
Crohn's disease
Monogenic immune-dysregulatory disorders
Monogenic systemic-onset juvenile idiopathic arthritis caused by mutations in LACC1
Inflammasome disorder caused by NLRP3 mutations
Inflammasome disorder caused by NLRP4 mutations
Immune-dysregulatory syndromes with chronic type I interferon signature caused by mutations in TMEM173/STING IFIH1/MDA5 and DDX58/RIG-I
Immune-dysregulatory syndromes caused by mutations in ADA2, TRNT1, and COPA, AP1S3, and TFNRSF11A
Immune-dysregulatory syndromes caused by mutations in PRKDC, STAT3, CTLA4, and PIK3R1
Idiopathic febrile syndromes
PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis)
Behçet syndrome
Proteasomal autoinflammatory syndromes
CANDLE syndrome/Nakajo-Nishimura syndrome
Other disorders
NLRP12-associated autoinflammatory disorder

polyserositis, synovitis, and pain. The episodes typically last 1–3 days. Amyloidosis is a well-known late complication (review: Portincasa et al. 2013). It is caused by mutations in MEFV, a gene encoding the protein pyrin. An autosomal-dominant form caused by heterozygous MEFV mutations is also known (Stoffels et al. 2014). Neutrophilic lobular panniculitis may belong to the widened spectrum of FMF. Periodic fever occurs in mevalonate kinase deficiency (OMIM 610377), an autosomal-recessive disorder characterized by hyperimmunoglobulin D syndrome and mevalonic aciduria, presenting with recurrent fever episodes often starting in infancy. Tumor necrosis factor receptor-associated periodic syndrome or TRAPS (familial Hibernian fever, OMIM 142680) is an uncommon autosomal-dominant disorder characterized by recurrent episodes of long-lasting fever and inflammatory changes in skin, muscles, skeletal system, serosal membranes, eye, and gastrointestinal tract. TRAPS is caused by mutations in the TNFRSF1A gene (TNF receptor superfamily 1A gene). In TRAPS, distinct circulating microRNAs were found, expression of microRNA-92b being inversely correlated with the number of fever attacks per year (Lucherini et al. 2013). PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne) is a further rare autoinflammatory disorder characterized by periodic fever, being caused by mutations in the PSTPIP1 gene (Demidowich et al. 2012). A variant of this PSTPIP1-associated condition has, in addition, hidradenitis suppurativa (PAPASH; Marzano et al. 2013).

The group of cryopyrin-associated periodic syndromes (CAPS) include several autosomal-dominant disorders, namely, CAPS proper, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (CINCA/NOMID). These disorders share a defect in the CIAS1 or NALP3/NLRP3 gene on chromosome 1, encoding the protein cryopyrin (review: Chang 2013). NALP3/NLRP3 is a component of the multiprotein complex called inflammasome, and CAPS are therefore a distinct group of inflammasomopathies. CAPS is the typical periodic fever syndrome associated with a cryopyrin anomaly. CINCA/NOMID is a complex disorder manifesting in neonates, with cutaneous, neurological, and osteoarticular signs and outbreaks of fever (Aksentijevich et al. 2002). CINCA is the abbreviation for chronic infantile neurological, cutaneous, and articular syndrome, and patients with this condition show recurrent fever, chronic meningitis, uveitis, sensineural hearing loss, urticarial skin rash, and a typical deforming arthropathy. CINCA syndrome (OMIM 607115) is caused by distinct CIAS1 mutations. Muckle-Wells syndrome is characterized by recurrent inflammatory attacks associated with chronic recurrent urticaria, sensineural deafness, periodic arthritis, and sometimes secondary amyloidosis. Familial cold autoinflammatory syndrome (FCAS) displays a phenotype that is less severe than patients with Muckle-Wells syndrome and has to be distinguished from acquired cold urticarial and familial atypical cold urticaria (FACU).

Autoimmune pyogenic disorders mainly comprise chronic non-bacterial osteomyelitis in children (CRMO; OMIM 259680), a chronic recurrent non-suppurative inflammation involving multiple skeletal sites and radiologically mimicking infectious osteomyelitis. Two genetic syndromes have CRMO as the dominant phenotype, i.e., Majeed syndrome and deficiency of the interleukin-1 receptor antagonist, suggesting a pathogenic role of interleukin-1. Majeed syndrome (OMIM 609628) is characterized by CRMO, congenital dyserythropoietic anemia, neutrophilic dermatosis (Sweet syndrome), and hepatosplenomegaly. The disorder was found to be caused by homozygous mutations in the LPIN2 gene. Interleukin-1-receptor antagonist deficiency (DIRA; OMIM 612852) is an autosomal-recessive disorder caused by mutations in the IL1RN gene, leading to a truncated protein that is not secreted, rendering immune cells hyperresponsive to interleukin-1beta stimulation. The patients suffer from osteitis with hyperostosis, periostitis, and pustulosis with subcorneal pustular dermatitis. A disorder mimicking CRMO is SAPHO syndrome, a rare condition that mainly affects bone and skin, with synovitis, acne, pustulosis, hyperostosis, and osteitis. LPIN2 or NOD2 variants were not detected in this syndrome.

Immune-mediated granulomatous diseases comprise Blau syndrome (see below), early-onset sarcoidosis, and NOD2-associated Crohn's disease. Early-onset sarcoidosis (OMIM 609464) is similar in its presentation to Blau syndrome and is also caused by mutations of NOD2.

Idiopathic febrile syndromes form a complex group of autoimmune conditions. Systemic-onset juvenile idiopathic arthritis is also termed juvenile or adolescent-onset Still's disease. It is a systemic inflammatory disorder within the spectrum of juvenile idiopathic arthritis, characterized by a chronic and often severe course and visceral involvement, including hepatosplenomegaly, lymphadenopathy, and anemia. The disorder can be complicated by macrophage activation syndrome or AA amyloidosis. A polymorphism in macrophage migration inhibitory factor has been implicated in this disorder. PFAPA stands for periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome. PFAPA usually starts in patients less than 5 years of age, has less than 20 episodes, and is not associated with significant long-term sequelae. SPAG7 is a candidate gene for PFAPA, encoding a protein expressed in tissues affected by the disorder and being functionally linked to inflammatory and antiviral responses. Behçet syndrome (OMIM 109650) is a systemic inflammatory condition involving both innate and adaptive immunity. It is an immune-mediated systemic small-vessel vasculitis that often presents with mucosal ulcerations, genital ulcers, and ocular disease, mainly uveitis. There is evidence that mutations in the NLRP3/cryopyrin inflammasome are pathogenically involved.

Autoinflammatory syndromes can also be caused by proteasomal disorders. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE syndrome; OMIM 256040) is caused by mutations in proteasome subunit beta type 8 (review: Gomes 2013), a gene reported to cause the JMP syndrome (joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy) in adults. In Japan, the disorder is known as Nakajo-Nishimura syndrome.

Microbial Sensing Proteins and Pattern Recognition Molecules: NLRs, NOD Proteins, Nodosomes, TLRs, and RIGs

NOD proteins are involved in innate immunity, the most ancestral and ubiquitous system of defense against microbial infection. The innate immune system employs different molecules that sense microbial pathogen-associated molecular patterns (PAMPs and PAMP-sensing proteins). These include Toll-like receptors, involved in the detection of microbes in the extracellular compartment, and a large group of molecules that detect intracellular microbes and their products, including RIG-1-like receptors, NOD-like receptors, and CARD components of inflammasomes (reviews: Inohara et al. 2002; Inohara and Nunez 2003; Kufer et al. 2006; Kanneganti et al. 2007; Le Bourhis et al. 2007; Rietdijk et al. 2008; Philpott and Girardin 2010; Bauernfeind and Hornung 2013). NOD proteins or Nod-like receptors are now members of the nucleotide-binding and oligomerization domain-like receptors (NLRs) containing family (review: Lamkanfi et al. 2007; Mathews et al. 2008). The NLR family contains more than 20 members, and these are grouped into molecules that contain either a CARD motif (see below) or a Pyrin motif. NLRs currently include the two major subfamilies, NLRC (the NODs) and NLRP (formerly called NALPs), and also comprise the MHC Class II transactivator (CIITA) and NAIP. NLR proteins are characterized by three structural domains: a C-terminal leucine-rich repeat domain able to sense a microbial motif, an intermediary nucleotide-binding site essential for the oligomerization of the molecule that is necessary for the signal transduction induced by different N-terminal effector motifs, such as a pyrin domain, a caspase-activating and recruitment domain (CARD), or a baculovirus inhibitor of apoptosis protein repeat (BIR) domain (review: Chamaillard et al. 2003).

NODs (newly termed NLRC) act as scaffolding proteins that assemble signaling platforms that trigger nuclear factor kappaB (NFkappaB) and mitogen-activated protein kinase signaling

pathways, while Pyrin molecules such as NALP3 regulate Il-1beta and IL-18 production (reviews: Mathews et al. 2008; Reitdijk et al. 2008; Franchi et al. 2009). Together with Toll-like receptors, NOD1 and NOD2 are cytoplasmic microbial sensors that trigger immune defense in response to bacterial peptidoglycans (Viala et al. 2004; Jiang et al. 2013; Keestra and Bäumler 2014). They act in a complex signaling cascade and induce, via muramyl dipeptide-induced activation of NRkappaB and RIP2 (Strober et al. 2006), antimicrobial effectors, such as nitric oxide and antimicrobial peptides. However, an isoform of NOD2, NOD2-C2, is capable of activating NFkappaB in the absence of muramyl dipeptide (Kramer et al. 2010). Activation of NFkappaB is a central functional platform of this pathway, and the activity status of NFkappaB is also regulated by factors that terminate its activation, e.g., the ubiquitin-editing enzyme A20/TNFAIP3 (Coomaert et al. 2009; Vereecke et al. 2009). This inhibiting action of AP20 is in turn modulated by a member of the ABIN family of proteins, ABIN3 (LIND), which binds to AP20 and is a lipopolysaccharide-inducible inhibitor of NFkappaB activation (Wullaert et al. 2007). NOD2 can also activate antiviral innate immune responses involving IRF3-dependent interferon-beta production after viral ssRNA recognition through a RIP2-independent mechanism requiring the mitochondrial adaptor protein MAVS (review: Lecat et al. 2010). Together, they form a cooperative system that is called the nodosome (Tattoli et al. 2007). NOD signaling also results in the activation of protein kinases and the production of chemokines. Hepatocytes express functional NOD1 and NOD2 receptors, and ligand-induced activation of hepatocyte NOD1 leads to activation of MAP kinases and expression of chemokines CCL5 (RANTES) and CXCL1 as part of the hepatic innate immune system (Scott et al. 2010). The chaperone (Hsp90; heat shock protein 90)-mediated function of NLR receptors in innate immunity depends on the co-chaperone Sgt1 and CHORD (cysteine- and histidine-rich)-containing protein 1 (Wu et al. 2008). CHORD domains are associated with CS domains, either with the same protein, as in the mammalian melusin and Chp1, or in separate but interacting proteins, and both CHORD and CS domains are independently capable of interacting with the chaperone Hsp90 (Zhang et al. 2010). NOD proteins undergo negative regulation via the splice variant of NOD2, NOD2-S (which inhibits NOD2/receptor-interacting protein kinase 2-induced signaling pathways; Rosenstiel et al. 2006), the ubiquitin-editing enzyme A20, pyrin domain-only proteins, and CARD proteins which all have a negative effect on NOD2 or NRLP3 signaling (review: Coll and O'Neill 2010). Also, olfactomedin 4, a glycoprotein upregulated in inflammatory bowel disease and *Helicobacter pylori* infection, exerts a negative feedback effect on NFkappaB through a direct association with NOD1 and NOD2 (Liu et al. 2010).

The function of NOD proteins is linked to autophagy, in that NOD2 recruits the critical autophagy protein, ATG16L1, to the plasma membrane during bacterial invasion and hence augments autophagy (Travassos et al. 2010). This is an important mechanism insofar as there is a critical link between autophagy and effective innate immunity. On the other hand, NLR-containing immunoamphisomes in dendritic cells regulate, via NOD2, the function of Toll-like receptors in that they amplify Toll-like receptor 7 (TLR7) signaling (Blanchet and Piguet 2010).

NLRPs

These caspase 1-activating receptors were previously termed, NALPs (Chamaillard et al. 2003). Like NODs, they contain a C-terminal leucine-rich repeat, which may be involved in the recognition of microbial pathogens, and a nucleotide-binding site for nucleoside triphosphates. The interaction with other proteins, e.g., ASC, is mediated via N-terminal pyrin domain. The family comprises in human 14 members (NLRP1-14).

Proteins with a CARD Domain

NOD proteins belong to a group of proteins which contain a homotypic interaction motif called the caspase recruitment domain (CARD; Le and

Harton 2013). Proteins possessing CARD are involved in the regulation of apoptosis or adaptive or innate immunity. Apart from NOD1 (CARD4) and Nod2 (CARD15), the group comprises NAC (NLRP1/NALP1/DEFCAP/CARD7), TUKAN (CARD8/Cardinal /NDPP/Dakar), CARD6 (which modulates NFkappaB activation by Nod1 and Cardiak; Stehlik et al. 2003a), caspase-9 and Apaf1 (involved in the intrinsic death pathway), Bcl10 and CARD11 (which mediate antigen receptor-induced NFkappaB activation), and Cardiak/Rip2/Rick (receptor-interacting protein (RIP)-like interacting caspase-like apoptosis regulatory protein kinase, which activates NFkappaB). Bcl10 is a signaling adaptor able to interact with Carma1, an interaction that is required for signaling from the T cell receptor to NFkappaB. Carma1 regulation of regulatory T cell development involves modulation of interleukin-2 receptor signaling (Lee et al. 2010). The association of Bcl10 with Carma1 is modulated by the calcium sensor, calmodulin, the interaction being localized to the CARD domain of Bcl10 (Edin et al. 2010). One CARD member, CARD6, has a domain structure different from other CARD proteins and is related to the superfamily of interferon-inducible GTPases. CARD6 interacts with receptor-interacting protein (RIP)-like interacting caspase-like apoptosis regulatory protein kinase (RICK) (Dufner and Mak 2006). CARD8 physically interacts with NOD2 and inhibits nodosome assembly and subsequent signaling upon muramyl-dipeptide stimulation, and CARD8 inhibits the direct bactericidal effect of NOD2 against intracellular infection with *Listeria monocytogenes* (Von Kampen et al. 2010). All inflammasomes require ASC (adaptor protein apoptosis-associated speck-like protein containing a CARD) for the activation of caspase-1 (Stutz et al. 2013), CARD playing a critical role in ASC foci formation and inflammasome signaling (Proell et al. 2013).

Toll-Like Receptors (TLRs)

Toll-like receptors (TLRs) have been established to play an essential role in the activation of innate immunity by recognizing specific patterns of microbial components. TLR signaling pathways arise from intracytoplasmic TIR domains which are conserved among all TLRs, and TLR signaling is modulated by other TIR-containing adaptors, such as MyD88, TIRAP, and TRIF. MyD88 is involved in the function of all TLRs, while TIRAP is specifically involved in the MyD88-dependent pathway via TLR2 and TLR4, and TRIF is implicated in the TRL3- and TLR4-mediated MyD88-independent pathway (review: Takeda and Akira 2004). The negative regulation of TLR signaling includes posttranscriptional regulation by miRNAs, posttranslational regulation by ubiquitination, and regulation by splice variants such as MyD88s, TRAM adaptor with GOLD domain, and IRAK2 isoforms (review: Coll and O'Neill 2010). Another negative regulation loop involves NOD2, which inhibits proapoptotic TLR4 signaling in enterocytes but not in macrophages (Richardson et al. 2010).

Virus-Sensing Proteins

Virus infection of mammalian cells elicits a variety of defense responses that are initiated by signals from virus-sensing receptors expressed by the host. The most important of these receptors are the ubiquitously expressed RIG-I-like receptor (RLR; retinoic acid-inducible gene-I-like receptors) family of DExDH/boxRNA helicases, which are potent RNA sensors (reviews: Nakhaei et al. 2009; Yoneyama and Fujita 2009; Zou et al. 2009; Rehwinkel and Reis e Sousa 2010). RIG-I detects invading viral RNA by recognition of 5′-triphosphate-containing viral RNA and activates the transcription factors NFkappaB and IRF3 through the mitochondrial protein MAVS. RNA bearing 5′-triphosphate strongly activates the RIG-I-IRF3 cascade, requiring polyubiquitin chains, and induces type I interferon-mediated antiviral immune responses. RIG-I binds specifically to K63-polyubiquitin chains through its tandem CARD domains in a manner that depends on

RNA and ATP. CARD domains therefore act as an ubiquitin sensor, and unanchored K63-polyubiquitin chains are signaling molecules in antiviral innate immunity (Zeng et al. 2010). A second intracellular viral sensor is MDA-5, which is also a DExDH/box RNA helicase.

NACHT-Containing Proteins

A further group of intracellular pathogen sensors are the NACHT (NAIP [neuronal apoptosis inhibitory protein], CIITA [MHC class II transcription activator], HET-E [incompatibility locus protein from *Podospora anserina*], and TP1 [telomerase-associated protein]) family proteins. CLAN (CARD, LRR [leucine-rich repeat], and NACHT domain-containing protein) (synonyms: CARD12, NLRc4, IPAF), an NACHT-containing molecule originally demonstrated to bind and activate pro-caspase-1, is also capable of influencing the functions of other members of the NACHT family, in that it associated with NALP1 [NACHT, LRR, and Pyrin protein 1]/NAC (nucleotide-binding domain and CARD-containing protein). The NACHT domain of CLAN binds all NACHT domains of CLAN itself, NOD1, NOD2, cryopyrin, NAC/NALP1, PAN2 (PAAD [pyrin, AIM (absent in melanoma), ASC (apoptosis-associated speck-like protein containing a CARD), and death domain-like and NACHT-containing protein), and NAIP. NAIP1 (neuronal apoptosis inhibitory protein 1) is involved in the recognition of distinct bacterial components, specifically the bacterial type III secretion needle protein (Yang et al. 2013). Interaction of CLAN with NOD1 and NOD2 inhibits NOD-induced NFkappaB activation (Damiano et al. 2004a). CLAN modulates endogenous caspase-1 activation and subsequent IL-1beta secretion from macrophages after exposure to lipopolysaccharides, peptidoglycan, and pathogenic bacteria (Damiano et al. 2004b). It is also a potent flagellin sensor but can also activate caspase-1 independent of bacterial flagellin and can restrict bacterial infection independently of caspase-1 (Abdelaziz et al. 2010).

The DNA Damage Sensor PARP1

PARP1 (poly[ADP-ribose] polymerase 1) is a DNA damage sensor that is cleaved by caspase in apoptosis. It is also cleaved in pyroptosis via the action of the NLRP3 and NLRC4 inflammasomes (Malireddi et al. 2010).

PAAD Proteins

Proteins containing PAAD and DD domains are a group of proteins that have a structure similar to that of NODs, and like NODs, they are involved in innate immunity and cause NFkappaB and caspase-1 activation. PAAD stands for [pyrin, AIM (absent in melanoma), ASC (apoptosis-associated speck-like protein containing a CARD)], and DD stands for (death domain-like). Several of these proteins utilize the adaptor protein ASC. For example, the PAAD-only protein-1 (POP1/ASC2) on chromosome 16 associates with ASC via PAAD-PAAD interactions and modulates NFkappaB and procaspase-1 regulation by this adaptor protein (Stehlik et al. 2003b).

NODs in Human Disease

NOD-like receptors play an important role in numerous human diseases (review: Zhong et al. 2013). NOD1 plays an important role in host defense and recognizes the minimal components of bacterial cell wall peptidoglycans, meso-diaminopimelic acid and meso-lanthionine (Takada and Uehara 2006; Uehara et al. 2006). NOD1 is expressed within the eye and its activation results in uveitis in an IL-1beta-dependent mechanism (Rosenzweig et al. 2009). NOD2 (CARD15) is composed of two N-terminal CARDs, a nucleotide-binding domain, and multiple C-terminal leucine-rich repeats. It is predominantly present in the monocyte/macrophage system and is a receptor for the ligand muramyl dipeptide (Grimes et al. 2012; Mo et al. 2012). Binding of this ligand to the NOD2 receptor activates NFkappaB (Ogura et al. 2001). This pathway activates primary FOXP3+ T lymphocytes.

This activation is functionally relevant to cell survival, as muramyl dipeptide-stimulated human FOXP3+ T cells are protected from death receptor Fas-mediated apoptosis (Rahman et al. 2010). Activated NOD2 ordinarily downregulates responses to Toll-like receptor stimulation, and thus cells lacking NOD2 are expected to mount increased responses to such stimulation. NOD2 is notable that variants in the ligand recognition domain are associated with Crohn's disease and other disorders such as Blau syndrome (reviews: Strober et al. 2008; Tigno-Aranjuez and Abbott 2012). Gene-wide analyses of single nucleotide polymorphisms in inflammatory bowel diseases have uncovered consistent variants and mutations in the NOD2, CARD15, interleukin-23 receptor, and autophagy-related 16-like 1 (ATG16L1) genes (reviews: Grant et al. 2008; Yao 2013). In Crohn's disease, the disease-associated NOD2 polymorphism causes failure of apoptosis protection in muramyl dipeptide-stimulated FOXP3+ T cells (Rahman et al. 2010). NOD2 activates autophagy in a manner requiring ATG16L1, another Crohn's disease susceptibility gene. NOD2 autophagy induction is required for bacterial handling and MHC class II antigen presentation in dendritic cells. Dendritic cells from Crohn's disease patients having the NOD2 or ATG16L1 variant display reduced autophagy induction after NOD2 triggering resulting in impaired bacterial clearance (Brain et al. 2010). ATG16L1 and NOD2 interact in an autophagy-dependent antibacterial pathway, and this pathway is impaired in the presence of Crohn's disease-associated NOD2 variants (Homer et al. 2010).

Inflammasomes

Several members of the NLR family of sensors (see above) can form multiprotein complexes called inflammasomes that trigger the activation of the cysteine protease caspase-1. Inflammasomes are components of the innate immune system (reviews: Sutterwala et al. 2007; Brodsky and Monack 2009; Pedra et al. 2009; Lamkanfi and Dixit 2009; Schroeder and Tschopp 2010). The caspase-1 inflammasome has a central role in pathway mediating innate immunity (Yu and Finlay 2008). Cell death mediated by inflammasomes is called pyroptosis (Bortoluci and Medzhitov 2010). Autoproteolytic maturation of caspase-1 zymogens within these inflammasomes leads to maturation and secretion of the pro-inflammatory cytokines interleukin-1beta and interleukin-18. The NLR proteins ICE protease-activating factor (IPAF/CLAN/NLRC4; detecting bacterial flagellins), ASC, NLRP1b, NLRP3/cryopyrin, NLRP4, and AIM2 (absent in melanoma) assemble caspase-1-activating inflammasomes in a stimulus-dependent manner (Lamkanfi and Dixit 2009; Broz et al. 2010). Based on these components of the inflammasome supramolecular complex, several types of inflammasomes have been proposed, viz., ASC inflammasome, AIM2 inflammasome, NLRP inflammasomes, and the Ipaf/CLAN12/NLRC4 inflammasome.

The ASC inflammasome contains ASC (apoptosis-associated speck-like protein containing a CARD) which is an important adaptor protein of inflammasomes, but ASC can also prime T cells in an inflammasome-independent manner (Ippagunta et al. 2010). ASC has a bipartite structure, consisting of an N-terminal pyrin domain and a C-terminal caspase recruitment domain (CARD). The pyrin domain of ASC is known to interact with various pyrin domain-containing intracellular danger signal sensors and pyrin domain-only proteins, such as POP-1 (Srimathi et al. 2008). ASC bridges activated NLRs with caspase-1. It translocates from the nucleus to the cytosol in response to inflammatory stimulation in order to promote an inflammasome response. Several isoforms of ASC exert an important influence on inflammasome structure and dynamics. Full-length ASC and the isoform ASC-b co-localize with NLRP3 and caspase-1, while the isoform inhibiting inflammasome assembly, ASC-c, co-localizes only with caspase-1 but not with NLRP3 (Bryan et al. 2010).

The AIM2 inflammasome is mainly characterized by the action of AIM2 which can bind DNA and engages the caspase-1-activating adaptor protein ASC to form a caspase 1-activating inflammasome. In response to double-stranded

viral and bacterial DNA, AIM2 regulates caspase 1-dependent maturation of IL-1beta and IL-18, as well as pyroptosis (Rathinam et al. 2010). The NLRP1 (NALP1) inflammasome is characterized by the presence of NLRP1 and recruits ASC as well as capsase-1 and caspase-5. NLRP1 is directly activated by muramyl dipeptide. The NLRP1 inflammasome is widely expressed in many cell types but is highly expressed in immune cells, particularly T cells and Langerhans cells. The NLRP3 (NALP3/cryopyrin) inflammasome is comprised of NLRP3, ASC, caspase-1, CARDINAL, and pyrin protein (which contains a pyrin domain). NLRP3 is an intracellular adaptor of the caspase-1 inflammasome (Mariathasan 2007) and mediates caspase-1 activation in response to a wide variety of bacterial ligands, dsRNA, and the endogenous danger signal uric acid (Lamkanfi et al. 2007). The *Mycobacterium tuberculosis* protein, ESAT-6, is a potent activator of an infection-inducible inflammasome consisting of NLRP3, ASC, and caspase-1, promoting the secretion of IL-1 beta (Mishra et al. 2010). The NLRP3 inflammasome also functions as a negative regulator of tumorigenesis during colitis-associated cancer (Allen et al. 2010). Mutations in NLRP genes cause several clinical syndromes. Mutations of the NLRP1 locus is associated with vitiligo-associated autoimmune disease. CIITA mutations cause the bare lymphocyte syndrome, and NLRP7 mutations may induce hydatidiform moles. Most important are mutations of NLRP3 which have been associated with a group of autoinflammatory disorders termed the cryopyrin-associated periodic syndromes (CAPS, cryopyrinopathies). CAPS include familial cold autoinflammatory syndrome of Muckle-Wells syndrome and chronic infantile neurologic, cutaneous, and articular syndrome (CINCA/neonatal-onset multisystem inflammatory disease, NOMID). CINCA/NOMID and Muckle-Wells syndrome exhibit constitutive increases in the secretion of IL-1beta and IL-18. Mutations in other components of the NLRP3 inflammasome platform include pyrin (encoded by the MEFV gene), mutated in autosomal-recessive familial Mediterranean fever. Both the NRLP3 and MEFV genes were also associated with psoriatic juvenile idiopathic arthritis.

The Ipaf inflammasome contains Ipaf (CARD12 or CLAN; new designation: NLRC4; Sutterwala and Flavell 2009), which is homologous to NLRP1 and NLRP3. It forms an inflammasome in response to flagellin stimulation and activates caspase-1. The recognition of flagellin by Ipaf is a specific process in that a second flagellin sensor, TLR5, responds more generally to flagellated bacteria, whereas Ipaf responds to bacteria that express both flagellin and distinct virulence factors, such as the *Salmonella* virulence factor transport systems (SPI1 type III secretion system and the Dot/lcm type IV secretion system) (Miao et al. 2007; Miao and Warren 2010). The Ipaf inflammasome contains a CARD domain, a central NACHT domain, and a C-terminal LRR, and activation of this complex induces the combined activation of the TLR and NLR pathways.

Pyroptosis (Pro-inflammatory Programmed Cell Death) and the Pyroptosome

Pyroptosis is a distinct form of programmed cell death that occurs by the action of inflammasomes. The term pyroptosis has been proposed from the Greek roots pyro, relating to fire or fever, and ptosis, denoting falling (Cookson and Brennan 2001; reviews: Fink and Cookson 2005; Bortoluci and Medzhitov 2010; Kepp et al. 2010). The mechanism and its components are packed in a subtype of the inflammasome termed pyroptosome. In contrast to apoptosis, pyroptosis requires the function of caspase-1, which is activated during pyroptosis by a large supramolecular complex termed the pyroptosome. Only one large pyroptosome is formed in each macrophage within minutes after infection, mainly with *Salmonella* and *Shigella*.

References

Abdelaziz DH, Amr K, Amer AO (2010) Nlrc4/Ipaf/CLAN/CARD12: more than a flagellin sensor. Int J Biochem Cell Biol 42:789–791

Aga F, Yamamoto Y, Tanaka K, Ono Y, Dobashi H, Nishiyama Y (2013) 18F-FDG PET/CT imaging of extensive systemic sarcoidosis with epididymal involvement. Clin Nucl Med 38:63–64

Ahmed HM, Liang DB, Giday SA, Montgomery EA, Farmer NM (2010) Necrotizing sarcoid granulomatosis: a case report of gastric involvement. J Hosp Med 5:113–114

Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, Stein L et al (2002) De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. Arthritis Rheum 46:3340–3348

Alam I, Levenson SD, Ferrell LD, Bass NM (1997) Diffuse intrahepatic biliary strictures in sarcoidosis resembling sclerosing cholangitis. Case report and review of the literature. Dig Dis Sci 42:1295–1301

Albu E, Saraiya RJ, Carvajal SJ, Sehonanda A, Balar N, Gerst PH (1995) Sarcoidosis presenting as obstructive jaundice. Am Surg 61:516–517

Allen C, TeKippe EM, Woodford RM, Uronis JM, Holl EK, Rogers AB, Herfarth HH et al (2010) The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. J Exp Med 207:1045–1056

Aravinthan A, Gelson W, Limbu A, Brais R, Rochardson P (2012) Hepatic sarcoidosis complicating treatment-naïve viral hepatitis. World J Hepatol 4:402–405

Arostegui JI, Arnal C, Merino R, Modesto C, Antonia CM, Moreno P, Garcia-Consuegra J et al (2007) NOD2 gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. Arthritis Rheum 56:3805–3813

Askling J, Grunewald J, Eklung A, Hillerdal G, Ekbom A (1999) Increased risk for cancer following sarcoidosis. Am J Respir Crit Care Med 160:1668–1672

Ayyala US, Padilla ML (2006) Diagnosis and treatment of hepatic sarcoidosis. Curr Treat Options Gastroenterol 9:475–483

Bakker GJ, Haan YC, Maillette de Buy Wenninger LJ, Beuers U (2012) Sarcoidosis of the liver: to treat or not to treat ? Neth J Med 70:349–356

Barton JC, McGuire BM, Acton RT (2009) HFE hemochromatosis and hepatic sarcoid. Am J Med Sci 337:386–390

Bass NM, Burroughs AK, Scheuer PJ, James DG, Sherlock S (1982) Chronic intrahepatic cholestasis due to sarcoidosis. Gut 23:417–421

Bauernfeind F, Hornung V (2013) Of inflammasomes and pathogens – sensing of microbes by the inflammasome. EMBO Mol Med 5:814–826

Baughman RP (1988) Sarcoidosis. Usual and unusual manifestations. Chest 94:165–170

Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H, Bresnitz EA, DePalo L et al (2001) Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 164:1885–1889

Becker ML, Rose CD (2005) Blau syndrome and related genetic disorders causing childhood arthritis. Curr Rheumatol Rep 7:427–433

Berger I, Katz M (1973) Portal hypertension due to hepatic sarcoidosis. Am J Gastroenterol 59:147–151

Bilir M, Mert A, Ozaras R, Yanardag H, Karayel T, Senturk H, Tahan V, Ozbay G, Sonsuz A (2000) Hepatic sarcoidosis: clinicopathologic features in thirty-seven patients. J Clin Gastroenterol 31:337–338

Blanchet FP, Piguet V (2010) Immunoamphisomes in dendritic cells amplify TLR signaling and enhance exogenous antigen presentation on MHC-II. Autophagy 6:816–818

Blich M, Edoute Y (2004) Clinical manifestations of sarcoid liver disease. Gastroenterol Hepatol 19:732–737

Bloom R, Sybert A, Mascatello VJ (1978) Granulomatous biliary tract obstruction due to sarcoidosis. Report of case and review of the literature. Am Rev Respir Dis 117:783–787

Bortoluci KR, Medzhitov R (2010) Control of infection by pyroptosis and autophagy: role of TLR and NLR. Cell Mol Life Sci 67:1643–1651

Brain O, Allan P, Simmons A (2010) NOD2-mediated autophagy and Crohn disease. Autophagy 6:412–414

Branson JH, Park JH (1954) Sarcoidosis – hepatic involvement: presentation of a case with fatal liver involvement, including autopsy findings and review of the evidence for sarcoid involvement of the liver as found in the literature. Ann Intern Med 40:111–154

Britt AR, Francis IR, Glazer GM, Ellis JH (1991) Sarcoidosis: abdominal manifestations at CT. Radiology 178:91–94

Brodsky IE, Monack D (2009) NLR-mediated control of inflammasome assembly in the host response against bacterial pathogens. Semin Immunol 21:199–207

Broz P, Newton K, Lakanfi M, Mariathasan S, Dixit VM, Monack DM (2010) Redundant roles for inflammasome receptors NLRP3 and NLRP4 in host defence against *Salmonella*. J Exp Med 207:1745–1755

Bruix J, Parés A, Burguera M, Rodes J (1980) Hepatic sarcoidosis and portal hypertension (in Spanish). Gastroenterol Hepatol 3:283–285

Bryan NB, Dorfleutner A, Kramer SJ, Yun C, Rojanasakul Y, Stehlik C (2010) Differential splicing of the apoptosis-associated speck like protein containing a caspase recruitment domain (ASC) regulates inflammasomes. J Inflamm (London) 7:23

Buxbaum J, Papademetriou M, Klipfel N, Selby R, Fong TL, Sharma O (2013) Biliary sarcoidosis: early diagnosis minimizes the need for surgery. Am J Respir Crit Care Med 187:556–559

Byrne JP, Cochrane AM, Williams DI, Williams R (1977) Cutaneous granulomata with primary biliary cirrhosis. Proc R Soc Med 70:897–898

Cain H, Kraus B (1977) Asteroid bodies: derivatives of the cytosphere. An electron microscopic contribution to the

pathology of the cytocentre. Virchows Arch B Cell Pathol 26:119–132
Casavilla FA, Gordon R, Wright HI, Gavaler JS, Starzl TE, Van Thiel DH (1993) Clinical course after liver transplantation in patients with sarcoidosis. Ann Intern Med 118:865–866
Caso F, Rigante D, Vitale A, Lucherini OM, Costa L, Atteno M, Compagnone A, Caso P et al (2013) Monogenic autoinflammatory syndromes: state of the art on genetic, clinical, and therapeutic issues. Int J Rheumatol 2013:513782
Caso F, Costa L, Rigante D, Vitale A, Cimaz R, Lucherini OM, Sfriso P, Verrecchia E, Tognon S, Bascherini V et al (2014) Caveats and truths in genetic, clinical, autoimmune and autoinflammatory issues in Blau syndrome and early onset sarcoidosis. Autoimmun Rev 13:1220–1229
Caso F, Galozzi P, Costa L, Sfriso P, Cantarini L, Punzi L (2015) Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. RMD Open 1:e000097
Chalasani P, Vohra M, Sheagren JN (2005) An association of sarcoidosis with hepatocellular carcinoma. Ann Oncol 16:1714–1715
Chamaillard M, Girardin SE, Viala J, Philpott DJ (2003) Nods, Nalps and Naip: intracellular regulators of bacterial-induced inflammation. Cell Microbiol 5:581–592
Chang C (2013) The pathogenesis of neonatal autoimmune and autoinflammatory diseases: a comprehensive review. J Autoimmun 41:100–110
Chawla Y, Dhiman RK (2008) Intrahepatic portal venopathy and related disorders of the liver. Semin Liver Dis 28:270–281
Cheitlin MD, Sullivan BH, Myers JE, Hench RF (1960) Portal hypertension in hepatic sarcoidosis. Gastroenterology 38:60–68
Coll RC, O'Neill LA (2010) New insights into the regulation of signalling by Toll-like receptors and Nod-like receptors. J Innate Immun 2:406–421
Cookson BT, Brennan MA (2001) Pro-inflammatory programmed cell death. Trends Microbiol 9: 113–114
Coomaert B, Carpentier I, Beyaert R (2009) A20: central gatekeeper in inflammation and immunity. J Biol Chem 284:8217–8221
Dagenais M, Dupaul-Chicoine J, Saleh M (2010) Function of NOD-like receptors in immunity and disease. Curr Opin Investig Drugs 11:1246–1255
Damiano JS, Oliveira V, Welsh K, Reed JC (2004a) Heterotypic interactions among NACHT domains: implications for regulation of innate immune responses. Biochem J 381:213–219
Damiano JS, Newman RM, Reed JC (2004b) Multiple roles of CLAN (caspase-associated recruitment domain, leucine-rich repeat, and NAIP CIIA HET-E, and TP1-containing protein) in the mammalian innate immune response. J Immunol 173:6338–6345
De Chadarévian JP, Raphael SA, Murphy GF (1993) Histologic, ultrastructural, and immunocytochemical features of the granulomas seen in a child with the syndrome of familial granulomatous arthritis, uveitis, and rash. Arch Pathol Lab Med 117:1050–1052
Delfosse V, de Leval L, De Roover A, Delwaide J, Honoré P, Boniver J, Detry O (2009) Budd-Chiari syndrome complicating hepatic sarcoidosis: definitive treatment by liver transplantation: a case report. Transplant Porc 41:3432–3434
Demidowich AP, Freeman AF, Kuhns DB, Aksentijevich I, Gallin JI, Turner ML, Kastner DL et al (2012) Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). Arthritis Rheum 64:2022–2027
Deniz K, Ward SC, Rosen A, Grewel P, Xu R (2008) Budd-Chiari syndrome in sarcoidosis involving liver. Liver Int 28:580–581
Desmet VJ (1990) Destructive intrahepatic bile duct diseases. Recenti Prog Med 81:203–217
Devaney K, Goodman Z, Epstein MS, Zimmerman HJ, Ishak KG (1993) Hepatic sarcoidosis – clinicopathologic features in 100 patients. Am J Surg Pathol 17:1272–1280
Dourakis SP, Saramadou R, Alexopoulou A, Kafiri G, Deutsch M, Koskinas J, Archimandritis AJ (2007) Hepatic granulomas: a 6-year experience in a single center in Greece. Eur J Gastroenterol Hepatol 19:101–104
Dow CT (2012) M. Paratuberculosis heat shock protein 65 and human diseases: bridging infection and autoimmunity. Autoimmune Disord 2012:150824
Drake WP, Dhason MS, Nadaf M, Shepherd BE, Vadivelu S, Hajizadeh R et al (2007) Cellular recognition of *Mycobacterium tuberculosis* ESAT-6 and KatG peptides in systemic sarcoidosis. Infect Immun 75:527–530
Drebber U, Kasper HU, Ratering J, Wedemeyer I, Schirmacher P, Dienes HP, Odenthal M (2008) Hepatic granulomas: histological and molecular pathological approach to differential diagnosis – a study of 442 cases. Liver Int 28:828–834
Dubaniewicz A, Trzonkowski P, Dubaniewicz-Wybieralska M, Dubaniewicz A, Singh M, Mysliwski A (2007) Mycobacterial heat shock protein-induced blood T lymphocytes subsets and cytokine pattern: comparison of sarcoidosis with tuberculosis and healthy controls. Respirology 12:346–354
Dufner A, Mak TW (2006) CARD tricks: controlling the interactions of CARD6 with RICK and microtubules. Cell Cycle 5:797–800
Ebert EC, Kierson M, Hagspiel KD (2008) Gastrointestinal and hepatic manifestations of sarcoidosis. Am J Gastroenterol 103:3184–3192
Edin S, Oruganti SR, Grundström C, Grundström T (2010) Interaction of calmodulin with Bcl10 modulates NF-kappaB activation. Mol Immunol 47:2057–2064
Elloumi H, Marzouk S, Tahri N, Bahloul Z, Azouz MM (2012) Sarcoidosis and liver involvement: a case series

of 25 patients (in French). Rev Med Interne 33:607–614
Farouj NE, Cadranel JF, Mofredi A, Jouannaud V, Lahmiri M, Lann PL, Cazier A (2011) Ductopenia related liver sarcoidosis. World J Hepatol 3:170–174
Ferreira A, Ramalho M, de Campos RO, Heredia V, Roque A, Vaidean G, Semelka RC (2013) Hepatic sarcoidosis: MR appearances in patients with chronic liver disease. Magn Reson Imaging 31:432–438
Fidler HM, Hadziyannis SJ, Dhillon AP, Sherlock S, Burroughs AK (1997) Recurrent hepatic sarcoidosis following liver transplantation. Transplant Proc 29:2509–2510
Fink SL, Cookson BT (2005) Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. Infect Immun 73:1907–1916
Foltz SJ, Johnson CD, Swensen SJ (1995) Abdominal manifestations of sarcoidosis in CT studies. J Comput Assist Tomogr 19:573–579
Franchi L, Warner N, Viani K, Nunez G (2009) Function of Nod-like receptors in microbial recognition and host defense. Immunol Rev 227:106–128
Gadde PS, Moscovic EA (1994) Asteroid bodies: products of unusual microtubule dynamics in monocyte-derived giant cells. An immunohistochemical study. Histol Histopathol 9:633–642
Ganne-Carrié N, Guettier C, Ziol M, Beaugrand M, Trinchet JC (2001) Sarcoidosis and the liver (in French). Ann Med Interne (Paris) 152:103–107
Gavilan F, Pereda T, Sousa JM, Serrano J, Gomez MA, Garcia I, Tamayo MJ, Martin C et al (2003) Hepatic cirrhosis with sarcoid granulomas. Differential diagnosis and liver transplantation: a case report. Transplant Proc 35:713–714
Gaya DR, Thorburn D, Oien KA, Morris AJ, Stanley AJ (2003) Hepatic granulomas: a 10 year single centre experience. J Clin Pathol 56:850–853
Giovinale M, Fonnesu C, Soriano A, Cerguaglia C, Curigliano V, Verrecchia E, De Socio G et al (2009) Atypical sarcoidosis: case reports and review of the literature. Eur Rev Med Pharmacol 13(Suppl 1):37–44
Goljan-Geremek A, Puscinska E, Bednarek M, Nowinski A, Kaminski D, Ptak J, Bestry I et al (2013) Fatal clinical outcome in a patient with sarcoidosis-lymphoma syndrome. Pneumonol Alergol Pol 81:542–549
Gomes AV (2013) Genetics of proteasome diseases. Scientifica (Cairo) 2013:637629
Grant SF, Baldassano RN, Hakonarson H (2008) Classification of genetic profiles of Crohn's disease: a focus on the ATG16L1 gene. Expert Rev Mol Diagn 8:199–207
Grimes CL, Ariyananada LZ, Melnyk JE, O'Shea EK (2012) The innate immune protein Nod2 binds directly to MDP, a bacterial cell wall fragment. J Am Chem Soc 134:13535–13537
Gupta S, Faughnan ME, Prud'homme GJ, Hwang DM, Munoz DG, Kopplin P (2008) Sarcoidosis complicated by cirrhosis and hepatopulmonary syndrome. Can Respir J 15:124–126
Hamazaki Y (1938) Über ein neues säurefeste Substanz führendes Spindelkörperchen der menschlichen Lymphdrüsen. Virchows Arch Cell Pathol 301:490–522
Harder H, Büchler MW, Fröhlich B, Ströbel P, Bergmann F, Neff W, Singer MV (2007) Extrapulmonary sarcoidosis of liver and pancreas: a case report and review of literature. World J Gastroenterol 13:2504–2509
Hashash JG, Proksell S, Behari J (2013) An unusual cause of cholestasis after liver transplantation. Sarcoidosis. Gastroenterology 145:e9–e10
Hercules H, Bethlem N (1984) Value of liver biopsy in sarcoidosis. Arch Pathol Lab Med 108:831–834
Hoeffel C, Bokemeyer C, Hoeffel JC, Gaucher H, Galanski M, Fornes P (1996) CT hepatic and splenic appearances with sarcoidosis. Eur J Radiol 23:94–96
Homer CR, Richmond AL, Ebert NA, Achkar JP, McDonald C (2010) ATG16L1 and NOD2 interact in an autophagy-dependent, anti-bacterial pathway implicated in Crohn's disease pathogenesis. Gastroenterology 139:1630–1641
Hughes P, McGavin CR (1997) Sarcoidosis and primary biliary cirrhosis with co-existing myositis. Thorax 52:201–202
Hughes GS, Kataria YP, O'Brien TF (1983) Sarcoidosis presenting as biliary cirrhosis: treatment with chlorambucil. South Med J 76:1440–1442
Inohara N, Nunez G (2003) NODs: intracellular proteins involved in inflammation and apoptosis. Nat Rev Immunol 3:371–382
Inohara N, Ogura Y, Nunez G (2002) Nods: a family of cytosolic proteins that regulate the host response to pathogens. Curr Opin Microbiol 5:76–80
Inoue M, Hino H, Minami H, Kameoka H, Nonaka T, Matsumoto I (1995) A case of sarcoidosis with hepatic lymph node hypertrophy (in Japanese). Nippon Naika Gakkai Zasshi 84:806–807
Inoue Y, Kawaguchi Y, Shimojo N, Yamaguchi K, Morita Y, Nakano T, Arima T, Tomiita M et al (2013) A case of infantile Takayasu arteritis with a p.D382E NOD2 mutation: an unusual phenotype of Blau syndrome/early-onset sarcoidosis ? Mol Rheumatology 23:837–839
Ippagunta SK, Brand DD, Luo J, Boyd KL, Calabrese C, Stienstra R, Van de Veerdonk FL et al (2010) Inflammasome-independent role of apoptosis-associated speck-like protein containing a CRAD (ASC) in T cell priming is critical for collagen-induced arthritis. J Biol Chem 285:12454–12462
Ishak KG (1998) Sarcoidosis of the liver and bile ducts. Mayo Clin Proc 73:467–472
Ivonye C, Elhammali B, Henriques-Forsythe M, Bennett-Gittens R, Oderinde A (2012) Disseminated sarcoidosis resulting in portal hypertension and gastrointestinal bleeding: a rare presentation. Can J Gastroenterol 26:508–509
James DG (1994) A comparison of Blau's syndrome and sarcoidosis. Sarcoidosis 11:100–101

James DG, Sherlock S (1994) Sarcoidosis of the liver. Sarcoidosis 11:2–6

Janssen CE, Rose CD, De Hertogh G, Martin TM, Bader Meunier B, Cimaz R, Harjacek M et al (2012) Morphologic and immunohistochemial characterization of granulomas in the nucleotide oligomerization domain2-related disorders Blau syndrome and Crohn disease. J Allergy Clin Immunol 129:1076–1084

Jiang W, Wang X, Zeng B, Liu L, Tardivel A, Wie H, Han J, Macdonald HR, Tschopp J et al (2013) Recognition of gut microbiota by NOD2 is essential for the homeostasis of intestinal intraepithelial lymphocytes. J Exp Med 210:2791

Jung G, Brill N, Poll LW, Koch JA, Wettstein M (2004) MRI of hepatic sarcoidosis: large confluent lesions mimicking malignancy. AJR Am J Roentgenol 183:171–173

Kahi CJ, Saxena R, Temkit M, Canlas K, Roberts S, Knox K, Wilkes D, Kwo PY (2006) Hepatobiliary disease in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 23:117–123

Kanneganti TD, Lamkanfi M, Nunez G (2007) Intracellular NOD-like receptors in host defence and disease. Immunity 27:549–559

Karagiannidis A, Karavalaki M, Koulaouzidis A (2006) Hepatic sarcoidosis. Ann Hepatol 5:251–256

Karlish AJ, Thompson RP, Williams R (1969) A case of sarcoidosis and primary biliary cirrhosis. Lancet 2:599

Keefe EB (1987) Sarcoidosis and primary biliary cirrhosis: literature review and illustrative case. Am J Med 83:977–980

Keestra AM, Bäumler AJ (2014) Detection of enteric pathogens by the nodosome. Trends Immunol 35:123–130

Keller K, Hofmann WJ, Kayser K, Limberg B, Lippert J, Werner A, Andrassy K, Hahn P et al (1997) Coincidence of primary sclerosing cholangitis and sarcoidosis – case report and review of the literature (in German). Z Gastroenterol 35:33–39

Kennedy PT, Zakaria N, Modawi SB, Papadopoulou AM, Murray-Lyon I, du Bois RM et al (2006) Natural history of hepatic sarcoidosis and its response to treatment. Eur J Gastroenterol Hepatol 18:721–726

Kepp O, Galluzzi L, Zitvogel L, Kroemer G (2010) Pyroptosis – a cell death modality of its kind ? Eur J Immunol 40:627–630

Khan IA, Irfan SM (2001) Cholestasis with hepatic fibrosis secondary to sarcoidosis – a case report. J Pak Med Assoc 51:89–92

Khare S, Luc N, Dorfleutner A, Stehlik C (2010) Inflammasomes and their activation. Crit Rev Immunol 30:463–487

Khubchandani RP, Hasija R, Touitou I, Khemani C, Wouters CH, Rose CD (2012) Blau arteritis resembling Takayasu disease with a novel NOD2 mutation. J Rheumatol 39:1888–1892

Kim SL, Gedgaudas-McClees RK, Waring JP (1992) Sarcoidosis with multiple hepatic and splenic nodules on dynamic computed tomography. Ann Intern Med 117:399–400

Kirkpatrick CJ, Curry A, Bisset DL (1988) Light- and electron-microscopic studies on multinucleated giant cells in sarcoid granuloma: new aspects of asteroid and Schaumann bodies. Ultrastruct Pathol 12:581–597

Kishor S, Turner ML, Borg BB, Kleiner DE, Cowen EW (2008) Cutaneous sarcoidosis and primary biliary cirrhosis: a chance association or related diseases? J Am Acad Dermatol 58:326–335

Kitamura Y, Motoi M, Terada T (1998) An autopsy case of ancient sarcoidosis associated with severe fibrosis in the liver and heart. Pathol Int 48:536–541

Klatskin G, Yesner R (1950) Hepatic manifestations of sarcoidosis and other granulomatous diseases. Yale J Biol Med 23:207–248

Kramer M, Bock J, Reichenbach D, Kaether C, Schreber S, Platzer M, Rosenstiel P, Huse K (2010) NOD2-C2 – a novel NOD2 isoform activating NF-kappaB in a muramyl dipeptide-independent manner. BMC Res Notes 3:224

Kufer TA, Banks DJ, Philpott DJ (2006) Innate immune sensing of microbes by Nod proteins. Ann N Y Acad Sci 1072:19–27

Kurokawa T, Kikuchi T, Ohta K, Imai H, Yoshimura N (2003) Ocular manifestations in Blau syndrome associated with a CARD15/Nod2 mutation. Ophthalmology 110:2040–2044

Kusielewicz D, Duchatelle V, Valeyre D, Battesti JP, Vissuzaine C, Costa T, Rautureau J (1988) Obstructive jaundice caused by granulomatous stenosis of the extrahepatic bile ducts in sarcoidosis (in French). Gastroenterol Clin Biol 12:664–667

Lamkanfi M, Dixit VM (2009) Inflammasomes: guardians of cytosolic sanctity. Immunol Rev 227:95–105

Lamkanfi M, Kanneganti TD, Franchi L, Nunez G (2007) Caspase-1 inflammasomes in infection and inflammation. J Leukoc Biol 82:220–225

Lazzarini LC, de Fatima do Amparo Teixeira M, Souza Rodrigues R, Marcos Nunes Valiante P (2008) Necrotizing sarcoid granulomatosis in a family of patients with sarcoidosis reinforces the association between both entities. Respiration 76:356–360

Le Bourhis L, Benko S, Girardin SE (2007) Nod1 and Nod2 in innate immunity and human inflammatory disorders. Biochem Soc Trans 35:1479–1484

Le Gall F, Loeuillet L, Delaval P, Thoreux PH, Desrues B, Ramée MP (1996) Necrotizing sarcoid granulomatosis with and without extrapulmonary involvement. Pathol Res Pract 192:306–313

Le HT, Harton JA (2013) Pyrin- and CARD-only proteins as regulators of NLR functions. Front Immunol 4:275

Lecat A, Piette J, Legrand-Poels S (2010) The protein Nod2: an innate receptor more complex than previously assumed. Biochem Pharmacol 80:2021–2031

Lee AJ, Wu X, Cheng H, Zhou X, Cheng X, Sun SC (2010) CARMA1 regulation of regulatory T cell development involves modulation of interleukin-2 receptor signaling. J Biol Chem 285:15696–15703

Leff JA, Ready JB, Repetto C, Goff JS, Schwarz M (1990) Coexistence of primary biliary cirrhosis and sarcoidosis. West J Med 153:439–441

Liu W, Yan M, Liu Y, Wang R, Li C, Deng C, Singh A, Coleman WG, Rodgers GP (2010) Olfactomedin 4 down-regulates innate immunity against *Helicobacter pylori* infection. Proc Natl Acad Sci U S A 107:11056–11061

Lloyd-Davies RW, Forbes GB (1965) Sarcoidosis of the gall bladder. Gastroenterology 49:287–290

Lucherini OM, Obici L, Ferracin M, Fulci V, McDermott MF, Merlini G, Muscari I, Magnotti F et al (2013) First report of circulating microRNAs in tumour necrosis factor receptor-associated periodic syndrome (TRAPS). PLoS One 8:e73443

Ludwig J, Wiesner RH, LaRusso NF (1988) Idiopathic adulthood ductopenia. A cause of chronic cholestatic liver disease and biliary cirrhosis. J Hepatol 7:193–199

Ludwig J, Colina F, Poterucha JJ (1995) Granulomas in primary sclerosing cholangitis. Liver 15:307–312

Maambo E, Brett AS, Vasudeva R, Burns RG (2007) Hepatobiliary sarcoidosis presenting as sclerosing cholangitis: long-term follow-up. Dig Dis Sci 52:3363–3365

Maamouri N, Ketari S, Habessi H, Nouira K, Ben Dhaou B, Boussema F, Cherif O et al (2009) Budd-Chiari syndrome in sarcoidosis (in French). Gastroenterol Clin Biol 33:147–148

Maddrey WC, Johns CJ, Boitnott JK, Iber FL (1970) Sarcoidosis and chronic hepatic disease: a clinical and pathologic study of 20 patients. Medicine 49:375–395

Malireddi RK, Ippagunta S, Lamkanfi M, Kanneganti TD (2010) Cutting edge: proteolytic inactivation of poly (ADP-ribose) polymerase 1 by the Nlrp3 and Nlrc4 inflammasomes. J Immunol 185:3127–3130

Mariathasan S (2007) ASC, Ipaf and Cryopyrin/Nalp3: bona fide intracellular adapters of the caspase-1 inflammasome. Microbes Infect 9:664–671

Marzano AV, Trevisan V, Gattorno M, Ceccherini I, De Simone C, Crosti C (2013) Pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH): a new autoinflammatory syndrome associated with a novel mutation of the PSTPIP1 gene. JAMA Dermatol 149:762–764

Mathews RJ, Sprakes MB, Mcdermott MF (2008) NOD-like receptors and inflammation. Arthritis Res Ther 10:228

Menias CO, Surabhi VR, Prasad SR, Wang HL, Narra VR, Chintapalli KN (2008) Mimics of cholangiocarcinoma: spectrum of disease. Radiographics 28:1115–1129

Menne WR (1952) Über bisher wenig beachtete Spindelkörperchen in menschlichen Lymphknoten. Zbl Allg Pathol 89:433–438

Mert A, Avsar S, Ozaras R, Bilir M, Yemisen M, Erturan S, Pekmezci S, Ozbay G (2004) Gall bladder involvement in sarcoidosis. J Clin Gastroenterol 38:612–613

Miao EA, Warren SE (2010) Innate immune detection of bacterial virulence factors via the NLRC4 inflammasome. J Clin Immunol 30:502–506

Miao EA, Andersen-Nissen E, Warren SE, Aderem A (2007) TLR5 and Ipaf: dual sensors of bacterial flagellin in the innate immune system. Semin Immunopathol 29:275–288

Mino RA, Murphy AI, Livingstone RG (1949) Sarcoidosis producing portal hypertension. Treatment by splenectomy and splenorenal shunt. Ann Surg 130:951–957

Mishra BB, Moura-Alves P, Sonawane A, Hacohen N, Griffiths G, Moita LF, Anes E (2010) Mycobacterium tuberculosis protein ESAT-6 is a potent activator of the NLRP3/ASC inflammasome. Cell Microbiol 12:1046–1063

Mo J, Boyle JP, Howard CB, Monie TP, Davis BK, Duncan JA (2012) Pathogen sensing by nucleotide-binding oligomerization domain-containing protein 2 8 NOD2) is mediated by direct binding to muramyl dipeptide and ATP. J Biol Chem 287:23057–23067

Morgenthau AS, Iannuzzi MC (2011) Recent advances in sarcoidosis. Chest 139:174–182

Mounajjed T, Oxentenko AS, Qureshi H, Smyrk TC (2013) Revisiting the topic of histochemically detectable copper in various liver diseases with special focus on venous outflow impairment. Am J Clin Pathol 139:79–86

Mueller S, Boehme MW, Hofmann WJ, Stremmel W (2000) Extrapulmonary sarcoidosis primarily diagnosed in the liver. Scand J Gastroenterol 35:1003–1008

Müller-Quernheim J, Prasse A, Zissel G (2012) Pathogenesis of sarcoidosis. Presse Med 41:e275–e287

Murphy JR, Sjogren MH, Kikendall JW, Peura DA, Goodman Z (1990) Small bile duct abnormalities in sarcoidosis. J Clin Gastroenterol 12:555–561

Nakanuma Y, Ohta G, Yamazaki Y, Doishita K (1979) Intrahepatic bile duct destruction in a patient with sarcoidosis and chronic intrahepatic cholestasis. Acta Pathol Jpn 29:211–219

Nakanuma Y, Ohta G, Takeshita H, Yamazaki Y, Doishita K, Shimizu M (1983) Florid duct lesions and extensive bile duct loss of the intrahepatic biliary tree in chronic liver disease other than primary biliary cirrhosis. Acta Pathol Jpn 33:1095–1104

Nakanuma Y, Kouda W, Harada K, Hiramatsu K (2001) Hepatic sarcoidosis with vanishing bile duct syndrome, cirrhosis, and portal phlebosclerosis. Report of an autopsy case. J Clin Gastroenterol 32:181–184

Nakata K, Iwata K, Kojima K, Kanai K (1989) Computed tomography of liver sarcoidosis. J Comput Assist Tomogr 13:707–708

Nakhaei P, Genin P, Civas A, Hiscott J (2009) RIG-I-like receptors: sensing and responding to RNA virus infection. Semin Immunol 21:215–222

Natalino MR, Goyette RE, Owensby LC, Rubin RN (1978) The Budd Chiari syndrome in sarcoidosis. JAMA 239:2657–2658

Nehls O, Hass HG, Weber P, Dette S, Lauer UM, Schlemmer HP, Oehlert M, Gregor M, Klump B (2006) Sarcoidosis mimicking cholangiocarcinoma. Endoscopy 38(Suppl 2):E65–E66

Ogata S, Horio T, Sugiura Y, Shimazaki H, Saito H, Aiko S, Nakanishi K, Kawai T (2010) Sarcoidosis-associated hepatocellular carcinoma. Acta Med Okayama 64:407–410

Ogura Y, Inohara N, Benito A, Chen FF, Yamaoka S, Nunez G (2001) Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF-kappaB. J Biol Chem 276:4812–4818

Okafuji I, Nishikomori R, Kanazawa N, Fujisawa A, Yamazaki S, Saito M, Yoshioka T, Kawai T, Sakai H, Tanizaki H et al (2009) Role of the NOD2 genotype in the clinical phenotype of Blau syndrome and early-onset sarcoidosis. Arthritis Rheum 60:242–250

Oketani M, Tsubouchi H, Hori T, Sakamoto K, Kawakami S, Yoshimitsu N, Matsuo T et al (1992) Sarcoidosis with tumorous hepatic and bone lesions mimicking disseminated malignancy: a case report. Gastroenterol Jpn 27:414–417

Onitsuka A, Katagiri Y, Kiyama S, Mimoto H, Nakamura T, Toda K, Shima H (2003) Hilar cholangiocarcinoma associated with sarcoid reaction in the regional lymph nodes. J Hepatobiliary Pancreatol Surg 10:316–320

Oswald-Richter KA, Drake WP (2010) The etiologic role of infectious antigens in sarcoidosis pathogenesis. Semin Respir Crit Care Med 31:375–379

Oswald-Richter K, Sato H, Hajizadeh R, Shepherd BE, Sidney J, Sette A, Newman LS, Drake WP (2010) Mycobacterial ESAT-6 and katG are recognized by sarcoidosis CD4+ T cells when presented by the American sarcoidosis susceptibility allele, DRB1*1101. J Clin Immunol 30:157–166

Panasci DJ, Gordon DH, Sadovsky R (1992) Sarcoidosis of the liver: evaluation with multiple imaging modalities. Comput Med Imaging Graph 16:55–58

Pedra JH, Cassel SL, Sutterwala FS (2009) Sensing pathogens and danger signals by the inflammasome. Curr Opin Immunol 21:10–16

Pereira-Lima J, Schaffner F (1987) Chronic cholestasis in hepatic sarcoidosis with clinical features resembling primary biliary cirrhosis. Report of two cases. Am J Med 83:144–148

Philpott DJ, Girardin SE (2010) Nod-like receptors: sentinels at host membranes. Curr Opin Immunol 22:428–434

Pillai P, Sobrin L (2013) Blau syndrome-associated uveitis and the NOD2 gene. Semin Ophthalmol 28:327–332

Popper HH, Klemen H, Colby TV, Churg A (2003) Necrotizing sarcoid granulomatosis – is it different from nodular sarcoidosis ? Pneumonologie 57:268–271

Porter GH (1961) Hepatic sarcoidosis: a cause of portal hypertension and liver failure: review. Arch Intern Med 108:205–216

Portincasa P, Scaccianoce G, Palasciano G (2013) Familial Mediterranean fever: a fascinating model of inherited autoinflammatory disorder. Eur J Clin Invest 43:1314–1327

Priori R, Bombardieri M, Spinelli FR, Merlin F, Miceli-Richard C, La Cava M, Scavalli AS et al (2004) Sporadic Blau syndrome with a double CARD15 mutation. Report of a case with lifelong follow-up. Sarcoidosis Vasc. Diffuse Lung Dis 21:228–231

Proell M, Gerlic M, Mace PD, Reed JC, Riedl SJ (2013) The CARD plays a critical role in ASC foci formation and inflammasome signalling. Biochem J 449:613–621

Pungpapong S, Steers JL, Wallace MB, Krishna M, Keaveny AP (2006) Hepatobiliary sarcoidosis mimicking Klatskin's cholangiocarcinoma. Gastrointest Endosc 64:124–125

Rahman MK, Midtling EH, Svingen PA, Xiong Y, Bell MP, Tung J, Smyrk T, Egan LJ, Faubion WA (2010) The pathogen recognition receptor NOD2 regulates human FOXP3+ T cell survival. J Immunol 184:7247–7256

Rathinam VA, Jiang Z, Waggoner SN, Sharma S, Cole LE, Waggoner L, Vanaja SK et al (2010) The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. Nat Immunol 11:395–402

Reau NS, Jensen DM (2008) Vanishing bile duct syndrome. Clin Liver Dis 12:203–217

Rehwinkel J, Reis e Sousa C (2010) RIGorous detection: exposing virus through RNA sensing. Science 327:284–286

Reid JD, Andersen ME (1988) Calcium oxalate in sarcoid granulomas. With particular reference to the small ovoid body and a note on the finding of dolomite. Am J Clin Pathol 90:545–558

Rezeig MA, Fashir BM (1997) Biliary tract obstruction due to sarcoidosis: a case report. Am J Gastroenterol 92:527–528

Richardson WM, Sodhi CP, Russo A, Siggers RH, Afrazi A, Gribar SC, Neal MD et al (2010) Nucleotide-binding oligomerization domain-2 inhibits Toll-like receptor-4 signaling in the intestinal epithelium. Gastroenterology 139:904–917

Rierdijk ST, Burwell T, Bertin J, Coyle AJ (2008) Sensing intracellular pathogens – NOD-like receptors. Curr Opin Pharmacol 8:261–266

Ro JY, Luna MA, Mackay B, Ramos O (1987) Yellow-brown (Hamazaki-Wesenberg) bodies mimicking fungal yeasts. Arch Pathol Lab Med 111:555–559

Romer FK, Hommelgaard P, Schou G (1998) Sarcoidosis and cancer revisited: a long-term follow-up study of 555 Danish sarcoidosis patients. Eur Respir J 12:906–912

Rose AS, Tielker MA, Knox KS (2008) Hepatic, ocular and cutaneous sarcoidosis. Clin Chest Med 29:509–524

Rose CD, Martin TM, Wouters CH (2011) Blau syndrome revisited. Curr Opin Rheumatol 23:411–418

Rosenstiel P, Huse K, Till A, Hampe J, Hellmig S, Sina C, Billmann S, von Kampen O et al (2006) A short isoform of NOD2/CARD15, NOD2-S, is an endogenous inhibitor of NOD2/receptor-interacting protein kinase 2-induced signaling pathways. Proc Natl Acad Sci U S A 103:3280–3285

Rosenzweig HL, Galster KT, Planck SR, Rosenbaum JT (2009) NOD1 is expressed in the eye and functionally

contributes to IL-1{beta}dependent ocular inflammation in mice. Invest Ophthalmol Vis Sci 50:1746–1753
Rudzki C, Ishak KG, Zimmerman HJ (1975) Chronic intrahepatic cholestasis of sarcoidosis. Am J Med 59:373–387
Russi EW, Bansky G, Pfaltz M, Spinas G, Hammer B, Senning A (1986) Budd Chiari syndrome in sarcoidosis. Am J Gastroenterol 81:71–75
Rybicki BA, Sinha R, Ivengar S, Gray-McGuire C, Elston RC, Iannuzzi MC, the SAGA Study Consortium (2007) Genetic linkage analysis of sarcoidosis phenotypes: the sarcoidosis genetic analysis (SAGA) study. Genes Immun 8:379–386
Saidha S, Sotirchos ES, Eckstein C (2012) Etiology of sarcoidosis: does infection play a role ? Yale J Biol Med 85:133–141
Saini SK, Rose CD (1996) Liver involvement in familial granulomatous arthritis (Blau syndrome). J Rheumatol 23:396–399
Sakai T, Maeda M, Takabatake M, Hayashi N, Ishii Y, Kitamura M, Saitoh R, Ishizaki T (1995) MR imaging of hepatosplenic sarcoidosis. Radiol Med 13:39–41
Sanchez GA, de Jesus AA, Goldbach-Mansky R (2013) Monogenic autoinflammatory diseases: disorders of amplified danger sensing and cytokine dysregulation. Rheum Dis Clin N Am 39:701–734
Sartori S, Galeotti R, Calia N, Gualandi M, Nielsen I, Trevisani L, Ceccotti P, Abbasciano V (2002) Sonographically guided biopsy and sonographic monitoring in the diagnosis and follow-up of 2 cases of sarcoidosis with hepatic nodules and inconclusive thoracic findings. J Ultrasound Med 21:1035–1039
Schroeder K, Tschopp J (2010) The inflammasomes. Cell 140:821–832
Scott GC, Berman JM, Higgins JL (1997) CT patterns of nodular hepatic and splenic sarcoidosis: a review of the literature. J Comput Assist Tomogr 21:369–372
Scott MJ, Chen C, Sun Q, Billiar TR (2010) Hepatocytes express functional NOD1 and NOD2 receptors: a role for NOD1 in hepatocyte CC and CXC chemokine production. J Hepatol 53:693–701
Sekine T, Amano Y, Hidaka F, Takagi R, Machida T, Naito Z, Kumita S (2012) Hepatosplenic and muscular sarcoidosis: characterization with MR imaging. Magn Reson Med Sci 11:83–89
Sfriso P, Caso F, Tognon S, Galozzi P, Gava A, Punzi L (2012) Blau syndrome, clinical and genetic aspects. Autoimmun Rev 12:44–51
Shay H, Berk JE, Sons M, Aegerter E, Weston JK, Adams AB (1951) The liver in sarcoidosis. Gastroenterology 19:441–459
Sherlock S (1987) The syndrome of disappearing intrahepatic bile ducts. Lancet 2:493–496
Sieracki JC, Fisher ER (1973) The ceroid nature of the so-called “Hamazaki-Wesenberg bodies”. Am J Clin Pathol 59:248–253
Smith G, Brownell I, Sanchez M, Prystowsky S (2008) Advances in the genetics of sarcoidosis. Clin Genet 73:401–412
Song Z, Marzilli L, Greenlee BM, Chen ES, Silver RF, Askin FB et al (2005) Mycobacterial catalase-peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis. J Exp Med 201:755–767
Srimathi T, Robbins SL, Dubas RL, Chang H, Cheng H, Roder H, Park YC (2008) Mapping of POP1-binding site on pyrin domain of ASC. J Biol Chem 283:15390–15398
Stanley NN, Fox RA, Whimster WF, Sherlock S, James DG (1972) Primary biliary cirrhosis or sarcoidosis – or both. N Engl J Med 287:1282–1284
Stehlik C, Hayashi H, Pio F, Godzik A, Reed JC (2003a) CARD6 is a modulator of NF-kappa B activation by Nod1- and Cardiak-mediated pathways. J Biol Chem 278:31941–31949
Stehlik C, Krajewska M, Welsh K, Krajewski S, Godzik A, Reed JC (2003b) The PAAD/PYRIN-only protein POP1/ASC2 is a modulator of ASC-mediated nuclear-factor-kappa B and pro-caspase-1 regulation. Biochem J 373:101–113
Stephan E, Khoury M, Nguyen-Khac Scheou A (1965) Pseudotumoral sarcoidosis of the liver. Apropos of a case (in French). Bull Mem Soc Med Hop Paris 116:1479–1484
Stoffels M, Szperl A, Simon A, Netea MG, Plantinga TS, van Deuren M, Kamphuis S et al (2014) MEFV mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease. Ann Rheum Dis 73:455–461
Strickland-Marmol LB, Fessler RG, Rojiani AM (2000) Necrotizing sarcoid granulomatosis mimicking an intracranial neoplasm: clinicopathologic features and review of the literature. Mod Pathol 13:909–913
Strober W, Murray PJ, Kitani A, Watanabe T (2006) Signalling pathways and molecular intercations of NOD1 and NOD2. Nat Rev Immunol 6:9–20
Strober W, Kitani A, Fuss I, Asano N, Watanabe T (2008) The molecular basis of NOD2 susceptibility mutations in Crohn’s disease. Mucosal Immunol 1(Suppl 1): S5–S9
Stutz A, Horvath GL, Monks BG, Latz E (2013) ASC speck formation as a readout for inflammasome activation. Methods Mol Biol 1040:91–101
Sutterwala FS, Flavell RA (2009) NLRC4/IPAF: a CARD carrying member of the NLR family. Clin Immunol 130:2–6
Sutterwala FS, Ogura Y, Flavell RA (2007) The inflammasome in pathogen recognition and inflammation. J Leukoc Biol 82:259–264
Suzuki K, Morise Z, Furuta S, Tanahashi Y, Takeura C, Kagawa T, Ikeda M, Sugioka A (2011) Hepatic sarcoidosis mimicking hilar cholangiocarcinoma: case report and review of the literature. Case Rep Gastroenterol 5:152–158
Symmans PJ, Brady K, Keen CE (1995) Calcium oxalate crystal deposition in epithelioid histiocytes of granulomatous lymphadenitis: analysis by light and electron microscopy. Histopathology 27:423–429

Takada H, Uehara A (2006) Enhancement of TLR-mediate innate immune responses by peptidoglycans through NOD signaling. Curr Pharm Des 12:4163–4172

Takeda K, Akira S (2004) TLR signaling pathways. Semin Immunol 16:3–9

Tan CB, Rashid S, Rajan D, Gebre W, Mustacchia P (2012) Case Rep Gastroenterol 6:183–189

Tattoli I, Travassos LH, Cameiro LA, Magalhaes JG, Girardin SE (2007) The nodosome: Nod1 and Nod2 control bacterial infections and inflammation. Semin Immunopathol 29:289–301

Tekeste H, Latour F, Levitt RE (1984) Portal hypertension complicating sarcoid liver disease: case report and review of the literature. Am J Gastroenterol 79:389–396

Thanos L, Zormpala A, Brountzos E, Nikita A, Kelekis D (2002) Nodular hepatic and splenic sarcoidosis in a patient with normal chest radiograph. Eur J Radiol 41:10–11

Thomas E, Micci D (1977) Chronic intrahepatic cholestasis with granulomas and biliary cirrhosis. JAMA 238:337–338

Tigno-Aranjuez JT, Abbott DW (2012) Ubiquitination and phosphorylation in the regulation of NOD2 signaling and NOD2-mediated disease. Biochim Biophys Acta 1823:2022–2028

Tombazzi C, Waters B, Ismail MK, Sylvestre PB, Martinez-Hernandez A, Riely CA (2008) Sarcoidosis mimicking primary sclerosing cholangitis requiring liver transplantation. Ann Hepatol 7:83–86

Travassos LH, Carneiro LA, Girardin S, Philpott DJ (2010) Nod proteins link bacterial sensing and autophagy. Autophagy 6:409–411

Trenn G, Gabbert HE, Schmitt-Gräff A, Reis HE (1999) Granulomatous hepatitis and myelitis: an unusual manifestation of extrapulmonary sarcoidosis (in German). Z Gastroenterol 37:159–163

Tripathi SV, Leslie KS (2013) Autoinflammatory diseases in dermatology: CAPS, TRAPS, HIDS, FMF, Blau, CANDLE. Dermatol Clin 31:387–404

Tsukada T, Katayama N, Taniguchi M, Miwa H, Kobayashi T, Deguchi K, Shirakawa S et al (1993) Liver sarcoidosis showing low-density intrahepatic septa on postcontrast computed tomography. Gastroenterol Jpn 28:730–733

Uehara A, Fujimoto Y, Kawasaki A, Kusumoto S, Fukase K, Takada H (2006) Meso-diaminopimelic acid and meso-lanthionine, amino acids specific to bacterial peptidoglycans, activate human epithelial cells through NOD1. J Immunol 177:1796–1804

van Brusselen D, Janssen CE, Scott C, Bevers N, Roskams T, Wouters C, Van Damma-Lombaerts R (2012) Budd-Chiari syndrome as presenting symptom of hepatic sarcoidosis in a child, with recurrence after liver transplantation. Pediatr Transplant 16:E58–E62

Van Maarsseveen TC, Vos W, van Diest PJ (2009) Giant cell formation in sarcoidosis: cell fusion or proliferation with non-division? Clin Exp Immunol 155:476–486

Van Steenbergen W, Fevery J, Vandenbrande P, Desmet V, Ponette E, Kerremans R, de Groote J (1987) Ulcerative colitis, primary sclerosing cholangitis, bile duct carcinoma, and generalized sarcoidosis. Report of a unique association. J Clin Gastroenterol 9:574–579

Vereecke L, Beyaert R, van Loo G (2009) The ubiquitin-editing enzyme A20 (TNFAIP3) is a central regulator of immunopathology. Trends Immunol 30:383–391

Viala J, Sansonetti P, Philpott DJ (2004) Nods and 'intracellular' innate immunity. C R Biol 327:551–555

Von Kampen O, Lipinski S, Till A, Martin SJ, Nietfeld W, Lehrach H, Schreiber S, Rosenstiel P (2010) Caspase recruitment domain-containing protein 8 (CARD8) negatively regulates NOD2-mediated signaling. J Biol Chem 285:19921–19926

Warshauer DM, Dumbleton SA, Molina PL, Yankaskas BC, Parker LA, Woosley JT (1994a) Abdominal CT findings in sarcoidosis: radiologic and clinical correlation. Radiology 192:93–98

Warshauer DM, Semelka RC, Ascher SM (1994b) Nodular sarcoidosis of the liver and spleen: appearance on MR images. J Magn Reson Imaging 4:553–557

Warshauer DM, Molina PL, Hammam SM, Koehler RE, Paulson EK, Bechtold RE, Perlmutter ML et al (1995) Nodular sarcoidosis of the liver and spleen: analysis of 32 cases. Radiology 195:757–762

Windler VE, Bützow GH, Klöppel G, Kempeneers I (1983) Hepatolienale granulomatose mit portaler hypertension. Z Gastroenterol 21:115–122

Winters R, Kida M, Cooper K (2007) Hamazaki-Wesenberg bodies in two patients with no history of sarcoidosis. J Clin Pathol 60:1169–1171

Wong VS, Adab N, Youngs GR, Sturgess R (1999) Hepatic sarcoidosis complicated by hepatocellular carcinoma. Eur J Gastroenterol Hepatol 11:353–355

Wu J, Luo S, Jiang H, Li H (2008) Mammalian CHORD-containing protein 1 is a novel heat shock protein 90-interacting protein. FEBS Lett 579:421–426

Wullaert A, Verstrepen L, Van Huffel S, Adib-Conquy M, Cornelis S, Kreike M, Haegman M et al (2007) LIND/ABIN-3 is a novel lipopolysaccharide-inducible inhibitor of NF-kappaB activation. J Biol Chem 282:81–90

Xerri L, Nosny Y, Minko D, Benkoel L, Nouhou H, Kohler JL, Chamlian A (1989) Association of sarcoidosis and primary biliary cirrhosis. Clinical and anatomopathologic study of a case followed for over 10 years (in French). Gastroenterol Clin Biol 13:513–516

Yang J, Zhao Y, Shi J, Shao F (2013) Human NAIP and mouse NAIP1 recognize bacterial type III secretion needle protein for inflammasome activation. Proc Natl Acad Sci U S A 110:14408–14413

Yao Q (2013) Nucleotide-binding oligomerization domain containing 2: structure, function, and disease. Semin Arthritis Rheum 43:125–130

Yeboah J, Afkhami M, Lee C, Sharma OP (2012) Necrotizing sarcoid granulomatosis. Curr Opin Pulm Med 18:493–498

Yoneyama M, Fujita T (2009) RNA recognition and signal transduction by RIG-I-like receptors. Immunol Rev 227:54–65

Yu HB, Finlay BB (2008) The caspase-1 inflammasome: a pilot of innate immune responses. Cell Host Microbe 4:198–208

Zeng W, Sun L, Jiang X, Chen X, Hou F, Adhikari A, Xu M, Chen ZJ (2010) Reconstitution of the RIG-I pathway reveals a signaling role of unanchored polyubiquitin chains in innate immunity. Cell 141:315–330

Zhang M, Kadota Y, Prodromou C, Shirasu K, Pearl LH (2010) Structural basis for assembly of hsp90-Sgt1-CHORD protein complexes: implications for chaperoning of NLR innate immunity receptors. Mol Cell 39:269–281

Zhong Y, Kinio A, Saleh M (2013) Functions of NOD-like receptors in human diseases. Front Immunol 4:333

Zou Chang M, Nie P, Secombes CJ (2009) Origin and evolution of the RIG-I like RNA helicase family. BMC Evol Biol 9:85

Hepatobiliary Manifestations of Chronic Granulomatous Diseases of Childhood

140

Contents

Abstract

The recurrent bacterial and fungal infections that complicate chronic granulomatous disease (CGD) can involve the hepatobiliary tract and induce abscesses and obstructing lesions. CGD is a heterogeneous group of primary immunodeficiency diseases, whereby phagocytes fail to kill certain bacteria and fungi after phagocytosis. CGD is a hereditary defect characterized by deficient production of reactive oxygen metabolites required to destroy intracellular microorganisms. This failure is related to several defects in NADPH oxidase. Pediatric patients with CGD frequently show hepatomegaly and bacterial liver abscesses, which are a clinical hallmark of CGD. The frequent and complex infections can also induce hepatobiliary granulomas and their secondary effects. Venopathy of portal vein branches is common in CGD and is associated with portal hypertension and splenomegaly.

Chronic Granulomatous Disease

Introduction

Chronic granulomatous disease (CGD; Bridges-Good syndrome; Quie syndrome; chronic granulomatous disorder; OMIM 306400; ICD-9: 288.1, ICD-10: D71) is a heterogeneous group of primary immunodeficiency diseases. In CGD, phagocytes fail to kill certain bacteria and fungi

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_140

after phagocytosis caused by a genetically defective respiratory burst (Berendes et al. 1957; Landing and Shirkey 1957; Bridges et al. 1959). Patients with CGD typically suffer from recurrent bacterial and fungal infections involving lungs, lymph nodes, soft tissue, bones, and liver (reviews: Segal et al. 2000; Heyworth et al. 2003; Loffredo 2011; Song et al. 2011).

Epidemiology

Based on a US registry, the minimum estimate of incidence was 1/200,000–1/250,000 live births, with about 20 new cases diagnosed each year (Winkelstein et al. 2000; Heyworth et al. 2003).

Clinical Manifestations

The clinical presentation of CGD is dominated by recurrent bacterial and fungal infections, excessive inflammation, and the sequelae of granuloma formation, related to phagocyte failure (Rosenzweig and Holland 2004; Khanna et al. 2005; Antachopoulos et al. 2007). Patients with CGD are particularly susceptible to catalase-positive microorganisms and certain Gram-negative bacteria (Ben-Ari et al. 2012) and often develop pneumonia, lymphadenitis, liver abscess, osteomyelitis, purulent dermatitis, and cellulitis.

The leading bacteria in CGD infections are *Staphylococcus aureus*, *Serratia marcescens*, *Streptococcus*, *Salmonella* species, *Klebsiella* species, *Pseudomonas* (*Burkholderia*) *cepacia*, *Psychrobacter immobilis*, and *Nocardia*, while the most important fungi include *Aspergillus fumigatus* and *Candida albicans* (Ben-Ari et al. 2012; Falcone et al. 2012; Sriaroon et al. 2014). In a large study, pneumonia was the most prevalent infectious disease (79 %), with *Aspergillus* being the most common infectious agent identified, followed by suppurative lymphadenitis (53 %, *Staphylococcus* the most prevalent cause), subcutaneous abscesses (42 %, mostly caused by *Staphylococcus*), liver abscess (27 %, again *Staphylococcus* the prevalent cause), and osteomyelitis (25 %, most often caused by *Serratia*) (Winkelstein et al. 2000). CGD can also promote mycobacterial infections, including *Mycobacterium fortuitum* and *M. avium* infections, disseminated *Mycobacterium flavescens* infection, and especially generalized BCGosis/BCGitis (review of the literature: Bustamante et al. 2007), the phagocytic respiratory burst playing an important role in the antimycobacterial defense (Lau et al. 1998). X-linked CGD has been reported to closely mimic juvenile sarcoidosis, with cervical and pulmonary granulomatous lymphadenopathy and high angiotensin-converting enzyme (Brunner et al. 2007). CGD is also characterized by exuberant inflammatory reactions and autoimmune phenomena, attributed to deficient anti-inflammatory signaling. For example, patients with CGD can develop an inflammatory bowel disease resembling Crohn's disease (Marciano et al. 2004; Marks et al. 2009). It has been suggested that impaired apoptotic cell clearance (efferocytosis) in CGD due to macrophage skewing contributes to enhanced inflammation, due to altered IL-4-dependent macrophage programming (Fernandez-Boyanapalli et al. 2009; review: Rieber et al. 2012). In addition, neutrophils from CGD patients only weakly inhibit gamma-delta T cells, while normal neutrophils are known to potently suppress gamma-delta T cell function (Sabbione et al. 2014).

Hepatic Manifestations of Granulomatous Disease

Hepatic Abscesses

Hepatosplenomegaly is present in up to 90 % of patients with CGD. Bacterial liver abscesses are a clinical hallmark of CGD (Chusid 1978; Mulholland et al. 1983; Lublin et al. 2002; Mamishi et al. 2011; Leiding et al. 2012; Székely et al. 2012). A hepatic abscess may be part of the initial presentation of CDG or may develop years after the diagnosis of CGD had been made. CGD can present as recurrent hepatic abscess in adult patients (Al-Khuwaitir et al. 2007). As found in a study on 368 patients, liver abscess was the most common hepatic manifestation of CGD (27 %), mostly caused by *Staphylococcus aureus*

(Winkelstein et al. 2000). In a study of 429 patients with CGD, liver involvement was found in 32 % of the patients (van den Berg et al. 2009). In contrast to sporadic liver abscess, which typically occurs as a single event and shows on CT images a thin enhancing rim with an internal liquefied, non-enhancing material, hepatic abscesses in CGD are often multiple lesions and have the tendency to remain enhancing without liquefaction (Garcia-Eulate et al. 2006). In fact, persistence of hepatic abscesses is a frequent phenomenon in CGD (Lublin et al. 2002). Macroscopically, abscesses often show multiple lobulated gray-to-yellow foci of up to several cm diameter. The lobulated areas have cavities filled with thick, purulent material typical for pus seen in staphylococcal infections, peripherally delimitated by granulation tissue and a fibrous reaction. Histologically, the abscesses show a purulent center with damaged neutrophil granulocytes, necrotic cell debris, fibrin-rich exudate, and macrophages. The periphery exhibits a demarcation zone composed of granulation tissue, an infiltrate of in part foamy macrophages, few epithelioid cells, lymphocytes, and plasma cells. In the vicinity of the abscess, macrophages with a ceroid-like, PAS-positive yellow-brown pigment may be seen.

Hepatic Granulomas in CGD

In a study of seven patients with CGD, with an age range of 5–41 years, hepatic histology was analyzed by biopsy or wedge resection in five and by autopsy in three cases. Histologically, the most consistent finding was the presence of foamy macrophages that contained a finely granular golden brown pigment, predominantly present in the portal tracts but also within the lobules. The presence of pigmented lipid-laden macrophages/histiocytes in the viscera was already noted in one of the first reports of CGD (Landing and Shirkey 1957). Four cases showed palisading granulomas with a giant cell reaction and central necrosis, lesions resembling *Candida* granulomas, and in part of these cases cultures for *Staphylococcus aureus* were positive. One case exhibited hyalinized portal tract and intralobular granulomas (Nakhleh et al. 1992). Among seven liver biopsies obtained from four pediatric patients with CGD, one biopsy showed granulomas and a second numerous classical pigmented macrophages in the sinusoids (Levine et al. 2005). In an analysis of the charts of 194 patients with CGD, liver abscess occurred in 35 %, and bioptic liver histology showed granulomas in 75 % and lobular hepatitis in 90 % of the specimens (Hussain et al. 2007).

Hepatic Vascular Anomalies in CGD

Venopathy of portal vein branches is common in CGD (80 %) and is associated with portal hypertension and splenomegaly. Venopathy of the central vein was also frequent (63 %) and was associated with the number of abscess episodes. Nodular regenerative hyperplasia (NRH) was seen in nine patients (Hussain et al. 2007). Mortality in CGD patients is associated with the development of non-cirrhotic portal hypertension (Feld et al. 2008). As in other disorders, NRH in CGD is likely to be caused by the vascular anomalies.

Differential Diagnosis

Combined immunodeficiency with autoimmune features caused by RAG1 mutations can evolve into a disorder resembling CGD (Reiff et al. 2013).

Molecular Mechanisms of Granulomatous Diseases

CGD is a hereditary defect of leukocyte function (Good et al. 1968) and is caused by the inability of phagocytes (neutrophils, monocytes, macrophages, eosinophils) to generate sufficient amounts of reactive oxygen metabolites required to kill microorganisms subsequent to their phagocytosis. This failure is caused by several defects of NADPH oxidase (Babior 2004), the key enzyme for this sequence of reactions (reviews: Curnutte 1993; Meischl and Roos 1998; Morel 2007). The superoxide-generating respiratory-burst oxidase

(NADPH oxidase) makes part of an enzyme complex that catalyzes the NADPH-dependent reduction of oxygen into the superoxide anion in phagocytic cells. The superoxide anion then generates other antimicrobial reactive oxygen intermediates, including H2O2, hydroxyl anion, and peroxynitrite anion. The activation of NADPH oxidase requires the translocation of the cytosolic enzyme subunits p47phox (phagocyte oxidase), p67phox, and the low molecular weight GTPase Rac to the membrane-bound flavocytochrome b558, a heterodimer consisting of the heavy chain gp91phox and the light chain p22phox (Leusen et al. 1996). The resulting enzyme complex transfers electrons from NADPH on the cytoplasmic side to oxygen on the vacuolar or extracellular side, thereby creating superoxide anions, the gp91phox subunit thought to contain the electron transport machinery of the oxidase as well as the NADPH- and FAD-binding sites (reviews: Segal et al. 2000; Vignais 2002). Phagocytic NADPH oxidase activity is regulated by phosphorylation of gp91phox/NOX2 by protein kinase C, which enhances its diaphorase activity and binding to Rac2, p67phox, and p47phox (Raad et al. 2009). In 1966, Holmes et al. detected an abnormality of phagocyte function in CGD (Holmes et al. 1966), while Quie et al. in 1967 demonstrated defective in vitro killing of bacteria by phagocytes obtained from CGD patients (Quie et al. 1967). Also in 1967, Bahner et al. reported a defective reduction of nitroblue tetrazolium by CGD phagocytes, proposing this phenomenon as a diagnostic test (Baehner et al. 1967). In 1968, a deficiency of reduced nicotinamide-adenine dinucleotide oxidase as a cause of CGD was found (Baehner and Karnovsky 1968). Subsequently, defective superoxide production from phagocytes in CGD was shown (Curnutte et al. 1974). The deficiency of the leukocyte oxidative burst in CGD favors infections above all with Gram-positive bacteria (Kaplan et al. 1968) and fungi (Kim et al. 1969). Defective NADPH oxidase expression in CGD was confirmed in 1975 (Hohn and Lehrer 1975), and the defective gene in X-linked CGD assigned to chromosome Xp21 (Segal 1987). The four components of the NADPH complex implicated in CGD are gp91phox, p22phox, p47phox, and p67phox. The X-linked variant of CGD is by far the most common (70 % of all cases of CGD), resulting in a greater number of affected males, but females with X-linked CGD are also known, attributed to skewed X inactivation. X-linked CGD is caused by alterations in the gp91phox gene (the CYBB gene localized to chromosome Xp21.1). It can involve deletions, frameshift, missense, nonsense, null, splice site, and intronic mutations of the CYBB gene (Noack et al. 2001; Brunner et al. 2007; Lewis et al. 2008; review: Song et al. 2011). Larger X-chromosomal deletions of the critical area cause the so-called contiguous gene syndrome, resulting in associations of the Kell phenotype (McLeod syndrome with X-linked CGD, Duchenne muscular dystrophy, and X-linked retinitis pigmentosa). X-linked CGD portends a worse prognosis with a higher annual mortality compared with the other genotypes.

Autosomal recessive CGD has been found to be caused by mutations of the p91phox (Umei et al. 1987), p22phox gene (Umei et al. 1987), p47phox gene (NCF1; Curnutte et al. 1987), and p67phox gene (Umei et al. 1987; Shamsian et al. 2008; van de Vosse et al. 2009).

Diffuse Hepatic Granulomatous Infiltration Syndrome

Introduction

In rare instances where the liver substance is heavily infiltrated by a granulomatous reaction in the absence of known causes of granulomatous hepatitis, including sarcoidosis, these alterations may be difficult to distinguish from a malignant process replacing the parenchyma.

Granulomatous infiltration of unknown cause with replacement of liver parenchyma has first been described in a 76-year-old man who had presented with fever, weight loss, and abnormal liver function tests (Millson et al. 2007). Ultrasound of the liver showed diffuse hepatomegaly, and MRI demonstrated a diffusely abnormal liver.

Pathology

Liver biopsies exhibited a granulomatous process that diffusely infiltrated and replaced the hepatic parenchyma, leaving portal areas and efferent veins in their original positions. Some granulomas had central necrosis, and most showed a peripheral zone of often large multinucleated pigmented CD68-positive epithelioid macrophages, becoming gradually replaced by loose fibrous tissue toward the center of the lesions. Obliterated efferent veins were found within the lesion, the obliteration being caused by an intimal fibrous thickening. The changes regressed after steroid therapy (Millson et al. 2007). A similar disorder had previously been reported, characterized by widespread granulomatous lesions in the liver and pure intrahepatic granulomatous venulitis, but tuberculosis and sarcoidosis were not formally excluded in this 72-year-old male patient (Nakanuma et al. 1980).

References

Al-Khuwaitir TS, Madani TA, Al-Qahtani T, Al-Tuwaijiri AS (2007) Chronic granulomatous disease with recurrent hepatic abscesses in an adult. Saudi Med J 28:1593–1596

Antachopoulos C, Walsh TJ, Roilides E (2007) Fungal infections in primary immunodeficiencies. Eur J Pediatr 166:1099–1117

Babior BM (2004) NADPH oxidase. Curr Opin Immunol 16:42–47

Baehner RL, Nathan DG (1967) Leukocyte oxidase: defective activity in chronic granulomatous disease. Science 155:835–836

Baehner RL, Karnovsky ML (1968) Deficiency of reduced nicotinamide-adenine dinucleotide oxidase in chronic granulomatous disease. Science 162:1277–1279

Ben-Ari J, Wolach O, Gavrieli R, Wolach B (2012) Infections associated with chronic granulomatous disease: linking genetics to phenotypic expression. Expert Rev Anti Infect Ther 10:881–894

Berendes H, Bridges RA, Good RA (1957) A fatal granulomatosis of childhood: the clinical study of a new syndrome. Minn Med 40:309–312

Bridges RA, Berendes H, Good RA (1959) A fatal granulomatous disease of childhood: the clinical, pathological, and laboratory features of a new syndrome. AMA J Dis Child 97:387–408

Brunner J, Dockter G, Rösen-Wolff A, Roesler J (2007) X-linked chronic granulomatous disease (CGD) caused by an intra-exonic splice mutation (CYBB exon 3, c.262C>A) is mimicking juvenile sarcoidosis. Clin Exp Rheumatol 25:336–338

Bustamante J, Sksu G, Vogt G, de Beaucoudrev L, Genel F, Chapgier A, Filipe-Santos O et al (2007) BCG-osis and tuberculosis in a child with chronic granulomatous disease. J Allergy Clin Immunol 120:32–38

Chusid MJ (1978) Pyogenic hepatic abscess in infancy and childhood. Pediatrics 62:554–559

Curnutte JT (1993) Chronic granulomatous disease: the solving of a clinical riddle at the molecular level. Clin Immunol Immunopathol 67:S2–S15

Curnutte JT, Whitten DM, Balior DM (1974) Defective superoxide production by granulocytes from patients with chronic granulomatous disease. N Engl J Med 290:593–597

Curnutte JT, Kuver R, Scott PJ (1987) Activation of neutrophil NADPH oxidase in a cell-free system. Partial purification of components and characterization of the activation process. J Biol Chem 262:5563–5569

Falcone EL, Hanses S, Stock F, Holland SM, Zelazny AM, Uzel G (2012) Streptococcal infections in patients with chronic granulomatous disease: case report and review of the literature. J Clin Immunol 32:649–652

Feld JJ, Hussain N, Wright EC, Kleiner DE, Hoofnagle JH, Ahlawat S, Anderson V et al (2008) Hepatic involvement and portal hypertension predict mortality in chronic granulomatous disease. Gastroenterology 134:1917–1926

Fernandez-Boyanapalli RF, Frasch SC, McPhillips K, Vandivier RW, Harry BL, Riches DW et al (2009) Impaired apoptotic cell clearance in CGD due to altered macrophage programming is reversed by phosphatidylserine-dependent production of IL-4. Blood 113:2047–2055

Garcia-Eulate R, Hussain N, Heller T, Kleiner D, Malech H, Holland S, Choyke PL (2006) CT and MRI of hepatic abscess in patients with chronic granulomatous disease. AJR Am J Roentgenol 187:482–490

Good RA, Quie PG, Winshorst DB, Page AR, Rodey GE, White J, Wolfson JJ, Holmes BH (1968) Fatal (chronic) granulomatous disease of childhood: a hereditary defect of leukocyte function. Semin Hematol 5:215–254

Heyworth PG, Cross AR, Curnutte JT (2003) Chronic granulomatous disease. Curr Opin Immunol 15:578–584

Hohn DC, Lehrer RI (1975) NADPH oxidase deficiency in X-linked chronic granulomatous disease. J Clin Invest 55:707–713

Holmes B, Quie PG, Windhorst DB, Good RA (1966) Fatal granulomatous disease of childhood. An inborn abnormality of phagocytic function. Lancet 1(7449):1225–1228

Hussain N, Feld JJ, Kleiner DE, Hoofnagle JH, Garcia-Eulate R, Ahlawat S, Koziel DE et al (2007) Hepatic abnormalities in patients with chronic granulomatous disease. Hepatology 45:675–683

Kaplan EL, Laxdal T, Quie PG (1968) Studies of polymorphonuclear leukocytes from patients with chronic granulomatous disease of childhood: bactericidal capacity for streptococci. Pediatrics 41:591–599

Khanna et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/16160105

Kim MH, Rodey GE, Good RA, Chilgren RA, Quie PG (1969) Defective candidacidal capacity of polymorphonuclear leukocytes in chronic granulomatous disease of childhood. J Pediatr 75:300–303

Landing BH, Shirkey HS (1957) A syndrome of recurrent infection and infiltration of viscera by pigmented lipid histiocytes. Pediatrics 20:431–438

Lau YL, Chan GC, Ha SY, Hui YF, Yuen KY (1998) The role of phagocytic respiratory burst in host defense against *Mycobacterium tuberculosis*. Clin Infect Dis 26:226–227

Leiding JW, Freeman AF, Marciano BE, Anderson VL, Uzel G, Malech HL, DeRavin S et al (2012) Corticosteroid therapy for liver abscess in chronic granulomatous disease. Clin Infect Dis 54:694–700

Leusen JH, Verhoeven AJ, Roos D (1996) Interactions between the components of the human NADPH oxidase: a review about the intrigues in the phox family. Front Biosci 1:d72–d90

Levine S, Smith VV, Malone M, Sebire NJ (2005) Histopathological features of chronic granulomatous disease (CGD) in childhood. Histopathology 47:508–516

Lewis EM, Singla M, Sergeant S, Koty PP, McPhail LC (2008) X-linked chronic granulomatous disease secondary to skewed X chromosome inactivation in a female with a novel CYBB mutation and late presentation. Clin Immunol 129:372–380

Loffredo L (2011) Chronic granulomatous disease. Intern Emerg Med 6(Suppl 1):125–128

Lublin M, Bartlett DL, Danforth DN, Kauffman H, Gallin JI, Malech HL, Shawker T, Choyke P et al (2002) Hepatic abscess in patients with chronic granulomatous disease. Ann Surg 235:383–391

Mamishi S, Ahmadi F, Ahmadi M, Rezaei N (2011) Liver abscess as the presenting manifestation of chronic granulomatous disease. Acta Microbiol Immunol Hung 58:297–301

Marciano BE, Rosenzweig SD, Kleiner DE, Anderson VL, Darnell DN, Anaya-O'Brien S et al (2004) Gastrointestinal involvement in chronic granulomatous disease. Pediatrics 114:462–468

Marks DJ, Miyagi K, Rahman FZ, Novelli M, Bloom SL, Segal AW (2009) Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn's disease. Am J Gastroenterol 104:117–124

Meischl C, Roos D (1998) The molecular basis of chronic granulomatous disease. Springer Semin Immunopathol 19:417–434

Millson CE, Guthrie JA, Sahay P, Wyatt JI (2007) Granulomatous infiltration with replacement of liver parenchyma: first case report. Eur J Gastroenterol Hepatol 19:715–717

Morel F (2007) Molecular aspects of chronic granulomatous disease. "The NADPH oxidase complex" (in French). Bull Acad Natl Med 191:377–390

Mulholland MW, Delaney JP, Simmons RL (1983) Gastrointestinal complications of chronic granulomatous disease: surgical implications. Surgery 94:569–575

Nakanuma Y, Ohta G, Doishita K, Maki H (1980) Granulomatous liver disease in the small hepatic and portal veins. Arch Pathol Lab Med 104:456–458

Nakhleh RE, Glock M, Snover DC (1992) Hepatic pathology of chronic granulomatous disease of childhood. Arch Pathol Lab Med 116:71–75

Noack D, Heyworth PG, Newburger PE, Cross AR (2001) An unusual intronic mutation in the CYBB gene giving rise to chronic granulomatous disease. Biochem Biophys Acta 1537:125–131

Quie et al. 1967. http://www.ncbi.nlm.nih.gov/pubmed/6021213

Raad H, Paclet MH, Boussetta T, Kroviarski Y, Morel F, Quinn MT, Gougerot-Pocidalo MA et al (2009) Regulation of the phagocyte NADPH oxidase activity: phosphorylation of gp91phox/NOX2 by protein kinase C enhances its diaphorase activity and binding to Rac2, p67phox, and p47phox. FASEB J 23:1011–1022

Reiff A, Bassuk AG, Church JA, Campbell E, Bing X, Fergusoan PJ (2013) Exome sequencing reveals RAG1 mutations in a child with autoimmunity and sterile chronic multifocal osteomyelitis evolving into disseminated granulomatous disease. J Clin Immunol 33:1289–1292

Rieber N, Hector A, Kuijpers T, Roos D, Hartl D (2012) Current concepts of hyperinflammation in chronic granulomatous disease. Clin Dev Immunol 2012:252460

Rosenzweig SD, Holland SM (2004) Phagocyte immunodeficiencies and their infections. J Allergy Clin Immunol 113:620–626

Sabbione F, Gabelloni ML, Ernst G, Gori MS, Salamone G, Oleastro M, Trevani A et al (2014) Neutrophils suppress γδ T-cell function. Eur J Immunol 44:819–830

Segal AW (1987) Absence of both cytochrome b-245 subunits from neutrophils in X-linked chronic granulomatous disease. Nature 326:88–91

Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM (2000) Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore) 79:170–200

Shamsian BS, Mansouri D, Pourpak Z, Rezaei N, Chavoshzadeh Z, Jadali F, Gharib A et al (2008) Autosomal recessive chronic granulomatous disease, IgA deficiency and refractory autoimmune thrombocytopenia responding to Anti-CD20 monoclonal antibody. Iran J Allergy Asthma Immunol 7:181–184

Song E, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G (2011) Chronic granulomatous disease: a review of the infectious and inflammatory complications. Clin Mol Allergy 9:10

Sriaroon P, Elizalde A, Perez EE, Leiding JW, Aldrovandi GM, Sleasman JW (2014) Psychrobacter immobilis septicemia in a boy with X-linked chronic granulomatous disease and fulminant hepatic failure. J Clin Immunol 34:39–41

Székely A, Péter M, Erdös M, Marodi L (2012) Hepatic abscess as the single manifestation of X-linked chronic granulomatous disease. Pediatr Blood Cancer 58:828–829

Umei T, Takeshige K, Minakami S (1987) NADPH-binding component of the superoxide-generating oxidase in unstimulated neutrophils and the neutrophils from the patients with chronic granulomatous disease. Biochem J 243:467–472

Van de Vosse E, van Wengen A, van Geelen JA, de Boer M, Roos D, van Dissel JT (2009) A novel mutation in NCF1 in an adult CGD patient with a liver abscess as first presentation. J Hum Genet 54:313–316

Van den Berg JM, van Koppen E, Ahlin A, Belohradsky BH, Bernatowska E, Corbeel L et al (2009) Chronic granulomatous disease: the European experience. PLoS One 4:e5234

Vignais PV (2002) The superoxide-generating NADPH oxidase: structural aspects and activation mechanism. Cell Mol Life Sci 59:1428–1459

Winkelstein JA, Marino MC, Johnston RB, Boyle J, Curnutte J, Gallin JI, Malech HL et al (2000) Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 79:155–169

Part XXVII

Hepatobiliary Mass Lesions Caused by Fibrosclerotic Lesions

Tumor-Like Fibrosclerotic Lesions of the Hepatobiliary Tract

141

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_141

Abstract

A spectrum of idiopathic tumor-like fibrosclerotic lesions can involve the biliary tract and cause stenotic lesions. Idiopathic retroperitoneal fibrosis denotes a group of still not well-defined disorders that include Albarran-Ormond syndrome, chronic periaortitis, inflammatory aortic aneurysms, sclerosing mesenteritis, sclerosing mediastinitis, orbital pseudotumor, and Riedel's thyroiditis. The mass-producing effect of fibrosing processes taking place in the retroperitoneal space or the mesentery can encroach upon the extrahepatic biliary tree and result in biliary obstruction. A second group of conditions is summarized under the term IgG4-related sclerosing disease, characterized by infiltrations of IgG4-expressing plasma cells associated with a chronic fibrosclerosing process. In the hepatobiliary tract, these disorders mainly present as IgG4-related cholangitis, IgG4-realted pseudotumors, and bile duct alterations secondary to IgG4-related autoimmune pancreatitis.

Hepatobiliary Involvement in Idiopathic Retroperitoneal Fibrosis and Related Disorders

Introduction

Idiopathic retroperitoneal fibrosis (IRPF; Albarran-Ormond syndrome; Gerota syndrome; Ormond's disease; fibrous retroperitonitis) denotes a group of progressive fibrosclerotic disorders now characterized by the development of fibrosis in several tissue compartments, i.e., not only in the retroperitoneal space as was previously thought. The eponyms associated with idiopathic retroperitoneal fibrosis (Albarran-Ormond syndrome and Gerota syndrome or Gerota's fasciitis) are John Kelso Ormond (1886–1978), an American urologist; Joaquin Maria Albarran y Dominguez (1860–1912), a Cuban urologist; and Dimitrie D. Gerota (1867–1939), a Romanian anatomist and surgeon. Dr. Albarran y Dominguez studied histology with Louis-Antoine Ranvier (Ranvier's nodes), and together with Halle, he described the Bacillus pyogenes, later to be named Bacterium coli. In 1906 he became the chairman of the Clinic of Urology at the Paris Necker Hospital and described the periureteric lesions found in the syndrome in 1905 (Albarran 1905). Ormond also published his findings based on the ureteral involvement in the disease in question (Ormond 1948). He summarized the main features of the syndrome in 1965, naming the condition idiopathic retroperitoneal fibrosis (Ormond 1965). Dr. Gerota was, in addition to his function as a professor of surgical anatomy and experimental surgery, also a professor at the Art Academy of Bucharest and teacher to the well-known sculptor Constantin Brancusi. Together, they performed the famous carved muscles study known as The Ecorché (1905). Gerota's fascia is named after him. Since the first descriptions of the condition, it has been recognized that retroperitoneal fibrosis and its variants makes part of a group of what is now called fibroinflammatory disorders, comprising retroperitoneal fibrosis sensu strictiori, chronic periaortitis and part of inflammatory aortic aneurysms, sclerosing mediastinitis, sclerosing mesenteritis, orbital pseudotumor, and Riedel's thyroiditis (reviews: Dehner and Coffin 1998; Alberti 2007). Fibrotic processes in the retroperitoneal space and the aortic/periaortic compartment are now recognized to cover an entire spectrum of lesions (Bulkley 1960; Sethia and Darke 1983; Mitchinson 1984, 1986; Martina et al. 1993; Amiya et al. 2005; Table 1).

Table 1 Idiopathic retroperitoneal fibrosis (IRPF) and the spectrum of fibroinflammatory disorders

Idiopathic retroperitoneal fibrosis sensu strictiori (Albarran-Ormond syndrome)
Chronic periaortitis/perianeurysmal retroperitoneal fibrosis
Inflammatory aortic aneurysms
Sclerosing mesenteritis
Sclerosing mediastinitis
Orbital pseudotumor
Riedel's thyroiditis
Several lesions from the spectrum of systemic IgG4-related sclerosing disease

More recently, chronic periaortitis has been proposed to represent a term under which the several manifestations of the disease may be listed, including idiopathic retroperitoneal fibrosis (the previous Albarran-Ormond or Gerota syndromes), perianeurysmal retroperitoneal fibrosis, and inflammatory abdominal aortic aneurysm (Jois et al. 2004; Vaglio and Buzio 2005; Vaglio et al. 2006a, 2007).

Fibroinflammatory Disorders Are Often Manifestations of Systemic IgG4-Related Sclerosing Disease

The aetiology and pathogenesis of the retroperitoneal fibrosis complex are only partially clarified. It has been reported that asbestos exposure is a risk factor for idiopathic retroperitoneal fibrosis. In addition, an increasing number of studies showed an association between these fibrotic disorders and autoimmune processes (Vaglio et al. 2003, 2006b). At least part of these conditions are pathogenetically related to an entity termed, IgG4-related autoimmune disease (IgG4-associated multifocal systemic fibrosclerosis; IgG4-related sclerosing disease; systemic IgG4-related plasmacytic syndrome, SIPS; Hyper-IgG4 disease; Neild et al. 2006). In this disorder, a moderate to marked infiltration of IgG4-positive plasma cells together with CD4- and/or CD8-positive T lymphocytes is noted in the target tissues, including peripancreatic, retroperitoneal, lung, salivary gland, and large bile duct tissues (-Kamisawa et al. 2003a; Hamed et al. 2007). Retroperitoneal fibrosis and chronic periaortitis develop in conjunction with the IgG4-related autoimmune disease (Yamashita et al. 2008), and a subset of inflammatory abdominal aortic aneurysms has a close relationship to IgG4-related periaortitis (Kasashima et al. 2008; Matsumoto et al. 2008; Sakata et al. 2008).

Pathology

The macroscopic presentation of retroperitoneal fibrosis is most frequently that of a firm or rubbery, unencapsulated fibrous plaque or flat mass of gray to whitish color, this mat with indistinct borders being sometimes several centimeters thick, firmly adherent to the posterior peritoneum and displacing it anteriorly. The main portion of the plaque is commonly at the level of the sacral promontorium, with variable extension upward and to the sides. Typically, the process envelopes the retroperitoneal structures, in particular the large- and medium-sized vessels and the ureters, but it may also involve the extrahepatic bile ducts.

Histologically, the tissue shows a chronic inflammation with lymphocytes, macrophages, and plasma cell infiltrates of variable density associated with fibrosis, which is cellular in early or active phases and later becomes hypocellular and sclerotic. The lymphocytic infiltrates are chiefly located around blood vessels, often with central core of CD20-positive B cells and a peripheral zone of CD3-positive T cells. Generally, T cells predominate in diffuse lymphocyte infiltrates (Corradi et al. 2007). Eosinophil and neutrophil granulocytes are present in variable numbers. In some phase of the disease, macrophages (in part foamy cells) predominate (Hughes and Buckley 1993). In the setting of adipose tissue invasion/replacement by the fibrotic process, lipogranulomas can develop. In cases associated with IgG4-related multifocal fibrosclerosis, many of the plasma cells are IgG4 positive and usually occur together with T lymphocytes, both CD4- and CD8-positive. In regard to mesenchymal cells found in the lesions of the disease spectrum, it has been suggested that myofibroblasts are involved in the development of inflammatory aortic aneurysm (Sakata et al. 2007).

Bile Duct Involvement in Idiopathic Retroperitoneal Fibrosis

The mass-producing process of IRPF can encroach upon the extrahepatic biliary system and sometimes mimic bile duct cancer. In the course of anterior extension of fibrosclerosis, it can involve the tissue of the hepatoduodenal ligament, the peripancreatic tissue, and tissues of the hepatic hilum, thus causing encasement and stenosis of extrahepatic bile ducts and leading to biliary obstruction with jaundice.

Selected References Hardy (1962), Schneider (1964), Renner et al. (1980), Lundström (1983), Wetter et al. (1991), Laitt et al. (1992), Cappell (1994), Chutaputti et al. (1995), Pereira-Lima et al. (1996), Dejaco et al. (1999), Lechiche et al. (2001), Tamura et al. (2003), Zhao et al. (2004), Fukui et al. (2005), Kamisawa et al. (2006a), Matsushita et al. (2009), and Quante et al. (2006).

The necropsy case of Schneider (1964) showed a plaque-like mass which completely surrounded several large retroperitoneal vessels, both ureters, body and head of the pancreas, the retroperitoneal part of the duodenum, and the distal end of the common bile duct. The liver was described as green owing to biliary obstruction. The 46-year-old male patient described by Dejaco et al. (1999) was presented with jaundice, and ultrasonography revealed a solid tumor in the porta hepatis about 2 cm in diameter and dilated intrahepatic bile ducts. Subsequent ERCP demonstrated a stenosis of the common bile duct, and a presumptive diagnosis of Klatskin tumor was made. Resection of the lesion histologically showed a manifestation of Ormond's disease, with chronic inflammatory and fibrotic fatty tissue surrounding a narrowed bile duct. Quante et al. (2006) described involvement of the hepatic ducts by the fibrotic process, causing a duct stricture suggesting malignancy. Extrahepatic bile duct stenosis caused by retroperitoneal fibrosis may thus mimic sclerosing cholangiocarcinoma (Klatskin tumor; Wetter et al. 1991; Dejaco et al. 1999). Apart from large bile ducts, extending retroperitoneal fibrosis may also compromise the venous inflow tract of the liver, causing portal hypertension and hypoplasia (or rather atrophy) of a liver lobe (Hisatomi et al. 2004).

IRPF can involve the pancreas and the peripancreatic tissues and subsequently the distal-most part of the common bile duct, causing biliary obstruction (Cappell 1994). In some cases, IRPF encased the pancreatic head, with formation of firm and grayish-white tissue that compressed the distal bile duct, or with generation of a fibrous pseudotumor (Chutaputti et al. 1995; Zhao et al. 2004). Apart from autoimmune pancreatitis, autoimmune disorders of bile ducts, in part related to IgG4 disease, occur in the setting of IRPF. The process can be associated with primary biliary cirrhosis (Sevenet et al. 1985), primary sclerosing cholangitis (Hellstrom and Perez-Stable 1966; Laitt et al. 1992; De Suray et al. 2009), and hepatobiliary inflammatory pseudotumors (De Suray et al. 2009). Also IRPF with concomitant autoimmune pancreatitis has been found to be associated with sclerosing cholangitis (Alpert and Jindrak 1972; Fukui et al. 2005).

Chronic periaortitis (or perianeurysmal retroperitoneal fibrosis) has been observed to sometimes be complicated by common bile duct obstruction (Quante et al. 1991; Remedios et al. 1991). In the 67-year-old female patient reported by Remedios and coworkers, an inflammatory abdominal aortic aneurysm with surrounding retroperitoneal fibrosis was resected. The patient died of a ruptured perinephric abscess, and autopsy revealed a firm 4 cm mass in the pancreatic head severely constricting the pancreatic duct and infiltrating part of the wall of the common bile duct adjacent to the ampulla. Histology of the mass showed extensive dense fibrosis in the peripancreatic tissue adjacent to the site of the previously resected inflammatory aneurysm (Remedios et al. 1991).

Bile Duct Disease in Sclerosing Mesenteritis

Sclerosing mesenteritis has rarely been found to be associated with an idiopathic form of stenosing bile duct fibrosis closely mimicking hilar/perihilar cholangiocarcinoma (Klatskin tumor; Medina-Franco et al. 2001). In this 64-year-old jaundiced male patient, abdominal ultrasound showed intrahepatic biliary dilatation without extrahepatic dilatation. ERCP demonstrated a hilar stricture compatible with Klatskin tumor. Dynamic contrast-enhanced helical CT scans revealed focal thickening of extrahepatic bile ducts as well as an infiltrative mass measuring 8.4 × 4.6 cm in the root of the mesentery. Laparotomy showed a dense infiltration in the proximal mesentery, extending to the hepatic hilar region. Histologically, the mesenteric lesion was sclerosing

mesenteritis, and the bile duct was extensively encased by this inflamed sclerotic tissue.

What Is Sclerosing Mesenteritis?

Sclerosing mesenteritis (SCM), first described in 1924 (Jura 1924), is known in the literature under several other terms, including retractile mesenteritis, fibrosing mesenteritis, liposclerotic mesenteritis, xanthogranulomatous mesenteritis, mesenteric lipodystrophy, mesenteric lipogranuloma, and mesenteric panniculitis (Panniculitis mesenterialis). Jura (1924) already employed the term, retractile and sclerosing mesenteritis (in the Italian publication: mesenterite retrattile e sclerosante). These different terms have caused considerable confusion, but they are currently thought to reflect different evolution phases and/or severity grades of the same disease process (Durst et al. 1977; Ghosh and Kum 2007). It is a chronic inflammatory process of unknown aetiology, located to the mesenteric adipose tissue (more frequently involving the small bowel meso than the colonic meso; in the small bowel mesenterium chiefly the mesenteric root), with a tendency to progress to extensive lipofibrosis or liposclerosis. The disease rarely involves the peripancreatic tissue, the omentum, or the pelvic adipose tissue. The disease may occur in conjunction with retroperitoneal fibrosis, which in this disease most probably reflects an extension of the disease from the mesenteric root to the retroperitoneal space (Sabaté et al. 1999). Peripancreatic involvement may cause the clinical presentation of pancreatic pseudotumor (Sheikh et al. 1999). That SCM may belong to the spectrum of multiorgan fibrosclerosing disorders is supported by the observation that SCM occurs in conjunction with idiopathic orbital inflammation (Sharma et al. 2006). The incidence of the disorder is not known, but postmortem studies have reported an incidence of up to 1 % (Streuli and Stamm 1994). The peak incidence is in the sixth to seventh decades, and males are more frequently affected than females (2:1). Patients usually present with abdominal discomfort or pain, nausea, weight loss, and, less commonly, fever of unknown origin. Probably caused by remodeling of the mesenteric lymph vessels by the inflammatory process, multiple mesenteric lymphatic cysts (Johnson et al. 1997) and/or chylous ascites may develop (Ehrenpreis et al. 2008). SCM may produce tumor-like mesenteric lesions; a palpable mass has been reported to be found in 50 % of the patients. The etiology and pathogenesis of SCM remain unclear. Potential causes that have been discussed include autoimmune causes, infections, and vascular disorders.

Idiopathic Sclerosing Peritonitis

Idiopathic sclerosing (encapsulating) peritonitis (idiopathic encapsulating peritonitis; abdominal cocoon syndrome) is a rare condition characterized by intraperitoneal fibrosclerosis, mainly reported in young adolescent women as a cause of small bowel obstruction. In this disorder, which can be associated with ascites, the small bowel is encased in an encapsulating fibrous sac or saclike membrane termed abdominal cocoon (Masuda et al. 1993). The firm nacreous fibrotic membrane may wrap the intestine in a concertina-like fashion (Da Luz et al. 2011). Apart from the idiopathic form, secondary sclerosing peritonitis occurs to be caused by intraperitoneal chemotherapy, peritoneal dialysis, practolol therapy, meconium peritonitis, tuberculous peritonitis, or the positioning of a peritoneal-jugular shunt in cirrhotic patients with refractory ascites (reviews: Cleffken et al. 2008; Minutolo et al. 2008). The idiopathic form, which is the main cause of abdominal cocoon, was first described in 1978 based on observation on ten girls with a narrow age range of 13–18 years (Foo et al. 1978). As the fibrous cocoon is associated with extensive adhesions, it may be expected that the structure of the hepatoduodenal ligament can be compromised.

Segmental Pericholangial Fibrosis

This is a rare benign fibrotic disorder observed in a child who underwent surgery to remove a hepatic hilar mass suspected to be malignant. It represents a fibrous disorder of unknown etiology located to the bifurcation of the hepatic duct, where the bile

duct wall and the surrounding tissue were markedly fibrotic. Histologically the resected lesion was characterized by a loose connective tissue containing myofibroblasts and chronic inflammatory cells, while more advanced fibrosis was noted in the adjacent soft tissues (Takabe et al. 1997). The potential relationship of this disorder to the spectrum of IRPF is currently unknown.

Fibrosing Thyroid Disease and Sclerosing Cholangitis

Riedel's thyroiditis, an IgG4-related disorder with or without associated multisystemic sclerosis (Dahlgren et al. 2010), may be combined with sclerosing cholangitis (Bartholomew et al. 1963; Brihaye et al. 2008).

IgG4-Related Disease of the Hepatobiliary Tract

Introduction

IgG4-related disease (synonyms: IgG4-related systemic disease; IgG4 syndrome; IgG4-related sclerosing disease; IgG4-reated systemic sclerosing disease; multifocal fibrosclerosis) is a systemic disorder that is characterized by extensive IgG4-positive plasma cells and T-lymphocyte infiltration of various organs, followed by a variable fibrosing process and obliterative phlebitis of the target tissues (reviews: Bateman and Deheragoda 2009; Cheuk and Chan 2010; Okazaki et al. 2010; Sato et al. 2010; Takahashi et al. 2010; Khosroshahi and Stone 2011a, b; Smyrk 2011; Zen and Nakanuma 2011; Carruthers et al. 2012; Divatia et al. 2012; Stone 2013; Mahajan et al. 2014). The disease was first identified based on the observation that patients with sclerosing pancreatitis (now autoimmune pancreatitis) have high serum IgG4 concentrations (Hamano et al. 2001) and that autoimmune pancreatitis is characterized by the presence of numerous IgG4+ plasma cells (Hamano et al. 2002). Clinical manifestations mainly involve the pancreas, the biliary tract, and the salivary glands, but also the retroperitoneal tissues, kidney, lung, prostate, and numerous other organs and tissues (review: Kamisawa and Okamoto 2008). The disorder has also been termed multifocal idiopathic fibrosclerosis, IgG4-related sclerosing disease, IgG4-related systemic disease, IgG4-related autoimmune disease, IgG4-related syndrome, IgG4-related plasmacytic syndrome (SIPS), and IgG4-related multiorgan lymphoproliferative syndrome. Also the term, hyper-IgG4 disease, has been proposed (Neild et al. 2006). The Japanese Research Committee for Systemic IgG4-related Sclerosing Disease appointed the term, IgG4-related disease, as a minimal consensus to all conditions of the disorder (review: Okazaki et al. 2010). The disorder is usually associated with an elevation of serum IgG4 levels, and the serial measurement of these levels is useful to determine the disease activity (Tabata et al. 2011). IgG4-related disease manifesting in the biliary tract is typically associated with stenosing duct lesions that mimic malignancy. On the other hand, IgG4-related disease of the pancreas and bile ducts cause significant morbidity, organ dysfunction, and malignancy (Huggett et al. 2014). The clinical entities associated with this disease are numerous, and a selection is shown in the Table 2. In all of these disease entities, the presence of IgG4-containing plasma cells in the lesions is a characteristic and diagnostically significant feature (Deheragoda et al. 2007).

Selected References Saeki et al. (2006), Tanabe et al. (2006), Chen and Montgomery (2008), Ito et al. (2008), Miwa et al. (2008), Takato et al. (2008), Kamisawa et al. (2003a, 2006a,b), Neild et al. (2006), Ohara et al. (2007), Kamisawa and Okamoto (2008), Zen and Nakanuma (2010), Khosroshahi and Stone (2011a,b), and Smyrk (2011).

IgG4-Associated Sclerosing Cholangitis

Sclerosing cholangitis (SC) is a heterogeneous disease entity with different etiologies and pathogenic pathways. The spectrum of SC chiefly

Table 2 Selection of reported organ manifestations of IgG4-related disease

Central nervous system
Sclerosing pachymeningitis
Pseudotumoral hypophysitis
Head and neck region
IgG4-related orbital inflammatory disease
IgG4-related scleritis
Sialadenitis (sometimes with Küttner tumor)
Sclerosing dacryoadenitis
IgG4-related Mikulicz's disease
Chronic rhinosinusitis
Thoracic organs
IgG4-related thyroiditis
IgG4-related esophagitis
Mediastinal fibrosis
Interstitial pneumonia (IgG4-positive pulmonary disease)
Cardiovascular system
Thoracic inflammatory aortic disease
Inflammatory aortic aneurysm
IgG4-related arteritis and periarteritis
IgG4-related pericarditis
Abdominal organs
IgG4-related autoimmune pancreatitis
IgG4-related cholangitis/cholangiopathy
IgG4-related hepatobiliary pseudotumors
Sclerosing mesenteritis
IgG4-related inflammatory bowel disease
Retroperitoneal space
Retroperitoneal fibrosis
Genitourinary tract
Tubulointerstitial nephritis
Ureteral inflammatory pseudotumor
IgG4-related epididymo-orchitis
IgG4-related prostatitis
Skin and associated structures
IgG4-related skin diseases
IgG4-related mastitis
Skeletal-articular system
IgG4-related arthritis
Peripheral nervous system
Perineural IgG4(+) plasma cell infiltration
Lymphoreticular system
IgG4-related lymphadenopathy

comprises primary sclerosing cholangitis (PSC), autoimmune-related SC, and secondary sclerosing cholangitis (SSC) caused by stenosing lesions of the biliary tract. One subset of autoimmune-related SC is associated with or caused by IgG4-related disease, with or without other manifestations of this disorder (IgG4-SC; Hamano et al. 2005; Hamed et al. 2007; Hayashi et al. 2007; Nakanuma and Zen 2007; Cheung and Lo 2008; Erdogan et al. 2008; Alderlieste et al. 2009; Fujita et al. 2010; Mizutani et al. 2012; Naitoh et al. 2012; Nakazawa et al. 2012, 2013; Novotny et al. 2012; Nowatari et al. 2012; Boonstra et al. 2014; Saito et al. 2013; Silveira 2013; Graham et al. 2014; Joshi and Webster 2014; Okazaki et al. 2014). The diagnostic criteria for this distinct type of cholangiopathy have recently been reviewed (Ohara et al. 2012). IgG4-SC typically affects patients 60–80 years old, 80–85 % being male, and usually manifests as obstructive jaundice and organ swelling mimicking cancer (Beuers et al. 2014). This type of SC is mostly found in conjunction with autoimmune pancreatitis (AIP) discussed in the following paragraph and may be associated with other IgG4-related disorders, such as retroperitoneal fibrosis and sclerosing sialadenitis (Hamed et al. 2007). IgG4-related SC without pancreatic manifestations is rare. Even less common are types of autoimmune but non-AIP-related SC without elevation of serum IgG4 (Sawai et al. 2011). IgG4-SC can clinically and radiologically mimic hilar cholangiocarcinoma/Klatskin tumor (Hamano et al. 2005; Cheung and Lo 2008; Nguyen-tat et al. 2012; Tabata et al. 2013) or other cholangiocarcinomas (Lytras et al. 2012; Maeda and Shimada 2012) and, in case of lesions in the distal common bile duct, resemble ampullary cancer (Aomatsu et al. 2012). Intrahepatic IgG4-related SC can result in sepsis caused by secondary suppurative cholangitis and can sometimes result in recurrent liver failure (Clendenon et al. 2011). The disorder is sometimes associated with hepatic inflammatory pseudotumors (Zen et al. 2004). IgG4-SC may show similar manifestations as eosinophilic cholangitis (Iwamuro et al. 2009). The disorder can be associated with other lesions found in IgG4-related sclerosing disease, such as autoimmune pancreatitis/AIP (discussed in the following paragraph), retroperitoneal fibrosis, and sclerosing sialadenitis (Hamed et al. 2007). IgG4-related SC has been observed together with

retroperitoneal fibrosis in the absence of AIP (Miura and Miyachi 2009; Rompa et al. 2010). Similar to type 1 autoimmune pancreatitis, IgG4-SC is associated with significant morbidity and mortality due to malignancy and organ failure involving the liver, kidney, and brain. In one study, malignancy occurred in 11 % shortly before or after the diagnosis of IgG4-related disease, with development of pancreatobiliary cancers (Huggett et al. 2014).

IgG4-SC presents with a characteristic pathology. Similar to PSC, bile ducts show a chronic fibrosclerosing process that results in marked stenosis of the involved parts. In the patients reported by Hamano and coworkers (Hamano et al. 2005), ERCP showed long-segment, smooth narrowing of the common bile duct, and in one case MRI revealed a mass-like lesion around the common bile duct that involved the portal vein. In contrast to PSC, where cellular infiltrates in the florid inflammatory phase are mainly lymphocytes, IgG4-SC shows IgG4-expressing plasma cells at high density, typically >50 IgG4-positive cells per high-powered field. In part of patients, dense infiltrates of IgG4-positive plasma cells were noted in portal tracts and associated with destructive cholangitis, suggesting an overlap between IgG4-SC and primary biliary cirrhosis (Takemoto et al. 2014). The presence of high-density infiltrates of IgG4-positve plasma cells in hilar areas of liver explants from patients with PSC was significantly associated with dominant biliary strictures and need for biliary stenting (Fischer et al. 2014), suggesting a causal relationship between IgG4(+) plasma cells and the pathogenesis of marked fibrosclerosing biliary changes.

IgG4-Related Sclerosing Cholangitis in Autoimmune Pancreatitis (AIP-Associated Sclerosing Cholangitis)

Autoimmune pancreatitis (AIP) is one of the chief manifestations of IgG4-related sclerosing disease (Kamisawa et al. 2003b; Kojima et al. 2007; Blejter et al. 2008; Okazaki et al. 2008; Smyrk 2011). AIP has been reported in 1961 as a peculiar type of pancreatitis associated with hypergammaglobulinemia (Sarles et al. 1961) and described in more detail in 1995 (Yoshida et al. 1995), and consensus diagnostic criteria for AIP have since been worked out (Asian Diagnostic Criteria, Japan-Korea Consensus: Otsuki et al. 2008; Mayo Clinic Diagnostic Criteria/HISORt Criteria: Chari et al. 2006; International Consensus Diagnostic criteria: Shimosegawa et al. 2011). AIP occurs in two histologic variants, i.e., lymphoplasmacytic sclerosing pancreatitis (LPSP; type 1 AIP, associated with elevated serum IgG4) and idiopathic duct-centric pancreatitis (IDCP; type 2 AIP) or granulocytic epithelial lesion-positive pancreatitis (Honolulu Consensus Document; Chari et al. 2011). In contrast to type 1 AIP, type 2 AIP seems to be confined to the pancreas (Deshpande et al. 2011). AIP was localized to the pancreatic head in 94 % of cases, with possible extension into the periphery of the gland and/or into the biliary tract (Esposito et al, 2008). It has later been found that AIP is closely related to the HLA DRB1*0405-DQB1*0401 haplotype (Kawa et al. 2002) and associated with inflammatory infiltrates rich in IgG4-containing plasma cells and that it is accompanied by elevated serum IgG4 levels (Hamano et al. 2001; Sadler et al. 2011). Immunohistochemically, deposition of IgG4 together with IgG and complement C3s has been detected at the basement membrane of pancreatic ducts and acini in AIP (Detlefsen et al. 2010). AIP can cause plasma cell-rich sclerosing mass lesions (pseudotumors) that may closely mimic pancreatic malignancy (Kajiwara et al. 2008).

AIP has been observed in association with several forms of IgG4-related sclerosing disease (reviews: Hirano et al. 2004; Kamisawa et al. 2010; Zhang and Smyrk 2010) and in particular with bile duct lesions mimicking primary sclerosing cholangitis (IgG4-associated cholangitis, see above; review: Björnsson et al. 2007), primary biliary cirrhosis, and Sjögren syndrome (Takuma et al. 2011). In 1963, two cases of PSC with pancreatic involvement seen at the Mayo Clinic were reported, and these cases may represent the first published examples of SC associated with AIP (Bartholomew et al. 1963). Sclerosing cholangitis can in fact develop subsequent to chronic

pancreatitis associated with Sjögren syndrome (Montefusco et al. 1984; Versapuech et al. 1986) and with AIP proper (Erkelens et al. 1999; Nakazawa et al. 2001, 2005; Horiuchi et al. 2002; Kuroiwa et al. 2002; Hirano et al. 2003; Pickartz et al. 2004; Prasad et al. 2004; Nishino et al. 2005, 2007; Kawa et al. 2007; Beristain et al. 2008; Esposito et al. 2008; Ong et al. 2011). In patients with this constellation, serum IgG4 levels are significantly higher than those in patients with primary sclerosing cholangitis (Hirano et al. 2006; Nishino et al. 2007; Hochwald et al. 2008), and the disease in these patients does not show an association with inflammatory bowel disease (Nakazawa et al. 2005). In one study, intra- and/or extrahepatic biliary tract involvement in AIH was 64 % (Esposito et al. 2008), and in another investigation on 16 patients with AIP, stricture of the extrahepatic bile duct was detected in 88 % and duct wall thickening in 94 % of the patients (Nishino et al. 2005). The overall rate of extrahepatic bile duct involvement in AIP is around 70 % (Zhang and Smyrk 2010). Sclerosing cholangitis associated with AIP seems to be a distinct disease that differs from classical primary sclerosing cholangitis (PSC), although there is some overlap (Webster et al. 2009). This has led to the concept of "AIP-associated sclerosing cholangitis" (AIP-SC; Uehara et al. 2005). The mean age at presentation was significantly higher in AIP associated with bile duct disease than in PSC (Kim et al. 2006). Radiologically, the extrahepatic duct was involved in AIP-SC, while both extrahepatic and intrahepatic bile ducts were involved in PSC. Cholangiography can discriminate PSC from AIP-SC, in that band-like stricture, beaded or pruned-tree appearance and diverticulum-like formation were significantly more frequent in PSC, and segmental stricture, long stricture with prestenotic dilatation, and stricture of the distal common bile duct were more common in AIP-SC (Nakazawa et al. 2004). These authors therefore classified cholangiograms of IgG4-related SC into four types. Stenosis with type 1 is located only in the lower part of the common bile duct; stenosis type 2 is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts; type 3 stenosis occurs in both the hilar hepatic region and the lower part of the common bile duct; and type 4 stenosis is detected only in the hilar region.

The clinical, radiological, and pathological features of IgG4-related SC and PSC are different (Zen et al. 2004; Nakanuma and Zen 2007; Deshpande et al. 2009; Cheuk and Chan 2010; Smyrk 2011). IgG4-related sclerosing cholangitis has a more marked male preponderance, involves middle-aged to elderly individuals (PSC: more commonly young adults), and often presents with obstructive jaundice. IgG4 cholangiopathy is histologically characterized by an inflammation with infiltrates showing a transmural and homogeneous distribution within the bile duct wall, whereas inflammatory changes in PSC tend to involve the inner parts of the duct wall. In contrast to PSC, erosive or ulcerous lesions, and onion-skin-type concentric periductal fibrosis, and/or xanthomatous changes are not features of AIP-SC. The diffuse transmural lymphoplasmacytic infiltration in AIP-SC is associated with marked interstitial fibrosis with a focal storiform pattern (similar to that seen in AIP) and occasional obliterative phlebitis. The biliary epithelium is usually spared of injury. Immunohistochemically, IgG4-containing plasma cells are frequent in the infiltrates of AIP-SC (Nishino et al. 2005; Nakanuma and Zen 2007; Ghazale et al. 2008; Naitoh et al. 2009) and can be assessed in biopsies from Vater's ampulla and the common bile duct (Kawakami et al. 2010), and the IgG4-positive plasma cell/mononuclear cell ratio was significantly higher in AIP-SC than in PSC (Uehara et al. 2005). Patients with AIP-SC have significantly higher numbers of IgG4+ plasma cells in ampullary biopsies than patients with PSC and pancreatobiliary carcinomas. In one study, 18 out of 27 patients (67 %) with AIP had more than 10 IgG4+ plasma cells in their ampullary biopsies (Kubota et al. 2008). PSC occurs in younger and AIP-SC in older patients, obstructive jaundice is more often found in AIP-SC, and whereas PSC is associated with inflammatory bowel disease, AIP-SC is associated with extrapancreatic manifestations of AIP (Kawa et al. 2007). AIP-SC may cause stenosing lesions closing mimicking hilar sclerosing carcinoma/Klatskin tumor (Cheung and Lo 2008). Sclerosing cholangitis may

develop in patients having developed a AIP-related pancreatic pseudotumor (Toosi and Heathcote 2004). Rarely, IgG4-negative sclerosing cholangitis is associated with AIP (Sewkani et al. 2005).

Primary Sclerosing Cholangitis Mimicking IgG4-Related Disease

Zen and coworkers described two patients of PSC associated with ulcerative colitis and typical bile duct histology, including duct erosion and xanthogranulomatous reaction, having undergone liver transplantation. The explants showed marked infiltration of IgG4-positive plasma cells, mainly in duct-associated xanthogranulomatous tissue, in the absence of typical features of IgG4-related SC (Zen et al. 2011).

Small Bile Duct Involvement in IgG4-Related Sclerosing Cholangitis

This disorder has been defined as damage of small intrahepatic bile ducts associated with infiltration of >/= 10 IgG4+ plasma cells per HPF and has been observed in 5 out of 22 (26 %) patients with IgG4-related disease. Patients with small duct involvement showed a higher incidence of intrahepatic bile duct strictures on cholangiography. Conversely, 57 % of patients with intrahepatic bile duct strictures on cholangiography had histologically evident small duct involvement. The number of IgG4+ plasma cells was correlated with the site of the most proximal stricture (Naitoh et al. 2011).

IgG4 Hepatopathy and IgG4-Related Hepatitis

IgG4 hepatopathy is a recently described disorder which presents with five histologic patterns: (1) evident portal tract inflammation with or without interface hepatitis, (2) large bile duct obstructive features, (3) portal sclerosis, (4) lobular hepatitis, and (5) canalicular cholestasis (Umemura et al. 2007). A subset of patients with interface hepatitis showing the features of autoimmune hepatitis (AIH) reveal high densities of IgG4+ plasma cells in the cellular infiltrates (IgG4-associated autoimmune hepatitis). This type of AIH was identified in 2007 (Umemura et al. 2007) in one patient showing an International Autoimmune Hepatitis Group (IAIHG) score of 18 and a high serum IgG4 concentration and was later confirmed in other patients (Chung et al. 2010; Castillo-Rama et al al. 2013; Yada et al. 2013) and found in over 3 % of Japanese patients with type 1 AIH (Umemura et al. 2011).

Hepatobiliary Pseudotumors in IgG4-Related Sclerosing Disease

Inflammatory pseudotumors developing in association with IgG4-related disease usually show histologic features that resemble those of ALK rearrangement-positive inflammatory myofibroblastic tumors (IMTs). Inflammatory pseudotumors occurring in patients with IgG4-related disease contain numerous IgG4-positive plasma cells, albeit there is considerable histologic overlap between these two lesion groups. It has been demonstrated that a subset of IMT exhibits an IgG4/IgG ratio that is within the range for IgG4-related sclerosing disease, a feature that is useful for the distinction of two types of IMT (Saab et al. 2011).

Hepatobiliary pseudotumors with high IgG4 plasmocyte cellularity have been observed by several authors, sometimes, but not always, in association with autoimmune pancreatitis/AIP (Sato et al. 2004; Kanno et al. 2005; Sasahira et al. 2005; Martin Malagon et al. 2006; Uchida et al. 2007; de Suray et al. 2009; Kim et al. 2011; Ahn et al. 2012; Hastir et al. 2014). In the case reported by Martin Malagon et al. (2006), a lesion of the inflammatory myofibroblastic tumor type was located in the distal common bile duct of a 51-year-old female patient suffering from lymphoplasmacytic sclerosing pancreatitis. In AIP, pseudotumoral masses have been observed synchronously in the pancreas and the gallbladder (Gumbs et al. 2005). In

another patient with AIP, multiple inflammatory pseudotumors were detected in the liver, associated with peripheral eosinophilia (Sasahira et al. 2005). Hepatic inflammatory pseudotumor may, apart from AIP, synchronously occur with other manifestations, including sclerosing cholangitis, retroperitoneal fibrosis, and sialadenitis (de Suray et al. 2009). Intrahepatic IgG4-related pseudotumor can clinically and radiologically mimic hepatocellular carcinoma (Hastir et al. 2014). Zen and coworkers (Zen et al. 2007) defined two types of hepatic inflammatory pseudotumors, fibrohistiocytic and lymphoplasmacytic. The lymphoplasmacytic type is histologically characterized by diffuse inflammatory cell infiltration, mainly by lymphocytes and plasma cells. The inflammatory cells may infiltrate perineural spaces. Parts of these pseudotumors reveal a significant eosinophil infiltration. Obliterative phlebitis with or without recanalization may be present. IgG4+ plasma cells were significantly more frequent in the lymphoplasmacytic variant. Some areas of pseudotumors display entrapped small bile ducts.

IgG4-Associated Ampullitis

In rare cases, ampullitis is characterized by an infiltrate showing numerous IgG4-positive plasma cells. This disorder was also observed in patients with inflammatory bowel disease, including Crohn's disease (Navaneethan et al. 2011). On the other hand, plasma cells can be increased in ampullary tissue due to extension of IgG4-related autoimmune pancreatitis into the ampullary region (Kawakami and Zen 2010).

Sclerosing Cholecystitis in Autoimmune Pancreatitis

Sclerosing cholecystitis is now well recognized to occur in association with IgG4-related disease (IgG4-related cholecystitis; Abraham et al. 2003; Fukui et al. 2005; Nishino et al. 2005; Kamisawa et al. 2006c; Wang et al. 2009; Leise et al. 2011; Lee et al. 2013; Feely et al. 2014). Thickening of the gallbladder wall was detected on ultrasonography and/or CT in 32 % of AIP patients (Kamisawa and Okamoto 2008) and in another study in 56 % (Nishino et al. 2005). In a study of gallbladders obtained from patients with lymphoplasmacytic sclerosing pancreatitis, 60 % of the gallbladders contained moderate or marked inflammatory infiltrates and lymphoid nodules, and gallbladders from these pancreatitis patients received the highest scores for deep inflammation of all groups compared (Abraham et al. 2003). IgG4-related sclerosing cholecystitis is most common in patients having AIP with extensive bile duct disease and where stenosis of the extrahepatic bile duct is frequent (Kamisawa et al. 2006c). Histologically, fibrosis/sclerosis is associated with a mucosal or transmural lymphoplasmacytic infiltration, the plasma cells containing IgG4 (Kamisawa et al. 2006c). In case of diffuse and marked plasmacytic inflammatory infiltration of the gallbladder wall, the lesion can mimic gallbladder cancer (Lee et al. 2013; Shin et al. 2013).

Locoregional Lymphadenopathy in IgG4-Associated Sclerosing Disease of the Hepatobiliary Tract (IgG4 Lymphadenopathy)

Lymph nodes draining IgG4-associated sclerosing cholangitis and pancreatitis are often enlarged, because the immune reaction driving the disease causes a marked expansion of the nodal cell populations involved and particularly lymphoblasts and IgG4-expressing plasma cells. In such lymph nodes, three histological patterns have been identified, i.e., interfollicular expansion by immunoblasts and plasma cells, follicular and germinal center hyperplasia, and Castleman-like alterations (Cheuk et al. 2008; Shimizu et al. 2010). Some patients with IgG4-related disease may develop generalized lymphadenopathy, sometimes with a histology mimicking multicentric Castleman's disease (Kamisawa et al. 2006a; Sato et al. 2009; Takenaka et al. 2011; review: Sato et al. 2010).

Malignancy Associated with IgG4-Related Sclerosing Disease

Generally, the incidence of total malignancies in patients with IgG4-related disease seems to not be different from control populations (Hirano et al. 2014), but certain neoplasms have been found in association with this disorder. Mucosa-associated lymphoid tissue lymphoma may arise from ocular adnexal IgG4-related disease and IgG4-producing lymphomas exist (review: Sato et al. 2010). In a study on 111 patients with IgG4-related disease with or without AIP and 331 patient-years of observation, 3 patients developed non-Hodgkin lymphoma 3–5 years after the diagnosis of IgG4-related disease. One of the patients showed lymphoma involvement of the liver (Takahashi et al. 2009). Peripheral T-cell lymphoma has been reported in a patient with IgG4-related disease (Kanda et al. 2011). Marginal zone lymphoma involving the meningeal dura has been observed in IgG4-related disease (Venkataraman et al. 2011). Several cases of ductal adenocarcinoma of the pancreas have been reported in association with IgG4-related AIP, and IgG4-related disease can rarely be complicated by cholangiocarcinoma (Douhara et al. 2013).

Differential Diagnosis

It has to be emphasized that IgG4-containing plasma cells may be observed in a wide array of immune reactions and inflammatory responses, in the absence of other features of IgG4-related disease (Strehl et al. 2011). IgG4-positive plasma cells were also found in peritumoral tissue of patients with hilar cholangiocarcinoma, other cholangiocarcinomas, and gallbladder carcinoma (Resheq et al. 2013; Harada and Nakanuma 2014), suggesting that cholangiocarcinoma cells in their function as nonprofessional antigen-presenting cells may indirectly induce an IgG4 reaction via an Il-10-mediated pathway (Harada and Nakanuma 2014). Interestingly, IgG4-positive plasma cells are also encountered in inflammatory myofibroblastic tumor, a rare mesenchymal neoplasm having an anaplastic lymphoma kinase (ALK) rearrangement in the majority of cases and histologically resembling IgG4-related reactive inflammatory pseudotumor (Saab et al. 2011), eventually suggesting a pathogenic link. Increased numbers of IgG4(+) plasma cells were observed in a subset of Rosai-Dorfman disease cases (Menon et al. 2014). There is one report describing an inflammatory angiomyolipoma of the liver showing dense infiltrates of IgG4-positive plasma cells (Agaimy and Märkl 2013).

Pathogenic Pathways

IgG4 has distinct functional properties (review: Nirula et al. 2011). IgG4 is known to be capable to undergo what is called half-antibody exchange in vivo and what causes the generation of recombined antibodies composed of two different binding specificities. The regulation of IgG4 synthesis in plasma cells is not fully understood but seems to depend on an aberrant acquired immunity based on T2-dominated immune responses. IgG4 production is partially driven by T helper 2 cytokines mediating allergic responses and IgE synthesis. In tissues affected by IgG4-related disease, mast cells are a source of T helper 2 and regulatory T-cell cytokines and are therefore suggested to play a role in pathogenic pathways of this disease (Takeuchi et al. 2014). Increased T-helper 2 cytokines produced in IgG4-related cholangitis disrupted the tight-junction-associated biliary epithelial cell barrier, the subsequent biliary leaks considered to contribute to the pathogenesis of chronic bile duct inflammation (Müller et al. 2013). It has been found that interleukin-13 is a T cell-derived cytokine that efficiently directs naïve human B cells to switch to IgG4 and IgE production (Punnonen et al. 1993). Observations in polyclonal IgG4 hypergammaglobulinemia have, however, shown that stimulation of IgG4 synthesis by plasmacytoid cells may be mediated by soluble T cell factors other than IL-13 (Boulanger et al. 2006). In IgG4-related sclerosing cholangitis, there is evidence that the chemotactic factor/receptor system CCl1-CCR8 is involved in the recruitment of lymphocytes (Zen et al. 2013).

References

Abraham SC, Cruz-Correa M, Argani P, Furth EE, Hruban RH, Boitnott JK (2003) Lymphoplasmacytic chronic cholecystitis and biliary tract disease in patients with lymphoplasmacytic sclerosing pancreatitis. Am J Surg Pathol 27:441–451

Agaimy A, Märkl B (2013) Inflammatory angiomyolipoma of the liver: an unusual case suggesting relationship to IgG4-related pseudotumor. Int J Clin Exp Pathol 6:771–779

Ahn KS, Kang KJ, Kim YH, Lim TJ, Jung HR, Kang YN, Kwon JH (2012) Inflammatory pseudotumors mimicking intrahepatic cholangiocarcinoma of the liver; IgG4-positivity and its clinical significance. J Hepatobiliary Pancreat Sci 19:405–412

Albarran J (1905) Retention rénale par periurétérite. Libération externe de l'uretère. Assoc Fr Urol 9:511

Alberti C (2007) Retroperitoneal fibroses: aetiopathogenesis and taxonomic assessment. Eur Rev Med Pharmacol Sci 11:375–382

Alderlieste YA, Elzen BDJ, Rauws EAJ et al (2009) Immunoglobulin G4-associated cholangitis: one variant of immunoglobulin G4-related systemic disease. Digestion 79:220–228

Alpert LI, Jindrak K (1972) Idiopathic retroperitoneal fibrosis and sclerosing cholangitis associated with a reticulum cell sarcoma. Report of a case. Gastroenterology 62:111–117

Amiya E, Ishizaka N, Watanabe A, Endo Y, Itou R, Yoshida S, Nangaku M, Nagai R (2005) Retroperitoneal fibrosis with periaortic and pericardial involvement. Circ J 69:760–762

Aomatsu N, Okita Y, Kato Y (2012) A case requiring differentiation of IgG4-related sclerosing disease from periampullary cancer (in Japanese). Gan To Kagaku Ryoho 39:2155–2157

Bartholomew LG, Cain JC, Woolner LB, Utz DC, Ferris DO (1963) Sclerosing cholangitis: its possible association with Riedel's struma and fibrous retroperitonitis. Report of two cases. N Engl J Med 269:8–12

Bateman AC, Deheragoda MG (2009) IgG4-related systemic sclerosing disease – an emerging and underdiagnosed condition. Histopathology 55:373–383

Beristain JL, Sabater L, Calatayud A, Calvete J, Rausell M, Liedo S, Tosca J, Sastre J, Aparisi L (2008) Autoimmune pancreatitis: inflammatory pseudotumor, multifocal fibrosclerosis, portal hypertension, and long-term outcome (in Spanish). Rev Esp Enferm Dig 100:652–658

Beuers U, Maillette de Buy Wenniger LJ, Doorenspleet M, Hubers L, Verheij J, van Gulik T et al (2014) IgG4-associated cholangitis. Dig Dis 32:605–608

Björnsson E, Chari ST, Smyrk TC, Lindor K (2007) Immunoglobulin G4 associated cholangitis: description of an emerging clinical entity based on review of the literature. Hepatology 45:1547–1554

Blejter J, Weller S, Pace R, Cusumano H, Giambini D (2008) Autoimmune pancreatitis: an adolescent case and review of literature. J Pediatr Surg 43:1368–1372

Boonstra K, Culver EL, de Buy Wenninger LM, van Heerde MJ, van Erpecum KJ et al (2014) Serum IgG4 and IgG1 for distinguishing IgG4-associated cholangitis from primary sclerosing cholangitis. Hepatology 59:1954–1963

Boulanger E, Fuentes V, Meignin V, Mougenot B, Labume S, Gouilleux-Gruart V, Cogné M et al (2006) Polyclonal IgG4 hypergammaglobulinemia associated with plasmacytic lymphadenopathy, anemia and nephropathy. Ann Hematol 85:833–840

Brihaye B, Lidove O, Sacré K, Laissy JP, Escoubet B, Valla D, Papo T (2008) Diffuse periarterial involvement in systemic fibrosclerosis with Riedel's thyroiditis, sclerosing cholangitis, and retroperitoneal fibrosis. Scand J Rheumatol 37:490–492

Bulkley GJ (1960) Retroperitoneal fibrosis. Q Bull Northwest Univ Med Sch 34:113

Cappell MS (1994) Obstructive jaundice due to retroperitoneal fibrosis involving the head of the pancreas. J Clin Gastroenterol 18:53–56

Carruthers MN, Stone JH, Khosroshani A (2012) The latest on IgG4-RD: a rapidly emerging disease. Curr Opin Rheumatol 24:60–69

Castillo-Rama M, Sebagh M, Sasatomi E, Randhawa P, Isse K, Salgarkar AD, Ruppert K et al (2013) "Plasma cell hepatitis" in liver allografts: identification and characterization of an IgG4-rich cohort. Am J Transplant 13:2966–2977

Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, Clain JE et al (2006) Diagnosis of autoimmune pancreatitis. The Mayo Clinic experience. Clin Gastroenterol Hepatol 4:1010–1016

Chari ST, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T (2011) Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu Consensus Document. Pancreatology 10:664–672

Chen and Montgomery 2008. http://www.ncbi.nlm.nih.gov/pubmed/18682417

Cheuk W, Chan JKC (2010) IgG4-related sclerosing disease. A crucial appraisal of an evolving clinicopathologic entity. Adv Anat Pathol 17:303–332

Cheuk W, Yuen HK, Chu SY, Chiu EK, Lam LK, Chan JK (2008) Lymphadenopathy of IgG4-related sclerosing disease. Am J Surg Pathol 32:671–681

Cheung MT, Lo IL (2008) IgG4-related sclerosing lymphoplasmacytic pancreatitis and cholangitis mimicking carcinoma of pancreas and Klatskin tumour. ANZ J Surg 78:252–256

Chung H, Watanabe T, Kudo M, Maenishi O, Wakatsuki Y, Chiba T (2010) Identification and characterization of IgG4-associated autoimmune hepatitis. Liver Int 30:222–231

Chutaputti A, Burrell MI, Boyer JL (1995) Pseudotumor of the pancreas associated with retroperitoneal fibrosis: a dramatic response to corticosteroid therapy. Am J Gastroenterol 90:1155–1158

Cleffken B, Sie G, Riedl R, Heineman E (2008) Idiopathic sclerosing encapsulating peritonitis in a young female – diagnosis of abdominal cocoon. J Pediatr Surg 43: e27–e30

Clendenon JN, Aranda-Michel J, Krishna M, Taner CB, Willingham DL (2011) Recurrent liver failure caused by IgG4 associated cholangitis. Ann Hepatol 10:562–564

Corradi D, Maestri R, Palmisano A, Bosio S, Greco P, Manenti L, Ferretti S, Cobelli R et al (2007) Idiopathic retroperitoneal fibrosis: clinicopathologic features and differential diagnosis. Kidney Int 72:742–753

Da Luz MM, Barral SM, Barral CM, Bechara CS, Lacerda-Filho A (2011) Idiopathic encapsulating peritonitis: report of two cases. Surg Today 41:1644–1648

Dahlgren M, Kosroshani A, Nielsen GP, Deshpande V, Stone JH (2010) Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. Arthritis Care Res (Hoboken) 62:1312–1318

De Suray N, Van Beers B, Sempoux C, Borschette C, Lonneux M, Deprez P, Geubel A (2009) Autoimmune pancreatitis, sclerosing cholangitis, liver inflammatory pseudotumors, retroperitoneal fibrosis, lymphadenopathy, and sialoadenits in a single patient: a multifaceted expression of a hitherto unrecognized systemic autoimmune syndrome? Pancreas 38:476–478

Deheragoda MG, Church NI, Rodriguez-Justo M, Munson P, Sandanayake N, Seward EW et al (2007) The use of immunoglobulin g4 immunostaining in diagnosing pancreatic and extrapancreatic involvement in autoimmune pancreatitis. Clin Gastroenterol Hepatol 5:1229–1234

Dehner LP, Coffin CM (1998) Idiopathic fibrosclerotic disorders and other inflammatory pseudotumors. Semin Diagn Pathol 15:161–173

Dejaco C, Ferenci P, Schober E, Kaserer K, Függer R, Novacek G, Gangl A (1999) Stenosis of the common bile duct due to Ormond's disease: case report an review of the literature. J Hepatol 31:156–159

Deshpande V, Sainani NI, Chung RT et al (2009) IgG4-associated cholangitis: a comparative histological and immunophenotypic study with primary sclerosing cholangitis on liver biopsy material. Mod Pathol 22:1287–1295

Deshpande V, Gupta R, Sainani N, Sahani DV, Virk R, Ferrone C, Khosroshahi A et al (2011) Subclassification of autoimmune pancreatitis: a histologic classification with clinical significance. Am J Surg Pathol 35:26–35

Detlefsen S, Bräsen JH, Zamboni G, Capelli P, Klöppel G (2010) Deposition of complement C3c, immunoglobulin (Ig)G4 and IgG at the basement membrane of pancreatic ducts and acini in autoimmune pancreatitis. Histopathology 57:825–835

Divatia M, Kim SA, Ro JY (2012) IgG4-related sclerosing disease, an emerging entity: a review of a multi-system disease. Yonsei Med J 53:15–34

Douhara A, Mitoro A, Otani E, Furukawa M, Kaji K, Uejima M, Sawai M, Yoshida M et al (2013) Cholangiocarcinoma developed in a patient with IgG4-related disease. World J Gastrointest Oncol 5:181–185

Durst AL, Freund H, Rosenmann E, Birnbaum D (1977) Mesenteric panniculitis: review of the literature and presentation of cases. Surgery 81:203–211

Ehrenpreis ED, Boiskin I, Schaefer K (2008) Chylous ascites in a patient with mesenteric panniculitis. J Clin Gastroenterol 42:327–328

Erdogan D, Kloek JJ, ten Kate FJ, Rauws EA, Busch OR, Gouma DJ et al (2008) Immunoglobulin G4-related sclerosing cholangitis in patients resected for presumed malignant bile duct strictures. Br J Surg 95:727–734

Erkelens GW, Vleggaar FP, Lesterhuis W, Van Buuren HR, van der Werf SD (1999) Sclerosing pancreatocholangitis responsive to steroid therapy. Lancet 354:43–44

Esposito I, Born D, Bergmann F, Longerich T, Welsch T, Giese NA, Büchler MW, Kleeff J, Friess H, Schirmacher P (2008) Autoimmune pancreatocholangitis, non-autoimmune pancreatitis and primary sclerosing cholangitis: a comparative morphological and immunological analysis. PLoS One 3:e2539

Feely MM, Gonzalo DH, Corbera M, Hughes SJ, Trevino JG (2014) IgG4-related cholecystitis presenting as biliary malignancy: report of three cases. J Gastrointest Surg 18:1710–1715

Fischer S, Trivedi PJ, Ward S, Greig PD, Therapondos G, Hirschfield GM (2014) Frequency and significance of IgG4 immunohistochemical staining in liver explants from patients with primary sclerosing cholangitis. Int J Exp Pathol 95:209–215

Foo KT, Ng KC, Rauff A, Foong WC, Sinniah R (1978) Unusual small intestinal obstruction in adolescent girls: the abdominal cocoon. Br J Surg 65:427–430

Fujita T, Kojima M, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Ochiai A, Kinoshita T (2010) Incidence, clinical presentation and pathological features of benign sclerosing cholangitis of unknown origin masquerading as biliary carcinoma. J Hepatobiliary Pancreat Surg 17:139–146

Fukui T, Okazaki K, Yoshizawa H, Ohashi S, Tamaki H, Kawasaki K, Matsuura M, Asada M et al (2005) A case of autoimmune pancreatitis associated with sclerosing cholangitis, retroperitoneal fibrosis and Sjögren's syndrome. Pancreatology 5:86–91

Ghazale A, Chari ST, Zhang L et al (2008) Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology 134:706–715

Ghosh P, Kum J (2007) Mesenteric panniculitis and sclerosing mesenteritis: a continuum of inflammation fibrosis. Clin Gastroenterol Hepatol 5:A32

Graham RP, Smyrk TC, Chari ST, Takahashi N, Zhang L (2014) Isolated IgG4-realted sclerosing cholangitis: a report of 9 cases. Hum Pathol 45:1722–1729

Gumbs AA, Kim J, Kiehna E, Brink JA, Salem RR (2005) Autoimmune pancreatitis presenting as simultaneous masses in the pancreatic head and gallbladder. JOP 6:455–459

Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T et al (2001) High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 344:732–738

Hamano H, Kawa S, Ochi Y et al (2002) Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet 359:1403–1404

Hamano H, Kawa S, Uehara T, Ochi Y, Takayama M, Komatsu K, Muraki T, Umino J et al (2005) Immunoglobulin G4-related lymphoplasmacytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma: part of a spectrum of autoimmune pancreatitis? Gastrointest Endosc 62:152–157

Hamed G, Tsushima K, Yasuo M, Kubo K, Yamazaki S, Kawa S, Hamano H, Yamamoto H (2007) Inflammatory lesions of the lung, submandibular gland, bile duct and prostate in a patient with IgG4-associated multifocal systemic fibrosclerosis. Respirology 12:455–457

Harada K, Nakanuma Y (2014) Cholangiocarcinoma with respect to IgG4 reaction. Int J Hepatol 2014:803876

Hardy JD (1962) Some lesions of the biliary tract. Idiopathic retroperitoneal fibrosis and other problems. Am J Surg 103:457–468

Hastir D, Verset L, Lucidi V, Demetter P (2014) IgG4 positive lymphoplasmacytic inflammatory pseudotumour mimicking hepatocellular carcinoma. Liver Int 34:961

Hayashi K, Nakazawa T, Ohara H, Ando T, Takada H, Tanaka H, Sasaki M, Kataoka H et al (2007) Autoimmune sclerosing cholangiopancreatitis with little pancreatic involvement by imaging findings. Hepatogastroenterology 54:2146–2151

Hellstrom HR, Perez-Stable EC (1966) Retroperitoneal fibrosis with disseminated vasculitis and intrahepatic sclerosing cholangitis. Am J Med 40:184–187

Hirano K, Shiratori Y, Komatsu Y, Yamamoto N, Sasahira N, Toda N et al (2003) Involvement of the biliary system in autoimmune pancreatitis: a follow-up study. Clin Gastroenterol Hepatol 1:453–464

Hirano K, Komatsu Y, Yamamoto N, Nakai Y, Sasahira N, Toda N, Tsayama H, Tada M et al (2004) Pancreatic mass lesions associated with raised concentration of IgG4. Am J Gastroenterol 99:2038–2040

Hirano K, Kawabe T, Yamamoto N, Nakai Y, Sasahira N, Tsujino T, Toda N, Isayama H et al (2006) Serum IgG4 concentrations in pancreatic and biliary diseases. Clin Chim Acta 367:181–184

Hirano K, Tada M, Sasahira N, Isayama H, Mizuno S, Takagi K, Watanabe T, Saito T et al (2014) Incidence of malignancies in patients with IgG4-related disease. Intern Med 53:171–176

Hisatomi K, Ohya T, Asayama M, Shibata M, Ito M, Sakurai Y, Sato Y (2004) Hypoplasia of the right hepatic lobe associated with portal hypertension and idiopathic retroperitoneal fibrosis. J Gastroenterol 39:685–691

Hochwald SN, Hemming AW, Draganov P, Vogel SB, Dixon LR, Grobmyer SR (2008) Elevation of serum IgG4 in western patients with autoimmune sclerosing pancreatocholangitis: a word of caution. Ann Surg Oncol 15:1147–1154

Horiuchi A, Kawa S, Hamano H, Hayama M, Ota H, Kiyosawa K (2002) ERCP features in 27 patients with autoimmune pancreatitis. Gastrointest Endosc 55:494–499

Huggett MT, Culver EL, Kumar M, Hurst JM, Rodriguez-Justo M, Chapman MH, Johnson GJ et al (2014) Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. Am J Gastroenterol. doi:10.1038/ajg.2014.223

Hughes D, Buckley PJ (1993) Idiopathic retroperitoneal fibrosis is a macrophage-rich process. Implications for its pathogenesis and treatment. Am J Surg Pathol 17:482–490

Iwamuro M, Yamamoto K, Kawamoto H, Terada R, Ogawa T, Nose S (2009) Eosinophilic cholangitis with initial clinical features indistinguishable from IgG4-related cholangitis. Intern Med 48:1143–1147

Johnson LA, Longacre TA, Wharton KA, Jeffrey RB (1997) Multiple mesenteric lymphatic cysts: an unusual feature of mesenteric panniculitis (sclerosing mesenteritis). J Comput Assist Tomogr 21:103–105

Jois RN, Gaffney K, Marshall T, Scott DG (2004) Chronic periaortitis. Rheumatology (Oxford) 43:1441–1446

Joshi D, Webster G (2014) Clinical observations in hepatology: IgG4 related sclerosing cholangitis. Hepatology. doi:10.1002/hep.27411

Jura V (1924) Sulla mesenterite retrattile e sclerosante. Policlinico 31:575–581

Kajiwara M, Kojima M, Konishi M, Nakagohri T, Takahashi S, Gotohda N, Hasebe T, Ochiai A, Kinoshita T (2008) Autoimmune pancreatitis with multifocal lesions. J Hepatobiliary Pancreat Surg 15:449–452

Kamisawa T, Okamoto A (2008) IgG4-related sclerosing disease. World J Gastroenterol 14:3948–3955

Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H (2003a) A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 38:982–984

Kamisawa T, Funata N, Hayashi Y, Tsuruta K, Okamoto A, Amemiya K, Egawa N, Nakajima H (2003b) Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. Gut 52:683–687

Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A (2006a) IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. Pancreatocology 6:132–137

Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A (2006b) IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. Pancreatology 6:132–137

Kamisawa T, Tu Y, Nakajima H, Egawa N, Tsuruta K, Okamoto A, Horiguchi S (2006c) Sclerosing cholecystitis associated with autoimmune pancreatitis. World J Gastroenterol 12:3736–3739

Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T (2010) Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol 7:401–409

Kanda G, Ryu T, Shirai T, Ijichi M, Hishima T, Kitamura S, Bandai Y (2011) Peripheral T-cell lymphoma that developed during the follow-up of IgG4-related disease. Intern Med 50:155–160

Kanno A, Satoh K, Kimura K, Masamune A, Asakura T, Unno M, Matsuno S, Moriya T, Shimosegawa T (2005) Autoimmune pancreatitis with hepatic inflammatory pseudotumor. Pancreas 31:420–423

Kasashima S, Zen Y, Kawashima A, Konishi K, Sasaki H, Endo M, Matsumoto Y, Kawakami K et al (2008) Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periqortitis. Am J Surg Pathol 32:197–204 http://www.ncbi.nlm.nih.gov/pubmed/18223321

Kawa S, Ota M, Yoshizawa K, Horiuchi A, Hamano H, Ochi Y et al (2002) HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. Gastroenterology 122:1264–1269

Kawa S, Hamano H, Umemura T, Kiyosawa K, Uehara T (2007) Sclerosing cholangitis associated with autoimmune pancreatitis. Hepatol Res 37(Suppl 3): S487–S495

Kawakami H, Zen Y (2010) Is IgG4 immunostaining of duodenal ampullary biopsies alone useful to diagnose autoimmune pancreatitis? Gastrointest Endosc 72:1328

Kawakami H, Zen Y, Kuwatani M, Eto K, Haba S, Yamato H, Shinada K, Kubota K, Asaka M (2010) IgG4-related sclerosing cholangitis and autoimmune pancreatitis: histological assessment of biopsies from Vater's ampulla and the bile duct. J Gastroenterol Hepatol 25:1648–1655

Khosroshahi A, Stone JH (2011a) IgG4-related systemic disease: the age of discovery. Curr Opin Rheumatol 23:72–73

Khosroshahi A, Stone JH (2011b) A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol 23:57–66

Kim JY, Kim MH, Jung JH, Song JH, Oh HC, Kwon SH, Lee TY, Lee SS, Seo DW et al (2006) Comparison of clinical findings between autoimmune pancreatitis with bile duct involvement and primary sclerosing cholangitis (in Korean). Korean J Gastroenterol 48:104–111

Kojima M, Sipos B, Klapper W, Frahm O, Knuth HC, Yanagishawa A et al (2007) Autoimmune pancreatitis: frequency, IgG4 expression, and clonality of T and B cells. Am J Surg Pathol 31:521–528

Kubota K, Kato S, Akiyama T, Yoneda M, Fujita K, Ogawa M, Inamori M, Kobayashi N et al (2008) Differentiating sclerosing cholangitis caused by autoimmune pancreatitis and primary sclerosing cholangitis according to endoscopic duodenal papillary features. Gastrointest Endosc 68:1204–1208

Kuroiwa T, Suda T, Takahashi T, Hirono H, Natsui M, Motoyama H, Nomoto M, Aoyagi Y (2002) Bile duct involvement in a case of autoimmune pancreatitis successfully treated with an oral steroid. Dig Dis Sci 47:1810–1816

Laitt RD, Hübscher SG, Buckels JA, Darby S, Elias E (1992) Sclerosing cholangitis associated with multifocal fibrosis: a case report. Gut 33:1430–1432

Lechiche C, De Sequin C, François F, Yeche S, Reynaud D, Maubon A, Dubois A (2001) Peri-aortic fibrosis: unusual case of jaundice. Ann Med Interne (Paris) 152:411–414

Lee YS, Lee SH, Lee MG, Lee SJ, Hwang JH, Shin E, Lee YJ (2013) Immunoglobulin g4-related disease mimicking unresectable gallbladder cancer. Gut Liver 7:616–620

Leise MD, Smyrk TC, Takahashi N, Sweetser SR, Vege SS, Chari ST (2011) IgG4-associated cholecystitis: another clue in the diagnosis of autoimmune pancreatitis. Dig Dis Sci 56:1290–1294

Lundström B (1983) Idiopathic retroperitoneal fibrosis and common bile duct stenosis. A case report. Acta Chir Scand 149:713–715

Lytras D, Kalaitzakis E, Webster GJ, Imber CJ, Amin Z, Rodriguez-Justo M, Pereira SP et al (2012) Cholangiocarcinoma of IgG4-associated cholangitis: how feasible it is to avoid unnecessary surgical interventions? Ann Surg 256:1059–1067

Maeda M, Shimada K (2012) A case of IgG4-related sclerosing cholangitis mimicking an intrahepatic cholangiocellular carcinoma. Jpn J Clin Oncol 42:153

Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH (2014) IgG4-related disease. Ann Rev Pathol Mech Dis 9:315–347

Martin Malagon A, Lopez-Tomassetti Fernandez E, Arteaga Gonzalez I, Carrillo Pallares A, Diaz Luis H (2006) Inflammatory myofibroblastic tumor of the distal common bile duct associated with lymphoplasmacytic sclerosing pancreatitis. Case report and review of the literature. Pancreatology 6:145–154

Martina FB, Nüesch R, Gasser TC (1993) Retroperitoneal fibrosis and chronic periaortitis: a new hypothesis. Eur Urol 23:371–374

Masuda C, Fujii Y, Kamiya T, Miyamoto M, Nakahara K, Hattori S, Ohshita H, Yokoyama H et al (1993) Idiopathic sclerosing peritonitis in a man. Intern Med 32:552–555

Matsumoto Y, Kasashima S, Kawashima A, Sasaki H, Endo M, Kawakami K, Zen Y, Nakanuma Y (2008) A case of multiple immunoglobulin G4-related periarteritis: a tumorous lesion of the coronary artery

and abdominal aortic aneurysm. Hum Pathol 39:975–980
Matsushita M, Fukui T, Uchida K, Nishio A, Okazaki K (2009) Atypical retroperitoneal fibrosis associated with biliary stricture: IgG4-related sclerosing disease? Scand J Gastroenterol 44:1146–1147
Medina-Franco H, Listinsky C, Mel Wilcox C, Morgan D, Heslin MJ (2001) Concomitant sclerosing mesenteritis and bile duct fibrosis simulating Klatskin's tumor. J Gastrointest Surg 5:658–660
Menon MP, Evbuomwan MO, Rosai J, Jaffe ES, Pittaluga S (2014) A subset of Rosai-Dorfman disease cases show increased IgG4-positive plasma cells: another red herring or a true association with IgG4-related disease? Histopathology 64:455–459
Minutolo V, Gagliano G, Angirillo G, Minutolo O, Morello A, Rinzivillo C (2008) Intestinal obstruction due to idiopathic sclerosing encapsulating peritonitis. Clinical report and review of literature. G Chir 29:173–176
Mitchinson MJ (1984) Chronic periaortitis and periarteritis. Histopathology 8:589–600
Mitchinson MJ (1986) Retroperitoneal fibrosis revisited. Arch Pathol Lab Med 110:784–786
Miura H, Miyachi Y (2009) IgG4-related retroperitoneal fibrosis and sclerosing cholangitis independent of autoimmune pancreatitis. A recurrent case after a 5-year-history of spontaneous remission. JOP 10:432–437
Miwa I, Maruyama Y, Kageoka M, Nagata K, Ohata A, Noda Y, Ikeya K, Matsui T, Koda K, Watanabe F (2008) Retroperitoneal fibrosis and Castleman disease in two patients with high IgG4 levels (in Japanese). Nippon Shokakibyo Gakkai Zasshi 105:1087–1092
Mizutani S, Suzuki H, Yoshida H, Arima Y, Kitayama Y, Uchida E (2012) Case of IgG4-related sclerosing cholangitis with a normal serum IgG4 level: report of a case. J Nippon Med Sch 79:367–372
Montefusco PP, Geiss AC, Bronzo RL, Randall S, Kahn E, McKinley MJ (1984) Sclerosing cholangitis, chronic pancreatitis, and Sjögren's syndrome: a syndrome complex. Am J Surg 147:822–826
Müller T, Beutler C, Pico AH, Otten M, Dürr A, Al-Abadi H, Guckelberger O, Meyer Zum Büschenfelde D et al (2013) Increased T-helper 2 cytokines in bile from patients with IgG4-related cholangitis disrupt the tight junction-associated biliary epithelial cell barrier. Gastroenterology 144:1116–1128
Naitoh I, Nakazawa T, Ohara H et al (2009) Endoscopic transpapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. J Gastroenterol 44:1147–1155
Naitoh I, Zen Y, Nakazawa T, Ando T, Hayashi K, Miyabe K, Yoshida M, Nojiri S et al (2011) Small bile duct involvement in IgG4-related sclerosing cholangitis: liver biopsy and cholangiography correlation. J Gastroenterol 46:269–276
Naitoh I, Nakazawa T, Hayashi K, Miyabe K, Shimizu S, Kondo H, Yoshiba M, Yamashita H et al (2012) A case of IgG4-related sclerosing cholangitis overlapped with primary biliary cirrhosis. Intern Med 51:1695–1699
Nakanuma Y, Zen Y (2007) Pathology and immunopathology of immunoglobulin G4-related sclerosing cholangitis: the latest addition to the sclerosing cholangitis family. Hepatol Res 37(Suppl 3):S478–S486
Nakazawa T, Ohara H, Yamada T, Ando H, Sano H, Kajino S, Hashimoto T, Nakamura S et al (2001) Atypical primary sclerosing cholangitis cases associated with unusual pancreatitis. Hepatogastroenterology 48:625–630
Nakazawa T, Ohara H, Sano H, Aoki S, Kobayashi S, Okamoto T, Imai H, Nomura T et al (2004) Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis. Gastrointest Endosc 60:937–944
Nakazawa T, Ohara H, Sano H, Ando T, Aoki S, Kobayashi S, Okamoto T, Nomura T et al (2005) Clinical differences between primary sclerosing cholangitis and sclerosing cholangitis with autoimmune pancreatitis. Pancreas 30:20–25
Nakazawa T, Naitoh I, Hayashi K, Okumura F, Miyabe K, Yoshida M, Yamashita H et al (2012) Diagnostic criteria for IgG4-related cholangitis based on cholangiographic classification. J Gastroenterol 47:79–87
Nakazawa T, Naitoh I, Hayashi K, Miyabe K, Simizu S, Joh T (2013) Diagnosis of IgG4-related sclerosing cholangitis. World J Gastroenterol 19:7661–7670
Navaneethan U, Liu X, Bennett AE, Walsh RM, Venkatesh PG, Shen B (2011) IgG4-associated ampullitis and cholangiopathy in Crohn's disease. J Crohn's Colitis 5:451–456
Neild GH, Rodriguez-Justo M, Wall C, Connolly JO (2006) Hyper-IgG4 disease: report and characterization of a new disease. BMC Med 4:23
Nguyen-tat M, Gamstätter T, Marquardt JU, Geissinger E, Schadmand-Fischer S, Lang H et al (2012) IgG4-related sclerosing cholangitis mimicking cholangiocarcinoma. Z Gastroenterol 50:1008–1012
Nirula A, Glaser SM, Kalled SL, Taylora FR (2011) What is IgG4? A review of the biology of a unique immunoglobulin subtype. Curr Opin Rheumatol 23:119–124
Nishino T, Toki F, Oyama H, Oi I, Kobayashi M, Takasaki K, Shiratori K (2005) Biliary tract involvement in autoimmune pancreatitis. Pancreas 30:76–82
Nishino T, Oyama H, Hashimoto E, Toki F, Oi I, Kobayashi M, Shiratori K (2007) Clinicopathological differentiation between sclerosing cholangitis with autoimmune pancreatitis and primary sclerosing cholangitis. J Gastroenterol 42:550–559
Novotny I, Dite P, Trna J, Lata J, Husova L, Geryk E (2012) Immunoglobulin G4-related cholangitis: a variant of IgG4-related systemic disease. Dig Dis 30:216–219
Nowatari T, Kobayashi A, Fukunaga K, Oda T, Sasaki R, Ohkohchi N (2012) Recognition of other organ involvement might assist in the differential diagnosis of IgG4-associated sclerosing cholangitis without apparent pancreatic involvement: report of two cases. Surg Today 42:1111–1115

Ohara H, Nakazawa T, Ando T, Joh T (2007) Systemic extrapancreatic lesions associated with autoimmune pancreatitis. J Gastroenterol 42(Suppl 18):15–21

Ohara H, Okazaki K, Tsubouchi H, Inui K, Kawa S, Kamisawa T, Tazuma S, Uchida K et al (2012) Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci 19:536–542

Okazaki K, Uchida K, Fukui T (2008) Recent advances in autoimmune pancreatitis: concept, diagnosis and pathogenesis. J Gastroenterol 43:409–418

Okazaki K, Kawa S, Kamisawa T, Shimosegawa T, Tanaka M, Reserach Committee for Intractable Pancreatic Disease and Japan Pancreas Society (2010) Japanese consensus guidelines for management of autoimmune pancreatitis: I. Concept and diagnosis of autoimmune pancreatitis. J Gastroenterol 45:249–265

Okazaki K, Uchida K, Koyabu M, Miyoshi H, Ikeura T, Takaoka M (2014) IgG4 cholangiopathy – current concept, diagnosis, and pathogenesis. J Hepatol 61:690–695

Ong SL, Garcea G, Puls F, Richards C, Mulcahy K, Grant A, Dennison AR, Berry DP (2011) IgG4-positive sclerosing cholangitis following autoimmune pancreatitis with deranged CA19.9. Int J Surg Pathol 19:84–87

Ormond JK (1948) Bilateral ureteral obstruction due to envelopment and compression by an inflammatory retroperitoneal process. J Urol (Baltimore) 59: 1072–1079

Ormond JK (1965) Idiopathic retroperitoneal fibrosis: a discussion of the etiology. J Urol (Baltimore) 94:385–390

Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, Park SW, Shimosegawa T et al (2008) Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea symposium on autoimmune pancreatitis. J Gastroenterol 43:403–408

Pereira-Lima JC, Krömer MU, Adamek HE, Riemann JF (1996) Cholestatic jaundice due to Ormond's disease (primary retroperitoneal fibrosis). Hepatogastroenterology 43:992–994

Pickartz T, Pickartz H, Lochs H, Ockenga J (2004) Overlap syndrome of autoimmune pancreatitis and cholangitis associated with secondary Sjogren's syndrome. Eur J Gastroenterol Hepatol 16:1295–1299

Prasad P, Salem RR, Mangla R, Aslanian H, Jain D, Lee J (2004) Lymphoplasmacytic sclerosing pancreatocholangitis: a case report and review of the literature. Yale J Biol Med 77:143–148

Punnonen J, Aversa G, Cocks BG, McKenzie ANJ, Menon S, Zurawski G, De Waal Melafyt R et al (1993) Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. Proc Natl Acad Sci U S A 90:3730–3734

Quante M, Appenrodt B, Randerath S, Theodossi A (1991) Chronic periaortitis presenting as common bile duct obstruction. Gut 32:713–714

Quante et al. 2006. http://www.ncbi.nlm.nih.gov/pubmed/18759151

Remedios D, Coppen M, Bradbeer J, Theodossi A (1991) Chronic periaortitis presenting as common bile duct obstruction. Gut 32:713–714

Renner IG, Ponto GC, Savage WT, Boswell WD (1980) Idiopathic retroperitoneal fibrosis producing common bile duct and pancreatic duct obstruction. Gastroenterology 79:348–351

Resheq YJ, Quaas A, von Renteln D, Schramm C, Lohse AW, Lüth S (2013) Infiltration of peritumoural but tumour-free parenchyma with IgG4-positive plasma cells in hilar cholangiocarcinoma and pancreatic adenocarcinoma. Dig Liver Dis 45:859–865

Rompa GT, Jablonska AK, Guzek MT, Dubowik MM, Marek IE, Smoczynski MK (2010) Sclerosing cholangitis associated with retroperitoneal fibrosis: a case of multisystem fibroinflammatory disorder. Hepatol Int 4:779–783

Saab ST, Hornick JL, Fletcher CD, Olson SJ, Coffin CM (2011) IgG4 plasma cells in inflammatory myofibroblastic tumor: inflammatory marker or pathogenic link? Mod Pathol 24:606–612

Sabaté et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10063848

Sadler R, Chapman RW, Simpson D, Soonawall ZF, Waldegrave EL, Burden JM, Misbah SA, Ferry BL (2011) The diagnostic significance of serum IgG4 levels in patients with autoimmune pancreatitis: a UK study. Eur J Gastroenterol Hepatol 23:139–145

Saeki T, Saito A, Hiura T, Yamazaki H, Emura I, Ueno M, Miyamura S, Gejyo F (2006) Lymphoplasmacytic infiltration of multiple organs with immunoreactivity for IgG4: IgG4-related systemic disease. Intern Med 45:163–167

Saito M, Shimura T, Hashimoto Y, Ishigame T, Yashima R, Koyama Y, Takenoshita S (2013) IgG4-related intrahepatic sclerosing cholangitis resulting in sepsis caused by secondary suppurative inflammation: report of a case. Surg Today 43:1175–1179

Sakata N, Nabeshima K, Iwasaki H, Tashiro T, Uesugi N, Nakashima O, Ito H, Kawanami T et al (2007) Possible involvement of myofibroblast in the development of inflammatory aortic aneurysm. Pathol Res Pract 203:21–29

Sakata N, Tashiro T, Uesugi N, Kawara T, Furuya K, Hirata Y, Iwasaki H, Kojima M (2008) IgG4-positive plasma cells in inflammatory abdominal aortic aneurysm: the possibility of an aortic manifestation of IgG4-related sclerosing disease. Am J Surg Pathol 32:553–559

Sarles H, Sarles JC, Muratore R et al (1961) Chronic sclerosis of the pancreas – an autoimmune disease? Am J Dig Sci 6:688–698

Sasahira N, Kawabe T, Nakamura A, Shimura K, Shimura H, Itobayashi E, Asada M et al (2005) Inflammatory pseudotumor of the liver and peripheral eosinophilia in autoimmune pancreatitis. World J Gastroenterol 11:922–925

Sato Y, Harada K, Nakanuma Y (2004) Hepatic inflammatory pseudotumour related to autoimmune pancreatitis. Histopathology 45:418–419

Sato Y, Kojima M, Takata K, Morito T, Asaoku H, Takeuchi T, Mizobuchi K, Fujihara M et al (2009) Systemic IgG4-related lymphadenopathy: a clinical and pathologic comparison to multicentric Castleman's disease. Mod Pathol 22:589–599

Sato Y, Notohara K, Kojima M, Takata K, Masaki Y, Yoshino T (2010) IgG4-related disease: historical overview and pathology of hematological disorders. Pathol Int 60:247–258

Sawai H, Matsubayashi H, Sasaki K, Tanaka M, Kakushima N, Takizawa K, Yamaguchi Y, Ono H (2011) A case of sclerosing cholangitis without pancreatic involvement thought to be associated with autoimmunity. Intern Med 50:433–438

Schneider CF (1964) Idiopathic retroperitoneal fibrosis producing vena caval, biliary, ureteral and duodenal obstructions. Ann Surg 159:316–320

Sethia B, Darke SG (1983) Abdominal aortic aneurysm with retroperitoneal fibrosis and ureteric entrapment. Br J Surg 70:434–436

Sevenet F, Capron-Chivrac D, Delcenserie R, Lelarge C, Delamarre J, Capron JP (1985) Idiopathic retroperitoneal fibrosis and primary biliary cirrhosis. A new association? Arch Intern Med 145:2124–2125

Sewkani A, Kapoor S, Sharma S, Naik S, Debbarma MK, Varshnev S (2005) IgG4 negative sclerosing cholangitis associated with autoimmune pancreatitis. JOP 6:269–273

Sharma V, Martin P, Marjoniemi VM (2006) Idiopathic orbital inflammation with sclerosing mesenteritis: a new association? Clin Experiment Ophthalmol 34:190–192

Sheikh RA, Prindiville TP, Arenson D, Ruebner BH (1999) Sclerosing mesenteritis seen clinically as pancreatic pseudotumor: two cases and a review. Pancreas 18:316–321

Shimizu I, Nasu K, Sato K, Ueki H, Akahane D, Sumi M, Ueno M, Ichikawa N, Asano N et al (2010) Lymphadenopathy of IgG4-related sclerosing disease: three case reports and review of the literature. Int J Hematol 92:751–756

Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH et al (2011) International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 40:352–358

Shin SW, Kim Y, Jeong WK, Kim J, Kim MY, Oh YH, Pyo JY (2013) Isolated IgG4-related cholecystitis mimicking gallbladder cancer: a case report. Clin Imaging 37:969–971

Silveira MG (2013) IgG4-associated cholangitis. Clin Liver Dis 17:255–268

Smyrk TC (2011) Pathological features of IgG4-related sclerosing disease. Curr Opin Rheumatol 23:74–79

Stone JH (2013) Extra-pancreatic features of autoimmune pancreatitis (IgG4-related disease). Pancreatopedia: Exocrine Pancreas Knowl Base. doi:10.3998/panc.2013.19

Strehl JD, Hartmann A, Agaimy A (2011) Numerous IgG4-positive plasma cells are ubiquitous in diverse localized non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. J Clin Pathol 64:237–243

Streuli and Stamm 1994. http://www.ncbi.nlm.nih.gov/pubmed/7876020

Tabata T, Kamisawa T, Takuma K, Egawa N, Setoguchi K, Tsuruta K, Obayashi T, Sasaki T (2011) Serial changes of elevated serum IgG4 levels in IgG4-related systemic disease. Intern Med 50:69–75

Tabata T, Kamisawa T, Hara S, Kuruma S, Chiba K, Kuwata G, Fujiwara T, Egashira H et al (2013) Differentiating immunoglobulin g4-related sclerosing cholangitis from hilar cholangiocarcinoma. Gut Liver 7:234–238

Takabe K, Nakatani Y, Kanaya H, Takimoto A, Endo I, Sekido H, Shimada H (1997) Segmental pericholangial fibrosis: a peculiar benign fibrosing disease at the hepatic hilum. J Pediatr Surg 32:1767–1770

Takahashi N, Ghazale AH, Smyrk TC, Mandrekar JN, Chari ST (2009) Possible association between IgG4-associated systemic disease with or without autoimmune pancreatitis and non-Hodgkin lymphoma. Pancreas 38:523–526

Takahashi H, Yamamoto M, Suzuki C, Naishiro Y, Shinomura Y, Imai K (2010) The birthday of a new syndrome: IgG4-related diseases constitute a clinical entity. Autoimmun Rev 9:591–594

Takato H, Yasui M, Ichikawa Y, Fujimura M, Nakao S, Zen Y, Minato H (2008) Nonspecific interstitial pneumonia with abundant IgG4-positive cells infiltration, which was thought as pulmonary involvement of IgG4-related autoimmune disease. Intern Med 47:291–294

Takemoto R, Miyake Y, Harada K, Nakanuma Y, Moriya A, Ando M, Hirohata M, Yamamoto K (2014) Overlap of IgG4-related sclerosing cholangitis and primary biliary cirrhosis. Intern Med 53:1429–1433

Takenaka K, Takada K, Kobayashi D, Moriguchi M, Harigai M, Miyasaka N (2011) A case of IgG4-related disease with features of Mikulicz's disease, and retroperitoneal fibrosis and lymphadenopathy mimicking Castleman's disease. Mod Rheumatol 21:410–414

Takeuchi M, Sato Y, Ohno K, Tanaka S, Takata K, Gion Y, Orita Y, Ito T, Tachibana T et al (2014) T helper 2 and regulatory T-cell cytokine production by mast cells: a key factor in the pathogenesis of IgG4-related disease. Mod Pathol 27:1126–1136

Takuma K, Kamisawa T, Igarashi Y (2011) Autoimmune pancreatitis and IgG4-related sclerosing cholangitis. Curr Opin Rheumatol 23:80–87

Tamura S, Yokoyama Y, Nakajo K, Morita T, Wada K, Onishi S (2003) A rare case of idiopathic retroperitoneal fibrosis involving obstruction of the mesenteric arteries, duodenum, common bile duct, and inferior vena cava. Intern Med 42:812–817

Tanabe T, Tsushima K, Yasuo M, Urushihata K, Hanaoka M, Koizumi T, Fujimoto K, Kubo K et al (2006) IgG4-associated multifocal systemic fibrosis complicating sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic involvement. Intern Med 45:1243–1247

Toosi MN, Heathcote J (2004) Pancreatic pseudotumor with sclerosing pancreato-cholangitis: is this a systemic disease? Am J Gastroenterol 99:377–382

Uchida K, Satoi S, Miyoshi H, Hachimine D, Ikeura T, Shimatani M, Matsushita M, Takaoka M et al (2007) Inflammatory pseudotumors of the pancreas and liver with infiltration of IgG4-positive plasma cells. Intern Med 46:1409–1412

Uehara T, Hamano H, Kawa S, Sano K, Honda T, Ota H (2005) Distinct clinicopathological entity'autoimmune pancreatitis-associated sclerosing cholangitis'. Pathol Int 55:405–411

Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K (2007) Immunoglobulin G4-hepatopathy: association of immunoglobulin G4-bearing plasma cells in liver with autoimmune pancreatitis. Hepatology 46:463–471

Umemura T, Zen Y, Hamano H, Joshita S, Ichijo T, Yoshizawa K, Kiyosawa K, Ota M et al (2011) Clinical significance of immunoglobulin G4-associated autoimmune hepatitis. J Gastroenterol 46(Suppl 1):48–55

Vaglio A, Buzio C (2005) Chronic periaortitis: a spectrum of diseases. Curr Opin Rheumatol 17:34–40

Vaglio A, Corradi D, Manenti L, Ferretti S, Garini G, Buzio C (2003) Evidence of autoimmunity in chronic periaortitis: a prospective study. Am J Med 114:454–462

Vaglio A, Greco P, Corradi D, Palmisano A, Martorana D, Ronda N, Buzio C (2006a) Autoimmune aspects of chronic periaortitis. Autoimmun Rev 5:458–464

Vaglio A, Salvarani C, Buzio C (2006b) Retroperitoneal fibrosis. Lancet 367:241–251

Vaglio A, Palmisano A, Corrado D, Salvarani C, Buzio C (2007) Retroperitoneal fibrosis: evolving concepts. Rheum Dis Clin North Am 33:803–817

Venkataraman G, Rizzo KA, Chavez JJ, Streubel B, Raffeld M, Jaffe ES, Pittaluga S (2011) Marginal zone lymphomas involving meningeal dura: possible link to IgG4-related disease. Mod Pathol 24:355–366

Versapuech JM, Labayle D, Grange D, Fischer D, Kemeny F, D'Hubert E (1986) Sclerosing cholangitis, chronic pancreatitis and Sjögren's syndrome (in French). Ann Med Interne (Paris) 137:147–151

Wang WL, Farris AB, Lauwers GY et al (2009) Autoimmune pancreatitis-related cholecystitis: a morphologically and immunologically distinctive form of lymphoplasmacytic sclerosing cholecystitis. Histopathology 54:829–836

Webster GJ, Pereira SP, Chapman RW (2009) Autoimmune pancreatitis/IgG4-associated cholangitis and primary sclerosing cholangitis – overlapping or separate diseases? J Hepatol 51:398–402

Wetter LA, Ring EJ, Pellegrini CA, Way LW (1991) Differential diagnosis of sclerosing cholangiocarcinomas of the common hepatic duct (Klatskin tumors). Am J Surg 161:57–62

Yada N, Kudo M, Chung H, Watanabe T (2013) Autoimmune hepatitis and immunoglobulin g4-associated autoimmune hepatitis. Dig Dis 31:415–420

Yamashita K, Haga H, Mikami Y, Kanematsu A, Nakashima Y, Kotani H, Ogawa O, Manabe T (2008) Degree of IgG4+ plasma cell infiltration in retroperitoneal fibrosis with or without multifocal fibrosclerosis. Histopathology 52:404–409

Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N (1995) Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci 40:1561–1568

Zen Y, Nakanuma Y (2010) IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol 34:1812–1819

Zen Y, Nakanuma Y (2011) Pathogenesis of IgG4-related disease. Curr Opin Rheumatol 23:114–118

Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, Kurumaya H, Katayanagi K et al (2004) IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol 28:1193–1203

Zen Y, Fujii T, Sato Y, Masuda S, Nakanuma Y (2007) Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease. Mod Pathol 20:884–894

Zen Y, Quaglia A, Portmann B (2011) Immunoglobulin G4-positive plasma cell infiltration in explanted livers for primary sclerosing cholangitis. Histopathology 58:414–422

Zen Y, Liberal R, Nakanuma Y, Heaton N, Portmann B (2013) Possible involvement of CCL1-CCR8 interaction in lymphocytic recruitment in IgG4-realted sclerosing cholangitis. J Hepatol 59:1059–1064

Zhang L, Smyrk TC (2010) Autoimmune pancreatitis and IgG4-related systemic disease. Int J Clin Exp Pathol 3:491–504

Zhao MF, Tian Y, Guo KJ, Ma ZG, Liao HH (2004) Common bile duct obstruction due to fibrous pseudotumor of pancreas associated with retroperitoneal fibrosis: a case report. World J Gastroenterol 10:3078–3079

Part XXVIII

Reactive Bile Duct Alterations Mimicking Biliary Tumors

Reactive Bile Duct Alterations Mimicking Biliary Cancer: Inflammatory Conditions

142

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_142

Abstract

Several inflammatory conditions of the biliary tract can mimic biliary cancer, resulting in biliary obstruction and jaundice. Following ulcerating cholangitis, granulation tissue formation can result in inflammatory polyps that may grow to rather large size to obstruct bile duct lumen. In part of cases, foreign bodies such as suture material induces granulation tissue polyps. Mass-forming lesions are also produced by various types of granulomatous cholangitis, including sarcoidosis, Crohn's disease, and tuberculosis. Duct stenosis may be caused by numerous mucosal lymph follicles (follicular cholangitis). A distinct form of recurrent cholangitis that may result in bile duct scarring and associated with stone casts is oriental cholangitis. Similar to the gallbladder, large bile ducts can undergo xanthogranulomatous inflammation. A rare condition is cholesterolosis of bile ducts, which can produce cholesterol polyps.

Inflammatory Polyps of the Bile Ducts

Introduction

Inflammatory polyps are defined as exophytically growing reactive lesions that develop in the context of deranged wound healing on epithelial surfaces and consist of granulation tissue. Inflammatory polyps ("granuloma of the biliary tract"; pyogenic granuloma of bile ducts; postsurgical granuloma) have been reported for all portions of the extrahepatic biliary tract, including the hepatic ducts (Hussain and Ahmed 2003), the bifurcation area (Nagayama et al. 1992), the common bile duct (Ro 1975; Stamatakis et al. 1979; Ezaki et al. 1994; Lee et al. 2007), the gallbladder (Sun et al. 2004), and the ampullary region (Shtamler et al. 1973; Norton et al. 2002). The lesions are mostly solitary, but multiple polyps of the choledochus have been observed (Adachi et al. 1991). Such polyps can grow to rather large size and may then cause biliary obstruction, e.g., reported for the hepatic duct, common bile duct (Ro 1975; Nagayama et al. 1992), and ampullary region. In cholangiograms, inflammatory polyps may mimic stones ("pseudocalculus"; Lautatzis et al. 1988).

Most biliary inflammatory polyps seem to be postsurgical lesions or develop in areas of ulceration caused by stone disease. A postsurgical etiology is suggested by the observation that inflammatory polyps occur in the vicinity of the cystic stump after cholecystectomy (Farkas et al. 1980) or in conjunction with choledochoduodenostomy (Lee et al. 2007).

Pathology

Macroscopically, the lesions appear as small (usually <1 cm) polypoid formations of reddish or grayish color, with either a glistening or finely granulated surface, the granulation being caused by the characteristic surface structure of granulation tissue. The polyps may be covered by a fibrinopurulent exudate or by bile-stained material.

Published histopathologic examinations of inflammatory bile duct polyp are very limited (Figs. 1, 2, 3, 4, 5, 6, and 7). In one study, the polypoid lesions in AIDS-related polypoid cholangitis were demonstrated to consist of granulation tissue (Collins et al. 1993).

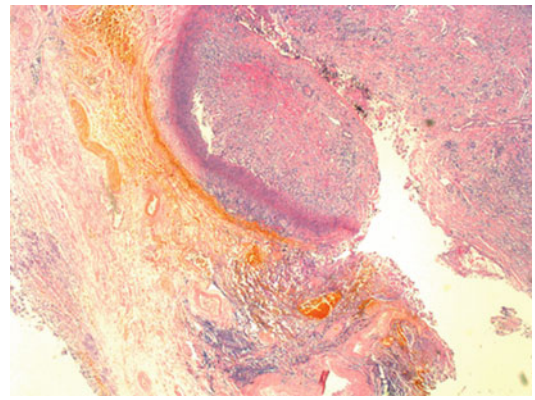

Fig. 1 Inflammatory polyp (granulation tissue polyp) in an ulcerated bile duct. The polyp is partly covered with fibrinoleukocytic exudate (hematoxylin and eosin stain)

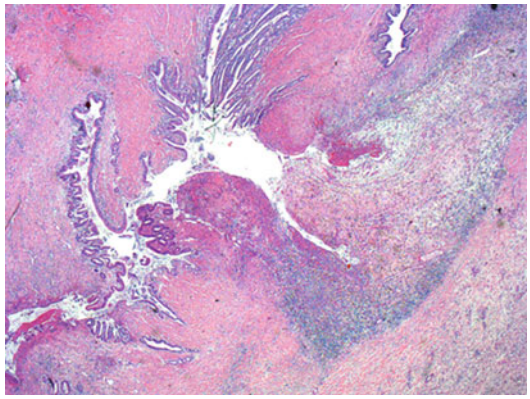

Fig. 2 Inflammatory polyps of the bile duct. The polyps have developed as granulation tissue overgrowths arising from the bottom of non-healing bile duct ulcers. The mucosa adjacent to the polyp in the center exhibits metaplastic epithelial changes (hematoxylin and eosin stain)

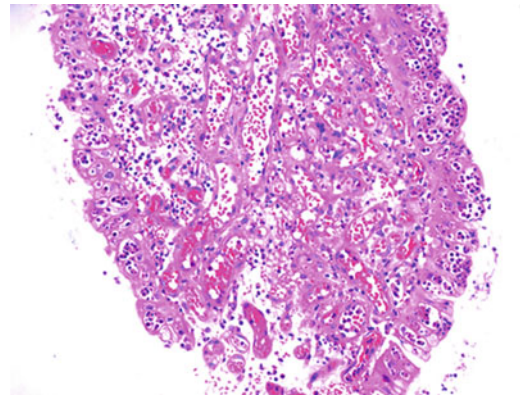

Fig. 4 Inflammatory bile duct polyp in the stage of granulation tissue formation. The highly vascularized tissue is covered by regenerating biliary epithelium. The latter is invaded by numerous neutrophils (hematoxylin and eosin stain)

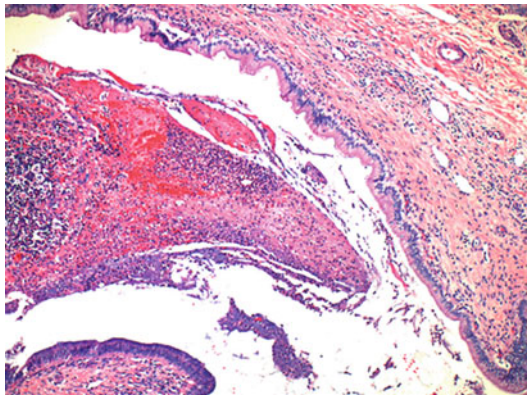

Fig. 3 Apical parts of inflammatory polyps of bile ducts may predominantly consist of fibrin- and leukocyte-rich exudate, as in the present case (hematoxylin and eosin stain)

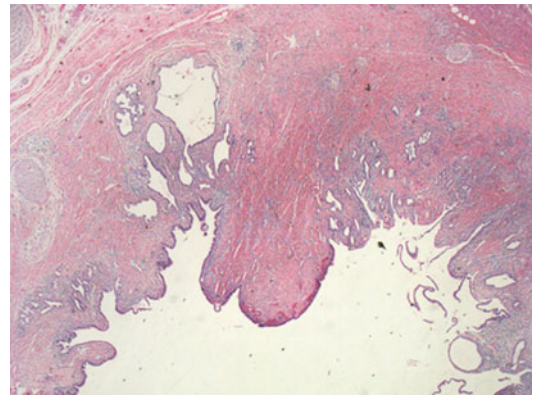

Fig. 5 Fibrous polyp of the bile duct (hematoxylin and eosin stain)

Other Types of Bile Duct Polyps Related to Inflammation and Hyperplasia

AIDS-Related Polypoid Cholangitis

A distinct situation is the occurrence of inflammatory bile duct polyps in patients with AIDS-related sclerosing cholangitis (ARSC; Forbes et al. 1993; Ducreux et al. 1995). Among 31 patients with this disorder, intraluminal polypoidal defects within the common bile duct and larger intrahepatic ducts were detected in eight cases (26 %), and it was proposed to term this condition AIDS-related polypoid cholangitis (Collins et al. 1993).

Suture Granuloma of Bile Ducts

Part of inflammatory lesions with a polypoid or nodular shape consist of a granulating inflammation centered on suture material. Such lesions have been termed suture granulomas. The lesions consist of a fibrosing granulation tissue with numerous macrophages and foreign body-type giant cells. The latter may contain suture thread fragments in their cytoplasm (Brauner et al. 1988). In case such

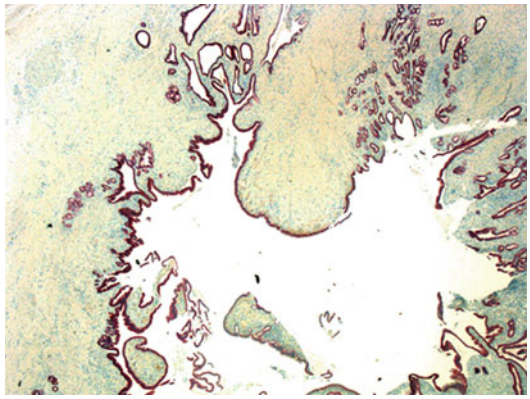

Fig. 6 Fibrous polyp of the bile duct. In contrast to adjacent bile duct mucosa, the cholangiocyte lining of the polyp is still immature and flat (cytokeratin 19 immunostain)

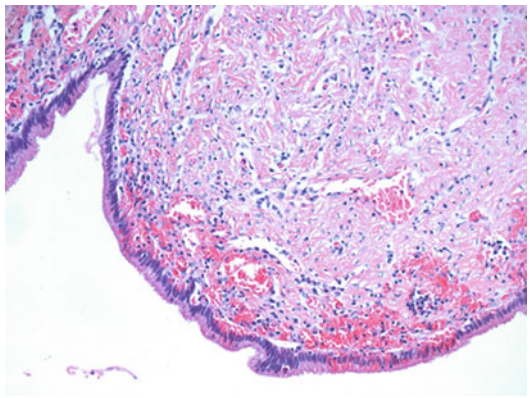

Fig. 7 Fibrous polyp of the bile duct. In the subepithelial area, remnants of granulation tissue are found, while deeper parts are fibrosed/scarred (hematoxylin and eosin stain)

"granulomas" grow to larger size, they may mimic cholangiocarcinoma (Gleeson and McMullin 1987; Murphy et al. 1990).

Mucosal Bile Duct Hyperplasia

There are rare instances where bile duct stenosis is caused by hyperplastic mucosal changes in the biliary tract. In a 71-year-old patient, a tumorous stenosing lesion of the distal bile duct was found. Abdominal ultrasonography revealed dilatation of the intra- and extrahepatic bile ducts and the pancreatic duct. Endoscopic examinations showed swelling and redness of the papilla of Vater with an irregular surface, and a biopsy displayed adenoma at this place. Cholangiography showed disruption of the common bile duct due to a polypoid lesion of its distal part, with occasional prolapse of the lesion into the duodenum. This lesion also compressed the orifice of the pancreatic duct. Histology of the sessile lesion disclosed nodular mucosal hyperplasia, with papillary superficial growths and hyperplasia of mucus gland cells (Kubota et al. 1996). It was suggested that this type of lesion may belong to the group of "adenomatous" or "adenofibromyomatous" hyperplasias occurring in the most distal part of the common bile duct and in the papillo-ampullary region (Zubov and Zubkov 1983; Hirota et al. 1989).

Granulomatous Cholangitis

Granulomatous Cholangitis in Sarcoidosis

In sarcoidosis, epithelioid cell granulomas with or without multinucleated giant cells of the Langhans type are often present in multiple organs, including the liver (Devaney et al. 1993; review: Ishak 1998). Granulomas may heal with leaving a trace, but numerous and in particular confluent granulomas form fibrosing/scarring conglomerates that produce a mass effect. Stenosing lesions cause obstructive jaundice (Bloom et al. 1978; Kusielewicz et al. 1988) and may mimic cholangiocarcinoma, e.g., Klatskin tumor (Pungpapong et al. 2006). On the other hand, granulomatous hepatitis in sarcoidosis was reported to cause biliary tract obstruction (Rezeig and Fashir 1997). Bile duct sarcoidosis may also resemble primary sclerosing cholangitis (Tombazzi et al. 2008). Granulomatous sarcoidotic cholangitis can lead to ductopenia, the underlying pathogenetic mechanism of the chronic cholestatic syndrome of sarcoidosis, discussed in a separate chapter.

Granulomatous Cholangitis in Tuberculosis

Scarring of tuberculous granulomas of the bile duct may be followed by biliary stricture and obstructive jaundice. Fibrous stricture is, however, nowadays a rare complication of biliary tract tuberculosis. It predominates in the common hepatic duct and in proximal and distal parts of the common bile duct (Fan et al. 1989; Kenneth et al. 1999; Kok and Yapp 1999; Prasad and Pandey 2001). This type of benign stricture may mimic bile duct malignancy/cholangiocarcinoma (Behera et al. 1997; Inal et al. 2000).

Crohn's Disease of the Bile Ducts

Crohn's disease and ulcerative colitis are considered as systemic diseases as they are associated with clinical and pathological manifestations involving organs outside the gastrointestinal tract (Rothfuss et al. 2006; Agrawal et al. 2007). Inflammatory lesions histologically compatible with Crohn's disease may develop in the wall of the bile ducts, albeit very rarely. Histologically proven Crohn's lesions of the common bile duct and the ampullary region have been reported to cause obstructive jaundice and acute pancreatitis. Biopsies of the papilla of Vater and common bile duct showed non-necrotizing expanding granulomas (Rivas et al. 2009). Ampullary stenosis with biliary obstruction has been reported in duodenal Crohn's disease (Foutch and Ferguson 1984; Spiess et al. 1992; Yung et al. 2005). Crohn's disease is also associated with a bile duct pathology resembling, or identical with, sclerosing cholangitis (Silbermintz et al. 2006).

Follicular Cholangitis

Segmental stricture/stenosis of the bile ducts found in patients with no history of biliary tract disease raise the suspicion of bile duct cancer (Maeda et al. 1998). Among inflammatory disorders clinically and radiologically mimicking cholangiocarcinoma, follicular cholangitis is a rare but rather typical example. Sclerosing and non-sclerosing forms are distinguished, but it is not known whether this reflects different evolution phases of the same process.

Follicular Lymphoplasmacytic Sclerosing Cholangitis

Among five patients with benign sclerosing cholangitis masquerading biliary tract carcinoma, two had cholangitis with prominent lymph follicle formation (Fujita et al. 2009). Follicular cholangitis can cause a wall thickening of extrahepatic ducts resulting in segmental stenosis and causing obstructive jaundice (Ajisaka et al. 2002). Radiological examinations in a 57-year-old female with a biliary stricture disclosed granular elevated lesions in the common hepatic duct and severe stenosis at the hepatic hilum. Under the tentative diagnosis of hepatic hilar bile duct cancer, the patient underwent extended right hepatectomy with bile duct resection. Histology showed a benign stricture of the bile duct associated with marked formation of lymph follicles with germinal centers (Aoki et al. 2003). In a 62-year-old male patient, this configuration led to the preoperative diagnosis of hilar cholangiocarcinoma and to subsequent resection of the extrahepatic bile duct and part of the right intrahepatic duct. The mucosa of the extrahepatic bile duct showed a coarse granulation and its wall was concentrically thickened to 0.5–0.7 cm. Histologically, the mucosal granulations were caused by prominent lymph follicles. The submucosa of the bile duct exhibited smooth muscle cells hyperplasia, diffuse neural hypertrophy, and diffuse lymph follicle formation (Lee et al. 2005). Among patients who had undergone surgery of the proximal extrahepatic bile duct from 1993 to 2008 on suspicion of proximal bile cancer, two were diagnosed with sclerosing follicular cholangitis, masquerading as hilar cholangiocarcinoma (Fujita et al. 2010).

Follicular Lymphoplasmacytic Non-sclerosing Cholangitis

The presence of lymph follicles, in part with germinal centers, is sometimes an incidental finding obtained during the workup of resected bile ducts (Fig. 8). The accumulation of lymphoid cells and plasmacytoid cells in the common bile duct associated with numerous lymph follicles may be massive, rising suspicion of a neoplastic lymphoproliferative process (Suzuki et al. 2004).

Follicular Cholangitis and Pancreatitis (Follicular Cholangiopancreatitis)

This is a distinct form of cholangiopancreatitis originally observed in five patients (Zen et al. 2012). Three of the patients presented with predominantly hilar bile duct stricture and two with a bulky pancreatic head. Four patients were treated surgically for suspected malignancy and one patient underwent liver transplantation with a clinical diagnosis of primary sclerosing cholangitis. Resected bile duct specimens showed a localized bile duct wall thickening in large hilar or perihilar bile ducts, associated with marked intrahepatic bile duct dilatation and liver atrophy (biliary-type atrophy). Whipple resection specimens of the two patients with pancreatic masses showed an ill-defined mass in the pancreatic head.

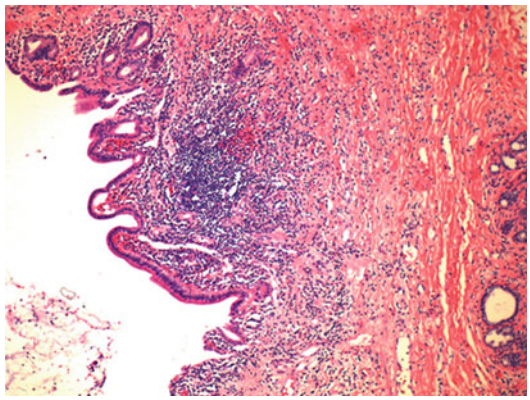

Fig. 8 Follicular cholangitis. The mucosa of the bile duct shows a well-developed lymph follicle without germinal center (hematoxylin and eosin stain)

Histologically, the biliary and pancreatic lesions showed similar features. There was a duct-centered lymphoplasmacytic infiltration with numerous lymph follicles, in part with germinal centers, associated with collagenous fibrous tissue deposition. The collagen-rich fibrosis differed from the storiform fibrosis typically seen in IgG4-related disease, and veno-obliterative lesions were not detected. Many plasma cells and occasional eosinophils were seen between the follicles. Immunohistochemically, only occasional IgG4-positive plasma cells were noted. The pathogenesis of this entity, which may clinically and radiologically be confounded with malignancy, is not yet known.

Pathogenesis

The pathogenesis of follicular cholangitis has not been clarified, but it is likely that it results from marked local immunostimulation driven by so far unknown antigens.

Differential Diagnosis

The histologic differential diagnosis of follicular cholangitis mainly comprises primary bile duct lymphoma (Kosuge et al. 1991; Joo et al. 2004).

Oriental Cholangitis

Introduction

Oriental cholangitis (synonyms: oriental cholangiohepatitis, recurrent cholangitis, recurrent pyogenic cholangitis, oriental infestational cholangitis, Hong Kong disease, intrahepatic pigment stone disease) is a progressive and potentially life-threatening hepatobiliary disease that is endemic in Asian countries and is characterized by episodic biliary obstruction, abdominal pain, and sepsis.

The cause of oriental cholangitis is unknown, but it is probably multifactorial, with parasites (e.g., *Clonorchis*) and bacterial infection thought

to play a role, including *Escherichia coli* and *Salmonella typhi* (reviews: Ong 1962; Stock and Fung 1962; Stock 1968; Seel and Park 1983; Reynolds et al. 1994). The disorder was first described in 1930 in a publication entitled "Common Duct Stones of Liver Origin" (Digby 1930). The author drew attention to the occurrence among the Chinese in Hong Kong of a syndrome to which Cook and coworkers gave the name "recurrent pyogenic cholangitis" in 1954 (Cook et al. 1954). Sporadic cases have been reported from outside of Asia, e.g., the United States (Kirby et al. 1995; Wilson et al. 1996; Honda et al. 2007). Such cases may be seen with increasing frequency because of the influx of immigrants from southeast Asia (Turner and Cramer 1983; Carmona et al. 1984; Sperling et al. 1997).

Clinical and Imaging Features

Oriental cholangitis is typically a disease of adults but also occurs in the pediatric age group (Bergman and Harris 1986). Patients typically present with symptoms and signs of recurrent cholangitis, namely, attacks of fever, chills, abdominal pain, and jaundice. Laboratory findings including leukocytosis and increased levels of bilirubin and alkaline phosphatase reflect the clinical features. Most patients have bile cultures positive for *Escherichia coli* (Ho and Wesson 1974), but there are also patients who are intrahepatic typhoid carriers (McFadzean and Ong 1966). The disorder is further characterized by the formation of pigmented, calcium bilirubinate stones that have a claylike consistency (the earthy stones of Aschoff) (Aschoff 1924) and often fill the ducts with casts (Federle et al. 1982).

Owing to obstruction, the gallbladder may be readily palpable for it is grossly distended (Stock 1968). During acute attacks, the gallbladder may perforate leading to biliary peritonitis. If jaundice is unrelieved, hepatic failure may ensue. Once established, there are periods of exacerbation and remission. During the former, obstruction of the larger ducts into which the infected segment drains occurs, and this results in back-flow infection of hitherto unaffected ducts. After recurrent attacks, biliary strictures develop behind which stones collect, associated with multiple honeycombed abscesses occur. Ultimately, the common bile duct is involved, and obstruction thereto is produced either by spasm of the sphincter or by stones (McFadzean and Ong 1966). Occasionally, a cholangiocarcinoma develops in the damaged ducts.

Imaging shows intrahepatic and extrahepatic bile duct strictures, often associated with primary bile duct stones and biliary obstruction (Scheible and Davis 1981; Sperling et al. 1997). Abdominal ultrasonography may reveal dilated common bile duct and common hepatic ducts, and numerous focal echogenicities with intense shadowing can be seen in the intrahepatic ducts, representing the multiple stones (Lim et al. 1990). However, some stones are isoechoic relative to the liver, lack acoustic shadowing, and may produce a cast in the dilated duct that can be missed at sonography (Chau et al. 1987). Sonography delineates bile duct dilatation in virtually all patients with oriental cholangitis, but the extrahepatic ducts are less often dilated than the intrahepatic ducts (66–79 % vs. 85–100 %; Chau et al. 1987; Lim et al. 1990). The stones detected with sonography may be either in the extrahepatic, the intrahepatic ducts, or both. In some patients, stones are located only in the segmental ducts. The detectability of stones with sonography depends on the stones' size, echogenicity, acoustic shadowing features, and location (Lee et al. 1986; Lim et al. 1990). Usually, intrahepatic stones are echogenic and shadowing, whereas some extrahepatic stones (around 25 %) do not cast shadow. Biliary mud/sludge or isoechoic bile duct stones filling the biliary tree as a cast may be missed as they sometimes appear as soft tissue masses and obscure visualization of intrahepatic ductal dilatation. CT demonstrates ductal dilatations, hyperattenuated stones or sludge, pneumobilia, intrahepatic stones forming casts, and parenchymal abnormalities such as biliary atrophy, the latter accompanied by intrahepatic bile duct crowding (Federle et al. 1982; Chan et al. 1989). Atrophy of the liver in oriental cholangitis is related to portal vein occlusion caused by the recurrent inflammatory process (Kusano

et al. 1992). The lateral segment of the left liver lobe is the most common and most early site of intrahepatic stones and intrahepatic ductal dilatation, and the posterior segment of the right liver lobe is the second most common site (Federle et al. 1982; Chan et al. 1989; Lim et al. 1990). Typically, ductal dilatation involves the first and second divisions of the intrahepatic ducts (Chan et al. 1989). This may be related to the more acute angulation of these ducts, resulting in less efficient drainage on this side of the biliary system (Ong 1962; Chan et al. 1989). Intrahepatic duct dilatation is often associated with strictures and impacted stones (Lim 1991), but strictures are rare in the extrahepatic ducts (Ong 1962), and the dilatation of the extrahepatic ducts generally is not related to the location of stones (Lim et al. 1990). Cholangiography typically shows a beaded appearance of the bile ducts, caused by alternating areas of strictures and dilatation (Chau et al. 1987; Kirby et al. 1995).

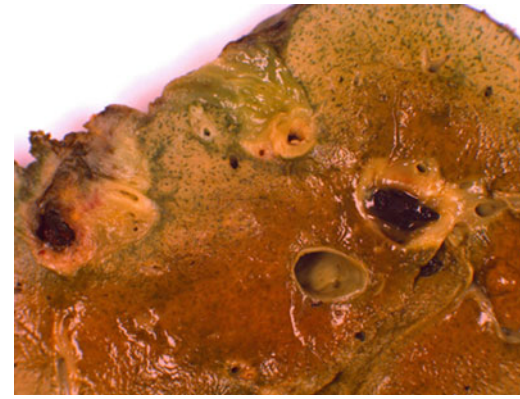

Fig. 9 Purulent intrahepatic cholangitis and pericholangitis

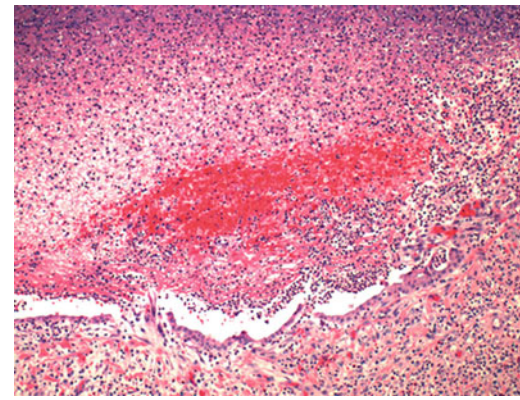

Fig. 10 Purulent and ulcerating cholangitis. The damaged and partially ulcerated mucosa exhibits a covering layer of fibrinopurulent and hemorrhagic exudate (hematoxylin and eosin stain)

Pathology

The main gross findings comprise dilated intrahepatic bile ducts with claylike stones that sometimes form large casts, bile duct scarring with strictures alternating with dilatations, biliary atrophy of the segments involved, and sometimes hepatic honey-combed abscesses located close to the altered bile ducts (Fig. 9). The common bile duct is grossly thickened and dilated, often to 2 cm or more in diameter, packed with soft and rather friable stones of all sizes and sometimes containing pus. The claylike stones may form a solid but friable cast of the entire common bile duct and its hepatic tributaries (Stock 1968; Chou and Chan 1980; Chan et al. 1989; Lim 1991). In some cases, parenchymal atrophy is associated with portal vein obstruction subsequent to pylephlebitis. The gallbladder is usually found to be grossly dilated, thin-walled, hardly inflamed, and rarely containing stones. The papilla of Vater is usually hypertrophied (Ong 1962), fibrosed, and rigid but patent, allowing passage of a large dilator without difficulty. In some cases, there is periampullary stricture due to fibrosis and passage of stones. It is thought that repeated passage of small pieces of stones or small stones through the sphincter of Oddi into the duodenum results in these ampullary changes (Ong 1962).

Histologically, the intrahepatic bile ducts show a purulent and ulcerating inflammation in early phases (Figs. 10 and 11). Later, they often show dilatation and fibrous strictures associated with a periductal lymphohistiocytic and often plasmacellular infiltration. In the lumina, one notes friable stony material stained with bile and sometimes containing purulent exudate in the stone clefts. In case of clonorchiasis, the stones

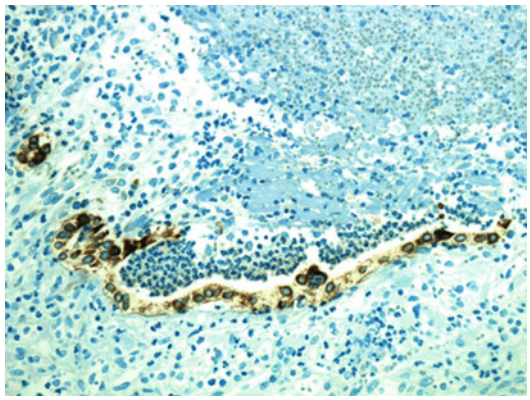

Fig. 11 Purulent ulcerating cholangitis. The injured epithelium detaches from the lamina propria, in part caused by the damaging action of neutrophils in the exudate (hematoxylin and eosin stain)

may contain *Clonorchis* eggs (Lim 1991). In the duct lumina, there are also pigmented mud, debris, and shed epithelial cells and frank pus. Fibrous tissue proliferates in the portal tracts, where also marked ductular proliferations are in evidence, associated with granulocytic ductulitis/periductulitis.

Cholangitis Glandularis Proliferans

Cholangitis grandularis proliferans (CGP; synonym: proliferative cholangitis) is defined as a histologic variant of primary sclerosing cholangitis (PSC). CGP is restricted to the extrahepatic bile ducts and typically presents as painless jaundice. In contrast to PSC, CGP mainly occurs in females and in the absence of inflammatory bowel disease. CGP may be associated with cholangiocarcinoma of the extrahepatic bile ducts (Richardson et al. 1993). However, whether CGP is a premalignant condition is not yet established.

Histopathologically, CGP is characterized by florid intramural proliferations of glandular elements in the extrahepatic bile ducts (Le Quesne and Ranger 1957; Krukowski et al. 1983; Graham et al. 1988). The main histologic differential diagnosis are situations with reactive proliferations of peribiliary glands.

Adenomyosis of the Bile Ducts

Whereas as adenomyosis (adenomyomatosis) is well known and common change in the gallbladder, adenomyosis primary to the extrahepatic bile ducts is a rare lesion. It mostly occurs in the common bile duct, where it can cause obstruction with jaundice (Lin 1983; Diel et al. 1989; Iwaki et al. 2008; Krutsay 2010). Adenomyosis has more often been found in the ampullary region (Huang et al. 1993; Treitschke et al. 2000; Kayahara et al. 2001). Histologically, regular cholangiocytes form invaginations of varying size, depth, and shape, with a sheath of smooth muscle cells. The glandular structures may develop hyperplastic changes (adenomyomatous hyperplasia; Iwaki et al. 2008; Numata et al. 2011). Circumscribed and tumor-like lesions are called adenomyoma and are discussed in a separate chapter. Adenomyosis of the bile duct has to be distinguished from cystically dilated peribiliary glands (Terada and Nakanuma 1990; Nakanuma et al. 1994; Fusai et al. 2005). Whether there is a pathogenic relationship between cystic peribiliary glands and adenomyosis is not known. But cystic peribiliary glands are not usually surrounded by smooth muscle bundles. Adenomyosis of the gallbladder has been found to be associated with benign stenosis of the terminal part of the common bile duct (Pera et al. 1971).

Fibroinflammatory Biliary Stricture

In older reports, non-traumatic benign inflammatory strictures of the extrahepatic bile ducts have been described, with a histology different from that of primary sclerosing cholangitis (Krukowski and Matheson 1989; Standfield et al. 1989). It has been found that benign fibrosing lesions and benign tumors cause 8–13.4 % of all biliary strictures (Hadjis et al. 1985; Corvera et al. 2005), and part of them form a masquerade of hilar cholangiocarcinoma. Later, it has been recognized that at least part of these disorders represent a distinct variant of cholangitis causing benign strictures that can clinically imitate a stenosing

neoplastic process. Fibroinflammatory stricture (FIBS) is a rare benign ductocentric myofibroblastic and inflammatory process that may mimic extrahepatic bile duct malignancy. In a study of 11 patients with FIBS, all presented with obstructive jaundice, and six patients had coexisting autoimmune disease. Radiographic features of bile duct cancer were seen in patients. Four patients had a definable mass associated with the extrapancreatic bile duct, while four patients had soft tissue infiltrating the porta hepatis. The preoperative CT scans showed residual biliary ductal dilatation following stenting in eight patients. ERC revealed a dominant stricture of the extrahepatic bile duct in all patients. Histologically, the bile ducts showed inflammatory and fibrosing changes, with a lymphoplasmacytic component in 45 %. All lesions except one expressed smooth muscle actin in the spindle cells of the fibrosed areas, hence representing myofibroblasts. In five cases, IgG4-positive plasma cells were found in the infiltrate, all of which had ductocentric lymphoplasmacytic inflammation (FIBS+IgG4) (Gamblin et al. 2009). The histopathologic and immunohistochemical findings, in particular the presence of IgG4-positive plasma cells, suggest that FIBS belongs to the growing group of IgG4-related sclerosing diseases. Other fibrosclerosing disorders of the large bile ducts have been found to contain IgG4-positive plasma cells, including IgG4-associated cholangitis (Webster et al. 2009) and lymphoplasmacytic sclerosing cholangitis (Kram et al. 2002; Takuma et al. 2011), which may mimic infiltrating hilar cholangiocarcinoma (Hamano et al. 2005).

Xanthogranulomatous Cholangitis (Xanthogranulomatous Cholangiopathy)

Introduction

Apart from xanthogranulomatous cholecystitis, inflammatory lesions characterized by the presence of numerous lipid-laden macrophages, rendering the involved tissue macroscopically yellow, xanthogranulomatous inflammations can also develop in the gastrointestinal tract, including stomach, pancreas, and colon (Oh et al. 2005; Kubosawa et al. 2007; Shima et al. 2008; Nishimura et al. 2011), and part of or the entire extrahepatic bile duct system, leading to mass lesions and stenosing alterations mimicking malignancy.

Involvement of Extrahepatic Bile Ducts in Xanthogranulomatous Cholecystitis

A xanthogranulomatous inflammation is well recognized in the gallbladder (Reed et al. 1994; Dixit et al. 1998; Guzman-Valdivia 2004). Xanthogranulomatous cholecystitis may rarely cause bile duct stenosis due to its extension into extrahepatic bile ducts (Kawana et al. 1990). The latter report refers to a female infant with obstructive jaundice who had a narrowing of the common bile duct due to surrounding xanthogranulomatous tissue. The biliary obstruction was released by cholecystectomy, resection of the choledochus, and hepaticojejunostomy.

Xanthogranulomatous Cholangitis

Xanthomatous choledochitis is a very rare stenosing bile duct disorder of unknown etiology. It is histologically characterized by the development of usually transmural inflammation rich in lipid-laden macrophages, similar to the histology of xanthogranulomatous cholecystitis, with marked thickening of the duct wall. One observation described a 9-month-old infant presenting with obstructive jaundice caused by a circumscribed xanthogranulomatous lesion located to the distal common bile duct (Prasil et al. 1999). The xanthogranulomatous inflammation may be restricted to the distal common bile duct, a lesion termed xanthogranulomatous choledochitis (Goldar-Najafi and Khettry 2003; Pantanowitz et al. 2004; Krishna et al. 2008; Ma et al. 2013). In the detailed report of Ma and coworkers (2013), the inflammatory process of the distal common bile duct presented in the form

gray-yellow protrusive lesions measuring up to 1.5 cm. Histologically, the fibroinflammatory process contained numerous foamy macrophages and multinucleated giant cells. Xanthogranulomatous cholangitis produces a type of stenosis of the common bile duct that may mimic cholangiocarcinoma (Pantanowitz et al. 2004; Kawate et al. 2006; Menias et al. 2008). Xanthogranulomatous cholangitis may involve the distal-most part of the common duct, extending into the ampullary tissue and mimicking ampullary cancer (Pottakkat et al. 2006). The xanthogranulomatous process may also develop in the pancreatic head itself and cause ampullary stenosis (xanthogranulomatous pancreatitis; Iyer et al. 2004). In few cases, the process involves the entire extrahepatic duct system. In a 34-year-old female patient, the xanthogranulomatous lesion reached from the hepatic ducts to the common bile duct, in the absence of gallstones (Kawate et al. 2006).

Xanthogranulomatous Changes in Primary Sclerosing Cholangitis

A subgroup of patients with primary sclerosing cholangitis (PSC) undergoing liver transplantation exhibited varying degrees of xanthogranulomatous cholangiopathy at the native liver hilum (Khettry et al. 2003; Keaveny et al. 2004). The presence of this alteration in the native liver hilum was associated with a higher rate of early posttransplant mortality or retransplantation (Keaveny et al. 2004). Histology of the lesions was characterized by an inflammatory reaction involving the hilar bile ducts with or without extension into the adjacent hilar soft tissues. The infiltrate contained foam cells, lymphocytes, plasma cells, and neutrophils.

Cholesterolosis of the Bile Ducts

Introduction

Biliary tract cholesterolosis is chiefly recognized for the gallbladder, where it consists in an accumulation of cholesteryl esters and triglycerides in macrophages at the level of the mucosa. This distinct alteration of the gallbladder mucosa has been described by Virchow in 1857 (Virchow 1857) and given the name of cholesterosis by Mentzer in 1925 (Mentzer 1925). Cholesterosis of the gallbladder has been categorized as one of the lesions representing so-called hyperplastic cholecystosis, referring to gallbladder adenoma, adenomyomatosis, and cholesterolosis (Govoni 1981; Berk et al. 1983; Csendes et al. 1998; 2003; Liu and Wang 2006). A prevalence of 4–8 % has been reported for gallbladder cholesterolosis, particularly in males. Apart from a diffuse involvement of the mucosa, resulting in the "strawberry gallbladder," cholesterolosis of the gallbladder may also be manifest in the form of cholesterol polyps with a size ranging from 2 to 10 mm (Sandri et al. 2003).

Cholesterolosis of the Extrahepatic Bile Ducts

In addition to the gallbladder, cholesterolosis also occurs in the extrahepatic bile ducts. The first report dates from 1958 (Fock 1958). This author described the findings obtained at choledochotomy in a 61-year-old woman who had had cholecystectomy but suffered from recurrent stone disease in the extrahepatic ducts. As soon as the common bile duct was opened, bright granular spots were noticed on its inner surface extending over the whole visible section of it. A biopsy revealed typical cholesterolosis. Extrahepatic bile duct cholesterolosis has preferentially been observed in the mucosa of the common bile duct (Fock 1958). Bile duct cholesterolosis has been observed in conjunction with bile duct carcinoma (Kin et al. 1994). The alteration occurs in the cystic duct (Gilloteaux et al. 1997) but has also been noted in the area of Vater's papilla (Peypoch 1971). Similar to the gallbladder, cholesterolosis of the common bile duct can present as endoluminal polypoid lesions, the so-called cholesterol polyps (Ikoma et al. 1995).

Selected References Grosse 1964; Fassati et al. 1967; Bontempini 1980; Okanobu

et al. 1985; Kamiya et al. 1986; Tokumura et al. 1991; Onodera et al. 1993; Ikoma et al. 1995; Arimoto et al. 1998; Akahori et al. 2002; Horaguchi et al. 2007; Fukatsu et al. 2008.

Gross Pathology

In the patient reported by Bontempini (1980), the resected common bile duct showed a typical "strawberry mucosa" ("coledoco al fragola" in the original Italian report), characterized by numerous miliary-sized lesions of yellowish-white color on a pink mucosal background. Similar to the gallbladder, common bile duct cholesterolosis can present as a cholesterol polyp. In the 73-year-old male patient reported by Ikoma and coworkers (1995), endoscopic retrograde cholangiography revealed a filling defect in the common bile duct 3 cm below the confluence of the cystic duct, and abdominal ultrasonography disclosed a small polypoid lesion at this site. Intraoperative cholangioscopy revealed two yellow polypoid tumors. Macroscopically, the excised specimen showed two flat polypoid lesions of 6 and 5 mm size, respectively, with a yellow and granular surface (Ikoma et al. 1995).

Histopathology

Except cholesterol polyps, cholesterolotic deposits of the common bile duct are usually rather small, but they closely resemble those seen in the gallbladder, i.e., characterized by the superficial mucosal accumulation of nests of foamy macrophages. The histology of cholesterol polyps of the extrahepatic bile ducts is characterized by clustered foamy macrophages that occupy the lamina propria and, by their expansion, cause the polypoid deformation of the mucosa (Ikoma et al. 1995). In two patients with bile duct cancer, foamy cell clusters representing a cholesterolosis phenotype have been described to be located in the stromal components of papillary cholangiocarcinoma, forming cholesterol polyps covered by malignant epithelium. These lesions were grossly visible as small yellow spots (Kin et al. 1994). In cholesterolosis of the cystic duct, electron microscopic examinations revealed that mucous secretory granules appeared dilated, and peculiar intracellular cholesterol deposits were detected in the apical and subapical regions of the cells and around condensed mitochondria (Gilloteaux et al. 1997). Similar ultrastructural changes have been observed in cholesterolosis of the gallbladder (Satoh and Koga 1997).

Differential Diagnosis

The differential diagnosis of ductal cholesterol polyp mainly includes gallbladder cholesterol polyps that may detach and be translocated to the common bile duct, eventually followed by polyp impaction and biliary obstruction (Takii et al. 1994).

References

Adachi et al. 1991. http://www.ncbi.nlm.nih.gov/pubmed/2030568

Agrawal D, Rukkannagari S, Kethu S (2007) Pathogenesis and clinical approach to extraintestinal manifestations of inflammatory bowel disease. Minerva Gastroenterol Dietol 53:233–248

Ajisaka H, Fujita H, Kaji M, Maeda K, Yabushita K, Konishi K, Uchiyama A, Miwa A (2002) Lymphoplasmacytic sclerosing pancreatocholangitis successfully treated by pancreatoduodenectomy. J Hepatobiliary Pancreat Surg 9:522–526

Akahori T, Ohyama T, Yasukawa J, Yoshikawa T (2002) A case of cholesterosis of the common bile duct (in Japanese). J Jpn Surg Assoc 63:2525–2528

Aoki T, Kubota K, Oka T, Hasegawa K, Hirai I, Makuuchi M (2003) Follicular cholangitis: another cause of benign biliary stricture. Hepato-Gastroenterology 50:639–642

Arimoto Y, Yamazaki O, Kawai S, Kubo N, Yamada S, Ko M et al (1998) A case of polypoid cholesterosis of the common bile duct (in Japanese). Jpn J Gastroenterol 95:348–352

Aschoff L (1924) Lectures on pathology. Hoeber, New York

Behera A, Kocher R, Dhavan S, Aggarwal S, Singh K (1997) Isolated CBD tuberculosis mimicking malignant obstruction. Am J Gastroenterol 92:2122–2123

Bergman KS, Harris BH (1986) Oriental cholangitis. J Pediatr Surg 21:573–575
Berk RN, van der Vegt JH, Lichtenstein JE (1983) The hyperplastic cholecystoses: cholesterolosis and adenomyomatosis. Radiology 146:593–601
Bloom R, Sybert A, Mascatello VJ (1978) Granulomatous biliary tract obstruction due to sarcoidosis. Report of a case and review of the literature. Am Rev Respir Dis 117:783–787
Bontempini L (1980) A remark about a cholesterolosis of the common bile duct (in Italian). Pathologica 72:409–412
Brauner M, Bokobza G, Legrand I, Hassan M (1988) Ultrasonic diagnosis of non-calculous intraluminal obstruction in the extrahepatic bile ducts. Apropos of 8 cases (in French). J Radiol 69:197–203
Carmona RH, Crass RA, Lim RC, Trunkey DD (1984) Oriental cholangitis. Am J Surg 148:117–124
Chan FL, Man SW, Leong LLY, Fan ST (1989) Evaluation of recurrent pyogenic cholangitis with CT: analysis of 50 patients. Radiology 170:165–169
Chau EMT, Leong LLY, Chan FL (1987) Recurrent pyogenic cholangitis: ultrasound evaluation compared with endoscopic retrograde cholangiopancreato-graphy. Clin Radiol 38:79–85
Chou ST, Chan CW (1980) Recurrent pyogenic cholangitis: a necropsy study. Pathology 12:415–428
Collins CD, Forbes A, Harcourt-Webster JN, Francis ND, Gleeson JA, Gazzard BG (1993) Radiological and pathological features of AIDS-related polypoid cholangitis. Clin Radiol 48:307–310
Cook J, Hou PC, Ho HC, McFadzean AJ (1954) Recurrent pyogenic cholangitis. Br J Surg 42:188–203
Corvera CU, Blumgart LH, Darvishian F, Klimstra DS, DeMatteo R, Fong Y, D'Angelica M et al (2005) Clinical and pathologic features of proximal biliary strictures masquerading as hilar cholangiocarcinoma. J Am Coll Surg 201:862–869
Csendes A, Smok G, Burdiles P, Diaz JC, Maluenda F, Korn O (1998) Histological findings of gallbladder mucosa in 95 control subjects and 80 patients with asymptomatic gallstones. Dig Dis Sci 43:931–934
Csendes A, Burdiles P, Smok G, Csendes P, Burgos A, Recio M (2003) Histologic findings of gallbladder mucosa in 87 patients with morbid obesity without gallstones compared to 87 control subjects. J Gastrointest Surg 7:547–551
Devaney K, Goodman ZD, Epstein MS, Zimmerman HJ, Ishak KG (1993) Hepatic sarcoidosis. Clinicopathologic features in 100 patients. Am J Surg Pathol 17:1272–1280
Diel R, Hamborg V, Krüger C (1989) Primary adenomyomatosis of the choledochus as a rare cause of obstructive jaundice (in German). Z Gastroenterol 27:228–232
Digby KH (1930) Common duct stones of liver origin. Br J Surg 17:578
Dixit VK, Prakash A, Guptra A, Pandey M, Gautam A, Kumar M, Shukla VK (1998) Xanthogranulomatous cholecystitis. Dig Dis Sci 43:940–942
Ducreux M, Buffet C, Lamy P, Beaugerie L, Fritsch J, Choury A, Ligoury C, Longuet P et al (1995) Diagnosis and prognosis of AIDS-related cholangitis. AIDA 9:875–880
Ezaki T, Okamura T, Yoshida Y, Kitamura M, Furuta A, Haratake J, Shirakusa T (1994) A small polypoid lesion in the lower common bile duct: a case study. Endoscopy 26:271
Fan ST, Ng IOL, Choi TK, Lai ECS (1989) Tuberculosis of the bile duct: a rare cause of biliary stricture. Am J Gastroenterol 84:413–414
Farkas I, Patko A, Kovari M (1980) Obstructive jaundice caused by postsurgical granuloma of the common bile duct. Endoscopy 12:250–253
Fassati LR, Doldi S, Tajana A (1967) Cholesterolosis of the common bile duct (in Italian). Arch Ital Chir 93:146–152
Federle MP, Cello JP, Laing FC, Jeffrey RB (1982) Recurrent pyogenic cholangitis in Asian immigrants. Radiology 143:151–156
Fock G (1958) Cholesterolosis of the common bile duct: report of a case. Acta Chir Scand 116:33–35
Forbes A, Blanshard C, Gazzard B (1993) Natural history of AIDS related sclerosing cholangitis: a study of 20 cases. Gut 34:116–121
Foutch PG, Ferguson DR (1984) Duodenal Crohn's disease complicated by common bile duct obstruction: report of a case and review of the literature. Am J Gastroenterol 79:520–524
Fujita T, Kojima M, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Ochiai A, Kinoshita T (2009) Incidence, clinical presentation and pathological features of benign sclerosing cholangitis of unknown origin masquerading as biliary carcinoma. J Hepato-Biliary Pancreat Surg 17:139–146
Fujita T, Kojima M, Kato Y, Gotohda N, Takahashi S, Konishi M, Kinoshita T (2010) Clinical and histopathological study of "follicular cholangitis": sclerosing cholangitis with prominent lymphocytic infiltration masquerading as hilar cholangiocarcinoma. Hepatol Res 40:1239–1247
Fukatsu H, Kawamoto H, Harada R, Fujii M, Tsutsumi K, Ogawa T, Ishida E, Okada H et al (2008) Cholesterolosis of the common bile duct with anomalous arrangement of the pancreatobiliary ductal system. Gastrointest Endosc 67:1172–1173
Fusai G, Tucker O, Nik Sulaiman NM, Karani J, Rela M, Portmann B (2005) Peribiliary cysts can mimic Caroli's disease: a case report. Int J Surg Pathol 13:379–382
Gamblin TC, Krasinskas AM, Slivka AS, Tublin ME, Demetris J, Shue E, Caro S et al (2009) Fibroinflammatory biliary stricture: a rare bile duct lesion masquerading as cholangiocarcinoma. J Gastrointest Surg 13:713–721
Gilloteaux J, Hawkins WS, Gilloteaux LC, Jasso J, Kelly TR (1997) Ultrastructural aspects of human cystic duct epithelium as a result of cholelithiasis and cholesterolosis. Microsc Res Tech 39:22–38

Gleeson MJ, McMullin JP (1987) Suture granuloma simulating a cholangiocarcinoma. Br J Surg 74:1181

Goldar-Najafi A, Khettry U (2003) Xanthogranulomatous choledochitis: a previously undescribed mass lesion of hepatobiliary and ampullary region. Semin Liver Dis 23:101–106

Govoni AF (1981) Hyperplastic cholecystosis: an analysis and review of the different pathologic and radiologic aspects. Radiol Diagn (Berlin) 22:557–588

Graham SM, Barwick K, Cahow CE, Baker CC (1988) Cholangitis glandularis proliferans. A histologic variant of primary sclerosing cholangitis with distinctive clinical and pathological features. J Clin Gastroenterol 10:579–583

Grosse H (1964) Cholesterolosis of the ductus choledochus (in German). Acta Hepatosplenol 11:293–299

Guzman-Valdivia G (2004) Xanthogranulomatous cholecystitis: 15 years' experience. World J Surg 28:254–257

Hadjis NS, Collier NA, Blumgart LH (1985) Malignant masquerade at the hilum of the liver. Br J Surg 72:659–661

Hamano H, Kawa S, Uehara T, Ochi Y, Takayama M, Komatsu K, Muraki T, Umino J et al (2005) Immunoglobulin G4-related lymphoplasmacytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma: part of a spectrum of autoimmune pancreatitis? Gastrointest Endosc 62:152–157

Hirota M, Ikei S, Mori K, Sakamoto K, Yamane T, Katafuchi S, Goto M, Akagi M (1989) Adenofibromyomatous hyperplasia of the extrahepatic bile duct. J Jpn Soc Clin Surg 50:1423–1428

Ho CS, Wesson DE (1974) Recurrent pyogenic cholangitis in Chinese immigrants. AJR Am J Roentgenol 122:368–374

Honda H, Liu D, Nishida SD, Young RS (2007) Oriental cholangiohepatitis from outside of Asia. Hawaii Med J 66:9–11

Horaguchi J, Fujita N, Noda Y, Kobayashi G, Ito K, Takasawa O, Obana T, Endo T et al (2007) Choledochocele associated with superficial spreading cancer with cholesterolosis of the bile duct. J Gastroenterol 42:318–324

Huang HL, Liu CL, Yang TL, Lin HJ (1993) Adenomyoma of the papilla of vater: a case report. Zonghua Yi Xue Za Zhi (Taipei) 51:386–388

Hussain D, Ahmed M (2003) Liver cyst with inflammatory hepatic duct polyp. J Coll Phys Surg Pak 13:418–420

Ikoma A, Ueno T, Tanaka K, Saisho A, Yoshida A, Taira A (1995) Cholesterol polyp of the common bile duct. Am J Gastroenterol 90:1534–1535

Inal M, Aksungur E, Akgüg E, Demirbas O, Oguz M (2000) Biliary tuberculosis mimicking cholangiocarcinoma: treatment with metallic biliary endoprosthesis. Am J Gastroenterol 95:1069–1071

Ishak KG (1998) Sarcoidosis of the liver and bile ducts. Mayo Clin Proc 73:467–472

Iwaki K, Shibata K, Ohta M, Endo Y, Uchida H, Tominaga M, Okunaga R, Kai S, Kitano S (2008) Adenomyomatous hyperplasia of the common bile duct: report of a case. Surg Today 38:85–89

Iyer VK, Aggarwal S, Mathur M (2004) Xanthogranulomatous pancreatitis: mass lesion of the pancreas simulating pancreatic carcinoma – a report of two cases. Indian J Pathol Microbiol 47:36–38

Joo YE, Park CH, Lee WS, Kim HS, Choi SK, Cho CK, Rew JS, Kim SJ, Maetani I (2004) Primary non-Hodgkin's lymphoma of the common bile duct presenting as obstructive jaundice. J Gastroenterol 39:692–696

Kamiya J, Nimura Y, Harakawa N, Shionoya S (1986) Studies on cholesterosis of the common bile duct (in Japanese). Nippon Shokakibyo Gakkai Zasshi 83:189–195

Kawana T, Suita S, Arima T, Hirayama Y, Ishii K, Minamishima I, Ueda K, Hirata T et al (1990) Xanthogranulomatous cholecystitis in an infant with obstructive jaundice. Eur J Pediatr 149:765–767

Kawate S, Ohwada S, Ikota H, Hamada K, Kashiwabara K, Morishita Y (2006) Xanthogranulomatous cholangitis causing obstructive jaundice: a case report. World J Gastroenterol 12:4428–4430

Kayahara M, Ohta T, Kitagawa H, Miwa K, Urabe T, Murata T (2001) Adenomyomatosis of the papilla of Vater: a case illustrating diagnostic difficulties. Dig Surg 18:139–142

Keaveny AP, Gordon FD, Goldar-Najafi A, Lewis WD, Pomfret EA, Pomposelli JJ et al (2004) Native liver xanthogranulomatous cholangiopathy in primary sclerosing cholangitis: impact on posttransplant outcome. Liver Transpl 10:115–122

Kenneth YY, Kok KYY, Samuel KS (1999) Tuberculosis of bile duct. A rare cause of obstructive jaundice. Am J Gastroenterol 29:161–164

Khettry U, Keaveny AP, Goldar-Najafi A, Lewis WD, Pomfret EA, Pomposelli JJ et al (2003) Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. Hum Pathol 34: 1127–1136

Kin Y, Nimura Y, Kamiya J, Kondo S, Nagino M (1994) Cholesterosis in bile duct carcinoma. Gastrointest Endosc 40:92–93

Kirby CL, Horrow MM, Rosenberg HK, Oleaga JA (1995) US case of the day. Oriental cholangiohepatitis. Radiographics 15:1503–1506

Kok KY, Yapp SK (1999) Tuberculosis of the bile duct: a rare cause of obstructive jaundice. J Clin Gastroenterol 29:161–164

Kosuge T, Makuuchi M, Ozaki H, Kinoshita T, Takenaka T, Mukai K (1991) Primary lymphoma of the common bile duct. Hepato-Gastroenterology 38:235–238

Kram MT, May LD, Cooperman A, Bernstein S, Abedeer R, Cohen PR (2002) Lymphoplasmacytic sclerosing pancreatitis and cholangitis. Gastrointest Endosc 55:588–590

Krishna RP, Kumar A, Singh RK, Sikora S, Saxena R, Kapoor VK (2008) Xanthogranulomatous

inflammatory stricture of extrahepatic biliary tract: presentation and surgical management. J Gastrointest Surg 12:836–841
Krukowski ZH, Matheson NA (1989) Benign non-traumatic inflammatory strictures of the extrahepatic biliary system. Br J Surg 76:1354
Krukowski ZH, McPhie JL, Farquharson AG, Matheson NA (1983) Proliferative cholangitis (cholangitis glandularis proliferans). Br J Surg 70:166–171
Krutsay M (2010) Adenomyosis of the common bile duct (in Hungarian). Magy Onkol 54:179–180
Kubosawa H, Yano K, Oda K, Shiobara M, Ando K, Nunomura M, Sarasgina H (2007) Xanthogranulomatous gastritis with pseudosarcomatous changes. Pathol Int 57:291–295
Kubota K, Bandai Y, Watanabe M, Toyoda H, Oka T, Makuuchi M (1996) Biliary stricture due to mucosal hyperplasia of the common bile duct: a case report. Hepato-Gastroenterology 43:147–151
Kusano S, Okada Y, Endo T, Yokoyama H, Ohmiya H, Atari H (1992) Oriental cholangiohepatitis: correlation between portal vein occlusion and hepatic atrophy. AJR Am J Roentgenol 158:1011–1014
Kusielewicz D, Duchatelle V, Valeyre D, Battesti JP, Vissuzaine C, Coste T, Rautureau J (1988) Obstructive jaundice caused by granulomatous stenosis of the extrahepatic bile ducts in sarcoidosis (in French). Gastroenterol Clin Biol 12:664–667
Lautatzis M, Shoenut JP, Scurrah J, Micflikier AB (1988) Pseudocalculus of the common bile duct. Can J Surg 31:37–38
Le Quesne LP, Ranger I (1957) Cholecystitis glandularis proliferans. Br J Surg 44:447–448
Lee JT, Yoo HS, Kim KW, Lee DY, Lee YH, Suh JH (1986) The capability of real time ultrasound in the detection of the biliary tract stones. J Korean Soc Med Ultrasound 5:33–40
Lee JY, Lim JH, Lim HK (2005) Follicular cholangitis mimicking hilar cholangiocarcinoma. Abdom Imaging 30:744–747
Lee CK, Dong SH, Jung SH, Jang JY, Kim HJ, Kim BH, Chang YW, Chang R, Kim YW (2007) Pyogenic granuloma of the common bile duct in a patient with choledochoduodenostomy. Endoscopy 39(suppl 1): E282–E283
Lim JH (1991) Oriental cholangiohepatitis: pathologic, clinical and radiologic features. AJR Am J Roentgenol 157:1–8
Lim JH, Ko YT, Lee DH, Hong KS (1990) Oriental cholangiohepatitis: sonographic findings in 48 cases. AJR Am J Roentgenol 155:511–514
Lin QT (1983) Adenomyomatosis of the common bile duct: report of 3 cases (in Chinese). Zonghua Wai Ke Za Zhi 21:360–361
Liu YL, Wang JT (2006) Hyperplastic cholecystoses: efforts should be made to recognize and treat them. Hepato-Biliary Pancreat Dis Int 5:334–336
Ma J, Fan H, Wei P, Kou JT, He Q (2013) Lower bile duct stenosis caused by xanthogranulomatous cholangitis complicated with jaundice. Chin Med J (Engl) 126:4600
Maeda S, Yamanaka N, Tanaka T, Tanaka W, Yasui C, Yamanaka J, Imakita M, Okada T et al (1998) Idiopathic benign biliary stricture. J Hepato-Biliary Pancreat Surg 5:463–466
McFadzean AJ, Ong GB (1966) Intrahepatic typhoid carriers. Br Med J 1:1567–1571
Menias CO, Surabhi VR, Prasad SR, Wang HL, Narra VR, Chintapalli KN (2008) Mimics of cholangiocarcinoma: spectrum of disease. Radiographics 28:1115–1129
Mentzer SH (1925) Cholesterosis of the gallbladder. Am J Pathol 1:383–388
Murphy JR, Shay SS, Moses FM, Braxton J, Jaques DP, Waong RKH (1990) Suture granuloma masquerading as malignancy of the biliary tract. Dig Dis Sci 35:1176–1179
Nagayama Y, Kobayashi N, Yamabe H (1992) Obstructive jaundice caused by polypoid inflammatory granuloma in a consanguineous case. Dig Dis Sci 37:613–617
Nakanuma Y, Sasaki M, Terada T, Harada K (1994) Intrahepatic peribiliary glands of humans. II. Pathologic spectrum. J Gastroenterol Hepatol 9:80–86
Nishimura M, Nishihara T, Hirose T, Ishikawa Y, Yamaoka R, Inoue H, Tatsuta M (2011) Xanthogranulomatous pancreatitis mimicking a malignant cystic tumor of the pancreas: report of a case. Surg Today 41:1310–1313
Norton ID, Gostout CJ, Baron TH, Geller A, Petersen BT, Wiersema MJ (2002) Safety and outcome of endoscopic snare excision of the major duodenal papilla. Gastrointest Endosc 56:239–243
Numata M, Morinaga S, Watanabe T, Tamagawa H, Yamamoto N, Shiozawa M, Kameda Y, Ohkawa S, Rino Y et al (2011) A case of adenomyomatous hyperplasia of the extrahepatic bile duct. Case Rep Gastroenterol 5:457–462
Oh YH, Seong SS, Jang KS, Chung YW, Park CH, Park YW, Han DS (2005) Xanthogranulomatous inflammation presenting as a submucosal mass of the sigmoid colon. Pathol Int 55:440–444
Okanobu K, Onishi N, Tomioka N et al (1985) A case of multiple polypoid cholesterolosis of the common bile duct (in Japanese). Tan to Sui 6:1427–1432
Ong GB (1962) A study of recurrent pyogenic cholangitis. Arch Surg 84:199–225
Onodera K, Ooe N, Sawa M, Maiya N, Kato K, Kusano M et al (1993) A case of cholesterosis of the common bile duct (in Japanese). J Jpn Surg Assoc 54:532–536
Pantanowitz L, Goldar-Najafi A, Nasser I (2004) Xanthogranulomatous choledochitis mimicking cholangiocarcinoma. Pathol Int 54:213–215
Pera C, Fernandez-Cruz L, Villa J (1971) Vesicular adenomyomatosis and its association with benign stenosis of the terminal part of the common bile duct (in Spanish). Rev Esp Enferm Apar Dig 34:569–586
Peypoch IA (1971) Colesterolosis de las vias biliares. Barcelona Quir 4:433

Pottakkat B, Saxena R, Nag HH, Kumari N, Krishnani N (2006) Ampullary xanthogranulomatous inflammation mimicking periampullary cancer: report of a case. J Pancreat (Onleine) 7:222–225

Prasad A, Pandey KK (2001) Tuberculous biliary strictures: uncommon cause of obstructive jaundice. Australas Radiol 45:365–368

Prasil P, Cayer S, Lemay M, Pelletier L, Cloutier R, Leclerc S (1999) Juvenile xanthogranuloma presenting as obstructive jaundice. J Pediatr Surg 34:1072–1073

Pungpapong S, Steers JL, Wallace MB, Krishna M, Keaveny AP (2006) Hepatobiliary sarcoidosis mimicking Klatskin's cholangiocarcinoma. Gastrointest Endosc 64:124–125

Reed A, Ryan C, Schwartz SI (1994) Xanthogranulomatous cholecystitis. J Am Coll Surg 179:249–252

Reynolds WR, Brinkman JD, Haney BD, Fiticsar JE (1994) Oriental cholangiohepatitis. Mil Med 159:158–160

Rezeig MA, Fashir BM (1997) Biliary tract obstruction due to sarcoidosis: a case report. Am J Gastroenterol 92:527–528

Richardson AJ, Grierson JM, Tait N, Williams SJ, Little JM (1993) A case of cholangitis glandularis proliferans and cholangiocarcinoma of the common bile duct. HPB Surg 6:205–209

Rivas JM, Erim T, Berho ME, Petras RE, Castro FJ (2009) Crohn's disease of the common bile duct and ampulla causing obstructive jaundice and acute pancreatitis. Am J Gastroenterol 104:1053–1055

Ro JO (1975) Extrahepatic obstructive jaundice due to inflammatory polyp of common bile duct. Postgrad Med 58:259–260

Rothfuss KS, Stange EE, Herrlinger KR (2006) Extraintestinal manifestations and complications in inflammatory bowel diseases. World J Gastroenterol 12:4819–4831

Sandri L, Colecchia A, Larocca A, Vestito A, Capodicasa S, Azzaroli F, Mazzella G et al (2003) Gallbladder cholesterol polyps and cholesterolosis. Minerva Gastroenterol Dietol 49:217–224

Satoh H, Koga A (1997) Fine structure of cholesterolosis in the human gallbladder and the mechanism of lipid accumulation. Microsc Res Tech 39:14–21

Scheible FW, Davis GB (1981) Oriental cholangiohepatitis: preoperative radiographic and ultrasonographic diagnosis. Gastrointest Radiol 6:269–271

Seel DJ, Park YK (1983) Oriental infestational cholangitis. Am J Surg 146:188–203

Shima Y, Saisaka Y, Furukita Y, Nishimura T, Horimi T, Nakamura T, Tanaka K, Shibuya Y et al (2008) Resected xanthogranulomatous pancreatitis. J Hepato-Biliary Pancreat Surg 15:240–242

Shtamler B, Suprin H, Keret D (1973) Symptomatic inflammatory polyp of Vater's ampulla (in Hebrew). Harefuah 84:605–607

Silbermintz A, Krishnan S, Banquet A, Markowitz J (2006) Granulomatous pneumonitis, sclerosing cholangitis, and pancreatitis in a child with Crohn's disease: response to infliximab. J Pediatr Gastroenterol Nutr 42:324–326

Sperling RM, Koch J, Sandhu JS, Cello JP (1997) Recurrent pyogenic cholangitis in Asian immigrants to the United States: natural history and role of therapeutic ERCP. Dig Dis Sci 42:865–871

Spiess SE, Braun M, Vogelzang RL, Craig RM (1992) Crohn's disease of the duodenum complicated by pancreatitis and common bile duct obstruction. Am J Gastroenterol 87:1033–1036

Stamatakis et al. 1979. http://www.ncbi.nlm.nih.gov/pubmed/454993

Standfield NJ, Salisbury JR, Howard ER (1989) Benign non-traumatic inflammatory strictures of the extrahepatic biliary system. Br J Surg 76:849–852

Stock FE (1968) Oriental cholangiohepatitis. Proc R Soc Med 61:223–224

Stock FE, Fung JH (1962) Oriental cholangiohepatitis. Arch Surg 84:409–412

Sun XJ, Shi JS, Han Y, Wang JS, Ren H (2004) Diagnosis and treatment of polypoid lesions of the gallbladder: report of 194 cases. Hepato-Biliary Pancreat Dis Int 3:591–594

Suzuki S, Tanaka S, Suzuki M, Imazato M, Hayashi T, Hanyu F, Kayano H, Ban S (2004) Mucosa-associated lymphoid tissue-type lymphoproliferative lesions of the common bile duct. Hepato-Gastroenterology 51:110–113

Takii Y, Shirai Y, Kanehara H, Hatakeyama K (1994) Obstructive jaundice caused by a cholesterol polyp of the gallbladder: report of a case. Surg Today 24:1104–1106

Takuma K, Kamisawa T, Igarashi Y (2011) Autoimmune pancreatitis and IgG4-related sclerosing cholangitis. Curr Opin Rheumatol 23:80–87

Terada T, Nakanuma Y (1990) Pathological observations of intrahepatic peribiliary glands in 1,000 consecutive autopsy livers. III. Survey of necroinflammation and cystic dilatation. Hepatology 12:1229–1233

Tokumura H, Shimizu F, Tezuka F (1991) Two cases of cholesterosis of the common bile duct (in Japanese). Jpn J Gastroenterol Surg 24:2046–2050

Tombazzi C, Waters B, Ismail MK, Sylvestre PB, Martinez-Hernandez A, Riely CA (2008) Sarcoidosis mimicking primary sclerosing cholangitis requiring liver transplantation. Ann Hepatol 7:83–86

Treitschke F, Beger HG, Meessen D, Schoenberg MH (2000) Benign tumors of the Vater's papilla (in German). Dtsch Med Wochenschr 125: 1030–1034

Turner WW, Cramer CR (1983) Recurrent oriental cholangiohepatitis. Surgery 93:397–401

Virchow R (1857) Über das Epithel der Gallenblase und über einen intermediären Stoffwechsel des Fettes. Virchows Arch 11:574–578

Webster GJ, Pereira SP, Chapman RW (2009) Autoimmune pancreatitis/IgG4-associated cholangitis and primary sclerosing cholangitis – overlapping or separate diseases? J Hepatol 51:398–402

Wilson MK, Stephen MS, Mathur M, Sheldon D, Storey D (1996) Recurrent pyogenic cholangitis or "oriental cholangiohepatitis" in occidentals: case reports of four patients. Aust NZ J Surg 66:649–652

Yung K, Oviedo J, Farraye FA, Becker JM, Andrews CW, Lichtenstein D (2005) Ampullary stenosis with biliary obstruction in duodenal Crohn's disease: a case report and review of the literature. Dig Dis Sci 50:1118–1121

Zen Y, Ishikawa A, Ogiso S, Heaton N, Portmann B (2012) Follicular cholangitis and pancreatitis – clinicopathological features and differential diagnosis of an under-recognized entity. Histopathology 60: 261–269

Zubov NA, Zubkov VG (1983) Hyperplastic changes in the major duodenal papilla in human opisthorchiasis. Arkh Patol 45:34–38

Reactive Bile Duct Alterations Mimicking Biliary Cancer: Eosinophilic Cholangitis/Cholangiopathy and Other Eosinophilic Disorders

143

Contents

Abstract

A distinct spectrum of disorders causing biliary obstruction is characterized by eosinophilic infiltration. Eosinophilic cholangiopathy denotes an alteration characterized by an increased infiltration of bile duct walls with eosinophils, associated with stenosing bile duct fibrosis. The disorder may be combined with eosinophilic cholecystitis. In part of cases, bile duct fibrosis is severe, mimicking sclerosing cholangitis. Rare forms show additional granuloma formation that also involves liver tissue (eosinophilic granulomatous cholangiohepatitis). In forms that extend into the liver substance, eosinophilic abscesses may develop. These intraparenchymal lesions can develop a vigorous inflammatory reaction followed by inflammatory fibrosis, ending up in mass lesions mimicking liver tumors (eosinophilic pseudotumors).

Eosinophilic Cholangiopathy and Eosinophilic Cholangitis

Introduction

Eosinophilic cholangiopathy (synonym: eosinophilic cholangitis) denotes an alteration characterized by an increased infiltration of bile duct walls with eosinophils (review: Nashed et al. 2010). A similar change can occur in the gallbladder (eosinophilic cholecystitis; Fox and Mainwaring 1972;

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_143

Kerstein et al. 1976; Leegard 1980), and in case both bile ducts and gallbladder are involved, the term eosinophilic cholangiopathy is applied. First reports on this spectrum of disorders related to eosinophilic infiltrations of the gallbladder (Albot et al. 1949; Fox and Mainwaring 1972), and Kerstein and coworkers described what is still called eosinophilic cholecystitis (Kerstein et al. 1976). Since then, several further examples of biliary tract eosinophilia have been reported, under variable situations of eosinophilia. Eosinophilic cholangitis can be combined with eosinophilic cholecystitis (Leegard 1980). Eosinophilic cholangiopathy also occurs in the pediatric age group (Murray and Woods 1981; Waguet et al. 2000).

Selected References: Leegard 1980; Butler et al. 1985; Tazawa 1996; Tenner et al. 1997; Rodgers et al. 2001; Abdalla and Vauthey 2002; Herrerias-Gutierrez 2003; Vauthey et al. 2003; Duseja et al. 2005; Reyes et al. 2005; Jeyaman et al. 2007; Matsumoto et al. 2007; Chen et al. 2009; Iwamuro et al. 2009; Dubay et al. 2010; Nashed et al. 2010.

Eosinophilic cholangitis is associated with eosinophilic gastroenteritis (Murray and Woods 1981; Schoonbroodt et al. 1995; Kuniyoshi et al. 1998; Jimenez-Saenz et al. 2003), supposed allergic reactions (Matsumoto et al. 2007), idiopathic hypereosinophilic syndrome (Sussman et al. 2008), and other forms of peripheral eosinophilia of unknown cause (Butler et al. 1985). Eosinophilic cholangitis has also been found in association with other and much rarer instances of eosinophilic organ inflammation, e.g., eosinophilic ureteritis (Platt et al. 1990). In one patient, eosinophilic cholangitis was associated with IgG4-related cholangitis (Iwamuro et al. 2009).

Eosinophilic gastroenteritis, in which probably most cases of eosinophilic cholangitis and cholecystitis have been noted, is a disorder of still unknown etiology and pathogenesis. Clinical features of eosinophilic gastroenteritis depend on which location of the gastrointestinal tract and on which tissue compartments are involved. In a clinical review of 220 cases, the stomach and the proximal small bowel were the single most common sites of involvement, while one third of patients were found to have two or more sites of disease, including the biliary tract. Peripheral eosinophilia is found in 20–90 % of cases (Naylor 1990). Mucosal involvement is the most commonly reported, whereas involvement of the subserosal/serosal compartment has been documented in less than 50 cases (Leveque et al. 1998). Eosinophilic cholangitis can also develop in conjunction with eosinophilic cholecystitis (Leegard 1980). In this situation it has been observed that the eosinophilic infiltration may extend into the tissue of the hepatic hilum and produce signs of biliary obstruction (Rosengart et al. 1990).

Clinical Features

As eosinophilic cholangitis can cause bile duct fibrosis, this disorder may induce extrahepatic biliary obstruction, but biliary obstruction has also been found due to dense eosinophilic duct infiltration alone, i.e., in the absence of relevant fibrosis (Murray and Woods 1981; Butler et al. 1985; Platt et al. 1990; Rosengart et al. 1990; Todd et al. 1990; Grauer et al. 1993; Tenner et al. 1997; Matsumoto et al. 2007; Chen et al. 2009; Nashed et al. 2010). Particularly critical stenosis in eosinophilic cholangitis involved the extrahepatic bifurcation (Rosengart et al. 1990) and the common bile duct (Platt et al. 1990; Grauer et al. 1993). These stenoses or strictures often masquerade common bile duct carcinoma (Rodgers et al. 2001; Chen et al. 2009) or hilar carcinoma (Rodgers et al. 2001). The stenosis is sometimes associated with marked dilatation of the extrahepatic and/or intrahepatic bile ducts (Butler et al. 1985; Platt et al. 1990).

Pathology

The information on macroscopic features of eosinophilic cholangitis is exceedingly sparse. In one resection specimen, the common bile duct showed an encasement by a thick fibroinflammatory mass causing stenosis and a partial

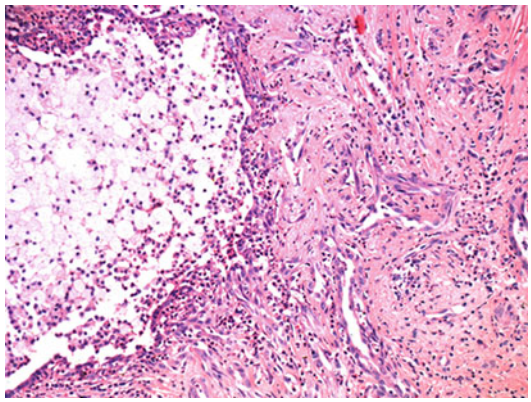

Fig. 1 Eosinophilic cholangitis. The lumen contains a loose exudate with eosinophils and foam cells. Eosinophils also infiltrate the lamina propria (hematoxylin and eosin stain)

effacement of the duct wall layers (Shanti et al. 2001).

The duct walls show a mixed cellular infiltration dominated by eosinophils, commonly with some admixture of lymphocytes, plasma cells, and macrophages (Fig. 1). Eosinophils are found to accumulate in small blood vessels, sometimes with typical eosinophil rolling and attachment to the endothelium. The eosinophils tend to be more frequent in inner and middle layers than in the subserosal compartment. In the case of dense infiltrations, Charcot-Leyden crystals may be seen. The eosinophils also invade the surface epithelium, similar to what is seen in eosinophilic gastroenteritis and with signs of cholangiocyte damage, and there may be infiltration by eosinophils of the peribiliary glands. In the case of dense accumulation of eosinophils in the duct wall, small eosinophilic abscesses may form (Song et al. 1997). The eosinophilic infiltration is sometimes associated with mural fibrosis (Song et al. 1997), even in the absence of clinical signs of sclerosing cholangitis (see below).

Eosinophilic Sclerosing Cholangitis

Eosinophilic cholangitis is known to cause fibrous thickening of the bile ducts walls (Song et al. 1997), but in some patients, there occurs a phenotype where duct sclerosis is a main feature. In fact, a subset of patients with eosinophilic cholangiopathy has been shown to develop all imaging signs of sclerosing cholangitis (Scheurlen et al. 1992; Grauer et al. 1993; Shimomura et al. 1996; Pometta et al. 2000; Miura et al. 2009), also in the pediatric age group (Ichikawa et al. 1997). As this disorder may be seen in association with hypereosinophilic syndrome ("hypereosinophilic sclerosing cholangitis"; Al-Abdulla et al. 2000), it has been suggested that sclerosing cholangitis develops secondary to eosinophilic infiltration of the bile ducts (Grauer et al. 1993; Ichikawa et al. 1997). In fact, marked eosinophilia can be the first manifestation of sclerosing cholangitis (Horiuchi et al. 2009). It has, however, to be added that eosinophilia accompanies PSC in a fraction of the patients (Mir-Madjlessi et al. 1986; in Japanese reports up to 40 %) and that PSC is also known to be associated with eosinophilic infiltration of the liver (Watanabe et al. 1995; Hartleb et al. 1998). Secondary sclerosing cholangitis with dilatation of both the intrahepatic and extrahepatic bile ducts has been described in eosinophilic cholecystitis (Miura et al. 2009).

Eosinophilic Granulomatous Cholangiohepatitis

Hepatic giant cell granulomas with surrounding eosinophilic infiltration (eosinophilic granulomas) have been observed in the context of eosinophilic gastroenteritis (Everett and Mitros 1980).

Eosinophilic Abscess

A mass-producing variant of eosinophilic cholangitis has been reported in a 33-year-old male patient presenting with jaundice and abdominal pain. ERCP showed strictures of the right and left hepatic ducts, and MRI disclosed a 4 cm-sized mass engulfing the junction of the hepatic ducts. Laparotomy showed a multilobulated mass involving the porta hepatis and the fundus of the gallbladder. Histologically, the nodules consisted of sheets

of eosinophils surrounded by a fibro-inflammatory reaction, the eosinophils undermining the surface epithelium. At some places, the tissue was necrotic and densely occupied by eosinophils, thus forming an eosinophilic abscess. The authors observed a similar pseudotumor in a 57-year-old female patient, again in the porta hepatis (Shanti et al. 2001). Eosinophilic liver abscesses occurring in the context of various disorders have been reviewed (Han and Kim 2003; Kang et al. 2004; Jin 2005). Eosinophilic liver abscess may produce nodular mass lesions and thus mimic intrahepatic malignancy (Byun et al. 2006; Kim et al. 2009; Shin 2010). Specifically, eosinophilic liver abscess exhibits contrast-enhancing features on CT and MR images during the hepatic arterial phase, closely mimicking hepatocellular carcinoma (Byun et al. 2006). The differential diagnostic of malignancy is even more important in patients in whom eosinophilic liver abscess was associated with GIT cancer, e.g., gastric carcinoma (Hong et al. 1993).

Eosinophilic Pseudotumor of the Liver and Biliary Tract

Eosinophilic pseudotumors of the liver are mass lesions that resemble eosinophilic hepatic abscesses in morphology, but that show less perifocal inflammatory changes. These lesions are most commonly caused by parasites, chiefly by *Toxocara canis*/visceral larva migrans, most cases being reported from Korea (Hartleb and Januszewski 2001; Jung et al. 2007; Jackson et al. 2010; Lee and Shin 2011), and less commonly by *Ascaris* (Kim et al. 2002). Histologically, a very dense accumulation of eosinophils with signs of eosinophil decay (apoptosis, necroptosis, necrosis) is found, associated with sometimes numerous Charcot-Leyden crystals and eventually remnants of parasites. Clinically, the mass lesions may closely mimic hepatic neoplasia (Jackson et al. 2010) or metastatic disease (Park et al. 2012). Eosinophilic pseudotumor can develop in the ampullary region and cause bile duct obstruction (O'Toole et al. 2003).

Biliary Obstruction Caused by Eosinophilic Inflammation of the Duodeno-ampullary Region

Biliary obstruction may be caused by eosinophilic infiltrates located to the ampullary region, duodenum, or small intestine in the context of eosinophilic gastroenteritis (Rumans and Lieberman 1987; Farahvash et al. 1990; Mohandas et al. 1990; Christopher et al. 2002; Madhotra et al. 2002; Polyak et al. 2002), by an eosinophilic papillary pseudotumor (O'Toole et al. 2003) or by a mass effect of eosinophilic pancreatitis (Eugene et al. 1984; Barthet et al. 1998; Euscher et al. 2000; Sheth et al. 2006).

Eosinophilic Inflammatory Fibroid Polyp of the Biliary Tract

Inflammatory fibroid polyps (synonym: granuloma with eosinophils) are rare lesions of the gastrointestinal tract, histologically often characterized by marked tissue eosinophilia. These polyps predominantly develop in the esophagus (Costa et al. 2000) and the stomach (Rigler et al. 1956; Johnstone and Morson 1978; Battin-Bertho et al. 1987; Hasegawa et al. 1997). The evolution of these polypous lesions has been proposed to follow four stages, viz., a nodular stage with small (<1 cm) lesions composed of spindle cells in a myxoid background, a fibrovascular stage (lesions around 1.5 cm of size) with endothelial proliferation and eosinophilia, and edematous and sclerotic stages, the lesion now being several centimeters in diameter (Kim and Kim 1988). At least part of gastrointestinal inflammatory polyps harbor spindle cells that are reactive for C34 (Hasegawa et al. 1997; Kim et al. 2000; Pantanowitz et al. 2004), but kit negative (Kim et al. 2000). As these distinct mesenchymal elements of polyps also express fascin, calponin, and CD35, a dendritic cell origin of these elements was proposed (Pantanowitz et al. 2004). Inflammatory polyps are very rare in the extrahepatic biliary tract (Ro 1975; Shepherd et al. 1986; Adachi et al. 1991; Adachi and Fukumoto 1996; Moulis 1996; Watananbe et al. 2002; Hussain and

Ahmed 2003). In some of these biliary tract polyps, a marked eosinophilic infiltration is noted, similar to that in the GIT counterparts. Eosinophils are more often seen in basal parts of the polyp than in its most luminal parts, and eosinophils are also noted in the duct wall immediately facing the stalk of the polyp.

Eosinophilic Ascites in Hepatobiliary Eosinophilic Inflammation

Eosinophilic ascites, sometimes massive, has been found in eosinophilic gastroenteritis evolving in conjunction with idiopathic hypereosinophilic syndrome (McNabb et al. 1979; Vandewiele et al. 1991) and also in the subserous/serosal form of eosinophilic gastroenteritis (Sanchez-Fayos et al. 1992; Fortman et al. 1993).

Hepatobiliary Eosinophilic Vascular Disorders

The extrahepatic bile ducts are very rarely involved by allergic granulomatous arteritis of the Churg-Strauss type. The inflamed mural vessels exhibit segmental fibroid necrosis, these foci being surrounded by epithelioid cells and numerous eosinophils. Allergic granulomatous angiitis can cause hepatic artery aneurysms that may rupture into the bile duct system (Nakamura et al. 1991). The disorder is also known to involve the gallbladder (Suzuki et al. 2005). Churg-Strauss syndrome is characterized by marked accumulation of circulating eosinophils in peripheral blood and affected tissues, associated with a distinct type of granulomatous vasculitis (reviews: Abril 2011; Vaglio et al. 2012). In contrast to eotaxin-1 and eotaxin-2, eotaxin-3 was markedly elevated in serum of Churg-Strauss syndrome patients, and the levels were significantly correlated with the peripheral eosinophil count. Immunohistochemically, there was a strong expression of eotaxin-3 in endothelial cells and inflammatory cells of affected tissues (Polzer et al. 2008). The biliary tract may be involved in eosinophilic mesenteric vasculitis (Abdulwahab et al. 2007).

Hypereosinophilic multiple thrombosis (HEMT) is a distinct syndrome characterized by the combination of chronic mature eosinophilia and multiple thrombus formation in several organs (Ishii et al. 1977, 1978). Hypereosinophilia also induces thrombophlebitis (Kanno et al. 2005; Terrier et al. 2006) and thrombotic microangiopathy (Liapis et al. 2005). Large thrombi have been observed in the heart (Kocaturk and Yilmaz 2005; Janoskuti et al. 2006), the CNS sinuses (Sakuta et al. 2007), the portal vein (Kikuchi et al. 2002; Monterrubio Villar et al. 2006), and the hepatic veins, with subsequent Budd-Chiari syndrome (Elouaer-Blanc et al. 1985; Vargas et al. 1993; Zylberberg et al. 1996; Becker et al. 2006).

Parasitic Eosinophilic Cholangitis and Cholecystitis

Hepatobiliary ascariasis is a well-recognized pathology: in a study of 500 Indian patients with this infestation, acute cholangitis was observed in 121 patients (Khuroo et al. 1990). Eosinophilic cholecystitis and cholangitis (sometimes obstructive) are known to occur due to *Clonorchis sinensis*, *Opisthorchis viverrini* and *O. felineus*, *Dicrocoelium dendriticum*, and *Fasciola hepatica* and *F. gigantica* (Sullivan and Koep 1980; Dias et al. 1996; Rim 2005; Lai et al. 2007; Rana et al. 2007). Severe eosinophilic cholangitis with parenchymal destruction has been observed due to hydatid disease. In such situation, small bile ducts may be replaced by epithelioid cell granulomas surrounded by an eosinophilic infiltrate (Raptou et al. 2009).

Bile Duct Rupture and Peripheral Eosinophilia

Rupture of extrahepatic bile ducts may be associated with subsequent peripheral eosinophilia. This phenomenon was, e.g., observed in an infant having spontaneous rupture of the common bile duct and leakage of bile into the abdominal cavity.

Blood eosinophilia raised to 16 % within 5 days after the bile duct event (Imanieh et al. 2006).

References

Abdalla EK, Vauthey JN (2002) Eosinophilic cholangiopathy. Surgery 131:237–238

Abdulwahab A, Almoallim H, Khan N (2007) Isolated eosinophilic mesenteric vasculitis with extensive thrombosis and splenic infarction in a 13-year-old boy. Clin Rheumatol 26:254–257

Abril A (2011) Churg-Strauss syndrome: an update. Curr Rheumatol Rep 13:489–495

Adachi K, Fukumoto S (1996) Inflammatory polyp of the extra-hepatic bile duct (in Japanese). Ryoikibetsu Shokogun Shirizu 9:149–151

Adachi K, Uno K, Mikami M, Kobayashi H, Hattori S, Ohtani M, Fukumoto S, Shimada Y (1991) A case of multiple choledochal inflammation polyps (in Japanese). Nihon Shokakibyo Gakkai Zasshi 88:213–216

Al-Abdulla NA, Schulick RD, Regan F (2000) Hypereosinophilic sclerosing cholangitis: findings using half-Fourier magnetic resonance imaging. Hepatogastroenterology 47:359–361

Albot G, Poileeux F, Olivier C et al (1949) Les cholécystites à éosinophiles. Presse Med 57:558–559

Barthet M, Hastier P, Buckley MJ, Bernard JP, Sastre B, Baroni JL et al (1998) Eosinophilic pancreatitis mimicking pancreatic neoplasia: EUS and ERCP findings: is nonsurgical diagnosis possible? Pancreas 17:419–422

Battin-Bertho R, Dauge MC, Toublanc M, Grossain M, Marche C, Bocquet L (1987) Fibro-inflammatory polyp with eosinophilic infiltration. Apropos of 3 cases of gastric polyps (in French). Ann Pathol 7:176–183

Becker V, Lersch C, Gaa J, Schmid RM (2006) Partial Budd-Chiari syndrome associated with a hypereosinophilic syndrome (in German). Z Gastroenterol 44:173–177

Butler TW, Feintuch TA, Caine WP (1985) Eosinophilic cholangitis, lymphadenopathy, and peripheral eosinophilia: a case report. Am J Gastroenterol 80:572–574

Byun JH, Yang DH, Yoon SE, Won HJ, Shin YM, Jeong YY, Jang SJ (2006) Contrast-enhancing hepatic eosinophilic abscess during the hepatic arterial phase: a mimic of hepatocellular carcinoma. AJR Am J Roentgenol 186:168–173

Chen WH, Yu CC, Wu CC, Jan YJ (2009) Eosinophilic cholangitis with obstructive jaundice mimicking bile duct carcinoma. J Hepatobiliary Pancreat Surg 16:242–245

Christopher V, Thompson MH, Hughes S (2002) Eosinophilic gastroenteritis mimicking pancreatic cancer. Postgrad Med J 78:498–499

Costa PM, Marques A, Tavora I, Oliveira E, Diaz M (2000) Inflammatory fibroid polyp of the esophagus. Dis Esophagus 13:75–79

Dias LM, Silva R, Viana HL, Palhinhas M, Viana RL (1996) Biliary fascioliasis: diagnosis, treatment and follow-up by ERCP. Gastrointest Endosc 43:616–620

Dubay D, Jhala N, Eloubeidi M (2010) Eosinophilic cholangitis. Clin Gastroenterol Hepatol 8:A22

Duseja A, Nada R, Dhiman RK, Chawla YK, Kalra N, Prashad S, Karwasra RK (2005) Eosinophilic cholangiopathy – a case report. Dig Dis Sci 50:1422–1425

Elouaer-Blanc L, Zafrani ES, Farcet JP, Saint-Marc Girardin MF, Mathieu D, Dhumeaux D (1985) Hepatic vein obstruction in idiopathic hypereosinophilic syndrome. Arch Intern Med 145:751–753

Eugene C, Gury B, Bergue A, Quevauvilliers J (1984) Icterus disclosing pancreatic involvement in idiopathic hypereosinophilic syndrome (in French). Gastroenterol Clin Biol 8:966–969

Euscher E, Vaswani K, Frankel W (2000) Eosinophilic pancreatitis: a rare entity that can mimic a pancreatic neoplasm. Ann Diagn Pathol 4:379–385

Everett GD, Mitros FA (1980) Eosinophilic gastroenteritis with hepatic eosinophilic granulomas. Report of a case with 30-year follow-up. Am J Gastroenterol 74:519–521

Farahvash MJ, Bastani B, Farahvash MR, Irvanlou G (1990) Eosinophilic gastroenteritis with biliary and partial duodenal obstruction. Am J Gastroenterol 85:1022–1024

Fortman LM, Johanson JF, Baskin WN, Greenlaw RL (1993) Eosinophilic ascites without eosinophilia: a unique presentation of serosal eosinophilic gastroenteritis. Am J Gastroenterol 88:1280–1281

Fox H, Mainwaring AR (1972) Eosinophilic infiltration of gallbladder. Gastroenterology 63:1049–1052

Grauer L, Padilla VM, Bouza L, Barkin JS (1993) Eosinophilic sclerosing cholangitis associated with hypereosinophilic syndrome. Am J Gastroenterol 88:1764–1769

Han JK, Kim SH (2003) Eosinophilic hepatic abscess (in Korean). Taehan Kan Hakhoe Chi 9:341–343

Hartleb M, Januszewski K (2001) Severe hepatic involvement in visceral larva migrans. Eur J Gastroenterol Hepatol 13:1245–1249

Hartleb M, Kajor M, Kaczor R, Nowak A (1998) Hepatic eosinophilic infiltration in primary sclerosing cholangitis. J Gastroenterol 33:134–135

Hasegawa T, Yang P, Kagawa N, Hirose T, Sano T (1997) CD34 expression by inflammatory fibroid polyps of the stomach. Mod Pathol 10:451–456

Herrerias-Gutierrez JM (2003) Biliary tract disease. A rare manifestation of eosinophilic gastroenteritis. Dig Dis Sci 48:624–627

Hong SW, Kim H, Park C, Lee SI (1993) Eosinophilic liver abscess in patients with gastric carcinoma. Kor J Pathol 27:27–33

Horiuchi K, Kakizaki S, Kosone T, Ichikawa T, Sato K, Takagi H, Mori M, Sakurai S et al (2009) Marked eosinophilia as the first manifestation of sclerosing cholangitis. Intern Med 48:1377–1382

Hussain D, Ahmed M (2003) Liver cyst with inflammatory hepatic duct polyp. J Coll Physicians Surg Pak 13:418–420

Ichikawa N, Taniguchi A, Akama H, Ishiguro H, Kurihara T, Terai C, Hara M, Kashiwazaki S (1997) Sclerosing cholangitis associated with hypereosinophilic syndrome. Intern Med 36:561–564

Imanieh MH, Mowla A, Zohouri D, Forootan HR, Karimi M (2006) Spontaneous perforation of the common bile duct with eosinophilia in an 18-month-old girl: a case report and review of the literature. Med Sci Monit 12:CS31–CS33

Ishii T, Koide O, Hosoda Y, Takahashi R (1977) Hypereosinophilic multiple thrombosis. A proposal of a new designation of disseminated eosinophilic "collagen disease". Angiology 28:361–375

Ishii T, Sternby NH, Hosoda Y (1978) Hypereosinophilic multiple thrombosis. Vasa 7:303–308

Iwamuro M, Yamamoto K, Kawamoto H, Terada R, Ogawa T, Nose S (2009) Eosinophilic cholangitis with initial clinical features indistinguishable from IgG4-related cholangitis. Intern Med 48:1143–1147

Jackson G, Kathuria M, Abraham B, Schmadig VJ (2010) Fine needle aspiration diagnosis of necrotizing eosinophilic abscess clinically mimicking hepatic neoplasia: a case report. Acta Cytol 54:60–62

Janoskuti L, Forhecz Z, Lengyel M (2006) Unique presentation of hypereosinophilic syndrome: recurrent mitral prosthetic valve thrombosis without endomyocardial disease. J Heart Valve Dis 15:726–729

Jeyaman R, Ramakrishna BS, Kurian G (2007) Eosinophilic cholangiopathy – a report of two cases. Indian J Gastroenterol 26:190–191

Jimenez-Saenz M, Villar-Rodriguez JL, Torres Y, Carmona I, Salas-Herrero E, Gonzalez-Vilches J, Herrerias-Gutierrez JM (2003) Biliary tract disease. A rare manifestation of eosinophilic gastroenteritis. Dig Dis Sci 48:624–627

Jin SY (2005) Eosinophilic liver abscess (in Korean). Korean J Hepatol 11:176–179

Johnstone JM, Morson BC (1978) Inflammatory fibroid polyp of the gastrointestinal tract. Histopathology 2:349–361

Jung JK, Jung JT, Lee CH, Kim EY, Kwon JG, Kim BS (2007) A case of hepatic abscess caused by toxocara (in Korean). Korean J Hepatol 13:409–413

Kang HR, Kwon HS, Song WJ et al (2004) Analysis of 54 cases of eosinophilic liver abscess – underlying diseases and clinical characteristics. Kor J Ashtma Allerg Clin Immunol 24:229–235

Kanno H, Ouchi N, Sato M, Wada T, Sawa T (2005) Hypereosinophilia with systemic thrombophlebitis. Hum Pathol 36:585–589

Kerstein MD, Sheehan DG, Gudjonsson B, Lewis J (1976) Eosinophilic cholecystitis. Am J Gastroenterol 66:349–352

Khuroo MS, Zargar SA, Mahajan R (1990) Hepatobiliary and pancreatic ascariasis in India. Lancet 335:1503–1506

Kikuchi K, Minami K, Miyakawa H, Ishibashi M (2002) Portal vein thrombosis in hypereosinophilic syndrome. Am J Gastroenterol 97:1274–1275

Kim YI, Kim WH (1988) Inflammatory fibroid polyps of gastrointestinal tract. Evolution of histologic patterns. Am J Clin Pathol 89:721–727

Kim MK, Higgins J, Cho EY, Ko YH, Oh YL (2000) Expression of CD34, bcl-2, and kit in inflammatory fibroid polyps of the gastrointestinal tract. Appl Immunohistochem Mol Morphol 8:147–153

Kim S, Maekawa Y, Matsuoka T, Imoto S, Ando K, Mita K, Kim H, Nakajima T, Ku K, Koterazawa T et al (2002) Eosinophilic pseudotumor of the liver due to Ascaris suum infection. Hepatol Res 23:306

Kim YS, Park SJ, Kim HK, Park JM (2009) A case of eosinophilic abscess mistaken for metastasis due to FDG uptake in PET-CT (in Korean). Korean J Gastroenterol 54:349–354

Kocaturk H, Yilmaz M (2005) Idiopathic hypereosinophilic syndrome associated with multiple intracardiac thrombi. Echocardiography 22:675–676

Kuniyoshi M, Ikeda K, Takano S, Okubo Y, Baba T, Tazoe A, Hail M, Hara Y (1998) Case of eosinophilic gastroenteritis complicated with eosinophilic cholecysto-cholangitis (in Japanese). Nippon Naika Gakkai Zasshi 87:1563–1565

Lai CH, Chin C, Chung HC, Liu H, Hwang JC, Lin HH (2007) Clonorchiasis-associated perforated eosinophilic cholecystitis. Am J Trop Med Hyg 76:396–398

Lee SH, Shin WG (2011) Eosinophilic liver abscess caused by *Toxocara canis* (in Korean). Korean J Gastroenterol 58:226–228

Leegard M (1980) Eosinophilic cholecystitis. Acta Chir Scand 146:295–296

Leveque L, Michiels C, Collet E, Jouve JL, Lorcerie B, Lambert D (1998) Eosinophilic ascites and urticaria. Rev Med Intern 19:334–337

Liapis H, Ho AK, Brown D, Mindel G, Gleich G (2005) Thrombotic microangiopathy associated with the hypereosinophilic syndrome. Kidney Int 67:1806–1811

Madhotra R, Eloubeidi MA, Cunningham JT, Lewin D, Hoffman B (2002) Eosinophilic gastroenteritis masquerading as ampullary adenoma. J Clin Gastroenterol 34:240–242

Matsumoto N, Yokoyama K, Nakai K, Yamamoto T, Otani T, Ogawa M, Tanaka N et al (2007) A case of eosinophilic cholangitis: imaging findings of contrast-enhanced ultrasonography, cholangioscopy, and intraductal ultrasonography. World J Gastroenterol 13:1995–1997

McNabb PC, Fleming CR, Higgins JA, Davis GL (1979) Transmural eosinophilic gastroenteritis with ascites. Mayo Clin Proc 54:119–122

Mir-Madjlessi SH, Sivak MV, Farmer RG (1986) Hypereosinophilia, ulcerative colitis, sclerosing cholangitis and bile duct carcinoma. Am J Gastroenterol 81:483–485

Miura F, Asano T, Amano H, Yoshida M, Toyota N, Wada K, Kato K, Takada T, Fukushima J et al (2009) Resected case of eosinophilic cholangiopathy presenting with secondary sclerosing cholangitis. World J Gastroenterol 15:1394–1397

Mohandas KM, Santhi Swaroop V, Desai DC, Jagannath P, Krishnamurthi S, DeSouza LJ (1990) Pancreatic and biliary obstruction due to eosinophilic gastroenteritis. Am J Gastroenterol 85:1540–1541

Monterrubio Villar J, Cordoba Lopez A, Macayo Sanchez AJ (2006) Idiopathic eosinophilia associated with portal vein and massive thrombosis: successful thrombolysis with streptokinase. Med Sci Monit 12:CS53–CS56

Moulis H (1996) Another inflammatory bile duct polyp. Endoscopy 28:330

Murray SM, Woods CJ (1981) Disseminated eosinophilic infiltration of a newborn infant, with perforation of the terminal ileum and bile duct obstruction. Arch Dis Child 56:66–71

Nakamura S, Yokoi Y, Suzuki S, Sakaguchi S, Muro H, Maeda M, Kawasaki H (1991) A case of melena caused by a hepatic aneurysm ruptured into the intrahepatic bile duct in a patient with allergic granulomatous angiitis. Jpn J Surg 21:471–475

Nashed C, Sakpal SV, Shusharina V, Chamberlain RS (2010) Eosinophilic cholangitis and cholangiopathy: a sheep in wolves clothing. HPB Surg 2010:906496

Naylor AR (1990) Eosinophilic gastroenteritis. Scott Med J 35:163–165

O'Toole D, Palazzo L, Vuillerme MP, Maire F, Levy P, Ruszniewski P (2003) Bile duct obstruction caused by an eosinophilic papillary pseudotumor. Gastrointest Endosc 58:445–448

Pantanowitz L, Antonioli DA, Pinkus GS, Shahsafaei A, Odze RD (2004) Inflammatory fibroid polyps of the gastrointestinal tract: evidence for a dendritic cell origin. Am J Surg Pathol 28:107–114

Park S, Kim YS, Kim YJ, Kyung SY, Park JW, Jeong SH, Lee SP (2012) Toxocariasis masquerading as liver and lung metastatic nodules in patients with gastrointestinal cancer: clinicopathologic study of five cases. Dig Dis Sci 57:155–160

Platt ML, Kiesling VJ, Vaccaro JA (1990) Eosinophilic ureteritis associated with eosinophilic cholangitis: a case report. J Urol 144:127–129

Polyak S, Smith TA, Mertz H (2002) Eosinophilic gastroenteritis causing pancreatitis and pancreatobiliary ductal dilation. Dig Dis Sci 47:1091–1095

Polzer K, Karonitsch T, Neumann T, Eger G, Haberler C, Soleiman A, Hellmich B et al (2008) Eotaxin-3 is involved in Churg-Strauss syndrome – a serum marker closely correlating with disease activity. Rheumatology (Oxford) 47:804–808

Pometta R, Callea F, Mangano M, Zuccoli E, Conte D (2000) Recurrent cholestasis and hypereosinophilia in a young female. Dig Liver Dis 32:630–633

Rana SS, Bhasin DK, Nanda M, Singh K (2007) Parasitic infestations of the biliary tract. Curr Gastroenterol Rep 9:156–164

Raptou G, Pliakos I, Hytiroglou P, Papayramidis S, Karkavelas G (2009) Severe eosinophilic cholangitis with parenchymal destruction on the left hepatic lobe due to hydrated disease. Pathol Int 59:395–398

Reyes M, Abraham C, Abedi M, Carucci LR, Schwartz LB (2005) Hypereosinophilic syndrome with hepatobiliary masses and obstructive jaundice. Ann Allergy Asthma Immunol 94:25–28

Rigler LG, Blank L, Hebbel R (1956) Granuloma with eosinophils; benign inflammatory fibroid polyps of the stomach. Radiology 66:169–176

Rim HJ (2005) Clonorchiasis: an update. J Helminthol 79:269–281

Ro JO (1975) Extrahepatic obstructive jaundice due to inflammatory polyp of common bile duct. Postgrad Med 58:259–260

Rodgers MS, Allen JP, Koea JB, McCall JL (2001) Eosinophilic cholangitis: a case of 'malignant masquerade'. HPB (Oxford) 3:235–239

Rosengart TK, Rotterdam H, Ranson JH (1990) Eosinophilic cholangitis: a self-limited cause of extrahepatic biliary obstruction. Am J Gastroenterol 85:582–585

Rumans MC, Lieberman DA (1987) Eosinophilic gastroenteritis presenting with biliary and duodenal obstruction. Am J Gastroenterol 82:775–778

Sakuta R, Tomita Y, Ohashi M, Nagai T, Murakami N (2007) Idiopathic hypereosinophilic syndrome complicated by central sinovenous thrombosis. Brain Dev 29:182–184

Sanchez-Fayos MP, Miranda R, Renedo L, Porres JC, Hernandez Guio C (1992) Eosinophilia and ascites as an expression of a subserous form of eosinophilic gastroenteritis (in Spanish). Rev Clun Esp 191:30–34

Scheurlen M, Mork H, Weber P (1992) Hypereosinophilic syndrome resembling chronic inflammatory bowel disease with primary sclerosing cholangitis. J Clin Gastroenterol 14:59–63

Schoonbroodt D, Horsmans Y, Laka A, Geubel AP, Hoang P (1995) Eosinophilic gastroenteritis presenting with colitis and cholangitis. Dig Dis Sci 40:308–314

Shanti CM, Lucas CE, Tyburski JG, Soulen RL, Lucas DR (2001) Eosinophilic abscess and eosinophilic pseudotumor presenting as bile duct masses: a report of 2 cases. Surgery 130:104–108

Shepherd HA, Laidlow JM, Ross AP, Vincenti A, Lane RH (1986) Extrahepatic biliary obstruction by a common bile duct inflammatory polyp in association with a gallstone, and treatment by endoscopic sphincterotomy. Endoscopy 18:66–68

Sheth A, Palmer R, Jordan PA, Manas K, Bhalodia A (2006) Eosinophilic gastroenteritis of the pancreas: an unusual cause of obstructive jaundice. J Clin Gastroenterol 40:623–625

Shimomura I, Takase Y, Matsumoto S, Kuyama J, Nakajima T, Maeda H, Sugase T, Hata A et al (1996) Primary sclerosing cholangitis associated with increased peripheral eosinophils and serum IgE. J Gastroenterol 31:737–741

Shin YM (2010) Hepatic eosinophilic abscess presenting as single nodular mass (in Korean). Korean J Hepatol 16:95–99

Song HH, Byun JY, Jung SE, Choi KH, Shinn KS, Kim BK (1997) Eosinophilic cholangitis: US, CT. and cholangiography findings. J Comput Assist Tomogr 21:21–253

Sullivan WG, Koep LJ (1980) Common bile duct obstruction with cholangiohepatitis in clonorchiasis. JAMA 243:2060–2061

Sussman DA, Bejarano PA, Regev A (2008) Eosinophilic cholangiopathy with concurrent eosinophilic colitis in a patient with idiopathic hypereosinophilic syndrome. Eur J Gastroenterol Hepatol 20:574–577

Suzuki M, Nabeshima K, Miyazaki M, Yoshimura H, Tagawa S, Shiraki K (2005) Churg-Strauss syndrome complicated by colon erosion, acalculous cholecystitis and liver abscesses. World J Gastroenterol 11:5248–5250

Tazawa J (1996) Eosinophilic cholangitis (in Japanese). Ryoikibetsu Shokogun Shirizu 9:17–19

Tenner S, Roston A, Lichtenstein D, Brooks D, Herlihy E, Carr-Locke D (1997) Eosinophilic cholangiopathy. Gastrointest Endosc 45:307–309

Terrier B, Piette AM, Kerob D, Cordoliani F, Tancrede E, Hamidou L, Lebbe C, Bletry O, Kahn JE (2006) Superficial venous thrombophlebitis as the initial manifestation of hypereosinophilic syndrome: study of the first 3 cases. Arch Dermatol 142:1606–1610

Todd KR, Heidrun R, John HCR (1990) Eosinophilic cholangitis: a self-limited cause of extrahepatic biliary obstruction. Am J Gastroenterol 85:582–585

Vaglio A, Moosig F, Zwerina J (2012) Churg-Strauss syndrome: update on pathophysiology and treatment. Curr Opin Rheumatol 24:24–30

Vandewiele IA, Maeyaert BM, Van Cutsem EJ, Geboes KR, Knockaert DC (1991) Massive eosinophilic ascites: differential diagnosis between idiopathic hypereosinophilic syndrome and eosinophilic gastroenteritis. Acta Clin Belg 46:37–41

Vargas CA, Maldonado O, Botero RC, Jeffers LJ, Parker T, Reddy KR, Schiff ER (1993) Budd-Chiari syndrome associated with the hypereosinophilic syndrome. Am J Gastroenterol 88:1802–1803

Vauthey JN, Loyer E, Chokshi P, Lahoti S (2003) Case 57: eosinophilic cholangiopathy. Radiology 227: 107–112

Waguet J, Benamara MA, Chardot C, Pariente D (2000) Common bile duct stenosis with hypereosinophilia and pancreatitis in childhood. Pediatr Radiol 30:383–385

Watanabe H, Ohira H, Kuroda M, Takagi T, Ishikawa H, Nishimaki T, Kasukawa R, Takahashi K (1995) Primary sclerosing cholangitis with marked eosinophilic infiltration of the liver. J Gastroenterol 30:524–528

Watananbe H, Iwase H, Sugitani M (2002) Inflammatory polyps in common bile duct caused by T-tube. Hepatogastroeneterology 49:894–896

Zylberberg H, Valla D, Viquie F, Casadevall N (1996) Budd-Chiari syndrome associated with 5q deletion and hypereosinophilia. J Clin Gastroenterol 23:66–68

Mechanical and Anatomical Causes of Bile Duct Obstruction

144

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_144

Abstract

Various mechanical and anatomical alterations can induce obstruction of the bile duct system, sometimes mimicking biliary cancer. Protruding tissue masses including biliary tumor thrombi and icteric-type hepatocellular carcinoma can massively obstruct bile ducts. A similar effect is produced by periductal tumor growths or compression by periductal enlarged lymph nodes occupied by metastatic disease (external compression). Intraductal blood clots may result in biliary obstruction. Other ductal and intraductal factors causing stenosis include bile duct webs and diaphragms, bile duct angulation, congenital and acquired bile duct diverticula, and bile duct intussusception and volvulus. The peripancreatic inflammatory and necrotic changes that occur in the setting of pancreatitis can cause stricture of extrahepatic bile ducts. A distinct form of derangement of intraductal flow is biliary sludge.

Bile Duct Obstruction Due To Protruding Tissue Masses

So-Called Biliary Tumor Thrombi

The term thrombus to denote the presence of tumor tissue within a ductal lumen is a misnomer, because thrombus is reserved for a distinct product of intravascular blood clotting. The phenomenon is characterized by ingrowth of a malignant tumor into a large bile duct, followed by detachment of a tumor fragment that may either float, obturate the lumen, or be transported in a distal direction. In the proper sense of the term, tumor "thrombus" denotes a free intraluminal tumor fragment rather than a pedunculated intraluminal polyp that is still fixed to the duct wall, e.g., with a vascular stalk.

Icteric-Type Hepatocellular Carcinoma

Intraluminal tumor masses of tumor fragments can cause biliary obstruction and jaundice, mostly reported for hepatocellular carcinoma (HCC) in the context of the distinct oncologic situation, *icteric hepatoma* or *icteric-type hepatocellular carcinoma* (defined by Lin et al. 1975). Since Mallory et al. (1947) first described a case of HCC accompanied with obstructive jaundice secondary to biliary hemorrhage from a tumor invading the cystic duct, several situations have been connected with the term, icteric hepatoma, and we here classify them into five types (Table 1).

Table 1 Types of icteric hepatoma (icteric-type hepatocellular carcinoma)

Type 1
Obstructive jaundice caused by direct invasion and stenosis of bile duct
Type 2
Obstructive jaundice caused by intraductal floating and distally migrating tumor debris
Type 3
Obstructive jaundice caused by tumor-induced intraductal blood clot/hemobilia
Type 4
Obstructive jaundice caused by extrinsic duct compression by tumor and/or nodal metastases and/or tumorous portal vein thrombosis
Type 5
Ectopic hepatocellular carcinoma (hilar or in the extrahepatic ducts)

First, the term is mostly used for those HCCs that cause obstructive jaundice by floating tumor debris in the common bile duct, as outlined below (Chen 2002). Other situations include direct invasion of ducts by HCC (Afroudakis et al. 1978), sometimes with polypoid intraluminal growth (Nonomura et al. 1983), hemorrhagic obturating clot formation (Creed and Fisher 1956), and hemobilia (Johns and Zimmerman 1961). A distinct situation is characterized by usually stenosing HCC apparently arising outside the liver substance proper. Whether all of these tumors are in fact ectopic HCC, or instances where the primary intrahepatic neoplasm has been missed, is sometimes difficult to judge (Badve et al. 1991; Buckmaster et al. 1994; Murakami et al. 2003; Tsushimi et al. 2005; Makino et al. 2006).

In most cases, invasion by HCC of the biliary tract system at some place must have taken place,

and, in fact, bile duct infiltration by HCC followed by intraluminal growth has been documented several times. Even small tumors can then, owing to intraluminal polypoid growth, cause biliary obstruction (Terada et al. 1989). A second mechanism is sometimes reported to consist of HCC rupture into large bile ducts (Chen et al. 1994), but as to how such a ruptured tumor gets access to duct lumina is not really known. In HCCs complicated by bile duct invasion, the levels of serum bilirubin and carbohydrate antigen 19-9 were significantly higher in the bile duct invasion group in comparison with patients with HCC who had no bile duct involvement. Macroscopically, confluent multinodular type and infiltrative HCC types were predominant in the bile duct invasion group, as were tumor with portal vein invasion and intrahepatic metastasis (Ikenaga et al. 2009b). In some HCCs with bile duct invasion, a fragment or fragments of the intracavitary growth may detach and be situated (frequently together with clotted blood) as a floating mass or tumor debris in the lumen (the "tumor thrombus"), and subsequently be dislocated to other places of the biliary tract (e.g., the ampullary region), analogous to an embolus ("tumor embolus").

Selected References Dickinson and Santulli (1962), Gerson und Schinella (1969), Brand et al. (1976), Kawakami et al. (1977), Afroudakis et al. (1978), Cleland and Adjukiewicz (1980), Jurco and Kim (1980), Joehl and Abt (1984), Roslyn et al. (1984), Oshima et al. (1986), Sarma et al. (1987), Komatsu et al. (1989), Kiev et al. (1990), Lau et al. (1990), Schutze et al. (1990), Lai et al. (1992), Kirk et al. (1994), Wang et al. (1995), Sastry et al. (1996), Nakajima et al. (1997), Satoh et al. (2000), Shiomi et al. (2001), Tamada et al. (2001),Tanizaki et al. (2001), Tseng et al. (2001), Nishio et al. (2002), Murakami et al. (2003), Peng et al. (2004), Hanaoka et al. (2006), Gabata et al. (2007), Kobayashi et al. (2008), Long et al. (2010, and Wang et al. (2010).

On MRI images, HCC tumor thrombi present as cord-like or columnar masses in the bile duct with proximal cholangiectasis. The tumor thrombi are slightly hypointense on T1-weighted and slightly hyperintense on T2-weighted images. On MRI-cholangiopancreatograms, the majority of the lesions present as filling defect in the bile duct, abrupt obstruction of the bile duct, and duct dilatation above the obstruction (Liu et al. 2010).

In few instances, the migration track from the primary ductal invasion site to the subsequent obturation site ("embolus") could be followed in detail, e.g., from the right hepatic duct to the common bile duct (Wind and Futterman 1977; Tsuzuki et al. 1979). Among 18 with intracommon bile duct manifestations of HCC, choledochoscopy revealed that the site of hepatoma rupture was from the right intrahepatic duct in nine patients, from the left hepatic duct in seven patients, and from the hepatic hilum in two patients (Jan and Chen 1999). Distal migration of intraluminal tumor fragments has also been observed in fibrolamellar carcinoma of the liver (Albaugh et al. 1984; Eckstein et al. 1988). In some instances, distal duct stenosis is not caused by tumor tissue as such, but rather by dislocated clots and/or blood associated with the more proximally located, invasive, and destructive tumor growth (hemobilia; van Sonnenberg und Ferrucci 1979; Fraser et al. 1989; Rhoe et al. 1989; Vagianos et al. 1993). Sandblom first introduced the term hemobilia, and this author already stated that hemobilia can cause biliary obstruction (Sandblom 1948).

How frequent are HCCs complicated by cancer thrombi in bile ducts? In a series of 140 necropsied patients with hepatocellular carcinoma, tumorous invasion of bile ducts was detected in 2.1 % (Carella et al. 1981). Among 238 autopsy and 21 surgical cases of HCC, 24 cases with prominent intrabile duct tumor growth were identified. Progressive obstructive jaundice had occurred during the course of most cases and was the presenting sign in nine patients. The average survival time of the cases was significantly shorter than that of HCC patients without intraductal tumor growth (Kojiro et al. 1982). In a study of 549 cases of HCC in Korea, the authors experienced ten cases with gross evidence of tumor thrombi in the bile duct system (Wang et al. 1999). In another study (from Taiwan),

intraductal HCC fragments were found in nine patients out of 3,921 patients with HCC (Huang et al. 1998). In a Japanese investigation, nine (1.66 %) out of 542 cases of HCC treated surgically disclosed macroscopic bile duct thrombi (Ueda et al. 1994). A retrospective study was undertaken to review 20 patients with obstructive jaundice secondary to ruptured HCC into common bile duct during a 12-year period. All these patients on initial examination had recurrent episodic jaundice and cholangitis, and 75 % showed liver cirrhosis (Chen et al. 1994). In China, where an estimated 300,000 new cases of HCC are diagnosed annually, it is estimated that 1–2 % (Ueda et al. 1994) or 2.3–9.2 % (cited in Xiangji et al. 2009) of HCC cases have coincident bile duct tumor thrombi, which represents 7,000–27,000 new cases of biliary tumor thrombi each year. In a study of 12,114 patients with HCC, 184 patients had tumors complicated by bile duct thrombi (1.84 %; Xiangji et al. 2009).

Other Tumors Causing Biliary Tumor Thrombi

Apart from HCC, other tumors have been reported to produce intraductal obstructive growths, including gallbladder carcinoma (Midorikawa et al. 2000; Rau et al. 2004), carcinoma of the cystic duct (Shibata and Toyoda 1995), cystic duct remnant carcinoma (Gabata et al. 2003), metastatic breast carcinoma (Papo et al. 1996), metastatic renal cell carcinoma (Ueda et al. 2002), and in particular manifestations of colorectal carcinoma. Liver metastases from colorectal cancer easily invade the Glisson's triads and may show prominent intrabiliary polypoid tumor growth (Riopel et al. 1997; Povoski et al. 2000; Takamatsu et al. 2004), sometimes with minimal invasion of the liver substance (Uehara et al. 2004). In a study of 149 patients with liver metastasis from colorectal cancer, 12 % had macroscopic intrabiliary growth, the size of the ingrowths ranging from 4 to 42 mm (Okano et al. 1999). In this study, two thirds of the tumors with macroscopic bile duct invasion were well-differentiated adenocarcinomas with a tendency for less vascular invasion. In another study of 217 patients who underwent hepatic resection for colorectal cancer metastasis, microscopic bile duct invasion was found in 89 patients (40.6 %) and of these, 23 patients (10.6 %) had macroscopic biliary extension. This subset of macroscopic biliary involvement exhibited less aggressive features (Kubo et al. 2002). A smaller percentage of macroscopic bile duct involvement, i.e., 5.8 %, was found in recent study of 103 patients (Sugiura et al. 2006).

Intraductal Tumor Tissue Prolapse

Prolapsed tumor tissue can cause intermittent jaundice, e.g., reported for prolapsed gastric tumor occluding the common bile duct (Rukstinat et al. 1970).

Biliary Obstruction Caused by Postoperative Intraductal Blood Clots

Obstructive jaundice has been seen to be caused by choledochal clots after cholecystectomy (Aguilar Lugue et al. 1983).

Prolapsed Masses and Gastroduodenal Intussusception Causing Ampullary Obstruction

The ampullary orifice can be blocked or stenosed by prolapse of polypoid malignant gastric tumors (Karl et al. 2004) or intussusception of gastric polyps, e.g., polyps in Gardner's syndrome (Herman et al. 1992).

Bile Duct Stenosis Due To Extrinsic Compression

Introduction

Apart from tumors and tumor-like lesions developing in the bile duct walls and causing stenosis/obstruction, the bile duct system can also undergo

stenosis by external compression by a large number of lesions.

Tumors

Several types of neoplasms, but mainly malignant ones, can exert extrinsic compression on large bile ducts and thus induce biliary obstruction. These lesions, e.g., comprise hepatocellular carcinoma (Joehl and Abt 1984; Thomsen et al. 1998; Murata et al.,2003; Camci et al. 2007), fibrolamellar carcinoma (Albaugh et al. 1984), cholangiocarcinomas, hepatobiliary cystadenoma (Erdogan et al. 2006), metastases (Liratzopoulos et al. 2006), non-Hodgkin's lymphoma (Jho et al. 2007), and Hodgkin's lymphoma (Di Sena et al. 2005). Similarly, malignancies of the pancreatic head can compress the distal-most part of the common bile duct.

Compression by Hepatic Cysts

Large nonparasitic liver cysts and cyst in polycystic disease can exert compression mainly on intrahepatic bile ducts (Salam and Keeffe 1989; Ishikawa et al. 2002; Lapeyre et al. 2002). Sudden duct compression can occur upon bleeding into such a cyst (von Woellwarth et al. 2000). Similarly, hemorrhage into cysts in hepatic polycystic disease can cause bile duct stenosis (Rosenfeld et al. 2001). Peribiliary cysts can rarely compress the bile duct and lead to obstructive jaundice (Ikenaga et al. 2009a).

Infectious and Parasitic Causes of Bile Duct Compression

Tuberculosis of bile duct-associated lymph nodes situated in the hepatoduodenal ligament can cause duct compression (Amarapurkar and Agrawal 2006), and periportal tuberculous lymphadenitis may encroach upon the extrahepatic duct system (Stanely et al. 1984). Echinococcus cysts caused by *E. granulosus* exhibit expanding growth and can displace and compress bile ducts (Colle et al. 2002), sometimes with effacement of the bile duct confluence (Martin Molinero et al. 1989).

Vascular Compression

Pulsatile vascular compression of the common bile duct is a rare cause of biliary obstruction. The extrahepatic bile duct system may be compressed by several arteries and their branches, including the right hepatic artery, gastroduodenal artery, cystic artery, proper hepatic artery, and variable branches of the common hepatic artery. Important in this context is the considerable variation of artery anatomy in this vascular compartment (Hiatt et al. 1994; Koops et al. 2004). The relations of these arteries to the biliary ducts have been studied in detail (Michels 1951). Jaundice due to common bile duct obstruction by an aberrant celiac artery was first reported in 1961 (Luttwak and Schwartz 1961).

The right hepatic artery can cause compressive jaundice (right hepatic artery syndrome; Taboga et al. 1969; Tsuchiya et al. 1984; Chung et al. 1994; Miyashita et al. 2005) and may promote the development of lithiasis (Kim et al. 1992b; Ju et al. 2000). A right hepatic artery originating from the gastroduodenal artery has also been shown to induce obstructive jaundice (Baek et al. 2008). Compression of the common bile duct can occur secondary to vascular rings (Goldberg and Doman 1988). Aneurysms of visceral arteries can cause bile duct compression and jaundice, including aneurysms of the abdominal aorta (Smith et al. 2002), hepatic artery (Lewis et al. 1982; Mazziotti et al. 2003), and gastroduodenal artery (Konstantakos et al. 2000; Sipahioglu et al. 2005). Common bile duct compression occurs secondary to visceral venous aneurysms, which most often develop in the portal vein (Sfyroeras et al. 2009). Cavernous transformation of the portal vein is known to compress the extrahepatic biliary tract (portal biliopathy; portal hypertensive biliopathy; Takehara et al. 1993; Chandra et al. 2001; Rosenthal et al. 2008). Enlarged collateral veins occurring in portal hypertension can compress the common bile

duct (Hunt 1965). These alterations are further discussed in a separate chapter.

Bile Duct Webs

Introduction

Bile duct webs (biliary webs; biliary septa; biliary diaphragms) are rare causes of biliary obstruction, likely to be congenital in nature, but presenting in later life due to the initial patency of these webs in allowing bile drainage (review: Margolis and Schein 2001). However, cases in the pediatric age group have been reported as well (Chapoy et al. 1981; Shih et al. 1992), including congenital septate biliary tree (Frexes et al. 1986). The webs present as septum-like folds usually located to the extrahepatic bile ducts. On imaging, webs typically appear as thin radiolucent rings with or without proximal duct dilatation. Webs are predominantly located in the common hepatic duct (Fisher et al. 1968; Furukawa et al. 1992; Kato et al. 1994), the right or left hepatic duct (Goldenberg et al. 1981), the hepatic duct junction (Devanesan et al. 1978), and the common bile duct (Ornet et al. 1966; Pinter et al. 1975; Chari and Harrison 1998; Baek et al. 2005; Shera and Shah 2008).

Congenital webs are extremely rare malformations of the extrahepatic bile ducts, with little more than 20 cases reported in the literature. A congenital origin in at least part of the cases is suggested by an association with congenital anomalies elsewhere in the biliary tract. Webs may be associated with choledochal cysts (Ando et al. 1995; Sharma et al. 1995; Dong et al. 2006). Septum of the common hepatic duct was reported to be associated with an anomalous junction of the biliopancreatic ductal system (Kato et al. 1994) or with complex hepatobiliary pancreatic anomalies characterized by dominant dorsal duct syndrome, with the dorsal pancreatic duct representing the only drainage system (Shera and Shah 2008). On the other hand, there may be instances where webs or septum-like formations develop subsequent to inflammatory changes of ducts. For example, biliary web has been noted in association with cholelithiasis (de Celis et al. 1985; Papaziogas et al. 2002; Baek et al. 2005), but gallstones may also develop as a complication of web-induced bile duct stenosis. Furthermore, webs are a cholangiographic feature in a subset of patients with primary sclerosing cholangitis (PSC; Gulliver et al. 1991).

Macroscopically, the diaphragms or septa are crescent shaped, bridge-like, or shaped like a swallow's nest (aortic valve-like), or they present as ringlike webs (perforated diaphragms). At choledochoscopy, the web may show a micropapillary texture and erosions (Baek et al. 2005).

In the few situations where histologic examination of resected webs or septa had been performed, these structures disclosed a fibrous stroma covered by ductal mucosa (Ando et al. 1995), sometimes with atrophy of the overlying mucosa (Furukawa et al. 1992) or, conversely, with signs of epithelial proliferation (Baek et al. 2005). The resected web in one patient with biliopancreatic maljunction showed a normal histology of the adjacent parts of the common hepatic duct (Kato et al. 1994).

Bile Duct Angulation

Angulation of the large bile duct is an anatomical variant of the duct's course between the confluens and the duodenal entry. These changes gained some actuality owing to the fact that they may produce ERCP difficulties (Affronti 2007) and that they may be involved in stone recurrence. It may occur as congenital anomaly in extrahepatic bile duct angulation; the common bile is seen as deviating to the right as it descends toward the duodenum (Warren 1987). Angulation is measured as the sharpest angle along the common bile duct from 1 cm below the bifurcation to 1 cm above the papilla. Angulation of the large duct is thought to dispose to bile stasis, and angulation of the common bile duct has earlier been found to associate with choledocholithiasis (Warren 1987) and to predispose to recurrent symptomatic bile duct stones (Keizman et al. 2006). In a recent systematic study on 232 consecutive

patients who had undergone endoscopic retrograde cholangiopancreatography for bile duct stones, symptomatic bile duct stones recurred in 16 %, and among these patients, angulation of the common bile duct (145° or less) was an independent risk factor (Keizman et al. 2006). Angulation may also occur as a secondary event, e.g., in association with extrahepatic portal venous obstruction (Khuroo et al. 1993), ampullary or pancreatic tumors (Reibscheid et al. 1973), or induced by T-tube (the elbow sign; Lee and Burhenne 1991).

Diverticula of Bile Ducts

Congenital Diverticula of the Biliary Tract

Congenital diverticula of the biliary tract are rare lesions classified according to the Alonso-Lej system and the Todani systems as being type II choledochal cysts. Alonso-Lej et al. first classified choledochal cysts into three types (Alonso-Lej et al. 1959). Due to the recognition of intrahepatic involvement, Todani and coworkers modified their classification into six types (Todani et al. 1977), later revised and refined (Todani et al. 1984, 2003; Todani 1997).

In an analysis of 878 patients, Yamaguchi found the frequency of type II lesions to be 1.4 % among all types of anomalies (Yamaguchi 1980). Mixed types I and II choledochal cysts with a fusiform common bile duct with a diverticulum originating from the midportion of the common bile duct have also been described (Kaneyama et al. 2005b). Congenital diverticula and ectasias of the biliary tract can develop in inborn disorders of connective tissue metabolism, e.g., multiple hollow organ dysplasia in Ehlers-Danlos syndrome (Kahn et al. 1988; Schippers and Dittler 1989) and Marfan syndrome (Merza and Raiser 1987). Congenital diverticula of the large bile ducts can, depending on their position, size, and geometry, cause inflammation and subsequent stenosis and can also contain gallstones (Kune 1965). Congenital diverticula of the common bile duct are a well-recognized entity.

Selected References Longo (1950), Alden and Sterner (1957), Kune (1965), Luchtman et al. (1971), Sapounov (1972), Pujol-Soler et al. (1975), Camelot et al. (1976), Koytcha et al. (1976), Kostiainen et al. (1983), Shamberger et al. (1985), Ehmke (1987), Mouroux et al. (1987), Solovel et al. (1987), Bastid and Sahel (1989), Bona et al. (1991), Mai et al. (1991), Gelmi et al. (1994), Sato et al. (2002), and Kaneyama et al. 2005b).

They may occur as an isolated lesion or in combination with other rare anomalies of the biliary tract, such as an accessory choledochus (Gelmi et al. 1994). A more common subset of choledochal diverticula develop in the intraduodenal part of the duct (low choledochal diverticula; Pujol-Soler et al. 1975; Kostiainen et al. 1983; Shamberger et al. 1985; Solovel et al. 1987; Bastid and Sahel 1989; Bona et al. 1991). The development of choledochal diverticula is sometimes associated with abnormalities of mucosal cell differentiation, e.g., gastric ectopic mucosa of the pyloric type (Mai et al. 1991).

Diverticulum of the common bile duct may undergo spontaneous rupture with formation of retroperitoneal biloma (Takahashi et al. 2005). Diverticula have rarely been observed in the hepatic duct (Eisen et al. 1963; Jackson and Maxwell 1964; Maxwell et al. 1967; Napoli 1970; Down 1974; Meyers et al. 1976; Schey et al. 1977; Farkas et al. 1980; Flowers and Ho 1998; Kaneyama et al. 2005a; Hashimoto et al. 2007; Fernandes et al. 2010). Hepatic duct diverticulum may occur in the common hepatic duct (hepatodochal diverticulum) or in the left or right hepatic duct and is considered to be a developmental anomaly. It is a rare disorder with the lowest incidence among congenital conditions that cause dilatation of the bile duct (Maxwell et al. 1967; Farkas et al. 1980). Common hepatic duct diverticulum has been shown to cause fatal obstructive cholangitis and sepsis (Flowers and Ho 1998). Diverticula can also develop in the cystic duct (Grassberger and Seyss 1967). Intrahepatic duct diverticula are rare and may occur as solitary or multiple lesions. This type of

diverticulum may be observed in association with pancreaticobiliary maljunction (Ikematsu et al. 1994).

Acquired Diverticula of the Biliary Tract

Acquired biliary tract diverticula and diverticulum-like lesions are known to occur in the context of primary sclerosing cholangitis (PSC). Such diverticula and/or bile duct webs have been considered by several authors to be highly typical cholangiographic features of PSC, although seen in only about a third of the cases (MacCarty et al. 1983), but in contrast to earlier reports (e.g., Rohrmann et al. 1978), these alterations are not specific for this disease (Gulliver et al. 1991; Tibble et al. 2003).

Cholangiographically, the spectrum of lesions ranges from the "beaded" cholangiographic appearance of ducts characteristic for PSC to usually small diverticular outpouchings (MacCarty et al. 1983). Biliary tract diverticula in PSC can occur together with webs or biliary septum formation (Gulliver et al. 1991), but septa also occur in conjunction with biliary tract malformations (Kato et al. 1994). Other conditions sometimes associated with acquired diverticula include common duct stones, postoperative structures, bile duct stent, and choledochoduodenostomy (Gulliver et al. 1991).

Duodenal Diverticula Associated with Common Bile Duct Disease and Biliary Obstruction

Periampullary duodenal diverticula which are common lesions, mainly in older patients, have been classified into three types, according to the position of the major duodenal papilla (Boix et al. 2006): type I, papilla inside the diverticulum; type II, papilla at the margin of the diverticulum; and type III, papilla near the diverticulum. From their critical position in regard to the choledochal entry, duodenal diverticula can cause biliary obstruction (Gudjonsson et al. 1988; Yoneyama et al. 2004). The distinct anatomic relations between the insertion of the choledochal duct into duodenal diverticula have been analyzed in detail based on 96 postmortem specimens. In every instance, the common bile duct either emptied into or immediately adjacent to the diverticulum (Wolfson and Miller 1978). Tissual anomalies associated with duodenal diverticula, such as the so-called mucosal rosette (a periampullary pseudotumor; Bellamy 1993; Price et al. 1993), may contribute to the pathogenesis of deranged flow. One pathogenic factor may be related to the fact that periampullary diverticula lead to pancreatobiliary reflux (Sugiyama and Atomi 2001). Sometimes, food impaction in a duodenal diverticulum induces biliary obstruction (Van der Linde et al. 1997). Intraduodenal diverticulum has been reported to be associated with double common bile duct causing cholangitis (Martins et al. 2007).

Bile Duct Intussusception and Volvulus

Intussusception

Spontaneous intussusception is known for the cystic duct; this event can cause common bile duct obstruction (Aseem and Cohn 1975). Invagination of the common bile duct into the jejunum has been observed in conjunction with choledochjejunostomy (Zografos and Androulakis 1998). It may also be caused by tumors located to the ampullary region (Van Kemmel and L'hermine 1973).

Volvulus

Volvulus is well known for the gallbladder, where it was described in 1898 already (Wendel 1898). It occurs in all age groups, with the highest incidence in elderly women, and a female-to-male ratio of 3:1 (review of literature: Shaikh et al. 2005). In contrast, volvulus is an exceptional event in the extrahepatic bile ducts. The choledochal duct may be dislodged, together with torsion, in case of large diaphragmatic

hernias, ending up with choledochal semivolvulus (Caldeiro et al. 2001).

Bile Duct Stenosis in Pancreatitis

The fibrotic process characterizing chronic pancreatitis often extends into the tissue surrounding the intrapancreatic part of the common bile duct, causing distal bile duct stenosis. In fact, chronic pancreatitis is one of the most frequent causes of biliary stricture/stenosis (McCollum and Jordan 1975; Warshaw et al. 1976; Schulte et al. 1977; Scott et al. 1977; Sarles and Sahel 1978; Yadegar et al. 1980; Wislooff et al. 1982; Eckhauser et al. 1983; Newton et al. 1983; Aranha et al. 1984; Stabile et al. 1987; Abdullah et al. 2007). In a study on 79 patients with moderate or advanced chronic pancreatitis, 46 % had ERCP evidence of distal common bile duct stenosis (Wislooff et al. 1982). In a retrospective analysis of 814 cases of chronic pancreatitis in Korea, biliary stricture was detected in 13.9 % (Ryu et al. 2005). In an Indian nationwide study on 1,086 patients with chronic pancreatitis of diverse etiology, biliary obstruction was found in 8.2 % (Balakrishnan et al. 2008). Distal bile duct stenosis can occur in any form of chronic pancreatitis, including groove pancreatitis (Castell-Monsalve et al. 2008) and autoimmune pancreatitis (Matsubara et al. 2005). Pancreatic pseudocysts developing in the context of chronic pancreatitis may compress the distal common bile duct and induce biliary obstruction (Gonzalez et al. 1965; Christensen et al. 1975; Falko et al. 1975; Chawla et al. 1977; Warshaw and Rattner 1980; Skellenger et al. 1983; Magyar et al. 1994; Noda et al. 1994; Cho et al. 2000; Yeh et al. 2003; Okabe et al. 2006). Persistent biliary obstruction caused by chronic pancreatitis can lead to secondary biliary cirrhosis (Warshaw et al. 1976; Abdullah et al. 2007). Bile duct obstruction also occurs in patients with acute gallstone pancreatitis (Petrosyan et al. 2009). Chronic fibrosing pancreatitis can be associated with pancreatolithiasis. Pancreatic stones may dislodge into the common channel of the pancreatobiliary ducts and cause obstruction and/or cholangitis (Kinoshita et al. 1996; Jain et al. 2005; Naitoh et al. 2008).

Biliary Obstruction Due To Biliary Sludge

Introduction

Sludge is the more or less solid material which results from slow settling of particles and gels dispersed in a viscid, mucin-rich liquid medium (Angelico et al. 1990; Lee 1990). The material of biliary sludge is a mixture of thickened bile with insoluble salts and sometimes collective collagen tissue from damaged bile duct walls. In more detail, the most common precipitates in gallbladder bile are cholesterol monohydrate crystals, calcium bilirubinate granules, calcium phosphate and calcium carbonate crystals, and calcium salts of fatty acids (Filly et al. 1980; Allen et al. 1981; Lee and Nicholls 1986; Jüngst et al. 1996; Keulemans et al. 1998).

By use of immunofluorescence, it was shown that sludge sediment appears as a mixture of vesicular aggregates and pigment particles which are linked by a gel matrix of mucin containing cholesterol monohydrate crystals, in part coated by IgA (de la Porte et al. 2000). Mucin in bile is supposed to accelerate the crystallization of cholesterol monohydrate (Levy et al. 1984; Smith 1987; Wilhelmi et al. 2004). In fact, hepatic bile is modified during residence in the gallbladder, contributing to eventual sludge formation (Ko et al. 2005b). A portion of biliary sludge contains comparatively large particles (1–3 mm) called microliths, the formation of which is an obligatory intermediate step in the development of gallstones. As a consequence of the sedimentation of sludge, the biliary tract (but particularly the gallbladder) may contain layered bile, with the lowest layer showing low-amplitude echogenicity on ultrasound (Jüngst et al. 2006). The components of sludge can be analyzed by use of bile microscopy (Delchier et al. 1986; Ros et al. 1986; Ko et al. 1999), including polarized light microscopy (Gogna et al. 1989).

Clinical Features of Sludge

Although the ultrasonic detection of gallbladder sludge is relatively frequent, the clinical importance remains unclear (Shaffer 2001). Sludge and microliths can cause deranged bile flow followed by colicky pain, cholecystitis, cholangitis, and acute pancreatitis and has thus been suggested to be of clinical relevance (Ohara and Schaefer 1990; Shaffer 2001; Pazzi et al. 2003; Jain 2004). However, only a fraction of patients with biliary sludge may develop clinical manifestations, because sludge spontaneously disappears in many patients (Lee et al. 1988). In a series of 286 patients with sludge, gallbladder sludge disappeared within a relatively short time in 71.4 % of patients, but gallbladder sludge was considered an important phenomenon because gallbladder stones or complications such as acute cholecystitis occurred in 19.6 % of patients (Janowitz et al. 1994). In the early phase of acute pancreatitis of suspected biliary origin, bile duct crystals were found in most cases (Kohut et al. 2001). In contrast, the relationship of bile duct crystals to sphincter of Oddi dysfunction is not clear (Rhee and Elta 2003). In some patients, sludge in the gallbladder or the common bile duct causes pseudotumorous masses, the so-called tumefactive sludge (Ando and Ito 1986; Kelly et al. 1993).

Imaging criteria of biliary sludge are filling defects or plug-like obstruction seen on cholangiograms or material filling the bile ducts seen on sonograms or CT scans (Barton et al. 1995; Gomez et al. 1998; Metrewell et al. 2004). Transabdominal ultrasound examination permits the visualization of sludge particles in bile, usually those of >2–3 mm in diameter. These represent the larger components of biliary sludge and consist of aggregated crystals or microliths suspended in the mucin-rich liquid phase.

What Are Typical Situations Where Biliary Sludge Develops ?

Biliary sludge is known to develop during pregnancy and the postpartum (usually reversible; Maringhini et al. 1988, 1993; Gilat and Konikoff 2000; increasing in frequency from the second trimester [5.1 %] to the postpartum [10.2 %]; Ko et al. 2005a; Bolukbas et al. 2006), in total parenteral nutrition (Messing et al. 1983; Murray and Hawkey 1992), in morbidly obese patients after rapid weight loss (Shiffman et al. 1991), during fasting after gastrointestinal tract surgery (Bolondi et al. 1985), in critically ill trauma patients (Toursarkissian et al. 1995), after choledochoduodenostomy (chronic biliary sludge or "sump syndrome"; Ell et al. 2006), in gastric and duodenal ulcer disease (Maev et al. 2006), in sickle cell disease (Walker and Serjeant 1996; Al-Salem and Qaisruddin 1998; Walker et al. 2000), and in beta-thalassemia major (Portincasa et al. 2004). Gallbladder sludge develops in approximately 70 % of patients after bone marrow transplantation, and sludge often develops in these patients without known predisposing factors (Teefey et al. 1994). This sludge mainly consists of calcium bilirubinate, while cholesterol crystals are almost absent (Ko et al. 1996). Biliary sludge is known to occur after liver transplantation (found by imaging in 13 % in a series of 400 transplanted livers; Barton et al. 1995). However, the development of this complication, in the absence of anastomotic obstruction in the common bile duct, has now become very rare, owing to improved techniques of biliary reconstruction and routine biliary flushing prior to cold preservation. The pathogenesis of sludge post-OLT is likely to be multifactorial, but cold ischemic damage to the bile duct wall may play a significant role (Chen et al. 1988).

Bile Plug Syndrome and Inspissated Bile Syndrome

The two disorders may be different, in that bile plug syndrome (synonym: gall plug syndrome) is commonly reserved for manifestations in large bile ducts, including the ampullary part (Bernstein et al. 1969; Lévy et al. 1979; Mahr et al. 1988), whereas inspissated bile syndrome mainly involves the intrahepatic tract (Hickey and Power 1956; Breunung and Mitschke 1968;

Lukacs et al. 1972). However, the two terms are frequently used synonymously in the literature. Inspissated bile syndrome has been observed in congenital hematological disorders, including hereditary spherocytosis (Kibel 1961), and in association with choledochal cyst (Lai et al. 1998). Bile plug syndrome can resolve spontaneously (Lang and Pinckney 1991), and the inspissated bile has also been shown to be dissolvable by use of mucolytic agents (Brown 1990). Bile plugs are visualized by means of several imaging techniques (Pfeiffer et al. 1986; Sty et al. 1987; Metrewell et al. 2004). Cystic fibrosis (CF) is associated with an inspissated bile syndrome, producing cholestasis secondary to plugging of macroscopically normal bile ducts by the viscid bile (Lindblad et al. 1992; Greenholz et al. 1997). In extreme neonatal forms of CF, with early profound cholestasis, the process can be associated with a marked decrease in bile ductal diameter, varying from hypoplasia (or atrophy?) to atresia. The involved ducts show a ductocentric fibrosis, and the disorder may require a Kasai-type portoenterostomy (Greenholz et al. 1997).

Inspissated Bile in Subacute Nonsuppurative Cholangitis (Cholangitis Lenta)

Subacute nonsuppurative cholangitis (cholangitis lenta) is an uncommon yet important histological finding in liver biopsies from pediatric liver transplant recipients. Apart from ductular proliferation in the absence of an acute inflammatory infiltrate, inspissated bile in ductules is a diagnostic feature (Lin et al. 2007).

Protein Plugs

Protein plugs manifest as filling defects occur in pancreaticobiliary maljunction associated with choledochal cysts. In one study, this phenomenon was found in 22 out of 55 (40 %) patients (Kaneko et al. 1997) and 34.1 % in another series of 126 pediatric patients (Ando et al. 1998).

Drug-Induced Pseudolithiasis

Reversible biliary sludge and/or lithiasis, named as pseudolithiasis, have been reported in patients treated with ceftriaxone, a widely used antimicrobial agent in pediatrics (Schaad et al. 1988; Kim et al. 1992a; Bor et al. 2004; Miloh et al. 2009). This type of sludge can cause acute cholecystitis and acute pancreatitis (Famularo et al. 1999). In a prospective study of 44 children, 11 patients developed pseudolithiasis 2–9 days after initiation of ceftriaxone therapy, and six children (54.5 %) developed this complication within the first 3 days. Pseudolithiasis resolved in all these children (Papadopoulou et al. 1999). It has been suggested that high ambient temperature may lead to easier pseudolithiasis owing to loss of fluid (Araz et al. 2007). The sludge associated with ceftriaxone contains calcium-ceftriaxone salt as a major component (Park et al. 1991).

Obstructive Mucobilia

Introduction

Mucobilia is defined as a condition in which mucin produced by nonneoplastic or neoplastic biliary cells accumulates within the bile duct lumina, admixed with variable proportions of bile, debris, and/or inflammatory exudates. Mucobilia can, due to the viscous character of mucins, interfere with bile flow and thus cause jaundice of the obstructive type (Hadjis et al. 1987; Chen 1998; Tu et al. 2003; Brown et al. 2010). Typical causes of mucobilia are listed in Table 2 (Chamberlain and Blumgart 2000; Kim

Table 2 Causes of mucobilia

Intraductal papillary mucinous neoplasms of the bile duct
Mucin-producing cholangiocarcinoma
Intrahepatic cholangiocarcinoma, intraductal papillary type
Metastatic colorectal carcinoma
Biliary cystadenocarcinoma
Cholangitis with mucus hypersecretion

et al. 2000; Yeh et al. 2004; Kuo et al. 2005; Koea 2012).

Some biliary tract neoplasms, and in particular intraductal papillary mucinous neoplasms, secrete copious mucin into the bile ducts, a change termed mucobilia. Mucin has a greater impact than the neoplasm itself on the cholangiogram and the clinical presentation. The tumor-bearing ducts show a disproportionate or aneurysmal dilatation caused by the accumulation and failing drainage of mucus (Tsou et al. 2008). Mucin as such is usually not detected by imaging examinations such as ultrasonography, CT, or MRI, because of the signal intensity of mucin being the same as that of water (Yeh et al. 2005). Viscid mucobilia can be found in cystic fibrosis. A large series found a high (96 %) incidence of common bile duct stenosis in patients with CF and liver disease (Gaskin et al. 1988). Apart from ductocentric fibrosis (sometimes resembling sclerosing cholangitis; Gaskin et al. 1988) and stenosis caused by pancreatic fibrosis (Lambert et al. 1981), the accumulation of viscid bile in the duct lumina plays a significant role. The mucostasis also involves the peribiliary glands, which are dilated and apparently increased in number (Bilton et al. 1990). In CF, the inspissated bile may show calcification/mineralization (inspissated calcified secretions; Bilton et al. 1990). Mucus plugs have been observed in congenital stenosis of the common bile duct (Vedantham et al. 1992).

In marked mucobilia, endoscopic retrograde cholangiography may show a disproportionate or aneurysmal dilatation of the tumor-bearing bile duct, but the neoplasm may be hidden in the mucin masses (Tsou et al. 2008). Copious mucus/mucin produced and secreted by biliary tract tumors may be discharged through a dilated ampullary orifice. However, this mechanism may also operate in pancreatic intraductal papillary mucinous tumors, where massive mucus discharge through the papilla can block the distal bile duct (Ito et al. 1977; Smith and Matzen 1985; Patel et al. 2005). In some instances, obstructive jaundice due to impaction of thick mucus produced by such tumors is caused by protrusion of mucus through a spontaneous biliopancreatic fistula (Kurihara et al. 2000).

Pathology

In cases with neoplastic mucobilia, the pathology presentation is determined by the type of underlying neoplasm. In intraductal tumors with a papillary growth pattern, the secreted mucus may engulf the tips of the papillae, and the displaced mucus masses contain detached tumor cells, apoptotic cells, debris, and exudate cells, mainly neutrophil granulocytes. Ulceration of the dilated and damaged bile duct wall can lead to extrusion of mucus into the periductal connective tissue, where it elicits a foreign body-type reaction, with accumulation of mucophages (so-called mucus granulomas). Mucobilia developing in the setting of cholangitis shows hypersecretion of epithelial mucin by hypertrophic and hyperplastic biliary and peribiliary gland cells.

Hemoduct and Hemocholecyst (Hemobilia)

Diverse causes, including trauma, infection, and malignant tumors, can lead to accumulation of fresh or coagulated blood in the biliary tract (hemobilia). Coagulated intraluminal blood can obstruct the biliary struct and mimic neoplastic obstructive disease (Seok et al. 2013). Malignant neoplasms and liver abscesses can invade the bile duct system and cause intraductal hemorrhage (Al-Qahtani 2014). Hemobilia can occur after bioptic trauma, including percutaneous liver biopsy, and may cause acute pancreatitis (Van Os and Petersen 1996; Jornod et al. 1999; Kim et al. 1999; Machicao et al. 2002; Sood et al. 2002; Li et al. 2009) or acute cholecystitis (Albuquerque et al. 2005; Edden et al. 2006). Biopsy-induced symptomatic hemobilia can develop as a delayed complication (Lichtenstein et al. 1992; Rossi et al. 2002). Hemobilia can also result from rupture of hepatic artery pseudoaneurysms (Rencuzogullari et al. 2014). Deep mucosal ulcerations may erode arteries and cause luminal

hemorrhage, e.g., cystic artery bleeding in the gallbladder (Contini et al. 2009). Hemobilia has been observed as a complication of photodynamic therapy for unresectable cholangiocarcinoma (Killeen et al. 2009).

References

Abdallah AA, Krige JE, Bornman PC (2007) Biliary tract obstruction in chronic pancreatitis. HPB (Oxford) 9:421–428

Affronti J (2007) Distal common bile duct angulation and common bile duct stones: who cares? Gastrointest Endosc 66:1161–1163

Afroudakis A, Bhuta SM, Ranganath KA, Kaplowitz N (1978) Obstructive jaundice caused by hepatocellular carcinoma. Report of three cases. Am J Dig Dis 23:609–617

Aguilar Lugue J, Pelaz Salomon A, Castro Lorenzo J, Manueco Santurtun M, Paramo Gomez P (1983) Obstructive jaundice caused by choledochal clots after cholecystectomy (in Spanish). Rev Esp Enferm Apar Dig 64:53–56

Albaugh JS, Keeffe EB, Krippaehne WW (1984) Recurrent obstructive jaundice caused by fibrolamellar hepatocellular carcinoma. Dig Dis Sci 29:762–767

Albuquerque W, Arantes V, de Paula farah K, Lambertucci JR (2005) Acute pancreatitis and acute cholecystitis caused by hemobilia after percutaneous ultrasound-guided liver biopsy. Endoscopy 37:1159–1160

Alden JF, Sterner ER (1957) Diverticulum of the common bile duct; a case report. Ann Surg 145:269–270

Allen B, Bernhoft R, Blanckaert N, Svanvik J, Filly R, Gooding G, Way L (1981) Sludge is calcium bilirubinate associated with bile stasis. Am J Surg 141:51–56

Alonso-Lej F, Rever WB, Pessagno DJ (1959) Congenital choledochal cyst, with a report of 2, and an analysis of 94 cases. Int Abstr Surg 108:1–30

Al-Qahtani HH (2014) Hemobilia due to liver abscess. A rare cause of massive upper gastrointestinal bleeding. Saudi Med J 35:604–606

Al-Salem AH, Qaisruddin S (1998) The significance of biliary sludge in children with sickle cell disease. Pediatr Surg Int 13:14–16

Amarapurkar A, Agrawal V (2006) Liver involvement in tuberculosis – an autopsy study. Trop Gastroenterol 27:69–74

Ando H, Ito T (1986) Ultrasonic characteristics of tumefactive biliary sludge: a thixotropic phenomenon. J Clin Ultrasound 14:289–292

Ando H, Ito T, Kaneko K, Seo T (1995) Congenital stenosis of the intrahepatic bile duct associated with choledochal cysts. J Am Coll Surg 181:426–430

Ando H, Kaneko K, Ito F, Seo T, Harada T, Watanabe Y, Ito T (1998) Surgical removal of protein plugs complicating choledochal cysts: primary repair after adequate opening of the pancreatic duct. J Pediatr Surg 33:1265–1267

Angelico M, De Santis A, Capocaccia L (1990) Biliary sludge: a critical update. J Clin Gastroenterol 12:656–662

Aranha GV, Prinz RA, Freeark RJ, Greenlee HB (1984) The spectrum of biliary tract obstruction from chronic pancreatitis. Arch Surg 119:595–600

Araz N, Okan V, Dermirci M, Araz M (2007) Pseudolithiasis due to ceftriaxone for meningitis in children: report of 8 cases. Tohoku J Exp Med 211:285–290

Aseem WM, Cohn PJ (1975) Case report: intussuscepted cystic duct causing common duct obstruction. Postgrad Med 58:125–128

Badve SS, Saxena R, Wagholikar UL (1991) Intraductal hepatocellular carcinoma with normal liver – case report. Indian J Cancer 28:165–167

Baek SH, Cheon YK, Cho YD, Lee JS, Shim CS, Kim BS (2005) A common bile duct web in association with common bile duct stone (in Korean). Korean J Gastroenterol 46:306–309

Baek YH, Choi SR, Lee JH, Kim MJ, Kim YH, Roh YH, Roh MH (2008) Obstructive jaundice due to compression of the common bile duct by right hepatic artery originated from gastroduodenal artery (in Korean). Korean J Gastroenterol 52:394–398

Balakrishnan V, Unnikrishnan AG, Thomas V, Choudhuri G, Veeraraju P, Singh SP et al (2008) Chronic pancreatitis. A prospective nationwide study of 1,086 subjects from India. JOP 9:593–600

Barton P, Maier A, Steininger R, Mühlbacher F, Lechner G (1995) Biliary sludge after liver transplantation: 1. Imaging findings and efficacy of various imaging procedures. AJR Am J Roentgenol 164:859–864

Bastid C, Sahel J (1989) Diverticulosis of the distal end of the choledochus demonstrated by retrograde endoscopic cholangiopancreatography. Apropos of 5 case reports (In French). Acta Gastroenterol Belg 52:33–38

Bellamy PR (1993) The mucosal rosette: a peri-ampullary pseudotumor within a duodenal diverticulum. Clin Radiol 47:117–118

Bernstein J, Braylan R, Brough AJ (1969) Bile-plug syndrome: a correctable cause of obstructive jaundice in infants. Pediatrics 43:273–276

Bilton D, Fox R, Webb AK, Lawler W, McMahon RF, Howat JM (1990) Pathology of common bile duct stenosis in cystic fibrosis. Gut 31:236–238

Boix J, Lorenzo-Zuniga V, Ananos F, Domenech E, Morillas RM, Gassuli MA (2006) Impact of periampullary duodenal diverticula at endoscopic retrograde cholangiopancreatography: a proposed classification of periampullary duodenal diverticula. Surg Laparosc Endosc Percutan Technol 16:208–211

Bolondi L, Gaiani S, Testa S, Labo G (1985) Gall bladder sludge formation during prolonged fasting after gastrointestinal tract surgery. Gut 26:734–738

Bolukbas FF, Bolukbas C, Horoz M, Ince AT, Uzunkov A, Ozturk A, Aka N, Demirci F et al (2006) Risk factors associated with gallstone and biliary sludge formation during pregnancy. J Gastroenterol Hepatol 21:1150–1153

Bona S, Boiselle JC, Harb J, Descombes P, Rouison D, Huguet C (1991) Intra-duodenal development of low choledochal diverticula. Apropos of 2 cases (in French). Ann Radiol (Paris) 34:273–277

Bor O, Dinleyici EC, Kebapci M, Aydogdu SD (2004) Ceftriaxone-associated biliary sludge and pseudocholelithiasis during childhood: a prospective study. Pediatr Int 46:322–324

Brand SN, Brandt LJ, Sprayregan S, Brenner S, Bernstein LH (1976) Extrahepatic biliary tract obstruction secondary to a hepatoma-containing blood clot in the common bile duct. Am J Dig Dis 21:905–909

Breunung M, Mitschke I (1968) The inspissated bile syndrome (gall plug syndrome) or syndrome of inspissated bile (in German). Kinderärztl Prax 36:491–503

Brown DM (1990) Bile plug syndrome: successful management with a mucolytic agent. J Pediatr Surg 25:351–352

Brown MA, Sakpal SV, Chamberlain RS (2010) Mucobilia: current aspects in the management of a rare cause of malignant biliary obstruction. J Hepato-Biliary-Pancreat Surg 17:205–210

Buckmaster MJ, Schwartz RW, Carnahan GE, Strodel WE (1994) Hepatocellular carcinoma embolus to the common hepatic duct with no detectable primary hepatic tumor. Am Surg 60:699–702

Caldeiro JC, Curcio A, Gigena VC, Barbarossa G (2001) Choledochal semi volvulus with jaundice due to hiatal hernia. Initial percutaneous management. Acta Gastroenterol Latinoam 31:329–332

Camci C, Gurakar A, Kohli V, Sharma S, Jabbour N (2007) Unusual presentation of recurrent hepatocellular carcinoma as obstructive jaundice 15 years after liver transplant. Exp Clin Transplant 5:713–715

Camelot G, Gaume JP, Carbillet JP, Schwager JC, Mantion G, Grandmottet P, Gillet M (1976) Congenital diverticula of the common bile duct. Review of the literature (in French). J Chir (Paris) 112:227–236

Carella G, Degott C, Benhamou JP (1981) Invasion of the lumen of the bile ducts by hepatocellular carcinoma. Liver 1:251–254

Castell-Monsalve FJ, Sousa-Martin JM, Carranza-Carranza A (2008) Groove Pancreatitis: MRI pathologic findings. Abdom Imaging 33:342–348

Cho HG, Min HY, Jang DS, Shin YW, Kim KR et al (2000) Two cases of chronic pancreatitis with pseudocyst complicated by obstructive jaundice. Yonsei Med J 41:522–527

Chamberlain RS, Blumgart LH (2000) Mucobilia in association with a biliary cystadenocarcinoma of the caudate duct: a rare cause of malignant biliary obstruction. HPB Surg 11:345–351

Chandra R, Kapoor D, Tharakan A, Chaudhary A, Sarin SK (2001) Portal biliopathy. J Gastroenterol Hepatol 16:1086–1092

Chapoy et al. 1981. http://www.ncbi.nlm.nih.gov/pubmed/7450427

Chari ST, Harrison ME (1998) Common bile duct webs. Am J Gastroenterol 93:2638–2639

Chawla SK, Chawla K, Sossi AJ, LoPresti PA (1977) Uncommon presentation of pancreatic pseudocyst. Am J Gastroenterol 68:154–160

Chen MF (1998) Mucobilia: the clinical spectrum, diagnosis and treatment. J Gastroenterol Hepatol 13:1084–1090

Chen MF (2002) Icteric type hepatocellular carcinoma: clinical features, diagnosis and treatment. Chang Gung Med J 25:496–501

Chen CL, Wang KL, Chuang JH, Lin JN, Chu MF, Chang CH (1988) Biliary sludge-cast formation following liver transplantation. Hepatogastroenterology 35:22–24

Chen MF, Jan YY, Jeng LB, Hwang TL, Wang CS, Chen SC (1994) Obstructive jaundice secondary to ruptured hepatocellular carcinoma into the common bile duct. Surgical experiences of 20 cases. Cancer 73:1335–1340

Christensen NM, Demling R, Mathewson C (1975) Unusual manifestations of pancreatic pseudocysts and their surgical management. Am J Surg 130:199–205

Chung JP, Kim KW, Chi HS et al (1994) Obstructive jaundice due to compression of the common hepatic duct by right hepatic artery – a case associated with the absence of the lateral segment of the left hepatic lobe. Yonsei Med J 35:231–238

Cleland P, Adjukiewicz A (1980) Hepatoma and obstructive jaundice. Postgrad Med J 56:371–372

Colle I, Van Vlierberghe H, Brenard R, Troisi R, de Hemptinne B, Navez B, De Coninck S et al (2002) Biliary complications of large Echinococcus granulosus cysts: report of 2 cases and review of the literature. Acta Clin Belg 57:349–354

Contini S, Uccelli M, Sassatelli R, Pinna F, Corradi D (2009) Gallbladder ulcer eroding the cystic artery: a rare cause of hemobilia. Am J Surg 198:e17–e19

Creed DL, Fisher ER (1956) Clot formation in the common duct; an unusual manifestation of primary hepatic carcinoma. AMA Arch Surg 73:261–265

De Celis G, Sirvent JM, Gine JJ, Caballero F, Sacristan B, Vidaller A, Margarit C (1985) Choledochal membrane and lithiasis causing obstructive jaundice (in Spanish). Rev Esp Enferm Apar Dig 68:433–435

De la Porte PL, Lafont H, Domingo N, Meyer G, Müller I, Zündt B, Jüngst D (2000) Composition and immunofluorescence studies of biliary "sludge" in patients with cholesterol or mixed gallstones. J Hepatol 33:352–360

Delchier JC, Benfredj P, Preaux AM, Metreau JM, Dhumeaux D (1986) The usefulness of microscopic bile examination in patients with suspected microlithiasis: a prospective evaluation. Hepatology 6:118–122

Devanesan J, deBlasi HP, Sable R, Hoe R, Kinkahabwala M (1978) Congenital hepatic duct obstruction with perforate diaphragms. Arch Surg 113:1452–1455

Di Sena V, Thuler FP, Macedo EP, Paulo GA, Della Libera E, Ferrari AP (2005) Obstructive jaundice secondary to bile duct involvement with Hodgkin's disease: a case report. Sao Paulo Med J 123:30–32

Dickinson SJ, Santulli T (1962) Obstruction of common bile duct by hepatoma. Surgery 52:800–802

Dong Q, Jiang B, Zhang H, Jiang Z, Lu H, Yang C, Cheng Y, Hao X (2006) Management strategy for congenital choledochal cysts with co-existing intrahepatic dilation and aberrant bile duct as well as other complicated biliary anomalies. Yonsei Med J 47:826–832

Down RH (1974) Solitary diverticulum of the hepatic ducts (two cases). Proc R Soc Med 67:217

Eckhauser FE, Knol JA, Strodel WE, Achem S, Nostrant T (1983) Common bile duct strictures associated with chronic pancreatitis. Am Surg 49:350–358

Eckstein RP, Bambach CP, Stiel D, Roche J, Goodman BN (1988) Fibrolamellar carcinoma as a cause of bile duct obstruction. Pathology 20:326–331

Edden Y, St Hilaire H, Benkov K, Harris MT (2006) Percutaneous liver biopsy complicated by hemobilia-associated acute cholecystitis. World J Gastroenterol 12:4435–4436

Ehmke H (1987) Choledochal diverticulum as a possible cause of right-sided upper abdominal pain (in German). Röfo 146:234–236

Eisen HB, Poller S, Maxwell JW, Jackson FC (1963) Hepatodochal diverticulum: a difficult Roentgen diagnosis. Radiology 81:276–278

Ell C, Boosfeld C, Henrich R, Rabenstein T (2006) Endoscopic treatment of the "sump syndrome" after choledochoduodenostomy: a new technique using an amplatzer septal occluder. Z Gastroenterol 44:1231–1235

Erdogan D, Busch OR, Rauws EA, van Delden OM, Gouma DJ, van Gulik TM (2006) Obstructive jaundice due to hepatobiliary cystadenoma or cystadenocarcinoma. World J Gastroenterol 12:5735–5738

Falko JM, Mekhjian HS, Thomas FB (1975) Silent pancreatic pseudocyst: an unusual cause of extrahepatic biliary obstruction. Am J Dig Dis 20:583–587

Famularo G, Polchi S, De Simone C (1999) Acute cholecystitis and pancreatitis in a patient with biliary sludge associated with the use of ceftriaxone: a rare but potentially severe complication. Ann Ital Med Int 14:202–204

Farkas IE, Patko A, Szebeni A, Tulassay Z (1980) Diverticulum of the bile duct. Diagnosis by endoscopic retrograde cholangiopancreatography and ultrasonography. Am J Gastroenterol 73:310–314

Fernandes ES, Bernardo RL, Fernandes MM, Araujo RM, Sebbe R, Monte A, Coelho JF et al (2010) Extrahepatic right hepatic duct diverticulum: a rare entity. Hepatobiliary Pancreat Dis Int 9:213–215

Filly RA, Allen B, Minton MJ, Bernhoft R, Way LW (1980) In vitro investigation of the origin of echoes with biliary sludge. J Clin Ultrasound 8:193–200

Fisher et al. 1968. http://www.ncbi.nlm.nih.gov/pubmed/5652512

Flowers MB, Ho KJ (1998) A rare common hepatic duct diverticulum causing fatal biliary obstruction and sepsis. Arch Pathol Lab Med 122:197–198

Fraser GM, Zirkin H, Krugliak P (1989) Blood clot in the biliary tree due to hepatocellular carcinoma. Isr J Med Sci 25:118–120

Frexes M, Neblett WW, Holcomb GW (1986) Spectrum of biliary disease in childhood. South Med J 79:1342–1349

Furukawa H, Hara T, Taniguchi T (1992) A case of septum formation of the common hepatic duct combined with an anomalous hepatic duct of the caudate lobe. Gastroenterol Jpn 27:102–107

Gabata T, Matsui O, Sanada J, Kadoya M, Ohmura K, Minato H (2003) Cystic duct remnant carcinoma with widespread invasion along the extrahepatic bile duct wall: dynamic CT findings. Abdom Imaging 28:79–82

Gabata T, Terayama N, Kobayashi S, Sanada J, Kadoya M, Matsui O (2007) MR imaging of hepatocellular carcinomas with biliary tumor thrombi. Abdom Imaging 32:470–474

Gaskin KJ, Waters DLM, Howman-Giles R, de Silva M, Earl JW, Martin HC, Kann AE, Brown JM, Dorney SF (1988) Liver disease and common bile duct stenosis in cystic fibrosis. N Engl J Med 318:340–346

Gelmi GF, Gallo G, Valenti G, Amendolara M, Meneghini G, Perri SG (1994) A rare case of accessory choledochus associated with diverticulum of the common bile duct (in Italian). G Chir 15:103–106

Gerson CD, Schinella RA (1969) Hepatoma presenting as extrahepatic biliary obstruction. Report of a case. Am J Dig Dis 14:42–47

Gilat T, Konikoff F (2000) Pregnancy and the biliary tract. Can J Gastroenterol 14(Suppl D):55D–59D

Gogna A, Kar P, Acharya NR, Anand VJ, Kapoor R (1989) Polarized light microscopic examination of human bile in the diagnosis of microlithiasis of the gallbladder. Trop Gastroenterol 10:167–172

Goldberg HJ, Doman DB (1988) Vascularing – an unusual cause of benign biliary stricture. Gastrointest Endosc 34:347–349

Goldenberg DA, Brooks WS, Galambos JT (1981) Unilateral cirrhosis: bleeding varices, right hepatic duct diaphragm, and left hepatic duct atresia. Dig Dis Sci 26:843–851

Gomez NA, Roldos FE, Andrade RA, Rojas JE, Alvarez LR (1998) Biliary sludge: a well-defined sonographic entity. Acta Gastroenterol Latinoam 28: 327–329

Gonzalez LL, Jaffe MS, Wiot JF, Altemeier WA (1965) Pancreatic pseudocyst: a cause of obstructive jaundice. Ann Surg 161:569–576

Grassberger A, Seyss R (1967) Diverticulum of the cystic duct (in German). Munch Med Wochenschr 109:2542–2543

Greenholz SK, Krishnadasan B, Marr C, Cannon R (1997) Biliary obstruction in infants with cystic fibrosis requiring Kasai portoenterostomy. J Pediatr Surg 32:175–179

Gudjonsson H, Gamelli RL, Kaye MD (1988) Symptomatic biliary obstruction associated with juxtapapillary duodenal diverticulum. Dig Dis Sci 33:114–121

Gulliver DJ, Baker ME, Putnam W, Baillie J, Rice R, Cotton PB (1991) Bile duct diverticula and webs: nonspecific cholangiographic features of primary sclerosing cholangitis. AJR Am J Roentgenol 157:281–285

Hadjis NS, Slater RN, Blumgart LH (1987) Mucobilia: an unusual cause of jaundice. Br J Surg 74:48–49

Hanaoka J, Shimada M, Ikegami T, Imura S, Morine Y, Kanemura H, Arakawa Y, Kurita N et al (2006) Hepatocellular carcinoma with massive bile duct tumor thrombus: report of a long-term survival. Hepatogastroenterology 55:2217–2220

Hashimoto M, Umemura R, Okuda C, Matsuda M, Watanabe G (2007) Hepatic duct diverticulum. Am J Surg 193:219–220

Herman LL, Kurtz RC, Brennan MF, Shike M (1992) Acute pancreatitis from intussusception of a gastric polyp in a patient with Gardner's syndrome. Dig Dis Sci 37:955–960

Hiatt JR, Gabbay J, Busuttil RW (1994) Surgical anatomy of the hepatic arteries in 1000 cases. Ann Surg 220:50–52

Hickey KM, Power WH (1956) The inspissated bile syndrome. J Irish Med Assoc 38:58–59

Huang GT, Sheu JC, Lee HS, Lai MY, Wang TH, Chen DS (1998) Icteric type hepatocellular carcinoma: revisited 20 years later. J Gastroenterol 33:53–56

Hunt AH (1965) Compression of the common bile-duct by an enlarging collateral in a case of portal hypertension. Br J Surg 52:636–637

Ikematsu Y, Eto T, Tomioka T, Matsumoto T, Tsunoda T, Kanematsu T (1994) Biliary diverticulum with pancreaticobiliary maljunction. Hepatogastroenterology 41:70–72

Ikenaga N, Chijiiwa K, Otani K, Ohuchida J, Uchiyama S (2009a) A case of peribiliary cyst presenting with obstructive jaundice. J Gastrointest Surg 13:174–176

Ikenaga N, Chijiiwa K, Otani K, Ohuchida J, Uchiyama S, Kondo K (2009b) Clinicopathologic characteristics of hepatocellular carcinoma with bile duct invasion. J Gastrointest Surg 13:492–497

Ishikawa H, Uchida S, Yokokura Y, Iwasaki Y, Horiuchi H, Hiraki M, Kinoshita H, Shirouzu K (2002) Nonparasitic solitary huge liver cysts causing intracystic hemorrhage or obstructive jaundice. J Hepato-Biliary-Pancreat Surg 9:764–768

Ito Y, Blackstone MO, Frank PH, Skinner DB (1977) Mucinous biliary obstruction associated with a cystic adenocarcinoma of the pancreas. Gastroenterology 73:1410–1412

Jackson FC, Maxwell JW (1964) Intrahepatic diverticulum – common hepatic bile duct. Arch Surg 89:706–708

Jain R (2004) Biliary sludge: when should it not be ignored ? Curr Treat Options Curr Treat Options Gastroenterol 7:105–109

Jain S, Kumar M, Arora A (2005) Pancreatic calculus impacted at ampulla of Vater causing sever cholangitis and septic shock. Trop Gastroenterol 26:144–145

Jan YY, Chen MF (1999) Obstructive jaundice secondary to hepatocellular carcinoma rupture into the common bile duct: choledochoscopic findings. Hepatogastroenterology 46:157–161

Janowitz P, Kratzer W, Zemmler T, Tudyka J, Wechsler JG (1994) Gallbladder sludge: spontaneous course and incidence of complications in patients without stones. Hepatology 20:291–294

Jho DH, Jho DJ, Chejfec G, Ahn M, Ong ES, Espat NJ (2007) Primary biliary B-cell lymphoma of the cystic duct causing obstructive jaundice. Am Surg 73:508–510

Joehl RJ, Abt AB (1984) Obstructive jaundice caused by hepatocellular carcinoma. J Surg Oncol 27:80–84

Johns WA, Zimmerman A (1961) Biliary obstruction due to hemobilia caused by liver cell carcinoma. Ann Surg 153:706–710

Jornod P, Wiesel PH, Pescatore P, Gonvers JJ (1999) Hemobilia, a rare cause of acute pancreatitis after percutaneous liver biopsy: diagnosis and treatment by endoscopic retrograde cholangiopancreatography. Am J Gastroenterol 94:3051–3054

Ju JW, Kim MC, Kim YH, Oh JY, Nam KJ, Rho MH (2000) Hepatocholelithiasis due to compression of the common hepatic duct by right hepatic artery. Korean J Hepato-Biliary-Pancreat Surg 4:241–245

Jüngst D, Del Pozo R, Christoph S, Miguel JF, Eder MI, Lange V, Frimberger E, Von Ritter C, Paumgartner G (1996) Sedimentation of biliary sludge: effect on composition of gallbladder bile from patients with cholesterol, mixed, or pigment stones. Scand J Gastroenterol 31:273–278

Jüngst C, Kullak-Ublick GA, Jüngst D (2006) Gallstone disease: microlithiasis and sludge. Best Pract Res Clin Gastroenterol 20:1053–1062

Jurco S, Kim H (1980) Extrahepatic biliary obstruction by hepatocellular carcinoma. Am J Gastroenterol 74:176–178

Kahn T, Reiser M, Gmeinwieser J, Heuck A (1988) The Ehlers-Danlos syndrome, type IV, with an unusual combination of organ malformations. Cardiovasc Intervent Radiol 11:288–291

Kaneko K, Ando H, Ito T, Watanabe Y, Seo T, Harada T, Ito F (1997) Protein plugs cause symptoms in patients with choledochal cysts. Am J Gastroenterol 92:1018–1021

Kaneyama K, Yamataka A, Urao M, Kobayashi H, Lane GJ, Miyano T (2005a) An extremely rare case of symptomatic right hepatic duct diverticulum located outside the liver. Pediatr Surg Int 21:1023–1026

Kaneyama K, Yamataka A, Kobayashi H, Lane GJ, Miyano T (2005b) Mixed type I and II choledochal cysts: a new clinical subtype ? Pediatr Surg Int 21:911–913

Karl T, Langwara H, Bahr R (2004) Prolapsed malignant polyp of the stomach causing acute pancreatitis (in German). Chirurg 75:75–79

Kato S, Nakagawa T, Kobayashi H, Arai E, Isetani K (1994) Septum formation of the common hepatic duct associated with an anomalous junction of the pancreaticobiliary ductal system and gallbladder cancer. Report of a case. Surg Today 24:534–537

Kawakami M, Kitamura T, Akanuma Y, Kosaka K, Kato Y (1977) A case of obstructive jaundice caused by intraluminal growth of hepatoma through the right hepatic duct (in Japanese). Nippon Naika Gakkai Zasshi 66:1753–1758

Keizman D, Shalom MI, Konikoff FM (2006) An angulated common bile duct predisposes to recurrent symptomatic bile duct stones after endoscopic stone extraction. Surg Endosc 20:1594–1599

Kelly IM, Lees WR, Russell RC (1993) Tumefactive biliary sludge: a sonographic pseudotumour appearance in the common bile duct. Clin Radiol 47:251–254

Keulemans YC, Mok KS, de Wit LT, Gouma DJ, Groen AK (1998) Hepatic bile versus gallbladder bile: a comparison of protein and lipid concentration and composition in cholesterol gallstone patients. Hepatology 28:11–16

Khuroo MS, Yattoo GN, Zargar SA, Javid G, Dar MY, Khan BA, Boda MI (1993) Biliary abnormalities associated with extrahepatic portal venous obstruction. Hepatology 17:807–813

Kibel MA (1961) Hereditary spherocytosis complicated by the inspissated bile syndrome. S Afr Med J 21:50–53

Kiev J, Dyslin DC, Vitenas P, Kerstein MD (1990) Obstructive jaundice caused by hepatoma fragments in the common hepatic duct. J Clin Gastroenterol 12:207–213

Killeen RP, Torreggiani WC, Malone DE, Brophy DP (2009) Hemobilia as a potential complication in patients treated with photodynamic therapy for unresectable cholangiocarcinoma. Gastrointest Cancer Res 3:80

Kim YS, Kestell MF, Lee SP (1992a) Gall-bladder sludge: lessons from ceftriaxone. J Gastroenterol Hepatol 7:618–621

Kim MH, Lee SK, Min YI et al (1992b) Secondary intrahepatic stones due to compression of common hepatic duct by right hepatic artery. Korean J Gastroenterol 24:901–905

Kim HJ, Shin JH, Lee YY, Lee JK, Yim BC, Park UT, Myung SJ, Lee SK, Kim MH, Min YI (1999) Hemobilia causing acute biliary pancreatitis after percutaneous liver biopsy. Endoscopy 31:S18–S19

Kim HJ, Kim MH, Lee SK, Yoo KS, Park ET, Lim BC, Park HJ, Myung SJ, Seo DW et al (2000) Mucin-hypersecreting bile duct tumor characterized by a striking homology with an intraductal papillary mucinous tumor (IPMT) of the pancreas. Endoscopy 32:389–393

Kinoshita H, Imayama H, Sou H, Shibata J, Ogami N, Tamae T, Nakayama T (1996) A case of obstructive icterus caused by incarceration of a pancreatic stone in the common channel of the pancreatobiliary ducts. Kurume Med J 43:79–85

Kirk JM, Skipper D, Joseph AE, Knee G, Grundy A (1994) Intraluminal bile duct hepatocellular carcinoma. Clin Radiol 49:886–888

Ko CW, Murakami C, Sekijima JH, Kim MH, McDonald GB, Lee SP (1996) Chemical composition of gallbladder sludge in patients after marrow transplantation. Am J Gastroenterol 91:1207–1210

Ko CW, Sekijima JH, Lee SP (1999) Biliary sludge. Ann Intern Med 130:301–311

Ko CW, Beresford SA, Schulte SJ, Matsumoto AM, Lee SP (2005a) Incidence, natural history, and risk factors for biliary sludge and stones during pregnancy. Hepatology 41:359–365

Ko CW, Schulte SJ, Lee SP (2005b) Biliary sludge is formed by modification of hepatic bile by the gallbladder mucosa. Clin Gastroenterol Hepatol 3:672–678

Kobayashi N, Kirikoshi H, Higurashi T, Iida H, Mawatari H, Endo H, Nozaki Y, Yoneda K et al (2008) Tumor fragment impacted at the major duodenal papilla causing obstructive jaundice in a patient with hepatocellular carcinoma. Gastrointest Endosc 68:999–1000

Koea JB (2012) Metastatic colorectal carcinoma presenting with mucobilia. ANZ J Surg 82:373–374

Kohut M, Nowak A, Nowakowska-Dulawa E, Kcazor R, Marek T (2001) The frequency of bile duct crystals in patients with presumed biliary pancreatitis. Gastrointest Endosc 54:37–41

Kojiro M, Kawabata K, Kawano Y, Shirai F, Takemoto N, Nakashima T (1982) Hepatocellular carcinoma presenting as intrabile duct tumor growth: a clinicopathologic study of 24 cases. Cancer 49:2144–2147

Komatsu R, Shima Y, Takahashi H, Shimamura Y, Watanabe E, Shimizu H (1989) hepatocellular carcinoma with intraductal tumor thrombus diagnosed by ultrasonography: report of two resected cases (in Japanese). Rinsho Hoshasen 34:941–944

Konstantakos AK, Coogan SM, Husni EA, Raaf JH (2000) Aneurysm of the gastroduodenal artery: an unusual cause of obstructive jaundice. Am Surg 66:695–698

Koops A, Wojciechowski B, Broering DC, Adam G, Krupski-Berdien G (2004) Anatomic variations of the hepatic arteries in 604 selective celiac and a superior mesenteric angiographies. Surg Radiol Ant 26:239–244

Kostiainen S, Paakkonen M, Merikoshi Y (1983) Diverticulum of the common bile duct. A case report. Acta Chir Scand 149:531–533

Koytcha F, Testart J, Teniere P (1976) A case of congenital diverticulum of the choledochus in an adult (in French). Sem Hop 52:1400–1404

Kubo M, Sakamoto M, Fukushima N, Yachida S, Nakanishi Y, Shimoda T, Yamamoto J, Moriya Y, Hirohashi S (2002) Less aggressive features of colorectal cancer with liver metastases showing macroscopic intrabiliary extension. Pathol Int 52:514–518

Kune GA (1965) Gall stones in diverticula of the lower common bile duct. Gut 6:95–98

Kuo CM, Changchien CS, Wu KL, Chuah SK, Chiu KW, Chiu YC, Chou YP, Kuo CH (2005) Mucin-producing cholangiocarcinoma: clinical experience of 24 cases in 16 years. Scand J Gastroenterol 40:455–459

Kurihara K, Nagai H, Kasahara K, Kanazawa K, Kanai N (2000) Biliopancreatic fistula associated with intraductal papillary-mucinous pancreatic cancer: institutional experience and review of the literature. Hepatogastroenterology 47:1164–1167

Lai ST, Lam KT, Lee KC (1992) Biliary tract invasion and obstruction by hepatocellular carcinoma: report of five cases. Postgrad Med J 68:961–963

Lai HS, Duh YC, Chen WJ (1998) Inspissated bile syndrome followed by choledochal cyst formation. Surgery 123:706–708

Lambert JR, Cole M, Crozier DN, Connon JJ (1981) Intrapancreatic common bile duct compression causing jaundice in an adult with cystic fibrosis. Gastroenterology 80:169–172

Lang EV, Pinckney LE (1991) Spontaneous resolution of bile-plug syndrome. AJR Am J Roentgenol 156:1225–1226

Lapeyre M, Mathieu D, Tailboux L, Rahmouni A, Kobeiter H (2002) Dilatation of the intrahepatic bile ducts associated with benign liver lesions: an unusual finding. Eur Radiol 12:71–73

Lau WY, Mok SD, Leung JW, Li AK (1990) Migrated tumour fragments in common bile ducts from hepatocellular carcinoma. Aust N Z J Surg 60:995–997

Lee SP (1990) Pathogenesis of biliary sludge. Hepatology 12:200S–205S

Lee SH, Burhenne HJ (1991) Extrahepatic bile duct angulation by T-tube: the elbow sign. Gastrointest Radiol 16:157–158

Lee SP, Nicholls JF (1986) Nature and composition of biliary sludge. Gastroenterology 90:677–686

Lee SP, Maher K, Nicholls JF (1988) Origin and fate of biliary sludge. Gastroenterology 94:170–176

Lévy JM, Kuss JJ, Karli A, Clerc G, Buck P, Weill-Bousson M, Lutz P, Mikail I (1979) Bile plug syndrome. A rare cause of curable cholestatic jaundice in the infant (in French). Arch Fr Pediatr 36:801–806

Levy PF, Smith BF, LaMont JT (1984) Human gallbladder mucin accelerates nucleation of cholesterol in artificial bile. Gastroenterology 87:270–275

Lewis DR, Kung H, Connon JJ (1982) Biliary obstruction secondary to hepatic artery aneurysm: cholangiographic appearance and diagnostic considerations. Gastroenterology 82:1446–1451

Li F, Mekeel KL, Eleid M, Harrison ME, Reddy KS, Moss AA, Mulligan DC (2009) Hemobilia and pancreatitis after liver transplant biopsy. Liver Transpl 15:350–351

Lichtenstein DR, Kim D, Chopra S (1992) Delayed massive hemobilia following percutaneous liver biopsy: treatment by embolotherapy. Am J Gastroenterol 87:1833–1838

Lin TY, Chen KM, Chen YR, Lin WS, Wang TH, Sung JL (1975) Icteric type hepatoma. Med Chir Dig 88:267–270

Lin CC, Sundaram SS, Hart J, Whitington PF (2007) Subacute nonsuppurative cholangitis (cholangitis lenta) in pediatric liver transplant patients. J Pediatr Gastroenterol Nutr 45:228–233

Lindblad A, Hultcrantz R, Strandvik B (1992) Bile-duct destruction and collagen deposition: a prominent ultrastructural feature of the liver in cystic fibrosis. Hepatology 16:372–381

Liratzopoulos N, Efremidou EI, Papageorgiou MS, Romanidis K, Minopoulos GJ, Manolas KJ (2006) Extrahepatic biliary obstruction due to a solitary pancreatic metastasis of squamous cell lung carcinoma. Case report. J Gastrointest Liver Dis 15:73–75

Liu Q, Chen J, Li H, Liang B, Zhang L, Hu T (2010) Hepatocellular carcinoma with bile duct tumor thrombi: correlation of magnetic resonance imaging features to histopathologic manifestations. Eur J Radiol 76:103–109

Long XY, Li YX, Wu W, Li L, Cao J (2010) Diagnosis of bile duct hepatocellular carcinoma thrombus without obvious intrahepatic mass. World J Gastroenterol 16:4998–5004

Longo OF (1950) Diverticulum of the common bile duct (in Spanish). Bol Trab Acad Argent Cir 34:224–228

Luchtman M, Martins MS, Scheidemantel RE (1971) Congenital diverticulum of the choledochus. Report of a case. Int Surg 55:280–282

Lukacs VF, Balazs M, Dénes J (1972) The clinical picture of inspissated bile syndrome (in German). Acta Paediatr Acad Sci Hung 13:139–150

Luttwak EM, Schwartz A (1961) Jaundice due to obstruction of the common duct by aberrant artery: demonstration of celiac anomaly by translumbar aortography and simultaneous choledochogram. Ann Surg 153: 134–137

MacCarty RL, laRusso NF, Wiesner RH, Ludwig J (1983) Primary sclerosing cholangitis: findings on cholangiography and pancreatography. Radiology 149:39–44

Machicao VI, Lukens FJ, Lange SM, Scolapio JS (2002) Arterioportal fistula causing acute pancreatitis and hemobilia after liver biopsy. J Clin Gastroenterol 34:481–484

Maev IV, Dicheva DT, Buragina TA, Penkina TV (2006) Frequency of the detection of biliary sludge in ulcerative disease (in Russian). Eksp Klin Gastroenterol 20–4:138

Magyar A, Tilhanyi T, Szlavik R, Flautner L (1994) Pancreatic pseudocysts causing compression symptoms. Acta Chir Hung 34:59–67

Mahr MA, Hugosson C, Nazar HM, Saad SA, Ali MA (1988) Bile-plug syndrome. Pediatr Radiol 19:61–64

Mai S, Paladino F, Donelli G, Mantovani LF (1991) A choledochal diverticulum. A case report (in Italian). Minerva Chir 46:1217–1222

Makino T, Nakamori S, Kashiwazaki M, Masuda N, Ikenaga M, Hirao M, Fujitani K et al (2006) An icteric type hepatocellular carcinoma with no detectable tumor in the liver: report of a case. Surg Today 36:633–637

Mallory TB, Castleman B, Parris EE (1947) Case record of Massachusetts general hospital, case 33441. N Engl J Med 237:673–676

Margolis M, Schein M (2001) Biliary web-a rare cause of extrahepatic biliary obstruction. Dig Surg 18:317–319

Maringhini A, Ciambra M, Baccelliere P, Raimondo M, Pagliaro L (1988) Sludge, stones, and pregnancy. Gastroenterology 95:1160–1161

Maringhini A, Ciambra M, Baccelliere P, Raimondo M, Orlando A, Tinè F, Grasso R, Randazzo MA et al (1993) Biliary sludge and gallstones in pregnancy: incidence, risk factors, and natural history. Ann Intern Med 119:116–120

Martin Molinero R, Placer Galan C, Jimenez Garrido M, Soleto Saez E (1989) Hepatic hydatid cyst with destruction of the biliary confluent. Apropos of 2 cases treated by direct reconstruction (in French). J Chir (Paris) 126:672–675

Martins PN, Benckert C, Vetzke-Schlieker W, Pratschke J, Tullius SG, Neuhaus P (2007) Intraduodenal diverticulum associated with a double common bile duct causing recurrent pancreatitis and cholangitis: report of a case. Surg Today 37:320–324

Matsubara T, Sakurai Y, Miura H, Kobayashi H, Shoji M, Nakamura Y, Imazu H, Hasegawa S et al (2005) Complete obstruction of the lower common bile duct caused by autoimmune pancreatitis: is biliary reconstruction really necessary ? J Hepato-Biliary-Pancreat Surg 12:76–83

Maxwell JW, Jackson FC, Davis WC, Eisen HB, Poller S (1967) Hepatodochal diverticulum: a new entity. Am Surg 33:153–158

Mazziotti S, Blandino A, Gaeta M, Lamberto S, Vinci V, Ascenti G (2003) Hepatic artery aneurysm, an unusual cause of obstructive jaundice: MR cholangiography findings. Abdom Imaging 28:835–837

McCollum WB, Jordan PH (1975) Obstructive jaundice in patients with pancreatitis without associated biliary tract disease. Ann Surg 182:116–120

Merza AP, Raiser MW (1987) Biliary tract manifestations of the Marfan syndrome. Am J Gastroenterol 82:779–782

Messing B, Bories C, Kunstlinger F, Bernier JJ (1983) Does total parenteral nutrition induce gallbladder sludge formation and lithiasis ? Gastroenterology 84:1012–1019

Metrewell C, So NM, Chu WC, Lam WW (2004) Magnetic resonance cholangiography in children. Br J Radiol 77:1059–1064

Meyers C, Reynes CJ, Freeark RJ (1976) Diverticulum of the hepatic duct: a rare anomaly. Radiology 119:38

Michels NA (1951) The hepatic, cystic and retroduodenal arteries and their relations to the biliary ducts. Ann Surg 133:503–524

Midorikawa Y, Kubota K, Komatsu Y, Hasegawa K, Koike Y, Mori M, Makuuchi M (2000) Gallbladder carcinoma with a tumor thrombus in the common bile duct: an unusual cause of obstructive jaundice. Surgery 127:473–474

Miloh T, Rosenberg HK, Kochin I, Kerkar N (2009) Inspissated bile syndrome in a neonate with cefotaxime: sonographic aid to diagnosis, management, and follow-up. J Ultrasound Med 28:541–544

Miyashita K, Shiraki K, Ito T, Taoka H, Nakano T (2005) The right hepatic artery syndrome. World J Gastroenterol 11:3008–3009

Mouroux J, Chazelet C, Deixonne B, Baumel H (1987) Congenital diverticulum of the bile ducts. Apropos of a case and review of the literature (in French). J Chir (Paris) 124:99–102

Murakami Y, Yokoyama T, Kanehiro T, Uemura K, Sasaki M, Morifuji M, Sueda T (2003) Successful diagnosis and resection of icteric type hepatocellular carcinoma. Hepatogastroenterology 50:1634–1636

Murata K, Shiraki K, Kawakita T, Yamamoto N, Okano H, Sakai T, Ohmori S, Deguchi M et al (2003) Hepatocellular carcinoma presenting with obstructive jaundice: a clinicopathological study of eight cases. Hepatogastroenterology 50:2057–2060

Murray FE, Hawkey CJ (1992) Therapeutic approaches to the problem of biliary sludge and gallstone formation during total parenteral nutrition. Clin Nutr 11:12–17

Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Okumura F, Togawa S, Kitajima Y et al (2008) A case of obstructive jaundice caused by impaction of a pancreatic stone in the papilla for which a needle knife precut papillotomy was effective. JOP 9:520–525

Nakajima Y, Ashikawa T, Sugihara K, Sakurazawa K, Menjou M, Sasabe M (1997) A case of the hepatocellular carcinoma with obstructive jaundice due to the tumor thrombus in the common hepatic duct (in Japanese). Nippon Shokakibyo Gakkai Zasshi 94:498–502

Napoli D (1970) Rare congenital anomaly of the biliary ways: diverticulum of the common hepatic duct (in Italian). Quad Radiol 35:503–510

Newton BB, Rittenbury MS, Anderson MC (1983) Extrahepatic biliary obstruction associated with pancreatitis. Ann Surg 197:645–653

Nishio H, Miyata K, Hanai M, Kato M, Yoneyama F, Kobayashi Y (2002) resection of an icteric type hepatoma with tumor thrombi filling the right posterior bile duct. Hepatogastroenterology 49:1682–1685

Noda T, Ueno N, Tamada K, Ichiyama M, Fukuda M, Tomiyama T, Nishizono T, Tano S et al (1994) A case of chronic pancreatitis with pseudocysts complicated by infection and obstructive jaundice. Am J Gastroenterol 89:2066–2069

Nonomura A, Ohta G, Kanai M, Kobayashi K (1983) Hepatocellular carcinoma presenting extrahepatic biliary obstruction. Acta Pathol Jpn 33:789–806

Ohara N, Schaeder J (1990) Clinical significance of biliary sludge. J Clin Gastroenterol 12:291–294

Okabe Y, Tsuruta O, Wada Y, Wada K, Suga H, Kudoh M, Kawahara R, Kodama T et al (2006) Endoscopic ultrasonography-guided cystogastrostomy for large pancreatic pseudocyst with obstructive jaundice – a case report. Kurume Med J 53:89–94

Okano K, Yamamoto J, Moriya Y, Akasu T, Kosuge T, Sakamoto M et al (1999) Macroscopic intrabiliary growth of liver metastases from colorectal cancer. Surgery 126:829–834

Ornet L, Petrucci JM, Morin G (1966) Intrahepatic biliary lithiasis with congenital diaphragm of the hepatocholedochus (in French). J Chir (Paris) 91:269–272

Oshima S, Okayasu I, Hatakeyama S (1986) Hepatocellular carcinoma presenting extrahepatic obstructive jaundice due to bile duct invasion – clinicopathological study of two cases. Bull Tokyo Med Dent Univ 33:91–97

Papadopoulou F, Efremidis S, Karyda S, Badouraki M, Karatza E, Panteliadis C, Malaka K (1999) Incidence of ceftriaxone-associated gallbladder pseudolithiasis. Acta Paediatr 88:1352–1355

Papaziogas B, Lazaridis C, Pavlidis T, Galanis I, Paraskevas G, Papaziogas T (2002) Congenital web of the common bile duct in association with cholelithiasis. J Hepatobiliary Pancreat Surg 9:271–273

Papo M, Fernandez J, Quer JC, Sirvent JJ, Richart C (1996) metastatic breast carcinoma presenting as obstructive jaundice. Am J Gastroenterol 91:2240–2241

Park HZ, Lee SP, Schy AL (1991) Ceftriaxone-associated gallbladder sludge. Identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. Gastroenterology 100:1665–1670

Patel A, Lambiase L, Decarli A, Fazel A (2005) Management of the mucin filled bile duct. A complication of intraductal papillary mucinous tumor of the pancreas. JOP 6:255–259

Pazzi P, Gamberini S, Buldrini P, Gullini S (2003) Biliary sludge: the sluggish gallbladder. Dig Liver Dis 35(Suppl 3):S39–S45

Peng SY, Wang JW, Liu YB, Cai XJ, Xu B, Deng GL, Li HJ (2004) Hepatocellular carcinoma with bile duct thrombi: analysis of surgical treatment. Hepatogastroenterology 51:801–804

Petrosyan M, Estrada JJ, Chan S, Rosen H, Berne TV, Mason RJ (2009) Natural progression of biochemical markers of biliary tract obstruction in patients with gallstone pancreatitis. Gastroenterol Res Pract 2009:820749

Pfeiffer WR, Robinson LH, Balsara VJ (1986) Sonographic features of bile plug syndrome. J Ultrasound Med 5:161–163

Pinter A, Pilaszanovich I, Schafer J, Weisenbach J (1975) Membraneous obstruction of the common bile duct. J Pediatr Surg 10:839–840

Portincasa P, Moschetta A, Berardino M, Di-Ciaula A, Vacca M, Baldassarre G, Pietrapertosa A et al (2004) Impaired gallbladder motility and delayed orocecal transit contribute to pigmentary gallstone and biliary sludge formation in beta-thalassemia major adults. World J Gastroenterol 10:2383–2390

Povoski SP, Klimstra DS, Brown KT, Schwartz LH, Kurtz RC, Jarnagin WR, Fong Y, Blumgart LH (2000) Recognition of intrabiliary hepatic metastases from colorectal adenocarcinoma. HPB Surg 11:383–390

Price J, Clarke A, Tait N (1993) The mucosal rosette: a peri-ampullary pseudotumor within a duodenal diverticulum. Clin Radiol 48:145–146

Pujol-Soler R, Fernandez-Cruz L, Garcia-Olives F (1975) Diverticula of the infundibulum of the choledochus (in Spanish). Rev Esp Enferm Apar Dig 45:559–566

Rau C, Marec F, Vibert E, Geslin G, Yzet T, Joly JP, Chatelain D, Duval H, Regimbeau JM (2004) Gallbladder cancer revealed by a jaundice caused by an endobiliary tumor thrombus (in French). Ann Chir 129:368–371

Reibscheid S, Lederman H, Ganc A, Larsson EJ, Vilela MP, Secaf F (1973) Direction and angulation of the extra-hepatic ducts in pancreatic and ampullary tumors: radiological sign for the differential diagnosis. Analysis of 47 cases by transparietal-hepatic cholangiography (in Portuguese). Rev Paul Med 82:139–144

Rencuzogullari A, Okoh AK, Akcam TA, Roach EC, Dalci K, Ulku A (2014) Hemobilia as a result of tight hepatic artery pseudoaneurysm rupture: an unusual complication of laparoscopic cholecystectomy. Int J Surg Case Rep 5:142–144

Rhee JY, Elta GH (2003) The relationship of bile duct crystals to sphincter of Oddi dysfunction. Curr Gastroenterol Rep 5:160–163

Rhoe BS, Kim H, Jin SY, Jang WI (1989) Hepatoma presenting as extrahepatic biliary obstruction due to hemobilia. Yonsei Med J 30:383–386

Riopel MA, Klimstra DS, Godellas CV, Blumgart LH, Westra WH (1997) Intrabiliary growth of metastatic colonic adenocarcinoma: a pattern of intrahepatic spread easily confused with primary neoplasia of the biliary tract. Am J Surg Pathol 21:1030–1036

Rohrmann CA, Ansel HJ, Freeny PC, Silverstein FE, Protell RL, Fenster LF, Ball T (1978) Cholangiographic abnormalities in patients with inflammatory bowel disease. Radiology 127:635–641

Ros E, Navarro S, Fernandez I, Reixach M, Ribo JM, Rodes J (1986) Utility of biliary microscopy for the prediction of the chemical composition of gallstones and the outcome of dissolution therapy with ursodeoxycholic acid. Gastroenterology 91:703–712

Rosenfeld L, Abergel A, Bonny C, Poincloux L, Gayard P, Garcier JM, Scribe-Outtas M et al (2001) Complicated polycystic liver disease with intracystic hemorrhage and obstructive jaundice (in French). Gastroenterol Clin Biol 25:818–822

Rosenthal MD, White GH, Stephen MS, Gallagher JJ, Sandroussi C (2008) Vascular biliopathy as a cause of common bile duct obstruction successfully treated by mesocaval shunt and endoscopic retrograde cholangiopancreatography biliary stent placement. Vascular 16:356–358

Roslyn JJ, Kuchenbecker S, Longmire WP, Tompkins RK (1984) Floating tumor debris. A cause of intermittent biliary obstruction. Arch Surg 119:1312–1315

Rossi P, Sileri P, Gentileschi P, Sica GS, Ercoli L, Coscarella G, De Majo A, Gaspari AL (2002) Delayed symptomatic hemobilia after ultrasound-guided liver

biopsy: a case report. Hepatogastroenterology 49:1659–1662
Rukstinat GJ, Saletta FJ, Tuleja CW (1970) Intermittent jaundice: the result of a prolapsed gastric tumor occluding the common bile duct. IMJ Ill Med J 137:595–597
Ryu JK, Lee JK, Kim YT, Lee DK, Seo DW, Lee KT, Kim HG, Kim JS, Lee HS et al (2005) Clinical features of chronic pancreatitis in Korea: a multicenter nationwide study. Digestion 72:207–211
Salam M, Keeffe EB (1989) Liver cysts associated with polycystic kidney disease: role of Tc-99m hepatobiliary imaging. Clin Nucl Med 14:803–807
Sandblom P (1948) Hemorrhage into the biliary tract following trauma – "traumatic hemobilia". Surgery 24:571
Sapounov S (1972) A case of choledochal diverticulum with secondary calculus formation (in German). Fortschr Geb Rontgenstr Nuklearmed 116:719–720
Sarles H, Sahel J (1978) Cholestasis and lesions of the biliary tract in chronic pancreatitis. Gut 19:851–857
Sarma DP, Weilbaecher TG, Deipairine EM (1987) Hepatocellular carcinoma causing obstructive jaundice. J Surg Oncol 34:192–193
Sastry RA, Raju GS, Kumar YR (1996) Icterus due to tumor emboli – a rare presentation of hepatoma. Indian J Gastroenterol 15:24–25
Sato R, Fujii T, Chiba A et al (2002) A case of Alonso-Lej's type II, congenital cystic dilatation of the common bile duct (in Japanese). gastroenterol. Endoscopy 44:1191–1197
Satoh S, Ikai I, Honda G, Okabe H, Takeyama O, Yamamoto Y, Yamamoto N, Iimuro Y et al (2000) Clinicopathologic evaluation of hepatocellular carcinoma with bile duct thrombi. Surgery 128:779–783
Schaad UB, Wedgwood-Krucko J, Tschaeppeler H (1988) Reversible ceftriaxone-associated pseudolithiasis in children. Lancet 2(8625):1411–1413
Schey WL, Pinsky SM, Lipschütz HS, Dragomer AS (1977) Hepatic duct diverticulum simulating a choledochal cyst. AJR Am J Roentgenol 128:318–320
Schippers E, Dittler HJ (1989) Multiple hollow organ dysplasia in Ehlers-Danlos syndrome. J Pediatr Surg 24:1181–1183
Schulte WJ, LaPorta AJ, Condon RE, Unger GF, Geenen JE, DeCosse JJ (1977) Chronic pancreatitis: a cause of biliary stricture. Surgery 82:303–309
Schutze K, Hentschel E, Dufek W (1990) Malignant bile duct obstruction by tumor embolism. Endoscopy 22:197–198
Scott J, Summerfield JA, Elias E, Dick R, Sherlock S (1977) Chronic pancreatitis: a cause of cholestasis. Gut 18:196–201
Seok DK, Ki SS, Wang JH, Moon ES, Lee TU (2013) Hemorrhagic cholecystitis presenting as obstructive jaundice. Korean J Intern Med 28:384–385
Sfyroeras GS, Antoniou GA, Drakou AA, Karathanos C, Giannoukas AD (2009) Visceral venous aneurysms: clinical presentation, natural history and their management : a systematic review. Eur J Vasc Endovasc Surg 38:498–505
Shaffer EA (2001) Gallbladder sludge: what is its clinical significance ? Curr Gastroenterol Rep 3:166–173
Shaikh AA, Charles A, Domingo S, Schaub G (2005) Gallbladder volvulus: report of two original cases and review of the literature. Am Surg 71:87–89
Shamberger RC, Treat MR, Ottinger LW (1985) Intraduodenal diverticula of the common bile duct. Gastrointest Endosc 31:333–335
Sharma AK, Wakhlu A, Sharma SS (1995) The role of endoscopic retrograde cholangiopancreatography in the management of choledochal cysts in children. J Pediatr Surg 30:65–67
Shera AH, Shah OJ (2008) Congenital common bile duct web in association with hepatobiliary pancreatic ductal anomalies. Eur J Pediatr Surg 18:350–351
Shibata Y, Toyoda S (1995) Carcinoma of the cystic duct protruding into the common bile duct: report of a case. Surg Today 25:1050–1053
Shiffman ML, Sugerman HJ, Kellum JM, Brewer WH, Moore EW (1991) Gallstone formation after rapid weight loss: a prospective study in patients undergoing gastric bypass surgery for treatment of morbid obesity. Am J Gastroenterol 86:1000–1005
Shih et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1339201
Shiomi M, Kamiya J, Nagino M, Uesaka K, Sano T, Hayakawa N, Kanai M, Yamamoto H, Nimura Y (2001) Hepatocellular carcinoma with biliary tumor thrombi: aggressive operative approach after appropriate preoperative management. Surgery 129: 692–698
Sipahioglu MH, Tokgöz B, Karahan OI, Ok E, Sav T, Oymak O, Utas C (2005) Obstructive icterus directly related to visceral artery aneurysm in a CAPD patient. Clin Nephrol 63:493–495
Skellenger ME, Patterson D, Foley NT, Jordan PH (1983) Cholestasis due to compression of the common bile duct by pancreatic pseudocysts. Am J Surg 145:343–348
Smith BF (1987) Human gallbladder mucin binds biliary lipids and promotes cholesterol crystal nucleation in model bile. J Lipid Res 28:1088–1097
Smith E, Matzen P (1985) Mucus-producing tumors with mucinous biliary obstruction causing jaundice: diagnosed and treated endoscopically. Am J Gastroenterol 80:287–289
Smith AD, Mohammed F, Watson GM, Howlett DC (2002) Common bile duct compression by an abdominal aortic aneurysm: an unusual cause of biliary tract dilatation. Eur J Gastroenterol Hepatol 14:767–769
Solovel G, Makkouk N, Favriel JM, Teissier JM, Petit J, Esso C (1987) Congenital diverticulum of the lower choledochus. Apropos of a case with intraduodenal development (in French). J Chir (Paris) 124:119–124
Sood A, Midna V, Kumar A, Sood N (2002) Acute pancreatitis with hemobilia following percutaneous liver biopsy. Indian J Gastroenterol 21:81–82

Stabile BE, Calabria R, Wilson SE, Passaro E (1987) Stricture of the common bile duct from chronic pancreatitis. Surg Gynecol Obstet 165:121–126

Stanley JH, Yantis PL, Marsh WH (1984) Periportal tuberculous adenitis: a rare cause of obstructive jaundice. Gastrointest Radiol 9:227–229

Sty JR, Wells RG, Schroeder BA (1987) Comparative imaging. Bile-plug syndrome. Clin Nucl Med 12:489–490

Sugiura T, Nagino M, Oda K, Ebata T, Nishio H, Arai T, Nimura Y (2006) Hepatectomy for colorectal liver metastases with macroscopic intrabiliary tumor growth. World J Surg 30:1902–1908

Sugiyama M, Atomi Y (2001) Periampullary diverticula cause pancreatobiliary reflux. Scand J Gastroenterol 36:994–997

Taboga V, Braggion G, Marchesin G (1969) Cholestasis caused by unnoticed anomaly of the right hepatic artery. Acta Chir Ital 25:491–497

Takahashi K, Okabe Y, Orino A, Imai Y, Yazumi S, Chiba T (2005) Spontaneous rupture of a biliary diverticulum in the distal common bile duct, with formation of a retroperitoneal biloma. Gastrointest Endosc 61:783–787

Takamatsu S, Teramoto K, Kawamura T, Kudo A, Noguchi N, Irie T, Ochiai T, Kumagai J et al (2004) Liver metastasis from rectal cancer with prominent intrabile duct growth. Pathol Int 54:440–445

Takehara H, Komi N, Okada A, Masamune K, Asai A (1993) A case of biliary stricture caused by cavernous transformation of the portal vein. Acta Paediatr Jpn 35:158–161

Tamada K, Isoda N, Wada S, Tomiyama T, Ohashi A, Satoh Y, Ido K, Sugano K (2001) Intraductal ultrasonography for hepatocellular carcinoma with tumor thrombi in the bile duct: comparison with polypoid cholangiocarcinoma. J Gastroenterol Hepatol 16:801–805

Tanizaki H, Furuse J, Yoshino M, Ogino T, Ishikura S, Satake M, Hasebe T (2001) Combination radiotherapy for hepatocellular carcinoma with intraductal tumor thrombus: a case report. Eur J Radiol 38:213–218

Teefey SA, Hollister MS, Lee SP, Jacobson AF, Higano CS, Bianco JA, Colacurcio CJ (1994) Gallbladder sludge formation after bone marrow transplantation: sonographic observations. Abdom Imaging 19: 57–60

Terada T, Nakanuma Y, Kawai K (1989) Small hepatocellular carcinoma presenting as intrabiliary pedunculated polyp and obstructive jaundice. J Clin Gastroenterol 11:578–583

Thomsen GH, Kruse A, Petersen A (1998) Hepatocellular carcinoma presenting as a tumor of the hilar and extrahepatic bile ducts. Eur J Gastroenterol Hepatol 10:803–804

Tibble J, Meenan JK, Wilkinson ML, McNair A (2003) Biliary diverticula in sclerosing cholangitis. Gastrointest Endosc 57:918

Todani T (1997) Congenital choledochal dilatation: classification, clinical features, and long-term results. J Hepato-Biliary-Pancreat Surg 4:276–282

Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K (1977) Congenital bile duct cysts: classification, operative procedures, and review of 37 cases including cancer arising from choledochal cyst. Am J Surg 134:263–269

Todani T, Watanabe Y, Fujii T, Toki A, Uemura S, Koike Y (1984) Congenital choledochal cyst with intrahepatic involvement. Arch Surg 119:1038–1043

Todani T, Watanabe Y, Toki A, Morotomi Y (2003) Classification of congenital biliary cystic disease: special reference to type Ic and IVA cysts with primary ductal stricture. J Hepato-Biliary-Pancreat Surg 10:340–344

Toursarkissian B, Kearney PA, Holley DT, Cheung R, Fried A, Strodel WE (1995) Biliary sludge in critically ill trauma patients. South Med J 88:420–424

Tseng JH, Hung CF, Ng KK, Wan YL, Yeh TS, Chiu CT (2001) Icteric-type hepatoma: magnetic resonance imaging and magnetic resonance cholangiographic features. Abdom Imaging 26:171–177

Tsou YK, Liu NJ, Wu RC, Lee CS, Tang JH, Hung CF, Jan YY (2008) Endoscopic retrograde cholangiography in the diagnosis and treatment of mucobilia. Scand J Gastroenterol 43:1137–1144

Tsuchiya R, Eto T, Harada N, Yamamoto K, Matsumoto T, Tsunoda T, Yamaguchi T et al (1984) Compression of the common hepatic duct by the right hepatic artery in intrahepatic gallstones. World J Surg 8:321–326

Tsushimi T, Enoki T, Harada E, Orita M, Noshima S, Masuda M, Hamano K (2005) Ectopic hepatocellular carcinoma arising in the bile duct. J Hepato-Biliary-Pancreat Surg 12:266–268

Tsuzuki T, Ogata Y, Iida S, Kasajima M, Takahashi S (1979) Hepatoma with obstructive jaundice due to the migration of a tumor mass in the biliary tract: report of a successful resection. Surgery 85:593–598

Tu JF, Zhu GB, Jiang FZ, Zhang QY (2003) Diagnosis and treatment of mucobilia: report of 8 cases. Hepatobiliary Pancreat Dis Int 2:106–109

Ueda M, Takeuchi T, Takayasu T, Takahashi K, Okamoto S, Tanaka A, Morimoto T et al (1994) Classification and surgical treatment of hepatocellular carcinoma (HCC) with bile duct thrombi. Hepatogastroenterology 41:349–354

Ueda K, Ohori M, Taka J, Kusano M (2002) Metastatic biliary polypoid thrombus from renal cell carcinoma: report of a case. Surg Today 32:458–461

Uehara K, Hasegawa H, Ogiso S, Sakamoto E, Igami T, Ohira S, Mori T (2004) Intrabiliary polypoid growth of liver metastasis from colonic adenocarcinoma with minimal invasion of the liver parenchyma. J Gastroenterol 39:72–75

Vagianos C, Karavias D, Dragotis C, Kalofonos H, Androulakis J (1993) Obstructive jaundice due to intracholedochal blood clot: an unusual early presentation of primary hepatic carcinoma. Br J Clin Pract 47:22–223

Van der Linde K, van der Linden GH, Beukers R, Cleophas TA (1997) Food impaction in a duodenal diverticulum as an unusual cause of biliary obstruction: case reports and review of the literature. Eur J Gastroenterol Hepatol 9:635–639

Van Kemmel M, L'Hermine C (1973) Invagination of the common bile duct, Wirsung's duct, Vater's ampulla and the duodenum caused by an ampullar tumor (in French). Sem Hop 49:1305–1308

Van Os EC, Petersen BT (1996) Pancreatitis secondary to percutaneous liver biopsy-associated hemobilia. Am J Gastroenterol 91:577–580

Van Sonnenberg E, Ferrucci JT (1979) Bile duct obstruction in hepatocellular carcinoma (hepatoma) – clinical and cholangiographic characteristics. Report of 6 cases and review of the literature. Radiology 130:7–13

Vedantham S, Taylor FC, Yousefzadeh DK, Udekwu P, Thistlethwaite JR, Whitington PF (1992) Abdominal pain in a young girl due to congenital stenosis of the common bile duct with mucus plug formation. J Pediatr Gastroenterol Nutr 15:440–443

Von Woellwarth J, Behrend M, Raab R (2000) Development of obstructive jaundice after hemorrhage into a benign, non-parasitic liver cyst (in German). Chirurg 71:963–965

Walker TM, Serjeant GR (1996) Biliary sludge in sickle cell disease. J Pediatr 129:443–445

Walker TM, Hambleton IR, Serjeant GR (2000) Gallstones in sickle cell disease: observations from The Jamaican Cohort study. J Pediatr 136:80–85

Wang JH, Wang LY, Lin ZY, Chen SC, Kang SC, Chuang WL, Lu SN, Hseih MY et al (1995) Doppler sonography of common hepatic duct tumor invasion in hepatocellular carcinoma: report of two cases. J Ultrasound Med 14:471–474

Wang HJ, Kim JH, Kim JH, Kim WH, Kim MW (1999) Hepatocellular carcinoma with tumor thrombi in the bile duct. Hepatogastroenterology 46:2495–2499

Wang YD, Xue HZ, Jiang QF, Shen Q, Wang LC, Zhang X, Lu B, Yu M, Li K (2010) Surgical operation and re-operation for hepatocellular carcinoma with bile duct thrombosis. Chin Med J (Engl) 123:2163–2170

Warren BL (1987) Association between cholangiographic angulation of the common bile duct and choledocholithiasis. S Afr J Surg 25:13–15

Warshaw AL, Rattner DW (1980) Fates and fallacies of common bile duct obstruction by pancreatic pseudocysts. Ann Surg 192:33–37

Warshaw AL, Schapiro RH, Ferrucci JT, Galdabini JJ (1976) Persistent obstructive jaundice, cholangitis and biliary cirrhosis due to common bile duct stenosis in chronic pancreatitis. Gastroenterology 70:562–567

Wendel AV (1898) Case of floating gall-bladder and kidney complicated by cholelithiasis with perforation of gall-bladder. Ann Surg 27:199–202

Wilhelmi M, Jüngst C, Mock M, Meyer G, Zündt B, Del Pozo R, Jüngst D (2004) Effect of gallbladder mucin on the crystallization of cholesterol in bile. Eur J Gastroenterol Hepatol 16:1301–1307

Wind G, Futterman S (1977) Obstructive jaundice secondary to hepatoma. Case report and literature review. Am J Gastroenterol 67:80–83

Wislooff F, Jakobsen J, Osnes M (1982) Stenosis of the common bile duct in chronic pancreatitis. Br J Surg 69:52–54

Wolfson NS, Miller FB (1978) Anatomic relationships of insertion of the common bile duct into primary duodenal diverticula. Surg Gynecol Obstet 146: 628–630

Xiangji L, Weifeng T, Bin Y, Chen L, Xiaoqing J, Balhe Z, Feng S, Mengchao W (2009) Surgery of hepatocellular carcinoma complicated with cancer thrombi in bile duct: efficacy for criteria for different therapy modalities. Langenbecks Arch Surg 394:1033–1039

Yadegar J, Williams RA, Passaro E, Wilson SE (1980) Common duct stricture from chronic pancreatitis. Arch Surg 115:582–586

Yamaguchi M (1980) Congenital choledochal cyst. Analysis of 1433 patients in the Japanese literature. Am J Surg 140:653–657

Yeh CL, Lai KH, Lo GH, Lin CK, Hsu PI, Chan HH, Tsai WL, Lin CP (2003) Endoscopic treatment in a patient with obstructive jaundice caused by pancreatic pseudocyst. J Chin Med Assoc 66:555–559

Yeh CN, Jan YY, Yeh TS, Hwang TL, Chen MF (2004) Hepatic resection of the intraductal papillary type of peripheral cholangiocarcinoma. Ann Surg Oncol 11:606–611

Yeh TS, Tseng JH, Chen TC, Liu NJ, Chiu CT, Jan YY et al (2005) Characterization of intrahepatic cholangiocarcinoma of the intraductal growth-type and its precursor lesions. Hepatology 42:657–664

Yoneyama F, Miyata K, Ohta H, Takeuchi E, Yamada T, Kobayashi Y (2004) Excision of a juxtapapillary duodenal diverticulum causing biliary obstruction: report of three cases. J Hepato-Biliary-Pancreat Surg 11:69–72

Zografos GC, Androulakis G (1998) Choledochojejunostomy with invagination of the bile duct into the jejunum. J Surg Oncol 68:120–121

145 Bile Duct Compression and Stenosis Due to Anomalies and Acquired Disorders of the Splanchnic Arterial Tree and the Portal Venous System

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_145

Abstract

Large bile ducts can be compressed and stenosed by various anomalies and acquired disorders of the splanchnic arterial tree and the portal venous system. Overall, compression of the extrahepatic biliary tract by arteries is a very uncommon condition. Compression may occur by the right hepatic artery resulting in the so-called hepatic duct compression syndrome. Aneurysms of the hepatic artery can cause intrabiliary stenosis and clot formation. Most of aneurysms inducing bile duct stenosis are extrahepatic alterations. Also dissecting aneurysms of the hepatic artery tree may rarely cause obstructive jaundice. Biliary obstruction can also be caused by pseudoaneurysms, cavitated arteriocentric hematomas without endothelial lining. Hepatic artery thrombosis, severe atherosclerosis, chemotherapy-associated vascular damage, and necrotizing arteritis, including periarteritis nodosa, are sometimes followed by bile duct necrosis and duct stenosis. A further cause of vascular obstruction of the biliary tree is portal biliopathy with cavernous transformation of the portal vein.

Bile Duct Compression Caused by Distinct Anatomical Features of Arteries

In the upper abdomen, compressions of hollow organs by arterial blood vessels mainly include the well-known stricture of the duodenum by the superior mesenteric artery, causing the so-called gas minus ileus. In contrast, compression of the extrahepatic biliary tract by arteries is an exceptional event. The bile duct can be compressed by the right hepatic artery at the hilus of the liver, resulting in what is called the hepatic duct compression syndrome or the right hepatic artery syndrome.

The hepatic artery has a rather complex anatomy, with several known and clinically sometimes relevant anomalies. The right hepatic artery has a variable point of origin, but in about 75 % of cases arises from the common hepatic artery and crosses the common hepatic duct posteriorly. Michels, in an autopsy series of 200 cases, defined the basic anatomic variations in hepatic artery, found variant pattern in 45 %, and specified ten major types (Michels 1966; Table 1). Michels also described the relations of the biliary ducts to the hepatic and cystic arteries

Table 1 Classifications of the hepatic artery tree anatomy

Michels classification (1966)		
Type 1	Normal	55 %
Type 2	Replaced LHA from LGA	
Type 3	Replaced RHA from SMA	
Type 4	Replaced RHA + LHA	
Type 5	Accessory LHA	
Type 6	Accessory RHA	
Type 7	Accessory RHA + LHA	
Type 8	Replaced RHA + accessory LHA or replaced LHA + accessory RHA	
Type 9	CHA from SMA	
Type 10	CHA from LGA	
Hiatt classification (1994)		
Type 1	Normal	75.7 %
Type 2	Replaced or accessory LHA	
Type 3	Replaced or accessory RHA	
Type 4	Replaced or accessory RHA + replaced or accessory LHA	
Type 5	CHA from SMA	
Type 6	CHA from aorta	

LHA left hepatic artery, *RHA* right hepatic artery, *CHA* common hepatic artery, *LGA* left gastric artery, *SMA* superior mesenteric artery

(Michels 1951). In a detailed anatomical study of 1,000 cases, 757 cases were of the normal type 1, with the common hepatic artery arising from the celiac axis to form the gastroduodenal and proper hepatic arteries and the proper hepatic dividing distally into right and left branches. One hundred six cases were of type 3, with a replaced or accessory right hepatic artery originating from the superior mesenteric artery. Ninety seven cases were of type 2, with a replaced or accessory left hepatic artery arising from the left gastric artery. Only 23 cases were of type 4, with both right and left hepatic arteries arising from the superior mesenteric and left gastric arteries, respectively. Fifteen cases showed type 5, with the entire common hepatic artery arising as a branch of the superior mesenteric artery, and two cases were of type 6, with the common hepatic artery originating directly from the aorta (Hiatt et al. 1994; Table 1).

The relationships between the hilar and intrahepatic parts of the hepatic artery and the portal vein also reveal variations. Based on a CT-arterial portography (CTAP) and CT-angiography (CTA) study in 147 patients, the combined anatomy of right anterior hepatic artery and portal vein with regard to segmentation was classified as dorsoventral (26.5 %), dorsoventral and inferior (10.9 %), multiple (18.4 %), and superior and inferior segments (1.4 %) (Ibukuro et al. 2012).

These anatomic arrangements may predispose to impingement, but this effect is extremely rare (Taboga et al. 1969; Doi et al. 1979; Kumada et al. 1981; Watanabe et al. 1982; Tsuchiya et al. 1984; Kim et al. 1992; Kondo et al. 1999; Izuishi et al. 2005; Miyashita et al. 2005; Gottlieb and Brophy 2007). Duplication of the hepatic artery may occur (Tokunaga et al. 2007). When biliary obstruction with jaundice is present, the compression of the duct is more frequently associated with a hepatic artery aneurysm or an aberrant anatomy. In the lateral type of right hepatic artery compression, the bile duct is compressed by the artery lateral to it, while in the transverse type, the bile duct is compressed by the artery crossing it. In the latter situation, intrahepatic stones may be caught at the involved level (Watanabe et al. 1982; Tsuchiya et al. 1984; Kim et al. 1992). A right hepatic artery anteriorly overriding the common hepatic duct has also been shown to cause duct compression and obstructive jaundice (Chung et al. 1994). As an anatomical variation, crossing between the hepatic artery and the common bile duct (arterio-biliary crossing) can occur, causing different grades of biliary obstruction (Manenti et al. 1981). Jaundice due to obstruction of the common duct has been observed to be caused by an aberrant celiac artery (Luttwak and Schwartz 1961). A compression of the common bile duct by the posterosuperior pancreaticoduodenal artery has also been reported (Watanabe et al. 2005). It may be expected that, owing to the variable anatomy of the celiac and hepatic artery system, other situations of bile duct impingement may occur. The types and frequencies of hepatic artery variations differ among larger studies addressing this question, also depending on the methods used. Among 600 patients analyzed by digital subtraction angiography, only 61.3 % had the standard hepatic arterial anatomy. 19.8 % had variant left hepatic arteries, 14.8 % had variant right hepatic arteries, and 4.7 % had a variant involving both left and right hepatic arteries. About 4 % had a variant origin of the common hepatic artery arising from either the superior mesenteric artery or the aorta, and double hepatic arteries were seen in 3.7 % of the patients (Covey et al. 2002).

In a selective celiac and superior mesenteric artery angiography study on 604 patients, normal textbook hepatic artery anatomy was found in 79.1 %, i.e., more frequently than in the former study (Koops et al. 2004). In an analysis of 60 cadaveric livers (minimum age of autopsied patients = 18 years; no liver pathology), 15 % of the livers had a median hepatic artery. A right hepatic artery originating from the superior mesenteric artery was found in 25 %, and a left hepatic artery coming from the left gastric artery in 3.3 %. The right and left hepatic arteries were accessory in 18.3 % and 3.3 % of the cases, respectively (Chaib et al. 2007). The celiomesenteric trunk is a rare but well-recognized anomaly (Petscavage and Maldjian 2007; Tosun et al. 2007). A very uncommon variation of the hepatic artery system is the formation of an arterial ring encircling the

common hepatic duct (Dusanovic et al. 1999). It is known that several non-hepatic arteries can originate from the hepatic arteries. In a systematic study, the most common non-hepatic artery was the right gastric artery, followed by the hepatic falciform artery, an accessory left gastric artery, the posterior superior pancreaticoduodenal artery, and the left phrenic artery. The left hepatic artery was the most frequent origin of non-hepatic arteries (Song et al. 2006). These compression syndromes must be distinguished from pseudo-obstruction of extrahepatic bile ducts from arterial pulsatile compression, resulting in an artifact. The right hepatic artery was found to be the causative vessel in 67 % among 234 patients analyzed (Watanabe et al. 2000).

Arterial Aneurysms

Aneurysms are a rare cause of hemobilia and intrabiliary clot formation sometimes followed by jaundice. The arteries most often involved are branches of the hepatic or gastroduodenal arteries (Fig. 1). Hepatic artery aneurysm comprises a reported incidence of 0.02 % and accounts for about 20 % of all visceral aneurysms. In the literature, the risk of rupture ranges from 14 % to 80 % of all hepatic artery aneurysms (Hashim et al. 2009). Most hepatic artery aneurysms (75–85 %) are extrahepatic, and the parent vessel is most commonly (65 %) the common hepatic artery (Countryman et al. 1983). Location to the right hepatic artery is less frequent, occurring in about 30 % of cases, and location to the left hepatic artery is rare (Boontje 1979; Graham et al. 1980; Shanley et al. 1996). A small part of hepatic artery aneurysms is located intrahepatically (Burns and Slakey 2009). Mycotic aneurysms historically accounted for most hepatic artery aneurysms, but accounted for only 4 % in a more recent review (Shanley et al. 1996). Inflammatory aneurysm of the hepatic artery is a complication of periarteritis nodosa (Park et al. 2006; Parent et al. 2010). Rare causes of hepatic artery aneurysms are inherited connective tissue disorders (see below) and prune belly syndrome, an uncommon disorder thought to be caused by mesodermal delay during ontogenesis (Alhawsawi et al. 2009).

A triad of abdominal pain, hemobilia, and jaundice is seen in less than one-third of the patients. Aneurysm of the hepatic artery may rupture into the biliary tract and cause hemobilia via an arterio-biliary fistula (Gracey 1970; Winchester et al. 1970; Balthazar 1977; Harlaftis and Akin 1977; Petrin et al. 1982; Chen et al. 1983; Casula et al. 1984; Zachary et al. 1986). True aneurysms of the hepatic artery may cause obstructive jaundice (Lal et al. 1989; Chandramohan et al. 2001; Bramis et al. 2002; Mazziotti et al. 2003). In most of these situations, the aneurysms are located in the extrahepatic branches of the hepatic artery, intrahepatic aneurysms as a cause of segmental bile duct stenoses being very uncommon (Salazar et al. 1984). Giant aneurysm of the hepatic artery can cause portal hypertension (Kantarci et al. 2009). Rarely, thrombosis of a hepatic artery aneurysm produces a mass that may be confounded with malignancy (Chhem and Groleau

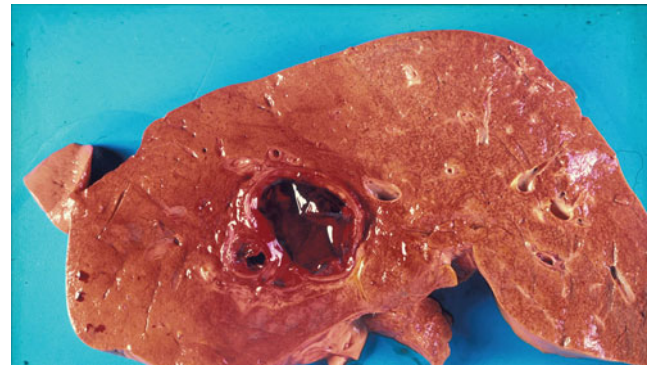

Fig. 1 Aneurysm of the hepatic artery, producing a mass effect

1989; Elmas et al. 1998). A similar situation has rarely been reported in aneurysms of the gastroduodenal artery (Sipahioglu et al. 2005; Aoufi et al. 2007), the splenic artery (Coulier et al. 2006), and the celiac artery (White et al. 1987). True aneurysm of the cystic artery is rare, but is a known cause of hemobilia (Kirchgatterer et al. 1998).

Aneurysms of the celiac artery, first described in 1745, are rare vascular lesions that represent only 3.6–4 % of splanchnic artery aneurysms, with estimated incidence of 0.005–0.01 %. Earlier, this aneurysm was associated with frequent morbidity and mortality; before 1950, more than 90 % of the patients presented with epigastric pain, and up to 87 % died of aneurysmal rupture, the diagnosis most frequently having been made at autopsy. More recently (1985–1995), 69 % of the patients presented with abdominal pain, and just 7 % presented with rupture, 14 % being asymptomatic, and with an overall mortality rate of 14 %. During the first half of the last century, the mean age at diagnosis was 39.7 years, men outnumbered women 9:1, and syphilis was the apparent cause in 31 % of cases. Since that time, the mean age at diagnosis has increased to 53.7 years and women constitute 44 % of those affected, perhaps reflecting a paucity in luetic infections (reviews: Graham et al. 1985; Stone et al. 2002; McMullan et al. 2006). In the patient described by White and coworkers (1987), a massive celiac artery aneurysm caused both biliary and portal obstruction, associated with portal hypertension and extensive retroperitoneal varices. Abdominal aortic aneurysms with or without rupture rarely compress the common bile and cause biliary obstruction (Dorrucci et al. 2001; Smith et al. 2002).

Dissecting Aneurysm of the Hepatic Artery Tree

Primary dissecting hepatic artery aneurysms, unaccompanied by aortic or other dissections, have been reported only few times (Callicot and Hoke 1968; Gurrero 1970; Hill et al. 1974; James 1976; Pinkerton et al. 1976; Larson et al. 1987; Derhy et al. 1988; Roh and LeSher 1989; Muller and Kim 1995; Garcia et al. 1996; Hashimoto et al. 1998; Nakamura et al. 1998; Al Hilli 2001). Dissecting aneurysm of the celiac axis and hepatic artery has been found to be associated with obstructive jaundice (Bret et al. 1987).

Pseudoaneurysms

Pseudoaneurysms are cavitated arteriocentric hematomas that lack an endothelial lining. Extrahepatic artery pseudoaneurysms are caused by several mechanisms, including artery dissection and traumatic vessel damage, but such lesions caused by visceral artery dissection with or without aortic dissection are very rare. Pseudoaneurysm causing fistula, hemobilia, or rupture into the gallbladder is known to occur in the hepatic artery (Natalini et al. 1978; Ahmed et al. 2001; Akatsu et al. 2004). One well-known cause of hepatic artery pseudoaneurysms is liver transplantation, where this complication usually occurs within the first 2 months of grafting, and is characterized with a high mortality rate (Tobben et al. 1988; Adani et al. 2008). Hepatic artery pseudoaneurysm can occur following laparoscopic cholecystectomy (Rivitz et al. 1996). Pseudoaneurysm of the hepatic artery with delayed fatal hemorrhage has been observed few days after percutaneous liver biopsy (Ahmed et al. 2001). Pseudoaneurysm of the cystic artery develops with or without associated cholecystitis and is known to be a rare cause of arterio-biliary fistula and hemobilia (Reddy 1983; Barba et al. 1994; England et al. 1998; Kaman et al. 1998; Maeda et al. 2002; Akatsu et al. 2007; Beuran et al. 2008; Moses et al. 2008). Pseudoaneurysm of the gastroduodenal artery as a cause of obstructive jaundice has been reported (Kossak et al. 2001). Pseudoaneurysm complicating a choledochal cyst was found to cause hematobilia. In this situation, pseudoaneurysm is caused by chronic inflammatory changes in the wall of the choledochal cyst, and the contiguity of the cyst to the hepatic artery could result in chronic pressure erosion, resulting in the pathologic

communication between the artery and the cyst (Eliscu and Weiss 1988). Pseudoaneurysms of visceral arteries can also cause biliary obstruction and may present as an intrahepatic mass, leading to considerable differential diagnostic difficulties (Widjaja et al. 1999).

Biliary Obstruction Associated with Arteritis

Clinical manifestations in the liver are not common in patients with polyarteritis nodosa (PN), although necrotizing arteritis in the liver as an autopsy finding is not infrequent. Hepatic artery aneurysms and hepatic infarction are the most common hepatic complications (Park et al. 2006; Parent et al. 2010). PN involves the hepatobiliary system either in conjunction with systemic vasculitis or as an isolated (organ-specific) involvement of the hepatic and biliary artery tree. The latter situation is best known for apparently isolated PN of the gallbladder. PN involving the bile duct arterial system can cause ductal wall necrosis (infarction) or segmental duct atrophy, followed by rupture and hemobilia (Cho et al. 2011). The lesions are histologically characterized by necrotizing arteritis of the bile duct arteries. The ischemic necroses of bile ducts induce a scarring reaction which may end up with a presentation that is similar to sclerosing cholangitis with duct stenosis (Wold and Baggenstoss 1949; Dillard and Black 1970; Alleman et al. 1986; Barquist et al. 1991; Parangi et al. 1991; Goritsas et al. 1997; Park et al. 2007). Ischemic and inflammatory damage to the duct wall may also be followed by cystic dilatation of the duct, likely through weakness of the duct structures (Doppman et al. 1979; Amir et al. 1984; Chang et al. 2003). Hepatic lobar atrophy has been observed in combined involvement of hepatic artery branches and of the hepatic portal tissue in PN (Nakazawa et al. 1992).

Systemic vasculitis (particularly PN and vasculitis occurring in lupus erythematodes) is associated with an increased risk of aneurysms developing in the visceral arteries, including the hepatic artery and often complicated by rupture and/or hemobilia (Glassman and Skerrett 1960; McCollum et al. 1979; Bookman et al. 1983; Trambert et al. 1989; Choy et al. 1997; Stambo et al. 2004; Yamazaki 2004; Park et al. 2006). PN can cause pseudoaneurysms that may, due to their sometimes considerable size, exert compression of the extrahepatic biliary system and induce obstructive jaundice (Dönmez et al. 2005).

Apart from the more frequent manifestations seen in PN and related disorders, other forms of vasculitis may involve the hepatobiliary arterial system. They include temporal arteritis (polymyalgia rheumatica; polymyalgia arteriitica; Heptinstall et al. 1954; von Knorring and Wasastjerna 1976; Lie 1978; Ogilvie et al. 1981; Rousselet et al. 1989), producing giant cell arteritis in hepatic artery branches and sometimes leading to ischemic cholangiopathy (Rousselet et al. 1989), and Churg-Strauss syndrome (Nishie et al. 2003). Necropsies of patients dying in the acute phase of arteritic polymyalgia are rare, particularly since the establishment of effective therapy. Therefore, the knowledge relating to biliary pathology is rudimentary. A rare arteritis that can cause hepatic artery aneurysms is allergic granulomatous arteritis (Churg-Strauss disease; Nakamura et al. 1991). Vasculitis of the peribiliary vessels causing ischemic necrosis was noted in Schönlein-Henoch purpura (Viola et al. 1999). A vasculitis involving peripheral arteries in portal tracts and associated with acute cholangitis has been observed in Kawasaki disease (Gear et al. 1992).

Biliary Tract Damage in Atherosclerosis and Calcifications of the Hepatic Arteries

Although involved in general atherosclerosis, atherosclerosis of the hepatic artery or the celiac trunk arteries is regarded as rare and difficult to assess clinically. Evident differences in the occurrence of atherosclerosis between hepatic and coronary arteries have systematically been analyzed by histologic investigations on autopsy material. It was found that, in contrast to coronary arteries, hepatic artery intimal thickening was incidental

during the first four decades of life and regular only later on. During all age periods studied, intimal thickness in hepatic arteries was less pronounced than that in coronary arteries. True atherosclerosis was detected during the eighth and ninth decades in the hepatic artery, i.e., about 4 decades later than in coronary arteries (Krus et al. 2000). In a UK-based medical review of the literature, there was no report of hepatic artery atherosclerosis preventing the use of a procured liver for transplantation, but the authors reported one such case for the first time (Maluf et al. 2004). A further case of reported hepatic artery atherosclerosis was observed in conjunction with celiac artery aneurysm (Papadimitriou et al. 2005). In the literature, most reports refer to hepatic artery calcifications which may cause differential diagnostic difficulties in regard to pneumobilia or intrahepatic stones (Desai et al. 1989; White and Wilson 1994; Christensen et al. 1995; Pai and Bude 2002). Atherosclerotic narrowing of the hepatic arteries of intrahepatic arteries was found to be associated with biliary stricture (Sajura et al. 2001), probably caused by postischemic fibrosis/scarring of the duct wall. In another patient, benign biliary stricture was found to be accompanied by fibrous replacement of the media of the accompanying artery (Hashikura et al. 1994). Calcifications of the hepatic artery, with variable stenosis, are well recognized as a complication of chronic renal failure, mainly in the context of chronic hemodialysis (Okuda et al. 2002, 2003), although in dialysis patients, the hepatic artery is less frequently involved than the abdominal aorta and the splenic artery (Okuda et al. 2002).

Hepatic artery calcification is also known in the rare autosomal-recessive disorder, idiopathic infantile arterial calcinosis (IIAC; OMIM; Wax et al. 2001). IIAC is characterized by calcifications in the arterial media and fibroproliferative changes in the intima of larger arteries, sometimes resulting in reduced vascular elasticity and blood flow. In a female neonate, hepatic arterial involvement resulted in reduced blood flow in the narrowed hepatic artery and in fatal progressive liver failure (Whitehall et al. 2003).

Bile Duct Damage in Hepatic Artery Thrombosis

Hepatic artery thrombosis can occur in grafted livers, reported to occur more frequently in children than in adults (Tzakis et al. 1985; Wozney et al. 1986; Bhattacharjya et al. 2001; Silva et al. 2006; Vaidya et al. 2007). In a series of 18 OLT patients with graft loss owing to bile duct necrosis, radiographic vascular studies suggested hepatic arterial thrombosis or stenosis in 11 cases (Krishna et al. 2005). In a study on 4,234 OLTs performed between 1984 and 2007, hepatic artery thrombosis was noted in 203 patients (5 %), associated with reduced graft survival (only 10 % graft salvage; Duffy et al. 2009). A similar figure was found in a systematic review of OLT (overall 4.4 %), the complication being more common children (8.3 %) vs. adults (2.9 %) (Bekker et al. 2009). Hepatic artery thrombosis is sometimes followed by biliary strictures requiring stenting as a late complication (Cook and Crofton 1997). Intrahepatic biliary necrosis has been observed in late post-OLT hepatic artery thrombosis, i.e., occurring after 6 months (Valente et al. 1996; Gunsar et al. 2003).

Biliary Tract Disorders in Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is well known to involve the hepatobiliary system, with an estimated prevalence ranging from 8 % to 31 % in retrospective studies. HHT causes pathologic changes of the hepatic artery, including arterial tortuosity, arteriovenous malformation, and hepatic artery aneurysm (Graham et al. 1964; Peery 1987; Milot et al. 2007; Miyabe et al. 2007). Anatomically, three different patterns of abnormal vascular communications can occur in the liver: portal vein to hepatic vein (portovenous), hepatic artery to hepatic vein (arteriovenous), and hepatic artery to portal vein (arterioportal). Only 5–8 % of patients with these vascular malformations are symptomatic (Khalid and Garcia-Tsao 2008). Anicteric cholestasis has been

noted in 73 % of a series of patients with HHT (Bernard et al. 1993). In fact, biliary tract manifestations are now well recognized in HHT, and according to shunt type and size, Garcia-Tsao has classified patients into three groups presenting with cardiac failure, biliary disease, or portal hypertension. Type 1 shunts can cause a cardiac and/or biliary-type clinical pattern. Cholestasis is the most frequent marker, indicating bile duct damage (specifically ischemia), even when the clinical evolution is dominated by cardiovascular signs (Garcia-Tsao et al. 2000; Lerut et al. 2006). Arteriovenous malformations, specifically tortuosities of the main hepatic and intrahepatic arteries located close to the bile ducts, may result in external bile duct compression with subsequent bile duct dilatation (Hatzidakis et al. 2002; Hayashi et al. 2008). In a series of 19 patients with HHT, five symptomatic patients had elevated alkaline phosphatase levels and radiographic evidence of bile duct anomalies similar to those of Carolis' disease or those in primary sclerosing cholangitis (Garcia-Tsao et al. 2000). Stenosis and/or dilatations are thought to be causes by ischemic necrosis and atrophy of the bile duct wall, biliary tract necrosis having been observed in HHT (McInroy et al. 1998). In a report on HHT based on the results of the European liver transplant registry, biliary necrosis causing hepatic failure was observed in 12/40 patients (Lerut et al. 2006). In this report, a biliary type of HHT was recognized, and the liver explants with this type of disease showed cholangitis associated with a diffuse and extreme modification of bile duct morphology, cystic bile duct dilatation, intrahepatic biliary sludge and/or stones, bile-stained necrotic areas, and biliary mucosal necrosis (Lerut et al. 2006). HHT may be associated with multiple intrahepatic bile duct stenosis, focal cystic bile duct dilatations along the course of the intrahepatic ducts, and large biliary cysts (Lin and Stall 2007). It has been proposed that arteriovenous shunts may cause hypoperfusion of the peribiliary plexus supplying the biliary tree, promoting bile duct ischemia with subsequent fibrosis and atrophy of the bile ducts, or even bile duct wall necrosis followed by biliary cysts (Garcia-Tsao et al. 2000; Asma et al. 2005). Postischemic bile duct cysts can become infected, with formation of numerous intrahepatic bile duct-derived cystic spaces measuring up to 4 cm (Hillert et al. 2001). It has been suggested that hepatolithiasis occurring in conjunction with HHT may be promoted by biliary stasis (Ball and Duggam 1990). The treatment of HHT-associated arteriovenous malformations by embolization may itself cause biliary complications, e.g., ischemic cholangitis (Chavan et al. 1998) and biliary necrosis (Odorico et al. 1998).

Biliary Obstruction Caused by Chemotherapy-Induced Cholangiopathy

Jaundice can develop in patients with liver cancer (mainly metastases of colorectal carcinoma) during hepatic arterial infusion chemotherapy (HAIC; hepatic artery infusion, HAI), particularly when fluoropyrimidines were used. Apart from hepatotoxic effects (chemical hepatitis), focal biliary obstruction mediated by chemotherapy-induced bile duct strictures (so-called iatrogenic sclerosing cholangitis; toxic biliary sclerosis; chemotherapy-induced sclerosing cholangitis, CISC) plays a significant role. In early phases of duct damage, bile duct infarction can develop, sometimes mimicking multiple liver metastases (Shrikhande et al. 2002; with literature review). Most strictures occur in the proximal parts of the extrahepatic bile duct system and at its bifurcation, and intrahepatic ducts show a variable degree of involvement (Daly et al. 1984; Botet et al. 1985; Hohn et al. 1985; Pien et al. 1985; Anderson et al. 1986; Laughlin 1986; Clark and Gallant 1987). In the study of Anderson and coworkers, the strictures were long, on the average 2–3 cm long, with smooth tapering both proximally and distally, they involved the proximal common bile duct 1–2 cm from its origin from the porta, and there was no evidence of beading as seen in primary sclerosing cholangitis (Anderson et al. 1986).

How frequent is chemotherapy-associated stenosing cholangiopathy? The estimated incidence ranges from 8 % to 26 %. Among 54 patients with liver metastases of colorectal

carcinoma treated with floxuridine HAI, 5 patients (9.2 %) developed biliary toxicity with jaundice and cholangitis/cholangiopathy, and extrahepatic biliary sclerosis was detected in 3 patients (Aldrighetti et al. 2001). The analysis of a randomized trial of the Northern California Oncology Group (NCGOG), comparing intravenous vs. intra-arterial FUDR in patients with hepatic colorectal carcinoma metastases, showed that among the first 25 patients in the intra-arterial higher-dose therapy arm (0.3 mg FUDR/kg/day), ten patients developed radiologically evident biliary strictures, and three developed permanent jaundice (Hohn et al. 1989). In a study of 11 patients with CISC, the mean age at presentation was 59.5 years, and cholangiographic findings revealed a stricture confined to the common hepatic duct in two patients, involving the hepatic hilum in seven patients, involving the right and/or left main hepatic ducts in nine patients, and extending to the intrahepatic radicles in two patients. The grade and extent of biliary strictures did not change in five, improved in one, recurred in two, and progressed in two patients over the follow-up period of 28.2 months (Alazmi et al. 2006). In a study of 17 patients with intra-arterial FUDR-induced cholestasis, all patients studied had segmental involvement at the common hepatic duct bifurcation. The cystic duct and the gallbladder were often involved, but the distal common bile duct was spared. Histologic features of periductal fibrosis were present in specimens obtained from liver biopsies in three patients and autopsy in two patients (Shea et al. 1986).

Pathogenetically, it has been proposed that that bile duct lesions are caused by toxic vascular damage followed by ischemic cholangiopathy (Ludwig et al. 1989; Hasegawa et al. 2000), demonstrating the importance of blood flow from the peribiliary vascular bed for the survival of the biliary mucosa (Clark and Gallant 1987). 5-fluorouracil is toxic to arterial endothelial cells and seems to exert a thrombogenic effect (Cwikiel et al. 1996; Kinhult et al. 2003). In a rat model, both 5-fluorouracil and peplomycin induced endothelial cell apoptosis upon intra-aortic injection, but the incidence of apoptosis was higher with 5-fluorouracil (Sudoh et al. 2004).

Portal Biliopathy and Bile Duct Varices

Introduction

Portal biliopathy is a term describing a spectrum of lesions and functional disturbances occurring in the bile ducts secondary to extrahepatic portal venous obstruction (EHPVO), specifically thrombosis of its extrahepatic portion as a major pathology of this vessel (Janssen et al. 2001; Garcia-Pagan et al. 2008). The conception of portal biliopathy was put forward in 1992 (Sarin et al. 1992), and this disorder was later worked out in more detail (Chandra et al. 2001; Akaki et al. 2002; He and Fan 2002; Condat et al. 2003; Perego et al. 2003; Rangari et al. 2003; Dhiman et al. 2007; Shin et al. 2007). EHPVO is a common cause of portal hypertension and constitutes up to 40 % of all patients with portal hypertension.

Portal biliopathy (synonyms: portal hypertensive biliopathy; cholangiopathy associated with portal hypertension; portal cavernoma-associated cholangiopathy) refers to a clinicopathologic complex comprising all abnormalities of the entire biliary tract (including extra- and intrahepatic bile ducts, cystic duct, and gallbladder) in patients with compromised portal venous circulation. The definition should not exclusively refer to portal hypertension, because some anomalies of the portal vein, such as aneurysm, may induce biliopathy in the absence of portal hypertension. On the other hand, changes similar to portal biliopathy have been recognized in patients with portal hypertension not related to EHPVO, such as cirrhosis of the liver or idiopathic portal hypertension, albeit with lesser frequency (review: Dhiman et al. 2007). Depending on the anatomic manifestations of portal biliopathy, this disorder has been cholangiographically classified in several types and subtypes (Table 2; Chandra et al. 2001). The etiology and pathogenesis of portal biliopathy are incompletely known, but, as outlined in the following paragraphs, mechanical and/or ischemic effects on bile ducts (compression, bulging, protrusion) caused by pathologically structured veins seem to prevail.

Table 2 Classification of cholangiography changes in portal biliopathy (Chandra et al. 2001)

Type I: Involvement of extrahepatic bile duct
Type II: Involvement of intrahepatic ducts only
Type IIIa: Involvement of extrahepatic bile duct and unilateral intrahepatic duct (left or right)
Type IIIb: Involvement of extrahepatic bile duct and bilateral intrahepatic ducts

Cavernous Transformation of the Portal Vein: Morphologic Aspects

Terms frequently employed in the literature referring to portal biliopathy are cavernous transformation of the portal vein and portal vein "cavernoma" (Gibson and Richards 1955). In fact, the terms describe at least two lesions that may occur alone or in combination. Cavernous transformation of the portal vein refers to a condition where, due to collateral blood accumulation/flow in obstruction of the extrahepatic portal vein, marked dilatation of the parabiliary venous plexus takes place (for the definition of parabiliary plexus, see the paragraph below on "Anatomical Substrates of Portal Biliopathy"). Hence, this change does not describe a cavernous change of the portal vein itself, but a complex remodeling of venous vessels associated with the portal vein in case of obstruction of the latter (Figs. 2, 3, and 4).

Morphologic studies have shown that cavernous transformation is not only dilatation of periportal venous collaterals but also neogenesis of vessels. An early study had shown that, on histological examination, cases of cavernous transformation show a combination of chronic recanalized portal vein thrombosis (Koga et al. 1986) and formation of paraportal hepatopetal collaterals (Bechtelsheimer and Conrad 1980). Sections of recanalized portal veins in fact show an endoluminal spongy network of new formed vascular channels, in some way reminiscent of cavernous hemangioma, thus explaining the term "cavernoma." This alteration is commonly associated with portal vein phlebosclerosis, itself caused by high venous pressure load (portal hypertension) and/or intimal

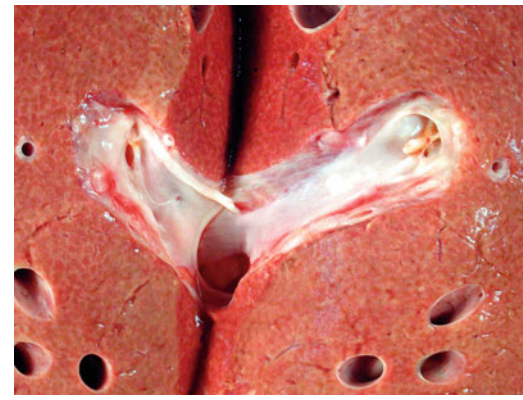

Fig. 2 Cavernous transformation of the portal vein. The portal venous branch is longitudinally opened and shows fibrous intraluminal strands and nets

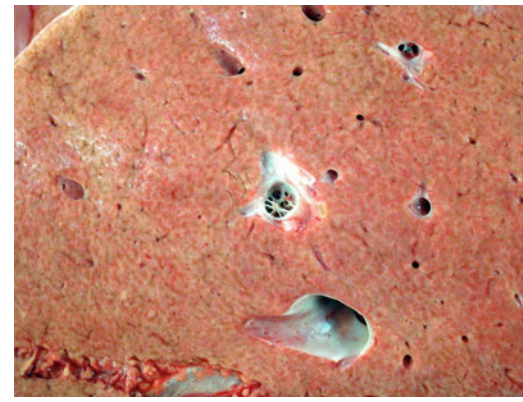

Fig. 3 Cavernous transformation of the portal vein. Net-like intraluminal fibrous strands in an intrahepatic portal vein branch

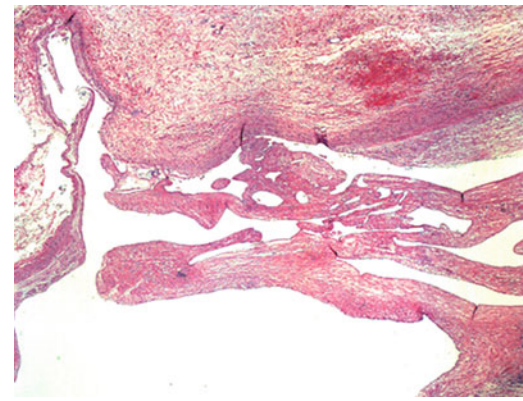

Fig. 4 Cavernous transformation of the portal vein. Organization of thrombus resulted in a fibrous intraluminal meshwork (Elastica-van Gieson stain)

integration of organized thrombotic material. The network of dilated and sometimes varicose venous vascular channels is mostly caused by expansion of veins of the parabiliary plexus. However, it has also been proposed that formation of collaterals starts with new growth of primitive sinusoidal vessels originating from the portal vein and protruding into the paraportal tissue, later to exhibit increasing venous differentiation up to the point of formation of varices (Bechtelsheimer and Conrad 1980). The grossly visible cavernous vein system commonly produces a sponge-like sheath around the portal vein and the large bile ducts, periductal collaterals being situated in the fibroadipose outer compartment of the hepatoduodenal ligament, but the dilated collateral may also involve the mural parts of the ducts (intramural cavernous transformation; intramural varices; Chow and Jeffrey 1999), sometimes producing a ductal mural cavernoma (Novellas et al. 2004). In the hepatic hilar region, variceal intramural collaterals may, also in conjunction with a fibrogenic/sclerosing reaction, result in an enhancing, vascular mass (Geyer et al. 2005). Even by use of Doppler sonography, the original portal vein may no longer be visualized within the mass of tortuous vessels. In addition, the phlebectatic changes seen in cavernous transformation can extend into the liver, this pattern consisting of numerous thin-walled vessels observed in the medium-sized portal tracts of the liver ("intrahepatic cavernous transformation"; Koga et al. 1986; Terada et al. 1988), a change also noted in situations of tumor-induced venous obstruction (Terada et al. 1990).

Biliopathy in Portal Vein Thrombosis or Cavernous Transformation of the Portal Vein (Cavernoma; Portal Cavernomatosis)

The first patient with symptomatic biliary obstruction due to EHPVO was reported in 1944 (Fraser and Broun 1944), Subsequently, several observations confirmed stenosis of the extrahepatic bile ducts by a thrombosed portal vein (Seez et al. 1980; Khuroo et al. 1993; D'Souza et al. 2009; Htun Oo et al. 2009). Among 17 patients with portal vein cavernoma, symptomatic biliary obstruction was detected in 82 % (Belhadjbrik et al. 2006). Compression of bile ducts with subsequent obstructive jaundice by cavernoma has been observed in children (Ruszinko et al. 2004) and has been shown to reversible upon portal decompression (Gauthier-Villars et al. 2005). The vascular anomalies and the subsequent changes of the bile ducts may mimic cholangiocarcinoma (Kessler et al. 2007).

The thrombosed vessel and/or associated venous (varicose) collaterals exert a compression effect usually on the common bile duct (Lohr et al. 1993), and in some instances, thrombosis of this vessel causing biliary obstruction may mimic a tumor (Nyman et al. 1996; Horie et al. 2005). The dilated, varicose collateral veins developing in EHPVO have been demonstrated to cause smooth indentations of the common bile duct, seen in cholangiography (Vleggaar et al. 1999), and duct stenoses, ductal narrowing, or duct wall irregularities have been found by use of MRI (Chevallier et al. 2006). The distinct changes of large bile ducts may suggest sclerosing cholangitis ("pseudosclerosing cholangitis"; Dilawari and Chawla 1992). Apart from mechanical compression, ischemic pathogenic pathways have been considered, because some biliary changes may persist after shunt surgery (Dhiman et al. 1999). Obstructive extrahepatic portal vein obstruction can be associated with portal vein calcification (calcified cavernous transformation) and can cause obstructive jaundice, the common bile duct being extrinsically compressed by the calcified cavernoma (Mackenzie et al. 1978).

Obstructive Cholestasis Caused by Aneurysms of the Portal Vein

Aneurysm of the extrahepatic portal vein is rare but is the most frequent visceral venous aneurysm, followed by aneurysms of inferior vena cava, superior mesenteric vein, splenic vein, and iliac veins (Barzilai and Kleckner 1956; Calligaro et al. 1995; De Gaetano et al. 2006). Extrahepatic portal vein aneurysms seem to be acquired

lesions, but congenital PV aneurysms have been reported as well (Gomez et al. 2004; Giavroglou et al. 2006), and they have also been observed in conjunction with Abernethy malformation/congenital extrahepatic portosystemic shunt (Kumar et al. 2008). Its clinical manifestations are variable (Lau et al. 2002). Intrahepatic portal vein aneurysms have also been described (Laumonier et al. 2005). There are few reports describing jaundice and/or recurrent cholestasis apparently caused by this venous pathology, biliary obstruction probably caused by the displacement of the biliary tract (Barzilai and Kleckner 1956; Hermann and Shafer 1965; Thomas 1967; Yamane et al. 2006).

In fact, one patient with this clinical constellation showed a markedly bent extrahepatic bile duct caused by the extrinsic pressure exerted by extrahepatic cystic portal vein aneurysm (Yamane et al. 2006). In the patient of Hermann and Shafer, suffering from obstructive cholestasis, laparotomy revealed a large (6 × 4 cm) saccular aneurysm of the extrahepatic portal vein. The portal vein emerged from the posterior and medial side of the aneurysm which lay at the junction of the splenic and superior mesenteric veins under the duodenum and pancreas and directly anterior to the inferior vena cava. On the artist's drawing (Fig. 5 of this publication), the close spatial relationship between the large aneurysm and the bile duct is in evidence (Hermann and Shafer 1965).

The etiology and pathogeneses of portal vein aneurysms have not yet been clarified. Ontogenetically, the PV system takes its origin from the vitelline and umbilical veins draining the splanchnic blood of the embryo. The so-called "congenital theory" of PV aneurysms postulates a failure in the regression of the right primitive vitelline vein, and a diverticular remnant of this vitelline vein may then enlarge to form a saccular aneurysm of the PV in later life. Other authors attribute the development of PV aneurysms to an inherent weakness of the venous wall. The hypothesis of a congenital origin of these aneurysms is supported by the detection of congenital/connatal lesions and the occurrence of this condition in children and young adults without a history of liver disease (review: Lau et al. 2002).

Biliopathy in Portal Vein Varicosis

Varicose deformation and dilatation of the portal vein in portal venous hypertension can compromise the structure and function of large bile ducts in several ways. The varicosities are known to exert external compression of bile ducts with consecutive obstructive jaundice (Varin et al. 2005).

Biliary Varices

Bile duct varices (biliary tract varicosis) usually occur in conjunction with extrahepatic portal venous obstruction (EPVO), in particular portal vein thrombosis and cavernous transformation of the portal vein (Williams et al. 1982; Kim and Chew 1988). Biliary varices are defined as multiple, large, serpiginous, anechogenic vascular channels in and/or surrounding the extrahepatic bile ducts. Bile duct varices can, via their pressure effect on the duct wall, induce reactive fibroinflammatory lesions with wall thickening (Denys et al. 1998) or produce changes mimicking duct involvement by tumor ("pseudocholangiocarcinoma sign"; Bayraktar et al. 1992; Gorgul et al. 1996; Strunk et al. 2001).

In a study of 21 patients with EPVO, CT and endoscopic ultrasonography showed varices in the wall of the common bile duct in 76 %, surrounding the common duct in 52 %, and in the gallbladder in 43 %. Among 34 patients with cavernous transformation of the portal vein studied by use of MRI, 67 % had paracholedochal portoportal collateral vessels, with 64 % showing visible luminal channels. Epicholedochal venous collaterals were observed in 23 % (Schaible et al. 2002). Biliary varices can cause obstructive cholestasis (Hunt 1965; Palazzo et al. 2000). Varices were the cause of obstructive jaundice in 14 %, but only when they were in the wall of the common bile duct (Palazzo et al. 2000). In the study of Schaible and coworkers (2002), 70 % of patients demonstrated biliary abnormalities due to portoportal collaterals, leading to duct stenosis in 23 %. The ductal walls were irregular in 20 % and thickened in 32 %.

Gallbladder and/or cystic vein varices are rather common in patients with EPVO

(Charnsangavej et al. 1984; Saigh et al. 1985; West et al. 1991; Chawla et al. 1994; Safadi et al. 1996; Gabata et al. 1997; Morales Perez et al. 1999; Radhi 2003). Among 50 patients with portal hypertension, gallbladder varices were identified in 12 % (West et al. 1991). The cystic vein can function as a bypass in portal vein thrombosis (Myking and Halvorsen 1971). Varicosis may mimic a tumor via thickening of the gallbladder wall (Saigh et al. 1985) or by producing an irregularly structured and voluminous cystic duct.

Anatomical Substrates of Portal Biliopathy

What Are the Pathways Draining Venous Blood from the Extrahepatic Bile Ducts?

Venous drainage of the extrahepatic ducts is mostly by veins that ascend along their course. They form the epicholedochal venous plexus of Saint (1961) and the paracholedochal venous plexus of Petren (Petren and Karlmark 1932). The former represents a fine reticular venous plexus on the common bile duct and hepatic ducts and is in intimate contact with their outer surface. The veins of this plexus vary in diameter, but normally are not larger than 1 mm. The latter consists of veins that run parallel to the common bile duct and are connected to the gastric veins, pancreaticoduodenal veins, portal vein, and liver directly. In a detailed analysis based on seven normal postmortem livers (Vellar 2001), it turned out that axial duct veins were found closely applied to the lateral margins of the bile duct. These were commonly two in number known as the 9 o'clock and 3 o'clock marginal vessels. A 6 o'clock vessel may also occur (three marginal veins). In the retropancreatic portion of the common bile duct, the two vessels tend to break up to form a plexus. These marginal vessels give branches which enter the liver substance superiorly, i.e., segments IV, V, caudate lobe, and caudate process. Other branches join the hilar venous plexus which then enter the caudate process or join the caudate portal venous branches. Marginal veins emptying into segment IV join portal venous branches supplying segment IV from the Rex recessus, while smaller vessels join small subcapsular vessels. In this study, the cystic veins always joined the 9 o'clock marginal vein, and they never joined the portal vein. A constant branch connects the 3 o'clock marginal vein with the right gastric vein (what is of importance in the light of the pathogenesis of bile duct varices in case of portal hypertension). The 9 o'clock and 3 o'clock marginal veins connect inferiorly, either individually or after anastomosing with each other, with the pancreaticoduodenal venous plexus, which in its turn drains into the superior mesenteric vein via the posterosuperior pancreaticoduodenal vein.

What Is the Anatomical Substrate of Gallbladder and Cystic Vein Varicosis ?

The venous system of the gallbladder is in direct communication with the portal vein system (Gabata et al. 1997). Venous blood from the gallbladder drains into the right portal vein directly or via the parabiliary venous plexus through the cystic vein, which also communicates with the deep cystic vein running directly into the liver and communicating with the right intrahepatic portal vein branches (Halvorsen and Myking 1971; Myking and Halvorsen 1971; Saigh et al. 1985; Couinaud 1988). In fact, the cystic vein is a direct bypass in portal vein obstruction (Myking and Halvorsen 1971). Contrast medium-supported helical CT imaging has shown that cholecystic venous blood most frequently enters peripheral portal venous branches of hepatic segment V (96 %) and segment IV (93 %). In order of decreasing frequency, cholecystic venous blood also drained to segments I, VI, VIII, III, and VII. The venous blood subsequently drained into the middle hepatic vein (75 %) or right hepatic vein (71 %; Yoshimitsu et al. 1997). Part of these venous channels are connected to the parabiliary venous system. This system originates from the pancreaticoduodenal and pyloroduodenal veins, runs along the common bile duct and the hepatic

artery, and divides in the liver hilum into a venous network within the hilar plate. This hilar plexus sends branches to the veins of the liver segments adjacent to the hilum, and, in 46 % of specimens studied, part of the cystic veins were anastomosed with the parabiliary system (Couinaud 1988).

What Is the Significance of the Cystic Vein?

In some texts on the hepatobiliary anatomy, a cystic vein proper is not specified, although cystic veins were known to classical anatomists, but analysis of the local vascular anatomy during laparoscopic cholecystectomy shows the presence of venous twigs that run parallel to the cystic duct and perpendicular to the common bile duct, bridging the gap between cystic artery and cystic duct, not crossing the common hepatic duct (Fine 1997). In regard to the drainage pathways of the cystic vein, the drainage routes had been studied mainly by the use of autopsy specimens or cast models (Sappey quoted by Kreider 1933; Kreider 1933; Zielke 1962; Halvorsen and Myking 1971; Satoh 1989). The description of the gallbladder veins by Sappey, a famous French anatomist, is as follows: The veins fall into two groups: those which originate in the superior (peritoneal) surface of the gallbladder and those which originate in the inferior surface. The former usually give rise to two trunks which, either separately or after uniting, empty into the right branch of the portal vein. The latter, 12 or 15 in number, representing so many small accessory portal veins, leave the gallbladder to ramify in the liver lobules which surround the gallbladder fossa (Sappey 1879). In a detailed analysis employing vascular gelatine injection, Kreider in principle confirmed these findings (Kreider 1933). His results showed that the gallbladder is covered with a plexus of usually paired and sometimes unpaired veins which accompany the branches of the cystic artery. This might, according to Krider, be called "cystic plexus" or "cystic plexus proper." The cystic plexus is drained by a number of unpaired cystic veins which are very irregular in number, size, and course and which arise from the smaller paired veins of the cystic plexus. Some of the cystic veins can be followed into large branches of the portal vein, and the others enter the liver at any point of the gallbladder fossa from its margin to its deepest point (the gallbladder fossa outlet veins according to my nomenclature). It has to be emphasized that, in the study of Vellar (2001; see above), cystic veins never entered the portal vein, but always joined the 9 o'clock marginal vein of bile ducts. The venous plexus of the gallbladder mucosa resembles the plexus of the duodenal mucosa and consists of a rich network of small veins, the interstices of which are filled with a network of extremely small veins. The gallbladder muscularis itself contains small veins, some of which unite the mucosal plexus with the cystic plexus. The gallbladder serosal veins take in general a lateral course toward the sides of the gallbladder. Some of them, and especially those in the middle of the peritoneal surface, communicate with the veins of the cystic plexus. The others run off to one side or the other into the liver (Kreider 1933). Based on a detailed autopsy study (100 randomly selected necropsies; ink injection into the cystic artery), Halvorsen and Myking (1971) largely confirmed the previous findings, although larger cystic veins were detected in only a fraction of cases, anatomically separated in five groups amounting to 8.5 %. The smaller veins of the gallbladder converge into larger veins that run on the sides of the gallbladder into the liver. The same pattern was described by Habighorst and coworkers after injection of X-ray contrast into the portal vein (Habighorst et al. 1965). In line with the conception of gallbladder fossa outlet veins and their drainage pathway, the authors always found ink in one and sometimes several large intrahepatic portal vein branches running under and parallel to the gallbladder fossa from the fundus of the gallbladder to the hilus of the liver. These veins were in most cases located 1–1.5 cm deep in the liver substance. The path of the connecting veins is not yet clearly known, although venous ostia were found in the portal vein probably belonging to cystic veins (Douglass et al. 1950).

In hemodynamic studies it has been found, by use of angio-CT, that all cystic veins drained

into the intrahepatic portal vein branches (cystic-intrahepatic inflow vessels). The cystic veins took either of two routes: one into the liver through the hepatic hilum, taken mainly by the portal branch for subsegment 4a (P4a), the anterior portal branch, and the umbilical portion of the portal branch and the other through the hepatic bed, taken mainly by S4a sinusoid, S5 sinusoid, P4a, and P5 (Sugita et al. 2000). In 70 % of the cases, cystic venous flow perfused either P4 or S5 (Kumaoka et al. 1998).

References

Adani GL, Avellini C, Baccarani U, Lorenzin D, Risaliti A, Gasparini D, Sponza M, Vit A et al (2008) Graft vessel wall pathology in a case of hepatic artery pseudoaneurysm in a liver transplant recipient. Transplant Proc 40:3800–3803

Ahmed A, Samuels SL, Keeffe EB, Cheung RC (2001) Delayed fatal hemorrhage from pseudoaneurysm of the hepatic artery after percutaneous liver biopsy. Am J Gastroenterol 96:233–237

Akaki S, Kobayashi H, Sasai N, Tsunoda M, Kuroda M, Kanazawa S, Togami I, Hiraki Y (2002) Bile duct stenosis due to portal cavernomas: MR portography and MR cholangiopancreatography demonstration. Abdom Imaging 27:58–60

Akatsu T, Hayashi S, Egawa T, Doi M, Nagashima A, Kitano M, Yamane T, Yoshii H, Kitajima M (2004) Hepatic artery pseudoaneurysm associated with cholecystitis that ruptured into the gallbladder. J Gastroenterol 39:900–903

Akatsu T, Tanabe M, Shimizu T, Handa K, Kawachi S, Aiura K, Ueda M, Shimazu M, Kitajima M (2007) Pseudoaneurysm of the cystic artery secondary to cholecystitis as a cause of hemobilia: report of a case. Surg Today 37:412–417

Al Hilli FA (2001) Primary dissecting hepatic artery aneurysm in pregnancy. Cardiovasc Pathol 10:99–101

Alazmi WM, McHenry L, Watkins JL, Fogel EL, Schmidt S, Sherman S, Lehman GL (2006) Chemotherapy-induced sclerosing cholangitis: long-term response to endoscopic therapy. J Clin Gastroenterol 40:353–357

Aldrighetti L, Arru M, Ronzoni M, Salvioni M, Villa E, Ferla G (2001) Extrahepatic biliary stenoses after hepatic arterial infusion (HAI) of floxuridine (FudR) for liver metastases from colorectal cancer. Hepato-Gastroenterology 48:1302–1307

Alhawsawi AM, Aljiffry M, Walsh MJ, Peltekian K, Molinari M (2009) Hepatic artery aneurysm associated with prune belly syndrome: a case report and review of the literature. J Surg Educ 66:43–47

Alleman MJA, Janssens AR, Spoelstra P, Kroon MJA (1986) Spontaneous intrahepatic hemorrhages in polyarteritis nodosa. Ann Intern Med 105:712–739

Amir R, Jacobs PH, Piepsz A (1984) Unusual cholescintigraphic findings in polyarteritis nodosa. Clin Nucl Med 9:585–587

Anderson SD, Holley HC, Berland LL, Van Dyke JA, Stanley RJ (1986) Causes of jaundice during hepatic artery infusion chemotherapy. Radiology 161:439–442

Aoufi S, Herrera Justiniano JM, Garcia-Agudo R, Garrido Serrano A, Marquez Galan JL (2007) An unusual cause of obstructive jaundice: giant gastroduodenal artery aneurysm (in Spanish). Gastroenterol Hepatol 30:114–116

Asma K, Dalila G, Olfa B, Malika R, Afef K, Najet B, Jamel K, Abdeljabbar G, Sarra S et al (2005) Cholangitis revealing an intrahepatic Osler's disease (in French). Tunis Med 83:495–498

Ball NJ, Duggam MA (1990) Hepatolithiasis in hereditary hemorrhagic telangiectasia. Arch Pathol Lab Med 114:423–425

Balthazar EJ (1977) Hemobilia: calcified hepatic artery aneurysm presenting with massive gastrointestinal bleeding. Gastrointest Radiol 2:71–74

Barba CA, Bret PM, Hinchey EJ (1994) Pseudoaneurysm of the cystic artery: a rare cause of hemobilia. Can J Surg 37:64–66

Barquist E, Goldstein N, Zinner MJ (1991) Polyarteritis nodosa presenting as a biliary stricture. Surgery 109:16–19

Barzilai R, Kleckner MS (1956) Hemocholecyst following ruptured aneurysm of portal vein. Arch Surg 72:725–727

Bayraktar Y, Balkanci F, Kayhan B, Ozenc A, Arslan S, Telatar H (1992) Bile duct varices or "pseudocholangiocarcinoma sign" in portal hypertension due to cavernous transformation of the portal vein. Am J Gastroenterol 87:1801–1806

Bechtelsheimer H, Conrad A (1980) Morphology of cavernous transformation of the portal vein (in German). Leber Magen Darm 10:99–106

Bekker J, Ploem S, de Jong KP (2009) Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. Am J Transplant 9:746–757

Belhadjbrik N, Kchaou-Oakaa A, Kharrat J, Elloumi H, Gargouri D, Kochlef A, Ghorbel A (2006) Biliary abnormalities associated to portal cavernoma. About 17 cases (in French). Tunis Med 84:291–295

Bernard G, Mion F, Henry L, Plauchu H, Paliard P (1993) Hepatic involvement in hereditary hemorrhagic telangiectasia: clinical, radiological., and hemodynamic studies of 11 cases. Gastroenterology 105:482–487

Beuran M, Chiotoroiu AL, Ayram M, Vartic M, Constantinescu G, Dorobat B, Rosu O, Diaconescu BI (2008) Management for pseudoaneurysm of cystic artery with an arterio-biliary fistula after laparoscopic cholecystectomy: a rare case of hemobilia (in Romanian). Chirurgia (Bucur) 103:689–694

Bhattacharjya S, Gunson BK, Mirza DF, Mayer DA, Buckels JA, McMaster P, Neuberger JM (2001) Delayed hepatic artery thrombosis in adult orthotopic liver transplantation – a 12-year experience. Transplantation 71:1592–1596

Bookman AAM, Goode E, McLoughlin MJ, Cohen Z (1983) Polyarteritis nodosa complicated by a ruptured intrahepatic aneurysm. Arthritis Rheum 26:106–108

Boontje AH (1979) Multiple aneurysms of the visceral branches of the abdominal aorta. VASA 8:42–50

Botet JF, Watson RC, Kemeny N, Daly JM, Yeh S (1985) Cholangitis complicating intraarterial chemotherapy in liver metastasis. Radiology 156:335–337

Bramis J, Felekouras E, Kontos M, Leonardou P, Griniatsos J, Bastounis E (2002) True giant common hepatic artery aneurysm associated with obstructive jaundice: a case report. Int Surg 87:142–146

Bret PM, Partensky C, Bretagnolle M, Paliard P, Burke M (1987) Obstructive jaundice by a dissecting aneurysm of celiac axis and hepatic artery. Dig Dis Sci 32:1431–1434

Burns L, Slakey DP (2009) Laparoscopic management of massive hemobilia from an intrahepatic aneurysm. JSLS 13:60–63

Callicot JH, Hoke HF (1968) Dissecting aneurysm of the common hepatic artery. Arch Pathol 85:681–685

Calligaro KD, Ahmad S, Dandora R, Dougherty MJ, Savarese RP, Doerr KJ, McAffee S, DeLaurentis DA (1995) Venous aneurysms: surgical indications and review of the literature. Surgery 117:1–6

Casula G, Scattone S, Cossu L, Simonetti G (1984) Hemobilia from ruptured hepatic artery aneurysm: angiographic demonstration of arteriobiliary fistula in a successfully treated case. Gastrointest Radiol 9:171–173

Chaib E, Bertevello P, Saad WA, Pinotti HW, Gama-Rodrigues J (2007) The main hepatic anatomic variations for the purpose of split-liver. Hepato-Gastroenterology 54:688–692

Chandra R, Kapoor D, Tharakan A, Chaudhary A, Sarin SK (2001) Portal biliopathy. J Gastroenterol Hepatol 16:1086–1092

Chandramohan, Khan AN, Fitzgerald S, Sherlock D, Tam E (2001) Sonographic diagnosis and follow-up of idiopathic hepatic artery aneurysm, an unusual cause of obstructive jaundice. J Clin Ultrasound 29:466–471

Chang HK, Chung J, Lee DH, Kim KT, Jang HJ (2003) A limited polyarteritis nodosa of the liver and gallbladder accompanied with a solitary cystic dilatation of the intrahepatic bile duct. Clin Exp Rheumatol 21:525

Charnsangavej C, Thornhill B, Chuang VP, Bernstein RG (1984) Gallbladder varices: a potential pathway in portal hypertension and portal vein occlusion. Cardiovasc Intervent Radiol 7:247–250

Chavan A, Galanski M, Wagner S, Caselitz M, Schlitt HJ, Gratz KF, Manns M (1998) Hereditary hemorrhagic telangiectasia: effective protocol for embolization of hepatic vascular malformations – experience in five patients. Radiology 209:735–739

Chawla et al. 1994. http://www.ncbi.nlm.nih.gov/pubmed/8109513

Chen MF, Chou FF, Wang CH, Jang YI (1983) Hematobilia from ruptured hepatic artery aneurysm. Report of two cases. Arch Surg 118:759–761

Chevallier P, Denys A, Novellas S, Schmidt S, Schnyder P, Bruneton JN (2006) Magnetic resonance cholangiography features of biliary abnormalities due to cavernous transformation of the portal vein. Clin Imaging 30:190–194

Chhem RK, Groleau S (1989) Echographic aspect of a hepatic artery aneurysm simulating a neoplastic mass of the porta hepatis (in French). Can Assoc Radiol J 40:222–223

Cho CJ, Kim YG, Lee SG, Lee CK, Kim JH, Koo BS, Yoo B (2011) Inflammatory and noninflammatory vascular disease causing hemobilia. J Clin Rheumatol 17:138–141

Chow L, Jeffrey RB (1999) Intramural varices of the bile duct: an unusual pattern of cavernous transformation of the portal vein. AJR Am J Roentgenol 173:1255–1256

Choy CWK, Smith PA, Frazer C, Jeffrey GP (1997) Ruptured hepatic artery aneurysm in polyarteritis nodosa: a case report and literature review. Aust NZ J Surg 67:906–908

Christensen MG, Lorentzen JE, Schroeder TV (1995) Revascularisation of atherosclerotic mesenteric arteries: experience in 90 consecutive patients. Eur J Vasc Endovasc Surg 9:509

Chung JP, Kim KW, Chi HS, Lee SI, Shin ET, Cho JH, Lee HW, Kang JK, Park IS (1994) Obstructive jaundice due to compression of the common hepatic duct by right hepatic artery – a case associated with the absence of the lateral segment of the left hepatic lobe. Yonsei Med J 35:231–238

Clark RA, Gallant TE (1987) Bile duct strictures associated with hepatic arterial infusion chemotherapy. Gastrointest Radiol 12:148–151

Condat B, Vilgrain V, Asselah T, O'Toole D, Rufat P, Zappa M, Moreau R, Valla D (2003) Portal cavernoma-associated cholangiopathy: a clinical and MR cholangiography coupled with MR portography imaging study. Hepatology 37:1302–1308

Cook GJ, Crofton ME (1997) Hepatic artery thrombosis and infarction: evolution of the ultrasound appearances in liver transplant recipients. Br J Radiol 70:248–251

Couinaud C (1988) The parabiliary venous system. Surg Radiol Anat 10:311–316

Coulier B, Mairy Y, Broze B, Ramboux A (2006) Giant splenic artery aneurysm presenting as unusual cause of obstructive jaundice. JBR-BTR 89:201–203

Countryman D, Norwood S, Register D, Torma M, Andrassy R (1983) Hepatic artery aneurysm. Report of an unusual case and review of the literature. Am Surg 49:51–54

Covey AM, Brody LA, Maluccio MA, Getrajdman GI, Brown KT (2002) Variant hepatic arterial anatomy revisited: digital subtraction angiography performed in 600 patients. Radiology 224:542–547

Cwikiel M, Eskilsson J, Wieslander JB, Stjernquist U, Albertsson M (1996) The appearance of endothelium in small arteries after treatment with 5-fluorouracil. An electron microscopic study of late effects in rabbits. Scanning Microsc 10:805–818

D'Souza MA, Desai D, Joshi A, Abraham P, Shah SR (2009) Bile duct stricture due to by portal biliopathy: treatment with one-stage portal-systemic shunt and biliary bypass. Indian J Gastroenterol 28:35–37

Daly JM, Kemeny N, Oderman P, Botet J (1984) Long-term hepatic arterial infusion chemotherapy: anatomic considerations, operative technique, and treatment morbidity. Arch Surg 119:936–941

De Gaetano AM, Andrisani MC, Gui B, Maresca G, Ionta R, Bonomo L (2006) Thrombosed portal vein aneurysm. Abdom Imaging 31:545–548

Denys A, Helenon O, Lafortune M, Correas JM, Patrriquin H, Moreau JF, Menu Y (1998) Thickening of the wall of the bile duct due to intramural collaterals in three patients with portal vein thrombosis. AJR Am J Roentgenol 171:455–456

Derhy S, Foster DW, Cauquil P, Bazin C, Roche A (1988) Dissection spontanée de l'artère hépatique. Aspects échographique et artériographiques; à propos d'un cas. Ann Radiol 31:301–304

Desai RK, Paushter DM, Armistead J (1989) Intrahepatic arterial calcification mimicking pneumobilia. A potential pitfall in the ultrasound evaluation of biliary tract disease. J Ultrasound Med 8:333–335

Dhiman RK, Puri P, Chawla Y, Minz M, Bapuraj JR, Gupta S, Nagi B, Suri S (1999) Biliary changes in extrahepatic portal venous obstruction: compression by collaterals or ischemic ? Gastrointest Endosc 50:646–652

Dhiman RK, Behera A, Chawla YK, Dilawari JB, Suri S (2007) Portal hypertensive biliopathy. Gut 56:1001–1008

Dilawari JB, Chawla YK (1992) Pseudosclerosing cholangitis in extrahepatic portal venous obstruction. Gut 33:272–276

Dillard BM, Black WC (1970) Polyarteritis nodosa of the gallbladder and bile ducts. Am Surg 36:423–427

Doi S, Yoshimoto S, Hikita K, Beppu M (1979) Compression of the common hepatic duct by right hepatic artery in a case with cholecystolithiasis (in Japanese). Stomatol Intest 14:687

Dönmez H, Men S, Dilli A, Soylu SO et al (2005) Giant gastroduodenal artery pseudoaneurysm due to polyarteritis nodosa as a cause of obstructive jaundice: imaging findings and coil embolization results. Cardiovasc Intervent Radiol 28:850–853

Doppman JL, Dunnick NR, Girton M, Fauci AS, Popovsky MA (1979) Bile duct cysts secondary to liver infarcts: report of a case and experimental production by small vessel hepatic artery occlusion. Radiology 130:1–5

Dorrucci V, Dusi R, Rombola G, Cordiano C (2001) Contained rupture of an abdominal aortic aneurysm presenting as obstructive jaundice: report of a case. Surg Today 31:331–332

Douglass BE, Baggenstoss AH, Hollinshead WH (1950) The anatomy of the portal vein and its tributaries. Surg Gynecol Obstet 91:562

Duffy JP, Hong JC, Farmer DG, Ghobrial RM, Yersiz H, Hiatt JR, Busuttil RW (2009) Vascular complications of orthotopic liver transplantation: experience in more than 4200 patients. J Am Coll Surg 208:896–903

Dusanovic AM, Ignjatovic DM, Knezevic PA, Todorovic M, Krgovic KL, Filipovic BR (1999) Arterial ring encircling the bile duct with coexisting anomalous liver irrigation. Dig Surg 16:72–75

Eliscu EH, Weiss GM (1988) Hematobilia due to a pseudoaneurysm complicating a choledochal cyst. AJR Am J Roentgenol 151:783–784

Elmas N, Calli C, Killi R, Memis A, Oyar O, Mentes A (1998) Partially thrombosed hepatic artery aneurysm mimicking pancreatic head carcinoma. Comput Med Imaging Graph 22:67–70

England RE, Marsh PJ, Ashleigh R, Martin DF (1998) Case report: pseudoaneurysm of the cystic artery: a rare cause of hemobilia. Clin Radiol 53:72–75

Fine A (1997) The cystic vein: the significance of a forgotten anatomic landmark. JSLS 1:263–266

Fraser J, Broun AK (1944) A clinical syndrome associated with a rare anomaly of vena portal system. Surg Gynecol Obstet 78:520–524

Gabata et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9000362

Garcia P, Garcia-Giannoli H, Meyran S, Valette PJ, Henry L, Dumout O (1996) Primary dissecting aneurysm of the hepatic artery: sonographic, CT and angiographic findings. Am J Roentgenol 166:1316–1318

Garcia-Pagan JC, Hernandez-Guerra M, Bosch J (2008) Extrahepatic portal vein thrombosis. Semin Liver Dis 28:282–292

Garcia-Tsao G, Korzenik JR, Young L, Henderson KJ, Jain D, Byrd B, Pollak JS, White RI (2000) Liver disease in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 343:931–936

Gauthier-Villars M, Franchi S, Gauthier F, Fabre M, Pariente D, Bernard O (2005) Cholestasis in children with portal vein obstruction. J Pediatr 146:568–573

Gear JH, Meyers KE, Steele M (1992) Kawasaki disease manifesting with acute cholangitis. A case report. S Afr Med J 81:31–33

Geyer M, Jung T, Bertschinger P (2005) Unusual mass in the hepatic portal of an 86-year-old woman. Ultraschall Med 26:231–233

Giavroglou C, Xinou E, Fotiadis N (2006) Congenital extrahepatic portal vein aneurysm. Abdom Imaging 31:241–244

Gibson JB, Richards RL (1955) Cavernous transformation of the portal vein. J Pathol Bact 70:81–95

Glassman E, Skerrett PV (1960) Rupture of an intrahepatic aneurysm due to polyarteritis nodosa. Am J Med 28:143–146

Gomez R, Bentsen DM, Burd RS (2004) Antenatal diagnosis of an extrahepatic portal vein aneurysm. South Med J 97:1023–1024

Gorgul A, Kayhan B, Dogan I, Unal S (1996) Disappearance of the pseudo-cholangiocarcinoma sign after TIPSS. Am J Gastroenterol 91:150–154

Goritsas CP, Repanti M, Papadaki E, Lazarou N, Andonopoulos AP (1997) Intrahepatic bile duct injury and nodular regenerative hyperplasia of the liver in a patient with polyarteritis nodosa. J Hepatol 26:727–730

Gottlieb K, Brophy MC (2007) Hepatic duct compression syndrome diagnosed by endoscopic ultrasound. J Gastrointest Liver Dis 16:350–351

Gracey L (1970) Jaundice due to hepatic artery aneurysm. Proc R Soc Med 63:1311

Graham WP, Eiseman B, Pryor R (1964) Hepatic artery aneurysm with portal vein fistula in a patient with familial hereditary telangiectasia. Ann Surg 159:362–367

Graham JM, McCollum CH, DeBakey ME (1980) Aneurysms of the splanchnic arteries. Am J Surg 140:797

Graham LM, Stanley JC, Whitehouse WM, Zelenock GB, Wakefield TW, Cronenwett JL, Lindenauer SM (1985) Celiac artery aneurysms: historic (1745–1949) versus contemporary (1950–1984) differences in etiology and clinical importance. J Vasc Surg 2:757–764

Gunsar F, Rolando N, Pastacaldi S, Patch D, Raimondo ML, Davidson B, Rolles K, Burroughs AK (2003) Late hepatic artery thrombosis after orthotopic liver transplantation. Liver Transpl 9:605–611

Gurrero EC (1970) Primary dissecting aneurysm of the hepatic artery. Arch Pathol 89:569–573

Habighorst LV, Albers P, Zeitler E (1965) Die Gefässe der Gallenblase im postmortalen Angiogramm. Fortschr Röntgenstr 103:63

Halvorsen JF, Myking AO (1971) The arterial supply and venous drainage of the gall-bladder. A study of one hundred autopsies. Acta Chir Scand 137:659–664

Harlaftis NN, Akin JT (1977) Hemobilia from ruptured hepatic artery aneurysm. Report of a case and review of the literature. Am J Surg 133:229–232

Hasegawa K, Kubota K, Aoki T, Hira I, Miyazawa M, Ohtomo K, Makuuchi M (2000) Ischemic cholangitis caused by transcatheter hepatic arterial chemoembolization 10 months after resection of the extrahepatic bile duct. Cardiovasc Intervent Radiol 23:304–306

Hashikura Y, Makuuchi M, Kawasaki S, Miwa S, Kobayashi A, Imai Y, Ota H (1994) Benign stricture of the intrahepatic bile duct with arterial involvement. Hepatogastroenterology 41:79–81

Hashim A, Allagaband S, Bajwa T (2009) Leaking hepatic artery aneurysm successfully treated with covered stent. Catheter Cardiovasc Interv 74:500–505

Hashimoto M, Ito I, Sato K (1998) Case report: dissecting aneurysm of the hepatic artery. Clin Radiol 53: 913–914

Hatzidakis AA, Gogas C, Papanikolaou N, Samonakis D, Kofteridis D, Gourtsoyiannis NC (2002) Hepatic involvement in hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease). Eur Radiol 12(suppl 3): S51–S55

Hayashi S, Baba Y, Ueno K, Nakajo M (2008) Small arteriovenous malformation of the common bile duct causing hemobilia in a patient with hereditary hemorrhagic telangiectasia. Cardiovasc Intervent Radiol 31(suppl 2):S131–S134

He ZP, Fan LJ (2002) Diagnosis and treatment of portal biliopathy. Hepatobiliary Pancreat Dis Int 1:581–586

Heptinstall RH, Porter KA, Barkley H (1954) Giant cell (temporal) arteritis. J Pathol Bacteriol 67:507–519

Hermann RE, Shafer WH (1965) Aneurysm of the portal vein and portal hypertension: first reported case. Ann Surg 162:1101–1104

Hiatt JR, Gabbay J, Busuttil RW (1994) Surgical anatomy of the hepatic arteries in 1000 cases. Ann Surg 220:50–52

Hill DE, Lobrill M, Edward JE (1974) Primary dissecting aneurysm of the hepatic artery. Arch Intern Med 133:471–474

Hillert C, Broering DC, Gundlach M, Knoefel WT, Izbicki JR, Rogiers X (2001) Hepatic involvement in hereditary hemorrhagic telangiectasia: an unusual indication for liver transplantation. Liver Transpl 7:266–268

Hohn D, Melnick J, Stagg R, Altman D, Friedman M, Ignoffo R, Ferrell L, Lewis B (1985) Biliary sclerosis in patients receiving hepatic arterial infusions of floxuridine. J Clin Oncol 3:98–102

Hohn DC, Stagg RJ, Friedman MA, Hannigan JF, Rayner A, Ignoffo RJ, Acord P, Lewis BJ (1989) A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group Trial. J Clin Oncol 7:1646–1654

Horie T, Shimizu I, Okazaki M, Fujiwara K, Fujiwara S, Yamamoto K, Iuchi A, Tanagami A et al (2005) A patient with adult extrahepatic portal obstruction, of which distinction from intrahepatic cholangiocarcinoma was difficult. J Med Invest 52:203–207

Htun OY, Olliff S, Haydon G, Thorburn D (2009) Symptomatic portal biliopathy: a single centre experience from the UK. Eur J Gastroenterol Hepatol 21:206–213

Hunt AH (1965) Compression of the common bile duct by an enlarging collateral vein in case of portal hypertension. Br J Surg 52:636–637

Ibukuro K, Takeguchi T, Fukuda H, Abe S, Tobe K, Tanaka R, Tagawa K (2012) Spatial relationship between intrahepatic artery and portal vein based on the fusion image of CT-arterial portography (CTAP) and CT-angiography (CTA): new classification for hepatic artery at hepatic hilum and the segmentation of right anterior section of liver. Eur J Radiol 81: e158–e165

Izuishi K, Toyama Y, Wakabayashi H, Usuki H, Maeta H (2005) Compression of the common hepatic duct by the right hepatic artery. Clin Imaging 29:342–344

James AW (1976) Primary dissecting aneurysm of the hepatic artery simulating acute myocardial infarction. Can Med Assoc J 114:110–111

Janssen HL, Wijnhoud A, Haagsma EB, van Uum SH, van Nieuwkerk CM, Adang RP et al (2001) Extrahepatic portal vein thrombosis: aetiology and determinants of survival. Gut 49:720–724

Kaman L, Kumar S, Behera A, Kateriya RN (1998) Pseudoaneurysm of the cystic artery: a rare cause of hemobilia. Am J Gastroenterol 93:1535–1537

Kantarci M, Karakaya A, Aydinii B, Yalcin Polat K, Ceviz M (2009) Giant hepatic artery aneurysm causing portal hypertension. Dig Liver Dis 41:913

Kessler A, Graif M, Konikoff F, Mercer D, Oren R, Carmiel M, Blachar A (2007) Vascular and biliary abnormalities mimicking cholangiocarcinoma in patients with cavernous transformation of the portal vein: role of color Doppler sonography. J Ultrasound Med 26:1089–1095

Khalid SK, Garcia-Tsao G (2008) Hepatic vascular malformations in hereditary hemorrhagic telangiectasia. Semin Liver Dis 28:247–258

Khuroo MS, Yattoo GN, Zargar SA, Javid G, Dar MY, Khan BA, Boda MI (1993) Biliary abnormalities associated with extrahepatic portal venous obstruction. Hepatology 17:807–813

Kim S, Chew FS (1988) Choledochal varices. AJR Am J Roentgenol 150:578–580

Kim MH, Lee SK, Min YI, Kwon TW, Ahn SH, Lee SG, Min PC (1992) secondary intrahepatic stones due to compression of common hepatic duct by right hepatic artery (in Korean). Korean J Gastroenterol 24:901

Kinhult S, Albertsson M, Eskilsson J, Cwikiel M (2003) Effects of probucol on endothelial damage by 5-fluorouracil. Acta Oncol 42:304–308

Kirchgatterer A, Allinger S, Spöttl A, Zisch R, Funk S, Messenbäck F, Haidenthaler A et al (1998) Aneurysm of teh cystic artery as a rare cause of hemobilia (in German). Wien Klin Wochenschr 110:298–301

Koga T, Kage M, Arakawa M, Fukuda K, Tanikawa K (1986) Extrahepatic portal obstruction in adults – report of an autopsy case. Gastroenterol Jpn 21:267–272

Kondo H, Kanematsu M, Shiratori Y, Moriwaki H, Hoshi H (1999) Potential pitfall of MR cholangiopancreatography: right hepatic arterial impression of the common hepatic duct. J Comput Assist Tomogr 23:60–62

Koops A, Wojciechowski B, Broering DC, Adam G, Krupski-Berdien G (2004) Anatomic variations of the hepatic arteries in 604 selective celiac and superior mesenteric angiographies. Surg Radiol Anat 26:239–244

Kossak J, Janik J, Debski J, Rytlewski R, Salacinski A (2001) Pseudoaneurysm of the gastroduodenal artery as a cause of obstructive jaundice. Med Sci Monit 7:759–761

Kreider PG (1933) The anatomy of the veins of the gallbladder. Surg Gynecol Obstet 57:475–482

Krishna M, Keaveny AP, Genco PV, Rosser BG, Dickson RC, Nguyen JH, Steers JL, Nakhleh RE (2005) Clinicopathological review of 18 cases of liver allografts lost due to bile duct necrosis. Transplant Proc 37:2221–2223

Krus S, Turjman MW, Fiejka E (2000) Comparative morphology of the hepatic and coronary artery walls. Part I. Differences in the distribution and intensity of non-atherosclerotic intimal thickening and atherosclerosis. Med Sci Monit 6:19–23

Kumada S, Nakano H, Kitamura K, Watahiki H, Takeda I, Ozawa H, Shibata T, Sugiyama K, Hachisuga K (1981) A case of obstructive jaundice due to compression of the common hepatic duct by right hepatic artery (right hepatic artery syndrome) (in Japanese). Biliary Tract Pancreas 2:533

Kumaoka H, Kikuyama M, Kitanaka H, Kayahara T, Horio Y, Matsubayashi Y, Tobe T (1998) Cystic vein: as a perfusion vein of hepatic portion-angiographical study (in Japanese). Nippon Shokakibyo Gakkai Zasshi 95:419–423

Kumar A, Kumar J, Aggarwal R, Srivastava S (2008) Abernethy malformation with portal vein aneurysm. Diagn Interv Radiol 14:143–146

Lal RB, Strohl JA, Piazza S, Aslam M, Ball D, Patel K (1989) Hepatic artery aneurysm. J Cardiovasc Surg (Torino) 30:509–513

Larson CJ, Geier GR, Edward WD (1987) Fatal acute dissection of the right hepatic artery after appendectomy. Arch Pathol Lab Med 111:300–302

Lau H, Chew DK, Belkin M (2002) Extrahepatic portal vein aneurysm: a case report an review of the literature. Cardiovasc Surg 10:58–61

Laughlin EH (1986) Common duct stricture associated with hepatic artery infusion of FUDR. J Surg Oncol 31:56–59

Laumonier H, Montaudon M, Corneloup O, Brunot S, Laurent F (2005) CT angiography of intrahepatic portal aneurysm. Abdom Imaging 30:755–757

Lerut J, Orlando G, Adam R, Sabba C, Pfitzmann R, Klempnauer J, Belghiti J, Pirenne J, Thevenot T et al (2006) Liver transplantation for hereditary hemorrhagic telangiectasia: report of the European liver transplant registry. Ann Surg 244:854–862

Lie JT (1978) Disseminated visceral giant cell arteritis. Am J Clin Pathol 69:299–305

Lin E, Stall L (2007) Spectrum of biliary abnormalities in hepatic hereditary hemorrhagic telangiectasia: demonstration by multidetector computed tomography. Emerg Radiol 14:461–463

Lohr JM, Kuchenreuter S, Grebmeier H, Hahn EG, Fleig WE (1993) Compression of the common bile duct due to portal-vein thrombosis in polycythemia vera. Hepatology 17:586–592

Ludwig J, Kim CH, Wiesner RH, Krom RA (1989) Floxuridine-induced sclerosing cholangitis: an ischemic cholangiopathy ? Hepatology 9:215–218

Luttwak EM, Schwartz A (1961) Jaundice due to obstruction of the common duct by aberrant artery: demonstration of celiac anomaly by translumbar aortography and simultaneous choledochogram. Ann Surg 153:134–137

Mackenzie RL, Tubbs HR, Laws JW, Dawson JL, Williams R (1978) Obstructive jaundice and portal vein calcification. Br J Radiol 51:953–955

Maeda A, Kunou T, Saeki S, Aono K, Murata T, Niinomi N, Yokoi S (2002) Pseudoaneurysm of the cystic artery with hemobilia treated by arterial embolization and elective cholecystectomy. J Hepatobiliary Pancreat Surg 9:755–758

Maluf D, Clark BD, Cotterell AH, Posner MP, Fisher RA (2004) Massive hepatic artery atherosclerosis of an otherwise suitable donor liver: a case report. Transplant Proc 36:1438–1441

Manenti A, Ragazzi P, Cerofolini E (1981) Arterio-biliary crossing on the common bile duct (in French). Acta Chir Belg 80:37–40

Mazziotti S, Blandino A, Gaeta M, Lamberto S, Vinci V, Ascenti G (2003) Hepatic artery aneurysm, an unusual cause of obstructive jaundice: MR cholangiography findings. Abdom Imaging 28:835–837

McCollum CN, Sloan ME, Davison AM, Giles GR (1979) Ruptured hepatic aneurysm in systemic lupus erythematosus. Ann Rheum Dis 38:396–398

McInroy B, Zajko AB, Pinna AD (1998) Biliary necrosis due to hepatic involvement with hereditary hemorrhagic telangiectasia. AJR Am J Roentgenol 170:413–415

McMullan DM, McBride M, Livesay JJ, Dougherty KG, Krajcer Z (2006) Celiac artery aneurysm: a case report. Tex Heart Inst J 33:235–240

Michels NA (1951) The hepatic, cystic and retroduodenal arteries and their relations to the biliary ducts with samples of the entire celiacal blood supply. Ann Surg 133:503–524

Michels 1966. http://www.ncbi.nlm.nih.gov/pubmed/5917302

Milot L, Dumortier J, Boillo O, Pilleul F (2007) Giant aneurysm of the main hepatic artery secondary to hereditary hemorrhagic telangiectasia: 3D contrast-enhanced MR angiography features. Gastroenterol Clin Biol 31:297–299

Miyabe K, Akita S, Kitajima Y, Hirai M, Naitoh I, Hayashi K, Okamoto T, Okayama Y et al (2007) Rupture of hepatic aneurysm complicating hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) for which hepatic arterial coil embolization was effective. J Gastroenterol Hepatol 22:2352–2357

Miyashita K, Shiraki K, Ito T, Taoka H, Nakano T (2005) The right hepatic artery syndrome. World J Gastroenterol 11:3008–3009

Morales Perez et al. 1999. http://www.ncbi.nlm.nih.gov/pubmed/10601769

Moses V, Keshava SN, Wann VC, Joseph P, Sitaram V (2008) Cystic artery pseudoaneurysm after laparoscopic cholecystectomy presenting as haemobilia: a case report. Trop Gastroenterol 29:107–109

Muller MF, Kim D (1995) Spontaneous dissection of the hepatic artery. Abdom Imaging 20:462–465

Myking AO, Halvorsen JF (1971) The cystic vein as a bypass in portal vein thrombosis. Acta Chir Scand 137:587–591

Nakamura S, Yokoi Y, Suzuki S, Sakaguchi S, Muro H, Maeda M, Kawasaki H (1991) A case of melena caused by a hepatic aneurysm ruptured into the intrahepatic bile duct in a patient with allergic granulomatous angiitis. Jpn J Surg 21:471–475

Nakamura S, Suzuki S, Hachiya T, Ochiai H, Konno H, Baba S, Baba S (1998) Primary dissection of the hepatic artery. Report of a case. Surg Today 28:1065–1068

Nakazawa K, Itoh N, Duan HJ, Komiyama Y, Shigamatsu H (1992) Polyarteritis nodosa with atrophy of the left hepatic lobe. Acta Pathol Jpn 42:662–666

Natalini G, Trancanelli V, Sciutti S, Vecchiarelli G, Corinaldesi D, Castori AC, Correnti S, Mercati U (1978) Hemobilia caused by rupture of a false aneurysm of the left branch of the hepatic artery (in Italian). Minerva Chir 33:651–655

Nishie M, Tomiyama M, Kamijo M, Kannari K, Tanosaki M, Baba M, Matsunaga M, Suda T (2003) Acute cholecystitis and duodenitis associated with Churg-Strauss syndrome. Hepato-Gastroenterology 50:998–1002

Novellas S, Chevallier P, Peroux JL, Bruneton JN (2004) Rare localization of a portal cavernoma in the wall of the common bile duct. Clin Imaging 28:132–134

Nyman R, al-Suhaibani H, Kagevi I (1996) Portal vein thrombosis mimicking tumour and causing obstructive jaundice. A case report. Acta Radiol 37:685–687

Odorico et al. 1998. http://www.ncbi.nlm.nih.gov/pubmed/9791159

Ogilvie AL, James PD, Toghill PJ (1981) Hepatic artery involvement in polymyalgia arteritica. J Clin Pathol 34:769–772

Okuda K, Kobayashi S, Hayashi H, Ohtake H, Nakajima Y, Yoshida K, Kashima H, Irie Y (2002) Case-control study of calcification of the hepatic artery in chronic hemodialysis patients: comparison with the abdominal aorta and splenic artery. J Gastroenterol Hepatol 17:91–95

Okuda K, Kobayashi S, Hayashi H, Nakajima K, Ohtake Y, Yoshida H, Kashima T, Irie Y (2003) Sonographic features of hepatic artery calcification in chronic renal failure. Acta Radiol 44:151–153

Pai SS, Bude RO (2002) Sonographic appearance of extensive hepatic arterial calcification mimicking pneumobilia. J Clin Ultrasound 30:38–41

Palazzo L, Hochain P, Helmer C, Cuillerier E, Landi B, Roseau G, Cugnenc PH, Barbier JP, Cellier C (2000) Biliary varices on endoscopic ultrasonography: clinical presentation and outcome. Endoscopy 32:520–524

Papadimitriou DK, Pitoulias GA, Tachtsi MD, Aslanidou EA, Lazaridis CN, Alexandrakis AG (2005) Celiac artery aneurysm associated with atherosclerotic common hepatic artery stenosis. VASA 34:136–139

Parangi S, Mehmet O, Blume RS, Bixon R, Laffey KJ, Perzin KH (1991) Hepatobiliary complications of polyarteritis nodosa. Arch Surg 126:909–912

Parent BA, Cho SW, Buck DG, Nalesnik MA, Gamblin TC (2010) Spontaneous rupture of hepatic artery aneurysm associated with polyarteritis nodosa. Am Surg 76:1416–1419

Park SS, Kim BU, Han HS, Goo JC, Han JH, Bae IH, Park SM (2006) Hemobilia from ruptured hepatic artery aneurysm in polyarteritis nodosa. Korean J Intern Med 21:79–82

Park HJ, Choi YJ, Kim JE, Ye YM, Park HS, Suh CH (2007) Successful treatment of pediatric systemic polyarteritis nodosa with cholestatic hepatitis. Clin Rheumatol 26:122–124

Peery WH (1987) Clinical spectrum of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Am J Med 82:989–997

Perego P, Cozzi G, Bertolini A (2003) Portal biliopathy. Surg Endosc 17:351–352

Petren T, Karlmark E (1932) Die extrahepatischen Gallengangsvenen und ihre pathologisch-anatomische Bedeutung (The veins of the extrahepatic biliary system and their pathologic-anatomic significance) (in German). Verh Anat Ges 41:139–143

Petrin P, Costantino V, Feltrin GP, Miotto D, Puttini L, Pedrazzoli S (1982) Hepatic artery aneurysm. Am J Gastroenterol 77:934–935

Petscavage JM, Maldjian P (2007) Celiomesenteric trunk: two variants of a rare anomaly. Australas Radiol 51(suppl):B306–B309

Pien EH, Zeman RK, Benjamin SB (1985) Iatrogenic sclerosing cholangitis following hepatic arterial chemotherapy infusion. Radiology 156:329–330

Pinkerton JA, Wood WG, Fowler D (1976) Fibrodysplasia with dissecting aneurysm of the hepatic artery. Surgery 79:721–723

Radhi JM (2003) Gallbladder varices. Pathology 35:358–359

Rangari M, Gupta R, Jain M, Malhotra V, Sarin SK (2003) Hepatic dysfunction in patients with extrahepatic portal venous obstruction. Liver Int 23:434–439

Reddy SC (1983) Pseudoaneurysm of cystic artery with upper gastrointestinal hemorrhage. South Med J 76:85–86

Rivitz SM, Waltman AC, Kelsey PB (1996) Embolization of an hepatic artery pseudo-aneurysm following laparoscopic cholecystectomy. Cardiovasc Intervent Radiol 19:43–46

Roh LS, LeSher A (1989) Dissecting aneurysm of the hepatic artery. Am J Forensic Med Pathol 10:67–70

Rousselet MC, Kettani S, Rohmer V, Saint-André JP (1989) A case of temporal arteritis with intrahepatic arterial involvement. Pathol Res Pract 185:329–331

Ruszinko V, Kovacs M, Szonyi L, Verebely T, Willner P (2004) Cavernous transformation of the portal vein causing jaundice, presenting in the form of Wilson's disease. Acta Chir Belg 104:457–458

Safadi R, Sviri S, Eid A, Levensart P (1996) Gallbladder varices: a case report and review of the literature. Eur J Med Res 1:506–508

Saigh et al. 1985. http://www.ncbi.nlm.nih.gov/pubmed/3892039

Saint JH (1961) The epicholedochal venous plexus and its importance as a means of identifying the common bile duct during operations on the extrahepatic biliary tract. Br J Surg 48:489–498

Sajura A, Umekita N, Inoue S, Maeshiro T, Miyamoto S, Matsui Y, Asakage M, Kawahara Y, Kitamura M (2001) Benign biliary stricture associated with atherosclerosis. Hepato-Gastroenterology 48:81–82

Salazar JE, Moore SM, Murray IF (1984) Intrahepatic aneurysm: a rare cause of segmental biliary obstruction. J Can Assoc Radiol J 35:206–208

Sappey PC (1879) Traité d'anatomie descriptive Adrien Delahaye. Paris

Sappey PC. Quoted by: Kreider PG (1933) The anatomy of the veins of the gallbladder. Surg Gynecol Obstet 57:475–482

Sarin SK, Bhatia V, Makwane U (1992) Portal biliopathy in extrahepatic portal vein obstruction. Ind J Gastroenterol 2:A82

Satoh T (1989) Study of the anatomy of the venous drainage of the gallbladder (in Japanese). Tando 3:227–233

Schaible R, Textor J, Schepke M, Wolff M, Schild H, Kreft B (2002) MRI in cavernous transformation of the portal vein: secondary biliary abnormalities and portoportal collaterals (in German). Röfo 174:1408–1414

Seez P, Liehr H, Schott H, Lehmann W (1980) Cavernous transformation of the portal vein causing bile drainage disturbance (in German). Leber Magen Darm 10:274–276

Shanley CJ, Shah NL, Messina LM (1996) Common splanchnic artery aneurysms: splenic, hepatic, and celiac. Ann Vasc Surg 10:315–322

Shea WJ, Demas BE, Goldberg HI, Hohn DC, Ferrell LD, Kerlan RK (1986) Sclerosing cholangitis associated with hepatic arterial FUDR chemotherapy: radiographic-histologic correlation. AJR Am J Roentgenol 146:717–721

Shin SM, Kim S, Lee JW, Kim CW, Lee TH, Lee SH, Kim GH (2007) Biliary abnormalities associated with portal biliopathy: evaluation on MR cholangiography. AJR Am J Roentgenol 188:W341–W347

Shrikhande S, Friess H, Kleeff J, Tempia A, Zimmermann A, Borner M, Büchler MW (2002) Bile duct infarction following intraarterial hepatic chemotherapy mimicking multiple liver metastasis: report of a case and review of the literature. Dig Dis Sci 47:338–344

Silva MA, Jambulingam PS, Gunson BK, Mayer D, Buckels JA, Mirza DF, Bramhall SR (2006) Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience from a single centre in the United Kingdom. Liver Transpl 12:146–151

Sipahioglu MH, Tokgöz B, Karahan OI, Ok E, Sav T, Oymak O, Utas C (2005) Obstructive jaundice directly related to visceral artery aneurysm in a CAPD patient. Clin Nephrol 63:493–495

Smith AD, Mohammed F, Watson GM, Howlett DC (2002) Common bile duct compression by an abdominal aortic aneurysm: an unusual cause of biliary tract dilatation. Eur J Gastroenterol Hepatol 14:767–769

Song SY, Chung JW, Lim HG, Park JH (2006) Nonhepatic arteries originating from the hepatic arteries:

angiographic analysis in 250 patients. J Vasc Interv Radiol 17:461–469
Stambo GW, Guiney MJ, Cannella XF, Germain BF (2004) Coil embolization of multiple hepatic artery aneurysms in a patient with undiagnosed polyarteritis nodosa. J Vasc Surg 39:1122–1124
Stone WM, Abbas MA, Gloviczki P, Fowl RJ, Cherry KJ (2002) Celiac arterial aneurysms: a critical reappraisal of a rare entity. Arch Surg 137:670–674
Strunk H, Textor J, Remig J (2001) Intramural bile duct varicosis ("pseudo-cholangiocarcinoma sign") in computed tomography (in German). Röfo 173: 765–766
Sudoh M, Kishimoto Y, Marumoto A, Inoue M, Sano A, Miura N, Horie Y, Hasegawa J, Ryoke K (2004) A new animal model of continuous catheterization for investigating mechanisms of arteritis associated with chemotherapy. Life Sci 74:3025–3032
Sugita M, Ryu M, Satake M, Kinoshita T, Konishi M, Inoue K, Shimada H (2000) Intrahepatic inflow areas of the drainage vein of the gallbladder: analysis by angio-CT. Surgery 128:417–421
Taboga V, Braggion G, Marchesin G (1969) Colostasi da anomalia non nota dell'arteria epatica destra. Acta Chir Ital 15:491
Terada T, Takegoshi T, Doishita K, Nakanuma Y (1988) Histological study of intrahepatic cavernous transformation in a patient with primary myelofibrosis and portal venous thrombosis. Virchows Arch A Pathol Anat Histopathol 412:339–345
Terada T, Nakanuma Y, Matsushita E (1990) Mapping of cavernous vessels in the liver in an autopsy case of hepatocellular carcinoma in comparison with imaging figures. J Clin Gastroenterol 12:109–113
Thomas 1967. http://www.ncbi.nlm.nih.gov/pubmed/6067019
Tobben PJ, Zajko AB, Sumkin JH et al (1988) Pseudoaneurysms complicating organ transplantation: roles of CT, duplex sonography, and angiography. Radiology 169:65–70
Tokunaga M, Ohyama S, Nunobe S, Hiki N, Fukunaga T, Seto Y, Yamaguchi T (2007) Advanced gastric cancer with a duplicated hepatic artery: preoperative diagnostic value of multidetector-row computed tomography for surgical resection. Gastric Cancer 10:191–195
Tosun O, Sanlidilek U, Cetin H, Ozdemir O, Kurt A, Sakarya ME, Tas I (2007) Unusual congenital aortic anomaly with rare common celiamesenteric trunk variation: MR angiography and digital subtraction angiography findings. Cardiovasc Intervent Radiol 30:1061–1064
Trambert J, Reinitz E, Buchbinder S (1989) Ruptured hepatic artery aneurysms in a patient with systemic lupus erythematosus: case report. Cardiovasc Intervent Radiol 12:32–34
Tsakis AG, Gordon RD, Shaw BW, Iwatsuki S, Starzl TE (1985) Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. Transplantation 40:667–671
Tsuchiya R, Eto T, Harada N, Yamamoto K, Matsumoto T, Tsunoda T, Yamaguchi T, Noda T, Izawa K (1984) Compression of the common hepatic duct by the right hepatic artery in intrahepatic gallstones. World J Surg 8:321–326
Vaidya S, Dighe M, Kolokythas O, Dubinsky T (2007) Liver transplantation. Vascular complications. Ultrasound Q 23:239–253
Valente JF, Alonso MH, Weber FL, Hanto DW (1996) Late hepatic artery thrombosis in liver allograft recipients is associated with intrahepatic biliary necrosis. Transplantation 61:61–65
Varin OC, Varin DS, Houben GM, de Hemptinne B (2005) Obstructive jaundice caused by portal varicosis (in Dutch). Ned Tijdschr Geneeskd 149:2979–2981
Vellar ID (2001) Preliminary study of the anatomy of the venous drainage of the intrahepatic and extrahepatic bile ducts and its relevance to the practice of hepatobiliary surgery. ANZ J Surg 71:418–422
Viola S, Meyer M, Fabre M, Tounian P, Goddon R, Dechelotte P, Valayer J, Gruner M, Bernard O (1999) Ischemic necrosis of bile ducts complicating Schönlein-Henoch purpura. Gastroenterology 117:211–214
Vleggaar FP, Van Buuren HR, Lameris JS (1999) Bile duct lesions in portal vein thrombosis (in Dutch). Ned Tijdschr Geneeskd 143:2057–2062
Von Knorring J, Wasastjerna C (1976) Liver involvement in polymyalgia rheumatica. Scand J Rheumatol 5:197–204
Watanabe H, Matsumoto T, Maekawa T (1982) Filling defects at the hepatic hilum due to compression by the right hepatic artery in cholangiogram. Gastrointest Radiol 7:263–267
Watanabe Y, Dohke M, Ishimori T, Amoh Y, Okumura A, Oda K, Hayashi T, Hiyama A, Dodo Y (2000) Pseudoobstruction of the extrahepatic bile duct due to artifact from arterial pulsatile compression: a diagnostic pitfall of MR cholangiopancreatography. Radiology 214:856–860
Watanabe H, Iwase H, Sugitani M, Watanabe T (2005) Compression of the common bile duct by the posterosuperior pancreaticoduodenal artery: case report. Abdom Imaging 30:214–217
Wax JR, Blackstone J, Pinette MG, Cartin A (2001) Hepatic vascular calcification: an early second trimester sonographic feature of idiopathic infantile arterial calcinosis. Am J Obstet Gynecol 185:1267–1268
West et al. 1991. http://www.ncbi.nlm.nih.gov/pubmed/2006274
White et al. 1987. http://www.ncbi.nlm.nih.gov/pubmed/3805111
White LM, Wilson SR (1994) Hepatic arterial calcification: a potential pitfall in the sonographic diagnosis of intrahepatic biliary calculi. J Ultrasound Med 13:141–144
Whitehall J, Smith M, Altamirano L (2003) Idiopathic infantile arterial calcification: sonographic findings. J Clin Ultrasound 31:497–501

Widjaja A, Rosenthal H, Bleck J, Walter B, Gölkel C, Rademaker J, Holstein A, Gebel M, Manns MP (1999) Pitfall: a pseudotumor within the left liver lobe presenting with abdominal pain, jaundice and severe weight loss. Ultraschall Med 20:268–272

Williams SM, Burnett DA, Mazer MJ (1982) Radiographic demonstration of common bile duct varices. Gastrointest Radiol 7:69–70

Winchester DP, Seed RW, Bergan JJ, Conn J (1970) Jaundice, hemobilia, and hemoperitoneum. Consequences of rupture of hepatic artery aneurysm. Am J Surg 120:384–387

Wold LE, Baggenstoss AH (1949) Gastrointestinal lesions in periarteritis nodosa. Mayo Clin Proc 24:28–35

Wozney P, Zajko AB, Bron KM, Point S, Starzl TE (1986) Vascular complications after liver transplantation: a 5-year experience. AJR Am J Roentgenol 147: 657–663

Yamane T, Uchiyama K, Nakamura M, Ishii T, Kuroda H, Hata D, Koido S, Kato T, Fujise K, Tajiri H (2006) A case of extrahepatic portal vein aneurysm with the remarkably bent bile duct by its displacement (in Japanese). Nippon Shokakibyo Gakkai Zasshi 103:1067–1072

Yamazaki K (2004) Systemic lupus erythematosus with hepatic aneurysm, valsalva sinus aneurysm and associated polyangiitis: aneurysmal wall remodeling with dense fibrosis and calcification mediated by residual smooth muscle cells. Lupus 13:54–59

Yoshimitsu K, Honda H, Kaneko K, Kuriowa T, Irie H, Chijiiwa K, Takenaka K, Masuda K (1997) Anatomy and clinical importance of cholecystic venous drainage: helical CT observations during injection of contrast medium into the cholecystic artery. AJR Am J Roentgenol 169:505–510

Zachary K, Geier S, Pellecchia C, Irwin G (1986) Jaundice secondary to hepatic artery aneurysm: radiological appearance and clinical features. Am J Gastroenterol 81:295–298

Zielke K (1962) Beitrag zur Frage von Verlauf und Mündungsgebiet der Gallenblasenvenen. Acta Hepatosplen (Stuttgart) 9:33

Postcholecystectomy Changes, Biliary Tract Mineralizations, and Intrabiliary Foreign Bodies

146

Contents

Abstract

Following cholecystectomy, several postcholecystectomy changes can simulate biliary tract cancer. Postsurgery strictures associated with fibrosis or scarring may mimic desmoplastic cancers. Also cystic duct remnants, including cystic duct remnant mucocele and bilomas, can induce alterations that may resemble a neoplastic process. In addition, carcinoma can develop within a cystic duct remnant following cholecystectomy. Thickening of the bile duct walls mimicking a neoplastic process can be caused by duct calcifications. Causes of calcifications include infections, infestations, metabolic diseases, calcification of sludge balls, and limy bile syndrome. Stenosis and obstruction of large bile ducts can be induced by various types of foreign bodes. A distinct form of bile duct obstruction is biliary tract bezoar, including phytobezoar, food bezoar, trichobezoar, and fungal bezoars. Bezoars are mimicked by masses that consist of blood, pus, or necrotic tissue (pseudobezoars).

Postcholecystectomy Changes Simulating Biliary Tract Tumor

Introduction

The most important postcholecystectomy disorder complex is summarized under the term postcholecystectomy syndrome (PCS). PCS refers to the

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_146

persistence of gastrointestinal and hepatobiliary signs and symptoms after cholecystectomy. There are a multitude of biliary and non-biliary causes of PCS (Deziel 1994; Kumar and Pande 2001; Tsoraides et al. 2007; Filip et al. 2009; Girometti et al. 2010; Jaunoo et al. 2010; Schofer 2010). A review of 1.6 million cholecystectomies, from 1992 to 1999, demonstrated a 0.5 % incidence of bile duct injury.

Postcholecystectomy Bile Duct Strictures

Extrahepatic biliary tract strictures caused by fibrosis/scarring are a well-known complication after cholecystectomy-induced bile duct injury (Agarwal et al. 2008; Grönroos 2008; Vitale et al. 2008). In a recent overview (1991–2006) on 292 patients who were referred for postcholecystectomy problems, 199 had cholecystectomy-related injuries, and 93 had other pathologies. Sixty-seven patients had bile duct injuries (Amsterdam Academic Medical Center's classification, types B, C, and D), and 46 patients had bile duct strictures (Vitale et al. 2008). In 15–20 % of patients with postcholecystectomy biliary strictures, portal hypertension occurs (Agarwal et al. 2008). Inflammatory scarring may involve distal parts of the common bile duct and can cause sphincter of Oddi dysfunction. Apart from scar-induced stricture, inflammatory and fibrosing reactions around foreign bodies may cause biliary obstruction with obstructive jaundice; e.g., post-surgical granuloma of the common bile duct (Farkas et al. 1980) and suture material induces foreign body reaction (Das et al. 2010).

Postcholecystectomy Syndrome and Cystic Duct Remnant

There is considerable variability in regard to the junction of the cystic duct with the common bile duct. The cystic duct may insert anywhere along the course of the common bile duct from the porta hepatis to the duodenum, and before the junction, the cystic duct may descend for a considerable distance immediately adjacent and parallel to the right side or posterior to the common hepatic duct (Linder and Green 1964).

In a prospective sonographic study of 139 patients, the average diameter of the normal distal cystic duct was 1.8 mm. In 95 % of the patients, the distal cystic duct was located posterior to the common bile duct and, in 5 % of the patients, anterior to the common bile duct (Parulekar 1989). Postcholecystectomy syndrome (PCS) is a rather common condition in patients with cholecystectomy and presents with a heterogenous set of signs and symptoms, including upper abdominal pain, gastrointestinal disorders, vomiting, and eventually jaundice (Colp 1944; Twiss and Carter 1948; Gants 1953; Cavallaro et al. 2009; Girometti et al. 2010; Perera et al. 2011). PCS may be associated with stone disease, including remnant gallbladder lithiasis (Demetriades et al. 2008; Pernice and Andreoli 2009), remnant cystic duct calculi/lithiasis of long cystic duct remnant, and choledocholithiasis (Bystrovskaia and Orlova 2008).

The Cystic Duct Remnant and the Postcholecystectomy Syndrome

The cystic duct remnant (retained cystic duct stump; Stahl 1962; Mathews and Hiatt 1966) is defined as a residual cystic duct greater than 1 cm in length. In few situations of inadequate surgery, the cystic duct stump may be associated with retained parts of the distal gallbladder (gallbladder remnant; Shaw et al. 2004; Demetriades et al. 2008). In laparoscopic cholecystectomy (ERCP study, $N = 113$), the length of the stump was up to 1 cm, 1–2 cm, 2–3 cm, and more than 3 cm in length in 34.5 %, 36.3 %, 24.8 %, and 4.4 % of the patients, respectively (Keiler et al. 1992).

The remnant is readily identifiable by sonography (Crowley and Hedvall 1985), and it is known to be an etiologic factor for several postcholecystectomy disorders, including stone

development in the remnant (the most frequent complication; Zhou et al. 2003), scarring, intestinal adhesions, and traumatic neuroma (the latter being discussed in a separate chapter). The lesion pattern causes complex disorders known under diverse terms, including the so-called cystic duct syndrome/cystic duct stump syndrome and the postcholecystectomy syndrome (Garlock and Hurwitt 1951; Hangos 1958). The postcholecystectomy syndrome refers to a wide spectrum of conditions that may pose a challenging diagnostic dilemma (Shaw et al. 2004), and only part of the disorders are attributable to remnant duct stones (Palanivelu et al. 2009), others being dysfunction of the sphincter of Oddi and, in developmental countries, biliary ascariasis. The symptoms occurring after cholecystectomy are often attributed to a long residual cystic duct (the long cystic duct stump; Salzer 1962) that may favor the development of secondary changes (Larmi et al. 1975; Hopkins et al. 1979). How frequent is the cystic duct stump, and how frequently does the stump cause biliary symptoms? Among 54 symptomatic patients with previous cholecystectomy, a stump was found by use of ERCP in 56 % of the patients, with a mean length of 23 mm (Aärimaa and Mäkelä 1981). In a randomized study of 80 patients comparing standard cholecystectomy with a technique to remove the entire cystic duct, 37 % versus 85 % of the patients, respectively, were free of biliary symptoms during an 8-year period (Jonson et al. 1991), suggesting a pathogenic role of the stump. Cystic duct remnant causes pain, biliary dyskinesia, and sludge formation (the cystic duct remnant syndrome; Perera et al. 2011; Selvaggi et al. 2011). Cystic duct remnants may undergo cystic dilatation (Perera et al. 2011) and are prone to develop calculi (remnant lithiasis; stump stones; Palanivelu et al. 2009; Sahoo and Kumar 2013). As such, unrecognized lithiasis of the cystic duct may be a relatively common event that leaves its traces in the postcholecystectomy stump. In a study of 143 consecutive cholecystectomies, cystic duct lithiasis was detected in 14.4 % of patients (Sezeur and Akel 2011). The remnant can undergo mucus retention with formation of a mucocele (Chatterjee et al. 2011). The formation of sludge and stones in the cystic duct remnant has been documented by sonography (Parulekar 1989). A rare entity is cystic duct remnant-enteric fistulization. Calculous obstruction of the cystic duct remnant or the common bile duct must be present for fistulization to occur (Woods et al. 1992). A long cystic duct remnant with stone formation can cause Mirizzi syndrome (Wani et al. 2010).

Cystic Duct Remnant Mucocele

A rare cause of biliary obstruction after liver transplantation is a tension mucocele of the remnant of the allograft cystic duct. A blind donor cystic duct remnant undergoes distension with mucus and causes extrinsic compression of the common hepatic duct. At liver transplantation, if the biliary anastomosis is done at the level where the allograft cystic duct is contiguous to the common bile duct, the orifice of the cystic duct may be incorporated into the suture line of the anastomosis. As the donor gallbladder is removed, this procedure may create a closed (blind) cystic duct remnant (Koneru et al. 1989; Zajko et al. 1990). Other pathogenic factors include a compromised mucus outflow from the remnant due to contraction of connective tissue in Calot's triangle, ischemic duct damage, and lack of nervous regulation (Liang et al. 2007). This complication has chiefly been found in adult liver graft recipients (Koneru et al. 1989; Zajko et al. 1990; Abcarian et al. 1994; Liang et al. 2007), but has also been reported for the pediatric age group (Pariente et al. 1991; Ahlavat et al. 2008). Cystic duct remnant mucocele presents both as nonobstructive and obstructive lesion. In regard to the prevalence of the nonobstructive cases, an anechoic ovoidal structure just before the portal vein and in proximity of the main bile duct was found in 2–4.5 % of patients (Caputo et al. 1995, 2000). In a series of eight patients with this type of mucocele, all patients had clinical and/or laboratory evidence of biliary obstruction or cholangitis from 2 weeks to 3.3 years following transplantation (Zajko et al. 1990).

Cystic Duct Leaks and Biloma Formation

A subset of patients with postcholecystectomy syndrome have biliary leaks, the chief locations being the gallbladder bed, subhepatic space, right paracolic gutter, lesser sac, and diffusely peritoneal cavity. Cystic duct leaks (cystic duct stump leaks) appear to complicate laparoscopic cholecystectomy more often than open cholecystectomy (Himal 1996; Barkun et al. 1997). Among 207 consecutive patients with postcholecystectomy bile leak, the leak site was the cystic duct stump in 78 % (Sandha et al. 2004). In one systematic study, the leaks post-laparoscopy presented at a median of 4 days after intervention (Woods et al. 1994). In another study ($N = 64$), biliary obstruction was noted in 31 % of the patients, however, in two thirds associated with stones (Barkun et al. 1997). Bile leakage from the cystic stump may result from clip displacement (Hanazaki et al. 1999; Adjepong 2000). Bile draining from the leak may form bilomas, e.g., in the subphrenic space (Albasini et al. 1995) and sometimes forming a cystic mass up to almost 10 cm in size (Meshikhes et al. 2007). Leakage-induced fluid collections in the gallbladder fossa may with time (after years) be demarcated and may seldom communicate via the cystic duct stump with the common bile duct, producing what has been termed a phantom gallbladder (Xing et al. 2007).

Cystic Duct Fistula

Cystic duct fistula is a rare complication of cholecystectomy (Nelson 1984). The fistula can drain into the subhepatic space (Agrawal et al. 1979) or the gastrointestinal tract (Chandar and Hookman 1980; Woods et al. 1992; Abiad and Sidani 2000).

Cystic Duct Remnant Carcinoma

Carcinoma originating from a cystic duct remnant is a rare complication. These adenocarcinomas invade the bile duct system and extend along the common bile duct and cause biliary obstruction (Phillips and Estrin 1969; Dixon and Christensen 1971; Gabata et al. 2003; Noji et al. 2003; Eum et al. 2008).

Calcinosis and Related Conditions of the Biliary Tract

Bile Duct Calcifications in Infections and Infestations

In hepatobiliary tuberculosis, large "chalky" and nodular calcifications are seen along the extrahepatic ducts, in particular the common bile duct (Maglinte et al. 1988). Bile duct calcification is also known to occur in the context of schistosomiasis/bilharziasis (Radhakrishnan et al. 1988; Fataar et al. 1996), discussed in a separate chapter.

Bile Duct Calcifications in Metabolic Diseases

Calcification/mineralization may also involve the small intrahepatic bile ducts and/or the ductules. Ductular epithelial lining calcification has been observed in uremia and suggested to be a result of elevated serum calcium and phosphate (Kurumaya et al. 1989). Chronic renal failure may, via secondary hyperparathyroidism, also cause hepatic artery calcifications producing hilar calcium signals, but the hepatic artery is far less frequently involved than the abdominal aorta and the splenic artery (Okuda et al. 2002). Calcifications of smaller artery branches accompanying the portal vein or the bile ducts also occur (Okuda et al. 2003). Hepatic artery calcifications may be mistaken for biliary calculi (White and Wilson 1994). Bile duct calcifications have been observed in calcifying primary and secondary amyloidosis (Kennan and Evans 1991; Levine 1994; Jacobs et al. 1997; Korkmaz and Kebapci 2004).

Calcifying Sludge Balls

Bile sludge masses are a substrate for mineral crystal formation, rarely resulting in calcified

roundish masses or sludge balls (Feuerstein et al. 1990).

Limy Bile Syndrome

Limy bile syndrome (synonyms: calcium milk bile, milk of calcium bile) is a rare condition in which a radiopaque gallbladder and/or bile ducts are noted on plain roentgenograms, caused by the accumulation of a thick, paste-like material in the biliary tract. The disorder was first described in 1911 (Churchman 1911; he described the material as "calcium soap"), and in 1926, the term milk of calcium (in German: Kalkmilchgalle) was coined (Volkmann 1926), followed by the term limy bile in 1933 (Knutsson 1933). The syndrome is caused by excessive calcium carbonate precipitation in the bile and is usually associated with distal biliary tract obstruction and sometimes with parenteral nutrition, although the etiology of the precipitation of this calcium salt is not known (Le Genissel et al. 1967; Sudhakar Krishnan and Lim 1983; Lazzari et al. 1985; Fowler et al. 1993; Moreaux and Roux 1994; Ballas et al. 2005). The syndrome also occurs in the pediatric age group, including newborns (review of the literature: Eymeri et al. 1989). Atomic absorption spectrophotometry and crystallographic analysis by the X-ray powder diffraction method and infrared spectrometry have confirmed that calcium carbonate is the major constituent of limy bile, mostly in the form of aragonite, followed by calcite and vaterite (Saito et al. 1986). It has been suggested that gallbladder stasis may play a pathogenic role (Naryshkin et al. 1987). Limy bile syndrome can cause cholecystitis without obstruction at the neck of the gallbladder (limy bile cholecystitis; Churchman 1911; Gya et al. 1990). Apart from the gallbladder, calcium milk bile can accumulate in the extrahepatic bile duct, in particular the common bile duct, and can cause obstructive jaundice (Tsukamoto et al. 2003; Ballas et al. 2005; Sasaki et al. 2010), but most such cases, a double localization (i.e., gallbladder plus bile duct) is observed (Sava et al. 1988).

Differential Diagnosis of Bile Duct Calcifications

Calcification can ensue in cholangiocarcinomas, particularly in mucinous cholangiocellular carcinoma (Nagakura et al. 1999).

Bile Duct Stenosis Associated with Porcelain Gallbladder

Chronic cholecystitis with extensive calcification/mineralization of the gallbladder wall (porcelain gallbladder) may be associated with extensive pericystic fibrosis that can lead to fibrous encasement of stenosis of the extrahepatic bile ducts (Snajdauf et al. 2006).

Foreign Bodies in Bile Ducts

Introduction

Several types of foreign bodies can be dislodged into the bile duct via luminal transport, migrate into bile duct tissues, or be introduced in the setting of surgical procedures (Table 1). Non-inert foreign bodies typically induce an inflammatory foreign body-type reaction, followed by fibrosis and eventually fibrotic bile duct stricture/stenosis, in some patients mimicking malignancy.

Table 1 Types of foreign bodies in the biliary tract

Metal clips
Suture material
Fragments of stents, tubes, catheters, or duct prostheses
Gelfoam
Food components (such as fish bones)
Toothpicks
Bezoars
Textile components
Rubber bands
Combat-related foreign bodies

Metal Clips

Clip migration after a laparoscopic procedure was first reported in 1992 (Hemmi et al. 1992; Matsuura et al. 1992; Onghena et al. 1992), and clips usually migrate to the common bile duct, where they can cause obstruction and jaundice (Hemmi et al. 1992; Raoul et al. 1992; Dias and Dharmaratne 2012), but have been identified at the hepatic duct as well (Ahn et al. 2005). Cystic duct clip migration into the common bile duct was observed following cholecystectomy (Rowe and Nikfarjam 2012). Surgical clip migration into the common bile duct has also been found after orthotopic liver transplantation (Alsulaiman et al. 2006). The mechanism of clip migration is poorly understood and can occur from days to years after laparoscopic cholecystectomy. It may be suggested that, via induction of a foreign body reaction and similar to foreign bodies situated elsewhere, leukocyte- and/or infection-mediated tissue necrosis ensues, followed by liberation of the clip through a tissue gap into the duct lumen. Endoclip migration from the cystic stump to the common bile duct has also been observed for polymer endoclips (Kissmeyer-Nielsen and Kiil 2005).

Metal clips, subsequent to migration or in situ, can serve as a nidus for formation of common bile duct and other duct gallstones (called "clip stones" or "clipoliths"; Mansvelt et al. 1993; Brogdon et al. 1996; Ray and Bhattacharya 2013) after open or laparoscopic cholecystectomy (Walker et al. 1979; Wittenberg et al. 1985; Davis et al. 1988; Martinez et al. 1995; Muehlenberg und Löffler 1995; Alberts et al. 1999; Yoshizumi et al. 2000; Lee et al. 2003; Chong et al. 2004; Mouzas et al. 2005; Steffen et al. 2007), thus being one well-identifiable cause of iatrogenic biliary stone (Chong 2005). In these situations, clips can in fact be found as a constituent of the gallstones (Mansoa et al. 2000).

Suture Material

Suture material can elicit a foreign body reaction in the bile duct. In one case, this granuloma generated a mass of 1.5 cm diameter, mimicking Klatskin tumor (Uzcatequi-Paz and Gonzalez-Paredes 2009). In another patient, a stenosing foreign body granuloma (suture granuloma) developed 18 years after duodenal surgery, mimicking cholangiocarcinoma (Murphy et al. 1990). Common bile duct stones may develop around nonabsorbable suture/ligature threads, either in situ or around sutures that had migrated into the common bile duct, a complication already reported at the end of the nineteenth century (Homans 1897; Sigler and Sahler 1969; Orr 1980; Lewis and Urdaneta 1981; Fink and Budd 1983; Ormann 1989; Son et al. 1999; Fortun et al. 2005; Kim et al. 2007), and part of the migrating sutures took their origin at the cystic stump (Leborgne et al. 1981).

Other Intrabiliary Foreign Bodies

A wide array of foreign bodies not related to surgical maneuvers have been reported. They comprise, among others, stents, fragments of damaged and sometimes migrating stents (the so-called stent cholangitis; Figs. 1 and 2; Johanson et al. 1992; Manouras et al. 2007), T-tubes and catheters, migrating bile duct prostheses (Zapata Morcillo et al. 2006), elastic rubber bands (Ochiai et al. 2012), migrating Gelfoam (Riddle et al. 2008), dislocated/migrating food

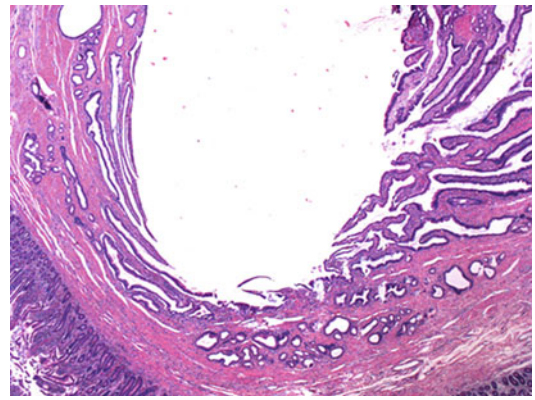

Fig. 1 Stent cholangitis in a biliodigestive anastomosis. Due to compression by the stent, the mucosa is flattened and partially atrophic (hematoxylin and eosin stain)

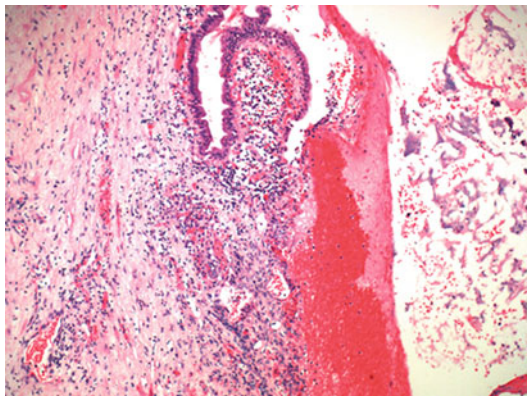

Fig. 2 Stent cholangitis. The stent (now removed) has damaged the bile duct mucosa and induced an ulcerating and fibrosing inflammation, eventually causing stenosis (hematoxylin and eosin stain)

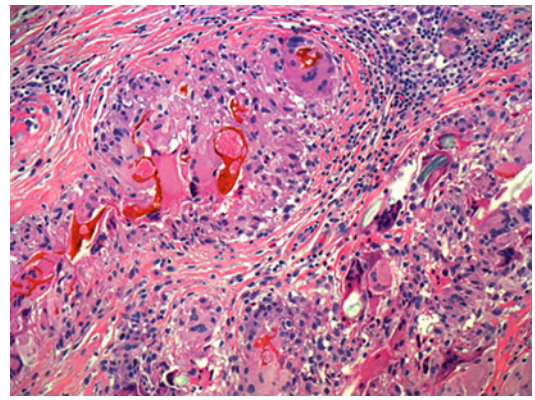

Fig. 4 Foreign body cholangitis. The *upper half* of the figure shows bile granulomas and the lower right corner granulomas with particulate foreign material (hematoxylin and eosin stain)

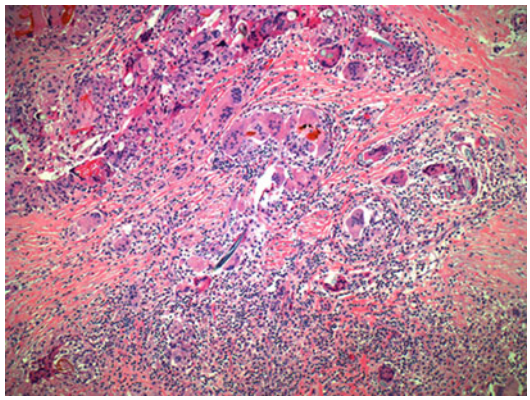

Fig. 3 Foreign body cholangitis. Several foreign body granulomas with multinucleated giant cells have accumulated in the mucosa (hematoxylin and eosin stain)

components (in particular fish bones, which may cause stone formation; Orda et al. 1986; Kaji et al. 2004; Kim et al. 2004; Patel et al. 2006), textile components (including obstructive textilomas; Cimsit et al. 2006), and combat-related foreign bodies, including bullets and shell splinters (Klein et al. 1981; Maheshwari et al. 2003; Kamona et al. 2005). Part of such foreign bodies may form the nidus of a stone, e.g., a T-tube fragment (Hoffman et al. 2008), a plastic biliary stent (Dokas et al. 2009), or a metal stent (Cheon et al. 2002). These foreign bodies can elicit a foreign body reaction (Figs. 3 and 4).

Biliary Tract Bezoars (Biliary Bezoars)

Bezoar (enterolith, gastrolith) is a concretion in the gastrointestinal tract caused by the intake of undigestible material such as plant fibers, hair, or constituents of tablets. The name stems from Arabic bazahr and Persian padzahr, meaning protecting against poison. The "stones" are frequently encountered in the GI tract of ruminants, including goats. Bezoar is then also the name of a goat (*Capra aegagrus*) which is a matriarchal candidate for ancestor of domestic goat (Takada et al. 1997). Bezoars can mineralize to become stonelike structures (bezoar stone, bezoardicum minerale). Such stones still have a certain value in traditional medicine, used as an antidote to poison. This action of bezoar was recorded by the famous French surgeon, Ambroise Paré (1510–1590), who performed a celebrated practical test with a bezoar stone which had been brought from Spain to Charles IX of France. Bezoar as a poison antidote was also used in Asia; Garcias ab Horto, a Portuguese physician of Goa, described a variety of bezoar called lapis malacensis (Malacca stone) found in the liver of a hedgehog and employed as an antidote for poisons in Malacca. A specimen was brought to Rome from Portugal by Cardinal Alexandrinus, and Mercato states that he had seen a test of its virtues as an antidote for poisons.

Table 2 Types of biliary tract bezoars

Phytobezoar (plant components)
Food bezoar
Trichobezoar (hair)
Mycotic bezoars (yeast bezoar, "fungal ball")
Pseudobezoars (hemobezoar; pyobezoar; necrobezoar; bezoars composed of blood clots, pus, or necrotic tissue)

Bile duct bezoars are composed of diverse materials (Table 2)

The formation of bile duct bezoars is a rare event, and these bodies usually occur in the common bile duct, particularly its distal segment. They have been detected in the context of choledochoenteric anastomosis (Siegel 1981), duodenal diverticulum (Armengol-Miro et al. 1977; Seyrig et al. 1989; van der Linde et al. 1997), postcholecystectomy choledochoduodenal fistula (Moghaddam et al. 2006), and clot bezoar after endoscopic sphincterotomy (Groth et al. 2006). Clinical manifestations are obstructive jaundice and cholangitis. In regard to constituents forming bezoars, the terminology and definitions are not consistently respected, in that bezoars should consist of ingested, albeit not necessarily foreign, material (e.g., foreign, phytobezoar; non-foreign, trichobezoar). Hence, "hemobezoars" (Groth et al. 2006) and "pyobezoars" are not true bezoars; otherwise compacted bile sludge and even gallstones would also be bezoars ("pseudobezoars"). The composition of biliary bezoars has been reported to be food components (food bezoar; Zuber-Jerger and Kullmann 2006), plant material (phytobezoar; Vitovec 1975; Malt 1979; Lamotte et al. 1995; Kim et al. 2006, 2013; Garlipp et al. 2012), fibrinoid material with cellular debris (Moghadaam et al. 2006), clumps of yeast (yeast bezoar; Perttala et al. 1975), and coagulated blood (hemobezoar; Groth et al. 2006). Interestingly, part of common bile duct gallstones may develop from bezoars. In a crystallographic investigation, foreign material was identified in part of gallstones, mainly suturing material (postcholecystectomy) and cellulose (Prochazka et al. 1999). Phytobezoar was reported to act as a nidus for gallstone formation (Cetta et al. 1993).

Foreign Material-Containing Gallstones

As already mentioned above, foreign material in the bile ducts can be a cause for cholelithiasis, the gallstone matter being deposited around a foreign body which acts as a nidus. In a study on 54 patients where gallstones were examined qualitatively using crystallographic analysis by X-ray powder diffraction and where foreign material was studied morphologically and by polarization microscopy, foreign material was detected in six patients (11.1 % of the cases), among which four had a history of previous cholecystectomy (Prochazka et al. 1999).

References

Aärimaa M, Mäkelä P (1981) The cystic duct stump and the postcholecystectomy syndrome. An analysis of 54 patients subjected to ERCP. Ann Chir Gynaecol 70:297–303

Abcarian PW, Emond JC, Ring EJ (1994) Cystic duct remnant mucocele in a liver transplant recipient. J Vasc Interv Radiol 5:127–130

Abiad F, Sidani M (2000) Biliary-colonic fistula through a cystic duct stump. Int Surg 85:231–233

Adjepong SE (2000) Bile leakage resulting from clip displacement of the cystic duct stump. Surg Endosc 14:96–97

Agarwal AK, Gupta V, Singh S, Agarwal S, Sakhuja P (2008) Management of patients of postcholecystectomy benign biliary stricture complicated by portal hypertension. Am J Surg 195:421–426

Agrawal RM, Mitre R, Brodmerkel GJ, Brooks DH (1979) The diagnosis of post-cholecystectomy cystic duct fistula utilizing endoscopic retrograde cholangiopancreatography. Endoscopy 11:193–196

Ahlawat SK, Fishbien TM, Haddad NG (2008) Cystic duct remnant mucocele in a liver transplant recipient. Pediatr Radiol 38:884–886

Ahn SI, Lee KY, Kim SJ, Cho EH, Choi SK, Hur YS, Cho YU, Hong KC et al (2005) Surgical clips found at the hepatic duct after laparoscopic cholecystectomy: a possible case of clip migration. Surg Laparosc Endosc Percutan Tech 15:279–282

Albasini JL, Aledo VS, Dexter SP, Marton J, Martin IG, McMahon MJ (1995) Bile leakage following laparoscopic cholecystectomy. Surg Endosc 9:1274–1278

Alberts MS, Fenoglio M, Ratzer E (1999) Recurrent common bile duct stones containing metallic clips following laparoscopic common bile duct exploration. J Laparoendosc Adv Surg Tech A 9:441–444

Alsulaiman R, Barkun J, Barkun A (2006) Surgical clip migration into the common bile duct after orthotopic liver transplantation. Gastrointest Endosc 64:833–834

Armengol-Miro JR, Villagrasa M, Formiguera J, Ramentol F, Prim P, Guardia J, Gomez JL (1977) Prepapillary intradiverticular bezoar as cause of obstructive jaundice. Removed by endoscopy. Endoscopy 9:247–249

Ballas KD, Alatsakis MB, Rafailidis SF, Psarras K, Sakadamis AK (2005) Limy bile syndrome: review of seven cases. ANZ J Surg 75:787–789

Barkun AN, Rezieg M, Mehta SN, Pavone E, Landry S, Barkun JS, Fried GM, Bret P, Cohen A (1997) Postcholecystectomy biliary leaks in the laparoscopic era: risk factors, presentation, and management. McGill Gallstone Treatment Group. Gastrointest Endosc 45:277–282

Brogdon BG, Neuffer FH, Siner JR (1996) Choledochal 'clipoliths' after cholecystectomy. South Med J 89:1111–1113

Bystrovskaia EV, Orlova IN (2008) Choledocholithiasis occurrence in postcholecystectomic syndrome (in Russian). Eksp Klin Gastroenterol 3:33–36

Caputo M, Spagnol A, Minguzzi MT, Papa S, Calculli L, Soro A, Grazi GL, Morganti M, Gavelli G (1995) Incidence of dilatation of residual cystic duct in liver transplantation. Our experience with 152 cases (in Italian). Radiol Med (Torino) 89:647–650

Caputo M, Piolanti M, Riccioli LA, Pazienza L, Fabbro E, Gruupioni F, Grazi G, Gavelli G (2000) Nonobstructive residual mucocele of the cystic duct. Reassessment of complications in our 13 years' experience with liver transplantation (in Italian). Radiol Med (Torino) 100:354–356

Cavallaro A, Cavallaro V, Trainiti M, Licciardello A, Cappellani A (2009) Post cholecystectomy syndrome: an out of date topic? Ann Ital Chir 80:403–406

Cetta F, Lombardo F, Rossi S (1993) Large foreign body as a nidus for a common duct stone in a patient without spontaneous biliary enteric fistula or previous abdominal surgery. HPB Surg 6:235–242

Chandar VP, Hookman P (1980) Choledochocolonic fistula through a cystic duct remnant. A case report. Am J Gastroenterol 74:179–181

Chatterjee S, Das D, Hudson M, Bassendine MF, Scott J, Oppong KE, Sen G, French JJ (2011) Mucocele of the cystic duct remnant after orthotopic liver transplant: a problem revisited. Exp Clin Transplant 9:214–216

Cheon YK, Moon JH, Cho YD, Kim YS, Lee MS, Shim CS (2002) Biliary metal stent as a nidus for bile duct stone. Korean J Intern Med 17:57–60

Chong VH (2005) Iatrogenic biliary stone. Surg Technol Int 14:147–155

Chong VH, Yim HB, Lim CC (2004) Clip-induced biliary stone. Singapore Med J 45:533–535

Churchman JW (1911) Acute cholecystitis with large amount of calcium soap in gall bladder. Bull Johns Hopkins Hosp 22:223–224

Cimsit B, Keskin M, Ozden I, Alper A (2006) Obstructive jaundice due to a textiloma mimicking a common bile duct stone. J Hepatobiliary Pancreat Surg 13:172–173

Colp R (1944) The postcholecystectomy syndrome and its treatment. Bull N Y Acad Med 20:203–219

Crowley SF, Hedvall SE (1985) Cystic duct remnant: sonographic diagnosis. J Ultrasound Med 4:261–263

Das K, Basu K, Ray S, Chatterjee S (2010) Suture material in the common bile duct casing recurrent postcholecystectomy pain. Endoscopy 42(Suppl 2):E258

Davis M, Hart B, Kleinman R (1988) Obstructive jaundice from open vessel clip. Gastrointest Radiol 13:259–260

Demetriades H, Pramateftakis MG, Kanellos I, Angelopoulos S, Mantzoros I, Betsis D (2008) Retained gallbladder remnant after laparoscopic cholecystectomy. J Laparoendosc Adv Surg Tech A 18:276–279

Deziel DJ (1994) Complications of cholecystectomy. Incidence, clinical manifestations, and diagnosis. Surg Clin North Am 74:809–823

Dias R, Dharmaratne P (2012) Ingested foreign body in the common bile duct. J Indian Assoc Pediatr Surg 17:31–32

Dixon JA, Christensen C (1971) Primary adenocarcinoma in cystic duct remnants. Am J Surg 121:610–611

Dokas S, Kalampakas A, Delivorias P, Sion M, Tsitouridis I (2009) Removal of a large stone growing around and encasing a plastic biliary stent: respect the ductal axis. Dig Liver Dis 41:319–321

Eum JS, Kim GH, Park CH, Kang DH, Song GA (2008) A remnant cystic duct cancer presenting as a duodenal submucosal tumor. Gastrointest Endosc 67:975–976

Eymeri JC, Hugon N, Jouanelle A, De Lagausie P, Rival JM (1989) The limy bile syndrome in newborn infants. Apropos of a case (in French). Chir Pediatr 30:209–212

Farkas I, Patko A, Kövari M (1980) Obstructive jaundice caused by postsurgical granuloma of the common bile duct. Endoscopy 12:250–253

Fataar S, al Ansari AG, Bassiony H, Satyanath S, Rudwan M (1996) Case report: calcified pancreas and bile ducts from schistosomiasis. Br J Radiol 69:1064–1066

Feuerstein IM, Shawker TH, Savarese DM (1990) CT demonstration of calcifying sludge balls. J Comput Assist Tomogr 14:325–326

Filip M, Saftoiu A, Popescu C, Gheonea DI, Iordache S, Sandulescu L, Ciurea T (2009) Postcholecystectomy syndrome – an algorithmic approach. J Gastrointest Liver Dis 18:67–71

Fink DL, Budd DC (1983) Chromic suture material as a nidus for common duct stone formation. Int Surg 68:151–152

Fortun P, Anagnostopoulos G, Laurence B (2005) Suture material as a nidus for common bile duct stones: taking a closer look. N Z Med J 118:U1318

Fowler CL, Soriano H, Ferry GD, Margraf LR, Harberg FJ (1993) Limy bile syndrome. J Pediatr Surg 28:1568–1569

Gabata T, Matsui O, Sanada J, Kadova M, Ohmura K, Minato H (2003) Cystic duct remnant carcinoma with widespread invasion along the extrahepatic bile duct wall: dynamic CT findings. Abdom Imaging 28:79–82

Gants RT (1953) Postcholecystectomy syndrome. US Armed Forces Med J 4:1457–1462

Garlipp B, Schulz HU, Böttcher S, Lemke A, Meyer F, Lippert H (2012) Phytobezoar in the common hepatic duct – rare cause of obstructive jaundice following pancreatoduodenectomy: case report and review of the literature (in German). Z Gastroenterol 50:1166–1170

Garlock JH, Hurwitt ES (1951) The cystic duct stump syndrome. Surgery 29:833–841

Girometti R, Brondani G, Cereser L, Como G, Del Pin M, Bazzocchi M, Zuiani C (2010) Post-cholecystectomy syndrome: spectrum of biliary findings at magnetic resonance cholangiopancreatography. Br J Radiol 83:351–361

Grönroos JM (2008) Endoscopic management of postcholecystectomy bile duct strictures. J Am Coll Surg 207:786–787

Groth S, Seewald S, Leong AT, Omar S, de Weerth A, Thonke F, Soehendra N (2006) Postendoscopic sphincterotomy hemobezoar (with video). Gastrointest Endosc 63:715

Gya D, Sali A, Vitetta L, Eu P, Arkles B (1990) Limy bile cholecystitis: an in vitro study and a case report. Aust N Z J Surg 60:998–1000

Hanazaki K, Igarashi J, Sodeyama H, Matsuda Y (1999) Bile leakage from clip displacement of the cystic duct stump: a potential pitfall of laparoscopic cholecystectomy. Surg Endosc 13:168–171

Hangos G (1958) Cystic duct stump syndrome (in German). Zentralbl Chir 83:1434–1436

Hemmi P, Diaz D, Steffen A, Othoniel J, Michel A, Dauverchain J (1992) Late jaundice after cholecystectomy by laparoscopy, caused by a endo-choledochal clip (in French). Gastroenterol Clin Biol 16:725–726

Himal HS (1996) The role of ERCP in laparoscopic cholecystectomy-related cystic duct stump leaks. Surg Endosc 10:653–655

Hoffman A, Kiesslich R, Galle PR, Neurath MF (2008) A 9-year retained T-tube fragment encased within a stone as a rare cause of jaundice. Z Gastroenterol 46:700–703

Homans J (1897) Gall-stones formed around silk sutures, twenty months after recovery from cholecystectomy. Ann Surg 26:114–116

Hopkins SF, Bivins BA, Griffen WO (1979) The problem of the cystic duct remnant. Surg Gynecol Obstet 148:531–533

Jacobs JE, Birnbaum BA, Furth EE (1997) Abdominal visceral calcification in primary amyloidosis: CT findings. Abdom Imaging 22:519–521

Jaunoo SS, Mohandas S, Almond LM (2010) Postcholecystectomy syndrome (PCS). Int J Surg 8:15–17

Johanson JF, Schmalz MJ, Geenen JE (1992) Incidence and risk factors for biliary and pancreatic stent migration. Gastrointest Endosc 38:341–346

Jonson G, Nilsson DM, Nilsson T (1991) Cystic duct remnants and biliary symptoms after cholecystectomy. A randomized comparison of two operative techniques. Eur J Surg 157:583–586

Kaji H, Asano N, Tamura H, Yuh I (2004) Common bile duct stone caused by a fish bone: report of a case. Surg Today 34:268–271

Kamona A, Mansour A, Qandeel M, Al-Eshaiker M (2005) Biliary obstruction secondary to combat-related foreign bodies: report of two cases. Abdom Imaging 30:748–749

Keiler A, Pernegger C, Hornof R, Wenzl S, Brandtner W (1992) The cystic stump after laparoscopic cholecystectomy (in German). Wien Klein Wochenschr 104:356–359

Kennan NM, Evans C (1991) Case report: hepatic and splenic calcification due to amyloid. Clin Radiol 44:60–61

Kim YH, Kim YJ, Park WK, Lee SK, Kwon JH, Woo SK (2004) Fish bone as a nidus for stone formation in the common bile duct: report of two cases. Korean J Radiol 5:210–213

Kim TO, Lee SH, Kim GH, Heo J, Kang DH, Song GA, Lee JW, Cho M (2006) Common bile duct stone caused by a phytobezoar. Gastrointest Endosc 63:324

Kim KH, Jang BI, Kim TN (2007) A common bile duct stone formed by suture material after open cholecystectomy. Korean J Intern Med 22:279–282

Kim Y, Park BJ, Kim MJ, Sung DJ, Kim DS, Yu YD, Lee JH (2013) Biliary phytobezoar resulting in intestinal obstruction. World J Gastroenterol 19:133–136

Kissmeyer-Nielsen P, Kiil J (2005) Endoclip on the cystic duct after laparoscopic cholecystectomy (in Danish). Ugeskr Laeger 167:2657–2658

Klein E, Schneebaum S, Feuchtwanger MM, Strauss S, Ben-Ari G (1981) Shell splinter in the common bile duct: a rare cause of obstructive jaundice. Am J Surg 141:376–377

Knutsson F (1933) On limy bile. Acta Radiol 14:453–462

Koneru B, Zajko AB, Sher L, Marsh JW, Tzakis AG, Iwatsuki S, Starzl TE (1989) Obstructing mucocele of the cystic duct after transplantation of the liver. Surg Gynecol Obstet 168:394–396

Korkmaz C, Kebapci M (2004) Addison's disease associated with widespread abdomino-pelvic visceral calcification due to secondary amyloidosis: a case report. Acta Radiol 45:800–802

Kumar V, Pande GK (2001) Complications of cholecystectomy in the era of laparoscopic surgery. Trop Gastroenterol 22:72–79

Kurumaya H, Yoshida K, Kono N, Nakanuma Y, Takeda S, Oiko Y (1989) Hepatic calcification in proliferated bile ductules in a uremic patient. Arch Pathol Lab Med 113:411–413

Lamotte M, Kochx M, Hautekeete M, Holvoet J, Hubens H (1995) Biliary phytobezoar: a medical curiosity. Am J Gastroenterol 90:1346–1348

Larmi TK, Mokka R, Kemppainen P, Seppälä A (1975) A critical analysis of the cystic duct remnant. Surg Gynecol Obstet 141:48–52

Lazzari G, Giorgi G, Gramellini F, Biscarini R (1985) A case of calcium milk bile. Echoradiographic aspects (in Italian). Radiol Med (Torino) 71:258–261

Le Genissel M, Lecomte P, Benejam Y, Vedel JP, Commandre F (1967) Limy bile (in French). Arch Fr App Dig 56:877–878

Leborgne J, Basque Y, Horeau JH, Sudry P, Le Neel JC (1981) Common bile duct stone formation on migrating ligature threads. A report on three cases (in French). J Chir (Paris) 118:343–347

Lee KW, Lee JW, Jeoung S, Jung BJ, Lee DH, Kim PS, Kim HG, Kim YS, Choi SK (2003) A case of common bile duct stone formed around a surgical clip after laparoscopic cholecystectomy. Korean J Gastroenterol 42:347–350

Levine E (1994) Abdominal visceral calcification in secondary amyloidosis: CT findings. Abdom Imaging 19:554–555

Lewis JW, Urdaneta LF (1981) Stone formation on silk suture after choledochoduodenostomy. South Med J 74:1280–1281

Liang TB, Zhao ZC, Jia CK, Zheng SS (2007) Mucocele formation of cystic bile duct remnant after orthotopic liver transplantation. Chin Med J 120: 254–256

Linder HH, Green RB (1964) Embryology and surgical anatomy of the extrahepatic biliary tree. Surg Clin North Am 44:1273–1285

Maglinte DD, Alvarez SZ, Ng AC, Lapena JL (1988) Patterns of calcifications and cholangiographic findings in hepatobiliary tuberculosis. Gastrointest Radiol 13:331–335

Maheshwari M, Chawla A, Dalvi A, Thapar P, Raut A (2003) Bullet in the common hepatic duct: a cause of obstructive jaundice. Clin Radiol 58:334–335

Malt RA (1979) Obstructing phytobezoar of an intrahepatic bile duct. Arch Surg 114:86–87

Manouras A, Archodovassilis F, Lagoudianakis EE, Tsekouras D, Genetzakis M, Pararas N et al (2007) Vertical rotation and impaction to the choledochal duct of a migrated biliary self-expanding metal stent. Surg Laparosc Endosc 17:416–417

Mansoa A, Martins A, Brito E, Melo M, Coito P (2000) Surgical clips as a nidus for stone formation in the common bile duct. Surg Endosc 14:1189

Mansvelt B, Harb J, Farkas B, Mourou M, Huguet C (1993) "Clip-stone" filiation within the biliary tract. HPB Surg 6:185–188

Martinez J, Combs W, Brady PG (1995) Surgical clips as a nidus for biliary stone formation: diagnosis and therapy. Am J Gastroenterol 90:1521–1524

Mathews RM, Hiatt WS (1966) Under the biliary tree: the cystic duct stump. J Kans Med Soc 67:583–588

Matsuura et al. 1992. http://www.ncbi.nlm.nih.gov/pubmed/1353215

Meshikhes AW, AbulRahi A, Al-Momen SA, Al-Safran Z, Al-Daolah QH (2007) An unusual bile collection after postcholecystectomy bile leakage. Surg Laparosc Endosc Percutan Tech 17:138–140

Moghaddam JA, Amini M, Adibnejad S (2006) Development of bile duct bezoars following cholecystectomy caused by choledochoduodenal fistula formation: a case report. BMC Gastroenterol 6:1

Moreaux J, Roux JM (1994) Limy bile. A surgical experience in 16 patients. Gastroenterol Clin Biol 18:550–555

Mouzas IA, Petrakis I, Vardas E, Kogerakis N, Skordilis P, Prassopoulos P (2005) Bile leakage presenting as acute abdomen due to a stone created around a migrated surgical clip. Med Sci Monit 11: CS16–CS18

Muehlenberg K, Löffler A (1995) Clip migration in the common bile duct and consecutive calculus formation after laparoscopic cholecystectomy (in German). Z Gastroenterol 33:108–111

Murphy JR, Shay SS, Moses FM, Braxton J, Jacques DP, Wong RK (1990) Suture granuloma masquerading as malignancy of the biliary tract. Dig Dis Sci 35:1176–1179

Nagakura S, Shirai Y, Yamai K, Hatakeyama K (1999) Calcification in mucinous cholangiocellular carcinoma. Hepatogastroenterology 46:465–466

Naryshkin S, Trotman BW, Raffensperger EC (1987) Milk of calcium bile. Evidence that gallbladder stasis is a key factor. Dig Dis Sci 32:1051–1055

Nelson AM (1984) Cystic duct fistula: a complication of cholecystectomy. Am J Gastroenterol 79:479–481

Noji T, Kondo S, Hirano S, Ambo Y, Tanaka E, Okushiba S, Katoh H (2003) Carcinoma of the cystic duct remnant with direct colonic invasion. Int J Gastrointest Cancer 34:117–120

Ochiai T, Yamamoto Y, Otsuji E (2012) Elastic rubber band migration into the common bile duct after C-tube drainage. J Gastrointest Surg 16:2343

Okuda K, Kobayashi S, Hayashi H, Ohtake H, Nakajima Y, Yoshida K, Kashima H, Irie Y (2002) Case-control study of calcification of the hepatic artery in chronic hemodialysis patients: comparison with the abdominal aorta and splenic artery. J Gastroenterol Hepatol 17:91–95

Okuda K, Kobayashi S, Hayashi H, Nakajima K, Ohtake Y, Yoshida H, Kashima T, Irie Y (2003) Sonographic features of hepatic artery calcification in chronic renal failure. Acta Radiol 44:151–153

Onghena T, Vereecken L, Dwey K, Loon C (1992) Common bile duct foreign body: an unusual case. Surg Laparosc Endosc 2:8–10

Orda R, Leviav A, Ratan I, Stadler J, Wiznitzer T (1986) Common bile duct stone caused by a foreign body. J Clin Gastroenterol 8:466–468

Ormann W (1989) A thread as a nidus of a common bile duct calculus: findings during endoscopic lithotripsy. Endoscopy 21:191–192

Orr KB (1980) Suture material as a nidus for formation of common bile duct stones. Aust N Z J Surg 50:493–494

Palanivelu C, Rangarajan M, Jategaonkar PA, Madankumar MV, Anand NV (2009) Laparoscopic management of remnant cystic duct calculi: a retrospective study. Ann R Coll Surg Engl 91:25–29

Pariente D, Bihet MH, Tammam S, Riou JY, Bernard O, Devictor D, Gauthier F, Houssin D, Chaumont P (1991) Biliary complications after transplantation in children: role of imaging modalities. Pediatr Radiol 21:175–178

Parulekar SG (1989) Sonography of the distal cystic duct. J Ultrasound Med 8:367–373

Patel VM, Barai RS, Thomas PR (2006) A wandering fish bone. Postgrad Med J 82:e9

Perera E, Bhatt S, Dogra VS (2011) Cystic duct remnant syndrome. J Clin Imaging Sci 1:2

Pernice LM, Andreoli F (2009) Laparoscopic treatment of stone recurrence in a gallbladder remnant: report of an additional case and literature review. J Gastronintest Surg 13:2084–2091

Perttala Y, Peltokallio P, leiviskä T, Sipponen J (1975) Yeast bezoar formation following gastric surgery. Am J Roentgenol Radium Ther Nucl Med 125:365–373

Phillips SJ, Estrin J (1969) Primary adenocarcinoma in a cystic duct stump. Report of a case and review of the literature. Arch Surg 98:225–227

Prochazka V, Krausova D, Kod'ousek R, Zamecnikova P (1999) Foreign material as a cause of choledocholithiasis. Endoscopy 31:383–385

Radakrishnan S, al Nakib B, Sivanandan R, Menon NK (1988) Hepatosplenic and small bowel calcification due to Schistosoma mansoni infection. Dig Dis Sci 33:1637–1640

Raoul JL, Bretagne JF, Siproudhis L, Heresbach D, Campion JP, Gosselin M (1992) Cystic duct clip migration into the common bile duct: a complication of laparoscopic cholecystectomy treated by endoscopic biliary sphincterotomy. Gastrointest Endosc 38:608–611

Ray S, Bhattacharya SP (2013) Endoclip migration into the common bile duct with stone formation: a rare complication after laparoscopic cholecystectomy. JSLS 17:330–332

Riddle C, Ahmed B, Doyle J, Connolly BL (2008) Migration of Gelfoam to the gallbladder after liver biopsy. Pediatr Radiol 38:806–809

Rowe D, Nikfarjam M (2012) Cystic duct clip migration into the common bile duct. Indian J Gastroenterol 31:86

Sahoo MR, Kumar A (2013) Stump stone 6 years after cholecystectomy: a possibility. BMJ Case Rep 2013. pii: bcr2012007957

Saito K, Omori H, Kanno S, Hirata Y, Okada T, Mori S, Nakadate K (1986) Chemical and crystallographic studies on 33 cases of calcium carbonate gallstone (so-called limy bile). Gastroenterol Jpn 21:162–166

Salzer G (1962) The long cystic duct stump, a cause of postcholecystectomy syndrome (in German). Langenbecks Arch Klin Chir Verh Dtsch Z Chir 299:560–566

Sandha GS, Bourke MJ, Haber GB, Kortan PP (2004) Endoscopic therapy for bile leak based on a new classification: results in 207 patients. Gastrointest Endosc 60:567–575

Sasaki T, Kato D, Matsuoka N, Yamashita Y (2010) Limy bile syndrome complicated by obstructive jaundice. Int Surg 95:49–53

Sava G, Millot P, Becmeur F, Vaxman F, Grenier JF (1988) Limy bile syndrome. Study of a case with double localization in the gallbladder and common bile duct (in French). Gastroenterol Clin Biol 12:156–159

Schofer JH (2010) Biliary causes of postcholecystectomy syndrome. J Emerg Med 39:406–410

Selvaggi F, Di Bartolomeo N, De Iuliis I, Del Ciotto N, Innocenti P (2011) Laparoscopic treated so-called reformed gallbladder in patient with postcholecystectomy chronic pain. G Chir 32:335–337

Seyrig JA, Chambon J, Fritsch J, Berger M, Liguory C, Chousterman M (1989) Cholestasis caused by an intradiverticular bezoar. Endoscopic treatment. Gastroenterol Clin Biol 13:741–743

Sezeur A, Akel K (2011) Cystic duct remnant calculi after cholecystectomy. J Visc Surg 148:e287–e290

Shaw C, O'Hanlon DM, Fenlon HM, McEntee GP (2004) Cystic duct remnant and the 'post-cholecystectomy syndrome'. Hepatogastroenterology 51:36–38

Siegel JH (1981) Biliary bezoar: the sump syndrome and choledochoenterostomy. Endoscopy 14:238–240

Sigler L, Sahler CO (1969) Silk: the nidus of a common bile duct calculus. Surgery 65:276–279

Snajdauf J, Petru O, Pycha K, Rygl M, Kalousova J, Keil R, Kodet R (2006) Porcelain gallbladder with extrahepatic bile duct obstruction in a child. Pediatr Surg Int 22:293–296

Son JM, Kim DI, Lee HJ, Mjung SJ, Kim HJ, Park ET, Lim BC, Yoo KS, Seo DW et al (1999) Suture material as a nidus of a common bile duct stone. Korean J Gastrointest Endosc 19:S198–S102

Stahl WM (1962) Retained cystic duct stump. Conn Med 26:377–380

Steffen M, Kronsbein H, Wesche L (2007) Metal clip as a nidus for formation of common bile duct stone following laparoscopic cholecystectomy. Z Gastroenterol 45:317–319

Sudhakar Krishnan MM, Lim KH (1983) "Limy bile" – case report and review of literature. Singapore Med J 24:374–376

Takada T, Kikkawa Y, Yonekawa H, Kawakami S, Amano T (1997) Bezoar (*Capra aegagrus*) is a matriarchal candidate for ancestor of domestic goat (*Capra hircus*): evidence from the mitochondrial DNA diversity. Biochem Genet 35:315–326

Tsoraides SS, Cha AI, Crawford DL (2007) Postcholecystectomy biliary symptoms. J Surg Educ 64:228–233

Tsukamoto T, Ohta Y, Shuto T, Hirohashi K, Kubo S, Tanaka H, Takemura S, Kinoshita H (2003) Limy bile: a case of obstructive jaundice and review of 26 cases. Osaka City Med J 49:67–70

Twiss JR, Carter RF (1948) The diagnosis and management of the postcholecystectomy syndrome. N Y State J Med 48:2245–2251

Uzcatequi-Paz E, Gonzalez-Paredes G (2009) Foreign body granuloma simulating malignant disease in the biliary tract (in Spanish). Gastroenterol Hepatol 32:32–35

Van der Linde K, van der Linden GH, Beukers R, Cleophas AJ (1997) Food impaction in a duodenal diverticulum as an unusual cause of biliary obstruction: case reports and review of the literature. Eur J Gastroenterol Hepatol 9:635–639

Vitale GC, Tran TC, Davis BR, Vitale M, Vitale D, Larson G (2008) Endoscopic management of postcholecystectomy bile duct strictures. J Am Coll Surg 206:918–923

Vitovec J (1975) A phytobezoar in the choledochous duct (in German). Rofo 123:593–594

Volkmann J (1926) Ueber Kalkmilchgalle. München Med Wochenschr 73:2014–2015

Walker WE, Avant GR, Reynolds VH (1979) Cholangitis with a silver lining. Arch Surg 114:214–215

Wani NA, Khan NA, Shah AI, Khan AQ (2010) Post-cholecystectomy Mirizzi's syndrome: magnetic resonance cholangiopancreatography demonstration. Saudi J Gastroenterol 16:295–298

White LM, Wilson ST (1994) Hepatic artery calcification: a potential pitfall in the sonographic diagnosis of intrahepatic biliary calculi. J Ultrasound Med 13:141

Wittenberg H, Freise J, Meyer HJ, Then P (1985) Gallstone formation following transmural migration of a surgical clip in the bile ducts. Case report (in German). Z Gastroenterol 23:139–142

Woods MS, Farha GJ, Street DE (1992) Cystic duct remnant fistulization to the gastrointestinal tract. Surgery 111:101–104

Woods MS, Shellito JL, Santoscoy GS, Hagan RC, Kilgore WR, Traverso LW, Kozarek RA, Brandabur JJ (1994) Cystic duct leaks in laparoscopic cholecystectomy. Am J Surg 168:560–563

Xing J, Rochester J, Messer CK, Reiter BP, Korsten MA (2007) A phantom gallbladder on endoscopic retrograde cholangiopancreatography. World J Gastroenterol 13:6274–6276

Yoshizumi T, Ikeda T, Shimizu T, Ohta S, Nagata S, Sonoda T, Sugimachi K (2000) Clip migration causes choledocholithiasis after laparoscopic cholecystectomy. Surg Endosc 14:1188

Zajko AB, Bennett MJ, Campbell WL, Koneru B (1990) Mucocele of the cystic duct remnant in eight liver transplant recipients: findings at cholangiography, CT, and US. Radiology 177:691–693

Zapata Morcillo E, Cosme Jimenez A, Arriola Manchola JA, Loyola Echaniz F et al (2006) Proximal migration of a distal common bile duct prosthesis to the left hepatic duct (in Spanish). Gastroenterol Hepatol 29:377–378

Zhou PH, Liu FL, Yao LQ, Qin XY (2003) Endoscopic diagnosis and treatment of post-cholecystectomy syndrome. Hepatobiliary Pancreat Dis Int 2: 117–120

Zuber-Jerger I, Kullmann F (2006) Prevention of food bezoar in the common bile duct by endoscopic stenting. Dig Liver Dis 38:529–530

Part XXIX

Tumors and Pseudotumors of the Gallbladder

Adenocarcinoma of the Gallbladder (Classical Gallbladder Cancer) 147

ICD-O code 8140/3 (intestinal type; 8144/3)

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_147

Abstract

Ordinary gallbladder carcinoma (adenocarcinoma) develops in a gallbladder that has undergone secondary changes, often due to long-standing cholelithiasis and associated alterations. Gallbladder carcinoma is detected in about 2–3 % of all cholecystectomy samples and accounts to approximately 60 % of all cancers of the extrahepatic biliary system. The neoplasm can be associated with epithelial precursor lesions and presents with various macroscopic growth patterns. Part of the tumors show, similar to cholangiocarcinomas, a marked desmoplastic stromal reaction and cause a circumscribed or diffuse thickening of the gallbladder wall. Other tumors grow a nodular lesion, sometimes large and obstructing the gallbladder lumen, or present in the form of polyps that grow into the lumen. Histologically, most of the neoplasms are glandular adenocarcinomas with various levels of cellular differentiation. The tumors can grow through the gallbladder wall, show perineural invasion, extend into the gallbladder bed, and invade, depending on stage, into the liver and adjacent organs.

Introduction

In the WHO classification of tumors, carcinoma of the gallbladder (CG) is defined as a malignant neoplasm, usually with biliary, intestinal, foveolar, or squamous differentiation, arising in the gallbladder (Alobores-Saavedra et al. 2010). In most cases, CG develops in an orthotopic gallbladder that may have undergone secondary changes, often due to long-standing cholelithiasis and associated alterations. Rarely, CG develops in gallbladder remnants after incomplete gallbladder resection (Cowley and Wood 1964; Tanga et al. 1973). In the present chapter, emphasis is placed in adenocarcinomas of the gallbladder, special types such as mucinous and squamous cell carcinomas being treated in another chapter. Carcinoma of the gallbladder and its relationship with gallstone disease and chronic cholecystitis have been studied since long.

Selected References: Beadles (1897), Musser (1889), Thomas and Nocia (1896), Warthin (1900), Treutlein (1901), Friedheim (1904), Proescher (1907), Riedel (1911), Smithies (1919), Magoun and Renshaw (1921), Deaver (1924), Lentze (1926), Luelsdorf (1927), Judd and Baumgartner (1929), Rolleston and McNee (1929), Finsterer (1932), Judd and Gray (1932), Seide and Geller (1933), Aiga (1935), Erdmann (1935), Boyce and McFetridge (1936), Cooper (1937), Jankelson (1937), Hochberg and Kogut (1939), Liebowitz (1939–1940), Mohardt (1939), Lam (1940), Lichtenstein and Tannenbaum (1940), Campbell (1941), Kirshbaum and Kozoll (1941), Greenlee et al. (1941), Warren and Balch (1940), Mattson (1942), Vadheim et al. (1944), Benjamin (1948), Burdette (1957), Koga et al. (1985), Levin (1999), Goldin and Roa (2009).

Epidemiology

CG is an important cancer of the gastrointestinal tract, with an estimated 6,000 new cases per year in the USA. In old autopsy series from a time period with a low rate of gallbladder surgery, the prevalence of CG in necropsies ranged from 5 % to 6 % (Kaumann 1909). In a more recent large autopsy series from Japan, CG was found in 2.1 % (Kimura et al. 1989). In a series of 540 consecutive cholecystectomies from Japan, CG was detected in 2.2 % (Terada 2013). Around 60 % of all cancers of the extrahepatic biliary system arise in the gallbladder (Narula 1971). There are marked differences in incidence from one region of the world to the other. Based on cancer registry data, it was found that the highest CG incidence rates worldwide were reported for women in Delhi, India (21.5/100,000); South Karachi, Pakistan (13.8/100,000); and Quito, Ecuador (12.9/100,000), and high incidences were found in Korea, Japan, and some Central and Eastern European countries (review: Randi et al. 2006). There are also differences in prevalence within

one the same country, due to ethnic variables. In North America, CG is more frequent in American Indians and Hispanic Americans than in whites or African Americans. In an autopsy series of 287 patients with CG, the ratio of men to women was 1:2.64–1:3.7 (Gupta et al. 1980; Sons et al. 1985), but in older series an even higher female preponderance was found (Kaufmann 1909). The average age of women at the time point of diagnosis was 70 years, and that of man, 69.5 years (Sons et al. 1985). The disease occurs on the average at a younger age in females than in males (Gupta et al. 1980). In part of patients, CG is diagnosed as an unsuspected lesion in cholecystectomy specimens (incidental CG; Varshney et al. 2002; Mazer et al. 2012). In a Korean study of 527 patients with gallbladder resection for benign biliary disease, unsuspected CG was found in 1.89 %, 50 % of these patients showing early CG with invasion confined to the mucosa (stage T1) (Kwon and Chang 1997). In a French registry of 218 cases of incidental CG, 67 patients were male and 151 female, with a median age at presentation of 64 years (Fuks et al. 2011). In a systematic review of 30 publications, 276 CGs were detected in Western studies reporting a total of 61,542 cholecystectomy specimens (prevalence of 0.4 %), and of these, 65 % were expected pre- or intraoperatively, while 344 cases of CG were found in 37,365 specimens from Asian studies (prevalence of 1.2 %), with 45 cases being expected pre- or intraoperatively (Swank et al. 2013). In one study analyzing cases of laparoscopic cholecystectomy, the ratio between incidental and non-incidental was 9 out of 19 (Cavallaro et al. 2012).

Clinical and Imaging Features

Dominating symptoms and signs in patients with CG are upper abdominal discomfort or pain, weight loss, jaundice, fatigue, and a palpable mass (Illingworth 1935; Cooper 1937; Kelly and Speed 1946; Danzis 1948; Sainburg and Garlock 1948; Arminski 1949; Cooke et al. 1953; Fortner and Pack 1958; Gerst 1961; Bossart et al. 1962; Chandler and Fletcher 1963; Polk 1966; Robertson and Carlisle 1967; Hardy and Volk 1970; Tanga and Ewing 1970; Solan and Jackson 1971; Krain 1972; Adson 1973; Ohlsson and Aronsen 1974; Donaldson and Busuttil 1975; Melson et al. 1976; Richard and Cantin 1976; Piehler and Crichlow 1977; Arnaud et al. 1979; Jönsson and Pettersson 1982; Pandey et al. 2001; Xu and Zou 2007; Giang et al. 2012). Jaundice was detected in CG patients in up to 58 % (Arnaud et al. 1995), suggesting that invasion and obstruction of extrahepatic bile ducts is a common feature of CG. Part of the increased gallbladder mass may be due to hydrops or hemocholecyst. CG can cause rupture of the gallbladder, eventually followed by biliary peritonitis (Bakaleinik 1976). Very rarely, mucus secreted by CG can accumulate in bile duct lumens and cause obstruction of the common bile duct (Hughes et al. 1997). CG can synchronously occur in conjunction with other neoplasms of the biliary tract, such as carcinoma of the common bile duct (Fujii et al. 2004).

CG can readily be identified by various ultrasonography and other imaging techniques (Pettersson 1974; Olken et al. 1978; Yeh 1979; Fultz et al. 1988; Franquet et al. 1991; Kumar and Aggarwal 1994; Rooholamini et al. 1994; Ohtani et al. 1996; Pandey et al. 2000; Levy et al. 2001; Schwartz et al. 2002; Oikarinen 2006; Lee et al. 2009). Invasive CG presents as wall thickening or polypoid growths in conventional and CT images (Melson et al. 1976; Levy et al. 2001; Levy et al. 2002) and ultrasonography images (Olken et al. 1978; Allibone et al. 1981). In contrast to advanced invasive CD, early CG may be difficult to identify by ultrasonography/US (Nilsson et al. 1989). In one study of 15 patients with pT1 and pT2 disease, US allowed diagnosis in only 5 patients (Kapoor et al. 1996). At US, CG may present as lumen-filling tumors, polypoid masses, or infiltrating masses (Kumar et al. 1990). On both US and CT images, distinguishing the protruding type of CG from polypoid adenomas may be difficult, but benign neoplasms have a more homogeneous texture, spaces between the lesion and the gallbladder wall, and a relatively normal configuration of the gallbladder wall (Jin et al. 2013). The depth of

invasion can be assessed by the use of endoscopic ultrasound/EUS. EUS examination of CG resulted in four distinct phenotypes of cancer growth, i.e., Type A (a pedunculated mass with a fine-nodular surface in an intact wall), Type B (a broad-based mass with an irregular surface and intact outer hyperechoic layer of adjacent wall), Type C (irregular outer hyperechoic layer due to mass echo), and Type D (outer hyperechoic layer disrupted by a mass echo). Each of these types correlated well with the histologically determined depth in cancer invasion (Fujita et al. 1999). CT images in CG show various patterns, including lesions classified as "massive," "thickened wall," or "intraluminal" (Itai et al. 1980).

Fig. 1 Gallbladder carcinoma. There is stone disease with a *large black* concrement in the gallbladder (to the *right*) and a smaller stone in the large bile duct. The liver shows several cancer metastases (necropsy specimen)

Pathology

Macroscopy

In their macroscopic presentation, CGs markedly differ between early and advanced cancers. The examination and documentation of macroscopic and other findings in cases of CG have been standardized (Henson et al. 2000).

Early carcinomas, which now comprise tumors of stages T1a and T1b (Cangemi et al. 2006), are usually manifest in the form of circumscribed thickenings of the mucosa or, less commonly, as small polypoid lesions having an adenoma-like morphology. The main gross presentations of early CG comprise flat, superficial-raised, sessile, or pedunculated lesions (Figs. 1, 2, 3, and 4; Tsuchiya 1991). Another classification divided early carcinomas into protruding or superficial lesions, whereby protruding tumors were further subdivided into pedunculated or sessile neoplasms, whereas superficial tumors were subdivided into elevated, flat, or depressed lesions. Among protruding tumors, the majority are sessile, and 88 % of these sessile tumors were accompanied by superficial elevated and/or flat tumors. Overall, 86 % of these early CGs were T1a and 14 % T1b (Wakai et al. 2012). Japanese investigators described that early carcinomas display granular, flat, or gastric area-like mucosal

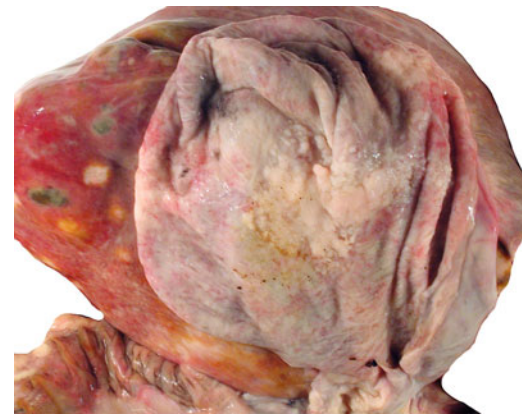

Fig. 2 Same specimen as in Fig. 1, after removal of stones. The gallbladder wall shows carcinoma in the form of a nodular plaque (*center*). Several liver metastases are seen (necropsy specimen)

patterns, which are however not specific for CG, as they may also occur in non-tumorous conditions of the gallbladder. Stereomicroscopic analyses of gallbladders with early CG of the flat type revealed three distinct patterns, i.e., grooved, pitted, or papillary, each of which further subdivided into regular or irregular. The frequency of the grooved (52.2 %) and papillary (52.2 %) patterns was significantly higher in CG than in nonneoplastic lesions, mostly with an irregular subtype, while there was no significant

Fig. 3 Carcinoma of the gallbladder with a component growing into the lumen. The large tumor has massively invaded the liver substance

Fig. 4 Carcinoma of the gallbladder. Transmural cancer growth, marked extension of the carcinoma into the liver, and intrahepatic metastatic disease are seen

difference for the pitted pattern (Ryozawa et al. 1997). In contrast to invasive CG, its precursor lesions, including high-grade dysplasia, are not detectable macroscopically (Renshaw and Gould 2012), and also early CG is detectable pre- and/or intraoperatively in 24 % of cases only (Wakai et al. 2012).

The main growth patterns found in advanced CG are a circumscribed form and a diffuse form of cancer. The circumscribed form presents in four patterns, i.e., a platelike pattern characterized by a firm, more or less delineated plaque causing wall thickening; a nodular pattern with soft or firm tumor nodules effacing the wall and eventually bulging into the lumen; a polypoid pattern with exophytic tumor masses growing into the lumen, forming cauliflower-like masses; and so-called scar cancer, where a grossly ill-defined cancer is situated in scar tissue found in a shrunken gallbladder containing impacted stones. Circumscribed tumor masses within the lumen are usually ulcerated at their surface. Large tumors with necrosis can cause gallbladder perforation. In the diffuse growth pattern of CG, the entire gallbladder wall is firm and sometimes thickened, due to diffuse cancer cell infiltration, without a visible tumor mass. Whereas circumscribed tumors can cause significant enlargement of the gallbladder, diffuse CG is often associated with gallbladder shrinkage. Infiltrative CG can invade the infundibulum and the cystic duct, causing effacement and destruction of the cystic duct, which may no longer be found at gross examination. In case the cystic duct is still open, the gallbladder contains bile and mucus, while complete cystic duct obstruction can result in gallbladder hydrops, but only in non-shrunken gallbladders. Among 287 autopsy cases, most tumors (67.7 %) showed a diffuse infiltrative growth and 32.3 % a polypoid-exophytic growth (Sons et al. 1985). Polypoid tumors were, however, not always found at a high frequency; in one report of 173 cases of CG, only 10 % showed a polypoid pattern (Tragermann 1953).

As CG often develops in gallbladders with long-standing inflammatory change, the organ can show pericholecystic scarring or is sometimes embedded in scar tissue filling the gallbladder fossa. The fibrous adhesions may contain accumulations of pus or even true abscesses, the latter most often in case of perforation, while gallbladder empyema is rather an uncommon CG (Zenker 1889; Haribhakti et al. 1997). CG presents a characteristic local invasion and metastatic pattern. Large cancers often show invasion of the liver substance, and infiltration of neighboring organs can be observed, most often transverse colon and duodenum, and less frequently stomach and pancreas. Rarely, the tumor protrudes through the gallbladder neck and cystic duct into the extrahepatic bile duct system, where it can produce a

tumor thrombus in the common bile duct (Xin-Wei et al. 2013). CG can invade the anterior abdominal wall. In very advanced CG, the tumor can form a large conglomerate inseparably situated between the liver, abdominal wall, stomach, pancreas, and colon, encroaching upon and stenosing large bile ducts and blood vessels, including the portal vein. Owing to its invasive features, CG can produce fistulations between the gallbladder and invaded neighboring organs, most often vesicocolonic fistula, and much rarer vesicoduodenal or vesicogastric fistulas.

Locoregional lymph node metastases may cause impressive lymphadenomegaly. CG commonly produces hepatic metastases, which are manifest as macroscopic metastases of micrometastases. Micrometastases are defined as discrete nodular hepatic lesions, having a diameter of less than 5 mm, or as metastatic deposits located within venous vessels of the liver. Micrometastases are more frequent within 1 cm of the gallbladder bed than 1–2 cm from it, suggesting cancer spread through the vascular network of the gallbladder fossa. Micrometastases showed a strong correlation with the extent of blood vessel invasion around the primary tumor and were often detected in patients with a primary tumor localized on the hepatic side and with more than 3 cm of subserosal invasion (Endo et al. 2004). Although CG invades the entire gallbladder wall and reaches the subserosal space, peritoneal spread (peritoneal carcinomatosis) is not a common feature and is preferentially seen in the diffuse (scirrhous) growth pattern of CG.

Histopathology

Gallbladder carcinoma presents with a wide spectrum of histologies, whereby tubular and solid adenocarcinoma (the "classical" types of CG) predominates (Figs. 5, 6, and 7; Albores-Saavedra et al. 2010; Table 1). The current WHO classification is based on previous classifications published by the WHO and by the Armed Forces Institute of Pathology/AFIP in 2000.

In fact, adenocarcinoma with various proportions of tubular, solid, and/or diffusely growing components is found in most cases (84.6 % in a large autopsy series; Sons et al. 1985). Adenocarcinoma usually grows in the form of nodular or polypoid masses, but diffuse mucosal carcinoma has also been described (Haratake et al. 2002).

Adenocarcinoma, Biliary Type

This is the most common adenocarcinoma of the gallbladder, and these neoplasms are usually well- to moderately differentiated lesions. Biliary-type adenocarcinoma consists of tubular gland-like structures of variable length, lined by columnar cells of varying height and cuboidal cells. The

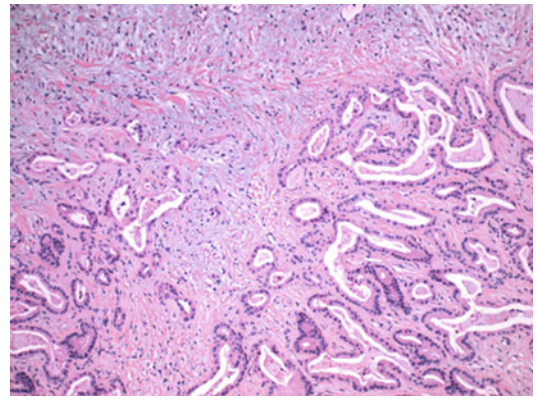

Fig. 5 Well-differentiated adenocarcinoma of the gallbladder (hematoxylin and eosin stain)

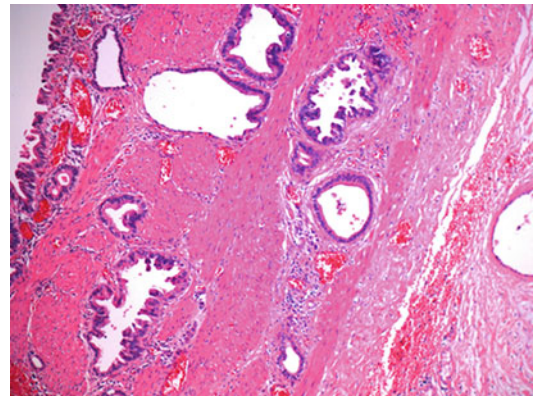

Fig. 6 Adenocarcinoma of the gallbladder with micropapillary components. The tumor has invaded the muscular layer and is clearly distinguishable from a dilated mucosal pocket (hematoxylin and eosin stain)

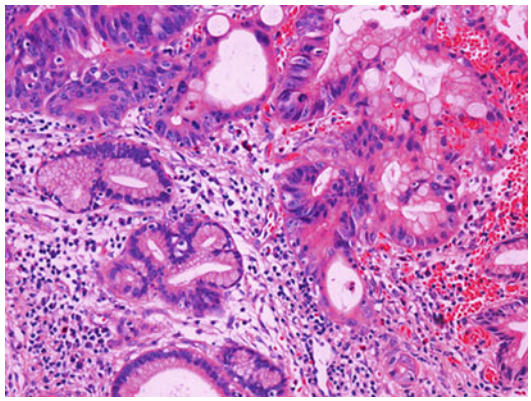

Fig. 7 Moderately differentiation adenocarcinoma of the gallbladder (to the *top* and *right*). Note the clear difference between cancerous tissue and the normal gallbladder glands seen to the *left* and *bottom* (hematoxylin and eosin stain)

Table 1 Histologic types of gallbladder carcinoma

Classical types of gallbladder carcinoma
Adenocarcinoma, biliary type
Adenocarcinoma, intestinal type
Adenocarcinoma, gastric foveolar type
Papillary carcinoma
Carcinoma in situ
Rare carcinoma variants
Signet ring cell carcinoma
Mucinous (colloid) carcinoma
Clear cell carcinoma
Cribriform carcinoma
Micropapillary carcinoma
Squamous cell carcinoma
Adenosquamous carcinoma
Carcinoma with lymphoid stroma
Giant cell carcinoma
Hepatoid carcinoma
Carcinoma with morule-like features
Adenocarcinoma with choriocarcinoma-like features
Small cell carcinoma
Undifferentiated carcinoma
Pleomorphic carcinoma
Carcinomas with sarcomatoid features

cells resemble the cells lining bile ducts and can reliably be identified in fine needle aspiration material (Yadav et al. 2013). Part of the neoplastic cells contain mucin that is sometimes secreted into the tubules, but not forming "mucin lakes" that characterize colloid carcinomas. Approximately a third of well-differentiated biliary-type CG shows focal intestinal differentiation, sometimes with formation of goblet cells. Part of gallbladder adenocarcinomas may contain cell types other than columnar cells, such as Paneth cells, and/or neuroendocrine cells (Koga et al. 1991). Some tumor contains numerous neuroendocrine cells that are reactive for peptide hormones and/or serotonin. Argentaffin cells as a component of CG are a rather uncommon finding, and only a few cells have been detected in one study (Azadeh and Parai 1980). A variant of well-differentiated adenocarcinoma of the gallbladder can mimic minimal deviation adenocarcinoma of the cervix (Tashiro et al. 2000). The nuclei of invasive CG are generally larger than those of in situ lesions, a phenomenon that has been objectively proven by the use of stereologic estimation of mean nuclear volume (Elpek et al. 1999). Classical adenocarcinoma of the gallbladder exhibits variable degrees of desmoplasia (stromal reaction), however, usually without the massive sclerosing stromal reaction characterizing Klatskin tumors. Similar to desmoplastic areas in cholangiocarcinomas, the stroma of CG can undergo secondary changes, including advanced fibrosis/sclerosis, hyalinization, and rarely osseous metaplasia (Cavazza et al. 1999), the latter discussed in more detail in a separate paragraph. In comparison with biliary-type carcinomas of the extrahepatic bile duct, desmoplasia of CG is usually less pronounced. CG may undergo necrosis, hemorrhage, and calcification (Parker and Joffe 1972; Rogers et al. 1973; Hori et al. 2008). Calcification of CG (see below) seems to be an inherent, albeit not yet clarified, feature of some forms of CG, as calcification can also occur in lymph node metastases of these carcinomas (Yun et al. 2011).

Adenocarcinoma, Intestinal Type

Intestinal-type CG is less common than CG and presents under two phenotypes. The more frequent one is characterized by tubular gland-like structures closely resembling those found in

colorectal carcinomas, composed of tall columnar cells with pseudostratified elongated or ovoid nuclei, with mitotic figures having left the basal position and found higher up in the cancer epithelium. Nuclear debris or apoptotic bodies may be found in the epithelial lining. The second, less common variant contains numerous goblet cells, intermingled with Paneth cells and neuroendocrine cells. Immunohistochemically, both variants are typically reactive for MUC2, CEA, and the transcription factor CDX2 (review: Albores-Saavedra et al. 2010).

Adenocarcinoma, Gastric Foveolar Type

This is a rare variant of well-differentiated adenocarcinoma that consists of tall columnar cells with abundant cytoplasm containing mucin and basally placed nuclei. The tumor cells are usually reactive for MUC5A. This carcinoma either occurs as a pure form or exists in combination with other adenocarcinoma variants.

Papillary Carcinoma of the Gallbladder

Papillary adenocarcinoma of the gallbladder is a distinct variety of CG characterized by a papillary growth pattern, a tendency for exophytic growth, and a more favorable biology of disease (Egeberg et al. 1949; Frank and Spjut 1967; Hart et al. 1972; Gunn and Dyte 1985; Akiyama et al. 1995; Onuma et al. 2013). Papillary carcinoma is rare and has been observed in only 4.2 % of all CG (Nuzzo et al. 2005). It has also been found in the setting of anomalous pancreaticobiliary junction (Nuzzo et al. 2005). The intraluminally growing component of papillary carcinomas is well-differentiated and consists of slender papillae covered by columnar cells. Less or even poorly differentiated cell populations have been noted at the base of the papillary structures by some authors (Glenn and Hays 1954; Lund 1960). Large papillary carcinomas may suffer from poor vascularization and undergo marked necrosis (Onuma et al. 2013). Previously, noninvasive and invasive forms of papillary carcinoma were lumped together. In a comparative analysis, it surfaced that noninvasive papillary carcinoma is a distinctive variant occurring more often in females, predominantly showing a biliary phenotype and rarely an intestinal phenotype, associated with cholelithiasis in the majority of cases, and revealing no metastasis and an excellent prognosis. In contrast and similar to ordinary CG, invasive papillary CG can produce lymph node metastasis and is associated with poor prognosis (Albores-Saavedra et al. 2005). A more favorable outcome thus depended on lymph node dissection (Wolma and Lynch 1961).

Intestinal-Type Carcinoma of the Gallbladder

Intestinal-type CG is a variant of well-differentiated adenocarcinoma of the gallbladder characterized by the presence of intestinal features (Albores-Saavedra et al. 1986). Part of these neoplasms resemble colorectal carcinoma, whereas others exhibit a composition characterized by absorptive columnar cells, numerous goblet cells, Paneth cells, and some neuroendocrine cells. The latter may be reactive for serotonin, somatostatin, cholecystokinin, and/or pancreatic polypeptide. The carcinomas are sometimes associated with intestinal metaplasia of the uninvolved mucosa (Albores-Saavedra et al. 1986).

Adenocarcinoma of the Gallbladder with Marked Desmoplasia

In contrast to Klatskin tumors, desmoplasia in CG is usually of moderate degree. There exists, however, a subset of gallbladder adenocarcinomas having marked stromal fibrosis (Wang et al. 2006). In these neoplasms, ultrasound shows that the gallbladder wall is irregularly thickened or exhibits nodosity, but the growth pattern is usually diffuse. A second form of CG associated with copious connective tissue formation is carcinoma

associated with porcelain gallbladder or hyalinizing cholecystitis. Carcinomas developing in this form of cholecystitis did not form distinct tumor masses or a significant wall thickening, but showed widely scattered and bland-appearing glands embedded in the thin band of hyaline stroma, often with microcalcifications and granular intraluminal debris (Patel et al. 2011).

Carcinoma In Situ

Carcinoma in situ (CIS) occurs in the gallbladder either as an isolated lesion or as a lesion associated with invasive carcinoma (Kott and Urca 1974; Albores-Saavedra et al. 1980). Similar to other organs, CIS of the gallbladder is considered to be a malignant neoplasm in its preinvasive phase of evolution. However, in a given case, it cannot be reliably judged whether CIS would have switched to an invasive phenotype in the future or rather persisted as a stable lesion. Among 200 consecutive cholecystectomy specimens removed for cholelithiasis or cholecystitis, CIS was identified in 3.5 %. CIS was also found in the mucosa adjacent to invasive CG in 79 % of surgical cases and in 52.9 % of autopsy cases (Albores-Saavedra et al. 1980). In an analysis of 18 cases of CIS of the gallbladder, all patients were females with an age range of 29–83 years at diagnosis (mean, 55 years). Macroscopically, the CIS lesions could not be distinguished from chronic cholecystitis, with one exception. Histologically, CIS presents as either a papillary lesion or a more common non-papillary lesion. CIS of the gallbladder may extend from the surface epithelium to invaginations and then to antral-type glands, the latter being associated with CIS in more than half of the cases (Albores-Saavedra et al. 1984).

Rare Variants of Gallbladder Carcinoma

A small fraction of CG is characterized by a histology different from adenocarcinoma. These rare carcinoma variants mostly share features with similar neoplasms occurring in other organs (Albores-Saavedra et al. 1981, 1996). The diverse forms of tumors are treated in separate chapters.

Mixed Carcinomas

A minority of CG shows more than one histologic component. Mucinous CG with a separate nodule of anaplastic carcinoma was observed (Mizuno et al. 1999), and there is a very rare reported case of gallbladder adenocarcinoma associated with a choriocarcinoma, sometimes with immunoreactivity for beta-HCG (Albores-Saavedra et al. 1981; Abu-Farsakh and Fraire 1991).

Invasion Patterns

Perineural invasion is a typical feature of CG, and this neoplasm shares this important prognostic alteration with carcinomas of the extrahepatic bile ducts. Cancer cell spread along perineural spaces follows the distinct anatomy of gallbladder nerves. These nerves form a mucosal plexus resembling the intestinal Meissner's plexus, transmural branches, and a nervous plexus on the exterior surface of the gallbladder, the latter plexus also containing ganglion cell clusters (Hermann 1952). Perineural invasion may be mimicked by florid pyloric gland metaplasia of the gallbladder, where the perineural space and the intraneural compartment may be infiltrated by cytologically bland cuboidal or columnar mucin-containing cells (Albores-Saavedra and Henson 1999). Invasive CG has a strong tendency to extend from the mucosa of the gallbladder, where the neoplasm takes its origin in most instances, into the muscle layer and from there into the subserosal space. In part of patients, invasive CG and also CIS were found to extend into Rokitansky-Aschoff sinuses (Albores-Saavedra et al. 2004). Similar to cholangiocarcinomas of the extrahepatic ducts, perineural invasion is a characteristic feature of CG. This type of invasion was identified in 10 of 14 CG (Nagakawa et al. 1993), and perineural

invasion extended to the extramural biliary or pancreatic nerve plexuses in part of cases.

Lymph Node Metastases

Lymph node metastases in CG are either of the macrometastatic or micrometastatic variant and are frequent events of spread. They prevail in the nodular infiltrative form of CG with a histology of moderately differentiated adenocarcinoma, but are less common in papillary adenocarcinoma (Sumiyoshi et al. 1991). In a study of 135 patients with CG undergoing radical resection, lymph node metastasis was found histologically in 44 % (Shirai et al. 2012). In case of micrometastases, the identification of small clusters of carcinoma cells spread to lymph nodes may be difficult by conventional histologic examinations. The detection rate depends in the size and geometry of micrometastases. Tiny aggregates of cancer cells can be detected by means of cytokeratin immunohistochemistry in histologically negative lymph nodes (Yokoyama et al. 1999; Natarajan et al. 2005; Sasaki et al. 2006). In one study, 7 out of 255 HE-negative lymph nodes (2.7 %) were found to be positive for micrometastases by the use of cytokeratin immunostaining (Tajima et al. 1999).

Lesions Associated with Gallbladder Carcinoma

In part of CG with transmural invasion, associated inflammatory infiltrates or populations of immunological effector cells may spill over into the liver substance of the gallbladder bed. Similar to other cancers, CG contains tumor-infiltrating lymphocytes (TILs). High levels of CD4(+) and CD8(+) cells were detected in 51–1 % and 37.8 % of CG cases, respectively, and also infiltrates of natural killer cells were observed (Nakakubo et al. 2003). Part of TILs are FoxP3+ and IL-17-producing T cells that affect tumor progression and prognosis in CG after surgery (Goeppert et al. 2013; Zhang et al. 2013). CG also contains tumor-associated macrophages (TAMs), but these cells are less frequent than TILs. The hepatic bed remaining after cholecystectomy can show various alterations, including granulation tissue, remnants of adherent adipose tissue with lipogranulomas, and sometimes foreign body-type granulomas. Rarely, eosinophil-containing necrotizing granulomas have been observed in the hepatic bed following tumor cholecystectomy, associated with peripheral eosinophilia (Ohtsuki et al. 2012).

Ultrastructural Findings

SEM pictures of well-differentiated CG revealed that CG cells are irregularly shaped columnar cells with less developed and pleomorphic microvilli, whereas transmission EM demonstrated well-developed cytoplasmic organelles, variably differentiated mucus granules, abundant lysosomes, and chromatin changes shared with other malignancies (Koga et al. 1991). In classical CG, mucin-producing secretory columnar cells predominate, intermingled with narrow and dark-staining pencil-like cells (Larraza-Hernandez et al. 1984).

Immunohistochemistry

CG, including its lymph node metastases, is consistently positive for cytokeratins 8 and 18 (Yokoyama et al. 1999). Part of CG are immunoreactive for CK7 and, less often, CK20 (Kalekou and Miliaras 2011). An entire panel of immunohistochemical stains, including cytokeratins, vimentin, epithelial membrane antigen, and carcinoembryonic antigen, is required to reliably diagnose poorly differentiated and undifferentiated forms of gallbladder carcinomas (Diebold-Berger et al. 1995). A significant fraction of CG expresses the mucins, MUC1 and MUC4. High MUC1 expression was correlated with more differentiated neoplasms, whereas a high MUC4 expression was correlated with a negative nodal status (Kim et al. 2012). However, a relationship between MUC1 expression and differentiation was not detected in another

investigation (Ghosh et al. 2005). MUC4 is preferentially expressed in the apex of cancer cells (Miyahara et al. 2008). Expression of CA 242 seems to be a promising marker in CG diagnosis (Rana et al. 2012). Intestinal-type CGs express an intestinal goblet cell marker (Hughes and Bhatal 2013), and CGs with features of pyloric gland metaplasia are reactive for class II mucins (Tatematsu et al. 1988). The majority of CGs express p53 protein in the nuclei (The et al. 1994; Doval et al. 2014). CGs express EGFR, Cox-2, and cyclin D1 (Doval et al. 2014). Part of CG expressed estrogen and progesterone receptors (Gupta et al. 2012). Other immunoreactivities in CG that may be useful in diagnosis of CG include CD151 (a member of the tetraspanin family; Matsumoto et al. 2014), CD117/c-Kit (Langner et al. 2004), EphB1 and Ephrin-B (Yuan et al. 2014), the von Hippel-Lindau gene product, maspin, IMP3, and S100P (Shi et al. 2013). Aberrant maspin expression was noted in focal and patchy areas of gallbladder epithelium and intestinal metaplasia of the gallbladder in patients with cholelithiasis (Maesawa et al. 2006); its expression seems to be involved in early carcinogenesis of CG (Kim et al. 2010). Maspin (mammary serine protease inhibitor) is a member of the serine protease inhibitor/non-inhibitor superfamily and plays a role in the biology of several cancers, where it is downregulated or overexpressed, suggesting differential roles in various cell types. Selectively increased cell adhesion by the expression of maspin is thought to contribute to the inhibition of metastatic spread (review: Berardi et al. 2013). CG shows variably elevated proliferation indices when examined by the use of PCNA or Ki-67 immunohistochemistry (Roa et al. 1993).

Secondary Changes of Gallbladder Carcinoma

CG can undergo marked necrosis, preferentially the exophytically growing forms (Sakurai et al. 2001; Hori et al. 2008). Due to necrosis/infarction, polypoid lesions may detach from the stalk and freely float in the lumen. Necrosis and/or accumulation of mucin, or exudate, can lead to the formation of cystic structures with carcinoma, eventually mimicking adenomyosis/adenomyomatosis at imaging (Tian et al. 2003; Yoshimitsu et al. 2005). Intratumoral cystic components were found in 3 of 35 proven CG by MR examination. All these tumors were well-differentiated adenocarcinomas and cystic changes were caused by abundant mucin production, mucin being accumulated in dilated Rokitansky-Aschoff sinuses (Yoshimitsu et al. 2005). In case of vesicointestinal, and particularly vesicocolonic fistulation, entry of intestinal bacteria into tumor can lead to puriform liquefaction or gangrene of cancer and, rarely, gas gangrene.

As already noted above, gallbladder carcinoma can undergo extensive calcification (Parker and Joffe 1972; Rogers et al. 1973): two main patterns of calcification occur. Calcified carcinomas may have calcium salt deposits mainly in the stroma, numerous mineralization grains being placed between stromal cells and/or along connective tissues fibers. The incidence of this change is not known, but may be more frequent in case one would test for microcalcifications by the use of the von Kossa stain. The second pattern is characterized by sometimes marked calcification in CG with high mucin content (Parker and Joffe 1972; Tian et al. 2003). In rare cases, calcification present in the primary tumor is also found in lymph node metastases (calcified nodal metastasis; Parker and Joffe 1972; Yun et al. 2011) or in liver metastases (Nakadaira et al. 2008). Calcifications and/or osseous metaplasia occurs on malignant gallbladder neoplasms other than CG, e.g., carcinosarcoma with calcified or bony components (Grote and Kaemmerer 1986; Ishida et al. 2012). Calcifications can also develop in mucinous cholangiocarcinoma (Nagakura et al. 1999).

A very rare secondary change in CG is osseous metaplasia (heterotopic ossification), which develops within tumor stroma and is characterized by the formation of immature bony tissue or osteoid within the spindle cell background (Cavazza et al. 1999). Heterotopic ossification in tumors may be induced by production of bone morphogenetic proteins (Imai et al. 2001; Komai et al. 2006). Carcinosarcomas of the gallbladder

can contain foci of osseous metaplasia (Nakagawa et al. 1996).

Precursor Lesions

Several investigations indicate that CGs derive from a foregut cell lineage and that at least a large part of CGs develop in the setting of a hyperplasia/metaplasia-dysplasia-carcinoma in situ-invasive carcinoma sequence, or a cascade leading from gallbladder adenoma with or without significant atypia to carcinoma (Sawyer 1970; Albores-Saavedra et al. 1980; Kozuka et al. 1982; Laitio 1983; Yamagiwa 1987; Yamamoto et al. 1989a, b; Aldridge and Bismuth 1990; Kim et al. 2001; Adsay 2007; Stancu et al. 2007; Trivedi et al. 2008; Feng et al. 2011; Hughes and Bhathal 2013; Segovia Lohse and Cuenca Torres 2013; Kijima et al. 2014).

The overall prevalence of metaplastic changes developing in chronic inflammatory gallbladder disease varies considerably among different studies and was higher than 25 % in some analyses. Metaplastic changes appear to be more frequent in cases with microlithiasis and are associated with chronic gallbladder wall thickening (Seretis et al. 2014). Intestinal metaplasia, in part with goblet cells, was found at rates of 4.0 % and 30.6 % in cases without and with cholelithiasis, respectively. Metaplasia was detected at rates of 69.8 % and 61.1 % in cases with dysplasia and carcinoma, respectively, suggesting that intestinal metaplasia of the gallbladder may precede dysplastic changes (Yamagiwa and Tomiyama 1986). The prevalence of dysplasia varies as a function of genetic background of patients, presence or absence of risk factors such as stone disease and chronic cholecystitis, and definitions/criteria employed to identify dysplasia. Overall, incidental gallbladder dysplasia (IGBD) seems to be a fairly common incidental histologic finding after cholecystectomy for gallstone disease (Solaini et al. 2014). In a Japanese study of 200 gallbladders removed for presumed benign disease, dysplasia was present in 14.5 % (12 % mild dysplasia, 2.5 % moderate to severe dysplasia), while epithelial hyperplasia was diagnosed in 27 % of cases (Mukada et al. 1985). In one analysis, over 80 % of invasive CG presented areas adjacent to flat dysplasia and carcinoma in situ (Rao et al. 2006). There is evidence that K-RAS mutations play a role in the development of premalignant gallbladder lesions and early carcinogenesis (Kim et al. 2000). In contrast to flat dysplasia, an adenoma-carcinoma sequence does not seem to be a pathway for gallbladder carcinogenesis as common as that of dysplasia, as adenomas are uncommon (less than 1 % of cholecystectomies), and adenomatous remnants in the neighboring mucosa to early CG were detected less than 3 % of cases (Roa et al. 2006). However, adenomatous residues were found in up to 19 % of invasive CG (Kozuka et al. 1982). In part of cases of CG, the invasive neoplasm is spatially associated with carcinoma in situ/CIS. CIS disclosed a superficial extension into Rokitansky-Aschoff sinuses and mucous glands (Yamaguchi et al. 1992). CG is known to occur in the setting of gallbladder papillomatosis (Kunisch et al. 1997). What is the time period required for the transformation of dysplasia to frank carcinoma? There is still scarce information regarding the timely evolution of gallbladder precursor lesions, owing to the fact that dysplastic lesions are silent, and early CGs are usually asymptomatic. In an investigation on resected gallbladders, the mean age of patients showing gallbladder dysplasia was 46.3 years, that of early CG 57.5 years, that of advanced CG 59 years, and that of CG with metastases 61.1 years (Roa et al. 1996), suggesting that the carcinogenic progression from dysplasia may require at least 15 years. In addition to precursor lesions, the role of cancer stem cells in the carcinogenesis of CG has been discussed. CG can contain CD133-positive cells classified as self-renewing potential carcinoma stem cells (Shi et al. 2011).

CG was identified in close spatial relationship with adenomyomatosis (Paraf and Potet 1988), but a causal relationship between adenomyomatosis and carcinogenesis remains uncertain. A recent investigation showed that the status of adenomyomatosis in gallbladders with CG was significantly associated with T stage, nodal metastasis, distant metastasis, and shorter survival, and

that adenomyomatosis-positive CG is more often diagnosed clinically in the advanced stages (Kai et al. 2011). CG can also arise in Rokitansky-Aschoff sinuses (Terada 2008), but such relationships are difficult to assess, as invasive CG and CIS can secondarily involve these sinuses (Albores-Saavedra et al. 2004).

Differential Diagnosis

CG may histologically be confounded with an entire spectrum of nonneoplastic lesions, including diverse forms of metaplasia, adenomyomatosis foci with atypia, regenerative changes in previously damaged Rokitansky-Aschoff sinuses, and hyperplastic Luschka ducts (Singhi et al. 2011; Giang et al. 2012). Mass-forming adenomyomatosis of the gallbladder may be masquerade as CG (Shimoji et al. 2001; Ray et al. 2012). Mucin-containing Rokitansky-Aschoff sinuses with extracellular mucin deposits may mimic mucinous adenocarcinoma of the gallbladder (Albores-Saavedra et al. 2009). Pseudotumorous lesions, e.g., intramural gallbladder hematomas (Tan et al. 2005) and gallstone granulomas (Tham and Ng 2001; Jung et al. 2011), may also mimic CG. Rare mass-producing specific inflammations of the gallbladder can produce presentations similar to that of cancer, including gallbladder tuberculosis (Hegler 1925; Ramia et al. 2006; Soufi et al. 2011; Verma et al. 2012), brucellosis (Ögredicie et al. 2010), and actinomycosis (Hefny et al. 2005; Lee et al. 2007).

Paraneoplastic Organ Changes in Gallbladder Carcinoma

A small subset of CG is associated with paraneoplastic features/syndromes (Table 2). The disorders comprise acanthosis nigricans (Lam 1940; Lichtenstein and Tannenbaum 1940; Campbell 1941; Werko 1945; Jacobs and Rigel 1981), bullous pemphigoid (Post et al. 1973), exfoliative dermatitis/erythrodermia (Kameyama et al. 2005), polymyositis (Adli et al. 2013), dermatomyositis (Yiannopoulos et al. 2002; Ni et al. 2013), neuropathy (Mitobe et al. 1970), paraneoplastic opsoclonus (Corcia et al. 1997), Guillain-Barré syndrome (Phan et al. 1999), erythrocytosis (Manigand et al. 1971), thrombocytosis (Wakabayashi et al. 1978), leukemoid reactions (Pozza et al. 1966), hemolytic anemia (Barletta et al. 1989; de la Sierra et al. 1989), Sweet's syndrome (Jindal et al. 2012), production of granulocyte colony-stimulating factor (Takahashi et al. 1985; Takeda et al. 1990; Furihata et al. 1999; Suzumura et al. 2014), hypercalcemia (Vilabona et al. 1986; Watanabe et al. 1989;), Cushing's syndrome (Brickner et al. 1961), synthesis and secretion of chorionic gonadotropin/beta-HCG (Fukuda and Ohnishi 1990; Sato et al. 2010), and AFP-producing CG (Sugaya et al. 1989) which is discussed in a separate paragraph. Paraneoplastic disorders of the CNS in CG should

Table 2 Paraneoplastic syndromes/disorders in gallbladder carcinoma

Cutaneous alterations
Acanthosis nigricans
Bullous pemphigoid
Erythrodermia
Soft tissue alterations
Dermatomyositis
Polymyositis
Hematological alterations
Erythrocytosis
Thrombocytosis
Leukemoid reactions
Production of granulocyte colony-stimulating factor
Autoimmune hemolytic anemia
Hemolytic microangiopathic anemia
Sweet's syndrome
Paraneoplastic thrombosis
Neuromuscular alterations
Neuropathy (sensory, mixed)
Opsoclonus
Guillain-Barré syndrome
Metabolic alterations
Paraneoplastic hypercalcemia
Cushing's syndrome
Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Paraneoplastic hyponatremia
AFP production

not be confounded with effects of metastases, e.g., myelopathy due to spinal metastases (Newman et al. 1977).

References

Abu-Farsakh H, Fraire AE (1991) Adenocarcinoma and (extragonadal) choriocarcinoma of the gallbladder in a young woman. Hum Pathol 22:614–615

Adli B, Pakzad M, Bangash MN, Rakei S (2013) Polymyositis as presenting manifestation of gallbladder carcinoma: a case report. Int J Surg Case Rep 4:665–668

Adsay NV (2007) Neoplastic precursors of the gallbladder and extrahepatic biliary system. Gastroenterol Clin North Am 36:889–900

Adson MA (1973) Carcinoma of the gallbladder. Surg Clin North Am 53:1203–1216

Aiga Y (1935) Über einen seltenen Fall von operativ dauernd geheiltem Gallenblasen-karzinom. Zentralbl f Chir 62:212–215

Akiyama T, Saito H, Kiriyama M, Tomita F, Kosaka T, Kita I, Takashima S, Matsunou H (1995) A case of gallbladder cancer associated with a common bile duct neuroma, and a cystic lesion of the liver with histologic findings similar to those of an inflammatory pseudotumor. J Gastroenterol 30:408–412

Albores-Saavedra and Henson 1999. http://www.ncbi.nlm.nih.gov/pubmed/10594857

Albores-Saavedra J, Alcantara-Vazquez A, Cruz-Ortiz H, Herrera-Goepfert R (1980) The precursor lesions of invasive gallbladder carcinoma. Hyperplasia, atypical hyperplasia and carcinoma in situ. Cancer 45:919–927

Albores-Saavedra J, Cruz-Ortiz H, Alcantara-Vazques A, Henson DE (1981) Unusual types of gallbladder carcinoma. A report of 16 cases. Arch Pathol Lab Med 105:287–293

Albores-Saavedra J, de Jesus Manrique J, Angeles-Angeles A, Henson DE (1984) Carcinoma in situ of the gallbladder. A clinicopathologic study of 18 cases. Am J Surg Pathol 8:323–333

Albores-Saavedra J, Nadji M, Henson DE (1986) Intestinal-type adenocarcinoma of the gallbladder. A clinicopathologic study of seven cases. Am J Surg Pathol 10:19–25

Albores-Saavedra J, Molberg K, Henson DE (1996) Unusual malignant epithelial tumors of the gallbladder. Semin Diagn Pathol 13:326–338

Albores-Saavedra J, Shukla D, Carrick K, Henson DE (2004) In situ and invasive adenocarcinoma of the gallbladder extending into or arising from Rokitansky-Aschoff sinuses: a clinicopathologic study of 49 cases. Am J Surg Pathol 28:621–628

Albores-Saavedra J, Tuck M, McLaren BK, Carrick KS, Henson DE (2005) Papillary carcinomas of the gallbladder: analysis of noninvasive and invasive types. Arch Pathol Lab Med 129:905–909

Albores-Saavedra J, Galliani C, Chable-Montero F, Batich K, Henson DE (2009) Mucin-containing Rokitansky-Aschoff sinuses with extracellular mucin deposits simulating mucinous carcinoma of the gallbladder. Am J Surg Pathol 33:1633–1638

Albores-Saavedra J, Adsay NV, Crawford JM, Klimstra DS, Klöppel G, Sripa B, Tsui WMS et al (2010) Carcinoma of the gallbladder and extrahepatic bile ducts. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds) Who classification of tumours of the digestive system, 4th edn. IARC, Lyon, pp 266–272

Aldridge MC, Bismuth H (1990) Gallbladder cancer: the polyp-cancer sequence. Br J Surg 77:363–364

Allibone GW, Fagan CJ, Porter SC (1981) Sonographic features of carcinoma of the gallbladder. Gastrointest Radiol 6:169–173

Arminski TC (1949) Primary carcinoma of the gallbladder. Cancer 2:379–398

Arnaud et al. 1979. http://www.ncbi.nlm.nih.gov/pubmed/474877

Arnaud JP, Casa C, Georgeac C, Serra-Maudet V, Jacob JP, Ronveray J, Bergamaschi R (1995) Primary carcinoma of the gallbladder – review of 143 cases. Hepatogastroenterology 42:811–815

Azadeh B, Parai SK (1980) Argentaffin cells, intestinal metaplasia, and antral metaplasia in carcinoma of the gall bladder. Histopathology 4:653–659

Babaleinik M (1976) Biliary peritonitis due to double perforation of carcinoma of the gallbladder: case report. Mil Med 141:551–553

Barletta R, Fiorentino E, Spano G, Coppotelli L, Fiorito S, Paradise M, Cordova C (1989) Considerations on a case of hemolytic microangiopathic anemia in a patient with adenocarcinoma of the gallbladder (in Italian). Recenti Prog Med 80:142–146

Barsoum GH, Windsor CW (1992) Parietal seeding of carcinoma of the gallbladder after laparoscopic cholecystectomy. Br J Surg 79:846

Beadles CF (1897) Primary carcinoma of the liver (gallbladder) associated with a large tumour on the thoracic wall. Trans Pathol Soc Lond 48:119–121

Benjamin EG (1948) Carcinoma of the gall bladder; an analysis of 70 cases. Minn Med 31:537–540

Berardi R, Morgese F, Onofri A, Mazzanti P, Pistelli M, Ballatore Z, Savini A, De Lisa M et al (2013) Role of maspin in cancer. Clin Transl Med 2:8

Bossart PA, Patterson AH, Zintel HA (1962) Carcinoma of the gallbladder. A report of seventy-six cases. Am J Surg 103:366–369

Boyce FF, McFetridge EM (1936) Carcinoma of the gallbladder; a critique based on an analysis of 25 cases from Charity Hospital in New Orleans. Int S Digest 21:67–79

Brickner PW, Lyons M, Landau SJ (1961) Cushing's syndrome associated with non-endocrine neoplasms. A review and a new case, the first with carcinoma of the gallbladder. Am J Med 31:632–639

Burdette WJ (1957) Carcinoma of the gallbladder. Ann Surg 145:832–844

Campbell DA (1941) A clinical study of carcinoma of the gallbladder. Ann Surg 113:1068–1069
Cangemi V, Fiori E, Picchi C, De Cesare A, Cangemi R, Galati G, Volpino P (2006) Early gallbladder carcinoma: a single-center experience. Tumori 92:487–490
Cavallaro A, Piccolo G, Panebianco V, Lo Menzo E, Berretta M, Zanghi A, Di Vita M et al (2012) Incidental gallbladder cancer during laparoscopic cholecystectomy: managing an unexpected finding. World J Gastroenterol 18:4019–4027
Cavazza A, De Marco L, Asioli S, Pastore L, Gardini G (1999) Stromal osseous metaplasia in metastatic adenocarcinoma of the gallbladder. Tumori 85:133–134
Chandler JJ, Fletcher WS (1963) A clinical study of primary carcinoma of the gallbladder. Surg Gynecol Obstet 117:297–300
Cooke L, Avery-Jones F, Keich MK (1953) Carcinoma of the gallbladder. A statistical study. Lancet 2:585–587
Cooper WA (1937) Carcinoma of the gallbladder. Arch Surg 35:431–448
Corcia P, De Toffol B, Hommet C, Saudeau D, Autret A (1997) Paraneoplastic opsoclonus associated with cancer of the gall bladder. J Neurol Neurosurg Psychiatry 62:293
Cowley LL, Wood V (1964) Carcinoma developing in a remnant of the gallbladder. Ann Surg 159:465–468
Danzis M (1948) Carcinoma of the gall bladder; a report of 26 cases. J Med Soc N J 45:274–277
De la Sierra A, Villalta J, Lozano M, Campa MT, Ingelmo M (1989) Autoimmune hemolytic anemia preceding by 6 years an adenocarcinoma of the gallbladder (in Spanish). Ann Med Int 6:481–482
De Stoll M (1771) Cited by Rolleston and McNee (1929)
Deaver JB (1924) Carcinoma of the gall-bladder. Am J Surg 38:105–107
Diebold-Berger S, Vaiton JC, Pache JC, d'Amore ES (1995) Undifferentiated carcinoma of the gallbladder. Report of a case with immunohistochemical findings. Arch Pathol Lab Med 119:279–282
Donaldson LA, Busuttil A (1975) A clinicopathologic review of 68 carcinomas of the gallbladder. Br J Surg 62:26–32
Doval DC, Azam S, Sinha R, Batra U, Mehta A (2014) Expression of epidermal growth factor receptor, p53, Bcl2, vascular endothelial growth factor, cyclooxygenase-2, cyclin D1, human epidermal receptor-2 and Ki-67: Association with clinicopathological profiles and outcomes in gallbladder carcinoma. J Carcinog 13:10
Egeberg RO, Van Orden MT, Kaplan L (1949) Primary papillary adenocarcinoma of the fundus of the gallbladder. Ann West Med Surg 3:66–68
Elpek GO, Gelen T, Güleç F, Sedele M, Karpuzoglu T, Süleymanlar I (1999) Stereologic estimation of mean nuclear volume in well-differentiated adenocarcinoma and carcinoma in situ of the gallbladder. Anal Quant Cytol Histol 21:445–448
Endo et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15175901
Erdmann JF (1935) Malignancy of the gallbladder. Ann Surg 101:1139–1143
Feng Z, Chen J, Wei H, Gao P, Shi J, Zhang J, Zhao F (2011) The risk factor of gallbladder cancer: hyperplasia of mucous epithelium caused by gallstones associates with p16/cyclinD1/CDK4 pathway. Exp Mol Pathol 91:569–577
Finsterer H (1932) Das Karzinom der Gallenblase. Med Klein 28:432–436
Fortner JG, Pack GT (1958) Clinical aspects of primary carcinoma of the gallbladder. AMA Arch Surg 77:742–750
Frank SA, Spjut HJ (1967) Inapparent carcinoma of the gallbladder. Am Surg 33:367–372
Franquet T, Montes M, Ruiz de Azua Y, Jimenez FJ, Cozcolluela R (1991) Primary gallbladder carcinoma: imaging findings in 50 patients with pathologic correlation. Gastrointest Radiol 16:143–148
Friedheim E (1904) Ueber primären Krebs der Leber, Gallengänge und Gallenblase. Beitr Klin Chir 44:188–204
Fujii T, Kaneko T, Sugimoto H, Okochi O, Inoue S, Takeda S, Nagasaka T, Nakao A (2004) Metachronous double cancer of the gallbladder and common bile duct. J Hepatobiliary Pancreat Surg 11:280–285
Fujita N, Noda Y, Kobayashi G, Kumira K, Yago A (1999) Diagnosis of the depth of invasion of gallbladder carcinoma by EUS. Gastrointest Endosc 50:659–663
Fuks D, Regimbeau JM, Le Treut YP, Bachellier P, Raventos A, Pruvot FR, Chiche L et al (2011) Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. World J Surg 35:1887–1897
Fukuda T, Ohnishi Y (1990) Gallbladder carcinoma producing human chorionic gonadotropin. Am J Gastroenterol 85:1403–1406
Fultz PJ, Skucas J, Weiss SL (1988) Comparative imaging of gallbladder cancer. J Clin Gastroenterol 10:683–692
Furihata M, Sonobe H, Ohtsuki Y, Enzan H, Tokuoka H, Nakanuma Y (1999) An immunohistochemical study on a case of granulocyte-colony stimulating factor-producing gall-bladder carcinoma. Pathol Int 49:1010–1013
Gerst PH (1961) Primary carcinoma of the gallbladder. A thirty year summary. Ann Surg 153:369–372
Ghosh M, Kamma H, Kawamoto T, Koike N, Miwa M, Kapoor VK, Krishnani N, Agrawal S et al (2005) MUC 1 core protein as marker of gallbladder malignancy. Eur J Surg Oncol 31:891–896
Giang TH, Ngoc TT, Hassell LA (2012) Carcinoma involving the gallbladder: a retrospective review of 23 cases – pitfalls in diagnosis of gallbladder carcinoma. Diagn Pathol 7:10
Glenn F, Hays DM (1954) The scope of radical surgery in the treatment of malignant tumors of the extrahepatic biliary tract. Surg Gynecol Obstet 99:529–541
Goeppert B, Frauenschuh L, Zucknick M, Stenzinger A, Andrulis M, Klauschen F, Joehrens K et al (2013) Prognostic impact of tumour-infiltrating immune cells on biliary tract cancer. Br J Cancer 109:2665–2674

Goldin RD, Roa JC (2009) Gallbladder cancer: a morphological and molecular update. Histopathology 55:218–229

Greenlee DP, Hamilton RC, Ferraro FP (1941) Primary carcinoma of the gallbladder. Arch Surg 42:598–610

Grote R, Kaemmerer H (1986) Carcinosarcoma of the gallbladder in the computed tomogram (in German). Rontgenblatter 39:17–20

Gunn IF, Dyte PH (1985) Papillary adenocarcinoma of the gallbladder. Med J Aust 142:362–363

Gupta S, Udupa KN, Gupta S (1980) Primary carcinoma of the gallbladder: a review of 328 cases. J Surg Oncol 14:35–44

Gupta et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22690257

Haratake J, Kasai T, Makino H (2002) Diffuse mucosal carcinoma of intrahepatic and extrahepatic bile ducts including gallbladder. Pathol Int 52:784–788

Hardy MA, Volk H (1970) Primary carcinoma of the gallbladder: a ten year review. Am J Surg 120:800–803

Haribhakti SP, Awashti S, Pradeep R, Kapoor VK, Kaushik SP (1997) Carcinoma gallbladder: atypical presentations and unusual associations. Trop Gastroenterol 18:32–34

Hart J, Modan B, Hashomer T (1972) Factors affecting survival of patients with gallbladder neoplasms. Arch Intern Med 129:931–934

Hefny AF, Torab FC, Joshi S, Sebastian M, Abu-Zidan FM (2005) Actinomycosis of the gallbladder: case report and review of the literature. Asian J Surg 28:230–232

Hegler C (1925) Tumorartige cholecystitis und cholangitis tuberculosa. Virchows Arch 254:272–276

Henson DE, Albores-Saavedra J, Compron CC (2000) Protocol for the examination of specimens from patients with carcinomas of the gallbladder, including those showing focal endocrine differentiation: a basis for checklists. Cancer Committee of the College of American Pathologists. Arch Pathol Lab Med 124:37–40

Hermann H (1952) Das Nervensystem der menschlichen Gallenblase und seine Veränderungen bei Cholelithiasis (The nervous system of the human gallbladder and its alterations in cholelithiasis). Virchows Arch 322:17–48

Hochberg LA, Kogut B (1939) Primary carcinoma of the gallbladder. Am J Surg 43:746–753

Hori et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18855999

Hughes NR, Bhathal PS (2013) Adenocarcinoma of gallbladder: an immunohistochemical profile and comparison with cholangiocarcinoma. J Clin Pathol 66:212–217

Hughes OD, Haray PN, Williams IM, Roberts R, Lewis MH (1997) Carcinoma of the gall-bladder producing mucous obstruction of the common bile duct: a cautionary note. J R Coll Surg Edinb 42:280–282

Illingworth CFW (1935) Carcinoma of the gallbladder. Br J Surg 23:4–18

Imai N, Iwai A, Hatakeyama S, Matsuzaki K, Kitagawa Y, Kato S, Kato S, Hokari R et al (2001) Expression of bone morphogenetic proteins in colon carcinoma with heterotopic ossification. Pathol Int 51:643–648

Ishida J, Ajiki T, Hara S, Ku Y (2012) Gallbladder calcification leads to discovery of carcinosarcoma of the gallbladder. Surgery 152:934–935

Itai Y, Araki T, Yoshikawa K, Furui S, Yashiro N, Tasaka A (1980) Computed tomography of gallbladder carcinoma. Radiology 137:713–718

Jacobs MI, Rigel DS (1981) Acanthosis nigricans and the sign of Leser-Trélat associated with adenocarcinoma of the gallbladder. Cancer 48:325–328

Jankelson IR (1937) Clinical aspects of primary carcinoma of the gall bladder. N Engl J Med 217:85–88

Jin W, Zhang C, He X, Xu Y, Wang L, Zhao Z (2013) Differences between images of large adenoma and protruding type of gallbladder carcinoma. Oncol Lett 5:1629–1632

Jindal R, Jain A, Mittal A, Shirazi N (2012) Sweet's syndrome as the presenting manifestation of gall bladder adenocarcinoma. BMJ Case Rep. 2012. pii: bcr2012006869

Jönsson PE, Pettersson BA (1982) Carcinoma of the gallbladder – a natural history type of study. J Surg Oncol 21:215–218

Judd ES, Baumgartner CJ (1929) Malignant lesions of the gallbladder. Arch Int Med 44:735–745

Judd ES, Gray HK (1932) Carcinoma of the gall bladder and bile ducts. Surg Gynecol Obstet 55:308–315

Jung YM, Son BK, Ahn SB, Kim DM, Kim EK (2011) Intramural gallbladder hematoma mimicking gallbladder neoplasm in a 55-year-old male patient. J Korean Surg Soc 81:216–220

Kai K, Ide T, Masuda M, Kitahara K, Miyoshi A, Miyazaki K, Noshiro H, Tokunaga O (2011) Clinicopathologic features of advanced gallbladder cancer associated with adenomyomatosis. Virchows Arch 459:573–580

Kalekou H, Miliaras D (2011) Cytokeratin 7 and 20 expression in gallbladder carcinoma. Pol J Pathol 62:25–30

Kameyama H, Shirai Y, Date K, Kuwabara A, Kurosaki R, Hatakeyama K (2005) Gallbladder carcinoma presenting as exfoliative dermatitis (erythroderma). Int J Gastrointest Cancer 35:154–155

Kapoor VK, Pradeep R, Haribhakti SP, Sikora SS, Kaushik SP (1996) Early carcinoma of the gallbladder: an elusive disease. J Surg Oncol 62:284–287

Kaufmann E (1909) Lehrbuch der speziellen pathologischen Anatomie, 5th edn., Reimer G, Berlin

Kelly FJ, Speed T (1946) Primary carcinoma of the gallbladder. Tex State J Med 42:327–329

Kijima H, Wu Y, Yosizawa T, Suzuki T, Tsugeno Y, Haga T, Seino H, Morohashi S, Hakamada K (2014) Pathological characteristics of early to advanced gallbladder carcinoma and extrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Sci 21:453–458

Kim SW, Her KH, Jang JY, Kim WH, Kim YT, Park YH (2000) K-ras oncogene mutation in cancer and

precancerous lesions of the gallbladder. J Surg Oncol 75:246–251
Kim et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11410326
Kim J, Jang KT, Kim KH, Park JW, Chang BJ, Lee KH, Lee JK, Heo JS, Choi DW et al (2010) Aberrant maspin expression is involved in early carcinogenesis of gallbladder cancer. Tumour Biol 31:471–476
Kim SM, Oh SJ, Hur B (2012) Expression of MUC1 and MUC4 in gallbladder adenocarcinoma. Korean J Pathol 46:429–435
Kimura W, Shimada H, Kuroda A, Morioka Y (1989) Carcinoma of the gallbladder and extrahepatic bile duct in autopsy cases of the aged, with special reference to its relationship to gallstones. Am J Gastroenterol 84:386–390
Kirshbaum JD, Kozoll DD (1941) Carcinoma of the gall bladder and extrahepatic bile ducts; a clinical and pathological study of 117 cases in 13,330 necropsies. Surg Gynecol Obstet 73:740–754
Koga A, Yamauchi S, Nakayama F (1985) Primary carcinoma of the gallbladder. Am Surg 51:529–533
Koga A, Momii S, Eguchi M, Makino T (1991) Ultrastructure of well-differentiated adenocarcinoma of the gallbladder. Ultrastruct Pathol 15:41–48
Komai Y, Morimoto S, Saito K, Urushibara M, Sakai K, Ikeda S (2006) Possible involvement of bone morphogenetic protein 2 in heterotopic ossification in metastatic lesion from urothelial carcinoma of bladder. Int J Urol 13:1126–1128
Kott I, Urca I (1974) Carcinoma in situ of the gallbladder. Med Chir Dig 3:181–182
Kozuka S, Tsubone N, Yasui A, Hachisuka K (1982) Relation of adenoma to carcinoma in the gallbladder. Cancer 50:2226–2234
Krain LS (1972) Gallbladder and extrahepatic bile duct carcinoma. Analysis of 1,808 cases. Geriatrics 27:111–117
Kumar A, Aggarwal S (1994) Carcinoma of the gallbladder: CT findings in 50 cases. Abdom Imaging 19:304–308
Kumar A, Aggarwal S, Berry M, Sawhney S, Kapur BM, Bhargava S (1990) Ultrasonography of carcinoma of the gallbladder: an analysis of 80 cases. J Clin Ultrasound 18:715–720
Kunisch M, Hoppe M, Bohle RM, Weimar B, Rauber K, Rau WS (1997) Gallbladder adenocarcinoma in villous adenomatosis (papillomatosis) of the gallbladder and common bile duct (in German). Rofo 166:454–456
Kwon SY, Chang HJ (1997) A clinicopathological study of unsuspected carcinoma of the gallbladder. J Korean Med Sci 12:519–522
Laitio M (1983) Histogenesis of epithelial neoplasms of human gallbladder I. Dysplasia Pathol Res Pract 178:51–56
Lam CR (1940) The present status of carcinoma of the gallbladder: a study of thirty-four clinical cases. Ann Surg 111:403–410
Langner C, Lemmerer M, Komprat P (2004) Analysis of KIT (CD117) expression in gallbladder carcinomas by tissue microarray. Eur J Surg Oncol 30:847–850
Larraza-Hernandez O, Henson DE, Albores-Saavedra J (1984) The ultrastructure of gallbladder carcinoma. Acta Morphol Hung 32:279–293
Lee YH, Kim SH, Cho MY, Rhoe BS, Kim MS (2007) Actinomycosis of the gallbladder mimicking carcinoma: a case report with US and CT findings. Korean J Radiol 8:169–172
Lee TY, Ko SF, Huang CC, Ng SH, Liang JL, Huang HY, Chen MC, Sheen-Chen SM (2009) Intraluminal versus infiltrating gallbladder carcinoma: clinical presentation, ultrasound and computed tomography. World J Gastroenterol 15:5662–5668
Lentze FA (1926) Gallensteine und Gallenblasencarcinom. Beitr Klin Chir 137:38–62
Levin B (1999) Gallbladder carcinoma. Ann Oncol 10 (Suppl 4):129–130
Levy AD, Murakata LA, Rohrmann CA (2001) Gallbladder carcinoma: radiologic-pathologic correlation. Radiographics 21:295–314
Levy AD, Murakata LA, Abbott RM, Rohrmann CA (2002) From the archives of the AFIP. Benign tumors and tumorlike lesions of the gallbladder and extrahepatic bile ducts: radiologic-pathologic correlation. Armed Forces Institute of Pathology. Radiographics 22:387–413
Lichtenstein GM, Tannenbaum W (1940) Carcinoma of the gallbladder: a study of seventy-five cases. Ann Surg 111:411–415
Liebowitz HR (1939–1940) Primary carcinoma of the gall bladder. Am J Digest Dis 6:381–387
Luelsdorf F (1927) Die Beziehungen gwischen Steinkrankheit and Krebs der gallenblase. Zschr Krebsforsch 24:395–405
Lund J (1960). Surgical indications in cholelithiasis: prophylactic cholecystectomy elucidated on the basis of long term followup of 526 nonoperated cases. Ann Surg 151–173
Maesawa C, Ogasawara S, Yashima-Abo A, Kimura T, Kotani K, Masuda S, Nagata Y et al (2006) Aberrant maspin expression in gallbladder epithelium is associated with intestinal metaplasia in patients with cholelithiasis. J Clin Pathol 59:328–330
Magoun JAH, Renshaw K (1921) Malignant neoplasia in the gall-bladder. Ann Surg 74:700–720
Manigand G, Paillas J, Demuth L, Testas P, Deparis M (1971) Polycythemia and cancer of the gallbladder. Discussion apropos of an anatomoclinical case on the paraneoplastic nature of erythrocytosis (in French). Presse Med 79:3–6
Matsumoto N, Morine Y, Utsunomiya T, Imura S, Ikemoto T, Arakawa Y, Iwahashi S et al (2014) Role of CD151 expression in gallbladder carcinoma. Surgery. doi:10.1016/j.surg.2014.04.053
Mattson H (1942) Carcinoma of the gall bladder; study of sixty cases. Minn Med 25:985–988

Mazer LM, Losada HF, Chaudry RM, Velazquez-Ramirez GA, Donohue JH, Kooby DA et al (2012) Tumor characteristics and survival analysis of incidental versus suspected gallbladder carcinoma. J Gastrointest Surg 16:1311–1317

Melson GL, Reiter F, Evens RG (1976) Tumorous conditions of the gallbladder. Semin Roentgenol 11:269–282

Mitobe F, Hasegawa A, Ida T, Watanabe N (1970) Primary cancer of the gall bladder with suspected neuropathy without any clinical evidence (in Japanese). Naika 25:163–166

Miyahara N, Shoda J, Ishige K, Kawamoto T, Ueda T, Taki R, Ohkohchi N, Hyodo I et al (2008) MUC4 interacts with ErbB2 in human gallbladder carcinoma: potential pathobiological implications. Eur J Cancer 44:1048–1056

Mizuno T, Eimoto T, Tada T, Tateyama H, Inagaki H, Murase T (1999) Mucinous tumor of the gallbladder with a separate nodule of anaplastic carcinoma. Arch Pathol Lab Med 123:1280–1284

Mohardt JH (1939) Carcinoma of the gall bladder; collective review. Int Abstr Surg 69:440–451

Mukada T, Andoh N, Matsushiro T (1985) Precancerous lesions of the gallbladder mucosa. Tohoku J Exp Med 145:387–394

Musser JH (1889) Primary cancer of the gall-bladder and bile-ducts. Boston M S J 121:525–529

Nagakawa T, Mori K, Nakano T, Kadoya M, Kobayashi H, Akiyama T, Kayahara M et al (1993) Perineural invasion of carcinoma of the pancreas and biliary tract. Br J Surg 80:619–621

Nagakura S, Shirai Y, Yamai K, Hatakeyama K (1999) Calcification in mucinous cholangiocellular carcinoma. Hepatogastroenterology 46:465–466

Nakadaira K, Kurosaki I, Ueki H (2008) Recurrent gallbladder carcinoma treated with combination chemotherapy with gemcitabine, CPT-11 and S-1 – a successful case with metastatic tumors replaced by marked calcification (in Japanese). Gan To Kagaku Ryoho 35:837–839

Nakagawa T, Yamakado K, Takeda K, Nakagawa T (1996) An ossifying carcinoasarcoma of the gallbladder: radiologic findings. AJR Am J Roentgenol 166:1233–1234

Nakakubo Y, Miyamoto M, Cho Y, Hida Y, Oshikiri T, Suzuoki M, Hiraoka K, Itoh T et al (2003) Clinical significance of immune cell infiltration within gallbladder cancer. Br J Cancer 89:1736–1742

Narula IM (1971) Historical review of carcinoma of the gallbladder. Indian J Hist Med 16:6–11

Natarajan S, Xu F, Gilchrist K, Weber SM (2005) Cytokeratin is a superior marker for detection of micrometastatic biliary tract carcinoma. J Surg Res 125:9–15

Newman RP, Jacobs L, Cumbo T (1977) Myelopathy due to spinal metastasis from adenocarcinoma of the gallbladder. Cancer 40:2338–2342

Ni QF, Liu GQ, Pu LY, Kong LL, Kong LB (2013) Dermatomyositis associated with gallbladder carcinoma: a case report. World J Hepatol 5:230–233

Nilsson P, Ekberg O, Aspelin P, Sigurjonsson SV, Genell S (1989) Ultrasonography in the diagnosis of gallbladder carcinoma. Rofo 150:171–175

Nuzzo G, Clemente G, Cadeddu F, Ardito F, Ricci R, Vecchio FM (2005) Papillary carcinoma of the gallbladder and anomalous pancreaticobiliary junction. Report of three cases and review of the literature. Hepatogastroenterology 52:1034–1038

Ögredici Ö, Erb S, Langer I, Pilo P, Kerner A, Haack HG, Cathomas G, Danuser J, Pappas G, Tarr PE (2010) Brucellosis reactivation after 28 years. Emerg Infect Dis 16:2021–2022

Ohlsson EG, Aronsen KF (1974) Carcinoma of the gallbladder. A study of 181 cases. Acta Chir Scand 140:475–480

Ohtani T, Shirai Y, Tsukada K, Muto T, Hatakeyama K (1996) Spread of gallbladder carcinoma: CT evaluation with pathologic correlation. Abdom Imaging 21:195–201

Ohtsuki Y, Kimura M, Watanabe R, Okada Y, Teratani Y, Kurabayashi A, Takeuchi T et al (2012) Marked infiltration of eosinophils in necrotizing granulomas in the resected hepatic bed after cholecystectomy resulting from gallbladder cancer and metastatic liver cancer is associated with peculiar peripheral eosinophilia. Med Mol Morphol 45:53–57

Oikarinen H (2006) Diagnostic imaging of carcinomas of the gallbladder and the bile ducts. Acta Radiol 47:345–358

Olken SM, Bledsoe R, Newmark H (1978) The ultrasonic diagnosis of primary carcinoma of the gallbladder. Radiology 129:481–482

Onuma M, Miura M, Fujisaka Y, Zuguchi M, Asonuma S, Umemura T, Iioka Y, Outou T et al (2013) A case of huge papillary adenocarcinoma of the gallbladder with marked necrosis (in Japanese). Nihon Shokakibyo Gakkai Zasshi 110:95–103

Pandey M, Sood BP, Shukla RC, Aryya NC, Singh S, Shukla VK (2000) Carcinoma of the gallbladder: role of sonography in diagnosis and staging. J Clin Ultrasound 28:227–232

Pandey M, Pathak AK, Gautam A, Aryya NC, Shukla VK (2001) Carcinoma of the gallbladder: a retrospective review of 99 cases. Dig Dis Sci 46:1145–1151

Paraf F, Potet F (1988) Gallbladder carcinoma arising in adenomyomatosis. Am J Gastroenterol 83:1439

Parker GW, Joffe N (1972) Calcifying primary mucus-producing adenocarcinoma of the gall-bladder. Br J Radiol 45:468–469

Patel et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21716080

Pettersson H (1974) Carcinoma of the gallbladder. A review of 158 cases. Acta Radiol Diagn (Stockh) 15:225–236

Phan TG, Hersch M, Zagami AS (1999) Guillain-Barré syndrome and adenocarcinoma of the gall bladder: a paraneoplastic phenomenon? Muscle Nerve 22:141–142

Piehler JM, Crichlow RW (1977) Primary carcinoma of the gallbladder. Arch Surg 112:26–30
Polk HC (1966) Carcinoma and the calcified gallbladder. Gastroenterology 50:582–585
Post B, Wilhelmi F, Jänner M (1973) Bullous pemphigoid as a cutaneous paraneoplastic syndrome in carcinoma of the gallbladder (in German). Hautarzt 24:193–197
Pozza G, Valentini R, Ponti GB, Giangrande A (1966) On a case of leukemoid reaction in the course of adenocarcinoma of the gallbladder (in Italian). Haematol Lat 9:29–36
Proescher F (1907) A remarkable case of carcinoma of the gall-bladder in a man 22 years old. JAMA 48: 481–483
Ramia JM, Muffak K, Fernandez A, Villar J, Garrote D, Ferron JA (2006) Gallbladder tuberculosis: false-positive PET diagnosis of gallbladder cancer. World J Gastroenterol 12:6559–6560
Rana S, Dutta U, Kochhar R, Rana SV, Gupta R, Pal R, Jain K, Srinivasan R, Nagi B et al (2012) Evaluation of CA 242 as a tumor marker in gallbladder cancer. J Gastrointest Cancer 43:267–271
Randi G, Franceschi S, La Vecchia C (2006) Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 118:1591–1602
Ray R, Dey R, Chatterjee S, Guha P (2012) Gallbladder adenomyomatosis with tubercular portal lymphadenopathy masquerading as gallbladder carcinoma. Arab J Gastroenterol 13:150–152
Renshaw AA, Gould EW (2012) Submitting the entire gallbladder in cases of dysplasia is not justified. Am J Clin Pathol 138:374–376
Richard PF, Cantin J (1976) Primary carcinoma of the gallbladder: study of 108 cases. Can J Surg 19:27–32
Riedel B (1911) Zur Diagnose und Therapie des Gallenblasenkarzinomes. Münch Med Wochenschr 58:1337–1340
Roa I, Araya J, Shiraishi T, Yatanai R, Villaseca M, Wistuba I, De-Aretxabala X (1993) Proliferating cell nuclear antigen in gallbladder carcinoma. Histopathology 23:179–183
Roa I, Araya JC, Villaseca M, De Aretxabala X, Riedemann P, Endoh K, Roa J (1996) Preneoplastic lesions and gallbladder cancer: an estimate of the period required for progression. Gastroenterology 111:232–236
Roa I, de Aretxabala X, Araya C, Roa J (2006) Preneoplastic lesions in gallbladder cancer. J Surg Oncol 93:615–623
Robertson WA, Carlisle BB (1967) Primary carcinoma of the gallbladder. Review of fifty-two cases. Am J Surg 113:738–742
Rogers LF, Lastra MP, Lin KT, Bennett D (1973) Calcifying mucinous adenocarcinoma of the gallbladder. Am J Gastroenterol 59:441–445
Rolleston HD, McNee JW (1929) Diseases of the liver, gall-bladder, and bile-ducts, 3rd edn. The Macmillan, London, p 691
Rooholamini SA, Tehrani NS, Razavi MK, Au AH, Hansen GC, Ostrzega N, Verma RC (1994) Imaging of gallbladder carcinoma. Radiographics 14:291–306
Ryozawa S, Watanabe H, Abe M, Ajioka Y, Nishikura K, Okita K (1997) Macroscopic and stereomicroscopic diagnosis of superficial flat-type early carcinomas of the gallbladder. J Gastroenterol 32:635–642
Sainburg FP, Garlock JH (1948) Carcinoma of the gall bladder; report of 75 cases. Surgery 23:201–205
Sakurai et al. 2001. http://www.ncbi.nlm.nih.gov/pubmed/11294297
Sasaki E, Nagino M, Ebata T, Oda K, Arai T, Nishio H, Nimura Y (2006) Immunohistochemically demonstrated lymph node micrometastasis and prognosis in patients with gallbladder carcinoma. Ann Surg 244:99–105
Sato S, Ishii M, Fujihira T, Ito E, Ohtani Y (2010) Gallbladder adenocarcinoma with human chorionic gonadotropin: a case report and review of literature. Diagn Pathol 5:46
Sawyer KC (1970) The unrecognized significance of papillomas, polyps, and adenomas of the gallbladder. Am J Surg 120:570–578
Schwartz LH, Black J, Fong Y, Jarnagin W, Blumgart L, Gruen D, Winston C, Panicek DM (2002) Gallbladder carcinoma: findings at MR imaging with MR cholangiopancreatography. J Comput Assist Tomogr 26:405–410
Segovia Lohse HA, Cuenca Torres OM (2013) Prevalence and sequence of metaplasia-dysplasia-carcinoma of the gallbladder. A single centre retrospective study. Cir Esp 91:672–675
Seide J, Geller W (1933) Beitrag zur Frage nach dem Zusammenhang von Galensteinleiden und Krebs der Gallenblase. Arch Verdauungskr 54:71–78
Seretis C, Lagoudianakis E, Gemenetzis G, Seretis F, Pappas A, Gougiotis S (2014) Metaplastic changes in chronic cholecystitis: implications for early diagnosis and surgical intervention to prevent the gallbladder metaplasia-dysplasia-carcinoma sequence. J Clin Med Res 6:26–29
Shi CJ, Gao J, Wang M, Wang X, Tian R, Zhu F, Shen M, Qin RY (2011) Cd133+ gallbladder carcinoma cells exhibit self-renewal ability and tumorigenicity. World J Gastroenterol 17:2965–2971
Shi J, Liu H, Wang HL, Prichard JW, Lin F (2013) Diagnostic utility of von Hippel-Lindau gene product, maspin, IMP3, and S100P in adenocarcinoma of the gallbladder. Hum Pathol 44:503–511
Shimoji H, Nakachi A, Matsubara H, Miyazato H, Isa T, Hiroyasu S, Shiraishi M, Muto Y (2001) Fundic adenomyomatosis bulged with the subserosal excessive of the gallbladder mimicking polypoid carcinoma: a case report with unusual imaging and morphological features. Clin Imaging 25:187–191
Shirai et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22594526
Singhi AD, Adsay NV, Swierczynski SL, Torbenson M, Anders RA, Hruban RH, Argani P (2011) Hyperplastic

Luschka ducts: a mimic of adenocarcinoma in the gallbladder fossa. Am J Surg Pathol 35:883–890
Smithies F (1919) Primary carcinoma of the gall-bladder; an analysis of twenty-three proved instances of the disease. Am J Med Sci 157:67–74
Solaini L, Sharma A, Watt J, Iosifidou S, Chin Aleong JA, Kocher HM (2014) Predictive factors for incidental gallbladder dysplasia and carcinoma. J Surg Res 189:17–21
Solan MJ, Jackson BT (1971) Carcinoma of the gallbladder – a clinical appraisal and review of 57 cases. Br J Surg 58:593–597
Sons HU, Borchard F, Joel BS (1985) Carcinoma of the gallbladder: autopsy findings in 287 cases and review of the literature. J Surg Oncol 28:199–206
Soufi M, Benamer S, Chad B (2011) Pseudotumoral gallbladder tuberculosis (in French). Rev Med Interne 32: e32–e33
Stancu M, Caruntu ID, Giusca S, Dobrescu G (2007) Hyperplasia, metaplasia, dysplasia and neoplasia lesions in chronic cholecystitis – a morphologic study. Rom J Morphol Embryol 48:335–342
Sugaya Y, Sugaya H, Kuronuma Y, Hisauchi T, Harada T (1989) A case of gallbladder carcinoma producing both alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA). Gastroenterol Jpn 24:325–331
Sumiyoshi K, Nagai E, Chijiiwa K, Nakayama F (1991) Pathology of carcinoma of the gallbladder. World J Surg 15:315–321
Suzumura K, Iimuro Y, Asano Y, Kuroda N, Hirano T, Yamanaka J, Okada T, Okamoto T et al (2014) Granulocyte-colony stimulating factor-producing gallbladder carcinoma. Int Surg 99:577–583
Swank HA, Mulder IM, Hop WC, van de Vijver MJ, Lange JF, Bemelman WA (2013) Routine histopathology for carcinoma in cholecystectomy specimens not evidence based: a systematic review. Surg Endosc 27:4439–4448
Tajima Y, Tomioka T, Ikematsu Y, Ichinose K, Inoue K, Kanematsu T (1999) Immunohistochemical demonstration of cytokeratin is useful for detecting micrometastatic foci from gallbladder carcinoma in regional lymph nodes. Jpn J Clin Oncol 29:425–428
Takahashi M, Fujiwara M, Kishi K, Sakai C, Sanada M, Moriyama Y, Shibata A (1985) CSF producing gall bladder cancer: case report and characteristics of the CSF produced by tumor cells. Int J Cell Cloning 3:294–303
Takeda T, Ichiyanagi A, Sano K, Yoshida J, Tsutsumi Y, Miyaji T (1990) A case of gallbladder cancer producing granulocyte-colony-stimulating factor. Gastroenterol Jpn 25:762–767
Tan SW, Lai SK, Ng KW, Chen P, Chen KH, Jiang CF (2005) Intramural gallbladder hematoma mimicking gallbladder neoplasm in a 33-year-old male. J Chin Med Assoc 68:146–149
Tanga MR, Ewing JB (1970) Primary malignant tumors of the gall-bladder: report of 43 cases. Surgery 67:418–426
Tanga MR, Bouchard A, Ewing JB (1973) Carcinoma developing in gall bladder remnants. J Indian Med Assoc 61:132–133
Tashiro T, Hirokawa M, Horiguchi H, Wakatsuki S, Sano T, Yada S (2000) Well-differentiated adenocarcinoma of the gallbladder mimicking minimal deviation adenocarcinoma of the cervix. APMIS 108:173–177
Tatematsu M, Ichinose M, Miki K, Tatematsu K, Kishikawa H, Ito N (1988) Gastric phenotype expression in human gallbladder cancers revealed by pepsinogen immunohistochemistry and mucin histochemistry. Virchows Arch A Pathol Anat Histopathol 413:25–32
Teh M, Wee A, Raju GC (1994) An immunohistochemical study of p53 protein in gallbladder and extrahepatic bile duct/ampullary carcinomas. Cancer 74:1542–1545
Terada T (2008) Gallbladder adenocarcinoma arising in Rokitansky-Aschoff sinus. Case Rep Pathol Int 58:806–809
Terada T (2013) Histopathologic features and frequency of gall bladder lesions in consecutive 540 cholecystectomies. Int J Clin Exp Pathol 6:91–96
Tham CH, Ng BK (2001) Gallstone granuloma: a rare complication of laparoscopic cholecystectomy. Singapore Med J 42:174–175
Thomas A, Nocia A (1896) Cancer primitive de la vésicule biliaire. Bull Soc Anat Paris 10:471–473
Tian H, Matsumoto S, Takaki H, Kiyosue H, Komatsu E, Okino Y, Mori H, Miyake H (2003) Mucin-producing carcinoma of the gallbladder: imaging demonstration in four cases. J Comput Assist Tomogr 27:150–154
Tragermann LJ (1953) Primary carcinoma of the gallbladder; review of 173 cases. Calif Med 78:431–437
Treutlein A (1901) Ueber eine Fall von primärem Gallenkrebs der Gallenblase. Centralbl Allg Pathol Pathol Anat 12:825–828
Trivedi V, Gumaste VV, Liu S, Baum J (2008) Gallbladder cancer: adenoma-carcinoma of dysplasia-carcinoma sequence? Gastroenterol Hepatol 4:735–737
Tsuchiya Y (1991) Early carcinoma of the gallbladder: macroscopic features and US findings. Radiology 179:171–175
Vadheim JL, Gray HK, Dockerty MB (1944) Carcinoma of the gallbladder; a clinical and pathologic study. Am J Surg 63:173–180
Varshney S, Butturini G, Gupta R (2002) Incidental carcinoma of the gallbladder. Eur J Surg Oncol 28:4–10
Verma R, Vij M, Pal L (2012) Gall bladder tuberculosis masquerading as carcinoma: dilemma resolved by aspiration cytology. Diagn Cytopathol 40:91–93
Villabona CM, Esteve M, Vidaller A, Escobedo AP, Pac MP, Petriz L (1986) Hypercalcemic crisis in gallbladder cancer. Acta Gastroenterol Belg 49:532–535
Wakabayashi T, Kishimoto H, Miwa Y, Riku S (1978) Cancer of gallbladder with severe thrombocytosis. Acta Pathol Jpn 28:627–635
Wakai T, Ajioka Y, Nagino N, Yamaguchi N, Shirai Y, Hatakeyama K (2012) Morphological features of early

gallbladder carcinoma. Hepatogastroenterology 59:1013–1017
Wang YK, Zhao W, Hao Y, Zhang Y, Guo YB, Meng NL, Ma L, Li J (2006) Clinicopathologic features of gallbladder adenocarcinoma with marked stromal fibrosis – a report of 19 cases (in Chinese). Ai Zheng 25:896–900
Warren R, Balch FG (1940) Carcinoma of the gall bladder; the etiological role of gallstones. Surgery 7:657–666
Warthin AS (1900) A case of primary adenocarcinoma of the gallbladder with secondaries in both adrenals, melanosis of skin (Addison's disease?), vitiligo, and hypertrophy of the pancreas. Phila Med J 6:38–40
Watanabe Y, Ogino Y, Ubukata E, Sakamoto Y, Matsuzaki O, Shimizu N (1989) A case of a gallbladder cancer with marked hypercalcemia and leukocytosis. Jpn J Med 28:722–726
Werko L (1945) Acanthosis nigricans associated with carcinoma of the gallbladder and plantar hyperkeratosis; report of a case. Acta Derm Venereol 26:70–83
Wolma FJ, Lynch JB (1961) Papillary carcinoma of the gallbladder. The importance of lymph node dissection in early cases. Arch Surg 83:657–660
Xin-Wei Y, Jue Y, Bao-Hua Z, Feng S (2013) An unusual gallbladder carcinoma with tumor thrombus in the common bile duct. J Cancer Res Ther 9:122–124
Xu LN, Zou SQ (2007) A clinicopathological analysis in unsuspected gallbladder carcinoma: a report of 23 cases. World J Gastroenterol 13:1857–1860
Yadav R, Jain D, Mathur SR, Sharma A, Iyer VK (2013) Gallbladder carcinoma: an attempt of WHO histological classification on fine needle aspiration material. Cytojournal 10:12
Yamagiwa H (1987) Dysplasia of gallbladder. Its pathological significance. Acta Pathol Jpn 37:747–754
Yamagiwa H, Tomiyama H (1986) Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. Acta Pathol Jpn 36:989–997
Yamaguchi A, Hachisuka K, Isogai M, Tsubone M (1992) Carcinoma in situ of the gallbladder with superficial extension into the Rokitansky-Aschoff sinuses and mucous glands. Gastroenterol Jpn 27:765–772
Yamamoto M, Nakajo S, Tahara E (1989a) Dysplasia of the gallbladder. Its histogenesis and correlation to gallbladder adenocarcinoma. Pathol Res Pract 185:454–460
Yamamoto M, Nakajo S, Tahara E (1989b) Histogenesis of well-differentiated adenocarcinoma of the gallbladder. Pathol Res Pract 184:279–286
Yeh HC (1979) Ultrasonography and computed tomography of carcinoma of the gallbladder. Radiology 133:167–173
Yiannopoulos G, Ravazoula P, Meimaris N, Stavropoulos M, Andonopoulos AP (2002) Dermatomyositis in a patient with adenocarcinoma of the gall bladder. Ann Rheum Dis 61:663–664
Yokoyama N, Shirai Y, Hatakeyama K (1999) Immunohistochemical detection of lymph node micrometastases from gallbladder carcinoma using monoclonal anticytokeratin antibody. Cancer 85:1465–1469
Yoshimitsu K, Irie H, Aibe H, Tajima T, Nishie A, Asayama Y, Matake K, Yamaguchi K et al (2005) Well-differentiated adenocarcinoma of the gallbladder with intratumoral cystic components due to abundant mucin production: a mimicker of adenomyomatosis. Eur Radiol 15:229–233
Yuan Y, Yang ZL, Miao XY, Liu ZR, Li DQ, Zou Q, Li JH, Liang LF, Zeng GX et al (2014) EphB1 and Ephrin-B, new potential biomarkers for squamous cell/adenosquamous carcinomas and adenocarcinomas of the gallbladder. Asian Pac J Cancer Prev 15:1441–1446
Yun EJ, Yoon DY, Choi CS, Bae SH, Seo YL, Chang SK, Lim KJ, Kwon JH, Kwon MJ et al (2011) Calcified carcinoma of the gallbladder with calcified nodal metastasis presenting as a porcelain gallbladder: a case report. Cancer Res Treat 43:71–74
Zenker H (1889) Der primäre Krebs der Gallenblase und seine Beziehungen zu Gallensteinen und Gallenblasennarbe. Thesis, University of Erlangen
Zhang Y, Huang Y, Qin M (2013) Tumour-infiltrating FoxP3+ and IL-17-producing T cells affect the progression and prognosis of gallbladder carcinoma after surgery. Scand J Immunol 78:516–522

Adenocarcinoma of the Gallbladder: Biology of Disease, Prognosticators, and Staging

148

Contents

Abstract

Biology of disease and progression of ordinary gallbladder carcinoma depends on several factors. For local spread, perineural and intraneural invasions are important risk factors. Gallbladder carcinoma often extends beyond the organ boundaries and invades the gallbladder bed, liver, and adjacent soft tissues. Lymph node metastasis is a characteristic feature of gallbladder carcinoma and a significant prognostic factor. Pericholedochal nodes are a common metastatic site, followed by the cystic node. There is a relationship between T stage and the incidence of locoregional lymph node metastases. The prognostically significant patterns of gallbladder cancer spread to the liver include hepatic bed type, hepatic hilum type, bed and hilum type, lymph node type, cystic duct type, and localized type. Gallbladder carcinoma can spread through intraluminal bile duct invasion. It produces a distinct pattern of distant metastases, although extraabdominal metastasis is overall uncommon in gallbladder carcinoma. Important prognosticators for tumor progression are tumor stage, lymph node stage, radicality of resection, perineural invasion, and the histologic grade.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_148

Biology of Disease

The natural course of CG is characterized by a high tendency for invasion, spread, and metastasis (Fahim et al. 1962). Most of the patients with CG present with advanced disease at the time point of diagnosis, precluding curative resection resulting in dismal prognosis (Dutta 2012). In some series, almost half of patients showed metastatic disease at the time point of diagnosis (Hamrick et al. 1982). The overall 5-year survival for patients with CG having undergone R0 curative resection was reported to range from 21 % to 69 % in diverse studies (review: Lai and Lau 2008).

Local Invasion

Perineural and intraneural invasions are important modes of local spread in CG. The incidence ranged from 22 % to more than 50 % (Vadheim et al. 1944; Kuwayti et al. 1957; Fahim et al. 1962; Ouchi et al. 1987; Nagakawa et al. 1993). Perineural cancer invasion has to be distinguished from perineural invasion observed in benign conditions, such as adenomyomatous hyperplasia (Albores-Saavedra et al. 2007) and pyloric gland metaplasia (Albores-Saavedra and Henson 1999). There is a correlation between the prevalence of perineural invasion and higher histologic grade (Fahim et al. 1962). CG often extends beyond the organ's boundaries and invades the gallbladder bed, the liver, soft tissues surrounding the bile ducts, and the hepatoduodenal ligament. In bile ducts located to the hepatoduodenal ligament, perineural invasion in the setting of bile duct infiltration is a sign of aggressive tumor disease (Kaneoka et al. 2003). Pathogenetically, expression of the neural cell adhesion molecule/NCAM by carcinoma cells seems to play an important role as a neurotrophic mechanism (Seki et al. 1995). The direct extension of CG tumor cells from the primary tumor to adjacent organs and structures is only partially elucidated. One mechanism involves mucosal and submucosal lymphatic vessel networks that connect neighboring organs. In patients with CG, cancer cells spread through lymphatic vessels in the submucosal layer of the common bile duct (Chikamoto et al. 2009). CG frequently invades blood vessels, in particular veins. The anatomy of the venous drainage of the gallbladder has been studied in detail (Habighorst et al. 1965; Halvorsen and Myking, 1971 9). The first authoritative investigation based on injection methods dates from 1932 (Karlmark 1932). This author demonstrated that the venules and small veins of the gallbladder form a continuous plexus localized to the adventitia of the organ. This plexus is, via venous bridges, connected with a similar plexus of the extrahepatic bile ducts. The plexus system is in turn drained by a variable number of cholecystic veins showing diverse types of arrangement. On the hepatic side of the gallbladder, the number of cholecystic veins ranges from 2 to 20, and these veins terminate in the quadrate lobe of the liver adjacent to the gallbladder bed. In contrast, the peritoneal side of the gallbladder shows usually only one cholecystic vein (rarely two). This vein drains either into the liver or into the periductal venous plexus, which in turn is connected to the veins of the quadrate lobe. In part of cases, this vein drains into the portal vein (review: Fahim et al. 1962). The significance of portal vein drainage is underlined by the observation of dilated gallbladder veins or gallbladder varices in the setting of portal hypertension (Marchal et al. 1985; Ralls et al. 1988; Kainberger et al. 1990). Veins that enter the quadrate lobe form a plexus of small vessel that finally drain into the hepatic vein of this lobe (Petrén 1932). Small veins of the cystic duct join at the neck of the gallbladder to form either single or double cystic veins which accompany the cystic duct to connect to the periductal veins (review: Fine 1997). This anatomical substrate suggests an important pathway for CG spread both into the region of the extrahepatic bile ducts and the hepatoduodenal ligament and the right-sided liver. In a study of 155 cases of CG, involvement of gallbladder vessels was identified in 13.9 %, invasion involving venules having a diameter of 500–1,200 μm to larger veins with a thick muscular wall. In large veins, traffic of cancer cells through the wall seems to take place via transmural invasion and/or extension along vasa

vasorum (Fahim et al. 1962). CG cancer cells can spread through lymphatic vessels in the submucosa of the common bile duct (Chikamoto et al. 2009).

Lymph Node Metastasis

Lymph node metastasis is a characteristic feature of CG that represents a significant prognostic factor. The incidence of lymph node metastasis in CG varies from 35 % to 75 % in diverse studies (Cooper 1937; Vadheim et al. 1944; Jones 1950; Willis 1953). Lymphatic spread may show a distinct distribution pattern, with the pericholedochal nodes being the most commonly affected, followed by the cystic node. Lymph node metastasis by CG cab develops in the absence of involvement of the liver (Cappell and Tudhope 1934). This distinct pattern results from the specific anatomy of the lymphatic drainage of the gallbladder. By means of Prussian blue injection into human fetuses 8–9 months old, Clermont (1909) had studied the lymphatic vessels of the gallbladder and gallbladder-associated lymph nodes in detail. The gallbladder wall harbors lymphatic plexus that traverses the entire wall and enters lymphatic collecting trunks that are mainly located on the inferior surface of the gallbladder. They are arranged like the letter "N," as they are present on both the left and the right borders and diagonally toward the left side of the gallbladder neck (Fahim et al. 1962). The left-sided collecting trunks empty into the cystic node which is situated in the acute angle formed between the cystic duct and the common hepatic duct, while the right-sided collecting trunks pass along the right border of the gallbladder neck and extend uninterrupted to empty into the pericholedochal nodes (reviewed by Fahim et al. 1962). Also the lymph from the cystic node ends in the pericholedochal nodes. The latter are usually two lymph nodes, termed the node of the hiatus and the superior pancreaticoduodenal node. The node of the hiatus was a constant finding in Clermont's investigation. It is situated to the right of the common duct, its lower pole being at the level of the attachment of the lesser omentum behind the superior portion of the duodenum. The node of the hiatus also receives lymph from the extrahepatic bile ducts and from the right liver lobe. Three to four efferent lymphatic vessels of the node of the hiatus continue to reach the superior pancreaticoduodenal node, which is located along the superior surface of the pancreas to the right of the common duct (summarized in Fahim et al. 1962). Efferent lymphatics of this node continue either to the preaortic peri-celiac nodes or to the three to four posterior pancreaticoduodenal nodes which are located around the vessel arcade in the posterior pancreaticoduodenal groove. From here, the lymph flows to the nodes around the superior mesenteric artery. Clermont (1909) found lymph nodes along the hepatic pedicle in relation to the hepatic artery, draining the left liver lobe only, but he did not find any Quénu-type hepatic hilar lymph nodes (proposed to exist by Edouard André Victor Alfred Quénu, 1852–1944, French surgeon active in anatomy and surgical pathology). Clermont's studies referred to human fetuses and infants and the situation in adults may differ from findings obtained in the prenatal and pediatric age group. The lymphatic system of the gallbladder was subject to more recent investigations on adult individuals. Ito and coworkers (1991) divided gallbladder lymphatic drainage into three pathways, i.e., the cholecystoretropancreatic pathway (the main pathway), having two routes, namely, one running spirally and posteriorly from the anterior surface of the common bile duct to the right and the other one running almost straight down from the posterior surface of the common bile duct. These routes end at a retroportal lymph node, termed by the authors the principal retroportal node. A second route connected the gallbladder with the celiac nodes, and a third ran in front of the portal vein to the superior mesenteric nodes.

There is a relationship between the T stage and the incidence of locoregional lymph node metastases. In one study, none of 15 patients with stage pT1 tumors had lymph node metastasis, while 60 of 96 patients with pT2-4 tumor disease had lymph node metastases. pT3-4 tumors displayed more lymph node involvement and significantly higher N2:N1 ratios (2.5) than pT2 tumors.

Patients with N2 disease had a worse prognosis than those with N1 (Tsukada et al. 1997). Overexpression of microRNA-155, associated with inflammation-induced carcinogenesis, in CG is closely correlated with the emergence of lymphatic metastasis and poor prognosis. In vitro assays revealed that aberrant expression of miRNA-155 enhanced CG cell proliferation and invasion (Kono et al. 2013).

Invasion of the Liver and Intrahepatic Metastasis

Among early sites of metastasis, the liver is often involved. In fact, hepatic metastasis is the most frequent mode of recurrence of advanced CG after radical resection, and microscopic liver metastases in CG are an independent prognostic factor (Endo et al. 2004). Infiltration and/or metastatic involvement of the liver was detected in up to 89 % of cases (Lam 1940; Vadheim et al. 1944; Glenn and Hays 1954; Burdette 1957; Sons et al. 1985). It may, however, sometimes be difficult to distinguish hepatic metastases in segments close to the gallbladder from direct invasion of the liver substance. The pathways leading to true hepatic metastases have been discussed, emphasis being placed on the anatomic relationships between gallbladder veins and the anterior portal vein (Shirai et al. 1995; Yoshimitsu et al. 1997, 2001; Ohtsuka et al. 1998; Lin et al. 2005; Table 1). The extent of microscopic angiolymphatic portal tract invasion correlated with the gross depth of direct invasion of the liver (Shirai et al. 1995).

Table 1 Patterns of gallbladder carcinoma spread to the liver

***Kondo system* (2002)**
Hepatic bed type
Hepatic hilum type
Bed and hilum type
Lymph node type
Cystic duct type
Localized type
***Wakai system* (2010)**
Direct invasion through the gallbladder bed
Portal tract invasion
True hepatic metastatic nodules

Kondo and coworkers (2002) identified six types of CG spread. In the hepatic bed type, a large mass in the fundus and body of the gallbladder invaded the liver substance through the gallbladder bed. In the hepatic hilum type, CG of the gallbladder neck infiltrates the hepatic hilum causing obstructive jaundice. In the bed and hilum type, huge masses occupying the entire gallbladder involve both the gallbladder bed and the hepatic hilum. In the lymph node type, enlarged metastatic lymph nodes are the most prominent feature. In the cystic duct type, a small mass arising from the cystic duct involves the common bile duct. In the localized type, tumor spread is localized to the gallbladder and presents at the earliest stage of any type (Kondo et al. 2002). In another study, the mode of hepatic spread was classified into three patterns, i.e., direct invasion through the gallbladder bed, portal tract invasion, and true hepatic metastatic nodules. A significant proportion of cases with portal tract invasion revealed invasion of hepatic lymphatic vessels as shown by D2-40/podoplanin immunohistochemistry (Wakai et al. 2010).

Intraductal Spread of Gallbladder Carcinoma

CG can spread through intraluminal invasion of the extrahepatic biliary tract. It was found in up to 4 % of cases (Fahim et al. 1962). Rarely, CG showed intraluminal implantation into bile ducts (so-called implantation metastasis or formation of intraluminal tumor "thrombi" or "emboli"; Hollings 1963; Al-Qudah 1994; Evans 1994; Midorikawa et al. 2000). In case intraluminal CG metastasis involves the confluence or the common bile duct, obstructive jaundice ensues (Hollings 1963; Midorikawa et al. 2000).

Distant Metastasis

CG produces a distinct pattern of distant metastases, although extraabdominal metastases are

overall uncommon in CG. The most common metastatic site is the lung (Tokunaga et al. 2005; Jeyaraj et al. 2013), followed by the central nervous system (Takano et al. 1991; Tayo et al. 2005), ovaries (Singh et al. 2010), soft tissues, and breast (Khangembam et al. 2013). In rare instances, pulmonary metastasis of CG presents with a lepidic growth patterns, i.e., cancer cells lining alveolar spaces (Tokunaga et al. 2005). Similar to carcinomas of the extrahepatic bile ducts, CG can produce ovarian metastases that sometimes present as Krukenberg tumors (Andrieux et al. 1972; Chicos et al. 2007). Solitary metastases to the skeleton occur, but are rather uncommon (Rominger et al. 1961; Prakash et al. 2010; Chaudhari et al. 2014; Puranik et al. 2014). Multiple osseous metastases are even less common (Commandre et al. 1965; Misra et al. 1997). Subcutaneous metastasis is also rare in CG, but may present as a rapidly progressive cancer disease (Heavey et al. 2014). Other rare sites comprise the orbita (Puglisi et al. 2005), heart (Gunjiganvi et al. 2013), adrenal gland (Sahoo et al. 2014), and uterus (Martinez-Roman et al. 2005; Kefeli et al. 2009).

The mechanisms leading to early and widespread metastasis in CG are only partially known. CG shows an upregulation of the prometastatic microRNA-20, closely associated with local cancer invasion and distant metastasis. A markedly increased level of TGF-beta1 is responsible for the elevation of microRNA-20a, which in turn promotes epithelial-mesenchymal transition thought to promote metastasis (Chang et al. 2013).

Implant Metastasis

Implant metastasis of CG can develop in cholecystectomy scars (Merz et al. 1993). In some patients, metastases of CG have been found at the port site (Karayannakis and Knight 1997; Reber et al. 1998; Ohmura et al. 1999; Winston et al. 1999; Nakagawa et al. 2000), trocar site (Copher et al. 1995), or umbilicus (Clair et al. 1993; Kessler and Mihaljevic 1994; Jacobi et al. 1995; Jeon et al. 1999) following laparoscopic cholecystectomy. The incidence of recurrence of incidental CG at the port site following laparoscopic cholecystectomy was 14 % in one study and was similar whether the primary tumor was confined to the gallbladder (T1/T2) or locally advanced (T3/T4; Z'graggen et al. 1998). In an international survey, it was found port site recurrence was identified in 17.1 % of 409 patients with a median of 180 days following laparoscopic cholecystectomy for nonapparent CG (Paolucci et al. 1999). Laparoscopic cholecystectomy with the finding of unsuspected CG may be followed by cutaneous seeding (Kim and Roy 1994), and laparoscopic removal of CG may cause peritoneal cancer dissemination (Pezet et al. 1992; Sailer et al. 1995; Marmorale et al. 1998; Ohtani et al. 1998; Shirai et al. 1998). Cancer spread to the peritoneum in the setting of laparoscopic cholecystectomy was mainly found in the presence of T3 tumors (Wysocki and Krzywon 2000). Rarely, CG gave rise to umbilical metastasis, alias Sister Mary Joseph's nodule, in the absence of laparoscopic surgery (Rousselot et al. 1964; Bork et al. 2002; Renner and Sticherling 2007). Sister Mary Joseph's nodule refers to a palpable tumor nodule bulging into the umbilicus due to a metastasis from an abdominal or pelvic malignancy. The eponym is related to Sister Mary Joseph Dempsey (1856–1939), surgical assistant of Dr. William J. Mayo at St. Mary's Hospital in Rochester, who drew Dr. Mayo's attention to the phenomenon of umbilical metastasis, the metastatic pathway probably involving lymphatics along the obliterated umbilical vein. Laparoscopic cholecystectomy can also be complicated by parietal seeding of carcinoma (Barsoum and Windsor 1992) or by seeding into the gallbladder fossa (Evrard et al. 1996). Seeding of CG along the intervention tract was observed following percutaneous transhepatic choledochoscopy (Yamakawa et al. 1983).

Prognosticators

A growing list of factors affecting prognosis of CG have been identified, relating to growth factors and their receptors, factors regulating

proliferation and apoptosis, adhesion molecules, factors regulating cell motility and locomotion, enzymes involved in tissue invasion, and angiogenic factors (review: Gomez-Roel et al. 2007).

Stage

Tumor stage (T stage) and lymph node metastases (N stage) are important prognosticators in CG. The T category is a decisive factor for predicting outcome (Kayahara and Nagakawa 2007; Cho et al. 2012). Early CG, limited in its extension to the intramucosal compartment (pT1a), is usually an incidental finding, but this stage is associated with good prognosis (Albores-Saavedra et al. 2011). The presence of lymph node metastases is an important predictor of outcome, whereby the number in involved lymph nodes independently determines prognosis after tumor resection (Sakata et al. 2010; Shirai et al. 2012). Distant positive lymph nodes have a particularly adverse effect on outcome (Meng et al. 2011). There is increasing evidence that the lymph node ratio (LNR) is an important prognostic factor for CG patients. LNR was a powerful predictor of disease-free survival in curatively resected patients, specifically in stage IIIB disease (Negi et al. 2011; Choi et al. 2013). In another investigation, however, the number of positive lymph nodes better predicted patient outcome after resection than LNR or location of positive nodes (Shirai et al. 2012). The presence of lymph node metastases in CG is associated with expression of the high molecular weight glycoprotein, DF3 (MUC 1). Lymph node metastasis was frequently found in the cytoplasmic DF3- and stromal DF3-positive CG, suggesting that DF3 expression plays important roles in cancer cell growth and metastasis of CG (Kashiwagi et al. 2000). The prognostic significance of nodal micrometastases in CG is not yet known in detail, but was shown to have an impact on survival (Sasaki et al. 2006) or even be an independent prognosticator for poor outcome (Nagakura et al. 2001). In one investigation, nodal micrometastases were found in 2.3 % of lymph nodes that were macrometastasis negative at conventional examination. Micrometastases correlated with non-micro-lymph node metastases on conventional tissue sections and were a significant prognostic factor, although they may reflect cancer cell spread to the whole body rather than an initial event of cancer spread (Tanabe et al. 2012). Distant metastases are a decisive factor for prognosis in patients with CG. Hepatic metastasis is the most common mode of recurrence of advanced CG after radical resection. Both macroscopic and microscopic liver metastases are involved in progressive disease and dismal prognosis.

Radicality of Resection

The presence or absence of carcinoma in the resection margin significantly affects outcome (Chakravarty et al. 2009). Carcinoma spread to the cystic duct is a prognosticator which indicates poor prognosis in CG patients, probably also linked to a high proportion of associated perineural invasion and lymph node metastasis (Nakata et al. 2007). It should be mentioned that high-grade dysplasia may rarely occur in the cystic duct margin in the absence of invasive CG (Bickenbach et al. 2011). Intraoperative frozen section is a common method to evaluate resection margins in the setting of cholecystectomies performed for CG, but has some interpretational drawbacks due to the presence of gallbladder structures that may be confounded with cancer, including glands and (atypical) Rokitansky-Aschoff sinuses. It has been demonstrated that frozen section and permanent diagnoses of the bile duct margin in CG may be inconsistent in up to 25 % of cases due to overdiagnosis in frozen sections and the “appearance” of carcinoma in permanent histology slides (Yamaguchi et al. 2005).

Incidental Versus Non-incidental CG

A significant fraction of CGs are incidental tumors detected in cholecystectomy specimens obtained via resection of suspected benign disease. Patients with incidental CG (IGC) had a longer survival rate compared to patients with

non-incidental CG (NIGC). In one study, the majority of patients with potentially curable disease had IGC (D'Hondt et al. 2013).

Histologic Type

With few exceptions, the histologic type of CG did not affect biology of disease (Glenn and Hays 1954). In a comparative study, well-differentiated or moderately differentiated tubular adenocarcinomas were associated with a longer survival time than poorly differentiated carcinomas, the latter also having a higher incidence of hematogenous metastases (Egawa et al. 2004). Most CG shows the histology of adenocarcinoma, and the relatively few neoplasms with distinct morphologies different from ordinary adenocarcinoma mainly comprise papillary and colloid carcinomas. In comparison with all other histologic types, papillary CG had the most favorable prognosis, in some series found in patients with long survival (Fahim et al. 1963; Frank and Spjut 1967; Hart et al. 1972; Ouchi et al. 1986; Henson et al. 1992).

Histologic Grade

Dedifferentiation is often observed in CG and is associated with poor prognosis. In an ECOG study on 30 patients with advanced CG divided into either low-grade or high-grade lesions, the 13-week low-grade CG patient survival was significantly longer than the 7-week high-grade CG patient survival (Johnson et al. 1987). In part of CG, less differentiated tumor cells form isolated single cells or clusters of fewer than five cancer cells at the invasive front. Similar to the respective situation in colorectal carcinomas, this phenomenon is termed tumor budding, a lesion that reflects prognosis, particularly for T2 tumors (Kai et al. 2011).

Invasion Patterns

The presence of perineural invasion is a negative prognosticator in patients with CG (Nagakawa et al. 1993; Yamaguchi et al. 2002; Noshiro et al. 2003; Nakata et al. 2007). In one study of 68 patients with CG, perineural invasion was demonstrated in 71 % of patients. The incidence of invasion was correlated with invasion of extrahepatic bile ducts, which was the only independent factor associated with perineural involvement. The 5-year survival rate of patients with perineural invasion was 7 % in comparison with 71 % of patients without detectable perineural invasion (Yamaguchi et al. 2002). Bile duct involvement portends poor prognosis in resected CG (Chan et al. 2005; Eil et al. 2013). In early CG, intraepithelial extension into Rokitansky-Aschoff sinus is an adverse prognostic factor (Roa et al. 2013). As in other carcinomas, vascular invasion is a negative prognostic factor in CG. Expression of vascular endothelial growth factor-C/VEGF-C was expressed in 63 % of CG, and this expression was associated with lymphatic vessel invasion and lymph node metastasis, suggesting that VEGF-C is involved in tumor progression through lymphangiogenesis and facilitation of lymphatic vessel invasion (Nakashima et al. 2003). Invasion of the hepatic artery is an important prognostic factor in patients with CG, as infiltration of this artery confers high risk and a poorer prognosis (Kobayashi et al. 2012).

Oncogene and Tumor Suppressor Gene Expression and Factors Involved in Chromatin and DNA Metabolism

A significant proportion of CG expresses p53. Fifty-eight percent of these cancers were immunoreactive for p53 in one analysis, seen more often in moderately or poorly differentiated neoplasms (Washington and Gottfried 1996). No significant correlation was found between p53 overexpression and T stage, lymph node metastasis, prognosis, or recurrence in patients with CG, but p53 overexpression was correlated with aneuploidy (Ajiki et al. 1996). p53 nuclear overexpressions in CG were not related to cancer differentiation, depth of gallbladder wall invasion, or patient survival (Hidalgo Grau et al. 2004).

Lack of correlation between p53 expression in CG and survival was found in another investigation (Washington and Gottfried 1996). On the other hand, other investigations reported a role of p53 gene mutation in the transition from premalignancy to malignancy (Ajiki et al. 1996; Moreno et al. 2005) and a correlation between p53 expression in CG and poor survival (Takagawa et al. 2005). An important regulator of chromatin, involved in silencing tumor suppressor genes, is the histone deacetylase (HDAC) system. The Myc oncogene pathway seems to be involved in carcinogenesis and progression of CG. N-myc downstream-regulated gene 1 (NDRG1), a member of the N-myc downstream-regulated gene family, is associated with inhibition of tumor metastasis and tumor suppression. In CG, NDRG1 was expressed in 63.8 % of cases, specifically at the invasive front of the tumors, but not in normal gallbladder epithelium. This expression was significantly associated with high histologic grade, advanced T stage, positive nodal metastasis, venous/lymphatic invasion, and poor survival (Zhang et al. 2012). In CG, overexpression of HDAC 2 in tumor cell nuclei is correlated with higher histologic grade, and predicts unfavorable prognosis (Du et al. 2013a). There is evidence that factors involved in chromatin replication and chromatin remodeling are altered in CG and affect biology of disease. Rsf-1/HBXAP, a nuclear protein with histone chaperon function and member of the remodeling and spacing factor complex which mediates ATPase-dependent chromatin remodeling, is expressed in CG, and its overexpression confers aggressiveness and is associated with disease-specific survival (Chen et al. 2011a). Decreased expression of the chromodomain helicase DNA-binding protein 5 in CG cells is correlated with a higher lymph node metastasis rate and shorter disease-free survival and overall survival (Du et al. 2013b). Dicer and Drosha, two enzymes critically involved in the processing of microRNA, are significantly less expressed in CG than in dysplastic gallbladder epithelia and were less expressed in poorly differentiated carcinomas with lymph node metastases in comparison with well-differentiated adenocarcinomas. Loss of expression of Dicer and Drosha was associated with decreased overall survival (Shu et al. 2012).

Transcription Factors and Associated Protein Signaling Networks

SOX4, a member of the SRY-related HMG-box (SOX) transcription factor family, plays a significant role in carcinogenic pathways of various malignancies. SOX4 was expressed in 75 % of CG, but in normal gallbladder epithelium. SOX4 expression in CG was significantly associated with low histologic grade, low pathological T stage, early clinical stage, and better disease-free and overall survival (Wang et al. 2012a).

Sonic hedgehog, its receptor, patched, and its downstream transcription factor, Gli1 protein, are overexpressed in CG. The expression of these factors was significantly correlated with stage, lymph node metastasis, venous and lymphatic invasion, liver invasion, and lower survival rates (Li et al. 2012). Expression of the N-myc downstream-regulated gene 2 (NDRG2), a protein that may reduce the metastatic potential of cancers, was detected in 37.6 % of CG. Tumors with downregulation of NDRG2 more often had lymph node metastases and lymphovascular invasion and tended to have higher TNM stage; the patients also had poor prognosis (Song et al. 2012). Caudal-related homeobox protein (CDX2), a homeodomain protein which plays an important role in the regulation of cell proliferation and differentiation of glandular epithelia and which is a regulator of intestinal metaplasia, is absent from the normal gallbladder, but is expressed in part of CG, mostly in well-differentiated tubular adenocarcinomas of the intestinal type (Wu et al. 2005).

Cell Cycle Regulation

High proliferative activity is generally associated with an aggressive phenotype of CG (Hui et al. 2002). CG expresses various factors involved in cell cycle regulation, including cyclin E (Mishra et al. 2009), cyclin D1, and p16 (Xuan

et al. 2005; Srivastava et al. 2013). The expression rate of cyclin D1 (68.3 %) in CG was significantly higher than in nonneoplastic disorders of the gallbladder, whereas the expression rates of p16 and retinoblastoma/Rb protein were significantly lower in CG compared to those in cholecystitis and adenoma (Ma et al. 2005). Cyclin D1 overexpression is a critical event in CG carcinogenesis and independently predicts decreased patient survival (Hui et al. 2000; Itoi et al. 2000). Loss of p16 in CG and bile duct cancers is associated with reduced survival of patients (Karamitopoulou et al. 2008), whereby loss of p16INK4 protein is correlated with overexpression of the retinoblastoma/Rb protein (Shi et al. 2000). In contrast, overexpression of cyclin E was not associated with depth of tumor invasion, tumor stage, or patient prognosis (Eguchi et al. 1999). p27 is a tumor suppressor protein which inhibits both Cdk2/cyclin E and Cdk2/cyclin A complexes and prevents transition to the S phase of the cell division cycle. Expression of p27 is expressed in CG and was correlated with clinical stage of CG (Xuan et al. 2005; Alsheyab et al. 2007), and low p27Kip1 expression in CG is an independent prognostic factor associated with poor prognosis (Filipits et al. 2003). The expression pattern of p27 is critically modulated by two SCF(Skp2) ubiquitin ligase-related proteins, Skp2 and cyclin-dependent kinase subunit 1/Cks1, which are involved in the posttranscriptional degradation of the p27 tumor suppressor. Reduced p21(WAF1/CIP1) expression is an early event in CG carcinogenesis and is of prognostic significance (Li et al. 2001; Puhalla et al. 2007). Expression of Skp2 was found to be an important and independent adverse prognosticator in CG (Li et al. 2007). Cyclooxygenase-2 (COX-2) plays a role in promoting cell proliferation, growth, and metastasis of carcinoma cells. Intense immunostaining of COX-2 was found in hyperplastic gallbladder lesions (65 %), pT2 CG (76 %), and advanced stage CG (64 %), including the associated stroma. In pT2 CG, expression of COX-2 in the stroma adjacent to the carcinoma cells in the subserosal layer correlated with aggressiveness of disease, including the tendency for distant metastasis (Kawamoto et al. 2002). The mammalian target of rapamycin (mTOR), a serine/threonine kinase, plays an essential role in the regulation of cell growth and is frequently deregulated in cancers. In CG, phospho-mTOR is an overexpression in early phases of cancer evolution, associated with poor prognosis (Leal et al. 2013). The sphingosine-1-phosphate receptor 1 (S1P1) is overexpressed in CG, and higher levels of S1P1 were significantly correlated with tumor differentiation, tumor mass, lymph node metastasis, invasion, and decreased survival time (Yuan et al. 2013). S1Ps are a class of G protein-coupled receptors that are a signaling target of sphingosine-1-phosphate and that are involved in the regulation of cell proliferation, cytoskeletal organization, and cell migration.

Other Factors Involved in Proliferation and Differentiation of Cells

Astrocyte elevated gene-1 is overexpressed in CG and is strongly correlated with the differentiation degree, stage, Ki-67 proliferation index, and liver invasion. Expression of this protein in CG is an independent prognostic marker for CG progression (Sun et al. 2011). Expression of connective tissue growth factor/CTGF in CG was correlated with better survival in two studies (Alvarez et al. 2008; Garcia et al. 2013), while in another investigation a role of CTGF expression in CG progression was found (Garcia et al. 2013). Part of CGs produce several classes of mucins (see below). Univariate analysis showed that MUC4 expression was significantly associated with poor survival, while expression of MUC1 and MUC2 was not correlated to survival. Backward stepwise multivariate analysis exhibited that MUC4 expression was a significant risk factor for poor outcome (Lee et al. 2012a). Expression of the multifunctional redox protein, human thioredoxin-1 (TRX-1), and its reducing enzyme, thioredoxin reductase (TRX-R), in CG affects tumor biology. Specifically, nuclear TRX-1 expression in cancer cells at the invasion front of CG is a significant prognostic marker (Nagano et al. 2012). Estrogen receptors (ERs) are

expressed in part of CG cells (Gupta et al. 2012). ERbeta isoform was expressed in most specimens, but preferentially in central tumor parts. Absent ERbeta expression at the invasive front was significantly associated with lymph node metastasis, advanced stage, lymphatic invasion, and poor prognosis (Sumi et al. 2004).

Chemokines, Cytokines, and Other Factors Involved in Immune Responses

Chemokine (C-X-C motif) ligand 12 (CXCL12), important for the progression of various malignancies, was differentially expressed in CG tissue, together with its receptor CXCR4, and the magnitude of expression was associated with high histologic grade and nodal metastasis, and expression was a significant risk factor for survival. CXCL12 increased anchorage-dependent and anchorage-independent growth, adhesiveness, and migration and invasive properties of CG cells (Lee et al. 2012b). Toll-like receptors (TLRs), which play a crucial role in inflammatory reactions, including chronic cholecystitis, are also operational in various pathways involved in carcinogenesis. TLR4 is mainly expressed in the glandular and luminal epithelia of the gallbladder. TLR4 expression was lower in CG in comparison with chronic cholecystitis and normal gallbladder (Huan et al. 2012).

Mechanisms of Apoptosis

There are intimate relationships between CG and apoptosis (Zhang et al. 2003). Positive rates of Fas were not significantly different among CG, dysplasia, and gallbladder adenoma, but positive rates of Fas ligand/FasL in carcinoma were significantly higher than that in chronic cholecystitis, suggesting that FasL expression in CG permits tumor cells to escape from immune surveillance by inducing apoptosis in lymphocytes infiltrating CG tissue (Xu et al. 2005). Higher expression of Bcl-2 in CG is considered to affect growth and progression of the tumors via inhibition of apoptosis (Mikami et al. 1999; Karamitoupoulou et al. 2008). Expression of the cellular Fas-associated death domain-like interleukin-1-converting enzyme inhibitory protein (c-FLIP), an antiapoptotic protein, is upregulated in CG, potentially conferring a growth advantage (Zong et al. 2009). Expression of p53-upregulated modulator of apoptosis (PUMA) was significantly higher in adenocarcinoma of the gallbladder than in adenoma and chronic cholecystitis, whereby PUMA expression was lower in small (less than 2-cm diameter) and well-differentiated CG with N0 than in poorly differentiated larger (>2 cm) CG with lymph node metastasis and invasion of surrounding tissues (Cai et al. 2013). Receptor-binding cancer antigen expressed on SiSo cells (RCAS1), a protein that induces apoptosis in immune effector cells expressing the RCAS1 receptor, was overexpressed in 70 % of CG, but not in precursor lesions. RCAS1 expression was associated with depth of tumor invasion, venous involvement, perineural invasion, tumor stage, and the presence of metastases (Oshikiri et al. 2001). Expression of heat shock protein 70-interacting protein (CHIP), a U-box-type E3 ubiquitin ligase, in CG is associated with poor prognosis (Liang et al. 2013).

Cell Adhesion and Motility

Deranged cell-to-cell or cell-to-matrix contact mediated by adhesion molecules plays a crucial role within the invasion cascade. Several factors involved in adhesion are altered in CG. Epithelial cell adhesion molecule (Ep-CAM) is overexpressed in almost two thirds of CG, and overexpression of this factor is related to decreased overall survival and is an independent prognostic factor (Varga et al. 2004; Prince et al. 2008). The L1 adhesion molecule, associated with prognosis in several malignancies, is not expressed in normal gallbladder epithelium, but was detectable in 63.8 % of CG, specifically in cells located to the invasive front of the neoplasm. Expression of L1 in CG cells was correlated with high histologic grade, advanced T stage, and venous and lymphatic invasion and was an independent negative prognosticator in multivariate

analysis (Choi et al. 2011). Expression of nectin-2, an adhesion molecule involved in calcium-independent cell adhesion, in CG is correlated to high T stage and poor prognosis (Miao et al. 2013). Thrombospondin-1 (TSP1), an extracellular glycoprotein that affects cell adhesion, motility, and growth, is mainly expressed in CG stromal cells and less so in cancer cells. Stromal expression of TSP1 increased as a function of increasing stage and was associated with lymph node metastasis and venous involvement, suggesting that TSP1 plays a role in CG spread and metastasis (Ohtani et al. 1999). Fascin, a protein interacting with thrombospondin-1, shows a marked overexpression in advanced CG, associated with aggressive clinical features and poor overall survival. Fascin, thrombospondin-1, and syndecan-1 interact to mediate this aggressive phenotype of CG (Roh et al. 2009). Syndecan-1 expression itself was detected in 58.1 % of CG, and syndecan-1-positive neoplasms more frequently showed lymph node metastasis and tended to have a deeper invasion depth and significantly shorter survival (Roh et al. 2008). Significant differences of E-cadherin and beta-catenin expression were detected between normal, inflamed, and cancerous gallbladder tissues (Puhalla et al. 2005). Loss of E-cadherin expression is high in CG (Priya et al. 2010), an alteration that may contribute to failure of intercellular adhesion, individualization of cells, and promotion of an invasive phenotype. N-cadherin and P-cadherin are biomarkers for invasion and metastasis in CG (Yi et al. 2014). Alterations of beta-catenin signaling are frequent events in CG, but these alterations seem to be minor contributors to CG carcinogenesis, but may be related to progression via loss of E-cadherin function (Kimura et al. 2003). Expression of the integrin-linked kinase (ILK) was found to be an independent poor prognostic predictor in CG (Li et al. 2013). CD97, a member of the EGF-TM7 adhesin family binding to its cellular receptor, CD55, plays an important role in invasiveness and aggressiveness of malignancies. It is a complement regulatory protein expressed by cells to protect them from bystander complement attack. CD97 and CD55 are absent or weakly expressed in normal gallbladder epithelium, but are overexpression CG, this expression being associated with high histologic grade, advanced T stage, angioinvasion, and reduced overall survival (Wu et al. 2012). CD44, a molecule involved in the metastatic pathway of cancers, exists in several variants or isoforms, including CD44s (standard variant), variant 3 (CD44v3), and variant 6 (CD44v6). CD44s is present in normal gallbladder epithelium and exhibits membranous immunostaining. In CG, CD44s is stained as strongly as normal epithelium, but reactivity for CD44v3 and CD44v6 was also found. CD44s is significantly less expressed in well-differentiated CG in the invasive component of the tumor than in the intramucosal part, and both CD44v3 and CD44v6 are more strongly expressed in poorly differentiated CG than in well-differentiated CG, but these expression patterns were not associated with outcome (Yanagisawa et al. 2001). Trefoil factor family protein 1/TFF1 (pS2), a factor that interacts with mucins to protect gastrointestinal epithelial cells and which promotes epithelial cell migration, is expressed in low-stage CG, and expression decreases as a function of increased grade and stage. Patients with TFF1-positive CG revealed a more favorable outcome compared with TFF1-negative neoplasms (Kornprat et al. 2005). As other carcinomas, CG displays alterations of the cytoskeleton and cytoskeletal proteins, changes that affect cell motility and cancer cell migration as a component of the invasion cascade. Cofilin-1, an actin-modulating protein that depolymerizes filamentous F actin and inhibits the polymerization of monomeric G actin, is expressed in CG, whereby expression was significantly associated with large tumor size, high T stage, lymph node metastasis, and decreased overall survival (Yang et al. 2013).

Mechanisms of Invasion and Spread

CG cells express several members of matrix metalloproteinases (MMPs), enzymes that have a central role in the tumor invasion cascade, as they facilitate the egress of cancer cells from the primary tumor and the locomotion and migration of

tumor cells in invaded tissues (Fan et al. 2002). MMP-9 and MMP-14 play a role in CG tumorigenesis (Karadag et al. 2008). MMP-1 and protease-activated receptor-1 are expressed in approximately 70 % of CG. CG expressing these two proteins more often showed lymph node metastasis, a deeper invasion depth, and more frequently lymphovascular invasion (Du et al. 2011). Expression of MMP-2 negatively affected the survival rate (Wu et al. 2009). In mucinous CG, which has a biology different from that of ordinary CG, MMP expression is lower (Karadag et al. 2008). The transcription and expression of MMPs in CG modulated by the neural precursor cell expressed developmentally downregulated 4-lik (Nedd4L) protein. Overexpression of Nedd4L in CG regulates the expression of MMP1 and MMP13 (Takeuchi et al. 2011). ADAM proteins, a multifunctional gene family of membrane proteins having a disintegrin and metalloprotease domain and involved in the metastatic cascade, are overexpressed in CG, this feature being associated with poor prognosis (Wu et al. 2011).

Expression of Differentiation Antigens and Factors Related to Cancer Cell Metabolism

Carcinoembryonic antigen (CEA), which may function as a metastatic potentiator via modulation of intercellular adhesion and cell migration, is expressed in CG cells and CG stromal cells. Lymph node metastasis was frequently found in cytoplasmic and stromal cell CEA-positive CG (Dowaki et al. 2000). Stromal expression of the mucin MUC1 in CG is associated with tumor aggressiveness and a tendency to form distant organ metastases (Kashiwagi et al. 2001; Kawamoto et al. 2004), while expression of MUC2 was not significantly related to lymphatic invasion, lymph node metastasis, or prognosis (Kashiwagi et al. 2001). Tumor-associated glycoprotein 72 is expressed more frequently in CG of larger size, with lymph node metastasis, with higher stage, and with poor differentiation, suggesting that expression of this antigen is a marker of CG aggressiveness (Ouyang et al. 2010). CD24, a small surface protein, is a marker of malignancy and poor prognosis in CG (Liu et al. 2011). Part of CGs express the hepatocyte antigen (Hep). Expression of Hep was negatively correlated to the grade of differentiation, tumor size, and lymph node metastasis, and elevated Hep expression was associated with increased overall survival, Hep expression being an independent prognostic predictor (Li et al. 2011). Forced expression of LAPTM4B in a CG cell line increased the invasive potential (Zhou et al. 2007, 2010). CG expresses neurotrophin, nerve growth factor, and the receptor TrkA (Artico et al. 2010), but the biologic significance of this expression has not yet been elucidated. Glucose uptake is generally augmented in cancer cells. The glucose transporter, GLUT1, is expressed in CG, and this elevated expression is strongly associated with cancer progression (Kim et al. 2002).

Angiogenesis and Lymphangiogenesis

Angiogenesis of tumors, induced and controlled by complex signaling pathways involving VEGF, plays a significant role in tumor progression, including CG (Giatromanolaki et al. 2002; Harino et al. 2008). Increased tumor vascularization caused by angiogenic mechanisms plays a significant role in cancer progression. A high microvessel density in CG determined by Chalkley counting was associated with worse prognosis (da Rocha et al. 2009). In CG, microvessel density was found to increase as a function of depth of invasion, suggesting a role of angiogenesis in the invasive process (Kalekou and Miliaras 2011). Microvessel density correlated with tumor stage and liver metastasis (Chen et al. 2011b). However, microvessel density was not an independent prognosticator in multivariate analysis (Sugawara et al. 1999). Average microvessel counts were lower in cases of well-differentiated carcinoma, small tumor size (less than 2-cm diameter), and negative nodes,

while higher microvessel counts and expression of CD146 in CG were associated with poor survival (Wang et al. 2012b). In a fraction of CG showing augmented angiogenesis, vascular endothelial growth factor/VEGF is expressed (Yamamoto et al. 1998; Giatromanolaki et al. 2003). The presence and expression level of VEGF were associated with tumor size, lymphatic invasion, and advanced disease stage (Okita et al. 1998; Letelier et al. 2014). Expression of platelet-derived endothelial growth factor/thymidine phosphorylase was detected in 63 % of CG, while hyperplastic epithelia or adenomas did not show significant expression. However, the magnitude of expression did not correlate with angiogenesis, but with depth of invasion, lymph node metastasis, and tumor stage (Yamamoto et al. 2000). Cyclooxygenase-2, which affects the expression of VEGF, induces angiogenesis in CG and is associated with poor prognosis (Zhi et al. 2005). A similar effect was found for the expression of inducible nitric oxide synthase (Niu et al. 2004). Tumor endothelial marker 8 (TEM8) protein is highly specific to angiogenesis in malignant neoplasms and is not required for normal adult angiogenesis. TEM8 is expressed in endothelial cells of CG, and its expression increased significantly with increasing CG stage (Maurya et al. 2011). TGF-beta, a protein with multiple functions, also promotes angiogenesis and is expressed in CG, where it augments angiogenesis and is associated with tumor progression (Kitamura et al. 2003).

CG shows vigorous lymphangiogenesis mediated by VEGF-C. TNF-alpha promotes formation of lymphatic vessels in CG through NF-kappaB-mediated upregulation of VEGF-C (Qiang et al. 2014). Expression of vascular endothelial growth factor-D in CG promotes growth, lymphangiogenesis, and lymphatic metastasis in CG and plays a role in CG progression (Lin et al. 2012).

Vasculogenic mimicry, a phenomenon associated with increased tumor-related mortality in several cancers, was observed in CG cell lines cultured in a 3D matrix, and vasculogenic mimicry in these cells was stimulated by HIF-1alpha. In CG analyzed in vivo, vasculogenic mimicry was also observed, and HIF-1alpha expression and vasculogenic mimicry were associated with poorer overall survival (Sun et al. 2012). Vasculogenic mimicry in CG is mediated by signaling pathways that involve PI3K/MMPs/Ln-5gamma2 and EphA2/FAK/paxillin networks (Lu et al. 2013).

Tumor Ploidy

Abnormal DNA contents were observed in 51 % of CG, whereby 44.4 % of tumors were aneuploid. In comparison, aneuploidy was detected in 81.3 % of metastatic lesions (Roa et al. 1993), suggesting effects of progressive genomic instability. Aneuploidy of CG was significantly associated with poorly differentiated adenocarcinoma, higher T stage, and a high mitotic index. A significant advantage in terms of 5-year survival was found in patients with diploid neoplasms in comparison with those having aneuploid tumors (Sato et al. 1993). In contrast, cytometric determination of DNA ploidy provided no prognostic information in CG as compared to conventional tumor staging in other studies (Yamamoto et al. 1990; Baretton et al. 1994).

MicroRNAs

MicroRNA-34 is associated with poor prognosis in CG through the regulation of telomere length in stem cells (Jin et al. 2014). An increased expression of microRNA-335 in CG predicts a favorable prognosis, but this miRNA is downregulated in the majority of CG, being one factor that may determine the aggressive biology of this cancer (Peng et al. 2013). Upregulation of the prometastatic microRNA-20a was closely associated with local invasion, distant metastasis, and poor prognosis (Chang et al. 2013). MicroRNA-155 was overexpressed in CG in comparison with nonneoplastic gallbladder, associated with the presence of nodal metastases and poor prognosis (Kono et al. 2013).

Staging

Determination of tumor stage is a decisive factor in prognostication of CG. However, up to 40 % of CG cases are diagnosed at an advance stage of disease (Henson et al. 1992), limiting the differential estimation of outcome as a function of stage. The current staging system formulated by the AJCC is shown in Table 2. It corresponds to the UICC system (Fong et al. 2006; Gore and Shelhamer 2007; Edge et al. 2010).

The advantages of pitfalls of the AJCC/UICC have recently been discussed (Adsay et al. 2012). The gallbladder does not have the distinct layering as other gastrointestinal organs do. Therefore, it was stated that the definitions of Tis/T1a/T1b may lack practicability, and therefore, the "early gallbladder carcinoma" category proposed in high regions may have to be recognized instead. Furthermore, it was proposed that documentation of hepatic versus serosal involvement should be performed in cases of advanced tumors (Adsay et al. 2012).

In addition to T stage, which describes depth of invasion and extension into adjacent organs and/or structures, other modes of invasion have been proposed as prognostically relevant parameters. T2 carcinomas with subserosal invasion form a distinct group of gallbladder cancers that may profit from radical surgery including resection of the gallbladder bed (Chijiiwa et al. 2001). In T2 tumors, free resection margins and the absence of perineural invasion and of lymph node metastasis are related to good prognosis. The depth of subserosal invasion in pT2 tumors has an impact on outcome in patients with pT2 neoplasms (Wakai et al. 2003). Depth of invasion of the subserosal layer was divided into three categories, i.e., ss1, ss2, and ss3, representing invasion of the upper, middle, or lower thirds of the subserosal layer, respectively (Sasaki et al. 2005). Expression of N-acetylglucosaminyl-transferase V, an enzyme that catalyzes the beta1-6 branching of N-acetyl-glucosamine on asparagine-like oligosaccharides of cellular proteins and enhances the malignant features of cancer cells, is expressed in CG located to the subserosal layer and correlates with postsurgical survival in pT2 tumors (Onuki et al. 2014). Expression of MUC1 mucins in the subserosal layer correlated with postsurgical prognosis (Kawamoto et al. 2001). A further prognostic feature related to stage is the mural invasion

Table 2 AJCC staging of gallbladder carcinoma (7th edition; Edge et al. 2010)

T			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor invades the lamina propria or muscular layer		
T1a	Tumor invades the lamina propria		
T1b	Tumor invades the muscular layer		
T2	Tumor invades perimuscular connective tissue; no extension beyond the serosa or into the liver		
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts		
T4	Tumor invades the main portal vein or hepatic artery or invades at least two extrahepatic organs or structures		
N			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein		
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes		
M			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage	*T*	*N*	*M*
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T1-3	N1	M0
IVA	T4	N0-1	M0
IVB	Any T	N2	M0
	Any T	Any N	M1

Generally, CGs of stages T1 and T2 are classified as early CG

There are some notable differences between the UICC staging system and the staging system of the Japanese Society of Biliary Surgery (JSBS) staging system (Japanese Society of Biliary Surgery 2001; Table 3)

Table 3 Gallbladder cancer extension classified according to the 2001 version of the classification of biliary tract carcinoma of JSBS (2001)

T (tumor categories)	
T1	S0, Hinf0, Binf0, PV0, A0
T2	S1, Hinf1, Binf1, PV0, A0
T3	S2, Hinf2, Binf2, PV1, A1
T4	S3, any Hinf, Binf3, PV2,3, A2,3
S (grade of serosal invasion)	
S0	No invasion of the serosa
S1	Doubtful invasion of the serosa
S2	Definite invasion of the serosa
S3	Invasion of other organs or structures
Hinf (grade of hepatic invasion)	
Hinf0	No direct invasion of the liver
Hinf1	Doubtful direct invasion of the liver
Hinf2	Definite direct invasion of the liver and invasion around the gallbladder bed
Hinf3	Mass formation because of direct invasion of the liver
Binf (grade of hepatoduodenal ligament (bile duct) invasion	
Binf0	No invasion of the hepatoduodenal ligament
Binf1	Doubtful invasion of the hepatoduodenal ligament
Binf2	Definite invasion of the hepatoduodenal ligament
Binf3	Severe invasion of the hepatoduodenal ligament
PV (grade of portal vein invasion)	
PV0	No invasion of any of portal veins
PV1	Doubtful invasion of portal veins
PV2	Definite invasion of portal veins
PV3	Severe invasion of portal veins (narrowing or constriction)
A (grade of hepatic artery invasion)	
A0	No invasion of any of hepatic arteries
A1	Doubtful invasion of hepatic arteries
A2	Definite invasion of hepatic arteries
A3	Severe invasion of hepatic arteries (narrowing or constriction)
N (lymph node involvement)	
N0	No evidence of lymph node metastasis
N1	Lymph node involvement in a primary lymph node group close to tumor
N2	Lymph node involvement in a secondary lymph node group
N3	Lymph node involvement in a tertiary lymph node group
N4	Lymph node involvement in the fourth lymph node group

(*continued*)

Table 3 (continued)

Staging system			
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0, N1	M0
Stage III	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
	Any T	N3	M0
Stage IVB	Any T	N4	M0
	Any T	Any N	M1

pattern of CG. Two intramural invasion patterns were defined as the infiltrative growth type (IG, infiltrative growth in the muscle layer without destruction) and a destructive growth type (DG, massive growth with destruction of the muscle layer; Okada et al. 2009a). Scirrhous growth was found more often in DG lesions, and the overall survival rate of patients with DG tumors was significantly lower than that of patients with IG tumors (Okada et al. 2009a). A negative effect of the DG pattern was also found in pT2 CG with a subserosa-invasive growth pattern (Okada et al. 2012). Tumors with a DG growth pattern show a higher proliferative activity, a poorer differentiation, a stromal laminin-5gamma2 chain expression, and a distant lymph node metastasis (Okada et al. 2009b).

References

Adsay NV, Bagci P, Tajiri T, Oliva I, Ohike N, Balci S, Ganzalez RS, Basturk O, Jang KT et al (2012) Pathologic staging of pancreatic, ampullary, biliary, and gallbladder cancers: pitfalls and practical limitations of the current AJCC/UICC TNM staging system and opportunities for improvement. Semin Diagn Pathol 29:127–141

Ajiki T, Onoyama H, Yamamoto M, Asaka K, Fujimori T, Maeda S, Saitoh Y (1996) p53 protein expression and prognosis in gallbladder carcinoma and premalignant lesions. Hepatogastroenterology 43:521–526

Albores-Saavedra J, Henson DE (1999) Pyloric gland metaplasia with perineural invasion of the gallbladder: a lesion that can be confused with adenocarcinoma. Cancer 86:2625–2631

Albores-Saavedra J, Keenportz B, Bejarano PA, Alexander AA, Henson DE (2007) Adenomyomatous hyperplasia

of the gallbladder with perineural invasion: revisited. Am J Surg Pathol 31:1598–1604
Albores-Saavedra J, Chable-Montero F, Angeles-Albores-D, Schwartz A, Klimstra DS et al (2011) Early gallbladder carcinoma: a clinicopathologic study of 13 cases of intramucosal carcinoma. Am J Clin Pathol 135:637–642
Al-Qudah MS (1994) Intraluminal implantation of gallbladder cancer into the bile ducts. Br J Surg 81:590
Alsheyab FM, Ziadeh MT, Bani-Hani KE (2007) Expression of p21 and p27 in gallbladder cancer. Saudi Med J 28:683–687
Alvarez H, Corvalan A, Roa JC, Argani P, Murillo F, Edwards J, Beaty R, Feldmann G et al (2008) Serial analysis of gene expression identifies connective tissue growth factor expression as a prognostic biomarker in gallbladder cancer. Clin Cancer Res 14:2631–2638
Andrieux J, Parache RM, Fery M (1972) A further case of Krukenberg's tumor manifesting a vesiculocholedochal cancer (in French). Chirurgie 98:219–223
Artico M, Bronzetti E, Alicino V, Ionta B, Bosco S, Grande C, Bruno M, Transquili Leali FM et al (2010) Human gallbladder carcinoma: role of neurotrophins, MIB-1, CD34 and CA15-3. Eur J Histochem 54:e10
Baretton G, Blasenbreu S, Vogt T, Löhrs U, Rau H, Schmidt M (1994) DNA ploidy in carcinoma of the gallbladder. Prognostic significance and comparison of flow and image cytometry on archival tumor material. Pathol Res Pract 190:584–592
Barsoum and Windsor 1992. http://www.ncbi.nlm.nih.gov/pubmed/1393498
Bickenbach KA, Shia J, Klimstra DS, DeMatteo RP, Fong Y, Kingham TP, Allen PJ et al (2011) High-grade dysplasia of the cystic duct margin in the absence of malignancy after cholecystectomy. HPB (Oxford) 13:865–868
Bork K, Schreiber J, Bräuninger W (2002) Umbilical metastasis of a gallbladder carcinoma: "Sister Mary Joseph's nodule" (in German). Dtsch Med Wochenschr 127:553–556
Burdette WJ (1957) Carcinoma of the gallbladder. Ann Surg 145:832–844
Cai W, Li Q, Yang Z, Miao X, Wen Y, Huang S, Ouyang J (2013) Expression of p53 upregulated modulator of apoptosis (PUMA) and C-myb in gallbladder adenocarcinoma and their pathological significance. Clin Transl Oncol 15:818–824
Cappell DF, Tudhope GR (1934) Unrevealed primary carcinoma of the gall-bladder. Glasgow Med J 122:185
Chakravarty KD, Yeh CN, Jan YY, Chen MF (2009) Factors influencing long-term survival in patients with T3 gallbladder adenocarcinoma. Digestion 79:151–157
Chan KM, Yeh TS, Yu MC, Jan YY, Hwang TL, Chen MF (2005) Gallbladder carcinoma with biliary invasion: clinical analysis of the differences from nonbiliary invasion. World J Surg 29:72–75
Chang Y, Liu C, Yang J, Liu G, Feng F, Tang J, Hu L, Li L, Jiang F, Chen C, Wang R et al (2013) MiR-20a triggers metastasis of gallbladder carcinoma. J Hepatol 59:518–527
Chaudhari S, Hatwal D, Bhat P (2014) A rare presentation of gallbladder carcinoma metastasis. J Clin Diagn Res 8:FD19–FD20
Chen TJ, Huang SC, Huang HY, Wei YC, Li CF (2011a) Rsf-1/HBXAP overexpression is associated with disease-specific survival of patients with gallbladder carcinoma. APMIS 119:808–814
Chen Y, Chen Y, Yu G, Ding H (2011b) Lymphangiogenic and angiogenic microvessel density in gallbladder carcinoma. Hepatogastroenterology 58:20–25
Chicos SC, Beznea A, Chebac GR, Ceausu M, Ceausu M (2007) The Krukenberg tumor caused by an adenocarcinoma of the gallbladder (in Romanian). Chirurgia (Bucur) 102:481–485
Chijiiwa K, Nakano K, Ueda J, Noshiro H, Nagai E, Yamaguchi K, Tanaka M (2001) Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. J Am Coll Surg 192:600–607
Chikamoto A, Tsuji T, Nakahara O, Sakamoto Y, Ikuta Y, Tanaka H, Takamori H, Hirota M et al (2009) Cancer cells spread through lymph vessels in the submucosal layer of the common bile duct in gallbladder carcinoma. J Hepatobiliary Pancreat Surg 16:557–561
Cho SY, Han SS, Park SJ, Kim YK, Kim SH, Woo SM, Lee WJ, Kim TH, Hong EK (2012) T-category reflects the histopathologic characteristics of gallbladder cancer. Eur J Surg Oncol 38:537–542
Choi SY, Jo YS, Huang SM, Liang ZL, Min JK, Hong HJ, Kim JM (2011) L1 cell adhesion molecule as a novel independent poor prognostic factor in gallbladder carcinoma. Hum Pathol 42:1476–1483
Choi BG, Kim CY, Cho SH, Kim HJ, Koh YS, Kim JC, Cho CK, Kim HJ, Hur YH (2013) Impact of lymph node ratio as a valuable prognostic factor in gallbladder carcinoma, focusing on stage IIIB gallbladder carcinoma. J Korean Surg Soc 84:168–177
Clair DG, Lautz DB, Brooks DC (1993) Rapid development of umbilical metastases after laparoscopic cholecystectomy for unsuspected gallbladder carcinoma. Surgery 113:355–358
Clermont D (1909) Lymphatiques des voies biliaires: cancer de la vésicule (anatomie pathologique et traitement chirurgical). Thesis, University of Toulouse, France
Commandre F, Dalbera-Gayraud L, Besson R, Berato J, Gilly R (1965) A case of cancer of the gallbladder with multiple osseous metastases (in French). Arch Mal Appar Dig Mal Nutr 54:1174–1176
Cooper WA (1937) Carcinoma of the gallbladder. Arch Surg 35:431–448
Copher JC, Rogers JJ, Dalton ML (1995) Trocar-site metastasis following laparoscopic cholecystectomy for unsuspected carcinoma of the gallbladder. Case report and review of the literature. Surg Endosc 9:348–350
D'Hondt M, Lapointe R, Benamira Z, Pottel H, Plasse M, Letourneau R, Roy A, Dagenais M (2013) Carcinoma of the gallbladder: patterns of presentation, prognostic

factors and survival rate. An 11-year single centre experience. Eur J Surg Oncol 39:548–553
da Rocha AO, Coutinho LM, Schall JG (2009) The prognostic value of angiogenesis by Chalkley counting in gallbladder carcinoma. Hepatogastroenterology 56:34–38
Dowaki S, Kijima H, Kashiwagi H, Ohtani Y, Tobita K, Tsukui M, Tanaka Y, Tazawa K et al (2000) CEA immunohistochemical localization is correlated with growth and metastasis of human gallbladder carcinoma. Int J Oncol 16:49–53
Du X, Wang S, Lu J, Cao Y, Song N, Yang T, Dong R, Zang L, Yang Y, Wu T, Li J (2011) Correlation between MMP1-PAR1 axis and clinical outcome of primary gallbladder carcinoma. Jpn J Clin Oncol 41:1086–1093
Du X, Zhao H, Zang L, Song N, Yang T, Dong R, Yin J, Wang C, Lu J (2013a) Overexpression of histone deacetylase 2 predicts unfavorable prognosis in human gallbladder carcinoma. Pathol Oncol Res 19:397–403
Du X, Wu T, Lu J, Zang L, Song N, Yang T, Zhao H, Wang S (2013b) Decreased expression of chromodomain helicase DNA-binding protein 5 is an unfavorable prognostic marker in patients with primary gallbladder carcinoma. Clin Transl Oncol 15:198–204
Dutta U (2012) Gallbladder cancer: can newer insights improve the outcome ? J Gastroenterol Hepatol 27:642–653
Edge SB, Byrd DR, Compton CC et al (eds) (2010) AJCC cancer staging manual, 7th edn. Springer, New York, pp 211–217
Egawa N, Tu Y, Kamisawa T, Amemiya K, Tsuruta K, Okamoto A, Funata N (2004) A comparative clinical study of gallbladder tubular adenocarcinoma according to the grade of differentiation. J Gastroenterol 39:975–980
Eguchi N, Fujii K, Tsuchida A, Yamamoto S, Sasaki T, Kajiyama G (1999) Cyclin E overexpression in human gallbladder carcinomas. Oncol Rep 6:93–96
Eil R, Hansen PD, Cassera M, Orloff SL, Sheppard BC, Diggs B, Billingsley KG (2013) Bile duct involvement portends poor prognosis in resected gallbladder carcinoma. Gastrointest Cancer Res 6:101–105
Endo I, Shimada H, Takimoto A, Fujii Y, Miura Y, Sugita M, Morioka D, Masunari H et al (2004) Microscopic liver metastasis: prognostic factor for patients with pT2 gallbladder carcinoma. World J Surg 28:692–696
Evans HJ (1994) Intraluminal implantation of gallbladder cancer into the bile ducts. Br J Surg 81:1393–1394
Evrard S, Mutter D, Bui A, Marescaux J (1996) Neoplastic seeding in the gallbladder fossa after laparoscopic cholecystectomy. Surgery 119:357
Fahim RB, McDonald JR, Richards JC, Ferris DO (1962) Carcinoma of the gallbladder: a study of its modes of spread. Ann Surg 156:114–124
Fahim RB, Ferris DO, McDonald JR (1963) Carcinoma of the gallbladder: a appraisal of its surgical treatment. Arch Surg 86:334
Fan YZ, Zhang JT, Yang HC, Yang YQ (2002) Expression of MMP-2, TIMP-2 protein and the ratio of MMP-2/TIMP-2 in gallbladder carcinoma and their significance. World J Gastroenterol 8:1138–1143
Filipits M, Puhalla H, Wrba F (2003) Low p27Kip1 expression is an independent prognostic factor in gallbladder carcinoma. Anticancer Res 23:675–679
Fine A (1997) The cystic vein: the significance of a forgotten anatomic landmark. JSLS 1:263–266
Fong Y, Wagman L, Gonen M, Crawford J, Reed W, Swanson R, Pan C, Ritchey J et al (2006) Evidence-based gallbladder cancer staging. Changing cancer staging by analysis of data from the National Cancer database. Ann Surg 243:767–774
Frank SA, Spjut HJ (1967) Inapparent carcinoma of the gallbladder. Am Surg 33:367–372
Garcia P, Leal P, Alvarez H, Brebi P, Ili C, Tapia O, Roa JC (2013) Connective tissue growth factor immunohistochemical expression is associated with gallbladder cancer progression. Arch Pathol Lab Med 137:245–250
Giatromanolaki A, Sivridis E, Koukourakis MI, Polychronidis A, Simopoulos C (2002) Prognostic role of angiogenesis in operable carcinoma of the gallbladder. Am J Clin Oncol 25:38–41
Giatromanolaki A, Koukourakis MI, Simopoulos C, Polychronidis A, Sivridis E (2003) Vascular endothelial growth (VEGF) expression in operable gallbladder carcinomas. Eur J Surg Oncol 29:879–883
Glenn F, Hays DM (1954) The scope of radical surgery in the treatment of malignant tumors of the extrahepatic biliary tract. Surg Gynecol Obstet 99:529–541
Gomez-Roel X, Arrieta O, Leon-Rodriguez E (2007) Prognostic factors in gallbladder and biliary tract cancer. Med Oncol 24:77–83
Gore RM, Shelhamer RP (2007) Biliary tract neoplasms: diagnosis and staging. Cancer Imaging 7:S15–S23
Gunjiganvi M, Singh KK, Harsha HS, Bipin T (2013) Cardiac metastasis from gallbladder carcinoma. Int J Surg Case Rep 4:1156–1158
Gupta P, Agarwal A, Gupta V, Singh PK, Pantola C, Amit S (2012) Expression and clinicopathological significance of estrogen and progesterone receptors in gallbladder cancer. Gastrointest Cancer Res 5:41–47
Habighorst LV, Albers P, Zeitler E (1965) Vessels of the gallbladder in postmortem angiography (in German). Fortschr Geb Rontgenstr Nuklearmed 103:63–70
Hamrick RE, Liner J, Hastings PR, Cohn I (1982) Primary carcinoma of the gallbladder. Ann Surg 195:270–273
Harino Y, Imura S, Kanemura H, Morine Y, Fujii M, Ikegami T, Uehara H, Shimada M (2008) Role of tumor angiogenesis in gallbladder carcinoma: with special reference to thymidine phosphorylase. Int J Clin Oncol 13:452–457
Hart J, Modan B, Hashomer T (1972) Factors affecting survival of patients with gallbladder neoplasms. Arch Intern Med 129:931–934
Heavey SF, Roeland EJ, Tipps AM, Datnow B, Sicklick JK (2014) Rapidly progressive subcutaneous metastases from gallbladder cancer: insight into a rare presentation

in gastrointestinal malignancies. J Gastrointest Oncol 5:E58–E64
Henson DE, Albores-Saavedra J, Corle D (1992) Carcinoma of the gallbladder. Histologic types, stage of disease, grade and survival rates. Cancer 170:1493–1497
Hidalgo Grau LA, Badia JM, Salvador CA, Manso TS, Canaleta JF, Nogues JM et al (2004) Gallbladder carcinoma: the role of p53 protein overexpression and Ki-67 antigen expression as prognostic markers. HPB (Oxford) 6:174–180
Hollings RM (1963) Tumour embolism of the common bile duct – a cause of jaundice in carcinoma of the gall-bladder. Med J Aust 2:618–620
Huan P, Maosheng T, Zhigian H, Long C, Xiaojun Y (2012) TLR4 expression in normal gallbladder, chronic cholecystitis and gallbladder carcinoma. Hepatogastroenterology 59:42–46
Hui AM, Li X, Shi YZ, Takayama T, Torzilli G, Makuuchi M (2000) Cyclin D1 overexpression is a critical event in gallbladder carcinogenesis and independently predicts decreased survival for patients with gallbladder carcinoma. Clin Cancer Res 6:4272–4277
Hui AM, Shi YZ, Li X, Sun L, Guido T, Takayama T, Makuuchi M (2002) Proliferative marker Ki-67 in gallbladder carcinomas: high expression level predicts early recurrence after surgical resection. Cancer Lett 176:191–198
Ito M, Mishima Y, Sato T (1991) An anatomical study of the lymphatic drainage of the gallbladder. Surg Radiol Anat 13:89–104
Itoi T, Shinohara Y, Takeda K, Nakamura K, Takei K, Sanada J, Horibe T, Saito T et al (2000) Nuclear cyclin D1 overexpression is a critical event associated with cell proliferation and invasive growth in gallbladder carcinogenesis. J Gastroenterol 35:142–149
Jacobi CA, Keller H, Mönig S, Said S (1995) Implantation metastasis of unsuspected gallbladder carcinoma after laparoscopy. Surg Endosc 9:351–352
Japanese Society of Biliary Surgery (2001) Classification of biliary tract carcinoma, 1st edn. Kanehara, Tokyo
Jeon HM, Kim JS, Lee CD, Kim EK, Kim SN (1999) Late development of umbilical metastasis after laparoscopic cholecystectomy for a gallbladder carcinoma. Oncol Rep 6:283–287
Jeyaraj P, Sio TT, Iott MJ (2013) An unusual case of isolated, serial metastases of gallbladder carcinoma involving the chest wall, axilla, breast and lung parenchyma. Rare Tumor 5:e7
Jin K, Xiang Y, Tang J, Wu G, Li J, Xiao H, Li C, Chen Y, Zhao J (2014) miR-34 is associated with poor prognosis of patients with gallbladder cancer through regulating telomere length in tumor stem cells. Tumour Biol 35:1503–1510
Johnson LA, Lavin PT, Dayal YY, Geller SA, Doos WG, Cooper HS, Gerber JE et al (1987) Gallbladder adenocarcinoma: the prognostic significance of histologic grade. J Surg Oncol 34:16–18
Jones CJ (1950) Carcinoma of the gallbladder: a clinical and pathologic analysis of fifty cases. Ann Surg 132:110–120
Kai K, Kohya N, Kitahara K, Masuda M, Miyoshi A, Ide T, Tokunaga O, Miyazaki K, Noshiro H (2011) Tumor budding and dedifferentiation in gallbladder carcinoma: potential for the prognostic factors in T2 lesions. Virchows Arch 459:449–456
Kainberger FM, Vergesslich KA, Eilenberger M, Poeltner S, Ponhold W (1990) Color-coded Doppler evaluation of cholecystic varices in portal hypertension. Pediatr Radiol 21:71–72
Kalekou H, Miliaras D (2011) Cytokeratin 7 and 20 expression in gallbladder carcinoma. Pol J Pathol 62:25–30
Kaneoka Y, Yamaguchi A, Isogai M, Harada T, Suzuki M (2003) Hepatoduodenal ligament invasion by gallbladder carcinoma: histologic patterns and surgical recommendation. World J Surg 27:260–265
Karadag N, Kirimlioglu H, Isik B, Yilmaz S, Kirimlioglu V (2008) Expression of matrix metalloproteinases in gallbladder carcinoma and their significance in carcinogenesis. Appl Immunohistochem Mol Morphol 16:148–152
Karamitopoulou E, Tornillo L, Zlobec I, Cioccari L, Carafa V, Borner M, Schaffner T et al (2008) Clinical significance of cell-cycle and apoptosis-related markers in biliary tract cancer: a tissue microarray-based approach revealing a distinctive immunophenotype for intrahepatic and extrahepatic cholangiocarcinoma. Am J Clin Pathol 130:780–786
Karayannakis AJ, Knight MJ (1997) Umbilical port metastasis from gallbladder carcinoma after laparoscopic cholecystectomy. Eur J Surg Oncol 23:186–187
Karlmark E (1932) Die Lokalisationstendenz bei Metastasierung durch die Venen in die Leber. Acta Pathol Microbiol Scand 18(Suppl 13):1–203
Kashiwagi H, Kijima H, Dowaki S, Ohtani Y, Tobita K, Tsukui M, Tanaka Y, Matsubayashi H et al (2000) DF3 expression in human gallbladder carcinoma: significance for lymphatic invasion. Int J Oncol 16:455–459
Kashiwagi H, Kijima H, Dowaki S, Ohtani Y, Tobita K, Yamazaki H, Nakamura M et al (2001) MUC1 and MUC2 expression in human gallbladder carcinoma: a clinicopathological study and relationship with prognosis. Oncol Res 8:485–489
Kawamoto T, Shoda J, Asano T, Ueda T, Furukawa M, Kawamoto T, Shoda J, Irimura T, Miyahara N, Furukawa M, Ueda T, Asano T, Kano M et al (2001) Expression of MUC1 mucins in the subserosal layer correlates with postsurgical prognosis of pathological tumor stage 2 carcinoma of the gallbladder. Clin Cancer Res 7:1333–1342
Kawamoto et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/11920595
Kawamoto T, Shoda J, Miyahara N, Suzuki H, Furukawa M, Todoriki T, Tanaka N et al (2004) Expression of MUC1 recognized by a monoclonal antibody MY.1E12is a useful biomarker for tumor

aggressiveness of carcinoma of the gallbladder. Clin Exp Metastasis 21:353–362
Kayahara M, Nagakawa T (2007) Recent trends of gallbladder cancer in Japan. An analysis of 4770 patients. Cancer 110:572–580
Kefeli M, Gonullu G, Can B, Malatyalioglu E, Kandemir B (2009) Metastasis of adenocarcinoma of the gall bladder to en endometrial polyp detected by endometrial curettage: case report and review of the literature. Int J Gynecol Pathol 28:343–346
Kessler T, Mihaljevic L (1994) Implantation metastasis of a gallbladder cancer at the umbilicus after laparoscopic cholecystectomy (in German). Chirurg 65: 564–565
Khangembam BC, Sharma P, Naswa N, Sahoo MK, Kumar R (2013) Solitary breast metastasis from recurrent gallbladder carcinoma simulating a second primary on 18F-FDG PET/CT. Clin Nucl Med 38:e433–e434
Kim HJ, Roy T (1994) Unexpected gallbladder cancer with cutaneous seeding after laparoscopic cholecystectomy. South Med J 87:817–820
Kim YW, Park YK, Yoon TY, Lee SM (2002) Expression of the GLUT1 glucose transporter in gallbladder carcinomas. Hepatogastroenterology 49:907–911
Kimura Y, Furuhata T, Mukaiya M, Kihara C, Kawakami M, Okita K, Yanai Y, Zenbutsu H et al (2003) Frequent beta-catenin alteration in gallbladder carcinomas. J Exp Clin Cancer Res 22:321–328
Kitamura K, Kasuya K, Tsuchida A, Mimuro A, Inoue K, Aoki T, Aoki T, Koyanagi Y (2003) Immunohistochemical analysis of transforming growth factor beta in gallbladder cancer. Oncol Rep 10:327–332
Kobayashi A, Oda T, Fukunaga K, Sasaki R, Ohkohchi N (2012) Invasion of the hepatic artery is a crucial predictor of poor outcomes in gallbladder carcinoma. World J Surg 36:645–650
Kondo S, Nimura Y, Kamiya J, Nagino M, Kanai M, Uesaka K, Hayakawa N (2002) Mode of tumor spread and surgical strategy in gallbladder carcinoma. Langenbecks Arch Surg 387:222–228
Kono H, Nakamura M, Ohtsuka T, Nagayoshi Y, Mori Y, Takahata S, Aishima S, Tanaka M (2013) High expression of microRNA-155 is associated with the aggressive malignant behavior of gallbladder carcinoma. Oncol Rep 30:17–24
Kornprat P, Rehak P, Lemmerer M, Gogg-Kamerer M, Langner C (2005) Analysis of trefoil factor family protein 1 (TFF1, pS2) expression in chronic cholecystitis and gallbladder carcinoma. Virchows Arch 446:505–510
Kuwayti K, Baggenstoss AH, Stauffer MH, Priestley JT (1957) Carcinoma of the major intrahepatic and extrahepatic bile ducts exclusive of the papilla of vater. Surg Gynec Obstet 104:357–366
Lai CH, Lau WY (2008) Gallbladder cancer – a comprehensive review. Surgeon 6:101–110
Lam CR (1940) The present status of carcinoma of the gallbladder: a study of thirty-four clinical cases. Ann Surg 111:403–410
Leal P, Garcia P, Sandoval A, Letelier P, Brebi P, Ili C, Alvarez H, Tapia O, Roa JC (2013) Immunohistochemical expression of phosphor-mTOR is associated with poor prognosis in patients with gallbladder adenocarcinoma. Arch Pathol Lab Med 137:552–557
Lee HK, Cho MS, Kim TH (2012a) Prognostic significance of muc4 expression in gallbladder carcinoma. World J Surg Oncol 10:224
Lee HJ, Lee K, Lee DG, Bae KH, Kim JS, Liang ZL, Huang SM, Suk OY, Kim HY et al (2012b) Chemokine (C-X-C motif) ligand 12 is associated with gallbladder carcinoma progression and is a novel independent poor prognostic factor. Clin Cancer Res 18:3270–3280
Letelier P, Garcia P, Leal P, Ili C, Buchegger K, Riquelme I, Sandoval A, Tapia O, Roa JC (2014) Immunohistochemical expression of vascular endothelial growth factor A in advanced gallbladder carcinoma. Appl Immunohistochem Mol Morphol 22:530–536
Li X, Hui AM, Shi YZ, Takayama T, Makuuchi M (2001) Reduced p21 (WAF1/CIP1) expression is an early event in gallbladder carcinogenesis and is of prognostic significance for patients with carcinomas of the gallbladder. Hum Pathol 32:771–777
Li SH, Li CF, Sung MT, Eng HL, Hsiung CY, Huang WW, Lin CN, Yu SC, Huang HY (2007) Skp2 is an independent prognosticator of gallbladder carcinoma among p27(Kip1)-interacting cell cycle regulators: an immunohistochemical study of 62 cases by tissue microarray. Mod Pathol 20:497–507
Li QL, Yang ZI, Liu JQ, Miao XY (2011) Expression of CDX2 and hepatocyte antigen in benign and malignant lesions of gallbladder and its correlation with histopathologic type and clinical outcome. Pathol Oncol Res 17:561–568
Li J, Wu T, Lu J, Cao Y, Song N, Yang T, Dong R, Yang Y, Zang L, Du X, Wang S (2012) Immunohistochemical evidence of the prognostic value of hedgehog pathway components in primary gallbladder carcinoma. Surg Today 42:770–775
Li J, Yang ZL, Ren X, Zou Q, Yuan Y, Liang L, Chen M, Chen S (2013) ILK and PRDX1 are prognostic markers in squamous cell/adenosquamous carcinomas and adenocarcinoma of gallbladder. Tumour Biol 34: 359–368
Liang ZL, Kim M, Huang SM, Lee HJ, Kim JM (2013) Expression of carboxyl terminus of Hsp70-interacting protein (CHIP) indicates poor prognosis in human gallbladder carcinoma. Oncol Lett 5:813–818
Lin HT, Liu GJ, Wu D, Lou JY (2005) Metastasis of primary gallbladder carcinoma in lymph node and liver. World J Gastroenterol 11:748–751
Lin W, Jiang L, Chen Y, She F, Han S, Zhu J, Zhou L, Tang N, Wang X, Li X (2012) Vascular endothelial growth factor-D promotes growth, lymphangiogenesis and lymphatic metastasis in gallbladder cancer. Cancer Lett 314:127–136
Liu B, Zhang Y, Liao M, Deng Z, Gong L, Jiang J, Lynn L, Wu K, Miao X (2011) Clinicopathologic and

prognostic significance of CD24 in gallbladder carcinoma. Pathol Oncol Res 17:45–50
Lu XS, Sun W, Ge CY, Zhang WZ, Fan YZ (2013) Contribution of the PI3k/MMPs/Ln-5g2 and EphA2/FAK/Paxillin signaling pathways to tumor growth and vasculogenic mimicry of gallbladder carcinomas. Int J Oncol 42:2103–2115
Ma HB, Hu HT, Di ZL, Wang ZR, Shi JS, Wang XJ, Li Y (2005) Association of cyclin D1, p16 and retinoblastoma protein expressions with prognosis and metastasis of gallbladder carcinoma. World J Gastroenterol 11:744–747
Marchal GJ, Van Holsbeeck M, Tshibwabwa-Ntumba E, Goddeeris PG, Fevery J, Oyen RH et al (1985) Dilatation of the cystic veins in portal hypertension: sonographic demonstration. Radiology 154: 187–189
Marmorale C, Scibé R, Siquini W, Massa M, Brunelli A, Landi E (1998) Parietal seeding of unsuspected gallbladder carcinoma after laparoscopic cholecystectomy. Ann Ital Chir 69:613–617
Martinez-Roman S, Frumovitz M, Deavers MT, Ramirez PT (2005) Metastatic carcinoma of the gallbladder mimicking an advanced cervical carcinoma. Gynecol Oncol 97:942–945
Maurya SK, Tewari M, Kumar M, Thakur MK, Shukla HS (2011) Expression pattern of tumor endothelial marker 8 protein in gallbladder carcinomas. Asian Pac J Cancer Prev 12:507–512
Meng H, Wang X, Fong Y, Wang ZH, Wang Y, Zhang ZT (2011) Outcomes of radical surgery for gallbladder cancer patients with lymphatic metastases. Jpn J Clin Oncol 41:992–998
Merz et al. 1993. http://www.ncbi.nlm.nih.gov/pubmed/8356516
Miao X, Yang ZL, Xiong L, Zou Q, Yuan Y, Li J, Liang L, Chen M, Chen S (2013) Nectin-2 and DDX3 are biomarkers for metastasis and poor prognosis of squamous cell/adenosquamous carcinomas and adenocarcinoma of gallbladder. Int J Exp Pathol 6:179–190
Midorikawa Y, Kubota K, Komatsu Y, Hasegawa K, Koike Y, Mori M, Makuuchi M (2000) Gallbladder carcinoma with a tumor thrombus in the common bile duct: an unusual cause of obstructive jaundice. Surgery 127:473–474
Mikami T, Yanagisawa N, Baba H, Koike M, Okayasu I (1999) Association of Bcl-2 protein expression with gallbladder carcinoma differentiation and progression and its relation to apoptosis. Cancer 85:318–325
Mishra PK, Jatawa SK, Raghuram GV, Pathak N, Jain A, Tiwari A, Varshney S, Maudar KK (2009) Correlation of aberrant expression of p53, Rad50, and cyclin-E proteins with microsatellite instability in gallbladder adenocarcinomas. Genet Mol Res 8:1202–1210
Misra S, Chaturvedi A, Misra NC (1997) Carcinoma gallbladder presenting with skeletal metastases. Indian J Gastroenterol 16:74
Moreno M, Pimentel F, Gazdar AF, Wistuba II, Miquel JF (2005) TP53 abnormalities are frequent and early events in the sequential pathogenesis of gallbladder carcinoma. Ann Hepatol 4:192–199
Nagakawa T, Mori K, Nakano T, Kadoya M, Kobayashi H, Akiyama T, Kayahara M et al (1993) Perineural invasion of carcinoma of the pancreas and biliary tract. Br J Surg 80:619–621
Nagakura S, Shirai Y, Yokoyama N, Hatakeyama K (2001) Clinical significance of lymph node micrometastasis in gallbladder carcinoma. Surgery 129:704–713
Nagano M, Hatakeyama K, Kai M, Nakamura H, Yodoi J, Asada Y, Chijiiwa K (2012) Nuclear expression of thioredoxin-1 in the invasion front is associated with outcome in patients with gallbladder carcinoma. HPB (Oxford) 14:573–582
Nakagawa S, Tada T, Furukawa H, Abe M, Hatakeyama K (2000) Late-type recurrence at the port site of unexpected gallbladder carcinoma after a laparoscopic cholecystectomy: report of a case. Surg Today 30:853–855
Nakashima T, Kondoh S, Kitoh H, Ozawa H, Okita S, Harada T, Shiraishi K, Ryozawa S et al (2003) Vascular endothelial growth factor-C expression in human gallbladder cancer and its relationship to lymph node metastasis. Int J Mol Med 11:33–39
Nakata T, Kobayashi A, Miwa S, Soeda J, Miyagawa S (2007) Impact of tumor spread to the cystic duct on the prognosis of patients with gallbladder carcinoma. World J Surg 31:155–161
Negi SS, Singh A, Chaudhary A (2011) Lymph nodal involvement as prognostic factor in gallbladder cancer: location, count or ratio ? J Gastrointest Surg 15:1017–1025
Niu XJ, Wang ZR, Wu SL, Geng ZM, Zhang YF, Qing XL (2004) Relationship between inducible nitric oxide synthase expression and angiogenesis in primary gallbladder carcinoma tissue. World J Gastroenterol 10:725–728
Noshiro H, Chijiiwa K, Yamaguchi K, Shimizu S, Sugitani A, Tanaka M (2003) Factors affecting surgical outcome for gallbladder carcinoma. Hepatogastroenterology 50:939–944
Ohmura Y, Yokoyama N, Tanada M, Takiyama W, Takashima S (1999) Port site recurrence of unexpected gallbladder carcinoma after a laparoscopic cholecystectomy: report of a case. Surg Today 29:71–75
Ohtani T, Takano Y, Shirai Y, Hatakeyama K (1998) Early intraperitoneal dissemination after radical resection of unsuspected gallbladder carcinoma following laparoscopic cholecystectomy. Surg Laparosc Endosc 8:58–62
Ohtani Y, Dowaki S, Kashiwagi H, Tobita K, Tsukui M, Tanaka Y, Tsuchida T, Tokunaga T et al (1999) Stromal expression of thrombospondin-1 is correlated with growth and metastasis of human gallbladder carcinoma. Int J Oncol 15:453–457
Ohtsuka M, Miyazaki M, Itoh H, Nakagawa K, Ambiru S, Shimizu H, Nakajima N, Akikusa B et al (1998) Routes of hepatic metastasis of gallbladder carcinoma. Am J Clin Pathol 109:62–68

Okada K, Kijima H, Imaizumi T, Hirabayashi K, Matsuyama M, Yazawa N, Oida Y et al (2009a) Wall-invasion pattern correlates with survival of patients with gallbladder adenocarcinoma. Anticancer Res 29:685–691

Okada K, Kijima H, Imaizumi T, Hirabayashi K, Matsuyama M, Yazawa N, Oida Y et al (2009b) Stromal laminin-5gamma2 chain expression is associated with the wall-invasion pattern of gallbladder adenocarcinoma. Biomed Res 30:53–62

Okada K, Kijima H, Imaizumi T, Hirabayashi K, Matsuyama M, Yazawa N, Dowaki S et al (2012) Clinical significance of wall invasion pattern of subserosa-invasive gallbladder carcinoma. Oncol Rep 28:1531–1536

Okita S, Kondoh S, Shiraishi K, Kaino S, Hatano S, Okita K (1998) Expression of vascular endothelial growth factor correlates with tumor progression in gallbladder cancer. Int J Oncol 12:1013–1018

Onuki K, Sugiyama H, Ishige K, Kawamoto T, Ota T, Ariizumi S, Yamato M, Kadota S et al (2014) Expression of N-acetylglucosaminyltransferase V in the subserosal layer correlates with postsurgical survival of pathological tumor stage 2 carcinoma of the gallbladder. J Gastroenterol 49:702–714

Oshikiri T, Hida Y, Miyamoto M, Hashida H, Katoh K, Suzuoki M, Nakakubo Y, Hiraoka K et al (2001) RCAS1 as a tumour progression marker: an independent negative prognostic factor In gallbladder cancer. Br J Cancer 85:1922–1927

Ouchi K, Goto H, Owada Y, Sato T (1986) Spreads of gallbladder carcinoma: significance of histological classification of the tumor (in Japanese). Nihon Geka Gakkai Zasshi 87:878–882

Ouchi K, Owada Y, Matsuno S, Sato T (1987) Prognostic factors in the surgical treatment of gallbladder carcinoma. Surgery 101:731–737

Ouyang M, Wu W, Zou Y, Zhou J, Wang Z, Wan X (2010) Immunoreactivity and prognostic value of tumor-associated glycoprotein 72 in primary gallbladder carcinoma. Surg Oncol 19:82–87

Paolucci V, Schaeff B, Schneider M, Gutt C (1999) Tumor seeding following laparoscopy: international survey. World J Surg 23:989–995

Peng HH, Zhang YD, Gong LS, Liu WD, Zhang Y (2013) Increased expression of microRNA-335 predicts a favorable prognosis in primary gallbladder carcinoma. Oncol Targets Ther 6:1625–1630

Petrén T (1932) Die extrahepatischen Gallengangsvenen und ihre pathologisch-anatomische Bedeutung. Verh Anat Ges 41:139–143

Pezet D, Fondrinier E, Rotman N, Guy L, Lemesle P, Lointier P, Chipponi J (1992) Parietal seeding of carcinoma of the gallbladder after laparoscopic cholecystectomy. Br J Surg 79:230

Prakash M, Aiyappan SK, Kumar A, Sreenivasan R, Yadav TD, Khandelwal N (2010) Solitary skeletal metastasis in carcinoma gallbladder: two case reports. Cancer Imaging 10:121–123

Prince S, Zeidman A, Dekel Y, Ram E, Koren R (2008) Expression of epithelial cell adhesion molecule in gallbladder carcinoma and its correlation with clinicopathologic variables. Am J Clin Pathol 129: 424–429

Priya TP, Kapoor VK, Krishnani N, Agrawal V, Agrawal S (2010) Role of E-cadherin gene in gall bladder cancer and its precursor lesions. Virchows Arch 456:507–514

Puglisi F, Capuano P, Gentile A, Lobascio P, Russo S, Martines G, Lograno G, Memeo V (2005) Retrobulbar metastasis from gallbladder carcinoma after laparoscopic cholecystectomy. A case report. Tumori 91:428–431

Puhalla H, Herberger B, Soleiman A, Filipits M, Laengle F, Gruenberger T, Wrba F (2005) E-cadherin and beta-catenin expression in normal, inflamed and cancerous gallbladder tissue. Anticancer Res 25:4249–4254

Puhalla H, Wrba F, Kandioler D, Lehnert M, Huynh A, Gruenberger T, Tamandi D et al (2007) Expression of p21 (Wafl/Cip1), p57 (Kip2) and HER2/neu in patients with gallbladder cancer. Anticancer Res 27:1679–1684

Puranik AD, Purandare N, Agrawal A, Shah S, Rangarajan V (2014) Bone marrow metastases in an otherwise operable gall bladder cancer: rare site of distant metastases detected on FDG PET/CT. Clin Nucl Med 39: e169–e172

Qiang D, Lei J, Xiaoqian W, Meiping W, Feifel S, Yanling C (2014) TNF-a promotes the lymphangiogenesis of gallbladder carcinoma through NF-kB-mediated up-regulation of VEGF-C. Cancer Sci. doi:10.1111/cas.12504

Ralls PW, Mayekawa DS, Lee KP, Colletti PM, Johnson MB, Halls JM (1988) Gallbladder wall varices: diagnosis with color flow Doppler sonography. J Clin Ultrasound 16:595–598

Reber PU, Baer HU, Patel AG, Schmied B, Büchler MW (1998) Port site metastases following laparoscopic cholecystectomy for unsuspected carcinoma of the gallbladder. Z Gastroenterol 36:901–907

Renner R, Sticherling M (2007) Sister Mary Joseph's nodule as a metastasis of gallbladder carcinoma. Int J Dermatol 46:505–507

Roa I, Araya JC, Shiraishi T, Yatani R, Wistuba I, Villaseca M, De Aretxbala X (1993) DNA content in gallbladder carcinoma: a flow cytometric study of 96 cases. Histopathology 23:459–464

Roa JC, Tapia O, Manterola C, Villaseca M, Guzman P, Araya JC, Bagci P, Saka B et al (2013) Early gallbladder carcinoma has a favorable outcome but Rokitansky-Aschoff sinus involvement is an adverse prognostic factor. Virchows Arch 463:651–661

Roh YH, Kim YH, Choi HJ, Lee KE, Roh MS (2008) Syndecan-1 expression in gallbladder cancer and its prognostic significance. Eur Surg Res 41:245–250

Roh YH, Kim YH, Choi HJ, Lee KE, Roh MS (2009) Fascin overexpression correlates with positive thrombospondin-1 and syndecan-1 expressions and a more aggressive clinical course in patients with

gallbladder cancer. J Hepatobiliary Pancreat Surg 16:315–321
Rominger CJ, Lockwood DW, Canino CW (1961) Carcinoma of the gallbladder with mandibular metastasis: report of case. J Oral Anesth Hosp Dent Serv 19:425–427
Rousselot R, Labram C, Janvier R (1964) Umbilical tumor, metastasis indicative of gallbladder cancer (in French). Bull Soc Fr Dermatol Syphiligr 71:670–672
Sahoo MK, Sharma P, Suman S, Jain TK, Bal C, Kumar R (2014) Gallbladder carcinoma metastasizing to adrenal gland: a rare site demonstrated with (18)F-FDG PET/CT. Clin Nucl Med 39:184–185
Sailer M, Debus S, Fuchs KH, Thiede A (1995) Peritoneal seeding of gallbladder cancer after laparoscopic cholecystectomy. Surg Endosc 9:1298–1300
Sakata J, Shirai Y, Wakai T, Ajioka Y, Hatakeyama K (2010) Number of positive lymph nodes independently determines the prognosis after resection in patients with gallbladder carcinoma. Ann Surg Oncol 17:1831–1840
Sasaki R, Uesugi N, Itabashi H, Fujita T, Takeda Y, Hoshikawa K, Takahashi M, Funato O et al (2005) Clinicopathological study of depth of subserosal invasion in patients with pT2 gallbladder carcinoma. J Surg Oncol 92:83–88
Sasaki E, Nagino M, Ebata T, Oda K, Arai T, Nishio H, Nimura Y (2006) Immunohistochemically demonstrated lymph node micrometastasis and prognosis in patients with gallbladder carcinoma. Ann Surg 244:99–105
Sato Y, Tanaka J, Koyama K, van Gulik TM, Lygidakis NJ, van der Heyde MN (1993) Tumor DNA content in gallbladder carcinoma. Hepatogastroenterology 40:375–379
Seki H, Koyama K, Tanaka J, Sato Y, Umezawa A (1995) Neural cell adhesion molecule and perineural invasion in gallbladder cancer. J Surg Oncol 58:97–100
Shi YZ, Hui AM, Li X, Takayama T, Makuuchi M (2000) Overexpression of retinoblastoma protein predicts decreased survival and correlates with loss of p16INK4 protein in gallbladder carcinomas. Clin Cancer Res 6:4096–4100
Shirai Y, Tsukada K, Ohtani T, Watanabe H, Hatakeyama K (1995) Hepatic metastases from carcinoma of the gallbladder. Cancer 75:2063–2068
Shirai Y, Ohtani T, Hatakeyama K (1998) Laparoscopic cholecystectomy may disseminate gallbladder carcinoma. Hepatogastroenterology 45:81–82
Shirai Y, Sakata J, Wakai T, Ohashi T, Ajioka Y, Hatakeyama K (2012) Assessment of lymph node status in gallbladder cancer: location, number, or ratio of positive nodes. World J Surg Oncol 10:87
Shu GS, Yang ZL, Liu DC (2012) Immunohistochemical study of Dicer and Drosha expression in the benign and malignant lesions of gallbladder and their clinicopathological significances. Pathol Res Pract 208:392–397
Singh S, Gupta P, Khanna R, Khanna AK (2010) Simultaneous breast and ovarian metastasis from gallbladder carcinoma. Hepatobiliary Pancreat Dis Int 9:553–554
Song SP, Zhang SB, Liu R, Yao L, Hao YQ, Liao MM, Zhang YD, Li ZH (2012) NDRG2 down-regulation and CD24 up-regulation promote tumor aggravation and poor survival in patients with gallbladder carcinoma. Med Oncol 29:1879–1885
Sons HU, Borchard F, Joel BS (1985) Carcinoma of the gallbladder: autopsy findings in 287 cases and review of the literature. J Surg Oncol 28:199–206
Srivastava V, Patel B, Kumar M, Shukla M, Pandey M (2013) Cyclin D1, retinoblastoma and p16 protein expression in carcinoma of the gallbladder. Asian Pac J Cancer Prev 14:2711–2715
Sugawara Y, Makuuchi M, Harihara Y, Noie T, Inoue K, Kubota K, Takayama T (1999) Tumor angiogenesis in gallbladder carcinoma. Hepatogastroenterology 46:1682–1686
Sumi K, Matsuyama S, Kitajima Y, Miyazaki K (2004) Loss of estrogen receptor beta expression at cancer front correlates with tumor progression and poor prognosis of gallbladder cancer. Oncol Rep 12: 979–984
Sun W, Fan YZ, Xi H, Lu XS, Ye C, Zhang JT (2011) Astrocyte elevated gene-1 overexpression in human primary gallbladder carcinomas: an unfavorable and independent prognostic factor. Oncol Rep 26:1133–1142
Sun W, Shen ZY, Zhang H, Fan YZ, Zhang WZ, Zhang JT, Lu XS, Ye C (2012) Overexpression of HIF-1a in primary gallbladder carcinoma and its relation to vasculogenic mimicry and unfavourable prognosis. Oncol Rep 27:1990–2002
Takagawa M, Muguruma N, Oguri K, Imoto Y, Okamoto K, Ii K, Ito S (2005) Prediction of prognosis in gallbladder carcinoma by mucin and p53 immunohistochemistry. Dig Dis Sci 50:1410–1413
Takano S, Yoshii Y, Owada T, Shirai S, Nose T (1991) Central nervous metastasis from gallbladder – case report. Neurol Med Chir (Tokyo) 31:782–786
Takeuchi T, Adachi Y, Nagayama T, Furihata M (2011) Nedd4L modulates the transcription of metalloproteinase-1 and -13 genes to increase the invasive activity of gallbladder cancer. Int J Exp Pathol 92:79–86
Tanabe M, Endo I, Masunari H, Sugita M, Morioka D, Ishikawa T, Ichikawa Y, Shimada H (2012) Is lymph-node micrometastasis in gallbladder cancer a significant prognostic factor? Hepatogastroenterology 59:31–35
Tayo JR, Al-Abdulkarim H, Al-Rayess M (2005) Brain metastasis as an manifestation of a gallbladder carcinoma. Neurosciences (Riyadh) 10:235–237
Tokunaga T, Arakawa H, Kuwashima Y (2005) A case of lepidic pulmonary metastasis from adenocarcinoma of the gallbladder mimicking acute interstitial pneumonia. Clin Radiol 60:1213–1215
Tsukada K, Kurosaki I, Uchida K, Shirai Y, Oohashi Y, Yokoyama N, Watanabe H et al (1997) Lymph node spread from carcinoma of the gallbladder. Cancer 80:661–667

Vadheim JL, Gray HK, Dockerty MB (1944) Carcinoma of the gallbladder; a clinical and pathologic study. Am J Surg 63:173–180

Varga M, Obrist P, Schneeberger S, Mühlmann G, Felgel-Farnholz C, Fong D, Zitt M et al (2004) Overexpression of epithelial cell adhesion molecule antigen in gallbladder carcinoma is an independent marker for poor survival. Clin Cancer Res 10:3131–3136

Wakai T, Shirai Y, Yokoyama N, Ajioka Y, Watanabe H, Hatakeyama K (2003) Depth of subserosal invasion predicts long-term survival after resection in patients with T2 gallbladder carcinoma. Ann Surg 10: 447–454

Wakai T, Shirai Y, Sakata J, Nagahashi M, Ajioka Y, Hatakeyama K (2010) Mode of hepatic spread from gallbladder carcinoma: an immunohistochemical analysis of 42 hepatectomized specimens. Am J Surg Pathol 34:65–74

Wang C, Zhao H, Lu J, Yin J, Zang L, Song N, Dong R, Wu T, Du X (2012a) Clinicopathological significance of SOX4 expression in primary gallbladder carcinoma. Diagn Pathol 7:41

Wang W, Yang ZL, Liu JQ, Jiang S, Miao XY (2012b) Identification of CD146 expression, angiogenesis, and lymphangiogenesis as progression, metastasis, and poor-prognosis related markers for gallbladder adenocarcinoma. Tumour Biol 33:173–182

Washington K, Gottfried MR (1996) Expression of p53 in adenocarcinoma of the gallbladder and bile ducts. Liver 16:99–104

Willis RA (1953) Pathology of tumors, 2nd edn. Mosby, St. Louis, p 997

Winston CB, Chen JW, Fong Y, Schwartz LH, Panicek DM (1999) Recurrent gallbladder carcinoma along laparoscopic cholecystectomy port tracks: CT demonstration. Radiology 212:439–444

Wu XS, Akiyama Y, Igari T, Kawamura T, Hiranuma S, Shibata T, Tsuruta K, Koike M et al (2005) Expression of homeodomain protein CDX2 in gallbladder carcinomas. J Cancer Res Clin Oncol 131:271–278

Wu W, Wang R, Liu H, Peng J, Huang D, Li B, Ruan J (2009) Prediction of prognosis in gallbladder carcinoma by CD147 and MMP-2 immunohistochemistry. Med Oncol 26:117–123

Wu K, Liao M, Liu B, Deng Z (2011) ADAM-17 overexpression in gallbladder carcinoma correlates with poor prognosis of patients. Med Oncol 28: 475–480

Wu J, Lei L, Wang S, Gu D, Zhang J (2012) Immunohistochemical expression and prognostic value of CD97 and its ligand CD55 in primary gallbladder carcinoma. J Biomed Biotechnol 2012:587672

Wysocki A, Krzywon J (2000) Does the laparoscopic cholecystectomy accelerate the intraperitoneal dissemination of previously unrecognized gallbladder cancer. Int J Surg Investig 2:313–317

Xu LN, Zou SQ, Wang JM (2005) Action of mechanism of Fas and Fas ligand in immune escape of gallbladder carcinoma. World J Gastroenterol 11:3719–3723

Xuan YH, Choi YL, Shin YK, Kook MC, Chae SW, Park SM, Chae HB, Kim SH (2005) An immunohistochemical study of the expression of cell-cycle-regulated proteins p53, cyclin D1, RB, p27, Ki67 and MSH2 in gallbladder carcinoma and its precursor lesions. Histol Histopathol 20:59–66

Yamaguchi R, Nagino M, Oda K, Kamiya J, Uesaka K, Nimura Y (2002) Perineural invasion has a negative impact on survival of patients with gallbladder carcinoma. Br J Surg 89:1130–1136

Yamaguchi K, Shirahane K, Nakamura M, Su D, Konomi H, Motoyama K, Sugitani A et al (2005) Frozen section and permanent diagnoses of the bile duct margin in gallbladder and bile duct cancer. HPB (Oxford) 7:135–138

Yamakawa T, Itoh S, Hirosawa K, Miyoshi T, Katoh K, Iizumi S, Kawabata K (1983) Seeding of gallbladder carcinoma along the tract after percutaneous transhepatic choledochoscopy. Am J Gastroenterol 78:649–651

Yamamoto M, Oda N, Tahara E (1990) DNA ploidy patterns in gallbladder adenocarcinoma. Jpn J Clin Oncol 20:83–86

Yamamoto S, Fujii K, Kitadai Y, Yamamoto S, Tsuchida A, Kajiyama G (1998) Expression of vascular endothelial growth factor in human gallbladder lesions. Oncol Rep 5:1065–1069

Yamamoto S, Kitadai Y, Tsuchida A, Saski T, Matsubara K, Kajiyama G (2000) Expression of platelet-derived endothelial cell growth factor/thymidine phosphorylase in human gallbladder lesions. Eur J Cancer 36:257–263

Yanagisawa N, Mikami T, Mitomi H, Saegusa M, Koike M, Okayasu I (2001) CD44 variant overexpression in gallbladder carcinoma associated with tumor dedifferentiation. Cancer 91:408–416

Yang ZL, Miao X, Xiong L, Zou Q, Yuan Y, Li J, Liang L, Chen M, Chen S (2013) CFL1 and Arp3 are biomarkers for metastasis and poor prognosis of squamous cell/adenosquamous carcinomas and adenocarcinomas of gallbladder. Cancer Invest 31:132–139

Yi S, Yang ZL, Miao X, Zou Q, Li J, Liang L, Zeng G, Chen S (2014) N-cadherin and P-cadherin are biomarkers for invasion, metastasis, and poor prognosis of gallbladder carcinomas. Pathol Res Pract 210:363–368

Yoshimitsu K, Honda H, Kaneko K, Kuroiwa T, Irie H, Chijiiwa K, Takenaka K, Masuda K (1997) Anatomy and clinical importance of cholecystic venous drainage: helical CT observations during injection of contrast medium into the cholecystic artery. AJR Am J Roentgenol 169:505–510

Yoshimitsu K, Honda H, Kuroiwa T, Irie H, Aibe H, Tajima T, Chijiiwa K, Shimada M, Masuda K (2001) Liver metastasis from gallbladder carcinoma: anatomic correlation with cholecystic venous drainage demonstrated by helical computed tomography during injection of contrast medium in the cholecystic artery. Cancer 92:340–348

Yuan LW, Liu DC, Yang ZL (2013) Correlation of S1P1 and ERp29 expression to progression, metastasis, and poor prognosis of gallbladder adenocarcinoma. Hepatobiliary Pancreat Dis Int 12:189–195

Z'graggen K, Birrer S, Maurer CA, Wehrli H, Klaiber C, Baer HU (1998) Incidence of port site recurrence after laparoscopic cholecystectomy for preoperatively unsuspected gallbladder carcinoma. Surgery 124:831–838

Zhang M, Pan JW, Ren TR, Zhu YF, Han YJ, Kühnel W (2003) Correlated expression of inducible nitric oxide synthase and P53, Bax in benign and malignant diseased gallbladder. Ann Anat 185:549–554

Zhang SB, Song SP, Li B, Zhou YS, Zhang YD (2012) Expression of N-myc downstream-regulated gene 1 in primary gallbladder carcinoma and its correlation with clinicopathological features and clinical outcome. Med Oncol 29:1866–1872

Zhi YH, Liu RS, Song MM, Tian Y, Long J, Tu W, Guo RX (2005) Cyclooxygenase-2 promotes angiogenesis by increasing vascular endothelial growth factor and predicts prognosis in gallbladder carcinoma. World J Gastroenterol 11:3724–3728

Zhou L, He XD, Chen J, Cui QC, Qu Q, Rui JA, Zhao YP (2007) Overexpression of LAPTM4B-35 closely correlated with clinicopathological features and postresectional survival of gallbladder carcinoma. Eur J Cancer 43:809–815

Zhou L, He XD, Yu JC, Zhou RL, Xiong FX, Qu Q, Rui JA (2010) Expression of LAPTM4B in gallbladder carcinoma cells: the role in invasive potential. Hepatogastroenterology 57:207–211

Zong H, Yin B, Chen J, Ma B, Cai D, He X (2009) Overexpression of c-FLIP confers the resistance to TRAIL-induced apoptosis on gallbladder carcinoma. Tohoku J Exp Med 217:203–208

Adenocarcinoma of the Gallbladder: Risk Factors and Pathogenic Pathways

149

Contents

Abstract

For ordinary adenocarcinoma of the gallbladder, several risk factors have been identified. The most important risk factors are cholelithiasis, female gender, advancing age, and an elevated maximum body mass index. Gallstones and associated inflammatory gallbladder disease are the most common risk factors for gallbladder cancer. At least three quarters of patients with gallbladder carcinoma have gallstones at the time point of diagnosis, but cholelithiasis seems to be a cofactor for carcinogenesis. There is a relationship between gallbladder carcinoma and chronic inflammatory disease of the gallbladder, including xanthogranulomatous cholecystitis. Also chronic sclerosing and hyalinizing cholecystitis with or without calcification is associated with gallbladder carcinoma. Other carcinogenic associations include anomalous pancreaticobiliary junction and an increasing number of genetic, epigenetic, and molecular alterations.

Cholelithiasis

The most important risk factors for carcinoma of the gallbladder (CG) are cholelithiasis, female gender, advancing age, and elevated maximum body mass index (Strom et al. 1995; Sheth et al. 2000; Pandey 2003; Miller and Jarnagin 2008; Rustagi and Dasanu 2012). Gallstones and

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_149

associated inflammatory gallbladder changes are the most common risk factors for CG (Slade 1905; Fawcett and Rippmann 1913; Luelsdorf 1926–1927; Goldschmidt 1963; Wenckert and Robinson 1966; Hardy and Volk 1970; Hart et al. 1971; Balaroutsos et al. 1974; Beltz and Condon 1974; Arnaud et al. 1979; Hamrick et al. 1982; Vitetta et al. 2000; Tazuma and Kajiyama 2001; Chen et al. 2014; Cariati et al. 2014). It is estimated that three quarters of patients with CG have gallstones at the time point of diagnosis (Balaroutsos et al. 1974). Piehler and Crichlow (1978), in a review of the literature, found a 73.9 % incidence in 2,000 cases. Overall, the risk of CG is approximately four to five times higher in patients with gallstones than in patients without gallstones (reviews: Lowenfels et al. 1985; Lowenfels et al. 1999). Currently, it is considered that gallstones as such are a cofactor for carcinogenesis, but formal proof that they directly cause CG is lacking (review: Shrikhande et al. 2010).

Chronic Inflammatory Gallbladder Disease

There is a relationship between CG and chronic inflammatory disease of the gallbladder, including xanthogranulomatous cholecystitis (Zhuang et al. 2013). Chronic sclerosing and hyalinizing cholecystitis with or without wall calcification (porcelain gallbladder) is associated with CG (Polk 1966; Berk et al. 1973; Stephen and Berger 2001; Khan et al. 2011; Patel et al. 2011; Gupta and Jauhari 2012; Wong and Weissglas 2013). Porcelain gallbladder is a rare condition which was found in only 0.06–0.80 % of cholecystectomy specimens. It is more common in female patients. A recent investigation demonstrated that the risk of harboring CG in patients with porcelain gallbladder is lower than recently anticipated (Schnelldorfer 2013), and in one study, no association between porcelain gallbladder and CG was identified (Towfigh et al. 2001). The significance of gallbladder polyps in predisposing to CG is probably overstated (Pilgrim et al. 2013). Environmental agents, such as heavy metals, have been proposed to be related to gallbladder carcinogenesis (Pandey 2006). In earlier times, thorotrastosis was a well-recognized cause of CG (Hashizume et al. 1980), but most patients who had been investigated by the use of Thorotrast are now no longer alive. Rarely, CG has been found in the setting of primary sclerosing cholangitis (Lewis et al. 2007). There is an association of higher CG risk and chronic salmonellosis (Welton et al. 1979; Caygill et al. 1995; Kumar et al. 2006; Andia et al. 2008; Tewari et al. 2010; Walawalkar et al. 2013). Chronic *Salmonella* carriage is a well-known feature in this infection, and *Salmonella* can form robust biofilms on gallbladder epithelium, the bacterium being able to adhere to and invade polarized gallbladder epithelial cells apically (Gonzalez-Escobedo and Gunn 2013; Gunn et al. 2014). *Salmonella* carriage can induce a smoldering inflammation promoting carcinogenesis and *Salmonella* secretes a genotoxic toxin (Nath et al. 2010). A case-control study in the USA showed that chronic typhoid carriers died of hepatobiliary cancer six times more often than matched controls (Welton et al. 1979). Also in Northern India, a potential association between chronic typhoid fever carriage (*Salmonella typhi* and *Salmonella paratyphi* A) and CG was observed (Nath et al. 1997, 2008).

Differences of CG frequencies in various populations suggest effects of genetic factors. Also familial CG supports a role of genetic mechanisms. In addition, there is evidence that genetic factors are involved in the pathogenesis of gallstone disease, therefore indirectly affecting gallbladder carcinogenesis.

Anomalous Pancreaticobiliary Junction

In Eastern countries, specifically in Japan, anomalous pancreaticobiliary junction is considered to be an important risk factor for CG (Kimura et al. 1985; Lin et al. 1988; Ozmen et al. 1991; Chijiiwa et al. 1993; Tseng et al. 1993; Hanada

et al. 1996; Uetsuji et al. 1996; Yang et al. 1997; Egami et al. 1998; Chao et al. 1999; Yoshida et al. 1999; Ng 2000; Elnemr et al. 2001; Nakayama et al. 2001; Sakurai et al. 2001; Yano et al. 2001; Takayashiki et al. 2002; Hu et al. 2003; Kang et al. 2007; Noda et al. 2007; Hori et al. 2008; review: Tsuchida et al. 2003). In an investigation of the Japanese Study Group of Pancreaticobiliary Maljunction (PBM), PBM was found in 52 (3 %) of 1,722 patients investigated with ERCP, and of these, 14 patients had developed CG (Egami et al. 1998). This association was identified in Western patients at a much lower frequency (Tuech et al. 2000). Detailed histologic studies have demonstrated that CG carcinogenesis in the presence of maljunction proceeds along a complex pathway, starting with hyperplastic mucosal changes in the gallbladder associated with upregulated cell kinetics, followed by various grades of metaplasia, dysplasia, and transition to carcinoma (Yamamoto et al. 1991; Sai et al. 2005; review: Hanada et al. 1999a). Epithelial cell proliferation of the gallbladder is increased in patients with maljunction (Hanada et al. 1996; Yang et al. 1997). Maljunction-induced increased gallbladder cell proliferation may be an event initiated early in life, as increased proliferative activity of mucosal epithelia was detected in children with maljunction (Tanno et al. 1999; Tokiwa et al. 1999). The mechanisms involved in the induction of this sequence of events are only partially known, but it is suggested that pancreatic juice reflux into the biliary tract followed by inflammation, epithelial cell loss, and consecutive hyperregeneration play a significant role (review: Chao et al. 1999). In fact, CG has been found in association with pancreaticobiliary reflux in the absence of maljunction (Sai et al. 2006). This pathway was found to be accompanied by p53 gene mutations and mutations in codon 12 of the K-RAS gene (Iwase et al. 1997; Chao et al. 1999; Hanada et al. 1999a, b; Masuhara et al. 2000). Point mutations of the K-RAS gene in CG have also been found in tumors that had developed in patients with congenital biliary dilatation (Tomono et al. 1996).

Genetic and Molecular Alterations

In CG, an array of genetic abnormalities has been identified, often involving chromosomes 3p, 8p, 9q, and 22q (Wistuba et al. 2002a; Malik 2004; Srivastava et al. 2011; Andrén-Sandberg 2012; Boutros et al. 2012; Maurya et al. 2012). Also aberrations of other chromosomal sites, including chromosomes 1p, 3p,4, 5p, 8p21, 9p, 9q, 13q, 16q, 17p, and 18q21, are considered to play pathogenic roles (Wistuba and Albores-Saavedra 1999; Kuroki et al. 2005; Dixit et al. 2012). Microsatellite instability was detectable in 17 % of CG patients (Yoshida et al. 2000). LOH at a locus on chromosome 3p is associated with abnormalities of the fragile histidine triad gene in CG (Wistuba et al. 2002a,b; Riquelme et al. 2007). Microsatellite instability (MSI) was detected in 17 % of CG, and there was an inverse correlation between MSI and the presence of LOH in CG (Yoshida et al. 2000).

Whole-exome and targeted gene sequencing of CG identified recurrent mutation in the ErbB pathway. Mutated ErbB signaling pathways were found in 36.8 % of CG samples (Li et al. 2014). Several investigations indicate that abnormalities in the TP53 (chromosome 17p13) and p16(Ink4)/CDKN2 (chromosome 9p21–22) gene loci are early and frequent events in the carcinogenesis of CG. The role of p53 gene alterations in CG is still not clarified (Ajiki et al. 1996b; Jonas et al. 1997; Kim et al. 2001a,b; Quan et al. 2001; Koda et al. 2003; Wang et al. 2006; Ghosh et al. 2013, review: Rai et al. 2011). Overall, p53 is expressed in CG with a high frequency (Fujii et al. 1996; da Rocha et al. 2004; Kalekou and Miliaras 2004; Wang et al. 2006). There is evidence that p53 expression is more prevalent in the gallbladder with gallstones in patients with CG (Misra et al. 2000). One subset of CG seems to develop de novo in the setting of predominant p53 gene mutations, with low rate of K-RAS mutations (Itoi et al. 1996). The expression rate of p53 seems to reflect the dysplasia-carcinoma sequence (Agrawal et al. 2010). p53 expression was found in 32.4 % of dysplastic lesions, 44.7 % of CIS, and 65.4 % of invasive carcinomas (Wistuba et al. 1996). Mutations of the TP53 locus seem to be associated with

the growth pattern of CG, as the incidence of p53 immunoreactivity was greater in flat CG than in polypoid CG (Hanada et al. 1997). In contrast to CG, p53 expression was not detectable in gallbladder adenoma but in carcinoma arising in adenoma (Takei et al. 1996). Mutations in the K-RAS gene have been identified in patients with CG, however, at a low frequency, in contrast to adenomas (Saetta et al. 1996; Saetta 2006; Pai et al. 2011; Javle et al. 2014). There is evidence that such mutations may occur either early or later in the carcinogenic pathway. In contrast to other studies, no mutations in K-RAS were found in adenoma or gallbladder dysplasia in one study, but in 20 % of established CG (Kim et al. 2001a). Conversely, an earlier investigation reported K-RAS gene mutation even in gallbladder dysplasia at an incidence similar to that in CG (Ajiki et al. 1996a). There is evidence that alterations in DNA repair genes may be involved in CG carcinogenesis (Srivastava et al. 2010). Altered gene expression patterns involved in CG carcinogenesis are also promoted by aberrant promoter hypermethylation as epigenetic mechanism (House et al. 2003; Takahashi et al. 2004; Garcia et al. 2009). The acquisition of epigenetic alterations of several gene promoter sites of tumor suppressors may contribute to carcinogenic pathways in chronic cholecystitis and dysplastic changes (House et al. 2003). A gene that frequently undergoes epigenetic inactivation in CG is 3p, which is therefore considered a site of candidate tumor suppressor genes (Riquelme et al. 2007).

Apart from the nuclear genome, CG also showed alterations in the mitochondrial genome. Mutation analysis of this genome, in particular the D-loop, showed a wide range of point mutations and polymorphisms in the mitochondrial genome of CG (Maurya et al. 2013).

Factors Involved in Growth and Cell Cycle Regulation

Proliferative activity of CG cells is correlated with overexpression of several factors regulating the cell division cycle, including cyclin E (Eguchi et al. 1999; Mishra et al. 2011). Nuclear expression of the p16(INK4a) gene product was expressed in 39.1 % of CG and 31.6 % of high-grade dysplastic gallbladder epithelia, but not in normal epithelium (Lynch et al. 2008). Inactivation of p16 in CG occurs through two pathways, i.e., via LOH at 9p21–22 and through homozygous gene deletion, the latter being a combination of LOH and promoter hypermethylation (Tadokoro et al. 2007). Cell proliferation in CG is also regulated by a novel member of the Krüppel C2H2-type zinc finger protein family, zinc finger X-chromosomal protein, which promotes growth, but also migration, of CG cells (Tan et al. 2013). Cell proliferation of CG cells is induced by the morphogen, hepatocyte growth factor/HGF (Li et al. 1998; Yang et al. 2012), whereby the cancer cells express the HGF receptor, c-Met (Sasaki et al. 2012). In CG, c-Met is immunohistochemically localized in the cell membrane (Sanada et al. 2010). CG also showed an aberrant activation of the Sonic hedgehog signaling pathway (Xie et al. 2014). ErbB2 signaling in CG is linked to MUC4 expression, as ErbB2 interacts with MUC4 at the carcinoma cell apex, associated with hyperphosphorylation of erbB2, MAPK, and Akt, and with the overexpression of cyclooxygenase-2. Experimentally, MUC4 amplifies cell proliferation in the presence of heregulin through potentiating the phosphorylation of ErbB2 and its signaling pathways (Miyahara et al. 2008).

Wnt/Beta-Catenin Signaling Pathway

In contrast to gallbladder adenomas, altered expression of beta-catenin, such as nuclear or cytoplasmic expression and loss of cell membrane expression, is not a common feature in gallbladder dysplasia and CG, but cytoplasmic and nuclear expression of beta-catenin in CG was correlated with a less aggressive behavior of the neoplasms (Chang et al. 2002).

Apoptosis

Apoptosis is a common phenomenon in CG and is regulated by diverse pro- and antiapoptotic factors. The frequency of apoptosis may increase

with CG progression (Sasatomi et al. 1996). One protein regulating apoptosis is p53. p53 gene mutations are a rather common event in CG and were observed in up to 35.7 % of cases (Kim et al. 2001b). There seems to be a positive correlation between expressions of p53 and Bcl-2 (Sasatomi et al. 1996). 65.4 % of CG revealed a decreased expression of Bax-interacting dactor-1/Bif-1, suggesting that loss of Bif-1 might play a role in gallbladder tumorigenesis (Kim et al. 2008). TSG101, a protein involved in resistance against apoptosis, is overexpressed in CG (Liu et al. 2011).

Invasion and Spread

As already specified above (paragraph on prognosticators), several types of matrix metalloproteinases (MMPs) are expressed in CG and are involved in the initiation and progression of the invasion cascade. Genetic variants of MMP-2, MMP-7, and MMP-9 are associated with higher susceptibility of gallbladder cancer (Sharma et al. 2012). Heparanase is a further enzyme playing a role in invasion and metastasis (Dutta and Poomachandra 2008; Wu et al. 2008). Heparanase is an endo-beta-glucuronidase which splits heparan sulfate and is frequently expressed in CG. Trophinin, an adhesion molecule that was first identified in human trophoblast cells and involved in embryo implantation, promotes cancer cell invasion in CG cells (Chang et al. 2009). Trophinin interacts with tastin and bystin, cytoplasmic proteins required for trophinin's activity as an adhesion molecule (Fukuda and Sugihara 2012). Invasive features of CG cells are also promoted hepatocyte growth factor/HGF interacting with the membranous c-Met receptor (Li et al. 1998). Part of CG exhibit overexpression of c-Met in cells of the invasive component, in association with expression of beta-catenin and cyclooxygenase-2 (Moon et al. 2005). However, other subsets of CG that have been analyzed revealed lack of c-Met expression in the invasive part of the tumor (Sanada et al. 2010).

Angiogenesis

As in other carcinomas and non-epithelial malignancies, tumor-induced angiogenesis is a critical mechanism in the setting of tumor growth and progression. A major driving force that induced angiogenic pathways is tumor hypoxia. Hypoxia-inducible factors 1alpha and 2alpha are upregulated in many CG, and this upregulation is strongly associated with increased expression of vascular endothelial growth factor/VEGF and augmented angiogenesis (Giatromanolaki et al. 2006). However, lower expression of hypoxia-inducible factor-1alpha and elevated expression of the von Hippel-Lindau (VHL) gene in CG are important markers for tumor progression, in that highly invasive tumors show decreased HIF-1alpha expression (Yang et al. 2011). VEGF-C, which has a central role in neoplastic lymphangiogenesis and angiogenesis through VEGF receptor 3 and VEGF receptor 2, respectively, expressed in endothelial cells, promotes progressive growth and invasion of CG (Chen et al. 2010). A further factor involved in tumor angiogenesis in CG is cyclooxygenase-2. Overexpression of this enzyme in CG cells is associated with increased angiogenesis, which in turn affects tumor progression and patient survival (Legan et al. 2009). Basigin (EMMPRIN/CD147), a multifunctional membrane glycoprotein involved in invasion and angiogenesis of diverse malignancies, is overexpressed in CG, expression pattern being correlated with stage and survival rate (Xiao and Tang 2009).

References

Agrawal V, Goel A, Krishnani N, Pandey R, Agrawal S, Kapoor VK (2010) p53, carcinoembryonic antigen and carbohydrate antigen 19.9 expression in gall bladder cancer, precursor epithelial lesions and xanthogranulomatous cholecystitis. J Postgrad Med 56:262–266

Ajiki T, Fujimori T, Onoyama H, Yamamoto M, Kitazawa S, Maeda S, Saitoh Y (1996a) K-ras gene mutation in gall bladder carcinomas and dysplasia. Gut 38:426–429

Ajiki T, Onoyama H, Yamamoto M, Asaka K, Fujimori T, Maeda S, Saitoh Y (1996b) p53 protein expression and

prognosis in gallbladder carcinoma and premalignant lesions. Hepatogastroenterology 43:521–526
Andia ME, Hsing AW, Andreotti G, Ferreccio C (2008) Geographic variation of gallbladder cancer mortality and risk factors in Chile: a population-based ecologic study. Int J Cancer 123:1411–1416
Andrén-Sandberg A (2012) Molecular biology of gallbladder cancer: potential clinical implications. N Am J Med Sci 4:435–441
Arnaud J, Graf P, Gramfort J, Adloff M (1979) Primary carcinoma of the gallbladder: review of 25 cases. Am J Surg 138:403–406
Balaroutos C, Bastounis E, Karamanakos P, Golematis B (1974) Primary carcinoma of the gallbladder: analysis of 22 cases. Am Surg 40:605–608
Beltz WR, Condon RE (1974) Primary carcinoma of the gallbladder. Am Surg 180:180–184
Berk RN, Armbruster TG, Saltzstein SL (1973) Carcinoma in the porcelain gallbladder. Radiology 106:29–31
Boutros C, Gary M, Baldwin K, Somasundar P (2012) Gallbladder cancer: past, present and an uncertain future. Surg Oncol 21:e183–e191
Cariati A, Piromalli E, Cetta F (2014) Gallbladder cancers: associated conditions, histological types, prognosis, and prevention. Eur J Gastroenterol Hepatol 26:562–569
Caygill CP, Braddick M, Hill MJ, Knowles RL, Sharp JC (1995) The association between typhoid carriage, typhoid infection and subsequent cancer at a number of sites. Eur J Cancer Prev 4:187–193
Chang HJ, Jee CD, Kim WH (2002) Mutation and altered expression of beta-catenin during gallbladder carcinogenesis. Am J Surg Pathol 26:758–766
Chang XZ, Yu J, Zhang XH, Yin J, Wang T, Cao XC (2009) Enhanced expression of trophinin promotes invasive and metastatic potential of human gallbladder cancer cells. J Cancer Res Clin Oncol 135:581–590
Chao TC, Wang CS, Jan YY, Chen HM, Chen MF (1999) Carcinogenesis in the biliary system associated with APDJ. J Hepatobiliary Pancreat Surg 6:218–222
Chen Y, Jiang L, She F, Tang N, Wang X, Li X, Han S, Zhu J (2010) Vascular endothelial growth-C promotes the growth and invasion of gallbladder cancer via an autocrine mechanism. Mol Cell Biochem 345:77–89
Chen YK, Yeh JH, Lin CL, Peng CL, Sung FC, Hwang IM, Kao CH (2014) Cancer risk in patients with cholelithiasis and after cholecystectomy: a nationwide cohort study. J Gastroenterol 49:923–931
Chijiiwa K, Tanaka M, Nakayama F (1993) Adenocarcinoma of the gallbladder associated with anomalous pancreaticobiliary ductal junction. Am Surg 59:430–434
da Rocha AO, Coutinho LM, Scholl JG, Leboutte LD (2004) The value of p53 protein expression in gallbladder carcinoma: analysis of 60 cases. Hepatogastroenterology 51:1310–1314
Dixit R, Kumar P, Tripathi R, Basu S, Mishra R, Shukla VK (2012) Chromosomal structural analysis in carcinoma of the gallbladder. World J Surg Oncol 10:198
Dutta U, Poomachandra KS (2008) Heparanase and gallbladder cancer: new insights into understanding tumor growth and invasion. J Gastroenterol Hepatol 23:343–344
Egami K, Onda M, Uchida E, Matsuda T, Watanabe A, Arima Y, Kim T, Tajiri T, Okazaki S et al (1998) Clinicopathological studies on association of gallbladder carcinoma and pancreaticobiliary maljunction. Nihon Ika Daigaku Zasshi 65:7–13
Eguchi N, Fujii K, Tsuchida A, Yamamoto S, Sasaki T, Kajiyama G (1999) Cyclin E overexpression in human gallbladder carcinomas. Oncol Rep 6:93–96
Elnemr A, Ohta T, Kayahara M, Kitagawa H, Yoshimoto K, Tani K, Shimizu K, Nishimura G et al (2001) Anomalous pancreaticobiliary ductal junction without bile duct dilatation in gallbladder cancer. Hepatogastroenterology 48:382–386
Fawcett J, Rippmann CH (1913) Carcinoma of the gallbladder associated with gallstones. Guy's Hosp Rep 52:41–80
Fujii K, Yokozaki H, Yasui W, Kuniyasu H, Hirata M, Kajiyama G, Tahara E (1996) High frequency of p53 gene mutation in adenocarcinomas of the gallbladder. Cancer Epidemiol Biomarkers Prev 5:461–466
Fukuda MN, Sugihara K (2012) Trophinin in cell adhesion and signal transduction. Front Biosci (Elite Ed) 4:342–350
Garcia P, Manterola C, Araya JC, Villaseca M, Guzman P, Sanhueza A, Thomas M et al (2009) Promoter methylation profile in preneoplastic and neoplastic gallbladder lesions. Mol Carcinog 48:79–89
Ghosh M, Sakhuja P, Singh S, Agarwal AK (2013) p53 and beta-catenin expression in gallbladder tissues and correlation with tumor progression in gallbladder cancer. Saudi J Gastroenterol 19:34–39
Giatromanolaki A, Sivridis E, Simopoulos C, Polychronidis A, Gatter KC, Harris AL, Koukourakis MI (2006) Hypoxia inducible factors 1alpha and 2alpha are associated with VEGF expression and angiogenesis in gallbladder carcinomas. J Surg Oncol 94:242–247
Goldschmidt A (1963) Cholelithiasis and primary carcinoma of the gallbladder. Proc Rudolf Virchows Med Soc 22:97–101
Gonzalez-Escobedo G, Gunn JS (2013) Gallbladder epithelium as a niche for chronic Salmonella carriage. Infect Immun 81:2920–2930
Gunn JS, Marshall JM, Baker S, Dongol S, Charles RC, Ryan ET (2014) Salmonella chronic carriage: epidemiology, diagnosis, and gallbladder persistence. Trends Microbiol. doi:10.1016/j.tim.2014.06.007
Gupta S, Jauhari RK (2012) Rare presentation of porcelain gall bladder: carcinoma gall bladder with a large intra-abdominal cystic swelling. BMJ Case Rep. 2012, bcr2012006894
Hamrick RE, Liner J, Hastings PR, Cohn I (1982) Primary carcinoma of the gallbladder. Ann Surg 195:270–273
Hanada K, Itoh M, Fujii K, Tsuchida A, Ooishi H, Kajiyama G (1996) K-ras and p53 mutations in stage

I gallbladder carcinoma with an anomalous junction of the pancreaticobiliary duct. Cancer 77:452–458

Hanada K, Itoh M, Fujii K, Tsuchida A, Hirata M, Iwao T, Eguchi N, Sasaki T, Matsubara K et al (1997) TP53 mutations in stage I gallbladder carcinoma with special attention to growth patterns. Eur J Cancer 33:1136–1140

Hanada K, Tsuchida A, Kajiyama G (1999a) Cellular kinetics and gene mutations in gallbladder mucosa with an anomalous junction of pancreaticobiliary duct. J Hepatobiliary Pancreat Surg 6:223–228

Hanada K, Tsuchida A, Iwao T, Eguchi N, Sasaki T, Morinaka K, Matsubara K, Kawasaki Y et al (1999b) Gene mutations of K-ras in gallbladder mucosa and gallbladder carcinoma with an anomalous junction of the pancreaticobiliary duct. Am J Gastroenterol 94:1638–1642

Hardy MA, Volk H (1970) Primary carcinoma of the gallbladder: a ten year review. Am J Surg 120:800–803

Hart J, Modan B, Shani M (1971) Cholelithiasis in the aetiology of gallbladder neoplasms. Lancet 1:1151–1153

Hashizume Y, Shinohara K, Koide O, Takei R (1980) Carcinoma of the gallbladder in thorotrastosis – case report (in Japanese). Rinsho Hoshasen 25:951–954

Hori T, Wagata T, Takemoto K, Shigeta T, Takuwa H, Hata K, Uemoto S, Yokoo N (2008) Spontaneous necrosis of solid gallbladder adenocarcinoma accompanied with pancreaticobiliary maljunction. World J Gastroenterol 14:5933–5937

House MG, Wistuba II, Argani P, Guo M, Schulick RD, Hruban RH, Herman JG et al (2003) Progression of gene hypermethylation in gallstone disease leading to gallbladder cancer. Ann Surg Oncol 10:882–889

Hu B, Gong B, Zhou DY (2003) Association of anomalous pancreaticobiliary ductal junction with gallbladder carcinoma in Chinese patients: an ERCP study. Gastrointest Endosc 57:541–545

Itoi T, Watanabe H, Ajioka Y, Oohashi Y, Takel K, Nishikura K, Nakamura Y, Horil A et al (1996) APC, K-ras codon 12 mutations and p53 gene expression in carcinoma and adenoma of the gall-bladder suggest two genetic pathways in gall-bladder carcinogenesis. Pathol Int 46:33–340

Iwase T, Nakazawa S, Yamao K, Yoshino K, Yoshino J, Inui K, Yamachika H, Kanemaki N et al (1997) Ras gene point mutations in gallbladder lesions associated with anomalous connection of pancreaticobiliary ducts. Hepatogastroenterology 44:1457–1462

Javle M, Rashid A, Churi C, Kar S, Zuo M, Eterovic AK, Nogueras-Gonzalez GM et al (2014) Molecular characterization of gallbladder cancer using somatic mutation profiling. Hum Pathol 45:701–708

Jonas S, Springmeier G, Tauber R, Wiedenmann B, Gessner R, Kling N, Lobeck H et al (1997) p53 hot-spot mutational analysis in advanced Western gallbladder carcinoma. World J Surg 21:768–772

Kalekou H, Miliaras D (2004) Immunohistochemical study of microvessel density, CD44 (standard form), p53 protein and c-erbB2 in gallbladder carcinoma. J Gastroenterol Hepatol 19:812–818

Kang CM, Kim KS, Choi JS, Lee WJ, Kim BR (2007) Gallbladder carcinoma associated with anomalous pancreaticobiliary duct junction. Can J Gastroenterol 21:383–387

Khan ZS, Livingstone EH, Huerta S (2011) Reassessing the need for prophylactic surgery in patients with porcelain gallbladder: case series and systematic review of the literature. Arch Surg 146:1143–1147

Kim YT, Kim J, Jang YH, Lee WJ, Ryu JK, Park YK, Kim SW, Kim WH, Yoon YB et al (2001a) Genetic alterations in gallbladder, adenoma, dysplasia and carcinoma. Cancer Lett 169:59–68

Kim YW, Huh SH, Park YK, Yoon TY, Lee SM, Hong SH (2001b) Expression of the c-erb-B2 and p53 protein in gallbladder carcinomas. Oncol Rep 8:1127–1132

Kim SY, Oh YL, Kim KM, Jeong EG, Kim MS, Yoo NJ, Lee SH (2008) Decreased expression of Bax-interacting factor-1 (Bif-1) in invasive urinary bladder and gallbladder cancers. Pathology 40:553–557

Kimura K, Ohto M, Saisho H, Unozawa T, Tsuchiya Y, Morita M, Ebara M, Matsutani S et al (1985) Association of gallbladder carcinoma and anomalous pancreaticobiliary ductal union. Gastroenterology 89:1258–1265

Koda M, Yashima K, Kawaguchi K, Andachi H, Hosoda A, Shiota G, Ito H, Murawaki Y (2003) Expression of Fhit, Mlh1, and P53 protein in human gallbladder carcinoma. Cancer Lett 199:131–138

Kumar S, Kumar S, Kumar S (2006) Infection as a risk factor for gallbladder cancer. J Surg Oncol 93:633–639

Kuroki T, Tajima Y, Matsuo K, Kanematsu T (2005) Genetic alterations in gallbladder carcinoma. Surg Today 35:101–105

Legan M, Luzar B, Marolt VF (2009) Expression of cyclooxygenase-2, glucose transporter-1 and angiogenesis in gallbladder carcinomas and their impact on prognosis. Scand J Gastroenterol 44:1101–1108

Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC (2007) Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. Am J Surg Pathol 31:907–913

Li H, Shimura H, Aoki Y, Date K, Matsumoto K, Nakamura T, Tanaka M (1998) Hepatocyte growth factor stimulates the invasion of gallbladder carcinoma cell lines in vitro. Clin Exp Metastasis 16:74–82

Li M, Zhang Z, Li X, Ye J, Wu X, Tan Z, Liu C, Shen B, Wang XA, Wu W, Zhou D et al (2014) Whole-exome and targeted gene sequencing of gallbladder carcinoma identifies recurrent mutations in the ErbB pathway. Nat Genet 46:872–876

Lin JT, Yu SC, Hsu SC, Wang TH, How SW, Chen DS (1988) Carcinoma of the gallbladder from an anomalous connection between the bile duct and the pancreatic duct. J Clin Gastroenterol 10:335–338

Liu DC, Yang ZL, Jiang S (2011) Identification of PEG10 and TSG101 as carcinogenesis, progression, and poor-prognosis related biomarkers for gallbladder adenocarcinoma. Pathol Oncol Res 17:859–866

Lowenfels AB, Lindström CG, Conway MJ, Hastings PR (1985) Gallstones and risk of gallbladder cancer. J Natl Cancer Inst 75:77–80

Lowenfels AB, Maisonneuve P, Boyle P, Zatonski WA (1999) Epidemiology of gallbladder cancer. Hepatogastroenterology 46:1529–1532

Luelsdorf F (1926–1927) Die Beziehungen zwischen Steinkrankheit und Krebs der Gallenblase. Ztschr Krebsforsch 24, p 395–405

Lynch BC, Lathrop SL, Ye D, Ma TY, Cerili LA (2008) Expression of the p16(INK4a) gene product in premalignant and malignant epithelial lesions of the gallbladder. Ann Diagn Pathol 12:161–164

Malik IA (2004) Gallbladder cancer: current status. Expert Opin Pharmacother 5:1271–1277

Masuhara S, Kasuya K, Aoki T, Yoshimatsu A, Tsuchida A, Koyanagi Y (2000) Relation between K-ras codon 12 mutation and p53 protein overexpression in gallbladder cancer and biliary ductal epithelia in patients with pancreaticobiliary maljunction. J Hepatobiliary Pancreat Surg 7:198–205

Maurya SK, Tewari M, Mishra RR, Shukla HS (2012) Genetic aberrations in gallbladder cancer. Surg Oncol 21:37–43

Maurya SK, Tewari M, Shukla HS (2013) Gallbladder carcinoma: high rate of mitochondrial d-loop mutations. Diagn Mol Pathol 22:119–122

Miller G, Jarnagin WR (2008) Gallbladder carcinoma. Eur J Surg Oncol 34:306–312

Mishra PK, Raghuram GV, Jatawa SK, Bhargava A, Varshney S (2011) Frequency of genetic alterations observed in cell cycle regulatory proteins and microsatellite instability in gallbladder adenocarcinoma: a translational perspective. Asian Pac J Cancer Prev 12:573–574

Misra S, Chaturvedi A, Goel MM, Mehrotra R, Sharma ID, Srivastava AN, Misra NC (2000) Overexpression of p53 protein in gallbladder carcinoma in North India. Eur J Surg Oncol 26:164–167

Miyahara N, Shoda J, Ishige K, Kawamoto T, Ueda T, Taki R, Ohkohchi N, Hyodo I et al (2008) MUC4 interacts with ErbB2 in human gallbladder carcinoma: potential pathobiological implications. Eur J Cancer 44:1048–1056

Moon WS, Park HS, Lee H, Pai R, Tarnawski AS, Kim KR, Jang KY (2005) Co-expression of cox-2. C-met and beta-catenin in cells forming invasive front of gallbladder cancer. Cancer Res Treat 37:171–176

Nakayama K, Konno M, Kanzaki A, Morikawa T, Miyashita H, Fujioka T, Uchida T et al (2001) Allelotype analysis of gallbladder carcinoma associated with anomalous junction of pancreaticobiliary duct. Cancer Lett 166:135–141

Nath G, Singh H, Shukla VK (1997) Chronic typhoid carriage and carcinoma of the gallbladder. Eur J Cancer Prev 6:557–559

Nath G, Singh YK, Kumar K, Gulati AK, Shukla VK, Khanna AK, Tripathi SK, Jain AK et al (2008) Association of carcinoma of the gallbladder with typhoid carriage in a typhoid endemic area using nested PCR. J Infect Dev Countries 2:302–307

Nath G, Gulati AK, Shukla VK (2010) Role of bacteria in carcinogenesis, with special reference to carcinoma of the gallbladder. World J Gastroenterol 16:5395–5404

Ng JW (2000) Carcinoma of the gallbladder associated with anomalous junction of the pancreaticobiliary duct. J Am Coll Surg 190:385–386

Noda Y, Fujita N, Kobayashi G, Ito K, Horaguchi J, Takasawa O, Obana T, Ishida K et al (2007) Histological study of gallbladder and bile duct epithelia in patients with anomalous arrangement of the pancreaticobiliary ductal system: comparison between those with and without a dilated common bile duct. J Gastroenterol 42:211–218

Ozmen V, Martin PC, Igci A, Cevikbas U, Webb WR (1991) Adenocarcinoma of the gallbladder associated with congenital choledochal cyst and anomalous pancreaticobiliary ductal junction. Eur J Surg 157:549–551

Pai RK, Mojtahed K, Pai RK (2011) Mutations in the RAS/RAF/MAP kinase pathway commonly occur in gallbladder adenomas but are uncommon in gallbladder adenocarcinomas. Appl Immunohistochem Mol Morphol 19:133–140

Pandey M (2003) Risk factors for gallbladder cancer: a reappraisal. Eur J Cancer Prev 12:15–24

Pandey M (2006) Environmental pollutants in gallbladder carcinogenesis. J Surg Oncol 93:640–643

Patel S, Roa JC, Tapia O, Dursun N, Bagci P, Basturk O, Cakir A, Losada H, Sarmiento J et al (2011) Hyalinizing cholecystitis and associated carcinomas: clinicopathologic analysis of a distinctive variant of cholecystitis with porcelain-like features and accompanying diagnostically challenging carcinomas. Am J Surg Pathol 35:1104–1113

Piehler JM, Crichlow RW (1978) Primary carcinoma of the gallbladder. Surg Gynecol Obstet 147:929–942

Pilgrim CH, Groeschl RT, Christinas KK, Gamblin TC (2013) Modern perspectives on factors predisposing to the development of gallbladder cancer. HPB (Oxford) 15:839–844

Polk HC (1966) Carcinoma and the calcified gallbladder. Gastroenterology 50:582–585

Quan ZW, Wu K, Wang J, Shi W, Zhang Z, Merrell RC (2001) Association of p53, p16, and vascular endothelial growth factor protein expressions with the prognosis and metastasis of gallbladder cancer. J Am Coll Surg 193:380–383

Rai R, Tewari M, Kumar M, Singh AK, Shukla HS (2011) p53: its alteration and gallbladder cancer. Eur J Cancer Prev 20:77–85

Riquelme E, Tang M, Baez S, Diaz A, Pruyas M, Wistuba II, Corvalan A (2007) Frequent epigenetic inactivation of chromosome 3p candidate tumor suppressor genes in gallbladder carcinoma. Cancer Lett 250:100–106

Rustagi T, Dasanu CA (2012) Risk factors for gallbladder cancer and cholangiocarcinoma: similarities, differences and updates. J Gastrointest Cancer 43:137–147

Saetta AA (2006) K-ras, p53 mutations, and microsatellite instability (MSI) in gallbladder cancer. J Surg Oncol 93:644–649

Saetta A, Lazaris AC, Davaris PS (1996) Detection of ras oncogene point mutations and simultaneous proliferative fraction estimation in gallbladder cancer. Pathol Res Pract 192:532–540

Sai JK, Suyama M, Nobukawa B, Kubokawa Y, Sato N (2005) Severe dysplasia of the gallbladder associated with occult pancreaticobiliary reflux. J Gastroenterol 40:756–760

Sai JK, Suyama M, Kubokawa Y (2006) A case of gallbladder carcinoma associated with pancreaticobiliary reflux in the absence of a pancreaticobiliary maljunction: a hint for early diagnosis of gallbladder carcinoma. World J Gastroenterol 12:4593–4595

Sakurai Y, Shoji M, Matsubara T, Suganuma M, Hasegawa S, Imazu H, Ochiai M et al (2001) Spontaneous necrosis of gallbladder carcinoma in patient with pancreaticobiliary maljunction. J Hepatobiliary Pancreat Surg 8:95–100

Sanada Y, Osada S, Tokuyama Y, Tanaka Y, Takahashi T, Yamaguchi K, Yoshida K (2010) Critical role of c-Met and Ki67 in progress of biliary carcinoma. Am Surg 76:372–379

Sasaki T, Kuniyasu H, Luo Y, Kato D, Shinya S, Fujii K, Ohmori H, Yamashita Y (2012) Significance of epithelial growth factor in the epithelial-mesenchymal transition of human gallbladder cancer cells. Cancer Sci 103:1165–1171

Sasatomi E, Tokunaga O, Miyazaki K (1996) Spontaneous apoptosis in gallbladder carcinoma. Relationships with clinicopathologic factors, expression of E-cadherin, bcl-2 protooncogene, and p53 oncosuppressor gene. Cancer 78:2101–2110

Schnelldorfer T (2013) Porcelain gallbladder: a benign process or concern for malignancy ? J Gastrointest Surg 17:1161–1168

Sharma KL, Misra S, Kumar A, Mittal B (2012) Higher risk of matrix metalloproteinase (MMP-2, 7, 9) and tissue inhibitor of metalloproteinase (TIMP-2) genetic variants to gallbladder cancer. Liver Int 32:1278–1286

Sheth S, Bedford A, Chopra S (2000) Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. Am J Gastroenterol 95:1402–1410

Shrikhande SV, Barretto SG, Singh S, Udwadia TE, Agarwal AK (2010) Cholelithiasis in gallbladder cancer: coincidence, cofactor, or cause! Eur J Surg Oncol 36:514–519

Slade GR (1905) Gall-stones and cancer. Lancet 1:1059–1062

Srivastava K, Srivastava A, Mittal B (2010) Polymorphisms in ERCC2, MSH2, and OGG1 DNA repair genes and gallbladder cancer risk in a population of Northern India. Cancer 116:3160–3169

Srivastava K, Srivastava A, Sharma KL, Mittal B (2011) Candidate gene studies in gallbladder cancer: a systematic review and meta-analysis. Mutat Res 728:67–79

Stephen AE, Berger DL (2001) Carcinoma in the porcelain gallbladder: a relationship revisited. Surgery 129:699–703

Strom BL, Soloway RD, Rios-Dalenz JL, Rodriguez-Martinez HA, West SL, Kinman JL et al (1995) Risk factors for gallbladder cancer. An international collaborative case-control study. Cancer 76:1747–1756

Tadokoro H, Shigihara T, Ikeda T, Takase M, Suyama M (2007) Two distinct pathways of p16 gene inactivation in gallbladder cancer. World J Gastroenterol 13:6396–6403

Takahashi T, Shivapurkar N, Riquelme E, Shigematsu H, Reddy J, Suzuki M, Miyajima K et al (2004) Aberrant promoter hypermethylation of multiple genes in gallbladder carcinoma and chronic cholecystitis. Clin Cancer Res 10:6126–6133

Takayashiki T, Miyazaki M, Kato A, Ito H, Nakagawa K, Ambiru S, Shimizu H, Furuya S et al (2002) Double cancer of gallbladder and bile duct associated with anomalous junction of the pancreaticobiliary ductal system. Hepatogastroenterology 49:109–112

Takei K, Watanabe H, Itoi T, Saito T (1996) p53 and Ki-67 immunoreactivity and nuclear morphometry of 'carcinoma-in-adenoma' and adenoma of the gall-bladder. Pathol Int 46:908–917

Tan Z, Zhang S, Li M, Wu X, Weng H, Ding Q, Cao Y, Bao R, Shu Y, Mu J, Ding Q et al (2013) Regulation of cell proliferation and migration in gallbladder cancer by zinc finger X-chromosomal protein. Gene 528:261–266

Tanno S, Obara T, Fujii T, Mizukami Y, Yanagawa N, Izawa T, Ura H, Kohgo Y (1999) Epithelial hyperplasia of the gallbladder in children with anomalous pancreaticobiliary ductal union. Hepatogastroenterology 46:3068–3073

Tazuma S, Kaijyama G (2001) Carcinogenesis of malignant lesions of the gall bladder. The impact of chronic inflammation and gallstones. Langenbecks Arch Surg 386:224–229

Tewari M, Mishra RR, Shukla HS (2010) Salmonella typhi and gallbladder cancer: report from an endemic region. Hepatobiliary Pancreat Dis Int 9:524–530

Tokiwa K, Ono S, Iwai N (1999) Mucosal cell proliferation activity of the gallbladder in children with anomalous arrangement of the pancreaticobiliary duct. J Hepatobiliary Pnacreat Surg 6:213–217

Tomono H, Nimura Y, Aono K, Nakashia I, Iwamoto T, Nakashima N (1996) Point mutations of the c-Ki-ras gene in carcinoma and atypical epithelium associated

with congenital biliary dilatation. Am J Gastroenterol 91:1211–1214

Towfigh S, McFadden DW, Cortina GR, Thompson JE, Tompkins RK, Chandler C et al (2001) Porcelain gallbladder is not associated with gallbladder carcinoma. Am Surg 67:7–10

Tseng LL, Chen JH, Yang KC (1993) Anomalous junction of pancreaticobiliary duct with carcinoma of the gallbladder: report of two cases. J Formos Med Assoc 92:178–181

Tsuchida A, Itoi T, Aoki T, Koyanagi Y (2003) Carcinogenetic process in gallbladder mucosa with pancreaticobiliary maljunction (Review). Oncol Rep 10:1693–1699

Tuech JJ, Pessaux P, Aube C, Regenet N, Cervi C, Bergamaschi R, Arnaud JP (2000) Cancer of the gallbladder associated with pancreaticobiliary maljunction without bile duct dilatation in a european patient. J Hepatobiliary Pancreat Surg 7:336–338

Uetsuji S, Okuda Y, Kwon AH, Komada H, Imamura A, Takai S, Kamiyama Y (1996) Gallbladder cancer with a low junction of the cystic duct or an anomalous pancreaticobiliary junction. Eur J Gastroenterol Hepatol 8:1213–1217

Vitetta L, Sali A, Little P, Mrazek L (2000) Gallstones and gall bladder carcinoma. Aust N Z J Surg 70:667–673

Walawalkar YD, Gaind R, Nayak V (2013) Study on Salmonella typhi occurrence in gallbladder of patients suffering from chronic cholelithiasis – a predisposing factor for carcinoma of gallbladder. Diagn Microbiol Infect Dis 77:69–73

Wang SN, Chung SC, Tsai KB, Chai CY, Chang WT, Kuo KK, Chen JS, Lee KT (2006) Aberrant p53 expression and the development of gallbladder carcinoma and adenoma. Kaohsiung J Med Sci 22:53–59

Welton JC, Marr JS, Friedman SM (1979) Association between hepatobiliary cancer and typhoid carrier state. Lancet 1:791–794

Wenckert A, Robertson B (1966) The natural course of gallstone disease: eleven-year review of 781 nonoperated cases. Gastroenterology 50:376–381

Wistuba II, Albores-Saavedra J (1999) Genetic abnormalities involved in the pathogenesis of gallbladder carcinoma. J Hepatobiliary Pancreat Surg 6:237–244

Wistuba II, Gazdar AF, Roa I, Albores-Saavedara J (1996) p53 protein overexpression in gallbladder carcinoma and its precursor lesions: an immunohistochemical study. Hum Pathol 27:360–365

Wistuba II, Ashfaq R, Maitra A, Alvarez H, Riquelme E, Gazdar AF (2002a) Fragile histidine triad gene abnormalities in the pathogenesis of gallbladder carcinoma. Am J Pathol 160:2073–2079

Wistuba II, Maitra A, Carrasco R, Tang M, Troncoso P, Minna JD, Gazdar AF (2002b) High resolution chromosome 3p, 8p, 9p and 22q allelotyping analysis in the pathogenesis of gallbladder carcinoma. Br J Cancer 87:432–440

Wong SM, Weissglas IS (2013) Gallbladder wall calcification and gallbladder cancer. J Am Coll Surg 216:1223–1224

Wu W, Pan C, Yu H, Gong H, Wang Y (2008) Heparanase expression in gallbladder carcinoma and its correlation to prognosis. J Gastroenterol Hepatol 23:491–497

Xiao GF, Tang HH (2009) Tumor-enhancing activity of Basigin expression in gallbladder carcinoma and its prognostic role. Mol Med Rep 2:503–508

Xie F, Xu X, Xu A, Liu C, Liang F, Xue M, Bai L (2014) Aberrant activation of Sonic hedgehog signaling in chronic cholecystitis and gallbladder carcinoma. Hum Pathol 45:513–521

Yamamoto M, Nakajo S, Tahara E, Ito M, Taniyama K, Shimamoto F, Miyoshi N, Hayashi Y et al (1991) Mucosal changes of the gallbladder in anomalous union with the pancreatico-biliary duct system. Pathol Res Pract 187:241–246

Yang Y, Fujii H, Matsumoto Y, Suzuki K, Kawaoi A, Suda K (1997) Carcinoma of the gallbladder and anomalous arrangement of the pancreaticobiliary ductal system: cell kinetic studies of gallbladder epithelial cells. J Gastroenterol 32:801–807

Yang Z, Yang Z, Xiong L, Huang S, Liu J, Yang L, Miao X (2011) Expression of VHL and HIF-1a and their clinicopathologic significance in benign and malignant lesions of the gallbladder. Appl Immunohistochem Mol Morphol 19:534–539

Yang L, Guo T, Jiang S, Yang Z (2012) Expression of ezrin, HGF and c-met and its clinicopathological significance in the benign and malignant lesions of the gallbladder. Hepatogastroenterology 59:1769–1775

Yano Y, Tasaka K, Okutani T, Maeda Y, Mori T, Tamura M, Hamada Y, Yokoyama T et al (2001) A case of undifferentiated carcinoma of the gallbladder with anomalous arrangement of the pancreaticobiliary ductal system. Oncol Rep 8:1281–1283

Yoshida T, Shibata K, Matsumoto T, Sasaki A, Hirose R, Kitano S (1999) Carcinoma of the gallbladder associated with anomalous junction of the pancreaticobiliary duct in adults. J Am Coll Surg 189:57–62

Yoshida T, Sugai T, Habano W, Nakamura S, Uesugi N, Funato O, Saito K (2000) Microsatellite instability in gallbladder carcinoma: two independent genetic pathways of gallbladder carcinogenesis. J Gastroenterol 35:768–774

Zhuang PY, Zhu MJ, Wang JD, Zhou XP, Quan ZW, Shen J (2013) Xanthogranulomatous cholecystitis: a clinicopathological study of its association with gallbladder carcinoma. J Dig Dis 14:45–50

Variant Adenocarcinomas of the Gallbladder

150

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_150

Abstract

The most common adenocarcinoma of the gallbladder is derived from the glandular epithelium. In addition, there are several variants of adenocarcinoma that are distinguished from the standard form by variant differentiation patterns. One form of gallbladder adenocarcinoma is characterized by abundant production and secretion of mucin, resulting in extracellular mucin lakes. This is mucinous carcinoma, a rare tumor of which only relatively few reports are published, mainly occurring in older patients. In contrast to ordinary gallbladder carcinoma, female preponderance is not present. A second variant of adenocarcinoma with mucin production is associated with deficient mucin secretion, resulting in signet-ring cells. Signet-ring cell carcinoma is a very rare gallbladder cancer with a highly aggressive course. There are several other, very rare variants of gallbladder adenocarcinoma. They include cribriform carcinoma, micropapillary carcinoma, cervix carcinoma-like carcinoma, carcinoma with morule-like features, clear cell carcinoma, carcinoma with lymphoid stroma, and undifferentiated carcinomas.

Mucinous Carcinoma of the Gallbladder

ICD-O code 8480/3

Introduction

In the WHO classification of tumors, mucinous adenocarcinoma of the gallbladder (MCG, mucoid adenocarcinoma, colloid carcinoma) is defined as a carcinoma in which more than 50 % of the tumor contains extracellular mucin. In case the extracellular mucin constitutes a predominant component of the tumor, with scattered tumor cells floating in mucin lakes, the terms colloid carcinoma or gelatinous carcinoma (carcinoma gelatinosum) are employed. MCGs are more common in the gallbladder than in the extrahepatic

bile ducts (Albores-Saavedra et al. 2010; Dursun et al. 2012; Yadav et al. 2013).

Epidemiology

MCG is a rare tumor, of which only relatively few reports are available. In a Japanese study of 540 consecutive cholecystectomies, 12 adenocarcinomas were detected, and of these only one was an MCG (Terada et al. 2013a). In an investigation of 606 primary gallbladder carcinomas, 2.5 % qualified for MCG according to the WHO criteria. The mean age was 65 years, and the female-to-male ratio was 1.1, i.e., clearly different from ordinary CG, where female patients prevail (Dursun et al. 2012).

Selected References Zamecnik et al. 1946; Hirsch et al. 1964; Parker and Joffe 1972; Rogers et al. 1973; Ishibashi et al. 1986; Araida et al. 1996; Tian et al. 2003; Huang et al. 2006; Yamamoto et al. 2010; Dursun et al. 2012; Jindal et al. 2012.

MCG seems to develop in connection with the same risk factors as in ordinary adenocarcinoma and has also been diagnosed in the setting of porcelain gallbladder (Joo et al. 2003) and sclerosing cholangitis in association with ulcerative colitis (Noda et al. 2009).

Clinical and Imaging Features

The clinical presentation of MCG is usually not different from that of other gallbladder adenocarcinomas, signs and symptoms being nonspecific in part of cases. However, some patients exhibit marked enlargement of the gallbladder, and viscous mucin accumulated in the gallbladder lumen may cause obstruction with jaundice and pain (Ishibashi et al. 1986; Ozeki et al. 1991; Tian et al. 2003). In one study, 67 % of patients presented with the clinical picture interpreted as acute cholecystitis (Dursun et al. 2012). Excessive drainage may require specific management (Hirsch et al. 1964).

On CT and MR images, the tumor often presents as a thickened gallbladder wall, a polypoid or cauliflower-like mass with a soft-tissue density, small calcified spots, and some laminated high viscosity fluid inside the gallbladder cavity (Nobusawa et al. 1994; Levy et al. 2001; Huang et al. 2006). Linear or curvilinear streaks seen in MR and MR cholangiopancreatography images are typical findings in MCG (Ishiguro et al. 2012). Cystic areas in an enlarged gallbladder are also a feature of MCG (Tian et al. 2003; Yoshimitsu et al. 2005).

Pathology

Macroscopy

Macroscopically, MCG presents under an entire spectrum of lesions, but nodular and polypoid tumor masses of sometimes large size predominate. In MCG with a very high content of mucin, the tumors are grossly gelatinous or glassy-transparent, whereby this feature is best visualized on cut surfaces. When cutting through the tumor, mucin typically sticks to the knife, and a thin mucin thread can be spun when slowly removing the knife from the tumor cut surface. The maximum of gelatinous features is found in colloid carcinoma, which may be associated with accumulation of viscid mucinous material in the gallbladder lumen. Mucin can be dislocated to the gallbladder neck and the cystic duct, causing obstruction and gluing eventual gallstones together to form a conglomerate mass. In the study of Dursun and coworkers (2012), mean and median tumor diameters were larger than those of conventional adenocarcinomas (4.8 cm and 3.4 cm vs. 2.9 cm and 2.5 cm, respectively; Dursun et al. 2012). Lymph node metastases and tumor deposits in a perineural location may also present as transparent, glassy nodules.

Histopathology

Mucinous adenocarcinoma shows mucin-forming tubular, cribriform, and solid components of

carcinomatous epithelium admixed with extracellular mucin deposits, the latter per definition amounting to more than 50 % of the tumor. The stromal reaction is usually not pronounced. In a minority of cases, well-defined stromal mucin nodules or mucin lakes with scanty tumor cells floating in the mucin (colloid carcinoma) are found, and there are cases that also show signet-ring cells (Dursun et al. 2012). Part of the cases, mainly those with an intraluminally growing component, show a papillary growth pattern at the surface and microcystic alterations with mucin lakes or nodules at the bottom of the lesion. In MCG with cystic components, the substrate of cysts are markedly enlarged gland-like structures containing mucin, which then leaks out and forms mucin lakes (Yoshimitsu et al. 2005). As often large neoplasms, MCG can undergo extensive necrosis. Rarely, MCG undergoes extensive calcification (Parker and Joffe 1972; Rogers et al. 1973;), as mucin accumulations represent a material that favors deposits of calcium salts. Within amphophilic or slightly basophilic extracellular mucus masses, tiny granules of strongly basophilic mineralizations are found, positive in the von Kossa stain, and these granules may coalesce to larger mineral deposits with cracks and fissures and, sometimes, a concentric structure.

Immunohistochemistry

MCG shares markers with ordinary adenocarcinomas of the gallbladder. Among 15 MCG, 57 % were CK7 positive, 29 % were CD20 positive, and 57 % expressed MUC1, 86 % MUC2, and 86 % MUC5AC, but none expressed MUC6 (Dursun et al. 2012). The MUC1 core mucin, which is often present in well-to-moderately differentiated gallbladder carcinomas, is a mucin that can leak out of the cells (Yamato et al. 1999).

Combined Gallbladder Carcinomas Containing a Mucinous Component

Combined neuroendocrine adenocarcinomas (MANEC, see the respective paragraph) may contain mucinous adenocarcinoma. In a 59-year-old male, a 4 cm-sized gelatinous and cauliflower-like gallbladder tumor was found, composed of biphasic large-cell neuroendocrine carcinoma and pure mucinous carcinoma (Russo et al. 2012).

Differential Diagnosis

MCG has to be distinguished from mucin-containing adenocarcinoma with less than 50 % mucin content and from signet-ring cell carcinoma. In some cases, mucocele of the gallbladder may mimic MCG. Mucin in mucoceles or in mucin-containing Rokitansky-Aschoff sinuses can leak upon rupture and elicit a vigorous macrophage reaction (mucophages), sometimes resembling neoplastic signet-ring cells. Numerous mucophages may accumulate to form nodules (mucin granulomas) that can be confound with mucin-containing tumor nodules. In case of doubt, immunohistochemistry by use of anti-CK antibodies (carcinoma cells are positive) and CD68 (macrophages are positive) is helpful to clarify the situation.

Signet-Ring Cell Carcinoma of the Gallbladder

ICD-O code 8490/3

Introduction

Signet-ring cell carcinoma (SRCC) is a rare and highly aggressive variant of adenocarcinoma characterized by accumulation of mucins within the cytoplasm of cancer cells. Due to a purported secretion defect, mucin is retained in the cell in the form of a large glycoprotein body that displaces and deforms the nucleus, resulting in a picture resembling a signet ring. SRCC occurs in several organs but most commonly develops in the stomach (linitis plastica), accounting for 15–30 % of all gastric cancers (Kim et al. 1994; Adachi et al. 2000). SRCC arising in the gallbladder is a highly uncommon neoplasm.

Epidemiology

The exact prevalence of SRCC among carcinomas of the gallbladder is not known, but the tumor is considered to be a rare lesion (Brandt-Rauf and Branwood 1980; Nishida et al. 1997; Krunic et al. 2007; Karabulut et al. 2008; Czyszczon and Alatassi 2010; Mondal 2010; Pavic et al. 2010; Pudasainin et al. 2011; Snyder et al. 2012; Agergaard et al. 2012). The lack of detailed data is in part due to the fact that histological typing was not performed in many published series and to the difficulty of identifying signet-ring cells in conventional histology preparations. In a Japanese series of 57 gallbladder carcinomas, 6 were of the SRCC type (Tatematsu et al. 1988). Among seven gallbladder adenocarcinomas, one was found to be SRCC (Khoo and Nurul 2008). SRCC of the gallbladder is usually a tumor of elderly individuals, but rare examples of SRCC occurring in young individuals are also known (22 years; Czyszczon and Alatassi 2010; 32 years; Mondal 2010). Males are more often affected than with ordinary gallbladder adenocarcinoma. The cancer was found in gallbladders with or without stone disease with associated chronic cholecystitis. In one patient, gallbladder SRCC was observed in the setting of anomalous pancreaticobiliary ductal union (Yamauchi et al. 2000).

Clinical and Imaging Features

Clinical presentation and imaging features are the same as those described for ordinary gallbladder adenocarcinoma, with the exception that SRCC are diffusely infiltrating neoplasms that do not give rise to polypoid lesions at imaging.

Pathology

Macroscopy

SRCC of the gallbladder is usually a mass-forming lesion associated with thickening of the gallbladder wall owing to diffuse infiltration. In one patient, the color of the tumor was described as yellowish white (Pudasainin et al. 2011).

Histopathology

The typical feature of SRCC is, similar to its gastric counterpart, a diffuse growth with sheets of signet-ring cells spreading laterally through the lamina propria of the mucosa and the muscle layer. The tumor cells are medium-sized to large, often about the size of a macrophage, with a well-defined surface membrane, a cup-shaped nucleus displaced to the cell periphery, and a slightly foamy (microvesicular) or clear, large vacuole that stains with PAS, mucicarmine, alkaline Alcian blue, and the Genta stain (Genta et al. 1994; El-Zimaity et al. 1997). In some cases, extracellular mucin is also visualized, representing a mixture of mucin-producing cells that either store or secrete the glycoproteins. Transmural growth with invasion of the subserosal space and infiltration of the gallbladder bed are found. SRCC can also give rise to tumor emboli, sometimes translocated to small pulmonary arteries, followed by pulmonary tumor thrombotic microangiopathy (Ohno et al. 2014).

Immunohistochemistry

SRCC of the upper gastrointestinal tract are generally immunoreactive for CKAE1/3 (100 %), CAM5.2, CK7, and EMA, rarely for CK19 and CK20, and not for CK14 (Pavic et al. 2010; Bazan et al. 2011; Terada 2013b). In SRCC of the stomach, reactivity for EMA was found in 57 %, CEA in 100 %, CA19-9 in 100 %, and p53 in 83 % (Terada 2013c), and the most frequently expressed mucins were MUC5AC and MUC6 (Terada 2013d). In gastric SRCC, variable proportions of tumors are positive for CDX-2 (Chu and Weiss 2004; Terada 2013b), but there are yet no respective data for SRCC of the gallbladder.

Signet-Ring Cell Carcinoma In Situ

This lesion is very rare and was not recognized on gross examination, but was found incidentally on microscopic analysis. Histologically, the alteration was very similar to that of in situ and intramucosal signet-ring cell carcinoma of the stomach. The neoplastic cells were confined to superficial parts of the mucosa, mainly to epithelial lining and epithelial invaginations, in the absence of dysplastic changes of the adjacent epithelium (Albores-Saavedra et al. 1996).

Combined/Composite Tumors Containing a SRCC Component

Gallbladder adenocarcinomas rarely contain components of neuroendocrine neoplasms (MANEC) and in this context may contain SRCC (Olinici and Vasiu 1991).

Biology of Disease

SRCC of the gallbladder is an aggressive and diffusely growing neoplasm that, similar to SRCC in other organs, tends to produce multiple lymph node metastases and distant metastases, often to the liver in a first phase of the disease (Mondal 2010; Bazan et al. 2011). Apart from pure SRCC, also other carcinomas with a component of signet-ring cell carcinoma (mixed SRCC carcinomas) may be expected to show a more aggressive course, as demonstrated for stomach tumors (Huh et al. 2013). In contrast to ordinary gallbladder adenocarcinoma, SRCC may metastasize to unusual sites, including the skin (Krunic et al. 2007). Similar to other SRCC (mainly those of the stomach), SRCC of the gallbladder can give to ovarian Krukenberg tumors (Unterweger et al. 1999; Ayhan et al. 2001; Jain et al. 2006; Kiyokawa et al. 2006). In study performed in Thailand, 7 % of metastatic ovarian tumors had their origin in the gallbladder/extrahepatic bile ducts (Khunamornpong et al. 2006).

Nonneoplastic Signet-Ring Cells in the Gallbladder (Benign Signet-Ring Cell Change)

Signet-ring cell change is a nonneoplastic condition that morphologically simulates SRCC (Wang et al. 2003). Nonneoplastic signet-ring cells or cells closely resembling malignant signet-ring cells have been observed in several organs under various pathologic conditions, including pseudomembranous colitis (Michal et al. 1998; Abdulkader et al. 2003), cholangitis (Dhingra and Wang 2011), and acute erosive gastropathy (Dimet et al. 2004). Rarely, focal collections of signet-ring cells both on the mucosal surface lining and within the lumen of glands or tubules have been detected in the gallbladder, in the absence of evidence for malignancy. In one case, the gallbladder epithelium exhibited multilayering, and part of the epithelial cells showed a small round basal or eccentric nucleus and a vacuolated Pas-, mucicarmine-, and Alcian blue-positive cytoplasm, resulting in a signet-ring cell appearance (Suri et al. 2001). Nonneoplastic signet-ring cells were found in ulcerative lesions of the gallbladder (Michal et al. 1998). In another investigation, the cells were immunoreactive for keratin AE1/AE3 and were regarded to be disrupted mucosal goblet cells with degenerative changes (Ragazzi et al. 2009).

Differential Diagnosis

Rarely, signet-ring cell carcinoma of the stomach or other parts of the gastrointestinal tract may metastasize to the gallbladder (Bilicli et al. 2012). SRCC has to be distinguished from other neoplastic conditions forming signet-ring cells, specifically signet-ring cell lymphomas that may occur in the gastrointestinal tract. SRCC must not be confounded with the presence of nonneoplastic signet-ring cells that may occur in several organs, including the gallbladder (see above; Suri et al. 2001; Ragazzi et al. 2009).

Pathogenic Pathways

Molecular pathways involved in the pathogenesis of gallbladder SRCC are largely unknown, but it may be anticipated that mechanisms operational in other SRCC also apply to the gallbladder counterpart. In colorectal SRCC, chromosomal instability manifested by LOH was a nearly universal finding, including cases with high-level microsatellite instability, associated with BRAF V600E mutation (Kakar et al. 2012). Gastric SRCC exhibited copy number alterations of MYC and TP53, and this feature was associated with aggressive biology at early and advanced stages (Sonoda et al. 2013). In gastric carcinomas, heat shock protein 70 (HSP70) expression is high in intestinal-type cancers with an aggressive course but not in SRCC (Lee et al. 2013). Gastric SRCC and mucinous carcinomas overexpress the COL4A3 protein, which belongs to the type IV collagen family and plays a role in cancer progression (Nie et al. 2013). Gastric SRCC reveal distinct patterns of epigenetic alterations, associated with overexpression of DNA methyltransferase 1 and decreased expression of DNA methyltransferase 3A, suggesting that these neoplasms may produce complex patterns of aberrant DNA methylation (He et al. 2013). A subset of pulmonary adenocarcinomas with signet-ring cell morphology is characterized with rearrangements of the ALK gene (ALK+ lung adenocarcinomas; Nishino et al. 2012).

Cribriform Carcinoma of the Gallbladder

Introduction

Cribriform carcinoma (carcinoma cribrosum) is defined as a low-grade infiltrating carcinoma with a cribriform pattern. A cribriform (sievelike) growth shows round or angular masses of cells embedded in a desmoplastic stroma, sharply punched out round spaces, and a nuclear grade I in at least 90 % of cells. Cribriform carcinoma has chiefly been observed in the breast (Page et al. 1983; Wells and Ferguson 1988; Venable et al. 1990; Stutz et al. 1994; Nishimura et al. 2005). In the breast, invasive cribriform carcinoma is a histologic subtype with the same excellent prognosis as that of invasive tubular carcinoma (Page et al. 1983). It now forms a distinctive clinicopathologic entity (Venable et al. 1990).

Cribriform Carcinoma of the Gallbladder

Cribriform carcinoma has been identified as a rare subtype of gallbladder adenocarcinoma (Albores-Saavedra et al. 1996). In a series of seven patients, five patients were female and two male, whose ages at diagnosis ranged from 31 to 72 years (average, 57 years), i.e., younger than patients with conventional adenocarcinomas of the gallbladder. Five patients had cholelithiasis. Estrogen or progesterone receptors were not detected in these tumors. Three patients having tumors with high nuclear grade died as a result of the neoplasm which had infiltrated the liver by direct extension, while three patients with low nuclear grade tumors confined to the gallbladder wall survived 4–7 years after cholecystectomy (Albores-Saavedra et al. 2008). It seems that cribriform carcinoma of the gallbladder differs from its counterpart in the breast by a more aggressive biology.

Micropapillary Carcinoma of the Gallbladder

Introduction

Micropapillary carcinoma is a distinct variant of adenocarcinoma histologically characterized by very delicate papillary structures often surrounded by a clear, “empty” halo. This lesion was first described in the breast and has since been observed in various organs. This neoplasm has been mentioned to have an aggressive behavior with a high propensity for lymphovascular invasion, multiple lymph node metastases, and poor clinical outcome.

Micropapillary Carcinoma of the Gallbladder

Among a series of 90 gallbladder carcinomas, 20 cases (22.2 %) showed small foci with the typical features of micropapillary carcinoma. Of these 20 cases, 17 also showed lymph node metastases, which was more frequent than in ordinary adenocarcinomas, showing that the presence of this features, even in a focal distribution, is a predictor of lymph node metastasis (Hara et al. 2010).

Cervix Carcinoma-Like Carcinoma of the Gallbladder

Introduction

Among well-differentiated adenocarcinomas of the gallbladder, a small subset is characterized by cell lineages different from biliary-type cells or intestinal-type cells. One very rare variant is adenocarcinoma mimicking minimal deviation adenocarcinoma of the cervix (Tashiro et al. 2000). Minimal deviation adenocarcinoma of the cervix (synonym, adenoma malignum) is a rare form of invasive adenocarcinoma characterized by well-differentiated, but abnormally shaped glands lined by mucin-containing columnar cells with basal nuclei (Gusserow 1870; Silverberg and Hurt 1975; Gilks et al. 1989). The per se contradictory term "adenoma malignum" was chosen to denote a histologic appearance of "adenoma" associated with an aggressive phenotype with fatal progression ("malignum").

Pathology

The index patient was a 71-year-old Japanese male undergoing cholecystectomy for suspected cancer. The resected gallbladder showed a small polypoid mass of 12 mm diameter. Histologically, the neoplasm was a well-differentiated adenocarcinoma composed of columnar cells with a clear or slightly eosinophilic cytoplasm, with ovoid-to-slightly elongated nuclei being basally placed, and with expression of gastric-type mucin. The carcinoma had infiltrated the gallbladder wall in the form of well-developed glands associated with slight desmoplastic reaction (Tashiro et al. 2000).

Carcinoma of the Gallbladder with Morule-Like Features

Introduction

Several types of carcinomas in various organs are characterized by the development of so-called morules, spherical clusters of small cells with clear ("empty") nuclei and a distinct immunophenotype (from Latin, morus: mulberry; the term is redundantly used, as morula or morule is already used as a term denoting the solid cellular mass of blastomeres formed by cleavage of a zygote). Papillary thyroid carcinoma (Camaselle-Teijeiro and Chan 1999; Hirokawa et al. 2010; Cetta et al. 2011, 2012; Schaeffer et al. 2011), colorectal carcinoma (Sarlin and Mori 1984; Ueo et al. 2005), endometrial carcinoma (Saegusa et al. 2007), papillary lung carcinoma (Moran et al. 2004), bronchioloalveolar carcinoma (Fornelli et al. 2003), well-differentiated fetal adenocarcinoma of the lung and pulmonary blastoma (Sekine et al. 2003; Makishi et al. 2006), intraductal papillary mucinous neoplasm of the pancreas (Tateno et al. 2012), and gallbladder carcinoma (Sakai et al. 2008). Morular features rarely also develop in benign neoplasm, including pulmonary sclerosing hemangioma associated with familial adenomatous polyposis (Hosaka et al. 2004).

Gallbladder Carcinoma with Morule-Like Features

A very rare variant of gallbladder carcinoma is characterized by tumor-associated lymphoid stroma and morule-like features (Sakai et al. 2008). A 53-year-old man showed a polypoid gallbladder tumor with a thin stalk, measuring 1.3 × 0.5 cm. Histology revealed a well-

differentiated tubular adenocarcinoma accompanied by multiple spindle cell nodules forming morules as a putative metaplastic reaction. The stroma of the carcinoma exhibited a dense lymphoid cell infiltration.

Pathology

Histopathology

Histologically, morules observed in several carcinoma localizations are well-defined spherical structures composed of small, oval-to-short spindle-shaped cells with bland nuclei, frequently accompanied by intranuclear clear inclusions or optically clear nuclei that are positive for biotin and biotin-binding enzymes, i.e., pyruvic acid carboxylase and propionyl-CoA carboxylase (Okamoto et al. 1995; Gamachi et al. 2003; Ueo et al. 2005). In addition to several types of carcinoma, morules with biotin-containing optically clear nuclei have also been found in benign epithelial neoplasms, e.g., colonic tubular adenoma (Sasaki et al. 1999). Morules are morphologically and qualitatively different from squamous metaplasia (Chinen et al. 2004) and do not express features of epithelial cells in part of these tumors, while they are cytokeratin positive in others.

Immunocytochemistry

Carcinomas with morule-like features developing in other organs display distinct immunophenotypes. Cells of morules fail to express epithelial and oncofetal markers (Makishi et al. 2006). Cytoplasmic expression of CD10 is a characteristic marker of morule-forming tumors in different organs, CD10 being a factor involved in morular metaplasia (Chiarelli et al. 2006; Cameselle-Teijeiro et al. 2008). Cells of the cribriform-morular carcinomas, including the morular variant of papillary thyroid carcinoma (Hirokawa et al. 2010; Koo et al. 2011), endometrial carcinoma (Saegusa et al. 2007), and colorectal carcinoma (Ueo et al. 2005), consistently demonstrate nuclear and cytoplasmic expression of beta-catenin. Aberrant beta-catenin expression is regarded as a common denominator for morular formation, and beta-catenin accumulation co-localizes with estrogen receptor-beta, suggesting a cross talk between beta-catenin signaling and Wnt signaling pathways (Nakatani et al. 2004). The morules in endometrioid proliferations of the uterus and ovary consistently express the intestinal transcription factor CDX2 (Houghton et al. 2008), which is also expressed in pyloric gland adenoma of the gallbladder (Wani et al. 2008). CDX2, which overlaps with nuclear expression of beta-catenin, has a functional role in beta-catenin signaling in the course of transdifferentiation in endometrial adenocarcinomas (Saegusa et al. 2007). In morular differentiation of endometrial carcinomas, SOX4 functions as a positive regulator of beta-catenin signaling (Saegusa et al. 2012). Morular cells also express cyclin D1 and p63 and display a low Ki-67 labeling index, i.e., less than 1 % (Ueo et al. 2005). Marked nuclear expression of beta-catenin was also detected in gallbladder carcinoma with morule-like features (Sakai et al. 2008).

AFP-Producing Carcinoma of the Gallbladder

Introduction

Similar to certain cholangiocarcinomas, a small subset of gallbladder carcinomas have been shown to produce alpha-fetoprotein/AFP (Bernades et al. 1972; Miyasaka et al. 1978; Haruta et al. 1987; Maruiwa 1987; Maruiwa et al. 1988, 1996; Sugaya et al. 1989; Brown and Roberts 1992; Ikeda et al. 1992; Watanabe et al. 1993; Ng and Ng 1995; Cocquyt et al. 1996; Ono et al. 1996; Tanigawa 1996; St Laurent et al. 1999). This rare tumor should not be confounded with AFP-producing hepatoid carcinoma of the gallbladder.

Clinical and Imaging Features

The clinical presentation is that of other gallbladder malignancies, i.e., upper right quadrant pain, a

palpable mass, weight loss, and eventually jaundice. The salient feature of these neoplasms is elevated serum AFP levels (above 1,000 ng/ml), sometimes leading to misinterpretations as to the nature of the tumor. Typically, serum AFP levels drop to normal following resection of the tumor (Brown and Roberts 1992). In some of the cases, proteins other than AFP have been produced by gallbladder adenocarcinomas, e.g., carcinoembryonic antigen and antigen 19-9 (Sugaya et al. 1989; Ono et al. 1996).

AFP-producing adenocarcinomas of the gallbladder are aggressive lesions that invade the liver substance and give rise to multiple metastases, in particular of the liver, causing hepatic failure in part of the patients (Ono et al. 1996). A more aggressive behavior of these neoplasms has also been detected in nude mouse models of tumor transplantation (Maruiwa 1987; Maruiwa et al. 1996).

Pathology

Macroscopy

Macroscopically, AFP-producing carcinomas of the gallbladder show the same growth pattern as other adenocarcinomas, including polypoid, pedunculated, or fungating lesions (Ikeda et al. 1992; Ng and Ng 1995).

Histopathology

AFP-producing gallbladder tumors are adenocarcinomas with a tubular, tubulo-papillary, or papillary growth pattern, not different from that of non-AFP-secreting carcinomas, but papillary adenocarcinoma seems to predominate (Ikeda et al. 1992; Ono et al. 1996). Other morphotypes have rarely been noted, e.g., undifferentiated carcinoma (Ng and Ng 1995; St Laurent et al. 1999) or carcinoma with a component of pleomorphic cells and giant cells (Ng and Ng 1995). In part of the cases, increasing production of AFP may be associated with morphological dedifferentiation of the carcinomas. In one patient with recurrent gallbladder carcinoma, serum AFP increased as a function of tumor progression, with dedifferentiation of the tumor in its metastases in comparison with the primary tumor (Cocquyt et al. 1996). AFP production has been found in a clear cell carcinoma of the gallbladder with neuroendocrine differentiation (Sentani et al. 2014).

Immunohistochemistry

The cells of the adenocarcinoma are immunoreactive for AFP, showing that AFP is in fact produced by this cell type (Haruta et al. 1987; Ikeda et al. 1992; Ng and Ng 1995).

Differential Diagnosis

Differential diagnosis includes other hepatic tumors showing a glandular phenotype and AFP production, including mixed hepatocellular carcinoma-cholangiocarcinoma and purely acinar hepatocellular carcinoma. Carcinosarcoma of the gallbladder has been found to sometimes produce AFP (Shimada et al. 2009)

Clear Cell Carcinoma of the Gallbladder

ICD-O code 8310/3

Introduction

Clear cell carcinoma (clear cell adenocarcinoma) of the gallbladder is an uncommon variant of carcinoma recognized in the World Health Organization classification of tumors of the gallbladder and extrahepatic bile ducts (Albores-Saavedra et al. 2010). Gallbladder clear cell carcinoma is composed predominantly of glycogen-rich clear cells with well-defined cell borders and central hyperchromatic nuclei (Bittinger et al. 1995; Vardaman and Albores-Saavedra 1995; Nomura et al. 1996; Piana et al. 2002; Sartelet et al. 2004;

Vaillo et al. 2004; Tajiri et al. 2006). Most of the cases showed a single morphology ("pure" clear cell carcinoma), but the tumor has also been described in combination with small cell carcinoma of the gallbladder (Piana et al. 2002).

Clinical and Imaging Features

Biologically, little is known about the natural history of these neoplasms, which in similar or the same phenotypes also occur in several other organs, including the extrahepatic bile ducts and the liver. In a series of seven cases, the clinical presentation was similar with conventional adenocarcinomas of the gallbladder, signs and symptoms including right upper quadrant pain, a palpable mass, jaundice, nausea, signs of obstruction, and/or signs of metastatic disease. Almost all cases were associated with cholelithiasis (Vardaman and Albores-Saavedra 1995). All these seven patients were females, and age at diagnosis ranged from 56 to 68 years (mean, 62 years). Two patients had elevated serum CEA levels, explained by the presence of conventional adenocarcinomas together with clear cell carcinoma. This component is usually CEA positive by immunohistochemistry and is presumably the source of the oncofetal antigen in serum. The prognosis of patients with clear cell carcinoma of the gallbladder is poor and related to the pathologic stage (Vardaman and Albores-Saavedra 1995).

Pathology

Macroscopy

Clear cell carcinoma may present as a solid growth, similar to gallbladder adenocarcinoma, but polypoid variants with endoluminal growth have also been observed (Sartelet et al. 2004). Of a series of seven cases, the anatomic location was known in five, and these neoplasms were located in the fundus and body of the gallbladder and infiltrated the full thickness of the wall. Four tumors extended into the liver, two had metastasized to locoregional lymph nodes, and one to the omentum and multiple peritoneal sites. Size of the primary tumor ranged from 5.4 to 7 cm in diameter (Vardaman and Albores-Saavedra 1995).

Histopathology

The tumor cells are of intermediate size and impress by their very well-defined cytoplasmic borders and a clear (sometimes water clear) cytoplasm. The clear cell aspect is caused by accumulation of abundant glycogen. Therefore, the cells display PAS-positive diastase-labile cytoplasmic granules but are consistently mucin negative. In contrast, foci of conventional adenocarcinoma intermingled with clear cell carcinoma in part of cases show mucin-containing cells. There are tumors where columnar cells show subnuclear and supranuclear vacuoles similar to those found in epithelia of secretory endometrium. The clear cells are arranged in sheets, nests, cords, trabeculae, and glandular structures. A papillary variant has also been reported (Sartelet et al. 2004). The sheets and cords are separated by collagen bundles and show a reticulin network of variable density. A minority of cases showed a predominantly glandular pattern (Vardaman and Albores-Saavedra 1995). Focal papillary structures consisting of cuboidal or columnar clear cells lined up on fine fibrovascular stalks are also found, and one variant of clear cell carcinoma shows a predominantly papillary growth pattern (Vardaman and Albores-Saavedra 1995; Sartelet et al. 2004). In the cases of Vardaman and Albores-Saavedra (1995), the majority of cases contained areas of conventional adenocarcinoma that represented 5–40 % of the neoplasms, but may not be present in metastatic deposits. A clear cell component can also occur in squamous cell carcinoma of the gallbladder (Vardaman and Albores-Saavedra 1995). In a patient with adenocarcinoma of the cystic duct, clear cell change was only found in lymph node metastases (Tajiri et al. 2006). Diagnosis of clear cell carcinoma

has been performed by use of fine needle aspiration cytology (Vaillo et al. 2004).

Immunohistochemistry

Clear cell carcinomas of the gallbladder share the immunophenotype, specifically the cytokeratin expression pattern, with adenocarcinoma of this organ (Bittinger et al. 1995). The tumor cells are reactive for epithelial membrane antigen/EMA but negative for vimentin (Sartelet et al. 2004). Staining was focally positive for CEA in the clear cells in a minority of cases (Vardaman and Albores-Saavedra 1995).

Alpha-Fetoprotein-Producing Clear Cell Carcinoma

Clear cell carcinomas that produce alpha-fetoprotein have been observed in the extrahepatic bile ducts (Miyazawa et al. 2006) and, very rarely, in the gallbladder. A metastasizing clear cell tumor of the gallbladder showed hepatoid areas with a trabecular growth pattern, sinusoid-like vascular channels, and immunoreactivity for AFP and CEA, associated with elevated serum AFP levels. The hepatoid components predominated in the metastases (Vardaman and Albores-Saavedra 1995). In another patient, AFP-producing clear cell carcinoma of the gallbladder was associated with adenocarcinoma showing neuroendocrine differentiation, poorly or undifferentiated carcinoma, and carcinoma in situ in the surrounding gallbladder mucosa (Sentani et al. 2014).

Differential Diagnosis

The predominant differential diagnosis of clear cell carcinoma primary to the gallbladder is renal cell carcinoma of the clear cell type. Renal cell carcinomas tend to metastasize to unusual sites, and among metastases occurring in the gallbladder, renal cell carcinoma holds the first position, followed by malignant melanoma (see the respective chapter). Intra-abdominally, the pancreas is a preferred location (Kassabian et al. 2000; Wente et al. 2005), but several reports also document renal cell carcinoma metastasis to the gallbladder (Satoh et al. 1991; Brasseur et al. 1999; Kechrid et al. 2000; Aoki et al. 2002; Nojima et al. 2008; Kücükakin et al. 2009). In one patient, an intraluminal polypoid metastasis of renal cell carcinoma mimicked a gallbladder polyp (Fang et al. 2010). Metastatic renal cell carcinoma may grow as a polypoid mass in the gallbladder (Botting et al. 1963; Satoh et al. 1991), a growth pattern also known for primary clear cell carcinoma. In such cases, immunohistochemistry will serve to solve the diagnostic difficulty. A more remote differential diagnosis is other clear cell neoplasms, e.g., clear cell carcinoid tumor of the gallbladder (Sinkre et al. 2001).

Carcinoma of the Gallbladder with Lymphoid Stroma

Carcinomas of the gallbladder are associated with an immune response of the host, presenting as a mainly lymphocytic infiltration in the tumor stroma. These infiltrates are usually low-density reactions and are discussed in a separate paragraph. Exceptionally, the infiltrates are dense or very dense, a phenomenon known from other carcinomas (e.g., certain breast carcinomas) and called lymphoid stroma. Carcinoma of the gallbladder with lymphoid stroma was first reported in 1984 (Muto et al. 1984), followed by two cases several years later (Kijima et al. 1999; Sakai et al. 2008).

Histologically, the tumor reveals adenocarcinoma with an expended stromal component. The latter contains a dense infiltrate chiefly composed of small lymphocytes, but plasma cells, macrophages, and eosinophils may also be seen in much lower numbers. As in other tumors with a lymphoid stroma, lymph follicles with germinal center can develop. Whether the presence of a lymphoid stroma regularly implies a more favorable prognosis is, owing to the few reported cases, not yet established.

Undifferentiated Carcinoma of the Gallbladder

ICD-O code 8020/3

Introduction

Apart from poorly differentiated adenocarcinoma, a small subset of gallbladder carcinoma are composed of cell lineages with a highly deviating, undifferentiated phenotype, rendering a distinction between carcinoma and sarcoma difficult in some cases. Undifferentiated carcinoma (UDC) is more frequently encountered in the gallbladder than in extrahepatic bile ducts. In the current WHO classification, UDC also comprises spindle cell carcinomas, small cell non-endocrine carcinoma, giant cell carcinomas (including those with osteoclast-like giant cells), and a nodular/lobular type superficially resembling breast carcinoma (Albores-Saavedra et al. 1996). These different variants have been described in several reports (Guo et al. 1988; Nishihara and Tsuneyoshi 1993; Kubota et al. 2000; Tanaka et al. 2002; Takahashi et al. 2004; Badmos et al. 2013). Spindle cell carcinomas of the gallbladder seem to form at least two morphological groups, one with an undifferentiated phenotype sometimes difficult to separate from carcinosarcomas of the gallbladder and the other characterized by a bland-looking population of spindle cells. Epithelial spindle cell tumors of the gallbladder are therefore further discussed in a separate paragraph, except the undifferentiated variant which is treated in the present paragraph. As gallbladder carcinomas comprising a combination of bona fide epithelial cells, transition forms, and vimentin-positive spindle cells, the mechanism of epithelial-to-mesenchymal transition may pathogenetically be involved, probably calling for a reappraisal of UDC definition in the future.

Pathology

Macroscopy

UDCs as rapidly growing neoplasms tend to form bulky tumors with often extensive necrosis, hemorrhage, and accumulated tumor debris and coagulated blood masses in the gallbladder lumen. Tumor hemorrhage can cause hemobilia (Kubota et al. 2000). The growth pattern is either mass forming, diffusely infiltrating, or endoluminal polypoid. Protruding forms with a tumor pedicle were also described (Takahashi et al. 2004).

Histopathology

The undifferentiated tumor cells in UDC may coexist with small neoplastic cells of the non-neuroendocrine type (Takahashi et al. 2004). Part of UDC contains an immature-looking epithelial component, either adenocarcinoma or squamous cell carcinoma or combined, and a highly atypical spindle cell component (undifferentiated spindle cell carcinoma; Nishihara and Tsuneyoshi 1993; Akatsu et al. 2005; Badmos et al. 2013). In variants with a squamous cell/keratinocyte lineage, a gradual transition between the squamous cell carcinoma and the spindle cell component was observed (Nishihara and Tsuneyoshi 1993). Spindle cell components in UDC have also been termed pseudosarcomatous type of carcinoma (Guo et al. 1988; Diebold-Berger et al. 1995). Part of UDC contains highly atypical giant cells of the non-osteoclast type (Manouras et al. 2009). A very rare variant of UDC histologically mimics lobular carcinoma of the breast (Albores-Saavedra et al. 1996).

Immunohistochemistry

Almost all spindle cell UDCs were positive for at least one of the epithelial markers (mostly AE1/AE3 and EMA, less often CEA), but part of the cells were also reactive for vimentin (Guo et al. 1988; Nishihara and Tsuneyoshi 1993).

Differential Diagnosis

UDCs with a prominent atypical spindle cell component have to be distinguished from "true" carcinosarcomas of the gallbladder.

Pleomorphic Carcinoma of the Gallbladder

ICD-O code 8020/3

Introduction

Pleomorphic carcinoma (pleomorphic giant cell carcinoma) is one of the least common primary cancers of the gallbladder, and only few cases have been reported (Appelman and Coopersmith 1970; Willén and Willén 1982; Alpers and Smuckler 1984; Takeda et al. 1990; Caruso et al. 1991; Omura et al. 1999; Kubota et al. 2000; Shimada et al. 2012). Some authors have classified pleomorphic carcinoma as a variant of undifferentiated carcinoma of the gallbladder (Guo and Enjoji 1988). The clinical presentation is that of other invasive carcinomas of the gallbladder. The neoplasm may be associated with a paraneoplastic syndrome, i.e., production of granulocyte colony-stimulating factor, causing leukocytosis in the peripheral blood (Takeda et al. 1990; Omura et al. 1999). Leukocytosis disappears immediately after cholecystectomy. Due to the small numbers of reported cases, no reliable data regarding outcome are available, but pleomorphic gallbladder carcinomas are highly aggressive lesions with a tendency to invade the liver and adjacent organs and poor prognosis.

Pathology

Macroscopy

As other high-grade carcinomas, pleomorphic carcinoma of the gallbladder produces ill-defined invasive masses with necrosis and hemorrhage. Polypoid tumors protruding into the gallbladder lumen have been described (Caruso et al. 1991).

Histopathology

The histology of these carcinomas is characterized by a growth that lack architectural cohesiveness and the organoid features of typical adenocarcinomas. The neoplastic cells are mononuclear or multinucleated (giant cells) and are generally large or at least of intermediate size, with an eosinophilic or amphophilic cytoplasm. Nuclei are highly irregular and pleomorphic, sometimes lobulated, with a coarse chromatin and large nucleoli. Numerous and in part highly atypical mitotic figures are noted. Some of the tumors contain atypical and pleomorphic spindle cells and squamous cells (Appelman and Coopersmith 1970; Alpers and Smuckler 1984; Shimada et al. 2012). The stroma is usually poorly developed. Extensive necrosis, apoptosis, and leukocyte-tumor cell phagocytosis are often present.

Immunohistochemistry

The tumor cells are reactive for cytokeratins, EMA, and carcinoembryonic antigen (Caruso et al. 1991), demonstrating the epithelial nature of this poorly differentiated neoplasm.

Differential Diagnosis

Due to the presence of multinucleated giant cells, pleomorphic carcinoma may be confounded with other giant cell neoplasms, specifically carcinoma with osteoclast-like giant cells. In the latter neoplasms, the giant cells possess more and isomorphic nuclei, and the cells lack pleomorphism. Pleomorphic carcinomas with a spindle cell component may resemble carcinosarcomas.

Undifferentiated Giant Cell Carcinoma (Anaplastic Carcinoma) of the Gallbladder

Undifferentiated carcinoma giant cell type is a rare variant of carcinoma that also occurs in the biliary tract (Dowaki et al. 2003; Oikawa et al. 2007; Ide et al. 2012).

In the very uncommon gallbladder tumors showing this morphology, it has been assumed

that anaplastic giant cell components may probably represent dedifferentiation of a preexisting adenocarcinoma.

References

Abdulkader I, Cameselle-Teijeiro J, Forteza J (2003) Signet-ring cells associated with pseudomembranous colitis. Virchows Arch 442:412–414

Adachi Y, Yasuda K, Inomata M, Sato K, Shiraishi N, Kitano S (2000) Pathology and prognosis of gastric carcinoma: well versus poorly differentiated type. Cancer 89:1418–1424

Agergaard Thging B, Roslind A, Wojdemann M (2012) Signet ring cell carcinoma of the gallbladder (in Danish). Ugeskr Laeger 174:948–949

Akatsu T, Ueda M, Shimazu M, Wakabayashi G, Aiura K, Tanabe M, Kawachi S et al (2005) Primary undifferentiated spindle-cell carcinoma of the gallbladder presenting as a liver tumor. J Gastroenterol 40:993–998

Albores-Saavedra J, Molberg K, Henson DE (1996) Unusual malignant epithelial tumors of the gallbladder. Semin Diagn Pathol 13:326–338

Albores-Saavedra J, Henson DE, Moran-Portela D, Lino-Silva S (2008) Cribriform carcinoma of the gallbladder: a clinicopathologic study of 7 cases. Am J Surg Pathol 32:1694–1698

Albores-Saavedra J, Adsay NV, Crawford JM, Klimstra DS, Klöppel G, Sripa B, Tsui WMS et al (2010) Carcinoma of the gallbladder and extrahepatic bile ducts. WHO classification of tumours of the digestive system. IARC, Lyon, pp 268–269

Alpers CE, Smuckler EA (1984) Pleomorphic carcinoma of the gallbladder: case report and ultrastructural study. Ultrastruct Pathol 6:29–38

Aoki T, Inoue K, Tsuchida A, Aoki T, Kasuya K, Kitamura K, Koyanagi Y, Shimizu T et al (2002) Gallbladder metastasis of renal cell carcinoma: report of two cases. Surg Today 32:89–92

Appelman HD, Coopersmith N (1970) Pleomorphic spindle-cell carcinoma of the gallbladder. Relation to sarcoma of the gallbladder. Cancer 25:535–541

Araida T, Kogure M, Takasaki K (1996) Mucin producing gallbladder cancer. Ryoikibetsu Shokogun Shirizu 9:352–355

Ayhan A, Guney I, Saygan-Karamursel B, Taskiran C (2001) Ovarian metastasis of primary biliary and gallbladder carcinomas. Eur J Gynaecol Oncol 22:377–378

Badmos KB, Salah Seada L, Fahad Al Rashid F, Oreiby HA (2013) Undifferentiated spindle cell carcinoma of the gallbladder: a report of a case, an immunohistochemical profile, and a review of the literature. Case Rep Pathol 2013:267194

Bazan F, Sanchez J, Aguilar G, Radosevic A, Busto M, Zuccarino F, Pijuan L, Risueño N (2011) Metastatic gallbladder adenocarcinoma with signet-ring cells: a case report. J Med Case Rep 5:458

Bernades P, Schlegel N, Potet F, Menaché D (1972) Cancer of the gallbladder with alpha-feto-protein. Disappearance of the protein after exeresis of the tumor (in French). Nouv Press Med 1:1297–1298

Bilicli A, Seker M, Öven Ustaalioglu BB, Hallaç Keser S, Cinaral F, Gümüs M (2012) Gallbladder metastasis secondary to gastric cancer as a first site of recurrence presented with acute cholecystitis: case report and literature review. Turk J Gastroenterol 23:764–768

Bittinger A, Altekrüger I, Barth P (1995) Clear cell carcinoma of the gallbladder. A histological and immunohistochemical study. Pathol Res Pract 191:1259–1265

Botting AJ, Harrison EG, Black BM (1963) Metastatic hypernephroma masquerading as a polypoid tumor of the gallbladder and review of metastatic tumors of the gallbladder. Mayo Clin Proc 38:225–232

Brandt-Rauf PW, Branwood AW (1980) Case report: an unusual case of gallbladder cancer in an automotive worker. CA Cancer J Clin 30:333–336

Brasseur P, Bissen L, Dupont H, Sukkarieh F (1999) Metastasis to the gallbladder secondary to a clear cell renal tumor (in French). J Radiol 80:739–740

Brown JA, Roberts CS (1992) Elevated serum alpha-fetoprotein levels in primary gallbladder carcinoma without hepatic involvement. Cancer 70:1838–1840

Camaselle-Teijeiro J, Chan JK (1999) Cribriform-morular variant of papillary carcinoma: a distinctive variant representing the sporadic counterpart of familial adenomatous polyposis-associated thyroid carcinoma? Mod Pathol 12:400–411

Cameselle-Teijeiro J, Alberte-Lista L, Chiarelli S, Buritica C, Gonçalves L, Gonzalez-Campora R et al (2008) CD10 is a characteristic marker of tumours forming morules with biotin-rich, optically clear nuclei that occur in different organs. Histopathology 52:389–392

Caruso RA, Famulari C, Giuffré G, Mazzeo G (1991) Pleomorphic carcinoma of the gallbladder: report of a case. Tumori 77:523–526

Cetta F, Ugolini G, Barellini L, Civitelli S, Carmellini M (2011) FAP associated cribriform morular variant of PTC: striking female prevalence and indolent course. Endocr J 58:817–818

Cetta F, Moltoni L, Barellini L, Monti M, Gotti G (2012) Familial adenomatous polyposis-associated papillary thyroid carcinoma shows an indolent course and usually, but not always, belongs to the cribriform-morular variant of papillary thyroid carcinoma. Acta Cytol 56:107–108

Chiarelli S, Buritica C, Litta P, Ciani S, Guarch R, Nogales FF (2006) An immunohistochemical study of morules in endometrioid lesions of the female genital tract: CD10 is a characteristic marker of morular metaplasia. Clin Cancer Res 12:4251–4256

Chinen K, Kamiyama K, Kinjo T, Arasaki A, Ihama Y, Hamada T, Iwamasa T (2004) Morules in endometrial carcinoma and benign endometrial lesions differ from squamous differentiation tissue and are not infected with human papillomavirus. J Clin Pathol 57:918–926

Chu PG, Weiss LM (2004) Immunohistochemical characterization of signet-ring cell carcinomas of the stomach, breast, and colon. Am J Clin Pathol 121:884–892

Cocquyt V, Pipeleers-Marichal M, Delvaux G, Van belle S (1996) Increasing serum levels of alpha-fetoprotein in a patient with relapsing gallbladder carcinoma. Am J Clin Oncol 19:465–468

Czyszczon IA, Alatassi H (2010) Signet ring cell carcinoma of the gallbladder in a 22-year-old man: a case report and review of the literature. Int J Surg Pathol 18:358–362

Dhingra S, Wang H (2011) Nonneoplastic signet-ring cell change in gastrointestinal and biliary tracts: a pitfall for overdiagnosis. Ann Diagn Pathol 15:490–496

Diebold-Berger S, Vaiton JC, Pache JC, d'Amore ES (1995) Undifferentiated carcinoma of the gallbladder. Report of a case with immunohistochemical findings. Arch Pathol Lab Med 119:279–282

Dimet S, Lazure T, Bedossa P (2004) Signet-ring cell change in acute erosive gastropathy. Am J Surg Pathol 28:1111–1112

Dowaki S, Kijima H, Kashiwagi H, Tobita K, Ohtani Y, Sugio Y, Sekka T, Osamura RY et al (2003) Undifferentiated spindle and giant cell carcinoma of the common bile duct. Tokai J Exp Clin Med 28:127–130

Dursun N, Escalona OT, Roa JC, Basturk O, Bagci P, Cakir A, Cheng J, Sarmiento J et al (2012) Mucinous carcinomas of the gallbladder: clinicopathologic analysis of 15 cases identified in 606 carcinomas. Arch Pathol Lab Med 136:1347–1358

El-Zimaity HMT, Itani K, Graham DY (1997) Early diagnosis of signet ring cell carcinoma of the stomach: role of the Genta stain. J Clin Pathol 50:867–879

Fang X, Gupta N, Shen SS, Tamboli P, Charnsangavej C, Rashid A, Wang H (2010) Intraluminal polypoid metastasis of renal cell carcinoma in gallbladder mimicking gallbladder polyp. Arch Pathol Lab Med 134:1003–1009

Fornelli A, Cavazza A, Cancellieri A, Rossi G, De Marco L (2003) Bronchioloalveolar carcinoma with nodular ("morule-like") features. Virchows Arch 442:407–408

Gamachi A, Kashima K, Daa T, Nakatani Y, Tsujimoto M, Yokoyama S (2003) Aberrant intranuclear localization of biotin, biotin-binding enzymes, and beta-catenin in pregnancy-related endometrium and morule-associated neoplastic lesions. Mod Pathol 16:1124–1131

Genta RM, Robason GO, Graham DY (1994) Simultaneous visualization of Helicobacter pylori and gastric morphology: a new stain. Hum Pathol 25:221–226

Gilks CB, Young RH, Aguirre P, DeLellis RA, Scully RE (1989) Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. Am J Surg Pathol 13:717–729

Guo KJ, Enjoji M (1988) Undifferentiated carcinoma of the gallbladder. Cancer 61:1872–1879

Guo KJ, Yamaguchi K, Enjoji M (1988) Undifferentiated carcinoma of the gallbladder. A clinicopathologic, histochemical, and immunohistochemical study of 21 patients with a poor prognosis. Cancer 61:1872–1879

Gusserow ALS (1870) Über Sarcome des Uterus. Arch Gynakol 1:240–251

Hara S, Kijima H, Okada K, Igarashi Y (2010) Invasive micropapillary variant of the gallbladder adenocarcinoma and its aggressive potential for lymph node metastasis. Biomed Res 31:89–95

Haruta J, Kanayama K, Tachino F, Hayakawa M, Kusakabe A, Kurokawa S, Oka Y et al (1987) A clinicopathological evaluation of AFP-positive gallbladder cancer – with special reference to two autopsy cases investigated by an immunological method (in Japanese). Gan No Rinsho 33:1839–1845

He M, Fan J, Jiang R, Tang WX, Wang ZW (2013) Expression of DNMTs and genomic DNA methylation in gastric signet ring cell carcinoma. Mol Med Rep 8:942–948

Hirokawa M, Maekawa M, Kuma S, Miyauchi A (2010) Cribriform-morular variant of papillary thyroid carcinoma – cytological and immunocytochemical findings of 18 cases. Diagn Cytopathol 38:890–896

Hirsch EF, Gerber L, Coffey RJ, Goldman ML (1964) Mucoid carcinoma of the gallbladder: clinical management of excessive drainage. Surgery 55:769–761

Hosaka N, Sasaki T, Adachi K, Sato T, Tanaka T, Miura Y, Sawai T, Toki J, Hisha H, Okamura A et al (2004) Pulmonary sclerosing hemangioma associated with familial adenomatous polyposis. Hum Pathol 35:764–768

Houghton O, Connolly LE, McCluggage WG (2008) Morules in endometrioid proliferations of the uterus and ovary consistently express the intestinal transcription factor CDX2. Histopathology 53:156–165

Huang CP, Chiou YY, Chou YH, Chiang JH, Chang CY (2006) Imaging findings in mucin-producing carcinoma of the gallbladder. J Formos Med Assoc 105:427–430

Huh CW, da Jung H, Kim JH, Lee YC, Kim H, Kim H, Yoon SO, Youn YH, Park H et al (2013) Signet ring cell mixed histology may show more aggressive behavior than other histologies in early gastric cancer. J Surg Oncol 107:124–129

Ide T, Miyoshi A, Kitahara K, Kai K, Noshiro H (2012) Spindle and giant cell type undifferentiated carcinoma of the proximal bile duct. Case Rep Gastroenterol 6:33–39

Ikeda M, Okada S, Morozumi A, Fujino MA, Matsumoto Y (1992) Alpha-fetoprotein producing carcinoma of the gallbladder associated with anomalous arrangement of the pancreaticobiliary ductal system – early detection through an attack of acute pancreatitis. Gastroenterol Jpn 27:669–673

Ishibashi H, Hachisuka K, Yamaguchi A, Isogai M, Fukada S, Kato S et al (1986) Mucin-producing gallbladder carcinoma: report of a case. Tan to Sui 7:1173–1178

Ishiguro S, Onaya H, Esaki M, Kosuge T, Hiraoka N, Mizuguchi Y, Arai Y (2012) Mucin-producing

carcinoma of the gallbladder: evaluation by magnetic resonance cholangiopancreatography in three cases. Korean J Radiol 13:637–642

Jain V, Gupta K, Kudva R, Rodrigues GS (2006) A case of ovarian metastasis of gall bladder carcinoma simulating primary ovarian neoplasm: diagnostic pitfalls and review of literature. Int J Gynecol Cancer 16(suppl 1): 319–321

Jindal T, Mandal SN, Kamal MR, Das AK, Karmakar D (2012) Occult mucin secreting adenocarcinoma of gall bladder with metastasis to urinary bladder. Updat Surg 64:239–240

Joo YE, Kim HS, Choi SK, Rew JS, Kim HJ, Kang HK, Juhng SW, Kim SJ (2003) Case of mucinous adenocarcinoma with porcelain gallbladder. J Gastroenterol Hepatol 18:995–998

Kakar S, Deng G, Smyrk TC, Cun L, Sahai V, Kim YS (2012) Loss of heterozygosity, aberrant methylation. BRAF mutation and KRAS mutation in colorectal signet ring cell carcinoma. Mod Pathol 25:1040–1047

Karabulut Z, Yildirim Y, Abaci I, Ilgici D, Ozyilkan O (2008) Signet-ring cell carcinoma of the gallbladder: a case report. Adv Ther 25:520–523

Kassabian A, Stein J, Jabbour N, Parsa K, Skinner D, Parekh D, Cosenza C, Selby R (2000) Renal cell carcinoma metastatic to the pancreas: a single-institution series and review of the literature. Urology 56:211–215

Kechrid M, Malik GH, Al-Mohaya S, Shaikh JF, Al-Wakeel JS, El Gamal H, Farouk H et al (2000) Renal cell carcinoma of contralateral kidney with secondaries in gallbladder eight years after nephrectomy. Saudi J Kidney Dis Transplant 11:587–592

Khoo JJ, Nurul AM (2008) A clinicopathological study of nine cases of gallbladder carcinoma in 1122 cholecystectomies in Johor. Malays J Pathol 30:21–26

Khunamornpong S, Suprasert P, Chiangmai WN, Siriaunkgul S (2006) Metastatic tumors to the ovaries: a study of 170 cases in northern Thailand. Int J Gynecol Cancer 16(suppl 1):132–138

Kijima H, Suto A, Takeshita T, Omiya H, Tsuchida T, Yamazaki H, Nakamura M, Ueyama Y (1999) Gallbladder carcinoma with lymphoid stroma: a case report with immunohistochemical analyses. J Clin Gastroenterol 28:256–258

Kim JP, Kim SC, Yang HK (1994) Prognostic significance of signet ring cell carcinoma of the stomach. Surg Oncol 3:221–227

Kiyokawa T, Young RH, Scully RE (2006) Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. Am J Surg Pathol 30:277–299

Koo JS, Jung W, Hong SW (2011) Cytologic characteristics and b-catenin immunocytochemistry on smear slide of cribriform-morular variant of papillary thyroid carcinoma. Acta Cytol 55:13–18

Krunic AL, Chen HM, Lopatka K (2007) Signet-ring cell carcinoma of the gallbladder with skin metastases. Australas J Dermatol 48:187–189

Kubota H, Kageoka M, Iwasaki H, Sugimoto K, Higuchi R, Honda S, Watanabe F, Koda K et al (2000) A patient with undifferentiated carcinoma of gallbladder presenting with hemobilia. J Gastroenterol 35:63–68

Kücükakin B, Olsen CH, Gögenur I (2009) Renal cell carcinoma with metachronous metastases to the gallbladder after two years (in Danish). Ugeskr Laeger 171:2486–2487

Lee HW, Lee EH, Kim SH, Roh MS, Jung SB, Choi YC (2013) Heat shock protein 70 (HSP70) expression is associated with poor prognosis in intestinal type gastric cancer. Virchows Arch 463:489–495

Levy AD, Murakata LA, Rohrmann CA (2001) Gallbladder carcinoma: radiologic-pathologic correlation. Radiographics 21:295–314

Makishi S, Kinjo T, Sawada S, Chinen K, Hirayasu T, Hamada T, Saito K, Iwamasa T (2006) Morule and morule-like features associated with carcinomas in various organs: report with immunohistochemical and molecular studies. J Clin Pathol 59:95–100

Manouras A, Genetzakis M, Lagoudianakis EE, Markogiannakis H, Papadima A, Agrogiannis G et al (2009) Undifferentiated giant cell type carcinoma of the gallbladder with sarcomatoid dedifferentiation: a case report and review of the literature. J Med Case Rep 3:6496

Maruiwa M (1987) Establishment of a new human gallbladder carcinoma cell line (KMG-A) from an alpha-fetoprotein-producing gallbladder carcinoma transplanted into nude mice. Kurume Med J 34: 133–146

Maruiwa M, Yano H, Kataoka A, Murakami T, Fukuda K, Sugihara S, Kojiro M (1988) Heterotransplantation of an alpha-fetoprotein-producing human gallbladder carcinoma into nude mice. Acta Pathol Jpn 38: 501–513

Maruiwa M, Yano H, Fukuda K, Ogasawara S, Hisaka T, Yamaguchi R, Kojiro M (1996) An alpha-fetoprotein-producing human gallbladder carcinoma cell line (KMG-C) shows more aggressive biologic behavior than an alpha-fetoprotein-non-producing cell line. Int J Oncol 8:1179–1188

Michal M, Chlumska A, Mukensnabl P (1998) Signet-ring cell aggregates stimulating carcinoma in colon and gallbladder mucosa. Pathol Res Pract 194:197–200

Miyasaka K, Kabashima T, Hamaguchi H, Hanada T, Mitsunaga K, Maejima S, Hatano M (1978) A case of alpha-fetoprotein strongly positive cholecystic cancer associated with porcelain gallbladder (in Japanese). Rinsho Hoshasen 23:589–592

Miyazawa M, Torii T, Toshimitsu Y, Kamizasa N, Suzuki T, Shinozuka N, Ishizawa K et al (2006) Alpha-fetoprotein-producing clear cell carcinoma of the extrahepatic bile ducts. J Clin Gastroenterol 40:555–557

Mondal SK (2010) Signet ring cell carcinoma of gallbladder with celiac lymph node metastasis in a young man. J Cancer Res Ther 6:379–381

Moran CA, Jagirdar J, Suster S (2004) Papillary lung carcinoma with prominent "morular" component. Am J Clin Pathol 122:106–109

Muto Y, Sho Y, Uchimura M (1984) Carcinoma with lymphoid stroma of the gallbladder – a case report. Jpn J Surg 14:399–404

Nakatani Y, Masudo K, Nozawa A, Inayama Y, Yamanaka S, Ito T, Kitamura H, Notohara K et al (2004) Biotin-rich, optically clear nuclei express estrogen receptor-beta: tumors with morules may develop under the influence of estrogen and aberrant beta-catenin expression. Hum Pathol 35:869–874

Ng WK, Ng WF (1995) Elevated serum alpha-fetoprotein in a patient with undifferentiated carcinoma of the gall bladder. J Clin Pathol 48:1061–1063

Nie XC, Wang JP, Zhu W, Xu XY, Xing YN, Yu M, Liu YP, Takano Y, Zheng HC (2013) COL4A3 expression correlates with pathogenesis, pathologic behaviors, and prognosis of gastric carcinomas. Hum Pathol 44:77–86

Nishida T, Iwasaki H, Johzaki H, Tanaka S, Watanabe R, Kikuchi M (1997) A human gall-bladder signet ring cell carcinoma cell line. Pathol Int 47:368–376

Nishihara K, Tsuneyoshi M (1993) Undifferentiated, spindle cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and flow cytometric study of 11 cases. Hum Pathol 24:1298–1305

Nishimura R, Ohsumi S, Teramoto N, Yamakawa T, Saeki T, Takashima S (2005) Invasive cribriform carcinoma with extensive microcalcifications in the male breast. Breast Cancer 12:145–148

Nishino M, Klepeis VE, Yeap BY, Bergethon K, Morales-Oyarvide V, Dias-Santagata D et al (2012) Histologic and cytomorphologic features of ALK-rearranged lung adenocarcinomas. Mod Pathol 25:1462–1472

Nobusawa H, Hashimoto T, Munechika H, Soejima K, Seino N, Kurashita Y, Gokan T et al (1994) US and CT findings of mucinous carcinomas of the gallbladder (in Japanese). Nippon Igaku Hoshasen Gakkai Zasshi 54:1359–1367

Noda H, Chiba F, Toyama N, Konishi F (2009) Mucin-producing carcinoma of the gallbladder associated with primary sclerosing cholangitis and ulcerative colitis. J Hepato-Biliary-Pancreat Surg 16:83–85

Nojima H, Cho A, Yamamoto H, Nagata M, Takiguchi N, Kainuma O, Souda H, Gunji H et al (2008) Renal cell carcinoma with unusual metastasis to the gallbladder. J Hepato-Biliary-Pancreat Surg 15:209–212

Nomura S, Shirota H, Nakamura T (1996) Clear cell carcinoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:345–347

Ohno Y, Kumagi T, Kuroda T, Koizumi M, Azemoto N, Yamanishi H, Oda M, Hirooka M, Abe M, Ikeda Y et al (2014) Signet-ring cell carcinoma of the gallbladder complicated by pulmonary tumor thrombotic microangiopathy. Intern Med 53:1125–1129

Oikawa H, Oka K, Nagakura S, Fukunaga M, Sando N, Kashimura J, Hakozaki H (2007) Spindle and giant cell type undifferentiated carcinoma arising in the common bile duct: a case report. Pathol Res Pract 203:179–184

Okamoto Y, Kashima K, Daa T, Yokoyama S, Nakayama I, Noguchi S (1995) Morule with biotin-containing intranuclear inclusions in thyroid carcinoma. Pathol Int 45:573–579

Olinici CD, Vasiu R (1991) Composite endocrine cell, typical adenocarcinoma and signet ring carcinoma of the gallbladder. Rom J Morphol Embryol 37: 171–173

Omura N, Abe S, Hirai K, Aoki T (1999) A case of granulocyte-colony stimulating factor producing gallbladder cancer. Am J Gastroenterol 94:273–275

Ono T, Komatsu M, Hoshino T, Ishii T, Fujii T, Oshima S, Mikami K, Umeki Y, Enomoto K et al (1996) Alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9-producing gallbladder cancer. J Gastroenterol 31:742–746

Ozeki Y, Matsubara N, Saiga T, Homma M, Koyama A, Ichikawa T et al (1991) Mucus-producing cancer of the gallbladder: report of a case. Gastroenterol Endosc 33:2439–2444

Page DL, Dixon JM, Anderson TJ, Lee D, Stewart HJ (1983) Invasive cribriform carcinoma of the breast. Histopathology 7:525–536

Parker GW, Joffe N (1972) Calcifying primary mucus-producing adenocarcinoma of the gall-bladder. Br J Radiol 45:468–469

Pavic I, Marusic Z, Mijic A, Balicevic D, Kruslin B, Tomas D (2010) A case of signet-ring cell carcinoma of the gallbladder: immunohistochemistry and differential diagnosis. Acta Clin Oncol 49:159–162

Piana S, Cavazza A, Corrado S, Putrino I, Gardini G (2002) Combined small cell carcinoma and clear cell carcinoma of the gallbladder: report of a case and review of the literature. Pathol Res Pract 198:821–824

Pudasainin S, Subedi N, Prasad KB, Rauniyar SK, Bhattacharya SK, Koirala R, Koirala S et al (2011) Signet ring cell carcinoma of the gallbladder: a case report. Nepal Med Coll J 13:308–310

Ragazzi M, Carbonara C, Rosai J (2009) Nonneoplastic signet-ring cells in the gallbladder and uterine cervix. A potential source of overdiagnosis. Hum Pathol 40:326–331

Rogers LF, Lastra MP, Lin KT, Bennett D (1973) Calcifying mucinous adenocarcinoma of the gallbladder. Am J Gastroenterol 59:441–445

Russo S, Russo F, Maiello FM, Paolini B, Carrabba A, De Gregorio A (2012) Biphasic large cell neuroendocrine carcinoma – pure mucinous carcinoma of the gallbladder (MANEC): a unique combination. Pathologica 104:185–189

Saegusa M, Hashimura M, Kuwata T, Hamano M, Wani Y, Okayasu I (2007) A functional role of Cdx2 in beta-catenin signaling during transdifferentiation in endometrial carcinomas. Carcinogenesis 28:1885–1892

Saegusa M, Hashimura M, Kuwata T (2012) Sox4 functions as a positive regulator of b-catenin signaling through upregulation of TCF4 during morular differentiation of endometrial carcinomas. Lab Investig 92:511–521

Sakai Y, Sano S, Koike H (2008) Morule-like features and tumour-associated lymphoid proliferation in gallbladder carcinoma. Ann Diagn Pathol 12:430–432

Sarlin JG, Mori K (1984) Morules in epithelial tumors of the colon and rectum. Am J Surg Pathol 8:281–285

Sartelet H, Simon M, Alowanou A, Yasser K, Pinteaux A (2004) Papillary tumor of the gallbladder: the clear cells carcinoma (in French). Ann Pathol 24:58–61

Sasaki A, Yokoyama S, Arita T, Inomata M, Kashima K, Nakayama I (1999) Morules with biotin-containing optically clear nuclei in colonic tubular adenoma. Am J Surg Pathol 23:336–341

Satoh H, Iyama A, Hidaka K, Nakashiro H, Harada S, Hisatsugu T (1991) Metastatic carcinoma of the gallbladder from renal cancer presenting as intraluminal polypoid mass. Dig Dis Sci 36:520–523

Schaeffer DF, Yoshida EM, Owen DA, Berean KW (2011) Familial adenomatous polyposis-rendering a diagnosis based on recognition of an unusual primary thyroid neoplasm. Case Rep Med 2011:767610

Sekine S, Shibata T, Matsuno Y, Maeshima A, Ishii G, Sakamoto M, Hirohashi S (2003) Beta-catenin mutations in pulmonary blastomas: association with morule formation. J Pathol 200:214–221

Sentani K, Uraoka N, Oue N, Yasui W (2014) Alpha-fetoprotein-producing clear cell carcinoma of the gallbladder with neuroendocrine differentiation. Med Mol Morphol 47:54–56

Shimada K, Iwase K, Aono T, Nakai S, Takeda S, Fujii M, Koma M, Nishikawa K et al (2009) Carcinosarcoma of the gallbladder producing alpha-fetoprotein and manifesting as leukocytosis with elevated serum granulocyte colony-stimulating factor: report of a case. Surg Today 39:241–246

Shimada M, Kadoya S, Tanada Y, Endo N, Murakami N, Matsui K (2012) Resected pleomorphic carcinoma of the gallbladder. Case Rep Gastroenterol 6:747–753

Silverberg SG, Hurt WG (1975) Minimal-deviation adenocarcinoma (adenoma malignum) of the cervix. A reappraisal. Am J Obstet Gynecol 121:971–975

Sinkre PA, Murakata L, Rabin L, Hoang MP, Albores-Saavedra J (2001) Clear cell carcinoid tumor of the gallbladder: another distinctive manifestation of von Hippel-Lindau disease. Am J Surg Pathol 25:1334–1339

Snyder JA, Carman R, Dimarco L (2012) Signet-ring cell carcinoma of the gallbladder after gastric bypass. J Gastrointest Cancer 43(Suppl 1):567–569

Sonoda A, Mukaisho K, Nakayama T, Diem VT, Hattori T, Andoh A, Fujiyama Y, Sugihara H (2013) Genetic lineages of undifferentiated-type gastric carcinomas analysed by unsupervised clustering of genomic DNA microarray data. BMC Med Genomics 6:25

St Laurent M, Esterl RM, Halff GA, Speeg KV (1999) Gallbladder carcinoma producing alpha-fetoprotein. J Clin Gastroenterol 28:155–158

Stutz JA, Evans AJ, Pinder S, Ellis IO, Yeoman LJ, Wilson AR, Sibbering DM (1994) The radiological appearances of invasive cribriform carcinoma of the breast. Nottingham Breast Team. Clin Radiol 49:693–695

Sugaya Y, Sugaya H, Kuronuma Y, Hisauchi T, Harada T (1989) A case of gallbladder carcinoma producing both alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA). Gastroenterol Jpn 24:325–331

Suri VS, Sakhuja P, Malhotra V, Gondal R, Sachdev AK, Negi SS (2001) Benign signet ring cell change with multilayering in the gallbladder mucosa- a case report. Pathol Res Pract 197:785–788

Tajiri K, Shimizu Y, Mihara H, Kawanishi Y, Orihara T, Takahashi H, Ishizawa S, Kawai S et al (2006) Cholangiocarcinoma at the cystic duct discovered by lymph node metastases with clear cell transformation. Intern Med 45:1045–1048

Takahashi Y, Fukushima J, Fukusato T, Shiga J (2004) Sarcomatoid carcinoma with components of small cell carcinoma and undifferentiated carcinoma of the gallbladder. Pathol Int 54:866–871

Takeda T, Ichiyanagi A, Sano K, Yoshida J, Tsutsumi Y, Miyaji T (1990) A case of gallbladder cancer producing granulocyte-colony-stimulating factor. Gastroenterol Jpn 25:762–767

Tanaka S, Ohta T, Kaji E, Kosaka T, Nagano T, Makino Y, Murakami I (2002) A case of undifferentiated carcinoma of the gallbladder which could be diagnosed from the autopsy (in Japanese). Nihon Shokakibyo Gakkai Zasshi 99:1366–1371

Tanigawa N (1996) Gallbladder carcinoma producing CEA, AFP, CA19-9, sialyl SSEA and CSF (in Japanese). Ryoikibetsu Shokogun Shirizu 9:237–239

Tashiro T, Hirokawa M, Horiguchi H, Wakatsuki S, Sano T, Yada S (2000) Well-differentiated adenocarcinoma of the gallbladder mimicking minimal deviation adenocarcinoma of the cervix. APMIS 108:173–177

Tatematsu M, Ichinose M, Miki K, Tatematsu K, Kishikawa H, Ito N (1988) Gastric phenotypic expression in human gallbladder cancers revealed by pepsinogen immunohistochemistry and mucin histochemistry. Virchows Arch A Pathol Anat Histol 413:25–32

Tateno Y, Esaki M, Shimada K, Ojima H, Kanai Y, Hiraoka N (2012) Morules in intraductal papillary mucinous neoplasm with an associated invasive carcinoma of the pancreas. Pancreas 41:651–652

Terada T (2013a) An immunohistochemical study of primary signet-ring cell carcinoma of the stomach and colorectum. I. Cytokeratin profile of 42 cases. Int J Clin Exp Pathol 6:703–710

Terada T (2013b) An immunohistochemical study of primary signet-ring cell carcinoma of the stomach and colorectum: III. Expressions of EMA, CEA, CA19-9, CDX-2, p53, Ki-67 antigen, TTF-1, vimentin, and p63 in normal mucosa and in 42 cases. In6, 613–621. t. Int J Clin Exp Pathol 6:630–638

Terada T (2013c) An immunohistochemical study of primary signet-ring cell carcinoma of the stomach and

colorectum: II. Expression of MUC1, MUC2, MUC5AC, and MUC6 in normal mucosa and in 42 cases. Int J Clin Exp Pathol 6:613–621

Terada T (2013d) Histopathologic features and frequency of gallbladder lesions in consecutive 540 cholecystectomies. Int J Clin Exp Pathol 6:91–96

Tian H, Matsumoto S, Takaki H, Kiyosue H, Komatsu E, Okino Y, Mori H, Miyake H (2003) Mucin-producing carcinoma of the gallbladder: imaging demonstration in four cases. J Comput Assist Tomogr 27:150–154

Ueo T, Kashima K, Daa T, Kondo Y, Sasaki A, Yokoyama S (2005) Immunohistochemical analysis of morules in colonic neoplasms: morules are morphologically and qualitatively different from squamous metaplasia. Pathobiology 72:269–278

Unterweger M, Caduff R, Bajka M, Klotz HP, Kubik-Huch RA (1999) Krukenberg syndrome in metastatic gallbladder adenocarcinoma with unknown primary tumor (in German). Praxis (Bern) 88:1320–1323

Vaillo A, Rodriguez-Recio FJ, Gutiérrez-Martin A, Ballestin C, Ruiz-Liso JM (2004) Fine needle aspiration cytology of clear cell carcinoma of the gallbladder with hepatic infiltration: a case report. Acta Cytol 48:560–564

Vardaman C, Albores-Saavedra J (1995) Clear cell carcinomas of the gallbladder and extrahepatic bile ducts. Am J Surg Pathol 19:91–99

Venable JG, Schwartz AM, Silverberg SG (1990) Infiltrating cribriform carcinoma of the breast: a distinctive clinicopathologic entity. Hum Pathol 21: 333–338

Wang K, Weinrach D, Lal A, Musunuri S, Ramirez J, Ozer O, Keh P, Rao MS (2003) Signet-ring cell change versus signet-ring cell carcinoma: a comparative analysis. Am J Surg Pathol 27:1429–1433

Wani Y, Notohara K, Fujisawa M (2008) Aberrant expression of an "intestinal marker" Cdx2 in pyloric gland adenoma of the gallbladder. Virchows Arch 453:521–527

Watanabe M, Hori Y, Nojima T, Kato H, Taketa K, Isogawa S, Yokoyama K, Nakagawa S (1993) Alpha-fetoprotein-producing carcinoma of the gallbladder. Dig Dis Sci 38:561–564

Wells CA, Ferguson DJ (1988) Ultrastructural and immunocytochemical study of a case of invasive cribriform breast carcinoma. J Clin Pathol 41:17–20

Wente MN, Kleeff J, Esposito I, Hartel M, Müller MW, Fröhlich BE, Büchler MW, Friess H (2005) Renal cancer cell metastasis into the pancreas: a single-center experience and overview of the literature. Pancreas 30:218–222

Willén R, Willén H (1982) Primary sarcoma of the gallbladder. A light and electronmicroscopical study. Virchows Arch (Pathol Anat) 396:91–102

Yadav R, Jain D, Mathur SR, Sharma A, Iyer VK (2013) Gallbladder carcinoma: an attempt of WHO histological classification on fine needle aspiration material. CytoJournal 10:12

Yamamoto A, Ozeki Y, Ito Y, Horita R, Saji S, Sugiyama H, Matsunaga K (2010) A case of well differentiated mucinous carcinoma of the gallbladder (in Japanese). Nippon Shokakibyo Gakkai Zasshi 107:1821–1827

Yamato T, Sasaki M, Watanabe Y, Nakanuma Y (1999) Expression of MUC1 and MUC2 mucin core proteins and their messenger RNA in gall bladder carcinoma: an immunohistochemical and in situ hybridization study. J Pathol 188:30–37

Yamauchi K, Ozeki Y, Sumi Y, Yamada T, Koyama H (2000) A case of signet ring cell carcinoma of the gallbladder with anomalous pancreaticobiliary ductal union (in Japanese). Nippon Shokakibyo Gakkai Zasshi 97:204–208

Yoshimitsu K, Irie H, Aibe H, Tajima T, Nishie A, Asayama Y, Matake K, Yamaguchi K et al (2005) Well-differentiated adenocarcinoma of the gallbladder with intratumoral cystic components due to abundant mucin production: a mimicker of adenomyomatosis. Eur Radiol 15:229–233

Zamecnik P, Mallory TB, Benedict E (1946) Colloid carcinoma of gall bladder, with widespread metastases. N Engl J Med 235:691–693

Gallbladder Carcinomas Not Related to Glandular Epithelia 151

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_151

Abstract

In addition to the common glandular carcinomas (adenocarcinoma) of the gallbladder, few other types of carcinoma can develop in this organ. Squamous cell carcinoma is a rare type of gallbladder malignancy clinically characterized by a more rapid and aggressive growth with infiltration of the liver and adjacent organs, but less frequent lymph node metastases in comparison with adenocarcinoma. This tumor accounts for only few percent of all gallbladder cancers. Macroscopically, squamous cell carcinoma usually produces large bulky lesions that efface the gallbladder wall. Adenosquamous carcinoma of the gallbladder is also rare and is diagnosed with an incidence similar to that of squamous cell carcinoma. Hepatoid carcinoma of the gallbladder is a rare variant of extrahepatic carcinoma which in several respects mimics hepatocellular carcinoma. Only few well-documented cases were reported for the gallbladder. These cancers are rapidly growing and highly aggressive lesions, similar to their counterparts in other organs. Very rare primary carcinomas of the gallbladder consist of small cells in the absence of neuroendocrine markers. Other very rare primary carcinomas of the gallbladder include anaplastic and pleomorphic carcinoma variants.

Squamous Cell Carcinoma of the Gallbladder

ICD-O code 8070/3

Introduction

Squamous cell carcinoma (SCC; epidermoid carcinoma) of the gallbladder is a rare type of carcinoma characterized by a more rapid and invasive, aggressive growth with infiltration of the liver and adjacent organs, less frequent lymph node metastasis in comparison with adenocarcinoma, and poorer outcome.

Epidemiology

SCC is a rare primary carcinoma of the gallbladder, accounting for only 0.5–12.7 % of all gallbladder malignancies. This neoplasm is predominantly seen among females between the fourth and sixth decades of life. In a clinicopathological review of 68 primary carcinomas of the gallbladder, SCCs amounted to 4.4 % (Donaldson and Busuttil 1975). In an autopsy study of 287 patients with gallbladder carcinoma, 3.7 % were SCCs (Sons et al. 1985). In a series of 29 non-adenocarcinoma types of gallbladder carcinoma, one lesion was SCC and 28 were adenosquamous carcinomas (Oohashi et al. 2002). Among 124 gallbladder malignancies observed in one center, 5 were SCCs (2.41 %), with a mean age at diagnosis of 50.2 years and a female/male ratio of 1.5:1 (del Pozo et al. 2005). A series of nine gallbladder carcinomas detected in 1,122 cholecystectomies contained one case of SCC (Khoo and Nurul 2008). A more recent clinicopathologic analysis of 606 gallbladder carcinomas revealed 41 tumors with a squamous cell differentiation, and eight of these neoplasms were pure SCC. The average patient age of the tumors with squamous cell differentiation was 65 years, with a female/male ratio of 3.8 (Roa et al. 2011). The relatively large range of incidence extracted from literature data is probably related to variable prevalences of risk factors, in particular chronic cholecystitis associated with stone disease. Another factor explaining marked differences in incidence is related to the fact that, in some reports and series, adenosquamous carcinoma, mucoepidermoid carcinoma, and secondary SCCs were lumped together with true primary SCC of the gallbladder. SCC of the gallbladder has been found in the setting of low-dose methotrexate use (Azad et al. 2009). SCC of the gallbladder may be combined with other primary gallbladder malignancies, e.g., adenocarcinoma (Hanada et al. 1986) or angiosarcoma (Kumar et al. 1994).

Selected References (Rabinovitch and Kieffer 1931; Milanes et al. 1950; Karlinger 1956;

Musconi 1963; Priola 1954; Karlinger 1956; Donaldson and Busuttil 1975; Piehler and Crichlow 1978; Cintorino et al. 1981; Karasawa et al. 1981; Crooks and Ermocilla 1985; Sons et al. 1985; Hanada et al. 1986; Alvarez Perez et al. 1988; Donohue et al. 1990; Gomez et al. 1990; Henson et al. 1992; Willcox and Chang 1993; Kumar et al. 1994; Khaira et al. 1995; Miyazaki et al. 1995; Bartlett et al. 1996; Shimoi and Ohkusa 1996a; Solivetti et al. 1996; Al-Hady and Al-Saed 1997; Botto Micca et al. 1997; Principe et al. 1997; Suganuma et al. 1997; Benoist et al. 1998; Das et al. 1998; Crawford 1999; Todoroki et al. 1999; Glehen et al. 2000; Gupta et al. 2000, 2004; Roppongi et al. 2000; Tomono et al. 2000; Kamat et al. 2001; Murata et al. 2001; Waisberg et al. 2001; Ishikawa et al. 2004; del Pozo et al. 2005; Mingoli et al. 2005; Chan et al. 2007; Kobayashi et al. 2007; Rao et al. 2007; Khoo and Nurul 2008; Hou et al. 2010; Damian et al. 2011; Kim et al. 2011; Rekik et al. 2011; Roa et al. 2011; Soyama et al. 2011; Gupta and Gupta 2012; Hosseinzadeh et al. 2012; Khan et al. 2012; Xu et al. 2012; Bouassida et al. 2013; Bourmèche et al. 2013; Kalayarasan et al. 2013; Chakrabarty et al. 2014; Kais et al. 2014).

Clinical and Imaging Features

The most important symptom is abdominal pain, occurring in 66 % of patients. The patients may present with colicky pain (mainly in those with stone disease), a right hypochondrial mass, or jaundice. The tumor may present as acute cholecystitis (Gupta et al. 2004; Damian et al. 2011) or gallbladder empyema (Kamat et al. 2001). Due to its invasive features, SCC can cause fistulations, e.g., biliary-colic fistula (Khaira et al. 1995). In one patient, SCC of the gallbladder was found to produce granulocyte-colony-stimulating factor (Murata et al. 2001). CT images reveal a thick-walled gallbladder (Rekik et al. 2011).

Pathology

Macroscopy

SCC of the gallbladder usually forms large bulky lesions that efface the gallbladder wall. On cut surfaces, the tumors are whitish and friable lesions, associated with often extensive necrosis and hemorrhage. In a minority of cases, the tumors display an endophytic and polypoid growth pattern, with formation of several vegetations sometimes extending from the fundus to the neck of the gallbladder (Mingoli et al. 2005) or with the tumor mass sometimes filling the dilated gallbladder lumen (endophytic carcinomas; Khan et al. 2012). Among 41 cancers with a squamous cell differentiation, including eight pure SCCs, 6 % of the tumors were polypoid (Roa et al. 2011). Very small lesions (minute SCC) have been described, e.g., in the form of a small and firm nodules incidentally found during cholecystectomy (Roppongi et al. 2000). In advanced-stage disease, the tumor invades the gallbladder fossa and the liver substance.

Histopathology

SCC of the gallbladder is an invasive lesion growing in the form of solid components which consist of a layered keratinocyte epithelium. The squamous cell cords are often several cells thick and grow along preexisting structures of the gallbladder wall, specifically blood vessels and nerves. In the cords, smaller cells prevail at the periphery, while more mature-looking keratinocytes predominate in central parts of the cords. In some cases, the smaller and peripherally placed cells show basaloid features. In the centers of the cords, the keratinocytes may form concentrically arranged clusters ("pearls"), with or without keratinization. The latter is seen as dyskeratosis or parakeratosis, while areas with formation of a stratum granulosum are less commonly seen (Xu et al. 2012). SCC can be present as early gallbladder carcinoma, with an intramucosal extension (Albores-Saavedra et al. 2011). Desmoplasia (stroma formation) is usually not pronounced. Large necrosis can occur,

associated with ulceration of the tumor. Peri-and/or intraneural invasion may be noted. Within the tumors and in the adjacent tissue, a cellular mixed infiltrate is noted. In a systematic study, tumor-infiltrating eosinophils were more frequent in SCCs and adenosquamous carcinomas than in adenocarcinoma (Roa et al. 2011). SCC of the gallbladder can be diagnosed by preoperative fine-needle aspiration cytodiagnosis (Gupta et al. 2000; Gupta and Gupta 2012).

SCC is sometimes associated with squamous cell metaplasia of the gallbladder surface epithelium or with squamous cell metaplastic changes situated in crypts or deeper parts of the glandular mucosa (Hanada et al. 1986; Roa et al. 2011). Among 41 gallbladder carcinomas with squamous cell differentiation, squamous cell metaplasia of adjacent mucosa was detected in 12 % of cases (Roa et al. 2011). These metaplastic areas may be located in gallbladder parts, showing mucosal atrophy and fibrosis in case of stone disease, and the metaplasia may in fact be found in flattened mucosae underlying an impacted stone. In squamous metaplasia, various degrees of keratinocyte dysplasia can occur, sometimes representing squamous cell carcinoma in situ. Such lesions may be in direct contact with invasive carcinoma, suggesting a dysplasia-carcinoma in situ-invasive carcinoma sequence or may exist as separate lesions, distant from otherwise invasive carcinoma components. SCC may also originate from metaplasia taking place in adenocarcinoma, as observed in some advanced cases of gallbladder carcinoma (Miyazaki et al. 1995; Tomono et al. 2000).

Biology of Disease

SCC of the gallbladder is aggressive and highly invasive neoplasms with an outcome that is poorer than that of adenocarcinoma, although they display a lower rate of locoregional lymph node metastasis, even in the presence of large primary tumors (Soyama et al. 2011; Chakrabarti et al. 2014). Gallbladder SCC can infiltrate the gallbladder bed, grow into the liver substance, and may be manifest in other sites (Kais et al. 2014). The biology of disease resembles that of adenosquamous carcinoma. Generally, SCC and adenosquamous carcinoma of the gallbladder present, in comparison with conventional adenocarcinoma, with a larger tumor size, a higher T stage, and a higher incidence of adjacent organ involvement, but a lower incidence of locoregional lymph node involvement (Kalayarasan et al. 2013). Whereas 5-year survival rates of adenocarcinoma have been reported to be in the range 32–38.5 % (Henson et al. 1992), the rarer SCC and adenosquamous carcinomas have shown 2-year survival rates of 10–22.3 %. This feature reflects what is known for other organs, where squamous and adenosquamous carcinomas showed a more unfavorable biology than adenocarcinoma, e.g., stomach and lung. The squamous component had a higher proliferative activity than the glandular component in gallbladder carcinomas (Nishihara et al. 1994b). Invasion of adjacent organs is a typical feature of SCC (Karaswa et al. 1981; Miyazaki et al. 1995; Mingoli et al. 2005; Khan et al. 2012). Like adenosquamous carcinoma, SCC is often diagnosed at an advanced stage, resulting in non-curative surgical resection and a poorer prognosis than in conventional gallbladder carcinoma (Kim et al. 2011). However, in a recent study where follow-up was available in 31 patients, the survival of patients with SCC/adenosquamous carcinomas was significantly worse than that of gallbladder adenocarcinomas, and this adverse prognosis persisted when compared with stage-matched advanced gallbladder adenocarcinoma cases (Roa et al. 2011).

Differential Diagnosis

Differential diagnosis mainly includes adenosquamous carcinoma with a predominant squamous cell component, invasion by a hepatic squamous cell carcinomas, and the very rare gallbladder metastasis of a squamous cell carcinoma situated elsewhere.

Pathogenic Pathways

SCC of the gallbladder was found to have coamplification of the HST1 and INT2 genes,

HST1 previously been found to be amplified in over 40 % of SCCs of the esophagus (Tsuda et al. 1989).

Adenosquamous Carcinoma of the Gallbladder

ICD-O code 8560/3

Introduction

Adenosquamous carcinoma of the gallbladder (ASC; synonym: adenoacanthoma) is a rare type of primary carcinoma of this organ. It is defined as an adenocarcinoma containing a squamous cell (keratinocyte) component constituting 25–99 % of the tumors. Adenocarcinomas containing less than 25 % squamous cells are classified as adenocarcinoma with focal squamous change. In older reports, the term adenoacanthoma was employed (Bartocci and Carratu 1964; Occhionero and Ricci 1964; Zambianchi 1965).

Epidemiology

ASC is a rare histologic type of gallbladder carcinoma, accounting for an estimated 5.3–10.6 % of all gallbladder carcinomas (Henson et al. 1992; Nishihara et al. 1994b; Albores-Saavedra et al. 1998). In an early analysis of 271 surgically resected gallbladder cancers, 20 patients had ASC (7.4 %; Nishihara et al. 1994a). In a study on 606 resected invasive gallbladder carcinomas, 41 cases (7 %) showed squamous differentiation, and 26 of these were ASC (Roa et al. 2011).

ASC is a tumor of older patients, most patients being older than 60 years at diagnosis. In the 20 patients with gallbladder ASC reported by Nishihara et al. (1994b), the mean age at diagnosis was 66.9 years. In a series of primary ASC and squamous cell carcinomas of the gallbladder, the average patient age at diagnosis was 65 years/range, 26–81 years, with a female/male ratio of 3.8 (Roa et al. 2011).

Selected References Kusakina and Nigmatulina 1980; Sato et al. 1981; Muto et al. 1982; Otsuka et al. 1982; Suster et al. 1987; Stamatiadis et al. 1989; Fukuda and Ohnishi 1990; Kojima et al. 1994; Nishihara et al. 1994b; Mingoli et al. 1995; Miyazaki et al. 1995; Nishihara et al. 1995; Shimoi and Ohkusa 1996b; Wagreich et al. 1998; Ercolani et al. 1999; Saito et al. 1999; Kondo et al. 2002; Oohashi et al. 2002; Ramia et al. 2002; Akcali et al. 2005; Fujita et al. 2005; Mingoli et al. 2005; Noske and Pahl 2006; Chan et al. 2007; Lada et al. 2007; Farah-Klibi et al. 2008; Horio et al. 2009; Bagdasaryan and Miroshnichenko 2011; Roa et al. 2011; Rustagi et al. 2011; Kim et al. 2012

Clinical and Imaging Features

Gallbladder ASC usually presents with upper abdominal pain, nausea, vomiting, and weight loss (Lada et al. 2007). In a comparative study, the clinical presentation of ASC was not different from that of adenocarcinoma. However, tumor stages in both ASC and squamous cell carcinomas of the gallbladder were significantly advanced and often included liver involvement (Chan et al. 2007). In a study of ten patients with ASC and four patients with squamous cell carcinoma, presentation with vomiting and an abdominal lump was more common than in patients with adenocarcinoma, and these tumors also presented with a larger tumor size, advanced T stage, and a higher incidence of adjacent organ involvement (Kalayarasan et al. 2013). ASC of the gallbladder may mimic Mirizzi syndrome. In one patient, the nodular growth pattern of the ASC was responsible for the finding of a benign-looking bile duct stenosis on examination by ERC (Horio et al. 2009). ASC of the gallbladder tends to invade not only the liver but also adjacent organs, sometimes with fistula formation, e.g., cholecysto-duodenal fistulas (Saito et al. 1999) or bilio-biliary fistulas (Ercolani et al. 1999). As a complication of ASC, tumor rupture has been described (Rustagi et al. 2011). Exceptionally, ASC of the gallbladder was associated with a paraneoplastic syndrome, e.g., a tumor producing

human chorionic gonadotropin (Fukuda and Ohnishi 1990).

Abdominal ultrasonography, CT, and MRI usually reveal an irregularly shaped solid mass with or without extension beyond the organ limits (Wagreich et al. 1998; Fujita et al. 2005). At endoscopic ultrasonography, ASC has been found to present with gallbladder wall thickening, similar to adenocarcinomas (Kim et al. 2012). In one patient, ASC was associated with congenital dilatation of the common bile duct (Otsuka et al. 1982).

Pathology

Macroscopy

Patients with ASC most often present with a large, non-cystic, and advanced-stage tumor mass replacing the gallbladder wall and the gallbladder fossa (Nishihara et al. 1994b; Mingoli et al. 1995; Miyazaki et al. 1995; Roa et al. 2011). In a minority of cases, a polypoid (endophytic) growth pattern is noted. Invasion of the liver substance and adjacent organs, mainly the duodenum, extrahepatic bile ducts, stomach, transverse colon, and pancreas, is a common finding at diagnosis. In ulcerated tumors, the surface of the defect is replaced by a gray-white, shaggy tumor mass. In stone disease, this mass may contain scattered, embedded calculi.

Histopathology

The typical histopathology of ASC is a tubular or papillary adenocarcinoma containing foci of squamous cells, often already visualized at low magnification. The transition between the adenocarcinoma components and the squamous cell components may be continuous or, more often, abrupt. For correct diagnosis, several fields have to be investigated, as the definition of ASC requires more than 25 % squamous cell components; otherwise the tumor is classified as adenocarcinoma with focal squamous change. As in pure squamous cell carcinomas, ASC tends to develop necrosis, sometimes extensive. The development of desmoplastic stroma is highly variable. Part of the tumors show a considerable desmoplasia, but scirrhous forms are the exception. In very rare cases, the desmoplastic stroma of ASC contained multinucleated giant cells of the osteoclast type (Grosso and Gonzalez 1992). ASC can present as early cancer with invasion limited to the proper muscle layer (Sato et al. 1981). ASC of the gallbladder can be diagnosed cytologically based on fine-needle aspiration (Yadav et al. 2013).

Variants of ASC of the Gallbladder

Probably due to the involvement of more than one lineage of cells differentiating in various directions, ASC can contain unusual cellular features in addition to the development of keratinocytes. A rare variant of ASC of the gallbladder is characterized by components showing atypical columnar epithelium with pseudostratification, mimicking gastric foveolar epithelium (Nishihara et al. 1995). Extensive spindle-cell transformation has been found in one case of ASC of the gallbladder. In areas showing interwoven fascicles of fusiform and poorly differentiated cells, keratin-positive cells were seen to merge with areas showing glandular and squamous cell features (Suster et al. 1987). ASC of the gallbladder was found in combination with other tumors, including pure squamous cell carcinoma or large-cell neuroendocrine carcinoma (Noske and Pahl 2006).

Immunohistochemistry

The glandular-type cells are positive for cytokeratins, epithelial membrane antigen, and carcinoembryonic antigen (Grosso and Gonzalez 1992). These cells express class II mucins (Nishihara et al. 1995). The squamous cells were positive for CK34BE12 and p63 (Rustagi et al. 2011). CD44 (standard) and CD44 variant members of a transmembrane glycoprotein adhesion molecule family are good markers of squamous epithelial differentiation (Georgolios et al. 2006) and can be used to detect a squamous cell lineage within an adenocarcinoma, including ASC (Ylagan et al. 2000). In ordinary gallbladder

adenocarcinoma, CD44 variant overexpression was associated with tumor dedifferentiation (Yanagisawa et al. 2001). In a PCNA study, a positive rate for immunostaining was larger in the squamous cell areas (mean 20.55 %) than in adenocarcinoma areas (11.40 %), suggesting a greater proliferative activity of the squamous component (Nishihara et al. 1994b).

Differential Diagnosis

The most important differential diagnosis is adenocarcinoma with focal squamous change, defined as an adenocarcinoma with less than 25 % squamous cell components. This distinction is properly made in large biopsies or resection specimens, while needle biopsies are problematic for the estimation of percentual representations, owing to marked sampling errors. A second potential differential diagnosis is metastatic ASC.

Biology of Disease

Similar to squamous cell carcinoma, ASC of the gallbladder is a tumor that is more invasive and more aggressive than ordinary adenocarcinoma, with a poor prognosis (Nishihara et al. 1994b; Ramia et al. 2002; Mingoli et al. 2005; Lada et al. 2007; Roa et al. 2011). It has been proposed that ASC of the gallbladder warrants resection only if curative resection is feasible (Oohashi et al. 2002). In fact, long-term survival following radical resection has been noted even in patients with advanced disease (Fujita et al. 2005).

Hepatoid Carcinoma of the Gallbladder

ICD-O code 8576/3

Introduction

Hepatoid adenocarcinoma (HAC; synonym: hepatoid carcinoma) is a rare variant of extrahepatic adenocarcinoma which mimics hepatocellular carcinoma (HCC) morphologically and in its functionality. Similar to HCCs, HACs produce and secrete alpha-fetoprotein (AFP), sometimes with very high serum levels (Akiyama et al. 2003; Su et al. 2013). HAC occurs in several organs, but most cases were observed in the stomach, followed by other parts of the gastrointestinal tract (including the pancreas), female genital tract, and lungs (Matsuta et al. 1991; Ishikura et al. 1997; Antonio et al. 2004). In fact, the first AFP-producing extrahepatic carcinoma with features of hepatic differentiation was observed in the stomach and termed hepatoid adenocarcinoma (Ishikura et al. 1985). HAC makes part of a complex group of non-HCC AFP-producing carcinomas. Not all carcinomas producing AFP are HAC. In the stomach, these lesions are generally classified as AFP-producing gastric cancer (AFPGC; Liu et al. 2012). AFPGC presents four histologic types: hepatoid, enteroblastic (fetal type), yolk sac tumor, and common adenocarcinoma type (Motoyama et al. 1993; Kinjo et al. 2012). Similar to gastric tumors, there is a distinct group of AFP-producing gallbladder carcinomas, lacking the histologic features of HAC. These lesions are discussed in a separate chapter.

HAC primary to the gallbladder is a very rare tumor with only relatively few well-documented cases (Katsuragi et al. 1989; Watanabe et al. 1993; Nishiwaki et al. 1997; Nakashima et al. 2000; Maitra et al. 2001a; Sakamoto et al. 2004; Sakamoto et al. 2005; Gakiopoulou et al. 2007; Koswara et al. 2007; van den Bos et al. 2007; Ellouze et al. 2011; Lee et al. 2011).

Clinical and Imaging Features

Patients with HAC present with abdominal discomfort or pain and a mass in the upper right abdominal compartment. HAC is associated with high levels of serum AFP in part of the cases (Katsuragi et al. 1989; van den Bos et al. 2007), but there is also HAC of the gallbladder lacking AFP production (Nakashima et al. 2000).

HAC is rapidly growing and highly aggressive, chemoresistant neoplasms that extensively metastasize to the liver, locoregional lymph nodes, and remote organs (Antonio et al. 2004; Lee et al. 2011). It has been proposed that hepatoid carcinomas, whether AFP producing or not, tend to fare worse than other AFP-producing carcinomas (Wee et al. 2004). On T1-weighted gradient-echo images, the tumor was hypointense to the adjacent liver substance, while fat-suppressed T2-weighted fast spin-echo images showed hyperintensity of the tumor. After injection of non-liver-specific gadolinium chelate, the lesion enhanced predominantly in the periphery (van den Bos et al. 2007).

Pathology

Macroscopy

The tumors are either solid growths of whitish color and firm consistency, or they present as large intraluminal polypoid masses.

Histopathology

Histologically, HAC displays a HCC-like trabecular pattern, the plates and nests composed of large cells with an eosinophilic and slightly granular cytoplasm and distinct cell borders. Nuclei are large and vesicular, often with an ovoid shape and prominent amphophilic or basophilic nucleoli. Part of the cells are PAS positive and stain with Victoria blue (Koswara et al. 2007). Due to these features, HAC often has a striking resemblance with HCC. Mitotic figures are regularly found and are sometimes present in large numbers, reflecting the rapid growth behavior of these neoplasms. In contrast to HCC, a sinusoidal vascular network is usually lacking. Desmoplasia is highly variable, but most tumors show only a delicate stromal component. HAC can consist of an HCC-like neoplasm in its entirety, but it may also be combined with typical adenocarcinoma, either intermingled or in the form of combined tumors (Sakamoto et al. 2004; Koswara et al. 2007; Ellouze et al. 2011) and with high-grade dysplasia of the gallbladder epithelium (Ellouze et al. 2011).

Immunohistochemistry

HAC shows marked reactivity for CK7 and CK19, mainly in components resembling adenocarcinoma, whereas CK20 is negative. Focally, CD10 is positive, suggesting focal canalicular differentiation (van den Bos et al. 2007; Ellouze et al. 2011). The neoplastic cells are reactive for AFP in part of the tumors (Katsuragi et al. 1989; Koswara et al. 2007; van den Bos et al. 2007). AFP reactivity is not restricted to HCC-like tumor cells but may also be detectable in glandular neoplastic cells (Koswara et al. 2007). In part of the cases, the cells have been shown to be positive for Hep Par1, suggesting a hepatocyte-like lineage (Maitra et al. 2001; Sakamoto et al. 2004; Ellouze et al. 2011). In other HAC, reactivity for glypican-3 was observed (Ushiku et al. 2010).

In HAC developing in organs other than the gallbladder, reactivity for P-glycoprotein and multidrug resistant-associated proteins (MRP) 1, 2, and 6 was significantly higher than in adenocarcinoma (Kamata et al. 2008). A marker distinguishing gastric HAC from HCC is the stem cell marker SALL4, which is diffusely expressed in HAC but is completely lacking in HCC (Ushiku et al. 2010; Ikeda et al. 2012).

Molecular Markers

In HAC located to other organs, novel markers distinguishing HAC from HCC have been investigated. Nasal epithelium carcinoma-associated protein/PLUNC has been shown to distinguish gastric HAC from primary HCC (Sentani et al. 2008).

Differential Diagnosis

HAC of the gallbladder has to be distinguished from HCC invading this organ or HCC metastasizing to the gallbladder (Tamura et al. 1993;

Han and Kim 2005; Murakami et al. 2008; Ando and Sakamoto 2009; Ryu et al. 2009). Since there is no peritoneal covering between the gallbladder and the liver fossa, gallbladder carcinoma easily and often invades the liver, whereas HCC rarely invades the gallbladder. Metastasis of HCC to the gallbladder can present massive intraluminal growth mimicking a primary gallbladder tumor (Terasaki et al. 1990) or may induce hemocholecyst (Chang et al. 1998). Gastric HAC often metastasizes to the liver and may eventually involve the gallbladder.

Pathogenic Pathways

The pathogenesis of HAC has not been clarified. One view suggests that adenocarcinoma acquires hepatic differentiation during tumor progression, while another hypothesis proposed that bipotential (progenitor) cells differentiate along two lineages, glandular and hepatoid (Sakamoto et al. 2004). There is molecular evidence of identical origin of gastric HAC with coexistent adenocarcinoma (Akiyama et al. 2003). It has been proposed that gastric AFP-producing carcinomas develop as common adenocarcinoma or enteroblastic carcinoma in the mucosa, which differentiate into HAC during the process of tumor invasion and proliferation, acquiring AFP production ability (Kinjo et al. 2012). HAC shares with HCC immunoreactivity for Hep Par1, regarded as a hepatocyte marker. Focal positivity for Hep Par1 was detected in 6/7 HAC of the gastrointestinal tract. This finding is no proof of a common cell lineage, but just underscores the fact that Hep Par1 expression is not unique to primary hepatocellular neoplasms (Maitra et al. 2001). Differential expression of transcription factors involved in hepatogenesis may be involved in the pathogenesis of HAC. In an AFP-producing lung carcinoma, expression of an important hepatogenic transcription factor, hepatocyte nuclear factor-4a, was restricted to hepatoid foci located in the tumor (Kishimoto et al. 2008).

Small Cell Carcinoma of the Gallbladder

Introduction

Small cell carcinoma (SCC; synonyms: small cell undifferentiated carcinoma, oat-cell carcinoma) of the gallbladder is an uncommon, aggressive malignancy that metastasized early and is associated with a poor prognosis. This tumor entity was first described in 1981 (Albores-Saavedra et al. 1981). Most SCC share with their bronchopulmonary counterpart the presence of neuroendocrine features (NE-SCC), but there seems to be small subset of undifferentiated SCC of the gallbladder that lack such features (non-neuroendocrine SCC; NNE-SCC). The exact origin and cell lineage of NNE-SCC are currently unknown, but this uncommon tumor is briefly discussed in descriptive terms.

Epidemiology

Overall, SCC of the gallbladder accounts for approximately 0.5 % of gallbladder carcinomas, according to SEER data (Henson et al. 1992), but higher incidences have been reported in other studies, e.g., 3.5 % (Moskal et al. 1999). In a further study of 284 cases of gallbladder carcinoma, eight were of the small cell type (Guo et al. 1988). Among 159 gallbladder carcinomas, 5 had the histology of small or oat-cell carcinoma (Albores-Saavedra et al. 1981). Small cell carcinoma (oat-cell carcinoma) of the gallbladder typically occurs in elderly women with cholelithiasis (Albores-Saavedra et al. 1984; Sons et al. 1985; Fujii et al. 2001), with a biology that is clearly different from that of gallbladder carcinoid tumors (Albores-Saavedra et al. 2009). Among 22 published cases, 86 % were women and 14 % males (female to male, 6:1). The mean age of the women was 64 years and of the men 60 years. Cholelithiasis was present in 91 % (Johnstone et al. 1993). In a review of 73 reported cases (Mahipal and Gupta 2011), age at diagnosis ranged from 25 to 86 years (median age: 67 years), with a clear female predominance (66 % female,

34 % male). In one study of 12 cases, the difference in gender was less prominent, i.e., female/male ratio of 5:7 (Maitra et al. 2001). The majority of tumors was associated with cholelithiasis (review: Moskal et al. 1999). In 72 % of the cases, the tumors were pure SCC, while 28 % of cases showed a combined morphology. In 68 % of the patients, the tumor was associated with cholelithiasis. From the National Cancer Institute's SEER program (1973–2005), 54 cases of SCC of the gallbladder were identified. The female/male ratio was 2.2, and the mean age at diagnosis was 67.5 years.

Clinical Features

The biology of disease is characterized by a rapidly progressing course, with frequent metastases to locoregional lymph nodes (70 %), liver (64 %), and lung (10 %) (Ron et al. 1992; Moskal et al. 1999; Matsuo et al. 2000; Mithal et al. 2000; Pavithran et al. 2001; Bahadur et al. 2005; Usmani et al. 2010; Mahipal and Gupta 2011). The 10-year survival for these tumors was 0 % (Albores-Saavedra et al. 2009). The mean survival is less than 7 months (Johnstone et al. 1993). In a later review of 73 cases, the median survival was 9 months (range: 1–198 months; Mahipal and Gupta 2011). However, successful treatment by surgery and adjuvant chemotherapy has been reported (Imai et al. 2008). Similar to SCCs of the lung, gallbladder SCC may be associated with paraneoplastic syndromes (Albores-Saavedra et al. 1981, 1984), e.g., paraneoplastic sensory neuropathy (Uribe-Uribe et al. 2009) or paraneoplastic hyponatremia (Ng et al. 2010).

General Pathologic Features

Macroscopically, small cell carcinoma tends to grow as protruding tumors that detach from the gallbladder wall, owing to extensive necrosis (Guo et al. 1988).

The neoplasms are similar at light and electron microscopic levels to those developing in other anatomic locations. The tumors consist of both small, round cells and elongated, spindle-shaped cells with a scarce, ill-defined cytoplasm and hyperchromatic nuclei with plump chromatin ("salt and pepper chromatin"). The tumors may contain multinucleated cells and foci of adenocarcinoma. The round cells are arranged in compact, solid sheets, with poor stroma. Rosette arrangements may occur. There is extensive necrosis with preservation of intact tumor tissue around blood vessels, as seen in other locations. The characteristic crush artifacts are seen (Albores-Saavedra et al. 1981; Guo et al. 1988; Johnstone et al. 1993; Muraina et al. 1996; Moskal et al. 1999; Matsuo et al. 2000). Intestinal metaplasia may develop (Kuwabara and Uda 1998). Immunohistochemically, part of the tumors are positive for cytokeratins and/or vimentin (Guo et al. 1988). Most of the tumors are typically positive for neuroendocrine lineage markers, especially chromogranin A (Matsuo et al. 2000; Nau et al. 2010) and synaptophysin and neuron-specific enolase (Cavazza et al. 1991). Ultrastructurally, the tumor cells contain typical, round neurosecretory granules (Albores-Saavedra et al. 1981; Larraza-Hernandez et al. 1984; Cavazzana et al. 1991). All small cell carcinomas of the gallbladder demonstrated inactivation of the pRB/p16 pathway; 67 % showed loss of pRB expression, and the other 33 % lost p16 expression. 83 % of the tumors accumulated high levels of p53, whereas activating K-ras mutations were not found (Parwani et al. 2003). For the gallbladder, several examples of mixed carcinomas consisting of adenocarcinoma and small cell carcinoma have been described (Muto et al. 1984; Duan et al. 1991; Nishihara et al. 1994a; Okamoto et al. 2003; Oshiro et al. 2008). Small cell carcinomas of the gallbladder may contain foci of adenosquamous carcinoma (Iida and Tsutsumi 1992). Squamous differentiation has been observed in small cell neuroendocrine carcinoma of the ampulla (Sugawara et al. 2004). Small cell carcinoma of the gallbladder was found to be combined with unusual other malignancies, such as clear cell carcinoma (Piana et al. 2002) or sarcomatoid carcinoma (Takahashi et al. 2004).

Non-neuroendocrine Type of Small Cell Carcinoma (NNE-SCC)

Small cell carcinoma of the gallbladder of the non-neuroendocrine type (NNE-SCC) forms an enigmatic and probably heterogeneous tumor group. Many of the examples of NNE-SCC described in the pre-immunohistochemistry era would now be reclassified as small cell neuroendocrine carcinomas (see below), but there remains a small group of neoplasms that represent undifferentiated carcinomas composed of small cells with scant cytoplasm in the absence of neuroendocrine marker expression. These neoplasms may exist as "pure" lesions or develop in combination with adenocarcinomas (Nishihara et al. 1994a; Moskal et al. 1999). Small cell carcinoma of the gallbladder may be situated in, or surrounded by, well-differentiated adenocarcinoma (Nishihara et al. 1994a), suggesting the emergence of an undifferentiated subclone.

Neuroendocrine Type of Small Cell Carcinoma (NE-SCC)

NE-SCC has first been described in 1981 by use of the term oat-cell carcinoma (Albores-Saavedra et al. 1981). Less than 100 cases have been reported since. These neoplasms are further discussed in the paragraph on neuroendocrine neoplasms of the gallbladder.

Selected References (Albores-Saavedra et al. 1984; Guo et al. 1988; Cavazzana et al. 1991; Duan et al. 1991; Iida and Tsutsumi 1992; Ron et al. 1992; Johnstone et al. 1993; Nishihara and Tsuneyoshi 1993; Muraina et al. 1996; Todoroki and Kawamoto 1996; Debois et al. 1998; Kuwabara and Uda 1998; Chuang et al. 1999; Matsuo et al. 2000; Mithal et al. 2000; Fujii et al. 2001; Maitra et al. 2001b; Pavithran et al. 2001; Lane et al. 2002; Piana et al. 2002; Okamoto et al. 2003; Parwani et al. 2003; Sengoz et al. 2003; Takahashi et al. 2004; Bahadur et al. 2005; Imai et al. 2008; Nishime et al. 2008; Uribe-Uribe et al. 2009; Nau et al. 2010; Ng et al. 2010; Usmani et al. 2010; Mahipal and Gupta 2011; Benkel et al. 2012).

Carcinoma of the Gallbladder with Osteoclast-Like Giant Cells

Introduction

Carcinomas with osteoclast-like giant cells are rare extraskeletal neoplasms composed of carcinoma of variable differentiation and numerous multinucleated giant cells in the stroma. This type of carcinoma most often occurs in the breast and in the pancreas, but it also develops in the extrahepatic bile duct system, including the gallbladder (Grosso and Gonzalez 1992; Ito et al. 1992; Amarapurkar et al. 2005; Akatsu et al. 2006; Albores-Saavedra et al. 2006). Carcinoma with osteoclast-like giant cells has to be distinguished from giant cell tumor with osteoclast-like giant cells or extraskeletal osteoclastoma, a benign neoplasm consisting of a mononuclear cell population and osteoclast-like giant cells, in the absence of carcinoma. Tumors located in the gallbladder may grow to relatively large and protruding lesions. As only very few cases have been documented, the biology of disease has not been systematically clarified. In one patient, the tumor metastasized to the liver, and this metastasis consisted predominantly of giant cells, with only a minor component of adenocarcinoma (Ito et al. 1992). The presence of giant cells in metastatic lesions has been confirmed in another study (Grosso and Gonzalez 1992).

Pathology

Histopathology

Histologically, the tumors reveal a basic proliferation of carcinoma being the main biologic feature of the neoplasm and an interstitium containing large multinucleated cells that are regarded as benign. The carcinomatous components were described as well-differentiated adenocarcinoma

(Ito et al. 1992) or adenosquamous carcinoma (Grosso and Gonzalez 1992; Akatsu et al. 2006). The carcinomatous components are spatially associated with monocytoid or macrophage-like mononuclear cells and multinuclear giant cells. The giant cells, representing fused macrophages, display a pale and slightly eosinophilic cytoplasm and contain dozens to more than 50 regularly structured nuclei which are ovoid and show a fine chromatin pattern, very much resembling nuclei of histiocytes. These osteoclast-like giant cells are usually distributed uniformly throughout the neoplasm. In the patient described by Ito and coworkers (1992), liver metastasis of the gallbladder carcinoma also showed osteoclast-like giant cells.

Immunohistochemistry

As in tumors with osteoclast-like giant cells located in other organs, the giant cells are reactive for markers of the monocyte/macrophage lineage, i.e., CD68 and HAM, whereas the macrophage-like mononuclear cells are CD163 positive (Albores-Saavedra et al. 2006).

Differential Diagnosis

Osteoclast-like giant cell tumor of the pancreas, where this lesion typically occurs, can metastasize to liver but also gallbladder (Sun et al. 1998). A second differential diagnosis is undifferentiated gallbladder carcinoma, giant cell type (Manouras et al. 2009), but the giant cells in this neoplasm are not osteoclast-like, CD68-positive elements, but epithelial tumor cells having a neoplastic character.

Carcinoma of the Gallbladder with Rhabdoid Features

Carcinomas with rhabdoid features are defined as usually poorly differentiated carcinomas containing a cell lineage resembling rhabdoid cells. In the gallbladder, a sarcomatoid carcinoma with rhabdoid features has been described. The tumor occurred in an elderly woman and presented macroscopically as a firm, solid, yellowish-gray, and granular mass with areas of necrosis. Histologically, the neoplasm was a biphasic sarcomatoid carcinoma consisting of pleomorphic cells, part of which of rhabdoid cell type, and neoplastic mucin-producing glandular structures. The rhabdoid cell co-expressed cytokeratins and vimentin, and ultrastructural examination revealed the typical cytoplasmic whorls of intermediate filaments. The tumor displayed an aggressive biology, with multiple intrahepatic metastases and omental seedings (Kim et al. 2003).

Differential Diagnosis

Differential diagnosis comprises metastases of other malignancies with rhabdoid features or the very rare primary rhabdoid tumor of the gallbladder (Suri et al. 2003).

References

Akatsu T, Kameyama K, Kawachi S, Tanabe M, Aiura K, Wakabayashi G, Ueda M et al (2006) Gallbladder carcinoma with osteoclast-like giant cells. J Gastroenterol 41:83–87

Akcali Z, Ozyilkan O, Sakalli H, Bal N, Noyan T (2005) Gallbladder adenosquamous cell carcinoma: report of two cases. Acta Gastroenterol Belg 68:440–442

Akiyama S, Tamura G, Endoh Y (2003) Histogenesis of hepatoid adenocarcinoma of the stomach: molecular evidence of identical origin with coexistent tubular adenocarcinoma. Int J Cancer 106:510–515

Albores-Saavedra J, Cruz-Ortiz H, Alcantara-Vazques A, Henson DE (1981) Unusual types of gallbladder carcinoma. A report of 16 cases. Arch Pathol Lab Med 105:287–293

Albores-Saavedra J, Soriano J, Larraza-Hernandez O, Aguirre J, Henson DE (1984) Oat cell carcinoma of the gallbladder. Hum Pathol 15:639–646

Albores-Saavedra J, Henson DE, Klimstra DS (1998) Tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater, 3rd edn. Armed Forces Institute of Pathology, Washington, DC, pp 63–92

Albores-Saavedra J, Grider DJ, Wu J, Henson DE, Goodman ZD (2006) Giant cell tumor of the extrahepatic biliary tree: a clinicopathologic study of 4 cases and comparison with anaplastic spindle and giant cell carcinoma with osteoclast-like giant cells. Am J Surg Pathol 30:495–500

Albores-Saavedra J, Batich K, Hossain S, Henson DE, Schwartz AM (2009) Carcinoid tumors and small-cell

carcinomas of the gallbladder and extrahepatic bile ducts: a comparative study based on 221 cases from the surveillance, epidemiology, and end results program. Ann Diagn Pathol 13:378–383

Albores-Saavedra J, Chable-Montero F, Angeles-Albores-D, Schwartz A, Klimstra DS et al (2011) Early gallbladder carcinoma: a clinicopathologic study of 13 cases of intramucosal carcinoma. Am J Clin Pathol 135:637–642

Al-Hady SM, Al-Saed A (1997) Primary keratinizing squamous cell carcinoma: an exceptional tumor of the gallbladder. Saudi J Gastroenterol 3:53–55

Alvarez-Perez JA, Vazquez Velsaco L, Gonzalez Gonzalez JJ, Seco Navedo M (1988) Epidermoid carcinoma of the gallbladder. Presentation of a new case (in Spanish). Rev Esp Enferm Apar Dig 74:691–692

Amarapurkar AD, Sangle N, Pandya JS, Jain A (2005) Unusual histologic variant of giant cell gall bladder carcinoma. J Postgrad Med 51:133–134

Ando K, Sakamoto Y (2009) A case of gallbladder metastasis from hepatocellular carcinoma. Jpn J Clin Oncol 39:540

Antonio J, Vitellas K, Frankel WL (2004) Hepatoid adenocarcinoma of the stomach. Ann Diagn Pathol 8:137–141

Azad A, Chionh F, Jayarajan J (2009) Gallbladder squamous cell carcinoma in the setting of low-dose methotrexate use. ANZ J Surg 79:662–663

Bagdasaryan R, Miroshnichenko H (2011) Adenosquamous cell carcinoma of the gallbladder. Med Health R I 94:19

Bahadur S, Shaukat A, Gibbs J, Litwin A, Nava H, Melnyk M, Javle M (2005) Cisplatin and gemcitabine for small cell carcinoma of the gall bladder. Am J Clin Oncol 28:425–426

Bartlett D, Fong Y, Fortner JG, Brennan MF, Blumgart LH (1996) Long-term results after resection for gallbladder cancer. Implications for staging and management. Ann Surg 224:639–646

Bartocci U, Carratu M (1964) Observations on adenoacanthoma of the gallbladder (in Italian). Gazz Int Med Chir 69:1465–1475

Benkel M, Brasch F, Neumann JD, Altendorf-Hofmann A, Sendt W (2012) Poorly differentiated neuroendocrine small-cell carcinoma of the gallbladder (in German). Zentralbl Chir 137:71–72

Benoist S, Panis Y, Fagniez PL, and the French University Association for Surgical Research (1998) Long-term results after curative resection for carcinoma of the gallbladder. Am J Surg 175:118–122

Botto Micca F, Coda R, Giordano F, Bona A, Bossotti M, Benedetto C (1997) Squamous carcinoma of the gallbladder. Anatomo-clinical study of a case with reference to oncogene expression (in Italian). Pathologica 89:77–80

Bouassida M, Mroua B, Douggaz A, Mighri MM, Touinsi H, Sassi S (2013) Primary pure squamous cell carcinoma of the gallbladder revealed by an acute angiocholitis (in French). Presse Med 42:110–113

Bourmèche M, Ben Salah H, Kallel M, Beyrouti MI, Makni S, Boudawara T, Frikha M et al (2013) A long survival after the treatment of a squamous cell carcinoma of the gallbladder (in French). Cancer Radiother 17:58–61

Cavazzana AO, Fassina AS, Tollot M, Ninfo V (1991) Small-cell carcinoma of gallbladder. An immunocytochemical and ultrastructural study. Pathol Res Pract 187:472–476

Chakrabarty I, Giri A, Ghosh N (2014) Cytohistopathological correlation of a case of squamous cell carcinoma of gallbladder with lymph node metastasis. Turk Patoloji Derg 30:81–84

Chan KM, Yu MC, Lee WC, Jan YY, Chen MF (2007) Adenosquamous/squamous cell carcinoma of the gallbladder. J Surg Oncol 95:129–134

Chang KM, Jeng KS, Yang FS, Chen BF (1998) Metastatic hepatocellular carcinoma presenting as hemocholecyst with perforation: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 61:613–618

Chuang SS, Lin CN, Chu CH, Chen FF (1999) Small cell carcinoma of the gallbladder: report of two cases. Pathol Oncol Res 5:235–238

Cintorino M, Cetta F, De Mauro D, Calfa C, Iudicone R, Del Vecchio MT (1981) Histogenesis of squamous cell carcinoma of the gallbladder. An anatomo-clinical case (in Italian). Arch De Vecchi Anat Patol 64:511–519

Crawford JM (1999) Carcinoma of the gallbladder. In: Cotran R, Kumar V, Collins T (eds) Robbins pathologic basis of diseases, 6th edn. W.B. Saunders, Philadelphia, p 899

Crooks D, Ermocilla R (1985) Primary squamous carcinoma of the gallbladder. Report of a case (in Spanish). Rev Med Panama 10:108–110

Damian U, Rumstadt B, Schilling D (2011) Acute squamous cell carcinoma of the gallbladder: a rare cause of acute cholecystitis (in German). Dtsch Med Wochenschr 136:1422–1425

Das DK, Tripathi RP, Bhambhani S, Chachra KL, Sodhani P, Malhotra V (1998) Ultrasound-guided fine-needle aspiration cytology diagnosis of gallbladder lesions: a study of 28 cases. Diagn Cytopathol 18:258–264

Debois JM, De Vriendt P, Charels K (1998) Small cell carcinoma of the gallbladder. Acta Chir Belg 98:110–112

Del Pozo AC, De Battista S, Velasco D, Pianzola H, Rodriguez J (2005) Epidermoid carcinoma of gallbladder: analysis of our casuistic (in Spanish). Acta Gastroenterol Latinoam 35:162–164

Donaldson LA, Busuttil A (1975) A clinicopathological review of 68 carcinomas of the gallbladder. Br J Surg 62:26–32

Donohue JH, Nagorney DM, Clive SG, Kenichi T, Douane MI, Martin AA (1990) Carcinoma of the gallbladder. Does radical resection improve outcome? Arch Surg 125:237–241

Duan HJ, Ishigame H, Ishii Z, Itoh N, Shigematsu H (1991) Small cell carcinoma of the gallbladder combined with adenocarcinoma. Acta Pathol Jpn 41:841–846

Ellouze S, Slim C, Ahmad G, Naourez G, Ali A, Héla M, Mariem K, Mohamed BA et al (2011) Hepatoid adenocarcinoma of the gallbladder. World J Surg Oncol 9:03

Ercolani G, Nagino M, Sano T, Kamiya J, Kondo S, Kanai M, Nishio H, Nimura Y (1999) Advanced adenosquamous carcinoma of the gallbladder with bilio-biliary fistula: an uncommon case treated by hepatopancreatoduodenectomy. Hepatogastroenterology 46:1650–1654

Farah-Klibi F, Ben rejeb M, Salah RB, Najeh N, Zaouche A, Ben Jilani S, Zermani R (2008) Adenosquamous carcinoma of the gallbladder (in French). Gastroenterol Clin Biol 32:632–634

Fujii H, Aotake T, Horiuchi T, Chiba Y, Imamura Y, Tanaka K (2001) Small cell carcinoma of the gallbladder: a case report and review of 53 cases in the literature. Hepatogastroenterology 48:1588–1593

Fujita T, Fukuda K, Ohmura Y, Nishi H, Mano M, Komatsubara S, Doihara H, Shimizu N (2005) Long-term survival of a patient with advanced adenosquamous carcinoma of the gallbladder after radical resection. J Hepatobiliary Pancreat Surg 12:147–150

Fukuda T, Ohnishi Y (1990) Gallbladder carcinoma producing human chorionic gonadotropin. Am J Gastroenterol 85:1403–1406

Gakiopoulou H, Givalos N, Liapis G, Agrogiannis G, Patsouris E, Delladetsima I (2007) Hepatoid adenocarcinoma of the gallbladder. Dig Dis Sci 52:3358–3362

Georgolios A, Batistatou A, Charalabopoulos A, Manolopoulos L, Charalabopoulos K (2006) The role of CD44 adhesion molecule in oral cavity cancer. Exp Oncol 28:94–98

Glehen O, Czyglik O, Donsbeck AV, Isaac S, Gilly FN, François Y, Vignal J (2000) Cancers vésiculaires de découverte fortuite. Ann Chir 125:137–143

Gomez N, Urrea I, Astudillio R (1990) Primary epidermoid carcinoma of the gallbladder. Acta Gastroenterol Latinoam 20:169–173

Grosso LE, Gonzalez JG (1992) Stromal osteoclast-like giant cells in an adenosquamous carcinoma of the gallbladder. Hum Pathol 23:703–706

Guo KJ, Yamaguchi K, Enjoji M (1988) Undifferentiated carcinoma of the gallbladder. A clinicopathologic, histochemical, and immunohistochemical study of 21 patients with a poor prognosis. Cancer 61:1872–1879

Gupta P, Gupta RK (2012) Preoperative diagnosis of squamous cell carcinoma of the gallbladder by ultrasound-guided aspiration cytology: clinical and cytological findings of nine cases. J Gastrointest Cancer 43:638–641

Gupta RK, Naran S, Lallu S, Fauck R, elAnsar A (2000) Fine needle aspiration cytodiagnosis of primary squamous cell carcinoma of the gallbladder. Report of two cases. Acta Cytol 44:467–471

Gupta S, Gupta SK, Aryya NC (2004) Primary squamous cell carcinoma of gallbladder presenting as acute cholecystitis. Indian J Pathol Microbiol 47:231–233

Han JK, Kim SH (2005) Hepatocellular carcinoma with unusual metastasis to the gallbladder (in Korean). Korean J Hepatol 11:180–182

Hanada M, Shimizu H, Takami M (1986) Squamous cell carcinoma of the gallbladder associated with squamous metaplasia and adenocarcinoma in situ of the mucosal columnar epithelium. Acta Pathol Jpn 36:1879–1886

Henson DE, Albores-Saavedra J, Corle D (1992) Carcinoma of the gallbladder: histologic types, stage of disease, grade, and survival rates. Cancer 70:1493–1497

Horio T, Ogata S, Sugiura Y, Aiko S, Kanai N, Matsunaga H, Maehara T (2009) Cholecystic adenosquamous carcinoma mimicking Mirizzi syndrome. Can J Surg 52:E71–E72

Hosseinzadeh M, Shokripur M, Salahi H (2012) Primary pure squamous cell carcinoma of gallbladder presenting as acute cholecystitis. Iran J Med Sci 37:271–273

Hou JZ, Zeng ZC, Sun J, Ji Y (2010) Conformal radiotherapy for squamous cell carcinoma of gallbladder: a case report. Case Rep Med 2010:645172

Iida Y, Tsutsumi Y (1992) Small cell (endocrine cell) carcinoma of the gallbladder with squamous and adenocarcinomatous components. Acta Pathol Jpn 42:119–125

Ikeda H, Sato Y, Yoneda N, Harada K, Sasaki M, Kitamura S, Sudo Y, Ooi A, Nakanuma Y (2012) a-Fetoprotein-producing gastric carcinoma and combined hepatocellular and cholangiocarcinoma show similar morphology but different histogenesis with respect to SALL4 expression. Hum Pathol 43:1955–1963

Imai H, Matsui S, Tokuyama Y, Osada S, Tomita H (2008) Small cell carcinoma of the gallbladder successfully treated by surgery and adjuvant chemotherapy. Am Surg 74:272–273

Ishikawa Y, Yoshida H, Mamada Y, Taniai N, Kawano Y, Mizuguchi Y, Kahsiwabara M et al (2004) Squamous cell carcinoma of gallbladder (in Japanese). J Nippon Med Sch 71:417–420

Ishikura H, Fukasawa Y, Ogasawara K, Natori T, Tsukada Y, Aizawa M (1985) An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report. Cancer 56:840–848

Ishikura H, Kishimoto T, Andachi H, Kakuta Y, Yoshiki T (1997) Gastrointestinal hepatoid adenocarcinoma: venous permeation and mimicry of hepatocellular carcinoma, a report of four cases. Histopathology 31:47–54

Ito M, Hsu CT, Naito S, Matsuo T, Onizuka S, Sekine I, Fujii H, Matsuoka Y (1992) Osteoclast-like giant cell tumor of the gallbladder. Virchows Arch A Pathol Anat Histopathol 420:359–366

Johnstone AK, Zuch RH, Anders KH (1993) Oat cell carcinoma of the gallbladder. A rare and highly lethal neoplasm. Arch Pathol Lab Med 117:1009–1012

Kais H, Hershkovitz Y, Sandbank J, Halevy A (2014) Port site metastases in squamous cell carcinoma of the gallbladder. Isr Med Assoc J 16:177–179

Kalayarasan R, Javed A, Sakhuja P, Agarwal AK (2013) Squamous variant of gallbladder cancer: is it different from adenocarcinoma? Am J Surg 206:380–385

Kamat R, Pandya J, Jashnati K, Antony AA (2001) Primary squamous cell carcinoma of gallbladder presenting as empyema. Bombay Hosp J 43:447–448

Kamata S, Kishimoto T, Kobayashi S, Miyazaki M (2008) Expression and localization of ATP binding cassette (ABC) family of drug transporters in gastric hepatoid adenocarcinomas. Histopathology 52:747–754

Karasawa T, Itoh K, Komukai M, Ozawa U, Sakurai I, Shikata T (1981) Squamous cell carcinoma of gallbladder. Report of two cases and review of the literature. Acta Pathol Jpn 31:299–308

Karlinger T (1956) Epidermoid carcinoma of the gallbladder; report of a case (in German). Zentralbl Pathol 81:689–695

Katsuragi M, Enomoto Y, Toyoda T, Nishimura Y, Uchida H, Ohnishi G, Tsutsumi M et al (1989) A case of gall bladder cancer with high level alpha-fetoprotein (in Japanese). Rinsho Hoshasen 34:371–374

Khaira HS, Awad RW, Thompson AK (1995) Squamous cell carcinoma of the gallbladder presenting with a biliary-colic fistula. Eur J Surg Oncol 21:581–582

Khan N, Afroz N, Haider N, Khan MA (2012) A case of pure endophytic squamous cell carcinoma of the gallbladder: a rare entity with aggressive behavior. Turk Patoloji Derg 28:181–183

Khoo JJ, Nurul AM (2008) A clinicopathological study of nine cases of gallbladder carcinoma in 1122 cholecystectomies in Johor, Malaysia. Malays J Pathol 30:21–26

Kim MJ, Yu E, Ro JY (2003) Sarcomatoid carcinoma of the gallbladder with a rhabdoid tumor component. Arch Pathol Lab Med 127:e406–e408

Kim WS, Jang KT, Choi DW, Choi SH, Heo JS, You DD, Lee HG (2011) Clinicopathologic analysis of adenosquamous/squamous cell carcinoma of the gallbladder. J Surg Oncol 103:239–242

Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, Jeon WK, Kim BI, Choi SH (2012) Clinical usefulness of endoscopic ultrasonography in the differential diagnosis of gallbladder wall thickening. Dig Dis Sci 57:508–515

Kinjo T, Taniguchi H, Kushima R, Sekine S, Oda I, Saka M, Gotoda T, Kinjo F, Fujita J et al (2012) Histologic and immunohistochemical analyses of a-fetoprotein-producing cancer of the stomach. Am J Surg Pathol 36:56–65

Kishimoto T, Yano T, Hiroshima K, Inayama Y, Kawachi K, Nakatani Y (2008) A case of a-fetoprotein-producing pulmonary carcinoma with restricted expression of hepatocyte nuclear factor-4a in hepatoid foci: a case report with studies of previous cases. Hum Pathol 39:1115–1120

Kobayashi A, Miyagawa S, Miwa S, Nomura K, Nakata T, Mihara M, Kusama K, Soeda J (2007) Radical surgery for advanced squamous cell carcinoma of the gallbladder: a report of three cases, including a 10-year survivor. Hepatogastroenterology 54:350–353

Kojima H, Sakaguchi Y, Fukui H, Tsujii T, Tsuruzono T, Nishimura K, Saito M (1994) A case of synchronous early gastric cancer and gallbladder adenosquamous carcinoma (in Japanese). Nihon Shokakibyo Gakkai Zasshi 91:80–83

Kondo M, Dono K, Sakon M, Shimizu J, Nagano H, Nakamori S, Umeshita K, Wakasa K et al (2002) Adenosquamous carcinoma of the gallbladder. Hepatogastroenterology 49:1230–1234

Koswara T, Marwoto W, Siregar NC, Gumay S, Azis H, Abdullah M, Himawan S (2007) Hepatoid carcinoma of the gallbladder. Acta Med Indones 39:179–182

Kumar A, Singh MK, Kapur BM (1994) Synchronous double malignant tumors of the gall bladder: a case-report of squamous cell carcinoma with an angiosarcoma. Eur J Surg Oncol 20:63–67

Kusakina GK, Nigmatulina AA (1980) Adenosquamous cancer of the gallbladder (in Russian). Arkh Patol 42:57–59

Kuwabara H, Uda H (1998) Small cell carcinoma of the gall-bladder with intestinal metaplastic epithelium. Pathol Int 48:303–306

Lada PE, Taborda B, Sanchez M, Tommasino J, Rosso FF, Gramatica L, Alecha GJ et al (2007) Adenosquamous and squamous carcinoma of the gallbladder (in Spanish). Cir Esp 81:202–206

Lane JE, Walker AN, Ayers GW, Foster JL, Williams JT (2002) Small-cell undifferentiated carcinoma of neuroendocrine type originating in the gallbladder. Curr Surg 59:495–497

Larraza-Hernandez O, Henson DE, Albores-Saavedra J (1984) The ultrastructure of gallbladder carcinoma. Acta Morphol Hung 32:279–293

Lee JH, Lee KG, Paik SS, Park HK, Lee KS (2011) Hepatoid adenocarcinoma of the gallbladder with production of alpha-fetoprotein. J Korean Surg Soc 80:440–444

Liu X, Sheng W, Wang Y (2012) An analysis of clinicopathological features and prognosis by comparing hepatoid adenocarcinoma of the stomach with AFP-producing gastric cancer. J Surg Oncol 106:299–303

Mahipal A, Gupta S (2011) Small-cell carcinoma of the gallbladder: report of a case and literature review. Gastrointest Cancer Res 4:135–136

Maitra A, Murakata LA, Albores-Saavedra J (2001a) Immunoreactivity for hepatocyte paraffin 1 antibody in hepatoid adenocarcinomas of the gastrointestinal tract. Am J Clin Pathol 115:698–694

Maitra A, Tascilar M, Hruban RH, Offerhaus GJ, Albores-Saavedra J (2001b) Small cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and molecular pathology study of 12 cases. Am J Surg Pathol 25:595–601

Manouras A, Genetzakis M, Lagoudianakis EE, Markogiannakis H, Papadima A, Agrogiannis G et al (2009) Undifferentiated giant cell type carcinoma of the gallbladder with sarcomatoid dedifferentiation: a

case report and review of the literature. J Med Case Rep 3:6496

Matsuo S, Shinozaki T, Yamaguchi S, Matsuzaki S, Takami Y, Hayashi T, Kanematsu T (2000) Small-cell carcinoma of the gallbladder: report of a case. Surg Today 30:89–93

Matsuta M, Ishikura H, Murakami K, Kagabu T, Nishiya I (1991) Hepatoid carcinoma of the ovary: a case report. Int J Gynecol Pathol 10:302–310

Milanes F, Causa A, Fernandez JT (1950) Epidermoid carcinoma of the gallbladder; anatomic and clinical studies of a case. Semin Med 57:983–988

Mingoli A, Brachini G, Petroni R, Antoniozzi A, Cavaliere F, Simonelli L, Chirletti P et al (2005) Squamous and adenosquamous cell carcinomas of the gallbladder. J Exp Clin Cancer Res 24:143–150

Mithal U, Heroor A, Khan K, Dudhat S, Jagannath P, Soman CS, Desouza LJ (2000) Small cell carcinoma of gall bladder. Indian J Gastroenterol 19:33

Miyazaki K, Tsutsumi N, Kiatahara K, Sasatomi E, Tokunaga O, Hisatsugu T (1995) Hepatopancreatoduodenectomy for squamous and adenosquamous carcinoma of the gallbladder. Hepatogastroenterology 42:47–50

Moskal TL, Zhang PJ, Nava HR (1999) Small cell carcinoma of the gallbladder. J Surg Oncol 70:54–59

Motoyama T, Aizawa K, Watanabe H, Fukase M, Saito K (1993) alpha-Fetoprotein producing gastric carcinomas: a comparative study of three different subtypes. Acta Pathol Jpn 43:654–661

Muraina OI, Tank R, Dhingra C, Vuletin JC, Colella F, Abdelsayed G, Pachter BR, Honikman L (1996) Small cell carcinoma of gallbladder: report of two cases. Am J Gastroenterol 91:792–794

Murakami M, Nagano H, Kobayashi S, Marubashi S, Noda T, Tomimaru T, Takeda Y et al (2008) A case of hepatocellular carcinoma with gall bladder metastasis (in Japanese). Gan To Kagaku Ryoho 35:2089–2091

Murata M, Tateishi H, Nishiyama H, Ito M, Zushi S, Imai Y, Nishikawa M, Kurokawa M et al (2001) A case of granulocyte-colony stimulating factor producing squamous cell carcinoma of the gall bladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 98:53–57

Musconi B (1963) Epidermoid carcinoma of the gallbladder. Etiopathogenetic considerations (in Italian). Arch Ital Mal Appar Dig 30:77–94

Muto Y, Uchimura M, Waki S, Hayshi T, Sameshima Y, Okamoto K (1982) Clinicopathologic study on adenosquamous carcinoma of the gallbladder and the bile duct (in Japanese). Jpn J Cancer Clin 28:440–444

Muto Y, Yamada M, Okamoto K, Uchimura M (1984) Small cell carcinoma of the gallbladder associated with an ordinary adenocarcinoma: a mixed type tumor. Ryukyu Med J 7:90–96

Nakashima H, Nagafuchi K, Satoh H, Takeda K, Yamasaki T, Yonemasu H, Kishikawa H (2000) Hepatoid adenocarcinoma of the gallbladder. J Hepatobiliary Pancreat Surg 7:226–230

Nau P, Liu J, Dillhoff M, Forster M, Hazey J, Melvin S (2010) Two cases of small cell carcinoma of the gallbladder. Case Rep Med 2010. pii:453624

Ng ES, Venkateswaran K, Ganpathi SI, Chuah BY (2010) Small cell gallbladder carcinoma complicated by paraneoplastic hyponatremia: a case report and literature review. J Gastrointest Cancer 41:264–268

Nishihara K, Tsuneyoshi M (1993) Small-cell carcinoma of the gallbladder – a clinicopathological, immunohistochemical and flow cytometric study of 15 cases. Int J Oncol 3:901–908

Nishihara K, Nagai E, Tsuneyoshi M, Nagashima M (1994a) Small-cell carcinoma combined with adenocarcinoma of the gallbladder. A case report with immunohistochemical and flow cytometric studies. Arch Pathol Lab Med 118:177–181

Nishihara K, Nagai E, Izumi Y, Yamaguchi K, Tsuneyoshi M (1994b) Adenosquamous carcinoma of the gallbladder: a clinicopathological, immunohistochemical and flow-cytometric study of twenty cases. Jpn J Cancer Res 85:389–399

Nishihara K, Takashima M, Furuta T, Haraguchi M, Tsuneyoshi M (1995) Adenosquamous carcinoma of the gall-bladder with gastric foveolar-type epithelium. Pathol Int 45:250–256

Nishime C, Ohnishi Y, Suemizu H, Tamaoki N, Kusumi T, Sato F, Yamazaki H, Nakamura M et al (2008) In vivo chemotherapeutic profile of human gallbladder small cell carcinoma. Biomed Res 29:251–256

Nishiwaki M, Kimura M, Gega M, Ohi Y, Nishioka A, Ashida H, Yamamura T, Utsunomiya J et al (1997) A case of adenocarcinoma of the gallbladder with lymph node metastasis showing hepatoid adenocarcinoma and producing alpha-fetoprotein (in Japanese). Nihon Shokakibyo Gakkai Zasshi 94:874–878

Noske A, Pahl S (2006) Combined adenosquamous and large-cell neuroendocrine carcinoma of the gallbladder. Virchows Arch 449:135–136

Occhionero F, Ricci G (1964) Adenoacanthoma of the gallbladder. Contribution to the knowledge of metaplastic processes (in Italian). Gazz Int Med Chir 69(suppl):3380–3386

Okamoto H, Miura K, Ogawara T, Fujii H, Matsumoto Y (2003) Small-cell carcinoma manifesting systemic lymphadenopathy combined with adenocarcinoma in the gallbladder: aggressiveness and sensitivity to chemotherapy. J Gastroenterol 38:801–805

Oohashi Y, Shirai Y, Wakai T, Nagakura S, Watanabe H, Hatakeyama K (2002) Adenosquamous carcinoma of the gallbladder warrants resection only if curative resection is feasible. Cancer 94:3000–3005

Oshiro H, Matsuo K, Mawatari H, Inayama Y, Yamanaka S, Nagahama K, Endo I, Shimada H et al (2008) Mucin-producing gallbladder adenocarcinoma with focal small cell and large cell neuroendocrine differentiation associated with pancreaticobiliary maljunction. Pathol Int 58:780–786

Otsuka S, Ito K, Hara A, Naruki Y, Matsuo K, Mizuochi K, Nakano M, Akima M (1982) Bile cytodiagnosis in a case of adenosquamous cell carcinoma of the gallbladder complicated by congenital dilatation of the common bile duct (in Japanese). Nihon Shokakibyo Gakkai Zasshi 79:1637–1642

Parwani AV, Geradts J, Caspers E, Offerhaus GJ, Yeo CJ, Cameron JL, Klimstra DS et al (2003) Immunohistochemical and genetic analysis of non-small cell and small cell gallbladder carcinoma and their precursor lesions. Mod Pathol 16:299–308

Pavithran K, Doval DC, Vaid AK, Verma RN (2001) Small cell carcinoma of the gall bladder: case report and review of literature. Trop Gastroenterol 22:170–171

Piana S, Carvazza A, Corrado S, Putino I, Gardini G (2002) Combined small cell carcinoma and clear cell carcinoma of the gallbladder: report of a case and review of the literature. Pathol Res Pract 198:821–824

Piehler JM, Crichlow RW (1978) Primary carcinoma of the gallbladder. Surg Gynecol Obstet 147:929–942

Principe A, Lugaresi ML, Lords RG, Golfieri R, Gallo MC, Bicchierri I, Polite E, Cavallari A (1997) Unsuspected carcinoma of the gallbladder: case report of trocar-site metastasis following laparoscopic cholecystectomy. Hepatogastroenterology 44:990–993

Priola I (1954) Primary carcinoma of the gallbladder with cornification of the flat epithelium (in Italian). Accad Medica 69:88–99

Rabinovitch J, Kieffer RS (1931) Squamous cell carcinoma of the gall bladder. Surg Gynecol Obstet 52:831–835

Ramia JM, Padilla D, Lopez R, Cubo T, Hernandez Calvo J (2002) Adenosquamous carcinoma of the gallbladder. What are the prognostic implications of this histologic variant? (in Spanish). Gastroenterol Hepatol 25:333–334

Rao S, Arya A, Aggarwal S, Gupta K, Arora R, Dhawan I (2007) Pure squamous cell carcinoma of the gall bladder. Indian J Pathol Microbiol 50:599–600

Rekik W, Ben Fadhel C, Boufaroua AL, Mestiri H, Khalfallah MT, Bouraoui S, Mzabi-Rgaya S (2011) Case report: primary pure squamous cell carcinoma of the gallbladder. J Visc Surg 148:e149–e151

Roa JC, Tapia O, Cakir A, Basturk O, Dursun N, Akdemir D, Saka B, Losada H, Bagci P et al (2011) Squamous cell and adenosquamous carcinomas of the gallbladder: clinicopathological analysis of 34 cases identified in 606 carcinomas. Mod Pathol 24:1069–1078

Ron IG, Wigler N, Ilie B, Chaitnik S (1992) Small cell carcinoma of the gallbladder: clinical course and response to chemotherapy. Tumori 78:207–210

Roppongi T, Takeyoshi I, Ohwada S, Sato Y, Fujii T, Honma M, Morishita Y (2000) Minute squamous cell carcinoma of the gallbladder: a case report. Jpn J Clin Oncol 30:43–45

Rustagi T, Rai M, Menon M (2011) Ruptured adenosquamous cell carcinoma of the gallbladder: case report and review of literature. Gastrointest Cancer Res 4:29–32

Ryu HS, Hwang ET, Choi CS, Kim TH, Yun KJ, Park DE (2009) A case of hepatocellular carcinoma invading the gallbladder misdiagnosed as a primary gallbladder carcinoma (in Korean). Korean J Hepatol 15:80–84

Saito A, Noguchi Y, Doi C, Mukai K, Fukuzawa K, Yoshikawa T, Amano T, Kondo J et al (1999) A case of primary adenosquamous/squamous cell carcinoma of gallbladder directly invaded duodenum. Hepatogastroenterology 46:204–207

Sakamoto K, Monobe Y, Kouno M, Moriya T, Sasano H (2004) Hepatoid adenocarcinoma of the gallbladder: case report and review of the literature. Pathol Int 54:52–56

Sakamoto K, Kimura N, Tokumura H, Ogasawara T, Moriya T, Sasano H (2005) Hepatoid adenocarcinoma of the gallbladder. Histopathology 47:649–651

Sato T, Koyama K, Yamauchi H, Matsuno S (1981) Early carcinoma of the gallbladder. Gastroenterol Jpn 16:459–464

Sengoz M, Abacioglu U, Salepci T, Eren F, Yumuk F, Turhal S (2003) Extrapulmonary small cell carcinoma: multimodality treatment results. Tumori 89:274–277

Sentani K, Oue N, Sakamoto N, Arihiro K, Aoyagi K, Sasaki H, Yasui W (2008) Gene expression profiling with microarray and SAGE identified PLUNC as a marker for hepatoid adenocarcinoma of the stomach. Mod Pathol 21:464–475

Shimoi K, Ohkusa T (1996a) Squamous cell carcinoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:338–340

Shimoi K, Ohkusa T (1996b) Adenosquamous cell carcinoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:314–317

Solivetti FM, Nasrollah N, Russo F, Spina C (1996) Epidermoid carcinoma of the gallbladder. Report of a rare case (in Italian). Radiol Med 91:661–662

Sons HU, Borchard F, Joel BS (1985) Carcinoma of the gallbladder: autopsy findings in 287 cases and review of the literature. J Surg Oncol 28:199–206

Soyama A, Tajima Y, Kuroki T, Tsuneoka N, Ohno S, Adachi T, Eguchi S, Kanematsu T (2011) Radical surgery for advanced pure squamous cell carcinoma of the gallbladder: report of case. Hepatogastroenterology 58:2118–2120

Stamatiadis AN, Papadimitriou C, Zombolas BT, Varatsos AA, Manouras AJ (1989) Adenosquamous carcinoma of the gallbladder (in Italian). Minerva Chir 44:2085–2087

Su JS, Chen YT, Wang RC, Wu CY, Lee SW, Lee TY (2013) Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: a literature review. World J Gastroenterol 19:321–327

Suganuma M, Marugami Y, Sakurai Y, Ochiai M, Hasegawa S, Imazu H, Matsubara T et al (1997) Cardiac metastasis from squamous cell carcinoma of gallbladder. J Gastroenterol 32:852–856

Sugawara G, Yamaguchi A, Isogai M, Watanabe Y, Kaneoka Y, Suzuki M (2004) Small cell neuroendocrine carcinoma of the ampulla of Vater with foci of squamous differentiation: a case report. J Hepatobiliary Pancreat Surg 11:56–60

Sun AP, Ohtsuki Y, Liang SB, Sonobe H, Iwata J, Furihata M, Takeuchi T, Qiu Y et al (1998) Osteoclast-like giant cell tumor of the pancreas with metastases to gallbladder and lymph nodes. A case report. Pathol Res Pract 194:587–594

Suri VS, Gondal R, Agarwal A, Malhotra V, Sakhuia P, Singhal S (2003) Primary rhabdoid tumor of the gallbladder: report of a case. Surg Today 33:464–466

Suster S, Huszar M, Herczeg E, Bubis JJ (1987) Adenosquamous carcinoma of the gallbladder with spindle cell features. A light microscopic and immunohistochemical study of a case. Histopathology 11:209–214

Takahashi Y, Fukushima J, Fukusato T, Shiga J (2004) Sarcomatoid carcinoma with components of small cell carcinoma and undifferentiated carcinoma of the gallbladder. Pathol Int 54:866–871

Tamura S, Kihara Y, Kakitsubata Y, Kakitsubata S, Iwata K, Higashi H, Setoguchi T et al (1993) Hepatocellular carcinoma invading the gallbladder: CT, arteriography and MRI findings. Clin Imaging 17:109–111

Terasaki S, Nakanuma Y, Terada T, Unoura M (1990) Metastasis of hepatocellular carcinoma to the gallbladder presenting massive intraluminal growth: report of an autopsy case. J Clin Gastroenterol 12:714–715

Todoroki T, Kawamoto T (1996) Oat cell carcinoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:251–255

Todoroki T, Kawamoto T, Otsuka M, Koike N, Yoshida S, Takada Y, Adachi S, Kashiwagi H et al (1999) Benefits for combining radiotherapy with aggressive resection for stage IV gallbladder cancer. Hepatogastroenterology 46:1585–1591

Tomono H, Fujioka S, Kato K, Aikawa K, Nimura Y (2000) Hepatopancreatoduodenectomy for squamous cell carcinoma of the gallbladder. Hepatogastroenterology 47:945–947

Tsuda T, Nakatani H, Tahara E, Sakamoto H, Terada M, Sugimura T (1989) HST1 and INT2 gene coamplification in a squamous cell carcinoma of the gallbladder. Jpn J Clin Oncol 19:26–29

Uribe-Uribe NO, Jimenez-Garduno AM, Henson DE, Albores-Saavedra J (2009) Paraneoplastic sensory neuropathy associated with small cell carcinoma of the gallbladder. Ann Diagn Pathol 13:124–126

Ushiku T, Shinozaki A, Shibahara J, Iwasaki Y, Tateishi Y, Funata N, Fukayama M (2010) SALL4 represents fetal gut differentiation of gastric cancer, and is diagnostically useful in distinguishing hepatoid gastric carcinoma from hepatocellular carcinoma. Am J Surg Pathol 34:533–540

Usmani S, Pazooki M, Bilgrami SF (2010) Small cell carcinoma of the gall-bladder: role of adjuvant chemotherapy. J Gastrointest Cancer 41:84–87

van den Bos IC, Hussain SM, Dwarkasing RS, Stoop H, Zondervan PE, Krestin GP, de Man RA (2007) Hepatoid adenocarcinoma of the gallbladder: a mimicker of hepatocellular carcinoma. Br J Radiol 80:e317–e320

Wagreich JM, Shapiro RS, Glajchen N, Seijo L (1998) MRI findings in adenosquamous carcinoma of the gallbladder. Clin Imaging 22:130–133

Waisberg J, Bromberg SH, Fares Franco MI, dos Santos PA, Castro MAP (2001) Squamous cell carcinoma of the gallbladder. Sao Paulo Med J/Rev Paul Med 119:43

Watanabe M, Hori Y, Njima T (1993) AFP producing carcinoma of the gallbladder. Dig Dis Sci 38:561–564

Wee A, Sampatanukul P, Vajragupta L (2004) Fine needle aspiration cytology of the liver. Year Book Publisher, Bangkok, pp 99–100

Willcox J, Chang FC (1993) Squamous cell carcinoma of the gallbladder. Kans Med 94:133–134

Xu WM, Li X, Hu QC, Song SL, Wang L, Wang YY (2012) Primary keratinizing squamous cell carcinoma of the gallbladder: report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 41:853–854

Yadav R, Jain D, Mathur SR, Sharma A, Iyer VK (2013) Gallbladder carcinoma: an attempt of WHO histological classification on fine needle aspiration material. Cytojournal 10:12

Yanagisawa N, Mikami T, Mitomi H, Saegusa M, Koike M, Okayasu I (2001) CD44 variant overexpression in gallbladder carcinoma associated with tumor dedifferentiation. Cancer 91:408–416

Ylagan LR, Scholes J, Demopoulos R (2000) Cd44: a marker of squamous differentiation in adenosquamous neoplasms. Arch Pathol Lab Med 124:212–215

Zambianchi C (1965) Adenoacanthoma of the gallbladder (in Italian). Ann Ital Chir 42:349–369

Cystic Epithelial Tumors and Mixed Neoplasms of the Gallbladder

152

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_152

Abstract

The gallbladder can be the primary site of rare cystic and mixed neoplasms. Cystadenoma and cystadenocarcinoma, now termed mucinous cystic neoplasms, very rarely develop in the wall of the gallbladder. These neoplasms can be restricted to the gallbladder or extend into the hepatoduodenal ligament. The malignant variant, cystadenocarcinoma, is an exceptionally rare neoplasm in the gallbladder. Sarcomatoid carcinomas, characterized by low differentiation and a marked spindle cell component, and various forms of carcinosarcoma can also develop as primary tumors in the gallbladder.

Cystadenoma and Cystadenocarcinoma of the Gallbladder

Introduction

Hepatobiliary cystadenoma and cystadenocarcinoma are rare primary neoplasms of the hepatobiliary tract, located in the liver substance of the extrahepatic biliary tract. Exceptionally, these tumors develop in the gallbladder. Cystadenomas and their malignant counterparts are characterized by conglomerates of macroscopically cystic lesions, the cysts being lined by a usually mucinous, much less often serous biliary-type epithelium. Underneath this epithelial lining, a cellular stroma may be in evidence, similar to the morphology found in other hepatobiliary cystadenomas and cystadenocarcinomas.

Cystadenoma of the Gallbladder

Relatively few reports documented the development of cystadenoma in the gallbladder (Botticelli and Ferrari De Gaetani 1968; Milicevic and Ostojic 1972; Mättig et al. 1982; Simmons et al. 1989; Devaney et al. 1994; Spector et al. 2003; Rooney et al. 2005; McCague et al. 2008; Gokalp et al. 2010). Similar to cystadenomas of the liver, gallbladder cystadenomas seem to prevail in females. Clinically, the tumors have caused upper abdominal pain, nausea, and vomiting, similar to other gallbladder tumors. Few patients experienced jaundice and/or fever. Cystadenoma may be limited to the gallbladder itself, producing a mass effect and sometimes massive gallbladder hydrops, but the neoplasms may also extend into the hepatoduodenal ligament and induce extrahepatic biliary obstruction (Mättig et al. 1982; Simmons et al. 1989). Sonography reveals medium-sized to large cystic lesions with multiple septal structures and sometimes papillary projections. On CT images, cystadenomas present as multilocular, multiseptated cystic structures originating from the gallbladder fossa. Low-density lesions (<30 H) with internal septa and nodules may be seen on CT.

Macroscopy

Macroscopically, gallbladder cystadenoma presents as well-delineated multicystic tumors with rather thin septa dividing the cysts from each other. In rare instances, cystadenoma formed a large polypoid mass that may prolapse into the common bile duct (McCague et al. 2008). The cysts contain a clear or opaque fluid that is sometimes viscid and with a positive spinning phenomenon (mucin-containing fluid). Some cysts may contain a hemorrhagic fluid or a coagulated proteinaceous matter.

Histopathology

Histologically, cysts are lined by a single layer of biliary-type epithelium or a pseudostratified biliary epithelium. Small papillary projections may develop. The cells are cuboid to prismatic, with a basally placed nucleus and a clear cytoplasm toward the cellular apex. In PAS and alkaline Alcian blue stains, the apical half of the cytoplasm shows accumulation of mucin. The nuclei resemble in shape and structure to cholangiocyte nuclei,

but they are slightly larger and may show a more coarse chromatin pattern, but nuclear atypias are usually of minor degree, and mitotic figures are hardly found. The subepithelial stroma is either poorly developed or may show the cellular features known from other hepatobiliary cystadenomas occurring in female patients.

Immunohistochemistry

Immunohistochemically, the tumor cells share an immunophenotype with cholangiocytes, being positive for cytokeratins 7 and 19. Whether stromal cells express sex steroid receptors, as seen in other hepatobiliary cystadenomas, is not known.

Cystadenoma Associated with Multiseptate Gallbladder

Gallbladder cystadenoma with transition to carcinoma has been found in conjunction with a multiseptate gallbladder, resulting in a unique clinico-radiologic phenotype (Sugawara et al. 2001). Multiseptate gallbladder is an extremely rare congenital anomaly characterized by multiple thin septa dividing the gallbladder lumen and sometimes resulting in a honeycomb appearance. The septa contain a muscular layer than is continuous with muscle of the gallbladder wall (Okuda et al. 1979; Isomoto et al. 1990; Strauss et al. 1993; Sugawara et al. 2001).

Cystadenocarcinoma of the Gallbladder

Cystadenocarcinoma of the gallbladder is even less common than cystadenoma. This phenomenon reflects what is known for other hepatobiliary cystadenomatous tumors, where carcinoma is an exceptional finding. In part of the cases, the tumor was clinically circumscribed, without evidence of malignancy, and diagnosis of carcinoma was found at histopathologic examination only (Nakagawa et al. 1990; Sistla et al. 2009). However, there are also observations documenting a clinically aggressive behavior of these neoplasms. In a 75-year-old man a multicystic tumor of 16 cm diameter was detected, showing the histology of cystadenocarcinoma. The neoplasm was invasive and had caused locoregional lymph node metastases. After extended resection, the patient remained without evidence of recurrence 12 months after surgery (Waldmann et al. 2006). In one patient, cystadenocarcinoma was associated with gallbladder cystadenoma (Terada et al. 2003), suggesting an adenoma-carcinoma sequence. In this case, dysplastic mucinous cells malignant papillotubular cells and invasive carcinoma cells were observed in the center of the tumor, while the cystadenoma component was localized to peripheral parts of the tumor. No ovarian-like stroma was detectable.

Differential Diagnosis

Radiologically, cystadenomatous tumors of the gallbladder may be mimicked by cystic gallbladder lymphangioma (Shikano et al. 2008), markedly cystic dilatation of Aschoff-Rokitansky sinuses, epithelial cysts of the gallbladder (Matsumoto et al. 2002), and hydatid gallbladder disease (Pitiakoudis et al. 2006). Very rarely, cystadenoma develops on the peritoneal surface and may involve the gallbladder niche (Krstic et al. 2005).

Spindle Cell Carcinoma (Sarcomatoid Carcinoma) of the Gallbladder

Introduction

Undifferentiated spindle cell carcinoma (SpCC) or sarcomatoid carcinoma of the gallbladder is a rare primary gallbladder malignancy. The nomenclature and classification of this type of carcinoma was complex and in part confusing, because at least three terms have been employed to denote this neoplasm, viz., spindle cell carcinoma, undifferentiated carcinoma (in part), sarcomatoid carcinoma, and carcinosarcoma. All three terms are based on the observation

that these carcinomas contain a spindle cell component that looks mesenchymal, suggesting the synchronous presence of an epithelial and non-epithelial cell lineage. This view has been changed by immunohistochemistry showing that the spindle cells co-express epithelial and mesenchymal markers. The finding of a bimodal differentiation pattern has led to the hypothesis that the spindle cell component is the dedifferentiated offspring of typical adenocarcinoma that co-occurs with spindle cell carcinoma in these lesions. A novel interpretation suggests that these neoplasms involve epithelial-mesenchymal transition.

In the present chapter, only carcinomas showing a spindle cell component, and not other heterologous components, are discussed. In addition, spindle cell carcinomas briefly discussed here are not those that are classified as "undifferentiated carcinoma" (Badmos et al. 2013; see the respective paragraph), although a marked overlap exists. The term carcinosarcoma should be reserved to malignancies in which the sarcomatous components consist of atypical mesenchymal elements other than cytokeratin-positive spindle cells, e.g., myosarcomatous, fibrosarcomatous, or osteosarcomatous components. The more precise definition of gallbladder carcinomas with a spindle cell component has to await novel criteria, including molecular features.

Epidemiology

Less than 20 cases have been reported, mostly involving patients older than 50 years, with females being more often involved than males (Iezzoni and Mills 1993; Nishihara and Tsuneyoshi 1993; Hotta et al. 2002; Arakawa et al. 2004; Takahashi et al. 2004; Akatsu et al. 2005; Kubota et al. 2006; Liu et al. 2009). In a study on 11 patients (8 women, 3 men), age at diagnosis ranged from 59 to 80 years (mean, 66.5 years) (Nishihara and Tsuneyoshi 1993). In a group of six patients, age at diagnosis ranged from 51 to 66 years (median, 58 years); five were females, one male (Liu et al. 2009).

Clinical and Imaging Features

Similar to other carcinomas of the gallbladder, the clinical presentation is nonspecific and consists of upper abdominal pain and fullness, weight loss, fever, and other systemic signs and symptoms of malignancy. On CT images, a thickening of the gallbladder wall is seen, similar to what is found on other invasive carcinomas of the gallbladder (Akatsu et al. 2005). SpCC are aggressive tumors with a poor outcome, even after curative resection and postoperative chemotherapy (Nishihara and Tsuneyoshi 1993; Liu et al. 2009).

Pathology

Macroscopy

The few cases where macroscopic features have been documented illustrate solid tumors with necrotic centers or polypoid lesions with an endoluminal growth pattern (Kubota et al. 2006).

Histopathology

The diagnostic feature of SpCC is hypercellular areas consisting of spindle cells that proliferate in a whirling or interlacing pattern. These elongated cells have a slightly eosinophilic or amphophilic cytoplasm and ovoid or oblong nuclei with minor atypia. Mitotic figures may be noted. SpCC may contain components of adenocarcinoma, with a gradual transition between the two different components (Akatsu et al. 2005). Foci of adenocarcinoma were detected in 8 out of 11 patients in one study. Two of the cases also had small foci of neoplastic squamous epithelium (Nishihara and Tsuneyoshi 1993). A case with undifferentiated small cell carcinoma was also described (Takahashi et al. 2004).

Immunohistochemistry

The neoplastic spindle cells are immunoreactive for cytokeratins, showing their epithelial character, but the cells also co-express vimentin

(Nishihara and Tsuneyoshi 1993; Kubota et al. 2006). In the largest published series (11 patients), AE1/AE3 was positive in nine, EMA in nine, and vimentin in eight cases (Nishihara and Tsuneyoshi 1993). The proliferative activity, as detected by Ki-67 immunostaining, was higher for spindle cells than for adenocarcinoma cells (Kubota et al. 2006).

Pathogenic Pathways

A common origin of spindle cells and conventional adenocarcinoma cells has been proposed, with spindle cells originating from carcinoma through dedifferentiation (Akatsu et al. 2005). A pluripotent progenitor cell may also be involved, similar to what has been proposed for carcinosarcomas (Ajiki et al. 2002). In SpCCs, homogeneous allelic losses (chromosomes 5q, 11q, 17p, and 18q) were identified in both the carcinomatous and sarcomatoid components, suggesting that SpCC had a single clonal origin (Arakawa et al. 2004). This hypothesis has also been formulated to explain the concurrent development of epithelial and mesenchymal cell lineages in carcinosarcomas. As the spindle cells in SpCC exhibit an epithelial immunophenotype, epithelial-mesenchymal transition (EMT) may also represent a pathogenic pathway operational in spindle cell carcinomas occurring in various organs.

Gallbladder Carcinoma with Osseous Stromal Metaplasia and Calcified Gallbladder Carcinoma

Introduction

Stromal osseous metaplasia (SOM) denotes an alteration in certain carcinomas characterized by the development of bone, mainly osteoid trabecules, within the fibroblastic (desmoplastic stroma), this bone being reactive rather than neoplastic. An alternative term is metaplastic stromal ossification. SOM has been found in several types of carcinomas, including colorectal carcinoma (Arnal Monreal et al. 1992; Pai et al. 1993), breast cancer (Kijima et al. 2006; Tsukuda et al. 2009), squamous cell carcinomas (Marioni et al. 2004), renal cell carcinoma (Kuroda et al. 2005), urothelial carcinoma (Mege-Lechevallier et al. 2007), ovarian carcinoma (Mukonoweshuro and Oriowolo 2005), and hepatocellular carcinoma (Leger et al. 1980; Maeda et al. 1986).

Stromal Osseous Metaplasia in Gallbladder Tumors

Extensive osseous metaplasia was observed in metastases of a gallbladder adenocarcinoma (Cavazza et al. 1999).

Differential Diagnosis

The main differential diagnosis are carcinosarcomas of the gallbladder having an osteosarcomatous component (Nakagawa et al. 1996). These lesions can be distinguished based on the atypical bone formation with malignant osteoblasts, while metaplastic bone in tumor stroma is reactive and presents as any immature normal bone.

Pathogenic Pathways

Tumor stroma cell populations contain mesenchymal stem cells that harbor an osteoprogenitor cell lineage. This type of pluripotent mesenchymal cells seems also to be present in the gallbladder wall, as bone metaplasia may occur in chronic cholecystitis and other reactive chronic gallbladder disorders (Indyk and Shipton 1957; Duchini 1967; Yosepovich et al. 2002).

Calcified Carcinoma of the Gallbladder

Calcified carcinoma is a very rare entity characterized by the presence of extensive calcification within an adenocarcinoma. In one case of calcified gallbladder carcinoma, the calcified deposits were

located within or replaced the glandular structures of the carcinoma, but were not detectable in the stroma. Extensive cancer calcification was also found in lymph node metastases (Yun et al. 2011).

Carcinosarcoma and "Malignant Mixed Tumors" of the Gallbladder

ICD-O code 8980/3

Introduction

Carcinosarcoma of the gallbladder is a very rare and highly aggressive tumor of unknown histogenesis characterized by malignancy of both epithelial and mesenchymal components of the same tissue, forming a complex mixture of neoplastic lineages. The term, carcinosarcoma, was coined in 1864 by Rudolf Virchow (1864). Carcinosarcomas can occur in almost all organs, but they are most common in the uterus. The first case of carcinosarcoma of the gallbladder was reported in 1907 by Landsteiner, who identified this type of tumor in a museum specimen (Landsteiner 1907). Since then, less than 100 cases have been reported in the literature.

Epidemiology

Carcinosarcoma of the gallbladder is one of the rarest malignancies of this organ and is reported to account for 1.7 % of all malignant gallbladder tumors (Born et al. 1984). The tumor is usually associated with cholelithiasis (present in 83 %; Roth et al. 1972) and mainly occurs in females in the sixth decade of their lives, the age range at diagnosis being from 45 to 91 years. In a review as of 2009 (Kohtani et al. 2009), only nine patients reported up to 2009 were older than 80 years at diagnosis, eight females and one male. After the first description in 1907 there was a time gap before very few additional tumors were reported (Kritsch 1925; Kleinknecht et al. 1931), followed by more cases to be described after the 1950s.

Selected References Klein et al. 1961; Knorr 1963; Billi 1964; Mehrotra et al. 1971; Wolfensberger 1971; Yamagiwa 1971; Roth et al. 1972; Sagi and Gyori 1972; Higgs et al. 1973; Lorenz 1974; Stempinski and Beger 1974; Herrero Zapatero et al. 1980; Mansori and Cho 1980; Zapatero et al. 1980; Cardia and Resta 1981; Aldovini et al. 1982; Carlson and McPherson 1982; Von Kuster and Cohen 1982; Yamagiwa et al. 1982; Miyamoto et al. 1983; Born et al. 1984; Coverlizza and Risio 1985; Lopez et al. 1985; Rodriguez Rodriguez et al. 1985; Bousquet et al. 1986; Grote and Kaemmerer 1986; Inoshita et al. 1986; Hasegawa et al. 1987; Herrera-Goepfert et al. 1987; Yamamoto et al. 1987; Lumsden et al. 1988; Ishihara et al. 1990; Mizuno et al. 1990; Nishihara et al. 1990; Sai et al. 1991; Kitagawa et al. 1992; Nakazawa et al. 1992; Emmoto et al. 1993; Fagot et al. 1994; Alvarez et al. 1995; Uesaka et al. 1995; Nakagawa et al. 1996; Taniguchi et al. 1996; Morrone et al. 1997; Nishikage et al. 1997; Rys et al. 1998; Tohsha et al. 1998; Eriguchi et al. 1999; Yavuz et al. 2000; Ajiki et al. 2002; Al-Sheneber et al. 2002; Hotta et al. 2002; Kim et al. 2003, 2012; Boulanger et al. 2004; Takahashi et al. 2004; Huguet et al. 2005; Sodergren et al. 2005; Kubota et al. 2006; Oberoi et al. 2006; Zhang et al. 2008; Agarwal et al. 2009; Kohtani et al. 2009; Liu et al. 2009; Okabayashi et al. 2009; Shimada et al. 2009; Uzun et al. 2009; Pu and Wu 2011; Krishnamurthy et al. 2011; Ishida et al. 2012; Park et al. 2012; Parreira et al. 2012; Sadamori et al. 2012; Khanna et al. 2013; Li et al. 2013; Wang et al. 2013 .

Clinical and Imaging Features

Clinical features include an upper abdominal mass, pain in the right hypochondrium (sometimes colicky pain, chiefly in the presence of stones), fever, malaise, and weight loss. Colicky pain may sometimes be due to the synchronous presence of gallstones, cholecystolithiasis being present in more than 70 % of patients. Carcinosarcoma of the

gallbladder can invade the extrahepatic bile duct system and form obstructing bile duct tumor thrombi (Wang et al. 2013). Carcinosarcoma may produce marked hemorrhage and cause hemobilia (Sadamori et al. 2012). Carcinosarcoma of the gallbladder may rarely produce paraneoplastic syndromes. Leukocytosis caused by secretion of granulocyte colony-stimulating factor by the tumor was observed (Shimada et al. 2009).

Carcinosarcoma of the gallbladder is a highly aggressive neoplastic disorder with a dismal prognosis which, so far, is usually treated by surgery, as optimal adjuvant chemotherapy and/or radiotherapy protocols are not yet available. In a literature review of 36 published cases of tumors treated with surgical resection, the 3-year overall survival rate was only 31.0 % and the median survival time was 7.0 months (Okabayashi et al. 2009). However, single cases with more favorable outcome following surgery and chemotherapy have also been reported (e.g., no evidence of disease 48 months after surgery; Kohtani et al. 2009). Currently, carcinosarcoma cannot yet stratified as to risk of progression and poor outcome, but tumor size seems to be a prognosticator, as tumors which were smaller than 5 cm in diameter were associated with long survival (Zhang et al. 2008). On the other hand, TNM stage is not a predictor of outcome. In studies comparing T stages II–IV it turned out that mean survival time was low regardless of the T status (Lumsden et al. 1988; Fagot et al. 1994; Liu et al. 2009).

Ultrasonography, CT, and ERCP usually disclose large and sometimes ill-defined gallbladder masses with or without associated gallstones (Hotta et al. 2002). A solid mass containing cystic patencies is sometimes seen on abdominal ultrasonography (Uzun et al. 2009). CT often shows a dilated gallbladder with irregular thickening of the wall and an intraluminal mass (Born et al. 1984; Eriguchi et al. 1999). Calcification within the tumor may be noted (Grote and Kaemmerer 1986) and may in fact lead to diagnosis (Ishida et al. 2012). On CT, the pericholecystic mass may invade adjacent organs, e.g., the hepatic flexure of the colon (Huguet et al. 2005). Rarely, the tumor presented with a huge cystic lesion (Emmoto et al. 1993).

Pathology

Macroscopy

Gallbladder carcinosarcomas are typically large and friable masses of whitish-gray color, showing variable degrees of hemorrhage and necrosis. The tumor can present with endophytic growth, forming polypoid masses (Bousquet et al. 1986; Inoshita et al. 1986; Lumsden et al. 1988; Fagot et al. 1994; Ajiki et al. 2002; Takahashi et al. 2004; Uzun et al. 2009). In tumors with chondroid and/or osteoid differentiation, cartilaginous components may be visualized as pale and transparent parts that are more form than the other tissues, while osteosarcoma may be seen as whitish and firm speckles with or without gross calcifications. In rare cases, the tumor can invade the bile duct system, forming bile duct tumor thrombi resulting in biliary obstruction (Wang et al. 2013).

Histopathology

The epithelial component is usually adenocarcinoma with variable tubular components, but squamous cell carcinoma and mixed adenocarcinoma and squamous cell carcinoma are also known (Herrera-Goepfert et al. 1987; Krishnamurthy et al. 2011; Park et al. 2012). Rarely, the carcinomatous component consisted of small cells and undifferentiated cells (Takahashi et al. 2004). At least at certain places, the diverse types of carcinoma cells blend more or less continuously with sarcoma cells, a characteristic feature of carcinosarcomas.

A frequent mesenchymal component are dense accumulations of spindle cells (Fagot et al. 1994; Hotta et al. 2002; Takahashi et al. 2004; Kubota et al. 2006; Uzun et al. 2009). This cell type is sometimes closely intermingled with epithelial cells forming tubules, or shows apparent transition to epithelial cells, suggesting epithelial-mesenchymal transition. In few cases, the spindle cell component has been termed, fibrosarcoma

(Von Kuster and Cohen 1982; Born et al. 1984). Spindle cell sarcoma has been found in combination squamous cell carcinoma (Kitagawa et al. 1992; Huguet et al. 2005). Chondroid neoplastic tissue is a well-known heterologous component (Mansori and Cho 1980; Von Kuster and Cohen 1982; Ajiki et al. 2002; Oberoi et al. 2006). These components appear as small and in part nodular islands of chondroid tissue with variable amounts of cartilage matrix and atypical chondroblasts. These foci sometimes show a direct transition into adenocarcinoma, a phenomenon that has led to terms such as adenocarcinoma with chondrosarcomatous component (Zheng et al. 2006). In contrast to the presence of chondroid/chondrosarcomatous tissue, an osteosarcomatous component is rare (Aldovini et al. 1982; Nakagawa et al. 1996). The tumor described by Aldovini et al. (1982) showed close intermingling of epithelial and mesenchymal components and malignant osteoblasts representing osteosarcoma and was interpreted as malignant mixed mesodermal tumor of the gallbladder. In gallbladder carcinosarcoma, adenocarcinoma can coexist with rhabdomyosarcoma of variable differentiation. In one case, the rhabdomyoblastic cells were immunoreactive for myoglobin, myosin, and muscle actin, and ultrastructurally they showed various stages of rhabdomyoblastic differentiation (Ishihara et al. 1990).

Leiomyosarcoma is a very rare component, or has at least only rarely identified as such (Yamagiwa 1971), what may be related to the lack of immunohistochemical techniques in older studies. In a minority of cases, the mesenchymal component presents as undifferentiated sarcoma with round and/or pleomorphic cells (Herrera-Goepfert et al. 1987). The presence of rhabdoid tumor tissue components in gallbladder carcinosarcoma is an exceptional finding. In one tumor observed in a 61-year-old female, the neoplasm revealed a biphasic sarcomatoid carcinoma with diffusely arranged pleomorphic cells, focally showing rhabdoid features, and neoplastic glands with focal mucin production. Immunohistochemically, the rhabdoid cells co-express cytokeratin and vimentin (Kim et al. 2003). Cases with combined heterologous elements are known, e.g., osteoid, cartilage, and rhabdomyoblasts. In one of such tumors, the metastases only showed a combination of adenocarcinoma and rhabdomyosarcoma (Inoshita et al. 1986).

Immunohistochemistry

In the light of the dual differentiation of carcinosarcomas, immunohistochemical investigations are an inevitable method for diagnosis and differential diagnosis. Spindle cell components are reactive for both cytokeratins and vimentin (Hotta et al. 2002; Uzun et al. 2009), suggesting that this cell lineage has undergone mesenchymal-epithelial transition (MET), although cytokeratin reactivity of spindle cells is sometimes weak (Kubota et al. 2006), and there are tumors in which spindle cells exclusively express vimentin (Khanna et al. 2013). Also the cells found in chondroid components express, in addition to vimentin, cytokeratins (Ajiki et al. 2002).

Variants of Carcinosarcoma of the Gallbladder

Exceptionally, synthesis and secretion of AFP was detected in these tumors, a phenomenon also present in subsets of bile duct and gallbladder carcinomas. In a 69-year-old male patient with elevated serum AFP, gallbladder carcinosarcoma was immunoreactive for AFP. This tumor also produced granulocyte colony-stimulating factor associated with peripheral leukocytosis as a paraneoplastic syndrome (Shimada et al. 2009).

Malignant Mixed Tumors of the Gallbladder

Several examples of malignant gallbladder neoplasms characterized by complex mixtures of carcinomatous and various mesenchymal components have previously been described by use of the terms, malignant mixed tumor or malignant

mixed mesodermal tumor. These lesions should now be classified as carcinosarcomas (Sagi and Gyori 1972; Higgs et al. 1973; Mansori and Cho 1980; Aldovini et al. 1982; Carlson and McPherson 1982; Von Kuster and Cohen 1982). However, some of the neoplasms exhibit a highly complex composition and appear as multilineage tumors. For example, mixed adenoneuroendocrine carcinoma of the gallbladder also showed squamous cell carcinomatous and osteosarcomatous differentiation (Shintaku et al. 2013).

Differential Diagnosis

Carcinosarcoma has to be distinguished from carcinomas with a spindle cell component, a feature also seen in variants of undifferentiated carcinoma of the gallbladder.

Pathogenesis

The histogenesis of carcinosarcoma has not been elucidated. Some authors proposed an origin from mesenchymal (stromal) cells present in adenocarcinomas and other types of carcinomas (Kadono et al. 2005). Potential pathogenic mechanisms also include epithelial-mesenchymal transition resulting in diverse types of heterologous components. Epithelial-mesenchymal transition has been documented in pulmonary carcinosarcoma (Thomas et al. 2012) and in uterine carcinosarcoma, where a role of the Akt/beta-catenin pathway (Saegusa et al. 2009) and of several species of microRNA (Castilla et al. 2011) has been discovered. Finally, an origin from a pluripotent tumor stem or progenitor cells capable to be primed for several cell lineages may be anticipated.

References

Agarwal T, Jain M, Goel A, Visayaragavan P, Gupta RK (2009) Carcinosarcoma of the gallbladder. Indian J Pathol Microbiol 52:244–245

Ajiki T, Nakamura T, Fujino Y, Suzuki Y, Takeyama Y, Ku Y, Kuroda Y, Ohbayashi C (2002) Carcinosarcoma of the gallbladder with chondroid differentiation. J Gastroenterol 37:966–971

Akatsu T, Ueda M, Shimazu M, Wakabayashi G, Aiura K, Tanabe M, Kawachi S, Kameyama K et al (2005) Primary undifferentiated spindle-cell carcinoma of the gallbladder presenting as a liver tumor. J Gastroenterol 40:993–998

Aldovini D, Piscioli F, Togni R (1982) Primary malignant mixed mesodermal tumor of the gallbladder. Report of a case and critical review of diagnostic criteria. Virchows Arch A Pathol Anat Histol 396:225–230

Al-Sheneber IF, Jaber T, Huttner I, Arseneau J, Loutfi A (2002) Carcinosarcoma of the gallbladder: a case report and review of the literature. Saudi J Gastroenterol 8:22–24

Alvarez JA, Fernandez R, Aramburo J, Fradejas JM, Velasco A, Moreno M (1995) Carcinosarcoma of the gallbladder (in Spanish). Gastroenterol Hepatol 18:81–83

Arakawa A, Fujii H, Matsumoto T, Hirai S, Suda K (2004) Loss of heterozygosity in clonal evolution with genetic progression and divergence in spindle cell carcinoma of the gallbladder. Hum Pathol 35:418–423

Arnal Monreal F, Lorenzo Patino MJ, Alvarez Garcia A (1992) Bone metaplasia in colorectal carcinoma (in Spanish). Rev Esp Enferm Dig 82:121–122

Badmos KB, Salah Seada L, Fahad Al Rashid F, Oreiby HA (2013) Undifferentiated spindle-cell carcinoma of the gallbladder: a report of a case, an immunohistochemistry profile, and a review of the literature. Case Rep Pathol 2013:267194

Billi C (1964) Su di un singolare caso di tumore della cholecisti. Acta Chir Ital 20:343–362

Born MW, Ramey WG, Ryan SF, Gordon PE (1984) Carcinosarcoma and carcinoma of the gallbladder. Cancer 53:2171–2177

Botticelli A, Ferrari De Gaetani C (1968) A case of cystic adenoma of the gallbladder (in Italian). Arch De Vecchi Anat Patol 52:729–741

Boulanger L, Picod G, Leduc F, Adams P, Bounoua F, Duval G (2004) Carcinosarcoma of the gallbladder (in French). J Chir (Paris) 141:52–54

Bousquet JC, You K, Cortez A, Grellet J, Vayre P (1986) Carcinosarcoma of the gallbladder. Echographic and anatomopathological diagnosis. Apropos of a case with review of the literature (in French). J Radiol 67:719–723

Cardia G, Resta L (1981) Recurrent carcinosarcoma of the gallbladder (in Italian). Pathologica 73:533–539

Carlson BR, McPherson FT (1982) Malignant mixed tumor of the gallbladder. J Miss State Med Assoc 23:133–135

Castilla MA, Moreno-Bueno G, Romero-Pérez L, Van De Vijver K, Biscuola M, Lopez-Garcia MA et al (2011) Micro-RNA signature of the epithelial-mesenchymal transition in endometrial carcinosarcoma. J Pathol 223:72–80

Cavazza A, De Marco L, Asioli S, Pastore L, Gardini G (1999) Stromal osseous metaplasia in metastatic adenocarcinoma of the gallbladder. Tumori 85:133–134

Coverlizza S, Risio M (1985) Malignant mixed tumors of the gallbladder. Report of a case and review of the literature(in Italian). Pathologica 77:209–213

Devaney K, Goodman ZD, Ishak KG (1994) Hepatobiliary cystadenoma and cystadenocarcinoma. A light microscopic and immunohistochemical study of 70 patients. Am J Surg Pathol 18:1078–1091

Duchini L (1967) Apropos of a case of ossification of the gallbladder. Contribution to the study of heterotopic ossifications (in Italian). Arch De Vecchi Anat Patol 50:537–552

Emmoto T, Nakanishi M, Ohsawa J, Nonaka M, Kanaoka S, Fukata R et al (1993) A case of carcinosarcoma of the gallbladder with a huge cystic lesion (in Japanese). Nippon Rinsho Geka Igakkai Zasshi 54:1312–1317

Eriguchi N, Aoyagi S, Hara M, Hashino K, Imamura M, Sato S, Imamura I, Kutami R, Jimi A (1999) A so-called carcinosarcoma of the gallbladder in a patient with multiple anomalies – a case report. Kurume Med J 46:175–179

Fagot H, Fabre JM, Ramos J, Laffay V, Guillon F, Domergue J, Baumel H (1994) Carcinosarcoma of the gallbladder. A case report and review of the literature. J Clin Gastroenterol 18:314–316

Gokalp G, Dusak A, Topal NB, Aker S (2010) Cystadenoma originating from the gallbladder. J Ultrasound Med 29:663–666

Grote R, Kaemmerer H (1986) Carcinosarcoma of the gallbladder in the computed tomogram (in German). Röntgenblätter 39:17–20

Hasegawa H, Takada T, Yasuda H, Uchiyama K, Tsuchiya S, Misu Y, Saitoh Y, Shikata J et al (1987) A case of huge carcinosarcoma of the gallbladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 84:1690–1694

Herrera-Goepfert R, Manrique Ortega JJ, Rodriguez-Martinez HA (1987) Carcinosarcoma of the gallbladder. Histol Histopathol 2:273–275

Herrero Zapatero A, Fuente Martin E, Martinez Alonso C, Orduna Domingo A, Rodrigo Saez L (1980) Carcinosarcoma of the gallbladder: description of a case and review of the literature (in Spanish). Rev Esp Enferm Apar Dig 57:57–64

Higgs WR, Mocega EE, Jordan PH (1973) Malignant mixed tumor of the gallbladder. Cancer 32:471–475

Hotta T, Tanimura H, Yokoyama S, Ura K, Yamaue H (2002) So-called carcinosarcoma of the gallbladder; spindle cell carcinoma of the gallbladder: report of a case. Surg Today 32:462–467

Huguet KL, Hughes CB, Hewitt WR (2005) Gallbladder carcinosarcoma: a case report and literature review. J Gastrointest Surg 9:818–821

Iezzoni JC, Mills SE (1993) Sarcomatoid carcinomas (carcinosarcomas) of the gastrointestinal tract: a review. Semin Diagn Pathol 10:176–187

Indyk JS, Shipton EA (1957) Heterotopic bone formation in the gall-bladder. Med J Aust 44:9–11

Inoshita S, Iwashita A, Enjoji M (1986) Carcinosarcoma of the gallbladder. Report of a case and review of the literature. Acta Pathol Jpn 36:913–920

Ishida J, Ajiki T, Hara S, Ku Y (2012) Gallbladder calcification leads to discovery of carcinosarcoma of the gallbladder. Surgery 152:934–935

Ishihara T, Kawano H, Takahashi M, Yokota T, Uchino F, Matsumoto N, Fukuyama N (1990) Carcinosarcoma of the gallbladder. A case report with immunohistochemical and ultrastructural studies. Cancer 66:992–997

Isomoto I, Matsunaga N, Ochi M, Hayashi K, Amamoto Y, Tachibana K, Furukawa M (1990) Multiseptate gallbladder: computed tomographic appearance. Radiat Med 8:55–57

Kadono J, Hamada N, Higashi M, Ishizaki N, Nakamura N, Sakata R (2005) Carcinosarcoma of the extrahepatic bile duct. J Hepato-Biliary Pancreat Surg 12:328–331

Khanna M, Khanna A, Manjari M (2013) Carcinosarcoma of the gallbladder: a case report and review of the literature. J Clin Diagn Res 7:560–562

Kijima Y, Umekita Y, Yoshinaka H, Owaki T, Sakamoto A, Yoshida H, Aikou T (2006) A case of breast carcinoma with cartilaginous and osseous metaplasia. Breast Cancer 13:214–219

Kim MJ, Yu E, Ro JY (2003) Sarcomatoid carcinoma of the gallbladder with a rhabdoid tumor component. Arch Pathol Lab Med 127:e406–e408

Kim HH, Hur YH, Jeong EH, Park EK, Koh YS, Kim JC, Kim HJ, Cho CK (2012) Carcinosarcoma of the gallbladder: report of two cases. Surg Today 42:670–675

Kitagawa T, Einame K, Suzuki H, Muto E, Takeda S, Kanda M (1992) A case of carcinosarcoma of the gallbladder associated with squamous cell carcinoma (in Japanese). Tando 6:85–90

Klein F, Dornetzhuber V, Kostolny I (1961) On a "carcinosarcoma" of the gallbladder wall (in German). Zbl Allg Pathol 102:17–20

Kleinknecht A, Nessmann V, Oberlin GC (1931) Epitheliosarcome de la vésicule biliaire. Bull Cancer (Paris) 20:476–485

Knorr G (1963) Carcinosarcoma of the gallbladder. Zbl Allg Pathol 105:37–41

Kohtani T, Masuda J, Hisaki T, Shimase K, Mizuguchi K (2009) Long-term survival of an elderly patient with carcinosarcoma of the gallbladder after cholecystectomy. Case Rep Gastroenterol 3:235–239

Krishnamurthy V, Shivalingiah SD, Ravishankar S, Manjunath GV (2011) Morphologic heterogeneity in carcinosarcoma of the gallbladder: report of a rare case. Case Rep Pathol 2011:929654

Kritsch N (1925) Eine Mischgeschwulst der Gallenblase. Moskowski Medizinski Zhurnal 5:9–12

Krstic M, Alempijevic T, Krstic S, Lausevic Z, Micev M, Saranovic D, Tomic D (2005) Peritoneal hepatobiliary cystadenoma – case report (in Serbian). Acta Chir Iugosl 52:99–101

Kubota K, Kakuta Y, Kawamura S, Abe Y, Inamori M, Kawamura H, Kirikoshi H, Kobayashi N et al (2006)

Undifferentiated spindle-cell carcinoma of the gallbladder: an immunohistochemical study. J Hepato-Biliary Pancreat Surg 13:468–471

Kuroda N, Iiyama T, Moriki T, Shuin T, Enzan H (2005) Chromophobe renal cell carcinoma with focal papillary configuration, nuclear basaloid arrangement and stromal osseous metaplasia containing fatty bone marrow element. Histopathology 46:712–713

Landsteiner K (1907) Plattenepithelkarzinom und Sarkom der Gallenblase in einem Falle von Cholelithiasis. Zschr Klein Med 62:427–433

Leger L, Lemaigre G, Prémont M, Salmon R, Klioua Z, Battesti JP (1980) Portal hypertension in sarcoidosis. Three cases including one with liver fibrosis and malignant hepatoma with osseous stroma (in French). Nouv Press Med 9:1021–1024

Li BF, Li PW, Shi R, Liu ZL, Liu YF (2013) Clinicopathologic analysis of gallbladder carcinosarcoma. Am Surg 79:E37–E39

Liu KH, Yeh TS, Hwang TL, Jan YY, Chen MF (2009) Surgical management of gallbladder sarcomatous carcinoma. World J Gastroenterol 15:1876–1879

Lopez GE, Strimel W, Herrera-Omelas L (1985) Carcinosarcoma of the gallbladder: report of a case. J Surg Oncol 29:224–226

Lorenz G (1974) Carcinosarcoma of the gallbladder (in German). Zentralbl Chir 99:1658–1660

Lumsden AB, Mitchell WE, Vohman MD (1988) Carcinosarcoma of the gallbladder: a case report and review of the literature. Am Surg 54:492–494

Maeda M, Kanayama M, Uchida T, Hasumura Y, Takeuchi J (1986) A case of hepatocellular carcinoma associated with ossification. A case report. Cancer 57:134–137

Mansori KS, Cho SY (1980) Malignant mixed of the gallbladder. Am J Clin Pathol 73:709–711

Marioni G, Altavilla G, Marino F, Marchese-Ragona R, Lelli-Mami G, Staffieri A (2004) Squamous cell carcinoma of the larynx with osteosarcoma-like stromal metaplasia. Acta Otolaryngol 124:870–873

Matsumoto M, Maruta M, Maeda K, Utsumi T, Sugioka A, Kuroda M (2002) Epithelial cyst of the gallbladder associated with adenocarcinoma. J Hepato-Biliary Pancreat Surg 9:389–392

Mättig H, Müller W, Liebe G, Schulz HG (1982) Benign papillary cystadenoma of the gallbladder with temporary incomplete cholestasis and concomitant pancreatitis. Diagnostic problems (in German). Zentralbl Chir 107:236–239

McCague A, Rosen M, O'Malley K (2008) Laparoscopic cholecystectomy of a polypoid gallbladder cystadenoma obstructing the common bile duct. Surg Laparosc Endosc Percutan Tech 18:209–212

Mege-Lechevallier F, Cherasse A, Ronze S, Colombel M, Scoazec JY (2007) Transitional carcinoma of the ureter with osseous metaplasia of the stroma: a case report (in French). Ann Pathol 27:43–46

Mehrotra TN, Gupta SC, Naithani YP (1971) Carcinosarcoma of the gall bladder. J Pathol 104:145–148

Milicevic D, Ostojic M (1972) Cystadenoma of the gallbladder (in Serbian). Srp Arh Celok Lek 100:261–263

Miyamoto Y, Morimatsu M, Takeuchi M (1983) Carcinosarcoma of the gallbladder (in Japanese). Byori to Rinsho 1065–1070

Mizuno K, Yokochi M, Ikeda K, Hamada S, Suzuki K et al (1990) A case of carcinosarcoma of the gallbladder with acute cholecystitis as the first diagnostic clue (in Japanese). Tando 4:499–504

Morrone C, Carlomagno G, Morrone F, Romeo F, De Stefano R (1997) Carcinosarcoma of the gallbladder (in Italian). Ann Ital Chir 68:375–378

Mukonoweshuro P, Oriowolo A (2005) Stromal osseous metaplasia in a low-grade ovarian adenocarcinoma. Gynecol Oncol 99:22–224

Nakagawa M, Matsumoto T, Suguro Y, Takanosu S (1990) A case of mucinous cystadenocarcinoma of the gallbladder (in Japanese). Nihon Geka Gakkai Zasshi 91:434–437

Nakagawa T, Yamakado K, Takeda K, Nakagawa T (1996) An ossifying carcinosarcoma of the gallbladder: radiologic findings. AJR Am J Roentgenol 166:1233–1234

Nakazawa T, Sotoyama K, Tsuchiya N, Naito Y, Honma J, Noto M, Nakazawa H, Takada I et al (1992) A case of common bile duct neoplasm with carcinosarcoma of the gallbladder (in Japanese). Nihon Naika Gakkai Zasshi 81:908–910

Nishihara K, Tsuneyoshi M (1993) Undifferentiated spindle cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and flow cytometric study of 11 cases. Hum Pathol 24:1298–1305

Nishihara S, Suwaki K, Moritani H, Toshimori T, Kondoh J, Oohara M et al (1990) Carcinosarcoma of the gallbladder. Report of a case (in Japanese). Tan to Sui 11:635–640

Nishikage T, Yamazaki S, Nagai K, Wakayama H, Miura N (1997) A case of carcinosarcoma of the gallbladder (in Japanese). Nippon Shokakigeka Gakkai Zasshi 30:1856–1860

Oberoi R, Iean A, Tangri R, Saharia A (2006) Carcinosarcoma of the gallbladder with chondroid differentiation: MRI findings. Indian J Radiol Imaging 16:491–493

Okabayashi T, Sun ZL, Montgomery RA, Hanazaki K (2009) Surgical outcome of carcinosarcoma of the gall bladder: a review. World J Gastroenterol 15:4877–4882

Okuda K, Nakajima M, Nakayama M, Nomura F (1979) Multiseptate gallbladder. Report of a case with a review of literature. Acta Hepatogastroenterol (Stuttg) 26:70–75

Pai SA, Bhasin SD, Krishnamurty SC (1993) Heterotopic ossification in colorectal adenocarcinoma. Indian J Pathol Microbiol 36:304–307

Park SB, Kim YH, Rho HL, Chae GB, Hong SK (2012) Primary carcinosarcoma of the gallbladder. J Korean Surg Soc 82:54–58

Parreira JM, Siqueira DE, Menacho AM, Pelizzari LL, Santos LC (2012) Carcinosarcoma of the gallbladder: case report. Arq Bras Cir Dig 25:65–66

Pitiakoudis MS, Tsaroucha AK, Deftereos S, Laftsidis P, Prassopoulos P, Simopoulos CE (2006) Primary hydatid disease in a retroplaced gallbladder. J Gastrointest Liver Dis 15:383–385

Pu JJ, Wu W (2011) Gallbladder carcinosarcoma. BMJ Case Rep 2011. pii:bcr0520103009

Rodriguez Rodriguez JM, Pérez Garcia M, Abdel-Lah BA, Pina Arroyo J, Ramos Boyero M et al (1985) Carcinosarcoma of the gallbladder (in Spanish). Rev Esp Enferm Apar Dig 67:357–361

Rooney TB, Schofer JM, Stanley MD, Banks SL (2005) Biliary cystadenoma of the gallbladder. AJR Am J Roentgenol 185:1571–1572

Roth J, Machnik G, Stiller D (1972) Carcinosarcoma of the gallbladder (in German). Zbl Allg Pathol 116:545–550

Rys J, Kruczak A, Iliszko M, Babinska M, Wasilewska A, Limon J, Niezabitowski A (1998) Sarcomatoid carcinoma (carcinosarcoma) of the gallbladder. Gen Diagn Pathol 143:321–325

Sadamori H, Fujiwara H, Tanaka T, Yanai H, Satoh D, Yagi T, Fujiwara T (2012) Carcinosarcoma of the gallbladder manifesting as cholangitis due to hemobilia. J Gastrointest Surg 16:1278–1281

Saegusa M, Hashimura M, Kuwata T, Okayasu I (2009) Requirement of the Akt/beta-catenin pathway for uterine carcinosarcoma genesis, modulating E-cadherin expression through the transactivation of slug. Am J Pathol 174:2107–2115

Sagi T, Gyori S (1972) Über eine maligne Mischgeschwulst der Gallenblase. Zbl Allg Pathol 116:177–182

Sai J, Ariyama J, Suyama M, Ogawa K, Ikari T, Sato K et al (1991) A case of carcinosarcoma of the gallbladder (in Japanese). Shokaki Naishikyo no Shinpo 39:420–423

Shikano T, Takeda S, Sakai M, Sugimoto H, Kanazumi M, Nomoto S, Nakao A (2008) Cystic lymphangioma of the gallbladder: report of a case. Surg Today 38:81–84

Shimada K, Iwase K, Aono T, Nakai S, Takeda S, Fujii M, Koma M, Nishikawa K, Matsuda C et al (2009) Carcinosarcoma of the gallbladder producing alpha-fetoprotein and manifesting as leukocytosis with elevated serum granulocyte colony-stimulating factor: report of a case. Surg Today 39:241–246

Shintaku M, Kataoka K, Kawabata K (2013) Mixed adenoneuroendocrine carcinoma of the gallbladder with squamous cell carcinomatous and osteosarcomatous differentiation: report of a case. Pathol Int 63:113–119

Simmons TC, Miller C, Pesigan AM, Lewin KJ (1989) Cystadenoma of the gallbladder. Am J Gastroenterol 84:1427–1430

Sistla SC, Sankar G, Basu D, Venkatesan B (2009) Biliary cystadenocarcinoma of the gall bladder: a case report. J Med Case Rep 3:75

Sodergren MH, Silva MA, Read-Jones SL, Hubscher SG, Mirza DF (2005) Carcinosarcoma of the biliary tract: two case reports and a review of the literature. Eur J Gastroenterol Hepatol 17:683–685

Spector SA, Fernandez VE, Vernon SE, Dunkin B, Livingstone AS (2003) Gallbladder cystadenoma and common bile duct obstruction. Int J Gastroenterol Cancer 34:151–155

Stempinski E, Beger HC (1974) Unsual case of a carcinosarcoma of the gallbladder (in German). Z Gastroenterol 12:485–489

Strauss S, Starinsky R, Alon Z (1993) Partial multiseptate gallbladder: sonographic appearance. J Ultrasound Med 12:201–203

Sugawara T, Kmai M, Sato M, Suzuki K, Okada N, Ono S (2001) Three cases of multiseptate gallbladder (in Japanese). Nihon Geka Gakkai Zasshi 102:358–362

Takahashi Y, Fukushima J, Fukusato T, Shiga J (2004) Sarcomatoid carcinoma with components of small cell carcinoma and undifferentiated carcinoma of the gallbladder. Pathol Int 54:866–871

Taniguchi H, Ohgaki M, Takahashi T (1996) Carcinosarcoma and so-called carcinosarcoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:270–272

Terada T, Takeuchi T, Taniguchi M (2003) Hepatobiliary cystadenocarcinoma with cystadenoma elements of the gall bladder in an old man. Pathol Int 53:790–795

Thomas VT, Hinson S, Konduri K (2012) Epithelial-mesenchymal transition in pulmonary carcinosarcoma: case report and literature review. Ther Adv Med Oncol 4:31–37

Tohsha T, Endoh H, Satoh T, Yashima Y, Satoh T (1998) A case of carcinosarcoma of the gallbladder. Nippon Syokakigeka Gakkai Zasshi 31:875–879

Tsukuda K, Tsuji H, Kunitomo T, Aokage K, Miyake T, Nakahara S, Masuda H (2009) Breast cancer with cartilaginous and/or osseous metaplasia diagnosed by lymph nodal metastasis: a case report. Acta Med Okayama 63:367–371

Uesaka K, Nimura Y, Hyakawa N, Iyomata S, Kondo S et al (1995) Carcinosarcoma of the gallbladder: a case report and review of the literature. J Hepato-Biliary Pancreat Surg 2:446–450

Uzun MA, Koksal N, Gunerhan Y, Celik A, Gunes P (2009) Carcinosarcoma of the gallbladder: report of a case. Surg Today 39:168–171

Virchow R (1864/1865) Die krankhaften Geschwülste, vol 2. August Hirschwald, Berlin, pp 181–182

Von Kuster LC, Cohen C (1982) Malignant mixed tumor of the gallbladder: report of two cases and a review of the literature. Cancer 50:1166–1170

Waldmann J, Zielke A, Moll R, Schweinsberg TS, Rothmund M, Langer P (2006) Cystadenocarcinoma of the gallbladder. J Hepato-Biliary Pancreat Surg 13:594–599

Wang Y, Gu X, Li Z, Xiang J, Chen Z (2013) Gallbladder carcinosarcoma accompanied with bile duct tumor thrombi: a case report. Oncol Lett 5:1809–1812

Wolfensberger C (1971) Carcinosarcoma of the gallbladder (in German). Schweiz Med Wochenschr 101:335–338

Yamagiwa H (1971) A case of carcinosarcoma of the gallbladder (in Japanese). Mieigaku 14:408–409

Yamagiwa H, Yoshimura H, Tomiyama H, Kawahara S, Ito F (1982) So-called carcinosarcoma (in Japanese). Rinsho Byori 30:1096–1102

Yamamoto A, Komuge T, Iuchi Y, Tokuoka S, Santo T (1987) A case of huge carcinosarcoma of the gallbladder (in Japanese). Hiroshima Igaky 40:1325–1326

Yavuz E, Bilgiç B, Cevikbaç U, Demiryont M (2000) Test and teach. Number ninety nine. Carcinosarcoma of the gallbladder. Pathology 32(41):63–64

Yosepovich A, Nass D, Zagatsky M, Kopolovic J (2002) Chronic cholecystitis with bone metaplasia. A case report. Pathol Res Pract 198:765–766

Yun EJ, Yoon DY, Choi CS, Bae SH, Seo YL, Chang SK, Lim KJ, Kwon JH et al (2011) Calcified carcinoma of the gallbladder with calcified nodal metastasis presenting as a porcelain gallbladder: a case report. Cancer Res Treat 43:71–74

Zapatero AH, Martin EF, Alonso CM, Domingo AO, Suez LR (1980) Carcinosarcoma de de vesicular biliar: descripcion de un caso y revision de la literature. Rev Esp Enferm Dig 57:57–64

Zhang L, Chen Z, Fukuma M, Lee LY, Wu M (2008) Prognostic significance of race and tumor size in carcinosarcoma of gallbladder: a meta-analysis of 68 cases. Int J Clin Exp Pathol 1:75–83

Zheng HF, Song QJ, Shen DH (2006) Adenocarcinoma of gallbladder with chondrosarcomatous component: report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 35:770

Benign/Borderline Epithelial Tumors and Dysplastic Alterations of the Gallbladder

153

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_153

Abstract

The gallbladder epithelium can give rise to a spectrum of adenomatous, borderline, and dysplastic lesions. Adenomas of the gallbladder are benign neoplasms of the glandular epithelium, often with various forms of differentiation. These tumors are usually small and solitary lesions that are asymptomatic in the majority of cases and often associated with cholelithiasis. Tubular, papillary, and tubulopapillary growth patterns are distinguished. Differentiation patterns include biliary type, pyloric-gland type, intestinal type, and foveolar type. Part of these neoplasms can contain Paneth cells, keratinocytes, neuroendocrine cells, or oncocytes. One special form is characterized by a solitary or diffuse papillary growth (gallbladder papilloma), a lesion sometimes associated with papillomatosis of the cystic duct and extrahepatic bile ducts. A small subset of preinvasive neoplastic gallbladder polyps show a complex mixture of papillary and tubular patterns and are termed intracholecystic papillary-tubular neoplasm.

Adenoma of the Gallbladder

ICD-O codes:

Adenoma	8140/0
Tubular Adenoma	8211/0

Introduction

Adenomas of the gallbladder (AG) are benign neoplasms of the glandular epithelium of the gallbladder, typically with various forms of differentiation. AG are usually small and solitary lesions that do not cause signs or symptoms in the majority of persons, but AG are significant as a potential origin of malignancy. Most AG are associated with cholelithiasis, in contrast to adenomas in the large bile ducts (reviews: Christensen and Ishak 1970; Albores-Saavedra et al. 1993, 2010, 2012; Zhang et al. 1994; Levy et al. 2002.

Epidemiology

AG is a rare lesion, whereas gallbladder polyps are relatively common alterations. Gallbladder polyps are found in approximately 5 % of the worldwide population (Myers et al. 2002; Lee et al. 2004). In a study of 194,767 asymptomatic patients undergoing ultrasonographic examinations, 10,926 patients revealed gallbladder polyps (5.6 %; Okamoto et al. 1999). The prevalence of AG is much lower, but the exact prevalence is not known. Some authors estimated that 95 % of gallbladder polyps are nonneoplastic (i.e., cholesterol polyps or inflammatory/hyperplastic polyps and polypoid adenomyosis), while AG are estimated to account for about 5 % of gallbladder polyps (Lillemoe 2006). Among 123 polyps, four cases of AG (3.2 %) were histologically diagnosed (Escalona et al. 2006). In one study, AG were found in 10 % of patients with gallbladder polyps (Ito et al. 2009).

An early investigation (Wellbrock 1934) showed AG in 69 gallbladders among a series of 9,550 cholecystectomies. Within a series of 1,847 cholecystectomies, 34 AG were identified (1.8 %). Nine carcinomas in situ developing in adenomas were found, and in 8 AG, invasive carcinomas were detected (all of well-differentiated types). Patients with carcinomas in AG were on average older than those with benign adenomas (Lee et al. 2010). In another study of 2,600 surgical specimens of cholecystectomy, an incidence of AG of 0.55 % was found (Zhou 1985). Farinon et al. (1991) found 9 AG among 2,145 cholecystectomies (0.4 %). AG occur more often in female patients (Zhou 1985; Albores-Saavedra et al. 2012). Very rarely, AG had been observed in the pediatric age group (Mogilner et al. 1991; Stringer et al. 2003; Ersöz et al. 2004).

Clinical and Imaging Features

Most AG, and in particular small lesions, are asymptomatic, but few patients experience abdominal pain or discomfort (Tanous et al. 1960; Perazo 1967; Botticelli et al. 1968; Hultén et al. 1970; Sawyer 1970; Brambs et al. 1986;

Logani et al. 1995; Terzi et al. 2000). In a minority of cases, large polypoid lesion may cause obstruction of the gallbladder outlet and is associated with recurrent biliary colic (Pila et al. 1991). Polypoid lesions of the gallbladder are commonly found on ultrasonography and CT images, and part of these lesions are polypoid AG that project into the gallbladder lumen (Kumagai et al. 2006; Tomic et al. 2011). AG can reliably be identified by MR, whereby a high b-value DWI (diffusion-weighted MR imaging) may be useful for differentiating between benign and malignant polypoid gallbladder lesions (Irie et al. 2011).

Pathology

Macroscopy

AG are usually flat, sessile, or pedunculated/polypoid lesions. They are commonly solitary tumors, but multiple AG are found in up to 10 % of cases (Lin and Hägerstrand 1983). In a study of 201 AG, 91 % were single lesions, but one gallbladder showed 102 adenomas (Albores-Saavedra et al. 2012). Most AG have a diameter of less than 20 mm. Most tubular AG display a lobular or globular contour, in contrast to the cauliflower-like configuration of papillary adenomas. The tumors show either a smooth or finely granulated surface and a whitish to pinkish or yellowish color. Large lesions can show superficial ulceration and/or small hemorrhages. The majority of AG have been found in association with cholelithiasis. In rare situations, tubulopapillary adenoma may cause intrabile duct tumor thrombus in the absence of malignancy (Yamamoto et al. 2014).

Histopathology

The histopathology of AG has been described and reviewed in detail (Table 1; Yamamoto et al. 1988; Ono and Masamune 1996a; Katabi 2010; Albores-Saavedra et al. 2010, 2012). AG can be divided into three types based on their growth pattern: tubular, papillary, and tubulopapillary.

Table 1 Growth patterns and differentiation patterns of adenomas of the gallbladder

Growth patterns
Tubular
Papillary
Tubulopapillary
Differentiation patterns (including "metaplasia")
Biliary type (normal counterpart of gallbladder epithelium)
Pyloric-gland type (pyloric-gland adenoma)
Intestinal type (intestinal-type adenoma)
Foveolar type (foveolar-type adenoma)
Other cellular components
Spindle cells
Paneth cells
Squamous epithelial cells (keratinocytes)
Neuroendocrine cells
Oxyphilic cells
Oncocytic cells

The papillary variant of AG is discussed in a separate paragraph. The main histologic differentiation patterns include pyloric-type, intestinal, foveolar, and biliary morphologies. Pyloric and intestinal adenomas are more common that in the extrahepatic bile ducts.

Pyloric and intestinal adenomas typically show a tubular-glandular growth pattern. In a large part of AG, a pyloric gland-type histology predominates (*tubular adenoma*, *pyloric-gland type*; *pyloric-gland adenoma*; Fig. 1), the most important member of so-called metaplastic adenoma (Yu and Kim 1985; Vieth et al. 2003; Constantea et al. 2008; Belekar et al. 2009). Small lesions have a globular or lobular shape, while large lesion develops a pedicle or stalk and project into the gallbladder lumen as polypoid lesions. Similar to colorectal adenomas with "metaplastic" changes, the question as to whether the occurrence of pyloric-type or intestinal-type epithelia in AG reflects true metaplasia is not yet settled. Pyloric-gland adenoma displays lobules of densely packed glands consisting of cells closely resembling the cells of pyloric glands, typically situated underneath a normal-looking biliary-type surface epithelium. Some of the glandular structures are cystically dilated. By definition, pyloric-

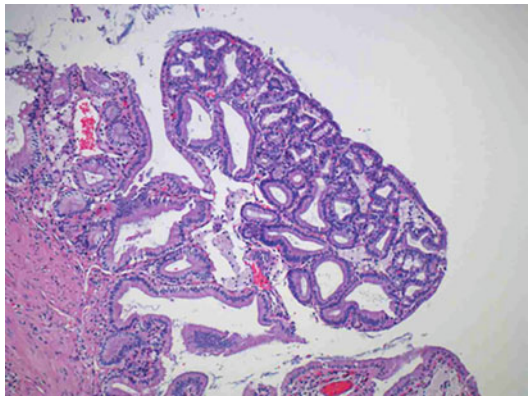

Fig. 1 Tubular adenoma of the gallbladder with polypous growth (hematoxylin and eosin stain)

gland AG have at least low-grade intraepithelial neoplasia, and particularly large lesions may show high-grade dysplasia or even carcinoma in situ or early invasive adenocarcinoma. In the study of Albores-Saavedra and coworkers (2012), high-grade dysplasia/carcinoma in situ was found in 27 % of 165 pyloric-gland adenomas and low-grade dysplasia in 15 %. In contrast, high-grade dysplasia was detected in 46 % of 28 intestinal adenomas, and foveolar adenomas only showed low-grade dysplasia.

The intestinal type of AG (*intestinal-type adenoma*) is less common than its pyloric counterpart. It is characterized by the presence of columnar intestinal cells arranged in a fashion closely resembling colorectal adenomas, often associated with dysplastic alterations. *Foveolar-type AG* is composed of tall columnar cells with basally placed hyperchromatic nuclei and a mucin-rich cytoplasm that expresses MUC5AC and MUC6. It is of importance to note that a biliary cell lineage (*biliary-type adenoma*) is involved in only a minority of cases of AG. Among 201 AG, 82 % were classified as pyloric, 14 % as intestinal, 2.4 % as foveolar, and 1.4 % as biliary (Albores-Saavedra et al. 2012).).

In addition to these main morphologies, some AG can contain other cellular elements of intestinal lineages, e.g., Paneth cells. Oxyphilic cells (Albores-Saavedra et al. 2012) and oncocytic elements (Lespi 1997) may occur. In tubular adenoma, squamous metaplasia was observed (Colovic et al. 2006). In some of these cases, the squamoid cell component undergoes a spindle cell change (Nishihara et al. 1991; Kushima et al. 1996). Rarely, spindle cell components lack intercellular bridges and signs of cytoplasmic keratinization (Yim et al. 1998). The latter type of AG is characterized by closely packed tubules of variable size arranged in lobules. Within these areas, spindle cell metaplasia is found in the form of solid morular foci of blunt spindle cells forming hypercellular nests and whirling arrangements situated between tubular profiles. Immunohistochemically, the spindle cells were reactive for one or more cytokeratins, but for vimentin (Yim et al. 1998), suggesting their epithelial lineage or the effect of epithelial-to-mesenchymal transition.

Immunohistochemistry

In contrast to adenocarcinoma, AG have a low level of MUC1 expression, whereas expression of MUC5AC is higher in AG than in gallbladder carcinoma cells (Xiong et al. 2012). In pyloric gland-type AG, 30 % or more of the epithelial cells were reactive for mucin MUC5AC in 38 % of the tumors, for human gastric mucin in 50 %, MUC6 in 100 %, and M-GGMC-1 in 93 %, while MUC2 was not detectable, supporting the presence of a pyloric-type cell lineage (Nagata et al. 2007). In the large study of Albores-Saavedra et al. (2012), MUC5AC and MUC6 labeled 95 % of pyloric gland-type adenomas, while MUC2 was found in 33 % of intestinal-type adenomas.

Immunohistochemically, part of AG share expression features with gallbladder carcinomas, but in regard to several markers, there is a marked difference between AG and gallbladder adenocarcinoma, and these differences also refer to molecular features (Wistuba et al. 1999). A subset of AG show nuclear reactivity for the tumor suppressor, p53 (Takei et al. 1996; Billo et al. 2000). In one analysis, expression of p53 was found in 16.6 % of AG, while it was seen in 83.3 % of gallbladder carcinomas (Arevalo et al. 2007). A similar figure was reported from another investigation (17.6 %; Wang et al. 2006). The pathways leading to p53 expression in AG are not yet known, as no p53 gene mutations were detectable in AG

(Kim et al. 2001). AG showed a significantly stronger cytoplasmic and nuclear expression of beta-catenin than gallbladder carcinomas, and beta-catenin exon 3 mutations were observed in 62.5 % of AG, but only 4.8 % of carcinomas, suggesting that abnormalities of the beta-catenin pathway may not play a central role in gallbladder carcinogenesis (Yanagisawa et al. 2001). Similarly, AG more commonly exhibit mutations in the RAS/RAF/MAP kinase signaling pathway than gallbladder carcinomas (Pai et al. 2011). S100A8 is overexpressed in gallbladder carcinomas in comparison with AG and other benign epithelial neoplasms (Wang et al. 2013). Expression of annexin A1 (ANXA1) and annexin A2 (ANXA2) is significantly higher in adenocarcinoma than in benign lesions, and benign gallbladder lesions such as AG with positive ANXA1 and/or ANXA2 expression show mild to severe epithelial atypia, suggesting that ANXA expression is a marker of progressive cancerization (Yang et al. 2010). Gallbladder carcinomas display a higher expression of the neurotrophic factor, brain-derived neurotrophic factor/BDNF than AG (Xiong et al. 2013), and more often express cyclin E than AG (Jin et al. 1997). In contrast to carcinomas, no decrease in expression of p27 (Kip1) was found in AG (Hui et al. 2000). Immunostaining for ERK1/2 was detected in 20 % of polypous AG, in contrast to 58.3 % in gallbladder adenocarcinoma (Li and Yang 2009). The progression along an adenoma-carcinoma sequence is associated by expression of cyclooxygenase-2 (Seki et al. 2002). Estrogen receptors can be detected in the gallbladder in various disease states, including AG (Yamamoto et al. 1990).

Gallbladder Adenoma and Carcinogenic Pathways

Pyloric-gland AG have, by definition, at least low-grade intraepithelial neoplasia. However, fraction of AG show severe epithelial dysplasia or carcinoma in situ, suggesting that there exists an adenoma-carcinoma sequence in the gallbladder (Kozuka et al. 1982; Pradines et al. 1988; Yamamoto et al. 1988; Nakajo et al. 1990; Chang et al. 1997; Watanabe et al. 1999; Sasatomi et al. 2000; Turrini et al. 2007; Ciurea et al. 2008; Trivedi et al. 2008). In fact, over 80 % of invasive gallbladder carcinomas present areas adjacent to epithelial dysplasia or carcinoma in situ (Roa et al. 2006). In a study of 17 AG, 72.7 % of metaplastic adenomas and 33.3 % of non-metaplastic adenomas showed foci of atypical gland proliferation (Nakajo et al. 1990). In patients with primary sclerosing cholangitis, gallbladder polyps were reported to be frequently malignant (Buckles et al. 2002). Whether these malignancies arising in or manifesting as polyps tend to originate from adenomas is not known.

Differential Diagnosis

In the setting of imaging approaches, the differential diagnosis between AG and cholesterol polyps based on ultrasonography may be difficult (Park et al. 2013). Apart from AG, sessile lesions are sometimes hyperplastic polyps (Sato et al. 1985).

Pathogenic Pathways

Polypous AG has been observed in Gardner's syndrome (Brevet et al. 2007) and in juvenile polyposis syndrome caused by SMAD4 mutation (Schwetz et al. 2012).

Villous Adenoma: A Rare Markedly Exophytic Variant of Papillary Adenoma

Introduction

Villous adenoma, a term still found in the literature, can be classified as a solitary papillary adenoma with a prominently exophytic growth mode. Similar to the large bile ducts, villous adenoma of the gallbladder is a very rare solitary adenoma with an arborizing papillary structure resembling the long villous structures seen in the respective colorectal adenomas (Kimura et al. 1994;

Nagahama et al. 1997; Krstic et al. 2007; Jin et al. 2013). Villous adenoma is a very rare lesion and was found only twice among 533 cholecystectomies (0.38 %) and in 1 patient among 1,300 randomly selected autopsies (0.08 %) (Kimura et al. 1994). There is overlap between lesion termed "villous" and those termed "papillary" (see below), the most important distinguishing features being the distinct gross presentation and the long finger-like projections in the former.

Pathology

Macroscopy

Villous adenoma is a solitary, polypoid tumor that may exceed a diameter of 5 cm and occupy a large part of the gallbladder lumen. It usually reveals as stalk and an exophytically growth part with a granular, cauliflower-like surface resembling villous adenomas of the colorectal region.

Histopathology

Villous adenoma displays a villous architecture with a regular arborization of long papilliform and densely crowded structures having a delicate fibrovascular stromal axis lined by a single layer of tall columnar cells with basally placed nuclei. The stromal axis may show apical edema (Krstic et al. 2007). Low-grade nuclear atypia is a common finding, but focal high-grade dysplasia or even carcinoma in situ have been reported (Krstic et al. 2007). The principal lesion may be accompanied by small tubular adenomas (Krstic et al. 2007). In villous adenoma with nuclear atypia, immunoreactivity for CEA and CA 19-9 was detected (Kimura et al. 1994).

Differential Diagnosis

Differential diagnosis includes papillary adenomas that do not show the elongated villous profiles of villous adenoma, although there is an overlap between the two lesion groups.

Solitary and Diffuse Papillary Adenoma (Papilloma): A Rare Form of Gallbladder Adenoma

ICD-O Code 8260/0

Introduction

Papillary adenoma (PA; synonyms: papilloma, villous papilloma, villous tumor) is a very rare form of adenoma of the gallbladder, characterized by a predominantly papillary growth pattern forming solitary or diffuse lesions in the gallbladder mucosa. Possibly or probably part of large (>1 cm) papillary lesions described in the literature rather belong to the novel category of preinvasive tumors called intracholecystic papillary-tubular neoplasms (see below).

Epidemiology

The incidence of papillary variants of gallbladder adenoma is not known, as most published observations referred to single cases. PA was apparently first described in 1899 (Ringel 1899). After this report, few other cases were published (Hansson 1905; Pels-Leusden 1906). PA of the gallbladder was described and classified in more detail in 1910 based on one case observed among 365 resected gallbladders (MacCarthy 1910). In a series of 2,168 gallbladders examined between 1907 and 1915, 85 specimens with one or more papillary lesions were seen, however without specifying the histopathologic features (Irwin and MacCarthy 1915). Abell found two PA among 288 cholecystectomies (Abell 1923). Swinton and Becker found 4 PA among 4,553 resected gallbladders (Swinton and Becker 1948). Relatively few observations were published in the first half of the twentieth century (Dominici 1911; Mayer 1911; Mayo 1915; Scoenlank 1915; Hruska 1916; Mölle 1916; Henry 1933; Phillips 1933; Kerr and Lendrum 1936; Brown and Cappell 1937; Greenwald 1944; Miller 1946; McHardy and Edwards 1948). In 1936, only 7 observations

of confirmed gallbladder PA were listed Kerr and Lendrum (1936). PA was since increasingly reported, with or without associated biliary tract papillomatosis.

Selected References Bagnoli and Pagni 1951; Delannoy et al. 1951; Lund and Burman 1951; Reynolds 1951; Ferrando 1952; Kane et al. 1952; Candiani 1954; Gagliardi and Gelbach 1957; Roy et al. 1957; Dunn and McCollum 1958; Scalvini 1958; Schnug 1958; DePrizio 1959; Marioni and Zucchi 1959; Baruah and Khaund 1960; Eiss et al. 1960; Loitman et al. 1962; Selzer et al. 1962; Lamarina 1963; Macbeath 1964; Makres et al. 1964; Mantero et al. 1964; Moretti and Forni 1964; Karaca et al. 1966; Toulet 1967; Bonandrini et al. 1970; Sawyer 1970; Miyar Gonzalez 1972; Kusakcioglu et al. 1974; McGregor and Cordiner 1974; Aoki et al. 1976; Leger et al. 1976; Picardi et al. 1978; Vadala et al. 1983; Falco et al. 1984; Chen and Yang 1987; Yamaguchi et al. 1989; Ono and Masamune 1996b; Di Rienzo et al. 1998.

Solitary lesions are much more common than the multicentric/diffuse forms, which represent a rare gallbladder pathology which was first described in 1911 (Dominici 1911). Further cases were described, only in part confirmed with histologic examination (Henry 1933; Brown and Cappell 1937; Marek 1955; Griffiths 1956; Cantey and Josey 1958; Morrison and Stewart 1956; Daneo and Rosso 1963; Graziani et al. 1965; Almagro 1985; Arunabh et al. 1988; Nakajo et al. 1988). In most cases, solitary or diffuse PA develops in the absence of preexisting underlying hepatobiliary disease, albeit a rare example of diffuse PA of the gallbladder was observed in the setting of ulcerative colitis and sclerosing cholangitis (Almagro 1985).

Clinical and Imaging Features

The clinical presentation depends on the growth patterns and the size of papillary lesions. Small solitary PA are often asymptomatic and are identified incidentally in the setting of cholecystectomy performed for other reasons. Large solitary villous lesions are sometimes associated with abdominal pain (Kao and Ruchim 1990) and acute abdomen (Mohandas et al. 1972) or may cause obstruction of the gallbladder outlet and lead to hydrops or even mucocele (Bazira et al. 1998), or biliary colic (Niv et al. 1986). In case of large PA, part of the tumor may detach, translocated distally as a floating fragment, and cause obstruction of the bile duct (Molina et al. 1988). Large lesions may rarely cause compression of the bile duct confluents and result in intermittent jaundice (Izinger 1964). Multiple PA often fill the entire gallbladder and can become symptomatic. Multiple PA of the gallbladder are most commonly symptomatic in patients where these lesions are associated with generalized bile duct system papillomatosis. PA has been observed in conjunction with regurgitation of pancreatic juice through an abnormally shaped pancreatobiliary union (Yamaguchi et al. 1989).

One of the early reports of gallbladder PA described a variant with intestinal-type epithelium and chloride secretion Kerr and Lendrum (1936). This papilloma deviated considerably in its histologic phenotype from ordinary gallbladder papillomas, in that it contained a partially intestinal cell lining with Paneth cells and enterochromaffin cells. In one patient, diffuse gallbladder PA was complicated with tuberculosis and granulomatous cholecystitis (Nakajo et al. 1988). In PA, abdominal sonography and imaging reveal characteristic filling defects caused by the exophytic mucosal lesions (Hilliard 1956; Pohlandt 1957; Carter et al. 1978; Porta et al. 1981). In case of diffuse biliary tract papillomatosis with involvement of the gallbladder, the exophytic lesions are visualized by use of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography/ERCP (Kliment et al. 2011).

Papilloma and Papillomatosis of the Gallbladder: Biology of Disease and Status as a Preneoplastic Disorder

PA can remain unchanged for long time periods after a growing phase and behave in a benign

manner. Exceptionally, they undergo circulation disorders followed by spontaneous amputation (Goinard and Pelissier 1958). However, similar to other forms of gallbladder adenoma, PA can undergo dysplastic changes resulting in carcinoma in situ and then invasive carcinoma, reflecting an adenoma-carcinoma sequence (Hruska 1916; Tabah and McNeer 1953; Ochsner and Gage 1956). Transformation into adenocarcinoma, sometimes of the papillary and exophytically growing type, was mainly found in patients with diffuse, multicentric gallbladder papillomatosis (Interlandi and Minchio 1979; Nakamura et al. 1987; Kunisch et al. 1997; Kosemehmetoglu et al. 2011). Either adenocarcinoma is detected as synchronous lesion (Khan and Singh 2012) or carcinoma is found in patients with gallbladder adenomas known or suspected for longer time periods, the latter situation being uncommon.

Pathology

Macroscopy

Solitary PA are sessile or polypoid lesions of gray to whitish or pinkish color measuring from a few mm to more than 1 cm in size. Larger lesion typically shows a finely granular surface caused by the clustered tips of the papillary structures. Large villous adenomas can reveal a gross morphology similar to that of colonic adenomas. In the diffuse (multicentric) form, the gallbladder mucosa is studded with numerous, mostly small papillary and sometimes racemose growths that may cover the entire mucosal surface, resulting in a velvety texture in early disease and ending up in a diffusely villous surface. Sometimes, few papillary lesions may be larger, resembling solitary villous adenomas.

Histopathology

Based on the prevailing cellular differentiation, four major patterns can be distinguished in gallbladder adenomas, i.e., biliary type, pyloric-gland type, intestinal type, and foveolar type. Overall, intestinal- and pyloric-type patterns are more common in gallbladder adenomas than in the extrahepatic bile ducts (Albores-Saavedra et al. 2010). Biliary- and pyloric-type epithelial lineages seem to be more prevalent in exophytically growing, papillary tumors, but they can contain other and sometimes rare components, such as Paneth cells and neuroendocrine cells Kerr and Lendrum (1936). In rare instances, gastric-type mucosa has been detected in PA (Ansari 1954; Almagro 1985). In rare cases of diffuse PA, Paneth cells were found to be numerous (Nakajo et al. 1988).

A rare variant of PA of the gallbladder shows signs of mucin hypersecretion, similar to one variant of large bile duct papillomatosis (mucin-hypersecreting papillomatosis). This variant can occur as a solitary lesion (Lauwers et al. 1995), or develop as a diffuse PA (Chung et al. 2006). Histologically, mucin-secreting PA shows a lining of papillary structures by a single layer of tall mucinous cells with a delicate fibrovascular stroma. Focal cellular tufting and nuclear atypia may be present. The columnar cells are Alcian blue-positive, but do not stain with the mucicarmine stain.

Papillary Adenoma and Papillomatosis of the Cystic Duct

PA is an even less common lesion in the cystic duct, as is mostly occurring as a solitary PA. Solitary PA of the cystic duct may rarely cause biliary colic (Loh et al. 1994). Similar to PA of the gallbladder, PA of the cystic duct may develop dysplasia and carcinoma, but these are exceptional observations (Lombard et al. 1967).

Differential Diagnosis

Macroscopically, large solitary PA may be confounded with exophytically growing papillary adenocarcinoma.

Intracholecystic Papillary-Tubular Neoplasm of the Gallbladder

A small subset of preinvasive neoplastic gallbladder polyps with a diameter of more than 1 cm display a complex mixture of tubular and papillary growth patterns associated with a broad spectrum of dysplasia. As these neoplasms have marked histologic similarity with intraductal papillary neoplasms of pancreas and bile duct and show similar cell lineages and mucin core protein expression, these tumors are proposed to be called intracholecystic papillary-tubular neoplasm or ICPN (Adsay et al. 2012; Jang 2014). Among the 123 cases reported by Adsay and coworkers (2012), the patients were predominantly female (2:1) with a mean age of 61 years and a medium tumor size of 2.2 cm. Pathologically, the main pattern was papillary in 43 %, tubulopapillary in 31 %, and tubular in 26 %. The predominant cell lineage was biliary in 50 % (66 % MUC1-positive), gastric foveolar in 16 % (all MUC5AC-positive), gastric in 20 % (almost all MUC6-positive), intestinal in 8 %, and oncocytic in 6 %. Among cases of a pyloric-gland adenoma pattern, 88 % had at least focal high-grade dysplasia and 18 % showed associated invasive carcinoma. Overall, factors significantly associated with invasive neoplasm were extent of high-grade dysplasia, a biliary or foveolar cell type, and the presence of papilla formation. ICPN rarely protrude into the large bile duct and thus cause obstructive jaundice (Hashimoto et al. 2014).

Fibroadenoma of the Gallbladder

Fibroadenoma of the gallbladder is an extremely rare tumor, histologically characterized by a polypoid endoluminal growth, a filamentous pedicle, and glandular epithelial structures embedded in abundant, loose, and edematous-looking connective tissue (Ochsner and Carrera 1959; Eguchi et al. 2001). Fibroadenoma can grow to large size (more than 11 cm) and fill the gallbladder lumen (Magata et al. 2009). Grossly, the polypoid masses exhibit a gray to reddish color, but they can also be greenish owing to bile stain.

Fibroadenoma of the Gallbladder with Borderline Malignancy

In one case of large fibroadenoma, histology showed hyperchromatic nuclei in part of the glandular cells, associated with disturbed polarity and nuclear immunostaining for p53 protein. Part of the stromal component revealed hypercellularity with irregular nuclei, increased proliferative activity, and p53 positivity (Magata et al. 2009). This very rare tumor may be related to carcinosarcoma of the gallbladder.

References

Abell I (1923) Papilloma and adenoma of gall-bladder. Ann Surg 77:276–280

Adsay V, Jang KT, Roa JC, Dursun N, Ohike N, Bagci P, Basturk O, Bandyopadhyay S, Cheng JD et al (2012) Intracholecystic papillary-tubular neoplasms (ICPN) of the gallbladder (neoplastic polyps, adenomas, and papillary neoplasms that are = >2.0 cm): clinicopathologic and immunohistochemical analysis of 123 cases. Am J Surg Pathol 36:1279–1301

Albores-Saavedra J, Vardaman CJ, Vuitch F (1993) Non-neoplastic polypoid lesions and adenomas of the gallbladder. Pathol Annu 1:145–177

Albores-Saavedra J, Adsay NV, Crawford JM, Klimstra DS, Klöppel G, Sripa D, Tsui WMS et al (2010) Carcinoma of the gallbladder and extrahepatic bile ducts. In: Bosman FT (ed) Who classification of tumours of the digestive system, 4th edn. IARC, Lyon, pp 266–273

Albores-Saavedra J, Chablé-Montero F, Gonzalez-Romo MA, Ramirez Jaramillo M, Henson DE (2012) Adenomas of the gallbladder. Morphologic features, expression of gastric and intestinal mucins, and incidence of high-grade dysplasia/carcinoma in situ and invasive carcinoma. Hum Pathol 43:1506–1513

Almagro UA (1985) Diffuse papillomatosis of the gallbladder. Am J Gastroenterol 80:274–278

Ansari IH (1954) Papilloma of gallbladder with epithelium of gastric mucosa (in German). Zentralbl Allg Pathol 92:355–359

Aoki Y, Okamura T, Kurimoto H, Taniguchi K (1976) Papilloma of the gallbladder. Am J Surg 131:614–617

Arevalo F, Arias Stella C, Monge E (2007) Immunoexpression of p53 and cyclin D1 in adenomas of the gallbladder (in Spanish). Rev Esp Enferm Dig 99:694–697

Arunabh SA, Shukla NK, Mathur M, Kapur MM (1988) Diffuse papillomatosis of gall bladder. J Assoc Physicians India 36:228–229

Bagnoli S, Pagni B (1951) Papilloma of the gallbladder (in Italian). Arch De Vecchi Anat Patol 16:1185–1203

Baruah BD, Khaund RR (1960) Papilloma of the gall bladder–a review (with a case report). Curr Med Pract 4:451–458

Bazira L, Thery Y, Habibou A, Tijdani A, Boukary BA, Rakotomala R, Illo A (1998) Diffuse papillomatosis of the gallbladder: case report of a hydropic gallbladder. Hepatogastroenterology 45:2044–2047

Belekar DM, Verma RA, Bhutala U (2009) Extensive pyloric metaplasia of tubulo-papillary adenoma of the gall bladder. Int J Surg 18. doi:10.5580/eca

Billo P, Marchegiani C, Capella C, Sessa F (2000) Expression of p53 in gallbladder carcinoma and in dysplastic and metaplastic lesions of the surrounding mucosa (in Italian). Pathologica 92:249–256

Bonandrini L, Mantellini E, Colombo P, Scarabelli L (1970) Benign tumors of the gallbladder. Illustration of cases of papilloma, adenoma and lipoma (in Italian). Minerva Chir 25:297–312

Botticelli A, Ferrari De Gaetani C (1968) A case of cystic adenoma of the gallbladder (in Italian). Arch De Vecchi Anat Pathol 52:729–741

Brambs HJ, Holstege A, Johannesson T (1986) Large adenoma of the gallbladder (in German). Rofo 145:475–477

Brevet M, Brehant O, Dumont F, Regimbeau JM, Dupas JL, Chatelain D (2007) Adenomatous polyposis of the gallbladder and Gardner's syndrome. A rare association (in French). Gastroenterol Clin Biol 31:425–427

Brown PR, Cappell DF (1937) Multiple villous papillomata of the gallbladder. Br J Surg 24:703–707

Buckles DC, Lindor KD, Larusso NF, Petrovic LM, Gores GJ (2002) In primary sclerosing cholangitis, gallbladder polyps are frequently malignant. Am J Gastroenterol 97:1138–1142

Candiani A (1954) Anatomo-pathological and clinical study of a case of gallbladder papilloma (in Italian). Acta Chir Ital 10:471–491

Cantey WC, Josey AI (1958) Papillomas of the gallbladder with report of a case. J S C Med Assoc 54:319–321

Carter SJ, Rutledge J, Hirsch JH, Vracko R, Chikos PM (1978) Papillary adenoma of the gall bladder: ultrasonic demonstration. J Clin Ultrasound 6:433–435

Chang JW, Whang YJ, Yun YK (1997) Clinicopathological significance for polypoid lesions of the gallbladder: the adenoma-carcinoma sequence. J Korean Surg Soc 53:432–438

Chen B, Yang GH (1987) Papilloma of the gallbladder: report of 11 cases (in Chinese). Zhonghua Wai Ke Za Zhi 25:100

Christensen AH, Ishak KG (1970) Benign tumors and pseudotumors of the gallbladder. Report of 180 cases. Arch Pathol 90:423–432

Chung JW, Kim MH, Choi EK, Lee SS, Seo DW, Lee SK (2006) Mucin-hypersecreting papillomatosis of the gallbladder. Gastrointest Endosc 64:435–436

Ciurea S, Matei E, Petrisor P, Luca L, Boros M, Herlea V, Popescu I et al (2008) Gallbladder adenoma with focal adenocarcinoma. Chirugia (Bucur) 103:355–358

Colovic R, Grubor N, Radak V, Micev M, Colovic N, Stojkovic M (2006) Tubular adenoma of the gallbladder with squamous metaplasia (in Serbian). Srp Arh Celok Lek 134:159–161

Constantea N, Axente D, Micu B (2008) A case of pyloric-type gallbladder adenoma. J Gastrointestin Liver Dis 17:116–117

Daneo P, Rosso C (1963) Gallbladder papillomatosis. Casuistic contribution (in Italian). Pathologica 55:495–502

Delannoy E, Soulier A, Devambez J (1951) Papilloma of the gallbladder and voluminous lithiasis of the choledochus (in French). Lille Chir 6:90–93

DePrizio CJ (1959) So-called papillomas of the gallbladder. Am J Gastroenterol 32:653

Di Rienzo M, Annunziata A, Russo A, Bartolacci M, Leombruni E, Picardi N (1998) Diagnostic and oncologic updating on gallbladder papilloma. Personal experience and review of the literature (in Italian). Ann Ital Chir 69:627–637

Dominici M (1911) Über einen seltenen Tumor der Gallenblase: klinischer und pathologisch-anatomischer Beitrag. Arch Klin Chir 96:487–493

Dunn FG, McCollum EB (1958) Benign papilloma of the gallbladder; case report. Grace Hosp Bull 36:31–33

Eguchi S, Matsuo S, Hidaka M, Azuma T, Yamaguchi S, Obata S, Kanematsu T (2001) Fibroadenoma of the gallbladder. J Clin Gastroenterol 32:459–460

Eiss S, Dimaio D, Caedo JP (1960) Multiple papillomas of the entire biliary tract: case report. Ann Surg 152:320–324

Ersöz C, Uguz A, Ergören Y, Koç Z (2004) A tubulopapillary adenoma of the gallbladder in a child of three years. Pediatr Surg Int 19:789–790

Escalona A, Leon F, Bellolio F, Pimentel F, Guajardo M, Gennero R, Cruz JP, Viviani P et al (2006) Gallbladder polyps: correlation between ultrasonographic and histopathological findings (in Spanish). Rev Med Chil 134:1237–1242

Falco E, Dolfi F, Lagana A, Magaldi M, Rocco C, Giurelli M (1984) Papillomas of the gallbladder. Review of the literature on the basis of a case observed by us (in Italian). Minerva Chir 39:569–572

Farinon AM, Pacella A, Cetta F, Sianesi M (1991) "Adenomatous polyps of the gallbladder " adenomas of the gallbladder. HPB Surg 3:251–258

Ferrando M (1952) A case of papilloma of the gallbladder (in Italian). Minerva Med 43:38–39

Gagliardi RA, Gelbach PD (1957) Papilloma of the gall bladder. Gastroenterology 32:666–674

Goinard P, Pelissier G (1958) Papillomas of the gallbladder & their spontaneous amputation (in French). Afr Fr Chir 16:307–312

Graziani D, Marks LM, Lim R, Friedell M, Swerdlow M (1965) Papillomatosis of the gallbladder Report of a case with intermittent jaundice and pain. Am J Gastroenterol 44:565–571

Greenwald W (1944) Papilloma of the gallbladder. Surgery 16:370–376

Griffiths E (1956) Papillomata of the gallbladder. Br J Surg 43:435–438

Hansson K (1905) Ein Fall von Papillom der Gallenblase. Nordiskt MedicinArk 38 No 4

Hashimoto S, Horaguchi J, Fujita N, Noda Y, Kobayashi G, Ito K, Koshida S, Kanno Y et al (2014) Intracholecystic papillary-tubular neoplasm of the gallbladder presenting with jaundice. Intern Med 53:2313–2317

Henry CKP (1933) Benign papillomata of gallbladder and biliary ducts. Can MAJ 38:300–302

Hilliard CH (1956) Papilloma of the gall bladder diagnosed radiologically. Br J Radiol 29:344

Hruska A (1916) Ein fall von krebsiger umwandlung eines papilloms der gallenlbase. Wien Klein Wschr 29:1263–1266

Hui AM, Li X, Shi YZ, Torzili G, Takayama T, Makuuchi M (2000) p27 (Kip1) expression in normal epithelia, precancerous lesions, and carcinomas of the gallbladder: association with cancer progression and prognosis. Hepatology 31:1068–1072

Hultén J, Johansson H, Olding L (1970) Adenomas of the gallbladder and extrahepatic bile ducts. Acta Chir Scans 136:203–207

Interlandi G, Minchio C (1979) Papillomatosis of the gallbladder with carcinoma (in Italian). Minerva Chir 34:1103–1108

Irie H, Kamochi N, Nojiri J, Egashira Y, Sasaguri K, Kudo S (2011) High b-value diffusion-weighted MRI in differentiation between benign and malignant polypoid gallbladder lesions. Acta Radiol 52:236–240

Irwin HC, MacCarty WC (1915) Papilloma of the gallbladder. Report of 85 cases. Ann Surg 61:725–729

Ito H, Hann LE, D'Angelica M, Allen P, Fong Y, Dematteo RP, Klimstra DS, Blumgart LH et al (2009) Polypoid lesions of the gallbladder: diagnosis and follow-up. J Am Coll Surg 208:570–575

Izinger E (1964) Gallbladder papilloma causing intermittent jaundice (in Hungarian). Magy Seb 17:59–63

Jang KT (2014) Hepatobiliary/pancreas pathology: SY11-2 intracholecystic papillary-tubular neoplasm of the gallbladder. Pathology 46(Suppl 2):S24

Jin YM, Yim H, Shim C (1997) Cyclin E expression in benign and malignant epithelial neoplasms of the gallbladder. Yonsei Med J 38:301–306

Jin W, Zhang C, Liu J, Zhao Z (2013) Large villous adenoma of gallbladder: a case report. Int J Surg Case Rep 4:175–177

Kane CF, Brown CH, Hoerr SO (1952) Papilloma of the gallbladder; report of eight cases. Am J Surg 83:161–164

Kao N, Ruchim M (1990) Gallbladder papilloma causing right upper quadrant pain. Am J Gastroenterol 85:334–335

Karaca F, Ozman M, Ozgür M (1966) Papillary adenoma of the gallbladder (in Turkish). Tip Fak Mecm 29:66–72

Katabi N (2010) Neoplasia of gallbladder and biliary epithelium. Arch Pathol Lab Med 134:1621–1627

Kerr AB, Lendrum AC (1935–1936) A chloride secreting papilloma of the gall-bladder ; a tumour of heterotopic intestinal epithelium containing Paneth cells and enterochromaffine cells and associated with massive chloride loss; with a critical review of papilloma of the gall-bladder. Br J Surg 23:615–639

Khan M, Singh I (2012) Multicentric papillomatosis with synchronous gallbladder malignancy. Trop Gastroenterol 33:86–87

Kim YT, Kim J, Jang YH, Lee WJ, Ryu JK, Park YK, Kim SW, Kim WH, Yoon YB et al (2001) Genetic alterations in gallbladder adenoma, dysplasia and carcinoma. Cancer Lett 169:59–68

Kimura W, Muto T, Esaki Y (1994) Incidence and pathogenesis of villous tumors of the gallbladder, and their relation to cancer. J Gastroenterol 29:61–65

Kliment M, Urban O, Straka M, Kudelka L, Fojtik P, Falt P (2011) Papillomatosis of the extrahepatic bile ducts and gallbladder diagnosed by endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). Endoscopy 43(Suppl 2):E321–E322

Kosemehmetoglu K, Akpinar E, Sokmensuer C, Harmaloglu E (2011) Papillary carcinoma with diffuse papillomatosis of gallbladder and cystic duct. Ann Diagn Pathol 15:140–144

Kozuka S, Tsubone N, Yasui A, Hachisuka K (1982) Relation of adenoma to carcinoma in the gallbladder. Cancer 50:2226–2234

Krstic M, Alempijevic T, Stimec B, Micev M, Milicevic M, Micic D, Jankovic G (2007) Gallbladder villous adenoma in a patient with acromegaly: a case report. World J Gastroenterol 13:3144–3146

Kumagai Y, Kotanagi H, Ishida H, Komatsuda T, Furukawa K, Yamada M, Ohuchi S et al (2006) Gallbladder adenoma: report of a case with emphasis on contrast-enhanced US findings. Abdom Imaging 31:449–452

Kunisch M, Hoppe M, Bohle RM, Weimar B, Rauber K, Rau WS (1997) Gallbladder adenocarcinoma in villous adenomatosis (papillomatosis) of the gallbladder and common bile duct (in German). Rofo 166:454–456

Kusakcioglu O, Aykam TB, Kusakcioglu A (1974) Papilloma of the gallbladder. Report of a case. Am J Gastroenterol 62:440–441

Kushima R, Remmele W, Stolte M, Borchard F (1996) Pyloric gland type adenoma of the gallbladder with squamoid spindle cell metaplasia. Pathol Res Pract 192:963–969

Lamarina A (1963) Contribution to the knowledge of papilloma of the gallbladder (in Italian). Osp Maggiore 58:689–705

Lauwers GY, Wahl SJ, Scott GV, DeRoux SJ (1995) Papillary mucinous adenoma arising in adenomyomatous hyperplasia of the gall bladder. J Clin Pathol 48:965–967

Lee KF, Wong J, Li JC, Lai PB (2004) Polypoid lesions of the gallbladder. Am J Surg 188:186–190

Lee SH, Lee DS, You IY, Jeon WJ, Park SM, Youn SJ, Choi JW, Sung R (2010) Histopathologic analysis of adenoma and adenoma-related lesions of the gallbladder (in Korean). Korean J Gastroenterol 55:119–126

Leger L, Chiche B, Soprani A, Louvel A (1976) Papilloma and papillary tumor of the gallbladder (in French. J Chir (Paris) 112:3–14

Lespi PJ (1997) Oncocytic metaplasia in a adenoma of the gallbladder. Histopathology 31:290–292

Levy AD, Murakata LA, Abbott RM, Rohrmann CA (2002) Benign tumors and tumor-like lesions of the gallbladder and extrahepatic bile ducts: radiologic-pathologic correlation. RadioGraphics 22:387–413

Li Q, Yang Z (2009) Expression of phospho-ERK1/2 and PI3-K in benign and malignant gallbladder lesions and its clinical and pathological correlations. J Exp Clin Cancer Res 28:65

Lillemoe KD (2006) Tumors of the gallbladder, bile ducts and ampulla. In: Feldman M, Friedman L, Brandt LJ (eds) Sleisinger and Fortran's gastrointestinal and liver disease. Saunders, Philadelphia, pp 1487–1502

Lin G, Hägerstrand I (1983) Multiple adenomas of the gallbladder. Case report. Acta Pathol Microbiol Immunol Scand 91:475–476

Logani KB, Sharma S, Agarwal K (1995) Tubular adenoma of the gallbladder. J Indian Med Assoc 93:402

Loh A, Kamar S, Dickson GH (1994) Solitary benign papilloma (papillary adenoma) of the cystic duct: a rare cause of biliary colic. Br J Clin Pract 48:167–168

Loitman BS, Cassel MA, Holtz S (1962) Papillomas of the gallbladder. Am J Roentgenol Radium Ther Nucl Med 88:783–791

Lombard R, Dehalleux E, Drèze C (1967) Cancerized papilloma of the cystic duct (in French). Acta Gastroenterol Belg 30:452–459

Lund NM, Burman CE (1951) A case of acute cholecystitis and obstruction due to a pedunculated papilloma, identical with an attack of acute cholecystitis and gallstones. Br J Surg 38:390–392

Macbeath WA (1964) Papillomas of the gallbladder. A technical consideration as illustrated by the three cases. Am J Surg 108:8–12

MacCarthy WC (1910) The pathology of the gall-bladder and some associated lesions. Ann Surg 51:651–669

Magata S, Kai K, Mori M, Edakuni G, Tokunaga O, Miyazaki K (2009) Fibroadenoma of the gallbladder with borderline malignancy: a poorly recognized gallbladder tumor. J Hepatobiliary Pancreat Surg 16:874–877

Makres G, Koutsikos S, Galanes N (1964) Papilloma of the gallbladder (in Swedish). Hell Cheirourgike 11:347–356

Mantero E, Ferrario R, Codega GF (1964) Papilloma of the gallbladder (in Italian). Quad Radiol 29:607–621

Marek S (1955) Papillomatosis of the gallbladder (in Czech). Cesk Gastroenterol Vyz 9:129–132

Marioni E, Zucchi C (1959) Papilloma of the gallbladder (in Italian). Arch Ital Chir 84:240–256

Mayer P (1911) Transformation of the gall-bladder into a papilliferous tumor. J Méd de Bruxelles 16(Suppl):85

Mayo CH (1915) Papillomas of the gall-bladder. Ann Surg 62:193–196

McGregor JC, Cordiner JW (1974) Papilloma of the gallbladder. Br J Surg 61:356–358

McHardy G, Edwards E (1948) Papilloma of the gallbladder; case report. New Orleans Med Surg J 100:573

Miller D (1946) Papilloma of the gallbladder. N Engl J Med 234:473–476

Miyar Gonzalez A (1972) Papillomatosis and cholesterosis of the gallbladder (in Spanish). Rev Esp Enferm Apar Dig 37:791–800

Mogilner JG, Dharan M, Siplovich L (1991) Adenoma of the gallbladder in childhood. J Pediatr Surg 26:223–224

Mohandas D, Saratchandra R, Bhaskar AG, Paul S (1972) Papilloma gallbladder presenting as acute abdomen. Am J Proctol 23:214–217

Molina LM, De Diego JA, Diez M, Delgado I, De Frutos L, Juarez D, Balibrea JL (1988) Obstruction of the bile duct by a papillary adenoma of the gallbladder. Hepatogastroenterology 35:91–93

Mölle H (1916) Ueber papillome der gallenblase, nebst mitteilung eines selbst beobachteten falles. Beitr Klein Chir 99:173–185

Moretti PM, Forni E (1964) Papilloma of the gallbladder. Considerations apropos of a personal observation (in Italian). Arch De Vecchi Anat Patol 44:255–265

Morrison RJG, Stewart PD (1956) Multiple villous papillomas of the gall-bladder. Br Med J 1:966

Myers RP, Shaffer EA, Beck PL (2002) Gallbladder polyps: epidemiology, natural history and management. Can J Gastroenterol 16:187–194

Nagahama M, Muto Y, Yamada M, Shiraishi M, Kusano T, Toda T (1997) Villous adenoma of the gallbladder: a case report. Hepatogastroenterology 44:681–684

Nagata S, Aijoka Y, Nishikura K, Watanabe G, Inoue T, Yamaguchi K, Watanabe H et al (2007) Co-expression of gastric and biliary phenotype in pyloric-gland type adenoma of the gallbladder: immunohistochemical analysis of mucin profile and CD10. Oncol Rep 17:721–729

Nakajo S, Yamamoto M, Urushihara T, Kajitani T, Tahara E (1988) Diffuse papillomatosis of the gallbladder complicated with tuberculosis. Acta Pathol Jpn 38:1473–1480

Nakajo S, Yamamoto M, Tahara E (1990) Morphometrical analysis of gallbladder adenoma and adenocarcinoma with reference to histogenesis and adenoma-carcinoma sequence. Virchows Arch A Pathol Anat Histopathol 417:49–56

Nakamura R, Kondoh M, Mori S, Sasou S (1987) Adenocarcinoma in papillomatosis of the gallbladder: a case report. Nihon Geka Hokan 56:525–530

Nishihara K, Yamaguchi K, Hashimoto H, Enjoji M et al (1991) Tubular adenoma of the gallbladder with squamoid spindle cell metaplasia. Report of three cases with immunohistochemical study. Acta Pathol Jpn 41:41–45

Niv Y, Kosakov K, Shcolnik B (1986) Fragile papilloma (papillary adenoma) of the gallbladder. A cause of recurrent biliary colic. Gastroenterology 91:999–1001

Ochsner SF, Carrera GM (1959) Fibroadenoma of gallbladder: report of a case with cholecystographic visualization. Arch Pathol 68:676–679

Ochsner S, Gage M (1956) Papilloma of the gallbladder with carcinoma-in-situ. Ochsner Clin Rep 2:27–31

Okamoto M, Okamoto H, Kitahara F, Kobayashi K, Karikome K, Miura K, Matsumoto Y, Fujino MA (1999) Ultrasonographic evidence of association of polyps and stones with gallbladder cancer. Am J Gastroenterol 94:446–450

Ono T, Masamune O (1996a) Gallbladder adenoma (pyloric gland type, intestinal type, proper epithelial type, papillary type, mucinous cystic type (in Japanese). Ryoikibetsu Shokogun Shirizu 9:308–310

Ono T, Masamune O (1996b) Gallbladder papilloma (in Japanese). Ryoikibetsu Shokogun Shirizu 9:324–325

Pai RK, Mojtahed K, Pai RK (2011) Mutations in the RAS/RAF/MAP kinase pathway commonly occur in gallbladder adenomas but are uncommon in gallbladder adenocarcinomas. Appl Immunohistochem Mol Morphol 19:133–140

Park CH, Chung MJ, Oh TG, Park JY, Bang S, Park SW, Kim H, Hwang HK, Lee WJ et al (2013) Differential diagnosis between gallbladder adenomas and cholesterol polyps on contrast-enhanced harmonic endoscopic ultrasonography. Surg Endosc 27:1414–1421

Pels-Leusden F (1906) Über papilläre wucherungen in der gallenblase und ihre beziehungen zur cholelithiasis and zum carcinoma. Langenbeck's Arch 5:80

Perazo RR (1967) Adenoma of the gallbladder (in Spanish). Prensa Med Argent 54:1804–1806

Phillips JR (1933) Papilloma of the gall-bladder. Am J Surg 21:38–42

Picardi N, Monti M, Pasta V (1978) Diagnostic and prognostic problems of papillomatosis of the gallbladder (in Italian). Ann Ital Chir 50:79–89

Pila Perez R, Pila Pelaez R, Reguero Jimenez J, Felix Leon J (1991) Adenoma of the gallbladder. Another cause of recurrent biliary colic (in Italian). Rev Esp Enferm Dig 80:345–347

Pohlandt K (1957) Cholecystographic diagnosis of benign tumors of the gallbladder (papillomas). Fortschr Geb Rontgenstr Nuklearmed 87:451–465

Porta E, Verrengia D, Coppola V, Muto R (1981) Echotomographic pattern of the gallbladder papilloma (in Italian). Radiol Med 67:27–30

Pradines P, Legrand I, Besson C, Brauner M (1988) Gallbladder adenoma with carcinoma in situ. Apropos of a case (in French). J Radiol 69:621–623

Reynolds FA (1951) Papilloma of gallbladder. Am J Surg 81:589–591

Ringel T (1899) Papilloma of the gall-bladder. Arch Klin Chir 59:161–166

Roa I, de Aretxabala X, Araya JC, Roa J (2006) Preneoplastic lesions in gallbladder cancer. J Surg Oncol 93:615–623

Roy H, Guha AC, Ghose SM (1957) Papilloma of the gallbladder. J Indian Med Assoc 28:273–275

Sasatomi E, Tokunaga O, Miyazaki K (2000) Precancerous conditions of gallbladder carcinoma: overview of histopathologic characteristics and molecular genetic findings. J Hepatobiliary Pancreat Surg 7:556–567

Sato H, Mizushima M, Ito J, Doi K (1985) Sessile adenoma of the gallbladder. Reappraisal of its importance as a precancerous lesion. Arch Pathol Lab Med 109:65–69

Sawyer KC (1970) The unrecognized significance of papillomas, polyps, and adenomas of the gallbladder. Am J Surg 120:570–578

Scalvini L (1958) Papilloma of the gallbladder (in Italian). Rass Int Clin Ter 38:547–556

Schnug GE (1958) So-called papillomas of the gallbladder. Am J Surg 96:296–301

Schwetz V, Uhrig S, Spuller E, Deutschmann A, Högeneauer C (2012) Manifestations of juvenile polyposis syndrome in SMAD4 mutation carriers of kindred. Eur J Gastroenterol Hepatol 24:988–994

Scoenlank A (1915) Über das papillom der gallenblase. Frankf Zschr Path 16:293–315

Seki S, Kitada T, Sakaguchi H, Hirohashi K, Kinoshita H (2002) Cyclooxygenase-2 expression in the adenoma-carcinoma sequence of human gallbladder. Am J Gastroenterol 97:2146–2147

Selzer DW, Dockerty MB, Stauffer MH, Priestley JT (1962) Papillomas (so-called) in the non-calculous gallbladder. Am J Surg 103:472–476

Stringer MD, Ceylan H, Ward K, Wyatt JI (2003) Gallbladder polyps in children–classification and management. J Pediatr Surg 38:1680–1684

Swinton NW, Becker WT (1948) Tumours of the gallbladder. Surg Clin North Am 28:669–672

Tabah EJ, McNeer G (1953) Papilloma of the gall-bladder with in situ carcinoma. Surgery 34:57–71

Takei K, Watanabe H, Itoi T, Saito T (1996) p53 and Ki-67 immunoreactivity and nuclear morphometry of 'carcinoma-in-adenoma' and adenoma of the gall-bladder. Pathol Int 46:426–435

Tanous JH, Ilano PC, Cruz A (1960) Adenoma of the gallbladder. J Int Coll Surg 34:298–301

Terzi C, Sökmen S, Seckin S, Albayrak L, Ugurlu M (2000) Polypoid lesions of the gallbladder: report of 100 cases with special reference to operative indications. Surgery 127:622–627

Tomic DV, Markovic AR, Alempijevic TM, Davidovic DB, Prsic DR, Vuckovic MS (2011) Ultrasound diagnosis of gallbladder polyps. Acta Chir Iugosl 58:31–35

Toulet J (1967) Vesicular papillomatosis (in French). Actual Hepatogastroenterol (Paris) 3:39–54

Trivedi V, Gumaste VV, Liu S, Baum J (2008) Gallbladder cancer: adenoma-carcinoma or dysplasia-carcinoma sequence ? Gastroenterol Hepatol (NY) 4:735–737

Turrini R, Lanzani G, Salmi A (2007) Gallbladder adenoma with focal adenocarcinoma: a case report (in Italian). Recenti Prog Med 98:505–508

Vadala G, Vadala V, Rizza G, Ingegneros L, Taranto S, Buffone A (1983) Papilloma of the gallbladder. Chir Ital 35:1014–1020

Vieth M, Kushima R, Borchard F, Stolte M (2003) Pyloric gland adenoma: a clinico-pathological analysis of 90 cases. Virchows Arch 442:317–321

Wang SN, Chung SC, Tsai KB, Chai CY, Chang WT, Kuo KK, Chen JS, Lee KT (2006) Aberrant p53 expression and the development of gallbladder carcinoma and adenoma. Kaosiung J Med Sci 22:53–59

Wang W, Ai KX, Yuan Z, Huang XY, Zhang HZ (2013) Different expression of S100A8 in malignant and benign gallbladder diseases. Dig Dis Sci 58: 150–162

Watanabe H, Date K, Toi T, Matsubayashi H, Yokoyama N, Yamano M, Ajioka Y, Nishikura K (1999) Histological and genetic changes in malignant transformation of gallbladder adenoma. Ann Oncol 10(4):136–139

Wellbrock WLA (1934) The occurrence and possible significance of adenoma of the gall bladder. Am J Surg 23:358–360

Wistuba II, Miguel JF, Gazdar AF, Albores-Saavedra J (1999) Gallbladder adenomas have molecular abnormalities different from those present in gallbladder carcinomas. Hum Pathol 30:21–25

Xiong L, Yang Z, Yang L, Liu J, Miao X (2012) Expressive levels of MUC1 and MUC5AC and their clinicopathologic significances in the benign malignant lesions of the gallbladder. J Surg Oncol 105:97–103

Xiong L, Deng X, Wen Y, Yang Z, Miao X (2013) Association of BDNF and BMPR1A with clinicopathologic parameters in benign and malignant gallbladder lesions. World J Surg Oncol 11:80

Yamaguchi K, Maeda S, Kitamura K (1989) papillary adenoma of the gallbladder associated with regurgitation of pancreatic juice through abnormally shaped union. Case report. Acta Chir Scand 155:549–552

Yamamoto M, Nakajo S, Tahara E (1988) Histological classification of epithelial polypoid lesions of the gallbladder. Acta Pathol Jpn 38:181–192

Yamamoto M, Nakajo S, Tahara E (1990) Immunohistochemical analysis of estrogen receptors in human gallbladder. Acta Pathol Jpn 40:14–21

Yamamoto K, Yamamoto F, Meada A, Igimi H, Yamamoto M, Yamaguchi R, Yamashita Y (2014) Tubulopapillary adenoma of the gallbladder accompanied by bile duct tumor thrombus. World J Gastroenterol 20:8736–8739

Yanagisawa N, Mikami T, Saegusa M, Okayasu I (2001) More frequent beta-catenin exon three mutations in gallbladder adenomas than in carcinomas indicate different lineages. Cancer Res 61:19–22

Yang LP, Yang ZL, Tan XG, Miao XY (2010) Expression of annexin A1 (ANXA1) and A2 (ANXA2) and its significance in benign and malignant lesions of gallbladder (in Chinese). Zhonghua Zhong Liu Za Zhi 32:595–599

Yim H, Jin YM, Shim C (1998) Tubular adenoma of the gallbladder with spindle cell metaplasia. J Korean Med Sci 13:295–298

Yu ES, Kim YI (1985) Metaplastic variant of the gallbladder adenoma: a report of a case. Korean J Pathol 19:350–354

Zhang ZX, Yin WH, Zhu ZY (1994) Adenoma of the gallbladder and its canceration: an analysis of 88 cases (in Chinese). Zhonghua Wai Ke Za Zhi 32:400–402

Zhou MJ (1985) Adenoma of the gallbladder–pathologic analysis of 14 cases (in Chinese). Zhonghua Zhong Liu Za Zhi 7:448–450

Hyperplastic Lesions and Metaplastic Changes of the Gallbladder 154

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_154

Abstract

Various types of hyperplastic lesions and metaplastic changes can develop in the gallbladder. Adenomatous hyperplasia of the gallbladder is a condition characterized by a hyperplasia of metaplastic pyloric-type glands and of deep-seated glands in the absence of cellular atypia. Macroscopically, this alteration presents in the form of a thick and nodular gallbladder mucosa, particularly in its diffuse form, but it can also produce polypoid lesions. The epithelial surface of the gallbladder and glandular epithelial can undergo focal to diffuse hyperplastic changes. In one rare form, papillary hyperplasia is present, usually in a diffuse pattern. Adenomyomatous hyperplasia is a reactive alteration characterized by hyperplastic and cystic changes in deep parts of the gallbladder mucosa associated with smooth muscle hypertrophy. This distinct hyperplasia exists in diffuse, segmental or annular, and localized or focal patterns. The gallbladder epithelium can be subject to various metaplastic changes, including pyloric gland metaplasia, antral gland metaplasia, intestinal metaplasia, and squamous cell metaplasia.

Adenomatous Hyperplasia of the Gallbladder

Introduction

Adenomatous hyperplasia of the gallbladder (AHGB) is a condition characterized by a hyperplasia of metaplastic pyloric-type glands and of deep-seated glands in the absence of cellular atypia. AHGB is sometimes interpreted as a pseudotumor of the gallbladder and has no known malignant potential so far (Christensen and Ishak 1970; Lee et al. 2004). The lesion has been included in the spectrum of cholecystitis glandularis proliferans, but AHGB can clearly develop in the absence of inflammatory change of the gallbladder (Kikiros et al. 2003).

Epidemiology

AHGB is often considered to be a rare lesion, but the incidence is difficult to assess owing to the lack of a consensus regarding diagnostic criteria (Piegza et al. 1978; Farinon et al. 1991; Tyagi et al. 1992; Baig et al. 2002; Kikiros et al. 2003; Stokes et al. 2007). Christensen and Ishak (1970) reviewed 180 tumors and pseudotumors of the gallbladder and identified AHGB in 18 cases/10 %. Elfving et al. (1969) reported the gallbladder mucosal hyperplasia was present in 22 % of their 104 patients who had presented with calculous cholecystitis. In a morphologic investigation of 415 cholecystectomy specimens, AHGB was detected in 10.1 % of the gallbladders (Tyagi et al. 1992). In a series of 40 patients from India with cholelithiasis undergoing cholecystectomy, a detailed histologic examination with numerous sections revealed five cases of AHGB. In a retrospective study evaluating gallbladder wall thickening in 342 patients who had undergone MR cholangiography prior to cholecystectomy, 144 patients revealed wall thickening defined as a wall thickness of 3 mm or more, and among these, no case of AHGB was found (Jung et al. 2005). The lesion is much rare in men than in females, with an estimated male to female ratio of 1:13 (Tyagi et al. 1992). Interestingly, AHGB was not seen in gallbladders containing pigment stones, but found in gallbladders containing mixed or cholesterol stones (Baig et al. 2002). AHGB has been observed in the pediatric age group (Kikiros et al. 2003).

Pathology

Macroscopy

Macroscopically, AHGB has been described as lesion with a thick and nodular gallbladder mucosa, at least in the diffuse form (Stokes et al. 2007). It can present as polypoid lesions (Farinon et al. 1991; Kikiros et al. 2003), the polyps being usually small but sometimes clustered to small groups of exophytic lesions.

Histopathology

AHGB is a focal or diffuse lesion (Tyagi et al. 1992). Histologically, the mucosa reveals elongated papillary folds with a fibrotic core and a mild lymphocytic infiltrate. The surface shows hyperplasia of metaplastic pyloric-type glands, while branching mucous glands are found in deeper layers, focally filling the lamina propria. Numerous deep-seated Rokitansky-Aschoff sinuses are common (Stokes et al. 2007). In contrast to adenomyomatosis, hypertrophy of the muscularis is not a feature in AHGB. Cellular atypia is consistently lacking. Tyagi and coworkers (1992) distinguished two types of AHGB: (1) spongious type described as prolonged but coalesced villi and (2) villous type, characterized by abnormally long and ramifying villi. In their material of 415 cholecystectomy specimens, 33.3 % were type 1, 52.4 % were type 2, and 14.3 % were mixed types.

Differential Diagnosis

Adenomyomatosis of the gallbladder resembles in several aspects AHGB, but shows hypertrophy of the muscle layer and extensive Rokitansky-Aschoff sinuses.

Mucosal Hyperplasia of the Gallbladder

Introduction

The surface epithelium and glandular epithelia of the gallbladder mucosa can undergo focal to diffuse hyperplastic changes that may be confounded with precursor lesion of cancer.

Papillary Hyperplasia of the Gallbladder

Introduction

Papillary hyperplasia of the gallbladder (PHGB) is a rare mucosal change characterized by a usually diffuse benign papillary proliferation of gallbladder epithelia (Albores-Saavedra et al. 1990). PHGB comes in two forms, i.e., primary PHGB and secondary PHGB often associated with pancreaticobiliary maljunction. As, in addition to the gallbladder, other parts of the biliary tract can be involved, PHGB may represent an organ-specific manifestation of a systemic biliary disorder. PHGB is usually not found in cholecystolithiasis.

Primary PHGB is a disorder that develops in the entire gallbladder mucosa in the absence of relevant background chronic inflammation-related gallbladder or bile duct disease. It has first been reported in 1990 based on the observation of a young female patient with a papillary hyperplastic lesion involving the mucosa of the entire gallbladder and the cystic and common bile ducts (Albores-Saavedra et al. 1990). Few other descriptions of this condition have since appeared (Celoria et al. 1994; Huang et al. 2001; Stringer et al. 2001; Umudum et al. 2006; Baba et al. 2014). The etiology of primary PHGB is not yet known.

Secondary PHGB is well known to develop in patients with pancreaticobiliary maljunction (PBMJ) (Yamato et al. 1999; Yamaguchi et al. 2009). PHGB in PBMJ exhibits senescent features including expression of p16(INK4A) and senescent-associated beta-galactosidase, low expression of the polycomb group protein EZH2, and low or increased proliferative activity. In contrast, secondary PHGB in PBMJ showing transformation into cancer showed upregulation of EZH2 (Yamaguchi et al. 2009).

Pathology

Macroscopy

Macroscopically, the gallbladder mucosa may be thickened and exhibits an increased granularity of its surface or a diffuse velvety structure, sometimes with tiny frond-like excrescences. In the investigation of Albores-Saavedra et al. (1990), the gallbladder mucosa was pink-yellow and bore numerous small papillary projections ranging from 0.2 to 0.8 cm in height.

Histopathology

Histologically, mucosal folds of the gallbladder are close to one another and taller than normal (Albores-Saavedra et al. 1990). The folds present a villous or papillary pattern with abnormal branching. The hyperplastic-hypertrophic folds are lined by normal-looking-well-differentiated columnar epithelial cells, usually without atypia in primary PHGB. The nuclei are basally or centrally placed. Part of cells exhibit subnuclear vacuoles, and an increased number of pencil-like cells are admixed with the columnar cells. Paneth cells, goblet cells, or argyrophilic cells are not present. In secondary PHGB, focal cellular and nuclear atypia/dysplasia can be found, precursor lesions of papillary gallbladder carcinoma associated with PBMJ (Kinoshita et al. 2002). In the vicinity of papillary to papillary-tubular carcinoma in PBMJ, atypical epithelial hyperplasia was described (Ohta et al. 1990). The nonneoplastic epithelium of secondary PHGB in PBMJ can express mucin core protein MUC1, similar to gallbladder carcinoma (Yamato et al. 1999). It has been proposed that reflux of pancreatic juice caused by maljunction may induce a distinct form of chronic inflammatory change in the gallbladder favoring the development of hyperplasic, dysplastic, and finally neoplastic alterations.

Differential Diagnosis

Differential diagnosis of PHGB includes papillomatosis of the gallbladder, multiple villous adenomas, and highly differentiated papillary carcinoma.

Glandular Hyperplasia of the Gallbladder

Glandular hyperplasia is a rare form of mucosal hyperplasia. It was observed in a small child with choledochal cyst, where the gallbladder mucosa displayed cribriform proliferation of the gland base of the mucosa, associated with the presence of hyperplastic glandular structures within lymph vessels, but in the absence of malignant change (Hirayama et al. 2009).

Adenomyomatous Hyperplasia

Introduction

Adenomyomatous hyperplasia/adenomyomatosis of the gallbladder (synonyms: diverticular disease of the gallbladder, adenomyosis of the gallbladder, cholecystitis glandularis proliferans, intramural diverticulosis of the gallbladder) is a well-recognized reactive alteration of the gallbladder, characterized by hyperplastic and cystic changes of deep parts of the mucosal epithelium associated with muscle hypertrophy. Together with cholesterolosis, adenomyomatosis has been allocated to a group of disorders termed hyperplastic cholecystoses, a term denoting reactive, benign alterations sharing a hyperplastic reaction of mucosal cells (Jutras 1960; Halin 1964; Feltner 1966; Jelaso et al. 1967; Lubera et al. 1967; Govoni 1981; Berk et al. 1983). It seems that most of the cases previously described as cholecystitis cystica in fact represent adenomyomatosis.

Selected References Eiserth 1938; Akerlund and Rudhe 1950; Caroli et al. 1951; King 1952, 1953; Zinober 1952; Burt and Masel 1955; Ross et al. 1955; Le Quesne and Ranger 1957; Rush et al. 1957; Goldberg and Dodgson 1958; Ludin 1960; Halpert 1961; Verhage and Van der Werff 1964; Brown et al. 1966; reviews: Owen and Bilhartz 2003.

Classification

Based on the distribution pattern and the extension of the lesions, adenomyomatosis is divided into three major types (Table 1).

Mass-forming lesions in localized or segmental adenomyomatosis are sometimes termed adenomyoma (Eiserth 1938; Maderna and Tritto 1959; Young 1959; Andrei and Nobile 1960; Caldone Firrao 1960; Ochsner 1962; Bricker and Halpert 1963; Jutras et al. 1964; Levesque

Table 1 Types of adenomyomatosis

Diffuse (generalized) adenomyomatosis, in which the entire gallbladder mucosa is involved
Segmental (annular) adenomyomatosis, whereby only one gallbladder segment is involved, with a ringlike involvement of one gallbladder part
Localized (focal) adenomyomatosis, whereby only a circumscribed part is involved, most often in the gallbladder fundus

et al. 1964; Tompkins 1967; Inoue and Matsuda 1978; Herrmann and Saul 1986). An adenomyoma is defined as a nodular mural lesion composed of fascicles of smooth muscle cells and clusters of dilated, hyperplastic biliary-type glands. The term is misleading insofar as "adenomyomas" developing in the setting of adenomyomatosis are not true benign neoplasms, but reactive nodular lesions. Focal/isolated adenomyomas mostly occur in the gallbladder fundus (Eiserth 1938).

Epidemiology

Lesions of the adenomyomatosis spectrum were first described by Sutherland (1898) and Eiserth (1938) under the term adenomyoma of the gallbladder. Since then, this entity has been further characterized in numerous reports. It seems that adenomyomatosis is detectable in 2–5 % of all cholecystectomies. In a study of 4,704 consecutive cholecystectomies, adenomyomatosis was detected in 2.4 % (Kim et al. 2010). In a further analysis of 30 patients, age at diagnosis ranged from 22 to 77 years (mean, 52.3 years), and the male to female ratio was 8:7. Twelve cases were segmental, ten were diffuse/generalized, and eight were fundal lesions. In 20 patients, the lesions were associated with gallstones (Kasahara et al. 1992). Gallbladder adenomyomatosis also occurs in the pediatric age group (Alberti et al. 1998; Zani et al. 2005; Akçam et al. 2008).

Selected References Colquhoun 1961; Katz and Rickard 1963; Fotopoulos and Crampton 1964; Seyss 1966; Bevan 1970; Heald 1970; Davies 1971; Frommhold and Lagemann 1971; McCormick and Lang 1971; Skapinker 1971; Ram and Midha 1975; Muto et al. 1978; Hidalgo and Lewicki 1980; Meguid et al. 1984; Kidney et al. 1986; Williams et al. 1986; Costa-Greco 1987; Halpert et al. 1989; Kasahara et al. 1992; Yang et al. 1996; Chang et al. 1998; Secil et al. 2005; Boscak et al. 2006; Dirks et al. 2006; Lin et al. 2011; Ray et al. 2012.

Clinical and Imaging Features

In most patients, adenomyomatosis is clinically silent. Some patients report vague abdominal pain or occasional colics, but these may be caused by accompanying gallstone disease. In fact, adenomyomatosis is often associated with cholecystolithiasis. Specifically, the segmental variant of adenomyomatosis seems to predispose to cholecystolithiasis (Nishimura et al. 2004). Among 64 cases of adenomyomatosis, 38 had black pigment stones, alone ($N = 22$) or in association with singe ($N = 12$) or multiple ($N = 4$) cholesterol gallstones. At least in initial phases of stone formation, Rokitansky-Aschoff sinuses were found close to small intraparietal vessels, and sometimes they contained black pigment microstones (Cariati and Cetta 2003). A subset of gallbladder adenomyomatosis is associated with anomalous pancreatobiliary ductal union (Wu et al. 1995; Chang et al. 1998). The fundal (localized) type of adenomyomatosis seems to differ from the other types in several respects. It has a lower frequency of gallstones and a lower inflammatory grade (Kim et al. 2010).

Sonographically, the main feature is a localized or generalized thickening of the gallbladder wall with a generally smooth outer contour. Small intramural cysts are identifiable in part of the cases, and gallbladder contractility is preserved, in contrast to malignancy (Rice et al. 1981; Raghavendra et al. 1983; Sagar and Naik 1984; Izumi et al. 1985; Fowler and Reid 1988; Brambs et al. 1990; Gerard et al. 1990; Hwang et al. 1998). The intramural foci may show "comet tail" reverberation artifacts, indicative of cholesterol crystals within Rokitansky-Aschoff sinuses. These

"comet tails" extend from the near wall into the anechoic lumen (Boscak et al. 2006; Mariani and Hsue 2011). Postcontrast CT images demonstrate the characteristic rosary sign or necklace sign, formed by the enhanced epithelial structures in the intramural diverticula surrounded by the non-enhancing hypertrophied muscle tissue (Chao et al. 1992; Zissin et al. 2003; Ching et al. 2007; Poonam et al. 2008; Stunell et al. 2008). The rosary or necklace signs are mostly found in the diffuse form of adenomyomatosis, while the segmental form often presents as a dumbbell-shaped gallbladder, and the localized form either presents as a polypoid structure or a nodular mass lesion ("adenomyoma"). The so-called pearl necklace sign is a typical feature of adenomyomatosis and is also well visualized at magnetic resonance cholangiopancreatography (MRCP; Haradome et al. 2003). The pocket-like wall lesions are best seen on CT in the fundal type of adenomyomatosis (Klose et al. 1991). In marked adenomyomatosis, CT imaging may result in findings mimicking gallbladder carcinoma (Agrawal et al. 2012). On MR, T1-weighted images reveal a diffusely thickened gallbladder wall and intramural cavities, which are hyperintense on T2-weighted images. The cavities represent Rokitansky-Aschoff sinuses (Yoshimitsu et al. 1999; Boscak et al. 2006). The phenotype of nonneoplastic and neoplastic gallbladder disease as displayed on MR images has been divided into four layered patterns, viz., type 1 shows two layers with a thin hypointense inner layer and thick hyperintense outer layer; type 2 has two layers of ill-defined margin; type 3 reveals multiple hyperintense cystic spaces in the gallbladder wall; and type 4 shows a diffuse nodular thickening without layering. Adenomyomatosis was correlated with type 3, while types 1 and 2 were typical for chronic and acute cholecystitis, respectively, and type 4 was a characteristic for gallbladder carcinoma (Jung et al. 2005).

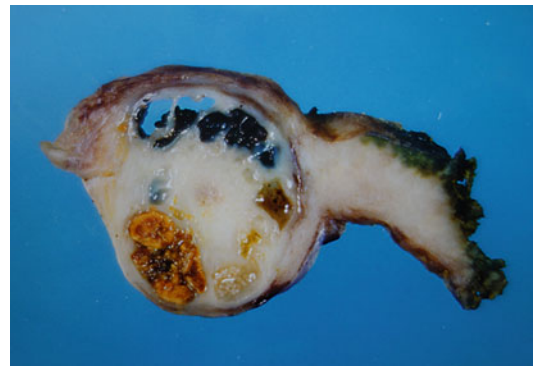

Fig. 1 Adenomyosis of the gallbladder. The cystic spaces contain black stones, and a brown concrement is impacted in scar tissue

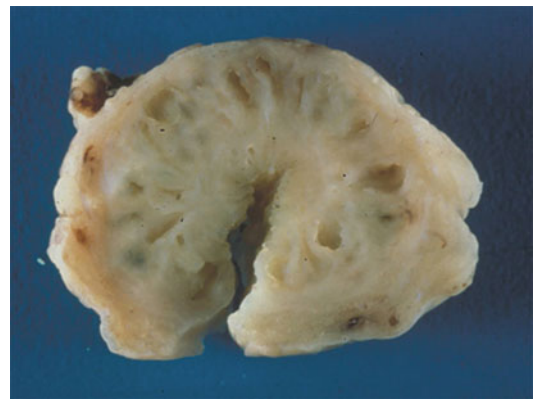

Fig. 2 Adenomyosis of the gallbladder with slit-like or microcystic spaces radially arranged around the gallbladder lumen

Pathology

Macroscopy

In most cases, the gallbladder wall is markedly thickened, up to 2 cm or even more. On sections, the wall shows multiple pockets or intramural cystic structures, which may contain gallstones, stone fragments, or glittering accumulations of cholesterol crystals (Figs. 1 and 2). Fundic adenomyomatosis can bulge with excessive subserosal fat tissue of the gallbladder, producing a mass lesion (Miyake et al. 1992; Shimoji et al. 2001).

Histopathology

Adenomyomatosis is characterized by hyperplastic mucosal pockets, cystically dilated Rokitansky-Aschoff sinuses, which are embedded

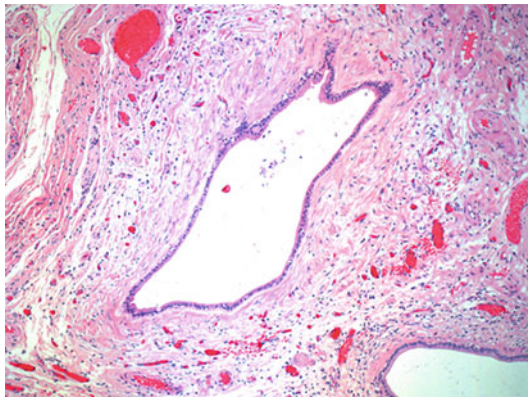

Fig. 3 Adenomyosis of the gallbladder. Cystic spaces are lined by a regular epithelium and surrounded by smooth muscle cells and a fibroblastic tissue (hematoxylin and eosin stain)

in a hyperplastic-hypertrophic muscle layer, usually with only minor or no inflammatory infiltrates, but with some fibrotic changes in advanced stages of the disease (Fig. 3). In part of the cases, Rokitansky-Aschoff sinuses are very prominent and appear as elongated and dilated, sometimes cystic epithelial pockets resembling diverticula. Hyperplastic changes may also be noted in more superficial epithelia of the mucosa. The mucosal pockets (Rokitansky-Aschoff sinuses) often contain inspissated bile, in part of the cases intermingled with stones, stone fragments, and/or cholesterol crystals. Adenomyoma, mostly seen in the fundal variant of adenomyomatosis (Ozgonul et al. 2010), is characterized by a nodule, predominantly fundic, of hypertrophic smooth muscle cells, containing distorted and in part cystically dilated glandular structures.

Differential Diagnosis

Radiologically, gallbladder cancer with intratumoral anechoic foci can be a mimic of adenomyomatosis (Ishizuka et al. 1998). Well-differentiated gallbladder adenocarcinoma with intratumoral cystic components and abundant mucin production may mimic adenomyomatosis (Yoshimitsu et al. 2005).

Is Adenomyomatosis a Precancerous Lesion?

So far, it is not known whether adenomyomatosis has any clinical significance and whether it will truly lead to inflammation or even cancer (Chan-Wilde et al. 1990). Based on the observation of dysplastic changes and the association of gallbladder carcinoma with adenomyomatosis, it has been suggested that adenomyomatosis might represent a premalignant condition (Bevan 1970; Aldridge et al. 1991; Funabiki et al. 1993; Kurihara et al. 1993; Imai et al. 2011). Diffuse adenomyomatosis was found to be associated with dysplastic gallbladder adenoma (Di Carlo et al. 2010). There is one reported case of papillary mucinous adenoma arising in adenomyomatous hyperplasia of the gallbladder (Lauwers et al. 1995). Early gallbladder adenocarcinoma has been found in association with adenomyomatosis (Fujita et al. 1988). A causal relationship between adenomyomatosis and carcinoma has been suggested based on a close spatial relationship of the two lesions (Paraf and Potet 1988). In one case, noninvasive carcinoma of the gallbladder was found in the mucosa overlying localized type of adenomyomatosis with a papillary adenoma in one of the cystic structures (Katoh et al. 1988). There is some evidence that the segmental form of adenomyomatosis predisposes to gallbladder carcinoma (Ootani et al. 1992; Kai et al. 2011). In a study of 4,560 consecutive patients undergoing cholecystectomies, 60 clinically noncancerous gallbladders with segmental adenomyomatosis were examined for epithelial alterations. Histology revealed previously unrecognized carcinoma in 6.6 % of cases, while the other types of adenomyomatosis did not show any significant increase in the incidence of gallbladder cancer, suggesting that segmental adenomyomatosis may represent a high-risk condition for carcinoma, especially in elderly patients (Nabatame et al. 2004).

Pathogenic Pathways

Etiology and pathogenesis of adenomyomatosis are not known. A pathogenic role of an increased

intra-gallbladder pressure has been suggested, with a pressure-induced dilatation and proliferation of Rokitansky-Aschoff sinuses, but this mechanistically oriented hypothesis fails to have any support.

Rokitansky-Aschoff Sinuses

Rokitansky-Aschoff sinuses (RAS or crypts), already discussed in the previous paragraph as a component of adenomyomatosis, are intramural diverticulum-like invaginations of gallbladder epithelium with an associated sheath of fibroblastoid cells with extracellular matrix. RAS extend down the gallbladder wall through smooth muscle gaps. The deep-most reaching RAS reach the peri-/extramuscular connective tissue (Zinober 1952; Ross et al. 1955; Rush et al. 1957; Halpert 1961; reviews: Albores-Saavedra and Henson 1984; Albores-Saavedra et al. 1998). In addition to their role in adenomyomatous hyperplasia, RAS are commonly found in gallbladder resection specimens irrespective of the presence of bona fide adenomyomatosis. In a Japanese series of 540 consecutive cholecystectomies, RAS were detected in 65 % of cases (Terada 2013).

Histologically, RAS are pocket-like, long, and often tortuous invaginations lined by a single layer of biliary-type columnar cells. At the bottom, RAS may show considerable branching, mainly at the gallbladder outlet and the first part of the cystic duct, causing crowded epithelial tubular clusters that may be confounded with well-differentiated adenocarcinoma. However, in contrast to carcinoma, epithelia of RAS lack any relevant atypia, reveal no increased mitotic activity, are in continuation with the mucosal surface, show an organoid/lobular texture, and lack the cellular stroma characterizing carcinoma. In addition, cells of RAS are not reactive for p53 protein and exhibit a very low proliferative activity based on MIB1 immunostaining (Dorantes-Heredia et al. 2013). RAS may accumulate mucin in their lumina which sometimes escapes into the extracellular space, simulating mucinous carcinoma of the gallbladder, but again the participating cells are p53 negative and low proliferative (Albores-Saavedra et al. 2009). In the course of chronic fibrosing cholecystitis, the necks of RAS may be stenosed or even obliterated, causing fluid stasis followed by cystic dilatation, sometimes with trapping of thickened bile, cholesterol crystals, or stones in the lumina. The etiology and pathogenesis of RAS are not yet known, although factors such as increased luminal pressure and weakness of the muscle layer have been discussed. It has also been proposed that chronic cholecystitis may weaken mural muscle bundles and hence reduce their capability to resist to outpouchings (Stalker et al. 1955).

Metaplastic Changes of the Gallbladder

Introduction

Similar to other organs of the gastrointestinal tract, the mucosa of the gallbladder can undergo several types of epithelial metaplasia, gastric metaplasia and intestinal metaplasia being the most common forms (Pessel et al. 1950). Apart from its differential diagnostic importance, metaplasia plays a role as a potential precursor lesion for carcinogenic pathways (Yamagiwa and Tomiyama 1986; Inada et al. 1989; Duarte et al. 1993; Lewis et al. 2007; Meirelles-Costa et al. 2010), an issue further discussed in the chapter on gallbladder carcinoma.

Gastric Metaplasia

General Features

Gastric gland metaplasia of the gallbladder is defined as the presence of gastric-type glands, either single or in groups, within the mucosa (lamina propria) or, less commonly, in the muscularis of the gallbladder. The areas of gastric metaplasia can contain pyloric, antral or mucous glands, or mixtures thereof. Neuroendocrine cells may also occur (Yamamoto et al. 1986). The frequency of gastric metaplasia of the gallbladder varies considerably among reports, ranging from 66 % to more than 80 %. The metaplastic changes

are often associated with chronic cholecystitis, and formation of lymph follicles (cholecystitis follicularis) has been found in association with metaplasia, but mainly in cases with *H. pylori* infection (Misra et al. 2007). Gastric metaplasia may also occur within adenocarcinomas of the gallbladder (Azadeh and Parai 1980).

Pyloric Gland Metaplasia

Pyloric gland metaplasia (pseudopyloric gland metaplasia) is identified in several parts of the gastrointestinal tract, including the gallbladder. PGM seems to be a common metaplastic change of the gallbladder (Fig. 4). Among 540 consecutive cholecystectomy specimens, PGM was detected in 54 % of cases (Terada 2013). PGM was classified into complete and incomplete types on the basis of mucin expression and immunoreactivities for pepsinogens I and II. The complete type of PGM is characterized by neutral mucins and weak pepsinogen I and strong pepsinogen II activities, like normal pyloric gland cells. The incomplete type contains acid mucins and was further subdivided into an incomplete type 1, having pepsinogen II but no pepsinogen I activity, and an incomplete type 2, with no pepsinogen activity (Tatematsu et al. 1987). The cells of PGM are reactive for the apomucin MUC6 (Sasaki et al. 1999). Interestingly, PGM can extend into the muscular wall and serosa of the gallbladder. In this florid PGM, metaplastic glands composed of cytologically bland cuboidal or columnar mucin-containing cells may show perineural and/or intraneural invasion, an intriguing alteration that can be confused with adenocarcinoma. The pathogenesis of this alteration has, similar to corresponding changes in other organs, not yet been clarified (Albores-Saavedra and Henson 1999). This metaplasia seems to develop from epithelial zones with increased proliferative activity (a transitional zone), and as this zone enlarges, shallow pits become apparent, containing pepsinogen II-positive cells and then the pits becoming deeper as the process advances, until the zone gradually resembles that of the normal gastric pylorus mucosa (Shimizu et al. 1996). PGM must not be confounded with pyloric gland adenoma of the gallbladder, which represents a small circumscribed tumor of the gallbladder mucosa composed of pyloric glands and sometimes aberrantly expressing an intestinal cell marker, Cdx2 (Sakamoto et al. 2007; Wani et al. 2008).

Antral Gland Metaplasia

In antral gland metaplasia (AGM), the metaplastic island consists of cuboidal to rather short columnar cells with cytoplasmic and nuclear features of antral cells (Fig. 5; Laitio 1976). The metaplastic antral glands contain sulfated and non-sulfated acid mucins (Buitrago Salassa and Javier Lespi

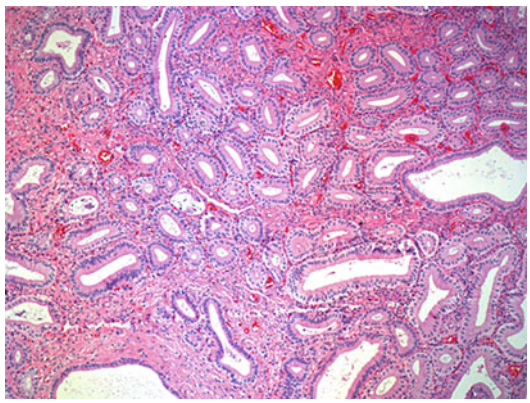

Fig. 4 Pyloric gland metaplasia of the gallbladder (hematoxylin and eosin stain)

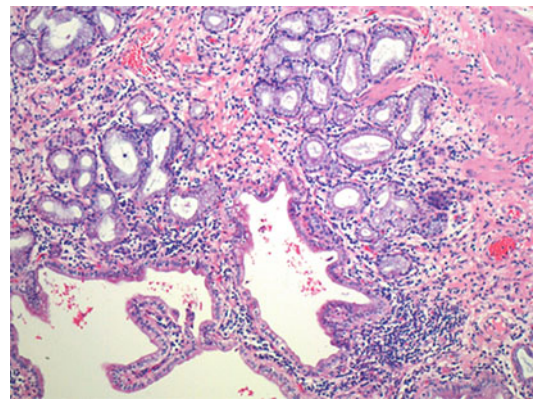

Fig. 5 Antral gland metaplasia of the gallbladder (hematoxylin and eosin stain)

2007). AGM may be mixed with pyloric gland metaplasia. Some reports described the presence of *Helicobacter pylori* in areas of gastric metaplasia (Misra et al. 2007), while other authors failed to detect *H. pylori* in these metaplastic lesions (Arnaout et al. 1990).

Gastric Heterotopia Versus Gastric Metaplasia

In contrast to metaplasia, which is an acquired condition, gastric heterotopia of the gallbladder is a rare congenital lesion that was first described in 1934 (Egyedi 1934). The lesion is discussed in more detail in a separate paragraph and may be confounded with gastric metaplasia of the gallbladder (Yamamoto et al. 1989). The diagnosis requires the identification of a focus composed of an entire (full-thickness) gastric-type mucosa, usually fundic, with PAS-positive foveolar cells, chief and parietal cells, and sometimes abundant pyloric glands (Isik et al. 2002; Ben Brahim et al. 2011). Gastric heterotopia often forms a bulged mucosal area or a polypoid lesion and less commonly an intramural nodular mass (Boyle et al. 1992; Vallera and Dawson 1992; Uchiyama et al. 1995; Leyman et al. 1996; Hamazaki and Fujiwara 2000; Sciumè et al. 2005; Cöl et al. 2007), whereas metaplastic lesions are commonly flat. Furthermore, gastric heterotopia is detected more frequently in younger adults and is mostly found in the gallbladder neck or even in the cystic duct (Isik et al. 2002), whereas metaplasia shows a more extended distribution. Gastric heterotopia may be associated with focal intestinal metaplasia with goblet cells in the surrounding gallbladder mucosa (Xeropotamos et al. 2001; Isik et al. 2002; Tavli et al. 2005).

Intestinal Metaplasia

Intestinal metaplasia (IM) of the gallbladder is characterized by the presence of areas composed of intestinal columnar cells, goblet cells, neuroendocrine cells and Paneth cells, and a distinct mucin expression mode (Ganesh et al. 2007). Complete IM was found in 9.8–85.7 % of gallbladders with gallstone disease, mainly in patients less than 40 years of age (Järvi and Laurén 1967; Kozuka and Hachisuka 1984; Dowling and Kelly 1986; Yamagiwa and Tomiyama 1986; Yamagiwa 1989; Jukemura 1996; Ghiur et al. 1997; Mukhopadhyay and Landas 2005; Fernandes et al. 2008; Sakamoto et al. 2009; Khan et al. 2011), but there are also reports with markedly lower frequencies of IM in cholelithiasis, e.g., 5.4 % (Jukemura 1996). Apart from geographical and genetic differences, variations in criteria used to identify IM may play a role for these marked differences. It was claimed that the frequency of IM increases as a function of increasing age, but this was not confirmed in all reports. Specifically, one study found a peak in incidence in individuals younger than 40 years (Fernandes et al. 2008). Histologic features consistent with IM were also identified in the pediatric age group, where the presence of intestinal gallbladder features seems to be a physiological trait (Zen et al. 2011). On the other hand, IM of the gallbladder in children has also been observed in the setting of pancreaticobiliary maljunction (Ono et al. 2011). Goblet cells are a feature of IM, but their mere presence as such does not suffice for a diagnosis of IM. Goblet cells were detected in more than half of gallbladder specimens in one study (Laitio 1980). Sporadic goblet cells commonly occurred in so-called goblet cell areas which, as small lesions, are usually located in the tops of gallbladder mucosal folds. IM develops when goblet cells also involve deeper parts of folds, associated with a change from sulfated mucins to non-sulfated mucins and the emergence of intestinal-type columnar cells and eventually enterochromaffin cells (Laitio 1975; Laitio and Nevalainen 1975a). Less commonly, IM can also contain Paneth cells (Laitio and Nevalainen 1975b). Ultrastructurally, intervening columnar cells (enterocyte-like cells) contain cytoplasmic mucin granules (Laitio and Nevalainen 1975b). IM cells express large intestinal mucin antigen/LIMA and small intestinal mucin antigen/SIMA (De Boer et al. 1981). Cells of IM are reactive for the transcription factor, Cdx2 (Sakamoto

et al. 2007, 2009). Based on the absence of the presence of endocrine cells, Albores-Saavedra and coworkers (1986) divided IM into two groups. The gallbladder with IM lacking endocrine cells contained isolated or small clusters of mature goblet cells, while those with endocrine cells, in addition to goblet cells, contained argyrophil and argentaffin cells and, less frequently, Paneth cells and gland-like structures resembling colonic crypts. Both groups showed pyloric gland and superficial gastric-type epithelium. The most common endocrine cells were serotonin-positive elements. Based on these findings, the involvement of an endodermal stem cell was suggested (Albores-Saavedra et al. 1986).

Squamous Cell Metaplasia

This is, in comparison with other forms of metaplasia, one of the least common variants. It is characterized by the replacement of a glandular gallbladder epithelium by a stratified squamous cell epithelium (keratinocytes) with or without keratinization (Fig. 6). Massive and diffuse squamous cell metaplasia with keratinization can result in a pseudoepidermoid cyst of the gallbladder, mimicking a gallbladder tumor (Teo et al. 2005). Extended squamous cell metaplasia of the gallbladder with dysplastic changes can occur in association with squamous cell carcinoma (Hanada et al. 1986). A component of squamous cell metaplasia was found in gastric heterotopia of the gallbladder (Daud et al. 2007) and in a tubular adenoma (Colovic et al. 2006).

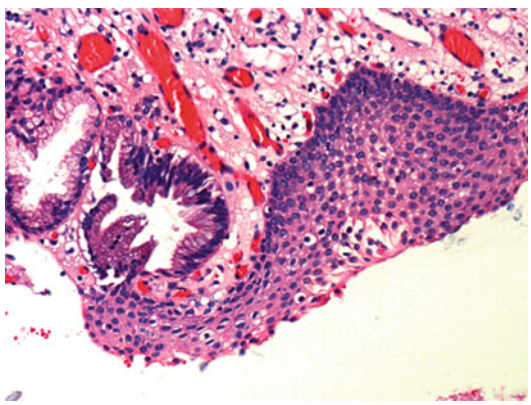

Fig. 6 Squamous cell metaplasia of the gallbladder (hematoxylin and eosin stain)

Other Forms of Epithelial Gallbladder Metaplasia

Ciliated gallbladder epithelium has been observed in a patient with duplication of the gallbladder (Raeburn 1969).

Mesenchymal Metaplastic Changes of the Gallbladder

Osseous metaplasia (or heterotopic bone) is a very rare alteration of the gallbladder, sometimes associated with chronic cholecystitis (Il'chenko et al. 2011; Rege and Vargas 2011). This type of metaplasia can present as a focal hyperdense lesion that may be confounded with a gallstone (Nelson and Kahn 2009). Osseous gallbladder metaplasia was observed in association with polypoid cholesterolosis (Ortiz-Hidalgo and Baquera-Heredia 2000). A similar type of metaplasia rarely develops in the stroma of gallbladder carcinomas (stromal osseous metaplasia; Cavazza et al. 1999).

Pathogenesis

Similar to other organs having a glandular mucosa, metaplastic changes in the gallbladder are thought to be caused, or their development favored, by chronic inflammatory disease, but the exact pathogenic pathways are not yet elucidated. There is recent evidence that several enterohepatic *Helicobacter* (*H.*) species can occur in inflammatory disorders and gallstone disease of the gallbladder and may play a pathogenic role, including *H. hepaticus*, *H. bilis*, *H. pullorum*, and *H. pylori* (Apostolov et al. 2005; Kobayashi et al. 2005; Hamada et al. 2009; Karagin et al. 2010; Lee et al. 2010; Boonyanugomol et al. 2012; Attaallah et al. 2013; Javed et al. 2013). *Helicobacter* infection of gallbladder mucosa in patients with chronic

cholecystitis was associated with metaplasia (Zhou et al. 2013). In one study, *H. pullorum* was only found in gallbladders with metaplasia (Karagin et al. 2010).

References

Agrawal S, Khurana J, Daruwala C (2012) Gallbladder adenomyomatosis: a malignant masquerader. Dig Liver Dis 44:e23

Akçam M, Buyukyavuz I, Ciris M, Eris N (2008) Adenomyomatosis of the gallbladder resembling honeycomb in a child. Eur J Pediatr 167:1079–1081

Akerlund A, Rudhe U (1950) Intramural small-cystic diverticulosis of the gallbladder. Acta Radiol 33:147–164

Alberti D, Callea F, Camoni G, Falchetti D, Rigamonti W, Caccia G (1998) Adenomyomatosis of the gallbladder in childhood. J Pediatr Surg 33:1411–1412

Albores-Saavedra J, Henson DE (1984) Tumors of the gallbladder and extrahepatic bile ducts, Atlas of tumor pathology, second series, fascicle 22. Armed Forces Institut of Pathology, Washington, DC

Albores-Saavedra J, Henson DE (1999) Pyloric gland metaplasia with perineural invasion of the gallbladder: a lesion that can be confused with adenocarcinoma. Cancer 86:2625–2631

Albores-Saavedra J, Nadji M, Henson DE, Ziegels-Weissman J, Mones JM (1986) Intestinal metaplasia of the gallbladder: a morphologic and immunocytochemical study. Hum Pathol 17:614–620

Albores-Saavedra J, Defortuna SM, Smothermon WE (1990) Primary papillary hyperplasia of the gallbladder and cystic and common bile ducts. Hum Pathol 21:228–231

Albores-Saavedra J, Henson DE, Klimstra DS (1998) Tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater, Atlas of tumo pathology, third series, fascicle 27. Armed Forces Institute of Pathology, Washington, DC

Albores-Saavedra J, Galliani C, Chable-Montero F, Batich K, Hensen DE (2009) Mucin-containing Rokitansky-Aschoff sinuses with extracellular mucin deposits simulating mucinous carcinoma of the gallbladder. Am J Surg Pathol 33:1633–1638

Aldridge MC, Gruffaz F, Castaing D, Bismuth H (1991) Adenomyomatosis of the gallbladder. A premalignant lesion? Surgery 109:107–110

Andrei A, Nobile F (1960) A characteristic benign tumor of the gallbladder: adenomyoma (in Italian). Atti Accad Fisiocrit Siena Med Fis 8:874–882

Apostolov E, Al-Soud WA, Nilsson I, Kornilovska I, Usenko V, Lyzogubov V, Gaydar Y et al (2005) Helicobacter pylori and other Helicobacter species in gallbladder and liver of patients with chronic cholecystitis detected by immunological and molecular methods. Scand J Gastroenterol 40:96–102

Arnaout AH, Abbas SH, Shousha S (1990) Helicobacter pylori is not identified in areas of gastric metaplasia of gall bladder. J Pathol 160:333–334

Attaallah W, Yener N, Ugurlu MU, Manukyan M, Asmaz E, Aktan AO (2013) Gallstones and concomitant gastric Helicobacter pylori infection. Gastroenterol Res Pract 2013:643109

Azadeh B, Parai SK (1980) Argentaffin cells, intestinal metaplasia and antral metaplasia in carcinoma of the gall bladder. Histopathology 4:653–659

Baba H, Wakabayashi M, Oba A, Tsubomoto T, Nakamura H, Sanada T, Kuwabara H et al (2014) Primary papillary hyperplasia of the gallbladder mimicking gallbladder cancer. Int Surg 99:247–251

Baig SJ, Biswas S, Das S, Basu K, Chattopadhyay G (2002) Histopathological changes in gallbladder mucosa in cholelithiasis: correlation with chemical composition of gallstones. Trop Gastroenterol 23:25–27

Ben Brahim E, Jouini R, Aboulkacem S, Jaouadi F, Labbene N, Cherif R, Helal Y, Sayed S et al (2011) Gastric heterotopia: clinical and histological study of 12 cases (in French). Tunis Med 89:935–939

Berk RN, van der Vegt JH, Lichtenstein JE (1983) The hyperplastic cholecystoses: cholesterolosis and adenomyomatosis. Radiology 146:593–601

Bevan G (1970) A calculous adenomyomatosis of the gallbladder. Gut 11:1029–1034

Bonnyanugomol W, Chomvarin C, Sripa B, Bhudhisawasdi V, Khuntikeo N, Hahnvajanawong C et al (2012) Helicobacter pylori in Thai patients with cholangiocarcinoma and its association with biliary inflammation and proliferation. HPB (Oxford) 14:177–184

Boscak AR, Al-Hawary M, Ramsburgh SR (2006) Best cases from the AFIP: adenomyomatosis of the gallbladder. Radiographics 26:941–946

Boyle L, Gallivan MV, Chun B, Lack EE (1992) Heterotopia of gastric mucosa and liver involving the gallbladder. Report of two cases with literature review. Arch Pathol Lab Med 116:138–142

Brambs HJ, Wrazidlo W, Schilling H (1990) The sonographic image of gallbladder adenomyomatosis (in German). Röfo 153:633–636

Bricker DL, Halpert B (1963) Adenomyoma of the gallbladder. Surgery 53:615–620

Brown HW, Goodsitt E, Snearly R (1966) Cholecystitis glandularis proliferans. Int Surg 45:650–654

Buitrago Salassa C, Javier Lespi P (2007) Detection of acid mucins in gastric metaplasia of the gallbladder (in Spanish). Acta Gastroenterol Latinoam 37:11–14

Burt LI, Masel H (1955) Cholecystitis glandularis proliferans; (diverticula of the gall-bladder). Med J Aust 42:270–272

Caldone Firrao G (1960) Adenomyoma of the gallbladder (in Italian). Policlinico Prat 67:1483–1488

Cariati A, Cetta F (2003) Rokitansky-Aschoff sinuses of the gallbladder are associated with black pigment gallstone formation: a scanning electron microscopy study. Ultrastruct Pathol 27:265–270

Caroli J, Paraf A, Beaugrand G (1951) Contribution to the study of multilobular gallbladders; radiological study of the Rokitansky-Aschoff sinuses; nature of this formation (in French). Arch Mal Appar Dig Mal Nutr 40:886–887

Cavazza A, De Marco L, Asioli S, Pastore L, Gardini G (1999) Stromal osseous metaplasia in metastatic adenocarcinoma of the gallbladder. Tumori 85:133–134

Celoria GC, Rodriguez Otero JC, Proske SA, Vallilengua C (1994) Papillary hyperplasia and cholesterolosis of the gallbladder. Medicine (B Aires) 54:31–34

Chang LY, Wang HP, Wu MS, Huang HT, Wang HH, Lin CC, Lin JT (1998) Anomalous pancreaticobiliary ductal union – an etiologic association of gallbladder cancer and adenomyomatosis. Hepato-Gastroenterology 45:2016–2019

Chan-Wilde C, Chew R, Foong WC, Wee A (1990) Adenomyomatosis of the gallbladder: the NUH experience. Ann Acad Singap 19:389–392

Chao C, Hsiao HC, Wu CS, Wang KC (1992) Computed tomographic finding in adenomyomatosis of the gallbladder. J Formos Med Assoc 91:467–469

Ching BH, Yeh BM, Westphalen AC, Joe BN, Qayyum A, Coakley FV (2007) CT differentiation of adenomyomatosis and gallbladder cancer. AJR Am J Roentgenol 189:62–66

Christensen AH, Ishak KG (1970) Benign tumors and pseudotumors of the gallbladder. Report of 180 cases. Arch Pathol 90:423–432

Cöl C, Boran C, Turkeli V, Dinler K, Kordon O, Erkol H, Sengul N (2007) Heterotopic gastric mucosa in gallbladder associated with kidney agenesis and congenital hip dysplasia. Acta Clin Belg 62:120–122

Colovic R, Grubor N, Radak V, Micev M, Colovic N, Stojkovic M (2006) Tubular adenoma of the gallbladder with squamous metaplasia (in Serbian). Srp Arh Celok Lek 134:159–161

Colquhoun J (1961) Adenomyomatosis of the gall-bladder (intramural diverticulosis). Br J Radiol 34:101–112

Costa-Greco MA (1987) Adenomyomatosis of the gallbladder. J Clin Ultrasound 15:198–199

Daud MS, Salomao FC, Salomao EC, Salomao BC (2007) Gastric heterotopia together with squamous metaplasia in the gallbladder. Acta Gastroenterol Latinoam 37:164–167

Davies W (1971) Six cases of gall-bladder adenomyomatosis (cholecystitis glandularis proliferans). Australas Radiol 15:148–155

De Boer WG, Ma J, Rees JW, Nayman J (1981) Inappropriate mucin production in gall bladder metaplasia and neoplasia – an immunohistological study. Histopathology 5:295–303

Di Carlo I, Toro A, Pulvirenti E, Zisa M, Galia A (2010) An unusual association of diffuse adenomyomatosis with dysplastic adenoma in chronic calculous cholecystitis: case presentation. BMC Gastroenterol 10:41

Dirks K, Deuerling J, Mühldorfer S (2006) Erscheinungsformen der Adenomyomatose der Gallenblase. Ultraschall Med 27:4

Dorantes-Heredia R, Chablé-Montero F, Henson DE, Albores-Saavedra J (2013) Rokitansky-Aschoff sinuses mimicking adenocarcinoma of the gallbladder: a study of 8 cases. Am J Surg Pathol 37:1269–1274

Dowling GP, Kelly JK (1986) The histogenesis of carcinoma of the gallbladder. Cancer 58:1702–1708

Duarte I, Llanos O, Domke H, Harz C, Valdiviedo V (1993) Metaplasia and precursor lesions of gallbladder carcinoma. Frequency distribution, and probability of detection in routine histologic samples. Cancer 72:1878–1884

Egyedi L (1934) Case of polypus of gallbladder containing aberrant gastric mucous membrane. Gyogyaszat 74:596–599

Eiserth P (1938) Adenomyome der Gallenblase. Virchows Arch Path Anat 302:717–723

Elfving G, Teir H, Degert H, Mäkelà V (1969) Mucosal hyperplasia in the gallbladder demonstrated by plastic models. Acta Pathol Microbiol Scand 77:384–388

Farinon AM, Pacella A, Cetta F, Sianesi M (1991) "Adenomatous polyps of the gallbladder" adenomas of the gallbladder. HPB Surg 3:251–258

Feltner WR (1966) Hyperplastic cholecystoses. Rocky Mt Med J 63:47–50

Fernandes JE, Franco MI, Suzuki RK, Tavares NM, Bromberg SH (2008) Intestinal metaplasia in gallbladders: prevalence study. Sao Paulo Med J 126:220–222

Fotopoulos JP, Crampton AR (1964) Adenomyomatosis of the gallbladder. Med Clin N Am 48:9–36

Fowler RC, Reid WA (1988) Ultrasound diagnosis of adenomyomatosis of the gall-bladder: ultrasonic and pathological correlation. Clin Radiol 39:402–406

Frommhold W, Lagemann K (1971) Adenomyomatosis of the gallbladder (in German). Fortschr Geb Röntgenstr Nuklearmed 115:464–475

Fujita N, Lee S, Kobayashi G, Yano A, Mochizuki F (1988) Early gallbladder carcinoma associated with adenomyomatosis of the gallbladder: report of a case (in Japanese). Nihon Shokakibyo Gakkai Zasshi 85:1536–1541

Funabiki T, Matsumoto S, Tsukada N, Kimura T, Yoshizaki S, Horibe Y (1993) A patient with early gallbladder cancer derived from a Rokitansky-Aschoff sinus. Surg Today 23:350–355

Ganesh IM, Subramani D, Halagowder D (2007) Mucin glycoarray in gastric and gallbladder epithelia. J Carcinog 6:10

Gerard PS, Berman D, Zafranloo S (1990) CT and ultrasound of gallbladder adenomyomatosis mimicking carcinoma. J Comput Assist Tomogr 14:490–491

Ghiur M, Pantelie C, Ghiur L (1997) Cholecystopathies with mucosal metaplasia of the intestinal type (in Romanian). Chirurgia (Bucur) 92:349–354

Goldberg HM, Dodgson MCH (1958) Cholecystitis cystica and related lesions. Br J Surg 45:374–378
Govoni AF (1981) Hyperplastic cholecystosis: an analysis and review of the different pathologic and radiologic aspects. Radiol Diagn (Berl) 22:557–588
Halin L (1964) Hyperplastic cholecystoses. J Am Osteopath Assoc 64:381–396
Halpert B (1961) Significance of the Rokitansky-Aschoff sinuses. Am J Gastroenterol 36:534–539
Halpert RD, Bedi DG, Tirman PJ, Gore DC (1989) Segmental adenomyomatosis of the gallbladder. A radiologic, sonographic and pathologic correlation. Am Surg 55:570–572
Hamada T, Yokota K, Ayada K, Hirai K, Kamada T, Haruma K, Chayama K, Oguma K (2009) Detection of Helicobacter hepaticus in human bile samples of patients with biliary disease. Helicobacter 14:545–551
Hamazaki K, Fujiwara T (2000) Heterotopic gastric mucosa in the gallbladder. J Gastroenterol 35:376–381
Hanada M, Shimizu H, Talami M (1986) Squamous cell carcinoma of the gallbladder associated with squamous metaplasia and adenocarcinoma in situ of the mucosal columnar epithelium. Acta Pathol Jpn 36:1879–1886
Haradome H, Ichikawa T, Sou H, Yoshikawa T, Nakamura A, Araki T, Hachiya J (2003) The pearl necklace sign: an imaging sign of adenomyomatosis of the gallbladder at MR cholangiopancreatography. Radiology 227:80–88
Heald RJ (1970) Adenomyomatosis as a source of error in the diagnosis of gall-bladder disease. Br J Surg 57:353–356
Herrmann PK, Saul WM (1986) Clinical pathology of adenomyoma of the gallbladder (in German). Zentralbl Allg Pathol 131:379–382
Hidalgo HJ, Lewicki AM (1980) Adenomyomatosis of the gallbladder. Am J Gastroenterol 73:81–84
Hirayama Y, Kubota M, Hasegawa G, Okuyama N, Ohtaki M, Kobayashi K, Tsukada M, Sato K, Nishikura K et al (2009) A case of a choledochal cyst associated with a lymphatic infiltration of a hyperplastic gallbladder epithelium. J Pediatr Surg 44:831–835
Huang CS, Lien HH, Jeng JY, Huang SH (2001) Role of laparoscopic cholecystectomy in the management of polypoid lesions of the gallbladder. Surg Laparosc Endosc Percutan Tech 11:242–247
Hwang JI, Chou YH, Tsay SH, Chiang JH, Chang CY, Boland GW, Mueller PR (1998) Radiologic and pathologic correlation of adenomyomatosis of the gallbladder. Abdom Imaging 23:73–77
II'chenko AA, Orlova IuN, Khomeriki SG (2011) Bone metaplasia in the gallbladder wall (in Russian). Eksp Klin Gastroenterol 8:86–90
Imai H, Osada S, Sasaki Y, Ikawa A, Takahashi T, Yamaguchi K, Hirose Y, Yoshida K (2011) Gallbladder adenocarcinoma with extended intramural spread in adenomyomatosis of the gallbladder with the pearl necklace sign. Am Surg 77:E57–E58
Inada A, Konishi F, Yamamichi N, Ito H (1989) Histogenesis of gallbladder cancer with special reference to metaplastic changes and distribution of various mucins and CEA (in Japanese). Nihon Geka Gakkai Zasshi 90:894–906
Inoue S, Matsuda H (1978) A case of adenomyoma of the gallbladder with gastric polyps (in Japanese). Nihon Shokakibyo Gakkai Zasshi 75:366–373
Ishizuka D, Shirai Y, Tsukada K, Hatakeyama K (1998) Gallbladder cancer with intratumoral anechoic foci: a mimic of adenomyomatosis. Hepato-Gastroenterology 45:927–929
Isik I, Sezer C, Dursun A (2002) Gastric heterotopia in the gallbladder: a case report. Turk J Gastroenterol 13:172–174
Izumi N, Koyama W, Irie T, Miyakawa H, Ito Y, Kanayama M, Hasumura Y, Takeuchi J (1985) Ultrasonography and computed tomography in adenomyomatosis of the gallbladder. Acta Radiol Diagn (Stockh) 26:689–692
Järvi O, Laurén P (1967) Intestinal metaplasia in the mucosa of the gallbladder and common bile duct with additional observations on pancreas heterotopy. Ann Med Exp Biol Fenn 45:213–223
Javed S, Mejias-Luque R, Kalali B, Bolz C, Gerhard M (2013) Helicobacter bilis gamma-glutamyltranspeptidase enhances inflammatory stress response via oxidative stress in colon epithelial cells. PLoS ONE 8:e73160
Jelaso D, Burdick CO, Brown RK (1967) Hyperplastic cholecystosis – segmental adenomyomatosis type. Report of two cases. Arch Surg 95:70–73
Jukemura J (1996) Colelitiase e risco de cancer de vesicula biliar, Thesis, Facultade de Medicina da Universitade de Sao Paulo, Brazil
Jung SE, Lee JM, Lee K, Rha SE, Choi BG, Kim EK, Hahn ST (2005) Gallbladder wall thickening: MR imaging and pathologic correlation with emphasis on layered pattern. Eur Radiol 15:694–701
Jutras JA (1960) Hyperplastic cholecystoses; Hickey lecture, 1960. Am J Roenetgenol Radium Ther Nucl Med 83:795–827
Jutras A, Levesque HP, Larini GP (1964) Adenomyoma and adenomyomatosis of the gallbladder (in Italian). Nunt Radiol 30:1223–1245
Kai K, Ide T, Masuda M, Kitahara K, Miyoshi A, Miyazaki K, Noshiro H, Tokunaga O (2011) Clinicopathologic features of advanced gallbladder cancer associated with adenomyomatosis. Virchows Arch 459:573–580
Karagin PH, Stenram U, Wadström T, Ljungh A (2010) Helicobacter species and common gut bacterial DNA in gallbladder with cholecystitis. World J Gastroenterol 16:4817–4822
Kasahara Y, Sonobe N, Tomiyoshi H, Imano M, Nakatani M, Urata T, Morishita A et al (1992) Adenomyomatosis of the gallbladder: a clinical survey of 30 surgically treated patients. Nihon Geka Hokan 61:190–198
Katoh T, Nakai T, Hayashi S, Satake T (1988) Noninvasive carcinoma of the gallbladder arising in localized type adenomyomatosis. Am J Gastroenterol 83:670–674

Katz JS, Rickard EH (1963) Adenomyosis of the gallbladder. S Afr Med J 37:1011–1014
Khan MR, Raza SA, Ahmad Z, Naeem S, Pervez S, Siddiqui AA, Ahmed M, Azami R (2011) Gallbladder intestinal metaplasia in Pakistani patients with gallstones. Int J Surg 9:482–485
Kidney M, Goiney R, Cooperberg PL (1986) Adenomyomatosis of the gallbladder: a pictorial exhibit. J Ultrasound Med 5:331–333
Kikiros C, Arunachalam P, Lam MH (2003) Adenomatous hyperplastic polyp of the gall bladder associated with cholelithiasis in a child. Pediatr Surg Int 19:118–199
Kim JH, Jeong IH, Han JH, Kim JH, Hwang JC, Yoo BM, Kim JH, Kim MW, Kim WH (2010) Clinical/pathological analysis of gallbladder adenomyomatosis; type and pathogenesis. Hepato-Gastroenterology 57:420–425
King ES (1952) Cholecystitis glandularis (Rokitansky-Luschka-Aschoff sinuses) and related conditions. Aust NZ J Surg 22:100–110
King ES (1953) Cholecystitis glandularis and diverticula of the gall-bladder. Br J Surg 41:156–161
Kinoshita H, Hara M, Hashino M, Nishimura K, Kodama T, Hamada S, Matsuo H, Yasunaga M et al (2002) A case of gallbladder cancer associated with pancreaticobiliary maljunction. Kurume Med J 49:61–65
Klose KC, Persigehl M, Biesterfeld S, Günther RW (1991) Adenomyomatosis of the gallbladder in CT (in German). Radiologie 31:73–81
Kobayashi T, Harada K, Miwa K, Nakanuma Y (2005) Helicobacter genus DNA fragments are commonly detectable in bile from patients with extrahepatic biliary diseases and associated with their pathogenesis. Dig Dis Sci 50:862–867
Kozuka S, Hachisuka K (1984) Incidence by age and sex of intestinal metaplasia in the gallbladder. Hum Pathol 15:779–784
Kurihara K, Mizuseki K, Ninomiya T, Shoji I, Kajiwara S (1993) Carcinoma of the gall-bladder arising in adenomyomatosis. Acta Pathol Jpn 43:82–85
Laitio M (1975) Goblet cells, enterochromaffin cells, superficial gastric-type epithelium and antral-type glands in the gallbladder. Beitr Pathol 156:343–358
Laitio M (1976) Intestinal, gastric body- and antral-type mucosal metaplasia in the gallbladder. Beitr Pathol 159:271–279
Laitio M (1980) Morphology and histochemistry of non-tumorous gallbladder epithelium. A series of 103 cases. Pathol Res Pract 167:335–345
Laitio M, Nevalainen T (1975a) Ultrastructure of endocrine cells in metaplastic epithelium of human gall bladder. J Anat 120:219–225
Laitio M, Nevalainen J (1975b) An electron microscopic study of intestinal metaplasia in human gallbladder. Beitr Pathol 155:297–308
Lauwers GY, Wahl SJ, Scott GV, DeRoux SJ (1995) Papillary mucinous adenoma arising in adenomyomatous hyperplasia of the gall bladder. J Clin Pathol 48:965–967
Le Quesne LP, Ranger I (1957) Cholecystitis glandularis proliferans. Br J Surg 44:447–458
Lee KF, Wong J, Li JC, Lai PB (2004) Polypoid lesions of the gallbladder. Am J Surg 188:186–190
Lee JW, Lee DH, Lee JI, Jeong S, Kwon KS, Kim HG, Shin YW, Kim YS, Choi MS et al (2010) Identification of Helicobacter pylori in gallstone, bile, and other hepatobiliary tissues of patients with cholecystitis. Gut Liver 4:60–67
Levesque HP, Longtin M, Jutras A (1964) Adenomyoma of the gallbladder. Anatomic and radiological findings (in French). Union Med Can 93:1487–1506
Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC (2007) Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. Am J Surg Pathol 31:907–913
Leyman P, Saint-Marc O, Hannoun L, Parc R (1996) Heterotopic gastric mucosa presenting as gallbladder polyps. Acta Chir Belg 96:128–129
Lin SH, Chang FY, Yang YS, Jin JS, Chen TW (2011) Rare gallbladder adenomyomatosis presenting as atypical cholecystitis: case report. BMC Gastroenterol 11:106
Lubera RJ, Climie AR, Kling GE (1967) Cholecystitis and the hyperplastic cholecystoses: a clinical, radiologic, and pathology study. Am J Dig Dis 12:696–704
Ludin H (1960) Pseudopolypous cholecystitis (cholecystitis glandularis proliferans) with lymphatic cysts of the adjacent parietal peritoneum (in German). Fortschr Geb Röntgenstr Nuklearmed 93:133–135
Maderna N, Tritto VA (1959) Adenomyoma of the gallbladder (in Italian). Riforma Med 73:1026–1030
Mariani PJ, Hsue A (2011) Adenomyomatosis of the gallbladder: the "good omen" comet. J Emerg Med 40:415–418
McCormick DL, Lang EK (1971) Adenomyomatosis and prominent Aschoff-Rokitansky sinuses of the gallbladder. J La State Med Soc 123:322–323
Meguid MM, Aun F, Bradford ML (1984) Adenomyomatosis of the gallbladder. Am J Surg 147:260–262
Meirelles-Costa AL, Bresciani CJ, Perez RO, Bresciani BH, Siqueria SA, Cocconello I (2010) Are histological alterations observed in the gallbladder precancerous lesions ? Clinics (Sao Paulo) 65:143–150
Misra V, Misra SP, Dwivedi M, Shouche Y, Dharne M, Singh PA (2007) Helicobacter pylori in areas of gastric metaplasia in the gallbladder and isolation of H. pylori DNA from gallstones. Pathology 39:419–424
Miyake H, Aikawa H, Hori Y, Mori H, Sakamoto I, Matsuoka Y, Himeno K, Yamashita H (1992) Adenomyomatosis of the gallbladder with subserosal fatty proliferation: CT findings in two cases. Gastrointest Radiol 17:21–23
Mukhopadhyay S, Landas SK (2005) Putative precursors of gallbladder dysplasia: a review of 400 routinely resected specimens. Arch Pathol Lab Med 129:386–390
Muto Y, Uchimura M, Waki S, Sameshima Y, Lin T, Matsumoto T, Kadono H, Tsugane Y et al (1978) Clinicopathological study of 37 cases of adenomyomatosis (localized type) of the gallbladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 75:1756–1767

Nabatame N, Shirai Y, Nishimura A, Yokoyama N, Wakai T, Hatakeyama K (2004) High risk of gallbladder carcinoma in elderly patients with segmental adenomyomatosis of the gallbladder. J Exp Clin Cancer Res 23:593–598

Nelson JJ, Kahn AG (2009) A case of bone metaplasia of the gallbladder epithelium. South Med J 102:322–324

Nishimura A, Shirai Y, Hatakeyama K (2004) Segmental adenomyomatosis of the gallbladder predisposes to cholecystolithiasis. J Hepatobiliary Pancreat Surg 11:342–347

Ochsner SE (1962) Adenomyoma of the gallbladder. Am J Roentgenol Radium Ther Nucl Med 88:778–782

Ohta T, Nagakawa T, Ueno K, Maeda K, Ueda N, Kayahara M, Akiyama T, Kanno M et al (1990) Clinical experience of biliary tract carcinoma associated with anomalous union of the pancreaticobiliary ductal system. Jpn J Surg 20:36–43

Ono S, Fumino S, Iwai N (2011) Implications of intestinal metaplasia of the gallbladder in children with pancreaticobiliary maljunction. Pediatr Surg Int 27:237–240

Ootani T, Shirai Y, Tsukada K, Muto T (1992) Relationship between gallbladder carcinoma and the segmental type of adenomyomatosis of the gallbladder. Cancer 69:2647–2652

Ortiz-Hidalgo C, Baquera-Heredia J (2000) Osseous metaplasia in polypoid cholesterolosis. Am J Surg Pathol 24:895

Owen CC, Bilhartz LE (2003) Gallbladder polyps, cholesterolosis, adenomyomatosis, and acute acalculous cholecystitis. Semin Gastrointest Dis 14:178–188

Ozgonul A, Bitiren M, Guldur ME, Sogut O, Yilmaz LE (2010) Fundal variant adenomyomatosis of the gallbladder: report of three cases and review of the literature. J Clin Med Res 2:150–153

Paraf F, Potet F (1988) Gallbladder carcinoma arising in adenomyomatosis. Am J Gastroenterol 83:1439

Pessel JF, Beairsto EB, Wise JB, Greeley JP, Rathmell TK (1950) Gastro-intestinal mucosa in the wall of the human gall-bladder. Gastroenterology 15:533–540

Piegza S, Tyszkiewicz S, Turczynski J, Szklarz Z (1978) Adenomatous hyperplasia in chronic cholecystitis and its significance in carcinogenesis (in Polish). Wiad Lek 31:1667–1670

Poonam Y, Ashu S, Rohini G (2008) Clinics in diagnostic imaging (121). Gallbladder adenomyomatosis. Singap Med J 49:262–264

Raeburn C (1969) Ciliated epithelium occurring in duplication of the gall bladder. J Pathol 97:402–403

Raghavednra BN, Subramanyam BR, Blathazar EJ, Horii SC, Megibow AJ, Hilton S (1983) Sonography of adenomyomatosis of the gallbladder: radiologic-pathologic correlation. Radiology 146:747–752

Ram MD, Midha D (1975) Adenomyomatosis of the gallbladder. Surgery 78:224–229

Ray R, Dey R, Chatterjee S, Guha P (2012) Gallbladder adenomyomatosis with tubercular portal lymphadenopathy masquerading as gallbladder carcinoma. Arab J Gastroenterol 13:150–152

Rege TA, Vargas SO (2011) Cholecystitis and cholelithiasis associated with an intramural fasciitis-like proliferation and osseous metaplasia. Pediatr Dev Pathol 14:80–83

Rice J, Sauerbrei EE, Semogas P, Cooperberg PL, Burhenne HJ (1981) Sonographic appearance of adenomyomatosis of the gallbladder. J Clin Ultrasound 9:336–337

Ross WD, Finby N, Evans JA (1955) Intramural diverticulosis of the gallbladder; Rokitansky-Aschoff sinuses. Radiology 64:366–372

Rush DK, Figiel LS, Figiel SJ (1957) Rokitansky-Aschoff sinuses; historical review and presentation of three cases. Grace Hosp Bull 35:53–61

Sagar G, Naik DR (1984) Ultrasound diagnosis of adenomyomatosis of the gall bladder. Br J Radiol 57:432–435

Sakamoto H, Mutoh H, Ido K, Satoh K, Hayakawa H, Sugano K (2007) A close relationship between intestinal metaplasia and Cdx2 expression in human gallbladders with cholelithiasis. Hum Pathol 38:66–71

Sakamoto H, Mutoh H, Ido K, Satoh S, Kumagai M, Hayakawa H, Tamada K, Sugano K (2009) Intestinal metaplasia in gallbladder correlates with high amylase levels in bile in patients with a morphologically normal pancreaticobiliary duct. Hum Pathol 40:1762–1767

Sasaki M, Yamato T, Nakanuma Y, Ho SB, Kim YS (1999) Expression of MUC2, MUC5AC and MUC6 apomucins in carcinoma, dysplasia and non-dysplastic epithelia of the gallbladder. Pathol Int 49:38–44

Sciumè C, Geraci G, Pisello E, Li VE, Facella T, Modica G (2005) Heterotopic gastric mucosa in the gallbladder: case report and literature review. Ann Ital Chir 76:93–97

Secil M, Karasu S, Sagol O, Coker A (2005) Combined segmental and focal adenomyomatosis involving the body of the gallbladder. J Clin Ultrasound 33:248–250

Seyss R (1966) Schizotonia of the gallbladder (segmental adenomyosis). Zentralbl Chir 91:1364–1366

Shimizu M, Kitoh K, Fujimitsu Y, Inada K, Ichinose M, Miki K, Yamao K, Nakazawa S et al (1996) Cellular differentiation and development of pyloric mucosal metaplasia in the human gall-bladder. Pathol Int 46:261–266

Shimoji H, Nakachi A, Matsubara H, Miyazato H, Isa T, Hiroyasu S, Shiraishi M, Muto Y (2001) Fundic adenomyomatosis bulged with the subserosal excessive fat of the gallbladder mimicking polypoid carcinoma: a case report with unusual imaging and morphological features. Clin Imaging 25:187–191

Skapinker S (1971) Adenomyomatosis of the gallbladder. S Afr J Surg 9:143–146

Stalker LK, Davies B, Guest TP (1955) Rokitansky-Aschoff sinuses as related to chronic cholecystitis. AMA Arch Surg 71:124–127

Stokes MC, Burnette R, Ballard B, Ross C, Beech DJ (2007) Adenomatous hyperplasia of the gallbladder. J Natl Med Assoc 99:959–961

Stringer MD, Abbott C, Arthur RJ, Lealman G (2001) Primary papillary hyperplasia of the gallbladder: a rare cause of biliary colic. J Pediatr Surg 36:1584–1586

Stunell H, Buckley O, Geoghegan T, O'Brien J, Ward E, Torreggiani W (2008) Imaging of adenomyomatosis of the gall bladder. J Med Imag Radiat Oncol 52:109–117

Sutherland LR (1898) Small adeno-myoma of the gallbladder. Glasg Med J 50:216–217

Tatematsu M, Furihata C, Miki K, Ichinose M, Shirai T, Tatematsu K, Ito N (1987) Complete and incomplete pyloric gland metaplasia of human gallbladder. Acta Pathol Jpn 37:39–46

Tavli L, Belviranli M, Erikoglu M, Esen H, Toy H (2005) Gastric heterotopia together with intestinal metaplasia in the gallbladder: case report and review of literature. Turk J Gastroenterol 16:160–162

Teo CH, Leow CK, Chang SA (2005) A pseudoepidermoid cyst arising from exuberant squamous metaplasia of the gallbladder. Arch Pathol Lab Med 129:e138–e140

Terada T (2013) Histopathologic features and frequency of gall bladder lesions in consecutive 540 cholecystectomies. Int J Clin Exp Pathol 6:91–96

Tompkins RK (1967) Surgical management of solitary adenomyoma of the gallbladder. Am Surg 33:415–418

Tyagi SP, Tyagi N, Maheshwari V, Ashraf SM, Sahoo P (1992) Morphological changes in diseased gall bladder: a study of 415 cholecystectomies at Aligarh. J Indian Med Assoc 90:178–181

Uchiyama S, Imai S, Suzuki T, Anita A, Takeda K, Sujino H, Kameda H (1995) Heterotopic gastric mucosa of the gallbladder. J Gastroenterol 30:543–546

Umudum H, Gunbatili E, Sanal M, Ceyhan K (2006) Primary diffuse papillary hyperplasia of the gallbladder. Pathology 38:591–592

Vallera DU, Dawson PJ (1992) Gastric heterotopia in the gallbladder. Path Res Pract 188:49–52

Verhage F, Van der Werff JJ (1964) Intramural diverticulosis (Rokitansky-Aschoff sinuses) in septate gallbladder. NY State J Med 64:3006–3009

Wani Y, Notohara K, Fujisawa M (2008) Aberrant expression of an "intestinal marker" Cdx2 in pyloric gland adenoma of the gallbladder. Virchows Arch 453:521–527

Williams I, Slavin G, Cox A, Simpson P, de Lacey G (1986) Diverticular disease (adenomyomatosis) of the gallbladder: a radiological-pathological survey. Br J Radiol 59:29–34

Wu MS, Wang HP, Shun CT, Yu SC, Wang TH, Lin JT (1995) Coexistence of anomalous pancreaticobiliary ductal union with adenomyomatosis of the gallbladder. Gastrointest Endosc 42:265–269

Xeropotamos N, Skopelitou AS, Batsis C, Kappas AM (2001) Heterotopic gastric mucosa together with intestinal metaplasia and moderate dysplasia in the gall bladder: report of two clinically unusual cases with literature review. Gut 48:719–723

Yamagiwa H (1989) Mucosal dysplasia of gallbladder: isolated and adjacent lesions to carcinoma. Jpn J Cancer Res 80:238–243

Yamagiwa H, Tomiyama H (1986) Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. Acta Pathol Jpn 36:989–997

Yamaguchi J, Sasaki M, Harada K, Zen Y, Sato Y, Ikeda H, Itatsu K, Yokoyama Y et al (2009) Papillary hyperplasia of the gallbladder in pancreaticobiliary maljunction represents a senescence-related lesion induced by lysolecithin. Lab Invest 89:1018–1031

Yamamoto M, Nakajo S, Tahara E (1986) Endocrine cells and lysozyme immunoreactivity in the gallbladder. Arch Pathol Lab Med 110:920–927

Yamamoto M, Murakami H, Ito M, Nakajo S, Tahara E (1989) Ectopic gastric mucosa of the gallbladder: comparison with metaplastic polyp of the gallbladder. Am J Gastroenterol 84:1423–1426

Yamato T, Kurumaya H, Ohama K, Yamamichi N, Watanabe Y, Harada K, Sasaki M et al (1999) Frequent expression of mucin core protein MUC1 in non-neoplastic gallbladder mucosa from patients with pancreaticobiliary maljunction. Liver 19:281–287

Yang WG, Wang SS, Weng YJ, Tsay SH, Chen CC, Chiang JH, Su CH, Lee FY, Lee SD (1996) Adenomyomatosis of the gallbladder. Zhonghua Yi Xue Za Zhi (Taipei) 58:12–17

Yoshimitsu K, Honda H, Jimi M, Kuroiwa T, Hanada K, Irie H, Tajima T, Takashima M et al (1999) MR diagnosis of adenomyomatosis of the gallbladder and differentiation from gallbladder carcinoma: importance of showing Rokitansky-Aschoff sinuses. AJR Am J Roentgenol 172:1535–1540

Yoshimitsu K, Irie H, Aibe H, Tajima T, Nishie A, Asayama Y, Matake K, Yamaguchi K et al (2005) Well-differentiated adenocarcinoma of the gallbladder with intratumoral cystic components due to abundant mucin production: a mimicker of adenomyomatosis. Eur Radiol 15:229–233

Young TE (1959) So-called adenomyoma of the gallbladder. Am J Clin Pathol 31:423–427

Zani A, Pacilli M, Conforti A, Casati A, Bosco S, Cozzi DA (2005) Adenomyomatosis of the gallbladder in childhood: report of a case and review of the literature. Pediatr Dev Pathol 8:577–580

Zen Y, Zen C, Quaglia A, Davenport M, Heaton N, Portmann B (2011) Intestinal phenotypes in pediatric gallbladder epithelium. Hum Pathol 42:1454–1458

Zhou D, Guan WB, Wang JD, Zhang Y, Gong W, Quan ZW (2013) A comparative study of clinicopathological features between chronic cholecystitis patients with and without Helicobacter pylori infection in gallbladder mucosa. PLoS ONE 8:e70265

Zinober M (1952) Rokitansky-Aschoff sinuses of the gall bladder; their demonstration during cholecystography. S Afr Med J 26:35

Zissin R, Osadchy A, Shapiro-Feinberg M, Gayer G (2003) CT of a thickened-wall gall bladder. Br J Radiol 76:137–143

Neuroendocrine Tumors of the Gallbladder

155

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_155

Abstract

Similar to the hepatobiliary tract, the gallbladder is a well-known origin of diverse types of neuroendocrine tumors. Previously, most of these neoplasms were classified as carcinoid tumors, irrespective of their grade of malignancy and differentiation. Today, the same classifications as used as in other anatomical locations are employed for gallbladder neuroendocrine tumors. As malignant neuroendocrine neoplasms, including those that arise in the hepatobiliary tract, can metastasize, the distinction between primary and metastatic gallbladder lesions may be difficult. Generally, solitary lesions and those with an endoluminal growth may more commonly represent primary neoplasms. As in other locations, grading of neuroendocrine neoplasms of the gallbladder is performed in accordance with the ENETS scheme.

ICD-O codes
Neuroendocrine tumor (NET)
NET G1 (carcinoid) 8240/3
NET G2 8249/3
Neuroendocrine carcinoma (NEC) 8246/3
Large cell NEC 8013/3
Small cell NEC 8041/3
MANEC 8244/3

Introduction

As in other locations, including the ampullary region and the extrahepatic bile ducts, neuroendocrine tumors primary to the gallbladder were preferentially termed carcinoids or carcinoid tumors, irrespective of their grade of malignancy and differentiation. The term carcinoid is now reserved for well-differentiated neuroendocrine tumors, according to the 2010 WHO classification (NET G1), while other forms of neuroendocrine tumors are allocated to distinct entities that are different from carcinoids. The novel WHO classification defines neuroendocrine neoplasms of the gallbladder as neoplasms with neuroendocrine differentiation, including NET, neuroendocrine carcinoma (NEC), and mixed adenoneuroendocrine carcinoma (MANEC) (Komminoth et al. 2010).

Classification of Neuroendocrine Neoplasms

Following the widely employed 2000 WHO classification of neuroendocrine tumors, the novel 2010 classification introduced new categories and nomenclatures, summarized in Table 1. The designation "neuroendocrine" instead of "endocrine" is now adopted to indicate that cell lineages involved in the neoplastic process express neural markers. The term, neuroendocrine neoplasm, can be employed as a synonym of neuroendocrine tumor.

The difference between WDET and WDEC was defined according to staging features in the WHO classification. The novel category, NET G2, does not necessarily translate into WDEC of the WHO 2000 classification. NEC should not be termed, NET G3, as NET is per definition a well-differentiated neoplasm.

Grading of Neuroendocrine Neoplasms

As in other locations, grading of gallbladder neuroendocrine tumors is now performed in accordance to the ENETS scheme (Rindi et al. 2006, 2007). The criteria are listed in Table 2. Pillars for this proliferation-based grading system are the mitotic count and the proliferation fraction assessed through the Ki-67 index. This grading

Table 1 WHO classifications (2000 and 2010) of neuroendocrine neoplasms

WHO 2000	WHO 2010
1. Well-differentiated endocrine tumor (WDET)	1. NET G1 (carcinoid)
2. Well-differentiated endocrine carcinoma (WDEC)	2. NET G2
3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	3. NEC (large cell or small cell type)
4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
5. Tumor-like lesions (TLL)	5. Hyperplastic and preneoplastic

Table 2 ENETS grading of neuroendocrine tumors

G1: Mitotic count <2 per 10 HPF and/or < = 2 % Ki-67 index
G2: Mitotic count 2–20 per 10 HPF and/or 3–20 % Ki-67 index
G3: Mitotic count >20 per 10 HPF and/or >20 % Ki-67 index

requires mitotic counts in at least 50 high-power fields (HPF), 1 HPF representing 2 mm^2 of tissue. Grading may, therefore, be difficult or not reliable in very small biopsy samples. The determination of the Ki-67 index (MIB1 immunostaining) requires the analysis of 500–2,000 tumor cells assessed in areas of homogeneous and strongest nuclear labeling (so-called "hot spots"). In case differences in grade determination between mitotic count and Ki-67 index occur, it is proposed that the higher grade be assumed.

Staging Systems for Neuroendocrine Neoplasms of the Gallbladder

In contrast to other gastrointestinal sites harboring neuroendocrine tumors, there is still no proposal for a TNM/staging classification of neuroendocrine neoplasms of the gallbladder. It has therefore been suggested that, for definitely malignant neuroendocrine neoplasms of the gallbladder, and in particular for NEC, the TNM system used for gallbladder adenocarcinomas be employed. Table 3 shows the TNM7 staging system for cancers of the gallbladder.

Epidemiology

Neuroendocrine tumors of the gallbladder are rare lesions that represent only 0.5 % of all gallbladder tumors and 0.2 % of all gastrointestinal neuroendocrine neoplasms (MacDonald 1956). Well-differentiated NETs (carcinoids) have a lower age at presentation in comparison with other gallbladder tumors (Godwin 1975), while NECs occur in an older category of patients.

Table 3 TNM7 Staging system for malignant neoplasms of the gallbladder

T			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor invades the lamina propria or muscle layer		
T1a	Tumor invades the lamina propria		
T1b	Tumor invades the muscle layer		
T2	Tumor invades the perimuscular connective tissue, no extension beyond the serosa or into the liver		
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, e.g., stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts		
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures		
N			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

General Clinical and Imaging Features

NET located to the distal part of the gallbladder can cause obstruction and may thus be associated with acute cholecystitis. Acute cholecystitis has also been observed in carcinoid tumor metastatic to the gallbladder, in the absence of stones (Saxton 1983). Even though NETs can synthesize a wide array of endocrine/neuroendocrine peptides, hormonal syndromes caused by these neoplasms are rare and include Zollinger-Ellison syndrome (Bernades et al. 1972) and ACTH secretion

syndrome (Spence and Burns-Cox 1975). Abdominal sonography and CT at admission usually reveal either intramural gallbladder masses, polypoid lesions (Salimi and Sharafuddin 1995), or tumors protruding into the gallbladder lumen, the latter morphology being rather typical for NEC (Chuang et al. 1999). In high-grade tumors, liver invasion is often seen at imaging.

Biology of Disease

In regard to biology of disease and tumor disease progression, neuroendocrine neoplasms of the gallbladder can be divided into two major groups that markedly differ in regard to tumor aggressiveness. The first group consists of NET showing a wide spectrum of behavior ranging from relatively bland tumors to metastasizing lesions, while the second group, the NEC, invariably shows a highly malignant phenotype with rapid evolution and high morbidity and mortality. In the NET group, the risk of malignant behavior depends on tumor size and proliferative activity (grade). NETs measuring 0.3–0.5 cm usually do not develop metastases, while gallbladder NETs with a diameter exceeding 2 cm often invade the liver and/or produce metastases. The overall risk for NET to cause regional or distant metastases is estimated to be 44 % and 11 %, respectively, with a 5-year survival rate of 41 %, based on the SEER database (reviewed in Komminoth et al. 2010). Patients with the aggressive NEC exhibit signs of disseminated disease at the time point of diagnosis in 40–50 %. MANEC tumors are considered to behave similar to ordinary gallbladder adenocarcinomas.

Neuroendocrine Tumor G1 (NET G1; Carcinoid) and NET G2 of the Gallbladder

Introduction

Well-differentiated neuroendocrine tumors (NET G1 and NET G2) are rare tumors. The first case has been reported in 1929 (Joel 1929), and a recent listing of the SEER database has 278 cases of gallbladder NET. However, only a minority of well-differentiated (G1) NETs are listed in this database, suggesting that G1 lesions may be very rare in the gallbladder, most gallbladder neuroendocrine neoplasms belonging to aggressive lesions discussed below (Eltawil et al. 2010; Lee et al. 2010). The female/male ratio of gallbladder carcinoids was 2.4, and the mean age at diagnosis was 64.5 years (Albores-Saavedra et al. 2009). NET may be detected incidentally, in the setting of cholecystectomies performed for other reasons, or are diagnosed because they are symptomatic lesions.

Selected References (Bosse 1943; Barnes 1952; Lanza et al. 1965; Nizze 1973; Gaffney and Coyle 1978; Sommariva et al. 1988; Yamamoto et al. 1989; Mochizuki 1991; Betancourt et al. 1992; Naseer and Kabir 1992; Porter et al. 1992; Deehan et al. 1993; Khetan et al. 1995; Kawaguchi et al. 1996; Nishigami et al. 1996; Psathakis et al. 1996; Lovera et al. 1997; Machado et al. 1998; Kaiho et al. 1999; Yokoyama et al. 2000; Angelini et al. 2003; Ozawa et al. 2003; Arjaneyulu et al. 2007; Geo et al. 2007; Virzi et al. 2008; Baikoussis et al. 2009; Kanakala et al. 2009; Zou et al. 2010; Ghosh et al. 2011; Lee et al. 2011; Mezi et al. 2011).

In principle, symptomatic gallbladder NETs are indistinguishable from gallbladder cancer (Tewari et al. 2009), and the carcinoid syndrome is estimated to occur in only 1 % or less of patients (Salimi and Sharafuddin 1995). A minority of gallbladder NETs are associated with the production and eventual secretion of hormonal peptides, including pancreatic polypeptide, somatostatin, gastrin, or ghrelin (Tanaka et al. 1992; Heymann et al. 1997; Walter et al. 2009), sometimes associated with Zollinger-Ellison syndrome (Barone et al. 1992). Angiographically, gallbladder carcinoids are hypervascular lesions fed by a sometimes dilated and finely neovascularized cystic artery, and this hypervascular phenotype is recapitulated in hepatic metastases (Kitagawa et al. 1986). NET with a differentiation grade G1 or G2 may

probably and in part be translated in what was previously called typical carcinoid. In a group of 101 gallbladder tumors diagnosed as carcinoid, 81 cases were "typical" and 20 cases were "atypical" carcinoids, the latter containing less differentiated neoplasms (Soga 2003).

Only well-differentiated NETs of the gallbladder are expected to have a better prognosis (Iype et al. 2009). Some authors defined "variant endocrinomas" developing in the gallbladder. "Classical" carcinoids were different from the variant group by exhibiting a younger average age, a higher incidence of associated cholelithiasis, a higher incidence of small tumors 50 mm or less, a smaller average tumor size, and a lower rate of metastases (Soga 2003). For classical gallbladder carcinoids, the 10-year survival rate was 36 % (Albores-Saavedra et al. 2009).

Pathology

Macroscopically, NETs are nodular or polypoid tumors of whitish, yellow, or tan color. Part of the lesions show an infiltrative growth into the gallbladder wall at macroscopic examination already. The neoplasms are usually small, less than 2 cm diameter in most cases, but they may grow to sizes exceeding 5 cm. Early lesions that measure only a few mm may be missed at gross examination (Porter et al. 1992). Most NETs are solitary lesions, but rare instances of multifocality exist. Rarely, tumors appear as clearly pedunculated lesions with a well-identifiable stalk (Oku et al. 2008).

In "typical" carcinoid (NET G1), small "endocrine type", uniform cells are arranged in the form of anastomosing trabecular, solid, nested, or alveolar structures surrounded by a richly vascularized stroma. Some NETs show tubular structures. The cells exhibit a slightly eosinophilic cytoplasm and round to oval nuclei with inconspicuous nucleoli. NET G2 has more cellular and nuclear unrest, with more frequent deviation of nuclear size and shape from the round endocrine nuclei and more frequent mitotic figures (see the paragraph on grading). Grimelius staining is variably positive (Nishigami et al. 1996), but Fontana-Masson staining is usually negative.

Ultrastructurally, the neoplastic cells contain typical and sometimes numerous neurosecretory granules in the cytoplasm (Kaiho et al. 1999). Immunohistochemically, NETs are strongly reactive for chromogranin A, synaptophysin, neuron-specific enolase, and CD56/N-CAM. The tumors can express cytokeratins (AE17AE3 and CK7), serotonin, and several hormonal peptides, including somatostatin, gastrin, and pancreatic polypeptide (Kaiho et al. 1999; Zou et al. 2010; Mezi et al. 2011).

Variants of Gallbladder NET/Carcinoid Tumors

One variant of NET G1 is characterized by a composition of clear cells (lipid-rich/clear cell neuroendocrine tumor; clear cell NET G1). Similar to their counterparts occurring in the pancreas (Ordonez and Silva 1997; Hoang et al. 2001), which may occur in the setting of von Hippel-Lindau disease (Singh et al. 2006) or in MEN I (Fryer et al. 2012), clear cell tumors of neuroendocrine lineage of the gallbladder can develop in von Hippel-Lindau disease (Sinkre et al. 2001), but clear cell NET G1 of the gallbladder can occur in the absence of this genetic disorder (Konishi et al. 2003; Ishida et al. 2012). These tumors are composed of cells with a cytoplasm that contains lipid droplets and sometimes displays a foamy structure. The clear aspect of the neoplastic cells is not caused by glycogen accumulations, as PAS staining gives a negative result. Similar to ordinary carcinoids, clear cell NET G1 are immunoreactive for chromogranin A and synaptophysin and may also express several neuroendocrine peptides, including somatostatin, gastrin, and pancreatic polypeptide (Konishi et al. 2003). Clear cell NETs associated with von Hippel-Lindau disease, but not sporadic cases, are reactive for alpha-inhibin (Sinkre et al. 2001; Konishi et al. 2003; Ishida et al. 2012). A very rare variant of NET G1 is signet-ring cell carcinoid, characterized by a neoplastic proliferation of numerous signet-ring cells admixed with chromogranin A-positive clear cells (Papotti et al. 1990). Goblet cell adenocarcinoid has been found as a component of a composite tumor (Muto et al. 1984).

Neuroendocrine Carcinoma (NEC) of the Gallbladder

Introduction

Neuroendocrine carcinomas (NECs) of the gallbladder are rare neoplasms, and patients with such lesions have a poor prognosis. NECs exhibit early and often numerous locoregional lymph node metastases and distant metastases, in a first round frequently to the liver (Bosl et al. 1980; McLean and Pedersen 1991; Kumar et al. 1992; Yoshizumi et al. 1992; Mizukami et al. 1998; Bhutani et al. 2001). However, modern chemotherapy schemes can now result in long-term remission in part of patients (Mizukami et al. 1998; Shimono et al. 2009; Elahi et al. 2013).

Small Cell NEC (SCNEC)

Small cell neuroendocrine carcinomas (SCNECs) of the gallbladder represent the more common variant of NEC and share many features with their counterparts developing in other organs, particularly those in the lung (see above; paragraph on small cell carcinomas). Gallbladder small cell NECs were also termed oat cell carcinoma (Albores-Saavedra et al. 1984). The prevalence of SCNEC of the gallbladder is estimated to be 1–5 % of all gastrointestinal neuroendocrine neoplasms (Albores-Saavedra et al. 1984). Similar to SCNEC of the ampullary region, patients with gallbladder SCNEC are older at presentation than those with NET/carcinoids, with a median age at diagnosis of 65 years (in one study, 69 years; Maitra et al. 2001). There is a female preponderance (76 % are female), and the tumors are often associated with cholelithiasis (72 %).

Selected References (Cavazzana et al. 1991; Ron et al. 1992; Nishihara and Tsuneyoshi 1993; Muraina et al. 1996; Chuang et al. 1999; Moskal et al. 1999; Matsuo et al. 2000; Fujii et al. 2001; Maitra et al. 2001; Lane et al. 2002; Jun et al. 2006; Imai et al. 2008; Nishime et al. 2008; Uribe-Uribe et al. 2009; Lee et al. 2010; Nau et al. 2010; Ng et al. 2010; Mahipal and Gupta 2011; Benkel et al. 2012; Chen et al. 2014).

Similar to LCNEC, SCNECs are very aggressive lesions with poor outcome (Lee et al. 2010). Seventy-five percent of the tumors had metastasized or extended locally beyond the gallbladder at surgery (Maitra et al. 2001). In an analysis of 28 pure SCNEC and 8 MANEC containing SCNEC, the tumors metastasized to lymph nodes in 88 %, the liver in 88 %, the lung in 23 %, and the peritoneum in 19 % (Moskal et al. 1999). In an analysis of 12 patients, mean survival was 10.7 months, with a range of 3–25 months (Maitra et al. 2001). Similar to other small cell undifferentiated carcinomas, SCNECs are sometimes associated with paraneoplastic syndromes, e.g., hyponatremia (Ng et al. 2010) or sensory neuropathy (Uribe-Uribe et al. 2009).

Pathology

Macroscopy

Macroscopically, the tumors are usually bulky lesions of whitish to tan color that may protrude into the gallbladder lumen. In one study of 12 cases, the neoplasms had an average size of 3 cm (Maitra et al. 2001). On cut sections, the tumors have a fleshy consistency or are friable masses. The carcinomas have been described as ill-defined or nodular gray-white to whitish masses showing hemorrhagic necrosis (Chuang et al. 1999). The tumors are often large at the time point of diagnosis and show a propensity for submucosal growth (Albores-Saavedra et al. 1984). SCC may also present as small nodular lesions of the gallbladder, but even small tumors can metastasize to local lymph nodes (Uribe-Uribe et al. 2009), again a feature also known for SCC of the lungs

Histopathology

Histologically, SCNECs exhibit loosely cohesive tumor cells that diffusely infiltrate the gallbladder wall, may form sheets and cords, and can show

extensive lymphovascular invasion. The tumor cells are small to medium sized, mostly somewhat larger than quiescent small lymphocytes, i.e., like oat cells of lung carcinoma. Apart from round cells, spindled, fusiform, or polygonal cells also occur. The cytoplasm is scanty and slightly eosinophilic to amphophilic. The nuclei are ovoid, spindle shaped, or indented, with the characteristic "salt and pepper" chromatin structure with either no visible nucleoli or two to three small nucleoli. Characteristic nuclear "moulding" (also written "molding") is seen on high-power examination. Nuclear "moulding" is a helpful artifact due to the flexible nuclear membrane: the nucleus of one tumor cell appears to be bumping into another nucleus, causing the two nuclei to look like part of a jigsaw puzzle. Many and in part abnormal mitotic figures are noted, as well as apoptotic bodies and foci of necrosis. There may be tingible bodies reflecting phagocytosis of nuclear debris, and emperipolesis of apoptotic bodies may be found. Prominent necrosis is usually found, with accumulations of shadow cells. Similar to small cell carcinoma of the lung, the tumors display the diagnostically helpful nuclear "crushed" artifact caused by section preparation and may show the Azzopardi phenomenon, i.e., basophilic chromatin containing damaged DNA coating vessel walls following liberation of chromatin/DNA from dead cells (Albores-Saavedra et al. 1984; Takei et al. 2007; Nau et al. 2010). Part of SCNECs may show rosette-like structures and tubules. The latter should represent definitively less than 30 % of the tumor, otherwise MANEC has to be considered (see below). In a series of 12 patients, invasion of the muscularis propria and perimuscular connective tissue was detected in 90 % (Maitra et al. 2001). Association with intestinal metaplasia of the gallbladder mucosa has been found, with goblet cells, pseudopyloric glands, and Paneth cells (Kuwabara and Uda 1998). Argyrophilic cells may be found in the Grimelius stain (Iida and Tsutsumi 1992; Nishihara and Tsuneyoshi 1993).

In more than a quarter of cases, SCNEC is combined with adenocarcinoma, squamous cell carcinoma, or other types of carcinoma (Duan et al. 1991; Iida and Tsutsumi 1992; Nishihara et al. 1994; Okamoto et al. 2003; Mahipal and Gupta 2011). In the series of 12 patients published by Maitra et al. (2001), half of the cases were combined with other neoplasms. Four had foci of adenocarcinoma, one had a component of squamous cell carcinoma, and one had a focus of carcinosarcoma. Combined SCC and clear cell carcinoma of the gallbladder have been observed (Piana et al. 2002). Sarcomatoid carcinoma of the gallbladder was found to have an SCC component (Takahashi et al. 2004).

Ultrastructurally, neurosecretory-type cytoplasmic granules were detected (Cavazzana et al. 1991; Fujii et al. 2001). Immunohistochemically, the tumor cells express neuroendocrine lineage markers, above all synaptophysin and chromogranin A (Cavazzana et al. 1991; Chuang et al. 1999; Mahipal and Gupta 2011). Synaptophysin expression is usually diffuse, whereas chromogranin A tends to involve scattered cells. In some cases, focal reactivity for epithelial markers was detectable, including cytokeratins, EMA, and CEA (Cavazzana et al. 1991). SCNEC may express serotonin, but this is a rare feature. Relatively few tumors expressed neuroendocrine peptides, such as somatostatin, or ACTH. On a molecular level, 100 % of SCNEC of the gallbladder demonstrated inactivation of the pRB/p16 pathway, and 67 % of these tumors accumulated high levels of p53, while activating K-ras mutations were not found (Parwani et al. 2003).

Large Cell NEC

Among NECs of the gallbladder, the large cell variant (LCNEC) is the less common in comparison with its small cell counterpart (Papotti et al. 2000; Jun et al. 2006; Shimono et al. 2009; Furrukh et al. 2013; Okuyama et al. 2013; Samad et al. 2013). LCNEC has been found in association with anomalous union of the pancreaticobiliary duct (Yoon et al. 2009). Exceptionally, LCNECs were associated with paraneoplastic syndromes, e.g., Cushing's syndrome caused by

production of ACTH by the tumor (Lin et al. 2010).

Macroscopically, the tumors resemble the phenotype described for SCNEC. Histologically, the neoplasms display an organoid growth pattern and consist of large cells with an amphophilic or slightly eosinophilic cytoplasm and large vesicular nuclei with prominent nucleoli. These cells are arranged in a diffuse, solid, or focally nesting pattern. In fine-needle aspiration preparations, rosette-like structures may be encountered in a background showing extensive necrotic debris (Samad et al. 2013). In some tumors, the cell size is situated between large and small cells (intermediate cell NEC; ICNEC), a tumor not listed as such in the 2010 WHO classification. Immunohistochemically, the tumor cells are reactive for synaptophysin, chromogranin A (Okuyama et al. 2013), and at least part of the cells are reactive for epithelial markers (AE1/AE3; Samad et al. 2013). The proliferation fraction (Ki-67 index) is high or very high (Okuyama et al. 2013; Samad et al. 2013).

Mixed Adenoneuroendocrine Carcinoma (MANEC) of the Gallbladder

Introduction

In the 2010 WHO classification, mixed adenoneuroendocrine carcinomas (MANECs) are defined as composite neoplasms in which areas of adenocarcinoma or squamous cell carcinoma intermingle with areas of neuroendocrine tumor (NET) or neuroendocrine carcinoma (NEC), each component comprising at least 30 %, or exceeding 30 %, of the neoplasm. In the light of the different cell lineages involved, a role of stem cells has been proposed as a pathogenic mechanism (Paniz Mondolfi et al. 2011).

The first description of a gastrointestinal tumor with an exocrine and a neuroendocrine component dates in 1924 (Cordier 1924). Tumors having a synchronous presentation of adenocarcinoma and (neuro)endocrine components were previously called adenocarcinoid, a term first coined in 1978 based on tumors of the appendix (Warkel et al. 1978; Cooper and Warkel 1978). In 1987, Lewin suggested to classify such neoplasm into three different subtypes: collision tumors, combined tumors, and amphicrine tumors (Lewin 1987). According to the WHO classification of tumors, these lesions are now termed mixed adenoneuroendocrine carcinoma or MANEC (synonyms: adenoendocrine carcinoma; mixed/composite glandular-endocrine cell carcinoma; composite carcinomatous and carcinoid tumor; carcinoid tumor with adenocarcinomatous differentiation). The neuroendocrine components display features overlapping those described in pure NETs or NECs, being formed by solid and/or trabecular structures with argyrophilic cells that are immunoreactive for neuroendocrine markers. The identification in adenocarcinoma of scattered neuroendocrine cells by immunohistochemistry does not qualify for the definition of MANEC. The spectrum of lesions ranges from pure NE tumors to pure non-endocrine carcinomas, as discussed in a review as of 2006 (Volante et al. 2006), and MANECs form a distinct window in this spectrum. The nomenclature and classification of these tumors has recently been refined (La Rosa et al. 2012; Table 4). Gastrointestinal MANECs, including those of the gallbladder, can be stratified in different prognostic categories according to grade of malignancy of each component. High-grade malignant MANECs are malignant composite or combined tumors formed by an adenomatous or carcinomatous component and by a poorly differentiated (small, intermediate, or large cell type) neuroendocrine carcinoma. Intermediate-grade malignant MANEC includes mixed adenocarcinoma-neuroendocrine carcinoma and amphicrine carcinoma. The first category consists of adenocarcinoma, and the neuroendocrine component is represented by a

Table 4 Classification of MANEC and related tumors (La Rosa et al. 2012)

High-grade malignant MANEC
Intermediate-grade malignant MANEC
Mixed adenocarcinoma-neuroendocrine tumor (adenocarcinoma-NET)
Mixed adenoneuroendocrine tumor (MANET)
Adenoma-neuroendocrine tumor (adenoma-NET)

differentiated neuroendocrine tumor which can show grade 1 (NET G1) or grade 2 (NET G2) differentiation. Amphicrine carcinoma represents a peculiar neoplasm in which exocrine and neuroendocrine features are coexpressed by the same neoplastic cells. Mixed adenocarcinoma-neuroendocrine tumor (adenocarcinoma-NET) is a composite tumor consisting of areas of adenocarcinoma and areas of grade 1 or grade 2 NET (synonyms: mucin-producing carcinoid; composite carcinoid-adenocarcinoma, composite carcinoid tumor, mixed adenocarcinoid tumor, and composite glandular-neuroendocrine mixed tumor). Mixed adenoneuroendocrine tumors or MANETs include neoplasms formed by well-differentiated neuroendocrine and exocrine cells which behave in an indolent manner. Adenoma-neuroendocrine tumor (adenoma-NET) is a very rare neoplasm characterized by both an adenomatous and a NET component (synonym: glandular-carcinoid tumor). It has to be emphasized that adenocarcinoma having cells showing immunoreactivity for neuroendocrine markers (adenocarcinoma with neuroendocrine features) in the absence of neuroendocrine cells should not be classified as MANEC.

MANEC and similar lesions are rare primary tumors of the gallbladder, less than 30 cases having been reported.

Selected References (Wisniewski and Toker 1972; Ito et al. 1980; Wada et al. 1983; Kotake et al. 1984; Muto et al. 1984; Noda et al. 1989; Fish et al. 1990; Peraza et al. 1990; Duan et al. 1991; Olinici and Waslu 1991; Iida and Tsutsumi 1992; Ohmori et al. 1993; Nishihara et al. 1994; Resnick et al. 1994; Eriguchi et al. 2000; Yannakou et al. 2001; Piana et al. 2002; Shimizu et al. 2006; Sosnik and Sosnik 2006; Tsuchiya et al. 2006; Oshiro et al. 2008; Sato et al. 2010; Paniz Mondolfi et al. 2011; Harada et al. 2012; Rastogi et al. 2012; Russo et al. 2012).

The rarity of reported cases of MANEC may be related to the lack of immune-histochemical studies in older studies. Among 49 gallbladder cancers of a recent investigation using immunohistochemistry for neuroendocrine markers, a neuroendocrine component occupying more than 30 % of the entire tumor was found in 5/49 cases/10 % (Harada et al. 2012), MANECs develop without recognizable association with preexisting disease in the large majority of cases. In one patient, an association with pancreaticobiliary maljunction was found (Oshiro et al. 2008).

Clinical and Imaging Features

The clinical presentation of MANECs is nonspecific and mainly consists of upper abdominal pain and a right upper abdominal mass. Signs of carcinoid syndrome are lacking. In MANEC cases containing aggressive neuroendocrine components, chiefly small of large cell parts, patients may present with advanced stage disease and associated symptoms and signs of cancer disease, including weight loss and fever. MANECs with small cell NEC (SCNEC) and large cell NEC (LCNEC) components have a poor outcome, whereas the biology of disease in MANECs having a carcinoid component is dominated by the adenocarcinoma component of the tumor (La Rosa et al. 2012). Exceptionally, MANECs are associated with hormonal hypersecretion, e.g., pancreatic polypeptide (Marrano et al. 1999).

Pathology

Apart from solid and nodular tumors, MANECs of the gallbladder are relatively often endophytically growing lesions, with a polypoid pattern. On cut surfaces the tumors are grayish or white or whitish-yellow to tan, depending on the proportion of adenocarcinoma vs. neuroendocrine components. MANEC may be deeply invasive lesions, penetrating the entire gallbladder wall and even infiltrating the fossa and the liver substance proper.

The histology of MANEC is characterized by adenocarcinoma and neuroendocrine elements randomly distributed through the gallbladder wall, closely juxtaposed, but also with transitions between the two components. Several combinations of morphologies have been described

Table 5 Types of adenocarcinoma and neuroendocrine tumors combined in MANEC and mixed adenocarcinoma-NET of the gallbladder

Adenocarcinoma, carcinoid tumor	(Wisniewski and Toker 1972; Wada et al. 1983; Kotake et al. 1984; Noda et al. 1989)
Undifferentiated carcinoma, carcinoid tumor	(Ito et al. 1980)
Adenocarcinoma, signet-ring cell carcinoma, ICNEC	(Olinici and Waslu 1991)
Tubular adenocarcinoma, ICNEC	(Eriguchi et al. 2000; Yannakou et al. 2001)
Adenocarcinoma, SCNEC	(Duan et al. 1991; Iida and Tsutsumi 1992; Nishihara et al. 1994; Okamoto et al. 2003; Shimizu et al. 2006; Tsuchiya et al. 2006; Elahi et al. 2013)
Clear cell carcinoma, SCNEC	(Piana et al. 2002)
Mucinous adenocarcinoma, SCNEC, LCNEC	(Oshiro et al. 2008; Russo et al. 2012)
Tubular adenocarcinoma, LCNEC	(Sato et al. 2010)
Papillary adenocarcinoma, LCNEC	(Paniz Mondolfi et al. 2011)

LCNEC large cell neuroendocrine carcinoma, *SCNEC* small cell neuroendocrine carcinoma, *ICNEC* intermediate cell neuroendocrine carcinoma

(Table 5). The differentiation and mucin production patterns of the adenocarcinoma component vary considerably among cases, and some adenocarcinomas may only show florid neuroendocrine cell nests (Sakaki et al. 2000). The reticulin pattern differs between the two parts, being dense in adenocarcinoma and delicate in the neuroendocrine parts. MANEC may contain a component of goblet cell adenocarcinoid as a rare differentiation mode (Muto et al. 1984). Where the two components merge, so-called transitional tumor cells showing both histological and cytological features may be seen. In these areas, argyrophil granules and mucin can be found in the same cells (Wada et al. 1983). One MANEC showed extensive Paneth cell metaplasia (Sakakai et al. 2000). The adenoid component of a small cell NEC-type MANEC may only be manifest in the form of intestinal metaplasia (Kuwabara and Uda 1998). Some of the tumors show necrosis and/or fibrosis.

The tumors may be associated with erosion or ulceration of the overlying mucosa, and hyperplastic epithelial changes are sometimes seen in the adjacent intact mucosa. Ultrastructurally, individual tumor cells were shown to have overlapping features of neuroendocrine and glandular differentiation (Paniz Mondolfi et al. 2011).

The adenocarcinoma cells express a marker pattern typical of ordinary gallbladder adenocarcinoma, while neuroendocrine tumor cells are reactive for neuron-specific enolase (NSE), chromogranin A, and synaptophysin (Noda et al. 1989; Eriguchi et al. 2000; Shimizu et al. 2006; Tsuchiya et al. 2006; Sato et al. 2010). So-called transitional tumor cells display common immunoreactivity for CEA, cancer antigen 19-9, CK19, epithelial cell adhesion molecule, and CD117 (Paniz Mondolfi et al. 2011).

Pathogenic Pathways

The histogenesis of MANEC has not yet been clarified, but several hypotheses of their pathogenesis have been proposed. One view consists of the coincidental neoplastic change in two different cell lineages; the other suggests the involvement of a progenitor cell developing into an endocrine and a glandular cellular phenotype. The second hypothesis is sometimes favored owing to the fact that so-called transitional cells are detectable in part of the tumors.

References

Albores-Saavedra J, Soriano J, Larraza-Hernandez O, Aguirre J, Henson DE (1984) Oat cell carcinoma of the gallbladder. Hum Pathol 15:639–646

Albores-Saavedra J, Batich K, Hossain S, Henson DE, Schwartz AM (2009) Carcinoid tumors and small-cell carcinomas of the gallbladder and extrahepatic bile ducts: a comparative study based on 221 cases from the surveillance, epidemiology, and end results program. Ann Diagn Pathol 13:378–383

Angelini C, Mussi C, Crippa S, Sartori P, Isimbaldi G, Bonardi C, Uggeri F (2003) Gallbladder carcinoid: a case report. Chir Ital 55:571–573
Arjaneyulu V, Shankar-Swarnalatha G, Rao SC (2007) Carcinoid tumor of the gall bladder. Ann Diagn Pathol 11:113–116
Baikoussis NG, Karvelas FP, Apostopoulos NV (2009) Primary carcinoid tumor of the gallbladder. Minerva Chir 64:119–120
Barnes TG (1952) Argentaffinoma (carcinoid) of the gall bladder; a case report. Surgery 32:723–727
Barone GW, Schaefer RF, Counce JS, Eidt JF (1992) Gallbladder and gastric argyrophil carcinoid associated with a case of Zollinger-Ellison syndrome. Am J Gastroenterol 87:392–394
Benkel M, Brasch F, Neumann JD, Altendorf-Hofmann A, Sendt W (2012) Poorly differentiated neuroendocrine small-cell carcinoma of the gallbladder (in German). Zentralbl Chir 137:71–72
Bernades P, Bonnefond A, Martin E, Bonfils S (1972) Zollinger-Ellison syndrome with carcinoid islet endocrine tumor with primary gallbladder localization (in French). Arch Fr Mal Appl Dig 61:759–766
Betancourt C, Clavier J, Zerpa H, Franceschi I (1992) Carcinoid tumor of the gallbladder (in Spanish). G E N 46:40–42
Bhutani V, Dutta U, Nagi B, Nijhawan R, Singh K (2001) Endocrine cell carcinoma of gall bladder. Indian J Gastroenterol 20:109–110
Bosl GJ, Yagoda A, Camara-Lopes LH (1980) Malignant carcinoid of the gallbladder: third reported case and review of the literature. J Surg Oncol 13:215–222
Bosse MD (1943) Carcinoid tumor of the gallbladder. Arch Pathol 35:898–899
Cavazzana AO, Fassina AS, Tollot M, Ninfo V (1991) Small-cell carcinoma of gallbladder. An immunohistochemical and ultrastructural study. Pathol Res Pract 187:472–476
Chen H, Shen YY, Ni XZ (2014) Two cases of neuroendocrine carcinoma of the gallbladder. World J Gastroenterol 20:11916–11920
Chuang et al. (1999). http://www.ncbi.nlm.nih.gov/pubmed/10491025
Cooper PH, Warkel RL (1978) Ultrastructure of the goblet cell type of adenocarcinoid of the appendix. Cancer 42:2687–2695
Cordier R (1924) Les cellules argentaffines dans les tumeurs intestinales. Arch Int Med Exp 1:5
Deehan DJ, Heys SD, Kernohan N, Eremin O (1993) Carcinoid tumour of the gall bladder: two case reports and a review of published works. Gut 34:1274–1276
Duan HJ, Ishigame H, Ishii Z, Itoh N, Shigematsu H (1991) Small cell carcinoma of the gallbladder combined with adenocarcinoma. Acta Pathol Jpn 41:841–846
Elahi F, Ahmadzadeh A, Yadollahzadeh M, Hassanpour K, Babaei M (2013) Neuroendocrine tumor of the gallbladder. Arch Iran Med 16:123–125
Eltawil KM, Gustafsson BI, Kidd M, Modlin IM (2010) Neuroendocrine tumors of the gallbladder: an evaluation and reassessment of management strategy. J Clin Gastroenterol 44:687–695
Eriguchi N, Aoyagi S, Noritomi T, Imamura M, Sato S, Fujiki K, Furukawa S, Shirozu K et al (2000) Adeno-endocrine cell carcinoma of the gallbladder. J Hepatobiliary Pancreat Surg 7:97–101
Fish DE, Al-Izzi M, George PP, Whitaker B (1990) Combined endocrine cell carcinoma and adenocarcinoma of the gallbladder. Histopathology 17:471–472
Fryer E, Serra S, Chetty R (2012) Lipid-rich ("clear cell") neuroendocrine tumors of the pancreas in MEN I patients. Endocr Pathol 23:243–246
Fujii H, Aotake T, Horiuchi T, Chiba Y, Imamura Y, Tanaka K (2001) Small cell carcinoma of the gallbladder: a case report and review of the literature. Hepatogastroenterology 48:1588–1593
Furrukh M, Qureshi A, Saparamadu A, Kumar S (2013) Malignant neuroendocrine tumour of the gallbladder with elevated carcinoembryonic antigen: case report and literature review. BMJ Case Rep. 2013. pii: bcr2013008778
Gaffney PR, Coyle LJ (1978) Carcinoid tumour of the gall bladder associated with a meningioma. Ir J Med Sci 147:318–321
Geo SK, Harikumar R, Kumar S, Kumar B, Gopinath A (2007) Gall bladder carcinoid: a case report and review of literature. Trop Gastroenterol 28:72–73
Ghosh M, Bhattacharyya NK, Ghoshsengupta S (2011) Carcinoid tumor of gall bladder – a case report. J Indian Med Assoc 109:198–199
Godwin JD (1975) Carcinoid tumors. An analysis of 2,837 cases. Cancer 36:560–569
Harada K, Sato Y, Ikeda H, Maylee H, Igarashi S, Okamura A, Masuda S, Nakanuma Y (2012) Clinicopathologic study of mixed adenoneuroendocrine carcinomas of hepatobiliary organs. Virchows Arch 460:281–289
Heymann MF, Fiche M, Dubois-Gordeeff A, Chetritt J, Cloarec D, Guiberteau B, Le Bodic MF (1997) Endocrine cell carcinoma (carcinoid tumour) of the gallbladder producing pancreatic polypeptide and somatostatin. Histopathology 30:606–607
Hoang MP, Hruban RH, Albores-Saavedra J (2001) Clear cell endocrine pancreatic tumor mimicking renal cell carcinoma: a distinctive neoplasm of von Hippel-Lindau disease. Am J Surg Pathol 25:602–609
Iida Y, Tsutsumi Y (1992) Small cell (endocrine cell) carcinoma of the gallbladder with squamous and adenocarcinomatous components. Acta Pathol Jpn 42:119–125
Imai H, Matsui S, Tokuyama Y, Osada S, Tomita H (2008) Small cell carcinoma of the gallbladder successfully treated by surgery and adjuvant chemotherapy. Am Surg 74:272–273
Ishida M, Shiomi H, Naka S, Tani T, Okabe H (2012) Clear cell neuroendocrine tumor G1 of the gallbladder without von Hippel-Lindau disease. Oncol Lett 4:1174–1176
Ito J, Mizushima M, Soto H (1980) Composite tumour exhibiting both carcinoid and undifferentiated carcinoma of the gallbladder. Tr Soc Pathol Jpn 69:3699

Iype S, Mirza TA, Propper DJ, Bhattacharya S, Feakins RM, Kocher HM (2009) Neuroendocrine tumours of the gallbladder: three cases and a review of the literature. Postgrad Med J 85:213–218

Joel W (1929) Karzinoidtumor der Gallenblase. Zbl Allg Pathol 46:14

Jun SR, Lee JM, Han JK, Choi BI (2006) High-grade neuroendocrine carcinomas of the gallbladder and bile duct: report of four cases with pathological correlation. J Comput Assist Tomogr 30:604–609

Kaiho T, Tanaka T, Tsuchiya S, Miura M, Saigusa N, Yanagisawa S, Takeuchi O, Kitakata Y et al (1999) A case of classical carcinoid tumor of the gallbladder: review of the Japanese published works. Hepatogastroenterology 46:2189–2195

Kanakala V, Kasaraneni R, Smith DA, Goulbourne IA (2009) Primary neuroendocrine neoplasm of the gallbladder. BMJ Case Rep. 2009. pii: bcr12.2008 1352

Kawaguchi M, Saito T, Morita S (1996) Carcinoid of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:261–264

Khetan N, Bose NC, Arya SV, Gupta HO (1995) Carcinoid tumor of the gallbladder: report of a case. Surg Today 25:1047–1049

Kitagawa K, Takashima T, Matsui O, Kadoya M, Haratake KJ, Tsuji M (1986) Angiographic findings in two carcinoid tumors of the gallbladder. Gastrointest Radiol 11:51–55

Komminoth P, Arnold R, Capella C, Klimstra DS, Klöppel G, Rindi G, Albores-Saavedra J et al (2010) Neuroendocrine neoplasms of the gallbladder and extrahepatic bile ducts. In: Bosman FT et al (eds) WHO classification of tumours of the digestive system. IARC, Lyon, pp 274–276

Konishi E, Nakashima Y, Smyrk TC, Masuda S (2003) Clear cell carcinoid tumor of the gallbladder. A case without von Hippel-Lindau disease. Arch Pathol Lab Med 127:745–747

Kotake K, Yoneyama K, Miyata J, Ishikawa H, Hayashi T (1984) Carcinoid with coexisting adenocarcinoma of the gallbladder. Report of a case. Am J Surg Pathol 39:1313

Kumar S, Agarwal S, Bhargava SK, Minocha VR (1992) Malignant carcinoid tumor of the gallbladder: a case report and review of literature. Trop Gastroenterol 13:78–84

Kuwabara H, Uda H (1998) Small cell carcinoma of the gall-bladder with intestinal metaplastic epithelium. Pathol Int 48:303–306

La Rosa S, Marando A, Sessa F, Capella C (2012) Mixed adenoneuroendocrine carcinoma (MANECs) of the gastrointestinal tract: an update. Cancer 4:11–30

Lane JE, Walker AN, Ayers GW, Foster JL, Williams JT (2002) Small-cell undifferentiated carcinoma of neuroendocrine type originating in the gallbladder. Curr Surg 59:495–497

Lanza P, Pezzoli G, Rocca E (1965) Carcinoid of the gallbladder. Review of the literature and presentation of a case (in Italian). Ann Ital Chir 41:1156–1168

Lee JM, Hwang S, Lee SG, Lee YJ, Park KM, Kim KH, Ahn CS, Kim MH, Lee SK et al (2010) Neuroendocrine tumors of the gallbladder: twelve cases in a single institution. Hepatogastroenterology 57:1064–1068

Lee JH, Lee KG, Oh YH, Paik SS, Park HK, Lee KS (2011) Carcinoid tumors of the extrahepatic biliary tract: report of four cases. Surg Today 41:430–435

Lewin K (1987) Carcinoid tumors and the mixed (composite) glandular-endocrine cell carcinomas. Am J Surg Pathol 11:S71–S86

Lin D, Suwantarat N, Kwee S, Miyashiro M (2010) Cushing's syndrome caused by an ACTH-producing large cell neuroendocrine carcinoma of the gallbladder. World J Gastrointest Oncol 2:56–58

Lovera M, Pirrotta A, Donida GL, Tampellini P, Saurgnani A, Cerqui F, Pelizzari E (1997) Carcinoid of the gallbladder. A report of a clinical case treated by video laparoscopic cholecystectomy (in Italian). Minerva Chir 52:1209–1213

MacDonald RA (1956) A study of 356 carcinoids of the gastrointestinal tract: report of four new cases of the carcinoid syndrome. Am J Med 21:867–878

Machado MC, Penteado S, Montagnini AL, Machado MA (1998) Carcinoid tumor of the gallbladder. Sao Paulo Med J 116:1741–1743

Mahipal A, Gupta S (2011) Small-cell carcinoma of the gallbladder: report of a case and literature review. Gastrointest Cancer Res 4:135–136

Maitra A, Tascilar M, Hruban RH, Offerhaus GJ, Albores-Saavedra J (2001) Small cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and molecular pathology study of 12 cases. Am J Surg Pathol 25:595–601

Marrano NN, Blevins LS, Gal AA, McGuire WP (1999) Pancreatic polypeptide hypersecretion associated with a neuroendocrine carcinoma of the gallbladder. Am J Med Sci 317:55–58

Matsuo S, Shinozaki T, Yamagichi S, Matsuzaki S, Takami Y, Hayashi T, Kanematsu T (2000) Small-cell carcinoma of the gallbladder: report of a case. Surg Today 30:89–93

McLean CA, Pedersen JS (1991) Endocrine cell carcinoma of the gallbladder. Histopathology 19:173–176

Mezi S, Petrozza V, Schillaci O, La Torre V, Cimadon B, Leopizzi M, Orsi E, La Torre F (2011) Neuroendocrine tumors of the gallbladder: a case report and review of the literature. J Med Case Rep 5:334

Mizukami Y, Nagashima T, Ikuta K, Chikamatsu E, Kurachi K, Kanemoto H, Yagi T et al (1998) Advanced endocrine cell carcinoma of the gallbladder: a patient with 12-year survival. Hepatogastroenterology 45:1462–1467

Mochizuki M (1991) Minute carcinoid tumor of the gallbladder. Acta Pathol Jpn 41:383–385

Moskal TL, Zhang PJ, Nava HR (1999) Small cell carcinoma of the gallbladder. J Surg Oncol 70:54–59

Muraina OI, Tank R, Dhingra C, Vuletin JC, Colella F, Abdelsayed G, Pachter BR et al (1996) Small cell carcinoma of gallbladder: report of two cases. Am J Gastroenterol 91:792–794

Muto Y, Okamoto K, Uichimura M (1984) Composite tumor (ordinary adenocarcinoma, typical carcinoid and goblet cell adenocarcinoid) of the gallbladder: a variety of composite tumor. Am J Gastroenterol 79:645–649

Naseer F, Kabir M (1992) Carcinoid tumour of gall bladder. J Pak Med Assoc 42:227–228

Nau P, Liu J, Dillhoff M, Forster M, Hazey J, Melvin S (2010) Two cases of small cell carcinoma of the gallbladder. Case Rep Med. 2010. pii: 453624

Ng ES, Venkateswaran K, Ganpathi SI, Chuah BY (2010) Small cell gallbladder carcinoma complicated by paraneoplastic hyponatremia: a case report and literature review. J Gastrointest Cancer 41:264–268

Nishigami T, Yamada M, Nakasho K, Yamamura M, Satomi M, Uematsu K, Ri G, Mizuta T et al (1996) Carcinoid tumor of the gall bladder. Intern Med 35:953–956

Nishihara K, Tsuneyoshi M (1993) Small-cell carcinoma of the gallbladder – a clinicopathological, immunohistochemical and flow cytometric study of 15 cases. Int J Oncol 3:901–908

Nishihara K, Nagai E, Tsuneyoshi M, Nagashima M (1994) Small-cell carcinoma combined with adenocarcinoma of the gallbladder. A case report with immunohistochemical and flow cytometric studies. Arch Pathol Lab Med 118:177–181

Nishime C, Ohnishi Y, Suemizu H, Tamaoki N, Kusumi T, Sato F, Yamazaki H, Nakamura M et al (2008) In vivo chemotherapeutic profile of human gallbladder small cell carcinoma. Biomed Res 29:251–256

Nizze H (1973) Carcinoid tumor of the gall bladder (in German). Zbl Allg Pathol 117:61–65

Noda M, Miwa A, Kitegawa M (1989) Carcinoid tumors of the gall bladder with adenocarcinomatous differentiation: a morphologic and immunohistochemical study. Am J Gastroenterol 84:953–957

Ohmori T, Furuya K, Okada K, Tabei R, Tao S (1993) Adenoendocrine cell carcinoma of the gallbladder: a histochemical and immunohistochemical study. Acta Pathol Jpn 43:268–274

Okamoto H, Miura K, Gawara T, Fujii H, Matsumoto Y (2003) Small-cell carcinoma manifesting systemic lymphadenopathy combined with adenocarcinoma in the gallbladder: aggressiveness and sensitivity to chemotherapy. J Gastroenterol 38:801–805

Oku T, Ono K, Nagamachi Y, Misu K, Senmaru N, Fujita M, Nagashima K, Fujii S et al (2008) Pedunculated carcinoid tumor of the gallbladder – analysis of the relationship between location and morphology in carcinoid tumor of the gallbladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 105:397–403

Okuyama Y, Fukui A, Enoki Y, Morishita H, Yoshida N, Fujimoto S (2013) A large cell neuroendocrine carcinoma of the gall bladder: diagnosis with 18FDG-PET/CT-guided biliary cytology and treatment with combined chemotherapy achieved a long-term stable condition. Jpn J Clin Oncol 43:571–574

Olinici CD, Waslu R (1991) Composite endocrine cell, typical adenocarcinoma and signet-ring carcinoma of the gallbladder. Rom J Morphol Embryol 110: 604–610

Ordonez NG, Silva EG (1997) Islet cell tumour with vacuolated lipid-rich cytoplasm: a new histological variant of islet cell tumour. Histopathology 31:157–160

Oshiro H, Matsuo K, Mawatari H, Inayama Y, Yamanaka S, Nagahama K, Endo I et al (2008) Mucin-producing gallbladder adenocarcinoma with focal small cell and large cell neuroendocrine differentiation associated with pancreaticobiliary maljunction. Pathol Int 58:780–786

Ozawa K, Kinoshita M, Kagata Y, Matsubara O (2003) A case of double carcinoid tumors of the gallbladder. Dig Dis Sci 48:1760–1761

Paniz Mondolfi AE, Slova D, Fan W, Attiyeh FF, Afthinos J, Reidy J, Pang Y, Theise ND (2011) Mixed adenoneuroendocrine carcinoma (MANEC) of the gallbladder: a possible stem cell tumor? Pathol Int 61:608–614

Papotti M, Galliano D, Monga G (1990) Signet-ring cell carcinoid of the gallbladder. Histopathology 17:255–259

Papotti M, Cassoni P, Sapino A, Passarino G, Krueger JE, Albores-Saavedra J (2000) Large cell neuroendocrine carcinoma of the gallbladder: report of two cases. Am J Surg Pathol 24:1424–1428

Parwani AV, Geradts J, Caspers E, Offerhaus GJ, Yeo CJ, Cameron JL, Klimstra DS et al (2003) Immunohistochemical and genetic analysis of non-small cell and small cell gallbladder carcinoma and their genetic precursor lesions. Mod Pathol 16:299–308

Peraza S, Delgado G, Gonzalez JE (1990) Neuroendocrine carcinoma and adenocarcinoma of the gallbladder: report of a case with immunocytochemical study (in Spanish). G E N 44:146–150

Piana S, Cavazza A, Corrado S, Putrino I, Gardini G (2002) Combined small cell carcinoma and clear cell carcinoma of the gallbladder: report of a case and review of the literature. Pathol Res Pract 198:821–824

Porter JM, Kalloo AN, Abernathy EC, Yeo CJ (1992) Carcinoid tumor of the gallbladder: laparoscopic resection and review of the literature. Surgery 112:106–110

Psathakis D, Wenk H, Müller G, Bruch HP (1996) Primary carcinoid tumor of the gallbladder. Hepatogastroenterology 43:167–168

Rastogi A, Bihari C, Singh S, Deka P, Bhatia V, Sarin S (2012) Adenoendocrine carcinoma of gallbladder in a patient with primary sclerosing cholangitis and ulcerative colitis. Trop Gastroenterol 33:158–160

Resnick MB, Jacobs DO, Brodsky GL (1994) Multifocal adenocarcinoma in situ with underlying carcinoid tumor of the gallbladder. Arch Pathol Lab Med 118:933–934

Rindi et al. (2006). http://www.ncbi.nlm.nih.gov/pubmed/16967267

Rindi et al. (2007). http://www.ncbi.nlm.nih.gov/pubmed/17674042

Ron IG, Wigler N, Ilie B, Chaitchik S (1992) Small cell carcinoma of the gallbladder: clinical course and response to chemotherapy. Tumori 78:207–210

Russo S, Russo F, Maiello FM, Paolini B, Carrabba A, De Gregorio A (2012) Biphasic large cell neuroendocrine carcinoma – pure mucinous carcinoma of the gallbladder (MANEC): a unique combination. Pathologica 104:185–189

Sakaki M, Hirokawa M, Sano T, Horiguchi H, Wakatsuki S, Ogata S (2000) Gallbladder adenocarcinoma with florid neuroendocrine cell nests and extensive Paneth cell metaplasia. Endocr Pathol 11:365–371

Salimi Z, Sharafuddin M (1995) Ultrasound appearance of primary carcinoid tumor of the gallbladder associated with carcinoid syndrome. J Clin Ultrasound 23:435–437

Samad A, Kaplan A, Arain M, Attam R, Jessurun J, Manivel JC, Pambuccian SE (2013) Endoscopic ultrasound-guided fine-needle aspiration diagnosis of large cell neuroendocrine of the gallbladder and common bile duct: report of a case. Diagn Cytopathol 41:1091–1095

Sato K, Imai T, Shirota Y, Ueda Y, Katsuda S (2010) Combined large cell neuroendocrine carcinoma and adenocarcinoma of the gallbladder. Pathol Res Pract 206:397–400

Saxton CR (1983) Unusual presentation of carcinoid tumor as acute cholecystitis. South Med J 76:947–948

Shimizu T, Tajiri T, Akimaru K, Arima Y, Yoshida H, Yokomuro S, Mamada Y, Taniai N et al (2006) Combined neuroendocrine cell carcinoma and adenocarcinoma of the gallbladder: report of a case. J Nihon Med Sch 73:101–105

Shimono C, Suwa K, Sato M, Shirai S, Yamada K, Nakamura Y, Makuuchi M (2009) Large cell neuroendocrine carcinoma of the gallbladder: long survival achieved by multimodal treatment. Int J Clin Oncol 14:351–355

Singh R, Basturk O, Klimstra DS, Zamboni G, Chetty R, Hussain S, La Rosa S, Yilmaz A et al (2006) Lipid-rich variant of pancreatic endocrine neoplasms. Am J Surg Pathol 30:194–200

Sinkre PA, Murakata L, Rabin L, Hoang MP, Albores-Saavedra J (2001) Clear cell carcinoid tumor of the gallbladder: another distinctive manifestation of von Hippel-Lindau disease. Am J Surg Pathol 25:1334–1339

Soga J (2003) Primary endocrinomas (carcinoids and variant neoplasms) of the gallbladder. A statistical evaluation of 138 reported cases. J Exp Clin Cancer Res 22:5–15

Sommariva S, Brigli G, Robutti F, Doaria FE, Doaria FL (1988) A rare case of carcinoid tumor of the gallbladder (in Italian). A rare case of carcinoid tumor of the gallbladder. Minerva Chir 43:1089–1094

Sosnik H, Sosnik K (2006) Double cancer of the gallbladder – a case report. Pol J Pathol 57:213–215

Spence RW, Burns-Cox CJ (1975) ACTH-secreting 'apudoma' of gallbladder. Gut 16:473–476

Takahashi Y, Fukushima J, Fukusato T, Shiga J (2004) Sarcomatoid carcinoma with components of small cell carcinoma and undifferentiated carcinoma of the gallbladder. Pathol Int 54:866–871

Takei H, Adesina AM, Bhattacharjee MB (2007) The Azzopardi phenomenon. Arch Pathol Lab Med 131:518

Tanaka K, Iida Y, Tsutsumi Y (1992) Pancreatic polypeptide-immunoreactive gallbladder carcinoid tumor. Acta Pathol Jpn 42:115–118

Tewari M, Kumar V, Mishra RR, Shukla HS (2009) Gallbladder carcinoid masquerading as gallbladder carcinoma. Hepatobiliary Pancreat Dis Int 8:326–328

Tsuchiya A, Endo Y, Yazawa T, Saito A, Inoue N (2006) Adenoendocrine cell carcinoma of the gallbladder: report of a case. Surg Today 36:849–852

Uribe-Uribe NO, Jimenez-Garduño AM, Henson DE, Albores-Saavedra J (2009) Paraneoplastic sensory neuropathy associated with small cell carcinoma of the gallbladder. Ann Diagn Pathol 13:124–126

Virzi G, Ragazzi S, D'Agati P, Caputo S, Mascali D, Ciaccio G, Scaravilli F, Piazza D (2008) Image of the month. Moderately differentiated neuroendocrine carcinoma of the gallbladder. Arch Surg 143:95–96

Volante M, Rindi G, Papotti M (2006) The grey zone between pure (neuro)endocrine and non-(neuro) endocrine tumors: a comment on concepts and classification of mixed exocrine-endocrine neoplasms. Virchows Arch 449:499–506

Wada A, Ishiguro S, Tafeishi R, Oshikawa O, Matsui Y (1983) Carcinoid tumor of the gallbladder associated with adenocarcinoma. Cancer 51:1911–1917

Warkel RL, Cooper PH, Helwig EB (1978) Adenocarcinoid, a mucin-producing carcinoid tumor of the appendix: a study of 39 cases. Cancer 42:2781–2793

Walter T, Chardon L, Hervieu V, Cohen R, Chayvialle JA, Scoazec JY, Lombard-Bohas C (2009) Major hyperghrelinemia in advanced well-differentiated neuroendocrine carcinomas: report of three cases. Eur J Endocrinol 161:639–645

Wisniewski M, Toker C (1972) Composite tumours of the gallbladder exhibiting both carcinomatous and carcinoid patterns. Am J Gastroenterol 58:633–637

Yamamoto M, Nakajo S, Miyoshi N, Nakai S, Tahara E (1989) Endocrine cell carcinoma (carcinoid) of the gallbladder. Am J Surg Pathol 13:292–302

Yannakou N, Rizos S, Parissi-Mathiou P, Samailis D, Charanioti S, Dervenis C (2001) Mixed (composite) glandular-endocrine carcinoma of the gallbladder. HPB (Oxford) 3:7–9

Yokoyama Y, Fujioka S, Kato K, Tomono H, Yoshida K, Nimura Y (2000) Primary carcinoid tumor of the gallbladder: resection of a case metastasizing to the liver and analysis of outcomes. Hepatogastroenterology 47:135–139

Yoon KW, Park CH, Lee WS, Joo YE, Kim HS, Choi SK, Rew JS, Lee JH (2009) A case of primary neuroendocrine carcinoma of the gallbladder associated with anomalous union of the pancreaticobiliary duct. Gut Liver 3:231–234

Yoshizumi Y, Sugiura Y, Morisaki Y, Shima S, Tanaka S (1992) Mitomycin-C-sensitive carcinoid tumor of the gallbladder: report of a case (in Japanese). Gan To Kagaku Ryoho 19:893–896

Zou YP, Li WM, Liu HR, Li N (2010) Primary carcinoid tumor of the gallbladder: a case report and brief review of the literature. World J Surg Oncol 8:12

Mesenchymal Tumors of the Gallbladder

156

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_156

Abstract

The gallbladder is the primary site of numerous types of mesenchymal tumors, but all these neoplasms are rare. Many of the small and solitary lesions are asymptomatic and are detected as incidental lesions in the setting of cholecystectomy for other reasons. Benign tumors include lipoma, various fibrous tumors, leiomyoma, gastrointestinal stromal tumor, schwannoma, neurofibroma, granular cell tumor, hemangioma, and lymphangioma. Several types of sarcomas were diagnosed in gallbladder specimens, in particular spindle cell sarcomas, myosarcomas, and angiosarcoma. Part of sarcomas show an endoluminal growth pattern, sometimes with formation of large polyps filling the gallbladder lumen. Part of sarcomatous gallbladder neoplasms described in the older literature are difficult to classify. Rarely, lymphomas develop in the gallbladder wall, in the apparent absence of manifestations elsewhere.

Lipoma of the Gallbladder

Introduction

Gallbladder lipoma is a rare benign adipocyte tumor that has been observed few times as an incidental finding in the course of cholecystectomy or as a slowly growing tumor that caused filling of the gallbladder or obstruction (Hillemand and Debbasch 1961; Bonandrini et al. 1970; Tokoro et al. 1991; Furukawa 1996; Takagi et al. 1996). Gallbladder lipoma may be associated with multiple lipomas of the gastrointestinal tract (Tokoro et al. 1991).

Pathology

Macroscopically, gallbladder lipomas are well-circumscribed, roundish yellow tumors of the soft consistency; these neoplasms also show elsewhere in the body. The histology is the same as in other lipomas, sometimes with small necrosis and

the formation of lipogranulomas. The slowly growing tumors can cause atrophy of the adjacent muscular layer of the gallbladder.

Differential Diagnosis

The principal differential diagnosis of gallbladder lipoma is the more common reactive increase of gallbladder-associated normal adipose tissue, i.e., lipomatosis (Miyake et al. 1987). On a biopsy, these two conditions may not be distinguishable.

Lipomatosis of the Gallbladder

Introduction

Lipomatosis of the gallbladder is defined as either a proliferation of mature adipose tissue in the subserosa of the gallbladder (the common variant) and/or an infiltration of the muscular wall of the gallbladder by adipose tissue, associated with myatrophy (the rare variant). Lipomatosis is one form of Jutras's hypertrophic cholecystosis, a group of disorders or abnormalities of the gallbladder different from inflammatory disease (Jutras et al. 1960). Gallbladder lipomatosis can be associated with adenomyomatosis (Miyake et al. 1992). Subserosal gallbladder lipomatosis is visualized on CT and MR images, with a typical mural stratification, the subserosal fatty layer being the last layer before the serosa stratum (Miyake et al. 1987; Oishi Tanaka et al. 2002).

Pathology

Macroscopically, a thick and lobulated layer of adipose tissue is found in the subserosal gallbladder space in the common form of lipomatosis. In this variant, the adipose tissue does not extend into the muscle layers. In contrast, the much less common transmural form shows lobules of fatty tissue also in the muscularis. Histologically, mature and normal-looking adipose tissue is the hallmark.

Differential Diagnosis

In contrast to the rare gallbladder lipoma, lipomatosis is not a nodular solitary lesion but forms a band-like accumulation of fatty tissue with a diffuse or lobular pattern.

Liposarcoma of the Gallbladder

Introduction

Liposarcoma is a member of the least common sarcomas developing in the gallbladder, together with rhabdomyosarcoma, angiosarcoma, and synovial sarcoma. Only few cases have been reported (Bader and Vallon 1983; Hamada et al. 2006). The tumors tended to invade adjacent structures and to spread within the abdominal cavity.

Pathology

As in other compartments of the body, gallbladder liposarcoma can grow to large or very large sizes. In one patient, the tumor measured 25 cm in diameter, with a weight of 3,300 g, and extended into the right liver lobe and the peritoneal cavity (Hamada et al. 2006). Several histologic types of this sarcoma were identified, including myxoid liposarcoma (Bader and Vallon 1983) and pleomorphic liposarcoma (Hamada et al. 2006).

Differential Diagnosis

Spindle cell components occurring in liposarcoma may lead to the erroneous diagnosis of fibrosarcoma or other spindle cell sarcomas. In liposarcoma lacking large droplet adipocytes, fat stains on frozen sections will lead to the correct diagnosis.

Leiomyoma of the Gallbladder

Introduction

Gallbladder leiomyomas either develop as sporadic and very rare benign tumors, or they occur in immunosuppressed individuals with or without

Epstein-Barr virus (EBV) infection. Sporadic leiomyomas of the gallbladder are usually small- or medium-sized nodular lesions that are mostly found incidentally in the course of cholecystectomies for other reasons (Gava and Cinti 1968; Christensen and Ishak 1970; Shou et al. 1987; Furukawa 1996; Palade et al. 2006; Wachter et al. 2010; Segura-Sampedro et al. 2012). Gallbladder leiomyomas of immunosuppressed patients, including children, were observed in HIV infection (Toma et al. 1997) and in EBV infection (Monforte-Muñoz et al. 2003). Monforte-Muñoz and associates reported an 8-year-old girl with SCID and bone marrow transplantation, who developed multiple gallbladder leiomyomas (leiomyomatosis) associated with other leiomyomas in the liver, spleen, pancreas, intestinal tract, and lung. The patient was EBV infected and developed extensive EBV-associated polymorphic lymphoproliferative disorder/PTLD. Pediatric HIV- and EBV-associated smooth muscle cell tumors of the gallbladder have been described in another clinical investigation (Mahlobo et al. 2012).

Pathology

Macroscopically, gallbladder leiomyomas are solitary or multiple nodular and whitish tumors of medium to high consistency, with a fibrillary or fasciculated texture on the cut surface. Histology typically shows fascicles of faintly eosinophilic and elongated smooth muscle cells with blunted nuclei. Mitotic figures are very rare, and necroses are usually absent. Immunohistochemically, the cells are markedly reactive for alpha-smooth muscle actin and vimentin but not for S100 protein.

Differential Diagnosis

Leiomyoma of the gallbladder may be confounded with other rare spindle cell tumors of this organ, including fibroma, myofibroblastic neoplasms, neurofibroma, well-differentiated leiomyosarcoma, and GISTs. The differential diagnostic separation of leiomyoma from GIST may be difficult and requires immunohistochemistry, leiomyomas being negative for CD117 and positive for smooth muscle actin.

Leiomyosarcoma of the Gallbladder

Introduction

Among gallbladder malignancies, primary leiomyosarcoma is one of the most infrequent types, with only relatively few reported cases. The first case may have been reported in 1893 (Schmidt 1893). By 1984, leiomyosarcoma accounted for 7 % of 105 cases of primary gallbladder sarcomas (Newmark et al. 1986). The tumor is mostly found in female patients in the sixth decade who have cholecystolithiasis (Yasuma and Yanaka 1971). Main symptoms and signs comprise pain radiating to the back or to the right lower quadrant, resembling cholecystitis. Gallbladder leiomyosarcoma carries a poor prognosis. It can invade the gallbladder fossa and the liver hilum and metastasizes to the liver (Garcia Marin et al. 2010).

Selected References Dello Russo and Paladino 1960; Gonzalomendoza and Aguilar 1963; Duchini 1965; Friedland 1971; Yasuma and Yanaka 1971; Willén and Willén 1982; Heitzman 1985; Newmark et al. 1986; Tarasov et al. 1987; Gutstein et al. 1988; Egorov 1989; Fotiadis et al. 1990; Yoshida et al. 1990; Muñoz et al. 1992; Kumar et al. 1993; Tocchi et al. 1993; Ikuno et al. 1996; Zeig et al. 1998; Danikas et al. 2001; Bernardos et al. 2004; Perez-Montiel et al. 2004; Palomeque et al. 2005; Elkaoui et al. 2008; Al-Daraji et al. 2009; Husain et al. 2009; Garcia Marin et al. 2010; Savlania et al. 2012.

Pathology

Gallbladder leiomyosarcomas usually form large, rubbery, or firm masses replacing the gallbladder. The neoplasms can grow to impressive sizes,

having a diameter of 17 cm and a weight of 3,100 g in one case (Palomeque et al. 2005). Large tumors often show central necrosis and hemorrhage. Part of the tumors display an endophytic growth, sometimes with large polypoid endoluminal masses with or without dilatation of the gallbladder lumen (Newmark et al. 1986; Perez-Montiel et al. 2004). Histology shows bundles and fascicles of eosinophilic spindle cells with elongated or blunt nuclei, variable nuclear atypias, and a usually slightly to moderately elevated mitotic count. However, poorly differentiated epithelioid leiomyosarcoma was also observed (Danikas et al. 2001). Immunohistochemically, the tumor expresses alpha-smooth muscle actin and vimentin (Garcia Marin et al. 2010).

Differential Diagnosis

Differential diagnostically, other spindle cell sarcomas and atypical hypercellular leiomyomas have to be considered.

Angioleiomyoma of the Gallbladder

Introduction

Angioleiomyoma (angiomyoma; vascular leiomyoma) is a benign myoid tumor that chiefly occurs in the soft tissues of the extremities, mostly the lower extremity (Hachisuga et al. 1984). The tumor was first described in 1868 by Aufrecht. It produces well-circumscribed nodules consisting of smooth muscle cells which have an intimate relationship to blood vessels. These tumors account for 5 % of all benign neoplasms of soft tissues. In the skin, angioleiomyoma is usually a solitary lesions, but multiple forms also occur. Histologically, angioleiomyoma is classified into three types, i.e., capillary or solid, the most common form characterized by the presence of numerous thin-walled slit-like vascular channels that rarely represent abortive arterial vessels; venous type, with vessels having thick walls; and the rare cavernous type, with dilated vessels that are rather poor in muscle cells. Due to the arterialization in a minority of cases, angioleiomyomas may present as pulsatile nodules. Less commonly, angioleiomyoma develops in inner organs, particularly intestine, genitourinary tract, and dura. Angioleiomyoma also occurs in the skeletal system.

Pathology

Angioleiomyoma rarely develops in the gallbladder (Aschl et al. 1999). Histologically, the nodular lesions are composed of a proliferation of smooth muscle cells forming bundles that surround numerous, thick-walled vessels with partially patent lumina.

Differential Diagnosis

The chief differential diagnosis is leiomyoma, a benign tumor that is well known to occur in the extrahepatic biliary tract.

Infantile Myofibromatosis of the Gallbladder

Exceptionally, gallbladder involvement with infantile myofibromatosis, a rare disorder discussed in another chapter, has been observed (Goldberg et al. 1988). This disorder is characterized by a proliferation of fibroblasts or and/or myofibroblasts which already appears at birth and progressively involves several organs and tissues. In the case reported by Goldberg and associates (1988), gallbladder infiltration was associated with involvement of the common bile duct, causing obstructive jaundice.

Fibroma of the Gallbladder

Primary fibroma of the gallbladder is among the most uncommon tumors of this organ, with only one report available (Furukawa 1996).

Fibrosarcoma and Not Further Specified Spindle Cell Sarcomas of the Gallbladder

Introduction

Primary fibrosarcoma of the gallbladder is a very rare malignancy (Landsteiner 1904; Lyons 1950; Daneo 1954; Chauvenet 1955; Longo and Ferraris 1957; Marrano and Freyrie 1963; Roselli et al. 1964; Tanga 1970; Mena and Montebruno 1971; Tamaki et al. 1971; Yasuma and Yanaka 1971; Vaittinen 1972; Chudacek 1973; Rose 1978; Willén and Willén 1982). In the light of revised classifications of fibroblastic and myofibroblastic sarcomas, it is difficult to judge as to how the tumors reported in the older literature would be classified today. Part of the cases may have represented myxofibrosarcoma or myofibroblastic sarcoma, tumors that are known to occur in the gallbladder (Husain et al. 2009), or myogenic sarcomas. Gallbladder fibrosarcoma was observed in conjunction with gallbladder carcinoma (Chudacek 1973).

Pathology

Macroscopically, fibrosarcomas are large and firm tumors with a fasciculated cut surface, sometimes with central necrosis and/or hemorrhage (Fig. 1). Histologically, the lesions present the same pattern as their soft tissue counterparts, i.e., a dense collection of fibroblastoid spindle cells forming bundles or fascicles, with variable degrees of nuclear atypia and usually a low mitotic count. Part of sarcomas derived from a fibroblastoid lineage show marked pleomorphisms and a low degree of differentiation (Fig. 2).

Myxofibrosarcoma is one of the most common sarcomas in the extremities of patients of older age, and is clinically characterized by a high prevalence of local recurrence, but a rather low overall risk of distant metastases. Primary visceral myxofibrosarcoma is an uncommon variant of this neoplasm. So far, there is a single observation of myxofibrosarcomatoid lesion in the gallbladder, with a fibromyxoid sarcoma-like/Evans-like morphology (Al-Daraji et al. 2009). Differential diagnostically, myxofibrosarcoma can metastasize to the intra-abdominal compartment, including the liver (Murahashi et al. 2012).

Differential Diagnosis

As already outlined above, fibrosarcoma has to be distinguished from other spindle cell sarcomas, in particular myofibroblastic sarcoma and myxofibrosarcoma. Inflammatory pseudotumors (inflammatory myofibroblastic tumors) of the gallbladder may histologically mimic spindle

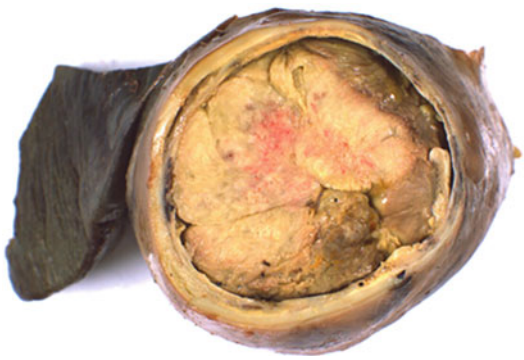

Fig. 1 Sarcoma of the gallbladder with an endophytic, "phyllodes-like" growth pattern. The neoplasm exhibits marked necrosis

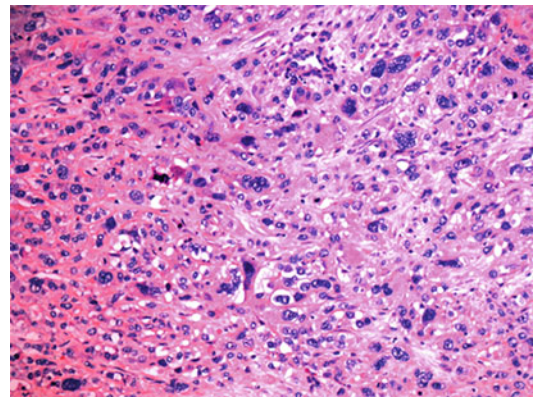

Fig. 2 Pleomorphic, poorly differentiated sarcoma of the gallbladder with tumor giant cells (hematoxylin and eosin stain)

cell sarcoma. Few cases of chronic cholecystitis can develop a marked, fasciitis-like and sometimes mass-forming connective tissue reaction that must not be confounded with sarcoma.

Schwannoma (Neurilemmoma) of the Gallbladder

Introduction

Schwannoma (neurinoma) is a common soft tissue tumor derived from Schwann cells of diverse types of nerves. Apart from soft tissues and the central nervous system, schwannoma develops in several visceral organs, including the hepatobiliary tract. In contrast to large extrahepatic bile ducts, schwannoma of the gallbladder is an uncommon neoplasm.

Pathology

Few cases of schwannoma primary to the gallbladder have been reported, and most were incidental findings obtained with cholecystectomy specimens (Debray et al. 1956; Christensen and Ishak 1970; Yamagiwa et al. 1991; Colovic et al. 2003; Ohta et al. 2010). In one patient, the lesion manifested as jaundice, and a diagnosis of bile duct cancer was considered, but cholecystectomy disclosed schwannoma of the gallbladder (Yamagiwa et al. 1991). In the patient reported by Ohta and associates (2010), laparoscopic cholecystectomy was performed due to a preoperative diagnosis of cholecystolithiasis. The surgical specimen revealed stones and chronic cholecystitis, associated with a small tumor that was manifest as wall thickening of the fundus. Histology showed the typical features of schwannoma.

Differential Diagnosis

Histologically, schwannoma of the gallbladder may be confounded with neurofibroma or traumatic neuroma. In small or damaged lesion, immunohistochemistry for S100 protein expression is helpful to detect the characteristic arrangement of Schwann cells in schwannomas.

Neurogenic Sarcoma of the Gallbladder

There is a single published observation of neurogenic sarcoma primary to the gallbladder (Rabinovitch and Trinidad 1952).

Granular Cell Tumor of the Gallbladder

Granular cell tumors (granular cell schwannomas) are lesions that are well known to occur in the extrahepatic bile duct system (see the respective chapter). In contrast, only few cases of granular cell tumor originating in the gallbladder have been observed (Ishii et al. 1977; Yamaguchi et al. 1985; Murakata and Ishak 2001). In one patient, the tumor was situated in the cystic duct and had caused mucocele of the gallbladder (Yamashina and Stemmermann 1984). As in other locations, the tumors are reactive for S100 protein and inhibin-alpha.

Neurofibroma and Neurofibrosarcoma of the Gallbladder

Introduction

Neurofibroma is a rare benign mesenchymal tumor of the gallbladder that develops with or without preceding neurofibromatosis type 1. In a review of seven published cases, age at presentation ranged from 44 to 77 years (average 61.6 years), with a slight female preponderance (Acebo et al. 1998). Most tumors are located in the gallbladder body and are detected incidentally in gallbladders resected for cholecystolithiasis (Arbab and Brasfield 1967; Christensen and Ishak 1970; Eggleston and Goldman 1982; Ilie and Behar 1985; Morizumi et al. 1988; Fuller and Williams 1991; Zhang 1991; Albores-

Saavedra et al. 1993; King and Williamson 1995; Acebo et al. 1998; Sucandy et al. 2010). Apart from asymptomatic lesions, a case presenting as chronic epigastric pain was reported (Sucandy et al. 2010).

Pathology

Macroscopically, solitary neurofibroma either presents as an intramural nodular tumor of whitish color that is well delineated and exhibits a rather form consistency or as and endophytically growing polypoid tumor. Among seven reviewed cases, five tumors appeared as the mural nodular variant, and two showed intraluminal growth. The size of the lesions ranged from 0.3 to 5.3 cm, with a mean diameter of 1.3 cm (Acebo et al. 1998). Gallbladder neurofibroma can present as multiple mural nodules (Sucandy et al. 2010). Histologically, diffuse or plexiform growth patterns occur, as seen in other neurofibromas.

Differential Diagnosis

Gallbladder neurofibroma may be confounded with neurinoma in the absence of immunohistochemical stains.

Neurofibrosarcoma

Malignant variants of neurofibroma, or neurofibrosarcoma, are extremely rare neoplasms of the gallbladder (Liu et al. 2013). In a 72-year-old female patient described by Liu et al. (2013), the gallbladder revealed a tumor with a maximum diameter of 7 cm that had reached the visceral surface of the organ. Histologically, the neoplasm was composed of fusiform to round cells with a slightly eosinophilic cytoplasm, with a fasciculated and weaving pattern. One to three mitoses per HPF were noted. Immunohistochemically, the cells were vimentin(++), NSE(+), S100 protein (+), and SMA(−).

Neuroma and Neuromatosis of the Gallbladder

Introduction

Neuromas (traumatic neuroma; amputation neuroma) are reactive proliferations of nerves that develop at the distal ends of proximal segments of severed nerves. They are characterized by a neural enmeshment of a disorganized overgrowth of axons, Schwann cells, and perineural cells, forming fascicles of variable dimension embedded in a fibrocollagenous tissue and representing an attempt for regeneration (Masson 1942; Stembridge 1951). Neuromas of the biliary tract and the gallbladder derive from the sympathetic and parasympathetic fibers arising from the greater and lesser splanchnic nerves. It has been shown that the area of the common bile duct bifurcation with the cystic duct is a particularly nerve-rich region (see the respective paragraph in the chapter of bile duct tumors).

Neuroma of the Gallbladder

Neuroma of the body of the gallbladder is a very rare lesion. A polypoid traumatic neuroma was incidentally found in a gallbladder resected for cholelithiasis. This neuroma was suggested to have developed following injury to the gallbladder during an unsuccessful cholecystectomy many years previously (Sano et al. 1985). In another patient, abdominal imaging revealed a protuberant lesion of the gallbladder, histologically representing neuroma in the absence of previous surgery and cholelithiasis (Matsuoka et al. 1996). There are also rare instances of cystic duct neuroma in the absence of previous surgery (Peison and Benisch 1985). More extensive involvement of the gallbladder, i.e., neuromatosis, has been described (Cosmacini et al. 1967). Traumatic neuroma had been found in a patient with double gallbladder, the lesion being present in the second gallbladder after removal of the first (Lefemine and Lazim 2009).

Postcholecystectomy Neuromas

Neuromas most commonly develop in the cystic duct after cholecystectomy, both open and laparoscopic, are the best known example of traumatic biliary tract neuroma, and develop with a highly variable delay following trauma, after cholecystectomy ranging from several months to more than 40 years (Hume and Buxton 1954; Gold 1962; Christensen and Ishak 1970; Bodner et al. 1978; Grigorjew 1981; Stibenz et al. 1984; Elhag and al Awadi 1992; Nagafuchi et al. 1998). The lesions occurred in up to 10 % of postcholecystectomy patients at autopsy in one study (Pickens et al. 1999). Neuroma of the cystic duct stump is a known cause of postcholecystectomy pain/postcholecystectomy syndrome. Cystic duct can extend into the wall of the large extrahepatic bile ducts and cause biliary obstruction (Iannelli et al. 2003).

Osteoma of the Gallbladder

A 39-year-old woman showed multiple osteomas in her gallbladder. She had presented with right upper quadrant abdominal pain, and ultrasonography displayed three small intraluminal gallbladder lesions with no apparent mobility. Pathological examination revealed three small polypoid osteomas covered with normal-looking mucosa (Chen 1994).

Osteosarcoma and Chondrosarcoma of the Gallbladder

Osteosarcoma

Extraskeletal osteosarcoma is a rare high-grade sarcoma which accounts for approximately 1 % of all malignant soft tissue neoplasms. The extrahepatic biliary tract is one of the least common sites for these tumors.

Pathology

Very few cases of osteosarcoma primary to the gallbladder have been described (Sartorio Riganti et al. 1959; Olgyai et al. 2006). Macroscopically, a bony consistency of the tumor mass may be recognizable. Histologically, a spindle cell sarcoma with interspersed neoplastic osteoid is found, with some CD68-positive osteoclasts (Olgyai et al. 2006).

Differential Diagnosis

The main differential diagnosis is variants of gallbladder carcinosarcoma containing tumor osteoid or even osteosarcoma-like components (Inoshita et al. 1986; Ishida et al. 2012; Parreira et al. 2012; Sadamori et al. 2012).

Chondrosarcoma

Edmondson (1967a) mentioned the possible existence of a chondrosarcoma of the gallbladder.

Synovial Sarcoma of the Gallbladder

Introduction

Synovial sarcoma is a high-grade soft tissue sarcoma that mostly develops in the extremities but also occurs in inner organs, including the gastrointestinal tract. In the hepatobiliary system, synovial sarcoma has been observed as a primary liver tumor several times, while a primary location to the gallbladder is an exceptional finding.

Pathology

There is a single report on synovial sarcoma primary to the gallbladder and common bile duct (Qayum et al. 2008).

Rhabdomyosarcoma of the Gallbladder

Introduction

Very few cases of gallbladder rhabdomyosarcoma (RMS) occurring in adult patients have been reported (Edmondson 1967b; Yasuma and Yanaka 1971; Willén and Willén 1982; Ben Rejeb et al. 1987, 1994; Al-Jaberi et al. 1994; Al-Daraji et al. 2009). Similar to hepatobiliary embryonal RMS in children, gallbladder RMS can grow with a botryoid pattern, i.e., with exophytic polypoid masses (Willén and Willén 1982). In the review of Ben Rejeb et al., it was specified that among seven patients described until 1994, six were females. Three tumors were of the embryonal type, three were of the alveolar type, and one was RMS NOS. In the pediatric age group, hepatobiliary rhabdomyosarcoma involving extra- and intrahepatic bile ducts is a well-recognized entity. However, only relatively few children presented with gallbladder RMS (Mihara et al. 1982). The case of Mihara and coworkers (1982) seems to be a combined RMS of both the common bile duct and the gallbladder, with formation of a polypoid filling defect in the duct and three RMS polyps in the gallbladder.

Pathology

In adult patients, gallbladder RMS can present as a large mass (up to 10 cm diameter; al-Jaberi et al. 1994), extensive necrosis, and hemorrhage in central parts of the mass being frequent. Histologically, embryonal, mixed embryonal, alveolar, and pure alveolar types were identified, the tumor cells being reactive for desmin and vimentin (Al-Jaberi et al. 1994). In pediatric gallbladder RMS, a polypoid/botryoid phenotype prevails, and the tumor is usually embryonal RMS (Mihara et al. 1982).

Differential Diagnosis

Apart from RMS, other gallbladder tumors can show rhabdomyoblastic or rhabdomyomatous differentiation, including carcinosarcomas and malignant stromal tumors (Furihata et al. 2005).

Gastrointestinal Stromal Tumor of the Gallbladder

Introduction

Gastrointestinal stromal tumor (GIST) chiefly develops in the GIT, mesentery and omentum, and much less commonly in the hepatobiliary tract (reviews: Steigen and Eide 2009; Liegl-Atzwanger et al. 2010; Foo et al. 2012). Only few reports have documented GIST primary to the gallbladder (Ortiz-Hidalgo et al. 2000; Mendoza-Marin et al. 2002; Jong et al. 2004; Peerlinck et al. 2004; Palomeque et al. 2005; Petrou et al. 2011; Kostov and Kobakov 2012). GISTs have been proposed to take their origin from interstitial cells of Cajal (ICCs) because of the expression of c-KIT (Sircar et al. 1999). ICCs (pacemaker cells of the GIT) are identified by their combined reactivity for CD117, CD34, and vimentin in the gut. In the first two reports on gallbladder GIST, emphasis had been placed that these neoplasms had the phenotype of ICCs (Ortiz-Hidalgo et al. 2000; Mendoza-Marin et al. 2002).

Gallbladder GIST can be divided into low-risk and high-risk categories, as proposed for other GISTs (Miettinen et al. 1999), and can show a malignant behavior (Mendoza-Marin et al. 2002; Jong et al. 2004; Park et al. 2004; Petrou et al. 2011), with invasion of the gallbladder fossa, the extrahepatic bile ducts, and the duodenum, and delayed metastasis to the liver (Park et al. 2004).

Pathology

Similar to GIST developing in the GIT, gallbladder GIST can grow to a large size and encase the entire gallbladder. Histologically, a spindle cell population predominates, with a morphologic pattern similar to that of GIST localized elsewhere. In malignant gallbladder GIST, tumor necrosis and a high rate of mitotic figures have been noted

(in one case more than 20/50 HPF; Park et al. 2004), i.e., showing the high-risk phenotype according to the risk of aggressive behavior of GIST proposed in the NIH consensus symposium of GIST (Fletcher et al. 2002).

Immunohistochemically, most gallbladder GISTs showed reactivity of the tumor cells for CD117/C-KIT, CD34, and vimentin (Ortiz-Hidalgo et al. 2000). However, rare cases with immunoreactivity for PDGFRA in the absence of CD117 staining have also been described, associated with a mutation of the PDGFRA gene involving codon 824 (Petrou et al. 2011).

"Gastrointestinal Stromal Tumor" with Rhabdmyomatous Differentiation of the Gallbladder

Furihata and coworkers (2005) described a malignant stromal gallbladder tumor, observed in a 68-year-old woman, histologically characterized by a spindle cell population showing a rhabdomyomatous differentiation in the absence of desmin immunostaining. The neoplastic cells were diffusely positive for CD117(c-KIT, suggesting an unusual variant of GIST derived from a mesenchymal stem cell capable to follow a rhabdomyomatous cell lineage.

Differential Diagnosis

By conventional histology, the most important morphologic differential diagnoses of gallbladder GIST comprise nerve sheath tumors and smooth muscle cell tumors.

Stromal Tumor of the Gallbladder with Phenotype of Interstitial Cells of Cajal

Stromal tumor of the gallbladder with the phenotype of interstitial cells of Cajal is a novel entity (Ortiz-Hidalgo et al. 2000; Mendoza-Marin et al. 2002). The first case was detected in a 69-year-old woman who had cholelithiasis and chronic cholecystitis. The gallbladder wall showed a hypocellular nodule of 2.4 cm diameter, composed of spindled cells that were immunoreactive for vimentin, CD34, and CD117. The CD117-positive cells were fusiform with elongated bipolar projections or dendritic-like cytoplasmic projections, representing interstitial cells of Cajal (ICC). In the uninvolved gallbladder wall, numerous CD117-positive ICCs were noted, suggesting that the tumor might have originated from ICC hyperplasia (Ortiz-Hidalgo et al. 2000). A malignant counterpart of this tumor was later observed in a 34-year-old woman who had suffered from upper quadrant abdominal pain. The gallbladder had a thickened wall and showed a polypoid growth arising in the neck region. In addition to the features described above, histology revealed numerous mitotic figures and necroses (Mendoza-Marin et al. 2002).

Hemangioma of the Gallbladder

Introduction

In contrast to the liver, where hemangioma is the most common benign tumor, primary hemangioma of the gallbladder is a very rare lesion. In most patients with this lesion, hemangiomas were incidentally discovered in the course of abdominal ultrasound and CT imaging performed for other reasons. Few patients with gallbladder hemangioma showed abdominal pain or signs mimicking cholangitis or choledocholithiasis.

Epidemiology

Hemangioma of the gallbladder was first mentioned in the 1960s in Robbins' textbook of pathology, but the first formal description of a hemangioma of the gallbladder area was that of Arbab and Brasfield (1967), who however reported on a cavernous hemangioma found in the gallbladder fossa in the course of a reoperation due to postcholecystectomy syndrome. Gallbladder hemangiomas are very uncommon lesions. In a review of benign gallbladder tumors, only

1 hemangioma was detected among 465 cases (Melson 1976). In a review of reported patients, the average age at presentation was 52.5 years, with a female to male ratio of 3:1 (Mayorga et al. 1997). In a more recent review of eight patients, six were male and two female, with an age at diagnosis ranging from 11 to 62 years (Crucitti et al. 2005). Cavernous hemangioma of the gallbladder was observed in conjunction with liver hemangioma (Moffat 1973) or was also identified in the setting of multiple visceral angiomatosis (Cabrera et al. 1977).

Clinical and Imaging Features

The clinical presentation of gallbladder hemangiomas is variable, signs and symptoms depending on the size of the lesions and their location within the organ. In part of cases, the lesion was asymptomatic and detected in the course of screening examinations. In the female patient described by Crucitti and coworkers (2005), abdominal ultrasound performed for screening revealed a solid and fixed echogenic mass arising from the gallbladder fundus, 2.8 × 2.2 cm in size, bulging into the lumen. In a compilation of eight cases, abdominal, epigastric, or back pain or discomfort, often vague, was experienced in six patients (Crucitti et al. 2005). However, gallbladder hemangioma of the cavernous type may also grow to impressive size and hence becoming symptomatic, causing voluminous enlargement of the organ and the clinical impression of a cystic mesenteric tumor (Mayorga et al. 1997).

Pathology

Macroscopically, gallbladder hemangiomas are nodular or polypoid and sometimes pedunculated, spongy, or bosselated tumors of red to blue-red color. Histologically, several types of hemangiomas were detected in the gallbladder wall, including cavernous hemangioma (Sewell and Miron 1969; Moffat 1973; Mayorga et al. 1997; Crucitti et al. 2005), arteriovenous hemangioma (Furukawa et al. 1997), and venous hemangioma (Jones et al. 1987). In the most common cavernous variant of hemangioma, histology disclosed densely packed dilated vascular channels with a lobular texture.

Differential Diagnosis

The most relevant differential diagnosis of gallbladder cavernous hemangioma are gallbladder varices, which may develop in the setting of portal hypertension or as a complication of other causes of gallbladder venous outflow disorders (Saigh et al. 1985; Chawla et al. 1994; Radhi 2003; Mishin 2005; Venerito et al. 2006; Besa et al. 2012; Moubarak et al. 2012). Dilated portosystemic collateral vessels of the gallbladder in liver cirrhosis make part of the inferior vena cava group (Moubarak et al. 2012). Similar to hemangiomas, gallbladder varices may undergo hemorrhage, even with associated rupture (Kevans et al. 2009). Other differential diagnoses comprise hypervascular tumors of the gallbladder or of the liver, close to the gallbladder fossa. Hepatic hemangioma located to the fossa region may masquerade as the gallbladder in case of gallbladder agenesis (Stephenson et al. 2010). Exceptional situations mimicking angiomatoid lesions of the gallbladder include mural and extramural proliferations of collateral vessels caused by gallbladder venous and arterial thrombosis in the setting of essential thrombocythemia (Picon-Coronel et al. 2011).

Angiosarcoma of the Gallbladder

Introduction

Among gallbladder sarcomas, primary angiosarcoma (AS) is among the least common malignancies. As in other localizations, gallbladder AS is a highly aggressive neoplasm (Delaini 1954; Vangelista 1954; Belelli 1956; Rosansky and Mullens 1982; Kawai et al. 1989; Kumar et al. 1989, 1994; Hittmair et al. 1991; Byers and McMahon 1994; White and Chan 1994; Costantini et al. 2005; Odashiro et al. 2005; Al-Daraji et al. 2009; Husain et al. 2009). gallbladder AS is usually an isolated lesion that is not associated with preexisting gallbladder lesions,

although one case of AS synchronously associated with squamous cell carcinoma was reported (Kumar et al. 1994).

Pathology

Macroscopically, gallbladder AS form nodular and often hemorrhagic lesions in the wall, or in outer parts of the gallbladder, sometimes extending into the gallbladder fossa. In the course of disease, widespread metastases mainly to the liver, spleen, and peritoneal surface develop (Odashiro et al. 2005). Histopathologically, gallbladder AS present the phenotype known from other locations of this tumor. A dominant proportion of gallbladder AS was of the epithelioid type (Byers and McMahon 1994; White and Chan 1994; Costantini et al. 2005).

Lymphangioma of the Gallbladder

Introduction

Intra-abdominal cystic lymphangiomas, including those developing in the gallbladder, are rare lesions that can be difficult to diagnose, because they radiologically mimic other cystic intra-abdominal alterations. Intra-abdominal lymphangiomas account for less than 5 % of all lymphangiomas. The most common site is the mesentery, followed by the omentum, mesocolon, small intestine, pancreas, liver, spleen, and retroperitoneal space. Approximately 60 % of the patients are younger than 5 years at presentation; the remaining cases do not manifest until the adult age group (Takiff et al. 1985; Roisman et al. 1989). Lymphangioma primary to the gallbladder is a rare lesion, with only few cases having been reported in the literature (Ohba et al. 1995; Amadori et al. 1999; Chung et al. 1999; Choi et al. 2002; Yang et al. 2003; Noh et al. 2005; Kim et al. 2007; Woo et al. 2007; Shikano et al. 2008; Boskovski et al. 2012; Bridda et al. 2012). Gallbladder lymphangioma has also been observed in the pediatric age group (Han et al. 2011).

Clinical and Imaging Features

The clinical presentation of gallbladder lymphangioma is non-specific and mainly consists of right upper quadrant pain, nausea, biliary pain, and sometimes a palpable mass. Owing to a pressure effect, biliary sludge may accumulate in the gallbladder, followed by gallbladder dysfunction. Ultrasonography and CT usually reveal cystic septated masses in the gallbladder wall or in the gallbladder fossa, in part of the cases with calcifications (Ohba et al. 1995), but sometimes the entire gallbladder is replaced by a multicystic mass effacing the gallbladder anatomy. T2-weighted MRI images reveal the septated aspect of most of the cystic lesions (Choi et al. 2002; Noh et al. 2005; Kim et al. 2007). Different signal intensities on T1- and T2-weighted images are due to different fat and fluid ratios within each cyst. Septa are enhanced on the delayed images, while the cystic portions are not. The gallbladder and its lumen may be compressed by the tumor. ERCP illustrated that there is no communication between the gallbladder lumen and the cystic spaces of the tumors (Choi et al. 2002). Angiography showed that the tumors are supplied by a branch of the cystic artery (Ohba et al. 1995).

Biology of Disease

Lymphangiomas are classified as simple, cavernous, or cystic tumors. The prognosis of gallbladder lymphangioma is generally good after complete surgical excision.

Pathology

Macroscopy

Most reported lymphangiomas of the gallbladder were cystic lesions of three morphotypes (Table 1). Multiloculated cystic lesions are grape-like masses with a sponge-like or honeycombed appearance. The cysts displace or replace the preexisting wall structures of the gallbladder and may bulge to the gallbladder lumen,

Table 1 Macroscopic presentation of gallbladder lymphangiomas

Multilocular cystic	Ohba et al. 1995; Shikano et al. 2008
Multiseptated cystic	Choi et al. 2002; Noh et al. 2005
Cystic	Yang et al. 2003; Kim et al. 2007; Woo et al. 2007; Boskovski et al. 2012

associated with atrophy of the mucosa and/or collapse of the lumen. In some of the thin-walled cysts, a fine vascular tree can be noted in the cyst walls. The cysts are sometimes under pressure; following incision, fluid may ooze out copiously. The wall of the cystic tumors can contain calcifications. In case hemorrhage into the spaces takes place, the cysts may have a bluish appearance.

Histopathology

Simple and cavernous lymphangiomas show lymphatic vascular channels that resemble, in their configuration and lumen width, to those found in capillary and cavernous hemangiomas. Cystic lymphangiomas consist of large cystic and usually globose spaces and exhibit a flat endothelial lining of the cystic spaces, whereas simple and cavernous tumors may show a cuboidal or flat lining. Cyst walls are often composed of connective tissue consisting of edematous fibrous tissue, and may contain few myocytes/myofibroblasts and a lymphocytic infiltrate, sometimes with lymph follicles. The lumina of the lymphatic channels contain a pale eosinophilic material (rich in protein, lymph) which can contain lymphocytes and sometimes a few erythrocytes.

Immunohistochemistry

The endothelial lining is reactive for factor VIII-associated antigen and CD31 (Woo et al. 2007). The cells are usually not reactive for CD34. Cells of lymphangiomas are reactive for podoplanin/D2-40 (Sinzelle et al. 2000; Kalof and Cooper 2009) and express VEGFR-3 (Norgall et al. 2007), but this has not yet been analyzed with gallbladder lymphangiomas.

Differential Diagnosis

The chief differential diagnoses comprise echinococcal cysts, lymphangiectasias, mixed cavernous hemangiomas, and wall cysts of the gallbladder.

"Hemangiopericytoma" and Related Tumors of the Gallbladder

Introduction

Hemangiopericytomas were originally described to be neoplasms derived from Zimmermann's pericytes. However, most of the tumors previously classified as hemangiopericytomas do not originate from pericytes, and most of the lesions are in fact solitary fibrous tumors (see the respective chapter on soft tissue tumors of the liver). However, there remains a small group of neoplasms of a truly pericytic lineage, i.e., myopericytomas, lesions that are related to myofibromatosis, glomangiopericytoma, and angioleiomyomas (Fletcher 1994; Granter et al. 1998).

Pathology

A single case of malignant hemangiopericytoma of the gallbladder has been described (Gupta et al. 1983). The tumor showed a pattern typical for this vascular neoplasm and displayed areas of necrosis, an increased mitotic activity, and metastases in locoregional lymph nodes and the right ovary. A giant cell-rich solitary fibrous tumor of the gallbladder was observed (Lazure et al. 2007). This well-demarcated tumor protruded into the lumen and showed a whorled and fibrous structure of the cut surface. The neoplasm was composed of uniform short spindle cells, often aligned like strings of beads between bands of hyalinized collagen. Myogenous sarcoma of the gallbladder

with a hemangiopericytomatous pattern was observed (Nestler et al. 2007).

Malignant Fibrous Histiocytoma (Undifferentiated Pleomorphic Sarcoma) of the Gallbladder

ICD-O code 8830/2

Introduction

Malignant fibrous histiocytoma (MFH) is a rare neoplasm with a high propensity for an aggressive biology. The original concept of MFH by Stout as his associates has undergone extensive changes, and today MFHs are classified as undifferentiated (high-grade) pleomorphic sarcoma/HGUPS (Erlandson and Antonescu 2004; Randall et al. 2004; Matushansky et al. 2009; Henderson and Hollmig 2012). The term MFH is still employed in this paragraph in order to refer to previous observations of this tumor in the gallbladder, all these lesions having been diagnosed as MFH.

Pathology

Few cases of MFH primary to the gallbladder were reported, showing the typical histology with spindle cells arranged in a storiform pattern, intermingled with pleomorphic tumor cells (the storiform pleomorphic pattern). The tumors were usually diagnosed in old patients and tended to metastasize to the liver (Kristofferson et al. 1983; Sasada et al. 1988; Sreekantaiah et al. 1992; Miyakawa and Hamano 1996; Orii et al. 1998; Tomono et al. 1998; Gruttadauria et al. 2001; Al-Daraji et al. 2009; Husain et al. 2009). Also the inflammatory variant of MFH has been observed in the gallbladder (Kato et al. 2002). The neoplasm was found in 70-year-old Japanese man and histologically consisted of ordinary MFH with xanthogranulomatous components, lymphocytes, foamy macrophages, and plasma cells. The tumor cells were reactive for granulocyte colony-stimulating factor, and it was suggested that part of the inflammatory reactions was due to this paracrine mechanism (Kato et al. 2002). In one case of ordinary MFH of the gallbladder, cytogenetic analysis revealed several chromosomal structural abnormalities, including reciprocal translocations and deletions, and chromosomes involved in rearrangements comprised chromosomes 1, 3, 10, 12, 4,16, and 19, while trisomies involved chromosomes 2, 8, 10, and 20 (Sreekantaiah et al. 1992).

References

Acebo E, Fernandez FA, Val-Bernal JF (1998) Solitary neurofibroma of the gallbladder. A case report and review of the literature. Gen Diagn Pathol 143:337–340

Albores-Saavedra J, Vardaman CJ, Vuitch F (1993) Non-neoplastic polypoid lesions and adenomas of the gallbladder. Pathol Ann Part 1:145–177

Al-Daraji WI, Makhlouf HR, Miettinen M, Montgomery EA, Goodman ZD, Marwaha JS et al (2009) Primary gallbladder sarcoma: a clinicopathologic study of 15 cases, heterogeneous sarcomas with poor outcome, except pediatric botryoid rhabdomyosarcoma. Am J Surg Pathol 33:826–834

Al-Jaberi TM, Al-Masri N, Tbukhi A (1994) Adult rhabdomyosarcoma of the gall bladder: case report and review of published works. Gut 35:854–856

Amadori G, Micciolo R, Poletti A (1999) A case of intra-abdominal multiple lymphangiomas in an adult in whom the immunological evaluation supported the diagnosis. Eur J Gastroenterol Hepatol 11:347–351

Arbab AA, Brasfield R (1967) Benign tumors of the gallbladder. Surgery 61:535–540

Aschl G, Wallner M, Tuppy H, Fröhler W, Kramar R (1999) Angioleiomyoma of the gallbladder: a rare cause of hemobilia in a patient on dialysis (in German). Dtsch Med Wochenschr 124:13–16

Bader H, Vallon H (1983) Liposarcoma of the gallbladder and the peritoneum. A case report (in German). Zbl Allg Pathol 127:45–49

Belelli E (1956) Case of primary angiosarcoma of the gallbladder (in Italian). Ann Ital Chir 33:1101–1114

Ben Rejeb A, Bouziani A, Khelil A (1987) Rhabdomyosarcome embryonnaire de type alvéolaire de la vésicule biliaire. A propos d'une observation. Arch Anat Cytol Pathol 35:5–8

Ben Rejeb A, Jabbes H, Essoussi M, Othmani S, Alaya MB, Bahri M (1994) Unusual localization of embryonal rhabdomyosarcoma of the gallbladder (in French). Ann Pathol 14:163–167

Bernardos L, Trujillo A, Huete A, Colon A, Martinez D, Calleja J, Camacho A (2004) Primary leiomyosarcoma

of the gallbladder (in Spanish). Rev Esp Enferm Dig 96:286–287
Besa C, Cruz JP, Huete A, Cruz F (2012) Portal biliopathy: a multitechnique imaging approach. Abdom Imaging 37:83–90
Bodner E, Aufschnaiter M, Hager J, Mikuz G (1978) Neuroma of the cystic nerve stump. No explanation for post-cholecystectomy pain (in German). Chirurg 49:424–427
Bonandrini L, Mantellini E, Colombo P, Scarabelli L (1970) Benign tumors of the gallbladder. Illustration of cases of papilloma, adenoma and lipoma (in Italian). Minerva Chir 25:297–312
Boskovski MT, Saad A, Israel GM, Salem RR (2012) Lymphangioma of the gallbladder in adults: review of the literature and a case report. J Gastrointest Surg 16:663–668
Bridda A, Dallagnese L, Frego M (2012) Is laparoscopic cholecystectomy safe for lymphangioma of the gallbladder? A complicated case mimicking subhepatic abscess. Updates Surg 64:73–76
Byers RJ, McMahon RF (1994) Epithelioid angiosarcoma of the gallbladder. Histopathology 25:502–503
Cabrera OR, Hernandez Viruel JA, Colinabarranco M, Villa FA (1977) Visceral multiple angiomatosis. Clinical case and review of the literature (in Spanish). Prensa Med Mex 42:325–330
Chauvenet A (1955) Two cases of gallbladder sarcoma (in French). J Med Bord 132:589–594
Chawla Y, Dilawari JB, Katariya S (1994) Gallbladder varices in portal vein thrombosis. AJR Am J Roentgenol 162:643–645
Chen KT (1994) Osteomas of the gallbladder. Arch Pathol Lab Med 118:755–756
Choi JY, Kim MJ, Chung JJ, Park SI, Lee JT, Yoo HS, Kim L, Choi JS (2002) Gallbladder lymphangioma: MR findings. Abdom Imaging 27:54–57
Christensen AH, Ishak KG (1970) Benign tumors and pseudotumors of the gallbladder. Report of 180 cases. Arch Pathol 90:423–432
Chudacek Z (1973) Combination of primary fibroblastic sarcoma and gallbladder carcinoma (in German). Fortschr Geb Röntgenstr Nuklearmed 118:344–345
Chung JH, Suh YL, Park IA, Jang JJ, Chi JG, Kim YI, Kim WH (1999) A pathologic study of abdominal lymphangiomas. J Korean Med Sci 14:257–262
Colovic R, Grubor N, Janciae-Zguricas M, Zogovi S (2003) Schwannoma of the gallbladder (in Croatian). Acta Chir Iugosl 50:135–137
Cosmacini G, Costa F, Limentani A (1967) So-called neuromatosis of the gallbladder (in Italian). Radiol Med 53:1108–1114
Costantini R, Di Bartolomeo N, Francomano F, Angelucci D, Innocenti P (2005) Epithelioid angiosarcoma of the gallbladder: case report. J Gastrointest Surg 9:822–825
Crucitti A, La Greca A, Antinori A, Antonacci V, Magistrelli P (2005) Cavernous hemangioma of the gallbladder. Case report and review of the literature. Tumori 91:432–435
Daneo P (1954) Sarcoma of the gallbladder (in Italian). Pathologica 46:367–371
Danikas D, Theodorou SJ, Singh R, Camal DE (2001) Leiomyosarcoma of the gallbladder: a case report. Am Surg 67:873–874
Debray C, Hardouin JP, Laumonier R, Martin E (1956) Neurinoma of gallbladder during chronic non-lithiasic cholecystitis (in French). Sem Hop 32:346–348
Delaini G (1954) A most rare mesenchymal tumor of the gallbladder: angioreticulosarcoma (in Italian). Arch Ital Urol 27:410–417
Dello RR, Paladino L (1960) On a case of leiomyosarcoma of the gallbladder (in Italian). Riforma Med 74:1309–1313
Duchini L (1965) Primary malignant leiomyoma of the gallbladder (in Italian). Arch de Vecchi Anat Patol 45:1037–1051
Edmondson HA (1967a) Tumors of the gallbladder and extrahepatic bile ducts. In: Firminger HI (ed) Atlas of tumor pathology, Sec. VII, Fasc. 26. Armed Forces Institute of Pathology, Washington, DC, pp 78–79
Edmondson HA (1967b) Tumours of the gallbladder and extrahepatic bile ducts. In: Atlas of tumour pathology, section 7. Armed Forces Institute of Pathology, Washington, DC, pp 82–83
Eggleston JF, Goldman RL (1982) Neurofibroma and elastosis of the gallbladder. Report of an unusual case. Am J Gastroenterol 77:335–337
Egorov VP (1989) Gigantic leiomyosarcoma of the gallbladder (in Russian). Arkh Patol 51:68–70
Elhag AM, al Awadi NZ (1992) Amputation neuroma of the gallbladder. Histopathology 21:586–587
Elkaoui H, Bouchentouf SM, Sall I, Baba H, Ait AA, Zentar A, Sair K, Ichou M, Sbiti Y (2008) Leiomyosarcoma of the gallbladder (in French). Gastroenterol Clin Biol 32:789–791
Erlandson RA, Antonescu CR (2004) The rise and fall of malignant fibrous histiocytoma. Ultrastruct Pathol 28:283–289
Fletcher CDM (1994) Haemangiopericytoma – a dying breed? Reappraisal of an "entity" and its variants. Curr Diagn Pathol 1:19–23
Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M et al (2002) Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 33:459–465
Foo WC, Liegl-Atzwanger B, Lazar AJ (2012) Pathology of gastrointestinal stromal tumors. Clin Med Insights Pathol 5:23–33
Fotiadis C, Gugulakis A, Nakopoulou L, Sechas M (1990) Primary leiomyosarcoma of the gallbladder. case report and review of the literature. HPB Surg 2:211–214
Friedland HM (1971) Leiomyosarcoma of the gallbladder. J Med Soc NJ 68:205–206

Fuller CE, Williams GT (1991) Gastrointestinal manifestation of type 1 neurofibromatosis (von Recklinghausen's disease). Histopathology 19:1–11

Furihata M, Fujimori T, Imura J, Ono Y, Furihata T, Shimoda M, Kato M, Kita J, Ohkura Y et al (2005) Malignant stromal tumor, so called "gastrointestinal stromal tumor", with rhabdomyomatous differentiation occurring in the gallbladder. Pathol Res Pract 201:609–613

Furukawa H (1996) Leiomyoma, lipoma, myxoma, and fibroma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:33–334

Furukawa H, Kanai Y, Mukai K, Yamasaki S (1997) Arteriovenous hemangioma of the gallbladder. CT and pathologic findings. AJR Am J Roentgenol 168:1383

Garcia MA, Bernardos GL, Martin GJ, Serralta de Colsa D, Turegano FF et al (2010) Primary leiomyosarcoma of the gallbladder. Rev Esp Enferm Dig 102:67–68

Gava L, Cinti C (1968) Leiomyoma of the gallbladder. Case report (in Italian). Minerva Chir 23:1209–1217

Gold E (1962) The clinical significance of amputation neuromas of the gallbladder (in German). Wien Klin Wochenschr 74:188–190

Goldberg NS, Bauer BS, Kraus H, Crussi FG, Esterly NB (1988) Infantile myofibromatosis: a review of clinicopathology with perspectives on new treatment choices. Pediatr Dermatol 5:37–46

Gonzalomendoza M, Aguilar JC (1963) Leiomyosarcoma of the gallbladder (in Spanish). Sem Med 123:2095–2096

Granter SR, Badizadegan K, Fletcher CDM (1998) Myofibromatosis in adults, glomangiopericytoma and myopericytoma. A spectrum of tumors showing perivascular myoid differentiation. Am J Surg Pathol 22:513–525

Grigorjew A (1981) Gallbladder neuroma (in Polish). Wiad Lek 34:767–768

Gruttadauria S, Doria C, Minervini MI, Doyle HR, Mandala L, Foglieni CS, Panarello G et al (2001) Malignant fibrous histiocytoma of the gallbladder: case report and review of the literature. Am Surg 67:714–717

Gupta S, Padmanabhan A, Khanna S (1983) Malignant hemangiopericytoma of the gallbladder. J Surg Oncol 22:171–174

Gutstein D, Cabra de Luna B, Garcia CM, Hernandez Aznar JF, Vara TC (1988) Primary leiomyosarcoma of the gallbladder (in Spanish). Rev Esp Enferm Apar Dig 74:158–160

Hachisuga T, Hashimoto H, Enjoji M (1984) Angioleiomyoma: a clinicopathologic reappraisal of 562 cases. Cancer 54:126–130

Hamada T, Yamagiwa K, Okanami Y, Fujii K, Nakamura I, Mizuno S, Yokoi H, Isaji S et al (2006) Primary liposarcoma of gallbladder diagnosed by preoperative imaging: a case report and review of literature. World J Gastroenterol 12:1472–1475

Han W, Zhang JZ, Wang HM (2011) Lymphangioma of the gallbladder in childhood: a case report and review of the literature. Chin Med J (Engl) 124: 4359–4360

Heitzman J (1985) Malignant leiomyosarcoma of the gallbladder (in Polish). Patol Pol 36:208–213

Henderson MT, Hollmig ST (2012) Malignant fibrous histiocytoma: changing perceptions and management challenges. J Am Acad Dermatol 67:1335–1341

Hillemand P, Debbasch L (1961) Lipoma of the gallbladder (in French). Arch Mal Appar Dig Mal Nutr 50:524

Hittmair A, Sandbichler P, Tötsch M, Mikuz G, Schmid KW (1991) Primary angiosarcoma of the gallbladder. Case report with review of the literature (in German). Pathologe 12:279–281

Hume RH, Buxton RW (1954) Postcholecystectomy amputation neuroma. Am Surg 20:698–708

Husain EA, Prescott RJ, Haider SA, Al-Mahmoud RW, Zelger BG, Zelger B, Al-daraji A (2009) Gallbladder sarcoma: a clinicopathological study of seven cases from the UK and Austria with emphasis on morphological subtypes. Dig Dis Sci 54:395–400

Iannelli A, Fabiani P, Karimdjee BS, Converset S, Saint-Paul MC, Gugenheim J (2003) Traumatic neuroma of the cystic duct with biliary obstruction. Report of a case. Acta Gastroenterol Belg 66:28–29

Ikuno N, Makiyama K, Yoshida N, Omagari K (1996) Leiomyosarcoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:335–337

Ilie B, Behar AJ (1985) Solitary neurofibroma of the gallbladder: report of three cases and literature review. Mt Sinai J Med 52:473–477

Inoshita S, Iwashita A, Enjoji M (1986) Carcinosarcoma of the gallbladder. Report of a case and review of the literature. Acta Pathol Jpn 36:913–920

Ishida J, Ajiki T, Hara S, Ku Y (2012) Gallbladder calcification leads to discovery of carcinosarcoma of the gallbladder. Surgery 152:934–935

Ishii T, Iri H, Yamamoto S, Shinozawa Y, Sudoh M (1977) Granular cell myoblastoma of the gallbladder. Am J Gastroenterol 68:38–44

Jones WP, Keller FS, Odrezin GT, Kelly DR (1987) Venous hemangioma of the gallbladder. Gastrointest Radiol 12:319–321

Jong KP, Seung HC, Lee S, Ki OM, Sang SY, Hae MJ (2004) Malignant gastrointestinal stromal tumor of the gallbladder. J Korean Med Sci 19:763–767

Jutras JA, Longtin JM, Levesque MD (1960) Hypertrophic cholecystoses. Hickey lecture. AJR Am J Roentgenol 93:795–827

Kalof AN, Cooper K (2009) D2-40 immunohistochemistry – so far! Adv Anat Pathol 16:62–64

Kato T, Kojima T, Shimizu T, Sasaki H, Abe M, Okushiba S, Kondo S, Kato H, Sato H (2002) Inflammatory malignant fibrous histiocytoma of the gallbladder: report of a case. Surg Today 32:81–85

Kawai T, Hirose Y, Ainota T, Miyazaki Y, Yamamoto Y, Ikeda M, Akahane Y, Fujino M et al (1989) A case of hemangiosarcoma of the gallbladder (in Japanese). Nihon Sokakibyo Gakkai Zasshi 86:2611–2616

Kevans D, MacNicholas R, Norris S (2009) Gallbladder wall variceal haemorrhage with associated rupture: a rare cause of mortality in the cirrhotic patient. Eur J Gastroenterol Hepatol 21:955–957

Kim JK, Yoo KS, Moon JH, Park KH, Chung YW, Kim KO, Park CH, Hahn T, Park SH et al (2007) Gallbladder lymphangioma: a case report and review of the literature. World J Gastroenterol 13:320–323

King W, Williamson DP (1995) Solitary neurofibroma of the gallbladder. J Ultrasound Med 14:315–316

Kostov DV, Kobakov GL (2012) Gastrointestinal stromal tumor of the gallbladder. HPB (Oxford) 14:150

Kristofferson AO, Domellöf L, Emdin SO, Kullenberg K (1983) Malignant fibrous histiocytoma of the gallbladder: a case report. J Surg Oncol 23:56–59

Kumar A, Lal BK, Singh MK, Kapur BM (1989) Angiosarcoma of the gallbladder. Am J Gastroenterol 84:1431–1433

Kumar S, Gupta A, Shrivastava UK, Bhargava SK (1993) Leiomyosarcoma of gallbladder: a case report. Indian J Pathol Microbiol 36:78–80

Kumar A, Singh MK, Kapur BM (1994) Synchronous double malignant tumors of the gallbladder. A case-report of squamous cell carcinoma with an angiosarcoma. Eur J Surg Oncol 20:63–67

Landsteiner K (1904) Über das Sarkom der Gallenblase. Wien Klin Wochenschr 17:163–165

Lazure T, Dimet S, Ndiaye N, Bourdin G, Ladouch-Badre A (2007) Giant cell-rich solitary fibrous tumour of the gallbladder. First case. Histopathology 50: 805–807

Lefemine V, Lazim TR (2009) Neuroma of a double gallbladder: a case report. Cases J 2:11

Liegl-Atzwanger B, Fletcher JA, Fletcher CD (2010) Gastrointestinal stromal tumors. Virchows Arch 456:11–127

Liu XF, Tang K, Sui LL, Xu G (2013) Neurofibrosarcoma of the gallbladder: a case report. World J Surg Oncol 11:189

Longo O, Ferraris A (1957) Sarcoma of the gallbladder (in French). Lyon Chir 53:349–352

Lyons AH (1950) Primary sarcoma of the gallbladder. Am J Surg 80:473–475

Mahlobo TT, Grieve A, Loveland JA (2012) Pediatric multifocal myofibroblastic tumors with involvement of the gallbladder: HIV- and Epstein-Barr virus-associated smooth muscle cell tumors. J Pediatr Surg 47: e1–e4

Marrano D, Freyrie V (1963) Primary sarcoma of the gallbladder (in Italian). Arch Ital Mal Appar Dig 30:539–556

Masson P (1942) Tumours encapsulées et benignes des nerfs (Encapsulated and benign tumors of nerves). Rev Can Biol 1:209

Matsuoka J, Tanaka N, Kojima K, Takai K, Hamaya K, Gochi A, Kamikawa Y, Orita K (1996) A case of traumatic neuroma of the gallbladder in the absence of previous surgery and cholelithiasis. Acta Med Okyama 50:273–277

Matushansky I, Charytonowicz E, Mills J, Siddiqi S, Hricik T, Cordon-Cardo C (2009) MFH classification: differentiating undifferentiated pleomorphic sarcoma in the 21st century. Expert Rev Anticancer Ther 9:1135–1144

Mayorga M, Hernando M, Val-Bernal JF (1997) Diffuse expansive cavernous hemangioma of the gallbladder. Gen Diagn Pathol 142:211–215

Melson GL (1976) Tumorous conditions of the gallbladder. Semin Roentgenol 11:269–272

Mena I, Montebruno D (1971) Sarcoma primario de la vesicula biliar (primary sarcoma of the gallbladder). Rev Med Chil 99:163–165

Mendoza-Marin M, Hoang MP, Albores-Saavedra J (2002) Malignant stromal tumor of the gallbladder with interstitial cells of Cajal phenotype. Arch Pathol Lab Med 126:481–483

Miettinen M, Sarlomo-Rikala M, Lasota J (1999) Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 30:1213–1220

Mihara S, Matsumoto H, Tokunaga F, Yano H, Ota M, Yamashita S (1982) Botryoid rhabdomyosarcoma of the gallbladder in a child. Cancer 49:812–818

Mishin I (2005) Gallbladder varices. Rom J Gastroenterol 14:165–168

Miyakawa R, Hamano K (1996) Malignant fibrous histiocytoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:243–244

Miyake H, Takeda H, Mori H, Hayashi K, Muta T, Ohshima T, Matsuo T (1987) CT findings in lipomatosis of the gallbladder. J Comput Assist Tomogr 11:165–166

Miyake H, Aikawa H, Hori Y, Mori H, Sakamoto I, Matsuoka Y, Himeno K, Yamashita H (1992) Adenomyomatosis of the gallbladder with subserosal fatty proliferation: CT findings in two cases. Gastrointest Radiol 17:21–23

Moffat JH (1973) Cavernous hemangioma of the gallbladder and liver. Can J Surg 16:172–175

Monforte-Muñoz H, Kapoor N, Saavedra JA (2003) Epstein-Barr virus-associated leiomyomatosis and posttransplant lymphoproliferative disorder in a child with severe combined immunodeficiency: case report and review of the literature. Pediatr Dev Pathol 6:449–457

Morizumi H, Sano T, Hirose T, Hizawa K (1988) Neurofibroma of the gallbladder seen as a papillary polyp. Acta Pathol Jpn 38:259–268

Moubarak E, Bouvier A, Boursier J, Lebigot J, Ridereau-Zins C, Thouveny F, Willoteaux S et al (2012) Portosystemic collateral vessels in liver cirrhosis: a three-dimensional MDCT pictorial review. Abdom Imaging 37:746–766

Muñoz E, Navarro A, Forcada P, Marco V, Veloso E, Marco C (1992) Primary leiomyosarcoma of the gallbladder (in Spanish). Rev Esp Enferm Dig 82: 243–244

Murahashi Y, Kaya M, Soma T, Sasaki M, Nagoya S, Wada T, Yamashita T (2012) Rapid multiorgan

dissemination of low-grade myxofibrosarcoma: a case report. Case Rep Med 2012:310805
Murakata LA, Ishak KG (2001) Expression of inhibin-alpha by granular cell tumors of the gallbladder and extrahepatic bile ducts. Am J Surg Pathol 25:1200–1203
Nagafuchi Y, Katuki M, Hisatome K, Higure A, Asami S, Itoh H (1998) A traumatic neuroma associated with obstructive jaundice after laparoscopic cholecystectomy. Hepato-Gastroenterology 45:424–427
Nestler G, Halloul Z, Evert M, Dombrowski F, Lippert H, Meyer F (2007) Myogenous sarcoma of the gallbladder with a hemangiopericytomatous pattern. J Hepato-Biliary Pancreat Surg 14:197–199
Newmark H, Kliewer K, Curtis A, DenBesten L, Enenstein W (1986) Primary leiomyosarcoma of gallbladder seen on computed tomography and ultrasound. Am J Gastroenterol 81:202–204
Noh KW, Bouras EP, Bridges MD, Narkleh RE, Nguyen JH (2005) Gallbladder lymphangioma: a case report and review of the literature. J Hepato-Biliary Pancreat Surg 12:405–408
Norgall S, Papoutsi M, Rössler J, Schweigerer L, Wilting J, Weich HA (2007) Elevated expression of VEGFR-3 in lymphatic endothelial cells from lymphangiomas. BMC Cancer 7:105
Odashiro AN, Pereira PR, Odashiro Miiji LN, Nguyen GK (2005) Angiosarcoma of the gallbladder: case report and review of the literature. Can J Gastroenterol 19:257–259
Ohba K, Sugauchi F, Orito E, Suzuki K, Ohno T, Mizoguchi N, Koide T, Terashima H et al (1995) Cystic lymphangioma of the gall-bladder: a case report. J Gastroenterol Hepatol 10:693–696
Ohta R, Hirata Y, Oneyama M, Takahashi Y, Kawahara Y, Kitamura M, Goto M, Sekikawa K et al (2010) Schwannoma of the gallbladder: report of a case. Fukushima J Med Sci 56:38–43
Oishi TY, Hori T, Nagata M, Itai Y (2002) Adenomyomatosis with marked subserosal fibrosis and lipomatosis of the gallbladder: mural stratification demonstrated with MR. Magn Reson Med Sci 1:125–128
Olgyai G, Horvath V, Banga P, Kocsis J, Buza N, Olah A (2006) Extraskeletal osteosarcoma located to the gallbladder. HPB (Oxford) 8:65–66
Orii K, Umemura T, Matsuzawa M, Yoshie T, Tamura Y, Yamamura N, Iijima Y, Nagata A et al (1998) A case of primary malignant fibrous histiocytoma of the gallbladder and a review of the cases in Japan (in Japanese). Nihon Shokakibyo Gakkai Zasshi 95:161–166
Ortiz-Hidalgo C, de Leon Bojorge B, Albores-Saavedra J (2000) Stromal tumor of the gallbladder with phenotype of interstitial cells of Cajal: a previously unrecognized neoplasm. Am J Surg Pathol 24:1420–1423
Palade R, Grigoriu M, Voiculescu D (2006) Gallbladder leiomyoma (in Romanian). Chirurgia (Bucur) 101:415–418
Palomeque A, Ramia JM, Muffak K, Alvarez MJ, Martinez AP, Garrote D, Ferron JA (2005) Mesenchymal tumor of the gallbladder (in Spanish). Rev Esp Enferm Dig (Madrid) 97:675–676
Park JK, Choi SH, Lee S, Min KO, Yun SS, Jeon HM (2004) Malignant gastrointestinal stromal tumor of the gallbladder. J Korean Med Sci 19:763–767
Parreira JM, Siqueira DED, Menacho AM, Pelizzari LL, dos Santos LCP (2012) Carcinosarcoma of the gallbladder: case report. ABCD Arq Bras Cir Dig 25:65–66
Peerlinck ID, Irvin TT, Sarsfield PT, Harington JM (2004) GIST (gastro-intestinal stromal tumour) of the gallbladder: a case report. Acta Chir Belg 104:107–109
Peison B, Benisch B (1985) Traumatic neuroma of the cystic duct in the absence of previous surgery. Hum Pathol 16:1168–1169
Perez-Montiel D, Mucientes F, Spencer L, Klaassen R, Suster S (2004) Polypoid leiomyosarcoma of the gallbladder: study of a case associated with adenomyomatous hyperplasia. Ann Diagn Pathol 8:358–363
Petrou A, Alexandrou P, Papalambros A, Saetta A, Fragkou P, Kontos M, Brennan N et al (2011) A malignant gastrointestinal stromal tumor of the gallbladder immunoreactive for PDGFRA and negative for CD 117 antigen (c-KIT). HPB Surg 2011:327192
Pickens A, Vickers SM, Brown KL, Reddy VV, Thompson JA (1999) An unusual etiology of biliary hilar obstruction and the potential role of acidic fibroblast growth factor in the development of a biliary neuroma. Am Surg 65:47–51
Picon-Coronel G, Chablé-Montero F, Angeles-Angeles A, Albores-Saavedra J (2011) Multiple venous and arterial thromboses of the gallbladder causing acute cholecystitis. A previously undescribed complication of essential thrombocythemia. Ann Hepatol 10:365–369
Qayum A, Riall TS, Srinivasan R, Salazar FA (2008) A patient with synovial cell sarcoma primary to the gallbladder and common bile duct. J Gastrointest Surg 12:609–611
Rabinovitch J, Trinidad S (1952) Primary neurogenic sarcoma of the gallbladder. Am J Surg 84:415–418
Radhi JM (2003) Gallbladder varices. Pathology 35:358–359
Randall RL, Albritton KH, Ferney BJ, layfield L (2004) Malignant fibrous histiocytoma of soft tissue: an abandoned diagnosis. Am J Orthop (Belle Mead NJ) 33:602–608
Roisman I, Manny J, Field S, Shiloni E (1989) Intra-abdominal lymphangioma. Br J Surg 76:485–489
Rosansky SJ, Mullens CC (1982) The hepatorenal syndrome associated with metastatic angiosarcoma of the gallbladder. Ann Intern Med 96:191–192
Rose AG (1978) Primary sarcoma of the gallbladder. S Afr Med J 53:909–910
Roselli A, Paulino F, Nobrega MW (1964) Sarcoma of the gallbladder: report of a case. Am J Dig Dis 9:698–703
Sadamori H, Fujiwara H, Tanaka T, Yanai H, Satoh D, Yagi T, Fujiwara T (2012) Carcinosarcoma of the

gallbladder manifesting as cholangitis due to hemobilia. J Gastrointest Surg 16:1278–1281
Saigh J, Williams S, Cawley K, Anderson JC (1985) Varices: a cause of focal gallbladder wall thickening. J Ultrasound Med 4:371–373
Sano T, Hirose T, Kagawa N, Hizawa K, Saito K (1985) Polypoid traumatic neuroma of the gallbladder. Arch Pathol Lab Med 109:574–576
Sartorio Riganti RJ, Mieres A, Val B (1959) Osteogenic sarcoma of the gallbladder (in Spanish). Sem Med 115:54–59
Sasada A, Yanagawa M, Hayashi S, Kita Y, Yoshimura M (1988) Primary malignant fibrous histiocytoma of the gallbladder: a case report (in Japanese). Nihon Geka Gakkai Zasshi 89:1306–1309
Savlania A, Behera A, Vaiphei K, Singh H, Dhiman RK, Duseja A, Chawla YK (2012) Primary leiomyosarcoma of gallbladder: a rare diagnosis. Case Rep Gastrointest Med 2012:287012
Schmidt HJ (1893) Primäres Leiomyosarkom der Gallenblase. Frankf Z Pathol 53:439–449
Segura-Sampedro JJ, Alamo-Martinez JM, Canete-Gomez J, Suarez-Artacho G, Gonzalez-Canton JR et al (2012) Gallbladder leiomyoma in absence of immune system disorders: an unusual diagnosis. Rev Esp Enferm Dig 104:382–384
Sewell JH, Miron MA (1969) Benign cavernous hemangioma of the gallbladder. Arch Pathol 88:30–31
Shikano T, Takeda S, Sakai M, Sugimoto H, Kanazumi N, Nomoto S, Nakao A (2008) Cystic lymphangioma of the gallbladder: report of a case. Surg Today 38:81–84
Shou CC, Chen ZH, Li XD, Wang X, Zhou XR (1987) Benign tumor and pseudotumor of the gallbladder – report of 40 patients (in Chinese). Zhonghua Zhong Liu Za Zhi 9:454–456
Sinzelle E, Duong Van Huyen JP, Breiteneder-Geleff S, Braunberger E, Deloche A et al (2000) Intrapericardial lymphangioma with podoplanin immunohistochemical characterization of lymphatic endothelial cells. Histopathology 37:93–94
Sircar K, Hewlett BR, Huizinga JD, Chorneyko K, Berezin I, Riddell RH (1999) Interstitial cells of Cajal as precursors of gastrointestinal stromal tumors. Am J Surg Pathol 23:377–389
Sreekantaiah C, Rao UN, Karakousis CP, Sandberg AA (1992) Cytogenetic findings in a malignant fibrous histiocytic of the gallbladder. Cancer Genet Cytogenet 59:30–34
Steigen SE, Eide TJ (2009) Gastrointestinal stromal tumors (GISTs): a review. APMIS 117:73–86
Stembridge VA (1951) Amputation neuroma following cholecystectomy. Ann Surg 134:1048–1051
Stephenson JA, Norwood M, Al-Leswas D, Al-Taan O, Beable R, Lloyd DM, Dennison AR (2010) Hepatic haemangioma masquerading as the gallbladder in a case of gallbladder agenesis: a case report and literature review. HPB Surg 2010:971609
Stibenz J, Kretzschmar U, Künzel W, Dittrich H (1984) Amputation neuroma as rare cause of so-called post-cholecystectomy syndrome (in German). Z Ges Inn Med 39:206–208
Sucandy I, Sharma D, Dalencourt G, Bertsch DJ (2010) Gallbladder neurofibroma presenting as chronic epigastric pain – case report and review of the literature. N Am J Med Sci 2:496–498
Takagi I, Watanabe T, Shibamoto Y, Toda G (1996) Lipoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:514–515
Takiff H, Calabria R, Yin L, Stabile BE (1985) Mesenteric cysts and intraabdominal cystic lymphangiomas. Arch Surg 120:1266–1269
Tamaki T, Yanagida S, Saito K (1971) A case of primary sarcoma of the gallbladder. Jpn J Cancer Clin 17:229–231
Tanga MR (1970) Sarcoma of the gallbladder. J Indian Med Assoc 55:22
Tarasov SS, Zhuk NN, Kulikova NG (1987) Leiomyosarcoma of the gallbladder (in Russian). Arkh Patol 49:69–71
Tocchi A, Codacci-Pisanelli M, Costa G, Lepre L, Agostini N, Maggiolini F (1993) Leiomyosarcoma of the gallbladder: a clinical case. G Chir 14:443–445
Tokoro Y, Furukawa H, Taniguchi T, Takahashi T, Hara T (1991) A case report of multiple lipomas of the alimentary tract and gall bladder combined with early gastric cancer (in Japanese). Nihon Shokakibyo Gakkai Zasshi 88:175–179
Toma P, Loy A, Pastorino C, Derchi LE (1997) Leiomyomas of the gallbladder and splenic calcifications in an HIV-infected child. Pediatr Radiol 27:92–94
Tomono H, Fujioka S, Kato K, Yoshida K, Nimura Y (1998) Malignant fibrous histiocytoma of the gallbladder. Hepato-Gastroenterology 45:1468–1472
Vaittinen E (1972) Sarcoma of the gallbladder. Ann Chir Gyn Fen 61:185–189
Vangelista G (1954) Case report of connective tumors of the gallbladder: a rare case of cholecystic angioreticulosarcoma (in Italian). Arch Ital Mal Appar Dig 20:464–477
Venerito M, Mönkemüller K, Malfertheiner P, Rickes S (2006) Hepatobiliary and pancreatic: gallbladder varices. J Gastroenterol Hepatol 21:1348
Wachter DL, Büttner MJ, Grimm K, Hartmann A, Agaimy A (2010) Leiomyoma of the gallbladder: a case report with review of the literature and discussion of the differential diagnosis. J Clin Pathol 63:177–179
White J, Chan YF (1994) Epithelioid angiosarcoma of the gallbladder. Histopathology 24:269–271
Willén R, Willén H (1982) Primary sarcoma of the gallbladder. A light and electronmicroscopical study. Virchows Arch A Pathol Anat Histol 396:91–102
Woo YS, Joo KR, Kim KY, Oh WT, Kim YH (2007) Unusual presentation of cystic lymphangioma of the gallbladder. Korean J Intern Med 22:197–200

Yamagiwa H, Kato K, Kurata M, Suzaki M, Sakai H, Kitagawa M, Itoh H (1991) A case of schwannoma of gallbladder (in Japanese). Med J Mie Univ 35:377–380

Yamaguchi K, Kuroki S, Daimaru Y, Hashimoto H, Enjoji M (1985) Granular cell tumor of the gallbladder. Report of a case. Acta Pathol Jpn 35:687–691

Yamashina M, Stemmermann GN (1984) Granular cell tumor: unusual cause for mucocele of gallbladder. Am J Gastroenterol 79:701–703

Yang HR, Jan YY, Huang SF, Yeh TS, Tseng JH, Chen MF (2003) Laparoscopic cholecystectomy for gallbladder lymphangiomas. Surg Endosc 17:1676

Yasuma T, Yanaka M (1971) Primary sarcoma of the gallbladder – reported three cases. Acta Pathol Jpn 21:285–304

Yoshida N, Mori N, Ishino T, Murata I, Makiyama K, Hara K (1990) A case of leiomyosarcoma of the gallbladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 87:865–871

Zeig DA, Memon MA, Kennedy DR, Woodward SA, Fitzgibbons RJ (1998) Leiomyosarcoma of the gallbladder – a case report and review of the literature. Acta Oncol 37:212–214

Zhang XH (1991) Polypoid lesions of the gallbladder: clinical and pathological correlations (in Chinese). Zhonghua Wai Ke Za Zhi 29:211–213

Melanocytic, Neuroectodermal, Germ Cell, Rhabdoid, Perivascular Epithelioid Cell, Hemolymphatic, and Metastatic Tumors of the Gallbladder

157

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_157

Abstract

The gallbladder is involved by a wide variety of non-epithelial tumors, apart from mesenchymal neoplasms. Visceral malignant melanoma develops in the biliary tract, including the gallbladder. As both primary and metastatic gallbladder melanomas may show similar of the same growth patterns, the differential diagnosis between these two conditions is often difficult. Primary gallbladder melanoma is more likely if the tumor shows a polypoid or lobulated and in particular papillary growth pattern, is a solitary lesion, and is associated with junctional activity in the adjacent mucosa. In contrast, metastatic lesions are more commonly multiple, flat, and without junctional changes. Apart from neuroendocrine tumors, other neuroectodermal neoplasms can develop as primary tumors in the gallbladder. Rare primary neoplasms in this organ include germ cell tumors, rhabdoid tumors, perivascular epithelioid cell tumors, and hemolymphatic neoplasms. Apart from malignant melanoma, numerous other malignancies can metastasize to the gallbladder, renal cell carcinoma being a particularly common metastasizing tumor.

Malignant Melanoma of the Gallbladder

Introduction

Visceral malignant melanoma is known to develop in the biliary tract (see the respective chapter) and also occurs as primary neoplasm in the gallbladder, albeit this is a rare malignancy. It has apparently first been reported in 1907 (Wieting and Hamdi 1907), and relatively few cases have since been reported.

Selected References Thayer et al. 1955; Walsh 1956; Jones 1961; Raffensperger et al. 1963; Debiec et al. 1966; Gabriele and Jouffre 1969; Tanga and Ewing 1970; Balthazar and Javors 1975; Peison and Rabin 1976; Sierra-Callejas and Warecka 1976; Hatae et al. 1978; Carle et al. 1981; Baumann et al. 1982; Anderson et al. 1983; Borja et al. 1984; Naguib and Aterman 1984; Seul and Lüchtrath 1984; Rudolph et al. 1985; Verbanck et al. 1986; Heath and Womack 1988; Guerini et al. 1990; Zhang et al. 1991; Habeck 1993; Hatanaka et al. 1993; Velez et al. 1995; Longwitz et al. 1996; Safioleas et al. 2006; Colaneri et al. 2010; Korkmaz et al, 2010; Gligorijevic et al. 2011; Pitlovic et al. 2011.

The morphology and clinical presentation of proven metastatic malignant melanoma of the gallbladder may closely mimic that of "true" or purported primary melanoma of the gallbladder, so that distinguishing these two situations is difficult and has led to the question whether primary malignant melanoma of the gallbladder exists (Higgins and Strutton 1995; Safioleas et al. 2006). Thus, at least part of the published primary gallbladder melanomas may in fact represent metastatic lesions. What are the criteria allowing the diagnosis of primary malignant melanoma of the gallbladder? The following criteria have been proposed: (1) Tumors must be solitary and arise from the mucosal surface of the gallbladder; (2) the lesions must either be papillary or polypoid; (3) they must either display junctional activity or have any other primary sites excluded by history taking, examination, and investigation (Heath and Womack 1988). By applying these criteria, part of the published cases may be deleted and reclassified as unrecognized metastatic lesions. However, also the criteria listed may be misleading, as it is, e.g., known that also metastatic gallbladder melanomas can grow with a polypoid pattern.

Clinical and Imaging Features

The clinical presentation is nonspecific, in particular as many cases remain clinically silent for longer time periods. In case the lesion becomes symptomatic and is suggestive of malignancy, gallbladder carcinomas are usually suspected. As with other gallbladder tumors encroaching upon the gallbladder outlet and/or the cystic duct, acute obstructive cholecystitis may occur in gallbladder

melanoma (Balthazar and Javors 1975). Acute cholecystitis in malignant melanoma may be severe and fulminant, associated with perforation of the gallbladder and biliary peritonitis (Heath and Womack 1988). Primary malignant melanoma of the gallbladder metastasizes to the liver, remote organs, and lymph nodes (Walsh 1956), but unusual metastasis pathways also occur, e.g., to the common bile duct (Verbanck et al. 1986).

Pathology

Macroscopy

Macroscopically, most primary gallbladder melanomas present as circumscribed nodular to lobulated black, friable masses. The growth pattern is characterized by large endophytic, polypoid, and friable masses in most of the reported cases, sometimes with a discrete vascular stalk. Polypoid formations with a papillary surface may form cushion-like structures or large vegetations. This phenotype is in contrast to the gross appearance of metastatic lesions which are more commonly flat, smaller, and multiple lesions (Willis 1948). In the study of metastatic lesions published by McFadden and coworkers (1979), the metastatic lesion was solitary in four cases, multiple in four cases, and diffuse in one case. Primary malignant melanomas of the gallbladder are also larger than most metastatic nodules, the polypoid formation having a diameter of sometimes more than 7 cm, while metastatic nodules described by Willis (1948) were often only a few mm in diameter. Part of the tumors display ulcerated nodules and show necroses in the center, where the tumors may be paler and hemorrhagic, but blackish necroses or black tumor fragments in the gallbladder lumen may also be encountered. In some cases, the gallbladder was filled with blackish sludge or with bile having suspended pigmented fragments and debris.

Histopathology

Histologically, malignant melanoma of the gallbladder shows the phenotype known from melanomas of the skin or other visceral melanomas. Spindled tumor cells with varying amounts of pigment granules (melanosomes) may dominate, but there are also tumor with large and polygonal, epithelioid cells of pleomorphic cells. Numerous and in part atypical mitotic figures are present. In larger nodules, extensive necrosis is noted. The tumors can contain numerous melanophages, mainly around necroses, where liberated melanosomes are phagocytosed by macrophages (Hatae et al. 1978). Small clusters of pigment granules as well as individual pigmented tumor cells may be noted within the columnar epithelial of the mucosa. A junctional activity may be present in lesions spreading within the gallbladder mucosa, characterized by pigmented cells situated between and beneath epithelia cells in small clumps or in isolation (Walsh 1956; Peison and Rabin 1976; Carle et al. 1981). This apparent junctional change has been proposed to be an argument for the primary nature of the tumor (Carle et al. 1981). In the gallbladder mucosa around the site of tumor attachment, and particularly in polypoid lesions having a stalk, there may be scattered single pigmented and in part dendritic cells between epithelial cells. The tumor invades the wall of the gallbladder, with pigmented nodules in the muscle layer and sometimes melanoma nodules in a subserosal position.

Immunohistochemistry

Both primary melanomas of the gallbladder and melanomas metastatic to the gallbladder display the immunohistochemical profile typical for malignant melanomas localized to other organs, including reactivity for HMB45/gp100, melan A, and MITF (Gassler et al. 2004).

Differential Diagnosis: Malignant Melanoma Metastatic to the Gallbladder

Malignant melanoma can metastasize to virtually any organ, most prominent metastatic sites being the lungs, liver, brain, and colon. Gastrointestinal

metastases of malignant melanoma have previously been thought to be uncommon, only 2–4 % of patients with malignant melanoma being diagnosed with gastrointestinal metastases during the course of their disease. However, through improved diagnostic techniques, more aggressive operative and diagnostic interventions, gastrointestinal involvement is now known to be more common. The most common sites of GIT metastases of melanoma include the small bowel (35–67 %), colon (9–15 %), and stomach (5–7 %). Malignant melanoma relatively often metastasizes to the gallbladder, a metastatic pattern that lacks a pathogenic explanation. Among patients with melanoma metastatic to the gastrointestinal tract, around 15 % showed metastases to the gallbladder (Das Gupta and Brasfield 1964). In a review of cases reported until 1979, the interval from diagnosis of the primary tumor until presentation with gallbladder metastases ranged from 3 to 13 years, with a mean of 5.8 years (McFadden et al. 1979).

Selected References Pautler and Gallavan 1951; Henriques 1955; Kazmann 1956; Zemlyn 1966; Gabriele and Jouffre 1969; Shimkin et al. 1972; McFadden et al. 1979; Daunt and King 1982; Vantomme et al. 1984; Murphy et al. 1987; Agosti et al. 1989; Stutte et al. 1989; Goldin 1990; Avila et al. 1994; Seelig and Schönleben 1997; Dong et al. 1999; Cellerino et al. 2000; Kohler et al. 2000; Guida et al. 2002; Gogas et al. 2003; Crippa et al. 2004; Gassler et al. 2004; Swiatoniowski et al. 2004; Rehani et al. 2006; Romero et al. 2006; Varsamidakis et al. 2006; Katz et al. 2007; Marone et al. 2007; Nelms et al. 2007; Tuveri and Tuveri 2007; Samplaski et al. 2008; Hamodat and Alhumidi 2009; Matsubayashi et al. 2012.

As already mentioned above, the similarity of presentation renders the diagnosis of primary gallbladder melanoma vs. metastatic melanoma difficult in a proportion of the cases. Melanoma metastatic to the gallbladder can cause acute, obstructive cholecystitis (Henriques 1955; Ostick and Haggani 1976; Langley et al. 1997; Vernadakis et al. 2009) or masquerading as cholelithiasis (Herrington 1965). Also hemobilia and biliary fistulae have been reported (Daunt and King 1982). However, most cases of gallbladder melanoma metastases are clinically asymptomatic during the patient's lifetime, also illustrated by the discrepancy in case reports vs. detection rates at autopsies (Das Gupta and Brasfield 1964; Goldin 1990; Dong et al. 1999). Overall, the prognosis of metastatic malignant melanoma to the gallbladder is dismal, with a median survival of 6–9 months, and long-term disease-free survival is achieved in only 1–2 % of patients (Dong et al. 1999; Gogas et al. 2003). In a more recent study of 13 patients, the median survival was 12 months following diagnosis, and only 1 patient survived more than 42 months (Katz et al. 2007).

Pathogenic Pathways

Few melanocytes are present in the normal gallbladder mucosa, and it has been suggested that malignant melanomas take their origin from these cells that have spread from the neural crest to the gallbladder during oncogenesis.

Primitive Neuroectodermal Tumor (PNET) of the Gallbladder

Introduction

Primitive neuroectodermal tumor (PNET)/extraosseous Ewing sarcoma most frequently develops in the soft tissues of the extremities and the paravertebral region, but is also known to occur in inner organs. Only one PNET originating in the gallbladder has been reported so far (Song et al. 2004).

Pathology

Histologically, the tumor reported by Song and associates (2004) showed monotonous round cells with a formation of Homer-Wright rosettes, with a morphology typical for PNET occurring elsewhere. The tumor cells were immunoreactive for MIC2/CD99 as well as for synaptophysin and

neuron-specific enolase. A chromosomal translocation, such as t(11;22)(q24;q12) or t(21;22)(q22;q12), was not detectable.

Differential Diagnosis

Differential diagnosis on conventionally stained sections mainly includes other small cell tumors occurring in the gallbladder, e.g., small cell carcinoma or lymphoma.

Paraganglioma of the Gallbladder

Introduction

Extraadrenal paragangliomas are uncommon neoplasms that have been reported in many locations, including the organ of Zuckerkandl, kidney, urethra, urinary bladder, prostate, uterus, vagina, retroperitoneal space, and gastrointestinal tract. While paragangliomas in the head, neck, and mediastinal regions are commonly associated with the parasympathetic system and are chromaffin negative and functionally inactive, retroperitoneal paragangliomas usually originate from the sympathetic nerve system. In the GIT, the duodenal ampulla is a predilection site, specifically for the gangliocytic variant of paraganglioma, whereas the hepatobiliary tract is seldom affected. Few reports documented paraganglioma primary to the gallbladder (Miller et al. 1972; Wolff 1973; Freschi and Sassi 1990; McDonald 1990; Hirano 2000; Cho et al. 2001; Mehra and Chung-Park 2005; Rodriguez-Merchan et al. 2006). The first three patients that had been described (Wolff 1973) were all woman aged 32, 52, and 59 years, respectively, at diagnosis. Gallbladder paraganglioma can develop in the setting of familial multiple endocrine neoplasm syndrome (Mehra and Chung-Park 2005).

Clinical and Imaging Features

Clinically, the tumor may be asymptomatic and detected during cholecystectomy performed for other reasons or may produce vague right upper quadrant pain or gastrointestinal bleeding (Mehra and Chung-Park 2005). In one patient, hemorrhagic gallbladder paraganglioma had caused cholecystoduodenal fistula (Miller et al. 1972). Associated cholecystitis, mostly chronic, was documented in several cases (Wolff 1973; Cho et al. 2001; Mehra and Chung-Park 2005). None of the gallbladder paragangliomas reported so far presented signs and symptoms related to the sympathetic system.

Pathology

Macroscopy

In the few reports where gross features were specified, the tumors were usually located in a subserosal position and were small and well-circumscribed masses, with a beefy, red to brown or red-tan and sometimes spongy cut surface, sometimes with small hemorrhages or necrotic foci (Cho et al. 2001; Mehra and Chung-Park 2005). There was no predilection of site within the gallbladder.

Histopathology

The histopathology of gallbladder paraganglioma is the same as that for other such tumors. The neoplasms are highly vascularized lesions with an expanding growth mode and are surrounded by a complete or incomplete fibrous capsule. The tumor cells are medium-sized, round to polygonal, with an eosinophil or amphophilic, finely granular cytoplasm. Few PAS-positive cytoplasmic globules may be present. The nuclei are ovoid, centrally placed, with a characteristically stippled ("salt-and-pepper") chromatin and small nucleoli. Very few mitotic figures are found. These cells are arranged in small islands or nests (Zellballen). This alveolar-like nesting pattern is best visualized in reticulin stains. Discrete cytoplasmic argyrophilia was detected in the Grimelius stain (Mehra and Chung-Park 2005).

Immunohistochemistry

The large cells forming nests are immunoreactive for chromogranin A, synaptophysin, and neuron-specific enolase, intermingled with S100 protein-positive sustentacular cells. The endothelia of intervening vascular channels are CD34 reactive (Mehra and Chung-Park 2005).

Differential Diagnosis

Gallbladder paraganglioma may occur as a component of multiple paragangliomas, involving the common bile duct and the liver in addition to the gallbladder (Ferrell et al. 1990).

Ganglioneuromatosis of the Gallbladder

Introduction

Ganglioneuromatosis is a well-recognized component of multiple endocrine neoplasia (MEN) type 2b (Carney et al. 1978). Ganglioneuromatosis of the gastrointestinal tract may precede pheochromocytoma and medullary thyroid carcinoma in patients with MEN 2b (Carney et al. 1976). Primary ganglioneuromatosis of the gallbladder is a very rare condition that may develop as an isolated tumor or occur as an extended infiltration of the organ (Carney et al. 1976; Chetty and Clark 1993; Sakuma et al. 2011). In one patient with extensive gallbladder ganglioneuromatosis, additional ectopic pheochromocytoma at the liver hilum was found (Sakuma et al. 2011).

Pathology

Macroscopically, the gallbladder shows a thickened wall and ropy, nodular appearance of the serosal surface (Chetty and Clark 1993). Histologically, the gallbladder wall contains numerous large and prominent nerve-like plexiform structures containing ganglion cells and associated proliferating Schwann cells. The mucosal surface is intact, and the neuroid structures are situated in deeper layers of the gallbladder. Some of the nerve-like profiles are dumbbell-shaped, simulating plexiform neurofibroma (Chetty and Clark 1993).

Differential Diagnosis

In the absence of easily detectable ganglion cells, e.g., due to a sampling error, the lesion may be misinterpreted as plexiform neurofibroma.

Malignant Rhabdoid Tumor of the Gallbladder

Malignant extrarenal rhabdoid tumors are well known to occur in the gastrointestinal tract and the liver, but are very uncommon in the biliary tract. The gallbladder is probably the least common primary site, with only few cases reported so far (Kim et al. 2003; Suri et al. 2003). In one case, the tumor was found in a 46-year-old man who had been operated on for cholelithiasis with chronic cholecystitis. Macroscopic examination of the gallbladder revealed a slight thickening in the body wall, in an area measuring about 1 cm in diameter. Histology showed rhabdoid tumor. The histopathologic presentation is that of rhabdoid tumors of other locations. Gallbladder carcinomas can rarely show a rhabdoid tumor component (Kim et al. 2003).

Germ Cell Tumors of the Gallbladder

Introduction

Similar to other parts of the hepatobiliary tract, germ cell tumors of various types can develop as primary tumors in the gallbladder. In the course of germ cell progenitor migration, some of the

progenitors may be integrated into the budding gallbladder primordium to later give rise to germ cell tumors.

Teratoma of the Gallbladder

Immature teratoma has been observed in the gallbladder of a 9-month-old girl who had presented with an abdominal mass. CT revealed a huge heterogeneous mass with cystic, solid, and calcified components, occupying the upper abdominal cavity and originating from the gallbladder. This teratoma was associated with gliomatosis peritonei in the presence of unaltered ovaries (Torikai et al. 2007).

Choriocarcinoma of the Gallbladder

Non-gestational choriocarcinoma can rarely originate in the gallbladder, similar to other parts of the hepatobiliary tract. Like choriocarcinomas located elsewhere, gallbladder choriocarcinoma displays a rapidly progressive course, with formation of hepatic metastases (Abu-Farsakh and Fraire 1991; Wang et al. 2001). Primary gallbladder choriocarcinoma has been found in conjunction with gallbladder adenocarcinoma (Abu-Farsakh and Fraire 1991).

Dermoid Cyst of the Gallbladder

A single observation described dermoid cyst arising in the gallbladder wall (Falcao and Leal 1975). It cannot be decided in this case whether this lesion was a component of a mature teratoma.

Differential Diagnosis

Gestational and non-gestational choriocarcinomas can widely metastasize within the abdominal cavity, including the gallbladder. Rare gallbladder adenocarcinomas with choriocarcinoma-like areas have been observed (Albores-Saavedra et al. 1981).

Perivascular Epithelioid Cell Tumors (PEComas) of the Gallbladder

Several types of perivascular epithelioid cells tumors (PEC tumors, PEComas) are known for the liver and its ligaments, angiomyolipomas being the most common. In contrast, only very few examples of gallbladder PEComas have been reported.

Among 35 cases of PEComa of the gastrointestinal tract, only 1 case was detected in the gallbladder (Doyle et al. 2013). Also malignant PEComa was observed as a primary neoplasm of the gallbladder (Zhao and Anders 2014). In an elderly male patient, a malignant PEComa of the urinary bladder had metastasized to the gallbladder (Sendo et al. 2013).

Myeloid Neoplasms of the Gallbladder

Alterations of the Gallbladder in Acute or Chronic Myeloid Leukemias

Acute myeloid leukemia can be a complicated by acute acalculous cholecystitis, with or without associated neutropenia (Hurley et al. 1992; Topeli et al. 1996). Acute cholecystitis is sometimes the presenting manifestation of acute myeloid leukemia (Bloom et al. 2002) and can develop in relapsing acute leukemia (Azin et al. 2014). In part of the cases, leukemic infiltration with immature myeloid cells of the gallbladder wall causes significant wall thickening and is causally linked to the initiation of acute inflammation (Bessmel'tsev and Abdulkadyrov 1992; Bloom et al. 2002; Shimizu et al. 2006; Solak et al. 2013). In part of cases, gallbladder infiltrates in the setting of acute myeloid leukemias can produce nodular lesions mimicking gallbladder carcinoma (e.g., in acute myelomonocytic leukemia; Tissot et al. 1981). Patients with chronic myeloid leukemia have a higher prevalence of gallstones (Ates et al. 2009).

Myeloproliferative Disorders

In the course of myelofibrosis, myeloproliferative infiltrates (myeloid metaplasia) can develop in the

gallbladder wall, causing wall thickening (Payan et al. 1989; Geddy and Wedgwood 1996; Thorns et al. 2002; Sahasrabudhe and Davenport 2005). Histologically, the gallbladder wall shows focal segmental or transmural infiltrates resembling extramedullary hematopoiesis, however with numerous immature myeloid cells and often with scattered or clustered atypical (dysplastic) megakaryocytes. A diffuse myeloid infiltrate can efface the architecture of the wall, however sometimes with sparing of the mucosa. The infiltrate can be associated with a reticulin fibrosis, similar to that in myelofibrosis of bone marrow (Geddy and Wedgwood 1996). Essential thrombocythemia can be complicated by multiple venous and arterial thrombosis of the gallbladder causing acute cholecystitis (Picon-Coronel et al. 2011).

Solid Myeloid Neoplasms of the Gallbladder (Extramedullary Myeloid Tumor)

Extramedullary myeloid tumor (EMMT); granulocytic sarcoma or chloroma has been observed in the gallbladder, forming solid tumors of variable size that can grossly resemble gallbladder carcinoma. Immunohistochemically, the neoplasms are reactive for myeloperoxidase, CD15, CD43, and CD117/c-Kit (Tuset et al. 1995; Ojima et al. 2005; Ukkola-Pons et al. 2010). Disseminated EMMT of organs including the gallbladder has also been found in the absence of bone marrow disease (Bartley et al. 2007).

Paraneoplastic Hematological Features of Gallbladder Carcinoma

Similar to other hepatobiliary cancers, carcinoma of the gallbladder can rarely induce paraneoplastic hematological syndromes, e.g., leukemoid reaction (Kumar et al. 2013). In one patient, severe thrombocytosis developed, in the autoptically proven absence of a myeloproliferative disorder (Wakabayashi et al. 1978).

Non-Hodgkin's Lymphomas of the Gallbladder

Introduction

The gallbladder is a rare site of primary non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphomas (HL). In most cases of lymphomatous involvement of this organ, infiltration takes place from the liver (either primary or secondary liver lymphomas extending into the gallbladder via the gallbladder fossa), or gallbladder infiltration is the manifestation of generalized lymphomatous disease. In certain situations, and in the absence of proof through autopsy, it is difficult to decide whether gallbladder lymphoma is truly a primary neoplasm or a manifestation of an otherwise not yet diagnosed lymphoma situated elsewhere.

Epidemiology

NHLs of the gallbladder are uncommon neoplasms that have mostly been published as single case reports. Among 1,452 gallbladder specimens examined over a 5-year period, only one case of lymphoma was found (Darmas et al. 2007).

Clinical Features

Clinically, gallbladder lymphomas often present as cholecystitis (Tishler et al. 1987; Huang et al. 2007) or a space-occupying lesion in the right upper abdomen, but part of the neoplasms are asymptomatic and are detected in the setting of cholecystectomy performed for other reasons. In one study, 92 % of gallbladder NHL presented with symptoms and signs of cholecystitis, cholelithiasis, or jaundice (Mani et al. 2010).

Types of NHL and Pathology

Almost all known types of NHL have been described for the gallbladder, but the type

distribution mirrors that of NHL of the gastrointestinal tract. From the literature it turned out that the most common NHLs (apparently) primary to the gallbladder were NHL of MALT, diffuse large B-cell NHL(DLBCL), and follicular lymphoma. The macroscopic presentation is often that of bulky and sometimes necrotic and/or hemorrhagic masses in the gallbladder wall and/or protruding into the lumen, i.e., a pattern formerly described as "lymphosarcoma." Less common is a presentation in the form of a diffuse infiltration of the wall with wall thickening (Botha and Kahn 1974; Neal et al. 1994; Chatila et al. 1996; Murakami et al. 1996; Bernardini et al. 2000; Gravel et al. 2001; Yokoe et al. 2003; Yamamoto et al. 2005; Ono et al. 2009; Willingham et al. 2009; Shah et al. 2011; Batur and Odev 2014). In a study of 13 cases, transmural involvement by lymphoma was identified in 71.4 %, while 28.6 % showed relative mucosal sparing with predominant smooth muscle and extramuscular involvement (Mani et al. 2010). Rarely, NHL presents as a gallbladder polyp (Mani et al. 2010; Acharya et al. 2014). The cystic lymph node and other locoregional lymph node may or may not be enlarged and involved (Mani et al. 2010). B-cell NHL was also diagnosed in the cystic duct (Jho et al. 2007).

Cases in which the type of gallbladder NHL can be identified from literature data include a broad spectrum of lesion (Table 1).

Table 1 Types of non-Hodgkin's lymphomas (NHLs) observed as primary or secondary lesions in the gallbladder

MALT NHL
Diffuse large B-cell NHL
Small B-cell NHL
Lymphoplasmacytic NHL
Follicular NHL
Extranodal marginal zone NHL
Mantle cell NHL
B-lymphoblastic NHL
Plasmablastic NHL
Burkitt's NHL
Primary effusion NHL
Intravascular large B-cell NHL
Peripheral T-cell NHL
T-cell lymphoblastic NHL
True histiocytic NHL

MALT NHL is the most common primary NHL of the gallbladder. It can form tumorous masses in the gallbladder, mimicking carcinoma, or present as a diffuse infiltration of the gallbladder wall. The histology and immunophenotype are the same as MALT lymphomas developing in other regions of the gastrointestinal tract (Mosnier et al. 1992; McCluggage et al. 1996; Stephen et al. 1998; Abe et al. 1999; Bickel et al. 1999; Tomori et al. 1999; Tsuchiya et al. 2001; Chim et al. 2002; Rajesh et al. 2003; Takano et al. 2004; Koshy et al. 2008; Bisig et al. 2009; Bagwan et al. 2011; Appukutty et al. 2013; Martinez Pérez et al. 2015; Mitra et al. 2014). The second most common NHL of the gallbladder is diffuse large B-cell NHL/DLBCL. It can produce bulky masses in the gallbladder, effacing the wall and sometimes filling the lumen, often with extensive necrosis. The tumor can infiltrate the gallbladder bed and extend into the liver. These are the neoplasms called "lymphocytic lymphosarcoma" or just "lymphosarcoma" in the older literature. The neoplastic cells are a medium-sized to large lymphoid cell with prominent nucleus, showing a B-cell phenotype. As in other locations, this NHL exhibits numerous mitotic figures and a high to very high proliferation fraction (Van Slyck and Schuman 1972; Tishler et al. 1987; Friedman et al. 1993; O'Boyle 1994; Huang et al. 2007; Kato et al. 2008; Sezgin et al. 2009; Mani et al. 2010; Tomonori et al. 2011; Kojima et al. 2014). DLBCL of the gallbladder can occur in combination with MALT NHL (Gardini et al. 2009). The third most common NHL of the gallbladder is follicular NHL, which is characterized by a B-cell population forming follicular structures with a distinctive immunophenotype (Ferluga et al. 2003; Jelic et al. 2004; Mani et al. 2010). The gallbladder can be involved in the setting of chronic lymphocytic leukemia and small B-cell NHL, characterized by a focal to diffuse and sometimes transmural

lymphoid cell infiltrate, the lymphocytes being small but slightly larger than normal unstimulated lymphocytes (Zhang 1985; Chatila et al. 1996; Sato et al. 2001; Psarras et al. 2014). Apart from secondary involvement, small B-cell NHL was also found as a primary gallbladder NHL (Psarras et al. 2014; Zelones and Coimbra 2014), but a not yet diagnosed generalized lymphoproliferative process is difficult to exclude in such cases. Rarely, lymphoplasmacytic NHL/Waldenström's macroglobulinemia was found in the gallbladder (Lin et al. 2003). The other NHLs listed in the table are rare to exceptional findings and include extranodal marginal zone lymphoma (Mani et al. 2010); mantle cell NHL that may develop as a primary gallbladder neoplasm, but also occurs as a metastatic process (Mani et al. 2010; Pherson et al. 2014); B-lymphoblastic NHL (Ozawa et al. 2012); primary (Kim et al. 2014), plasmablastic lymphoma (Mani et al. 2010); primary effusion lymphoma (Mani et al. 2010); intravascular large B-cell lymphoma (Duan et al. 2011; Yadav et al. 2014); Burkitt's lymphoma (Balonga et al. 1996; Gonzalez Lopez et al. 2010); T-cell lymphoma (Farah et al. 2012); T-cell lymphoblastic NHL (Mitropoulos et al. 2000); and true "histiocytic" lymphoma (Sagi and Györi 1972; Gillespie et al. 1977). A very unusual lymphoproliferative process that has been detected in the gallbladder is angiotropic lymphoma (formerly malignant angioendotheliomatosis). Angiotropic (intravascular) lymphoma (originally described as "angioendotheliomatosis proliferans systematisata; Pfleger and Tappeiner 1959) is a rare and mostly fatal neoplasm in which malignant T- or B-lymphoid cells proliferate within the lumina of small blood vessels, whereby B-cell populations predominate. The lesion was also termed intravascular malignant lymphomatosis and often involves the skin and the central nervous system (Wick et al. 1981; Keahey et al. 1982; Bhawan et al. 1985; Mori et al. 1985; Wrotnowski et al. 1985; Carrol et al. 1986; Dominguez et al. 1986; Sheibani et al. 1986; Theaker et al. 1986; Otrakji et al. 1988; Piérard et al. 1988; Fredericks et al. 1991; Helm et al. 1992; Periciario et al. 1995; Erös et al. 2002; Mandal et al. 2007). This malignancy primarily occurs in the skin and the central nervous system, but visceral forms have also been described. The term, malignant angioendotheliomatosis had formerly been employed to denote this neoplastic process, but this term is misleading for lymphomas, as the tumor cells are not endothelial cells, and true neoplastic angioendotheliomatosis is now restricted to rare forms of intravascularly disseminated angiosarcomas (Lin et al. 1997). Few cases of this rare tumor have been described in the gallbladder. Capillaries and other small vessels were filled with, and distended by, large round to oval lymphoid cells with a vesicular nucleus with one or more nucleoli. The mitotic rate was low (Laurino and Melato 1990; DiGiuseppe et al. 1994; Duan et al. 2011). In one case, gallbladder involvement developed in the course the Asian variant of intravascular lymphoma (Kuroda et al. 2007).

Differential Diagnosis

The main differential diagnosis of primary NHL of the gallbladder is metastasis/manifestation of NHL originating elsewhere (Arista Nasr and Lome-Maldonado 1993; Nakai et al. 2011). The gallbladder is sometimes involved in patients with acute lymphoblastic leukemia (Kosucu et al. 2012) or chronic lymphocytic leukemia (Bessmel'tsev and Abdulkadyrov 1991; Chim et al. 2001; Dasanu et al. 2010; Imenpour et al. 2011). Gallbladder involvement by large cell NHL was diagnosed in a patient witch Richter's syndrome (Maryniak and Konecki 1991). The time interval between diagnosis of the primary NHL and its later manifestations in the gallbladder may be long, e.g., 12 years in a patient with follicular NHL (Viswanathan et al. 2011). Very rarely, the gallbladder is the site of reactive lymphocytic proliferations forming a mass, i.e., pseudolymphoma (Hussain et al. 1976). This issue is treated below. Chronic cholecystitis can be associated with lymphoid hyperplasia, often with lymph follicles and germinal centers (Albores-Saavedra et al. 1989; Hayasaka et al. 1996). This lesion, which can

mimic follicular NHL, is termed lymphofollicular (follicular) cholecystitis (Estrada et al. 1960; Hatae and Kikuchi 1979).

Plasmacytoma of the Gallbladder

Plasmacytoma can occur as an apparently primary malignancy of the gallbladder (Hwang et al. 2010). Extramedullary plasmacytoma was also observed in the gallbladder fossa, several months following cholecystectomy (Majerovic et al. 2012). Medullary and extramedullary plasmacytomas can rarely metastasize to the gallbladder (Kondo et al. 1995; Schuster et al. 2007).

Castleman's Disease of the Gallbladder

Castleman's disease as a primary lesion was observed in the gallbladder fossa (Lee et al. 1991).

Langerhans Cell Neoplasms of the Gallbladder

A 74-year-old woman with Langerhans cell sarcoma primary to the gallbladder, associated with involvement of regional lymph nodes, has been described. The neoplastic cells were reactive for CD1a, langerin, and S100 protein, but electron microscopic examination failed to demonstrate Birbeck granules (Zhao et al. 2009). Xanthoma disseminatum can involve the gallbladder (Knobler et al. 1990), with formation of mucosal xanthomas.

Hemophagocytic Lymphohistiocytosis of the Gallbladder

Predominantly in the pediatric age group, hemophagocytic lymphohistiocytosis is known to involve the gallbladder, clinico-radiologically presenting with thickening of the gallbladder wall (Chateil et al. 1999; Fitzgerald and MacClain 2003; Schmidt et al. 2004).

Hodgkin's Lymphoma

Only very few reports have specified involvement of the gallbladder in patients with Hodgkin's disease (HD). In a 44-year-old male patient, acalculous cholecystitis developed due to HD. At surgical exploration, the gallbladder was thickened, erythematous, and tense. An enlarged lymph node was detected in Calot's triangle, and the cystic duct was thickened, leathery, and firm, causing gallbladder obstruction. Histologic examination showed infiltration of the gallbladder by HD at the level of the cystic duct (Dainko 1970). In a second case, HD of the gallbladder presented as a complex mass detected by CT (Orton and Saigh 1996). Involvement of locoregional lymph nodes can cause compression of the cystic duct with non-visualization of the gallbladder (Wee et al. 1970). Apart from the cystic duct, HD is known to infiltrate other parts of the extrahepatic bile duct system, associated with obstructive jaundice (Justin-Besançon et al. 1963; Ochoa and Keene 1970).

Pseudolymphomas and Lymphoid Hyperplasias of the Gallbladder

There is group of conditions of the gallbladder characterized by a reactive proliferation of lymphoid cells, sometimes mimicking a tumor and specifically lymphoma. Part of the lesions show a focal to diffuse hyperplasia of lymphocytes, while others are characterized by nodular lesions or tumor-like masses.

Lymphoid hyperplasias and pseudolymphomas are manifest as one of few patterns compiled in Table 2.

Reactive lymphoid hyperplasias of the gallbladder have been reported several times (Hayasaka et al. 1996). Lymphoid hyperplasia may be associated with chronic cholecystitis, but the etiology remains, with few exceptions, unknown. A marked lymphoid hyperplasia of the gallbladder wall has been observed in chronic cholecystitis caused by *Salmonella* Typhi (chronic typhoid cholecystitis; Mallory and

Table 2 Patterns of pseudolymphomas and lymphoid hyperplasias of the gallbladder

Follicular lymphoid hyperplasia
Focal pattern
Diffuse pattern
Non-follicular lymphoid hyperplasia
Focal pattern
Diffuse pattern
Nodular lymphoid hyperplasia (pseudolymphoma)

Lawson 1931). In the majority of cases, lymphoid hyperplasia presents in the form of a focal or diffuse production of lymphoid follicles with or without germinal centers (Perrin 1953; Estrada et al. 1960; Pennino and Avallone 1965; Hatae and Kikuchi 1979; Albores-Saavedra et al. 1989; Rana et al. 2014). This condition has also been termed, "follicular cholecystitis." In one study, "chronic follicular cholecystitis" was detected in 6.2 % of cholecystectomy specimens (Tyagi et al. 1992). Macroscopically, the mucosa was described as velvety, granular, or nodular (Albores-Saavedra et al. 1989). In few cases, follicular hyperplasia results in polypoid mucosal lesion growing to a size of up to 0.9 cm, resembling gallbladder adenomas (Albores-Saavedra et al. 1989). In contrast to polypoid non-Hodgkin's lymphomas, polypoid follicular pseudolymphomas are lined by a normal-looking, non-damaged gallbladder epithelium. In follicular lymphoid hyperplasia, the gallbladder wall is histologically studded with lymphoid follicles with germinal centers. The follicles may occupy the mucosa or show a transmural distribution. Large follicles can bulge into the gallbladder lumen. Typically germinal centers display macrophages with phagocytosed pycnotic nuclei (tingible bodies). In part of the cases, this follicular reaction is the sign of an immune response to unknown antigens in the absence of a true cholecystitis. However, other cases showed an associated inflammation and fibrosis of the gallbladder wall. In such situations, the follicles are accompanied by an infiltrate that contains plasma cells, neutrophils, and eosinophils (Albores-Saavedra et al. 1989).

Lymphoid hyperplasia can result in nodular lesions in the gallbladder wall (nodular lymphoid hyperplasia; Sauerbrei and Castelli 1979). Nodular lymphoid hyperplasia appears as solitary or multiple nodules composed of dense lymphoid infiltrates. In a minority of cases, lymphoid hyperplasia is detectable as single mass within the gallbladder wall. Such nodules are usually well demarcated and lack a capsule. Histologically, nodular mass lesions are either diffuse lymphocyte proliferations or, more commonly, lesions that consist of numerous lymphoid follicles with germinal centers (Hussain et al. 1976; Yamamoto et al. 2012). In contrast to follicular non-Hodgkin's lymphomas, germinal centers in lymphoid pseudotumors exhibit a typical arrangement of germinal cells and macrophages with tingible bodies.

Differential Diagnosis

The main differential diagnosis is primary non-Hodgkin's lymphoma of the gallbladder, the main follicular variants. Also chronic lymphocytic leukemia can cause an infiltration of the gallbladder wall that may be confounded with lymphoid hyperplasia (Dasanu et al. 2010).

Metastatic Disease of the Gallbladder

Introduction

Metastases to the gallbladder are unusual lesions (Botting et al. 1963). In a series of 1,000 autopsies, metastatic involvement of the gallbladder was detected in only 5.8 % of patients (Abrams et al. 1950). Among a series of 417 gallbladder malignancies in Korea, 4.8 % were metastases of diverse cancers (Yoon et al. 2009). Gallbladder metastases most commonly occur in patients with malignant cutaneous melanoma, renal cell carcinoma, and breast carcinoma (Khan et al. 2010). The reasons why these three malignant neoplasms so clearly dominate metastatic gallbladder disease are currently unknown. At gallbladder imaging, alterations that raise suspicion for gallbladder

metastases include polypoid endoluminal lesion, multiplicity of these vegetations, a broad base of polyps, only limited mural thickening, presence of contrast enhancement, absence of gallstones, and gallbladder bed infiltration (Abacheril and Metzger 2008; Barretta et al. 2011).

Common Types of Metastases

Malignant Melanoma

Cutaneous malignant melanoma (MM) can metastasize to virtually any organ, but organs and structures most typically involved are the regional lymph nodes, lungs, liver, brain, and the lower gastrointestinal tract. The gallbladder, due to still unknown reasons, is one of the most frequent metastatic sites of MM in the upper abdominal visceral system and accounts for about 50 % of all metastases to the biliary tract. Autopsy investigation have demonstrated that gallbladder metastases occur in up to 15 % of patients with metastatic MM of the GI tract, while gallbladder metastases are less often diagnosed during lifetime (Das Gupta and Brasfield 1964). This discrepancy is thought to be due to the observation that MM metastatic to the gallbladder seldom causes symptomatic disease. Gallbladder metastasis of MM may represent the first metastatic site of this neoplasm (Gwynne and Abbas 2008) and can also occur in stage I cutaneous MM (Cellerino et al. 2000). Gallbladder metastasis of MM can occur after a delay of 10 years or more (Gawenda et al. 1995). Owing to its polypoid growth pattern, metastatic gallbladder MM may be suspected by use of imaging examinations (Rehani et al. 2006), including ultrasonography (Zemlyn 1966; Miselli et al. 1988; Stutte et al. 1989; Hahn et al. 1993; Avila et al. 1994; Bedo et al. 1996; Holloway and King 1997; Vesnin et al. 1999; Andreano et al. 2010). Probably due to tumor necrosis and an associated inflammatory reaction, metastatic MM can cause, or be associated with, acute cholecystitis (Henriques 1955; Ostick and Haggani 1976; McFadden et al. 1979; Bundy and Ritchie 1982; Bugnon et al. 1987; Langley et al. 1997; Vernadakis et al. 2009). Similar to other gallbladder metastases, MM can cause gallbladder obstruction, sometimes inducing gallbladder colic (Paolini et al. 1999; Ligeron-Esbrayat and Guillot 2002; Nelms et al. 2007). The prognosis of metastatic MM to the gallbladder is poor, with a median survival time of 6–9 months (Langley et al. 1997; Dong et al. 1999; Katz et al. 2007), but postcholecystectomy survival times of up to 13.5 months have been reported (Dong et al. 1999).

Selected References Henriques 1955; Gavala and Nicolo 1960; Herrington 1965; Bertheussen and Hansen 1971; Shimkin et al. 1972; Arnaud et al. 1978; Orbuch et al. 1981; Vantomme et al. 1984; Murphy et al. 1987; Agosti et al. 1989; Goldin 1990; Guerini et al. 1990; Abdelli et al. 1996; Seelig and Schönleben 1997; Sparwasser et al. 1997; Kohler et al. 2000; Guida et al. 2002; Gogas et al. 2003; Qu et al. 2003; Crippa et al. 2004; Gassler et al. 2004; Swiatoniowski et al. 2004; Romero et al. 2006; Varsamidakis et al. 2006; Tuveri and Tuveri 2007; Samplaski et al. 2008; Alimova et al. 2009; Cicin et al. 2009; Matsubayashi et al. 2012.

Renal Cell Carcinoma (RCC)

RCC metastatic to the gallbladder is, as such, a rare manifestation of this malignancy that usually occurs in men, but is the second most frequent gallbladder metastasis after malignant melanoma. Gallbladder metastasis of RCC may develop after considerable delay, sometimes exceeding 6–10 years (Kechrid et al. 2000; Ricci et al. 2008). In a large series, 58.3 % of the lesions were metachronous deposits that were diagnosed at an average of 9.1 years after primary diagnosis of RCC (Ishizawa et al. 2006). RCC metastases to the gallbladder may either be the only metastatic manifestation of this cancer, or it may occur in conjunction with RCC metastases in other organs (Ricci et al. 2008). Furthermore, gallbladder metastases can occur synchronously or metachronously (Kücükakin et al. 2009; Chung et al. 2012). In analogy with other types of metastases, RCC metastatic to the gallbladder can induce, or mimic, acute cholecystitis (Golbey et al. 1991; Sand et al. 2009). Due to tumor

ulceration and necrosis, hemobilia can develop (Fullarton and Burgoyne 1991). Macroscopically, RCC metastases often show a polypoid or pedunculated configuration, resembling endoluminal gallbladder carcinomas and sometimes freely floating in the gallbladder lumen (Nagler et al. 1994; Nojima et al. 2008; Patel et al. 2009; Fang et al. 2010). The lesions may radiologically mimic gallbladder calculi (Lajolo et al. 2005). In a minority of cases, intraluminal growth is massive, with marked enlargement of the gallbladder (Terasaki et al. 1990). As the renal primary tumor, clear cell RCC metastasis of the gallbladder usually has a yellow color, with focal hemorrhage and necrosis (Ghaouti et al. 2013). Histology showed that the most common type of RCC metastatic to the gallbladder is the clear cell (hypernephroid) type (Nojima et al. 2008). In contrast to primary clear cell carcinoma of the gallbladder, RCC clear cells are negative for CK7 and CEA (Nojima et al. 2008).

Selected References Botting et al. 1963; Osman et al. 1978; Harder and Heindorff 1983; Fullarton and Burgoyne 1991; Golbey et al. 1991; Nagler et al. 1994; Coskun et al. 1995; King et al. 1995; Pagano et al. 1995; Lombardo et al. 1996; Uchiyama et al. 1997; Celebi et al. 1998; Brasseur et al. 1999; Aoki et al. 2002; Limani et al. 2003; Park et al. 2003, 2007; Ishizawa et al. 2006; Pandey et al. 2006; Nojima et al. 2008; Kawahara et al. 2010; Decoene et al. 2011; Chung et al. 2012; Collin and Sabbagh 2012; Robledo et al. 2012; Ghaouti et al. 2013; Jain and Chopra 2013.

Breast Carcinoma

Breast carcinoma is a malignancy that often shows widespread metastasis, specifically the lymph nodes, lung, bone, pleura, brain, and soft tissues, whereas the gastrointestinal and hepatobiliary tracts are less often involved. In the bile duct system, the gallbladder is the most commonly affected organ (Beaver et al. 1986; Rubin and Tate 1989; Pappo et al. 1991; Crawford et al. 1996; Shah et al. 2000; Doval et al. 2006; Manouras et al. 2008; Jones et al. 2009; Herrera et al. 2010; Di Vita et al. 2011; Riaz et al. 2012). Gallbladder metastasis in disseminated breast cancer was reported to occur in 4–7 % of patients (Lee 1983), with a delay between breast cancer diagnosis and gallbladder metastasis ranging from 18 months to more than 10 years (Zagouri et al. 2007). Most patients are asymptomatic in regard to the gallbladder (Riaz et al. 2012), but breast cancer metastasis to gallbladder can cause hydrops of the gallbladder (Essola et al. 2012) or acute cholecystitis (Beaver et al. 1986; Crawford et al. 1996; Boari et al. 2005; Doval et al. 2006; Zagouri et al. 2007; Al-Rawi et al. 2012), and in part of these patients, acute cholecystitis is the presenting feature of breast cancer (Manouras et al. 2008). Breast cancer metastasis can also induce obstructive alterations (Pappo et al. 1991) followed by hydrops (Murguia et al. 2006) or biliary colic (Rubin and Tate 1989).

Interestingly, most cases of breast cancer metastatic to the gallbladder are histologically lobular carcinoma of the breast (Di Vita et al. 2011). In a review of 13 cases extracted from the literature, 8 were lobular carcinomas (Khan et al. 2010). Less often, ductal carcinoma of the breast was found as gallbladder metastasis, including the papillary subtype (Murguia et al. 2006).

Hepatocellular Carcinoma

Apart from direct invasion of the gallbladder fossa and the gallbladder itself, hepatocellular carcinoma (HCC) is known to produce true hematogenous gallbladder metastases (Maruo et al. 1994; Nishida et al. 1997; Lane and Walker 2002; Han and Kim 2005; Terashima et al. 2007; Ando and Sakamoto 2009; Murakami et al. 2010; Kanzaki et al. 2011; Monden et al. 2011; Wakasugi et al. 2012). There seems to be a relationship between the intrahepatic site of HCC and gallbladder metastasis. The majority of reported cases had a primary tumor in segments S4 or S5, and most cases had portal vein thrombosis, suggesting a role of distinct vascular relationships (review: Wakasugi et al. 2012). Four possible routes for the trafficking of HCC cells to the gallbladder have been proposed: a hematogenous route via the portal venous system (mostly

associated with portal vein thrombosis), a lymphatic route, a route through direct invasion from the liver, and a route using pathways via peritoneal dissemination (Nakashima et al. 1983). These authors suggested that the portal vein system route was the most important metastatic pathway for the gallbladder. In fact, all gallbladder veins enter the right anterior branch of the portal vein system through the liver bed of the gallbladder via Carnot's triangle (Sugita et al. 2000), suggesting a backward venous spread to the gallbladder in case of HCC-associated portal vein thrombosis. Differential diagnostically, HCC metastases to the gallbladder have to be distinguished from direct invasion of the gallbladder by HCC from tumors that are situated close to the gallbladder bed (Ueno et al. 2001; Namkoong et al. 2004; Ryu et al. 2009).

Rare Types of Metastases

Uncommon metastases to the gallbladder include prostate carcinoma (Colombat et al. 1999; Maxwell et al. 2009), gastric carcinoma (Bellucci 1967; Bilici et al. 2012), rectal carcinoma (Abacheril and Metzger 2008), squamous cell carcinoma of the lung (Jeong et al. 2012), pulmonary large cell carcinoma (Tanaka et al. 2009) and other non-small cell carcinomas of the lung (Nassenstein and Kissler 2004), osteoclast-like giant cell tumor of the pancreas (Sun et al. 1998), carcinoma of the uterine cervix (Martinez-Roman et al. 2005), medullary plasmocytoma (Schuster et al. 2007), and perivascular epithelioid tumors (Sendo et al. 2013). Similar to more common types of metastases, rare metastatic gallbladder neoplasms can also cause acute cholecystitis, e.g., carcinoma of the stomach (Bilici et al. 2012).

References

Abacheril C, Metzger J (2008) Single metastasis in the gallbladder arising from adenocarcinoma of the rectum. South Med J 101:1183–1184

Abdelli N, Thiefin G, Diebold MD, Rodriguez JD, Varini E, Zeitoun P (1996) Endoscopic retrograde cholangiography in a metastatic melanoma of the gallbladder presenting as a gallstone migration. Endoscopy 28:402

Abe Y, Takatsuki H, Okada Y, Saito A, Kimura T, Nishimura J (1999) Mucosa-associated lymphoid tissue type lymphoma of the gallbladder associated with acute myeloid leukemia. Intern Med 38:442–444

Abrams HL, Spiro R, Goldstein N (1950) Metastases in carcinoma: analysis of 1000 autopsied cases. Cancer 3:74–85

Abu-Farsakh H, Fraire AE (1991) Adenocarcinoma and (extragonadal) choriocarcinoma of the gallbladder in a young woman. Hum Pathol 22:614–615

Acharya V, Ngai J, Whitelaw D, Motallebzadeh R (2014) Primary gallbladder lymphoma presenting as a polyp. BMJ Case Rep. doi:10.1136/bcr-2013-202715

Agosti R, De Giorgio R, Gaudio M, Paparo GF, Stanghellini V, Saragoni A, Corinaldesi R (1989) Isolated metastasis to the gallbladder of a malignant melanoma of the skin. Report of a case. Pathologica 81:333–338

Albores-Saavedra J, Cruz-Ortiz H, Alcantara-Vazques A, Henson DE (1981) Unusual types of gallbladder carcinoma. A report of 16 cases. Arch Pathol Lab Med 105:287–293

Albores-Saavedra J, Gould E, Manivel-Rodriguez C, Angeles-Angeles A, Henson DE (1989) Chronic cholecystitis with lymphoid hyperplasia. Rev Invest Clin 41:159–164

Alimova E, Gorin I, Gressier L, Hugol D, Bouillot JL, Cavalcanti A, Terrier-Lacombe MJ et al (2009) Metastatic melanoma of the gallbladder: two cases (in French). Ann Dermatol Venereol 136:368–370

Al-Rawi H, Al-Jafari M, Mathew H (2012) Metastatic breast cancer mimicking cholecystitis. A rare clinical presentation. Saudi Med J 33:1128–1130

Anderson JB, Hughes RG, Williamson RC (1983) Malignant melanoma of the gallbladder. Postgrad Med J 59:390–391

Ando K, Sakamoto Y (2009) A case of gallbladder metastasis from hepatocellular carcinoma. Jpn J Clin Oncol 39:540

Andreano A, Laeseke P, Lava M, Zimbaro F, Daniela V, Meloni MF (2010) Asymptomatic metastatic melanoma of the gallbladder diagnosed with contrast-enhanced ultrasonography. J Ultrasound Med 29:1133–1137

Aoki T, Inoue K, Tsuchida A, Aoki T, Kasuya K, Kitamura K, Koyanagi Y, Shimizu T (2002) Gallbladder metastasis of renal cell carcinoma: report of two cases. Surg Today 32:89–92

Appukutty SJ, Worthington T, Bagwan IN (2013) Gall bladder malignancy: an unusual association. J Gastrointestin Liver Dis 22:217–219

Arista Nasr J, Lome-Maldonado C (1993) Diffuse small lymphoplasmacytic lymphoma of the GI tract associated with massive intestinal amyloidosis. Rev Invest Clin 45:71–75

Arnaud JP, Miclo S, Aprahamian M, Weill-Bousson M, Adloff M (1978) Intestinal and gallbladder metastases

from a nevoepithelioma. Apropos of a case revealed by occult bleeding (in French). J Chir (Paris) 115:29–34

Ates F, Erkurt MA, Karincaoglu M, Aladag M, Aydogdu I (2009) Prevalence of gallstones in patients with chronic myelocytic leukemia. Med Princ Pract 18:175–179

Avila NA, Shawker TH, Fraker D (1994) Color-flow Doppler ultrasonography in metastatic melanoma of the gallbladder. J Clin Ultrasound 22:342–347

Azin A, Racz JM, Carolina Jimenez M, Sunil S, Porwit A, Jackson T, Okrainec A, Quereshy F (2014) Relapse of acute myeloid leukemia manifested by cholecystitis: a case report and review of the literature. Int J Surg Case Rep 5:302–305

Bagwan IN, Ping B, Lavender I, de Sanctis S (2011) Incidental presentation of gall bladder MALT lymphoma. J Gastrointest Cancer 42:61–64

Balonga C, Lencina R, Reus M, Garre C, de las Heras M (1996) Burkitt's lymphoma: atypical localization (in Spanish). Rev Esp Enferm Dig 88:439–441

Balthazar EJ, Javors B (1975) The radiology corner. Malignant melanoma of the gallbladder. Am J Gastroenterol 64:332–335

Barretta ML, Catalano O, Setola SV, Granata V, Marone U, D'Errico Gallipoli A (2011) Gallbladder metastasis: spectrum of imaging findings. Abdom Imaging 36:729–734

Bartley AN, Nelson CL, Nelson DH, Fuchs DA (2007) Disseminated extramedullary myeloid tumor of the gallbladder without involvement of the bone marrow. Am J Hematol 82:65–68

Batur A, Odev K (2014) Primary lymphoma of the gallbladder accompanied by cirrhosis: CT and MRI findings. BMJ Case Rep. doi:10.1136/bcr-2013-203101

Baumann C, Petropoulos P, Hahnloser P (1982) Malignant melanoma of the gallbladder (in French). Rev Med Suisse Romande 102:903–906

Beaver BL, Denning DA, Minton JP (1986) Metastatic breast carcinoma of the gallbladder. J Surg Oncol 31:240–242

Bedo F, Hoffer L, Bély M, Fekete G (1996) Isolated metastasis in the gallbladder from malignant cutaneous melanoma discovered by ultrasound (in Hungarian). Orv Hetil 137:1427–1428

Bellucci G (1967) A rare case metastasis in the gallbladder from gastric carcinoma (in Italian). Arch De Vecchi Anat Patol 49:315–326

Bernardini D, Giovannini M, Monges G, Sahel J, Capodano G, Seitz JF (2000) Gallbladder lymphoma: a rare cause jaundice (in French). Gastroenterol Clin Biol 24:1132–1133

Bertheussen KJ, Hansen A (1971) Gallbladder metastasis from malignant melanoma (in Danish). Ugeskr Laeger 133:1165–1166

Bessmel'tsev SS, Abdulkadyrov KM (1991) Ultrasonographic examination of the liver and abdominal lymph nodes in patients with chronic lymphocytic leukemia (in Russian). Ultrasonographic examination of the liver and abdominal lymph nodes in patients with chronic lymphocytic leukemia (in Russian). Gematol Transfuziol 36:9–11

Bessmel'tsev SS, Abdulkadyrov KM (1992) Ultrasonography of the gallbladder in patients with hemoblastoses (in Russian). Klin Med (Mosk) 70:46–49

Bhawan J, Wolff SM, Ucci AA, Bhan AK (1985) Malignant lymphoma and malignant angioendotheliomatosis: one disease. Cancer 55:570–576

Bickel A, Eitan A, Tsilman B, Cohen HI (1999) Low-grade B cell lymphoma of mucosa-associated lymphoid tissue (MALT) arising in the gallbladder. Hepatogastroenterology 46:1643–1646

Bilici A, Seker M, Oven Ustaalioglu BB, Keser SH, Cinaral F, Gümüs M (2012) Gallbladder metastasis secondary to gastric cancer as a first site of recurrence presented with acute cholecystitis: case report and literature review. Turk J Gastroenterol 23: 764–768

Bisig B, Copie-Bergman C, Baia M, Gaulard P, Delbecque K, Fassotte MF, Boniver J, de Leval L (2009) Primary mucosa-associated lymphoid tissue lymphoma of the gallbladder: report of a case harboring API2/MALT1 gene fusion. Hum Pathol 40:1504–1509

Bloom SH, Coad JE, Greeno EW, Ashrani AA, Hammerschmidt DE (2002) Cholecystitis as the presenting manifestation of acute myeloid leukemia: report of a case. Am J Hematol 70:254–256

Boari B, Pansini G, Pedriali M, Cavazzini L, Manfredini R (2005) Acute cholecystitis as a presentation of metastatic breast carcinoma of the gallbladder: a case report. J Am Geriatr Soc 53:2041–2043

Borja SR, Meyer WR, Cahill JP (1984) Malignant melanoma of the gallbladder. Report of a case. Cancer 54:929–931

Botha JB, Kahn LB (1974) Primary lymphoma of the gall bladder. Case report and review of the literature. S Afr Med J 48:1345–1348

Botting AJ, Harrison EG, Black BM (1963) Metastatic hypernephoma masquerading as a polypoid tumor of the gallbladder and review of metastatic tumors of the gallbladder. Proc Staff Meet Mayo Clin 38:225–232

Brasseur P, Bissen L, Dupont H, Sukkarieh F (1999) Metastasis to the gallbladder to a clear cell renal tumor (in French). J Radiol 80:739–740

Bugnon PY, Servais B, Gautier-Benoit C (1987) Isolated gallbladder metastasis of malignant melanoma disclosed by cholecystitis (in French). Gastroenterol Clin Biol 11:615–616

Bundy AL, Ritchie WG (1982) Ultrasonic diagnosis of metastatic melanoma of the gallbladder presenting as acute cholecystitis. J Clin Ultrasound 10:285–287

Carle G, Lessells AM, Best PV (1981) Malignant melanoma of the gallbladder: a case report. Cancer 48:2318–2322

Carney JA, Go VLW, Sizemore GW, Hayles AB (1976) Alimentary tract ganglioneuromatosis: a major component of the syndrome of multiple endocrine neoplasia, type 2b. N Engl J Med 295:1287–1291

Carney JA, Sizemore GW, Hayles AB (1978) Multiple endocrine neoplasia, type 2b. Pathobiol Annu 8:105–153

Carrol TJ, Schelper RL, Goeken JA, Kemp JD (1986) Neoplastic angioendotheliomatosis: immunopathologic and morphologic evidence for intravascular malignant lymphomatosis. Am J Clin Pathol 85:169–175

Celebi I, Güzelsoy M, Yörükoglu K, Kirkali Z (1998) Renal cell carcinoma with gallbladder metastasis. Int J Urol 5:288–290

Cellerino P, Corsi F, Morandi E, Foschi D, Trabucchi E (2000) Metastatic melanoma of the gallbladder. Eur J Surg Oncol 26:815–816

Chateil J, Brun M, Perel Y, Pillet P, Micheau M, Diard F (1999) Abdominal ultrasound findings in children with hemophagocytic lymphohistiocytosis. Eur Radiol 9:474–477

Chatila R, Fiedler PN, Vender RJ (1996) Primary lymphoma of the gallbladder; case report and review of the literature. Am J Gastroenterol 91:2242–2244

Chetty R, Clark SP (1993) Cholecystitis, cholelithiasis, and ganglioneuromatosis of the gall bladder: an unusual presentation of MEN type 2b. J Clin Pathol 46:1061–1063

Chim CS, Loong F, Chung LP (2001) Chronic lymphocytic leukemia involving the gallbladder. Br J Haematol 115:717

Chim CS, Liang R, Loong F, Chung LP (2002) Primary mucosa-associated lymphoid tissue lymphoma of the gallbladder. Am J Med 112:505–507

Cho YU, Kim JY, Choi SK, Hur YS, Lee KY, Kim SJ, Ahn SI, Hong KC et al (2001) A case of hemorrhagic gallbladder paraganglioma causing acute cholecystitis. Yonsei Med J 42:352–356

Chung PH, Srinivasan R, Linehan WM, Pinto PA, Bratslavsky G (2012) Renal cell carcinoma with metastases to the gallbladder: four cases from the National Cancer Institute (NCI) and review of the literature. Urol Oncol 30:476–481

Cicin I, Usta U, Sezer A, Canbaz S, Uzunoglu S, Karagol H, Genchellac H, Karasalihoglu AR et al (2009) Synchronous tonsil, gallbladder, and cardiac metastases without any other visceral metastases of malignant melanoma. Onkologie 32: 197–199

Colaneri RP, Nunes Bdos S, Herman P (2010) Melanoma of the gallbladder misdiagnosed as gallbladder cancer. Hepatobiliary Pancreat Dis Int 9:108–109

Collin Y, Sabbagh R (2012) An unusual case of pancreatitis revealing a metachronous renal cell carcinoma metastasis to the gallbladder. Can J Urol 19:6392–6394

Colombat M, Carton S, Dron B (1999) Vesicular metastasis of a prostatic adenocarcinoma (in French). Gastroenterol Clin Biol 23:990–991

Coskun F, Cetinkaya M, Cengiz O, Adsan O, Kulacoglu S, Eroglu A (1995) Metastatic carcinoma of the gallbladder due to renal cell carcinoma in the ectopic kidney. Acta Chir Belg 95:56–58

Crawford DL, Yen IT, Moore JT (1996) Metastatic breast carcinoma presenting as cholecystitis. Am Surg 62:745–747

Crippa S, Bovo G, Romano F, Mussi C, Uggeri F (2004) Melanoma metastatic to the gallbladder and small bowel: report of a case and review of the literature. Melanoma Res 14:427–430

Dainko EA (1970) Acalculous cholecystitis due to Hodgkin's disease. Calif Med 112:28–30

Darmas B, Mahmoud S, Abbas A, Baker AL (2007) Is there any justification for the routine histological examination of straightforward cholecystectomy specimens? Ann R Coll Surg Engl 89:238–241

Das Gupta TK, Brasfield R (1964) Metastatic melanoma: a clinicopathologic study. Cancer 17:1323–1339

Dasanu CA, Mesologites T, Homsi S, Ichim TE, Alexandrescu DT (2010) Chronic lymphocytic leukemia presenting with cholecystitis-like symptoms and gallbladder wall invasion. South Med J 103: 482–484

Daunt N, King DM (1982) Metastatic melanoma in the biliary tree. Br J Radiol 55:873–874

Debiec H, Kirylowicz K, Herba T (1966) 2 cases of malignant melanoma of the gallbladder (in Polish). Przegl Lek 22:463–465

Decoene J, Ameye F, Lerut E, Oyen R, Van Poppel H, Joniau S (2011) Renal cell carcinoma with synchronous metastasis to the calcaneus and metachronous metastases to the ovary and gallbladder. Case Rep Med 2011:671645

Di Vita M, Zanghi A, Lanzafame S, Cavallaro A, Piccolo G, Berretta M, Grosso G, Cappellani A (2011) Gallbladder metastases of breast cancer: from clinical-pathological patterns to diagnostic and therapeutic strategy. Clin Ter 162:451–456

DiGiuseppe JA, Nelson WG, Seifter EJ, Boitnott JK, Mann RB (1994) Intravascular lymphomatosis: a clinicopathologic study of 10 cases and assessment of response to chemotherapy. J Clin Oncol 12:2573–2579

Dominguez FE, Rosen LB, Coleman Kramer H (1986) Malignant angioendotheliomatosis proliferans. Report of an autopsied case studied with immunoperoxidase. Am J Dermatopathol 8:419–425

Dong XD, DeMatos P, Priteo VG, Seigler HF (1999) Melanoma of the gallbladder: a review of cases seen at Duke University Medical Center. Cancer 85:32–39

Doval DC, Bhatia K, Pavithran K, Sharma JB, Vaid AK, Hazarika D (2006) Breast carcinoma with metastasis to the gallbladder: an unusual case report with a short review of literature. Hepatobiliary Pancreat Dis Int 5:305–307

Doyle LA, Hornick JL, Fletcher CD (2013) PEComa of the gastrointestinal tract: clinicopathologic study of 35 cases with evaluation of prognostic parameters. Am J Surg Pathol 37:1769–1782

Duan X, Lapus A, Brown RE, Chen L (2011) Intravascular large B-cell lymphoma presenting as cholecystitis and pancytopenia: case report with literature review. Ann Clin Lab Sci 41:262–266

Erös N, Karolyi Z, Kovacs A, Takacs I, Radvanyi G, Kelenyi G (2002) Intravascular B-cell lymphoma. J Am Acad Dermatol 47(Suppl):S260–S262

Essola B, Malvaux P, Landenne J, Kargar S, Dopchie C, Waignein F, Sleiman WB et al (2012) Gallbladder metastasis from breast carcinoma: a new case report (in French). Rev Med Brux 33:171–175

Estrada RL, Brown NM, James CE (1960) Chronic follicular cholecystitis. Radiological, pathological and surgical aspects. Br J Surg 48:205–209

Falcao D, Leal AT (1975) Dermoid cyst of the gallbladder. Ann Chir Gynaecol Fenn 64:236–238

Fang X, Gupta N, Shen SS, Tamboli P, Charnsangavej C, Rashid A, Wang H (2010) Intraluminal polypoid metastasis of renal cell carcinoma in gallbladder mimicking gallbladder polyp. Arch Pathol Lab Med 134:1003–1009

Farah SS, Morris P, Dubrava Z, Du Guesclin A, Nagash N (2012) Angioblastic T-cell lymphoma of the gall bladder. ANZ J Surg 82:752–753

Ferluga D, Luzar B, Gadzijev EM (2003) Follicular lymphoma of the gallbladder and extrahepatic bile ducts. Virchows Arch 442:136–140

Ferrell KD, Ng A, Rouch D, Chua GT (1990) Nonfunctioning paraganglioma of the liver, gallbladder and common bile duct. Indiana Med 83:822–824

Fitzgerald NE, MacClain KL (2003) Imaging characteristics of hemophagocytic lymphohistiocytosis. Pediatr Radiol 33:392–401

Fredericks RK, Walker FO, Elster A, Challa V (1991) Angiotropic intravascular large-cell lymphoma (malignant angioendotheliomatosis): report of a case and review of the literature. Surg Neurol 35:218–223

Freschi M, Sassi I (1990) Paraganglioma of the gallbladder (in Italian). Pathologica 82:459–463

Friedman EP, Lazda E, Grant D, Davis J (1993) Primary lymphoma of the gallbladder. Postgrad Med J 69:585–587

Fullarton GM, Burgoyne M (1991) Gallbladder and pancreatic metastases from bilateral renal carcinoma presenting with hematobilia and anemia. Urology 38:184–186

Gabriele R, Jouffre C (1969) Un cas de mélanome de la vésicule biliaire. Lyon Chir 65:682–685

Gardini A, Saragoni L, La Barba G, Garcea D (2009) Simultaneous occurrence of primary diffuse large B-cell lymphoma and extranodal marginal zone (MALT) B-cell lymphoma in the gallbladder: a case report. Pathologica 101:230–234

Gassler N, Banafsche N, Quentmeier A, Otto HF, Helmke BM (2004) Secondary malignant melanoma of the gallbladder. A contribution to the differential diagnosis of pigmented lesions of the gallbladder (in German). Pathologe 25:155–159

Gavala S, Nicolo A (1960) Radiological aspect of intestinal and gallbladder metastases of melanoblastoma of the back (in Italian). Ann Radiol Diagn (Bologna) 33:155–163

Gawenda M, Franzen D, Lorenzen J, Müller U (1995) Brain and gallbladder metastases 10 years after local excision of a cutaneous malignant melanoma (in German). Dtsch Med Wochenschr 120:289–292

Geddy PM, Wedgwood KR (1996) Myelofibrosis presenting as chronic cholecystitis. J Clin Pathol 49:428–429

Ghaouti M, Znati K, Jahid A, Zouaidia F, Bernoussi Z, El Fakir Y, Mahassini N (2013) A gallbladder tumor revealing metastatic clear cell renal carcinoma: report of a case and review of literature. Diagn Pathol 8:4

Gillespie JJ, Ayala AG, MacKay B, Silliman YE (1977) Diagnosis of lymphoma from a cholecystectomy specimen: case report and review of the literature. South Med J 70:353–354

Gligorijevic J, Zivkovic V, Djordjevic B, Dimov I (2011) Primary gallbladder melanoma in dysplastic nevus syndrome: report of a case and literature review. Turk J Gastroenterol 22:626–630

Gogas J, Mantas D, Gogas H, Kouskos E, Markopoulos C, Vgenopoulou S (2003) Metastatic melanoma in the gallbladder: report of a case. Surg Today 33:135–137

Golbey S, Gerard PS, Frank RG (1991) Metastatic hypernephroma masquerading as acute cholecystitis. Clin Imaging 15:293–295

Goldin EG (1990) Malignant melanoma metastatic to the gallbladder. Case report and review of the literature. Am Surg 56:369–373

Gonzalez Lopez JA, Artigas Raventos V, Rodriguez Blanco M, Marinello FG, Trias Folch M (2010) Primary Burkitt's lymphoma of the gallbladder (in Spanish). Cir Esp 88:204–205

Gravel J, Lallier M, Garel L, Brochu P, Champagne J, Alvarez F (2001) Primary non-Hodgkin lymphoma of the extrahepatic biliary tract and gallbladder in a child. J Pediatr Gastroenterol Nutr 32:598–601

Guerini A, Gottardi D, Galassi A, Armani A, Bionadani L, Candiani V, Venza E (1990) Malignant melanoma of the gallbladder. Case report and review of the literature. Arch Anat Cytol Pathol 38:168–170

Guida M, Cramarossa A, Gentile A, Benvestito S, De Fazio M, Sanbiasi D, Crucitta E et al (2002) Metastatic malignant melanoma of the gallbladder: a case report and review of the literature. Melanoma Res 12:619–625

Gwynne S, Abbas T (2008) The gallbladder as the first site of metastatic disease in a patient with melanoma. Hematol Oncol Stem Cell Ther 1:197–198

Habeck JO (1993) Primary malignant melanoma of the gallbladder. Case report and literature review (in German). Zentralbl Pathol 139:367–371

Hahn ST, Park SH, Choi HS, Kim CY, Shinn KS, Kim CS (1993) Ultrasonographic features of metastatic melanoma of the gallbladder. J Clin Ultrasound 21:542–546

Hamodat M, Alhumidi A (2009) Malignant melanoma of the gall bladder, a case report and literature review. Internet J Pathol 9:1–7

Han JK, Kim SH (2005) Hepatocellular carcinoma with unusual metastasis to the gallbladder (in Korean). Korean J Hepatol 11:180–182

Harder VV, Heindorff H (1983) Metastasis from renal cell carcinoma to the gallbladder (in Danish). Ugeskr Laeger 145:3261

Hatae Y, Kikuchi M (1979) Lymph follicular cholecystitis. Acta Pathol Jpn 29:67–72

Hatae Y, Kikuchi M, Segawa M, Yonemitsu K (1978) Malignant melanoma of the gallbladder. Pathol Res Pract 163:281–287

Hatanaka N, Miyata M, Kamiike W, Okumura K, Hashimoto T, Yamaguchi T, Kishino Y et al (1993) Radical resection of primary malignant melanoma of the gallbladder with multiple metastases: report of a case. Surg Today 23:1023–1036

Hayasaka T, Hirose Y, Itoh T (1996) Reactive lymphoid hyperplasia (RLH) of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:326–328

Heath DI, Womack C (1988) Primary malignant melanoma of the gall bladder. J Clin Pathol 41:1073–1077

Helm TN, Bergfeld WF, Elston D (1992) Angiotropic lymphoma: malignant angioendotheliomatosis. Cutis 50:204–206

Henriques CQ (1955) A case of secondary melanoma of the gallbladder presenting as acute cholecystitis. Br J Surg 42:663–665

Herrera FA, Hassanein AH, Cosman BC, Bouvet M (2010) Breast carcinoma metastatic to the gallbladder and urinary bladder. Eur Rev Med Pharmacol 14: 883–886

Herrington JL (1965) Metastatic malignant melanoma of the gallbladder masquerading as cholelithiasis. Am J Surg 109:676–678

Higgins CM, Strutton GM (1995) Malignant melanoma of the gall bladder – does primary melanoma exist? Pathology 27:312–314

Hirano T (2000) Paraganglioma of the gallbladder: report of a rare case. Am J Gastroenterol 95:1607–1608

Holloway BJ, King DM (1997) Ultrasound diagnosis of metastatic melanoma of the gallbladder. Br J Radiol 70:1122–1125

Huang WT, Chuang SS, Huang CC, Lu CL, Eng HL (2007) Primary diffuse large B-cell lymphoma of the gallbladder with cholelithiasis masquerading as acute cholecystitis: case report and literature review. N Z Med J 120: U2470

Hurley R, Weisdorf DJ, Jessurun J, Vercellotti GM, Miller WJ (1992) Relapse of acute leukemia presenting as acute cholecystitis following bone marrow transplantation. Bone Marrow Transplant 10:387–389

Hussain SA, English WE, Lytle LH, Thomas DW (1976) Pseudolymphoma of the gallbladder. Am J Gastroenterol 65:152–155

Hwang DW, Lim CS, Jang JY, Lee SE, Yoon SO, Jeon YK, Uk Lee K, Kim SW (2010) Primary hematolymphoid malignancies involving the extrahepatic bile duct or gallbladder. Leuk Lymphoma 51:1278–1287

Imenpour H, Castagnola M, De Silva G, Zupo S, Truini M, Merlo E, Anselmi L (2011) Incidental finding of peripheral B-cell non-Hodgkin lymphoma, lymphocytic/CLL type, of the gallbladder in a patient with chronic cholecystitis. Pathologica 103:307–310

Ishizawa T, Okuda J, Kawanishi T, Kitagawa T, Yakumaru K, Sekikawa T (2006) Metastatic renal cell carcinoma of the gallbladder. Asian J Surg 29: 145–148

Jain D, Chopra P (2013) Metastatic renal cell carcinoma of gall bladder. Saudi J Kidney Dis Transpl 24:100–104

Jelic TM, Barreta TM, Yu M, Frame JN, Estallila OC, Mellen PF, New man SS et al (2004) Primary, extranodal, follicular non-Hodgkin lymphoma of the gallbladder: case report and a review of the literature. Leuk Lymphoma 45:381–387

Jeong YS, Han HS, Lim SN, Kim MJ, Han JH, Kang MH, Ryu DH, Lee OJ, Lee KH et al (2012) Gallbladder metastasis of non-small cell lung cancer presenting as acute cholecystitis. Chin J Cancer Res 24:249–252

Jho DH, Jho DJ, Chejfec G, Ahn M, Ong ES, Espat NJ (2007) Primary biliary B-cell lymphoma of the cystic duct causing obstructive jaundice. Am Surg 73:508–510

Jones CH (1961) Malignant melanoma of the gallbladder. J Pathol Bacteriol 81:423–430

Jones M, Mathew J, Abdullah KE, McCulloch T, Cheung KL (2009) Ruptured gallbladder as the first presentation of breast cancer. World J Surg Oncol 7:50

Justin-Besançon L, Laroche C, Nenna A, Etienne JP (1963) Jaundice caused by choledochal obstruction in Hodgkin's disease, surgical by-pass (in French). Sem Hop 39:2571–2574

Kanzaki R, Yamada T, Gotoh K, Takahashi H, Murata M, Tomita Y, Yano M, Ohigashi H et al (2011) Surgical resection for hepatocellular carcinoma with metastasis to the gallbladder: report of a case. Surg Today 41:285–291

Kato H, Naganuma T, Iizawa Y, Kitagawa M, Tanaka M, Isaji S (2008) Primary non-Hodgkin's lymphoma of the gallbladder diagnosed by laparoscopic cholecystectomy. J Hepatobiliary Pancreat Surg 15:659–663

Katz SC, Bowne WB, Wolcock JD, Busam KJ, Jaques DP, Coit DG (2007) Surgical management of melanoma of the gallbladder: a report of 13 cases and review of the literature. Am J Surg 193:493–497

Kawahara T, Ohshiro H, Sekiguchi Z, Furuya M, Namura K, Itoh H, Sano F, Kawaji K et al (2010) Gallbladder metastasis from renal cell carcinoma. Case Rep Oncol 3:30–34

Kazmann H (1956) Malignant melanoma of the gallbladder. Am J Surg 92:469–471

Keahey TM, Guerry DP, Tuthill RJ, Bondi EE (1982) Malignant angioendotheliomatosis proliferans treated with doxorubicin. Arch Dermatol 118:512–514

Kechrid M, Malik GH, Al-Mohaya S, Shaikh JF, Al-Wakeel JS, El Gamal H, Farouk H et al (2000) Renal cell carcinoma of contralateral kidney with

secondaries in gallbladder eight years after nephrectomy. Saudi J Kidney Dis Transpl 11:587–592
Khan ZS, Huth J, Kapur P, Huerta S (2010) Indications and recommended approach for surgical intervention of metastatic disease to the gallbladder. World J Surg Oncol 8:80
Kim MJ, Yu E, Ro JY (2003) Sarcomatoid carcinoma of the gallbladder with a rhabdoid tumor component. Arch Pathol Lab Med 127:e406–e408
Kim HJ, Lee TJ, Choi YS (2014) Primary B-lymphoblastic lymphoma of gallbladder involving mandibular bone. Int J Hematol 99:790–793
King DH, Centeno AS, Saldivar VA, Sarosdy MF (1995) Renal cell carcinoma metastatic to the gallbladder or prostate: two case reports. Urology 46:722–725
Knobler RM, Neumann RA, Gebhart W, Radaskiewicz T, Ferenci P, Widhalm K (1990) Xanthoma disseminatum with progressive involvement of the central nervous and hepatobiliary systems. J Am Acad Dermatol 23:341–346
Kohler U, Jacobi T, Sebastian G, Nagel M (2000) Laparoskopische Cholecystektomie bei einer isolierten Gallenblasenmetastase eines malignen Melanoms (Laparoscopic cholecystectomy in isolated gallbladder metastasis of malignant melanoma). Chirurg 71:1517–1520 (in German)
Kojima F, Ishida M, Fujie Y, Okabe H (2014) Postsurgical long-term disease-free survival in a case of primary diffuse large B-cell lymphoma of the gallbladder without adjuvant therapy. Am Surg 80:58–60
Kondo H, Kainuma O, Itami J, Minoyama A, Nakada H (1995) Extramedullary plasmacytoma of maxillary sinus with later involvement of the gall bladder and subcutaneous tissues. Clin Oncol (R Coll Radiol) 7:330–331
Korkmaz T, Seber S, Turhal S (2010) Primary melanoma of the gallbladder. J BUON 15:892
Koshy M, Zhao F, Garofalo MC (2008) Primary MALT lymphoma of the gallbladder. Case report. J Gastrointestin Liver Dis 17:207–210
Kosucu P, Kul S, Gunes G, Ilmaz M, Ersoz S, Ozdemir F (2012) Multiple relapses extramedullary localization of acute lymphoblastic leukemia. Bratisl Lek Listy 113:46–49
Kücükakin B, Olsen CH, Gögenur I (2009) Renal cell carcinoma with metachronous metastases to the gallbladder after two years (in Danish). Ugeskr Laeger 171:2486–2487
Kumar P, Chandra K, Madhok R, Nigam P (2013) Leukaemoid reaction (paraneoplastic syndrome) in adenocarcinoma of gall bladder. J Assoc Physicians India 61:356–357
Kuroda N, Mizobuchi M, Shimamaura Y, Taniguchi Y, Daibata M, Miyoshi I, Ichimura T et al (2007) An Asian variant of intravascular lymphoma: unique clinical and pathological manifestation in the gallbladder. APMIS 115:371–375
Lajolo PP, Del Giglio A, Speranzini M, Rossetti C, Pettinati J (2005) Metastatic melanoma of the gallbladder mimicking bladder calculi (in Portuguese). Rev Assoc Med Bras 51:74
Lane JE, Walker AN (2002) Metastatic hepatocellular carcinoma of the gallbladder. Digest Surg 19:267–268
Langley RG, Bailey EM, Sober AJ (1997) Acute cholecystitis from metastatic melanoma to the gall-bladder in a patient with a low-risk melanoma. Br J Dermatol 136:279–282
Laurino L, Melato M (1990) Malignant angioendotheliomatosis (angiotropic lymphoma) of the gallbladder. Virchows Arch A Pathol Anat Histopathol 417:243–246
Lee YT (1983) Breast carcinoma: pattern of metastasis at autopsy. J Surg Oncol 23:175–180
Lee T, Lee SK, Chou TY, Ho YJ (1991) Castleman's disease: 6 cases report (in Chinese). Zhonghua Yi Xue Za Zhi (Taipei) 48:237–241
Ligeron-Esbrayat C, Guillot B (2002) Hepatic colic revealing vesicular metastasis of melanoma (in French). Presse Med 31:1893–1894
Limani K, Matos C, Hut F, Gelin M, Closset J (2003) Metastatic carcinoma of the gallbladder after a renal cell carcinoma. Acta Chir Belg 103:233–234
Lin BT, Weiss LM, Battifora H (1997) Intravascularly disseminated angiosarcoma: true neoplastic angioendotheliomatosis? Report of two cases. Am J Surg Pathol 21:1138–1143
Lin P, Bueso-Ramos C, Wilson CS, Mansoor A, Medeiros LJ (2003) Waldenstrom macroglobulinemia involving extramedullary sites: morphologic and immunophenotypic findings in 44 patients. Am J Surg Pathol 27:1104–1113
Lombardo FP, Hertford DE, Shanahan EM, Kazam E (1996) Doppler ultrasonographic evaluation of renal cell carcinoma metastasis to the gallbladder. J Ultrasound Med 15:725–728
Longwitz D, Schulz HG, Bosse A (1996) Malignant melanoma of the gallbladder (in German). Ultraschall Med 17:195–198
Majerovic M, Bogdanic B, Drinkovic N, Kinda SB, Jakic-Razumovic J, Gasparovic V (2012) Extramedullary plasmacytoma imitating neoplasm of the gallbladder fossa after cholecystectomy. Coll Antropol 36:331–333
Mallory TB, Lawson GM (1931) Chronic typhoid cholecystitis. Am J Pathol 7:71
Mandal AK, Savvidou L, Slater RM, Cockett W, Wiggins J, Missouris CG (2007) Angiotropic lymphoma: associated chromosomal abnormalities. Eur J Intern Med 18:432–434
Mani H, Climent F, Colomo L, Pittaluga S, Raffeld M, Jaffe ES (2010) Gall bladder and extrahepatic bile duct lymphomas: clinicopathological observations and biological implications. Am J Surg Pathol 34:1277–1286
Manouras A, Lagoudianakis EE, Genetzakis M, Pararas N, Papadima A, Kekis PB (2008) Metastatic breast carcinoma initially presenting as acute cholecystitis: a case report and review of the literature. Eur J Gynecol Oncol 29:179–181
Marone U, Caracao C, Losito S, Daponte A, Chiofalo MG, Mori S, Cerra R, Pezzullo L et al (2007) Laparoscopic

cholecystectomy for melanoma metastatic to the gallbladder: is it an adequate surgical procedure? Report of a case and review of the literature. World J Surg Oncol 5:141

Martinez Pérez A, Camarasa Lillo N, Domingo Del Pozo C, Vazquez Tarragon A, Castro Garcia C (2015). MALT lymphoma of the gallbladder (in Spanish). Gastroenterol Hepatol 38:320–322

Martinez-Roman S, Frumovitz M, Deavers MT, Ramirez PT (2005) Metastatic carcinoma of the gallbladder mimicking an advanced cervical carcinoma. Gynecol Oncol 97:942–945

Maruo H, Watahiki Y, Ohsaku M, Kosaka A, Morii I (1994) A case of hepatocellular carcinoma with metastasis to the gallbladder and the omentum. Gastroenterology 17:1379–1383

Maryniak RK, Konecki R (1991) 2 cases of Richter's syndrome (in Polish). Acta Haematol Pol 22:165–169

Matsubayashi H, Kiyohara Y, Sasaki K, Kanemoto H, Urikura K, Kawata N, Kimura H et al (2012) Metastatic malignant melanoma of the gallbladder diagnosed by cytology of endoscopic naso-gallbladder drainage fluid. J Dig Dis 13:190–194

Maxwell D, Safley TL, Payne F, Richmond BK (2009) Isolated metastasis to the gallbladder arising from adenocarcinoma of the prostate. Am Surg 75:431–432

McCluggage WG, Mackle E, Mccusker G (1996) Primary low grade malignant lymphoma of mucosa-associated lymphoid tissue of gallbladder. Histopathology 29:285–287

McDonald EC (1990) Nonneoplastic paraganglionic tissue in the gallbladder wall. J Tenn Med Assoc 83:225–226

McFadden PM, Krementz ET, McKinnon WM, Pararo LL, Ryan RF (1979) Metastatic melanoma of the gallbladder. Cancer 44:1802–1808

Mehra S, Chung-Park M (2005) Gallbladder paraganglioma: a case report with review of the literature. Arch Pathol Lab Med 129:523–526

Miller TA, Weber TR, Appelman HD (1972) Paraganglioma of the gallbladder. Arch Surg 105:637–639

Miselli A, Ugolotti U, Ghirarduzzi A, Violi V (1988) Metastatic melanoma of the gallbladder. Preoperative ultrasonographic documentation (in Italian). Radiol Med 75:260–262

Mitra S, Mukherjee S, Chakraborty H (2014) Mucosa associated lymphoid tissue lymphoma of gallbladder: a rare presentation. Indian J Pathol Microbiol 57:502–503

Mitropoulos FA, Angelopoulou MK, Siakantaris MP, Rassidakis G, Vayiopoulos GA et al (2000) Primary non-Hodgkin's lymphoma of the gall bladder. Leuk Lymphoma 40:123–131

Monden K, Nakagohri T, Kojima M, Kato Y, Gotohda N, Takahashi S (2011) A case of gallbladder metastasis from hepatocellular carcinoma (in Japanese). Jpn J Gastroenterol Surg 44:259–265

Mori S, Itoyama S, Mohri N, Shibuya A, Hirose T, Takanashi R, Oshimi K, Mizoguchi H et al (1985) Cellular characteristics of neoplastic angioendotheliosis. An immunohistological marker study of 6 cases. Virchows Arch (A) 407:167–175

Mosnier JF, Brousse N, Sevestre C, Fléjou JF, Delteil C, Hénin D, Potet F (1992) Primary low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue arising in the gallbladder. Histopathology 20:273–275

Murakami H, Takahashi Y, Binnaka T, Kitagawa S (1996) Malignant lymphoma of the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:245–247

Murakami M, Kobayashi S, Marubashi S, Eguchi H, Takeda Y, Tanemura M, Wada H et al (2010) Isolated metastasis to the gallbladder from hepatocellular carcinoma. Hepatol Res 40:793–798

Murguia E, Quiroga D, Canteros G, Sanmartino C, Barreiro M, Herrera J (2006) Gallbladder metastases from ductal papillary carcinoma of the breast. J Hepatobiliary Pancreat Surg 13:591–593

Murphy MN, Lorimer SM, Glennon PE (1987) Metastatic melanoma of the gallbladder: a case report and review of the literature. J Surg Oncol 34:68–72

Nagler J, McSherry CK, Miskovitz P (1994) Asymptomatic metachronous metastatic renal adenocarcinoma to the gallbladder. Report of a case and guidelines for evaluation of intraluminal polypoid gallbladder masses. Dig Dis Sci 39:2476–2479

Naguib SE, Aterman K (1984) Presumed malignant melanoma of the gallbladder: report of a case and a review of the literature. Am J Dermatopathol 6:231–243

Nakai M, Toyoki Y, Ishido K, Kudo D, Kimura N, Yamana D, Hakamada K (2011) A case of malignant lymphoma of the gallbladder after chemotherapy for malignant lymphoma of the skin and right intraocular (in Japanese). Gan To Kagaku Ryoho 38: 2442–2444

Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K (1983) Pathology of hepatocellular carcinoma in japan. 232 consecutive cases autopsied in ten years. Cancer 51:863–877

Namkoong KY, Kang MJ, Im HM, Kim MS, Ko BS, Ahn HT, Lee JR, Kim JO (2004) A case of hepatocellular-cholangiocarcinoma invading the gallbladder (in Korean). Korean J Hepatol 10:148–153

Nassenstein K, Kissler M (2004) Gallbladder metastasis of non-small cell lung cancer. Onkologie 27:398–400

Neal MR, Shah HR, Angtuaco TL (1994) Case of the day. 6. Diagnosis: lymphoma of the gall bladder. J Ultrasound Med 13:337–338

Nelms JK, Patel JA, Atkinson DP, Raves JJ (2007) Metastatic malignant melanoma of the gallbladder presenting as biliary colic: a case report and review of literature. Am Surg 73:833–835

Nishida J, Tanaka M, Suto K, Sasaki Y, Yamagata K, Aizawa T (1997) A case of metastatic gallbladder tumor derived from hepatocellular carcinoma (in Japanese). Nihon Shokakibyo Gakkai Zasshi 94:857–860

Nojima H, Cho A, Yamamoto H, Nagata M, Takiguchi N, Kainuma O, Souda H, Gunji H et al (2008) Renal cell carcinoma with unusual metastasis to the gallbladder. J Hepatobiliary Pancreat Surg 15:209–212

O'Boyle MK (1994) Gallbladder wall mass on sonography representing large-cell non-Hodgkin's lymphoma in an AIDS patient. J Ultrasound Med 13:67–68

Ochoa JI, Keene WR (1970) Obstructive jaundice in Hodgkin's disease due to infiltration of the biliary ducts. J Fla Med Assoc 57:21–23

Ojima H, Hasegawa T, Matsuno Y, Sakamoto M (2005) Extramedullary myeloid tumor (EMMT) of the gallbladder. J Clin Pathol 58:211–213

Ono A, Tanoue S, Yamada Y, Takaji Y, Okada F, Matsumoto S, Mori H (2009) Primary malignant lymphoma of the gallbladder: a case report and literature review. Br J Radiol 82:e15–e19

Orbuch SJ, Porta J, Garrido C, Perazzo DL (1981) Melanoma with gallbladder metastasis. Report of a case (in Spanish). Acta Gastroenterol Latinoam 11:533–536

Orton DF, Saigh JA (1996) CT of Hodgkin's lymphoma limited to the gallbladder. Abdom Imaging 21:238–239

Osman J, Regan RJ, Dathan JR (1978) Bilateral renal carcinoma with metastasis in gall bladder and associated with a strongly positive ANA. Br J Urol 50:212

Ostick DG, Haggani MT (1976) Obstructive cholecystitis due to metastatic melanoma. Postgrad Med J 52:710–712

Otrakji CL, Voigt W, Amador A, Nadji M, Gregorios JB (1988) Malignant angioendotheliomatosis – a true lymphoma: a case of intravascular malignant lymphomatosis studied by southern blot hybridization analysis. Hum Pathol 19:475–478

Ozawa T, Kosugi S, Noda T, Take H (2012) Gall bladder B-lymphoblastic lymphoma showing carcinoma-like appearance. Intern Med 51:663–664

Pagano S, Ruggeri P, Franzoso F, Brusamolino R (1995) Unusual renal cell carcinoma metastasis to the gallbladder. Urology 45:867–869

Pandey D, Kane SV, Shukla PJ, Shrikhande SV, Tongaonkar HB (2006) Isolated gall bladder metastasis from renal cell carcinoma. Indian J Gastroenterol 25:161–162

Paolini O, Rampal A, Caroli-Bosc FX, Desruelles F, Ortonne JP, Delmont JP (1999) Vesicular metastasis of malignant melanoma revealed by recurrent hepatic colic crisis (in French). Gastroenterol Clin Biol 23:412–414

Pappo I, Feigin E, Uziely B, Arnir G (1991) Biliary and pancreatic metastases of breast carcinoma: is surgical palliation indicated? J Surg Oncol 46:211–214

Park JS, Chae YS, Hong SJ, Shin DH, Choi JS, Kim BR (2003) Metastatic renal cell carcinoma of the gallbladder. Yonsei Med J 44:355–358

Park JH, Lee SH, Park H (2007) Metachronous metastatic renal cell carcinoma to the gallbladder (in Korean). Korean J Gastroenterol 49:127–130

Patel S, Zebian B, Gurjar S, Pavithran N, Singh K, Liston T, Grant J (2009) An unusual gall-bladder polyp – site of metastatic renal cell carcinoma: a case report. Cases J 2:172

Pautler EE, Gallavan EM (1951) Melanoma of brain and gallbladder. AMA Arch Pathol 51:238–245

Payan HM, Grossman IW, Pelaez M (1989) Acute surgical abdomen and myelofibrosis. Mod Pathol 2:270–272

Peison B, Rabin L (1976) Malignant melanoma of the gallbladder: report of three cases and review of the literature. Cancer 37:2448–2454

Pennino P, Avallone L (1965) Chronic follicular cholecystitis (in Italian). Rass Int Clin Ter 45:370–376

Perniciario C, Winkelmann RK, Daoud MS, Su WP (1995) Malignant angioendotheliomatosis is an angiotropic intravascular lymphoma. Immunohisto-chemical, ultrastructural, and molecular genetic studies. Am J Dermatopathol 17:242–248

Perrin TG (1953) Histology of a case of proliferative follicular cholecystitis (in Spanish). Rev Clin Esp 51:305–308

Pfleger L, Tappeiner J (1959) Zur Kenntnis der systematisierten Endotheliomatose der cutanen Blutgefässe (Reticuloendotheliose?). Hautarzt 10:359–363

Pherson M, Yon JR, Wilhelm S, Toscano MP, Kruse EJ (2014) Mantle cell lymphoma metastasis to the gallbladder. Ann Surg 80:e198–e199

Picon-Coronel G, Chablé-Montero F, Angeles-Angeles A, Albores-Saavedra J (2011) Multiple venous and arterial thromboses of the gallbladder causing acute cholecystitis. A previously undescribed complication of essential thrombocythemia. Ann Hepatol 10:365–369

Piérard GE, Soyeur-Broux M, Fridman V, Sadzot B, De La Brassinne M, Monnen G et al (1988) Lymphome angiotrope de type angioendothéliomatose proliférante systémique. Ann Dermatol Venereol 115:333–336

Pitlovic V, Latic F, Pitlovic H, Rupcic M, Jurisic D, Latic A (2011) Primary malignant melanoma of gallbladder. Med Glas Ljek Komore Zenicko-Doboj Kantona 8:71–73

Psarras K, Symeonidis N, Vlachaki E, Baltatzis M, Papatolios G, Pavlidis E, Mouratidou C et al (2014) Primary gallbladder small lymphocytic lymphoma as a rare postcholecystectomy finding. Case Rep Hematol 2014:716071

Qu G, Kaur JS, Seward JB (2003) Metastatic melanoma presenting as cardiac mass and hemobilia. Am J Med Sci 325:157–159

Raffensperger EC, Brason FW, Triano G (1963) Primary melanoma of the gallbladder. Am J Dig Dis 8:356–363

Rajesh LS, Nada R, Yadav TD, Joshi K (2003) Primary low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue of the gallbladder. Histopathology 43:300–301

Rana S, Jairajpuri ZS, Khan S, Hassan MJ, Jetley S (2014) Gall bladder lymphoid hyperplasia: masqurading as lymphoma. J Can Res Ther 10:749–751

Rehani B, Strohmeyer P, Jacobs M, Mantil J (2006) Gallbladder metastasis from malignant melanoma: diagnosis with FDG PET/CT. Clin Nucl Med 31:812–813

Riaz N, Ahmed R, Afzal S, Masood N (2012) Breast carcinoma with asymptomatic metastasis to the gallbladder. Singapore Med J 53:e136–e138

Ricci V, Carbone SF, Testi W, Malatesti R, Lo Gatto M, Dell'Avanzato R, Ginanneschi C et al (2008) Single gallbladder and multiple pancreatic metastases from renal cell carcinoma sixteen years after nephrectomy. Chir Ital 60:311–314

Robledo AB, Millet SB, Orbis Castellanos JF, Montalva Oron EM, Salom Fuster J et al (2012) Metastasis of the gallbladder in clear cell renal carcinoma. Oncol Lett 3:1136–1138

Rodriguez-Merchan B, Lozoya R, Allende E, Mesa J (2006) Paraganglioma of the gallbladder (in Spanish). Med Clin (Barc) 127:158

Romero M, Bianchi L, Vilana R (2006) Melanoma metastasis to the gallbladder (in Spanish). Radiologia 48:321–323

Rubin A, Tate JJ (1989) Breast carcinoma metastatic to the gallbladder. J Clin Pathol 42:1223–1224

Rudolph A, Bothe J, Bonk U (1985) Malignes Melanom der gallenblase. Chirurg 56:469–471

Ryu HS, Hwang ET, Choi CS, Kim TH, Kim HC, Yun KJ, Park DE (2009) A case of hepatocellular carcinoma invading the gallbladder misdiagnosed as a primary gallbladder carcinoma (in Korean). Korean J Hepatol 15:80–84

Safioleas M, Agapitos E, Kontzoglou K, Stamatakos M, Safioleas P, Mouzopoulos G, Kostakis A (2006) Primary melanoma of the gallbladder: does it exist? Report of a case and review of the literature. World J Gastroenterol 12:4259–4261

Sagi T, Györi S (1972) Primary gallbladder reticulosarcoma (in German). Zentralbl Allg Pathol 116:174–176

Sahasrabudhe N, Davenport A (2005) Myeloid metaplasia in the gall bladder: a case report. J Clin Pathol 58:998–999

Sakuma T, Hirota M, Ohashi H, Kakudo K, Kawano K (2011) Extensive ganglioneuromatosis of gallbladder. Int J Surg Pathol 19:524–526

Samplaski MK, Rosato EL, Witkiewicz AK, Mastrangelo MJ, Berger AC (2008) Malignant melanoma of the gallbladder: a report of two cases and review of the literature. J Gastrointest Surg 12:1123–1126

Sand M, Bechara FG, Kopp J, Krins N, Behringer D, Mann B (2009) Gallbladder metastasis from renal cell carcinoma mimicking acute cholecystitis. Eur J Med Res 14:90–92

Sato THG, Masuo K, Mochizuki T, Sanada Y (2001) A case of malignant lymphoma of the gallbladder. Jpn J Gastroenterol Surg 34:1308–1311

Sauerbrei E, Castelli M (1979) Hypogammaglobulinemia and nodular lymphoid hyperplasia of the gut. J Can Assoc Radiol 30:62–63

Schmidt MH, Sung L, Shuckett BM (2004) Hemophagocytic lymphohistiocytosis in children: abdominal US findings within 1 week of presentation. Radiology 230:685–689

Schuster D, Klosterhalfen B, Fiedler C, Prescher A (2007) Metastasis of medullary plasmocytoma as the cause of acute cholecystitis (in German). Dtsch Med Wochenschr 132:612–615

Seelig MH, Schönleben K (1997) Laparoscopic cholecystectomy for a metastasis of a malignant melanoma in the gallbladder. Z Gastroenterol 35:673–675

Sendo H, Harada H, Hasegawa H, Yasuda T, Ohara T, Oshikiri T, Tanaka K, Fujino Y et al (2013) A case of gallbladder metastasis from a malignant perivascular epithelioid cell tumor of the bladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 110:861–868

Seul B, Lüchtrath H (1984) Malignes Melanom der Gallenblase. Chirurg 55:179–181

Sezgin O, Altintas E, Polat A, Tombak A (2009) Ultrasonographic features of a large B-cell lymphoma of the gallbladder. Turk J Gastroenterol 20:239–240

Shah RJ, Koehler A, Long JD (2000) Bile peritonitis secondary to breast cancer metastatic to the gallbladder. Am J Gastroenterol 95:1379–1381

Shah KG, Molmenti EP, Idrovo JP, Nicastro J, Coppa G (2011) Primary gallbladder lymphomas. Am Surg 77:360–361

Sheibani K, Battifora H, Winberg CD, Burke JS, Ben-Ezra J, Ellinger GM, Quigley NJ et al (1986) Further evidence that "malignant angioendotheliomatosis" is an angiotropic large-cell lymphoma. N Engl J Med 314:943–948

Shimizu T, Tajiri T, Akimaru K, Arima Y, Yokomuro S, Yoshida H, Mamada Y, Tainai N et al (2006) Cholecystitis caused by infiltration of immature myeloid cells: a case report. J Nippon Med Sch 73:97–100

Shimkin PM, Soloway MS, Jaffe E (1972) Metastatic melanoma of the gallbladder. Am J Roentgenol Radium Ther Nucl Med 116:393–395

Sierra-Callejas JL, Warecka K (1976) Primary malignant melanoma of the gallbladder. Virchows Arch A Pathol Anat Histol 370:233–238

Solak A, Solak I, Genç B, Sahin N (2013) The role of diffusion-weighted examination in non-polypoid gallbladder malignancies: a preliminary study. Turk J Gastroenterol 24:148–153

Song DE, Choi G, Jun SY, Ro JY (2004) Primitive neuroectodermal tumor of the gallbladder. Arch Pathol Lab Med 128:571–573

Sparwasser C, Krupeinski M, Radomsky J, Pust RA (1997) Gallbladder metastasis of renal cell carcinoma. A case report and review of the literature. Urol Int 58:257–258

Stephen MR, Farquharson MA, Sharp RA, Jackson R (1998) Sequential malt lymphomas of the stomach, small intestine, and gall bladder. J Clin Pathol 51:77–79

Stutte H, Muller PH, d'Hoedt B, Striebel W (1989) Ultrasonographic diagnosis of melanoma metastases in liver, gallbladder, and spleen. J Ultrasound Med 8:541–547

Sugita M, Ryu M, Satake M, Kinoshita T, Konishi MA, Inoue K (2000) Intrahepatic inflow areas of the drainage vein of the gallbladder: analysis by angio-CT. Surgery 128:417–421

Sun AP, Ohtsuki Y, Liang SB, Sonobe H, Iwata J, Furihata M, Takeuchi T, Qiu Y et al (1998) Osteoclast-like giant cell tumor of the pancreas with metastases to gallbladder and lymph nodes. A case report. Pathol Res Pract 194:587–594

Suri VS, Gondal R, Agarwal A, Malhotra V, Sakhuja P, Singhal S (2003) Primary rhabdoid tumor of the gallbladder: report of a case. Surg Today 33:464–466

Swiatoniowski G, Mazur G, Halon A, Rozumek G, Dabrowska M, Zawisza R, Prdulak E (2004) Malignant melanoma with gall bladder metastasis as a second neoplasm in the course of prostate cancer. Pathol Oncol Res 10:243–245

Takano Y, Katsurada J, Kawamura M, Sakamoto N, Watanabe Y, Kanno S (2004) A case of primary low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) of gallbladder. Yakuri To Rinsho 14:397

Tanaka T, Sekimura A, Tanaka H, Tonegawa K, Ogawa K, Haneda H (2009) Gallbladder metastasis of large cell lung cancer (in Japanese). Kyobu Geka 62:1069–1072

Tanga MR, Ewing JB (1970) Primary malignant tumors of the gallbladder: report of 43 cases. Surgery 67:418–426

Terasaki S, Nakanuma Y, Terada T, Unoura M (1990) Metastasis of hepatocellular carcinoma to the gallbladder presenting massive intraluminal growth: report of an autopsy case. J Clin Gastroenterol 12:714–715

Terashima T, Yamashita T, Arai K, Kakinoki K, Kagaya T, Sakai Y (2007) A case of metastatic gallbladder tumor of the hepatocellular carcinoma (in Japanese). Kanzo 48:363–369

Thayer KH, Williams OO, Rowe D (1955) Malignant melanoma of the gallbladder; report of a case and review of the literature. Ariz Med 12:15–18

Theaker JM, Gatter KC, Esiri MM, Easterbrook P (1986) Neoplastic angioendotheliomatosis – further evidence supporting a lymphoid origin. Histopathology 10:1261–1270

Thorns C, Rohrmoser B, Feller A, Horny HC (2002) Chronic cholecystitis and myeloid metaplasia. Histopathology 41:273–275

Tishler M, Rahmani R, Shilo R, Armon S, Abramov AL (1987) Large-cell lymphoma presenting as acute cholecystitis. Acta Haematol 77:51–52

Tissot JD, Schneider P, Hürlimann J, Saraga EP, Cech P, Ramelet AA (1981) Tumors and myelomonocytic leukemia (in French). Schweiz Med Wochenschr 111:389–393

Tomonori N, Yukinari S, Ai M, Yoshinobu A (2011) Gallbladder involvement of diffuse large B-cell lymphoma mimicking gallbladder carcinoma. Acta Gastroenterol Belg 74:479–480

Tomori H, Nagahama M, Miyazato H, Shiraishi M, Muto Y, Toda T (1999) Mucosa-associated lymphoid tissue (MALT) of the gallbladder: a clinicopathological correlation. Int Surg 84:144–150

Topeli A, Demiroglu H, Dundar S (1996) Acalculous cholecystitis in patients with acute leukemia. Br J Clin Pract 50:224–225

Torikai M, Tahara H, Kaji T, Shimono R, Yano T, Yoshioka T, Kawakami K, Takamatsu H (2007) Immature teratoma of gallbladder associated with gliomatosis peritonei, a case report. J Pediatr Surg 42: E25–E27

Tsuchiya T, Shimokawa I, Higami Y, Ohtani H, Shigeoka Y, Ohshima K, Tanaka K et al (2001) Primary low-grade MALT lymphoma of the gallbladder. Pathol Int 51:965–969

Tuset E, Ribera JM, Vaquero M, Jimenez C, Milla F, Junca J, Fores A, Feliu E (1995) Granulocytic sarcoma: a study of 5 cases (in Spanish). Med Clin (Barc) 104:377–380

Tuveri M, Tuveri A (2007) Isolated metastatic melanoma to the gallbladder: is laparoscopic cholecystectomy indicated?: a case report and review of the literature. Surg Laparosc Endosc Percutan Tech 17:141–144

Tyagi SP, Tyagi N, Mheshwari V, Ashraf SM, Sahoo P (1992) Morphological changes in diseased gall bladder: a study of 415 cholecystectomies at Aligarh. J Indian Med Assoc 90:178–181

Uchiyama T, Suzki M, Fukuhara K, Unno M, Ise H, Matsuno S (1997) Gallbladder metastasis from renal cell carcinoma – a report of a case (in Japanese). Nihon Shokakibyo Gakkai Zasshi 94:68–72

Ueno N, Kanamura T, Kawaguchi K, Tanaka K, Inoue K, Idei Y, Yamamoto M (2001) A hepatocellular carcinoma with lymph node metastasis and invasion into the gallbladder: preoperative difficulty ruling out a gallbladder carcinoma. Oncol Rep 8:331–335

Ukkola-Pons E, Weber-Donat G, Minvielle F, Bonardel G, Baccialone J, Jeanbourquin D et al (2010) Gallbladder chloroma: a case report (in French). J Radiol 91:239–240

Van Slyck EJ, Schuman BM (1972) Lymphocytic lymphosarcoma of the gallbladder. Cancer 30:810–816

Vantomme L, Van Reepinghen P, Aubry A, Fievez M (1984) Malignant melanoma of the gallbladder (in French). Acta Chir Belg 84:23–26

Varsamidakis N, Panagiotou P, Yettimis E (2006) Isolated gallbladder metastatic melanoma. HPB (Oxford) 8:73

Velez AF, Penetrante RB, Spellman JE, Orozco A, Karakousis CP (1995) Malignant melanoma of the gallbladder: report of a case and review of the literature. Am Surg 61:1095–1098

Verbanck JJ, Rutgeerts LJ, van Aelst FJ, Tytgat JH, Decoster JM, Noyez DN, Theunynck PJ et al (1986) Primary malignant melanoma of the gallbladder, metastatic to the common bile duct. Gastroenterology 91:214–218

Vernadakis S, Rallis G, Danias N, Serafimidis C, Christodoulou E, Troulinakis M, Legakis N et al (2009) Metastatic melanoma of the gallbladder: an unusual clinical presentation of acute cholecystitis. World J Gastroenterol 15:3434–3436

Vesnin AG, Semenow II, Negustorov IF, Anisimov W, Turkevich EA (1999) Ultrasound diagnosis of melanoma metastasis into the gallbladder (in Russian). Vopr Onkol 45:690–692

Viswanathan SR, Khalpey Z, Ashley SW (2011) Gallbladder lymphoma. Med Oncol 28:810–812
Wakabayashi T, Kishimoto H, Miwa Y, Riku S (1978) Cancer of gallbladder with severe thrombocytosis. Acta Pathol Jpn 28:627–635
Wakasugi M, Ueshima S, Akamatsu H, Tori M, Oshita M, Tsujimoto M, Nishida T (2012) Gallbladder metastasis from hepatocellular carcinoma. Report of a case and review of literature. Int J Surg Case Rep 3:455–459
Walsh TS (1956) Primary melanoma of the gallbladder with cervical metastasis and fourteen and a half year survival: first histologically proved case. Cancer 9:518–522
Wang JC, Angeles S, Chak P, Platt AB, Nimmagadda N (2001) Choriocarcinoma of the gallbladder: treated with cisplatin-based chemotherapy. Med Oncol 18:165–169
Wee GC, Hagen G, Torres A, Shieber W (1970) Hodgkin's disease of the cystic node as a cause of nonvisualization of the gallbladder. Am J Gastroenterol 54:272–276
Wick MR, Banks PM, McDonald TJ (1981) Angioendotheliomatosis of the nose with fatal systemic dissemination. Cancer 48:2510–2517
Wieting H, Hamdi G (1907) Über die physiologische und pathologische Melaninpigmentierung und den epithelialen Ursprung der Melanoblastome. Ein primäres Melanoblastom der Gallenblase. Beitr Pathol Anat 42:23–84
Willingham DL, Menke DM, Satyanarayana R (2009) Gallbladder lymphoma in primary sclerosing cholangitis. Clin Gastroenterol Hepatol 7:A26
Willis RA (1948) Pathology of tumors, 2nd edn. Butterworth & Co., Ltd., London, p 914
Wolff M (1973) Paraganglioma of the gallbladder. Arch Surg 107:493
Wrotnowski U, Mills SE, Cooper PH (1985) Malignant angioendotheliomatosis. An angiotropic lymphoma? Am J Clin Pathol 83:224–248
Yadav S, Chisti MM, Rosenbaum L, Barnes MA (2014) Intravascular large B cell lymphoma presenting as cholecystitis: diagnostic challenges persist. Ann Hematol 93:1259–1260
Yamamoto T, Kawanishi M, Yoshiba H, Kanehira E, Itoh H (2005) Primary non-Hodgkin's lymphoma of the gallbladder. AJR Am J Roentgenol 184(3 suppl):S86–S87
Yamamoto S, Tsukamoto T, Kanazawa A, Shimizu S, Mikamori M, Fujiwara Y, Nagahara H et al (2012) Lymphoid hyperplasia detected as a single mass in the gallbladder: report of a case. Surg Today 42:1244–1247
Yokoe M, Mizuno Y, Hattori K, Kanankura M, Nishi Y, Kumada K, Katsumi K, Takano Y et al (2003) A case of malignant lymphoma of the gallbladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 100:1219–1223
Yoon WJ, Yoon YB, Kim YJ, Ryu JK, Kim YT (2009) Metastasis to the gallbladder: a single-center experience of 20 cases in South Korea. World J Gastroenterol 15:4806–4809
Zagouri F, Sergentanis IN, Koulocheri D, Nonni A, Bousiotou A, Domeyer P, Michalopoulos NV et al (2007) Bilateral synchronous breast carcinomas followed by metastasis to the gallbladder: a case report. World J Surg Oncol 5:101
Zelones JT, Coimbra R (2014) Gallbladder small lymphocytic lymphoma in a patient with chronic cholecystitis and choledocholithiasis. Am Surg 80:E173–E174
Zemlyn S (1966) Metastatic melanoma of the gallbladder. Radiology 87:744–745
Zhang MZ (1985) Primary malignant lymphoma of the gallbladder – a case report (in Chinese). Zhonghua Zhong Liu Za Zhi 7:70–71
Zhang ZD, Myles J, Pai RP, Howard JM (1991) Malignant melanoma of the biliary tract: a case report. Surgery 109:323–328
Zhao L, Anders KH (2014) Malignant perivascular epithelioid cell tumor of the gallbladder: a case report and review of literature. Arch Pathol Lab Med 138:1238–1241
Zhao G, Luo M, Wu ZY, Liu Q, Zhang B, Gao RL, Zhang ZQ (2009) Langerhans cell sarcoma involving gallbladder and peritoneal lymph nodes: a case report. Int J Surg Pathol 17:347–353

Tumor-Like Inflammatory Changes of the Gallbladder

158

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_158

Abstract

Several forms of tumor-like inflammatory lesions develop in the gallbladder. Similar to the liver and bile ducts, inflammatory pseudotumors can develop in the gallbladder. They include inflammatory myofibroblastic tumors, with clonal and reactive variants, inflammatory tumors developing as a foreign body reaction, and pseudotumors in the setting of IgG4-related sclerosing disease. Inflammatory pseudotumors of the gallbladder can grow to a size exceeding 10 cm and mimic cancer. Reactive endoluminal inflammatory processes of the gallbladder are called inflammatory polyps, a rather common complication of cholecystitis. Histologically, granulation polyps and inflammatory fibroid polyps are distinguished. A gallbladder inflammation that may closely resemble a malignant process is xanthogranulomatous cholecystitis, a chronic inflammatory and sometimes destructive process characterized by massive accumulation of lipid-containing macrophages and other leukocytes, later followed by a fibrosing lesion. Xanthogranulomatous cholecystitis is associated with gallbladder carcinoma in part of the patients. Another distinct form of cholecystitis with a fibrosing reaction and wall thickening is lymphoplasmacytic sclerosing cholecystitis.

Inflammatory Pseudotumor (Inflammatory Myofibroblastic Tumor) of the Gallbladder

Introduction

Inflammatory pseudotumors (myofibroblastic inflammatory tumors) are well-defined tumorous lesions of the hepatobiliary tracts (see the respective chapter), but are very uncommon alterations of the gallbladder. As in other locations, pseudotumors can be divided into several entities, as summarized in Table 1.

Clinical and Imaging Features

The clinical features of inflammatory gallbladder tumors are known from relatively few case reports only (Shou et al. 1987; Ikeda et al. 1990; Corsi and Bosman 1995; Behranwala et al. 2005; Jain et al. 2005; Mssrouri et al. 2011; Muduly et al. 2012; Rammohan et al. 2012). Inflammatory pseudotumor may clinically present as active cholecystitis, i.e., epigastric or right upper quadrant pain, nausea, vomiting, and fever. In case of large lesions, an upper abdominal mass may be in evidence. In the serum, elevated inflammatory markers are found. The lesions clinicoradiologically mimic gallbladder carcinoma or other gallbladder malignancies in part of the cases (Jain et al. 2005) and sometimes initially present as a gallbladder neoplasm (Behranwala et al. 2005).

Apparently, clonal myofibroblastic tumors of the gallbladder may be HIV and EBV associated and can present as multifocal lesions in the pediatric age group (Mahlobo et al. 2012). Reactive inflammatory pseudotumor has been observed secondary to spilled intra-abdominal gallstones, i.e., as an excessive inflammatory foreign body-type reaction. The lesion may cause extensive adhesions between the diaphragm and the parietal wall with the gallbladder (Rammohan et al. 2012). Gallbladder pseudotumors developing in the setting of IgG4-related disease are sometimes large and ill-defined lesions that mimic gallbladder cancer (Lee et al. 2013).

Table 1 Clinicopathological forms of inflammatory pseudotumors of the gallbladder

Inflammatory myofibroblastic tumor (most of the previously reported cases of inflammatory pseudotumor)
Localized (mass-forming) and diffuse forms
Clonal versus reactive variants
Inflammatory pseudotumors. In the setting of marked foreign body-type reactions
Pseudotumors in the setting of IgG4-related sclerosing disease
Calcifying fibrous pseudotumor

Pathology

Macroscopy

Inflammatory pseudotumor of the gallbladder presents as localized or diffuse thickening of the gallbladder wall or as a mass resembling gallbladder cancer. The masses may exceed 10 cm

in diameter (Behranwala et al. 2005). In case of marked accumulation of lipid-laden macrophages (pseudoxanthomatous reaction), the cut surface shows yellowish spots; otherwise, the tissue is grayish-red, depending on its vascularization.

Histopathology

The histology of inflammatory pseudotumors has been outlined in detail elsewhere. Part of the tumors correspond to clonal myofibroblastic tumors as described in more detail in another chapter. These lesions consist of a proliferation of myoid spindle cells with or without ALK positivity. Reactive forms are chiefly characterized by a proliferation of fibroblasts and myofibroblasts, intermingled with an inflammatory infiltrate containing various numbers of lymphocytes, macrophages (in part foam cells), plasma cells, and granulocytes. In some cases, numerous CD68-positive macrophages were detected (Ozsan et al. 2013). One variant of reactive pseudotumor of the gallbladder is characterized by calcifications (calcifying fibrous pseudotumor; Mourra et al. 2004).

Differential Diagnosis

The most important differential diagnosis of inflammatory pseudotumor of the gallbladder is the group of myofibroblastic and other spindle cell sarcomas.

Inflammatory Polyps of the Gallbladder

Introduction

Inflammatory polyps of the gallbladder are reactive endoluminal lesions which are either sessile or have a short stalk and head and mainly consisting of granulation tissue or fibrovascular tissue with variable amounts of leukocytic infiltrate cells (Majeski 1986; Albores-Saavedra et al. 1993; Owen and Bilhartz 2003). As their size can reach one cm in diameter, inflammatory polyps can produce pseudotumorous lesions that mimic gallbladder neoplasms, in particular polypoid carcinoma. Most inflammatory polyps are associated with chronic cholecystitis.

Epidemiology

The overall prevalence of gallbladder polyps as assessed by ultrasonography in a European population was 4.6 % in men and 4.3 % in women (Jorgensen and Jensen 1990). Among apparently healthy Japanese, the prevalence of gallbladder polyps was highest in middle-aged men, but this observation mainly related to cholesterol polyps (Segawa et al. 1992). Bland inflammatory polyps of the gallbladder are uncommon lesions, however with variable published incidences (Christensen and Ishak 1970, Kubota et al. 1995; Terzi et al. 2000; Myers et al. 2002; Wu et al. 2003; Sun et al. 2004; Ito et al. 2009; Zielinski et al. 2009; Terada 2013).

In a histologic examination of polyps found in 72 patients, cholesterol polyps were in present in 47, adenomas in 8, cancers in 16, and an inflammatory polyp in 1 (Kubota et al. 1995). Among 40 patients with pathologically confirmed polypoid lesions of the gallbladder and mean age of 43.9 years, 57.5 % had cholesterol polyps, 12.5 % inflammatory polyps, 10 % adenocarcinomas, 7.5 % xanthomatous polyps, and 5 % papillary adenomas, and 1 each of the patients had mixed polyp, neurofibroma, and adenomatoid proliferation polyp (Zhang 1991). Terzi et al. (2000) registered no inflammatory polyp among their 74 reported benign polypoid lesions of the gallbladder. A Japanese study documented 7 inflammatory polyps among 70 surgical cases of small polypoid lesions (Sadamoto et al. 2002). In a Chinese series of 260 cases of polypoid gallbladder, 4 lesions were inflammatory polyps (Wu et al. 2003). Roa et al. (2004) noted a prevalence of 2 % inflammatory polyps among 219 gallbladders with polyps of Chilean patients. In an investigation from Korea referring to 396 patients with

confirmed polypoid lesions of the gallbladder, inflammatory polyp accounted for 1.7 %, in comparison with 51.2 % cholesterol polyps (Kwon et al. 2009).

Classification

Several forms of inflammatory polyps of the gallbladder can be distinguished on morphologic and/or molecular grounds. The polyp types are summarized in Table 2. Most inflammatory polyps are bland lesions that correspond in their morphology to reactive polypoid lesions occurring elsewhere in mucosa-containing organs (so-called granulation polyps; Liao et al. 1996).

In the gastrointestinal tract, inflammatory polyps with hyperplastic epithelial changes and having juvenile-like features were found in the setting of neurofibromatosis type 1. Similar lesions may be expected to occur in the gallbladder.

Clinical and Imaging Features

As inflammatory polyps of the gallbladder are small lesions usually not exceeding 10 mm in diameter, they do per se not cause clinical signs and symptoms, the latter being related to underlying gallbladder disease, in particular cholecystitis and stone disease (Christensen and Ishak 1970). Inflammatory polyps are often hypoechoic solitary lesions (Hallgrimmsson and Skaane 1988). On CT, small polypoid lesions, i.e., those less than 10 mm in size, may not be detectable in unenhanced images (Furukawa et al. 1995). Inflammatory polyps may radiologically mimic early polypoid carcinoma (Kyokane et al. 1994; Maeyama et al. 1998; Susumu et al. 2009). A polyp size exceeding 10 mm and age over 60 years suggest malignancy (Koga et al. 1988; Yang et al. 1992; Sugiyama et al. 1999; Yeh et al. 2001; Lee et al. 2004).

Table 2 Types of inflammatory polyps of the gallbladder

Ordinary inflammatory polyp (granulation polyp)
Pyogenic granuloma of the gallbladder
Inflammatory fibroid polyp
Polypoid lesions in xanthogranulomatous cholecystitis

Pathology

Macroscopy

Inflammatory polyps are mostly solitary and sessile lesions. Similar to cholesterol polyps, they generally have a diameter of less than 10 mm, while most cancerous polyps exceed 10 mm in size at the time point of diagnosis (Kubota et al. 1995). In contrast to inflammatory polyps, cholesterol polyps are multiple lesions in about two thirds of cases (Sun et al. 2004). In fresh state, the polyps are reddish to grayish-brown, depending on the grade of hyperemia, density of leukocytes infiltration, and eventual hemosiderosis. The surface of the polyps is either granular, as in any granulation tissue growing out of a mucosal surface, or glistening in case of epithelial covering.

Histopathology

Early lesions show the typical features of a highly vascular granulation tissue with only poor fibroblastic/myofibroblastic reaction (Fig. 1). The vascular stroma of older polyps is typically edematous and displays a cellular infiltrate dominated by lymphocytes, macrophages, and plasma cells. Toward the surface of the polyp, neutrophils may be encountered, and the surface itself is often covered by a thin layer of fibrin-containing exudate. The new formed vessels may show neutrophil leukodiapedesis. Part of polyps show a partial or, less commonly, complete lining of their surface by a columnar epithelium with signs of cell damage, leukocytes transmigration, and regenerative alterations. The epithelial cells are usually flat and can show nuclear atypia related to regeneration.

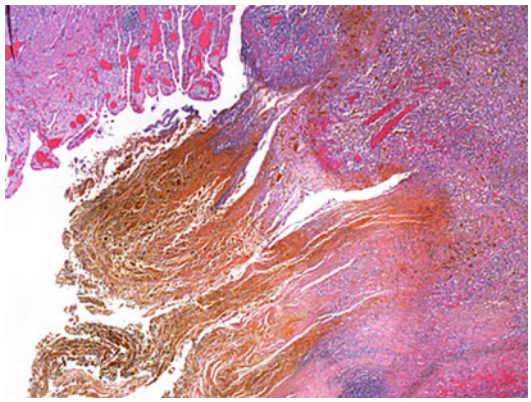

Fig. 1 Inflammatory polyps of the gallbladder. The granulation tissue polyps are covered with bile-containing exudate (hematoxylin and eosin stain)

Inflammatory Fibroid Polyp of the Gallbladder

Inflammatory fibroid polyps (IFP; Vanek's polyp) are benign lesions occurring in the gastrointestinal tract, specifically in the stomach and small bowel, but IFP also occur in the colon, rectum, esophagus, and gallbladder (Morales-Fuentes et al. 2011; Liu et al. 2013). The lesion was first described by Vanek in 1949, using the term "submucosal granuloma." In contrast to ordinary inflammatory polyp, IFP may grow to larger size and can develop a nodular surface (Kim et al. 2003; Liu et al. 2013). IFP are polypoid lesions consisting of a fibrovascular tissue infiltrated by several classes of inflammatory cells, including eosinophils and mast cells. About half of cases show perivascular onion skinning, and part of the lesions reveal a short fascicular growth pattern, and eosinophilia of the lesion was present in 94 % in one study (Liu et al. 2013). IFP developing in stomach and small bowel commonly show mutations in platelet-derived growth factor receptor alpha (PDGFRA), similar to some GISTs, a finding that was suggested to indicate a neoplastic nature of IFP (Schildhaus et al. 2009; Bjerkehagen et al. 2013). Activating PDGFRA mutations occur in exons 12, 14, and 18, whereby exon 12 mutations prevailed in the small intestine, while exon 18 mutations occurred frequently in the stomach (Huss et al. 2012). IFP is a very rare lesion in the gallbladder (Fogt et al. 1998; Kim et al. 2003). In one patient with IFP of the gallbladder, a PDGFRA mutation was detected, similar to its gastrointestinal counterparts (Martini et al. 2013).

Gallbladder Polyps in Acromegaly

Patients with uncontrolled acromegaly have an increased mortality rate compared with the general population, cardiovascular disease accounting for about 60 % of the mortality. These patients also bear an increased risk of developing several types of neoplasms, both benign and malignant, such as carcinomas of breast, colorectum, and prostate, and other types of epithelial tumors, approximately 15 % of mortality being due to cancer. In a retrospective analysis of 140 patients with active acromegaly, colon carcinoma was found in 10, thyroid cancer in 5, breast cancer in 4, and gastric cancer in 2. The risk of developing these cancers was significantly higher than that for a matched control group (Kurimoto et al. 2008).

Patients with acromegaly also reveal a higher incidence of benign lesions, including gallbladder polyps, which were found in up to 14 % of patients (Kurimoto et al. 2008). In another investigation on newly diagnosed acromegaly, the relative risk for gallbladder polyps in acromegaly patients was 6.29, mostly for patients older than 50 years of age and higher growth hormone serum levels (Annamalai et al. 2011). The histopathology of these polyps has not been determined, however with one reported patient with a villous gallbladder adenoma (Krstic et al. 2007).

Differential Diagnosis

Hemobilia with a blood clot in the gallbladder lumen, e.g., subsequent to needle biopsy, may sonographically mimic a polyp (Kwon et al. 2002; Lin et al. 2005). Polypoid benign tumors with a fibrous component may be confounded with a reactive polyp, e.g., polypous

neurofibroma (Morizumi et al. 1988) and polypoid adenomyoma (Sasatomi et al. 1997). Exceptionally, a pseudopolyp-like lesion of the gallbladder was found following penetration of a biopsy needle into the gallbladder, the penetrating needle causing an elevation of the inner gallbladder layer at the entrance site, sonographically mimicking a polyp (Barzilai et al. 1997).

Xanthogranulomatous Cholecystitis

Introduction

Xanthogranulomatous cholecystitis (XGC) is a chronic inflammatory and sometimes destructive process of the gallbladder characterized by massive accumulation of lipid-containing macrophages (foamy macrophages), rendering the tissue macroscopically yellowish as in xanthomas, later followed by fibrosis and eventually extension into neighboring organs. In the context of tumors, XGC is important for two reasons. First, it may clinico-radiologically mimic gallbladder cancer. Secondly, XGC is associated with gallbladder carcinoma in part of the patients, although a role of XGC as a premalignant condition is not settled.

Epidemiology

XGC was first described in 1970 as "fibroxanthogranulomatous inflammation" (Christensen and Ishak 1970). Since then, numerous cases have been reported for adult patients, first under a variety of names, including "ceroid or ceroid-like histiocytic granuloma of the gallbladder." Takahashi and coworkers (1976) reported the incidence in Japan to be 1–2 % of all surgically removed gallbladders. In a retrospective 3-year study, 13 cases of XGC (7 females, 6 males) were identified in 724 gallbladders (1.8 %), with an estimated incidence of 1.7 cases per 100,000 population per year (Roberts and Parsons 1987). Among 1,425 cholecystectomies, 35 cases of XGC were identified (2.4 %; Cardenas-Lailson et al. 2005). In a recent review of 29 studies from Europe, India, Far East, and Americas, covering 1,599 patients, the overall incidence of XGC was 1.3–1.9 %, with the exception of India where it was 8.8 % (Hale et al. 2014). Analysis of clinical data of 39 patients with XGC revealed a male to female ratio of 30:9 and an average age at diagnosis of 62.2 years. There was an association with gallbladder stones in 94.9 % (Han and Chen 2012). In other studies, a female preponderance was found (74 %; Cardenas-Lailson et al. 2005). Rarely, XGC develops in the pediatric age group and has even been diagnosed in infants (Kim et al. 2013).

Selected References: (Takahashi et al. 1976; Amazon and Rywlin 1980), and "biliary granulomatous cholecystitis" (Mehrotra and Bhatnagar 1982), later followed by the term now consistently employed, XGC (Bluth et al. 1979; Goodman and Ishak 1981; Reyes et al. 1981; Fligiel and Lewin 1982; Parsons et al. 1986; Hanada et al. 1987; Roberts and Parsons 1987; Franco et al. 1990; Ladefoged and Lorentzen 1993; Houston et al. 1994; Dixit et al. 1998; Eriguchi et al. 2001; Pinocy et al. 2003; Guzman-Valdivia 2004; Kansakar et al. 2008; Wang et al. 2009a; Rastogi et al. 2010; Cecava and Andrews 2011; Singal et al. 2011; Han and Chen 2012; Jain et al. 2012).

Clinical and Imaging Features

XGC may present with atypical clinical manifestations and is sometimes difficult to diagnose, although many patients show a clinical presentation that is similar to ordinary cholecystitis (Han and Chen 2012). XGC can undergo an aggressive inflammatory course (Psarras et al. 2012), with extension into adjacent organs, above all the liver and transverse colon, and development of cholecystoenteric fistulas (Parsons et al. 1986; Fu et al. 2012). XGC may be associated with xanthogranulomatous changes in other organs, e.g., xanthogranulomatous gastritis (Guarino et al. 1993). In one patient, XGC was associated with primary sclerosing cholangitis (Mori et al. 2010).

Sonography delivers characteristic features in patients with XGC, including a diffuse or focal thickening of the gallbladder wall and oval or flat wall nodules of low echogenicity, the latter ranging in size from 5 to 12 mm (Bluth et al. 1979; Kim et al. 1998; De Gaetano et al. 1985; Parra et al. 2000; Cecava and Andrews 2011; Ueda et al. 2011). On CT images, gallbladders in XGC are homogeneously enhanced in the early vascular phase and remain enhanced for more than 1 min, gallbladder enhancement being either smooth and regular as in ordinary cholecystitis or coarse and irregular (De Gaetano et al. 1985; Cossi et al. 1987; Hanada et al. 1987; Casas et al. 1996; Chun et al. 1997; Kim et al. 1999; Parra et al. 2000; Bhattacharya et al. 2011; Ueda et al. 2011). Part of the cases exhibit a disrupted mucosal line, this feature being more often associated with liver infiltration (Zhao et al. 2013). On contrast-enhanced CT images, intramural hypoattenuating nodules occupying more than 60 % of the gallbladder wall were suggestive of XGC (Jain et al. 2012). XGC can produce masses of the gallbladder that radiologically closely resemble malignancy (Agarwal et al. 2013).

Pathology

Macroscopy

Macroscopically, gallbladders with XGC usually show a marked increase in wall thickness. There may be adhesions on the serosal surface, and the gallbladder is sometimes adherent to the liver and difficult to dissect with the fossa. On cut surfaces, the organ shows a yellowish, patchy discoloration, sometimes with formation of yellowish nodules that bulge into the mucosa. The nodular infiltrate disrupts the mucosal surface, sometimes with ulceration. Large-nodule yellow lesions are soft in the center, due to partial necrosis. Three distribution subtypes of the lesions have been proposed, i.e., multinodular, focal, and diffuse (Franco et al. 1990). In case of marked inflammatory nodularity and fibrotic changes, an inflammatory pseudotumor can result. XGC can result in fistula formation, predominantly cholecystoenteric fistulas.

Histopathology

The histopathology of XGC has been described in detail (Roberts and Parsons 1987; Dao et al. 1989; Singh et al. 1989; Franco et al. 1990). The lesion is chiefly characterized by a dense focal to disuse and sometimes nodular infiltrate composed of numerous foamy macrophages, lymphocytes, and plasma cells, with only a minor participation of granulocytes. The lipid-laden macrophages appear in two forms, i.e., round to oval and large macrophages with a foamy to spongy cytoplasm and spindle-shaped macrophages/histiocytes with elongated nuclei and a granular cytoplasm, which can contain ceroid (Gal et al. 1984; Roberts and Parsons 1987). Giant cells of the Touton type may occur. Foci of xanthogranulomatous tissue are often centered at Rokitansky-Aschoff sinuses. Tumor-like nodules predominantly consist of spindle-shaped cells. Large accumulations of inflammatory cells can result in full-thickness, destructive lesions of the gallbladder, with variable extension into subserosal fat and eventual extension into the gallbladder fossa and beyond the serosal lining. The inflammatory process can also involve the mucosa, with formation of ulcers and mucosal xanthogranulomatous nodules. In most cases, depositions of cholesterol crystals with or without formation of cholesterol granulomas, hemosiderosis, and extravasated bile are present (Roberts and Parsons 1987). Progressively, the inflammation is accompanied by fibrosis which may be patchy or segmental, with formation of sclerosed masses.

Immunohistochemistry

As in other chronic inflammatory disorders, macrophages in XGC are reactive for CD68 and CD163. Inflammatory cells in this cholecystitis are positive for GLUT-1 and GLUT-3. As glucose transporter-1 mediates the transport of fluorodeoxyglucose/(18)F-FDG through GLUT-3, this expression pattern may explain the positive result on F-FDG PET imaging (Sawada et al. 2013).

Differential Diagnosis

The principal clinico-radiological differential diagnosis is gallbladder cancer.

Xanthogranulomatous Cholecystitis and Gallbladder Cancer

As XGC results in an increase of tissue mass, a thickening of the gallbladder wall, a reduced gallbladder contractility, invasion of adjacent organs, and increased cancer marker levels in serum, it may clinically and radiologically mimic gallbladder cancer.

Selected References: (Düber et al. 1984; Maeda et al. 1994; Ros and Goodman 1997; Yoshida et al. 1997; Adachi et al. 1998; Enomoto et al. 2003; Baykara and Karahan 2004; Rao et al. 2005; Spinelli et al. 2006; Clarke et al. 2007; Makino et al. 2009; Sharma et al. 2009; Chang et al. 2010; Rastogi et al. 2010; Maker and Maker 2012; Martins et al. 2012; Zhang et al. 2012; Agarwal et al. 2013).

XGC can present with right upper quadrant pain associated with jaundice, and with an enlarged and firm gallbladder adherent to adjacent organ, in particular with an unclear border between gallbladder and liver, resulting in the clinico-radiological aspect of malignancy during cholecystectomy (Martins et al. 2012). The increase of tissue mass can result in chronic inflammatory pseudotumor (Howard et al. 1991; Roels et al. 1999). As inflammation can markedly extend beyond the gallbladder limits in XGC, an invasive process with infiltration of liver and colon can result (Pinocy et al. 2003). XGC can also be associated with liver abscess suggesting metastasis of gallbladder cancer (Eriguchi et al. 2002). At gallbladder imaging, there is an overlap between the two conditions, but there are also some features serving to distinguish the two entities (Uchiyama et al. 2009; Goshima et al. 2010; Shetty et al. 2012). In a study of 68 patients with XGC, focal thickening of the gallbladder wall as seen on CT images, early enhancement of the gallbladder, and lymph node enlargement were seen more often in coexisting gallbladder cancer. In contrast-enhanced CT images of XCG, the mucosal lining is intact and enhancing, while it is disrupted in cancer (Jain et al. 2012). Fine needle aspiration cytology can distinguish between XGC-mimicking cancer and bona fide malignancy (Hijoka et al. 2010).

XGC may be associated with gallbladder carcinoma, raising the question whether XGC is a premalignant condition (Benbow and Taylor 1988; Benbow 1989; Lopez et al. 1991; Lee et al. 2003; Kwon and Sakaida 2007; Ghosh et al. 2011; Al-Abed et al. 2012). In an immunohistochemical investigation 65 cases of XGC, epithelial nuclear reactivity for p53 protein was found in 3 % of XGC in comparison with 52 % in gallbladder carcinoma, suggesting that XGC is not a premalignant condition (Ghosh et al. 2011). Another study showed that 16 % of gallbladder cancers were associated with XGC, but failed to show p53 protein expression in epithelia of XGC lesions (Agrawal et al. 2010). In one case of XGC, no p53 gene mutation was found by use of PCR and single-strand conformational polymorphism analysis (Takada et al. 2002). A recent global study found that the incidence of gallbladder carcinoma associated with XGC was lowest in European studies (3.3 %), varying from 5.1 % to 5.9 % in the other regions analyzed (India, Far East, the Americas).

Etiology and Pathogenesis

XGC may result from an excessive inflammatory response to mostly unknown antigens, mainly involving an increased cell-mediated immune response with massive recruitment of monocytes/macrophages (Nakashiro et al. 1995). Based on the accumulation of large amounts of lipids in macrophages, a role of biliary lipids has been proposed, e.g., through an inflammatory response to extravasated bile from ruptured

Rokitansky-Aschoff sinuses (Christensen and Ishak 1970; Takahashi et al. 1976; Fligiel and Lewin 1982). Certain infections may promote the development of XGC, e.g., *Candida albicans* infection in immunosuppressed patients (Brown et al. 1996) and *Escherichia coli*. The role of *E. coli* in the pathogenesis of XGC was found to involve scavenger receptor class A and CXCL16-CXCR6 interaction (Sawada et al. 2007).

Lymphoplasmacytic Sclerosing Cholecystitis

Introduction

Lymphoplasmacytic sclerosing cholecystitis (LPSC) is a rare and in part mass-forming inflammatory gallbladder disease that is most often associated with distinct other pathologies, i.e., IgG4-related sclerosing disease, autoimmune pancreatitis, and primary sclerosing cholangitis (PSC) (Kamisawa et al. 2006; Wang et al. 2009b; Kazantsev and Lishchuk 2011). LPSC developing in the setting of IgG4-related sclerosing diseases is a distinct entity and is different from sclerosing cholecystitis related to PSC. Alterations of the gallbladder resembling IgG4-related sclerosing disease and above all occurring in patients with autoimmune pancreatitis are increasingly observed and have in part been termed IgG4-associated cholecystitis (Wang et al. 2009b; Kawakami et al. 2010; Leise et al. 2011).

In patients with PSC, one or more gallbladder abnormalities were found in 41 % of patients, cholecystitis amounting to 25 % (Said et al. 2008). Diffuse lymphoplasmacytic acalculous cholecystitis is a distinctive form of chronic cholecystitis associated with PSC (Jessurun et al. 1998) and also occurs in patients with ulcerative colitis (Herzog and Goldblum 1996). Among 72 gallbladders from 100 consecutive liver explants for PSC, lymphoplasmacytic chronic cholecystitis was present in 49 % (Lewis et al. 2007), but this form of inflammation is not associated with an increase in the number of IgG4-positive plasma cells. Diffuse lymphoplasmacytic chronic cholecystitis is also a distinct alteration in extrahepatic biliary disease (Abraham et al. 2003).

Pathology

Thickening of the gallbladder was detected 75 % (Kamisawa et al. 2006). Histologically, dense lymphoplasmacytic infiltrates either involve the gallbladder mucosa or form a transmural alteration. These infiltrates are associated with a marked fibrosclerosis of the wall. Eosinophilia, phlebitis, and extramural inflammatory nodules are further morphologic features of LPSC. In LPSC associated with IgG4-related sclerosing disease or autoimmune pancreatitis, the plasma cell population contains a significant fraction of IgG4-positive cells (Kamisawa et al. 2006; Leise et al. 2011).

LPSC can be localized and result in a gallbladder pseudotumor. In a patient with autoimmune pancreatitis, ultrasound examination revealed a mass at the fundus of the gallbladder, and CT scans showed a well-enhanced mass. Histologically, the tumor-like nodules consisted of lymphoplasmacytic infiltrates, irregular fibrosis, numerous IgG4-positive plasma cells, and adenomyomatosis (Kawakami et al. 2010).

Noninfectious Granulomatous Cholecystitis

Apart from granulomas or granuloma-like lesions occurring in xanthogranulomatous cholecystitis, sometimes with formation of so-called ceroid granulomas, other conditions of the gallbladder can contain epithelioid granulomas (Table 3).

The gallbladder is rare site of sarcoidosis, with formation of typical fibrosclerosing granulomas having giant cells and eventually Schaumann bodies (Lloyd-Davies and Forbes 1965; Mert et al. 2004). In rheumatoid arthritis, rheumatoid nodules with central fibrinoid necrosis and peripheral palisading histiocytes were found (Sandhu

Table 3 Granulomatous disorders of the gallbladder

Xanthogranulomatous cholecystitis
Sarcoidosis
Rheumatoid nodules (rheumatismus nodosus visceralis)
Granulomas in other autoimmune disorders (systemic lupus erythematosus, polyarteritis nodosa, granulomatous vasculitis)
Crohn's disease
Ulcerative colitis (IBD)
Cholesterol granulomas
Ceroid granulomas
Foreign body granulomas

and Choy 2013). In autoimmune vasculitis/angiitis, granulomas can accompany the vascular inflammatory process, e.g., in polyarteritis nodosa and necrotizing granulomatous vasculitis/Churg-Strauss syndrome (Lasser and Ghofrany 1976). The gallbladder is a well-known site of polyarteritis nodosa (PN) and is sometimes the only localization of isolated PN (Kumar et al. 2003; Juliano et al. 2009). Systemic lupus erythematosus is also known to manifest in the gallbladder (Vergara-Fernandez et al. 2009). Crohn's disease can rarely involve the gallbladder.

Macroscopically, the mucosa is often granular and nodular, with broad longitudinal ulcers and a thickened wall. Well-formed noncaseating granulomas can be found from the lamina propria to the subserosa (McClure et al. 1984; Bouteloup et al. 1997; Rettally et al. 2003; Andoh et al. 2006). Chronic granulomatous cholecystitis has been observed in the setting of chronic ulcerative colitis (Goldgraber and Kirsner 1960). In gallbladders with ulcerous inflammation, cholesterol-containing fragments of stones come into contact with mucosal macrophages, leading to cholesterol granulomas. Ceroid accumulating in the gallbladder mucosa can induce epithelioid cell induction followed by ceroid granuloma formation. Ceroid granulomas are in part associated with chronic cholecystitis and may produce a mass effect mimicking gallbladder cancer. Macroscopically, they are characterized by intramural or mucosal yellow-brown nodules. Mucosal ulceration or rupture of Rokitansky-Aschoff sinuses with bile leakage has been implicated as a pathogenic mechanism (Duarte et al. 1994).

Emphysematous Cholecystitis, Pneumocholecystitis, Pneumobilia, and Gallbladder Pneumatosis

Introduction

Few gallbladder disorders are characterized by the accumulation of gas in the gallbladder lumen and/or the gallbladder wall. As gangrenous inflammations play to most significant role, such lesions associated with an increase of gallbladder mass may be confounded with necrotic malignancy complicated by gas-forming infection.

Emphysematous Cholecystitis

Emphysematous cholecystitis (the "effervescent gallbladder") is a life-threatening variant of acute cholecystitis characterized by the presence of gas in the lumen and the wall of the gallbladder associated with necrotizing inflammation. The disorder has previously also been termed pneumocholecystitis or gangrenous pneumocholecystitis (Heifetz and Senturia 1948; Abel and Rousselot 1952; Lemmens and Louyest 1969). Infection with gas-forming bacteria, such as *Clostridium* species, *E. coli*, and *Salmonella* Derby, plays a decisive role. Predisposing conditions include ischemic gallbladder wall damage (atherosclerosis, cholecystic arterial thrombosis, thromboembolism, vasculitis, systemic hypoperfusion, gallbladder torsion), diabetes mellitus, and old age. CT images show gas in the gallbladder lumen (with an air-fluid level) and within the wall. Air may extensively dissect the gallbladder wall and escape into the abdominal cavity, with formation of pneumoperitoneum (Ohtani et al. 1996; Modini et al. 2008; Carrascosa and Salcines-Caviedes 2012). Luminal gas may also be transported into lower segments of the biliary tract, causing pneumobilia (Harley et al. 1978; Johnson et al. 1984). Emphysematous cholecystitis still has a high mortality (up to 15 %; Moanna et al. 2006).

Selected References: (Friedman and Poster 1955; Mentzer et al. 1975; Harley et al. 1978;

Goodman 1979; McMillin 1985; Gerritsen 1986; Nemcek et al. 1988; Lorenz and Steffen 1990; Ohtani et al. 1996; Garcia-Sancho Tellez et al. 1999; Ise et al. 2002; Konno et al. 2002; Lallemand et al. 2003; Chiu et al. 2004; Bouras et al. 2005; Moanna et al. 2006; Safioleas et al. 2006; Tanaka et al. 2007; Modini et al. 2008; Papavramidis et al. 2008; Uesaka et al. 2009; Wu et al. 2010; Verbeeck et al. 2011; Carrascosa and Salcines-Caviedes 2012; Kurguzov et al. 2012).

Histologically, necrosis or even extensive infarctoid changes are found, usually with a rather poor infiltration owing to limited access of leukocytes owing to vascular occlusion. However, diffuse granulocytic infiltrates (phlegmon) may occur. In longer-standing disease, eosinophilia and a gas reaction with macrophages and giant cells may ensue (Hino et al. 1989).

Gallbladder Pneumatosis

Gallbladder pneumatosis (pneumatosis cystoides), similar to its counterpart in the intestinal tract, is a rare condition characterized by the presence of gas bubbles in the mucosa or deeper parts of the gallbladder wall (Goudet et al. 1995). Gas situated in the tissue may elicit a foreign body-type reaction with accumulation of macrophages and multinucleated giant cells at the transition zone between gas and tissue (the so-called gas reaction). The pathogenesis of gallbladder pneumatosis has not been clarified, but it may develop from the ascent of gas from intestinal pneumatosis, following diagnostic interventions, or as a late change after emphysematous cholecystitis.

References

Abel WG, Rousselot LM (1952) Pneumocholecystitis; report of a case. N Engl J Med 246:662–663

Abraham SC, Cruz-Correa M, Argani P, Furth EE, Hruban RH, Boitnott JK (2003) Diffuse lymphoplasmacytic chronic cholecystitis is highly specific for extrahepatic biliary tract disease but does not distinguish between primary and secondary sclerosing cholangiopathy. Am J Surg Pathol 27:1313–1320

Adachi Y, Iso Y, Moriyama M, Kasai T, Hashimoto H (1998) Increased serum CA 19-9 in patients with xanthogranulomatous cholecystitis. Hepatogastroenterology 45:77–80

Agarwal AK, Kalayarasan R, Javed A, Sakhuja P (2013) Mass-forming xanthogranulomatous cholecystitis masquerading as gallbladder cancer. J Gastrointest Surg 17:1257–1264

Agrawal V, Goel A, Krishnani N, Pandey R, Agrawal S, Kapoor VK (2010) p53, carcinoembryonic antigen and carbohydrate antigen 19.9 expression in gall bladder cancer, precursor epithelial lesions and xanthogranulomatous cholecystitis. J Postgrad Med 56:262–266

Al-Abed Y, Elsherif M, Firth J, Borgstein R, Myint F (2012) Simultaneous xanthogranulomatous cholecystitis and gallbladder cancer in a patient with a large abdominal aortic aneurysm. Korean J Intern Med 27:338–341

Albores-Saavedra J, Vardaman CJ, Vuitch F (1993) Non-neoplastic polypoid lesions and adenomas of the gallbladder. Pathol Annu 28:145–177

Amazon K, Rywlin AM (1980) Ceroid granulomas of the gall bladder. Am J Clin Pathol 73:123–127

Andoh A, Endo Y, Kushima R, Hata K, Tsujikawa T, Sasaki M, Mekata E, Tani T et al (2006) A case of Crohn's disease involving the gallbladder. World J Gastroenterol 12:977–978

Annamalai AK, Gayton EL, Webb A, Halsall DJ, Rice C, Ibram F, Chaudhary AN et al (2011) Increased prevalence of gallbladder polyps in acromegaly. J Clin Endocrinol Metab 96:E1120–E1125

Barzilai M, Ish-Shalom N, Lerner A (1997) Gallbladder pseudopolyp formation following percutaneous liver biopsy. Pediatr Surg Int 12:422–423

Baykara M, Karahan OI (2004) Xanthogranulomatous cholecystitis mimicking carcinoma of gallbladder. Tani Girisim Radyol 10:56–58

Behranwala KA, Straker P, Wan A, Fisher C, Thompson JN (2005) Inflammatory myofibroblastic tumour of the gallbladder. World J Surg Oncol 3:24

Benbow EW (1989) Xanthogranulomatous cholecystitis associated with carcinoma of the gallbladder. Postgrad Med J 65:528–531

Benbow EW, Taylor PM (1988) Simultaneous xanthogranulomatous cholecystitis and primary adenocarcinoma of gallbladder. Histopathology 12:672–675

Bhattacharya B, Katta US, Facciuto M (2011) Image of the month. Xanthogranulomatous cholecystitis. Arch Surg 146:627–628

Bjerkehagen B, Aaberg K, Steigen SE (2013) Do not be fooled by fancy mutations: inflammatory fibroid polyps can harbor mutations similar to those found in GIST. Case Rep Med 2013:845801

Bluth EI, Katz MM, Merritt CR, Sullivan MA, Mitchell WT (1979) Echographic findings in xanthogranulomatous cholecystitis. J Clin Ultrasound 7:213–214

Bouras G, Lunca S, Vix M, Marescaux J (2005) A case of emphysematous cholecystitis managed by laparoscopic surgery. JSLS 9:478–480

Bouteloup C, Guédon C, François A, Hemet J, Lerebours E (1997) Gallbladder involvement in Crohn disease (in French). Gastroenterol Clin Biol 21:153–155

Brown H, Talamini M, Westra WH (1996) Xanthogranulomatous cholecystitis due to invasive Candida albicans in a patient with AIDS. CID 22:186–187

Cardenas-Lailson LE, Torres-Gomez B, Medina-Sanchez-S, Mijares-Garcia JM, Hernandez-Calleros J (2005) Epidemiology of xanthogranulomatous cholecystitis (in Spanish). Cir Cir 73:19–23

Carrascosa MF, Salcines-Caviedes JR (2012) Emphysematous cholecystitis. CMAJ 184, E81

Casas D, Pérez-Andrés R, Jimenez JA, Mariscal A, Cuadras P, Salas M, Gomez-Plaza MC (1996) Xanthogranulomatous cholecystitis: a radiological study of 12 cases and a review of the literature. Abdom Imaging 21:456–460

Cecava ND, Andrews R (2011) Case report of xanthogranulomatous cholecystitis, review of its sonographic and magnetic resonance findings, and distinction from other gallbladder pathology. J Radiol Case Rep 5:19–24

Chang BJ, Kim SH, Park HY, Lim SW, Kim J, Lee KH, Lee KT, Rhee JC, Lim JH et al (2010) Distinguishing xanthogranulomatous cholecystitis from the wall-thickening type of early-stage gallbladder cancer. Gut Liver 4:518–523

Chiu HH, Chen CM, Mo LR (2004) Emphysematous cholecystitis. Am J Surg 188:325–326

Christensen AH, Ishak KG (1970) Benign tumours and pseudotumours of the gall bladder. Arch Pathol 90:423–432

Chun KA, Ha HK, Yu ES, Shinn KS, Kim KW, Lee DH, Kang SW, Auh YH (1997) Xanthogranulomatous cholecystitis: CT features with emphasis on differentiation from gallbladder carcinoma. Radiology 203: 93–97

Clarke T, Matsuoka L, Jabbour N, Mateo R, Genyk Y, Selby R, Gagandeep S (2007) Gallbladder mass with a carbohydrate antigen 19-9 level in the thousands: malignant or benign pathology ? Report of a case. Surg Today 37:342–344

Corsi A, Bosman C (1995) Chronic cholecystitis with features of diffuse inflammatory pseudotumour: a clinico-pathological case study and review of the literature. Ital J Gastroenterol 27:252–255

Cossi AF, Scholz FJ, Aretz HT, Larsen CR (1987) Computed tomography of xanthogranulomatous cholecystitis. Gastrointest Radiol 12:154–155

Dao AH, Wong SW, Adkins RB (1989) Xanthogranulomatous cholecystitis. A clinical and pathologic study of twelve cases. Am Surg 55:32–35

De Gaetano AM, Breda M, Maresca G, Danza F, Vecchio F, Colagrande C (1985) Xanthogranulomatous cholecystitis: echographic and CT patterns. Rays 10:63–67

Dixit VK, Prakash A, Gupta A, Pandey M, Gautam A, Kumar M, Shukla VK (1998) Xanthogranulomatous cholecystitis. Dig Dis Sci 43:940–942

Duarte Z, Guevara U, Vuong PN (1994) Ceroid granulomas of the gallbladder. A clinicopathologic study of nine cases. Arch Anat Cytol Pathol 42:5–9

Düber C, Störkel S, Wagner PK, Müller J (1984) Xanthogranulomatous cholecystitis mimicking carcinoma of the gallbladder: CT findings. J Comput Assist Tomogr 8:1195–1198

Enomoto T, Todoroki T, Koike N, Kawamoto T, Matsumoto H (2003) Xanthogranulomatous cholecystitis mimicking stage IV gallbladder cancer. Hepatogastroenterology 50:1255–1258

Eriguchi N, Aoyagi S, Tamae T, Kanazawa N, Nagashima J, Nishimura K, Hamada S et al (2001) Xanthogranulomatous cholecystitis. Kurume Med J 48:219–221

Eriguchi N, Aoyagi S, Horiguchi H, Tamae T, Uchida S, Hiraki M, Nishimura K, Kawabata M et al (2002) Xanthogranulomatous cholecystitis with a liver abscess and metastatic endophthalmitis: report of a case. Surg Today 32:285–288

Fligiel S, Lewin KJ (1982) Xanthogranulomatous cholecystitis: case report and review of the literature. Arch Pathol Lab Med 106:302–304

Fogt F, Zimmerman RL, Buyske J (1998) Inflammatory fibroid polyp of the gallbladder. Histopathology 33:583–584

Franco V, Aragona F, Genova G, Florena AM, Stella M, Campesi G (1990) Xanthogranulomatous cholecystitis. Histopathological study and classification. Pathol Res Pract 186:383–390

Friedman C, Poster H (1955) Emphysematous cholecystitis. NY State J Med 55:1720–1723

Fu CK, Hsieh TY, Chan DC, Lee HS, Huang TY (2012) Xanthogranulomatous cholecystitis presenting with duodenal ulcer and cholecystoenteric fistula. Endoscopy 44(Suppl 2):E213–E214

Furukawa H, Takayasu K, Mukai K, Inoue K, Kyokane T, Shimada K, Kosuge T, Ushio K (1995) CT evaluation of small polypoid lesions of the gallbladder. Hepatogastroenterology 42:800–810

Gal R, Kolkov Z, Beitner S, Kessler E (1984) Xanthogranulomatous cholecystitis containing ceroid. Arch Pathol Lab Med 108:774–775

Garcia-Sancho Tellez L, Rodriguez-Montes JA, Fernandez de Lis S, Garcia-Sancho Martin L (1999) Acute emphysematous cholecystitis. Report of twenty cases. Hepatogastroenterology 46:2144–2148

Gerritsen GP (1986) Emphysematous cholecystitis. Int Surg 71:115–116

Ghosh M, Sakhuja P, Agarwal AK (2011) Xanthogranulomatous cholecystitis: a premalignant condition? Hepatobiliary Pancreat Dis Int 10:179–184

Goldgraber MB, Kirsner JB (1960) Chronic granulomatous cholecystitis and chronic fibrosing choledochitis associated with chronic ulcerative colitis. A case report. Gastroenterology 38:821–828

Goodman L (1979) Emphysematous cholecystitis. Md State Med J 28:64–66

Goodman ZD, Ishak KG (1981) Xanthogranulomatous cholecystitis. Am J Surg Pathol 5:653–659

Goshima S, Chang S, Wang JH, Kanematsu M, Bae KT, Federle MP (2010) Xanthogranulomatous cholecystitis: diagnostic performance of CT to differentiate from gallbladder cancer. Eur J Radiol 74:e79–e83

Goudet P, Hagemann B, Cercueil JP, Becker F, Bernard A, Tatou E, Cougard P, Viard H (1995) Gallbladder pneumatosis. An ultrasonic pitfall (in French). Ann Chir 49:187

Guarino M, Reale D, Micoli G, Tricomi P, Cristofori E (1993) Xanthogranulomatous gastritis: association with xanthogranulomatous cholecystitis. J Clin Pathol 46:88–90

Guzman-Valdivia G (2004) Xanthogranulomatous cholecystitis: 15 years' experience. World J Surg 28:254–257

Hale et al. (2014). http://www.ncbi.nlm.nih.gov/pubmed/23991684

Hallgrimmsson P, Skaane P (1988) Hypoechoic solitary inflammatory polyp of the gallbladder. J Clin Ultrasound 16:603–604

Han SH, Chen YL (2012) Diagnosis and treatment of xanthogranulomatous cholecystitis: a report of 39 cases. Cell Biochem Biophys 64:131–135

Hanada K, Nakata H, Nakayama T, Tsukamoto Y, Terashima H, Kuroda Y, Okuma R et al (1987) Radiologic findings in xanthogranulomatous cholecystitis. AJR Am J Roentgenol 148:727–730

Harley WD, Kirkpatrick RH, Ferrucci JT (1978) Gas in the bile ducts (pneumobilia) in emphysematous cholecystitis. AJR Am J Roentgenol 131:661–663

Heifetz CJ, Senturia HR (1948) Acute pneumocholecystitis. Surg Gynecol Obstet 86:424–433

Herzog K, Goldblum JR (1996) Gallbladder adenocarcinoma and acalculous chronic lymphoplasmacytic cholecystitis associated with ulcerative colitis. Mod Pathol 9:194–198

Hijoka S, Mekky MA, Bhatia V, Sawaki A, Mizuno N, Hara K, Hosoda W, Shimizu Y et al (2010) Can EUS-guided FNA distinguish between gallbladder cancer and xanthogranulomatous cholecystitis? Gastrointest Endosc 72:622–627

Hino K, Saito I, Ohumi T, Omoto K, Ideguchi S, Yamamoto R, Wada A, Yamamoto S et al (1989) A case of acute emphysematous cholecystitis with infiltration of giant cells and eosinophils in the gallbladder wall (in Japanese). Nihon Shokakibyo gakkai Tasshi 86:265–269

Houston JP, Collins MC, Cameron I, Reed MW, Parsons MA, Roberts KM (1994) Xanthogranulomatous cholecystitis. Br J Surg 81:1030–1032

Howard TJ, Bennion RS, Thompson JE (1991) Xanthogranulomatous cholecystitis: a chronic inflammatory pseudotumor of the gallbladder. Am Surg 57:821–824

Huss S, Wardelmann E, Goltz D, Binot E, Hartmann W, Merkelbach-Bruse S, Büttner R, Schildhaus HU (2012) Activating PDGFRA mutations n inflammatory fibroid polyps occur in exon 12, 14 and 18 and are associated with tumour localization. Histopathology 61:59–68

Ikeda H, Oka T, Imafuku I, Yamada S, Yamada H, Fujiwara K, Hirata M, Idezuki Y, Oka H (1990) A case of inflammatory pseudotumor of the gallbladder and bile duct. Am J Gastroenterol 85:203–206

Ise N, Andoh H, Furuya T, Sato T, Yasui O, Yoshioka M, Iida M, Takahashi T, Kotanagi H et al (2002) Acute emphysematous cholecystitis preceded by symptoms of ileus: report of a case. Surg Today 32:183–185

Ito H, Hann LE, D'Angelica M, Allen P, Fong Y, Dematteo RP, Klimstra DS, Blumgart LH, Jarnagin WR (2009) Polypoid lesions of the gallbladder: diagnosis and follow-up. J Am Coll Surg 208:570–575

Jain D, Das A, Gupta V, Gulati M (2005) Inflammatory pseudotumor of gall bladder fossa of liver. Indian J Gastroenterol 24:79–80

Jain S, Saluja SS, Sharma AK, Sant H, Mishra PK (2012) Xanthogranulomatous cholecystitis: catching the culprit – clinical and imaging analysis. Dig Surg 29:187–193

Jessurun J, Bolio-Solis A, Manivel JC (1998) Diffuse lymphoplasmacytic acalculous cholecystitis: a distinctive form of chronic cholecystitis associated with primary sclerosing cholangitis. Hum Pathol 29:512–517

Johnson H, Sloane RE, Perlman DM (1984) Pneumobilia as the sole radiographic finding in emphysematous cholecystitis. J Ultrasound Med 3:R29

Jorgensen T, Jensen KH (1990) Polyps in the gallbladder. A prevalence study. Scand J Gastroenterol 25:281–286

Juliano J, Wilson KD, Gertner E (2009) Vasculitis of the gallbladder: case report and spectrum of disease. J Clin Rheumatol 15:75–77

Kamisawa T, Tu Y, Nakajima H, Egawa N, Tsuruta K, Okamoto A, Horiguchi S (2006) Sclerosing cholecystitis associated with autoimmune pancreatitis. World J Gastroenterol 12:3736–3739

Kansakar PB, Rodrigues G, Khan SA (2008) Xanthogranulomatous cholecystitis: a clinicopathological study from a tertiary care health institution. Kathmandu Univ Med J 6:472–475

Kawakami H, Eto K, Kuwatani M, Asaka M (2010) Localized lymphoplasmacytic sclerosing cholecystitis in a patient with autoimmune pancreatitis. Intern Med 49:2359–2360

Kazantsev IA, Lishchuk SV (2011) IgG4-related sclerosing disease (in Russian). Arkh Patol 73:40–43

Kim PN, Ha HK, Kim YH, Lee MG, Kim MH, Auh YH (1998) US findings of xanthogranulomatous cholecystitis. Clin Radiol 53:290–292

Kim PN, Lee SH, Gong GY, Kim JG, Ha HK, Lee YJ, Lee MG, Auh YH (1999) Xanthogranulomatous cholecystitis: radiologic findings with histologic correlation that focuses on intramural nodules. AJR Am J Roentgenol 172:949–953

Kim DH, Kim SR, Song SY, Lee JK, Heo J, Kim SH (2003) A large fibrous polyp of the gallbladder mimicking a polypoid carcinoma. J Gastrointest 38:1009–1012

Kim SH, Kim HY, Jung SE, Park KW, Choi YH, Kim WS, Park SH (2013) Xanthogranulomatous cholecystitis in 2-month-old infant. J Korean Surg Soc 85:191–194

Koga A, Watanabe K, Fukuyama T, Takiguchi S, Nakayama F (1988) Diagnosis and operative indications for polypoid lesions of the gallbladder. Arch Surg 123:26–29

Konno K, Ishida H, Naganuma H, Sato M, Komatsuda T, Sato A, Ishida J, Sakai T et al (2002) Emphysematous cholecystitis: sonographic findings. Abdom Imaging 27:191–195

Krstic M, Alempijevic T, Stimec B, Micev M, Milicevic M, Micic D, Jankovic G (2007) Gallbladder villous adenoma in a patient with acromegaly: a case report. World J Gastroenterol 13:3144–3146

Kubota K, Bandai Y, Noie T, Ishizaki Y, Teruya M, Makuuchi M (1995) How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? Surgery 177:481–487

Kumar B, Krishnani N, Misra R, Pandey R (2003) Isolated necrotizing vasculitis of gallbladder: a report of two cases and review of literature. Indian J Pathol Microbiol 46:429–431

Kurguzov OP, Godzhello MA, Kurguzova DO (2012). The acute emphysematous cholecystitis (in Russian). Khirurgiia (Mosk.) (3): 77–83

Kurimoto M, Fukuda I, Hizuka N, Takano K (2008) The prevalence of benign and malignant tumors in patients with acromegaly at a single institute. Endocr J 55:67–71

Kwon AH, Sakaida N (2007) Simultaneous presence of xanthogranulomatous cholecystitis and gallbladder cancer. J Gastroenterol 42:703–704

Kwon TK, Jeon SH, Park HW, Jung WJ, Hwang JY, Park KS, Cho KB, Hwang JS, Ahn SH et al (2002) A case of intraluminal gallbladder hematoma after percutaneous liver biopsy (in Korean). Taehan Kan Hakhoe Chi 8:486–489

Kwon W, Jang JY, Lee SE, Hwang DW, Kim SW (2009) Clinicopathologic features of polypoid lesions of the gallbladder and risk factors of gallbladder cancer. J Korean Med Sci 24:481–487

Kyokane T, Akita Y, Katayama M, Kitagawa Y, Shichino S, Sato T (1994) A case of inflammatory polyp of the gallbladder with was difficult to differentiate from cancer (in Japanese). Nihon Shokakibyo Gakkai Zasshi 91:1062–1066

Ladefoged C, Lorentzen M (1993) Xanthogranulomatous cholecystitis. A clinicopathological study of 20 cases and review of the literature. APMIS 101:869–875

Lallemand B, De Keuleneer R, Maassarani F (2003) Emphysematous cholecystitis. Acta Chir Belg 103:230–232

Lasser A, Ghofrany S (1976) Necrotizing granulomatous vasculitis (allergic granulomatosis) of the gallbladder. Gastroenterology 71:660–662

Lee HS, Joo KR, Kim DH, Park NH, Jeong YK, Suh JH, Nam CW (2003) A case of simultaneous xanthogranulomatous cholecystitis and carcinoma of the gallbladder. Korean J Intern Med 18:53–56

Lee KF, Wong J, Li JC, Lai PB (2004) Polypoid lesions of the gallbladder. Am J Surg 188:186–190

Lee YS, Lee SH, Lee MG, Lee SJ, Hwang JH, Shin E, Lee YJ (2013) Immunoglobulin G4-related disease mimicking unresectable gallbladder cancer. Gut Liver 7:616–620

Leise MD, Smyrk TC, Takahashi N, Sweetser SR, Vege SS, Chari ST (2011) IgG4-associated cholecystitis: another clue in the diagnosis of autoimmune pancreatitis. Dig Dis Sci 56:1290–1294

Lemmens HA, Louyest J (1969) Gas gangrene of the gallbladder or gangrenous pneumocholecystitis. Arch Chir Neerl 21:332–342

Lewis JT, Talwalkar JA, Rosen CB, Smyrk TC, Abraham SC (2007) Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. Am J Surg Pathol 31:907–913

Liao CM, Watanabe H, Itoi T, Matsubayashi H (1996) Granulation polyp of the gallbladder, inflammation of the Rokitansky-Aschoff sinus (in Japanese). Ryoikibetsu Shokogun Shirizu 9:321–323

Lin CL, Chang JJ, Lee TS, Lui KW, Yen CL (2005) Gallbladder polyp as a manifestation of hemobilia caused by arterial-portal fistula after percutaneous liver biopsy: a case report. World J Gastroenterol 11:305–307

Liu TC, Lin MT, Montgomery EA, Singhi AD (2013) Inflammatory fibroid polyps of the gastrointestinal tract: spectrum of clinical, morphologic, and immunohistochemistry features. Am J Surg Pathol 37: 586–592

Lloyd-Davies RW, Forbes GB (1965) Sarcoidosis of the gall bladder. Gastroenterology 49:287–290

Lopez JI, Elizalde JM, Calvo MA (1991) Xanthogranulomatous cholecystitis associated with gallbladder adenocarcinoma. A clinicopathological study of 5 cases. Tumori 77:358–360

Lorenz RW, Steffen HM (1990) Emphysematous cholecystitis: diagnostic problems and differential diagnosis of gallbladder gas accumulations. Hepatogastroenterology 37(Suppl 2):103–106

Maeda T, Shimada M, Matsumata T, Adachi E, Taketomi A, Tashiro Y, Tsuneyoshi M et al (1994) Xanthogranulomatous cholecystitis masquerading as gallbladder carcinoma. Am J Gastroenterol 89:628–630

Maeyama R, Yamaguchi K, Noshiro H, Takashima M, Chijiwa K, Tanaka M (1998) A large inflammatory polyp of the gallbladder masquerading as gallbladder carcinoma. J Gastroenterol 33:770–774

Mahlobo TT, Grieve A, Loveland JA (2012) Pediatric multifocal myofibroblastic tumors with involvement of the gallbladder: HIV-and Epstein-Barr virus-associated smooth muscle cell tumors. J Pediatr Surg 47:e1–e14

Majeski JA (1986) Polyps of the gallbladder. J Surg Oncol 32:16–18

Maker AV, Maker VK (2012) Malignant masquerade of xanthogranulomatous cholecystitis on intraoperative ultrasound of the liver. J Surg Oncol 106:525–526

Makino I, Yamaguchi T, Sato N, Yasui T, Kita I (2009) Xanthogranulomatous cholecystitis mimicking gallbladder carcinoma with a false-positive result on fluorodeoxyglucose PET. World J Gastroenterol 15:3691–3693

Martini M, Santoro L, Familiari P, Costamagna G, Ricci R (2013) Inflammatory fibroid polyp of the gallbladder bearing a platelet-derived growth factor receptor alpha mutation. Arch Pathol Lab Med 137:721–724

Martins PN, Sheiner P, Facciuto M (2012) Xanthogranulomatous cholecystitis mimicking gallbladder cancer and causing obstructive cholestasis. Hepatobiliary Pancreat Dis Int 11:549–552

McClure J, Banerjee SS, Schofield PS (1984) Crohn's disease of the gall bladder. J Clin Pathol 37:526–518

McMillin K (1985) Computed tomography of emphysematous cholecystitis. J Comput Assist Tomogr 9:330–332

Mehrotra ML, Bhatnagar BNS (1982) Biliary granulomatous cholecystitis. J Indian Med Assoc 79:144–145

Mentzer RM, Golden GT, Chandler JG, Horsley JS (1975) A comparative appraisal of emphysematous cholecystitis. Am J Surg 129:10–15

Mert A, Avsar S, Ozaras R, Bilir M, Yemisen M, Erturan S, Pekmezci S, Ozbay G (2004) Gall bladder involvement in sarcoidosis. J Clin Gastroenterol 38:612–613

Moanna A, Bajaj R, del Rio C (2006) Emphysematous cholecystitis due to Salmonella derby. Lancet Infect Dis 6:118–120

Modini C, Clementi I, Simonelli L, Antoniozzi A, Assenza M, Ciccarone F, Bartolucci P et al (2008) Acute emphysematous cholecystitis as a cause of pneumoperitoneum. Chir Ital 60:315–318

Morales-Fuentes GA, de Ariño-Suarez M, Zarate-Osomo A, Rodriguez-Jerkov J, Terrazas-Espitia F et al (2011) Vanek's polyp or inflammatory fibroid polyp. Case report and review of the literature. Cir Cir 79:242–245

Mori A, Doi R, Yonenaga Y, Nakabo S, Yazumi S, Nakaya J, Kono F, Manabe T, Uemoto S (2010) Xanthogranulomatous cholecystitis complicated with primary sclerosing cholangitis: report of a case. Surg Today 40:777–782

Morizumi H, Sano T, Hirose T, Hizawa K (1988) Neurofibroma of the gallbladder seen as a papillary polyp. Acta Pathol Jpm 38:259–268

Mourra N, Bell S, Parc R, Fléjou JF (2004) Calcifying fibrous pseudotumour: fist case report in the gallbladder. Histopathology 44:84–86

Mssrouri R, Soufi M, Settaf A, Chad B (2011) Inflammatory pseudotumour of the gallbladder (in French). Rev Prat 61:610

Muduly D, Deo SV, Shukla NK, Manjunath NM, Durgapal P, Kallianpur A (2012) Inflammatory myofibroblastic tumor of gall bladder. Trop Gastroenterol 33:297–299

Myers RP, Shaffer EA, Beck PL (2002) Gallbladder polyps: epidemiology, natural history and management. Can J Gastroenterol 16:187–194

Nakashiro H, Haraoka S, Fujiwara K, Harada S, Hisatsugu T, Watanabe T (1995) Xanthogranulomatous cholecystitis. Cell composition and a possible pathogenetic role of cell-mediated immunity. Pathol Res Pract 191:1078–1086

Nemcek AA, Gore RM, Vogelzang RL, Grant M (1988) The effervescent gallbladder: a sonographic sign of emphysematous cholecystitis. AJR Am J Roentgenol 150:575–577

Ohtani Y, Tanaka Y, Tsukui M, Goto K, Moriya H, Tobita K, Sekka T, Saito Y, Makuuchi H et al (1996) Acute emphysematous cholecystitis associated with pneumobilia: a case report. Tokai J Exp Clin Med 21:33–36

Owen CC, Bilhartz LE (2003) Gallbladder polyps, cholesterolosis, adenomyomatosis, and acute acalculous cholecystitis. Semin Gastrointest Dis 14:178–188

Ozsan I, Ozsoy M, Sahin E, Ortaç R, Aydin U (2013) Inflammatory myofibroblastic tumor of the gallbladder. Balk Med J 30:323–326

Papavramidis TS, Michalopoulos A, Papadopoulos VN, Paramythiotis D, Karadimou V et al (2008) Emphysematous cholecystitis: a case report. Cases J 1:73

Parra JA, Acinas O, Bueno J, Güezmes A, Fernandez MA, Farinas MC (2000) Xanthogranulomatous cholecystitis : clinical, sonographic, and CT findings in 26 patients. AJR Am J Roentgenol 174:979–983

Parsons MA, Harris SC, Grainger RG, Ross B, Smith JAR, Williams JL (1986) Fistula and sinus formation in xanthogranulomatous cholecystitis. Br J Urol 58:488–493

Pinocy J, Lange A, König C, Kaiserling E, Becker HD, Kröber SM (2003) Xanthogranulomatous cholecystitis resembling carcinoma with extensive tumorous infiltration of the liver and colon. Langenbecks Arch Surg 388:48–51

Psarras K, Baltatzis ME, Symeonidis N, Pavlidis ET, Miha A, Pavlidis TE, Sakantamis AK (2012) A severe case of xanthogranulomatous cholecystitis along with a review of CT indications for nonoperative management including percutaneous drainage. Surg Laparosc Endosc Percutan Tech 22:e42–e44

Rammohan A, Srinivasan UP, Jeswanth S, Ravichandran P (2012) Inflammatory pseudotumour secondary to spilled intra-abdominal gallstones. Int J Surg Case Rep 3:305–307

Rao RV, Kumar A, Sikora SS, Saxena R, Kapoor VK (2005) Xanthogranulomatous cholecystitis: differentiation from associated gall bladder carcinoma. Trop Gastroenterol 26:31–33

Rastogi A, Singh DK, Sakhuja P, Gondal R (2010) Florid xanthogranulomatous cholecystitis masquerading as invasive gallbladder cancer leading to extensive surgical resection. Indian J Pathol Microbiol 53:144–147

Rettally CA, Trevino HH, Molina K, Kane SV (2003) Crohn's disease involving the gallbladder. Case report and review of the literature. Am J Gastroenterol 98:509–511

Reyes CV, Jablokow VR, Reid R (1981) Xanthogranulomatous cholecystitis : report of seven cases. Am Surg 47:322–325

Roa I, de Aretxabala X, Morgan R, Molina R, Araya JC, Roa J, Ibacahe G (2004) Clinicopathological features of gallbladder polyps and adenomas (in Spanish). Rev Med Chil 132:673–679

Roberts KM, Parsons MA (1987) Xanthogranulomatous cholecystitis: clinicopathological study of 13 cases. J Clin Pathol 40:412–417

Roels K, Bogaert J, Van Hoe L, Vanbeckevoort D, Delvaux S (1999) Xanthogranulomatous cholecystitis associated with a xanthogranulomatous pseudotumor on the left diaphragm. Eur Radiol 9:1139–1141

Ros PR, Goodman ZD (1997) Xanthogranulomatous cholecystitis versus gallbladder carcinoma. Radiology 203:10–12

Sadamoto Y, Oda S, Tanaka M, Harada N, Kubo H, Eguchi T, Nawata H (2002) A useful approach to the differential diagnosis of small polypoid lesions of the gallbladder, utilizing an endoscopic ultrasound scoring system. Endoscopy 34:959–965

Safioleas M, Stamatakos MK, Mouzopoulos GJ, Tziorzis G, Chagiconstantinu K, Revenas K (2006) Emphysematous cholecystitis. Review of five cases and report of septic musculoskeletal complications. Chirurgia (Bucur) 101:61–64

Said K, Glaumann H, Bergquist A (2008) Gallbladder disease in patients with primary sclerosing cholangitis. J Hepatol 48:598–605

Sandhu SK, Choy G (2013) Vasculitis of the gallbladder in early rheumatoid arthritis. BMJ Case Rep. doi:10.1136/bcr-2012-008228

Sasatomi E, Miyazaki K, Mori M, Satoh T, Nakano S, Tokunaga O (1997) Polypoid adenomyoma of the gallbladder. J Gastroenterol 32:704–707

Sawada S, Harada K, Isse K, Sato Y, Sasaki M, Kaizaki Y, Nakanuma Y (2007) Involvement of *Escherichia coli* in pathogenesis of xanthogranulomatous cholecystitis with scavenger receptor class A and CXCL16-CXCR6 interaction. Pathol Int 57:652–663

Sawada S, Shimada Y, Sekine S, Shibuya K, Yoshioka I, Matsui K, Okumura T, Yoshida T et al (2013) Expression of GLUT-1 and GLUT-3 in xanthogranulomatous cholecystitis induced a positive result on (18) F-FDG PET : report of a case. Int Surg 98:372–378

Schildhaus HU, Büttner R, Binot E, Merkelbach-Bruse S, Wardelmann E (2009) Inflammatory fibroid polyps are true neoplasms with PDGFRA mutations (in German). Pathologe 30(Suppl 2):117–120

Segawa K, Arisawa T, Niwa Y, Suzuki T, Tsukamoto Y, Goto H, Hamajima E, Shimodaira M, Ohmiya N (1992) Prevalence of gallbladder polyps among apparently healthy Japanese : ultrasonographic study. Am Gastroenterol 87:630–633

Sharma D, Babu R, Sood G, Kapoor G, Solanki RS, Thomas S (2009) Xanthogranulomatous cholecystitis masquerading as malignancy with liver metastasis. ANZ J Surg 79:946–947

Shetty GS, Abbey P, Prabhu SM, Narula MK, Anand R (2012) Xanthogranulomatous cholecystitis: sonographic and CT features and differentiation from gallbladder carcinoma: a pictorial essay. Jpn J Radiol 30:480–485

Shou CC, Chen ZH, Li XD, Wang X, Zhou XR (1987) Benign tumor and pseudotumor of the gallbladder – report of 40 patients (in Chinese). Zhonghua Zhong Liu Za Zhi 9:454–456

Singal R, Gupta S, Pande P, Singh B, Mittal A, Naredi B, Kenwar DB (2011) Xanthogranulomatous cholecystitis: case series in a rural area, clinicopathological study and review of literature. Acta Gastroenterol Latinoam 41:331–334

Singh UR, Agarwal S, Misra K (1989) Histopathological study of xanthogranulomatous cholecystitis. Indian J Med Res 90:285–288

Spinelli A, Schumacher G, Pascher A, Lopez-Hanninen E, Al-Abadi H, Benckert C et al (2006) Extended surgical resection for xanthogranulomatous cholecystitis mimicking advanced gallbladder carcinoma : a case report and review of the literature. World J Gastroenterol 12:2293–2296

Sugiyama M, Xie XY, Atomi Y, Saito M (1999) Differential diagnosis of small polypoid lesions of the gallbladder: the value of endoscopic ultrasonography. Ann Surg 229:498–504

Sun XJ, Shi JS, Han Y, Wang JS, Ren H (2004) Diagnosis and treatment of polypoid lesions of the gallbladder: report of 194 cases. Hepatobiliary Pancreat Dis Int 3:591–594

Susumu S, Matsuo S, Tsutsumi R, Azuma T, Obata S, Hayashi T (2009) Inflammatory polyp of the gallbladder mimicking early polypoid carcinoma. Case Rep Gastroenterol 3:255–259

Takada M, Horita Y, Okuda S, Okumoto S, Samizo M, Wada T, Kuroda Y, Maeda S (2002) Genetic analysis of xanthogranulomatous cholecystitis: precancerous lesion of gallbladder cancer ? Hepatogastroenterology 49:935–937

Takahashi K, Oka K, Hakozaki H, Kojima M (1976) Ceroid-like histiocytic granuloma of gall bladder. Acta Pathol Jpn 26:25–46

Tanaka S, Kubota D, Oba K, Lee SH, Yamamoto T, Uenishi T, Tanaka H, Kubo S et al (2007) Gallbladder torsion-induced emphysematous cholecystitis in a 16-year-old boy. J Hepatobiliary Pancreat Surg 14:608–610

Terada T (2013) Histopathologic features and frequency of gall bladder lesions in consecutive 540 cholecystectomies. Int J Clin Exp Pathol 6:91–96

Terzi C, Sökmen S, Seckin S, Albayrak L, Ugurlu M (2000) Polypoid lesions of the gallbladder: report of 100 case with special reference to operative indications. Surgery 127:622–627

Uchiyama K, Ozawa S, Ueno M, Hayami S, Hirono S, Ina S, Kawai M, Tani M, Yamaue H (2009) Xanthogranulomatous cholecystitis: the use of preoperative CT findings to differentiate it from

gallbladder carcinoma. J Hepatobiliary Pancreat Surg 16:33–338

Ueda J, Yoshida H, Arima Y, Mamada Y, Taniai N, Mineta S, Yoshioka M, Kawano Y, Naito Z, Uchida E (2011) A case of xanthogranulomatous cholecystitis preoperatively diagnosed with contrast-enhanced ultrasonography. J Nippon Med Sch 78:194–198

Uesaka K, Seima Y, Tokura M, Shimada Y (2009) A case of emphysematous cholecystitis with cholecystic arterial thrombosis and gallbladder infarction (in Japanese). Nihon Shokakibyo Gakkai Zasshi 106:222–227

Verbeeck N, Hartmann KM, Weber J, Martin M (2011) Exceptional, potentially fatal combination of emphysematous pancreatitis and gas-forming cholecystitis: successful multidisciplinary conservative treatment supported by repeated CT-staging. JBR-BTR 94:71–74

Vergara-Fernandez O, Zeron-Medina J, Mendez-Probst C, Salgado-Nesme N, Borja-Cacho D et al (2009) Acute abdominal pain in patients with systemic lupus erythematosus. J Gastrointest Surg 13:1351–1357

Wang M, Zhang T, Zang L, Lu A, Mao Z, Li J, Dong F, Hu W, Jiang Y, Zheng M (2009a) Surgical treatment for xanthogranulomatous cholecystitis: a report of 74 cases. Surg Laparosc Endosc Percutan Tech 19:231–233

Wang WL, Farris AB, Lauwers GY, Deshpande V (2009b) Autoimmune pancreatitis-related cholecystitis: a morphologically and immunologically distinctive form of lymphoplasmacytic sclerosing cholecystitis. Histopathology 54:829–836

Wu AJ, Li YQ, Du LA (2003) Relationship between cholecystolithiasis and polypoid gallbladder. J Zhejiang Univ Sci 4:620–625

Wu JM, Lee CY, Wu YM (2010) Emphysematous cholecystitis. Am J Surg 200:e53–e54

Yang HL, Sun YG, Wang Z (1992) Polypoid lesions of the gallbladder: diagnosis and indications for surgery. Br J Surg 79:227–229

Yeh CN, Jan YY, Chao TC, Chen MF (2001) Laparoscopic cholecystectomy for polypoid lesions of the gallbladder: a clinicopathologic study. Surg Laparosc Endosc Percutan Tech 11:176–181

Yoshida J, Chijiiwa K, Shimura H, Yamaguchi K, Kinukawa N, Honda H, Tanaka M (1997) Xanthogranulomatous cholecystitis versus gallbladder cancer: clinical differentiating factors. Am Surg 63:367–371

Zhang XH (1991) Polypoid lesions of the gallbladder. Clinical and pathological correlations (in Chinese). Zhonghua Wai Ke Za Zhi 29:211–213

Zhang LF, Hou CS, Liu JY, Xiu DR, Xu Z, Wang LX, Ling XF (2012) Strategies for diagnosis of xanthogranulomatous cholecystitis masquerading as gallbladder cancer. Chin Med J (Engl) 125:109–113

Zhao F, Lu PX, Yan SX, Wang GF, Yuan J, Zhang SZ, Wang YX (2013) CT and MR features of xanthogranulomatous cholecystitis: an analysis of consecutive 49 cases. Eur J Radiol 82:1391–1397

Zielinski MD, Atwell TD, Davis PW, Kendrick ML, Que FG (2009) Comparison of surgically resected polypoid lesions of the gallbladder to their pre-operative ultrasound characteristics. J Gastrointest Surg 13:19–25

Noninflammatory Tumor-Like Changes of the Gallbladder

159

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_159

Abstract

The gallbladder can be subject to an entire spectrum of noninflammatory tumor-like changes. A typical example is cholesterolosis of the gallbladder, defined by a mucosal lesion characterized by accumulation of cholesteryl esters and triglycerides in foamy macrophages. Multiple mucosal yellowish to white lesions produce a macroscopically striking lesion termed strawberry gallbladder. Large accumulations of foamy cells give rise to cholesterol polyps that may protrude into the gallbladder lumen and mimic a neoplastic polyp. These polyps may undergo ulceration followed by secondary inflammatory changes. The adipose tissue situated around the gallbladder can undergo steatonecrosis followed by formation of numerous lipogranulomas. The gallbladder is rarely involved with malakoplakia, a reactive lesion more commonly occurring in the urogenital tract. Gallbladder malakoplakia presents in the form of yellowish plaques or nodules and histologically consists of large macrophages with distinct calcifications, the Michaelis-Gutmann bodies. The gallbladder is the site of endometriosis, endometrioma, several types of metaplasia, and tissue ectopias, whereby misplaced pancreatic tissue is the most common variant.

Cholesterolosis of the Gallbladder

Introduction

Cholesterolosis (synonyms: cholesterosis, cholesterinosis) is defined by a mucosal lesion of the gallbladder characterized by accumulation of cholesteryl esters and triglycerides in macrophages, which show the morphology of foam cells. Cholesterolosis was first described by Rudolf Virchow in 1857 (Virchow 1857). Typically, cholesterolosis displays a multifocal mucosal distribution, with multiple yellowish and sharply delineated foci distributed on the dark red-green background of the mucosa, a phenotype which somewhat resembles the morphology of the skin of a strawberry ("strawberry gallbladder"). Cholesterolosis can, however, produce endophytic lesions manifest as polyps, lesions that may radiologically mimic true gallbladder tumors.

Selected References: MacCarty 1919; Judd and Mentzer 1927a; Mackay 1937; Arnell 1941; Lewis and Peterson 1943; Womack and Haffner 1944; Mitty and Rousselot 1957; Reid 1962; Salmenkivi 1964; Heino and Ritama 1965; Andersson and Bergdahl 1971; Jacyna and Bouchier 1987; Csendes et al. 1998; Izzo et al. 2001; Owen and Bilhartz 2003.

Epidemiology

Cholesterolosis of the gallbladder is a common lesion. In a study of 633 consecutive necropsies, 134 strawberry gallbladders (diffuse cholesterolosis), 61 polypous forms, and 29 combined forms were found. None of the persons was under 15 years, and only three were under 20 years of age (Mentzer 1925). In a study of 1,000 surgical cases of cholesterolosis of the gallbladder, 26 % of the stone-free and 82 % of the gallstone cases occurred in females. The age incidence in the two groups was essentially alike, the greatest number of cases in each group occurring between the ages of 35 and 40 years (Judd and Mentzer 1927a). In 1,323 cholecystectomy preparations, cholesterolosis was detected in 15.6 % of cases (Celoria et al. 1994). In a more recent hospital-based retrospective study, 549 patients underwent cholecystectomy and hepatic resection for hepatocellular carcinoma, the prevalence of cholesterolosis of the gallbladder was 6.6 %, and the prevalence of cholesterol polyp of the gallbladder was 0.9 % (Lai 2011).

Among 549 consecutive patients who had cholecystectomies for various gallbladder disorders, 13.4 % had cholesterolosis. Cholesterolosis with coexistent gallstones was documented in 63.3 %, and 85.1 % of the cases were reported to have abnormally high fasting serum cholesterol levels (Khairy et al. 2004). The prevalence of cholesterolosis is higher in obese patients, being 38 % in obese vs. 6 % in nonobese patients in one study (Dittrick et al. 2005) and 37 % in another

(Csendes et al. 2003). In a study of 1,000 cases of gallbladder cholesterolosis, stones were present in half of the specimens, and multiple stones were found in 69 %, 99 % of the stones being cholesterol stones. Cholesterolosis alone, as the typical strawberry gallbladder, was the diagnosis in 53 % of the stone-free group and in 82 % of the stone group, and polypous cholesterolosis was detected in 47 % and 18 %, respectively. Diffuse and local/polypous forms were combined in 34 % of the stone-free and in 10 % of the stone-containing specimens (Judd and Mentzer 1927b).

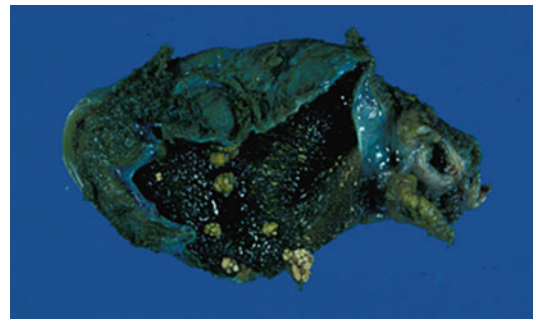

Fig. 1 Cholesterolosis of the gallbladder with cholesterol polyps

Clinical and Imaging Features

Isolated cholesterolosis is clinically silent in most cases. In the era preceding CT and MRI studies, imaging for cholesterolosis using X-ray was associated with a high percentage of errors (Judd and Mentzer 1927b; Damore et al. 2001), although other authors consider ultrasonography as an efficient tool (Price et al. 1982; Sandri et al. 2003). In an ultrasonography study of 853 patients who underwent laparoscopic cholecystectomy, 56 had gallbladder polyps, including cholesterolosis polyps, 75 % of them being smaller than 10 mm. Overall US-based diagnosis of gallbladder polyp was inaccurate in 82 % (Akyürek et al. 2005).

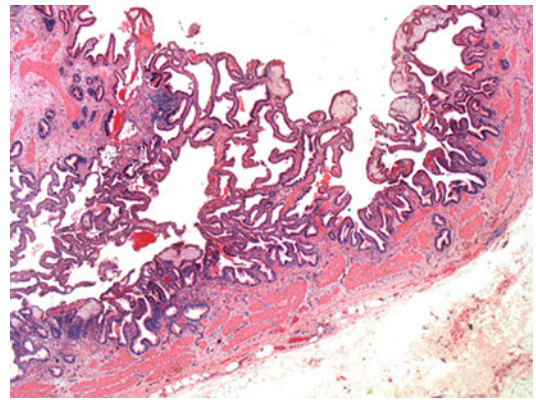

Fig. 2 Cholesterolosis of the gallbladder. Foamy, lipid-rich macrophages have accumulated in the tips of mucosal folds (hematoxylin and eosin stain)

Pathology

Macroscopy

Macroscopically, cholesterolosis of the gallbladder shows small yellowish elevations when the mucosa is inspected in the fresh specimen (Fig. 1). These elevations form circumscribed lesions or coalesce to form short bar-like or hook-like structures or an incomplete network reflecting the fine mucosal fold pattern of the gallbladder (Cooke 1931; Lewis and Peterson 1943; Feldman and Feldman 1954). The lesions, which occupy the tips of mucosal ridges, are 1 mm in diameter or less. Seventy-eight percent of cases showed grossly visible fatty changes (cholecystosteatosis) in the wall of the gallbladder (Judd and Mentzer 1927a).

Histopathology

The histology of gallbladder cholesterolosis has been studied in detail (Guerra et al. 1963). The lamina propria of the mucosa and in particular the tips of the delicate mucosal folds are densely infiltrated by large and clear, markedly vacuolated macrophages (foamy cells, Figs. 2 and 3). Cholesterolosis is often associated with papillary epithelial hyperplasia of the gallbladder (Elfving et al. 1968; Celoria et al. 1994) and sometimes with adenomyosis (Helpap and Huegel 1988). The foamy macrophage accumulations can develop regressive changes, associated with release of cholesteryl esters into the extracellular

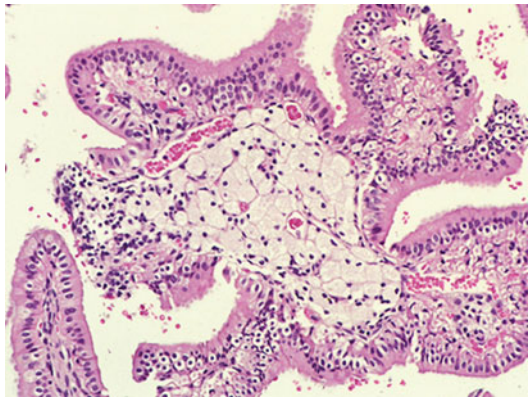

Fig. 3 Cholesterolosis of the gallbladder at higher magnification (hematoxylin and eosin stain)

space, an inflammatory response of the foreign-body type, and formation of cholesterol crystals and cholesterol granulomas, with foreign-body giant cells apposed to crystals (Womack and Haffner 1944). In old lesions, collections of cholesterol granulomas, sometimes in band-like formations, may be noted in deep layers of the gallbladder, in part of the cases associated with formation of lymph follicles and germinal centers. This process can induce mucosal ulceration, granulation tissue, and scarring, sometimes followed by inspissated bile depositions and dystrophic calcifications of the gallbladder wall (Womack and Haffner 1944). Exceptionally, osseous metaplasia can develop in such lesions (Ortiz-Hildalgo and Baquera-Heredia 2000). Released cholesterol and its esters may be transported to locoregional lymph nodes, where they can form "metastatic" cholesterol granulomas in the subcapsular sinus (Womack and Haffner 1944). Rarely, cholesterolosis has been found in association with carcinoma in situ (Akiyama et al. 1996).

Electron Microscopic Findings

Cholesteryl ester-laden macrophages in cholesterolosis show numerous protruded processes, which also contain organelles, lipid droplets, and abundant lysosomes. In foam cells, the cytoplasm is filled with large lipid droplets containing cholesteryl esters. Adjacent epithelial cells also show ultrastructural signs of high cholesterol content, with small lipid droplets and a well-developed agranular endoplasmic reticulum (Nevalainen and Laitio 1972; Koga 1985; Satoh and Koga 1997). Epithelial cells of the cystic duct in cholesterolosis of the gallbladder showed mucous secretory granules that appear dilated, and peculiar intracellular cholesterol deposits are detectable in the apical and subapical region of cells and around condensed mitochondria (Gilloteaux et al. 1997), suggesting that the cystic duct mucosa may participate in cholesterolosis of precursor lesions of this condition.

Tumor-Like Cholesterol Polyps of the Gallbladder

In clinico-radiologic work-ups, tumorous lesions of the gallbladder larger than 10 mm have a high incidence of malignancy. In rare instances, cholesterol polyps of the gallbladder can grow to sizes exceeding 1 cm, forming large papillary masses with a diameter of up to 3 cm and thus mimicking gallbladder cancer (Kaido et al. 2004).

Pathogenesis

Cholesterolosis of the gallbladder is considered to be multifactorial, and first ideas about pathogenic pathways date back to more than 50 years (Graham and Elman 1932). As part of investigations documented a correlation between high serum cholesterol levels and the prevalence of cholesterolosis of the gallbladder (Khairy et al. 2004), excess of cholesterol production was regarded as a pathogenic factor. However, in a study on 446 patients with cholesterolosis associated with gallstones and 190 patients without stones, cholesterolosis was not associated with high plasma cholesterol levels (Méndez-Sanchez et al. 1997). In patients with cholesterolosis, a positive correlation was obtained between the cholesterol saturation of bile and the content of

esterified cholesterol in the gallbladder mucosa (Sahlin et al. 1995). Free sterols can be transferred from bile to the gallbladder mucosa (Tilvis et al. 1982), where free cholesterol is esterified within cells, mainly mucosal macrophages. Cholesteryl ester accumulation is not caused by reduced efflux of cholesterol due to a defective sterol 27-hyroxylase mechanism (Strömsten et al. 2004). There is evidence that cholesteryl ester synthesis of gallbladder mucosa might play a role in the pathogenesis of cholesterolosis, as the activity of acylCoA-cholesterol ester acyltransferase is increased (Watanabe et al. 1998).

Steatonecrosis, Panniculitis, and Lipogranulomas of the Gallbladder

Severe transmural and specifically fistulating and perforating cholecystitis can induce necrosis and inflammation in the pericholecystic adipose tissue (panniculitis). This process can lead to numerous and in part cystic lipogranulomas, eventually producing a mass effect. Fat necrosis (steatonecrosis, adiponecrosis) of the gallbladder is uncommonly found in patients with acute pancreatitis (Chitkara 1995). It presents as whitish flecks or patches in the subadventitional adipose tissue, identical to the lesions found in peripancreatic adipose tissue. Steatonecrosis of the gallbladder may be marked and associated with direct extension from fat necrosis of the hepatoduodenal ligament, causing an ill-defined mass (Schein et al. 1993). A rare instance of membranous fat necrosis of the gallbladder has been reported (Ohtsuki et al. 2012). Membranous fat necrosis (synonyms: membranocystic change, lipomembranous panniculitis) is usually observed in skin-related diseases but may become a systemic alteration. The tissue contains wavy sudanophilic fluffy membranes that can elicit vigorous foreign-body reactions with giant cells. Gallbladder panniculitis can rarely be a manifestation of the panniculitis disorder, Weber-Christian disease (Ishida et al. 1993).

Cholecystosteatosis (Nonalcoholic Fatty Gallbladder Disease)

Obesity may cause fatty infiltration of multiple internal organs, including liver, heart, kidney, and pancreas, associated with organ and tissue dysfunction. Adipose tissue and tissues having fat overload form a dynamic endocrine organ regulating energy expenditure and adipokine turnover. Obesity is also associated with cholecystosteatosis. Cholecystosteatosis (synonym: nonalcoholic fatty gallbladder disease, NAFGBD) denotes increased fat deposition in the gallbladder wall (review, Pitt 2007). Increased gallbladder tissue lipids comprise free fatty acids, phospholipids, and triglycerides (Goldblatt et al. 2006; Mathur et al. 2008). It has been found that there is a relation between the type of cholecystitis and total gallbladder wall fat. Patients with acalculous and calculous cholecystitis have increased gallbladder fat compared to nondiseased controls, and this increased fat may lead to poor gallbladder emptying and biliary symptoms and signs (Al-Azzawi et al. 2007). Increased lipids enhance inflammatory reactions of the gallbladder (steatocholecystitis) resulting in an abnormal wall structure and decreased contractility (review: Tsai 2009).

Malakoplakia of the Gallbladder

Malakoplakia is a rare and unusual inflammatory process first described in the early 1900s (see the chapter on malakoplakia of the liver). Very few cases of gallbladder malakoplakia have been reported (Hanada et al. 1981; Charpentier et al. 1983; Hide et al. 2001; Agnarsdottir et al. 2004; Di Tommaso et al. 2005; Vaiphei et al. 2012). Gallbladder malakoplakia has been found in association with diabetes mellitus type 2 (Vaiphei et al. 2012). Macroscopically, yellowish plaques or nodules were noted. Histopathologically, accumulation of large macrophages with von Kossa-positive Michaelis-Gutmann bodies, associated with lymphocytic infiltration, is the hallmark. In

hematoxylin and eosin-stained sections, Michaelis-Gutmann bodies appear as targetoid cytoplasmic inclusions, and these bodies are PAS positive with and without diastase treatment and are also positive for the colloidal iron stain.

In the presence of typical targetoid, von Kossa-positive Michaelis-Gutmann bodies, the macrophage-rich lesions can hardly be confounded with other granulomatous inflammatory lesions.

Endometriosis and Endometrioma of the Gallbladder

Introduction

Endometriosis is defined as the presence of functioning endometrial tissue outside the uterine cavity. The prevalence of endometriosis has been estimated to be between 8 % and 18 % in young women. Endometriosis outside the pelvic cavity and ovaries mainly involves the abdominal wall, the gastrointestinal tract, and the urinary tract. Rare locations include muscle tissue, inguinal canal, umbilicus, mediastinum, bronchi, pleura, and even nasal region (nasolacrimal endometriosis). Endometriosis, which is well documented for the liver (see the respective paragraph), very rarely occurs in the gallbladder (Saadat-Gilani et al. 2007; Saldaña et al. 2010; Iafrate et al. 2013). Clinically, gallbladder endometriosis was manifest as chronic and vague or colicky abdominal pain, most severe in the right hypochondrium and accentuated during menstruation, and eventually an upper abdominal mass (Iafrate et al. 2013). The cyclic pain is thought to be caused by intrafocal bleeding during menstruation. Gallbladder endometriosis may be an isolated manifestation of this disorder or may be accompanied by endometriotic nodules situated elsewhere, e.g., the abdominal wall (Iafrate et al. 2013).

Pathology

Macroscopically, endometriotic foci may be situated in any part of the gallbladder but predominate in the fundus. The foci may adhere to the gallbladder surface or form internal nodules. The lesions may grow to macroscopic size and mimic cancer (gallbladder endometrioma; Saldaña et al. 2010). Histopathologically, endometriotic foci show preserved or markedly altered endometrial tissue consisting of endometrial glands in various phases of proliferation or secretion and the typical cellular stroma. Secondary changes mainly comprise fresh and old hemorrhage, with accumulation of hemosiderin-containing macrophages and free hemosiderin granules, necrosis, and fibrosis.

As endometriosis is an estrogen-dependent disease, endometriotic foci express estrogen receptors, a phenomenon which may help in the correct classification of stromal foci in the hepatobiliary tract (review: Burns and Korach 2012). Biologically, active estrogens are available to endometriotic tissue via several mechanisms, specifically aromatase activity. The rapid estrogen effects on endometriotic tissue are mediated by both membrane-associated estrogen receptors alpha and G protein-coupled receptor 30/GPER (Plante et al. 2012; Samartzis et al. 2012). Estrogen receptor-beta levels are more than 100 times higher in endometriosis than in normal endometrial tissue (Bulun et al. 2012). Also the estrogen-regulated genes, GREB1, c-MYC, and cyclin D1, are overexpressed in endometriotic foci (Pellegrini et al. 2012).

Differential Diagnosis

Endometriosis occurs in the liver and can be situated close to the gallbladder. Endometriosis sometimes develops on the undersurface of the diaphragm (Triponez et al. 2010).

Osseous Metaplasia of the Gallbladder

Introduction

Osseous metaplasia (heterotopic bone) denotes a tissue alteration characterized by the development of immature and/or mature bone within

connective tissue of various organs. Osseous metaplasia of the gallbladder wall is an uncommon finding and has mainly been observed in the setting of chronic fibrosing cholecystitis (Indyk and Shipton 1957; Duchini 1967; Yosepovich et al. 2002; Nelson and Kahn 2009; Rege and Vargas 2011).

Pathology

Histologically, one most often notes a delicate network of osteoid trabecules lined by osteoblasts, embedded in a collagenous matrix with or without associated lymphocytic infiltration ("cholecystitis ossificans"). Mature mineralized bone may also develop in part of the cases. Osseous metaplasia sometimes exclusively involves the gallbladder mucosa (Nelson and Kahn 2009). In one patient with cholecystitis and cholelithiais, osseous metaplasia of the gallbladder wall was associated with a fasciitis-like fibroblastoid proliferation containing osteoclast-like giant cells (Rege and Vargas 2011).

Differential Diagnosis

Ossifications occur in part of gallbladder carcinosarcomas (Nakagawa et al. 1996). Impacted calcified gallstones may mimic circumscribed osseous metaplasia.

Pancreatic Ectopia of the Gallbladder

Introduction

Misplaced pancreatic tissue (ectopic pancreas, heterotopic pancreas) can occur in the wall of the gallbladder. This alteration was first described by Poppi in 1916. Since then, numerous descriptions of this clinicopathologic entity have appeared in the literature.

Selected References: Mutschmann 1946; Elfving 1959; Monfreda et al. 1967; Dolan et al. 1974; Qizilbash 1976; Ben-Baruch et al. 1986; Lai and Tompkins 1986; Collard et al. 1989; Jarde et al. 1989; Murakami and Tsutsumi 1989; Jeng et al. 1991; Hadzi-Nikolov et al. 1997; Kondi-Paphiti et al. 1997; Bhana and Chetti 1999; Mboti et al. 2003; Meshikhes et al. 2003; Pilloni et al. 2006; Beltran et al. 2007; Elpek et al. 2007; Neupert et al. 2007; Shiwani and Gosling 2008; Bromberg et al. 2009; Al-Shraim et al. 2010; Cerullo et al. 2011; Gucer et al. 2011; Klimis et al. 2011; Sroczynski et al. 2013.

Instead of pancreatic heterotopia or ectopia, the term pancreatic choristoma of the gallbladder is employed to denote this lesion (Beltran et al. 2007). At least half of the cases are located to the gallbladder neck, which embryologically is more close to the pancreas anlage.

Clinical Features

In the majority of cases, heterotopic pancreatic tissue in the gallbladder is an asymptomatic, incidentally found alteration. In part of patients, the lesion can induce, or be associated with, acute or chronic cholecystitis in part of patients (Bhana and Chetty 1999; Mboti et al. 2003; Elpek et al. 2007; Shiwani and Gosling 2008; Bromberg et al. 2009; Al-Shraim et al. 2010; Klimis et al. 2011; Elhence et al. 2012; Sroczynski et al. 2013). Cholecystitis may be related to obstruction, as it was found in pancreatic heterotopia located to the gallbladder neck (Weppner et al. 2009; Limaiem et al. 2012). The lesion rarely presents with symptoms and signs of pancreatitis, as the ectopic pancreatic tissue can undergo acute inflammation, similar to the orthotopic organ (Qizilbash 1976; Pilloni et al. 2006). Sometimes, pancreatic heterotopia gives rise to a suspicious tumefaction (Collard et al. 1989; Foucault et al. 2012), and in one patient, the heterotopia was associated with hypertrophic ectopic pancreatic ducts mimicking an adenomyoma (Pilloni et al. 2006). One case with malignant change of pancreatic heterotopia of the gallbladder was reported (Jeng et al. 1991). The lesion may be associated with high levels of

amylasuria (Klimis et al. 2011) or may cause an elevation of pancreatic enzymes in gallbladder bile (Sato et al. 2012).

Pathology

Macroscopically, pancreatic heterotopia is usually manifest as a mere thickening of the gallbladder wall, with circumscribed nodules of pancreatic tissue embedded in fibrous stroma. The heterotopia can, however, also present as gross, tumor-like nodules of 1 cm diameter or even more (Mboti et al. 2003). Histologically, all cellular systems of the normal pancreas can be present, including acinar cells, duct cells, and endocrine islet-type cells or fully developed islets of Langerhans with expression of insulin and somatostatin (Pilloni et al. 2006; Beltram et al. 2007). In some cases, large parts of the gallbladder wall are involved by pancreatic exocrine tissue, the pancreatic ductules and ducts resembling Rokitansky-Aschoff sinuses (Pilloni et al. 2006). Pancreatic heterotopia can be associated with synchronous heterotopic gastric mucosa of the gallbladder (Jaerve and Meurman 1964).

Ectopic Liver of the Gallbladder

Introduction

Ectopic liver tissue (liver choristoma, accessory liver, hepar succenturiatum) is a rare condition that most often involves the pancreas, stomach, gastrohepatic ligament, umbilical ligament, gallbladder, omentum, adrenal glands, esophagus, and thoracic cavity, including mediastinum, lung, and heart. Ectopic liver of the gallbladder is a rare clinical entity that is usually asymptomatic and observed incidentally in the setting of laparoscopy, cholecystectomy for other reasons, or autopsy. Ectopia of liver tissue in the gallbladder wall was first described in 1922 under the term supernumerary liver lobe implanted on the inferior surface of the gallbladder (Corsy 1922).

Epidemiology

Overall, the incidence of ectopic liver in the abdominal and thoracic cavities has been estimated from 0.24 % to 0.47 %. The incidence of ectopic liver of the gallbladder is probably low but seems to be the most common intra-abdominal site of liver ectopia (Griniatsos et al. 2002; Algin et al. 2008; Triantafyllidis et al. 2009). In a study of 5,500 autopsies, only three cases were detected (0.05 %; Eiserth 1940). In a more recent investigation on 1,060 laparoscopies, three cases were identified (0.28 %; Watanabe et al. 1989).

Clinical Features

Most cases of ectopic liver of the gallbladder are incidental findings without symptoms and signs. However, ectopic liver can produce a mass lesion that may be confounded with a gallbladder tumor (Hamdani and Baron 1994). In unusual situations, ectopic liver can undergo secondary changes that are symptomatic, including torsion of pedunculated lesions, acute hemorrhage, compression, obstruction of the gallbladder, or malignant transformation.

Selected References: Eiserth 1940; Klein 1955; Bassis and Izenstark 1956; Horanyi and Fuesy 1963; Ashby 1969; Costero et al. 1975; Collan et al. 1978; Torchio and Maconi 1978; Natori et al. 1986; Fellbaum et al. 1987; Tejada and Danielson 1989; Watanabe et al. 1989; Castro Viera et al. 1990; Iacconi and Masoni 1990; Svane and Knudtzon 1991; Hamdani and Baron 1994; Kodama and Yokoyama 1996; Sato et al. 1998; Djuricic et al. 1999; Acar et al. 2002; Griniatsos et al. 2002; Sakarya et al. 2002; Lundy et al. 2005; Wang and Liu 2006; Koh and Hunt 2007; Triantafyllidis et al. 2009; Catani et al. 2011; Dettmer et al. 2011; Nagar et al. 2011; Martinez et al. 2013.

Pathology

Macroscopy

Most cases of liver ectopia of the gallbladder showed liver tissue attached to the outer surface of the organ. The lesion may be pedunculated and forming a polypoid structure, with a thick or thin stalk of variable length connecting it with the gallbladder and containing blood vessels (Lundy et al. 2005; Triantafyllidis et al. 2009). Very few reports documented the presence of ectopic liver tissue in inner parts or the gallbladder wall (intramural ectopia) or even the mucosa (Torchio and Maconi 1978; Natori et al. 1986). Ectopic liver tissue of the gallbladder usually manifests as small brownish nodules measuring from a few mm to 1 or 2 cm (Natori et al. 1986), but lesions measuring several cm in diameter have also been observed (Lundy et al. 2005). Due to circulation failure, ectopic liver tissue can undergo necrosis associated with acute hemorrhage, the lesion presenting as a dark red nodule on the gallbladder surface (Nagar et al. 2011).

Histopathology

Histologically, the ectopic liver tissue usually shows a normal architecture, although the lobules may be deformed and/or undersized (Griniatsos et al. 2002). In at least part of the cases, ectopic liver contained portal tracts with small bile ducts, arteries, and venous branches. The ectopic liver tissue is sometimes cholestatic, with accumulation of bile in canaliculi (Svane and Knudtzon 1991). Interestingly, these livers or liverlets do however not always show cholestasis, although a connection to the gallbladder lumen or the cystic duct cannot, or not easily, be identified. Hepatocytes located in ectopic liver may undergo changes similar to that of orthotopic hepatocytes, apart from cholestasis, such as fatty change (Eiserth 1940), hemosiderosis (Tejada and Danielson 1989), and cirrhosis (Watanabe et al. 1989). In one case of ectopic liver localized to the gallbladder fundus, retention of alpha-1-antitrypsin was detected in the ectopic hepatocytes (Dettmer et al. 2011).

Ectopic Liver and Malignancy

Ectopic liver tissue has a propensity to develop hepatocellular carcinoma/HCC, especially in oriental patients (see the respective chapter; Arakawa et al. 1999; Caygill and Gatenby 2004; Leone et al. 2004). In the study of Arakawa and coworkers (1999), which focused at ectopias other than those of the gallbladder, 22 out of 48 cases developed HCC. HCC can also develop in ectopic liver of the gallbladder (Tamura et al. 1985; Arakawa et al. 1999). Interestingly, the incidence of HCC is much lower in ectopic liver tissue of the gallbladder: only one of 33 cases developed cancer (Arakawa et al. 1999). The reason for this striking difference is unknown. Ectopic liver of the gallbladder may have less time to undergo carcinogenesis, because the involved gallbladders may be removed early. It has also been suggested that the difference might be related to the finding that ectopic liver attached to the gallbladder is an anomaly occurring later in ontogenesis and is thus well differentiated and composed of more stable tissue (Griniatsos et al. 2002).

Pathogenic Pathways

It is assumed that ectopic liver of the gallbladder arises from residual liver primordial cells located in the caudal part of the liver primordium.

Thyroid Ectopia of the Gallbladder

In the course of thyroid anlage descent, groups or clusters of thyrocyte precursors can lodge at various non-eutopic sites and thus give rise to ectopic tissue. The most common sites of ectopic thyroid tissue are lingual, sublingual, thyroglossal, laryngotracheal, and lateral cervical sites. Thyroid ectopia in the gallbladder wall has been reported few times (Harach 1998; Ihtiyar et al. 2003; Venditti

et al. 2007; Cassol et al. 2010; Liang et al. 2010; review, Klubo-Gwiezdzinska et al. 2011).

Macroscopically, thyroid ectopia can produce a gallbladder mass (Liang et al. 2010), but this is a highly unusual event as ectopic thyroid tissue is usually detected histologically as an incidental finding. Histology is characterized by normal-looking thyroid tissue, with or without a lobular texture, follicles sometimes being embedded in a collagenous matrix. A potential differential diagnosis of thyroid ectopia is gallbladder metastasis of well-differentiated follicular thyroid carcinoma.

Pathogenic Pathways

Similar to thyroid ectopia in the liver (see the respective paragraph), ectopic thyroid tissue in the gallbladder wall is thought to arise via aberrant migration of thyroidocyte progenitors in the course of the thyroid anlage descent from the foramen cecum to the mediastinum. The descending thyroid anlage is, in a certain phase of embryogenesis, in close contact with the mesenchyme of the future septum transversum, and cell exchange may occur during this developmental phase.

Adrenocortical Ectopia

Very rarely, ectopic adrenal cortex was found in the form of small nodular structures in the subserosal space of the gallbladder (Busuttil 1974).

Gastric Mucosal Heterotopia in the Gallbladder

Introduction

Gastric mucosal heterotopia (GMH) of the gallbladder is a congenital abnormality characterized by the presence of usually circumscribed areas of gastric mucosa replacing the original gallbladder mucosa. Gallbladder GMH was first described in 1934, based on a polypoid lesion (Egyedi 1934), and relatively few observations have been documented since.

Selected References: Williams and Humm 1953; Curtis and Sheahan 1969; Summers et al. 1970; Bentivegna and Hirschl 1972; Keramidas et al. 1977; Mooney et al. 1979; Adam et al. 1989; Pradines et al. 1989; Boyle et al. 1992; Vallera et al. 1992; Schimpl et al. 1994; Uchiyama et al. 1995; Hamazaki and Fujiwara 2000; Inoue et al. 2000; Xeropotamos et al. 2001; Isik et al. 2002; Lombay et al. 2003; Madrid et al. 2003; Sciumè et al. 2005; Cöl et al. 2007; Triki et al. 2008; Hayama et al. 2010; Bulus et al. 2012; Liang et al. 2013.

GMH of the gallbladder is an uncommon condition, while pseudopyloric or pyloric gland metaplastic epithelium in the gallbladder is a common finding, detectable in 66–84 % of cholecystectomy specimens, whereas intestinal metaplasia is present in 12–52 % of gallbladders and is often associated with pyloric metaplasia (review, Xeropotamos et al. 2001). Gallbladder GMH is almost equally distributed among sexes, with an age range at diagnosis of 6–77 years, a considerable proportion of cases being reported for the pediatric age group. In almost a third of cases, gallstones were present. GMH can lead to mucosal defects, including peptic ulcerations (Kehrer and De Minjer 1951; Larsen et al. 1985), sometimes causing massive hemobilia (Adam et al. 1989; Yoon et al. 2005), and hematemesis and melena (Larsen et al. 1985). GMH may occur in gallbladders with preexisting anatomical abnormalities, including duplicate gallbladder (Bailie et al. 2003), or anomalous union of the pancreatobiliary duct (Wakiyama et al. 1998). Apart from the gallbladder, GMH can develop in the cystic duct (Orizio et al. 2011). GMH and intestinal metaplasia of the gallbladder are considered to be precancerous (Yamagiwa and Tomiyama 1986). Etiology and pathogenesis of gastric mucosal heterotopias are not known.

Pathology

Macroscopy

Macroscopically, gallbladder GMH can present as a flat or plaque-like lesion, but GMH growing

as pedunculated or sessile polypous masses is also well known (Yamamoto et al. 1988, 1989; Schimpl et al. 1994; Uchiyama et al. 1995; Leyman et al. 1996; Sciumè et al. 2005; Hayama et al. 2010). In case of polypoid lesions, gallbladder carcinoma may suspected based on imaging results (Hayama et al. 2010), also because polypous GMH may grow to a size exceeding 2 cm. Gallbladder GMH can also present as a firm nodular mass or as a multiloculated lesion (Xeropotamos et al. 2001). Large GMH masses can cause symptom-producing tumors (Bentivegna and Hirschl 1972). On CT images, GMH appears as a slightly high density area which is intermediately enhanced early after bolus injection of contrast medium (Inoue et al. 2000). The lesions are often located in the gallbladder fundus, but GMH also occurs in the gallbladder neck (Sciumè et al. 2005).

Histopathology

Histologically, GMH reveals a gastric-type superficial epithelium and associated gastric glands, including pyloric glands, corpus glands, and fundic glands, chief cells and parietal/oxyntic cells being present (Runge et al. 1978). The epithelium overlying the glandular structures may show hyperplastic changes. Neuroendocrine/APUD cells have been found in part of the cases (Vallera et al. 1992). GMH can be associated with extensive adjacent pyloric and/or pseudopyloric metaplasia, staining red with the Alcian blue-PAS stain (Xeropotamos et al. 2001), or intestinal gallbladder metaplasia (Tavli et al. 2005). It can undergo secondary changes, such as cystic change (Popkharitov et al. 2008) or squamous metaplasia (Daud et al. 2007). Gallbladder GMH can be associated with other types of heterotopia/ectopia, such as pancreas and thyroid tissue (Murakami and Tsutsumi 1999), or with adenoma of the gallbladder (Summers et al. 1970). On gastric-type epithelium of the gallbladder, no *Helicobacter pylori* was detected (Arnaout et al. 1990).

Table 1 Types of gallbladder ectopia

Retroposition of the gallbladder
Intrahepatic gallbladder
Left-sided gallbladder (transposition)
Gallbladder interposition
Extraabdominal gallbladder

Ectopic Gallbladder

Ectopic gallbladder, albeit a rare condition, has clinical significance because it can lead to misdiagnosis and misinterpretation as a tumorous lesion. Several types of gallbladder ectopia are known (Table 1).

A retroposed gallbladder (retrohepatic gallbladder) may suggest the presence of a cystic tumor on the underside of the liver (Feldman and Venta 1988; Chowbey et al. 2004). A retrohepatic gallbladder can be contained in the coronary ligament (Principe et al. 1979). Ectopic gallbladder may be situated within the liver substance, with or without stones (Glasionov 1961; Schulz et al. 1975; Velchik and Noel 1987; Lobo et al. 2007), and can mimic an intrahepatic cystic tumor (Schneider et al. 1979). If it is situated away from the peritoneum, signs of acute cholecystitis may be absent. In some cases, ectopic gallbladder has an own mesenterium (mesovesicula) containing feeding vessels (Popli et al. 2010), the ectopic gallbladder then being a hanging lesion that can undergo torsion and gangrenous infarction (the "floating gallbladder"; Havrilla et al. 1978). A floating gallbladder on a long "mesovesicula" can also herniate through the foramen of Winslow into the lesser sac, with signs of strangulation (Blanton et al. 1974). In rare instances, the gallbladder is situated in a suprahepatic position (Faintuch et al. 1979; Youngwirth et al. 1983; Sheu et al. 1995), sometimes associated with malformations of the right liver (Hsu et al. 1994) or inverted liver (Hibbs and Ahmad 2010). It can also occur intrathoracically (Labitzke 1991), and in few instances, the gallbladder was transposed to the left underside of the liver (gallbladder transposition; Duimstra and Greenfield 1977; Keller et al. 1982; Wong et al. 2001; Dhulkotia et al. 2002) or was malpositioned in the

region of extrahepatic bile ducts (gallbladder interposition; Walia et al. 1986). The gallbladder can be situated on the left side of the common bile duct and the cystic duct, arising from the right hepatic duct (Chung et al. 1997).

Reactive Vascular Mass Lesions of the Gallbladder

Introduction

Similar to extrahepatic and intrahepatic bile ducts, the gallbladder can be involved in a variety of reactive vascular alterations that may produce mass effects or pseudotumors mimicking neoplastic disease. The most important changes include gallbladder varices and pseudoaneurysms of the cystic artery.

Gallbladder Varices

In part of patients with portal hypertension, ectopic varices (varicose veins) as dilated venous collaterals can develop in the wall of the gallbladder.

Selected References: Malusev 1951; Salam et al. 1979; Lebrec and Benhamou 1985; West et al. 1991; Chawla et al. 1994, 1995; Safadi et al. 1996; Gabata et al. 1997; Palazzo et al. 2000; Chu et al. 2002; Radhi 2003; Ito et al. 2009; de Alcantara et al. 2013.

It is estimated that the incidence of gallbladder varices in cirrhotic and non-cirrhotic portal hypertension amounts to up to 30 % (West et al. 1991; Chawla et al. 1994; Helbich et al. 1994; Rathi et al. 1996). Gallbladder varices have also been described in the pediatric age group (Helbich et al. 1994; Rathi et al. 1996). The varices may or may not be associated with extrahepatic portal vein occlusion (West et al. 1991) but are sometimes associated with portal vein cavernoma (Lebrec and Benhamou 1985). Varices cause fixed filling defects (Rosen and Wilson 1980) and thickening of the gallbladder wall suspicious of malignancy (Saigh et al. 1985). Rupture of varices leads to variceal bleeding, sometimes followed by life-threatening or fatal abdominal hemorrhage (Holmlund and Lundström 1977; Chu et al. 2002; Kevans et al. 2009; Vilallonga et al. 2012). The dilated gallbladder veins can be visualized by means of color Doppler sonography (Kainberger et al. 1990; Helbich et al. 1994; Safadi et al. 1996; Mishin 2005). A direct communication of the varices to intrahepatic portal vein branches can be demonstrated by Doppler sonography and CT (Gabata et al. 1997).

Aneurysmatic Changes and Related Vascular Disorders

The most common alteration in this group is cystic artery pseudoaneurysm (CAP). Pseudoaneurysms (synonyms: false aneurysm, aneurysma spurium, aneurysma falsum) are characterized by a periarterial hematoma following a tear in the arterial wall involving intima and media but leaving the adventitia intact in classical cases. However, in some of these aneurysms, the hematoma will break through the adventitia with time. CAP is most often observed in the setting of acute cholecystitis (Machida et al. 2008; Hague et al. 2010; Dewachter et al. 2012; Fung et al. 2013) and can develop as a complication of xanthogranulomatous cholecystitis (Ahmed et al. 2010). CAP can protrude into the gallbladder lumen, producing masses of up to 2 cm in diameter (Ahmed et al. 2010). This vascular lesion can cause acute internal hemorrhage (Fung et al. 2013) and hemoperitoneum (Ghoz et al. 2007), sometimes with fatal outcome (Olbrycht 1965). Pseudoaneurysms can also develop in the right hepatic artery and rupture into the gallbladder (Schubert et al. 1980; Lin et al. 2010). Percutaneous liver biopsy can be complicated by arterial-portal fistula causing a gallbladder polyp as a manifestation of hemorrhage (Lin et al. 2005).

Arteriovenous and Other Vascular Malformations of the Gallbladder

Arteriovenous malformations of the gallbladder are very unusual alterations characterized with the presence of serpentine around and within the gallbladder wall. Angiographically, dilated and tortuous cystic artery branches, a racemose vascular network, and early filling branches of the cystic vein have been noted (Tajima et al. 1997; Osada et al. 2007). The gallbladder is rarely involved in the setting of Osler-Weber-Rendu disease, with multiple telangiectasias in the gallbladder wall (Baba et al. 1995).

Gallbladder Hemorrhage and Hematoma

Introduction

Gallbladder hematomas can occur under various conditions, including trauma, inflammation, coagulation disorders, vascular accidents, and malignant neoplasms. More commonly, blood accumulates within the gallbladder lumen and produces a hemocholecyst, but various conditions also cause intramural gallbladder bleeding which results in wall thickening, mass effect, and sometimes extensive wall dissection. Gallbladder hemorrhages and hematomas can be divided into several anatomical categories (Table 2).

Hemorrhagic Cholecystitis

Gallbladder hemorrhage is a relatively rare complication of hemorrhagic cholecystitis (Parekh and Corvera 2010) and is sometimes associated with pathological coagulopathy or the administration of anticoagulative therapies (Morris et al. 2008; Chen et al. 2010), uremia (Lai and Tarng 2009), or cytostatic therapy. Hemorrhagic cholecystitis can result in hemobilia (Bazzoni et al. 1993) or in gallbladder rupture with massive intraperitoneal bleeding (Tavernaraki et al. 2011). Hemorrhagic cholecystitis, with its alteration in wall structure and contractility, may simulate gallbladder carcinoma (Gremmels et al. 2004).

Table 2 Categories of gallbladder hemorrhage and hematoma

Hemorrhagic cholecystitis
Intraluminal hematoma (hemocholecyst, hematocele)
Intramural gallbladder hematoma
Hemorrhagic tumors

Intraluminal Hematoma (Hemocholecyst)

Acute or continuous bleeding into the gallbladder lumen causes the formation of a blood clot that may completely fill the lumen (hemocholecyst, gallbladder hematocele, Scharling and Geisinger 1993) and which reveals characteristic sonographic and CT features (Grant and Smirniotopoulos 1983; Kauzlaric and Barmeir 1985). Intraluminal blood masses may be mixed with bile, gallstones, mucus, exudate, and tissue debris. Intraluminal blood escapes through the cystic duct and hence causes hemobilia in more distal parts of the biliary tract. In severe and rapidly progressing hemorrhage, gallbladder rupture may result. Important causes of hemocholecyst mainly comprise blunt trauma with gallbladder contusion (Sandblom 1948; Saad et al. 1979; Fröschle et al. 1990; McNabney et al. 1990; Erb et al. 1994), gallbladder malignancy (Faure et al. 1969; Uchiyama et al. 1998; John et al. 1999; Heise et al. 2000; Kubota et al. 2000), coagulation disorders (e.g., hemophilia; Shimura et al. 2000), complications of anticoagulant therapy (Brawner et al. 1966; Mikou et al. 2004; Zangrandi et al. 2009), chemotherapy, radiofrequency ablation therapy of malignant liver tumors (Yamamoto et al. 2003; Shin et al. 2011), benign tumors and polyps (Cappell et al. 1993), hemorrhagic cholecystitis (Ku et al. 2004), ruptured artery and venous aneurysms and pseudoaneurysms (Barzilai and

Kleckner 1956; Hakami et al. 1976; Miura et al. 1998), and venous hemorrhage in portal hypertension (Krustev et al. 2002). In the setting of portal hypertension, gallbladder varices may develop, followed by variceal hemorrhage (Chu et al. 2002; Kevans et al. 2009). Intraluminal gallbladder hematoma was also induced by percutaneous liver biopsy (Kwon et al. 2002). Hemocholecyst can present as a tumorous mass and may mimic a gallbladder neoplasm (Jung et al. 2011).

Intramural Hematoma

Intramural hematoma of the gallbladder is less common than hemocholecyst (Tesler and Cantor 1957; Pilling 1979). Hematoma confined to the wall results in a mass that exerts pressure. The hematoma may remain confined to the wall or may rupture into the gallbladder lumen or through the serosal covering into the peritoneal cavity. Hematoma of the gallbladder wall may be associated with infiltrating hematoma of the hepatic pedicle (Dao et al. 1989). Intramural hematoma as a "pushing" or infiltrating mass can mimic a gallbladder neoplasm on sonographic, CT, or MR images (Tan et al. 2005; Jung et al. 2011).

Hemorrhagic Tumors

Malignancies of the gallbladder can give rise to hemorrhage, both hemocholecyst and mural hematomas at the site of the tumor, whereby the tumors themselves may be hemorrhagic (Petrin 1966; Faure et al. 1969; Piotrowski et al. 1975; Calmat et al. 1979; Fourdan et al. 1994; Osawa et al. 1996; Jones et al. 1997). Metastases to the gallbladder also cause hemorrhage and hemobilia, e.g., metastases of renal cell carcinoma (Fullarton and Burgoyne 1991) or of hepatocellular carcinoma (Chang et al. 1998). In addition to malignant tumors, also benign gallbladder neoplasms can give rise to tumor hemorrhage (Cho et al. 2001).

Pathology

Macroscopy

In acute hemorrhagic cholecystitis, the gallbladder wall is thickened, with edema and bleeding in the extramuscular tissue. The mucosa has lost its fine texture and appears as a dark red to blackish surface with overlying blood coagula and exudate on ulcerated parts. On cut sections, the wall has lost its layers and is visualized as a dark red and often friable tissue. Hemocholecyst is macroscopically characterized by liquid or coagulated blood filling the gallbladder lumen. In recently developing cases, the blood is easily removable from the mucosa, while with time the coagulated blood may adhere to the mucosal surface. In formalin-fixed specimen, the blood forms a dark and hard mass that usually falls off when cutting through the organ. Intramural hematomas, which are either an isolated phenomenon or are combined with hemocholecyst, appear as blood masses of variable size that dissect the gallbladder wall and may bulge into the lumen, mimicking a hemorrhagic tumor.

References

Acar T, Taçyildiz R, Karakayali S (2002) Ectopic liver tissue attached to the gallbladder. Acta Chir Belg 102:210–211

Adam R, Fabiani B, Bismuth H (1989) Hematobilia resulting from heterotopic stomach in the gallbladder neck. Surgery 105:564–569

Agnarsdottir M, Willén R, El Hag IA (2004) Three cases of malakoplakia of the gallbladder. Ups J Med Sci 109:255–259

Ahmed I, Tanveer UH, Sajjad Z, Munazza B, Azeem UD, Basit S (2010) Cystic artery pseudo-aneurysm: a complication of xanthogranulomatous cholecystitis. Br J Radiol 83:e165–e167

Akiyama T, Sahara H, Seto K, Saitou H, Kiriyama M, Tomita F, Kosaka T, Kita I et al (1996) Gallbladder cancer associated with cholesterosis. J Gastroenterol 31:470–474

Akyürek N, Salman B, Irkörücü O, Sare M, Tatliciolglu E (2005) Ultrasonography in the diagnosis of true gallbladder polyps: the contradiction in the literature. HPB (Oxford) 7:155–158

Al-Azzawi HH, Nakeeb A, Saxena R, Maluccio MA, Pitt HA (2007) Cholecystosteatosis: an explanation for

increased cholecystectomy rates. J Gastrointest Surg 11:835–842
Algin et al. (2008) http://www.ncbi.nlm.nih.gov/pubmed/21490853
Al-Shraim M, Rabie ME, Elhakeem H, Kandeel A, Shah MT, Jamil S (2010) Pancreatic heterotopia in the gallbladder associated with chronic cholecystitis. A rare combination. JOP 11:464–466
Andersson A, Bergdahl L (1971) Acalculous cholesterosis of the gallbladder. Arch Surg 103:342–344
Arakawa M, Kimura Y, Sakata K, Kubo Y, Fukushima T, Okuda K (1999) Propensity of ectopic liver to hepatocarcinogenesis: case reports and a review of the literature. Hepatology 29:57–61
Arnaout AH, Abbas SH, Shousha S (1990) Helicobacter pylori is not identified in areas of gastric metaplasia of gall bladder. J Pathol 160:333–334
Arnell O (1941) Cholesterolosis vesicae felleae. Acta Chir Scand 85:511–524
Ashby EC (1969) Accessory liver lobe attached to the gallbladder. Br J Surg 56:311–312
Baba R, Hashimoto E, Yashiro K, Nagasako K, Hayashi N, Nishikawa T, Ludwig J (1995) Multiple abdominal telangiectases and lymphangiectases. A limited form of Osler-Weber-Rendu disease? J Clin Gastroenterol 21:154–157
Bailie AG, Wyatt JI, Sheridan MB, Stringer MD (2003) Heterotopic gastric mucosa in a duplicate gallbladder. J Pediatr Surg 38:1401–1403
Barzilai R, Kleckner MS (1956) Hemocholecyst following ruptured aneurysm of portal vein: report of a case. AMA Arch Surg 72:725–727
Bassis ML, Izenstark JL (1956) Ectopic liver: its occurrence in the gall bladder. AMA Arch Surg 73:204–206
Bazzoni C, Serini M, Ongari M, Squazzini C, Alleva M, Lombardi C (1993) Massive hemobilia caused by necrotic hemorrhagic cholecystitis. Report of a case (in Italian). Minerva Chir 48:857–860
Beltran et al. (2007) http://www.ncbi.nlm.nih.gov/pubmed/18180840
Ben-Baruch D, Sandbank Y, Wollock Y (1986) Heterotopic pancreatic tissue in the gallbladder. Acta Chir Scand 152:557–558
Bentivegna S, Hirschl S (1972) Heterotopic gastric mucosa in the gallbladder presenting as a symptom-producing tumor. A case report. Am J Gastroenterol 57:423–428
Bhana BD, Chetty R (1999) Heterotopic pancreas – an unusual cause of cholecystitis. S Afr J Surg 37:105–107
Blanton DE, Bream CA, Mandel SR (1974) Gall bladder ectopia: a review of anomalies of position. AJR Am J Roentgenol 121:396
Boyle L, Gallivan MV, Chun B, Lack EE (1992) Heterotopia of gastric mucosa and liver involving the gallbladder. Report of two cases with literature review. Arch Pathol Lab Med 116:138–142
Brawner J, Trivedi H, Sataline LR (1966) Hemocholecyst. Report of a case associated with anticoagulation therapy. Ohio State Med J 62:1028–1030
Bromberg SH, Franco MI, Franca LCM, Neto CC (2009) Pancreatic heterotopia in the gallbladder: a case report and literature review. Einstein J Biol Med 7:215–218
Bulun SE, Monsavais D, Pavone ME, Dyson M, Xue Q, Attar E, Tokunaga H et al (2012) Role of estrogen receptor-b in endometriosis. Semin Reprod Med 30:39–45
Bulus H, Yildiz M, Alimogullari M, Simsek G, Köklü S, Koçak E (2012) Gastric heterotopia within the gallbladder wall in a patient with chronic cholecystitis. Am Surg 78:E51–E52
Burns KA, Korach KS (2012) Estrogen receptors and human disease: an update. Arch Toxicol 86:1491–1504
Busuttil A (1974) Ectopic adrenal within the gall-bladder wall. J Pathol 113:231–233
Calmat A, Riquet M, Clot JP, Kariotakis E, Mercadier M (1979) Acute haemocholecystitis due to carcinoma of the gallbladder (in French). Ann Chir 33:371–373
Cappell MS, Marks M, Kirschenbaum H (1993) Massive hemobilia and acalculous cholecystitis due to benign gallbladder polyp. Dig Dis Sci 38:1156–1161
Cassol CA, Noria D, Asa SL (2010) Ectopic thyroid tissue within the gall bladder: case report and brief review of the literature. Endocr Pathol 21:263–265
Castro Viera GA, Sanuy ME, Camara HA, Cordoba OC (1990) Accessory liver in gallbladder. Apropos of a case report (in Spanish). Rev Esp Enferm Dig 77:295–296
Catani M, De Milito R, Romagnoli F, Mingazzini P, Silvestri V, Usai V, Romeo V, Modini C (2011) Ectopic liver nodules: a rare finding during cholecystectomy. G Chir 32:255–258
Caygill CP, Gatenby PA (2004) Ectopic liver and hepatocarcinogenesis. Eur J Gastroenterol Hepatol 16:727–729
Celoria GC, Rodriguez Otero JC, Proske SA, Vallilengua C (1994) Papillary hyperplasia and cholesterolosis of the gallbladder. Medicina (B Aires) 54:31–34
Cerullo G, Marrelli D, Di Mare G, Onorati M, Tripodi S, Neri A, Roviello F (2011) Heterotopic pancreatic tissue in the gallbladder. Two case reports and brief review of the literature. G Chir 32:259–262
Chang KM, Jeng KS, Yang FS, Chen BF (1998) Metastatic hepatocellular carcinoma presenting as hemocholecyst with perforation: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 61:613–618
Charpentier P, Prade M, Bognel C, Gadenne C, Duvillard P (1983) Malakoplakia of the gallbladder. Hum Pathol 14:827–828
Chawla Y, Dilawari JB, Kataiya S (1994) Gallbladder varices in portal vein thrombosis. AJR Am J Roentgenol 162:643–645
Chawla A, Dewan R, Sarin SK (1995) The frequency and influence of gallbladder varices on gallbladder functions in patients with portal hypertension. Am J Gastroenterol 90:2010–2014
Chen YY, Yi CH, Chen CL, Huang SC, Hsu YH (2010) Hemorrhagic cholecystitis after anticoagulation therapy. Am J Med Sci 340:338–339

Chitkara YK (1995) Pathology of the gallbladder in gallstone pancreatitis. Arch Pathol Lab Med 119:355–359

Cho YU, Kim JY, Choi SK, Hur YS, Lee KY, Kim SJ, Ahn SI, Hong SC, Woo ZH et al (2001) A case of hemorrhagic gallbladder paraganglioma causing acute cholecystitis. Yonsei Med J 42:352–356

Chowbey PK, Wadhwa A, Sharma A, Khullar R, Soni V, Baijal M (2004) Ectopic gallbladder: laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech 14:26–28

Chu EC, Chick W, Hillebrand DJ, Hu KQ (2002) Fatal spontaneous gallbladder variceal bleeding in a patient with alcoholic cirrhosis. Dig Dis Sci 47:2682–2685

Chung CC, Leung KL, Lau WY, Li AK (1997) Ectopic gallbladder revisited, laparoscopically: a case report. Can J Surg 40:464–466

Cöl C, Boran C, Turkeli V, Dinler K, Kordon O, Erkol H, Sengul N (2007) Heterotopic gastric mucosa in gallbladder associated with kidney agenesis and congenital hip dysplasia. Acta Clin Belg 62:120–122

Collan Y, Hakkileuoto A, Hastgacka J (1978) Ectopic liver. Ann Chir Gynaecol 67:27–29

Collard P, Mazy V, Jardon-Jeghres C, Focan C (1989) Local tumefaction of the gallbladder wall due to pancreatic heterotopia. J Belge Radiol 72:471–473

Cooke HH (1931) A pathological study of the "strawberry" gallbladder. Thesis, University of Minnesota

Corsy F (1922) Lobe supérnumeraire du foie implanté sur la face inférieure de la vésicule biliaire. C R Seances Soc Biol 86:695–697

Costero C, Quilantan R, Meléndez J (1975) Ectopic liver located in the gallbladder (in Spanish). Rev Invest Clin 27:55–58

Csendes A, Smok G, Burdiles P, Diaz JC, Maluenda F, Korn O (1998) Histological findings of gallbladder mucosa in 95 control subjects and 80 patients with asymptomatic gallstones. Dig Dis Sci 43:931–934

Csendes A, Burdiles P, Smok G, Csendes P, Burgos A, Recio M (2003) Histologic findings of gallbladder mucosa in 87 patients with morbid obesity without gallstones compared to 87 control subjects. J Gastrointest Surg 7:547–551

Curtis LE, Sheahan DG (1969) Heterotopic tissues in the gallbladder. Arch Pathol 88:677–683

Damore LJ, Cook CH, Fernandez KL, Cunningham J, Ellison EC, Melvin WS (2001) Ultrasonography incorrectly diagnoses gallbladder polyps. Surg Laparosc Endosc Percutan Tech 11:88–91

Dao TH, Rotman N, Mathieu D, Vasile N (1989) Infiltrating hematoma of the hepatic pedicle and gallbladder wall. Ultrasonographic and x-ray computed tomographic aspects (in French). J Radiol 70:431–433

Daud MS, Salomao FC, Salomao EC, Salomao BC (2007) Gastric heterotopia together with squamous metaplasia in the gallbladder. Acta Gastroenterol Latinoam 37:164–167

De Alcantara RV, Yamada RM, Cardoso SR, de Fatima M, Servidoni CP, Hessel G (2013) Ultrasonography predictors of esophageal varices. J Pediatr Gastroenterol Nutr 57:700–703

Dettmer M, Cathomas G, Willi N (2011) Alpha-1-antitrypsin retention in an ectopic liver. Diagn Pathol 6:16

Dewachter L, Dewaele T, Rosseel F, Crevits I, Aerts P, De Man R (2012) Acute cholecystitis with pseudoaneurysm of the cystic artery. JBR-BTR 95:136–137

Dhulkotia A, Kumar S, Kabra V, Shukla HS (2002) Aberrant gallbladder situated beneath the left lobe of liver. HPB (Oxford) 4:39–42

Di Tommaso L, Arizzi C, Roncalli M (2005) Malacoplakia of the gallbladder. Histopathology 46:474–475

Dittrick GW, Thompson JS, Campos D, Bremers D, Sudan D (2005) Gallbladder pathology in morbid obesity. Obes Surg 15:238–242

Djuricic S, Zlatkovic M, Stankonic I, Plamenac P (1999) Heterotopic liver tissue in the fundus of the gallbladder. Srp Arh Celok Lek 127:412–415

Dolan RV, Remine WH, Dockery MB (1974) The fate of heterotopic pancreatic tissue. Arch Surg 109: 762–765

Duchini L (1967) Apropos of a case of ossification of the gallbladder. Contribution to the study of heterotopic ossifications (in Italian). Arch de Vecchi Anat Patol 50:537–552

Duimstra F, Greenfield RE (1977) Left liver lobe gall bladder. S D J Med 30:7–9

Egyedi L (1934) Case of polypus of gallbladder containing gastric mucosa membrane tissue. Gyogyaszat 74:596–599

Eiserth P (1940) Beiträge zur Kenntnis der Nebenlebern. Virchows Arch A Pathol Anat Histopathol 307:307–313

Elfving G (1959) Heterotopic pancreatic tissue in the gall bladder wall: report of a case. Acta Chir Scand 118:32–36

Elfving G, Palmu A, Teir H (1968) Cholesterolosis and mucosal hyperplasia of gallbladder. Ann Chir Gynaecol Fenn 57:28–30

Elhence P, Bansal R, Agrawal N (2012) Heterotopic pancreas in gall bladder associated with chronic cholecystolithiasis. Int J Appl Basic Med Res 2:142–143

Elpek GO, Bozova S, Küpesiz GY, Ogüs M (2007) An unusual cause of cholecystitis: heterotopic pancreatic tissue in the gallbladder. World J Gastroenterol 13:313–315

Erb RE, Mirvis SE, Shanmuganathan K (1994) Gallbladder injury secondary to blunt trauma: CT findings. J Comput Assist Tomogr 18:778–784

Faintuch J, Machado MC, de Mendonça LK, das Neves MM, Raia AA (1979) Suprahepatic gallbladder – a rare ectopia of the gallbladder (in Portuguese). Rev Hosp Clin Fac Med Sao Paulo 34:260–264

Faure GJ, Maupin JM, Barbier H (1969) Acute hemobilia and hemoperitoneum caused by cancer of the gallbladder (in French). J Chir (Paris) 98:529–532

Feldman M, Feldman M (1954) Cholesterosis of the gallbladder; an autopsy study of 165 cases. Gastroenterology 27:641–648

Feldman L, Venta L (1988) Percutaneous cholecystostomy of an ectopic gallbladder. Gastrointest Radiol 13:256–258

Fellbaum C, Beham A, Schmid C (1987) Isolated accessory liver (hepar succenturiatum) at the neck of the gallbladder. Case report with review of the literature (in German). Wien Klin Wochenschr 99:825–827

Foucault A, Veilleux H, Martel G, Lapointe R, Vandenbroucke-Menu F (2012) Heterotopic pancreas presenting as suspicious mass in the gallbladder. JOP 13:700–701

Fourdan O, Prat F, Fritsch J, Brocheriou I, Choury D, Etienne JP (1994) Hemobilia revealing calculosis and cancer of the gallbladder. Value of retrograde choledochoscopy (in French). Gastroenterol Clin Biol 18:901–902

Fröschle G, Brümmer P, Gebhardt J (1990) Isolated gallbladder hematoma and covered perforation following blunt abdominal trauma (in German). Zentralbl Chir 115:365–368

Fullarton GM, Burgoyne M (1991) Gallbladder and pancreatic metastases from bilateral renal carcinoma presenting with hematobilia and anemia. Urology 38:184–186

Fung AK, Vosough A, Olson S, Aly EH, Binnie NR (2013) An unusual cause of acute internal haemorrhage: cystic artery pseudoaneurysm secondary to acute cholecystitis. Scott Med J 58:e23–e26

Gabata T, Matsui O, Kadoya M, Yoshikawa J, Ueda K, Nobata K, Kawamori Y, Takashima T (1997) Gallbladder varices: demonstration of direct communication to intrahepatic portal veins by color Doppler sonography and CT during arterial portography. Abdom Imaging 22:82–84

Ghoz A, Kheir E, Kotru A, Halazun K, Kessel D, Patel JJ, Lodge JP (2007) Hemoperitoneum secondary to rupture of cystic artery pseudoaneurysm. Hepatobiliary Pancreat Dis Int 6:321–323

Gilloteaux J, Hawkins WS, Gilloteaux LC, Jasso J, Kelly TR (1997) Ultrastructural aspects of human cystic duct epithelium as a result of cholelithiasis and cholesterolosis. Microsc Res Tech 39:22–38

Glasionov IM (1961) On intrahepatic localization of the gall-bladder (in Russian). Khirurgiia (Mosk) 37:116–117

Goldblatt MI, Swartz-Basile DA, Al-Azzawi HH, Trans KQ, Nakeeb A, Pitt HA (2006) Nonalcoholic fatty gallbladder disease: the influence of diet in lean and obese mice. J Gastrointest Surg 10:193–201

Graham EA, Elman R (1932) The pathogenesis of the 'strawberry' gallbladder. Arch Surg 24:14–22

Grant EG, Smirniotopoulos JG (1983) Intraluminal gallbladder hematoma: sonographic evidence of hemobilia. J Clin Ultrasound 11:507–509

Gremmels JM, Kruskal JB, Parangi S, Kane RA (2004) Hemorrhagic cholecystitis simulating gallbladder carcinoma. J Ultrasound Med 23:993–995

Griniatsos J, Riaz AA, Isla AM (2002) Two cases of ectopic liver attached to the gallbladder wall. HPB (Oxford) 4:191–194

Gucer H, Bagci P, Coskunoglu EZ, Karadag C (2011) Heterotopic pancreatic tissue located in the gallbladder wall. A case report. JOP 12:152–154

Guerra L, Perna AM, Lotti G, Siccardi A (1963) Cholesterolosis of the gallbladder. Anatomopathological study (in Italian). Pathologica 55:471–484

Hadzi-Nikolov D, Resl M, Herzig B, Svetlik M (1997) Heterotopic pancreatic tissue in the wall of the gallbladder (in Czech). Cesk Patol 33:146–148

Hague J, Brennand D, Raja J, Amin Z (2010) Cystic artery pseudoaneurysms in hemorrhagic acute cholecystitis. Cardiovasc Intervent Radiol 33:1287–1290

Hakami M, Beheshti G, Amirkhan A (1976) Hemobilia caused by rupture of cystic artery aneurysm. Am J Proctol 27:56–57

Hamazaki K, Fujiwara T (2000) Heterotopic gastric mucosa in the gallbladder. J Gastroenterol 35:376–381

Hamdani SD, Baron RL (1994) Ectopic liver simulating a mass in the gallbladder wall: imaging findings. AJR Am J Roentgenol 162:647–648, 16, 294–297

Hanada M, Tujimura T, Kimura M (1981) Cholecystic granulomas in gallstone disease. A clinicopathologic study of 17 cases. Acta Pathol Jpn 31:221–231

Harach HR (1998) Ectopic thyroid tissue adjacent to the gallbladder. Histopathology 32:90–91

Havrilla TR, Reich NE, Haaga JR, Seidelmann FE, Cooperman AM, Alfidi RJ (1978) Computed tomography of the gall bladder. AJR Am J Roentgenol 130:1059

Hayama S, Suzuki Y, Takahashi M, Hazama K, Fujita M, Kondo S, Katoh H (2010) Heterotopic gastric mucosa in the gallbladder: report of two cases. Surg Today 40:783–787

Heino AE, Ritama V (1965) Observations on cholesterosis of the gall-bladder. An autopsy study. Ann Chir Gynaecol Fenn 54:387–391

Heise CP, Giswold M, Eckhoff D, Reichelderfer M (2000) Cholecystitis caused by hemocholecyst from underlying malignancy. Am J Gastroenterol 95:805–808

Helbich T, Breitenseher M, Heinz-Peer G, Vergesslich K, Granditsch G, Kainberger F (1994) Color Doppler ultrasound of gallbladder varicose veins in children. A rare sign of portal hypertension. Ultraschall Med 15:126–130

Helpap B, Huegel A (1988) Cholesterosis and adenomyomatosis of the gallbladder (cholecystosis) (in German). Pathologe 9:70–77

Hibbs H, Ahmad U (2010) Inverted liver with suprahepatic, anteriorly displaced gallbladder. J La State Med Soc 162:150–152

Hide G, Desai S, Bloxham CA (2001) Malakoplakia of the gall-bladder: imaging and histological features. Clin Radiol 56:326–328

Holmlund D, Lundström B (1977) Extrahepatic obstruction of the portal vein with bleeding from the

gallbladder. Report of a case. Acta Radiol Diagn (Stockh) 18:680–684
Horanyi J, Fuesy F (1963) Accessory liver in the wall of the gallbladder (in Hungarian). Magy Seb 16:294–297
Hsu KL, Chou FF, Shern JY, Yang AD (1994) Suprahepatic gallbladder with agenesis of the right lobe of the liver: report of a case. J Formos Med Assoc 93:320–323
Iacconi P, Masoni T (1990) Accessory liver. Report of 2 cases. Acta Chir Belg 90:228–230
Iafrate F, Ciolina M, Iannitti M, Baldassari P, Pichi A, Rengo M, De Cecco CN, Laghi A (2013) Gallbladder and muscular endometriosis: a case report. Abdom Imaging 38:120–124
Ihtiyar E, Isikoy S, Algin C, Sahin A, Erkasap S, Yasar B (2003) Ectopic thyroid in the gallbladder: report of a case. Surg Today 33:777–780
Indyk JS, Shipton EA (1957) Heterotopic bone formation in the gall-bladder. Med J Aust 44:9–11
Inoue Y, Shibata T, Niinobu T, Ishida T, Sato T, Hanada M (2000) Heterotopic gastric mucosa in the gallbladder: sonographic and CT findings. Abdom Imaging 25:198–200
Ishida T, Nakamura H, Hori S, Marukawa T, Mitani T, Murakami T, Nishikawa M, Nakanishi K et al (1993) Acalculous cholecystitis (panniculitis) associated with Weber-Christian disease. Clin Imaging 17:56–58
Isik I, Sezer C, Dursun A (2002) Gastric heterotopia in the gallbladder: a case report. Turk J Gastroenterol 13:172–174
Ito K, Fujita T, Shimizu A, Sasaki K, Tanabe M, Matsunaga N (2009) Imaging findings of unusual intra- and extrahepatic portosystemic collaterals. Clin Radiol 64:200–207
Izzo L, Boschetto A, Brachini G, Binda B, Lamazza A, Caramanico L, Corigliano N et al (2001) "Strawberry" gallbladder: review of the literature and our experience (in Italian). G Chir 22:33–36
Jacyna MR, Bouchier IAD (1987) Cholesterolosis: a physical cause of "functional" disorder. Br Med J 295:619–620
Jaerve and Meurman (1964) http://www.ncbi.nlm.nih.gov/pubmed/14188064
Jarde O, Barrat JP, Degardin P, Maingueux P, Tardif B (1989) Aberrant pancreas in the gallbladder. J Chir 126:476–477
Jeng KS, Yang KC, Kuo SH (1991) Malignant degeneration of heterotopic pancreas. Gastrointest Endosc 37:196–198
John A, Ramachandran TM, Ashraf S, Nair MS, Devi RS (1999) Carcinoma of gallbladder presenting as hemobilia. Indian J Gastroenterol 18:88–89
Jones RL, Mackie G, Taylor SA (1997) Case report: gallbladder carcinoma – an unusual cause of haemobilia. Clin Radiol 52:962–963
Judd ES, Mentzer SH (1927a) Cholesterosis of the gall bladder. I. A clinical study. Calif West Med 27:337–339
Judd ES, Mentzer SH (1927b) Cholesterosis of the gall bladder. II. The surgical aspects. Cal West Med 27:487–489
Jung YM, Son BK, Ahn SB, Kim DH, Kim EK (2011) Intramural gallbladder hematoma mimicking gallbladder neoplasm in a 55-year-old male patient. J Korean Surg Soc 81:216–220
Kaido T, Kano M, Suzaki S, Yanagibashi K, Shiota M (2004) Large cholesterol polyp of the gallbladder mimicking gallbladder carcinoma. Abdom Imaging 29:100–101
Kainberger FM, Vergesslich KA, Eilenberger M, Poeltner S, Ponhold W (1990) Color-coded Doppler evaluation of cholecystic varices in portal hypertension. Pediatr Radiol 21:71–72
Kauzlaric D, Barmeir E (1985) Sonography of intraluminal gallbladder hematoma. J Clin Ultrasound 13:291–294
Kehrer JK, De Minjer A (1951) Peptic ulcer of the gallbladder. Arch Chir Neerl 3:151–156
Keller D, Gayral F, Larrieu H (1982) Malposition of the gallbladder under the left lobe of the liver. A case report (in French). Ann Chir 36:243–245
Keramidas DC, Skondras C, Anagnostou D, Doulas N (1977) Gastric heterotopia in the gallbladder. J Pediatr Surg 12:759–762
Kevans D, MacNicholas R, Norris S (2009) Gallbladder wall variceal haemorrhage with associated rupture: a rare cause of mortality in the cirrhotic patient. Eur J Gastroenterol Hepatol 21:955–957
Khairy GA, Guraya SY, Murshid KR (2004) Cholesterolosis. Incidence, correlation with serum cholesterol level and the role of laparoscopic cholecystectomy. Saudi Med J 25:1226–1228
Klein F (1955) Accessory liver of microscopic size in the gallbladder wall (in German). Zentralbl Allg Pathol 93:466–469
Klimis T, Roukounakis N, Kafetzis I, Mouziouras V, Karantonis I, Andromanakos N (2011) Heterotopic pancreas of the gallbladder associated with chronic cholecystitis and high levels of amylasuria. JOP 12:458–460
Klubo-Gwiezdzinska J, Manes RP, Chia SH, Burman KD, Stathatos NA, Deeb ZE et al (2011) Clinical review: ectopic cervical thyroid carcinoma – review of the literature with illustrative case series. J Clin Endocrinol Metab 96:2684–2691
Kodama T, Yokoyama T (1996) Heterotopic tissues in the gallbladder (heterotopic gastric mucosa, heterotopic intestinal epithelium, heterotopic pancreatic tissue and ectopic liver in the gallbladder (in Japanese). Ryoikibetsu Shokogun Shirizu 9:360–362
Koga A (1985) Fine structure of the human gallbladder with cholesterosis with special reference to the mechanism of lipid accumulation. Br J Exp Pathol 66:605–611
Koh CE, Hunt R (2007) Ectopic liver encountered during laparoscopic cholecystectomy. Asian J Surg 30:227–229
Kondi-Paphiti A, Antoniou AG, Kotsis T, Polimeneas G (1997) Aberrant pancreas in the gallbladder wall. Eur Radiol 7:1064–1066

Krustev N, Mendizova A, Velev M (2002) Hemobilia caused by gallbladders's polyps in liver cirrhosis (in - Bulgarian). Khirurgiia (Sofia) 58:42–44

Ku J, DeLaRosa J, Kang J, Hoyt D, Coimbra R (2004) Acute cholecystitis with a hemocholecyst as an unusual presentation of gallbladder cancer: report of a case. Surg Today 34:973–976

Kubota H, Kageoka M, Iwasaki H, Sugimoto K, Higuchi R, Honda S, Watanabe F et al (2000) A patient with undifferentiated carcinoma of gallbladder presenting with hemobilia. J Gastroenterol 35:63–68

Kwon TK, Jeon SH, Park HW, Jung WJ, Hwang JY, Park KS, Cho KB, Hwang JS et al (2002) A case of intraluminal gallbladder hematoma after percutaneous liver biopsy (in Korean). Taehan Kan Hakhoe Chi 8:486–489

Labitzke R (1991) Congenital intrathoracic ectopic gallbladder – a currently unreported developmental disorder. Attempt at a classification of abnormal gallbladder sites (in German). Chirurg 62:755–758

Lai SW (2011) Pathologic evaluation of gallbladder in patients who underwent cholecystectomy and hepatic resection for hepatocellular carcinoma. Am J Med Sci 341:305–307

Lai YC, Tarng DC (2009) Hemorrhagic acalculous cholecystitis: an unusual location of uremic bleeding. J Chin Med Assoc 72:484–487

Lai EC, Tompkins RK (1986) Heterotopic pancreas. Review of a 26 year experience. Am J Surg 151:697–700

Larsen EH, Diederich PJ, Sorensen FB (1985) Peptic ulcer in the gallbladder. A case report. Acta Chir Scand 151:575–576

Lebrec D, Benhamou JP (1985) Ectopic varices in portal hypertension. Clin Gastroenterol 14:105–121

Leone N, De Paolis P, Carrera M, Carucci P, Musso A, David E, Brunello F, Fronda GR et al (2004) Ectopic liver and hepatocarcinogenesis: report of three cases with four years' follow-up. Eur J Gastroenterol Hepatol 16:731–735

Lewis KM, Peterson CW (1943) Cholesterosis of the gallbladder: observations on twenty-five cases without stones. Ann Surg 117:450–455

Leyman P, Saint-Marc O, Hannoun L, Parc R (1996) Heterotopic gastric mucosa presenting as gallbladder polyps. Acta Chir Belg 96:128–129

Liang K, Liu JF, Wang YH, Tang GC, Teng LH, Li F (2010) Ectopic thyroid presenting as a gallbladder mass. Ann R Coll Surg Engl 92:W4–W6

Liang YL, Liang X, Wang YF, Cai XJ (2013) Heterotopic gastric mucosa with mild dysplasia in the gallbladder. Chin Med J (Engl) 126:978–979

Limaiem F, Jedidi S, Hassan F, Korbi S, Aloui S, Lahmar A, Bouraoui S, Mzabi S (2012) Pancreatic heterotopia in the gallbladder neck associated with chronic cholecystitis. Pathologica 104:446–448

Lin CL, Chang JJ, Lee TS, Lui KW, Yen CL (2005) Gallbladder polyp as a manifestation of hemobilia caused by arterial-portal fistula after percutaneous liver biopsy: a case report. World J Gastroenterol 11:305–307

Lin YH, Lee RC, Hsia CY, Chen HC, Chiang JH, Tseng HS, Chang CY (2010) Right hepatic artery pseudoaneurysm ruptured into the gallbladder demonstrated by magnetic resonance angiography. J Chin Med Assoc 73:331–333

Lobo SW, Menezes RG, Mamata S, Baral P, Knachan T, Hunnargi SA, Bodhe AV, Bhat NB (2007) Ectopic partial intrahepatic gall bladder with cholelithiasis – a rare anomaly. Nepal Med Coll J 9:286–288

Lombay B, Kiss A, Szabo L (2003) Heterotopic gastric mucosa in the gallbladder. Pediatr Radiol 33:587

Lundy J, Johnson E, Edwards K, Rivera D (2005) Laparoscopic management of gallbladder-associated ectopic liver. JSLS 9:485–487

MacCarty WC (1919) The frequency of strawberry gallbladder. Ann Surg 69:131–139

Machida H, Ueno E, Shiozawa S, Fujimura M, Tsuchiya A, Kim DH, Ogawa K, Aiba M (2008) Unruptured pseudoaneurysm of the cystic artery with acute calculous cholecystitis incidentally detected by computed tomography. Radiat Med 26:384–387

Mackay WA (1937) Cholesterosis of the gallbladder: a review, supplemented by personal observations on 87 cases. Br J Surg 24:570–594

Madrid C, Berrocal T, Gorospe L, Prieto C, Gamez M (2003) Heterotopic gastric mucosa involving the gallbladder and biliary tree. Pediatr Radiol 33: 129–132

Malusev D (1951) Varices of the gallbladder (in Serbian). Srp Arh Celok Lek 49:775–779

Martinez CA, de Resende HC, Rodrigues MR, Sato DT, Brunialti CV, Palma RT (2013) Gallbladder-associated ectopic liver: a rare finding during a laparoscopic cholecystectomy. Int J Surg Case Rep 4:312–315

Mathur A, Al-Azzawi HH, Lu D, Yancey KW, Swartz-Basile DA, Nakeeb A, Pitt HA (2008) Steatocholecystitis: the influence of obesity and dietary carbohydrates. J Surg Res 147:290–297

Mboti F, Maassarani F, de Keuleneer R (2003) Cholecystitis associated with heterotopic pancreas. Acta Chir Belg 103:110–112

McNabney WK, Rudek R, Pemberton LB (1990) The significance of gallbladder trauma. J Emerg Med 8:277–280

Méndez-Sanchez N, Tanimoto MA, Cobos E, Roldan-valadez E, Uribe M (1997) Cholesterolosis is not associated with high cholesterol levels in patients with and without gallstone disease. J Clin Gastroenterol 25:518–521

Mentzer SH (1925) Cholesterosis of the gall bladder. Am J Pathol 1:383–388

Meshikhes AW, Al-Jaroof AH, Atassi R (2003) Heterotopic pancreas in the gall bladder. Saudi Med J 24:907–908

Mikou MM, Mouaffak Y, Benyacob A, Modaddek A, Faroudy M, Ababou A, Lazreq C et al (2004) Haemocholecyst: a rare complication of anticoagulant

treatment (in French). Ann Fr Anesth Reanim 23:733–736
Mishin I (2005) Gallbladder varices. Rom J Gastroenterol 14:165–168
Mitty WF, Rousselot LM (1957) Cholesterosis of the gall bladder. Gastroenterology 32:910–916
Miura K, Hoshino T, Komatsu M, Ono T, Sato T, Tanaka J, Masamune O (1998) A case of hemorrhage into the gallbladder probably due to rupture of pseudoaneurysm formed by cystic artery (in Japanese). Nihon Shokakibyo Gakkai Zasshi 95:450–454
Monfreda G, Draghi L, Peloso R (1967) Heterotopic pancreatic tissue. Radiological aspects (in Italian). Quad Radiol 32:449–471
Mooney B, O'Malley E, Dempsey J (1979) Gastric heterotopia in a gall bladder. Ir J Med Sci 148:50–53
Morris DS, Porterfield JR, Sawyer MD (2008) Hemorrhagic cholecystitis in an elderly patient taking aspirin and cilostazol. Case Rep Gastroenterol 2:203–207
Murakami M, Tsutsumi Y (1989) Aberrant pancreatic tissue accompanied by heterotopic gastric mucosa in the gall-bladder. Pathol Int 49:580–582
Murakami M, Tsutsumi Y (1999) Aberrant pancreatic tissue accompanied by heterotopic gastric mucosa in the gall-bladder. Pathol Int 49:580–582
Mutschmann PN (1946) Aberrant pancreatic tissue in the gallbladder wall. Am J Surg 72:282–283
Nagar S, Koffron A, Raofi V (2011) A case of hemorrhagic necrosis of ectopic liver tissue within the gallbladder wall. HPB Surg 2011:389381
Nakagawa T, Yamakado K, Takeda K, Nakagawa T (1996) An ossifying carcinosarcoma of the gallbladder: radiologic findings. AJR Am J Roentgenol 166:1233–1234
Natori T, Hawkin S, Aizawa M, Asai T, Kameda Y, Ikuyohashi K (1986) Intra-cholecystic ectopic liver. Acta Pathol Jpn 36:1213–1216
Nelson JJ, Kahn AG (2009) A case of bone metaplasia of the gallbladder epithelium. South Med J 102: 322–324
Neupert G, Appel P, Braun S, Tonus C (2007) Heterotopic pancreas in the gallbladder. Diagnosis, therapy, and course of a rare developmental anomaly of the pancreas (in German). Chirurg 78:261–264
Nevalainen T, Laitio M (1972) Ultrastructure of gallbladder with cholesterolosis. Virchows Arch B Cell Pathol 10:237–242
Ohtsuki Y, Hatano H, Okada Y, Lee GH, Furihata M (2012) Case report: membranous fat necrosis of the gallbladder as the cause of peculiar foreign body reaction in a patients with severe chronic cholecystitis. Biomed Res India 23:457–460
Olbrycht J (1965) Sudden death due to internal hemorrhage into the peritoneal cavity from a ruptured periarteritic aneurysma of the cystic artery (in German). Beitr Gerichtl Med 23:160–170
Orizio P, Villanacci V, Bassotti G, Falchetti D, Torri F, Ekema G (2011) Heterotopic gastric mucosa in the cystic duct. Int J Surg Pathol 19:364–365
Ortiz-Hidalgo C, Baquera-Heredia J (2000) Osseous metaplasia in polypoid cholesterosis. Am J Surg Pathol 24:895
Osada H, Honda N, Takahashi T, Oku S, Watanabe W, Okada T, Ohno H, Hondo M, Nishimura K (2007) Arteriovenous malformation of the gallbladder: CT and angiographic findings. Radiat Med 25:73–75
Osawa H, Mori Y, Inoue F (1996) Case report: malignant haemobilia detected in the gallbladder – retrograde cholangiographic findings. Br J Radiol 69:79–81
Owen CC, Bilhartz LE (2003) Gallbladder polyps, cholesterolosis, adenomyomatosis, and acute acalculous cholecystitis. Semin Gastrointest Dis 14:178–188
Palazzo L, Hochain P, Helmer C, Cuillerier E, Landi B, Roseau G, Cugnenc PH, Barbier JP et al (2000) Biliary varices on endoscopic ultrasonography: clinical presentation and outcome. Endoscopy 32:520–524
Parekh J, Corvera CU (2010) Hemorrhagic cholecystitis. Arch Surg 145:202–204
Pellegrini C, Gori I, Achtari C, Hornung D, Chardonnens E, Wunder D, Fiche M, Canny GO (2012) The expression of estrogen receptors as well as GREB1, c-MYC, and cyclin D1, estrogen-regulated genes implicated in proliferation, is increased in peritoneal endometriosis. Fertil Steril 98:1200–1208
Petrin C (1966) Massive hemobilia in the course of carcinoma and lithiasis of the gallbladder (in Italian). Chir Ital 18:770–782
Pilling DW (1979) Haematoma of the wall of the gallbladder. Br J Radiol 52:840–841
Pilloni L, Cois A, Uccheddu A, Ambu R, Coni P, Faa G (2006) Complete pancreatic heterotopia of gallbladder with hypertrophic duct simulating an adenomyoma. World J Gastroenterol 12:1786–1787
Piotrowski M, Kostecka W, Dyk T (1975) Hemocholecyst – hemorrhage into the gallbladder in the course of gallbladder carcinoma (in Polish). Wiad Lek 28:1069–1072
Pitt HA (2007) Hepato-pancreatic-biliary fat: the good, the bad and the ugly. HPB (Oxford) 9:92–97
Plante BJ, Lessey BA, Taylor RN, Wang W, Bagchi MK, Yuan L, Scotchie J, Fritz MA et al (2012) G protein-coupled estrogen receptor (GPER) expression in normal and abnormal endometrium. Reprod Sci 19:684–693
Popkharitov AI, Gulubova MV, Dandov AD, Sivrev DP (2008) Heterotopic gastrointestinal cyst mimicking chronic cholecystitis: a case report. J Med Case Rep 2:173
Popli MB, Popli V, Solanki Y (2010) Ectopic gall bladder: a rare case. Saudi J Gastroenterol 16:50
Pradines P, Brauner M, Legrand I, Sibony M, Garin B (1989) Heterotopic gastric mucosa in the gallbladder. AJR Am J Roentgenol 152:432
Price RJ, Stewart ET, Foley WD, Dodds WJ (1982) Sonography of polypoid cholesterolosis. AJR Am J Roentgenol 139:1197–1198

Principe A, Spangaro M, Lapilli A, Vecchi R, Volta L, De Lorenzi P (1979) Congenital anomalies of the gallbladder: a case of retrohepatic gallbladder contained in the coronary ligament (in Italian). Minerva Chir 34:879–884

Qizilbash AH (1976) Acute pancreatitis occurring in heterotopic pancreatic tissue in the gallbladder. Can J Surg 19:413–414

Radhi JM (2003) Gallbladder varices. Pathology 35:358–359

Rathi PM, Soni A, Nanivadekar SA, Sawant P, Bhatnagar MS, Upadhyay AP (1996) Gallbladder varices: diagnosis in children with portal hypertension on duplex sonography. J Clin Gastroenterol 23:228–231

Rege TA, Vargas SO (2011) Cholecystitis and cholelithiasis associated with an intramural fasciitis-like proliferation and osseous metaplasia. Pediatr Dev Pathol 14:80–83

Reid JD (1962) Cholesterolosis of the gallbladder: its nature and pathogenesis. N Z Med J 61:384–391

Rosen IE, Wilson SR (1980) Varices of the gallbladder. J Can Assoc Radiol 31:73–74

Runge et al. (1978) http://www.ncbi.nlm.nih.gov/pubmed/580715

Saad SA, Rush BF, Devanesan JD, Lazaro EJ (1979) Traumatic hematocele of the gallbladder with hemobilia. J Trauma 19:67–69

Saadat-Gilani K, Bechmann L, Frilling A, Gerken G, Canbay A (2007) Gallbladder endometriosis as a cause of occult bleeding. World J Gastroenterol 13:4517–4519

Safadi R, Sviri S, Eid A, Levensart P (1996) Gallbladder varices: a case report and review of the literature. Eur J Med Res 1:506–508

Sahlin S, Stahlberg D, Einarsson K (1995) Cholesterol metabolism in liver and gallbladder mucosa of patients with cholesterolosis. Hepatology 21:1269–1275

Saigh J, Williams S, Cawley K, Anderson JC (1985) Varices: a cause of focal gallbladder wall thickening. J Ultrasound Med 4:371–373

Sakarya A, Erhan Y, Aydede H, Kara E, Ilkgül O, Ciftdogan C (2002) Ectopic liver (choristoma) associated with the gallbladder encountered during laparoscopic cholecystectomy: a case report. Surg Endosc 16:1106

Salam AA, Goldman M, Smith D, Hill HL (1979) Gastric, intestinal, and gallbladder varices: hemodynamic and therapeutic considerations. South Med J 72:402–408

Saldaña DG, de Acosta DA, Aleman HP, Gebrehiwot D, Torres E (2010) Gallbladder endometrioma associated with obstructive jaundice and a serous ovarian cystic adenoma. South Med J 103:1250–1252

Salmenkivi K (1964) Cholesterosis of the gall-bladder. A clinical study based on 269 cholecystectomies. Acta Chir Scand 105(Suppl 324):1–193

Samartzis N, Samartzis EP, Noske A, Fedier A, Dedes KJ, Caduff R, Fink D, Imesch P (2012) Expression of the G protein-coupled estrogen receptor (GPER) in endometriosis: a tissue microarray study. Reprod Biol Endocrinol 10:30

Sandblom P (1948) Hemorrhage into the biliary tract following trauma; traumatic hemobilia. Surgery 24:571–586

Sandri L, Colecchia A, Larocca A, Vestito A, Capodicasa S, Azzaroli F, Mwangemi C et al (2003) Gallbladder cholesterol polyps and cholesterolosis. Minerva Gastroenterol Dietol 49:217–224

Sato S, Watanabe M, Nagasawa S, Niigaki M, Sakai S, Akagi S (1998) Laparoscopic observations of congenital anomalies of the liver. Gastrointest Endosc 47:136–140

Sato A, Hashimoto M, Sasaki K, Matsuda M, Watanabe G (2012) Elevation of pancreatic enzymes in gallbladder bile associated with heterotopic pancreas. A case report and review of the literature. JOP 13:235–238

Satoh H, Koga A (1997) Fine structure of cholesterolosis in the human gallbladder and the mechanism of lipid accumulation. Microsc Res Tech 39:14–21

Scharling ES, Geisinger KR (1993) Case of the day. Hemobilia: intraluminal gallbladder hematoma. J Ultrasound Med 12:244–245

Schein M, Assalia A, Schmulevski P, Meislin V, Hashmonai M (1993) Infected peri-pancreatic necrosis causing gallbladder necrosis by direct extension. HPB Surg 7:77–79

Schimpl G, Schaffler G, Sorantin E, Ratschek M, Klimpfinger M (1994) Polypoid gastric heterotopia in the gallbladder: clinicopathological findings and review of the literature. J Pediatr Gastroenterol Nutr 19:129–131

Schneider EA, Eisner M, Fridrich R (1979) Scintigraphic demonstration of an intrahepatic gall-bladder presenting as a focal liver lesion. Br J Radiol 52:754–755

Schubert GE, Klasmeier H, Lius W, Roth A (1980) Spurious aneurysm of the hepatic artery in the lumen of the gallbladder with hemobilia. Sonographic, angiographic, and pathological-anatomical findings (in German). Rofo 132:88–90

Schulz RC, Shields JB, Fletcher JW, Donati RM (1975) Liver scanning and the intrahepatic gallbladder: case report. J Nucl Med 16:1029–1030

Sciumè C, Geraci G, Pisello E, Li Volsi E, Facella T, Modoca G (2005) Heterotopic gastric mucosa in the gallbladder: case report and literature review. Ann Ital Chir 76:93–97

Sheu BS, Lin XZ, Chen CY, Chow NH, Lin PW, Tsai HM (1995) Suprahepatic gallbladder and right lobe anomaly of the liver in patients with biliary cancers. Dig Dis Sci 40:2411–2416

Shimura T, Kojima T, Tsutsumi S, Yoshida T, Uchiumi H, Kuwano H (2000) Gallbladder hematoma in a patient with hemophilia B, report of a case. Hepatogastroenterology 47:939–941

Shin KY, Heo J, Kim JY, Lee SJ, Jang SY, Park SY, Jung MK, Cho CM, Tak WY et al (2011) A case of

hemocholecyst associated with hemobilia following radiofrequency ablation therapy for hepatocellular carcinoma. Korean J Hepatol 17:148–151

Shiwani MH, Gosling J (2008) Heterotopic pancreas of the gallbladder associated with chronic cholecystitis. JOP 9:30–32

Sroczynski M, Sebastian M, Halon A, Rudnicki J, Sebastian A, Agrawal AK, Piekarz P (2013) Pancreatic heterotopia in the gallbladder: an incidental finding after cholecystectomy. Folia Histochem Cytobiol 51:174–177

Strömsten A, von Bahr S, Bringman S, Saeki M, Sahlin S, Björkhem I, Einarsson C (2004) Studies on the mechanism of accumulation of cholesterol in the gallbladder mucosa. Evidence that sterol 27-hydroxylase is not a pathogenetic factor. J Hepatol 40:8–13

Summers FH, Zinberg SS, Kotkin M, Toch H, Sarkaria DS (1970) Heterotopic gastric mucosa with adenoma of the gall bladder. JAMA 214:597

Svane S, Knudtzon J (1991) Ectopic liver in the gallbladder and cholestasis. Tidsskr Nor Laegeforen 111:2643–2644

Tajima H, Hosaka J, Tajima N, Kumazaki T (1997) Arteriovenous malformation of the gallbladder. Eur Radiol 7:333–334

Tamura S, Yanaginuma N, Fujiwara K (1985) A case of ectopic liver cancer – hepatocellular carcinoma that developed in the gallbladder. Jpn J Gastroenterol 82:2448

Tan SW, Lai SK, Ng KW, Chen P, Chen KH, Jiang CF (2005) Intramural gallbladder hematoma mimicking gallbladder neoplasm in a 33-year-old male. J Chin Med Assoc 68:146–149

Tavernaraki K, Sykara A, Tavernaraki E, Chondros D, Lolis ED (2011) Massive intraperitoneal bleeding due to hemorrhagic cholecystitis and gallbladder rupture: CT findings. Abdom Imaging 36:565–568

Tavli L, Belviranli M, Erikoglu M, Esen H, Toy H (2005) Gastric heterotopia together with intestinal metaplasia in the gallbladder: case report and review of literature. Turk J Gastroenterol 16:160–162

Tejada E, Danielson C (1989) Ectopic or heterotopic liver (choristoma) associated with the gallbladder. Arch Pathol Lab Med 113:950–952

Tesler J, Cantor PJ (1957) Hematoma of the gall bladder. Gastroenterology 33:308–312

Tilvis RS, Aro J, Strandberg TE, Lempinen M, Miettinen TA (1982) Lipid composition of bile and gallbladder mucosa in patients with acalculous cholesterolosis. Gastroenterology 82:607–615

Torchio B, Maconi G (1978) Nodule of ectopic hepatic parenchyma in the wall of the gallbladder. Minerva Chir 33:39–44

Triantafyllidis I, Papapavlou L, Nikoloudis N, Economou A, Andreadis E, Chrissidou M et al (2009) Ectopic liver tissue attached to the gallbladder wall: a case report. Cases J 2:6786

Triki E, Brigand C, Meyer C (2008) Heterotopic gastric mucosa in the gallbladder (in French). J Chir (Paris) 145:376–377

Triponez F, Alifano M, Bobbio A, Regnard JF (2010) Endometriosis-related spontaneous diaphragmatic rupture. Interact Cardiovasc Thorac Surg 11:485–487

Tsai CJ (2009) Steatocholecystitis and fatty gallbladder disease. Dig Dis Sci 54:1857–1863

Uchiyama S, Imai S, Suzuki T, Arita A, Takeda K, Sujino H, Kameda H (1995) Heterotopic gastric mucosa of the gallbladder. J Gastroenterol 30:543–546

Uchiyama K, Aida N, Shibuya T, Tanaka S (1998) Early carcinoma of the gallbladder accompanied by hemobilia: report of a case. Surg Today 28:763–767

Vaiphei K, Singh P, Verma GR (2012) Gallbladder malakoplakia in type 2 diabetes mellitus: a rare entity. BMJ Case Rep 2012. pii: bcr201206601

Vallera DU, Dawson PJ, Path FR (1992) Gastric heterotopia in the gallbladder. Case report and review of the literature. Pathol Res Pract 188:49–52

Velchik MG, Noel AW (1987) False-positive liver scan due to an intrahepatic gallbladder detected by cholescintigraphy. Clin Nucl Med 12:50–52

Venditti M, Hay RW, Kulaga A, Demetrick DJ (2007) Diagnosis of ectopic tissue versus contamination by genetic fingerprinting in a routine surgical pathology specimen. Hum Pathol 38:378–382

Vilallonga R, Gonzalez O, Bergamini S, Fort JM, Armengol M (2012) Gallbladder variceal bleeding in a patient with alcoholic cirrhosis: a rare entity. Rev Esp Enferm Dig 104:153–154

Virchow R (1857) Über das Epithel der Gallenblase und über einen intermediären Stoffwechsel des Fettes. Virchows Arch Pathol Anat Histol 11:574–598

Wakiyama S, Yoshimura K, Shimada M, Kajiyama K, Sugimachi K (1998) Heterotopic gastric mucosa in a gallbladder with an anomalous union of the pancreatobiliary duct: a case report. Hepatogastroenterology 45:1488–1491

Walia HS, Abraham TK, Baraka A (1986) Gall-bladder interposition: a rare anomaly of the extrahepatic ducts. Int Surg 71:117–121

Wang Y, Liu FJ (2006) Ectopic liver tissue in the gallbladder serosa: a case report (in Chinese). Zhonhua Gan Zang Bing Za Zhi 14:369

Watanabe M, Matsura T, Takatori Y, Ueki K, Kobatake T, Hidaka M, Hirakawa H, Fukumoto S et al (1989) Five cases of ectopic liver and a case of accessory lobe of the liver. Endoscopy 21:39–42

Watanabe F, Hanai H, Kaneko E (1998) Increased acylCoA-cholesterol ester acyltransferase activity in gallbladder mucosa in patients with gallbladder cholesterolosis. Am J Gastroenterol 93:1518–1523

Weppner JL, Wilson MR, Ricca R, Lucha PA (2009) Heterotopic pancreatic tissue obstructing the gallbladder neck: a case report. JOP 10:532–534

West MS, Garra BS, Horii SC, Hayes WS, Cooper C, Silverman PM, Zeman RK (1991) Gallbladder varices:

imaging findings in patients with portal hypertension. Radiology 179:179–182

Williams MJ, Humm JJ (1953) Heterotopia composed of gastric epithelium and smooth muscle in the wall of the gall bladder; a case report. Surgery 34:133–139

Womack NA, Haffner H (1944) Cholesterolosis: its significance in the badly damaged gallbladder. Ann Surg 119:391–401

Wong LS, Rusby J, Ismail T (2001) Left-sided gall bladder: a diagnostic and surgical challenge. ANZ J Surg 71:557–558

Xeropotamos N, Skopelitou AS, Batsis C, Kappas AM (2001) Heterotopic gastric mucosa together with intestinal metaplasia and moderate dysplasia in the gall bladder: report of two clinically unusual cases with literature review. Gut 48:719–723

Yamagiwa H, Tomiyama H (1986) Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. Acta Pathol Jpn 36:989–997

Yamamoto M, Nakajo S, Tahara E (1988) Histological classification of epithelial polypoid lesions of the gallbladder. Acta Pathol Jpn 38:181–192

Yamamoto M, Murakami H, Ito M, Nakajo S, Tahara E (1989) Ectopic gastric mucosa of the gallbladder: comparison with metaplastic polyp of the gallbladder. Am J Gastroenterol 84:1423–1426

Yamamoto T, Kubo S, Hirohashi K, Tanaka S, Uenishi T, Ogawa M, Sakabe K, Hai S et al (2003) Secondary hemocholecyst after radiofrequency ablation therapy for hepatocellular carcinoma. J Gastroenterol 38:399–403

Yoon AJ, Cowles RA, Stylianos S, O-Toole KM (2005) Heterotopic gastric mucosa in the gallbladder: a rare cause of massive hemobilia. J Pediatr Gastroenterol Nutr 40:606–608

Yosepovich A, Nass D, Zagatsky M, Kopolovic J (2002) Chronic cholecystitis with bone metaplasia. A case report. Pathol Res Pract 198:765–766

Youngwirth LD, Peters JC, Perry MC (1983) The suprahepatic gallbladder. An unusual anatomical variant. Radiology 149:57–58

Zangrandi F, Piotto A, Tregnaghi A, Pelizzo MR (2009) Hemocholecyst associated with antithrombotic therapy. Can J Surg 52:E297–E298

Cysts of the Gallbladder 160

Contents

Abstract

The gallbladder is the site of various types of cysts that can mimic cystic neoplasms. Gallbladder cysts have been classified as congenital, acquired, and neoplastic cysts. Congenital cysts mainly include congenital simple epithelial cysts, ciliated foregut cyst, dermoid cysts, cystic choristomas derived from ectopic gastric mucosa, mesothelial cysts, duplication cysts, and bronchogenic cysts. Simple cysts may have a muscular wall but are not communicating with the gallbladder lumen. Acquired cysts are retention cysts, dilated Rokitansky-Aschoff sinuses, adenomyomatosis, cystic changes of fistulas, cystic abscesses, inflammatory pseudocysts, and parasitic cysts. Retention cysts are caused by obstructive gallbladder changes induced by stones, tumors, or sludge.

General Remarks and Classification

Cysts of the gallbladder wall represent a heterogeneous group of lesions that may be confounded with other alterations characterized by cyst formation, including necrotic tumors and abscesses. Gallbladder cysts have been classified as congenital, acquired, and neoplastic cysts, as summarized in Table 1 (Jacobs et al. 1991).

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_160

Table 1 Congenital and acquired cysts of the gallbladder

Congenital cysts
Congenital simple epithelial cyst
Ciliated foregut cyst
Dermoid cyst
Mesothelial cyst
Cystic choristoma
Gallbladder duplication cyst
Congenital cystic malformation
Bronchogenic cyst
Acquired cysts
Retention cyst
Dilated Rokitansky-Aschoff sinuses
Adenomyomatosis
Cyst from traction of a peridiverticular adhesion
Cystic change of fistula
Cystic abscess
Pseudocyst
Parasitic cyst
Neoplastic cysts

Congenital Cysts of the Gallbladder

Congenital cysts of the gallbladder are very rare lesions that are characterized by a muscle layer and lack of communication with the gallbladder lumen (Cureton and Newcombe 1961). Such cysts sometimes contain a simple cholangiocellular epithelium without further differentiation (simple epithelial cyst; Ochsner and Blalock 1964; Fitzer 1978; Jacobs et al. 1991; Asada et al. 1993; Fujisawa et al. 1995) and are either unilocular or multilocular (Cureton and Newcombe 1961). Epithelial gallbladder cysts may be associated with preneoplastic changes and adenocarcinoma (Matsumoto et al. 2002). Congenital cysts are thought to be caused by incomplete development of a second gallbladder primordium (formation of aberrant vesicles), isolation of a congenital diverticulum, or cystic transformation of a Luschka duct. Part of congenital epithelial cysts with a muscularis are lined by a ciliated epithelium containing variable amounts of goblets cells, thus corresponding to the type of ciliated cyst found in the liver (ciliated foregut cysts of the gallbladder; see the respective paragraph). Further types of congenital cyst characterized by an abnormal epithelial differentiation are the very rare dermoid cyst (Falcao and Leal 1975) and mesothelial cyst (Hoffman et al. 1989). Heterotopic gastrointestinal mucosa of the gallbladder has been found to form a cystic choristoma (Popkharitov et al. 2008). Intra-abdominal bronchogenic cyst has been detected alongside the gallbladder (Kim et al. 2004). A congenital cystic change of the gallbladder can also be caused by duplication of the gallbladder, one component of the double organ undergoing cyst formation (Kothari et al. 2005). An unusual lesion of unknown cause is giant congenital cystic malformation of the gallbladder (Lobe et al. 1986).

Congenital cysts also develop in the cystic duct (congenital cystic duct cyst; cystic malformation of the cystic duct; Pracy 1949; Bode and Aust 1983; Champetier et al. 1987; Serena Serradel et al. 1991) and are sometimes associated with an anomalous pancreaticobiliary junction (Weiler et al. 2003).

Acquired Cysts of the Gallbladder

Acquired cysts can develop following obstructive changes, e.g., by a tumor (retention cyst; Sworn and Gay 1975; Yamada et al. 1996). Retention cysts can occur following cholecystectomy and are located proximal to the stump (Prudkov and Titov 2001). Part of the acquired retention cysts may contain bile, gallstones, or stone fragments such as cholesterol crystal clusters.

Rokitansky-Aschoff sinuses may, especially in cases of sinus neck obstruction, undergo marked cystic change. Cysts are also a feature of gallbladder adenomyomatosis; these cysts may grow to a size detectable by sonography (Hwang et al. 1998; Brambs et al. 1990). Very rare are pseudocysts following pancreatitis (Jelen et al. 1974). In case of extensive squamous metaplasia of the gallbladder mucosa developing in chronic cholecystitis, a pseudoepidermoid cyst can arise (Teo et al. 2005).

Parasitic Cysts

A rather frequent cause of acquired gallbladder cysts is echinococcosis, forming hydatid cysts in

the gallbladder wall or cysts attached to the gallbladder adventitia (Soldevilla 1950; Cabanie and Lamy 1960; Rigas et al. 1979; Safioleas et al. 2004; Pitiakoudis et al. 2006). Hydatid cysts of the gallbladder may undergo marked calcification, sometimes mimicking porcelain gallbladder (Benedetti-Valentini 1954; Krasniqi et al. 2010) and may develop a cholecysto-hydatid fistula (Murtaza et al. 2008; Sabat et al. 2008).

Differential Diagnosis

Differential diagnosis of gallbladder cysts includes hydrops of the gallbladder, mucocele, cholecystocele (Deshmukh et al. 1999), gallbladder diverticulum, gallbladder varicosis (Saigh et al. 1985), cystadenoma of the gallbladder (Spector et al. 2003), and gallbladder lymphangioma (Choi et al. 2002).

Epithelial Cysts of the Gallbladder

Introduction

Apart from ciliated foregut cyst, which is treated in a separate chapter, several other types of congenital or acquired gallbladder cysts are recognized, cystic lesions that have to be distinguished from cystic neoplasms of the gallbladder.

Non-ciliated Epithelial Cysts

Non-ciliated epithelial gallbladder cysts (synonym: epithelial inclusion cyst) are congenital malformative lesions that are thought to result from the segregation of a part of the gallbladder anlage during ontogenesis. In contrast to true diverticula, these cysts do not communicate with the main gallbladder lumen (Cureton and Newcombe 1961; Ochsner and Blalock 1964; Sworn and Gay 1975; Fitzer 1978; Berulava 1980; Jacobs et al. 1991; Asada et al. 1993; Fujisawa et al. 1995; Mori et al. 2002). Most of these cysts are unilocular, but multilocular cysts have also been described (Cureton and Newcombe 1961). Solitary cysts are located within the gallbladder wall, are attached to the outside of the gallbladder (e.g., the fundus), or protrude into the gallbladder lumen. Histologically, the cysts are lined by a single layer of non-ciliated columnar epithelium of the biliary type. The cyst epithelium can undergo dysplastic changes and development of carcinoma in situ (Sworn and Gay 1975). Extensive congenital cystic changes can exceptionally result in giant congenital cystic malformation of the gallbladder (Lobe et al. 1986).

Ciliated Foregut Cyst of the Gallbladder

Introduction

Ciliated foregut cysts form a minority of epithelial gallbladder cysts. These cysts are either an incidental finding in abdominal ultrasound examinations or may produce a mass effect in the right upper abdominal compartment, without acute inflammatory signs (Raeburn 1969; Kakitsubata et al. 1995; Nam et al. 2000; Hirono et al. 2002; Muraoka et al. 2003; Koletsa et al. 2005; Bulut and Karayalçin 2010).

Pathology

Macroscopically, ciliated foregut cysts are thin-walled cysts with a fibrous wall and glistening inner surface, the lumen containing a clear or slightly blurry but viscous fluid. The cysts can protrude into the gallbladder lumen (Kakitsubata et al. 1995; Muraoka et al. 2003), but most cysts are in fact located to the level of the submucosa. A communication to the gallbladder lumen is usually lacking, with few exceptions (Koletsa et al. 2005). Histologically, a fibrous wall is lined by a pseudostratified columnar ciliated epithelium with interspersed goblet cells (magenta stained in the PAS stain), sometimes with an underlying layer of smooth muscle cells.

Differential Diagnosis

As in the liver, old and secondarily altered ciliated foregut cysts can show loss of differentiated ciliated cells, the lining being replaced by a simple biliary-type cuboidal epithelium. Such lesions may look like any epithelial cyst, not otherwise specified. The presence of smooth muscle cells in the cyst wall favors a diagnosis of ciliated foregut cyst, even in the absence of ciliated cells.

Pseudoepidermoid Cyst

The gallbladder mucosa is known to undergo squamous metaplasia, which rarely results in the formation of pseudoepidermoid cysts clinically mimicking a gallbladder tumor (Teo et al. 2005).

Duplication Cyst

Congenital duplication of the gallbladder, caused by doubling of the gallbladder anlage, can give rise to cyst lined by the same type of epithelium as the gallbladder partner itself (Kothari et al. 2005).

Bronchogenic Cyst of the Gallbladder

Bronchogenic cysts are cystic lesions derived from ontogenically misplaced bronchial anlages and are characterized by an epithelial lining of ciliated respiratory epithelium with or without associated other bronchial wall components. Bronchogenic cysts prevail in the intrathoracic compartment but may also occur intra-abdominally. Rare examples have been observed in the gallbladder (Kim et al. 2004).

Apart from bronchogenic cyst developing in the gallbladder, such lesions also emerge at the inferior surface of the liver, next to the gallbladder, mimicking a cystic gallbladder tumor (Kim et al. 2004). There are several reports on subdiaphragmatic bronchogenic cysts (reviewed in Kim et al. 2004).

Retention Cyst of the Gallbladder

Marked stenosis or obstruction of the gallbladder causes dilatation of the organ (hydrops), sometimes with accumulation of mucin-rich fluid (mucocele). These mechanisms can give rise to acquired epithelium-lined cysts or retention cysts (Yamada et al. 1996).

Acquired Honeycomb Gallbladder

Honeycomb gallbladder is an acquired, rare form of pseudo-multiseptate gallbladder associated with chronic calculous cholecystitis. Ultrasonography shows a hyperechoic collection with acoustic shadowing on the inferior surface of the liver. Macroscopically, multiple septum-like structures arise from the gallbladder wall and bridge the lumen from side to side, resulting in a honeycomb pattern caused by inflammatory interfold adhesions and synechia (Sasaki et al. 2004).

Congenital Cysts of the Cystic Duct

A deranged development of the cystic duct in the phase of its canalization can result in the formation of a congenital cystic dilatation of this duct, forming a large cyst, eventually containing calculi (cystic malformation of the cystic duct; Pracy 1949; Champetier et al. 1987; Serena Serradel et al. 1991). It has been proposed that cystic malformation of the cystic duct may be classified as type VI cyst in Todani's classification of biliary tract cysts (Maheshwari 2012).

Mesothelial Cyst of the Gallbladder

Apart from gallbladder cysts with either a simple or a ciliated epithelium, few cysts have a mesothelial lining and are termed mesothelial gallbladder cyst (Hoffman et al. 1989).

Differential Diagnosis

Solitary gallbladder cysts may mimic hydrops of the gallbladder (Ghosh and Meyers 1990; Panico et al. 2011), mucocele (Escobar and Neel 2011), true gallbladder diverticulum, diaphragm of the gallbladder (St-Vil et al. 1992), or hydatid disease (Krasniqi et al. 2010). Solitary cysts have also to be distinguished from ciliated foregut cysts of the gallbladder (Kakitsubata et al. 1995) and from carcinomas undergoing marked cystic change (Hiraki et al. 2010). Multilocular epithelial cysts must be distinguished from other multicystic lesions, including echinococcosis, cystadenoma, and cystic lymphangioma. Cysts located in the vicinity of the gallbladder may radiologically be confounded with gallbladder cysts or with the gallbladder itself, e.g., omental cysts (Giyanani et al. 1986).

References

Asada Y, Miura S, Konishi F, Munemoto Y, Kasahara Y, Saitou H, Mitsui T, Iida Y et al (1993) Epithelial inclusion cyst of the gallbladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 90:3070–3075

Benedetti-Valentini S (1954) Calcified echinococcic cysts simulating porcellaneous gallbladder (in Italian). Minerva Chir 9:1176–1179

Berulava OI (1980) Stenosis of the pylorus in combination with a gallbladder cyst (in Russian). Khirurgiia (Mosk) 6:99–100

Bode WE, Aust JB (1983) Isolated cystic dilatation of the cystic duct. Am J Surg 145:828–829

Brambs HJ, Wrazidlo W, Schilling H (1990) The sonographic image of gallbladder adenomyomatosis (in German). Rofo 153:633–636

Bulut AS, Karayalçin K (2010) Ciliated foregut cyst of the gallbladder: report of a case and review of the literature. Pathol Res Int 2010:193535

Cabanie G, Lamy L (1960) Hydatid malformation of the gallbladder from a voluminous cyst of the liver (in French). Bull Soc Pathol Exot Fil 53:41–43

Champetier P, Partensky C, Ponchon T (1987) Cystic malformations of the cystic duct. Surg Radiol Anat 9:287–291

Choi JY, Kim MJ, Chung JJ, Park SI, Lee JT, Yoo HS, Kim L, Choi JS (2002) Gallbladder lymphangioma: MR findings. Abdom Imaging 27:54–57

Cureton RJR, Newcombe JF (1961) Multilocular cyst of the gallbladder. Br J Surg 48:577–580

Deshmukh SS, Gandhi RK, Patel RV, Narshetty GS, Kadam NN, Kadam SN (1999) Cystic duct atresia with cholecystocele. Aust N Z J Surg 69:889–890

Escobar MC, Neel JA (2011) Pathology in practice. Gallbladder mucocele rupture, bile peritonitis, cholestasis, and liver inflammation and necrosis. J Am Vet Med Assoc 239:65–67

Falcao D, Leal AT (1975) Dermoid cyst of the gallbladder. Ann Chir Gynaecol Fenn 64:236–238

Fitzer PM (1978) Epithelial cyst of the gallbladder. Va Med 105:231–232

Fujisawa T, Tomofuji Y, Kuroda N, Hagino H, Sakamoto N, Sakashita M, Maeda M, Kouno T (1995) A case of intramural cyst in the gallbladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 92:1309–1314

Ghosh BC, Meyers HF (1990) Hydrops of the gallbladder. Mil Med 155:A6

Giyanani VL, Jackson MK, Gerlock AJ, McDonald JC (1986) Omental cyst mimicking the gallbladder. J Clin Ultrasound 14:131–133

Hiraki M, Yakushiji H, Hashiguchi K, Harada S, Kohya N, Kai K, Yamaguchi K, Mori D et al (2010) Gallbladder carcinoma with a large monolocular cystic cancerous component. Oncol Lett 1:995–998

Hirono S, Tanimura H, Yokoyama S, Uchiyama K, Tani M, Onishi H, Yamaue H (2002) Clinical features of ciliated foregut cyst of the gallbladder: a rare entity of cystic lesion in the gallbladder. Dig Dis Sci 47:1817–1820

Hoffman CJ, Hales ED, Malachowski ME, Pietrafitta JJ (1989) Mesothelial cyst of the gallbladder. J Clin Ultrasound 17:50–52

Hwang JI, Chou YH, Tsay SH, Chiang JH, Chang CY, Boland GW, Mueller PR (1998) Radiologic and pathologic correlation of adenomyomatosis of the gallbladder. Abdom Imaging 23:73–77

Jacobs E, Ardichvili D, D'Avanzo E, Penneman R, Van Gansbeke D (1991) Cyst of the gallbladder. Dig Dis Sci 36:1796–1802

Jelen J, Marzymska G, Wujkowski S (1974) Pseudocyst of the gallbladder treated surgically (in Polish). Wad Lek 27:2171–2176

Kakitsubata Y, Kakitsubata S, Marutsuka K, Watanabe K (1995) Epithelial cyst of the gallbladder demonstrated by ultrasonography: case report. Radiat Med 13:309–310

Kim KH, Kim JI, Ahn CH, Kim JS, Ku YM, Shin OR, Lee EJ, Lim KW (2004) The first case of intraperitoneal bronchogenic cyst in Korea mimicking a gallbladder. J Korean Med Sci 19:470–473

Koletsa T, Tzioufa V, Michalopoulos A, Apostolides S, Papadopoulos B, Hytiroglou P (2005) Ciliated hepatic foregut cyst communicating with the gallbladder. Virchows Arch 446:200–201

Kothari PR, Kumar T, Jiwane A, Paul S, Kutumbale R, Kulkarni B (2005) Unusual features of gall bladder duplication cyst with review of the literature. Pediatr Surg Int 21:552–554

Krasniqi A, Limani D, Gashi-Luci L, Spahija G, Dreshaj IA (2010) Primary hydatid cyst of the gallbladder: a case report. J Med Case Reports 4:29

Lobe TE, Hayden CK, Merkel M (1986) Giant congenital cystic malformation of the gallbladder. J Pediatr Surg 21:447–448

Maheshwari P (2012) Cystic malformation of cystic duct: 10 cases and review of literature. World J Radiol 4:413–417

Matsumoto M, Maruta M, Maeda K, Utsumi T, Sugioka A, Kuroda M (2002) Epithelial cyst of the gallbladder associated with adenocarcinoma. J Hepatobiliary Pancreat Surg 9:389–392

Mori T, Hasegawa H, Ogiso S, Sakamoto E, Shibahara H, Igami T, Ohira S, Uehara K et al (2002) A case of the cyst of the gallbladder (in Japanese). Nihon Shokakibyo Gakkai Zasshi 99:631–634

Muraoka A, Watanabe N, Ikeda Y, Kokudo Y, Tatemoto A, Sone Y, Kagawa S, Tsumura M et al (2003) Ciliated foregut cyst of the gallbladder: report of a case. Surg Today 33:718–721

Murtaza B, Malik IB, Mahmood A, Sharif MA, Saeed S, Satti AA (2008) Cholecysto-hydatid cyst fistula. J Coll Physicians Surg Pak 18:778–780

Nam ES, Lee HI, Kim DH, Choi CS, Kim YB, Shin HS (2000) Ciliated foregut cyst of the gallbladder: a case report and review of the literature. Pathol Int 50:427–430

Ochsner SF, Blalock JB (1964) Epithelial cyst of the gallbladder. Am J Surg 198:419–420

Panico MR, Vallone G, Mollica C, Nicolai E, Di Cosmo N, Vajro P (2011) Massive hydrops of the gallbladder mimicking a choledochal cyst. J Pediatr Surg 46:1015–1018

Pitiakoudis MS, Tsarpucha AK, Deftereos S, Laftsidis P, Prassopoulos P, Simopoulos CE (2006) Primary hydatid disease in a retroplaced gallbladder. J Gastrointestin Liver Dis 15:383–385

Popkharitov AI, Gulubova MV, Dandov AD, Sivrev DP (2008) Heterotopic gastrointestinal cyst mimicking chronic cholecystitis: a case report. J Med Case Reports 2:173

Pracy DS (1949) Congenital cyst of the cystic duct containing calculi. Br Med J 2:217

Prudkov MI, Titov KV (2001) Cholecystogenic cyst after mucoclasis of the gallbladder as a cause of postcholecystectomy syndrome (in Russian). Vestn Khir Im I Grek 160:79–80

Raeburn C (1969) Ciliated epithelium occurring in a duplication of the gallbladder. J Pathol 97:402–403

Rigas AM, Karatzas GM, Markidis NC, Bonikos DS, Sotiropoulou GG, Skalkeas G (1979) Primary hydatid cyst of the gallbladder. Br J Surg 66:406

Sabat SB, Barhate KP, Deshmukh MP (2008) Cholecysto-hydatid cyst fistula. J Ultrasound Med 27:299–301

Safioleas M, Stamoulis I, Theocharis S, Moulakakis K, Makris S, Kostakis A (2004) Primary hydatid disease of the gallbladder: a rare clinical entity. J Hepatobiliary Pancreat Surg 11:352–356

Saigh J, Williams S, Cawley K, Anderson JC (1985) Varices: a cause of focal gallbladder wall thickening. J Ultrasound Med 4:371–373

Sasaki M, Tokunaga Y, Minami N (2004) The honeycomb gallbladder: a new category of acquired pseudomultiseptate gallbladder. J Hepatobiliary Pancreat Surg 11:375–378

Serena Serradel AF, Santamaria Linares E, Herrera Goepfert R (1991) Cystic dilatation of the cystic duct: a new type of biliary cyst. Surgery 109:320–322

Soldevilla V (1950) Hydatid cyst of the gallbladder simulating carcinoma (in Spanish). Rev Esp Enferm Apar Dig Nutr 9:484–488

Spector SA, Fernandez VE, Vernon SE, Dunkin B, Livingstone AS (2003) Gallbladder cystadenoma and common bile duct obstruction. Int J Gastrointest Cancer 34:151–155

St-Vil D, Luks FI, Hancock BJ, Garel L, Brochu P, Blanchard H, Bensoussan AL (1992) Diaphragm of the gallbladder: a case report. J Pediatr Surg 27:1301–1303

Sworn MJ, Gay P (1975) A fundal cyst of the gallbladder: an unusual abdominal mass. Med J Aust 23:307–308

Teo CH, Leow CK, Chang SA (2005) A pseudoepidermoid cyst arising from exuberant squamous metaplasia of the gallbladder. Arch Pathol Lab Med 129:e138–e140

Weiler H, Grandel A, Frühmorgen P (2003) Congenital cystic dilatation of the cystic duct associated with an anomalous pancreaticobiliary junction (in German). Ultraschall Med 24:197–201

Yamada M, Hoshino U, Daitoh K, Tasaki M, Satoh M (1996) Retention cyst of the gallbladder (In Japanese). Ryoikibetsu Shokogun Shirizu 9:456–458

Tumor-Like Infections and Infestations of the Gallbladder (Infectious and Parasitic Pseudotumors)

161

Contents

Abstract

Similar to liver and bile ducts, the gallbladder can be subject to several types of tumor-like infections and infestations. The gallbladder is a well-known site of actinomycosis. Gallbladder actinomycosis presents with the clinical picture of acute or subacute calculous cholecystitis. The inflammation is an aggressive process and can extend into the gallbladder fossa and from there to the liver substance. Tuberculosis can involve the gallbladder, but is one of the rarest forms of abdominal tuberculosis. It can present as an ulcerating cholecystitis or a tumor-like granulomatous process mimicking cancer. Other bacterial infections of the gallbladder with mass lesions comprise brucellosis and several types of mycosis. The gallbladder is sometimes involved in hydatid disease and other parasitoses.

Actinomycosis of the Gallbladder

Introduction

Actinomycosis is an important infectious disease of the hepatobiliary tract, discussed in a separate chapter. However, the gallbladder is the least common anatomical site of hepatobiliary actinomycosis, with only few single cases having been reported. Gallbladder actinomycosis can cause extensive destruction of the organ and is

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_161

associated with an invasive process that may closely mimic gallbladder malignancy.

Microbiology

The microbiological features of *Actinomyces* (*A.*) are discussed in detail elsewhere. In gallbladder actinomycosis, *A. israelii* and *A. naeslundii* have been identified as causative agents.

Clinical Features

Gallbladder actinomycosis usually presents with the symptoms and signs of acute or subacute calculous cholecystitis, with abruptly starting upper quadrant abdominal pain and fever (Coleman et al. 1969; Marrie et al. 1977; Smithers et al. 1983; Freland et al. 1987; van Steensel and Kwan 1988; Gerich et al. 1990; Mutter et al. 1993; Acevedo et al. 2008; Lee et al. 2009). Sonography showed a thickened and edematous gallbladder wall, as in other forms of acute cholecystitis (Hefny et al. 2005). The inflammatory process may extend into the gallbladder fossa and from there to the liver, causing liver abscess (Brewer and Allen 1980). Due to the tissue-destructive feature of the infection, fistulas between the gallbladder and common bile duct, duodenum, or stomach may develop (Bledsoe et al. 2008). Clinically and radiologically, gallbladder actinomycosis can mimic gallbladder malignancy (Lee et al. 2007), but gallbladder actinomycosis has also been observed in association with gallbladder adenocarcinoma (Merle-Melet et al. 1995; El Amine et al. 2013). Actinomycosis can also develop in the cholecystic duct remnant following cholecystectomy (Ormsby et al. 1998).

Pathology

Macroscopy

In gallbladder actinomycosis, the serosa is hyperemic and sometimes coarsely granular due to the presence of actinomycotic colonies, the so-called sulfur granules. This phenomenon is caused by the destructive growth of the infectious process, invading the gallbladder wall in a cancer-like manner to reach the serosal surface. The gallbladder wall itself is thickened and edematous or hemorrhagic, with foci of purulent exudate. Extension to the serosa can cause fistulation, with escape of purulent bile onto the serosal surface.

Histopathology

Histomorphology is dominated by a severe suppurative and later granulating inflammation, often with destruction of the preexisting layers of the gallbladder wall and extension into adjacent tissues. Microabscesses may be seen (Hefny et al. 2005). In the purulent exudate, typical microbial drusen forming sulfur granules are present (Lee et al. 2009); for more details, see the respective chapter on liver actinomycosis. These bacterial colonies are composed of Gram-positive, filamentous organisms.

Differential Diagnosis

Radiologically, retroperitoneal actinomycosis, e.g., associated with dropped gallstones (Ramia et al. 2004), can mimic the destructive process characterizing gallbladder actinomycosis.

Tuberculosis of the Gallbladder

Introduction

Abdominal tuberculosis is one of the most common forms of extrapulmonary tuberculosis, with a prevalence in developing countries as high as 12 %. Abdominal localizations of the infection increase in number during the last years, mainly due to acquired immunodeficiency, intravenous drug abuse, and the emergence of virulent mycobacterial strains with multiresistance. Among

abdominal manifestations of tuberculosis, tuberculosis of the gallbladder (cholecystitis tuberculosa) is one of the rarest forms but is still diagnosed in endemic areas. It was estimated that gallbladder tuberculosis accounts for about 1 % of all cases of abdominal tuberculosis (Goyal et al. 1998). The rarity of gallbladder tuberculosis, in comparison with the much more common tuberculosis of the liver, has been proposed to be due to a protective effect of bile against mycobacterial infection.

Epidemiology

Gaucher is said to be the first to have reported gallbladder tuberculosis in 1870 (cited in Lazarus and Eisenberg 1934). Gaucher's patient had, at necropsy, pulmonary tuberculosis and tuberculous involvement of several inner organs, including the liver. The gallbladder showed a hazelnut-sized tuberculous mass.

The first histologically proven case of gallbladder tuberculosis was, however, only reported in 1894 (Heddaeus 1894). This author described a 44-year-old female who presented with a fistulating tumor in the right upper abdomen. The fistula was surgically explored and revealed a connection with the gallbladder which contained caseous necroses. In 1908, Simmonds summarized five cases observed to this time point (Braquehaye 1901; Kisch 1902; Beitzke 1905; Knotte 1907), and reported his own case, a 9-month-old child suffering from miliary tuberculosis and showing miliary foci in the gallbladder mucosa (Simmonds 1908). The 41-year-old female patient described by Braquehaye (1901) is probably the first case of isolated gallbladder tuberculosis. The patient had no evidence of other sites of tuberculosis and was healed following cholecystectomy alone. In the patient of Kisch (1902), a 57-year-old female patient, gallbladder tuberculosis was associated with nodular hepatic tuberculosis and generalized organ tuberculosis and had led to a cholecystocolonic fistula. Several other cases were reported in the first 20 years of the twentieth century, only in part with histologic confirmation (Calabrée 1910). A first extensive compilation of cases appeared in a thesis as of 1922 (Altmeyer 1922). In 1955, 36 proven cases of gallbladder tuberculosis have been compiled, together with a series of questionable cases (Weitz 1955).

Whereas gallbladder tuberculosis is very rarely seen in western countries, studies from southern, southeast, and east Asia document that this disorder is more common in these regions, mainly in patients with abdominal tuberculosis. In a study from India covering the time period between 1996 and 2010, seven out of 209 patients who had undergone biliary tract surgery with a preoperative diagnosis of gallbladder carcinoma or carcinoma of the common bile duct in fact had biliary tract tuberculosis (Govindasamy et al. 2011). Gallbladder tuberculosis develops most often in women over 30 years of age (Duan et al. 1992; Abu-Zidan and Zayat 1999). In the majority of cases, it develops in the setting of abdominal tuberculosis, but rare cases of isolated gallbladder tuberculosis are also known (Lazarus and Eisenberg 1934; Piper et al. 1987; Gupta et al. 1998; Ruhl et al. 2003). The presence of gallstones is detected in more than 90 % of cases of gallbladder tuberculosis, cholelithiasis therefore considered as a condition favoring tuberculous infection of the gallbladder (Bergdahl and Boquist 1972; Ziarek et al. 1975). Rarely, gallbladder tuberculosis has also been diagnosed in patients with pulmonary tuberculosis (Rozmanic et al. 2001) and has been observed in a gallbladder affected by biliary papillomatosis (Nakajo et al. 1988).

Clinical and Imaging Features

The clinical and imaging features of gallbladder tuberculosis have been described in numerous reports, mostly on the basis of single cases. Simmonds (1908) divided gallbladder tuberculosis into two forms: (a) acute gallbladder tuberculosis, characterized by multiple mucosal

ulcerations containing acid-fast bacilli and/or miliary tubercles/granulomas, and (b) chronic granulomatous cholecystitis. Leader (1952) proposed to distinguish a diffuse or miliary form from a local form, the latter being subdivided into a focal or nodular form, consisting of single or multiple conglomerate tubercles forming tumor-like tuberculomas, and a tubular form, also involving the intrahepatic bile ducts. Weitz (1955) proposed four clinical groups of gallbladder tuberculosis, i.e., (a) acute or subacute miliary tuberculosis in children having ulcerated tubercles of the gallbladder mucosa; (b) gallbladder tuberculosis in patients with severe generalized tuberculosis, often with extensive pulmonary phthisis, tubercles in mediastinal and mesenterial lymph nodes, splenic tuberculosis, tuberculous lesions in the intestinal tract and liver, and terminal miliary spread with leptomeningitis; (c) isolated gallbladder tuberculosis; and (d) other or miscellaneous forms. Another clinical classification with four forms distinguishes (a) involvement of the gallbladder as a component of miliary tuberculosis in children and adults, (b) gallbladder tuberculosis as a component of disseminated abdominal tuberculosis, (c) isolated gallbladder tuberculosis in the absence of tuberculous disease elsewhere, and (d) involvement of the gallbladder in the setting of immunosuppression.

Clinically, gallbladder tuberculosis may present with a right hypochondrial mass, jaundice, findings suggestive of gallbladder empyema, and low-grade fever/fever of unknown origin. In 70–90 % of cases, gallbladder tuberculosis was associated with the presence of gallstones (Bergdahl and Boquist 1972; Ziarek et al. 1975; Rouas et al. 2003). Gallbladder tuberculosis may present as acute abdomen caused by gallbladder perforation (Hahn et al. 1995), and tuberculosis of the gallbladder neck may be a cause of cholecystitis. In the course of imaging studies, the preoperative diagnosis is often confused with various other gallbladder diseases (Ramia et al. 2006). Sonographic and CT studies revealed several typical patterns of tuberculous gallbladder disease, including micronodular lesions of the gallbladder wall, diffuse or circumscribed wall thickening, and a tumor-like gallbladder mass (Ben et al. 1995; Jain et al. 1995; Abu-Zidan and Zayat 1999; Xu et al. 2011).

Selected References Rankin and Massie 1926; Lazarus and Eisenberg 1934; Arias 1950; Leader 1952; Schwartz et al. 1954; Weitz 1955; Farkas 1960; Wohlgemuth et al. 1960; Giordano et al. 1961; Burakov 1965; Pfeifer and Reiher 1966; Rybkowski 1966; Krejczy and Krejczy 1967; Mlynek and Engel 1968; Erdelyi and Fenyvesi 1969; Kretschmar and Rosenkranz 1969; Bergdahl and Boquist 1972; Ziarek et al. 1975; Czerwinski 1979; Luez et al. 1979; Misgar et al. 1980; Eroukhmanoff et al. 1982; Ahmad et al. 1983; Grassini et al. 1984; Piper et al. 1987; Abascal et al. 1988; Arlandis Felix et al. 1990; Ben et al. 1995; Ikai et al. 1996; Jassem et al. 1996; D'Agta et al. 1997; Zhang et al. 1997; Goyal et al. 1998; Gupta et al. 1998; Kumar et al. 2000; Garg et al. 2001; Yu and Liu 2002; Banerjee and Sen 2003; Pandya et al. 2003; Ruhl et al. 2003; El Malki et al. 2006; Kapoor et al. 2006; Ramia et al. 2006; Saluja et al. 2007; Sobnach et al. 2010; Leong et al. 2011; Soufi et al. 2011; Verma et al. 2012, 2013; Rejab et al. 2013.

Pathology

Macroscopy

Cholecystectomy specimens in gallbladder tuberculosis show a markedly thickened wall, mainly of the fundus. The serosal surface may show adhesions and sometimes tiny white to gray nodules representing caseating granulomas (miliary lesions). Cut surfaces of the gallbladder wall show small to large caseiform necrosis of ovoid to highly irregular shape. Typically, and in contrast to pyogenic abscesses, these necroses are cream-white instead of dark-yellow, have the consistency of a thick and viscous fluid, and stick to the knife and to the gloves. In rare cases, tuberculous necrosis is not whitish in color but shows a

quince-yellow tinge. In cases with extensive gallbladder destruction, theses caseating masses may fill the gallbladder lumen or may protrude through transmural defects of the gallbladder wall. In long-standing disease, the necrosis becomes compact and putty-like, with or without calcifications. Large and in particular conglomerated lesions may resemble a necrotic malignancy of the gallbladder.

Histopathology

The histology of the lesions is that of a granulomatous inflammation with caseating necrosis and the presence of Langhans giant cells, as in other forms of tuberculosis. Tuberculosis can cause transmural destruction of the gallbladder wall, with extension to the peritoneal surface (Peritonitis tuberculosa), invasion of the gallbladder fossa, and gallbladder perforation with development of bilomas (Hahn et al. 1995). In acute forms of gallbladder tuberculosis, mucosal ulcerations with a necrotic center develop, these lesions containing numerous acid-fast bacilli and representing an anergic reaction. Gallbladder tuberculosis is sometimes associated with tuberculous lesions of the liver, including miliary hepatic tuberculosis (Mirski and Zielinski 1972). The tuberculous infection can involve tissues in the draining area of the gallbladder, including lymph vessels and perilymphangial tissues. Following cholecystectomy, the tuberculous inflammation may continue from these remaining tissue compartments, eventually giving rise to postoperative fistulas (Gupta et al. 1998).

Tuberculosis of Lymph Nodes Associated with Gallbladder

As in other organs, tuberculosis of the gallbladder undergoes lymphogenous spread to locoregional lymph nodes, sometimes forming a primary complex. Lymph nodes that are typically involved comprise the cystic node, lymph nodes of the hepatoduodenal ligament, and peripancreatic lymph nodes (Remmele and Lennert 1957; Vojtisek and Zrustova 1965). In case the cystic node is affected by tuberculosis, the gallbladder is almost always infected (Prasad and Pandey 2001). Tuberculosis detected in these lymph node systems is, however, not always associated with gallbladder tuberculosis. Rarely, isolated cystic duct tuberculosis was diagnosed (De Melo et al. 2004; Sidhu et al. 2007), and isolated peripancreatic tuberculous lymphadenitis was found as a rare manifestation of abdominal tuberculosis (Huang et al. 2013).

Gallbladder Tuberculosis as a Disorder Mimicking Gallbladder Malignancy

As gallbladder tuberculosis can form large necrotic mass lesions (tuberculomas), this specific inflammation may clinically and radiologically mimic malignant neoplasms of the gallbladder, specifically gallbladder carcinoma (Hegler 1925; Rankin and Massie 1926; Ben et al. 1995; Garg et al. 2001; Bikhchandani et al. 2005; Verma et al. 2012). Conglomerate tuberculous lesions with confluent caseating necrosis can replace the gallbladder, invade the gallbladder fossa, and may involve the liver substance. Such aggressive mass lesions are termed pseudotumoral gallbladder tuberculosis (Soufi et al. 2011).

Differential Diagnosis

The “classical” histological presentation of tuberculosis can hardly be confounded with other disease processes, except certain rare mycoses.

Pathways of Infection

It seems that gallbladder tuberculosis is often associated with abdominal extra-gallbladder tuberculosis (Xu et al. 2011), suggesting that the gallbladder is secondarily involved via so far not

well-known routes of microbial spread. It has been proposed that the gallbladder becomes involved by the contiguous spread of mycobacteriosis from adjacent infected lymph nodes and lymph vessels, the peritoneum, an enterohepatic route, or via a hematogenous route (review: Abu-Zidan and Zayat 1999). An interesting finding is the observation of gallstones in up to 90 % of patients with gallbladder tuberculosis, suggesting a pathogenic role of lithiasis in biliary tract tuberculosis (Bergdahl and Boquist 1972; Ziarek et al. 1975).

Brucellosis

Species of *Brucella*, in particular *Brucella melitensis*, can cause acute acalculous or calculous cholecystitis (Morris et al. 1979; Fasquelle et al. 1999; Miranda et al. 2001; Kanafani et al. 2005; Al-Otaibi 2010). Exceptionally, mass lesions ("brucellomas") caused by *Brucella* infection develop in the gallbladder. A female patient who had had febrile brucellosis developed, after a period of 19 years, right upper quadrant pain. CT examinations revealed a mass contiguous with the gallbladder and extending intrahepatically, suspicious of cancer. The resection specimen showed mass-forming granulomatous cholecystitis and PCR of tissue resulted in the diagnosis of *Brucella* infection (Ögredici et al. 2010).

Mycoses of the Gallbladder

Due to the induction of purulent inflammation and a granulomatous response, fungal infections of the gallbladder may rarely induce infectious pseudotumors. However, most fungal infections of the gallbladder are characterized by acute cholecystitis. Fungi that causes gallbladder disease include *Candida albicans*, *Candida lusitaniae*, *Candida famata*, *Candida tropicalis*, *Mucor*, and *Torulopsis glabrata* (Warren and Marsh 1982; Diebel et al. 1996; Santos et al. 2004; Yildirim et al. 2008; Lacarrière et al. 2011; Jajoo et al. 2012; Araujo et al. 2013). In the course of fungal septicemia, *Candida tropicalis* produced gallbladder masses (Jajoo et al. 2012). In the setting of gastrointestinal basidiobolomycosis (*Basidiobolus ranarum*), tumor-like lesions mimicking malignancy relatively often develop in liver and gallbladder (Vikram et al. 2012).

Echinococcosis of the Gallbladder

Introduction

Echinococcosis, which presents in two forms caused by two species, i.e., hydatid disease and alveolar echinococcosis, is endemic in certain regions of the world and is known to typically involve the hepatobiliary tract. However, and in contrast to the liver, gallbladder echinococcosis is a very rare disease, even in endemic areas. Secondary involvement of the gallbladder by echinococcosis of the liver is more frequent than bona fide primary gallbladder echinococcosis. The reason for the uncommon involvement of the gallbladder is currently unknown. Gallbladder involvement may result in tumor-like masses that are sometimes confounded with malignancy.

Hydatid Disease of the Gallbladder

Echinococcus granulosus/*hydatidosus* is the more common species to involve the gallbladder, several reports having described the clinicopathological features of this rare entity (Putnik and Ciric 1953; Ansimov 1962; Khrokhlov 1967; Greida 1973; Rigas et al. 1979; Bacciu et al. 1980; Raza et al. 2003; Safioleas et al. 2004; Pitiakoudis et al. 2006; Krasniqi et al. 2010). Among 183 patients with abdominal hydatid cysts, only 12 patients had only extrahepatic abdominal involvement (6.5 %), involvement of the gallbladder amounting to only 0.6 %, being as rare as adrenal echinococcosis (Wani et al. 2005). The gallbladder may secondarily be involved via expansion of bile duct hydatidosis into the gallbladder following rupture of hydatids (Yücesoy and Poçan 2014). Ultrasonographically, the cysts

typically produce an annular pattern with undulating membranes and signs of membrane detachment (Ivanis et al. 1994; Kapoor et al. 2000). The cystic parasite elicits a marked inflammatory and fibrosing reaction in the gallbladder wall, sometimes with acute cholecystitis or even gallbladder phlegmon (Makokha 1961; Mizaushev and Emuzov 1979), leading to an ill-defined cystic mass lesion that may mimic gallbladder malignancy (Soldevilla 1950). Gallbladder hydatid cysts may undergo suppuration associated with gallbladder empyema (Celoria et al. 1980).

Echinococcus alveolaris of the Gallbladder

Primary alveolar echinococcosis of the gallbladder is a very rare manifestation of this parasite (Pautov 1964).

Pathology

Macroscopy

Echinococcus hydatidosus/granulosus of the gallbladder manifests as a monocystic or multicystic parasite similar to other localizations, in particular the liver. The cyst walls are firm and fixed by connective tissue with adjacent wall components. The cysts usually grow extramucosally, but they can markedly narrow the gallbladder lumen, as they bulge into the gallbladder cavity. Upon opening of the cysts, a jelly-like material appears, containing whitish lamellae that form complex and sometimes concentric structures. Secondary daughter cysts and grape-like, milky-white collections of embryonal parasites forming coralliform colonies are often seen. In the wall of the cysts, patchy calcifications are often noted (Tkebuchava 1966; Krasniqi et al. 2010). Hydatid cysts of the gallbladder can sometimes undergo massive calcification, with calcium salt deposits involving entire cysts and the pericystic tissue, resulting in a gross presentation resembling porcelain gallbladder (Benedetti-Valentini 1954).

Histopathology

The histopathology of gallbladder echinococcosis is the same as that of other hepatobiliary manifestations of this parasite.

Differential Diagnosis

The most important differential diagnosis is echinococcosis of the liver encroaching upon, invading, or rupturing into the gallbladder (Ivanov 1957; Cangiotti et al. 1994; Abou-Khalil et al. 1996; Murtaza et al. 2008; Rabbani et al. 2011). Fistulous communications between hepatic hydatid cysts and the gallbladder are described (Kumar et al. 2004; Adaletli et al. 2005; Murtaza et al. 2008). Hepatic hydatid cysts may rupture into the gallbladder, with subsequent obstruction of the cystic duct by a daughter cyst acting as a ball valve and causing acalculous cholecystitis (Abou-Khalil et al. 1996). Bile sludge can radiologically mimic hydatid cyst membranes (Kara et al. 2010). Rupture of hepatic hydatid cysts into the biliary tract may elicit eosinophilic cholecystitis (Alfaro et al. 1995).

Pathogenic Pathways

Apart from the portal circulation, it has been suggested that echinococcus embryos can spread via other routes to the gallbladder, including the biliary tract (Cangiotti et al. 1994; Raza et al. 2003), the peritoneal cavitary pathway (Cangiotti et al. 1994), or the lymphatic system via lymphatic transport of oncospheres from the intestine to the gallbladder (Rigas et al. 1979; Safioleas et al. 2004). Based on the observation of hydatid cysts located inside the gallbladder, two groups proposed dissemination of embryos (brood capsules) through the biliary tract/cystic duct, but such a pathway has never been proven (Cangiotti et al. 1994; Raza et al. 2003; reviewed in Krasniqi et al. 2010).

Other Infestations of the Gallbladder

Schistosomiasis (bilharziosis) often involves the gallbladder in certain endemic areas, and deposition of eggs with schistosomulae causes granulomatous schistosomal cholecystitis (Rappaport et al. 1975, Sharara et al. 2001). The gallbladder can be infested by *Ascaris lumbricoides*, a nematode parasite that can ascend bile ducts and migrate through the cystic duct (review: Khanduri et al. 2014). A very rare parasitosis of the gallbladder is cysticerosis (Punia et al. 2010). Paragonimiasis, a common parasitosis of the lungs, exceptionally infests the hepatobiliary tract, including the gallbladder (Salinas et al. 1999).

References

Abascal J, Martin F, Abreu L, Pereira F, Herrera J, Ratia T, Menendez J (1988) Atypical hepatic tuberculosis presenting as an obstructive jaundice. Am J Gastroenterol 83:1183–1186

Abou-Khalil S, Smith BM, Maclean JD, Poenaru D, Fried GM, Bret P, Barkun AN (1996) Acute cholecystitis and cholangitis caused by Echinococcus granulosus. Am J Gastroenterol 91:805–807

Abu-Zidan FM, Zayat I (1999) Gallbladder tuberculosis: case report and review of the literature. Hepatogastroenterology 46:2804–2806

Acevedo F, Baudrand R, Letelier LM, Gaete P (2008) Actinomycosis: a great pretender. Case reports of unusual presentations and a review of the literature. Int J Infect Dis 12:358–362

Adaletli I, Yilmaz S, Cakir Y, Kervancioglu R, Bayram M (2005) Fistulous communication between a hepatic hydatid cyst and the gallbladder: diagnosis with MR cholangiopancreatography. AJR Am J Roentgenol 185:1211–1213

Ahmad MN, Zargar HU, Shahdad NA, Sapru A, Kaur S (1983) Tuberculosis of gallbladder (a case report). J Postgrad Med 29:258–260

Alfaro Torres J, Fernandez Fernandez L, Hörndler Argarate C, Ruiz Liso JM, Sanz Anguela JM et al (1995) Eosinophilic cholecystitis associated with rupture of hepatic hydatid cyst of the bile ducts (in Spanish). Rev Esp Enferm Dig 87:899–902

Al-Otaibi FE (2010) Acute acalculous cholecystitis and hepatitis caused by Brucella melitensis. J Infect Dev Ctries 4:464–467

Altmeyer F (1922) Ueber die Tuberkulose der Gallenblase und gleichzeitige Uterustuberkulose. Thesis, Cologne

Ansimov AF (1962) On echinococcosis of the gallbladder and bile ducts (in Russian). Khirurgia (Mosk) 38:106–107

Araujo PS, Medeiros Z, Melo FL, Maciel MA, Melo HR (2013) Candida famata-induced fulminating cholecystitis. Rev Soc Bras Med Trop 46:795–796

Arias Vallejo E (1950) Acute tuberculous cholecystitis. Gastroenterology 16:501–504

Arlandis Felix FJ, Villalobos Talero J, Mazure Lenhoff RA, Cabrerizo Comitre E, Polo Camacho M et al (1990) Tuberculosis of the biliary system: presentation of a case and review of the literature (in Spanish). Rev Espan Enferm Dig 78:43–45

Bacciu PP, Marongiu GM, Dettori G, Gherli T, Biglioli P (1980) Echinococcosis of the gallbladder: pathogenetic considerations (in Italian). Chir Ital 32:783–789

Banerjee S, Sen S (2003) Tuberculosis of the gallbladder. J Indian Med Assoc 101:556–557

Beitzke K (1905) Ueber einen Fall von tuberkulöser Cholecystitis. Zentralbl Path 16:106

Ben RJ, Young T, Lee HS (1995) Hepatobiliary tuberculosis presenting as a gallbladder tumor. Scand J Infect Dis 27:415–417

Benedetti-Valentini S (1954) Calcified echinococcoic cysts simulating porcellanous gallbladder (in Italian). Minerva Chir 9:1176–1179

Bergdahl L, Boquist L (1972) Tuberculosis of the gallbladder. Br J Surg 59:289–292

Bikhchandani J, Malik VK, Kumar V, Sharma S (2005) Hepatic tuberculosis mimicking carcinoma gall bladder. Indian J Gastroenterol 24:25

Bledsoe SE, Oliver AE, Delgado DG, Kent RB (2008) Concomitant cholecystoduodenal fistula and cholecystocholedochal fistula due to actinomyces. Am Surg 74:133–135

Braquehaye MJ (1901) Bull Soc Chir Paris 27:1082, cited in Knotte (1907) and Altmeyer (1922)

Brewer JH, Alen MJ (1980) Actinomycosis of the gallbladder with liver abscess. South Med J 73:1070–1072

Burakov GG (1965) Tuberculosis of the gallbladder. Probl Tuberkuletza 43:79–80

Calabrée L (1910) A propos de deux cas inédits de tuberculose de la vésicule biliaire. Rev Internat Tubercul 18:110

Cangiotti L, Muiesan P, Begni A, de Cesare V, Pouchè A, Giulini SM, Tiberio G (1994) Unusual localizations of hydatid disease: a 18 year experience. G Chir 15:83–86

Celoria G, Beatini M, Larghero GC, Paulazzo D (1980) A case of empyema of the gallbladder adjacent to a suppurated echinococcal cyst (in Italian). Arch Maragliano Patol Clin 36:67–68

Coleman RM, Georg LK, Rozzell AR (1969) Actinomyces naeslundii as an agent of human actinomycosis. Appl Microbiol 18:420–426

Czerwinski L (1979) Isolated gallbladder tuberculosis (in Polish). Polski Przeglad Chirurgiczny 51:173–174

D'Agta A, Funto I, Lazzi S, Bonocompagni G (1997) Video laparoscopic cholecystectomy in a case of biliary

lithiasis associated with gallbladder tuberculosis. Minerva Chir 52:1103–1108
De Melo VA, de Melo GB, Silva RL, Piva N, Almeida ML (2004) Tuberculosis of the cystic duct lymph node. Braz J Infect Dis 8:112–114
Deycke C (1910) Primary tuberculosis of the gallbladder with stone formation (in German). Dtsch Med Wochenschr 2171
Diebel LN, Raafat AM, Dulchavsky SA, Brown WJ (1996) Gallbladder and biliary tract candidiasis. Surgery 120:764–765
Duan JG, Liu CL, Chen Y (1992) One case of gallbladder tuberculosis. Chin J Radiol 26:379
El Malki HO, Benkabbou A, Mohsine R, Ifrine L, Belkouchi A, Balafrei S (2006) Gallbladder tuberculosis (in French). Can J Surg 49:135–136
El-Amine O, Lahmar A, Zamali N, Bouraoui S, Sabbagh S, Khalfallah T, Mzabi-Regaya S (2013) Actinomycosis associated adenocarcinoma of the gallbladder (in French). Tunis Med 91:74–75
Erdelyi B, Fenyvesi E (1969) Isolated tuberculosis of the gallbladder. Orv Hetil 110:1934–1937
Eroukhmanoff P, Bazelly B, Cohen-Solal JL, Milleron B, Favre M, Flabeau F (1982) Tuberculosis of the gallbladder: apropos of a case with histological identification (in French). Nouv Presse Med 11:3795–3796
Farkas S (1960) Cholecystitis tuberculosa (in German). Zentralbl Chir 85:2312–2314
Fasquelle D, Charignon G, Rami M (1999) Acute cholecystitis in a patient with brucellosis. Eur J Clin Microbiol Infect Dis 18:599–600
Freland C, Massoubre B, Horeau JM, Caillon J, Drugeon HB (1987) Actinomycosis of the gallbladder due to Actinomyces naeslundii. J Infect 15:251–257
Garg P, Godara R, Karwasra RK, Jain R, Yadav V (2001) A palpably enlarged hard gall bladder can be tubercular. Indian J Gastroenterol 20:120
Gerich RP, Vainagii MV, Shapoval AL, Visitskaia NI (1990) Actinomycosis of the gallbladder (in Russian). Klin Khir 9:67–68
Giordano FP, Bogetti H, Interguglielmo R (1961) Tuberculosis of the gallbladder (in Spanish). Bol Trab Soc Cir B Aires 45:247–254
Govindasamy M, Srinivasan T, Varma V, Mehta N, Yadav A, Kumaran V, Nundy S (2011) Biliary tract tuberculosis – a diagnostic dilemma. J Gastrointest Surg 15:2172–2177
Goyal SC, Goyal R, Malhotra V, Kaushik K (1998) Tuberculosis of the gall bladder. Indian J Gastroenterol 17:108
Grassini M, Cavanenghi D, Amerio GM, Sorisio V (1984) Apropos of a case of tuberculosis of the gallbladder (in Italian). Minerva Chir 39:573–575
Greida BP (1973) Echinococcosis of the gallbladder (in Russian). Klin Khir 5:49–50
Gupta NM, Khaitan A, Singh V, Radotra B (1998) Isolated gallbladder tuberculosis with postoperative biliary fistula. Endoscopy 30:S73–S74
Hahn ST, Park SH, Shin WS, Kim CY, Shinn KS (1995) Gallbladder tuberculosis with perforation and intrahepatic biloma. J Clin Gastroenterol 20:84–86
Heddaeus A (1894) Tuberkulose der Gallenblase. Bruns' Beitr 12:440
Hefny AF, Torab FC, Joshi S, Sebastian M, Abu-Zidan FM (2005) Actinomycosis of the gallbladder: case report and review of the literature. Asian J Surg 28:230–232
Hegler C (1925) Tumor-like cholecystitis and cholangitis tuberculosa (in German). Virchows Arch Pathol Anat Physiol Klin Med 254:272–276
Huang CT, Lo CY, Lee TH (2013) Isolated peripancreatic tuberculous lymphadenopathy: a rare manifestation of abdominal tuberculosis mimicking pancreatic cystic neoplasm. J Dig Dis 14:105–108
Ikai M, Itoh M, Sano H, Joh T, Yokoyama Y, Takeuchi T (1996) Tuberculosis of the gallbladder. Ryokibetsu Shokogun Shirizu 9:219–221
Ivanis N, Rubinic M, Gudovic A, Zeidler F (1994) Ultrasound image of an echinococcus daughter cyst in the gallbladder (in German). Ultraschall Med 15: 269–271
Ivanov PA (1957) Rupture of echinococcus liver cyst into gallbladder (in Russian). Khirurgia (Mosk) 33: 116–117
Jain R, Sawhney S, Bhargava D, Berry M (1995) Gallbladder tuberculosis: sonographic appearance. J Clin Ultrasound 23:327–329
Jajoo M, Kumar V, Goyal VK, Garg A (2012) Candida tropicalis infection in a term neonate with gall bladder masses and infective endocarditis. Asian Pac J Trop Med 5:410–412
Jassem E, Smialek U, Wojcikiewicz K, Jaskiewicz J, Mierzejewska E (1996) Gallbladder tuberculosis and stomach cancer (in Polish). Pneumologia I Allergol Polska 64:85–87
Kanafani ZA, Sharara AI, Issa IA, Kanj SS (2005) Acute calculous cholecystitis associated with brucellosis: a report of two cases and review of the literature. Scand J Infect Dis 37:927–930
Kapoor A, Sarma D, Gandhi D (2000) Sonographic diagnosis of a ruptured primary hydatid cyst of the gallbladder. J Clin Ultrasound 28:51–52
Kapoor S, Sewkani A, Naik S, Sharma S, Jain A, Varshney S (2006) Myriad presentations of gall bladder tuberculosis. Indian J Gastroenterol 25:103–104
Kara T, Akpinar E, Sarikaya B, Dagoglu G, Akhan D (2010) Bile sludge that mimics hydatid cyst membranes: a potential pitfall for ultrasound. J Gastrointest Liver Dis 19:126
Khanduri S, Parashari UC, Agrawal D, Bhadury S (2014) Ascariasis of the gallbladder: a rare case report and a review of the literature. Trop Doct 44:50–52
Khrokhlov NF (1967) Echinococcosis of gallbladder and bile ducts (in Russian). Sov Zdravookhr Kirg 3:26–27
Kisch A (1902) Ueber einen Fall von Cholecystitis tuberculosa chronica. Prager Med Wochenschr 27:61–65

Knotte E (1907) Ueber einen Fall von schwerer Allgemeintuberkulose mit Herz-und Gallenblasentuberkulose. Thesis, Leipzig

Krasniqi A, Limani D, Gashi-Luci L, Spahija G, Dreshaj IA (2010) Primary hydatid cyst of the gallbladder: a case report. J Med Case Rep 4:29

Krejczy K, Krejczy H (1967) A case of tuberculosis of the gallbladder (in Polish). Grizlica I Choroby Pluc 35:491–492

Kretschmar KH, Rosenkranz M (1969) Gallbladder tuberculosis. Zentralbl f Allg Pathol Pathol Anat 112:281–285

Kumar K, Ayub M, Kumar M, Keswani NK, Shukla HS (2000) Tuberculosis of the gallbladder. HPB Surg 11:401–404

Kumar A, Upadhyaya DN, Singh S, Kumar M, Ansari MA (2004) Cholecysto-hydatid cyst fistula. Indian J Gastroenterol 23:76–77

Lacarrière E, Lacaze L, Schwarz L, Huet E, Lemoine F, Scotté M (2011) First case of gastrointestinal mucormycosis in an immunocompromised patient with gallbladder and duodenum involvement. Infection 39:595–598

Lazarus JA, Eisenberg AA (1934) Tuberculosis of the gallbladder, report of a case of primary tuberculous cholecystitis. Am J Surg 24:166–173

Leader SA (1952) Tuberculosis of the liver and gallbladder with abscess formation: a review and case report. Ann Intern Med 37:594–606

Lee YH, Kim SH, Cho MY, Rhoe BS, Kim MS (2007) Actinomycosis of the gallbladder mimicking carcinoma: a case report with US and CT findings. Korean J Radiol 8:169–172

Lee JH, Hwang ET, Kim KH, Jo HJ, Kim TH, Choi SC, Choi CS (2009) A case of actinomycosis of gallbladder presenting as acute cholecystitis (in Korean). Korean J Gastroenterol 53:261–264

Leong BD, Chan KW, Ramu P, Kumar VM, Chuah JA (2011) Tuberculosis of gallbladder with candidiasis, a rare entity. Med J Malaysia 66:146–147

Luez J, Deregnaucourt G, Benoit M (1979) Tuberculosis of the gallbladder. Lille Medical 24:97–99

Makokha NS (1961) A case of acute hydatid cholecystitis (in Russian). Laboratorio 39:139–140

Marrie T, Stiver HG, Molgat A, Stark RG, Norris D (1977) Actinomycosis of the gallbladder. Can J Surg 20:147–149

Merle-Melet M, Mory F, Stempfel B, Maurer P, Régent D, Parent S, Tortuyaux JM et al (1995) Actinomyces naeslundii, acute cholecystitis, and carcinoma of the gallbladder. Am J Gastroenterol 90:1530–1531

Miranda RT, Gimeno AE, Rodriguez TF, de Arriba JJ, Olmo DG, Solera J (2001) Acute cholecystitis caused by Brucella melitensis: case report of review. J Infect 42:77–78

Mirski Z, Zielinski A (1972) Isolated tuberculosis of the gallbladder and miliary tuberculosis of the liver discovered by means of biopsy (in Polish). Gruzlica 40:561–562

Misgar MS, Kariholu PL, Bhat DN, Fazili F, Yousuf M, Muhajid S (1980) Tuberculosis of gall bladder. J Indian Med Assoc 74:196–197

Mizaushev BA, Emuzov SK (1979) Rare case of acute phlegmonous cholecystitis in combination with echinococcosis of the gallbladder and mechanical jaundice (in Russian). Vestn Khir Im I I Grek 122:93–94

Mlynek HJ, Engel C (1968) Contribution to the clinical aspects and morphology of gallbladder tuberculosis. Zenralbl Chir 93:1332–1336

Morris SJ, Greenwald RA, Turner RL, Tedesco FJ (1979) Brucella-induced cholecystitis. Am J Gastroenterol 71:481–484

Murtaza B, Malik IB, Mahmood A, Sharif MA, Saeed S, Satti AA (2008) Cholecysto-hydatid cyst fistula. J Coll Physicians Surg Pak 18:778–780

Mutter D, Mendoza-Burgos L, Evrard S, Keller P, Vix M, Marescaux J (1993) Gallbladder actinomycosis. A rare entity (in French). Presse Med 22:784

Nakajo S, Yamamoto M, Urushihara T, Kajitani T, Tahara E (1988) Diffuse papillomatosis of the gallbladder complicated with tuberculosis. Acta Pathol Jpn 38:1473–1480

Ögredici Ö, Erb S, Langer I, Pilo P, Kerner A, Haack HG, Cathomas G, Danuser J et al (2010) Brucellosis reactivation after 28 years. Emerg Infect Dis 16:2021–2022

Ormsby AH, Bauer TW, Hall GS (1998) Actinomycosis of the cholecystic duct: case report and review. Pathology 30:65–67

Pandya JS, Palep JH, Shinkre NB, Patil NN, Palan VA (2003) Primary biliary tuberculosis – an unusual case. Indian J Surg 65:440–441

Pautov FN (1964) A case of primary alveolar echinococcosis of the gallbladder (in Russian). Med Parazitol (Mosk) 33:423–425

Pfeifer K, Reiher P (1966) Tuberculosis of the gallbladder (in German). Dtsch Gesundheitsw 21:1448–1451

Piper C, Gamstatter G, Bettendorf U, von Egidy H (1987) Gallbladder tuberculosis. Review and case report of a patient with advanced renal failure. Leber Magen Darm 17:381–382

Pitiakoudis MS, Tsaroucha AK, Deftereos S, Laftsidis P, Prassopoulos P, Simopoulos CE (2006) Primary hydatid disease in a retroplaced gallbladder. J Gastrointestin Liver Dis 15:383–385

Prasad A, Pandey KK (2001) Tuberculous biliary strictures: uncommon cause of obstructive jaundice. Australas Radiol 45:365–368

Punia RP, Garg S, Bisht B, Dalal U, Mohan H (2010) Clinico-pathological spectrum of gallbladder disease in children. Acta Paediatr 99:1561–1564

Putnik M, Ciric S (1953) Hydatid cyst of the gallbladder. Srp Arh Celok Lek 81:531–532

Rabbani K, Narjis Y, Diffaa A, Jalal H, Zoughari L, Benelkhaiat R, Louzi A, Finech B et al (2011) Calcified liver hydatid cyst compressing the gall bladder. Arab J Gastroenterol 12:166–167

Ramia JM, Mansilla A, Villar J, Muffak K, Garrote D, Ferron JA (2004) Retroperitoneal actinomycosis due to dropped gallstones. Surg Endosc 18:345–349

Ramia JM, Muffak K, Fernandez A, Villar J, Garrote D, Ferron JA (2006) Gallbladder tuberculosis: false-positive PET diagnosis of gallbladder cancer. World J Gastroenterol 12:6559–6560

Rankin FW, Massie FM (1926) Primary tuberculosis of the gall bladde. Ann Surg 83:800–806

Rappaport I, Albukerk J, Schneider IJ (1975) Schistosomal cholecystitis. Arch Pathol 99:227–228

Raza MH, Harris SH, Khan R (2003) Hydatid cyst a gall bladder. Indian J Gastroenterol 22:67–68

Rejab H, Guirat A, Ellouze S, Trigui A, Mizouni A, Triki H, Boudaouara T, Beyrouti MI (2013) Primitive gallbladder tuberculosis. A case report with review of the literature. Ann Ital Chir 84:1–3

Remmele W, Lennert K (1957) Die Tuberkulose der Gallenwegs-Lymphknoten. Pathologie und Klinik eines wenig bekannten Krankheitsbildes. Beitr Klin Tuberkulose 117:327–343

Rigas AM, Karatzas GM, Markidis NC, Bonikos DS, Sotiropoulou GG, Skalkeas G (1979) Primary hydatid cyst of the gallbladder. Br J Surg 66:406

Rouas L, Mansouri F, Jahid A, Zouaidia F, Saidi H, Nabih N, Benabdellah M, Laraqui L et al (2003) Gallbladder tuberculosis associated with cholelithiasis (in French). Rev Med Liege 58:757–760

Rozmanic V, Kilvain S, Ahel V, Banac S, Gazdik M (2001) Pulmonary tuberculosis with gallbladder involvement: a review and case report. Pediatr Int 43:511–513

Ruhl KM, Krones CJ, Hermanns B, Schumpelick V (2003) Tuberculosis of the gall bladder (in German). Chirurg 74:478–481

Rybkowski W (1966) A case of tuberculous hepatic cirrhosis and tuberculous inflammation of the gallbladder (in Polish). Wiad Lek 19:1007–1009

Safioleas M, Stamoulis I, Theocharis S, Moulakakis K, Makris S, Kostakis A (2004) Primary hydatid disease of the gallbladder: a rare clinical entity. J Hepatobiliary Pancreat Surg 11:352–356

Salinas C, Gutierrez G, Casavilca S (1999) Gallbladder paragonimiasis: report of one case (in Spanish). Rev Gastroenterol Peru 19:57–58

Saluja SS, Ray S, Pal S, Kukaraja M, Srivastava DN, Sahni P, Chattopadhyay TK (2007) Hepatobiliary and pancreatic tuberculosis: a two decade experience. BMC Surg 7:10

Santos LD, Rogan KA, Kennerson AR (2004) Cytologic diagnosis of suppurative cholecystitis due to Candida albicans and actinomyces. A report of 2 cases. Acta Cytol 48:407–410

Schwartz M, Gilman RA, Settle J (1954) Tuberculous cholecystitis: report of a case and review of the literature. Am Rev Tuberc 70:734–738

Sharara AI, Abi-Saad G, Haddad M, Mansour A, Tawil A (2001) Acute granulomatous schistosomal cholecystitis. Eur J Gastroenterol Hepatol 13:1001–1003

Sidhu DS, Singh M, Jindal RK, Gupta S, Simpy K (2007) Isolated cystic duct lymph node tuberculosis. J Indian Med Assoc 105:460

Simmonds A (1908) Ueber Gallenblasentuberkulose. Zentralbl Allg Path Pathol Anat 19:225

Smithers BM, Wall DR, Weedon D (1983) Actinomycosis of the gall bladder. Aust NZ J Surg 53:587–588

Sobnach S, Van der Linde GD, Kahn D, Bhyat A (2010) Primary tuberculosis of the gallbladder in an HIV-positive patient. S Afr J Surg 48:100

Soldevilla V (1950) Hydatid cyst of the gallbladder simulating carcinoma (in Spanish). Rev Esp Enferm Apar Dig Nutr 9:484–488

Soufi M, Benamer S, Chad B (2011) Pseudotumoral gallbladder tuberculosis (in French). Rev Med Interne 32:e32–e33

Tkebuchava GI (1966) Calcified echinococcosis of the gallbladder (in Russian). Khirurgia (Mosk) 42:134–135

Van Steensel CJ, Kwan TS (1988) Actinomycosis of the gallbladder. Neth J Surg 40:23–25

Verma R, Vij M, Pal L (2012) Gall bladder tuberculosis masquerading as carcinoma: dilemma resolved by aspiration cytology. Diagn Cytopathol 40:91–93

Verma SK, Mishra AK and Jaiswal AK (2013) Tuberculosis of gallbladder neck: a cause of cholecystitis with cholelithiasis. BMJ Case Rep 2013. pii:bcr2012008007. http://www.ncbi.nlm.nih.gov/pubmed/23413288

Vikram HR, Smilack JD, Leighton JA, Crowell MD, De Petris G (2012) Emergence of gastrointestinal basidiobolomycosis in the United States, with a review of worldwide cases. Clin Infect Dis 54:1685–1691

Vojtisek V, Zrustova M (1965) Tuberculosis of the gallbladder and its lymph nodes (in French). Lyon Chir 61:828–837

Wani RA, Malik AA, Chowdri NA, Wani KA, Nagash SH (2005) Primary extrahepatic abdominal hydatidosis. Int J Surg 3:125–127

Warren GH, Marsh S (1982) Granulomatous Torulopsis glabrata cholecystitis in a diabetic. Am J Clin Pathol 78:406–410

Weitz G (1955) Tuberculosis of the gallbladder (in German). Langenbecks Arch Klin Chir Ver Dtsch Z Chir 280:318–336

Wohlgemuth B, Herrmann W, Vogel K (1960) On the clinical aspects and morphology of gallbladder tuberculosis (in German). Zentralbl Chir 85:2327–2333

Xu XF, Yu RS, Qiu LL, Shen J, Dong F, Chen Y (2011) Gallbladder tuberculosis: CT findings with histopathologic correlation. Korean J Radiol 12:196–202

Yildirim M, Ozaydin I, Sahin I, Yasar M (2008) Acute calculous cholecystitis caused by Candida lusitaniae:

an unusual causative organism in a patient without underlying malignancy. Jpn J Infect Dis 61:138–139

Yu R, Liu Y (2002) Gallbladder tuberculosis: case report. Chin Med J (Engl) 115:1259–1261

Yücesoy AN, Poçan S (2014) Secondary gallbladder hydatidosis and nonfragmented germinative membrane sourced obstructive jaundice caused by intrabiliary ruptured hepatic hydatid cyst (a case report): two rare complication of the intrabiliary ruptured hepatic hydatid cyst. Hepatobiliary Surg Nutr 3:209–211

Zhang YM, Guo GR, Ning GN (1997) One case of gallbladder tuberculosis. Chin J Tuberc Respir Dis 20:190

Ziarek S, Deddouche M, Zoubir Y, Taleb M (1975) Tuberculosis of the gallbladder. Apropos of three cases (in French). Med Chir Dig 4:219–222

Tumors and Tumor-Like Lesions of the Cystic Duct

162

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_162

Abstract

Adenocarcinoma of the cystic duct is a neoplasm that takes its origin from the mucosa of the cystic duct. The tumor is sometimes classified as a distinct subtype of gallbladder carcinoma. It is a rare malignancy which accounts to only 2–6 to 12.6 % of all extrahepatic bile duct malignancies. The neoplasm mainly occurs in male and in persons older than 60 years of age. Individuals with this tumor less commonly have gallstones in comparison with gallbladder cancer patients. For diagnosis, the tumor must be restricted to the cystic duct, with no evidence of a neoplastic process in gallbladder or other bile ducts. There are attempts to classify cystic duct carcinoma in regard to growth patterns and spread, including a hepatic hilum type and a cystic confluence type. There are other very rare primary neoplasms of the cystic duct, including neuroendocrine tumors and various types of mesenchymal neoplasms.

Carcinoma of the Cystic Duct

ICD-O code 8140/3

Introduction

Carcinoma of the cystic duct is an adenocarcinoma taking its origin from the mucosa of the cystic duct. It is a rare malignancy, for which preoperative diagnosis is often difficult (Hellner 1925; Farrar 1951). Some authors considered cystic duct carcinoma as a distinct subgroup of gallbladder carcinoma (Nakata et al. 2009).

Anatomy and Physiology of the Cystic Duct

The cystic duct connects the gallbladder with the extrahepatic bile ducts, and its point of insertion into the extrahepatic duct marks the division between the common hepatic duct and the common bile duct. Normally, the cystic duct measures 2–4 cm in length, with a diameter of 1–5 mm, and often shows a serpentine or tortuous course. In 49.9 % of cases, the cystic duct enters the extrahepatic duct from the right lateral aspect, in 18.4 % from the medial aspect and in 31.7 % from an anterior or posterior position. The cystic duct runs parallel to the extrahepatic duct and spirals around the duct. It has a parallel course relative to the extrahepatic bile duct in 10.6 % of patients and varies in length from 1.5 to 9.5 cm (mean, 3–4 cm). Of these parallel cystic ducts, 17 % have a spiral course (Turner and Fulcher 2001). Variants with a longer cystic duct and a lower insertion exist. The anatomy of the cystic duct is variable, with five main macroscopic variations (formation of a fibrous mesocysticum; long cystic duct with low entry into common hepatic duct; cystic duct joining the common hepatic duct on its left; accessory right hepatic duct, and absence of cystic duct, the gallbladder neck directly joining the common hepatic duct). Very rare variations include situations where the cystic opens directly into duodenum and where the cystic duct is absent due to the two hepatic ducts directly entering the gallbladder (Flint 1923; McGregor 1950; Toufeeq 1953). The cystic duct is fed by the cystic artery, which has many possible origins, with the right hepatic artery being the most common (Hugh et al. 1992; Chen et al. 2000; Balija et al. 2001; Mlakar et al. 2003). The topographic relationships between the cystic artery and the cystic duct have been analyzed in detail, with the formulation of distinct group patterns (Ding et al. 2007). Group I or the Calot's triangle type consists of cases with a classical single cystic artery originating from the right hepatic artery within Calot's triangle and of double cystic artery, with a single cystic artery from the right hepatic artery dividing into anterior and posterior branches. In Group II, the cystic artery approaches the gallbladder outside Calot's triangle, with four subgroups: (a) cystic artery originating from the gastroduodenal artery, (b) cystic artery originating from the variant right hepatic artery, (c) cystic artery originating directly from the liver parenchyma, and (d) cystic artery originating from the left hepatic artery. Group III is the compound cystic artery type according to Ding

et al. (2007). This group includes cases where a single cystic artery is accompanied by several types of additional arteries approaching the cystic duct and cases with multiple cystic arteries.

The cystic duct is a complex conduit that allows low-viscosity hepatic bile to enter the gallbladder under low pressure and the expulsion of a more viscous gallbladder bile. It was assumed that the spiral valve of Heister has the central role in these mechanisms, but there are novel findings illustrating that this view has to be revised. The spiral mucosal folds or valves of Heister have first been described in 1732, and the role of these folds remains somewhat obscure (Mentzer 1926; Dasgupta and Stringer 2005). The spiral folds contain muscle cells responsive to neural and hormonal stimuli and considered to play a role in bile transport (Dasgupta and Stringer 2005). Based on cholangiographic 3D models of the inner geometry of the cystic duct, it was found that the most significant geometric parameter affecting resistance was the baffle clearance (lumen size), followed by the number of baffles (the number of folds in the valve of Heister (Ooi et al. 2004). However, the term spiral valve may be misleading, as in over half of casts, spiraling was not the dominant feature of the cystic duct, and a "valve" implies active resistance of flow in one direction, while the internal baffles of the cystic duct serve to regulate bile flow in both directions (Bird et al. 2006). Hydrodynamically, the lumen of the cystic duct seems to serve as a passive resistor striving to provide a constant amount of resistance to control the flow of bile out of the gallbladder (Al-Atabi et al. 2012). In addition, modifications of the bile remaining in the gallbladder for a certain time and admixed with new bile entering the gallbladder alter bile rheology, thus affecting flow through the cystic conduit.

Definitions and Classifications

Diagnostic criteria for carcinoma restricted to the cystic duct have been worked out by Farrar (1951): the tumor must be restricted to the cystic duct; there must be no neoplastic process in the gallbladder, hepatic, or common bile ducts; and histologic examination must confirm the presence of carcinoma. The Farrar definition excludes advanced carcinoma originating from the cystic duct and only applies to tumors originating from the cystic duct and being limited to this part of the extrahepatic duct system (Nakata et al. 2009). As part of the cancers taking their origin in the cystic duct later extend into the gallbladder neck and/or the hepatic ducts, the Farrar definition has practical limitations. As an alternative definition, cystic duct carcinoma has been described as a gallbladder tumor, the center of which is located in the cystic duct (Ozden et al. 2003).

Table 1 Classifications of cystic duct carcinoma

Kubota and Yokoyama system (Kubota et al. 2008; Yokoyama et al. 2008)
Hepatic hilum type
Cystic confluence type
Kim system (Kim et al. 2007)[a]
Type I
Type II
Type III

[a]Types defined in the following paragraph

There are recent attempts to classify cystic duct carcinomas in regard to their locoregional spread (Table 1).

Cystic duct carcinomas extending into adjacent tissues and hence no longer fulfilling the Farrar criteria principally show two patterns of invasion: the hepatic hilum pattern (hepatic hilum type) and the confluence invasive pattern (cystic confluence type). In the first pattern, carcinoma invades structures in or around the hepatic hilum, whereas the second pattern is characterized by extension of tumor into the common hepatic duct and the confluence region (Kubota et al. 2008; Yokoyama et al. 2008). Dividing cystic duct carcinoma with extraductal extension into these two types has clinical and biological implications. Perineural and vascular invasion were more common in the hepatic hilum type, which more often occurred in female patients and was associated with a poorer prognosis than that of the cystic confluence type, the later occurring more frequently in males (Yokoyama et al. 2008). Kim and coworkers (2007) defined three types of cystic duct

carcinoma, based on the extent of infiltration. Type I is characterized by a carcinoma confined within the cystic duct (the original Farrar-type carcinoma); in Type II, carcinoma having its center located in the cystic duct extends to the gallbladder neck and infundibulum or bile duct of the cystic duct side, without obstructive jaundice; in Type III, carcinoma with its center in the cystic duct extends up to the gallbladder body or bile duct on the contralateral side of the cystic duct opening, causing obstructive jaundice.

Epidemiology

Carcinoma of the cystic duct is the least common carcinoma of the extrahepatic biliary tract. It amounts to only 2.6–12.6 % of all extrahepatic bile duct malignancies (Glenn and Hill 1955; Nakata et al. 2009). The tumor usually strikes elderly men, and many patients were more than 60 years old at diagnosis. In a review of Western and Japanese cases, mean age at presentation was 62 years, with a male to female ratio of 3.5:1 (Chijiiwa and Torisu 1993). Patients with this form of cancer have a much lower rate of accompanying gallstones than gallbladder carcinoma patients. Few cases were diagnosed in the setting of pancreaticobiliary maljunction (Kawarada and Das 2001; Sato et al. 2001). Rarely, carcinoma of the cystic duct has been found in the setting of hepatobiliary fluke disease, e.g., opisthorchiasis (Chainuvati et al. 1976), or in association with xanthogranulomatous cholecystitis (Abue et al. 2011). Cystic duct carcinoma rarely occurs in conjunction with gallbladder carcinoma (Itoh et al. 2008).

Clinical and Imaging Features

The clinical features of carcinoma of the cystic duct are usually nonspecific and consist of right upper abdominal discomfort or pain, sometimes colicky, and a palpable right hypochondrial mass, which may either be due to the tumor itself or due to enlargement of the gallbladder. In a review of 23 published cases, 81 % presented with right upper quadrant abdominal pain, 41 % with abdominal mass, and a minority with other symptoms and signs (Baraka et al. 1990). Few patients presented with acute cholecystitis (Chan et al. 2005). Part of the cases were identified incidentally, e.g., in the course of abdominal examinations due to the suspicion for other disease. The massive stenosis or obstruction of the cystic duct caused by the tumor can lead to gallbladder hydrops (Pack and Teng 1968), eventually perforation of the gallbladder (Parker 1965) and induction of limy bile (Takahashi et al. 2007). Hydrops in the presence of cystic duct carcinoma was misinterpreted as gallbladder empyema (Rivkind et al. 1989). In some patients, the tumor had mimicked Mirizzi syndrome (John et al. 1982; Walker and Kanzer 1982). In few cases, the carcinoma infiltrated the region of the extrahepatic duct confluence and thus caused stenosis and obstructive jaundice (De Waele et al. 1984; Baraka et al. 1990; Radin et al. 1990; Holzinger et al. 1998; Nemoto et al. 2003). Obstructive jaundice was mainly detected in patients with extended tumor disease, i.e., with tumors not fulfilling Farrar's criteria for restricted cystic duct carcinoma. In a group of 15 patients, among whom 13 had cancer that did not fit Farrar's criteria, 67 % had jaundice (Nakata et al. 2009).

Selected References (Hellner 1925; Farrar 1951; Irons 1955; Rabinovitch et al. 1960; Smith et al. 1962, 1967; Vaittinen 1972; Geoffroy and Maffioli 1975; Nishimura et al. 1975; Manabe and Sugie 1978; Kogire et al. 1985; Radin et al. 1990; Galler et al. 1991; Napolitano and Morgana 1992; Nari et al. 2001; Kim et al. 2007; Yokoyama et al. 2008; Kiu et al. 2009; Aoki and Nara 2010).

Abdominal ultrasound often shows a distended gallbladder or swelling of the gallbladder, mostly without stones (Kubota et al. 2008). Less commonly, atrophy of the gallbladder was noted. Endoscopic ultrasonography reveals a stenosing and infiltrative tumor which extends into the gallbladder, the extrahepatic bile ducts, or both (Shiba et al. 2011). ERCP reveals a stenosis or block at the level of the cystic duct, sometimes associated

with dilated bile ducts (Borghese et al. 1999; Takahashi et al. 2007). Transhepatic cholangiography revealed a curvilinear compression along the lateral aspect of the common hepatic duct, a picture similar to that found in Mirizzi syndrome (Baraka et al. 1990). The mass replacing the cystic duct and the gallbladder neck is visualized by means of CT and MRCP (Furukawa et al. 1999; Abe et al. 2003).

Pathology

Macroscopy

In most cases, cystic duct carcinomas are firm masses of whitish color that obstruct the duct or, due to markedly invasive growth, efface the duct (Abe et al. 2003). In cases fulfilling the Farrar criteria for restricted cystic duct cancer, the tumors are nodular lesions without infiltration of adjacent tissues. Cystic duct carcinoma can protrude into the common bile duct through the orifice of the cystic duct (Shibata and Toyoda 1995), sometimes forming an intraductal tumor thrombus (Aoki and Nara 2010). The gross description of cystic duct cancer based on resection specimens is sometimes not an easy task, specifically in cases with extension of disease into the junctional area or to the hepatic hilum or in situations where anatomic variations of the duct are present (see above).

Histopathology

The majority of cases with documented histology showed moderately to well-differentiated adenocarcinoma with variable desmoplasia (Fig. 1; Yamaguchi et al. 1991; Ozden et al. 2003; Takahashi et al. 2007). A subset of carcinomas are mucin-producing lesions (Nemoto et al. 2003). Less commonly, exophytically growing tumors with a papillary phenotype were observed (Shibata and Toyoda 1995). There is a relationship between the two main histologic presentations of cystic duct carcinoma and the local extension mode. In cases restricted to the cystic duct (typical Farrar-type lesions), tubular and papillary adenocarcinomas prevail, while those neoplasms which extend

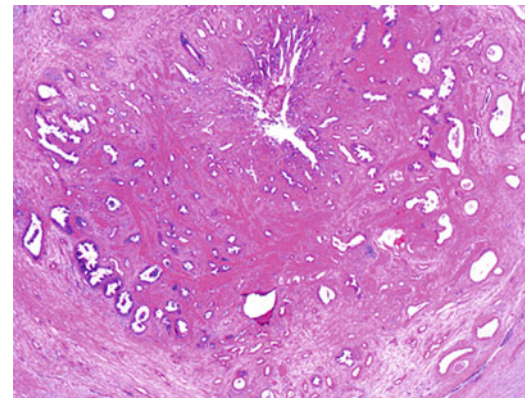

Fig. 1 Adenocarcinoma of the cystic duct. The lumen is severely stenosed by a concentrically growing tubular carcinoma with desmoplasia (hematoxylin and eosin stain)

beyond the cystic duct are chiefly composed of moderately to poorly differentiated adenocarcinoma (Kubota et al. 2008). Exceptionally, clear-cell adenocarcinoma was identified (Tajiri et al. 2006), a phenotype also occurring in other parts of the biliary tract, including the gallbladder. Similar to carcinomas of other parts of the extrahepatic biliary system, cystic duct carcinoma reveals a high rate of perineural invasion. The tumor can also spread superficially to the gallbladder (Sasaki et al. 2011). A sarcoid granulomatous reaction in lymph nodes has been found in a patient with cystic duct carcinoma, similar to granulomatous reactions identified in patients with other adenocarcinomas (Klein et al. 1994).

Precursor Lesions

Carcinoma in situ and dysplastic epithelial changes were rarely observed in the cystic duct (Gilloteaux and Combetta 2005). Typical cholecystocytes were associated with pleomorphic cells of poor differentiation and cells ultrastructurally containing modified mucus vesicles with heterogeneous fatty deposits. Development of carcinoma from papilloma or papillomatosis of the cystic duct has been reported (Lombard et al. 1967; Kosemehmetoglu et al. 2011). In one patient, papillary adenocarcinoma was found to have arisen within a pedunculated cystic duct polyp (Lebovics et al. 1993).

Rare Other Carcinomas of the Cystic Duct

Very few other apparently primary malignancies of the cystic duct have been described. In contrast to the gallbladder (see below), very few published cases of small-cell carcinoma primary to the cystic duct are known (Sonoda et al. 2003). The clinical presentation may be complex, as cystic duct malignancies tend to involve the hepatic ducts or the common bile duct and hence cause signs related to these structures. In a male patient presenting with pain and jaundice, imaging showed a small nodule in the cystic duct invading the common bile duct, with dilatation of the proximal biliary system (Sonoda et al. 2003).

Differential Diagnosis

Carcinomas arising in the distal part of the gallbladder or the gallbladder neck may be confounded with cystic duct carcinoma. A considerable proportion of gallbladder carcinomas show cancer spread to the cystic duct. Among 42 patients operated for advanced gallbladder carcinoma, 31 % revealed cancer spread to the cystic duct (Nakata et al. 2007).

Staging

Staging of cystic duct cancer is performed as for gallbladder carcinoma. About half of patients revealed advanced stage disease at the time point of diagnosis. In a series of 31 cases, stage at presentation was T2 in 3, T3 in 12, and T4 in 16 patients, and 42 % of patients had lymph node metastases (Ozden et al. 2003).

Biology of Disease

In comparison with gallbladder cancer and carcinomas of other parts of the extrahepatic biliary tract, carcinoma restricted to the cystic duct has an outcome that is superior to that of other cancer locations (Benchellal et al. 2008; Berretta et al. 2010). In particular, patients with early-stage disease and undergoing complete resection may show a favorable course (Yamaguchi et al. 1991). Patients who present with higher stage at diagnosis have a poorer outcome. In a study of 31 patients, of whom 16 had stage T4 tumor disease, actuarial 5-year survival rate excluding hospital deaths was 22 % (Ozden et al. 2003). Similar to gallbladder cancer, carcinoma of the cystic duct may show early local recurrence or, in some patients, follow an aggressive course, sometimes with systemic spread (Redmond and Majeranowski 1954; Holzinger et al. 1998). Locoregional lymph nodes are found in a fraction of patients. In one study, five of eight patients displayed lymph node metastases along the hepatoduodenal ligament (Chan et al. 2005), and a second investigation found lymph node metastases in 42 % (Ozden et al. 2003).

Benign Epithelial Neoplasms of the Cystic Duct

Introduction

Very few examples of benign primary epithelial tumors of the cystic duct are known from the literature. These lesions are homologous to those found in other parts of the hepatobiliary tract.

Bile Duct Adenoma of the Cystic Duct

Bile duct adenoma (biliary adenoma) of the cystic duct is a very uncommon neoplasm that is very similar, if nor identical, to biliary adenomas situated elsewhere in the bile duct system (Yopp et al. 2008). Adenomas of the cystic duct can cause duct obstruction or, very rarely, Mirizzi syndrome (Kunisaki et al. 2005). Macroscopically, these adenomas are usually small and well-circumscribed nodular lesions. Histologically, they are characterized by densely packed tubular profiles composed of bland-looking bile duct epithelial cells, but variants with dysplastic changes have also been found (Satoh et al. 1999).

Papillary Adenoma of the Cystic Duct

Papillary adenoma of the cystic duct is a very rare benign neoplasm that shares morphologic features with its counterpart in the large extrahepatic bile ducts and the gallbladder (Loh et al. 1994; Ho and Lee 2006). Due to its exophytic growth, papillary adenoma can cause duct obstruction followed by biliary colic (Loh et al. 1994).

Pyloric Gland Adenoma of the Cystic Duct

Pyloric gland adenoma of the cystic duct, histologically characterized by closely packed pyloric-type glands lined by mucus-secreting cells, has been observed in a 62-year-old male patients who presented with a 2 cm-sized protruding tumor of the cystic duct (Schaefer et al. 2012).

Neuroendocrine Tumors of the Cystic Duct

Introduction

In contrast to the remaining parts of the biliary tract, only very few cases of neuroendocrine neoplasms primary to the cystic duct have been reported in the literature. For the current classification of neuroendocrine tumors, see the other chapters treating these neoplasms. Cystic duct neuroendocrine tumors included somatostatinoma (Goodman et al. 1984), carcinoid tumor (Nicolescu and Popescu 1986; Chittal and Ra 1989; Rugge et al. 1992; Shah et al. 1998; Hermina et al. 1999), and well-differentiated neuroendocrine carcinoma (Felekouras et al. 2009).

Clinical Features

Cystic duct neuroendocrine tumors may be asymptomatic (Aronsky et al. 1999; Stavridi et al. 2007; Ioannidis et al. 2012), but neoplasms growing to a certain size may cause duct obstruction followed by a painfully distended gallbladder (Goodman et al. 1984) or colicky pain crises (Rugge et al. 1992).

Biology of Disease

Most of the few cases reported showed a benign course of the disease, but metastasis in the cystic node was found in one patient (Hermina et al. 1999). In one patient, a 60-year-old female, a malignant variant in the form of a well-differentiated neuroendocrine carcinoma was observed (Felekouras et al. 2009).

Pathology

Macroscopy

As in other locations, neuroendocrine tumors of the cystic duct are well-circumscribed, firm roundish nodular tumors of a yellow to tan color. Most lesions are small and do not exceed 1 cm in diameter, while malignant variants may grow to larger size (Felekouras et al. 2009).

Histopathology

Similar to other locations in the biliary tract, neuroendocrine tumors of the cystic duct are composed of medium-sized cells with an eosinophilic and slightly granular cytoplasm and finely stippled nuclei ("slat-and-pepper" pattern). The tumor cells were reported to be argentaffin (Goodman et al. 1984). The cells arranged in the form of nests and solid structures, with intervening thin-walled vascular channels.

Electron Microscopy

In one case of somatostatinoma of the cystic duct, the tumor cells contained relatively few dense granules (Rugge et al. 1992), measuring 135–475 nm in a case of somatostatinoma (Goodman et al. 1984).

Immunohistochemistry

The neoplasms express neuroendocrine lineage markers (chromogranin A, synaptophysin, neuron-specific enolase; Rugge et al. 1992) and, in case of specific differentiations, certain hormones (Goodman et al. 1984).

Lymphomas of the Cystic Duct

Very few examples of malignant non-Hodgkin's lymphomas (NHL) apparently primary to the cystic duct have been described. The NHL histologically included extranodal follicular lymphoma (Ferluga et al. 2003) and diffuse large B-cell lymphoma, anaplastic variant (Jho et al. 2007). In other patients, the cystic duct was involved in the setting of NHL affecting other organs and tissues, e.g., histiocytic lymphoma (Tartar and Balfe 1990). In one patient, Hodgkin's lymphoma of the cystic duct node was found as a cause of non-visualization of the gallbladder (Wee et al. 1970).

Granular Cell Tumor of the Cystic Duct

Introduction

Granular cell tumor (GCT; granular cell schwannoma; formerly termed granular cell myoblastoma or Abrikossoff's tumor) is an uncommon benign neoplasm of unknown histogenesis, morphologically characterized by solid growth of large cells with a strikingly granular cytoplasm. Apart from skin, oral cavity, and soft tissues, the biliary tract is one of the more common localizations, but GCT of the cystic duct is a very unusual tumor that almost exclusively occurred in women (Fialho and Hilario 1952; Serpe et al. 1960; Goldman et al. 1967; Mackay et al. 1968; Christensen and Ishak 1970; Abt et al. 1971; LiVolsi et al. 1973; Reul et al. 1975; Barber 1984; Yamashina and Stemmermann 1984; Hobbiss et al. 1987; Timberlake and Tachovsky 1988; Ferri Romero et al. 1994, Karakozis et al. 2000). In a review of 15 patients, 14 were female and 1 was male, with an age range at presentation of 15–61 years (Savage and Devitt 1977).

Clinical Features

Symptomatic GCT of the cystic duct has only been reported as a rare finding, mostly presenting as nonspecific right upper quadrant pain or epigastric pain (Fialho and Hilario 1952; Serpe et al. 1960; Goldman et al. 1967; Mackay et al. 1968; Christensen and Ishak 1970; Abt et al. 1971; LiVolsi et al. 1973; Reul et al. 1975; Ferri Romero et al. 1994). The tumor can induce recurrent biliary colic and cholecystitis (Barber 1984; Karakozis et al. 2000), and cystic duct stenosis can result in gallbladder mucocele (Yamashina and Stemmermann 1984).

Pathology

Macroscopy

The tumors are small and roundish, often yellow to tan, and rather well-circumscribed lesions, but ill-defined and seemingly invasive forms are also encountered. In case of cystic duct stenosis caused by the tumor, the gallbladder may be dilated and show a thickened wall due to chronic cholecystitis. Hydrops or mucocele may be present (Reul et al. 1975; Yamashina and Stemmermann 1984).

Histopathology

GCT consists of a proliferation of large polygonal or elongated cells with markedly granular and eosinophilic cytoplasm and often centrally placed, small, round, and dark nuclei. The cytoplasmic granules are strongly positive with the PAS reaction. The tumor cells are embedded within a loose fibrous stroma rich in mucopolysaccharides and sometimes

encircle prominent nerve fibers or are even located within nerves.

Immunohistochemistry

GCT are immunoreactive for S100 protein, alpha-inhibin, and calretinin (Murakata and Ishak 2001; Fine and Li 2003).

Differential Diagnosis

GCT also occurred above the junction of the cystic duct and the common hepatic duct and can infiltrate the cystic duct (Bilanovic et al. 2008). Due to granular and eosinophilic cytoplasm, GCT may be confounded with other neoplasms having these features, such as neuroendocrine neoplasms and paragangliomas. GCT are consistently negative for neuroendocrine markers.

Metastatic Disease and Cancer Invasion of the Cystic Duct

Introduction

A variety of malignancies can metastasize to the biliary tract and the gallbladder and rarely also to the cystic duct. Metastases to the gallbladder are dominated by renal cell carcinoma, malignant melanoma, hepatocellular carcinoma, and breast cancer, and similar preferences have been noted for the cystic duct. Reported cystic duct metastases included breast cancer (Andry et al. 1986), malignant melanoma (O'Connell et al. 1984), rectal carcinoma (Wakahara et al. 2011), and hepatocellular carcinoma (Clark and Schulz 1947).

Clinical Features

As with other tumors located to the cystic duct, metastases can lead to duct stenosis or obstruction followed by acalculous cholecystitis or biliary colic (Andry et al. 1986).

Differential Diagnosis

Metastasis to the cystic duct has to be distinguished from direct invasion of the duct by cancers, including gallbladder carcinoma (Nakata et al. 2007), which can result in cystic duct obstruction (Miyayama et al. 2003). The presence of two cystic lymph nodes (Sekaran and Anwar 2008) can be confounded with a primary or secondary cystic duct tumor. The same diagnostic problem may arise metastatic disease of the cystic node (Arai et al. 1997), in tuberculosis of the cystic duct lymph node (de Melo et al. 2004), or in various inflammatory alterations of this node (Williams and Whittaker 1965).

Tumor-like Inflammatory Changes of the Cystic Duct

There are very few reported instances of acute or chronic inflammatory changes of the cystic duct resulting in tumor-like tissue mass augmentation. These lesions include primary chronic inflammation of the cystic duct of unknown cause (Labo and Rosa 1965; "primary cystic duct cholangitis"), inflammatory cystic duct polyps (Roig Vila et al. 1995), malakoplakia (Sahel et al. 1976), and manifestations of Kawasaki disease (Liebmann et al. 1982).

Primary cystic duct inflammation ("chronic cysticitis," Labo and Rosa 1965)

This is the most important inflammatory change of the cystic duct, and owing to fibroplasia, it can result in pseudotumoral thickenings of the duct. It has been proposed that primary inflammation of the cystic duct may be more common than generally supposed. It may arise at the same time as a chronic diffuse cholecystitis or be the initial stage of it. Or it may also be associated with cholelithiasis (Labo and Rosa 1965). The usually painful lesions radiologically present as a threadlike duct, rigid duct, rosary-like duct, pearl lace duct, or in the form of a swan neck, sometimes associated with a hypotonic gallbladder (Labo and Rosa 1965). Histologically, both atrophic chronic cysticitis and hypertrophic chronic cysticitis have been described, whereby

the latter can be associated with fibrous pericysticitis. In some cases, these inflammatory changes are accompanied by cystic duct cholesterolosis (Labo and Rosa 1965).

Heterotopias in the Cystic Duct

Introduction

Heterotopias and metaplastic alterations are rather common pathologies in the gallbladder, but are much less frequently encountered in the cystic duct. Heterotopias include heterotopic pancreatic tissue (Inceoglu et al. 1993; Bhana and Chetty 1999; Mrak et al. 2010; Lee et al. 2013), gastric mucosa (Lamont et al. 1991; Orizio et al. 2011), and heterotopic duodenum (Galloway 1984).

Clinical Features

Heterotopias in the cystic duct can, due to their mass-forming effect, lead to stenosis, obstruction, inflammatory changes, including cholecystitis, and eventually biliary colic. This phenomenon has, e.g., been observed in pancreatic heterotopia (Inceoglu et al. 1993; Bhana and Chetty 1999; Mrak et al. 2010).

Pathology

The macroscopic and histologic features of cystic duct heterotopias are the same as those of the gallbladder (see the respective paragraph). Pancreatic heterotopia may be exocrine or mixed exocrine-endocrine, sometimes with islets in normal proportion, and was in one patient associated with segmental adenomyomatosis of the gallbladder (Lee et al. 2013). The heterotopic pancreatic tissue can localize to the mucosa and submucosa, forming a nodule or a polypoid lesion, but it can also be situated deeply, in an intramural location (Mrak et al. 2010). Heterotopic gastric mucosa can contain all gastric mucosal cell types (Lamont et al. 1991).

Cystic Alterations of the Cystic Duct

Few examples of congenital and acquired cystic alterations of the cystic are known and enter the differential diagnosis of cystic neoplastic processes of the extrahepatic biliary tract. Very rare are congenital cystic dilatations solely confined to the cystic duct (Bode and Aust 1983). Congenital cystic duct dilatation is sometimes associated with an anomalous pancreaticobiliary ductal junction (Weiler et al. 2003). Among acquired lesions, stone disease with impaction of a calculus in the cystic duct can cause marked inflammatory dilatation of the cystic duct mimicking a cyst (Tanaka et al. 2008). Cystic dilatation was also diagnosed following cholecystectomy (Dhanjal et al. 2005).

Tumors of the Cystic Duct Remnant

Introduction

The cystic duct remnant, which has variable lengths and residual mucosal surfaces, can undergo several types of secondary changes, mostly inflammatory, but several types of tumorous lesions can also develop.

Carcinoma of the Cystic Duct Stump

Cystic duct remnant carcinoma is a very rare complication (Phillips and Estrin 1969; Dixon and Christensen 1971; Gabata et al. 2003). Adenocarcinoma of the stump can show widespread invasion along the common bile duct wall, causing wall thickening (Gabata et al. 2003). Invasion may also extend beyond the limits of the extrahepatic biliary tract, e.g., into the transverse colon (Noji et al. 2003) or the duodenum (Eum et al. 2008). After cholecystectomy, high-grade dysplasia of the cystic duct margin has been observed in the absence of malignancy in the gallbladder (Bickenbach et al. 2011).

Amputation Neuroma of the Cystic Duct Stump

Postsurgical amputation neuromas can develop at the cystic stump and are a typical form of nonneoplastic tumor-like lesion (Rosenberg and Matzner 1957; Loutsch 1961; Palagiano and D'Addato 1963; Mattler et al. 1965; Joske and Finlay-Jones 1966; Berge and Haeger 1967; Maheshwari and Agarwal 1969; Doberauer and Kühlmayer 1973; Bodner et al. 1978; Prinz et al. 1979; Cimaschi et al. 2006).

Pseudotumors of the Cystic Duct Stump

Mass-forming pseudoaneurysm arising from the cystic artery stump was detected following laparoscopic cholecystectomy (Nakase et al. 2008). Granuloma at the cystic remnant-common bile duct junction was found in one patient (Farkas et al. 1980). Empyema of the cystic duct stump may be confounded with a tumor-like mass (Brodman and Ghazi 1971).

References

Abe H, Tanaka K, Sugiyama S, Katamoto T, Makuuchi M (2003) CT findings of cystic duct carcinoma two years before obstructive jaundice. Hepatogastroenterology 50:24–26

Abt AB, Geinberg E, Kaunitz S (1971) Granular cell myoblastoma of the extrahepatic biliary tree. Mount Sinai J Med 38:457–461

Abue M, Suzuki M, Miyazaki T, Nomura E, Uchimi K, Noguchi T, Suzuki S, Onodera H et al (2011) A case of early cystic duct carcinoma concomitant with xanthogranulomatous cholecystitis (XGC) (in Japanese). Nihon Shokakibyo Gakkai Zasshi 108:1743–1751

Al-Atabi M, Ooi RC, Luo XY, Chin SB, Bird NC (2012) Computational analysis of the flow of bile in human cystic duct. Med Eng Phys 34:1177–1183

Andry G, Turnbull AD, Botet J, Kurtz RC (1986) Cholesonographic characteristics of cystic duct metastasis causing acute acalculous cholecystitis: case report. J Surg Oncol 31:178–181

Aoki M, Nara S (2010) A case of solid adenocarcinoma arising from the cystic duct with tumor thrombus in the common bile duct. Jpn J Clin Oncol 40:819

Arai T, Tanaka M, Noto K, Sakamoto Y, Kawachi Y (1997) Cystic lymph node metastasis caused by a Bellini duct carcinoma. Br J Urol 79:135–136

Aronsky D, Z'graggen K, Stauffer E, Lange J, Klaiber C (1999) Primary neuroendocrine tumors of the cystic duct. Digestion 60:493–496

Balija M, Huis M, Stulhofer M, Nikolic V (2001) Contribution to the nomenclature of variations of the cystic artery. Chirurg 72:154–158

Baraka A, al Mokhtar NY, Madda JP, Amirrad M, Asfar S (1990) Primary carcinoma of the cystic duct causing obstructive jaundice. JR Soc Med 83:746–747

Barber CJ (1984) Granular cell tumour of the cystic duct. A cause of cholecystitis. JR Coll Surg Edinb 29:56–57

Benchellal ZA, Soro KG, Orain I, Poret H, Ferhi AH, Darquies-Chevalley J (2008) Thirteen-year disease-free survival after surgery for cystic duct carcinoma: a case report. Case Rep Gastroenterol 2:428–432

Berge T, Haeger K (1967) Clinical significance of the amputation neuroma and length of the cystic duct remnant. Acta Chir Scand 133:55–60

Berretta M, Di Benedetto F, Lleshi A, Ristagno M, Cappellani A, Bearz A, Berretta S et al (2010) Long term survival in a patient with adenocarcinoma of the cystic duct. J Chemother 22:436–437

Bhana BD, Chetty R (1999) Heterotopic pancreas – an unusual cause of cholecystitis. S Afr J Surg 37:105–107

Bickenbach KA, Shia J, Klimstra DS, DeMatteo RP, Fong Y, Kingham TP, Allen PJ et al (2011) High-grade dysplasia of the cystic duct margin in the absence of malignancy after cholecystectomy. HPB (Oxford) 13:865–868

Bilanovic D, Boricic I, Zdravkovic D, Randjelovic T, Stanisavljevic N, Tokovic B (2008) Granular cell tumor of the common hepatic duct presenting as cholangiocarcinoma and acute acalculous cholecystitis. Acta Chir Iugosl 55:99–101

Bird NC, Ooi RC, Luo XY, Chin SB, Johnson AG (2006) Investigation of the functional three-dimensional anatomy of the human cystic duct: a single helix? Clin Anat 19:528–534

Bode WW, Aust JB (1983) Isolated cystic dilatation of the cystic duct. Am J Surg 145:828–829

Bodner E, Aufschnaiter M, Hager J, Mikuz G (1978) Neuroma of the cystic nerve stump. No explanation for post-cholecystectomy pain (in German). Chirurg 49:424–427

Borghese M, Gabriele R, Antoniozzi A, Teneriello F, Caporale A, Giuliani A, Lombardo F, Rengo M (1999) Primary carcinoma of the cystic duct: a case report and review of the literature (in Italian). G Chir 20:35–40

Brodman HR, Ghazi A (1971) Empyema of the cystic duct stump. Am Surg 37:427–430

Chainuvati T, Paosawadhi A, Sripranoth M, Manasatih S, Viranuvatti V (1976) Carcinoma of the cystic duct associated with opisthorchiasis. Southeast Asian J Trop Med Public Health 7:482–486

Chan KM, Yeh TS, Tseng JH, Liu NJ, Jan YY, Chen MF (2005) Clinicopathological analysis of cystic duct carcinoma. Hepatogastroenterology 52:691–694

Chen TH, Shyu JF, Chen CH, Ma KH, Wu CW, Lui WY, Liu JC (2000) Variations of the cystic artery in Chinese adults. Surg Laparosc Endosc Percutan Tech 10:154–157

Chijiiwa K, Torisu M (1993) Primary carcinoma of the cystic duct. J Clin Gastroenterol 16:309–313

Chittal SM, Ra PM (1989) Carcinoid of the cystic duct. Histopathology 15:643–646

Christensen AH, Ishak KG (1970) Benign tumours and pseudotumours of the gall bladder. Report of 180 cases. Arch Pathol 90:423–432

Cimaschi D, De Cesare V, Pulcini G, Cervi E, Belloni M, Liserre B, Cervi GC (2006) A case of amputation neuroma of the bile duct following video-laparoscopic cholecystectomy (in Italian). G Chir 27:31–36

Clark W, Schulz MD (1947) Hepatoma, with invasion of cystic duct and metastasis to third lumbar vertebra. N Engl J Med 237:673–676

Dasgupta D, Stringer MD (2005) Cystic duct and Heister's "valves". Clin Anat 18:81–87

De Melo VA, de Melo GB, Silva RL, Piva N, Almeida ML (2004) Tuberculosis of the cystic duct lymph node. Braz J Infect Dis 8:112–114

De Waele B, Beaurang J, Smekens L, Pipeleers-Marichal M (1984) Carcinoma of cystic duct leading to obstructive jaundice. Dig Dis Sci 29:865–867

Dhanjal NS, Sharif AW, Rosenfelder NA, Lim AK, Taylor-Robinson SD (2005) Cystic duct dilatation after cholecystectomy in fibropolycystic liver disease. J Hepatol 43:192

Ding YM, Wang B, Wang WX, Wang P, Yan JS (2007) New classification of the anatomic variations of cystic artery during laparoscopic cholecystectomy. World J Gastroenterol 13:5629–5634

Dixon JA, Christensen C (1971) Primary adenocarcinoma in cystic duct remnants. Am J Surg 121:610–611

Doberauer B, Kühlmayer R (1973) Cysticus stump neurinoma as a rare cause for postcholecystectomy syndrome (in German). Chirurg 44:39–41

Eum JS, Kim GH, Park CH, Kang DH, Song GA (2008) A remnant cystic duct cancer presenting as a duodenal submucosal tumor. Gastrointest Endosc 67:975–976

Farkas I, Patko A, Kövari M (1980) Obstructive jaundice caused by postsurgical granuloma of the common bile duct. Endoscopy 12:250–253

Farrar DA (1951) Carcinoma of the cystic duct. Br J Surg 39:183–185

Felekouras E, Petrou A, Bramis K, Prassas E, Papaconstantinou I, Dimitriou N, Pazaiti A et al (2009) Malignant carcinoid tumor of the cystic duct: a rare cause of bile duct obstruction. Hepatobiliary Panceat Dis Int 8:640–646

Ferluga D, Luzar B, Gadzijev EM (2003) Follicular lymphoma of the gallbladder and extrahepatic bile ducts. Virchows Arch 442:136–140

Ferri Romero J, Carrion Tomas A, Estrada Caballero JL, Fernandez Gimenez F, Ceballos Gil S et al (1994) Granular cell tumor of the bile duct: an infrequent location (in Spanish). Rev Esp Enferm Dig 85:217–219

Fialho F, Hilario J (1952) Granular cell rhabdomyoma of the cystic duct (myoblastoma) (in Portuguese). Rev Bras Med 9:616–618

Fine SW, Li M (2003) Expression of calretinin and the alpha-subunit of inhibin in granular cell tumors. Am J Clin Pathol 119:259–264

Flint ER (1923) Abnormalities of the right hepatic, cystic, and gastroduodenal arteries, and of the bile-ducts. Br J Surg 10:509–519

Furukawa H, Muramatsu Y, Fukushima N, Kosuge T (1999) Carcinoma oft eh cystic bile duct: MRCP and CT appearance. AJR Am J Roentgenol 173:1141

Gabata T, Matsui O, Sanada J, Kadoya M, Ohmura K, Minato H (2003) Cystic duct remnant carcinoma with widespread invasion along the extrahepatic bile duct wall: dynamic CT findings. Abdom Imaging 28:79–82

Galler L, Feinberg GL, Scarano JJ (1991) Case report: cystic duct carcinoma. NJ Med 88:337–339

Galloway PG (1984) Heterotopic duodenum in the cystic duct. Arch Pathol Lab Med 108:666–668

Geoffroy H, Maffioli C (1975) Carcinoma of the cystic duct. Report of a case and review of the literature (in French). Arch Fr Mal App Dig 64:239–247

Gilloteaux J, Combetta J (2005) Carcinoma in situ of the cystic duct. Ultrastruct Pathol 29:79–84

Glenn F, Hill MR (1955) Extrahepatic biliary tract cancer. Cancer 8:1218–1225

Goldman LI, Lemole G, Ellis R, Rosemond GP (1967) Granular cell myoblastoma of the cystic duct. JAMA 200:1185–1186

Goodman ZD, Albores-Saavedra J, Lundblad DM (1984) Somatostatinoma of the cystic duct. Cancer 53:498–502

Hellner H (1925) Das Karzinom des Ductus cysticus (Carcinoma of the cystic duct). Beitr Klin Chir 134:554

Hermina M, Starling J, Warner TF (1999) Carcinoid tumor of the cystic duct. Pathol Res Pract 195:707–709

Ho CM, Lee PH (2006) Image of the month. Papillary adenoma of the cystic duct. Arch Surg 141:315

Hobbiss JH, Hasleton P, Kahn MK, Turner L (1987) Granular cell myoblastoma of the cystic duct: a case report and review of the literature. JR Coll Surg Edinb 32:117–118

Holzinger F, Schilling M, Z'graggen K, Stain S, Baer HU (1998) Carcinoma of the cystic duct leading to obstructive jaundice. A case report and review of the literature. Dig Surg 15:273–278

Hugh TB, Kelly MD, Li B (1992) Laparoscopic anatomy of the cystic artery. Am J Surg 163:593–595

Inceoglu R, Dosluoglu HH, Kullu S, Ahiskali R, Doslu FA (1993) An unusual cause of hydropic gallbladder and biliary colic – heterotopic pancreatic tissue in the cystic duct: report of a case and review of the literature. Surg Today 23:532–534

Ioannidis O, Cheva A, Paraskevas G, Chatzopoulos S, Kotronis A, Papadimitriou N et al (2012) Neuroendocrine tumor of the cystic duct. Acta Gastroenterol Belg 75:357–360

Irons HS (1955) Carcinoma of cystic duct; case report of a successful resection. Surgery 38:396–401

Itoh T, Fuji N, Taniguchi H, Yasukawa S, Yasuda H, Wakabayashi N, Watanabe T et al (2008) Double cancer of the cystic duct and gallbladder associated with low junction of the cystic duct. J Hepatobiliary Pancreat Surg 15:338–343

Jho DH, Jho DJ, Chejfec G, Ahn M, Ong ES, Espat NJ (2007) Primary biliary B-cell lymphoma of the cystic duct causing obstructive jaundice. Am Surg 73:508–510

John M, Walker B, Kanzer F (1982) Carcinoma of the cystic duct mimicking the Mirizzi syndrome. Am J Gastroenterol 77:936–937

Joske RA, Finlay-Jones LR (1966) Amputation neuroma of the cystic-duct stump. Br J Surg 53:766–768

Karakozis S, Gongora E, Zapas JL, He P, Krishnan J, Kirkpatrick JR (2000) Granular cell tumors of the biliary tree. Surgery 128:113–115

Kawarada Y, Das BC (2001) Primary carcinoma of the cystic duct associated with pancreaticobiliary maljunction. J Gastroenterol 36:289–290

Kim WC, Lee DH, Ahn SI, Kim JM (2007) A case of cystic duct carcinoma treated with surgery and adjuvant radiotherapy: a proposal for new classification. J Gastrointestin Liver Dis 16:437–440

Kiu V, Wang HP, Wu YM (2009) Cystic duct tubular adenocarcinoma. Dig Surg 26:369–370

Klein M, Kaminsky P, Deibener J, Cocciale MP, Duc M (1994) Sarcoid reactions in cystic duct carcinoma. Chest 106:1304–1305

Kogire M, Kitamura O, Yamada T, Noda H, Asano M, Yoshida A (1985) Carcinoma of the cystic duct: a case report. Nihon Geka Hokan 54:508–513

Kosemehmetoglu K, Akpinar E, Sokmensuer C, Hamaloglu E (2011) Papillary carcinoma with diffuse papillomatosis of gallbladder and cystic duct. Ann Diagn Pathol 15:140–144

Kubota K, Kakuta Y, Inayama Y, Yoneda M, Abe Y, Inamori M, Kirikoshi H, Saito S et al (2008) Clinicopathologic study of resected cases of primary carcinoma of the cystic duct. Hepatogastroenterology 55:1174–1178

Kunisaki SM, Hertl M, Bodner BE, Cosimi AB (2005) Mirizzi syndrome secondary to an adenoma of the cystic duct. J Hepatobiliary Pancreat Surg 12:159–162

Labo G, Rosa L (1965) Primary chronic inflammation of the cystic duct. Postgrad Med J 41:243–246

Lamont N, Winthrop AL, Cole FM, Langer JC, Issenman RM, Finkel KC (1991) Heterotopic gastric mucosa in the gallbladder: a cause of chronic abdominal pain in a child. J Pediatr Surg 26:1293–1295

Lebovics E, Le Guyader H, Savino J, Moldes O, Weisberger J, Rosenthal WS (1993) Papillary adenocarcinoma arising within a pedunculated cystic duct polyp. Am J Gastroenterol 88:1278–1280

Lee SW, Yun SP, Seo HI (2013) Heterotopic pancreas of the gallbladder associated with segmental adenomyomatosis of the gallbladder. J Korean Surg Soc 84:309–311

Liebmann LI, Mikelic V, Joh MM, Wilson FM (1982) Hydrops of the gallbladder in an adult with Kawasaki disease. JAMA 247:827–829

LiVolsi VA, Perzin KH, Badder EM (1973) Granular cell tumours of the biliary tract. Arch Pathol 95:13–17

Loh A, Kamar S, Dickson GH (1994) Solitary benign papilloma (papillary adenoma) of the cystic duct: a rare cause of biliary colic. Br J Clin Pract 48:167–168

Lombard R, Dehalleux E, Drèze C (1967) Cancerized papilloma of the cystic duct (in French). Acta Gastroenterol Belg 30:452–459

Loutsch H (1961) Apropos of a case of amputation neuroma of the cystic stump (in French). Mem Acad Chir (Paris) 87:324–330

Mackay B, Elliott GB, MacDougall JA (1968) Granular cell myoblastoma of the cystic duct: report of a case with electron-microscope observations. Can J Surg 11:44–51

Maheshwari VK, Agarwal GP (1969) Post-cholecystectomy cystic duct neuroma. A case report. Indian J Pathol Bacteriol 12:126–127

Manabe T, Sugie T (1978) Primary carcinoma of the cystic duct. Arch Surg 113:1202–1204

Mattler EA, Barberis CR, Salama AA, Rossai J (1965) Postcholecystectomy syndrome – amputation neuroma of the cystic duct (in Spanish). Rev Argent Cir 8:93–94

McGregor L (1950) Synopsis of surgical anatomy, 7th edn. John Wright & Sons, Bristol, pp 66–67

Mentzer SH (1926) The valves of Heister. Arch Surg 13:511–522

Miyayama S, Matsui O, Akakura Y, Yamamoto T, Nishida H, Minami T, Kozaka K et al (2003) Percutaneous cholecystocholedochostomy for cholecystitis and cystic duct obstruction in gallbladder carcinoma. J Vasc Interv Radiol 14:261–263

Mlakar B, Gadzijev EM, Ravnik D, Hribernik M (2003) Anatomical variations of the cystic artery. Eur J Morphol 41:31–34

Mrak K, Eberl T, Tschmelitsch J, Langner C (2010) Heterotopic pancreatic tissue in the cystic duct: complicating factor or coexisting pathology. South Med J 103:471–473

Murakata LA, Ishak KG (2001) Expression of inhibin-alpha by granular cell tumors of the gallbladder and extrahepatic bile ducts. Am J Surg Pathol 25:1200–1203

Nakase Y, Takagi T, Fukumoto K, Kassai K, Yamagami T, Itani K, Miyagaki T (2008) Hemobilia and cystic artery stump pseudoaneurysm associated with liver abscess after laparoscopic cholecystectomy: report of a case. Surg Today 38:567–571

Nakata T, Kobayashi A, Miwa S, Soeda J, Miyagawa S (2007) Impact of tumor spread to the cystic duct on the

prognosis of patients with gallbladder carcinoma. World J Surg 31:155–161
Nakata T, Kobayashi A, Miwa S, Soeda J, Uehara T, Miyagawa S (2009) Clinical and pathological features of primary carcinoma of the cystic duct. J Hepatobiliary Pancreat Surg 16:75–82
Napolitano S, Morgana R (1992) Primary carcinoma of the cystic duct. A rarity in surgery (in Italian). Minerva Chir 47:1493–1496
Nari G, Ponce O, Ramirez Utrera E (2001) Primary cancer of the cystic duct; a case report. Acta Gastroenterol Latinoam 31:403–404
Nemoto A, Goshima H, Yoshimine S, Higashiguchi T, Takagi K, Fujii K, Kato H (2003) Mucin-producing carcinoma of the cystic duct that caused obstructive jaundice. Hepatogastroenterology 50:1250–1254
Nicolescu PG, Popescu A (1986) Carcinoid tumor of the cystic duct. Morphol Embryol (Bucur) 32:275–277
Nishimura A, Mayama S, Nakano K, Seki Y, Tanaka N (1975) Carcinoma of the cystic duct: case report. Jpn J Surg 5:109–117
Noji T, Kondo S, Hirano S, Ambo Y, Tanaka E, Okushiba S, Katoh H (2003) Carcinoma of the cystic duct remnant with direct colonic invasion. Int J Gastrointest Cancer 34:117–120
O'Connell JB, Whittemore DM, Russell JC, Ellis WA, Becker DR (1984) Malignant melanoma metastatic to the cystic and common bile ducts. Cancer 53:184–186
Ooi RC, Luo XY, Chin SB, Johnson AG, Bird NC (2004) The flow of bile in the human cystic duct. J Biomech 37:1913–1922
Orizio P, Villanacci V, Bassotti G, Falchetti D, Torri F, Ekema G (2011) Heterotopic gastric mucosa in the cystic duct. Int J Surg Pathol 19:364–365
Ozden I, Kamiya J, Nagino M, Uesaka K, Oda K, Sano T, Kamiya S, Nimura Y (2003) Cystic duct carcinoma: a proposal for a new "working definition". Langenbecks Arch Surg 387:337–342
Pack GT, Teng PK (1968) Carcinoma of cystic duct leading to hydrops of gallbladder. JAMA 203:153–154
Palagiano V, D'Addato M (1963) Amputation neuroma of the cystic duct (in Italian). Acta Chir Ital 19:581–597
Parker RH (1965) Carcinoma of the cystic duct with gallbladder perforation. Ann Intern Med 63:475–480
Phillips SJ, Estrin J (1969) Primary adenocarcinoma in a cystic duct stump. Report of a case and review of the literature. Arch Surg 98:225–227
Prinz RA, Greenlee HB, Caporale FS (1979) Amputation neuroma of the cystic duct: a treatable cause of postcholecystectomy pain. Ann Surg 45:543–544
Rabinovitch J, Arlen M, Grayzel D, Roberts M, Rabinovitch P (1960) Primary carcinoma of the cystic duct. Report of two cases. Arch Surg 80:424–433
Radin DR, Chandrasoma P, Ralls PW (1990) Carcinoma of the cystic duct. Gastrointest Radiol 15:49–52
Redmond AD, Majeranowski JF (1954) Systemic spread of a cystic duct carcinoma: a case report. Ann Intern Med 40:632–640
Reul GJ, Rubio PA, Berkman NL (1975) Granular cell myoblastoma of the cystic duct. A case associated with hydrops of the gallbladder. Am J Surg 129:583–584
Rivkind AI, Sherman Y, Rabinovici R (1989) Cystic duct carcinoma mimicking empyema of the gallbladder. Am Surg 55:314–315
Roig Vila JV, Castells Ferrer P, Flors Alandi C, Blasco Segura T, Garcia Armengol J (1995) Acute cholecystitis caused by cystic polyp (in Spanish). Rev Esp Enferm Dig 87:752–753
Rosenberg J, Matzner MJ (1957) Neuroma in a dilated stump of the cystic duct: preoperative visualization by intravenous cholangiography. Am J Gastroenterol 27:471–478
Rugge M, Sonego F, Militello C, Guido M, Ninfo V (1992) Primary carcinoid tumor of the cystic and common bile ducts. Am J Surg Pathol 16:802–807
Sahel J, Scheiner C, Lebreuil G, Sarles H (1976) Malacoplakia of the cystic duct (in French). Arch Fr Mal App Dig 65:585–590
Sasaki K, Matsuda M, Hashimoto M, Harano T, Fujii T, Watanabe G (2011) Early cystic duct carcinoma of new classification. Int J Surg Case Rep 2:246–249
Sato M, Watanabe Y, Kikkawa H, Kohtani T, Suzuki H, Nezu K, Yoshida M, Kawachi K et al (2001) Carcinoma of the cystic duct associated with pancreaticobiliary maljunction. J Gastroenterol 36:276–280
Satoh H, Hirano T, Ogawa Y, Minamishima Y, Saitoh S, Takashima M, Koga K, Imaizumi N et al (1999) Adenoma arising from the cystic duct and extending to the confluence of the extrahepatic biliary tract. J Hepatobiliary Pancreat Surg 6:186–189
Savage and Devitt 1977. http://www.ncbi.nlm.nih.gov/pubmed/200901
Schaefer IM, Cameron S, Middel P, Homayounfar K, Schwörer H, Vieth M, Veits L (2012) Pyloric gland adenoma of the cystic duct with malignant transformation: report of a case with review of the literature. BMC Cancer 12:570
Sekaran P, Anwar S (2008) The presence of two cystic nodes. Clin Anat 21:807–808
Serpe SJ, Todd D, Baruch H (1960) Cholecystitis due to granular cell myoblastoma of the cystic duct. Am J Dig Dis 5:824–826
Shah IA, Schlageter MO, Wong SX, Gani OS (1998) Carcinoid tumor of the cystic duct. Dig Surg 15:372–373
Shiba H, Misawa T, Ito R, Imazu H, Suzuki M, Yanaga K (2011) Preoperative diagnosis of early cystic duct cancer using endoscopic ultrasonography and endocholangioscopy: report of a case. J Gastrointest Surg 15:1477–1479
Shibata Y, Toyoda S (1995) Carcinoma of the cystic duct protruding into the common bile duct: report of a case. Surg Today 25:1050–1053
Smith VM, Feldman M, Warner CG (1962) Neoplasms of the cystic and hepatic ducts. Am J Dig Dis 7:804–816

Smith BB, Huergo M, Cullin PS (1967) Carcinoma of the cystic duct. Tex Med 63:75–77

Sonoda Y, Yamaguchi K, Nagai E, Nakamuta M, Ito T, Eguchi T, Chijiiwa K, Tanaka M (2003) Small cell carcinoma of the cystic duct: a case report. J Gastrointest Surg 7:631–634

Stavridi F, Chong H, Chan S, Goldsmith C, Reddy M, Glees J, Benepal T (2007) Neuroendocrine tumour of the cystic duct: a case report and literature review. J Gastrointest Cancer 38:32–33

Tajiri K, Shimizu Y, Mihara H, Kawanishi Y, Orihara T, Takahashi H, Ishizawa S, Kawai S et al (2006) Cholangiocarcinoma at the cystic duct discovered by lymph node metastases with clear cell transformation. Intern Med 45:1045–1048

Takahashi S, Homma H, Aikyama T, Mesawa S, Kojke K, Hirata K, Kogawa K, Kawano Y et al (2007) A case of primary carcinoma of the cystic duct with limy bile (in Japanese). Nihon Shokakibyo Gakkai Zasshi 104:394–400

Tanaka S, Yamamoto T, Ishihara K, Ono K (2008) Acute inflammatory dilation of the cystic duct induced by a stone. Dig Surg 25:309

Tartar VM, Balfe DM (1990) Lymphoma in the wall of the bile ducts: radiologic imaging. Gastrointest Radiol 15:53–57

Timberlake GA, Tachovsky TJ (1988) Granular cell myoblastoma of the cystic duct. Mil Med 153: 98–99

Toufeeq AK (1953) Abnormalities of cystic duct, cystic artery and right hepatic artery. J Natl Med Assoc 45:409–413

Turner MA, Fulcher AS (2001) The cystic duct: normal anatomy and disease processes. RadioGraphics 21:3–22

Vaittinen E (1972) Carcinoma of the cystic duct. Ann Chir Gynaecol Fenn 61:190–194

Wakahara T, Tsukamoto T, Toyokawa A, Iwasaki T, Hamabe Y, Teramura K (2011) A case of cystic duct metastasis from rectal cancer (in Japanese). Nihon Shokakibyo Gakkai Zasshi 108:2023–2029

Walker JM, Kanzer BF (1982) Carcinoma of the cystic duct mimicking the Mirizzi syndrome. Am J Gastroenterol 77:936–938

Wee GC, Hagen G, Torres A, Shieber W (1970) Hodgkin's disease of the cystic node as a cause of nonvisualization of the gallbladder. Am J Gastroenterol 54:272–276

Weiler H, Grandel A, Frühmorgen P (2003) Congenital cystic dilatation of the cystic duct associated with an anomalous pancreaticobiliary ductal junction (in German). Ultraschall Med 24:197–201

Williams G, Whittaker JS (1965) Diagnostic problems in biliary duct lymph nodes. J Clin Pathol 18:43–46

Yamaguchi K, Nishihara K, Tsuneyoshi M (1991) Carcinoma of the cystic duct. J Surg Oncol 48:282–286

Yamashina M, Stemmermann GN (1984) Granular cell tumor: unusual cause for mucocele of gallbladder. Am J Gastroenterol 79:701–703

Yokoyama Y, Nishio H, Ebata T, Abe T, Igami T, Oda K, Nimura Y, Nagino M (2008) New classification of cystic duct carcinoma. World J Surg 32:621–626

Yopp AC, Pulipati R, Chorost MI, Horovitz JH (2008) Cystic duct biliary adenoma. Surgery 143:150–151

Part XXX

Peritoneal Tumors and Tumor-Like Lesions

Tumors, Tumor-Like Lesions, and Metaplastic Lesions of the Peritoneum

163

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_163

Abstract

The parietal and visceral peritoneum, including the serosal surface covering the liver, is subject to various neoplastic and nonneoplastic alterations. In part of these lesions, tumors and tumor-like processes can involve the liver and cause differential diagnostic problems. Depending on the type of lesions, circumscribed focal masses or a diffuse process associated with thickening of the liver capsule can develop. Several types of primary peritoneal malignancies are known, including primary papillary serous carcinoma, primary psammocarcinoma, primary peritoneal clear cell carcinoma, anaplastic giant cell carcinoma, hepatoid carcinoma, mesodermal (Müllerian) adenosarcoma, and malignant mesothelioma. A distinct neoplastic process known to involve the liver is pseudomyxoma peritonei most frequently associated with mucinous malignancies of the appendix and ovaries. Gliomatosis peritonei may involve large parts of the serosal surface. Numerous forms of reactive alterations of the peritoneum can give rise to small tumor-like lesions. They mainly include various types of metaplasia, granulomas, endometriosis, and deciduosis.

Introduction

The parietal and visceral peritoneum is subject to various neoplastic and nonneoplastic alterations. Inner organs, including the liver and the gallbladder, can be involved when the visceral surface of the peritoneum is affected. In such situations, tumors and tumor-like lesions can be found on the liver capsule, the free surface of the gallbladder, in the gallbladder fossa, and in the subdiaphragmatic space. Depending on the type of lesions, discrete focal masses or a diffuse process resulting in a thickening of the liver capsule may ensue. In this chapter, several entities primarily involving the peritoneum are discussed.

Primary Papillary Serous Carcinoma of the Peritoneum

Introduction

Primary papillary serous carcinoma of the peritoneum (PPSCP; synonyms: extraovarian primary peritoneal carcinoma, EOPPC; extraovarian pelvic serous tumor; multifocal extraovarian serous carcinoma; peritoneal carcinomatosis of unknown primary tumor site) is an uncommon primary low-grade carcinoma of the peritoneal surface that is histologically indistinguishable from papillary serous carcinoma of the ovaries. PPSCP typically develops a diffuse peritoneal growth pattern, while it spares or only superficially invades the ovaries. In the first description of this neoplasm, the author thought it to be a mesothelioma of the pelvic peritoneum (Swerdlow 1959), but the distinction between peritoneal carcinoma and mesothelioma was emphasized in 1977 (Kannerstein et al. 1977).

Epidemiology

PPSCP was first described in 1959 (Swerdlow 1959) and is a disease of females of the middle-aged to older group (Foyle et al. 1981; Lele et al. 1988). Among the cases reported in the literature, around 10 % of females diagnosed with serous ovarian carcinoma actually suffered from PPSCP. PPSCP is an exceptional finding in males (Shah et al. 1998; Shmueli et al. 2001). In the context of peritoneal cancer work-ups, more and more cases of primary peritoneal carcinomas have been identified.

Selected References Raju et al. (1989), Chew et al. (1995), Trauner et al. (1995), Zhou et al. (1995), Taus et al. (1997), Chopra et al. (2000), Koutselini et al. (2001), Morita et al. (2004), Puvaneswary and Proietto (2004), Nakao et al. (2009), Agarwal et al. (2010), Bhuyan et al. (2010), Hwang et al. (2010), Liu et al. (2011). In three studies, the mean age at presentation was 53.3 years (range, 46–59) (Chew et al. 1995), 56 years (range,

40–74 years) (Zhou et al. 1995), and 63 years (range, 44–74 years) (Iavazzo et al. 2008).

Clinical Findings

The tumor presentation is characterized by peritoneal, omental, and mesenterial masses of an exophytically growing tumor in the absence of a primary ovarian malignancy (Liu et al. 2011). The most common presenting features are abdominal pain and distention, and almost all patients present with ascites, often massive (Chew et al. 1995). The serum CA125 levels are markedly elevated (Rosen et al. 1992; Zhou et al. 1995; Furukawa et al. 1999; Iavazzo et al. 2008; Bhuyan et al. 2010). Similar to papillary serous ovarian carcinoma, rising longitudinal levels of CA125 may be significant in the detection of PPSCP (Skates et al. 2003). PPSCP may extend beyond the abdominal cavity and involve the pleural surface (Suh et al. 2008). The carcinoma can metastasize to locoregional lymph nodes and remote organs, including the bronchopulmonary tract (Nakao et al. 2009) and the brain (Sakakibara et al. 2011). The outcome of PPSCP seems to strongly depend on disease extension and amount of residual disease after therapy. In a study of 18 patients, the median overall survival time was 10 months, the figure reflecting the extent of spread of the disease at diagnosis and the relatively limited proportion of patients profiting from optimal cytoreductive surgery (Taus et al. 1997).

Imaging Findings

Patients with PPSCP present with an imaging picture that resembles that of diffuse peritoneal ovarian cancer spread, often associated with massive ascites (Chopra et al. 2000; Morita et al. 2004; Puvaneswary and Proietto 2004). On CT images, the parietal peritoneum of the pelvis showed diffuse enhancement with nodular thickening, and omental caking was seen in the majority of patients with advanced disease. Some of the tumors, i.e., those with psammoma bodies, reveal multiple calcifications (Stafford-Johnson et al. 1998). Typically, the ovaries exhibit a normal size but may display a fine enhancing surface nodularity owing to tumor growth on the ovarian surface (Chopra et al. 2000). The tumor often involves the tissues surrounding the sigmoid colon (Zissin et al. 2001) and may in fact mimic sigmoid cancer (Chand et al. 2007). In the course of disease, PPSCP extends into the upper abdominal compartment (Taus et al. 1997), where involvement of the transverse colon associated with omental tumor formation develops (Furukawa et al. 1999). Upper abdominal involvement can be associated with pleural effusions (Zissin et al. 2001), sometimes massive and bilateral (Kaira et al. 2006).

Pathology

Macroscopy

Macroscopically, the visceral and parietal peritoneums are studded with more or less prominent whitish to reddish nodules with a granulated surface. This pattern is seen at laparoscopy (Trauner et al. 1995). These nodules are commonly 2–5 mm in diameter, but few larger nodules may be noted, especially within the infiltrated omentum. In the intra-abdominal adipose tissue, nodules may coalesce and form an omental cake and/or a firm mesenterial plaque. The small bowel and colon (particularly the sigmoid) may be engulfed by thick and nodular tumor masses, causing a conglomerate of firmly adherent loops. In part of the cases, small cysts filled with a gray and partially gelatinous material are present. The exophytic growths extend into the subdiaphragmatic space (Chew et al. 1995) and to the liver surface. PPSCP can metastasize to the liver (Shmueli et al. 2001).

Histopathology

The histopathology resembles that of papillary serous carcinoma of the ovary. The papillary structures consist of medium-sized serous cells. Part of the cells contain mucin, and even signet ring cells may be noted. One subset of PPSCP

are high-grade neoplasms often showing high mitotic rate, invasion, and necrosis (Truong et al. 1990). However, part of PPSCP are low grade (grade 1), and histologically these tumors mimic the invasive implants of ovarian serous borderline tumors, lack high-grade nuclear atypia, show tissue and/or lymphovascular invasion, and have significant solid epithelial proliferations (Weir et al. 1998). Within the papillary growth, small calcifications or even psammoma bodies may be noted (Liu et al. 2011). The tumor can be diagnosed by use of fine needle aspiration combined with immunocytochemistry (Alberti et al. 2007).

Immunohistochemistry

The tumor cells are positive for cytokeratins (cytokeratins 7 and 20 but not keratins 5/6), epithelial membrane antigen (EMA), Lewis Y antigen, CD15, and placental alkaline phosphatase (Zhou et al. 1995; Shmueli et al. 2001). There is marked positivity for CA125 (Furukawa et al. 1999). The tumor cells are reactive for Ber-EP4, MOC-31, CA19-9, and Leu-M1 (Ordonez 2006). About a third of the tumors are vimentin-positive (Truong et al. 1990). Similar to other carcinomas situated in the peritoneum, but in contrast to mesothelioma, PPSCP is positive for claudin 4 (Facchetti et al. 2007). A large proportion of tumors was found to be positive for estrogen receptors (Barnetson et al. 2006). There is usually no or only limited immunoreactivity for polyclonal CEA or monoclonal CEA (Raju et al. 1989; Truong et al. 1990). Immunostaining for Leu-M1, calretinin, thrombomodulin, or CD44H is negative (Attanoos et al. 2002). The tumors exhibit marked nuclear positivity for p53 protein (Nishimura et al. 2000).

Variants of PPSCP

Primary Peritoneal Serous Borderline Tumors

Peritoneal serous micropapillomatosis of low malignant potential (serous borderline tumor of the peritoneum) is a variant of PPSCP with no detectable invasive growth (Biscotti and Hart 1992). Serous borderline tumors histologically resemble the noninvasive implants of ovarian serous borderline tumors, lack invasion, and do not show nuclear atypia of the degree seen in grade 2 or grade 3 serous carcinoma. Clinically, it is usually manifest at an earlier age than PPSCP. In 19 patients with this neoplasm, mean age at diagnosis was 48 years (Weir et al. 1998).

Primary Psammocarcinoma of the Peritoneum

Primary psammocarcinoma of the peritoneum is a serous carcinoma characterized by the presence of large deposits of psammoma bodies and low-grade cytologic atypia (Whitcomb et al. 1999; Bilgin et al. 2006). This variant of carcinoma was diagnosed at earlier age, i.e., 40 years in one study (Weir et al. 1998). The diagnosis requires the presence of at least 75 % psammoma bodies, no more than moderate cytological atypia, tissue or lymphovascular space invasion, and rare epithelial solid proliferations less than 15 cells across (Weir et al. 1998). Similar to PPSCP, the tumor can be associated with elevated serum CA125 (Whitcomb et al. 1999). Primary peritoneal psammocarcinoma revealed a favorable outcome in part of the patients, resembling the biology of low malignant potential tumors of the ovaries, but examples with an aggressive course are also known, with recurrent disease and metastasis (Poggi et al. 1998; Akbulut et al. 2007; Bodnar et al. 2009).

Differential Diagnosis

The chief differential diagnosis is serous papillary ovarian cancer with peritoneal spread. Histologically, the two neoplasms are in principle indistinguishable. Therefore, diagnosis of PPSCP requires that the ovaries are free of tumor, except the involvement of the ovarian peritoneal surface by a noninvasive papillary

tumor growth in PPSCP. A second important differential diagnosis is papillary peritoneal mesothelioma in females, which can mainly be distinguished by use of immunohistochemistry, as mesotheliomas, but not PPSCP, are positive for calretinin, thrombomodulin, and podoplanin (Zhou et al. 1995; Koutselini et al. 2001; Attanoos et al. 2002; Ordonez 2006). In contrast to PPSCP, peritoneal mesotheliomas do not express estrogen receptors (Barnetson et al. 2006).

Pathogenic Pathways

PPSCP is thought to originate from extragonadal mesothelial cell systems which have a Müllerian differentiation potential. Already in 1972, the female peritoneum was described as a part of the secondary Müllerian system (Lauchalan 1972). A Müllerian potential of peritoneum is supported by the observation of extraovarian malignant mixed Müllerian tumors arising from the peritoneum (Mira et al. 1995; Kanis et al. 2011). Another hypothesis proposed that pathways leading to serous carcinogenesis of the ovaries and the peritoneum involve the traffic of preneoplastic/neoplastic cells from the tubal fimbria, originating from serous tubal intraepithelial carcinomas (STICs), or mediated by a generic secretory cell outgrowth (SCOUT) in the fallopian tube that is associated with altered PAX2 expression (Mehra et al. 2011). Whether the multiple nodules and papillary formations in PPSCP are monoclonal or oligo/polyclonal growths is not yet known. In one study, DNA sequence analysis of the p53 gene showed diverse point mutations at codons 167 and 192 in two of four anatomically different tumors, suggesting polyclonality of some PPSCP neoplasms (Nishimura et al. 2000). The proportion of p53 immunoreactive cells was higher in cases of high-grade pelvic serous neoplasms, reflecting to importance of p53 gene mutations in this subset of neoplasms (Chang et al. 2011). Rare situations have shown familial papillary serous carcinomas of the cervix, peritoneum, and ovary (Kaplan et al. 1998).

Primary Peritoneal Clear Cell Carcinoma

Introduction

In the abdominal cavity, clear cell carcinoma is mostly derived from the ovaries and often associated with endometriosis. The neoplasms are characterized by clear epithelial cells containing abundant glycogen and the presence, at least at some places, of hobnail cells. Very few clear cell carcinomas involving the peritoneal surface in the absence of a genital tract tumor have been described (Lee et al. 1991; Ichimura et al. 2001; Terada and Kawaguchi 2005; Takano et al. 2009; Muezzinoglu et al. 2011). All patients were women 45 years of age or older at diagnosis. The tumors are interpreted to have a Müllerian derivation.

Clinical Features

The tumors presented with upper abdominal and pelvic tumor masses, sometimes associated with ascites. The tumors can grow around intra-abdominal organs such as the stomach and the spleen (Terada and Kawaguchi 2005). The neoplasm may be associated with elevated serum CA19-9 levels (Ichimura et al. 2001).

Pathology

Macroscopy

Macroscopically, part of the described tumors were solid growths with cystic parts, encapsulated by fibrous tissues (Terada and Kawaguchi 2005).

Histopathology

The neoplasms consist of proliferations of polygonal cells arranged in solid nests, tubular, or papillary patterns, the latter sometimes with a hobnail appearance. At least half of the cell populations showed cells with a clear cytoplasm, prominent

cell borders, and round hyperchromatic nuclei with prominent nucleoli. PAS-positive intracytoplasmic hyaline globules were recognized in a few areas (Terada and Kawaguchi 2005). The stromal axes of papillary structures contain an Alcian blue-positive myxoid substance. Histologically, associated endometriosis was either present (Muezzinoglu et al. 2011) or absent (Takano et al. 2009).

Immunohistochemistry

In a study of two tumors, the neoplastic cells were positive for cytokeratin AE1/AE3, polyclonal cytokeratin, cytokeratin MNF116, cytokeratin 34betaE12, epithelial membrane antigen (EMA), CA125, CA19-9, and p53 protein, whereas no reactivity for vimentin and for steroid hormone receptors was found (Terada and Kawaguchi 2005).

Primary Peritoneal Anaplastic Giant Cell Carcinoma

This is an extremely rare type of a primary peritoneal carcinoma that was observed in a 72-year-old woman who had presented with lower abdominal pain. CT revealed a diffuse omental thickening (omental cake). Pathologic examination of resection specimens revealed extensive omental replacement by tumor but only superficial surface cortical involvement of both ovaries, and the neoplasm was composed of diffusely arranged anaplastic tumor giant cells (Lu et al. 2008).

Diffuse Hepatoid Adenocarcinoma of the Peritoneal Cavity

Hepatoid adenocarcinoma is a rare malignancy that occurs mostly in the gastrointestinal tract and the ovaries. A primary localization in the peritoneal surface is very rare and was observed in a 68-year-old man presenting with massive ascites and markedly elevated serum and ascitic AFP levels. CT revealed multiple nodular lesions disseminated exclusively in the peritoneal cavity. Laparoscopic biopsy displayed the morphology of diffuse hepatoid adenocarcinoma (Kitamura et al. 2006).

Primary Peritoneal Mesodermal (Müllerian) Adenosarcoma

Introduction

One–3 % of all female genital tract tumors are stromal malignancies, and of these mesodermal (Müllerian) mixed tumors or adenosarcomas account for 8–10 % of cases (Clement and Scully 1974). Histologically, the neoplasms contain a neoplastic but benign-looking or mildly atypical epithelial element and a sarcomatous, usually low-grade stromal component. Müllerian adenosarcomas are typically neoplasms arising in the corpus of the uterus, but the tumor also occurs in the uterine cervix and ovary and more rarely in the vagina and fallopian tube (review: McCluggage 2010). A small fraction of the tumors originate from the peritoneum, including the pouch of Douglas (Kerner et al. 1989; Ohno et al. 1989; De Jonge et al. 1995; Thylan 1996; Kato et al. 2000; Visvalingam et al. 2001; Kanngurn et al. 2005; Magro et al. 2005; Gong et al. 2008; Patrelli et al. 2011). In part of the cases, the tumor was associated with endometriosis (Dincer et al. 2002; Huang et al. 2009).

Clinical and Imaging Features

The clinical presentation is dominated by the effects of tumor masses occupying the peritoneal surface in diverse sites of the abdominal cavity. Patients usually have pain in the lower or upper abdomen. CT images document the often large solid masses that encroach upon and invade intra-abdominal organs (Gong et al. 2008).

Pathology

Macroscopy

The gross presentation is that of bulky tumors that protrude from the peritoneal surface and cause tumorous adhesions between the peritoneum and organs and between involved organs.

Histopathology

Typically, adenosarcomas show a biphasic pattern and a low-power phyllode-like architecture with leaflike projections consisting of a neoplastic stroma, lined by a variety of benign-looking Müllerian-type epithelia, including cuboid to prismatic glandular epithelium and squamous epithelium. The epithelium lines slit-like or antler-shaped cavities situated between the phyllode-like stromal projections. The glandular epithelium may show a variety of metaplastic changes, including ciliated and strongly eosinophilic cells. A characteristic feature are intraglandular stromal protrusions. The stroma exhibits a rather low cellularity, but cell density is typically higher close to the epithelial linings, causing the development of a so-called cambium. To be classified as sarcomatous, the stroma should show two or more mitotic figures per 10 HPFs (Verschraegen et al. 1998; review: McCluggage 2010). In regard to stromal predominance, Müllerian adenosarcomas exist as lesions without sarcomatous overgrowth (MA-NSO) or with sarcomatous overgrowth (MA-SO). The stroma is usually low grade and of the endometrial or fibroblastic type, but high-grade sarcomatous components also occur, e.g., the sarcomatous component may show an extensive rhabdomyosarcomatous element (Kato et al. 2000). Within the neoplastic stromal tissue, fetal-type cartilage can develop (Kanngurn et al. 2005). Adenosarcomas with an important component of mesenchymal tumor tissue may be difficult to diagnose, because large areas can display a low cellularity and infrequent mitotic figures.

Immunohistochemistry

The epithelial cell populations are cytokeratin-positive, while the stromal cells are reactive for vimentin, alpha-SMA, desmin, CD10, WT1, and steroid hormone receptors. Expression of estrogen receptors predominates in MA-NSOs and I much less common in MA-SOs (Soslow et al. 2008; Gallardo and Prat 2009).

Pseudomyxoma Peritonei

Introduction

Pseudomyxoma peritonei (PMP) was first described by K.F. Rokitansky in 1842 and is a complex life-threatening intra-abdominal disease or syndrome characterized by multifocal to diffuse peritoneal epithelial implants derived from mucinous tumors, secreting copious mucin, and causing dissecting gelatinous ascites (Yan et al. 2001; Jacquemin and Laloux 2005; Buell-Gutbrod and Gwin 2013). PMP is a serious condition that may show a very aggressive course, however depending on the type of disease (see below; Touloumis et al. 2013; Wang et al. 2014). Most primary tumors causing PMP formerly seemed to be located to the appendix or the ovaries (Young 2004; Jacquemin and Laloux 2005; Lee et al. 2008; Smeenk et al. 2008). Less common lesions that can give rise to PMP comprise intraductal papillary mucinous neoplasm of bile ducts (Jhuang and Hsieh 2012), neoplastic mesenteric cysts (Zappa and Sugarbaker 2010), ruptured mucinous cystadenoma of the spleen (Kapoor et al. 2007), mucinous adenocarcinoma of the urachus (Yan et al. 2006), malignant transformation of tailgut cyst (retrorectal hamartoma; Zappa et al. 2009), and colonic polyps (Goldstein et al. 2006).

The identification of primary mucinous ovarian tumors as origin of PMP is hampered by the fact that a considerable fraction of the patients have concurrent mucinous appendiceal tumors, leading to the concept that in most patients ovarian involvement is in fact a secondary

phenomenon, i.e., following an appendiceal primary tumor (Ronnett et al. 1995a, 1997; Pai and Longacre 2005). The pathogenic pathway leading to this distinct mode of peritoneal spread of the disease is only partially known. Recent studies show that PMP is, in principle, a disease of MUC2-expressing goblet cells. Secreted MUC2 accounts for the voluminous deposits of extracellular mucin, typically with a mucin-to-cell ratio exceeding 10:1. Primary epithelial cell cultures derived from PMP express MUC2 whose levels can be epigenetically regulated and are upregulated in response to *Pseudomonas aeruginosa*. Importantly, the levels of mucin deposition are not related to the grade of malignancy but rather reflect the constitutive levels of expression observed in normal goblet cells of the appendix (O'Connell et al. 2002). The neoplastic goblet cells of PMP strongly express a member of the human Reg protein family, the regenerating protein (Reg)-like protein (REPL, Reg IV), a secreted protein of C-lectin type (Heiskala et al. 2006). Reg proteins are involved in regeneration, proliferation, and differentiation of cells in the pancreas, liver, and gastrointestinal mucosa. PMP may involve extended areas of the peritoneal surface and as such can grow onto and eventually into the liver. In 5.4 % of patients, PMP showed pleural extension (Pestieau et al. 2000).

Classification

Based on systematic clinicopathologic studies, PMP is now viewed as three pathologically and prognostically distinct disease processes (Table 1; Ronnett et al. 1995b).

The first type (the classical clinical syndrome of PMP) is *disseminated peritoneal adenomucinosis* (*DPAM*) characterized by copious mucinous ascites and histologically bland peritoneal mucinous tumors. The morphology shows bland to low-grade adenomatous mucinous epithelium associated with abundant extracellular mucin and fibrosis. In most cases, DPAM is causally attributed to a ruptured appendiceal mucinous tumor and usually follows a rather indolent clinical course when surgically treated but may recur over months to years. The second type is *peritoneal mucinous carcinomatosis* (*PMCA*) characterized by copious and diffuse peritoneal mucinous carcinoma. Clinically resembling DPAM, histology shows invasive mucinous adenocarcinoma derived from the GIT. PMCA has a significantly more aggressive course. The third type, *peritoneal mucinous carcinomatosis with intermediate or discordant features* (*PMCA I/D*), displays intermediate or discordant histologic features and is derived from well-differentiated mucinous adenocarcinomas associated with adenomas but manifests a clinical course very similar to cases of pure peritoneal carcinomatosis (Ronnett et al. 1997). In a study of 101 patients with PMP of appendiceal origin, 58 patients had DPAM, 23 had PMCA, and 20 had PMCA I/D, and DPAM and PMCA I/D exhibited a roughly equal incidence of parenchymal (beyond the serosa) organ invasion (Bradley et al. 2006). For patients with PMP of appendiceal origin, a new classification system has recently been proposed, a three-tiered grading system designated PMP1, PMP2, and PMP3 (Shetty et al. 2013). PMP1 included many patients with abundant extracellular mucin and columnar nonstratified epithelium without atypia or dysplasia. In PMP3 cases, part of the lesions contained any percentage of signet ring cells, the presence of signet ring cells having an impact on survival.

Table 1 Classification of pseudomyxoma peritonei (PMP)

Disseminated peritoneal adenomucinosis (DPAM)
Peritoneal mucinous carcinomatosis (PMCA)
Peritoneal mucinous carcinomatosis with intermediate or discordant features (PMCA I/D)

Liver Involvement in PMP

Macroscopy

PMP lesions that develop around the liver usually result in a characteristic scalloping of the liver and spleen margins and often in omental thickening, with production of a so-called omental cake. In the setting of upper abdominal PMP, the liver can directly be involved in part of the patients (Youssef and Moran 2011). Notches of myxoid tumor tissue

can form on the surface of the liver (Qi et al. 2015). During laparotomy or laparoscopy, or at necropsy, liver involvement by PMP is manifest as transparent and viscous masses overlying the liver capsule (Nikolic et al. 2012). In case of hemorrhage or infection, the mucoid material may change from a transparent aspect to brownish-red or yellowish masses. Owing to the organ movements, the material may be pushed into ridges or granular structures. In advanced stages, only a fibrosclerotic thickening of the liver surface is seen. In rare cases, PMP can produce intrahepatic metastases (Lang et al. 1995; Serrano Lira et al. 1995; Gupta et al. 2000), characterized by mucinous adenocarcinoma deposits. Recurrent appendiceal PMP and its mucus may accumulate at the liver hilus/porta hepatis. Among 140 patients with recurrence of appendiceal PMP following complete cytoreduction, 5 % had disease recurrence in and around the porta hepatis (Sugarbaker and Bijelic 2008). PMP was found to originate from low-grade intraductal papillary mucinous neoplasm of bile duct (Jhuang and Hsieh 2012).

Histopathology

PMP tissue and mucinous material covering the liver surface in case of DPAM show lakes of mucus dissecting fibrous tissue, sometimes with a lymphocytic reaction and the formation of macrophage accumulations or mucus granulomas. Suspended in the mucus masses one notes aggregates or "flakes" of well-differentiated mucinous epithelium, sometimes with goblet cell features. The mucus-induced dissection may extend into the subserosal compartment, what is difficult to distinguish from tumor invasion. In case of PMCA, epithelial formations of mucinous adenocarcinoma are seen, and subserosal invasion is easily detectable.

Immunohistochemistry

Immunohistochemically, the PMP tissue is diffusely reactive for cytokeratin 20, CDX-2, MUC2, and MUC5AC. CDX-2 is a useful marker to confirm the appendiceal origin of PMP (Nonaka et al. 2006). MUC2 expression was found to be highest in the PMCA type of PMP and was found to be associated with enteric bacteria in PMP tissue (Semino-Mora et al. 2008). Expression of MUC5AC by the atypical goblet cells is not specific for PMP (O'Connell et al. 2002).

Biology of Disease

As already mentioned above, the classes/types of PMP have an impact on prognosis of the disease. Patients with the DPAM type of PMP have a significantly more favorable prognosis than patients with PMCA, having 5-year and 10-year survival rates of 75 % and 68 %, respectively. In contrast, patients with PMCA I/D had 5-year and 10-year survival rates of 50 % and 21 % and those with PMCA 14 % and 3 %, respectively (Ronnett et al. 2001). Negative prognostic determinants after complete cytoreduction and hyperthermic intraperitoneal chemotherapy of PMP comprised previous chemotherapy, the PMCA pattern, and elevated serum CA125 (Baratti et al. 2009). The biology of PMP seems to be influenced by its inflammatory microenvironment, in particular the expression of IL-6. This cytokine response may be linked to a core microbiome associated with PMP, in that 16S amplicon-based sequencing, direct in situ hybridization analysis, and culturing methods identified numerous bacterial taxa that were consistently present in all PMP patients tested (Gilbreath et al. 2013).

Gliomatosis Peritonei

Introduction

Gliomatosis peritonei (GP), first reported under this name in 1906 (Neuhäuser 1906) but already described in 1905 (Fleischmann 1905), is characterized by the emergence of numerous peritoneal, or more precisely subperitoneal, foci consisting of glial tissue. This is a rare, mostly benign condition occurring both in children and in adults and

chiefly associated with immature and mature teratomas of the ovary (Fortt and Mathie 1969; Robboy and Scully 1970; Okamoto et al. 2007) and sometimes with teratomas located elsewhere. Exceptionally, GP is associated with growing teratoma syndrome (so-called chemotherapeutic retroconversion; Amsalem et al. 2004). The highest incidence of GP was found in the first two decades of life in regard to the time point of first tumor (teratoma) operation (average age based on a literature review, 15.4 years; Müller et al. 2002). GP, particularly in the presence of numerous and large glial foci, is known to cause ascites, of unknown pathogenic mechanism (Hsieh and Liu 2009). Rarely, ovarian teratoma-based GP is associated with both ascites and pleural effusion (hydrothorax). This is termed Pseudo-Meigs' syndrome in GP (Khan et al. 2005). The complex biology of disease of gliomatosis peritonei (GP) is usually a benign condition, and immature teratomas, when associated with mature glial implants within the peritoneum, have a better prognosis irrespective of the original tumor grade (Robboy and Scully 1970). However, there are descriptions of cases of mature gliomatosis peritonei which seem to have evolved into malignancy (Shefren et al. 1991).

Gliomatosis Peritonei of the Liver Surface

An involvement of the liver surface has already been observed in the first patient reported (Fleischmann 1905). The nodules are usually composed of mature-looking glial tissue and either form macroscopically visible nodules of up to 3.5 cm size (*nodular GP*; Harms et al. 1989; average, 0.26 cm; Müller et al. 2002) or microscopic foci found in random peritoneal biopsies (miliary GP). There may be signs of chronic inflammation or immune reaction, perifocal fibrosis, calcifications, or psammoma bodies. The cells of the foci are immunoreactive for GFAP, vimentin, S100 protein, and NSE (Harms et al. 1989; Müller et al. 2002). In part of the cases, a close spatial relationship between a teratoma and GP was found. In the case described by Torikai and coworkers (Torikai et al. 2007), a 9-month-old girl had a cystic and partly calcified immature teratoma hanging beneath the liver and in continuity with the fundus of the gallbladder. In the adjacent omentum and peritoneum, numerous nodules up to 2 mm in diameter were seen, histologically characterized by mature gliomatous tissue. The tridermal primary tumor also contained immature neural tissue.

Pathogenic Pathways

In regard to the causes of GP, at least five theories of pathogenesis have been proposed, viz., implants representing all three germ layers, with survival of glial tissue; immature neural tissue spreading in the abdominal cavity, with subsequent glial differentiation; extrusion from a teratoma of mature glial tissue itself; the differentiation of pluripotent Müllerian stem cells along a glial cell pathway; and primary multiplicity of lesions as a so-called field effect (Müller et al. 2002). A lymphatic spread of target cells is suggested by the observation of nodular/nodal gliomatosis involving locoregional lymph nodes. The complexity of pathogenic pathways in GP is underlined by the morphologic unity, soft tissue gliomatosis, where glial tissue foci occur at diverse sites, with or without association with teratomas or sequestered encephaloceles (McDermott et al. 1996). The glial implant theory of GP is suggested by the observation that GP can occur as a complication of a ventriculoperitoneal shunt, in the absence of any ovarian lesions (Lovell et al. 1989), suggesting an implantation pathway also known to work for peritoneal manifestations of malignant intracranial tumors in patients with such shunts.

Molecular studies have put the implantation theories of GP into question. In investigations employing polymorphic microsatellite loci as markers, it turned out that glial implants in GP seem to arise from cells within the peritoneum (presumably Müllerian stem cells) and not from associated ovarian teratomas (Ferguson et al. 2001; Kwan et al. 2004). Another microsatellite marker study of tumors of immature ovarian

teratoma and its recurrences, and GP, demonstrated mutually exclusive genetic differences among the lesions, establishing the lineages as genetically distinct (Best et al. 2004).

Metaplastic and Tumor-like Lesions of the Hepatic Peritoneum

Introduction

The peritoneum, including that covering the liver, can undergo a multitude of reactive changes that are characterized by focal or multiple mass-producing lesions that can mimic a neoplastic process. In case these alterations are markedly expressed on the hepatic serosa, multiple tumor-like lesions mimicking, e.g., metastatic disease can develop.

Epithelial Metaplasia, Hyperplasia, and Related Lesions of the Mesothelium

Squamous Cell Metaplasia

The peritoneal mesothelium can undergo squamous cell metaplasia, with or without keratinization (Schatz and Colgan 1991). This metaplasia was most often found in chronic peritonitis, e.g., in patients with peritoneal tuberculosis. It has also been observed in patients on continuous ambulatory peritoneal dialysis/CAPD (Selgas et al. 1995) and is sometimes followed by the development of benign glandular inclusions thought to derive from totipotential subcoelomic mesenchymal cells (Chen 1981).

Peritoneal Keratin Granulomas

In cases with keratinization, cornified cells can detach from the epithelial, enter the subserosal space, and elicit a vigorous foreign body reaction, with formation of keratin granulomas. Such granulomas can, however, also develop in the setting of peritoneal spread of squamous cell neoplasms or after rupture of ovarian dermoid cysts.

In general, release of cornified squamous epithelial cells from the "sealed" epithelial into connective tissue elicits a vigorous foreign body reaction mediated by activated macrophages and their fused offspring, multinucleated foreign body giant cells. This response results in the formation of granulomas that contain decaying cornified squamous cells and keratin lamellae, the keratin granuloma. In some situations, these granulomas also contain cholesterol crystals with adherent giant cells (mixed keratin and cholesterol granulomas). Keratin granulomas are well known to occur in the setting of squamous cell carcinomas, e.g., following radiation therapy or chemotherapy where damaged or dead cancer cells induce a local granulomatous reaction (Safall and Azar 1966; Reddy et al. 1975; Westra et al. 1998), but the granulomas may also be found in the vicinity of squamous cell carcinomas in the absence of therapy (Leshin et al. 1992). Keratin granulomas also occur in the neighborhood of benign lesions, e.g., ruptured epidermoid/trichilemmal cysts and dermoid cysts. In this situation, a lipogranulomatous reaction can emerge, directed against the fatty cyst contents.

Apart from squamous cell metaplasia, keratin granulomas situated in the peritoneal surface mainly occur in patients with gynecological cancers containing a squamous component (Chen 1999). In these instances, squamous cancer cells can either leave the tumor when it invades the peritoneum or escape through the Fallopian tube. Peritoneal keratin granulomas, sometimes multiple, have been observed in the context of uterine adenoacanthoma (Chen et al. 1978), endometrioid adenocarcinoma with squamous differentiation (Kim and Scully 1990; Wotherspoon et al. 1989; van der Horst and Evans 2008; Uehara et al. 2011), ovarian carcinomas with squamous differentiation (Wu et al. 2006), and ruptured ovarian teratoma (Phupong et al. 2004). Oil-containing peritoneal keratin granulomas were found as a complication of ovarian dermoid (Kurrein and Fothergill 1961). In male patients, peritoneal keratin granulomas can be related to peritoneal squamous metaplasia or peritoneal inclusion cysts with squamous metaplasia. Following rupture of such cysts, large inflammatory

tumor-like lesions containing keratin granulomas can develop, also involving the liver surface (Tripathy et al. 2010).

Mucinous Metaplasia

Mucinous metaplasia of the peritoneum is a very rare condition, characterized by the presence of mucin-producing glandular or prismatic cells lining the peritoneal surface (Saran et al. 2008).

Mesothelial Hyperplasia

The mesothelial covering of the peritoneal surface can, under several circumstances, develop adenomatoid epithelial structures that may pose diagnostic difficulties in regard to the exclusion of malignant disease (Michal 1997). Hyperplasia of the peritoneal mesothelium is a reactive process that presents in the form of nodular, papillary, tubular, or mixed mesothelial growths (Rosai and Dehner 1975; Clement and Young 1993; Churg et al. 2000; Lee et al. 2014). The alteration can occur in association with a variety of gynecological disorders (Oparka et al. 2011) but can also occur in the setting of peritoneal inflammatory disorders. This alteration is usually characterized by linear arrays of widely spaced and horizontally oriented, simply constructed and non-branching tubules and nests of mesothelial cells, sometimes embedded in a stroma-like connective tissue. The lesions are more commonly found in the tunica vaginalis ("florid mesothelial hyperplasia"; Lee et al. 2014). Mesothelial hyperplasia may be confounded with mesothelioma, in particular benign papillary mesothelioma (Goepel 1981), but whereas the latter express insulin-like growth factor II messenger RNA-binding protein 3/IMP3, reactive hyperplastic mesothelial cells do not (Shi et al. 2011).

Endometriosis

The peritoneum is a rather common site of extragenital endometriosis, either with grossly detectable lesions or in a microscopic form (Khan et al. 2014). Peritoneal endometriosis has a high lymph vessel density associated with the expression of lymphatic growth factors (VEGF-C/VEGF-D) in stromal cells and macrophages (Reichelt et al. 2012). Apart from locally induced and activated stromal cells, macrophages play a significant role in the pathogenesis of peritoneal endometriosis, via secretion of a distinct set of cytokines (Beste et al. 2014). Endometriosis can transform into a mucinous epithelium with eventual development of dysplastic changes (Mai and Burns 1999) and may in some instances resemble a placental site nodule or placental site (Santos et al. 1999). A variant of peritoneal endometriosis is peritoneal stromal endometriosis, characterized histologically by small nodules or plaques of endometrium-type stroma, sometimes with a whorled pattern, increased vascularity, and red cell extravasation. The stromal foci are situated in the submesothelial tissue and protrude above the surface. The lesions may be accompanied by circumscribed mesothelial hyperplasia (Boyle and McCluggage 2009). Stromal endometriosis occurs either in conjunction with classical endometriosis, or as a lesion of its own.

Endosalpingiosis

Endosalpingiosis denotes the presence of endosalpingeal, Fallopian tube-type prismatic, and at least in part ciliated epithelia in extratubal tissues, including the peritoneum. The cells can form multiple simple glands that are lined by a single layer of cells, sometimes with development of cystic structures.

Strumosis Peritonei

Strumosis (synonyms: metastatic ovarian strumosis, strumatosis) is defined as the presence of implants of mature follicular thyroid tissues in the peritoneal tissue. The source of peritoneal strumosis is struma ovarii in ovarian teratoma (Brogsitter et al. 2004; Muallem et al. 2012; Navarro et al. 2012), struma ovarii in connection

with other ovarian tumors (Sibio et al. 2010), and isolated struma ovarii (Balasch et al. 1993; Karseladze and Kulinitch 1994). Peritoneal strumosis can cause thyrotoxicosis (Kim et al. 2009) and may be difficult to differentiate from spread of highly differentiated follicular thyroid carcinoma (Roth and Karseladze 2008).

Sertoli Cell Tumor Implants

In very cases, Sertoli cell tumor of the ovary produced benign peritoneal implants (Onida et al. 2010).

Deciduosis of the Peritoneum

Associated with pregnancy, the peritoneal covering of the liver may be involved in ectopic decidual change, a lesion termed deciduosis or ectopic decidual reaction (deciduosis peritonei), and thought to result from the differentiation of extrauterine stromal cells to a decidual cell lineage (Kwan and Pang 1964; Zaytsev and Taxy 1987; Buttner et al. 1993; Fenjvesi and Zivkovic 2005; Kinra et al. 2006; Shukla et al. 2008; Bolat et al. 2012; Stewart 2013). In part of cases, the peritoneal surface and the omentum are studded with numerous whitish grain-like lesions, varying in diameter from 1 to 5 mm. Peritoneal deciduosis can cause hemorrhage (Hulme-Moir and Ross 1969). It may grossly mimic peritoneal tubercles or miliary peritoneal tuberculosis (Shukla et al. 2008) or metastatic nodules (Piccinni et al. 2002). Hepatic peritoneal deciduosis has, however, not yet been specified in the reports on peritoneal decidual change. Deciduosis has been observed to be accompanied by lipofuscinosis peritonei (White and Chan 1994). A decidual reaction of the peritoneum sometimes results in mass lesions (gross deciduosis, pseudotumoral deciduosis), even obstructing labor (Malpica et al. 2002).

Peritoneal deciduosis, in particular pseudotumoral deciduosis, has to be distinguished histologically from deciduoid mesothelioma (Mourra et al. 2005).

Peritoneal Stromal Luteinization

The submesothelial stromal cells of the peritoneum can undergo functioning extraovarian stromal luteinization (Aneiros-Fernandez et al. 2010).

Melanosis Peritonei

Melanosis peritonei (MP) is a very rare condition characterized by the presence of melanin-containing cells, either melanocytes or – more commonly – melanin-containing macrophages (melanophages, melanophores) in the subperitoneal tissue, including that of the liver. In MP, the peritoneal surface shows a grossly gray to black pigmentation, in a focal to multifocal or even diffuse distribution pattern. Focal melanosis may grossly mimic deposits of malignant melanomas in the course of laparotomy or laparoscopy. MP has most often been encountered in association with melanin-containing lesions covered by peritoneum, such as inflammatory processes (particularly peritoneal tuberculosis), Addison's disease, ovarian dermoid cysts/mature teratoma, ovarian cystadenomas, and gonadal melanogenic neoplasms (Crampton 1832; Gluge 1841; Afonso et al. 1962; Lee and Pontifex 1975; Fukushima et al. 1984; Kagiya et al. 1990; Hesseling and De Wilde 1998; Jaworski et al. 2001; Kim et al. 2002, 2010; Liu et al. 2007). Exceptional associations are melanophage-containing enteric duplication cysts (Jung et al. 1996; Nada et al. 2000) and gastric triplication (De la Torre Mondragon et al. 1997). In MP associated with ovarian teratomas, a spread of germ cell derivatives has been suggested. In non-teratomatous cysts, a gastrointestinal-type squamous epithelium may be a target structure for melanocyte homing, similar to the epidermis. Melanophages are thought to be transferred to the peritoneal/subperitoneal tissue via lymphatic spread, to mainly form perivascular and perineural accumulations of melanosome-containing macrophages, sometimes with formation of pigment cell nodules (Jung et al. 1996). Also a (phagocytic?) uptake of melanin granules by mesothelial cells has been

described (Kim et al. 2002). A condition macroscopically resembling MP is the peritoneal deposition of iron-containing pigments (Jaworski et al. 2001).

Melanotic Peritoneal Cyst

There is a report on a patient having a multilocular cyst lined by heavily pigmented mesothelial cells. Light and electron microscopy revealed that this pigment was melanin, and underneath the pigmented lining there were scattered melanocytes with a dendritic shape. This type of pigmented cyst may represent a manifestation of primary melanosis peritonei (Drachenberg and Papadimitriou 1990).

Melanotic Alterations of the Peritoneum in Neoplastic Melanocyte Processes

Malignant melanocytic neoplasms can induce melanotic lesions of the peritoneum (Hefaiedh et al. 2009; Lim et al. 2012). These lesions may result from accumulations of melanophages having phagocytosed melanosomes escaped from decayed melanoma cells or represent foci of regressed melanoma metastases. More frequent are growing, i.e., non-necrotic melanin-containing peritoneal metastases of melanoma, with primary lesions both in extra-abdominal and intra-abdominal sites (Gao et al. 2010; Lim et al. 2012), including ocular melanoma (Knapp 1868). Peritoneal deposits of malignant melanoma can develop after a long delay, occurring 10 or more years after diagnosis of the primary tumor (Lee et al. 2003). Apart from malignant melanoma, neurocutaneous melanocytosis and malignant meningeal melanosis can give rise to peritoneal metastases (Kurokawa et al. 2013), in part via tumor cell spreading from ventriculoperitoneal shunting for the treatment of hydrocephalus occurring in this disorder (Faillace et al. 1984; Gattuso et al. 1995; Cajaiba et al. 2008).

Peritoneal Pigmentation in Peutz-Jeghers Syndrome

Apart from its gastrointestinal hamartomatous polyposis phenotype, Peutz-Jeghers syndrome is characterized by circumscribed mucosal pigmentations, especially in the intraoral area. In rare cases, peritoneal pigmentation has been observed (Hirasawa et al. 2012).

Non-melanin Pigmentations of the Peritoneum

Multiple black patches of the peritoneum grossly resembling endometriosis and caused by focal accumulation of carbon particles ("peritoneal tattoos") have been observed following spillage and spread of India ink from preoperative endoscopic tattooing (Algoe et al. 2008; Cappell et al. 2010; Tutticci et al. 2010; Stemmer and Shurshalina 2014).

Reactive Peritoneal Cysts

Peritoneal inclusion cysts are a relatively common finding. They mostly develop following a peritoneal insult and occur in a wide age range and mostly in females (82.5 %; Veldhuis et al. 2013). There are rare instances of multilocular peritoneal inclusion cyst, small but grossly visible thin-walled cysts being lined by a single layer of flat mesothelial cells. The cysts may contain retained ovarian fluid (Bharwani and Crofton 2013). Part of the lesions are accompanied by mural mesothelial proliferations. These lesions have to be distinguished from primary peritoneal serous borderline tumor (PPSBT) (Go et al. 2012), multicystic peritoneal mesothelioma (Vallerie et al. 2009), and primary or secondary peritoneal hydatidosis (echinococcosis; Goel et al. 2010; Kushwaha et al. 2012; Hegde and Hiremath 2013; Lissandrin et al. 2013). Part of peritoneal pseudocysts are caused by accumulation of cerebrospinal fluid due to ventriculoperitoneal shunts (Lejeune et al. 1984; Chandra et al. 1992).

Granulomatous and Other Inflammatory Reactions in Peritoneal Tissues

Numerous inflammatory, infectious, and neoplastic conditions can induce a granulomatous peritoneal reaction (peritonitis granulomatosa), e.g., miliary tuberculosis. Granulomas with a necrotic but not caseating center are seen secondary to diathermy ablation of endometriotic peritoneal lesions. Lost gallstones or gallstone fragments can settle in the peritoneum and elicit a vigorous inflammation, sometimes with gallstone granulomas (so-called gallstone peritonitis). A peritoneal macrophage/histiocytic reaction (histiocytic nodules, histiocytic nodulosis, mucicarminophilic histiocytosis) occurs in association with the deposition of oxidized regenerated cellulose (Gonzalez-Campora et al. 1997; Tang et al. 2009). Nodular macrophage/histiocyte aggregates of the peritoneum have also been observed in patients with ovarian cancer (Lv et al. 2012).

Chronic peritonitis can cause circumscribed, tumor-like plaques of fibrosis or scarring. A distinct variant of fibrosing peritonitis is sclerosing peritonitis, a condition mimicking a desmoplastic tumor manifestation. As a specific entity or syndrome, sclerosing peritonitis can be associated with luteinized thecomas/thecomatosis of the ovary (Clement et al. 1994; Iwasa et al. 1996; Werness 1996; Staats et al. 2008; Levavi et al. 2009; Mellembakken et al. 2010), ovarian fibromatosis (Frigerio et al. 1997), and benign cystic ovarian teratoma (Stenram 1997). Sclerosing peritonitis can also be induced by foreign material, e.g., talcum powder, and also occurs as an idiopathic lesion (Burstein et al. 1990). In part of patients, sclerosing peritonitis presents as an encapsulating fibrosis or "abdominal cocoon" (Wirnsberger et al. 1992; Serafimidis et al. 2006).

Myxoglobulosis of the Peritoneal Cavity

Myxoglobulosis (von Hansemann) is a distinct pathology of the vermiform appendix, characterized by the presence of small globules within thickened, viscous mucus, their size ranging from millet grains to sago seeds (Hentz 1932; Uhle and Wilkinson 1954; Navarrete-Reyan et al. 1969). Myxoglobulosis can manifest in the peritoneal cavity, the form of whitish-gray nodules or globules measuring up to 1 cm in diameter. Many of these lesions were filled with mucinous material. Electron microscopically, the globules were covered by mesothelial cells with microvilli (Tanimura and Imachi 1989).

Peritoneal Changes in Mucinous Ascites

Mucinous ascites is an uncommon condition characterized by accumulation of mucin in the peritoneal cavity in the absence of pseudomyxoma peritonei. It is caused by leakage of mucin from ruptured mucin-producing lesions of the gastrointestinal tract or the ovaries, usually a benign appendiceal mucocele. Mucinous ascites can be differentiated from the ominous pseudomyxoma peritonei microscopically by the absence of epithelial cells amidst mucin pools in the former. Rarely, mucinous ascites is caused by mucinous metaplasia of the mesothelial peritoneal lining (Saran et al. 2008).

References

Afonso JF, Martin G, Nisco FS, Albaret RR (1962) Melanogenic ovarian tumors. Am J Obstet Gynecol 84:667–676

Agarwal R, Sharma S, Guleria K, Radhakrishnan G, Radhika AG (2010) Primary peritoneal carcinoma: a diagnostic dilemma. Arch Gynecol Obstet 282:115–116

Akbulut M, Kelten C, Bir F, Soysal ME, Duzcan SE (2007) Primary peritoneal serous psammocarcinoma with recurrent disease and metastasis: a case report and review of the literature. Gynecol Oncol 105:248–251

Alberti N, Serrano-Egea A, Garcia-Garcia E, Ballestin C, Pérez-Barrios A, Lopez-Rios F (2007) Primary papillary serous carcinoma of the peritoneum: report of a case with diagnosis by fine needle aspiration and immunocytochemistry. Acta Cytol 51:203–206

Algoe KK, Chen H, Schned AR, Whiteside JL (2008) Intraperitoneal India ink deposits appearing as

endometriosis in a patient with chronic pelvic pain. Obstet Gynecol 112:448–450

Amsalem H, Nadjari M, Prus D, Hiller N, Benshushan A (2004) Growing teratoma syndrome vs. chemotherapeutic retroconversion: case report an review of the literature. Gynecol Oncol 92:357–360

Aneiros-Fernandez J, Carballo P, Molina S, Munoz E, Nogales FF (2010) Functioning extraovarian stromal luteinization of the peritoneum. Histopathology 56:654–656

Attanoos RL, Webb R, Dojcinov SD, Gibbs AR (2002) Value of mesothelial and epithelial antibodies in distinguishing diffuse peritoneal mesothelioma in females from serous papillary carcinoma of the ovary and peritoneum. Histopathology 40:237–244

Balasch J, Pahisa J, Marquez M, Ordi J, Fabregues F, Puerto B, Vanrell JA (1993) Metastatic ovarian strumosis in an in-vitro fertilization patient. Hum Reprod 8:2075–2077

Baratti D, Kusamura S, Nonaka D, Cabras AD, Laterza B, Deraco M (2009) Pseudomyxoma peritonei: biological features are the dominant prognostic determinants after complete cytoreduction and hyperthermic intraperitoneal chemotherapy. Ann Surg 249:243–249

Barnetson RJ, Burnett RA, Downie I, Harper CM, Roberts F (2006) Immunohistochemical analysis of peritoneal mesothelioma and primary and secondary serous carcinoma of the peritoneum: antibodies to estrogen and progesterone receptors are useful. Am J Clin Pathol 125:67–76

Best DH, Butz GM, Moller K, Coleman WB, Thomas DB (2004) Molecular analysis of an immature ovarian teratoma with gliomatosis peritonei and recurrence suggests genetic independence of multiple tumors. Int J Oncol 25:17–25

Beste MT, Pfäffle-Doyle N, Prentice EA, Morris SN, Lauffenburger DA, Isaacson KB, Griffith LG (2014) Molecular network analysis of endometriosis reveals a role for c-Jun-regulated macrophage activation. Sci Transl Med 6:222ra16

Bharwani N, Crofton ME (2013) Peritoneal pseudocysts: aetiology, imaging appearances, and natural history. Clin Radiol 68:828–836

Bhuyan P, Mahapatra S, Mahapatra S, Sethy S, Parida P, Satpathy S (2010) Extraovarian primary peritoneal papillary serous carcinoma. Arch Gynecol Obstet 281:561–564

Bilgin T, Ozuysal S, Cankiliç H (2006) Primary psammocarcinoma of the peritoneum. Int J Gynecol Cancer 16(Suppl 1):129–131

Biscotti CV, Hart WR (1992) Peritoneal serous micropapillomatosis of low malignant potential (serous borderline tumors of the peritoneum). A clinicopathologic study of 17 cases. Am J Surg Pathol 16:467–475

Bodnar L, Wcislo G, Gomas M, Gasowska-Bodnar A, Wisniewski P, Stec R, Baranowski W, Szcylik G (2009) Serous peritoneal psammocarcinoma with an aggressive course: a case and review of the literature. Ginekol Pol 80:632–636

Bolat F, Canpolat T, Tarim E (2012) Pregnancy-related peritoneal ectopic decidua (deciduosis): morphological and clinical evaluation. Turk Patholoji Derg 28:56–60

Boyle DP, McCluggage WG (2009) Peritoneal stromal endometriosis: a detailed morphological analysis of a large series of cases of a common and under-recognized form of endometriosis. J Clin Pathol 62:530–533

Bradley RF, Stewart JH, Russell GB, Levine EA, Geisinger KR (2006) Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol 30:551–559

Brogsitter C, Wonsak A, Würl K, Kotzerke J (2004) Peritoneal strumosis. Eur J Nucl Med Mol Imaging 31:1057

Buell-Gutbrod R, Gwin K (2013) Pathologic diagnosis, origin, and natural history of pseudomyxoma peritonei. Am Soc Clin Oncol Educ Book 33:221–225

Burstein M, Galun E, Ben-Chetrit E (1990) Idiopathic sclerosing peritonitis in a man. J Clin Gastroenterol 12:698–701

Buttner A, Bassler R, Theele C (1993) Pregnancy-associated ectopic decidua (deciduosis) of the greater omentum. An analysis of 60 biopsies with cases of fibrosing deciduosis and leiomyomatosis peritonealis disseminata. Pathol Res Pract 189:352–359

Cajaiba MM, Benjamin D, Halaban R, Reyes-Mugica M (2008) Metastatic peritoneal neurocutaneous melanocytosis. Am J Surg Pathol 32:156–161

Cappell MS, Courtney JT, Amin M (2010) Black macular patches on parietal peritoneum and other extraintestinal sites from intraperitoneal spillage and spread of India ink from preoperative endoscopic tattooing: an endoscopic, surgical, gross pathologic, and microscopic study. Dig Dis Sci 55:2599–2605

Chandra S, Bhatnagar V, Mitra DK (1992) Intraperitoneal CSF pseudocysts following ventriculo-peritoneal shunts. Indian Pediatr 29:1438–1440

Chand M, Moore PJ, Clarke AD, Nash GF, Hickish T (2007) A diagnostic dilemma following risk-reducing surgery for BRCA1 mutation – a case report of primary papillary serous carcinoma presenting as sigmoid cancer. World J Surg Oncol 5:102

Chang MC, Cibas ES, Crum CP, Kindelberger DW (2011) High-grade and low-grade pelvic serous neoplasms demonstrate differential p53 immunoreactivity in peritoneal washings. Acta Cytol 55:79–84

Chen KT (1981) Benign glandular inclusions of the peritoneum and periaortic lymph nodes. Diagn Gynecol Obstet 3:265–268

Chen KT (1999) Cytology of peritoneal keratin granulomas. Diagn Cytopathol 20:105–107

Chen KT, Kostich ND, Rosai J (1978) Peritoneal body granulomas to keratin in uterine adenoacanthoma. Arch Pathol Lab Med 102:174–177

Chew S, Tham KF, Lim FK, Ratnam SS (1995) Papillary serous carcinoma of the peritoneum. J Obstet Gynaecol 21:341–347, Tokyo 1995

Chopra S, Laurie LR, Chintapalli KN, Valente PT, Dodd GD (2000) Primary papillary serous carcinoma of the peritoneum: CT-pathologic correlation. J Comput Assist Tomogr 24:395–399

Churg A, Colby TV, Cagle P, Corson J, Gibbs AR, Gilks B, Grimes M, Hammar S et al (2000) The separation of benign and malignant mesothelial proliferations. Am J Surg Pathol 24:1183–1200

Clement PB, Scully RE (1974) Mullerian adenosarcoma of the uterus. A clinicopathologic analysis of ten cases of a distinctive type of Mullerian mixed tumor. Cancer 34:1138–1152

Clement PB, Young RH (1993) Florid mesothelial hyperplasia associated with ovarian tumors: a potential source of error in tumor diagnosis and staging. Int J Gynecol Pathol 12:51–58

Clement PB, Young RH, Hanna W, Scully RE (1994) Sclerosing peritonitis associated with luteinized thecomas of the ovary. A clinicopathological analysis of six cases. Am J Surg Pathol 18:1–13

Crampton J (1832) Case of melanosis. Boston Med Surg J 5:344–346

De Jonge MJ, van Dam PA, Van Marck E, Prove A, van Oosterom AT (1995) Primary extrauterine müllerian adenosarcoma of the peritoneum. Gynecol Oncol 57:126–130

De la Torre Mondragon L, Daza DC, Bustamante AP, Fascinetto GV (1997) Gastric triplication and peritoneal melanosis. J Pediatr Surg 32:1773–1775

Dincer AD, Timmins P, Pietrocola D, Fisher H, Ambros RA (2002) Primary peritoneal mullerian adenosarcoma with sarcomatous overgrowth associated with endometriosis: a case report. Int J Gynecol Pathol 21:65–68

Drachenberg CB, Papadimitriou JC (1990) Melanotic peritoneal cyst. Light-microscopic and ultrastructural studies. Arch Pathol Lab Med 114:463–467

Facchetti F, Lonardi S, Gentili F, Bercich L, Falchetti M, Tardanico R, Baronchelli C et al (2007) Claudin 4 identifies a wide spectrum of epithelial neoplasms and represents a very useful marker for carcinoma versus mesothelioma diagnosis in pleural and peritoneal biopsies and effusions. Virchows Arch 451:669–680

Faillace WJ, Okawara SH, McDonald JV (1984) Neurocutaneous melanosis with extensive intracerebral and spinal cord involvement. Report of two cases. J Neurosurg 61:782–785

Fenjvesi A, Zivkovic S (2005) Deciduosis peritonei – a case report (in Serbian). Med Pregl 58:196–199

Ferguson AW, Katabuchi H, Ronnett BM, Cho KR (2001) Glial implants in gliomatosis peritonei arise from normal tissue, not from the associated teratoma. Am J Pathol 159:51–55

Fleischmann C (1905) Teratoma peritonei mit ausgebreiteten Disseminationen. Z Geburtshilfe Gynaecol 56:396–415

Fortt RW, Mathie IK (1969) Gliomatosis peritonei caused by ovarian teratoma. J Clin Pathol 22:348–353

Foyle A, Al-Jabi M, McCaughey WT (1981) Papillary peritoneal tumors in women. Am J Surg Pathol 5:241–249

Frigerio L, Taccagni GL, Mariani A, Mangili G, Ferrari A (1997) Idiopathic sclerosing peritonitis associated with florid mesothelial hyperplasia, ovarian fibromatosis, and endometriosis: a new disorder of abdominal mass. Am J Obstet Gynecol 176:721–722

Fukushima M, Sharpe L, Okagaki T (1984) Peritoneal melanosis secondary to a benign dermoid cyst of the ovary: a case report with ultrastructural study. Int J Gynecol Pathol 2:403–409

Furukawa T, Ueda J, Takahashi S, Higashino K, Shimura K, Tsujimura T, Araki Y (1999) Peritoneal serous papillary carcinoma: radiological appearance. Abdom Imaging 24:78–81

Gallardo A, Prat J (2009) Mullerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma. Am J Surg Pathol 33:278–288

Gao R, Liu NF, Sheng XG (2010) Malignant ovarian melanoma with extensive pelvic and peritoneal metastasis: a case report and literature review. Chin J Cancer 29:460–462

Gattuso P, Carson HJ, Attal H, Castelli MJ (1995) Peritoneal implantation of meningeal melanosis via ventriculoperitoneal shunt: a case report and review of the literature. Diagn Cytopathol 13:257–259

Gilbreath JJ, Semino-Mora C, Friedline CJ, Liu H, Bodi KL, McAvoy TJ, Francis J et al (2013) A core microbiome associated with the peritoneal tumors of pseudomyxoma peritonei. Orphanet J Rare Dis 8:105

Gluge G (1841) Abhandlungen zur Physiologie und Pathologie. Anatomisch-mikroskopische Untersuchungen. Friedrich Mauke, Jena, p 115

Go HS, Hong HS, Kim JW, Woo JY (2012) CT appearance of primary peritoneal serous borderline tumour: a rare epithelial tumour of the peritoneum. Br J Radiol 85: e22–e25

Goel MM, Verma N, Sagar M (2010) Disseminated intra-abdominal hydatidosis causing acute intestinal obstruction – a rare presentation. BMJ Case Rep pii: bcr0620103066

Goepel JR (1981) Benign papillary mesothelioma of peritoneum: a histological, histochemical and ultrastructural study of six cases. Histopathology 5:21–30

Goldstein PJ, Cabanas J, da Silva RG, Sugarbaker PH (2006) Pseudomyxoma peritonei arising from colonic polyps. Eur J Surg Oncol 32:764–766

Gong J, Yu X, Xu J, Wang X (2008) CT imaging of a primary malignant mixed mullerian tumor arising from the peritoneum. Clin Imaging 32:390–392

Gonzalez-Campora R, Illanes-Moreno M, Parra-Martin J, Villar-Rodriguez JL, Loscertales-Abril J et al (1997) Extensive peritoneal histiocyte reaction to oxidized regenerated cellulose. Surgery 121:471–473

Gupta MD, Kapoor S, Jain A, Gangwal P, Madan K, Das K, Chakravorty A, Kar P (2000) Occult primary adenocarcinoma causing pseudomyxoma peritonei

with pleural and hepatic metastases. Indian J Gastroenterol 19:189–190
Harms D, Janig U, Gobel U (1989) Gliomatosis peritonei in childhood and adolescence: clinicopathological study of 13 cases including immunohistochemical findings. Pathol Res Pract 184:422–430
Hefaiedh R, Fekih M, Kacem IH, Matri S, Boubaker J, Filali A (2009) Peritoneal melanosis: a rare localization of the melanoma: a case report (in French). Tunis Med 87:719–720
Hegde N, Hiremath B (2013) Primary peritoneal hydatidosis. BMJ Case Rep pii: bcr2013200435
Heiskala K, Giles-Komar J, Heiskala M, Andersson LC (2006) High expression of RELP (Reg IV) in neoplastic goblet cells of appendiceal mucinous cystadenoma and pseudomyxoma peritonei. Virchows Arch 448:295–300
Hentz VG (1932) Myxoglobulosis of the appendix. Ann Surg 96:456–459
Hesseling M, De Wilde RL (1998) Zur Differentialdiagnose laparoskopisch nachweisbarer herdförmiger Läsionen des Peritoneums. Geburtsh Frauenheilk 58:272–281
Hirasawa A, Akahane T, Tsuruta T, Kobayashi Y, Masuda K, Banno K, Fujii T, Susumu N et al (2012) Lobular endocervical glandular hyperplasia and peritoneal pigmentation associated with Peutz-Jeghers syndrome due to a germline mutation of STK11. Ann Oncol 23:2990–2992
Hsieh and Liu 2009. http://www.ncbi.nlm.nih.gov/pubmed/19453084
Huang GS, Arend RC, Sakaris A, Hebert TM, Goldberg GL (2009) Extragenital adenosarcoma: a case report, review of the literature, and management discussion. Gynceol Oncol 115:472–475
Hulme-Moir I, Ross MS (1969) A case of early postpartum abdominal pain due to haemorrhagic deciduosis peritonei. J Obstet Gynaecol Br Commonw 76:746–749
Hwang JH, Song SH, Kim KA, Shin BK, Lee JK, Lee NW, Lee KW (2010) Primary serous papillary carcinoma of the peritoneum mimicking pelvic actinomycosis: a case report and brief literature review. Eur J Gynaecol Oncol 31:214–216
Iavazzo C, Vorgias G, Katsoulis M, Kalinoglou N, Dertimas V, Aktivos T (2008) Primary peritoneal serous papillary carcinoma: clinical and laboratory characteristics. Arch Gynecol Obstet 278:53–56
Ichimura T, Ishiko O, Nishimura S, Kojima T, Shimura K (2001) Primary peritoneal clear cell carcinoma: excellent results from paclitaxel and carboplatin combination chemotherapy. Oncol Rep 8:1243–1245
Iwasa Y, Minamiguchi S, Konishi I, Onodera H, Zhou J, Yamabe H (1996) Sclerosing peritonitis associated with luteinized thecoma of the ovary. Pathol Int 46:510–514
Jacquemin G, Laloux P (2005) Pseudomyxoma peritonei: review on a cluster of peritoneal mucinous diseases. Acta Chir Belg 105:127–133
Jaworski RC, Boadle R, Greg J, Cocks P (2001) Peritoneal "melanosis" associated with a ruptured ovarian dermoid cyst: report of a case with electron-probe energy dispersive X-ray analysis. Int J Gynecol Pathol 20:386–389
Jhuang JY, Hsieh MS (2012) Pseudomyxoma peritonei (mucinous carcinoma peritonei) preceded by intraductal papillary neoplasm of the bile duct. Hum Pathol 43:1148–1152
Jung YC, Chen CJ, Tzeng CC (1996) Melanosis peritonei associated with enteric duplication cyst. A case report. Am J Surg Pathol 20:181–186
Kagiya A, Fukushi A, Tachizaki T, Saito Y, Iwazaki K (1990) A case of melanosis ovarii et peritonei (in Japanese). Nihon Sanka Fujinka Gakkai Zasshi 42:1571–1574
Kaira K, Takise A, Endou K, Yanagitani N, Sunaga N, Mori M (2006) A case of primary peritoneal serous papillary carcinoma initially presented by massive bilateral pleural effusions. Eur J Gynaecol Oncol 27:197–199
Kanis M, Kesterson JP, Shroff S, Lele S, Mhawech-Fauceglia P (2011) Malignant mixed Müllerian tumor of primary peritoneal origin. Ann Diagn Pathol 15:273–277
Kannerstein M, Churg J, McCaughey WT, Hill DP (1977) Papillary tumors of the peritoneum in women. Mesothelioma or papillary carcinoma. Am J Obstet Gynecol 127:306–314
Kanngurn S, Somran J, Art-Ong C, Lamlertthon W, Porncharoenpong S (2005) Primary peritoneal adenosarcoma with stromal overgrowth and fetal type cartilage: a case report and literature review. J Med Assoc Thai 88:849–854
Kaplan EJ, Caputo TA, Shen PU, Sassoon RI, Soslow RA (1998) Familial papillary serous carcinoma of the cervix, peritoneum, and ovary: a report of the first case. Gynecol Oncol 70:289–294
Kapoor S, Naik S, Sharma S, Varshney S (2007) Pseudomyxoma peritonei due to a ruptured mucinous cystadenoma of the spleen. Eur Surg 39:314–316
Karseladze AI, Kulinitch SI (1994) Peritoneal strumosis. Pathol Res Pract 190:1082–1085
Kato N, Zhe J, Endoh Y, Motoyama T (2000) Extrauterine Müllerian adenosarcoma of the peritoneum with an extensive rhabdomyosarcomatous element and a marked myxoid change. Pathol Int 50:347–351
Kerner H, Lichtig C, Beck D (1989) Extrauterine müllerian adenosarcoma of the peritoneal mesothelium: a clinicopathologic and electron microscopic study. Obstet Gynecol 73:510–513
Khan J, McClennan BL, Qureshi S, Martell M, Iyer A, Bokhari SJ (2005) Meigs syndrome and gliomatosis peritonei: a case report and review of the literature. Gynecol Oncol 98:313–317
Khan KN, Fujishita A, Kitajima M, Hiraki K, Nakashima M, Masuzaki H (2014) Occult microscopic endometriosis: undetectable by laparoscopy in normal peritoneum. Hum Reprod 29:462–472

Kim KR, Scully RE (1990) Peritoneal keratin granulomas with carcinomas of endometrium and ovary and atypical polypoid adenomyoma of endometrium. A clinicopathological analysis of 22 cases. Am J Surg Pathol 14:925–932

Kim NR, Suh YL, Song SY, Ahn G (2002) Peritoneal melanosis combined with serous cystadenoma of the ovary: a case report and literature review. Pathol Int 52:724–729

Kim D, Cho HC, Park JW, Lee WA, Kim YM, Chung PS, Park SG, Ahn WS, Han SJ et al (2009) Struma ovarii and peritoneal strumosis with thyrotoxicosis. Thyroid 19:305–308

Kim SS, Nam JH, Kim SM, Choi YD, Lee JH (2010) Peritoneal melanosis associated with mucinous cystadenoma of the ovary and adenocarcinoma of the colon. Int J Gynecol Pathol 29:113–116

Kinra P, Sen A, Sharma JC (2006) Ectopic decidual reaction: a case report. Med J Armed Forces India 62:280–281

Kitamura H, Ikeda K, Honda T, Ogino T, Nakase H, Chiba T (2006) Diffuse hepatoid adenocarcinoma in the peritoneal cavity. Intern Med 45:1087–1091

Knapp H (1868) Die intraoculären Geschwülste. Nach eigenen klinischen Beobachtungen und anatomischen Untersuchungen. Müllersche Hofbuchhandlung, Carlsruhe

Koutselini HA, Lazaris AC, Thomopoulou G, Papayannopoulou A, Kairi-Vasilatou E (2001) Papillary serous carcinoma of the peritoneum: case study and review of the literature on the differential diagnosis of malignant peritoneal tumors. Adv Clin Path 5:99–104

Kurokawa R, Kim P, Kawamoto T, Matsuda H, Hayashi S, Yamazaki S, Hatamochi A et al (2013) Intramedullary and retroperitoneal melanocytic tumor associated with congenital blue nevus and nevus flammeus: an uncommon combination of neurocutaneous melanosis and phacomatosis pigmentovascularis – case report. Neurol Med Chir (Tokyo) 53:730–734

Kurrein F, Fothergill RJ (1961) Oleo-keratin granuloma in peritoneum: a rare complication of ovarian dermoid. J Obstet Gynaecol Br Commonw 68:124–127

Kushwaha JK, Sonkar AA, Verma AK, Pandey SK (2012) Primary disseminated extrahepatic abdominal hydatid cyst: a rare disease. BMJ Case Rep pii: bcr0220125808

Kwan D, Pang LS (1964) Deciduosis peritonei. J Obstet Gynaecol Br Commonw 71:804–806

Kwan MY, Kalle W, Lau GT, Chan JK (2004) Is gliomatosis peritonei derived from the associated ovarian teratoma? Hum Pathol 35:685–688

Lang H, Jähne J, Flemming P, Meyer HJ, Pichlmayr R (1995) Pseudomyxoma peritonei of appendiceal origin – a report of seven cases and a review of published reports. Eur J Surg 161:355–360

Lauchalan SC (1972) The secondary Müllerian system. Obstet Gynecol Surv 27:133–146

Lee D, Pontifex AH (1975) Melanosis peritonei. Am J Obstet Gynecol 122:526–527

Lee KR, Verma U, Belinson J (1991) Primary clear cell carcinoma of the peritoneum. Gynecol Oncol 41:259–262

Lee EY, Heiken JP, Huettner PC (2003) Late recurrence of malignant melanoma presenting as peritoneal "carcinomatosis". Abdom Imaging 28:284–286

Lee JK, Song SH, Kim I, Lee KH, Kim BG, Kim JW, Kim YT, Park SY, Cha MS, Kang SB (2008) Retrospective multicenter study of a clinicopathologic analysis of pseudomyxoma peritonei associated with ovarian tumors (KGOG 3005). Int J Gynecol Cancer 18:916–920

Lee S, Illei PB, Han JS, Epstein JI (2014) Florid mesothelial hyperplasia of the tunica vaginalis mimicking malignant mesothelioma: a clinicopathologic study of 12 cases. Am J Surg Pathol 38:54–59

Lejeune JP, Sion S, Verbeck P, Combelles G, Dhellemmes P, Torrealba JG (1984) Peritoneal csf pseudocysts. Rare complication of ventriculoperitoneal shunts (in French). Neurochirurgie 30:235–239

Lele SB, Piver MS, Matharu J, Tsukada Y (1988) Peritoneal papillary carcinoma. Gynecol Oncol 31:315–320

Leshin B, Prichard EH, White WL (1992) Dermal granulomatous inflammation to cornified cells. Significance near cutaneous squamous cell carcinoma. Arch Dermatol 128:649–652

Levavi H, Sabah G, Heifetz M, Feinmesser M (2009) Sclerosing peritonitis associated with bilateral luteinized thecoma, linked to anticonvulsant therapy. Eur J Gynaecol Oncol 30:695–700

Lim CS, Thompson JF, McKenzie PR, McCarthy SW, Scolyer RA (2012) Peritoneal melanosis associated with metastatic melanoma involving the omentum. Pathology 44:255–257

Lissandrin R, Agliata S, Brunetti E (2013) Secondary peritoneal echinococcosis causing massive bilateral hydronephrosis and renal failure. Int J Infect Dis 17: e141–e142

Liu YL, Nie ZY, Lu LJ, Hui YZ (2007) Peritoneal "melanosis": report of a case (in Chinese). Zhonghua Bing Li Xue Za Zhi 36:572–573

Liu Q, Lin JX, Shi QL, Wu B, Ma HH, Sun GQ (2011) Primary peritoneal serous papillary carcinoma: a clinical and pathological study. Pathol Oncol Res 17:713–719

Lovell MA, Ross GW, Cooper PH (1989) Gliomatosis peritonei associated with a ventriculoperitoneal shunt. Am J Clin Pathol 91:485–487

Lu X, Zhang C, Liu F, Sung CJ, Steinhoff MM, Lawrence WD (2008) Primary peritoneal anaplastic giant cell carcinoma: case report of an unusual and highly malignant müllerian neoplasm. Arch Pathol Lab Med 132:109–112

Lv Y, Li P, Zheng J, Wang L, Yun J, Huang G, Yan Q, Li Z, Luo P, Li S, Harn L, Yi J et al (2012) Nodular histiocytic aggregates in the greater omentum of patients with ovarian cancer. Int J Surg Pathol 20:178–184

Magro F, Pereira C, Carneiro F, Lopes JM, Teixeira A, Sarmento C, Lima J, Saraiva A et al (2005) Colon stenosis in a patient with ulcerative colitis as a manifestation of mixed müllerian tumor of the peritoneum. Scand J Gastroenterol 40:1251–1254

Mai KT, Burns BF (1999) Development of dysplastic mucinous epithelium from endometriosis of the appendix. Histopathology 35:368–372

Malpica A, Deavers MT, Shahab I (2002) Gross deciduosis peritonei obstructing labor: a case report and review of the literature. Int J Gynecol Pathol 21:273–275

McCluggage WG (2010) Mullerian adenosarcoma of the female genital tract. Adv Anat Pathol 17:122–129

McDermott MB, Glasner SD, Nielsen PL, Dehner LP (1996) Soft tissue gliomatosis. Morphologic unity and histogenetic diversity. Am J Surg Pathol 20: 148–155

Mehra K, Mehrad M, Ning G, Drapkin R, McKeon FD, Xian W, Crum CP (2011) STICS, SCOUTs and p53 signatures; a new language for pelvic serous carcinogenesis. Front Biosci (Elite Ed) 3:625–634

Mellembakken JR, Engh V, Tanbo T, Czernobilsky B, Edelstein E, Lunde O, Roth LM (2010) Mitotically active cellular luteinized thecoma of the ovary and luteinized thecomatosis associated with sclerosing peritonitis: case studies, comparison, and a review of the literature. Pathol Res Pract 206:744–748

Michal M (1997) Benign epithelial structures on the surface of appendices. Pathology 29:267–269

Mira JL, Fenoglio-Preiser CM, Husseinzadeh N (1995) Malignant mixed müllerian tumor of the extraovarian secondary Müllerian system. Report of two cases and review of the English literature. Arch Pathol Lab Med 119:1044–1049

Morita H, Aoki J, Taketomi A, Sato N, Endo K (2004) Serous surface papillary carcinoma of the peritoneum: clinical, radiologic, and pathologic findings in 11 patients. AJR Am J Roentgenol 183:923–928

Mourra N, de Chaisemartin C, Goubin-Versini I, Parc R, Flejou JF (2005) Malignant deciduoid mesothelioma: a diagnostic challenge. Arch Pathol Lab Med 129:403–406

Muallem MZ, Harter P, Heitz F, El-Balat A, Fissler-Eckhoff A, Menzel C, du Bois A (2012) Struma ovarii recurrence with peritoneal strumosis: a case report. J Solid Tumor 2:46–50

Muezzinoglu B, Corak S, Yucesoy I (2011) Primary peritoneal clear cell adenocarcinoma associated with endometriosis. Appl Immunohistochem Mol Morphol 19:384–385

Müller AM, Söndgen D, Strunz R, Muller KM (2002) Gliomatosis peritonei: a report of two cases and review of the literature. Eur J Obstet Gynecol Reprod Biol 100:213–222

Nada R, Vaiphei K, Rao KL (2000) Enteric duplication cyst associated with melanosis peritonei. Indian J Gastroenterol 19:140–141

Nakao M, Oguri T, Maeno K, Ota C, Takakuwa O, Iwashima Y, Miyazaki M, Kutsuna T et al (2009) Endobronchial metastasis from primary serous carcinoma of the peritoneum. Intern Med 48:1165–1168

Navarrete Reyna A, Stewart CV, Collis LC (1969) Myxoglobulosis. Tex Med 65:52–55

Navarro P, Lopez L, Gonzalez M, Sangros M, Lievano P, Alvarez S, Abos D (2012) Peritoneal strumosis: an extension study with (99m)TC-pertechnetate (in Spanish). Rev Esp Med Nucl Imagen Mol 31:97–100

Neuhäuser H (1906) Ueber die teratoiden Geschwülste des Eierstocks. Arch Gynäk 79:696–719

Nikolic O, Djurdjevic S, Stojanovic S, Basta Nikolic M, Mocko Kacanski M, Secen S (2012) Pseudomyxoma peritonei – case report. Eur J Gynaecol Oncol 33:227–229

Nishimura M, Wakabayashi M, Hashimoto T, Shibata J, Ueyama H, Ebina M, Fujiyama Y et al (2000) Papillary serous carcinoma of the peritoneum: analysis of clonality of peritoneal tumors. J Gastroenterol 35:540–547

Nonaka D, Kusamura S, Baratti D, Casali P, Younan R, Deraco M (2006) CDX-2 expression in pseudomyxoma peritonei: a clinicopathological study of 42 cases. Histopathology 49:381–387

O'Connell JT, Tomlinson JS, Roberts AA, McGonigle KF, Barsky SH (2002) Pseudomyxoma peritonei is a disease of MUC2-expressing goblet cells. Am J Pathol 161:551–564

Ohno S, Kuwano H, Mori M, Sakata H, Mori A, Shinohara K (1989) Malignant mixed mesodermal tumour of the peritoneum with a complete response to cyclophosphamide. Eur J Surg Oncol 15:287–291

Okamoto D, Ishigami K, Yoshimitsu K, Irie H, Tajima T, Asayama Y, Hirakawa M, Ushijima Y et al (2007) Gliomatosis peritonei associated with immature ovarian teratoma: a mimicker of peritoneal dissemination of malignant diseases. J Comput Assist Tomogr 31:317–319

Onida GA, Bosincu L, Dessole S, Nicolae A, Preda O, Cossu-Rocca P, Aneiros-Fernandez J et al (2010) Sertoli cell tumor with benign peritoneal implants associated with gonadoblastoma. Int J Gynecol Pathol 29:423–426

Oparka R, McCluggae WG, Herrington CS (2011) Peritoneal mesothelial hyperplasia associated with gynaecological disease: a potential diagnostic pitfall that is commonly associated with endometriosis. J Clin Pathol 64:313–318

Ordonez NG (2006) The diagnostic utility of immunohistochemistry and electron microscopy in distinguishing between peritoneal mesotheliomas and serous carcinomas: a comparative study. Mod Pathol 19:34–48

Pai RK, Longacre TA (2005) Appendiceal mucinous tumors and pseudomyxoma peritonei: histologic features, diagnostic problems, and proposed classification. Adv Anat Pathol 12:291–311

Patrelli TS, Silini EM, Gizzo S, Berretta R, Franchi L, Thai E, Lukanovic A, Nardelli GB et al (2011)

Extragenital Müllerian adenosarcoma with pouch of Douglas location. BMC Cancer 11:171

Pestieau SR, Esquivel J, Sugarbaker PH (2000) Pleural extension of mucinous tumor in patients with pseudomyxoma peritonei syndrome. Ann Surg Oncol 7:199–203

Phupong V, Sueblinvong T, Triratanachat S (2004) Ovarian teratoma with diffuse peritoneal reactions mimicking advanced ovarian malignancy. Arch Gynecol Obstet 270:189–191

Piccinni DJ, Spitale LS, Cabalier LR, Dionisio de Cabalier ME (2002) Decidua in the peritoneal surface mimicking metastatic nodules. Findings during cesarean section (in Spanish). Rev Fac Cien Med Univ Nac Cordoba 59:113–116

Poggi SH, Bristow RE, Nieberg RK, Berek JS (1998) Psammocarcinoma with an aggressive course. Obstet Gynecol 92:659–661

Puvaneswary M, Proietto T (2004) Primary papillary serous carcinoma of the peritoneum: four cases and review of computed tomography findings. Australas Radiol 48:421–425

Qi ZH, Cai S, Li JC, Lin K, Zhang Y, Xiao MS, Su N (2015) Ultrasonographic features of pseudomyxoma peritonei and their comparison with computed tomographic findings (in Chinese). Zhongguo Yi Xue Ke Xue Yuan Xue Bao 37:424–429

Raju U, Fine G, Greenawald KA, Ohorodnik JM (1989) Primary papillary serous neoplasia of the peritoneum: a clinicopathologic and ultrastructural study of eight cases. Hum Pathol 20:426–436

Reddy CR, Rajakumari K, Jayasimha P (1975) Keratin granulomas in squamous cell carcinomas treated by irradiation. Indian J Cancer 12:327–333

Reichelt U, Keichel S, Barcena de Arellano ML, Chiantera V, Schneider A, Mechnser S (2012) High lymph vessel density and expression of lymphatic growth factors in peritoneal endometriosis. Reprod Sci 19:876–882

Robboy SJ, Scully RE (1970) Ovarian teratoma with glial implants on the peritoneum: an analysis of 12 cases. Hum Pathol 1:643–653

Ronnett BM, Kurman RJ, Zahn CM, Shmookler BM, Jablonski KA, Kass ME, Sugarbaker PH (1995a) Pseudomyxoma peritonei in women: a clinicopathologic analysis of 30 cases with emphasis on site of origin, prognosis, and relationship to ovarian mucinous tumors of low malignant potential. Hum Pathol 26:509–524

Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM (1995b) Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol 19: 1390–1408

Ronnett BM, Shmookler BM, Sugarbaker PH, Kurman RJ (1997) Pseudomyxoma peritonei: new concepts in diagnosis, origin, nomenclature, and relationship to mucinous borderline (low malignant potential) tumors of the ovary. Anat Pathol 2:197–226

Ronnett BM, Yan H, Kurman RJ, Shmookler BM, Wu L, Sugarbaker PH (2001) Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. Cancer 92:85–91

Rosai J, Dehner LP (1975) Nodular mesothelial hyperplasia in hernia sacs: a benign reactive condition simulating a neoplastic process. Cancer 35:165–175

Rosen HR, Rosen AC, Preiser J, Stierer M, Klein M, Hanak H (1992) Non-ovarian peritoneal papillary serous carcinoma with high CA125 levels. Arch Gynecol Obstet 251:199–202

Roth LM, Karseladze AI (2008) Highly differentiated follicular carcinoma arising struma ovarii: a report of 3 cases, a review of the literature, and a reassessment of so-called peritoneal strumosis. Int J Gynecol Pathol 27:213–222

Safall H, Azar HA (1966) Keratin granulomas in irradiated squamous cell carcinoma of various sites. Cancer Res 26:500–508

Sakakibara Y, Endo S, Yoshida Y, Tanaka Y, Hashimoto T, Ohara T (2011) A case of serous surface papillary carcinoma of the peritoneum metastatic to the brain (in Japanese). No Shinkei Geka 39:607–610

Santos LD, Fernando SS, Yong JL, Killingsworth MC, Wu XJ, Kennerson AR (1999) Placental site nodules and plaques: a clinicopathological and immunohistochemical study of 25 cases with ultrastructural findings. Pathology 31:328–336

Saran RK, Majumdar K, Kaur S, Mishra PK, Gondal R (2008) Organizing mucinous ascites masquerading as pseudomyxoma peritonei: a process possibly caused by metaplasia but not neoplasia. J Surg Educ 65:221–224

Schatz JE, Colgan TJ (1991) Squamous metaplasia of the peritoneum. Arch Pathol Lab Med 115:397–398

Selgas R, Fernandez de Castro M, Viguer JM, Burgos E, Bajo MA, Carcamo C, Vara F (1995) Transformed mesothelial cells in patients on CAPD for medium-to long-term periods. Perit Dial Int 15:305–311

Semino-Mora C, Liu H, McAvoy T, Nieroda C, Studeman K, Sardi A, Dubois A (2008) Pseudomyxoma peritonei: is disease progression related to microbial agents? A study of bacteria, MUC2 and MUC5AC expression in disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. Ann Surg Oncol 15:1414–1423

Serafimidis C, Katsarolis I, Vernadakis S, Rallis G, Giannopoulos G, Legakis N, Peros G (2006) Idiopathic sclerosing encapsulating peritonitis (or abdominal cocoon). BMC Surg 6:3

Serrano Lira F, Gil Madre J, Madruga Galan F, Pérez Cabezas M, Sanchez Diaz E (1995) Peritoneal pseudomyxoma and liver metastasis (in Spanish). Rev Esp Enferm Dig 87:684–685

Shah IA, Jayram L, Gani OS, Fox IS, Stanley TM (1998) Papillary serous carcinoma of the peritoneum in a man: a case report. Cancer 82:860–866

Shefren G, Collin J, Soriero O (1991) Gliomatosis peritonei with malignant transformation: a case report and review of the literature. Am J Obstet Gynecol 164:1617–1621

Shetty S, Natarajan B, Thomas P, Govindarajan V, Sharma P, Loggie B (2013) Proposed classification of pseudomyxoma peritonei: influence of signet ring cells on survival. Am Surg 79:1171–1176

Shi M, Fraire AE, Chu P, Cornejo K, Woda BA, Dresser K, Rock KL, Jiang Z (2011) Oncofetal protein IMP3, a new diagnostic biomarker to distinguish malignant mesothelioma from reactive mesothelial proliferation. Am J Surg Pathol 35:878–882

Shmueli E, Leider-Trejo L, Schwartz I, Aderka D, Inbar M (2001) Primary papillary serous carcinoma of the peritoneum in a man. Ann Oncol 12:563–567

Shukla S, Pujani M, Singh SK (2008) Ectopic decidual reaction mimicking peritoneal tubercles: a report of three cases. Indian J Pathol Microbiol 51:519–520

Sibio S, Borrini F, Sammartino P, Accarpio F, Biacchi D, Caprio G, Iafrate F, Baccheschi AM (2010) Predominant Brenner combined with struma ovarii containing a papillary microcarcinoma associated with benign peritoneal strumosis: report of a case and histologic features. Endocr Pathol 21:199–203

Skates S, Troiano R, Knapp RC (2003) Longitudinal CA125 detection of sporadic papillary serous carcinoma of the peritoneum. Int J Gynecol Cancer 13:693–696

Smeenk RM, Bruin SC, van Velthuysen ML, Verwaal VJ (2008) Pseudomyxoma peritonei. Curr Probl Surg 45:527–575

Soslow RA, Ali A, Oliva E (2008) Mullerian adenosarcomas: an immunophenotypic analysis of 35 cases. Am J Surg Pathol 32:1013–1021

Staats PN, McCluggage WG, Clement PB, Young RH (2008) Luteinized thecomas (thecomatosis) of the type typically associated with sclerosing peritonitis: a clinical, histopathologic, and immunohistochemical analysis of 27 cases. Am J Surg Pathol 32:1273–1290

Stafford-Johnson DB, Bree RL, Francis IR, Korobkin M (1998) CT appearance of primary papillary serous carcinoma of the peritoneum. AJR Am J Roentgenol 171:687–689

Stemmer SM, Shurshalina A (2014) Colonoscopic tattoo dye spillage mimics endometriosis on laparoscopy. J Minim Invasive Gynecol 21:704–707

Stenram U (1997) Sclerosing peritonitis in a case of benign cystic ovarian teratoma. A case report. APMIS 105:414–416

Stewart CJ (2013) Deciduoid mesothelial hyperplasia of the pelvic peritoneum. Histopathology 63:598–600

Sugarbaker PH, Bijelic L (2008) The porta hepatis as a site of recurrence of mucinous appendiceal neoplasms treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. Tumori 94:694–700

Suh JH, Kim YH, Chang ED (2008) Primary papillary serous carcinoma of the peritoneum diagnosed by video-assisted thoracoscopic surgery: report of a case. Surg Today 38:743–746

Swerdlow M (1959) Mesothelioma of the pelvic peritoneum resembling papillary cystadenocarcinoma of the ovary. Am J Obstet Gynecol 77:197–200

Takano M, Yoshikawa T, Kato M, Aida S, Goto T, Furuya K, Kikuchi Y (2009) Primary clear cell carcinoma of the peritoneum: report of two cases and a review of the literature. Eur J Gynaecol Oncol 30:575–578

Tang KW, Lamaro V, Jaworksi R (2009) Peritoneal histiocytic reaction associated with oxidized regenerated cellulose, a form of mucicarminophilic histiocytosis. Pathology 41:598–600

Tanimura A, Imachi M (1989) Pseudomyxoma peritonei with myxoglobulosis – a case report and the pathogenesis of the myxoglobules. Gan No Rinsho 35:1795–1799

Taus P, Petru E, Gücer F, Pickel H, Lahousen M (1997) Primary serous papillary carcinoma of the peritoneum: a report of 18 patients. Eur J Gynaecol Oncol 18:171–172

Terada T, Kawaguchi M (2005) Primary clear cell adenocarcinoma of the peritoneum. Tohoku J Exp Med 206:271–275

Thylan S (1996) Primary extrauterine mullerian adenosarcoma of the peritoneum. Gynecol Oncol 60:333

Torikai M, Tahara H, Kaji T, Shimono R, Yano T, Yoshioka T, Kawakami K, Takamatsu H (2007) Immature teratoma of the gallbladder associated with gliomatosis peritonei, a case report. J Pediatr Surg 42:E25–E27

Touloumis Z, Galyfos G, Kavouras N, Menis M, Lavant L (2013) Aggressive pseudomyxoma peritonei: a case report with an unusual clinical presentation. Case Rep Oncol Med 2013:926963

Trauner M, Klimpfinger M, Stauber RE, Schreiber F, Stöger H, Kreis GJ (1995) Laparoscopic diagnosis of peritoneal serous papillary carcinoma. Endoscopy 27:337–341

Tripathy K, Misra A, Sethi S, Biswal P, Mohanty P, Gouda K, Dash A, Mahapatra S (2010) Peritoneal keratin granuloma masquerading as disseminated carcinoma. Case Rep Gastroenterol 4:31–34

Truong LD, Maccato ML, Awalt H, Cagle PT, Schwartz MR, Kaplan AL (1990) Serous surface carcinoma of the peritoneum: a clinicopathologic study of 22 cases. Hum Pathol 21:99–110

Tutticci N, Cameron D, Croese J, Roche E (2010) Peritoneal deposits with carbon pigmentation associated with endoscopic submucosal tattooing of a rectal cancer. Endoscopy 42(Suppl 2):E136

Uehara K, Yasuda M, Ichimura T, Yamaguchi H, Nagata K, Kayano H, Sasaki A, Murata S et al (2011) Peritoneal keratin granuloma associated with endometrioid adenocarcinoma of the uterine corpus. Diagn Pathol 6:104

Uhle AO, Wilkinson WR (1954) Myxoglobulosis of the appendix. J Int Coll Surg 21:79–83

Vallerie AM, Lerner JP, Wright JD, Baxi LV (2009) Peritoneal inclusion cysts: a review. Obstet Gynecol Surv 64:321–334

Van der Horst C, Evans AJ (2008) Peritoneal keratin granulomas complicating endometrial carcinoma: a report of two cases and review of the literature. Int J Gynecol Cancer 18:549–553

Veldhuis WB, Akin O, Goldman D, Mironov S, Mironov O, Soslow RA, Barakat RR, Hricak H (2013) Peritoneal inclusion cysts: clinical characteristics and imaging features. Eur Radiol 23:1167–1174

Verschraegen CF, Vasuratna A, Edwards C, Freedman R, Kudelka AP, Tornos C, Kavanagh JJ (1998) Clinicopathologic analysis of Mullerian adenosarcoma: the M.D. Anderson Cancer Center experience. Oncol Rep 5:939–944

Visvalingam S, Jaworski R, Blumenthal N, Chan F (2001) Primary peritoneal mesodermal adenosarcoma: report of a case and review of the literature. Gynecol Oncol 81:500–505

Wang H, Wang X, Ju Y, Wang J, Zhang X, Cheng Y, Sun J, Hu Y (2014) Clinicopathological features and prognosis of pseudomyxoma peritonei. Exp Ther Med 7:185–190

Weir MM, Bell DA, Young RH (1998) Grade 1 peritoneal serous carcinomas: a report of 14 cases and comparison with 7 peritoneal serous psammocarcinomas and 19 peritoneal serous borderline tumors. Am J Surg Pathol 22:849–862

Werness BA (1996) Luteinized thecoma with sclerosing peritonitis. Arch Pathol Lab Med 120:303–306

Westra WH, Forastiere AA, Eisele DW, Lee DJ (1998) Squamous cell granulomas of the neck: histologic regression of metastatic squamous cell carcinoma following chemotherapy and/or radiotherapy. Head Neck 20:515–521

Whitcomb BP, Kost ER, Hines JF, Zahn CM, Hall KL (1999) Primary peritoneal psammocarcinoma: a case presenting with an upper abdominal mass and elevated CA-125. Gynecol Oncol 73:331–334

White J, Chan YF (1994) Lipofuscinosis peritonei associated with pregnancy-related ectopic decidua. Histopathology 25:83–85

Wirnsberger GH, Ganser K, Domej W, Sauseng G, Moore D, Moczygemba M, Krejs GJ (1992) Sclerosing encapsulating peritonitis: differential diagnosis to peritoneal encapsulation and abdominal cocoon – a case report. Z Gastroenterol 30:534–537

Wotherspoon AC, Benjamin E, Boutwood AA (1989) Peritoneal keratin granulomas from transtubal spread of endometrial carcinoma with squamous metaplasia (adenoacanthoma). Case report. Br J Obstet Gynaecol 96:236–240

Wu TI, Chang TC, Hsueh S, Lai CH (2006) Ovarian endometroid carcinoma with diffuse pigmented peritoneal keratin granulomas: a case report and review of the literature. Int J Gynecol Cancer 16:426–429

Yan H, Pestieau SR, Shmookler BM, Sugarbaker PH (2001) Histopathologic analysis in 46 patients with pseudomyxoma peritonei syndrome: failure versus success with a second-look operation. Mod Pathol 14:164–171

Yan TD, Sugarbaker PH, Brun EA (2006) Pseudomyxoma peritonei from mucinous adenocarcinoma of the urachus. J Clin Oncol 24:4944–4946

Young RH (2004) Pseudomyxoma peritonei and selected other aspects of the spread of appendiceal neoplasms. Semin Diagn Pathol 21:134–150

Youssef H, Moran BJ (2011) On or in the liver? Two cases with diffuse pseudomyxoma peritonei and synchronous hepatic pathology. Tech Coloproctol 15:85–87

Zappa L, Sugarbaker PH (2010) Mesenteric cyst: report of a case resulting in pseudomyxoma peritonei. Tumori 96:332–335

Zappa L, Godwin TA, Sugarbaker PH (2009) Tailgut cyst, an unusual cause of pseudomyxoma peritonei. Tumori 95:514–517

Zaytsev P, Taxy JB (1987) Pregnancy-associated ectopic decidua. Am J Surg Pathol 11:526–530

Zhou J, Iwasa Y, Konishi I, Kann N, Kannagi R, Kobashi Y, Kim YC, Yamabe H (1995) Papillary serous carcinoma of the peritoneum in women. A clinicopathologic and immunohistochemical study. Cancer 76:429–436

Zissin R, Hertz M, Shapiro-Feinberg M, Bernheim J, Altaras M, Fishman A (2001) Primary serous papillary carcinoma of the peritoneum: CT findings. Clin Radiol 56:740–745

Part XXXI

General Pathology of Hepatobiliary Tumors: Etiology and Pathogenesis of Hepatocellular Carcinoma

Etiology and Pathogenesis of Hepatocellular Carcinoma: Inflammatory and Toxic Causes

164

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_164

Abstract

The main risk factors for the development of hepatocellular carcinoma (HCC) include chronic fibrosing liver disease and cirrhosis. Hepatic fibrosis and cirrhosis are most commonly caused by hepatitis virus infection and numerous nonviral factors. Worldwide, hepatitis B virus and hepatitis C virus infections play a central role as etiologic factors for liver cirrhosis and associated HCC, but in addition to their pro-cirrhosis effect, these viruses can also act as oncogenic agents. A second group of important hepatic inflammatory conditions that increase risk for HCC are various forms of nonalcoholic steatohepatitis and associated metabolic disorders. Hepatotoxic factors that increase HCC risk include alcohol (alcoholic liver disease, in part associated with fibrosing inflammation), aflatoxin, iron (mainly in hemochromatosis), pesticides, and a large spectrum of other toxic molecules. Certain drugs, in particular sex steroids and their derivates, can augment liver cancer risk. Apart from the various types of hemochromatosis, other inborn errors of metabolism bear an increased HCC risk, including Wilson's disease, glycogenoses, and tyrosinemia.

Introduction

The main risk factors for the development of HCC include chronic fibrosing liver disease and cirrhosis, most commonly caused by hepatitis viruses and a long list of nonviral factors involved in human hepatic carcinogenesis (reviews: Jaskiewicz et al. 1991; Okuda 1995; Kew 2000; Anzola 2004; Abdel-Hamid 2009; Dragani 2010; Tsai and Chung 2010; Hamed and Ali 2013; Njei et al. 2015; Table 1). Although more than 80 % of HCC develop in cirrhotic livers, there is a substantial fraction of tumors that are detected in non-cirrhotic livers, with a high variable background of underlying liver changes (Brancatelli et al. 2002).

Table 1 Nonviral factors involved in hepatocellular carcinoma

Alcohol toxicity (alcoholic liver disease; ALD)
Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH)
Chronic fibroinflammatory liver diseases other than viral
Toxic agents other than alcohol
Aflatoxin
Iron
Betel ingredients
Pesticides
N-nitroso compounds
Smoking
Drugs
Androgenic steroids
Oral contraceptives
Inborn errors of metabolism
Hereditary hemochromatosis
Porphyrias
Wilson's disease
Glycogenoses
Tyrosinemia
Others
Parasitosis of the liver
Radioactive agents
Thorotrast
Genetic predisposition (familial HCC)

Hepatitis B Virus (HBV) Infection: A Major Cause of Hepatocellular Carcinoma

Introduction

The hepatitis B and C viruses belong to the most important etiologies for HCC worldwide. In regions with high-level endemicity of HBV infection, HBV as a cause of HCC exceeded HCV as a cause of HCC by a factor of about four. HCCs related to HBV or HCV differ epidemiologically. In a large nationwide Korean cohort ($N = 4{,}630$), the annual incidence rate of HBV-related HCC peaked at the 50–59 age group, whereas the annual incidence rate of HCV-related HCC increased gradually to the =>70 age group. In HBV-related cancers, large tumors and portal vein invasion at timepoint of diagnosis were more frequent, whereas tumor multiplicity was more

common in the HCV group. In addition, HBV-related stage IV tumors were associated with poorer survival than HCV-related stage IV cancers (Sinn et al. 2014).

Hepatitis B Virus (HBV) and HBV-Induced Infectious Disease

Hepatitis B virus (HBV) is a very common member of the *Hepadnavirus* family. The viral particle has been described in detail, as have its protein components which are instrumental in the virus's interaction with host cells and are important antigens for immune reactions raised by the host. The HBV genome is a partially double-stranded DNA with a sequence of about 3,200 nucleotides and a minus strand and a plus strand. The minus strand harbors four open reading frames, encoding pre-S/S envelope proteins, core (pre-C/C) proteins, and X protein.

HBV infection is markedly influenced and regulated by several human genes which affect viral cell binding and entry, synthesis and release of virions, and induction of a host response (review: Zeng 2014). The HBV virion seems to interact with a putative hepatocyte receptor via a myristoylated N-terminal preS1-domain of the HBV large envelope protein/HBV-L (Schieck et al. 2013). Upon binding to host cells, the HBV genome is transferred to the nucleus where it becomes a covalently closed circular DNA, which then serves as a template for transcription of viral DNA through the action of reverse HBV polymerase, to be translated into viral proteins. HBV polymerase is devoid a proofreading ability, and is error prone in its transcribing activity, this being a major reason for the development of HBV genome mutations. HBV exists in the form of several genotypes which have distinct clinical and treatment implications (review: Lin and Kao 2011). There exists a relationship between HBV genotypes and HCC development. HBV genotype C strains with spontaneous YMDD mutations were an independent risk factor for HCC in cirrhotic patients (Yang et al. 2013).

In HBV infection, hepatocytes can show ground-glass changes caused by the cytoplasmic deposition of HBsAg. In comparison with those without HCC, cases with HCC had a significantly higher prevalence of type II ground-glass hepatocytes, with a geographically clustered pattern, and associated with higher grades of hepatic fibrosis. It was suggested that this phenomenon might represent clonal proliferation of hepatocytes with mutated hepatitis B surface antigen (Mathai et al. 2013). Infection of HCC cells can result in the cytoplasmic expression of HBV surface antigen (HBsAg; Wu and Lam 1979). Two patterns of distribution and staining of HBsAg in HCC cells were recognized, i.e., confinement of reactivity to solitary or small groups of positive cells where a large HBsAg-positive body resembling a ground glass inclusion was found and a larger area in HCC where all cells show a diffuse peripheral or perinuclear staining of the cytoplasm (Wu 1979).

HBV Infection and Hepatocellular Carcinoma

HBV infection is one of the most important hepatocarcinogenic factors worldwide (reviews: Tarocchi et al. 2014; Trépo et al. 2014). It is estimated that more than 50 % of HCCs arise in HBV carriers. At least 350 million people worldwide are chronically infected with HBV and are at high risk of HCC. Of all HCCs, 80–90 % develop in cirrhotic livers. As, depending on the viral type, 20–50 % of patients will develop hepatic cirrhosis, cirrhosis is the main liver alteration promoting HCC, which manifests at an annual rate of 1–7 % in HCV-infected patients and 3–8 % in HBV-infected patients (Kew and Popper 1984; Arbuthnot and Kew 2001; Raptis et al. 2003; Lee and Lee 2007; Kew 2010b; Tsai and Chung 2010). HBV induces HCC mainly through two pathways, i.e., induction of inflammation and cirrhosis, a carcinogenic pathway shared with other factors inducing HCC, and via a direct mechanism involving genomic integration and expression of the HBx gene product and other HBV-encoded proteins. HBV also affects

carcinogenic pathways by inducing epigenetic changes through methylation on genes regulating cell proliferation, cell adhesion, and several signaling pathways, including p16INK4A, GSTP1, E-cadherin, RASSF1A, and p21WAF1/CIP1 genes (Rongrui et al. 2014).

Chronic active hepatitis induced by HBV and HCV causes chronic fibrosing hepatopathy ending up in cirrhosis. In the setting of this apparently linear process, hepatocyte regeneration is continuously turned on and results in a probably stepwise emergence of clonally aberrant liver cell populations that start to accumulate transforming mutations due to a complex selection process. This pathway can be histologically followed as a hyperplasia-dysplasia sequence . A crucial step in the hepatocarcinogenic capabilities of HCV is its genomic integration into the host cell genomes. Integration of the HBV genome into the human genome is present in over 80–90 % of HBV-related HCCs and in most instances precedes HCC development. HBV genomic integration is also found in non-tumorous liver in patients with chronic HBV infection. HBV genome integrants have a complex pattern of position in the human genome and were considered to be either random or nonrandom. Integrants prefer fragile sites in the genome or regions which are prone to instability. HBV integration promotes several genetic alterations in the human genome, including deletions, translocations, fusion transcripts, amplifications of genes, and genomic instability. Integration of HBV DNA does not seem to compromise or affect cellular oncogenes or tumor suppressor genes directly, but integrants are often situated close to human repetitive sequences and are capable to transpose to other chromosome regions through reintegration. Generally, integration-induced genomic instability may cause misexpression of oncogenes, tumor suppressors, growth factors, and microRNAs, contributing to cell transformation and carcinogenesis. Frequent targets of HBV genome integration comprise cyclins, PDGFR, calcium signaling gene products, retinoic acid receptor beta, and telomerase. Most HCCs with genomic HBV integration have the integrated HBV X gene and/or truncated pre-S/S genes.

Selected References (Kew et al. 1980; Mori et al. 1980; Beasley et al. 1981; Linsell 1984; Beasley 1988; Chen and Chen 1999; Reeves and DeMatteo 2000; Coleman 2003; Wang et al. 2004; Feitelson and Lee 2007; Lee and Lee 2007; Tsai and Chung 2010; Ng and Wu 2012; Sung et al. 2012; Bai et al. 2013; Bharadwaj et al. 2013; Guerreri et al. 2013; Tarocchi et al. 2014).

Among HBV genome-encoded proteins, the HBV X protein (HBX) plays a central part in the regulation of viral gene expression and replication by transactivating promoters and enhancers that are important for persistent viral infection. The HBX gene often remains functional following integration of HBV DNA into the host cell genome in the course of hepatocarcinogenesis. However, as the HBV DNA is prone to numerous mutations due to the proofreading failures of HBV polymerase, the HBX protein is also subject to mutations which play a role in hepatocarcinogenesis and HCC progression (Xie et al. 2014). The HBX protein is a 154 amino acid residue protein that generally functions as a promiscuous transcriptional activator of polymerase II and III promoters (Henkler and Koshy 1996). HBX and its mutated forms can interfere with numerous cellular processes, including cell cycle induction and progression, apoptotic pathways, signal transduction, transcription regulation, protein degradation, and oxidative stress responses. Part of these HBX-induced deregulations, modified by mutations, plays a role in hepatocarcinogenesis in a complex manner that is only partially understood (reviews: Ali et al. 2014). HBX transactivates numerous cytoplasmic signaling components, including Ras/Raf/MAPK, JNK, PKC, JAK/STAT, PI3K, AP-1, AP-2, Smad, and Wnt, and interferes with cellular calcium signaling (Liu et al. 2011). It causes inactivation of negative growth regulators, inhibition of cell senescence factors, and promotion of telomerase. HBx also acts as an antiapoptotic protein. On the other hand, expression of HBx can induce the expression of the Fas/Fas ligand system. HBX also disrupts a balanced expression of circadian

rhythm genes in HCC. Integration of wild-type and mutated HBV into the host genome markedly compromises genomic stability. Subsequent to integration into host DNA, HBX induces genomic instability mainly via compromising excision repair that is dependent on p53. HBx leads to transcriptional repression of the p53 gene and therefore inactivates several cell pathways that depend in p53, including apoptosis, cell cycle progression, DNA repair, and tumor suppression. The HBx protein modulates the expression of PTEN by inhibiting the function of p53 which promotes PTEN expression via p53-mediated transcription.

Selected References (Su et al. 1998; Murakami 2001; Wu et al. 2001; Chung et al. 2003; Wang et al. 2003; Chan and Oi-Lin Ng 2005; Tanaka et al. 2006; Kew 2011; Ng and Lee 2011; Gong et al. 2013; Motavaf et al. 2013; Xu et al. 2013; Amaddeo et al. 2014; Ji et al. 2014; Tong et al. 2014; Yang et al. 2014; Park 2015).

HBX protein is involved in a distinct feature of HCCs associated with previous or actual hepatitis B virus infection, i.e., ploidy and cell nuclearity. Significantly higher DNA ploidy values with a reduction in the percentage of binucleated hepatocytes were detected in such HCCs (Gramantieri et al. 1996). HBX activates mitogenic Polo-like kinase 1 attenuating DNA damage checkpoint and DNA repair resulting in partial polyploidy (Studaeh et al. 2010).

HBx protein also interacts with distinct sets of microRNAs (Xu et al. 2013). It inhibits tumor suppressor miR-205 through inducing hypermethylation of miR-205 promoter to enhance carcinogenesis (Zhang et al. 2013b). There is also evidence that HBx can cause epigenetic modifications via modulation of methyltransferase transcription (review; Kew 2011). A transactivational function is also exerted by truncated pre-S/S integrated gene products. These proteins can transactivate various host cell genes, such as c-Myc, c-Fos, and Ras (Schluter et al. 1994; Luber et al. 1996), and can upregulate human telomerase. Mutant large pre-S protein can activate endoplasmic reticulum stress-induced oxidative DNA damage and by this promote genomic instability.

Hepatitis C Virus (HCV) Infection

HCV Virus: Its Genotypes, Viral Genome, and Gene Products

Hepatitis C virus (HCV; genus *Hepacivirus* in the family *Flaviviridae*) is a small RNA virus with a genome of about 9.6 kb length. HCV infection is a leading factor in etiology and pathogenesis of chronic liver disease, with about 170–200 million persons infected worldwide, and is a major cause of chronic hepatitis, liver steatosis, and cirrhosis. It has been estimated that HCV infection accounts for 27 % of cirrhosis and 25 % of HCC worldwide (Alter 2007; Rustgi 2007; Banerjee et al. 2010; Jang and Chung 2011; Wang et al. 2012; Thomas 2013; Koike 2014; Lee et al. 2014). The microbiology of HCV is complex, as the virus exists as seven genotypes, 67 subtypes, and numerous so-called pseudo-species (Messina et al. 2015). Distinct genotypes are now recognized to induce characteristic phenotypes of HCV-induced disease. For example, genotype 1 is associated with aggressive disease, increased insulin resistance, and higher risks for cirrhosis and HCC, while genotype 3 is associated with increased risk of steatosis and fibrosis (review: Ripoli and Pazienza 2011). In a meta-analysis, patients infected with HCV genotype 1b had almost double the risk to develop HCC than those infected with other genotypes, mainly in patients with early stage of disease (Raimondi et al. 2009). Recent studies showed that also the HCV genotype 3 is independently associated with a higher HCC incidence in patients with ongoing HCV-induced cirrhosis (Nkontchou et al. 2011). Genotype 5 was neither more nor less hepatocarcinogenic than other HCV genotypes (Kedda et al. 1997). HCV prevalence is highest in Egypt, and China has the largest number of HCV-infected individuals (an estimated 29.8 million; Hajarizadeh et al. 2013). Acute HCV infection is often not detected, due to its generally asymptomatic nature. About 25 % of HCV-infected persons with acute infection

undergo spontaneous clearance, but the majority, i.e., 75 %, progress to chronic HCV infection, which is a major risk factor for liver cirrhosis, and chronic HCV infection is an established risk factor for HCC. The biology of HCV-induced liver disease is also influenced by the fact that, according to recent views, HCV infection must be regarded as a systemic disease rather than a disorder limited to the liver (reviews: Antonelli et al. 2008; Craxi et al. 2008). The estimation of HCV-related risk is complex, because this type of viral infection is associated with other risk factors occurring in HCV-infected patients, including HBV infection, alcoholic liver disease, iron toxicity, and HIV infection (Dimitroulis et al. 2013).

The genome of HCV harbors a long reading frame flanked by untranslated 5′ and 3′ sequences. The positive-strand RNA of the virus encodes a single large polyprotein that is processed by viral and host proteases into at least ten structural and nonstructural proteins. Proteins derived from the NH2-terminal third of the polyprotein provide three structural components of HCV, i.e., core and two envelope glycoproteins, E1 and E2. The core protein is the principal building block of the nucleocapsid, has RNA-binding activity, and exists in several forms with varying molecular weights. The nonstructural protein N2 is involved in polyprotein processing and virus assembly, while five other nonstructural proteins (NS3, NS4A/4B, NS5A/5B) operate in viral RNA replication. NS3 is a serine protease capable of cleaving the polyprotein at four distinct sites and is also an RNA helicase and a component of the RNA replicase complex. Replication of HCV is modulated by several microRNAs (Hou and Bonkovsky 2013; Lee et al. 2014; Li et al. 2014), whereby the most important is the liver-specific microRNA-122 (miR-122). Binding of miR-122 to HCV genomic RNA stabilizes the RNA against nucleolytic degradation in an Argonaute protein-dependent manner, but interaction of miR-122 with HCV RNA also promotes viral RNA translation directed by the internal ribosome entry site located downstream of the miR-122-binding site (Conrad and Niepmann 2014).

Infection Mode of HCV

HCV molecular biology, replication features, and immune responses induced by the virus have been studied in detail and reviewed (Irshad and Dhar 2006; Perrault and Pécheur 2009; Ashfaq et al. 2011; De Giorgi et al. 2013; Kim and Chang 2013). In the liver, hepatocytes are the main reservoir of HCV. HCV enters host cells through a complex mechanism mediated by the viral E2 envelope glycoprotein core structure (Kong et al. 2013). Cell entry requires at least three host cell molecules, i.e., the tetraspanin CD81, scavenger receptor BI (SR-BI), and the tight junction protein claudin1. The highly conserved large extracellular loop of CD81 binds the HCV envelope protein complex E1/E2 (Helle and Dubuisson 2008; Ahmad et al. 2011; Houldsworth et al. 2014). Envelope proteins E1 and E2 interact in a cross talk that is involved in membrane fusion and modulation of the E1/E2 binding to entry receptors (Douam et al. 2014). The expression of viral entry receptors is augmented via cell polarization, whereby tight junctions provide a barrier for viral access to receptors (Mee et al. 2008). On the other hand, HCV infection reduces hepatocellular polarity in a VEGF-dependent manner, in that VEGF depolarizes hepatocytes (Mee et al. 2010). Claudin1 is highly expressed in hepatocytes during HCV infection and has high potential for phosphorylation and O-glycosylation (Ahmad et al. 2011). Claudin1 and CD81 form a complex that is localized to the basolateral surface of polarized cells (Harris et al. 2010). However, claudin use for HCV entry is isolate dependent, and differential claudin1 usage by HCV isolates may evolve based on variable expression of claudins in human liver cells (Haid et al. 2014). There is recent evidence that transferrin receptor 1 plays a role in HCV infection at the level of glycoprotein-mediated entry and acts after CD81, as it is involved in HCV particle internalization (Martin and Uprichard 2013). Infection of the liver with HCV is promoted by factors produced from sinusoidal endothelial cells/SEC. SEC secrete bone morphogenetic protein4/BMP4 as an endothelial-expressed proviral factor that facilitates HCV

infection of the liver. BMP4 expression in SEC is negatively regulated by vascular endothelial growth factor-A/VEGF-A through a VEGFR2-primed activation of p38 MAPK (Rowe et al. 2014).

Hepatocellular Carcinoma in Hepatitis C Virus Infection

Chronic HCV infection is a major risk factor for the development of HCC, and the involved pathogenic pathways have been studied and reviewed in detail.

Selected References (Hasan et al. 1990; Kew 1994; Branda and Wands 2006; Levrero 2006; Jin 2007; Ashfaq et al. 2011; Zheng et al. 2011; Bühler and Bartenschlager 2012; Jeong et al. 2012; Selimovic et al. 2012; Hoshida et al. 2014; Koike 2014; Shlomai et al. 2014; Lin et al. 2015).

In particular, HCV genotype 1b increases the cumulative lifetime risk of HCC (Lee et al. 2014). HCV infection alone can promote the development of HCC, although there is also evidence that risk factors not directly related to the virus modify cancer development, such as age, male gender, severity of liver disease, alcohol abuse, and other viruses (Bruno et al. 2011). Epstein-Barr virus/EBV may act as a helper virus by promoting replication of HCV in the infected liver (Akhter et al. 2003). HCV viral components are operational in several phases or steps of the HCC hepatocarcinogenesis pathway, including the induction of inflammation and genotoxic effects, as HCV can directly or indirectly induce DNA damage (Idilman et al. 1998; Jahan et al. 2012; Rusyn and Lemon 2014; Shawki et al. 2014).

HCV and its viral proteins promote hepatocarcinogenesis through the induction of chronic liver inflammation and hepatic cirrhosis, a main risk factor for liver cancer (Jin 2007). The chronic inflammatory response induced by HCV is not only a crucial element in the pathway leading to cirrhosis, but also affects signaling pathways that promote hepatocarcinogenesis, e.g., TGF-beta signaling (Matsuzaki et al. 2007). Inflammatory responses followed by fibrosis and hepatocarcinogenesis induced by HCV are also modulated by oxidative stress caused by HCV. HCV manipulates the pro- and antioxidant balance in cells and tissues, in part by its influence on lipid metabolism and lipoxigenation (review: Paracha et al. 2013). HCV can also cause hepatic iron overload, which contributes to cell damage and inflammation and is associated with poor prognosis (Drakesmith and Prentice 2008). In HCV-infected cirrhotic livers, leptin receptor somatic mutations are frequent and associated with HCC. Such mutations could disrupt leptin receptor signaling and increase susceptibility to liver carcinogenesis (Ikeda et al. 2014).

HCV infection can elicit a distinct type of hepatic steatosis that may be complicated by inflammatory changes (Syed et al. 2010; Filipe and McLauchlan 2015). As outlined in later paragraph, steatosis and steatohepatitis are now well-established risk factors for the development of HCC. Overall, 6 % of HCV patients have steatosis/steatohepatitis, more often in the presence of HCV genotype 3. HCV-induced steatosis/steatohepatitis is mainly observed in the setting of a distinct spectrum of metabolic abnormalities, comprising insulin resistance, hyperuricemia, reversible hypercholesterolemia, arterial hypertension, and expansion of visceral adipose tissue, a constellation termed hepatitis C-associated dysmetabolic syndrome/HCADS (review: Lonardo et al. 2014). The mechanisms involved in HCV-induced hepatic steatosis and steatohepatitis are not fully clarified, but include downregulation of very low-density lipoproteins/VLDLs, inhibition of adipose triglyceride lipase-mediated lipid mobilization, upregulation of lipoprotein and cholesterol receptors, upregulation of master regulator sterol response element binding protein, HCV core protein interaction with lipid droplet accumulation, HCV interaction with microsomal triglyceride transfer protein/MTP, and attenuated mitochondrial lipid beta-oxidation.

Apart from inducing a necroinflammatory response and hepatic fibrosis, HCV and its diverse viral-specific proteins directly interfere with

numerous functions and signaling pathways of the host cell, and this complex interactome is now considered to play an important role in hepatocarcinogenesis (review: Jin 2007). Four HCV components, namely, HCV core, NS3, NS4B, and NS5A, have been demonstrated to exhibit transformation potential in cultured cells (review: Banerjee et al. 2010). HCV viral proteins cause beta-catenin stabilization as an important carcinogenic pathway. Both HCV core and NS5A induce an accumulation of wild-type beta-catenin known to be involved in HCC pathogenesis (review: Levrero 2006). Beta-catenin-mediated transcriptional activity is elevated by NS5A protein (Milward et al. 2010), and this protein inactivates a component of the beta-catenin signaling pathway, glycogen synthase kinase-3beta, and increases the subsequent accumulation of beta-catenin in HCC cells (Park et al. 2009). HCV interferes with the tumor suppressor, PML/promyelocytic leukemia protein, a central component of PML nuclear bodies (Herzer et al. 2014). HCV proteins trigger numerous stress responses of host cells, including endoplasmic reticulum stress (unfolded protein responses), apoptosis, autophagy, and cell cycle arrest (review: Ke and Chen 2012). By inducing the production of reactive oxygen species (ROS) via affecting the levels of the mitochondrial chaperone, prohibitin, and blunting of antioxidant system, HCV markedly exacerbates oxidative stress, an effect involved in the development of HCC (Fujinaga et al. 2011). There is evidence that HCV viral proteins directly affect the cell division cycle of infected cells. In HCV-infected hepatoma cells, a decrease in the proportions of cells in G1 and S phases and an increase of cells in the G2/M phase were detected, associated with marked decreases of mitosis markers, such as phosphohistone 3. The presence of HCV and its proteins seems to cause cell cycle arrest at the level of initiation of mitosis (Kannan et al. 2011). HCV protein NS5A participates in the oncogenic transformation of hepatocyte precursors and induces epithelial-mesenchymal transition (Akkari et al. 2012). The NS5A protein also promotes genomic instability through downregulation of the spindle gene Aspm, thus inducing an aberrant mitotic cell cycle (Wu et al. 2008). Part of HCV's effects on signaling pathways regulating cell proliferation, apoptosis, and cell migration is mediated by a deregulated expression of microRNAs operational in the HCV viral life cycle (Shrivastava et al. 2013). Similar to HBV, HCV also exerts direct effects on cellular mechanisms via epigenetic changes, causing aberrant methylation on SOCS-1, Gadd45beta, MGMT, STAT1, and APC (Rongrui et al. 2014). The HCV core protein also epigenetically silences the Wnt antagonist, secreted frizzled-related protein/SFRP, causing activation of the Wnt signaling pathway and contributing to HCC aggressiveness via induction of epithelial-mesenchymal transition (Quan et al. 2014).

Nonalcoholic Fatty Liver Disease (NAFL) and Nonalcoholic Steatohepatitis (NASH)

NAFL and NASH are associated with hepatocellular carcinoma.

Both NAFL and NASH may cause progressive liver fibrosis and cirrhosis, followed by HCC in part of the patients, both in Western and Eastern countries (metabolic syndrome-associated HCC).

Selected References (Cotrim et al. 2000; Bugianesi et al. 2002; El-serag et al. 2006; Siegel and Zhu 2009; Blonski et al. 2010; Starley et al. 2010; Kawai et al. 2011; Welzel et al. 2011; Baffy et al. 2012; Jain et al. 2012; Rosmorduc and Fartoux 2012; Sun and Karin 2012; Torres and Harrison 2012; Michelotti et al. 2013; Rahman et al. 2013; Rosmorduc 2013; Yilmaz et al. 2013; Alzahrani et al. 2014; Dongiovanni et al. 2014; Kikuchi et al. 2014).

HCCs developing in NAFLD belong to the category of the so-called non-B, non-C HCC (Nishikawa and Osaki 2013) and have become the most rapidly growing indication for liver transplantation in patients with HCC in the USA (Wong et al. 2014). With a current epidemic of the metabolic syndrome, the number of patients with

NAFL/NASH increases, and it is expected that this increase will translate into an increased incidence of HCC (reviews: Hashimoto and Tokushige 2012; Mangia and Ripoli 2013; Rahman et al. 2013). In a nationwide Japanese survey of 14,530 HCC patients, NAFLD was the cause in 2.0 % and alcoholic liver disease in 7.2 % (Tokushige et al. 2011). As NAFL and NAFLD are strongly linked to obesity with or without diabetes mellitus, obesity-related HCC is regarded as an entity of major worldwide concern (Caldwell et al. 2004; Regimbeau et al. 2004; Shen et al. 2012; Michelotti et al. 2013). HCC in patients with active NASH is either a large solitary mass or a multifocal tumor and may precede clinically advanced disease (Iannaccon et al. 2007, Chagas et al. 2009). There is now strong evidence that HCC can develop already in simple fatty liver, i.e., in the absence of significant fibroinflammatory disease or cirrhosis (Chagas et al. 2009; Ikura et al. 2011; Alexander et al. 2013). However, a systematic review of available data showed that NAFLD or NASH cohorts with few or no cases of cirrhosis had a minimal risk for HCC, while cohorts of NASH and cirrhosis had a consistently higher risk, but the HCC risk was lower than that in cohorts with HCV-associated cirrhosis (White et al. 2012). In patients with NAFLD-associated HCC, the tumor disease is often accompanied by signs of metabolic disorders (Duan et al. 2012). In particular, metabolic disease associated with diabetes mellitus increases the risk of HCC (review: Blonski et al. 2010).

Apart from the procarcinogenic effect of liver cirrhosis as a late sequela of NAFL/NASH, the pathogenic pathways leading from fatty liver with or without associated inflammation to HCC are only partially known. There is evidence that mechanisms causing hepatocarcinogenesis in the metabolic syndrome involve interactions between several signaling pathways deregulated in insulin resistance, including oxidative stress, adiponectin actions, inflammatory cytokine networks and oncogene activation, and insulin resistance as such (review: Siddique and Kowdley 2011). There is also a complex relationship between NAFLD-induced chronic liver damage and hepatocyte injury caused by diabetes mellitus. Diabetes as such also increases the risk of HCC, such a risk correlated with long duration of diabetes (Hassan et al. 2010). The abnormal lipid metabolism characterizing NAFLD, with the emergence of unusual fatty acids, may as such be involved in hepatocarcinogenesis. Metabolites derived from excessive glucose, lipid, and insulin cause oxidative stress, which compromise genomic stability and promote pathologic polyploidization (Gentric et al. 2015). These metabolites also perturb epigenetic gene regulation via DNA methylation, RNA interference, and histone modifications (Tian et al. 2013). In steatosis, histone macroH2A1 isoforms undergo changes in HCC, with macroH2A1.2 specifically upregulated in steatosis-associated HCC (Rappa et al. 2013). NFLD is associated with a profound change in the life history of hepatocytes, consistent with hepatocyte senescence caused by shortening of hepatocyte telomeres (Aravinthan et al. 2013). In murine HCC models, proteomic and lipidomic signatures were different between HCC and NASH, with a significantly altered fatty acid profile in HCC characterized by a conversion of saturated fatty acids to monounsaturated fatty acids (Muir et al. 2013). During hepatocarcinogenesis from NASH, silencing of microRNA-122 through hypermethylation is an early event (Takaki et al. 2014).

HCC developing in livers with NAFLD or NASH often shows a phenotype not different from HCC emerging in other conditions. However, as specified in a separate chapter, part of the tumors exhibit a steatohepatitic morphology (steatohepatitic HCC), being more frequent in patients with NAFLD-associated cirrhosis and significantly associated with metabolic risk factors (Salomao et al. 2010, 2012; Gupta et al. 2014).

NAFL, NAFLD, and NASH: Frequent Hepatic Disorders with Complex Clinical Sequelae

NAFL (nonalcoholic fatty liver), NAFLD (nonalcoholic fatty liver disease), and NASH (nonalcoholic steatohepatitis) are considered to

be hepatic manifestations of the metabolic syndrome, and therefore a novel term has been coined, MAFLD (metabolic syndrome-associated fatty liver disease; Balmer and Dufour 2011). NAFLD encompasses a wide spectrum of disease pathology, ranging from the seemingly benign accumulation of neutral fat (simple hepatic steatosis; NAFL) to progressive NASH associated with necroinflammation and fibrosis (Sugimoto and Takei 2011; Farrell et al. 2012; Mak et al. 2012; Lomonaco et al. 2013). In Western countries, NAFLD is a relatively frequent disorder and has become the most common chronic hepatic disease, with an estimated prevalence of 20–30 % (reviews: Milic and Stimac 2012; Loomba and Sanyal 2013).

The pathogenic mechanisms involved in NAFLD are still incompletely elucidated (Watanabe et al. 2007; Koo 2013; Schuppan and Schattenberg 2013). On a higher homeostatic level, interactions between hepatocytes, hepatic stellate cells, hepatic macrophages, and progenitor cells are involved in a complex cross talk that regulates signaling pathways of lipid metabolism and the hepatic metabolome (Beyoglu and Idle 2013; Carpino et al. 2013). There is genetic predisposition for NAFLD (Anstee and Day 2013), genome-wide association studies having identified several genetic modifiers, including the patatin-like phospholipase domain-containing 3 (PNPLA3; adiponutrin) gene variant I148M (Trépo et al 2011; Dongiovanni et al. 2013; Ezzikouri et al. 2014). Alterations in PNPLA3 expression may be related to hepatocarcinogenesis. A higher risk of HCC was observed for subjects with a homozygous genetic variation in PNPLA3 (Hassan et al. 2013). Carriage of the PNPLA3 rs 738409 C>G polymorphism confers an increased risk of NAFLD-associated HCC (Guyot et al. 2013; Liu et al. 2014). In the pathogenesis of steatosis, the main pathways include excessive availability of plasma fatty acids, increased lipogenesis from carbohydrates, decreased lipolysis, and sequelae of oxidative cell and tissue damage. Lipogenesis from glucose is a crucial process that depends on insulin action and is under the control of a specific transcription factor, sterol regulatory element binding protein 1c (SREBP-1c), activated by insulin and carbohydrate response element binding protein (ChREBP) activated by glucose. SREBP-1c, which is proteolytically activated in the endoplasmic reticulum by the maturating action of insulin, itself activates glycolytic and lipogenic gene expression (Ferré and Foufelle 2010). Lipid metabolism in adipocytes and hepatocytes is critically regulated by the action of adipocytokines, in particular adiponectin (Gatselis et al. 2014). Lack of a major member of this group, adiponectin, as observed in NAFLD, drives steatosis and inflammation, while its presence has an antitumor property and is thought to counteract hepatocarcinogenic pathways (review: Wieser et al. 2012). NAFLD and NASH are associated with significant oxidative stress, whereby lipoperoxidation plays an important role. Through formation of oxidated nucleotides such as 8-hydroxy-2'-deoxyguanosine, this stress response can cause oxidative DNA damage which may be involved in carcinogenesis (Tanaka et al. 2013).

There is a complex link between NAFLD and HCV infection, and in pathways leading to HCC, both disorders may contribute in a concerted manner (Ohata et al. 2003; Pekow et al. 2007; Patel and Harrison 2012). Part of patients with HCV-induced chronic hepatitis exhibit hepatic steatosis, in particular those with the genotype 3. HCV infection is also associated with hypobetalipoproteinemia and hypocholesterolemia (Felmlee et al. 2013). The procancerogenic effects of HCV and cirrhosis are thought to be augmented by the effects of fat accumulation, including lipoperoxidation, action of oxygen radicals, and persistent activation of peroxisome proliferator-activated receptor-alpha, the latter causing marked changes in the lipid metabolism and oxidative stress (review: Koike et al. 2010). Although there is a strong relationship between HCV infection, the metabolic syndrome, and NAFLD, the metabolic syndrome is also associated with cryptogenic HCC, i.e., not related to either HBV, HCV, or alcoholic liver disease (Lee et al. 2013). The progression of NAFLD and hence the occurrence of cirrhosis and HCC are influenced by gut microbiota, through a pathway involving NLRP6 and NLRP3 inflammasomes and the

effector protein interleukin-18, which negatively regulate progression of fatty liver disease (Henao-Mejia et al. 2012).

Other Inflammatory Disorders Promoting Hepatocarcinogenesis in Humans

Introduction

The distinct cellular and molecular environment that develops in the liver in various inflammatory diseases is considered an important factor favoring the emergence of liver cancer (Berasain et al. 2009). Numerous types of chronic hepatic inflammation share common pathways favoring hepatocarcinogenesis. They include ongoing enhanced hepatocyte or cholangiocyte regeneration with an increased risk of accumulating cancerogenic mutations, remodeling of hepatic parenchyma with altered vascular relations, accumulation of immunologic effector cells that secrete cytokines and chemokines favoring abnormal cell growth and angiogenesis, and local induction of oxidative stress associated with genotoxic radical release.

Autoimmune Hepatitis

HCC developing in patients with autoimmune hepatitis (AIH) is a rare situation (Pauwels et al. 1987; Thung et al. 1990; Park et al. 2000; Hardee et al. 2003; Ward et al. 2008; Watanabe et al. 2009; Trivedi and Cullen 2011; Wong et al. 2011; Yamamoto et al. 2011). In some patients of earlier reports of probable autoimmune disease-related HCC, the old term lupoid hepatitis was employed (Satake et al. 1988; Motoo et al. 1989). It is difficult to judge the significance of this association in older reports, because part of them were published before the era of HCV screening, suggesting that part of patients had HCV infection associated with autoimmune features or frank AIH (Geramizadeh et al. 2013). The frequency of HCC in patients with AIH and cirrhosis is estimated to range from 1 % to 9 %, with an annual incidence in cirrhotic patients of 1.1–1.9 % (Wong et al. 2011; Czaja 2013). In Japan, survey results showed that HCC developed in 5.1 % of patients with AIH, with cirrhosis of the liver observed in elderly individuals (Ohira et al. 2013). In Japanese AIH patients, hepatic cirrhosis at presentation was predictive of the development of HCC in AIH (Hino-Arinaga et al. 2012; Migita et al. 2012). In some patients, AIH-associated HCC developed in a liver with cirrhosis and precancerous lesions (Ward et al. 2008), suggesting a dysplasia-HCC pathway in part of AIH patients. HCC was also observed in the setting of IgG4-associated de novo AIH after liver transplantation (Zhao et al. 2013).

Primary Biliary Cirrhosis

Patients with primary biliary cirrhosis (PBC) reveal an increased risk of HCC (Krasner et al. 1979; Mallet et al. 1981; Silveira et al. 2008; Watanabe et al. 2009; Kuiper et al. 2010; Macaron et al. 2010; Imam et al. 2012; Floreani and Farinati 2013). Reported risk factors for HCC comprise age, male sex, cirrhosis, and portal hypertension. Among 210 patients with PBC who were followed up for a median period of 8.5 years, 11 patients (5.2 %) developed HCC (Tomiyama et al. 2013). In studies from Spain and Italy, the prevalences were 3.34 % and 3.36 %, respectively (Cavazza et al. 2009). In surveys from Japan, the incidence and mortality of HCC in PBC patients were significantly higher as compared with the general Japanese population. Among 179 PBC patients, 13 developed HCC (Hosonuma et al. 2013). Using data from two Japanese national surveys, it turned out that 71/2,946 patients with PBC, or 2.4 %, developed HCC. HCC patients associated with PBC showed a significantly poorer prognosis than those without (Harada et al. 2013). In a review of 29 cases, more than 70 % of patients were aged over 65 years, the resected tumors were solitary in 79 %, and the median maximum tumor diameter was 37 mm (Sasaki et al. 2014).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC), which develops in about 8.5 % of patients with Crohn's disease, is typically complicated by cholangiocarcinoma, a neoplasm which arises in 10–20 % of patients with long-standing PSC. Rarely, HCC has been found as a late complication of PSC. The prevalence of HCC in patients with PSC is estimated to be around 2 % (Ismail et al. 1991; Votte-Lambert et al. 1993; Guckelberger et al. 1998; Leidenius et al. 2001; Oya et al. 2004; Demarchi et al. 2007). PSC patients with cholangiocarcinoma had a shorter median duration of PSC compared with PSC patients having HCC (Leidenius et al. 2001). HCC also developed in small-duct PSC, a disorder in which the disease either starts in or exclusively involves the small intrahepatic bile ducts (Ali and Shah 2010). HCC has been observed in Crohn's disease in the absence of signs of PSC (Ishida et al. 2010). In addition to ordinary HCC, fibrolamellar hepatocellular carcinoma was observed in a patient with ulcerative colitis and PSC (Snook et al. 1989), and also combined hepato-cholangiocarcinoma was found in association with PSC (Wee et al. 1985). HCC was also observed in the setting of other autoimmune disorders, e.g., Sjögren's syndrome (Yan et al. 2013).

Sarcoidosis

Sarcoidosis of the liver can be complicated by HCC, but sarcoidosis-associated HCC is a rare condition (Askling et al. 1999; Wong et al. 1999; Chalasani et al. 2005; Pila Pérez et al. 2007; Ogata et al. 2010; Arai et al. 2014). As hepatic sarcoidosis can induce hepatic fibrosis and remodeling, this process may be an important risk factor for liver cancer. In one patient with sarcoidosis, HCC was associated with established liver cirrhosis (Chalasani et al. 2005). On the other hand, HCC can elicit a sarcoid granulomatous reaction in the liver (Adachi et al. 1993).

Toxic Compounds as Etiologic Agents for HCC

Aflatoxins

Aflatoxins (AF) are secondary difuranocoumarin-derived mycotoxins produced by a polyketide pathway by the fungi, *Aspergillus flavus* and *Aspergillus parasiticus*. Together with *Fusarium*, *Aspergillus* is the mycotoxigenic genus of greatest concern (Bhatnagar et al. 2002; Kew 2010a, 2012, 2013; Felizardo and Camara 2013; Woloshuk and Shim 2013). The two *Aspergillus* species are widely spread and grow in large numbers in grain and seed products and in vegetable staple food, in particular stapled maize, rice, sorghum, and ground nuts. The two fungi produce AF best at temperatures ranging from 25 to 32 centigrades, a relative humidity of 85 %, and a moisture of greater than 12 % but less than 16 %, illustrating that optimal conditions will exist in certain subtropical and tropical countries. High risks for AF production by contaminating fungi are also related to suboptimal storage facilities, food drying, routine food and staple monitoring, and mold exposure control, due to infrastructural and/or financial shortcomings. In developing countries, staple food is often restricted to few types of vegetables (e.g., rice) that provide the principal food, resulting in the chronic intake of large mycotoxin amounts in case of staple food contamination (review: Kew 2013). Among AF, the most potent carcinogenic agent is AFB1. Exposure of AFB1 in parts of Asia and Latin America and chiefly in Africa may begin early in life (already in utero), followed by episodes of intoxication in adulthood. These episodes are markedly influenced by geographical factors, seasonal factors, agricultural and crop storage practices, and individual food preparation and preference habits (review: Bosch and Peers 1991).

The toxic effects that occur following AFB1 ingestion are summarized under the term aflatoxicosis (Williams et al. 2004). Depending on utilized food sources with variable prevalence of fungal contamination, it is estimated that more than four billion persons living in developing

countries are chronically exposed to largely uncontrolled amounts of this toxin (Enwonwu 1984; review: Williams et al. 2004). Apart from the promotion of liver cancer, AFB1 causes several other toxic effects in man and animals and modulates the course of several diseases in humans, including infections such as HIV infection, because AFB1 affects the function of the immune system.

The hepatocarcinogenic effect of AFB1 has been demonstrated in numerous investigations, case reports, and reviewed several times (Linsell and Peers 1972, 1977; Lutwick 1979; Yuen et al. 2009; Hamid et al. 2013; Kew 2013). It is estimated that between 25,000 and 155,000 persons with HCC worldwide have attracted this cancer due to AFB1 exposure and that about 40 % of these persons live in sub-Saharan Africa (review: Kew 2013). Reviews of available results revealed a high degree of positive correlation between calculated ingestion levels of AFB1 and the adult incidence rates of HCC (Peers and Linsell 1977). AFB1 is also the most potent experimental hepatocarcinogen. Reduced AF exposure (diminished maize consumption) associated with universal HBV vaccination caused a decline in liver cancer mortality in an endemic Chinese region (Chen et al. 2013). In the body, AFB1 is metabolized by the cytochrome P450 system to highly active metabolites, including AFB1-8,9-exo-epoxide, which is in turn converted into 8,9-dihydroxy-8-(N7) gualnyl-9-hydroxy AFB1 adduct. This adduct is then metabolized into AFB1 formamidopyrimidine adduct. These adducts are mutagenic and also alter p53 by inducing an arginine to serine mutation at codon 249. AFB1 negatively regulates the WNT/beta-catenin signaling pathway, a pathway critically involved in hepatocarcinogenesis, via activating miR-33a, a microRNA that downregulates beta-catenin (Fang et al. 2013). The destabilizing action of AFB1 metabolites on DNA is modified by differential expression of the DNA repair genes, XRCC4 and XRCC5, linked to genetic polymorphisms (Long et al. 2013). One mechanism of AFB1-mediated carcinogenesis is its induction of a global DNA hypomethylation, suggesting that AFB1 affects epigenetic pathways (Zhang et al. 2012). There are interactions between AFB1 and dietary iron overload in hepatic mutagenesis, in that the two agents exert a multiplicative effect (Asare et al. 2007).

The carcinogenic effects of AF as such are difficult to assess as many individuals with AF exposure also have other hepatic disorders promoting liver cancer, mainly hepatitis virus infections and in particular HBV infection (Peers et al. 1987). The potency of AFB1 in HBsAg+ individuals is substantially higher (with a factor of about 30) than in HBsAg-negative persons (Henry et al. 2002). The cellular changes induced by hepatitis viral infection are thought to modify the hepatocytes' ability to handle AFB1. For example, it was proposed that HBV-infected hepatocytes are predisposed to AFB1-induced DNA damage and that a combination of viral infection and AFB1 toxicity augments the overall cellular oxidative stress (Wild and Montesano 2009).

Ochratoxin A

Apart from AF, another potential contributor to high incidences of HCC in Asia and sub-Saharan Africa is dietary exposure to ochratoxin A (OTA). OTA is an isocoumarin-derived mycotoxin produces by the fungus, *Aspergillus ochraceus*. This fungus chiefly grows on stapled barley, corn/maize, or wheat, but OTA can be found in a wide array of other foods and beverages, including cereals, beer, wine, coffee, cocoa, and spices. Even some meat and milk products were found to contain OTA. OTA is potent immunosuppressive and carcinogenic agent that induces liver and kidney tumors in experimental animals. However, no epidemiological data are available so far to prove the role of OTA in human HCC (review: Felizardo and Camara 2013).

Alcohol Toxicity and Alcoholic Liver Disease

Chronic alcohol intake and alcoholic liver disease (ALD) are a major risk factor for HCC worldwide

(Marrero et al. 2005; Persson et al. 2013; Purohit et al. 2013; reviews: Morgan et al. 2004; Borro and Testino 2013). Heavy alcohol consumption particularly increases the incidence of HCC in patients infected with hepatitis viruses (Lin et al. 2013). It is estimated that heavy alcoholic consumption for at least 5 years increases the risk of HCC by nearly fivefold, and the risk seems to be roughly proportional to the amount of alcohol consumed (Donato et al. 2002; Munaka et al. 2003). However, the risk of HCC in individuals who consume low or moderate amounts remains unknown.

The pathogenesis of alcohol-associated HCC is complex and involves abnormal regenerative hepatocyte responses following chronic liver cell injury, liver cirrhosis as a general HCC risk factor, induction of inflammation with production of procarcinogenic cytokines, and activation of carcinogenic signaling pathways. In majority of ALD patients with HCC, liver cirrhosis was present (Schütte et al. 2012). A further pathogenic group involves patients who have, in addition to ALD, chronic HCV and/or HBV infections which per se can promote carcinogenesis (Kudo et al. 2014). Hepatitis virus infections can modulate the progression of ALD and may thus exert an impact on hepatocarcinogenesis. For example, the presence of HBV core antibody was associated with more advanced liver disease in alcoholic patients with cirrhosis (Zhang et al. 2013a). Metabolites of alcohol are highly active substances that interfere with numerous cellular pathways. A major catabolic product of ethyl alcohol, acetaldehyde, is known to form DNA adducts, the best known being the mutagenic N(2)-ethyl-2′-deoxyguanosine, a genotoxic molecule (Brooks and Theravathu 2005). In the alcohol-preferring rat model of hepatocarcinogenesis, alcohol activated the hedgehog signaling pathway and the associated downstream gene targets (Chan et al. 2014). There are also epigenetic events in liver cancer associated with alcoholic liver disease. Ethanol exposure can alter the histone acetylation status and interact with regulating miRNAs that control transcriptional events (French 2013).

Occupational Toxins

Occupational exposure to chemicals may be a risk factor for HCC development, although relatively few studies have addressed this problem. Potential occupational substances having a hepatocarcinogenic effect include vinyl chloride, organic solvents, pesticides, polychlorinated biphenyl, and arsenic (review: Uccello et al. 2012).

Drugs and Hepatocellular Carcinoma

Androgens

Sex steroids play an important role in hepatic tumorigenesis, albeit mainly for benign hepatocytic tumors and tumor-like lesions (review: Giannitrapani et al. 2006). HCC, sometimes associated with peliosis hepatis, occurs or occurred as a complication of androgen therapy applied for several indications, including Fanconi's anemia (hereditary aplastic anemia), osteoporosis, and body building (Bernstein et al. 1971; Johnson et al. 1972; Henderson et al. 1973; Ziegenfuss and Carabasi 1973; Meadows et al. 1974; Anthony 1975; Farrell et al. 1975; Holder et al. 1975; Kew et al. 1976; Abbondanzo et al. 1986; Kosaka et al. 1996; Gelfand and Wiita 1997; Velazquez and Alter 2004; Ozenne et al. 2008). However, apart from a role of androgen therapy, Fanconi anemia patients may also have a higher HCC risk due to hepatic iron overload (Ozenne et al. 2008). Liver cell tumors following androgen administration and interpreted as "hepatoma" may not always had been "true" ordinary HCC, as some of the lesions regressed after discontinuation of the drug (Farrell et al. 1975). There is evidence that the synthetic androgenic substance, oxymetholone, used for the treatment of aplastic anemias and osteoporosis, is most often associated with HCC, sometimes after a delay of more than 10 years (Linares et al. 1991; Kosaka et al. 1996; Velazquez and Alter 2004). However, HCC in patients with Fanconi's anemia has been observed in the pediatric age group (Abbondanzo et al. 1986).

HCC has also been observed in individuals treated with danazol (Buamah 1985; Weill et al. 1988; Crampon et al. 1998; Confavreux et al. 2003). This relatively weakly androgenic substance is a derivative of the synthetic steroid, ethisterone, a modified progesterone (17-alpha-ethinyl testosterone), and acts by suppressing the increase of luteinizing hormone during the mid-menstrual cycle. It had been or is used for the treatment of fibrocystic breast disease, hereditary angioedema, and endometriosis, but its use in endometriosis has largely been replaced by other drugs.

Androgens, which are converted to estrogens in the liver by the action of aromatase, bind to specific hepatic androgen receptors. Part of human HCC express androgen receptor (Nagasue et al. 1995), in one study 67.7 % (Vizoso et al. 2007). Androgens binding to the androgen receptor enhance HCC cell growth and apoptosis resistance via activation of PEG10 (paternally expressed gene 10; Jie et al. 2007). Activation of the androgen receptor signaling pathway is thought to play a role in carcinogenesis. In HCC cell lines, activation of androgen receptors promotes cell migration and invasion, in part via expression of the metastasis-promoting gene, ID1 (Ao et al. 2012). The cell cycle-regulated kinase (CCRK) is a direct androgen receptor-regulated gene that drives beta-catenin-dependent hepatocarcinogenesis (Feng et al. 2011). The androgen pathway of hepatocarcinogenesis involves upregulation of miRNA-216a and a subsequent suppression of the tumor suppressor in lung cancer-1 (TSCL1) gene (Chen et al. 2012). Differential functions and expression patterns of androgen receptors are considered to play a role in the striking sexual dimorphism of HCC, with males clearly predominating, also in HBV-associated HCC (Kalra et al. 2008; Yeh and Chen 2010). A cooperation of HBV X (HBVx) protein with androgen receptor signaling pathways contributes to this dimorphism. HBVx correlates with high levels of androgen receptor in HCC and induces androgen receptor expression by stimulating its transcription in a promoter methylation-independent manner (Zhu et al. 2011). HBVx protein enhances the transcriptional activity of the androgen receptor through c-Src and glycogen synthase kinase-3beta kinase pathways (Yang et al. 2009). On the other hand, the androgen pathway can increase the transcription of HBV via direct binding to the androgen-responsive elements sites in viral enhancer I, a possible explanation for a higher HBV titer in male carriers and an increased risk of HCC (Wang et al. 2009). In addition to HBV, HCV infection also affects androgen receptor metabolism, in that HCV viral proteins engage in cross talk with the androgen receptor signaling pathway. HCV core protein activates STAT3, which in turn enhances androgen receptor-mediated transcription (Kanda et al. 2008). Androgen-mediated facilitation of HCC depends on Foxa1/Foxa2, suggesting that Foxa factors and their targets are central for the sexual dimorphism of HCC (Li et al. 2012). Irrespective of the role exerted by androgens in hepatocarcinogenic pathways, all antiandrogenic clinical trials failed in advanced HCC. There is now evidence that hepatic androgen receptor expressions in mice play dual yet opposite roles to promote HCC initiation but suppress HCC metastasis. Hepatic androgen receptors can enhance anoikis and suppress migration of HCC cells through suppression of p38 phosphorylation/activation and the nuclear factor kappB/MMP-9 pathway, respectively (Ma et al. 2012).

Estrogens

HCC has also been observed following long-term estrogen therapy (Sotaniemi et al. 1975) or oral contraceptive use (Davis et al. 1975; Glassberg and Rosenbaum 1976; Henderson et al. 1976; Balasz et al. 1977; Leclère et al. 1977; Pryor et al. 1977; Schmidt 1977; Christopherson et al. 1978; Menzies-Gow 1978; Trias et al. 1978; Amtrup et al. 1980; Shar and Kew 1982; Henderson et al. 1983; Neuberger et al. 1986). In one patient, HCC was diagnosed in pregnancy associated with earlier oral contraceptive administration (Christensen et al. 1981). There are observations of liver cell adenoma associated with oral contraceptive use transformed

into HCC (Gyorffy et al. 1989; Korula et al. 1991). There were indications that oral contraceptive use may increase the risk of HCC in countries with extremely low rates for HCC (Palmer et al. 1989; Prentice 1991). However, the question as to whether there is an etiologic relation between oral contraceptives and HCC is complex, in contrast to benign liver tumors (Baum et al. 1973). Even in early investigations, an etiologic association of HCC and oral contraceptives was not found, an apparent association being interpreted as probably coincidental (Goodman and Ishak 1982). Older studies were, at least in part, not based on carefully selected patient groups and were based on patients using pills that are no longer employed. WHO collaborative multinational case-control studies provided no evidence that short-term use of oral contraceptives enhances the risk of liver cancer in countries where the determinants of this neoplasm are similar to those observed in the countries where the analysis was performed (Anonymous 1989; Thomas 1991). An eventual effect of oral contraceptives on HCC risk may be related to the type of preparation used. There is evidence that a potential association with liver cancer is smaller for recent low-dose preparations (La Vecchia and Bosetti 2009). In the multicenter international liver tumor study (MILTS), a small subgroup of HCC cases without liver cirrhosis and with negative serology for HBV and HCV, there was evidence of an association with duration of oral contraceptive use, but no such trend was observed in the group employing preparations containing cyproterone acetate. Altogether, there was no evidence for an increased risk of HCC associated with cyproterone acetate or cyproterone acetate-like oral contraceptives (Thomas et al. 1997). In an inception cohort study from the UK, comparing 339,000 woman years of observation for never oral contraceptive users and 744,000 woman years for ever users, oral contraception was not associated with overall increased risk of cancer (Hannaford et al. 2007). However, female sex steroid use may alter the pathology and behavior of HCC, in that there is some evidence that such a therapy or administration may induce hypervascularity of tumors and a tendency for bleeding (Hromas et al. 1985). In a literature search published in 2009, no systematic study of contraceptive use among women with hepatocellular adenoma or with malignant liver tumors was identified (Kapp and Curtis 2009).

Hepatocellular Carcinoma in Non-cirrhotic Nodular Lesions of the Liver

A considerable fraction of HCC develops in non-cirrhotic liver, but a minority of them are found in association with other hepatocytic nodular lesions. There are few observations suggesting that HCC can arise in a background of nodular regenerative hyperplasia/NRH (Nzeako et al. 1996; Russmann et al. 2001). An analysis of 804 patients with non-cirrhotic HCC resulted in 23 patients having NRH (Nzeako et al. 1996). A higher incidence of HCC was observed in patients with obstruction of the inferior vena cava in the hepatic portion in chronic Budd-Chiari syndrome, a cause of hepatic venous outflow obstruction (HVOO). Hepatic parenchymal lesions are reported in up to 40 % of patients with Budd-Chiari syndrome, and the most common benign nodular lesions are large regenerative nodules and nodular lesions resembling focal nodular hyperplasia (Zhou et al. 2000; Ibarrola et al. 2004; Newerla et al. 2012). In more than 50 % of patients with chronic Budd-Chiari syndrome, thrombotic events in the portal vein occur (Cazals-Hatem et al. 2003), followed by increased arterial flow compensating low portal venous flow, a hemodynamic situation favoring large regenerative nodules (Tanaka and Wanless 1998). The reported time lag from diagnosis of Budd-Chiari syndrome and HCC ranged from several years to several decades. The pathogenesis has not been clarified, but may be linked to ongoing hepatocyte damage caused by HVOO followed by abnormally increased cell turnover (Nakamura and Takezawa 1982; Havlioglu et al. 2003; Jang et al. 2003; Walldorf et al. 2009). The fact that several types of nodular regenerative lesions commonly develop in Budd-Chiari syndrome supports the view that continuously increased hepatocyte regeneration is a

typical feature of this condition. In two patients Budd-Chiari syndrome complicated by HCC was associated with hepatic fibrosis and liver cirrhosis, respectively (Takayasu et al. 1994). The vena cava can show diverse types of membranous obstruction (MOVC) that most commonly involve the infra-or retrohepatic portion of the vein (Kimura et al. 1965), but less frequently, suprahepatic MOVC occurs (Gips et al. 1972; Suchato et al. 1977). Similar to chronic Budd-Chiari syndrome, MOVC causes hepatic hyperregeneration with nodular lesions (Gips 1972). MOVC, caused by postthrombotic fibrous stricture or a congenital web, is a disorder complicated by Budd-Chiari syndrome (Ciesek et al. 2010; Chen et al. 2011). It is often complicated by HCC, but as this vascular abnormality is rare, it contributes with only a minor fraction to the overall causes of HCC (Nakamura 1982; Okuda 1982; Simson 1982; Hautekeete et al. 1990; Seo et al. 1998; Katoh and Shigematsu 1999; Karia et al. 2000; Matsui et al. 2000; Takamura et al. 2004; Kew and Hodgkinson 2006; Mohan et al. 2009; Srinivas et al., 2012). MOVC has mainly been found in South Africa, India, and Japan and overall seems to be complicated by HCC in 3.7–47.5 % of patients, depending on the populations studied (reviews: Hautekeete et al. 1990; Mohan et al. 2009). Subjects affected are often younger and have a poorer prognosis. In a Korean study of 98 patients with MOVC, liver nodules were detected in 37 patients (38 %), 23 of whom had HCC and 14 of whom had benign nodules. The cumulative incidence of HCC at 1, 5, and 10 years was 7.3 %, 13.5 %, and 31.8 %, respectively (Gwon et al. 2010). In a South African series of patients, 6 of 15 individuals with membranous caval obstruction had concomitant HCC (40 %; Kew et al. 1989). Another investigation on 44 black patients with membranous caval obstruction from South Africa found HCC in 47.5 % of these patients (Simson 1982).

References

Abbondanzo SL, Manz HJ, Klappenbach RS, Gootenberg JE (1986) Hepatocellular carcinoma in an 11-year-old girl with Fanconi's anemia. Report of a case and review of the literature. J Pediatr Hematol Oncol 8:334–337

Abdel-Hamid NM (2009) Recent insights on risk factors of hepatocellular carcinoma. World J Hepatol 1:3–7

Adachi S, Ueda H, Ishikawa T, Ozaki A (1993) A case report of sarcoid reactions with hepatocellular carcinoma and two early gastric carcinomas (in Japanese). Nihon Geka Gakkai Zasshi 94:534–537

Ahmad W, Shabbiri K, Ijaz B, Asad S, Sarwar MT, Gull S, Kausar H, Fouzia K, Shahid I et al (2011) Claudin-1 required for HCV virus entry has high potential for phosphorylation and *O*-glycosylation. Virol J 8:229

Akhter S, Liu H, Parbhu R, DeLucca C, Bastian F, Garry RF, Schwartz M, Thung SN et al (2003) Epstein-Barr virus and human hepatocellular carcinoma. Cancer Lett 192:49–57

Akkari L, Grégoire D, Floc'h N, Moreau M, Hernandez C, Simonin Y, Rosenberg AR et al (2012) Hepatitis C viral protein NS5A induces EMT and participates in oncogenic transformation of primary hepatocyte precursors. J Hepatol 57:1021–1028

Alexander J, Torbenson M, Wu TT, Yeh MM (2013) Non-alcoholic fatty liver disease contributes to hepatocarcinogenesis in non-cirrhotic liver: a clinical and pathological study. J Gastroenterol Hepatol 28:848–854

Ali S, Shah V (2010) Small-duct primary sclerosing cholangitis with hepatocellular carcinoma requiring liver transplantation. Hepatobiliary Pancreat Dis Int 9:208–212

Ali A, Abdel-Hafiz H, Suhail M, Al-Mars A, Zakaria MK, Fatima K, Ahmad S, Azhar E, Chaudhary A, Qadri I (2014) Hepatitis B virus. HBx mutants and their role in hepatocellular carcinoma. World J Gastroenterol 20:10238–10248

Alter MJ (2007) Epidemiology of hepatitis C virus infection. World J Gastroenterol 13:2436–2441

Alzahrani B, Iseli TJ, Hebbard LW (2014) Non-viral causes of liver cancer: does obesity led inflammation play a role ? Cancer Lett 345:223–229

Amaddeo G, Cao Q, Ladeiro Y, Imbeaud S, Nault JC, Jaoui D, Gaston-Mathe Y, Laurent C et al (2014) Integration of tumour and viral genomic characterisations in HBV-related hepatocellular carcinomas. Gut. doi:10.1136/gutjnl-2013-306228

Amtrup F, Slottved J, Svanholm H (1980) Liver cell carcinoma in young women possibly induced by oral contraceptives. Acta Obstet Gynecol Scand 59:567–569

Anonymous (1989) Combined oral contraceptives and liver cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer 43:254–259

Anstee QM, Day CP (2013) The genetics of NAFLD. Nat Rev Gastroenterol Hepatol 10:645–655

Anthony PP (1975) Hepatoma associated with androgenic steroids. Lancet 1:685–686

Antonelli A, Ferri C, Galeazzi M, Giannitti C, Manno D, Mieli-Vergani G, Menegatti E et al (2008) HCV

infection: pathogenesis, clinical manifestations and therapy. Clin Exp Rheumatol 26(1 Suppl 48):S39–S47
Anzola M (2004) Hepatocellular carcinoma: role of hepatitis B and hepatitis C viruses proteins in hepatocarcinogenesis. J Viral Hepat 11:383–393
Ao J, Meng J, Zhu L, Nie H, Yang C, Li J, Gu J, Lin Q, Long W, Dong X, Li C (2012) Activation of androgen receptor induces ID1 and promotes hepatocellular carcinoma cell migration and invasion. Mol Oncol 6:507–515
Arai T, Akita S, Sakon M, Fujii T, Tanaka H, Ishii K, Miwa S (2014) Hepatocellular carcinoma associated with sarcoidosis. Int J Surg Case Rep 5:562–565
Aravinthan A, Scarpini C, Tachtatzis P, Verma S, Penrhyn-Lowe S, Harvey R, Davies SE et al (2013) Hepatocyte senescence predicts progression in non-alcohol-related fatty liver disease. J Hepatol 58:549–556
Arbuthnot P, Kew M (2001) Hepatitis B virus and hepatocellular carcinoma. Int J Exp Pathol 82:77–100
Asare GA, Bronz M, Naidoo V, Kew MC (2007) Interactions between aflatoxin B1 and dietary iron overload in hepatic mutagenesis. Toxicology 234:157–166
Ashfaq UA, Javed T, Rehman S, Nawaz Z, Riazuddin S (2011) An overview of HCV molecular biology, replication and immune responses. Virol J 8:161
Askling J, Grunewald J, Eklund A, Hillerdal G, Ekbom A (1999) Increased risk for cancer following sarcoidosis. Am J Respir Crit Care Med 160:1668–1672
Baffy et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22326465
Bai F, Yano Y, Fukumoto T, Takebe A, Tanaka M, Kuramitsu K, Anggorowati N et al (2013) Quantification of pregenomic RNA and covalently closed circular DNA in hepatitis B virus-related hepatocellular carcinoma. Int J Hepatol, 2013:849290
Balasz et al. 1977. http://www.ncbi.nlm.nih.gov/pubmed/189270
Balmer ML, Dufour JF (2011) Non-alcoholic steatohepatitis – from NAFLD to MAFLD (in German). Ther Umsch 68:183–188
Banerjee A, Ray RB, Ray R (2010) Oncogenic potential of hepatitis C virus proteins. Viruses 2:2108–2112
Baum JK, Holtz F, Bookstein JJ, Klein EW (1973) Possible association between benign hepatomas and oral contraceptives. Lacent 2:929
Beasley RP (1988) Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 61:1942–1956
Beasley RP, Hwang LY, Lin CC, Chien CS (1981) Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan. Lancet 2:1129–1133
Berasain C, Castillo J, Perugorria MJ, Latasa MU, Prieto J, Avila MA (2009) Inflammation and liver cancer: new molecular links. Ann NY Acad Sci 1155:206–221
Bernstein et al. 1971. http://www.ncbi.nlm.nih.gov/pubmed/4324228
Beyoglu D, Idle JR (2013) The metabolomic window into hepatobiliary disease. J Hepatol 59:842–858
Bharadwaj M, Roy G, Dutta K, Misbah M, Husian M, Hussian S (2013) Tackling hepatitis B virus-associated hepatocellular carcinoma – the future is now. Cancer Metast Rev 32:229–268
Bhatnagar D, Yu J, Ehrlich KC (2002) Toxins of filamentous fungi. Chem Immunol 81:167–206
Birch NC, Radio S, Horslen S (2003) Metastatic hepatocellular carcinoma in a patient with Niemann-Pick disease, type C. J Pediatr Gastroenterol Nutr 37:624–626
Blonski W, Kotlyar DS, Forde KA (2010) Non-viral causes of hepatocellular carcinoma. World J Gastroenterol 16:3603–3615
Borro P, Testino G (2013) Surveillance for hepatocellular carcinoma in alcoholic patients. Am J Gastroenterol 108:1811
Bosch FX, Peers F (1991) Aflatoxins: data on human carcinogenic risk. IARC Sci Publ 105:48–53
Brancatelli G, Federle MP, Grazioli L, Carr BI (2002) Hepatocellular carcinoma in noncirrhotic liver: CT, clinical, and pathologic findings in 39 U.S. residents. Radiology 222:89–94
Branda M, Wands JR (2006) Signal transduction cascades and hepatitis B and C related hepatocellular carcinoma. Hepatology 43:891–902
Brooks J, Theravathu JA (2005) DNA adducts from acetaldehyde: implications for alcohol-related carcinogenesis. Alcohol 35:187–193
Bruno S, Savojardo D, Almasio PL, Mondelli MU (2011) Critical reappraisal of risk factors for occurrence of hepatocellular carcinoma in patients with hepatitis C virus. Hepatol Med 3:21–28
Buamah PK (1985) An apparent danazol-induced primary hepatocellular carcinoma: case report. J Surg Oncol 28:114–116
Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, Musso A, De Paolis P et al (2002) Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology 123:134–140
Bühler S, Bartenschlager R (2012) Promotion of hepatocellular carcinoma by hepatitis C virus. Dig Dis 30:445–452
Caldwell SH, Crespo DM, Kang HS, Al-Osaimi MS (2004) Obesity and hepatocellular carcinoma. Gastroenterology 127:S97–S103
Carpino G, Renzi A, Onori P, Gaudio E (2013) Role of hepatic progenitor cells in nonalcoholic fatty liver disease development: cellular cross-talks and molecular networks. Int J Mol Sci 14:20112–20130
Cavazza et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19585656
Cazals-Hatem D, Vilgrain V, Genin P, Denninger MH, Durand F, Belghiti J, Valla D et al (2003) Arterial and portal circulation and parenchymal changes in Budd-Chiari syndrome: a study of 17 explanted livers. Hepatology 37:510–519
Chagas et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19787150

Chalasani P, Vohra M, Sheagren JN (2005) An association of sarcoidosis with hepatocellular carcinoma. Ann Oncol 16:1714–1715

Chan DW, Oi-Lin NI (2005) Knock-down of hepatitis B virus X protein reduces the tumorigenicity of hepatocellular carcinoma cells. J Pathol 208:372–380

Chan IS, Guy CD, Machado MV, Wank A, Kadiyala V, Michelotti G, Choi S, Swiderska-Syn M et al (2014) Alcohol activates the hedgehog pathway and induces related procarcinogenic processes in the alcohol-preferring rat model of hepatocarcinogenesis. Alcohol Clin Exp Res 38:787–800

Chen PJ, Chen DS (1999) Hepatitis B virus infection and hepatocellular carcinoma: molecular genetics and clinical perspectives. Semin Liver Dis 19:253–262

Chen H, Cheng Y, Ning S, Chen Y (2011) Budd-Chiari syndrome caused by multiple membranous obstruction of the inferior vena cava in a young man. Ann Vasc Surg 1139:e5–e7

Chen PJ, Yeh SH, Liu WH, Lin CC, Huang HC, Chen CL, Chen DS, Chen PJ (2012) Androgen pathway stimulates microRNA-216a transcription to suppress the tumor suppressor in lung cancer-1 gene in early hepatocarcinogenesis. Hepatology 56:632–643

Chen JG, Egner PA, Ng D, Jacobson LP, Muñoz A, Zhu YR, Qian GS, Wu F, Yuan JM et al (2013) Reduced aflatoxin exposure presages decline in liver cancer mortality in an endemic region of China. Cancer Prev Res (Phila) 6:1038–1045

Christensen SE, Andersen VR, Vilstrup H (1981) A case of hepatoma in pregnancy associated with earlier oral contraception. Acta Obstet Gynecol Scand 60:519

Christopherson WM, Mays ET, Barrows G (1978) Hepatocellular carcinoma in young women on oral contraceptives. Lancet 2:38–39

Chung TW, Lee YC, Ko JH, Kim CH (2003) Hepatitis B virus X protein modulates the expression of pTEN by inhibiting the function of p53, a transcriptional activator in liver cells. Cancer Res 63:3453–3458

Ciesek S, Rifai K, Bahr MJ, Boozari B, Steinmann E, Helfritz E, Wedemeyer H, Manns MP et al (2010) Membranous Budd-Chiari syndrome in Caucasians. Scand J Gastroenterol 45:226–234

Coleman WB (2003) Mechanisms of human hepatocarcinogenesis. Curr Mol Med 3:573–588

Confavreux C, Sève P, Broussole C, Renaudier P, Ducerf C (2003) Danazol-induced hepatocellular carcinoma. QJM 96:317–318

Conrad KD, Niepmann M (2014) The role of microRNAs in hepatitis C virus RNA replication. Arch Virol 159:849–862

Cotrim HP, Parana R, Braga E, Lyra L (2000) Nonalcoholic steatohepatitis and hepatocellular carcinoma: natural history? Am J Gastroenterol 95:3018–3019

Crampon D, Barnoud R, Durand M, Ponard D, Jacquot C, Sotto JJ, Letoublon C, Zarski JP (1998) Danazol therapy: an unusual aetiology of hepatocellular carcinoma. J Hepatol 29:1035–1036

Craxi A, Laffi G, Zignego AL (2008) Hepatitis C virus (HCV) infection. Syst Dis 29:85–95

Czaja AJ (2013) Hepatocellular carcinoma and other malignancies in autoimmune hepatitis. Dig Dis Sci 58:1459–1476

Davis M, Portmann B, Searle M, Wright R, Williams R (1975) Histological evidence of carcinoma in a hepatic tumour associated with oral contraceptives. Br Med J 4:496–498

De Giorgi V, Buonaguro L, Worschech A, Tornesello ML, Izzo F, Marincola FM, Wang E et al (2013) Molecular signatures associated with HCV-induced hepatocellular carcinoma and liver metastasis. PLoS ONE 8, e56153

Demarchi B, Bresso F, Novero D, Palestro G, Sapone N, Pellicano R, Bonardi R, Smedile A, Rizzetto M, Astegiano M (2007) Hepatocellular carcinoma complicating primary sclerosing cholangitis in Crohn's disease. A case report. Minerva Gastroenterol Dietol 53:279–283

Dimitroulis D, Valsami S, Spartalis E, Pikoulis E, Kouraklis G (2013) Hepatocellular carcinoma in patients co-infected with hepatitis C virus and human immunodeficiency virus. World J Hepatol 5:323–327

Donato F, Tagger A, Gelati U, Parrinello G, Boffetta P, Albertini A, Decarli A, Trevisi P et al (2002) Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 155:323–331

Dongiovanni P, Anstee QM, Valenti L (2013) Genetic predisposition in NAFLD and NASH: impact on severity of liver disease and response to treatment. Curr Pharm Des 19:5219–5238

Dongiovanni P, Romeo S, Valenti L (2014) Hepatocellular carcinoma in nonalcoholic fatty liver: role of environmental and genetic factors. World J Gastroenterol 20:12945–12955

Douam et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24038151

Dragani TA (2010) Risk of HCC: genetic heterogeneity and complex genetics. J Hepatol 52:252–257

Drakesmith H, Prentice A (2008) Viral infection and iron metabolism. Nat Rev Microbiol 6:541–552

Duan XY, Qiao L, Fan JG (2012) Clinical features of nonalcoholic fatty liver disease-associated hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 11:18–27

El-Serag HB, Hampel H, Javadi F (2006) The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 4:369–380

Enwonwu CO (1984) The role of dietary aflatoxin in the genesis of hepatocellular cancer in developing countries. Lancet 2:956–958

Ezzikouri S, Alaoui R, Tazi S, Nadir S, Elmdaghri N, Pineau P, Benjelloun S (2014) The adiponutrin I148M variant is a risk factor for HCV-associated liver cancer in North-African patients. Infect Genet Evol 21:179–183

Fang et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/24015284

Farrell GC, Joshua DE, Uren RF, Baird PJ, Perkins KW, Kroneneberg H (1975) Androgen-induced hepatoma. Lancet 1:430–432

Farrell GC, van Rooyen D, Gan L, Chitturi S (2012) NASH is an inflammatory disorder: pathogenic, prognostic and therapeutic implications. Gut Liver 6:149–171

Feitelson MA, Lee J (2007) Hepatitis B virus integration, fragile sites, and hepatocarcinogenesis. Cancer Lett 252:157–170

Felizardi RJ, Camara NO (2013) Hepatocellular carcinoma and food contamination: aflatoxins and ochratoxin A as a great prompter. World J Gastroenterol 19:3723–3725

Felmlee DJ, Hafirassou ML, Lefevre M, Baumert TF, Schuster C (2013) Hepatitis C virus, cholesterol and lipoproteins – impact for the viral life cycle and pathogenesis of liver disease. Viruses 5:1292–1324

Feng H, Cheng AS, Tsang DP, Li MS, Go MY, Cheung YS, Zhao GJ, Ng SS, Lin MC et al (2011) Cell cycle-related kinase is a direct androgen receptor-regulated gene that drives β-catenin/ T cell factor-dependent hepatocarcinogenesis. J Clin Invest 121:3159–3175

Ferré P, Foufelle F (2010) Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c. Diabetes Obes Metab 12(Suppl 2):83–92

Filipe A, McLauchlan J (2015) Hepatitis C virus and lipid droplets: finding a niche. Trends Mol Med 21:34–42

Floreani A, Farinati F (2013) Risk factors associated with hepatocellular carcinoma in primary biliary cirrhosis. Hepatology 58:1520–1521

French SW (2013) Epigenetic events in liver cancer resulting from alcoholic liver disease. Alcohol Res 35:57–67

Fujinaga H, Tsutsumi T, Yotsuyanagi H, Moriya K, Koike K (2011) Hepatocarcinogenesis in hepatitis C: HCV shrewdly exacerbates oxidative stress by modulating both production and scavenging of reactive oxygen species. Oncology 81(Suppl 1):11–17

Gatselis NK, Nitaios G, Makaritsis K, Dalekos GN (2014) Adiponectin: a key playmaker adipocytokine in non-alcoholic fatty liver disease. Clin Exp Med 14:121–131

Gelfand MM, Wiita B (1997) Androgen and estrogen-androgen hormone replacement therapy: a review of the safety literature, 1941 to 1996. Clin Ther 19:383–404

Gentric G, Maillet V, Paradis V, Couton D, L'Hermitte A, Panasyuk G, Fromenty B, Celton-Morizur S, Desdouets C (2015) Oxidative stress promotes pathologic polyploidization in nonalcoholic fatty liver disease. J Clin Invest. doi:10.1172/JCI73957

Geramizadeh B, Nikeghbalian S, Shamsaifar A, Kazemi K, Malekhosseini SA (2013) Hepatocellular carcinoma in two patients with autoimmune hepatitis, a single center experience and review of the literature. Hepat Mon 13, e7957

Giannitrapani L, Soresi M, La Spada E, Cervello M, D'Alessandro N, Montalto G (2006) Sex hormones and risk of liver tumor. Ann N Y Acad Sci 1089:228–236

Gips CH (1972) Membranous obstruction of the inferior vena cava as a cause of macronodular cirrhosis. Lancet 2:655–656

Gips CH, Blickman JR, Bredée JJ, Dorlas JC, Eygelaar A, Hekking EJ, Hoedemaeker PJ et al (1972) Membranous obstruction of the suprahepatic segment of the inferior vena cava. Diagnostic and therapeutic considerations; the importance of anticoagulation. Folia Med Neerlandica 15:228–239

Glassberg and Rosenbaum 1976. http://www.ncbi.nlm.nih.gov/pubmed/55736

Gong P, Zhang X, Zhang J, Zhang J, Luo H, Wang Z (2013) Hepatitis B virus X in the proliferation of hepatocellular carcinoma cells. Front Biosci 18:1256–1265

Goodman ZD, Ishak KG (1982) Hepatocellular carcinoma in women: probably lack of etiologic association with oral contraceptive steroids. Hepatology 2:440–444

Gramantieri L, Melchiorri C, Chieco P, Gaiani S, Stecca B, Casali A, Bolondi L (1996) Alteration of DNA ploidy and cell nuclearity in human hepatocellular carcinoma associated with HBV infection. J Hepatol 25:848–853

Guckelberger O, Bechstein WO, Nüssler NC, Radke C, Neuhaus P (1998) Hepatocellular carcinoma in patients suffering from primary sclerosing cholangitis. J Hepatol 29:513–514

Guerreri F, Belloni L, Pediconi N, Levrero M (2013) Molecular mechanisms of HBV-associated hepatocarcinogenesis. Semin Liver Dis 33:147–156

Gupta N, Rastogi A, Bihari C (2014) Steatohepatitic hepatocellular carcinoma – a case report with literature review. Indian J Surg Oncol 5:161–163

Guyot E, Sutton A, Rufat P, Laquillier C, Mansouri A, Moreau R, Ganne-Carrrié N et al (2013) PNPLA3 rs738409, hepatocellular carcinoma occurrence and risk model prediction in patients with cirrhosis. J Hepatol 58:312–318

Gwon D, Ko GY, Yoon HK, Sung KB, Kim JH, Lee SS, Lee JM, Ohm JY, Shin JH (2010) Hepatocellular carcinoma associated with membranous obstruction of the inferior vena cava: incidence, characteristics, and risk factors and clinical efficacy of TACE. Radiology 254:617–626

Gyorrfy EJ, Bredfeldt JE, Black WC (1989) Transformation of hepatic cell adenoma to hepatocellular carcinoma due to oral contraceptive use. Ann Intern Med 110:489–490

Haid S, Grethe C, Dill MT, Heim M, Kaderali L, Pietschmann T (2014) Isolate-dependent use of claudins for cell entry by hepatitis C virus. Hepatology 59:24–34

Hajarizadeh B, Grebely J, Dore GJ (2013) Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol 10:553–562

Hamed MA, Ali SA (2013) Non-viral factors contributing to hepatocellular carcinoma. World J Hepatol 5:311–322

Hamid AS, Tesfamariam IG, Zhang Y, Zhang ZG (2013) Aflatoxin B1-induced hepatocellular carcinoma in developing countries: geographical distribution, mechanism of action and prevention. Oncol Lett 5:1087–1092

Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ (2007) Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioners's oral contraceptive study. BMJ 335:651

Harada K, Hirohara J, Ueno Y, Nakano T, Kakuda Y, Tsubouchi H, Ichida T, Nakanuma Y (2013) Incidence of and risk factors for hepatocellular carcinoma in primary biliary cirrhosis: national data from Japan. Hepatology 57:1942–1949

Hardee JT, Breth GF, El-Serag HB (2003) Hepatocellular carcinoma associated with autoimmune hepatitis. J Clin Gastroenterol 37:271–272

Harris HJ, Davis C, Mullins JG, Hu K, Goodall M, Farquhar MJ, Mee CJ, McCaffrey K et al (2010) Claudin association with CD81 defines hepatitis C virus entry. J Biol Chem 285:21092–21102

Hasan F, Jeffers LJ, De Medina M, Reddy KR, Parker T, Schiff ER, Houghton M et al (1990) Hepatitis C-associated hepatocellular carcinoma. Hepatology 12:589–591

Hashimoto E, Tokushige K (2012) Hepatocellular carcinoma in non-alcoholic steatohepatitis: growing evidence of an epidemic? Hepatol Res 42:1–14

Hassan MM, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, Javle M, Moghazy DM et al (2010) Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer 116:1938–1946

Hassan MM, Kaseb A, Etzel CJ, El-Serag H, Spitz MR, Chang P, Hale KS, Liu M et al (2013) Genetic variation in the PNPLA3 gene and hepatocellular carcinoma in USA: risk and prognosis prediction. Mol Carcinog 52(Suppl 1):139–147

Hautekeete ML, Brenard R, Hadengue A, Degott C, Babany G, Arrive L, Lebrec D et al (1990) Membranous obstruction of the inferior vena cava and hepatocellular carcinoma in a Caribbean patient. J Clin Gastroenterol 12:214–217

Havlioglu N, Brunt EM, Bacon BR (2003) Budd-Chiari syndrome and hepatocellular carcinoma: a case report and review of the literature. Am J Gastroenterol 98:201–204

Helle F, Dubuisson J (2008) Hepatitis C virus entry into host cells. Cell Mol Life Sci 65:100–112

Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL et al (2012) Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature 482:179–185

Henderson JT, Richmond J, Sumerling MD (1973) Androgenic-anabolic steroid therapy and hepatocellular carcinoma. Lancet 1:934

Henderson BE, Benton B, Edmondson HA (1976) Letter: hepatocellular carcinoma and oral contraceptives. JAMA 236:560

Henderson BE, Preston-Martin S, Edmondson HA, Peters RL, Pike MC (1983) Hepatocellular carcinoma and oral contraceptives. Br J Cancer 48:437–440

Henkler FF, Koshy R (1996) Hepatitis B virus transcriptional activators: mechanisms and possible role in oncogenesis. J Viral Hepat 3:109–121

Henry SH, Bosch FX, Bowers JC (2002) Aflatoxin, hepatitis and worldwide liver cancer risks. Adv Exp Med Biol 504:229–233

Herzer K, Gerken G, Hofmann TG (2014) Hepatitis C-associated liver carcinogenesis: role of PML nuclear bodies. World J Gastroenterol 20:12367–12371

Hino-Arinaga T, Ide T, Kuromatsu R, Miyajima I, Ogata K, Kuwahara R, Hisamochi A et al (2012) Risk factors for hepatocellular carcinoma in Japanese patients with autoimmune hepatitis type 1. J Gastroenterol 47:569–576

Holder LE, Gnarra DJ, Lampkin BC, Nishiyama H, Perkins P (1975) Hepatoma associated with anabolic steroid therapy. Am J Roentgenol Ther Nucl Med 124:638–642

Hoshida Y, Fuchs BC, Bardeesy N, Baumert TF, Chung RT (2014) Pathogenesis and prevention of hepatitis C virus-induced hepatocellular carcinoma. J Hepatol 61(Suppl 1):S79–S90

Hosonuma K, Sato K, Yanagisawa M, Kakizaki S, Takagi H, Hirato J, Mori M (2013) Incidence, mortality, and predictive factors of hepatocellular carcinoma in primary biliary cirrhosis. Gastroenterol Res Pract 2013:168012

Houldsworth et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24122777

Hromas RA, Srigley J, Murray JL (1985) Clinical and pathological comparison of young adult women with hepatocellular carcinoma with and without exposure to oral contraceptives. Am J Gastroenterol 80:479–485

Huang P, Xu X, Wang L, Zhu B, Wang X, Xia J (2014) The role of EGF-EGFR signaling pathway in hepatocellular carcinoma inflammatory microenvironment. J Cell Mol Med 18:218–230

Iannaccone R, Piacentini F, Murakami T, Paradis V, Belghiti J, Hori M, Kim T, Durand F et al (2007) Hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: helical CT and MR imaging findings with clinical-pathologic comparison. Radiology 243:422–430

Ibarrola C, Castellano VM, Colina F (2004) Focal hyperplastic hepatocellular nodules in hepatic venous outflow obstruction: a clinicopathological study of four patients and 24 nodules. Histopathology 44:172–179

Idilman R, De Maria N, Colantoni A, Van Thiel DH (1998) Pathogenesis of hepatitis B and C-induced hepatocellular carcinoma. J Viral Hepat 5:285–299

Ikeda A, Shimizu T, Matsumoto Y, Fujii Y, Eso Y, Inuzuka T, Mizuguchi A, Shimizu K et al (2014) Leptin receptor somatic mutations are frequent in HCV-infected cirrhotic liver and associated with hepatocellular carcinoma. Gastroenterology 146:222–232

Ikura Y, Mita E, Nakamori S (2011) Hepatocellular carcinomas can develop in simple fatty livers in the setting of oxidative stress. Pathology 43:167–168

Imam MH, Silveira MG, Sinakos E, Gossard AA, Jorgensen R, Keach J, DeCook AC et al (2012) Long-term outcomes of patients with primary biliary cirrhosis and hepatocellular carcinoma. Clin Gastroenterol Hepatol 10:182–185

Irshad M, Dhar I (2006) Hepatitis C virus core protein: an update on its molecular biology, cellular functions and clinical implications. Med Princ Pract 15:405–416

Ishida M, Naka S, Shiomi H, Tasujikawa T, Andoh A, Nakahara T, Saito Y, Kurumi Y et al (2010) Hepatocellular carcinoma occurring in a Crohn's disease patient. World J Gastroenterol 16:3215–3218

Ismail T, Angrisani L, Hübscher S, McMaster P (1991) Hepatocellular carcinoma complicating primary sclerosing cholangitis. Br J Surg 78:360–361

Jahan S, Ashfaq UA, Qasim M, Khaliq S, Saleem MJ, Afzal N (2012) Hepatitis C virus to hepatocellular carcinoma. Infect Agent Cancer 7:2

Jain D, Nayak NC, Saigal S (2012) Hepatocellular carcinoma in nonalcoholic fatty liver cirrhosis and alcoholic cirrhosis: risk factor analysis in liver transplant recipients. Eur J Gastroenterol Hepatol 24:840–848

Jang JY, Chung RT (2011) Chronic hepatitis C. Gut Liver 5:117–132

Jang JW, Yoon SK, Bae SH, Choi JY, Chung KW, Sun HS (2003) Rapidly progressing Budd-Chiari syndrome complicated by hepatocellular carcinoma. Korean J Intern Med 18:191–195

Jaskiewicz K, Stephen A, Banach L (1991) Hepatocellular carcinoma in a rural population at risk. Anticancer Res 11:2187–2190

Jeong SW, Jang JY, Chung RT (2012) Hepatitis C virus and hepatocarcinogenesis. Clin Mol Hepatol 18:347–356

Ji X, Zhang Q, Du Y, Liu W, Li Z, Hou X, Cao G (2014) Somatic mutations, viral integration and epigenetic modification in the evolution of hepatitis B virus-induced hepatocellular carcinoma. Curr Genomics 15:469–480

Jie X, Lang C, Jian Q, Chaoqun L, Dehua Y, Yi S, Yanping J, Luokun X, Qiuping Z et al (2007) Androgen activates PEG10 to promote carcinogenesis in hepatic cancer cells. Oncogene 26:5741–5751

Jin DY (2007) Molecular pathogenesis of hepatitis C virus-associated hepatocellular carcinoma. Front Biosci 12:222–233

Johnson FL, Lerner KG, Siegel M, Faegler JR, Majerus PW, Hartmann JR, Thomas ED (1972) Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. Lancet 2: 1273–1276

Kalra M, Mayes J, Assefa S, Kaul AK, Kaul R (2008) Role of sex steroid receptors in pathobiology of hepatocellular carcinoma. World J Gastroenterol 14:5945–5961

Kanda T, Steele R, Ray R, Ray RB (2008) Hepatitis C virus core protein augments androgen receptor-mediated signaling. J Virol 82:11066–11072

Kannan RP, Hensley LL, Evers LE, Lemon SM, McGivern DR (2011) Hepatitis C virus infection causes cell cycle arrest at the level of initiation of mitosis. J Virol 85:7989–8001

Kapp N, Curtis KM (2009) Hormonal contraceptive use among women with liver tumors: a systematic review. Contraception 80:387–390

Karia K, Mathur SK, Amarapurkar D, Punamiya SJ (2000) Hepatocellular carcinoma in association with membranous obstruction of inferior vena cava. Indian J Gastroenterol 19:90–91

Katoh M, Shigematsu H (1999) Primary liver carcinoma complicating membranous obstruction of the inferior vena cava. Pathol Int 49:253–257

Kawai H, Nomoto M, Suda T, Kamimura K, Tsuchiya A, Tamura Y, Yano M, Takamura M et al (2011) Multicentric occurrence of hepatocellular carcinoma with nonalcoholic steatohepatitis. World J Hepatol 3:15–23

Ke PY, Chen SS (2012) Hepatitis C virus and cellular stress response: implications to molecular pathogenesis of liver diseases. Viruses 4:2251–2290

Kedda MA, Kew MC, Coppin A (1997) Hepatocarcinogenic effect of genotype 5 of hepatitis C virus. Trop Gastroenterol 18:153–155

Kew MC (1994) Hepatitis C virus and hepatocellular carcinoma. FEMS Microbiol Rev 14:211–219

Kew MC (2000) Epidemiology of hepatocellular carcinoma and its viral risk factors. Acta Gastroenterol Belg 63:227–229

Kew MC (2010a) Hepatocellular carcinoma in African Blacks. Recent progress in etiology and pathogenesis. World J Hepatol 2:65–73

Kew MC (2010b) Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. Pathol Biol (Paris) 58:273–277

Kew MC (2011) Hepatitis B virus x protein in the pathogenesis of hepatitis B virus-induced hepatocellular carcinoma. J Gastroenterol Hepatol 26(Suppl 1):144–152

Kew MC (2012) Hepatocellular carcinoma in developing countries: prevention, diagnosis and treatment. World J Hepatol 4:99–104

Kew MC (2013) Aflatoxins as a cause of hepatocellular carcinoma. J Gastrointest Liver Dis 22:305–310

Kew MC, Hodgkinson HJ (2006) Membranous obstruction of the inferior vena cava and its causal relation to hepatocellular carcinoma. Liver Int 26:1–7

Kew MC, Popper H (1984) Relationship between hepatocellular carcinoma and cirrhosis. Semin Liver Dis 4:136–146

Kew MC, Van Coller B, Prowse CM, Skikne B, Wolfsdorf JI, Isdale J, Krawitz S, Altman H et al (1976) Occurrence of primary hepatocellular cancer and peliosis hepatis after treatment with androgenic steroids. S Afr Med J 50:1233–1237

Kew MC, Ray MB, Desmet VJ, Desmyter J (1980) Hepatitis-B surface antigen in tumour tissue and

non-tumorous liver in black patients with hepatocellular carcinoma. Br J Cancer 41:399–406
Kew MC, McKnight A, Hodgkinson J, Bukofzer S, Esser JD (1989) The role of membranous obstruction of the inferior vena cava in the etiology of hepatocellular carcinoma in Southern African blacks. Hepatology 9:121–125
Kikuchi L, Oliveira CP, Carrilho FJ (2014) Nonalcoholic fatty liver disease and hepatocellular carcinoma. Biomed Res Int 2014:106247
Kim CW, Chang KM (2013) Hepatitis C virus: virology and life cycle. Clin Mol Hepatol 19:17–25
Kimura C, Matsuda S, Maetani S, Iwahashi K, Terada M, Hrooka M, Yamamoto K (1965) Obstruction of inferior vena cava with special reference to membranous obstruction of its hepatic portion. Thoraxchir Vask Chir 12:430–439
Koike K (2014) The oncogenic role of hepatitis C virus. Recent Results Cancer Res 193:97–111
Koike K, Tsutsumi T, Yotsuyanagi H, Moriya K (2010) Lipid metabolism and liver disease in hepatitis C viral infection. Oncology 78(Suppl 1):24–30
Kong L, Giang E, Nieusma T, Kadam RU, Cogburn KE, Hua Y, Dai X, Stanfield RL et al (2013) Hepatitis C virus E2 envelope glycoprotein core structure. Science 342:1090–1094
Koo SH (2013) Nonalcoholic fatty liver disease: molecular mechanisms for the hepatic steatosis. Clin Mol Hepatol 19:210–215
Korula J, Yellin A, Kanel G, Campofiori G, Nichols P (1991) Hepatocellular carcinoma coexisting with hepatic adenoma. Incidental discovery after long-term oral contraceptive use. West J Med 155:416–418
Kosaka A, Takahashi H, Yajima Y, Tanaka M, Okamura K, Mizumoto R, Katsuta K (1996) Hepatocellular carcinoma associated with anabolic steroid therapy: report of a case and review of the Japanese literature. J Gastroenterol 31:450–454
Krasner N, Johnson PJ, Portmann B, Watkinson G, Macsween RN, Williams R (1979) Hepatocellular carcinoma in primary biliary cirrhosis: report of four cases. Gut 20:255–258
Kudo A, Tanaka S, Ban D, Matsumura S, Irie T, Ochiai T, Nakamura N, Arii S, Tanabe M (2014) Alcohol consumption and recurrence of non-B or non-C hepatocellular carcinoma after hepatectomy: a propensity score analysis. J Gastroenterol 49: 1352–1361
Kuiper EM, Hansen BE, Adang RP, van Nieuwkerk CM, Timmer R, Drenth JP, Spoelstra P et al (2010) Relatively high risk for hepatocellular carcinoma in patients with primary biliary cirrhosis not responding to ursodeoxycholic acid. Eur J Gastroenterol Hepatol 22:1495–1502
La Vecchia C, Bosetti C (2009) Oral contraceptives and neoplasms other breast and female genital tract. Eur J Cancer Prev 18:407–411
Leclère J, Meot B, Marchal F, Mizrahi R, Collard F, Rauber G, Hartemann P (1977) Liver cell carcinoma associated with oral contraceptives (in French). Ann Endocrinol (Paris) 38:361–362
Lee AT, Lee CG (2007) Oncogenesis and transforming viruses: the hepatitis B virus and hepatocellular carcinoma – the etiopathologic link. Front Biosci 12:234–245
Lee SS, Jeong SH, Byoun YS, Chung SM, Seong MH, Sohn HR, Min BY, Jang ES et al (2013) Clinical features and outcome of cryptogenic hepatocellular carcinoma compared to those of viral and alcoholic hepatocellular carcinoma. BMC Cancer 13:335
Lee MH, Yang HI, Yuan Y, L'Italien G, Chen CJ (2014a) Epidemiology and natural history of hepatitis C virus infection. World J Gastroenterol 20:9270–9280
Lee CH, Kim JH, Lee SW (2014b) The role of microRNAs in hepatitis C virus replication and related liver diseases. J Microbiol 52:445–451
Lee MH, Yang HI, Lu SN, Jen CL, You SL, Wang LY, L'Italien G, Chen CJ, Yuan Y et al (2014c) Hepatitis C virus genotype 1b increases cumulative lifetime risk of hepatocellular carcinoma. Int J Cancer 135:1119–1126
Leidenius M, Höckersted K, Broomé U, Ericzon BG, Friman S, Olausson M, Schrumpf E (2001) Hepatobiliary carcinoma in primary sclerosing cholangitis: a case control study. J Hepatol 34:792–798
Levrero M (2006) Viral hepatitis and liver cancer: the case of hepatitis C. Oncogene 25:3834–3847
Li Z, Tuteja G, Schug J, Kaestner KH (2012) Foxa1 and Foxa2 are essential for sexual dimorphism in liver cancer. Cell 148:72–83
Li X, Yang W, Ye W, Jin L, He J, Lou L (2014) microRNAs: novel players in hepatitis C virus infection. Clin Res Hepatol Gastroenterol. doi:10.1016/j.clinre.2014.04.008
Lin and Kao 2011. http://www.ncbi.nlm.nih.gov/pubmed/21199523
Lin CW, Lin CC, Mo LR, Chang CY, Perng DS, Hsu CC, Lo GH, Chen YS, Yen YC et al (2013) Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol 58:730–735
Lin MV, King LY, Chung RT (2015) Hepatitis C virus-associated cancer. Annu Rev Pathol 10:345–370
Linares M, Pastor E, Gomez A, Grau E (1991) Hepatocellular carcinoma and squamous cell carcinoma in a patient with Fanconi's anemia. Ann Hematol 63:54–55
Linsell A (1984) Primary liver cancer: global epidemiology and main aetiological factors. Ann Acad Med Singapore 13:185–189
Linsell CA, Peers FG (1972) The aflatoxins and human liver cancer. Recent Results Cancer Res 39:125–129
Linsell CA, Peers FG (1977) Aflatoxin and liver cell cancer. Trans R Soc Trop Med Hyg 71:471–473
Liu J, Wang Z, Tang J, Shan X, Zhang W, Chen Q, Zhou F, Chen K, Huang A, Tang N (2011) Hepatitis C virus core protein activates Wnt/β-catenin signaling through multiple regulation of upstream molecules in the SMMC-7721 cell line. Arch Virol 156:1013–1023

Liu YL, Patman GL, Leathart JB, Piguet AC, Burt AD, Dufour JF, Day CP, Daly AK et al (2014) Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol 61:75–81

Lomonaco R, Sunny NE, Bril F, Cusi K (2013) Nonalcoholic fatty liver disease: current issues and novel treatment approaches. Drugs 73:1–14

Lonardo A, Adinolfi LE, Restivo L, Ballestri S, Romagnoli D, Baldelli E, Nascimbeni F, Loria P (2014) Pathogenesis and significance of hepatitis C virus steatosis: an update on survival strategy of a successful pathogen. World J Gastroenterol 20:7089–7103

Long XD, Zhao D, Wang C, Huang XY, Yao JG, Ma Y, Wei ZH, Liu M, Zeng LX et al (2013) Genetic polymorphisms in DNA repair genes XRCC4 and XRCC5 and aflatoxin B1-related hepatocellular carcinoma. Epidemiology 24:671–681

Loomba R, Sanyal AJ (2013) The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 10:686–690

Luber B, Arnold N, Sturzl M, Höhne M, Schirmacher P, Lauer U et al (1996) Hepatoma-derived integrated HBV DNA causes multistage transformation in vitro. Oncogene 12:1597–1608

Lutwick LI (1979) Relation between aflatoxin, hepatitis-B virus, and hepatocellular carcinoma. Lancet 1: 755–757

Ma WL, Hsu CL, Yeh CC, Wu MH, Huang CK, Jeng LB, Hung YC, Lin TY, Yeh S et al (2012) Hepatic androgen receptor suppresses hepatocellular carcinoma metastasis through modulation of cell migration and anoikis. Hepatology 56:176–185

Macaron C, Hanouneh IA, Zein NN (2010) Incidence and risk factors of hepatocellular carcinoma in patients with primary biliary cirrhosis. Hepatology 52:2239

Mak KM, Kwong AJ, Chu E, Hoo NM (2012) Hepatic steatosis, fibrosis, and cancer in elderly cadavers. Anat Rec (Hoboken) 295:40–50

Mallet L, Petite JP, Amat D, Bloch F, Juillet Y, Camilléri JP, Housset E (1981) Hepatocellular carcinoma and primary biliary cirrhosis: report of one case (in French). Gastroenterol Clin Biol 5:379–384

Mangia A, Ripoli M (2013) Insulin resistance, steatosis and hepatitis C virus. Hepatol Int 7(Suppl 2):782–789

Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS (2005) Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol 42:218–224

Martin DN, Uprichard SL (2013) Identification of transferrin receptor 1 as a hepatitis C virus entry factor. Proc Natl Acad Sci U S A 110:10777–10782

Mathai AM, Alexander J, Kuo FY, Torbenson M, Swanson PE, Yeh MM (2013) Type II ground-glass hepatocytes as a marker of hepatocellular carcinoma in chronic hepatitis B. Hum Pathol 44:1665–1671

Matsui S, Ichida T, Watanabe M, Sugitani S, Suda T, Takahashi T, Asakura H (2000) Clinical features and etiology of hepatocellular carcinoma arising in patients with membranous obstruction of the inferior vena cava: in reference to hepatitis viral infection. J Gastroenterol Hepatol 15:1205–1211

Matsuzaki K, Murata M, Yoshida K, Sekimoto G, Uemura Y, Sakaida N, Kaibori M et al (2007) Chronic inflammation associated with hepatitis C virus infection perturbs hepatic transforming growth factor beta signaling, promoting cirrhosis and hepatocellular carcinoma. Hepatology 46:48–57

Meadows AT, Naiman JL, Valdes-Dapena M (1974) Hepatoma associated with androgen therapy for aplastic anemia. J Pediatr 84:109–110

Mee et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/17959672

Mee et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/19944696

Menzies-Gow N (1978) Hepatocellular carcinoma associated with oral contraceptives. Br J Surg 65:316–317

Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E (2015) Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 61:77–87

Michelotti GA, Machado MV, Diehl AM (2013) NAFLD, NASH and liver cancer. Nat Rev Gastroenterol Hepatol 10:656–665

Migita K, Watanabe Y, Jiuchi Y, Nakamura Y, Saito A, Yagura M, Ohta H, Shimada M et al (2012) Hepatocellular carcinoma and survival in patients with autoimmune hepatitis (Japanese National Hospital Organization – autoimmune hepatitis prospective study). Liver Int 32:837–844

Milic S, Stimac D (2012) Nonalcoholic fatty liver disease/steatohepatitis: epidemiology, pathogenesis, clinical presentation and treatment. Dig Dis 30:158–162

Milward A, Mankouri J, Harris M (2010) Hepatitis C virus NS5A protein interacts with β-catenin and stimulates its transcriptional activity in a phosphoinositide-3 kinase-dependent fashion. J Gen Virol 91:373–381

Mohan P, Sukumar R, Surendran R, Sathyabhama C, Jayanthi V (2009) Hepatocellular carcinoma in membranous obstruction of the inferior vena cava – a causal or casual presentation. J Gastrointest Liver Dis 18:254–255

Morgan TR, Mandayam S, Jamal MM (2004) Alcohol and hepatocellular carcinoma. Gastroenterology 127: S87–S96

Mori W, Machinami R, Tanaka K (1980) Pathology of hepatocellular carcinoma. Pathol Res Pract 169:4–20

Motavaf M, Safari S, Saffari JM, Alavian SM (2013) Hepatitis B virus-induced hepatocellular carcinoma: the role of the virus x protein. Acta Virol 57:389–396

Motoo Y, Wakatsuki T, Tanaka N, Hinoue Y, Kobayashi K, Hattori N, Matsui O, Izumi R et al (1989) Resected case of hepatocellular carcinoma associated with lupoid hepatitis. J Gastroenterol Hepatol 4:295–298

Muir K, Hazim A, He Y, Peyressatre M, Kim DY, Song X, Beretta L (2013) Proteomic and lipidomic signatures of lipid metabolism in NASH-associated hepatocellular carcinoma. Cancer Res 73:4722–4731

Munaka M, Kohshi K, Kawamoto T, Takasawa S, Nagata N, Itoh H, Oda S, Katoh T (2003) Genetic polymorphisms of tobacco- and alcohol-metabolizing enzymes and the risk of hepatocellular carcinoma. J Cancer Res Clin Oncol 129:355–360

Murakami S (2001) Hepatitis B virus X protein: a multifunctional viral regulator. J Gastroenterol 36:651–660

Nagasue N, Yu L, Yukaya H, Kohno H, Nakamura T (1995) Androgen and estrogen receptors in hepatocellular carcinoma and surrounding liver parenchyma: impact on intrahepatic recurrence after hepatic resection. Br J Surg 82:542–547

Nakamura S (1982) Membranous obstruction of the inferior vena cava and hepatocellular carcinoma. Gastroenterology 83:728

Nakamura S, Takezawa Y (1982) Obstruction of the inferior vena cava in the hepatic portion and hepatocellular carcinoma. Tohoku J Exp Med 138:119–120

Neuberger J, Forman D, Doll R, Williams R (1986) Oral contraceptives and hepatocellular carcinoma. Br Med J (Clin Res Ed) 292:1355–1357

Newerla C, Schaeffer F, Terraciano L, Hohmann J (2012) Multiple FNH-like lesions in a patient with chronic Budd-Chiari syndrome: Gd-EOB-enhanced MRI and Br1 CEUS findings. Case Rep Radiol 2012:685486

Ng SA, Lee C (2011) Hepatitis B virus X gene and hepatocarcinogenesis. J Gastroenterol 46:974–990

Ng J, Wu J (2012) Hepatitis B- and hepatitis C-related hepatocellular carcinomas in the United States: similarities and differences. Hepat Mon 12, e7635

Nishikawa H, Osaki Y (2013) Non-B, non-C hepatocellular carcinoma (review). Int J Oncol 43:1333–1342

Njei B, Rotman Y, Ditah I, Lim JK (2015) Emerging trends in hepatocellular carcinoma incidence and mortality. Hepatology 61:191–199

Nkontchou G, Ziol M, Aout M, Lhabadie M, Baazia Y, Mahmoudi A, Roulot D, Ganne-Carrie N et al (2011) HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. J Viral Hepat 18:e516–e522

Nzeako UC, Goodman ZD, Ishak KG (1996) Hepatocellular carcinoma and nodular regenerative hyperplasia: possible pathogenetic relationship. Am J Gastroenterol 91:879–884

Ogata et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/21173811

Ohata K, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, Abiru S, Nakagawa Y et al (2003) Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. Cancer 97:3036–3043

Ohira H, Abe K, Takahashi A, Zeniya M, Ichida T (2013) Clinical features of hepatocellular carcinoma in patients with autoimmune hepatitis in Japan. J Gastroenterol 48:109–114

Okuda K (1982) Membranous obstruction of the inferior vena cava: etiology and relation to hepatocellular carcinoma. Gastroenterology 82:376–379

Okuda K (1995) Hepatocellular carcinomas associated with hepatitis B and C virus infections: are they any different ? Hepatology 22:1883–1885

Oya H, Sato Y, Yamamoto S, Takeishi T, Kobayashi T, Hatakeyama K (2004) Living related donor liver transplantation for primary sclerosing cholangitis with hepatocellular carcinoma and Crohn's disease: a case report. Transplant Proc 36:2297–2298

Ozenne V, Paradis V, Vuillerme MP, Vilgrain V, Leblanc T, Belghiti J, Imbert A, Valla DC, Degos F (2008) Liver tumours in patients with Fanconi anaemia: a report of three cases. Eur J Gastroenterol Hepatol 20:1036–1039

Palmer JR, Rosenberg L, Kaufman DW, Warshauer ME, Stolley P, Shapiro S (1989) Oral contraceptive use and liver cancer. Am J Epidemiol 130:878–882

Paracha UZ, Fatima K, Algahtani M, Chaudhary A, Abuzenadah A, Damanhouri G, Qadri I (2013) Oxidative stress and hepatitis C virus. Virol J 10:251

Park et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19726098

Park YM (2015) Clinical utility of complex mutations in the core promoter and proximal precore regions of the hepatitis B virus genome. World J Hepatol 7:113–120

Park SZ, Nagorney DM, Czaja AJ (2000) Hepatocellular carcinoma in autoimmune hepatitis. Dig Dis Sci 45:1944–1948

Patel A, Harrison SA (2012) Hepatitis C virus infection and nonalcoholic steatohepatitis. Gastroenterol Hepatol (NY) 8:305–312

Pauwels A, Desaint B, Legendre C, Cardranel JF, Florent C, Lévy VG (1987) Hepatocellular carcinoma and autoimmune chronic active hepatitis (in French). Gastroenterol Clin Biol 11:432–433

Peers FG, Linsell CA (1977) Dietary aflatoxins and human primary liver cancer. Ann Nutr Aliment 31:1005–1017

Peers F, Bosch X, Kaldor J, Linsell A, Plujimen M (1987) Aflatoxin exposure, hepatitis B virus infection and liver cancer in Swaziland. Int J Cancer 39:545–553

Pekow JR, Bhan AK, Zheng H, Chung RT (2007) Hepatic steatosis is associated with increased frequency of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. Cancer 109:2490–2496

Perrault M, Pécheur EI (2009) The hepatitis C virus and its hepatic environment: a toxic but finely tuned partnership. Biochem J 423:303–314

Persson EC, Schwartz LM, Park Y, Trabert B, Hollenbeck AR, Graubard BI, Freedman ND et al (2013) Alcohol consumption, folate intake, hepatocellular carcinoma, and liver disease mortality. Cancer Epidemiol Biomarkers Prev 22:415–421

Pila PR, Pila PR, Rosales TP, Holguin Priteo VA, Alzate Giraldo LF (2007) Sarcoidosis and fibrolamellar carcinoma of the liver (in Spanish). An Med Interna 24:431–434

Prentice RL (1991) Epidemiologic data on exogenous hormones and hepatocellular carcinoma and selected other cancers. Prev Med 20:38–46

Pryor AC, Cohen RJ, Goldman RL (1977) Hepatocellular carcinoma in a woman on long-term oral contraceptives. Cancer 40:884–888

Purohit V, Rapaka R, Kwon OS, Song BJ (2013) Roles of alcohol and tobacco exposure in the development of hepatocellular carcinoma. Life Sci 92:3–9

Quan H, Zhou F, Nie D, Chen Q, Cai X, Shan X, Zhou Z, Chen K, Huang A, Li S, Tang N (2014) Hepatitis C virus core protein epigenetically silences SFRP1 and enhances HCC aggressiveness by inducing epithelial-mesenchymal transition. Oncogene 33:2826–2835

Rahman R, Hammoud GM, Almashhrawi AA, Ahmed KT, Ibdah JA (2013) Primary hepatocellular carcinoma and metabolic syndrome: an update. World J Gastrointest Oncol 5:186–194

Raimondi S, Bruno S, Mondelli MU, Maisonneuve P (2009) Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. J Hepatol 50:1142–1154

Rappa F, Greco A, Podrini C, Cappello F, Fori M, Bourgoin L, Peyrou M, Marino A et al (2013) Immunopositivity for histone H2A1 isoforms marks steatosis-associated hepatocellular carcinoma. PLoS One 8:e54458

Raptis I, Koskinas J, Emmanouil T, Hadziyannis S (2003) Changing relative roles of hepatitis B and C viruses in the aetiology of hepatocellular carcinoma in Greece. Epidemiological and clinical observations. J Viral Hepat 10:450–454

Reeves ME, DeMatteo RP (2000) Genes and viruses in hepatobiliary neoplasia. Semin Surg Oncol 19:8

Regimbeau JM, Colombat M, Mognol P, Durand F, Abdalla E, Degott C, Degos F et al (2004) Obesity and diabetes as a risk factor for hepatocellular carcinoma. Liver Transpl 10(Suppl 1):S69–S73

Ripoli M, Pazienzia V (2011) Impact of HCV genetic differences on pathobiology of disease. Expert Rev Anti Infect Ther 9:747–759

Rongrui L, Na H, Zongfang L, Fanpu J, Shiwen J (2014) Epigenetic mechanism involved in the HBV/HCV-related hepatocellular carcinoma tumorigenesis. Curr Pharm Des 20:1715–1725

Rosmorduc O (2013) Relationship between hepatocellular carcinoma, metabolic syndrome and non-alcoholic fatty liver disease: which clinical arguments? Ann Endocrinol 74:115–120

Rosmorduc O, Fartoux L (2012) HCC and NASH: how strong is the clinical demonstration? Clin Res Hepatol Gastroenterol 36:202–208

Rowe IA, Galsinh SK, Wilson GK, Parker R, Durant S, Lazar C, Branza-Nichita N et al. (2014) Paracrine signals from liver sinusoidal endothelium regulate hepatitis C virus replication. Hepatology 59:375–384

Russmann S, Zimmermann A, Krähenbühl S, Kern B, Reichen J (2001) Veno-occlusive disease, nodular regenerative hyperplasia and hepatocellular carcinoma after azathioprine treatment in a patient with ulcerative colitis. Eur J Gastroenterol Hepatol 13:287–290

Rustgi VK (2007) The epidemiology of hepatitis C infection in the United States. J Gastroenterol 42:513–521

Rusyn I, Lemon SM (2014) Mechanisms of HCV-induced liver cancer: what did we learn from in vitro and animal studies. Cancer Lett 345:210–215

Salomao M, Yu WM, Brown RS, Emond JC, Lefkowitch JH (2010) Steatohepatitic hepatocellular carcinoma (SH-HCC): a distinctive histological variant of HCC in hepatitis C virus-related cirrhosis with associated NAFLD/NASH. Am J Surg Pathol 34:1630–1636

Salomao M, Remotti H, Vaughan R, Siegel AB, Lefkowitch JH, Moreira RK (2012) The steatohepatitic variant of hepatocellular carcinoma and its association with underlying steatohepatitis. Hum Pathol 43:737–746

Sasaki K, Matsuda M, Ohkura Y, Kawamura Y, Inoue M, Suzuki Y, Hashimoto M, Ikeda K et al. (2014) Clinical significance of hepatectomy for primary biliary cirrhosis patients with hepatocellular carcinoma: report of a single center case series and review of the published work. Hepatol Res 44:474–480

Satake Y, Takada K, Ikeda K, Shiosaka T, Fujia S, Kobayashi Y (1988) A case of primary liver cell cancer complicating lupoid hepatitis. Jpn J Med 27:83–86

Schieck A, Schulze A, Gähler C, Müller T, Haberkorn U, Alexandrov A, Urban S, Mier W (2013) Hepatitis B virus hepatotropism is mediated by specific receptor recognition in the liver and not restricted to susceptible hosts. Hepatology 58:43–53

Schluter V, Meyer M, Hofschneider PH, Koshy R, Caselmann WH (1994) Integrated hepatitis B virus X and 3‘truncated preS/S sequences derived from human hepatomas encode functionally active transactivators. Oncogene 9:3335–3344

Schmidt G (1977) Hepatocellular carcinoma: a possible complication of oral contraceptive steroids. Med J Aust 1:215–217

Schuppan D, Schattenberg JM (2013) Non-alcoholic steatohepatitis: pathogenesis and novel therapeutic approaches. J Gastroenterol Hepatol 28(Suppl 1):68–76

Schütte K, Bornschein J, Kahl S, Seidensticker R, Arend J, Ricke J, Malfertheiner P (2012) Delayed diagnosis of HCC with chronic alcoholic liver disease. Liver Cancer 1:257–266

Selimovic D, El-Khattouti A, Ghozlan H, Youssef H, Abdelkader O, Hassan M (2012) Hepatitis C virus-related hepatocellular carcinoma: an insight into molecular mechanisms and therapeutic strategies. World J Hepatol 4:342–355

Seo JB, Chung JW, Park JH, Kim SH, Kim TK, Han JK, Choi BI, Han MC (1998) Benign obstruction of the hepatic inferior vena cava complicated by hepatocellular carcinoma: combined interventional management. AJR Am J Roentgenol 170:655–659

Shar SR, Kew MC (1982) Oral contraceptives and hepatocellular carcinoma. Cancer 49:407–410

Shawki SM, Meshaal SS, El Dash AS, Zayed NA, Hanna MO (2014) Increased DNA damage in hepatitis C

virus-related hepatocellular carcinoma. DNA Cell Biol 33:884–890
Shen C, Zhao CY, Zhang R, Qiao L (2012) Obesity-related hepatocellular carcinoma: roles of risk factors altered in obesity. Front Biosci (Landmark Ed) 17: 2356–2370
Shlomai A, de Jong YP, Rice CM (2014) Virus associated malignancies: the role of viral hepatitis in hepatocellular carcinoma. Semin Cancer Biol 26:78–88
Shrivastava S, Mukherjee A, Ray RB (2013) Hepatitis C virus infection, microRNA and liver disease progression. World J Hepatol 5:479–486
Siddique A, Kowdley KV (2011) Insulin resistance and other metabolic risk factors in the pathogenesis of hepatocellular carcinoma. Clin Liver Dis 15:281–296
Siegel AB, Zhu AX (2009) Metabolic syndrome and hepatocellular carcinoma: two growing epidemics with a potential link. Cancer 115:5651–5661
Silveira MG, Suzuki A, Lindor KD (2008) Surveillance for hepatocellular carcinoma in patients with primary biliary cirrhosis. Hepatology 48:1149–1156
Simson IW (1982) Membranous obstruction of the inferior vena cava and hepatocellular carcinoma in South Africa. Gastroenterology 82:171–178
Sinn DH, Gwak GY, Cho J, Paik SW, Yoo BC (2014) Comparison of clinical manifestations and outcomes between hepatitis B virus- and hepatitis C virus-related hepatocellular carcinoma: analysis of a nationwide cohort. PLoS ONE 9, e113184
Snook JA, Kelly P, Chapman RW, Jewell DP (1989) Fibrolamellar hepatocellular carcinoma complicating ulcerative colitis with primary sclerosing cholangitis. Gut 30:243–245
Sotaniemi EA, Alavaikko MJ, Kaipanen WJ (1975) Primary liver cancer associated with long-term oestrogen therapy. Ann Clin Res 7:287–289
Srinivas et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22572493
Starley BQ, Calcagno CJ, Harrison SA (2010) Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology 51:1820–1832
Studaeh et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20624918
Su Q, Schroder CH, Hofmann WJ, Otto G, Pichlmayr R, Bannasch P (1998) Expression of hepatitis B virus X protein in HBV-infected human livers and hepatocellular carcinomas. Hepatology 27:1109–1120
Suchato et al. 1977. http://www.ncbi.nlm.nih.gov/pubmed/858736
Sugimoto K, Takei Y (2011) Clinicopathological features of non-alcoholic fatty liver disease. Hepatol Res 41:911–920
Sun and Karin 2012. http://www.ncbi.nlm.nih.gov/pubmed/22120206
Sung WK, Zheng H, Li S, Chen R, Liu X, Li Y, Lee NP, Ariyaratne PN, Tennakoon C et al (2012) Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma. Nat Genet 44:65–769
Syed GH, Amako Y, Siddiqui A (2010) Hepatitis C virus hijacks host lipid metabolism. Trends Endocrinol Metab 21:33–40
Takaki Y, Saito Y, Takasugi A, Toshimitsu K, Yamada S, Muramatsu T, Kimura M, Sugiyama K, Suzuki H, Arai E et al (2014) Silencing of microRNA-122 is an early event during hepatocarcinogenesis from non-alcoholic steatohepatitis. Cancer Sci 105:1254–1260
Takamura M, Ichida T, Yokoyama J, Matsuda Y, Nomoto M, Aoyagi Y (2004) Recurrence of hepatocellular carcinoma 102 months after successful eradication and removal of membranous obstruction of the inferior vena cava. J Gastroenterol 39:681–684
Takayasu K, Muramatsu Y, Moriyama N, Wakao F, Makuuchi M, Takayama T, Kosuge T et al (1994) Radiological study of idiopathic Budd-Chiari syndrome complicated by hepatocellular carcinoma. A report of four cases. Am J Gastroenterol 89: 249–253
Tanaka M, Wanless IR (1998) Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. Hepatology 27:488–496
Tanaka Y, Kanai F, Ichimura T, Tateishi K, Asaoka Y, Guleng B, Jazag A, Ohta M et al (2006) The hepatitis B virus X protein enhances AP-1 activation through interaction with Jab1. Oncogene 25:635–642
Tanaka S, Miyanishi K, Kobune M, Kawano Y, Hoki T, Kubo T, Hayashi T, Sato T et al (2013) Increased hepatic oxidative DNA damage in patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. J Gastroenterol 48:1249–1258
Tarocchi M, Polvani S, Marroncini G, Galli A (2014) Molecular mechanism of hepatitis B virus-induced hepatocarcinogenesis. World J Gastroenterol 20:11630–11640
Thomas DB (1991) The WHO Collaborative Study on neoplasia and Steroid Contraceptives: the influence of combined oral contraceptives on risk of neoplasms in developing and developed countries. Contraception 43:695–710
Thomas DL (2013) Global control of hepatitis C: where challenge meets opportunity. Nat Med 19:850–858
Thomas D, Brechot C, Spitzer WO, Watanabe S, Beral V, Meirik O (1997) Oral contraceptives and liver cancer: results of the multicenter international liver tumor study (MILTS). Contraception 56:275–284
Thung SN, Bach N, Fasy TM, Jordon D, Schaffner F (1990) Hepatocellular carcinoma associated with autoimmune chronic active hepatitis. Mt Sinai J Med 57:165–168
Tian Y, Wong VW, Chan HL, Cheng AS (2013) Epigenetic regulation of hepatocellular carcinoma in non-alcoholic fatty liver disease. Semin Cancer Biol 23:471–482
Tokushige K, Hashimoto E, Horie Y, Taniai M, Higuchi S (2011) Hepatocellular carcinoma in Japanese patients with nonalcoholic fatty liver disease, alcoholic liver disease, and chronic liver disease of unknown etiology:

report of the nationwide survey. J Gastroenterol 46:1230–1237
Tomiyama Y, Takenaka K, Kodama T, Kawanaka M, Sasaki K, Nishina S, Yoshioka N et al (2013) Risk factors for survival and the development of hepatocellular carcinoma in patients with primary biliary cirrhosis. Intern Med 52:1553–1559
Tong HV, Bock CT, Velavan TP (2014) Genetic insights on host and hepatitis B virus in liver diseases. Mutat Res Rev Mutat Res 762:65–75
Torres DM, Harrison SA (2012) Nonalcoholic steatohepatitis and noncirrhotic hepatocellular carcinoma: fertile soil. Semin Liver Dis 32:30–38
Trépo E, Pradat P, Potthoff A, Momozawa Y, Quertinmont E, Gustoto T, Lemmers A et al (2011) Impact of patatin-like phospholipase-3 (rs738409 C>G) polymorphism on fibrosis progression and steatosis in chronic hepatitis C. Hepatology 54:60–69
Trépo C, Chan HL, Lok A (2014) Hepatitis B virus infection. Lancet 384:2053–2063
Trias R, Rius X, Autonell J, Algaba F (1978) Hepatocarcinoma and oral contraceptives. Lancet 1:821
Trivedi PJ, Cullen S (2011) Autoimmune hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Dig Dis Sci 56:276–278
Tsai WL, Chung RT (2010) Viral hepatocarcinogenesis. Oncogene 29:2309–2324
Uccello M, Malaquarnera G, Corriere T, Biondi A, Basile F, Malaquarnera M (2012) Risk of hepatocellular carcinoma in workers exposed to chemicals. Hepat Mon 12, e5943
Velazquez and Alter 2004. http://www.ncbi.nlm.nih.gov/pubmed/15495253
Vizoso FJ, Rodriguez M, Altadill A, Gonazelz-Diéguez ML, Linares A, Gonzalez LO et al (2007) Liver expression of steroid hormones and apolipoprotein D receptors in hepatocellular carcinoma. World J Gastroenterol 13:3221–3227
Votte-Lambert A, Samuel D, Reynes M, Bismuth H, Capron JP (1993) Hepatocellular carcinoma complicating primary sclerosing cholangitis (in French). Gastroenterol Clin Biol 17:604–605
Walldorf J, Tannapfel A, Holzhausen HJ, Wittekind C, Seufferlein T, Settmacher U et al (2009) Rapid development of hepatocellular carcinoma in isolated thrombosis of hepatic veins (classic Budd-Chirai syndrome): case report and review of literature. BMJ Case Rep bcr07.2009.2057
Wang XZ, Chen XC, Chen YX, Zhang LJ, Li D, Chen FL, Chen ZX, Chen HY, Tao QM (2003) Overexpression of HBxAg in hepatocellular carcinoma and its relationship with Fas/FasL system. World J Gastroenterol 9:2671–2675
Wang Y, Lau SH, Sham JS, Wu MC, Wang T, Guan XY (2004) Characterization of HBV integrants in 14 hepatocellular carcinomas: association of truncated X gene and hepatocellular carcinogenesis. Oncogene 23:142–148
Wang SH, Yeh SH, Lin WH, Wang HY, Chen DS, Chen PJ (2009) Identification of androgen response elements in the enhancer I of hepatitis B virus: a mechanism for sex disparity in chronic hepatitis B. Hepatology 50:1392–1402
Wang Y, Li J, Chen J, Liu L, Peng Z, Ding J, Ding K (2012) From cirrhosis to hepatocellular carcinoma in HCV-infected patients: genes involved in tumor progression. Eur Rev Med Pharmacol Sci 16:995–1000
Ward SC, Deniz K, Roayale S, Qin L (2008) Multifocal hepatocellular carcinoma and precancerous lesions in a patient with autoimmune hepatitis-related cirrhosis. Semin Liver Dis 28:123–127
Watanabe S, Horie Y, Kataoka E, Sato W, Dohmen T, Ohshima S, Goto T, Suzuki A (2007) Non-alcoholic steatohepatitis and hepatocellular carcinoma: lessons from hepatocyte-specific phosphatase and tensin homolog (PTEN)-deficient mice. J Gastroenterol Hepatol 22(Suppl 1):S96–S100
Watanabe T, Soga K, Hirono H, Hasegawa K, Shibasaki K, Kawai H, Aoyagi Y (2009) Features of hepatocellular carcinoma in cases with autoimmune hepatitis and primary biliary cirrhosis. World J Gastroenterol 15:231–239
Wee A, Ludwig J, Coffey RJ, LaRusso NF, Wiesner RH (1985) Hepatobiliary carcinoma associated with primary sclerosing cholangitis and chronic ulcerative colitis. Hum Pathol 16:719–726
Weill BJ, Menkès CJ, Cormier C, Louvel A, Dougados M, Houssin D (1988) Hepatocellular carcinoma after danazol therapy. J Rheumatol 15:447–449
Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA (2011) Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. Hepatology 54:463–471
White DL, Kanwal F, El-Serag HB (2012) Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol 10:1342–1359
Wieser V, Moschen AR, Tilg H (2012) Adipocytokines and hepatocellular carcinoma. Dig Dis 30:508–513
Wild CP, Montesano R (2009) A model of interaction: aflatoxins and hepatitis viruses in liver cancer aetiology and prevention. Cancer Lett 286:22–28
Williams JH, Phillips TD, Jolly PE, Stiles JK, Jolly CM, Aggarwal D (2004) Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences, and interventions. Am J Clin Nutr 80:1106–1122
Woloshuk CP, Shim WB (2013) Aflatoxins, fumonisins, and trichothecenes: a convergence of knowledge. FEMS Microbiol Rev 37:94–109
Wong VS, Adab N, Youngs GR, Sturgess R (1999) Hepatic sarcoidosis complicated by hepatocellular carcinoma. Eur J Gastroenterol Hepatol 11:353–355

Wong RJ, Gish R, Frederick T, Bzowej N, Frenette C (2011) Development of hepatocellular carcinoma in autoimmune hepatitis patients: a case series. Dig Dis Sci 56:578–585

Wong RJ, Cheung R, Ahmed A (2014) Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 59:2188–2195

Wu PC (1979) Patterns of hepatitis B surface antigen. Localization in cells of hepatocellular carcinoma. Arch Pathol Lab Med 103:165–168

Wu PC, Lam KC (1979) Cytoplasmic hepatitis B surface antigen and the ground-glass appearance in hepatocellular carcinoma. Am J Clin Pathol 71:229–234

Wu CG, Salvay DM, Forgues M, Valerie K, Farnsworth J, Markin RS, Wang XW (2001) Distinctive gene expression profiles associated with hepatitis B virus x protein. Oncogene 20:3674–3682

Wu et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18728014

Xie Y, Liu S, Zhao Y, Guo Z, Xu J (2014) X protein mutations in hepatitis B virus DNA predict postoperative survival in hepatocellular carcinoma. Tumour Biol 35:10325–10331

Xu et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23321675

Yamamoto K, Hiura M, Tabaru A, Honma Y, Narita R, Abe S, Shimajiri S, Okamoto K et al (2011) Rapid progression of hepatocellular carcinoma in a patient with autoimmune hepatitis. Intern Med 50: 1409–1413

Yan MX, Yang J, Sun Q, Liu CH, Wang YG, Wang WQ (2013) Hepatocellular carcinoma that arose from primary Sjögren's syndrome. Ann Hepatol 12: 824–829

Yang WJ, Chang CJ, Yeh SH, Lin WH, Wang SH, Tsai TF, Chen DS, Chen PJ (2009) Hepatitis B virus X protein enhances the transcriptional activity of the androgen receptor through c-Src and glycogen synthase kinase-3beta kinase pathways. Hepatology 49:1515–1524

Yang JH, Zhang H, Chen XB, Chen G, Wang X (2013) Relationship between hepatocellular carcinoma and hepatitis B virus genotype with spontaneous YMDD mutations. World J Gastroenterol 19:3861–3865

Yang SL, Yu C, Jiang JX, Liu LP, Fang X, Wu C (2014) Hepatitis B virus X protein disrupts the balance of the expression of circadian rhythm genes in hepatocellular carcinoma. Oncol Lett 8:2715–2720

Yeh SH, Chen PJ (2010) Gender disparity of hepatocellular carcinoma: the roles of sex hormones. Oncology 78(Suppl 1):172–179

Yilmaz Y, Colak Y, Kurt R, Senates E, Eren F (2013) Linking nonalcoholic fatty liver disease to hepatocellular carcinoma: from bedside to bench and back. Tumori 99:10–16

Yuen MF, Hou JL, Chutaputti A, Asia Pacific Working Party on prevention of Hepatocellular Carcinoma (2009) Hepatocellular carcinoma in the Asia pacific region. J Gastroenterol Hepatol 24:346–353

Zeng Z (2014) Human genes involved in hepatitis B virus infection. World J Gastroenterol 20:7696–7706

Zhang YJ, Wu HC, Yazici H, Yu MW, Lee PH, Santella RM (2012) Global hypomethylation in hepatocellular carcinoma and its relationship to aflatoxin B exposure. World J Hepatol 4:169–175

Zhang M, Wu R, Jiang J, Minuk GY, Niu J (2013a) The presence of hepatitis B core antibody is associated with more advanced liver disease in alcoholic patients with cirrhosis. Alcohol 47:553–558

Zhang T, Zhang J, Cui M, Liu F, You X, Du Y, Gao Y, Zhang S, Lu Z, Ye L, Zhang X (2013b) Hepatitis B virus X protein inhibits tumor suppressor miR-205 through inducing hypermethylation of miR-205 promoter to enhance carcinogenesis. Neoplasia 15:1282–1291

Zhao XY, Rakhda MI, Wang TI, Jia JD (2013) Immunoglobulin G4-associated de novo autoimmune hepatitis after liver transplantation for chronic hepatitis B- and C-related cirrhosis and hepatocellular carcinoma: a case report with literature review. Transplant Proc 45:824–827

Zheng S, Tansey WP, Hiebert SW, Zhao Z (2011) Integrative network analysis identifies key genes and pathways in the progression of hepatitis C virus induced hepatocellular carcinoma. BMC Med Genomics 4:62

Zhou H, Wolff M, Pauleit D, Fischer HP, Pfeifer U (2000) Multiple macroregenerative nodules in liver cirrhosis due to Budd-Chiari syndrome. Case reports and review of the literature. Hepato-Gastroenterology 47:522–527

Zhu R, Zhang JS, Zhu YZ, Fan J, Mao Y, Chen Q, Zhu HG (2011) HBx-induced androgen receptor expression in HBV-associated hepatocarcinoma is independent of the methylation status of its promoter. Histol Histopathol 26:23–35

Ziegenfuss J, Carabasi R (1973) Androgens and hepatocellular carcinoma. Lancet 1:262

Etiology and Pathogenesis of Hepatocellular Carcinoma: Hepatocellular Carcinoma Associated with Inborn Errors of Metabolism and Hepatobiliary Malformations

165

Contents

Abstract

Chronic iron overload causes a broad array of cell and tissue injuries and is an important cause of hepatocellular carcinoma (HCC). Among inborn errors of metabolism, hereditary hemochromatosis with its massive iron overload is the most important risk factor for HCC. In addition to hemochromatosis and few other, rare congenital disorders if iron metabolism, there are several acquired conditions with chronic iron overload of the liver, including transfusional iron overload, metabolic syndrome, dietary iron overload in sub-Saharan Africa, and other forms of nutritional iron overload. Hereditary hemochromatosis exists in several types caused by mutations of the genes for HFE, hemojuvelin, hepcidin, transferrin receptor 2, and ferroportin. Patients with cirrhotic hemochromatosis have approximately a 20–200 times higher risk of developing HCC than a non-cirrhotic control group. In this disorder, the annual incidence of HCC is 4 % once cirrhosis has established, illustrating the important role of cirrhosis as an HCC risk factor. Typically, HCC that develops in hemochromatosis does not store stainable iron, resulting in iron-free nodules or masses in an iron-overloaded cirrhotic background.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_165

Chronic Iron Overload of the Liver as a Hepatic Carcinogen

Introduction

Iron is a critical metal for numerous cellular processes and holds a central position in oxidative phosphorylation. As a toxic element, body iron must be tightly regulated (reviews: Fleming 2005; Anderson and Frazer 2006; Siah et al. 2006; Wang and Pantopoulos 2011). Several hereditary and acquired disorders of iron homeostasis result in chronic iron overload known to cause chronic liver disease and cirrhosis (reviews: Franchini 2006; Siah et al. 2006; Table 1).

Genetically caused hepatic iron overload includes hereditary hemochromatosis (reviews: Beutler 2006; Franchini and Veneri 2005; Adams 2009; Allen 2010; Babitt and Lin 2011; Pietrangelo et al. 2011; Kanwar and Kowdley 2013), thalassemias, hereditary spherocytosis, hemoglobin H disease (Chim et al. 1998), and 3-oxo-delta-steroid 5beta-reductase deficiency (Ueki et al. 2009). Hemochromatosis was already described in the nineteenth century, and its hereditary nature was described in 1935 by Sheldon. Hereditary hemochromatosis is caused by several genetic defects affecting critical proteins involved in iron homeostasis (Babitt and Lin 2011; Pietrangelo et al. 2011; Santos et al. 2012; Table 2).

Table 1 Causes of chronic iron overload

Congenital disorders
Hereditary hemochromatosis (several types)
Inborn errors of metabolism associated with iron overload
Neonatal hemochromatosis (gestational alloimmune liver disease)
Congenital non-hereditary disorders with iron overload (e.g., Pearson's syndrome)
Acquired disorders
Transfusional iron overload (transfusion siderosis)
Metabolic syndrome
Dietary iron overload in sub-Saharan Africa (African iron overload)
Other forms of nutritional iron overload

Type 1 Hereditary Hemochromatosis

The most common defect in hereditary hemochromatosis is deficiency of the HFE protein, mostly caused by the C282Y mutation. Males that are homozygous for C282Y often develop iron overload-related disease, but this effect is less common in females (Allen et al. 2008). Inappropriately low secretion of the iron hormone, hepcidin, which negatively regulates iron absorption, is considered the mechanisms for iron overload in this disorder (Alexander and Kowdley 2009). As the most common form of hemochromatosis is type 1, caused by HFE mutations, this is also the form with the highest number of patients with HCC. Patients with cirrhotic hemochromatosis have approximately a 20–200 times higher risk of developing HCC than a non-cirrhotic control group. In hereditary HFE hemochromatosis, the annual incidence of HCC is 4 % once cirrhosis has been established (review: Villanueva et al. 2010). In HFE-related hemochromatosis, there is a relationship between types of mutations and risk for HCC. Meta-analysis of nine studies showed that the Y allele of C282Y was associated with HCC risk (Jin et al. 2010). However, data regarding the relationship between the genotype and HCC incidence vary from one study to the other, some analyses failing to show that HFE mutations increase the risk for HCC, except C282Y homozygosity (Cauza et al. 2003). In a study of 66,000 cases, the odds ratio for HCC in homozygous C282Y patients was 11 (Ellervik et al. 2007). In a meta-analysis of nine studies, it turned out that Y allele of C282Y was associated with HCC in European alcoholic liver cirrhosis patients (Jin et al. 2010). In one study from the UK, only a very small proportion of HFE C282Y homozygotes developed HCC (Willis et al. 2005), and another investigation demonstrated that the C282Y heterozygous genotype was significantly more common in HCC patients, suggesting that this genotype plays a more important role in hepatocarcinogenesis (Hellerbrand et al. 2003). Patients with homozygous or heterozygous C282Y mutations combined with homozygosity for the transferrin receptor Ser allele showed an increased risk for HCC (Beckman et al. 2000).

Table 2 Types of hereditary (primary) hepatic iron overload

Disease	Transmission	Defect	Locus	OMIM
HH type 1	ar	HFE	6p21	235200
HH type 2A	ar	Hemojuvelin	1q21	608374
HH type 2B	ar	Hepcidin	19q13	606464
HH type 3	ar	TF receptor 2	7q22	604250
HH type 4	ad	Ferroportin	2q32	606069
Neonatal hemochromatosis		Unknown		231100
Aceruloplasminemia	ar	Ceruloplasmin	3q24-q25	604290
Atransferrinemia	ar	Transferrin	3q22.1	209300
3-Oxo-delta-steroid 5beta reductase deficiency	ar	ODSBR	7q33	235555
Δ-Aminolevulinate synthase 1 mutations	ar	ALAS	3p21.2	125290
Hereditary xerocytosis	ad	PIEZO1	16q24.3	194380
Trichohepatoenteric syndrome 1	ar	TTC37	5q15	222470
GRACILE syndrome	ar	BCS1L	2q35	603358

Abbreviations: *HH* hereditary hemochromatosis, *TF* transferrin, *ODSBR* 3-oxo-delta-steroid 5beta-reductase, *ALAS* aminolevulinate synthase, *ar* autosomal recessive, *ad* autosomal dominant

There is an association between heterozygosity for HFE gene mutations and hepatitis viruses in HCC, in that multivariate analysis reveled that C282Y heterozygous males were 3.8-fold more likely to be HBV positive and that H63D heterozygous females were 6.0-fold more likely to be HCV positive than wild-type subjects. These associations may modulate hepatocellular iron accumulation and oxygen stress responses (Fracanzani et al. 2005).

HCC in hereditary hemochromatosis is usually associated with liver cirrhosis (Tiniakos and Williams 1988). Iron-storing liver cirrhosis has been described in the early twentieth century already, in part using the terms pigment cirrhosis or, in French, cirrhosis bronzée (Achard and Leblanc 1921; Flinn and von Glahn 1929; Lubarsch 1929; Wegelin 1929; Rosenthal 1932). However, the absence of relevant chronic fibrosing liver disease or cirrhosis was observed part of hemochromatosis patients with HCC (Fellows et al. 1988; Sheehan et al. 1989; Kew 1990; Goh et al. 1999; Köhler et al. 1999; Britto et al. 2000; Pellisè et al. 2001; Von Delius et al. 2006; Hiatt et al. 2007; Singh et al. 2012). In a literature review of 2012, 14 case reports of hemochromatosis patients with HCC in the absence of cirrhosis were found; ten of them had evidence of hepatic iron overload, and the remaining patients lacked significant iron storage in their livers (Singh et al. 2012). However, there are also reports that did not find any patient with HCC in non-cirrhotic hemochromatosis (Fargion et al. 1994). In a non-cirrhotic HFE hemochromatosis patient with HCC, HBV DNA integration in tumor tissue was found (Pollicino et al. 2013), suggesting that occult viral infection may contribute to hepatocarcinogenesis in non-cirrhotic hemochromatosis patients. Primary HCC in hemochromatosis was observed in spite of adequate iron removal through multiple phlebotomies (Hurst et al. 1961; Hines et al. 1971) or after reversal of cirrhosis (Blumberg et al. 1988), suggesting that, at least in part of patients, a basic hepatic defect caused by iron overload may persist even after elimination of risk factors.

Type 2 Hereditary Hemochromatosis (Juvenile Hemochromatosis)

Hereditary hemochromatosis type 2, or juvenile hemochromatosis, is a group of autosomal recessive disorders that affects females and males equally, clinically characterized by early-onset iron overload followed by severe organ dysfunction usually before the age of 30 years. The clinical spectrum is similar to that in HFE-related hemochromatosis, but the signs of organ involvement appear much earlier and progression is more

rapid. In untreated disease, manifestations of heart involvement predominate, with cardiac failure being the most important cause of premature death. Type 2 hemochromatosis appears in two forms, subtype 2A and subtype 2B.

Subtype 2A Hereditary Hemochromatosis

Subtype 2A hemochromatosis (OMIM 608374) is caused by mutations in the hemojuvelin gene. Hemojuvelin plays a central role in iron homeostasis via the hemojuvelin-hepcidin axis, whereby the function of hepcidin as a master regulator of iron handling interacts with hemojuvelin (Zhang 2010). Hemojuvelin belongs to the repulsive guidance molecular family (RGM family), members including RGMa, RGMb (Dragon), and RGMs (hemojuvelin). The regulation of hemojuvelin expression is only partially known. Hemojuvelin is anchored to the cell membrane via GPI, binds the proteins neogenin and BMP2 and BMP4, and can be shed from membranes, this shedding being inhibited in response to iron via the action of neogenin (Zhang et al. 2007). TNFalpha downregulated hemojuvelin expression through transcription suppression within the hemojuvelin promoter (Salama et al. 2012). Hemojuvelin is degraded by matriptase-2, an enzyme that belongs to the family of type II transmembrane serine proteases (Meynard et al. 2011; Wysocka et al. 2014), and by the furin family of protein convertases. Matriptase-2 is directly upregulated by hypoxia-inducible factor-1 (Maurer et al. 2012) and is a negative regulator of hepcidin expression (Silvestri et al. 2008). Matriptase-2 also downregulates BMP/SMAD signaling and via this pathway directly regulates iron homeostasis (Finberg et al. 2010). RGM family proteins exhibit differential BMP-binding properties, whereby membrane-anchored hemojuvelin preferentially binds to BMP6 (Wu et al. 2012), an interaction that is important in the regulation of systemic iron homeostasis in that hemojuvelin-BMP-binding enhances hepcidin expression in hepatocytes. Loss of matriptase-2 increases bone morphogenetic protein-dependent signaling. Downregulation of hemojuvelin prevents inhibitory effects of bone morphogenetic proteins 4 and 6 on iron metabolism, in particular hepcidin expression in HCC (Maegdefrau et al. 2011). Hemojuvelin expression is increased in adipocytes of obese individuals (Luciani et al. 2011), suggesting a signaling pathway for abnormal iron homeostasis occurring in obesity and the metabolic syndrome.

Subtype 2B Hereditary Hemochromatosis

Subtype 2B hemochromatosis (OMIM 606464) is caused by mutations in the HAMP gene encoding the protein hepcidin. Only few cases of this subtype have been reported. Hepcidin has a central role in iron homeostasis and is the most critical systemic iron-regulating hormone (Nemeth and Ganz 2006; Ganz 2007; Lee and Beutler 2009; Camaschella and Silvestri 2011; Kaplan et al. 2011; Singh et al. 2011; Ganz and Nemeth 2012; Adams 2014; D'Anna and Roque 2013; Wu et al. 2013; Zhao et al. 2013; Ruchala and Nemeth 2014). Hepcidin modulates systemic iron balance through a limitation of dietary iron absorption and release of iron from macrophage stores. The pathway for hepcidin-dependent regulation of tissue and plasma iron distribution involved the induction by hepcidin of the degradation of its receptor, the cellular iron exporter ferroportin (Nemeth et al. 2004; Lee and Beutler 2009; Preza et al. 2013). Ferroportin exports iron into plasma from enterocytes, from macrophage iron stores, and from hepatocytes that store liver iron (review: Ganz and Nemeth 2012). Hepcidin synthesis is under the control of serine protease, TMPRSS6 (matriptase-2), an iron sensor (Du et al. 2008; Lee et al. 2009), and is mediated by the bone morphogenetic protein/BMP type I receptors ALK2 and ALK3, and hepcidin induction in response to inflammatory reactions requires cooperative BMP signaling (Finberg 2013), BMP4 and BMP6 being a key endogenous regulator of hepcidin expression (Andriopoulos et al. 2009). BMP4-induced hepcidin expression in turn requires a hemojuvelin-neogenin interaction (Zhang et al. 2009). SMAD7 is a potent inhibitor of hepcidin expression and abolishes hepcidin activation by BMPs (Mleczko-Sanecka et al. 2010). Expression of hepcidin is also under

control of innate immune and infectious stimuli (Armitage et al. 2011) and interleukin-22 (Smith et al. 2013), but hepcidin expression is also subject to an autoregulatory pathway in which prohepcidin regulates expression of the hepcidin gene via binding of prohepcidin to the inflammation-regulated STAT3-binding site in the hepcidin gene promoter (Lane et al. 2013). The proteins HFE, transferrin receptor 2, and hemojuvelin form a membrane-associated multiprotein complex with hepcidin (D'Alessio et al. 2012). Interaction of HFE protein with the transferrin receptor 2 is required for transferrin-induced hepcidin expression. In the autosomal dominant iron storage disorder, ferroportin deficiency, mutant ferroportin is resistant to hepcidin-mediated internalization, whereby an alteration at C326 produces the most severe interaction defect (Fernandes et al. 2009).

Type 3 Hereditary Hemochromatosis

Type 3 hereditary hemochromatosis (OMIM 604250) is caused by mutations in the transferrin receptor 2 (TfR2) gene and is an autosomal recessive disorder (review: Chen and Enns 2012). Transferrin receptors regulated to homeostasis of the transferrin ligand and have a central role in iron metabolism (Gkouvatsos et al. 2012). It is characterized by a phenotype that is close to that of HFE hemochromatosis and exhibits a variable age of onset and a widespread geographical distribution (McDonald et al. 2013; Radio et al. 2014). TfR2 is selectively expressed in the liver and is a homologue of TfR1 and is a molecule with a central role in iron homeostasis, but the details of its function are only partially known. TfR2 is crucial for iron sensing in human hepatocytes (Rapisarda et al. 2010). TfR2 and HFE form a stable complex at the cell surface which increases cellular uptake of transferrin-bound iron (Waheed et al. 2008). The HFE-TfR2 interaction is also required for transferrin-induced hepcidin expression (Nemeth et al. 2005; Girelli et al. 2011). HFE and transferrin receptor 2 regulate furin expression through mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/Erk) signaling, indicating that transferrin receptor 2 and HFE are involved in holotransferrin-dependent signaling for the regulation of furin, which in turn may control hepcidin expression (Poli et al. 2010). In contrast to wild-type TfR2, which is expressed both in endocytic structures and on the cell surface, mutated TfR2 is retained in the endoplasmic reticulum and is, therefore, not available as a surface receptor (Wallace et al. 2008).

Type 4 Hereditary Hemochromatosis

Ferroportin 1 (IREG1/MTP1) mutations are the cause of hemochromatosis type 4 (also called ferroportin disease; Détivaud et al. 2013). Ferroportin is a transmembrane channel protein involved in the exit control of iron out of macrophages, erythrocytes, and hepatocytes. The macrophage-monocyte system holds a central role in iron homeostasis (Kong et al. 2013). Ferroportin forms a characteristic transport channel, the ferroportin pore, with a critical tryptophan residue at position 42 of the extracellular end of the pore (Gac et al. 2013). Ferroportin is regulated by its interactions with other iron proteins and by iron-responsive microRNA-485-3p (Sangokoya et al. 2013). In contrast to other types of hemochromatosis, ferroportin disease is an autosomal dominant disorder. It is characterized by failure of iron release from macrophage stores and marked accumulation of stainable iron in hepatic Kupffer cells. Patients with ferroportin disease show early increase in serum ferritin in spite of low transferrin saturation and a decreased availability of iron for circulating transferrin. They also display marginal anemia with low tolerance to phlebotomy. Anemia leads to compensatory increase of iron absorption, which in concert with deficient iron release from cells contributes to iron overload, a "more in-less out" effect (Devalia et al. 2002; Wallace et al. 2004; reviews: Pietrangelo 2004; De Domenico et al. 2006; Mayr et al. 2010). In advanced disease (third and fourth decades of life), parenchymal iron overload becomes significant, but the clinical phenotype is generally milder than that in HFE-related hemochromatosis.

Ferroportin disease can be followed by HCC development (Corradini et al. 2007; Rosmorduc et al. 2008). Ferroportin mutations not only occur in Western countries, but were also detected in the Asia-Pacific region (Solomon Islands; Arden et al. 2003). Ferroportin overexpression in murine macrophages significantly impaired macrophage-mediated cellular immunity, associated with impaired nitric oxide/NO production in response to antigenic stimulation (Johnson et al. 2010). HCC tissue showed a lesser expression of ferroportin than noncancerous liver tissue, and ferroportin levels declined along with the progression of liver cancer (Wang et al. 2013).

Pathology of Hepatocellular Carcinoma in Hemochromatosis

HCC as a complication of chronic hepatic iron overload has most often been observed in the various forms of hereditary hemochromatosis.

Selected References Hibbs 1927; Keith and McNair 1930; Orr 1930; Rosenthal 1932; Point et al. 1957; Nash and Kaung 1962; Cliff 1969; Seshadri et al. 1982; Toyokuni 1996; Willis et al. 1997; Pleass and Garden 1998; Fargion et al. 1994; Beckman et al. 2000; Deugnier and Turlin 2001; Fargion et al. 2001; Haddow et al. 2003; Huang 2003; Lwakatare et al. 2003; Kowdley 2004; Harrison and Bacon 2005; Kew and Asare 2007; Ko et al. 2007; Edgren et al. 2008; Adams 2009; Chen and Chloupkova 2009; Kew 2009; Toyokuni 2009; Blonski et al. 2010; Villanueva et al. 2010; and Gan et al. 2011.

But it also occurs in congenital hemochromatosis (Quante et al. 2011), patients with thalassemic syndromes (Parfrey and Squier 1978) and spherocytosis (Barry et al. 1968; Takegoshi et al. 1984). Irrespective of cause, chronic hepatic iron overload leads to fibrogenesis and progressive hepatic fibrosis ending up with cirrhosis and, in part of patients, cirrhosis-associated HCC (reviews: Chen and Chloupkova 2009; Kew 2009). HCC developing in hemochromatosis is known for more than 100 years (Runte 1901; Loehlein 1907).

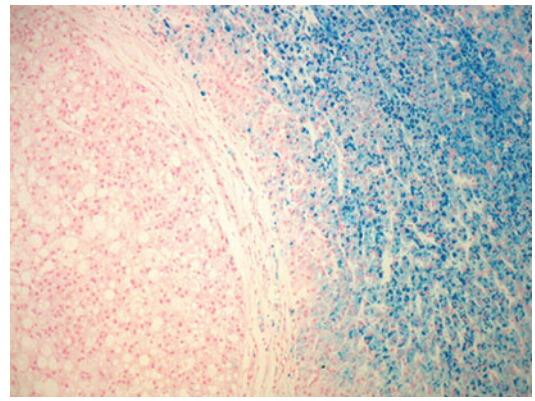

Fig. 1 Hepatocellular carcinoma developing in hereditary hemochromatosis. In this iron stain, the HCC is devoid of stainable iron (*left* of figure), in contrast to marked iron overload of the liver (Perls iron stain)

In most cases, HCC developing in hemochromatosis does not store stainable iron, while the adjacent cirrhotic or non-cirrhotic liver tissue exhibits marked to massive cytoplasmic iron overload (Fig. 1; Bothwell et al. 1965).

Macroscopically, the pale or greenish tumors are easily recognized on a background of a chocolate-brown cirrhotic liver. Iron overload in cirrhotic liver in hemochromatosis has a characteristic distribution and pattern, easily detectable in liver biopsies (Bassett et al. 2011). The stainable iron found in iron-storing hepatocytes is mainly hemosiderin, a structure constructed of crystalline lattices containing ferritin (Richter 1958), but cells may also show a diffuse nongranular background staining in Perls stain, thought to be due to the accumulation of ferritin, an iron/oxygen biomineral contained in protein nanocages (the ferritin nanocage protein superfamily; Andrews 2010; Bevers and Theil 2011; Zhang and Orner 2011; Theil 2013). In some cases, iron-containing nuclear inclusions are found (Altmann 1977). There are few and intriguing exceptions in the form of HCC in hemochromatosis that accumulate significant amounts of stainable iron. In rare cases, accumulation of stainable iron in HCC tissue may be caused by intratumoral hemorrhage (Runte 1901). In one

investigation, HCC arising in hemochromatosis showed frequent biliary differentiation (Morcos et al. 2001). The liver in hereditary hemochromatosis frequently shows sublobular nodules of hepatocytes that are free of stainable iron or displaying much less iron than the adjacent tissue of pigment cirrhosis. These lesions were called iron-free foci. In a study of 185 patients with untreated hereditary hemochromatosis, such lesions were observed in 7.6 % of patients, all men, with an age range of 38–76 years, with hepatic fibrosis or cirrhosis. Ten of these patients had dysplastic features in the iron-free foci, and the foci disclosed increased proliferative activity, suggesting that the foci are preneoplastic lesions (Deugnier et al. 1993).

The molecular mechanisms leading to the exclusion of iron accumulation in HCC cells are only partially clarified. Expression for most of the iron regulatory genes, including hepcidin, transferrin receptor 2, transferrin, ceruloplasmin, and iron regulatory protein 1/IRP1, was significantly downregulated in HCC tissue (Tseng et al. 2009). Also the expression of hepcidin mRNA was uniformly suppressed in HCC (Kijima et al. 2008), suggesting that a reduction of hepcidin in iron-depleted HCC cells reflects a physiologic consequence of the demand for iron in rapidly growing neoplastic cells. A very small subset of HCCs in HCC have shown iron overload of tumor cells, due to so far unknown reasons.

Hepatocellular Carcinoma in Other Genetic Disorders that Affect Iron Metabolism

HCC can develop in patients with thalassemia minor, thalassemia intermedia, and thalassemia major (OMIM 604131) (Borgna-Pignatti et al. 1986, 2004, 2014; Mancuso et al. 2006; Mancuso 2010; Restivo Pantalone et al. 2010; Musallam et al. 2012; Gomatos et al. 2013). Among 36 reported cases of thalassemia-associated HCC, 61 % were found in thalassemia intermedia (Maakaron et al. 2013). HCC emerging in thalassemic syndromes is a rather recent development that is linked to the now longer survival of thalassemic patients (Borgna-Pignatti et al. 2004). A prospective study estimated that the HCC incidence in beta-thalassemia is approximately 2 %, but a more recent study on 144 patients reported an HCC incidence of 5.3 % (Triantos et al. 2013). HCC was found in thalassemia with HCV infection also in the absence of liver cirrhosis (Mancuso et al. 2005). Currently, it is still difficult to judge as to what role iron overload as such is played in HCC of thalassemic patients, because these patients are, due to numerous blood transfusions, often infected with hepatitis viruses, in particular HCV (Ansari et al. 2013; review: Mancuso 2010). In a review of 22 cases of HCC occurring in patients with thalassemic syndrome, 86 % of the patients had been infected with HCV (Borgna-Pignatti et al. 2004), whereas a Greek investigation reported 57/144 patients infected with HCV (Triantos et al. 2013). In regard to the potential role of iron in thalassemia-associated HCC, it was proposed that the main risk factor for HCC was HCV infection in thalassemia major patients but iron activity in thalassemia intermedia patients (Fragatou et al. 2010). HCC was observed in association with hemochromatosis developing in hereditary spherocytosis (Takegoshi et al. 1984), hemoglobin H disease (Chim et al. 1998), and 3-oxo-delta-steroid 5beta-reductase deficiency (Ueki et al. 2009). Hereditary hematologic disorders requiring multiple transfusions can develop transfusion-induced secondary hemochromatosis followed by HCC, e.g., congenital hypoplastic anemia or Blackfan-Diamond syndrome (Steinherz et al. 1976). Several other inborn errors of metabolism are associated with hepatic iron overload, including Δ-aminolevulinate synthase mutations (Lee et al. 2009) and hereditary xerocytosis (dehydrated hereditary stomatocytosis with or without pseudohyperkalemia and/or perinatal edema), characterized by hemolytic anemia, primary erythrocyte dehydration, and iron overload in several organs (Assis et al. 2013). The disorder is caused by gain-of-function mutations in the inactivating eukaryotic cation-selective mechanosensitive ion channel, PIEZO1 (Zarychanski et al. 2012; Albouisson et al. 2013).

Hepatocellular Carcinoma in Acquired Chronic Iron Overload

There are several disorders characterized by acquired iron overload. They include transfusional iron overload, neonatal hemochromatosis, mainly caused by gestational alloimmune liver disease (Bonilla et al. 2012; Whitington 2012; Lopriore et al. 2013) but also found in rare chromosomal anomalies, such as duplication of 16p (Schwaibold et al. 2014), alcoholic liver disease, NAFLD, and dietary iron overload. HCC can develop in acquired forms of iron overload. In general, the risk for HCC development is higher in any type of cirrhosis with increased iron levels (Jaskiewicz et al. 1997; Ito et al. 1999). NAFLD caused by or related to the metabolic syndrome is often associated with hepatic iron overload (Fujita and Takei 2011) and is known to be complicated by HCC. Iron overload in NASH leads, similar to other iron overload situations of the liver, to oxidative DNA damage (Fujita et al. 2009) which in turn results in a promutagenic situation. Patients with other forms of secondary hemochromatosis, e.g., those with hematologic disorders, may also develop HCC (Chung et al. 2003). A further type of chronic overload that may be complicated by HCC is dietary (nutritional) iron overload of rural sub-Saharan Africa, a condition that had previously been termed "Bantu siderosis" or "siderosis in the Bantu" and is now termed African iron overload (Strachan 1929; Bothwell and Bradlow 1960; Gangaidzo and Gordeuk 1995; Mandishona et al. 1998; Moyo et al. 1998; Kew and Asare 2007). The term "Bantu siderosis" would imply that this disorder is restricted to Bantu ethnics; however, significant African iron overload is also known from Uganda, East Africa, Ghana, and Nigeria (review: Gangaidzo and Gordeuk 1995). In former times, severe iron overload was common in sub-Saharan Africa, with a prevalence of more than 10 % in some populations, mainly in South Africa (Gordeuk et al. 1986; Gordeuk 1992). The pathogenesis of African iron overload is not fully clarified. The traditional view has it that this form of dietary iron overload is linked to the consumption of local alcoholic fermented beverage brewed in iron-rich containers (Bothwell et al. 1964). However, the pathogenesis is probably more complex with genetic factors playing a role. There is strong evidence that African iron overload in fact augments the risk for HCC (Mandishona et al. 1998). In an original autopsy series on 114 subjects, 8.8 % with markedly increased hepatic iron storage died from HCC in comparison with 1 patient out of 159 patients (0.6 %) without iron overload (Strachan 1929). In a rural-based liver biopsy study in the Transkei, South Africa, a combination of cirrhosis and severe hepatic iron overload was detected in 38 % of 203 biopsy specimens from 246 patients with HCC (Jaskiewicz et al. 1991).

Iron and Hepatocarcinogenic Pathways

Apart from cirrhosis as an established risk factor for HCC, iron accumulation as such is considered to play a hepatocarcinogenic role, as excess cell and tissue iron has known mutagenic and proliferative effects (reviews: Deugnier et al. 2008; Fargion et al. 2011). The pathogenic pathways of iron-induced HCC are complex. Iron acts as a modulating cofactor in chronic liver disease and is known to accelerate the development of hepatocyte damage (Tirnitz-Parker et al. 2013), but also seems to be a cofactor in tumor cell proliferation (Steegmann-Olmedillas 2011). Free ionized iron is a potent inducer of reactive oxygen species (ROS)/intermediates causing disruption of the cellular redox balance. Via this mechanism, free iron-related oxidative stress causes lipoperoxidation, the resulting highly reactive metabolites leading to DNA injury with formation of mutagenic aberrant nucleotides, such as 8-hydroxy-2′-deoxy-guanosine, which causes G:C to T:A transversions, DNA unwinding, and DNA strand breaks (Asare et al. 2006; Toyokuni 2008; Kew 2009). In hemochromatosis, polymorphism of the patatin-like phospholipase domain-containing-3 (PNPLA3) gene, a gene involved in the pathogenesis of steatosis and hepatic fibrosis, may represent a permissive factor for progression (Valenti et al. 2012). This polymorphism also plays a role fibrosis progression and steatosis in chronic hepatitis C (Trépo et al. 2011) and in the

severity of NASH (Rotman et al. 2010; Speliotes et al. 2010). The genetic alterations occurring in hereditary hemochromatosis lead to epigenetic changes which are already found in nonneoplastic hepatocytes (Lehmann et al. 2007). It also to be expected that mitochondria, with their central role in apoptosis, participate in the regulation of iron metabolism in carcinogenic pathways. Mitochondria possess several proteins involved in iron homeostasis, including mitoferrins 1 and 2; mitochondrial ferritin; ABCBs 6, 7, and 10; and frataxin (Shaw et al. 2006; Richardson et al. 2010; Huang et al. 2011).

Hepatocellular Carcinoma in Inborn Errors of Metabolism Other than Hemochromatosis

Introduction

Several inborn errors of metabolism are risk factors for the development of HCC (Table 3). However, due to the low incidence of most of these congenital disorders, the overall contribution of inborn metabolic diseases to hepatocarcinogenesis is relatively weak.

Table 3 Inborn errors of metabolism complicated by hepatocellular carcinoma

Disorders of copper metabolism
Wilson's disease
Porphyrias
Acute intermittent porphyria
Glycogen storage diseases
Glycogenosis type Ia
Glycogenosis type III
Glycogenosis type IV
Glycogenosis type VI
Disorders of lipid and glycolipid metabolism
Familial hypobetalipoproteinemia
Cholesterol ester storage disease
Gaucher's disease
Niemann-Pick's disease
Urea cycle disorders
Arginase deficiency
Disorders of amino acid and protein metabolism
Tyrosinemia
Type II citrullinemia
Alpha-1-antitrypsin deficiency
Dubin-Johnson syndrome
Cholestatic disorders

Wilson's Disease and Other Disorders of Copper Metabolism

Several disorders of copper metabolism are known, both inborn errors of metabolism and acquired disorders (Table 4). Wilson's disease (OMIM 277900) is a rare autosomal recessive disorder of copper transport and metabolism, with an incidence of approximately 1 in 40,000 live births, caused by mutations in the ATP7b gene located to chromosome 13q14.3 (Samuel Alexander Kinnier Wilson, 1912; reviews: Kodama et al. 2012; Broussolle et al. 2013; Kaler 2013; Trocello et al. 2013). The gene product is called ATPase Cu(2+)-transporting beta polypeptide (review: Cox and Moore 2002). Most patients with Wilson's disease are compound heterozygotes in regard to mutated ATP7b gene, a phenomenon which complicates the establishment of genotype-phenotype correlations.

Copper that is an essential element is required for the production of cuproenzymes that include cytochrome C oxidase, lysyl oxidase, dopamine β-hydroxylase, one type of superoxide dismutase, tyrosinase, ascorbic acid oxidase, and ceruloplasmin (Lalioti et al. 2009). As copper is a toxic metal, uptake, transport, storage, and elimination are tightly controlled. Copper transport is accomplished by two ATPases, ATP7a and ATP7b, of which ATP7b is mainly expressed in hepatocytes and mutated in Wilson's disease (review: Rosencrantz and Schilsky 2011). In hepatocytes, copper is delivered to the trans-Golgi network by ATOX1 and then transported across the Golgi through the action of ATP7b which is located in the trans-Golgi membrane (Hasan et al. 2012; Huster et al. 2012). Copper accumulated in the trans-Golgi compartment via this mechanism is incorporated into apo-ceruloplasmin, reduced to holo-

Table 4 Disorders of copper metabolism

Inborn disorders		
Disorder	*Gene involved*	*OMIM number*
Wilsons' disease	ATP7b	OMIM 277900
Menkes disease	ATP7a	OMIM 309400
Occipital horn syndrome	ATP7a	OMIM 304150
X-linked distal hereditary motor neuropathy	ATP7a	
MEDNIK syndrome	AP1S1	
Aceruloplasminemia	Ceruloplasmin	OMIM 604290
Congenital cataracts, hearing loss, and neurodegeneration	SLC33A1	OMIM 614482
Acquired disorders		
Idiopathic copper toxicosis		

ceruloplasmin, and then transported as ceruloplasmin into the blood. The transport of copper to bile also requires ATP7b. In addition to this ATPase, the COMM domain-containing protein1/COMMD1 (previously termed MURR1; Sarkar and Roberts 2011) is also active in biliary excretion of copper. Failure of ATP7b function leads to markedly impaired copper transport out of hepatocytes and copper storage in these cells (review: Kodama et al. 2012).

The histopathologic spectrum of liver lesions caused by Wilson's disease is very variable, ranging from minor cellular alterations associated with the presence of stainable copper to cirrhosis with or without marked hepatocellular injury (reviews: Johncilla and Mitchell 2011; Sini et al. 2013). Wilson's disease is known to be associated with HCC, usually in the setting of Wilsonian liver cirrhosis (Vachon et al. 1973; Kamakura et al. 1975; Wilkinson et al. 1983; Guan et al. 1985; Polio et al. 1989; Cheng et al. 1992; Kumagi et al. 2005; Xu et al. 2007; Ikegawa et al. 2011), albeit controversial informations have been presented referring to HCC incidences. In one study, HCC in Wilson's disease was reported as an extremely rare event (Cheng et al. 1992), while another study arrived at an opposite conclusion (Sternlieb 2000). HCC in the setting of Wilson's disease can already develop in childhood and may occur in non-cirrhotic livers (Thattil and Dufour 2013). As copper is a metal that generates reactive oxygen species, oxidative cell injury may be a crucial mechanism involved in carcinogenesis. Copper (Cu2+) causes apoptosis of several cell systems, including erythrocytes (eryptosis; Lang et al. 2012).

Mutations of the second copper-transporting ATPase, ATP7a, causes Menkes disease (kinky hair disease or steely hair disease, OMIM 309400), occipital horn syndrome, and X-linked distal hereditary motor neuropathy. Similar to ATP7b, the Menkes copper transport protein ATP7a is located to the trans-Golgi network and is an intestinal copper transporter (Dierick et al. 1997). Hepatic copper storage is also a feature of the MEDNIK syndrome, characterized by mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratoderma. The disorder is caused by AP1S1 gene mutations. This gene encodes delta-1A, the small subunit of the adaptor protein 1 complex critically involved in clathrin coat assembly and regulation of trafficking between trans-Golgi network, endosomes, and the plasma membrane (Montpetit et al. 2008; Martinelli et al. 2013).

There are several acquired disorders of copper metabolism, including idiopathic copper toxicosis (Hayashi et al. 2012). A distinct situation is the complex of disorders summarized under the term Indian childhood cirrhosis (ICC). ICC is a distinct disease that has been endemic in most parts of India and interpreted to be the result of excess dietary copper intake. ICC presents with a phenotype similar to that of Wilson's disease, but is not caused by ARTP7 gene mutations. ICC has now disappeared from most areas of India, but still exists in Andhra Pradesh and other parts of India

(Singh et al. 1959; Pandit and Bhave 1996; Tanner 1998; Sriramachari and Nayak 2008; Nayak and Chitale 2013; Patra et al. 2013). A clinically related disorder is North American Indian childhood cirrhosis (NAIC, OMIM 604901), described in aboriginal children from northwestern Quebec and characterized as distinct form of neonatal familial cholestasis, severe fibrosis, and marked involvement of bile ducts (Drouin et al. 2000). NAIC is associated with mutations of the human ribosome biogenesis factor, hUTP4/Cirhin (Chagnon et al. 2002; Richter et al. 2007; Freed and Baserga 2010). Cirhin is localized to the nucleolus (Yu et al. 2005) and is a component of the small ribosomal subunit processome and interacts with Cirip, a functional, alternative splice variant of the HIVEP1 protein. An interaction factor of Cirhin is a nucleolar protein, NOL11, required for pre-rRNA transcription and processing (Freed et al. 2012). The function of Cirhin in the development of the hepatobiliary system has been studied in a zebra fish gene knockdown model (Wilkins et al. 2013). An Indian childhood cirrhosis-like condition has also been observed in Japan (Nagasaka et al. 1999). A form of non-Indian childhood cirrhosis (NICC) with copper storage has been observed in Europe and proposed to be associated with exogenic infantile copper intoxication (Müller et al. 1999; Müller-Höcker 1999). A further variant is endemic Tyrolean childhood cirrhosis which was observed in more than 130 infants and children in western Austria between 1900 and 1974. The disorder has disappeared from this area since 1974 and is not an allelic variant of Wilson's disease but may represent a disease requiring both genetic and environmental factors in the sense of an ecogenetic disorder (Müller et al. 1996; Wijmenga et al. 1998; Tanner 1999; Pandit and Bhave 2002).

Porphyrias

Several forms of porphyria are associated with HCC in part of involved patients, including acute intermittent porphyria, variegate porphyria (an acute porphyria caused by partial deficiency of protoporphyrinogen oxidase), hereditary coproporphyria, and sporadic porphyria cutanea tarda.

Selected References Andant et al. 1997; Bengtsson and Hardell 1986; Berman and Braun 1962; Bjersing et al. 1996; Cassiman et al. 2008; Deybach and Puy 2011; Lim and Mascaro 1995; Lithner and Wetterberg 1984; Salata et al. 1985; Schneider-Yin et al. 2010; and Stewart 2012.

In patients with porphyria cutanea tarda, the pathogenesis of liver tumors is particularly complex, as this form of porphyria is associated with HCV and HBV infection, hemochromatosis/iron overload, and specifically alcoholic liver disease, known causes of HCC (Ryan Caballes et al. 2012). Relatively few patients develop HCC in porphyria cutanea tarda, with a yearly incidence of less than 1 % per patient year of follow-up (Kordac 1972; Packe and Clarke 1985; Gisbert et al. 2004; Whittle et al. 2010), and risk factors for HCC were the presence of liver cirrhosis, male sex, and age over 51 (Salata et al. 1985). Porphyria cutanea tarda can occur in combination with hereditary hemochromatosis, the condition being complicated with HCC (Mogl et al. 2007). On the other hand, HCC can induce pseudo-porphyria through production of large amounts of porphobilinogen (Pierach et al. 1984; Ochiai et al. 1997) or porphyrins, resulting in acquired cutaneous porphyria (Keczkes and Barker 1976).

Glycogen Storage Diseases

A minority of the many types of glycogen storage disease can be associated with HCC. Most observations documenting such an association refer to glycogenosis type Ia, an autosomal recessive disorder caused by deficiency of glucose-6-phosphatase (von Gierke's disease, OMIM 232200).

Selected References Zangeneh et al. 1969; Grossman et al. 1981; Limmer et al. 1988; Conti and Kemeny 1992; Bianchi 1993; Franco et al. 2005; Okuda et al. 2009; Manzia

et al. 2011; Ochi et al. 2011; Bashir et al. 2012; and Mikuriya et al. 2012.

Glycogenosis type Ia is a very rare disorder, with an incidence of 1 in 100,000 to 1 in 300,000 live births, and is chiefly characterized by hepatomegaly, a rounded doll-like face, growth retardation, hypoglycemia during fasting, and a hemorrhagic diathesis caused by impaired platelet aggregation. A well-known and common hepatic complication of this glycogenosis is the emergence of liver cell adenoma, which was detected by sonography in up to 73 % of patients (Talente et al. 1994). In contrast, HCC and focal nodular hyperplasia (FNH) are less common events. In one study of 22 patients with glycogenosis type Ia and liver tumors, liver cell adenoma, HCC, FNH, and hepatoblastoma accounted for 16, 3, 2, and 1 case, respectively (Sumimoto et al. 1988). HCC in patients with glycogenosis type Ia can synchronously be associated with other hepatic nodular lesions, e.g., focal nodular hyperplasia (Mikuriya et al. 2012). In part of reported HCC in patients with the type Ia disorder, transition from liver cell adenoma to HCC was observed, in one report in 50 % of cases (Bianchi 1996). For both adenoma and HCC occurring in glycogenosis, the pathogenic pathways of tumorigenesis are not known.

Other glycogenoses sometimes complicated by HCC are glycogenosis type III (debrancher enzyme deficiency, Cori or Forbes disease, OMIM 232400; Shimizu et al. 1982; Haagsma et al. 1997; Siciliano et al. 2000; Cosme et al. 2005; Demo et al. 2007), glycogenosis type IV (brancher enzyme deficiency, Andersen disease, OMIM 232500; de Moor et al. 2000; Onal et al. 2009), and glycogenosis type VI (phosphorylase deficiency, Hers disease, OMIM 232700; Manzia et al. 2011). In glycogenosis type III, development of HCC may be related to liver cirrhosis known to occur in a subset of patients of this disorder, although hepatic involvement is considered mild and self-limiting in most patients (Haagsma et al. 1997; Siciliano et al. 2000; Demo et al. 2007). In some patients with glycogenosis, potential nodular precursor lesions developed, including adenomatous hyperplasia in a female patient with glycogenosis type VIII (phosphorylase kinase deficiency, OMIM 306000; Shiomi et al. 1989).

Lipid and Glycolipid Disorders

Among disorders of lipid and glycolipid metabolism, Gaucher's disease (glucocerebrosidosis) is sometimes complicated by HCC (Arends et al. 2013). Familial hypobetalipoproteinemia (OMIM 615558) is characterized by fatty liver and is in most cases caused by defects in the APOB gene, encoding a short apolipoprotein B-48 and a longer apolipoprotein B-100. In most APOB mutations, both of these apolipoproteins are short versions which fail to transport fat and cholesterol. Three genetic forms are known, i.e., premature stop codon specifying mutations of APOB, a form linked to a susceptibility locus on chromosome 3p21, and a form linked neither to APOB nor to chromosome 3p21 (Schonfeld et al. 2005). There are several reports documenting associated liver cirrhosis and hepatocellular carcinoma (Lonardo et al. 1998; Cefalu et al. 2013). A related disorder is caused by mutations in the ANGPTL3 gene (angiopoietin-like 3 protein), associated with combined hypolipidemia, extremely low levels of serum low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, and low triglycerides (Musunuru et al. 2010; Noto et al. 2012). HCC was found in patients with cholesterol ester storage disease (Riva et al. 2008) and Niemann-Pick's disease (Pennington et al. 1996; Birch et al. 2003).

Amino Acid and Protein Disorders

Tyrosinemia

Tyrosinemias form a group of hereditary disorders characterized by elevated serum tyrosine levels and, dependent on the type of disease, several patterns of clinical sequelae. Hereditary tyrosinemia type I (tyrosinemia I, OMIM 276700) is an autosomal recessive disorder caused by deficiency of fumarylacetoacetase, the

last enzyme of tyrosine catabolism. Tyrosinemia I causes progressive liver disease that results in micro- and macronodular cirrhosis in early childhood and is associated with secondary renal tubular dysfunction leading to hypophosphatemic rickets (Fanconi syndrome) (review: Russo et al. 2001). HCC occurs in about a third of patients with the chronic form of hereditary tyrosinemia I (Gentz et al. 1969; Weinberg et al. 1976; Day et al. 1987; Dehner et al. 1989; Castilloux et al. 2007). In chronic tyrosinemia I, HCC may develop after a long delay, e.g., in a patient aged 37 years, despite a favorable biological environment in the liver (Kim et al. 2000), and in the presence of so-called "silent" tyrosinemia (Castilloux et al. 2007). In a review performed in 1976, 16 cases of HCC in patients surviving beyond 2 years of age (37 %) had been reported in 43 patients with tyrosinemia I. This incidence was considerably higher than that known for the development of HCC in adults with macronodular liver cirrhosis, suggesting additional factors playing a role in the pathogenesis of HCC (Weinberg et al. 1976). The morphology of HCC in tyrosinemia is not different from other HCCs.

Livers in tyrosinemia I may show multiple hepatic nodules that are not HCC (Day et al. 1987; Shteyer et al. 2011). These nodules appear as high-attenuation hepatic foci on CT scans, but may not be visualized on sonograms. Pathologically, the lesions are regenerating nodules (Day et al. 1987). In acute tyrosinemia type I, hepatic remodeling with micronodularity of the liver may develop. This alteration is sometimes associated with focal fatty change, resulting in multiple intrahepatic mass lesions mimicking HCC (Tazawa et al. 1990). Hepatoblastoma has been found in a patient with tyrosinemia I following treatment with NTBC (Nobili et al. 2010).

Alpha-1-Antitrypsin Deficiency

HCC is a reported complication of alpha-1-antitrypsin deficiency (AATD; Kew et al. 1978; Köhnlein and Welte 2008). AATD is now classified as a serpinopathy, a group of disorders characterized by inappropriate conformational change and self-association or polymerization of serpin (serine proteinase inhibitor) molecule within the endoplasmic reticulum (Knaupp et al. 2010). AATD is a rather common congenital metabolic disorder characterized by numerous mutations, however, with the Z allele being predominantly associated with liver disease. PiZZ homozygotes occur in about 1 in 2000–5000 births in Western countries (review: Teckman 2013). HCC in AATD chiefly occurs in male patients and develops in several AATD genotypes. HCC was found as a complication of ATAD in the PiZZ phenotype, but there are also reported cases for the MZ phenotype, heterozygous ATA deficiency regarded as a cofactor for chronic liver disease and HCC, in the PiSZ genotype, and the Mmalton variant. The prevalence of HCC in patients with ATA deficiency was comparable to that of HCC in patients with cirrhosis of other etiologies. Apart from HCC, AATD may also confer genetic risk for cholangiocarcinoma.

Selected References Eriksson and Hägerstrand 1974; Rawlings et al. 1974; Schleissner and Cohen 1975; Palmer and Wolfe 1976; Rubel et al. 1982; Reid et al. 1987; Propst et al. 1994; Elzouki and Eriksson 1996; Zhou and Fischer 1998; Zhou et al. 2000; Rudnick and Perlmutter 2005; Mihalache et al. 2011; and Perlmutter and Silverman 2011.

The pathogenic pathways leading to HCC in ATA deficiency are incompletely known, but cirrhosis and other cirrhosis-related risk factors and the associated chronic augmentation of liver cell turnover are proposed to be involved (Perlmutter 2006; Topic et al. 2012). Patients with ATA-related cirrhosis showed a high prevalence of hepatitis viral infection (Propst et al. 1992). The abnormally folded AAT polymers that accumulate in the cisterns of the endoplasmic reticulum impair luminal protein mobility and sensitize the cell to endoplasmic reticulum stress (Ordonez et al. 2013), a factor known to be involved in neoplastic transformation. In fact, continuously augmented cell loss and compensatory hepatocyte regeneration are considered a driving force for carcinogenesis in AATD (Perlmutter 2006). The

cytotoxic effects exerted by the abnormally folded serpin are counteracted by the degeneration of the abnormal proteins by both proteasomal and autophagic pathways (Kamimoto et al. 2006), and these pathways may fail in the course of abnormal regeneration. In the course of disease, ATA undergoes stepwise changes in the degree of fucosylation ending up with a HCC-specific modification (Comunale et al. 2010).

Citrullinemia

HCC was found as a complication of asymptomatic adult-onset type II citrullinemia caused by mutations in the SLC25A13 gene and associated with citrin deficiency (Hagiwara et al. 2003; Tsai et al. 2006; Soeda et al. 2008). Downregulation of citrin, a mitochondrial aspartate-glutamate carrier primarily expressed in hepatocytes, is associated with hepatocyte apoptosis through the mitochondrial death pathway (Sawada et al. 2007), and this deregulation of cell survival and compensatory mechanisms may be involved in carcinogenesis. On the other hand, citrullinemia type II causes hepatic steatosis (Tsai et al. 2006), which as such is a known risk factor for HCC.

Inborn Cholestatic Syndromes and Disorders of Bilirubin Metabolism

Congenital disorders associated with severe cholestasis are known to be a risk factor for HCC, including progressive familial intrahepatic cholestasis/PFIC (Ugarte and Gonzalez-Crussi 1981; Knisely et al. 2006; Davit-Spraul et al. 2010), Alagille syndrome (Kim et al. 2005; Tsai et al. 2010), biliary atresia (Hol et al. 2008; Hadzic et al. 2011), and congenital liver fibrosis (Adams 1986). In PFIC, PFIC2 caused by mutations in ABCB11 encoding the bile salt pump/BSEP has a higher risk of HCC in comparison with PFIC1 (Davit-Spraul et al. 2010). Several types of disorders of bilirubin metabolism can be complicated by HCC, e.g., Dubin-Johnson syndrome (Okamura et al. 1980; Sakamoto et al. 1987; Shikada et al. 2004).

References

Achard C, Leblanc A (1921) Cirrhosis bronze. Bull Mém Soc Méd Hôp Paris 45:1689

Adams PC (1986) Hepatocellular carcinoma associated with arteriohepatic dysplasia. Dig Dis Sci 31:438–442

Adams PC (2009) The natural history of untreated HFE-related hemochromatosis. Acta Haematol 122:134–139

Adams PC (2014) Hepcidin in hemochromatosis: the message or the messenger? Hepatology 59:749–750

Albouisson et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23695678

Alexander J, Kowdley KV (2009) HFE-associated hereditary hemochromatosis. Genet Med 11:307–313

Allen MK (2010) Hereditary hemochromatosis: a literature review and case report. Physiother Can 62:276–284

Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, McLaren CE et al (2008) Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med 358:221–230

Altmann HW (1977) Iron containing nuclear inclusions in human pigmentary cirrhosis (in German). Virchows Arch B Cell Pathol 23:277–290

Andant C, Puy H, Deybach JC, Soulé JC, Nordmann Y (1997) Occurrence of hepatocellular carcinoma in a case of hereditary coproporphyria. Am J Gastroenterol 92:1389–1390

Anderson GJ, Frazer DM (2006) Iron metabolisms meets signal transduction. Nature Genet 38:503–504

Andrews SC (2010) The ferritin-like superfamily: evolution of the biological iron storeman from a rubrerythrin-like ancestor. Biochim Biophys Acta 1800:691–705

Andriopoulos B, Corradini E, Xia Y, Faasse SA, Chen S, Grgurevic L, Knutson MD et al (2009) BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism. Nat Genet 41:482–487

Ansari S, Azarkivan A, Halagi F (2013) Incidence of hepatocellular carcinoma in patients with thalassemia who had hepatitis C. Acta Med Iran 51:404–407

Arden KE, Wallace DF, Dixon JL, Summerville L, Searle JW, Anderson GJ, Ramm GA et al (2003) A novel mutation in ferroportin1 is associated with haemochromatosis in a Solomon Island patient. Gut 52:1215–1217

Arends M, van Dussen L, Biegstraaten M, Hollak CE (2013) Malignancies and monoclonal gammopathy in Gaucher disease; a systematic review of the literature. Br J Haematol 161:832–842

Armitage AE, Eddowes LA, Gileadi U, Cole S, Spottiswoode N, Selvakumar TA, Ho LP et al (2011) Hepcidin regulation by innate immune and infectious stimuli. Blood 118:4129–4139

Asare GA, Mossaranda KS, Kew MC, Paterson AC, Kahler-Venter CP, Siziba K (2006) Hepatocellular carcinoma caused by iron overload: a possible mechanism of direct hepatocarcinogenicity. Toxicology 219:41–52

Assis RA, Kassab C, Seguro FS, Costa FF, Silveira PA, Wood J, Hamerschlak N (2013) Iron overload in a

teenager with xerocytosis: the importance of nuclear magnetic resonance imaging. Einstein (Sao Paulo) 11:528–532
Babitt JL, Lin HY (2011) The molecular pathogenesis of hereditary hemochromatosis. Semin Liver Dis 31:280–292
Barry M, Scheuer P, Sherlock S, Ross CF, Williams R (1968) Hereditary spherocytosis with secondary haemochromatosis. Lancet 2:481–485
Bashir MR, Merkle EM, Kishnani PS (2012) Challenges in screening for hepatocellular carcinoma in the glycogen storage disease type 1a population. Intern Med 51:1811
Bassett ML, Hickman PE, Dahlstrom JE (2011) The changing role of liver biopsy in diagnosis and management of haemochromatosis. Pathology 43:433–439
Beckman LE, Hägerstrand I, Stenling R, Van Landeghem GF, Beckman L (2000) Interaction between haemochromatosis and transferrin receptor genes in hepatocellular carcinoma. Oncology 59:317–322
Bengtsson NO, Hardell L (1986) Porphyrias, porphyrins and hepatocellular carcinoma. Br J Cancer 54:115–117
Berman J, Braun A (1962) Incidence of hepatoma in porphyria cutanea tarda. Rev Czech Med 8:290
Beutler E (2006) Hemochromatosis: genetics and pathophysiology. Annu Rev Med 57:331–347
Bevers LE, Theil EC (2011) Maxi-and mini-ferritins: minerals and protein nanocages. Prog Mol Subcell Biol 52:29–47
Bianchi L (1993) Glycogen storage disease I and hepatocellular tumours. Eur J Pediatr 152(Suppl 1):S63–S70
Birch NC, Radio S, Horslen S (2003) Metastatic hepatocellular carcinoma in a patient with Niemann-Pick disease, type C. J Pediatr Gastroenterol Nutr 37:624–626
Bjersing L, Andersson C, Lithner F (1996) Hepatocellular carcinoma in patients from northern Sweden with acute intermittent porphyria: morphology and mutations. Cancer Epidemiol Biomarkers Prev 5:393–397
Blonski W, Kotlyar DS, Forde KA (2010) Non-viral causes of hepatocellular carcinoma. World J Gastroenterol 16:3603–3615
Blumberg RS, Chopra S, Ibrahim R, Crawford J, Farraye FA, Zeldis JB, Berman MD (1988) Primary hepatocellular carcinoma in idiopathic hemochromatosis after reversal of cirrhosis. Gastroenterology 95:1399–1402
Bonilla S, Prozialek JD, Malladi P, Pan X, Yu S, Melin-Aldana H, Whitington PF (2012) Neonatal iron overload and tissue siderosis due to gestational alloimmune liver disease. J Hepatol 56:1351–1355
Borgna-Pignatti C, De Stefano P, Sessa F, Avato F (1986) Hepatocellular carcinoma in thalassemia major. Med Pediatr Oncol 327–328
Borgna-Pignatti C, Vergine G, Lombardo T, Cappellini MD, Cianciulli P, Maggio A et al (2004) Hepatocellular carcinoma in the thalassaemia syndromes. Br J Haematol 124:114–117
Borgna-Pignatti C, Garani MC, Forni GL, Cappelini MD, Cassinerio E, Fidone C et al (2014) Hepatocellular carcinoma in thalassaemia. An update of the Italian Registry. Br J Haematol 167:121–126
Bothwell TH, Bradlow BA (1960) Siderosis in the Bantu. A combined histopathological and chemical study. Arch Pathol 70:279–292
Bothwell TH, Seftel H, Jacobs P (1964) Iron overload in Bantu subjects. Studies on the availability of iron in Bantu beer. Am J Clin Nutr 14:47–51
Bothwell TH, Abrahams C, Bardlow BA, Charlton RW (1965) Idiopathic and Bantu hemochromatosis. Comparative histological study. Arch Pathol 79:163–168
Britto MR, Thomas LA, Balaratnam N, Griffiths AP, Duane PD (2000) hepatocellular carcinoma arising in non-cirrhotic liver in genetic haemochromatosis. Scand J. Gastroenterol 35:889–893
Broussolle E, Trocello JM, Woimant F, Lachaux A, Quinn N (2013) Samuel Alexander Kinnier Wilson. Wilson's disease, Queen square and neurology. Rev Neurol (Paris) 169:927–935
Camaschella C, Silvestri L (2011) Molecular mechanisms regulating hepcidin revealed by hepcidin disorders. Sci World 11:1357–1366
Cassiman D, Vannoote J, Roelandts R, Libbrecht L, Roskams T, Van den Oord J, Fevery J et al (2008) Porphyria cutanea tarda and liver disease. A retrospective analysis of 17 cases from a single centre and review of the literature. Acta Gastroenterol Belg 71:237–242
Castilloux J, Laberge AM, Martin SR, Lallier M, Marchand V (2007) ''Silent" tyrosinemia presenting as hepatocellular carcinoma in a 10-year-old girl. J Pediatr Gastroenterol Nutr 44:375–377
Cauza E, Peck-Radosavljevic M, Ulrich-Pur H, Datz C, Gschwantler M, Schöniger-Hekele M et al (2003) Mutations of the HFE gene in patients with hepatocellular carcinoma. Am J Gastroenterol 98:442–447
Cefalu AB, Pirruccello JP, Noto D, Gabriel S, Valenti V, Gupta N, Spina R, Tarugi P et al (2013) A novel APOB mutation identified by exome sequencing cosegregates with steatosis, liver cancer, and hypocholesterolemia. Arterioscler Thromb Vasc Biol 33:2021–2025
Chagnon P, Michaud J, Mitchell G, Mercier J, Marion JF, Drouin E, Rasquin-Weber A et al (2002) A missense mutation (R565W) in cirhin (FLJ4728) in North American Indian childhood cirrhosis. Am J Hum Genet 71:1443–1449
Chen J, Chloupkova M (2009) Abnormal iron uptake and liver cancer. Cancer Biol Ther 8:1699–1708
Chen J, Enns CA (2012) Hereditary hemochromatosis and transferrin receptor 2. Biochim Biophys Acta 1820:256–263
Cheng WS, Govindarajan S, Redeker AG (1992) Hepatocellular carcinoma in a case of Wilson's disease. Liver 12:42–45
Chim CS, Chan V, Todd D (1998) Hemosiderosis with diabetes mellitus in untransfused hemoglobin H disease. Am J Hematol 57:160–163
Chung H, Kudo M, Kawasaki T, Kitano M, Minami Y, Suetomi Y, Onda H (2003) Hepatocellular carcinoma associated with secondary haemochromatosis in non-cirrhotic liver: a case report. Hepatol Res 26:254–258

Cliff JM (1969) Longstanding haemochromatosis with polyarthritis and terminal hepatoma. Proc R Soc Med 62:641

Comunale MA, Rodemich-Betesh L, Hafner J, Wang M, Norton P, Di Bisceglie AM et al (2010) Linkage specific fucosylation of alpha-1-antitrypsin in liver cirrhosis and cancer patients: implications for a biomarker of hepatocellular carcinoma. PLoS One 5, e12419

Conti JA, Kemeny N (1992) Type Ia glycogenosis associated with hepatocellular carcinoma. Cancer 69:1320–1322

Corradini E, Ferrara F, Pollicino T, Vegetti A, Abbati GL, Losi L, Raimondo G, Pietrangelo A (2007) Disease progression and liver cancer in the ferroportin disease. Gut 56:1030–1032

Cosme A, Montalvo I, Sanchez J, Ojeda E, Torrado J, Zapata E, Bujanda L, Gutierrez A et al (2005) Type III glycogen storage disease associated with hepatocellular carcinoma (in Spanish). Gastroenterol Hepatol 28:622–625

Cox and Moore 2002. http://www.ncbi.nlm.nih.gov/pubmed/12539960

D'Alessio F, Hentze MW, Muckenthaler MU (2012) The hemochromatosis proteins HFE, TfR2, and HJV form a membrane-associated protein complex for hepcidin regulation. J Hepatol 57:1052–1060

D'Anna MC, Roque ME (2013) Physiological focus on the erythropoietin –hepcidin-ferroportin axis. Can J Physiol Pharmacol 91:338–345

Davit-Spraul et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20422496

Day DL, Letourneau JG, Allan BT, Sharp HL, Ascher N, Dehner LP, Thompson WM (1987) Hepatic regenerating nodules in hereditary tyrosinemia. AJR Am J Roentgenol 149:391–393

De Domenico I, Ward DM, Musci G, Kaplan J (2006) Iron overload due to mutations in ferroportin. Haematologica 91:92–95

de Moor RA, Schweizer JJ, van Hoek B, Wasser M, Vink R, Maaswinkel-Mooy PD (2000) Hepatocellular carcinoma in glycogen storage disease type IV. Arch Dis Child 82:479–480

Dehner LP, Snover DC, Sharp HL, Ascher N, Nakhleh R, Day DL (1989) Hereditary tyrosinemia type I (chronic form): pathologic findings in the liver. Hum Pathol 20:149–158

Demo E, Frush D, Gottfried M, Koepke J, Boney A, Bali D, Chen YT, Kishnani PS (2007) Glycogen storage disease type III – hepatocellular carcinoma a long-term complication ? J Hepatol 46:492–498

Détivaud L, Island ML, Jouanolle AM, Ropert M, Bardou-Jacquet E, Le Lan C, Mosser A et al (2013) Ferroportin diseases: functional studies, a link between genetic and clinical phenotype. Hum Mutat 34:1529–1536

Deugnier Y, Turlin B (2001) Iron and hepatocellular carcinoma. J Gastroenterol Hepatol 16:491–494

Deugnier YM, Charalambous P, Le Quilleuc D, Turlin B, Searle J, Brissot P, Powell LW et al (1993) Preneoplastic significance of hepatic iron-free foci in genetic hemochromatosis: a study of 185 patients. Hepatology 18:1363–1369

Deugnier Y, Brissot P, Loréal O (2008) Iron and the liver: update 2008. J Hepatol 48:S113–S123

Devalia V, Carter K, Walker AP, Perkins SJ, Worwood M, May A, Dooley JS (2002) Autosomal dominant reticuloendothelial iron overload associated with a 3-base pair deletion in the ferroportin 1 gene (SLC11A3). Blood 100:695–697

Deybach JC, Puy H (2011) Hepatocellular carcinoma without cirrhosis: think acute hepatic porphyrias and vice versa. J Intern Med 269:521–524

Dierick HA, Adam AN, Escara-Wilke JF, Glover TW (1997) Immunocytochemical localization of the Menkes copper transport protein (ATP7A) to the trans-Golgi network. Hum Mol Genet 6:409–416

Drouin E, Russo P, Tuchweber B, Mitchell G, Rasquin-Weber A (2000) North American Indian cirrhosis in children: a review of 30 cases. J Pediatr Gastroenterol Nutr 31:395–404

Du X, She E, Gelbart T, Truksa J, Lee P, Xia Y, Kohovananth K, Mudd S, Mann N et al (2008) The serine protease TMPRSS6 is required to sense iron deficiency. Science 320:1088–1092

Edgren G, Nyrén O, Melbye M (2008) Cancer as a ferrotoxic disease: are we getting hard stainless evidence ? J Natl Cancer Inst 100:976–977

Ellervik C, Birgens H, Tybjaerg-Hansen A, Nordestgaard BG (2007) hemochromatosis genotypes and risk of 31 disease endpoints: meta-analyses including 66,000 cases and 226,000 controls. Hepatology 46:1071–1080

Elzouki AN, Eriksson S (1996) Risk of hepatobiliary disease in adults with severe alpha 1-antitrypsin deficiency (PiZZ): is chronic viral hepatitis B or C an additional risk factor for cirrhosis and hepatocellular carcinoma ? Eur J Gastroenterol Hepatol 8:989–994

Eriksson S, Hägerstrand I (1974) Cirrhosis and malignant hepatoma in alpha 1-antitrypsin deficiency. Acta Med Scand 195:451–458

Fargion S, Fracanzani AL, Piperno A, Braga M, D'Alba R, Ronchi G, Fiorelli G (1994) Prognostic factors for hepatocellular carcinoma in genetic hemochromatosis. Hepatology 20:1426–1431

Fargion S, Stazi MA, Fracanzani AL, Mattioli M, Sampietro M, Tavazzi D, Bertelli C et al (2001) Mutations in the HFE gene and their interaction with exogenous risk factors in hepatocellular carcinoma. Blod Cells Mol Dis 27:505–511

Fargion S, Valenti L, Fracanzani AL (2011) Beyond hereditary hemochromatosis: new insights into the relationship between iron overload and chronic liver diseases. Dig Liver Dis 43:89–95

Fellows IW, Stewart M, Jeffcoate WJ, Smith PG, Toghill PJ (1988) Hepatocellular carcinoma in primary haemochromatosis in the absence of cirrhosis. Gut 29:1603–1606

Fernandes A, Preza GC, Phung Y, De Domenico I, Kaplan J, Ganz T, Nemeth E (2009) The molecular

basis of hepcidin-resistant hereditary hemochromatosis. Blood 114:437–443
Finberg KE (2013) Regulation of systemic iron homeostasis. Curr Opin Hematol 20:208–214
Finberg KE, Whittlesey RL, Fleming MD, Andrews NC (2010) Down-regulation of Bmp/Smad signaling by Tmprss6 is required for maintenance of systemic iron homeostasis. Blood 115:3817–3826
Fleming RE (2005) Advances in understanding the molecular basis for the regulation of dietary iron absorption. Curr Opin Gastroenterol 21:201–206
Flinn FB, von Glahn WC (1929) Pigment cirrhosis of the liver. J Exp Med 49:5
Fracanzani AL, Fargion S, Stazi MA, Valenti L, Amoroso P, Cariani E, Sangiovanni A et al (2005) Association between heterozygosity for HFE mutations and hepatitis viruses in hepatocellular carcinoma. Blood Cells Mol Dis 35:27–32
Fragatou S, Tsourveloudis I, Manesis G (2010) Incidence of hepatocellular carcinoma in a thalassemia unit. Hemoglobin 34:221–226
Franchini M (2006) Hereditary iron overload: update on pathophysiology, diagnosis, and treatment. Am J Hematol 81:202–209
Franchini M, Veneri D (2005) Recent advances in hereditary hemochromatosis. Ann Hematol 84:347–352
Franco LM, Krishnamurthy V, Bali D, Weinstein DA, Arn P, Clary B, Boney A, Sullivan J et al (2005) Hepatocellular carcinoma in glycogen storage disease type Ia: a case series. J Inherit Metab Dis 28:153–162
Freed EF, Baserga SJ (2010) The C-terminus of Utp4, mutated in childhood cirrhosis, is essential for ribosome biogenesis. Nucleic Acids Res 38: 4798–4806
Freed EF, Prieto JL, McCann KL, McStay B, Baserga SJ (2012) NOL11, implicated in the pathogenesis of North American Indian childhood cirrhosis, is required for pre-rRNA transcription and processing. PLoS Genet 8, e1002892
Fujita N, Takei Y (2011) Iron overload in nonalcoholic steatohepatitis. Adv Clin Chem 55:105–132
Fujita N, Miyachi H, Tanaka H, Takeo M, Nakagawa N, Kobayashi Y, Iwasa M, Watanabe S et al (2009) Iron overload is associated with hepatic oxidative damage to DNA in nonalcoholic steatohepatitis. Cancer Epidemiol Biomarkers Prev 18:424–432
Gac GL, Ka C, Joubrel R, Gourlaouen I, Lehn P, Mornon JP, Férec C, Callebaut I (2013) Structure-function analysis of the human ferroportin iron exporter (SLC40A1): effect of hemochromatosis type 4 disease mutations and identification of critical residues. Hum Mutat 34:1371–1380
Gan EK, Powell LW, Olynyk JK (2011) Natural history and management of HFE-hemochromatosis. Semin Liver Dis 31:293–301
Gangaidzo IT, Gordeuk VR (1995) Hepatocellular carcinoma and African iron overload. Gut 37:727–730
Ganz T (2007) Molecular control of iron transport. J Am Soc Nephrol 18:394–400
Ganz T, Nemeth E (2012) Hepcidin and iron homeostasis. Biochim Biophys Acta 1823:1434–1443
Gentz J, Heinrich J, Lindblad B, Lindstedt S, Zetterström R (1969) Enzymatic studies in a case of hereditary tyrosinemia with hepatoma. Acta Paediatr Scand 58:393–396
Girelli D, Trombini P, Busti F, Campostrini N, Sandri M, Pelucchi S, Westerman M et al (2011) A time course of hepcidin response to iron challenge in patients with HFE and TFR2 hemochromatosis. Haematologica 96:500–506
Gisbert JP, Garcia-Buey L, Alonso A, Rubio S, Hernandez A, Pajares JM, Garcia-Diez A et al (2004) Hepatocellular carcinoma risk in patients with porphyria cutanea tarda. Eur J Gastroenterol Hepatol 16:689–692
Gkouvatsos K, Papanikolaou G, Pantopoulos K (2012) regulation of iron transport and the role of transferrin. Biochim Biophys Acta 1820:188–202
Goh J, Callagy G, McEntee G, O'Keane JC, Bomford A, Crowe J (1999) Hepatocellular carcinoma arising in the absence of cirrhosis in genetic haemochromatosis: three case reports and review of literature. Eur J Gastroenterol Hepatol 11:915–919
Gomatos IP, Alexakis N, Koskinas J, Smparounis SA, Katsaragakis S, Konstadoulakis MM et al (2013) Management of hepatocellular carcinoma in homozygous β-thalassemia cirrhotic patients. Am Surg 79:111–113
Gordeuk VR (1992) Hereditary and nutritional iron overload. Baillres Clin Haematol 5:169–186
Gordeuk VR, Boyd RD, Brittenham GM (1986) Dietary iron overload persists in rural sub-Saharan Africa. Lancet 1:1310–1313
Grossman H, Ram PC, Coleman RA, Gates G, Rosenberg ER, Bowie JD, Wilkinson RH (1981) Hepatic ultrasonography in type I glycogen storage disease (von Gierke disease). Detection of hepatic adenoma and carcinoma. Radiology 141:753–756
Guan R, Oon CJ, Wong PK, Foong WC, Wee A (1985) Primary hepatocellular carcinoma associated with Wilson's disease in a young woman. Postgrad Med J 61:357–359
Haagsma EB, Smit GP, Niezen-Koning KE, Gouw AS, Meerman L, Slooff MJ (1997) Type IIIb glycogen storage disease associated with end-stage cirrhosis and hepatocellular carcinoma. Hepatology 25: 537–540
Haddow JE, Palomaki GE, McClain M, Craig W (2003) Hereditary haemochromatosis and hepatocellular carcinoma in males: a strategy for estimating the potential for primary prevention. J Med Screen 10:11–13
Hadzic N, Quaglia A, Portmann B, Paramalingam S, Heaton ND, Rela M, Mieli-Vergani G et al (2011) Hepatocellular carcinoma in biliary atresia: King's College Hospital experience. J Pediatr 159:617–622
Hagiwara N, Sekijima Y, Takei Y, Ikeda S, Kawasaki S, Kobayashi K, Saheki T (2003) Hepatocellular carcinoma in a case of adult-onset type II citrullinemia. Intern Med 42:978–982

Harrison SA, Bacon BR (2005) Relation of hemochromatosis with hepatocellular carcinoma: epidemiology, natural history, pathophysiology, screening, treatment, and prevention. Med Clin North Am 89: 391–409

Hasan NM, Gupta A, Polishchuk E, Yu CH, Polishchuk R, Dmitriev OY, Lutsenko S (2012) Molecular events initiating exit of a copper-transporting ATPase ATP7B from the trans-Golgi network. J Biol Chem 287:36041–36050

Hayashi H, Shinohara T, Goto K, Fujita Y, Murakami Y, Hattori A, Tatsumi Y, Shimizu A et al (2012) Liver structures of a patient with idiopathic copper toxicosis. Med Mol Morphol 45:105–109

Hellerbrand C, Pöppl A, Hartmann A, Schölmerich J, Lock G (2003) HFE C282Y heterozygosity in hepatocellular carcinoma: evidence for an increased prevalence. Clin Gastroenterol Hepatol 1:279–284

Hiatt T, Trotter JF, Kam I (2007) Hepatocellular carcinoma in a noncirrhotic patient with hereditary hemochromatosis. Am J Med Sci 334:228–230

Hibbs DK (1927) Hemochromatosis and primary carcinoma of the liver. Trans Chicago Path Soc 12:331

Hines C, Davis WD, Ferrante WA (1971) Hepatoma developing in hemochromatosis in spite of adequate treatment by multiple phlebotomies. Am J Dig Dis 16:349–355

Hol L, van den Bos IC, Hussain SM, Zondervan PE, de Man RA (2008) Hepatocellular carcinoma complicating biliary atresia after Kasai portoenterostomy. Eur J Gastroenterol Hepatol 20:227–231

Huang X (2003) Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. Mutat Res 533:153–171

Huang ML, Lane DJ, Richardson DR (2011) Mitochondrial mayhem: the mitochondrion as a modulator of iron metabolism and its role in disease. Antioxid Redox Signal 15:3003–3019

Hurst PE, Kakulas BA, Walters MN (1961) Hepatoma developing in treated haemochromatosis: report of a case. Med J Aust 48:18–21

Huster D, Kühne A, Bhattacharjee A, Raines L, Jantsch V, Noe J, Schirrmeister W et al (2012) Diverse functional properties of Wilson disease ATP7B variants. Gastroenterology 142:947–956

Ikegawa S, Hiraoka A, Shimizu Y, Hidaka S, Tazuya N, Ichiryu M, Nakahara H, Tanabe A et al (2011) Hepatocellular carcinoma in a case of Wilson's disease treated with radiofrequency ablation therapy. Intern Med 50:1433–1437

Ito K, Mitchell DG, Gabata T, Hann HW, Kim PN, Fujita T, Awaya H, Honjo K, Matsunaga N (1999) Hepatocellular carcinoma: association with increased iron deposition in the cirrhotic liver at MR imaging. Radiology 212:235–240

Jaskiewicz et al. 1991. http://www.ncbi.nlm.nih.gov/pubmed/1663722

Jaskiewicz K, Banach L, Lancaster E (1997) Hepatic siderosis, fibrosis and cirrhosis: the association with hepatocellular carcinoma in high-risk population. Anticancer Res 17:3897–3899

Jin F, Qu LS, Shen XZ (2010) Association between C282Y and H63D mutations of the HFG gene with hepatocellular carcinoma in European populations: a meta-analysis. J Exp Clin Cancer Res 29:18

Johncilla M, Mitchell KA (2011) Pathology of the liver in copper overload. Semin Liver Dis 31:239–244

Johnson EE, Sandgren A, Cherayil BJ, Murray M, Wessling-Resnick M (2010) Role of ferroportin in macrophage-mediated immunity. Infect Immun 78:5099–5106

Kaler SG (2013) Inborn errors of copper metabolism. Handb Clin Neurol 113:1745–1754

Kamakura K, Kimura S, Igarashi S et al (1975) A case of Wilson's disease with hepatoma. J Jpn Soc Intern Med 64:232–238

Kamimoto T, Shoji S, Hidvegi T, Mizushima N, Umebayashi K, Perlmutter DH, Yoshimori T (2006) Intracellular inclusions containing mutant alpha1-antitrypsin Z are propagated in the absence of autophagic activity. J Biol Chem 281:4467–4476

Kanwar P, Kowdley KV (2013) Diagnosis and treatment of hereditary hemaochromatosis: an update. Expert Rev Gastroenterol Hepatol 7:517–530

Kaplan J, Ward DM, De Domenico I (2011) The molecular basis of iron overload disorders and iron-linked anemias. Int J Hematol 93:14–20

Keczkes K, Barker DJ (1976) Malignant hepatoma associated with acquired hepatic cutaneous porphyria. Arch Dermatol 112:78–82

Keith WD, McNair AY (1930) Hemochromatosis, diabetes mellitus, primary carcinoma of the liver. Canad Med Ass J 22:529

Kew MD (1990) Pathogenesis of hepatocellular carcinoma in hereditary hemochromatosis: occurrence in noncirrhotic patients. Hepatology 11:1086–1087

Kew MC (2009) Hepatic iron overload and hepatocellular carcinoma. Cancer Lett 286:38–43

Kew MC, Asare GA (2007) Dietary iron overload in the African and hepatocellular carcinoma. Liver Int 27:735–741

Kew MC, Turnbull R, Prinsloo I (1978) Alpha1-antitrypsin deficiency and hepatocellular cancer. Br J Cancer 37:635–638

Kijima H, Sawada T, Tomosugi N, Kubota K (2008) Expression of hepcidin mRNA is uniformly suppressed in hepatocellular carcinoma. BMC Cancer 8:167

Kim SZ, Kupke KG, Ierardi-Curto L, Holme E, Greter J, Tanguay RM, Poudrier J et al (2000) Hepatocellular carcinoma despite long-term survival in chronic tyrosinemia I. J Inherit Metab Dis 23:791–804

Kim B, Park SH, Yang HR, Seo JK, Kim WS, Chi JG (2005) Hepatocellular carcinoma occurring in Alagille syndrome. Pathol Res Pract 201:55–60

Knaupp AS, Levina V, Robertson AL, Pearce MC, Bottomley SP (2010) Kinetic instability of the serpin Z alpha1-antitrypsin promotes aggregation. J Mol Biol 396:375–383

Knisely AA, Strautnieks SS, Meier Y, Stieger B, Byrne JA, Portmann BC, Bull LN et al (2006) Hepatocellular carcinoma in ten children under five years of age with bile salt export pump deficiency. Hepatology 44:478–486

Ko C, Siddaiah N, Berger J, Gish R, Brandhagen D, Sterling RK, Cotler SJ, Fontana RJ et al (2007) Prevalence of hepatic iron overload and association with hepatocellular cancer in end-stage liver disease: results from the National Hemochromatosis Transplant Registry. Liver Int 27:1394–1401

Kodama H, Fujisawa C, Bhadhprasit W (2012) Inherited copper transport disorders: biochemical mechanisms, diagnosis, and treatment. Curr Drug Metab 13:237–250

Köhler HH, Höhler T, Küsel U, Kirkpatrick CJ, Schirmacher P (1999) Hepatocellular carcinoma in a patient with hereditary hemochromatosis and noncirrhotic liver. A case report. Pathol Res Pract 195:509–513

Köhnlein T, Welte T (2008) Alpha-1 antitrypsin deficiency: pathogenesis, clinical presentation, diagnosis, and treatment. Am J Med 121:3–9

Kong WN, Lei YH, Chang YZ (2013) The regulation of iron metabolism in the mononuclear phagocyte system. Expert Rev Hematol 6:411–418

Kordac V (1972) Frequency of occurrence of hepatocellular carcinoma in patients with porphyria cutanea tarda in long-term follow-up. Neoplasma 19: 135–139

Kowdley KV (2004) Iron, hemochromatosis, and hepatocellular carcinoma. Gastroenterology 127(Suppl 1): S79–S86

Kumagi T, Horiike N, Abe M, Kurose K, Iuchi H, Masumoto T, Joko K, Akbar SF, Michitaka K et al (2005) Small hepatocellular carcinoma associated with Wilson's disease. Intern Med 44:439–443

Lalioti et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19482593

Lane DJ, Huang ML, Richardson DR (2013) Hepcidin, show some self-control ! How the hormone of iron metabolism regulates its own expression. Biochem J 452:e3–e5

Lang F, Lang E, Föller M (2012) Physiology and pathophysiology of eryptosis. Transfus Med Hemother 39:308–314

Lee PL, Beutler E (2009) Regulation of hepcidin and iron-overload disease. Annu Rev Pathol 4:489–515

Lee P, Rice L, McCarthy JJ, Beutler E (2009) Severe iron overload with a novel aminolevulinate synthase mutation and hepatitis C infection. A case report. Blood Cells Mol Dis 42:1–14

Lehmann U, Wingen LU, Brakensiek K, Wedemeyer H, Becker T, Heim A, Metzig K et al (2007) Epigenetic defects of hepatocellular carcinoma are already found in non-neoplastic liver cells from patients with hereditary haemochromatosis. Hum Mol Genet 16:1335–1342

Lim HW, Mascaro JM (1995) The porphyrias and hepatocellular carcinoma. Dermatol Clin 13:135–142

Limmer J, Fleig WE, Leupold D, Bittner R, Ditschuneit H, Beger HG (1988) Hepatocellular carcinoma in type I glycogen storage disease. Hepatology 8:531–537

Lithner F, Wetterberg L (1984) Hepatocellular carcinoma in patients with acute intermittent porphyria. Acta Med Scand 215:272

Loehlein W (1907) Drei Fälle von primärem Leberkarcinom. Beitr Pathol Anart Allgem Pathol 42:545–558

Lonardo A, Tarugi P, Ballarini G, Bagni A (1998) Familial heterozygous hypobetalipoproteinemia, extrahepatic primary malignancy, and hepatocellular carcinoma. Dig Dis Sci 43:2489–2492

Lopriore E, Mearin ML, Oepkes D, Devlieger R, Whitington PF (2013) Neonatal hemochromatosis: management, outcome, and prevention. Prenat Diagn 33:1221–1225

Lubarsch O (1929) Über Leberzirrhose insbesondere die Pigmentzirrhose. Dtsch Med Wochenschr 55:1749

Luciani N, Brasse-Lagnel C, Poli M, Anty R, Lesueur C, Cormont M, Laguerriere A et al (2011) Hemojuvelin: a new link between obesity and iron homeostasis. Obesity (Silver Spring) 19:1545–1551

Lwakatare F, Hayashida Y, Yamashita Y (2003) MR imaging of hepatocellular carcinoma arising in genetic hemochromatosis. Magn Reson Med Sci 2:57–59

Maakaron JE, Cappellini MD, Graziadei G, Ayache JB, Taher AT (2013) Hepatocellular carcinoma in hepatitis-negative patients with thalassemia intermedia: a closer look at the role of siderosis. Ann Hepatol 12:142–146

Maegdefrau U, Arndt S, Kivorski G, Hellerbrand C, Bosserhoff AK (2011) Downregulation of hemojuvelin prevents inhibitory effects of bone morphogenetic proteins on iron metabolism in hepatocellular carcinoma. Lab Invest 91:1615–1623

Mancuso A (2010) Hepatocellular carcinoma in thalassemia: a critical review. World J Hepatol 2:171–174

Mancuso A, Rigano P, Renda D, Di Salvo V, Pignatti CB, Guddo F, Buccellato A, Nicoli N et al (2005) Hepatocellular carcinoma on cirrhosis-free liver in a HCV-infected thalassemic. Am J Hematol 78:158–159

Mancuso A, Sciarrino E, Renda MC, Maggio A (2006) A prospective study of hepatocellular carcinoma incidence in thalassemia. Hemoglobin 30:119–124

Mandishona E, MacPhail AP, Gordeuk VR, Kedda MA, Paterson AC, Rouault TA et al (1998) Dietary iron overload as a risk factor for hepatocellular carcinoma in Black Africans. Hepatology 27:1563–1566

Manzia TM, Angelico R, Toti L, Cillis A, Ciano P, Orlando G, Anselmo A, Angelico M et al (2011) Glycogen storage disease type Ia and VI associated with hepatocellular carcinoma: two case reports. Transplant Proc 43:1181–1183

Martinelli D, Travaglini L, Drouin CA, Ceballos-Picot I, Rizza T, Bertini E, Carrozzo R et al (2013) MEDNIK syndrome: a novel defect of copper metabolism treatable by zinc acetate therapy. Brain 136:872–881

Maurer E, Gütschow M, Stirnberg M (2012) Matriptase-2 (TMPRSS6) is directly up-regulated by hypoxia

inducible factor-1: identification of a hypoxia-responsive element in the TMPRSS6 promoter region. Biol Chem 393:535–540

Mayr R, Janecke AR, Schranz M, Griffiths WJ, Vogel W, Pietrangelo A, Zoller H (2010) Ferroportin disease: a systematic meta-analysis of clinical and molecular findings. J Hepatol 53:941–949

McDonald CJ, Wallace DF, Crawford DH, Subramaniam VN (2013) Iron storage disease in Asia-Pacific populations: the importance of non-HFE mutations. J Gastroenterol Hepatol 28:1087–1094

Meynard D, Vaja V, Sun CC, Corradini E, Chen S, Lopez-Otin C, Grgurevic L, Hong CC et al (2011) Regulation of TMPRSS6 by BMP6 and iron in human cells and mice. Blood 118:747–756

Mihalache F, Höblinger A, Grünhage F, Krawczyk M, Gärtner BC, Acalovschi M, Sauerbruch T et al (2011) Heterozygosity for the alpha1-antitrypsin Z allele may confer genetic risk of cholangiocarcinoma. Aliment Pharmacol Ther 33:389–394

Mikuriya Y, Oshita A, Tashiro H, Amano H, Kobayashi T, Arihiro K, Ohdan H (2012) Hepatocellular carcinoma and focal nodular hyperplasia of the liver in a glycogen storage disease patient. World J Hepatol 4:191–195

Mleczko-Sanecka K, Casanovas G, Ragab A, Breitkopf K, Müller A, Boutros M, Dooley S et al (2010) SMAD7 controls iron metabolism as a potent inhibitor of hepcidin expression. Blood 115:2657–2665

Mogl MT, Pascher A, Presser SJ, Schwabe M, Neuhaus P, Nuessler NC (2007) An unhappy triad: hemochromatosis, porphyria cutanea tarda and hepatocellular carcinoma – a case report. World J Gastroenterol 13:1998–2001

Montpetit A, Côté S, Brustein E, Drouin CA, Lapointe L, Boudreau M, Meloche C, Drouin R et al (2008) Disruption of AP1S1, causing a novel neurocutaneous syndrome, perturbs development of the skin and spinal cord. PLoS Genet 4, e1000296

Morcos M, Dubois S, Bralet MP, Belghiti J, Degott C, Terris B (2001) Primary liver carcinoma in genetic hemochromatosis reveals a broad histologic spectrum. Am J Clin Pathol 116:738–743

Moyo VM, Makunike R, Gangaidzo IT, Gordeuk VR, McLaren CE, Khumalo H, Saungweme T et al (1998) African iron overload and hepatocellular carcinoma (HA-7-0-080). Eur J Haematol 60:28–34

Müller T, Feichtinger H, Berger H, Müller W (1996) Endemic Tyrolean infantile cirrhosis: an ecogenetic disorder. Lancet 347:877–880

Müller T, van de Sluis B, Müller W, Pearson P, Wijmenga C (1999) Non-Indian childhood cirrhosis. Eur J Med Res 4:293–297

Müller-Höcker J (1999) Pathomorphology of the liver in exogenic infantile copper intoxication in Germany. Eur J Med Res 4:229–232

Musallam KM, Cappellini MD, Wood JC, Taher AT (2012) Iron overload in non-transfusion-dependent thalassemia: a clinical perspective. Blood Rev 26(Suppl 1): S16–S19

Musunuru K, Pirruccello JP, Do R, Peloso GM, Guiducci C, Sougnez C, Garimella KV et al (2010) Exome sequencing, ANGPTL3 mutations, and familial combined hypolipidemia. N Engl J Med 363:2220–2227

Nagasaka H, Kobayashi K, Yorifuji T, Kage M, Kimura A, Takayanagi M, Kikuta H et al (1999) Indian childhood cirrhosis-like disease in a Japanese boy undergoing liver transplantation. J Pediatr Gastroenterol Nutr 29:598–600

Nash HL, Kaung DT (1962) Carcinoma of the liver, hemochromatosis, and polycythemia: a case report. J Iowa State Med Soc 52:789–791

Nayak NC, Chitale AR (2013) Indian childhood cirrhosis (ICC) & ICC-like diseases: the changing scenario of facts versus notions. Indian J Med Res 137:1029–1042

Nemeth E, Ganz T (2006) Regulation of iron metabolism by hepcidin. Annu Rev Nutr 26:323–342

Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, Kaplan J (2004) Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 306:2090–2093

Nemeth E, Roetto A, Garozzo G, Ganz T, Camaschella C (2005) Hepcidin is decreased in TFR2 hemaochromatosis. Blood 105:1803–1806

Nobili V, Jenkner A, Francalanci P, Castellano A, Holme E, Callea F, Dionisi-Vici C (2010) Tyrosinemia type 1: metastatic hepatoblastoma with a favorable outcome. Pediatrics 126:e235–e238

Noto D, Cefalu AB, Valenti V, Fayer F, Pinotti E, Ditta M, Spina R, Vigna G, Yue P et al (2012) Prevalence of ANGPTL3 and APOB gene mutations in subjects with combined hypolipidemia. Arterioscler Thromb Vasc Biol 32:805–809

Ochi H, Hiraoka A, Uehara T, Hidaka S, Kawasaki H, Furuya K, Hirooka M, Abe M et al (2011) Abdominal imaging findings of a patient with hepatocellular carcinoma associated with glycogen storage disease type 1a. Intern Med 50:2317–2322

Ochiai T, Morishima T, Kondo M (1997) Symptomatic porphyria secondary to hepatocellular carcinoma. Br J Dermatol 136:129–131

Okamura J, Monden M, Horikawa S, Sikujara O, Kosaki G, Seki K, Kuroda C, Sakurai M (1980) Hepatocellular carcinoma in a case of Dubin-Johnson syndrome treated successfully with right extended lobectomy. Jpn J Surg 10:343–347

Okuda Y, Ota H, Mikami K, Nagase H, Mukai R, Okada K, Ide Y, Yanagisawa T, Maruyama K et al (2009) A case of glycogen storage disease type I with hepatocellular carcinoma (in Japanese). Gan To Kagaku Royho 36:2362–2364

Onal IK, Turhan N, Oztas E, Arhan M, Akcoren Z, Oguz P, Akdogan M, Onal ED et al (2009) Hepatocellular carcinoma in an adult patient with type IV glycogen storage disease. Acta Gastroenterol Belg 72:377–378

Ordonez A, Snapp EL, Tan L, Miranda E, Marciniak SJ, Lomas DA (2013) Endoplasmic reticulum polymers

impair luminal protein mobility and sensitize to cellular stress in alpha1-antitrypsin deficiency. Hepatology 57:2049–2060
Orr JW (1930) Primary carcinoma of the liver in a case of hemochromatosis. Lancet 1:1400
Packe GE, Clarke CW (1985) Is porphyria cutanea tarda a risk factor in the development of hepatocellular carcinoma ? A case report and review of the literature. Oncology 42:44–47
Palmer PE, Wolfe HJ (1976) Alpha-antitrypsin deposition in primary hepatic carcinomas. Arch Pathol Lab Med 100:232–236
Pandit and Bhave 1996. http://www.ncbi.nlm.nih.gov/pubmed/8615370
Pandit AN, Bhave SA (2002) Copper metabolic defects and liver disease: environmental aspects. J Gastroenterol Hepatol 17(Suppl 3):S403–S407
Parfrey PS, Squier M (1978) Thalassaemia minor, iron overload, and hepatoma. Br Med J 1:416
Patra S, Vij M, Kancherala R, Samal SC (2013) Is Indian childhood cirrhosis an extinct disease now ? – an observational study. Indian J Pediatr 80:651–654
Pellisè M, Gnzalez-Abraldes J, Navasa M, Miquel R, Bruguera M (2001) Hepatocellular carcinoma in a patient with hereditary hemochromatosis without cirrhosis (in Spanish). Gastroenterol Hepatol 24:132–134
Pennington DJ, Sivit CJ, Chandra RS (1996) Hepatocellular carcinoma in a child with Niemann-Pick disease: imaging findings. Pediatr Radiol 26:220–221
Perlmutter DH (2006) Pathogenesis of chronic liver injury and hepatocellular carcinoma in alpha-1-antitrypsin deficiency. Pediatr Res 60:233–238
Perlmutter DH, Silverman GA (2011) Hepatic fibrosis and carcinogenesis in α1-antitrypsin deficiency: a prototype for chronic tissue damage in gain-of-function disorders. Cold Spring Harb Perspect Biol 3:pII:a005801
Pierach CA, Bossenmaier IC, Cardinal RA, Weimer MK (1984) Pseudo-porphyria in a patient with hepatocellular carcinoma. Am J Med 76:545–548
Pietrangelo A (2004) The ferroportin disease. Blood Cells Mol Dis 32:131–138
Pietrangelo A, Caleffi A, Corradini E (2011) Non-HFE hepatic iron overload. Semin Liver Dis 31:302–318
Pleass H, Garden OJ (1998) Early diagnosis of hepatocellular carcinoma in haemochromatosis influences surgical management. Scott Med J 43:114–115
Point WW, MacMahon HE, Patterson JF (1957) Clinicopathologic conference: hemochromatosis, alcoholic cirrhosis and carcinoma of liver. Bull Tufts N Engl Med Cent 3:50–58
Poli M, Lusciei S, Gandini V, Maccarinelli F, Finazzi D, Silvestri L, Roetto A, Arosio P (2010) Transferrin receptor 2 and HFE regulate furin expression via mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/Erk) signaling. Implications for transferrin-dependent hepcidin regulation. Haematologica 95:1832–1840
Polio J, Enriquez RE, Chow A, Wood WM, Bradshaw JP (1989) Hepatocellular carcinoma in Wilson's disease. Case report and review of the literature. J Clin Gastroenterol 11:220–224
Pollicino T, Vegetti A, Saitta C, Ferrara F, Corradini E, Raffa G, Pietrangelo A, Raimondo G (2013) Hepatitis B virus DNA integration in tumour tissue of a non-cirrhotic HFE-haemochromatosis patient with hepatocellular carcinoma. J Hepatol 58:190–193
Preza GC, Pinon R, Ganz T, Nemeth E (2013) Cellular catabolism of the iron-regulatory peptide hormone hepcidin. PLoS One 8, e58934
Propst T, Propst A, Dietze O, Judmaier G, Braunsteiner H, Vogel W (1992) High prevalence of viral infection in adults with homozygous and heterozygous alpha 1-antitrypsin deficiency and chronic liver disease. Ann Intern Med 117:641–645
Propst T, Propst A, Dietze O, Judmaier G, Braunsteiner H, Vogel W (1994) Prevalence of hepatocellular carcinoma in alpha-1-antitrypsin deficiency. J Hepatol 21:1006–1011
Quante M, Benckert C, Thelen A, Ulhmann D, Bartels M, Moche M, Dollinger M, Wittekind C, Jonas S (2011) Liver transplantation to treat hepatocellular carcinoma in iron-free foci in congenital hemochromatosis: case report. Transplant Proc 43:2066–2069
Radio FC, Majore S, Binni F, Valiante M, Ricerca BM, De Bernardo C, Morrone A, Grammatico P (2014) TFR2-related hereditary hemochromatosis as a frequent cause of primary iron overload in patients from Central-Southern Italy. Blood Cells Mol Dis 52:83–87
Rapisarda C, Puppi J, Hughes RD, Dhawan A, Farnaud S, Evans RW, Sharp PA (2010) Transferrin receptor 2 is crucial for iron sensing in human hepatocytes. Am J Physiol Gastrointest Liver Physiol 299: G778–G783
Rawlings W, Moss J, Cooper HS, Hamilton SR (1974) Hepatocellular carcinoma and partial deficiency of alpha-1-antitrypsin (MZ). Ann Intern Med 81:771–773
Reid CL, Wiener GJ, Cox DW, Richter JE, Geisinger KR (1987) Diffuse hepatocellular dysplasia and carcinoma associated with the Mmalton variant of alpha 1-antitrypsin. Gastroenterology 93:181–187
Restivo Pantalone G, Renda D, Valenza F, D'Amato F, Vitrano A, Cassara F, Rigano P et al (2010) Hepatocellular carcinoma in patients with thalassaemia syndromes: clinical characteristics and outcome in a long term single centre experience. Br J Haematol 150:245–247
Richardson DR, Lane DJ, Becker EM, Huang ML, Whitnall M, Suryo Rahmanto Y et al (2010) Mitochondrial iron trafficking and the integration of iron metabolism between the mitochondrion and cytosol. Proc Natl Acad Sci U S A 107:10775–10782
Richter GW (1958) Electron microscopic hemosiderin: presence of ferritin and occurrence of crystalline lattices in hemosiderin deposits. J Biophys Biochem Cytol 4:55–58
Richter A, Mitchell GA, Rasquin A (2007) North American Indian childhood cirrhosis (NAIC) (in French). Med Sci (Paris) 23:1002–1007

Riva S, Spada M, Sciveres M, Minervini M, Cintorino D, Maggiore G, Gridelli B (2008) Hepatocarcinoma in a child with cholesterol ester storage disease. Dig Liver Dis 40:784

Rosencrantz R, Schilsky M (2011) Wilson disease: pathogenesis and clinical considerations in diagnosis and treatment. Semin Liver Dis 31:245–259

Rosenthal SR (1932) Hemochromatosis and primary carcinoma of the liver. Report of a case, with review of the literature and discussion of the pathogenesis. Arch Pathol 13:88–105

Rosmorduc O, Wendum D, Arrivé L, Elnaggar A, Ennibi A, Hannoun L, Charlotte F et al (2008) Phenotypic expression of ferroportin disease in a family with the N144H mutation. Gastroenterol Clin Biol 32:321–327

Rotman Y, Koh C, Zmuda JM, Kleiner DE, Liang TJ, NASH CRN (2010) The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. Hepatology 52:894–903

Rubel LR, Ishak KG, Benjamin SB, Knuff TE (1982) alpha-1-antitrypsin deficiency and hepatocellular carcinoma. Association with cirrhosis, copper storage, and Mallory bodies. Arch Pathol Lab Med 106:678–681

Ruchala P, Nemeth E (2014) The pathophysiology and pharmacology of hepcidin. Trends Pharmacol Sci 35:155–161

Rudnick DA, Perlmutter DH (2005) Alpha-1-antitrypsin deficiency: a new paradigm for hepatocellular carcinoma in genetic liver disease. Hepatology 42: 514–521

Runte J (1901) Der primäre Leberkrebs. Thesis, Bayrische Julius-Maximilians-Universität, Würzburg, Germany

Russo PA, Mitchell GA, Tanguay RM (2001) Tyrosinemia: a review. Pediatr Dev Pathol 4:212–221

Ryan Caballes F, Sendi H, Bonkovsky HL (2012) Hepatitis C, porphyria cutanea tarda and liver iron: an update. Liver Int 32:880–893

Sakamoto A, Mori I, Kawai K, Tsuchiyama H (1987) Dubin-Johnson syndrome associated with hepatocellular carcinoma – report of an autopsy case. Gan No Rinsho 33:1361–1367

Salama MF, Bayele HK, Srai SS (2012) Tumour necrosis factor alpha downregulates human hemojuvelin expression via a novel response element within its promoter. J Biomed Sci 19:83

Salata H, Cortés JM, Enriquez de Salamanca R, Oliva H, Castro A, Kusak E, Carreno V et al (1985) Porphyria cutanea tarda and hepatocellular carcinoma. Frequency of occurrence and related factors. J Hepatol 1:477–487

Sangokoya C, Doss JF, Chi JT (2013) Iron-responsive miR-485-3p regulates cellular iron homeostasis by targeting ferroportin. PLoS Genet 9, e1003408

Santos PC, Krieger JE, Pereira AC (2012) Molecular diagnostic and pathogenesis of hereditary hemochromatosis. Int J Mol Sci 13:1497–1511

Sarkar B, Roberts EA (2011) The puzzle posed by COMMD1, a newly discovered protein binding Cu (II). Metallomics 3:20–27

Sawada S, Kinjo T, Makishi S, Tomita M, Arasaki A, Iseki K, Watanabe H, Kobayashi K et al (2007) Downregulation of citrin, a mitochondrial AGC, is associated with apoptosis of hepatocytes. Biochem Biophys Res Commun 364:937–944

Schleissner LA, Cohen AH (1975) Alpha1-antitrypsin deficiency and hepatic carcinoma. Am Rev Respir Dis 111:863–868

Schneider-Yin X, van Tuyll van Serooskerken AM, Went P, Tyblewski W, Poblete-Gutierrez P et al (2010) Hepatocellular carcinoma in variegate porphyria: a serious complication. Acta Derm Venereol 90:512–515

Schonfeld G, Lin X, Yue P (2005) Familial hypobetalipoproteinemia: genetics and metabolism. Cell Mol Life Sci 62:1372–1378

Schwaibold EM, Bartels I, Küster H, Lorenz M, Burfeind P, Adam R, Zoll B (2014) De novo duplication of chromosome 16p in a female infant with signs of neonatal hemochromatosis. Mol Cytogenet 7:7

Seshadri MS, Dayal AK, Bhaktaviziam A (1982) Hepatoma in hemaochromatosis. J Assoc Physicians India 30:333–335

Shaw GC, Cope JJ, Li L, Corson K, Hersey C, Ackermann GE, Gwynn B, Lambert AJ et al (2006) Mitoferrin is essential for erythroid iron assimilation. Nature 440:96–100

Sheehan F, Connolly CE, McCarthy CF (1989) Hepatocellular carcinoma in idiopathic haemochromatosis. Gut 30:889

Shikada Y, Matsumata T, Suehiro T, Sugimachi K (2004) Hepatocellular carcinoma in a case of Dubin-Johnson syndrome treated successfully with a central bilateral segmentectomy. Hepatogastroenterology 51:833–836

Shimizu J, Shiraishi H, Sakurabayashi S, Sugiura F, Takizawa H, Miyazaki K et al (1982) A report on an adult case of type III glycogenosis with primary liver cancer and liver cirrhosis. Nippin Shokakibyo Gakkai Zasshi 79:2328–2332

Shiomi S, Saeki Y, Kim K, Nishiguchi S, Seki S, Kuroki T, Kobayashi K, Harihara S et al (1989) A female case of type VIII glycogenosis who developed cirrhosis of the liver and hepatocellular tumor. Gastroenterol Jpn 24:711–714

Shteyer E, Simanovsyk N, Koplewitz B, Korman SH (2011) Multiple hepatic lesions in a girl with tyrosinemia: not always hepatocellular carcinoma. J Pediatr 158:513–513.e1

Siah CW, Ombiga J, Adams LA, Trinder D, Olynyk JK (2006) Normal iron metabolism and the pathophysiology of iron overload disorders. Clin Biochem Rev 27:5–16

Siciliano M, De Candia E, Ballarin S, Vecchio FM, Servidei S, Annese R, Landolfi R et al (2000) hepatocellular carcinoma complicating liver cirrhosis in type

IIIa glycogen storage disease. J Clin Gastroenterol 31:80–82
Silvestri L, Pagani A, Nai A, De Domenico I, Kaplan J, Camaschella C (2008) The serine protease matriptase-2 (TMPRSS6) inhibits hepcidin activation by cleaving membrane hemojuvelin. Cell Metab 8:502–511
Singh A, Jolly SS, Balasubrahmanyan M (1959) Indian childhood cirrhosis. Br Med J 1:278–279
Singh B, Arora S, Agarwal P, Gupta SK (2011) Hepcidin: a novel peptide hormone regulating iron metabolism. Clin Chim Acta 412:823–830
Singh P, Kaur H, Lerner RG, Patel R, Rafiyath SM, Singh Lamba G (2012) Hepatocellular carcinoma in non-cirrhotic liver without evidence of iron overload in a patient with primary hemochromatosis. Review J Gastrointest Cancer 43:36–39
Sini M, Sorbello O, Sanna F, Battolu F, Civolani A, Fanni D, Faa G, Demelia L (2013) Histologic evolution and long-term outcome of Wilson's disease: results of a single-center experience. Eur J Gastroenterol Hepatol 25:111–117
Smith CL, Arvedson TL, Cooke KS, Dickmann LJ, Forte C, Li H, Merriam KL, Perry VK et al (2013) IL-22 regulates iron availability in vivo through the induction of hepcidin. J Immunol 191:1845–1855
Soeda J, Yazaki M, Nakata T, Miwa S, Ikeda S, Hosoda W, Iijima M, Kobayashi K et al (2008) Primary liver carcinoma exhibiting dual hepatocellular-biliary epithelial differentiations associated with citrin deficiency: a case report. J Clin Gastroenterol 42:855–860
Speliotes EK, Butler JL, Palmer CD, Voight BF, GIANT Consortium, MiGen Consortium, NASH CRN, Hirschhorn JN (2010) PNLPA3 variants specifically confer increased risk for histologic nonalcoholic fatty liver disease but not metabolic disease. Hepatology 52:904–912
Sriramachari S, Nayak NC (2008) Indian childhood cirrhosis: several dilemmas resolved. Indian J Med Res 128:93–96
Steegmann-Olmedillas JL (2011) The role of iron in tumour cell proliferation. Clin Tranl Oncol 13:71–76
Steinherz PG, Canale VC, Miller DR (1976) Hepatocellular carcinoma, transfusion-induced hemochromatosis and congenital hypoplastic anemia (Blackfan-Diamond syndrome). Am J Med 60:1032–1035
Sternlieb I (2000) Hepatology. A century of progress. In: Wilson's disease: clinics in liver disease, vol 4, no 1. W. B. Saunders, Philadelphia
Stewart MF (2012) Review of hepatocellular cancer, hypertension and renal impairment as late complications of acute porphyria and recommendations for patient follow-up. J. Clin Pathol 65:976–980
Strachan AS (1929) Haemosiderosis and haemochromatosis in South African natives with a comment on etiology of haemochromatosis. Thesis, University of Glasgow, Glasgow
Sumimoto S, Motoi T, Mikawa H, Honde H, Kobayashi N, Tanaka K, Ozawa K, Sudo M et al (1988) Type Ia glycogen storage disease with multiple hepatic adenomas and a highly differentiated hepatic carcinoma: a case report and review of the literature. Ann Paedfiatr Jpn 34:47–55
Takegoshi T, Nishino T, Tanino M, Nonokura A, Ohta G (1984) An autopsy case of hemochromatosis and hepatoma combined with hereditary spherocytosis. Jpn J Med 23:48–52
Talente GM, Colemen RA, Alter C, Baker L, Brown BI, Cannon RA, Chen YT, Crigler JF et al (1994) Glycogen storage disease in adults. Ann Intern Med 120:218–226
Tanner MS (1998) Role of copper in Indian childhood cirrhosis. Am J Clin Nutr 67(suppl):1074S–1081S
Tanner MS (1999) Indian childhood cirrhosis and Tyrolean childhood cirrhosis. Disorders of a copper transport gene ? Adv Exp Med Biol 448:127–137
Tazawa Y, Kikuchi M, Kurobane I, Watanabe A, Nakai H, Nariswa K, Tada K (1990) An acute form of tyrosinemia type I with multiple intrahepatic mass lesions. J Pediatr Gastroenterol Nutr 10:536–539
Teckman JH (2013) Liver disease in alpha-1 antitrypsin deficiency: current understanding and future therapy. COPD 10(Suppl 1):35–43
Thattil R, Dufour JF (2013) Hepatocellular carcinoma in a non-cirrhotic patient with Wilson's disease. World J Gastroenterol 19:2110–2113
Theil EC (2013) Ferritin: the protein nanocage and iron biomineral in health and in disease. Inorg Chem 52:12223–12233
Tiniakos and Williams 1988. http://www.ncbi.nlm.nih.gov/pubmed/2839215
Tirnitz-Parker JE, Glanfield A, Olynyk JK, Ramm GA (2013) Iron and hepatic carcinogenesis. Crit Rev Oncog 18:391–407
Topic A, Ljujic M, Radojkovic D (2012) Alpha-1-antitrypsin in pathogenesis of hepatocellular carcinoma. Hepat Mon 12, e7042
Toyokuni S (1996) Iron-induced carcinogenesis: the role of redox regulation. Free Radic Biol Med 20:553–566
Toyokuni S (2008) Molecular mechanisms of oxidative stress-induced carcinogenesis. from epidemiology to oxygenomics. IUBMB Life 60:441–447
Toyokuni S (2009) Role of iron in carcinogenesis: cancer as a ferrotoxic disease. Cancer Sci 100:9–16
Trépo E, Pradat P, Potthoff A, Momozawa Y, Quertinmont E, Gustoto T, Lemmers A et al (2011) Impact of patatin-like phospholipase-3 (rs738409 C>G) polymorphism on fibrosis progression and steatosis in chronic hepatitis C. Hepatology 54:60–69
Triantos C, Kourakli A, Kalafateli M, Giannakopoulou D, Koukias N, Thomopoulos K et al (2013) Hepatitis C in patients with β-thalassemia major. A single-centre experience. Ann Hematol 92:739–746
Trocello JM, Broussolle E, Girardot-Tinant N, Pelosse M, Lachaux A, Lloyd C, Woimant F (2013) Wilson's disease, 100 years later…. Rev Neurol (Paris) 169:936–943
Tsai CW, Yang CC, Chen HL, Hwu WL, Wu MZ, Liu KL, Wu MS (2006) Homozygous SLC25A13 mutation in a Taiwanese patient with adult-onset citrullinemia

complicated with steatosis and hepatocellular carcinoma. J Formos Med Assoc 105:852–856

Tsai S, Gurakar A, Anders R, Lam-Himlin D, Boitnott J, Pawlik TM (2010) Management of large hepatocellular carcinoma in adult patients with Alagille syndrome: a case report and review of literature. Dig Dis Sci 55:3052–3058

Tseng HH, Chang JG, Hwang YH, Yeh KT, Chen YL, Yu HS (2009) Expression of hepcidin and other iron-regulatory genes in human hepatocellular carcinoma and its clinical implications. J Cancer Res Clin Oncol 135:1413–1420

Ueki I, Kimura A, Chen HL, Yurifuji T, Mori J, Itoh S, Maruyama K, Ishige T, Takei H et al (2009) SRD5B1 gene analysis needed for the accurate diagnosis of primary 3-oxo-Delta-steroid 5beta-reductase deficiency. J Gastroenterol Hepatol 24:776–785

Ugarte N, Gonzalez-Crussi F (1981) Hepatoma in siblings with progressive familial cholestatic cirrhosis of childhood. Am J Clin Pathol 76:172–177

Vachon A, Paliard P, Grimaud JA, Peyrot-Guillard L, Reiss T (1973) Les étapes de l'atteinte hépatique de la dégénérescence hépatolenticulaire: lesions précoces, hypertension portale et dégénérescence cancéreuse. A propos de 4 observations. Lyon Med 230:591–598

Valenti L, Maggioni P, Piperno A, Rametta R, Pelucchi S, Mariani R, Dongiovanni P et al (2012) Patatin-like phospholipase domain containing-3 gene I148M polymorphism, steatosis, and liver damage in hereditary hemochromatosis. Wordl J Gastroenterol 18:2813–2820

Villanueva A, Newell P, Hoshida Y (2010) Inherited hepatocellular carcinoma. Best Pract Res Clin Gastroenterol 24:725–734

Von Delius S, Lersch C, Schulte-Frohlinde E, Fend F, Dobritz M, Schmid RM, Eckel F (2006) Hepatocellular carcinoma associated with hereditary hemochromatosis occurring in non-cirrhotic liver. Z Gastroenterol 44:39–42

Waheed A, Britton RS, Grubb JH, Sly WS, Fleming RE (2008) HFE association with transferrin receptor 2 increases cellular uptake of transferrin-bound iron. Arch Biochem Biophys 474:193–197

Wallace DF, Clark RM, Harley HAJ, Subramaniam VN (2004) Autosomal dominant iron overload due to a novel mutation of ferropoertin1 associated with parenchymal iron loading and cirrhosis. J Hepatol 40:710–713

Wallace DF, Summerville L, Crampton EM, Subramaniam VN (2008) Defective trafficking and localization of mutated transferrin receptor 2: implications for type 3 hereditary hemochromatosis. Am J Physiol Cell Physiol 294:C383–C390

Wang J, Pantopoulos K (2011) Regulation of cellular iron metabolism. Biochem J 434:365–381

Wang Q, Zhou J, Zhong D, Wang Q, Huang J (2013) Ferroportin in the progression and prognosis of hepatocellular carcinoma. Eur J Med Res 18:59

Wegelin H (1929) Ein Fall von Pigmentzirrhose. Verhandl Deutsch Path Ges 24:97

Weinberg AG, Mize CE, Worthen HG (1976) The occurrence of hepatoma in the chronic form of hereditary tyrosinemia. J Pediatr 88:434–438

Whitington PF (2012) Gestational alloimmune liver disease and neonatal hemochromatosis. Semin Liver Dis 32:325–332

Whittle C, Hepp J, Armas R, Schultz M (2010) Porphyria cutanea tarda, hemosiderosis and hepatocellular carcinoma: report of one case (in Spanish). Rev Med Chil 138:581–585

Wijmenga C, Müller T, Murli IS, Brunt T, Feichtinger H, Schönitzer D, Houwen RH et al (1998) Endemic Tyrolean infantile cirrhosis is not an allelic variant of Wilson's disease. Eur J Hum Genet 6:624–628

Wilkins BJ, Lorent K, Matthews RP, Pack M (2013) p53-mediated biliary defects caused by knockdown of cirh1a, the zebrafish homolog of the gene responsible for North American Indian childhood cirrhosis. PLoS One 10, e77670

Wilkinson ML, Portmann B, Williams R (1983) Wilson's disease and hepatocellular carcinoma: possible protective role of copper. Gut 24:767–771

Willis G, Wimperis JZ, Lonsdale R, Jennings BA (1997) Haemochromatosis gene mutation in hepatocellular cancer. Lancet 350:565–566

Willis G, Bardley V, Fellows IW, Lonsdale R, Wimperis JZ, Jennings BA (2005) Hepatocellular carcinoma and the penetrance of HFE C282Y mutations: a cross sectional study. BMC Gastroenterol 5:17

Wu Q, Sun CC, Lin HY, Babitt JL (2012) Repulsive guidance molecule (RGM) family proteins exhibit differential binding kinetics for bone morphogenetic proteins (BMPs). PLoS One 7, e46307

Wu XN, Su D, Wang L, Yu FL (2013) Roles of the hepcidin-ferroportin axis and iron in cancer. Eur J Cancer Rev

Wysocka M, Gruba N, Miecznikowska A, Poppow-Stellmaszyk J, Gütschow M, Stirnberg M et al (2014) Substrate specificity of human matriptase-2. Biochimie 97:121–127

Xu R, Bu-Ghanim M, Fiel MI, Schiano T, Cohen E, Thung SN (2007) Hepatocellular carcinoma associated with an atypical presentation of Wilson's disease. Semin Liver Dis 27:122–127

Yu B, Mitchell GA, Richter A (2005) Nucleolar localization of cirhin, the protein mutated in North American Indian childhood cirrhosis. Exp Cell Res 311:218–228

Zangeneh F, Limbeck GA, Brown BI, Emch JR, Arcasoy MM, Goldenberg VE, Kelley VC (1969) Hepatorenal glycogenosis (type I glycogenosis) and carcinoma of the liver. J Pediatr 74:73–83

Zarychanski R, Schulz VP, Houston BL, Maksimova Y, Houston DS, Smith B, Rinehart J et al (2012) Mutations in the mechanotransduction protein PIEZO1 are associated with hereditary xerocytosis. Blood 120:1908–1915

Zhang AS (2010) Control of systemic iron homeostasis by the hemojuvelin-hepcidin axis. Adv Nutr 1:38–45

Zhang Y, Orner BP (2011) Self-assembly in the ferritin nano-cage protein superfamily. Int J Mol Sci 12:5406–5421

Zhang AS, Anderson SA, Meyers KR, Hernandez C, Eisenstein RS, Enns CA (2007) Evidence that inhibition of hemojuvelin shedding in response to iron is mediated through neogenin. J Biol Chem 282:12547–12556

Zhang AS, Yang F, Wang J, Tsukamoto H, Enns CA (2009) Hemojuvelin-neogenin interaction is required for bone morphogenic protein-4-induced hepcidin expression. J Biol Chem 284:22580–22589

Zhao N, Zhang AS, Enns CA (2013) Iron regulation by hepcidin. J Clin Invest 123:2337–2343

Zhou H, Fischer HP (1998) Liver carcinoma in PiZ alpha-a-antitrypsin deficiency. Am J Surg Pathol 22: 742–748

Zhou H, Ortiz-Pallardo ME, Ko Y, Fischer HP (2000) Is heterozygous alpha-1-antitrypsin deficiency type PIZ a risk factor for primary liver carcinoma ? Cancer 88:2668–2676

Etiology and Pathogenesis of Hepatocellular Carcinoma: Chromosomal Alterations, Oncogenes, Tumor Suppressors, and Associated Signaling Networks

166

Contents

Abstract

In addition to the common viral and nonviral causes of hepatocellular carcinoma (HCC), etiology and pathogenesis of this malignancy depend on a wide array of chromosomal alterations, oncogenes, tumor suppressors, and associated signaling networks. HCC is associated with various recurrent chromosomal aberrations that are in part detectable in early-stage HCC already. Certain of these aberrations occur at high frequency and are alterations that can be employed in a diagnostic setting, e.g., chromosomal loci 8p and 8q, and several other loci with gains or losses. The loci defined by these LOH patterns harbor genes involved in hepatocarcinogenic pathways. The main gene products encoded by these genes include transcription factors (e.g., p53), receptor tyrosine kinases and other kinases, GTPases (such as Ras), components of the Wnt/beta-catenin signaling pathway, TGF-beta1 and associated signaling proteins, PTEN, and the Hedgehog signaling pathway.

Hepatocellular Carcinoma in Chromosomal Breakage Syndromes

Several progeroid disorders are characterized by early development of a phenotype of premature aging resembling "old man" appearance, a lipodystrophy phenotype, and the emergence of malignancies at young age. These features are

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_166

particularly characteristic for neonatal progeroid syndrome or Wiedemann-Rautenstrauch syndrome (OMIM 264090; review: Hou 2009), while adult progeria or Werner syndrome is characterized by a thin body. HCC can develop in progeroid syndromes (Ruijs et al. 2003) and in adult progeria/Werner syndrome, which has a defect in fibulin 3 expression (Okano et al. 2011).

Familial Clustering of Hepatocellular Carcinoma

There are relatively few reports documenting familial clustering of HCC, apart from cases related to inborn errors of metabolism as outlined above. Familial primary HCC was first reported to occur in three adult male siblings in 1965 (Kaplan and Cole 1965), and a second observation referred to three brothers with HCC, aged 11, 22, and 31 years, at diagnosis (Hagstrom and Dee Baker 1968). Familial occurrence of early-onset HCC was observed in patients showing a new segmental progeroid syndrome with genomic instability. The patients showed biallelic germline mutations in SPRTN (also termed C1orf124, DVC1, or Spartan), a protein involved in the prevention of DNA replication stress during general DNA replication and replication-related G2/M checkpoint regulation (Lessel et al. 2014). DNA-protein cross-links (DPCs) are highly toxic compounds which interfere with DNA transactions. Such cross-links can be repaired by Spartan (SprT-like domain-containing protein)/DVC1 (DNA damage protein targeting VCP), a protease of the eukaryotic DPC protease family which allows translesional DNA synthesis, a DNA damage tolerance process allowing DNA replication machinery to replicate past nucleotide lesions. Spartan/DVC1 is deficient in a progeroid syndrome and is a PCNA (proliferating cell nuclear antigen)-interacting protein. Binding to PCNA is a crucial step in lesion repair, because DNA damage-induced PCNA ubiquitination serves as a molecular mark to orchestrate postreplication repair. Spartan is directed to sites of DNA damage in a mechanism dependent on PCNA ubiquitination, PIP box, and UBZ domain, and Spartan interacts with Rad18, the E3 ubiquitin ligase that modifies PCNA (Centore et al. 2012; Ghosal et al. 2012).

Oncogenes, Tumor Suppressors, and Other Molecular Features in Hepatocarcinogenesis

Introduction

Liver cancers, in particular HCC, are subject to multiple genetic/genomic changes that involve genes that regulate growth, differentiation, apoptosis, and invasion and involved in hepatocarcinogenic pathways. The molecular signatures that are progressively identified in liver cancers will result in novel molecular classification that can serve for improved treatment stratifications.

Selected References Buendia 2002, 2007; Feitelson et al. 2002; Coleman 2003; Dufour et al. 2007; Martin and Dufour 2008; Wong and Ng 2008; Feo et al. 2009; Hoshida et al. 2009; McGivern and Lemon 2009; Merle and Trepo 2009; Totoki et al. 2011; van Malenstein et al. 2011; Calvisi et al. 2012; Li and Mao 2013; Nishida and Kudo 2013; Ramakrishna et al. 2013; Kirstein and Vogel 2014; Zhang et al. 2014.

Chromosomal Loci Involved in Hepatocarcinogenesis

HCC is characterized by a wide array of recurrent chromosomal aberrations that are sometimes detectable in early-stage HCC already (Piao et al. 1998; Homayounfar et al. 2013). Certain of these aberrations occur at high frequency and are, therefore, leading alterations that can be employed in a diagnostic setting, e.g., the loci 8p23 and 8q (Nagai et al. 1997; Chang et al. 2002). Recurrent losses of several loci in HCC mainly involve chromosome arms 1p, 4q, 6q, 8p, 9p, 10q,13q, 16q, and 17p, and chromosomal gains mainly involve 1q, 6p, 8q, 17q, and 20q, whereby loss of 4q and 16q seems to occur

predominantly in HBV-related HCC (Laurent-Puig et al. 2001; Nishida et al. 2003). LOH of 8p is already detectable in nodular precursor lesions (dysplastic nodules) HCC at relatively high frequency, and less often, dysplastic nodules display LOH of other chromosomes, such as 11p13 (Kahng et al. 2003). The loci defined by these LOH pattern harbor genes that play important roles in hepatocarcinogenic pathways. In the following paragraphs, reference is made for some of these loci in case the respective genes have been studied in detail.

Genetic Alterations in Hepatocellular Carcinoma: Genomic Signatures as an Instrumentarium for Risk Stratification and Personalized Treatments

HCCs show distinct patterns of recurrent gene alterations that involve several regulation and signaling pathways and include numerous (hundreds) altered genes. Patterns, e.g., comprise changes of tumor suppressors, growth regulators, the p53 pathway involved in apoptosis, chromatin remodelers, and components of the Wnt pathway. The detailed analysis of such genomic alterations and the evaluation of diverse omics result in the formulation of mutational landscapes of HCC and characteristic molecular signatures that may serve for improved cancer stratifications, transcriptome classifications, and future therapies.

Selected References Chen et al. 2002, 2010, Boyault et al. 2007; Jia et al. 2011; Totoki et al. 2011, 2014; Coban and Barton 2012; Fujimoto et al. 2012; Guichard et al. 2012; Han 2012; Roessler et al. 2012; Nakagawa and Shibata 2013; Jhunjhunwala et al. 2014; Shibata and Aburatani 2014; Takai et al. 2014; Woo et al. 2014; Fujimoto et al. 2015; Wang et al. 2015).

An array-based comparative genomic hybridization (AB-CGH) study revealed 722 dysregulated genes in HCC (Skawran et al. 2008). Liver cancers develop in the setting of complex mutation patterns of tumor oncogenes and tumor suppressor genes. The broad array of tumor suppressors, growth factors, and signaling pathways operational in HCC pathogenesis and biology have been reviewed, and important genes are summarized in Table 1 (Ozturk 1999; Dufour et al. 2007; Pang and Poon 2007; Wong and Ng 2008).

Table 1 Tumor suppressors and oncogenes in hepatocellular carcinoma

Transcription factors
p53
c-Myc
C-Fos
HOX
FOX
KLF6 (Krüppel-like factor 6)
RUNX3
Receptor tyrosine kinases
HGF/c-Met
EGFR
Other kinases
Hippo
GTPases
Ras
DLC1 (deleted in liver cancer 1)
Other suppressors or oncogenic systems
Wnt/beta-catenin signaling cascade
Hedgehog signaling pathway
PTEN
TGF-beta1 and associated proteins

Deregulation of Receptor Tyrosine Kinases in Hepatocarcinogenic Pathways

Introduction

HCC is, in its development and progression, characterized by abnormal expression and deregulation of several receptor tyrosine kinases (RTKs). RTKs are cell surface receptors for numerous growth factors, hormones, and cytokines and represent at least 58 of the 90 tyrosine kinase genes of

Table 2 Classes of receptor tyrosine kinases

Receptor	
RTK class I (EGF receptor family/ErbB family)	
	EGFR/Erb-1
	ErbB2/Her2
	ErbB3/Her3
	ErbB4/Her4
RTK class II (insulin receptor family)	IGF1R
RTK class III (platelet-derived growth factor receptor (PDGFR) family)	PDGFRA
	PDGFRB
	CSF1R/Fms
	Kit/CD117
RTK class IV (fibroblast growth factor receptor (FGFR) family)	FGFR1-4
RTK class V (VEGF receptor family)	VEGFR1-3
RTK class VI (HGF receptor family)	
RTK class VII (Trk (tropomyosin receptor kinase) family)	
RTK class VIII (Eph (ephrin receptor family))	
	EphA1-8
	EphB1-6
RTK class IX (AXL receptor family)	
RTK class X (LTK receptor family)	
RTK class XI (TIE receptor family/angiopoietin receptors)	Tie1, Tie2
RTK class XII (ROR receptor family)	
RTK class XIII (DDR receptor family)	
RTK class XIV (RET receptor family)	
RTK class XV (KLG receptor family)	
RTK class XVI (RYK receptor family)	
RTK class XVII (MuSK receptor family)	

the human genome. In contrast to non-receptor tyrosine kinases, RTKs contain a typical hydrophobic transmembrane domain composed of 25–38 amino acid residues, an N-terminal extracellular region, and an intracellular C-terminal region. The conserved C-terminal domain acts as the kinase proper that catalyzes receptor autophosphorylation followed by interaction with downstream targets. The kinases are divided into almost 20 classes (Table 2).

Hepatocyte Growth Factor and c-Met in Hepatic Carcinogenesis

Hepatocyte growth factor (HGF; scatter factor; gene on chromosome 7q21.11) is an important morphogen that regulates growth, cell migration, the construction of distinct tissue structures in development, regeneration, and wound healing. HGF binds to its receptor, c-Met.

HGF belongs to the plasminogen subfamily of S1 peptidases, however, without peptidase activity, and is produced as an inactive precursor that is cleaved by a serine protease into an alpha chain and a beta chain that unite to form an active heterodimer via disulfide bond formation. The processing serine protease of HGF is termed HGF activator (HGFA), which is itself regulated by two Kunitz-type serine proteinase inhibitors, HGFA inhibitor type 1/HAI-1 (SPINT1) and type 2/HAI-2. The HGF-HGFA system is located in a pericellular compartment and tightly regulates the HGF/c-MET interactome. HGF is usually secreted by mesenchymal and stromal cells in a paracrine fashion and acts as a multifunctional cytokine mainly on cells with epithelial lineages (Nakamura 1991; Matsumoto and Nakamura

1992; Kankuri et al. 2005). In addition to diverse types of epithelial cells, HGF also acts on hematopoietic cells and endothelial cells. It promotes angiogenesis both in normal vessel systems and in vascular tumors and has an effect on endothelial barriers (Higginbotham et al. 2014; Sanders et al. 2014; Young et al. 2014). c-Met (MET; hepatocyte growth factor receptor (HGFR); on chromosome 7q31.2) is a receptor tyrosine kinase encoded by the MET gene (MET proto-oncogene). The receptor kinase is produced as a single-chain precursor protein that is posttranslationally processed to yield alpha and beta subunits which are linked to form a mature receptor for HGF. The alpha subunit is an extracellular highly glycosylated domain, while the beta subunit is the transmembrane domain. HGF is the only ligand for c-Met.

The HGF/c-Met receptor signaling pathway is involved in development, growth, and progression of HCC and other malignancies (Suzuki et al. 1994; Ueki et al. 1997; Whittaker et al. 2010; Gao et al. 2011; Ang et al. 2013; Chu et al. 2013; Goyal et al. 2013; Graveel et al. 2013; Lee et al. 2013). HGF promotes experimental hepatocarcinogenesis in part via c-Met autocrine activation in transgenic mice (Horiguchi et al. 2002). The expression patterns of c-Met in HCC and fibrolamellar carcinoma are variable, in that both increase or decrease were found (Schoedel et al. 2003), but its expression tends to be higher in high-grade HCC (Zhao and Zimmermann 1998). HCCs with a c-Met-related expression signature display an aggressive phenotype (Kaposi-Novak et al. 2006). c-Met-positive HCC more often showed portal vein invasion and were associated with lower recurrence-free survival rates (Kondo et al. 2013). Epigenetic upregulation of HGF and c-Met promotes EMT and an aggressive phenotype in HCC (Ogunwobi et al. 2013).

The mechanisms involved in HGF/c-Met-induced hepatocarcinogenesis are complex and proceed along several pathways. HGF induces c-Met expression through upregulation of the c-Met promoter activity. A second pathway involves osteopontin in HCC, induced by the frequently overexpressed transcription factor late SV40 factor (LSF), osteopontin thereby activating c-Met through an interaction between osteopontin and its cell surface receptor CD44 (Yoo et al. 2011). In its oncogenic action for HCC, upregulated c-Met is synergistic to inactivation of the Ras/MAPK pathway negative regulator, Sprouty2 (Lee et al. 2008, 2010). In HCC cells, the HGF/c-Met signaling system also acts via an epigenetic regulator, mixed-lineage leukemia (MLL), which is required for invasion and metastatic spread of HCC (Marquardt and Thorgeirsson 2013; Takeda et al. 2013). In hepatocarcinogenesis, the HGF/c-Met signaling pathway interacts with MUC1 expression in cancer cells. Co-expression of c-Met and MUC1 was associated with the differentiation status of HCC, whereby HGF-induced c-Met phosphorylation downregulated MUC1 expression (Bozkaya et al. 2012). HGF binding to c-met can induce epithelial-mesenchymal transition (EMT), a process modulated by a frequently mutated tumor suppressor, CMTM8 (Zhang et al. 2012). The action of c-Met in HCC is antagonized by an HCC tumor suppressor, leukocyte cell-derived chemotaxin 2 (LECT2), which suppresses HCC vascular invasion by recruitment of protein tyrosine phosphatase 1B (Chen et al. 2014). HGF signaling is regulated by chromatin remodeling and associated factors. Histone deacetylation regulates chromatin remodeling and activates HGF signaling by repressing microRNA-449 in HCC cells, c-Met being a target for this microRNA (Buurman et al. 2012).

Epidermal Growth Factor Receptors in Liver Cancer

The EGFR family is a receptor tyrosine kinase family of four structurally related proteins. These surface receptors bind members of the epidermal growth factor/EGF family of extracellular protein/growth factor ligands. Marked overexpression of EGFRs is a hallmark of several cancers, excessive EGFR signaling being a strong driving force for tumorigenesis and cancer progression. EGFR or ErbB1 (gene on chromosome 7p11.2) binds EGF and TGFalpha and several other ligands. Upon binding of a ligand, the monomeric receptor is

activated to become an active homodimer. The receptor can also pair with other members of the family to generate activated heterodimers, such as Erb2/Her2/neu. Dimerization of EGFR activates the intracellular kinase domain to produce autophosphorylation of the C-terminal domain of the receptor. This is followed by activation of numerous downstream target proteins that is associated with the phosphorylated tyrosine residues of EGFR via their phosphotyrosine-binding domains. This interaction promotes downstream signaling along diverse signal transduction pathways, including MAPK, JNK, and Akt pathways, which are the final mediator for the regulation of cell proliferation and differentiation.

EGFR has a complex role in HCC biology, because its function not only affects HCC cells themselves but also stromal cells, vascular cells, and leukocytes infiltrating the tumor. The EGFR signaling system is situated within an extensive network of interactions and cross-talks with other signaling pathways, including other growth factors, cytokines, and inflammatory mediators (Berasain et al. 2011; Berasain and Avila 2014). EGF signaling promotes hepatic fibrosis and the development of cirrhosis and can, via these tumorigenic conditions, favor the development of liver cancer (Fuchs et al. 2014). EGFR/Erb-1 is overexpressed in many HCCs, in some analyses correlated with tumor cell differentiation and an aggressive tumor phenotype (Buckley et al. 2008). Distinct patterns of EGF/EGFR gene polymorphisms were related to the risk of HBV- and HCV-associated HCC (Abu Dayyeh et al. 2011). HER2/EGFR2 is also overexpressed in part of HCC, albeit at much lower frequency than Erb-1 (Hsu et al. 2002; Bacaksiz et al. 2008). HER2 was detected in HBx-expressing HCCs and was associated with poor prognosis. HBx augments HER2 protein levels in HCC cells through promotion of HER2 mRNA stability, mediated by induction of the RNA-binding protein HuR (Hung et al. 2014). In HCC cells, an direct interaction between cell surface beta1, 4-galactosyltransferase 1, and EGFR inhibits EGFR activation (Tang et al. 2013). Expression of EGFR in HCC is suppressed by the activity of microRNA-302b which directly targets EGFR and is frequently downregulated in HCC (Wang et al. 2013). This downregulation is a major cause of high EGFR expression levels in HCC. EGF signaling can induce cytokeratin 19 expression in HCC, an effect that is associated with higher growth abilities and a more aggressive phenotype (Yoneda et al. 2011).

The EGF/EGFR signaling platform is situated at a critical node between hepatocarcinogenic pathways and inflammatory signals (Berasain et al. 2009). EGF/EGFR induces a pro-inflammatory niche in HCC through induced production of CXCL5 and CXCL8 from HCC cells (Huang et al. 2014). In human HCC, EGFR is expressed in tumor-associated macrophages (TAMs). Based on murine HCC models, it turned out that EGFR is required for TAMs to transcriptionally induce IL-6, which is then involved in stimulation of hepatocyte proliferation and carcinogenesis. In humans, presence of EGFR-expressing TAMs is associated with more aggressive tumor biology and poor survival (Lanaya et al. 2014). TNF-alpha, which is produced by macrophages, triggers shedding of the EGFR ligand in HCC, amphiregulin, by the sheddase ADAM17, highlighting a further link between inflammation and liver cancer. ADAM17 is upregulated in the course of hepatocarcinogenesis (Berasain et al. 2012).

The Hippo Signaling Pathway in Hepatocellular Carcinoma

The Salvador-LATS-MST1/2 (Hippo) pathway is a complex kinase signaling platform that comprises the kinases Hippo and LATS1/LATS2 (warts in *Drosophila*), the adaptor proteins Salvador (AV1) and Mats, the transcriptional coactivator YAP (Yorkie in *Drosophila*), the Hippo activator Willin/Expanded, the upstream regulator KIBRA, and several Hippo-associated proteins. The Hippo pathway plays a key role in the control of cell number, tissue mass, and organ size in development and adults but also affects other cell functions, such as cytokinesis and cytoskeletal rearrangement (Genevet et al. 2010). The core of the signaling platform consists of a kinase

cascade in which Hippo (MST in humans) phosphorylates the nuclear DBF-2-related kinase LATS, which in turn phosphorylates and inactivates YAP/Yorkie. The phosphorylation of these proteins is influenced by an upstream effector of the Hippo pathway, KIBRA. YAP (Yes-associated protein) is a transcriptional coactivator that binds to the transcription factor TEAD (TEAD1-4 in humans, Scalloped in *Drosophila*) in its inactive, unphosphorylated form to promote cell growth and inhibit apoptosis via activation of transcriptional targets. The Hippo pathway affects cytokinesis and cell proliferation also through its effect on spindle formation and is involved in the generation of apico-basal cell polarity (Genevet and Tapon 2011). The mammalian (MST2) sterile 20-like kinase 2 and the scaffold protein SAV1 (Salvador) directly interact with the Nek2 kinase, a NIMA (never in mitosis A)-related kinase implicated in disconnecting the centrosomes via disjoining the linker proteins C-Nap1 and rootletin (Mardin et al. 2010).

Through its role in growth control and regulation of cell population and organ size, Hippo signaling exerts an influence on cancerogenesis and tumor progression (Harvey and Tapon 2007; Grusche et al. 2010). YAP, a target of Hippo, is an important oncogenic driver in liver carcinogenesis (review: Liu et al. 2010). YAP interacts with the Notch signaling cascade as it upregulates Jagged-1 and activates the Notch pathway and a proliferative response in human HCC (Tschaharganeh et al. 2013). Apart from the main components of the Hippo kinase platform, associated proteins are also involved in hepatic carcinogenic pathways. KIBRA, a protein acting upstream of the Hippo pathway, functions as a tumor suppressor that regulates Hippo signaling in conjunction with Merlin and Willin, forming a complex localized to the apical domain of epithelial cells and directly binding to Hippo/LATS (Yu et al. 2010). Several Hippo-associated proteins have functions that may mediate invasive features of cancer cells and by this modulate cancer by mechanisms other than growth control. Zyxin is a regulator of Hippo signaling in invertebrates and mammals. Zyxin is overexpressed in HCC and upregulates its motile phenotype, as in other cancers (Sy et al. 2006; Yamamura et al. 2013). The function of zyxin in cell motility is linked to its being a component of epithelial podosomes (Spinardi et al. 2004) and to its role in FAT signaling (Grusche et al 2010; Rauskolb et al. 2011). The four FAT proteins in mammals (FAT 1–4) associated with two Dachsous proteins (Dachsous 1–2) are very large cell adhesion molecules/cadherins that regulate planar cell polarity (Sharma and McNeill 2013) and are involved in cancer development. FAT4 which is critically involved in maintenance of planar cell polarity and inhibition of cell proliferation is recurrently mutated in HCC (Katoh 2012). Cell polarization is a prerequisite for cell locomotion and is regulated by other proteins that are linked to the Hippo pathway, including Crumbs, Par/partitioning defective, and Scribble, of which the apical polarity protein Crumbs controls the activity of YAP, the progrowth target of the Hippo kinase cassette (Grzeschik et al. 2010; Ngok et al. 2014; Ribeiro et al. 2014). Crumbs appears to act as a potential tumor suppressor involved in the regulation of epithelial-mesenchymal transition in cancer (Laprise 2011). The Hippo activator Willin (a FERM-domain protein like merlin) and the polarity protein Par3 regulate epithelial apical constriction involved in polarized phenotype (Ishiuchi and Takeichi 2011). On the other, elements of the cytoskeleton influences the function of the Hippo pathway. The cilia-associated protein NPHP4, mutated in one form of nephronophthisis, acts as a potent negative regulator of Hippo signaling, directly interacting with kinase LATS1 and inhibiting LATS1-mediated phosphorylation of YAP (Habbig et al. 2011).

Wnt/Beta-Catenin Signaling

Introduction

The Wnt/beta-catenin signaling pathway is a key regulation platform for numerous cellular functions, both in normal cells and in cancer. The pathway is initiated by binding of Wnt ligands to their frizzled (Fz) receptors. Wnt signaling comprises 19 Wnt ligands in humans. These ligands

are highly conserved secreted glycoproteins that bind to ten types of frizzled receptors and play a central role in cell fating, priming of progenitor cells, induction of differentiation, and tissue homeostasis.

The Wnt signaling cascades include three pathways. In the canonical pathway, Wnt ligands activate target genes through stabilization of beta-catenin followed by its nuclear translocation and activation of distinct target genes. The canonical pathway is mediated by Wnt1 class ligands, comprising Wnt1, Wnt3, Wnt3a, Wnt7a, Wnt7b, and Wnt8a. In two noncanonical pathways, Wnt ligands promote activation of RhoA and Jun kinase, while a third pathway involves intracellular calcium release and activation of protein kinase C/PKC and calmodulin-dependent protein kinase II (review: Lee et al. 2006). In the canonical pathway, formation of a Wnt/Fz complex is followed by phosphorylation-mediated activation of the cytoplasmic protein Dishevelled, which regulates the activity of an intracellular signaling complex composed of beta-catenin, glycogen synthase kinase 3beta (GSK3beta), Axin, and the adenomatous polyposis coli/APC protein. The scaffolding protein Axin promotes proteasomal degradation of beta-catenin, a step that requires phosphorylation of beta-catenin by GSK3beta. Activated Dishevelled binds to Axin and promotes its binding to GSK3beta, thus preventing its beta-catenin phosphorylation, leading to bypassing proteasomal degradation of beta-catenin and nuclear beta-catenin translocation. This sequence of events leads from Wnt-receptor binding to the transcriptional activation of several target genes. In the noncanonical Wnt pathways such as Wnt/frizzled-PCP (planar cell polarity) signaling, Dishevelled signals via Daam1-Rho axis and the Rac1 axis, whereby Dishevelled has also important functions in Wnt-microtubule signaling (Gao and Chen 2010).

Wnt/Beta-Catenin Signaling in Liver Cancer

The Wnt/beta-catenin signaling cascade is critically involved in cancer development, including hepatocarcinogenesis, and may represent a future treatment target (Morin 1999; Prunier et al. 2004; Lee et al. 2006; Dahmani et al. 2011). This signal pathway exerts a strong influence on growth and expansion of the hepatocyte lineage, including neoplastic hepatocytes. Activated beta-catenin drives the expression of target genes required for cell cycle progression and proliferation. In the liver, Wnt/beta-catenin signaling holds a central position of growth regulation of the hepatocyte lineage and its precursor cells, including EpCAM(+) hepatic stem cells (Yamashita et al. 2007). HGF-mediated and beta-catenin-mediated pathways cooperate in hepatocyte proliferation during ontogenesis and regeneration (Apte et al. 2006; Nejak-Bowen et al. 2010), and transgenic mice expressing an oncogenic form of beta-catenin develop hepatomegaly caused by uncontrolled hepatocyte growth (Cadoret et al. 2001). In transgenic HCC mice, 50 % of hepatic tumors had somatic mutations within the beta-catenin gene, leading to deregulated Wnt/beta-catenin signaling (de la Coste et al. 1998). There is strong evidence that a deregulated Wnt/beta-catenin pathway is strongly involved in hepatocarcinogenesis in humans, both HCCs and hepatoblastomas.

Selected References Huang et al. 1999; Kondo et al. 1999; Legoix et al. 1999; Nhieu et al. 1999; Wong et al. 2001; Taniguchi et al. 2002; Ban et al. 2003; Cui et al. 2003; Toan et al. 2005; Cavard et al. 2008; Kim et al. 2008; Takigawa and Brown 2008; Nejak-Bowen and Monga 2011; Pez et al. 2013; Lu et al. 2014.

Specifically, the canonical Wnt signaling is often activated due to overexpression and/or somatic mutations in components of the Wnt signal cascade in HCC (de la Coste et al. 1998; Miyoshi et al. 1998). An aberrant nuclear accumulation of beta-catenin, detectable with immunohistochemistry, already occurs in early phases of hepatocarcinogenesis and is a frequent finding in HCC, more often in poorly differentiated than in moderately or well-differentiated tumors (Terris et al. 1999; Murata et al. 2001; Wong et al. 2001; Tien et al. 2005; Wang et al. 2009;

Li et al. 2011). Nuclear beta-catenin accumulation in HCC is associated with increased cell proliferation (Nhieu et al. 1999). Nuclear reactivity for beta-catenin is also present in tumorous lesions undergoing transformation to HCC, such as telangiectatic adenoma (Hechtman et al. 2011). HCC with exon-3 mutations represented a distinct phenotype characterized by a higher percentage of large tumor size and macro- and microvascular invasion (Cieply et al. 2009). Intracellular accumulation of beta-catenin was correlated with cyclin D1 expression and a higher proliferation index (Ueta et al. 2002). Mutational activation of beta-catenin signaling in HCC is correlated with induction of glutamine synthetase, glutamate transporter-1, and G-protein-coupled receptor 49 but not ornithine transcarbamylase (Zucman-Rossi et al. 2007; Austinat et al. 2008; Cieply et al. 2009). Distinct distribution patterns of beta-catenin in HCC are associated with E-cadherin expression, affecting cell adhesion features of neoplastic cells, mechanism of epithelial-to-mesenchymal transition (EMT), and biology of disease (Ihara et al. 1996; Garcia et al. 1998; Nuruki et al. 1998). Beta-catenin undergoes a complex cross talk with snail to induce EMT in HCCs, a process requiring activity of the ERK1/2 signaling pathway (Zucchini-Pascal et al. 2013). Decreased E-cadherin expression on HCC cells is associated with beta-catenin mislocalization and HCC invasion and metastasis (Du et al. 2009), suggesting a role of reduced cell adhesion for tumor cell individualization and spread. Nuclear beta-catenin expression is correlated with the Edmondson-Steiner grade (Wang et al. 2009). Approximately 20 % of human HCC harbor activating mutations with exon 3 of the beta-catenin gene (Kondo et al. 1999; Fujie et al. 2001; Yuan et al. 2011). Expression of beta-catenin in HCC is more abundant in late-stage tumors, neoplasms with a high proliferative rate, and metastatic HCCs (Lai et al. 2011). Deregulation of beta-catenin expression may be associated with other carcinogenic alterations. Hepatitis C virus (HCV) core protein promotes hepatoma cell growth through enhancement of canonical Wnt/beta-catenin signaling, specifically via inactivation of GSK-3beta, contributing to upregulation of c-Myc, cyclin D1, WISP2, and CTGF (Liu et al. 2011; Higgs et al. 2013). Beta-catenin gene mutations were associated with high exposure to aflatoxin B1 (Devereux et al. 2001), whereby aflatoxin B1 negatively regulates Wnt/beta-catenin signaling through upregulating and activating microRNA-33a, a miR that potently inhibits expression of beta-catenin (Fang et al. 2013). Presence or absence of beta-catenin mutations in HCC may be associated with distinct chromosomal aberrations. Chromosome 1p, 4q, and 16p deletions were associated with the absence of beta-catenin mutations (Legoix et al. 1999).

In addition to the typical alterations of beta-catenin expression, HCCs show various changes of Wnt ligand functions and of Wnt/frizzled signaling (Lee et al. 2006; Bogaerts et al. 2014). Part of these Wnt dysregulations are directly or indirectly caused by factors that drive hepatocarcinogenesis. HCV nonstructural protein 5A activates beta-catenin signaling cascades through inactivation of glycogen synthase kinase 3beta and subsequent beta-catenin accumulation (Park et al. 2009). HCV core protein can activate the Wnt signaling cascade through upregulation of gene expression of canonical Wnt ligands Wnt2, Wnt3, Wnt3a, Wnt8b, Wnt10a, and Wnt10b and of frizzled receptors 2, 5, 6, 7, and 9 and of LRP5/6 co-receptors (Liu et al. 2011). On the other hand, blockade of Wnt signaling in HCC cells inhibits tumor growth and angiogenesis (Hu et al. 2009). Loss of Wnt5a is downregulated in the majority of HCCs and acts as a tumor suppressor, decreased expression being associated with aggressive tumor biology (Geng et al. 2012), but in part of HCC, Wnt5a mRNA levels were higher than in para-carcinoma tissues (Li et al. 2014). In vitro, overexpression of Wnt5a in human HCC cells was associated with decrease of cell proliferation and migration, suggesting that Wnt5a acts as a tumor suppressor gene in HCC (Bi et al. 2014). HCC can also display altered expression patterns of Wnt/Frizzled receptors. Expression of frizzled-7 is an early event in hepatocarcinogenesis and affects growth and tumor cell migration (Merle et al. 2004, 2005). A functional interaction between frizzled-7 and Wnt3 causes activation

of Wnt/beta-catenin signaling in HCC cells, associated with TCF transcriptional activity and cell proliferation (Kim et al. 2008). Conversely, soluble frizzled-7 receptor protein inhibits Wnt signaling and results in reduced HCC cell viability and growth (Wei et al. 2011). Glypican-3, which is highly expressed in the majority of HCCs, may form a complex with Wnt by stabilizing the interaction between Wnt and the frizzled receptor, leading to activation of downstream signaling pathways (Gao and Ho 2011). There is an increased group of frizzled-related proteins (FRPs) that modulate the Wnt-frizzled receptor system. Secreted FRPs are WNT antagonists that directly bind to Wnt, have a role in the regulation of cell proliferation and differentiation, and act as tumor suppressors because their expression is often downregulated in diverse cancers via promoter hypermethylation (Shi et al. 2007). Epigenetic inactivation of secreted FRPs (SFRPs) is a common finding in HCC (Takagi et al. 2008). SFRP silencing activates the canonical Wnt pathway and increases cell proliferation in HCC (Kaur et al. 2012). The secreted frizzled-related protein 1 (SFRP1) is a tumor suppressor located to chromosome 8p12-p11.1 (a common LOH region in HCC) and a beta-catenin antagonist that is frequently inactivated in tumors via promoter hypermethylation (Wu et al. 2012). Secreted SFRP1 belongs to the FRP family of proteins that possess a cysteine-rich domain homologous to the Wnt-binding site of frizzled proteins. Downregulation of SFRP1 is a common event in HCC (Shih et al. 2006, 2007) and can contribute to oncogenesis of human HCC, while overexpression of this protein inhibits cell growth (Huang et al. 2007). SFRP1 is epigenetically silenced in HCC (Wu et al. 2012). SFRP1 silencing is promoted by HCV core protein, an effect that enhances HCC aggressiveness by inducing epithelial-mesenchymal transition (EMT) (Quan et al. 2014). In patients with HBV-related liver disease, serum levels of secreted frizzled-related protein 5 (SFRP5) differentially decrease as a function of disease status, lowest levels characterizing patients with HCC (Peng et al. 2014). A further protein that interacts with Wnt is the Wnt coreceptor low-density lipoprotein receptor-related protein-6 (LRP6), which forms a signaling complex with Wnt ligand and frizzled receptor to activate a downstream signaling cascade. Upregulation of LRP6 promotes hepatocarcinogenesis and enhances cell invasion (Tung et al. 2012). Apart from beta-catenin dysregulation, other members of the Wnt/frizzled downstream signaling cascade may be altered in liver cancer. Mutations of AXIN1 and AXIN2 have been documented in both HCCs and hepatoblastomas (Clevers 2000; Satoh et al. 2000; Taniguchi et al. 2002). In contrast to beta-catenin activation in HCC, Axin-mutated HCC did not show induction of glutamine synthetase or glutamate transporter-1 (Zucman-Rossi et al. 2007).

Mechanisms

Activation of the Wnt7-beta-catenin signaling cascade causes upregulation of a large set of target genes that play a role in diverse cell functions (Lee et al. 2007). Wnt/beta-catenin signaling may regulate the Ras/MAPK and PI3K/SAPK signaling pathways via regulation of the phosphorylation status of ERK1/2, JNK/SAPK, and Akt1 protein in HCC cells (Wang et al. 2011). The signal pathway regulates cell cycle progression in HCC cells through affecting cyclin A and cyclin E (Wang et al. 2009). Activation of the canonical beta-catenin pathway results in overexpression of the multifunctional protein Cyr61 (CCN1) via binding to the Cyr61 promoter. Cyr61/CCN is a secreted ECM-associated protein of the CCN family. One well-known member of this family is CCN2 or connective tissue growth factor (CTGF). Cyr61 is involved in the regulation of diverse cellular activities, mainly cell adhesion, proliferation, differentiation, apoptosis, migration, and senescence, through interaction with integrin receptors and heparan sulfate proteoglycans. Overexpression of Cyr61 promotes progression of HCC (Li et al. 2012). Oncogenic beta-catenin promotes an inflammatory response characterized by invariant NKT (iNKT) and chemokine-like chemotactic factor leukocyte cell-derived chemotaxin 2 (LECT2) production,

leading to liver tumorigenesis and an aggressive phenotype of HCC (Anson et al. 2012). TGF-beta cooperates with Ras to activate nuclear beta-catenin in the setting of epithelial-mesenchymal transition (EMT) of hepatocytes. Another pathway of EMT in HCC involves SIRT2 (sirtuin2) which mediates EMT through the GSK-3beta/beta-catenin pathway (Chen et al. 2013). Beta-catenin signaling enhances hypoxia-induced EMT in HCC cells through cross talk with HIF-1alpha signaling (Zhang et al. 2013). The nuclear beta-catenin accumulation results in dedifferentiation of hepatocytes to become an early liver progenitor phenotype. This phenomenon also occurs in HCC showing signs of EMT and tumor recurrence (Zulehner et al. 2010). Wnt/beta-catenin signaling activates expression of four microRNA-181 family members in HCC (Ji et al. 2011).

The canonical Wnt pathway is counteracted by several factors that may also operate in HCC. Major inhibitors of beta-catenin signaling are Dickkopf (DKK) proteins, a family of four secreted proteins (DKK1–DKK4) of which however not all members are beta-catenin inhibitors. DKKs modulate beta-catenin signaling in HCC (Fatima et al. 2011). There is a stepwise upregulation of DKK1 in HCC tissues, higher transcript levels associated with more aggressive tumor behavior, venous invasion, and higher stage (Tung et al. 2011). An elevated expression of DKK1 in HCC is associated with cytoplasmic/nuclear beta-catenin accumulation, instead of membrane expression, and aggressive tumor biology (Yu et al. 2009). On the other hand, DKK4 hampers cell proliferation, reduces colony formation and retards cell migration, probably represents a potential tumor suppressor, and is downregulated in many HCCs (Fatima et al. 2012). The transcription factor SOX1 (sex determining region Y-box 1) is frequently downregulated in HCC via promoter hypermethylation and functions as a tumor suppressor in these tumors by antagonizing the WNT/beta-catenin signaling pathway (Tsao et al. 2012). The candidate tumor suppressor SRY-box containing gene 17 (SOX17) negatively regulates beta-catenin signaling and inhibits HCC cell growth (Jia et al. 2010). The Wnt/beta-catenin pathway is inhibited by an inhibitor of a key regulator of the cascade at the APC complex level, Dishevelled, i.e., HDPR1 (Dapper in *Xenopus*). Downregulation of HDPR1 was found in 58 % of HCC, due to epigenetic hypermethylation of the promoter or allelic loss of its locus, and the decrease is associated with accumulation of beta-catenin (Yau et al. 2005). The dishevelled-associated protein Prickle-1 negatively regulates beta-catenin signaling via promotion of Dishevelled ubiquitination and degradation in HCC (Chan et al. 2006). The beta-catenin pathway is also regulated by microRNAs. MicroRNA-214 targets beta-catenin and by this mechanisms suppresses stem cell-like traits, invasion, and recurrence of human HCC (Xia et al. 2012).

Apart from the canonical pathway, HCC can show features of activation of the noncanonical Wnt-mediated signaling pathway. The noncanonical cascade member Wnt11 is downregulated in human HCC cell lines, while upregulated Wnt11 inhibits HCC cell proliferation and migration via activated protein kinase C, which antagonizes canonical signaling through phosphorylation of beta-catenin (Toyama et al. 2010).

Novel Genes and Gene Products Deregulated in Liver Cancer and Representing Valid or Potential Oncogenes/Tumor Suppressors

Retinoblastoma Gene

The retinoblastoma gene (RB1) is relatively rarely mutated in HCC. RB1, localized to chromosome 13q14.2, encodes a protein that is a negative regulator of cell cycle by binding to the transcription factor E2F. However, RB1 showed imprint abnormalities in a high proportion of HCC patients, 40 % of HCC specimens showing hyper- or hypomethylation at the CpG island in intron 2 of the RB1 gene, loss of imprinting representing an important mechanism for RB1 pathway inactivation in HCC (Anwar et al. 2014).

Insulin-Like Growth Factors

Components of the insulin-like growth factor signaling system and associated proteins are altered in HCC and considered to be potential tumor suppressors. Liver cancer development is also influenced by IGF-binding proteins. Insulin-like growth factor-2 mRNA-binding proteins 1, 2, and 3 belong to a conserved protein family of RNA-binding oncofetal proteins involved in cell proliferation, morphology, differentiation, and cell shape control (Bell et al. 2013). One of these factors is IGF2-binding protein 1 (IGF2BP1), a protein strongly upregulated in HCC and involved in the promotion of proliferation (Gutschner et al. 2014). Another IGFBP is insulin-like growth factor-binding protein-7, which is itself downregulated by the oncogene astrocyte-elevated gene 1 (AEG-1) and acts as a potential tumor suppressor in HCC (Chen et al. 2011).

Tumor Suppressors

A factor that is important as a hepatocyte lineage determinant and differentiation factor is hepatocyte nuclear factor 4 (HNF4), which is a marker of HCC progression and might be a tumor suppressor (Lazarevich et al. 2010). LIS1 (human lissencephaly-1 mutated in the Miller-Dieker lissencephaly syndrome) is a gene assigned to chromosome 17p13.3 and frequently altered in liver cancer cells. LIS1 is downregulated in HCC and acts as tumor suppressor (Xing et al. 2011). The gene Ptpn11, which encodes the tyrosine phosphatase Shp2, is a proto-oncogene that is altered in several malignancies, especially several types of leukemia. It has a tumor suppressor function in the liver (Bard-Chapeau et al. 2011). The X-chromosome-linked tumor suppressor TSPX is altered in several cancers. In the setting of hepatocarcinogenic pathways, TSPX interacts with HBV X protein (HBx) and promotes its degradation via a proteasomal pathway, mutations of TSPX predisposing to human liver cancer (Kido et al. 2011). LZAP (C53, Cdk5rap3) is a putative tumor suppressor that is an activator pf p53. Specifically, it inhibits p38 MAPK by facilitating p38 association with wild-type p53-induced phosphatase 1 (An et al. 2011; Zhao et al. 2011). LZAP selectively inhibits NF-kappa B and promotes cell proliferation and an invasive phenotype of cancer cells (Wang et al. 2007). WW domain-containing oxidoreductase (WWOX) is a tumor suppressor with a reduced expression in several cancers. WWOX is downregulated in HCC, associated with cytoplasmic accumulation with beta-catenin and strong nuclear TCF4 expression, suggesting activation of the Wnt/beta-catenin signaling cascade (Li et al. 2013).

References

Abu Dayyeh BK, Yang M, Fuchs BC, Karl DL, Yamada S, Shinsky JJ, O'Brien TR et al (2011) A functional polymorphism in the epidermal growth factor gene is associated with risk for hepatocellular carcinoma. Gastroenterology 141:141–149

An H, Lu X, Liu D, Yarbrough WG (2011) LZAP inhibits p38 MAPK (p38) phosphorylation and activity by facilitating p38 association with the wild-type p53 induced phosphatase 1 (WIP1). PLoS One 6:e16427

Ang CS, Sun MY, Huitzil-Melendez DF, Chou JF, Capanu M, Jarnagin W, Fong Y et al (2013) c-MET and HGF mRNA expression in hepatocellular carcinoma: correlation with clinicopathological features and survival. Anticancer Res 33:3241–3245

Anson M, Crain-Denoyelle AM, Baud V, Chereau F, Gougelet A, Terris B, Yamagoe S et al (2012) Oncogenic β-catenin triggers an inflammatory response that determines the aggressiveness of hepatocellular carcinoma in mice. J Clin Invest 122:586–599

Anwar SL, Krech T, Hasemeier B, Schipper E, Schweitzer N, Vogel A, Kreipe H, Lehmann U (2014) Deregulation of RB1 expression by loss of imprinting in human hepatocellular carcinoma. J Pathol 233:392–401

Apte U, Zeng G, Muller P, Tan X, Micsenyi A, Cieply B, Dai C, Liu Y, Kaestner KH et al (2006) Activation of Wnt/beta-catenin pathway during hepatocyte growth factor-induced hepatomegaly in mice. Hepatology 44:992–1002

Austinat M, Dunsch R, Wittekind C, Tannapfel A, Gebhardt R, Gaunitz F (2008) Correlation between beta-catenin mutations and expression of Wnt-signaling target genes in hepatocellular carcinoma. Mol Cancer 7:21

Bacaksiz A, Sahin FI, Bilezikci B, Yilmaz Z (2008) Determination of HER-2/Neu status in hepatocellular carcinoma cases. Genet Test 12:211–214

Ban KC, Singh H, Krishnan R, Seow HF (2003) GSK-3beta phosphorylation and alteration of beta-catenin in hepatocellular carcinoma. Cancer Lett 199:201–208

Bard-Chapeau EA, Li S, Ding J, Zhang SS, Zhu HH, Princen F, Fang DD, Han T et al (2011) Ptpn11/Shp2 acts as a tumor suppressor in hepatocellular carcinogenesis. Cancer Cell 19:629–639

Bell JL, Wächter K, Mühleck B, Pazaitis N, Köhn M, Lederer M, Hüttelmaier S (2013) Insulin-like growth factor 2 mRNA-binding proteins (IHG2BPs): post-transcriptional drivers of cancer progression? Cell Mol Life Sci 70:2657–2675

Berasain C, Avila MA (2014) The EGFR signalling system in the liver: from hepatoprotection to hepatocarcinogenesis. J Gastroenterol 49:9–23

Berasain C, Perugorria MJ, Latasa MU, Castillo J, Goni S, Santamaria M, Prieto J et al (2009) The epidermal growth factor receptor: a link between inflammation and liver cancer. Exp Biol Med (Maywood) 234:713–725

Berasain C, Ujue Latasa M, Urtasun R, Goni S, Elizalde M, Garcia-Irigoyen O, Azcona M et al (2011) Epidermal growth factor receptor (EGFR) crosstalks in liver cancer. Cancers (Basel) 3:2444–2461

Berasain C, Nicou A, Garcia-Irigoyen O, Latasa MU, Urtasun R, Elizalde M, Salis F et al (2012) Epidermal growth factor receptor signaling in hepatocellular carcinoma: inflammatory activation and a new intracellular regulatory mechanism. Dig Dis 30:524–531

Bi L, Liu X, Wang C, Cao Y, Mao R, Li P, Geng M (2014) Wnt5a involved in regulation of the biological behavior of hepatocellular carcinoma. Int J Clin Exp Pathol 7:987–995

Bogaerts E, Heindryckx F, Vandewynckel YP, Van Grunsven LA, Van Vlierberghe H (2014) The roles of transforming growth factor-β, Wnt, Notch and hypoxia on liver progenitor cells in primary liver tumours (review). Int J Oncol 44:1015–1022

Boyault S, Rickman DS, de Reyniès A, Balabaud C, Rebouissou S, Jeannot E, Hérault A, Saric J, Belghiti J, Franco D et al (2007) Transcriptome classification of HCC is related to gene alterations and to new therapeutic targets. Hepatology 45:42–52

Bozkaya G, Korhan P, Cokakli M, Erdal E, Sagol O, Karademir S, Korch C, Atabey N (2012) Cooperative interaction of MUC1 with the HGF/c-Met pathway during hepatocarcinogenesis. Mol Cancer 11:64

Buckley AF, Burgart LJ, Sahai V, Kakar S (2008) Epidermal growth factor receptor expression and gene copy number in conventional hepatocellular carcinoma. Am J Clin Pathol 129:245–251

Buendia MA (2002) Genetic alterations in hepatoblastoma and hepatocellular carcinoma: common and distinctive pathways. Med Pediatr Oncol 39:530–535

Buendia MA (2007) Tumor suppressors in hepatocellular carcinoma: many are called, but few are chosen. J Hepatol 46:546–548

Buurman R, Gürlevik E, Schäffer V, Eilers M, Sandbothe M, Kreipe H, Wilkens L, Schlegelberger B et al (2012) Histone deacetylases activate hepatocyte growth factor signaling by repressing microRNA-449 in hepatocellular carcinoma cells. Gastroenterology 143:811–820

Cadoret A, Ovejero C, Saadi-Kheddouci S, Souil E, Fabre M, Romagnolo B, Kahn A, Perret C (2001) Hepatomegaly in transgenic mice expressing an oncogenic form of beta-catenin. Cancer Res 61:3245–3249

Calvisi DF, Frau M, Tomasi ML, Feo F, Pascale RM (2012) Deregulation of signalling pathways in prognostic subtypes of hepatocellular carcinoma: novel insights from interspecies comparison. Biochim Biophys Acta 1826:215–237

Cavard C, Colnot S, Audard V, Benhamouche S, Finzi L, Torre C, Grimber G, Godard C et al (2008) Wnt/beta-catenin pathway in hepatocellular carcinoma pathogenesis and liver physiology. Future Oncol 4:647–660

Centore RC, Yazinski SA, Tse A, Zou L (2012) Spartan/C1orf124, a reader of PCNA ubiquitinylation and a regulator of UV-induced DNA damage response. Mol Cell 46:625–635

Chan DW, Chan CY, Yam JW, Ching YP, Ng IO (2006) Prickle-1 negatively regulates Wnt/beta-catenin pathway by promoting Dishevelled ubiquitination/degradation in liver cancer. Gastroenterology 131:1218–1227

Chang J, Kim NG, Piao Z, Park C, Park KS, Paik YK, Lee WJ, Kim BR, Kim H (2002) Assessment of chromosomal losses and gains in hepatocellular carcinoma. Cancer Lett 182:193–202

Chen X, Cheung ST, So S, Fan ST, Barry C, Higgins J, Lai KM, Ji J, Dudoit S, Ng IO et al (2002) Gene expression patterns in human liver cancers. Mol Biol Cell 13:1929–1939

Chen CF, Hsu EC, Lin KT, Tu PH, Chang HW, Lin CH, Chen YJ, Gu DL, Lin CH, Wu JY, Chen YT, Hsu MT et al (2010) Overlapping high-resolution copy number alterations in cancer genomes identified putative cancer genes in hepatocellular carcinoma. Hepatology 52:1690–1701

Chen D, Yoo BK, Santhekadur PK, Gredler R, Bhutia SK, Das SK, Fuller C, Su ZZ et al (2011) Insulin-like growth factor-binding protein-7 functions as a potential tumor suppressor in hepatocellular carcinoma. Clin Cancer Res 17:6693–6701

Chen J, Chan AW, To KF, Chen W, Zhang Z, Ren J, Song C, Cheung YS, Lai PB et al (2013) SIRT2 overexpression in hepatocellular carcinoma mediates epithelial to mesenchymal transition via akt/GSK-3β/β-catenin signaling. Hepatology 57:2287–2298

Chen CK, Yang CY, Hua KT, Ho MC, Johansson G, Jeng YM, Chen CN, Chen MW et al (2014) Leukocyte cell-derived chemotaxin 2 antagonizes MET receptor activation to suppress hepatocellular carcinoma vascular invasion by protein tyrosine phosphatase 1B recruitment. Hepatology 59:974–985

Chu JS, Ge FJ, Zhang B, Wang Y, Silvestris N, Liu LJ, Zhao CH, Lin L, Brunetti AE et al (2013) Expression and prognostic value of VEGFR-2, PDGFR-β, and c-Met in advanced hepatocellular carcinoma. J Exp Clin Cancer Res 32:16

Cieply B, Zeng G, Proverbs-Singh T, Geller DA, Monga SP (2009) Unique phenotype of hepatocellular cancers with exon-3 mutations in beta-catenin gene. Hepatology 49:821–831

Clevers H (2000) Axin and hepatocellular carcinomas. Nat Genet 24:206–208

Coban Z, Barton MC (2012) Integrative genomics: liver regeneration and hepatocellular carcinoma. J Cell Biochem 113:2179–2184

Coleman WB (2003) Mechanisms of human hepatocarcinogenesis. Curr Mol Med 3:573–588

Cui J, Zhou X, Liu Y, Tang Z, Romeih M (2003) Wnt signaling in hepatocellular carcinoma: analysis of mutation and expression of beta-catenin, T-cell factor-4 and glycogen synthase kinase 3-beta genes. J Gastroenterol Hepatol 18:280–287

Dahmani R, Just PA, Perret C (2011) The Wnt/β-catenin pathway as a therapeutic target in human hepatocellular carcinoma. Clin Res Hepatol Gatroenterol 35:709–713

De la Coste A, Romagnolo B, Billuart P, Renard CA, Buendia MA, Soubrane O, Fabre M et al (1998) Somatic mutations of the beta-catenin gene are frequent in mouse and human hepatocellular carcinomas. Proc Natl Acad Sci U S A 95:8847–8851

Devereux TR, Stern MC, Flake GP, Yu MC, Zhang ZQ, London SJ, Taylor JA (2001) CTNNB1 mutations and beta-catenin protein accumulation in human hepatocellular carcinomas associated with high exposure to aflatoxin B1. Mol Carcinog 31:68–73

Du GS, Wang JM, Lu JX, Li Q, Ma CQ, Du JT, Zou SQ (2009) Expression of P-aPKC-iota, E-cadherin, and beta-catenin related to invasion and metastasis in hepatocellular carcinoma. Ann Surg Oncol 16:1578–1586

Dufour JF, Huber O, Kozma SC, Lu X, Toftgard R (2007) Tumour suppressors in liver carcinogenesis. J Hepatol 47:860–867

Fang Y, Feng Y, Wu T, Srinivas S, Yang W, Fan J, Yang C, Wang S (2013) Aflatoxin B1 negatively regulates Wnt/β-catenin signaling pathway through activating miR-33a. PLoS One 8:e73004

Fatima S, Lee NP, Luk JM (2011) Dickkopfs and Wnt/β−catenin signalling in liver cancer. World J Clin Oncol 2:311–325

Fatima S, Lee NP, Tsang FH, Kollings FT, Ng IO, Poon RT, Fan ST, Luk JM (2012) Dickkopf 4 (DKK4) acts on Wnt/β-catenin pathway by influencing β-catenin in hepatocellular carcinoma. Oncogene 31:4233–4244

Feitelson MA, Sun B, Satiraglu Tufan NL, Liu J, Pan J, Lian Z (2002) Genetic mechanisms of hepatocarcinogenesis. Oncogene 21:2593–2604

Feo F, Frau M, Tomasi ML, Brozzetti S, Pascale RM (2009) Genetic and epigenetic control of molecular alterations in hepatocellular carcinoma. Exp Biol Med 234:726–736

Fuchs BC, Hoshida Y, Fujii T, Wei L, Yamada S, Lauwers GY, McGinn CM, DePeralta DK et al (2014) Epidermal growth factor receptor inhibition attenuates liver fibrosis and development of hepatocellular carcinoma. Hepatology 59:1577–1590

Fujie H, Moriya K, Shintani Y, Tsutsumi T, Takayama T, Makuumi M, Kimura S, Koike K (2001) Frequent beta-catenin aberration in human hepatocellular carcinoma. Hepatol Res 20:39–51

Fujimoto A, Totoki Y, Abe T, Boroevich KA, Hosoda F, Nguyen HH, Aoki M, Hosono N, Kubo M, Miya F, Arai Y et al (2012) Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. Nat Genet 44:760–764

Fujimoto A, Furuta M, Shiraishi Y, Gotoh K, Kawakami Y, Arihiro K, Nakamura T, Ueno M, Ariizumi S, Nguyen HH et al (2015) Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. Nat Commun 6:6120

Gao C, Chen YG (2010) Dishevelled: the hub of Wnt signaling. Cell Signal 22:717–727

Gao W, Ho M (2011) The role of glypican-3 in regulating Wnt in hepatocellular carcinomas. Cancer Rep 1:14–19

Gao JJ, Inagaki Y, Xue X, Qu XJ, Tang W (2011) c-Met: a potential therapeutic target for hepatocellular carcinoma. Drug Discov Ther 5:2–11

Garcia S, Martini F, De Micco C, Andrac Hardwigsen J, Sappa P, Lavaut MN, Le Treut YP et al (1998) Immunoexpression of E-cadherin and beta-catenin correlates to survival of patients with hepatocellular carcinomas. Int J Oncol 12:443–447

Genevet A, Tapon N (2011) The Hippo pathway and apicobasal cell polarity. Biochem J 436:213–224

Genevet A, Wehr MC, Brain R, Thompson BJ, Tapon N (2010) Kibra is a regulator of the Salvador/Warts/Hippo signaling network. Dev Cell 18:300–308

Geng M, Cao YC, Chen YJ, Jiang H, Bi LQ, Liu XH (2012) Loss of Wnt5a and Ror2 protein in hepatocellular carcinoma associated with poor prognosis. World J Gastroenterol 18:1328–1338

Ghosal G, Leung JW, Nair BC, Fong KW, Chen J (2012) Proliferating cell nuclear antigen (PCNA)-binding protein C1orf124 is a regulator of translesion synthesis. J Biol Chem 287:34225–34233

Goyal L, Muzumdar MD, Zhu AX (2013) Targeting the HGF/c-Met pathway in hepatocellular carcinoma. Clin Cancer Res 19:2310–2318

Graveel CR Tolbert D, Vande Woude GF (2013) MET: a critical player in tumorigenesis and therapeutic target. Cold Spring Harb Perspect Biol 5(7) [Pub Med 23818496]

Grusche FA, Richardson HE, Harvey KF (2010) Upstream regulation of the hippo size control pathway. Curr Biol 20:R574–R582

Grzeschik NA, Parsons LM, Allott ML, Harvey KF, Richardson HE (2010) Lgl, aPKC, and Crumbs regulate the Salvador7Warts/Hippo pathway through two distinct mechanisms. Curr Biol 20:573–581

Guichard C, Amaddeo G, Imbeaud S, Ladeiro Y, Pelletier L, Maad IB, Calderaro J et al (2012) Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. Nat Genet 44:694–698

Gutschner T, Hämmerle M, Pazaitis N, Bley N, Fiskin E, Uckelmann H, Heim A, Gross M et al (2014) Insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) is an important protumorigenic factor in hepatocellular carcinoma. Hepatology 59: 1900–1911

Habbig S, Bartram MP, Müller RU, Schwarz R, Andriopoulos N, Chen S, Sägmüller JG et al (2011) NPHP4, a cilia-associated protein, negatively regulates the Hippo pathway. J Cell Biol 193:633–642

Hagstrom RM, Baker TD (1968) Primary hepatocellular carcinoma in three male siblings. Cancer 22:142–150

Han ZG (2012) Functional genomic studies: insights into the pathogenesis of liver cancer. Annu Rev Genomics Hum Genet 13:171–205

Harvey K, Tapon N (2007) The Salvador-Warts-Hippo pathway – an emerging tumour-suppressor network. Nat Rev Cancer 7:182–191

Hechtman JF, Raoufi M, Fiel MI, Taouli B, Facciuto M, Schiano TD, Blouin AG, Thung SN (2011) Hepatocellular carcinoma arising in a pigmented telangiectatic adenoma with nuclear β-catenin and glutamine synthase positivity: case report and review of the literature. Am J Surg Pathol 35:927–932

Higginbotham K, Tian Y, Gawlak G, Moldobeava N, Shah A, Birukova AA (2014) hepatocyte growth factor triggers distinct mechanisms of Asef and Tiam1 activation to induce endothelial barrier enhancement. Cell Signal 26:2306–2316

Higgs MR, Lerat H, Pawlotsky JM (2013) Hepatitis C virus-induced activation of β-catenin promotes c-Myc expression and a cascade of pro-carcinogenetic events. Oncogene 32:4683–4693

Homayounfar K, Schwarz A, Enders C, Cameron S, Baumhoer D, Ramadori G, Lorf T, Gunawan B, Sander B (2013) Etiologic influence on chromosomal aberrations in European hepatocellular carcinoma identified by CGH. Pathol Res Pract 209:380–387

Horiguchi N, Takayama H, Toyoda M, Otsuka T, Fukusato T, Merlino G, Takagi H, Mori M (2002) Hepatocyte growth factor promotes hepatocarcinogenesis through c-Met autocrine activation and enhanced angiogenesis in transgenic mice treated with diethylnitrosamine. Oncogene 21:1791–1799

Hoshida Y, Nijman SM, Kobayashi M, Chan JA, Brunet J, Chiang DY, Villanueva A et al (2009) Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. Cancer Res 69:7385–7392

Hou JW (2009) Natural course of neonatal progeroid syndrome. Pediatr Neonatol 50:102–109

Hsu C, Huang CL, Hsu HC, Lee PH, Wang SJ, Cheng AL (2002) HER-2/neu overexpression is rare in hepatocellular carcinoma and not predictive of anti-HER-2/neu regulation of cell growth and chemosensitivity. Cancer 94:415–420

Hu J, Dong A, Fernandez-Ruiz V, Shan J, Kawa M, Martinez-Anso E, Prieto J, Qian C (2009) Blockade of Wnt signaling inhibits angiogenesis and tumor growth in hepatocellular carcinoma. Cancer Res 69:6951–6959

Huang H, Fujii H, Sankila A, Mahler-Araujo BM, Matsuda M, Cathomas G, Ohgaki H (1999) Beta-catenin mutations are frequent in human hepatocellular carcinomas associated with hepatitis C virus infection. Am J Pathol 155:1795–1801

Huang et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17626620

Hung CM, Huang WC, Pan HL, Chien PH, Lin CW, Chen LC, Chien YF, Lin CC et al (2014) Hepatitis B virus X upregulates HuR protein level to stabilize HER2 expression in hepatocellular carcinoma cells. Biomed Res Int 2014:827415

Ihara A, Koizumi H, Hashizume R, Uchikoshi T (1996) Expression of epithelial cadherin and alpha- and beta-catenins in nontumoral livers and hepatocellular carcinomas. Hepatology 23:1441–1447

Ishiuchi T, Takeichi M (2011) Willin and Par3 cooperatively regulate epithelial apical constriction through aPKC-mediated ROCK phosphorylation. Nat Cell Biol 13:860–866

Jhunjhunwala S, Jiang Z, Stawiski EW, Gnad F, Liu J, Mayba O, Du P, Diao J, Johnson S, Wong KF, Gao Z, Li Y et al (2014) Diverse modes of genomic alteration in hepatocellular carcinoma. Genome Biol 15:436

Ji J, Yamashita T, Wang XW (2011) Wnt/beta-catenin signaling activates microRNA-181 expression in hepatocellular carcinoma. Cell Biosc 1:4

Jia Y, Yang Y, Liu S, Herman JG, Lu F, Guo M (2010) SOX17 antagonizes WNT/β-catenin signaling pathway in hepatocellular carcinoma. Epigenetics 5: 743–749

Jia D, Wei L, Guo W, Zha R, Bao M, Chen Z, Zhao Y, Ge C, Zhao F, Chen T, Yao M et al (2011) Genome-wide copy number analyses identified novel cancer genes in hepatocellular carcinoma. Hepatology 54:1227–1236

Kahng YS, Lee YS, Kim BK, Park WS, Lee JY, Kang CS (2003) Loss of heterozygosity of chromosome 8p and 11p in the dysplastic nodule and hepatocellular carcinoma. J Gastroenterol Hepatol 18:430–436

Kankuri E, Cholujova D, Comajova M, Vaheri A, Bizik J (2005) Induction of hepatocyte growth factor/scatter factor by fibroblast clustering directly promotes tumor cell invasiveness. Cancer Res 65:9914–9922

Kaplan L, Cole SL (1965) Fraternal primary hepatocellular carcinoma in three male adult siblings. Am J Med 39:305–311

Kaposi-Novak P, Lee JS, Gomez-Quiroz L, Coulouarn C, Factor VM, Thorgeirsson SS (2006) Met-regulated expression signature defines a subset of human hepatocellular carcinomas with poor prognosis and aggressive phenotype. J Clin Invest 116:1582–1595

Katoh 2012. http://www.ncbi.nlm.nih.gov/pubmed/23076869

Kaur P, Mani S, Cros MP, Scoazec JY, Chemin I, Hainaut P, Herceq Z (2012) Epigenetic silencing of sFRP1 activates the canonical Wnt pathway and contributes to increased cell growth and proliferation in hepatocellular carcinoma. Tumour Biol 33:325–336

Kido T, Ou JH, Lau YF (2011) The X-linked tumor suppressor TSPX interacts and promotes degradation of the hepatitis B viral protein HBx via the proteasome pathway. PLoS One 6:e22979

Kim YD, Park CH, Kim HS, Choi SK, Rew JS, Kim DY, Koh YS, Jeung KW, Lee KH et al (2008) Genetic alterations of Wnt signaling pathway-associated genes in hepatocellular carcinoma. J Gastroenterol Hepatol 23:110–118

Kirstein MM, Vogel A (2014) The pathogenesis of hepatocellular carcinoma. Dig Dis 32:545–553

Kondo Y, Kanai Y, Sakamoto M, Genda T, Mizokami M, Ueda R, Hirohashi S (1999) Beta-catenin accumulation and mutation of exon 3 of the beta-catenin gene in hepatocellular carcinoma. Jpn J Cancer Res 90:1301–1309

Kondo S, Ojima H, Tsuda H, Hashimoto J, Morizane C, Ikeda M, Ueno H, Tamura K et al (2013) Clinical impact of c-Met expression and its gene amplification in hepatocellular carcinoma. Int J Clin Oncol 18:207–213

Lai TY, Su CC, Kuo WW, Yeh YL, Kuo WH, Tsai FJ, Tsai CH, Weng YJ, Huang CY et al (2011) β-catenin plays a key role in metastasis of human hepatocellular carcinoma. Oncol Rep 26:415–422

Lanaya H, Natarajan A, Komposch K, Li L, Amberg N, Chen L, Wculek SK, Hammer M et al (2014) EGFR has a tumour-promoting role in liver macrophages during hepatocellular carcinoma formation. Nat Cell Biol. doi:10.1038/ncb3031

Laprise P (2011) Emerging role for epithelial polarity proteins of the Crumbs family as potential tumor suppressors. J Biomed Biotechnol 2011:868217

Laurent-Puig P, Legoix P, Bluteau O, Belghiti J, Franco D, Binot F, Monges G, Thomas G et al (2001) Genetic alterations associated with hepatocellular carcinomas define distinct pathways of hepatocarcinogenesis. Gastroenterology 120:1763–1773

Lazarevich NL, Shavochkina DA, Fleishman DI, Kustova IF, Morozova OV, Chuchuev ES et al (2010) Deregulation of hepatocyte nuclear factor 4 (HNF4) as a marker of epithelial tumors progression. Exp Oncol 32:167–171

Lee HC, Kim M, Wands JR (2006) Wnt/Frizzled signaling in hepatocellular carcinoma. Front Biosc 11:1901–1915

Lee HS, Park MH, Yang SJ, Park KC, Kim NS, Kim YS, Kim DI, Yoo HS, Choi EJ et al (2007) Novel candidate targets of Wnt/beta-catenin signaling in hepatoma cells. Life Sci 80:690–698

Lee SA, Ho C, Roy R, Kosinski C, Patil MA, Tward AD, Fridyland J, Chen X (2008) Integration of genomic analysis and in vivo transfection to identify sprouty 2 as a candidate tumor suppressor in liver cancer. Hepatology 47:1200–1210

Lee SA, Ladu S, Evert M, Dombrowski F, De Murtas V, Chen X, Calvisi DF (2010) Synergistic role of Sprouty2 inactivation and c-Met up-regulation in mouse and human hepatocarcinogenesis. Hepatology 52: 506–517

Lee SJ, Lee J, Sohn I, Mao M, Kai W, Park CK, Lim HY (2013) A survey of c-Met expression and amplification in 287 patients with hepatocellular carcinoma. Anticancer Res 33:5179–5186

Legoix P, Bluteau O, Bayer J, Perret C, Balabaud C, Belghiti J, Franco D, Thomas G (1999) Beta-catenin mutations in hepatocellular carcinoma correlate with a low rate of loss of heterozygosity. Oncogene 18:4044–4046

Lessel D, Vaz B, Halder S, Lockhart PJ, Marinovic-Terzic I, Lopez-Mosqueda J, Philipp M, Sim JC, Smith KR et al (2014) Mutations in SPRTN cause early onset hepatocellular carcinoma, genomic instability and progeroid features. Nat Genet 46:1239–1244

Li S, Mao M (2013) Next generation sequencing reveals genetic landscape of hepatocellular carcinomas. Cancer Lett 340:247–253

Li YS, Liu M, Nakata Y, Tang HB (2011) β-catenin accumulation in nuclei of hepatocellular carcinoma cells up-regulates glutathione-S-transferase M3 mRNA. World J Gastroenterol 17:1772–1778

Li ZQ, Ding W, Sun SJ, Li J, Pan J, Zhao C, Wu WR, Si WK (2012) Cyr61/CCN1 is regulated by Wnt/β-catenin signaling and plays an important role in the progression of hepatocellular carcinoma. PLoS One 7:e35754

Li YP, Wu CC, Chen WT, Huang YC, Chai CY (2013) The expression and significance of WWOX and β-catenin in hepatocellular carcinoma. APMIS 121:120–126

Li P, Cao Y, Li Y, Zhou L, Liu X, Geng M (2014) Expression of Wnt-5a and β-catenin in primary hepatocellular carcinoma. Int J Clin Exp Pathol 7:3190–3195

Liu AM, Xu MZ, Chen J, Poon RT, Luk JM (2010) Targeting YAP and Hippo signaling pathway in liver cancer. Expert Opin Ther Targets 14:855–868

Liu J, Ding X, Tang J, Cao Y, Hu P, Zhou F, Shan X, Cai X, Chen Q, Ling N, Zhang B et al (2011) Enhancement of canonical Wnt/β-catenin signaling activity by HCV core protein promotes cell growth of hepatocellular carcinoma cells. PLoS One 6:e27496

Lu LC, Shao YY, Lee YH, Hsieh MS, Hsiao CH, Lin HH, Kao HF, Ma YY, Yen FC et al (2014) β-catenin (CTNNB1) mutations are not associated with prognosis in advanced hepatocellular carcinoma. Oncology 87:159–166

Mardin BR, Lange C, Baxter JE, Hardy T, Scholz SR, Fry AM, Schiebel E (2010) Components of the Hippo pathway cooperate with Nek2 kinase to regulate centrosome disjunction. Nat Cell Biol 12:1166–1176

Marquardt JU, Thorgeirsson SS (2013) Linking MLL and the HGF-MET signaling pathway in liver cancer. J Clin Invest 123:2780–2783

Martin J, Dufour JF (2008) Tumor suppressor and hepatocellular carcinoma. World J Gastroenterol 14:1720–1737

Matsumoto K, Nakamura T (1992) Hepatocyte growth factor: molecular structure, roles in liver regeneration, and other biological functions. Crit Rev Oncog 3:27–54

McGivern DR, Lemon SM (2009) Tumor suppressors, chromosomal instability, and hepatitis C virus-associated liver cancer. Annu Rev Pathol Mech Dis 4:399–415

Merle P, Trepo C (2009) Molecular mechanisms underlying hepatocellular carcinoma. Viruses 1:852–872

Merle et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15480989

Merle P, Kim M, Herrmann M, Gupte A, Lefrançois L, Califano S, Trépo C, Tanaka S et al (2005) Oncogenic role of the frizzled-7/beta-catenin pathway in hepatocellular carcinoma. J Hepatol 43:854–862

Miyoshi Y, Iwao K, Nagasawa Y, Aihara T, Sasaki Y, Imaoka S, Murata M, Shimano T et al (1998) Activation of the beta-catenin gene in primary hepatocellular carcinomas by somatic alterations involving exon 3. Cancer Res 58:2524–2527

Morin PJ (1999) Beta-catenin signaling and cancer. Bioessays 21:1021–1030

Murata M, Miyoshi Y, Ohsawa M, Shibata K, Ohta T, Imai Y, Nishikawa M, Iwao K et al (2001) Accumulation of beta-catenin in the cytoplasm and the nuclei during the early hepatic tumorigenesis. Hepatol Res 21:126–135

Nagai H, Pineau P, Tiollais P, Buendia MA, Dejean A (1997) Comprehensive allelotyping of human hepatocellular carcinoma. Oncogene 14:2927–2933

Nakagawa H, Shibata T (2013) Comprehensive genome sequencing of the liver cancer genome. Cancer Lett 340:234–240

Nakamura T (1991) Structure and function of hepatocyte growth factor. Prog Growth Factor Res 3:67–85

Nejak-Bowen KN, Monga SP (2011) Beta-catenin signaling, liver regeneration and hepatocellular cancer: sorting the good from the bad. Semin Cancer Biol 21:44–58

Nejak-Bowen KN, Thompson MD, Singh S, Bowen WC, Dar MJ, Khillan J, Dai C, Monge SP (2010) Accelerated liver regeneration and hepatocarcinogenesis in mice overexpressing serine-45 mutant beta-catenin. Hepatology 51:1603–1613

Ngok SP, Lin WH, Anastasiadis PZ (2014) Establishment of epithelial polarity – GEF who's minding the GAP? J Cell Sci 127:3205–3215

Nhieu JT, Renard CA, Wei Y, Cherqui D, Zafrani ES, Buendia MA (1999) Nuclear accumulation of mutated beta-catenin in hepatocellular carcinoma is associated with increased cell proliferation. Am J Pathol 155:703–710

Nishida N, Kudo M (2013) Recent advancements in comprehensive genetic analyses for human hepatocellular carcinoma. Oncology 84(Suppl 1):93–97

Nishida N, Nishimura T, Ito T, Komeda T, Fukuda Y, Nakao K (2003) Chromosomal instability and human hepatocarcinogenesis. Histol Histopathol 18:897–909

Nuruki K, Toyoyama H, Ueno S, Hamanoue M, Tanabe G, Aikou T, Ozawa M (1998) E-cadherin but not N-cadherin expression is correlated with the intracellular distribution of catenins in human hepatocellular carcinomas. Oncol Rep 5:1109–1114

Ogunwobi OO, Puszyk W, Dong HJ, Liu C (2013) Epigenetic upregulation of HGF and c-Met drives metastasis in hepatocellular carcinoma. PLoS One 8:e63765

Okano H, Isono Y, Tanaka H, Ishihara Y, Matsusaki S, Aoki M, Sase T, Saitou T, Mukai K et al (2011) Primary liver tumor associated with Werner syndrome (adult progeria). Hepatol Res 41:1260–1265

Ozturk M (1999) Genetic aspects of hepatocellular carcinogenesis. Semin Liver Dis 19:235–242

Pang RW, Poon RT (2007) From molecular biology to targeted therapies for hepatocellular carcinoma: the future is now. Oncology 72(Suppl 1):30–44

Park CY, Choi SH, Kang SM, Kang JI, Ahn BY, Kim H, Jung G, Choi KY, Hwang SB (2009) Nonstructural 5A protein activates β-catenin signaling cascades: implication of hepatitis C virus-induced liver pathogenesis. J Hepatol 51:853–864

Peng C, Xiao X, Kang B, He S, Li J (2014) Serum secreted frizzled-related protein 5 levels differentially decrease in patients with hepatitis B virus-associated chronic infection and hepatocellular carcinoma. Oncol Lett 8:1340–1344

Pez F, Lopez A, Kim M, Wands JR, Caron de Fromentel C, Merle P (2013) Wnt signaling and hepatocarcinogenesis: molecular targets for the development of innovative anticancer drugs. J Hepatol 59:1107–1117

Piao Z, Park C, Park JH, Kim H (1998) Allelotype analysis of hepatocellular carcinoma. Int J Cancer 75:29–33

Prunier C, Hocevar BA, Howe PH (2004) Wnt signaling: physiology and pathology. Growth Factors 22:141–150

Quan H, Zhou F, Nie D, Chen Q, Cai X, Shan X, Zhou Z, Chen K, Huang A, Li S, Tang N (2014) Hepatitis C virus core protein epigenetically silences SFRP1 and enhances HCC aggressiveness by inducing epithelial-mesenchymal transition. Oncogene 33:2826–2835

Ramakrishna G, Rastogi A, Trehanpati N, Sen B, Khosla R, Sarin SK (2013) From cirrhosis to hepatocellular carcinoma: new molecular insights on inflammation and cellular senescence. Liver Cancer 2:367–383

Rauskolb C, Pan G, Reddy BV, Oh H, Irvibe KD (2011) Zyxin links fat signaling to the hippo pathway. PLoS Biol 9:e1000624

Ribeiro P, Holder M, Frith D, Snijders AP, Tapon N (2014) Crumbs promotes expanded recognition and degradation by the SCF (Slimb/β-TrCP) ubiquitin ligase. Proc Natl Acad Sci U S A 111:E1980–E1989

Roessler S, Long EL, Budhu A, Chen Y, Zhao X, Ji J, Walker R, Jia HL, Ye QH et al (2012) Integrative genomic identification of genes on 8p associated with

hepatocellular carcinoma progression and patient survival. Gastroenterology 142:957–966
Ruijs MW, van Andel RN, Oshima J, Madan K, Nieuwint AW, Aalfs CM (2003) Atypical progeroid syndrome: an unknown helicase gene defect ? Am J Med Genet A 116A:295–299
Sanders AJ, Ye L, Li J, Mason MD, Jiang WG (2014) Tumour angiogenesis and repulsive guidance molecule B: a role in HGF-and BMP-7-mediated angiogenesis. Int J Oncol 45:1304–1312
Satoh S, Daigo Y, Furukawa Y, Kato T, Miwa N, Nishiwaki T, Kawasoe T, Ishiguro H et al (2000) AXIN1 mutations in hepatocellular carcinomas, and growth suppression in cancer cells by virus-mediated transfer of AXIN1. Nat Genet 24:245–250
Schoedel KE, Tyner VZ, Kim TH, Michalopoulos GK, Mars WM (2003) HGF, MET, and matrix-related proteases in hepatocellular carcinoma, fibromalellar variant, cirrhotic and normal liver. Mod Pathol 16:14–21
Sharma P, McNeill H (2013) Fat and Dachsous cadherins. Prog Mol Biol Transl Sci 116:215–235
Shi Y, He B, You L, Jablons DM (2007) Roles of secreted frizzled-related proteins in cancer. Acta Pharmacol Sin 28:1499–1504
Shibata T, Aburatani H (2014) Exploration of liver cancer genomes. Nat Rev Gastroenterol Hepatol 11:340–349
Shih YL, Shyu RY, Hsieh CB, Lai HC, Liu KY, Chu TY, Lin YW (2006) Promoter methylation of the secreted frizzled-related protein 1 gene SFRP1 is frequent in hepatocellular carcinoma. Cancer 107:579–590
Shih YL, Hsieh CB, Lai HC, Yan MD, Hsieh TY, Chao YC, Lin YW (2007) SFRP1 suppressed hepatoma cells growth through Wnt canonical signaling pathway. Int J Cancer 121:1028–1035
Skawran B, Steinemann D, Weigmann A, Flemming P, Becker T, Flik J, Kreipe H, Schlegelberger B et al (2008) Gene expression profiling in hepatocellular carcinoma. Upregulation of genes in amplified chromosome regions. Mod Pathol 21:505–516
Spinardi L, Rietdorf J, Nitsch L, Bono M, Tacchetti C, Way M, Marchisio PC (2004) A dynamic podosome-like structure of epithelial cells. Exp Cell Res 295:360–374
Suzuki K, Hayashi N, Yamada Y, Yoshihara H, Miyamoto Y, Ito Y, Ito T, Katayama K et al (1994) Expression of the c-met protooncogene in human hepatocellular carcinoma. Hepatology 20:1231–1236
Sy SM, Lai PB, Pang E, Wong NL, To KF, Johnson PJ, Wong N (2006) Novel identification of zyxin upregulations in the motile phenotype of hepatocellular carcinoma. Mod Pathol 19:1108–1116
Takagi H, Sasaki S, Suzuki H, Toyota M, Maruyama R, Nojima M, Yamamoto H, Omata M et al (2008) Frequent epigenetic inactivation of SFRP genes in hepatocellular carcinoma. J Gastroenterol 43:378–389
Takai A, Dang HT, Wang XW (2014) Identification of drivers from cancer genome diversity in hepatocellular carcinoma. Int J Mol Sci 15:11142–11160
Takeda S, Liu H, Sasagawa S, Dong Y, Trainor PA, Cheng EH, Hsieh JJ (2013) HGF-MET signals via the MLL-ETS2 complex in hepatocellular carcinoma. J Clin Invest 123:3154–3165
Takigawa Y, Brown AM (2008) Wnt signaling in liver cancer. Curr Drug Targets 9:1013–1024
Tang W, Weng S, Zhang S, Wu W, Dong L, Shen X, Zhang S, Gu J, Xue R (2013) Direct interaction between surface β1,4-galactosyltransferase 1 and epidermal growth factor receptor (EGFR) inhibits EGFR activation in hepatocellular carcinoma. Biochem Biophys Res Commun 434:449–454
Taniguchi K, Roberts LR, Aderca IN, Dong X, Qian C, Murphy LM, Nagorney DM et al (2002) Mutational spectrum of beta-catenin, AXIN1, and AXIN2 in hepatocellular carcinomas and hepatoblastomas. Oncogene 21:4863–4871
Terris B, Pineau P, Bregeaud L, Valla D, Belghiti J, Tiollais P, Degott C, Dejean A (1999) Close correlation between beta-catenin gene alterations and nuclear accumulation of the protein in human hepatocellular carcinomas. Oncogene 18:6583–6588
Tien LT, Ito M, Nakao M, Niino D, Serik M, Nakashima M, Wen CY, Yatsuhashi H et al (2005) Expression of beta-catenin in hepatocellular carcinoma. World J Gastroenterol 11:2398–2401
Toan LT, Ito M, Nakao M, Niino D, Serik M, Nakashima M, Wen CY, Yatsuhashi H et al (2005) Expression of beta-catenin in hepatocellular carcinoma. World J Gastroenterol 11:2398–2401
Totoki Y, Tatsuno K, Yamamoto S, Arai Y, Hosoda F, Ishikawa S, Tsutsumi S, Sonoda K et al (2011) High-resolution characterization of a hepatocellular carcinoma genome. Nat Genet 43:464–469
Totoki Y, Tatsuno K, Covington KR, Ueda H, Creighton CJ, Kato M, Tsuji S, Donehower LA, Slagle BL et al (2014) Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. Nat Genet 46:1267–1273
Toyama T, Lee HC, Koga H, Wands JR, Kim M (2010) Noncanonical Wnt11 inhibits hepatocellular carcinoma cell proliferation and migration. Mol Cancer Res 8:254–265
Tsao CM, Yan D, Shih YL, Yu PN, Kuo CC, Lin WC, Li HJ, Lin YW (2012) SOX1 functions as tumor suppressor by antagonizing the WNT/β-catenin signaling pathway in hepatocellular carcinoma. Hepatology 56:2277–2287
Tschaharganeh DF, Chen X, Latzko P, Malz M, Gaida MM, Felix K, Ladu S, Singer S et al (2013) Yes-associated protein up-regulated Jagged-1 and activates the NOTCH pathway in human hepatocellular carcinoma. Gastroenterology 144:1530–1542
Tung EK, Mak CK, Fatima S, Lo RC, Zhao H, Zang C, Dai H, Poon RT, Yuen MF et al (2011) Clinicopathological and prognostic significance of serum and tissue Dickkopf-1 levels in human hepatocellular carcinoma. Liver Int 31:1494–1504

Tung EK, Wong BY, Yau TO, Ng IO (2012) Upregulation of the Wnt co-receptor LRP6 promotes hepatocarcinogenesis and enhances cell invasion. PLoS One 7:e36565

Ueki T, Fujimoto J, Suzuki T, Yamamoto H, Okamoto E (1997) Expression of hepatocyte growth factor and its receptor c-met proto-oncogene in hepatocellular carcinoma. Hepatology 25:862–866

Ueta T, Ikeguchi M, Hirooka Y, Kaibara N, Terada T (2002) Beta-catenin and cyclin D1 expression in human hepatocellular carcinoma. Oncol Rep 9:1197–1203

Van Malenstein H, van Pelt J, Verslype C (2011) Molecular classification of hepatocellular carcinoma anno 2011. Eur J Cancer 47:1789–1797

Wang J, An H, Mayo MW, Baldwin AS, Yarbrough WG (2007) LZAP, a putative tumor suppressor, selectively inhibits NF-kappaB. Cancer Cell 12:239–251

Wang X, Meng X, Sun X, Liu M, Gao S, Zhao J, Pei F, Yu H (2009) Wnt/beta-catenin signaling pathway may regulate cell cycle and expression of cyclin A and cyclin E protein in hepatocellular carcinoma cells. Cell Cycle 8:1567–1570

Wang XH, Meng XW, Sun X, Liu BR, Han MZ, Du YJ, Song YY, Xu W (2011) Wnt/β-catenin signaling regulates MAPK and Akt1 expression and growth of hepatocellular carcinoma cells. Neoplasma 58:239–244

Wang L, Yao J, Shi X, Hu L, Li Z, Song T, Juang C (2013) MicroRNA-302b suppresses cell proliferation by targeting EGFR in human hepatocellular carcinoma SMMC-7721 cells. BMC Cancer 13:448

Wang J, Zuo Y, Man YG, Avital I, Stojadinovic A, Liu M, Yang X, Varghese RS, Tadesse MG, Ressom HW (2015) Pathway and network approaches for identification of cancer signature markers from omics data. J Cancer 6:54–65

Wei W, Chua MS, Grepper S, So SK (2011) Soluble frizzled-7 receptor inhibits Wnt signaling and sensitizes hepatocellular carcinoma cells towards doxorubicin. Mol Cancer 10:16

Whittaker S, Marais R, Zhu AK (2010) The role of signaling pathways in the development and treatment of hepatocellular carcinoma. Oncogene 29:4989–5005

Wong CM, Ng IO (2008) Molecular pathogenesis of hepatocellular carcinoma. Liver Int 28:160–174

Wong CM, Fan ST, Ng IO (2001) Beta-catenin mutation and overexpression in hepatocellular carcinoma: clinicopathologic and prognostic significance. Cancer 92:136–145

Woo HG, Kim SS, Cho H, Kwon SM, Cho HJ, Ahn SJ, Park ES, Lee JS, Cho SW, Cheong JY (2014) Profiling of exome mutations associated with progression of HBV-related hepatocellular carcinoma. PLoS One 9: e115152

Wu Y, Li J, Sun CY, Zhou Y, Zhao YF, Zhang SJ (2012) Epigenetic inactivation of the canonical Wnt antagonist secreted frizzled-related protein 1 in hepatocellular carcinoma cells. Neoplasma 59:326–332

Xia H, Ooi LL, Hui KM (2012) MiR-214 targets β-catenin pathway to suppress invasion, stem-like traits and recurrence of human hepatocellular carcinoma. PLoS One 7:e44206

Xing Z, Tang X, Gao Y, Da L, Song H, Wang S, Tiollais P, Li T, Zhao M (2011) The human LIS1 is downregulated in hepatocellular carcinoma and plays a tumor suppressor function. Biochem Biophys Res Commun 409:193–199

Yamamura M, Noguchi K, Nakano Y, Segawa E, Zushi Y, Takaoka K, Kishimoto H et al (2013) Functional analysis of Zyxin in cell migration and invasive potential of oral squamous cell carcinoma cells. Int J Oncol 42:873–880

Yamashita T, Budhu A, Forgues M, Wang XW (2007) Activation of hepatic stem cell marker EpCAM by Wnt-beta-catenin signaling in hepatocellular carcinoma. Cancer Res 67:10831–10839

Yau TO, Chan CY, Chan KL, Lee MF, Wong C:M, Fan ST, Ng IO (2005) HDPR1, a novel inhibitor of the WNT/beta-catenin signaling, is frequently downregulated in hepatocellular carcinoma: involvement of methylation-mediated gene silencing. Oncogene 24:1607–1614

Yoneda N, Sato Y, Kitao A, Ikeda H, Sawada-Kitamura S, Miyakoshi M, Harada K, Sasaki M et al (2011) Epidermal growth factor induces cytokeratin 19 expression accompanied by increased growth abilities in human hepatocellular carcinoma. Lab Invest 91:262–272

Yoo BK, Gredler R, Chen D, Santhekadur PK, Fisher PB, Sarkar D (2011) c-Met activation through a novel pathway involving osteopontin mediates oncogenesis by the transcription factor LSF. J Hepatol 55:1317–1324

Young RJ, Fernando M, Hughes D, Brown NJ, Wolf PJ (2014) Angiogenic growth factor expression in benign and malignant vascular tumours. Exp Mol Pathol 97:148–153

Yu B, Yang X, Xu Y, Yao G, Shu H, Lin B, Hood L, Wang H, Yang S, Gu J, Fan J et al (2009) Elevated expression of DKK1 is associated with cytoplasmic/nuclear beta-catenin accumulation and poor prognosis in hepatocellular carcinomas. J Hepatol 50: 948–957

Yu J, Zheng Y, Dong J, Klusza S, Deng WM, Pan D (2010) Kibra functions as a tumor suppressor protein that regulates Hippo signaling in conjunction with Merlin and Expanded. Dev Cell 18:288–299

Yuan RH, Jeng YM, Hu RH, Lai RL, Lee PH, Cheng CC, Hsu HC (2011) Role of p53 and β-catenin mutations in conjunction with CK19 expression on early tumor recurrence and prognosis of hepatocellular carcinoma. J Gastrointest Surg 15:321–329

Zhang W, Mendoza MC, Pei X, Ilter D, Mahoney SJ, Zhang Y, Ma D, Blenis J, Wang Y (2012) Down-regulating of CMTM8 induces epithelial-to-mesenchymal transition-like changes via c-MET/extracellular signal-regulated kinase (ERK) signaling. J Biol Chem 287:11850–11858

Zhang Q, Bai X, Chen W, Ma T, Hu QD, Liang C, Xie S, Chen C, Hu LQ, Xu S, Liang T (2013) Wnt/β-catenin signaling enhances hypoxia-induced epithelial-mesenchymal transition in hepatocellular carcinoma via crosstalk with hif-1α signaling. Carcinogenesis 34:962–973

Zhang Y, Qiu Z, Wei L, Tang R, Lian B, Zhao Y, He X, Xie L (2014) Integrated analysis of mutation data from various sources identifies key genes and signaling pathways in hepatocellular carcinoma. PLoS One 9:e100854

Zhao M, Zimmermann A (1998) Liver cell dysplasia: reactivities for c-met protein, Rb protein, E-cadherin and transforming growth factor-beta 1 in comparison with hepatocellular carcinoma. Histol Histopathol 13:657–670

Zhao JJ, Pan K, Li JJ, Chen YB, Chen JG, Lv L, Wang DD, Pan QZ, Chen MS, Xia JC (2011) Identification of LZAP as a new candidate tumor suppressor in hepatocellular carcinoma. PLoS One 6:e26608

Zucchini-Pascal N, Peyre L, Rahmani R (2013) Crosstalk between beta-catenin and snail in the induction of epithelial to mesenchymal transition in hepatocellular carcinoma: role of the ERK1/2 pathway. Int J Mol Sci 14:20768–20792

Zucman-Rossi J, Benhamouche S, Godard C, Boyault S, Grimber G, Balabaud C, Cunha AS et al (2007) Differential effects of inactivated Axin1 and activated beta-catenin mutations in human hepatocellular carcinomas. Oncogene 26:774–780

Zulehner G, Mikula M, Schneller D, van Zijl F, Huber H, Sieghart W, Grasl- Kraupp B et al (2010) Nuclear beta-catenin induces an early liver progenitor phenotype in hepatocellular carcinoma and promotes tumor recurrence. Am J Pathol 176:472–481

Etiology and Pathogenesis of Hepatocellular Carcinoma: Transcription Factors, Signal Pathways Regulating Proliferation and Apoptosis, and Telomeres/ Telomerases

167

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_167

Abstract

Etiology and pathogenesis of hepatocellular carcinoma (HCC) involve deregulation of various transcription factors, signal pathways that control cell proliferation, differentiation and apoptosis, and the telomere/telomerase system. A major mutated transcription factor in HCC is the TP53/p53 gene, one of the most commonly mutated gene in human cancer. p53 is a multifunctional transcription factor that plays an important role in the DNA damage response network, cell cycle regulation, DNA repair, cellular senescence, and apoptosis. Other deregulated transcription factors in HCC include Krüppel-like proteins involved in cell and tissue homeostasis and in cell survival, the c-Fos/c-Jun oncogene system, the human FOX gene family, the Myc proto-oncogene, HOX gene product, and the RUNX transcription factor. The multifunctional protein transforming growth factor beta1 (TGF1) and TGF1-related signaling pathways play a significant role in HCC pathogenesis. GTPases and GTPase-related proteins such as DLC1 (deleted in liver cancer 1) and Ras are involved in early hepatocarcinogenic pathways. HCC pathogenesis also involves deregulation of telomeres and telomerases, a system that controls orderly replication, genomic stability, and regulation of cell senescence.

Deregulated Transcription Factors in Liver Cancer

p53, A Major Mutated Transcription Factor in Hepatocellular Carcinoma

The TP53/p53 gene is the most commonly mutated gene in human cancers (Vogelstein et al. 2000; Olivier et al. 2010; Olivier and Taniere 2011; Seton-Rogers 2014). This encodes the p53 protein, a multifunctional transcription factor playing important roles in DNA damage response network, cell cycle regulation, DNA repair, cellular senescence, and apoptosis (Beckerman and Prives 2010). In principle, p53 prevents abnormal proliferation of numerous cell lineages by guarding against cellular stress and genotoxic damage. As a major transcription factor, p53 exerts its effects via transactivation and transrepression of numerous target genes acting in arrest of cell proliferation or induction of cell death, i.e., operating as a factor that determines cell mass homeostasis. p53 is a major proapoptotic factor by its function as a prooxidant molecule and is a major target of certain hepatocarcinogenic substances, in particular aflatoxins (see above). More than 80 % of p53 gene mutations that occur in cancers involve the transcription/DNA-binding domain of the protein, whereby these mutations prevent p53 from binding to DNA. By use of modern techniques, in particular parallel pyrosequencing, also rare or low-abundance p53 mutations are detectable, having led to an important increase in known mutations in many types of cancers. Apart from mutations of the gene, the function of p53 can be blunted by other mechanisms that interfere with the function of wild-type p53. Many factors can cause altered expression, stability, or activity of p53 in cancers in the absence of p53 mutations, i.e., under maintenance of the wild-type transcription factor.

As stringent control of p53 function is necessary for cell growth homeostasis and survival, p53 interacts with several controlling proteins. p53 mainly interacts with two structurally related proteins that counteract the potentially lethal effects of p53, MDM2 and MDM4. MDM2 (E3 ubiquitin-protein ligase homologue) is an oncogene and encodes a protein which is a potent inhibitor of p53 function (Toledo and Wahl 2007; Perry 2010). The MDM2 gene is a target for transcriptional activation by p53, resulting in MDM2-p53 autoregulatory feedback loop that regulates p53 activity. The activity of the inhibitor MDM2 is blocked by microRNA-339-5p which directly targets MDM2 (Jansson et al. 2014). This microRNA is downregulated in tumors harboring wild-type p53. MDM2 is also a direct target of microRNA-221 in HCC, this microRNA therefore activating the p53 axis by inhibiting MDM2 (Fornari et al. 2014). An MDM2 antagonist that may restore p53 function in HCC cells is Nutlin-3.

On the other hand, Nutlin-3 can also downregulate p53 phosphorylation on serine392 and induce apoptosis in HCC (Shi et al. 2014). MDM2 is amplified or overexpressed in numerous human malignancies. Distinct polymorphisms in the MDM2 gene (at codons 285, 309, and 344) are associated with increased HCC risk, showing that MDM2 is a potential oncogene (Peng et al. 2013; Chen et al. 2014a; Rebbani et al. 2014).

Mutations of TP53 are a well-known etiologic feature in human HCC, cause function failure of p53, and abolish the proapoptotic function of p53, resulting in increased tumor cell survival. TP53 mutations in HCC affect tumor biology and are associated with poor outcome (Tannapfel et al. 2001; Peng et al. 2002; Edamoto et al. 2003; Hussain et al. 2007; Tornesello et al. 2013; Zhan et al. 2013). Such mutations can occur spontaneously or are induced by external factor, the best known example being aflatoxin B1 exposure that is associated with a point mutation at codon 249, as discussed above. In HCC, an important mutational hot spot is R249S, a mutation strongly associated with aflatoxin toxicity and high HCC risk. In patients with HCC, TP53 mutations, in particular those involving the hot spots R249S and V157F, are associated with an aggressive course and poor prognosis (Villanueva and Hoshida 2011). When associated with chronic HBV infection, the leading mutation (Ser249) shows a multiplicative effect of HCC risk (Aguilar et al. 1994; Kirk et al. 2005; Qi et al. 2014). p53 activity can be directly abrogated by HBV infection. The HBx protein, critically involved in HBV-associated hepatocarcinogenesis, can specifically bind to the carboxy-terminus of p53 and suppress p53-induced apoptosis. HBx protein can also decrease binding of p53 to proteins involved in nucleotide excision repair, augmenting the risk of further mutations within DNA (Wang et al. 1994). In patients with HVC-related HCC, unusual mutations of TP53 have been detected, e.g., distinct so-called microindel mutations, infrequent mutations resulting in inserted and deleted sequences at the same nucleotide position and causing truncation of the p53 protein with loss of the DNA-binding domain (Long et al. 2013). p53 represses certain proteins involved in apoptosis regulation. For example, the prosurvival function of the cellular apoptosis susceptibility / importin-alpha1 transport cycle is repressed by p53 in HCC (Winkler et al. 2014). The Notch1 receptor, which plays an important role in liver cell fating and growth, differentially regulates oncogenesis by wild-type p53 overexpression and p53 mutation in HCC (Lim et al. 2011). p53 is transcriptionally regulated by the tumor suppressor gene downregulated in HCC, FHL2 (four and a half LIM protein 2), a LIM domain-only protein. FHL2 binds to and activates the TP53 promoter in hepatic cells. The hot spot mutation 747G>T in HCC is potentially associated with a higher expression of FHL2 in HCC tumor tissue (Xu et al. 2014).

Apart from its role in the regulation of apoptosis and its status as a tumor suppressor, p53 induces other pathogenic pathways that may play a role in liver cancer development, in particular proliferation and cell cycle regulation. This is linked to distinct functions of p53 in the transcriptional regulation of genes involved in mitotic entry, centrosome duplication, and cytokinesis. For example, p53 regulates expression of polo-like kinases which are central to the control of these growth processes (Ward and Hudson 2014). Certain mutated p53 proteins may achieve gain of oncogenic functions via production of oxidative and nitrosative stress (Hussain et al. 2007). A rather frequent polymorphism at codon 72 resulting in the change of arginine to proline is correlated with risk for HCC in distinct subpopulations infected with hepatitis viruses (Hu et al. 2014). However, the proline variant was also correlated with HCC in an HCV-independent manner, suggesting the p53 alterations can promote HCC in the absence of other well-established exogenous risk factors (Ezzikouri et al. 2007). Sustained p53 activation subsequent to DNA damage promotes inflammation-associated mechanisms that can lead to carcinogenesis, supporting the view that p53 can act in a dichotomous manner rather than exclusively acting as a tumor suppressor. In HCC models, constant activation of wild-type p53 resulted in pro-tumorigenic inflammation via

induction of the potential inflammatory molecule, high-mobility group protein 1 (HMGB1) (Yan et al. 2013). A protein with a significant homology to p53 and showing functional similarities to p53 is p73. LOH of p73 is observed in a significant proportion of HCC patients, and tumors with p73 LOH were more often detected in livers without cirrhosis and were associated with poorer patient outcome (Aoki et al. 2004).

Krüppel-Like Transcription Factors

The zinc finger transcription factors, Krüppel-like factors (KLFs), form a family with 17 members (KLF1–KLF17) in mammals. KLFs have a central role in regulation of cell and tissue homeostasis under normal and neoplastic conditions and critically affect cell proliferation, differentiation, survival, and stress responses. The factors are also operational in ontogenesis and the development of numerous organs and tissues and are involved in the reprogramming of somatic stem cells into pluripotent stem cells, a mechanism also playing a role in carcinogenic pathways (review: McConnell and Yang 2010).

KLF6 is a major factor among KLFs acting in cancer biology and is frequently mutated in several human cancers and significantly involved in the regulation of growth, angiogenesis, and apoptosis in cancer cells (Yin et al. 2007). Specifically, KLF6 is capable to regulate a group of genes that belong to the carcinoembryonic gene family, involved in carcinogenesis (review: Andreoli et al. 2010). Three splice variants of KLF6 exist, termed SV1, SV2, and SV3. Alternative splicing of KLF6 is mediated by hepatocyte growth factor to promote growth through SRSF1 (Muñoz et al. 2012). Allelic loss of KLF6 was found only in a variable fraction of HCC cases, varying from around 4 % to 49 % of tumors (Kremer-Tal et al. 2004; Pan et al. 2006; Song et al. 2006; Wang et al. 2007a, 2010a; Lee et al. 2010). Downregulation of KLF6 was already detectable in macroregenerative nodules occurring in cirrhosis (Bureau et al. 2008). The SV2 splice variant of KLF6, which displays antiproliferative and proapoptotic functions, is variably expressed in HCC and HCC cells (Hanoun et al. 2010; Zhenzhen et al. 2012). A frequent upregulated downstream transcript of KLF6 is the PTTG1 (pituitary tumor-transforming gene 1; Lee et al. 2010) oncogene, and a further KLF6-mediated pathway is transactivation of the E-cadherin promoter (DiFeo et al. 2006). The expression patterns of KLF6 and its splice variants are in itself regulated by TGF-beta via a Smad3-Sp1/specificity protein1-LKF6 interaction (Botella et al. 2009).

Other members of the KLF family show expression patterns in HCC that differ from those for KLF6. KLF4 is expressed in the cytoplasm of HCC cells, immunoreactivity being correlated with cell differentiation and decreased proliferative activity (Hsu et al. 2014). In HCC cells, KLF4 suppresses a critical epithelial-mesenchymal transition (EMT)-related transcription factor, Slug, thus reverting EMT in these tumors (Lin et al. 2012). KLF8 plays important roles in cell cycle regulation and oncogenic transformation. Expression of KLF8 in HCC is correlated with nuclear beta-catenin expression, suggesting that KLF8 interacts with the Wnt/beta-catenin pathway and induces typical signaling targets, including c-Myc, cyclin D1, and Axin1 (Yang et al. 2012). KLF8 expression in HCC also positively correlated with expression of focal adhesion kinase/FAK and MMP-9, suggesting that KLF8 affects mechanisms that function in tumor invasion (Han et al. 2013). In fact, upregulation of KLF8 in HCC promotes tumor invasion and is associated with poor prognosis (Li et al. 2010).

KLF9, assigned to chromosome 9q13 and inhibitor of cell proliferation and inducer of apoptosis, is downregulated in HCC tissue in comparison with nonneoplastic liver (Fu et al. 2014). KLF15 indirectly affects hepatocarcinogenesis via its role on HBV infection pathways. It activates HBV gene expression (HBs and core protein expression) and viral DNA replication via promoter interaction (Zhou et al. 2011). KLF17, which plays a role in regulating epithelial-mesenchymal transition (EMT), is downregulated in HCC, associated with increased tumor cell motility, invasion capacity, and upregulation of EMT-promoting factors (Liu et al. 2013). The pro-invasive function of KLF17 in HCC is

modulated by microRNA-9 which targets this transcription factor (Sun et al. 2013).

c-Fos/c-Jun Oncogene System

c-Fos (chromosome 14q24.3) is a proto-oncogene and the human homologue of the retroviral oncogene v-fos. It is a member of the FOS family that comprises c-Fos, FosB, Fra-1, Fra-2, and smaller FosB splice variants. The c-Fos basic leucine zipper protein forms a heterodimer with c-Jun to form the AP-1 complex (activator protein-1 complex) which acts as a transcription factor and binds to AP-1-specific sites at promoter and enhancer regions of target genes (Abate and Curran 1990). c-Fos cannot form homodimers. Its expression is stimulated by growth factors, tumor promoters, cytokines, and ultraviolet radiation, expression being characterized as a very early response (immediate early gene). Protein stability is modulated by posttranslational phosphorylation by MAPK, protein kinase A or protein kinase C. The oncogene Jun, the homologue of transforming gene of avian sarcoma virus 17, is assigned to chromosome 1p32.1 and a member of the JUN-FOS family of basic leucine zipper proteins acting as a potent transcription factor.

Together with other oncogenes, Fos is involved in the regulation of liver regeneration (Corral et al. 1985; Thompson et al. 1986; Coni et al. 1990, 1993; Morello et al. 1990; Haritani et al. 1991; Hsu et al. 1992). Fos possesses a tumor-suppressive function in various cancer types (Tulchinsky 2000; Durchdewald et al. 2009) and suppresses HCC development in vivo (Mikula et al. 2003). c-Fos is overexpressed in at least part of HCC in comparison with surrounding liver tissue, often coordinated with expression of c-Jun (Tabor 1994; Yuen et al. 2001), and Fos is upregulated in HCC precursors (Alexandre et al. 1994; Feng et al. 2001). c-Fos expression in HCC is in part regulated by epigenetic promoter methylation (Choi et al. 1996). Fos overexpression in hepatocytes increases their proliferation capacity via stabilization of cyclin D1 (Güller et al. 2008). Elevated Fos is a mediator of c-Myc-induced apoptotic signaling in HCC cells (Kalra and Kumar 2004). Elevated levels of Fos in HCC cells are associated with a metastatic phenotype. In HCC sublines with a high spontaneous metastatic potential show derepression of Fos due to downregulation of microRNA-139 which inhibits Fos by direct targeting (Fan et al. 2013). Fos may also indirectly affect carcinogenic pathways. The protein acts as a positive regulator of hepatitis C virus propagation and may thus favor pathologic processes linked to HCV infection (Kang et al. 2011).

Human FOX Gene Family in Hepatocarcinogenesis

The human forkhead-box (FOX) gene family is a large gene family with more than 40 members. FOX proteins are transcription factors. Members of the FOX subfamilies A–G, I–L, and Q were grouped into class 1 FOX proteins, whereas members of subfamilies H and M–P were grouped into class 2 FOX proteins.

FOX proteins, in part as fusion partners of other proteins, are involved in the regulation of cell proliferation and apoptosis and are dysregulated in cancerogenic pathways of various neoplasms (Fu and Tindall 2008; Kloet and Burgering 2011). FOX proteins are DNA-binding proteins that control the transcription of multiple target genes that regulate genes involved in cell growth, proliferation, differentiation, and survival and control DNA repair (reviews: Katoh and Katoh 2004; Zhang et al. 2011; Katoh et al. 2013). Human O class FOX proteins (FOXO) are transcription factors that are activated in response to numerous stimuli, including several growth factors, insulin, nutrients, and oxidative stress. Their subcellular localization is regulated by phosphorylation and ubiquitination.

Within the FOXO group of transcription factors, FOXO3 located at chromosome 6q21 acts as a tumor suppressor in HCC, inducing the expression or proapoptotic genes or interfering with the Wnt and MAPK signaling pathways (Lu et al. 2009; Xie et al. 2012; Carbajo-Pescador et al. 2014). The tumor suppressor candidate

FOXP1 (chromosome 3p13) is overexpressed in HCC tissue in comparison with nonneoplastic liver, associated with larger tumor size and higher stage (Zhang et al. 2012). FOXP3 (scurfin, on Xp11.23) was found in some hepatoma cell lines and detected immunohistochemically in 48 % of human HCC, expression being related to high risk (Wang et al. 2010b). FOXC1 (6p25.3) is critically involved in regulation of epithelial-mesenchymal transition and cell locomotion/migration, associated with higher Snail expression. It is upregulated in HCC, where it promotes metastatic spread and an aggressive course (Xia et al. 2013). FOXC1 also induces microvascular invasion in HCC (Xu et al. 2012). Presence of detectable FOXJ1 (on 17q.25) in HCC cells was associated with high histologic grade, an elevated proliferative activity, metastatic spread, and poor survival (Chen et al. 2013). FOXM1 (on 12p13.33) is a master regulator of tumor metastasis and is often expressed in HCC (Lin et al. 2010; Raychaudhuri and Park 2011). Its expression in HCC is induced by HBx protein and is correlated with a metastatic phenotype (Sun et al. 2011; Xia et al. 2012). The class I FOX protein FOXQ1 on 6p25.3 is overexpressed in HCC, FOXQ1 expression being associated with large tumor diameter, high serum AFP, later stage grouping, and aggressive tumor biology (Wang et al. 2013).

Myc Gene Expression in Hepatocellular Carcinoma

The Myc proto-oncogene is located on chromosome 8q24.21 and encodes a multifunctional DNA-binding protein activating or repressing transcription of numerous target genes, but predominantly those involved in control of growth and cell cycle progression. c-Myc is also implicated in the regulation of DNA replication. Malignant transformation and growth related to Myc results from a deregulation and altered balance in the expression of targeted gene products under the control of Myc.

The oncogene c-Myc is implicated in development of HCC (Yuen et al. 2001; Wang et al. 2012a). c-Myc interacts with SIRT1 in a positive feedback loop, and the two proteins act synergistically to promote hepatocellular proliferation; in human HCC SIRT1 expression positively correlates with expression of c-Myc and p53 (Jang et al. 2012). c-Myc expression and function in hepatocarcinogenic pathways interact with HBV X protein. HBx protein and c-Myc cooperate to support ribosome biogenesis and cellular transformation (Shukla and Kumar 2012). Amplifications of c-Myc in HCC are late genetic alteration in these neoplasms and are correlated with poor prognosis (Wang et al. 2002). Similar to other cancers, Myc function in HCC is controlled by microRNAs. MicroRNA-744 can target Myc, causing inhibition of cell growth, while decreased expression of this microRNA in HCC promotes Myc-induced cell proliferation (Lin et al. 2014). In HCC, genes and proteins interacting with Myc can also display altered expression patterns. Part of HCC showed upregulation of N-Myc downstream-regulated gene 1 (NDRG1), associated with a more aggressive tumor phenotype and poorer survival (Lu et al. 2014).

HOX Gene Pathways in Liver Cancer

Hox genes (homeotic genes) form a group of related genes that regulate the development of distinct body plans. For example, Hox proteins determine anterior-posterior axis, body segmentation, and symmetries of internal organs. Hox genes encode transcription factors that share a distinct sequence termed the homeobox. Interestingly, the alignment and organization of Hox genes along chromosomes characterized by distinct clusters are the same as the order of expression along the anterior-posterior axis of the organism, a phenomenon called colinearity (Duboule 1998). Colinearity seems to be related by a self-regulation process that determines the precise temporal and spatial expression of clustered Hox genes (Sheth et al. 2014).

Hox gene expression is deregulated in HCC. There is a significant difference in the expression of locus A HOX genes (HOXA genes), located on chromosome 7, between normal liver and HCC. Overexpression of HOXA1 correlates with

aggressive behavior and poor prognosis in patients with HCC, whereas downregulation of HOXA1 inhibits growth, migration, and invasion of HCC cells (Zha et al. 2012). In part of HCCs, a consistent overexpression of HOXA13 occurs, leading to the action of several gene targets that regulate the HCC cell cycle (review: Cillo et al. 2011). Specifically, there is a protein-protein interaction between HOXA13 and elF4E nuclear bodies, affecting the nuclear export of specific mRNA, such as c-Myc, VEGF, and cyclin D1 (Cillo et al. 2011).

RUNX Transcription Factor

RUNX3 (runt-related transcription factor 3) is a tumor suppressor that is downregulated in various cancers and involved in development of HCC. In HCC, RUNX3 expression is frequently decreased or even lost by epigenetic promoter hypermethylation or hemizygous deletion. Decreased expression is associated with the induction of epithelial-mesenchymal transition (EMT), reduced apoptosis, and tumor progression (Shiraha et al. 2011). In HCC cancer cell lines, an inverse correlation was found between RUNX3 expression and JAG ligand, RUNX3 expression via this pathway reducing HCC cancer stem cells (Nishina et al. 2011).

Transforming Growth Factor-Beta Signaling and TGF-Related Pathways in Hepatocarcinogenesis

Transforming growth factor-beta1 (TGF-beta1, chromosome 19q13.2) is a multifunctional protein that regulates proliferation, differentiation, survival, and apoptosis in numerous cell lineages. TGF-beta1 belongs to the TGF-beta superfamily, a large family of structurally related proteins, divided into four families (or subfamilies), i.e., decapentaplegic Vg-related family (bone morphogenetic proteins (BMPs) and growth differentiation factors), activin/inhibin family, TGF-beta family (TGF-beta1, TGF-beta2, and TGF-beta3), and a mixed family. Mature dimeric TGF-beta proteins interact with a conserved family of cell surface serine/threonine-specific protein kinase receptors. These receptors generate signals by use of a family of proteins termed Smads. Smads are intracellular proteins transducing signals from TGF-beta ligands to the nucleus for activating gene transcription. Smads are transcription factors that consist of trimers of two receptor-regulated Smads (Smad1-3, Smad 5 and Smad 8/9) and one co-Smad (Smad 4). TGF-beta1 affects the cell cycle progression by inducing p15 and p21 proteins which block cyclin-CDK complexes required for retinoblastoma (Rb) phosphorylation. Via this pathway, TGF-beta1 blocks progression through the G1 phase of cycle and suppresses expression of c-Mac, a protein required for G1 progression. TGF-beta1 induces apoptosis through the Smad pathway and DAXX (death-associated protein 6) pathway. In the liver, TGF-beta1 is a potent inhibitor of cell proliferation, acts in the termination mechanism of liver regeneration, plays a role in liver fibrosis and cirrhosis, and is frequently overexpressed in HCC (Abou-Shady et al. 1999; Kim et al. 2003; Paik et al. 2003; Ji et al. 2006; Lu et al. 2008; Giannelli et al. 2011). It is an inhibitor of hepatocyte DNA synthesis and may induce apoptosis, but the role of TGF-beta signaling in hepatocarcinogenesis is complex and not yet fully clarified. This may be due to fact that the hepatic action of TGF-beta strongly depends on its balanced expression, in that underexpression or overexpression can cause increased hepatocyte turnover and by that an increased risk of malignant transformation (Rossmanith and Schulte-Hermann 2001).

There is evidence that TGF-beta signaling plays a dichotomous role in hepatic carcinogenesis in that, on the one hand, it seems to suppress HCC development, but on the other hand is retained for HCC survival and maintenance of a malignant and aggressive phenotype (Mu et al. 2013). A procarcinogenic effect of TGF-beta also depends on its association with p53 loss (Morris et al. 2012). The carcinogenic action of TGF-beta in the liver may depend on a "dosage effect" related to differential expression patterns. Notwithstanding its antiproliferative action, overexpression of TGF-beta in HCC is

correlated with the tumor's malignant potential, probably also influenced by TGF-beta-induced stromagenesis/desmoplasia (Yamazaki et al. 2011; Gupta et al. 2014). TGF-beta is capable to induce epithelial-mesenchymal transition in HCC and by this promote spread and metastasis (Giannelli et al. 2005; Reichl et al. 2012). It also triggers HCC invasiveness through promotion of alpha3beta1 integrin expression and motility on laminin 5 substrates (Giannelli et al. 2002). TGF-beta1 phosphorylates beta1 integrin via Smad2 and Smad3, leading to its activation for invasion (Fransvea et al. 2009). On the other hand, blocking of TGF-beta1 upregulates E-cadherin and reduces invasion of HCC cells (Fransvea et al. 2008). Several members of the ECM-related CCN protein family interact with TGF signaling in cancers. Connective tissue growth factor (CTGF, CCN2) is upregulated in HCC cells through stimulation by epidermal growth factor receptor (EGFR) ligands, dependent on YAP expression, and CTGF expression promotes DNA synthesis and cell survival and downregulates TRAIL expression (Abou-Shady et al. 2000; Chu et al. 2008; Jia et al. 2011; Urtasun et al. 2011).

GTPases and GTPase-Related Proteins in Liver Cancer

Deleted in Liver Cancer 1 (DLC1) Tumor Suppressor Gene

The deleted in liver cancer 1 (DLC1) gene is a potent tumor suppressor gene located to chromosome 8p, plays a significant role in hepatocarcinogenesis, and encodes a regulator of the Rho family of small GTPases, i.e., a Rho GTPase-activating protein or RhoGAP. On chromosome 8p, DLC makes part of a cluster of six genes that are involved in liver carcinogenesis. Loss of DLC1 expression mediated by genetic and epigenetic mechanisms has been associated with the development of numerous human cancers, and two related genes, DLC2 and DLC3, may also represent tumor suppressors. DLCs affect growth of normal and cancer cells via their action as regulators of Rho GTPases which are key factors in cell proliferation. Apart from growth regulation, DLC1 also regulates functions of the cytoskeleton and cell motility, important aspects for tumor cell invasion and spread (Durkin et al. 2007; Liao and Lo 2008; Zimonjic and Popescu 2012). DLC1 presents as three isoforms (alpha, beta, and gamma), whereby DLC1 alpha is the most prominent form in normal human tissues. The function of DLC1 and DLC2 is regulated by differential phosphorylation mediated by Akt kinase.

DLC1 repression HCC has an influence on several biologic aspects of this cancer. In HCC, DLC1 negatively regulates Rho/ROCK/MLC pathway and ROCK-dependent actomyosin contractility. DLC1 abrogates Rock-mediated cytoskeletal reorganization, including formation of stress fibers and focal adhesions (Wong et al. 2008). Downregulation of DLC1 therefore favors a motile and invasive phenotype. In vitro, DLC1 overexpression inhibits growth of HCC cells. DLC1 is frequently inactivated in HCC tumors, through hemizygous and homozygous genomic deletion and epigenetic promoter hypermethylation (Wolosz et al. 2014), whereby remnant expression is found in tumor stroma. HCC can also harbor polymorphisms and missense mutation of DLC1 (Park et al. 2003). Similar to DLC1, a second RhoGAP protein, DLC2, has growth suppressor function, is underexpressed in HCC, and is probably involved in liver carcinogenesis (Ching et al. 2003).

Ras Signaling Pathways

Ras family proteins, named after their presence in rat **s**arcoma, are widely expressed in tissues and organs and belong to a superfamily of small GTPases regulating numerous cell functions, but in particular cell proliferation, differentiation, and survival. Human cell lineages possess three Ras genes, termed HRAS, KRAS, and NRAS, located on chromosomes 11p15.5, 12p12.1, and 1p13.2, respectively.

Ras genes encoding Ras proteins are the mostly commonly altered oncogenes in human

malignancies. Ras proteins are G proteins or guanosine-nucleotide-binding proteins, i.e., single-subunit small GTPases, which function as binary signaling switches. In the off position, Ras binds to GDP, while in the on position, they bind to GTP. The shift between GDP and GTP, and therefore the movement of the switch, is accomplished by the inherent GTPase function of Ras. The function of this switch is modulated by guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). GAP stabilizes Ras and accelerates its switch function, while GEF releases GDP from Ras, facilitating Ras activation. The GTP-bound Ras state has affinities to numerous downstream effectors that mediate the signaling effects. Mutations and epigenetic alterations of the Ras-mitogen-activated protein kinase (MAPK) pathway are among the most common changes observed in various cancers. It is estimated that 20–30 % of all human cancers harbor mutations of Ras family genes, whereby mutations cause inappropriate activation of Ras genes. Constitutional overactivation of this pathway is known to cause overlapping syndromes termed RASopathies (Zenker 2011). Altered Ras and Raf oncogenes are also involved in the pathogenesis of genomic instability and aneuploidy (review: Kamata and Pritchard 2011).

The Ras pathway is significantly upregulated in part of HCC compared with nonneoplastic liver, however with markedly varying incidence. The frequency of K-Ras mutations in HCCs varied markedly and ranged from 2 % to more than 90 % (Liu et al. 1994; Colombino et al. 2012). Mutation of H-Ras in HCC amounted to 71 % in one study (Sui et al. 2012). Ras expression is synergized with Notch1 expression to transform hepatic cells (Fan et al. 2011). Ras expression in HCC promotes cell growth by alternative splicing-mediated inactivation of Krüppel-like 6 (KLF6), a tumor suppressor and zinc finger transcription factor that inhibits proliferation by transcriptional activation of p21 (Yea et al. 2008). In HCC cells, the Ras/Raf/MEK/ERK pathway is stimulated by diacylglycerol (DAG) kinase, an enzyme having a key position in the DAG-protein kinase signaling cascade. In particular, DAG kinase alpha is involved in HCC progression by activation of the MAPK pathway (Takeishi et al. 2012). Deregulation of Ras pathway components affects the biology of HCC. Patients with Ras, Raf-1, or pMEK1 overexpression had poorer overall survival (Chen et al. 2011a). Mutations of H-Ras occurred more often in high-risk tumors with metastatic recurrence than in low-risk neoplasms (Sui et al. 2012). In the absence of Ras mutations, inactivation/downregulation of GAPs/Ras GTPase-activating proteins (Ras GAPs), mainly RASAL1, DAB2IP, and NF1, promote unrestrained activity of wild-type Ras in human HCC (Calvisi et al. 2011).

HCCs revealed frequent downregulation of Ras association domain family (RASSF) proteins both in the early and late stages of carcinogenic pathways. Reduced RASSF1A expression is related to TNM stage, metastatic spread, portal vein invasion, and multiple tumor nodes (Hu et al. 2010). Inactivation of RASSF is associated with LOH of 3p21.3 in tumors, including HCC.

Whereas inactivation of the RASSF1A tumor suppressor is a widespread phenomenon in cancers, downregulation of RASSF2 and RASSF5 is so far limited to certain HCC subsets (Calvisi et al. 2012). Inactivation of RASSF1A in HCC is predominantly accomplished by epigenetic mechanisms, in that more than 90 % of HCCs were methylated at the RASSF1A CpG island (Dammann et al. 2005). RASSF1A expression in HCC cells inhibits cell growth via blunted proliferation (Guan et al. 2009). Epigenetic RASSF1A promoter hypermethylation presented as a prognostic marker for HCC (Saelee et al. 2010). A Ras effector gene acting via RASSF1A is the putative tumor suppressor NORE1B which is epigenetically silenced in the majority of HCC (Macheiner et al. 2009). Several proteins that modify the function of the Ras signaling pathway have been identified in HCC. Important modulators of the RTK/Ras/MAPK pathway are Sprouty proteins. Sprouty (SPRY) orchestrates a complex regulatory platform in the cell and mediates the cross talk among different signaling pathways depending on the MAPK/ERK pathway (Masoumi-Moghaddam et al. 2014). SPRY

genes are differentially expressed in HCC, whereby SPRY1, SPRY2, and SPRY3 are probably involved in carcinogenesis (Sirivatanauksorn et al. 2012). SPRY2 is downregulated in many HCC and may therefore represent a tumor suppressor in this malignancy (Fong et al. 2006; Song et al. 2012), and inactivation of SPRY2 accelerates Akt-driven hepatocarcinogenesis through activation of MAPK and PKM2 pathways (Wang et al. 2012b). The negative regulator of the Ras/Raf-1/ERK pathway, Spred2, increases growth in HCC when downregulated, while overexpression augments caspase-3 and apoptosis (Ma et al. 2011). A Ras-related protein is ARHI (aplasia Ras homologue member I or DIRAS3) which is an imprinted tumor suppressor gene with lost expression in certain cancers. ARHI binds to importins and impairs nuclear import of cargo proteins (Huang et al. 2009a), and is frequently downregulated in HCC, where its suppression is associated with tumor growth and angiogenesis (Huang et al. 2009b; Zhao et al. 2010).

PTEN Signaling in Liver Cancers

PTEN (phosphoinositide 3-kinase/phosphatase and tensin homologue, on chromosome 10q 23.31) is an ubiquitously expressed tumor suppressor and important signaling platform that acts through its lipid phosphatase domain and is centrally involved in growth regulation. In this signal node, PTEN operates as phosphoinositide phosphatase terminating PI3K signaling by dephosphorylating PtdIns(3,4)P and PtdIns (3,4,5)P(3). In its function as a regulator of specific gene expression, growth, cytoskeletal organization, integrin-mediated cell adhesion, and apoptosis, PTEN is expected to play a role in carcinogenic pathways (Tamura et al. 1999). PTEN also negatively regulates the MAPK pathway through its protein phosphatase activity.

In the liver, PTEN regulates several functions of hepatocytes and is also involved in the handling of hepatitis viruses by these cells. HCV infection downregulates PTEN and modulates cholesterol metabolism, favoring macrovesicular steatosis of the liver (Peyrou et al. 2013). PTEN is instrumental in the regulation of stem cell biology. In the liver, it controls the expansion of CD133-positive liver cancer stem cells (Rountree et al. 2009). Deregulation of PTEN occurs in various malignancies (review: Peyrou et al. 2010), and PTEN deregulation is a well-known feature of HCC (Wang et al. 2007b; Wu et al. 2007). Generally, failure of the tumor suppressor PTEN is associated with more aggressive malignancies, also high-grade and invasive HCCs (Hou et al. 2014). This pathway depends on nuclear localization of PTEN, a step that is already observed in hepatocytes infected with HCV and depending on transportin-2 depletion (Bao et al. 2014). PTEN is often downregulated in HCC, mainly via point mutations and associated with poor patient outcome (Yao et al. 1999; Hu et al. 2003, 2007; Zhang et al. 2004; Wu et al. 2007; Zhao et al. 2013), but was found to be expressed in other HCC, mostly at low levels in comparison with nonneoplastic liver (Dong-Dong et al. 2003; Wang et al. 2007b). LOH of HCC with downregulated PTEN localizes to chromosomes 10q23.3 (Fujiwara et al. 2000). Loss of PTEN expression in HCC enhanced tumor cell migration and invasion via Akt/Sp-1 transcription factor/MMP-2 activation, illustrating that downregulation of PTEN can confer an invasive and aggressive phenotype (Sze et al. 2011). The expression of PTEN in human HCC is regulated by aberrant expression of microRNA-21, exerting an influence on cell growth, migration, and invasion (Meng et al. 2007).

Hedgehog Signaling in Hepatocarcinogenesis

Sonic hedgehog (SHH) located to chromosome 7q36.6 encodes a secreted protein that is involved in the regulation of cell fates in the course of ontogenesis and produces inductive signals during embryogenesis. Hedgehog signaling pathway also plays a central role in regulation of growth homeostasis in the adult organism. Mammals possess three *Drosophila* hedgehog homologues termed DHH (desert hedgehog), IHH (Indian hedgehog), and SHH (sonic hedgehog), of which

SHH is the most intensively studied homologue. SHH is associated to membrane lipid rafts via covalent attachment of a cholesterol moiety and a palmitic acid, but it can be secreted into the extracellular matrix with the help of the transporter-like protein Dispatched and the glypican family member heparan sulfate proteoglycan Dlp. The SHH ligand binds on target cells to the Patched-1 (PTCH1) receptor, a molecule homologous to the Niemann-Pick disease protein NPC1. In the absence of SHH ligand binding, PTCH1 inhibits the downstream effector smoothened (SMO) via removing oxysterols from SMO through a sterol sensor/sterol pump contained in PTCH1. All three mammalian hedgehog homologues also bind to a second receptor, PTCH2. The effectors of this signaling pathway are the Gli proteins (glioma-associated oncogene homologue), DNA-binding zinc finger domain proteins. Gli transcription factors (Gli1, Gli2, and Gli3) inhibit transcription of SHH targets via binding to Gli-responsive genes. Transcriptional control by Gli proteins is in part tissue specific, with certain Gli proteins preferentially expressed in distinct tissues. An important negative regulator of SHH signaling is the Rab family GTPase, Rab23, which is involved in the regulation of certain development steps during ontogenesis.

The SHH signaling cascade promotes cell proliferation, specifically the growth of progenitor cells located to various tissues, and is involved in hepatic homeostasis. Due to its central role in growth control and regulation of developmental pathways shared by normal and transforming cells, altered and dysregulated hedgehog signaling is firmly linked to cancer development (review: Toftgard 2000). In the liver, early steps of SHH-linked carcinogenesis may strongly depend on dysregulated hedgehog signaling in immature cholangiocytes, stellate cells, and myofibroblasts, as mature hepatocytes lack hedgehog pathway activity. Hedgehog signaling in hepatic stellate cells (HSCs) is embedded in a network of factors linking hepatocytes with HSCs, e.g., glypican 3 which regulates HSC viability in a hedgehog-dependent manner (Magistri et al. 2014). In contrast, hepatoma cell lines in culture show expression of hedgehog species, PTCH1, smoothened, and Gli1. Production and secretion of hedgehog ligands by malignant hepatocytes influences the metabolic function of myofibroblasts and probably stromal cells via stimulation of glycolysis (Chan et al. 2012). Activation of the hedgehog signaling pathway is a frequent event in HCC, whereby expression of SHH, PTCH1, and Gli1 was observed at high rates (Huang et al. 2006; Patil et al. 2006; Sicklick et al. 2006; Calvisi et al. 2012; Che et al. 2012; Zheng et al. 2013). Expression of smoothened was observed in about 60 % of examined HCC, and hedgehog target genes PTCH1 and Gli1 were found in over 50 % of the tumors (Huang et al. 2006). Hedgehog-related hepatocarcinogenesis is in part linked to HBV infection. Blockade of hedgehog signaling delayed liver cancer development induced by HBx protein, suggesting the HBx-promoted carcinogenesis is partially dependent on the activation of the hedgehog pathway (Arzumanyan et al. 2012). In HCC cells, Gli1 activation and Gli1 nuclear localization are stimulated by HbX protein (Kim et al. 2011). The SHH pathway is involved in the generation of epithelial-mesenchymal transition (EMT) in HCC. Gli1 drives EMT in HCC, in part by upregulating caveolin-1, a strong inducer of EMT (Gai et al. 2014). TGF-beta1, which strongly induces EMT in HCC, promotes EMT in this neoplasm by activation of the SHH and Wnt pathways (Steinway et al. 2014), suggesting the presence of a complex interacting hedgehog-TGF-Wnt signaling platform. Gli1 mediates TGF-beta1-driven EMT in HCC through upregulation of the pro-EMT factor SNAI1 (Zheng et al. 2012).

HCC overexpressing components of the hedgehog signaling pathway show increased proliferation and invasiveness (Cheng et al. 2009), while downregulation of Gli1 inhibited HCC cell migration and invasion (Chen et al. 2014b). Gli1 was upregulated in HCCs with high histological grade, advanced nodal stage, and intrahepatic metastases (Zhang et al. 2014). The pro-invasive and pro-metastatic effects of hedgehog signaling in HCC in part depend on increased expression of MMP-9 via an activated ERK pathway (Lu et al. 2012). Expression of PTCH-1 and Gli1

in HCC predicts recurrence of HCC following tumor resection (Jeng et al. 2013). However, among the various components of the hedgehog system, only expression of the transcriptional factor Gli1 was associated with clinicopathologic features of HCC and indicated poor prognosis (Che et al. 2012). The frequent dysregulation of hedgehog signaling components in HCC may render this pathway amenable to novel therapies (Kappler and von Schweinitz 2012). There is recent evidence that cholangiocarcinoma also shows dysregulated hedgehog signaling (Kim et al. 2012).

Telomeres and Telomerase

Introduction

Telomeres are highly important molecular structures that generate the physical ends of linear chromosomes. They function as a cap to protect chromosomal end from "erosion" and from being mistaken as a DNA double-strand break and maintain ordered replication, genomic stability, and the regulation of cell senescence. Telomeres with a proper length protect genes located close to chromosomal ends from being truncated. Telomere dysregulation has direct consequences for aging and cancerogenesis, including hepatic oncogenesis. As a function of senescence and aging, telomere length changes, also reflected by expression levels of the thermogenic skeletal muscle hormone, irisin (Rana et al. 2014). In mammalian cells, telomeres consist of long telomeric double-stranded DNS/ssDNA overhangs composed of six proteins. The six human telomeric proteins TRF1, TRF2, RAP1, TIN2, POT1, and TPP1 have distinct functions and form a telomeric complex termed the telosome or shelterin. The term shelterin was chosen in analogy to other chromosomal protein complexes such as condensin and cohesin (de Lange 2005). This complex is critically required for telomere protection and maintenance and length control (Okamoto et al. 2008; Denchi 2009). A highly controlled interaction between three proteins, TIN2, TTP1, and POT1, in the cytoplasm regulates assembly and function of the telosome in the nucleus (O'Connor et al. 2006; Chen et al. 2007). The human telomere ssDNA overhangs are protected by POT1 and TPP1. Within the telosome, TRF1 and TRF2 are connected to POT1 through TIN2 and TPP1, whereby TIN2 is a key telosome element (Chen et al. 2007). Both in normal cells and neoplastic cells, telomere function is modulated by several controlling factors. Human TEN1 is a component of the mammalian CST complex (telomere-capping complex) containing CTC1-STN1-TEN1. CTC1 and STN1 act in telomere duplex replication and genome-wide restart of replication following DNA fork stalling. The three CST proteins are at the telomere and maintain telomere integrity, and TEN1 is required for G-overhang processing and genome-wide replication restart (Kasbek et al. 2013). During each cell division, telomeres typically shorten due to the fact that DNA polymerase is unable to fully replicate the 3′ end of chromosomes (the so-called end-replication problem), because the synthesis of Okazaki fragments requires RNA primers attaching ahead on the lagging DNA strand. In order to avoid progressive telomere shorting as a function of cell cycling, cells express a reverse transcriptase that maintains telomere length by adding newly synthesized DNA to the shortening ends. This enzyme, the telomerase (hTERT), consists of the transcriptase proper (TERT) and the telomerase RNA component (TERC) employed as a template to produce telomeric DNA.

Telomere Abnormalities in Liver Cancer and Its Precursors

The basic effect of telomere dysregulation in carcinogenic pathways is related to uncorrected or incompletely corrected telomere shortening leading to progressive genomic instability. Both precursor lesions in the liver and HCC accumulate numerous telomere dysfunctions, mainly telomere shortening which affects genomic stability and the balance between immortality and senescence of cancer cells (Ohashi et al. 1996; Huang et al. 1998; Oh et al. 2003, 2005; Ozturk

et al. 2009; Fu et al. 2012; El-Idrissi et al. 2013; Jung et al. 2014). Telomere length varies through chronic liver disease ending up with cancer by predominantly increasing shorter telomeres (telomere shortening effect), whose length is a good indicator for malignant potential (Yokota et al. 2003; Carulli and Anzivino 2014). However, certain subsets of HCC show long telomeres, a feature that is related to higher telomerase activity (see below), cell immortalization, and invasive capacity (Ko and Jung 2014). Shortening of telomeres causes telomere dysfunction; these short telomeres can undergo fusion, producing dicentric chromosomes and breakage-fusion-bridge cycles, finally resulting in large-scale genomic rearrangements and marked genomic instability (Murnane 2006, 2012). Genomic instability caused by telomere shortening in HCC, e.g., shows up in increasing aneuploidy of chromosome 8, a chromosome with common LOH events in HCC (Plentz et al. 2005). In HCC precursor cells, telomere shortening coincided with inactivation of cell cycle checkpoints (Plentz et al. 2007). Telomere shortening in HCC is associated with upregulation of the telomere proteins TRF1, TRF2, and TIN2 (Oh et al. 2005), possibly reflecting a compensatory mechanism. Telomere maintenance in HCC is regulated by the class III histone deacetylase, sirtuin 1, which is upregulated in HCC. Sirtuins are generally involved in senescence and pathogenic pathways of genomic instability (McGuinness et al. 2011). There is a positive correlation between expression levels and advancement in tumor grades. SIRT1 silencing causes telomere dysfunction and the emergence of telomere dysfunction-induced liver foci (Chen et al. 2011b).

Telomerase (hTERT) reactivation in cancers is a mechanism to achieve telomere maintenance and to avoid progressive telomere erosion. HCCs and their nodular precursors show an upregulation of telomerase (hTERT) that may in advanced liver cancer result in long telomeres and effect that plays a role in cancer progression (Huang et al. 1998; Oh et al. 2008). Variations in telomere length may also characterize distinct subsets of HCC. HCCs show TERT promoter mutations that affect telomere length and maintenance (Pinyol et al. 2014). HCCs with stemness-related protein expression, tumors showing a highly aggressive phenotype, display increased telomere length, increased expression of hTERT and shelterin complex proteins, and increased chromosomal instability (Kim et al. 2013). However, telomerase activation was not only found in dysplastic nodules but also in large regenerative nodules occurring in cirrhosis, suggesting that increased telomerase activity is not necessarily a feature of malignancy (Hytiroglou et al. 1998). Telomerase expression in HCC, or its reactivation following hepatectomy, predicted recurrence (Kobayashi et al. 2002). HCC and its precursor lesions revealed a high frequency of hTERT promoter somatic mutations, occurring as one of the earliest recurrent genetic defects (Nault et al. 2013). In one investigation, telomerase activity, telomere length, and hTERT expression in HCC were independent of the hepatitis virus status (Saini et al. 2009). A protein encoded by the DKC1 gene, dyskerin, is an essential nucleolar protein involved in cell cycle regulation and is required for the pseudouridylation of ribosomal RNA and the stabilization of the telomerase RNA component. Overexpression of dyskerin in HCC was correlated with MYC and MIK67 expression and is an unfavorable prognostic factor in patients with HCC (Liu et al. 2012). Leptin expression is highly correlated with hTERT expression levels in HCC, mediated through binding of STAT3 and Myc/Max/mad network proteins on the hTERT promoter (Stefanou et al. 2010). hTERT expression in HCC is also subject to epigenetic regulation via methylation of the hTERT promoter, the CpG island methylator phenotype (Zhang et al. 2008; Iliopoulos et al. 2009).

References

Abate C, Curran T (1990) Encounters with Fos and Jun on the road to AP-1. Semin Cancer Biol 1:19–26

Abou-Shady M, Baer HU, Friess H, Berberat P, Zimmermann A, Graber H, Gold LI et al (1999) Transforming growth factor betas and their signaling receptors in human hepatocellular carcinoma. Am J Surg 177:209–215

Abou-Shady M, Friess H, Zimmermann A, di Mola FF, Guo XZ, Baer HU, Büchler MW (2000) Connective tissue growth factor in human liver cirrhosis. Liver 20:296–304

Aguilar F, Harris CC, Sun T, Hollstein M, Cerutti P (1994) Geographic variation of p53 mutational profile in nonmalignant human liver. Science 264:1317–1319

Alexandre K, Fokan D, Galand P (1994) Immunohistochemical expression of the C-fos protein in preneoplastic and neoplastic lesions during hepatocarcinogenesis in rats. Int J Oncol 4:429–434

Andreoli V, Gehrau RC, Bocco JL (2010) Biology of Krüppel-like factor 6 transcriptional regulator in cell life and death. IUBMB Life 62:896–905

Aoki T, Miyamoto A, Marubashi S, Nagano H, Umeshita K, Fujiwara Y, Dono K, Nakamori S et al (2004) Clinical value of alterations in p73 gene, related to p53, at 1p36, in human hepatocellular carcinoma. Int J Oncol 24:441–446

Arzumanyan A, Sambandam V, Clayton MM, Choi SS, Xie G, Diehl AM, Yu DY, Feitelson MA (2012) Hedgehog signaling blockade delays hepatocarcinogenesis induced by hepatitis B virus X protein. Cancer Res 72:5912–5920

Bao W, Florea L, Wu N, Wang Z, Banaudha K, Qian J, Houzet L, Kumar R, Kumar A (2014) Loss of nuclear PTEN in HCV-infected human hepatocytes. Infect Agent Cancer 9:23

Beckerman R, Prives C (2010) Transcriptional regulation by p53. Cold Spring Harb Perspect Biol 2:a000935

Botella LM, Sanz-Rodriguez F, Komi Y, Fernandez-L A, Varela E, Garrida-Martin EM et al (2009) TGF-beta regulates the expression of transcription factor KLF6 and its splice variants and promotes co-operative transactivation of common target genes through a Smad3-Sp1-KLF6 interaction. Biochem J 419:485–495

Bureau C, Péron JM, Bouisson M, Danjoux M, Selves, Bioulac-Sage P, Balabaud C et al (2008) Expression of the transcription factor Klf6 in cirrhosis, macronodules, and hepatocellular carcinoma. J Gastroenterol Hepatol 23:78–86

Calvisi DF, Ladu S, Conner EA, Seo D, Hsieh JT, Factor VM, Thorgeirsson SS (2011) Inactivation of Ras GTPase-activating proteins promotes unrestrained activity of wild-type Ras in human liver cancer. J Hepatol 54:311–319

Calvisi DF, Evert M, Dombrowski F (2012) Pathogenetic and prognostic significance of inactivation of RASSF proteins in human hepatocellular carcinoma. Mol Biol Int 2012:849874

Carbajo-Pescador S, Mauriz JL, Garcia-Palomo A, Gonzalez-Gallego J (2014) FoxO proteins: regulation and molecular targets in liver cancer. Curr Med Chem 21:1231–1246

Carulli L, Anzivino C (2014) Telomere and telomerase in chronic liver disease and hepatocarcinoma. Wordl J Gastroenterol 20:6287–6292

Chan IS, Guy CD, Chen Y, Lu J, Swiderska-Syn M, Michelotti GA, Karaca G, Xie G et al (2012) Paracrine hedgehog signaling drives metabolic changes in hepatocellular carcinoma. Cancer Res 72:6344–6350

Che L, Yuan YH, Jia J, Ren J (2012) Activation of sonic hedgehog signaling pathway is an independent potential prognosis predictor in human hepatocellular carcinoma patients. Chin J Cancer Res 24:323–331

Chen LY, Liu D, Songyang Z (2007) Telomere maintenance through spatial control of telomeric proteins. Mol Cell Biol 27:5898–5909

Chen L, Shi Y, Jiang CY, Wei LX, Wang YL, Dai GH (2011a) Expression and prognostic role of pan-Ras, Raf-1, pMEK1 and pERK1/2 in patients with hepatocellular carcinoma. Eur J Surg Oncol 37:513–520

Chen J, Zhang B, Wong N, Lo AW, To KF, Chan A-W, Ng MH, Ho CY, Cheng SH et al (2011b) Sirtuin 1 is upregulated in a subset of hepatocellular carcinomas where it is essential for telomere maintenance and tumor cell growth. Cancer Res 71:4138–4149

Chen HW, Huang XD, Li HC, He S, Ni RZ, Chen CH, Peng C, Wu G, Wang GH et al (2013) Expression of FOXJ1 in hepatocellular carcinoma: correlation with patients' prognosis and tumor cell proliferation. Mol Carcinog 52:647–659

Chen QW, Chn H, Cheng JS, Meng ZQ (2014a) MDM2 SNP309T>G polymorphism and hepatocellular carcinoma risk: a meta-analysis. Tumour Biol 35:4147–4151

Chen JS, Li HS, Huang JQ, Zhang LJ, Chen XL, Wang Q, Lei J, Feng JT, Liu Q et al (2014b) Down-regulation of Gli-1 inhibits hepatocellular carcinoma cell migration and invasion. Mol Cell Biochem 393:283–291

Cheng WT, Xu K, Tian DY, Zhang ZG, Liu LJ, Chen Y (2009) Role of Hedgehog signaling pathway in proliferation and invasiveness of hepatocellular carcinoma cells. Int J Oncol 34:829–836

Ching YP, Wong CM, Chan SF, Leung TH, Ng DC, Jin DY, Ng IO (2003) Deleted in liver cancer (DLC) 2 encodes a RhoGAP protein with growth suppressor function and is underexpressed in hepatocellular carcinoma. J Biol Chem 278:10824–10830

Choi EK, Uyeno S, Nishida N, Okumoto T, Fujimura S, Aoki Y, Nata M, Sagisaka K et al (1996) Alterations of c-fos gene methylation in the processes of aging and tumorigenesis in human liver. Mutat Res 354:123–128

Chu CY, Chang CC, Prakash E, Kuo ML (2008) Connective tissue growth factor (CTGF) and cancer progression. J Biomed Sci 15:675–685

Cillo C, Schiavo G, Cantile M, Bihl MP, Sorrentino P, Carafa V, D'Armiento M, Roncalli M et al (2011) The HOX gene network in hepatocellular carcinoma. Int J Cancer 129:2577–2587

Colombino M, Sperlongano P, Izzo F, Tatangelo F, Botti G, Lombardi A, Accardo M et al (2012) BRAF and PIK3CA genes are somatically mutated in hepatocellular carcinoma among patients from South Italy. Cell Death Dis 3:e259

Coni P, Pichiri-Coni G, Ledda-Columbano GM, Rao PM, Rajalakshmi S, Sarma DS et al (1990) Liver hyperplasia is not necessarily associated with increased expression of c-fos and c-myc mRNA. Carcinogenesis 11:835–839

Coni P, Simbula G, de Prati AC, Menegazzi M, Suzuki H, Sarma DS, Ledda-Columbano GM et al (1993) Differences in the steady-state levels of c-fos, c-jun and c-myc messenger RNA during mitogen-induced liver growth and compensatory regeneration. Hepatology 17:1109–1116

Corral M, Tichonicky L, Guguen-Guillouzo C, Corcos D, Raymondjean M, Paris B, Kruh J et al (1985) Expression of c-fos oncogene during hepatocarcino-genesis, liver regeneration and in synchronized HTC cells. Exp Cell Res 160:427–434

Dammann R, Schagdarsurengin U, Seidel C, Strunnikova M, Rastetter M, Baier K, Pfeifer GP (2005) The tumor suppressor RASSF1A in human carcinogenesis. An update. Histol Histopathol 20:645–663

De Lange T (2005) Shelterin: the protein complex that shapes and safeguards human telomeres. Genes Dev 19:2100–2110

Denchi EL (2009) Give me a break: how telomeres suppress the DNA damage response. DNA Repair (Amst) 8:1118–1126

DiFeo A, Narla G, Camacho-Vanegas O, Nishio H, Rose SL, Buller RE, Friedman SL et al (2006) E-cadherin is a novel transcriptional target of the KLF6 tumor suppressor. Oncogene 25:6026–6031

Dong-Dong L, Xi-Ran Z, Xiang-Rong C (2003) Expression and significance of new tumor suppressor gene PTEN in primary liver cancer. J Cell Mol Med 7:67–71

Duboule D (1998) Vertebrate hox gene regulation: clustering and/or colinearity ? Curr Opin Genet Dev 8:514–518

Durchdewald M, Angel P, Hess J (2009) The transcription factor Fos: a Janus-type regulator in health and disease. Histol Histopathol 24:1451–1461

Durkin ME, Yuan BZ, Zhou X, Zimonjic DB, Lowy DR, Thorgeirsson SS, Popescu NC (2007) DLC-1: a Rho GTPase-activating protein and tumour suppressor. J Cell Mol Med 11:1185–1207

Edamoto Y, Hara A, Biernat W, Terracciano L, Cathomas G, Riehle HM, Matsuda M et al (2003) Alterations of RB1, p53 and Wnt pathways in hepatocellular carcinomas associated with hepatitis C, hepatitis B and alcoholic liver cirrhosis. Int J Cancer 106:334–341

El-Idrissi M, Hervieu V, Merle P, Mortreux F, Wattel E (2013) Cause-specific telomere factors deregulation in hepatocellular carcinoma. J Exp Clin Cancer Res 32:64

Ezzikouri S, El Feydi AE, Chafik A, Benazzouz M, El Kihal L, Afifi R et al (2007) The pro variant of the p53 codon 72 polymorphism is associated with hepatocellular carcinoma in Moroccan population. Hepatol Res 37:748–754

Fan R, Chen P, Zhao D, Tong JL, Li J, Liu F (2011) Cooperation of deregulated Notch signaling and Ras pathway in human hepatocarcinogenesis. J Mol Histol 42:473–481

Fan Q, He M, Deng X, Wu WK, Zhao L, Tang J, Wen G, Sun X, Liu Y (2013) Derepression of c-Fos caused by microRNA-139 down-regulation contributes to the metastasis of human hepatocellular carcinoma. Cell Biochem Funct 31:319–324

Feng DY, Zheng H, Tan Y, Cheng RX (2001) Effect of phosphorylation of MAPK and Stat3 and expression of c-fos and c-jun proteins on hepatocarcinogenesis and their clinical significance. World J Gastroenterol 7:33–36

Fong CW, Chua MS, McKie AB, Ling SH, Mason V, Li R, Yusoff P, Lo TL, Leung HY et al (2006) Sprouty 2, an inhibitor of mitogen-activated protein kinase signaling, is down-regulated in hepatocellular carcinoma. Cancer Res 66:2048–2058

Fornari F, Milazzo M, Galassi M, Callegari E, Veronese A, Miyaaki H, Sabbioni S, Mantovani V et al (2014) p53/mdm2 feedback loop sustains miR-221 expression and dictates the response to anticancer treatments in hepatocellular carcinoma. Mol Cancer Res 12: 203–216

Fransvea E, Angelotti U, Antonaci S, Giannelli G (2008) Blocking transforming growth factor-beta up-regulates E-cadherin and reduces migration and invasion of hepatocellular carcinoma cells. Hepatology 47:1557–1566

Fransvea E, Mazzocca A, Antonaci S, Giannelli G (2009) Targeting transforming growth factor (TGF)-betaRI inhibits activation of beta1 integrin and blocks vascular invasion in hepatocellular carcinoma. Hepatology 49:839–850

Fu Z, Tindall DJ (2008) FOXOs, cancer and regulation of apoptosis. Oncogene 27:2312–2319

Fu X, Wan S, Hann HW, Myers RE, Hann RS, Au J, Chen B, Xing J, Yang H (2012) Relative telomere length: a novel- non-invasive biomarker for the risk of non-cirrhotic hepatocellular carcinoma in patients with chronic hepatitis B infection. Eur J Cancer 48:1014–1022

Fu DZ, Cheng Y, He H, Liu HY, Liu YF (2014) The fate of Krüppel-like factor 9-positive hepatic carcinoma cells may be determined by the programmed cell death protein 5. Int J Oncol 44:153–160

Fujiwara Y, Hoon DS, Yamada T, Umeshita K, Gotoh M, Sakon M, Nishisho I, Monden M (2000) PTEN/MMAC1 mutation and frequent loss of heterozygosity identified in chromosome 10q in a subset of hepatocellular carcinomas. Jpn J Cancer Res 91:287–292

Gai X, Lu Z, Tu K, Liang Z, Zheng X (2014) Caveolin-1 is up-regulated by GLI1 and contributes to GLI1-driven EMT in hepatocellular carcinoma. PLoS One 9:e84551

Giannelli G, Fransvea E, Marinosci F, Bergamini C, Colucci S, Schiraldi D, Antonaci S (2002) Transforming growth factor-beta1 triggers

hepatocellular carcinoma invasiveness via alpha3beta1 integrin. Am J Pathol 161:183–193

Giannelli G, Bergamini C, Fransvea E, Sgarra C, Antonaci S (2005) Laminin-5 with transforming growth factor-beta1 induces epithelial to mesenchymal transition in hepatocellular carcinoma. Gastroentereology 129:1375–1383

Giannelli G, Mazzocca A, Fransvea E, Lahn M, Antonaci S (2011) Inhibiting TGF-β signaling in hepatocellular carcinoma. Biochim Biophys Acta 1815:214–223

Guan HG, Xue WJ, Qian HX, Zhou XJ, Qin L, Lan J (2009) RASSF1A expression inhibits cell growth and enhances cell chemosensitivity to mitomycin in BEL-7402 hepatocellular carcinoma cells. Chin Med J (Engl) 122:1328–1332

Güller M, Toualbi-Abed K, Legrand A, Michel L, Mauviel A, Bernuau D, Daniel F (2008) c-Fos overexpression increases the proliferation of human hepatocytes by stabilizing nuclear cyclin D1. World J Gastroenterol 14:6339–6346

Gupta DK, Singh N, Sahu DK (2014) TGF-β mediated crosstalk between malignant hepatocyte and tumor microenvironment in hepatocellular carcinoma. Cancer Growth Metastasis 7:1–8

Han S, Han L, Sun H, Zan X, Zhou Z, Xu K, Yao Y, Liu Q (2013) Krüppel-like factor expression and correlation with FAK, MMP-9 and E-cadherin expression in hepatocellular carcinoma. Mol Med Rep 8:81–88

Hanoun N, Bureau C, Diab T, Gayet O, Dusetti N, Selves J, Vinel JP, Buscail L, Cordelier P et al (2010) The SV2 variant of KLF6 is down-regulated in hepatocellular carcinoma and displays anti-proliferative and pro-apoptotic functions. J Hepatol 53:880–888

Haritani H, Esumi M, Uchida T, Shikata T (1991) Oncogene expression in the liver tissue of patients with nonneoplastic liver disease. Cancer 67:2594–2598

Hou W, Liu J, Chen P, Wang H, Ye BC, Qiang F (2014) Mutation analysis of key genes in RAS/RAF and PI3K/PTEN pathways in Chinese patients with hepatocellular carcinoma. Oncol Lett 8:1249–1254

Hsu JC, Bravo R, Taub R (1992) Interactions among LRF-1, JunB, c-Jun, and c-Fos define a regulatory program in the G1 phase of liver regeneration. Mol Cell Biol 12:4654–4665

Hsu HT, Wu PR, Chen CJ, Hsu LS, Yeh CM, Hsing MT, Chiang YS, Lai MT, Yeh KT (2014) High cytoplasmic expression of Krüppel-like factor 4 is an important prognostic factor of better survival in hepatocellular carcinoma. Int J Mol Sci 15:9894–9906

Hu TH, Huang CC, Lin PR, Chang HW, Ger LP, Lin YW, Changchien CS, Lee CM et al (2003) Expression and prognostic role of tumor suppressor gene PTEN/MMAC1/TEP1 in hepatocellular carcinoma. Cancer 97:1929–1940

Hu TH, Wang CC, Huang CC, Chen CL, Hung CH, Chen CH, Wang JH, Lu SN et al (2007) Down-regulation of tumor suppressor gene PTEN, overexpression of p53, plus high proliferating cell nuclear antigen index predict poor patient outcome of hepatocellular carcinoma after resection. Oncol Rep 18:1417–1426

Hu L, Chen G, Yu H, Qiu X (2010) Clinicopathological significance of RASSF1A reduced expression and hypermethylation in hepatocellular carcinoma. Hepatol Int 4:423–432

Hu S, Zhao L, Yang J, Hu M (2014) The association between polymorphism of P53 codon72 Arg/Pro and hepatocellular carcinoma susceptibility: evidence from a meta-analysis of 15 studies with 3,704 cases. Tumour Biol 35:3674–3656

Huang GT, Lee HS, Chen CH, Chiou LL, Lin YW, Lee CZ, Chen DS, Sheu JC (1998) Telomerase activity and telomere length in human hepatocellular carcinoma. Eur J Cancer 34:1946–1949

Huang S, He J, Zhang X, Bian Y, Yang L, Xie G, Zhang K, Tang W, Stelter AA, Wang Q et al (2006) Activation of the hedgehog pathway in human hepatocellular carcinomas. Carcinogenesis 27:1334–1340

Huang S, Chang IS, Lin W, Ye W, Luo RZ, Lu Z, Lu Y, Zhang K, Liao WS, Tao T et al (2009a) ARHI (DIRAS3), an imprinted tumour suppressor gene, binds to importins and blocks nuclear import of cargo proteins. Biosc Rep 30:159–168

Huang J, Lin Y, Li L, Qing D, Teng XM, Zhang YL, Hu X, Hu Y, Yang P, Han ZG (2009b) ARHI, as a novel suppressor of cell growth and downregulated in human hepatocellular carcinoma, could contribute to hepatocarcinogenesis. Mol Carcinog 48:130–140

Hussain SP, Schwank J, Staib F, Wang XW, Harris CC (2007) TP53 mutations and hepatocellular carcinoma: insights into the etiology and pathogenesis of liver cancer. Oncogene 26:2166–2176

Hytiroglou P, Kotoula V, Thung SN, Tsokos M, Fiel MI, Papadimitriou CS (1998) Telomerase activity in precancerous hepatic nodules. Cancer 82:1831–1838

Iliopoulos D, Satra M, Drakaki A, Poultsides GA, Tsezou A (2009) Epigenetic regulation of hTERT promoter in hepatocellular carcinomas. Int J Oncol 34:391–399

Jang KY, Noh SJ, Lehwald N, Tao GZ, Bellovin DI, Park HS, Moon WS, Felsher DW et al (2012) SIRT1 and c-Myc promote liver tumor cell survival and predict poor survival of human hepatocellular carcinomas. PLoS One 7:e45119

Jansson MD, Damas ND, Lees M, Jacobsen A, Lund AH (2014) miR-339-5p regulates the p53 tumor-suppressor pathway by targeting MDM2. Oncogene. doi:10.1038/onc.2014.130

Jeng KS, Sheen IS, Jeng WJ, Lin CC, Lin CK, Su JC, Yu MC, Fang HY (2013) High expression of patched homolog-1 messenger RNA and glioma-associated oncogene-1 messenger RNA of sonic hedgehog signaling pathway indicates a risk of postresection recurrence of hepatocellular carcinoma. Ann Surg Oncol 20:464–473

Ji GZ, Wang XH, Miao L, Liu Z, Zhang P, Zhang FM, Yang JB (2006) Role of transforming growth factor-beta1-smad signal transduction pathway in patients with

hepatocellular carcinoma. World J Gastroenterol 12:644–648

Jia XQ, Cheng HQ, Li H, Zhu Y, Li YH, Feng ZQ, Zhang JP (2011) Inhibition of connective tissue growth factor overexpression decreases growth of hepatocellular carcinoma cells in vitro and in vivo. Chin Med J (Engl) 124:3794–3799

Jung SW, Park NH, Shin JW, Park BR, Kim CJ, Lee JE, Shin ES, Kim JA, Chung YH (2014) Prognostic impact of telomere maintenance gene polymorphisms in hepatocellular carcinoma patients with chronic hepatitis B Hepatology 59:1912–1920

Kalra N, Kumar V (2004) c-Fos is a mediator of the c-myc-induced apoptotic signaling in serum-deprived hepatoma cells via the p38 mitogen-activated protein kinase pathway. J Biol Chem 279:25313–25319

Kamata T, Pritchard C (2011) Mechanisms of aneuploidy induction by RAS and RAF oncogenes. Am J Cancer Res 1:955–971

Kang SM, Lim S, Won SJ, Shin YJ, Lim YS, Ahn BY, Hwang SB (2011) c-Fos regulates hepatitis C virus propagation. FEBS Lett 585:3236–3244

Kappler R, von Schweinitz D (2012) A better way forward: targeting hedgehog signaling in liver cancer. Front Biosc (Schol Ed) 4:277–286

Kasbek C, Wang F, Price CM (2013) Human TEN1 maintains telomere integrity and functions in genome-wide replication restart. J Biol Chem 288:30139–30150

Katoh M, Katoh M (2004) Human FOX gene family (review). Int J Oncol 25:1495–1500

Katoh M, Igarashi M, Fukuda H, Nakagama H, Katoh M (2013) Cancer genetics and genomics of human FOX family genes. Cancer Lett 328:198–206

Kim YJ, Lee HS, Im JP, Min BH, Kim HD, Jeong JB, Yoon JH, Kim CY, Kim MS et al (2003) Association of transforming growth factor-beta1 gene polymorphisms with a hepatocellular carcinoma risk in patients with chronic hepatitis B virus infection. Exp Mol Med 35:196–202

Kim HY, Cho HK, Hong SP, Cheong J (2011) Hepatitis B virus X protein stimulates the Hedgehog-Gli activation through protein stabilization and nuclear localization of Gli1 in liver cancer cells. Cancer Lett 309:176–184

Kim YJ, Park SB, Park JY, Park SW, Chung JB, Song SY, Bang S (2012) The sonic hedgehog pathway as a treatment target for extrahepatic biliary tract cancer. Mol Med Rep 5:12–16

Kim H, Yoo JE, Cho JY, Oh BK, Yoon YS, Han HS, Lee HS, Jang JJ, Jeong SH et al (2013) Telomere length, TERT and shelterin complex proteins in hepatocellular carcinomas expressing "stemness"-related markers. J Hepatol 59:746–752

Kirk GD, Lesi OA, Mendy M, Szymanska K, Whittle H, Goedert JJ et al (2005) 249(ser) TP53 mutation in plasma DNA, hepatitis B viral infection, and risk of hepatocellular carcinoma. Oncogene 24:5858–5867

Kloet DE, Burgering BM (2011) The PKB/FOXO switch in aging and cancer. Biochim Biophys Acta 1813:1926–1937

Ko E, Jung G (2014) Positive association of long telomeres with the invasive capacity of hepatocellular carcinoma cells. Biochem Biophys Res Commun 447: 358–363

Kobayashi T, Sugawara Y, Shi YZ, Makuuchi M (2002) Telomerase expression and p53 status in hepatocellular carcinoma. Am J Gastroenterol 97:3166–3171

Kremer-Tal S, Reeves HL, Narla G, Thung SN, Schwartz M, Difeo A, Katz A, Bruix J et al (2004) Frequent inactivation of the tumor suppressor Kruppel-like factor 6 (KLF6) in hepatocellular carcinoma. Hepatology 40:1047–1052

Lee UE, Ghiassi-Nejad Z, Paris AJ, Yea S, Narla G, Walsh M, Friedman SL (2010) Tumor suppressor activity of KLF6 mediated by downregulation of the PTTG1 oncogene. FEBS Lett 584:1006–1010

Li JC, Yang XR, Sun HX, Xu Y, Zhou J, Qiu SJ, Ke AW, Cui YH, Wang ZJ, Wang WM et al (2010) Up-regulation of Krüppel-like factor 8 promotes tumor invasion and indicates poor prognosis for hepatocellular carcinoma. Gastroenterology 139:2146–2157

Liao YC, Lo SH (2008) Deleted in liver cancer-1 (DLC-1): a tumor suppressor not just for liver. Int J Biochem Cell Biol 40:843–847

Lim SO, Park YM, Kim HS, Quan X, Yoo JE, Park YN, Choi GH, Jung G (2011) Notch1 differentially regulates oncogenesis by wildtype p53 overexpression and p53 mutation in grade III hepatocellular carcinoma. Hepatology 53:1352–1362

Lin M, Guo LM, Liu H, Du J, Yang J, Zhang LJ, Zhang B (2010) Nuclear accumulation of glioma-associated oncogene 2 protein and enhanced expression of forkhead-box transcription factor M1 protein in human hepatocellular carcinoma. Histol Histopathol 25:1269–1275

Lin ZS, Chu HC, Yen YC, Lewis BC, Chen YW (2012) Krüppel-like factor 4, a tumor suppressor in hepatocellular carcinoma cells reverts epithelial mesenchymal transition by suppressing slug expression. PLoS One 7:e43593

Lin F, Ding R, Zheng S, Xing D, Hong W, Zhou Z, Shen J (2014) Decrease expression of microRNA-744 promotes cell proliferation by targeting c-Myc in human hepatocellular carcinoma. Cancer Cell Int 14:58

Liu P, Fléjou JF, Feldmann G, Bernuau D (1994) Activation of ras oncogene in livers with cirrhosis. J Hepatol 21:1103–1108

Liu B, Zhang J, Huang C, Liu H (2012) Dyskerin overexpression in human hepatocellular carcinoma is associated with advanced clinical stage and poor patient prognosis. PLoS One 7:e43147

Liu FY, Deng YL, Li Y, Zeng D, Zhou ZZ, Tian DA, Liu M (2013) Down-regulated KLF17 expression is associated with tumor invasion and poor prognosis in hepatocellular carcinoma. Med Oncol 30:425

Long J, Wang Y, Li M, Tong WM, Jia JD, Huang J (2013) Correlation of TP53 mutations with HCV positivity in hepatocarcinogenesis: identification of a novel TP53

microindel in hepatocellular carcinoma with HCV infection. Oncol Rep 30:119–124

Lu Y, Wu LQ, Li CS, Wang SG, Han B (2008) Expression of transforming growth factors in hepatocellular carcinoma and its relation with clinicopathological parameters and prognosis. Hepatobiliary Pancreat Dis Int 7:174–178

Lu M, Ma J, Xue W, Cheng C, Wang Y, Zhao Y, Ke Q, Liu H, Liu Y, Li P, Cui X, He S et al (2009) The expression and prognosis of FOXO3a and Skp2 in human hepatocellular carcinoma. Pathol Oncol Res 15:679–687

Lu JT, Zhao WD, He W, Wei W (2012) Hedgehog signaling pathway mediates invasion and metastasis of hepatocellular carcinoma via ERK pathway. Acta Pharmacol Sin 33:691–700

Lu WJ, Chua MS, So SK (2014) Suppressing N-myc downstream regulated gene 1 reactivates senescence signaling and inhibits tumor growth in hepatocellular carcinoma. Carcinogenesis 35:915–922

Ma XN, Liu XY, Yang YF, Xiao FJ, Li QF, Yan J, Zhang QW, Wang LS, Li XY et al (2011) Regulation of human hepatocellular carcinoma cells by Spred2 and correlative studies on its mechanism. Biochem Biophys Res Commun 410:803–808

Macheiner D, Gauglhofer C, Rodgarkia-Dara C, Grusch M, Brachner A, Bichler C, Kandioler D et al (2009) NORE1B is a putative tumor suppressor in hepatocarcinogenesis and may act via RASSF1A. Cancer Res 69:235–242

Magistri P, Leonard SY, Tang CM, Chan JC, Lee TE, Sicklick JK (2014) The glypican 3 hepatocellular carcinoma marker regulates human hepatic stellate cells via hedgehog signaling. J Surg Res 187:377–385

Masoumi-Moghaddam S, Amini A, Morris DL (2014) The developing story of Sprouty and cancer. Cancer Metastasis Rev 33:695–720

McConnell BB, Yang VW (2010) Mammalian Krüppel-like factors in health and diseases. Physiol Rev 90:1337–1381

McGuinness D, McGuinness DH, McCaul JA, Shiels PG (2011) Sirtuins, bioageing, and cancer. J Aging Res 2011:235754

Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T (2007) MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. Gastroenterology 133:647–658

Mikula M, Goltzmann J, Fischer AN, Wolschek MF, Thallinger C, Schulte-Hermann R et al (2003) The proto-oncoprotein c-Fos negatively regulates hepatocellular tumorigenesis. Oncogene 22:6725–6738

Morello D, Lavenu A, Babinet C (1990) Differential regulation and expression of jun, c-fos and c-myc proto-oncogenes during mouse liver regeneration and after inhibition of protein synthesis. Oncogene 5:1511–1519

Morris SM, Baek JY, Koszarek A, Kanngurn S, Knoblaugh SE, Grady WM (2012) Transforming growth factor-beta signaling promotes hepatocarcinogenesis induced by p53 loss. Hepatology 55:121–131

Mu X, Lin S, Yang J, Chen C, Chen Y, Herzig MC, Washburn K, Halff GA, Walter CA et al (2013) TGF-β signaling is often attenuated during hepatotumorigenesis, but is retained for the malignancy of hepatocellular carcinoma cells. PLoS One 8:e63436

Muñoz U, Puche JE, Hannivoort R, Lang UE, Cohen-Naftaly M, Friedman SL (2012) Hepatocyte growth factor enhances alternative splicing of the Kruppel-like factor 6 / KLF6) tumor suppressor to promote growth through SRSF1. Mol Cancer Res 10:1216–1227

Murnane JP (2006) Telomeres and chromosome instability. NA Repair (Amst) 5:1082–1092

Murnane JP (2012) Telomere dysfunction and chromosome instability. Mutat Res 730:28–36

Nault JC, Mallet M, Pilati C, Calderaro J, Bioulac-Sage P, Laurent C, Laurent A, Cherqui D et al (2013) High frequency of telomerase reverse-transcriptase promoter somatic mutations in hepatocellular carcinoma and preneoplastic lesions. Nat Commun 4:2218

Nishina S, Shiraha H, Nakanishi Y, Tanaka S, Matsubara M, Takaoka N, Uemura M et al (2011) Restored expression of the tumor suppressor gene RUNX3 reduces cancer stem cells in hepatocellular carcinoma by suppressing Jagged1-Notch signaling. Oncol Rep 26:523–531

O'Connor MS, Safari A, Xin H, Liu D, Songyang Z (2006) A critical role for TPP1 and TIN2 interaction in high-order telomeric complex assembly. Proc Natl Acad Sci U S A 103:11874–11879

Oh BK, Jo Chae K, Park C, Kim K, Jung Lee W, Han KH, Nyun Park Y (2003) Telomere shortening and telomerase reactivation in dysplastic nodules of human hepatocarcinogenesis. J Hepatol 39:786–792

Oh BK, Kim YJ, Park C, Park YN (2005) Up-regulation of telomere-binding proteins, TRF1, TRF2, and TIN2 is related to telomere shortening during human multistep hepatocarcinogenesis. Am J Pathol 166:73–80

Oh BK, Kim H, Park YN, Yoo JE, Choi J, Kim KS, Lee JJ, Park C (2008) High telomerase activity and long telomeres in advanced hepatocellular carcinomas with poor prognosis. Lab Invest 88:144–152

Ohashi K, Tsutsumi M, Nakajima Y, Kobitsu K, Nakano H, Konishi Y (1996) Telomere changes in human hepatocellular carcinomas and hepatitis virus infected noncancerous livers. Cancer 77(8 Suppl):1747–1751

Okamoto K, Iwano T, Tachibana M, Shinkai Y (2008) Distinct roles of TRF1 in the regulation of telomere structure and lengthening. J Biol Chem 283:23981–23988

Olivier M, Taniere P (2011) Somatic mutations in cancer prognosis and prediction: lessons from TP53 and EGFR genes. Curr Opin Oncol 23:88–92

Olivier M, Hollstein M, Hainaut P (2010) TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Pring Harb Perspect Biol 2:a001008

Ozturk M, Arslan-Ergul A, Bagislar S, Senturk S, Yuzugullu H (2009) Senescence and immortality in hepatocellular carcinoma. Cancer Lett 286:103–113

Paik SY, Park YN, Kim H, Park C (2003) Expression of transforming growth factor-beta1 and transforming growth factor-beta receptors in hepatocellular carcinoma and dysplastic nodules. Mod Pathol 16:86–96

Pan XC, Chen Z, Chen F, Chen XH, Jin HY, Xu XY (2006) Inactivation of the tumor suppressor Krüppel-like factor 6 (KLF6) by mutation of decreased expression in hepatocellular carcinoma. J Zheijiang Univ Sci B 7:830–836

Park SW, Durkin ME, Thorgeirsson SS, Popescu NC (2003) DNA variants of DLC-1, a candidate tumor suppressor gene in human hepatocellular carcinoma. Int J Oncol 23:133–137

Patil MA, Zhang J, Ho C, Cheung ST, Fan ST, Chen X (2006) Hedgehog signaling in human hepatocellular carcinoma. Cancer Biol Ther 5:111–117

Peng CY, Chen TC, Hung SP, Chen MF, Yeh CT, Tsai SL, Chu CM, Liaw YF (2002) Genetic alterations of INK4alpha/ARF locus and p53 in human hepatocellular carcinoma. Anticancer Res 22:1265–1271

Peng Q, Lao X, Chen Z, Lai H, Deng Y, Wang J, Mo C, Sui J, Wu J, Zhai L, Yang S et al (2013) TP53 and MDM2 gene polymorphisms, gene-gene interaction, and hepatocellular carcinoma risk: evidence from an updated meta-analysis. PLoS One 8:e82773

Perry ME (2010) The regulation of the p53-mediated stress response by MDM2 and MDM4. Cold Spring Harb Perspect Biol 2:a000968

Peyrou M, Bourgoin L, Foti M (2010) PTEN in liver diseases and cancer. World J Gastroenterol 16:4627–4633

Peyrou M, Clément S, Maier C, Bourgoin L, Branche E, Conzelmann S, Kaddai V et al (2013) PTEN protein phosphatase activity regulates hepatitis C virus secretion through modulation of cholesterol metabolism. J Hepatol 59:420–426

Pinyol R, Tovar V, Llovet JM (2014) TERT promoter mutations: gatekeeper and driver of hepatocellular carcinoma. J Hepatol 61:685–687

Plentz RR, Schlegelberger B, Flemming P, Gebel M, Kreipe H, Manns MP, Rudolph KL et al (2005) Telomere shortening correlates with increasing aneuploidy of chromosome 8 in human hepatocellular carcinoma. Hepatology 42:522–526

Plentz RR, Park YN, Lechel A, Kim H, Nellessen F, Langkopf BH, Wilkens L, Destro A et al (2007) Telomere shortening and inactivation of cell cycle checkpoints characterize human hepatocarcinogenesis. Hepatology 45:968–976

Qi LN, Bai T, Chen ZS, Wu FX, Chen YY, De Xiang B, Peng T, Han ZG, Li LQ (2014) The p53 mutation spectrum in hepatocellular carcinoma from Jiangxi, China: role of chronic hepatitis B virus infection and aflatoxin B1 exposure. Liver Int. doi:10.1111/liv.12460

Rana KS, Arif M, Hill EJ, Aldred S, Nagel DA, Nevill A, Randeva HS, Bailey CJ et al (2014) Plasma irisin levels predict telomere length in healthy adults. Age (Dord) 36:995–1001

Raychaudhuri P, Park HJ (2011) FoxM1: a master regulator of tumor metastasis. Cancer Res 71:4329–4333

Rebbani K, Ezzikouri S, Marchio A, Kandil M, Pineau P, Benjelloun S (2014) MDM2 285G>C and 344T>A gene variants and their association with hepatocellular carcinoma: a Moroccan case-control study. Infect Agent Cancer 9:11

Reichl P, Haider C, Grubinger M, Mikulits W (2012) TGF-β in epithelial to mesenchymal transition and metastasis of liver carcinoma. Curr Pharm Des 18:4135–4147

Rossmanith W, Schulte-Hermann R (2001) Biology of transforming growth factor in hepatocarcinogenesis. Microsc Res Tech 52:430–436

Rountree CB, Ding W, He L, Stiles B (2009) Expansion of CD133-expressing liver cancer stem cells in liver-specific phosphatase and tensin homolog deleted on chromosome 10-deleted mice. Stem Cells 27:290–299

Saelee P, Wongkham S, Chariyalertsak S, Petmitr S, Chuensumran U (2010) RASSF1A promoter hypermethylation as a prognostic marker for hepatocellular carcinoma. Asian Pac J Cancer Prev 11:1677–1681

Saini N, Srinivasan R, Chawla Y, Sharma S, Chakraborti A, Rajwanshi A (2009) Telomerase activity, telomere length and human telomerase reverse transcriptase expression in hepatocellular carcinoma is independent of hepatitis virus status. Liver Int 29:1162–1170

Seton-Rogers S (2014) p53 and cellular plasticity. Nat Rev Cancer 14:577

Sheth R, Bastida MF, Kmita M, Ros M (2014) "Self-regulation", a new facet of Hox genes' function. Dev Dyn 243:182–191

Shi X, Liu J, Ren L, Mao N, Tan F, Ding N, Yang J, Li M (2014) Nutlin-3 downregulates p53 phosphorylation on serine392 and in duces apoptosis in hepatocellular carcinoma cells. BMB Rep 47:221–226

Shiraha H, Nishina S, Yamamoto K (2011) Loss of runt-related transcription factor 3 causes development and progression of hepatocellular carcinoma. J Cell Biochem 112:745–749

Shukla SK, Kumar V (2012) Hepatitis B virus X protein and c-Myc cooperate in the upregulation of ribosome biogenesis and in cellular transformation. FEBS J 279:3859–3871

Sicklick JK, Li YX, Jayaraman A, Kannangai R, Qi Y, Vivekananadan P, Ludlow JW et al (2006) Dysregulation of the hedgehog pathway in human hepatocarcinogenesis. Carcinogenesis 27:748–757

Sirivatanauksorn Y, Sirivatanauksorn V, Srisawat C, Khongmanee A, Tongkham C (2012) Differential expression of sprouty genes in hepatocellular carcinoma. J Surg Oncol 105:273–276

Song J, Kim CJ, Cho YG, Kim SY, Nam SW, Lee SH, Yoo NJ, Lee JY, Park WS (2006) Genetic and epigenetic alterations of the KLF6 gene in hepatocellular carcinoma. J Gastroenterol Hepatol 21:1286–1289

Song K, Gao Q, Zhou J, Qiu SJ, Qiu SJ, Huang XW, Wang XY, Fan J (2012) Prognostic significance and clinical relevance of Sprouty 2 protein expression in human hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 11:177–184

Stefanou N, Papanikolaou V, Furukawa Y, Nakamura Y, Tsezou A (2010) Leptin as a critical regulator of hepatocellular carcinoma development through modulation of human telomerase reverse transcriptase. BMC Cancer 10:442

Steinway SN, Gomez Tejeda Zanudo J, Ding W, Rountree CB, Feith DJ, Loughran TP et al (2014) Network modeling of TGFβ signaling in hepatocellular carcinoma epithelial-to-mesenchymal transition reveals joint Sonic hedgehog and Wnt pathway activation. Cancer Res 74:5963–5977

Sui G, Ma X, Liu S, Niu H, Dong Q (2012) Study of the correlation between H-ras mutation and primary hepatocellular carcinoma. Oncol Lett 4:779–782

Sun HC, Li M, Lu JL, Yan DW, Zhou CZ, Fan JW, Qin XB, Tang HM, Peng ZH (2011) Overexpression of forkhead box M1 protein associated with aggressive tumor features and poor prognosis of hepatocellular carcinoma. Oncol Rep 25:1533–1539

Sun Z, Han Q, Zhou N, Wang S, Lu S, Bai C, Zhao RC (2013) MicroRNA-9 enhances migration and invasion through KLF17 in hepatocellular carcinoma. Mol Oncol 7:884–894

Sze KM, Wong KL, Chu GK, Lee JM, Yau TO, Ng IO (2011) Loss of phosphatase and tensin homolog enhances cell invasion and migration through AKT/Sp-1 transcription factor/matrix metalloproteinase 2 activation in hepatocellular carcinoma and has clinicopathologic significance. Hepatology 53:1558–1569

Tabor E (1994) Tumor suppressor genes, growth factor genes, and oncogenes in hepatitis B virus-associated hepatocellular carcinoma. J Med Virol 42:357–365

Takeishi K, Taketomi A, Shirabe K, Toshima T, Motomura T, Ikegami T, Yoshizumi T et al (2012) Diacylglycerol kinase alpha enhances hepatocellular carcinoma progression by activation of Ras-Raf-MEK-ERK pathway. J Hepatol 57:77–83

Tamura M, Gu J, Tran H, Yamada KM (1999) PTEN gene and integrin signaling in cancer. J Natl Cancer Inst 91:1820–1828

Tannapfel A, Busse C, Weinans L, Benicke M, Katalinic A, Geissler F, Hauss J, Wittekind C (2001) INK4a-ARF alterations and p53 mutations in hepatocellular carcinomas. Oncogene 20:7104–7109

Thompson NL, Mead JE, Braun L, Goyette M, Shank PR, Fausto N (1986) Sequential protooncogene expression during rat liver regeneration. Cancer Res 46:3111–3117

Toftgard R (2000) Hedgehog signalling in cancer. Cell Mol Life Sci 57:1720–1731

Toledo F, Wahl GM (2007) MDM2 and MDM4: p53 regulators as targets in anticancer therapy. Int J Biochem Cell Biol 39:1476–1482

Tornesello ML, Buonaguro L, Tatangelo F, Botti G, Izzo F, Buonaguro FM (2013) Mutations in TP53, CTNNB1 and PIK3CA genes in hepatocellular carcinoma associated with hepatitis B and hepatitis C virus infections. Genomics 102:74–83

Tulchinsky E (2000) Fos family members: regulation, structure and role in oncogenic transformation. Histol Histopathol 15:921–928

Urtasun R, Latasa MU, Demartis MI, Balzani S, Goñi S, Garcia-Irigoyen O, Elizalde M et al (2011) Connective tissue growth factor autocriny in human hepatocellular carcinoma: oncogenic role and regulation by epidermal growth factor receptor/yes-associated protein-mediated activation. Hepatology 54:2149–2158

Villanueva A, Hoshida Y (2011) Depicting the role of TP53 in hepatocellular carcinoma progression. J Hepatol 55:724–725

Vogelstein B, Lane D, Levine AJ (2000) Surfing the p53 network. Nature 408:307–310

Wang XW, Forrester K, Yeh H, Feitelson MA, Gu JR, Harris CC (1994) Hepatitis B virus X protein inhibits p53 sequence-specific DNA binding, transcriptional activity, and association with transcription factor ERCC3. Proc Natl Acad Sci U S A 91:2230–2234

Wang Y, Wu MC, Sham JS, Zhang W, Wu WQ, Guan XY (2002) Prognostic significance of c-myc and AIB1 amplification in hepatocellular carcinoma. A broad survey using high-throughput tissue microarray. Cancer 95:2346–2352

Wang SP, Zhou HJ, Chen XP, Ren GY, Ruan XX, Zhang Y, Zhang RL, Chen J (2007a) Loss of expression of Kruppel-like factor 6 in primary hepatocellular carcinoma and hepatoma cell lines. J Exp Clin Cancer Res 26:117–124

Wang L, Wang WL, Zhang Y, Zhang Y, Guo SP, Zhang J, Li QL (2007b) Epigenetic and genetic alterations of PTEN in hepatocellular carcinoma. Hepatol Res 37:389–396

Wang S, Kang L, Chen X, Zhou H (2010a) Frequent down-regulation and deletion of KLF6 in primary hepatocellular carcinoma. J Huazhong Univ Sci Technolog Med Sci 30:470–476

Wang WH, Jiang CL, Yan W, Zhang YH, Yang JT, Zhang C, Yan B, Zhang W et al (2010b) FOXP3 expression and clinical characteristics of hepatocellular carcinoma. World J Gastroenterol 16:5502–5509

Wang Y, Li J, Chen J, Liu L, Peng Z, Ding J, Ding K (2012a) From cirrhosis to hepatocellular carcinoma in HCV-infected patients: genes involved in tumor progression. Eur Rev Med Pharmacol Sci 16:995–1000

Wang C, Delogu S, Ho C, Lee SA, Gui B, Jiang L, Ladu S, Cigliano A, Dombrowski F et al (2012b) Inactivation of Spry2 accelerates AKT-driven hepatocarcinogenesis via activation of MAPK and PKM2 pahways. J Hepatol 57:577–583

Wang W, He S, Ji J, Huang J, Zhang S, Zhang Y (2013) The prognostic significance of FOXQ1 oncogene

overexpression in human hepatocellular carcinoma. Pathol Res Pract 209:353–358
Ward A, Hudson JW (2014) p53-dependent and cell specific epigenetic regulation of the polo-kinases under oxidative stress. PLoS One 9:e87918
Winkler J, Ori A, Holzer K, Sticht C, Dauch D, Eiteneuer EM, Pinna F, Geffers R, Ehemann V et al (2014) Prosurvival function oft he cellular apoptosis susceptibility(importin-α1 transport cycle is repressed by p53 in liver cancer. Hepatology 60:884–895
Wolosz D, Walczak A, Wilczynski GM, Szparecki G, Wilczek E, Gornicka B (2014) Deleted in liver cancer 1 expression and localization in hepatocellular carcinoma tissue sections. Oncol Lett 8:785–788
Wong CC, Wong CM, Ko FC, Chan LK, Ching YP, Yam JW, Ng IO (2008) Deleted in liver cancer 1 (DLC1) negatively regulates Rho/ROCK/MLC pathway in hepatocellular carcinoma. PLoS One 3:e2779
Wu SK, Wang BJ, Yang Y, Feng XH, Zhao XP, Yang DL (2007) Expression of PTEN, PPM1A and P-Smad2 in hepatocellular carcinomas and adjacent liver tissues. World J Gastroenterol 13:4554–4559
Xia L, Huang W, Tian D, Zhu H, Zhang Y, Hu H, Fan D, Nie Y, Wu K (2012) Upregulated FoxM1 expression induced by hepatitis B virus X protein promotes tumor metastasis and indicates poor prognosis in hepatitis B virus-related hepatocellular carcinoma. J Hepatol 57:600–612
Xia L, Huang W, Tian D, Zhu H, Qi X, Chen Z, Zhang Y, Hu H, Fan D, Nie Y, Wu K (2013) Overexpression of forkhead box C1 promotes tumor metastasis and indicates poor prognosis in hepatocellular carcinoma. Hepatology 57:610–624
Xie C, Song LB, Wu JH, Li J, Yun JP, Lai JM, Xie DY, Lin BL, Yuan YF, Li M, Gao ZL (2012) Upregulator of cell proliferation predicts poor prognosis in hepatocellular carcinoma and contributes to hepatocarcinogenesis by downregulating FOXO3a. PLoS One 7:e40607
Xu ZY, Ding SM, Zhou L, Xie HY, Chen KJ, Zhang W, Xing CY, Guo HJ, Zheng SS (2012) FOXC1 contributes to microvascular invasion in primary hepatocellular carcinoma via regulating epithelial-mesenchymal transition. Int J Biol Sci 8:1130–1141
Xu J, Zhou J, Li MS, Ng CF, Ng YK, Lai PB, Tsui SK (2014) Transcriptional regulation of the tumor suppressor FHL2 by p53 in human kidney and liver cells. PLoS One 9:e99359
Yamazaki K, Masugi Y, Sakamoto M (2011) Molecular pathogenesis of hepatocellular carcinoma: altering transforming growth factor-β signaling in hepatocarcinogenesis. Dig Dis 29:284–288
Yan HX, Wu HP, Zhang HL, Ashton C, Tong C, Wu H, Qian QJ, Wang HY, Ying QL (2013) p53 promotes inflammation-associated hepatocarcinogenesis by inducing HMGB1 release. J Hepatol 59:762–768
Yang T, Cai SY, Zhang J, Lu JH, Lin C, Zhai J, Wu MC, Shen F (2012) Krüppel-like factor 8 is a new wnt/beta-catenin signaling target gene and regulator in hepatocellular carcinoma. PLoS One 7:e39668
Yao YJ, Ping XL, Zhang H, Chen FF, Lee PK, Ahsan H, Chen CJ, Lee PH, Peacocke M et al (1999) PTEN/MMAC1 mutations in hepatocellular carcinomas. Oncogene 18:3181–3185
Yea S, Narla G, Zhao X, Garg R, Tal-Kremer S, Hod E, Villanueva A, Loke J, Tarocchi M et al (2008) Ras promotes growth by alternative splicing-mediated inactivation of the KLF6 tumor suppressor in hepatocellular carcinoma. Gastroenterology 134:1521–1531
Yin D, Komatsu N, Miller CW, Chumakov AM, Marschesky A, McKenna R, Black KL et al (2007) KLF6: mutational analysis and effect on cancer cell proliferation. Int J Oncol 30:65–72
Yokota T, Suda T, Igarashi M, Kuoiwa T, Waguri N, Kawai H, Mita Y, Aoyagi Y (2003) Telomere length variation and maintenance in hepatocarcinogenesis. Cancer 98:110–118
Yuen MF, Wu PC, Lai VC, Lau JY, Lai CL (2001) Expression of c-Myc, c-Fos, and c-jun in hepatocellular carcinoma. Cancer 91:106–112
Zenker M (2011) Clinical manifestations of mutations in RAS and related intracellular signal transduction factors. Curr Opin Pediatr 23:443–451
Zha TZ, Hu BS, Yu HF, Tan YF, Zhang Y, Zhang K (2012) Overexpression of HOXA1 correlates with poor prognosis in patients with hepatocellular carcinoma. Tumour Biol 33:2125–2134
Zhan P, Ji YN, Yu LK (2013) TP53 mutation is associated with a poor outcome for patients with hepatocellular carcinoma: evidence from meta-analysis. Hepatobiliary Surg Nutr 2:260–265
Zhang L, Yu Q, He J, Zha X (2004) Study of the PTEN gene expression and FAK phosphorylation in human hepatocarcinoma tissues and cell lines. Mol Cell Biochem 262:25–33
Zhang C, Guo X, Jiang G, Zhang L, Yang Y, Shen F, Wu M, Wei L (2008) CpG island methylator phenotype association with upregulated telomerase activity in hepatocellular carcinoma. Int J Cancer 123:998–1004
Zhang X, Tang N, Hadden TJ, Rishi AK (2011) Akt, FoxO and regulation of apoptosis. Biochim Biophys Acta 1813:1978–1986
Zhang et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22422806
Zhang J, Tu K, Yang W, Li C, Yao Y, Zheng X, Liu Q (2014) Evaluation of jagged2 and Gli1 expression and their correlation with prognosis in human hepatocellular carcinoma. Mol Med Rep 10:749–754
Zhao X, Li J, Zhuo J, Cai L (2010) Reexpression of ARHI inhibits tumor growth and angiogenesis and impairs the mTOR/VEGF pathway in hepatocellular carcinoma. Biochem Biopys Res Commun 403:417–421
Zhao B, Zhu Y, Cui K, Gao J, Yu F, Chen L, Li S (2013) Expression and significance of PTEN and miR-92 in hepatocellular carcinoma. Mol Med Rep 7:1413–1416

Zheng X, Vittar NB, Gai X, Fernandez-Barrena MG, Moser CD, Hu C, Almada LL et al (2012) The transcription factor GLI1 mediates TGFβ1 driven EMT in hepatocellular carcinoma via a SNAI1-dependent mechanism. PLoS One 7:e49581

Zheng X, Zeng W, Gai X, Xu Q, Li C, Liang Z, Tuo H, Liu Q (2013) Role of the hedgehog pahway in hepatocellular carcinoma (review). Oncol Rep 30:2020–2026

Zhenzhen Z, De'an T, Limin X, Wie Y, Min L (2012) New candidate tumor-suppressor gene KLF6 and its splice variant KLF6 SV2 counterbalancing expression in primary hepatocarcinoma. Hepatogastroenterology 59: 473–476

Zhou J, Tan T, Tian Y, Zheng B, Ou JH, Huang EJ, Yen TS (2011) Krüppel-like factor 16 activates hepatitis B virus gene expression and replication. Hepatology 54:109–121

Zimonjic DB, Popescu NC (2012) Role of DLC1 tumor suppressor gene and MYC oncogene in pathogenesis of human hepatocellular carcinoma: potential prospects for combined targeted therapeutics (review). Int J Oncol 41:393–406

Etiology and Pathogenesis of Hepatocellular Carcinoma: Epigenetic Mechanisms

168

Contents

Abstract

Etiology and pathogenesis of liver cancer strongly depend on various epigenetic mechanisms that result in gene silencing. By the action of epigenetic processes, heritable changes in gene expression patterns are maintained over numerous cell generation and play an important role in carcinogenic pathways. Major epigenetic mechanisms that operate in hepatocellular carcinoma (HCC) include DNA methylation, histone modifications, chromatin modifiers, microRNAs, RNA editing (RNA editome), and lncRNAs. DNA methylation that involves numerous CpG sites and results in distinct DNA methylome signatures is an important pathway in HCC. In these neoplasms, CpG-methylated sites are predominantly located within gene-promoter regions and CpG islands, and their presence is associated with biology of disease in HCC. Part of HCCs show various types of histone modifications which play a role in hepatocarcinogenesis. HCCs also show distinct deregulations of chromatin modifiers that cause gene silencing, in particular polycomb repressive complexes. Liver cancers exhibit highly complex patterns of microRNA expression, resulting in distinct microRNAomes that will provide diagnostic and stratification signatures.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_168

Introduction: General Features of the Liver Cancer Epigenome

By the action of epigenetic mechanisms, heritable changes in gene expression patterns are maintained over numerous generations and play an important role in carcinogenic pathways, including liver cancers. Epigenetic mechanisms operational in HCCs include alterations in DNA methylation (methylome), histone modifications, chromatin modifiers, microRNAs, RNA editing (RNA editome), and lncRNAs (reviews: Liu et al. 2012; Liu et al. 2014a; Raggi et al. 2014). Importantly, epigenetically driven changes in gene expression in HCCs are influenced by environmental factors. Specifically, hepatitis virus infections, alcohol toxicity, and fungal hepatotoxins elicit epigenetic alterations of genes through altered promoter methylation, histone modifications, and RNA-mediated gene silencing (Herceg and Paliwal 2011).

DNA Methylation as an Epigenetic Mechanism: Methylation Profiles in Liver Cancer (the HCC Methylome or Methylation Epigenome)

By the use of genome-wide profiling of DNA methylation, numerous CpG sites modified by methylation were identified in HCCs in comparison with the normal or cirrhotic liver tissue (Raggi and Invernizzi 2013; Dong and Wang 2014). CpG-methylated sites are predominantly located within promoter regions and CpG islands, and their presence is associated with biology of disease in HCCs (Zhu 2006; Hernandez-Vargas et al. 2010; Shen et al. 2012; Song et al. 2013; Mah and Lee 2014; Nishida et al. 2014). In one study on patients with HBV- or HCV-associated HCCs, methylation patterns were associated with tumor progression stage and involved distinct genes involved in growth regulation and signaling (APC, RASSFIA, CDKN2A, and FZD7), and certain hypermethylated genes (e.g., NAT2, CSPG2, and DNMT1) were exclusively associated with HBV-related HCC (Hernandez-Vargas et al. 2010). Song and coworkers detected promoter CpG island DNA methylation loci in diverse signaling networks affecting cell development, gene expression, and cell death (Song et al. 2013). Analysis of epigenetic methylation patterns in HCCs results in the detection of methylation-based prognostic signatures based on the identification of relevant hepatocarcinogenic genes (Yu et al. 2002). Certain clusters of methylated genes indicate tumors with progenitor cell features and are potent epidrivers (Villanueva et al. 2015).

Several candidate tumor suppressors for HCC have been identified to be regulated by promoter hypermethylation, including p16INK4 (Roncalli et al. 2002; Qin et al. 2004; Zang et al. 2011), RASSF1A/Ras association domain family 1A gene (Schagdarsurengin et al. 2003), RUNX3 (Yang et al. 2014b), RIZ1/retinoblastoma-interacting zinc finger gene (Zhang et al. 2010), ZIC1 tumor suppressor (Wang et al. 2014a), tumor suppressor DACH1/human dachshund homolog 1 (Zhu et al. 2013), adenomatous polyposis coli gene/APC (Xu et al. 2014), endothelin receptor type B (Hsu et al. 2006), smad-interacting protein-1/SIP1 (Acun et al. 2011), TGF-beta1 target gene and transcriptional repressor HEYL (Kuo et al. 2014), bone morphogenetic protein-6 (He et al. 2014a), and secreted frizzled-related proteins (Lin et al. 2014). DNA methylation can also modify the expression of several microRNAs in HCC, including microRNA-148a, microRNA-195, microRNA-375, and microRNA-378 (He et al. 2015). There is a negative feedback regulatory loop between microRNA-148a and DNMT1 in HCC cell proliferation, in that DNM1, which is a target of this miR, is inversely correlated with the expression of microRNA-148a (Long et al. 2014).

The activity of DNA methyltransferase 1/DNMT1 in human HCC can be upregulated by growth factors, specifically insulin-like growth factor 1 signaling upregulates DNMT1 via an Akt/beta-transducin repeat-containing protein-mediated ubiquitin proteasome pathway (Fang et al. 2015). Cancer gene methylation frequencies in HCC are modulated by hepatitis virus infections

and environmental carcinogenic factors. Generally, HBX induces epigenetic modifications in hepatocarcinogenesis (Park et al. 2007). Hepatitis B virus inhibits the expression of the metastasis inhibitor KAI1/CD82 through hypermethylation of its promoter in HCC cells (Yu et al. 2014) and downregulates the suppressor of cytokine signaling/SOCS1 by hypermethylation (Zhang et al. 2013b). HBX promotes hypermethylation of p16INK4a through upregulation of DNMT1 and DNMT3 (Zhu et al. 2010). A high frequency of RASSF1A hypermethylation in human HCC was associated with aflatoxin B1 exposure (Zhang et al. 2002), and K-Ras and p16 methylation was more common in workers exposed to vinyl chloride (Weihrauch et al. 2001).

Histone Modifications

In nucleosomes, 145 DNA base pairs are wrapped around a histone octamer consisting H2A, H2B, H3, and H4 histones. Histones packed within nucleosome octamers have a protruding tail which is subject to posttranslational modifications, the histone modifications as an epigenetic feature. Histone modifications serve to switch gene transcription on or off. The modifications include methylation and acetylation of lysine and arginine, phosphorylation of serine and threonine, and ubiquitination of lysine. Histone acetylation is mediated by two families of enzymes, the histone acetyltransferases (causing the "on" position of gene transcription) and histone deacetylases (causing the "off" position of gene transcription).

Part of HCCs show various types of histone modifications which play a role in carcinogenesis and are associated with tumor biology (Magerl et al. 2010; Cai et al. 2011a; He et al. 2012; Hung et al. 2014a). For example, a high level of H3 histone lysine trimethylation is correlated with an aggressive course and poor prognosis of HCC (He et al. 2012). The generation of histone modifications in HCCs is also related to epigenetic alterations in chromatin patterning (see the following paragraph).

Chromatin Modifiers (Polycomb Repressive Complexes)

A distinct form of heritable gene silencing is mediated by chromatin-modifying complexes containing polycomb group proteins. Specifically, polycomb proteins generate silencing platforms termed polycomb repressive complexes (PRCs). Two major PRCs are known. PRC1 consists of a core protein (BMI), RING1A and RING1B ubiquitin ligases for the histone H2AK119, and the protein CBX7 which binds to histone H3K27. PRC2 consists of EZH1/EZH2 (a methyltransferase causing gene silencing by trimethylating histone H3K27), SUZ12/suppressor of zeste 12 homolog, EED1, and RbAp48. Deregulation of PRCs and the associated epigenetic alterations are involved in cancerogenesis (Piunti and Pasini 2011; Lin et al. 2011).

HCCs show various aberrations of PRC-based epigenetic mechanisms (Au et al. 2013). In HCCs, expression levels of EZH1/EZH2 are frequently elevated, high expression correlated with aggressive, metastatic features and poor prognosis (Sudo et al. 2005; Cai et al. 2011b). EZH2 as a methyltransferase represses target genes in part through histone modifications in cancers (Simon and Lange 2008). HCCs show EZH2-induced trimethylation of histone H3 lysine 27 (H3K27me3), affecting the expression of several genes, including cyclin-dependent kinase inhibitors and Notch signaling (Gao et al. 2014). Enhanced EZH2 in HCC silences Wnt antagonists, thereby activating Wnt/beta-catenin signaling involved in hepatocarcinogenesis (Cheng et al. 2011). EZH2, together with c-Myc, silences the tumor-suppressing microRNA-101 in HCC (Wang et al. 2013) and multiple microRNAs involved in liver cancer metastasis (Au et al. 2012).

The PRC pathways are connected with effects exerted by HBV X protein. HBX-mediated hepatocyte transformation is associated with downregulation of the PRC2 component, SUZ12 in a polo-like kinase 1-dependent manner (Wang et al. 2011), a mechanism that activates mitogenic polo-like kinase 1 (Studach et al. 2010). Loss of

SUZ12 caused by this mechanism in turn results in derepression of PRC2 target genes involved in stem and progenitor cell biology, including EpCAM, DLK1, DKK2, and BAMBI (Wang et al. 2011; Studach et al. 2012).

MicroRNAs in Hepatocarcinogenesis

General Remarks

MicroRNAs (miRNAs or miRs) are small noncoding RNA molecules with a length of about 22 nucleotides. They are involved in posttranscriptional regulation of gene expression via base-pairing with complementary sequences within processed mRNA molecules. Targeted mRNAs are silenced by this interaction and afterward actively disassembled (target degradation). The human genome encodes more than 1,000 microRNAs with a complex catalog of targets forming a microRNAome. Functional maturation of microRNAs requires a stepwise cleavage of precursor hairpin transcripts by the Drosha and Dicer RNase III enzymes, but there exist at least two alternative (noncanonical) pathways. One is based on a splicing-mediated miR biogenetic mechanisms related to the action of short hairpin introns called mirtrons. In the mirtron pathway, spliceosome-excised introns are direct Dicer substrates (Ruby et al. 2007; Westholm and Lai 2011). A third pathway is, in contrast to mirtrons, independent of Dicer, but requires Drosha for processing (the simtrons; Havens et al. 2012). Both mirtrons and simtrons interact with Argonaute proteins and function in silencing of target transcripts. The microRNAome is the complete set of microRNAs/miRNAs (or a so-called microRNA atlas) of an organism or a certain normal or neoplastic cell lineage (Murray et al. 2010). The whole human microRNAome will be determined in order to arrive at the complete target miRNA network (Satoh and Tabunoki 2011).

The MicroRNAome in Cancerogenesis

MicroRNAs and the microRNAome have an important role in cancer and cancerogenesis, including liver cancer (Koturbash et al. 2011: Khare et al. 2013). MicroRNAs that have a central role in cancer development are termed oncogenic microRNAs or oncomiRs. In the future, distinct microRNA signatures will characterize individual tumors, in the sense of a oncomiRome. MicroRNAomes of neoplasms may serve to develop novel tumor classifications and to arrive at "micromanaging" classifications by creating a map of tumor-specific miRNA signatures (Vilar et al. 2011).

The MicroRNAome in Hepatobiliary Cancer

There is increasing evidence that microRNAs, due to their action on multiple targets, play a significant role in the development of liver cancer, and in HCC progression (review: Gong et al. 2015). In HCC, microRNAs often display aberrant expression profiles and seem to act as oncogenes or tumor suppressors. Certain microRNA species are almost exclusively associated with HCC or related to distinct HCC types and subtypes, implying microRNAs or hepatic oncomiRs a significance for diagnosis and risk stratification. Furthermore, an aberrant expression of HCC oncomiRs generates typical molecular signatures for these tumors, correlated with clinical parameters and potential drug sensitivities (Gramantieri et al. 2008; Ji and Wang 2009; ElHefnawi et al. 2013; Gailhouste and Ochiya 2013; Giordano and Columbano 2013; Greene et al. 2013; Sun et al. 2013a; D'Anzeo et al. 2014; Hung et al. 2014b; Kou et al. 2014; Saito et al. 2014; Table 1). But also important predisposing conditions are markedly influenced by the action of microRNAs. For example, HCV infection, playing an critical role in hepatocarcinogenesis, is regulated on several levels by distinct miR species (reviews: Kumar 2011; Hou and Bonkovsky 2013). In particular, microRNA-122 is highly enriched in the liver infected with HCV and interacts with HCV, suggesting that HCV has subverted the host gene-silencing machinery (Gupta et al. 2014). In cancer cells, microRNA-mediated gene regulation may be interconnected with signaling pathways, e.g., the Wnt/beta-catenin

Table 1 MicroRNAs (miRs) expressed in liver cancer and/or upregulated or downregulated in hepatitis virus-induced hepatocellular carcinoma (Modified after Hou and Bonkovsky (2013), Sun et al. (2013a), D'Anzeo et al. (2014), and Hung et al. (2014))

Upregulated microRNAs	Main target(s)
miR-10a	Eph4, CADM1
miR-17-5p	p38 signaling pathway
miR-18a	ER1alpha
miR-18b	TIMP3
miR-21	PTEN, RhoB, PDCD4
miR-23a	PGC-1a, G6PC
miR-130a	RUNX3
mir-135a	FOXM1
miR-143	FNDC3B
miR-155	SOCS1, DKK1, APC, PTEN
miR-181	TIMP3
miR-182	MTSS1
mirR-210	VMP1, AIFM3
miR-216a	TSLC1
miR-221	CDK inhibitors
miR-224	NF-kappaB pathway, Smad4
miR-301a	Gax
miR-373	PPP6C
miR-490-3p	ERCIC3
miR-519d	CDKN1A/p21, PTEN, Akt 3
miR-550a	CPEB4
miR-590-5p	TGFRII
miR-615-5p	IGF-II
miR-657	TLE1, NF-jB
Downregulated microRNAs	
Let-7a	caspase-3
Let-7b	HMGA2
Let-7c	PPARalpha
miR-1	ETI1
miR-7a	c-Myc, caspase-3, Bcl-xl
miR-26a/b	IL-6, cyclin D2
miR-29a	SPARC
miR-34a	c-Met, CCL22
miR-101	C-Fos, SOX-9, EZH2
miR-122	c-Myc,ADAM-1,Wnt-1 IL-6, TNF,IGF-1R
miR-124	ROCK2, EZH2, CDK6, SMYD3
miR-125a/125b	VEGF-A, Mcl-1, Bcl-2, SIRT7
miR-138	CCND3
miR-139	c-Fos, ROCK2
miR-145	IGF-1R, beta-catenin, IRS1/2
miR-195	VEGF, cyclin D1, CDK6, E2F3
miR-199a/b-3p	c-Met, mTOR, caveolin-2, PAK4
miR-200a	HDAC4
miR-203	ABCE1
miR-206	suppressor of cell proliferation
mirR-214	catenin, HDGF
miR-219-5p	GPC3
miR-223	STMN1
miR-375	AEG-1, ATG7
miR-376a	PIK3R1
miR-449	c-Met
miR-450a	DNMT3a
miR-520e	cyclin D1, MEKK2

signaling cascade (Sun et al. 2013b). Similar to other microRNAs, oncomiRs associated with HCC may be distributed among cells via exosomes/microvesicles, a mechanism potentially involved in the generation of metastatic niches and establishment of cancer fields.

In what follows a selection of the microRNAs listed in the Table are discussed in some more detail. MicroRNA-21, which negatively regulates several targets and involved in the development of several cancers, displays elevated expression levels in HCC, where it regulates multiple programs that enhance proliferation, apoptosis, and invasive pathways by mainly targeting PTEN, PDCD4, and RECK (Liu et al. 2010). MicroRNA-23 may be involved in the onset of HCC, as its expression is correlated with TNM stage and tumor size (Bao et al. 2014). Expression of microRNA-26a in HCC suppresses angiogenesis by targeting the HGF/c-Met signaling pathway (Yang et al. 2014a). MicroRNA-21 is inducible by the HBx protein and favors cell proliferation by targeting programmed cell death protein 4 and PTEN (Bao et al. 2013; Damania et al. 2014). MicroRNA-29c acts as a tumor suppressor by directly targeting a factor involved in cellular senescence and regulation of telomere function, sirtuin 1/SIRT1. MiR-29c potently suppresses SIRT1, and loss of miR-29c expression in HCC causes aberrant SIRT1 expression promoting tumor progression (Bae et al. 2014). MicroRNA-101 is an important tumor-suppressive miR in human HCCs and is

epigenetically repressed by the zeste homolog 2/EZH2 unit of the polycomb repressive complex 2/PRC2 in a c-Myc-mediated manner (Wang et al. 2014b). MicroRNA-106b-25/microRNA-17-92 forms polycistronic clusters that are involved in HCC oncogenesis and are regulated by c-Myc (Tan et al. 2014). MicroRNA-122 is a liver-specific miR which suppresses proliferation and induces apoptosis (Xu et al. 2012) and is significantly downregulated in most HCCs. It regulates hepatic tumorigenesis by targeting Akt3, suggesting that microRNA-122 acts as tumor suppressor (Nassirpour et al. 2013). MicroRNA-148a is a tumor suppressor in HCC and involved in HBV-induced hepatocarcinogenesis. HBV infection promotes expression of this miR through HBx-mediated upregulation of the URG11 gene, URG11 protein modulating the expression of several miRs (Yuan et al. 2012). This microRNA also suppresses epithelial-mesenchymal transition/EMT and metastasis by targeting Met/Snail signaling (Zhang et al. 2014). MicroRNA-657 directly targets transducin-like enhancer protein 1/TLE1 and activates NF-kappaB pathways (Zhang et al. 2013a). MicroRNA-206 is downregulated in HCC. Low levels of this miR are associated with poor tumor differentiation, multiple tumors, advanced stage, and lymph node metastasis. MicroRNA-206 is a suppressor of cell proliferation and promoter of apoptosis (Yunqiao et al. 2014). MicroRNA-218 modulates HCC proliferation through targeting of the PTEN/Akt/PIP3K pathway (Xiao et al. 2014). In several HCC cell systems, microRNA-612 showed inhibitory effects on cell proliferation, migration, invasion, and metastasis, Akt being a direct target. This microRNA also suppresses the stemness of HCC by reducing the number and size of tumor spheres and colony formation in vitro (Tang et al. 2014). Expression of microRNA-657 can be induced by hepatitis viral proteins and is increased in HCC, where it augments proliferative activity. In a miRNA analysis of the human bile, real-time PCR has identified miRNA-9 as a potential diagnostic biomarker for biliary tract cancer (Shigehara et al. 2011). Certain microRNAs can exert an influence in the growth pattern of HCCs. Simultaneous silencing of microRNA-141 and microRNA-200 promoted the development of HCC with bile duct thrombus formation via activation of epithelial-mesenchymal transition (Yeh et al. 2014).

Several microRNAs have been analyzed in regard to their impact on HCC biology and aggressiveness in more detail (reviewed in Sun et al. 2013a). HCC with poor prognosis, or shorter disease-free survival, or shorter overall survival, and aggressive course were characterized by downregulation of miRs let-7g, 19, 22, 26, 29, 99a, 122, 124, 139, 145, and 199b or upregulation of miRs 10b, 21, 17-5p, 135a, 155, 182, 221, and 222. Upregulation of miR-125b was associated with good survival.

Long Noncoding RNAs in Liver Cancer

Long noncoding RNAs (lncRNAs) are functional RNA molecules that are not translated into a protein, but play significant roles in numerous biological processes and in cancerogenic pathways (review: GENCODE consortium v7 catalog of lncRNAs, Derrien et al. 2012). LncRNAs are transcribed as large RNA transcripts with a length greater than 200 nucleotides, i.e., about ten times longer than microRNAs and longer than other short/small noncoding RNAs, such as piRNAs, snoRNAs, and endogenous siRNAs (Deng and Sui 2013; Shi et al. 2013). LncRNAs form a large group of RNAs. It is estimated that at least four times more lncRNAs than coding RNA sequences are present. The FANTOM (Functional Annotation of Mammalian cDNA) project identified approximately 35,000 noncoding transcripts from around 10,000 distinct loci, but this figure may become greater in the future. LncRNAs are transcribed within intergenic stretches and are predominantly transcribed as complex interlaced networks of overlapping sense and antisense transcripts that frequently include protein-coding genes. LncRNAs function in the regulation of life cycles of numerous genes and affect

chromosome remodeling, transcription (via targeting transcriptional activators or repressors and RNA polymerase II), availability of transcription factors, splicing regulation, siRNA-directed gene regulation, posttranscriptional processing, interactions with microRNAs, epigenetic silencing, and imprinting (Rinn and Chang 2012). Via these interactions, lncRNAs regulate cell growth and differentiation. Specifically, numerous lncRNA species that affect differentiation of various cell lineages have been identified (list and review: Hu et al. 2012). In cancer, lncRNAs expression is associated with modulation of invasion, spread, metastasis, and recurrence (Qiu et al. 2013).

Alterations of lncRNA expression play a role in various liver disorders, including cancer and its precursors (Takahashi et al. 2014). Dysregulation of lncRNA has been observed in HCC, whereby both up- and downregulations were observed for numerous (more than 200) lncRNAs (Panzitt et al. 2007; Hou and Bonkovsky 2013; Pan et al. 2013; Wang and Li 2013; He et al. 2014b; Huang et al. 2014; Liu et al. 2014b; Zhao et al. 2014; Zhu et al. 2014b). Mainly in HCV-associated HCC, several species of lncRNA are differentially expressed (Hou and Bonkovsky 2013). LncRNAs are also involved in the biology of hepatitis virus infections. In HBx transgenic mice, a distinct pattern of lncRNA develops compared with wild-type mice. HBx protein downregulates lncRNA-Dreh (for downregulated expression by HBx), which can inhibit HCC growth and metastasis and acts as a tumor suppressor in the pathogenesis of HBV-related HCC. This lncRNA has a human homolog (hDREH), which is often downregulated in HCCs (Huang et al. 2013). The pathways leading from dysregulated lncRNA expression and carcinogenesis are not yet clarified, but modifications in the proliferative behavior of target cells may play a central role. In the setting of liver regeneration, a distinct type of lncRNA termed lncRNA associated with liver regeneration/lncRNA-LALR1 is expressed and accelerates hepatocyte proliferation via activation of the Wnt/beta-catenin signaling cascade (Xu et al. 2013).

RNA Editing and the RNA Editome in Hepatocellular Carcinoma: Diversification of the Tumor Transcriptome

A posttranscriptional modification of RNA is characterized by enzyme-mediated conversion of nucleotides within RNA, processes causing extensive transcriptome diversity. A common RNA editing is adenosine-to-inosine conversion (termed A-to-I editing). A-to-I editing is accomplished by adenosine deaminase/ADA which induces adenosine deamination to yield inosine. The editing process involves both coding and noncoding regions of DNA (Athanasiadis et al. 2004). ADAs that are specific for double-stranded RNA are termed ADAR (adenosine deaminases that act on RNA), forming a family with ADAR1 and ADAR2 being prominent members (George et al. 2014). A second form of RNA editing is characterized by cytidine to uridine conversion, mediated by APOBEC-1. A third form of RNA editing, guanosine-to-adenosine conversion, involves the APOBEC-3 protein.

RNA editing generates considerable RNA and protein diversity, with aberrant diversity patterns in cancers (Schaub and Keller 2002; Paz et al. 2007; Dominissini et al. 2011). During malignant transformation of cells and progression of cancers, A-to-I editing results in complex patterns of RNA modifications, the so-called RNA editome. In HCCs, the editing rate is significantly higher than in adjacent nonneoplastic liver tissues (Kang et al. 2015). The RNA editome of HCC is markedly disrupted and showed hyper-and hypoediting of numerous genes, including not only the recoding editing of exons but also the editing in noncoding chromosomal regions (microRNAs; Alu-repetitive elements; Li et al. 2013; Qi et al. 2014). Genome-wide analysis of editing in HCC revealed several tumor-specific edits in part relating to cancer genes (Kang et al. 2015). HCCs often display a severely disrupted A-to-I RNA-editing balance, mainly caused by differential expression patterns of ADAR1 and ADAR2 (Chan et al. 2014). In HCC, ADA2 mediates the editing of

complementary antisense transcripts as a mechanism regulating the biosynthesis of specific microRNAs (Yang et al. 2006; Liu et al. 2013).

Interspersed Nuclear Elements/ Transposable Elements/Endogenous Retrotransposons in Liver Cancer

Retroposons or transposable elements comprise about 44 % of the human genome (Cordaux and Batzer 2009). Active retroelements come in three classes and can induce mutations. They comprise long interspersed elements (LINEs; around 500,000 copies), short interspersed elements (SINEs; approximately 1.5 million copies), and SVAs (SINE-R, VNTR, Alus; around 3,000 copies). LINE-1 retrotransposons (6.4 kb long) represent mobile genetic elements that account for up to 21 % of the human genome (Adams et al. 1980). LINE-1 retrotransposons have two open reading frames that encode proteins that act in retrotransposition, i.e., a ribonucleoprotein p40 and a reverse transcriptase. These two proteins operate in the "copy and paste" mechanism to generate a new DNA template for further retrotransposition (review: Rahrmann and Largaespada 2013). Novel LINE-1 insertions can change gene functions and by this induce pathological genome expression patterns associated with carcinogenesis. Altered gene expression is linked to the generation, during retrotransposition, of two single-strand breaks that may create the potential for double-strand break, translocations, deletions, or recombinations. Part of endogenous LINE-type retrotransposons are silenced by epigenetic promoter methylation, but active (non-silenced) LINEs have been observed in several normal cell lineages and in cancer cells. LINE-1 alterations (germline retrotransposition events) are involved in HCC and are associated with altered expression of tumor suppressors (Rahrmann and Largaespada 2013; Shukla et al. 2013). Hypomethylation of LINE-1 was detected in a majority of HCCs, but not in nonneoplastic liver tissue (Takai et al. 2000). Epigenetic hypomethylation of LINE-1 in HCC is associated with poor prognosis through activation of c-Met (Zhu et al. 2014a).

References

Acun T, Oztas E, Yagci T, Yakicier MC (2011) SIP1 is downregulated in hepatocellular carcinoma by promoter hypermethylation. BMC Cancer 11:223

Adams JW, Kaufman RE, Kretschmer PJ, Harrison M, Nienhuis AW (1980) A family of long reiterated DNA sequences, one copy of which is next to the human beta globin gene. Nucl Acids Res 8:6113

Athanasiadis A, Rich A, Maas S (2004) Widespread A-to-I RNA editing of Alu-containing mRNAs in the human transcriptome. PLoS Biol 2:e391

Au SL, Wong CC, Lee JM, Fan DN, Tsang FH, Ng IO, Wong CM (2012) Enhancer of zeste homolog 2 epigenetically silences multiple tumor suppressor microRNAs to promote liver cancer metastasis. Hepatology 56:622–631

Au SL, Ng IO, Wong CM (2013) Epigenetic dysregulation in hepatocellular carcinoma: focus on polycomb group proteins. Front Med 7:231–241

Bae HJ, Noh JH, Kim JK, Eun JW, Jung KH, Kim MG, Chang YG, Shen Q, Kim SJ et al (2014) MicroRNA-29c functions as a tumor suppressor by direct targeting oncogenic SIRT1 in hepatocellular carcinoma. Oncogene 33:2557–2567

Bao L, Yan Y, Xu C, Ji W, Shen S, Xu G, Zeng Y, Sun B, Qian H, Chen L, Wu M et al (2013) MicroRNA-21 suppresses PTEN and hSulf-1 expression and promotes hepatocellular carcinoma progression through AKT/ERK pathways. Cancer Lett 337:226–236

Bao L, Zhao J, Dai X, Wang Y, Ma R, Su Y, Cui H, Niu J, Bai S, Xiao Z, Yuan H et al (2014) Correlation between miR-23a and onset of hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 38:318–330

Cai MY, Hou JH, Rao HL, Luo RZ, Li M, Pei YQ, Lin MC, Guan XY, Kung HF, Zeng YX, Xie D (2011a) High expression of H3K27me3 in human hepatocellular carcinomas correlates closely with vascular invasion and predicts worse prognosis in patients. Mol Med 17:12–20

Cai MY, Tong ZT, Zheng F, Liao YJ, Wang Y, Rao HL, Chen YC, Wu QL, Liu YH, Guan XY, Lin MC, Zeng YX et al (2011b) EZH2 protein: a promising immunomarker for the detection of hepatocellular carcinomas in liver needle biopsies. Gut 60:967–976

Chan TH, Lin CH, Qi L, Fei J, Li Y, Yong KJ, Liu M, Song Y, Chow RK, Ng VH, Yuan YF, Tenen DG, Guan XY et al (2014) A disrupted RNA editing balance mediated by ADARs (Adenosine DeAminases that act on RNA) in human hepatocellular carcinoma. Gut 63:832–843

Cheng AS, Lau SS, Chen Y, Kondo Y, Li MS, Feng H, Ching AK, Cheung KF, Wong HK, Tong JH, Jin H, Choy KW et al (2011) EZH2-mediated concordant repression of Wnt antagonists promotes β-catenin-dependent hepatocarcinogenesis. Cancer Res 71:4028–4039

Cordaux R, Batzer MA (2009) The impact of retrotransposons on human genome evolution. Nat Rev Genet 10:691–703

D'Anzeo M, Faloppi L, Scartozzi M, Giampieri R, Bianconi M, Del Prete M, Silvestris N et al (2014) The role of micro-RNAs in hepatocellular carcinoma: from molecular biology to treatment. Molecules 19:6393–6406

Damania P, Sen B, Dar SB, Kumar S, Kumari A, Gupta E, Sarin SK, Venugopal SK (2014) Hepatitis B virus induces cell proliferation via HBx-induced microRNA-21 in hepatocellular carcinoma by targeting programmed cell death protein4 (PDCD4) and phosphatase and tensin homologue (PTEN). PLoS One 9:e91745

Deng G, Sui G (2013) Noncoding RNA in oncogenesis: a new era of identifying key players. Int J Mol Sci 14:18319–18349

Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D et al (2012) The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evaluation, and expression. Genome Res 22:1775–1789

Dominissini D, Moshitch-Moshkovitz S, Amariglio N, Rechavi G (2011) Adenosine-to-inosine RNA editing meets cancer. Carcinogenesis 32:1569–1577

Dong Y, Wang A (2014) Aberrant DNA methylation in hepatocellular carcinoma tumor suppression (review). Oncol Lett 8:963–968

ElHefnawi M, Soliman B, Abu-Shahba N, Amer M (2013) An integrative meta-analysis of microRNAs in hepatocellular carcinoma. Genomics Proteomics Bioinformatics 11:354–367

Fang QL, Yin YR, Xie CR, Zhang S, Zhao WX, Pan C, Wang XM, Yin ZY (2015) Mechanistic and biological significance of DNA methyltransferase 1 upregulated by growth factors in human hepatocellular carcinoma. Int J Oncol 46:782–790

Gailhouste L, Ochiya T (2013) Cancer-related microRNAs and their role as tumor suppressors and oncogenes in hepatocellular carcinoma. Histol Histopathol 28:437–451

Gao et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24916103

George CX, John L, Samuel CE (2014) An RNA editor, adenosine deaminase acting on double-stranded RNA (ADAR1). J Interferon Cytokine Res 34:437–446

Giordano S, Columbano A (2013) MicroRNAs: new tools for diagnosis, prognosis, and therapy in hepatocellular carcinoma? Hepatology 57:840–847

Gong J, He XX, Tian A (2015) Emerging role of microRNA in hepatocellular carcinoma (review). Oncol Lett 9:1027–1033

Gramantieri L, Fornari F, Callegari E, Sabbioni S, Lanza G, Croce CM, Bolondi L, Negrini M (2008) MicroRNA involvement in hepatocellular carcinoma. J Cell Mol Med 12:2189–2204

Greene CM, Varley RB, Lawless MW (2013) MicroRNAs and liver cancer associated with iron overload: therapeutic targets unraveled. World J Gastroenterol 19:5212–5226

Gupta P, Cairns MJ, Saksena NK (2014) Regulation of gene expression by microRNA in HCV infection and HCV-mediated hepatocellular carcinoma. Virol J 11:64

Havens MA, Reich AA, Duelli DM, Hastings ML (2012) Biogenesis of mammalian microRNAs by a non-canonical processing pathway. Nucleic Acids Res 40:4626–4640

He C, Xu J, Zhang J, Xie D, Ye H, Xiao Z, Cai M, Xu K, Zeng Y, Li H, Wang J (2012) High expression of trimethylated histone H3 lysine 4 is associated with poor prognosis in hepatocellular carcinoma. Hum Pathol 43:1425–1435

He Y, Cui Y, Xu B, Gu J, Wang W, Luo X (2014a) Hypermethylation leads to bone morphogenetic protein 6 downregulation in hepatocellular carcinoma. PLoS One 9:e87994

He Y, Meng XM, Huang C, Wu BM, Zhang L, Lv XW, Li J (2014b) Long noncoding RNAs: novel insights into hepatocellular carcinoma. Cancer Lett 344:20–27

He XX, Kuang SZ, Liao JZ, Xu CR, Chang Y, Wu YL, Gong J, Tian DA, Guo AY, Lin JS (2015) The regulation of microRNA expression by DNA methylation in hepatocellular carcinoma. Mol Biosyst 11:532–539

Herceg Z, Paliwal A (2011) Epigenetic mechanisms in hepatocellular carcinoma: how environmental factors influence the epigenome. Mutat Res 727:55–61

Hernandez-Vargas H, Lambert MP, Le Calvez-Kelm F, Gouysse G, McKay-Chopin S, Tavtigian SV, Scoazec J-Y et al (2010) Hepatocellular carcinoma displays distinct DANN methylation signatures with potential as clinical predictors. PLoS One 5:e9749

Hou W, Bonkovsky HL (2013) Non-coding RNAs in hepatitis C-induced hepatocellular carcinoma: dysregulation and implications for early detection, diagnosis and therapy. World J Gastroenterol 19:7836–7845

Hsu LS, Lee HC, Chau GY, Yin PH, Chi CW, Lui WY (2006) Aberrant methylation of EDNRB and p16 genes in hepatocellular carcinoma (HCC) in Taiwan. Oncol Rep 15:507–511

Hu W, Alvarez-Dominguez JR, Lodish HF (2012) Regulation of mammalian cell differentiation by long non-coding RNAs. EMBO Rep 13:971–983

Huang JF, Guo YJ, Zhao CX, Yuan SX, Wang Y, Tang GN, Zhou WP, Sun SH (2013) Hepatitis B virus X protein (HBx)-related long noncoding RNA (lncRNA) down-regulated expression by Hbx (Dreh) inhibits hepatocellular carcinoma metastasis by targeting the intermediate filament protein vimentin. Hepatology 57:1882–1892

Huang JL, Zheng L, Hu YW, Wang Q (2014) Characteristics of long non-coding RNA and its relation to hepatocellular carcinoma. Carcinogenesis 35:507–514

Hung SY, Lin HH, Yeh KT, Chang JG (2014a) Histone-modifying genes as biomarkers in hepatocellular carcinoma. Int J Clin Exp Pathol 7:2496–2507

Hung CH, Chiu YC, Chen CH, Hu TH (2014b) MicroRNAs in hepatocellular carcinoma: carcinogenesis, progression, and therapeutic target. Biomed Res Int 2014:486407

Ji J, Wang XW (2009) New kids on the block: diagnostic and prognostic microRNAs in hepatocellular carcinoma. Cancer Biol Ther 8:1686–1693

Kang L, Liu X, Gong Z, Zheng H, Wang J, Li Y, Yang H, Hardwick J, Dai H, Poon RT, Lee NP, Mao M, Peng Z et al (2015) Genome-wide identification of RNA editing hepatocellular carcinoma. Genomics 105:76–82

Khare S, Zhang Q, Ibdah JA (2013) Epigenetics of hepatocellular carcinoma: role of microRNA. World J Gastroenterol 19:5439–5445

Koturbash I, Zemp FJ, Pogribny I, Kovalchuk O (2011) Small molecules with big effects: the role of the microRNAome in cancer and carcinogenesis. Mutat Res 722:94–105

Kou JT, Fan H, Han D, Li L, Li P, Zhu J, Ma J, Zhang ZH, He Q (2014) Association between four common microRNA polymorphisms and the risk of hepatocellular carcinoma and HBV infection. Oncol Lett 8:1255–1260

Kumar A (2011) MicroRNA in HCV infection and liver cancer. Biochim Biophys Acta 1809:694–699

Kuo KK, Jian SF, Li YJ, Wan SW, Weng CC, Fang K, Wu DC, Cheng KH (2014) Epigenetic inactivation of TGFβ1 target gene HEYL, a novel tumor suppressor, is involved in the P53 induced apoptotic pathway in hepatocellular carcinoma. Hepatol Res. doi:10.1111/hepr.12414

Li Y, Chen L, Chan TH, Guan XY (2013) Hepatocellular carcinoma: transcriptome diversity regulated by RNA editing. Int J Biochem Cell Biol 45:1843–1848

Lin YW, Chen HM, Fang JY (2011) Gene silencing by the Polycomb group proteins and association with cancer. Cancer Invest 29:187–195

Lin YW, Shih YL, Lien GS, Suk FM, Hsieh CB, Yan MD (2014) Promoter methylation of SFRP3 is frequent in hepatocellular carcinoma. Dis Markers 2014:351863

Liu C, Yu J, Yu S, Lavker RM, Cai L, Liu W, Yang K, He X, Chen S (2010) MicroRNA-21 acts as an oncomir through multiple targets in human hepatocellular carcinoma. J Hepatol 53:98–107

Liu WR, Shi YH, Peng YF, Fan J (2012) Epigenetics of hepatocellular carcinoma: a new horizon. Chin Med J 125:2349–2360

Liu WH, Chen CH, Yeh KH, Li CL, Wu YJ, Chen DS, Chen PJ, Yeh SH (2013) ADAR2-mediated editing of miR-214 and miR-122 precursor and antisense RNA transcripts in liver cancers. PLoS One 8:e81922

Liu M, Jiang L, Guan XY (2014a) The genetic and epigenetic alterations in human hepatocellular carcinoma: a recent update. Protein Cell 5:673–691

Liu WT, Lu X, Tang GH, Ren JJ, Liao WJ, Ge PL, Huang JF (2014b) LncRNAs expression signatures of hepatocellular carcinoma revealed by microarray. World J Gastroenterol 20:6314–6321

Long XR, He Y, Huang C, Li J (2014) MicroRNA-148a is silenced by hypermethylation and interacts with DNA methyltransferase 1 in hepatocellular carcinogenesis. Int J Oncol 44:1915–1922

Magerl C, Ellinger J, Braunschweig T, Kremmer E, Koch LK, Höller T, Büttner R, Lüscher B, Gütgemann I (2010) H3K4 dimethylation in hepatocellular carcinoma is rare compared with other hepatobiliary and gastrointestinal carcinomas and correlates with expression of the methylase Ash2 and the demethylase LSD1. Hum Pathol 41:181–189

Mah WC, Lee CGL (2014) DNA methylation: potential biomarker in hepatocellular carcinoma. Biomarker Res 2:5

Murray BS, Choe SE, Woods M, Ryan TE, Liu W (2010) An in silico analysis of microRNAs: mining the microRNAome. Mol Biosyst 6:1853–1862

Nassirpour R, Mehta PP, Yin MJ (2013) miR-122 regulates tumorigenesis in hepatocellular carcinoma by targeting AKT3. PLoS One 8:e79655

Nishida N, Nishimura T, Nakai T, Chishina H, Arizumi T, Takita M, Kitai S, Yada N, Hagiwara S, Inoue T, Minami Y et al (2014) Genome-wide profiling of DNA methylation and tumor progression in human hepatocellular carcinoma. Dig Dis 32:658–663

Pan YF, Qin T, Feng L, Yu ZJ (2013) Expression profile of altered long non-coding RNAs in patients with HBV-associated hepatocellular carcinoma. J Huazhong Univ Sci Technolog Med Sci 33:96–101

Panzitt K, Tschernatsch MM, Guelly C, Moustafa T, Stradner M, Strohmaier HM, Buck CR et al (2007) Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, a noncoding RNA. Gastroenterology 132:330–342

Park IY, Sohn BH, Yu E, Suh DJ, Chung YH, Lee JH, Surzycki SJ, Lee YI (2007) Aberrant epigenetic modifications in hepatocarcinogenesis induced by hepatitis B virus X protein. Gastroenterology 132:1476–1494

Paz N, Levanon EY, Amariglio N, Heimberger AB, Ram Z, Constantini S, Barbash ZS, Adamsky K, Safran M, Hirschberg A et al (2007) Altered adenosine-to-inosine RNA editing in human cancer. Genome Res 17:1586–1595

Piunti A, Pasini D (2011) Epigenetic factors in cancer development: polycomb group proteins. Future Oncol 7:57–75

Qi L, Chan TH, Tenen DG, Chen L (2014) RNA editome imbalance in hepatocellular carcinoma. Cancer Res 74:1301–1306

Qin Y, Liu JY, Li B, Sun ZL, Sun ZF (2004) Association of low p16INK4a and p15INK4b mRNAs expression with their CpG islands methylation with human hepatocellular carcinogenesis. World J Gastroenterol 10:1276–1280

Qiu MT, Hu JW, Yin R, Xu L (2013) Long noncoding RNA: an emerging paradigm of cancer research. Tumour Biol 34:613–620

Raggi C, Invernizzi P (2013) Methylation and liver cancer. Clin Res Hepatol Gastroenterol 37:564–571

Raggi C et al (2014) Epigenetic reprogramming modulates malignant properties of liver cancer. Hepatology 59:2251–2262

Rahrmann EP, Largaespada DA (2013) Retrotransposons: a new and credible source of inherited and somatically acquired hepatocellular carcinoma mutations. J Hepatol 59:616–617

Rinn JL, Chang HY (2012) Genome regulation by long noncoding RNAs. Annu Rev Biochem 81:145–166

Roncalli M, Bianchi P, Bruni B, Laghi L, Destro A, Di Gioia S, Gennari L, Tommasini M, Malesci A, Coggi G (2002) Methylation framework of cell cycle gene inhibitors in cirrhosis and associated hepatocellular carcinoma. Hepatology 36:427–432

Ruby JG, Jan CH, Bartel DP (2007) Intronic microRNA precursors that bypass Drosha processing. Nature 448:83–86

Saito Y, Hibino S, Saito H (2014) Alterations of epigenetics and microRNA in hepatocellular carcinoma. Hepatol Res 44:31–42

Satoh J, Tabunoki H (2011) Comprehensive analysis of human microRNA target networks. BioData Min 4:17

Schagdarsurengin U, Wilkens L, Steinmann D, Flemming P, Kreipe HH, Pfeifer GP et al (2003) Frequent epigenetic inactivation of the RASSF1A gene in hepatocellular carcinoma. Oncogene 22: 1866–1871

Schaub M, Keller W (2002) RNA editing by adenosine deaminases generates RNA and protein diversity. Biochimie 84:791–803

Shen J, Wang S, Zhang YJ, Kappil M, Wu HC, Kibirya MG, Wang Q, Jasmine F, Ahsan H, Lee PH, Yu MW, Chen CJ et al (2012) Genome-wide DNA methylation profiles in hepatocellular carcinoma. Hepatology 55:1799–1808

Shi X, Sun M, Liu H, Yao Y, Song Y (2013) Long non-coding RNAs: a new frontier in the study of human diseases. Cancer Lett 339:159–166

Shigehara K, Yokomuro S, Ishibashi O, Mizuguchi Y, Arima Y, Kawahigashi Y, Kanda T et al (2011) Real-time PCR-based analysis of the human bile microRNAome identifies miR-9 as a potential diagnostic biomarker for biliary tract cancer. PLoS One 6: e23584

Shukla R, Upton KR, Muñoz-Lopez M, Gerhardt DJ, Fisher ME, Nguyen T, Brennan PM et al (2013) Endogenous retrotransposition activates oncogenic pathways in hepatocellular carcinoma. Cell 153:101–111

Simon JA, Lange CA (2008) Roles of the EZH2 histone methyltransferase in cancer epigenetics. Mutat Res 647:21–29

Song MA, Tiirikainen M, Kwee S, Okimoto G, Yu H, Wong LL (2013) Elucidating the landscape of aberrant DNA methylation in hepatocellular carcinoma. PLoS One 8:e55761

Studach LL, Wang WH, Weber G, Tang J, Hulliner RL, Malbrue R, Liu X, Andrisani O (2010) Polo-like kinase 1 activated by the hepatitis B virus X protein attenuates both the DNA damage checkpoint and DANN repair in partial polyploidy. J Biol Chem 285:30282–30293

Studach LL, Menne S, Cairo S, Buendia MA, Hullinger RL, Lefrançois L, Merle P, Adrisani OM (2012) Subset of Suz1/PRC2 target genes is activated during hepatitis B virus replication and liver carcinogenesis associated with HBV X protein. Hepatology 56:1240–1251

Sudo T, Utsunomiya T, Mimori K, Nagahara H, Ogawa K, Inue H, Wakiyama S, Fujita H, Shirouzu K, Mori M (2005) Clinicopathological significance of EZH2 mRNA expression in patients with hepatocellular carcinoma. Br J Cancer 92:1754–1758

Sun J, Lu H, Wang X, Jin H (2013a) MicroRNAs in hepatocellular carcinoma: regulation, function, and clinical implications. Sci World J 2013:924206

Sun X, He Y, Huang C, Ma TT, Li J (2013b) Distinctive microRNA signature associated of neoplasms with the Wnt/β-catenin signaling pathway. Cell Signal 25:2805–2811

Takahashi K, Yan I, Haga H, Patel T (2014) Long noncoding RNA in liver diseases. Hepatology 60:744–753

Takai D, Yagi Y, Habib N, Sugimura T, Ushijima T (2000) Hypomethylation of LINe1 retrotransposon in human hepatocellular carcinomas, but not in surrounding liver cirrhosis. Jpn J Clin Oncol 30:306–309

Tan W, Li Y, Lim SG, Tan TM (2014) miR-106b-25/miR-17-92 clusters: polycistrons with oncogenic roles in hepatocellular carcinoma. World J Gastroenterol 20:5962–5972

Tang J, Tao ZH, Wen D, Wan JL, Liu DL, Zhang S, Cui JF, Sun HC, Wang L, Zhou J et al (2014) MiR-612 suppresses the stemness of liver cancer via Wnt/β-catenin signaling. Biochem Biophys Res Commun 447:210–215

Vilar E, Tabernero J, Gruber SB (2011) Micromanaging the classification of colon cancer: the role of the microRNAome. Clin Cancer Res 17:7207–7209

Villanueva A, Portela A, Sayols S, Battiston C, Hishida Y, Mendez-Gonzalez J, Imbeaud S, Letouzé E, Hernandez-Gea V et al (2015) DNA methylation-based prognosis and epidrivers in hepatocellular carcinoma. Hepatology. doi:10.1002/hep.27732

Wang Z, Li X (2013) The role of noncoding RNA in hepatocellular carcinoma. Gland Surg 2:25–29

Wang WH, Studach LL, Andrisani OM (2011) ZNF198 and SUZ12 are down-regulated in hepatitis B virus (HBV) X protein-mediated hepatocyte transformation and in HBV replication. Hepatology 53:1137–1147

Wang K, Lim HY, Shi S, Lee J, Deng S, Xie T, Zhu Z, Wang Y, Pocalyko D, Yang WJ et al (2013) Genomic landscape of copy number aberrations enables the identification of oncogenic drivers in hepatocellular carcinoma. Hepatology 58:706–717

Wang YY, Jiang JX, Ma H, Han J, Sun ZY, Liu ZM, Xu ZG (2014a) Role of ZIC1 methylation in hepatocellular carcinoma and its clinical significance. Tumour Biol 35:7429–7433

Wang L, Zhang X, Jia LT, Hu SJ, Zhao J, Yang JD, Wen WH, Wang Z, Wang T et al (2014b) c-Myc-mediated epigenetic silencing of MicroRNA-101 contributes to dysregulation of multiple pathways in hepatocellular carcinoma. Hepatology 59:1850–1863

Weihrauch M, Benicke M, Lehnert G, Wittekind C, Wrbitzky R, Tannapfel A (2001) Frequent k-ras -2 mutations and p16(INK4A) methylation in hepatocellular carcinomas in workers exposed to vinyl chloride. Br J Cancer 84:982–989

Westholm JQ, Lai EC (2011) Mirtrons: microRNA biogenesis via splicing. Biochimie 93:1897–1904

Xiao ZD, Jiao CY, Huang HT, He LJ, Zhao JJ, Lu ZY, Liu LX (2014) miR-218 modulate hepatocellular carcinoma cell proliferation through PTEN/AKT/PI3K pathway and HoxA10. Int J Clin Exp Pathol 7:4039–4044

Xu J, Zhu X, Wu L, Yang R, Yang Z, Wang Q, Wu F (2012) MicroRNA-122 suppresses cell proliferation and induces cell apoptosis in hepatocellular carcinoma by directly targeting Wnt/β-catenin pathway. Liver Int 32:752–760

Xu D, Yang F, Yuan JH, Zhang L, Bi HS, Zhou CC, Liu F, Wang F, Sun SH (2013) Long noncoding RNAs associated with liver regeneration 1 accelerates hepatocyte proliferation during liver regeneration by activating Wnt/β-catenin signaling. Hepatology 58:739–751

Xu B, Nie Y, Liu X, Feng S, Yang Z, Wang Z, Zheng Q, Luo X (2014) Quantitative analysis of APC promoter methylation in hepatocellular carcinoma and its prognostic implications. Oncol Lett 7:1683–1688

Yang W, Chendrimada TP, Wang Q, Higuchi M, Seeburg PH, Shiekhattar R, Nishikura K (2006) Modulation of microRNA processing and expression through RNA editing by ADAR deaminases. Nat Struct Mol Biol 13:13–21

Yang X, Zhang XF, Lu X, Jia HL, Liang L, Dong QZ, Ye QH, Qin LX (2014a) MicroRNA-26a suppresses angiogenesis in human hepatocellular carcinoma by targeting hepatocyte growth factor-cMet pathway. Hepatology 59:1874–1885

Yang Y, Ye Z, Xiao G, Luo G, Yang H (2014b) Clinicopathological significance of RUNX3 gene hypermethylation in hepatocellular carcinoma. Tumour Biol 35:10333–10340

Yeh TS, Wang F, Chen TC, Yeh CN, Yu MC, Jan YY, Chen MF (2014) Expression profile of microRNA-200 family in hepatocellular carcinoma with bile duct tumor thrombus. Ann Surg 259:346–354

Yu J, Ni M, Zhang H, Gao B, Gu J, Chen J, Zhang L, Wu M, Zhen S, Zhu J (2002) Methylation profiling of twenty promoter-CpG islands of genes which may contribute to hepatocellular carcinogenesis. BMC Cancer 2:29

Yu G, Bing Y, Li W, Xia L, Liu Z (2014) Hepatitis B virus inhibits the expression of CD82 through hypermethylation of its promoter in hepatoma cells. Mol Med Rep 10:2580–2586

Yuan K, Lian Z, Sun R, Clayton MM, Ng IO, Feitelson MA (2012) Role of miR-148a in hepatitis B associated hepatocellular carcinoma. PLoS One 7:e35331

Yunqiao L, Vanke H, Jun X, Tangmeng G (2014) MicroRNA-206, down-regulated in hepatocellular carcinoma, suppresses cell proliferation and promotes apoptosis. Hepatogastroenterology 61:1302–1307

Zang JJ, Xie F, Xu JF, Qin YY, Shen RX, Yang JM, He J (2011) P16 gene hypermethylation and hepatocellular carcinoma: a systematic review and meta-analysis. World J Gastroenterol 17:3043–3048

Zhang YJ, Ahsan H, Chen Y, Lunn RM, Wang LY, Chen SY, Lee PH, Chen CJ, Santella RM (2002) High frequency of promoter hypermethylation of RASSF1A and p16 and its relationship to aflatoxin B1-DNA adduct levels in human hepatocellular carcinoma. Mol Carcinog 35:85–92

Zhang C, Li H, Wang Y, Liu W, Zhang Q, Zhang T, Zhang X, Han B, Zhou G (2010) Epigenetic inactivation of the tumor suppressor gene RIZ1 in hepatocellular carcinoma involves both DNA methylation and histone modifications. J Hepatol 53: 889–895

Zhang L, Yang L, Liu X, Chen W, Chang L, Chen L, Loera S, Chu P, Huang WC et al (2013a) MicroRNA-657 promotes tumorigenesis in hepatocellular carcinoma by targeting transducin-like enhancer protein 1 through nuclear factor kappa B pathways. Hepatology 57:1919–1930

Zhang X, Wang J, Cheng J, Ding S, Li M, Sun S, Zhang L, Liu S, Chen X, Zhuang H, Lu F (2013b) A integrated analysis of SOCS1 down-regulation in HBV infection-related hepatocellular carcinoma. J Viral Hepat. doi:10.1111/jvh.12137

Zhang JP, Zeng C, Xu L, Gong J, Fang JH, Zhuang SM (2014) MicroRNA-148a suppresses the epithelial-mesenchymal transition and metastasis of hepatoma cells by targeting Met/Snail signaling. Oncogene 33:4069–4076

Zhao J, Greene CM, Gray SG, Lawless MW (2014) Long noncoding RNAs in liver cancer: what we know in 2014. Expert Opin Ther Targets 22:1–12

Zhu J (2006) DNA methylation and hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 13:265–273

Zhu YZ, Zhu R, Shi LG, Mao Y, Zheng GJ, Chen Q, Zhu HG (2010) Hepatitis B virus X protein promotes hypermethylation of p16(INK4A) promoter through upregulation of DNA methyltransferases in hepatocarcinogenesis. Exp Mol Pathol 89:268–275

Zhu H, Wu K, Yan W, Hu L, Yuan J, Dong Y, Li Y, Jing K, Yang Y, Guo M (2013) Epigenetic silencing of DACH1 induces loss of transforming growth factor-β1 antiproliferative response in human hepatocellular carcinoma. Hepatology 58:2012–2022

Zhu C, Utsunomiya T, Ikemoto T, Yamada S, Morine Y, Imura S, Arakawa Y, Takasu C et al (2014a) Hypomethylation of long interspersed nuclear element-1 (LINE-1) is associated with poor prognosis via activation of c-Met in hepatocellular carcinoma. Ann Surg Oncol 21(suppl 4):S729–S735

Zhu J, Liu S, Ye F, Shen Y, Tie Y, Zhu J, Jin Y, Zheng X, Wu Y, Fu H (2014b) The long noncoding RNA expression profile of hepatocellular carcinoma identified by microarray analysis. PLoS One 9:e101707

Part XXXII

General Pathology of Hepatobiliary Tumors: Structural and Functional Changes of Nuclei

Nucleus, Nuclear Structure, and Nuclear Functional Changes in Liver Cancer

169

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_169

Abstract

Cancers, including those of the hepatobiliary tract, display a wide variety of cellular and nuclear abnormalities that reflect the fundamental biologic disorder, characterizing malignancies. Part of nuclear abnormalities are important for cancer diagnosis and are generally summarized under the term nuclear atypia. The spectrum of nuclear abnormalities in cancer, and the associated mechanisms, is however highly complex. The major forms of nuclear and cellular abnormalities in cancer cells include pleomorphic, anisokaryosis, anaplasia, micronuclei, hyperchromasia, coarse chromatin patterns, chromatin bridges, macronucleoli, irregular nuclear membranes, and abnormal mitotic figures. Generally, the severity of chromatin abnormalities used in histologic and cytologic diagnosis, such as hyperchromasia, coarse chromatin, and changes in nuclear size and shape, depends on the dedifferentiation of cancer cells, the changes gradually increasing in malignancies of higher grade. There are direct causal links between the fundamental derangement of high-order chromatin organization that occurs in and characterizes cancers and the diagnostically important patterns of altered nuclear morphology.

General Aspects of Cancer Cell Morphology

Cellular and Nuclear Abnormalities of Cancer Cells

Cancers, including those of the hepatobiliary tract, show a wide variety of cellular and nuclear abnormalities that reflect the severe biologic disorder characterizing cancer and are useful for diagnosis (Klebs 1889; von Hansemann 1897; Willis 1948; Cameron 1952; Rather 1978; Cohen et al. 1991; Bignold 2003; Bignold 2004; Wee and Nilsson 2003; Bignold et al. 2006b; Rynearson and Sussman 2011). Part of the abnormalities visualized in tissue sections or cytologic smears are described by distinct terms (Table 1).

Pleomorphism, Nuclear Size, and Nuclear Shape

Pleomorphism relates to marked overall changes of the cell body and its cytoplasm and alterations in shape, size, and chromatin pattern of nuclei in cancer cells and usually reflects a mutator phenotype of carcinogenesis (Bignold 2003; Zink et al. 2004). Typical alterations of nuclear in cancer cells comprise malleable nuclei with crush artifacts, grooves, clefts, polylobulation, indentations, folds, and undulations (Figs. 1, 2, 3, 4, 5, 6, and 7).

Apart from frequent and general changes in chromatin structure (Table 1), chromatin changes comprise asymmetric aggregates of heterochromatin, dispersed heterochromatin, and loss of heterochromatin aggregates (Zink et al. 2004). The mechanisms governing nuclear size and shape are still not well elucidated. There is evidence that the control of nuclear size and nuclear shape is coupled in a complex manner (Walters et al. 2012; Jevtic et al. 2014). Nuclear shape, which undergoes dramatic changes in cancer cells, is strongly regulated by the nuclear envelope and its connections with both the cytoskeleton and chromatin. The nuclear envelope can undergo several types of characteristic alterations in cancer cells. In malignant neoplastic cells with genetically stable, near-diploid background, the nuclear envelope can show intranuclear invaginations that contain cytoplasm and are manifest as so-called intranuclear inclusions. Also nuclear grooves found in certain neoplasms are thought to derive from nuclear lamina abnormalities. In genomically highly unstable tumors, severe shape anomalies of the nuclear envelope are more common (Fischer 2014). Cancer cells can show transient nuclear envelope rupturing during interphase, associated with the mislocalization of nucleoplasmic and cytoplasmic proteins and sometimes entrapment of cytoplasmic organelles in the nuclear space (nuclear invaginations;

Table 1 Terminology of cellular and nuclear abnormalities of cancer cells

Pleomorphism	Variable size and shape of cells and/or nuclei in cells of the same type
Anisokaryosis	Variation in nuclear size
Macrokaryosis	Increased nuclear size
Nuclear/cytoplasmic ratio	Increased N/C ratio of 1:2 or more suggests cancer
Anaplasia	Process leading to undifferentiation (von Hansemann definition)
Micronucleus	Small abnormal nucleus forming whenever a chromosome or chromosome fragment is not incorporated into one of daughter nuclei
Broken eggs	Small amounts of genetic material attached to the nucleus by a Feulgen-positive filament
Nuclear buds	Protrusions of nuclei formed from chromatin bridges
Nucleotesimals	Nuclear appendages connected with the nucleus by lamellar bridges
Atypical naked nuclei	HCC nuclei apparently devoid of cytoplasm in cytologic smears
Hyperchromasia	Increased basophilic staining of nuclear components due to a change in structure, density, and/or amount of chromatin
Coarse chromatin pattern	Ropy or cord-like chromatin pattern
Irregular chromatin distribution	Distribution of chromatin particles is different from normal cells of the same lineage (e.g., salt-and-pepper chromatin; irregular granular chromatin)
Chromatin bridge	Stringlike DNA matter connecting nuclei of two daughter cells. Telomeres of sister chromatids fuse and fail to segregate into daughter cells during anaphase (anaphase bridges). The bridge may be seen in the next interphase (interphase bridge)
Macronucleoli	Nucleoli increased in size (diameter of more than 5 μm)
Anisonucleoliosis	Variation in nucleolar shape or size (also within the same nucleus)
Angular nucleoli	Nucleoli have an angular shape or are fusiform, instead of being round or ovoid
Irregular nuclear membrane	Nuclear membrane is wrinkled or shows grooves, gaps, invaginations, or blebs

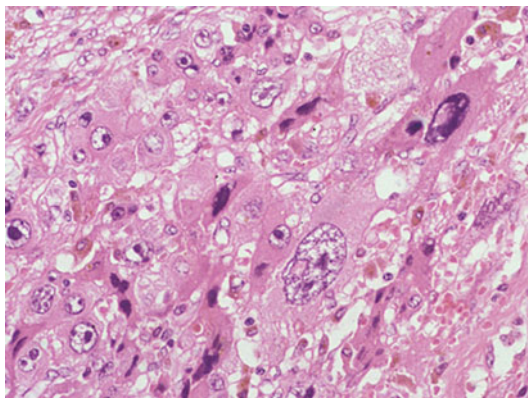

Fig. 1 Marked pleomorphism in a poorly differentiated hepatocellular carcinoma. One of the neoplastic cells shows a polyploid, massively enlarged nucleus; a second cell (to the *top* and *right*) exhibits hyperchromasia and irregular chromatin distribution (hematoxylin and eosin stain)

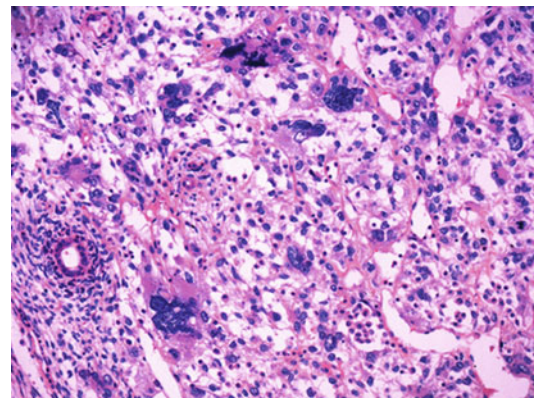

Fig. 2 Nuclear pleomorphism with formation of tumor giant cells (hematoxylin and eosin stain)

Figs. 8 and 9). Through the gaps produced by envelope rupture, chromatin particles can escape, resulting in micronucleus-like structures (Vargas et al. 2012).

Anaplasia

The concept of anaplasia found in malignancies has first been formulated by von Hansemann (1893). David Paul von Hansemann, a German pathologist (1858–1920) and assistant of Virchow

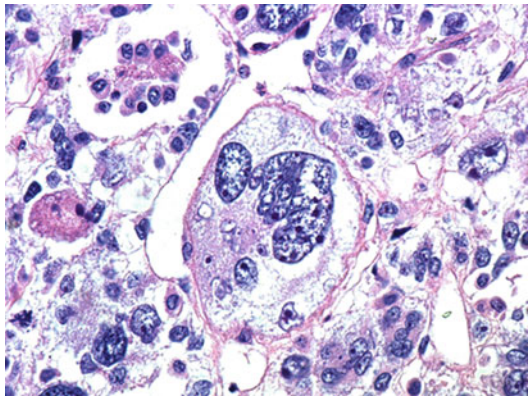

Fig. 3 Striking nuclear pleomorphism with a multilobulated polyploid giant nucleus and production of separate smaller nuclei following endomitosis (hematoxylin and eosin stain)

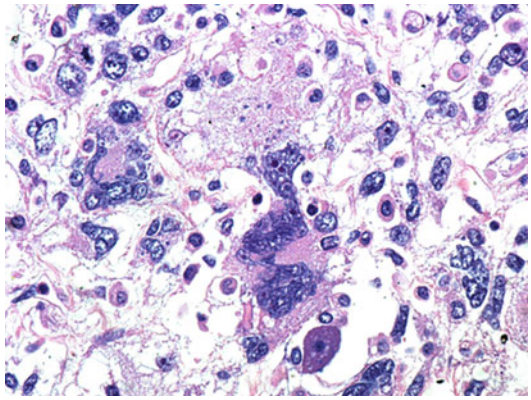

Fig. 4 Massive pleomorphism with incomplete cytokinesis of a tumor giant cell, resulting in a dumbbell-shaped cell, multinuclearity, and micronuclei (hematoxylin and eosin stain)

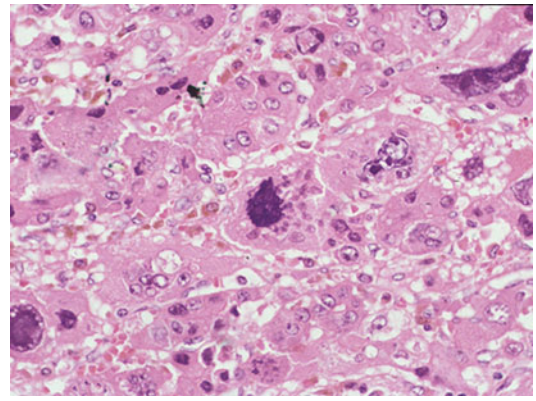

Fig. 5 Hepatocellular carcinoma with cellular and nuclear pleomorphism. A tumor giant cell in the center has an enlarged hyperchromatic nucleus which underwent karyopyknosis due to mitotic catastrophe. This cell displays several small nuclei following endomitosis (hematoxylin and eosin stain)

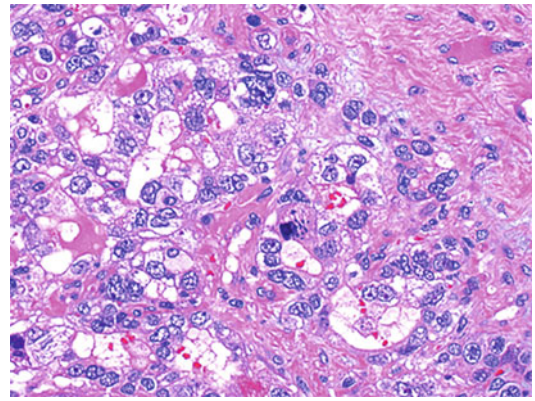

Fig. 6 Several tumor cells show strongly basophilic micronuclei (hematoxylin and eosin stain)

(Wagner 1999), is also known for the Hansemann cells, macrophages containing Michaelis-Gutmann bodies in malakoplakia. As reviewed by Whitman (1919), pleomorphism of cancer cells and the presence of atypical, irregular mitoses had been described before (e.g., Arnold 1880). Von Hansemann found, in a carcinoma of the larynx, hyperchromatism and large numbers of tripolar and multipolar mitotic figures, but also noted so-called hypochromatism caused by an actual reduction in total chromosome number in some cancer cells, in one case with a monaster having only nine chromosomes. Von Hansemann used his term hypochromatism exclusively for cells with a reduced chromosome number, whereas this term is now also employed in a less specific manner for situations with an apparently reduced amount of chromatin, diminished stainability of chromatin, or a loose chromatin structure. The investigator related these abnormalities to delayed chromosomal splitting, resulting in highly asymmetrical division with one daughter cell receiving a reduced chromosome set. Chromosomal splitting failure is supported by the observation that one daughter cell may contain an odd number of chromosomes (Von Hansemann

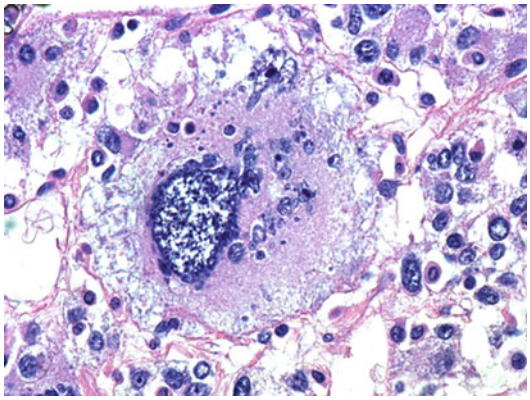

Fig. 7 Highly pleomorphic tumor giant cell with a polyploid nucleus, small separate nuclei, and several condensed micronuclei (hematoxylin and eosin stain)

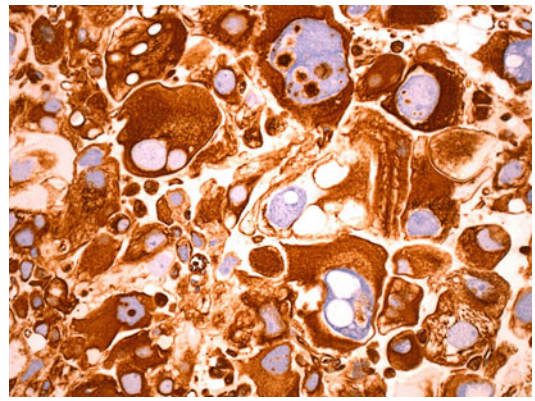

Fig. 9 In this cytokeratin stain, part of nuclear invaginations exhibit a brown reaction product which represents cytoskeletal components of cytoplasm invaginated into abnormal nuclei (cytokeratin immunostain)

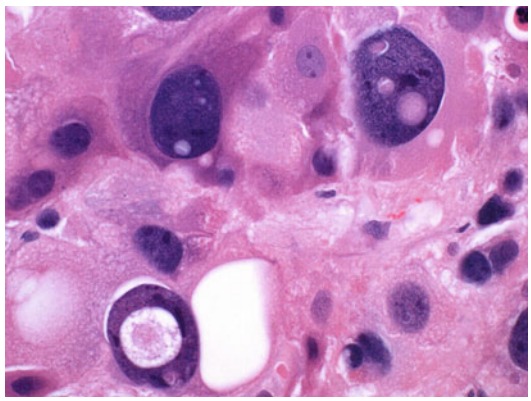

Fig. 8 Pleomorphic neoplasm with polyploid nuclei. Part of the nuclei show one to several so-called nuclear vacuoles, which in most cases are cytoplasmic invaginations caused by abnormal reassembly of nuclei and nuclear membranes (hematoxylin and eosin stain)

1890, 1891). Together with de Vries, von Hansemann believed that asymmetrical mitosis has a strong impact on cell fate due to a disordered distribution of chromosomal constituents that transmit properties of cells and termed pangenes or idioplasmae (now the genes). In 1914, Boveri speculated that malignant transformation and cancer were associated with these chromosomal abnormalities and are therefore credited with the first chromosomal theory of cancer, based on the observations of von Hansemann and others before him (Boveri 1914; Bignold et al. 2006a). The term anaplasia as formulated by von Hansemann is the mere process of disorder leading to undifferentiation and not the nuclear changes due to undifferentiation. This has led to some misunderstandings in the literature (Whitman 1919). Even today, the nuclear changes in undifferentiated cancer cells are called "anaplasia," although the term denotes aberrant growth.

In contrast to anaplasia, metaplasia is a form of cell lineage infidelity that can occur in normal, dysplastic and neoplastic cells and may be related to so-called embryonic reversion of cells. Based on the concept of histologic substitution, the term metaplasia was introduced by Virchow in 1870 (review: Bignold 2005). There is evidence that cancerogenic pathways can proceed through a phase of metaplasia, thus having a preneoplastic or premalignant status under certain conditions, but metaplastic changes found in neoplasms may also exist ab initio, as several tumors characteristically contain "foreign" cell lineages and pathways of differentiation as an inherent feature.

Micronuclei

A micronucleus is small and highly abnormal nucleus that is formed in cells with various types of DNA damage, such as ionizing radiation, genotoxic chemicals, or certain mutations. The

development of micronuclei in malignancies is associated with mutagenetic stresses and, in general, genomic instability (Iarmarcovai et al. 2006; Bolt et al. 2011; Fenech et al. 2011; Samanta and Dey 2012; Bhatia and Kumar 2014). Micronuclei are tiny basophilic spherical extranuclear objects that are seen to budd off daughter cells after mitosis. The bodies are often seen at light microscopy in the vicinity of a large nucleus. Micronuclei can contain non-incorporated chromosomes, chromosome fragments, or chromatids (Heddle et al. 1991; Norppa and Falck 2003). In solid tumors, more than 70 % of micronuclei contained material from unstable chromosomes (Gisselsson et al. 2001). Micronuclei typically show a massive collapse of nuclear membrane associated with irreversible loss of compartmentalization (Hatch et al. 2013). Micronuclei can themselves damage cells and are related to apoptosis (Utani et al. 2010), because micronuclear damaged DNA induces a defective cell cycle checkpoint arrest and DNA repair response (Terradas et al. 2010). Micronuclei are detectable in liver cancers and their precursor lesions (de Almeida et al. 2004). In the course of hepatocarcinogenesis, there is a stepwise increase in the number of micronuclei from normal hepatocytes to atypical cells to HCC cells. Micronuclei increase as a function of decreased differentiation of HCCs (Guido et al. 2008; Wen et al. 2013). An increased rate of micronuclei was found in human hepatoma cells transfected with the HBV HBX gene, suggesting that genomic instability with micronuclei can be driven by hepatocarcinogenic viral products (Livezey et al. 2002).

Micronuclei can form after mitosis from lagging chromatids or chromatin bridges between anaphase chromosomes and can persist for about one cell cycle. If cells containing micronuclei enter mitosis, they produce either daughter cells without micronuclei or, more often, cells with additional micronuclei (Utani et al. 2010). Chromosomal anaphase bridges are an important cause of micronuclei. Micronuclei that develop through this mechanisms have incomplete nuclear pore complexes, nuclear import defects, and a chromatin with greatly reduced transcriptional activity (Hoffelder et al. 2004). In addition, interphase nuclear budding is a chief mechanism for micronucleation, resulting in lamin B1-positive and lamin B1-negative micronuclei. Lamin B1-negative micronuclei located to cytoplasmic blebs are often connected with the nucleus by a thin chromatin stalk, whereby chromatin is extruded through lamina gaps (nuclear herniation, blister formation), suggesting that in micronucleogenesis cytoplasmic membrane blebbing and nuclear budding are coupled (Utani et al. 2011). The pathogenic role of nuclear blebs is supported by the finding that similar to micronuclei they frequently contain unstable chromosomes or parts of them (Gisselsson et al. 2001).

"Broken Eggs" and Nucleotesimals

Broken eggs (BE) are small amounts of genetic material attached to the main nucleus through a Feulgen-positive filament (da Silva et al. 2007). Similar to micronuclei, BE are sensitive markers of genotoxic damage and chromosomal instability. In comparison with normal hepatocytes, BE were significantly more frequent in precursor lesions, with a progressive increase from large regenerative nodules to dysplastic nodules and HCCs (Guido et al. 2008). There are other forms of nuclear fragmentation, resulting in abnormal paranuclear structures. In certain tumors, an amitotic process causes small nuclear appendages connected with the main nucleus via lamellar bridges. Such appendages were called nucleotesimals (Elias and Fong 1978).

Nuclear Morphology and Chromatin Structure in Liver Cancer

General Morphologic Features of Liver Cancer Nuclei

In hepatocellular carcinoma (HCC), alterations of nuclear size, shape, and structure strongly depend on the differentiation grade of these neoplasms. Well-differentiated (grade 1) HCCs display nuclei that resemble those of normal or regenerating

hepatocytes. In early tumors, nuclear anomalies may be minor ("minimum deviation carcinomas"), a phenomenon that causes diagnostic difficulties when assessing small liver nodules. In the course of decreasing differentiation and tumor progression, nuclei become larger and show hyperchromasia of peripheral parts, a more coarse chromatin pattern, and more variable shapes. The abnormal chromatin structure of HCC nuclei is clearly shown in ultrastructural studies (Theron and Mekel 1964; Ghadially and Parry 1966; Toker and Trevino 1966; Ruebner et al. 1967; Schaff et al. 1971; Horvath et al. 1972; Ma and Blackburn 1973). HCC nuclei can show an increase of the granular component (Hruban 1979). In some HCCs, intranuclear invaginations of cytoplasm can be found ("nuclear vacuoles"; Livni et al. 1977). Well-differentiated cholangiocarcinomas exhibit nuclei with a structure that is similar to that of normal cholangiocytes of medium-sized or large bile ducts, whereas moderately or poorly differentiated cancers show a broad array of marked nuclear anomalies similar to those of other adenocarcinomas. Morphologic abnormalities observable in liver cancers can be assessed quantitatively by means of morphometric methods or the determination of fractal dimensions (Kerenji et al. 2000).

Chromatin in Liver Cancer Cells

As outlined above, the often massive derangements occurring in the nuclei of cancer cells are reflected in alterations of chromatin structure and function. As a general rule, the magnitude of chromatin abnormalities, such as hyperchromasia, coarse chromatin, and the associated changes in nuclear shape and size, depends on the dedifferentiation of hepatic tumor cells, chromatin changes being usually minor in benign hepatocyte and cholangiocyte neoplasms and gradually increasing in malignancies of higher grades. In hepatocellular adenomas, the chromatin structure resembles that of normal hepatocytes, but nucleoli may be larger. In contrast, chromatin texture is coarser already in well-to-moderately differentiated HCCs and is highly abnormal in G3 or G4 lesions. In principle, chromatin structure and stainability deviate from those of hepatocytes as a function of higher liver cancer cell grade. Whereas an experienced eye may still recognize the hepatocyte-type nucleus in G1 and G2 HCCs, higher-grade neoplasms have atypical chromatin that may belong to any other poorly differentiated neoplasm, rendering diagnosis more and more difficult.

Part of genotoxic effects that change chromatin structure and function in cancer cells can be counteracted by several mechanisms, particularly the DNA damage response (DDR), a process that coordinately regulates DNA repair in conjunction with cell cycle progression. DDR requires sensing of chromatin injury and a machine that can decompact chromatin to have access to damaged components. This is brought about by posttranslational histone modifications affecting nucleosome accessibility and several ATP-dependent chromatin remodeling systems (Clapier and Cairns 2009; Luijsterburg and van Attikum 2011).

High-Order Chromatin Organization Determines Nuclear Structure, Size, and Shape

As many of the nuclear abnormalities that occur in cancer cells relate to abnormal configurations of chromatin, essential features of diverse forms of chromatin and their definitions are briefly presented. Chromatin is the entire ensemble of genomic DNA and numerous associated proteins (the chromatin proteome), consisting of a highly ordered and dynamic structure confined within the nucleus (review: van Steensel 2011). Basic structures of chromatin that form the building blocks for higher-level structures are the chromatin fiber (diameter of 10 nm; the previous 30 nm fiber is not a constant finding; Maeshima et al. 2014) and nucleosomes, of which about $3 \times 10(7)$ are present per human nucleus. The higher order of chromatin possesses several levels of organization. In the nucleus, chromosomes occupy distinct territories with preferred nuclear locations. There is evidence for a complex suprachromosomal order. Chromosome territories of the nucleus contain

open chromatin compartments having active genes, closed chromatin compartments comprising inactive genes, and interchromatin domain compartments that include complexes for the transcription, splicing, DNA replication, and repair machineries (Cremer et al. 2000). Each of these compartments has a distinct proteome of regulatory and enzymatic proteins. The chromatin proteome accounts for approximately 10 % of the cell's proteins. These proteins form complexes with DNA, RNA, and among themselves, forming an intricate chromatin interactome. To explain the complexity of chromatin self-organization and chromatin folding, models have been developed, e.g., the strings and binders switch model (Barbieri et al. 2012, 2013).

The composition, ordering, and remodeling of chromatin are well-studied features, but notwithstanding this knowledge, the relationships between chromatin and nuclear morphologies have not yet been fully elucidated (Zink et al. 2004; Reddy and Feinberg 2013). Chromatin is a highly dynamic matter regulated by chromatin factors and codes (Zhou and Troyanskaya 2014) and undergoing complex functional and structural changes in cancer cells, whereby cancer-associated chromosomal and genomic changes transcribe into alterations in chromatin structure (e.g., "coarse chromatin pattern"; Zhang et al. 2000). For gene positioning and expression, chromatin is arranged in a basic 30 nm fiber and loops, chromatin loops allowing a long-range physical contact between regulatory DNA sequences and transcribing genes (reviews: Dean 2011; Holwerda and de Laat 2012; Ghirlando and Felsenfeld 2013). Within transcriptional chromatin domains, genes to be transcribed are clustered in transcriptional units called "gene bodies," which are modified in their function via DNA methylation, also in liver cancers (Tischoff and Tannapfel 2008; reviews: Jones 2012; Huh et al. 2013).

Condensed Chromatin

Condensed chromatin is any kind of chromatin occurring in the form of dense particles irrespective of the cause of condensation. Chromatin condensation serves to pack the almost two meters of DNA and associated proteins into nucleosomes, chromatin domains, and chromosome territories, resulting in the high-order structure of chromatin (Grigoryev 2012; Hirano 2012a).

Euchromatin

Euchromatin is defined as a lightly packed chromatin abundant in gene concentration, often in state of active transcription. About 92 % of the human genome is euchromatic. Euchromatin possesses the typical string and nucleosomal pattern, has the 10 nm fibril as the basic structural unit, and appears as light-colored bands (low-compaction structure) in G band preparations, while heterochromatin stains dark. In mammalian cells, condensed euchromatin is detectable in tissue-specific pattern and is also called, "functional heterochromatin." Euchromatin is the active chromatin form engaged in the transcription of DNA into mRNA.

Heterochromatin

Heterochromatin is a chromatin form with tightly packed DNA and exists in two forms, constitutive and facultative heterochromatin. Heterochromatin was first defined by Emil Heitz in 1928 and was later found to predominantly localize to the nuclear periphery and around the nucleolus. Constitutive heterochromatin is repetitive and generates structural functions including telomeres and centromeres and acts as an attractor for expression and repression signals. It can mainly affect the function of genes in its vicinity (position-effect variegation). Heterochromatin plays a role in the maintenance of chromosome integrity (Fadloun et al. 2013). Facultative heterochromatin is not repetitive and may, under certain condition, lose its compact structure and become transcriptionally active. Peripheral heterochromatin provides a "protected area" for epigenetically silent genes and gene-poor DNA. This positioning of chromatin sub-compartments depends on lamina-associated and nucleolus-associated chromatin domains (LADs and NADs; Wu and Yao 2013;

Padeken and Heun 2014). A protein associated with the nuclear lamina, PRR14, participates in the tethering of heterochromatin to the inner nuclear membrane surface. PRR14 binds to anaphase chromosomes via HP1 and then mediates the association with nuclear lamina in telophase (Poleshko and Katz 2014). Heterochromatin in the proper sense denotes constitutive heterochromatin, i.e., a form of chromatin that is always condensed at interphase. The generation of heterochromatin as a dynamic platform strongly depends on histone modifications, specifically it requires epigenetic methylation of histone H3 and the subsequent recruitment of chromodomain proteins, including heterochromatin protein HP1 (Grewal and Jia 2007). HP1 binds lysine 9-methylated histone H3, a hallmark of heterochromatin (Nishibuchi and Nakayama 2014).

Crowded Chromatin

In contrast to organelles with their lipid membranes, intranuclear structures are not separated from each other by membranes but employ other ways for compartmentalization. The compaction mode of chromatin exerts a direct influence on the local crowding state of chromatin and has been suggested to play a role in the generation of distinct chromatin patterns, but crowded chromatin is not sufficient for heterochromatin formation (Walter et al. 2013).

Chromatin Remodeling, Insulation, and Compartmentalization

Chromatin remodeling denotes a complex and dynamical process that serves to modify chromatin architecture to permit access of condensed genomic DNA to the transcription machinery (Clapier and Cairns 2009). Remodeling is mainly mediated by two systems, i.e., covalent histone-modifying complexes and ATP-dependent chromatin remodeling. The latter operates at the level of nucleosome regulation and consists of at least five chromatin remodeling complexes, of which the SWI/SNF complex holds a remarkable place in malignancy because it contains proteins mutated in several cancers (SMARCB1, the hSNF5/INI1 protein). Nucleoplasmin is also involved in chromatin remodeling (Arregi et al. 2011). The term, chromatin insulator, is employed for two nuclear phenomena. On the one hand, chromatin components are compartmentalized by chromatin insulator proteins (Vogelmann et al. 2011). Insulator-related proteins, but not the insulators themselves, colocalize with nuclear speckles and form so-called insulator bodies (Golovnin et al. 2008). Insulator-related proteins found in insulator bodies include the Drosophila Suppressor of Hairy wing (Su(Hw)), modifier of mdg4, and centrosomal 190 kDa/p190. The posttranslational modification of insulator proteins by small ubiquitin-like modifier (SUMO) and intact p190 protein is crucial for insulator body formation, insulator bodies functioning as a depot of sumoylated proteins that are involved in insulation (Golovnin et al. 2012). On the other hand, DNA sequence elements termed insulators are long-range interactors that either barrier elements that block the propagation of heterochromatic structures into adjacent euchromatin (modulators of chromatin domain boundaries; Wei et al. 2005) or enhancer-blocking elements that interfere with interactions between enhancers and promoters when placed between them (Gaszner and Felsenfeld 2006; Bushey et al. 2008; Amouyal 2010; Giles et al. 2010; Vogelmann et al. 2011; Barkess and West 2012; Dixon et al. 2012; Ghirlando et al. 2012; Yang and Corces 2012). Enhancer-blocking elements are DNA elements that disrupt the communication between a regulatory sequence (enhancers or silencers) and a promoter. DNA insulators must reside between an enhancer or silencer and promoter to exert an inhibitory action.

Chromatin Compaction

As visualized by light microscopy of normal and cancer cells, chromatin is compacted in the course of mitosis into discrete mitotic chromosomes. This highly ordered compaction or condensation is brought about by a nonhistone protein complex,

the condensins (Hirano 2012b; Piazza et al. 2013). Condensin forms a multisubunit structural maintenance of chromosome (SMC) protein complex (Cuylen and Haering 2011). Condensin I is required for the establishment of the intrinsic higher-order structure of chromosomes (Gassmann et al. 2004). Condensin II induces axial compaction of interphase chromosomes, disrupts interchromosomal interactions, and promotes the dispersal of pericentric heterochromatin, therefore functioning as a protein that compartmentalizes chromatin into discrete chromosomal territories (Bauer et al. 2012). Condensin is recruited and attracted by monopolin, a protein complex which cross-links multiple kinetochore complexes to prevent merotelic attachments that might cause chromosomal missegregation (Dudas et al. 2011; Burrack et al. 2013).

Segregation of compacted chromosomes depends on a distinct chromatin environment at centromeres. Pericentric heterochromatin controls the histone variant composition of centromeres and hence affects the segregation process (Boyarchuk et al. 2014). In the course of mitosis, the pericentromere becomes a spring consisting of cohesin, condensin, and a rosette of intramolecular chromatin loops, which determine the position of cohesin, radially displaced from condensin (Stephens et al. 2013). Cohesin is the multisubunit complex that produces segregation of compacted chromosomes in the course of mitosis and which mediates cohesion between replicated sister chromatids (Peters et al. 2008; Brooker and Berkowitz 2014; Tapia-Alveal et al. 2014). Components of the cohesin complex can undergo mutations, resulting in cohesinopathies (Cornelia de Lange syndrome; Roberts syndrome) and several types of cancer (Losada 2014; Solomon et al. 2014). In mammalian cells, cohesin interacts with distinct chromosomal sites and colocalizes with a protein that induces long-range DNA interactions, CTCF, thus producing a link between cohesin function and genome organization (Bose and Geron 2010). Through these mechanisms, cohesin also controls gene transcription through multiple mechanisms (Dorsett and Kassis 2014) and affects, in cooperation with CTCF, chromatin architecture (Feig and Odom 2013; Sofueva et al. 2013; Wallace and Bosco 2013; Ball et al. 2014; Zuin et al. 2014). The maintenance of sister chromatid cohesion also depends on the microtubule and kinetochore protein, astrin, which regulates separase activity (Thein et al. 2007). Separase is a cysteine protease that severs the connection of aligned sister chromatids and promotes centriole disengagement at the end of mitosis.

Senescence-Associated Heterochromatin Foci (SAHF)

In senescence of cellular systems, a stable proliferation arrest is associated with profound alteration in chromatin organization. The hallmark of this process is the development of punctate DNA foci in senescent cells, termed senescence-associated heterochromatin foci (SAHF) (Kosar et al. 2011; Aird and Zhang 2013; Chandra and Narita 2013). SAHFs are specialized senescence-associated, highly compacted domains of facultative heterochromatin that largely exclude other domains of chromatin at telomeres and pericentromeres (Zhang and Adams 2007). A distinct form of heterochromatinization in SAHF is a means to maintain a functional chromatin complement in the absence of DNA replication and depends a spatial repositioning of chromatin and on the function of lamin B1 (Corpet and Stucki 2014). SAHFs contain typical heterochromatin-associated proteins, including heterochromatin protein 1, HMGA proteins, and the histone H2A variant macroH2A. A complex of histone chaperones, histone repressor A (HIRA), and antisilencing function 1a (ASF1a) play a key role in the formation of SAHFs (Zhang et al. 2007), and SAHF biogenesis is also promoted by the chromatin remodeling factor acting downstream of the oncogene, BRCA1 (Tu et al. 2013). BRG1 in SAHF formation is preceded by senescence-associated distension of satellites (SADS) associated with higher-order unfolding of satellite heterochromatin (Swanson et al. 2013).

Nuclear Envelope-Limited Chromatin

Nuclear envelope-limited chromatin appears in the form of very thin sheets (envelope-limited chromatin sheets, ELCS). ELCS are a form of condensed chromatin that forms structural units of about 17–30 nm in diameter that forms an ordered layer or several layers of definite geometry at the level of the nuclear envelope (Haynes and Davies 1973; Kuvichkin 2012). TEM cross sections show a picture resembling a sandwich of apposed nuclear envelopes separated by about 30 nm, containing a layer of parallel chromatin fibers (Eltsov et al. 2014). ELCS appears to develop from excessive nuclear envelope growth caused by complex heterochromatin-nuclear envelope interactions (Olins and Olins 2009). ELCS cannot be visualized in normal or cancer cells by the use of light microscopy. The function of ELCS is not well known, but ELCS is predominantly associated with M phase arrest, mitosis restitution, and delayed apoptosis in endopolyploid cells, suggesting that uncoupling of mitosis from DNA replication plays a role in ELCS induction (Erenpreisa et al. 2002).

Lamina-Associated Domains

Lamina-associated domains or LADs consist of a relatively large fraction of mammalian genome that is inactive and organized along the nuclear lamina via interaction of numerous lamina-associated sequences (LASs) enriched in the GAGA motif (Guelen et al. 2008; Bickmore and van Steensel 2013; Luperchio et al. 2014). LADs have a role in the modulation of gene expression, in that lamins generate contacts with gene promoters (Lund and Collas 2013; Collas et al. 2014). Lamina interactions are generated during mitosis and involves localized recruitment of lamin B during late anaphase. LAD is bound by the transcriptional repressor cKrox, suggesting that LAD is a chromatin compartment related to chromatin silencing (Zullo et al. 2012).

Interchromatin and Intrachromatin Connections

Interactions between diverse chromatin domains are mediated by groups of distinct proteins, specifically a set of coiled-coil domain-containing complexes termed cohibin, cohesin, condensin, and monopolin. These complexes perform the regulation of DNA-DNA connections across the genome (review: Poon and Mekhail 2011).

Argyrophilic Nucleolar Organizers and Fibrillar Centers in Liver Cancer

Introduction

Nucleolar organizer regions (NORs) are characterized by loops of ribosomal DNA that are transcribed to ribosomal RNA by RNA polymerase 1; NORs are localized to the short arms of the five acrocentric chromosomes, i.e., chromosomes 13, 14, 15, 21, and 22 in humans (Fakan and Hernandez-Verdun 1986). NORs embed coding genes for the synthesis of 18S and 28S ribosomal RNA. Ultrastructurally, NORs are evident as fibrillar centers within nuclei, associated with the dense fibrillary component of interphase. NORs can be visualized based on their argyrophilic staining features (argyrophilic NORs or AgNORs). These structures are argyrophilic because they are associated with acidic proteins containing sulfhydryl and carboxy groups that precipitate silver ions (Shiro et al. 1993). By the use of silver stains, NORs appear as dark brown or black spots in light microscopy.

Nucleolar Organizer Regions in Liver Cancer

Generally, NORs are more frequently detectable in HCCs and preneoplastic lesions than in normal or cirrhotic liver (Crocker and McGovern 1988; Bufo and Frassanito 1992; Shimizu et al. 1995). NORs are more frequent in HCC than in hepatocytes of normal or cirrhotic liver (Anselmi et al. 1990; Nonomura et al. 1990a; Parveen et al. 2006). The number of NORs in normal human hepatocytes was 1.3–1.7, while it was

2.4–3.5 in cirrhosis and 3.0–7.9 in HCC (Jain et al. 1998). In HCCs, two types of AgNORs were detected, type 1 NORs being large and medium-sized dots with well-defined margins, and these NORs were in close association with nucleoli, and type 2 NORs being fine single dots and clusters without well-defined margins. Smaller and irregular type 1 NORs and more numerous type 2 NORs were associated with decreasing HCC differentiation (Shiro et al. 1993). The presence and number of NORs have an impact on the biology of HCCs. A significant correlation was found between the number of NORs and proliferative activity of HCCs (Nagao et al. 1995). The number of NORs was correlated with tumor grade and size, portal vein invasion, and survival in HCC patients (Shimizu et al. 1995). Also in various types of cholangiocarcinomas, the number of NORs is increased in comparison with normal controls (Nonomura et al. 1990b). Similar to HCC, the number of AgNORs was related to tumor differentiation and size (Hayashi et al. 1995).

Nuclear Envelope and Associated Structures

Nuclear Envelope

The nuclear core is surrounded by a double bilayer termed nuclear envelope. The nuclear envelope was compared to a "cocoon" that harbors and protects all the nuclear and genomic machinery (Chow et al. 2012; Strambio-De-Castilla 2013). In the course of mitosis, the nuclear envelope undergoes extensive structural remodeling, which begins with the retraction of nuclear membranes into the endoplasmic reticulum (ER) at onset of mitosis and finalizing with the re-enclosure of postmitotic chromatin by ER-derived membranes (reviews: Kanoh 2013; Wandke and Kutay 2013). Embedded in the nuclear envelope are the nuclear pore complexes (NPCs) that mediate mRNA transport. However, recent evidence showed that NPCs are not the only gates for mRNA exit, as mRNAs can traverse the double envelope membrane at sites other than NPCs. Important nuclear envelope proteins are the nesprin-1, nesprin-2, nesprin-3, and nesprin-4, which connect nuclei with elements of the cytoskeleton (Rajgor and Shanahan 2013). Nesprin-1/nesprin-2 isoforms tether actin through their N-terminal actin binding domain, while nesprin-3 binds plectin and associated with intermediate filaments. Nesprins affect nuclear size and nuclear shrinkage. Complete nesprin-2 (nesprin-2 giant) overexpression leads to increased nuclear size (Lu et al. 2012).

Nuclear envelope reassembly at the end of mitosis depends on the close gathering of neighboring chromosomes that form a compact cluster. These clusters seem to produce a signal that the new envelope is generated around the entire chromosome mass and not around single chromosomes. This process is mediated by the chromokinesin Kid (kinesin 10) which localizes to the boundaries of anaphase and telophase chromosomes and is involved in the shortening of anaphase chromosome masses along the spindle axis. By this mechanism, Kid prevents the formation of postmitotic multinucleated cells (Ohsugi et al. 2008).

Nuclear Lamina

The nuclear lamina is the inner layer of the nuclear envelope and is mainly composed of a meshwork of several lamins. Nuclear lamins are type V intermediate filaments that are posttranslationally modified and which determine the structure of the nuclear lamina and serve as chromatin-interacting proteins which affect the organization of chromosomes within the nucleus (Dechat et al. 2010). A-/C-type lamins exhibit marked invaginations into the interior of the nucleus, representing channels for the transport of regulatory cargo to and from nuclear and nucleolar compartments. A-type lamin channels interact with polycomb group bodies, genomic regions of DNA repair, heterochromatin proteins, and UBF-positive regions of nucleoli, and A-/C-type lamin channels interact with nuclear pores and PML bodies (Legartova et al. 2014).

Nuclear Pore Complex

The nuclear pore complex (NPC) is a distinct multiunit structural component and the nuclear membrane and mediates the selective passage of certain molecules into and out of the nucleus. As such, the NPC is a highly selective bidirectional transporter for a large number of protein and ribonucleoprotein cargoes (Peters 2009; Wente and Rout 2011; Natalizio and Wente 2013). NPCs play a central role in the transfer of mRNA into ribosomal compartments (Brickner and Brickner 2012; Adams and Wente 2013; Natalizio and Wente 2013). The basket of the NPC is a distinct structure composed of eight specific protein filaments which protrude into the nucleoplasm and converge in a ring distal to the NPC. These basket proteins (nucleoporins; reviews: Doye and Hurt 1997; Wälde and Kehlenbach 2010; Chatel and Fahrenkrog 2011; Burns and Wente 2014) interact with other NPC proteins, the spindle organizer, the proteasome, silencing factors, and components of messenger ribonucleoproteins (mRNPs) (Liashkovich et al. 2012). Nucleoporins with a filamentous domain structure occupy the center and line the diffusion conduit of the NPC and gate protein diffusion across the NPC (Patel et al. 2007). The basket seems to reduce chromatin crowding around the central transporter of the NPC and is considered to be the docking site for mRNPs during nuclear export (Niepel et al. 2013). A further major component of the NPC basket is the nucleoporin translocated promoter region (Tpr), a protein involved in nuclear transport, chromatin organization, and mitosis, and associated with cancer and aging (Rajanala and nandicoori 2012; Snow et al. 2013; Snow and Paschal 2014).

The transport of karyophilic proteins into and from the nucleus is accomplished by a family of specific proteins, the karyopherins (KPNs), which possess nuclear localization signals (NLSs) and belong to the nuclear pore complex family. Generally, karyopherin-mediated protein transfer takes place through nuclear pores. Karyopherins can operate as importins (proteins mediating traffic into the nucleus) and exportins (out of the nucleus). Importin beta facilitates transport of protein cargo in the karyoplasm, whereby it first binds to importin alpha, which attaches cargo in the cytoplasm. Importin alpha exists in six forms, alpha1 to alpha6 (KPNA1 to KPNA6). Importin beta is encoded by the KPNB1 gene. A further beta-karyopherin is transportin-1 which mediates the nuclear import of the RNA-binding protein hnRNP A1. Transportin-3 mediates the nuclear import of splicing factors (Maertens et al. 2014). Nuclear localization of beta-catenin, a Wnt-related signaling protein mutated in HCCs and hepatoblastomas, is mediated by importin beta-5 in cooperation with the IQGAP1 protein (Goto et al. 2013). Importin 8, another beta-karyopherin, regulates the transport of mature microRNAs into the nucleus (Wei et al. 2014). Exportin 5, encoded by the XPO5 gene, mediates the nuclear export of microRNAs (Muqbil et al. 2013).

Nuclear Budding and Blebbing of the Nuclear Lamina in Cancer Cells

Structures protruding from the nucleus in the form of blebs are mainly found in a progeria syndrome and in diverse cancer cells. Blebs have been observed in regions where the fibers in the lamin meshwork have a greater separation (Funkhouser et al. 2013).

Nucleus-Cytoskeleton Connections (LINC Complexes), Chromosome Movements, and Nuclear Positioning

Nucleoskeleton and LINC Complexes

The nuclear envelope is linked to the cytoskeleton via distinct envelope proteins that transfer cytoskeletal forces to the nuclear lamina through a nuclear envelope bridge (the LINC complex). Linker of nucleoskeleton and cytoskeleton (LINC) complexes span the double membrane of the nuclear envelope and provide the machinery that links the nucleoskeleton with the cytoskeleton via a distinct set of proteins (reviews: Ostlund et al. 2009; Zhong et al. 2010; Lombardi and

Lammerding 2011; Simon and Wilson 2011; Rothballer et al. 2013). These proteins comprise SUN (Sad1 and UNC-84), spanning the inner nuclear membrane and KASH (Klarsicht, ANC-1, and Syne/nesprin homology) residing in the outer nuclear membrane (Sosa et al. 2012). These proteins can associate cytoskeletal proteins, including actin, microtubules, intermediate filaments, and centrosomal proteins, with the nuclear surface and the nucleoskeleton (Starr and Fridolfsson 2010). In the lumen of the nuclear envelope, the SUN and KASH domain proteins assemble to form a nuclear envelope bridge which mediates binding to cytoskeletal proteins (Rothballer et al. 2013). Specifically, nesprin-2 giant and nesprin-3 anchor actin cap fibers to the nucleus (Chambliss et al. 2013). The nucleoskeleton itself includes nuclear pore-linked filaments, A-type and B-type intermediate filaments, nuclear mitotic apparatus (NuMA) networks, spectrins, titin, actin variants/isoforms, and more than ten myosin and kinesin motors. This multiprotein system plays an central role in interskeleton signaling, nuclear positioning and movements, and chromosome motility.

Nuclear Positioning

For its proper function and the establishment of nuclear-organelle interactions, the cell must set the nucleus into distinct intracellular positions. Nuclear position is actively regulated by the mechanisms of intracellular nucleus movements, in particular also nuclear rotation (Sleeman 2004; Starr 2011). Movements are chiefly mediated by the microtubular system, but the actin cytoskeleton and dynein are also involved (Wu et al. 2011). Specifically, the actin machine is active during centrosome orientation in polarized cells, where the actin cytoskeleton moves the centrosome to the cell center, while the nucleus is shifted to the cell rear, thus orienting the centrosome between the nucleus and the rear end. The moving nucleus is connected with the actin cytoskeleton by a linear array of nuclear envelope membrane proteins, the transmembrane actin-associated nuclear (TAN) lines, mainly composed of nesprin-2G, Samp1, and SUN2 (reviews: Luxton et al. 2011; Osorio and Gomes 2014). Nuclear movements require the LINC complex components nesprin-2G and SUN2, and Samp1 is required for its association with SUN2 and lamin A/C (Borrego-Pinto et al. 2012). TAN line formation is mediated by the diaphanous formin, FHOD1, which interacts with nesprin-2G (Kutscheidt et al. 2014). A-type lamins anchor TAN lines through the action of a nuclear membrane protein, emerin, which organizes actin flow for nuclear movement (Chang et al. 2013). Nuclear positioning is also mediated by nuclear pore proteins (NUPs), including nucleoporins (Ruben et al. 2011).

Chromosome Movements, Chromokinesins, and Gene Positioning

Genes must be expressed and repressed at the right time and right place. Gene expression and positioning strongly depend on condensed regions of heterochromatin, the latter acting as a subnuclear silencing compartment (Jost et al. 2012). Chromosomes perform directed movements during the cell division cycle (chromosome oscillations; Campas and Sens 2006). The directed movements depend on a proper position within the spindle and are related to the chromosomal passenger complex, a complex driving chromosome segregation and cytokinesis, and composed of Aurora kinase B, INCENP, survivin and borealin, and centralspindlin (Watanabe 2010; Lewellyn et al. 2011; van der Horst and Lens 2014). Several theories have been formulated to explain the mechanisms behind these movements. One direction of thinking involves a machinery similar to that operational in microtubule-kinesin-driven organelle movements. In a second theory, mitotic chromosome motions were correlated with electrostatic forces. Positively charged kinetochore-associated molecules, such as Ndc80/hec1, have been implicated as likely interaction partners for negatively charged microtubule ends to generate electrostatic-dependent poleward forces that drive chromosome motion. This scheme explains dynamic tracking/coupling of kinetochores to microtubules, and the simultaneous

depolymerization of kinetochore microtubules as poleward force is generated (review: Shain and Gagliardi 2011).

The first system of chromosome-associated motors functions conventionally in moving chromosomes along microtubules of the spindle apparatus. The second system of chromatin-associated motors is involved in preventing chromosome loss and spindle formation, via docking microtubules to chromosome arms. A third system involves kinetochore motors which operate in spindle checkpoint activity (review: Brunet and Vernos 2001). Chromosome-associated motors comprise several classes of kinesin motors (chromokinesins; Mazumdar and Misteli 2005; Vanneste et al. 2011). Members of the kinesin-8 subfamily are plus end-directed motors that accumulate at the plus ends of kinetochore microtubules. Kinetochore translocation is strongly coupled at the depolymerizing microtubule end. The so-called Pac-Man hypothesis suggests that poleward movement of chromosomes during anaphase is brought about by disassembly of kinetochore microtubules at the kinetochore, generation of the poleward force taking place exclusively at or very close to the kinetochore, and the required energy coming from coupled disassembly of these microtubules (Pickett-Heaps and Forer 2001). Kinesin 8/Kif18A destabilizes microtubules via its depolymerizing activity and is capable to walk along microtubules for long distances, depending on a non-motor microtubule binding site (Mayr et al. 2011). Kinetochores and their proteins control the movements of duplicated chromosomes by interacting with spindle microtubules during mitosis and meiosis. They create a complex protein interface with microtubules (review: Akiyoshi and Siggins 2012). Kinetochore function in mitosis depends on the identification of microtubule attachment points. At the onset of mitosis, but no longer at metaphase, the protein CLIP-170 localizes to kinetochores and facilitates the formation of kinetochore-microtubule attachments, through direct capture of microtubules at the kinetochore . The polymer end of microtubules is the critical interface to kinetochores and is therefore stringently controlled. A distinct kinesin, mitotic centromere-associated kinesin (MCAK), a member of the kinesin-13 family, is a potent depolymerase of microtubules by removing tubulin subunits from the polymer end. This depolymerization corrects erroneous attachments of microtubule-kinetochore. The expression and activity of MCAK itself are regulated by mitotic kinases, including Aurora A/B, polo-like kinase 1, and cyclin-dependent kinase 1 (Sanhaji et al. 2011). Kinetochore-microtubule attachment during the organization of the mitotic spindle also depends on multiple asters (MAST)/Orbit, a member of a family of non-motor microtubule-associated proteins. MAST/Orbit is required for the maintenance of spindle bipolarity and chromosome congression (Maiato et al. 2002). Kinetochore-microtubule interactions are furthermore regulated by BUB1, BUB3, and BUBR1 proteins, core spindle checkpoint kinases which interact with the CENP-E microtubule motor (Maia et al. 2007). The spindle assembly checkpoint (SAC) presents initiation of anaphase until all chromosomes have been congressed in the spindle plane and have accomplished bipolar attachments within the mitotic spindle, in order to ensure fidelity of chromosome segregation and to strictly avoid eventual chromosome loss during mitosis. BUB1, BUB3, and BUBR1 SAC kinases play a critical role in this crucial process (Logarinho and Bousbaa 2008).

Mitotic Centromere Movements and Their Regulation

At the metaphase plate, alignment of chromosomes takes place, representing a visible signature of metazoan cell division. Centromeres direct the assembly of kinetochores, microtubule attachment sites allowing chromosome segregation in the spindle. The kinetochore-associated protein complex, Ndc80, binds to a centromere receptor of this complex, histone-fold protein Cnn1 (CENP-T), thus coupling chromosome movement to kinetochore-dependent spindle dynamics. In order to arrange chromosomes in the metaphase plane, mechanisms to cancel centromere motion and to arrest centromeres in the spindle midzone plane are required. Restricting centromere

movement to the spindle midzone is linked to centromere attenuation by kinesin-8/Kif18A which promotes microtubule pausing. Kinesin Kif18A is a motile kinesin depolymerase which is crucial for attenuating chromosome oscillations (Gardner et al. 2008), chromosome congression, and dampening of microtubule plus-end dynamics (Du et al. 2010). In addition, polar ejection forces spatially confine chromosomes to the metaphase plane through position-dependent regulation of kinetochore tension and centromere switch rates, and polar ejection forces are antagonistically modulated by chromokinesins.

Chromatin Movements (Chromobility)

The interphase nucleus is functionally compartmentalized, including preferential interior localization of gene-rich and early-replicating chromosome regions versus peripheral localization of gene-poor and late-replicating chromosome regions. The generation of such dynamic compartments in nuclei depends on distinct features of chromatin dynamics, long-range directional movements of target components, gene positioning, and chromosome territory relocation (Hübner and Spector 2010). The genomic DNA in mammalian cells is organized into chromatin domain of about 1 Mbp size which are the basic units for DNA compaction, replication, and transcription. These chromatin domains undergo translational movements and configurational changes. In the interphase nucleus, chromatin and chromatin components move in a constrained random walk, having an impact on genome expression dynamics and DNA-based reactions. In addition to translational movements, chromatin domains exhibit rapid oscillatory motions, early S-phase replicated chromatin domains showing the highest levels of motion, and late S-phase chromatin the lowest. Chromatin mobility is increased at sites of DNA double-strand breaks, a process requiring Mec1, Rad9, and the homologous recombination machinery. The process of chromatin movement is termed chromobility and is thought to be accomplished by the action of nuclear chromatin motors (Bridger 2011). Chromatin parts, gene loci, and entire chromosomal domains can move rapidly, with relocation of parts of the genome within less than 15 min over a number of microns (Bridger 2011).

Interorganelle DNA Migration

In eukaryotic cells, DNA is known to be exchanged between mitochondria, which are endosymbiosis-derived DNA-containing organelles, and the nucleus. This interorganelle DNA migration is a process that began early in evolution and resulted in a massive relocation of organelle genes to the nuclear genome, followed by retargeting of the nuclear gene components to their ancestral compartment, and others now function in new subcellular locations. There is also gene transfer from plastids to the nucleus, a process that played and still plays a role in genome evolution (Bock and Timmis 2008). However, almost all present-day nuclear transfers of mitochondrial or plastid DNA give rise to noncoding sequences, dubbed nuclear mitochondrial DNAs (NUMTs), and nuclear plastid DNAs (NUPTs) (reviews: Richly and Leister 2004; Kleine et al. 2009). Mitochondrial genomes often contain large numbers of plastid DNA (ptDNA)-derived sequences (MTPTs), whereby the intercompartmental transfer of ptDNA is markedly reduced in species with only a single plastid per cell (monoplastidic species) versus those with many plastids per cell (polyplastidic species). This is termed the limited transfer window hypothesis (Barbrook et al. 2006). MTPTs are restricted to the mitochondrial genomes of polyplastidic species and are absent from those of monoplastidic species (Smith 2011). Interorganelle DNA transfer is ongoing and ubiquitous and can produce genetic diversity by reshaping genes through adding novel exons. Plastid or nuclear gene sequences have also contributed to the biogenesis of mitochondrial tRNA genes (review: Leister and Kleine 2011).

Nucleolus

Morphology of Nucleoli in Liver Cancer

The nucleolus is, after chromatin, the most striking nuclear structure seen at light microscopy. Nucleoli occur in cancer cells as single spherical object of variable diameter or as few to several smaller structures of round or ovoid shape. Depending on the relationship between proteins and RNAs, the staining of nucleoli ranges from eosinophilic to amphophilic and slightly basophilic. Apart from their size, shape, and staining features, nucleoli may show typical intranuclear distribution pattern in various cancers. In well-differentiated hepatocellular carcinoma, nucleoli resemble in the shape to those of normal hepatocytes, but they are larger and show a strong eosinophilia (macroeosinophilic nucleoli). As cell differentiation decreases, nucleoli become larger and multiple, and their staining shifts from eosinophilic to amphophilic or even basophilic, the latter in grade 4 lesions. Nucleolar hypertrophy is a typical feature of HCC nuclei and can be quantitatively assess by determination of the nucleolar index. In comparison with normal human hepatocytes, nucleoli with a size of 7 μ^2 or greater were considered to be hypertrophic. The nucleolar index was obtained by calculating the percentage of liver cells having a nucleoli with 7 μ^2 or greater (Trerè et al. 2003). HCCs were significantly more common in the group with a nucleolar index of 2.5 or greater. Nucleoli in HCCs revealed ultrastructural abnormalities, including a condensation of the fibrillar component (Ruebner et al. 1967; Horvath et al. 1972; Smetana et al. 1972; Hruban 1979).

Both HCCs and cholangiocarcinomas can show abnormal expression patterns of the nucleolar protein, dyskerin (Liu et al. 2012; Vasuri et al. 2015). In intrahepatic cholangiocarcinomas, expression of dyskerin was associated with more aggressive tumor biology (Vasuri et al. 2015). Similarly, HCC expressing dyskerin presented with advanced clinical stage and poor patient prognosis (Liu et al. 2012). Dyskerin, a protein mutated in dyskeratosis congenita, is one of the three subunits of the telomerase ribonucleoprotein complex. It is involved in the regulation of telomere length (Gu et al. 2009), but it also possesses functions that are independent on its action on telomeres, including regulation of mitosis (Alawi and Lin 2013; Angrisani et al. 2014).

Nucleolus: Structure

In tissue sections and smears, nucleoli are not homogeneous structures but show a finely granular or homogeneous background with more dense areas. The nucleolus possesses a fine internal network of proteins called the nucleolar matrix or nucleolar skeleton (Zbarsky 1981; Schwarzacher and Wachtler 1993; Chen et al. 1999; Raska et al. 2006). In cell spreads, nucleolar organization shows a network corresponding to the nucleolonema (NCN; Estable 1966; Deltour and Motte 1990; Sato et al. 2005). This network reveals units comparable to the rDNA transcriptional units in length and is associated with tufts of fibrils and granules (Ghosh and Paweletz 1996). Ultrastructural investigations demonstrate that the nucleolus consists of three major components: a dense fibrillar component (DFC), a granular component (GC), and a fibrillar center (FC) (review: Schwarzacher and Wachtler 1993). DFC and FC are integrated in the NCN, whereby FCs predominantly occur in amniote organisms. The NCN is a fundamental substructure of the nucleolus, whereby the DFC corresponds to the matrix of the NCN, and the FC is a counterpart of argyrophilic lacunae localized in the NCN (Mirre and Stahl 1981; Kniebiehler et al. 1983; Sato 1992; Sato et al. 2005). High-voltage electron microscopy in thick sections has shown that argyrophilic FC components in compact nucleoli show a knotted ropelike structure in which knots are constituted of one central fibrillar center surrounded at some distance by loops of the dense fibrillar component and in which the rope is constituted of dense fibrillar component. In reticulated nucleoli, argyrophilic deposits are confined to the surface of the nucleolonema as several strands twisted at the periphery of the fibrillar

component (Ploton et al. 1987). FCs are low-electron density patches within DFCs and change their size and features under different physiological conditions and during the cell cycle. The volume of FCs doubles from G1 to G2 in Ehrlich tumor cells (Lepoint and Goessens 1982), and the number of FCs gradually increases from G1 to G2 (Junera et al. 1995). FCs are depots of inactive rRNA genes. The DFC is present as a network of strands that surround FCs, but DFC can also reach out to the nucleolar periphery. In DFCs, pre-rRNA synthesis and early rRNA-processing events take place, while GC is the site of late rRNA-processing events and assembly of ribosomal particles. There is a clear relationship between the functional status and the morphology and structure of the nucleolus. This has an impact on the understanding of nucleolar changes in cancer cell nuclei. In hyposynthetic cells, i.e., those with a low-level protein synthesis and ribosome biogenesis, nucleoli are small and show a single FC and poor DFC, resulting in ring-shaped nucleoli. In active cells, including growing cancer cells, a large network of DFC contains numerous FCs, and GC occupies peripheral parts (compact nucleoli). Newly stimulated cells exhibit a prominent DFC, but only few and small FCs (reticulate nucleoli; Schwarzacher and Wachtler 1993). During mitosis, the nucleolus is decomposed and postmitotically reassembled by a highly controlled process.

Nucleolus: Nucleologenesis and Function

The biogenesis of nucleoli (nucleologenesis) takes place in the nucleus around distinct genetic loci termed nucleolar-organizing regions (NORs). A typical NOR consists of tandem repeats of ribosomal RNA (rRNA) genes, of which more than 200 clustered copies are present in the human genome on five different chromosomes. Nucleoli play a central role in ribosomal RNA/rRNA synthesis and processing and ribosome subunit assembly (the "ribosome factory"; Boisvert et al. 2007; Cmarko et al. 2008; Bartova et al. 2010; Dundr 2012). Nucleolar ribonucleoproteins are localized to components of the NCN. Non-nucleosomal DNA filaments form roundish agglomerates with a spatial distribution which is superimposable on that of FCs (Derenzini et al. 1983). Ribosomal DNA (rDNA) is specifically localized to the FCs, but rDNA transcription does not seem to take place in these structures. rDNA transcription is localized to the boundary region between FC and DFC, rRNA transcripts being processed outward within the DFC (Sato et al. 2005). This distribution pattern is also reflected by the intranucleolar distribution of fibrillarin, fibrillarin staining shifting from the FCs to adjacent regions (Snaar et al. 2000; Jamison et al. 2010). During S phase of the cell cycle, catalytically active telomerase holoenzyme is initially assembled in DFC. The telomerase RNP is retained in the nucleolus via interaction of hTERT with nucleolin. Following this step, the telomerase RNP is transported to Cajal bodies (Lee et al. 2014).

In the course of ribosome biogenesis, the initial step involves transcription of rRNA genes by two RNA polymerases (pol I and III) within the nucleolus, in association with regulatory proteins forming the preinitiation complex (PIC). The PIC contains promoter selectivity factor (SLI), transcription initiation factors (SLI), and upstream binding factor (UBF). In humans, rRNA genes transcribed in the nucleolus by pol I result in the rRNA transcripts 5.8S, 18S, and 28S, whereas the 5S transcript (a component of the 60S ribosomal subunit) is transcribed by pol III in the nucleoplasm, later to be transferred to the nucleolus. For ribosome biogenesis, different and highly dynamic pre-ribosomal complexes are formed. These complexes contain specific proteins required for the production of the various types of rRNA transcripts. For the 18S transcript, Dbp4 (a DEAD-box RNA helicase), Bfr2, and Enp2 are required, whereby the latter two proteins associate with U3 small nucleolar RNA/snoRNA, the U3-specific protein Mpp10, and various pre-18S ribosomal RNA species. These proteins are components of the small-subunit (SSU) processome (Turner et al. 2009; Soltanieh et al. 2014). The SSU

processome is a large (80S) ribonucleoprotein complex that corresponds to the terminal knobs seen in EM (Bernstein et al. 2004; Phipps et al. 2011; Feng et al. 2013). During transcription of rRNA genes, the highly specific molecular organization of the respective partners in the nucleolus can be visualized. Active rRNA genes are present in the form of characteristic Christmas trees.

Apart from proteins directly participating in the ribosome factory, the nucleolus contains other proteins involved in nucleolar functions (nucleolar proteome). Nucleolin is a phosphoprotein widely distributed in the nucleolus. The protein has numerous functions, and its levels reflect the functional activity of the organelle. It has helicase and ATPase activities and can bind RNA via its RNA recognition motifs (review: Tajrishi et al. 2011). As noted above, nucleolin is also involved in the turnover of telomerase in nucleoli. A further nucleolar protein is fibrillarin, involved in pre-rRNA processing during ribosomal biogenesis and in the maintenance of nuclear shape. Nucleophosmin (B23) is a protein which is predominantly localized in the nucleolus. Nucleophosmin is overexpression in many human cancer cells and plays a regulatory role during differentiation of liver cancer cells (Xu et al. 2014). Nucleophosmin targets the ARF tumor suppressor to the nucleolus and inhibits its function (Korgaonkar et al. 2005). ARF is a nucleolar protein that activates checkpoints in a p53-dependent manner by binding Mdm2, an antagonist of p53. From its position in the nucleolus, ARF acts as a sensor of signals that relate to cell growth and proliferation (Maggi et al. 2014). The nucleolus contains the lipid phosphatase PTEN which plays a role in regulating nucleolar homeostasis and morphology (Li et al. 2014). The nucleolus contains at least ten species of mature microRNAs. Their accumulation in the nucleolus depends on the protein CRM1 which is associated with the trafficking of small nucleolar RNAs (Bai et al. 2014). MicroRNAs can affect nucleolar structure and function. Expression of microRNA-122 in HCC cells results in more prominent nucleoli in these cells (Jin et al. 2014).

Functions of the Nucleolus Other Than the Ribosome Factory

The nucleolus and its machinery are in constant interaction with the nucleoplasm and several nuclear bodies (see below) and act as a complex sensor of various nuclear and cytoplasmic functions (Olson et al. 2002; Sirri et al. 2008; Thiry et al. 2011). The nucleolus is involved in nuclear and chromatin organization, cell cycle regulation, stress responses, and aging. Nucleolar proteins interact with heterochromatin and mediate the organization of heterochromatin around the nucleolus (nucleolus-associated chromatin domains, NADs; Padeken and Heun 2014). The relationship between the nucleolus and the cell cycle is complex, and cell cycle features have a strong influence on both function and size of nucleoli (Derenzini et al. 1998; Tsai and Pederson 2014). During mitosis, the ribosome factory comes to a halt, requiring a sensor system of the nucleolus that monitors the position of the cell with respect to interphase versus cycling.

References

Adams RL, Wente SR (2013) Uncovering nuclear pore complexity with innovation. Cell 152:1218–1221

Aird KM, Zhang R (2013) Detection of senescence-associated heterochromatin foci (SAHF). Methods Mol Biol 965:185–196

Akiyoshi B, Siggins S (2012) Reconstituting the kinetochore-microtubule interface: what, why, and how. Chromosoma 121:235–250

Alawi F, Lin P (2013) Dyskerin localizes to the mitotic apparatus and is required for orderly mitosis in human cells. PLoS ONE 8:e80805

Amouyal M (2010) Gene insulation. Part II: natural strategies in vertebrates. Biochem Cell Biol 88:885–898

Angrisani A, Vicidomini R, Turano M, Furia M (2014) Human dyskerin: beyond telomeres. Biol Chem 395:593–610

Anselmi L, Sementa AR, Borgiani L, Banderali A, Rovida S (1990) Nucleolar organizer regions (NORs) in normal and pathological liver: a quantitative analysis. Pathologica 82:653–662

Arnold J (1880) Bemerkungen zu den Mitteilungen des Herrn Dr. Pautynski. Virchows Arch 79:407–409

Arregi I, Falces J, Banuelos S, Urbaneja MA, Taneva SG (2011) The nuclear transport machinery recognizes nucleoplasmin-histone complexes. Biochemistry 50:7104–7110

Bai B, Liu H, Laiho M (2014) Small RNA expression and deep sequencing analyses of the nucleolus reveal the presence of nucleolus-associated microRNAs. FEBS Open Biol 4:441–449

Ball AR, Chen YY, Yokomori K (2014) Mechanisms of cohesin-mediated gene regulation and lessons learned from cohesinopathies. Biochim Biophys Acta 1839:191–202

Barbieri M, Chotalia M, Fraser J, Lavitas LM, Dostie J, Pombo A, Nicodemi M (2012) Complexity of chromatin folding is captured by the strings and binders switch model. Proc Natl Acad Sci U S A 109:16173–16178

Barbieri M, Chotalia M, Fraser J, Lavitas LM, Dostie J, Pombo A, Nicodemi M (2013) A model of the large-scale organization of chromatin. Biochem Soc Trans 41:508–512

Barbrook AC, Howe CJ, Purton S (2006) Why are plastid genomes retained in non-photosynthetic organisms? Trends Plant Sci 11:101–108

Barkess G, West AG (2012) Chromatin insulator elements: establishing barriers to set heterochromatin boundaries. Epigenomics 4:67–80

Bartova E, Harnicarova Horakova A, Uhlirova R, Raska I, Galiova G, Orlova D, Kozubek S (2010) Structure and epigenetics of nucleoli in comparison with non-nucleolar compartments. J Histochem Cytochem 58:391–403

Bauer CR, Hartl TA, Bosco G (2012) Condensin II promotes the formation of chromosome territories by inducing axial compaction of polyploid interphase chromosomes. PLoS Genet 8:e1002873

Bernstein KA, Gallagher JE, Mitchell BM, Granneman S, Baserga SJ (2004) The small-subunit processome is a ribosome assembly intermediate. Eukaryot Cell 3:1619–1626

Bhatia A, Kumar Y (2014) Relevance of microscopic indicators of chromosomal instability in routine reporting of malignancies. Diagn Cytopathol 42:181–188

Bickmore WA, van Steensel B (2013) Genome architecture: domain organization of interphase. Cell 152:1270–1284

Bignold LP (2003) Pathogenetic mechanisms of nuclear pleomorphism of tumour cells based on the mutator phenotype theory of carcinogenesis. Histol Histopathol 18:657–664

Bignold LP (2004) Chaotic genomes make chaotic cells: the mutator phenotype theory of carcinogenesis applied to clinicopathological relationships of solid tumors. Cancer Invest 22:338–343

Bignold LP (2005) Embryonic reversions and lineage infidelities in tumour cells: genome-based models and role of genetic instability. Int J Exp Pathol 86:67–79

Bignold LP, Coghlan BLD, Jersmann HPA (2006a) Hansemann, Boveri, chromosomes and the gametogenesis-related theories of tumours. Cell Biol Int 30:640–644

Bignold LP, Coghland BLD, Jersmann HPA (2006b) Cancer morphology, carcinogenesis and genetic instability: a background. In: Bignold LP (ed) Cancer: cell structures, carcinogens and genomic instability. Birkhäuser, Basel

Bock R, Timmis JN (2008) Reconstructing evolution: gene transfer from plastids to the nucleus. Bioessays 30:556–566

Boisvert FM, van Koningsbruggen S, Navascues J, Lamond AI (2007) The multifunctional nucleolus. Nat Rev Mol Cell Biol 8:574–585

Bolt HM, Steart JD, Hengstler JG (2011) A comprehensive review about micronuclei: mechanisms of formation and practical aspects in genotoxicity testing. Arch Toxicol 85:861–862

Borrego-Pinto J, Jegou T, Osorio DS, Auradé F, Gorjanacz M, Koch B, Mattaj IW et al (2012) Samp1 is a component of TAN lines and is required for nuclear movement. J Cell Sci 125:1099–1105

Bose T, Geron JL (2010) Cohesinopathies, gene expression, and chromatin organization. J Cell Biol 189:201–210

Boveri T (1914) Zur Frage der Entstehung maligner Tumoren. Fischer Verlag, Jena. English translation: Boveri M (1929) The origin of malignant tumors. Williams & Wilkins, Baltimore

Boyarchuk E, Filipescu D, Vassias I, Cantaloube S, Almouzni G (2014) Pericentric heterochromatin state during the cell cycle controls the histone variant composition of centromeres. J Cell Sci 127:3347–3359

Brickner DG, Brickner JH (2012) Interchromosomal clustering of active genes at the nuclear pore complex. Nucleus 3:487–492

Bridger JM (2011) Chromobility: the rapid movement of chromosomes in interphase nuclei. Biochem Soc Trans 39:1747–1751

Brooker AS, Berkowitz KM (2014) The roles of cohesins in mitosis, meiosis, and human health and disease. Methods Mol Biol 1170:229–266

Brunet S, Vernos I (2001) Chromosome motors on the move. From motion to spindle checkpoint activity. EMBO Rep 2:669–673

Bufo P, Frassanito F (1992) Hepatocellular carcinoma and preneoplastic lesions of the liver: evaluation of argyrophilic nucleolar organizer regions (AgNORs). Boll Soc Ital Biol Sper 68:707–714

Burns LT, Wente SR (2014) From hypothesis to mechanism. Uncovering nuclear pore complex links to gene expression. Mol Cell Biol 34:21114–22120

Burrack LS, Applen Clancey SE, Chacon JM, Gardner MK, Berman J (2013) Monopolin recruits condensin to organize centromere DNA and repetitive DNA sequences. Mol Biol Cell 24:2807–2819

Bushey AM, Dorman ER, Corces VG (2008) Chromatin insulators: regulatory mechanisms and epigenetic inheritance. Mol Cell 32:1–9

Cameron GR (1952) Pathology of the cell. Charles C. Thomas, Springfield

Campas O, Sens P (2006) Chromosome oscillations in mitosis. Phys Rev Lett 97:128102

Chambliss AB, Khatau SB, Erdenberger N, Robinson DK, Hodzic D, Longmore GD et al (2013) The LINC-anchored actin cap connects the extracellular milieu to the nucleus for ultrafast mechanotransduction. Sci Rep 3:1087

Chandra T, Narita M (2013) High-order chromatin structure and the epigenome in SAHFs. Nucleus 4:23–28

Chang W, Folker ES, Worman HJ, Gundersen GG (2013) Emerin organizes actin flow for nuclear movement and centrosome orientation in migrating fibroblasts. Mol Biol Cell 24:3869–3880

Chatel G, Fahrenkrog B (2011) Nucleoporins: leaving the nuclear pore complex for a successful mitosis. Cell Signal 23:1555–1562

Chen J, Shen Y, Jiao R, Zhai Z (1999) Composition and structure of nucleolar skeleton (nucleolar matrix): actin and fibrillarin are two main protein components of nucleolar skeleton. Sci China C Life Sci 42:34–42

Chow KH, Factor RE, Ullman KS (2012) The nuclear envelope environment and its cancer connections. Nat Rev Cancer 12:196–209

Clapier CR, Cairns BR (2009) The biology of chromatin remodeling complexes. Annu Rev Biochem 78:273–304

Cmarko D, Smigova J, Minichova L, Popov A (2008) Nucleolus: the ribosome factory. Histol Histopathol 23:1291–1298

Cohen MB, Haber MM, Holly EA, Ahn DK, Bottles K, Stoloff AC (1991) Cytologic criteria to distinguish hepatocellular carcinoma from nonneoplastic liver. Am J Clin Pathol 95:125–130

Collas P, Lund EG, Oldenburg AR (2014) Closing the (nuclear) envelope on the genome: how nuclear lamins interact with promoters and modulate gene expression. Bioessays 36:75–83

Corpet A, Stucki M (2014) Chromatin maintenance and dynamics in senescence: a spotlight on SAHF formation and the epigenome of senescent cells. Chromosoma 123:423–436

Cremer T, Kreth G, Koester H, Fink RH, Heintzmann R, Cremer M, Solovei I, Zink D, Cremer C (2000) Chromosome territories, interchromatin domain compartment, and nuclear matrix: an integrated view of the functional nuclear architecture. Crit Rev Eukaryot Gene Expr 10:179–212

Crocker J, McGovern J (1988) Nucleolar organiser regions in normal, cirrhotic, and carcinomatous livers. J Clin Pathol 41:1044–1048

Cuylen S, Haering CH (2011) Deciphering condensin action during chromosome segregation. Trends Cell Biol 21:552–559

Da Silva AE, Rados PV, da Silva Lauxen I, Gedoz L, Villarinho EA, Fontanella V (2007) Nuclear changes in tongue epithelial cells following panoramic radiography. Mutat Res 632:121–125

De Almeida TM, Leitao RC, Andrade JD, Beçak W, Carrilho FJ, Sonohara S (2004) Detection of micronuclei formation and nuclear anomalies in regenerative nodules of human cirrhotic livers and relationship to hepatocellular carcinoma. Cancer Genet Cytogenet 150:16–21

Dean A (2011) In the loop: long range chromatin interactions and gene regulation. Brief Funct Genom 10:3–10

Dechat T, Adam SA, Taimen P, Shimi T, Goldman RD (2010) Nuclear lamins. Cold Spring Harb Perspect Biol 2:a000547

Deltour R, Motte P (1990) The nucleolonema of plant and animal cells: a comparison. Biol Cell 68:5–11

Derenzini M, Hernandez-Verdun D, Pession A, Novello F (1983) Structural organization of chromatin in nucleolar organizer regions of nucleoli with a nucleolonema-like and compact ribonucleoprotein distribution. J Ultrastruct Res 84:161–172

Derenzini M, Trerè D, Pession A, Montanaro L, Sirri V, Ochs RL (1998) Nucleolar function and size in cancer cells. Am J Pathol 152:1291–1297

Dixon JR, Selvaraj S, Yue F, Kim A, Li Y, Shen Y, Hu M, Liu JS, Ren B (2012) Topological domains in mammalian genomes identified by analysis of chromatin interactions. Nature 485:376–380

Dorsett D, Kassis JA (2014) Checks and balances between cohesin and Polycomb in gene silencing and transcription. Curr Biol 24:R535–R539

Doye V, Hurt E (1997) From nucleoporins to nuclear pore complexes. Curr Open Cell Biol 9:401–411

Du Y, English CA, Ohi R (2010) The kinesin Kif18A dampens microtubule plus-end dynamics. Curr Biol 20:374–380

Dudas A, Polakova S, Gregan J (2011) Chromosome segregation: monopolin attracts condensin. Curr Biol 21:R634–R636

Dundr M (2012) Nuclear bodies: multifunctional companions of the genome. Curr Opin Cell Biol 24:415–422

Elias and Fong (1978) http://www.ncbi.nlm.nih.gov/pubmed/730149

Eltsov M, Sosnovski S, Olins AL, Olins DE (2014) ELCS in ice: cryo-electron microscopy of nuclear envelope-limited chromatin sheets. Chromosoma 123:303–312

Erenpreisa J, Ivanov A, Cragg M, Selivanova G, Illidge T (2002) Nuclear envelope-limited chromatin sheets are part of mitotic death. Histochem Cell Biol 117:243–255

Estable C (1966) Morphology, structure, and dynamics of the nucleonema. Natl Cancer Inst Monogr 23:91–105

Fadloun A, Eid A, Torres-Padilla ME (2013) Mechanisms and dynamics of heterochromatin formation during mammalian development: closed paths and open questions. Curr Top Dev Biol 104:1–45

Fakan S, Hernandez-Verdun D (1986) The nucleolus and the nucleolar organizer regions. Biol Cell 56:189–206

Feig and Odom (2013) http://www.ncbi.nlm.nih.gov/pubmed/24270571

Fenech M, Kirsch-Volders M, Natarajan AT, Surrales J, Croft J, Parry J, Norppa H (2011) Molecular mechanisms of micronucleus, nucleoplasmic bridge and

nuclear bud formation in human cells. Mutagenesis 26:125–132
Feng JM, Tian HF, Wen JF (2013) Origin and evolution of the eukaryotic SSU processome revealed by a comprehensive genomic analysis and implications for the origin of the nucleolus. Genome Biol Evol 5:2255–2267
Fischer AH (2014) The diagnostic pathology of the nuclear envelope in human cancers. Adv Exp Med Biol 773:49–75
Funkhouser CM, Sknepnek R, Shimi T, Goldman AE, Goldman RD, Olvera de la Cruz M (2013) Mechanical model of blebbing in nuclear lamin meshworks. Proc Natl Acad Sci U S A 110:3248–3253
Gardner MK, Odde DJ, Bloom K (2008) Kinesin-8-molecular motors: putting the brakes on chromosome oscillations. Trends Cell Biol 18:307–310
Gassmann R, Vagnarelli P, Hudson D, Earnshaw WC (2004) Mitotic chromosome formation and the condensin paradox. Exp Cell Res 296:35–42
Gaszner M, Felsenfeld G (2006) Insulators: exploiting transcriptional and epigenetic mechanisms. Nat Rev Genet 7:703–713
Ghadially FN, Parry EW (1966) Ultrastructure of a human hepatocellular carcinoma and surrounding non-neoplastic liver. Cancer 19:1989–2004
Ghirlando R, Felsenfeld G (2013) Chromatin structure outside and inside the nucleus. Biopolymers 99:225–232
Ghirlando R, Giles K, Gowher H, Xiao T, Xu Z, Yao H, Felsenfeld G (2012) Chromatin domains, insulators, and the regulation of gene expression. Biochim Biophys Acta 1819:644–651
Ghosh S, Paweletz N (1996) Nucleolar organization as revealed in cell spreads. Cell Biol Int 20:465–470
Giles KE, Gowher H, Ghirlando R, Jin C, Felsenfeld G (2010) Chromatin boundaries, insulators, and long-range interactions in the nucleus. Cold Spring Harb Symp Quant Biol 75:79–85
Gisselsson D, Björk J, Höglund M, Mertens F, Dal Cin P, Akerman M, Mandahl N (2001) Abnormal nuclear shape in solid tumors reflects mitotic instability. Am J Pathol 158:199–206
Golovnin A, Melnikova L, Volkov I, Kostuchenko M, Galkin AV, Georgiev P (2008) 'Insulator bodies' are aggregates of proteins but not of insulators. EMBO Rep 9:440–445
Golovnin A, Volkov I, Georgiev P (2012) SUMO conjugation is required for the assembly of Drosophila Su (Hw) and Mod(mdg4) into insulator bodies that facilitate insulator complex formation. J Cell Sci 125:2064–2074
Goto T, Sato A, Adachi S, Iemura S, Natsume T, Shibuya H (2013) IQGAP1 protein regulates nuclear localization of b-catenin via importin-b5 protein in Wnt signaling. J Biol Chem 288:36351–36360
Grewal SI, Jia S (2007) Heterochromatin revisited. Nat Rev Genet 8:35–46
Grigoryev SA (2012) Nucleosome spacing and chromatin higher-order folding. Nucleus 3:493–499
Gu B, Bessler M, Mason PJ (2009) Dyskerin, telomerase and the DNA damage response. Cell Cycle 8:6–10
Guelen L, Pagie L, Brasset E, Meuleman W, Faza MB, Talhout W, Eussen BH, de Klein A et al (2008) Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions. Nature 453:948–951
Guido M, Fassan M, Giacomelli L, Cillo U, Farinati F, Burra P, Fagiuoli S, Rugge M (2008) Micronuclei and broken eggs in human liver carcinogenesis. Anticancer Res 28:2507–2511
Hatch EM, Fischer AH, Deerinck TJ, Hetzer MW (2013) Catastrophic nuclear envelope collapse in cancer cell micronuclei. Cell 154:47–60
Hayashi H, Maeda T, Adachi E, Shimada M, Matsumata T, Takenaka K (1995) Argyrophilic nucleolar organizer regions (AgNOR) of resected intrahepatic cholangiocellular carcinomas. Hepatogastroenterology 42:440–444
Haynes ME, Davies HG (1973) Observations on the origin and significance of the nuclear envelope-limited monolayers of chromatin unit threads associated with the cell nucleus. J Cell Sci 13:139–171
Heddle JA, Cimino MC, Hayashi M, Romagna F, Shelby MD, Tucker JD, Vanparys P et al (1991) Micronuclei as an index of cytogenetic damage: past, present, and future. Environ Mol Mutagen 18:277–291
Hirano T (2012a) Chromosome territories meet a condensin. PLoS Genet 8:e1002939
Hirano T (2012b) Condensins: universal organizers of chromosomes with diverse functions. Genes Dev 26:1659–1678
Hoffelder DR, Luo L, Burke NA, Watkins SC, Gollin SM, Saunders WS (2004) Resolution of anaphase bridges in cancer cells. Chromosome 112:389–397
Holwerda S, de Laat W (2012) Chromatin loops, gene positioning, and gene expression. Front Genet 3:217
Horvath E, Kovacs K, Ross RC (1972) Ultrastructural findings in a well-differentiated hepatoma. Digestion 7:74–82
Hruban Z (1979) Ultrastructure of hepatocellular tumors. J Toxicol Environ Health 5:403–433
Hübner MR, Spector DL (2010) Chromatin dynamics. Annu Rev Biophys 39:471–489
Huh I, Zeng J, Park T, Yi SV (2013) DNA methylation and transcriptional noise. Epigenet Chromatin 6:9
Iarmarcovai G, Botta A, Orsière T (2006) Number of centromeric signals in micronuclei and mechanisms of aneuploidy. Toxicol Lett 166:1–10
Jain R, Malhotra V, Kumar N, Sarin SK (1998) Nucleolar organizer regions in cirrhosis and hepatocellular carcinoma. Trop Gastroenterol 19:100–101
Jamison JM, Gilloteaux J, Perlaky L, Thiry M, Smetana K, Neal D, McGuire K, Summers JL (2010) Nucleolar changes and fibrillarin redistribution following apatone treatment of human bladder carcinoma cells. J Histochem Cytochem 58:635–651

Jevtic P, Edens LJ, Vukovic LD, Levy DL (2014) Sizing and shaping the nucleus: mechanisms and significance. Curr Opin Cell Biol 28C:16–27

Jin JC, Zhang X, Jin XL, Qian CS, Jiang H, Ruan Y (2014) MicroRNA-122 regulation of the morphology and cytoarchitecture of hepatoma carcinoma cells. Mol Med Rep 9:1376–1380

Jones (2012) http://www.ncbi.nlm.nih.gov/pubmed/22641018

Jost KL, Bertulat B, Cardoso MC (2012) Heterochromatin and gene positioning: inside, outside, any side? Chromosoma 121:555–563

Junera HR, Masson C, Geraud G, Hernandez-Verdun D (1995) The three-dimensional organization of ribosomal genes and the architecture of the nucleoli vary with G1, S and G2 phases. J Cell Sci 108:3427–3441

Kanoh J (2013) Release of chromosomes from the nuclear envelope: a universal mechanism for eukaryotic mitosis? Nucleus 4:100–104

Kerenji AS, Bozovic ZL, Tasic MM, Budimlija ZM, Klem IA, Polzovic AF (2000) Fractal dimension od hepatocytes' nuclei in normal liver vs hepatocellular carcinoma (HCC) in human subjects – preliminary results. Arch Oncol 8:47–50

Klebs E (1889) Die allgemeine Pathologie (General pathology), vol 2. G. Fischer Verlag, Jena

Kleine T, Maier UG, Leister D (2009) DNA transfer from organelles to the nucleus: the idiosyncratic genetics of endosymbiosis. Annu Rev Plant Biol 60:115–138

Kniebiehler B, Mirre C, Stahl A (1983) Multiplication of nucleolar fibrillar centres and absence of rDNA amplification in mouse oocyte during meiotic prophase I. Tissue Cell 15:159–166

Korgaonkar C, Hagen J, Tompkins V, Frazier AA, Allamargot C, Quelle FW, Quelle DE (2005) Nucleophosmin (B23) targets ARF to nucleoli and inhibits its function. Mol Cell Biol 25:1258–1271

Kosar M, Bartkova J, Hubackova S, Hodny Z, Lukas J, Bartek J (2011) Senescence-associated heterochromatin foci are dispensable for cellular senescence, occur in a cell type-and insult-dependent manner and follow expression of p16 (ink4a). Cell Cycle 10:457–468

Kutscheidt S, Zhu R, Antoku S, Luxton GW, Stagljar I, Fackler OT, Gundersen GG (2014) FHOD1 interaction with nesprin-2G mediates TAN line formation and nuclear movement. Nat Cell Biol 16:708–715

Kuvichkin VV (2012) Isolation of chromatin DNA tightly bound to the nuclear envelope of HeLa cells. J Membr Biol 245:683–690

Lee JH, Lee YS, Jeong SA, Khadka P, Roth J, Chung IK (2014) Catalytically active telomerase holoenzyme is assembled in the dense fibrillar component on the nucleolus during S phase. Histochem Cell Biol 141:137–152

Legartova S, Stixova L, Laur O, Kozubek S, Sehnalova P, Bartiva E (2014) Nuclear structures surrounding internal lamin invaginations. J Cell Biochem 115:476–487

Leister and Kleine (2011) http://www.ncbi.nlm.nih.gov/pubmed/22017974

Lepoint A, Goessens G (1982) Quantitative analysis of Ehrlich tumour cell nucleoli during interphase. Exp Cell Res 137:456–459

Lewellyn L, Carvalho A, Desai A, Maddox AS, Oegema K (2011) The chromosomal passenger complex and centralspindlin independently contribute to contractile ring assembly. J Cell Biol 193:155–169

Li P, Wang D, Li H, Yu Z, Chen X, Fang J (2014) Identification of nucleolus-localized PTEN and its function in regulating ribosome biogenesis. Mol Biol Rep 41:6383–6390

Liashkovich I, Meyring A, Oberleithner H, Shahin V (2012) Structural organization of the nuclear pore permeability barrier. J Control Release 160:601–608

Liu B, Zhang J, Huang C, Liu H (2012) Dyskerin overexpression in human hepatocellular carcinoma is associated with advanced clinical stage and poor patient prognosis. PLoS ONE 7:e43147

Livezey KW, Negorev D, Simon D (2002) Increased chromosomal alterations and micronuclei formation in human hepatoma HepG2 cells transfected with the hepatitis B virus HBX gene. Mutat Res 505:63–74

Livni N, Behar A, Brautbar N (1977) Ultrastructure of hepatocellular carcinoma in a cirrhotic liver. Isr J Med Sci 13:590–599

Logarinho E, Bousbaa H (2008) Kinetochore-microtubule interactions "in check" by Bub1, Bub3 and BubR1: the dual task of attaching and signalling. Cell Cycle 7:1763–1768

Lombardi ML, Lammerding J (2011) Keeping the LINC: the importance of nucleocytoskeletal coupling in intracellular force transmission and cellular function. Biochem Soc Trans 39:1729–1734

Losada A (2014) Cohesin in cancer: chromosome segregation and beyond. Nat Rev Cancer 14:389–393

Lu W, Schneider M, Neumann S, Jaeger VM, Taranum S, Munck M, Cartwright S et al (2012) Nesprin interchain associations control nuclear size. Cell Mol Life Sci 69:3493–3509

Luijsterburg MS, van Attikum H (2011) Chromatin and the DNA damage response: the cancer connection. Mol Oncol 5:349–367

Lund E, Collas P (2013) Nuclear lamins: making contacts with promoters. Nucleus 4:424–430

Luperchio TR, Wong X, Reddy KL (2014) Genome regulation at the peripheral zone: lamina associated domains in development and disease. Curr Opin Genet Dev 25:50–61

Luxton GG, Gomes ER, Folker ES, Worman HJ, Gundersen GG (2011) TAN lines: a novel nuclear envelope structure involved in nuclear positioning. Nucleus 2:173–181

Ma MH, Blackburn CRB (1973) Fine structure of primary liver tumors and tumor-bearing liver in man. Cancer Res 33:1766–1774

Maertens GN, Cook NJ, Wang W, Hare S, Gupta SS, Öztop I, Lee K, Pye VE, Cosnefroy O et al (2014)

Structural basis for nuclear import of splicing factors by human transportin 3. Proc Natl Acad Sci U S A 111:2728–2733
Maeshima K, Imai R, Tamura S, Nozaki T (2014) Chromatin as dynamic 10-nm fibers. Chromosoma 123:225–237
Maggi LB, Winkeler CL, Miceli AP, Apicelli AJ, Brady SN, Kuchenreuther MJ, Weber JD (2014) ARF tumor suppression in the nucleolus. Biochim Biophys Acta 1842:831–839
Maia AF, Lopes CS, Sunkel CE (2007) BubR1 and CENP-E have antagonistic effects upon the stability of microtubule-kinetochore attachments in Drosophila S2 cell mitosis. Cell Cycle 6:1367–1378, Genetics 185, 113–127
Maiato H, Sampaio P, Lemos CL, Findlay J, Carmena M, Earnshaw WC, Sunkel CE (2002) MAST/Orbit has a role in microtubule-kinetochore attachment and is essential for chromosome alignment and maintenance of spindle bipolarity. J Cell Biol 157:749–760
Mayr MI, Storch M, Howard J, Mayer TU (2011) A non-motor microtubule binding site is essential for the high processivity and mitotic function of kinesin-8 Kif18A. PLoS ONE 6:e27471
Mazumdar M, Misteli T (2005) Chromokinesins: multitalented players in mitosis. Trends Cell Biol 15:349–355
Mirre C, Stahl A (1981) Ultrastructural organization, sites of transcription and distribution of fibrillar centres in the nucleolus of the mouse oocyte. J Cell Sci 48:105–126
Muqbil I, Bao B, Abou-Samra AB, Mohammad RM, Azmi AS (2013) Nuclear export mediated regulation of microRNAs: potential target for drug intervention. Curr Drug Targets 14:1094–1100
Nagao T, Ishida Y, Yamazaki K, Kondo Y (1995) Nucleolar organizer regions in hepatocellular carcinoma related to the cell cycle, cell proliferation and histologic grade. Pathol Res Pract 191:967–972
Natalizio BJ, Wente SR (2013) Postage for the messenger: designating routes for nuclear mRNA export. Trends Cell Biol 23:365–373
Niepel M, Molloy KR, Williams R, Farr JC, Meinema AC, Vecchietti N, Cristea IM et al (2013) The nuclear basket proteins Mlp1p and Mlp2p are part of a dynamic interactome including Esc1p and the proteasome. Mol Biol Cell 24:3920–3938
Nishibuchi G, Nakayama J (2014) Biochemical and structural properties of heterochromatin protein 1: understanding its role in chromatin assembly. J Biochem 156:11–20
Nonomura A, Mizukami Y, Matsubara F, Nakanuma Y (1990a) Identification of nucleolar organizer regions in non-neoplastic and neoplastic hepatocytes by the silver-staining technique. Liver 10:229–238
Nonomura A, Matsubara F, Mizukami Y, Izumi R, Nakanuma Y, Kurumaya H, Watanabe K, Takayanagi N (1990b) Demonstration of nucleolar organizer regions in intrahepatic bile duct carcinoma by the silver-staining technique. Liver 10:269–277
Norppa H, Falck GC (2003) What do human micronuclei contain? Mutagenesis 18:221–233
Ohsugi M, Adachi K, Horai R, Kakuta S, Sudo K, Kotaki H, Tokai-Nishizumi N, Sagara H et al (2008) Kid-mediated chromosome compaction ensures proper nuclear envelope formation. Cell 132:771–782
Olins DA, Olins AL (2009) Nuclear envelope-limited chromatin sheets (ELCS) and heterochromatin higher order structure. Chromosoma 118:537–548
Olson MO, Hingorani K, Szebeni A (2002) Conventional and nonconventional roles of the nucleolus. Int Rev Cytol 219:199–266
Osorio and Gomes (2014) http://www.ncbi.nlm.nih.gov/pubmed/24563363
Ostlund C, Folker ES, Choi JC, Gomes ER, Gundersen GG, Worman HJ (2009) Dynamics and molecular interactions of linker of nucleoskeleton and cytoskeleton (LINC) complex proteins. J Cell Sci 122:4099–4108
Padeken J, Heun P (2014) Nucleolus and nuclear periphery: velcro for heterochromatin. Curr Opin Cell Biol 28C:54–60
Parveen S, Bukhari MH, Khan SA, Naveed IA, Chaudhry NA, Tahseen M (2006) AgNOR stain in normal, cirrhotic and carcinomatous liver. Biomedica 22:59–61
Patel SS, Belmont BJ, Sante JM, Rexach MF (2007) Natively unfolded nucleoporins gate protein diffusion across the nuclear pore complex. Cell 129:83–96
Peters R (2009) Translocation through the nuclear pore: Kaps pave the way. BioEssays 31:466–477
Peters JM, Tedeschi A, Schmitz J (2008) The cohesin complex and its roles in chromosome biology. Gene Dev 22:3089–3114
Phipps KR, Charette J, Baserga SJ (2011) The small subunit processome in ribosome biogenesis – progress and prospects. Wiley Interdiscip Rev RNA 2:1–21
Piazza I, Haering CH, Rutkowska A (2013) Condensin: crafting the chromosome landscape. Chromosoma 122:175–190
Pickett-Heaps JD, Forer A (2001) Pac-Man does not resolve the enduring problem of anaphase chromosome movement. Protoplasma 215:16–20
Ploton D, Beorchia A, Menager M, Jeannesson P, Adnet JJ (1987) The three-dimensional ultrastructure of interphasic and metaphasic nucleolar argyrophilic components studied with high-voltage electron microscopy in thick sections. Biol Cell 59:113–120
Poleshko A, Katz RA (2014) Specifying peripheral heterochromatin during nuclear lamina reassembly. Nucleus 5:32–39
Poon BPK, Mekhail K (2011) Cohesin and related coiled-coil domain-containing complexes physically and functionally connect the dots across the genome. Cell Cycle 16:2669–2682
Rajanala K, Nandicoori VK (2012) Localization of nucleoporin Trp to the nuclear pore complex is

essential for Trp mediated regulation of the export of unspliced RNA. PLoS ONE 7:e29921
Rajgor D, Shanahan CM (2013) Nesprins: from the nuclear envelope and beyond. Expert Rev Mol Med 15:e5
Raska I, Shaw PJ, Cmarko D (2006) Structure and function of the nucleolus in the spotlight. Curr Opin Cell Biol 18:325–334
Rather LJ (1978) The genesis of cancer. A study in the history of ideas. The Johns Hopkins University Press, Baltimore
Reddy KL, Feinberg AP (2013) Higher order chromatin organization in cancer. Semin Cancer Biol 23:109–115
Richly and Leister (2004) http://www.ncbi.nlm.nih.gov/pubmed/15014143
Rothballer A, Schwartz TU, Kutay U (2013) LINCing complex functions at the nuclear envelope: what the molecular architecture of the LINC complex can reveal about its function. Nucleus 4:29–36
Ruben GJ, Kirkland JG, Macdonoush T, Chen M, Dubey RN, Gartenberg MR, Kamakaka RT (2011) Nucleoporin mediated nuclear positioning and silencing of HMR. PLoS ONE 7:e21923
Ruebner BH, Gonzalez-Licea A, Slusser RJ (1967) Electron microscopy of some human hepatomas. Gastroenterology 53:18–30
Rynearson AL, Sussman CR (2011) Nuclear structure, organization, and oncogenesis. J Gastrointest Cancer 42:112–117
Samanta S, Dey P (2012) Micronucleus and its applications. Diagn Cytopathol 40:84–90
Sanhaji M, Friel CT, Wordeman L, Louwen F, Yuan J (2011) Mitotic centromere-associated kinesin (MCAK): a potential cancer drug target. Oncotarget 2:935–947
Sato S (1992) Identification of the plant nucleolonema using silver staining of serial ultrathin sections. Biotech Histochem 67:149–152
Sato S, Yano H, Makimoto Y, Kaneta T, Sato Y (2005) Nucleolonema as a fundamental substructure of the nucleolus. J Plant Res 118:71–81
Schaff Z, Lapis K, Safrany L (1971) The ultrastructure of primary hepatocellular cancer in man. Virchows Arch A Pathol Pathol Anat 352:340–538
Schwarzacher HG, Wachtler F (1993) The nucleolus. Anat Embryol (Berl) 188:515–536
Shain DH, Gagliardi LJ (2011) Can molecular cell biology explain chromosome motions? Theor Biol Med Model 8:16
Shimizu K, Izumi R, Ii T, Muraoka K, Inoue T, Fukushiam W, Sakamoto K, Tani T, Hashimoto T, Yagi M, Miyazaki I et al (1995) Prognostic significance of nucleolar organizer regions in hepatocellular carcinoma. Hepatology 21:393–397
Shiro T, Seki T, Naitoh Y, Inoue K, Okamura A (1993) A correlation of argyrophilic nucleolar organizer regions with stages of hepatocellular carcinoma. Cancer 71:44–49
Simon DN, Wilson KL (2011) The nucleoskeleton as a genome-associated dynamic 'network of networks'. Nat Rev Mol Cell Biol 12:695–708
Sirri V, Urcuqui-Inchima S, Roussel P, Hernandez-Verdun D (2008) Nucleolus: the fascinating nuclear body. Histochem Cell Biol 129:13–31
Sleeman JE (2004) Dynamics of the mammalian nucleus: can microscopic movements help us to understand our genes? Phil Trans R Soc Lond A 362:2775–2793
Smetana K, Gyorkey F, Gyorkey P, Busch H (1972) Studies on nucleoli and cytoplasmic fibrillar bodies of human hepatocellular carcinomas. Cancer Res 32:925–932
Smith (2011) http://www.ncbi.nlm.nih.gov/pubmed/21803764
Snaar S, Wiesmeijer K, Jochemsen AG, Tanke HJ, Dirks RW (2000) Mutational analysis of fibrillarin and its mobility in living human cells. J Cell Biol 151:653–662
Snow CJ, Paschal BM (2014) Roles of the nucleoporin Trp in cancer and aging. Adv Exp Med Biol 773:309–322
Snow CJ, Dar A, Dutta A, Kehlenbach RH, Paschal BM (2013) Defective nuclear import of Trp in Progeria reflects the Ran sensitivity of large cargo transport. J Cell Biol 201:541–557
Sofueva S, Yaffe E, Chan WC, Georgopoulou D, Vietri Rudan M, Mira-Bontenbal H et al (2013) Cohesin-mediated interactions organize chromosomal domain architecture. EMBO J 32:3119–3129
Solomon DA, Kim JS, Waldman T (2014) Cohesin gene mutations in tumorigenesis: from discovery to clinical significance. BMB Rep 47:299–310
Soltanieh S, Lapensee M, Dragon F (2014) Nucleolar proteins Bfr2 and Enp2 interact with DEAD-box RNA helicase Dbp4 in two different complexes. Nucleic Acids Res 42:3194–3206
Sosa BA, Rothballer A, Kutay U, Schwartz TU (2012) LINC complexes form by binding of three KASH peptides to domain interfaces of trimeric SUN proteins. Cell 149:1035–1047
Starr DA (2011) Watching nuclei move. Insights into how kinesin-1 and dynein function together. BioArchitecture 1:9–13
Starr DA, Fridolfsson HN (2010) Interactions between nuclei and the cytoskeleton are mediated by SUN-KASH nuclear-envelope bridges. Annu Rev Cell Dev Biol 26:421–444
Stephens AD, Quammen CW, Chang B, Haase J, Taylor RM, Bloom K (2013) The spatial segregation of pericentric cohesin and condensin in the mitotic spindle. Mol Biol Cell 24:3909–3919
Strambio-De-Castilla C (2013) Jumping over the fence: RNA nuclear export revisited. Nucleus 4:95–99
Swanson EC, Manning B, Zhang H, Lawrence JB (2013) Higher-order unfolding of satellite heterochromatin is a consistent and early event in cell senescence. J Cell Biol 203:929–942
Tajrishi MM, Tuteja R, Tuteja N (2011) Nucleolin: the most abundant multifunctional phosphoprotein of nucleolus. Commun Integr Biol 4:267–275
Tapia-Alveal et al (2014) http://www.ncbi.nlm.nih.gov/pubmed/24981336

Terradas M, Martin M, Tusell L, Genesca A (2010) Genetic activities in micronuclei: is the DNA entrapped in micronuclei lost for the cell? Mutat Res 705:60–67

Thein KH, Kleylein-Sohn J, Nigg EA, Gruneberg U (2007) Astrin is required for the maintenance of sister chromatid cohesion and centrosome integrity. J Cell Biol 178:345–354

Theron JJ, Mekel RC (1964) Electron microscopical studies of human malignant hepatoma cells. Tijdschr Gastroenterol 36:152–164

Thiry M, Lamaye F, Lafontaine DLJ (2011) The nucleolus. When two became three. Nucleus 2:289–293

Tischoff I, Tannapfel A (2008) DNA methylation in hepatocellular carcinoma. World J Gastroenterol 14:1741–1748

Toker C, Trevino N (1966) Ultrastructure of human primary hepatic carcinoma. Cancer 19:1594–1606

Trerè D, Borzio M, Morabito A, Borzio F, Roncalli M, Derenzini M (2003) Nucleolar hypertrophy correlates with hepatocellular carcinoma development in cirrhosis due to HBV infection. Hepatology 37:72–78

Tsai RY, Pederson T (2014) Connecting the nucleolus to the cell cycle and human disease. FASEB J 28:3290–3296

Tu Z, Zhuang X, Yao YG, Zhang R (2013) BRG1 is required for formation of senescence-associated heterochromatin foci induced by oncogenic RAS or BRCA1 loss. Mol Cell Biol 33:1819–1829

Turner AJ, Knox AA, Priteo JL, McStay B, Watkins NJ (2009) A novel small-subunit processome assembly intermediate that contains the U3 snoRNP, nucleolin, RRP5, and DBP4. Mol Cell Biol 29:3007–3017

Utani K, Kohno Y, Okamoto A, Shimizu N (2010) Emergence of micronuclei and their effects on the fate of cells under replication stress. PLoS ONE 5:e10089

Utani K, Okamoto A, Shimizu N (2011) Generation of micronuclei during interphase by coupling between cytoplasmic membrane blebbing and nuclear budding. PLoS ONE 6:e27233

van der Horst A, Lens SMA (2014) Cell division: control of the chromosomal passenger complex in time and space. Chromosoma 123:25–42

Van Steensel B (2011) Chromatin: constructing the big picture. EMBO J 30:1885–1895

Vanneste D, Ferreira V, Vernos I (2011) Chromokinesins: localization-dependent functions and regulation during cell division. Biochem Soc Trans 39:1154–1160

Vargas JD, Hatch EM, Anderson DJ, Hetzer MW (2012) Transient nuclear envelope rupturing during interphase in human cancer cells. Nucleus 3:88–100

Vasuri F, Rocchi L, Degiovanni A, Guinchi F, Brandi G, Trerè D, Maontanaro L, D'Errico-Grigioni A (2015) Dyskerin expression in human fetal, adult and neoplastic intrahepatic bile ducts: correlations with cholangiocarcinoma aggressiveness. Histopathology 66:244–251

Vogelmann J, Valeri A, Guillou E, Cuvier O, Nollmann M (2011) Roles of chromatin insulator proteins in higher-order chromatin organization and transcription regulation. Nucleus 2:358–369

Von Hansemann DP (1890) Über asymmetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung (On the asymmetrical cell division in epithelial cancers and its biological significance). Virchows Arch F Path Anat 119:299–326

Von Hansemann DP (1891) Über pathologische Mitosen (On pathological mitoses). Virchows Arch Path Anat 123:356–370

Von Hansemann DP (1893) Studien über die Spezificität, den Altruismus und die Anaplasie der Zellen, mit besonderer Berücksichtigung der Geschwülste. A. Hirschwald, Berlin

Von Hansemann DP (1897) Die microscopische Diagnose der bösartigen Geschwülste (The microscopic diagnosis of malignant tumors), 2nd edn. A. Hirschwald, Berlin

Wagner RP (1999) Rudolph Virchow and the genetic basis of somatic ecology. Genetics 151:917–920

Wälde S, Kehlenbach RH (2010) The part and the whole: functions of nucleoporins in nucleocytoplasmic transport. Trends Cell Biol 20:461–469

Wallace HA, Bosco G (2013) Condensins and 3D organization of the interphase nucleus. Curr Genet Med Rep 1:219–229

Walter A, Chapuis C, Huet S, Ellenberg J (2013) Crowded chromatin is not sufficient for heterochromatin formation and not required for its maintenance. J Struct Biol 184:445–453

Walters AD, Bommakanti A, Cohen-Fix O (2012) Shaping the nucleus: factors and forces. J Cell Biochem 113:2813–2821

Wandke C, Kutay U (2013) Enclosing chromatin: reassembly of the nucleus after open mitosis. Cell 152:1222–1225

Watanabe Y (2010) Temporal and spatial regulation of targeting aurora B to the inner centromere. Cold Spring Harb Symp Quant Biol 75:419–423

Wee A, Nilsson B (2003) Highly well differentiated hepatocellular carcinoma and benign hepatocellular lesions. Can they be distinguished on fine needle aspiration biopsy? Acta Cytol 47:16–26

Wei GH, Liu DP, Liang CC (2005) Chromatin domain boundaries: insulators and beyond. Cell Res 15:292–300

Wei Y, Li L, Wang D, Zhang CY, Zen K (2014) Importin 8 regulates the transport of mature microRNAs into the cell nucleus. J Biol Chem 289:10270–10275

Wen CH, Lin CH, Tsao SC, Su YC, Tsai MH, Chai CY (2013) Micronucleus scoring in liver fine needle aspiration cytology. Cytopathology 24:391–395

Wente SR, Rout MP (2011) The nuclear pore complex and nuclear transport. Cold Spring Harb Perspect Biol 2:a000562

Whitman RC (1919) Somatic mutations as a factor in the production of cancer: a critical review of v. Hansemann's theory of anaplasia in the light of modern knowledge of genetics. J Cancer Res 4:181–202

Willis RA (1948) Pathology of tumours. Butterworths, London

Wu F, Yao J (2013) Spatial compartmentalization at the nuclear periphery characterized by genome-wide mapping. BMC Genomics 14:591

Wu J, Lee KC, Dickinson RB, Lele TP (2011) How dynein and microtubules rotate the nucleus. J Cell Physiol 226:2666–2674

Xu DH, Liu F, Li X, Chen XF, Jing GJ, Wu FY, Shi SL, Li QF (2014) Regulatory role of nucleophosmin during the differentiation of human liver cancer cells. Int J Oncol 45:264–272

Yang J, Corces VG (2012) Insulators, long-range interactions, and genome function. Curr Opin Genet Dev 22:86–92

Zbarsky IB (1981) Nuclear skeleton structures in some normal and tumor cells. Mol Biol Rep 7:139–148

Zhang R, Adams PD (2007) Heterochromatin and its relationship to cell senescence and cancer therapy. Cell Cycle 6:784–789

Zhang WH, Zhu SN, Lu SL, Huang YL, Zhao P (2000) Three-dimensional image of hepatocellular carcinoma under confocal laser scanning microscope. World J Gastroenterol 6:344–347

Zhang R, Chen W, Adams PD (2007) Molecular dissection of formation of senescence-associated heterochromatin foci. Mol Cell Biol 27:2343–2358

Zhong Z, Wilson KL, Dahl KN (2010) Beyond lamins other structural components of the nucleoskeleton. Methods Cell Biol 98:97–119

Zhou J, Troyanskaya OG (2014) Global quantitative modeling of chromatin factor interactions. PLoS Comput Biol 10:e1003525

Zink D, Fischer AH, Nickerson JA (2004) Nuclear structure in cancer cells. Nat Rev Cancer 4:677–687

Zuin J, Dixon JR, van der Reijden MI, Ye Z, Kolovos P, Brouwer RW, van de Corput MP et al (2014) Cohesin and CTCF differentially affect chromatin architecture and gene expression in human cells. Proc Natl Acad Sci U S A 111:996–1001

Zullo JM, Demarco IA, Piqué-Regi R, Gaffney DJ, Epstein CB, Spooner CJ, Luperchio TR (2012) DNA sequence-dependent compartmentalization and silencing of chromatin at the nuclear lamina. Cell 149:1474–1487

Nucleus, Nuclear Structure, and Nuclear Functions: Pathogenesis of Nuclear Abnormalities in Cancer

170

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_170

Abstract

The numerous types of structural abnormalities of cancer cell nuclei are directly associated with functional disorders of nuclear homeostasis, DNA replication and its fidelity, and cell division, this general disorder being a hallmark of malignant transformation. Basically, the nuclear abnormalities seen in cytologic and histologic preparations reflect progressive chromosomal and genomic instability and their effects on the higher-order structure of chromatin. The diverse types of chromatin are organized within the nuclear space in a specific fashion and occupy distinct intranuclear compartments. These patterns are massively altered in progressing cancer cells, involving disturbed arrangement of chromatin fibers, abnormal heterochromatin generation, disordered production of euchromatin strings, failure of nonrandom positioning of interphase chromosomes within the nuclear matrix, abnormal attachment of chromosomes to the nuclear membrane, and anomalies of intranuclear chromosome movements.

Pathogenic Pathways of Structural Nuclear Abnormalities in Cancer: General Aspects

The numerous types of structural abnormalities of cancer cell nuclei are directly associated with functional disorders of nuclear homeostasis, DNA replication and its fidelity, and cell division. In particular, structural nuclear abnormalities reflect chromosomal instability (CIN) and genomic instability (von Hansemann 1893; Boveri 1914; reviews: Cheng and Loeb 1993, 1997; Bignold et al. 2006; Thompson et al. 2010). Apart from abnormal chromosome numbers and asymmetrical division being at the base of von Hansemann's concept of anaplasia, numerous structural anomalies found in the nuclei of cancer cells have not yet been sufficiently explained (review: Bignold 2003). This mainly holds true for chromatin changes found in interphase cancer nuclei and described as "coarse chromatin," "stippled chromatin," "hyperchromatism," and "chromatin clumping."

There is evidence that components of diverse types of chromatin are arranged in distinct and dynamic patterns within the nuclear space. These patterns are strikingly different in living cells in comparison with fixed and stained entire nuclei on smears or cut nuclei appearing in histologic sections. Specifically, unfolded chromosomes occupy domains in the nucleus during interphase, providing a uniform density of fine chromatin fibers throughout the living nucleus. In contrast, interphase chromatin is seen in preparations of fixed cells as coarse clumps (heterochromatin) or strings and fibers (euchromatin) (Bignold 2003). Dynamic chromatin patterns are also caused by a nonrandom positioning of interphase chromosomes within the nuclear matrix, chromosomal attachment to nuclear membrane, intranuclear chromosome movements, orientations of chromosomal domains toward nuclear pores during transcription, and connections between chromatin and components of the cytoskeleton.

Pathogenesis of Chromosomal Instability in Cancer: Disordered Centrosome Cycles and Centrosome Amplification (Polycentrosomy)

Centrosomes and Centrioles as Drivers of Cytokinesis

Centrosomes and centrioles are critical structures in the orderly distribution of chromosomes during cell division. The centrosome holds a chief position in the regulation of division, organization of cell polarity and motility, and cilium-dependent sensing and signaling. The centrosome is the main microtubule-organizing center of cells and templates the assembly of the primary cilium. At mitotic entry, the division cycle involves nucleus-centrosome coupling in prophase, requiring recruitment of dynein to nuclear surface, regulated by the protein Asunder (Jodoin et al. 2012). Cytokinesis requires the interaction of centrosomes and centrosome-associated proteins with other effectors, e.g., centralspindlin, which

connects the mitotic spindle to the plasma membrane (Lekomtsev et al. 2012; White and Glotzer 2012; Glotzer 2013).

It is to be expected that disorders of centrosome function in cancer cells have effects far beyond a mere derangement of cell division. Several factors control the structure and function of centrosomes. Two kinases are particularly essential for centrosome duplication, i.e., polo-like kinase 1 (PLK1) and PLK4. PLK1 has several targets that directly affect centrosome biogenesis and function. PLK1 phosphorylates the Wnt signaling protein Axin, which dynamically regulates the centrosome's association with gamma-tubulin (Ruan et al. 2012). Liver kinase B1 (LKB1) controls centrosome function mediated by PLK1 and maintains genomic stability (Werle et al. 2014). A further protein involved in the centrosome cycle is the Fanconi anemia protein, FancJ, which activates PLK1 (Zou et al. 2013). PLK4 possesses an autoregulated instability which limits centrosome duplication to once per normal cell cycle (Holland et al. 2010). In addition, the function of PLK4 is regulated via its phosphorylation by stress-activated protein kinase kinase kinases (SAPKKKs), cooperatively with p53 protein (Nakamura et al. 2013).

Centriole duplication is a process by which two new daughter centrioles are produced from preexisting mother centrioles (Browntree and Rogers 2013). Centriole duplication is regulated by the proteins PLK4, centrobin, centrosomal proteins of 152 kDa (CEP152), 192 kDa (CEP192), and 135 kDa (CEP135), STIL (SCL/TAL1 interrupting locus; SIL; Vulprecht et al. 2012), and centrosomal protein 4.1-associated protein (CPAP/CENPJ), whereby the shape and number of centrioles are controlled by a CPAP-centrobin interaction on centrioles (Gudi et al. 2014).

A Damaged Centrosome Cycle Induces Centrosome Amplification

Boveri (1914) had reported that supernumerary centrosomes can cause chromosome missegregation in sea urchin eggs. It is now established that deregulation of centrosome structure and function, and a disordered centrosome cycle, are central to the pathogenesis of chromosomal instability in cancer (reviews: D'Assoro et al. 2002; Lingle et al. 2005; Ganem et al. 2009; Duensing and Duensing 2010). Specifically, mechanisms causing centrosome amplification play the main role in this pathway, whereby numerous chemical carcinogens and ionizing radiation are well known to cause centrosome duplication. Other causes include failure of cytokinesis and alterations of regulators of centrosome structure and function, e.g., via mutations. The fate of cells with such errors depends on whether the centrosome cycle and the chromosome cycle remain coupled or not (Lingle et al. 2005). In case of maintained coupling, cells enter the G2 phase of the cycle with duplicated centrosomes and a 4N chromosome complement. In the uncoupled state, cells go through one or more rounds of centrosome/centriole duplication in the absence of chromosome replication. Subsequent division will result in 4N cells with multiple centrosomes and formation of multipolar spindles and multipolar mitotic figures. This is a mechanism that is frequent in poorly differentiated cancer cells and cancer cells altered by radiotherapy. Centrosome amplification is a key mechanism for the generation of an aneuploid cellular offspring, as further outlined in a following paragraph. The centrosome-driven biogenesis of spindles and spindle pole bodies is directly associated with nuclear function, as spindle pole bodies are inserted in the nuclear envelope (Jaspersen and Ghosh 2012), the latter itself being a chromatin organizer (Zuleger et al. 2011).

Centrosome Cycle Anomalies in Cancer: Centrosome Clustering as a Repair Mechanism Protecting Against Abnormal Centrosome Cycles and Polycentrosomy

As centrosome cycle anomalies and polycentrosomy are ruinous for normal spindle biogenesis and an orderly cell division, centrosome amplification causes cell division failure, chaotic genomes, and cell death in cancer cells.

In general, multipolar spindles are antagonistic to cell viability, however depending on the ploidy status of cells involved. For example, supernumerary centrosomes in aneuploid cancer cells may be unable to nucleate microtubules and thus generate multipolar mitosis, due to lack of functional centrioles. In contrast, diploid cancer cells possess a functional centriole and are capable to nucleate microtubules and create spindles (Ghadimi et al. 2000; Difilippantonio et al. 2009). Can, therefore, cancer cells circumvent the disastrous effects of centrosome amplification ? Even in the presence of two or more centrosomes, part of neoplastic cells can obviously divide in a successful manner, due to suppression of multipolar mitosis (Kwon et al. 2008). This is usually accomplished through clustering of supernumerary centrosomes into bipolar arrays, whereby extra centrosomes undergo coalescence into two functional spindle poles (centrosome clustering; Brinkley 2001; Godinho et al. 2009). Through this mechanism, a clone of aneuploidy cancer cells emerges. Within this aneuploidy clone, selection mechanisms will promote the development of cells with bipolar spindles, e.g., via selective inactivation of extra centrosomes.

Centrosome clustering is a highly complex process that is mediated by APC/C (cyclosome), whereby the motor kinesin Eg5 is a substrate of APC/C-CDH1, inhibition of APC/C resulting in stabilization of Eg5, while increased Eg5 levels prevent centrosome clustering (Drosopoulos et al. 2014). Successful cell division, both of normal and cancer cells, depends on a highly conserved and tightly controlled program that regulates nuclear envelope breakdown, chromosome condensation and alignment, spindle formation, sister chromatid separation, anaphase motors, cytokinesis, and restoration of nuclei. The successful performance of this program not only depends on the switching on of several control and checkpoint proteins but also the selective and timely degradation and elimination of distinct proteins. This is accomplished by the proteasomal pathway and the action of several E-type ubiquitin ligases that generate ubiquitin chains containing target proteins. One of these ligases that are central to cell division is the anaphase-promoting complex. The anaphase-promoting complex or cyclosome (APC/C) is a molecular machine that regulated sister chromatid segregation and the exit from mitosis via catalyzing the ubiquitinylation of several cell cycle regulators, including cyclins. APC/C consist of a large multi-subunit complex of E3 RING-cullin ubiquitin ligase and is constructed of 14 proteins (He et al. 2014; Zhang et al. 2013a, 2014). The function of this complex is controlled by several cofactors, reversible phosphorylation, and distinct inhibitors (review: Barford 2011). A heterotrimeric protein complex, Ska (spindle- and kinetochore-associated protein complex) which is required for anaphase onset, enhances binding of APC/C to chromosomes and promotes exit from mitosis (Sivakumar et al. 2014). The cyclosome is inhibited by the spindle assembly checkpoint/SAC and unattached kinetochores transduce the SAC via the intramitotic production of a APC/C inhibitor. In addition, nuclear pore complexes in interphase cells also inhibit APC/C through assembling a premitotic anaphase inhibitor (Rodriguez-Bravo et al. 2014).

Apart from its effects on mitosis, centrosome amplification has additional effects on cancer cell behavior. Centrosome amplification can, similar to certain mutated oncogenes, trigger cell invasion. The pathway involves augmented centrosomal microtubule nucleation and an increase in Rac1 activity, which disrupts cell-cell adhesion and promotes invasion (Godinho et al. 2014).

Aneuploidy

Polyploidy and Aneuploidy in Normal Hepatocytes

As expected based on findings in other malignant neoplasm, hepatocellular and cholangiocellular neoplasms display various types of aneuploidy. However, also normal hepatocytes can become aneuploid, showing that aneuploidy is not necessarily a feature of malignancy (Gupta 2000). Between 30 % and 90 % of human hepatocytes

were found to be aneuploid, whereby polyploidy and aneuploidy in the liver are closely linked (Celton-Morizur and Desdouets 2010; Gentric et al. 2012; Duncan et al. 2012; Duncan 2013). Polyploidy plays a pivotal role for the development of binuclear hepatocytes (Toyoda et al. 2005; Guidotti et al. 2003), is a sign of terminal differentiation and cell senescence (Gentric et al. 2012), and is induced by partial hepatectomy, which attenuates hepatocyte replication (Sigal et al. 1999). Hepatocytes of mice may become polyploid and then undergo ploidy reversal to become aneuploid, a process termed ploidy conveyor (Duncan et al. 2010).

Aneuploidy in Hepatocellular and Cholangiocellular Malignancies

Aneuploidy is a well-recognized feature of hepatocellular carcinoma (HCC) and has been found in 37 % to more than 70 % of HCCs (Balsells et al. 1996; Eissa et al. 1997), associated with a high count of argyrophilic nucleolar organizer regions (AgNOR). Both higher aneuploidy and AgNOR counts are also detectable in dysplastic HCC precursor lesions (Attallah et al. 2009). On the other hand, there are HCCs with a "minimal deviation phenotype" that are diploid (Nowell and Morris 1969). DNA ploidy in HCCs was not correlated with age, sex, tumor stage, or underlying liver disease (Nagasue et al. 1992; Hamazaki et al. 1993; Ng et al. 1994). However, there is some evidence that aneuploidy is associated with dedifferentiation (Wilkens et al. 2004) and certain differentiation patterns of HCCs. Higher rates of aneuploidy or hyperploidy were detected in HCCs rich in Mallory-Denk bodies in comparison with standard HCCs (Hoso and Nakanuma 1989).

Accelerated mitotic progression is associated with mitotic defects, chromosome missegregation, and aneuploidy in HCC, caused by overexpression of a distinct oncogene, chromodomain helicase/ATPase DNA-binding protein 1-like (CHD1L) gene, which in turn activated its target, and translationally controlled tumor protein (TCTP); TCTP promotes the ubiquitin-proteasome degradation of Cdc25C during mitotic progression, causing the failure in the dephosphorylation of Cdk1 on Tyr15 and decreased Cdk1 activity, which in turn provokes a faster mitotic exit and chromosome missegregation (Chan et al. 2012). A spindle checkpoint protein, CENP-E, which plays a significant role in the function of the spindle organization checkpoint and the process of chromosome separation, displays a reduced expression in HCC, causing chromosome misseparation and hence aneuploidy (Liu et al. 2009). Aneuploid hepatocellular carcinoma cells often harbor gain of 1q and partial loss of 13q, while cholangiocarcinoma cell lines showed loss of 8p in combination with a relative gain of 8q (Wilkens et al. 2012).

Ploidy and -Somy: Definitions and Terms

The term ploidy denotes the number of sets of chromosomes in a cell. Haploid (N) is the number of chromosomes in a gamete, which is also monoploid (see below). The normal human chromosome set is diploid, i.e., the presence of two sets of chromosomes. A monoploid chromosome number is the number of chromosomes in a single (nonhomologous) set and is, therefore, different from the haploid number. The monoploid number is the number of unique chromosomes in a single complete set. An exact multiple of haploid chromosome complement is called euploid, while a chromosome complement showing a chromosome number other than the diploid 46 in humans is termed heteroploid. Specifically, euploidy is a condition in which a cell has an integral multiple of the monoploid number. In humans, the normal set is 46, an integer multiple ($\times 2$) of 23, but a situation of 69 (an integer multiple of 3; $3 \times 23 = 69$) would also be called an euploid state. *Monoploidy* denotes the loss of an entire set of chromosomes. Monoploid organisms with one half of the normal chromosome number are rare in nature due to unmasking of recessive lethal mutations, but there are examples of monoploid invertebrates originating from unfertilized eggs, such as male bees (drones) and worker ants. *Aneuploidy* is defined as an abnormal chromosomal

situation where one or more chromosomes of a normal set are lacking or are present in more than their normal number of copies. In this sense, aneuploidy is any non-euploid state. Missing or extra chromosomes are a frequent cause of birth defects and are well known to occur in cancer cells. The chief mechanism of aneuploidy is failure of proper separation of chromosomes in the course of cell division (see below). Aneuploidy exists in one of several variants. Nullisomy is a condition with loss of both pairs of homologous chromosomes (chromosomal composition = 2N−2). Monosomy is characterized by the loss of a single chromosome (2N−1). In balanced translocations or deletions, partial monosomy can develop. Here, only a portion of the chromosome is present in a single copy. In doubly monosomy, one chromosome from each of two pair of homologous chromosome is missing (2N−1−1). Disomy (the presence of two chromosome copies) is the normal situation for humans, whereas it is abnormal or aneuploid in organisms that normally are triploid or above. Uniparental disomy denotes a condition where both copies of a chromosome derive from the same parent. In trisomy, gain of an extra copy of a certain chromosome takes place (2N+1). A common example is trisomy 21, the cause of Down's syndrome. In tetrasomy, an extra pair of homologous chromosomes is gained (2N +1). Tetrasomy is rarely found in autosomes (nonsex chromosomes). An isochromosome is defined as a chromosome having the same genetic material on both arms. *Polyploidy* is a condition in which cells have multiple sets of chromosomes beyond the normal set. *Clastogenesis* is a mechanism that results in additions, deletions, or rearrangements of parts of the chromosomes.

Mechanisms of Aneuploidy

In general, aneuploidy is caused by mechanisms that cause a deranged separation of chromosomes during cell division. The most important mechanisms are nondisjunction, chromosomal misalignment, multipolar spindles, monopolar spindles, inactive mitotic checkpoints, sister chromatid cohesion, and merotelic attachment. In nondisjunction, a failure of chromosomal alignment control results in a situation where a chromosome pair is not lined up on the mitotic plate in time. During division, this pair lags behind and will not enter a daughter cell. In the condition of multiple spindles, common in cancer cells, more than two spindle poles are generated. This will result in one daughter cell for each spindle pole, each daughter cells having any complement of chromosomes. In malignant cells, multiple and defective spindle may, however, abolish the cell's capacity to divide, resulting in complex endomitotic polyploid states. In the case of a monopolar spindle, only a single daughter cell can emerge, having a double copy of chromosomes. Inactive mitotic checkpoints are responsible for nondisjunction at multiple chromosomes, in some situations of all chromosomes, as these checkpoints normally control the progression of the entire chromosome sets to the mitotic apparatus. Construction, maintenance, and timely removal of sister chromatid cohesion prior to the mitotic act itself are critical processes that are tightly regulated. The main regulator of this process is a protein complex termed cohesion. Failure of cohesion function and nonremoval of sister chromatid cohesion leads to aneuploidy (Barbero 2011). Centromeric chromatin is also involved in the maintenance of a normal karyotype.

Aneuploidy and the Kinetochore

The kinetochore, a large protein complex localized to the centromeric chromatin domain, is the docking site for mitotic spindle microtubules and a target for the controlling action of the spindle checkpoint. In the course of metaphase, spindle microtubules from the two opposing spindle poles capture each pair of sister kinetochores and create tension across sister kinetochores (Jia et al. 2013). The cross-linking of kinetochore components and microtubule attachment sites during anaphase is mediated by the monopolin complex chiefly compose of two proteins (Corbett et al. 2010). The spindle checkpoint serves to detect improper attachments between microtubules and kinetochores, and in case such misattachments happen,

it switches off the anaphase-promoting complex and delays anaphase onset. Failure of the checkpoint leads to premature sister chromatid separation and aneuploidy. Orderly progression through mitosis also depends on a proper interaction between anchoring proteins and mitotic kinases, including the protein gravin which interacts, in its phosphorylated form, with the mitotic kinase PLK1 (polo-like kinase 1). Gravin is closely linked to the mitotic spindle checkpoint protein, CDK1, a protein interacting with Mad2 (Chila et al. 2013). Gravin phosphorylated by CDK1/cyclin B1 localizes to centrosomes and spindle of dividing cells where it acts as a scaffold for PLK1. Depletion of gravin, what occurs in part of malignant neoplasms, impacts mitotic progression, causes misalignment of chromosomes, and induces aneuploidy (review: Canton and Scott 2013). Kinases that perform surveillance of the division process include Aurora kinases (Aurora-A, Aurora-B, and Aurora-C). Deranged expression patterns of Aurora kinases are causally linked with the generation of aneuploidy and cancerogenesis, whereby the expression of these kinases is modulated by de novo synthesis, stability factors, phosphorylation, and ubiquitin-dependent degradation. Aneuploidy can also be induced by epigenetic mechanisms (Herrera et al. 2008).

An intriguing mechanism of aneuploidization is heterotypic tumor/cell-in-cell structure. This mechanism is characterized by the phenomenon that one living and intact cell (and not an apoptotic cell) enters into another living cell, usually occurring between homotypic cancer cells and immunologic effector cells. T and B cells, monocytes, and natural killer cells are known to invade tumor cells, and these cells can penetrate directly into the nucleus of tumor cells, causing multinucleation and thereafter aneuploidy (Chen et al. 2013).

Merotelic Kinetochores as a Source of Aneuploidy

Kinetochores have binding sites for about 20–25 kinetochore microtubules. Kinetochores bound to kinetochore microtubules oscillate between poleward and away-from-the-pole movements. These oscillations are coupled to changes in length of kinetochore microtubules (Amaro et al. 2010; Wan et al. 2012). Kinetochores can become merotelic in prometaphase if they attach to microtubules from opposite poles rather than to just one pole as normal. Merotelic kinetochore orientation is a misattachment of kinetochores in which a single kinetochore is attached to microtubules from both spindle poles instead of just one (Cimini et al. 2004; Gregan et al. 2011). These merotelic attachments, which are not always detected by the mitotic spindle checkpoint, support chromosome bi-orientation and alignment near the metaphase plate, and are a cause of aneuploidy (Cimini et al. 2001). In anaphase initiation, merotelic kinetochores are not properly segregated, may lag behind, or even move in the direction of the wrong pole. This leads to lagging chromosomes in anaphase (Cimini et al. 2002). Therefore, merotelic kinetochores are a major mechanism for the generation of aneuploidy (Salmon et al. 2005). The effect of merotelic kinetochores can be corrected by an increase in the ratio of kinetochoric microtubules attached to the correct versus incorrect pole during pre-anaphase, resulting in eventual kinetochore reorientation. A second correction mechanism seem to involve an increased in microtubule ratio to opposite poles in anaphase, promoting segregation of merotelically oriented chromosomes to the correct pole.

Aneuploidy and Other Causes of Multilateral Genomic Instability and Their Role in Cancerogenic Pathways (Cancer Chromosomal Instability, CIN)

Aneuploidy is consistently found in most, if not all, cancers and is strong driving force for cancerogenic pathways (Duesberg et al. 1998, 1999, 2004; Sen 2000; Duesberg and Rasnick 2000; Duesberg and Li 2003; Weaver and Cleveland 2009; Nguyen and Ravid 2010; Ried et al. 2012; Honma et al. 2014; Ricke and van Deursen 2013; Takeshita et al. 2013; Zasadil

et al. 2013) and may be associated with somatic mosaicism (Sen 2000). Aneuploidy destabilizes the karyotype as it unbalances thousands of genes and causes progressive genomic instability, an altered transcriptome and proteome, and finally a novel cellular phenome (Pavelka and Rancati 2013). Cancer chromosomal instability (CIN) is defined as an excessive rate of numerical and structural genomic changes in neoplasms (Bayani et al. 2007). CIN is associated with aneuploidy and is a major factor for intratumor heterogeneity and is a marker for aggressive tumor biology (Zasadil et al. 2013). Progressive CIN leads to an increasing deviation of the cancer clones from their normal counterparts in regard to genotype and genomics, creating something like a "novel species." CIN is characterized by increased DNA replicating stress and proneness to faulty information copying circumvented by the generation of novel and sometimes thriving copies. Cells in a state of aneuploidy more often acquire mutations that eventually result in their malignant transformation, aneuploidy driving a mutator phenotype (Kolodner et al. 2011). Many of the random novel karyotypes thus induced perish, but part of them survive and give rise to abnormal karyotypes that acquire replicative autonomy and a cancer phenotype – similar to a deviant form of speciation (the speciation theory of carcinogenesis). According to this theory, cancer is a chromosomal disease strongly dependent on the generation of aneuploidy and genomic instability (Duesberg et al. 2005, 2006; review: Duesberg et al. 2011). CIN is normally abolished by the action of CIN-suppressor genes, such as PIGN (MCD4), MEX3C (RKHD2), and ZNF516 (KIAA0222) encoded on chromosome 18q that are often altered in CIN, CIN being associated with aneuploidy (Burrell et al. 2013). Abnormal, aneuploidy genotypes evolving in the course of genomic instability result in the selection of specific clones that gain individuality as autonomously replicating entities (Fabarius et al. 2008). There is increasing evidence that distinct protein groups affecting the fidelity of chromosome separation during mitosis are involved in aneuploidy and genomic instability in cancers. One group of proteins involved in this pathway are mitotic kinases. Aurora kinases link chromosome segregation and cell division to cancer susceptibility. During carcinogenesis, missegregation of chromosomes due to deregulated Aurora kinase activity results in aneuploidy or polyploidization (review: Meraldi et al. 2004). In gastric cancer cells, high Aurora-B kinase expression in nuclei is correlated with aneuploidy and TP53 mutations, but not with microsatellite instability (Honma et al. 2013).

Aneuploidy is not the single mechanism responsible for genomic instability. A mechanism of genomic instability is deregulation of the centrosome cycle, a process that is operational in many cancers (reviews: Fukasawa 2005; Vitre and Cleveland 2012). Centrosome composition is controlled by the tumor suppressor phosphatase and tensin homolog (PTEN) and Akt during mitosis. Specifically, PTEN localization at mitotic centrosomes peaks between prophase and metaphase, paralleling the centrosomal localization of gamma-tubulin (Leonard et al. 2013). Centrosome deregulation is closely linked to centrosome amplification caused by environmental factors such as ionizing radiation, failure of cytokinesis, and activating mutations affecting centrosome structure and function. Centrosome duplication as a first step of amplification promotes cells to enter the G2 phase of the cycle in tetraploid state (4N). But such cells fail to terminate mitosis and tend to reenter the G1 phase of cycle as 4N cells with amplified centrosomes. In case centrosome duplication is uncoupled from chromosome replication, further centrosomal amplification round will result in multipolar spindles that may cause aneuploidy, as outlined above (Lingle et al. 2005). Centrosome amplification is also the cause for polyploid karyotype states occurring in cancers (Duensing and Duensing 2010).

Genomic instability is also thought to be linked to telomere dynamics (Cheung and Deng 2008), specifically to erosion and/or amplification of the TTAGGG repeat sequences present at chromosomal termini. Telomeres are specialized domains at chromosomal ends made up of 5′-TTAGGG-3′ repeats and a number of telomere-associated proteins (the "telomerome"). The telomere is capable to form a loop structure to conceal the DNA end and protecting it from breaks and degradation.

Correct telomere function determines the domain of individual chromosomes within the nuclear compartment and protects chromosomes from damage, telomere failure leading to karyotype destabilization (Cheung and Deng 2008). Amplification of telomeric DNA is associated with aggressive malignancy, in particular metastatic cancers (Pathak et al. 2002).

Mitotic Catastrophe as a Protection Against Aneuploidy

Mitotic catastrophe (MIC) is a mechanism designed to sense mitotic failure leading to cell death or senescence. MIC is a very powerful pathway to circumvent and counteract progressive aneuploidy and genomic instability. Several pathogenic pathways can induce MIC. One mechanism of MIC consists in the generation of non-bipolar mitotic spindles that cause failure of cell division and death. In cancer cells, apoptin, a protein from chicken anemia virus, can cause MIC and selective tumor cell death through failure to progress through anaphase and telophase (Lanz et al. 2013). More details on MIC are presented in the chapter on cell death and apoptosis.

Chromosomal and Genomic Instability as a Driving Force for Cancerogenesis: Further Mechanisms

Introduction

Errors in genome replication fidelity cause chromosome instability (CIN) leading to aneuploidy and the promotion of cancerogenic pathways (see above; Abbas et al. 2013). CIN can promote cancerogenesis through gene amplifications and deletions (structural CIN) and gains and losses of chromosomes (numerical CIN or nCIN) (reviews: Foijer 2010; Thompson et al. 2010). Traditional mechanisms for CIN comprise cohesion defects, supernumerary centrosomes, defects in kinetochore-microtubule attachment dynamics, and defects in cell cycle regulation. Genomic instability in contrast to CIN can be generated via mutational events resulting in sometimes characteristic mutational signatures in cancers (Alexandrov et al. 2013; Helleday et al. 2014). Genomic instability can also develop through localized hypermutations, a disorder called kataegis. Recently, several catastrophic genomic disorders resulting in copy number variation (CNV) have been described (Lupski and Stankiewicz 2005; Zhang et al. 2009; Liu et al. 2011). Several of these disorders lead to "genome chaos" (chaotic genomes), a massive form of CIN found in several types of cancer (Liu et al. 2014). The finding very important for cancerogenesis is that even in the presence of massive and rapidly evolving genome damage, viable clones with unstable genomes can emerge (Lane and Clarke 2012).

Nonallelic Homologous Recombination (NAHR) and Nonhomologous End Joining (NHEJ)

NAHR and NHEJ are two mechanisms that result in a "genome chaos" (Liu et al. 2014). NAHR is a major cause of CNV that occurs when the control of allelic recombination fails (Liu et al. 2012). It can occur on interchromosome, intrachromosome, intrachromatid, and sister chromatid exchange levels. Random rejoining of chromosomal fragments can occur through nonhomologous end joining (NHEJ).

Chromoanagenesis

In chromoanagenesis, large numbers of complex rearrangements occur at one or a few chromosomal loci in a single catastrophic event. The term seems to cover the two events, chromothripsis and chromoanasynthesis (Holland and Cleveland 2012).

Chromothripsis

Chromothripsis (chromosome shattering) describes a distinct form of "acute" genomic

rearrangement occurring in one single massive jump instead of numerous small steps (Stephens et al. 2011). Hence, chromothripsis is a form of CIN that opposes the traditional theory that cancer results from a multistep process. It is a catastrophic one-off event rather than the gradual accumulation of genomic alterations typical for many other oncogenic pathways (Rajapakse et al. 2011; Forment et al. 2012; Jones and Jallepailli 2012; Zhang et al. 2013b; Cai et al. 2014; Kinsella et al. 2014) and is the cause of clustered chromosomal rearrangements in subsets of malignant neoplasms. Some cancer cells can thus contain chromosomes with hundreds or thousands of clustered intra- and interchromosomal rearrangements, which involve a single chromosome or a chromosome arm (Kloosterman et al. 2011), and these rearrangements cause rapid genome evolution. It is currently thought that chromothripsis results from breakage and inaccurate reassembly of chromosomes, i.e., "shattering" of chromosomes followed by aberrant "stitching together" (reviews: Forment et al. 2012; Righolt and Mai 2012). The process shows large numbers of complex rearrangements in circumscribed regions of single chromosomes or chromosome arms, clustering of chromosomal breakpoints, prevalence of rearrangements involving a single haplotype, randomness of joining features, and randomness of DNA fragment order along resulting abnormal chromosomes. However, the exact mechanisms are not yet elucidated, and the view that chromothripsis results from a single event has been criticized (Sorzano et al. 2013). In chromothripsis, mitotic entry takes place before completion of DNA replication within the micronucleus occurred, with a defect in disassembling the micronuclear envelope that encapsulates the chromosome fragments for random reassembly in the following interphase (Holland and Cleveland 2012).

Chromothripsis has been observed in hepatocellular carcinoma (HCC). In one study, chromothripsis was detectable in 5.7 % of HCCs recurrently affecting chromosome arms 1q and 8q (Fernandez-Banet et al. 2014).

Chromoanasynthesis

Chromoanasynthesis is another type of constitutional complex genome rearrangement (Liu et al. 2011). In contrast to chromothripsis, the authors detected frequent copy number gains with interspersed regions containing duplication or triplication of one parental allele, but no LOH, and proposed microhomology, mediated breakage-induced repair as the major mechanism for inducing the translocations. In summary, chromoanasynthesis denotes a genomic disorder in which locally defective DNA replication causes serial, microhomology-mediated template switching resulting in local rearrangements with CNV (Holland and Cleveland 2012; Pihan 2013).

Chromoplexy

Chromoplexy denotes a type of complex DNA rearrangements that occurs in cancer cells. Similar to chromothripsis, chromoplexy is characterized by scrambling of genetic material of one or more chromosomes as multiple strands and then ligated to each other in a new configuration. In contrast to chromothripsis, where one or two chromosomes are involved in the shattering process, chromoplexy involves DNA segments from multiple chromosomes and shows fewer rearrangements than the hundreds or thousands found in chromothripsis. In addition, chromoplexy can occur in multiple subsequent rounds, what does not occur in chromothripsis.

Chromosome Pulverization

Chromosome pulverization is a form of genomic chaos characterized by massive errors in mitotic chromosome segregation that generate DNA breaks through the formation of micronuclei. In case errors produce lagging chromosomes, whole-chromosome-containing micronuclei can develop. These micronuclei cause whole-chromosome aneuploidy because they undergo marked subsequent changes, i.e., defective and

asynchronous DNA replication that results in DNA damage and extensive chromosomal fragmentation ("pulverization") within the micronucleus. As such, pulverization can be regarded as a form of chromothripsis with its genome instability, because micronuclei with fragmented chromosomes can persist and may be distributed to daughter cells (Crasta et al. 2012).

Kataegis

Kataegis (from Greek, "thunder") denotes a pattern of localized hypermutation occurring in certain cancer genomes (Nik-Zainal et al. 2012). Hypermutated regions that occur in kataegis often colocalize with regions of somatic genome rearrangement. Kataegic hypermutation almost exclusively involves cytosine to thymine switches, possibly caused by the action of AID/APOBEC cytosine deaminase (Lada et al. 2012). This cytosine deaminase, when dysregulated, can induce localized hypermutation with simultaneous, closely spaced or clustered multiple mutations (Roberts and Gordenin 2014). Localized hypermutation can also originate from DNA damage (e.g., alkylation) within long single-stranded DNA (ssDNA) formed at resected double-strand breaks and dysfunctional replication forks, clustered mutations emerging along the track of DNA synthesis (Roberts et al. 2012; Sakofsky et al. 2014).

Nuclear Bodies

Introduction

Nuclear bodies comprise a group of distinct structures of the nuclear architecture involved in a wide array of nuclear functions (reviews: Dundr 2011, 2012). The bodies form, as their name implies, morphologically visible, dot-like or point-like structures that, as they may be numerous and associated with distinct chromatin domains or the nucleolus, have an impact on the overall inner texture of the nucleus. The dynamic bodies therefore also contribute to the nuclear changes found in cancer cells, although the bodies are not easily identifiable in conventional sections. Part of the nuclear bodies are involved in the handling of RNA or ribonucleoprotein complexes, while others are distinct multiprotein signalosomes. The principal categories of nuclear bodies are listed in Table 1.

Table 1 Nuclear bodies

Promyelocytic leukemia bodies (PML bodies)
Nuclear speckles
Nuclear paraspeckles
P-bodies (mRNA processing bodies)
S1-1 nuclear bodies
Nuclear stress bodies (nuclear stress granules)
U bodies
Histone locus bodies
Cajal body
DDX1 bodies
Cleavage bodies
Gemini bodies (gems)
Polycomb group bodies
HSF1 granules

Promyelocytic Leukemia Bodies/PML Nuclear Bodies: General Aspects

Promyelocytic leukemia bodies (PML bodies) play an important role in the pathogenesis of diverse malignancies and are therefore treated in some more detail. These bodies are named after their specific component, the promyelocytic leukemia protein (PML). The PML gene was originally found at the t(15;17) translocation site of acute promyelocytic leukemia. The PML protein is the core component of a nuclear substructure that contains more than 70 proteins, the PML body or PML nuclear body (PML-NBs). PML-NBs are also termed nuclear dots, PML oncogenic domains (PODs) nuclear domain 10, or Kr-bodies. PML-NBs represent punctate structures that originally were detected as an autoantigenic target in primary biliary cirrhosis, but they are also found in the nuclei of cancer cells, including liver cancer. Proteins other than PML cover a broad range of protein types, such as Sp100, nuclear matrix proteins, and proteins of

the nuclear pore complex, whereby part of these proteins are SUMOylated, a process involved in PML-NB biogenesis (Shen et al. 2006). PML protein (synonym: TRIM 19) belong to the group of tripartite motif (TRIM) proteins having a coiled-coil region that facilitates oligomerization, a process important for PML body formation (Batty et al. 2012). The PML protein is a scaffold protein with several functions, including the control of cell growth, apoptosis and survival, DNA repair, senescence, telomere maintenance, and nuclear storage of proteins (reviews: Salomoni et al. 2012; Mazza and Pelicci 2013).

PML and PML-NBs serve as DNA damage sensors (Dellaire et al. 2006). The number and size of PML-NBs changes as a function of cell cycle phase and changes in chromatin structures or DNA damage. The number of PML-NBs increases in S phase and, as response to DNA damage, the latter effect being the result of DNA injury sensing. PML protein interacts with chromatin and ATM kinase which in turn phosphorylates the KRAB-associated protein 1 (KAP1), inducing in an increase in PML-NB number (Kepkay et al. 2011). Originally thought to be an exclusively nuclear protein, PML is now known to act in the cytoplasm as well, where it affects several mechanisms of cellular homeostasis (Carracedo et al. 2011; Jin et al. 2014). In particular, PML is a key regulator of cytokine signaling and affects immune responses, inflammation, and cytokine-induced apoptosis (Terris et al. 1995; Maarifi et al. 2014). Differential expression of PML in liver cancers may, therefore, exert an influence on tumor-associated inflammation and antitumor immune reactions. Breakdown of the nuclear envelope during mitosis is associated with formation of stable interactions of PML-NBs with early endosomes and spindle poles, this interaction remaining through mitosis and dissociated in the daughter cells (Palibrk et al. 2014).

PML Nuclear Bodies in Liver Cancer

PML expression has a determinant function in cancer stem cells and carcinogenic pathways, including hepatocarcinogenesis. PML is required for cancer stem cell maintenance (review: Zhou and Bao 2014). In many established solid tumors, immunohistochemical expression of PML is reduced or even absent. Generally, low expression of PML is associated with high-grade morphology, aggressive tumor biology, and poor outcome (Mazza and Pelicci 2013). However, HCCs show an upregulation of PML-NBs. Overexpression of PML was detected in 50 % of HCCs (Chan et al. 1998). The amount of PML and the number and size of PML-NBs increased gradually in the progression from liver cirrhosis, dysplastic nodules, to HCCs, and this overexpression was strongest in HBV-related cancers (Yoon and Yu 2001). However, HCV seems to interfere with the PML tumor suppressor (Herzer et al. 2014). In hepatocarcinogenic pathways, PML protein links DNA damage response and DNA repair to HBV-related tumorigenic pathways. PML deficiency facilitates genomic instability and promotes HBV-induced hepatocarcinogenesis (Chung and Wu 2013), and downregulation of PML also fosters HCV-associated hepatocarcinogenesis, a process associated with impaired expression of the proapoptotic factor TRAIL (Herzer et al. 2012). In HCV-infected cells, the HCV core protein promotes PML localization to PML-NBs where it colocalizes with p53. In PML-NBs, HCV core protein interacts with the PML isoform IV, a key regulator of p53 activity, and via this reaction inhibits the proapoptotic action of p53 (Herzer et al. 2005). Expression of PML and PML bodies in HCC negatively affects apoptosis of cancer cells (Herzer et al. 2014).

References

Abbas T, Keaton MA, Dutta A (2013) Genomic instability in cancer. Cold Spring Harb Perspect Biol 5:a012914

Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati AV, Bignell GR, Bolli N et al (2013) Signatures of mutational processes in human cancer. Nature 500:415–421

Amaro AC, Samora CP, Holtackers R, Wang E, Kingston IJ, Alonso M, Lampson M et al (2010) Molecular control of kinetochore-microtubule dynamics and chromosome oscillations. Nat Cell Biol 12:319–329

Attallah AM, Tabll AA, El-Nashar E, El-Bakry KA, El-Sadany M, Ibrahim T, El-Dosoky I (2009) AgNORs count and DNA ploidy in liver biopsies from patients with schistosomal liver cirrhosis and hepatocellular carcinoma. Clin Biochem 42:1616–1620

Balsells J, Caragol I, Allende E, Diaz I, Charco R, Lazaro JL, Murio E, Margarit C (1996) DNA ploidy study of resected hepatocellular carcinoma in cirrhotic liver. J Hepatol 25:854–858

Barbero JL (2011) Sister chromatid cohesion control and aneuploidy. Cytogenet Genome Res 133:223–233

Barford D (2011) Structural insights into anaphase-promoting complex function and mechanism. Philos Trans R Soc Lond B Biol Sci 366:3605–3624

Batty EC, Jensen K, Freemont PS (2012) PML nuclear bodies and other TRIM-defined subcellular compartments. Adv Exp Med Biol 770:39–58

Bayani J, Selvarajah S, Maire G, Vukovic B, Al-Romaih K, Zielenska M, Squire JA (2007) Genomic mechanisms and measurement of structural and numerical instability in cancer cells. Semin Cancer Biol 17:5–18

Bignold LP (2003) Pathogenetic mechanisms of nuclear pleomorphism of tumour cells based on the mutator phenotype theory of carcinogenesis. Histol Histopathol 18:657–664

Bignold LP, Coghlan BLD, Jersmann HPA (2006) Hansemann, Boveri, chromosomes and the gametogenesis-related theories of tumours. Cell Biol Int 30:640–644

Boveri T (1914) Zur Frage der Entstehung maligner Tumoren. Fischer Verlag, Jena. (English translation: Boveri M (1929) The origin of malignant tumors. Williams & Wilkins, Baltimore)

Brinkley BR (2001) Managing the centrosome numbers game: from chaos to stability in cancer cell division. Trends Cell Biol 11:18–21

Browntree CW, Rogers GC (2013) Show me your license, please: deregulation of centriole duplication mechanisms that promote amplification. Cell Mol Life Sci 70:1021–1034

Burrell RA, McClelland SE, Endesfelder D, Groth P, Weller MC, Shaikh N, Domingo E et al (2013) Replication stress links structural and numerical cancer chromosomal instability. Nature 494:492–496

Cai H, Kumar N, Bagheri HC, von Mering C, Robinson MD, Baudis M (2014) Chromothripsis-like patterns are recurring but heterogeneously distributed features in a survey of 22,347 cancer genome screens. BMC Genomics 15:82

Canton DA, Scott JD (2013) Anchoring proteins encounter mitotic kinases. Cell Cycle 12:863–864

Carracedo A, Ito K, Pandolfi PP (2011) The nuclear bodies inside out: PML conquers the cytoplasm. Curr Opin Cell Biol 23:360–366

Celton-Morizur S, Desdouets C (2010) Polyploidization of liver cells. Adv Exp Med Biol 676:123–135

Chan JY, Chin W, Liew CT, Chang KS, Johnson PJ (1998) Altered expression of the growth and transformation suppressor PML gene in human hepatocellular carcinomas and in hepatitis tissues. Eur J Cancer 34:1015–1022

Chan TH, Chen L, Liu M, Hu L, Zheng BJ, Poon VK, Huang P, Yuan YF, Huang JD et al (2012) Translationally controlled tumor protein induces mitotic defects and chromosome missegregation in hepatocellular carcinoma development. Hepatology 55:491–505

Chen YH, Wang S, He MF, Wang Y, Zhao H, Zhu HY, Yu XM, Ma J, Che XJ, Wang JF et al (2013) Prevalence of heterotypic tumor/immune cell-in-cell structure in vitro and in vivo leading to formation of aneuploidy. PLoS One 8:e59418

Cheng KC, Loeb LA (1993) Genomic instability and tumor progression: mechanistic considerations. Adv Cancer Res 60:121–156

Cheng KC, Loeb LA (1997) Genomic stability and instability: a working paradigm. Curr Top Microbiol Immunol 221:1–16

Cheung AL, Deng W (2008) Telomere dysfunction, genome instability and cancer. Front Biosci 13:2075–2090

Chila R, Celenza C, Lupi M, Damia G, Carrassa L (2013) Chk1-Mad2 interaction: a crosslink between the DNA damage checkpoint and the mitotic spindle checkpoint. Cell Cycle 12:1083–1090

Chung YL, Wu ML (2013) Promyelocytic leukaemia protein links DNA damage response and repair to hepatitis B virus-related hepatocarcinogenesis. J Pathol 230:377–387

Cimini D, Howell B, Maddox P, Khodjakov A, Degrassi F, Salmon ED (2001) Merotelic kinetochore orientation is a major mechanism of aneuploidy in mitotic mammalian tissue cells. J Cell Biol 153:517–527

Cimini D, Fioravanti D, Salmon ED, Degrassi F (2002) Merotelic kinetochore orientation versus chromosome mono-orientation in the origin of lagging chromosomes in human primary cells. J Cell Sci 115:507–515

Cimini D, Cameron LA, Salmon ED (2004) Anaphase spindle mechanics prevent mis-segregation of merotelically oriented chromosomes. Curr Biol 14:2149–2155

Corbett KD, Yip CK, Ee LS, Walz T, Amon A, Harrison SC (2010) The monopolin complex crosslinks kinetochore components to regulate chromosome-microtubule attachments. Cell 142:556–567

Crasta K, Ganem NJ, Dagher R, Lantermann AB, Ivanova EV, Pan Y, Nezi L, Protopopov A et al (2012) DNA breaks and chromosome pulverization from errors in mitosis. Nature 482:53–58

D'Assoro et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12214243

Dellaire G, Ching RW, Ahmed K, Jalali F, Tse KCK, Bristow RG, Bazett-Jones DP (2006) Promyelocytic leukemia nuclear bodies behave as DNA damage sensors whose response to DNA double-strand breaks is regulated by NBS1 and the kinases ATM, Chk2, and ATR. J Cell Biol 175:55–66

Difilippantinio MJ, Ghadimi BM, Howard T, Camps J, Nguyen QT, Ferris DK, Sackett DL et al (2009) Nucleation capacity and presence of centrioles define a distinct category of centrosome abnormalities that induces multipolar mitoses in cancer cells. Environ Mol Mutagen 50:672–696

Drosopoulos K, Tang C, Chao WC, Linardopoulos S (2014) APC/C is an essential regulator of centrosome clustering. Nat Commun 5:3686

Duensing A, Duensing S (2010) Centrosomes, polyploidy and cancer. Adv Exp Med Biol 676:93–103

Duesberg P, Li R (2003) Multistep carcinogenesis: a chain reaction of aneuploidizations. Cell Cycle 2:202–210

Duesberg P, Rasnick D (2000) Aneuploidy, the somatic mutation that makes cancer a species of its own. Cell Motil Cytoskeleton 47:81–107

Duesberg P, Rausch C, Rasnick D, Hehlmann R (1998) Genetic instability of cancer cells is proportional to their degree of aneuploidy. Proc Natl Acad Sci U S A 95:13692–13697

Duesberg P, Rasnick D, Li R, Winters L, Rausch C, Hehlmann R (1999) How aneuploidy may cause cancer and genetic instability. Anticancer Res 19: 4887–4906

Duesberg P, Fabarius A, Hehlmann R (2004) Aneuploidy, the primary cause of the multilateral genomic instability of neoplastic and preneoplastic ells. IUBMB Life 56:65–81

Duesberg P, Li R, Fabarius A, Hehlmann R (2005) The chromosomal basis of cancer. Cell Oncol 27:293–318

Duesberg P, Li R, Fabarius A, Hehlmann R (2006) Aneuploidy and cancer: from correlation to causation. Contrib Microbiol 13:16–44

Duesberg P, Mandrioli D, McCormack A, Nicholson JM (2011) Is carcinogenesis a form of speciation ? Cell Cycle 10:2100–2114

Duncan AW (2013) Aneuploidy, polyploidy and ploidy reversal in the liver. Semin Cell Dev Biol 24:347–356

Duncan AW, Taylor MH, Hickey RD, Hanlon Newell AE, Lenzi ML, Olson SB, Finegold MJ et al (2010) The ploidy conveyor of mature hepatocytes as a source of genetic variation. Nature 467:707–710

Duncan AW, Hanlon Newell AE, Smith L, Wilson EM, Olson SB, Thayer MJ, Strom SC et al (2012) Frequent aneuploidy among normal human hepatocytes. Gastroenterology 142:25–28

Dundr M (2011) Seed and grow: a two-step model for nuclear body biogenesis. J Cell Biol 193:605–606

Dundr M (2012) Nuclear bodies: multifunctional companions of the genome. Curr Opin Cell Biol 24:415–422

Eissa S, Wahed M, Ismail A, Amer K, Khalifa A, Einaggar A (1997) DNA ploidy in hepatic cirrhosis, dysplasia and carcinoma. Oncol Rep 4:443–445

Fabarius A, Li R, Yerganian G, Hehlmann R, Duesberg P (2008) Specific clones of spontaneously evolving karyotypes generate individuality of cancers. Cancer Genet Cytogenet 180:89–99

Fernandez-Banet J, Lee NP, Chan KT, Gao H, Liu X, Sung WK, Tan W, Fan ST et al (2014) Decoding complex patterns of genomic rearrangements in hepatocellular carcinoma. Genomics 103:189–203

Foijer F (2010) CINister thoughts. Biochem Soc Trans 38:1715–1721

Forment JV, Kaidi A, Jackson SP (2012) Chromothripsis and cancer: causes and consequences of chromosome shattering. Nat Rev Cancer 12:663–670

Fukasawa K (2005) Centrosome amplification, chromosome instability and cancer development. Cancer Lett 230:6–19

Ganem NJ, Godinho SA, Pellman D (2009) A mechanism linking extra chromosomes to chromosomal instability. Nature 460:278–282

Gentric G, Desdouets C, Celton-Morizur S (2012) Hepatocytes polyploidization and cell cycle control in liver physiopathology. Int J Hepatol 2012:282430

Ghadimi BM, Sackett DL, Difilippantonio MJ, Schröck E, Neumann T, Jauho A, Auer G et al (2000) Centrosome amplification and instability occurs exclusively in aneuploidy, but not in diploid colorectal cancer cell lines, and correlates with numerical chromosomal aberrations. Gene Chromosome Cancer 27:183–190

Glotzer M (2013) Cytokinesis: centralspindlin moonlights as a membrane anchor. Curr Biol 23:R145–R147

Godinho et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19156503

Godinho SA, Picone R, Burute M, Dagher R, Su Y, Leung CT, Polyak K, Brugge JS et al (2014) Oncogene-like induction of cellular invasion from centrosome amplification. Nature 510:167–171

Gregan J, Polakova S, Zhang L, Tolic-Norrelykke IM, Cimini D (2011) Merotelic kinetochore attachment: causes and effects. Trends Cell Biol 21:374–381

Gudi R, Zou C, Dhar J, Gao Q, Vasu C (2014) Centrobin-centrosomal protein 4.1.-associated protein (CPAP) interaction promotes CPAP localization to the centrioles during centriole duplication. J Biol Chem 289:15166–15178

Guidotti JE, Brégerie O, Robert A, Debey P, Brechot C, Desdouets C (2003) Liver cell polyploidization: a pivotal role for binuclear hepatocytes. J Biol Chem 278:19095–19101

Gupta S (2000) Hepatic polyploidy and liver growth control. Semin Cancer Biol 10:161–171

Hamazaki K, Kato T, Yunoki Y, Mori M, Gochi A, Mimura H, Orita K (1993) An analysis of DNA ploidy pattern of hepatocellular carcinoma. Acta Med Okayama 47:413–416

He Y, Tollini L, Kim TH, Itahana Y, Zhang Y (2014) The anaphase-promoting complex/cyclosome is an E3 ubiquitin ligase for Mdm2. Cell Cycle 13:2101–2109

Helleday T, Eshtad S, Nik-Zainal S (2014) Mechanisms underlying mutational signatures in human cancers. Nat Rev Genet. doi:10.1038/nrg3729

Herrera LA, Prada D, Andonegui MA, Dueñas-Gonzalez A (2008) The epigenetic origin of aneuploidy. Curr Genomics 9:43–50

Herzer K, Weyer S, Krammer PH, Galle PR, Hofmann TG (2005) Hepatitis C virus core protein inhibits tumor

suppressor protein promyelocytic leukemia function in human hepatoma cells. Cancer Res 65:10830–10837
Herzer K, Carbow A, Sydor S, Sowa JP, Biesterfeld S, Hofmann TG, Galle PR, Gerken G et al (2012) Deficiency of the promyelocytic leukemia protein fosters hepatitis C-associated hepatocarcinogenesis in mice. PLoS One 7:e44474
Herzer K, Gerken G, Hofmann TG (2014) Hepatitis C-associated liver carcinogenesis: role of PML nuclear bodies. World J Gastroenterol 20:12367–12371
Holland AJ, Cleveland DW (2012) Chromoanagenesis and cancer: mechanisms and consequences of localized, complex chromosomal rearrangements. Nat Med 18:1630–1638
Holland AJ, Lan W, Niessen S, Hoover H, Cleveland DW (2010) Polo-like kinase 4 kinase activity limits centrosome overduplication by autoregulating its own stability. J Cell Biol 188:191–198
Honma K, Nakanishi R, Nakanoko T, Ando K, Saeki H, Oki E, Iimori M, Kitao H, Kakeji Y et al (2014) Contribution of Aurora-A and –B expression to DNA aneuploidy in gastric cancers. Surg Today 44:454–461
Hoso M, Nakanuma Y (1989) Cytophotometric DNA analysis of hepatocellular carcinoma with Mallory bodies. Virchows Arch A Pathol Anat Histopathol 416:51–55
Jaspersen SL, Ghosh S (2012) Nuclear envelope insertion of spindle pole bodies and nuclear pore complexes. Nucleus 3:1–11
Jia L, Kim S, Yu H (2013) Tracking spindle checkpoint signals from kinetochores to APC/C. Trends Biochem Sci 38:302–311
Jin G, Gao Y, Lin HK (2014) Cytoplasmic PML: from molecular regulation to biological functions. J Cell Biochem 115:812–818
Jodoin JN, Shboul M, Sitaram P, Zein-Sabatto H, Reversade B, Lee E, Lee LA (2012) Human Asunder promotes dynein recruitment and centrosomal tethering to the nucleus at mitotic entry. Mol Biol Cell 23:4713–4724
Jones MJ, Jallepailli PV (2012) Chromothripsis: chromosomes in crisis. Dev Cell 23:908–917
Kepkay R, Attwood KM, Ziv Y, Shiloh Y, Dellaire G (2011) KAP1 depletion increases PML nuclear body number in concert with ultrastructural changes in chromatin. Cell Cycle 10:308–322
Kinsella M, Patel A, Bafna V, (2014) The elusive evidence for chromothripsis. Nucleic Acids Res 42:8231–8242
Kloosterman WP, Hoogstraat M, Paling O, Tavakoli-Yaraki M, Renkens I, Vermaat JS et al (2011) Chromothripsis is a common mechanism driving genomic rearrangements in primary and metastatic colorectal cancer. Genome Biol 12:R103
Kolodner RD, Cleveland DW, Putnam CD (2011) Cancer. Aneuploidy drives a mutator phenotype in cancer. Science 333:942–943
Kwon M, Godinho SA, Chandhok NS, Ganem NJ, Azioune A, Thery M, Pellman D (2008) Mechanisms to suppress multipolar divisions in cancer cells with extra centrosomes. Genes Dev 22:2189–2203
Lada AG, Dhar A, Boissy RJ, Hirano M, Rubel AA, Rogozin IB, Pavlov YI (2012) AID/APOBEC cytosine deaminase induces genome-wide kataegis. Biol Direct 7:47
Lane AB, Clarke DJ (2012) Genome instability: does genetic diversity amplification drive tumorigenesis ? Bioessays 34:963–972
Lanz HL, Zimmerman RM, Brouwer J, Noteborn MH, Backendorf C (2013) Mitotic catastrophe triggered in human cancer cells by the viral protein apoptin. Cell Death Dis 4:e487
Lekomtsev S, Su KC, Pye VE, Blight K, Sundaramoorthy S, Takaki T, Collinson LM et al (2012) Centralspindlin links the mitotic spindle to the plasma membrane during cytokinesis. Nature 492:276–279
Leonard MK, Hill NT, Bubulya PA, Kadakia MP (2013) The PTEN-Akt pathway impacts the integrity and composition of mitotic centrosomes. Cell Cycle 12:1406–1415
Lingle WL, Lukasiewicz K, Salisbury JL (2005) Deregulation of the centrosome cycle and the origin of chromosomal instability in cancer. Adv Exp Med Biol 570:393–421
Liu Z, Ling K, Wu X, Cao J, Liu B, Li S, Si Q, Cai Y, Yan C, Zhang Y, Weng Y (2009) Reduced expression of cenp-e in human hepatocellular carcinoma. J Exp Clin Cancer Res 28:156
Liu P, Erez A, Nagamani SCS, Dhat SU, Kolodziejska KE, Dharmadhikari AV, Cooper ML et al (2011) Chromosome catastrophes involve replication mechanisms generating complex genomic rearrangements. Cell 146:889–903
Liu P, Carvalho CM, Hastings PJ, Lupski JR (2012) Mechanisms for recurrent and complex human genomic rearrangements. Curr Opin Genet Dev 22:211–220
Liu G, Stevens JB, Horne SD, Abdallah BY, Ye KJ, Bremer SW, Ye CJ, Chen DJ et al (2014) Genome chaos: survival strategy during crisis. Cell Cycle 13:528–537
Lupski JR, Stankiewicz P (2005) Genomic disorders: molecular mechanisms for rearrangements and conveyed phenotypes. PLoS Genet 1:e49
Maarifi G, Chelbi-Alix MK, Nisole S (2014) PML control of cytokine signaling. Cytokine Growth Factor Rev. doi:10.1016/j.cytogfr.2014.04.006
Mazza M, Pelicci PG (2013) Is PML a tumor suppressor? Front Oncol 3:174
Meraldi P, Honda R, Nigg EA (2004) Aurora kinases link chromosome segregation and cell division to cancer susceptibility. Curr Opin Genet Dev 14:29–36
Nagasue N, Yamanoi A, Takemoto Y, Kimoto T, Uchida M, Chang YC, Taniura H, Kohno H et al (1992) Comparison between diploid and aneuploid hepatocellular carcinomas: a flow cytometric study. Br J Surg 79:667–670
Nakamura T, Saito H, Takekawa M (2013) SAPK pathways and p53 cooperatively regulate PLK4 activity and centrosome integrity under stress. Nat Commun. doi:10.1038/ncomms2752

Ng IO, Lai EC, Ho JC, Cheung LK, Ng MM, So MK (1994) Flow cytometric analysis of DNA ploidy in hepatocellular carcinoma. Am J Clin Pathol 102:80–86

Nguyen HG, Ravid K (2010) Polyploidy: mechanisms and cancer promotion in hematopoietic and other cells. Adv Exp Med Biol 676:105–122

Nik-Zainal S, Alexnadrov LB, Wedge DC, Van Loo P, Greenman CD, Raine K, Jones D et al (2012) Mutational processes molding the genomes of 21 breast cancers. Cell 149:979–993

Nowell PC, Morris HP (1969) Chromosomes of "minimal deviation" hepatomas: a further report on diploid tumors. Cancer Res 29:969–970

Palibrk V, Lang E, Lang A, Schink KO, Rowe AD, Boe SO (2014) promyelocytic leukemia bodies tether to early endosomes during mitosis. Cell Cycle 13:1749–1755

Pathak S, Multani AS, Furlong CL, Sohn SH (2002) Telomere dynamics, aneuploidy, stem cells, and cancer (review). Int J Oncol 20:637–641

Pavelka N, Rancati G (2013) Never in neural: A systems biology and evolutionary perspective on how aneuploidy contributes to human diseases. Cytogenet Genome Res 139:193–205

Pihan GA (2013) Centrosome dysfunction contributes to chromosome instability, chromoanagenesis, and genome reprograming in cancer. Front Oncol 3:277

Rajapakse I, Scalzo D, Groudine M (2011) Losing control. Cancer's catastrophic transition. Nucleus 2:1–4

Ricke RM, van Deursen JM (2013) Aneuploidy in health, disease, and aging. J Cell Biol 201:11–21

Ried T, Hu Y, Difilippantonio MJ, Ghadimi M, Grade M, Camps J (2012) The consequences of chromosomal aneuploidy on the transcriptome of cancer cells. Biochim Biophys Acta 1819:784–793

Righolt C, Mai S (2012) Shattered and stitched chromosomes – chromothripsis and chromoanasynthesis – manifestations of a new chromosome crisis? Gene Chromosome Cancer 51:975–981

Roberts SA, Gordenin DA (2014) Clustered and genome-wide transient mutagenesis in human cancers: Hypermutation without permanent mutators or loss if fitness. Bioessays. doi:10.1002/bies.201300140

Roberts SA, Sterling J, Thompson C, Harris S, Mav D, Shah R, Klinczak LJ, Kryukov GV et al (2012) Clustered mutations in yeast and in human cancers can arise from damaged long single-strand DNA regions. Mol Cell 46:424–435

Rodriguez-Bravo V, Maciejowski J, Corona J, Buch HK, Collin P, Kanemaki MT, Shah JV et al (2014) Nuclear pores protect genome integrity by assembling a premitotic and Mad1-dependent anaphase inhibitor. Cell 156:1017–1031

Ruan K, Ye F, Li C, Liou YC, Lin SC, Lin SY (2012) PLK1 interacts and phosphorylates Axin that is essential for proper centrosome formation. PLoS One 7:e49184

Sakofsky CJ, Roberts SA, Malc E, Mieczkowski PA, Resnick MA, Gordenin DA et al (2014) Break-induced replication is a source of mutation clusters underlying kataegis. Cell Rep. doi:10.1016/j.celrep.2014.04.053

Salmon ED, Cimini D, Cameron LA, DeLuca JG (2005) Merotelic kinetochores in mammalian tissue cells. Philos Trans R Soc Lond B Biol Sci 360:553–568

Salomoni P, Dvorkina M, Michod D (2012) Role of promyelocytic leukaemia protein in cell death regulation. Cell Death Dis 3:e247

Sen S (2000) Aneuploidy and cancer. Curr Opin Oncol 12:82–88

Shen TH, Lin HK, Scaglioni PP, Yung TM, Pandolfi PP (2006) The mechanisms of PML-nuclear body formation. Mol Cell 24:331–339

Sigal SH, Rajvanshi P, Gorla GR, Sokhi RP, Saxena R, Gebhard DR, Reid LM et al (1999) Partial hepatectomy-induced polyploidy attenuates hepatocyte replication and activates cell aging events. Am J Physiol 276:G1260–G1272

Sivakumar S, Daum JR, Tipton AR, Rankin S, Gorbsky GJ (2014) The spindle and kinetochore-associated (Ska) complex enhances binding of the anaphase-promoting complex/cyclosome (APC/C) to chromosomes and promotes mitotic exit. Mol Biol Cell 25:594–605

Sorzano CO, Pascual-Montano A, Sanchez de Diego A, Martinez-A C, van wely KH (2013) Chromothripsis: breakage-fusion-bridge over and over again. Cell Cycle 12:2016–2023

Stephens PJ, Greenman CD, Fu B, Yang F, Bignell GR, Mudie LJ, Pleasance ED et al (2011) Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell 144:27–40

Takeshita M, Koga T, Takayama K, Ijichi K, Yano T, Maehara Y, Nakanishi Y, Sueshi K (2013) Aurora-B overexpression is correlated with aneuploidy and poor prognosis in non-small lung cancer. Lung Cancer 80:85–90

Terris B, Baldin V, Dubois S, Degott C, Fléjou JF, Hénin D, Dejean A (1995) PML nuclear bodies are general targets for inflammation and cell proliferation. Cancer Res 55:1590–1597

Thompson SL, Bakhoum SF, Compton DA (2010) Mechanisms of chromosomal instability. Curr Biol 20: R285–R295

Toyoda H, Bregerie O, Vallet A, Nalpas B, Pivert G, Brechot C, Desdouets C (2005) Changes to hepatocyte ploidy and binuclearity profiles during human chronic viral hepatitis. Gut 54:297–302

Vitre BD, Cleveland DW (2012) Centrosomes, chromosome instability (CIN) and aneuploidy. Curr Opin Cell Biol 24:809–815

Von Hansemann DP (1893) Studien über die Spezificität, den Altruismus und die Anaplasie der Zellen, mit besonderer Berücksichtigung der Geschwülste. A. Hirschwald, Berlin

Vulprecht J, David A, Tibelius A, Castiel A, Konotop G, Liu F, Bestvater F, Raab MS et al (2012) STIL is required for centriole duplication in human cells. J Cell Sci 125:1353–1362

Wan X, Cimini D, Cameron LA, Salmon ED (2012) The coupling between sister kinetochore directional

instability and oscillations in centromere stretch in metaphase PtK1 cells. Mol Biol Cell 23:1035–1046
Weaver BA, Cleveland DW (2009) The role of aneuploidy in promoting and suppressing tumors. J Cell Biol 185:935–937
Werle K, Chen J, Xu HG, Zhao RX, He Q, Lu C, Cui R, Liang J, Li YL, Xu ZX (2014) Liver kinase B1 regulates the centrosome via PLK1. Cell Death Dis 5:e1157
White EA, Glotzer M (2012) Centralspindlin: at the heart of cytokinesis. Cytoskeleton (Hoboken) 69: 882–892
Wilkens L, Flemming P, Gebel M, Bleck J, Terkamp C, Wingen L, Kreipe H, Schlegelberger B (2004) Induction of aneuploidy by increasing chromosomal instability during dedifferentiation of hepatocellular carcinoma. Proc Natl Acad Sci U S A 101:1309–1314
Wilkens L, Hammer C, Glombitza S, Müller DE (2012) Hepatocellular and cholangiolar carcinoma-derived cell lines reveal distinct sets of chromosomal imbalances. Pathobiology 79:115–126
Yoon GS, Yu E (2001) Overexpression of promyelocytic leukemia protein and alteration of PML nuclear bodies in early stage of hepatocarcinogenesis. J Korean Med Sci 16:433–438
Zasadil LM, Britigan EM, Weaver BA (2013) 2n or not 2n: aneuploidy, polyploidy and chromosomal instability in primary and tumor cells. Semin Cell Dev Biol 24:370–379
Zhang F, Carvalho CM, Lupski JR (2009) Complex human chromosomal and genomic rearrangements. Trends Genet 25:298–307
Zhang Z, Yang J, Kong EH, Chao WC, Morris EP, da Fonseca PC, Barford D (2013a) Recombinant expression, reconstitution and structure of human anaphase promoting complex (APC/C). Biochem J 449:365–371
Zhang CZ, Leibowitz ML, Pellman D (2013b) Chromothripsis and beyond: rapid genome evolution from complex chromosomal rearrangements. Genes Dev 27:2513–2530
Zhang J, Wan L, Dai X, Sun Y, Wei W (2014) Functional characterization of anaphase promoting complex/cyclosome (APC/C) E3 ubiquitin ligases in tumorigenesis. Biochim Biophys Acta 1845:277–293
Zhou W, Bao S (2014) PML-mediated signaling and its role in cancer stem cells. Oncogene 33:1475–1484
Zou J, Tian F, Li J, Pickner W, Long M, Rezvani K, Wang H, Zhang D (2013) FancJ regulates interstrand crosslinker induced centrosome amplification through the activation of polo-like kinase 1. Biol Open 2:1022–1031
Zuleger N, Robson MI, Schirmer EC (2011) The nuclear envelope as a chromatin organizer. Nucleus 2:339–349

Part XXXIII

General Pathology of Hepatobiliary Tumors: Mitochondrial Biology

Mitochondrial Biology in Hepatobiliary Tumors: Changes of the Cellular Energy Factory

171

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_171

Abstract

Within carcinogenic pathways involving abnormal stress responses and deregulation of cell death pathways, mitochondria play a significant role. Apart from their role as the principal energy machines of the cell, mitochondria hold a central role in the regulation of various forms of apoptosis, exert an influence on cell structure and shape, and engage in complex interactions with other cellular organelles. Numerous of these functions can be deranged in the course of malignant transformation of cells, having led to the concept of a mitochondrial malignancy theory. Hepatocellular carcinomas (HCCs) vary in their cellular content of mitochondria and the presence of mitochondrial structural abnormalities. In part of poorly differentiated HCCs, biogenesis and proliferation of mitochondria through fission are impaired, a process that causes mitochondriopenia or sarcopenia. Few HCCs and cholangiocarcinomas show markedly increased numbers of mitochondria, resulting in an oncocytic phenotype. Anomalies in microstructure include diminished cristae, matrix inclusions, density changes of the matrix, altered ratio of short versus elongated cristae, and complex shape changes. At least part of these mitochondrial anomalies are associated with complex alterations of mitochondrial DNA, including losses and mutations.

Introduction: Mitochondrial Malignancy Theory

Apart from the established role of oncogene products (oncoproteins), tumor suppressor proteins, viruses, chemical, and radiation inducing malignant transformation and tumorigenesis, there is evidence that hypoxia, oxygen-induced cell damage, and stress of nutrient deprivation also represent factors capable to promote carcinogenesis. These factors can accelerate senescence, hence exerting a selection pressure on cell systems involved. Cells capable to overcome and escape from cellular senescence form a fit subset of cells

with novel features, including proneness to malignant transformation. In the mechanisms that circumvent hypoxia-induced senescence, mitochondria play a central role.

Mitochondria (the cellular "powerhouse") and mitochondrial dysfunction are involved in cancerogenesis, cancer cell metabolism, growth and differentiation, and apoptosis (Modica-Napolitano et al. 2007; Grandemange et al. 2009; Chatterjee et al. 2011; Scatena 2012; Davila and Zamorano 2013; Gasparre et al. 2013; Wang et al. 2013b). Mitochondria of cancer cells differ in many respects from their counterparts of normal cells, in that they have changed their metabolism, in particular their oxidative phosphorylation, and their interactions with other organelles (Gogvadze et al. 2008). Overall, mitochondrial respiration is decreased in most cancer cells. Increased knowledge of mitochondrial functions in cancer cells will have an influence on the design of anticancer drugs (Tatarkova et al. 2012), including drugs that destabilize mitochondria, e.g., the mitocans (Neuzil et al. 2013).

Cancer Mitochondrioma and Mitochondrial Morphology in Hepatocellular and Cholangiocellular Carcinomas

Hepatocellular carcinomas vary in their cellular content of mitochondria and the presence of mitochondrial structural anomalies (Ghandially and Parry 1966; Schaff et al. 1971; Hruban 1979; Isomura and Nakashima 1980). The deranged functional status of HCC mitochondria, in part related to losses and mutations in mtDNA, manifests in several ways, although many, if not most, of the ultrastructural changes are nonspecific. The alterations include diminished cristae (Schaff et al. 1971), electron-dense mitochondrial inclusions (Schaff et al. 1971), density changes of the mitochondrial matrix, alterations in the ratio of short versus elongated mitochondria, and complex shape changes. In one ultrastructural morphometric study, the mitochondria of HCC cells revealed a higher numerical density and surface density of internal membranes and cristae than mitochondria of hepatocytes in cirrhosis (Wu et al. 1984). A liver cell tumor with large oxyphilic cells that harbor a rich ER and prominent mitochondria is fibrolamellar hepatocellular carcinoma (Caballero et al. 1985). Similar to other oncocytomas, oncocytic HCC is characterized by a marked increase in the number of mitochondria (Fukunaga et al. 1996), but it is not yet known whether this phenomenon is associated with an increased rate of mtDNA mutations. Clear cell HCC showed scarce and ballooned mitochondria (Clayton et al. 2012). In contrast to HCCs, cholangiocarcinomas may show abundant organelles, also in poorly differentiated variants (Alpert et al. 1974; Stitnimankarn et al. 1978).

Proliferative Status and Respiration of Mitochondria in Cancer Cells

In part of poorly differentiated HCC, biogenesis and proliferation of mitochondria are impaired, resulting in mitochondriopenia/sarcopenia. In contrast, fibrolamellar carcinoma is characterized by upregulation of mitochondriopoiesis, probably related to mutations in mtDNA (Vivekanandan et al. 2010). Induction of increased mitochondrial biogenesis and augmentation of oxidative phosphorylation hamper cancer progression through decrease in cell proliferation and invasiveness (Wang and Moraes 2011).

Alterations of Mitochondrial DNA in Liver Cancer

Introduction

Mitochondrial DNA (mtDNA) is a circular, covalently closed, double-stranded, and maternally inherited DNA of which between 100 and 10,000 separate copies exist in human cells, while a single mitochondrion contains two to ten mtDNA copies. MtDNA forms a chromosome equivalent, but it is confined in distinct mitochondrial nucleoids (Tauber et al. 2013). Nucleoids exist in complex clusters containing several accessory proteins, the DNA polymerase gamma complex and its

associated proteins, the DNA-compacting mitochondrial transcription factor A/TFAM, and the core transcription initiation factor TFB2M. The actions of the transcription factors TFAM and TFB2M on promoters and their interaction with mitochondrial RNA polymerase differ from those of the nuclear transcription machinery (Han et al. 2011; Yadav et al. 2014; Agaronyan et al. 2015; Morozov et al. 2015). The two strands of mtDNA differ in their nucleotide composition, the heavy strand (H strand) being guanine rich and the light strand (L strand) being cytosine rich. MtDNA encodes for a relatively small number of mitochondrial proteins, most of the approximately 1500 protein types being encoded by nuclear DNA and imported into mitochondria. In human cells, the H strand encodes 28 genes and the L strand 9 genes for a total of 37 genes, of which 13 genes encode mitochondrial proteins, 22 genes encode transfer RNAs/tRNAs, and two genes encode small and large subunits of ribosomal RNA/rRNA.

mtDNA is replicated by the action of DNA polymerase gamma complex. The catalytic polymerase proper is encoded by the POLG gene and two accessory subunits by the POLG2 gene. This complex associates with the Twinkle helicase and mitochondrial SSB proteins to form the mtDNA replisome (McKinney and Oliveira 2013). Twinkle helicase, a DNA unwinding enzyme mutated in certain mitochondriopathies, is an essential protein required for synthesis of nascent D-loop strands and complete mtDNA replication (Milenkovic et al. 2013). mtSSB protein/single-stranded DNA-binding protein directs origin-specific initiation of mtDNA replication, as it covers the parental heavy strand, which is displaced during mtDNA replication. The SSB protein blocks primer synthesis on the displaced strand and restricts initiation of light-stranded mtDNA synthesis to the specific origin of light-stranded DNA synthesis (Miralles Fusté et al. 2014).

Alterations of mtDNA in Liver Cancer

The maintenance of a function mitochondrial genome is crucial for mitochondrial functions. MtDNA function is compromised by mutations, whereby mtDNA mutates much faster than nuclear DNA. mtDNA point mutations and deletions occur somatically and accumulate with increasing age. Such mutations can occur together with wild-type mtDNA, a condition termed heteroplasmy. Mutant mtDNA can undergo clonal expansion within single cells, giving rise to complex and severe diseases (mitochondriopathies) and eventually cancer (reviews: Gaude and Frezza 2014; Kim 2014; Carelli et al. 2015). Similar to nuclear DNA, mtDNA is subject to base excision repair (Prakash and Doublié 2015). Apart from mtDNA, also mitochondrial tRNAs can under cancerogenic mutations (Wang et al. 2015c).

In cancer, the mtDNA genome undergoes genomic instability which exerts dramatic influences on mitochondrial structure and function (Copeland and Longley 2014; Ju et al. 2014). mtDNA copy numbers are reduced in HCCs (Yin et al. 2004), this reduction being correlated with tumor size and the presence of cirrhosis and with shortened 5-year survival (Yamada et al. 2006), suggesting that severe alterations in mtDNA markedly affect HCC biology. Several types of somatic mitochondrial DNA (mtDNA) alterations, including mtDNA loss, sequence polymorphisms, and mtDNA D-loop mutations, have been identified in cancers, including HCC (Lee et al. 2004; Wong et al. 2004; Yin et al. 2004, 2010; Stuart and Brown 2006; Lu et al. 2009; Gwak et al. 2011; Wang et al. 2011a; Jin et al. 2012; Hsu et al. 2013). It is likely that loss of mtDNA and mtDNA mutations is significantly involved in mitochondrial dysfunction, and mtDNA mutations act as clonal markers in HCC, specifically in multicentric HCC (Nomoto et al. 2002). In solid neoplasms, an elevated expression of normal or mutated mtDNA genes coding for components of the electron transfer machinery may affect the capability of cancer cells to adapt to novel energy situations, in particular hypoxia (Copeland et al. 2002). In HCCs, somatic mtDNA mutations and a general decrease in mtDNA copy number are common events (Hsu et al. 2013). Deletion of mtDNA was also observed in liver changes preceding HCC, i.e., viral hepatitis, liver cirrhosis, and hyperplastic liver nodules (Yamamoto et al. 1992; Nishikawa et al. 2001; Shao et al. 2004). Loss of mtDNA in HCC cells

is associated with angiogenic and invasive potential (Cheon et al. 2010). The link between mtDNA mutations and carcinogenesis, liver cancer cell behavior, and tumor progression is not yet well known (review: Wang et al. 2013b). However, a higher frequency of mtDNA D-loop (displacement loop) mutations was detected in less-differentiated HCCs (Tamori et al. 2004). There is evidence that the inflammatory process induced by hepatitis viruses contributes to the rate of mtDNA mutations (Wheelhouse et al. 2005). Mutations in the mitochondrial genome have also been identified in cholangiocarcinomas (Muisuk et al. 2015).

Epigenetic Alterations of mtDNA and Mitochondrial Gene Expression (Mitochondrial Epigenetics)

Introduction

Expression of nuclear genes is markedly modified by several epigenetic mechanisms which include DNA methylation, histone modifications, chromatin modifiers, and microRNAs. There is increasing evidence that also mtDNA gene expression is subject to such epigenetic mechanisms, potentially playing a role in cancerogenic pathways (mitoepigenetic phenomena in cancer; Ferreira et al. 2015).

Mitochondrial Epigenetic Methylome

Similar to nuclear DNA, gene expression regulation in mtDNA has been suggested to be accomplished by promoter methylation on cytosine residues, a still disputed issue (Maresca et al. 2015). In nuclear DNA, methylation is performed by DNA(cytosine-5)-methyltransferase 1/DNMT1. DNMT1 is responsible for maintaining the nuclear genome methylation patterns during DNA replication and repair. As the great majority of mitochondrial proteins are encoded by nuclear DNA, nuclear methylation gene-silencing patterns are imported into mitochondria. There is, however, some evidence that mtDNA methylation occurs through the action of a mitochondrial isoform of DNMT1 (Iacobazzi et al. 2013). Cytosine methylation of mtDNA has been detected in hepatocytes and was associated with the severity of nonalcoholic fatty liver disease (Pirola et al. 2013).

Epigenetic methylation of certain nuclear genes can affect replication of mtDNA. DNA methylation seems to occur at exon 2 of mtDNA polymerase gamma A/POLGA, and DNA demethylation of POLGA is an essential regulator of mtDNA copy number. Cancer cells are only capable to modulate POLGA DNA methylation and mtDNA copy number in the presence of a DNA demethylation agent that inhibits de novo DNMT activity (Kelly et al. 2012; Lee et al. 2015).

Mitochondrial MicroRNAs/MitomiRs: Translocated Nuclear MiRs and MitomiRs

Certain microRNAs encoded by nuclear DNA (MiRs) are imported into mitochondria where they epigenetically regulate gene expression patterns. Mitochondria are therefore a distinct destination for certain MiR subsets that have been outsourced from nuclei (Bandiera et al. 2011). However, the translocation of microRNAs and other small RNAs to mitochondria and other organelles is not yet clarified (Sripada et al. 2012a). MicroRNA-532-3p regulates mitochondrial fission through targeting apoptosis repressor with caspase recruitment domain (Wang et al. 2015b). Based on the central role of mitochondria in programmed cell death, it may be expected that other microRNAs are involved in apoptosis, what has already been documented for nuclear microRNAs in cancer (Wang and Lee 2009).

In addition to translocation of nuclear microRNAs to mitochondria, there is evidence that mitochondria-specific MiRs (termed mitomiRs) are encoded by mtDNA, in part predicted by respective sequence analysis of mtDNA (Barey et al. 2011; Shinde and Bhadra 2015). MitomiRs are considered to act as vectors that sense and respond dynamically to the changing microenvironments of mitochondria (Bandiera et al. 2013). Several aging-related

mitomiRs may play a direct role in controlling mitochondrial function by regulating mitochondrial protein expression and affecting inflammatory responses (Rippo et al. 2014). Similar to entire cells, it might be expected that mitomiRs can be released as cargo of exosomes. It was shown that stimulated human mast cells can secrete mitochondrial components/particles that can induce inflammatory responses in an autocrine and paracrine manner (Zhang et al. 2012).

Circulating Mitochondrial DNA and Mitochondrial Fragments

Damaged and permeabilized cells of malignant neoplasms, including liver cancer, can release mitochondrial fragments, such as membranes, cristae and matrix components (mitochondremia), and mitochondrial DNA. Circulating free mtDNA reflects tumor cell death and chemotherapeutic effects on cancer cells (Huang et al. 2014). As outlined in more detail below, mitochondria and mitochondrial components released by cells can act as danger signals and provide damage-associated molecular patterns/DAMPs which may provoke inflammatory responses (Maeda and Fadeel 2014). In particular, circulating free mtDNA can act as a specific form of DAMP-termed mitochondrial DNA damage-associated molecular patterns (mtDNA DAMPs).

Mitochondrial Oxygen Stress: A Pathway Involved in Hepatocarcinogenesis

Reactive Oxygen Species (ROS) Production and ROS-Induced Oncogenic Transformation

Oxystress and the production of reactive oxygen species (ROS), including ROS released from mitochondria, contribute to carcinogenesis and cancer biology in general through the induction of DNA damage and the deregulation of signaling pathways (reviews: Wallace 2005; Fang et al. 2007; Fogg et al. 2011; Cardin et al. 2014; Sullivan and Chandel 2014). Oxystress susceptibility versus resistance is in part determined by genetic factors. OSGIN1/oxidative stress-induced growth inhibitor 1 is a tumor suppressor that is downregulated or mutationally altered in human HCC (Liu et al. 2014c). There is increasing evidence that hypoxia is associated with a progressive elevation of mitochondrial production of reactive oxygen species (ROS). Over time this may lead to stabilization of damaged cells through increased hypoxia-inducible factor (HIF)-2alpha, enabling cells to survive with persistently elevated ROS levels (review: Ralph et al. 2010). Apart from HIF, altered redox states of mitochondria are linked to distinct mitochondrial membrane proteins. Reactive oxygen species modulator-1/ROMO1 is a mitochondrial protein and oncomarker associated with control of redox states and cancer growth that acts through induction of NF-kappaB (Shyamsunder et al. 2015). The paradoxial increase of ROS in cancer cells suffering from hypoxia is not fully clarified but is probably related to altered oxygen sensing by mitochondria and changes in HIF availability (Chandel 2010). ROS generated by mitochondrial complex III are required for hypoxic activation of HIF, a mechanism that is involved in ROS handling in hypoxic cancer cells (Guzy and Schumacker 2006; Klimova and Chandel 2008). Through HIF signaling, hypoxia induces enlarged mitochondria in cancer cells. Hypoxic cancer cells undergo HIF-1-dependent and mitofusin-1-mediated alteration in morphology from a tubular network to markedly enlarged organelles. This change protects the cells from apoptotic stimuli as the mitochondria conserve ATP production and transmembrane potential (Chiche et al. 2010).

ROS-induced oxidative stress can be reduced by several protective pathways. HIF-2alpha can counteract DNA mismatch repair, causing the progressive accumulation of mitochondrial ROS-induced oxidative DNA alterations and associated mutations. In case such stabilized cells overcome senescence and maintain proliferative capacity, they may be candidates for malignant transformation (ROS-induced oncogenic transformation; Ralph et al. 2010). A potent anti-oxystress factor is the molecular chaperone,

mortalin, a protein of the HSP 70 family located primarily to mitochondria (Luo et al. 2010; Yang et al. 2011; Flachbartova and Kovacech 2013). Mortalin, together with Tid1, serves as a protein disaggregating machine which carries the scavenging of toxic protein aggregates (Iosefson et al. 2012). In HCCs, mortalin is overexpressed and increases as a function of stage (Chen et al. 2011), suggesting a protection mechanism directed against the deleterious effects of oxidative protein damage. Mortalin also interacts with p53 protein (wild type and mutant types) in HCC cells, inactivating the transcriptional and proapoptotic functions of p53 (Lu et al. 2011b). On the other hand, mortalin silencing in HCC cells promotes apoptosis via disinhibition of p53 (Lu et al. 2011a).

Cell Death Pathways Induced by Mitochondrial Oxystress

Mitochondrial oxystress can induce several cell death pathways both in normal and neoplastic cells, including liver cancer. Mitophagy (mitochondrial autophagy), the controlled elimination of superfluous mitochondria (see below), is involved in the reorganization of the mitochondrial complement in normal and cancer cells. Parts of undifferentiated cancer cells are poor in organelles and may, despite their energy requirements, contain less mitochondria than normal counterparts. Apart from deranged mitochondrial biogenesis, elimination of "unwanted" mitochondria by a selection process may be involved in the process of sarcopenia/mitochondriopenia. An important driving force for mitophagy in neoplastic cells is hypoxia, associated redox disorders, and other stressors (Kim et al. 2011; Frank et al. 2012; Chourasia et al. 2015; Wei et al. 2015). Several proteins mediate hypoxic damage of mitochondria. The hypoxia-inducible BH3-only proteins BNIP3, BNIP3L, and NIX react to hypoxia and potently induce mitophagy in cancer cells (Mellor and Harris 2007; Bellot et al. 2009; Ding et al. 2010; Feng et al. 2013; Ney 2015). Cancer cells subject to hypoxia show increased mitophagy rates induced by the mitochondrial outer-membrane protein FUNDC1, a receptor for hypoxia-induced mitophagy and interacting partner of LC3 (Liu et al. 2012). In HCCs, an autophagy-promoting protein, damage-regulated autophagy modulator/DRAM is translocated to mitochondria and induces mitophagy leading to apoptosis. In such cells, translocation of DRAM is inhibited by phosphorylated Akt, a mechanism protecting HCC cells from apoptosis (Liu et al. 2014b). In addition to mechanisms inherent to cancer cells, factors involved in cancerogenesis itself can affect mitophagy. For example, hepatitis C virus/HCV can modulate mitophagy through mitochondrial translocation of Parkin, a protein critically involved in mitophagy (see below; Kim et al. 2013a; Hara et al. 2014).

Regulation of the Mitochondrial Matrix and Mitochondrial Proteomes in Cancer Cells

In both normal and neoplastic cells, the mitochondrial matrix contains a set of specific proteins that are imported into the matrix by the translocase of the outer membrane, i.e., the TOM complex, and the presequence translocase of the inner mitochondrial membrane, i.e., the TIM23 complex (Albrecht et al. 2006; Qiu et al. 2013). In conjunction with other dysfunctions of cancer mitochondria, the mitochondrial matrix of cancer cells undergoes complex alterations that affect the turnover of mitochondrial proteins and of mtDNA. Proteins located to the mitochondrial matrix are degraded by three specific mitochondrial proteases of the AAA+ superfamily (Lon, ClpXP, and m-AAA proteases). By regulating the quantity and availability of mitochondrial proteins, these proteases exert a strong influence on the assembly of inner membrane and matrix proteins, composition of the oxidative phosphorylation platforms/tablets, nucleoid formation, and mitochondrial network dynamics (Goard and Schimmer 2014). In cancer cells, the expression patterns of matrix proteases are altered, a mechanism that affects numerous mitochondrial functions in cancer.

Mammalian mitochondria contain up to 1400 different proteins which form the mitochondrial

proteome. These proteins are in part produced in the cytoplasm and enter mitochondria via targeting/recognition signals, but other members of the proteome are synthesized by mitochondrial ribosomes (Herrmann et al. 2012). Apart from changes in mitochondrial DNA, liver cancer cells show differential upregulations and downregulation of mitochondrial proteins (Ye et al. 2013). These proteome and subproteome alterations are thought to play a role not only in carcinogenesis but also in tumor cell biology, in particular invasion and spread.

Mitochondrial Alterations Induced by Hepatitis Viruses

Hepatitis Viruses as Inducers of Oxidative Stress

Both hepatitis B and hepatitis C virus infections exert significant effects on oxygen metabolism in mitochondria and are potent mediators of oxidative stress. Through these pathways, HBV and HCV can contribute to oxystress-promoted carcinogenesis. The HBV protein HB X interacts with the inner mitochondrial membrane protein COXIII, causing upregulation of COX III protein and increased activity of cytochrome c oxidase/COX, associated with enhanced production of ROS (Lim et al. 2010; Hino et al. 2014; Zheng et al. 2014; Zou et al. 2015). Via ROS generation, HB X protein affects cell death pathway, but this protein can also directly induce apoptotic pathways (Rawat et al. 2012). Mitochondrial oxidative stress is also mediated by the action of hepatitis C virus/HCV, a virus known to promote mitochondrial dysfunction. Specifically, HCV promotes the mitochondrial production of ROS (Simula and De Re 2010; Brault et al. 2013; Hino et al. 2014). HCV is well known to alter the redox state of hepatocytes, associated with structural changes of mitochondria, and HCV core protein-induced dysfunction of the respiratory chain results in ROS overproduction (Korenaga et al. 2005a, b; Piccoli et al. 2006, 2009). HCV proteins, including core and NS5a proteins, contribute the generation of ROS through mechanisms mediated by binding of these proteins to mitochondria and endoplasmic reticulum/ER. Mitochondrial HCV core protein binding induces calcium uptake, mitochondrial superoxide production, and sensitization of mitochondria to calcium- and ROS-induced membrane permeability transition. HCV core protein redistributes cytochrome c from mitochondrial to cytosolic compartments (Okuda et al. 2002). The core and NS5a proteins of HCV cause ER stress and calcium(2+) release from ER. This results in a shift of calcium from ER to mitochondria, causing mitochondrial electron transport changes followed by increased ROS production (Wang and Weinman 2006, 2013). HCV triggers mitochondrial permeability transition with production of ROS leading to DNA damage (Machida et al. 2006). HCV also affects oxygen metabolism in mitochondria through iron-mediated pathways. Generally, iron accumulation in the liver exacerbates oxidative stress. ROS-mediated oxystress is modulated by proteins that regulate mitochondrial iron homeostasis, including the NEET family of proteins containing 2Fe-2S clusters (Stehlingh et al. 2014; Tamir et al. 2014). HCV core protein enhances mitochondrial iron uptake and ROS generation (Sekine et al. 2015).

Antiviral Effects of Mitochondria

Mitochondria hold an important position in antiviral defense and the generation of antiviral immunity (reviews: Scott 2010; Ohta and Nishiyama 2011). RNA viral components interact with a mitochondrial membrane adaptor protein, mitochondrial antiviral signaling protein/MAVS which is a member of the RIG-I signaling pathway and plays a crucial role in orchestrating the innate host response mediated by interferon-beta/IFN-beta. RIG-I signaling via MAVS involves the NF-kappaB pathways and also coordinates apoptotic and metabolic pathways. This signaling system connects mitochondria with other organelles participating in stress responses, as MAVS is also present in membranes of the endoplasmic reticulum and peroxisomes (Belgnaoui et al. 2011; Zemerli and Arnoult 2012). MAVS

makes part of a defense platform (HCV pathogen-associated molecular patterns/PAMPs) that also comprises Toll-IL-1 receptor domain-containing adaptor inducing IFN-beta/TRIF (review: Heim 2013). HCV as an RNA virus can circumvent the MAVS-induced innate antiviral immune reaction by cleavage and inactivation of MAVS through the viral protease, NS3-4A (Li et al. 2005; Anggakusuma et al. 2015). Another protein is involved in sensing of HCV and inducing innate immunity of the helicase MDA5 (Cao et al. 2015).

Other Mitochondrial Effects of Hepatitis Viruses

HBV affects the turnover of the mitochondrial protein, mitofusin-2, a protein involved in mitochondrial fusion and apoptosis (see below). HB X protein inhibits p53-mediated upregulation of mitofusin-2 in HCC cells (Wang et al. 2012b). This may exert an effect on tumor cell apoptosis, as mitofusin-2 triggers mitochondrial calcium influx from the endoplasmic reticulum to induce apoptosis in HCC (Wang et al. 2015a).

Mitochondria: Role in Inflammasome Biology and Immunity

Introduction

Inflammasomes constitute distinct and large molecular platforms that are activated by stress factors to serve as cell damage sensors and trigger inflammation and an innate immune response through the maturation of pro-inflammatory cytokines to produce IL-1beta and IL-18. Nod-like receptor family protein 3/NLRP3 is the most prominent inflammasome (reviews: Gross et al. 2011; Leemans et al. 2011). Danger signals that can activate the NLRP3 inflammasome include pathogen-associated molecular patterns, the inflammasomes thereby acting as microbial sensors (review: Franchi et al. 2010). Apart from bacterial products, components of parasites such as the malarial hemozoin are also capable to operate as danger signals for the inflammasome (Dostert et al. 2009). Host-derived damaging compounds such as reactive oxygen species/ROS and uric acid crystals also activate the inflammasome (Gasse et al. 2009). Due to their position in mechanisms dealing with cellular stress responses and innate immunity, inflammasomes play an important role in carcinogenic pathways.

Inflammasomes: The Mitochondrial Connection

One of the major common pathways for inflammasome activation is ROS (Tschopp and Schroder 2011). ROS are, e.g., produced through activation of NADPH oxidase upon phagocytosis of exogenous substances such as silica and asbestos (Dostert et al. 2008). A main source of ROS is mitochondria, organelles which are induced to secrete ROS upon various activation stimuli, including membrane damage, hypoxia, and increased metabolic rates (Brookes et al. 2004). In fact, there is a close association between dysfunctional mitochondria and the NLRP3 inflammasome, and inflammasomes are activated by mitochondrial oxystress (Tschopp 2011; Gurung et al. 2015; Usui et al. 2015). ROS produced by mitochondria are endogenous damage-associated molecular patterns/DAMPs (Kapetanovic et al. 2015) and fuel the inflammasome (Sorbara and Girardin 2011). Oxidized mtDNA released during apoptosis from mitochondria directly binds and activates the NLRP3 inflammasome, suggesting a link between apoptosis and inflammasome activation (Shimada et al. 2012; review: Martinon 2012). On the other hand, autophagy proteins inhibit the release of mitochondrial DNA and thus regulate innate immune responses mediated by the activated inflammasome (Kepp et al. 2011). However, not all inflammasomes are linked to organelles. The activated endogenous apoptosis-associated speck-like protein containing a CARD (ASC) pyroptosome is produced in the cytoplasm and co-localizes with NLRP3 and caspase-1, but not with organelles (Wang et al. 2013a).

Inflammasomes, Mitochondria, and Innate Immunity

Through inflammasome activation, mitochondria are linked to, and can trigger, inflammatory responses that operate in innate immunity (West et al. 2011; Cloonan and Choi 2012; Weinberg et al. 2015). Mitochondrial DAMPs/mtDAMPs (mitochondrial danger signals or mitochondrial alarmins) are potent drivers of innate immune reactions through activation of inflammasomes, a process mediated by pattern recognition receptors such as Toll-like receptors/TLRs (Said-Sadier and Ojcius 2012). NLRP3 inflammasomes activated by mitochondria-derived ROS not only generate inflammatory cytokines (interleukin-beta1, IL-18) but also modulate glycolytic and lipogenetic pathways and thus promote the metabolic syndrome (reviews: Tschopp 2011; Salminen et al. 2012). The caspase-1-dependent pro-inflammatory process induced by inflammasomes can activate the innate immune system, initiating pyroptosis (an inflammatory form of programmed cell death; see the respective chapter on apoptosis) and influencing adaptive immunity (Sutterwala et al. 2014).

Necroptosis: A Form of Cell Death Involved in Mitochondria-Induced Inflammation and Innate Immunity

As further discussed in the chapter on apoptosis, necroptosis is a pathway of regulated, caspase-independent necrosis that involves the proteins RIPK1, RIPK3, and MLKL. An alternate pathway to induce necroptosis involves the antiapoptotic protein CFLAR (CASP8 and FADD-like apoptosis regulator) long isoform (CFALRL) (He and He 2013). Necroptosis is induced by death receptors, TNF-alpha, interferons, intracellular DNA and RNA sensors, and, what is important in the setting of immunity, damage pattern recognition receptors such as Toll-like receptors (Kaczmarek et al. 2013; Pasparakis and Vandenabeele 2015). Necroptosis induction is also linked to mitophagy (Mizumura et al. 2014). In the case of TNF-alpha-induced necroptosis, TNF-alpha stimulation leads to the activation of the kinase receptor-interacting protein 1/RIP1, which then binds with and activates RIP3 to form the necrosome. RIP3 interacts with and activates the pseudokinase, mixed lineage kinase domain-like/MLKL, which induces necroptosis through the induction of mitochondrial damage and mitochondrial ROS production, linking mitochondrial dysfunction with necroptosis (Ye et al. 2012; Marshall and Baines 2014). In the course of necroptosis, damaged cells can release part of their organelle inventory into the extracellular space and into circulation. Mitochondria released from necroptotic cells act as danger signals or alarmins (DAMPs) and by this induce inflammatory signaling (Sangiuliano et al. 2014). Such mitochondria are phagocytosed by macrophages and dendritic cells, leading to the modulation of cytokine secretion by macrophages and dendritic cell maturation (Maeda and Fadeel 2014), both processes being instrumental in the induction of inflammation and innate immunity. In liver inflammation and liver cancer, Kupffer cells, monocytes, macrophages, stellate cells, dendritic cells, and endothelial cells form an interacting network of non-epithelial cells that transmit necroptotic death signals into inflammatory responses (Brenner et al. 2013).

Inflammasomes in Liver Cancer

Chronic necroinflammation promoting ongoing hepatocyte regeneration, liver cirrhosis, cell senescence, and telomere shortening is a key process inducing hepatocarcinogenesis. Inflammasomes, and specifically the NLRP3 inflammasome, play an important role in this process. Due to their capability as inflammasome activators, mitochondria rendered dysfunctional by various endogenous and exogenous factors, including hepatitis viruses, hold a critical position in this pathogenic pathway (Ramakrishna et al. 2013). In early carcinogenic steps, HCC evolution may be driven by inflammasome actions, but later phases of HCC are characterized by marked deregulation of the NLRP3 inflammasome, its components significantly downregulated or even lost. This suggests distinct inflammasome and innate immunity

expression patterns along HCC evolution and progression (Wei et al. 2014). In carcinomas, inflammasome regulation also involves cells that are components of the tumor stroma. The stroma contains tumor-associated macrophages/TAMs. In these cells, inflammasomes are activated upon cellular danger signals, including ROS from dysfunctional mitochondria, and initiate cytokine-mediated inflammatory responses that modulate tumor cell survival, growth, motility, and invasion. Mesenchymal stromal cells and mesenchymal stem cells homing to stroma negatively regulate NLRP3 inflammasome activation in macrophages (Oh et al. 2014), suggesting a complex interaction network among stromal cells.

Mitochondrial Biogenesis and Morphogenesis

Mitochondrial Dynamics

Mitochondria constantly fuse and divide. The number and shapes of mitochondria in a given cell are subject to a dynamic process (generally termed mitochondrial dynamics) which changes as a function of diverse metabolic requirements (Chen and Chan 2010; Westermann 2010; Ferree and Shirihai 2012; Wang et al. 2012a; Youle and Van der Bleik 2012). In addition to mitochondrial morphology, mitochondria are also dynamic in terms of organelle turnover and intracellular organelle movements. Mitochondrial dynamics results from a controlled equilibrium between mitochondrial fusion and fission in order to maintain a set of functional organelles (the chondriome) that is capable to meet the metabolic requirements of cells. Cycles of mitochondrial fusion and fission play an important role in organelle homeostasis and in the maintenance of mitochondrial integrity, as the fusion/fission cycle exchanges mDNA, proteins, and lipids of damaged or altered mitochondria with those of "healthy" mitochondria (reviews: Benard and Karbowski 2009; Otera et al. 2013; van der Bliek et al. 2013). Mitochondrial fusion and fission also play an important role in the regulation of the cell cycle (Mitra 2013) and apoptosis (Wasilewski and Scorrano 2009; Karbowski 2010).

Mitochondrial Shaping

The maintenance of a distinct shape is a decisive feature of mitochondrial homeostasis (Scorrano 2013). Dynamic morphogenesis of mitochondria and the establishment of organelle shapes (shaping) depend on the activity of several proteins, including mitofusins (Mfn) 1 and 2, optic atrophy1 (Opa1), and Drp1. Independently of mitochondrial fusion, Opa1 regulates the crista remodeling pathway of apoptosis. Specifically, Opa1 oligomers produced by the inner membrane rhomboid protease Parl are disrupted early during the apoptotic process (Scorrano 2007).

Mitochondrial Fusion

Mitofusin 1, a GTPase mutated in some forms of Charcot-Marie-Tooth disease, is an essential mitochondrial outer-membrane protein and a key mediator of mitochondrial fusion (Cerveny et al. 2007). Mitofusins are related to dynamin, a large GTPase required for vesicle endocytosis. Mitofusins form oligomers and cleave GTP to generate mitochondrial membrane rearrangements resulting in fusion. The two known mitofusins are generally involved in mitochondrial dynamics and can form homo- and heterooligomers, but mitofusin 1 has generally a higher GTPase activity than mitofusin 2. The function of mitofusin-2 is modified by a binding protein, MARCH-V, that also binds ubiquitinated forms of Drp1. Overexpression of MARCH-V promotes the formation of long tubular mitochondria in a manner that depends on mitofusin 2 activity (Nakamura et al 2006). Mitofusin 2 has additional activities, e.g., it is required for axonal mitochondrial transport via its interaction with the Miro/Milton complex (Misko et al. 2010). In damaged mitochondria, Parkin interacts with mitofusin 1 and promotes its enhanced turnover through proteasomal degradation, a process that serves to selectively identify and eliminate injured mitochondria (Glauser et al. 2011). Normal fusion of mitochondria into elongated tubular structures requires the action of the Bcl-2 family proteins, Bax and Bak, whereby Bax seems to induce mitochondrial fusion by activating the assembly of the

large GTPase Mfn2/mitofusin (Karbowski et al. 2006). Mitochondrial fusion and structure biogenesis are also dependent on the protein optic atrophy 1/Opa1. Opa1, a mitochondrial fusion GTPase, independently from mitochondrial fusion regulates the crista remodeling pathway. Oligomers of a membrane bound and a soluble form of Opa1, produced by Parl, an inner membrane rhomboid protease (presenilin-associated rhomboid-like), are disrupted early during apoptosis, leading to remodeling of the mitochondrial cristae (Scorrano 2007). Crista remodeling requires Parl, which participates in the production of a soluble form of Opa1. Parl itself is regulated by proteolysis to generate a cleaved form, which in turn modulates the shape of the mitochondrial reticulum (Pellegrini and Scorrano 2007). Caspases indirectly regulate cleavage of Opa1 (Loucks et al. 2009). The opening of fusion pores by Opa1 exerts an influence on mitochondrial energy conservation events manifesting as so-called mitochondrial flashes associated with fluctuations in mitochondrial membrane potential (Santo-Domingo et al. 2013).

Mitochondrial Fission (Mitochondrial Division)

Fission of the mitochondrial organelle is the crucial mechanism that increases the number of mitochondria per cell and thus regulates the organelle complement of cells relative to their functions. Mitochondrial fission during mitosis is a complex process that is thought to involve sensors deciding about fission dynamics and the proper distribution of mitochondria to daughter cells (Nezich and Youle 2013). The establishment of a certain degree of symmetry of organelle distribution during cell division is in part linked to the interaction of mitochondria with elements of the cytoskeleton, a central pacemaker of mitosis. The main factors for controlled fission of mitochondria are the fission proteins DRP1 (the mitochondrial fission GTPase, dynamin-related protein 1; DRP1-dependent mitochondrial division), which undergoes complex posttranslational regulation (Santel and Fank 2008), Fis1, and the mitochondrial fission factor/Mff (review: Elgass et al. 2013). DRP1 is a self-assembling GTPase that is recruited to both mitochondrial and peroxisomal membranes to execute organelle fission. Dynamins are large GTPases that belong to a protein superfamily which includes classical dynamins, dynamin-like proteins, Opa1, Mx proteins, mitofusins, and guanylate-binding proteins/atlastins. DRP1 is required for the mitochondrial fragmentation taking place during mitosis. Mitotic mitochondrial fission depends on the relocation of DRP1 to the outer mitochondrial membrane to coordinate membrane scission. The transfer of DRP1 to mitochondrial membranes is promoted by Fis1, a docking protein which acts as the DRP1 receptor. The proper placement and assembly of DRP1 at membrane scission sites or the disassembly step of fission complexes is regulated by the mitochondrial E3 ubiquitin ligase, MARCH5 (Karbowski et al. 2007). Docking and SUMOylation of DRP1 are promoted by Bax/Bak (Wasiak et al. 2007). DRP1 undergoes phosphorylation by the mitotic kinase cyclin B-CDK1, a process mediated by the small Ras-like GTPase RALA and its effector RALBP1 (Kashatus et al. 2011). RALA and RALB are activated downstream of oncogenic Ras, whereby RALB is mainly involved in tumor cell survival and metastasis (Kashatus and Counter 2011; Kashatus 2013). The mitotic kinase Aurora A promotes RALA relocalization to mitochondrial membranes, where it recruits the effector RALBP1 and DRP1 (Kashatus and Counter 2011). The two adaptor proteins, MiD49 and MiD51, recruit DRP1 to the mitochondrial surface in a Fis1- and Mff-independent manner (Palmer et al. 2011, 2013; Loson et al. 2013). The enzymatic activity of DRP1 is prompted by binding of mutant huntingtin to DRP1 (Song et al. 2011). The dynamics of DRP1 also depends on its interaction with the PTEN-induced kinase PINK1 (Deng et al. 2008; Liu et al. 2011). The mitochondrial expression of DRP1 is also controlled by a mitochondrial protein that regulates various mitochondrial functions, TRAP1/tumor necrosis factor receptor-associated protein 1 (Takamura et al. 2012). DRP1 activity is inhibited by annexin a6, which binds to DRP1. On the other hand,

binding of $Ca^{(2+)}$ to annexin a6 relieves this inhibition, DRP1 being liberated to induce fission (Chlystun et al. 2013). In viral hepatitis, DRP1 expression is stimulated by HCV, which also induces DRP1 phosphorylation and translocation to mitochondria (Kim et al. 2014).

Fis1 and Mff are DRP1-receptor/effector proteins. Fis1 can, however, also accomplish mitochondrial fission independently of DRP1, via its self-interaction through formation of dimers and oligomers. The fission factor Fis1 fragments mitochondria; downregulation of Fis1 results in mitochondrial elongation reflecting fission failure. Fis1 also affects proper cell division by interplay with the cell cycle machinery at G2/M (Lee et al. 2014). The expression of Fis1 is regulated by microRNA-484 (Wang et al. 2012c). An important mitochondrial fission protein is mitochondrial fission factor/MFF. MFF and Fis1 are both tail anchored in the mitochondrial outer membrane, but they form separate protein complexes (Gandre-Babbe and van der Bliek 2008).

Mitochondrial fission seems to depend on interorganelle interactions and interactions between mitochondria and components of the cytoskeleton. Fission is promoted by ER-mitochondrial interactions. Inverted formin 2/INF2 located to ER membranes can induce actin polymerization, whereby actin filaments accumulate between ER and mitochondria and result in initial mitochondrial constriction, which then allows secondary DRP1-driven constriction and fission (Korobova et al. 2013). For mitochondrial fission to occur, mitochondrial movements must come to a halt. This requires that microtubules connected with mitochondria and their associated proteins/motors stop their traction. In situations, where mitochondrial fission is blocked, the traction of microtubules causes tubular structures extending from mitochondria, the so-called mitochondrial extensions (Bowes and Gupta 2008).

Complex Factor Networks Regulating Mitochondrial Biogenesis and Morphogenesis

Several other proteins are required for mitochondrial function and regulation of the fission/fusion cycle. Leucine zipper EF hand-containing transmembrane protein 1 (LETM1), encoded by the WHSC1 gene deleted in Wolf-Hirschhorn syndrome (Bergemann et al. 2005), is an essential mitochondrial protein that is evolutionarily conserved throughout the eukaryotic kingdom (Schlickum et al. 2004). The tubular shape of mitochondria is maintained by LETM1 via its interaction with the AAA+-ATPase BCS1L, the latter stimulating the assembly of the LETM1 complex (Tamai et al. 2008). Downregulation of LETM1 leads to Drp1-independent fragmentation of the mitochondrial network and to necrosis-like death, without activation of caspases and not protected by Bcl-2 (Dimmer et al. 2008), suggesting that LEMP1 has a central position in the maintenance of mitochondrial network integrity. Functionally, LETM1 acts in a distinct mitochondrial Ca^{2+} uptake pathway (Hajnoczky and Csordas 2010; Waldeck-Weiermair et al. 2011). It also serves as an anchor protein for complex formation with the mitochondrial ribosome protein L36, whereby it regulates mitochondrial biogenesis (Piao et al. 2009). Mitochondrial function is also strongly regulated by huntingtin, mutated forms of which cause Huntington's disease (Bossy-Wetzel et al. 2008). Expectedly, microRNAs affect the morphology and function of mitochondria (Li et al. 2012; Sripada et al. 2012a). Parts of regulatory microRNAs are located to the mitochondria and have been termed mitomiRs, microRNAs that act as vectors that sense and respond to changing cellular microenvironments (Bandiera et al. 2013). In HCC cells, microRNA-122 negatively regulates mitochondrial shape and induces organelle swelling (Jin et al. 2014).

For the construction of mitochondrial cristae, members of the prohibitin family are essential (Merkwirth and Langer 2009). Prohibitins (PHB) form the mitochondrial PHB complex that possesses two homologous subunits, PHB1 and PHB2, which form a high molecular weight complex in the inner mitochondrial membrane. Another protein regulating biogenesis of cristae is mitofilin, a mitochondrial inner membrane protein acting as a membrane anchor (An et al. 2012; Zerbes et al. 2012a). Mitofilin controls cristae remodeling and through this mechanism regulates

cytochrome c release during apoptosis (Yang et al. 2012). Mitofilin is a component of the mitochondrial inner membrane organizing system or MINOS, which consists of three spatially arrayed clusters, i.e., mitofilin, MINOS1, and CHCHD3 (Alkhaja et al. 2012; Jans et al. 2013). MINOS is required for cristae biogenesis and for keeping cristae membranes attached to the inner membrane through so-called crista junctions (Zerbes et al. 2012b). The MINOS clusters interact with a cardiolipin-binding protein facing the intermembrane space, APOOL, involved in cristae biogenesis (Weber et al. 2013). MINOS is also critically involved in protein biogenesis of the mitochondrial outer membrane (Bohnert et al. 2012).

Mitochondrial morphology is controlled by an outer-membrane mitochondria-anchored protein ligase (MAPL). Overexpression of MAPL leads to mitochondrial fragmentation. The protein is also incorporated within unique, Drp1-independent, 70–100 nm-diameter mitochondria-derived vesicles which selectively incorporate their cargo. MAPL-containing mitochondrial vesicles fuse with a subset of peroxisomes, a mechanism involved in the complex mitochondria-peroxisome interaction. A further factor exerting an influence of mitochondrial shape is ubiquitin-specific protease 30 (USP30), a deubiquitinating enzyme that is embedded in the mitochondrial outer membrane. Depletion of USP30 induces elongated and interconnected mitochondria in a mitofusin-dependent fashion (Nakamura and Hirose 2008). Rearrangement of mitochondria networks, mitochondrial segregation, elongation, and unfurling are controlled by Drp1 and Milton, a kinesin-associated protein (Aldridge et al. 2007).

Mitochondria-Endoplasmic Reticulum Interactions

Interorganelle communication is an important aspect of cell biology and depends on distinct organelle distribution patterns, organelle movements, and tethering between different organelles. Mitochondria interact with the endoplasmic reticulum (ER) through a physical association mediated by the mitochondria-associated ER membrane or MAM (Pizzo and Pozzan 2007; Giorgi et al. 2009; Lebiedzinska et al. 2009; Rowland and Voeltz 2012; Wideman et al. 2013). Communications between the endoplasmic reticulum (ER) and mitochondria are important for diverse metabolic mechanisms, but specifically for calcium(2+) homeostasis and lipid biosynthesis. MAM is critically involved in efficient transfer of Ca^{2+} from ER to mitochondria. The MAM is a platform for the intermembrane transport of cholesterol, phospholipids, and ceramides and allows direct calcium transmission to mitochondria (Fujimoto and Hayashi 2011). Proteins that mediate the ER-mitochondria contact include calnexin, calreticulin, ERp44, ERp57, grp75, and the sigma-1 receptor at the MAM (Hayashi et al. 2009). The mitochondrial GTPase, mitofusin-2, localizes also to ER membranes where it interacts with mitofusins located to the outer mitochondrial membrane, thus generating interorganellar bridges (Merkwirth and Langer 2008; de Brito and Scorrano 2009). The mitofusin2-mediated mitochondria-ER contacts are regulated by the mitochondrial ubiquitin ligase MITOL (Sugiura et al. 2013). An ER-mitochondria encounter structure (ERMES) tethering complex has been identified in yeast, which plays a role in phospholipid exchange between the two organelles (Kommann et al. 2009; Kommann and Walter 2010; Michel and Kommann 2012). This organelle tethering system is phylogenetically conserved; in yeast cells, the ER has a role in tethering mitochondria specifically at the tip of the growing bud, and mitochondrial anchoring to the bud tip requires the tethering factor Mmr1 (McBride 2011). In eukaryotic cells, ERMES is also involved in the coordination of mitochondrial protein import, mitochondrial DNA replication, and mitochondrial dynamics. Five ERMES proteins are known in yeast so far, the ER-anchored protein Mmm1 and three mitochondria-associated proteins, Mdm10, Mdm12, and Mdm34, involved in the regulation of mitochondrial protein synthesis and morphology. A fifth component, the calcium 2+-binding Miro GTPase Gem1, is an integral

component of ERMES (Kommann et al. 2011; Stroud et al. 2011; Nguyen et al. 2012). Gem1 regulates the number and size of the ERMES complexes. The metazoan Gem1 ortholog Miro1 localizes to sites of ER-mitochondrial contacts (Kommann et al. 2011). Apart from its central role in intracellular calcium homeostasis, the mitochondria-ER interface is also involved in the regulation of apoptosis (Grimm 2012). The mitochondrial fission protein Fission 1 homologue (Fis1) conveys an apoptosis signal from mitochondria to ER membranes by interacting with Bap31 at the ER. The Fis1-Bap31 complex (ARCosome) forms an ER-mitochondrial bridge and undergoes an association with procaspase-8- (Igasawa et al. 2011). The ERMES complex discussed above is critically involved in mitophagy and the formation of mitophagosomes (Böckler and Westermann 2014).

Mitochondria-Derived Vesicles and the Peroxisomal Connection

The biogenesis and function of mitochondria and peroxisomes are tightly coupled. Their growth and division are mediated by common fission machineries (reviews: Schrader 2006; Delille et al. 2009). hFis1, a tail-anchored membrane protein interacting with the dynamin-like fission protein DLP1, regulates the membrane fission of both organelles (Koch et al. 2005), whereby hFis1 is targeted to peroxisomes through the action of Pex19p, a peroxisomal membrane protein import factor (Delille and Schrader 2008). hFis1 and DLP1 interact with Pex11pbeta, involved in the morphogenesis of peroxisomes (Kobayashi et al. 2007). These complex interactions between mitochondria and peroxisomes also depend on a specific mitochondrial cargo transport system, the mitochondria-derived vesicles/MDVs (review: Andrade-Navarro et al. 2009). MDVs are capable to fuse with peroxisomes and deliver cargo to these organelles (review: Schumann and Subramani 2008). MDVs are formed independently of the known mitochondrial fission GTPase DRP1 and are enriched for a mitochondrial small ubiquitin-like modifier (SUMO) E3 ligase called MAPL. Seventy to 100 nm-diameter MDVs contain MAPL, an outer-membrane mitochondria-anchored protein ligase with a RING-finger domain (Neuspiel et al. 2008). This MAPL seems to have a regulatory function controlling mitochondrial morphology. MAPL-containing MDVs fuse with a subset of peroxisomes. In contrast, MDVs containing TOM20 and lacking MAPL do not fuse with peroxisomes. MDVs involved in the peroxisomal connection transport cargo from mitochondria to peroxisomes. The regulation of MAPL from mitochondria to peroxisomes is itself regulated by the retromer complex, a component of vesicle transport from endosomes to the Golgi complex. Vps35 and Vps36 are found in complex with MAPL, Vps35 being recruited from MDVs (Braschi et al. 2010). The delivery of cargo from MDVs to peroxisomes is selective and does not require mitochondrial depolarization and is independent of ATG5 and LC3, suggesting that vesicle delivery complements mitophagy (Soubannier et al. 2012.

Mitochondrial Ribosomes

Synthesis of respiratory chain complexes depends on the expression of mtDNA-encoded subunits. This protein synthesis is performed by mitochondrial ribosomes inserted into membranes. Mitochondrial ribosomes are involved in the synthesis of only relatively few hydrophobic membrane proteins serving as subunits of the respiratory chain (review: Agrawal and Sharma 2012). Mitochondrial ribosome biogenesis is controlled by the mitochondrial transcription termination factor 3/MTERF3 (Wredenberg et al. 2013). Membrane-bound mitochondrial ribosomes and their specific proteins interact with human mitochondrial RNA polymerase (Surovtseva and Shadel 2013) and distinct ribosome-binding proteins which facilitate mitochondrial translation and include ObgH1, Mtg1, Mdm38, Mba1, and Oxa1 (Bauerschmitt et al. 2010; Kotani et al. 2013). Transfer RNA required for ribosomal protein synthesis travels from cytoplasm to mitochondria (Rubio and Hopper 2011). Protein synthesized by mitochondrial ribosomes leaves the organelle through a specifically tailored

ribosomal polypeptide tunnel (Gruschke and Ott 2010). Ribosome recycling in mitochondria is mediated by mitochondrial ribosome recycling factor/mtRRF (Rorbach et al. 2008). Mitochondrial ribosomes are specifically recognized by the mitochondrial release factor, mtRF1a (Duarte et al. 2012), a factor which recycles stalled ribosomes resulting from truncated stop-codon-less mRNAs (Huynen et al. 2012).

Mitochondrial Calcium Signaling

Calcium(2+) can efficiently be transported into the mitochondrial matrix, whereby hormone-stimulated calcium influx proceeds via open IP3 receptors and ryanodine receptors, resulting in a higher intra-matrix calcium concentration than in the cytosol. Furthermore, an interorganellar tether between the ER (see above) and the outer mitochondrial membrane includes the IP3 receptor and the voltage-dependent anion-selective channel/VDAC providing a shortcut for released calcium to cross the outer mitochondrial membrane (review: Hajnoczky and Csordas 2010). The mitochondrial calcium signaling system is closely linked with the cytoplasm through distinct proteins, including MUCU1, NCLX, and LETM1 (review: Hajnoczky and Csordas 2010).

Movements of Mitochondria (Mitokinesis)

Introduction

The entire set of mitochondria (the chondriome) within a given cell forms a dynamic network, within which individual mitochondria are distributed in a characteristic and function-oriented manner rather than being randomly distributed in the cell. This distinct arrangement of mitochondria in cells requires movements of mitochondria. Intracellular movements of mitochondria affect a variety of cellular behaviors both in normal and neoplastic cells. The cellular functions affected by mitokinesis include proliferation, differentiation, and apoptosis, as well as mitochondrial metabolic activity (Boldogh and Pon 2007; Frederick and Shaw 2007; Fagarasanu et al. 2010). Mitochondrial movements that determine intracellular organelle distribution are also important for the generation of cell polarity and hence for cell motility and invasive properties. Mitochondrial movements take place in all cells studied so far, but the longest distances traveled by mitochondria take place in axonal transport of these organelles. The movement of mitochondria to distinct parts of the cell body not only determines cytokinesis as such but also the strength of the cytokinetic response. An anterior localization of mitochondria in cancer cells, in between the nucleus and the leading edge, correlates with faster cell locomotion and increased directional persistence (Desai et al. 2013). Therefore, mitokinesis has a direct impact on the mode of cancer cell motility and invasion.

Mitokinesis Is Regulated by Distinct Ras Superfamily Components and by the Parkin/PINK1 System

Mitokinesis is critically regulated by members of the Ras signaling pathway. Essential regulators of mitochondrial morphogenesis and calcium-dependent sensors of mitochondrial motility are Miro GTPases, a unique subgroup of Ras superfamily proteins (Reis et al. 2009). Miro interacts with the protein kinase PINK1. Both Miro and Milton associate with mitochondria and regulate mitochondrial attachment to microtubules via the kinesin heavy chain (Koutsopoulos et al. 2010; Kane and Youle 2011). PINK1 and Parkin are Parkinson disease-associated proteins, whereby Parkin acts downstream of PINK1 in maintaining mitochondrial function and integrity. PINK1, a Ser/Thr kinase, translocates Parkin, an ubiquitin ligase, to mitochondria and regulates mitochondrial remodeling processes (review: Koh and Chung 2010). PINK1 forms a multiprotein mitochondrial complex with the adaptor proteins, Miro and Milton, and PINK1 also interacts with mitofilin, suggesting a role for PINK1 in mitochondrial trafficking along microtubular tracks (Weihofen et al. 2009). PINK1 phosphorylates

Miro, a process that activates proteasomal degradation of Miro in a Parkin-dependent manner. The subsequent removal of the adaptor Miro from the mitochondrion detaches kinesin from the mitochondrial surface and therefore arrests mitochondrial motility (Wang et al. 2011b). Mitochondrial motility is linked to distinct components of the cytoskeleton. Mitochondria are specifically connected with several proteins of the cytoskeleton. In budding yeast cells, inheritance of mitochondria into the emerging bud sites is regulated by bidirectional transport along the cytoskeleton (Frederick and Shaw 2007). Mitochondrial movements within cells and cell processes are mediated by three types of molecular motor proteins traveling along the cytoskeletal scaffold. The predominance of cytoskeletal motors varies in different species. In yeast and other fungi and in plant cells, the main engine is based on the actin system (Boldogh and Pon 2006), while in eukaryotic cells mitochondria predominantly move along microtubular tracks (Frederick and Shaw 2007), but the actin system is also involved. In yeast cells, the spatial organization of mitochondria is microtubule dependent (Das et al. 2010). For the function of microtubular track in mitokinesis, two different types of motors are required, viz., dyneins and kinesins. Dyneins deliver mitochondria toward the minus end of microtubules, while kinesins transport the organelles toward both the plus and minus ends of microtubules, depending on the position of the motor domain at the N- or the C-terminus. Among the 14 known families of kinesins, two kinesins are known to operate in mitokinesis: the kinesin heavy chain (KHC; also termed KIF5) and KIF1Balpha (Nangaku et al. 1994; Tanaka et al. 1998). KHC/KIF5 belongs to the kinesin 1 family and exists in three isoforms, two of them restricted to brain cells. KHC/KIF5 docks mitochondria by use of distinct adaptor proteins. In mammalian cells, Miro1/2, OIP106/GRIF-1, and syntabulin are adaptors that allow KHC/KIF5 to associate with mitochondria (Brickley et al. 2005; Cai et al. 2005; Fransson et al. 2006). Miro1 and Miro2 are proteins located in the outer mitochondrial membrane. HUMMR (hypoxia upregulated mitochondrial movement regulator) is a mitochondrial protein which interacts with adaptor proteins Miro1 and Miro2 and therefore affects kinesin interaction with the mitochondria and microtubules (Li et al. 2009). While present in normoxia, HUMMR protein abundance is markedly induced by hypoxia through a HIF-1alpha-dependent mechanism. In axons, HUMMR biases mitochondrial movement in the anterograde direction in response to hypoxia (Li and Rempe 2010). Mitofusin 2, an outer mitochondrial membrane protein, interacts with the Miro/Milton complex and is necessary for transport of axonal mitochondria (Misko et al. 2010). In the nematode *Caenorhabditis elegans*, a further kinesin variant, KLP6, has been identified and shown to regulate morphology and transport of mitochondria in neural cells (Tanaka et al. 2011). The kinesin system is also involved in movements of the Golgi apparatus (Marks et al. 1994). In fission yeasts, an additional microtubule-dependent but motor-independent mechanism for mitochondria positioning has been identified, and the protein mmb1p binds to mitochondria and microtubules by attaching tubular mitochondria to the MT lattice at multiple discrete interaction sites (Fu et al. 2011).

The involvement of the actin system in mitochondrial motility pathway has been documented for several types of mammalian cells, including neurons and their axons. In humans, a myosin, Myo19, functions in actin-based mitokinesis (Quintero et al. 2008). In epithelial cells, the actin cytoskeleton controls the movement of intracellular organelles. Mitochondria and lysosomes moving actively at rest stopped rapidly within seconds after an intracellular Ca^{2+} rise induced by activation of P2Y(2) purinergic receptors in an F-actin-dependent manner (Jung et al. 2012). A third cytoskeletal protein system that affects mitokinesis is the intermediate filament vimentin. In cells lacking vimentin or in which vimentin organization is disrupted, the motility of mitochondria is increased relative to intact cells with normal vimentin networks. A vimentin peptide of residues 41–94 directly binds to mitochondria and links these organelles to other components of the cytoplasm and/or the cytoskeleton (Nekrasova et al. 2011).

Mitoptosis

Introduction

Mitoptosis (programmed destruction of mitochondria) is a mitochondrial suicide process by which cells can deal with impaired, malfunctioning, or damaged mitochondria. It is thought that mitoptosis plays an important role in various disease processes (review: Mijaljica et al. 2010; Apostolova et al. 2011). Mitoptosis was first hypothesized to take place in cells undergoing apoptosis (Skulachev 2002) and to accompany apoptosis as a pathway to eliminate mitochondria in a caspase-independent manner (Karbowski and Youle 2003). Mitoptosis occurs when mitochondria hydrolyze glycolytic ATP instead of producing respiratory ATP (uncoupling of oxidative phosphorylation; "energy catastrophe"). Survival of cells with this type of disorder is associated with selective elimination of "unloved" mitochondria by mitoptosis. Elimination of aged mitochondria through mitoptosis is thought to be regulated by mechanisms related to mitochondrial genome germ line variations that become more relevant and frequent as a function of age (Rose et al. 2002).

Mitoptosis as an Effector of Chondriome Organization: The Mitochondrial Thread-Grain Transition

Mitochondria perform a broad array of interconnected functions and form a dynamic, interconnected network that is intimately integrated with other cellular compartments and organelles (Nunnari and Suomalainen 2012). Mitochondria are now known to play a crucial role in cell signaling events, interorganelle communications, modulating nuclear functions, and regulating cell survival and death. Signaling gates serving as ports of cross-talk include mitochondrial porins, e.g., the voltage-dependent anion channel or VDAC (Shoshan-Barmatz et al. 2010). In many cell systems, the entire set of mitochondria (termed the chondriome) forms characteristic spatial arrangements called the mitochondrial reticulum. The distinct features of this intracellular positioning of individual mitochondria in the reticulum allow the cell to organize a united intracellular power-transmitting system (or a "powerhouse"). In this reticulum, mitochondria also act as important signaling platforms (Tait and Green 2012). As the cell is a dynamic system continuously adapting to novel situations, the mitochondrial reticulum has to be dynamic as well. The reticulum can, e.g., be changed by damage of certain mitochondria or mitochondrial senescence, may alter its network through mitochondrial movements, may change in numbers or shape changes, or may change its organization through interorganelle associations, e.g., with the ER. In these situations, decomposition of extended mitochondria to small and roundish organelles takes place, a process called thread-grain transition (Skulachev et al. 2004). Morphologically, elongated mitochondria undergo a segmentation, bead-like small organelle parts being connected with their neighbors via a thin, threadlike structure. It was assumed that this transition serves to isolate a damaged part of a mitochondrion from the intact parts, the isolated "grain" then undergoing mitoptosis and being engulfed by an autophagosome.

Mechanisms of Mitoptosis

Mitoptosis has been proposed to occur in two variants: inner membrane mitoptosis in which only the internal matrix and cristae are lost while the external mitochondrial envelope remains unaltered and outer-membrane mitoptosis, where only swollen internal cristae are detectable (Tinari et al. 2007). It may be assumed that both of these pathways will then result in mitoptotic organelle loss. Mitoptosis is characterized by a series of distinct steps (Lyamzeav et al. 2008): fission of mitochondrial filaments, clustering of the resulting roundish mitochondria in the perinuclear area, occlusion of mitochondrial clusters by a membrane and formation of the mitoptotic body, decomposition of mitochondria inside the mitoptotic body to small vesicles, protrusion of the mitoptotic body from the cell, and disruption of the boundary

membrane of the body. Mitoptosis is sometimes, but not consistently, associated with mitochondrial autophagy (Kundu and Thompson 2005; Lyamzeav et al. 2008). The increased fragmentation of mitochondria in the initial phase of mitoptosis is due to increased fission via the recruitment of a dynamin-like GTPase Drp1 to mitochondria and to a block of mitochondrial fusion, fission and fusion being counteracting mechanisms. In early mitoptosis, Bax-/Bak-mediated release of DDT/TIMM8a, a mitochondrial intermembrane space protein, into the cytosol occurs, where it binds to and promotes the mitochondrial redistribution of Drp1, a mediator of mitochondrial fission. In a first step, this redistribution causes mitochondrial outer-membrane permeabilization (MOMP), whereby intermembrane space proteins are released, including DDT/TIMM8a and the proapoptotic cytochrome c (Arnoult et al. 2005). In situations of proteasome inhibition, mitoptosis can occur independent from Bax/Bak, in that proteasome inhibitors induce a rapid and simultaneous upregulation of several BH3-only proteins, including BIK, BIM, MCL-1S, NOXA, and PUMA, in the mitochondria, causing mitochondrial membrane permeabilization, degradation of the mitochondrial reticulum, and irreversible changes of the mitochondrial ultrastructure (Lomonosova et al. 2009).

The integrity of mitochondria strongly depends on Ca^{2+} homeostasis within the organelle. This homeostasis depends on calcium transfer from the endoplasmic reticulum (ER) to the mitochondria, via a distinct functional and structural interorganelle association (ERMES; see above). Alpha-synuclein positively affects calcium transfer from the ER to mitochondria, augmenting the mitochondrial Ca^{2+} transients elicited by agonists that induce Ca^{2+} release from the ER. This effect depends on the number of ER-mitochondria interactions in the setting of ERMES (Cali et al. 2012). Reactive oxygen species (ROS) initiate mitoptosis in order to rid the intracellular population of mitochondria from those that are ROS overproducing (Skulachev 2006). Loss of the mitochondrial Lon protease, which catalyzes the degradation of oxidatively modified mitochondrial matrix proteins, chaperones the assembly of inner membrane complexes, and participates in the regulation of mitochondrial gene expression and genome integrity, leads to mitoptosis (Bota et al. 2005).

Protection Against Mitoptosis

As the maintenance of a normally constructed chondriome in its reticulum network is essential for cellular homeostasis, there are physiological mechanisms counteracting mitochondrial decay. During starvation, mitochondria fuse into highly connected networks, protecting mitochondria from damage-induced degradation through an interorganelle rescue mechanism. This distinct alteration of the chondriome is dependent on the inactivation of the fission protein Drp1, through targeting of two different phosphorylation sites. This rapid inhibition of mitochondrial fission, which characterizes one step in mitoptosis, leads to unopposed mitochondrial fusion to form a stable network (Rambold et al. 2011).

Physiological Mitoptosis

Reticulocyte maturation to erythrocytes is the final step of erythropoiesis that occurs in the blood circulation. In the course of reticulocyte maturation, a distinct two-step elimination program takes place, leading to loss or elimination of organelles, including the nucleus (followed by nucleophagy by macrophages), mitochondria, Golgi apparatus, lysosomes, and components of the endoplasmic reticulum. Part of the cellular protein substance of reticulocytes is eliminated by exosome release (Blanc et al. 2005). Close to red cell maturation, a second and last step is a cleaning session that clears the remaining mitochondria via mitoptosis (Géminard et al. 2002).

Mitoptosis in Cancer

Massive mitoptosis can cause cell death due to the intracellular liberation of cell death proteins normally hidden in the intermembrane space of mitochondria.

Mitophagy

Introduction

Mitophagy is the selective autophagic degradation of damaged and/or superfluous mitochondria and is regarded as an essential process for mitochondrial quality and quality control (reviews: Kim et al. 2007; Tolkovsky 2009; Mijaljica et al. 2010; Novak and Dikic 2011; Okamoto and Kondo-Okamoto 2012; Rambold and Lippincott-Schwartz 2011; Wang and Klionsky 2011; Hirota et al. 2012; May et al. 2012; Novak 2012; Zhang 2013; Dengjel and Abeliovich 2014; Liu et al. 2014a; Redmann et al. 2014; Shimizu et al. 2014; Song et al. 2014). Mitophagy is the major instrument of the cell to regulate mitochondrial number and mass, and there is a regulatory cross-talk between mitochondrial function and dysfunction and mitochondrial abundance (Michel et al. 2011), suggesting the presence of a mitochondrial abundance sensor. However, how mitochondria are selected for mitophagy is only partially known, although the mitochondrial permeability transition (MPT) is critically involved in the initiation of the process (Mijaljica et al. 2007). Mitophagy belongs to the group of autophagic processes, which also comprise pexophagy, ER-phagy, ribophagy, golgiphagy, and nucleophagy. Autophagy, as discussed in a separate chapter, serves removing of altered proteins and dysfunctional organelles (Kondo-Okamoto et al. 2012). Mitophagy is an essential component of the regulatory systems controlling mitochondrial numbers and mass. Apart from mitochondrial quality control, mitophagy is an instrument to guarantee the maintenance of adequate mitochondrial abundance (Michel and Kornmann 2012).

Structural Features of Mitophagy

In response to inducers of mitophagy, mitochondria undergo fragmentation. This morphologic alteration accompanies the exposure of so-called "eat-me" signals. These signals result in the engulfment of mitochondria by autophagosomes (Gomes and Scorrano 2013).

Causes of Mitochondrial Injury Leading to Mitophagy

Injury of mitochondrial DNA, e.g., mtDNA mutations, can result in mitophagy (de Gilkerson et al. 2012; De Vries et al. 2012). Mutations in the gene for ATPase type 13A2 (ATP13A2), involved in autosomal-recessive Parkinsonism (Kufor-Rakeb syndrome), are associated with a higher frequency of mtDNA lesions, increased oxygen consumption rates, fragmentation of the mitochondrial network, and mitophagy (Grünewald et al. 2012). Oxygen damage via reactive oxygen species (ROS) as potential mitochondrial damaging agents can normally be neutralized within the mitochondria through enzymatic activity. In case this system is overcharged, mitochondrial damage and mitophagy can occur (Lee et al. 2012). Elimination of mitochondria being overcharged with oxidized proteins via mitophagy is a mechanism suppressing cell damage by mitochondrial oxidative products (Kurihara et al. 2012). But also hypoxia causes mitochondrial injury leading to mitophagy (see above).

PINK1- and Parkin-Mediated Mitophagy

The Parkinson disease-related proteins PINK1 (PTEN-induced kinase 1; a mitochondrially localized serine/threonine kinase) and Parkin (PARK2; a cytosolically localized E3 ubiquitin ligase) are guardians of mitochondrial fidelity, regulate mitochondrial homeostasis (Scarffe et al. 2014), and are essential for targeting mitochondria for mitophagy (Matsuda and Tanaka 2010; Huang et al. 2011; Kane and Youle 2011; Springer and Kahle 2011; Youle and Narendra 2011; Jin and Youle 2012). The mitochondrial turnover of PINK1 and Parkin is tightly controlled. The mitochondrial intramembrane protease PARL cleaves human PINK1 within its conserved membrane anchor. Mature PINK1 is then free to be released into the cytosol or the mitochondrial intermembrane space.

In PINK1-dependent mitophagy and following uncoupling of the outer mitochondrial membrane

potential, the canonical import of PINK1 and PARL-catalyzed processing is blocked, leading to the accumulation of the PINK1 precursor. Accumulation of PINK1 precursor and its targeting to the outer mitochondrial membrane triggers mitophagy (Meissner et al. 2011). Generally, loss of PINK1 function causes oxidative stress via production of ROS and mitochondrial damage (Cui et al. 2011). Endogenous PINK1 forms a 700 kDa complex with the translocase of the outer membrane (TOM) on depolarized mitochondria. Association of PINK1 with TOM complex allows rapid reimport of PINK1 to rescue depolarized mitochondria from mitophagy (Lazarou et al. 2012). In Parkin-dependent mitophagy, PINK1 which is located in the mitochondrial outer membrane recruits Parkin from the cytosol to the mitochondria as a first step leading to autophagous destruction of the organelle. Complexes containing upstream Atg proteins (autophagy-related proteins), including ULK1 (the mammalian homologue of Agt1), Atg12, Atg14, DFCP1, WIPI-1, and Atg16L1, can associate with depolarized mitochondria. Atg9A and ULK1 structures are also recruited to damaged mitochondria as well as to the autophagosome formation site in the earliest steps of mitophagy, while the autophagosomal LC3 (MT-associated protein 1 light chain 3) family of proteins is involved in later stages of mitophagy (Itakura et al. 2012). LC3 interacts with microtubule-associated protein 1S/MAP1S bridging autophagic components with the microtubular system (Xie et al. 2011). In human endothelial cells, targeted mitochondrial damage upregulated the autophagy factors LC3B, Atg5, and Atg12, and this upregulation resulted in an improved mitochondrial membrane potential, enhanced ATP production, and an antiapoptotic effect (Mai et al. 2012). One of the effectors of the mitophagic cascade, Ulk1, is phosphorylated by AMP-activated protein kinase connecting energy sensing to mitophagy (Egan et al. 2011) and is regulated by the Hsp90-Cdc37 chaperone complex (Joo et al. 2011).

Parkin itself as an ubiquitin E3 ligase ubiquitinates intracellular proteins and via this mechanism induces clearance of cellular molecular debris and of organelles, including mitophagy, whereby ubiquitinylated outer mitochondrial membrane proteins, including mitofusins 1 and 2, are targeted for proteasomal degradation (Gegg et al. 2010; Chan and Chan 2011; Karbowski and Youle 2011; Khandelwal et al. 2011). In the pathway of mitophagy, Parkin binds to Ambra1 (activating molecule in beclin 1-regulated autophagy), a protein that promotes autophagy (Van Humbeeck et al. 2011a,b). The function of Parkin in mitophagy is synergistically regulated by the three ubiquitin-conjugating enzymes, UBE2N, UBE2L3, and UBE2D2/3 (Geisler et al. 2014). The autophagy protein beclin 1 interacts with Park2 and regulates Park2 translocation to mitochondria and mitophagy (Choubey et al. 2014). A protein that regulates mitophagy is the diabetes susceptibility factor clec16a, a membrane-associated endosomal protein that interacts with the E3 ubiquitin ligase Nrdp1, a target of the master regulator of mitophagy, Parkin (Soleimanpour et al. 2014). Parkin-induced mitophagy is counteracted by the mitochondrial deubiquitinase USP30, a protein which removes ubiquitin attached by Parkin onto damaged mitochondria (Bingol et al. 2014) and by the deubiquitinase USP15 (Cornelissen et al. 2014). PINK1 and Parkin also exert important effects on mitochondrial motility. PINK1 phosphorylates Miro, a component of the primary motor/adaptor complex that anchors kinesin to the mitochondrial surface. The phosphorylation of Miro activates proteasomal degradation of Miro in a Parkin-dependent manner. By thus stopping mitochondria in their tracks, the PINK1/Parkin pathway may quarantine damaged mitochondria prior to their mitophagic clearance (Wang et al. 2011).

Execution of Mitophagic Pathways

Bnip3 (Nip3-like protein X; NIX), an atypical BH3-only protein causing mitochondrial dysfunction and cell death, can under certain circumstances also protect against cell death by inducing mitophagy. Bnip3 activation is a pro-mitophagic signal, and this pathway involves impairment of mitochondrial oxidative phosphorylation and is independent of apoptosis (Thomas et al. 2011). This response requires

homodimerization of Bnip3, and clearance of mitochondria is mediated in part via binding of Bnip3 to the microtubule-associated protein 1 light chain 3 (LC3) on the autophagosome (Hanna et al. 2012). On the other hand, Bnip3-mediated mitophagy is inhibited by activation of the p53-TIGAR axis (Hoshino et al. 2012). Mdivi (mitochondrial division inhibitor) attenuates mitochondrial division in cells by selectively inhibiting the mitochondrial division dynamin-related protein (Cassidy-Stone et al. 2008). Dynamin-related protein 1 (Drp1) docks at mitochondria, regulating their positioning and activity (Baixauli et al. 2011). Mdivi is also a mitophagy inhibitor that operates via inhibition of Drp1 (Park et al. 2011; Givvimani et al. 2012). FUNDC1, a mitochondrial outer-membrane protein, is a receptor for hypoxia-induced mitophagy. Hypoxia leads to dephosphorylation of FUNDC1 and enhances its interaction with LC3 for selective mitophagy (Liu et al. 2012). Following mitophagy, organelle remnants can enter a lysosomal degradation pathway, whereby a distinct system of mitochondria-derived vesicles (MDVs) generates the contact with lysosomes to deliver degradable cargo (Soubannier et al. 2012).

Other Factors Regulating Mitophagy

The Parkinson disease GWAS risk factor locus SREBF1 (sterol regulatory element-binding transcription factor 1) is a regulator of mitophagy (Ivatt et al. 2014). The ATM gene mutated in ataxia telangiectasia plays a role in mitochondrial homeostasis. Atm-deficient thymocytes in mice show an altered mitochondrial homeostasis, suggesting that ATM plays a role in regulating mitophagy (Valentin-Vega and Kastan 2012). Melatonin, a highly efficient antioxidant, is involved in the control of mitophagy (Coto-Montes et al. 2012). Mitophagy is also mediated by the C2 domain-containing protein, SMURF1 (Orvedal et al. 2011). Mitophagy is also promoted by proteins of the HCV virion (Kim et al. 2014).

Sequelae of Inhibited Mitophagy

It has been shown that inhibition or blockade of mitophagy leads to the accumulation of damaged, ROS-generating mitochondria, which in turn activates the NLRP3 inflammasome, a pathway positively regulated by reactive oxygen species/ROS. The NLR3P inflammasome acts as a sensor of damaged mitochondria, explaining the frequent association of mitochondrial damage and inflammatory diseases (Zhou et al. 2011).

References

Agaronyan K, Morozov YI, Anikin M, Temiakov D (2015) Mitochondrial biology. Replication-transcription switch in human mitochondria. Science 347:548–551

Agrawal RK, Sharma MR (2012) Structural aspects of mitochondrial translational apparatus. Curr Opin Struct Biol 22:797–803

Albrecht R, Rehling P, Chacinska A, Brix J, Cadamuro SA, Volkmer R, Guiard B et al (2006) The Tim21 binding domain connects the preprotein translocases of both mitochondrial membranes. EMBO Rep 7:1233–1238

Aldridge AC, Benson LP, Siegenthaler MM, Whigham BT, Stowers RS, Hales KG (2007) Roles for Drp1, a dynamin-related protein, and milton, a kinesin-associated protein, in mitochondrial segregation, unfurling and elongation during Drosophila spermatogenesis. Fly (Austin) 1:38–46

Alkhaja AK, Jans DC, Nikolov M, Vukotic M, Lytovchenko O, Ludewig F, Schliebs W et al (2012) MINOS1 is a conserved component of mitofilin complexes and required for mitochondrial function and cristae organization. Mol Biol Cell 23:247–257

Alpert LI, Zak FG, Werthamer S, Bochetto JF (1974) Cholangiocarcinoma: a clinicopathologic study of five cases with ultrastructural observations. Hum Pathol 5:709–728

An J, Shi J, He Q, Lui K, Liu Y, Huang Y, Sheikh MS (2012) CHCM1/CHCHD6, novel mitochondrial protein linked to regulation of mitofilin and mitochondrial cristae morphology. J Biol Chem 287: 7411–7426

Andrade-Navarro MA, Sanchez-Pulido L, McBride HM (2009) Mitochondrial vesicles: an ancient process providing new links to peroxisomes. Curr Opin Cell Biol 21:560–567

Anggakusuma, Frentzen A, Gürlevik E, Yuan Q, Steinmann E, Ott M, Staeheli P, Schmid-Burgk J, Schmidt T, Hornung V et al (2015) Control of hepatitis C virus replication in mouse liver-derived cells by

MAVS-dependent production of type I and type III interferons. J Virol 89:3833–3845
Apostolova N, Blas-Garcia A, Esplugues JV (2011) Mitochondria sentencing about cellular life and death: a matter of oxidative stress. Curr Pharm Des 17:4047–4060
Arnoult D, Rismanchi N, Grodet A, Roberts RG, Seeburg DP, Estaquier J, Sheng M et al (2005) Bax/Bak-dependent release of DDT/TIMM8a promotes Drp1-mediated mitochondrial fission and mitoptosis during programmed cell death. Curr Biol 15:2112–2118
Baixauli F, Martin-Cofreces NB, Morlino G, Carrasco YR, Calabia-Linares C, Veiga E et al (2011) The mitochondrial fission factor dynamin-related protein 1 modulates T-cell receptor signalling at the immune synapse. EMBO J 30:1238–1250
Bandiera S, Rüberg S, Girard M, Cagnard N, Hanein S, Chrétien D, Munnich A, Lyonnet S, Henrion-Caude A (2011) Nuclear outsourcing of RNA interference components to human mitochondria. PLoS One 6:e20746
Bandiera S, Matégot R, Girard M, Demongeot J, Henrion-Caude A (2013) MitomiRs delineating the intracellular localization of microRNAs at mitochondria. Free Radic Biol Med 64:12–19
Barey E, Saint-Auret G, Bonnamy B, Damas D, Boyer O, Gidrol X (2011) Pre-microRNA and mature microRNA in human mitochondria. PLoS One 6:20220
Bauerschmitt H, Mick DU, Deckers M, Vollmer C, Funes S, Kehrein K, Ott M, Rehling P et al (2010) Ribosome-binding proteins Mdm38 and Mba1 display overlapping functions for regulation of mitochondrial translation. Mol Biol Cell 21:1937–1944
Belgnaoui SM, Paz S, Hiscott J (2011) Orchestrating the interferon antiviral response through the mitochondrial antiviral signaling (MAVS) adapter. Curr Opin Immunol 23:564–571
Bellot G, Garcia-Medina R, Gounon P, Chiche J, Roux D, Pouysségur J, Mazure NM (2009) Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains. Mol Cell Biol 29:2570–2581
Benard G, Karbowski M (2009) Mitochondrial fusion and division: regulation and role in cell viability. Semin Cell Dev Biol 20:365–374
Bergemann AD, Cole F, Hirschhorn K (2005) The etiology of Wolf-Hirschhorn syndrome. Trends Genet 21:188–195
Bingol B, Tea JS, Phu L, Reichelt M, Bakalrski CE, Song Q, Foreman O, Kirkpatrick DS et al (2014) The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature 509:370–375
Blanc L, De Gassart A, Géminard C, Bette-Bobillo P, Vidal M (2005) Exosome release by reticulocytes – an integral part of the red blood cell differentiation system. Blood Cells Mol Dis 35:21–26
Böckler S, Westermann B (2014) ER-mitochondria contacts as sites of mitophagosome formation. Autophagy 10:7
Bohnert M, Wenz LS, Zerbes RM, Horvath SE, Stroud DA, von der Malsburg K, Müller JM et al (2012) Role of mitochondrial inner membrane organizing system in protein biogenesis of the mitochondrial outer membrane. Mol Biol Cell 23:3948–3956
Boldogh IR, Pon LA (2006) Interactions of mitochondria with the actin cytoskeleton. Biochim Biophys Acta 1763:450–462
Boldogh IR, Pon LA (2007) Mitochondria on the move. Trends Cell Biol 17:502–510
Bossy-Wetzel E, Petrilli A, Knott AB (2008) Mutant huntingtin and mitochondrial dysfunction. Trends Neurosci 31:609–616
Bota DA, Ngo JK, Davies KJ (2005) Downregulation of the human Lon protease impairs mitochondrial structure and function and causes cell death. Free Radic Biol Med 38:665–677
Bowes T, Gupta RS (2008) Novel mitochondrial extensions provide evidence for a link between microtubule-directed movement and mitochondrial fission. Biochem Biophys Res Commun 376:40–45
Braschi E, Goyon V, Zunino R, Mohanty A, Xu L, McBride HM (2010) Vps35 mediates vesicle transport between the mitochondria and peroxisomes. Curr Biol 20:1310–1315
Brault C, Levy PL, Bartosch B (2013) Hepatitis C virus-induced mitochondrial dysfunctions. Viruses 5:954–980
Brenner C, Galluzzi L, Kepp O, Kroemer G (2013) Decoding cell death signals in liver inflammation. J Hepatol 59:583–594
Brickley K, Smith MJ, Beck M, Stephenson FA (2005) GRIF-1 and OIP106, members of a novel gene family of coiled-coil domain proteins, association in vivo and in vitro with kinesin. J Biol Chem 280:14723–14732
Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu SS (2004) Calcium, ATP, and ROS: a mitochondrial love-hate triangle. Am J Physiol Cell Physiol 287: C817–C833
Caballero T, Aneiros J, Lopez-Caballero J, Gomez-Morales M, Nogales F (1985) Fibrolamellar hepatocellular carcinoma. An immunohistochemical and ultrastructural study. Histopathology 9:445–456
Cai Q, Gerwin C, Sheng ZH (2005) Syntabulin-mediated anterograde transport of mitochondria along neuronal processes. J Cell Biol 170:959–969
Cali T, Ottolini D, Negro A, Brini M (2012) Alpha-synuclein controls mitochondrial calcium homeostasis by enhancing endoplasmic reticulum-mitochondria interactions. J Biol Chem 287:17914–17929
Cao X, Ding Q, Lu J, Tao W, Huang B, Zhao Y, Niu J, Liu YJ, Zhong J (2015) MDA5 plays a critical role in interferon response during hepatitis C virus infection. J Hepatol 62:771–778
Cardin R, Piciocchi M, Bortolami M, Kotsafti A, Barzon L, Lavezzo E, Sinigaglia A et al (2014) Oxidative damage in the progression of chronic liver disease to

hepatocellular carcinoma: an intricate pathway. World J Gastroenterol 20:3078–3086
Carelli V, Maresca A, Caporali L, Trifunov S, Zanna C, Rugolo M (2015) Mitochondria: biogenesis and mitophagy balance in segregation and clonal expansion of mitochondrial DNA mutations. Int J Biochem Cell Biol pii:S1357-2725(15)00033-3
Cassidy-Stone A, Chipuk JE, Ingerman E, Song C, Yoo C, Kuwana T, Kurth MJ, Shaw JT et al (2008) Chemical inhibition of the mitochondrial division dynamin reveals its role in Bax/Bak-dependent mitochondrial outer membrane permeabilization. Dev Cell 14:193–204
Cerveny KL, Tamura Y, Zhang Z, Jensen RE, Sesaki H (2007) Regulation of mitochondrial fusion and division. Trends Cell Biol 17:563–569
Chan NC, Chan DC (2011) Parkin uses the UPS to ship off dysfunctional mitochondria. Autophagy 7:771–772
Chandel NS (2010) Mitochondrial regulation of oxygen sensing. Adv Exp Med Biol 661:339–354
Chatterjee A, Dasgupta S, Sidransky D (2011) Mitochondrial subversion in cancer. Cancer Prev Res 4: 638–654
Chen H, Chan DC (2010) Physiological functions of mitochondrial fusion. Ann N Y Acad Sci 1201:21–25
Chen X, Xu B, Li H, Yang L, Zuo J, Liu W, Liu C (2011) Expression of mortalin detected in human liver cancer by tissue microarrays. Anat Rec (Hoboken) 294:1344–1351
Cheon H, Moon HE, Lee MS, Kim SS (2010) Loss of mitochondrial DNA enhances angiogenic and invasive potential of hepatoma cells. Oncol Rep 23:779–786
Chiche J, Rouleau M, Gounon P, Brahimi-Horn MC, Pouysségur J, Mazure NM (2010) Hypoxic enlarged mitochondria protect cancer cells from apoptotic stimuli. J Cell Physiol 222:648–657
Chlystun M, Campanella M, Law AL, Duchen MR, Fatimathas L, Levine TP, Gerke V et al (2013) Regulation of mitochondrial morphogenesis by annexin a6. PLoS One 8:e53774
Choubey V, Cagalinec M, Liiv J, Safiulina D, Hickey MA, Kuum M, Liiv M, Anwar T et al (2014) BECN1 is involved in the initiation of mitophagy: it facilitates PARK2 translocation to mitochondria. Autophagy 10:1105–1119
Chourasia AH, Boland ML, Macleod KF (2015) Mitophagy and cancer. Cancer Metab 3:4
Clayton FE, Furth EE, Xu T, Yao Y, Hwang PG, Bing Z (2012) A case of primary clear cell hepatocellular carcinoma in a non-cirrhotic liver: an immunohistochemical and ultrastructural study. Rare Tumor 4:e29
Cloonan SM, Choi AM (2012) Mitochondria: commanders of innate immunity and disease? Curr Opin Immunol 24:32–40
Copeland WC, Longley MJ (2014) Mitochondrial genome maintenance in health and disease. DNA Repair (Amst) 19:190–198
Copeland WC, Wachsman JT, Johnson FM, Penta JS (2002) Mitochondrial alterations in cancer. Cancer Invest 20:557–569
Cornelissen T, Haddad D, Wauters F, Van Humbeeck C, Mandemakers W, Koentjoro B et al (2014) The deubiquitinase USP15 antagonizes Parkin-mediated mitochondrial ubiquitination and mitophagy. Hum Mol Genet oii:ddu244
Coto-Montes A, Boga JA, Rosales-Corral S, Fuentes-Broto L, Tan DX, Reiter RJ (2012) Role of melatonin in the regulation of autophagy and mitophagy: a review. Mol Cell Endocrinol 361:12–23
Cui T, Fan C, Gu L, Gao H, Liu Q, Zhang T, Qi Z, Zhao C, Zhao H, Cai Q, Yang H (2011) Silencing of PINK1 induces mitophagy via mitochondrial permeability transition in dopaminergic MN9D cells. Brain Res 1394:1–13
Das M, Chiron S, Verde F (2010) Microtubule-dependent spatial organization of mitochondria in fission yeast. Methods Cell Biol 97:203–221
Davila AF, Zamorano P (2013) Mitochondria and the evolutionary roots of cancer. Phys Biol 10:026008
de Brito OM, Scorrano L (2009) Mitofusin-2 regulates mitochondrial and endoplasmic reticulum morphology and tethering: the role of Ras. Mitochondrion 9:222–226
De Vries RL, Gilkerson RW, Przedborski S, Schon EA (2012) Mitophagy in cells with mtDNA mutations: being sick is not enough. Autophagy 8:699–700
Delille HK, Schrader M (2008) Targeting of hFis1 to peroxisomes is mediated by Pex19p. J Biol Chem 283:31107–31115
Delille HK, Alves R, Schrader M (2009) Biogenesis of peroxisomes and mitochondria: linked by division. Histochem Cell Biol 131:441–446
Deng et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18799731
Dengjel J, Abeliovich H (2014) Musical chairs during mitophagy. Autophagy 10:706–707
Desai SP, Bhatia SN, Toner M, Irimia D (2013) Mitochondrial localization and the persistent migration of epithelial cancer cells. Biophys J 104:2077–2088
Dimmer KS, Navoni F, Casarin A, Trevisson E, Endele S, Winterpacht A, Salviati L, Scorrano L (2008) LETM1, deleted in Wolf-Hirschhorn syndrome is required for normal mitochondrial morphology and cellular viability. Hum Mol Genet 17:201–214
Ding WX, Ni HM, Li M, Liao Y, Chen X, Stolz DB, Dorn GW, Yin XM (2010) Nix is critical to two distinct phases of mitophagy, reactive oxygen species-meditated autophagy induction and Parkin-ubiquitin-p62-mediated mitochondrial priming. J Biol Chem 285:27879–27890
Dostert C, Pétrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J (2008) Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science 320:674–677
Dostert C, Guarda G, Romero JF, Menu P, Gross O, Tardivel A, Suva ML et al (2009) Malarial hemozoin is a Nalp3 inflammasome activating danger signal. PLoS One 4:e6510
Duarte I, Nabuurs SB, Magno R, Huynen M (2012) Evolution and diversification of the organellar release factor family. Mol Biol Evol 29:3497–3512

Egan DF, Shackelford DB, Mihaylova MM, Gerlino S, Kohnz RA, Mair W, Vasquez DS et al (2011) Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. Science 331:456–461

Elgass K, Pakay J, Ryan MT, Palmer CS (2013) Recent advances into the understanding of mitochondrial fission. Biochim Biophys Acta 1833:150–161

Fagarasanu A, Mast FD, Knoblach B, Rachubinski RA (2010) Molecular mechanisms of organelle inheritance: lessons from peroxisomes in yeast. Nat Rev Mol Cell Biol 11:644–654

Fang J, Nakamura H, Iyer AK (2007) Tumor-targeted induction of oxystress for cancer therapy. J Drug Target 15:475–486

Feng D, Liu L, Zhu Y, Chen Q (2013) Molecular signaling toward mitophagy and its physiological significance. Exp Cell Res 319:1697–1705

Ferree A, Shirihai O (2012) Mitochondrial dynamics: the intersection of form and function. Adv Exp Med Biol 748:13–40

Ferreira A, Serafim TL, Sardao VA, Cunha-Oliveira T (2015) Role of mtDNA-related mitoepigenetic phenomena in cancer. Eur J Clin Invest 45(Suppl. 1):44–49.

Flachbartova Z, Kovacech B (2013) Mortalin – a multipotent chaperone regulating cellular processes ranging from viral infection to neurodegeneration. Acta Virol 57:3–15

Fogg VC, Lanning NJ, Mackeigan JP (2011) Mitochondria in cancer: at the crossroads of life and death. Chin J Cancer 30:526–539

Franchi L, Munoz-Planillo R, Reimer T, Eigenbrot T, Nunez G (2010) Inflammasomes as microbial sensors. Eur J Immunol 40:611–615

Frank M, Duvezin-Caubet S, Koob S, Occhipinti A, Jagasia R, Petcherski A, Ruonala MO, Priault M, Salin B, Reichert AS (2012) Mitophagy is triggered by mild oxidative stress in a mitochondrial fission dependent manner. Biochim Biophys Acta 1823:2297–2310

Fransson S, Ruusala A, Aspenstrom P (2006) The atypical Rho GTPases Miro 1 and Miro-2 have essential roles in mitochondria trafficking. Biochem Biophys Res Commun 344:500–510

Frederick RL, Shaw JM (2007) Moving mitochondria, establishing distribution of an essential organelle. Traffic 8:1668–1675

Fu C, Jain D, Costa J, Velve-Casquillas G, Tran PT (2011) mmb1p binds mitochondria to dynamic microtubules. Curr Biol 21:1431–1439

Fujimoto M, Hayashi T (2011) New insights into the role of mitochondria-associated endoplasmic reticulum membrane. Int Rev Cell Mol Biol 292:73–117

Fukunaga N, Fujioka A, Tanaka K, Toyama R (1996) Oncocytic hepatocellular carcinoma with numerous globular hyaline bodies. Pathol Int 46:286–291

Gandre-Babbe S, van der Bliek AM (2008) The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammalian cells. Mol Biol Cell 19:2402–2412

Gasparre G, Porcelli AM, Lenaz G, Romeo G (2013) Relevance of mitochondrial genetics and metabolism in cancer development. Cold Spring Harb Perspect Biol 5 pii:a011411

Gasse P, Riteau N, Charron S, Girre S, Fick L, Pétrilli V, Tschopp J, Lagente V, Quesniaux VF et al (2009) Uric acid is a danger signal activating NALP3 inflammasome in lung injury inflammation and fibrosis. Am J Respir Crit Care Med 179:903–913

Gaude E, Frezza C (2014) Defects in mitochondrial metabolism and cancer. Cancer Metab 2:10

Gegg ME, Cooper JM, Chau KY, Rojo M, Schapira AH, Taanman JW (2010) Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. Hum Mol Genet 19:4861–4870

Geisler S, Vollmer S, Golombek S, Kahle PJ (2014) UBE2N, UBE2L3 and UBE2D2/3 ubiquitin-conjugating enzyme are essential for parkin-dependent mitophagy. J Cell Sci pii:jcs.146035

Géminard C, de Gassert A, Vidal M (2002) Reticulocyte maturation: mitoptosis and exosome release. Biocell 26:205–215

Ghandially FN, Parry EW (1966) Ultrastructure of a human hepatocellular carcinoma and surrounding non-neoplastic liver. Cancer 19:1989–2004

Gilkerson RW, de Vries RL, Lebot P, Wikstrom JD, Torgyekes E, Shirihai OS, Przedborski S et al (2012) Mitochondrial autophagy in cells with mtDNA mutations results from synergistic loss of transmembrane potential and mTORC1 inhibition. Hum Mol Genet 21:978–990

Giorgi C, De Stefani D, Bononi A, Rizzuto R, Pinton P (2009) Structural and functional link between the mitochondrial network and the endoplasmic reticulum. Int J Biochem Cell Biol 41:1817–1827

Givvimani S, Munjal C, Tyagi N, Sen U, Metreveli N, Tyagi SC (2012) Mitochondrial division/mitophagy inhibitor (Mdivi) ameliorates pressure overload induced heart failure. PLoS One 7:e32388

Glauser L, Sonnay S, Stafa K, Moore DJ (2011) Parkin promotes the ubiquitination and degradation of the mitochondrial fusion factor mitofusin 1. J Neurochem 118:636–645

Goard CA, Schimmer AD (2014) Mitochondrial matrix proteases as novel therapeutic targets in malignancy. Oncogene 33:2690–2699

Gogvadze V, Orrenius S, Zhivotosky B (2008) Mitochondria in cancer cells: what is so special about them? Trends Cell Biol 18:165–173

Gomes LC, Scorrano L (2013) Mitochondrial morphology in mitophagy and macroautophagy. Biochem Biophys Acta 1833:205–212

Grandemange S, Herzig S, Martinou JC (2009) Mitochondrial dynamics and cancer. Semin Cancer Biol 19:50–56

Grimm S (2012) The ER-mitochondria interface: the social network of cell death. Biochim Biophys Acta 1823:327–334

Gross O, Thomas CJ, Guarda G, Tschopp J (2011) The inflammasome: an integrated view. Immunol Rev 243:136–151

Grünewald A, Arns B, Seibler P, Rakovic A, Münchau A, Ramirez A, Sue CM, Klein C (2012) ATP3A2 mutations impair mitochondrial function in fibroblasts from patients with Kufor-Rakeb syndrome. Neurobiol Aging

Gruschke S, Ott M (2010) The polypeptide tunnel exit of the mitochondrial ribosome is tailored to meet the specific requirements of the organelle. Bioessays 32:1050–1057

Gurung P, Lukens JR, Kanneganti TD (2015) Mitochondria: diversity in the regulation of the NLRP3 inflammasome. Trends Mol Med 21:193–201

Guzy RD, Schumacker PT (2006) Oxygen sensing by mitochondria at complex III: the paradox of increased reactive oxygen species during hypoxia. Exp Physiol 91:807–819

Gwak GY, Lee DH, Moon TG, Choi MS, Lee JH, Koh KC, Paik SW, Joh JW, Yoo BC (2011) The correlation of hepatitis B virus pre-S mutation with mitochondrial D-loop mutations and common deletions in hepatocellular carcinoma. Hepatogastroenterology 58: 522–528

Hajnoczky G, Csordas G (2010) Calcium signalling: fishing out molecules of mitochondrial calcium transport. Curr Biol 20:R888–R891

Han B, Izumi H, Yasuniwa Y, Akiyama M, Yamaguchi T, Fujimoto N, Matsumoto T, Wu B, Tanimoto A, Sasaguri Y, Kohno K (2011) Human mitochondrial transcription factor A functions in both nuclei and mitochondria and regulates cancer cell growth. Biochem Biophys Res Commun 408:45–51

Hanna et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22505714

Hara Y, Yanatori I, Ikeda M, Kiyokage E, Nishina S, Tomiyama Y, Toida K, Kishi F, Kato N, Imamura M, Chayama K et al (2014) Hepatitis C virus core protein suppresses mitophagy by interacting with parkin in the context of mitochondrial depolarization. Am J Pathol 184:3026–3039

Hayashi T, Rizzuto R, Hajnoczky G, Su TP (2009) MAM: more than just a housekeeper. Trends Cell Biol 19:81–88

He MX, He YW (2013) CFLAR/c-FLIPL: a star in the autophagy, apoptosis and necroptosis alliance. Autophagy 9:791–793

Heim MH (2013) Innate immunity and HCV. J Hepatol 58:564–574

Herrmann JM, Longen S, Weckbecker D, Depuydt M (2012) Biogenesis of mitochondrial proteins. Adv Exp Med Biol 748:41–64

Hino K, Hara Y, Nishina S (2014) Mitochondrial reactive oxygen species as a mystery voice in hepatitis C. Hepatol Res 44:123–132

Hirota Y, Kang D, Kanki T (2012) The physiological role of mitophagy: new insights into phosphorylation events. Int J Cell Biol 2012:354914

Hoshino A, Mtaoba S, Iwai-Kanai E, Nakamura H, Kimata M, Nakaoka M, Katamura M et al (2012) p53-TIGAR axis attenuates mitophagy to exacerbate cardiac damage after ischemia. J Mol Cell Cardiol 52:175–184

Hruban Z (1979) Ultrastructure of hepatocellular tumors. J Toxicol Environ Health 5:401–431

Hsu CC, Lee HC, Wei YH (2013) Mitochondrial DNA alterations and mitochondrial dysfunction in the progression of hepatocellular carcinoma. World J Gastroenterol 19:8880–8886

Huang C, Andres AM, Ratliff EP, Hernandez G, Lee P, Gottlieb RA (2011) Preconditioning involves selective mitophagy mediated by Parkin and p62/SQSTM1. PLoS One 6:e20975

Huang CY, Chen YM, Wu CH, Tsai CM, Lee YC, Perng RP, Whang-Peng J (2014) Circulating free mitochondrial DNA concentration and its association with erlotinib treatment in patients with adenocarcinoma of the lung. Oncol Lett 7:2180–2184

Huynen MA, Duarte I, Chrzanowska-Lightowlers ZM, Nabuurs SB (2012) Structure based hypothesis of a mitochondrial ribosome rescue mechanism. Biol Direct 7:14

Iacobazzi V, Castegna A, Infantino V, Andria G (2013) Mitochondrial DNA methylation as a next-generation biomarker and diagnostic tool. Mol Genet Metab 110:25–34

Igasawa R, Mahul-Mellier AL, Datler C, Pazarentzos E, Grimm S (2011) Fis1 and Bap31 bridge the mitochondria-ER interface to establish a platform for apoptosis induction. EMBO J 30:556–568

Iosefson O, Sharon S, Goloubinoff P, Azem A (2012) Reactivation of protein aggregates by mortalin and Tid1 – the human mitochondrial Hsp70 chaperone system. Cell Stress Chaperones 17:57–66

Isomura T, Nakashima T (1980) Ultrastructure of human hepatocellular carcinoma. Acta Pathol Jpn 30:713–726

Itakura E, Kishi-Itakura C, Koyama-Honda I, Mizushima N (2012) Structures containing Atg9A and the ULK1 complex independently target depolarized mitochondria at initial stages of Parkin-mediated mitophagy. J Cell Sci 125:1488–1499

Ivatt RM, Sanchez-Martinez A, Godena VK, Brown S, Ziviani E, Whitworth AJ (2014) Genome-wide RNAi screen identifies the Parkinson disease GWAS risk locus SREBF1 as a regulator of mitophagy. Proc Natl Acad Sci U S A 111:8494–8499

Jans DC, Wurm CA, Riedel D, Wenzel D, Stagge F, Deckers M, Rehling P, Jakobs S (2013) STED super-resolution microscopy reveals an array of MINOS clusters along human mitochondria. Proc Natl Acad Sci U S A 110:8936–8941

Jin SM, Youle RJ (2012) PINK1-and parkin-mediated mitophagy at a glance. J Cell Sci 125:795–799

Jin Y, Yu Q, Zhou D, Chen L, Huang X, Xu G, Huang J, Gao X, Gao Y, Shen L (2012) The mitochondrial DNA 9-bp deletion polymorphism is a risk factor for hepatocellular carcinoma in the Chinese population. Genet Test Mol Biomarkers 16:330–334

Jin JC, Zhang X, Jin XL, Qian CS, Jiang H, Ruan Y (2014) MicroRNA-122 regulation of the morphology and

cytoarchitecture of hepatoma carcinoma cells. Mol Med Rep 9:1376–1380
Joo JH, Dorsey FC, Joshi A, Hennessy-Walters KM, Rose KL, McCastlain K, Zhang J et al (2011) Hsp90-Cdc37 chaperone complex regulates Ulk1- and Atg13-mediated mitophagy. Mol Cell 43:572–585
Ju YS, Alexandrov LB, Gerstung M, Martincorena I, Nik-Zainal S, Ramakrishna M, Davies HR, Papaemmanuil E et al (2014) Origins and functional consequences of somatic mitochondrial DNA mutations in human cancer. Elife. doi:10.7554/eLife.02935
Jung SR, Seo JB, Shim D, Hille B, Koh DS (2012) Actin cytoskeleton controls movement of intracellular organelles in pancreatic duct epithelial cells. Cell Calcium 51:459–469
Kaczmarek A, Vandenabeele P, Krysko DV (2013) Necroptosis: the release of damage-associated molecular patterns and its physiological relevance. Immunity 38:209–223
Kane LA, Youle RJ (2011) PINK1 and parkin flag Miro to direct mitochondrial traffic. Cell 147:721–723
Kapetanovic R, Bokil NJ, Sweet MJ (2015) Innate immune perturbations, accumulating DAMPs and inflammasome dysregulation: a ticking time bomb in ageing. Ageing Res Rev. doi:10.1016/j.arr.2015.02.005
Karbowski M (2010) Mitochondria on guard: role of mitochondrial fusion and fission in the regulation of apoptosis. Adv Exp Med Biol 687:131–142
Karbowski M, Youle RJ (2003) Dynamics of mitochondrial morphology in healthy cells and during apoptosis. Cell Death Differ 12:1484–1489
Karbowski M, Youle RJ (2011) Regulating mitochondrial outer membrane proteins by ubiquitination and proteasomal degradation. Curr Opin Cell Biol 232:476–482
Karbowski M, Norris KL, Cleland MM, Jeong SY, Youle RJ (2006) Role of Bax and Bak in mitochondrial morphogenesis. Nature 443:658–662
Karbowski M, Neutzner A, Youle RJ (2007) The mitochondrial E3 ubiquitin ligase MARCH5 is required for Drp1 dependent mitochondrial division. J Cell Biol 178:71–84
Kashatus DF (2013) Ral GTPases in tumorigenesis: emerging from the shadows. Exp Cell Res 319:2337–2342
Kashatus DF, Counter CM (2011) Breaking up is hard to do: RalA., mitochondrial fission and cancer. Small GTPases 2:329–333
Kashatus DF, Lim KH, Brady DC, Pershing NL, Cox AD, Counter CM (2011) RALA and RALBP1 regulate mitochondrial fission at mitosis. Nat Cell Biol 13:1108–1115
Kelly RD, Mahmud A, McKenzie M, Trounce IA, St. John JC (2012) Mitochondrial DNA copy number is regulated in a tissue specific manner by DNA methylation of the nuclear-encoded DNA polymerase gamma A. Nucleic Acids Res 40:10124–10138
Kepp O, Galluzzi L, Kroemer G (2011) Mitochondrial control of the NLRP3 inflammasome. Nat Immunol 12:199–200
Khandelwal PJ, Herman AM, Hoe HS, Rebeck GW, Moussa CE (2011) Parkin mediates beclin-dependent autophagic clearance of defective mitochondria and ubiquitinated Abeta in AD models. Hum Mol Genet 20:2091–2102
Kim A (2014) Mitochondrial DNA somatic mutation in cancer. Toxicol Res 30:235–242
Kim I, Rodriguez-Enriquez S, Lemasters JJ (2007) Selective degradation of mitochondria by mitophagy. Arch Biochem Biophys 462:245–253
Kim JH, Kim HY, Lee YK, Yoon YS, Xu WG, Yoon JK, Choi SE, Ko YG, Kim MJ et al (2011) Involvement of mitophagy in oncogenic K-Ras-induced transformation: overcoming a cellular energy deficit from glucose deficiency. Autophagy 7:1187–1198
Kim SJ, Syed GH, Siddiqui A (2013a) Hepatitis C virus induces the mitochondrial translocation of Parkin and subsequent mitophagy. PLoS Pathog 9:e1003285
Kim SJ, Khan M, Quan J, Till A, Subramani S, Siddiqui A (2013b) Hepatitis B virus disrupts mitochondrial dynamics: induces fission and mitophagy to attenuate apoptosis. PLoS Pathog 9:e1003722
Kim SJ, Syed GH, Khan M, Chiu WW, Sohail MA, Gish RG, Siddiqui A (2014) Hepatitis C virus triggers mitochondrial fission and attenuates apoptosis to promote viral persistence. Proc Natl Acad Sci U S A 111:6413–6418
Klimova T, Chandel NS (2008) Mitochondrial complex III regulates hypoxic activation of HIF. Cell Death Differ 15:660–666
Kobayashi S, Tanaka A, Fujiki Y (2007) Fis1, DLP1, and Pex11p coordinately regulate peroxisome morphogenesis. Exp Cell Res 313:1675–1686
Koch A, Yoon Y, Bonekamp NA, McNiven MA, Schrader M (2005) A role for Fis1 in both mitochondrial and peroxisomal fission in mammalian cells. Mol Biol Cell 16:5077–5086
Koh H, Chung J (2010) PINK1 and Parkin to control mitochondria remodeling. Anat Cell Biol 43:179–184
Kommann B, Walter P (2010) ERMES-mediated ER-mitochondria contacts: molecular hubs for the regulation of mitochondrial biology. J Cell Sci 123:1389–1393
Kommann B, Currie E, Collins SR, Schuldiner M, Nunnari J, Weissman JS, Walter P (2009) An ER-mitochondria tethering complex revealed by a synthetic biology screen. Science 325:477–481
Kommann B, Osman C, Walter P (2011) The conserved GTPase Gem1 regulates endoplasmic reticulum-mitochondria connections. Proc Natl Acad Sci U S A 108:14151–14156
Kondo-Okamoto N, Noda NN, Suzuki SW, Nakatogawa H, Takahashi I, Matsunami M et al (2012) Autophagy-related protein 32 acts as autophagic degron and directly initiates mitophagy. J Biol Chem 287:10631–10638
Korenaga M, Okuda M, Otani K, Wang T, Li Y, Weinman SA (2005a) Mitochondrial dysfunction in hepatitis C. J Clin Gastroenterol 39:S162–S166
Korenaga M, Wang T, Li Y, Showalter LA, Chan T, Sun J, Weinman SA (2005b) Hepatitis C virus core protein

inhibits mitochondrial electron transport and increases reactive oxygen species (ROS) production. J Biol Chem 280:37418–37488

Korobova F, Ramabhadran V, Higgs HN (2013) An actin-dependent step in mitochondrial fission mediated by the ER-associated formin INF2. Science 339:464–467

Kotani T, Akabane S, Takeyasu K, Ueda T, Takeuchi N (2013) Human G-proteins, ObgH1 and Mtg1, associate with the large mitochondrial ribosome subunit and are involved in translation and assembly of respiratory complexes. Nucleic Acids Res 41:3713–3722

Koutsopoulos OS, Laine D, Oselleame L, Chudakov DM, Parton RG, Frazier AE et al (2010) Human Miltons associate with mitochondria and induce microtubule-dependent remodeling of mitochondrial networks. Biochim Biophys Acta 1803:564–574

Kundu M, Thompson CB (2005) Macroautophagy versus mitochondrial autophagy: a question of fate? Cell Death Differ 12:1484–1489

Kurihara Y, Kanki T, Aoki Y, Hirota Y, Saigusa T, Uchiumi T, Kang D (2012) Mitophagy plays an essential role in reducing mitochondrial production of reactive oxygen species and mutation of mitochondrial DNA by maintaining mitochondrial quantity and quality in yeast. J Biol Chem 287:3265–3272

Lazarou M, Jin SM, Kane LA, Youle RJ (2012) Role of PINK1 binding to the TOM complex and alternate intracellular membranes in recruitment and activation of the E3 ligase parkin. Dev Cell 22:320–333

Lebiedzinska M, Szabadkai G, Jones AW, Duszynski J, Wieckowski MR (2009) Interactions between the endoplasmic reticulum, mitochondria, plasma membrane and other subcellular organelles. Int J Biochem Cell Biol 41:1805–1816

Lee HC, Li SH, Lin JC, Wu CC, Yeh DC, Wei YH (2004) Somatic mutations in the D-loop and decrease in the copy number of mitochondrial DNA in human hepatocellular carcinoma. Mutat Res 547:71–78

Lee J, Giordano S, Zhang J (2012) Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling. Biochem J 441:523–540

Lee S, Park YY, Kim SH, Nguyen OT, Yoo YS, Chan GK, Sun X, Cho H (2014) Human mitochondrial Fis1 links to cell cycle regulators at G2/M transition. Cell Mol Life Sci 171:711–725

Lee W, Johnson J, Gough DJ, Donoghue J, Cagnone GL, Vaghjiani V, Brown KA, Johns TG, St. John JC (2015) Mitochondrial DNA copy number is regulated by DN methylation and demethylation of POLGA in stem and cancer cells and their differentiated progeny. Cell Death Dis 6:e1664

Leemans JC, Cassel SL, Sutterwala FS (2011) Sensing damage by the NLRP3 inflammasome. Immunol Rev 243:152–162

Li Y, Rempe PA (2010) During hypoxia, HUMMR joins the mitochondrial dance. Cell Cycle 9:50–57

Li XD, Sun L, Seth RB, Pineda G, Chen ZJ (2005) Hepatitis C virus protease NS3/4A cleaves mitochondrial antiviral signaling protein off the mitochondria to evade innate immunity. Proc Natl Acad Sci U S A 102:17717–17722

Li Y, Lim S, Hoffman D, Aspenstrom P, Federoff HJ, Rempe DA (2009) HUMMR, hypoxia- and HIF-1alpha-inducible protein, alters mitochondrial distribution and transport. J Cell Biol 185:1065–1081

Li P, Jiao J, Gao G, Prabhakar BS (2012) Control of mitochondrial activity by miRNAs. J Cell Biochem 113:1104–1110

Lim W, Kwon SH, Cho H, Kim S, Lee S, Ryu WS, Cho H (2010) HBx targeting to mitochondria and ROS generation are necessary but insufficient for HBV-induced cyclooxygenase-2 expression. J Mol Med (Berl) 88:359–369

Liu W, Acin-Perez R, Geghman KD, Manfredi G, Lu B, Li C (2011) Pink1 regulates the oxidative phosphorylation machinery via mitochondrial fission. Proc Natl Acad Sci U S A 108:12920–12924

Liu L, Feng D, Chen G, Chen M, Zheng Q, Song P, Ma Q, Zhu C, Wang R, Qi W et al (2012) Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol 14:177–185

Liu L, Sasakibara K, Chen Q, Okamoto K (2014a) Receptor-mediated mitophagy in yeast and mammalian systems. Cell Res. doi:10.1038/cr.2014.75

Liu K, Shi Y, Guo XH, Ouyang YB, Wang SS, Liu DJ, Wang AN, Li N, Chen DX (2014b) Phosphorylated AKT inhibits the apoptosis induced by DRAM-mediated mitophagy in hepatocellular carcinoma by preventing the translocation of DRAM to mitochondria. Cell Death Dis 5:e1078

Liu M, Li Y, Chen L, Chan TH, Song Y, Fu L, Zeng TT, Dai YD, Zhu YH, Li Y, Chen J, Yuan YF, Guan XY (2014c) Allele-specific imbalance of oxidative stress-induced growth inhibitor 1 associates with progression of hepatocellular carcinoma. Gastroenterology 146:1084–1096

Lomonosova E, Ryerse J, Chinnadurai G (2009) BAX/BAK-independent mitosis during cell death induced by proteasome inhibition? Mol Cancer Res 7:1268–1284

Loson OC, Song Z, Chen H, Chan DC (2013) Fis1, Mff, MiD49 and MiD51 mediate Drp1 recruitment in mitochondrial fission. Mol Biol Cell 24:659–667

Loucks FA, Schroeder EK, Zommer AE, Hilger S, Kelsey NA, Bouchard RJ, Blackstone C et al (2009) Caspases indirectly regulate cleavage of the mitochondria fusion GTPase OPA1 in neurons undergoing apoptosis. Brain Res 1250:63–74

Lu J, Sharma LK, Bai Y (2009) Implications of mitochondrial DNA mutations and mitochondrial dysfunction in tumorigenesis. Cell Res 19:802–815

Lu WJ, Lee NP, Kaul SC, Lan F, Poon RT, Wadhwa R, Luk JM (2011a) Induction of mutant p53-dependent apoptosis in human hepatocellular carcinoma by targeting stress protein mortalin. Int J Cancer 129:1806–1814

Lu WJ, Lee NP, Kaul SC, Lan F, Poon RT, Wadhwa R, Luk JM (2011b) Mortalin-p53 interaction in cancer cells is stress dependent and constitutes a selective target for cancer therapy. Cell Death Differ 18:1046–1056

Luo WI, Dizin E, Yoon T, Cowan JA (2010) Kinetic and structural characterization of human mortalin. Protein Expr Purif 72:75–81

Lyamzeav KG, Nepryakhina OK, Saprunova VB, Bakeeva LE, Pletjushkina OY et al (2008) Novel mechanism of elimination of malfunctioning mitochondria (mitosis): formation of mitoptotic bodies and extrusion of mitochondrial material from the cell. Biochem Biophys Acta 1777:817–825

Machida K, Cheng KT, Lai CK, Jeng KS, Sung VM, Lai MM (2006) Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DANN damage and STAT3 activation. J Virol 80:7199–7207

Maeda A, Fadeel B (2014) Mitochondria released by cells undergoing TNF-α-induced necroptosis act as danger signals. Cell Death Dis 5:e1312

Mai S, Muster B, Bereiter-Hahn J, Jendrach M (2012) Autophagy proteins LC3B, ATG5 and ATG12 participate in quality control after mitochondrial damage and influence lifespan. Autophagy 8:47–62

Maresca A, Zaffagnini M, Caporali L, Carelli V, Zanna C (2015) DNA methyltransferase 1 mutations and mitochondrial pathology: is mtDNA methylated? Front Genet 6:90

Marks DL, Larkin JM, McNivel MA (1994) Association of kinesin with the Golgi apparatus in rat hepatocytes. J Cell Sci 107:2417–2426

Marshall KD, Baines CP (2014) Necroptosis: is there a role for mitochondria? Front Physiol 5:323

Martinon F (2012) Dangerous liaisons: mitochondrial DNA meets the NLRP3 inflammasome. Immunity 36:313–315

Matsuda N, Tanaka K (2010) Uncovering the roles of PINK1 and parkin in mitophagy. Autophagy 6:952–954

May AI, Devenish RJ, Prescott M (2012) The many faces of mitochondrial autophagy: making sense of contrasting observations in recent research. Int J Cell Biol 2012:431684

McBride HM (2011) Mitochondrial-ER tethering: the inheritance of a functional unit. Curr Biol 21:R949–R951

McKinney EA, Oliveira MT (2013) Replicating animal mitochondrial DNA. Genet Mol Biol 36:308–315

Meissner C, Lorenz H, Weihofen A, Selkoe DJ, Lemberg MK (2011) The mitochondrial intramembrane protease PARL cleaves human Pink1 to regulate Pank1 trafficking. J Neurochem 117:856–867

Mellor HR, Harris AL (2007) The role of the hypoxia-inducible BH3-only proteins BNIP3 and BNIP3L in cancer. Cancer Metastasis Rev 26:553–566

Merkwirth C, Langer T (2008) Mitofusin 2 builds a bridge between ER and mitochondria. Cell 135:1165–1167

Merkwirth C, Langer T (2009) Prohibitin function within mitochondria: essential roles for cell proliferation and cristae morphogenesis. Biochim Biophys Acta 1793:27–32

Michel AH, Kommann B (2012) The ERMES complex and ER-mitochondria connections. Biochem Soc Trans 40:445–450

Michel S, Wanet A, De Pauw A, Rommelaere G, Arnould T, Renard P (2011) Crosstalk between mitochondrial (dys)function and mitochondrial abundance. J Cell Physiol 227:2297–2310

Mijaljica D, Prescott M, Devenish RJ (2007) Different fates of mitochondria: alternative ways for degradation? Autophagy 3:4–9

Mijaljica D, Prescott M, Devenish RJ (2010) Mitophagy and mitoptosis in disease processes. Methods Mol Biol 648:93–106

Milenkovic D, Matic S, Kühl I, Ruzzenente B, Freyer C, Jemt E, Park CB, Falkenberg M, Larsson NG (2013) TWINKLE is an essential mitochondrial helicase required for synthesis of nascent D-loop strands and complete mtDNA replication. Hum Mol Genet 22:1983–1993

Miralles Fusté J, Shi Y, Wanrooij S, Zhu X, Jemt E, Persson Ö, Sabouri N, Gustafsson CM, Falkenberg M (2014) In vivo occupancy of mitochondrial single stranded DNA binding protein supports the strand displacement mode of DNA replication. PLoS Genet 10:e1004832

Misko A, Jiang S, Wegorzewska I, Milbrandt J, Baloh RH (2010) Mitofusin 2 is necessary for transport of axonal mitochondria and interacts with Miro/Milton complex. J Neurosci 30:4232–4240

Mitra K (2013) Mitochondrial fission-fusion as an emerging key regulator of cell proliferation and differentiation. Bioessays 35:955–964

Mizumura K, Cloonan SM, Nakahira K, Bhashyam AR, Cervo M, Kitada T, Glass K, Owen CA, Mahmood A, Washko GR et al (2014) Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. J Clin Invest 124:3987–4003

Modica-Napolitano JS, Kulawiec M, Singh KK (2007) Mitochondria and human cancer. Curr Mol Med 7:121–131

Morozov YI, Parshin AV, Agaronyan K, Cheung AC, Anikin M, Cramer P, Temiakov D (2015) A model for transcription initiation in human mitochondria. Nucleic Acid Res pii:gkv235

Muisuk K, Silsirivanit A, Imtawil K, Bunthot S, Pukhem A, Pairojkul C, Wongkham S, Wongkham C (2015) Novel mutations in cholangiocarcinoma with low frequencies revealed by whole mitochondrial genome sequencing. Asian Pac J Cancer Prev 16:1737–1742

Nakamura N, Hirose S (2008) Regulation of mitochondrial morphology by USP30, a deubiquitinating enzyme present in the mitochondrial outer membrane. Mol Biol Cell 19:1903–1911

Nakamura N, Kimura Y, Tokuda M, Honda S, Hirose S (2006) MARCH-V is a novel mitofusin 2 – and Drp1-binding protein able to change mitochondrial morphology. EMBO Rep 7:1019–1022

Nangaku M, Sato-Yoshitake R, Okada Y, Noda Y, Takemura R, Yamazaki H, Hirokawa N (1994) KIF1B, a novel microtubule plus end-directed monomeric motor protein for transport of mitochondria. Cell 79:1209–1220

Nekrasova OE, Mendez MG, Chernoivanenko IS, Tyurin-Kuzmin PA, Kuczmarski ER et al (2011) Vimentin intermediate filaments modulate the motility of mitochondria. Mol Biol Cell 22:2282–2289

Neuspiel M, Schauss AC, Braschi E, Zunino R, Rippstein P, Rachubinski RA, Andrade-Navarro MA et al (2008) Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. Curr Biol 18:102–108

Neuzil J, Dong LF, Rohlena J, Truksa J, Ralph SJ (2013) Classification of mitocans, anti-cancer drugs acting on mitochondria. Mitochondrion 13:199–208

Ney PA (2015) Mitochondrial autophagy: origins, significance, and role of BNIP3 and NIX. Biochim Biophys Acta pii:S0167-4889(15)00072-5

Nezich CL, Youle RJ (2013) Make or break for mitochondria. Elife 2:e00804

Nguyen TT, Lewandowska A, Choi JY, Markgraf DF, Junker M, Bilgin M, Eising CS et al (2012) Gem1 and ERMES do not directly affect phosphatidylserine transport from ER to mitochondria or mitochondrial inheritance. Traffic 13:880–890

Nishikawa M, Nishiguchi S, Shiomi S, Tamori A, Koh N, Takeda T, Kubo S, Hirohashi K et al (2001) Somatic mutation of mitochondrial DNA in cancerous and noncancerous liver tissue in individuals with hepatocellular carcinoma. Cancer Res 61:1843–1845

Nomoto S, Yamashita K, Koshikawa K, Nakao A, Sidransky D (2002) Mitochondrial D-loop mutations as clonal markers in multicentric hepatocellular carcinoma and plasma. Clin Cancer Res 8:481–487

Novak I (2012) Mitophagy: a complex mechanism of mitochondrial removal. Antioxid Redox Signal 17:794–802

Novak I, Dikic I (2011) Autophagy receptors in developmental clearance of mitochondria. Autophagy 7:301–303

Nunnari J, Suomalainen A (2012) Mitochondria: in sickness and in health. Cell 148:1145–1159

Oh JY, Ko JH, Lee HJ, Yu JM, Choi H, Kim MK, Wee WR, Prockop DJ (2014) Mesenchymal stem/stromal cells inhibit the NLRP3 inflammasomes by decreasing mitochondrial reactive oxygen species. Stem Cells 32:1553–1563

Ohta A, Nishiyama Y (2011) Mitochondria and viruses. Mitochondrion 11:1–12

Okamoto K, Kondo-Okamoto N (2012) Mitochondria and autophagy: critical interplay between the two homeostasis. Biochim Biophys Acta 1820:595–600

Okuda M, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM, Weinman SA (2002) Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterology 122:366–375

Orvedal A, Sumpter R, Xiao G, Ng A, Zou Z, Tang Y, Narimatsu M, Gilpin C, Sun Q et al (2011) Image-based genome-wide siRNA screen identifies selective autophagy factors. Nature 480:113–117

Otera H, Ishihara N, Mihara K (2013) New insights into the function and regulation of mitochondrial fission. Biochim Biophys Acta 1833:1256–1268

Palmer CS, Osellame LD, Laine D, Koutsopoulos OS, Frazier AE, Ryan MT (2011) MiD49 and MiD51, new components of the mitochondrial fission machinery. EMBO Rep 12:565–573

Palmer CS, Elgass KD, Parton RG, Osellame LD, Stojanovski D, Ryan MT (2013) Adaptor proteins MiD49 and MiD51 can act independently of Mff and Fis1 in Drp1 recruitment and are specific for mitochondrial fission. J Biol Chem 288:27584–27593

Park SW, Kim KY, Lindsey JD, Dai Y, Heo H, Nguyen DH, Ellisman MH, Weinreb RN et al (2011) A selective inhibitor of drp1, mdivi-1, increases retinal ganglion cell survival in acute ischemic mouse retina. Invest Ophthalmol Vis Sci 52:2837–2843

Pasparakis M, Vandenabeele P (2015) Necroptosis and its role in inflammation. Nature 517:311–320

Pellegrini L, Scorrano L (2007) A cut short to death: parl and opa1 in the regulation of mitochondrial morphology and apoptosis. Cell Death Differ 14: 1275–1284

Piao L, Li Y, Kim SJ, Byun HS, Huang SM, Hwang SK, Yang KJ, Park KA, Won M et al (2009) Association of LETM1 and MRLP36 contributes to the regulation of mitochondrial ATP production and necrotic cell death. Cancer Res 69:3397–3404

Piccoli C, Scrima R, D'Aprile A, Ripoli M, Lecce L, Boffoli D, Capitanio N (2006) Mitochondrial dysfunction in hepatitis C virus infection. Biochim Biophys Acta 1757:1429–1437

Piccoli C, Quarato G, Ripoli M, D'Aprile A, Scrima R, Cela O, Boffoli D, Moradpour D, Capitanio N (2009) HCV infection induces mitochondrial bioenergetic unbalance: causes and effects. Biochim Biophys Acta 1787:539–546

Pirola CJ, Gianotti TF, Burgueno AL, Rey-Funes M, Loidl CF, Mallardi P, Martino JS, Castano GO, Sookoian S (2013) Epigenetic modification of liver mitochondrial DNA is associated with histological severity of nonalcoholic fatty liver disease. Gut 62:1356–1363

Pizzo P, Pozzan T (2007) Mitochondria-endoplasmic reticulum choreography: structure and signaling dynamics. Trends Cell Biol 17:511–517

Prakash A, Doublié S (2015) Base excision repair in the mitochondria. J Cell Biochem. doi:10.1002/jcb.25103

Qiu J, Wenz LS, Zerbes RM, Oeljeklaus S, Bohnert M, Stroud DA, Wirth C, Ellenrieder L et al (2013) Coupling of mitochondrial import and export translocases by receptor-mediated supercomplex formation. Cell 154:596–608

Quintero OA, DiVito MM, Adikes RC, Kortan MB, Case LB, Lier AJ, Panaretos NS et al (2008) Human Myo19 is a novel myosin that associates with mitochondria. Nature 422:759–765

Ralph SJ, Rodriguez-Enriquez S, Neuzil J, Saavedra E, Moreno-Sanchez R (2010) The causes of cancer revisited: "mitochondrial malignancy" and ROS-induced oncogenic transformation – why mitochondria are targets for cancer therapy. Mol Aspects Med 31:145–170

Ramakrishna G, Rastogi A, Trehanpati N, Sen B, Khosla R, Sarin SK (2013) From cirrhosis to hepatocellular carcinoma: new molecular insights on inflammation and cellular senescence. Liver Cancer 2:367–383

Rambold AS, Lippincott-Schwartz J (2011) Mechanisms of mitochondria and autophagy crosstalk. Cell Cycle 10:4032–4038

Rambold AS, Kostelecky B, Lippincott-Schwartz J (2011) Fuse or die: shaping mitochondrial fate during starvation. Commun Integr Biol 4:752–754

Rawat S, Clippinger AJ, Bouchard MJ (2012) Modulation of apoptotic signaling by the hepatitis B virus X protein. Viruses 4:2945–2972

Redmann M, Dodson M, Boyer-Guittaut M, Darley-Usmar V, Zhang J (2014) Mitophagy mechanisms and role in human diseases. Int J Biochem Cell Biol 53C:127–133

Reis K, Fransson A, Aspenström P (2009) The Miro GTPases: at the heart of the mitochondrial transport machinery. FEBS Lett 583:1391–1398

Rippo MR, Olivieri F, Monsurro V, Prattichizzo F, Albertini MC, Procopio AD (2014) MitomiRs in human inflammaging: a hypothesis involving miR-181a, miR-34a and miR-146a. Exp Gerontol 56:154–163

Rorbach J, Richter R, Wessels HJ, Wydro M, Pekalski M, Farhoud M, Kühl I, Gaisne M et al (2008) The human mitochondrial ribosome recycling factor is essential for cell viability. Nucleic Acids Res 36:5787–5799

Rose G, Passarino G, Franscheschi C, De Benedictis G (2002) The variability of the mitochondrial genome in human aging: a key for life and death? Int J Biochem Cell Biol 34:1449–1460

Rowland AA, Voeltz GK (2012) Endoplasmic reticulum-mitochondria contacts: function of the junction. Nat Rev Mol Cell Biol 13:607–625

Rubio MA, Hopper AK (2011) Transfer RNA travels from the cytoplasm to organelles. Wiley Interdiscip Rev RNA 2:802–817

Said-Sadier N, Ojcius DM (2012) Alarmins, inflammasomes and immunity. Biomed J 35:437–449

Salminen A, Ojala J, Kaarniranta K, Kauppinen A (2012) Mitochondrial dysfunction and oxidative stress activate inflammasomes: impact on the aging process and age-related diseases. Cell Mol Life Sci 69:2999–3013

Sangiuliano B, Pérez NM, Moreira DF, Belizario JE (2014) Cell death-associated molecular-pattern molecules: inflammatory signaling and control. Mediators Inflamm 2014:821043

Santel A, Fank S (2008) Shaping mitochondria: the complex posttranslational regulation of the mitochondrial fission protein DRP1. IUBMB 60:448–455

Santo-Domingo J, Giacomello M, Poburko D, Scorrano L, Demaurex N (2013) OPA1 promotes pH flashes that spread between contiguous mitochondria without matrix protein exchange. EMBO J 32:1927–1940

Scarffe LA, Stevens DA, Dawson VL, Dawson TM (2014) Parkin and PINK1: much more than mitophagy. Trends Neurosci 37:315–324

Scatena R (2012) Mitochondria and cancer: a growing role in apoptosis, cancer cell metabolism and dedifferentiation. Adv Exp Med Biol 942:287–308

Schaff Z, Lapis K, Safrany L (1971) The ultrastructure of primary hepatocellular cancer in man. Virchows Arch A 352:340–358

Schlickum S, Moghekar A, Simpson JC, Steglich C, O'Brien RJ, Winterpacht A, Endele SU (2004) LETM1, a gene deleted in Wolf-Hirschhorn syndrome, encodes an evolutionarily conserved mitochondrial protein. Genomics 83:254–261

Schrader M (2006) Shared components of mitochondrial and peroxisomal division. Biochim Biophys Acta 1763:531–541

Schumann U, Subramani S (2008) Special delivery from mitochondria to peroxisomes. Trends Cell Biol 18:253–256

Scorrano L (2007) Multiple functions of mitochondria-shaping proteins. Novartis Found Symp 287:47–55

Scorrano L (2013) Keeping mitochondria in shape: a matter of life and death. Eur J Clin Invest 43:886–893

Scott I (2010) The role of mitochondria in the mammalian antiviral defense system. Mitochondrion 10:316–320

Sekine S, Ito K, Watanabe H, Nakano T, Moriya K, Shintani Y, Fujie H, Tsutsumi T, Miyoshi H, Fujinaga H, Shinzawa S et al (2015) Mitochondrial iron accumulation exacerbates hepatic toxicity caused by hepatitis C virus core protein. Toxicol Appl Pharmacol 282:237–243

Shao JY, Gao HY, Li YH, Zhang Y, Lu YY, Zeng YX (2004) Quantitative detection of common deletion of mitochondrial DNA in hepatocellular carcinoma and hepatocellular nodular hyperplasia. World J Gastroenterol 10:1560–1564

Shimada K, Crother TR, Karlin J, Dagvadori J, Chiba N, Chen S, Ramanujan VK et al (2012) Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 36:401–414

Shimizu S, Honda S, Arakawa S, Yamaguchi H (2014) Alternative macroautophagy and mitophagy. Int J Biochem Cell Biol 50:64–66

Shinde S, Bhadra U (2015) A complex genome-microRNA interplay in human mitochondria. Biomed Res Int 2015:206382

Shoshan –Barmatz V, de Pinto V, Zweckstetter M, Raviv Z, Keinan N, Arbel N (2010) VDAC, a multi-functional mitochondrial protein regulating cell life and death. Mol Aspects Med 31:227–285

Shyamsunder P, Verma RS, Lyakhovich A (2015) ROMO1 regulates RedOx states and serves as an inducer of NF-kB-driven EMT factors in Fanconi anemia. Cancer Lett 361:33–38

Simula MP, De Re V (2010) Hepatitis C virus-induced oxidative stress and mitochondrial dysfunction: a focus on recent advances in proteomics. Proteomics Clin Appl 4:782–793

Skulachev VP (2002) Programmed cell death phenomena: from organelle to organism. Ann N Y Acad Sci 959:214–237

Skulachev VP (2006) Bioenergetic aspects of apoptosis, necrosis and mitoptosis. Apoptosis 11:473–485

Skulachev VP, Bakeeva LE, Chernyak BV, Domnina LV, Minin AA, Pletjushkina OY et al (2004) Thread-gain transition of mitochondrial reticulum as a step of mitoptosis and apoptosis. Mol Cell Biochem 256–257:341–358

Soleimanpour SA, Gupta A, Bakay M, Ferrari AM, Groff DN, Fadista J, Spruce LA et al (2014) The diabetes susceptibility gene clec 16a regulates mitophagy. Cell 157:1577–1590

Song W, Chen J, Petrilli A, Liot G, Kinglmayr E, Zhou Y, Poquiz P, Tjong J, Pouladi MA et al (2011) Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. Nat Med 17:377–382

Song Y, Xiao Y, Wang JM, Chen Q (2014) The different molecular mechanisms of mitophagy between yeast and mammals. Crit Rev Eukaryot Gene Expr 24:29–38

Sorbara MT, Girardin SE (2011) Mitochondrial ROS fuel the inflammasome. Cell Res 21:558–560

Soubannier V, McLelland GL, Zunino R, Braschi E, Rippstein P, Fon EA, McBride HM (2012) A vesicular pathway shuttles cargo from mitochondria to lysosomes. Curr Biol 22:135–141

Springer W, Kahle PJ (2011) Regulation of PINK1-Parkin-mediated mitophagy. Autophagy 7:266–278

Sripada L, Tomar D, Singh R (2012a) Mitochondria: one of the destinations of miRNAs. Mitochondrion 12:593–599

Sripada L, Tomar D, Prajapati P, Singh R, Singh AK, Singh R (2012b) Systematic analysis of small RNAs associated with human mitochondria by deep sequencing: detailed analysis of mitochondrial associated miRNA. PLoS One 7:e44873

Stehlingh O, Wilbrecht C, Lill R (2014) Mitochondrial iron-sulfur protein biogenesis and human disease. Biochimie 100:61–77

Stitnimankarn T, Thakerngpol K, Damrongsak C, Chinapak O, Sindhvananda K (1978) Ultrastructure of cholangiocarcinoma associated with opisthorchiasis. Southeast Asian J Trop Med Public Health 9:558–567

Stroud DA, Oeljeklaus S, Wiese S, Bohnert M, Lewandrowski U, Sickmann A, Guiard B et al (2011) Composition and topology of the endoplasmic reticulum-mitochondria encounter structure. J Mol Biol 413:743–750

Stuart JA, Brown MF (2006) Mitochondrial DNA maintenance and bioenergetics. Biochim Biophys Acta 1757:79–89

Sugiura A, Nagashima S, Tokuyama T, Arno T, Matsuki Y, Ishido S, Kudo Y, McBride HM et al (2013) MITOL regulates endoplasmic reticulum-mitochondria contacts via mitofusin2. Mol Cell 51:20–34

Sullivan LB, Chandel NS (2014) Mitochondrial reactive oxygen species and cancer. Cancer Metab 2:17

Surovtseva YV, Shadel GS (2013) Transcription-independent role for human mitochondrial RNA polymerase in mitochondrial ribosome biogenesis. Nucleic Acid Res 41:2479–2488

Sutterwala FS, Haasken S, Cassel SL (2014) Mechanism of NLRP3 inflammasome activation. Ann N Y Acad Sci 1319:82–95

Tait SW, Green DR (2012) Mitochondria and cell signaling. J Cell Sci 125:807–815

Takamura H, Koyama Y, Matsuzaki S, Yamada K, Hattori T, Miyata S, Takemoto K et al (2012) TRAP1 controls mitochondrial fusion/fission balance through Drp1 and Mff expression. PLoS One 7:e51912

Tamai S, Iida H, Yokota S, Sayano T, Kiguchiya S, Ishihara N, Hayashi J, Mihara K et al (2008) Characterization of the mitochondrial protein LETM1, which maintains the mitochondrial tubular shapes and interacts with the AAA-ATPase BCS1L. J Cell Sci 121:2588–2600

Tamir S, Paddock ML, Darash-Yahana-Baram M, Holt SH, Sohn YS, Agranat L, Michaeli D, Sofleth JT, Lipper CH et al (2014) Structure function analysis of NEET proteins uncovers their role as key regulators of iron and ROS homeostasis in health and disease. Biochim Biophys Acta pii:S0167-4889(14)00373-5

Tamori A, Nishiguchi S, Nishikawa M, Kubo S, Koh N, Hirohashi K, Shiomi S, Inoue M (2004) Correlation between clinical characteristics and mitochondrial D-loop DNA mutations in hepatocellular carcinoma. J Gastroenterol 39:1063–1068

Tanaka Y, Kanai Y, Okada Y, Nonaka S, Takeda S, Harada A, Hirokawa N (1998) Targeted disruption of mouse conventional kinesin heavy chain, kif5B, results in abnormal perinuclear clustering of mitochondria. Cell 93:1147–1158

Tanaka K, Sugirura Y, Ichishita R, Mihara K, Oka T (2011) KLP6: a newly identified kinesin that regulates the morphology and transport of mitochondria in neuronal cells. J Cell Sci 124:2457–2465

Tatarkova Z, Kuka S, Petras M, Racay P, Lehotsky J, Dobrota D, Kaplan P (2012) Why mitochondria are excellent targets for cancer therapy. Klin Onkol 25:421–426

Tauber J, Dlaskova A, Santorova J, Smolkova K, Alan L, Spacek T, Plecita-Hlavata L, Jaburek M, Jezek P (2013) Distribution of mitochondrial nucleoids upon mitochondrial network fragmentation and network reintegration in HEPG2 cells. Int J Biochem Cell Biol 45:593–603

Thomas RL, Kubli DA, Gustafsson AB (2011) Bnip3-mediated defects in oxidative phosphorylation promote mitophagy. Autophagy 7:775–777

Tinari A, Garofalo T, Sorice M, Esposti MD, Malorini W (2007) Mitoptosis: different pathways for mitochondrial execution. Autophagy 3:282–284

Tolkovsky AM (2009) Mitophagy. Biochim Biophys Acta 1793:1508–1515

Tschopp J (2011) Mitochondria: sovereign of inflammation? Eur J Immunol 41:1196–1202

Tschopp J, Schroder K (2011) NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? Nat Rev Immunol 10:210–215

Usui F, Shirasuna K, Kimura H, Tatsumi K, Kawashima A, Karasawa T, Yoshimura K, Aoki H, Tsutsui H, Noda T, Sagara J et al (2015) Inflammasome activation by mitochondrial oxidative stress in macrophages leads to the development of angiotensin II-induced aortic aneurysm. Arterioscler Thromb Vasc Biol 35:127–136

Valentin-Vega Y, Kastan MB (2012) A new role for ATM. Regulating mitochondrial function and mitophagy. Autophagy 8:840–841

Van der Bliek AM, Shen Q, Kawajiri S (2013) Mechanisms of mitochondrial fission and fusion. Cold Spring Harb Perspect Biol

Van Humbeeck C, Cornelissen T, Hofkens H, Mandemakers W, Gevaert K, De Strooper B, Vandenberghe W (2011a) Parkin interacts with ambra1 to induce mitophagy. J Neurosci 31:10249–10261

Van Humbeeck C, Cornelissen T, Vandenberghe W (2011b) Ambra1: a parkin-binding protein involved in mitophagy. Autophagy 7:1555–1556

Vivekanandan P, Daniel H, Yeh MM, Torbenson M (2010) Mitochondrial mutations in hepatocellular carcinomas and fibrolamellar carcinomas. Mod Pathol 23: 790–798

Waldeck-Weiermair M, Jean-Quartier C, Rost R, Khan MJ, Vishnu N, Bondarenko AI et al (2011) Leucine zipper EF hand-containing transmembrane protein 1 (Letm1) and uncoupling proteins 2 and 3 (UCP2/3) contribute to two distinct mitochondrial Ca2+ uptake pathways. J Biol Chem 286:28444–28455

Wallace DC (2005) Mitochondria and cancer: Warburg addressed. Cold Spring Harb Symp Quant Biol 70:363–374

Wang K, Klionsky DJ (2011) Mitochondria removal and autophagy. Autophagy 7:297–300

Wang Y, Lee CG (2009) MicroRNA and cancer – focus on apoptosis. J Cell Mol Med 13:12–23

Wang X, Moraes CT (2011) Increases in mitochondrial biogenesis impair carcinogenesis at multiple levels. Mol Oncol 5:399–409

Wang T, Weinman SA (2006) Causes and consequences of mitochondrial reactive oxygen speciesgeneration in hepatitis C. J Gastroenterol Hepatol 21(Suppl. 3): S34–S37

Wang T, Weinman SA (2013) Interactions between hepatitis C virus and mitochondria: impact on pathogenesis and innate immunity. Curr Pathobiol Rep 1:179–187

Wang C, Zhang F, Fan H, Peng L, Zhang R, Liu S, Guo Z (2011a) Sequence polymorphisms of mitochondrial D-loop and hepatocellular carcinoma outcome. Biochem Biophys Res Commun 406:493–496

Wang X, Winter D, Ashrafi G, Schlehe J, Wong YL, Selkoe D, Rice S, Stehen J, LaVoie MJ et al (2011b) PINk1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. Cell 147:893–906

Wang S, Xiao W, Shan S, Jiang C, Chen M, Zhang Y, Lü S, Chen J, Zhang C, Chen Q et al (2012a) Multi-patterned dynamics of mitochondrial fission and fusion in a living cell. PLoS One 7:e19879

Wang W, Zhou D, Wei J, Wu Z, Cheng X, Sun Q, Xie H, Zhou L, Zheng S (2012b) Hepatitis B virus X protein inhibits p53-mediated upregulation of mitofusin-2 in hepatocellular carcinoma cells. Biochem Biophys Res Commun 421:355–360

Wang K, Long B, Jiao JQ, Wang JX, Liu JP, Li Q, Li PF (2012c) miR-484 regulates mitochondrial network through targeting Fis1. Nat Commun 3:781

Wang Y, Yang C, Mao K, Chen S, Meng G, Sun B (2013a) Cellular localization of NLRP3 inflammasome. Protein Cell 4:425–431

Wang W, Sun Q, Wu Z, Zhou D, Wie J, Xie H, Zhou L, Zheng S (2013b) Mitochondrial dysfunction-related genes in hepatocellular carcinoma. Front Biosci (Landmark Ed) 18:1141–1149

Wang W, Xie Q, Zhou X, Yao J, Zhu X, Huang P, Zhang L, Wei J, Xie H, Zhou L, Zheng S (2015a) Mitofusin-2 triggers mitochondria Ca^{2+} influx from the endoplasmic reticulum to induce apoptosis in hepatocellular carcinoma cells. Cancer Lett 358:47–58

Wang JX, Zhang XJ, Feng C, Sun T, Wang K, Wang Y, Zhou LY, Li PF (2015b) MicroRNA-532-3p regulates mitochondrial fission through targeting apoptosis repressor with caspase recruitment domain in doxorubicin cardiotoxicity. Cell Death Dis 6:e1677

Wang HR, Li YW, Wu JL, Guo SL (2015c) Mitochondrial mutations in patients with myelodysplastic syndromes. Mitochondrial DNA 26:1–3

Wasiak S, Zunino R, McBride HM (2007) Bax/Bak promote sumoylation of DRP1 and its stable association with mitochondria during apoptotic cell death. J Cell Biol 177:439–450

Wasilewski M, Scorrano L (2009) The changing shape of mitochondrial apoptosis. Trends Endocrinol Metab 20:287–294

Weber TA, Koob S, Heide H, Wittig I, Head B, van der Bliek A, Brandt U, Mittelbronn M et al (2013) APOOL is a cardiolipin-binding constituent of the Mitofilin/MINOS protein complex determining cristae morphology in mammalian mitochondria. PLoS One 8:e63683

Wei Q, Mu K, Li T, Zhang Y, Yang Z, Jia X, Zhao W, Huai W, Gu P, Han L (2014) Deregulation f the NLRP3 inflammasome in hepatic parenchymal cells during liver cancer progression. Lab Invest 94:52–62

Wei H, Liu L, Chen Q (2015) Selective removal of mitochondria via mitophagy: distinct pathways for different mitochondrial stresses. Biochim Biophys Acta. doi:10.1016/j.bbamacr.2015.03.013

Weihofen A, Thomas KJ, Ostaszewski BL, Cookson MR, Selkoe DJ (2009) Pink1 forms a multiprotein complex with Miro and Milton, linking Pink1 function to mitochondrial trafficking. Biochemistry 48: 2045–2052

Weinberg SE, Sena LA, Chandel NS (2015) Mitochondria in the regulation of innate and adaptive immunity. Immunity 42:406–417

West AP, Shadel GS, Ghosh S (2011) Mitochondria in innate immune responses. Nat Rev Immunol 11:389–402

Westermann B (2010) Mitochondrial fusion and fission in cell life and death. Nat Rev Mol Cell Biol 11:872–884

Wheelhouse NM, Lai PB, Wigmore SJ, Ross JA, Harrison DJ (2005) Mitochondrial D-loop mutations and deletion profiles of cancerous and noncancerous liver tissue in hepatitis B virus-infected liver. Br J Cancer 92:168–1272

Wideman JG, Gawryluk RM, Gray MW, Dacks JB (2013) The ancient and widespread nature of the ER-mitochondria encounter structure. Mol Biol Evol 30:2044–2049

Wong LJ, Tan DJ, Bai RK, Yeh KT, Chang J (2004) Molecular alterations in mitochondrial DNA of hepatocellular carcinomas: is there a correlation with clinicopathological profile? J Med Genet 41:e65

Wredenberg A, Lagouge M, Bratic A, Metodiev MD, Spahr H, Mourier A, Freyer C et al (2013) MTERF3 regulates mitochondrial ribosome biogenesis in invertebrates and mammals. PLoS Genet 9:e1003178

Wu PC, Lai CL, Liddel RH (1984) Quantitative morphology of mitochondria in hepatocellular carcinoma and chronic liver disease. Arch Pathol Lab Med 108:914–916

Xie R, Nguyen S, McKeehan K, Wang F, McKeehan WL, Liu L (2011) Microtubule-associated protein 1S (MAP1S) bridges autophagic components with microtubules and mitochondria to affect autophagosomal biogenesis and degradation. J Biol Chem 286:10367–10377

Yadav N, Pliss A, Kuzmin A, Rapali P, Sun L, Prasad P, Chandra D (2014) Transformations of the macromolecular landscape at mitochondria during DNA-damage-induced apoptotic cell death. Cell Death Dis 5:e1453

Yamada S, Nomoto S, Fujii T, Kaneko T, Takeda S, Inoue S, Kanazumi N, Nakao A (2006) Correlation between copy number of mitochondrial DNA and clinic-pathologic parameters of hepatocellular carcinoma. Eur J Surg Oncol 32:303–307

Yamamoto H, Tanaka M, Katayama M, Obayashi T, Nimura Y, Ozawa T (1992) Significant existence of deleted mitochondrial DNA in cirrhotic liver surrounding hepatic tumor. Biochem Biophys Res Commun 182:913–920

Yang H, Zhou X, Liu X, Yang L, Chen Q, Zhao D, Zuo J, Liu W (2011) Mitochondrial dysfunction induced by knockdown of mortalin is rescued by Parkin. Biochem Biophys Res Commun 410:114–120

Yang RF, Zhao GW, Liang ST, Zhang Y, Sun LH, Chen HZ, Liu DP (2012) Mitofilin regulates cytochrome c release during apoptosis by controlling mitochondrial cristae remodeling. Biochem Biophys Res Commun 428:93–98

Ye YC, Wang HJ, Tashiro S, Onodera S, Ikejima T (2012) RIP1-mediated mitochondrial dysfunction and ROS production contributed to tumor necrosis factor alpha-induced L929 cell necroptosis and autophagy. Int Immunopharmacol 14:674–682

Ye Y, Huang A, Huang C, Liu J, Wang B, Lin K, Chen Q, Zeng Y, Chen H, Tao X et al (2013) Comparative mitochondrial proteomic analysis of hepatocellular carcinoma from patients. Proteomics Clin Appl 7:403–415

Yin PH, Lee HC, Chau GY, Wu YT, Li SH, Lui WY, Wei YH, Liu TY, Chi CW (2004) Alteration of the copy number and deletion of mitochondrial DNA in human hepatocellular carcinoma. Br J Cancer 90:2390–2396

Yin PH, Wu CC, Lin JC, Chi CW, Wei YH, Lee HC (2010) Somatic mutations of mitochondrial genome in hepatocellular carcinoma. Mitochondrion 10:174–182

Youle RJ, Narendra DP (2011) Mechanisms of mitophagy. Nat Rev Mol Cell Biol 12:9–14

Youle RJ, van der Bliek AM (2012) Mitochondrial fission, fusion, and stress. Science 337:1062–1065

Zemerli N, Arnoult D (2012) Mitochondrial anti-viral immunity. Int J Biochem Cell Biol 44:1473–1476

Zerbes RM, van der Klei IJ, Veenhuis M, Pfanner N, van der Laan M, Bohnert M (2012a) Mitofilin complexes: conserved organizers of mitochondrial membrane architecture. Biol Chem 393:1247–1261

Zerbes RM, Bohnert M, Stroud DA, von der Malsburg K, Kram A, Oeljeklaus S, Warscheid B et al (2012b) Role of MINOS in mitochondrial membrane architecture: cristae morphology and outer membrane interactions differentially depend on mitofilin domains. J Mol Biol 422:183–191

Zhang J (2013) Autophagy and mitophagy in cellular damage control. Redox Biol 1:19–23

Zhang B, Asadi S, Weng Z, Sismanopoulos N, Theoharides TC (2012) Stimulated human mast cells secrete mitochondrial components that have autocrine and paracrine inflammatory actions. PLoS One 7: e49767

Zheng BY, Fang XF, Zou LY, Huang YH, Chen ZX, Li D, Zhou LY, Chen H, Wang XZ (2014) The co-localization of HBx and COXIII upregulates COX-2 promoting HepG2 cell growth. Int J Oncol 45:1143–1150

Zhou R, Yazdi AS, Menu P, Tschopp J (2011) A role for mitochondria in NLRP3 inflammasome activation. Nature 469:221–225

Zou LY, Zheng BY, Fang XF, Li D, Huang YH, Chen ZX, Zhou LY, Wang XZ (2015) HBx co-localizes with COXIII in HL-7702 cells to upregulate mitochondrial function and ROS generation. Oncol Rep 33:2461–2467

Part XXXIV

General Pathology of Hepatobiliary Tumors: Growth and Its Regulation

General Aspects of Liver Regeneration and Hepatobiliary Cancer Growth

172

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_172

Abstract

Uncontrolled, progressive proliferative growth is a key feature of cancers. The net mass increase of tumors depends, apart from secondary phenomena contributing to mass such as blood vessels and leukocyte infiltrates, on the balance between increase of cell number through proliferation and cell loss caused by apoptosis and necrosis. Cell proliferation of hepatocellular carcinoma (HCC) mimicks the kinetic features known for hepatocytes in the setting of liver regeneration, but critical control mechanisms that operate in normal liver regeneration are no longer active. This already involves a first step of proliferation, i.e priming of cells for cell cycle entry. In contrast to normal hepatocytes, which have to be initiated to cross the cycle checkpoint in depence of cell production demand, HCC cells seem to be capable to pass without stop from one division cycle to the next. This deregulated replication can involve failure in the control of numerous factors orchestrating the cell division cycle, including checkpoint proteins, proteins involved in DNA synthesis and synthesis termination, proteins of the mitotic apparatus and cytoskeleton, and factors preparing daughter cells for a new division round.

Introduction

With respect to proliferative growth of liver cancers, much has been learned by the study of liver regeneration. In fact, normal hepatocyte regeneration is one of the best known examples of regenerative responses, and the cell kinetic and molecular features of this process have been elucidated in rodent models and in the human liver to a high level of detail.

Selected reviews: (Michalopoulos 1990, 2013, 2014; Fausto and Webber 1993; Columbano and Shinozuka 1996; Fausto 2000; Zimmermann 2004; Alison and Lin 2011; Kang et al. 2012).

Previously, most of the knowledge regarding liver regeneration has been employed to better understand the capacity of the human liver to recover and to restitute its cell mass following injury, surgical resection, and transplantation. The time has now come to utilize this wealth of information for the study of abnormal growth and growth control patterns, taking place in liver cancer, and to gain knowledge suitable to generate more efficient anticancer drugs. Both hepatocellular and cholangiocellular cancers share in their growth regulation numerous pathways with their normal counterparts. They very often utilize the same or similar regulatory factors which however are subject to distinct and far-reaching deregulations.

Cell Proliferation in the Normal Resting and Regenerating Liver: Lessons for the Understanding of Liver Cancer Growth

General Aspects

In the normal resting liver, physiologic hepatocyte turnover goes at low pace, with about one cell in 20,000–40,000 cells being in cell cycle at a given time point. In the course of regeneration of the normal resting adult liver, several hepatic cell lineages have to be replaced in accordance with the required liver cell mass. An adjustment of liver mass to the requirements of the entire body may involve a controlling system, the so-called hepatostat (Michalopoulos 2014), an instrument that not only senses the actual state of cell turnover and regulates the compensatory replacement of cells that had been lost but also monitors the size, geometry, and composition of the liver lobules and other structural-functional units of the liver. The functional cell mass of the liver consists of several specialized cell types, of which the hepatocytes form the major part and which differ considerably in their turnover (Paget 1954; Francavilla et al. 1988; Fleig 1998). Hepatocytes are mature and highly specialized cells, but they are not terminally differentiated but are in proliferative quiescence (the G0 phase). In hepatic regeneration, hepatocytes are stimulated to rapidly enter a cell division cycle. This regenerative response involves a sequence of distinctive

phases: (1) an initiation or priming phase, in which G0 hepatocytes enter a state of replicative competence; (2) a proliferation phase, where expansion of the hepatocyte population takes place; and (3) a termination phase, where cell proliferation is suppressed to terminate regeneration at a defined set point. These three "phases" are not independent events, but overlap and are linked in their progression in a complex manner. In addition, proliferation in the expansion phase subsequently requires a distinct remodeling process representing a "fourth phase" of regeneration.

Timely Sequence, Morphology, and Involved Cells of Liver Regeneration

Following the stimulation of regeneration, hepatocyte proliferation starts after an interval of about 24 h, reflecting the priming of G0 cells and the shift from G0 to the G1/S checkpoint and then into the S phase of cycle. In the normal non-cirrhotic liver, regenerative proliferation of hepatocytes starts in the periportal zone 1 of the liver lobule and extends to the pericentral zone 3 by 36–48 h. Tritiated thymidine incorporation into murine hepatocyte nuclei was maximal at 36 h (Lorup 1977). After an initial burst of proliferation, the rate of progression into DNA synthesis in the rat liver is at 3–4 % per hour, whereby most cells divide once and a few twice (Fabrikant 1968). Proliferation of non-parenchymal cells lags behind, the delay amounting to 24–48 h or even later (Fabrikant 1968; Crofton et al. 1978; Bouwens et al. 1986; Wacker et al. 1986; Wake et al., 1989; Table 1).

Most hepatocytes are engaged in proliferation after 3 days (the expansion phase), and this phase is associated with the formation of hepatocyte accumulations of eight to ten cells (the hepatocyte clusters) arranged around immature or disintegrating sinusoidal vascular channels. The emergence of hepatocyte clusters, characterized by cells with an amphophilic to slightly eosinophilic cytoplasm and a partially immature morphology, is closely associated with the effacement of the normal sinusoidal network (Figs. 1 and 2). This is accompanied by loss of a typical space of Disse and a degradation of perisinusoidal extracellular matrix (ECM) through metalloproteinases (Michalopoulos and DeFrances 1997). As the perisinusoidal space with its mesenchymal cells is effaced, hepatocyte clusters are depleted of mature hepatic stellate cells (HSCs), suggesting that hepatocytes might transiently engage in some sort of autonomous proliferation, related to the lack of stop signals released by mesenchymal cells. By 48 h post-partial hepatectomy (PH),

Table 1 Start of proliferation of diverse liver cells following stimulation of regeneration: timescale

Hepatocytes	24 h
Cholangiocytes	48 h
Kupffer cells/macrophages	72 h
Sinusoidal endothelial cells	96 h

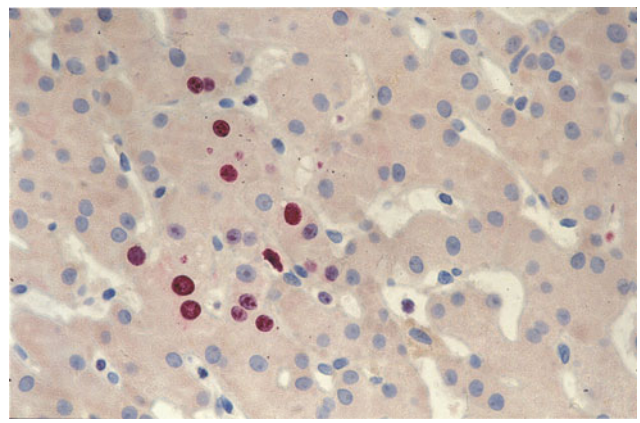

Fig. 1 Proliferative focus in liver regeneration. Several nuclei in a cluster express proliferating cell nuclear antigen (*PCNA*), and also a mitotic figure (metaphase, *close to the middle*) is labeled. Note that in the area of this proliferative cluster, hepatocyte plate architecture is partly effaced (PCNA immunostaining)

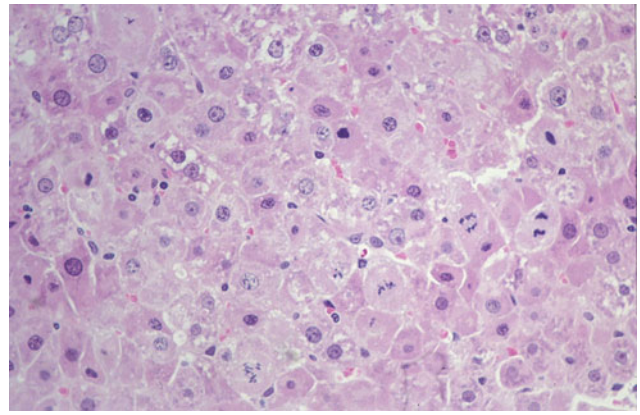

Fig. 2 Liver regeneration in the expansion phase. The liver cell plate structure is effaced and replaced by numerous proliferating hepatocytes (hematoxylin and eosin stain)

insinuation of small vessels ensues (resinusoidalization), associated with resynthesis of ECM proteins, the reconstitution of a space of Disse, and the repopulation of this space with regenerating HSC, which can exert growth control on hepatocytes. The resulting parenchymal unit (the "protolobula") is still oversized, and the final achievement of a normal lobule requires termination of hepatocyte regeneration and remodeling mechanisms depending on apoptosis. It seems that the new liver lobule is reshaped through a "top-to-bottom" control system, i.e., via controlled elimination of superfluous cells until the final dimension of the lobule determined by some master clock is achieved. The fate and functions of non-hepatocyte liver cells in regeneration are outlined in more detail below.

Molecular Regulation of the Initiation Phase of Liver Regeneration

Hepatocytes pass through a priming stage prior to proliferation (Mead et al. 1990). Priming, i.e., the gain of cell cycling competence by quiescent G0 hepatocytes, involves a set of upregulated regulatory factors, including hepatocyte growth factor/HGF, IL-10 mediated by p38MAPK, IL-6 mediated by STAT3, and TNF-alpha and JAK/STAT mediated by Ras/ERK and STAT3 (Fausto et al. 1995; Li et al. 2014). The main cellular sources for IL-6 and TNF-alpha are non-parenchymal cells, i.e., sinusoidal endothelia, Kupffer cells, and hepatic stellate cells (HSCs). ICAM-1-deficient mice exhibit impaired hepatocyte regeneration, because ICAM-1 triggers release of TNF-alpha and IL-6 from Kupffer cells following IL-6 binding to the gp130 receptor. TNF-alpha and IL-6 trigger the arrival at the cell cycle checkpoint and G0/G1 transition of the cell cycle. IL-6-deficient and TNFR-1-deficient animals fail to accomplish initiation and a hepatocyte regenerative response (Streetz et al. 2000). C/EBPbeta also critically controls the G1/S checkpoint. The importance of this pathway is illustrated by C/EBPbeta/NF-IL-6 knockout mice, showing a blunted regeneration. IL-6 can also cause cell cycle arrest and delayed proliferation during the first day of regeneration after partial hepatectomy, associated with activation of DNA repair enzymes to guarantee accurate replication and restoration of hepatic mass (Tachibana et al. 2014). Several mechanisms stimulate the IL-6 surge necessary for initiation. Peroxisome proliferator-activated receptor-alpha (Pparalpha) induces the IL-6R; Pparalpha null mice lack IL-6R gene induction and show delayed liver regeneration (Anderson et al. 2002). C/EBPbeta/NF-IL-6 binds to the IL-6 promoter region and enhances expression of IL-6. Promoter interaction is modulated by C/EBP homologous protein (CHOP), which interferes with NF-IL-6 action insofar as CHOP dimerizes more preferentially with an inhibitory

isoform of NF-IL-6 (LIP, liver-enriched inhibitory protein) than with a positively acting isoform (LAP, liver-enriched activator protein), CHOP upregulating IL-6 production without binding to its promoter (Hattori et al. 2003). The proper timing of G1/S checkpoint transition is controlled by a protein that regulates the Akt and STAT3 signaling pathway, protein tyrosine phosphatase of liver regeneration-1/Prl-1 (Jiao et al. 2015).

Apart from the key initiation factors, there are other pathways that can induce initiation. Rodents with dysfunctional leptin signaling exhibit a profound impairment of liver regeneration. Leptin-deficient ob/ob mice show an exaggerated activation of NF-kappaB and STAT3 during the initiation/priming phase, but an abrogation of TNF-alpha and IL-6 release at the time of G1/S transition (Leclercq et al. 2003). In early phases of liver regeneration, bile acid signaling plays a role in initiation. Bile acids promote regeneration through activating their receptors, farnesoid X receptor (FXR) and G protein-coupled BA receptor 1 (GPBAR1) (Fan et al. 2015). The activity of the farnesoid X receptor itself is regulated by sirtuin 1 (SIRT1), a molecule that controls central metabolic functions such as lipogenesis, protein synthesis, gluconeogenesis, and bile acid homeostasis (Garcia-Rodriguez et al. 2014). Bile acids are involved in a regulatory loop, in that remnant liver primed to undergo regeneration cannot handle bile acids returning via portal circulation (enterohepatic cycle).

Proliferation/Expansion Phase: Checkpoints and Growth Factors

Progression of primed/competent hepatocytes through G1 and subsequent replicative cycling mainly depends on hepatocyte growth factor (HGF) and transforming growth factor-alpha (TGF-alpha) signaling, after which the proliferation process seems to proceed autonomously under the control of cyclins and cyclin-dependent kinases. However, a complex network of other factors regulates the delicate transition of primed hepatocytes into the S phase of the cell division cycle (Fujiyoshi and Ozaki 2011).

Subsequent to priming/initiation, several immediate early-phase genes related to hepatocyte proliferation are induced within 2 h. They comprise c-fos, c-Jun, and others (Taub 1996). c-Jun serves as a major c-Jun-N-terminal kinase (JNK) target in proliferation. JNK is strongly activated minutes after PH; the JNK/c-Jun pathway is a critical component of the early proliferative response and induces the G0 to G1 transition via cyclin D1. A further rapidly induced factor is insulin-like growth factor-binding protein 1 (IGFBP-1). IGFBP-1-deficient mice display reduced and delayed hepatocyte DNA replication after PH (Leu et al. 2003). Some of the proteins involved in priming, expansion, and termination may be modified by enzymes converting (inactive) proproteins via limited proteolysis to the active species. Nine mammalian proprotein convertases have been identified so far, eight belonging to the yeast kexin subfamily of subtilases. A K-like subtilase, neural apoptosis-regulated convertase 1 (NARC-1), peaks on days 2–3 post PH, whereas other convertases (PC5, PACE4, furin) peak on day 1, suggesting that these enzymes are active in the bioavailability of growth factors. Furthermore, the bioavailability of growth factors depends on the liberation of these factors from storage in the ECM by the action of plasmin and plasmin-like enzymes, as found in experiments using mice deficient in urokinase or in plasminogen activator (uPA), showing an impaired liver regeneration.

Expression of HGF has been detected in hepatic stellate cells (HSCs), hepatic macrophages/Kupffer cells, and in sinusoidal endothelial cells. Kupffer cells are capable to simulate HGF secretion by HSCs (Takeishi et al. 1999). As HSCs diminish in number along the regeneration pathway, their stimulatory action is reduced by the end of regeneration, probably contributing to the termination phase. HGF is secreted as an inactive single-chain protein (scHGF), proteolytically cleaved at the Arg-Val-Val site to form the active two-chain HGF (tcHGF). The HGF receptor, c-Met, can bind both forms, but is only activated by tcHGF. Cleavage is accomplished by urokinase-type plasminogen activator (uPA),

tissue-type plasminogen activator, coagulation factor XIIIa, and hepatocyte growth factor activator (HGFA). The activity of HGFA is itself regulated by two Kunitz-type serine protease inhibitors, HGFA inhibitor type 1 (HAI-1) and type 2 (HAI-2), having different roles (Naganuma et al. 2003). TGF-alpha has a central place in the stimulation of hepatocyte proliferation and is regulated by beta-catenin signaling (Torre et al. 2011). Hepatocyte growth is furthermore regulated by H/MFREP-1 (human/murine fibrinogen-related protein-1), a liver-specific protein of the fibrinogen superfamily, eventually acting as a "molecular facilitator" in the regenerative response. Other factors that control hepatocyte proliferation include hepassocin, augmenter of liver regeneration (ALR), a mammalian FAD-dependent sulfhydryl oxidase that also plays a role in HCC (Schaefer-Ramadan et al. 2013; Yu et al. 2014b), EGF, heparin-binding epidermal growth factor-like growth factor (HB-EGF), and lal-1 (liver annexin like-1). Part of these growth factors are modulated by surface molecules on hepatocytes which interfere with growth factor receptor binding, e.g., integrins which can inhibit growth factor signaling (Patman 2014; Speicher et al. 2014).

Cell cycle progression itself is regulated by cyclin expression and activation of cyclin-dependent kinases (CDKs). For example, S-phase entry and progression critically depends on the formation of cyclin E-CDK2 and cyclin A-CDK2 complexes. Cyclin B associates with CDK1 (Cdc2) to achieve progression from G2 to M. CDK-mediated cell cycle progression is modulated by CDK inhibitors (CDKIs). Finally the G2/M transition in hepatocytes is regulated by a cell cycle-dependent nuclear protein, Citron kinase as a downstream target of Rho-GTPase, and Citron kinase loss in knockouts induces apoptosis in a subset of cells (Liu et al. 2003). The orderly expression of cyclin A and the Wee1/Cdc2/cyclinB1 pathway and entry into M phase is regulated by the production of the transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), a protein involved in proliferation and apoptosis (Zou et al. 2015).

Termination of the Regeneration Process

Subsequent to the expansion phase, the growth response must finally be terminated. Major factors involved in the termination response comprise transforming growth factor-beta (TGF-beta), the activins, integrin-linked kinase, glypican-3, and Yes-associated protein (YAP) (review: Kang et al. 2012). Loss of proliferative capacity of hepatocytes may also be induced by epithelial-mesenchymal transition, fundamentally altering the epithelial character of hepatocytes (Xue et al. 2013).

TGF-beta and activin regulate hepatic organ mass and tonically inhibit DNA synthesis in hepatocytes. The cation-independent mannose 6-phosphate receptor (CIMPR) is overexpressed in hepatocytes during regeneration. Induction of its gene occurs in mid-G1 phase, and CIMPR mediates latent pro-TGF-beta activation, thus acting by targeting TGF-beta to hepatocytes during the termination response of regeneration (Villevalois-Cam et al. 2003). The action of TGF-beta itself is mediated by Smads serving as intracellular signals in this pathway. Two transcriptional repressors of the TGF-beta/Smad pathway, SnoN and Ski, are upregulated during regeneration, and they antagonize TGF-beta-mediated termination via binding to Smad proteins (Macias-Silva et al. 2002). In addition to an inhibition of hepatocyte proliferation, TGF-beta1 also induces hepatocyte apoptosis by a c-Jun-independent mechanism, and this effect may contribute to the termination response, but may also be involved in lobule remodeling. The TGF-beta family member, bone morphogenetic protein (BMP) 4, is a paracrine inhibitor of liver regeneration (Do et al. 2012) and may be involved in the termination process.

Activins and their receptors and follistatin exhibit a distinctive timely expression pattern during regeneration. Activin A (the homodimer of the inhibin betaA chain) and follistatin (an activin-binding protein) inhibit and promote hepatocyte proliferation, respectively. Activin A is an inhibitor of hepatocyte DNA synthesis, can induce a reduction of liver mass, and promotes apoptosis in hepatocytes, blocked by follistatin (Rodgarkia-

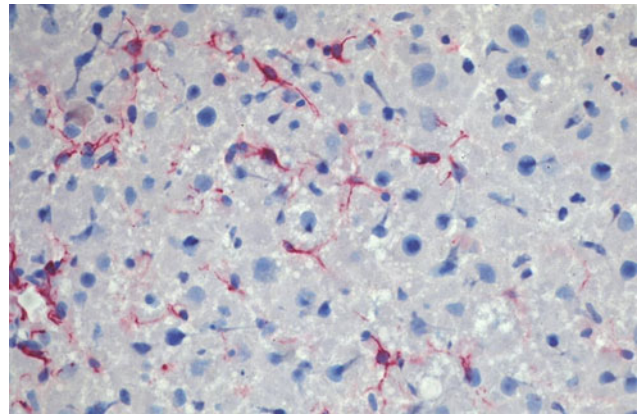

Fig. 3 Liver regeneration in the expansion phase. Desmin-reactive hepatic stellate cells with long processes have populated a proliferating hepatocyte cluster, but a Disse space has not yet been formed (frozen section, desmin immunostaining)

Dara et al. 2006; Kreidl et al. 2009). This response is dependent on activin receptors and on Smad2 protein relocated to the nucleus. Following partial hepatectomy in the rat, expression of betaA- and betaC-activins significantly dropped at 12 h post surgery and remained low until 168 h post hepatectomy, while a peak follistatin expression takes place at 24–48 h, coincident with an increase of hepatocyte mitosis (Gold et al. 2005). After rat liver injury or PH, hepatocyte activin A receptors are downregulated by 24 h and normalize by 72 h (Date et al. 2000), a phenomenon possibly involved in rendering hepatocytes responsive to mitogenic stimuli.

Termination of liver regeneration is also induced by the C/EBPalpha-HDAC1 complex and chromatin-remodeling proteins (Jin et al. 2014). Termination of regeneration is also regulated by proteins that are deregulated in liver cancer, i.e., C/EBP family proteins that interact with chromatin-remodeling proteins (Jin et al. 2015). A fine tuning of proliferation versus proliferative quiescence is also accomplished by Hippo signaling in mammalian liver regeneration. Loss of Hippo signaling, such as in liver cancers, results in ongoing, uncontrolled cell growth. The Hippo pathway includes a core kinase cascade that consists of Ste20-like kinases (in *Drosophila* called Hippo) and the cofactor Salvador, activating the large tumor suppressor Lats1/2 which in turn inhibits two transcriptional coactivators, YAP and TAZ (Hong et al. 2015).

Termination of hepatocyte regeneration requires, and goes in parallel with, the restauration of the normal sinusoidal and littoral phenotypes and the repopulation by hepatic stellate cells

Close to the end of regeneration and linked to termination, insinuation of vascular channels (the later sinusoids, resinusoidalization), formation of the perisinusoidal space of Disse, reequipment of Disse space by HSC (Fig. 3), and the resynthesis of the perisinusoidal extracellular matrix (ECM) take place.

These are processes that are crucial not only for the reconstruction of the regenerated lobule by remodeling but also for the termination of regeneration as such, because sinusoidal and littoral cells are the principal sources of termination signals. The morphogenesis of a sinusoidal system is linked to liver regeneration as such, in that endothelial cell-derived angiopoietin-2 controls regeneration as a spatiotemporal rheostat (Hu et al. 2014). A reconstructed sinusoidal system creates the homing microenvironment for blood-borne monocytes that differentiate into hepatic macrophages/Kupffer cells, a cell system that is involved in regeneration signaling (Chazaud 2014).

Resinusoidalization requires endothelial cell proliferation, exerting an important influence on hepatic regeneration (Wang et al. 2014b). In addition to VEGFs, sinusoidal cell regeneration is in part regulated by semaphorin 3E secreted by damaged hepatocytes (Yagai et al. 2014). The role of endothelial cells increasing in number during resinusoidalization is underlined by the recent finding that mice administered circulating VEGF-A had enlarged livers due to increased

proliferation of hepatocytes and non-parenchymal cells, and the sinusoidal endothelial cell-derived paracrine mediators promoting growth were IL-6 and HGF (LeCouter et al. 2003).

The repopulation of the developing liver lobule by HSC and their differentiated offspring, in particular their homing to the newly formed Disse space in the phase of resinusoidalization, depends on proliferation and migration of these cells. HSC shows a migration response to PDGF-BB, to epithelial growth factor (EGF), and to TGF-beta1, a key molecule of termination, augmenting the chemoinvasive response of HSC to PDGF and bFGF. A resynthesis of the previously degraded perisinusoidal ECM is required for full regeneration, and the ECM is synthesized by HSC transiently differentiated to myofibroblasts. This is illustrated by mice deficient in the Forkhead Box (Fox) f1 transcription factor, showing defective stellate cell activation and abnormal liver regeneration associated with aberrantly elevated TGF-beta1 expression (Kalininchenko et al. 2003). The importance of only a transient and well-controlled ECM increase is documented by observations obtained with mice bearing a mutated collagen-I gene conferring collagenase resistance (r/r mice); these animals exhibit a persistent activation and a reduced apoptosis of stellate cells, a failure of ECM degradation, and a diminished hepatocyte regeneration (Issa et al. 2003). Epithelial cells require contact with ECM to inhibit detachment-induced apoptosis (anoikis), and the reconstitution of a perisinusoidal ECM will therefore stabilize the newly formed hepatocyte population.

The final construction of the liver lobule and its zonation is regulated by the Wnt/beta-catenin signaling pathway (Gebhardt and Hovhannisyan 2010). Wnt signaling is the major upstream effector of beta-catenin activity in pericentral hepatocytes and determines the definition of zone, whereby Kupffer cells are the major source of Wnt secretion (Yang et al. 2014b). Lobule reconstruction also depends on the function of ductules and peribiliary stellate/myofibroblastic cells, ductular/myofibroblastic "units" probably serving as pacemakers of remodeling, similar to processes occurring in pancreatic regeneration (Zimmermann et al. 2002). There is some evidence that the shaping of the future lobule also critically depends on a close interaction between vascular endothelial cells and hepatocytes.

MicroRNAs as Regulators of Cell Proliferation in Liver Regeneration

A complex network of microRNAs regulates hepatocyte proliferation during liver regeneration (Song et al. 2010; Chaveles et al. 2012; Schug et al. 2013; Chen and Verfaillie 2014; Finch et al. 2014). MicroRNAs therefore provide an important instrument for the control of adequate cell replacement in the liver and hence participate in the master clock that determines initiation, progression, and termination of regeneration. In rodent models, microRNAs are subject to marked upregulations or downregulations, depending on the regeneration phases. In post-partial hepatectomy rats, early regeneration (hours, 3–18) was characterized by upregulation of 40 % of microRNAs, while at 24 h, around 70 % of microRNAs were downregulated. It was suggested that upregulation of microRNAs in early regeneration is required for priming of G0 hepatocytes for cell cycle entry (initiation, Shu et al. 2011). MicroRNA-21 is upregulated in the initiation/priming phase and promotes proliferation competence via targeting NF-kappaB signaling (Marquez et al. 2010). In the expansion phase, microRNA-127 is downregulated, facilitating hepatocyte proliferation in rat liver regeneration (Pan et al. 2012). The downregulation of distinct microRNA species in the proliferation/expansion phase reflects a phenomenon that is also observed in liver cancer (see below). Inhibited microRNA expression in the setting of ongoing proliferation includes microRNA-26a, microRNA-150, microRNA-503, and microRNA-663 (Zhou et al. 2012; Salehi et al. 2013), whereas upregulated microRNAs include microRNA-21, microRNA-122, and microRNA-221 (John et al. 2014). MicroRNA-21 targets PTEN (Yan-nan et al. 2014), and its surge in early regeneration facilitates rapid cyclin D1

translation and cell cycle progression (Ng et al. 2012). MicroRNA-221 enhances hepatocyte proliferation by targeting p27, p57, and Arnt (Yuan et al. 2013). Downregulation of microRNA-26a during the proliferative phase of regeneration enhances hepatocyte proliferation through targeting the cell cycle proteins CCND2 and CCNE2 (Zhou et al. 2012). In late regeneration, microRNA-34a is upregulated in hepatocytes of rats and is associated with the suppression of hepatocyte proliferation (Chen et al. 2011), suggesting that this MiR plays a role in the termination phase of regeneration. Similarly, downregulation of microRNA-23b activates TGF-beta17Smad3 signaling and thus contributes to the termination of regeneration (Yuan et al. 2011).

Safeguards of Aberrant Cell Replication During Regeneration

The proliferation of hepatocytes in regeneration is characterized by a massive surge of cell production, a process that ends with termination and zonation of the lobule. As in any markedly upregulated proliferation, like that found in cancers, unlimited cell production bears the risk of replication errors and the production of aberrant cells. Such a danger is not only inherent to cancers, but is also present in the transient, apparently "uncontrolled" growth surge in liver regeneration, where cells are disconnected for a certain time period. The mechanisms protecting proliferating hepatocytes from damage and transformation are incompletely known. One safeguard mechanism counteracting abnormal DNA replication induced by deregulated proliferation stimuli is the replication stress response (RSR), a mechanism leading to cell cycle restriction and/or apoptosis and therefore to a blockade of unwanted cells. In transformed cells, RSR is bypassed giving rise to viable aberrantly proliferating cells, whereas RSR is preserved in normal regenerating hepatocytes. A key component of RSR is the COP9 signalosome, a conserved regulator of cullin ring-type ubiquitin ligases (Panattoni et al. 2014).

Remodeling of the Growing Lobule

As outlined above, the primordial post-regeneration liver lobule is oversized and therefore requires remodeling to achieve its final dimension, which is crucial for metabolic zonation and the generation of proper vascular relationships. The radius of a normal liver lobule has to be controlled tightly in order to maintain an oxygenation gradient and proper oxygen extraction by lobule cells from lobule inflow to outflow. The remodeling of the post-regeneration liver lobules is also closely connected with the reconstitution of metabolic zonation. Metabolic zonation denotes the phenomenon that hepatocytes differ in the type of their metabolic activity and in their biology as a function of the cells' position within the lobule. Periportal hepatocytes differ from pericentral hepatocytes in their enzyme expression patterns. For example, enzymes active in drug metabolism are predominantly expressed in the pericentral zone. This metabolic zonation is not present at the termination phase of regeneration, and hepatocytes have to be programmed to achieve their distinct metabolic signature in the course of lobule remodeling (Torre et al. 2010; Gougelet et al. 2014). The control of liver zonated gene expression is regulated by a convergence of canonical Wnt signaling on hepatocyte nuclear factor (HNF) 4alpha-driven transcription (Colletti et al. 2009; Berasain and Avila 2014). Within the Wnt pathway, beta-catenin is a central molecule regulating zonation and in particular affects zonated lipid metabolism and the pathogenesis of steatosis (Behari et al. 2014). Several pathogenic factors can interfere with metabolic zonation, including hypoxia, toxic agents, and hepatitis C virus proteins (König et al. 2013; Moreau et al. 2015).

It appears that superfluous hepatocytes in the post-regeneration lobule are eliminated through apoptosis. Interestingly, TNF-alpha not only induces regeneration but also apoptosis. TNF-alpha-induced hepatocyte apoptosis is modulated by acidic sphingomyelinase (ASMase), as seen in ASMase knockout mice, by promoting the mitochondrial targeting of glycosphingolipids

(Garcia-Ruiz et al. 2003). Furthermore, hepatocyte cytokeratins/keratins (K) have an impact on cell survival. The K8/K18 system plays a significant role in providing resistance to stress and apoptosis in hepatocytes and in preserving hepatocyte integrity. K8/K18 provides resistance to Fas-mediated apoptosis through a modulation of Fas targeting to the cell surface. K18 is a caspase substrate, and transgenic mice overexpressing mutant human K18 develop hepatocyte fragility via keratin filament disruption, which predisposes hepatocytes to Fas- but not TNF-mediated apoptosis (Ku et al. 2003). The mechanism apparently involved is that K18 may sequester TNFR1-associated death domain protein (TRADD) to attenuate interactions between TRADD and activated TNFR1. The balance between apoptosis and hepatocyte survival is critical for appropriate remodeling of future fully regenerated lobules. Based on IGF-binding protein-1 (IGFBP-1)-deficient mice, it has been shown that IGFBP-1 functions as a hepatic survival factor counteracting the TGF-beta1 proapoptotic signal. Protection against caspase-8-mediated hepatocyte apoptosis is also accomplished by senescence marker protein-30 (SMP30), as based on studies with SMP30-/- mutant mice. A potent antiapoptotic agent against TNF-alpha-mediated liver cell loss is the TNF superfamily member LIGHT binding to lymphotoxin-beta receptor, inhibiting caspase-3 processing on the apoptotic protease cascade.

Liver Regeneration: Role of Stem/Progenitor Cells

In the normal liver, virtually, all newly formed hepatocytes are derived from preexisting mature hepatocytes (Yanger et al. 2014). Notwithstanding the fact that most cells that participate in parenchymal regeneration of a liver with competent cell systems are hepatocytes, stem or progenitor cells come into action in situations where remnant hepatocytes are injured and partially or completely incompetent for regeneration (Haque et al. 1996; Thorgeirsson 1996; Fausto and Campbell 2003; Santoni-Rugiu et al. 2005; Best et al. 2015; Huch 2015). Therefore, facultative hepatic stem cells enter the stage in situations of severe chronic or acute overwhelming liver injury (Itoh and Miyajima 2014; Shin and Kaestner 2014; Than and Newsome 2014). The liver possesses two stem/progenitor cell systems, i.e., fetal progenitor cells derived from foregut endoderm and competent to differentiate into hepatocyte and cholangiocyte lineages and adult hepatic progenitor cells that can contribute to liver regeneration under certain circumstances. Adult hepatic progenitor cells are in part resident cells normally situated within small bile ductules, in part cells derived from circulating stem cells. Circulating progenitor cells in part have the features of mesenchymal stem cells, and also local mesenchymal cells, including myofibroblastic cells, can contribute to the hepatocyte generation (Swiderska-Syn et al. 2014). Adult hepatic stem cells express a set of markers, including delta-like 1 homologue (DLK1), CD13, CD133, and LIV2 (reviews: Kamiya and Inagaki 2015). In rodents, progenitor cells termed oval cells develop in many instances of liver injury, and these cells express hepatic stem cell markers, including CK19 (Chiu et al. 2007).

The role of circulating stem cells derived from the bone marrow in the regenerating liver is not fully elucidated. Apparently, only few hepatocytes originate from circulating stem cells and are mainly generated by cell fusion (Oh et al. 2007). In contrast, circulating progenitor cells are a significant source of sinusoidal endothelial cells and hepatic leukocytes, the latter being an essential production place for growth factors and signaling substances involved in liver regeneration (Grompe 2005). Progenitor cells play an important role in the reconstitution of parenchyma in liver cirrhosis. The repopulation of regions of parenchymal extinction in human cirrhosis proceeds through hepatocyte buds located in broad septa, buds being clusters of cells reflecting a characteristic progenitor pathway and providing a progeny that represents up to 70 % of hepatocytes (Stueck and Wanless 2015). The action of hepatic progenitor cells in the setting of liver regeneration strongly depends on the hepatic microenvironment, where a close

interaction between progenitor cells, recruited inflammatory cells, the ECM and stored growth factors, and signaling factors takes place (Santoni-Rugiu et al. 2005). The capacity of progenitor cells to produce hepatocytes depends on a tight regulatory system, which also involves microRNAs, including microRNA-122 (Tanimizu et al. 2014). Circulating stem cells, including mesenchymal stem cells, can affect hepatocyte regeneration through signals released from stem cell-derived exosomes (Tan et al. 2014).

Fate and Function of Non-parenchymal Liver Cells in Hepatic Regeneration

Cholangiocytes and Bile Ducts

Cholangiocytes are capable of proliferating in the adult organism, however, at a low rate under resting conditions. Nevertheless, the proliferative activity of cholangiocytes in normal livers is higher than that of hepatocytes, suggesting a higher normal cell turnover (Rubin et al. 1995). Proliferation is enhanced in several conditions of liver injury, including inflammation, regeneration, and repair (Sutton and Spurgeon 1966; Marongiu et al. 2014). In the course of liver regeneration, regenerating cholangiocytes of the type normally found in ductules are found as small cell nests or, in some situations, as foci of ductular proliferation. These structures are situated in close association with altered portal spaces and remain there up to 2 weeks post-partial hepatectomy in rodent models (Seres-Sturm et al. 1981). Part of regenerating cholangiocytes enter the regenerating lobule, similar to models of rat liver transplantation (grade IV ductular proliferations, Zhao et al. 1993, 1995), and are in close relation with immature hepatocyte clusters. In the course of lobular remodeling, these proliferations recede and leave a normal complement of ductules, probably accomplished by tightly controlled apoptosis. However, cells of primitive ductules in hepatic injury may also derive from hepatocytes, this conversion depending on Notch-Hes1 signaling (Sekiya and Suzuki 2014). Regenerative proliferation of cholangiocytes is regulated by factors secreted by local monocytes/macrophages and other immune cells, including granulocyte colony-stimulating factor and stem cell factor. These factors also affect remodeling of the biliary system, through the action of S100 calcium-binding protein A4/S100A4 and microRNA-181b (Meng et al. 2012).

Proliferating cholangiocytes can acquire a phenotype of neuroendocrine cells. These cells secrete neuropeptides, hormones, growth factors, and cytokines and participate in a multifaceted cross talk with other liver cells, e.g., during regeneration (Alvaro et al. 2007). Newly formed cholangiocytes can convert into hepatocytes and thus contribute to parenchymal cell replacement (Tanimizu et al. 2013). Regenerating biliary epithelial cells can originate from progenitor cells. The biliary tree harbors multipotent stem cells. In portal tracts, these cells are located in ductules or in von Hering's passages, while in medium-sized to large bile ducts, they are mainly found in peribiliary glands (Cardinale et al. 2010, 2012; Sutton et al. 2012). In peribiliary tubuloalveolar glands, progenitor cells are located at the bottom of glands and are phenotypically heterogeneous, but express liver-specific transcription factors (SOX9/17) and several endodermal markers. In the course of priming/maturation, these cells shift to the bile duct surface, where they can, upon stimulation, become cholangiocytes or hepatocytes (Carpino et al. 2012). Subsequent to specific cell lineage priming, these progenitor cells give rise to cholangiocytes and hepatocytes (Cardinale et al. 2011).

Kupffer Cells/Macrophages

Kupffer cells as hepatic ED2+ macrophages and major component of hepatic littoral cells play an important role in liver homeostasis and regeneration (You et al. 2013). In the course of hepatocyte expansion, the sinusoidal architecture of the liver lobule is desintegrated, and with this the residence and the homing place for hepatic macrophages/Kupffer cells, which is normally situated within the sinusoidal lumen. The repopulation of newly formed sinusoids after the termination phase of liver regeneration is not fully elucidated. Apart from local macrophages that proliferate during

regeneration and find their way to the newly formed vascular channels, homing of circulating monocytes into sinusoids and the subsequent differentiation onto mature hepatic macrophages/Kupffer cells take place. After partial hepatectomy in the rat, ECD2+ cells remaining in the liver increase rapidly from day 2 to 5, with a maximum replicating ED2+ macrophages at day 2 (Ukai et al. 1990). Peak mitotic activity of Kupffer cells following partial hepatectomy in the rat occurred at 48 h (Widmann and Fahimi 1975). In the course of rodent liver regeneration, macrophages first infiltrate the periportal parenchyma and then shift to the pericentral zone, suggesting a hepatic zonation of homing factors (Baier et al. 2005).

Kupffer cells as monocyte-derived hepatic macrophages exert several effects of regenerating hepatocytes (review: Takeishi et al. 1999). Through a paracrine mechanism, Kupffer cells regulate regeneration of hepatocytes via secretion of IL-6 and TNF-alpha. As these two factors hold a key position in liver regulation, innate immune mechanisms mediated by monocytes/macrophages play a significant role (Shiratori et al. 1996; Aldeguer et al. 2002; Iimuro et al. 2007), an interleukin playing a central role in the initiation phase of regeneration (see below). The release of TNF-alpha and IL-6 by macrophages/Kupffer cells is triggered by intercellular adhesion molecule-1 (ICAM-1), which binds to macrophages and recruits leukocytes to the liver (Selzner et al. 2003). Hepatic macrophages can affect the morphogenesis of ductular reactions via macrophage-mediated signaling of TNF-like weak inducer of apoptosis (TWEAK) (Bird et al. 2013). Kupffer cells affect hepatic perfusion during liver regeneration via modulation of vasoactive peptides (Abshagen et al. 2008).

Sinusoidal Endothelial Cells

As outlined in more detail above, the terminal phase of liver regeneration requires the reconstitution of a sinusoidal microvascular bed (the so-called insinuation). Insinuation and angiogenesis mediated by angiopoietin-2 in general play a significant role in complete liver regeneration (Uda et al. 2013; Wang et al. 2014b). Sinusoidal endothelial cells (SECs) originate from local endothelial cells, local progenitors, and circulating precursor cells (Krause et al. 2010; Moniaux and Faivre 2011). The recruitment of progenitor cells of SEC is regulated by a surge of hepatic vascular endothelial growth factor (VEGF) (Wang et al. 2012b). In the early phase of liver regeneration, SECs downregulate their production of angiopoietin-2, which in turn reduces SEC-derived release of TGF-beta1, hence releasing an important hepatocyte proliferation break (Hu et al. 2014). In the later termination phase, this mechanism is reversed (see below). VEGF signaling produced by SECs and epithelial cells has a central place not only in sinusoidal regeneration but also in the generation of the distinct three-dimensional sinusoidal network and in lobule zonation (Mochida et al. 1998; Walter et al. 2014). Sinusoidal regeneration in late liver regeneration is mediated by semaphorin 3E secreted by hepatocytes (Yagai et al. 2014). SECs express vascular endothelial growth factor (VEGF)-A receptor-2/VEGFR2 which promotes hepatocyte proliferation via upregulation of the transcription factor Id1 and release of HGF (Ding et al. 2010). Induction of Id1 also takes place through upregulation of CXCR7 and CXCR4 in sinusoidal endothelial cells, deploying pro-regenerative angiogenic factors (Ding et al. 2014). SEC production and function in liver regeneration are strongly influenced by platelets (Nowatari et al. 2012; Murata et al. 2014). Platelets streaming through an intact sinusoidal system promote SEC proliferation and induce the secretion of IL-6 and VEGF by these cells (Kawasaki et al. 2010). This effect strongly depends on a close interaction between thrombocytes and SECs. SECs avidly bind platelets in an integrin-dependent and immobilized fibrinogen-dependent manner. This binding leads to NF-kappaB activation and cytokine secretion in SECs, and in upregulation of P-selectin, which in turn promotes homing and adhesion of leukocytes (Lalor et al. 2013). This may also be a mechanism resulting in the local recruitment of circulating stem cells.

SECs are engaged in a close interaction with hepatocytes, Kupffer cells, hepatic stellate cells

(HSCs), and Pit cells. SECs and their progenitors directly affect hepatocyte regeneration (Gamble et al. 2011; Wang et al. 2012a). These cells are capable to secrete HGF at low level, but part of their bone marrow-derived progenitors are rich in HGF (Ping et al. 2006; DeLeve 2013). The role of SECs in expansion and termination of regeneration is closely linked to their influence on hepatic angiogenesis (Ding et al. 2010, 2014; Uda et al. 2013; Huebert and Shah 2014). SECs coordinate liver regeneration as vascular pacemakers via angiopoietin-2 (Wang et al. 2014b), forming a spatiotemporal rheostat based on autocrine-acting angiopoietin-2 signaling (Hu et al. 2014). Similar to hepatocytes and HCC cells, endothelial cells are subject to stimulation by various growth factors. The response to growth factor stimulation is negatively regulated in these cells by the expression of four types of Sprouty proteins that are modulators of mitogen-activated protein kinase (MAPK) signaling (Mason et al. 2006; Cabrita and Christofori 2008).

Hepatic Stellate Cells, Myofibroblasts, and Other Hepatic Mesenchymal Cells

As outlined above, hepatic stellate cells (HSCs) repopulate the newly formed perisinusoidal/Disse spaces in the course of resinusoidalization of parenchyma in later phases of regeneration. HSCs proliferate in regeneration, can actively migrate to the perisinusoidal space, and undergo complex interactions with regenerating hepatocytes and SECs. HSC-hepatocyte signaling is associated with formation of direct physical contacts between these two cell types, via generation of tight junction-mediated connections (Mabuchi et al. 2004). The appropriate number of stellate cells after a proliferative surge is controlled by apoptosis. TGF-beta1 and IFN-alpha downregulate apoptosis in stellate cells, whereas CD95/CD95L and p53 protein promote apoptosis. The mechanisms involved include the TRAIL receptor-2/death receptor-5 expressed on activated stellate cells (Taimr et al. 2003). HSCs engage in growth factor-mediated signaling for hepatocytes and promote regeneration (Antoine et al. 2009; Yin et al. 2013). They secrete HGF, a process regulated by the tumor suppressor, cylindromatosis (CYLD) gene (Pannem et al. 2014). HSCs are a specific source of delta-like 1 homologue (DLK1), a protein that regulates cyclins and cyclin-dependent kinases and positively controls regeneration (Zhu et al. 2012). HSCs are central to the generation of a hepatic mesenchyme and extracellular matrix that provides a scaffold and growth factor storage facility for regeneration. Liver regeneration is promoted by trophic factors produced by hepatic mesenchymal cells (Fouraschen et al. 2014), part of which originate from HSCs. A C-type lectin produced by HSCs, endosialin, inhibits hepatocyte proliferation and is upregulated in the liver undergoing fibrosis (Mogler et al. 2015). Part of mesenchymal cells of the hepatic microenvironment are derived from mesenchymal stem cells (MSCs), which therefore play a role in the replacement of mesenchymal cells in the course of liver regeneration. In addition, MSCs can directly affect hepatocyte regeneration through the secretion of factors that promote proliferation (Fouraschen et al. 2012). Part of these MSC-derived pro-regenerative factors are released by exosomes (Tan et al. 2014). As bone marrow-derived stromal/mesenchymal cells with progenitor features can transform into functional hepatocytes, such mesenchymal cells may contribute to liver cell replacement in regeneration (Hang and Xia 2014). There is also evidence that HSCs and myofibroblastic cells can contribute to the production of progenitor cells (Kordes et al. 2014; Swiderska-Syn et al. 2014).

Immune Effector Cells

Whereas the kinetics of the four major cell types listed above are well known in liver regeneration, less information is available concerning blood vessel regeneration and the reconstitution of cells mediating hepatic innate immunity, i.e., natural killer cells/Pit cells and other immune effector cells. Cytokines and chemokines released by immune and inflammatory cells of the hepatic microenvironment can modulate parenchymal regeneration (Budhu and Wang 2006; Dong et al. 2007; Bishayee 2014). Interleukin-17 produced by gamma-delta T cells promotes hepatic

regeneration in a dectin-1-dependent manner (Rao et al. 2014). IL-17 also activates HSCs, which hold a central place in liver regeneration, promotes growth of liver cancer (Ma et al. 2014), and facilitates growth of liver cancer through recruitment of myeloid-derived suppressor cells (Hammerich and Tacke 2014). Elements of the local immune effector cell system secrete other pro-inflammatory cytokines that are important for liver regeneration. Expression of fibroblast growth factor-inducible 14 (Fn14), the receptor for TNF-like weak inducer of apoptosis (TWEAK), is induced early in liver regeneration and remains high throughout the expansion phase (Karaca et al. 2014). This factor is also involved in growth of HCCs (Li et al. 2013a). Adiponectin produced in the hepatic microenvironment is required for an efficient early cytokine response to hepatocyte loss, but is inhibitory to later growth factor actions, suggesting the adiponectin fine-tunes the progression of liver regeneration via modulation of signaling networks (Correnti et al. 2015). Cytokines produced by cells of the inflammatory niche also modulate the function of progenitor cells in the regenerating liver (Lowes et al. 2003; Strick-Marchand et al. 2008). Myeloid-derived suppressor cells are induced from circulating monocytes by activated HSCs in a CD44-dependent manner (Hoechst et al. 2013) and are expanded by HGF/c-Met derived from multipotent human mesenchymal stromal cells (Yen et al. 2013). On the other hand, natural killer cells of the liver can negatively regulate hepatic regeneration (Sun and Gao 2004). NK-mediated overactivation of innate immunity has to be blunted in regeneration in order to reduce its harmful effects. A coinhibitory receptor, T cell Ig and ITIM domain/TIGIT, safeguards liver regeneration via negatively regulating NK cell-hepatocyte cross talk (Bi et al. 2014). In patients with hepatocellular carcinoma, the natural killer response is disarmed by the action of myeloid-derived suppressor cells (Hoechst et al. 2009). The production and secretion of cytokines and chemokines by hepatic immune cells is modulated by factors involved in the regulation of hepatocyte and HCC cell proliferation. Augmenter of liver regeneration (ALR, hepatopoietin; see below) reduces activity of resident NK cells (Tanigawa et al. 2000) and induces a reduction of interferon-gamma in liver-resident NK cells and thus abolishes the inhibitory effects of interferon on hepatocyte regeneration (Polimeno et al. 2000).

The innate immune system of the liver and its effects on liver regeneration are markedly influenced by procedures related to the induction of hepatic regeneration, above all various surgical interventions. Laparotomy/open surgery results in suppression of the Th1 lymphocyte population and enhances the release of cytokines by macrophages. In contrast to laparoscopical surgery, open full laparotomy in a rat model was associated with increased function of peritoneal macrophages and enhanced TNF-alpha production (Lee et al. 2003). Laparoscopy and the associated CO2 pneumoperitoneum affect the function of peritoneal macrophages, with evidence of suppressed macrophage function and reduced secretion of TNF-alpha (Carter and Whelan 2001; Ost et al. 2008).

Effect of Liver Regeneration on Malignant Hepatic Tumors

Primary and metastatic malignancies of the liver develop and grow in normal liver; liver with fatty, other metabolic, or inflammatory changes; or in cirrhotic livers. The presence of a normal liver or a preexistent liver disease significantly affects growth patterns and fates of malignant neoplasms. The different growth mode of metastatic tumors in fatty or cirrhotic livers is discussed in the respective chapter on metastatic liver disease. A specific situation occurs for recurrent liver tumors that emerge in livers post resection with ongoing liver regeneration. Cellular and molecular changes taking place after surgical resection can result in a complex alteration of tumor growth and tumor cell kinetics. Generally, the surge of growth factors, cytokines, chemokines, angiogenic factors, and signaling pathways that are central to liver regeneration can affect growth of tumors (de Jong et al. 1996; Christophi et al. 2008). Liver regeneration following hepatic resection can facilitate tumor growth and activate metastases (Takita et al. 1966; Mizutani et al. 1992; Ikeda

et al. 1995; Harun et al. 2007; Paschos and Bird 2010; Shi et al. 2011; Shi and Line 2014) and can provide a novel microenvironment that may favor the homing of circulating tumor cells. Hepatic resection followed by regeneration is associated with upregulation of cyclin D1, VEGF, and VEGFRs affecting tumor growth (Shi et al. 2011). Activation of the renin-angiotensin system in the regenerating liver can stimulate hepatic tumor growth and recurrence (review: Koh et al. 2010). In murine models, upregulation of c-Met following partial hepatectomy enhanced the yield of hepatic metastases following tumor cell injection (Harun et al. 2014). In addition to the promotion of HCC recurrence, liver regeneration may also favor the development and growth of hepatic metastasis, but such an effect was not found in all animal experimentations (Panis et al. 1990). Liver regeneration and the associated remodeling of parenchyma may favor the homing of circulating tumor cells and/or the activation of dormant tumor cells that had already settled in the pre-metastatic niches of the liver before emergence of regeneration (Paschos and Bird 2010). Following partial hepatectomy, cells of the hepatic microenvironment secrete macrophage inflammatory protein-2 (MIP-2) which contributes to regeneration-induced acceleration of hepatic metastatic tumor growth. MIP-2 stimulates the process of engraftment, but not metastatic growth as such (Kollmar et al. 2006, 2008). Major liver resection and subsequent regenerative responses stimulate stromal cells in the liver and promote the emergence of metastases, in part through the action of upregulated TGF-beta (Momiyama et al. 2012). As important effectors of proliferative signals, cancer-associated fibroblasts (CAFs) modulate the regenerative response of hepatocytes located in peritumoral parenchyma (Cesselli et al. 2011). Liver regeneration following experimental partial hepatectomy also positively affected the yield of lung metastasis after injection of cancer cells, through a so far unknown mechanism (Ikeda et al. 1995). Furthermore, liver regeneration per se promotes accelerated hepatocarcinogenesis through chronic inflammation-induced double-strand DNA breaks (Barash et al. 2010).

Morphology of Proliferating Liver Cancer Cells

Liver cancer cells (HCCs and cholangiocarcinomas) in proliferation show an increased rate of mitotic figures, expressed as mitotic index (MI) (mitoses per N high-power fields). The MI of HCCs varies considerably among different tumors and is, also in G4 tumors, usually lower than many other poorly differentiated carcinomas, e.g., small cell carcinomas. MI correlates with survival in patients with HCC (Chapel et al. 1996). But also nuclear features in interphase cells suggest growth activity, e.g., increased nuclear size and large nucleoli indicating protein synthesis. In HCCs, the nuclear area correlates with cell differentiation and proliferative activity. Subjectively, one may obtain the impression that G3 and G4 HCCs possess smaller nuclei in comparison with better differentiated tumors, but this is flawed by the effects of increased nucleus/cytoplasm ratios. Morphometrically, the mean nuclear area of poorly differentiated HCCs was larger than that of moderately and well-differentiated tumors, and this increase was correlated with elevated proliferative activity (Ikeguchi et al. 1998). Ultrastructurally, HCC cells show persistence of nucleoli throughout all stages of cell division, and the Golgi apparatus retains its discrete entity of laminar and vesicular components during mitosis. Apparent penetration of RER into the mitotic apparatus is seen in metaphase and anaphase (Chang and Gibley 1968).

Cell Kinetics of Hepatocellular Carcinoma and Cholangiocarcinoma

There is a limited number of studies of the cell kinetics of human HCCs. The growth features of experimental HCCs have been studied by use of the assessment of incorporation of tritium-labeled thymidine (MacDonald 1961). In murine hepatoma models, the relative rate of DNA synthesis in individual tumor cells was about one half the relative rate in 21-h regenerating liver cells, and all of the tumors exhibited a H3-TdR-labeling

index between 9.6 and 12.9 (Chang et al. 1968). Tumor volume doubling time (TVDT) is an indicator of tumor growth rate and is associated with tumor biology in HCC. TVDTs in HCC are related to the differentiation grade. In one study, mean TVDTs in Edmondson grades 1–3 were 138.3, 94.9, and 32.2 days, respectively, whereby TVDT is correlated with AFP doubling times (Shingaki et al. 2013). Proliferative activity and tumor doubling times of HCCs were correlated with survival for patients with HCC treated with hepatectomy or in combination with systemic chemotherapy (Silvestrini et al. 1992).

Immunohistochemical Methods To Assess Cell Proliferation: Proliferating Cell Nuclear Antigen (PCNA)

Introduction

Proliferating cell nuclear antigen (PCNA) is a 36-kDa protein that serves as a regulator of the cell cycle. It is a cofactor of DNA polymerase delta in the S phase of cycle and is involved in DNA repair during DNA synthesis (Mozzherin et al. 1997; Prosperi 1997; Li et al. 2013b). A role of PCNA in DNA repair was also observed in HCC (Gramantieri et al. 2003). PCNA also promotes the activity of the DNA damage repair enzyme, DNA polymerase zeta (Garg et al. 2005). PCNA is differentially expressed in the cell cycle phases. It starts to accumulate in G1 to reach the highest expression level in the S phase, to decrease in G2/M. PCNA is a valuable antigen to immunohistochemically estimate the proliferative activity of neoplasms (determination of PCNA labeling index (LI), number of labeled nuclei per 100 nuclei analyzed), but has to be applied with certain cautions (Robbins et al. 1987; Hall et al. 1990; McCormick and Hall 1992). PCNA has, however, a rather slow turnover, leading to the effect that remaining immunoreactivity may persist in the next cycle, causing a potential interpretation artifact.

PCNA Labeling in Hepatocellular Carcinoma

PCNA labeling was detected in 57–100 % of HCCs (Kawakita et al. 1992; Nakopoulou et al. 1995; Shehata et al. 2006; Alenzi et al. 2010; Lai et al. 2014) and increases as a function of increasing tumor grade (Adachi et al. 1993; Ojanguren et al. 1993; Taniai et al. 1993; Wu and Tseng 1994; Suehiro et al. 1995; Hino et al. 1996, 1997), also in small HCCs, where high LIs were correlated with capsular and vascular invasion (Kitamoto et al. 1993). PCNA labeling also reflects higher tumor size (Osada et al. 2004) and the invasive phenotype of large HCCs (Ng et al. 1994), suggesting that proliferative activity exerts an influence on tumor cell invasion. In some studies, the PCNA LI was correlated with biology of disease in patients with HCC: The higher the PCNA LI, the worse the prognosis (Soini et al. 1996; Zeng et al. 2002), whereby tumors with a PCNA LI of less than 15 % had a better outcome (Nishimori et al. 1994). The PCNA LI increases along the hepatocarcinogenesis axis, being lower in nodular precursor lesions than in small HCCs and higher in malignant foci located in the interior of dysplastic nodules (Terada and Nakanuma 1992a; Zhao et al. 1994). PCNA LI in HCCs was positively correlated with increased numbers of tumor foci and advanced tumor invasiveness and stage (Shehata et al. 2006). The PCNA LI is, expectedly, also elevated in the regenerating liver, e.g., in viral hepatitis, whereby there was no difference in PCNA Li between HCV and HBV infections (Nakamura et al. 1993). A high PCNA Li is associated with upregulation of other proteins in HCCs, including the membrane traffic-related molecular alpha-taxilin (Ohtomo et al. 2010), the genomic stability maintenance protein growth arrest and DNA damage 45-alpha (GADD45-alpha) (Gramantieri et al. 2005), and PTEN (Hu et al. 2007). On the other hand, there are proteins that inhibit the function of PCNA, such as the CDK inhibitor, p21(Cip1/Waf1), which also modifies the interaction of PCNA

with other proteins (Oku et al. 1998; Tsurimoto 1999). Expression of the autophagy regulator Beclin-1 in HCC is associated with decreased PCNA labeling (Qiu et al. 2014). The PCNA-dependent DNA replication is mediated through a p21(Cip1)-like PCNA-binding motif in a subunit of DNA polymerase delta (Ducoux et al. 2001).

PCNA Labeling in Cholangiocarcinomas

PCNA is expressed in most or all cholangiocarcinomas, albeit with variable labeling indices (Ohashi et al. 1994; Terada and Nakanuma 1996; Rijken et al. 1998; Batheja et al. 2000). Similar to other neoplasms, proliferative activity is higher in cholangiocarcinomas with lower differentiation. Whereas well-differentiated cholangiocarcinomas showed a mean PCNA LI of 10.8 %, moderately or poorly differentiated tumors exhibited an index of 24.0 % and 26.0 %, respectively. The anatomical location of tumors along the biliary tree had no relation to the PCNA LI (Minato and Nakanuma 1993). The PCNA LI increases from hyperplastic lesions of intrahepatic bile ducts to dysplasia, to adenocarcinoma in situ (Terada and Nakanuma 1992b), a phenomenon also observed in surface epithelium and glands of stone-containing bile ducts (Lee and Sheen 1999), suggesting a gradual increase in proliferation as a function of the carcinogenic pathway. This is also reflected by the expression patterns of interphase nucleolar organizer regions (AgNORs) (Terada et al. 1992b). The number of AgNORs per nucleus of intrahepatic cholangiocarcinoma was related to tumor size and differentiation (Hayashi et al. 1995). The PCNA LI in intrahepatic cholangiocarcinoma varies as a function of the gross growth pattern. PCNA LI was significantly higher in periductal extension and spicula-forming tumor types than in the mass-forming type (Ohashi et al. 1994). In ampullary carcinomas, the rate of PCNA positivity correlated with tumor size (Crucitti et al. 1999).

Immunohistochemical Methods To Assess Cell Proliferation: Ki-67 Antigen

Introduction

The Ki-67 protein (also known as MKI67) is a cellular marker for cell proliferation (Gerdes et al. 1983). During interphase, Ki-67 protein is present in the nuclear matrix and is located to the nucleolus, whereas it is relocated to chromosomal surfaces during mitosis. In the cell division cycle, Ki-67 is present in all cycle phases (G1, S, G2, M), but it is not detectable in the G0 phase (Scholzen and Gerdes 2000). The protein is required for the assembly of the perichromosomal layer and is a cell cycle-regulated, protein phosphatase-1 binding protein that is involved in phospho-regulation of the nucleolar protein, nucleophosmin, and other proteins that are necessary for the construction of the mitotic chromosome periphery (Booth et al. 2014). The perichromosomal layer (synonyms: perichromosomal sheath, chromosomal coat, chromosome surface domain) is a distinct specialized chromosome domain involved in synthesis of messenger RNA, ribosome assembly, repair of DNA double-strand breaks, telomere maintenance, and apoptosis regulation (Van Hooser et al. 2005). Ki-67 contributes to the recruitment of protein phosphatase 1gamma to the perichromosomal layer of anaphase chromosomes (Takagi et al. 2014) and contributes to chromatin compaction (Kametaka et al. 2002). A Ki-67 antigen-related perichromosomal protein implicated in higher-order chromatin structure is chmadrin (Takagi et al. 1999). In proliferating and quiescent cells, the Ki-67 protein is associated with ribosomal RNA and regulates its transcription (Bullwinkel et al. 2006). The original Ki-67 antibody and the monoclonal antibody MIB-1 are directed against different epitopes of the same antigen and detect the Ki-67 antigen in normal and neoplastic replicating cells, also in HCCs and cholangiocarcinomas (Gerdes et al. 1983; Ng 1998).

Ki-67 Labeling in Hepatocellular Carcinoma

The Ki-67/MIB-1 proliferation index in HCC varies considerably and ranged from 15 % to 50 % (Grigioni et al. 1989). The number of MIB-1-positive cells in HCC correlates with the total mean number of nucleolar organizer regions (AgNORs) (Nagao et al. 1995). Similar to PCNA, Ki-67 expression is correlated with HCC grade (Ng et al. 1995; Kalogeraki et al. 2002; Witjes et al. 2013). Even well-differentiated HCCs display higher MIB1 indices than dysplastic nodules/adenomatous hyperplasia (Than et al. 1995), and there is a gradual increase of Ki-67 labeling from regenerative nodules to HCCs (Quaglia et al. 2006). The MIB-1 LI was elevated in HCCs and was found to be significantly higher in poorly differentiated tumors than in well-differentiated ones and was also higher in nonencapsulated tumors, but was not correlated with invasiveness (Ng et al. 1995), in contrast to PCNA labeling (see above). High Ki-67 labeling in HCCs is correlated with overexpression of an important regulator of cell cycle, centromere protein A (CENP-A) (Li et al. 2011). Elevated Ki-67 indices reflect more aggressive disease and poor prognosis (Colleoni et al. 1995). The regulation of Ki-67 in HCC cells is not yet well understood. A regulator of HCC growth and invasion, myocyte enhancer factor 2C, interacts with Ki-67 (Bai et al. 2014).

Ki-67 Labeling in Cholangiocarcinomas

Generally, cholangiocarcinomas show higher Ki-67 labeling indexes than well- to moderately differentiated HCCs. Specifically sarcomatoid components in cholangiocarcinomas exhibit a high proliferative activity that may exceed 40 % (Settakorn et al. 2005; Aishima et al. 2006; Iguchi et al. 2009). Also in combined hepatocellular-cholangiocarcinomas, the Ki-67 LI is lower in the HCC component than in the cholangiocarcinoma component (Wakasa et al. 2007). In extrahepatic cholangiocarcinomas, MIB-1 and/or AgNOR levels were associated with more aggressive disease, lymph node metastases, and poorer survival (Yamada et al. 1995; Shrestha et al. 1998; Suto et al. 1998; Murakami et al. 2003). In hilar cholangiocarcinoma, Ki-67 expression increased with stage of disease and invasion of cancer cells (Zhao et al. 2014). In patients with distal cholangiocarcinoma, a significant correlation was found between a low MIB-1 index and survival (Rijken et al. 1998). In intrahepatic cholangiocarcinomas, the Ki-67 LO correlated with overexpression of MDM2, an oncoprotein that binds to Tp53 and inhibits p53-mediated transactivation (Horie et al. 2000). The Ki-67/MIB-1 labeling index was a powerful prognostic factor in ampullary carcinoma (Shyr et al. 1999), and elevated Ki-67 levels may serve to distinguish ampullary adenomas from carcinomas (Kubota et al. 2013).

Assessment of Proliferative Activity in Liver Cancer: Additional Parameters

S-phase cells of HCCs can be assessed by in situ hybridization for histone 3 mRNA. Histone 3 accumulates in the cytoplasm during S phase and then decreases as cells approach G2. The histone H3 labeling index is elevated in HCCs and correlates with other proliferation markers, including PCNA and Ki-67/MIB1 (Nagao et al. 1996). The MIB1 LI is correlated with the number of nucleolar organizing regions (AgNORs) (Nagao et al. 1995). PRO2000/ANCCA is a candidate gene located within a region of chromosome 8q in HCC, and its expression was found in a high proportion of HCCs, more in poorly differentiated ones, and correlated with the Ki-67 index. Its expression was correlated with number of tumor nodules, TNM stage, portal vein invasion, and recurrence, suggesting a role as prognosticator (Yang et al. 2014a).

Initiation of Cell Cycle and Replication Control in Liver Cancer

Control of DNA Replication Initiation in Normal and Liver Cancer Cells

It is very important that only one DNA replicative round occurs per cell division cycle to avoid aneuploidy and genomic instability, alterations that often occur in cancers, including liver cancers. This control step, DNA licensing, is executed by the nuclear protein, geminin. Geminin is a substrate of the anaphase-promoting complex (APC/C). From the S phase of the cycle to the end of mitosis, geminin inhibits the replication factor Cdt1, which promotes assembly of the prereplication license complex, thus preventing the assembly of this complex. In G1, the APC/C mediates degradation of geminin via ubiquitination. By this machinery, the geminin-Cdt1 system guarantees a mono-round replication. This platform is linked to proteins that load helicase onto DNA, the MCM (minichromosome) maintenance helicases (see below). In the prereplication license complex, Cdt1 cooperates with the cell cycle protein Cdc6 to promote loading of MCMs onto the chromatin-bound origin recognition complex (ORC) via chromatin unfolding, to initiate DNA replication. In contrast, geminin prevents loading of MCM onto ORC by binding to Cdt1 and modulating its activity and stability. Geminin availability is itself regulated by its partner molecules, the Idas, whereby heterodimeric geminin-Ida complexes inhibit geminin function (reviews: Caillat and Perrakis 2012; Caillat et al. 2013). A central step in DNA replication initiation is the loading of replicative helicase at DNA replication origins to form a replicative fork. The loading causes each replication origin to be unwound and assembles functional bidirectional replisomes just once in each cell cycle. This step must be tightly regulated, as its failure will result in DNA damage and genomic instability, as in many cancers. The principal helicase loader is the MCM2-7 ATPase system, forming a hexameric ring. This ring forms the core of the DNA helicase and is first loaded at replication origins in an inactive form. ORC, Cdc6, and Cdt1 assemble two MCM2-7 hexamers into one double hexamer around dsDNA. This ring loading occurs through a DNA entry gate comprised of the MCM2 and MCM5 subunits. The helicase is activated by formation of a holo-helicase complex containing MCM2-7, Cdc45, and GINS proteins (Boos et al. 2012; Kang et al. 2014; Samel et al. 2014).

Geminin shows distinct expression patterns in HCC (Quaglia et al. 2006). Specifically, geminin is frequently amplified in these cancers and functionally linked with cyclin-dependent kinase 13 (Cdc13) (Kim et al. 2012). Although geminin is a negative regulator of DNA replication, its expression in HCCs reflects growth patterns, in that geminin-negative tumors represent resting tumors, while geminin-positive tumors are slowly growing or expanding lesions (Quaglia et al. 2006). Overexpression of MCM2 in HCCs characterizes tumors with poor differentiation (Sun et al. 2010), while MCM-negative tumors are resting lesions (Quaglia et al. 2006).

G1/S Transition Checkpoint and Mitosis Checkpoint Controls in Cancer Cells

The entry of cycling cells into cell cycle and cell division is controlled by checkpoint proteins acting at the G1/S transition. This checkpoint control, together with replication initiation control discussed above, is one of the major mechanisms to regulate cell cycle entry and progression. The most important factors controlling this checkpoint are several forms of checkpoint kinases and associated regulatory proteins. Checkpoint kinase 1 (CHK1) is an enzyme that is essential for preventing mitosis in response to DNA damage and functions as a mitogen-dependent protein kinase that suppresses p21 and p57, but not p27, activation (Ullah et al. 2011). Following checkpoint recovery upon completion of DNA repair

after DNA damage, Greatwall and Polo-like kinase 1 coordinate to promote checkpoint recovery (Peng et al. 2011). Polo-like kinase 1 (Plk1) is a member of the serine/threonine kinases as it represents the mammalian counterpart of *Drosophila* polo. Plk1 has a central role in the biogenesis of the mitotic spindle and chromosome segregation and in DNA damage repair (van Vugt and Medema 2005). Plk1 is recruited to centrosomes, kinetochores, and the spindle midzone and is critically involved in the initiation and progression of cytokinesis (Petronczki et al. 2008; Burkard et al. 2009). Plk1 is expressed in the nuclei of proliferating cells, but immunoreactivity disappears in the course of cell differentiation (Yuan et al. 1997).

After G1/S checkpoint control, control of mitosis entry is a second major regulatory machinery. Control of mitosis entry critically involves cyclin-dependent kinase 1, a mitotic driver enzyme involved in the ordered phosphorylation of numerous proteins required for cell division. The phosphorylated status of these proteins is maintained all through mitosis, but has to be abolished at mitotic exit through phosphatic dephosphorylation to become ready for a next cycle round. This is accomplished by protein phosphatase 2A (PP2A), which in turn is negatively regulated by the kinase Greatwall that phosphorylates the protein ARPP-19 and converts it into a potent phosphatase 2A inhibitor (Haccard and Jessus 2011; Wang et al. 2014a). Greatwall kinase is a serine/threonine kinase of the AGC family that is essential for the promotion of correct mitosis timing, having Endos as a substrate (Burgess et al. 2010; Rangone et al. 2011; Vigneron et al. 2011). PP2A-mediated dephosphorylation of Akt to repress mTORC1 signaling is enhanced by REDD1 regulated in DNA damage and development 1 (Dennis et al. 2014). An intracellular inhibitor of protein phosphatase 2A is cancerous inhibitor of PP2A (CIP2A), a target of bortezomib, which regulates cell proliferation via the Akt-mTOR signaling pathway (De et al. 2014; Lei et al. 2014). Inhibition of CIP2A by erlotinib reactivates PPA2 (Yu et al. 2014a). PP2A and CIP2A play a role in carcinogenic pathways. PP2A promotes hepatic carcinogenesis in a mouse model through inhibition of p53 (Duong et al. 2014). The hepatocarcinogenic HCV virus induces upregulation of PP2A associated with dysregulation of histone modifications (Duong et al. 2010). CIP2A is highly expressed in HCC and predicts poor prognosis (He et al. 2012; Huang et al. 2012).

Role of Cell Ploidy in Normal and Cancer Cells: Protection from Replicative Overshoot

Polyploidy, a situation characterized by an increase in the number of chromosomes sets, is a widely distributed phenomenon in nature, but is not a common feature in higher vertebrate cells. In humans, polyploidy usually results from a diploid-polyploid conversion whereby additional sets of chromosomes originate from the same individual (autopolyploidy). In the adult liver, progressive polyploidization takes place physiologically in the postnatal period. Tetraploid binucleated hepatocytes emerge upon stimulation with insulin signaling via PI3K/Akt signaling pathways, and hepatocyte polyploidization generally reflects terminal differentiation and senescence, associated with increased autofluorescence, accumulation of lipofuscin, loss of replicative capacity and regenerative power, and an increased apoptotic rate (reviews: Sigal et al. 1999; Gupta 2000; Gentric et al. 2012a, b; Gentric and Desdouets 2014). The generation of polyploid hepatocytes is a complex process that occurs not only physiologically but also in situations of so-called replicative stress responses. The latter can ensue under excessive proliferation stimuli leading to cell restriction and/or apoptosis. This is an important counterregulation mechanism that protects tissues and organs from replicative overshoot, but is thought to be bypassed in cancer. A repressor of replicative stress responses is the COP9 signalosome, a regulator of cullin-ring ligases, important members of ubiquitin ligases. Inactivation of this signalosome in the liver results in the activation of S- and G2-phase checkpoints, irreversible cell cycle arrest, polyploidization, and cell death (Panattoni et al. 2014). Polyploid cells

in primary HCC exhibit a reduced proliferative activity (Gerlyng et al. 1992).

References

Abshagen K, Eipel C, Kalff JC, Menger MD, Vollmar B (2008) Kupffer cells are mandatory for adequate liver regeneration by mediating hyperperfusion via modulation of vasoactive proteins. Microcirculating 15:37–47

Adachi E, Hashimoto H, Tsuneyoshi M (1993) Proliferating cell nuclear antigen in hepatocellular carcinoma and small cell liver dysplasia. Cancer 72:2902–2909

Aishima S, Kuroda Y, Asayama Y, Taguchi K, Nishihara Y, Taketomi A, Tsuneyoshi M (2006) Prognostic impact of cholangiocellular and sarcomatous components in combined hepatocellular cholangiocarcinoma. Hum Pathol 37:283–291

Aldeguer X, Debonera F, Shaked A, Krasinkas AM, Gelman AE, Que X, Zamir GA, Hiroyasu S, Kovalovich KK et al (2002) Interleukin-6 from intrahepatic cells of bone marrow origin is required for normal murine liver regeneration. Hepatology 35:40–48

Alenzi GFQ, El-Nashar EM, Al-Ghamdi SS, Abbas MY, Hamad AM, El-Saeed OM et al (2010) Investigation of Bcl-2 and PCNA in hepatocellular carcinoma: relation to chronic HCV. J Egypt Natl Cancer Inst 22:87–94

Alison MR, Lin WR (2011) Hepatocyte turnover and regeneration: virtually a virtuoso performance. Hepatology 53:1393–1396

Alvaro D, Mancino MG, Glaser S, Gaudio E, Marzioni M, Francis H, Alpini G (2007) Proliferating cholangiocytes: a neuroendocrine compartment in the diseased liver. Gastroenterology 132:415–431

Anderson SP, Yoon L, Richard EB, Dunn CS, Cattley RC, Corton JC (2002) Delayed liver regeneration in peroxisome proliferator-activated receptor-alpha-null mice. Hepatology 36:544–554

Antoine M, Tag CG, Gressner AM, Hellerbrand C, Kiefer P (2009) Expression of E-selectin ligand-1 (CFR/ESL-1) on hepatic stellate cells: implications for leukocyte extravasation and liver metastasis. Oncol Rep 21:357–362

Bai XL, Hang Q, Ye LY, Liang F, Sun X, Chen Y, Hu QD, Fu QH, Su W, Chen Z, Zhuang ZP, Liang TB (2014) Myocyte enhancer factor 2C regulation of hepatocellular carcinoma via vascuar endothelial growth factor and Wnt/β-catenin signaling. Oncogene.doi:10.1038/onc.2014.337

Baier PK, Baumgartner U, Hempel S, Wolff-Vorbeck G, von Dobschuetz E, Hopt UT (2005) Kupffer cells infiltrate liver tissue early after ischemia-reperfusion and partial hepatectomy. Eur Surg Res 37:290–297

Barash H, Gross E, Edrei Y, Ella E, Israel A, Cohen I, Corchia N, Ben-Moshe T, Pappo O, Pikarsky E, Goldenberg D et al (2010) Accelerated carcinogenesis following liver regeneration is associated with chronic inflammation-induced double-strand DNA strand breaks. Proc Natl Acad Sci U S A 107:2207–2212

Batheja N, Suriawinata A, Saxena R, Ionescu G, Schwartz M, Thung SN (2000) Expression of p53 and PCNA in cholangiocarcinoma and primary sclerosing cholangitis. Mod Pathol 13:1265–1268

Behari J, Li H, Liu S, Stedanovic-Racic M, Alonso L, O'Donnell CP, Shiva S, Singamsetty S, Watanabe Y, Singh VP et al (2014) β-catenin links hepatic metabolic zonation eith lipid metabolism and diet-induced obesity in mice. Am J Pathol 184:3284–3298

Berasain C, Avila MA (2014) Deciphering liver zonation: new insights into the β-catenin, Tcf4, and HNF4α triad. Hepatology 59:2080–2082

Best et al. 2015. http://www.ncbi.nlm.nih.gov/pubmed/25713804

Bi J, Zheng X, Chen Y, Wei H, Sun R, Tian Z (2014) TIGIT safeguards liver regeneration through regulating natural killer cell-hepatocyte crosstalk. Hepatology 60:1389–1398

Bird et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23576749

Bishayee A (2014) The role of inflammation and liver cancer. Adv Exp Med Biol 816:401–435

Boos D, Frigola J, Diffley JF (2012) Activation of the replicative DNA helicase: breaking up is hard to do. Curr Opin Cell Biol 24:423–430

Booth DG, Takagi M, Sanchez-Pulido L, Petfalski E, Vargiu G, Samejima K, Imamoto N, Ponting CP, Tollervey D et al (2014) Ki-67 is a PP1-interacting protein that organises the mitotic chromosome periphery. Elife 3:e01641

Bouwens L, Baekeland M, Wisse E (1986) Cytokinetic analyses of the expanding Kupffer-cell population in rat liver. Cell Tissue Kinet 19:217–226

Budhu A, Wang XW (2006) The role of cytokines in hepatocellular carcinoma. J Leukoc Biol 80:1197–1213

Bullwinkel J, Baron-Lühr B, Lüdemann A, Wohleberg C, Gerdes J, Scholzen T (2006) Ki-67 protein is associated with ribosomal RNA transcription in quiescent and proliferating cells. J Cell Physiol 206:624–635

Burgess A, Vigneron S, Brioudes E, Labbé JC, Lorca T, Castro A (2010) Loss of human Greatwall results in G2 arrest and multiple mitotic defects due to deregulation of the cyclin B-Cdc2/PP2A balance. Proc Natl Acad Sci U S A 107:12564–12569

Burkard et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19468302

Cabrita MA, Christofori G (2008) Sprouty proteins, masterminds of receptor tyrosine kinase signaling. Angiogenesis 11:53–62

Caillat C, Perrakis A (2012) Cdt1 and geminin in DNA replication initiation. Subcell Biochem 62:71–87

Caillat C, Pefani DE, Gillespie PJ, Taraviras S, Blo JJ, Lygerou Z, Perrakis A (2013) The geminin and Idas coiled coils preferentially form a heterodimer that inhibits Geminin function in DNA replication licensing. J Biol Chem 288:31624–31634

Cardinale V, Wang Y, Carpino G, Alvaro D, Reid L, Gaudio E (2010) Multipotent stem cells in the biliary tree. Ital J Anat Embryol 115:85–90

Cardinale V, Wang Y, Carpino G, Cui CB, Gatto M, Rossi M, Berloco PB, Cantefore A, Wauthier E, Furth ME, Inverardi L et al (2011) Multipotent stem/progenitor cells in human biliary tree give rise to hepatocytes, cholangiocytes, and pancreatic islets. Hepatology 54:2159–2172

Cardinale V, Wang Y, Carpino G, Mendel G, Alpini G, Gaudio E, Reid LM, Alvaro D (2012) The biliary tree – a reservoir of multipotent stem cells. Nat Rev Gastroenterol Hepatol 9:231–240

Carpino G, Cardinale V, Onori P, Franchitto A, Berloco PB, Rossi M, Wang Y, Semeraro R, Anceschi M, Brunelli R et al (2012) Biliary tree stem/progenitor cells in glands of extrahepatic and intrahepatic bile ducts : an anatomical in situ study yielding evidence of maturational lineages. J Anat 220:186–199

Carter JJ, Whelan RL (2001) The immunologic consequences of laparoscopy in oncology. Surg Oncol Clin N Am 10:655–677

Cesselli D, Beltrami AP, Poz A, Marzinotto S, Comisso E, Bergamin N, Bourkoula E, Pucer A, Puppato E, Toffoletto B et al (2011) Role of tumor associated fibroblasts in human liver regeneration, cirrhosis, and cancer. Int J Hepatol. 2011. art. ID 120925

Chang JP, Gibley CW (1968) Ultrastructure of tumor cells during mitosis. Cancer Res 28:521–534

Chang LO, Morris HP, Looney WB (1968) Rates of incorporation of tritium-labeled thymidine into the mitochondrial and nuclear DNA of normal rat liver, regenerating liver, and four hepatomas with different growth rates and their host livers. Br J Cancer 22:860–866

Chapel F, Guettier C, Chastang C, Rached AA, Mathieu D, Tepper M, Beaugrand M et al (1996) Needle biopsy of hepatocellular carcinoma: assessment of prognostic contribution of histologic parameters including proliferating cell nuclear antigen labeling and correlations with clinical outcomes. Group d'Etude Traitement Carcinoma Hépatocellulaire Cancer 77:864–871

Chaveles I, Zaravinos A, Habeos IG, Karavias DD, Maroulis I, Spandidos DA, Karavias D (2012) MicroRNA profiling in murine liver after partial hepatectomy. Int J Mol Med 29:747–755

Chazaud B (2014) Macrophages: supportive cells for tissue repair and regeneration. Immunobiology 219:172–178

Chen Y, Verfaillie CM (2014) MicroRNAs: the fine modulators of liver development and function. Liver Int 34:976–990

Chen H, Sun Y, Dong R, Yang S, Pan C, Xiang D, Miao M, Jiao B (2011) Mir-34a is upregulated during liver regeneration in rats and is associated with the suppression of hepatocyte proliferation. PLoS One 6:e20238

Chiu et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17628501

Christophi C, Harun N, Fifis T (2008) Liver regeneration and tumor stimulation – a review of cytokine and angiogenic factors. J Gastrointest Surg 12: 966–980

Colleoni M, Biasin MR, Boni L, Nelli P, Manente P, Gaion F, Perasole A, Infantolino D (1995) Evaluation of Ki-67 expression as a prognostic feature in hepatocellular carcinoma in cirrhosis. Eur J Cancer 31A:1547–1548

Colletti M, Cicchini C, Conigliaro A, Santangelo L, Alonzi T, Pasquini E, Tripodi M, Amicone L (2009) Convergence of Wnt signaling on the HNF4alpha-driven transcription in controlling liver zonation. Gastroenterology 137:660–672

Columbano A, Shinozuka H (1996) Liver regeneration versus direct hyperplasia. FASEB J 10:1118–1128

Correnti JM, Cook D, Aksamitiene E, Swarup A, Ogunnaike B, Vadigepalli R, Hoek JB (2015) Adiponectin fine-tuning of liver regeneration dynamics revealed through cellular network modelling. J Physiol 593:365–383

Crofton RW, Diesselhoff-den Dulk MM, van Furth R (1978) The origin, kinetics, and characteristics of the Kupffer cells in the normal steady state. J Exp Med 148:1–17

Crucitti A, Masettii R, Breccia C, Coppola R, Magistrelli P, Nuzzo G, Maggiano N, Picciocchi A (1999) Ampullary carcinoma: prognostic significance of ploidy, cell-cycle analysis and proliferating cell nuclear antigen (PCNA). Hepatogastroenterology 46:1187–1191

Date M, Matsuzaki K, Matsushita M, Tahashi Y, Sakitani K, Inoue K (2000) Differential regulation of activin A for hepatocyte growth and fibronectin synthesis in rat liver injury. J Hepatol 32:251–260

De Jong KP, Slooff MJ, de Vries EG, Brouwers MA, Terpstra OT (1996) Effect of partial liver rescetion on tumour growth. J Hepatol 25:109–121

De P, Carlson J, Leyland-Jones B, Dey N (2014) Oncogenic nexus of cancerous inhibitor of protein phosphatase 2A (CIP2A): an oncoprotein with many hands. Oncotarget 5:4581–4602

DeLeve LD (2013) Liver sinusoidal endothelial cells and liver regeneration. J Clin Invest 123:1861–1866

Dennis MD, Coleman CS, Berg A, Jefferson LS, Kimball SR (2014) REDD1 enhances protein phosphatase 2A-mediated dephosphorylation of Akt to repress mTORC1 signaling. Sci Signal 7:ra68

Ding BS, Nolan DJ, Butler JM, James D, Babazadeh AO, Rosenwaks Z, Mittal V, Kobayashi H, Shido K, Lyden D et al (2010) Inductive angiocrine signals from sinusoidal endothelium are required for liver regeneration. Nature 468:310–315

Ding BS, Cao Z, Lis R, Nolan DJ, Guo P, Simons M, Penfold ME, Shido K, Rabbany SY, Rafli S (2014) Divergent angiocrine signals from vascular niche balance liver regeneration and fibrosis. Nature 505:97–102

Do N, Zhao R, Ray K, Ho K, Dib M, Ren X, Kuzontkoski P, Terwilliger E, Karp SJ (2012) BMP4

is a novel paracrine inhibitor of liver regeneration. Am J Physiol Gastrointest Liver Physiol 303: G1220–G1227

Dong Z, Wei H, Sun R, Tian Z (2007) The roles of innate immune cells in liver injury and regeneration. Cell Mol Immunol 4:241–252

Ducoux M, Urbach S, Baldacci G, Hübscher U, Koundriokoff S, Christensen J, Hughes P (2001) Mediation of proliferating cell nuclear antigen (PCNA)-dependent DNA replication through a conserved p21 (Cip1)-like PCNA-binding motif present in the third subunit of human DNA polymerase delta. J Biol Chem 276:49258–49566

Duong FH, Christen V, Lin S, Heim MH (2010) Hepatitis C virus-induced up-regulation of protein phosphatase 2A inhibits histone modification and DNA damage repair. Hepatology 51:741–751

Duong FH, Dill MT, Matter MS, Makowska Z, Calabrese D, Dietsche T, Ketterer S et al (2014) Protein phosphatase 2A promotes hepatocellular carcinogenesis in the diethylnitrosamine mouse model through inhibition of p53. Carcinogenesis 35:114–122

Fabrikant JI (1968) The kinetics of cellular proliferation in regenerating liver. J Cell Biol 36:551–565

Fan M, Wang X, Xu G, Yan Q, Huang W (2015) Bile acid signaling and liver regeneration. Biochim Biophys Acta 1849:196–200

Fausto N (2000) Liver regeneration. J Hepatol 32:19–31

Fausto N, Campbell JS (2003) The role of hepatocytes and oval cells in liver regeneration and repopulation. Mech Dev 120:117–130

Fausto N, Webber EM (1993) Control of liver growth. Crit Rev Eukaryot Gene Expr 3:117–135

Fausto N, Laird AD, Webber EM (1995) Liver regeneration. 2. Role of growth factors and cytokines in hepatic regeneration. FASEB J 9:1527–1536

Finch ML, Marquardt JU, Yeoh GC, Callus BA (2014) Regulation of microRNAs and their role in liver development, regeneration and disease. Int J Biochem Cell Biol 54:288–303

Fleig WE (ed) (1998) Normal and malignant liver growth, International Falk Workshop. Martin-Luther-Universität, Halle

Fouraschen SM, Pan Q, de Ruiter PE, Farid WR, Kazemier G, Kwekkeboom J, Ijzermans JN, Metselaar HJ, Tilanus HW et al (2012) Secreted factors of human liver-derived mesenchymal stem cells promote liver regeneration early after partial hepatectomy. Stem Cells Dev 21:2410–2419

Fouraschen SM, Hall SR, de Jonge J, van der Laan LJ (2014) Support of hepatic regeneration by trophic factors from liver-derived mesenchymal stroma/stem cells. Methods Mol Biol 1213:89–104

Francavilla A, Ove P, Polimeno L, Coetzee M, Makowka L, Barone M, Van Thiel DH et al (1988) Regulation of liver size and regeneration: importance in liver transplantation. Transplant Proc 20:494–497

Fujiyoshi M, Ozaki M (2011) Molecular mechanisms of liver regeneration and protection for treatment of liver dysfunction and diseases. J Hepatobiliary Pancreat Sci 18:13–22

Gamble J, Vadas M, McCaughan G (2011) Sinusoidal endothelium is essential for liver regeneration. Hepatology 54:731–733

Garcia-Rodriguez JL, Barbier-Torres L, Fernandez-Alvarez-S, Gutierrez-de Juan V et al (2014) SIRT1 controls liver regeneraion by regulating bile acid metabolism through farnesoid X receptor and mammalian target of rapamycin signaling. Hepatology 59:1972–1983

Garcia-Ruiz C, Colell A, Mari M, Morales A, Calvo M, Enrich C, Fernandez-Checa JC (2003) Defective TNF-alpha-mediated hepatocellular apoptosis and liver damage in acidic sphingomyelinase knockout mice. J Clin Invest 11:197–208

Garg P, Stith CM, Majka J, Burgers PM (2005) Proliferating cell nuclear antigen promotes translesion synthesis by DNA polymerase zeta. J Biol Chem 280:23446–23450

Gebhardt R, Hovhannisyan A (2010) Organ patterning in the adult stage: the role of Wnt/beta-catenin signaling in liver zonation and beyond. Dev Dyn 239:45–55

Gentric G, Desdouets C (2014) Polyploidization in liver tissue. Am J Pathol 184:322–331

Gentric G, Desdouets C, Celton-Morizur S (2012a) Hepatocytes polyploidization and cell cell cycle control in liver physiopathology. Int J Hepatol 2012:282430

Gentric G, Celton-Morizur S, Desdouets C (2012b) Polyploidy and liver proliferation. Clin Res Hepatol Gastroenterol 36:29–34

Gerdes J, Schwab U, Lemke H, Stein H (1983) Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J Cancer 31:13–20

Gerlyng P, Grotmol T, Eristein B, Stokke T, Seglen PO (1992) Reduced proliferative activity of polyploid cells in primary hepatocellular carcinoma. Carcinogenesis 13:1795–1801

Gold EJ, Zhang X, Wheatley AM, Mellor SL, Cranfield M, Risbridger GP, Groome NP, Fleming JS (2005) betaA- and betaC-activin, follistatin, activin receptor mRNA and betaC-activin peptide expression during rat liver regeneration. J Mol Endocrinol 34:505–515

Gougelet A, Torre C, Veber P, Sartor C, Bachelot L, Denechaud PD, Godard C, Moldes M, Burnol AF, Dubuquoy C et al (2014) T-cell factor 4 and β-catenin chromatin occupancies pattern zonal liver metabolism in mice. Hepatology 59:2344–2357

Gramantieri L, Trerè D, Chieco P, Lacchni M, Giovannini C, Piscaglia F, Cavallari A et al (2003) In human hepatocellular carcinoma in cirrhosis proliferating cell nuclear antigen (PCNA) is involved in cell proliferation and cooperates with P21 in DNA repair. J Hepatol 39:997–1003

Gramantieri L, Chieco P, Giovannini C, Lacchini M, Treré D, Grazi GL, Venturi A, Bolondi L (2005) GADD45-alpha expression in cirrhosis and hepatocellular carcinoma: relationship with DNA repair and proliferation. Hum Pathol 36:1154–1162

Grigioni WF, D'Errico A, Bacci F, Gaudio M, Mazziotti A, Gozzetti G, Mancini AM (1989) Primary liver neoplasms: evaluation of proliferative index using MoAb Ki67. J Pathol 158:23–29

Gupta S (2000) Hepatic polyploidy and liver growth control. Semin Cancer Biol 10:161–171

Haccard O, Jessus C (2011) Greatwall kinase, ARPP-19 and protein phosphatase 2A: shifting the mitosis paradigm. Results Probl Cell Differ 53:219–234

Hall PA, Levison DA, Woods AL, Yu CC, Kellock DB, Watkins JA, Barnes DM et al (1990) Proliferating cell nuclear antigen (PCNA) immunolocalization in paraffin sections: an index of cell proliferation with evidence of deregulated expression in some neoplasma. J Pathol 162:285–294

Hammerich L, Tacke F (2014) Interleukins in chronic liver disease: lessons learned from experimental mouse models. Clin Exp Gastroenterol 7:297–306

Hang HL, Xia Q (2014) Role of BMSCs in liver regeneration and metastasis after hepatectomy. World J Gastroenterol J Gastroenterol 20:126–132

Haque S, Haruna Y, Saito K, Nalesnik MA, Atillasoy E, Thung SN, Gerber MA (1996) Identification of bipotential progenitor cells in human liver regeneration. Lab Invest 75:699–705

Harun N, Nikfarjam M, Muralidharan V, Christophi C (2007) Liver regeneration stimulates tumor metastases. J Surg Res 138:284–290

Harun N, Costa P, Christophi C (2014) Tumour growth stimulation following partial hepatectomy in mice is associated with increased upregulation of c-Met. Clin Exp Metastasis 31:1–14

Hattori T, Ohoka N, Hayashi H, Onozaki K (2003) C/EBP homologous protein (CHOP) up-regulates IL-6 transcription by trapping negative regulating NF-IL6 isoform. FEBS Lett 541:33–39

Hayashi H, Maeda T, Adachi E, Shimada M, Matsumata T, Takenaka K (1995) Argyrophilic nucleolar organizer regions (AgNOR) of resected intrahepatic cholangiocellular carcinomas. Hepatogastroenterology 42:440–444

He H, Wu G, Li W, Cao Y, Liu Y (2012) CIP2A is highly expressed in hepatocellular carcinoma and predicts poor prognosis. Diagn Mol Pathol 21:143–149

Hino N, Higashi T, Nouso K, Nakatsukasa H, Tsuji T (1996) Apoptosis and proliferation of human hepatocellular carcinoma. Liver 16:123–129

Hino N, Higashi T, Nouso K, Nakatsukasa H, Urabe Y, Kinugasa N, Yoshida K, Ashida K et al (1997) Proliferating cell nuclear antigen and grade of malignancy in small hepatocellular carcinoma – evaluation in US-guided specimens. Hepatogastroenterology 44:245–250

Hoechst B, Voigtlaender T, Ormandy L, Gamrekelashvili J, Zhao F, Wedemeyer H, Lehner F, Manns MP, Greten TF et al (2009) Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. Hepatology 50:799–807

Hoechst B, Schildberg FA, Sauerborn P, Gäbel YA, Gevensleben H, Goltz D, Heukamp LC, Türler A, Ballmaier M et al (2013) Activated human hepatic stellate cells induce myeloid derived suppressor cells from peripheral blood monocytes in a CD44-dependent fashion. J Hepatol 59:528–535

Hong L, Cai Y, Jiang M, Zhou D, Chen L (2015) The Hippo signaling pathway in liver regeneration and tumorigenesis. Acta Biochim Biophys Sin (Shanghai) 47:46–52

Horie S, Endo K, Kawasaki H, Terada T (2000) Overexpression of MDM2 protein in intrahepatic cholangiocarcinoma: relationship with p53 overexpression, Ki-67 labeling, and clinicopathological features. Virchows Arch 437:25–30

Hu TH, Wang CC, Huang CC, Chen CL, Hung CH, Chen CH, Wang JH, Lu SN et al (2007) Down-regulation of tumor suppressor gene PTEN, overexpression of p53, plus high proliferating cell nuclear antigen index predict poor patient outcome of hepatocellular carcinoma after resection. Oncol Rep 18:1417–1426

Hu J, Srivastava K, Wieland M, Runge A, Mogler C, Besemfelder E, Terhardt D, Vogel MJ et al (2014) Endothelial cell-derived angiopoietin-2 controls liver regeneration as a spatiotemporal rheostat. Science 343:416–419

Huang P, Qiu J, You J, Hong J, Li B, Zhou K, Chen G, Yuan Y, Zou R (2012) Expression and prognostic significance of CIP2A mRNA in hepatocellular carcinoma and nontumoral liver tissues. Biomarkers 17:422–429

Huch 2015. http://www.ncbi.nlm.nih.gov/pubmed/25567279

Huebert RC, Shah VH (2014) Sinusoidal endothelial cells direct traffic at the intersection of regeneration and fibrosis. Hepatology 60:754–756

Iguchi T, Yamashita N, Aishima S, Kuroda Y, Terashi T, Sugimachi K, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2009) A comprehensive analysis of immunohistochemical studies in intrahepatic cholangio-carcinoma using the survival tree model. Oncology 76:293–300

Iimuro Y, Seki E, Son G, Tsutsui H, Nakanishi K, Fujimoto J (2007) Role of innate immune response in liver regeneration. J Gastroenterol Hepatol 22(Suppl 1): S57–S58

Ikeda Y, Matsumata T, Takenaka K, Sasaki O, Soejima K, Sugimachi K (1995) Preliminary report of tumor metastasis during liver regeneration after hepatic resection in rats. Eur J Surg Oncol 21:188–190

Ikeguchi M, Sato N, Hirooka Y, Kaibara N (1998) Computerized nuclear morphometry of hepatocellular carcinoma and its relation to proliferative activity. J Surg Oncol 68:225–230

Issa R, Zhou X, Trim N, Millward-Sadler H, Krane S, Benyon C, Iredale J (2003) Mutation in collagen-1 that confers resistance to the action of collagenase results in failure of recovery from CCl4-induced liver fibrosis, persistence of activated hepatic stellate cells, and diminished hepatocyte regeneration. FASEB J 17:47–49

Itoh and Miyajima 2014. http://www.ncbi.nlm.nih.gov/pubmed/24115180

Jiao Y, Ye DZ, Li Z, Teta-Bissett M, Peng Y, Taub R, Greenbaum LE, Kaestner KH (2015) Protein tyrosine phosphatase of liver regeneration-1 is required for normal timing of cell cycle progression during liver regeneration. Am J Physiol Gastrointest Liver Physiol 308: G85–G91

Jin J, Hong IH, Lewis K, Iakova P, Breaux M, Jiang Y, Sullivan E, Jawanmardi N et al (2014) Cooperation of C/EBP family proteins and chromatin remodeling proteins is essential for termination of liver regeneration. Hepatology.doi:10.1002/hep.27295

Jin J, Hong IH, Lewis K, Iakova P, Breaux M, Jiang Y, Sulliva E, Jawanmardi N, Timchenko L, Timchenko NA (2015) Cooperation of C/EBP family proteins and chromatin remodeling proteins is essential for termination of liver regeneration. Hepatology 61:315–325

John K, Hadem J, Krech T, Wahl K, Manns MP, Dooley S, Batkai S, Thum T, Schulze-Osthoff K, Bantel H (2014) MicroRNAs play a role in spontaneous recovery from acute liver failure. Hepatology 60:1346–1355

Kalininchenko VV, Bhattacharyya D, Zhou Y, Gusarova GA, Kim W, Shin B, Costa RH (2003) Foxf1 +/- mice exhibit defective stellate cell activation and abnormal liver regeneration following CCl4 injury. Hepatology 37:107–117

Kalogeraki A, Garbagnati F, Santinami M, Zoras O (2002) DNA fragmentation and cell proliferation correlated with tumor grade in patients with hepatocellular carcinoma. Cancer 96:301–305

Kametaka et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/12485163

Kamiya and Inagaki 2015. http://www.ncbi.nlm.nih.gov/pubmed/24773763

Kang LI, Mars WM, Michalopoulos GK (2012) Signals and cells involved in regulating liver regeneration. Cells 1:1261–1292

Kang S, Warner MD, Bell SP (2014) Multiple functions for Mcm2-7 ATPase motifs during replication initiation. Mol Cell. doi:10.1016/j.molecel.2014.06.033

Karaca G, Swiderska-Syn M, Xie G, Syn WK, Krüger L, Machdao MV, Garman K, Choi SS, Michelotti GA, Burkly LC et al (2014) TWEAK/Fn14 signaling is required for liver regeneration after partial hepatectomy in mice. PLoS One 9:e83987

Kawakita N, Seki S, Sakaguchi H, Yanai A, Kuroki T, Mizoguchi Y, Kobayashi K, Monna T (1992) Analysis of proliferating hepatocytes using a monoclonal antibody against proliferating cell nuclear antigen/cyclin in embedded tissues from various liver diseases fixed in formaldehyde. Am J Pathol 140:513–520

Kawasaki T, Murata S, Takahashi K, Nozaki R, Ohshiro Y, Ikeda N, Pak S, Myronovych A, Hisakura K, Fukunaga K et al (2010) Activation of human liver sinusoidal endothelial cell by human platelets induces hepatocyte proliferation. J Hepatol 53:648–654

Kim HE, Kim DG, Lee KJ, Son JG, Song MY, Park YM, Kim JJ, Cho SW, Chi SG et al (2012) Frequent amplification of CENPF, GMNN and CDK13 genes in hepatocellular carcinomas. PLoS 7:e43223

Kitamoto M, Nakanishi T, Kira S, Kawaguchi M, Nakashio R, Suemori S, Kajiyama G et al (1993) The assessment of proliferating cell nuclear antigen immunohistochemical staining in small hepatocellular carcinoma and its relationship to histologic characteristics and prognosis. Cancer 72:1859–1865

Koh SL, Ager EI, Christophi C (2010) Liver regeneration and tumour stimulation: implications of the renin-angiotensin system. Liver Int 30:1414–1426

Kollmar O, Menger MD, Schilling MK (2006) Macrophage inflammatory protein-2 contributes to liver resection-induced acceleration of hepatic metastatic tumor growth. World J Gastroenterol 12:858–867

Kollmar O, Junker B, Rupertus K, Scheuer C, Menger MD, Schilling MK (2008) Liver resection-associated macrophage inflammatory protein-2 stimulates engraftment but not growth of colorectal metastasis at extrahepatic sites. J Surg Res 145:295–302

König M, Holzhütter HG, Berndt N (2013) Metabolic gradients as key regulators in zonation of tumor energy metabolism: a tissue-scale model-based study. Biotechnol J 8:1058–1069

Kordes C, Sawitza I, Götze S, Herebian D, Häussinger D (2014) Hepatic stellate cells contribute to progenitor cells and liver regeneration. J Clin Invest 124:5503–5515

Krause P, Rave-Fränk M, Wolff HA, Becker H, Christiansen H, Koenig S (2010) Liver sinusoidal endothelial and biliary cell repopulation following irradiation and partial hepatectomy. World J Gastroenterol 16:3928–3935

Kreidl E, Oztürk D, Metzner T, Berger W, Grusch M (2009) Activins and follistatins: emerging roles in liver physiology and cancer. World J Hepatol 1:17–27

Ku NO, Soetikno RM, Omary MB (2003) Keratin mutation in transgenic mice predisposes to Fas but not TNF-induced apoptosis and massive liver injury. Hepatology 37:1006–1014

Kubota K, Fujita Y, Sato T, Watanabe S, Hosono K, Yoneda M, Kirikoshi H, Hisatomi K et al (2013) Tumor diameter and Ki-67 expression in biopsy could be diagnostic markers discriminating from adenoma and early stage cancer in patients with ampullary tumors. J Hepatobiliary Pancreat Sci 20:531–537

Lai JP, Chen ZM, Lok T, Chan OT, Himmelfarb E, Zhai Q, Lin F, Wang HL (2014) Immunohistochemical stains of proliferating cell nuclear antigen, insulin-like growth factor 2 and clusterin help distinguish malignant from benign liver nodular lesions. J Clin Pathol 67:464–469

Lalor PF, Herbert J, Bicknell R, Adams DH (2013) Hepatic sinusoidal endothelium avidly binds platelets in an integrin-dependent manner, leading to platelet and endothelial activation and leukocyte recruitment. Am J Physiol Gastrointest Liver Physiol 304: G469–G478

Leclercq IA, Field J, Farrell GC (2003) Leptin-specific mechanisms for impaired liver regeneration in ob/ob mice after toxic injury. Gastroenterology 124:1451–1464

LeCouter J, Moritz DR, Li B, Phillips GL, Liang XH, Gerber HP, Hillan KJ, Ferrara N (2003) Angiogenesis-independent endothelial protection of liver: role of VEGFR-1. Science 299:890–893

Lee KT, Sheen PC (1999) Proliferating cell nuclear antigen expression in peribiliary glands of stone-containing intrahepatic bile ducts. Dig Dis Sci 44:2251–2256

Lee et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/14569448

Lei N, Peng B, Zhang JY (2014) CIP2A regulates cell proliferation via the AKT signaling pathway in human lung cancer. Oncol Rep.doi:10.3892 / or.2014.3375

Leu JI, Crissey MA, Craig LE, Taub R (2003) Impaired hepatocyte DNA synthetic response posthepatectomy in insulin-like growth factor binding protein 1 –deficient mice with defects in C/EBPbeta and mitogen-activated protein kinase/extracellular signal-regulated kinase regulation. Mol Cell Biol 23:1251–1259

Li Y, Zhu Z, Zhang S, Yu D, Yu H, Liu L, Cao X, Wang L, Gao H, Zhu M (2011) ShRNA-targeted centromere protein A inhibits hepatocellular carcinoma growth. PLoS One 6:e17794

Li N, Hu WJ, Shi J, Xue J, Guo WX, Zhang Y, Guan DX, Liu SP, Cheng YQ, Wu MC, Xie D, Liu SR, Cheng SQ (2013a) Roles of fibroblast growth factor-inducible 14 in hepatocellular carcinoma. Asian Pac J Cancer Prev 14:3509–3514

Li J, Holzschu DL, Sugiyama T (2013b) PCNA is efficiently loaded on the DNA recombination intermediate to modulate polymerase d, h, and z activities. Proc Natl Acad Sci U S A 110:7672–7677

Li M, Zhou X, Mei J, Geng X, Zhou Y, Zhang W, Xu C (2014) Study of the activity of the signaling pathways regulating hepatocytes from G0 phase into G1 phase during rat liver regeneration. Cell Mol Biol Lett 19:181–200

Liu H, Di Cunto F, Imarisio S, Reid LM (2003) Citron kinase is a cell cycle-dependent, nuclear protein required for G2/M transition of hepatocytes. J Biol Chem 278:2541–2548

Lorup C (1977) An autoradiographic study of the 3H-uridine and 3H-thymidine incorporation in the regenerating mouse liver. Cell Tissue Kinet 10:477–485

Lowes KN, Croager EJ, Olynyk JK, Abraham LJ, Yeoh GC (2003) Oval cell-mediated liver regeneration: role of cytokines and growth factors. J Gastroenterol Hepatol 18:4–12

Ma S, Cheng Q, Cai Y, Gong H, Wu Y, Yu X, Shi L, Wu D, Dong C, Liu H (2014) IL-17A produced by γδ T cells promotes tumor growth in hepatocellular carcinoma. Cancer Res 74:1969–1982

Mabuchi A, Mullaney I, Sheard P, Hesssian P, Zimmermann A, Senoo H, Wheatley AM (2004) Role of hepatic stellate cells in the early phase of liver regeneration in rat: formation of tight adhesion to parenchymal cells. Comp Hepatol 3(Suppl):S29

MacDonald RA (1961) "Lifespan" of liver cells. Autoradiographic study using tritiated thymidine in normal, cirrhotic, and partially hepatectomized rats. Arch Intern Med 107:335–343

Macias-Silva M, Li W, Leu JI, Crissey MA, Taub R (2002) Up-regulated transcriptional repressors SnoN and Ski bind Smad proteins to antagonize transforming growth factor-beta signals during liver regeneration. J Biol Chem 277:28483–28490

Marongiu F, Serra MP, Sini M, Marongiu M, Contini A, Laconi E (2014) Cell turnover in the repopulated rat liver: distinct lineages for hepatocytes and the biliary epithelium. Cell Tissue Res 356:333–340

Marquez RT, Wendlandt E, Galle CS, Keck K, McCaffrey AP (2010) MicroRNA-21 is upregulated during the proliferative phase of liver regeneration, targets Pellino-1, and inhibits NF-kappaB signaling. Am J Physiol Gastrointest Liver Physiol 298:G535–G541

Mason JM, Morrison DJ, Basson MA, Licht JD (2006) Sprouty proteins: multifaceted negative-feedback regulators of receptor tyrosine kinase signaling. Trends Cell Biol 16:45–54

McCormick D, Hall PA (1992) The complexities of proliferating cell nuclear antigen. Histopathology 21:591–594

Mead JE, Braun L, Martin DA, Fausto N (1990) Induction of replicative competence ("priming") in normal liver. Cancer Res 50:7023–7030

Meng F, Francis H, Glaser S, Han Y, DeMorrow S, Stokes A, Staloch D, Venter J, White M, Ueno Y, Reid LM, Alpini G (2012) Role of stem cell factor and granulocyte colony-stimulating factor in remodeling during liver regeneration. Hepatology 55:209–221

Michalopoulos GK (1990) Liver regeneration: molecular mechanisms of growth control. FASEB J 4:176–187

Michalopoulos GK (2013) Principles of liver regeneration and growth homeostasis. Compr Physiol 3:485–513

Michalopoulos GK (2014) Advances in liver regeneration. Expert Rev Gastroenterol Hepatol 26:1–11

Michalopoulos GK, DeFrances MC (1997) Liver regeneration. Science 276:60–66

Minato H, Nakanuma Y (1993) Cell kinetic and morphological studies of human cholangiocellular carcinoma. Acta Pathol Jpn 43:111–120

Mizutani J, Hiraoka T, Yamashita R, Miyauchi Y (1992) Promotion of hepatic metastases by liver resection in the rat. Br J Cancer 65:794–797

Mochida S, Ishikawa K, Toshima K, Inao M, Ikeda H, Matsui A, Shibuya M, Fujiwara K (1998) The mechanisms of hepatic sinusoidal endothelial cell regeneration: a possible communication sysem associated with vascular endothelial growth factor in liver cells. J Gastroenterol Hepatol 13(Suppl):S1–S5

Mogler C, Wieland M, König C, Hu J, Runge A, Korn C, Besemfelder E, Breitkopf-Heinlein K, Komljenovic D, Dooley S et al (2015) Hepatic stellate cell-expressed endosialin balances fibrogenesis and hepatocyte proliferation during liver damage. EMBO Mol Med. doi:10.15252/emmm.201404246

Momiyama M, Kumamoto T, Suetsugu A, Kishimoto H, Chishima T, Tanaka K, Akiyama H, Ichikawa Y,

Bouvet M et al (2012) Major liver resection stimulation stromal recruitment and metastasis compared with repeated minor resection. J Surg Res 178:280–287
Moniaux N, Faivre J (2011) Key role of sinusoidal endothelial cells in the triggering of liver regeneration. J Hepatol 55:488–490
Moreau M, Rivière B, Vegna S, Aoun M, Gard C, Ramos J, Assenat E, Hibner U (2015) Hepatitis C viral proteins perturb metabolic liver zonation. J Hepatol 62:278–285
Mozzherin DJ, Shibutani S, Tan CK, Downey KM, Fisher PA (1997) Proliferating cell nuclear antigen promotes DNA synthesis past template lesions by mammalian DNA polymerase delta. Proc Natl Acad Sci USA 94:6126–6131
Murakami M, Sasaki T, Kuwada Y, Yamasaki S, Kuwahara K, Chayama K (2003) Prognostic value of p53 and Ki-67 expression in resected or biopsy specimens of bile duct carcinoma. Oncol Rep 10:1091–1096
Murata S, Maruyama T, Nowatari T, Takahashi K, Ohkohchi N (2014) Signal transduction of platelet-induced liver regeneration and decrease of liver fibrosis. Int J Mol Sci 15:5412–5425
Naganuma S, Itoh H, Uchiyama S, Tanaka H, Nagaike K, Miyata S, Uchinokura S et al (2003) Characterization of transcripts generated from mouse hepatocyte growth factor activator inhibitor type 2 (HAI-2) and HAI-2-related small peptide (H2RSP) genes: chimeric mRNA transcribed from both HAI-2 and H2RSP genes is detected in human but not in mouse. Biochem Biophys Res Commun 302:345–353
Nagao T, Ishida Y, Yamazaki K, Kondo Y (1995) Nucleolar organizer regions in hepatocellular carcinoma related to the cell cycle, cell proliferation and histologic grade. Pathol Res Pract 191:967–972
Nagao T, Ishida Y, Kondo Y (1996) Determination of S-phase cells by in situ hybridization for histone H3 mRNA in hepatocellular carcinoma: correlation with histologic grade and other cell proliferative markers. Mod Pathol 9:99–104
Nakamura T, Hayama M, Sakai T, Hotchi M, Tanaka E (1993) Proliferative activity of hepatocytes in chronic viral hepatitis as revealed by immunohistochemistry for proliferating cell nuclear antigen. Hum Pathol 24:750–753
Nakopoulou L, Janinis J, Giannopoulou I, Lazaris AC, Koureas A, Zacharoulis D (1995) Immunohistochemical expression of p53 protein and proliferating cell nuclear antigen in hepatocellular carcinoma. Pathol Res Pract 191:1208–1213
Ng IO (1998) Prognostic significance of pathological and biological factors in hepatocellular carcinoma. J Gastroenterol Hepatol 13:666–670
Ng IO, Lai EC, Fan ST, Ng M, Chan AS, So MK (1994) Prognostic significance of proliferating cell nuclear antigen expression in hepatocellular carcinoma. Cancer 73:2268–2274
Ng IO, Na J, Lai EC, Fan ST, Ng M (1995) Ki-67 antigen expression in hepatocellular carcinoma using monoclonal antibody MIB1. A comparison with proliferating cell nuclear antigen. Am J Clin Pathol 104:313–318
Ng R, Song G, Roll GR, Frandsen NM, Willenbring H (2012) A microRNA-21 surge facilitates rapid cyclin D1 translation and cell cycle progression in mouse liver regeneration. J Clin Invest 122:1097–1108
Nishimori H, Tsukishiro T, Nambu S, Okada K, Shimizu Y, Miyabayashi C, Higuchi K, Watanabe A (1994) Analyses of proliferating cell nuclear antigen-positive cells in hepatocellular carcinoma: comparisons with clinical findings. J Gastroenterol Hepatol 9:425–432
Nowatari T, Fukunaga K, Ohkohchi N (2012) Regulation of signal transduction and role of platelets in liver regeneration. Int J Hepatol 2012:542479
Oh et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17383429
Ohashi K, Nakajima Y, Tsutsumi M, Kanehiro H, Fukuoka T, Hisanaga M, Taki J, Nakae D et al (1994) Clinical characteristics and proliferating activity of intrahepatic cholangiocarcinoma. J Gastroenterol Hepatol 9:442–446
Ohtomo N, Tomiya T, Tanoue Y, Inoue Y, Nishikawa T, Ikeda H, Seyama Y, Kokudo N et al (2010) Expression of a-taxilin in hepatocellular carcinoma correlates with growth activity and malignant potential of the tumor. Int J Oncol 37:1417–1423
Ojanguren I, Ariza A, Llatjos M, Castella E, Mate JL, Navas-Palacios JJ (1993) Proliferating cell nuclear antigen expression in normal, regenerative, and neoplastic liver: a fine-needle aspiration cytology and biopsy study. Hum Pathol 24:905–908
Oku T, Ikeda S, Sasaki H, Fukuda K, Morioka H, Ohtsuka E, Yoshikawa H, Tsurimoto T (1998) Functional sites of human PCNA which interact with p21 (Cip1/Waf1), DNA polymerase delta and replication factor C. Genes Cells 3:357–369
Osada S, Saji S, Kuno T (2004) Clinical significance of combination study of apoptotic factors and proliferating cell nuclear antigen in estimating the prognosis of hepatocellular carcinoma. J Surg Oncol 85:48–54
Ost MC, Patel KP, Rastinehad AR, Chu PY, Anderson AE, Smith AD, Lee BR (2008) Pneumoperitneum with carbon dioxide inhibits macrophage tumor necrosis factor-alpha secretion: source of transitional-cell carcinoma port-site metastasis, with prophylactic irrigation strategies to decrease laparoscopic oncologic risks. J Endourol 22:105–112
Paget GE (1954) Mitotic activity in the human liver. J Pathol Bacteriol 67:401–406
Pan C, Chen H, Wang L, Yang S, Fu H, Zheng Y, Miao M, Jiao B (2012) Down-regulation of MiR-127 facilitates hepatocyte proliferaton during rat liver regeneration. PLoS One 7:e39151
Panattoni M, Maiorino L, Lukacz A, Zentilin L, Mazza D, Sanvito F, Sitia G, Guidotti LG et al (2014) The COP9 signalosome is a repressor of replicative stress responses and polyploidization in the regenerating liver. Hepatology 59:2331–2343
Panis Y, Nordlinger B, Delelo R, Herve JP, Infante J, Kuhnle M, Ballet F (1990) Experimental colorectal

liver metastases. Influence of sex, immunological status and liver regeneration. J Hepatol 11:53–57

Pannem RR, Dorn C, Hellerbrand C, Massumi R (2014) Cylindromatosis gene CYLD regulates hepatocyte growth factor expression in hepatic stellate cells through interaction with histone deacetylase 7. Hepatology 60:1066–1081

Paschos KA, Bird NC (2010) Liver regeneration and its impact on post-hepatectomy metastatic tumour recurrence. Anticancer Res 6:2161–2170

Patman G (2014) Liver: loss of integrin β1 impairs liver regeneration and HCC progression. Nat Rev Gastroenterol Hepatol 11:392

Peng A, Wang L, Fisher LA (2011) Greatwall and Polo-like kinase 1 coordinate to promote checkpoint recovery. J Biol Chem 286:28996–29004

Petronczki M, Lénart P, Peters JM (2008) Polo on the rise – from mitotic entry to cytokinesis with Plk1. Dev Cell 14:646–659

Ping C, Xiaoling D, Jin Z, Jiahong D, Jiming D, Lin Z (2006) Hepatic sinusoidal endothelial cells promote hepatocyte proliferation early after partial hepatectomy in rats. Arch Med Res 37:576–583

Polimeno L, Margiotta M, Marangi L, Lisowsky T, Azzarone A, Ierardi E, Frassanito MA, Francavilla R, Francavilla A (2000) Molecular mechanisms of augmenter of liver regeneration as immunoregulator: its effect on interferon-gamma expressiion in rat liver. Dig Liver Dis 32:217–225

Prosperi E (1997) Multiple roles of the proliferating cell nuclear antigen: DNA replication, repair and cell cycle control. Prog Cell Cycle Res 3:193–210

Qiu DM, Wang GL, Chen L, Xu YY, He S, Cao XL, Qin J, Zhou JM, Zhang YX et al (2014) The expression of beclin-1, an autophagic gene, in hepatocellular carcinoma associated with clinical pathological and prognostic significance. BMC Cancer 14:327

Quaglia A, McStay M, Stoeber K, Loddo M, Caplin M, Fanshawa T, Williams G, Dhillon A (2006) Novel markers of cell kinetics to evaluate progression from cirrhosis to hepatocellular carcinoma. Liver Int 26:424–432

Rangone H, Wegel E, Gatt MK, Yeung E, Flowers A, Debski J, Dadlez M, Janssens V et al (2011) Suppression of Scant identifies Endos as a substrate of Greatwall kinase and a negative regulator of protein phosphatase 2A in mitosis. PLoS Genet 7:e1002225

Rao R, Graffeo CS, Gulati R, Jamal M, Narayan S, Zambirinis CP, Barilla R, Deutsch M, Greco SH, Ochi A, Tomkötter L et al (2014) Interleukin 17-producing γδT cells promote hepatic regeneration in mice. Gastroenterology 147:473–484

Rijken AM, Umezawa A, van Gulik TM, Bosma A, Polak MM, Offerhaus GJ, Obertop H et al (1998) Prognostic value of cell proliferation (Ki-67 antigen) and nuclear DNA content in clinically resectable, distal bile duct carcinoma. Ann Surg Oncol 5:699–705

Robbins BA, de la Vega D, Ogata K, Tan EM, Nakamura RM (1987) Immunohistochemical detection of proliferating cell nuclear antigen in solid human malignancies. Arch Pathol Lab Med 111:841–845

Rodgarkia-Dara C, Vejda S, Erlach N, Losert A, Bursch W, Berger W, Schulte-Hermann R et al (2006) The activin axis in liver biology and disease. Mutat Res 613:123–137

Rubin EM, Martin AA, Thung SN, Gerber MA (1995) Morphometric and immunohistochemical characterization of human liver regeneration. Am J Pathol 147:397–404

Salehi S, Brereton HC, Arno MJ, Darling D, Quaglia A, O'Grady J, Heaton N, Aluvihare VR (2013) Human liver regeneration is characterized by the corrdinated expression of istinct microRNA governing cell cycle fate. Am J Transplant 13:1282–1295

Samel SA, Fernandez-Cid A, Sun J, Riera A, Tognetti S, Herrera MC, Li H, Speck C (2014) A unique DNA entry gate serves for regulated loading of the eukaryotic replicative helicase MCM2-7 onto DNA. Genes Dev 28:1653–1666

Santoni-Rugiu E, Jelnes P, Thorgeirsson SS, Bisgaard HC (2005) Progenitor cells in liver regeneration: molecular responses controlling their activation and expansion. APMIS 113:876–902

Schaefer-Ramadan S, Gannon SA, Thorpe C (2013) Human augmenter of liver regeneration: probing the catalytic mechanism of a Flavin-dependent sulfhydryl oxidase. Biochemistry 52:8323–8332

Scholzen T, Gerdes J (2000) The Ki-67 protein: from the known and the unknown. J Cell Physiol 182:311–322

Schug J, Mckenna LB, Walton G, Hand N, Mukherjee S, Essuman K, Shi Z, Gao Y, Markley K, Nakagawa M, Kameswaran V et al (2013) Dynamic recruitment of microRNAs to their mRNA targets in the regenerating liver. BMC Genomics 14:264

Sekiya S, Suzuki A (2014) Hepatocytes, rather than cholangiocytes, can be the major source of primitive ductules in the chronically injured mouse liver. Am J Pathol 184:1468–1478

Selzner N, Selzner M, Odermatt B, Tian Y, Van Rooijen N, Clavien PA (2003) ICAM-1 triggers liver regeneration through leukocyte recruitment and Kupffer cell-dependent release of TNF-alpha/IL-6 in mice. Gastroenterology 124:692–700

Seres-Sturm L, Maros T, Seres-Sturm M (1981) Regeneration of intrahepatic biliary ducts after subtotal hepatectomy in rats. Morphol Embryol (Bucur) 27:7–9

Settakorn J, Kaewpila N, Burns GF, Leong AS (2005) FAT, E-cadherin, beta catenin, HER 2/neu, Ki67 immunoexpression, and histological grade in intrahepatic cholangiocarcinoma. J Clin Pathol 58:1249–1254

Shehata MA, Nosseir HR, Nagy HM, Farouk G (2006) Cyclin dependent kinase inhibitor p27(kip1) expression and subcellular localization in relation to cell proliferation in hepatocellular carcinoma. Egypt J Immunol 13:115–130

Shi JH, Line PD (2014) Effect of liver regeneration on malignant hepatic tumors. World J Gastroenterol 20:16167–16177

Shi JH, Huitfeldt HS, Suo ZH, Line PD (2011) Growth of hepatocellular carcinoma in the regenerating liver. Liver Transplant 17:866–874

Shin and Kaestner 2014. http://www.ncbi.nlm.nih.gov/pubmed/24439810

Shingaki N, Tamai H, Mori Y, Moribata K, Enomoto S, Deguchi H, Ueda K, Inoue I et al (2013) Serologicl and histological indices of hepatocellular carcinoma and tumor volume doubling time. Mol Clin Oncol 1:977–981

Shiratori Y, Hongo S, Hikiba Y, Ohmura K, Nagura T, Okano K, Kamii K, Tanaka T, Komatsu Y, Ochiai T, Tsobouchi H et al (1996) Role of macrophages in regeneration of liver. Dig Sci 41:1939–1946

Shrestha ML, Miyake H, Kikutsuji T, Tashiro S (1998) Prognostic significance of Ki-67 and p53 antigen expression in carcinomas of bile duct and gallbladder. J Med Invest 45:95–102

Shu J, Kren BT, Xia Z, Wong PY, Li L, Hanse EA, Min MX, Li B, Albrecht JH, Zeng Y, Subramanian S, Steer CJ et al (2011) Genomewide microRNA down-regulation as a negative feedback mechanism in the early phases of liver regeneration. Hepatology 54:609–619

Shyr YM, Su CH, Wu LH, Li AF, Chiu JH, Wu CW, Lui WY (1999) Prognostic value of MIB-1 index and DNA ploidy in resectable ampulla of Vater carcinoma. Ann Surg 229:523–527

Sigal SH, Rajvanshi P, Gorla GR, Sokhi RP, Saxena R, Gebhard DR, Reid LM et al (1999) Partial hepatectomy-induced polyploidy attenuates hepatocyte replication and activates cell aging events. Am J Physiol 276:G1260–G1272

Silvestrini R, Costa A, Regalia E (1992) Cell kinetics in the study of hepatocellular carcinoma. Ital J Gastroenterol 24:43–45

Soini Y, Virkajärvi N, Lehto VP, Pääkkö P (1996) Hepatocellular carcinomas with a high proliferation index and a low degree of apoptosis and necrosis are associated with a shortened survival. Br J Cancer 73:1025–1030

Song G, Sharma AD, Roll GR, Ng R, Lee AY, Blelloch RH, Frandsen NM, Willenbring H (2010) MicroRNAs control hepatocyte proliferation during liver regeneration. Hepatology 51:1735–1743

Speicher T, Siegenthaler B, Bogorad RL, Ruppert R, Petzold T, Padrissa-Altes S, Bachofner M, Anderson DG, Koteliansky V et al (2014) Knockdown and knockout of β1-integrin in hepatocytes impairs liver regeneration through inhibition of growth factor signalling. Nat Commun 5:3862

Streetz KL, Luedde T, Manns MP, Trautwein C (2000) Interleukin 6 and liver regeneration. Gut 47:309–312

Strick-Marchand H, Masse GX, Weiss MC, Di Santo JP (2008) Lymphocytes support oval cell-dependent liver regeneration. J Immunol 181:2764–2771

Stueck and Wanless 2015. http://www.ncbi.nlm.nih.gov/pubmed/25644399

Suehiro T, Matsumata T, Itasaka H, Yamamoto K, Kawahara N, Sugimachi K (1995) Clinicopathologic features and prognosis of resected hepatocellular carcinomas of varied sizes with special reference to proliferating cell nuclear antigen. Cancer 76:399–405

Sun R, Gao B (2004) Negative regulation of liver regeneration by innate immunity (natural killer cells/interferon-gamma). Gastroenterology 127:1525–1539

Sun M, Wu G, Li Y, Fu X, Huang Y, Tang R, Guo Y, Qiu M, Mao Y, Zhao F, Li L et al (2010) Expression profile reveals novel prognostic biomarkers in hepatocellular carcinoma. Front Biosci (Elite Ed) 2:829–840

Suto T, Sugai T, Nakamura S, Funato O, Nitta H, Sasaki R, Kanno S, Saito K (1998) Assessment of the expression of p53, MIB-1 (Ki-67 antigen), and argyrophilic nucleolar organizer regions in carcinoma of the extrahepatic bile duct. Cancer 82:86–95

Sutton PM, Spurgeon PJ (1966) Mitoses in bile duct epithelium following acute carbon tetrachloride poisoning. Br J Exp Pathol 47:545–549

Sutton ME, op den Dries S, Koster MH, Lisman T, Gouw AS, Porte RJ (2012) Regeneration of human extrahepatic biliary epithelium: the peribiliary glands as progenitor cell compartment. Liver Int 32:554–559

Swiderska-Syn M, Syn WK, Xie G, Krüger L, Machado MV, Karaca G, Michelotti GA, Choi SS, Premont RT, Diehl AM (2014) Myofibroblastic cells function as progenitors to regenerate murine liver after partial hepatectomy. Gut 63:1333–1344

Tachibana S, Zhang X, Ito K, Ota Y, Cameron AM, Williams GM, Sun Z (2014) Interleukin-6 is required for cell cycle arrest and activation of DNA repair enzymes after partial hepatectomy in mice. Cell Biosci 4:6

Taimr P, Higuchi H, Kocova E, Rippe RA, Friedman S, Gores GJ (2003) Activated stellate cells express TRAIL receptor-2/death receptor-5 and undergo TRAIL-mediated apoptosis. Hepatology 37:87–95

Takagi M, Matsuoka Y, Kurihara T, Yoneda Y (1999) Chmadrin: a novel Ki-67 antigen-related perichromosomal protein possibly implicated in higher order chromatin structure. J Cell Sci 112:2463–2472

Takagi M, Nishiyama Y, Taguchi A, Imamoto N (2014) Ki67 antigen contributes to the timely accumulation of protein phosphatase 1γ on anaphase chromosomes. J Biol Chem 289:22877–22887

Takeishi T, Hirano K, Kobayashi T, Hasegawa G, Hatakeyama K, Naito M (1999) The role of Kupffer cells in liver regeneration. Arch Histol Cytol 62:413–422

Takita S, Nishijima H, Kishino Y, Kawahigashi T, Toyota S (1966) Studies on the hepatic metastasis in injuried and regenerating livers. Tokushima J Exp Med 12:107–115

Tan CY, Lai RC, Wong W, Dan YY, Kim SK, Ho HK (2014) Mesenchymal stem cell-derived exosomes promote hepatic regeneration in drug-induced liver injury models. Stem Cell Res Ther 5:76

Taniai M, Tomimatsu M, Okuda H, Saito A, Obata H (1993) Immunohistochemical detection of proliferating cell nuclear antigen in hepatocellular carcinoma: relationship to histological grade. J Gastroenterol Hepatol 8:420–425

Tanigawa K, Sakaida I, Masuhara M, Hagiya M, Okita K (2000) Augmenter of liver regeneration (ALR) may promote liver regeneration by reducing natural killer (NK) cell activity in human liver diseases. J Gastroenterol 35:112–119

Tanimizu N, Nakamura Y, Ichinohe N, Mizuguchi T, Hirata K, Mitaka T (2013) Hepatic biliary epithelial cells acquire epithelial integrity but lose plasticity to differentiate into hepatocytes in vitro during development. J Cell Sci 126:5239–5246

Tanimizu N, Kobayashi S, Ichinohe N, Mitaka T (2014) Downregulation of miR122 by grainyhead-like 2 restricts the hepatocytic differentiation potential of adult liver progenitor cells. Development 141:4448–4456

Taub R (1996) Liver regeneration 4: transcriptional control of liver regeneration. FASEB J 10:413–427

Terada T, Nakanuma Y (1992a) Cell proliferative activity in adenomatous hyperplasia of the liver and small hepatocellular carcinoma. An immunohistochemical study demonstrating proliferating cell nuclear antigen. Cancer 70:591–598

Terada T, Nakanuma Y (1992b) Cell kinetic analyses and expression of carcinoembryonic antigen, carbohydrate antigen 19-9 and DU-PAN-2 in hyperplastic, pre-neoplastic and neoplastic lesions of intrahepatic bile ducts in livers with hepatolithiasis. Virchows Arch A Pathol Anat Histopathol 420:327–335

Terada T, Nakanuma Y (1996) Expression of apoptosis, proliferating cell nuclear antigen, and apoptosis-related antigens (bcl-2, c-myc, Fas, Lewis(y) and p53) in human cholangiocarcinomas and hepatocellular carcinomas. Pathol Int 46:764–770

Terada T, Nakanuma Y, Ohta T, Nagakawa T (1992) Histological features and interphase nucleolar organizer regions in hyperplastic, dysplastic and neoplastic epithelium of intrahepatic bile ducts in hepatolithiasis. Histopathology 21:233–240

Than and Newsome 2014. http://www.ncbi.nlm.nih.gov/pubmed/24453286

Than KW, Okayasu I, Akashi T (1995) Histopathological and immunohistochemical analysis of adenomatous hyperplasia and hepatocellular carcinoma: cellularity, thickness of cell cord, and Ki-67 proliferative activity. Bull Tokyo Med Dent Univ 42:67–81

Thorgeirsson SS (1996) Hepatic stem cells in liver regeneration. FASEB J 10:1249–1256

Torre C, Perret C, Colnot S (2010) Molecular determinants of liver zonation. Prog Mol Biol Transl Sci 97: 127–150

Torre C, Benhamouche S, Mitchell C, Godard C, Veber P, Letourneur F, Cagnard N et al (2011) The transforming growth factor-a and cyclin D1 genes are direct targets of b-catenin signaling in hepatocyte proliferation. J Hepatol 55:86–95

Tsurimoto T (1999) PCNA binding proteins. Front Biosci 4:D849–D858

Uda Y, Hirano T, Son G, Iimuro Y, Uyama N, Yamanaka J, Mori A, Arii S, Fujimoto J (2013) Angiogenesis is crucial for liver regeneration after partial hepatectomy. Surgery 153:70–77

Ukai K, Terashima K, Imai Y, Shinzawa H, Okuyama Y, Takahashi T, Ishikawa M (1990) Proliferation kinetics of rat Kupffer cells after partial hepatectomy. Immunohistochemical and ultrastructural analysis. Acta Pathol Jpn 40:623–634

Ullah Z, de Renty C, DePamphilis ML (2011) Checkpoint kinase 1 prevents cell cycle exit linked to terminal cell differentiation. Mol Cell Biol 31:4129–4143

Van Hooser AA, Yuh P, Heald R (2005) The perichromosomal layer. Chromosoma 114:377–388

van Vugt MA, Medema RH (2005) Getting in and out of mitosis with Polo-like kinase-1. Oncogene 24:2844–2859

Vigneron S, Gharbe-Ayachi A, Raymond AA, Burgess A, Labbé JC, Labesse G, Monserrat B et al (2011) Characterization of the mechanisms controlling Greatwall activity. Mol Cell Biol 31:2262–2275

Villevalois-Cam L, Rescan C, Gilot D, Ezan F, Loyer P, Desbuquois D et al (2003) The hepatocyte is a direct target for transforming-growth factor beta activation via the insulin-like growth factor II/mannose 6-phosphate receptor. J Hepatol 38:156–163

Wacker HH, Radzun HJ, Parwaresch MR (1986) Kinetics of Kupffer cells as shown by parabiosis and combined autoradiographic/immunohistochemical analysis. Virchows Arch B Cell Pathol Incl Mol Pathol 51:71–78

Wakasa T, Wakasa K, Shutou T, Hai S, Kubo S, Hirohashi K, Umeshita K, Monden M (2007) A histopathological study on combined hepatocellular and cholangiocarcinoma: cholangiocarcinoma component is originated from hepatocellular carcinoma. Hepatogastroenterology 54:508–513

Wake K, Decker K, Kirn A, Knook DL, McCuskey RS, Bouwens L, Wisse E (1989) Cell biology and kinetics of Kupffer cells in the liver. Int Rev Cytol 118:173–229

Walter TJ, Cast AE, Huppert KA, Huppert SS (2014) Epithelial VEGF signaling is required in the mouse liver proper sinusoid endothelial cell identity and hepatocyte zonation in vivo. Am J Physiol Gastrointest Liver Physiol 306:G840–G862

Wang L, Wang X, Xie G, Wang L, Hill CK, DeLeve LD (2012a) Liver sinusoidal endothelial cell progenitor cells promote liver regeneration in rats. J Clin Invest 122:1567–1573

Wang L, Wang X, Wang L, Chiu JD, van de Ven G, Gaarde WA, Deleve LD (2012b) Hepatic vascular endothelial growth factor regulates recruitment of rat liver sinusoidal endothelial cell progenitor cells. Gastroenterology 143:1555–1563

Wang P, Malumbres M, Archambault V (2014a) The Greatwall-PP2A axis in cell cycle control. Methods Mol Biol 1170:99–111

Wang R, Huebert RC, Shah VH (2014b) Sinusoidal endothelial cells coordinate liver regeneration and angiogenesis via angiopoietin-2: an ode to Prometheus. Gastroenterology 147:533–534

Widmann JJ, Fahimi HD (1975) Proliferation of mononuclear phagocytes (Kupffer cells) and endothelial

cells in regenerating rat liver. A light and electron microscopic cytochemical study. Am J Pathol 80: 349–366

Witjes CD, ten Kate FJ, Verhoef C, de Man RA, Ijzermans JN (2013) Immunohistochemical characteristics of hepatocellular carcinoma in non-cirrhotic livers. J Clin Pathol 66:687–691

Wu JD, Tseng HH (1994) The expression of proliferating cell nuclear antigen in hepatocellular carcinoma. Zhonghua Yi Xue Za Zhi (Taipei) 53:198–203

Xue ZF, Wu XM, Liu M (2013) Hepatic regeneration and the epithelial to mesenchymal transition. World J Gastroenterol 19:1380–1386

Yagai T, Miyajima A, Tanaka M (2014) Semaphorin 3E secreted by damaged hepatocytes regulates the sinusoidal regeneration and liver fibrosis during liver regeneration. Am J Pathol 184:2250–2259

Yamada Y, Yamauchi H, Kakizaki K, Suzuki H (1995) Expression of Ki-67 by monoclonal antibody MIB-1 in carcinoma of the middle and lower bile duct. Tohoku J Exp Med 177:375–377

Yang J, Huang J, Luo L, Chen Z, Guo Y, Guo L (2014a) Significance of PRO2000/ANCCA expression, a novel proliferation-associated protein in hepatocellular carcinoma. Cancer Cell Int 14:33

Yang J, Mowry LE, Nejak-Bowen KN, Okabe H, Diegel CR, Lang RA, Williams BO et al (2014b) Beta-catenin signaling in murine liver zonation and regeneration: a Wnt-Wnt-situation! Hepatology. doi:10.1002/hep.27082

Yanger K, Knigin D, Zong Y, Maggs L, Gu G, Akiyama H, Pikarsky E, Stanger BZ (2014) Adult hepatocytes are generated by self-duplication rather than stem cell differentiation. Cell Stem Cell 15:340–349

Yan-nan B, Zhao-yan Y, Li-xi L, Jiang Y, Qing-Jie X, Yong Z (2014) MicroRNA-21 accelerates hepatocyte proliferation in vitro via PI3K/Akt signaling by targeting PTEN. Biochem Biophys Res Commun 443:802–807

Yen BL, Yen ML, Hsu PJ, Liu KJ, Wang CJ, Bai CH, Sytwu HK (2013) Multipotent human mesenchymal stromal cells mediate expansion of myeloid-derived suppressor cells via hepatocyte growth factor/c-met and STAT3. Stem Cell Rep 1:139–151

Yin C, Evason KJ, Asahina K, Stainier DY (2013) Hepatic stellate cells in liver development, regeneration, and cancer. J Clin Invest 123:1902–1910

You Q, Holt M, Yin H, Li G, Hu CJ, Ju C (2013) Role of hepatic resident and infiltrating macrophages in liver repair after acute injury. Biochem Pharmacol 86:836–843

Yu HC, Hung MH, Chen YL, Chu PY, Wang CY, Chao TT, Liu CY, Shiau CW et al (2014a) Erlotinib derivative inhibits hepatocellular carcinoma by targeting CIP2A to reactivate protein phosphatase 2A. Cell Death Dis 5: e1359

Yu HY, Zhu MH, Xiang DR, Li J, Sheng JF (2014b) High expression of 23 kDa protein of augmenter of liver regeneration (ALR) in human hepatocellular carcinoma. Onco Targets Ther 7:887–893

Yuan J, Hörlin A, Hock B, Stutte HJ, Rübsamen-Waigmann H, Strebhardt K (1997) Polo-like kinase, a novel marker for cellular proliferation. Am J Pathol 150:1165–1172

Yuan B, Dong R, Shi D, Zhu Y, Zhao Y, Miao M, Jiao B (2011) Down-regulation of miR-23b may contribute to activation of the TGF-β1/Smad3 signalling pathway during the termination stage of liver regeneration. FEBS Lett 585:927–934

Yuan Q, Loya K, Rani B, Möbius S, Balakrishnan A, Lamle J, Cathomen T, Vogel T, Manns MP, Ott M, Cantz T, Sharma AD (2013) MicroRNA-221 overexpression accelerates hepatocyte proliferation during liver regeneration. Hepatology 57:299–310

Zeng WJ, Liu GY, Xu J, Zhou XD, Zhang YE, Zhang N (2002) Pathological characteristics. PCNA labeling index and DNA index in prognostic evaluation of patients with moderately differentiated hepatocellular carcinoma. World J Gastroenterol 8:1040–1044

Zhao D, Zimmermann A, Wheatley AM (1993) Morphometry of the liver after liver transplantation in the rat: significance of an intact arterial supply. Hepatology 17:310–317

Zhao M, Zhang NX, Du ZY, Laissue JA, Zimmermann A (1994) Three types of liver cell dysplasia (LCD) in small cirrhotic nodules are distinguishable by karyometry and PCNA labelling, and their features resemble distinct grades of hepatocellular carcinoma. Histol Histopathol 9:73–83

Zhao D, Zimmermann A, Kuznetsova LV, Wheatley AM (1995) Regression of bile duct damage and bile duct proliferation in the non-rearterialized transplanted rat liver is associated with spontaneous graft rearterializatin. Hepatology 21:1353–1360

Zhao W, Zhang B, Guo X, Zhang X, Hu J, Hu X, Lu Y (2014) Expression of Ki-67, Bax and p73 in patients with hilar cholangiocarcinoma. Cancer Biomark 14:197–202

Zhou J, Ju W, Wang D, Wu L, Zhu X, Guo Z, He X (2012) Down-regulation of microRNA-26a promotes mouse hepatocyte proliferation during liver regeneration. PLoS One 7:e33577

Zhu NL, Asahina K, Wang J, Ueno A, Lazaro R, Miyaoka Y, Miyajima A, Tsukamoto H (2012) Hepatic stellate cell-derived delta-like homolog 1 (DLK1) protein in liver regeneration. J Biol Chem 287:10355–10367

Zimmermann A (2004) Regulation of liver regeneration. Nephrol Dial Transplant 19(Suppl 4):iv6–iv10

Zimmermann A, Gloor B, Kappeler A, Uhl W, Friess H, Büchler MW (2002) Pancreatic stellate cells contribute to regeneration early after acute necrotising pancreatitis in humans. Gut 51:574–578

Zou Y, Hu M, Lee J, Nambiar SM, Garcia V, Bao Q, Chan JY, Dai G (2015) Nrf2 is essential for timely M phase entry of replicating hepatocytes during liver regeneration. Am J Physiol Gastroentest Liver Physiol 308: G262–G268

Growth Regulation in Hepatobiliary Cancer: Involvement of Growth Factors

173

Contents

Abstract

Cell proliferation in the regenerating liver and in liver neoplasms requires a complex system of growth factors that promote or inhibit proliferative growth. In hepatocellular carcinoma (HCC), protumorigenic growth factor signaling is frequently deregulated. Growth factors that are involved in liver cancer and specifically in HCC are those that also operate in normal liver regeneration, with some exceptions. The most important growth factors active in expansion and progression of HCC include hepatocyte growth factor (HGF) and its receptor Met, insulin-like growth factors, transforming growth factors alpha and beta, and epidermal growth factor. HGF and Met have been implicated in human hepatocarcinogenesis. HGF is up-regulated in part of HCCs, and amplification of Met characterizes subsets of HCC, whereby Met activation does not only affect growth, but also invasion and spread, suggesting that abnormal growth factor and growth factor receptor expression in cancers exerts complex effects on tumor biology.

Introduction

Liver regeneration and neoplasms of the hepatocyte lineages require a complex system of growth factors that promote or inhibit cell growth (reviews: Fausto 1991; Breuhahn et al. 2006; Breuhahn and Schirmacher 2010; Zender et al. 2010). In

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_173

hepatocellular carcinomas, protumorigenic growth factor signaling is frequently deregulated, whereby both diverse growth factors and/or their receptors may be upregulated. Growth factors that are involved in liver cancers are those that also operate in normal liver regeneration, with some exceptions. The most important growth factors active in liver cancer include hepatocyte growth factor, insulin-like growth factors, transforming growth factors alpha and beta, and epidermal growth factor. These growth factors and their receptors are or will be interesting targets for molecular therapies. In addition to these major factors, numerous other factors known to play a role in liver regeneration are identified in liver cancers, but their roles are less well understood.

Hepatocyte Growth Factor

Hepatocyte growth factor (HGF; scatter factor) is a multifunctional protein that is expressed in several organs and tissues and is, therefore, not specific for hepatocyte growth regulation. In the liver it is synthesized and secreted by non-hepatocyte cells, including hepatic stellate cells and their differentiated offspring. HGF interacts with its c-Met receptor which is itself regulated by a factor, modulating several tyrosine kinase receptors, decorin. HGF induces growth stimulation in various cell types, including hepatocytes in primary culture, but also growth inhibition in certain tumor cell lines. The opposing effects of HGF are caused by differences in downstream target signaling of the HGF receptor, c-Met. HGF induces redistribution of p21(CIP1) and p27(KIP1) via ERK-dependent p16(INK4a) upregulation, leading to cell cycle arrest at G1 (Han et al. 2005).

HGF and c-Met have been implicated in human hepatocarcinogenesis, and HGF is expressed in part of HCCs (Huitzil et al. 2008; Ang et al. 2013). In HCC, HGF is secreted by cancer-associated fibroblasts/CAFs and alphaSMA-reactive myofibroblasts and increases the proliferative activity of HCC cells (Jia et al. 2013). The HGF receptor c-Met is implicated in proliferation, invasion, and spread of numerous malignancies. Cancer cells having c-Met gene amplification can activate alternative signaling pathways to escape c-Met inhibition (Wang et al. 2009). In HCC, abnormal expression patterns of c-Met are detectable (Ueki et al. 1997; Huitzil et al. 2008; Ang et al. 2013; Kondo et al. 2013). Overexpression of c-Met in HCC defines tumor subtypes with increased vascular invasion and elevated microvessel density/angiogenesis (Kaposi-Novak et al. 2006), poor to moderate differentiation and increased proliferation (Suzuki et al. 1994), and shorter 5-year survival (Ueki et al. 1997).

Insulin-Like Growth Factors, Epidermal Growth Factor, and Neuregulins

Insulin-Like Growth Factors and Their Receptors

Insulin-like growth factors (IGFs) are polypeptides with sequence homology to insulin. IGFs exhibit strong proproliferative and antiapoptotic properties and consist of two major IGF family members, IGF-1 and IGF-2. These two ligands bind to membrane-bound receptors, IGFR1 and the mannose-6-phosphate receptor/IGFR2, respectively. The kinase activity of IGFR1 is triggered by clustering of syndecan-1, thus coupling IGFR1 function to inside-out integrin activation (Beauvais and Rapraeger 2010). IGFR2 plays an important role in trafficking IGFs to lysosomes. Both IGFs also bind to the insulin receptor isoform A. The bioavailability and function of IGFs within the so-called IGF axis is modulated by six secreted IGF-binding proteins (IGFBP1-6). Receptor binding results in the phosphorylation of several intracellular targets, in the activation of PI3K and Akt/protein kinase C, and finally in the activation of several genes involved in growth regulation (cyclin B, Myc, Fos, p27kip1).

IGFs have an important role in the promotion of cell growth and are commonly deregulated in many cancers, including HCC (Rashad et al. 2014; Liu et al. 2015). IGF-2 is highly expressed in fetal tissues but is downregulated in the normal adult liver via four epigenetically controlled promoters. IGF-2 is upregulated in a significant proportion of HCCs and their precursor lesions via reactivation of a fetal-type promoter

patterns and promotes growth in an autocrine manner. The expression pattern of IGF-2 in HCCs is modulated via IGFR2, which is downregulated in a major subset of these tumors (review: Breuhahn et al. 2006).

Expression of IGF-1 in HCCs follows more complex pathways, with both upregulation and downregulation occurring in phase-dependent manners (Ikeda et al. 2013; Yan et al. 2013). Development of HCC is accompanied by a significant reduction in serum IGF-1 levels, regulated by microRNA-190b (Hung et al. 2014). In contrast, IGF-1 may be elevated in HCC tumor tissue itself but is low in adjacent liver tissue. IGF-1 upregulation in HCC was associated with poorer median survival (Chun et al. 2014). Expression of IGFR1 beta was detectable in more than 50 % of HCC, but less than 10 % of normal liver samples, and in HCC was associated with poor differentiation (Liu et al. 2011).

HCCs express IGF-binding proteins/IGFBPs in complex patterns. The liver is the major source of at least two IGFBPs, IGFBP-1 and IGFBP-3, proteins that usually serve to attenuate the effects of IGFs at the receptor levels, thereby limiting the pro-growth effects of IGFs. In HCCs, the expression of IGFBPs 1, 3, and 4 is significantly downregulated, what results in failure of IGF inhibition and growth stimulation (Gong et al. 2000). HCCs also revealed upregulation of insulin-like growth factor 2-binding protein 1/IGF2BP1, a protein which enhances expression of c-Myc and Ki-67 proteins and potently regulates cell proliferation (Gutschner et al. 2014). HCCs also express insulin-like growth factor-2 mRNA-binding protein 3/IMP3, an oncofetal protein expressed in various cancers (Wachter et al. 2012).

Epidermal Growth Factor and Its Receptors

Epidermal growth factor receptor (EGFR, ErbB-1, HER1 in humans) belongs to the ErbB subfamily of transmembrane tyrosine kinase receptors, the other members being HER2/c-neu (ErbB-2), HER3 (ErbB-3), and Her4 (ErbB-4). EGFR can bind eight ligands in humans (TGF-alpha, EGF, heparin-binding EGF, amphiregulin, betacellulin, epiregulin, epigen, and crypto (review: Breuhahn et al. 2006). Upon ligand binding, EGFR dimerizes to form a homodimer which achieves intracellular protein tyrosine kinase activity. Active kinase autophosphorylates several receptor tyrosine residues leading to downstream activation of signaling pathways, mainly MAPK, Akt, and JNK pathways, causing DNA synthesis and cell proliferation. Receptor monomer dimerization occurs following ligand binding, but also the cytoplasmic protein plakophilin-2 enhances ligand-dependent and independent EGFR dimerization. EGFRs are internalized via endocytosis, mediated by Rab GTPases, a process deregulated in cancer cells (Grandal and Madshus 2008).

Members of the epidermal growth factor/EGF family are upregulated in subsets of HCCs and play an important role in growth regulation of these neoplasms (Higashiyama et al. 2008; Berasain et al. 2009; Nalesnik and Michalopoulos 2012). A single nucleotide polymorphism 61*G in the EGF gene has been identified in part of HCCs (Yuan et al. 2013). Individuals with the G/G EGF genotype had a higher adjusted risk for HCC than those with genotype A/A, and higher serum levels of EGF were seen among subjects with at least one G allele (Abu Dayyeh et al. 2011). In subsets of HCC, phosphorylated ErbB-3/HER3 and its ligands, the neuregulins, are upregulated, forming an autocrine loop affecting growth and invasion (Hsieh et al. 2011).

In many HCCs, the EGF receptor system (EGFR) plays a role as a signaling platform where different growth signals can converge (Berasain et al. 2009, 2011). EGFR is frequently overexpressed in HCCs, associated with extra EGFR gene copies and gains of chromosome 7 (Harada et al. 1999; Moon et al. 2006; Buckley et al. 2008). Inhibition of EGFR attenuates hepatocarcinogenesis, suggesting that the EGF-EGFR signaling system is critically involved in the development of liver cancer (Fuchs et al. 2014). High expression of EGFR is a marker of poorly differentiated HCCs, and EGFR polymorphisms in HCC are associated with prognosis (Wang et al. 2014). The homologue of EGFR, the c-erbB-2 oncogene, is

expressed in a minority of HCCs and is absent in cholangiocarcinoma (Collier et al. 1992). The mechanisms of growth-promoting effects of EGF/EHGR in HCCs are not fully clarified. EGFR transactivation in HCC cells is induced by TNF-alpha which triggers amphiregulin shedding from tumor cells, whereby amphiregulin is necessary for TNF-alpha activation of ERK1/2 and Akt signaling (Berasain et al. 2012). EGF can induce the expression of cytokeratin 19 in HCC cells, an alteration which is associated with increased growth capability (Yoneda et al. 2011).

Apart from its action on HCC cells, EGFR also affects the tumor microenvironment and the biology of tumor-associated cells located in stroma. The EGF-EGFR signaling system is involved in the generation of an inflammatory microenvironment in HCCs (Huang et al. 2014) and stimulates macrophages to produce interleukin-6, which in turn triggers the proliferation of HCC cells (Lanaya et al. 2014). EGFR expressed in tumor vessel endothelia promotes tumor angiogenesis, and tumors with EGFR expression show a higher microvessel density than those without expression (Moon et al. 2006).

Amphiregulin

Amphiregulin is a member of the EGF family and a ligand of EGFR. Amphiregulin is produced as a large precursor that is proteolytically cleaved and shed from cell surfaces by metalloproteinases. A protease involved in amphiregulin shedding is ADAM17, an enzyme upregulated in liver regeneration and HCCs (Berasain et al. 2012). Amphiregulin expression is not found in the normal liver but is upregulated during liver regeneration and in liver cirrhosis. It has functions in regulating immunity, inflammation, and tissue repair in normal and cancerous tissues (Zaiss et al. 2015). Amphiregulin is involved in HCC cell proliferation, is overexpressed in HCC tissues, and plays a role in hepatocarcinogenesis (Berasain et al. 2007). Amphiregulin gene expression is regulated by beta-catenin signaling in human HCC cells, and its upregulation participates in the induction of cyclin D1 and cell proliferation elicited by FGF19 (Latasa et al. 2012).

Transforming Growth Factor-Alpha

Two structurally related growth factors, transforming growth factor-alpha (TGF-alpha) and epidermal growth factor (EGF), act through a common cell surface receptor, the epidermal growth factor receptor (EGFR). Members of the TGF-alpha/EGF family occur as transmembrane-anchored factors that can be released through ectodomain shedding mediated by ADAM17. TGF-alpha is a potent mitogenic protein. In normal liver, TGF-alpha is expressed in cholangiocytes, but only occasionally and weakly in hepatocytes, and not in Kupffer cells. In part of HCCs, expression of TGF-alpha is deregulated, however, to variable degrees in published studies. TGF-alpha was found in the cytoplasm of HCC cells, and levels of mRNA were significantly elevated in part of cases (Harada et al. 1999; Yeh et al. 2007; Pannain et al. 2012). It was expressed at a high level from 31.9 % to more than 80 % of human HCC, preferentially in tumors growing in cirrhotic liver (Hsia et al. 1992; Pannain et al. 2012). TGF-alpha seems to mainly act in early stages of hepatocarcinogenesis and correlates with tumor proliferation and differentiation (Kira et al. 1997). TGF-alpha can show complex expression pattern in HCC, depending on the distribution of lineages with different levels of cell differentiation. Zones with high differentiation usually show prominent TGF-alpha expression, while poorly differentiated foci revealed lower levels of expression (Morimitsu et al. 1995; Zhang et al. 2004).

Transforming Growth Factor-Beta Superfamily Members

Transforming Growth Factor-Beta

Transforming growth factor-beta (TGF-beta) acts as a potent inhibitor of hepatocyte proliferation and is a critical termination signal of liver regeneration. It also mediates p53-dependent apoptosis in HCC cells (Wang et al. 2006). In its regulation of cell cycle progression and cell differentiation, TGF-beta operates through Smad protein

signaling. In their intranuclear action, Smads are negatively regulated by two nuclear proto-oncogenes, Ski and SnoN, which directly interact with Smad2, Smad3, and Smad4 and repress their capability to activate TGF-beta target genes.

TGF-beta is often overexpressed in HCC, and HCC cells show TGF-beta receptor-dependent growth inhibition in response to TGF-beta (Yamazaki et al. 2011). Based on RNA analysis, marked overexpression of TGF-beta1, TGF-beta2, and TGF-beta3 was found in HCCs. All three TGF-beta isoforms were also detected in HCC by immunohistochemistry (Abou-Shady et al. 1999). TGF-beta receptors are expressed in HCCs in various manners, but generally TGF-betaRs are expressed at low levels. Part of the tumors show decreased TGF-betaRII protein expression (Musch et al. 2005). HCC also shows diverse alterations in Smad signaling. In HCC cell lineages, Smad5 levels are either maintained or upregulated by an increase in gene dosage via a copy number gain, reflected by aberration in the long arm of chromosome 5 in part of HCCs (Zimonjic et al. 2003).

TGF-beta mediates a complex crosstalk between HCC cells and tumor microenvironment in HCC (Gupta et al. 2014). A distortion of TGF-beta signaling in HCC cells accelerates the malignant potential of the cells by enhancing stroma-induced cell growth (Sugano et al. 2003), suggesting that cancer cell-stroma interactions and epithelial-mesenchymal transition/EMT play an important role in TGF-beta-induced tumor progression. TGF-beta-induced hepatocyte EMT is modulated by microRNA-181a, overexpressed in cirrhosis and HCC (Brockhausen et al. 2014).

Bone Morphogenetic Proteins

Bone morphogenetic proteins/BMPs, TGF-beta superfamily members, play a role in the regulation of proliferation and differentiation of normal and cancer cells. BMP9, which triggers Smad 1, Smad 5, and Smad 8 phosphorylation and upregulates inhibitor of DNA binding 1/Id1 expression, is a proliferative and survival factor in HCC (Herrera et al. 2013). The activin/follistatin system, members of the TGF-beta superfamily, is also involved in hepatocarcinogenesis and regulation of HCC cell growth (Deli et al. 2008). Activins are disulphide-linked homo- or heterodimers formed from four different beta subunits termed beta(A), beta(B), beta(C), and beta(E). Activin A (beta(A) beta(A)) is a potent regulator of cell proliferation, apoptosis, and architecture of the liver, involved in the termination process of regeneration. The activity of activin A is counteracted by follistatin. Follistatin was overexpressed, while both activin subunits beta(A) and beta(E) were downregulated in the majority of human HCCs (Grusch et al. 2006).

Other Growth Regulatory Factors Promoting Cell Proliferation in Liver Cancers

Augmenter of Liver Regeneration

Augmenter of liver regeneration (ALR; encoded by the GFER gene; hepatic stimulatory substance; hepatopoietin) is a pleiotropic effector of growth for several cell systems, although it was originally identified as a liver cell growth factor involved in hepatocyte regeneration. In the liver, ALR is only expressed in hepatocytes and is a survival factor for these cells in that it protects them against apoptosis (Ilowski et al. 2011). ALR induces hepatocyte proliferation in an EGF receptor-independent manner (Ilowski et al. 2010). ALR is upregulated in subsets of human HCCs and stimulates autonomous growth of cancer cells (Thasler et al. 2005; Tang et al. 2009; Yu et al. 2010). These neoplasms in part show stable cytoplasmic expression of the 15 kDa isoform of ALR, whereby ALR expression is associated with reduced angioinvasion and less metastases (Dayoub et al. 2011).

Fibroblast Growth Factors

Fibroblast growth factors (FGFs), members of a large family of growth factors, and their receptors

are deregulated in many cancers, including HCCs and cholangiocarcinomas (Sandhu et al. 2014). In HCC, FGFs are often aberrantly expressed in conjunction with the reregulation of other growth factors, mainly HGF and TGF-beta (Gupta et al. 2014). In recent studies, more than 80 % of HCCs revealed overexpression of at least one FGF and/or FGFR. The main FGF family members upregulated in HCCs were FGF8, FGF17, and FGF18, all these three FGFs involved in autocrine and paracrine growth and survival signaling (Gauglhofer et al. 2011). Also the FGF19-FGFR4 signaling pathway is involved in development and growth of HCC (Lin and Desnoyers 2012). The isoform B of fibroblast growth factor receptor 2/FGFR2-IIIb is highly expressed in hepatocytes and acts in growth regulation. Lack of FGFR2-IIIb expression in HCCs is associated with more aggressive biology and reduced proliferative activity (Amann et al. 2010). Upregulation of FGF17 and FGF18 stimulates the growth of HCC-derived myofibroblasts, while FGF8, FGF17, and FGF18 induce the proliferation of endothelial cells, illustrating that the FGF system of growth factors also affects the growth of stromal and vascular cells of liver cancers (Gauglhofer et al. 2011).

In addition to FGFs, HCCs can also express FGF receptors/FGFRs. Human HCCs can present FGFR3, whereby higher expression levels are found in tumors of high grade (Qiu et al. 2005). A subset of HCCs expresses FGFR4, expression being associated with stage and TGF-beta1 expression. It surfaced that deregulated expression of FGFR4 is a key driver of an aggressive and rapidly growing phenotype of HCC (Ho et al. 2009; Chen et al. 2013b; Gauglhofer et al. 2014). FGFR4 signaling in HCC cells suppressed by its co-receptor Klotho-beta, a factor upregulated in subsets of HCC (Poh et al. 2012). Expression of FGFR2 in HCCs drives poor differentiation and an aggressive tumor phenotype (Harimoto et al. 2010). 13.6 % of intrahepatic cholangiocarcinomas showed a fusion of FGFR2 tyrosine kinase involving AHCYL1 and BICC1 as fusion partners. Expression of these fusion proteins promotes enhanced proliferation and transforming ability (Arai et al. 2014).

Krüppel-Like Factors

Krüppel-like factor 6 (KLF6) is an oncogene and ubiquitously expressed zinc finger transcription factor that is deregulated in numerous cancers. KLF6 is frequently inactivated in HCC, with LOH of the KLF6 gene found in up to 39 % of primary HCC. Downregulation of KLF6 is an early event in the course of hepatocarcinogenesis (Kremer-Tal et al. 2007). While wild-type KLF6 inhibits cell proliferation, mutant KLF6 in cancer cells can promote proliferation (Kremer-Tal et al. 2004, 2007). In HCC there is a correlation between activated Ras signaling and increased KLF6 alternative splicing. In cultured HCC cells, Ras signaling increases the expression of KLF6 SV1, thereby enhancing proliferation (Yea et al. 2008).

Antagonists of Proliferation in Liver Cancers

Glypican-3, which can enhance the pro-growth action of several growth factors, can itself inhibit HCC growth through induction of apoptosis (Pan et al. 2013). HCRP1/hepatocellular carcinoma-related protein 1, assigned to chromosome 8p21, encodes a growth inhibitory protein and is downregulated in HCC (Xu et al. 2003). Depletion of Aurora A kinase in HCC cells leads to upregulation of FoxO1 to induce cell cycle arrest (Lee et al. 2013). Overexpression of signal transducer and activator of transcription 1/STAT1 significantly reduced the proliferative activity of HCC cells and augments apoptosis (Chen et al. 2013a). Nogos (neurite outgrowth inhibitor proteins) form a family of three major members. Nogo-B is elevated in and plays a role for liver cirrhosis. Nogo-C is an inhibitor of cell proliferation and is extremely downregulated in HCC, associated with large tumor size and worse prognosis (Liu et al. 2014).

Substances Stimulating Liver Cancer Growth Produced by Platelets and Cells of the Tumor Microenvironment

Proliferation Stimulators Derived from Platelets

Platelets traffic to the microcirculation of liver cancers and may interact with tumor endothelia, where they can undergo viscous metamorphosis and aggregation, followed by the release of thrombocyte granule factors. Platelet aggregation associated with vascular thrombosis is a common event in liver cancer and is triggered by invading tumor cells. Endothelia of sinusoids and sinusoid-like vascular channels bind platelets in an integrin-dependent manner leading to platelet recruitment (Lalor et al. 2013). Subsequent to endothelial cell binding, platelets can induce hepatocyte proliferation (Takahashi et al. 2013) and endothelial cell apoptosis and therefore participate in regeneration and tumor-associated microvascular remodeling (Lisman and Porte 2010; Goubran et al. 2014).

Upon activation, platelets can release numerous factors from their dense and alpha granules. Through tumor cell-induced aggregation and formation of direct tumor cell-platelet contacts, cancer can induce thrombocyte activation and thus promote growth factor release. Platelet factors stimulate hepatocyte proliferation through induction of HGF and insulin-like growth factor 1/IGF-1 (Matsuo et al. 2008). Signal transducer and activator of transcription 3/STAT3 activation by IL-6 derived from SECs and Kupffer cells promotes regeneration upon contact with platelets (Murata et al. 2014). One source of this pathway, the Kupffer cells, fails in liver cancer, as HCCs do not contain Kupffer cells in any significant amount. However, platelets can stimulate liver cell proliferation even in the absence of Kupffer cells and secretion of TNF-alpha, due to their induction of HGF and IGF-1.

As platelets express P-selectin, they exert an influence on cancer cell homing to stroma and premetastatic niches (Coupland and Parish 2014) and tumor-stromal cell interactions which promote cell growth. Platelets can influence tumor growth also by induction of recruitment of growth-promoting immunomodulatory cells into stroma (Sitia 2014). Platelets can affect growth of cancer cells by release of platelet microparticles (PMPs; the former "platelet dust"). PMPs are fragments or microvesicles shed from the plasma membrane of thrombocytes undergoing activation, stress, or apoptosis. Via their cargo, PMPs can act in platelet-cancer loops that affect numerous functions of cancer cells, including growth and apoptosis (Goubran et al. 2015; Burnouf et al. 2014). The fragments measure 0.1–1.0 μm and represent the majority of circulating microparticles. Their cargo, which includes procoagulant phosphatidylserine, growth factors, and signal substances, modulates inflammatory responses in tumor microenvironment and cancer cell growth and invasion. Platelets can also have an effect on cancer cell growth by favoring tumor cell survival. Thrombocytes, via their close interaction with both endothelia and tumor cells, can protect cancer cells from shear-induced damage (Egan et al. 2014). Also the survival of nonneoplastic cells located to cancers is influenced by platelets. Phagocytosis of platelets by endothelial cells enhances the survival of these cells via inhibition of apoptosis by platelet constituents (Jiang et al. 2015). This mechanism may have an effect on the release of caspase-3-containing microparticles released by detached and apoptotic endothelial cells (Abid Hussein et al. 2005), whereby endothelial cells undergoing apoptosis become proadhesive for nonactivated platelets (Bombeli et al. 1999). Platelets diminish apoptosis in another cellular component of tumor microenvironment, i.e., monocytes. In monocytes that phagocytose platelets, apoptosis is inhibited by induced downregulation of caspase-3 and caspase-9 and upregulation of heat shock protein 70 (Lang et al. 2002). Neutrophils, which play a role in cancer cell invasion and growth, engage in complex interactions with platelets. Polarized neutrophils reveal a protruding domain that serves a scanning device for activated platelets via selectin

ligand PSGL-1. This interaction causes receptor redistribution and exerts a proinflammatory action (Sreeramkumar et al. 2014).

Proliferation Stimulators Derived from Cells of the Tumor Microenvironment/ Stroma

As outlined in detail in the chapters referring to primary liver cancer, hepatic metastases, and tumor stroma, the microenvironment or stroma of liver malignancies contains a complex set of mesenchymal cells that provide a niche for tumor progression and spread but also directly influence tumor cell growth. The stromal cell types capable to promote proliferation of HCC cells include hepatic stellate cells/HSCs, myofibroblasts/ MFBs, cancer-associated fibroblasts/CAFs, and tumor-associated macrophages/TAMs. HSCs interact with HCC cells in a complex manner, in that HCC cells determine the fate and growth of HSCs, and HSCs exert an influence on HCC proliferation, utility, and invasion (Amann et al. 2009; Carloni et al. 2014). HSCs can indirectly promote HCC growth via secretion of VEGFs which induce tumor angiogenesis (Lin et al. 2015). The activation of proangiogenic genes in HSCs is in turn stimulated by HCC cells, illustrating the intricate mutual influence tumor cells and stromal cells exert on each other (Sancho-Bru et al. 2010). HCCs specifically modulate the generation and function of HSCs located to their microenvironment. HCC cells under hypoxic conditions secrete platelet-derived growth factor-BB which in turn activates HSC proliferation, migration, and expression of VEGFA (Lu et al. 2015). HCC cells can secrete angiogenin which activates stromal HSCs and through this pathway tumor progression (Barcena et al. 2015). MFBs possess multifactorial proteomes and secretomes that can modulate HCC cell behavior (Slany et al. 2013). MFBs are a major source for hepatocyte growth factor/HGF in HCCs (Neaud et al. 1999; Guirouilh et al. 2001). HCCs themselves stimulate secretion of HGF by MFBs via a posttranscriptional mechanism (Guirouilh et al. 2000). MFBs can also promote tumor cell growth via affecting the extracellular matrix scaffold and its associated proteins. Neuropilin-1 produced by MFBs provides communications between these cells and soluble fibronectin which in turn promotes integrin-dependent fibronectin fibril assembly and thus a growth-promoting matrix (Yaqoob et al. 2012). Similar to HSCs, HCC cells can regulate the production and differentiation of MFBs and therefore generate cells which in turn modulate the cancer cells that gave rise to their production. For example, HCCs can secrete lysophostatidic acid which promotes the differentiation of peritumoral fibroblasts into MFBs (Mazzocca et al. 2011). A third group of stromal spindle cells, CAFs, are capable to secrete HGF and hence stimulate HCC cell proliferation (Jia et al. 2013). CAFs also upregulate CCL2, CCL26, interleukin-6, and LOXL2 genes related to proliferation of HCC cells (Lin et al. 2012).

References

Abid Hussein MN, Nieuwland R, Hau CM, Evers LM, Meesters EW, Sturk A (2005) Cell-derived microparticles contain caspase 3 in vitro and in vivo. J Thromb Haemost 3:888–896

Abou-Shady M, Baer HU, Friess H, Berberat P, Zimmermann A, Graber H, Gold LI et al (1999) Transforming growth factor betas and their signaling receptors in human hepatocellular carcinoma. Am J Surg 177:209–215

Abu Dayyeh BK, Yang M, Fuchs BC, Karl DL, Yamada S, Sninsky JJ, O'Brien TR, Dienstag JL, Tanabe KK, Chung RT et al (2011) A functional polymorphism in the epidermal growth factor gene is associated with risk for hepatocellular carcinoma. Gastroenterology 141:141–149

Amann T, Bataille F, Spruss T, Mühlbauer M, Gäbele E, Schölmerich J, Kiefer P, Bosserhoff AK, Hellerbrand C (2009) Activated hepatic stellate cells promote tumorigenicity of hepatocellular carcinoma. Cancer Sci 100:646–653

Amann T, Bataille F, Spruss T, Dettmer K, Wild P, Liedtke C, Mühlbauer M, Kiefer P, Oefner PJ, Trautwein C, Bosserhoff AK et al (2010) Reduced expression of fibroblast growth factor receptor 2IIIb in hepatocellular carcinoma induces a more aggressive growth. Am J Pathol 176:1433–1442

Ang CS, Sun MY, Huitzil-Melendez DF, Chou JF, Capanu M, Jarnagin W, Fong Y et al (2013) c-MET and HGF mRNA expression in hepatocellular carcinoma: correlation with clinicopathological features and survival. Anticancer Res 33:3241–3245

Arai Y, Totoki Y, Hosoda F, Shirota T, Hama N, Nakamura H, Ojima H, Furuta K, Shimada K, Okusaka T, Kosuge T et al (2014) Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology 59:1427–1434

Barcena C, Stefanovic M, Tutusaus A, Martinez-Nieto GA, Martinez L, Garcia-Ruiz C, de Mingo A, Caballeria J, Fernandez-Checa JC et al (2015) Angiogenesis secretion from hepatoma cells activates hepatic stellate cells to amplify a self-sustained cycle promoting liver cancer. Sci Rep 5:7916

Beauvais DM, Rapraeger AC (2010) Syndecan-1 couples the insulin-like growth factor-1 receptor to inside-out integrin activation. J Cell Sci 123:3796–3807

Berasain C, Castillo J, Perugorria MJ, Prieto J, Avila MA (2007) Amphiregulin: a new growth factor in hepatocarcinogenesis. Cancer Lett 254:30–41

Berasain C, Perugorria MJ, Latasa MU, Castillo J, Goni S, Santamaria M, Prieto J, Avila MA (2009) The epidermal growth factor receptor: a link between inflammation and liver cancer. Exp Biol Med (Maywood) 234:713–725

Berasain C, Ujue Latasa M, Urtasun R, Goni S, Elizalde M, Garcia-Irigoyen O, Azcona M, Prieto J, Avila MA (2011) Epidermal growth factor receptor (EGFR) crosstalks in liver cancer. Cancers (Basel) 3:2444–2461

Berasain C, Nicou A, Garcia-Irigoyen O, Latasa MU, Urtasun R, Elizalde M, Salis F, Perugorria MJ, Prieto J, Recio JA et al (2012) Epidermal growth factor receptor signaling in hepatocellular carcinoma: inflammatory activation and a new intracellular regulatory mechanism. Dig Dis 30:524–531

Bombeli T, Schwartz BR, Harlan JM (1999) Endothelial cells undergoing apoptosis become proadhesive for nonactivated platelets. Blood 93:3831–3838

Breuhahn K, Schirmacher P (2010) Signaling networks in human hepatocarcinogenesis – novel aspects and therapeutic options. Prog Mol Biol Transl Sci 97:251–277

Breuhahn K, Longerich T, Schirmacher P (2006) Dysregulation of growth factor signaling in human hepatocellular carcinoma. Oncogene 25:3787–3800

Brockhausen J, Tay SS, Grzelak CA, Bertolino P, Bowen DG, d'Avigdor WM, Teoh N et al (2014) miR-181a mediates TGF-b-induced hepatocyte EMT and is dysregulated in cirrhosis and hepatocellular cancer. Liver Int. doi:10.1111/liv.12517

Buckley AF, Burgart LJ, Sahai V, Kakar S (2008) Epidermal growth factor receptor expression and gene copy number in conventional hepatocellular carcinoma. Am J Clin Pathol 129:245–251

Burnouf T, Goubran HA, Chou ML, Devos D, Radosevic M (2014) Platelet microparticles: detection and assessment of their paradoxical functional roles in disease and regenerative medicine. Blood Rev 28:155–166

Carloni V, Luong TV, Rombouts K (2014) Hepatic stellate cells and extracellular matrix in hepatocellular carcinoma: more complicated than ever. Liver Int 34:834–843

Chen G, Wang H, Xie S, Ma J, Wang G (2013a) STAT1 negatively regulates hepatocellular carcinoma cell proliferation. Oncol Rep 29:2303–2310

Chen Z, Xie B, Zhu Q, Xia Q, Jiang S, Cao R, Shi L, Qi D, Li X, Cai L (2013b) FGFR4 and TGF-β1 expression in hepatocellular carcinoma: correlation with clinicopathological features and prognosis. Int J Med Sci 10:1868–1875

Chun YS, Huang M, Rink L, Von Mehren M (2014) Expression levels of insulin-like growth factors and receptors in hepatocellular carcinoma: a retrospective study. World J Surg Oncol 12:231

Collier JD, Guo K, Mathew J, May FE, Bennett MK, Corbett IP, Bassendine MF, Burt AD (1992) c-erbB2 oncogene expression in hepatocellular carcinoma and cholangiocarcinoma. J Hepatol 14:377–380

Coupland LA, Parish CR (2014) Platelets, selectins, and the control of tumor metastasis. Semin Oncol 41:422–434

Dayoub R, Wagner H, Bataille F, Stöltzing O, Spruss T, Buechler C, Schlitt HJ, Weiss TS (2011) Liver regeneration associated protein (ALR) exhibits antimetastatic potential in hepatocellular carcinoma. Mol Med 17:221–228

Deli A, Kreidl E, Santifaller S, Trotter B, Seir K, Berger W, Schulte-Hermann R, Rodgarkia-Dara C et al (2008) Activins and activin antagonists in hepatocellular carcinoma. World J Gastroenterol 14:1699–1709

Egan K, Cooke N, Kenny D (2014) Living in shear: platelets protect cancer cells from shear induced damage. Clin Exp Metastasis 31:697–704

Fausto N (1991) Growth factors in liver development, regeneration and carcinogenesis. Prog Growth Factor Res 3:219–234

Fuchs BC, Hoshida Y, Fujii T, Wei L, Yamada S, Lauwers GY, McGinn CM, DePeralta DK, Chen X, Kuroda T, Lanuti M et al (2014) Epidermal growth factor receptor inhibition attenuates liver fibrosis and development of hepatocellular carcinoma. Hepatology 59:1577–1590

Gauglhofer C, Sagmeister S, Schrottmaier W, Fischer C, Rodgarkia-Dara C, Mohr T, Stättner S, Bichler C, Kandioler D et al (2011) Up-regulation of the fibroblast growth factor 8 subfamily in human hepatocellular carcinoma for cell survival and neoangiogenesis. Hepatology 53:854–864

Gauglhofer C, Paur J, Schrottmaier WC, Wingelhofer B, Huber D, Naegelen I, Pirker C, Mohr T, Heinzle C, Holzmann K et al (2014) Fibroblast growth factor receptor 4: a putative key driver for the aggressive phenotype of hepatocellular carcinoma. Carcinogenesis 35:2331–2338

Gong Y, Cui L, Minuk GY (2000) The expression of insulin-like growth factor binding proteins in human hepatocellular carcinoma. Mol Cell Biochem 207:101–104

Goubran HA, Stakiw J, Radosevic M, Burnouf T (2014). Platelets effects on tumor growth. Semin Oncol 41:359–369

Goubran HA, Burnouf T, Stakiw J, Seghatchian J (2015). Platelet microparticle: a sensitive physiological "fine tuning" balancing factor in health and disease. Transfus Apher Sci 52:12–18

Grandal MV, Madshus IH (2008) Epidermal growth factor receptor and cancer: control of oncogenic signalling by endocytosis. J Cell Mol Med 12:1527–1534

Grusch M, Drucker C, Peter-Vörösmarty B, Erlach N, Lackner A, Losert A, Macheiner D et al (2006) Deregulation of the activin/follistatin system in hepatocarcinogenesis. J Hepatol 45:673–680

Guirouilh J, Castroviejo M, Balabaud C, Desmoulière A, Rosenbaum J (2000) Hepatocarcinoma cells stimulate hepatocyte growth factor secretion in human liver myofibroblasts. Int J Oncol 17:777–781

Guirouilh J, le Bail B, Boussarie L, Balabaud C, Bioulac-Sage P, Desmoulière A, Schuppan D, Rosenbaum J (2001) Expression of hepatocyte growth factor in human hepatocellular carcinoma. J Hepatol 34:78–83

Gupta DK, Singh N, Sahu DK (2014) TGF-β mediated crosstalk between malignant hepatocyte and tumor microenvironment in hepatocellular carcinoma. Cancer Growth Metastasis 7:1–8

Gutschner T, Hämmerle M, Pazaitis N, Bley N, Fiskin E, Uckelmann H, Heim A, Gross M, Hofmann N, Geffers R, Slawran B et al (2014) Insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) is an important protumorigenic factor in hepatocellular carcinoma. Hepatology 59:1900–1911

Han J, Tsukada Y, Hara E, Kitamura N, Tanaka T (2005) Hepatocyte growth factor induces redistribution of p21 (CIP1) and p27(KIP1) through ERK-dependent p16 (INK4a) up-regulation, leading to cell cycle arrest at G1 in HepG2 hepatoma cells. J Biol Chem 280:31548–31556

Harada K, Shiota G, Kawasaki H (1999) Transforming growth factor-alpha and epidermal growth factor receptor in chronic liver disease and hepatocellular carcinoma. Liver 19:318–325

Harimoto N, Taguchi K, Shirabe K, Adachi E, Sakaguchi Y, Toh Y, Okamura T, Kayashima H, Taketomi A, Maehara Y (2010) The significance of fibroblast growth factor receptor 2 expression in differentiation of hepatocellular carcinoma. Oncology 78:361–368

Herrera B, Garcia-Alvaro M, Cruz S, Walsh P, Fernandez M, Roncero C, Fabregat I et al (2013) BMP9 is a proliferative and survival factor for human hepatocellular carcinoma cells. PLoS One 8:e69535

Higashiyama S, Iwabuki H, Morimoto C, Hieda M, Inoue H, Matsushita N (2008) Membrane-anchored growth factors, the epidermal growth factor family: beyond receptor ligands. Cancer Sci 99:214–220

Ho HK, Pok S, Streit S, Ruhe JE, Hart S, Lim KS, Loo HL, Aung MO, Lim SG, Ullrich A (2009) Fibroblast growth factor receptor 4 regulates proliferation, anti-apoptosis and alpha-fetoprotein secretion during hepatocellular carcinoma progression and represents a potential target for therapeutic intervention. J Hepatol 50:118–127

Hsia CC, Axiotis CA, Di Bisceglie AM, Tabor E (1992) Transforming growth factor-alpha in human hepatocellular carcinoma and coexpression with hepatitis B surface antigen in adjacent liver. Cancer 70:1049–1056

Hsieh SY, He JR, Hsu CY, Chen WJ, Bera R, Lin KY, Shih TC, Yu MC, Lin YJ, Chang CJ, Weng WH, Huang SF (2011) Neuregulin/erythroblastic leukemia viral oncogene homolog 3 autocrine loop contributes to invasion and early recurrence of human hepatoma. Hepatology 53:504–516

Huang P, Xu X, Wang L, Zhu B, Wang X, Xia J (2014) The role of EGF-EGFR signalling pathway in hepatocellular carcinoma inflammatory microenvironment. J Cell Mol Med 18:218–230

Huitzil FD, Sun MY, Capanu M, Blumgart LH, Jarnagin WR, Fong Y, DeMatteo RP et al (2008) Expression of the c-met and HGF in resected hepatocellular carcinoma (rHCC): correlation with clinicopathological features (CP) and overall survival (OS). J Clin Oncol 26:4599

Hung TM, Ho CM, Liu YC, Lee JL, Liao YR, Wu YM, Ho MC, Chen CH, Lai HS, Lee PH (2014) Up-regulation of microRNA-190b plays a role for decreased IGF-1 that induces insulin resistance in human hepatocellular carcinoma. PLoS One 9:e89446

Ikeda Y, Kajiyama K, Yamashita Y, Ikegami T, Uchiyama H, Soejima Y, Kawanaka H, Ikeda T, Morita M, Oki E, Saeki H et al (2013) Differential expression of insulin-like growth factor 1 in human primary liver cancer. Fukuoka Igaku Zasshi 104:334–338

Ilowski M, Putz C, Weiss TS, Brand S, Jauch KW, Hengstler JG, Thasler WE (2010) Augmenter of liver regeneration causes different kinetics of ERK1/2 and Akt/PKB phosphorylation than EGF and induces hepatocytes proliferation in an EGF receptor independent and liver specific manner. Biochem Biophys Res Commun 394:915–920

Ilowski M, Kleespies A, de Toni EN, Donabauer B, Jauch KW, Hengstler JG, Thasler WE (2011) Augmenter of liver regeneration (ALR) protects human hepatocytes against apoptosis. Biochem Biophys Res Commun 404:148–152

Jia CC, Wang TT, Liu W, Fu BS, Hua X, Wang GY, Li J, Li X, Wu XY, Tai Y, Zhou J et al (2013) Cancer-associated fibroblasts from hepatocellular carcinoma promote malignant cell proliferation by HGF secretion. PLoS One 8:e63243

Jiang P, Ren YL, Lan Y, Li JL, Luo J, Li J, Cai JP (2015) Phagocytosis of platelets enhances endothelial cell survival under serum deprivation. Exp Bio Med (Maywood) 240:876–883

Kaposi-Novak P, Lee JS, Gomez-Quiroz L, Coulouarn C, Factor VM, Thorgeirsson SS (2006) Met-regulated expression signature defines a subset of human hepatocellular carcinomas with poor prognosis and aggressive phenotype. J Clin Invest 116:1582–1595

Kira S, Nakanishi T, Suemori S, Kitamoto M, Watanabe Y, Kajiyama G (1997) Expression of transforming growth

factor alpha and epidermal growth factor receptor in human hepatocellular carcinoma. Liver 17:177–182
Kondo S, Ojima H, Tsuda H, Hashimoto J, Morizane C, Ikeda M, Ueno H, Tamura K et al (2013) Clinical impact of c-Met expression and its gene amplification in hepatocellular carcinoma. Int J Clin Oncol 18:207–213
Kremer-Tal S, Reeves HL, Narla G, Thung SN, Schwartz M, Difeo A, Katz A, Bruix J et al (2004) Frequent inactivation of the tumor suppressor Kruppel-like factor 6 (KLF6) in hepatocellular carcinoma. Hepatology 40:1047–1052
Kremer-Tal S, Narla G, Chen Y, Hod E, DiFeo A, Yea S, Lee JS, Schwartz M, Thung SN et al (2007) Downregulation of KLF6 is an early event in hepatocarcinogenesis, and stimulates proliferation while reducing differentiation. J Hepatol 46:645–654
Lalor PF, Herbert J, Bicknell R, Adams DH (2013) Hepatic sinusoidal endothelium avidly binds platelets in an integrin-dependent manner, leading to platelet and endothelial activation and leukocyte recruitment. Am J Physiol Gastrointest Liver Physiol 304: G469–G478
Lanaya H, Natarajan A, Komposch K, Li L, Amberg N, Chen L, Wculek SK, Hammer M, Zenz R, Peck-Radosavljevic M et al (2014) EGFR has a tumour-promoting role in liver macrophages during hepatocellular carcinoma formation. Nat Cell Biol 16:972–981
Lang D, Dohle F, Terstesse M, Bangen P, August C, Pauels HG, Heidenreich S (2002) Down-regulation of monocyte apoptosis by phagocytosis of platelets: involvement of a caspase-9, caspase-3, and heat shock protein 70-dependent pathway. J Immunol 168:6152–6158
Latasa MU, Salis F, Urtasun R, Garcia-Irigoyen O, Elizalde M, Uriarte I, Santamaria M et al (2012) Regulation of amphiregulin gene expression by β-catenin signaling in human hepatocellular carcinoma cells: a novel crosstalk between FGF19 and the EGFR system. PLoS One 7:e52711
Lee SY, Lee G, Woo DH, Park NH, Cha HJ, Moon YH, Han IS (2013) Depletion of Aurora A leads to upregulation of FoxO1 to induce cell cycle arrest in hepatocellular carcinoma cells. Cell Cycle 12:67–75
Lin BC, Desnoyers LR (2012) FGF19 and cancer. Adv Exp Med Biol 728:183–194
Lin ZY, Chuang YH, Chuang WL (2012) Cancer-associated fibroblasts up-regulate CCL2, CCL26, IL-6 and LOXL2 genes related to promotion of cancer progression in hepatocellular carcinoma cells. Biomed Pharmacother 66:525–529
Lin N, Chen Z, Lu Y, Li Y, Hu K, Xu R (2015) Role of activated hepatic stellate cells in proliferation and metastasis of hepatocellular carcinoma. Hepatol Res 45:326–336
Lisman T, Porte RJ (2010) The role of platelets in liver inflammation and regeneration. Semin Thromb Hemost 36:170–174
Liu X, Jiang W, Aucejo F, Kim R, Miller C, Byrne M, Lopez R, Yerian L (2011) Insulin-like growth factor I receptor β expression in hepatocellular carcinoma. Hum Pathol 42:882–891
Liu X, Cui SJ, Zhu SJ, Geng DC, Yu L (2014) Nogo-C contributes to HCC tumorigenesis via suppressing cell growth and its interactome analysis with comparative proteomics research. Int J Clin Exp Pathol 7:2044–2055
Liu Q, Xu Z, Mao S, Chen W, Zeng R, Zhou S, Liu J (2015) Effect of hypoxia inducible factor-1α, insulin-like growth factor I and vascular endothelial growth factor expression in hepatocellular carcinoma HepG2 cells. Oncol Lett 9:1142–1148
Lu Y, Lin N, Chen Z, Xu R (2015) Hypoxia-induced secretion of platelet-derived growth factor-BB by hepatocellular carcinoma cells increases activated hepatic stellate cell proliferation, migration and expression of vascular endothelial growth factor-A. Mol Med Rep 11:691–697
Matsuo R, Ohkohchi N, Murata S, Ikeda O, Nakano Y, Watanabe M, Hisakura K, Myronovych A, Kubota T, Narimatsu H et al (2008) Platelets strongly induce hepatocyte proliferation with IGF-1 and HGF in vitro. J Surg Res 145:279–286
Mazzocca A, Dituri F, Lupo L, Quaranta M, Antonaci S, Giannelli G (2011) Tumor-secreted lysophostatidic acid accelerates hepatocellular carcinoma progression by promoting differentiation of peritumoral fibroblasts in myofibroblasts. Hepatology 54:920–930
Moon WS, Park HS, Yu KH, Park MY, Kim KR, Jang KY, Kim JS, Cho BH (2006) Expression of betacellulin and epidermal growth factor receptor in hepatocellular carcinoma: implications for angiogenesis. Hum Pathol 37:1324–1332
Morimitsu Y, Hsia CC, Kojiro M, Tabor E (1995) Nodules of less-differentiated tumor within or adjacent to hepatocellular carcinoma: relative expression of transforming growth factor-alpha and its receptor in the different areas of tumor. Hum Pathol 26:1126–1132
Murata S, Maruyama T, Nowatari T, Takahashi K, Ohkohchi N (2014) Signal transduction of platelet-induced liver regeneration and decrease of liver fibrosis. Int J Mol Sci 15:5412–5425
Musch A, Rabe C, Paik MD, Berna MJ, Smitz V, Hoffmann P, Nischalke HD, Sauerbruch T et al (2005) Altered expression of TGF-beta receptors in hepatocellular carcinoma – effects of a constitutively active TGF-beta type I receptor mutant. Digestion 71:78–91
Nalesnik MA, Michalopoulos GK (2012) Growth factor pathways in development and progression of hepatocellular carcinoma. Front Biosci (Schol Ed) 4:1487–1515
Neaud V, Faouzi S, Guirouilh J, Monvoisin A, Rosenbaum J (1999) Hepatocyte growth factor secreted by human liver myofibroblasts increases invasiveness of hepatocellular carcinoma cells. Curr Top Pathol 93:195–203
Pan Z, Chen C, Long H, Lei C, Tang G, Li L, Feng J, Chen F (2013) Overexpression of GPC3 inhibits hepatocellular carcinoma cell proliferation and invasion through induction of apoptosis. Mol Med Rep 7:969–974

Pannain VL, Morais JR, Damasceno-Ribeiro O, Avancini-Alves V (2012) Transforming growth factor a immunoreactivity. A study in hepatocellular carcinoma and in non-neoplastic liver tissue. Ann Hepatol 11:495–499

Poh W, Wong W, Ong H, Aung MO, Lim SG, Chua BT, Ho HK (2012) Klotho-beta overexpression as a novel target for suppressing proliferation and fibroblast growth factor receptor-4 signaling in hepatocellular carcinoma. Mol Cancer 11:14

Qiu WH, Zhou BS, Chu PG, Chen WG, Chung C, Shih J, Hwu P, Yeh C, Lopez R, Yeh Y (2005) Over-expression of fibroblast growth factor receptor-3 in human hepatocellular carcinoma. World J Gastroenterol 11:5266–5272

Rashad NM, El-Shal AS, Abd Elbary EH, Abo Warda MH, Hegazy O (2014) Impact of insulin-like growth factor 2, insulin-like growth factor receptor 2, insulin receptor substrate 2 genes polymorphisms on susceptibility and clinicopathological features of hepatocellular carcinoma. Cytokine 68:50–58

Sancho-Bru P, Juez E, Moreno M, Khurdayan V, Morales-Ruiz M, Colmenero J, Arroyo V, Brenner DA, Ginès P, Bataller R (2010) Hepatocarcinoma cells stimulate the growth, migration and expression of pro-angiogenic genes in human hepatic stellate cells. Liver Int 30:31–41

Sandhu DS, Baichoo E, Roberts LR (2014) Fibroblast growth factor signaling in liver carcinogenesis. Hepatology 59:1166–1173

Sitia G (2014) Platelets promote liver immunopathology contributing to hepatitis B virus-mediated hepatocarcinogenesis. Semin Oncol 41:402–405

Slany A, Haudek-Prinz V, Zwicki H, Stättner S, Grasl-Kraupp B, Gerner C (2013) Myofibroblasts are important contributors to human hepatocellular carcinoma: evidence for tumor promotion by proteome profiling. Electrophoresis 34:3315–3325

Sreeramkumar V, Adrover JM, Ballesteros I, Cuartero MI, Rossaint J, Bilbao I, Nacher M, Pitaval C, Radovanovic I et al (2014) Neutrophils scan for activated platelets to initiate inflammation. Science 346:1234–1238

Sugano Y, Matsuzaki K, Tahashi Y, Furukawa F, Mori S, Yamagata H, Yoshida K et al (2003) Distortion of autocrine transforming growth factor beta signal accelerates malignant potential by enhancing cell growth as well as PAI-1 and VEGF production in human hepatocellular carcinoma cells. Oncogene 22:2309–2321

Suzuki K, Hayashi N, Yamada Y, Yoshihara H, Miyamoto Y, Ito Y, Ito T, Katayama K et al (1994) Expression of the c-met protooncogene in human hepatocellular carcinoma. Hepatology 20:1231–1236

Takahashi K, Kozuma Y, Suzuki H, Tamura T, Maruyama T, Fukunaga K, Murata S, Ohkohchi N (2013) Human platelets promote liver regeneration with Kupffer cells in SCID mice. J Surg Res 180:62–72

Tang L, Sun H, Zhang L, Deng JC, Guo H, Zhang L, Liu Q (2009) Effects of the augmenter of liver regeneration on the biological behavior of hepatocellular carcinoma. Saudi Med J 30:1001–1009

Thasler WE, Schlott T, Thelen P, Hellerbrand C, Bataille F, Lichtenauer M, Schlitt HJ, Jauch KW, Weiss TS (2005) Expression of augmenter of liver regeneration (ALR) in human liver cirrhosis and carcinoma. Histopathology 47:57–66

Ueki T, Fujimoto J, Suzuki T, Yamamoto H, Okamoto E (1997) Expression of hepatocyte growth factor and its receptor c-met proto-oncogene in hepatocellular carcinoma. Hepatology 25:862–866

Wachter DL, Kristiansen G, Soll C, Hellerbrand C, Breuhahn K, Fritzsche F, Agaimy A, Hartmann A, Riener MO (2012) Insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression in hepatocellular carcinoma. A clinicopathological analysis with emphasis on diagnostic values. Histopathology 60:278–286

Wang CL, Wan YL, Liu YC, Huang ZQ (2006) TGF-beta1/SMAD signaling pathway mediates p53-dependent apoptosis in hepatoma cell lines. Chin Med Sci J 21:33–35

Wang S, Pashtan I, Tsutsumi S, Xu W, Neckers L (2009) Cancer cells harboring MET gene amplification activate alternative signaling pathways to escape MET inhibition but remain sensitive to hep90 inhibitors. Cell Cycle 8:2050–2056

Wang W, Ma XP, Shi Z, Zhang P, Ding DL, Huang HX, Saiyin HG, Chen TY, Lu PX, Wang NJ, Yu H, Sun J et al (2014) Epidermal growth factor receptor pathway polymorphisms and the prognosis of hepatocellular carcinoma. Am J Cancer Res 5:396–410

Xu Z, Liang L, Wang H, Li T, Zhao M (2003) HCRP1, a novel gene that is downregulated in hepatocellular carcinoma, encodes a growth-inhibitory protein. Biochem Biophys Res Commun 311:1057–1066

Yamazaki K, Masugi Y, Sakamoto M (2011) Molecular pathogenesis of hepatocellular carcinoma: altering transforming growth factor-b signaling in hepatocarcinogenesis. Dig Dis 29:284–288

Yan XD, Yao M, Wang L, Zhang HJ, Yan MJ, Gu X, Shi Y, Chen J, Dong Z, Yao DF (2013) Overexpression of insulin-like growth factor-I receptor as a pertinent biomarker for hepatocytes malignant transformation. World J Gastroenterol 19:6084–6092

Yaqoob U, Cao S, Shergill U, Jagavelu K, Geng Z, Yin M, de Assuncao TM, Cao Y, Szabolcs A, Thorgeirsson S et al (2012) Neuropilin-1 stimulates growth in increasing fibronectin fibril assembly in the tumor microenvironment. Cancer Res 72:4047–4059

Yea S, Narla G, Zhao X, Garg R, Tal-Kremer S, Hod E, Villanueva A, Loke J, Tarocchi M et al (2008) Ras promotes growth by alternative splicing-mediated inactivation of the KLF6 tumor suppressor in hepatocellular carcinoma. Gastroenterology 134: 1521–1531

Yeh MM, Larson AM, Campbell JS, Fausto N, Rulyak SJ, Swanson PE (2007) The expression of transforming growth factor-alpha in cirrhosis, dysplastic nodules, and hepatocellular carcinoma: an

immunohistochemical study of 70 cases. Am J Surg Pathol 31:681–689

Yoneda N, Sato Y, Kitao A, Ikeda H, Sawada-Kitamura S, Miyakoshi M, Harada K, Sasaki M, Matsui O, Nakanuma Y (2011) Epidermal growth factor induces cytokeratin 19 expression accompanied by increased growth abilities in human hepatocellular carcinoma. Lab Invest 91:262–272

Yu HY, Xiang DR, Huang HJ, Li J, Sheng JF (2010) Expression level of augmenter of liver regeneration in patients with hepatic failure and hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 9:492–498

Yuan JM, Fan Y, Ognjanovic S, Wang R, Van Den Berg D, Govindarajan S, Yu MC (2013) Genetic polymorphisms of epidermal growth factor in relation to risk of hepatocellular carcinoma: two case-control studies. BMC Gastroenterol 13:32

Zaiss DM, Gause WC, Osborne LC, Artis D (2015) Emerging functions of amphiregulin in orchestrating immunity, inflammation, and tissue repair. Immunity 42:216–226

Zender L, Villanueva A, Tovar V, Sia D, Chiang DY, Llovet JM (2010) Cancer gene discovery in hepatocellular carcinoma. J Hepatol 52:921–929

Zhang J, Wang WL, Li Q, Qiao Q (2004) Expression of transforming growth factor-alpha and hepatitis B surface antigen in human hepatocellular carcinoma tissues and its significance. World J Gastroenterol 10:830–833

Zimonjic DB, Durkin ME, Keck-Waggoner CL, Park SW, Thorgeirsson SS, Popescu NC (2003) SMAD5 gene expression, rearrangements, copy number, and amplification at fragile site FRA5C in human hepatocellular carcinoma. Neoplasia 5:390–396

Growth Regulation in Hepatobiliary Cancer: Regulators of the Cell Division Cycle

174

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_174

Cyclins: Key Switches for Cell Cycle Entry and Progression

Introduction

The entry into the progression through and the exit from cell cycle is a multistep process that its regulated by numerous factors, both in normal and neoplastic cells (reviews: Ford and Pardee 1999; John et al. 2001; Vermeulen et al. 2003; Murray 2004; Fung and Poon 2005). Cyclins regulate the cell division cycle in a cycle phase-specific manner and are key switches for G1/S entry and entry into mitosis. Their expression changes in a cyclical fashion along the cell cycle, hence their name. However, not all cyclins known today show this oscillating pattern. Cyclins that show phase-specific expression fluctuations activate cyclin-dependent kinases/CDKs by formation of specific cyclin-CDK complexes that are the drivers of cell cycle entry and progression through phosphorylation of numerous substrates. In addition to CDK-interacting cyclins, there are several orphan cyclins which have no known CDK partner. In order to activate CDKs in a tightly controlled fashion, cyclins are synthesized in a transcriptionally regulated manner and eliminated via proteasomal degradation at defined set points (Udvardy 1996). This cycle of synthesis and destruction forms the substrate of the master clock which determinates the orderly function of the cell division cycle, a process fundamentally deregulated in cancer cells (Johnson and Walker 1999; Stacey 2010; Bloom and Cross 2007).

Types and Functions of Cyclins

The numerous known cyclins are members of several families (families A to L, O, T, and Y). Several cyclin types consist of subtypes. The cyclins most important for cell cycle regulation form two main groups, summarized in Table 1.

G1/S cyclins rise in G1 and fall in early S phase. In the G1/S transition and in S, cyclin-CDK complexes start to induce DNA synthesis, the hallmark of S phase. In G2, M cyclin concentrations start to increase, and their complexing of CDKs is the mechanism for M entry (the G2/M transition).

Table 1 Major cyclins centrally involved in cell cycle regulation

G1/S cyclins (*control of G1 to S transition*)	
Cyclin A and the cyclin A-CDK2 complex	Active in S phase
Cyclin D and the cyclin D-CDK4 complex	G1/S transition
Cyclin D and the cyclin D-CDK6 complex	G1/S transition
Cyclin E and the cyclin E-CDK2 complex	G1/S transition
G2/M cyclins (*control of G2 to M transition*)	
Cyclin A and the cyclin A-CDK1 complex	G2/M transition
Cyclin B and the cyclin B-CDK1 complex	G2/M transition

Cyclin A

Cyclin A exists in two forms, cyclin A1 and cyclin A2, the genes being located on chromosomes 13q12.3–q13 and 4q27, respectively. Cyclin A can activate two different CDKs and functions in both S and M phases of cell cycle (Pines and Hunter 1992). It starts to accumulate during S, whereby its phase-specific synthesis is controlled at the transcription level involving several transcription factors, specifically E2F regulated by Rb protein, and is rapidly destroyed before metaphase via ubiquitination and proteasomal degradation. With its cyclin box, cyclin A interacts with a distinct domain of its two CDK partners, CDK1 (p34) and CDK2, termed PSTAIRE to form cyclin-CDK complexes. The cyclin A-CDK2 complex is required for passage into S, while the cyclin A-CDK1 complex is required for entry into M phase of the cell cycle. In the course of G1/S transition, newly synthesized cyclin A associates in the nucleus with CDK2, replacing cyclin E which was active before S as an initiator of the DNA pre-replication complex, rendering chromatin ready for DNA synthesis. At a distinct level, the novel cyclin A-CDK2 complex terminates the

assembly of the initiating cyclin E-CDK2 complex and then initiates DNA synthesis. During the cycle, cyclin A has a second important function. Via Cdc6, it ensures that DNA is replicated only one per cell cycle through inhibition of additional replication complex formation. In late G2, cyclin A associates with CDK1, a complex required for the activation of the cyclin B-CDK1 complex which is necessary for G2/M transition. Afterward, cyclins A and B are degraded and therefore switched off, until a new synthesis round will take place. Cyclins A and B possess a destruction box, and cyclins D and E have a PEST sequence, domains that are required for ubiquitin-mediated cyclin proteolysis in proteasomes at the end of the controlled cycle phase (Hershko 1999). The synthesis-degradation cycle found for cyclin A is exemplary for the timely expression of cyclins along the cell division cycle and illustrated as to how a cyclin switch can be put into on or off positions. In addition to its action on CDKs, cyclin A can promote microtubule detachment from kinetochores in prometaphase and is therefore directly involved in control of faithful chromosome segregation, protecting from microtubule-kinetochore binding errors.

Cyclin B

As outlined in the preceding paragraph, cyclin B is a mitotic cyclin involved, together with its partner CDK1, in the regulation of G2/M transition. Cyclin B exists in three forms (cyclins B1, B2, and B3), allocated to chromosomes 5q12, 15q21.3, and Xp11, respectively. The three B-type cyclins differ in their subcellular localization. Both B1 and B2 can associate with CDK1. Through tightly controlled synthesis, activity of the cyclin B-CDK1 complex (also termed mitosis-promoting factor, MPF) rises during the S phase of the cycle until M and is then abruptly degraded (Hershko 1999; Parry and O'Farrell 2001). In contrast to cyclins A and B, CDK1 is constitutively expressed all through the cycle (see below). The cyclin B-CDK1 complex activates its activating phosphatase, Cdc25, and inhibits its inhibiting kinase, Wee1. This process is associated with inhibiting of the phosphatase that counteracts the complex (Domingo-Sananes et al. 2011). The cyclin B1-CDK1 complex phosphorylates a microtubule-bundling protein, PRC1, which plays a critical role in the biogenesis of mitotic spindles and the spindle midzone. PRC1 phosphorylation by the cyclin 1 kinase complex is promoted by the mitotic kinase TOPK (Abe et al. 2007). There is recent evidence that cyclin B3 is a mitotic cyclin promoting metaphase-anaphase transition and being a late-destroyed cyclin subject to degradation by the APC/C-Cdc20 complex late in metaphase (Yuan and O'Farrell 2015). The cyclin B-CDK2 complex closely interacts with microtubule-associated serine-threonine kinase-like protein or MAST-L, the human orthologue of Greatwall kinase (Voets and Wolthuis 2010). This kinase promotes mitotic entry and maintenance of mitosis by inhibiting the protein phosphatase 2A/PP2A, a phosphatase which dephosphorylates cyclin B-CDK2 substrates (Burgess et al. 2010; Gharbi-Ayachi et al. 2010; Glover 2012; Lorca and Castro 2013; Wang et al. 2014a). MAST-L promotes cyclin B1 destruction by enforcing Cdc20-independent binding of cyclin B1 to the cyclosome (Voets and Wolthuis 2015).

Cyclin C

Cyclin C, encoded by the CCNC gene cyclin D1 (encoded by the gene CCDC on chromosome 6q16.2), is a cell cycle protein that regulates transition from G1 to S. Cyclin C interacts with CDK8, and this complex phosphorylates the C-terminal domain of the large subunit of RNA polymerase II, whereby this activity peaks in the G1 phase as a preparation for entry into S. The cyclin C-CDK8 complex is also present in some mammalian mediator-like protein complexes which repress activated transcription. Activated CDK8 phosphorylates cyclin H, repressing the ability of transcription initiation factor IIH to activate transcription.

Cyclin D

Cyclin D exists in three forms (cyclins D1, D2, and D3) and is a G1/S cyclin that is synthesized during G1 and promotes G1/S transition. The genes of the three D-type cyclins are localized on chromosomes 11q13, 12p13, and 6p21, respectively. Cyclins D are synthesized in response to growth factors and are regulated by downstream mitogen receptors through Ras/MAP kinase and Wnt/beta-catenin signaling. The MAP kinase ERK activates the transcription factors Myc and AP-1, causing transcription of the cyclin D, CDK4, and CDK6 genes to form complexes driving G1/S transition. Cyclin D can interact with four CDKs, i.e., CDK2, CDK4, CDK5, and CDK6. The cyclin D-CDK4/CDK6 complex that forms in late G1 phosphorylates and thus inhibits the Rb protein (see below), leading to induction of several proteins required for S phase, including cyclin E. Cyclin D1 has functions that are independent of CDK-mediated cell cycle progression. It regulates transcription factors, coactivators, and corepressors involved in chromatin remodeling. The expression of cyclin D and its complexes are also regulated by p21 and p27 (Kip1) proteins (see below). For their function, cyclin D1-cyclin-dependent kinase 2 complexes require the scaffold protein p21 for their assembly, activation, and substrate specificity (Jahn et al. 2013). Stabilized nuclear localization of cyclin D1 is mediated by c-Fos overexpression (Güller et al. 2008). After S, cyclin D-CDK complexes are rapidly inactivated by CDK-inhibiting proteins, above all INK4 family proteins (p14, p15, p16, and p18).

Cyclin E

Cyclin E is a G1/S transition cyclin that binds to CDK2. It exists in two forms, cyclin E1 and cyclin E2, the genes located to chromosomes 19q12 and 8q22.1, respectively. The cyclin E-CDK2 complex plays a central role in the regulation of G1 and the G1/S transition. The complex inhibits Rb protein through its phosphorylation and thus promotes progression through G1 via release of the transcription factor E2F from its binding to Rb. The cyclin E complex can also phosphorylate the cell cycle inhibiting TGF-beta pathway mediator Smad3, inhibiting its function and thus facilitating cell cycle progression. The cyclin E-CDK2 complex is involved in the centrosome cycle via phosphorylating nucleophosmin, which then detaches from unduplicated centrosomes and triggering centrosome duplication.

Cyclin F and Other Cyclins

There are several other cyclins that may affect cell cycle progression in an indirect way. Cyclin F (CCNF gene on chromosome 16p13.3) interacts with CP110, a protein that is essential for centrosome duplication. Cyclin F and CP110 associate on the centriole during G2, followed by CP110 proteolytic degradation after ubiquitination by the SCF/cyclin F ubiquitin ligase complex. Cyclin G, assigned to chromosome 5q34, is a cyclin that is induced by p53 upon DNA damage. It differs from other cyclins in that it lacks a protein-destabilizing/PEST sequence, but depends on its proteasome-mediated degradation on a cyclin box (Piscopo and Hinds 2008). Cyclin G is one of the earliest p53 target genes, and cyclin G-mediated p53 regulation is dependent upon ataxia-telangiectasia-mutated/ATM protein, which activates p53 in response to DNA damage (Ohtsuka et al. 2004). A partner of cyclin G is cyclin G-associated kinase/GAK, an enzyme that peaks in G1. Cyclin H (the CCNH gene assigned to 5q14.3) is a cyclin that is regulated by the cyclin C-CDK8 complex and interacts with the transcription factor IIH. Cyclin H forms a complex with CDK7 which stabilizes a protein that promotes epithelial-mesenchymal transition/EMT in cancer, C-terminal binding protein 2/CtBP2 (Wang et al. 2013). Cyclin I forms a complex with CDK5, this complex activating MEK/ERK pathways and resulting in increased Bcl-2 and Bcl-X(L) expression and enhanced survival of postmitotic cells (Brinkkoetter et al. 2009, 2010). The subcellular distribution and in particular the nuclear accumulation of CDK5, an

atypical CDK, are determined by cyclin I (Hagmann et al. 2015). Cyclin K (CCNK on chromosome 14q32.2) has a dual role in regulating the expression of CDKs and modulating RNA polymerase II activity.

Cyclin Deregulation in Liver Cancer

Cyclins play an important role in growth regulation of cells of the hepatocyte lineage, both normal and neoplastic. Cyclin deregulation is involved in atypical hepatocyte regeneration and hepatocarcinogenesis (Kitamura et al. 1998). In these pathogenic pathways, the various cyclins occupy distinct roles. In HCC, various patterns of cyclin deregulation have been detected, part of them exerting an influence on cancer growth and invasion (Masaki et al. 2003).

Cyclin A was upregulated in about half of HCCs (Zhou et al. 2003; Bahnassy et al. 2011). Cyclin D1 is subject to a common polymorphism (G870A) in exon 4 of the CCDN1 gene. This polymorphism may increase the risk of HCC (Hu et al. 2014). Cyclin D1 is upregulated in up to two thirds of HCCs (Bahnassy et al. 2011), but was downregulated in part of HCCs (Lu et al. 2013). HBx protein stabilizes cyclin D1 and increases its nuclear accumulation (Chen et al. 2015). Cyclin D1 upregulation is associated with increased levels of macrophage inhibitory factor/MIF in HCCs (Huang et al. 2014). Part of cyclin D1 expression depends on etiological factors, such as hepatitis virus infections. HBx protein promotes hepatic stem cell proliferation via upregulation of cyclin D1 mediated by MEK/ERK and PI3K/Akt signaling pathways (Wang et al. 2014b). In HCCs, cyclin D3 is significantly upregulated. This is associated with decreased expression of microRNA-138 which targets cyclin D3 (Huang et al. 2015). Stabilization of cyclin D1 in nuclei induces proliferation of hepatocytes (Güller et al. 2008). Cyclin D1 is a mediator of c-Met- and beta-catenin-induced hepatocarcinogenesis (Patil et al. 2009). Cyclin E facilitates dysplastic hepatocytes to bypass the G1/S checkpoint in the course of hepatocarcinogenesis (Pok et al. 2013). In established HCCs, cyclin E was overexpressed in up to about 50 %, and this expression pattern was correlated with differentiation, invasion, and metastasis (Zhou et al. 2003; Bahnassy et al. 2011). The pro-growth effect of cyclin E is associated with expression of HOXA7 (Li et al. 2015a). Cyclin F, capable to generate the Skp1-Cul1-F-box protein ubiquitin ligase complex, controls centrosome duplication and prevents genomic instability. Cyclin F oscillates in the course of the cell cycle with a pattern similar to that of cyclin A. In HCC, this cyclin is significantly decreased, downregulation being associated with growth, low differentiation, and tumor multiplicity (Fu et al. 2013). In most HCCs, cyclin G1 is downregulated in comparison with normal hepatic tissue (Cui et al. 2013). However, expression of cyclin G1 expands liver tumor-initiating cells by Sox induction through Akt/mTOR signaling (Wen et al. 2013). In HCC cells, cyclin G1 suppresses p53 activity by Notch3 (Giovannini et al. 2014). Cyclin G1 can mediate epithelial-mesenchymal transition/EMT through PI3K/Akt signaling, a process that affects tumor cell growth and invasion (Wen et al. 2012). In HCCs, expression of cyclin G1 is regulated by microRNA-122a which directly targets this cyclin (Gramantieri et al. 2007b; Fornari et al. 2009). Cyclin J (CCNJ) is downregulated in HCC through epigenetic promoter hypermethylation in the majority of cases, associated with enhanced growth and aggressive tumor biology (Takano et al. 2015).

Regulation of Cyclins in Liver Cancer by microRNAs

The function of cyclins in liver cancer is also regulated by microRNAs, which by this pathway exert an influence on cancer cell growth (see below). Downregulating to cyclin D3 (CCND3) by microRNA-503 inhibits the G1/S transition of cell cycle in HCC cells (Xiao et al. 2013). Cyclin D3 is also targeted by microRNA-138 which induces cell cycle arrest in HCC (Wang et al. 2012). MicroRNA-520 b targets cyclin D1

and via this effect inhibits growth of HCC cells. In clinical HCC tissues, microRNA-520b expression is markedly reduced (Zhang et al. 2012). CCNE1, an important mediator of G1/S transition and tumor suppressor, is targeted by microRNA-7 in HCCs (Zhang et al. 2014a).

Cyclin-Dependent Kinases

Introduction

Cyclin-dependent kinases (CDKs) are a family of protein kinases that interact with diverse cyclins and hold a central role in cell cycle regulation (reviews: Morgan 1997; Ekholm and Reed 2000; Vermeulen et al. 2003; Malumbres and Barbacid 2005; Suryadinata et al. 2010). CDKs phosphorylate substrates at serine and threonine residues and are therefore by definition serine-threonine kinases. For having full kinase activity, CDKs have to bind distinct cyclins.

Types of Cyclin-Dependent Kinases and Their Function as Cell Cycle Regulators

So far, more than ten CDKs have been identified, but only a fraction of them play crucial roles in cell cycle regulation (Table 2). It has been emphasized that certain CDKs can interact with more than one type of cyclin.

In contrast to cyclins, whose expression oscillates along the cell cycle in a characteristic manner, CDKs are constitutively expressed during the entire cell cycle, and their kinase activity pattern is determined by the phase-specific expression of their cyclin-binding partners. Apart from their activation through the binding cyclins, CDK activity is also regulated by phosphorylation on serine, threonine, or tyrosine residues produced by distinct CDK kinases. For example, CDK1 is activated through phosphorylation via the cyclin H-CDK7 complex/CAK. Most of these phosphorylations of CDKs augment their binding capacity for cyclins. CDKs are also activated by a distinct group of activators that interact with specific CDKs. For the CDK5 activator p35, LZAP is a binding protein that can act as a tumor suppressor in various neoplasms. Conversely, a group of proteins is active in inhibiting CDKs. The two main families of CDK inhibitor proteins are the INK4 family and the Cip/Kip family (see below). CDKs are also subject to inhibition by various other CDK inhibitors/CDKNs. CDKN1B affects the G1/S transition, while CDKN3 belongs to the protein phosphatase family. CDKs are dephosphorylated by CDK-associated protein phosphatase (KAP), a dual-specificity phosphatase that mainly dephosphorylates CDK2 and inhibits cell cycle progression (Hannon et al. 1994). KAP dephosphorylates CDK2 on threonine 160 in a cyclin-dependent manner.

Table 2 Major cyclin-dependent kinases (CDKs) and their binding cyclins

CDK	Cyclins	Activity in cell cycle phase
CDK4	Cyclins D1–D3	G1 and G1/S transition
CDK6	Cyclins D1–D3	G1 and G1/S transition
CDK2	Cyclin E	G1/S transition
CDK2	Cyclin A	S
CDK1	Cyclin A	G2/M transition
CDK1	Cyclin B	M

Deregulation of Cyclin-Dependent Kinases and Their Regulators in Liver Cancer

Similar to cyclins, several CDKs are subject to deregulation in liver cancers. Overexpression of CDK1 and CDK2 in cancer is generally associated with high aggressiveness and poor prognosis and is correlated with poor differentiation in HCCs (Shen et al. 2010). HCCs show enhanced expression of CDK4, mostly associated with downregulation of cyclin D1 (Lu et al. 2013). CDK4-/CDK6-dependent cell cycle progression in HCC cells is inhibited by p16 (INK4a) in an Rb protein-independent manner (Rivadeneira et al. 2010). Usually involved in the biology of neuronal cells, CDK5 also plays a role in cancer progression. Expression and activity of CDK5 were increased in HCC tissue and were associated with proliferative activity. In these cells, the enzyme is most

active in cells in G2/M phase of cycle. CDK5 regulates DNA damage response by phosphorylating ataxia-telangiectasia-mutated (ATM) kinase (Ehrlich et al. 2015). CDK10 is a Cdc2-related kinase that is important for the progression from G2 to M phases of the cell cycle. In HCCs, expression of CDK10 is markedly reduced in comparison with normal surrounding liver tissue, closely linked to tumor progression (Zhong et al. 2012). A Cdc2-related protein kinase is PFTK1, which is frequently upregulated in HCC. It interacts with cyclin Y to activate noncanonical Wnt signaling in HCC (Sun et al. 2014). Subsets of HCCs show upregulation of KAP, the CDK-associated protein phosphatase (Lin et al. 2013). The function of CDKs is inhibited by CDKN1/p57, implicated in various cancers. In HCC cells, expression of CDKN1 induces tumor cell senescence via the activity of the Notch target gene Hes1 (Giovannini et al. 2012).

A binding protein for the CDK5 activator p35, LZAP, is significantly decreased in HCC, associated with enhanced growth of the tumors (Zhao et al. 2011). Subsets of HCC exhibit aberrant transcripts of the CDK phosphatase KAP (Yeh et al. 2000). HCCs display downregulation of the CDK inhibitor CDKNB1 via direct targeting by microRNA-452, causing dramatically increased proliferation via induction of G1/S transition (Zheng et al. 2014). The CDK phosphatase-type inhibitor, CDKN3, is upregulated in HCC and promotes tumor cell proliferation by stimulating G1/S transition (Xing et al. 2012).

Retinoblastoma (Rb) Protein as an Inhibitor of Cell Cycle Pathways

Introduction

As outlined in the preceding paragraphs, entry into and progression through the cell division cycle is a tightly controlled process that is closely linked to cell production demands and which possesses several brakes to avoid cell production overshoots. A distinct array of proteins act as switches operating as "on" or "off" signals for cell cycling (Matsuda et al. 2013a). Phosphorylation is a common mechanism to maneuver the position of these switches.

Retinoblastoma Protein

Retinoblastoma protein (Rb, gene locus Rb1 on chromosome 13q14.2) is a tumor suppressor protein that is deregulated in numerous cancers. The main function of Rb is to prevent excessive cell proliferation by the inhibition of cell cycle progression until a cell is programmed to undergo division. At that time point, Rb is phosphorylated by a kinase to pRb, which is inactive and therefore releases cell cycle progression. For its function, active Rb binds to and inhibits a transcription factor of the E2F family, E2F1. In a complex with the dimerization partner DP, non-inhibited E2F1 releases a cell into S phase, while an inhibited complex keeps the cell waiting in G1. E2F1 and other E2F members are maximally expressed in late G1 and are present in association with E2F-regulated promoters during the G1/S transition. Rb protein is the switch that decides upon the activity of the E2F complex. The Rb switch in turn depends in its activity on cyclin-dependent kinases (see above) which phosphorylate it and thus cancel its action on E2F. Rb protein itself can interact with a host of proteins (review: Giacinti and Giordano 2006).

Deregulation of Rb Protein in Liver Cancers

Inactivation of Rb is a frequent event in HCCs and is an important mechanism for unlimited cell cycling in these neoplasms (Mayhew et al. 2007; Machida et al. 2009; Ahn et al. 2014). However, mutations of the Rb gene as a cause of Rb silencing is a relatively uncommon event in HCC. In contrast, Rb exhibits imprint abnormalities in a high proportion of primary HCCs, loss of imprinting being a major mechanism for Rb inactivation (Anwar et al. 2014). There is a significant correlation between loss of Rb and Rb gene methylation, emphasizing the significance of epigenetic mechanisms (Edamoto et al. 2003; Zhang

et al. 2014a). Loss of E2F inhibition in HCC due to Rb inactivation leads to activation of E2F target pathways. The E2F1 target, stathmin1, is frequently upregulated in HCCs with low AFP levels and promotes polyploidy and invasion in these cancers (Hsieh et al. 2010; Chen et al. 2013a). Ef2 promotes transcription of the Notch signaling pathway, which in turn serves as a negative feedback mechanism to slow down HCC growth (Viatour et al. 2011). HCCs with positive immunoreactivity for Rb protein showed a higher rate of intrahepatic metastasis (Naka et al. 1998). Apart from Rb, its target E2F also shows deregulation in various cancers, including HCC (Zhan et al. 2014).

Rb protein interacts with proteins that are deregulated in liver cancer. One group consists of retinoblastoma-binding proteins. The histone demethylase Rb-binding protein 2/RBP2 is overexpressed in HCC and negatively regulated by microRNA-212 (Liang et al. 2013). Rb is regulated by the expression of distinct microRNAs (Li et al. 2015b). MicroRNA-645, which is expressed in subsets of HCCs, downregulates Rb and by this effect enhances proliferative activity of tumor cells (Hernandez et al. 2013). Conversely, microRNA-26a/b activates pRb and in cooperation with cyclin E1 and CDK6 inhibits the G1/S transition (Zhu et al. 2012). In addition to its direct effects on cell cycle regulation, Rb protein affects other cell functions that may indirectly contribute to deregulated proliferation. For example, the Rb expression mode has striking effects on responses to genotoxic hepatocarcinogens (Reed et al. 2009, 2010, 2014). Rb potentiates the innate immune response in hepatocytes, while loss of Rb function in hepatocarcinogenesis alters the local innate immune status and favors tumor development (Hutcheson et al. 2014).

CDK Inhibitors and Their Deregulation in Liver Cancer

Introduction

The activity of CDKs is counteracted by a group of several CDK inhibitors which can either bind and inhibit CDKs directly or bind cyclin-CDK complexes. Two families of CDK inhibitors exist, the INK4 family and the Cip/Kip family (Table 3).

Table 3 Cyclin-dependent kinase inhibitors

INK4 family	*Members*	*Function*
	p15 (INK4b)	Inhibition of G1-associated CDKs
	p16 (INK4a)	(CDK4, CDK6)
	p18 (INK4c)	
	p19 (INK4d)	
Cip/Kip family		
	p21 (Cip1)	Inhibition of G1 cyclin-CDK
	p27 (Kip1)	Complexes and cyclin B-CDK1
	p57 (Kip2)	

p15 (INK4b, CDKN2B)

p15 (INK4b, CDK inhibitor 2B, CDKN2B, MTS2) is an INK4 family member CDK inhibitor that blocks the cell cycle at the G1/S transition via inhibition of CDK4 and CDK6 complexes. The gene is located to chromosome 9p21.3, where it lies adjacent to the p16 gene. p15 is frequently deregulated in various cancers, including HCC, via deletion of 9p (Liew et al. 1999; Shao et al. 2000). Downregulation of p15 causes promotion of growth, while ectopic expression of p15 is associated with inhibition of cell proliferation (Qin et al. 2004). Homozygous deletions of p15 exons were detected in part of HCCs, but are less frequent than those of p16 (Jin et al. 2000). In HCCs, p15 expression is also silenced by hypermethylation of its gene, found in up to 49 % of HCC cases (Roncalli et al. 2002; Pang et al. 2003; Yang et al. 2003; Qin et al. 2004; Fukai et al. 2005; Ko et al. 2008; Dong and Wang 2014; Zekri et al. 2014b; Zhang et al. 2014a). A p15 promoter hypermethylation status was associated with elevated serum AFP levels in HCC (Zhang et al. 2007). Expression of p15 in

HCCs is regulated by mitogen-activated protein kinase ERK5. Downregulation of ERK5 is associated with increased expression of p15 and p27 and leads to decreased cell proliferation, whereas enhanced ERK5 expression in HCC is associated with increased proliferation (Rovida et al. 2014). p15 induction is mediated by TGF-beta-induced complex of Smad2, Smad3, Smad4, and Sp1 (Feng et al. 2000). Downregulation of p15 by both genetic and epigenetic mechanisms was also found in cholangiocarcinomas (Chinnasri et al. 2009).

p16 (INK4a, CDKN2A, MTS1)

The 9p21.3 chromosomal INK4alpha/ARF locus encodes the proteins p14 (ARF) and p16 (INK4alpha), both functioning to mediate cell cycle arrest via the p53 and Rb protein pathways, respectively. p14 (ARF) shares exon 2 with p16 in a different reading frame. It is an upstream regulator of the Rb-CDK4 pathway and binds to MDM2 causing a stabilization of functional p53 (Horie et al. 2000). Part of HCCs showed inactivation of p14 (ARF) in up to 20 % of cases (Tannapfel et al. 2001; Peng et al. 2002). Inactivation of p14 (ARF) was frequently associated with the concomitant inactivation of p16 (INK4a), but inactivating hypermethylation of p14 occurred independently of that of p16 (Tannapfel et al. 2001). p14 (ARF) inactivation occurred more often in HCV-associated HCC. Inactivation is either caused by homozygous deletion (Peng et al. 2002) or epigenetic hypermethylation (Herath et al. 2002). Overexpression of p14 (ARF) may be a less common alteration in HCC than changes of other cycle regulators. It was mainly observed in poorly differentiated neoplasms in Japan (Ito et al. 2004). p16 protein is a G1-specific cell cycle inhibitor that prevents the association of cyclin-dependent kinase 4/CDK4 and CDK6 with cyclin D1. In HCCs, the p16/cyclin D1/Rb protein pathway is disrupted in the majority of cases, in up to 66 % of cases (Chaubert et al. 1997; Jin et al. 2000; Azechi et al. 2001; Tannapfel et al. 2001; Matsuda and Ichida 2006; Matsuda et al. 2008, 2013a; Dong and Wang 2014). Inactivation of p16 in HCC was found more often in advanced stage tumors (Hui et al. 1996). p16 downregulation is caused by allelic loss of chromosome 9 in subsets of HCC (Liew et al. 1999). Part of HCCs show aberrant p16 (INK4a) transcription caused by hypermethylated promoters, epigenetic silencing resulting in significant downregulation of p16 (Roncalli et al. 2002; Zhang et al. 2002; Qin et al. 2004; Fukai et al. 2005; Matsuda 2008; Shiraz et al. 2011; Zang et al. 2011; Matsuda et al. 2013a; Dong and Wang 2014; Mah and Lee 2014; Zekri et al. 2014a). Silencing of p16 in HCC via methylation was associated with poor prognosis in recurrent early-stage tumors (Ko et al. 2008). In patients with HBV-associated liver cirrhosis and HCC, there was a gradual transition from normal to cirrhotic to cancerous tissue with respect to p16 promoter hypermethylation, suggesting that this epigenetic change is an early event associated with hepatitis virus infection (Li et al. 2004; Wang et al. 2012; Zhang et al. 2014a). There is evidence that hepatitis C virus core protein can induce downregulation of p16 by promoter methylation (Park et al. 2011). p16 downregulation promotes cancer cell growth, while experimental activation of p16 inhibited proliferation of HCC cells (Huang et al. 2003). Loss of p16 protein in HCCs is closely related to the functional inactivation of p27 and contributes to p27 sequestration by cyclin D1-cyclin-dependent kinase 4 complexes (Matsuda et al. 2003). Inactivation is associated with overexpression of inhibitors of differentiation and DNA-binding-1/Id-1, which opposes Ets-mediated activation of p16 (Lee et al. 2003). On the other hand, Id-1 is downregulated by HGF through ERK-dependent and ERK-independent signaling pathways, resulting in increased expression of p16 (INK4a) in HCC cells (Ushio et al. 2009). These aberrant proteins regulate pRb phosphorylation by binding with cyclin-dependent kinase (CDK) 4 (Cho et al. 2003). Apart from its effects on tumor growth, p16 stimulates Cdc42 GTPase-dependent migration of HCC cells (Chen et al. 2013b). Deregulation of p16 also plays a

role in the induction of metastasis of HCC cells (Chen et al. 2007).

p16 (INK4a) is extensively expressed in a minority of bile duct cancers, but is present in most bile duct adenomas and ductular proliferations (Sasaki et al. 2014). p16 is downregulated in a significant fraction of cholangiocarcinomas (Tannapfel et al. 2000b; Ito et al. 2001a; Kang et al. 2002; Tannapfel et al. 2002; Karamitopoulou et al. 2008; Gonda et al. 2012; Ruys et al. 2014). In extrahepatic and intrahepatic cholangiocarcinomas, the p16 promoter was hypermethylated and epigenetically silenced in 50–76 % (Lee et al. 2002; Tannapfel et al. 2002; Yang et al. 2005; Chinnasri et al. 2009). In addition to epigenetic inactivation, a minority of cholangiocarcinomas exhibited recurrent homozygous deletions and mutations of the p16 (INK4a) locus (Tannapfel et al. 2002; Maehura et al. 2014). Functional promoter mutations of the p16 gene were detected in primary sclerosing cholangitis/PSC and PSC-associated cholangiocarcinoma (Ahrendt et al. 1999; Taniai et al. 2002; DeHaan et al. 2007). Loss of p16 is observable in intraepithelial neoplasia of bile ducts, whereby the decrease of expression becomes more prominent in a stepwise manner with increasing grade of BillN (Sasaki et al. 2008; Schlitter et al. 2014). Inactivation of p16 is a frequent event in intraductal papillary neoplasms, e.g., those arising in hepatolithiasis (Ishikawa et al. 2004). The expression of p16 in cholangiocarcinoma and precursor lesions is regulated in the catalytic subunit of the polycomb repressive complex 2, enhancer of zeste homologue 2/EZH2, a driving force for an accelerated cell cycle (Nakagawa et al. 2013). Another malignant hepatic neoplasm with abnormalities of the p16 pathway is angiosarcoma (Weihrauch et al. 2002).

p18 (INK4c, CDKN2C)

p18 (INK4c, CDKN2C) is encoded by a gene on chromosome 1p32.3 and is an inhibitor that strongly interacts with CDK6 and weakly with CDK4, but not with other CDKs. By inhibiting cyclin D-CDK4/CDK6 complexes, p18 blocks the cell cycle at the level of the G1/S transition. Immunohistochemically, a frequent loss of p18 was detected in HCCs, especially in poorly differentiated neoplasms. In p18-positive HCCs, p18 interacted with CDK4 rather than with CDK6 (Morishita et al. 2004). The pathogenesis of p18 decrease in HCC is not fully clarified. In contrast to other CDKNs, the p18 gene is not epigenetically methylated (Roncalli et al. 2002). The expression levels of p18 in HCCs are negatively regulated by lncRNA highly upregulated in liver cancer (HULC), which is dramatically upregulated in HCC and is inducible by hepatitis B virus X protein. High HULC levels are associated with decrease of p18 expression (Du et al. 2012). In collaboration with p53, p18 can suppress hepatocarcinogenesis in murine models (Damo et al. 2005).

p19 (INK4d, CDKN2D)

p19 (INK4d, CDKN2D) inhibits G1-associated cyclin-CDK complexes, in particular those which contain CDK4 and CDK6. The gene is located to chromosome 19p13.2. Overexpression of p19 rapidly induces arrest in G1 phase. This inhibitor shows frequent loss of expression in HCC, although the exact role of p19 in cell cycle regulation of these cancers is not well elucidated. Downregulation of p19 in HCC is associated with increased growth, poor differentiation, and aggressive biology (Morishita et al. 2011). p19 controls oncogenic function of STAT3 (signal transducer and activator of transcription 3) in HCC cells (Schneller et al. 2011). In addition to its effects on cell proliferation, p19 also modulates the invasive behavior of HCC cells. Experimental knockdown of p19 in HCC cell lines promotes cell invasion, while reintroduction of p19 restores the migratory capacity (Chen et al. 2008).

p21 (Cip1, CDKN1A)

The cyclin-dependent kinase (CDK) inhibitor p21 (Cip1, CDKN1A, wild-type p53-activated fragment1, Waf1) is assigned to chromosome 6p21.2

and plays an important role in response to DNA damage. Its overexpression results in cell cycle arrest. p21 is upregulated following ionizing radiation in a p53-dependent manner. It also inhibits the function of PCNA. p21 (Cip1) associates with cyclin D1, cyclin E, and CDK2 and is a very potent and tight-binding inhibitor of CDK. The inhibitor mediates p53 suppression on tumor cell growth. p21 expression is transcriptionally suppressed by histone deacetylase 2/HDAC2 through the Sp1-binding site enriched proximal region of the p21 promoter (Noh et al. 2011).

In the normal liver, tightly regulated p21 is required for sustained regeneration, while deregulated p21 provides a mechanism promoting liver cancer development (Goldenberg and Eferl 2014; Marhenke et al. 2014). p21 has been implicated as tumor suppressor and is deregulated in most HCC cases by immunohistochemical assessment (Zhang et al. 2009), in part associated with epigenetic p21 variants (Liu et al. 2013). Also precursor lesions of HCC, specifically small cell dysplasia, display downregulation of p21 (Park 2014). p21 gene polymorphisms individually or in combination with p27 polymorphisms increase the risk for HCC (Liu et al. 2013). In contrast to p53, p21 may serve as an early-event molecular carcinogen in HCC (Abdou et al. 2016; Ehedego et al. 2015). Targeted activation of p21 expression is a potent mechanism for inhibiting HCC cell growth (Kosaka et al. 2012). In HCCs, expression of p21 was correlated with a high PCNA LI and favorable risk, but not with p53 expression (Kao et al. 2007), while HCCs with p21 downregulation had advanced stage disease (Naka et al. 1998). MicroRNA-423 promotes cell growth in HCCs and regulates the G1/S transition by targeting p21 (Lin et al. 2011). MicroRNA-105 and microRNA-218, which are suppressed in HCCs, target the PI3K/Akt signaling pathway resulting in upregulation of p21 (Shen et al. 2014; Xiao et al. 2014). In subsets of HCC, p21 is upregulated, mainly in poorly differentiated tumor, but rather in late stages of tumor progression (Park et al. 2003).

The deregulated function of p21 in liver cancer is connected with a complex network of factors affecting cell proliferation. In HCCs, downregulation of p21 is induced by Notch3 signaling (Giovannini et al. 2013). In these neoplasms, overexpression of upregulator of cell proliferation (URGCP/URG4) increases cellular entry into G1/S transition associated with downregulation of p21 (Xie et al. 2012). Overexpression of URGCP/URG4 in the presence of the HBV X protein may function as a hepatocarcinogenic oncogene (Dodurga et al. 2012). The redistribution of p21 activity in HCCs is promoted by hepatocyte growth factor through ERK-dependent p16 upregulation, leading to cell cycle arrest at G1 (Han et al. 2005). Upregulation of p21 (Cip1) in hepatoma cells mediated by ERK-dependent and ERK-independent signaling affects HGF-induced inhibition of cell proliferation (Shirako et al. 2008).

Bile duct cancers and gallbladder cancers also show deregulation of p21 expression (Ito et al. 2000, 2001; Kim et al. 2009). In cholangiocarcinoma, absence of p21 expression predicted poor outcome, also in patients with no lymph node metastases and partly in patients with biologically less aggressive phenotypes (Kim et al. 2009). In cholangiocarcinomas, p21 is a downstream target of ligands of peroxisome proliferator-activated receptor gamma (PPARgamma), which by this pathway suppresses cancer cell growth (Han et al. 2003).

p27 (Kip1, CDKN1B)

Cyclin-dependent kinase inhibitor p27 (Kip1, CDKN1B) is a CDK inhibitor that plays a key role in controlling cell cycle by negatively regulating the progression through the G1 phase of the cycle and entry into S phase, causing G1 arrest. p27 blocks the kinase activities of CDK2-cyclin A and CDK2-cyclin E complexes (Borrellio et al. 2011; Wander et al. 2011). The protein is frequently expressed in cell differentiation, but is often downregulated in cancer cells. The expression of p27 (Kip1) is regulated by the far upstream element (FUSE), FUSE binding protein1 (FBP1; Matsushita et al. 2013), which activates translation of p27 (Kip1) mRNA via its internal ribosomal entry site (Zheng and Miskimins 2011).

Cytoplasmic mislocalization of p27 (Kip1), contributing to epithelial tumorigenesis, is induced by constitutive overactivation of the Ras signaling pathway, via oncogenic N-Ras-mediated activation of the Ral-GEF pathway (Tazat et al. 2013). p27 (Kip1) induces the accumulation of the repressor complexes of E2F, inhibits expression of the E2F-regulated genes, and inhibits expression of cyclin A and cyclin E (Shiyanov et al. 1997). p27 is degraded to permit cycle progression, degradation being mediated by ubiquitin-dependent targeting of p27 by SCF-Skp2, the F-box protein of the Skp1-Cullin-F-box protein (SCF) E3 ubiquitin ligase complex (Binné et al. 2007). Skp2 itself is involved in liver tumor development in cooperation with N-Ras and Akt (Delogu et al. 2015). Skp2-mediated degradation of p27 regulates the progression of cycling cells into mitosis via downregulation of CDK2 activity (Nakayama et al. 2004; Pagano 2004). The expression levels of Skp2 are regulated by Notch1 signaling that induces Skp2 transcription (Sarmento et al. 2005) and by the phosphorylation of the ezrin-radixin-moesin-binding phosphoprotein 50/EBP50 by Akt (Song et al. 2015). p27 is also regulated by Skp2-mediated ubiquitination induced by the cell cycle regulator Cks1 (S-phase kinase-associated protein 2), which is also involved in hepatocarcinogenesis (Lee et al. 2011; Qi et al. 2015). Cks1 itself is suppressed by the dual-specificity phosphatase 1/DUSP1 (Calvisi et al. 2008; Hao et al. 2015). Ubiquitination of p27 by the Skp-Cul1-F-box complex is regulated by the kinesin family member, KIP14, which is upregulated in HCCs (Xu et al. 2014), and by EGF, which upregulates Skp2/Cks1 (Kim et al. 2014). In addition, there exists an early phase, Skp2-independent ubiquitination pathway for p27 degradation (Hara et al. 2001; Kotoshiba et al. 2014).

p27 (Kip1) expression in HCCs is complex, variable, and linked to tumor stage. It was significantly decreased in part of HCCs, but was expressed in others, sometimes at high levels (Hui et al. 1998; Tannapfel et al. 2000a; Qin and Ng 2001; Armengol et al. 2003; Matsuda et al. 2003, 2013b; McAllister et al. 2003; Claudio et al. 2004; Lei et al. 2005; Shehata et al. 2006; Matsuda 2008; He et al. 2011). In HCCs, p27 expression is related to hepatocarcinogenic pathways (Bassullu et al. 2012) and predicts recurrence (Ito et al. 1999) and was inversely correlated with the expression of c-Jun activation domain-binding protein1/JAB1, associated with a shift of p27 and JAB1 from cytoplasm to nucleus (Chen et al. 2010; Qin et al. 2010; Yachida et al. 2010). In early stages of hepatocarcinogenesis, p27 may be overexpressed (Yachida et al. 2008), but p27 underexpression was also frequent in early stages of HCC and is an independent predictor of recurrence in these lesions (Armengol et al. 2003). Downregulation of p27 in HCCs is linked to expression of microRNA-221 (Fornari et al. 2008), whereby microRNA-221 expression is correlated with higher stage and aggressive biology (Fu et al. 2011). In HCCs with high p27 expression, this mode was associated with epigenetic downregulation of p16 and poor prognosis (Matsuda et al. 2003). In HCCs expressing p27 (Kip1), the proliferation index was significantly lower than in those lacking p27 (Kip1) expression (Jing et al. 2005). Hepatocyte growth factor/HGF induces the redistribution of p21 (Cip11) and p27 (Kip1) in HCC via upregulation of ERK-dependent p16 (INK4a), causing cell arrest at G1 (Han et al. 2005). In some HCCs, p27 gene mutations were found and suggested to affect HCC cancer risk (Chen et al. 2000; Liu et al. 2013). Downregulation of p27 by microRNA-222 overexpression in HCC promotes cancer cell proliferation (Yang et al. 2014a). Kinesin family member 14/KIF14 is involved as an oncogene in HCC. Silencing of KIF14 interferes with cell cycle progression by blocking p27 (Kip1) ubiquitination pathway in HCC cells (Xu et al. 2014). In HCCs, p27 (Kip1) also promotes migration and invasive capacity of tumor cells (Wang et al. 2008). Nuclear expression of Skp2, a mediator of ubiquitination-associated degradation of p27, promotes cycling in HCC and predicts poor prognosis (Shin et al. 2012; Zhang et al. 2012). In HCC cells, degradation of p27 is mediated by the ubiquitin ligase Pirh2, which is overexpressed in these neoplasms (Hattori et al. 2007; Huang

et al. 2011) and via this mechanism promotes tumor cell growth by overcoming the G1 arrest. Pirh2 overexpression is not specific for HCCs, but was also observed in other cancers (Shimada et al. 2009).

Downregulation of p27 also plays a role in aberrant cell cycle progression in cholangiocarcinomas. In these neoplasms, low or absent p27 expression predicts an aggressive biology and poor survival (Fiorentino et al. 2001; Taguchi et al. 2001; Hashimoto et al. 2009; Ruys et al. 2014). In cholangiocarcinomas, p27 expression decreased progressively from proximal to distal in the biliary tree and correlated with location-related differences in outcome (Jarnagin et al. 2006). Downregulation of p27 in cholangiocarcinoma is induced by activation and increased expression of the ubiquitination mediator, Skp2 (see above; Luo et al. 2015). On the other hand, TGF-beta can exert an antitumor effect in cancers via upregulation of p27 (Lee et al. 2013).

p57 (Kip2, CDKN1C)

p57 (Kip2) or CDK inhibitor 1C (CDKN1C, KIP2) is a member of the KIP (kinase inhibitory protein) family of CDKNs and a potential tumor suppressor gene. It is encoded by an imprinted gene located at chromosome 11p15.4, whereby the paternally inherited allele is transcriptionally repressed and methylated. It negatively regulates the cell cycle by inhibiting G1 cyclin-CDK complexes and the cyclin B-CDK1 complex, but it also modulates certain functions of the cytoskeleton (review: Pateras et al. 2009). p57 is the only CDKN that is induced by TGF-beta, a mechanism which is important for the termination phase of liver regeneration (see above). p57 is targeted by microRNA-221 whose overexpression accelerates hepatocyte proliferation in liver regeneration, and p57 (Kip2) is downregulated by Akt in the setting of HER2/Neu oncogenic pathways (Zhao et al. 2013b).

p57 expression is deregulated in various cancers, including liver cancer. Immunohistochemistry and molecular studies documented a frequent loss of p57 (Kip2) expression in HCCs (Guo et al. 2011; Hu et al. 2013a), particularly in moderately and poorly differentiated neoplasms, associated with higher PCNA labeling and poor survival (Ito et al. 2001b; Nan et al. 2005; Hu et al. 2013). HCCs with positivity for p57 (Kip2) and a low PCNA LI had a significantly better prognosis (Nakai et al. 2002). The mechanisms of p57 downregulation in HCCs are only partially known. Gene deletions or point mutations in the p57 gene are no frequent events in HCC (Bonilla et al. 1998). Downregulation of Notch1 and Notch3 in HCC cell lines resulted in a decrease of the Notch target gene Hes1, which in turn transcriptionally represses p57 (Giovannini et al. 2012). In human HCCs, p57 expression is negatively controlled by microRNA-221, which directly targets CDKN1C and is upregulated in the majority of HCCs, this increase favoring a growth phenotype (Fonari et al. 2008).

In extrahepatic cholangiocarcinoma and intrahepatic cholangiocarcinoma, p57 expression is downregulated in comparison with normal cholangiocytes, and a decreased p57 labeling index is related to increased proliferative activity and tumor progression (Ito et al. 2002).

Mitotic Cell Cycle Progression

Introduction: Anaphase-Promoting Complex (Cyclosome), Spindle Assembly Checkpoint, and Associated Protein Networks

In the control of segregation of sister chromatids during mitosis, the multiprotein anaphase-promoting complex (APC/C) or cyclosome has a central place. In association with its activating protein, Cdc20, APC/C is critically involved in the destruction of securin, leading to the activation of separase, a protease that cleaves the kleisin subunit of the cohesin complex, to abolish cohesion between sister chromatids (reviews: Sczaniecka and Hardwick 2008; Meadows and Millar 2015). Overall, exit from mitosis and the separation of sister chromatids require inactivation of cyclin B1-CDK1 kinase activity, APC/C, and inhibition of the anaphase inhibitor Pds1.

Orderly progression through M and exit from M are tightly regulated by APC/C, a large multiprotein cullin-RING E3 ubiquitin ligase having two activating subunits, Cdc20 (cell division cycle 20) and Cdh1 (reviews: Barford 2011; Chang and Barford 2014; Chang et al. 2014). Cdc20 activates APC/C from the onset of M through the metaphase-anaphase transition, whereas Cdh1 activates the cyclosome from anaphase through G1. Cdh1 also activates APC/C to inhibit the anaphase inhibitor securin. The APC/C complex recognizes its substrates by the aid of Cdc20, which can interact with a recognition motif in cyclins, BubR1, Bub1, and Acm1 (Di Fiore et al. 2015). Exit from mitosis involves accumulation of cyclin kinase inhibitors as well as cyclin proteolysis mediated by APC/C, both processes depending on CDK14 phosphatase, whose release from the nucleolus during anaphase leads to dephosphorylation and activation of an APC/C-activating subunit. The active CDK14 phosphatase hold a central position in reversing the activity of mitosis-associated cyclins and in exit from mitosis (review: Queralt and Uhlmann 2008). Release of CDK14 phosphatase depends on APC/C bound to Cdc20 that mediates proteolysis of Pds1 and the S-phase cyclin 5 (Shirayama et al. 1999; Irniger 2002). The APC/C-Cdc20 complex has a crucial role in cyclin destruction at the end of mitosis (Sudakin et al. 1995; Irniger 2002) and is subject to regulation by Rb protein. Excess transcription factor E2F1 due to Rb protein inactivation recruits Cdc20 and the APC/C-Cdc20 complex (Nath et al. 2015). An inhibitor of APC/cyclosome, early mitotic inhibitor-1 (Emi1), is an important cell cycle regulator that promotes S-phase and M-phase entry. In order to prevent premature degradation/inhibition of securin, the nuclear transport factors Nup98 and Rae1 associate with APC/C(Cdh1)-securin complexes. Nup98 and Rae1 escape from these complexes in late metaphase, as soon as all kinetochores are attached to spindle microtubules, leading to prompt ubiquitination of securin by APC/C (review: Baker et al. 2007).

Genomic stability and premature chromosome segregation are ensured by the function of the spindle assembly checkpoint (SAC). The SAC prevents the APC/C from recognizing cyclin B and securin by promoting the incorporation of Cdc20 into a complex termed mitotic checkpoint complex (Izawa and Pines 2015). During mitosis, the activity of the cyclosome is inhibited by products of the BUB and MAD genes, which form the mitotic checkpoint which is a fail-safe unit to ensure accurate chromosome segregation during mitosis, avoiding that unaligned chromosomes prematurely enter anaphase. The mitotic checkpoint complex consists of BubR1, Bub3, Mad2, and Cdc20 (Lara-Gonzalez et al. 2011) and is a complex that is subject to a "wait anaphase" signal provided by unattached kinetochores. It is assumed that a single unattached kinetochore can amplify the "wait anaphase" signal through a kinase cascade consisting of hBubR1, hBub1, and Mps1. The components of the mitotic checkpoint interact with the APC/C complex through a Cdc20-binding box in the BubR1 protein, providing a means to form BubR1-Ccd20 interactions to control APC/C activity (Diaz-Martinez et al. 2015). The APC/C complex also directly affects the mitotic checkpoints, in that one APC/C subunit, APC15, releases mitotic checkpoints and makes it responsive to kinetochore attachment (Mansfeld et al. 2011).

Control of mitosis progression is affected by NIMA-related kinases, of which the Nek (never in mitosis gene A-related kinases) family of cell cycle kinases plays a significant role. Specifically, Nek2, Nek6, Nek7, and Nek9 regulate mitotic events and associated processes, including centriole functions related to microtubule organization and cilia formation (O'Regan et al. 2007), whereas Nek1, Nek10, and Nek11 are implicated in DNA damage response (Fry et al. 2012). Nek6 and Nek7 kinases are required for mitotic spindle biogenesis, whereby both Neks localize to spindle poles, while only Nek6 also localizes to spindle microtubules in metaphase and anaphase and to the midbody during cytokinesis (O'Regan and Fry 2009). In the spindle generation process, the Nek7-associated protein Nek7-interactor RGS2 localizes to the spindle in a Nek7-dependent manner and contributes to spindle morphology and mitotic spindle pole integrity (de Souza et al. 2015). The activation of Nek6 and Nek7

depends on a kinase cascade mediated by the NIMA kinase system, Nercc1/Nek9 activated in mitosis (Belham et al. 2003).

Deregulated Cyclosome and Nek Functions in Liver Cancer

The APC/C interacting protein, Cdc20, is upregulated in HCC tissues in more than two thirds of cases. This increased expression is associated with increased Ki-67 labeling and TNM stage (Li et al. 2014a). The APC/C complex is inhibited by early mitotic inhibitor-1 (Emi1). Emi1 is highly expressed in HCCs, expression being correlated with stage and poor outcome. Emi1 expression in HCC goes in parallel with upregulation of the Emi1 substrates, cyclins A and B, and Skp2, while p27 (Kip1) is downregulated (Zhao et al. 2013a). Nek6 required for mitotic cell cycle progression is overexpressed in clinical HCC samples and HCC cell lines, and ectopic overexpression of Nek6 promotes cell proliferation. This Nek regulates the transcription of cyclin B via Cdc2 activation, inducing the accumulation of G0/G1 cells (Zhang et al. 2014b).

Complex Signaling Pathways Linking Cancer Growth with Other Features of Neoplastic Cells

Wnt/Beta-Catenin Signaling

Introduction

The Wingless/Wnt signaling pathway holds a central position in ontogenesis and oncogenesis. It works through a multiprotein-signaling cascade and activates several targets, in particular factors of the TCF/LEF HMG domain family. Activation of Wnt signaling results in cytoplasmic accumulation of beta-catenin (Armadillo in *Drosophila*), followed by nuclear translocation and interaction with TCFs to generate a transcriptional complex. In the absence of Wnt signaling, the negative regulator GSK3beta (glycogen synthase kinase 3) is activated, causing proteasomal degradation of cytoplasmic beta-catenin and lack of nuclear beta-catenin. In deficiency of nuclear beta-catenin, TCFs mediate target gene enhancement by the corepressor Groucho (review: Barker et al. 2000). Beta-catenin exerts a regulating influence on the growth of normal and neoplastic cells. However, as Wnt/beta-catenin signaling affects, apart from growth control, several other functions that are important for cancer cell biology, including cell differentiation, cell motility and adhesion, apoptosis, and invasion, this signaling pathway is briefly discussed separately.

Wnt/Beta-Catenin Signaling in Normal Liver Growth

Beta-catenin is critically involved in physiological liver growth (Monga 2014). In the normal liver, beta-catenin overexpression induced in mice provides a growth advantage during liver regeneration (Nejak-Bowen et al. 2010), and inhibition of beta-catenin in hepatoma cells inhibits growth and promotes apoptosis (Liyan et al. 2011), underlining the role of Wnt/beta-catenin in hepatocyte growth regulation. Factors involved in hepatocyte growth regulation, i.e., TGF-alpha and cyclin D1, are direct targets of beta-catenin signaling (Torre et al. 2011).

Wnt/Beta-Catenin Signaling in Liver Cancer

Oncogenic activation of the complex beta-catenin/Wnt signaling pathway is a frequent event in HCC, and activating mutations of beta-catenin markedly affect tumor growth regulation (Lee et al. 2006, 2014; Ding et al. 2014; Li et al. 2014b; Lu et al. 2014; Vilarinho et al. 2014; Wands and Kim 2014; review: Buendia 2002). Beta-catenin mutations that stabilize beta-catenin were found in 13–31 % of HCC (Edamoto et al. 2003) and promote hepatocyte proliferation and inhibit TNFalpha-induced apoptosis (Shang et al. 2004). HCC- and hepatoblastoma-associated beta-catenin mutations often involved the degradation box of the beta-catenin gene, resulting in failure of

proteasomal degradation of cytoplasmic beta-catenin and persistent nuclear expression, where the protein is detectable by immunohistochemistry. In HCC cells, Wnt/beta-catenin signaling regulates the cell cycle via expression of cyclin A and cyclin E (Wang et al. 2009b). SUMO-specific protease 2/SENP2, which plays an important role in the control of HCC cell growth, modulates the stability of beta-catenin in these tumors by SUMOylation (Shen et al. 2012). The stability of beta-catenin is also promoted by its interaction with SOX10, a tumor promoter that is upregulated in HCCs (Zhou et al. 2014). The Wnt/beta-catenin signaling pathway can also affect growth of HCCs via its regulation of angiogenic factor expression (Qu et al. 2014). In HCCs, a distinct pathway involved in the modification of beta-catenin degradation depends on the ubiquitin-like protein FAT10 (Yuan et al. 2014). A factor that counteracts Wnt/beta-catenin signaling in HCC is SOX17, an antagonist of canonical Wnt signaling which is downregulated in HCC (Yang et al. 2014b). In normal hepatocytes and HCC cells, secreted frizzled-related proteins/SFRPs function as negative regulators of Wnt signaling. In HCC, hypermethylation of SFRP1, SFRP2, and SFRP5 is frequent, causing SFRP downregulation in these neoplasms and inhibition of SFRP-mediated suppression of proliferation (Shih et al. 2007). One of the co-receptors of the Wnt/beta-catenin pathway is low-density lipoprotein receptor-related protein-6/LRP6, which forms a signaling complex with Wnt ligand and frizzled receptor to activate downstream signaling. Upregulation of LRP6 promotes hepatocarcinogenesis via hyperactivation of Wnt/beta signaling (Tung et al. 2012). For its activity, LRP6 requires caveolar endocytosis modulated by Wnt3a and Dickkopf1/Dkk1 (Yamamoto et al. 2008) and by the Rab GTPase RAB8B (Demir et al. 2013).

Notch Signaling in Liver Cancer

Notch receptor signaling is a highly conserved mechanism that plays a role in cell fating and control of cell growth. Mammals have four different Notch receptors, termed Notch1, Notch2, Notch3, and Notch4. Notch receptors are activated by contact with cells that bear Notch ligands at their surface. Notch ligands are transmembrane proteins that are members of the Delta/Serrate/LAG-2 (DSL) family. In mammals and humans, the ligands are known as Delta-like and Jagged/Jag. Notch signaling, counteracted by Numb signaling, plays an important role in several functions and diseases of the liver (Morel et al. 2013). During hepatic ontogenesis, Notch signaling is critically involved in the morphogenesis of the ductal plate and tubulogenesis (Strazzabosco and Fabris 2012; Geisler and Strazzabosco 2014).

Notch is involved in carcinogenic pathways and progression of numerous malignancies. Activated Notch signaling in mice livers induces the formation of HCC-like tumors (Villanueva et al. 2012). However, the effects of Notch expression vary considerably as a function of the cell system studied, having oncogenic or tumor-suppressive functions. In hepatocytes and HCC cells, Notch signaling is activated by the ligand Jag-1 which is upregulated by the transcriptional regulator YAP/Yes-associated protein (Tschaharganeh et al. 2013). Notch modulates the fate and behavior of hepatic progenitor cells (Bogaerts et al. 2014), and its expression pattern in cultured HCC cell lines is modulated by HBV X protein, in that HBx upregulated the expression of Notch1, Jagged-1, and Hes1 at the transcriptional level by binding to the Notch1 intracellular domain (Wang et al. 2012) . It was shown that Notch1 overexpression acting on various cell cycle regulators inhibited proliferation of HCC cells by inducing G0/G1 cell cycle arrest (Qi et al. 2003). On the other hand, there is evidence for a prooncogenic function of Notch in HCC. In comparison with cirrhotic tissue, HCCs can show aberrant nuclear expression of Notch1 and Notch3 (Gao et al. 2008; Giovannini et al. 2009; Wang et al. 2009a). Notch1 activation increased the proliferative activity in human HCC cell lines (Gao et al. 2012), while Notch1 signaling inhibited growth in another human HCC cell system through induction of cell cycle (G0/G1) arrest and apoptosis (Qi et al. 2003). In HCC cells,

cytoplasmic expression of Notch1, cytoplasmic expression of Notch3, coexistent nuclear expression of Notch3, and cytoplasmic Notch4 overexpression were observed, whereby Notch1 and Notch4 expression were markers for poor prognosis (Ahn et al. 2013). Expression of Notch3 decreased the invasive capacity of HCC by regulating MMP expression in one study (Zhou et al. 2013). On the other hand, an aberrant expression of Notch3 was associated with bigger tumor size, tumor multiplicity, and metastatic spread and predicts poor survival for HCCs (Hu et al. 2013b). In HCCs, Notch3 is a regulator of cell self-renewal by interacting with the beta-catenin signaling pathway (Zhang et al. 2015). Notch4 was downregulated in 80 % of HCC, but in Notch4-positive HCCs, this receptor was frequently expressed in endothelial cells (Gramantieri et al. 2007a). Notch signaling is the pathway by which the RUNX3 transcription factor suppresses HCC. RUNX3 directly interacts with the intracellular Notch1 domain and thus suppresses Notch signaling (Gao et al. 2010). Numb overexpression itself in HCC promotes cell proliferation (Wu et al. 2014).

Hippo Signaling Pathway in Liver Cancer

Hippo denotes a distinct kinase involved in a complex signaling pathway. The Hippo pathway consists of a core kinase cascade in which Hippo or MST1/MST2 in mammals phosphorylates the protein kinase Warts/LATS1/LATS2 to become active. LATS1 and LATS2 are nuclear DBF-2-related kinases that phosphorylate and inactivate Yes-associated protein/YAP (Yorkie in *Drosophila*), a transcriptional coactivator binding to TEAD-type transcription factors in its active, unphosphorylated form to activate expression of targets promoting cell proliferation and preventing apoptosis. Hippo signaling is critically involved in the control of organ size by regulating cell proliferation versus apoptotic rates. The Hippo-WW45/adaptor for Hippo kinase pathway controls liver size by controlling liver cell fate and restraining hepatic oval cell proliferation (Lee et al. 2010; Yimlamai et al. 2014). This signaling pathway also plays a role in the development of cancer, including HCC (reviews: Liu et al. 2012; Jie et al. 2013).

Carcinogenesis, including hepatocarcinogenesis, is modulated by two important downstream effectors of the Hippo kinase pathway, i.e., Yes-associated protein/YAP and PDZ-binding motif/TAZ. Increased expression of YAP was observed in HCC cells, with marked nuclear YAP immunoreactivity being present in most tissues. This expression pattern was associated with prominent induction of glypican-3, connective tissue growth factor/CTGF, and survivin, three YAP target genes, and downregulated expression of LATS kinase, the main upstream regulator of YAP (Li et al. 2012). Via YAP, the Hippo pathway is linked to Notch signaling, as YAP upregulated the Jagged-1 ligand and activates Notch (Tschaharganeh et al. 2013). A direct target of YAP and TAZ is the epidermal growth factor family member, amphiregulin. YAP, TAZ, and amphiregulin were expressed in the majority of HCCs, YAP expression being a prognostic factor (Han et al. 2014).

Hedgehog Signaling Pathways in Liver Cancer

The Hedgehog signaling pathway plays a central role in development (segment polarity), adult stem cell biology, and regulation of growth homeostasis in the adult organism. In *Drosophila*, Hedgehog is the ligand and an intracellular signaling molecule, while mammals possess three Hedgehog homologues termed DHH, IHH, and SHH/sonic Hedgehog, of which SHH is most intensively studied homologue. The SHH ligand, which is produced by cleavage from a precursor and has a cholesterol moiety at the carboxyl end serving as a trafficking and secretion signal, binds on target cells to the Patched-1 receptor/PTCH1, a molecule homologous to the Niemann-Pick disease protein NPC1. In the absence of SHH ligand binding, PTCH1 inhibits a downstream effector termed Smoothened/SMO via removing oxysterols from SMO

through a sterol sensor/sterol pump contained in PTCH1. Full complementation of SMO with sterols allows it to remain within cell membranes. All three mammalian Hedgehog homologues also bind to a second receptor, PTCH2. The effectors of this signaling pathway are the Gli proteins (glioma-associated oncogene homologue), DNA-binding zinc finger domain proteins. Gli transcription factors (Gli1, Gli2, and Gli3) inhibit transcription of SHH targets via binding to Gli-responsive genes. Transcriptional control by Gli proteins is in part tissue specific, with certain Gli proteins preferentially expressed in distinct tissues. Gli1 plays an important role in DNA folding in chromosomes via recruitment of histone deacetylase complexes. An important negative regulator of SHH signaling is the Rab family GTPase, Rab23, which is involved in the regulation of certain development steps during ontogenesis.

The SHH signaling cascade promotes cell proliferation, specifically the growth of progenitor cells located to various tissues, and is involved in hepatic homeostasis (Omenetti et al. 2011) and hepatitis C virus replication (Choi et al. 2011). SHH also regulates viability and turnover of hepatic stellate cells, in part modulated by glypican-3 (Magistri et al. 2014). The pathway is deregulated in several cancers, including liver cancer (review: Zheng et al. 2013). As SHH drives the growth and development of endodermal progenitors to become liver cells, a regression of neoplastic liver cells to immature precursor-like cells may anticipate deranged SHH signaling. HCC cell lineages in culture express Hedgehog signaling components and show overexpression of SMO, which may act as an oncogene and drive hepatocarcinogenesis (Sicklick et al. 2006). Activation of the Hedgehog signaling pathway is a frequent event in HCC, whereby expression of SHH, PTCH1, and Gli1 was observed at high rates (2006). HCC overexpressing components of the Hedgehog signaling pathway show increased proliferation and invasiveness (Cheng et al. 2009). In HCC cells, Gli1 activation and Gli1 nuclear localization are stimulated by the HBV X protein (HBx) (Kim et al. 2011). The negative SHH regulator Rab23 is overexpressed in subsets of HCC and HCC cell lines (Sun et al. 2012).

References

Abdou AG, Abd-Elwahed M, Badr M, Helmy M, Soliman EA, Maher D (2016) The differential immunohistochemical expression of p53, c-Jun, c-Myc, and p21 between HCV-related hepatocellular carcinoma with and without cirrhosis. Appl Immunohistochem Mol Morphol 24:75–87

Abe Y, Takeuchi T, Kagawa-Miki L, Ueda N, Shigemoto K, Yasukawa M, Kito K (2007) A mitotic kinase TOPK enhances Cdk1/cyclinB1-dependent phosphorylation of PRC1 and promotes cytokinesis. J Mol Biol 370:231–245

Ahn et al. (2013) http://www.ncbi.nlm.nih.gov/pubmed/23742774

Ahn SM, Jang SJ, Shim JM, Kim D, Hong SM, Sung CO, Baek D, Haq F, Ansari AA, Lee SY, Chun SM, Choi S et al (2014) Genomic portrait of resectable hepatocellular carcinomas: implications of RB1 and FGF19 aberrations for patient stratification. Hepatology 60:1972–1982

Ahrendt SA, Eisenberger CF, Yip L, Rashid A, Chow JT, Pitt HA, Sidransky D (1999) Chromosome 9p21 loss and p16 inactivation in primary sclerosing cholangitis-associated cholangiocarcinoma. J Surg Res 84:88–93

Anwar SL, Krech T, Hasemeier B, Schipper E, Schweitzer N, Vogel A, Kreipe H, Lehmann U (2014) Deregulation of RB1 expression by loss of imprinting in human hepatocellular carcinoma. J Pathol 233:392–401

Armengol C, Boix L, Bachs O, Solé M, Fuster J, Sala M, Llovet JM, Rodes J, Bruix J (2003) p27(Kip1) is an independent predictor of recurrence after surgical resection in patients with small hepatocellular carcinoma. J Hepatol 38:591–597

Azechi H, Nishida N, Fukuda Y, Nishimura T, Minata M, Katsuma H, Kuno M, Ito T et al (2001) Disruption of the p16/cyclin D1/retinoblastoma protein pathway in the majority of human hepatocellular carcinomas. Oncology 60:346–354

Bahnassy AA, Zekri AR, Loutfy SA, Mohamed WS, Moneim AA, Salem SE, Sheta MM, Omar A, Al-Zawahry H (2011) The role of cyclins and cyclin dependent kinases in development and progression of hepatitis C virus-genotype 4-associated hepatitis and hepatocellular carcinoma. Exp Mol Pathol 91:643–652

Baker DJ, Dawlaty MM, Galardy P, van Deursen JM (2007) Mitotic regulation of the anaphase-promoting complex. Cell Mol Life Sci 64:589–600

Barford D (2011) Structure, function and mechanism of the anaphase promoting complex (APC/C). Q Rev Biophys 44:153–190

Barker N, Morin PJ, Clevers H (2000) The Yin-Yang of TCF/beta-catenin signaling. Adv Cancer Res 77:1–24

Bassullu N, Turkmen I, Dayangac M, Yagiz Korkmaz P, Yasar R, Akyildiz M, Yaparak O, Tokat Y, Yuzer Y, Bulbul Dogusoy G (2012) The predictive and prognostic significance of c-erb-B2, EGFR, PTEN, mTOR, PI3K, p27, and ERCC1 expression in hepatocellular carcinoma. Hepat Mon 12:e7492

Belham C, Roig J, Caldwell JA, Aoyama Y, Kemp BE, Comb M, Avruch J (2003) A mitotic cascade of NIMA family kinases. Nercc1/Nek9 activates the Nek6 and Nek7 kinases. J Biol Chem 278:34897–34909

Binné UK, Classon MK, Dick FA, Wei W, Rape M, Kaelin WG, Näär AM, Dyson NJ (2007) Retinoblastoma protein and anaphase-promoting complex physically interact and functionally cooperate during cell-cycle exit. Nat Cell Biol 9:225–232

Bloom J, Cross FR (2007) Multiple levels of cyclin specificity in cell-cycle control. Nat Rev Mol Cell Biol 8:149–160

Bogaerts E, Heindryckx F, Vandewynckel YP, Van Grusnven LA, Van Vlierberghe H (2014) The roles of transforming growth factor-b, Wnt, Notch and hypoxia on liver progenitor cells in primary liver tumours (review). Int J Oncol 44:1015–1022

Bonilla F, Orlow I, Cordon-Cardo C (1998) Mutational study of p16CDKN2/MTS1/INK4A and p57KIP2 genes in hepatocellular carcinoma. Int J Oncol 12:583–588

Borriello A, Caldarelli I, Bencivenga D, Criscuolo M, Cucciolla V, Tramontano A, Oliva A et al (2011) p57Kip2 and cancer: time for a critical appraisal. Mol Cancer Res 9:1269–1284

Brinkkoetter PT, Olivier P, Wu JS, Henderson S, Krofft RD, Pippin JW, Hockenbery D, Roberts JM, Shankland SJ (2009) Cyclin I activates Cdk5 and regulates expression of Bcl-2 and Bcl-XL in postmitotic mouse cells. J Clin Invest 119:3089–3101

Brinkkoetter PT, Pippin JW, Shankland SJ (2010) Cyclin I-Cdk5 governs survival in post-mitotic cells. Cell Cycle 9:1729–1731

Buendia MA (2002) Genetic alterations in hepatoblastoma and hepatocellular carcinoma: common and distinctive aspects. Med Pediatr Oncol 39:530–535

Burgess A, Vigneron S, Brioudes E, Labbé JC, Lorca T, Castro A (2010) Loss of human Greatwall results in G2 arrest and multiple mitotic defects due to deregulation of the cyclin B-Cdc2/PP2A balance. Proc Natl Acad Sci U S A 107:12564–12569

Calvisi DF, Pinna F, Meloni F, Ladu S, Pellegrino R, Sini M, Daino L, Simile MM, De Miglio MR, Virdis P, Frau M et al (2008) Dual-specificity phosphatase 1 ubiquitination in extracellular signal-regulated kinase-mediated control of growth in human hepatocellular carcinoma. Cancer Res 68:4192–4200

Chang L, Barford D (2014) Insights into the anaphase-promoting complex: a molecular machine that regulates mitosis. Curr Opin Struct Biol 29:1–9

Chang L, Zhang Z, Yang J, Yang J, McLaughlin SH, Barford D (2014) Molecular architecture and mechanism of the anaphase-promoting complex. Nature 513:388–393

Chaubert P, Gayer R, Zimmermann A, Fontolliet C, Stamm B, Bosman F, Shaw P (1997) Germ-line mutations of the p16INK4(MTS1) gene occur in a subset of patients with hepatocellular carcinoma. Hepatology 25:1376–1381

Chen TC, Ng KF, Lien JM, Jeng LB, Chen MF, Hsieh LL (2000) Mutational analysis of the p27(kip1) gene in hepatocellular carcinoma. Cancer Lett 153:169–173

Chen YW, Klimstra DS, Mongeau ME, Tatem JL, Boyartchuk V, Lewis BC (2007) Loss of p53 and Inka/Arf cooperate in a cell autonomous fashion to induce metastasis of hepatocellular carcinoma cells. Cancer Res 67:7589–7596

Chen YW, Pailwal S, Draheim K, Grossman SR, Lewis BC (2008) p19Arf inhibits the invasion of hepatocellular carcinoma cells by binding to C-terminal binding protein. Cancer Res 68:476–482

Chen L, Yuan D, Wang GL, Wang Y, Wu YY, Zhu J (2010) Clinicopathological significance of expression of Tspan-1, Jab1 and p27 in human hepatocellular carcinoma. J Korean Med Sci 25:1438–1442

Chen YL, Uen YH, Li CF, Horng KC, Chen LR, Wu WR, Tseng HY, Huang HY, Wu LC, Shiue YL (2013a) The E2F transcription factor 1 transactivates stathmin 1 in hepatocellular carcinoma. Ann Surg Oncol 20:4041–4054

Chen YW, Chu HC, Ze-Shiang L, Shiah WJ, Chou CP, Klimstra DS, Lewis BC (2013b) p16 stimulates CDC42-dependent migration of hepatocellular carcinoma cells. PLoS One 8:e69389

Chen et al. (2015) http://www.ncbi.nlm.nih.gov/pubmed/25712050

Cheng WT, Xu K, Tian DY, Zhang ZG, Liu LJ, Chen Y (2009) Role of Hedgehog signaling pathway in proliferation and invasiveness of hepatocellular carcinoma cells. Int J Oncol 34:829–836

Chinnasri P, Pairojkul C, Jearanaikoon P, Sripa B, Budhisawasdi V, Tantimavanich S, Limpaiboon T (2009) Preferentially different mechanisms of inactivation of 9p21 gene cluster in liver fluke-related cholangiocarcinoma. Hum Pathol 40:817–826

Cho JW, Jeong YW, Han SW, Park JB, Jang BC, Baek WK, Kwon TK, Park JW et al (2003) Aberrant p16INK4A RNA transcripts expressed in hepatocellular carcinoma cell lines regulate pRb phosphorylation by binding with CDK4, resulting in delayed cell cycle progression. Liver Int 23:194–200

Choi SS, Bradrick S, Qiang G, Mostafavi A, Chaturvedi G, Weinman SA, Diehl AM et al (2011) Up-regulation of Hedgehog pathway is associated with cellular permissiveness for hepatitis C virus replication. Hepatology 54:1580–1590

Claudio PP, Russo G, Kumar CA, Minimo C, Farina A, Tutton S, Nuzzo G, Giuliante F et al (2004) pRb2/p130, vascular endothelial growth factor, p27(KIP1), and

proliferating cell nuclear antigen expression in hepatocellular carcinoma: their clinical significance. Clin Cancer Res 10:3509–3517

Cui X, Yu L, Wang Y, He S, Zhang Y, Wan C, Shi J, Jiang W, Zhang J, Mei G, Ni R (2013) The relationship between cyclin G1 and survival in patients treated surgically for HCC. Hepatogastroenterology 60:153–159

Damo LA, Snyder PW, Franklin DS (2005) Tumorigenesis in p27/p53- and p18/p53-double null mice: functional collaboration between the Rb and p53 pathways. Mol Carcinog 42:109–120

De Souza EE, Hehnly H, Perez AM, Meirelles GV, Smetana JH, Doxsey S, Kobard J (2015) Human Nek7-interactor RGS2 is required for mitotic spindle organization. Cell Cycle 14:656–667

DeHaan RD, Kipp BR, Smyrk TC, Abraham SC, Roberts LR, Halling KC (2007) An assessment of chromosomal alterations detected by fluorescence in situ hybridization and p16 expression in sporadic and primary sclerosing cholangitis-associated cholangiocarcinomas. Hum Pathol 38:491–499

Delogu S, Wang C, Cigliano A, Utpatel K, Sini M, Longerich T, Waldburger N, Breuhahn K, Jiang L, Ribback S, Dombrowski F et al (2015) SKP2 cooperates with N-Ras or AKT to induce liver tumor development in mice. Oncotarget 6:2222–2234

Demir K, Kirsch N, Beretta CA, Erdmann G, Ingelfinger D, Moro E, Argenton F, Carl M et al (2013) RAB8B is required for activity and caveolar endocytosis of LRP6. Cell Rep 4:1224–1234

Di Fiore B, Davey NE, Hagting A, Izawa D, Mansfeld J, Gibson TJ, Pines J (2015) The ABBA motif binds APC/C activators and is shared by APC/C substrates and regulators. Dev Cell 32:358–372

Diaz-Martinez LA, Tian W, Li B, Warrington R, Jia L, Brautigam CA, Luo X, Yu H (2015) The Cdc20-binding Phe box of the spindle checkpoint protein BubR1 maintains the mitotic checkpoint complex during mitosis. J Biol Chem 290:2431–2443

Ding X, Yang Y, Han B, Du C, Xu N, Huang H, Cai T, Zhang A, Han ZG, Zhou W, Chen L (2014) Transcriptomic characterization of hepatocellular carcinoma with CTNNB1 mutation. PLoS One 9:e95307

Dodurga Y, Yonguc GN, Avci CB, Bagci G, Gunduz C, Satiroglu-Tufan NL (2012) Investigation of microRNA expression changes in hepG2 cell line in presence of URG4/URGCP and in absence of URG4/URGCP suppressed by RNA interference. Mol Biol Rep 39:11119–11124

Domingo-Sananes MR, Kapuy O, Hunt T, Novak B (2011) Switches and latches: a biochemical tug-of-war between the kinases and phosphatases that control mitosis. Philos Trans R Soc Lond B Biol Sci 366:3584–3589

Dong Y, Wang A (2014) Aberrant DNA methylation in hepatocellular carcinoma tumor suppression (review). Oncol Lett 8:963–968

Du Y, Kong G, You X, Zhang S, Zhang T, Gao Y, Ye L, Zhang X (2012) Elevation of highly up-regulated in liver cancer (HULC) by hepatitis B virus X protein promotes hepatoma cell proliferation via down-regulating p18. J Biol Chem 287:26302–26311

Edamoto Y, Hara A, Biernat W, Terracciano L, Cathomas G, Riehle HM, Matsuda M et al (2003) Alterations of RB1, p53 and Wnt pathways in hepatocellular carcinomas associated with hepatitis C, hepatitis B and alcoholic liver cirrhosis. Int J Cancer 106:334–341

Ehedego H, Boekschoten MV, Hu W, Doler C, Haybaeck J, Gassler N, Mller M, Liedtke C, Trautwein C (2015) p21 ablation in liver enhances DNA damage, cholestasis, and carcinogenesis. Cancer Res 75:1144–1155

Ehrlich SM, Liebl J, Ardelt MA, Lehr T, De Toni EN, Mayr D, Brandl L, Kirchner T, Zahler S, Gerbes AL, Vollmar AM (2015) Targeting cyclin dependent kinase 5 in hepatocellular carcinoma – a novel therapeutic approach. J Hepatol. doi:10.1016/j.hep.2015.01.031

Ekholm SV, Reed SI (2000) Regulation of G(1) cyclin-dependent kinases in the mammalian cell cycle. Curr Opin Cell Biol 12:676–684

Feng XH, Lin X, Derynck R (2000) Smad2, Smad3 and Smad4 cooperate with Sp1 to induce p15(Ink4B) transcription in response to TGF-beta. EMBO J 19:5178–5193

Fiorentino M, Altimari A, D'Errico A, Gabusi E, Chieco P, Masetti M, Grigioni WF (2001) Low p27 expression is an independent predictor of survival for patients with either hilar or peripheral intrahepatic cholangiocarcinoma. Clin Cancer Res 7:3994–3999

Ford HL, Pardee AB (1999) Cancer and the cell cycle. J Cell Biochem Suppl 32–33:166–172

Fornari F, Gramantieri L, Ferracin M, Veronese A, Sabbioni S, Calin GA, Grazi GL et al (2008) MiR-221 controls CDKN1C/p57 and CDKN1B/p27 expression in human hepatocellular carcinoma. Oncogene 27:5651–5661

Fornari et al. (2009) http://www.ncbi.nlm.nih.gov/pubmed/19584283

Fry AM, O'Regan L, Sabir SR, Bayliss R (2012) Cell cycle regulation by the NEK family of protein kinases. J Cell Sci 125:4423–4433

Fu X, Wang Q, Chen J, Huang X, Chen X, Cao L, Tan H, Li W, Zhang L, Bi J, Su Q et al (2011) Clinical significance of miR-221 and its inverse correlation with p27Kip1 in hepatocellular carcinoma. Mol Biol Rep 38:3029–3035

Fu J, Qiu H, Cai M, Pan Y, Cao Y, Liu L, Yun J, Zhang CZ (2013) Low cyclin F expression in hepatocellular carcinoma associates with poor differentiation and unfavorable prognosis. Cancer Sci 104:508–515

Fukai K, Yokosuka O, Imazeki F, Tada M, Mikata R, Miyazaki M, Ochiai T, Saisho H (2005) Methylation status of p14ARF, p15INK4b, and p16INK4a genes in human hepatocellular carcinoma. Liver Int 25:1209–1216

Fung TK, Poon RY (2005) A roller coaster ride with the mitotic cyclins. Semin Cell Dev Biol 16:335–342

Gao J, Song Z, Chen Y, Xia L, Wang J, Fan R, Du R, Zhang F, Hong L, Song J, Zou X, Xu H, Zheng G, Liu J, Fan D (2008) Deregulated expression of Notch receptors in human hepatocellular carcinoma. Dig Liver Dis 40:114–121

Gao J, Chen Y, Wu KC, Liu J, Zhao YQ, Pan YL, Du R, Zheng GR, Xiong YM et al (2010) RUNX3 directly interacts with intracellular domain of Notch1 and suppresses Notch signaling in hepatocellular carcinoma cells. Exp Cell Res 316:149–157

Gao J, Dong Y, Zhang B, Xiong Y, Xu W, Cheng Y, Dai M, Yu Z, Xu M, Zheng G (2012) Notch1 activation contributes to tumor cell growth and proliferation in human hepatocellular carcinoma HepG2 and SMMC7721 cells. Int J Oncol 41:1773–1781

Geisler and Strazzabosco (2014) http://www.ncbi.nlm.nih.gov/pubmed/24930574

Gharbi-Ayachi A, Labbé JC, Burgess A, Vigneron S, Strub JM, Brioudes E, Van-Dorsselaer A, Castro A, Lorca T (2010) The substrate of Greatwall kinase, Arpp19, controls mitosis by inhibiting protein phosphatase 2A. Science 330:1673–1677

Giacinti C, Giordani A (2006) RB and cell cycle progression. Oncogene 25:5220–5227

Giovannini C, Gramantieri L, Chieco P, Minguzzi M, Lago F, Pianetti S, Ramazzotti E et al (2009) Selective ablation of Notch3 in HCC enhances doxorubicin's death promoting effect by a p53 dependent mechanism. J Hepatol 50:969–979

Giovannini C, Gramantieri L, Minguzzi M, Fornari F, Chieco P, Grazi GL, Bolondi L (2012) CDKN1C/P57 is regulated by the Notch target gene Hes1 and induces senescence in human hepatocellular carcinoma. Am J Pathol 181:413–422

Giovannini C, Baglioni M, Baron Toaldo M, Ventrucci C, D'Adamo C, Cipone M, Chieco P, Gramantieri L, Bolondo L (2013) Notch3 inhibition enhances sorafenib cytotoxic efficacy by promoting GSK3b phosphorylation and p21 down-regulation in hepatocellular carcinoma. Oncotarget 4:1618–1631

Giovannini C, Minguzzi M, Baglioni M, Fornari F, Giannone F, Ravaioli M, Cescon M, Chieco P, Bolondi L, Gramantieri L (2014) Suppression of p53 by Notch3 is mediated by cyclin G1 and sustained by MDM2 and miR-221 axis in hepatocellular carcinoma. Oncotarget 5:10607–10620

Glover DM (2012) The overlooked greatwall: a new perspective on mitotic control. Open Biol 2:120023

Goldenberg D, Eferl R (2014) p21Waf1/Cip1 revisited: oncogenic function in hepatocellular carcinoma. Gut 63:1372–1373

Gonda TA, Glick MP, Sethi A, Poneros JM, Palmas W, Iqbal S, Gonzalez S, Nandula SV, Emond JC, Brown RS et al (2012) Polysomy and p16 deletion by fluorescence in situ hybridization in the diagnosis of indeterminate biliary strictures. Gastrointest Endosc 75:74–79

Gramantieri L, Giovannini C, Lanzi A, Chieco P, Ravaioli M, Venturi A, Grazi GL, Bolondi L (2007a) Aberrant Notch3 and Notch4 expression in human hepatocellular carcinoma. Liver Int 27:997–1007

Gramantieri L, Ferracin M, Fornari F, Veronese A, Sabbioni S, Liu CG, Calin GA, Giovannini C, Ferrazzi E, Grazi GL et al (2007b) Cyclin G1 is target of miR-122a, a microRNA frequently down-regulated in human hepatocellular carcinoma. Cancer Res 67:6092–6099

Güller M, Toualbi-Abed K, Legrand A, Michel L, Mauviel A, Bernuau D, Daniel F (2008) c-Fos overexpression increases the proliferation of human hepatocytes by stabilizing nuclear cyclin D1. World J Gastroenterol 14:6339–6346

Guo H, Lv Y, Tian T, Hu TH, Wang WJ, Sui X, Jiang L, Ruan ZP, Nan KJ (2011) Downregulation of p57 accelerates the growth and invasion of hepatocellular carcinoma. Carcinogenesis 32:1897–1904

Hagmann H, Taniguchi Y, Pippin JW, Kauerz HM, Benzing T, Shankland SJ, Brinkkoetter PT (2015) Cyclin I and p35 determine the subcellular distribution of Cdk5. Am J Physiol Cell Physiol 308: C339–C347

Han C, Demetris AJ, Michalopoulos GK, Zhan Q, Shelhamer JH, Wu T (2003) PPARgamma ligands inhibit cholangiocarcinoma cell growth through p53-dependent GADD45 and p21 pathway. Hepatology 38:167–177

Han et al. (2005) http://www.ncbi.nlm.nih.gov/pubmed/16014626

Han SX, Bai E, Jin GH, He CC, Guo XJ, Wang LJ, Li M, Ying X, Zhu Q (2014) Expression and clinical significance of YAP, TAZ, and AREG in hepatocellular carcinoma. J Immunol Res 2014:261365

Hannon et al. (1994) http://www.ncbi.nlm.nih.gov/pubmed/8127873

Hao PP, Li H, Lee MJ, Wang YP, Kim JH, Yu GR, Lee SY, Leem SH, Jang KY, Kim DG (2015) Disruption of a regulatory loop between DUSP1 and p53 contributes to hepatocellular carcinoma development and progression. J Hepatol. doi:10.1016/j.jhep.2014.12.033

Hara T, Kamura T, Nakayama K, Oshikawa K, Hatakeyama S, Nakayama K (2001) Degradation of p27(Kip1) at the G(0)-G(1) transition mediated by a Skp-2-independent ubiquitination pathway. J Biol Chem 276:48937–48943

Hashimoto N, Yachida S, Okano K, Wakabayashi H, Imaida K, Kurokohchi K, Masaki T, Kinoshita H, Tominaga M et al (2009) Immunohistochemically detected expression of p27(Kip1) and Skp2 predicts survival in patients with intrahepatic cholangiocarcinomas. Ann Surg Oncol 16:395–403

Hattori T, Isobe T, Abe K, Kikuchi H, Kitagawa K, Oda T, Uchida C, Kitagawa M (2007) Pirh2 promotes ubiquitin-dependent degradation of the cyclin-dependent kinase inhibitor p27Kip1. Cancer Res 67:10789–10795

He S, Lu M, Xue W, Wang Y, Zhao Y, Gao S, Ke Q, Liu Y, Li P, Cui X, Cheng C, Shen A (2011) Phosphorylated p27Kip1 on Thr157 is an important prognosis in human

hepatocellular carcinoma in vivo and in vitro. Med Oncol 28:94–104
Herath NI, Kew MC, Walsh MD, Young J, Powell LW, Leggett BA, MacDonald GA (2002) Reciprocal relationship between methylation and loss of heterozygosity at the p14(ARF) locus in Australian and South African hepatocellular carcinomas. J Gastroenterol Hepatol 17:301–307
Hernandez et al. (2013) http://www.ncbi.nlm.nih.gov/pubmed/23864307
Hershko A (1999) Mechanisms and regulation of the degradation of cyclin B. Philos Trans R Soc B-Biol Sci 354:1571–1575
Horie S, Endo K, Kawasaki H, Terada T (2000) Overexpression of MDM2 protein in intrahepatic cholangiocarcinoma: relationship with p53 overexpression, Ki-67 labeling, and clinicopathological features. Virchows Arch 437:25–30
Hsieh SY, Huang SF, Yu MC, Yeh TS, Chen TC, Lin YJ, Chang CJ, Sung CM, Lee YL, Hsu CY (2010) Stathmin 1 overexpression associated with polyploidy, tumor-cell invasion, early recurrence, and poor prognosis in human hepatoma. Mol Carcinog 49:476–487
Hu TH, Wang CC, Huang CC, Chen CL, Hung CH, Chen CH, Wang JH, Lu SN et al (2007) Down-regulation of tumor suppressor gene PTEN, overexpression of p53, plus high proliferating cell nuclear antigen index predict poor patient outcome of hepatocellular carcinoma after resection. Oncol Rep 18:1417–1426
Hu T, Guo H, Wang W, Yu S, Han L, Jiang L, Ma J, Yang C, Guo Q, Nan K (2013a) Loss of p57 expression and RhoA overexpression are associated with poor survival of patients with hepatocellular carcinoma. Oncol Rep 30:1707–1714
Hu L, Xue F, Shao M, Deng A, Wei G (2013b) Aberrant expression of Notch3 predicts poor survival for hepatocellular carcinomas. Biosci Trends 7:152–156
Hu Z, Zhou Z, Xiong G, Wang Y, Lai Y, Deng L, Yang J (2014) Cyclin D1 G870A polymorphism and the risk of hepatocellular carcinoma in a Chinese population. Tumour Biol 35:5607–5612
Huang JZ, Xia SS, Ye QF, Jiang HY, Chen ZH (2003) Effects of p16 gene on biological behaviours in hepatocellular carcinoma cells. World J Gastroenterol 9:84–88
Huang X, Qian X, Cheng C, He S, Sun L, Ke Q, Zhang L, Pan X, He F, Wang Q et al (2011) Expression of Pirh2, a p27(Kip1) ubiquitin ligase, in hepatocellular carcinoma: correlation with p27(Kip1) and cell proliferation. Hum Pathol 42:507–515
Huang XH, Jian WH, Wu ZF, Zhao J, Wang H, Li W, Xia JT (2014) Small interfering RNA (siRNA)-mediated knockdown of macrophage migration inhibitory factor (MIF) suppressed cyclin D1 expression and hepatocellular carcinoma cell proliferation. Oncotarget 5:5570–5580
Huang B, Li H, Huang L, Luo C, Zhang Y (2015) Clinical significance of microRNA 138 and cyclin D3 in hepatocellular carcinoma. J Surg Res 193:718–723
Hui AM, Sakamoto M, Kanai Y, Ino Y, Gotoh M, Yokota J, Hirohashi S (1996) Inactivation of p16INK4 in hepatocellular carcinoma. Hepatology 24:575–579
Hui AM, Sun L, Kanai Y, Sakamoto M, Hirohashi S (1998) Reduced p27Kip1 expression in hepatocellular carcinomas. Cancer Lett 132:67–73
Hutcheson J, Bourgo RJ, Balaji U, Ertel A, Witkiewicz AK, Knudsen ES (2014) Retinoblastoma protein potentiates the innate immune response in hepatocytes: significance for hepatocellular carcinoma. Hepatology 60:1231–1240
Irniger S (2002) Cyclin destruction in mitosis: a crucial task of Cdc20. FEBS Lett 532:7–11
Ishikawa A, Sasaki M, Sato Y, Ohira S, Chen MF, Huang SF, Oda K, Nimura Y, Nakanuma Y (2004) Frequent p16ink4a inactivation is an early and frequent event of intraductal papillary neoplasm of the liver arising I hepatolithiasis. Hum Pathol 35:1505–1514
Ito Y, Matsuura N, Sakon M, Miyoshi E, Noda K, Takeda T, Umeshita K, Nagano H, Nakamori S, Dono K, Tsujimoto M et al (1999) Expression and prognostic roles of the G1-S modulators in hepatocellular carcinoma: p27 independently predicts the recurrence. Hepatology 30:90–99
Ito Y, Takeda T, Sakon M, Monden M, Tsujimoto M, Matsuura N (2000) Expression and clinical significance of the G1-S modulators in carcinoma of the extrahepatic bile duct. Anticancer Res 20:337–344
Ito Y, Takeda T, Sasaki Y, Sakon M, Yamada T, Ishiguro S, Imaoka S, Tsujimoto M, Matsuura N (2001a) Expression and clinical significance of the G1-S modulators in intrahepatic cholangiocellular carcinoma. Oncology 60:242–251
Ito Y, Takeda T, Sakon M, Tsujimoto M, Monden M, Matsuura N (2001b) Expression of p57/Kip2 protein in hepatocellular carcinoma. Oncology 61:221–225
Ito Y, Takeda T, Sasaki Y, Sakon M, Yamada T, Ishiguro S, Imaoka S, Tsujimoto M et al (2002) Expression of p57/Kip2 protein in extrahepatic bile duct carcinoma and intrahepatic cholangiocellular carcinoma. Liver 22:145–149
Ito T, Nishida N, Fukuda Y, Nishimura T, Komeda T, Nakao K (2004) Alteration of the p14(ARF) gene and p53 status in human hepatocellular carcinomas. J Gastroenterol 39:355–361
Izawa D, Pines J (2015) The mitotic checkpoint complex binds a second CDC20 to inhibit active APC/C. Nature 517:631–634
Jahn SC, Law ME, Corsino PE, Rowe TC, Davis BJ, Law BK (2013) Assembly, activation, and substrate specificity of cyclin D1/Cdk2 complexes. Biochemistry 52:3489–3501
Jarnagin WR, Klimstra DS, Hezel M, Gonen M, Fong Y, Roggin K, Cymes K, DeMatteo RP, D'Angelica M, Blumgart LH et al (2006) Differential cell cycle-regulatory protein expression in biliary tract adenocarcinoma: correlation with anatomic site, pathologic variables, and clinical outcome. J Clin Oncol 24:1152–1160

Jie L, Fan W, Weiqi D, Yingqun Z, Ling X, Miao S, Ping C, Chuanyong G (2013) The hippo-yes association protein pathway in liver cancer. Gastroenterol Res Pract 2013:187070

Jin M, Piao Z, Kim NG, Park C, Shin EC, Park JH, Jung HJ, Kim CG, Kim H (2000) p16 is a major inactivation target in hepatocellular carcinoma. Cancer 89:60–68

Jing Z, Nan KJ, Hu ML (2005) Cell proliferation, apoptosis and the related regulators p27, p53 expression in hepatocellular carcinoma. World J Gastroenterol 11:1910–1916

John PC, Mews M, Moore R (2001) Cyclin/Cdk complexes: their involvement in cell cycle progression and mitotic division. Protoplasma 216:119–142

Johnson DG, Walker CL (1999) Cyclins and cell cycle checkpoints. Annu Rev Pharmacol Toxicol 39:295–312

Kang YK, Kim WH, Jang JJ (2002) Expression of G1-S modulators (p53, p16, p27, cyclin D1, Rb) and Smad4/Dpc4 in intrahepatic cholangiocarcinoma. Hum Pathol 33:877–883

Kao JT, Chuah SK, Huang CC, Chen CL, Wang CC, Hung CH, Chen CH, Wang JH et al (2007) P21/WAF1 is an independent survival prognostic factor for patients with hepatocellular carcinoma after resection. Liver Int 27:772–781

Karamitopoulou E, Tornillo L, Zlobec I, Cioccari L, Carafa V, Borner M, Schaffner T, Brunner T, Diamantis I, Zimmermann A et al (2008) Clinical significance of cell cycle- and apoptosis-related markers in biliary tract cancer: a tissue microarray-based approach revealing a distinctive immunophenotype for intrahepatic and extrahepatic cholangiocarcinomas. Am J Clin Pathol 130:780–786

Kim WB, Han HJ, Lee HJ, Park SS, Song TJ, Kim HK, Suh SO, Kim YC, Choi SY (2009) Expression and clinical significance of cell cycle regulatory proteins in gallbladder and extrahepatic bile duct cancer. Ann Surg Oncol 16:23–34

Kim HY, Cho HK, Hong SP, Cheong J (2011) Hepatitis B virus X protein stimulates the Hedgehog-Gli activation through protein stabilization and nuclear localization of Gli1 in liver cancer cells. Cancer Lett 309:176–184

Kim JY, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, Jeon WK, Kim BI, Kim DH, Chae SW, Sohn JH (2014) Epidermal growth factor upregulates Skp2/Cks1 and p27(kip1) in human extrahepatic cholangiocarcinoma cells. World J Gastroenterol 20:755–773

Kitamura T, Watanabe S, Sato N (1998) Liver regeneration, liver cancers and cyclins. J Gastroenterol Hepatol 13(Suppl):S96–S99

Ko E, Kim Y, Kim SJ, Joh JW, Ong S, Park CK, Park J, Kim DH (2008) Promoter hypermethylation of the p16 gene is associated with poor prognosis in recurrent early-stage hepatocellular carcinoma. Cancer Epidemiol Biomarkers Prev 17:2260–2267

Kosaka M, Kang MR, Yang G, Li LC (2012) Targeted p21WAF1/CIP1 activation by RNAa inhibits hepatocellular carcinoma cells. Nucleic Acids Ther 22:335–343

Kotoshiba S, Gopinanthan L, Pfeiffenberger E, Rahim A, Vardy LA, Nakayama K, Nakayama KI, Kaldis P (2014) p27 is regulated independently of Skp2 in the absence of Cdk2. Biochim Biophys Acta 1843:436–445

Lara-Gonzalez P, Scott MI, Diez M, Sen O, Taylor SS (2011) BubR1 blocks substrate recruitment to the APC/C in a KEN-box-dependent manner. J Cell Sci 124:4332–4345

Lee et al. (2002) http://www.ncbi.nlm.nih.gov/pubmed/12213730

Lee TK, Man K, Ling MT, Wang XH, Wong YC, Lo CM, Poon RT, Ng IO, Fan ST (2003) Over-expression of Id-1 induces cell proliferation in hepatocellular carcinoma through inactivation of p16INK4a/RB pathway. Carcinogenesis 24:1729–1736

Lee HC, Kim M, Wands JR (2006) Wnt/Frizzled signaling in hepatocellular carcinoma. Front Biosci 11:1901–1915

Lee KP, Lee JH, Kim TS, Kim TH, Park HD, Byun JS, Kim MC, Jeong WI, Calvisi DF et al (2010) The Hippo-Salvador pathway restrains hepatic oval cell proliferation, liver size, and liver tumorigenesis. Proc Natl Acad Sci U S A 107:8248–8253

Lee EK, Kim DG, Kim JS, Yoon Y (2011) Cell-cycle regulator Cks1 promotes hepatocellular carcinoma by supporting NF-kB-dependent expression of interleukin-8. Cancer Res 71:6827–6835

Lee et al. (2013) http://www.ncbi.nlm.nih.gov/pubmed/23420090

Lee JM, Yang J, Newell P, Singh S, Parwani A, Friedman SL, Nejak-Bowen KN, Monga SP (2014) b-Catenin signaling in hepatocellular cancer: implications in inflammation, fibrosis, and proliferation. Cancer Lett 343:90–97

Lei PP, Zhang ZJ, Shen LJ, Li JY, Zou Q, Zhang HX (2005) Expression and hypermethylation of p27 kip1 in hepatocarcinogenesis. World J Gastroenterol 11:4587–4591

Li X, Hui AM, Sun L, Hasegawa K, Torzilli G, Minagawa M, Takayama T, Makuuchi M (2004) p16INK4A hypermethylation is associated with hepatitis virus infection, age, and gender in hepatocellular carcinoma. Clin Cancer Res 10:7484–7489

Li H, Wolfe A, Septer S, Edwards G, Zhong X, Abdulkarim AB, Ranganathan S, Apte U (2012) Deregulation of Hippo kinase signalling in human hepatic malignancies. Liver Int 32:38–47

Li J, Gao JZ, Du JL, Huang ZX, Wei LX (2014a) Increased CDC20 expression is associated with development and progression of hepatocellular carcinoma. Int J Oncol 45:1547–1555

Li P, Cao Y, Li Y, Zhou L, Liu X, Geng M (2014b) Expression of Wnt-5a and b-catenin in primary hepatocellular carcinoma. Int J Clin Exp Pathol 7:3190–3195

Li Y, Yang XH, Fang SJ, Qin CF, Sun RL, Liu ZY, Jiang BY, Wu X, Li G (2015a) HOXA7 stimulates human

hepatocellular carcinoma proliferation through cyclin E1/CDK2. Oncol Rep 33:990–996

Li L, Tang J, Zhang B, Yang W, LiuGao M, Wang R, Tan Y, Fan J, Chang Y, Fu J, Jiang F, Chen C, Yang Y, Gu J et al (2015b) Epigenetic modification of MiR-429 promotes liver tumour-initiating cell properties by targeting Rb binding protein 4. Gut 64:156–167

Liang X, Zeng J, Wang L, Fang M, Wang Q, Zhao M, Xu X, Liu Z, Li W, Li W, Liu S, Yu H, Jia J, Chen C (2013) Histone demethylase retinoblastoma binding protein 2 is overexpressed in hepatocellular carcinoma and negatively regulated by hsa-miR-212. PLoS One 8: e69784

Liew CT, Li HM, Lo KW, Leow CK, Lau WY, Hin LY, Lim BK, Lai PB, Chan JY, Wang XQ, Wu S, Lee JC (1999) Frequent allelic loss on chromosomal 9 in hepatocellular carcinoma. Int J Cancer 81:319–324

Lin J, Huang S, Wu S, Ding J, Zhao Y, Liang L, Tian Q, Zha R, Zhan R, He X (2011) MicroRNA-423 promotes cell growth and regulates G1/S transition by targeting p21Cip1/Waf1 in hepatocellular carcinoma. Carcinogenesis 32:1641–1647

Lin WR, Lai MW, Yeh CT (2013) Cyclin-dependent kinase-associated protein phosphatase is overexpressed in alcohol-related hepatocellular carcinoma and influences xenograft tumor growth. Oncol Rep 29:903–910

Liu AM, Xu Z, Luk JM (2012) An update on targeting Hippo-YAP signaling in liver cancer. Expert Opin Ther Targets 16:243–247

Liu F, Wei YG, Luo LM, Wang WT, Yan LN, Wen TF, Xu MQ, Yang JY, Li B (2013) Genetic variants of p21 and p27 and hepatocellular cancer risk in a Chinese Han population: a case-control study. Int J Cancer 132:2056–2064

Liyan W, Xun S, Xiangwei M (2011) Effect of b-catenin siRNA on proliferation and apoptosis of hepatoma cell line SMMC-7721 and HepG-2. Hepatogastroenterology 58:1757–1764

Lorca T, Castro A (2013) The Greatwall kinase: a new pathway in the control of the cell cycle. Oncogene 32:537–543

Lu JW, Lin YM, Chang JG, Yeh KT, Chen RM, Tsai JJ, Su WW, Hu RM (2013) Clinical implications of reregulated CDK4and cyclin D1 expression in patients with human hepatocellular carcinoma. Med Oncol 30:379

Lu LC, Shao YY, Lee YH, Hsieh MS, Hsiao CH, Lin HH, Kao HF, Ma YY, Yen FC et al (2014) b-catenin (CTNNB1) mutations are not associated with prognosis in advanced hepatocellular carcinoma. Oncology 87:159–166

Luo J, Zhou Y, Wang B, Li Q, Chen Y, Lan H (2015) Immunohistochemically detected expression of Skp2, p27kip1, and p-p27(Thr187) in patients with cholangiocarcinoma. Tumour Biol 36:5119–5125

Machida K, Liu JC, McNamara G, Levine A, Duan L, Lai MM (2009) Hepatitis C virus causes uncoupling of mitotic checkpoint and chromosomal polyploidy through the Rb pathway. J Virol 83:12590–12600

Maehura K, Natsugoe S, Takao S (2014) Molecular mechanism of cholangiocarcinoma carcinogenesis. J Hepato-Biliary-Pancreat Sci 21:754–760

Magistri P, Leonard SY, Tang CM, Chan JC, Lee TE, Sicklick JK (2014) The glypican 3 hepatocellular carcinoma marker regulates human hepatic stellate cells via hedgehog signaling. J Surg Res 187:377–385

Mah WC, Lee CG (2014) DNA methylation: potential biomarker in hepatocellular carcinoma. Biomark Res 2:5

Malumbres M, Barbacid M (2005) Mammalian cyclin-dependent kinases. Trends Biochem Sci 30:630–641

Mansfeld J, Collin P, Collins MO, Choudhary JS, Pines J (2011) APC15 drives the turnover of MCC-CDC20 to make the spindle assembly checkpoint responsive to kinetochore attachment. Nat Cell Biol 13:1234–1243

Marhenke S, Buitrago-Molina LE, Endig J, Orlik J, Schweitzer N, Klett S, Longerich T, Geffers R, Sanchez Munoz A et al (2014) p21 promotes sustained liver regeneration and hepatocarcinogenesis in chronic cholestatic liver injury. Gut 63:1501–1512

Masaki T, Shiratori Y, Rengifo W, Igarashi K, Yamagata M, Kurokohchi K, Uchida N, Miyauchi Y, Yoshiji H, Watanabe S et al (2003) Cyclins and cyclin-dependent kinases: comparative study of hepatocellular carcinoma versus cirrhosis. Hepatology 37:534–543

Matsuda Y (2008) Molecular mechanism underlying the functional loss of cyclin dependent kinase inhibitors p16 and p27 in hepatocellular carcinoma. World J Gastroenterol 14:1734–1740

Matsuda Y, Ichida T (2006) p16 and p27 are functionally correlated during the process of hepatocarcinogenesis. Med Mol Morphol 39:169–175

Matsuda Y, Ichida T, Genda T, Yamagiwa S, Aoyagi Y, Asakura H (2003) Loss of p16 contributes to p27 sequestration by cyclin D(1)-cyclin-dependent kinase 4 complexes and poor prognosis in hepatocellular carcinoma. Clin Cancer Res 9:3389–3396

Matsuda Y, Wakai T, Kubota M, Takamura M, Yamagiwa S, Aoyagi Y, Osawa M, Fujimaki S, Sanpei A, Genda T et al (2013a) Clinical significance of cell cycle inhibitors in hepatocellular carcinoma. Med Mol Morphol 46:185–192

Matsuda Y, Wakai T, Hirose Y, Osawa M, Fujimaki S, Kubota M (2013b) p27 is a critical prognostic biomarker in non-alcoholic steatohepatitis- related hepatocellular carcinoma. Int J Mol Sci 14:23499–23515

Matsushita K, Tamura M, Tanaka N, Tomonaga T, Matsubara H, Shimada H, Levens D et al (2013) Interactions between SAP155 and FUSE-binding protein-interacting repressor bridges c-Myc and p27Kip1 expression. Mol Cancer Res 11:689–698

Mayhew CN, Carter SL, Fox SR, Sexton CR, Reed CA, Srinivasan SV, Liu X, Wikenheiser-Brokamp K, Boivin GP et al (2007) RB loss abrogates cell cycle control and genome integrity to promote liver tumorigenesis. Gastroenterology 133:976–984

McAllister SS, Becker-Hapak M, Pintucci G, Pagano M, Dowdy SF (2003) Novel p27(kip1) C-terminal scatter

domain mediates Rac-dependent cell migration independent of cell cycle arrest functions. Mol Cell Biol 23:216–228
Meadows and Millar (2015) http://www.ncbi.nlm.nih.gov/pubmed/25619242
Monga SP (2014) Role of regulation of b-catenin signaling during physiological liver growth. Gene Expr 16:51–62
Morel CM, Fiorotto R, Fabris L, Strazzabosco M (2013) Notch signalling beyond liver development: emerging concepts in liver repair and oncogenesis. Clin Res Hepatol Gastroenterol 37:447–454
Morgan DO (1997) Cyclin-dependent kinases : engines, clocks, and microprocessors. Annu Rev Cell Dev Biol 13:261–291
Morishita et al. (2004) http://www.ncbi.nlm.nih.gov/pubmed/15349907
Morishita A, Gong J, Deguchi A, Tani J, Miyoshi H, Yoshida H, Yoneyama H, Mori H et al (2011) Frequent loss of p19IMK4D expression in hepatocellular carcinoma: relationship to tumor differentiation and patient survival. Oncol Rep 26:1363–1368
Murray AW (2004) Recycling the cell cycle: cyclins revisited. Cell 116:221–234
Naka T, Toyota N, Kaneko T, Kaibara N (1998) Protein expression of p53, p21WAF1, and Rb as prognostic indicators in patients with surgically treated hepatocellular carcinoma. Anticancer Res 18:555–564
Nakagawa S, Okabe H, Sakamoto Y, Hayashi H, Hashimoto D, Yokoyama N, Sakamoto K, Kuroki H, Mima K, Nitta H et al (2013) Enhancer of zeste homolog 2 (EZH2) promotes progression of cholangiocarcinoma cells by regulating cell cycle and apoptosis. Ann Surg Oncol 20(Suppl 3):S667–S675
Nakai S, Masaki T, Shiratori Y, Ohgi T, Morishita A, Kurokohchi K, Watanabe S, Kuriyama S (2002) Expression of p57(KIP2) in hepatocellular carcinoma: relationship between tumor differentiation and patient survival. Int J Oncol 20:769–775
Nakayama K, Nagahama H, Minamishima YA, Miyake S, Ishida N, Hatakeyama S, Kitagawa M, Iemura S, Natsume T et al (2004) Skp2-mediated degradation of p27 regulates progression into mitosis. Dev Cell 6:661–672
Nan KJ, Guo H, Ruan ZP, Jing Z, Liu SX (2005) Expression of p57(kip2) and its relationship with clinicopathology, PCNA and p53 in primary hepatocellular carcinoma. World J Gastroenterol 11:1237–1240
Nath S, Chowdhury A, Dey S, Roychoudhury A, Ganguly A, Bhattacharyya D, Roychoudhury S (2015) Deregulation of Rb-E2F1 axis causes chromosomal instability by engaging the transactivation function of Cdc20-anaphase-promoting complex/cyclosome. Mol Cel Biol 35:356–369
Nejak-Bowen KN, Thompson MD, Singh S, Bowen WC, Dar MJ, Khillan J, Dai C, Monge SP (2010) Accelerated liver regeneration and hepatocarcinogenesis in mice overexpressing serine-45 mutant beta-catenin. Hepatology 51:1603–1613
Noh JH, Jung KH, Kim JK, Eun JW, Bae HJ, Xie HJ, Chang YG, Kim MG, Park WS, Lee JY, Nam SW (2011) Aberrant regulation of HDAC2 mediates proliferation of hepatocellular carcinoma cells by deregulating expression of G1/S cell cycle proteins. PLoS One 6:e28103
O'Regan L, Fry AM (2009) The Nek6 and Nek7 protein kinases are required for robust mitotic spindle formation and cytokinesis. Mol Cell Biol 29:3975–3990
O'Regan L, Blot J, Fry AM (2007) Mitotic regulation by NIMA-related kinases. Cell Div 2:25
Ohtsuka T, Jensen MR, Kim HG, Kim KT, Lee SW (2004) The negative role of cyclin G in ATM-dependent p53 activation. Oncogene 23:5405–5408
Omenetti A, Choi S, Michelotti G, Diehl AM (2011) Hedgehog signaling in the liver. J Hepatol 54:366–373
Pagano M (2004) Control of DNA synthesis and mitosis by the Skp2-p27-Cdk1/2 axis. Mol Cell 14:414–416
Pang A, Ng IO, Fan ST, Kwong YL (2003) Clinicopathologic significance of genetic alterations in hepatocellular carcinoma. Cancer Genet Cytogenet 146:8–15
Park YN (2014) Hepatobiliary/pancreas pathology: SY11-1 hepatocellular dysplasia: large and small cell changes. Pathology 46(Suppl 2):S23
Park YN, Chae KJ, Kwon KW, Oh BK, Lee KS, Lee WJ, Park C (2003) p53 and p21WAF1/CIP1 in hepatitis B virus related hepatocarcinogenesis. Hepatogastronenterology 50:1292–1296
Park SH, Lim JS, Lim SY, Tiwari I, Jang KL (2011) Hepatitis C virus core protein stimulates cell growth by down-regulating p16 expression via DNA methylation. Cancer Lett 310:61–68
Parry DH, O'Farrell PH (2001) The schedule of destruction of three mitotic cyclins can dictate the timing of events during exit from mitosis. Curr Biol 11:671–683
Pateras IS, Apostolopoulou K, Niforou K, Kotsinas A, Gorgoulis VG (2009) p57KIP2: "Kip"ing the cell under control. Mol Cancer Res 7:1902–1919
Patil MA, Lee SA, Macias E, Lam ET, Xu C, Jones KD, Ho C, Rodriguez-Puebla M, Chen X (2009) Role of cyclin D1 as a mediator of c-Met-and beta-catenin-induced hepatocarcinogenesis. Cancer Res 69:253–261
Peng CY, Chen TC, Hung SP, Chen MF, Yeh CT, Tsai SL, Chu CM, Liaw YF (2002) Genetic alterations of INK4alpha/ARF locus and p53 in human hepatocellular carcinoma. Anticancer Res 22:1265–1271
Pines J, Hunter T (1992) Cyclins A and B1 in the human cell cycle. CIBA Found Symp 170:187–196
Piscopo DM, Hinds PW (2008) A role for the cyclin box in the ubiquitin-mediated degradation of cyclin G1. Cancer Res 68:5581–5590
Pok S, Wen V, Shackel N, Alsop A, Pyakurel P, Fahrer A, Farrell GC, Teoh NC (2013) Cyclin E facilitates dysplastic hepatocytes to bypass G1/S checkpoint in hepatocarcinogenesis. J Gastroenterol Hepatol 28:1545–1554
Qi R, An H, Yu Y, Zhang M, Liu S, Xu H, Guo Z, Cheng T, Cao X (2003) Notch1 signaling inhibits growth of

human hepatocellular carcinoma through induction of cell cycle arrest and apoptosis. Cancer Res 63: 8323–8329

Qi M, Liu D, Zhang S, Hu P, Sang T (2015) Inhibition of S-phase kinase-associated protein 2-mediated p27 degradation suppresses tumorigenesis and the progression of hepatocellular carcinoma. Mol Med Rep 11:3934–3940

Qin LF, Ng IO (2001) Expression of p27(KIP1) and p21 (WAF1/CIP1) in primary hepatocellular carcinoma: clinicopathologic correlation and survival analysis. Hum Pathol 32:778–784

Qin Y, Liu JY, Li B, Sun ZL, Sun ZF (2004) Association of low p16INK4a and p15INK4b mRNAs expression with their CpG islands methylation with human hepatocellular carcinogenesis. World J Gastroenterol 10:1276–1280

Qin J, Wang Z, Wang Y, Ma L, Ni Q, Ke J (2010) JAB1 expression is associated with inverse expression of p27 (kip1) in hepatocellular carcinoma. Hepatogastroenterology 57:547–553

Qu B, Liu BR, Du YJ, Chen J, Cheng YQ, Xu W, Wang XH (2014) Wnt/b-catenin signaling pathway may regulate the expression of angiogenic growth factors in hepatocellular carcinoma. Oncol Lett 7:1175–1178

Queralt E, Uhlmann F (2008) Cdk-counteracting phosphatases unlock mitotic exit. Curr Opin Cell Biol 20:661–668

Reed CA, Mayhew CN, McClendon AK, Yang X, Witkiewicz A, Knudsen ES (2009) RB has a critical role in mediating the in vivo checkpoint response, mitigating secondary DNA damage and suppressing liver tumorigenesis initiated by aflatoxin B1. Oncogene 28:4434–4443

Reed CA, Mayhew CN, McClendon AK, Knudsen ES (2010) Unique impact of RB loss on hepatic proliferation: tumorigenic stresses uncover distinct pathways of cell cycle control. J Biol Chem 285:1089–1096

Reed C, Hutcheson J, Mayhew CN, Witkiewicz AK, Knudsen ES (2014) RB tumor suppressive function in response to xenobiotic hepatocarcinogens. Am J Pathol 184:1853–1859

Rivadeneira DB, Mayhew CN, Thangavel C, Sotillo E, Reed CA, Grana X, Knudsen ES (2010) Proliferative suppression by CDK4/6 inhibition: complex function of the retinoblastoma pathway in liver tissue and hepatoma cells. Gastroenterology 138:1920–1930

Roncalli M, Bianchi P, Bruni B, Laghi L, Destro A, Di Gioia S, Gennari L, Tommasini M, Malesci A, Coggi G (2002) Methylation framework of cell cycle gene inhibitors in cirrhosis and associated hepatocellular carcinoma. Hepatology 36:427–432

Rovida E, Di Maira G, Tusa I, Cannito S, Paternostro C, Navari N, Vivoli E, Deng X, Gray NS, Esparis-Ogando A et al (2014) The mitogen-activated protein kinase ERK5 regulates the development and growth of hepatocellular carcinoma. Gut. doi:10.1136/gutjnl-2014-306761

Ruys et al. (2014) http://www.ncbi.nlm.nih.gov/pubmed/24081803

Sarmento LM, Huang H, Limon A, Gordon W, Fernandes J, Tavares MJ, Miele L, Cardoso AA, Classon M, Carlesso N (2005) Notch1 modulates timing of G1-S progression by inducing SKP2 transcription and p27 Kip1 degradation. J Exp Med 202:157–168

Sasaki M, Yamaguchi J, Itatsu K, Ikeda H, Nakanuma Y (2008) Over-expression of polycomb group protein EZH2 relates to decreased expression of p16 INK4a in cholangiocarcinogenesis in hepatolithiasis. J Pathol 215:175–183

Sasaki M, Matsubara T, Kakuda Y, Sato Y, Nakanuma Y (2014) Immunostaining for polycomb group protein EZH2 and senescent marker p16INK4a may be useful to differentiate cholangiocellular carcinoma from ductular reaction and bile duct adenoma. Am J Surg Pathol 38:364–369

Schlitter AM, Born D, Bettstetter M, Specht K, Kim-Fuchs C, Riener MO, Jeliazkova P, Sipos B, Siveke JT, Terris B et al (2014) Intraductal papillary neoplasms of the bile duct: stepwise progression to carcinoma involves common molecular pathways. Mod Pathol 27:73–86

Schneller D, Machat G, Sousek A, Proell V, van Zijl F, Zulehner G, Huber H, Mair M, Muellner MK, Nijman SM, Eferl R et al (2011) p19(ARF)/p14(ARF) controls oncogenic functions of signal transducer and activator of transcription 3 in hepatocellular carcinoma. Hepatology 54:164–172

Sczaniecka MM, Hardwick KG (2008) The spindle checkpoint: how do cells delay anaphase onset ? SEB Exp Biol Ser 59:243–256

Shang XZ, Zhu H, Lin K, Tu Z, Chen J, Nelson DR, Liu C (2004) Stabilized beta-catenin promotes hepatocyte proliferation and inhibits TNFalpha-induced apoptosis. Lab Invest 84:1332–1341

Shao J, Li Y, Li H, Wu Q, Hou J, Liew C (2000) Deletion of chromosomes 9p and 17 associated with abnormal expression of p53, p16/MTS1 and p15/MTS2 gene protein in hepatocellular carcinomas. Chin Med J (Engl) 113:817–822

Shehata MA, Nosseir HR, Nagy HM, Farouk G (2006) Cyclin dependent kinase inhibitor p27(kip1) expression and subcellular localization in relation to cell proliferation in hepatocellular carcinoma. Egypt J Immunol 13:115–130

Shen DY, Fang ZX, You P, Liu PG, Wang F, Huang CL, Yao XB, Chen ZX, Zhang ZY (2010) Clinical significance and expression of cyclin kinase subunits 1 and 2 in hepatocellular carcinoma. Liver Int 30:119–125

Shen HJ, Zhu HY, Yang C, Ji F (2012) SENP2 regulates hepatocellular carcinoma cell growth by modulating the stability of b-catenin. Asian Pac J Cancer Prev 13:3583–3587

Shen G, Rong X, Zhao J, Yang X, Li H, Jiang H, Zhou Q, Ji T, Huang S, Zhang J, Jia H (2014) MicroRNA-105

suppresses cell proliferation and inhibits PI3K/AKT signaling in human hepatocellular carcinoma. Carcinogenesis 35:2748–2755

Shih YL, Hsieh CB, Lai HC, Yan MD, Hsieh TY, Chao YC, Lin YW (2007) SFRP1 suppressed hepatoma cells growth through Wnt canonical signaling pathway. Int J Cancer 121:1028–1035

Shimada M, Kitagawa K, Dobashi Y, Isobe T, Hattori T, Uchida C, Abe K, Kotake Y et al (2009) High expression of Pirh2, an E3 ligase for p27, is associated with low expression of p27 and poor prognosis in head and neck cancers. Cancer Sci 100:866–872

Shin E, Kim SH, Jeong HY, Jang JJ, Lee K (2012) Nuclear expression of S-phase kinase-associated protein 2 predicts poor prognosis of hepatocellular carcinoma. APMIS 120:349–357

Shirako E, Hirayama N, Tsukada Y, Tanaka T, Kitamura N (2008) Up-regulation of p21CIP1 expression mediated by ERK-dependent and –independent pathways contributes to hepatocyte growth factor-induced inhibition of HepG2 hepatoma cell proliferation. J Cell Biochem 104:176–188

Shirayama M, Toth A, Galova M, Nasmyth K (1999) APC (Cdc20) promotes exit from mitosis by destroying the anaphase inhibitor Pds1 and cyclin Clb5. Nature 402:203–207

Shiraz OB, Galehdari H, Yavarian M, Geramizadeh B (2011) Possible down regulation of the p16 gene promoter in individuals with hepatocellular carcinoma. Hepat Mon 11:719–723

Shiyanov P, Hayes S, Chen N, Pestov DG, Lau LF, Raychaudhuri P (1997) p27Kip1 induces an accumulation of the repressor complexes of E2F and inhibits expression of the E2F-regulated genes. Mol Biol Cell 8:1815–1827

Sicklick JK, Li YX, Jayaraman A, Kannangai R, Qi Y, Vivekanandan P, Ludlow JW et al (2006) Dysregulation of the Hedgehog pathway in human hepatocarcinogenesis. Carcinogenesis 27:748–757

Song GJ, Leslie KL, Barrick S, Mamonova T, Fitzpatrick JM, Drombosky KW, Peyser N, Wang B, Pellegrini M, Bauer PM et al (2015) Phosphorylation of ezrin-radixin-moesin-binding phosphoprotein 50 (EBP50) by Akt promotes stability and mitogenic function of S-phase kinase-associated protein-2 (Skp2). J Biol Chem 290:2879–2887

Stacey DW (2010) Three observations that have changed our understanding of cyclin D1 and p27Kip1 in cell cycle control. Genes Cancer 1:11989–1199

Strazzabosco M, Fabris L (2012) Notch signaling in hepatocellular carcinoma: guilty in association ! Gastroenterology 143:1430–1434

Sudakin V, Ganoth D, Dahan A, Heller H, Hershko J, Luca FC, Ruderman JV, Hershko A (1995) The cyclosome, a large complex containing cyclin-selective ubiquitin ligase activity, targets cyclins for destruction at the end of mitosis. Mol Biol Cell 6:185–197

Sun HJ, Liu YJ, Li N, Sun ZY, Zhao HW, Wang C, Li H, Ma FM, Shi SM, Xu XQ et al (2012) Sublocalization of Rab23, a mediator of Sonic hedgehog signaling pathway, in hepatocellular carcinoma cell lines. Mol Med Rep 6:1276–1280

Sun T, Co NN, Wong N (2014) PFTK1 interacts with cyclin Y to activate non-canonical Wnt signaling in hepatocellular carcinoma. Biochem Biophys Res Commun 449:163–168

Suryadinata R, Sadowski M, Sarcevic B (2010) Control of cell cycle progression by phosphorylation of cyclin-dependent kinase (CDK) substrates. Biosci Rep 30:243–255

Taguchi K, Aishima S, Asyama Y, Kajiyama K, Kinukawa N, Shimada M, Sugimachi K, Tsuneyoshi M (2001) The role of p27kip1 protein expression on the biological behavior of intrahepatic cholangiocarcinoma. Hepatology 33:1118–1123

Tainai M, Higuchi H, Burgart LJ, Gores GJ (2002) p16INK4a promoter mutations are frequent in primary sclerosing cholangitis (PSC) and pSC-associated cholangiocarcinoma. Gastroenterology 123:1090–1098

Takano N, Hishida M, Inokawa Y, Hayashi M, Kanda M, Nishikawa Y, Iwata N, Kobayashi D, Tanaka C, Yamada S et al (2015) CCNJ detected by triple combination array analysis as tumor-related gene of hepatocellular carcinoma. Int J Oncol. doi:10.3892/ijo.2015.2892

Tannapfel A, Grund D, Katalinic A, Uhlmann D, Köckerling F, Haugwitz U, Wasner M et al (2000a) Decreased expression of p27 protein is associated with advanced tumor stage in hepatocellular carcinoma. Int J Cancer 89:350–355

Tannapfel A, Benicke M, Katalinic A, Uhlmann D, Köckerling F, Hauss J, Wittekind C (2000b) Frequency of p16(INK4A) alterations and K-ras mutations in intrahepatic cholangiocarcinoma of the liver. Gut 47:721–727

Tannapfel A, Busse C, Weinans L, Benicke M, Katalinic A, Geissler F, Hauss J, Wittekind C (2001) INK4a-ARF alterations and p53 mutations in hepatocellular carcinomas. Oncogene 20:7104–7109

Tannapfel A, Sommerer F, Benicke M, Weinans L, Katalinic A, Geissler F, Uhlmann D, Hauss J, Wittekind C (2002) Genetic and epigenetic alterations of the INK4a-ARF pathway in cholangiocarcinoma. J Pathol 197:624–631

Tazat K, Harsat M, Goldshmid-Shagal A, Ehrlich M, Henis YI (2013) Dual effects of Ral-activated pathways on p27 localization and TGF-b signaling. Mol Biol Cell 24:1812–1824

Torre C, Benhamouche S, Mitchell C, Godard C, Veber P, Letourneur F, Cagnard N et al (2011) The transforming growth factor-a and cyclin D1 genes are direct targets of b-catenin signaling in hepatocyte proliferation. J Hepatol 55:86–95

Tschaharganeh DF, Chen X, Latzko P, Malz M, Gaida MM, Felix K, Ladu S, Singer S et al (2013) Yes-associated protein up-regulates Jagged-1 and activates the Notch pathway in human hepatocellular carcinoma. Gastroenterology 144:1530–1542

Tung EK, Wong BY, Yau TO, Ng IO (2012) Upregulation of the Wnt co-receptor LRP6 promotes hepatocarcinogenesis and enhances cell invasion. PLoS One 7:e36565

Udvardy A (1996) The role of controlled proteolysis in cell-cycle regulation. Eur J Biochem 240:307–313

Ushio K, Hashimoto T, Kitamura N, Tanaka T (2009) Id1 is down-regulated by hepatocyte growth factor via ERK-dependent and ERK-independent signaling pathways, leading to increased expression of p16INK4a in hepatoma cells. Mol Cancer Res 7:1179–1188

Vermeulen K, Van Bockstaele DR, Berneman ZN (2003) The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. Cell Prolif 36:131–149

Viatour P, Ehmer U, Saddic LA, Dorrell C, Andersen JB, Lin C, Zmoos AF, Mazur PK, Schaffer BE, Ostermeier A et al (2011) Notch signaling inhibits hepatocellular carcinoma following inactivation of the RB pathway. J Exp Med 208:1963–1976

Vilarinho S, Erson-Omay EZ, Harmanci AS, Morotti R, Carrion-Grant G, Baranoski J et al (2014) Pediatric hepatocellular carcinoma due to somatic CTNNB1 and NFE2L2 mutations in the setting of inherited bi-allelic ABCB11 mutations. J Hepatol. doi:10.1016/j.jhep.2014.07.003

Villanueva A, Alsinet C, Yanger K, Hoshida Y, Zong Y, Toffanin S, Rodriguez-Carunchio L et al (2012) Notch signaling is activated in human hepatocellular carcinoma and induces tumor formation in mice. Gastroenterology 143:1660–1669

Voets E, Wolthuis RM (2010) MASTL is the human orthologue of Greatwall kinase that facilitates mitotic entry, anaphase and cytokinesis. Cell Cycle 9:3591–3601

Voets E, Wolthuis RM (2015) MASTL promotes cyclin B1 destruction by enforcing Cdc20-independent binding of cyclin B1 to the APC/C. Biol Open. doi:10.1242/bio.201410793

Wander SA, Zhao D, Slingerland JM (2011) p27: a barometer of signaling deregulation and potential predictor of response to targeted therapies. Clin Cancer Res 17:12–18

Wands JR, Kim M (2014) WNT/b-catenin signaling and hepatocellular carcinoma. Hepatology 60:452–454

Wang XQ, Lui EL, Cai Q, Ching WY, Liu KS, Poon RT, Fan ST (2008) p27Kip1 promotes migration of metastatic hepatocellular carcinoma cells. Tumour Biol 29:217–223

Wang M, Xue L, Cao Q, Lin Y, Ding Y, Yang P, Che L (2009a) Expression of Notch1, Jagged1 and beta-catenin and their clinicopathological significance in hepatocellular carcinoma. Neoplasma 56:533–541

Wang X, Meng X, Sun X, Liu M, Gao S, Zhao J, Pei F, Yu H (2009b) Wnt/beta-catenin signaling pathway may regulate cell cycle and expression of cyclin A and cyclin E protein in hepatocellular carcinoma cells. Cell Cycle 8:1567–1570

Wang Y, Cheng J, Xu C, Liu S, Jiang S, Xu Q, Chen X, Zhuang H, Lu F (2012) Quantitative methylation analysis reveals gender and age differences in p16INK4a hypermethylation in hepatitis B virus-related hepatocellular carcinoma. Liver Int 32:420–428

Wang Y, Liu F, Mao F, Hang Q, Huang X, He S, Wang Y, Cheng C, Wang H, Xu G, Zhang T, Shen A (2013) Interaction with cyclin H/cyclin-dependent kinase 7 (CCNh/CDK7) stabilizes C-terminal binding protein 2 (CtBP2) and promotes cancer cell migration. J Biol Chem 288:9028–9034

Wang P, Malumbres M, Archambault V (2014a) The Greatwall-PP2A axis in cell cycle control. Methods Mol Biol 1170:99–111

Wang HY, Yang SL, Liang HF, Li CH (2014b) HBx protein promotes oval cell proliferation by up-regulation of cyclin D1 via activation of the MEK/ERK and PI3K/Akt pathways. Int J Mol Sci 15:3507–3518

Weihrauch M, Markwarth A, Lehnert G, Wittekind C, Wrbitzky R, Tannapfel A (2002) Abnormalities of the ARF-p53 pathway in primary angiosarcomas of the liver. Hum Pathol 33:884–892

Wen W, Ding J, Sun W, Fu J, Chen Y, Wu K, Ning B, Han T, Huang L, Chen C, Xie D, Li Z, Feng G, Wu M, Xie W et al (2012) Cyclin G1-mediated epithelial-mesenchymal transition via phosphoinositide 3-kinase/Akt signaling facilitates liver cancer progression. Hepatology 55:1787–1798

Wen W, Han T, Chen C, Huang L, Sun W, Wang X, Chen SZ, Xiang DM, Tang L, Cao D, Feng GS, Wu MC, Ding J et al (2013) Cyclin G1 expands liver tumor-initiating cells Sox2 induction via Akt/mTOR signaling. Mol Cancer Ther 12:1796–1804

Wu J, Shen SL, Chen B, Nie J, Peng BG (2014) Numb promotes cell proliferation and correlates with poor prognosis in hepatocellular carcinoma. PLoS One 9:e95849

Xiao et al. (2013) http://www.ncbi.nlm.nih.gov/pubmed/23967867

Xiao ZD, Jiao CY, Huang HT, He LJ, Zhao JJ, Lu ZY, Liu LX (2014) miR-218 modulate hepatocellular carcinoma cell proliferation through PTEN/AKT/PI3K pathway and HoxA10. Int J Clin Exp Pathol 7:4039–4044

Xie C, Song LB, Wu JH, Li J, Yun JP, Lai JM, Xie DY, Lie BL, Yuan YF, Li M et al (2012) Upregulator of cell proliferation predicts poor prognosis in hepatocellular carcinoma and contributes to hepatocarcinogenesis by downregulating FOXO3a. PLoS One 7:e40607

Xing C, Xie H, Zhou L, Zhou W, Ding S, Wei B, Yu X, Su R, Zheng S (2012) Cyclin-dependent kinase inhibitor 3 is overexpressed in hepatocellular carcinoma and promotes tumor cell proliferation. Biochem Biophys Res Commun 420:29–35

Xu H, Choe C, Shin SH, Park SW, Kim HS, Jung SH, Yim SH, Kim TM, Chung YJ (2014) Silencing of KIF14 interferes with cell cycle progression and cytokinesis by blocking the p27(Kip1) ubiquitination pathway in hepatocellular carcinoma. Exp Mol Med 46:e97

Yachida S, Sakamoto M, Imaida K, Yokohira M, Saoo K, Okano K, Wakabayashi H et al (2008) p27(Kip1) is overexpressed in very early stages of hepatocarcinogenesis. Cancer Sci 99:2152–2159

Yachida S, Imaida K, Yokohira M, Hashimoto N, Suzuki S, Okano K, Wakabayashi H et al (2010) Jun activation domain binding protein 1 is overexpressed from the very early stages of hepatocarcinogenesis. Ann Surg Oncol 17:3386–3393

Yamamoto H, Sakane H, Yamamoto H, Michiue T, Kikuchi A (2008) Wnt3a and Dkk1 regulate distinct internalization pathways of LRP6 to tune the activation of beta-catenin signaling. Dev Cell 15:37–48

Yang B, Guo M, Herman JG, Clark DP (2003) Aberrant promoter methylation profiles of tumor suppressor genes in hepatocellular carcinoma. Am J Pathol 163:1101–1107

Yang B, House MG, Guo M, Herman JG, Clark DP (2005) Promoter methylation profiles of tumor suppressor genes in intrahepatic and extrahepatic cholangiocarcinoma. Mod Pathol 18:412–420

Yang et al. (2014a) http://www.ncbi.nlm.nih.gov/pubmed/24955159

Yang T, Li XN, Li L, Wu QM, Gao PZ, Wang HL, Zhao W (2014b) Sox17 inhibits hepatocellular carcinoma progression by downregulation of KIF14 expression. Tumour Biol 35:11199–11207

Yeh CT, Lu SC, Chen TC, Peng CY, Liaw YF (2000) Aberrant transcripts of the cyclin-dependent kinase-associated protein phosphatase in hepatocellular carcinoma. Cancer Res 60:4697–4700

Yimlamai D, Christodoulou C, Galli GG, Yanger K, Pepe-Mooney B, Gurung B, Shrestha K et al (2014) Hippo pathway activity influences liver cell fate. Cell 157:1324–1338

Yuan K, O'Farrell PH (2015) Cyclin B3 is a mitotic cyclin that promotes the metaphase-anaphase transition. Curr Biol. doi:10.1016/j.cub.2015.01.053

Yuan R, Wang K, Hu J, Yan C, Li M, Yu X, Liu X, Lei J, Guo W, Wu L, Hong K,Shao J (2014) Ubiquitin-like protein FAT10 promotes the invasion and metastasis of hepatocellular carcinoma by modifying B-catenin degradation. Cancer Res 74:5287–5300

Zang JJ, Xie F, Qin YY, Shen RX, Yang JM, He J (2011) P16 gene hypermethylation and hepatocellular carcinoma: a systematic review and meta-analysis. World J Gastroenterol 17:3043–3048

Zekri AR, Nassar AA, El-Din El-Rouby MN, Shousha HI, Barakat AB, El-Desouky ED, Zayed NA, Ahmed OS et al (2014a) Disease progression from chronic hepatitis C to cirrhosis and hepatocellular carcinoma is associated with increasing DNA promoter methylation. Asian Pac J Cancer Prev 14:6721–6726

Zekri AR, Bahnasy AA, Shoeab FE, Mohamed WS, El-Dahshan DH, Ali FT, Sabry GM, Dasgupta N, Daoud SS (2014b) Methylation of multiple genes in hepatitis C virus associated hepatocellular carcinoma. J Adv Res 5:27–40

Zhan L, Huang C, Meng XM, Song Y, Wu XQ, Miu CG, Zhan XS, Li J (2014) Promising roles of mammalian E2Fs in hepatocellular carcinoma. Cell Signal 26:1075–1081

Zhang YJ, Ahsan H, Chen Y, Lunn RM, Wang LY, Chen SY, Lee PH, Chen CJ, Santella RM (2002) High frequency of promoter hypermethylation of RASSF1A and p16 and its relationship of aflatoxin B1-DNA adduct levels in human hepatocellular carcinoma. Mol Carcinog 35:85–92

Zhang C, Li Z, Cheng Y, Jia F, Li R, Wu M, Li K, Wei L (2007) CpG island methylator phenotype association with elevated serum alpha-fetoprotein level in hepatocellular carcinoma. Clin Cancer Res 13:944–952

Zhang MF, Zhang ZY, Fu J, Yang YF, Yun JP (2009) Correlation between expression of p53, p21/WAF1, and MDM2 proteins and their prognostic significance in primary hepatocellular carcinoma. J Transl Med 7:110

Zhang J, Han C, Wu T (2012) MicroRNA-26a promotes cholangiocarcinoma growth by activating b-catenin. Gastroenterology 143:246–256

Zhang JC, Gao B, Yu ZT, Liu XB, Lu J, Xie F, Luo HJ, Li HP (2014a) Promoter hypermethylation of p14(ARF), RB, and INK4 gene family in hepatocellular carcinoma with hepatitis B virus infection. Tumour Biol 35:2795–2802

Zhang B, Zhang H, Wang D, Han S, Wang K, Yao A, Li X (2014b) Never in mitosis gene A-related kinase 6 promotes cell proliferation of hepatocellular carcinoma via cyclin B modulation. Oncol Lett 8:1163–1168

Zhang Q, Lu C, Fang T, Wang Y, Hu W, Qiao J, Liu B, Liu J, Chen N, Li M, Zhu R (2015) Notch3 functions as a regulator of cell self-renewal by interacting with the β-catenin pathway in hepatocellular carcinoma. Oncotarget 6:3669–3679

Zhao JJ, Pan K, Li JJ, Chen YB, Chen JG, Lv L, Wang DD, Pan QZ, Chen MS, Xia JC (2011) Identification of LZAP as a new candidate tumor suppressor in hepatocellular carcinoma. PLoS One 6:e26608

Zhao Y, Tang Q, Ni R, Huang X, Wang Y, Lu C, Shen A, Wang Y, Li C, Yuan Q, Chen H, Cheng C, He S (2013a) Early mitotic inhibitor-1, an anaphase-promoting complex/cyclosome inhibitor, can control tumor cell proliferation in hepatocellular carcinoma: correlation with Skp2 stability and degradation of p27(Kip1). Hum Pathol 44:365–373

Zhao R, Yang HY, Shin J, Phan L, Fang L, Che TF, Su CH, Yeung SC, Lee MH (2013b) CDK inhibitor p57 (Kip2) is downregulated by Akt during HER2-mediated tumorigenicity. Cell Cycle 12:935–943

Zheng Y, Miskimins WK (2011) Far upstream element binding protein 1 activates translation of p27(Kip1) mRNA through its internal ribosomal entry site. Int J Biochem Cell Biol 43:1641–1648

Zheng X, Zeng W, Gai X, Xu Q, Li C, Liang Z, Tuo H, Liu Q (2013) Role of the Hedgehog pathway in hepatocellular carcinoma (review). Oncol Rep 30:2020–2026

Zheng et al. (2014) http://www.ncbi.nlm.nih.gov/pubmed/24381057

Zhong XY, Xu XX, Yu JH, Jiang GX, Yu Y, Tai S, Wang ZD, Cui YF (2012) Clinical and biological significance of Cdk10 in hepatocellular carcinoma. Gene 498:68–74

Zhou Q, He Q, Liang LJ (2003) Expression of p27, cyclin E and cyclin A in hepatocellular carcinoma and its clinical significance. World J Gastroenterol 9:2450–2454

Zhou L, Zhang N, Song W, You N, Li Q, Sun W, Zhang Y, Wang D, Dou K (2013) The significance of Notch1 compared with Notch3 in high metastasis and poor overall survival in hepatocellular carcinoma. PLoS One 8:e57382

Zhou D, Bai F, Zhang X, Hu M, Zhao G, Zhao Z, Liu R (2014) SOX10 is a novel oncogene in hepatocellular carcinoma through Wnt/b-catenin/TCF4 cascade. Tumour Biol 35:9935–9940

Zhu Y, Lu Y, Zhang Q, Liu JJ, Li TJ, Yang JR, Zeng C, Zhuang SM (2012) MicroRNA-26a/b and their host genes cooperate to inhibit the G1/S transition by activating the pRb protein. Nucleic Acids Res 40:4615–4625

Growth Regulation in Hepatobiliary Cancer: Epigenetic Mechanisms 175

Contents

Regulation of Cell Proliferation in Liver Cancer by MicroRNAs/OncomiRs

Introduction

MicroRNAs (miRs) form a large class of noncoding RNAs that typically consist of only about 22 nucleotides. They act as endogenous suppressors of gene expression through binding to the 3′-untranslated region of target mRNAs. This suppression results in mRNA degradation and hence translation repression. As microRNAs affect numerous mRNAs involved in cell proliferation, differentiation, apoptosis, and invasion, they play significant roles in cancer pathogenesis. Among the more than 1,000 species of microRNAs, an increasing number are altered in their expression in liver cancers (Callegari et al. 2013; Gailhouste et al. 2013; Khare et al. 2013; Xiong et al. 2013; Hung et al. 2014; Saito et al. 2014). They can affect both proliferation and suppression of proliferation in liver cancers (Table 1). In their pro-proliferative and antiproliferative actions, microRNAs employ a wide array of factors, the expression of which they regulate. There is increasing evidence that, similar to signal substances and growth factors, microRNAs can be transported from their sources to tumor cells via microvesicles/exosomes, a system forming an intricate signaling platform within tumors that may be amenable to future treatment strategies.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_175

Table 1 MicroRNAs with an altered expression in liver cancers

	Tumor type	Mechanism
Promoters of cell proliferation		
MiR-21	HCC	Targeting PTEN, RECK, and PDCD4
MiR-24	HCC	Targeting Sox7
MiR-26a	CC	Activation of beta-catenin
MiR-31	CC	Suppression of RASA1
MiR-93	HCC	Targeting PTEN and CDKN1A
MiR-96	HCC	Targeting the ephrin 5A suppressor
MiR-182	HCC	Targeting the ephrin 5A suppressor
MiR-199a-3p	HCC	Targeting caveolin-2
MiR-221	HCC	Targeting CDKN1B and CDKN1C
MiR-222	HCC	Downregulation of p27
MiR-224	HCC	Activation of Akt signaling
MiR-331-3p	HCC	Targeting PHLPP
MiR-362-3p	HCC	Targeting Tob2
MiR-371-5p	HCC	Downregulation of PRPF4B
MiR-421	CC	Regulation of FXR expression
MiR-452	HCC	Targeting CDK inhibitor 1
MiR-675	HCC	Targeting Twist1 and Rb
MiR-1269	HCC	Downregulation of FOXO1
Suppressors of cell proliferation		
MiR-1	HCC	Targeting endothelin-1
MiR-7	HCC	Targeting cullin 5; targeting CCNE1
MiR-26a	HCC	ERalpha signaling
MiR-29a	HCC	Targeting SPARC
MiR-99a	HCC	Cell cycle arrest via cyclin D1
MiR-101-3p	HCC	Rab5a pathway
MiR-122	HCC	Targeting beta-catenin
MiR-124	HCC	Targeting PIK3CA
MiR-126	HCC	Targeting Sox2
MiR-127	HCC	Downregulation of Sept7
MiR-137	HCC	Targeting Akt2
MiR-138	CC	Targeting RhoC
MiR-138	HCC	Targeting cyclin D3
MiR-140-5p	HCC	Targeting TGF-beta receptor 1, FGF9
MiR-144	HCC	Targeting E2F3
MiR-145	HCC	Targeting IGF signaling and ADAM17
MiR-148b	HCC	Targeting the Wnt/beta-catenin pathway
MiR-152	HCC	Targeting several signaling pathways
MiR-185	HCC	Targeting DNMT1/PTEN/Akt pathway
MiR-193b	HCC	Induction of cell cycle arrest
MiR-195	HCC	Targeting multiple cycle regulators
MiR-198	HCC	Repression of mitogenic factors
MiR-199a	HCC	Targeting FZD7
MiR-202	HCC	Downregulation of LRP6
MiR-203	HCC	Targeting survivin
MiR-206	HCC	?
MiR-214	HCC	Suppression of beta-catenin
MiR-219-5p	HCC	Targeting glypican-3
MiR-302b	HCC	Targeting EGFR
MiR-302c	HCC	Suppression of EndoMT
MiR-342-3p	HCC	Suppression of NF-kappaB pathway
MiR-363	HCC	Downregulation of S1PR1
MiR-376a	HCC	Targeting p85alpha/PIK3R1
MiR-424	HCC	Targeting c-Myb
MiR-429	HCC	Targeting Notch1
MiR-451	HCC	Suppression of IKK-b
MiR-494	CC	G2/M arrest
MiR-503	HCC	Downregulation of cyclin D3 and E2F3
MiR-506	HCC	Targeting YAP mRNA 3′UTR
MiR-511	HCC	Targeting PIK3R3
MiR-517a and -517c	HCC	G2/M arrest via targeting Pyk2
MiR-520b	HCC	Targeting MEKK2 and cyclin D1
MiR-610	HCC	Suppression of LRP6
MiR-612	HCC	Wnt/beta-catenin signaling
MiR-744	HCC	Targeting c-Myc

MiR microRNA, *HCC* hepatocellular carcinoma, *CC* cholangiocarcinoma

MicroRNAs as Promoters of Cell Proliferation in Liver Cancer

MicroRNA-21 is an oncomiR that promotes HCC proliferation by targeting several factors, including PTEN, PDCD4, and RECK. Hepatitis B virus X protein induces cell proliferation through microRNA-21 targeting programmed cell death protein 4/PDCD4 and PTEN (Damania et al. 2014). Proliferation and invasion of HCC cells are promoted by microRNA-24, which is upregulated in HCC and targets the sex-determining region Y (SRY)-box 7/Sox7, a putative tumor suppressor (Ma et al. 2014). Human cholangiocarcinoma shows increased levels of microRNA-26a, associated with elevated proliferative activity via targeting glycogen synthase kinase-3beta and subsequent (Zhanget al. 2012). In intrahepatic cholangiocarcinoma, microRNA-31 was significantly upregulated, associated with increased proliferation due to suppression of RASA1 signaling (Hu et al. 2013). MicroRNA-93 promotes proliferation in HCC and activates the c-Met/PI3K/Akt signaling pathway by targeting PTEN and CDKN1A (Ohta et al. 2015). Both microRNA-96 and microRNA-182 promote cell proliferation in HCC and are upregulated in this tumor. The microRNAs act through targeting ephrin 5A, which is a tumor suppressor in HCC (Wang et al. 2015). MicroRNA-199a-3p, underexpressed in HCC, promotes cell proliferation via targeting caveolin-2 (Shatseva et al. 2011). MicroRNA-222 overexpression augments cell proliferation in HCC via downregulation of the cycle inhibitor p27 at a posttranslational level (Yang et al. 2014a). In human HCC, microRNA-221 promotes cell proliferation by targeting CDKN1B/p27 and CDKN1C/p57 (Fornari et al. 2008). MicroRNA-224 functions as a proliferation-stimulating oncomiR in HCC cells by activating Akt signaling (Ma et al. 2012). MicroRNA-331-3p is one of the most markedly overexpressed microRNAs in HCC, highly associated with metastases. It promotes proliferation of HCC by targeting PHLPP PH domain and leucine-rich repeat protein phosphatase, an enzyme which dephosphorylates Akt (Chang et al. 2014). Expression of microRNA-362-3p in HCC results in enhanced proliferation via direct targeting of Tob2, a member of the Tob family of antiproliferative, cell cycle-regulating proteins that interact with the CCR4-NOT transcription complex (Shen et al. 2015). Through downregulation of pre-mRNA processing factor 4 homolog B/PRPF4B, microRNA-371-5p facilitates G1/S transition in HCC cells (Liu et al. 2013b). Expression of microRNA-421 in cholangiocarcinoma promotes proliferation and acts as an oncomiR via downregulation of FXR/farnesyl X receptor (Zhong et al. 2012). Certain HCC showed overexpression of microRNA-452, associated with dramatic enhancement of cell proliferation via induction of G1-S transition. This MiR directly targets cyclin-dependent kinase inhibitor 1B/CDKN1B (Zheng et al. 2014). Expression of microRNA-675 in HCC tissue confers cell cycle activation and a proliferation phenotype linked to downregulation of Rb and Twist1 (Hernandez et al. 2013). HCCs show overexpression of microRNA-1269, which promotes cell proliferation through directly suppressing FOXO1 associated with deregulation of p21, cyclin D1, phosphorylated Rb, and Ki-67 expression (Yang et al. 2014b).

MicroRNAs as Suppressors of Cell Proliferation in Liver Cancer

Through targeting of endothelin-1, microRNA-1 inhibits proliferation of HCC cells (Li et al. 2012). Overexpression of microRNA-7 in HCC cells induces G1/S arrest via targeting cullin 5/CUL5 (Ma et al. 2013). The same MiR also targets CCNE1, a tumor suppressor which blocks the G1/S transition (Zhang et al. 2014a). Tumor-specific expression of microRNA-26a suppresses HCC cell growth via modulation of estrogen receptor signaling (Chen et al. 2011). Expression of microRNA-29a in HCC cells suppresses cell proliferation via inhibition of Akt/mTOR

phosphorylation downstream of SPARC (Zhu et al. 2012). Cell cycle arrest at G1 in HCC is induced by microRNA-99a via a mechanism involving cyclin D1 (Li et al. 2011). Hepatitis B virus can downregulate microRNA-101-3p. This leads to blunting of the antiproliferative effect of this microRNA via targeting the Rab5a pathway (Sheng et al. 2014). MicroRNA-122 suppresses cell proliferation and induces apoptosis by targeting beta-catenin. It is, however, downregulated in most HCCs (Xu et al. 2012). MicroRNA-124 is downregulated. It suppresses cell proliferation by targeting phosphoinositide-3-kinase catalytic subunit alpha/PIK3CA (Lang and Ling 2012). By targeting Sox2 (sex-determining region Y-box 2), microRNA-126 inhibits cell proliferation and induces apoptosis in HCC cells (Zhao et al. 2015). Suppression of HCC cell growth by microRNA-127 is caused by a G2/M block mediated by downregulation of Sept7, a septin protein involved in cytokinesis and microtubule turnover (Zhou et al. 2014b). FoxD3-regulated microRNA-137 suppresses growth and metastasis in HCC by targeting Akt2 (Liu et al. 2014a). MicroRNA-138 is downregulated in cholangiocarcinoma, associated with enhanced proliferation and invasion via upregulation of the RhoC/p-ERK/MMP-2/MMP-9 pathway (Wang et al. 2013a). In HCCs, microRNA-138 was downregulated in 77.8 % of cases, and this miR induces cell cycle arrest by targeting cyclin D3 (Wang et al. 2012c). Tumor growth and metastasis of HCC is suppressed by microRNA-140-5p via its targeting of transforming growth factor-beta receptor 1 and fibroblast growth factor 9 (Yang et al. 2013). Proliferation and metastasis of HCC is suppressed by microRNA-144 by targeting the E2F transcription factor 3, whereby this inhibitory microRNA is markedly reduced in HCC (Cao et al. 2014). In HCC, the levels of microRNA-145 are markedly decreased, inversely associated with abundance of insulin receptor substrate 1/IRS1, a key mediator of insulin-like growth factor/IGF signaling. IRS1 is a direct target of miR-145, which inhibits HCC cell proliferation via compromising downstream Akt/FOXO1 signaling (Wang et al. 2014). MicroRNA-145 also inhibits cell proliferation in HCC by directly targeting ADAM17 (a disintegrin and metalloproteinase 17) (Liu et al. 2014b). In human HCCs, microRNA-148b is significantly downregulated. This alteration is associated with increased growth, because microRNA-148b suppresses HCC cell proliferation by targeting the Wnt/beta-catenin pathway (Zhang et al. 2015). HCC shows a downregulation of microRNA-152, an miR that suppresses cell growth and inhibits invasion via targeting of Wnt-1, DNMT1, ERK1/ERK2, Akt, and TFRS6B (Dang et al. 2014). MicroRNA-185 decreases cell proliferation in HCC cells via targeting of the DNMT1/PTEN/Akt signaling pathway, but is downregulated in HCC (Qadir et al. 2014). MicroRNA-193b is downregulated in most HCCs, while its expression suppresses proliferation by inducing cell cycle arrest through regulation of CCND1 and ETS1 (Xu et al. 2010a). Targeting multiple cell cycle regulators is the mechanism of suppressed proliferation in HCC by microRNA-195 (Furuta et al. 2013). Suppression of several mitogenic factors is the effect exerted by microRNA-198 in HCC cells (Elfimova et al. 2013). In HCCs, low expression levels of microRNA-199a are associated with malignant potential and poor prognosis. This MiR regulates cell proliferation by targeting the frizzled type 7 receptor/FZD7 (Song et al. 2014). MicroRNA-202 suppresses HCC cell proliferation through downregulation of low-density lipoprotein receptor-related protein 6/LRP6 (Zhang et al. 2014b). Targeting of survivin is the mechanism by which microRNA-203 inhibits proliferation of HCC cells (Wei et al. 2013a). MicroRNA-206 is downregulated in HCC and suppresses cell proliferation by an unknown mechanism (Yunqiao et al. 2014). Through suppression of beta-catenin signaling via targeting of the beta-catenin mRNA, microRNA-214 inhibits cell growth in HCC (Wang et al. 2012a). A block in the G1/S transition is induced in HCC cells by microRNA-219-5p which decreases the expression levels of glypican-3 (Huang et al. 2012). Targeting of EGFR is the mechanism whereby microRNA-302b suppresses cell proliferation in human HCC cells (Wang et al. 2013b). MicroRNA-302c can inhibit growth of HCC by

suppressing endothelial-mesenchymal transition of endothelial cells (Zhu et al. 2014). MicroRNA-342-3p is a suppressor of HCC cell proliferation via its suppressive action of the NF-kappaB pathway (Zhao and Zhang 2015). MicroRNA-376a targets PIK3R1 (p85alpha) and via this pathway suppresses proliferation (Zheng et al. 2012). MicroRNA-363 suppresses the proliferation of HCC cells via downregulation of S1PR1/sphingosine-1-phosphate receptor 1 (Zhou et al. 2014a). MicroRNA-424 is downregulated in HVV and suppresses cell proliferation and migration by targeting of c-Myb (Yu et al. 2014). MicroRNA-429 directly targets Notch1 and via this mechanism represses cell proliferation and induces apoptosis (Gao and Liu 2014). The expression of microRNA-451 is markedly suppressed in HCC cells, what promotes proliferation, because miR-451 is a suppressor of proliferation via downregulation of cyclin D1 and c-Myc through inhibition of NF-kappaB pathway initiated by direct targeting of the IKBKB 3′-untranslated region (Li et al. 2013). MicroRNA-494 is a major modulator of cell cycle progression from G2 to M phases. In cholangiocarcinoma cells, it induces cycle arrest at the G2/M transition via targeting pituitary tumor-transforming gene1 and topoisomerase IIalpha (Yamanaka et al. 2012). This microRNA is downregulated in cholangiocarcinoma (Olaru et al. 2011). MicroRNA-503 is often downregulated in HCC. It suppresses the proliferative activity of HCC cells by G1-phase arrest, mediated by downregulation of cyclin D3 and suppression of the Rb/E2F signaling pathway (Xiao et al. 2013). Proliferation of HCC cells is suppressed via expression of microRNA-506 through targeting YAP/Yes-associated protein mRNA 3′UTR (Wang et al. 2014). MicroRNA-511 inhibits growth and metastasis of human HCC by targeting phosphoinositide-3-kinase regulatory subunit 3/PIK3R3 (Cao et al. 2015). MicroRNA-517a and microRNA-517c inhibit cell proliferation by blocking G2/M transition via targeting Pyk2, a focal adhesion kinase-related protein tyrosine kinase (Liu et al. 2013a). Targeting MEKK2 (mitogen-activated protein kinase kinase kinase 2) and cyclin D1 and a decrease of Rb protein phosphorylation are the mechanisms by which microRNA-520b inhibits growth of HCC cells (Zhang et al. 2012a). Human HCCs show a downregulation of microRNA-610, associated with enhanced cell proliferation. This MiR decreases Wnt/beta-catenin signaling through suppression of lipoprotein receptor-related protein 6/LRP6 and transducin beta-like protein1/TBL1X (Zeng et al. 2014). MicroRNA-612 has inhibitory effects on cell proliferation, migration, invasion, and metastasis of HCC and suppresses the stemness of liver cancer through Wnt/beta-catenin signaling (Tang et al. 2014). MicroRNA-744 is often downregulated in HCC tissues, whereby this MiR acts as a tumor suppressor by targeting c-Myc (Lin et al. 2014a).

Effects of Hepatitis B- and Hepatitis C Virus-Associated Proteins on Growth and Proliferation of Liver Cancers

Hepatitis B Virus

Hepatitis B virus (HBV) plays a major role in hepatocarcinogenic pathways worldwide (Rivière et al. 2014). The genome of HBV encodes several proteins that can affect cell cycle regulation in normal hepatocytes, regenerating liver cells, and liver cancer cells.

A central role the regulation of HCC cell proliferation is played by the HBV X protein (HB X protein; reviews: Madden and Slagle 2001; Gearhart and Bouchard 2010; Kew 2011; Gong et al. 2013; Lin et al. 2014b). HB X protein directly stimulates cell proliferation by promoting the reinitiation of DNA replication by regulating the expression of the replication licensing factor CDC6 (Pandey and Kumar 2012). Ectopic expression of HB X protein in HCC cells stabilizes cyclin D1, mainly in S phase, and increases cyclin D1 nuclear accumulation via ERK-mediated inactivation of GSK-3beta (Chen et al. 2015a). HB X protein can upregulate the expression of Notch1, jagged-1, and Hes-1 in HCC, leading to enhanced proliferation (Wang et al. 2012b). One mechanism in this pathway is characterized by HB X protein-induced reduction of Notch1 cleavage (Xu et al. 2010b).

In HCC cells, HB X protein interacts with and activates the endoplasmic reticulum stress-associated protein, cAMP-responsive, element-binding protein H/CREBH, resulting in expression of AP-1 target genes and cell proliferation (Cho et al. 2015). HB X protein regulates the expression of a cell contact protein, LIM and SH3 protein1/LASP-1, a focal adhesion protein, which is overexpressed in HCC and mediates cell proliferation (Tang et al. 2012).

HBV and its proteins are associated with complex patterns of microRNA expression in HCCs (review: Xie et al. 2014). Several pathways modulating microRNA expression in HBV-associated HCCs are mediated by HB X protein (Wang et al. 2010). HB X protein-induced upregulation of microRNA-221 results in proliferation of HBV-related HCC cells by targeting estrogen receptor-alpha, which functions as a tumor promoter (Chen et al. 2015b). The protein downregulates the expression of microRNA-16, abolishing the proliferation-suppressing function of this microRNA in HCC cells (Wu et al. 2011). On the other hand, Hb X enhances the expression of a microRNA that increases proliferation in HCC, microRNA-148a (Yuan et al. 2012). HB X protein is capable to modulate growth of HCC cells by affecting apoptosis. It induces microRNA-21 in these cells, followed by targeting programmed cell death protein 4/PDCD4 (Damania et al. 2014). HB X protein downregulates microRNA-338, a microRNA which inhibits cell proliferation by targeting cyclin D1 (Fu et al. 2012). It also downregulates microRNA-216b in HCC, associated with increased growth and invasion (Liu et al. 2015). MicroRNA-132 hypermethylation in HBV-associated HCCs is promoted by HB X protein, leading to downregulation of this microRNA (Wei et al. 2013b). Downregulation of microRNA-15b by HB X protein enhances HCC cell proliferation through fucosyltransferase 2-induced Globo H expression, Globo H being a cancer-associated carbohydrate antigen highly expressed in various cancers (Wu et al. 2014). MicroRNA-101 is downregulated by HB X protein and induces aberrant DNA methylation by targeting DNA methyltransferase (Wei et al. 2013c). HB X protein can also affect liver tumor cell growth by modulating the function of stromal cells. It activates hepatic stellate cells through upregulation of TGF-beta1, associated with pro-growth effects of these cells (Chen et al. 2014). HBV can affect cell proliferation by mechanisms other than HB X protein. HBV core promoter mutations can promote cell proliferation through upregulation transcription of S-phase kinase-associated protein 2 by activating the transcription factor E2F1 (Huang et al. 2013).

Hepatitis C Virus

Hepatitis C virus (HCV) is a major risk for the development of HCC. It possesses a complex intraviral protein interaction network that can affects numerous functions in host cells of the virus (Hagen et al. 2014). Several pathways to promote cell proliferation are mediated by HCV core protein. The protein downregulates the CDK inhibitor p16 and via this mechanisms overcomes stress-induced premature senescence (Lim et al. 2012). It can promote HCC cell proliferation through enhancement of TGF-alpha expression (Sato et al. 2006), activate the MAPK/ERK signaling cascade in a EGF- and TGF-alpha-independent manner (Hayashi et al. 2000), downregulate the cell cycle inhibitor p21 (Shiu et al. 2013), enhance canonical Wnt/beta-catenin signaling to promote cell growth (Liu et al. 2011), and promote heparin-binding EGF-like growth factor expression and Akt activation (Nakamura et al. 2011). HCV core protein induces TGF-beta-dependent epithelial-mesenchymal transition/EMT and by itself activates latent TGF-beta via thrombospondin to drive interactions between hepatocytes and stroma (Benzoubir et al. 2013). It also epigenetically silences the Wnt antagonist secreted frizzled-related protein/SFRP1 via promoter methylation and enhances growth and invasion of HCC by induction of EMT (Quan et al. 2014).

Similar to HBV-associated proteins, HCV core protein can modulate microRNAs regulating cell proliferation. HCV core protein downregulates microRNA-152, leading to

upregulation of Wnt1 associated with enhanced cell proliferation of cultured HCC cells (Huang et al. 2014). On the other hand, the protein upregulates microRNA-155 to activate Wnt signaling (Zhang et al. 2012b).

Morphogenetic Fields, Liver Regeneration, and Cancer Growth

Growth, differentiation, and the generation of distinct tissue patterns are regulated by morphogenetic fields during ontogenesis, to a large part driven by the effects of homeotic genes which are also active in cancers. Morphogenetic fields denote complex patterns that determine the behavior of cells in a nonlocal manner and which represent molecular super-platforms that determine molecular pathways and networks in larger areas of tissues (the "fields"). Morphogenetic fields have been viewed as large-scale systems of physical properties that store and transmit patterning information for ordered growth and shape generation in embryogenesis, regeneration, and morphostasis/aging, but probably also cancer (Levin 2012). Such patterning systems may operate through transcriptional, epigenetic, and molecular networks determined by a "master patterner" and/or may work via endogenous bioelectrical signals (Seo 2012; Adams and Levin 2013; Levin 2013, 2014). Deregulated bioelectric gradients as a cause of massively altered geometric features of cancer tissues have been proposed as a major factor for carcinogenesis (Chernet and Levin 2013).

References

Adams DS, Levin M (2013) Endogenous voltage gradients as mediators of cell-cell communication: strategies for investigating bioelectrical signals during pattern formation. Cell Tissue Res 352:95–122

Benzoubir N, Lejamtel C, Battaglia S, testoni B, Benassi B, Gondeau C, Perrin-Cocon L, desterke C, Thiers V, Samuel D et al (2013) HCV core-mediated activation of latent TGF-β via thrombospondin drives the crosstalk between hepatocytes and stromal environment. J Hepatol 59:1160–1168

Callegari E, Elamin BK, Sabbioni S, Gramantieri L, Negrini M (2013) Role of microRNAs in hepatocellular carcinoma: a clinical perspective. Onco Targets Ther 6:1167–1178

Cao T, Li H, Hu Y, Ma D, Cai X (2014) miR-144 suppresses the proliferation and metastasis of hepatocellular carcinoma by targeting E2F3. Tumour Biol 35:10759–10764

Cao G, Dong W, Meng X, Liu H, Liao H, Liu S (2015) MiR-511 inhibits growth and metastasis of human hepatocellular carcinoma cells by targeting PIK3R3. Tumour Biol 36:4453–4459

Chang RM, Yang H, Fang F, Xu JF, Yang LY (2014) miR-331-3p promotes proliferation and metastasis of hepatocellular carcinoma by targeting PHLPP. Hepatology. doi:10.1002/hep.27221

Chen L, Zheng J, Zhang Y, Yang L, Wang J, Ni J, Cui D, Yu C, Cai Z (2011) Tumor-specific expression of MicroRNA-26a suppresses human hepatocellular carcinoma growth via cyclin-dependent and – independent pathways. Mol Ther 19:1521–1528

Chen HY, Chen ZX, Huang RF, Lin N, Wang XZ (2014) Hepatitis B virus X protein activates human hepatic stellate cells through upregulating TGFβ1. Genet Mol Res 13:8645–8656

Chen X, Zhang L, Zheng S, Zhang T, Li M, Zhang X, Zeng Z, McCrae M, Zhao J, Zhuang H, Lu F (2015a) Hepatitis B virus X protein stabilizes cyclin D1 and increases cyclin D1 nuclear accumulation through ERKs-mediated inactivation of GSK-3β. Cancer Prev Res (Phila) pii: canpreves.0384.2014

Chen JJ, Tang YS, Huang SF, Ai JG, Wang HX, Zhang LP (2015a) HBx protein-induced upregulation of microRNA-221 promotes aberrant proliferation in HBV-related hepatocellular carcinoma by targeting estrogen receptor-α. Oncol Rep 33:792–798

Chernet B, Levin M (2013) Endogenous voltage potentials and the microenvironment: biolelectric signals that reveal, induce and normalize cancer. J Clin Exp Oncol 2013(suppl.1): pii: S1-002

Cho HK, Kim SY, Kyaw YY, Win AA, Koo SH, Kim HH, Cheong J (2015) HBx induces the proliferation of hepatocellular carcinoma cells via AP1 over-expressed as a result of ER stress. Biochem J 466:115–121

Damania P, Sen B, Dar SB, Kumar S, Kumari A, Gupta E, Sarin SK, Venugopal SK (2014) Hepatitis B virus induces cell proliferation via HBx-induced microRNA-21 in hepatocellular carcinoma by targeting programmed cell death protein 4 (PDCD4) and phosphatase and tensin homologue (PTEN). PLoS One 9, e97145

Dang YW, Zeng J, He RQ, Rong MH, Luo DZ, Chen G (2014) Effects of miR-152 on cell growth inhibition, motility suppression and apoptosis induction in hepatocellular carcinoma cells. Asian Pac J Cancer Prev 15:4969–4976

Elfimova N, Sievers E, Eischeid H, Kwiecinski M, Noetel A, Hunt H, Becker D, Frommolt P et al (2013) Control of mitogenic and motogenic pathways by

miR-198, diminishing hepatoma cell growth and migration. Biochim Biophys Acta 1833:1190–1198
Fornari et al. (2008) http://www.ncbi.nlm.nih.gov/pubmed/18521080
Fu X, Tan D, Hou Z, Hu Z, Liu G (2012) miR-338-3p is down-regulated by hepatitis B virus X and inhibits cell proliferation by targeting the 3′-UTR region of cyclinD1. Int J Mol Sci 13:8514–8539
Furuta M, Kozaki K, Tanimoto K, Tanaka S, Arii S, Shimamura T, Niida A, Miyano S et al (2013) The tumor-suppressive miR-497-195 cluster targets multiple cell-cycle regulators in hepatocellular carcinoma. PLoS One 8:e60155
Gailhouste L, Gomez-Santos L, Hagiwara K, Hatada I, Kitagawa N, Kawaharada K et al (2013) miR-148a plays a pivotal role in the liver by promoting the hepatospecific phenotype and suppressing the invasiveness of transformed cells. Hepatology 58:1153–1165
Gao H, Liu C (2014) miR-429 represses cell proliferation and induces apoptosis in HBV-related HCC. Biomed Pharmacother 68:943–949
Gearhart TL, Bouchard MJ (2010) The hepatitis B virus X protein modulates hepatocyte proliferation pathways to stimulate viral replication. J Virol 84:2675–2686
Gong P, Zhang X, Zhang J, Zhang J, Luo H, Wang Z (2013) Hepatitis B virus X protein in the proliferation of hepatocellular carcinoma cells. Front Biosc (Landmark Ed) 18:1256–1265
Hagen N, Bayer K, Rösch K, Schindler M (2014) The intraviral protein interaction network of hepatitis C virus. Mol Cell Proteomics 13:1676–1689
Hayashi et al. (2000) http://www.ncbi.nlm.nih.gov/pubmed/11050045
Hernandez JM, Elahi A, Clark CW, Wang J, Humphries LA, Centeno B, Bloom G, Fuchs BC, Yeatman T, Shibata D (2013) miR-675 mediates downregulation of Twist and Rb in AFP-secreting hepatocellular carcinoma. Ann Surg Oncol 20(suppl3):S625–S635
Hu C, Huang F, Deng G, Nie W, Huang W, Zeng X (2013) miR-31 promotes oncogenesis in intrahepatic cholangiocarcinoma cells via the direct suppression of RASA1. Exp Ther Med 6:1265–1270
Huang N, Lin J, Ruan J, Su N, Qing R, Liu F, He B, Lv C, Zheng D, Luo R (2012) MiR-219-5p inhibits hepatocellular carcinoma cell proliferation by targeting glypican-3. FEBS Lett 586:884–891
Huang Y, Tai AW, Tong S, Lok AS (2013) HBV core promoter mutations promote cellular proliferation through E2F1-mediated upregulation of S-phase kinase-associated protein 2 transcription. J Hepatol 58:1068–1073
Huang S, Xie Y, Yang P, Chen P, Zhang L (2014) HCV core protein-induced down-regulation of microRNA-152 promoted aberrant proliferation by regulating Wnt1 in HepG2 cells. PLoS One 9, e81730
Hung CH, Chiu YC, Chen CH, Hu TH (2014) MicroRNAs in hepatocellular carcinoma: carcinogenesis, progression, and therapeutic target. Biomed Res Int 2014:486407
Kew MC (2011) Hepatitis B virus x protein in the pathogenesis of hepatitis B virus-induced hepatocellular carcinoma. J Gastroenterol Hepatol 26(suppl 1):144–152
Khare S, Zhang Q, Ibdah JA (2013) Epigenetics of hepatocellular carcinoma: role of microRNA. World J Gastroenterol 19:5439–5445
Lang Q, Ling C (2012) MiR-124 suppresses cell proliferation in hepatocellular carcinoma by targeting PIK3CA. Biochem Biophys Res Commun 426:247–252
Levin M (2012) Morphogenetic fields in embryogenesis, regeneration, and cancer: non-local control of complex patterning. Biosystems 109:243–261
Levin M (2013) Reprogramming cells and tissue patterning via bioelectrical pathways: molecular mechanisms and biomedical opportunities. Wiley Interdiscip Rev Syst Biol Med 5:657–676
Levin M (2014) Molecular bioelectricity: how endogenous voltage potentials control cell behavior and instruct pattern regulation in vivo. Mol Cell Biol 25:3835–3850
Li D, Liu X, Lin L, Hou J, Li N, Wang C, Wang P, Zhang Q, Zhang P, Zhou W, Wang Z et al (2011) MicroRNA-99a inhibits hepatocellular carcinoma growth and correlates with prognosis of patients with hepatocellular carcinoma. J Biol Chem 286:36677–36685
Li D, Yang P, Li H, Cheng P, Zhang L, Wie D, Su X, Peng J, Gao H, Tan Y, Zhao Z, Li Y, Qi Z, Rui Y (2012) MicroRNA-1 inhibits proliferation of hepatocarcinoma cells by targeting endothelin-1. Life Sci 91:440–447
Li HP, Zeng XC, Zhang B, Long JT, Zhou B, Tan GS, Zeng WX, Chen W, Yang JY (2013) miR-451 inhibits cell proliferation in human hepatocellular carcinoma through direct suppression of IKK-b. Carcinogenesis 34:2443–2451
Lim JS, Park SH, Jang KL (2012) Hepatitis C virus core protein overcomes stress-induced premature senescence by down-regulating p16 expression via DNA methylation. Cancer Lett 321:154–161
Lin F, Ding R, Zheng S, Xing D, Hong W, Zhou Z, Shen J (2014a) Decrease expression of microRNA-744 promotes cell proliferation by targeting c-Myc in human hepatocellular carcinoma. Cancer Cell Int 14:58
Lin L, Yin X, Hu X, Wang Q, Zheng L (2014b) The impact of hepatitis B virus x protein and microRNAs in hepatocellular carcinoma: a comprehensive analysis. Tumour Biol 35:11695–11700
Liu J, Ding X, Tang J, Cao Y, Hu P, Zhou F, Shan X, Cai X, Chen Q, Ling N, Zhang B, Bi Y, Chen K, Ren H, Huang A et al (2011) Enhancement of canonical Wnt/β/-catenin signaling activity by HCV core protein promotes cell growth of hepatocellular carcinoma cells. PLoS One 6, e27496
Liu RF, Xu X, Huang J, Fei QL, Chen F, Li YD, Han ZG (2013a) Down-regulation of miR-517a and miR-517c promotes proliferation of hepatocellular carcinoma cells via targeting Pyk2. Cancer Lett 329:164–173
Liu RY, Diao CF, Zhang Y, Wu N, Wan HY, Nong XY, Liu M, Tang H (2013b) miR-371-5p down-regulates

pre mRNA processing factor 4 homolog B (PRPF4B) and facilitates the G1/S transition in human hepatocellular carcinoma cells. Cancer Lett 335:351–360

Liu LL, Lu SX, Li M, Li LZ, Fu J, Hu W, Yang YZ, Luo RZ, Zhang CZ, Yun JP (2014a) FoxD3-regulated microRNA-137 suppresses tumour growth and metastasis in human hepatocellular carcinoma by targeting AKT2. Oncotarget 5:5113–5124

Liu Y, Wu C, Wang Y, Wen S, Wang J, Chen Z, He Q, Feng D (2014b) MicroRNA-145 inhibits cell proliferation by directly targeting ADAM17 in hepatocellular carcinoma. Oncol Rep 32:1923–1930

Liu FY, Zhou SJ, Deng YL, Zhang ZY, Zhang EL, Wu ZB, Huang ZY, Chen XP (2015) MiR-216b involved in pathogenesis and progression of hepatocellular carcinoma through HBx-miR-216b-IGF2BP2 signaling. Cell Death Dis 6:e1670

Ma D, Tao X, Gao F, Fan C, Wu D (2012) miR-224 functions as an onco-miRNA in hepatocellular carcinoma cells by activating AKT signaling. Oncol Lett 4:483–488

Ma C, Qi Y, Shao L, Liu M, Li X, Tang H (2013) Downregulation of miR-7 upregulates Cullin 5 (CUL5) to facilitate G1/S transition in human hepatocellular carcinoma cells. IUBMB Life 65:1026–1034

Ma Y, She XG, Ming YZ, Wan QQ (2014) miR-24 promotes the proliferation and invasion of hCC cells by targeting SOX7. Tumour Biol 35:10731–10736

Madden CR, Slagle BL (2001) Stimulation of cellular proliferation by hepatitis B virus X protein. Dis Markers 17:153–157

Nakamura H, Aoki H, Hino O, Moriyama M (2011) HCV core protein promotes heparin binding EGF-like growth factor expression and activates Akt. Hepatol Res 41:455–462

Ohta K, Hoshino H, Wang J, Ono S, Iida Y, Hata K, Huang SK, Colquhoun S, Hoon DS (2015) MicroRNA-93 activates c-Met/PI3K/Akt pathway activity in hepatocellular carcinoma by directly inhibiting PTEN and CDKN1A. Oncotarget 6:3211–3224

Olaru AV, Ghiaur G, Yamanaka S, Luvsanjav D, An F, Popescu I, Alexandrescu S et al (2011) MicroRNA down-regulated in human cholangiocarcinoma control cell cycle through multiple targets involved in the G1/S checkpoint. Hepatology 54:2089–2098

Pandey V, Kumar V (2012) HBx protein of hepatitis B virus promotes reinitiation of DNA replication by regulating expression and intracellular stability of replication licensing factor CDC6. J Biol Chem 287:20545–20554

Qadir XV, Han C, Lu D, Zhang J, Wu T (2014) miR-185 inhibits hepatocellular carcinoma growth by targeting the DNMT1/PTEN/Akt pathway. Am J Pathol 184:2355–2364

Quan H, Zhou F, Nie D, Chen Q, Cai X, Shan X, Zhou Z, Chen K, Huang A, Li S, Tang N (2014) Hepatitis C virus core protein epigenetically silences SFRP1 and enhances HCC aggressiveness by inducing epithelial-mesenchymal transition. Oncogene 33:2826–2835

Rivière L, Ducroux A, Buendia MA (2014) The oncogenic role of hepatitis B virus. Recent Results Cancer Res 193:59–74

Saito Y, Hibino S, Saito H (2014) Alterations of epigenetics and microRNA in hepatocellular carcinoma. Hepatol Res 44:31–42

Sato Y, Kato J, Takimoto R, Takada K, Kawano Y, Miyanishi K, Kobune M, Sato Y, Takayama T, Matunaga T, Niitsu Y (2006) Hepatitis C virus core protein promotes proliferation of human hepatoma cells through enhancement of transforming growth factor alpha expression via activation of nuclear factor-kappaB. Gut 55:1801–1808

Seo JW (2012) What the literature says on bioelectricity? Basic Appl Pathol 5:81–82

Shatseva T, Lee DY, Deng Z, Yang BB (2011) MicroRNA miR-199a-3p regulates cell proliferation and survival by targeting caveolin-2. J Cell Sci 124:2826–2836

Shen H, Li W, Tian Y, Xu P, Wang H, Zhang J, Li Y (2015) Upregulation of miR-362-3p modulates proliferation and anchorage-independent growth by directly targeting Tob2 in hepatocellular carcinoma. J Cell Biochem. doi:10.1002/jcb.25110

Sheng Y, Li J, Zou C, Wang S, Cao Y, Zhang J, Huang A, Tang H (2014) Downregulation of miR-101-3p by hepatitis B virus promotes proliferation and migration of hepatocellular carcinoma cells by targeting Rab5a. Arch Virol 159:2397–2410

Shiu TY, Huang SM, Shih YL, Chu HC, Chang WK, Hsieh TY (2013) Hepatitis C virus core protein down-regulates p21(Waf1/Cip1) and inhibits corcumin-induced apoptosis through microRNA-345 targeting in human hepatoma cells. PLoS One 8, e61089

Song J, Gao L, Yang G, Tang S, Xie H, Wang Y, Wang J, Zhang Y, Jin J, Gou Y, Yang Z, Chen Z, Wu K, Liu J et al (2014) MiR-199a regulates cell proliferation and survival by targeting FZD7. PLoS One 9, e110074

Tang R, Kong F, Hu L, You H, Zhang P, Du W, Zheng K (2012) Role of hepatitis B virus X protein in regulating LIM and SH3 protein 1 (LASP-1) expression to mediate proliferation and migration of hepatoma cells. Virol J 9:163

Tang J, Tao ZH, Wen D, Wan JL, Liu DL, Zhang S, Cui JF, Sun HC, Wang L, Zhou J et al (2014) MiR-612 suppresses the stemness of liver cancer via Wnt/b-catenin signaling. Biochem Biophys Res Commun 447:210–215

Wang Y, Lu Y, Toh ST, Sung WK, Tan P, Chow P, Chung AY, Jooi LL, Lee CG (2010) Lethal-7 is down-regulated by the hepatitis B virus x protein and targets signal transducer and activator of transcription 3. J Hepatol 53:57–66

Wang X, Chen J, Li F, Lin Y, Zhang X, Lv Z, Jiang J (2012a) Mir-214 inhibits cell growth in hepatocellular carcinoma through suppression of b-catenin. Biochem Biophys Res Commun 428:525–531

Wang F, Zhou H, Yang Y, Xia X, Sun Q, Luo J, Cheng B (2012b) Hepatitis B virus X promotes the growth of hepatocellular carcinoma by modulation of the Notch signaling pathway. Oncol Rep 27:1170–1176

Wang W, Zhao LJ, Tan YX, Ren H, Qi ZT (2012c) MiR-138 induces cell cycle arrest by targeting cyclin D3 in hepatocellular carcinoma. Carcinogenesis 33:1113–1120

Wang Q, Tang H, Yin S, Dong C (2013a) Downregulation of microRNA-138 enhances the proliferation, migration and invasion of cholangiocarcinoma cells through the upregulation of RhoC/p-ERK/MMP-2/MMP-9. Oncol Rep 29:2046–2052

Wang L, Yao J, Shi X, Hu L, Li Z, Song T, Huang C (2013b) MicroRNA-302b suppresses cell proliferation by targeting EGFR in human hepatocellular carcinoma SMMC-7721 cells. BMC Cancer 13:448

Wang Y, Cui M, Sun BD, Liu FB, Zhang XD, Ye LH (2014) MiR-506 suppresses proliferation of hepatoma cells through targeting YAP mRNA 3′UTR. Acta Pharmacol Sin. doi:10.1038/aps.2014.59

Wang TH, Yeh CT, Ho JY, Ng KF, Chen TC (2015) OncomiR miR-96 and miR-182 promote cell proliferation and invasion through targeting ephrinA5 in hepatocellular carcinoma. Mol Carcinog. doi:10.1002/mc.22286

Wei W, Wanjun L, Hui S, Dongyue C, Xinjun Y, Jisheng Z (2013a) miR-203 inhibits proliferation of HCC cells by targeting survivin. Cell Biochem Funct 31:82–85

Wei X, Tan C, Tang C, Ren G, Xiang T, Qiu Z, Liu R, Wu Z (2013b) Epigenetic repression of miR-132 expression by the hepatitis B virus x protein in hepatitis B virus-related hepatocellular carcinoma. Cell Signal 25:1037–1043

Wei X, Xiang T, Ren G, Tan C, Liu R, Xu X, Wu Z (2013c) miR-101 is down-regulated by the hepatitis B virus x protein and induces aberrant DNA methylation by targeting DNA methyltransferase 3A. Cell Signal 25:439–446

Wu G, Yu F, Xiao Z, Xu J, Tang W, Wang J, Song E (2011) Hepatitis B virus X protein downregulates expression of the miR-16 family in malignant hepatocytes in vitro. Br J Cancer 105:146–153

Wu CS, Yen CJ, Chen JN, Huang WC, Wu CY, Yu YL (2014) Downregulation of microRNA-15b by hepatitis B virus X enhances hepatocellular carcinoma proliferation via fucosyltransferase 2-induced Globo H expression. Int J Cancer 134:1638–1647

Xiao F, Zhang W, Chen L, Chen F, Xie H, Xing C, Yu X, Ding S, Chen K, Guo H et al (2013) MicroRNA-503 inhibits the G1/S transition by downregulating cyclin D3 and E2F3 in hepatocellular carcinoma. J Trans Med 11:195

Xie KL, Zhang YG, Liu J, Zeng Y, Wu H (2014) MicroRNAs associated with HBV infection and HBV-related HCC. Theranostics 4:1176–1192

Xiong W, Sun LP, Chen XM, Li HY, Huang SA, Jie SH (2013) Comparison of microRNA expression profiles in HCC-derived microvesicles and the parental cells and evaluation of their roles in HCC. J Huazhong Univ Sci Technolog Med Sci 33:346–352

Xu C, Liu S, Fu H, Li S, Tie Y, Zhu J, Xing R, Jin Y, Sun Z, Zheng X (2010a) MicroRNA-193b regulates proliferation, migration and invasion in human hepatocellular carcinoma cells. Eur J Cancer 46:2828–2836

Xu J, Yun X, Jiang J, Wei Y, Wu Y, Zhang W, Liu Y, Wang W, Wen Y, Gu J (2010b) Hepatitis B virus X protein blunts senescence-like growth arrest of human hepatocellular carcinoma by reducing Notch1 cleavage. Hepatology 52:142–154

Xu J, Zhu X, Wu L, Yang R, Yang Z, Wang Q, Wu F (2012) MicroRNA-122 suppresses cell proliferation and induces cell apoptosis in hepatocellular carcinoma by directly targeting Wnt/b-catenin pathway. Liver Int 32:752–760

Yamanaka S, Campbell NR, An F, Kuo SC, Potter JJ, Mezey E, Maitra A, Selaru FM (2012) Coordinated effects of micro-RNA-494 induce G2/M arrest in human cholangiocarcinoma. Cell Cycle 11:2729–2738

Yang H, Fang F, Chang R, Yang L (2013) MicroRNA-140-5p suppresses tumor growth and metastasis by targeting transforming growth factor β receptor 1 and fibroblast growth factor 9 in hepatocellular carcinoma. Hepatology 58:205–217

Yang YF, Wang F, Xiao JJ, Song Y, Zhao YY, Cao Y, Bei YH, Yang CQ (2014a) MiR-222 overexpression promotes proliferation of human hepatocellular carcinoma hepG2 cells by downregulating p27. Int J Clin Exp Med 7:893–902

Yang XW, Shen GZ, Cao LQ, Jiang XF, Peng HP, Shen G, Chen D, Xue P (2014b) MicroRNA-1269 promotes proliferation in human hepatocellular carcinoma via downregulation of FOXO1. BMC Cancer 14:909

Yu L, Ding GF, He C, Sun L, Jiang Y, Zhu L (2014) MicroRNA-424 is down-regulated in hepatocellular carcinoma and suppresses cell migration and invasion through c-Myb. PLoS One 9, e91661

Yuan K, Lian Z, Sun B, Clayton MM, Ng IO, Feitelson MA (2012) Role of miR-148a in hepatitis B associated hepatocellular carcinoma. PLoS One 7, e35331

Yunqiao L, Vanke H, Jun X, Tangmeng G (2014) MicroRNA-206, down-regulated in hepatocellular carcinoma, suppresses cell proliferation and promotes apoptosis. Hepatogastroenterology 61:1302–1307

Zeng XC, Liu FQ, Yan R, Yi HM, Zhang T, Wang GY, Li Y, Jiang N (2014) Downregulation of miR-610 promotes proliferation and tumorigenicity and activates Wnt/β-catenin signaling in human hepatocellular carcinoma. Mol Cancer 13:261

Zhang W, Kong G, Zhang J, Wang T, Ye L, Zhang X (2012a) MicroRNA-520b inhibits growth of hepatoma cells by targeting MEKK2 and cyclin D1. PLoS One 7, e31450

Zhang Y, Wei W, Cheng N, Wang K, Li B, Jiang X, Sun S (2012b) Hepatitis C virus-induced up-regulation of microRNA-155 promotes hepatocarcinogenesis by activating Wnt signaling. Hepatology 56:1631–1640

Zhang X, Hu S, Zhang X, Wang L, Zhang X, Yan B, Zhao J, Yang A, Zhang R (2014a) MicroRNA-7 arrests cell cycle in G1 phase by directly targeting CCNE1 in human hepatocellular carcinoma cells. Biochem Biophys Res Commun 443:1078–1084

Zhang Y, Zheng D, Xiong Y, Xue C, Chen G, Yan B, Ye C (2014b) miR-202 suppresses cell proliferation in human hepatocellular carcinoma by downregulating LRP6 post-transcriptionally. FEBS Lett 588:1913–1920

Zhang JG, Shi Y, Hong DF, Song M, Huang D, Wang CY, Zhao G (2015) MiR-148b suppresses cell proliferation and invasion in hepatocellular carcinoma by targeting WNT1/β-catenin pathway. Sci Rep 5:8087

Zhao L, Zhang Y (2015) miR-342-3p affects hepatocellular carcinoma cell proliferation via regulating NF-kB pathway. Biochem Biophys Res Commun 457:370–377

Zhao C, Li Y, Zhang M, Yang Y, Chang L (2015) miR-126 inhibits cell proliferation and induces cell apoptosis of hepatocellular carcinoma cells partially by targeting Sox2. Hum Cell 28:91–99

Zheng Y, Yin L, Chen H, Yang S, Pan C, Lu S, Miao M, Jiao B (2012) miR-376a suppresses proliferation and induces apoptosis in hepatocellular carcinoma. FEBS Lett 586:2396–2403

Zheng Q, Sheng Q, Jiang C, Shu J, Chen J, Nie Z, Lv Z, Zhang Y (2014) MicroRNA-452 promotes tumorigenesis in hepatocellular carcinoma by targeting cyclin-dependent kinase inhibitor 1B. Mol Cell Biochem 389:187–195

Zhong XY, Yu JH, Zhang WG, Wang ZD, Dong Q, Tai S, Cui YF, Li H (2012) MicroRNA-421 functions as an oncogenic miRNA in biliary tract cancer through down-regulating farnesoid X receptor expression. Gene 493:44–51

Zhou P, Huang G, Zhao Y, Zhong D, Xu Z, Xu Z, Zeng Y, Zhang Y, Li S, He F (2014a) MicroRNA-363-mediated downregulation of S1PR1 suppresses the proliferation of hepatocellular carcinoma cells. Cell Signal 26:1374–1354

Zhou J, Lu S, Yang S, Chen H, Shi H, Miao M, Jiao B (2014b) MicroRNA-127 post-transcriptionally downregulates Sept7 and suppresses cell growth in hepatocellular carcinoma cells. Cell Physiol Biochem 33:1537–1546

Zhu XC, Dong QZ, Zhang XF, Deng B, Jia HL, Ye QH, Qin LX, Wu XZ (2012) microRNA-29a suppresses cell proliferation by targeting SPARC in hepatocellular carcinoma. Int J Mol Med 30:1321–1326

Zhu K, Pan Q, Jia Q, Dai Z, Ke AW, Zeng HY, Tang ZY, Fan J, Zhou J (2014) MiR-302c inhibits tumor growth of hepatocellular carcinoma by suppressing the endothelial-mesenchymal transition of endothelial cells. Sci Rep 4:5524

Part XXXV

General Pathology of Hepatobiliary Tumors: Necrobiology of Liver Cancer

Necrobiology of Liver Cancer: Apoptosis and Related Forms of Cell Death

176

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_176

Abstract

Proliferative growth of cancers, including hepatocellular carcinoma (HCC) and other liver cancers, is counteracted by cell loss induced by various mechanisms of cell death. An intricate process to control cell mass in normal and neoplastic tissues is apoptosis, a complex form of tightly controlled cell death, and its numerous variants. Loss of tumor substance can also occur through necrosis which, in contrast to previous views, is a complex and controlled process rather than a passive phenomenon. In HCC, apoptosis is present as spherical eosinophilic bodies devoid of nuclei, the so-called apoptotic bodies, associated with drop-out of involved cells. The apoptotic response in HCC can be quantitatively assessed by immunohistochemical and molecular methods. Apoptosis in HCC not only involves the cancer cells, but also several classes of stromal cells, including cancer-associated fibroblasts and myofibroblasts, and stromal leukocytes. Death of these cells markedly affects the structure and function of the tumoral microenvironment.

Introduction

Proliferative expansion of cancers, including hepatocellular carcinoma and cholangiocarcinoma, is counteracted by discrete or sometimes massive cell loss mediated by several mechanisms. Loss of tumor substance can occur through necrosis, e.g., due to poor blood supply, a process that had previously been regarded as a "passive" phenomenon throughout, but is now known to be a controlled process in at least part of the situations. An intricate mechanism to control cell mass in normal tissues, and particular during morphogenesis and ontogenesis, is apoptosis in its diverse manifestations. In addition to normal tissues, apoptosis is an important pathway in the restriction of growth of malignant neoplasms and is therefore a promising field for the design of future anticancer therapies.

Classification of Cell Death

The Nomenclature Committee on Cell Death (NCCD) proposed unified criteria for the definition of cell death and of its various morphologies. The 2009 recommendations of the NCCD have been published (Kroemer et al. 2009) and are summarized in Table 1. Historically, the forms of cell death occurring in normal and cancer cells have been allocated to three types of death. Type I cell death corresponds to apoptotic cell death, type II cell death describes autophagic cell death, and type III cell death is defined as a form of non-lysosomal vesiculate degradation. Since, several other forms of apoptotic and non-apoptotic forms of cell death have been described, leading to a complex situation that requires reassessment of definitions and classifications. In many of the now recognized forms of cell death, the underlying molecular mechanisms have been elucidated, resulting in molecular definitions of cell death subroutines formulated by the NCCD (Galluzzi et al. 2012).

Morphology and Biology of Apoptosis in Liver Cancers

Hepatocellular Carcinoma

In hepatocellular carcinoma (HCC), apoptotic tumor cells present as spherical eosinophilic bodies with a dense cytoplasm. These apoptotic bodies or apoptotic corpses are no longer connected

Table 1 Forms (types) of cell death

Apoptosis
Anoikis
Non-apoptotic forms of cell death (excluding necrosis)
Necrosis
Necroptosis
Phenoptosis
Autoschizis
Autophagy
Angiophagy
Cancerophagy
Netosis

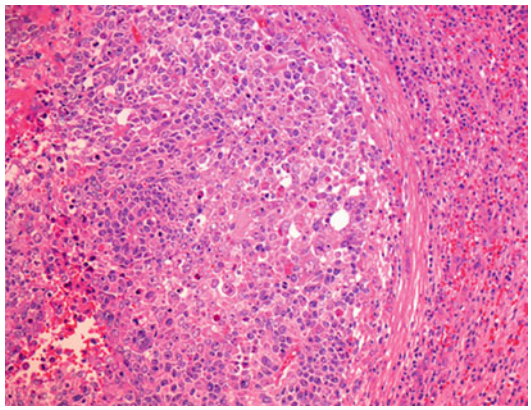

Fig. 1 Nodule of poorly differentiated hepatocellular carcinoma with apoptosis. Mainly in central parts, tumor cell drop-out with formation of apoptotic bodies is observed (hematoxylin and eosin stain)

with neighboring neoplastic cells, but seem to freely float in the tissual background (so-called drop-out or drop-out necrosis, a misnomer; Fig. 1). Apoptotic bodies occurring in well-differentiated HCCs having large and eosinophilic cells closely resemble apoptotic hepatocytes found in viral hepatitis, the Councilman bodies (Councilman-Rocha Lima bodies or "red bodies") originally described in yellow fever hepatitis (Councilman 1890; Rocha Lima 1912). Part of apoptotic bodies may contain small basophilic speckles, remnants of fragmented nuclei, or DNA. In bile-storing HCCs, apoptotic bodies sometimes stain yellow due to accumulation of intracellular bile. Apoptotic bodies are a rather rare finding in HCCs. In one study, apoptotic bodies were found in HCCs with a frequency of 4.2 (average; range 0–15) per 500 tumor cells (Paiva et al. 2002).

Apoptosis of HCC may be associated with a local immune response characterized by dense infiltrates of lymphocytes and plasma cells (medullary-like HCC; Zimmermann et al. 2002). In this situation, dying tumor cells and apoptotic bodies/corpses are surrounded by lymphoid cells and plasma cells that are sometimes in direct contact with the cancer cells. At the periphery of the inflamed area, lymph follicles with germinal centers can develop. In this area, also numerous S100 protein-reactive stellate cells accumulate, suggesting the presence of antigen-presenting cells. In HCCs with a marked apoptosis and immune reaction, parts of the neoplasm can undergo so-called spontaneous regression, as discussed in a separate chapter. In advanced tumor regression, clusters of apoptotic and atrophic HCC cells remain in a stroma densely populated by immune cells. In some cases, remnant cancer cells are only visualized by use of immunohistochemistry.

The apoptotic response of HCC cells can be assessed by use of immunohistochemical and molecular methods. HCC cells undergoing apoptosis expressed FasL, but not Fas (Zimmermann et al. 2002), while other studies found elevated expression of both Fas and FasL (Kubo et al. 1998; Roskams et al. 2000; Fukuzawa et al. 2001; Lee et al. 2001; Hammam et al. 2012; Fingas et al. 2013). Fas/FasL expression was decreased in proportion to the malignancy grade of HCCs (Ito et al. 1998, 2000a; Fukuzawa et al. 2001). In one investigation, FasL expression was only found in moderately or poorly differentiated HCCs (Ito et al. 2000a), and FasL expression was associated with worse prognosis after hepatectomy (Lee et al. 2004). Fas and FasL expression in HCC was significantly lower than in normal liver tissue (Kubo et al. 1998), and Fas is present in the cytoplasm of HCC cells rather than on the membrane (Higaki et al. 1996). Fas/FasL expression in HCC was enhanced in tumor margins (Fukuzawa et al. 2001). FasL expression in HCC cells was induced by HBV X protein (Shin et al. 1999). It was proposed that HCC cells expressing FasL may evade immune surveillance by inducing apoptosis in infiltrating T cells that express Fas. A strong expression of Fas and FasL was observed in hepatocytes surrounding HCCs, suggesting that normal liver cells have the ability to induce apoptosis in an autocrine or paracrine manner (Roskams et al. 2000). HCCs and HCC cell lines can express TRAIL/TNF-related apoptosis-inducing ligand receptor (Okano et al. 2003; Shiraki et al. 2005; Fingas et al. 2013). A fraction of HCCs express FADD

and TRADD proteins, whereby FADD expression was lower in HCC than in adjacent liver tissue and increased as a function of decreasing tumor differentiation. In contrast, expression of TRADD paralleled that of differentiation (Sun et al. 2000). The protein Bid, a mitochondrial membrane death ligand that oligomerizes Bak to release cytochrome c, showed a deceased expression in HCC cells, deficient Bid expression tendering cells resistant to apoptosis induced by Fas (Chen et al. 2001). In contrast to normal cholangiocytes, only very few HCC cells were positive for the anti-apoptotic protein, Bcl-2 (Terada and Nakanuma 1996). HCCs undergoing apoptosis express caspase-3 (Karamitopoulou et al. 2007). Sixty-eight percent of HCCs showed immunoreactivity for the executioner caspase-3, expression being correlated with elevated serum AFP levels (Persad et al. 2004). However, in subsets of HCC, caspase-3 is downregulated compared to non-tumor cells (Fujikawa et al. 2000). In contrast to normal hepatocytes, caspase-8 showed a strong nuclear staining of HCC cells, and low cytoplasmic and high nuclear staining intensity of caspase-8 correlated with impaired survival after hepatectomy (Koschny et al. 2013).

HCC apoptosis was analyzed by in situ DNA end labeling (TUNEL method). With this approach, the apoptotic rate was higher in HCCs showing a hepatocyte-like lineage and neuroendocrine features (Zhao and Zimmermann 1997b). HCC apoptosis can be assessed by nick end labeling (Terada and Nakanuma 1996). dUTP-biotin nick end labeling revealed end labeling indices of 0.35, 0.81, and 26.7 in well-, moderately, and poorly differentiated HCCs, respectively, suggesting an increased tumor cell turnover in high-grade lesions (Hino et al. 1996).

Cholangiocarcinoma

As in HCCs, malignant tumor progression in cholangiocarcinomas is related to failure to activate apoptosis (review: Celli and Que 1998). In comparison with HCC, morphologically

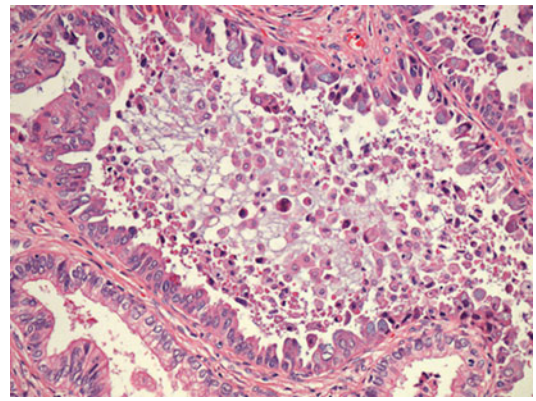

Fig. 2 In this cholangiocarcinoma, numerous neoplastic cells have been shed from the cell lining (drop-out), followed by accumulation of apoptotic cells within the tubule lumen (hematoxylin and eosin stain)

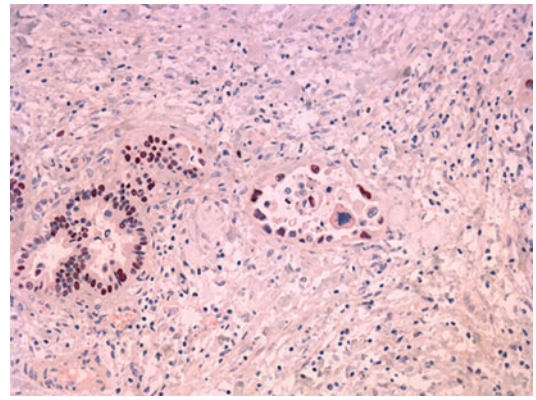

Fig. 3 Tumor cells in a proliferative cycle can suffer from drop-out and apoptosis. In this cholangiocarcinoma stained for proliferative activity, a cell in mitosis has been released from the cell lining of a tubule, is now an isolated element within the lumen, and will undergo apoptosis or anoikis (hematoxylin and eosin stain)

detectable apoptosis is less readily seen in part of cholangiocarcinomas, due to the high stromal content of these neoplasms. Apoptotic bodies are mostly found in mass-forming lesions having less stroma, and in tumors with an intraductal growth pattern (Figs. 2, 3, and 4). In solid growths, apoptotic bodies are predominantly found in central parts of the cancer strands. In intraductal cholangiocarcinomas, apoptotic cells may detach from tumor and float in the lumen, sometimes admixed with bile, mucus, or inflammatory exudate.

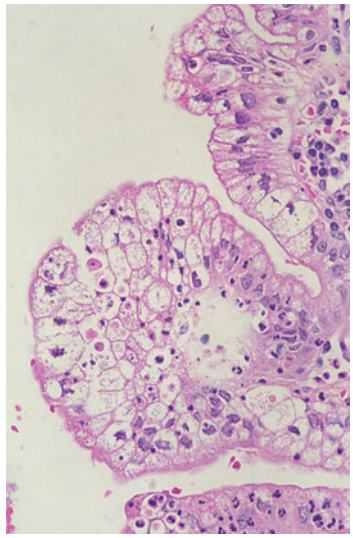

Fig. 4 Well-differentiated papillary cholangiocarcinoma. Apoptotic tumor cells are observed within the epithelial lining in the form of eosinophilic bodies that sometimes contain pycnotic nuclei or nucleus/chromatin remnants (hematoxylin and eosin stain)

Cholangiocarcinoma cells express several pro-and anti-apoptotic factors that can be assessed by immunohistochemistry to identify apoptotic cells. Cholangiocarcinomas express both Fas and FasL, whereby Fas expression decreased as a function of poor differentiation, while FasL was more often expressed in tumors with moderate or poor differentiation (Ito et al. 2000b). The percentage of Fas-expressing cells was higher in extrahepatic cholangiocarcinomas compared with intrahepatic tumors (Jhala et al. 2005). In intrahepatic cholangiocarcinomas, FasL was upregulated in early stages, whereas Fas was downregulated at progressed stages (Shimonishi et al. 2000). Hilar cholangiocarcinoma expresses FasL, associated with high levels of cell death among tumor-infiltrating lymphocytes (Li and Zou 2001). Pro-apoptotic TRAIL receptor was present in all cholangiocarcinomas, while TRAIL decoy receptors lacking the death domain were not expressed, but were detectable in normal hepatic tissue (Tanaka et al. 2000). Nuclear expression of the anti-apoptotic protein survivin is found in subsets of cholangiocarcinomas, associated with poor outcome (Javle et al. 2004). Cholangiocarcinomas and their dysplastic precursor lesions are reactive for the anti-apoptotic proteins Bcl-xL and Mcl-1 (Okaro et al. 2001). Immunoreactivity of Bcl-2 in cholangiocarcinoma cells seems to vary considerably. Bcl-2 was not detected in 1 investigation (Okaro et al. 2001); was found in 1 tumor among 20 cholangiocarcinomas (Terada and Nakanuma 1996); was present in 31.7 % of tumors in another study, where its expression was inversely related to nodal metastasis, perineural invasion, vascular invasion, and the proliferative status (Ito et al. 2000c); and was found in 8 out of 11 cholangiocarcinomas, similar to metastatic adenocarcinomas (Charlotte et al. 1994).

Liver Metastasis of Carcinomas

Regressive changes in liver metastasis of colorectal carcinomas are dominated by necrosis (see below). Apoptotic bodies are more frequently found in peripheral parts of the masses, close to the invasive border. The bodies appear as irregularly shaped, but often oval eosinophilic and homogeneous structures that are often situated as single objects or small clusters in the lumens of damaged adenocarcinoma tubules. These bodies represent condensed tumor cells having undergone drop-out from the epithelial lining of tubules. The apoptotic bodies may be accompanied by nuclear debris, cytoplasmic fragments, few neutrophils, and macrophages. In central parts of metastases, necrosis and apoptosis can occur together. In patients with colorectal carcinoma liver metastasis, apoptotic circulating tumor cells (CTCs) can be observed (Allen et al. 2014).

The mechanisms governing apoptosis and other forms of cell death in colorectal liver metastasis are only partially elucidated. Growth of metastasis depends on a shift in balance between proliferation and apoptosis. Apoptosis occurred more frequently in metastatic foci than in primary tumors of human colorectal carcinoma (Tatebe et al. 1996). There is evidence that this shift is regulated by factors derived from the primary tumor. For example, outgrowth of human hepatic colorectal cancer metastases occurs following resection of the primary

tumor, associated with a significant decrease of apoptosis in the metastasis (Peeters et al. 2006). This finding suggests that primary tumors secrete a factor that favors apoptosis in metastasis. In contrast, other studies did not find a difference of apoptosis behavior between primary and metastatic colorectal cancers (Seong et al. 2004). Development and progression of hepatic colorectal cancer metastases are regulated by differential expression of microRNA-192 which affects tumor cell apoptosis (Geng et al. 2014). Colorectal cancer cells associated with progression of disease exhibit low expression of M30, an early apoptosis indicator. This apoptosis resistance mechanism is important for metastasis (Kykalos et al. 2013). Liver metastasis of colorectal cancer is inhibited by cancer-derived CXCL16, a chemokine produced in the cancer microenvironment by CD8(+) T cells and natural killer cells (Kee et al. 2013), whereby chemokine-induced cell death may play a role. In fact, CXCL16 can suppress experimental hepatic colorectal cancer metastasis by promoting TNF-alpha-induced apoptosis by tumor-associated macrophages (Kee et al. 2014).

Cell Death in Tumor-Associated Microenvironments

Apoptosis and Necrosis of Stromal Cells

Stromal cells, myofibroblasts, and cancer-associated fibroblasts (CAFs), being the most important members, are critical for growth and spread of carcinomas (Mertens et al. 2013). Stromal cells of cancers, including liver carcinomas, are both locally produced via proliferation of resident mesenchymal cells and recruited from circulated mesenchymal stem cells. Recruitment of stromal cells is in part mediated by cancer cells and their products. Cholangiocarcinoma cells recruit stromal cells through secreting PDGF-D, which simulates migration of cancer-associated fibroblasts/CAFs via PDGFRbeta and Rho GTPase (Cadamuro et al. 2013). Such factors exert a prosurvival effect on stromal cells and shift cell turnover from loss through cell death to expansion. Apart from carcinoma cells, stromal cells of HCCs and cholangiocarcinomas can undergo apoptosis, a mechanism shaping the stromal composition. The turnover of the important myofibroblast precursor, hepatic stellate cell/HSC, is strongly regulated by apoptosis. Uncontrolled HSC proliferation in stromal expansion and fibrosis is counteracted by the Fas/Fas ligand pro-apoptotic system (Saile et al. 1997). Activated HSCs express the TRAIL receptor-2/death receptor-5 and are subject to TRAIL-mediated apoptosis, a mechanism that affects myofibroblast production and composition of the extracellular matrix (Taimr et al. 2003). The stromal population of mature, differentiated myofibroblasts is regulated by a balance between proliferation, growth arrest, differentiation, and apoptosis (Gressner 1998). Detection of this phenomenon requires special methods, such as immunostaining for pro-apoptotic factors or TUNEL assays. Activated stromal cells, predominantly myofibroblasts and cancer-associated fibroblasts/CAFs, can be primed for apoptosis by platelet-derived growth factor (PDGF) isomers via Puma-mediated Bak activation (Rizvi et al. 2014), a pathway that may be used in future treatment strategies. Stromal hepatic stellate cells and myofibroblasts are also sensitive to H_2O_2-mediated apoptosis, showing that oxidative stress is an important pro-apoptotic factor for these cell types (Larochelle et al. 2004; Thirunavukkarasu et al. 2004). Apoptosis of stromal cells, e.g., myofibroblasts, can be counteracted by various factors, including TGF-beta1 (Zhang and Phan 1999).

CAFs and myofibroblasts, which themselves are subject to cell death pathways, can affect cancer cell fate and progression by a complex balance between the promotion of growth and cell death. On the one hand, these stromal cells can drive the progression of cancer metastasis (Karagiannis et al. 2012), promote apoptosis resistance of cancer cells (Sirica 2011), and secrete PDGF-BB that induces hedgehog survival signaling in cholangiocarcinoma (Fingas et al. 2011). Apoptosis of stromal myofibroblasts is associated with upregulated MT1-matrix metalloproteinase (MMP) protein expression which induces pro-MMP-2 activation and in turn a proinvasive phenotype (Preaux et al. 2002). Deletion of CAFs suppresses tumor growth (Mertens et al. 2013). On the other hand,

bone marrow-derived stromal cells can increase the apoptosis rate of cancer cells and inhibit tumor metastasis (Hang and Xia 2014).

Apoptosis in Tumor-Associated Endothelial Cells and Angiogenic Compartments

The generation and turnover of endothelial cells located to tumor-associated blood vessels result from a delicate balance of proliferation and apoptosis. The shaping of a vascular network in progressing tumors depends on remodeling accomplished by apoptosis and other forms of cell death, a phenomenon that was studied in detail in involuting infantile hemangiomas (Razon et al. 1998). It is supposed that angiogenic systems in cancers are controlled by sensors that monitor the required number of endothelial and other vascular cells and provide signals to delete superfluous cells via apoptosis, similar to what seems to happen in ontogenesis. Limitation of neovessel density executed by receptor-mediated apoptosis is in part induced by thrombospondin-1 (Jimenez et al. 2000). Survival of endothelial cells during vasculogenesis and angiogenesis is influenced by pro-and anti-apoptotic factors secreted by cells of the stroma and tumor cells. Angiopoietin-1 and its receptor Tie-2 control survival of endothelial cells and by this regulate capillary tube formation (Hayes et al. 1999), acting as some sort of vasculogenic/angiogenic pacemaker. The morphogenesis of a functional neovessel network depends on survival of newly produced endothelial cells. VEGF, a strong promoter of angiogenesis, also markedly induces two members of the inhibitor of apoptosis/IAP family of proteins, survivin and XIAP (Tran et al. 1999), providing a potent survival strategy for these cells.

In the setting of programmed vascular regression, which also occurs in remodeling tumor vessel networks, macrophages can kill capillary endothelial cells in the G1 phase of the cell cycle (Diez-Roux et al. 1999). Also stromal cells are operational in endothelial cell apoptosis. Stromal tissue inhibitor of metalloproteinase-3/TIMP3, a potent inhibitor of angiogenesis, promotes endothelial cell apoptosis through a caspase-independent mechanism and targeting of a focal adhesion kinase/FAK-dependent survival pathway (Qi and Anand-Apte 2015). Apoptosis of endothelial cells can also be induced by solid tumor cells (Kebers et al. 1998) and is induced by ionizing radiation. Radiation-induced apoptosis of endothelial cells is dose dependent and occurs in a discrete wave 6–10 h after irradiation (Langley et al. 1997). Immortalized endothelial cells undergo p53-mediated apoptosis in a telomerase-independent manner (Maxwell et al. 1997). Apoptosis of tumor-associated endothelial cells plays a role in tumor spread and progression. Colorectal cancer liver metastasis in a mouse model is suppressed by apolipoprotein (a) kringle V via induction of apoptosis in tumor-associated endothelial cells (Ahn et al. 2014).

Apoptosis and Other Cell Death Forms in Cells Involved in Immune Responses and in Pro-apoptotic Pathways

HCCs, other primary liver cancers, and metastases are populated by various classes of leukocytes, mainly lymphocytes, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells, dendritic cells, plasma cells, and granulocytes. Immunologic effector cells, including lymphocytes, monocytes, and TAMs, generate an inflammatory microenvironment in HCC which affects tumor progression, including metastasis (Galdiero et al. 2013). Here, TAMs have a pivotal role (Shirabe et al. 2012; Capece et al. 2013), and these cells induce apoptosis in tumor cells and nonneoplastic partner cells in stroma, including lymphocytes, and are also subject to apoptosis which regulates TAMs' cell turnover (Yao et al. 2014). Caspase-independent cell death of TAMs is also induced by autophagy (Xu et al. 2006). The fate of TAMs in the stromal niche is strongly dependent on the influx and survival of their precursors, the monocytes, which in turn derive from blood and hence from bone marrow. Monocytes can undergo apoptosis

induced by several mechanisms, but they are protected from apoptosis through regulation of TREM-1 (Cai et al. 2013). Triggering receptor expressed on myeloid cells 1 (TREM-1) is a signaling molecule that modulates several types of immune reactions and inflammatory responses and holds a critical position in the pathogenesis of infections and sepsis (Bouchon et al. 2000; Gibot 2006). TREM-1 is coupled to the ITAM-containing adaptor DAP12 (Tessarz and Cerwenka 2008). Bruton tyrosine kinase/Btk is a positive regulator in the ITAM-mediated TREM-1/DAP12 pathway (Ormsby et al. 2011). TREM-1 is selectively expressed on blood neutrophils and subsets of monocytes, but is also aberrantly expressed on diverse cancer cells. TREM-1 prolongs macrophage survival via induction of the anti-apoptotic protein Bcl-2 (Yuan et al. 2014), a mechanism that is probably important for maintenance of functional TAM populations. In cancers, expression of TREM-1 depends on an intricate interaction between tumor cells and stromal leukocytes. Cancer cells can directly upregulate TREM-1 expression in TAMs, and TREM-1 secretion by TAMs is in turn associated with cancer recurrence and poorer survival (Ho et al. 2008). TREM-1 is expressed in HCC cells, where it promotes proliferation, inhibits apoptosis of these tumor cells, and is associated with poor survival (Duan et al. 2015). On the other hand, TREM-1 is also produced by stromal hepatic stellate cells associated with HCC. TREM-1 which is produced by peritumoral stellate cells promotes migratory behavior of HCC cells and confers an aggressive tumor phenotype (Liao et al. 2012). TREM-1 controls Kupffer cell activation and by this affects hepatocarcinogenesis (Wu et al. 2012). Expression of TREM-1 is associated with tumor progression via its inhibition of tumor cell apoptosis and enhancing angiogenesis in colorectal cancer (Lee et al. 2014).

T cells and natural killer cells accumulate in the stroma of liver cancers, in part recruited by the action of activated stromal monocytes (Kuang et al. 2010). In some variants of HCCs, lymphocytic infiltration is dense and results in HCCs with lymphoid stroma. Infiltration by CD8(+) lymphocytes is associated with tumor cell apoptosis in HCCs (Ikeguchi et al. 2004). The sometimes dense lymphocytic infiltration in HCC is generated by the action of chemokines and chemokine receptors in part produced by stromal cells. CD8 (+) T cells infiltrating HCC play a role in apoptosis of these tumors, and apoptosis in HCC is regulated by the suppression of Fas/FasL expression mediated by tumor-infiltrating lymphocytes (Fukuzawa et al. 2001). In metastases, the CXCL16/CXCR6 axis, upregulated in various cancers, functions as an inducer for lymphocyte build-up around tumor sites (Deng et al. 2010; Koizumo et al. 2007). Fas/FasL on membranes or in the cytoplasm of HCC cells was increased in areas with lymphocytic infiltration surrounding cancer, a response mainly mediated by CD8(+) T cells (Fukuzawa et al. 2001). Apart from mechanisms promoting influx/homing of cells, the number of tumor-infiltrating lymphocytes/TILs is regulated by the balance of proliferation/immigration versus apoptosis. Intratumoral activated hepatic stellate cells can induce T-cell apoptosis (Xia et al. 2013), suggesting a distinct interactome between stromal cells and TILs. Expression of pro-apoptotic FasL is more frequent in liver metastases of colorectal carcinoma than in matched primary tumors, associated with increased apoptotic elimination of tumor-infiltrating lymphocytes/TILs (Mann et al. 1999).

Leukocyte-tumor cell interactions in part depend on the highly variable longevity of leukocytes, a phenomenon that affects the fine-tuning of mechanisms in the tumor microenvironment. Whereas subsets of lymphocytes are long-lived, and also TAMs can show an extended life-span, neutrophils have a very short survival time as soon as they have left the blood stream to settle within tissues. Short-lived neutrophils infiltrating the peritumoral tissue compartment links inflammatory responses to progression of HCC by fostering angiogenesis, mediated through the secretion of pro-angiogenic MMP-9. Neutrophils are recruited to this site by IL-17 secreted by HCC cells (Kuang et al. 2011). Neutrophils can also promote motility of cancer cells through a hyaluronan-mediated toll-like receptor 4/PI3K activation pathway (Wu et al. 2011). These mechanisms are blunted by early death of neutrophils, an effect that requires continuous replacement of lost neutrophils

egressing from the blood. Death of extravascular neutrophils is a complex process that involves both apoptosis and necrosis. Neutrophils in tumors are also subject to autophagy. HCC cells can release soluble factors that trigger an increase of functional autophagy-specific protein LC3 and autophagosomes in neutrophils. Increased neutrophil autophagy was correlated with sustained production of pro-metastatic oncostatin M and matrix metalloproteinase-9 (Li et al. 2015b).

Apoptosis in Hepatocellular Carcinoma and Cholangiocarcinoma: A Major Mechanism to Control Tumor Growth and Spread

General Remarks

Most liver cancers are in an unbalance regarding cell proliferation and apoptosis (Fabregat 2009; Guo et al. 2010), resulting in a serious derangement of cell number homeostasis that causes progressive cancer growth with intervening periods of growth silence or even tumor regression (reviews: Kountouras et al. 2003). Apoptosis in HCCs may be induced by factors involved in HCC etiology. For example, HCV viral proteins can induce mitochondrial dysfunction and may, through this pathway, lead to mitochondria-mediated apoptosis (Brault et al. 2013), and apoptotic signaling is modulated by the HBV X protein (Rawat et al. 2012). Binding of HBsAg to the ECHS1 binding protein enhances apoptosis through the mitochondrial pathway (Xiao et al. 2013). ECHS1 (enoyl-CoA hydratase short chain 1) is a protein that is overexpressed in various cancers, including HCC, and interacts with STAT3 (signal transducer and activator of transcription 3) and negatively regulates STAT3 signaling (Chang et al. 2013).

Pro-apoptotic Factor Expression in Hepatocellular Carcinoma

HCC cells can express a wide array of pro-apoptotic factors with highly variable expression patterns (Table 2).

Table 2 Pro-apoptotic factors expressed in hepatocellular carcinoma

Fas/Fas ligand system
Bcl-2 superfamily members
Bax (Bcl-2-like protein 4)
Bak
Bok
Bim
Bid
BAD
Noxa
Puma
TGF-beta/Smad signaling pathway
p53 protein
Smac/DIABLO
TRAIL
PATZ 1 transcription factor
Omentin-1
Tat-interacting protein 30
Klotho protein
Krüppel-like factor 9
Adiponectin
DFNA5
Delta-like 3 downregulation
RhoA and RhoC proteins
DCL-1

There are significant differences in the expression of apoptosis-related factors/proteins between normal hepatic tissue and HCCs. HCC tissue expresses Fas (APO-1; CD95) more weakly and less frequently than noncancerous liver tissue, and while Fas is present in normal hepatocytes both on the cell membrane and in the cytoplasm, cell surface expression of Fas is variable in HCCs and HCC cell lines (Hamazaki et al. 1995; Higaki et al. 1996; Yano et al. 1996; Lee et al. 2001; Shin et al. 1998). In HCCs that express Fas, the expression pattern varies from few single cells to a honeycomb pattern. Low Fas expression is mainly found in HCCs of poor differentiation and an invasive phenotype (Ito et al. 1998, 2000a), while Fas ligand expression was detected in moderately and poorly differentiated tumors (Ito et al. 2000a) and was an indication of worse prognosis (Lee et al. 2004). Downregulation of Fas and upregulation of FasL in HCCs are regarded as important elements in evasion from

immune surveillance (Hammam et al. 2012). On the other hand, CD8(+) T cells that infiltrate peripheral parts of HCCs lead to upregulation of the Fas/FasL system in HCC cells to increase tumor cell apoptosis (Fukuzawa et al. 2001; Ikeguchi et al. 2004). Notwithstanding the fact that HCC cell can express Fas at low levels, these cells are often resistant to Fas-mediated apoptosis (Kubo et al. 1998). This is usually not an active process but rather the consequence of inadequate apoptotic stimulation (Natoli et al. 1995). Interestingly, HCCs can be surrounded by a population of normal hepatocytes that strongly express Fas and Fas ligand/FasL, suggesting that cancer may induce apoptosis in peritumoral cells (Roskams et al. 2000). Fas-related death signals, i.e., cFLIP (cellular FLICE-inhibitory protein), FADD (Fas-associated death domain), and NF-kappaB, are modulated in HCCs by the Wilms' tumor 1 gene (Uesugi et al. 2013). Fas also plays a role apoptosis and growth control of cholangiocarcinomas (Pan et al. 1999).

In HCC cells, apoptosis is potently induced by the TGF-beta signaling pathway, involving functional cooperation with Smad proteins and activator protein-1/AP-1 (Herzer et al. 2008). Pro-apoptotic signaling of TGF-beta1 is regulated by growth factors and integrin receptors located in the ECM (Ozaki et al. 2011). p53, frequently expressed in HCCs, promotes apoptosis, in interaction with several other proteins (Zhao and Zimmermann 1997a). One of the interacting partners of p53 in the apoptotic cascade is the transcription factor, PATZ1, which binds p53-dependent gene promoters (Valentino et al. 2013). Certain apoptosis-inducing proteins utilize the pro-apoptotic pathway of p53, e.g., nutlin-3 (Zheng et al. 2010). A promoter of apoptosis in HCC cells is the adipokine omentin-1, a protein which promotes apoptosis via regulating Sirt1-dependent p53 deacetylation (Zhang and Zhou 2013). The process of p53-induced apoptosis is a complex, multistep process. Generally, p53 mediates the transactivation of either cell cycle-regulating or pro-apoptotic target genes. The decision to enter an apoptotic pathway depends on the transcriptional regulator AATF. Genotoxic stress causes phosphorylation of AATRF through the p38MAPK/MK2 checkpoint kinase complex, followed by nuclear localization of AATF. In the nuclear compartment, AATF binds to Puma, Bax, and Bak promoters to suppress the DNA damage-induced expression of these pro-apoptotic p53 target genes (Höpker et al. 2012). HCC cells can express the second mitochondria-derived activator of caspase, Smac/DIABLO, a pro-apoptotic protein that releases inhibition of the IAP family from caspase-3 to induce apoptosis. Overexpression of Smac in HCCs promotes TRAIL-induced cell death (Okano et al. 2003).

Apoptosis is induced in HCCs by expression of the Tat-interacting protein 30/TIP30, a death pathway requiring mitochondrial participation. For TIP30-induced apoptosis, translocation of Bax is essential, and the process requires release of cytochrome c and Smac/DIABLO (Shi et al. 2008). Expression of klotho, a tumor suppressor involved in several cancers, including HCC, induces apoptosis in HCC cells through regulation of IGF-1R phosphorylation and subsequent activation of downstream Akt-p70S6K and ERK signaling (Shu et al. 2013). HCC cell apoptosis is promoted by the transcription factor, Krüppel-like factor 9/KLF9 via programmed cell death protein 5 (Fu et al. 2014). Apoptosis in HCC is promoted by DFNA5, a tumor suppressor that plays a role, as a mutated protein, in one form of autosomal dominant hearing loss (Wang et al. 2013a). DFNA5 is a pro-apoptotic protein that has been detected in several cancers (Op de Beeck et al. 2011) and is a paralog of DFNAB59/pejvakin, a protein involved in auditory neuropathy. Adiponectin impairs HCC progression by inducing apoptosis via modulation of c-Jun N-terminal kinase and mTOR pathways (Xing et al. 2015). Apoptosis in HCC cells is induced by downregulation of Delta-like 3, which is silenced in these neoplasms (Maemura et al. 2013). Apoptosis in HCC cells is regulated by several Rho proteins, including RhoA and RhoC and their expression inducers. RhoC is a key regulator of both growth and apoptosis in HCC cells (Xie et al. 2012). Apoptosis is induced in HCC cell populations by DLC-1 protein (DLC,

deleted in liver cancer), a pro-apoptotic GTPase-activating protein encoded by a gene on 8p21.3–22. DLC-1 is specific for RhoA and Cdc42, and its gene is frequently deleted in HCC (Wong et al. 2003), one mechanism for HCC apoptosis resistance. Restoration of DLC-1 expression in HCC cells induces apoptosis and inhibits cancer expansion (Zhou et al. 2004). A pro-apoptotic protein is Siva-1, a protein which induces both extrinsic (receptor-mediated) and intrinsic (non-receptor-mediated) apoptosis (Resch et al. 2009). Siva-1 binds to CD27, a component of the TNFR family. Siva-1 forms a functional complex with tyrosine kinase 2, a complex that augments the pro-apoptotic effects (Shimoda et al. 2010). A further binding partner of Siva-1 is pyrin, a protein mutated in familial Mediterranean fever/FMF. Through its binding, pyrin can recruit Siva to the apoptotic protein ASC specks (Balci-Peynircioglu et al. 2008). In mammalian cells, the open conformation of PTEN has a pro-apoptotic activity, counteracted by the tumor suppressor, p27Kip1, an enzyme that binds cyclin/CDK complexes in the nucleus but also exerts cytoplasmic functions (Andrés-Pons et al. 2012). Apoptosis of HCC cells is induced by suppression of serine/threonine kinase involved in centrosome separation and mitotic bipolar spindle formation, STK15/Aurora A/BTAK (Gao et al. 2008). A pro-apoptotic protein in HCCs acting in a caspase-independent manner is TIPE1 (tumor necrosis factor alpha-induced protein 8-like), a TIPE family member involved in apoptosis regulation. TIPE1 induces apoptosis in HCC cells by negatively regulating Rac1 and its downstream p65 and c-Jun N-terminal kinase pathways (Zhang et al. 2014). Certain microRNAs promote apoptosis in HCC cells. microRNA-141 promotes HCC apoptosis by targeting hepatocyte nuclear factor 3 beta (Lin et al. 2014). MicroRNA-1 induces apoptosis of HCC cells by targeting and downregulating the apoptosis inhibitor-5/API-5 (Li et al. 2015a). MicroRNA-206, markedly downregulated in HCC, is a promoter of apoptosis. Loss of this microRNA in HCC is associated with poor differentiation and advanced tumor stage (Yunqiao et al. 2014).

Downregulation of Apoptosis in Hepatocellular Carcinoma and Cholangiocarcinoma

An imbalance between pro-apoptotic and anti-apoptotic factors plays a significant role in the progression of HCCs and cholangiocarcinomas. As in normal tissues with cellular turnover, several types or species of anti-apoptotic factors are variably expressed in liver cancers (Table 3).

Important anti-apoptotic proteins in HCCs are endogenous inhibitors of apoptosis proteins (IAPs), key regulators of apoptosis, signal transduction pathways, and cytokinesis (Notarbartolo et al. 2004; Augello et al. 2009). IAPs were first identified as baculovirus proteins and in humans include XIAP, c-IAP1, c-IAP2, NIAP, survivin, Bruce, ILP-2, and livin/ML-IAP. IAPs are expressed in HCC and contribute to inhibition of apoptosis (Li et al. 2013). Apart from their role as apoptosis inhibitors, IAPs are regulators of innate immunity and inflammation and can act as E3 ubiquitin ligases acting on the Rho kinase Rac and thus modulate cell migration. IAPs are antagonized in HCC cells by a protein that is released

Table 3 Anti-apoptotic factors expressed in liver cancer

Inhibitor of apoptosis proteins (IAPs)
XIAP
c-IAP1
c-IAP2
NIAP
Survivin
Livin/ML-IAP
Bcl-2 superfamily members
Bcl-2
Bcl-xL
Bcl-W
Mcl-1
Bcl-B
BRE protein
Krüppel-like factor 6 (KLF6)
Glypican-3 (in part)
SERPINB3
DEK
Period1
Timeless
GRIM-19

from mitochondria in response to apoptotic stimuli, i.e., Smac/DIABLO (second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pl).

HCC cells are often resistant to TNF-related apoptosis-inducing ligand/TRAIL, a member of the TNF family. TRAIL is regulated by two death receptors, TRAIL receptor-1 (TRAIL-R1) and TRAIL-R2, and two decoy receptors (Chen et al. 2003). TRAIL resistance of HCC cells may be caused by downregulation of TRAIL-R1 and TRAIL-R2 in these cells (Shin et al. 2002). Generally, the expression of these two proteins is lower in HCCs than in normal liver, and reduced TRAIL-R1 and TRAIL-R2 expression goes in parallel with a decrease of caspase-3 activity (Yano et al. 2003). In HCCs, TRAIL-R1 downregulation and upregulation of TRAIL-R2 and TRAIL-R4 correlated with tumor dedifferentiation (Koschny et al. 2013).

Bcl-2, an anti-apoptotic factor, is variably expressed in HCCs, and its role in these cancers is not clarified. A positive linear correlation was found between Bcl-2 expression and p53 protein expression, and Bcl-2 expression was inversely proportional with histologic grade (El-Emshaty et al. 2014). Expression of Bcl-2 in HCC is subject to regulation by B cell translocation gene 1/BTG1. In these tumors, BTG1 is downregulated, resulting in reduced apoptosis (Sun et al. 2014). Bcl-2 is frequently overexpressed in cholangiocarcinoma cells and alters the threshold for apoptosis (Harnois et al. 1997).

Survivin is an important suppressor of apoptosis, but it also accelerates cancer cell proliferation. In HCCs, expression of survivin was found in 41–74 % of tumors (Ikeguchi et al. 2002; Moon and Tarnawski 2003; Chau et al. 2007; Augello et al. 2009), and cancers without detectable survivin expression showed significantly higher apoptosis rates, whereas expression of survivin was associated with poor prognosis (Ikeguchi et al. 2002; Cho et al. 2010). Expression of survivin in HCCs is correlated with high risk of disease recurrence (Fields et al. 2004; Ye et al. 2007). Among survivin-positive HCCs, 63 % showed punctate nuclear staining, while the remaining tumors displayed cytoplasmic staining. A nuclear transfer of survivin was associated with poorer differentiation (Moon and Tarnawski 2003). Increased nuclear expression of survivin in HCCs is associated with p53 protein expression (Kannangai et al. 2005). Survivin expression in HCCs is inhibited by Smac/DIABLO (Bao et al. 2006). Nuclear survivin expression was also detected in cholangiocarcinomas (Javle et al. 2004; Kannangai et al. 2005; Shen et al. 2009). In addition to nuclear immunoreactivity, also cytoplasmic immunostaining for survivin was observed in cholangiocarcinomas, strong nuclear survivin expression being correlated with poor prognosis (Javle et al. 2004). Survivin is downregulated by p16 reactivation in HCC resulting in anoikis (Hu et al. 2011). In addition to survivin, a second IAP is overexpressed in HCC, i.e., livin/ML-IAP. Smac is a potent suppressor of survivin in liver cancer (Bao et al. 2006).

Expression of the anti-apoptosis protein Bcl-xL in HCC correlates with an aggressive growth phenotype and poor survival (Watanabe et al. 2004). BRE, a protein that binds to the cytoplasmic domains of TNFR1 and Fas, is overexpressed in HCCs and acts as an anti-apoptotic factor (Chan et al. 2008). Krüppel-like factor 6/KLF6 is a transcription factor that protects HCC cells from apoptosis via a Bcl-2-mediated mechanism (Sirach et al. 2007). In HBV-associated HCC, downregulation of Notch1 through the action of upregulated microRNA-429 suppresses apoptosis (Gao and Liu 2014). In HCV-associated HCCs, decreased apoptosis is mediated through downregulation of p21 ras (Baddour et al. 2013). Overexpression of glypican-3, a membrane-associated heparan sulfate proteoglycan expressed in many HCCs and involved in cell proliferation and survival, can both induce apoptosis (Pan et al. 2013) and counteract apoptosis, while targeting of glypican-3 with microRNA-520c-3p induces apoptosis in HCC cells (Miao et al. 2014). SERPINB3, which is progressively expressed from dysplastic nodules to HCCs, is a potent inhibitor of apoptosis (Pontisso 2014). Overexpression of DEK, an oncogene originally found as one of the partners of the translocation-associated DEK-CAN fusion

gene in a subtype of acute myeloid leukemia, in HCC confers poor prognosis via inhibition of apoptosis (Yi et al. 2015). An anti-apoptotic factor expressed in HCCs and pancreatic cancer is the clock gene, Period1/Per (Sato et al. 2009). Also the endogenous clock protein timeless is overexpressed in some HCCs and counteracts apoptosis (Elgohary et al. 2015). Expression of the tumor suppressor GRIM-19, a mitochondrial respiratory chain complex I protein, in HCC suppresses tumor growth via stimulation of apoptosis (Kong et al. 2014).

Part of the mechanisms involved in anti-apoptosis in liver cancer operate through inhibition of pro-apoptotic factors. HBV infection can inhibit TGF-beta-induced apoptosis of HCC cells (Liu et al. 2014b). The HBV core protein can inhibit Fas-mediated apoptosis of HCC cells through modulating the expression of mFas/FasL and sFas expression (Liu et al. 2014a). HCC cells can circumvent apoptosis via acquisition of resistance to TRAIL/TNF-related apoptosis-inducing ligand, a pro-apoptotic member of the TNF family (Shin et al. 2002). Loss of the pro-apoptotic protein FADD in HCC cells promotes an anti-apoptotic phenotype (Sun et al. 2000). Expression of an anti-apoptotic protein, BIRC6, in HCC results in blunted apoptosis through facilitating the degradation of the pro-apoptotic protein, p53 (Tang et al. 2015). HBV can inhibit apoptosis in HBV-related HCC by upregulation of microRNA-181 and consecutive downregulation of Fas expression (Zou et al. 2014).

Elimination of Apoptotic Bodies

Clearance of Apoptotic Bodies and Efferocytosis

The condensed cell corpses resulting from apoptosis and related death mechanisms (the apoptotic bodies) are structures that contain numerous and in part altered proteins that can exert diverse functions, including pathological signaling functions and cell injury. It is, therefore, important to provide prompt clearance of apoptotic bodies. This process includes engulfment of apoptotic bodies followed by degradation of the engulfed particles (Fadeel et al. 2004; Ravichandran and Lorenz 2007; Fullard et al. 2009). In epithelia, clearance of apoptotic cellular fragments can be visualized by immunohistochemical staining with M30 antibody. M30 recognizes a neo-epitope formed early in the apoptotic cascade by caspase cleavage of cytokeratin 18 (Leers et al. 2002). A special form of the apoptotic body clearance process is efferocytosis. Efferocytosis is a process characterized by the recognition and removal of apoptotic cells by phagocytes predominantly in the setting of inflammation. Engulfment and clearance of apoptotic bodies/corpses involve three membrane proteins, low-density lipoprotein receptor-related protein-1/LRP, ABCA1, and the LRP adaptor protein GULP/CED-6 (Su et al. 2002; Kiss et al. 2006). GULP acts via the mammalian engulfment receptor Jedi-1, an interaction which mediates phagocytosis of apoptotic bodies through a clathrin-dependent mechanism (Sullivan et al. 2014).

Factors Operational in Clearance of Apoptotic Bodies

In the process of apoptotic body clearance, stabilins as scavenger receptors play a significant role. Stabilin-1(CLEVER-1) is specifically expressed in alternatively activated macrophages (type II macrophages) and certain endothelial cells (Kzhyshkowska 2010; Palani et al. 2011). In the liver, stabilin-1 and stabilin-2 are involved in the clearance of oxidized low-density lipoproteins by sinusoidal endothelial cells (Li et al. 2011). Stabilin-1 is located is recruited to sites of surface recognition and engulfment of apoptotic corpses by macrophages (Park et al. 2009). Cell corpse clearance via engulfment also strongly depends on a receptor for membrane phosphatidylserine on apoptotic cells, stabilin-2, which itself has thymosin beta44 as its downstream molecule (Lee et al. 2008). A stabilin-2 domain modulates pH-dependent recognition of phosphatidylserine in apoptotic cells (Kim et al. 2010). Stabilin-2-mediated corpse engulfment requires the presence of the adaptor protein

GULP, a likely downstream effector in the stabilin-2 signaling pathway (Park et al. 2008). GULP is also involved in stabilin-1-mediated phagocytosis (Park et al. 2010). Engulfment of apoptotic cells also requires caspase activity (Shklyar et al. 2013) and the presence of three receptor kinases, Tyro-3, Axl, and Mer, collectively termed TAM receptors (Lemke 2013; Nguyen et al. 2013). The elimination of dying or dead neutrophils depends on the presence of lysophosphatidylserine on neutrophils acting as a clearance and proresolution signal and on Rac1 activity increasing the numbers of macrophages efferocytosing apoptotic cells (Frasch et al. 2011). Engulfment of apoptotic bodies by various phagocytic cells is negatively regulated by PTEN by modulating activation of Rac GTPase (Mondal et al. 2011). Efferocytosis is negatively regulated by cellular expression of the high mobility group box 1/HMGB1 protein, a conserved protein with numerous intracellular and extracellular functions. HMGB1, through its association with Src kinase and an inhibition of interactions between Src kinase and focal adhesion kinase, decreases phagocytic ability of macrophages for apoptotic cells (Banerjee et al. 2011).

Recognition of Apoptotic Cells by Leukocytes

How are apoptotic corpses recognized by phagocytes? Apoptotic cells and their bodies express surface molecules that are sensed by phagocytes which can obviously "analyze" the surface patterns or "surface code" of dead versus living cells, providing "find-me" or "stay away" signals (Biermann et al. 2013; Hochreiter-Hufford and Ravichandran 2013). A critical surface address is phosphatidylserine, which is expressed on apoptotic cells, is recognized by phagocytes, and is an "eat-me" signal (Toda et al. 2012; Biermann et al. 2013). Apoptotic and pyroptotic cells release a nucleotide-type "find-me signal" and "eat-me signal" (Elliott et al. 2009; Wang et al. 2013b). These "find-me" signals are mediated by the plasma membrane channel pannexin 1, an ATP nucleotide release channel which increases membrane permeability during apoptosis (Chekeni et al. 2010; Sandilos and Bayliss 2012). Proteolytic enzymes can confuse the recognition of apoptotic cells by phagocytes (Guzik et al. 2007; Guzik and Potempa 2008). Under special situations, not entire cells but rather parts of cells are eliminated by engulfment. Human intrahepatic cholangiocytes can engulf blebs from their apoptotic peers (Rong et al. 2013).

Apoptosis: The Phenomenon and Mechanisms of Programmed Cell Death

Introduction

Apoptosis is, apart from necrosis, the best known form of cell death (reviews: Saraste 1999; Fink and Cookson 2005; Fietta 2006; Elmore 2007; Duprez et al. 2009). This classical form of programmed cell death is morphologically characterized by cell shrinkage, membrane damage, chromatin condensation and fragmentation, degradation of the nucleosomal structures, and formation of an eosinophilic dense body representing the shrunken cell, the apoptotic body, or apoptotic corpse. The duration of classical apoptosis ranges from 12 to 24 h. Classical apoptosis requires activation of the caspase cascade (review: Elmore 2007). Apoptotic bodies have long been known, a typical example being the Councilman body found in livers with acute or active hepatitis. The other forms of cell death are discussed in later paragraphs.

Detection of Apoptosis and Apoptotic Cells

Apart from morphologic detection of apoptosis, which in light microscopic preparations depends on the presence of apoptotic bodies, numerous cytochemical, immunohistochemical,

Table 4 Methods for detecting apoptosis and apoptotic cells

Immunostaining for membrane molecules (Fas/CD95, FasL, TNFR1/CD120a, TNFR2/CD120b, TRAIL receptors, and others)
Immunostaining for cytoplasmic molecules (Bcl-2, Bid, caspases, IAPs, and others)
Annexin V staining (phospholipid externalization, annexin V binding)
Cytochrome c immunohistochemistry
Detection of phosphatidylserine, and apoptosis marker, on cell surfaces
Caspase assays (caged fluorophores, FRET; carboxyfluorescein caspase activity assay; flow cytometry)
Caspase cleavage product assays (cytokeratin 18 cleavage; poly-ADP-ribose polymerase/PARP cleavage)
Cathepsin assay
Exclusion assays for detection of membrane damage (trypan blue exclusion, propidium iodide exclusion)
Chromatin condensation assays
Visualization of altered DNA by DNA fluorochrome staining (acridine orange)
Labeling of DNA strand breaks by nick translation (ISNT) using exogenous DNA polymerase
Labeling of cells by end labeling (TUNEL), using exogenous terminal transferase for end labeling of DNA fragments
DNA fragmentation assays (non-radioactive DNA fragmentation assay; radioactive assays, alkaline elution analysis, DNA "ladders" in agarose gel electrophoresis, radioactive ladder analysis, ELISA of histone-complexed DNA fragments, 3H-TdR-based JAM test, nucleosome quantification ELISA, anti-single stranded DNA antibody assay)
ATP bioluminescence assay
Mitochondrial function and integrity assays (permeability transition by vital dye staining, membrane potential assay, mitochondrial antigen staining, cytochrome c release assays, Smac/DIABLO assays)
Cell death detection ELISA
Cellometer imaging cytometry

DNA fragmentation (internucleosomal DNA cleavage) assays are based on the phenomenon that, in early apoptosis, genomic DNA is cleaved into distinct fragments prior to cell membrane disintegration/cell lysis (prelytic DNA fragmentation). The DNA fragments have a characteristic size and form rungs in a ladder as seen in agarose gel electrophoresis or in radioactive ladder analysis

and molecular methods have been developed to identify apoptosis in cultured cells and tissues (reviews: Willingham 1999; Saraste and Pulkki 2000; Martinez et al. 2010; Table 4).

Pathways to Apoptosis

General Remarks

Apoptosis as a highly regulated process required a complex network of proteins. The diverse manifestations of apoptosis have been defined and standardized (Fink and Cookson 2005; Kroemer et al. 2009; Galluzzi et al. 2012). Previously, apoptosis had been clearly separated from necrosis, these two death processes having been regarded as completely unrelated. Recent findings have changed this view, as outlined below (Nikoletopoulou et al. 2013). Apoptosis signaling is initiated by several stress factors, including nutrient deprivation, hypoxia, heat, infections, ionizing radiation, and increased intracellular calcium concentration. Via intermediate factors, these stressors can trigger the release of a complex array of pro-apoptotic signals by a damaged cell. Two conserved protein families are central to apoptosis, i.e., the Bcl-2 family controlling mitochondrial integrity and a group of cysteinyl aspartate-specific proteases, the caspase family.

The Intrinsic Pathway to Apoptosis

The intrinsic pathway operates through mitochondria. Mitochondria play a crucial role in the initiation of apoptosis by delivering an array of pro-apoptotic factors that induce caspase activation, while the extrinsic pathway (see below) does not directly involve mitochondria (review: Otera and Mihara 2012). Mitochondria-induced apoptosis is closely linked to mitochondrial fusion and fission and crista disorganization. Via this pathway, apoptosis is connected with the function of key mediators of fusion and fission, mitofusins, and the intermembrane space GTPase OPA1. In the setting of apoptosis, the mitochondrial network disintegrates into small spherical structures, a process also regulated by the pro-apoptotic and anti-apoptotic Bcl-2 family proteins. This mitochondrial fragmentation is independent from caspases and is associated with crista disorganization and subsequent cytochrome c release. However, mitochondrial fragmentation is not always

associated with apoptosis. The fragmentation process is closely linked to the decay of crista folds, cristae remodeling, and opening of crista junctions to release cytochrome c, the protein OPA1 required for crista integrity. Disruption of OPA1 complexes during early apoptosis leads to widening of cristae and release of cytochrome c into the intermembrane space. Fission and fragmentation of mitochondria is counteracted by a organelle-protecting process initiated in mitochondrial damage, called stress-induced mitochondrial hyperfusion (SIMH). Under stress such as exposure to UV irradiation and cytotoxic drugs, the mitochondrial network becomes highly connected, forming a hyperfused structure.

Under normal conditions, mitochondrial integrity is maintained by the action of anti-apoptotic Bcl-2 family members which inhibit the pro-apoptotic Bcl-2 members, Bax and Bak, to induce mitochondrial injury. Following cell stress, anti-apoptotic Bcl-2 members are antagonized by the activation of the Bcl-2-homology 3 proteins (BH3-only proteins), Bim, tBid and Noxa, which relieve Bax and Bak inhibition. The BH3-domain protein, Bim, can activate Bak and Bax directly (Czabotar et al. 2009), but its interactions with prosurvival proteins are complex (Mérino et al. 2009). Specifically, Bax and Bak can also mediate apoptosis without association with the BH3-only activators, Bim, Bid, and Puma (Willis et al. 2007). The BH3 domain protein, Noxa, interacts with several partners, but specifically with Puma and Mcl-1. Like Puma, Noxa is induced by the transcription factor p53, but Noxa, together with the pro-apoptotic Bcl-2 family member Bok, is also transcriptionally induced by MAL, the myocardin-related transcription factor A/MRTF-A (Shaposhnikov et al. 2012). Noxa and Puma synergistically induce apoptosis (Wensveen et al. 2011). This pathway involves the anti-apoptotic Bcl-2 protein, Mcl-1 which is a gateway to TRAIL sensitization (Kim et al. 2008). In p53-induced apoptosis, Puma can be caught at the mitochondrial surface by Mcl-1, and upon DNA damage, Noxa releases Puma from Mcl-1 and thus induces apoptosis (Nakajima and Tanaka 2011).

Active Bax and Bak oligomerize and form a channel in mitochondria through which a chief mediator of apoptosis, cytochrome c, is released into the cytosol. Here, cytochrome c forms a multiprotein platform with Apaf-1 and ATP to recruit and activate procaspase-9, a superstructure termed the apoptosome. Apoptosomes are highly complex signaling platforms that assemble the protein network required for apoptotic cell death. The apoptosome is the critical structure in the mitochondrial apoptotic pathway. Its assembly is initiated by the binding of cytochrome c to the apoptotic protease-activating factor (Apaf-1) in an ATP-dependent manner (reviews: Cecconi 1999; Dickens et al. 2012; Reubold and Eschenburg 2012; Yuan and Akey 2013). This step results in the construction of a characteristic heptameric "wheel" composed of seven Apaf-1 residues and seven molecules of cytochrome 2. This heptamer is now capable to activate the initiator caspase-9, which then switches the downstream caspase cascade into action. Activation of procaspase-9 on the apoptosome is a crucial step in the intrinsic cell death pathway. The holoapoptosome possesses procaspase-9 recruitment domains that form a CARD-CARD disk that is flexibly tethered to the apoptosome, whereby disk assembly and procaspase-9 binding generate an asymmetric proteolysis machine (Yuan et al. 2010, 2011). Procaspase-9 activated in the apoptosome platform then activates the downstream executioner caspases caspase-3, caspase-6, and caspase-7, enzymes that directly mediate the apoptotic process.

The Caspase Machinery: Execution of the Intrinsic Pathway of Apoptosis

In the course of the orderly cellular suicide program of apoptosis, a critical role is played by the sequential activation of several caspases, a family of cysteine proteases. Procaspases are synthesized as single-chain zymogens that, for full activation, require a complex and highly regulated process linked to activation complexes. Initiator caspases, mainly caspase-2, caspase-8, caspase-9, and caspase-10, are sequentially activated from procaspases in activation platforms having caspase-activating protein complexes that also

provide a chip-like distinct spatial arrangement of procaspases facilitating self-activation. These platforms include DISC (death-inducing signaling complex) which activates caspase-8 and caspase-10; the apoptosome, which activates caspase-9; the PIDDosome, which activates caspase-2 (review: Park 2012); and the apoptosome, which activates procaspase-9.

Generally, caspase-activating complexes contain members of the death domain/DD superfamily. The large DD superfamily consists of four subfamilies: (1) the death domain/DD subfamily, (2) the death effector domain/DED subfamily, (3) the caspase recruitment domain/CARD subfamily, and (4) the pyrin domain/PYD subfamily (Park 2012). Each of these subfamilies comprises between 7 and 32 species in the human genome. Pyrin domains are located at the N-termini of several proteins functioning in apoptotic and inflammatory signaling pathways (Fairbrother et al. 2001). Caspases active in apoptosis can be recruited by a distinct family of proteins, i.e., proteins with a caspase recruitment domain (CARD) motif. However, certain CARD proteins have anti-apoptotic effects. CARDINAL, a novel CARD protein, potently suppresses NF-kappaB activation (Bouchier-Hayes et al. 2001). The pro-apoptotic DRAL-caspase-9 complex is triggered by the sonic hedgehog-Patched receptor system. Patched interacts with the adaptor protein DRAL/downregulated in rhabdomyosarcoma LIM-domain protein. Via this binding, Patched recruits a protein complex that contains DRAL, one of the caspase recruitment domain (CARD)-containing proteins TUCAN (family member, 8) or NALP1 (NLR family, pyrin domain containing 1), and apical caspase-9 (Mille et al. 2009). Apart from the activation of caspases, TUCAN/CARDINAL and DRAL-containing proteins participate in the modulation of NF-kappaB activation (Stilo et al. 2002).

Activation of initiator caspases results in the activation of the executioner caspases caspase-3, caspase-6, and caspase-7. Executioner caspases such as caspase-3 and caspase-7 are also involved in signal transduction pathways inside target cells, through their capability to interact with several kinases, phosphatases, and other signaling molecules. Via such pathways, caspase-3 can, e.g., in an apparently paradoxical manner, control cell proliferation and tissue regeneration (Boland et al. 2013). Caspase-3, caspase-7, and caspase-9 are potently inhibited by the X-linked inhibitor of apoptosis (XIAP). The activity of XIAP is impaired by mitochondrial Smac (second mitochondria-derived activator of caspase) release during apoptosis. In a feedback loop, XIAP itself inhibits the release of Smac by mitochondria (Flanagan et al. 2010). In comparison with other caspases, caspase-2 has a more restricted role and selectively cleaves only a relatively small group of proteins, including cytoskeletal proteins (Vakifahmetoglou et al. 2013), but has a central role in the PIDDosome, a structure discussed in more detail below.

Factors Modulating the Intrinsic Pathway

There is a group of highly conserved proteins that potently inhibit apoptosis, i.e., the inhibitors of apoptosis proteins/IAPs. IAPs have a central, but indirect role in caspase regulation of the modulation of immune signaling. c-IAP1 and c-IAP2, unlike XIAP, do not directly inhibit caspases, but interact with tumor necrosis factor receptor/TNFR-associated factor 2/TRAF2, resulting in the recruitment of TNFR1. In addition to their function as factors counteracting apoptosis, IAPs also affect cell shape and cell motility, due to their interaction with MAPK, NF-kappaB, and Rho GTPase signaling pathways. IAPs are critically important regulators of apoptosis in hepatic cells. Main members of IPA comprise survivin, livin, c-IAP1, c-IAP2, NIAP, and XIAP. A potent IAP is X-linked inhibitor of apoptosis/XIAP protein, a protein which inhibits caspase-3, caspase-7, and caspase-9. The activity of XIAP is in turn inhibited during apoptosis by mitochondrial Smac/DIABLO (second mitochondria-derived activator of caspase) release, while cytosolic XIAP feeds back to mitochondria to impair Smac release. c-IAPs (cellular IAPs) and XIAP can also act as endogenous inhibitors of the ripoptosome, in that they can limit RIP1 kinase recruitment.

The Ripoptosome

A specific intracellular protein platform is required to mediate cell death induced by c-IAPs (cellular inhibitors of apoptosis proteins). The ripoptosome is a large multiprotein platform of around 2MDa (Tebev et al. 2011). c-IAPs promote the spontaneous formation of the ripoptosome complex (Imre et al. 2011) or necrosome, containing RIP1, FADD, caspase-8, caspase-10, and caspase inhibitor cFLIP isoforms. It can stimulate caspase-8-mediated apoptosis as well as caspase-independent necrosis. Ripoptosome assembly requires RIP1's kinase activity. The ripoptosome platform is mainly generated upon genotoxic stress or loss of IAPs. The ripoptosome as a distinct signaling platform can switch modes between apoptosis and necroptosis and critically influences the outcome of membrane-bound receptor triggering (Feoktistova et al. 2011, 2012).

The Extrinsic Pathway to Apoptosis

The extrinsic apoptotic pathway is initiated by stimulation of death receptors of the tumor necrosis factor receptor (TNFR) family, including TNFR1, TNFR2, Fas, and TRAIL receptor. Fas interacts with its ligand, FasL. TNF receptor 1 (TNFR1) is an ubiquitous death receptor that is involved in both normal and malignant cells. One important factor related to TNF signaling is TRAIL (tumor necrosis factor-related apoptosis-inducing ligand; Apo-2L) which interacts with specific cellular receptors, e.g., TRAIL-R, DR4, and DR5 (Thornburn 2004; Kim et al. 2013). Notwithstanding its pro-apoptotic action, TRAIL is constitutively expressed in tissues. Its effects are modulated by the differential expression of four TRAIL receptors, DR1–DR4, which bind TRAIL but differ markedly in their ability to transduce the death signal (MacFarlane 2003). TRAIL can be induced on the surface of HCC cells by cytokines and certain cytostatic drugs (Shiraki et al. 2005). Apoptosis induced by these death ligands and receptors is executed by the formation of death-inducing signaling complex (DISC). On the cell surface, several members of the TNF death receptor superfamily are arranged to form DISC which activates procaspase-8 (Schleich et al. 2013). On human cells, eight death receptor members attributed to four structurally homologous groups or clades form a functional DISC, i.e., the p75 (NTR) clade (p75 neutrotropin receptor, death receptor-6, and ectodysplasin A receptor), the TNF receptor 1 clade (TNFR1 and DR3), the CD95 clade (CD95/Fas/APO-1), and the TNF-related apoptosis-inducing ligand receptor (TRAIL-R) clade (TRAIL-R1 and TRAIL-R2). In the DISC complex, Fas-associated death domain (FADD) recruits initiator caspase-8 or caspase-10. In the DISC, activation of procaspase-8 leads to induction of death receptor-mediated apoptosis (Lavrik and Krammer 2012).

Death-Fold Complexes: PIDDosome, MyDDosome, and Fas/FADD-DISC

The Death-Fold Superfamily of Proteins

The death-fold superfamily is composed of four homologous subfamilies characterized by homotypic restricted interactions (review: Kersse et al. 2011). The building blocks for the construction of the multimeric complexes include the death domains (DDs), the death effector domains (DEDs), the caspase recruitment domains (CARDs), and the pyrin domains (PYDs). These domains are engaged in the formation of three major multimeric death-fold complexes, i.e., the PIDDosome, the MyDDosome, and the Fas/FADD-DISC (Mace and Riedl 2010; Kersse et al. 2011; Dickens et al. 2012).

PIDDosome

The PIDDosome is an oligomeric signaling complex that activates caspase-2 under genotoxic stress, whereby the PIDDosome can act as a sensor for DNA damage (Tinel and Tschopp 2004; Bouchier-Hayes and Green 2012; Janssens and Tinel. 2012; Manzl et al. 2012; McCoy

et al. 2012; Jang et al. 2013). This platform consists of PIDD (p53-induced protein with a death domain/DD), RAIDD (receptor-interacting protein/RIP-associated ICH-1/CED-3 homologous protein with a death domain/DD), and procaspase-2 and is capable to activate caspase-2 via interaction of the partners in the complex. Assembly of the PIDDosome is accomplished by PIDD mediating and stabilizing the interaction between RAIDD and caspase-2. Caspase-2 CARD is an insoluble protein that is solubilized by its binding partner, RAIDD CARD (Jang and Park 2013). Depending on the differential activation of its components, the PIDDosome can exert various functions. Specifically, the PIDD component can operate as a switch for signaling either to cell survival or cell death. This PIDD switch functions in relation to the phosphorylation status of the PIDD death domain. Phosphorylation by ATM/Tel1 (ataxia telangiectasia mutated), a conserved phosphatidylinositol 3-kinase (PIKK) that acts in response to DNA damage and regulates telomere maintenance, results in RAIDD binding, caspase-2 activation, and cell death, while the non-phosphorylated state of PIDD fails in caspase-2 activation and engages prosurvival RIP1 (Ando et al. 2012).

MyDDosome

The so-called MyDDosome (or Myddosome) is a protein complex involved in signaling by Toll-like receptors/TLRs and the interleukin-1 superfamily, a signaling cascade critically involved in innate immunity. This signaling requires the adaptor protein, myeloid differentiation primary response protein 88/MyD88. MyD88 is a component of the MyDDosome, together with IRAK kinases, MyDD adaptor-like, and TRIF-related adaptor molecule (Motshwene et al. 2009; George et al. 2011; review: Gay et al. 2011). The central complex of the MyDDosome is formed by a helical assembly of the MyD88-IRAK4-IRAK2 complex. In this complex, MyD88 recruits IRAK4, and the MyD88-IRAK4 complex recruits the IRAK4 substrates IRAK2 or the related IRAK1 (Lin et al. 2010). The significance of MyD88 in innate immunity is illustrated by the observation that individuals with rare MyD88 point mutations suffer from life-threatening infections.

References

Ahn JH, Yu HK, Lee HJ, Hong SW, Kim SJ, Kim JS (2014) Suppression of colorectal cancer liver metastasis by apolipoprotein(a) kringle V in a nude mouse model through the induction of apoptosis in tumor-associated endothelial cells. PLoS One 9:e93794

Allen JE, Saroya BS, Kunkel M, Dicker DT, Das A, Peters KL, Joudeh J, Zhu J, El-Deiry WS (2014) Apoptotic circulating tumor cells (CTCs) in the peripheral blood of metastatic colorectal cancer patients are associated with liver metastasis but not CTCs. Oncotarget 5:1753–1760

Ando K, Kernan JL, Liu PH, Sanda T, Logette E, Tschopp J, Look AT, Wang J, Bouchier-Hayes L et al (2012) PIDD death-domain phosphorylation by ATM controls prodeath versus prosurvival PIDDosome signaling. Mol Cell 47:681–693

Andrés-Pons A, Gil A, Oliver MD, Sotelo NS, Pulido R (2012) Cytoplasmic p27Kip1 counteracts the pro-apoptotic function of the open conformation of PTEN by retention and destabilization of PTEN outside of the nucleus. Cell Signal 24:577–587

Augello C, Caruso L, Maggioni M, Donadon M, Montorsi M, Santambrogio R, Torzilli G et al (2009) Inhibitors of apoptosis proteins (IAPs) expression and their prognostic significance in hepatocellular carcinoma. BMC Cancer 9:125

Baddour N, Farrag E, Zeid A, Bedewy E, Taher Y (2013) Decreased apoptosis in advanced-stage/high-grade hepatocellular carcinoma complicating chronic hepatitis C is mediated through the downregulation of p21 ras. Chin J Cancer Res 25:281–288

Balci-Peynircoiglu B, Waite AL, Hu C, Richards N, Staubach-Grosse A, Yilmaz E, Gumucio DL (2008) Pyrin, product of the MEFV locus, interacts with the proapoptotic protein. Siva J Cell Physiol 216:595–602

Banerjee S, de Freitas A, Friggeri A, Zmijewski JW, Liu G, Abraham E (2011) Intracellular HMGB1 negatively regulates efferocytosis. J Immunol 187:4686–4694

Bao ST, Gui SQ, Lin MS (2006) Relationship between expression of Smac and survivin and apoptosis of primary hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 5:580–583

Biermann M, Maueröder C, Brauner JM, Chaurio R, Janko C, Herrmann M, Muñoz LE (2013) Surface code – biophysical signals for apoptotic cell clearance. Phys Biol 10:065007

Boland K, Flanagan L, Prehn JHM (2013) Paracrine control of tissue regeneration and cell proliferation by caspase-3. Cell Death Dis 4:e725

Bouchier-Hayes L, Green DR (2012) Caspase-2: the orphan caspase. Cell Death Differ 19:51–57

Bouchier-Hayes L, Conroy H, Egan H, Adrain C, Creagh EM, MacFarlane M, Martin SJ (2001) CARDINAL, a novel caspase recruitment domain protein, is an inhibitor of multiple NF-kappa B activation pathways. J Biol Chem 276:44069–44077

Bouchon A, Dietrich J, Colonna M (2000) Cutting edge: inflammatory responses can be triggered by TREM-1, a novel receptor expressed on neutrophils and monocytes. J Immunol 164:4991–4995

Brault C, Levy PL, Bartosch B (2013) Hepatitis C virus-induced mitochondrial dysfunctions. Viruses 5:954–980

Cadamuro M, Nardo G, Indraccolo S, Dall'olmo L, Sambado L, Moserle L, Franceschet I, Colledan M, Massani M et al (2013) Platelet-derived growth factor-D and Rho GTPases regulate recruitment of cancer-associated fibroblasts in cholangiocarcinoma. Hepatology 58:1042–1053

Cai M, Chen Q, Chen C, Liu X, Hou J, Zeng C, Shu Q, Fang X (2013) Activation of triggering receptor expressed on myeloid cells-1 protects monocyte from apoptosis through regulation of myeloid cell leukemia-1. Anesthesiology 118:1140–1149

Capece D, Fischietti M, Verzella D, Gaggiano A, Cicciarelli G, Tessitore A, Zazzeroni F, Alesse E (2013) The inflammatory microenvironment in hepatocellular carcinoma: a pivotal role for tumor-associated macrophages. Biomed Res Int 2013:187204

Cecconi F (1999) Apaf1 and the apoptotic machinery. Cell Death Differ 6:1087–1098

Celli A, Que FG (1998) Dysregulation of apoptosis in the cholangiopathies and cholangiocarcinoma. Semin Liver Dis 18:177–185

Chan BC, Ching AK, To KF, Leung JC, Chen S, Li Q, Lai PB, Tang NL, Shaw PC et al (2008) BRE is an antiapoptotic protein in vivo and overexpressed in human hepatocellular carcinoma. Oncogene 27:1208–1217

Chang Y, Wang SX, Wang YB, Zhou J, Li WH, Wang N, Fang DF, Li HY, Li AL et al (2013) ECHS1 interacts with STAT3 and negatively regulates STAT3 signaling. FEBS Lett 587:607–613

Charlotte F, L'Herminé A, Martin N, Geleyn Y, Nollet M, Gaulard P, Zafrani ES (1994) Immunohistochemical detection of bcl-2 protein in normal and pathological human liver. Am J Pathol 144:460–465

Chau GY, Lee AF, Tsay SH, Ke YR, Kao HL, Wong FH, Tsou AP, Chau YP (2007) Clinicopathological significance of surviving expression in patients with hepatocellular carcinoma. Histopathology 51:204–218

Chekeni FB, Elliott MR, Sandilos JK, Walk SF, Kinchen JM, Lazarowski ER, Armstrong AJ et al (2010) Pannexin 1 channels mediate 'find-me' signal release and membrane permeability during apoptosis. Nature 467:863–867

Chen GG, Lai PB, Chan PK, Chak EC, Yip JH, Ho RL, Leung BC, Lau WY (2001) Decreased expression of Bid in human hepatocellular carcinoma is related to hepatitis B virus X protein. Eur J Cancer 37:1695–1702

Chen XP, He SQ, Wang HP, Zhao YZ, Zhang WG (2003) Expression of TNF-related apoptosis-inducing ligand receptors and antitumor effects of TNF-related apoptosis-inducing ligand in human hepatocellular carcinoma. World J Gastroenterol 9:2433–2440

Cho S, Lee JH, Cho SB, Yoon KW, Park SY, Lee WS, Park CH, Joo YE, Kim HS et al (2010) Epigenetic methylation and expression of caspase 8 and survivin in hepatocellular carcinoma. Pathol Int 60:203–211

Councilman WT (1890) Report on etiology and prevention of yellow fever. Public Health Bull 2:151–159

Czabotar PE, Colman PM, Huang DC (2009) Bax activation by Bim? Cell Death Differ 16:1187–1191

Deng L, Chen N, Li Y, Zheng H, Lei Q (2010) CXCR6/CXCL16 functions a s a regulator in metastasis and progression of cancer. Biochim Biophys Acta 1806:42–49

Dickens LS, Powley IR, Hughes MA, MacFarlane M (2012) The 'complexities' of life and death: death receptor signalling platforms. Exp Cell Res 318:1269–1277

Diez-Roux G, Argilla M, Makarenkova H, Ko K, Lang RA (1999) Macrophages kill capillary cells in G1 phase of the cell cycle during programmed vascular regression. Development 126:2141–2147

Duan M, Wang ZC, Wang XY, Shi JY, Yang LX, Ding ZB, Gao Q, Zhou J, Fan J (2015) TREM-1, an inflammatory modulator, is expressed in hepatocellular carcinoma cells and significantly promotes tumor progression. Ann Surg Oncol 22:3121–3129

Duprez L, Wirawan E, Vanden Berghe T, Vandenabeele P (2009) Major cell death pathways at a glance. Microbes Infect 11:1050–1062

El-Emshaty HM, Saad EA, Toson EA, Abdel Malak CA, Gadelhak NA (2014) Apoptosis and cell proliferation: correlation with BCL-2 and P53 oncoprotein expression in human hepatocellular carcinoma. Hepatogastroenterology 61:1393–1401

Elgohary N, Pellegrino R, Neumann O, Elzawahry HM, Saber MM, Zeeneldin AA, Geffers R, Ehemann V et al (2015) Protumorigenic role of Timeless in hepatocellular carcinoma. Int J Oncol 46:597–606

Elliott MR, Chekeni FB, Trampont PC, Lazarowski ER, Kadl A, Walk SF, Park D et al (2009) Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature 461:282–286

Elmore S (2007) Apoptosis: a review of programmed cell death. Toxicol Pathol 35:495–516

Fabregat I (2009) Dysregulation of apoptosis in hepatocellular carcinoma cells. World J Gastroenterol 15:513–520

Fadeel B, Orrenius S, Pervaiz S (2004) Buried alive: a novel approach to cancer treatment. FASEB J 18:1–4

Fairbrother WJ, Gordon NC, Humke EW, O'Rourke KM, Starovasnik MA, Yin JP et al (2001) The PYRIN domain: a member of the death domain-fold superfamily. Protein Sci 10:1911–1918

Feoktistova M, Geserick P, Kellert B, Dimitrova DP, Langlais C, Hupe M, Cain K, MacFarlane M

et al (2011) cIAPs block ripoptosome formation, a RIP1/caspase-8 containing intracellular cell death complex differentially regulated by cFLIP isoforms. Mol Cell 43:449–463

Feoktistova M, Geserick P, Panayotova-Dimitrova D, Leverkus M (2012) Pick your poison: the ripoptosome, a cell death platform regulating apoptosis and necroptosis. Cell Cycle 11:460–467

Fields AC, Cotsonis G, Sexton D, Santoianni R, Cohen C (2004) Survivin expression in hepatocellular carcinoma: correlation with proliferation, prognostic parameters, and outcome. Mod Pathol 17:1378–1385

Fietta P (2006) Many ways to die: passive and active cell death styles. Riv Biol 99:69–83

Fingas CD, Bronk SF, Werneburg NW, Mott JL, Guicciardi ME, Cazanave SC, Mertens JC et al (2011) Myofibroblast-derived PDGF-BB promotes Hedgehog survival signaling in cholangiocarcinoma cells. Hepatology 54:2076–2088

Fingas CD, Altinbas A, Schlattjan M, Beilfuss A, Sowa JP, Sydor S, Bechmann LP et al (2013) Expression of apoptosis- and vitamin D pathway-related genes in hepatocellular carcinoma. Digestion 87:176–181

Fink SL, Cookson BT (2005) Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. Infect Immun 73:1907–1916

Flanagan L, Sebastia J, Tuffy LP, Spring A, Lichawska A, Devocelle M, Prehn JH et al (2010) XIAP impairs Smac release from the mitochondria during apoptosis. Cell Death Dis 1:e49

Frasch SC, Fernandez-Boyanapalli RF, Berry KZ, Leslie CC, Bonvehtre JV, Murphy RC et al (2011) Signaling via macrophage G2A enhances efferocytosis of dying neutrophils by augmentation of Rac activity. J Biol Chem 286:12108–12122

Fu DZ, Cheng Y, He H, Liu HY, Liu YF (2014) The fate of Krüppel-like factor 9-positive hepatic carcinoma cells may be determined by the programmed cell death protein 5. Int J Oncol 44:153–160

Fujikawa K, Shiraki K, Sugimoto K, Ito T, Yamanaka T, Takase K, Nakao T (2000) Reduced expression of ICE/caspase1 and CPP32/caspase3 in human hepatocellular carcinoma. Anticancer Res 20:1927–1932

Fukuzawa K, Takahashi K, Furuta K, Tagaya T, Ishikawa T, Wada K, Omoto Y, Koji T et al (2001) Expression of Fas/Fas ligand (FasL) and its involvement in infiltrating lymphocytes in hepatocellular carcinoma (HCC). J Gastroenterol 36:681–688

Fullard JF, Kale A, Baker NE (2009) Clearance of apoptotic corpses. Apoptosis 14:1029–1037

Galdiero MR, Garlanda C, Jaillon S, Marone G, Mantovani A (2013) Tumor associated macrophages and neutrophils in tumor progression. J Cell Physiol 228:1404–1412

Galluzzi L, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV, Dawson TM et al (2012) Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ 19:107–120

Gao P, Wang R, Shen JJ, Lin F, Wang X, Dong K, Zhang HZ (2008) Hypoxia-inducible enhancer/alpha-fetoprotein promoter-driven RNA interference targeting STK15 suppresses proliferation and induces apoptosis in human hepatocellular carcinoma cells. Cancer Sci 99:2209–2217

Gao, Liu 2014. http://www.ncbi.nlm.nih.gov/pubmed/25312821

Gay NJ, Gangloff M, O'Neill LA (2011) What the Myddosome structure tells us about the initiation of innate immunity. Trends Immunol 32:104–109

Geng L, Chaudhuri A, Talmon G, Wisecarver JL, Are C, Brattain M, Wang J (2014) MicroRNA-192 suppresses liver metastasis of colon cancer. Oncogene 33:5332–5340

George J, Motshwene PG, Wang H, Kubarenko AV, Rautanen A, Mills TC, Hill AV et al (2011) Two human MYD88 variants, S34Y and R98C., interfere with MyD88-IRAK4-myddosome assembly. J Biol Chem 286:1341–1353

Gibot S (2006) Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia and severe sepsis. Semin Respir Crit Care Med 27:29–33

Gressner AM (1998) The cell biology of liver fibrogenesis – an imbalance of proliferation, growth arrest and apoptosis of myofibroblasts. Cell Tissue Res 292:447–452

Guo H, Nan K, Hu T, Meng J, Hui W, Zhang X, Qin H, Sui C (2010) Prognostic significance of co-expression of nm23 and p57 protein in hepatocellular carcinoma. Hepatol Res 40:1107–1116

Guzik K, Potempa J (2008) Friendly fire against neutrophils: proteolytic enzymes confuse the recognition of apoptotic cells by macrophages. Biochimie 90:405–415

Guzik K, Brzowska M, Smagur J, Krupa O, Sieprawska M, Travis J, Potempa J (2007) A new insight into phagocytosis of apoptotic cells: proteolytic enzymes divert the recognition and clearance of polymorphonuclear leukocytes by macrophages. Cell Death Differ 14:171–182

Hamazaki K, Gochi A, Matsubara N, Mori M, Orita K (1995) Expression of fas antigen and Bcl-2 protein in hepatocellular carcinoma. Acta Med Okayama 49:227–230

Hammam O, Mahmoud O, Zahran M, Aly S, Hosny K, Helmy A, Anas A (2012) The role of fas/fas ligand system in the pathogenesis of liver cirrhosis and hepatocellular carcinoma. Hepat Monit 12:e6132

Hang HL, Xia Q (2014) Role of BMSCs in liver regeneration and metastasis after hepatectomy. World J Gastroenterol 20:126–132

Harnois DM, Que FG, Celli A, LaRusso NF, Gores GJ (1997) Bcl-2 is overexpressed and alters the threshold for apoptosis in a cholangiocarcinoma cell line. Hepatology 26:884–890

Hayes AJ, Huang WQ, Mallah J, Yang D, Lippman ME, Li LY (1999) Angiopoietin-1 and its receptor Tie-2 participate in the regulation of capillary-like tubule

formation and survival of endothelial cells. Microvasc Res 58:224–237
Herzer K, Grosse-Wilde A, Krammer PH, Galle PR, Kanzler S (2008) Transforming growth factor-beta-mediated tumor necrosis factor-related apoptosis-inducing ligand expression and apoptosis in hepatoma cells requires functional cooperation between Smad proteins and activator protein-1. Mol Cancer Res 6:1169–1177
Higaki K, Yano H, Kojiro M (1996) Fas antigen expression and its relationship with apoptosis in human hepatocellular carcinoma and noncancerous tissues. Am J Pathol 149:429–437
Hino N, Higashi T, Nouso K, Nakatsukasa H, Tsuji T (1996) Apoptosis and proliferation of human hepatocellular carcinoma. Liver 16:123–129
Ho CC, Liao WY, Wang CY, Lu YH, Huang HY, Chen HY, Chan WK, Chen HW, Yang PC (2008) TREM-1 expression in tumor-associated macrophages and clinical outcome in lung cancer. Am J Respir Crit Care Med 177:763–770
Hochreiter-Hufford A, Ravichandran KS (2013) Clearing the dead: apoptotic cell sensing, recognition, engulfment, and digestion. Cold Spring Harb Perspect Biol 5: a008748
Höpker K, Hagmann H, Khurshid S, Chen S, Schermer B, Benzing T, Reinhardt HC (2012) Putting the brakes on p53-driven apoptosis. Cell Cycle 11:4122–4128
Hu et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/20971978
Ikeguchi M, Ueda T, Sakatani T, Hirooka Y, Kaibara N (2002) Expression of survivin messenger RNA correlates with poor prognosis in patients with hepatocellular carcinoma. Diagn Mol Pathol 11:33–40
Ikeguchi M, Oi K, Hirooka Y, Kaibara N (2004) CD8+ lymphocytes infiltration and apoptosis in hepatocellular carcinoma. Eur J Surg Oncol 30:53–57
Imre G, Larisch S, Rajalingam K (2011) Ripoptosome: a novel IAP-regulated cell death-signalling platform. J Mol Cell Biol 3:324–326
Ito Y, Takeda T, Umeshita K, Sakon M, Wakasa K, Matsuura N, Monden M (1998) Fas antigen expression in hepatocellular carcinoma tissues. Oncol Rep 5:41–44
Ito Y, Monden M, Takeda T, Eguchi H, Umeshita K, Nagano H, Nakamori S, Dono K et al (2000a) The status of Fas and Fas ligand expression can predict recurrence of hepatocellular carcinoma. Br J Cancer 82:1211–1217
Ito Y, Takeda T, Sasaki Y, Sakon M, Yamada T, Ishiguro S, Imaoka S, Tsujimoto M et al (2000b) Expression of Fas and Fas ligand reflects the biological characteristics but not the status of apoptosis of intrahepatic cholangiocellular carcinoma. Int J Mol Med 6:581–586
Ito Y, Takeda T, Sasaki Y, Sakon M, Monden M, Yamada T, Ishiguro S, Imaoka S et al (2000c) Bcl-2 expression in cholangiocellular carcinoma is inversely correlated with biologically aggressive phenotypes. Oncology 59:63–67
Jang TH, Park HH (2013) PIDD mediates and stabilizes the interaction between RAIDD and caspase-2 for the PIDDosome assembly. BMB Rep 46:471–476
Jang TH, Seo EK, Park HH (2013) Analysis of mutation effect on PIDDosome core complex. Appl Biochem Biotechnol 170:210–218
Janssens S, Tinel A (2012) The PIDDosome. DNA-damage-induced apoptosis and beyond. Cell Death Differ 19:13–20
Javle MM, Tan D, Yu J, LeVea CM, Li F, Kuvshinoff BW, Gibbs JF (2004) Nuclear survivin expression predicts poor outcome in cholangiocarcinoma. Hepatogastroenterology 51:1653–1657
Jhala NC, Vickers SM, Argani P, McDonald JM (2005) Regulators of apoptosis in cholangiocarcinoma. Arch Pathol Lab Med 129:481–486
Jimenez B, Volpert OV, Crawford SE, Febbraio M, Silverstein RL, Bouck N (2000) Signals leading to apoptosis-dependent inhibition of neovascularization by thrombospondin-1. Nat Med 6:41–48
Kannangai R, Wang J, Liu QZ, Sahin F, Torbenson M (2005) Survivin overexpression in hepatocellular carcinoma is associated with p53 dysregulation. Int J Gastrointest Cancer 35:53–60
Karagiannis GS, Poutahidis T, Erdman SE, Kirsch R, Riddell RH, Diamandis EP (2012) Cancer-associated fibroblasts drive the progression of metastasis through both paracrine and mechanical pressure on cancer tissue. Mol Cancer Res 10:1403–1418
Karamitopoulou E, Cioccari L, Jakob S, Vallan C, Schaffner T, Zimmermann A, Brunner T (2007) Active caspase 3 and DNA fragmentation as markers for apoptotic cell death in primary and metastatic liver tumours. Pathology 39:558–564
Kebers F, Lewalle JM, Desreux J, Munaut C, Devy L, Foidart JM, Noel A (1998) Induction of endothelial cell apoptosis by solid tumor cells. Exp Cell Res 240:197–205
Kee JY, Ito A, Hojo S, Hashimoto I, Igarashi Y, Tsukada K, Irimura T, Shibahara N, Nakayama T, Yoshie O, Sakurai H et al (2013) Chemokine CXCL16 suppresses liver metastasis of colorectal cancer via augmentation of tumor-infiltrating natural killer T cells in a murine model. Oncol Rep 29:975–982
Kee JY, Ito A, Hojo S, Hashimoto I, Igarashi Y, Tsuneyama K, Tsukada K, Irimura T, Shibahara N, Takasaki I, Inujima A et al (2014) CXCL16 suppresses liver metastasis of colorectal cancer by promoting TNF-α-induced apoptosis by tumor-associated macrophages. BMC Cancer 14:949
Kersse K, Verspurten J, Vanden Berghe T, Vandenabeele P (2011) The death-fold superfamily of homotypic interaction motifs. Trends Biochem Sci 36:541–552
Kim SH, Ricci MS, El-Deiry WS (2008) Mcl-1. a gateway to TRAIL sensitization. Cancer Res 68:2062–2064
Kim S, Bae DJ, Hong M, Park SY, Kim IS (2010) The conserved histidine in epidermal growth factor-like

domains of stabilin-2 modulates pH-dependent recognition of phosphatidylserine in apoptotic cells. Int J Biochem Cell Biol 42:1154–1163

Kim EY, Ryu JH, Kim AK (2013) CAPE promotes TRAIL-induced apoptosis through the upregulation of TRAIL receptors via activation of p38 and suppression of JNK in SK-Hep1 hepatocellular carcinoma cells. Int J Oncol 43:1291–1300

Kiss RS, Ma Z, Nakada-Tsukui K, Brugnera E, Vassilou G, McBride HM, Ravichandran KS, Marcel YL (2006) The lipoprotein receptor-related protein-1 (LRP) adapter protein GULP mediates trafficking of the LRP ligand prosaposin, leading to sphingolipid and free cholesterol accumulation in late endosomes and impaired efflux. J Biol Chem 281:12081–12092

Koizumi K, Hojo S, Akashi T, Yasumoto K, Saiki I (2007) Chemokine receptors in cancer metastasis and cancer cell-derived chemokines in host immune response. Cancer Sci 98:1652–1658

Kong D, Zhao L, Du Y, He P, Zou Y, Yang L, Sun L, Wang H, Xu D, Meng X, Sun X (2014) Overexpression of GRIM-19, a mitochondrial respiratory chain complex I protein, suppresses hepatocellular carcinoma growth. Int J Clin Exp Pathol 7:7497–7507

Koschny R, Brost S, Hinz U, Sykora J, Batke EM, Singer S, Breuhahn K, Stremmel W et al (2013) Cytosolic and nuclear caspase-8 opposite impact on survival after liver resection for hepatocellular carcinoma. BMC Cancer 13:532

Kountouras J, Zavos C, Chatzopoulos D (2003) Apoptosis in hepatocellular carcinoma. Hepatogastroenterology 50:242–249

Kroemer G, Galluzzi L, Vandenabeele P, Abrams J, Alnemri ES, Baehrecke EH, Blagosklonny MV et al (2009) Classification of cell death: recommendations of the Nomenclature Committee on cell Death 2009. Cell Death Differ 16:3–11

Kuang DM, Peng C, Zhao Q, Wu Y, Chen MS, Zheng L (2010) Activated monocytes in peritumoral stroma of hepatocellular carcinoma promote expansion of memory T helper 17 cells. Hepatology 51:154–164

Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L (2011) Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol 54:948–955

Kubo K, Matsuzaki Y, Okazaki M, Kato A, Kobayashi N, Okita K (1998) The Fas system is not significantly involved in apoptosis in human hepatocellular carcinoma. Liver 18:117–123

Kykalos S, Dimitroulis D, Ntikoudi E, Karayiannakis A (2013) The clinical significance of apoptosis and M30 expression in colonic cancer progression. J Recept Signal Transduct Res 33:255–259

Kzhyshkowska J (2010) Multifunctional receptor stabilin-1 in homeostasis and disease. Sci World J 10:2039–2053

Langley RE, Bump EA, Quartuccio SG, Medeiros D, Braunhut SJ (1997) Radiation-induced apoptosis in microvascular endothelial cells. Br J Cancer 75:666–672

Larochelle S, Langlois C, Thibault I, Lopez-Vallé CA, Roy M, Moulin V (2004) Sensitivity of myofibroblasts to H2O2-mediated apoptosis and their antioxidant cell network. J Cell Physiol 200:263–271

Lavrik IN, Krammer PH (2012) Regulation of CD95/Fas signaling at the DISC. Cell Death Differ 19:36–41

Lee SH, Shin MS, Lee HS, Bae JH, Lee HK, Kim HS, Kim SY, Jang JJ, Joo M et al (2001) Expression of Fas and Fas-related molecules in human hepatocellular carcinoma. Hum Pathol 32:250–256

Lee WC, Yu MC, Chen MF (2004) Prognostic impact of Fas ligand on hepatocellular carcinoma after hepatectomy. World J Surg 28:792–796

Lee SJ, So IS, Park SY, Kim IS (2008) Thymosin beta4 is involved in stabilin-2-mediated apoptotic cell engulfment. FEBS Lett 582:2161–2166

Lee WS, Park YL, Kim N, Oh HH, Son DJ, Kim MY, Oak CY, Chung CY, Park HC, Kim JS, Myung DS, Cho SB et al (2014) Myeloid cell leukemia-1 is associated with tumor progression by inhibiting apoptosis and enhancing angiogenesis in colorectal cancer. Am J Cancer Res 5:101–113

Leers MP, Björklund V, Björklund B, Jörnvall H, Nap M (2002) An immunohistochemical study of the clearance of apoptotic cellular fragments. Cell Mol Life Sci 59:1358–1365

Lemke G (2013) Biology of the TAM receptors. Cold Spring Harb Perspect Biol 5:a009076

Li ZY, Zou SQ (2001) Fas counterattack in cholangiocarcinoma: a mechanism for immune evasion in human hilar cholangiocarcinomas. World J Gastroenterol 7:860–863

Li R, Oteiza A, Sorensen KK, McCourt P, Olsen R, Smedsrod B, Svistounov D (2011) Role of liver sinusoidal endothelial cells and stabilins in elimination of oxidized density lipoproteins. Am J Physiol Gastrointest Liver Physiol 300:G71–G81

Li G, Chang H, Zhai YP, Xu W (2013) Targeted silencing of inhibitors of apoptosis proteins with siRNAs: a potential anti-cancer strategy for hepatocellular carcinoma. Asian Pac J Cancer Prev 14:4943–4952

Li D, Liu Y, Peng JJ, Tan Y, Zou Q, Song XF, Du M, Yang ZH, Tan Y, Zhou JJ, Xu T, Fu ZQ, Feng JQ et al (2015a) MicroRNA1 promotes apoptosis of hepatocarcinoma cells by targeting apoptosis inhibitor-5 (API-5). FEBS Lett 589:68–76

Li XF, Chen DP, Ouyang FZ, Chen MM, Wu Y, Kuang DM, Zheng L (2015b) Increased autophagy sustains the survival and pro-tumourigenic effects of neutrophils in human hepatocellular carcinoma. J Hepatol 62:131–139

Liao R, Sun TW, Yi Y, Wu H, Li YW, Wang JX, Zhou J, Shi YH, Cheng YF, Qiu SJ, Fan J (2012) Expression of TREM-1 in hepatic stellate cells and prognostic value in hepatitis B-related hepatocellular carcinoma. Cancer Sci 103:984–992

Lin SC, Lo YC, Wu H (2010) Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL-1R signalling. Nature 465:885–890

Lin et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/25425543

Liu W, Lin YT, Yan XL, Ding YL, Wu YL, Chen WN, Lin X (2014a) Hepatitis B virus core protein inhibits Fas-mediated apoptosis of hepatoma cells via regulation of mFas/FasL and sFas expression. FASEB J pii:fj.14–263822

Liu N, Jiao T, Huang Y, Liu W, Li Z, Ye X (2014b) HBV regulates apoptosis and tumorigenesis through miR15a-Smad7-TGF-β pathway. J Virol pii: JVI.02784–14

Mace PD, Riedl SJ (2010) Molecular cell death platforms and assemblies. Curr Opin Cell Biol 22:828–836

MacFarlane M (2003) TRAIL-induced signalling and apoptosis. Toxicol Lett 139:89–97

Maemura K, Yoshikawa H, Yokoyama K, Ueno T, Kurose H, Uchiyama K, Otsuki Y (2013) Delta-like 3 is silenced by methylation and induces apoptosis in human hepatocellular carcinoma. Int J Oncol 42:817–822

Mann B, Gratchev A, Böhm C, Hanski ML, Foss HD, Demel G, Trojanek B, Schmidt-Wolf I, Stein H, Riecken EO et al (1999) FasL is more frequently expressed in liver metastases of colorectal cancer than in matched primary carcinomas. Br J Cancer 79:1262–1269

Manzl C, Peintner L, Krumschnabel G, Bock F, Labi V, Drach M, Newbold A, Johnstone R et al (2012) PIDDosome-independent tumor suppression by caspase-2. Cell Death Differ 19:1722–1732

Martinez MM, Reif RD, Pappas D (2010) Detection of apoptosis: a review of conventional and novel techniques. Anal Methods 2:996–1004

Maxwell SA, Capp D, Acosta SA (1997) Telomerase activity in immortalized endothelial cells undergoing p53-mediated apoptosis. Biochem Biophys Res Commun 241:642–645

McCoy F, Eckard L, Nutt LK (2012) Janus-faced PIDD: a sensor for DNA damage-induced cell death or survival ? Mol. Cell 47:667–668

Mérino D, Giam M, Hughes PD, Siggs OM, Heger K, O'Reilly LA, Adams JM, Strasser A et al (2009) The role of BH3-only protein Bim extends beyond inhibiting Bcl-2-like prosurvival proteins. J Cell Biol 186:355–362

Mertens JC, Fingas CD, Christensen JD, Smoot RL, Bronk SF, Werneburg NW et al (2013) Therapeutic effects of deleting cancer-associated fibroblasts in cholangiocarcinoma. Cancer Res 73:897–907

Miao HL, Lei CJ, Qiu ZD, Liu ZK, Li R, Bao ST, Li MY (2014) MicroRNA-520c-3p inhibits hepatocellular carcinoma cell proliferation and invasion through induction of cell apoptosis by targeting glypican-3. Hepatol Res 44:338–348

Mille F, Thibert C, Fombonne J, Rama N, Guix C, Hayashi H, Corset V, Reed JC et al (2009) The Patched dependence receptor triggers apoptosis through a DRAL-caspase-9 complex. Nat Cell Biol 11:739–746

Mondal S, Ghosh-Roy S, Loison F, Li Y, Jia Y, Harris C, Williams DA, Luo HR (2011) PTEN negatively regulates engulfment of apoptotic cells by modulating activation of RAC GTPase. J Immunol 187:5783–5794

Moon WS, Tarnawski AS (2003) Nuclear translocation of survivin in hepatocellular carcinoma: a key to cancer cell growth? Hum Pathol 34:1119–1126

Motshwene PG, Moncrieffe MC, Grossmann JG, Kao C, Ayaluru M, Sanderock AM et al (2009) An oligomeric signaling platform formed by the Toll-like receptor signal transducers MyD88 and IRAK-4. J Biol Chem 284:25404–25411

Nakajima W, Tanaka N (2011) Noxa induces apoptosis in oncogene-expressing cells through catch-and-release mechanism operating between Puma and Mcl-1. Biochem Biophys Res Commun 413:643–648

Natoli G, Ianni A, Costanzo A, De Petrillo G, Ilari I, Chirillo P, Balsano C, Levrero M (1995) Resistance to Fas-mediated apoptosis in human hepatoma cells. Oncogene 11:1157–1164

Nguyen KQ, Tsou WI, Kotenko S, Birge RB (2013) TAM receptors in apoptotic cell clearance, autoimmunity, and cancer. Autoimmunity 46:294–297

Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N (2013) Crosstalk between apoptosis, necrosis and autophagy. Biochim Biophys Acta 1833:3448–3459

Notarbartolo M, Cervello M, Giannitrapani L, Meli M, Poma P, Dusonchet L, Montalto G, D'Alessandro N (2004) Expression of IAPs and alternative splice variants in hepatocellular carcinoma tissues and cells. Ann N Y Acad Sci 1028:289–293

Okano H, Shiraki K, Inoue H, Kawakita T, Saitou Y, Enokimura N, Yamamoto N, Sugimoto K et al (2003) Over-expression of Smac promotes TRAIL-induced cell death in human hepatocellular carcinoma. Int J Mol Med 12:25–28

Okaro AC, Deery AR, Hutchins RR, Davidson BR (2001) The expression of antiapoptotic proteins Bcl-2, Bcl-X (L), and Mcl-1 in benign, dysplastic, and malignant biliary epithelium. J Clin Pathol 54:927–932

Op de Beeck K, Van Camp G, Thys S, Cools N, Callebaut I, Vrijens K, Van Nassauw L et al (2011) The DFNA5 gene, responsible for hearing loss and involved in cancer, encodes a novel apoptosis-inducing protein. Eur J Hum Genet 19:965–973

Ormsby T, Schlecker E, Ferdin J, Tessarz AS, Angelisova P, Köprülü AD, Borte M, Warnatz K, Schulze I, Ellmeier W et al (2011) Btk is a positive regulator in the TREM-1/DAP12 signaling pathway. Blood 118:936–945

Otera, Mihara 2012. http://www.ncbi.nlm.nih.gov/pubmed/22536251

Ozaki I, Hamajima H, Matsuhashi S, Mizuta T (2011) Regulation of TGF-b1-induced pro-apoptotic signaling by growth factor receptors and extracellular matrix receptor integrins in the liver. Front Physiol 2:78

Paiva C, Oshima CT, Lanzoni VP, Forones NM (2002) Apoptosis, PCNA and p53 in hepatocellular carcinoma. Hepatogastroenterology 49:1058–1061

Palani S, Maksimow M, Miiluniemi M, Auvinen K, Jalkanen S, Salmi M (2011) Stabilin-1/CLEVER-1 a type 2 macrophage marker, is an adhesion and scavenging molecule on human placental macrophages. Eur J Immunol 41:2052–2063

Pan G, Vickers SM, Pickens A, Phillips JO, Ying W, Thompson JA, Siegal GP, McDonald JM (1999) Apoptosis and tumorigenesis in human cholangiocarcinoma cells. Involvement of Fas/APO-1 (CD95) and calmodulin. Am J Pathol 155:193–203

Pan Z, Chen C, Long H, Lei C, Tang G, Li L, Feng J, Chen F (2013) Overexpression of GPC3 inhibits hepatocellular carcinoma cell proliferation and invasion through induction of apoptosis. Mol Med Rep 7:969–974

Park HH (2012) Structural features of caspase-activating complexes. Int J Mol Sci 13:4807–4818

Park SY, Kang KB, Thapa N, Kim SY, Lee SJ, Kim IS (2008) Requirement of adaptor protein GULP during stabilin-2-mediated cell corpse engulfment. J Biol Chem 283:10593–10600

Park SY, Jung MY, Lee SJ, Kang KB, Gratchev A, Riabov V, Kzhyshkowska J, Kim IS (2009) Stabilin-1 mediates phosphatidylserine-dependent clearance of cell corpses in alternatively activated macrophages. J Cell Sci 122:3365–3373

Park SY, Kim SY, Kang KB, Kim IS (2010) Adaptor protein GULP is involved in stabilin-1-mediated phagocytosis. Biochem Biophys Res Commun 398:467–472

Peeters CF, de Waal RM, Wobbes T, Westphal JR, Ruers TJ (2006) Outgrowth of human liver metastases after resection of the primary colorectal tumor: a shift in the balance between apoptosis and proliferation. Int J Cancer 119:1249–1253

Persad R, Liu C, Wu TT, Houlihan PS, Hamilton SR, Diehl AM, Rashid A (2004) Overexpression of caspase-3 in hepatocellular carcinomas. Mod Pathol 17:861–867

Pontisso P (2014) Role of SERPINB3 in hepatocellular carcinoma. Ann Hepatol 13:722–727

Preaux AM, D'Ortho MP, Bralet MP, Laperche Y, Mavier P (2002) Apoptosis of human hepatic myofibroblasts promotes activation of matrix metalloproteinase-2. Hepatology 36:615–622

Qi JH, Anand-Apte B (2015) Tissue inhibitor of metalloproteinase-3 (TIMP3) promotes endothelial apoptosis via a caspase-independent mechanism. Apoptosis 20:523–534

Ravichandran KS, Lorenz U (2007) Engulfment of apoptotic cells: signals for a good meal. Nat Rev Immunol 7:964–974

Rawat S, Clippinger AJ, Bouchard MJ (2012) Modulation of apoptotic signaling by the hepatitis B virus X protein. Viruses 4:2945–2972

Razon MJ, Kräling BM, Mulliken JB, Bischoff J (1998) Increased apoptosis coincides with onset of involution in infantile hemangioma. Microcirculation 5:189–195

Resch U, Schichl YM, Winsauer G, Gudi R, Prasad K, de Martin R (2009) Siva1 is a XIAP-interacting protein that balances NFkappaB and NK signaling to promote apoptosis. J Cell Sci 122:2651–2661

Reubold TF, Eschenburg S (2012) A molecular view on signal transduction by the apoptosome. Cell Signal 24:1420–1425

Rizvi S, Mertens JC, Bronk SF, Hirsova P, Dai H, Roberts LR, Kaufmann SH, Gores GJ (2014) Platelet-derived growth factor primes cancer-associated fibroblasts for apoptosis. J Biol Chem 289:22835–22849

Rocha Lima H (1912) Zur pathologischen Anatomie des Gelbfiebers. Verh Dtsch Ges Pathol 15:163–182

Rong GH, Yang GX, Ando Y, Zhang W, He XS, Leung PS, Coppel RL, Ansari AA et al (2013) Human intrahepatic biliary epithelial cells engulf blebs from their apoptotic peers. Clin Exp Immunol 172:95–103

Roskams T, Libbrecht L, Van Damme B, Desmet V (2000) Fas and Fas ligand: strong co-expression in human hepatocytes surrounding hepatocellular carcinoma; can cancer induce suicide in peritumoral cells? J Pathol 191:150–153

Saile B, Knittel T, Matthes N, Schott P, Ramadori G (1997) CD95/CD95L-mediated apoptosis of the hepatic stellate cell. A mechanism terminating uncontrolled hepatic stellate cell proliferation during hepatic tissue repair. Am J Pathol 151:1265–1272

Sandilos JK, Bayliss DA (2012) Physiological mechanisms for the modulation of pannexin 1 channel activity. J Physiol 590:6257–6266

Saraste A (1999) Morphologic criteria and detection of apoptosis. Herz 24:189–195

Saraste A, Pulkki K (2000) Morphologic and biochemical hallmarks of apoptosis. Cardiovasc Res 45:528–537

Sato F, Nagata C, Liu Y, Suzuki T, Kondo J, Morohashi S, Imaizumi T, Kato Y, Kijima H (2009) PERIOD1 is an anti-apoptotic factor in human pancreatic and hepatic cancer cells. J Biochem 146:833–838

Schleich K, Krammer PH, Lavrik IN (2013) The chains of death: a new view on caspase-8 activation at the DISC. Cell Cycle 12:193–194

Seong J, Cho JH, Yang WI, Chung EJ, Kim NK (2004) Apoptosis and proliferation in paired primary colorectal adenocarcinomas and liver metastases. Yonsei Med J 45:187–192

Shaposhinikov D, Descot A, Schilling J, Posern G (2012) Myocardin-related transcription factor A regulates expression of Bok and Noxa and is involved in apoptotic signalling. Cell Cycle 11:141–150

Shen YC, Hu FC, Jeng YM, Chang YT, Lin ZZ, Chang MC, Hsu C, Cheng AL (2009) Nuclear overexpression of mitotic regulatory proteins in biliary tract cancer: correlation with clinicopathologic features and patient survival. Cancer Epidemiol Biomarkers Prev 18:417–423

Shi M, Yan SG, Xie ST, Wang HN (2008) Tip30-induced apoptosis requires translocation of Bax and involves mitochondrial release of cytochrome c and Smac/DIABLO in hepatocellular carcinoma cells. Biochim Biophys Acta 1783:263–274

Shimoda HK, Shide K, Kameda T, Matsunaga T, Shimoda K (2010) Tyrosine kinase 2 interacts with the proapoptotic protein Shiva-1 and augments its apoptotic functions. Biochem Biophys Res Commun 400:252–257

Shimonishi T, Isse K, Shibata F, Aburatani I, Tsuneyama K, Sabit H, Harada K, Miyazaki K et al (2000) Up-regulation of fas ligand at early stages and down-regulation of Fas at progressed stages of intrahepatic cholangiocarcinoma reflect evasion from immune surveillance. Hepatology 32:761–769

Shin EC, Shin JS, Park JH, Kim JJ, Kim H, Kim SJ (1998) Expression of Fas-related genes in human hepatocellular carcinomas. Cancer Lett 134:155–162

Shin EC, Shin JS, Park JH, Kim H, Kim SJ (1999) Expression of fas ligand in human hepatoma cell lines: role of hepatitis-B virus X (HBX) in induction of Fas ligand. Int J Cancer 82:587–591

Shin EC, Seong YR, Kim CH, Ahn YS, Kim K, Kim SJ, Hong SS, Park JH (2002) Human hepatocellular carcinoma cells resist to TRAIL-induced apoptosis, and the resistance is abolished by cisplatin. Exp Mol Med 34:114–122

Shirabe K, Mano Y, Muto J, Matono R, Motomura T, Toshima T, Takeishi K, Uchiyama H, Yoshizumi T, Taketomi A et al (2012) Role of tumor-associated macrophages in the progression of hepatocellular carcinoma. Surg Today 42:1–7

Shiraki K, Yamanaka T, Inoue H, Kawakita T, Enokimura N, Okano H, Sugimoto K et al (2005) Expression of TNF-related apoptosis-inducing ligand in human hepatocellular carcinoma. Int J Oncol 26:1273–1281

Shklyar B, Levy-Adam F, Mishnaevski K, Kurant E (2013) Caspase activity is required for engulfment of apoptotic cells. Mol Cell Biol 33:3191–3201

Shu G, Xie B, Ren F, Liu DC, Zhou J, Li Q, Chen J, Yuan L, Zhou J (2013) Restoration of klotho expression induces apoptosis and autophagy in hepatocellular carcinoma cells. Cell Oncol (Dordr) 36:121–129

Sirach E, Bureau C, Péron JM, Paradayol L, Vinel JP, Buscail L, Cordeiler P (2007) KLF6 transcription factor protects hepatocellular carcinoma-derived cells from apoptosis. Cell Death Differ 14:1202–1210

Sirica AE (2011) The role of cancer-associated myofibroblasts in intrahepatic cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 9:44–54

Stilo R, Leonardi A, Formisano L, Di Jeso B, Vito P, Liguoro D (2002) TUCAN/CARDINAL and DRAL participate in a common pathway for modulation of NF-kappaB activation. FEBS Lett 521:165–169

Su HP, Nakada-Tsukui K, Tosello-Trampont AC, Li Y, Bu G, Henson PM, Ravichandran KS (2002) Interaction of CED-6/GULP, an adapter protein involved in engulfment of apoptotic cells with CED-1 and CD91/low density lipoprotein receptor-related protein (LRP). J Biol Chem 277:11772–11779

Sullivan CS, Scheib JL, Ma Z, Dang RP, Schafer JM, Hickman FE, Brodsky FM et al (2014) The adaptor protein GULP promotes Jedi-1-mediated phagocytosis through a clathrin-dependent mechanism. Mol Biol Cell 25:1925–1936

Sun BH, Zhao XP, Wang BJ, Yang DL, Hao LJ (2000) FADD and TRADD expression and apoptosis in primary hepatocellular carcinoma. World J Gastroenterol 6:223–227

Sun GG, Lu YF, Cheng YJ, Yang CR, Liu Q, Jing SW, Han XC (2014) Expression of BTG1 in hepatocellular carcinoma and its correlation with cell cycles, cell apoptosis, and cell metastasis. Tumour Biol 35:11771–11779

Taimr P, Higuchi H, Kocova E, Rippe RA, Friedman S, Gores GJ (2003) Activated stellate cells express the TRAIL receptor-2/death receptor-5 and undergo TRAIL-mediated apoptosis. Hepatology 37:87–95

Tanaka S, Sugimachi K, Shirabe K, Shimada M, Wands JR (2000) Expression and antitumor effects of TRAIL in human cholangiocarcinoma. Hepatology 32:523–527

Tang W, Xue R, Weng S, Wu J, Fang Y, Wang Y, Ji L, Hu T, Liu T, Huang X, Chen S, Shen X, Zhang S et al (2015) BIRC6 promotes hepatocellular carcinogenesis: interaction of BIRC6 with p53 facilitating p53 degradation. Int J Cancer 136:E475–E487

Tatebe S, Ishida M, Kasagi N, Tsujitani S, Kaibara N, Ito H (1996) Apoptosis occurs more frequently in metastatic foci than in primary lesions of human colorectal carcinomas: analysis by terminal-deoxynucleotidyl-transferase-mediated dUTP-biotin nick end labeling. Int J Cancer 65:173–177

Tenev T, Bianchi K, Darding M, Broemer M, Langlais C, Wallberg F, Zachariou A, Lopez J et al (2011) The ripoptosome, a signaling platform that assembles in response to genotoxic stress and loss of IPAs. Mol Cell 43:432–448

Terada T, Nakanuma Y (1996) Expression of apoptosis, proliferating cell nuclear antigen, and apoptosis-related antigens (bcl-2, c-myc, Fas, Lewis(y) and p53) in human cholangiocarcinomas and hepatocellular carcinomas. Pathol Int 46:764–770

Tessarz AS, Cerwenka A (2008) The TREM-1/DAP12 pathway. Immunol Lett 116:111–116

Thirunavukkarasu C, Watkins S, Harvey SA, Gandhi CR (2004) Superoxide-induced apoptosis of activated rat hepatic stellate cells. J Hepatol 41:567–575

Thorburn A (2004) Death receptor-induced cell killing. Cell Signal 16:139–144

Tinel A, Tschopp J (2004) The PIDDosome, a protein complex implicated in activation of caspase-2 in response to genotoxic stress. Science 304:843–846

Toda S, Hanayama R, Nagata S (2012) Two-step engulfment of apoptotic cells. Mol Cell Biol 32:118–125

Tran J, Rak J, Sheehan C, Saibil SD, LaCasse E, Korneluk RG, Kerbel RS (1999) Marked induction of the IAP family antiapoptotic proteins survivin and XIAP by VEGF in vascular endothelial cells. Biochem Biophys Res Commun 264:781–788

Uesugi K, Hiasa Y, Tokumoto Y, Mashiba T, Koizumi Y, Hirooka M, Abe M, Matsuura B et al (2013) Wilms'

tumor 1 gene modulates Fas-related death signals and anti-apoptotic functions in hepatocellular carcinoma. J Gastroenterol 48:1069–1080

Vakifahmetoglu-Norberg H, Norberg E, Perdomo AB, Olsson M, Ciccosanti F, Orrenius S et al (2013) Caspase-2 promotes cytoskeleton protein degradation during apoptotic cell death. Cell Death Dis 4:e940

Valentino T, Palmieri D, Vitiello M, Pierantoni GM, Fusco A, Fedele M (2013) PATZ1 interacts with p53 and regulates expression of p53-target genes enhancing apoptosis or cell survival based on the cellular context. Cell Death Dis 4:e963

Wang CJ, Tang L, Shen DW, Wang C, Yuan QY, Gao W, Wang YK, Xu RH, Zhang H (2013a) The expression and regulation of DFNA5 in human hepatocellular carcinoma DFNA5 in hepatocellular carcinoma. Mol Biol Rep 40:6525–6531

Wang Y, Yang C, Mao K, Chen S, Meng G, Sun B (2013b) Cellular localization of NLRP3 inflammasome. Protein Cell 4:425–431

Watanabe et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15179366

Wensveen FM, Derks IA, van Gisbergen KP, de Bruin AM, Meijers JC, Yigittop H et al (2011) BH3-only protein Noxa regulates apoptosis in activated B cells and controls high-affinity antibody formation. Blood 119:1440–1449

Willingham MC (1999) Cytochemical methods for the detection of apoptosis. J Histochem Cytochem 47:1101–1109

Willis SN, Fletcher JI, Kaufmann T, van Delft MF, Chen L, Czabotar PE, Ierino H et al (2007) Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. Science 315:856–859

Wong CM, Lee JM, Ching YP, Jin DY, Ng IO (2003) Genetic and epigenetic alterations of DLC-1 gene in hepatocellular carcinoma. Cancer Res 63:7646–7651

Wu Y, Zhao Q, Peng C, Sun L, Li XF, Kuang DM (2011) Neutrophils promote motility of cancer cells via a hyaluronan-mediated TLR4/PI3K activation loop. J Pathol 225:438–447

Wu J, Li J, Salcedo R, Mivechi NF, Trinchieri G, Horuzsko A (2012) The proinflammatory myeloid cell receptor TREM-1 controls Kupffer cell activation and development of hepatocellular carcinoma. Cancer Res 72:3977–3986

Xia YH, Wang ZM, Chen RX, Ye SL, Sun RX, Xue Q, Huang Y (2013) T-cell apoptosis induced by intratumoral activated hepatic stellate cells is associated with lung metastasis in hepatocellular carcinoma. Oncol Rep 30:1175–1184

Xiao CX, Yang XN, Huang QW, Zhang YQ, Lin BY, Liu JJ, Liu YP, Jazag A, Guleng B et al (2013) ECHS1 acts as a novel HBsAg-binding protein enhancing apoptosis through the mitochondrial pathway in HepG2 cells. Cancer Lett 330:67–73

Xie S, Zhu M, Lv G, Zhang Q, Wang G (2012) The role of RhoC in the proliferation and apoptosis of hepatocellular carcinoma cells. Med Oncol 29:1802–1809

Xing SQ, Zhang CG, Yuan JF, Yang HM, Zhao SD, Zhang H (2015) Adiponectin induces apoptosis in hepatocellular carcinoma through differential modulation of thioredoxin proteins. Biochem Pharmacol 93:221–231

Xu Y, Kim SO, Li Y, Han J (2006) Autophagy contributes to caspase-independent macrophage cell death. J Biol Chem 281:19179–19187

Yano H, Fukuda K, Haramaki M, Momosaki S, Ogasawara S, Higaki K, Kojiro M (1996) Expression of Fas and anti-Fas-mediated apoptosis in human hepatocellular carcinoma cell lines. J Hepatol 25:454–464

Yano Y, Hayashi Y, Nakaji M, Nagano H, Seo Y, Ninomiya T, Yoon S, Wada A, Hirai M et al (2003) Different apoptotic regulation of TRAIL-caspase pathway in HBV- and HCV-related hepatocellular carcinoma. Int J Mol Med 11:499–504

Yao Z, Zhang P, Guo H, Shi J, Liu S, Liu Y, Zheng D (2014) RIP1 modulates death receptor mediated apoptosis and autophagy in macrophages. Mol Oncol pii: S1571-7891(14)00289-0

Ye CP, Qiu CZ, Huang ZX, Su QC, Zhuang W, Wu RL, Li XF (2007) Relationship between surviving expression and recurrence, and prognosis in hepatocellular carcinoma. World J Gastroenterol 13:6264–6268

Yi HC, Liu YL, You P, Pan JS, Zhou JY, Liu ZJ, Zhang ZY (2015) Overexpression of DEK gene is correlated with poor prognosis in hepatocellular carcinoma. Mol Med Rep 11:1318–1323

Yuan S, Akey CW (2013) Apoptosome structure, assembly, and procaspase activation. Structure 21:501–515

Yuan S, Yu X, Topf M, Ludtke SJ, Wang X, Akey CW (2010) Structure of an apoptosome-procaspase-9 CRAD complex. Structure 18:571–583

Yuan S, Yu X, Asara JM, Heuser JE, Ludtke SJ, Akey CW (2011) The holo-apoptosome: activation of procaspase-9 and interactions with caspase-3. Structure 19:1084–1096

Yuan Z, Syed MA, Panchal D, Joo M, Colonna M, Brantly M, Sadikot RT (2014) Triggering receptor expressed on myeloid cells 1 (TREM-1)-mediated Bcl-2 induction prolongs macrophage survival. J Biol Chem 289:15118–15129

Yunqiao L, Vanke H, Jun X, Tangmeng G (2014) MicroRNA-206, down-regulated in hepatocellular carcinoma, suppresses cell proliferation and promotes apoptosis. Hepatogastroenterology 61:1302–1307

Zhang HY, Phan SH (1999) Inhibition of myofibroblast apoptosis by transforming growth factor beta(1). Am J Respir Cell Mol Biol 21:658–665

Zhang YY, Zhou LM (2013) Omentin-1, a new adipokine, promotes apoptosis through regulating Sirt1-dependent p53 deacetylation in hepatocellular carcinoma cells. Eur J Pharmacol 698:137–144

Zhang Z, Liang X, Gao L, Ma H, Liu X, Pan Y, Yan W, Shan H, Wang Z, Chen YH et al (2014) TIPE1 induces apoptosis by negatively regulating Rac1 activation in hepatocellular carcinoma cells. Oncogene. doi:10.1038/onc.2014.208

Zhao M, Zimmermann A (1997a) Apoptosis in human hepatocellular carcinoma and in liver cell dysplasia is

correlated with p53 protein immunoreactivity. J Clin Pathol 50:394–400

Zhao M, Zimmermann A (1997b) Apoptosis in hepatocellular carcinomas with neuroendocrine differentiation. Histol Histopathol 12:973–980

Zheng T, Wang J, Song X, Meng X, Pan S, Jiang H, Liu L (2010) Nutlin-3 cooperates with doxorubicin to induce apoptosis of human hepatocellular carcinoma cells through p53 or p73 signaling pathways. J Cancer Res Clin Oncol 136:1597–1604

Zhou X, Thorgeirsson SS, Popescu NC (2004) Restoration of DLC-1 gene expression induces apoptosis and inhibits both cell growth and tumorigenicity in human hepatocellular carcinoma cells. Oncogene 23:1308–1313

Zimmermann A, Kappeler A, Friess H, Büchler MW (2002) Hepatocellular carcinoma with an unusual medullary-like histology and signs of regression ("medullary-like hepatocellular carcinoma"). Dig Liver Dis 34:748–763

Zou C, Chen J, Chen K, Wang S, Cao Y, Zhang J, Sheng Y, Huang A, Tang H (2014) Functional analysis of miR-181a and Fas involved in hepatitis B virus-related hepatocellular carcinoma pathogenesis. Exp Cell Res pii:S0014-4827(14)00503-5

Necrobiology of Liver Cancer: Other Forms of Cell Death Related or Not Related to Apoptosis

177

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_177

Abstract

In addition to classical apoptosis, necrobiologic processes active in cancer also include various forms of cell death related to apoptosis. These alternative and complex pathways are only incompletely studied in hepatobiliary tumors, but may play a significant role in the future, also for the development of novel therapies. A mode of cell death that occurs following detachment of cells from the extracellular matrix (ECM) is termed anoikis. As the ECM is highly abnormal in cancers, anoikis is an important death modality for tumor cells. An increasing number of cell death forms are independent from caspase pathways and are therefore not related to apoptosis. They include pyroptosis, pyronecrosis, ferroptosis, methuosis, parthanatos, paraptosis, caspase-independent mitotic death, oncosis, oxytosis, phenoptosis, and autoschizis. A distinct form of cell-in-cell death that occurs in various cancers characterizes emperipolesis, peripolesis, entosis, emperitosis, and cell cannibalism.

Introduction

In addition to classical apoptosis, which is the best known example of programmed cell death both in normal and neoplastic cells, there are several other cell death pathways that are either related to classical apoptosis or involve caspase-independent pathways and are thus not related to apoptosis (Duprez et al. 2009; Tables 1 and 2).

Table 1 Forms of cell death related to apoptosis

Anoikis
Synoikis
Lipoapoptosis

Table 2 Forms of cell death not related to apoptosis

Caspase-independent forms of cell death (numerous forms; see Table 3)
Protruded type of cell death
Pseudoapoptosis
Emperipolesis
Peripolesis
Entosis
Emperitosis
Cell cannibalism
Mitotic catastrophe

Anoikis and Synoikis

Anoikis and Homeless Cells

Anoikis ("death of homelessness") is defined as a mode of cell death that ensues upon cell detachment from the extracellular matrix (ECM), or the attachment of epithelial cells to an inappropriate matrix or substrate (Horbinski et al. 2010; Taddei et al. 2012; Paoli et al. 2013). Anoikis is an important prerequisite for metastatic spread in cancers (Kim et al. 2012). Regulators of anoikis include Mcl-1, Cav-1, Bcl-xL, c-FLIP, Bit1 and MAPK (Tan et al. 2013). Loss of matrix attachment depends on distinct alterations in composition and function of the cytoskeleton. The proapoptotic GTP-binding protein, death-associated protein 3 (DAP3), is critical for induction of anoikis. DAP3 is associated with FADD and activation of caspase-8 (Miyazaki et al. 2004). DAP kinase (DAPK), which undergoes activation upon induction by various death stimuli, and DAPK-induced cell death are associated with loss of matrix attachment (Ivanovska et al. 2014). DAPK is a Ca2+/calmodulin-regulated serine/threonine kinase that participates, as a member of a distinct interactome, in several signaling cascades, including the NLRP3 inflammasome (Bialik and Kimchi 2014). Anoikis is regulated by distinct signaling pathways (Zhan et al. 2004). Anoikis is an important mechanism to prevent and impair ectopic cell growth to inappropriate ECMs and is a guarantee for the maintenance of organ-typic tissue organization (review: Horbinski et al. 2010).

Anoikis in Various Neoplasms and Liver Cancers

Anoikis plays a significant role in fating of cancer cells. In particular, it markedly affects the

pathways that lead to individualization of tumor cells, a critical step in the early phases of invasive cascades. Specifically, it counteracts escape of viable cells from the primary tumor. Anoikis prevents shed epithelial cells and tumor cells from colonizing elsewhere and hence maintains normal architecture of normal tissues and may keep tumor architecture in control (Horbinski et al. 2010). Resistance to anoikis is a major mechanism that facilitates invasion and spread of cancer and is associated with anchorage-independent growth and epithelial-mesenchymal transition (EMT). Numerous pathways can lead to anoikis resistance, including changes in adhesion molecule expression patterns, increased growth factor/growth factor receptor expression, induction of EMT and associated pro-metastatic niches, and upregulation of pro-survival signaling (review: Paoli et al. 2013).

Anoikis resistance of HCC cells is a major mechanism promoting invasion and metastatic spread (Cao et al. 2009; Tan et al. 2013). A cancer microenvironment that undergoes remodeling associated with an altered extracellular matrix (ECM) protein platform can exert effects on HCC cell anoikis. MicroRNA-26a, which targets alpha5 integrin, promotes anoikis in HCC (Zhang et al. 2015). An elevated autocrine expression of the ECM protein, epidermal growth factor-like repeats, and discoidin I-like domains 3 (EDIL3) in HCC protects from tumor anoikis through integrin activation, creating a receptive microenvironment for the survival of detached HCC cells (Feng et al. 2014). Anoikis resistance is linked to the generation of epithelial-mesenchymal transition (EMT). Resistance to anoikis can be conferred by EMT via an E-cadherin-mediated pathway (Kumar et al. 2011). CD44 can provide an EMT signal pathway for the acquisition of a mesenchymal phenotype in HCC cells, resulting in anchorage-independent cell survival (Okabe et al. 2014). MicroRNA-424-5p, which reverses EMT and anoikis resistance in HCC, is downregulated in these tumors (Zhang et al. 2015).

A mitogen-activated protein kinase (MAPK) pathway is pivotal for anoikis resistance in HCC cells (Cao et al. 2014) and resistance requires expression of a membrane protease, RHBDL2 (Cheng et al. 2014). In HCCs, anoikis resistance is induced by an oncogene involved in tumor metastasis, AEG-1. AEG-1-promoted resistance is activated via the PI3K/Akt pathway and is characterized by the regulation of Bcl-2 and Bad (Zhou et al. 2014). Defects in the death receptor pathway of caspase activation can render tumor cells resistant to anoikis and hence promote metastasis (Simpson et al. 2008). The kinase receptor-interacting protein (RIP) is an upstream negative regulator of the NAD-dependent deacetylase, sirtuib-3 (SIRT3) in anoikis resistance (Kamarajan et al. 2012). Another protein that can regulate anoikis resistance in tumors is the CUB domain-containing protein 1, an SFK-binding phosphoprotein associated with anchorage independence of cancer cells (Uekita et al. 2007). HCC cells are protected from anoikis by the action of p21-activated kinase 1 (PAK1), which is upregulated by HBV X protein (Xu et al. 2012). Acquisition of anoikis resistance in HCC is produced through upregulation of CD147 (Ke et al. 2012) and by the aging suppressor gene product, Klotho, via activation of VEGFR2/PAK1 (Chen et al. 2013). Autophagy induced in different stages of tumorigenesis supports anoikis resistance (Sun et al. 2013; Yang et al. 2013). In HCC there is also a relationship between autophagy and anoikis. Induction of autophagy through upregulation of BNIP3 in HCC cells contributes to anoikis resistance via an mTORC1 signaling pathway (Sun et al. 2014).

Synoikis

There are mechanisms that allow tumor cells to circumvent anoikis. A distinct anti-anoikis mechanism is a process called synoikis (Shen and Kramer 2004). Synoikis denotes a tumor cell behavior in which tumor cell-cell contacts form a tissue-like population that promotes proliferation and survival in the absence of interactions with the extracellular matrix. Hepatoma cells can enter a synoikis-like survival mode mediated by angiopoietin-like 47ANGPTL4 (Zhang et al. 2008), a protein acting in lipid metabolism and

as an apoptosis survival factor for endothelial cells.

Lipoapoptosis: A Cell Death Mechanism for Steatotic Hepatocytes and Hepatocellular Carcinomas with Steatosis and Steatohepatitic Changes

An important proinflammatory mechanism in steatohepatitis and inflammatory changes in steatotic HCCs is lipoapoptosis induced by saturated free fatty acids (FFAs). Oxidative stress induced by lipotoxic molecules, in particular palmitate and stearate, plays a central role in pathways leading to lipoapoptosis and lipoapoptosis-associated hepatic inflammation. Saturated FFAs accumulate in hepatocytes in situations of compromised triglyceride synthesis, neutral fat being a safeguard by binding palmitate (Unger and Orci 2002; Malhi and Gores 2008; Alkhouri et al. 2009; Cazanave and Gores 2010; Zambo et al. 2013).

In hepatocytes, FFAs are well-known compounds to induce lipoapoptosis in a c-Jun-NH2-terminal kinase (JNK)-dependent pathway (Malhi et al. 2006). FFAs shift insulin-induced hepatocyte proliferation toward CD95/Fas-dependent apoptosis (Sommerfeld et al. 2015). Among fatty acids, palmitate is centrally involved in the induction of lipoapoptosis. Accumulation of palmitate in cells activates the endoplasmic reticulum stress response, resulting in induction of proapoptotic transcription factor C/EBP homologous protein (CHOP). CHOP-mediated lipoapoptosis is modulated by microRNA-615-3p which is repressed by palmitate to allow maximal expression of CHOP (Miyamoto et al. 2014). Palmitate activated by fatty acid transport protein 4 promotes an apoptosis cascade in hepatocytes characterized by increased JNK, PUMA, caspase-3, PARP-1 activation, and Rac1-mediated cytoskeletal reorganization (Seessle et al. 2015). One component of this pathway, the BH3-only protein PUMA, is a potent proapoptotic protein. PUMA expression is JNK1-dependent and contributes to lipoapoptosis in hepatocytes (Cazanave et al. 2009). Palmitate also promotes calcium release from the endoplasmic reticulum and thus induces mitochondrial dysfunction which induces oxidative stress (Egnatchik et al. 2014). FFAs can stimulate proteasomal degradation of cellular inhibitors of apoptosis protein 1 and 2 (cIPAP1 and cIAP2) in hepatocytes and thus promote apoptosis depending on death receptor 5 (DR5)-mediated signaling (Akazawa et al. 2013). Palmitate-induced lipoapoptosis is counteracted by several mechanisms. Lipoapoptosis mediated by palmitate-promoted upregulation of Bim and PUMA is attenuated by palmitoleate (Akazawa et al. 2010). MicroRNA-296 reduces lipoapoptosis in liver cells by directly targeting PUMA (Cazanave et al. 2011). Palmitate and stearate can also induce lipoapoptosis in cholangiocytes via caspase activation, nuclear translocation of FOXO3, and increased proapoptotic PUMA expression (Natarajan et al. 2014). In HCC cells in vitro, reduction of oxidative stress attenuates lipoapoptosis induced by hypoxia (Hwang et al. 2015).

Autosis

Autosis is a Na+,K+-ATPase-regulated form of stress-induced cell death promoted by a cell-penetrating autophagy-inducing peptide, Tat-Beclin 1, a derivative of Beclin 1. Stress factors involved in autosis comprise hypoxia and nutrient starvation. Morphologically, autosis is characterized by increased autophagosomes/autolysosomes and nuclear convolution at early stages of the process and focal swelling of the perinuclear space at later stages (Liu et al. 2013).

Protruded Type of Cell Death

Protruded type of cell death is a distinct form of parenchymal cell death that has first been observed in adrenal gland cells of normal rats (Chen-Pan et al. 1996). Protruded cells (p-cells) are characterized by an electron-lucent cytoplasm and ruptured membranes and their egress from the parenchymal tissue compartment into capillary

lumina. The egress of p-cells is either through endothelial gaps or following "rupture" of the capillary endothelial lining. The cytoplasmic matrices of dying p-cells were seen to scatter in the capillary lumen where the nuclei and mitochondria remained morphologically intact. A similar phenomenon has been observed in intercalated cell populations of the medullary collecting duct of the developing rat kidney, where superfluous intercalated cells are deleted by apoptosis followed by extrusion into the duct lumen (Kim et al. 1996).

Pseudoapoptosis

Pseudoapoptosis generally defines a death process that resembles initial stages of apoptosis, but is, in contrast to apoptosis, a reversible process. Cells undergoing pseudoapoptosis show blebbing, a deranged mitochondrial function, membrane lipid asymmetries, and a disorder of calcium homeostasis, but these changes can be reversed rapidly.

Non-apoptotic Forms of Cell Death

Introduction

Apart from apoptosis and its variants, several forms of ordered non-apoptotic cell death are known. Caspase-independent forms of cell death play an important role as safeguard mechanisms to protect the host from harmful cells in case of caspase failure ("regulated necrosis"; reviews: Bröker et al. 2005; Table 3).

Table 3 Forms of non-apoptotic cell death

Pyroptosis
Pyronecrosis
Ferroptosis
Methuosis
Parthanatos
Paraptosis
CIMD (caspase-independent mitotic death)
Oncosis
Oxytosis
Enucleation-induced cell death
Phenoptosis
Autoschizis

Pyroptosis and the Pyroptosome

Pyroptosis is defined as a caspase-1-dependent, NLRP3 (Nod-like receptor family protein 3)-, and AIM2-inflammasome-mediated form of inflammatory programmed cell death, mostly triggered in macrophages by various, in part microbial, stimuli (reviews: Kohl and Grütter 2004; Fink and Cookson 2005). In contrast to apoptosis, pyroptosis results in the release of PAMPS (pathogen-associated molecular patterns) and immune system-activating cytokines. The activation of pyroptosis causes secretion of interleukin-1beta and pore-mediated cytolysis. Caspase-1 (synonym: interleukin-1-converting enzyme) is chiefly active as a mediator of inflammation by proteolytically processing interleukin-1beta from an inactive precursor to the active form and as an inducer of a rapid apoptosis program in macrophages as a response to intracellular bacteria, called pyroptosis. Pyroptosis is characterized by formation of a supramolecular assembly of several proteins, the pyroptosome (Fernandes-Alnemri et al. 2007; Fernandes-Alnemri and Alnemri 2008). The pyroptosome is located in the cytoplasm, not linked to an organelle, and co-localizes with NLRP3 (Wang et al. 2013b). PYNOD/NLRP10, an NLR-like protein that consists of a pyrin domain and a NOD, is an inhibitor of inflammatory reactions mediated by caspase-1 and the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC). PYNOD co-localizes with ASC and inhibits caspase-1-mediated processing of interleukin-1beta without inhibiting caspase-4-mediated caspase-1 processing (Wang et al. 2004; Imamura et al. 2010). ASC, which binds directly to caspase-1, is critical for caspase-1 activation in pyroptosis. ASC itself is one of the two only human proteins that contain a caspase recruitment domain or CARD together with a pyrin, AIM, ASC, and death domain-like (PAAD)/PYRIN/DAPIN domain. Proteins with CARD regulate caspases,

and ASC binds by its CARD to procaspase-1 to regulate the activity of this enzyme (Stehlik et al. 2003).

The initiation of pyroptosis requires the activity of cytosolic pattern recognition receptors (PRRs), molecules that act as sensors for the detection of various endogenous and exogenous danger-associated molecular patterns (including pathogen-associated molecular patterns, PAMPs; Broz and Monack 2011). The principal structures involved are Nod-like receptors containing a pyrin domain (PYD) (NLRPs) and AIM2-like receptors (ALRs), structures also involved in carcinogenesis (reviews: Drexler and Yazdi 2013; Ratsimandresey et al. 2013). Inflammasomes in their role in pyroptosis interact in a complex manner with components of the caspase system. An inhibitor of caspase-8, c-FLIP (cellular FLICE-inhibitory protein), is a contributor to canonical inflammasome (NLRP3 and AIM2) activation for the generation of caspase-1 and active interleukin-1beta. Specifically, c-FLIP is required for full NLRP3 inflammasome assembly and NLRP3 mitochondrial localization (Wu et al. 2014). NLRP3 activation also induces a form of programmed necrotic cell death through induction of the protein ASC (apoptosis-associated speck-like protein containing a CARD), a process that leads to neutrophil-mediated inflammation (Satoh et al. 2013).

Pyronecrosis

The term pyronecrosis has been employed to described a form of necrotic cell death occurring in macrophages infected with *Shigella flexneri* (Willingham et al. 2007). In contrast to pyroptosis, pyronecrosis does not require caspase-1. The process involves the pattern recognition receptor NALP3/cryopyrin/CIAS1 and the apoptosis regulator protein apoptosis-associated speck-like protein containing a CAR (ASC). Pyronecrosis can also be induced by intracellular *Staphylococcus aureus*, but the bacterium can also induce anti-apoptotic programs in phagocytes (Fraunholz and Sinha 2012). Human macrophages infected with high burdens of ESAT-6-expressing *Mycobacterium tuberculosis* undergo pyronecrosis (Welin et al. 2011).

Ferroptosis

Ferroptosis is a form of non-apoptotic cell death that is iron dependent (Dixon et al. 2012). Ferroptosis is triggered by the oncogenic RAS-selective lethal small molecule erastin, a member of the RAS-selective lethal compounds (RSL). Erastin targets voltage-dependent anion channels 2 and 3 and blocks cysteine uptake by the cysteine/glutamate antiporter (Dixon et al. 2012). RSL-induced cell death proceeds in the absence of caspase activation and chromatin fragmentation and is associated with increased intracellular levels of reactive oxygen species (ROS). The deficiency in cysteine leads to failure of antioxidant protection, leading to iron-dependent cell death. An essential regulator of ferroptosis in cancer cells is glutathione peroxidase (Yang et al. 2014). In cancer cells, ferrostatin-1 is a potent pharmacological inhibitor of ferroptosis (Dixon et al. 2012). Ferroptosis occurs in HCCs, and this form of iron-dependent cell death has also been observed following sorafenib exposure (Louandre et al. 2013).

Methuosis

In the non-apoptotic cell death mode termed methuosis (from Greek, *methuo*, to drink to intoxication), excessive stimuli can induce cytoplasmic uptake and accumulation of small bubbles that gradually merge into giant vacuoles, causing decreased metabolic activity of the involved cell, decay of cell membranes, and cell death. Cell shrinkage and nuclear fragmentation as in apoptosis are absent (Cai et al. 2013). The vacuoles originate from non-clathrin endocytic compartments and are distinct from lysosomes and autophagosomes (Overmeyer et al. 2011). Methuosis is mechanistically characterized by alterations in the trafficking of clathrin-independent endosomes and can be induced by the expression of active Ras, with the important

downstream effectors small GTPases, Rac1, ARf6, and the Arf6 GTPase-activating protein GIT1 (Bhanot et al. 2010).

Parthanatos

Parthanatos is a form of caspase-independent programmed cell death induced by apoptosis-inducing factor (AIF) release from mitochondria and its translocation into the nucleus, where it initiates DNA cleavage (David et al. 2009). An important inducer of parthanatos is mitochondrial oxidative stress (Andrabi et al. 2008; Chiu et al. 2011). The stress response in the nucleus involves poly-ADP-ribose (PAR) polymer, which is generated in the nucleus and transported to mitochondria to mediate AIF release following lethal PARP-1 activation (Wang et al. 2009a). Parthanatos is associated with ATP consumption due to NAD+ depletion by poly(ADP-ribose) polymerase 1 (PARP-1)-dependent poly-ADP-ribosylation (PARylation) on target proteins (Koh et al. 2005; Huang et al. 2013; Mashimo et al. 2013; Virag et al. 2013). Binding of poly-ADP-ribose (PAR) to AIF is a critical event for PARP-1-dependent parthanatos (Wang et al. 2011). Parthanatos results in cell and tissue demise resembling necrosis.

Paraptosis

Paraptosis is a form of active caspase-independent type III cell death characterized by vacuolization of the cytoplasm, rounding of cells, and other features resembling cell necrosis (Sperandio et al. 2000; Hoa et al. 2009). Paraptosis may be a distinct form of oncosis. The process needs gene activation. In contrast to apoptosis, paraptosis has no nuclear fragmentation and DNA fragmentation, lacks membrane blebbing, and reveals only minor chromatin condensation. Mitochondrial swelling is a late phenomenon. Damaged parapoptotic cells release danger signals, including high mobility group B-1, heat shock proteins, and proteases. Several types of cancer drugs can induce paraptosis, including taxol. Paraptosis depends on failure of large potassium channels (Hoa et al. 2009). Paraptosis is mediated by mitogen-activated protein kinases (MAPKs) and inhibited by AIP-1/Alix. Apoptosis is not inhibited by AIP-1/Alix (Sperandio et al. 2004). Alix (apoptosis-linked-gene-2-product; ALG-2) acts as a mediator of exosome biogenesis, in a syndecan-syntenin-Alix complex (Baietti et al. 2012; Bissig and Gruenberg 2014; Ghossoub et al. 2014). Alix also mediates egress of naked hepatitis B virus capsid particles from HBV-replicating cells (Bardens et al. 2011).

Caspase-Independent Mitotic Death (CIMD)

There is a form of mitotic cell death that is independent of caspase activation, a process termed caspase-independent mitotic death (CIMD) (reviews: Bröker et al. 2005; Kitagawa and Niikura 2008). CIMD mainly involves proteolytic pathways mediated by cathepsins, calpains, serine proteases, and DNases, all these enzymes participating in an activation cascade that ends up in the cleavage of numerous cellular proteins, nuclear proteins, DNA, and in cell disintegration (Torriglia and Leprêtre 2009). CIMD depends on p73, a p53 homologue and inducer of apoptosis (Ozaki and Nakagawara 2005), and also depends on apoptosis-inducing factor and endonuclease G (Niikura et al. 2007). CIMD is induced during early mitosis by partial depletion of the spindle checkpoint protein, BUB, and defective kinetochore-microtubule attachments. This process is mediated by an interactor of BUB1, i.e., BUB3, which upon escape from BUB1 binding interacts with p73 (Niikura et al. 2010). CIMD may serve to eliminate cells that are at risk to marked chromosome mis-segregation.

Oncosis

Oncosis is a prelethal condition characterized by marked cell swelling, organelle swelling, increased cell membrane permeability, and membrane blebbing. Failure of membrane ion pumps

due to energy exhaustion seems to be in the center of pathogenesis. Oncosis is predominantly found in situations of induced ATP depletion, e.g., by toxic agents. A second pathway involves deranged calcium homeostasis and increased cytoplasmic Ca2+ activating calpain-type proteases that destabilize cellular membranes (review: Fink and Cookson 2005).

Oxytosis

Oxytosis is an oxidative stress-induced form of cell death originally observed in nerve cells exposed to excess glutamate in the extracellular medium (Tan et al. 2001). The process is also termed oxidative glutamate toxicity or glutamate-induced oxytosis. Excess glutamate inhibits cellular uptake of cysteine, required for the synthesis of the protective molecule glutathione. Failure of glutathione production results in excess of mitochondria-produced reactive oxygen species followed by calcium influx, finally leading to cell death.

Enucleation-Induced Cell Death

A novel mechanism of cell death that is considered to play a role in cancer cells is enucleation. In vitro it is associated with the formation of an induced cytoplasmic network of stress fibers that extrude the nucleus from the cell, followed by cell death. Intact nuclei are found in the vicinity of the cytoplasts for a certain time (Paunescu et al. 2014).

Phenoptosis

Phenoptosis is a term that has been coined to denote a system of programmed cell death that purifies a population from individuals that have become unwanted or are damaging the entire system (Skulachev 1999). For example, phenoptosis may purify an entire organ from cells that no longer fulfill the required functions or damage the organ's homeostasis. It could be envisaged that such a system performs a surveillance and protection function, e.g., recognizing mutated and potentially neoplastic cells and eliminating them via apoptosis.

More than a century ago, August Weismann had formulated the hypothesis that death of old individuals had been established in nature and its biological evolution as a kind of adaptation, in order to rejuvenate the population (Weissmann 1889). This hypothesis was strongly criticized by Medawar (1952).

Autoschizis

Autoschizis is a form of cancer cell death characterized by a decrease in cell size occurring subsequent to loss of cytoplasm via self-excision, in the absence of organelle loss. In cells undergoing autoschizis, also nuclei decrease in size and exhibit chromatin decondensation. Degraded chromatin is present in cytoplasmic autophagosomes. Nucleoli segregate their components and are fragmented into small pieces. Cell death then develops through karyorrhexis and karyolysis (Gilloteaux et al. 2001, 2004, 2006; Jamison et al. 2002).

Cell-in-Cell Death in Cancer: Cell-in-Cell Structures, Emperipolesis, Peripolesis, Entosis, Emperitosis, and Cannibalism

CICS, Emperipolesis, and Peripolesis

Upon cell contact, cells can form cell-in-cell structures (CICS), characterized by a process through which one or more cells (the effector cell) penetrate into the cytoplasm of another cell (the host or target cell; reviews: Xia et al. 2008; Yang and Li 2012; He et al. 2013). In humans, CICS physiologically occur among stem and progenitor cells and certain immune cells such as T-cells. Classically, penetration of cells as CICS effector cells into other cells is termed emperipolesis (McFarland 1970; Xia et al. 2008; Figs. 1 and 2). A similar process is peripolesis, a phenomenon in which a cell (usually a lymphocyte) attaches itself to another cell, mostly

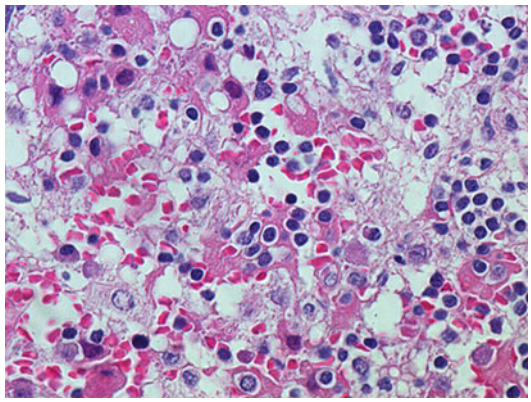

Fig. 1 Tumor cell emperipolesis. Cells with spherical and partly pycnotic nuclei are engulfed by phagocytic cells (hematoxylin and eosin stain)

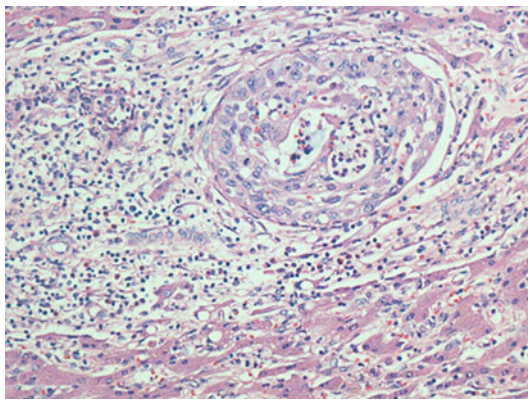

Fig. 2 Neutrophil emperipolesis by carcinoma cells (hematoxylin and eosin stain)

a macrophage or veiled cell, and proceeds to circle around it (Lyons et al. 1992). Cells of a distinct type can form CICS among themselves (homotypic CICS), but also different cell types can produce CICS (heterotypic CICS). Heterotypic CICS of normal cells are, e.g., granular leukocytes in megakaryocytes. In neoplasms, heterotypic CICS are a hallmark of Rosai-Dorfman disease, but they also occur in other neoplasms, such as carcinomas, where tumor cells can form cell-in-cell structures with leukocytes or stromal cells (Wang et al. 1976). Certain cancer cells can internalize platelets (Bhatia and Dey 2013). Homotypic CICS are also known for various cancers, showing tumor cells within tumor cells (tumor cell-tumor cell emperipolesis; Humble et al. 1956; Burns 1967; Chemnitz and Bichel 1973). The entry of effector cells into host cells can result in various fates of the cells involved. Emperipoletic lymphocytes can survive in their host cells, at least for a certain time. Immune effector cells surviving in tumor cells can attack their host cells by directly inserting into the nucleus of their tumor host cells (so-called lymphocyte-mediated cancer cell lysis; Wei and Hang 1989; Hang et al. 1991). However, it is assumed that in CICS most of the entering cells will undergo three major forms of cell death, i.e., cannibalism, entosis (non-apoptotic cell-in-cell death), and emperitosis (killer cell-mediated apoptotic cell-in-cell death; review: He et al. 2013).

Cellular Cannibalism: Cancer Cells Eat Their Way Free

Cannibalism is characterized by the phenomenon that normal cells and cancer cells can internalize other cells, such as neighboring tumor cells, leukocytes, and stromal cells, and "eat" them, a process that seems to augment their thriving and proliferative capacity (Sharma and Dey 2011; Caruso et al. 2012; Fais and Fauvarque 2012). In fact, tumor cells as cannibal cells may "eat" everything on their way, and often feed on sibling tumor cells, but also on cells encountered in their microenvironment, e.g., lymphocytes, natural killer cells, and granulocytes (Lugini et al. 2006; Qian and Shi 2009; Singhal et al. 2011). Cannibalizing of lymphocytes by tumor cells may damage the local antitumor immune response by inducing lymphocytopenia. There is evidence that metastatic tumor cells often employ cannibalism at the metastatic site, particularly under low nutrient supply (Fais 2007). The finding of cannibal tumor cells that internalize and eat nontumorous cells such as neutrophils and lymphocytes (Caruso et al. 2012) is termed xeno-cannibalism (Sarode and Sarode 2014b), while feeding on sibling cells is called self-cannibalism or macroautophagy (Malorni et al. 2007; Matarrese et al. 2008). Certain cancers also show homotypic cell cannibalism, a process regulated by the nuclear protein 1 (Cano et al. 2012). Cannibalism is not restricted to cancer cells and was also found in granuloma

cells (Sarode and Sarode 2014a). Cells involved in cannibalism employ the actin cytoskeleton, ezrin, and caveolin-1 to engulf and internalize their "victims," followed by the formation of a cannibalistic vacuole which fuses with lysosomes to form enzyme-containing caveosomes. Cell death in cannibalism is mediated by lytic enzymes of lysosomes. Interestingly, this process mimics a phylogenetically very old and conserved mechanism that is, e.g., well-known from feeding amoebas. It is assumed that cannibalism provides the cannibal cell with additional nutrients that serve for growth and invasion. However, there are also indications that self- and xeno-cannibalism can result in cellular "hyperphagia" that ends up with an autophagic reaction leading to cell death (Tinari et al. 2008).

Entosis

A second form of CICS-associated cell death is termed entosis (Overholtzer et al. 2007; Routray et al. 2014). Entosis is in part similar to cannibalism and is strongly dependent on light chain 3 (LC3). Entosis is also called LC3-associated phagocytosis, or LAP. However, in homotypic entosis, a living tumor cell is internalized intactly into a sibling cell of the same type (Yang and Li 2012). In the course of entosis, invading homotypic effector cells are enveloped in a target cell vacuole followed by recruitment of LC3 to the vacuole membrane, a process that requires Rho-dependent signaling, actin polymerization, and adherens junctions that bind the cells involved together. Autophagy-associated proteins such as Atg5, Atg7, and the lipid kinase VPS34, rather than autophagosomal proteins, are involved in the process (Kim and Overholtzer 2013). The vacuole then fuses with target cell lysosomes, but cell death is caused by lysosome-mediated caspase-3-independent cell death (review: He et al. 2013) and is related to autophagic processes (Florey et al. 2011). Autophagic proteins lipidate LC3 onto phagosomes and other macroendocytotic vacuole membranes and are required for entotic degradation of cargo (Florey and Overholtzer 2012). Entosis can impair metastatic spread by eliminating potential metastatic cells that have detached from the ECM pro-metastatic niche, i.e., disturbance of cytokinesis; entosis is also thought to compromise the future replicative capacity of target cells via induction of an aneuploid or multinucleated state in surviving cells (Janssen and Medema 2011; Krajcovic et al. 2011; Krajcovic and Overholtzer 2012).

Emperitosis

In emperitosis, natural killer (NK) cells are internalized by cancer cells. Many of these heterotypic CICS result in NK cell death within the tumor cell host ("strike-back effect"; He et al. 2013), in part by re-picking up of secreted granzyme B back into the effector cell causing suicide (Wang et al. 2013a), but part of the internalized NK effector cells can kill the host cancer cell by release of cytotoxic proteins. In both situations, cell death proceeds through apoptosis. Internalization of NK cells into cancer cells requires ezrin and leads to a form of programmed cell death (Wang et al. 2009b). Active granzyme B converts entosis to emperitosis (Salvesen 2014), and rapid uptake of granzyme B leads to emperitosis, a death mechanism of immune killer cells inside tumor cells (Wang et al. 2013a). Granzyme B induces extramitochondrial reactive oxygen species production via caspase-dependent NADHP oxidase activation (Aguilo et al. 2010). Granzyme B itself can be degraded by autophagy, a pathway involved in the escape of cancer cells from NK-mediated lysis (Viry et al. 2014).

Mitotic Catastrophe

Introduction

Mitotic catastrophe (MC; anaphase catastrophe) is defined as a type of cell death occurring during mitosis and a mechanism for avoiding genomic instability. In principle, MC results from a combination of deficient cell cycle checkpoints (specifically the spindle checkpoint) and cellular damage. Failure of these checkpoints and failing cell cycle arrest before or at mitosis causes an

attempt of aberrant chromosome segregation, ending up with apoptosis at the metaphase/anaphase transition (reviews: Castedo and Kroemer 2004; Castedo et al. 2004; Vitale et al. 2011). Only parts of cells in MC fulfill a complete apoptotic program. These cells start to divide asymmetrically in the next round of cell division and form aneuploidy daughter cells. This is an important mechanism that explains the common occurrence of aneuploid cells in malignant neoplasms.

What are the pathways leading to MC? The tuning of an orderly progression through G2 is regulated by cyclin-CDK levels (Oikonomou and Cross 2011), and deviations from these orderly gradients may cause G2/M failure. Maintenance of the G2 cell cycle checkpoint arrest for premitotic DNA quality control and repair is regulated by the WEE1 kinase and pushed forward by Cdc25 (De Witt Hamer et al. 2011). Premitotic repair itself is accomplished by homologous recombination proteins which are associated with centrosomes (Cappelli et al. 2011). A prolonged mitotic phase caused by abnormal chromosome segregation allows cells to reenter the subsequent G1 phase without cytokinesis (the so-called mitotic slippage). This has been shown to induce a p53-dependent cell death program, the MC (Gonçalves et al. 2011). The process of MC is also induced by depletion of centrosomal proteins (Kimura et al. 2013) and the viral protein apoptin (Lanz et al. 2013). The gammaH2AX-ATM (ataxia telangiectasia mutated)-p53 pathway triggers apoptosis in MC (Niida et al. 2005; Imre et al. 2011). The polo-like kinase family member serum-inducible kinase (Snk/Plk2) is a p53 target gene. At the mitotic checkpoint, p53-dependent activation of Snk/Plk2 prevents MC following spindle damage, while silencing of Snk/Plk2 induces MC (Burns et al. 2003). Stabilized p53 prevents caspase-independent mitotic death, counteracted by polo-like kinase 1, which in turn is suppressed by p21/Waf1 (Lin et al. 2011, 2014). Stabilization of p53 during this process is accomplished by Nqo1, which acts as a gatekeeper for proteasomal degradation of p53 (Bui and Shin 2011). MC-induced cell death is associated with a characteristic rearrangement of the actin-containing cytoskeleton (Grzanka et al. 2011).

Morphological Features of MC in Cancer Cells

The abnormal segregation of chromosomes in MC, the asymmetrical cell division that may follow MC, and the distinct type of cell death accompanying MC lead to a wide array of cytological abnormalities of tumor cells. They comprise aneuploidy, aberrant mitotic figures, bizarre and giant nuclei, multiple micronuclei, nuclear blebs, strings and pockets, nuclear invaginations, multinucleated tumor giant cells, centrosome aberrations, and signs of cell death, eventually with apoptotic bodies (Caruso et al. 2011a, b). It has been suggested that highly aggressive tumors characterized by pleomorphic giant cells are those having frequently undergone MC. MC may thus be a target for cancer therapy (review: Galimberti et al. 2011).

MC Is More Often Found in Cancer Cells

In contrast to normal cells, which are capable to repair damaged DNA during a G1 arrest, cancer cells often lack a sufficiently long G1 phase and depend in regard to DNA control and repair on a G2 arrest. The molecular switch for the G2/M transition, the Wee1 kinase, is often overexpressed in cancer cells, one mechanism why cancer cells prematurely enter mitosis and hence undergo MC (review: De Witt Hamer et al. 2011). A further system involved in the induction of MC in tumors involves miRNAs. The tumor-suppressive miRNA/mir-663 gene induces MC-associated growth arrest in human gastric cancer cells (Pan et al. 2010). MC in tumors is also induced by cancer therapy, in particular radiation (Hendry and West 1997; Shinomiya 2001; Eriksson and Stigbrand 2010) and chemotherapy (Portugal et al. 2010). This form of MC in tumor cells is associated with treatment-induced senescence of these cells (Roninson et al. 2001). In radiation-induced MC, one potential mechanism is centrosome amplification, which is induced by radiation and which can result in the formation of multipolar mitotic spindles (Dodson et al. 2007).

In addition to a p53-related cell death pathway, p53 null cells or cells with defective p53 can undergo MC-associated cell death in the absence of a G1 checkpoint as a result of mechanical disruption induced by centrosome overduplication/amplification (Fragkos and Beard 2011). Cells overexpressing the centrosome protein CP110 or depleted of cyclin F, which targets CP110 for destruction, have more than two centrosomes and undergo MC. p27(Kip1) sequesters cyclin F, which prevents its interaction with and the subsequent degradation of CP110, resulting in centrosome amplification (Sharma et al. 2012). DNA-damage-induced centrosome amplification itself is a common event in malignant neoplasms and promotes genomic instability (Pannu et al. 2012). Centrosome amplification is mediated by Ckh1, which causes G2 checkpoint activation after DNA damage. Overriding G2 checkpoint leads to mitotic slippage, cell cycle reentry in G1, and subsequent G1 arrest associated with senescence or MC (Poehlmann et al. 2011). Centrosome amplification can occur through centriole disengagement (Inanç et al. 2010). Centrosome amplification is also induced by MCT-1, a centrosomal oncoprotein involved in mitosis. Knockdown of MCT-1 protein results in intercellular bridging, chromosome mis-congregation, cytokinesis delay, and MC (Shih et al. 2012). MC in tumor cells has been proposed to be an oncosuppressive mechanism that avoids genomic instability and causes transformed cells with a defective DNA to enter MC-associated apoptosis which eliminates the "dangerous" defective cells (review: Vitale et al. 2011). However, malignant neoplasms can also circumvent MC and its effects. In some malignancies, survivin (BIRC5) is upregulated and protects the cells from MC-associated cell death (Lamers et al. 2011). In HBV-positive hepatocellular carcinoma cells, disruption of kinase activities of ATM and ATR results in formation of multinucleated giant cells and promotes MC (Wang et al. 2012).

References

Aguilo JI, Anel A, Catalan E, Sebastian A, Acin-Pérez R, Naval J, Wallich R, Simon MM et al (2010) Granzyme B of cytotoxic T cells induces extramitochondrial reactive oxygen species production via caspase-dependent NADPH oxidase activation. Immunol Cell Biol 88:545–554

Akazawa Y, Cazanave S, Mott JL, Elmi N, Bronk SF, Kohno S, Charlton MR, Gores GJ (2010) Palmitoleate attenuates palmitate-induced Bim and PUMA up-regulation and hepatocyte lipoapoptosis. J Hepatol 52:586–593

Akazawa Y, Guicciardi ME, Cazanave SC, Bronk SF, Werneburg NW, Kakisaka K, Nakao K, Gores GJ (2013) Degradation of cIAPs contributes to hepatocyte lipoapoptosis. Am J Physiol Gastrointest Liver Physiol 305:G611–G619

Alkhouri N, Dixon LJ, Feldstein AE (2009) Lipotoxicity in nonalcoholic fatty liver disease: not all lipids are created equal. Expert Rev Gastroenterol Hepatol 3:445–451

Andrabi SA, Dawson TM, Dawson VL (2008) Mitochondrial and nuclear cross talk in cell death: parthanatos. Ann NY Acad Sci 1147:233–241

Baietti MF, Zhang Z, Mortier E, Melchior A, Degeest G, Geeraerts A, Ivarsson Y, Depoortere F et al (2012) Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. Nat Cell Biol 14:677–685

Bardens A, Döring T, Stieler J, Prange R (2011) Alix regulates egress of hepatitis B virus naked capsid particles in an ESCRT-independent manner. Cell Microbiol 13:602–619

Bhanot H, Young AM, Overmeyer JH, Maltese WA (2010) Induction of nonapoptotic cell death by activated Ras requires inverse regulation of Rac1 and Arf6. Mol Cancer Res 8:1358–1374

Bhatia A, Dey P (2013) Platelet internalization within the cancer cells: what is the significance? Diagn Cytopathol 41:659–660

Bialik S, Kimchi A (2014) The DAP-kinase interactome. Apoptosis 19:316–328

Bissig C, Gruenberg J (2014) ALIX and the multivesicular endosome: ALIX in Wonderland. Trends Cell Biol 24:19–25

Bröker LE, Kruyt FA, Giaccone G (2005) Cell death independent of caspases: a review. Clin Cancer Res 11:3155–3162

Broz P, Monack DM (2011) Molecular mechanisms of inflammasome activation during microbial infections. Immunol Rev 243:174–190

Bui CB, Shin J (2011) Persistent expression of Nqo1 by p62-mediated Nrf2 activation facilitates p53-dependent mitotic catastrophe. Biochem Biophys Res Commun 412:347–352

Burns ER (1967) Tumor cell-tumor emperipolesis. Exp Cell Res 48:229–231

Burns TF, Fei P, Scata KA, Dicker DT, El-Deiry WS (2003) Silencing of the novel p53 target gene Snk/Plk2 leads to mitotic catastrophe in paclitaxel (taxol)-exposed cells. Mol Cell Biol 23:5556–5571

Cai HB, Liu JK, Fan Q, Li X (2013) Methuosis: a novel type of cell death (in Chinese). Nan Fang Yi Ke Da Xue Xue Bao 33:1844–1847

Cano CE, Sandi MJ, Hamidi T, Calvo EL, Turrini O, Bartholin L, Loncle C, Secq V et al (2012) Homotypic cell cannibalism, a cell-death process regulated by the nuclear protein 1, opposes to metastasis in pancreatic cancer. EMBO Mol Med 4:964–979

Cao L, Han L, Zhang Z, Li J, Qu Z, Du J, Liang X, Liu Y, Liu H, Shi Y, Liu S, Gao L et al (2009) Involvement of anoikis-resistance in the metastasis of hepatoma cells. Exp Cell Res 315:1148–1156

Cao L, Zhang Z, Han L, Du J, Liang X, Liu Y, Sun W (2014) Mitogen-activated protein kinase pathway is pivotal for anoikis resistance in metastatic hepatoma cells. Mol Med Rep 9:1121–1127

Cappelli E, Townsend S, Griffin C, Thacker J (2011) Homologous recombination proteins are associated with centrosomes and are required for mitotic stability. Exp Cell Res 317:1203–1213

Caruso R, Fedele F, Luciano R, Branca G, Parisi C, Paparo D, Parisi A (2011a) Mitotic catastrophe in malignant epithelial tumors: the pathologist's viewpoint. Ultrastruct Pathol 35:66–71

Caruso RA, Fedele F, Crisafulli C, Paparo D, Parisi A, Luciano R, Cavallari V (2011b) Abnormal nuclear structures (micronuclei, nuclear blebs, strings, and pockets) in a case of anaplastic giant cell carcinoma of the thyroid: an immunohistochemical and ultrastructural study. Ultrastruct Pathol 35:14–18

Caruso RA, Fedele F, Finocchiaro G, Arena G, Venuti A (2012) Neutrophil-tumor cell phagocytosis (cannibalism) in human tumors: an update and literature review. Exp Oncol 34:306–311

Castedo M, Kroemer G (2004) Mitotic catastrophe: a special case of apoptosis (in French). J Soc Biol 198:97–103

Castedo M, Perfettini JL, Roumier T, Andreau K, Medema R, Kroemer G (2004) Cell death by mitotic catastrophe: a molecular definition. Oncogene 23:2825–2837

Cazanave SC, Gores GJ (2010) Mechanisms and clinical implications of hepatocyte lipoapoptosis. Clin Lipidol 5:71–85

Cazanave SC, Mott JL, Elmi NA, Bronk SF, Wernburg NW, Akazawa Y, Kahraman A, Garrison SP, Zambetti GP et al (2009) JNK1-dependent PUMA expression contributes to hepatocyte lipoapoptosis. J Biol Chem 284:26591–26602

Cazanave SC, Mott JL, Elmi NA, Bronk SF, Masuoka HC, Charlton MR, Gores GJ (2011) A role for miR-296 in the regulation of lipoapoptosis by targeting PUMA. J Lipid Res 52:1517–1525

Chemnitz J, Bichel P (1973) Tumour cell-tumour cell emperipolesis studied by transmission electron microscopy. Exp Cell Res 82:319–324

Chen L, Liu H, Liu J, Zhu Y, Xu L, He H, Zhang H, Wang S, Wu Q, Liu W, Liu Y et al (2013) Klotho endows hepatoma cells with resistance to anoikis via VEGFR2/PAK1 activation in hepatocellular carcinoma. PLoS One 8:e58413

Cheng TL, Lai CH, Jiang SJ, Hung JH, Liu SK, Chang BI, Shi GY, Wu HL (2014) RHBDL2 is a critical membrane protease for anoikis resistance in human malignant epithelial cells. Sci World J 2014:902987

Chen-Pan C, Yamamoto Y, Ito Y, Pan IJ, Hayashi Y (1996) A new type of cell death, the protruded type, observed in the adrenal gland of normal rats. J Vet Med Sci 58:373–376

Chiu LY, Ho FM, Shiah SG, Chang Y, Lin WW (2011) Oxidative stress initiates DNA damager MNNG-induced poly (ADP-ribose) polymerase-1-dependent parthanatos cell death. Biochem Pharmacol 81:459–470

David KK, Andrabi SA, Dawson TM, Dawson VL (2009) Parthanatos, a messenger of death. Front Biosci (Landmark Ed) 14:1116–1128

De Witt Hamer PC, Mir SE, Noske D, Van Noorden CJ, Würdinger T (2011) WEE1 kinase targeting combined with DNA-damaging therapy catalyzes mitotic catastrophe. Clin Cancer Res 17:4200–4207

Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN et al (2012) Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 149:1060–1072

Dodson H, Wheatley SP, Morrison CG (2007) Involvement of centrosome amplification in radiation-induced mitotic catastrophe. Cell Cycle 6:364–370

Drexler SK, Yazdi AS (2013) Complex roles of inflammasomes in carcinogenesis. Cancer J 19:468–472

Duprez L, Wirawan E, Vanden Berghe T, Vandenabeele P (2009) Major cell death pathways at a glance. Microbes Infect 11:1050–1062

Egnatchik RA, Leamy AK, Jacobson DA, Shiota M, Young JD (2014) ER calcium release promotes mitochondrial dysfunction and hepatic cell lipotoxicity in response to palmitate overload. Mol Metab 3:544–553

Eriksson D, Stigbrand T (2010) Radiation-induced cell death mechanisms. Tumour Biol 31:363–372

Fais S (2007) Cannibalism: a way to feed on metastatic tumors. Cancer Lett 258:155–164

Fais S, Fauvarque MO (2012) TM9 and cannibalism: how to learn more about cancer by studying maoebae and invertebrates. Trends Mol Med 18:4–5

Feng MX, Ma MZ, Fu Y, Li J, Wang T, Xue F, Zhang JJ, Qin WX, Gu JR, Zhang ZG, Xia Q (2014) Elevated autocrine EDIL3 protects hepatocellular carcinoma from anoikis through RGD-mediated integrin activation. Mol Cancer 13:226

Fernandes-Alnemri T, Alnemri ES (2008) Assembly, purification, and assay of the activity of the ASC pyroptosome. Methods Enzymol 442:251–270

Fernandes-Alnemri T, Wu J, Yu JW, Datta P, Miller B, Jankowski W, Rosenberg S et al (2007) The pyroptosome: a supramolecular assembly of ASC dimers mediating inflammatory cell death via caspase-1 activation. Cell Death Differ 14:1590–1604

Fink SL, Cookson BT (2005) Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. Infect Immun 73:1907–1916

Florey O, Overholtzer M (2012) Autophagy proteins in macroendocytic engulfment. Trends Cell Biol 22:374–380

Florey O, Kim SE, Sandoval CP, Haynes CM, Overholtzer M (2011) Autophagy machinery mediates macroendocytic processing and entotic cell death by targeting single membranes. Nat Cell Biol 13:1335–1343

Fragkos M, Beard P (2011) Mitotic catastrophe occurs in the absence of apoptosis in p53-null cells with a defective G1 checkpoint. PLoS One 6:e22946

Fraunholz M, Sinha B (2012) Intracellular Staphylococcus aureus: live-in and let die. Front Cell Infect Microbiol 2:43

Galimberti F, Thompson SL, Ravi S, Compton DA, Dmitrovsky E (2011) Anaphase catastrophe is a target for cancer therapy. Clin Cancer Res 17:1218–1222

Ghossoub R, Lembo F, Rubio A, Gaillard CB, Bouchet J, Vitale N, Slavik J, Machala M et al (2014) Syntenin-ALIX exosome biogenesis and budding into multivesicular bodies are controlled by ARF6 and PLD2. Nat Commun 5:3477

Gilloteaux J, Jamison JM, Arnold D, Summers JL (2001) Autoschizis: another cell death for cancer cells induced by oxidative stress. Ital J Anat Embryol 106(suppl 1):79–92

Gilloteaux J, Jamison JM, Lorimer HE, Jarjoura D, Taper HS, Calderon PB, Neal DR et al (2004) Autoschizis: a new form of cell death for human ovarian carcinoma cells following ascorbate-menadione treatment. Nuclear and DNA degradation. Tissue Cell 36:197–209

Gilloteaux J, Jamison JM, Arnold D, Neal DR, Summers JL (2006) Morphology and DNA degeneration during autoschizic cell death in bladder carcinoma T24 cells induced by ascorbate and menadione treatment. Anat Rec A Discov Mol Cell Evol Biol 288:58–83

Gonçalves AP, Maximo V, Lim J, Singh KK, Soares P, Videira A (2011) Involvement of p53 in cell death following cell cycle arrest and mitotic catastrophe induced by rotenone. Biochim Biophys Acta 1813:492–499

Grzanka D, Marszalek A, Izdebska M, Gackowska L, Andrzej Szczepanski M, Grzanka A (2011) Actin cytoskeleton reorganization correlates with cofilin nuclear expression and ultrastructural changes in cho aa8 cell line after apoptosis and mitotic catastrophe induction by doxorubicin. Ultrastruct Pathol 35:130–138

Hang ZB, Wei YQ, Wang YP, Xu NR (1991) Direct ultrastructural evidence of lymphocyte-mediated cancer cell lysis in the microenvironment of Chinese nasopharyngeal carcinoma. Hum Pathol 22:320–325

He MF, Wang S, Wang Y, Wang X (2013) Modeling cell-in-cell structure into its biological significance. Cell Death Dis 4:e630

Hendry JH, West CM (1997) Apoptosis and mitotic cell death: their relative contributions to normal-tissue and tumour radiation response. Int J Radiat Biol 71:709–719

Hoa et al. (2009) http://www.ncbi.nlm.nih.gov/pubmed/19247496

Horbinski C, Mojesky C, Kyprianou N (2010) Live free or die. Tales of homeless (cells) in cancer. Am J Pathol 177:1044–1052

Hu H, Li Z, Chen J, Wang D, Ma J, Wang W, Li J, Wu H, Li L, Wu M, Qian Q, Chen J et al (2011) P16 reactivation induces anoikis and exhibits antitumour potency by downregulating Akt/survivin signalling in hepatocellular carcinoma cells. Gut 60:710–721

Huang CT, Huang DY, Hu CJ, Wu D, Lin WW (2013) Energy adaptive response during parthanatos is enhanced by PD98059 and involves mitochondrial function but not autophagy induction. Biochim Biophys Acta 1843:531–543

Humble JG, Jayne WHW, Pulvertaft RJV (1956) Biological interaction between lymphocytes and other cells. Br J Haematol 2:283–294

Hwang SY, Yu SJ, Lee JH, Kim HY, Kim YJ (2015) Reduction of oxidative stress attenuates lipoapoptosis exacerbated by hypoxia in human hepatocytes. Int J Mol Sci 16:3323–3334

Imamura R, Wang Y, Kinoshita T, Suzuki M, Noda T, Sagara J, Taniguchi S, Okamoto H et al (2010) Anti-inflammatory activity of PYNOD and its mechanism in humans and mice. J Immunol 184:5874–5884

Imre G, Norberg HV, Imreh S, Zhivotovsky B (2011) Chromosomal breaks during mitotic catastrophe trigger γH2AX-ATM-p53-mediated apoptosis. J Cell Sci 124:2951–2963

Inanç B, Dodson H, Morrison CG (2010) A centrosome-autonomous signal that involves centriole disengagement permits centrosome duplication in G2 phase after DNA damage. Mol Biol Cell 21:3866–3877

Ivanovska J, Mahadevan V, Schneider-Stock R (2014) DAPK and cytoskeleton-associated functions. Apoptosis 19:329–338

Jamison JM, Gilloteaux J, Taper HS, Calderon PB, Summers JL (2002) Autoschizis: a novel cell death. Biochem Pharmacol 63:1773–1783

Janssen A, Medema RH (2011) Entosis: aneuploidy by invasion. Nat Cell Biol 13:199–201

Kamarajan P, Alhazzazi TY, Danciu T, D'Silva NJ, Verdin E, Kapila YL (2012) Receptor-interacting protein (RIP) and sirtuin-3 (SIRT3) are on opposite sides of anoikis and tumorigenesis. Cancer 118:5800–5810

Ke X, Li L, Dong HL, Chen ZN (2012) Acquisition of anoikis resistance through CD147 upregulation: a new mechanism underlying metastasis of hepatocellular carcinoma cells. Oncol Lett 3:1249–1254

Kim SE, Overholtzer M (2013) Autophagy proteins regulate cell engulfment mechanisms that participate in cancer. Semin Cancer Biol 23:329–336

Kimura et al. (2013) http://www.ncbi.nlm.nih.gov/pubmed/23598415

Kim J, Cha JH, Tisher CC, Madsen KM (1996) Role of apoptotic and nonapoptotic cell death in removal of intercalated cells from developing rat kidney. Am J Physiol 270:F575–F592

Kim YN, Koo KH, Sung JY, Yun UJ, Kim H (2012) Anoikis resistance: an essential prerequisite for tumor metastasis. Int J Cell Biol 2012:306879

Kitagawa K, Niikura Y (2008) Caspase-independent mitotic death (CIMD). Cell Cycle 7:1001–1005

Koh DW, Dawson TM, Dawson VL (2005) Mediation of cell death by poly 8 ADP-ribose) polymerase-1. Pharmacol Res 52:5–14

Kohl A, Grütter MG (2004) Fire and death: the pyrin domain joins the death-domain superfamily. CR Biol 327:1077–1086

Krajcovic M, Overholtzer M (2012) Mechanisms of ploidy increase in human cancers: a new role for cell cannibalism. Cancer Res 72:1596–1601

Krajcovic M, Johnson NB, Sun Q, Normand G, Hoover N, Yao E, Richardson AL et al (2011) A non-genetic route to aneuploidy in human cancers. Nat Cell Biol 13:324–330

Kumar S, Park SH, Cieply B, Schupp J, Killiam E, Zhang F, Rimm DL, Frisch SM (2011) A pathway for the control of anoikis sensitivity by E-cadherin and epithelial-to-mesenchymal transition. Mol Cell Biol 31:4036–4051

Lamers F, van der Ploeg I, Schild L, Ebus ME, Koster J, Hansen BR, Koch T, Versteeg R et al (2011) Knockdown of survivin (BIRC5) causes apoptosis in neuroblastoma via mitotic catastrophe. Endocr Relat Cancer 18:657–668

Lanz HL, Zimmermann RME, Brouwer J, Noteborn MHM, Backendorf C (2013) Mitotic catastrophe triggered in human cancer cells by the viral protein apoptin. Cell Death Dis 4:e487

Lin YC, Sun SH, Wang FF (2011) Suppression of Polo like kinase 1 (PLK1) by p21(Waf1) mediates the p53-dependent prevention of caspase-independent mitotic death. Cell Signal 23:1816–1823

Lin YC, Chen YN, Lin KF, Wang FF, Chou TY, Chen MY (2014) Association of p21 with NF-YA suppresses the expression of Polo-like kinase 1 and prevents mitotic death in response to DNA damage. Cell Death Dis 5:e987

Liu Y, Shoji-Kawata S, Sumpter RM, Wei Y, Ginet V, Zhang L, Posner B, Tran KA et al (2013) Autosis is a Na+, K+-ATPase-regulated form of cell death triggered by autophagy-inducing peptides, starvation, and hypoxia-ischemia. Proc Natl Acad Sci U S A 110:20364–20371

Louandre C, Ezzoukhry Z, Godin C, Barbare JC, Mazière JC, Chauffert B, Galmiche A (2013) Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib. Int J Cancer 133:1732–1742

Lugini L, Matarrese P, Tinari A, Lozupone F, Federici C, Iessi E, Gentile M, Luciani F et al (2006) Cannibalism of liver lymphocytes by human metastatic but not primary melanoma cells. Cancer Res 66:3629–3638

Lyons DJ, Gautam A, Clark J, Harries MG, Mitchell EB, Milledge JS, Balfour BM (1992) Lymphocyte macrophage interactions: peripolesis of human alveolar macrophages. Eur Respir J 5:59–66

Malhi H, Gores GJ (2008) Molecular mechanisms of lipotoxicity in nonalcoholic fatty liver disease. Semin Liver Dis 28:360–369

Malhi H, Bronk SF, Werneburg NW, Gores GJ (2006) Free fatty acids induce JNK-dependent hepatocyte lipoapoptosis. J Biol Chem 281:12093–12101

Malorni W, Matarrese P, Tinari A, Farrace MG, Piacentini M (2007) Xeno-cannibalism: a survival "escamotage". Autophagy 3:75–77

Mashimo M, Kato J, Moss J (2013) ADP-ribosyl-acceptor hydrolase 3 regulates poly (ADP-ribose) degradation and cell death during oxidative stress. Proc Natl Acad Sci U S A 110:18964–18969

Matarrese P, Ciarlo L, Tinari A, Piacentini M, Malorni W (2008) Xeno-cannibalism as an exacerbation of self-cannibalism: a possible fruitful survival strategy for cancer cells. Curr Pharm Des 14:245–252

McFarland W (1970) Emperipolesis. N Engl J Med 282:168

Medawar PB (1952) An unsolved problem in biology. H.K. Lewis, London

Miyamoto Y, Mauer AS, Kumar S, Mott JL, Malhi H (2014) Mmu-miR-615-3p regulates lipoapoptosis by inhibiting C/EBP homologous protein. PLoS One 9: e109637

Miyazaki T, Shen M, Fujikura D, Tosa N, Kim HR, Kon S, Uede T, Reed JC (2004) Functional role of death-associated protein 3 (DAP3) in anoikis. J Biol Chem 279:44667–44672

Natarajan SK, Ingham SA, Mohr AM, Wehrkamp CJ, Ray A, Roy S, Cazanave SC, Phillippi MA, Mott JL (2014) Saturated free fatty acids induce cholangiocyte lipoapoptosis. Hepatology 60:1942–1956

Niida H, Tsuge S, Katsuno Y, Konishi A, Takeda N, Nakanishi M (2005) Depletion of Chk1 leads to premature activation of Cdc2-cyclin B and mitotic catastrophe. J Biol Chem 280:39246–39252

Niikura Y, Dixit A, Scott R, Perkins G, Kitagawa K (2007) BUB1 mediation of caspase-independent mitotic death determines cell fate. J Cell Biol 178:283–296

Niikura Y, Ogi H, Kikuchi K, Kitagawa K (2010) BUB3 that dissociates from BUB1 activates caspase-independent mitotic death (CIMD). Cell Death Differ 17:1011–1024

Oikonomou C, Cross FR (2011) Rising cyclin-CDK levels order cell cycle events. PLoS One 6:e20788

Okabe H, Ishimoto T, Mima K, Nakagawa S, Hayashi H, Kuroki H, Imai K, Nitta H, Saito S, Hashimoto D et al (2014) CD44s signals the acquisition of the mesenchymal phenotype required for anchorage-independent cell survival in hepatocellular carcinoma. Br J Cancer 110:958–966

Overholtzer M, Mailleux AA, Mouneinme G, Normand G, Schnitt SJ, King RW, Cibas ES et al (2007) A nonapoptotic cell death process, entosis, that occurs by cell-in-cell invasion. Cell 131:966–979

Overmeyer JH, Young AM, Bhanot H, Maltese WA (2011) A chalcone-related small molecular that indices methuosis, a novel form of non-apoptotic cell death, in glioblastoma cells. Mol Cancer 10:69

Ozaki T, Nakagawara A (2005) p73, a sophisticated p53 family member in the cancer world. Cancer Sci 96:729–737

Pan J, Hu H, Zhou Z, Sun L, Peng L, Yu L, Sun L, Liu J, Yang Z, Ran Y (2010) Tumor-suppressive mir-663 gene induces mitotic catastrophe growth arrest in human gastric cancer cells. Oncol Rep 24:105–112

Pannu V, Rida PC, Ogden A, Clewley R, Cheng A, Karna P, Lopus M, Mishra RC et al (2012) Induction of robust de novo centrosome amplification, high-grade spindle multipolarity and metaphase catastrophe: a novel chemotherapeutic approach. Cell Death Dis 3:e346

Paoli P, Giannoni E, Chiarugi P (2013) Anoikis molecular pathways and its role in cancer progression. Biochim Biophys Acta 1833:3481–3498

Paunescu V, Bojin FM, Gavriliuc OI, Taculescu EA, Ianos R, Ordodi VL, Iman VF et al (2014) Enucleation: a possible mechanism of cancer cell death. J Cell Mol Med. doi:10.1111/jcmm.12271

Poehlmann A, Habold C, Walluscheck D, Reissig K, Bajboui K, Ullrich O, Hartig R et al (2011) Cutting edge: Chk1 directs senescence and mitotic catastrophe in recovery from G2 checkpoint arrest. J Cell Mol Med 15:1528–1541

Portugal J, Mansilla S, Bataller M (2010) Mechanisms of drug-induced mitotic catastrophe in cancer cells. Curr Pharm Des 16:69–78

Qian Y, Shi Y (2009) Natural killer cells go inside: entosis versus cannibalism. Cell Res 19:1320–1321

Ratsimandresey RA, Dorfleutner A, Stehlik C (2013) An update on PYRIN domain-containing pattern recognition receptors: from immunity to pathology. Front Immunol 4:440

Roninson IB, Broude EV, Chang BD (2001) If not apoptosis, then what? Treatment-induced senescence and mitotic catastrophe in tumor cells. Drug Resist Updat 4:303–313

Routray S, Shankar AA, Swain N (2014) Does entosis curb the detached cancer cells better? Oral Oncol 50:e9–e11

Salvesen GS (2014) Dying from within: granzyme B converts entosis to emperipolesis. Cell Death Differ 21:3–4

Sarode SC, Sarode GS (2014a) Cellular cannibalism in central and peripheral giant cell granuloma of the oral cavity can predict biological behavior of the lesion. J Oral Pathol Med 43:459–463

Sarode SC, Sarode GS (2014b) Neutrophil-tumor cell cannibalism in oral squamous cell carcinoma. J Oral Pathol Med 43:454–458

Satoh T, Kambe N, Matsue H (2013) NLRP3 activation induces ASC-dependent programmed necrotic cell death, which leads to neutrophilic inflammation. Cell Death Dis 4:e644

Seessle J, Liebisch G, Schmitz G, Stremmel W, Chamulitrat W (2015) Palmitate activation by fatty acid transport protein 4 as a model system for hepatocellular apoptosis and steatosis. Biochim Biophys Acta 1851:549–565

Sharma N, Dey P (2011) Cell cannibalism and cancer. Diagn Cytopathol 39:229–233

Sharma SS, Ma L, Bagui TK, Forinash KD, Pledger WJ (2012) A p27 (Kip1) mutant that does not inhibit CDK activity promotes centrosome amplification and micronucleation. Oncogene 31:3989–3998

Shen X, Kramer RH (2004) Adhesion-mediated squamous cell carcinoma survival through ligand-independent activation of epidermal growth factor receptor. Am J Pathol 165:1315–1329

Shih HJ, Chu KL, Wu MH, Wu PH, Chang WW, Chu JS, Wang LH, Takeuchi H et al (2012) The involvement of MCT-1 oncoprotein in inducing mitotic catastrophe and nuclear abnormalities. Cell Cycle 11:934–952

Shinomiya N (2001) New concepts in radiation-induced apoptosis:'premitotic apoptosis' and 'postmitotic apoptosis'. J Cell Mol Med 5:240–253

Simpson CD, Anyiwe K, Schimmer AD (2008) Anoikis resistance and tumor metastasis. Cancer Lett 272:177–185

Singhal N, Handa U, Bansal C, Mohan H (2011) Neutrophil phagocytosis by tumor cells – a cytological study. Diagn Cytopathol 39:553–555

Skulachev VP (1999) Phenoptosis: programmed cell death of an organism. Biochemistry (Mosc) 64:1418–1426

Sommerfeld A, Reinehr R, Häussinger D (2015) Free fatty acids shift insulin-induced hepatocyte proliferation towards CD95-dependent apoptosis. J Biol Chem 290:4398–4409

Sperandio S, de Belle I, Bredesen DA (2000) An alternative, nonapoptotic form of programmed cell death. Proc Natl Acad Sci U S A 97:14376–14381

Sperandio S, Poksay K, de Belle I, Lafuente MJ, Liu BM, Nasir J, Bredesen DE (2004) Paraptosis: mediation by MAP kinases and inhibition by AIP-1/Alix. Cell Death Differ 11:1066–1075

Stehlik C, Lee SH, Dorfleutner A, Stassinopoulos A, Sagara J, Reed JC (2003) Apoptosis-associated speck-like protein containing a caspase recruitment domain is a regulator of procaspase-1 activation. J Immunol 171:6154–6163

Sun K, Deng W, Zhang S, Cai N, Jiao S, Song J, Wie L (2013) Paradoxical roles of autophagy in different stages of tumorigenesis: protector for normal or cancer cells. Cell Biosci 3:35

Sun L, Li T, Wei Q, Zhang Y, Jia X, Wan Z, Han L (2014) Upregulation of BNIP3 mediated by ERK/HIF-1α pathway induces autophagy and contributes to anoikis resistance of hepatocellular carcinoma cells. Future Oncol 10:1387–1398

Taddei ML, Giannoni E, Fiaschi T, Chiarugi P (2012) Anoikis: an emerging hallmark in health and diseases. J Pathol 226:380–393

Tan S, Schubert D, Maher P (2001) Oxytosis: a novel form of programmed cell death. Curr Top Med Chem 1:497–506

Tan K, Goldstein D, Crowe P, Yang JL (2013) Uncovering a key to the progress of metastasis in human cancers: a review of critical regulators of anoikis. J Cancer Res Clin Oncol 139:1795–1805

Tinari A, Matarrese P, Minetti M, Malorni W (2008) Hyperphagia by self-and xeno-cannibalism: cell death by indigestion?: a reminiscence of the Phedrus Fabula "Rana Rupta et Bos"? Autophagy 4:128–130

Torriglia A, Leprêtre C (2009) LEI/L-DNase II: interplay between caspase-dependent and independent pathways. Front Biosci (Landmark Ed) 14:4836–4847

Uekita T, Jia L, Narisawa-Saito M, Yokota J, Kiyono T, Sakai R (2007) CUB domain-containing protein 1 is a novel regulator of anoikis resistance in lung adenocarcinoma. Mol Cell Biol 27:7649–7660

Unger RH, Orci L (2002) Lipoapoptosis: its mechanism and its diseases. Biochim Biophys Acta 1585:202–212

Virag L, Robaszkiewicz A, Rodriguez-Vargas JM, Oliver FJ (2013) Poly (ADP-ribose) signaling in cell death. Mol Aspects Med 34:1153–1167

Viry E, Baginska J, Berchem G, Noman MZ, Medves S, Chouaib S, Janji B (2014) Autophagic degradation of GZMB/branzyme B: a new mechanism of hypoxic tumor cell escape from natural killer cell-mediated lysis. Autophagy 10:173–175

Vitale I, Galluzzi L, Castedo M, Kroemer G (2011) Mitotic catastrophe: a mechanism for avoiding genomic instability. Nat Rev Mol Cell Biol 12:385–392

Wang NS, Seemayer TA, Ahmed MN, Knaack J (1976) Giant cell carcinoma of the lung. A light and electron microscopic study. Hum Pathol 7:3–16

Wang Y, Hasegawa M, Imamura R, Kinoshita T, Kondo C, Konaka K, Suda T (2004) PYNOD, a novel Apaf-1/CED4-like protein is an inhibitor of ASC and caspase-1. Int Immunol 16:777–786

Wang Y, Dawson VL, Dawson TM (2009a) Poly (ADP-ribose) signals to mitochondrial AIF: a key event in parthanatos. Exp Neurol 218:193–202

Wang S, Guo Z, Xia P, Liu T, Wang J, Li S, Sun L, Wen Q, Zhou M, Mal L, Ding X et al (2009b) Internalization of NK cells into tumor cells requires ezrin and leads to programmed cell-in-cell death. Cell Res 19:1350–1362

Wang Y, Kim NS, Haince JF, Kang HC, David KK, Andrabi SA, Poirier GG, Dawson VL et al (2011) Poly (ADP-ribose) bidning to apoptosis-inducing factor is critical for PAR polymerase-1-dependent cell death (parthanatos). Sci Signal 4(167):ra20

Wang H, Zuo B, Wang H, Ren L, Yang P, Zeng M, Duan D, Liu C, Li M (2012) CGK733 enhances multinucleated cell formation and cytotoxicity induced by taxol in Chk1-deficient HBV-positive hepatocellular carcinoma cells. Biochem Biophys Res Commun 422:103–108

Wang S, He MF, Chen Y, Wang MY, Yu XM, Bai J, Zhu HY, Wang YY, Zhao H et al (2013a) Rapid reuptake of granzyme B leads to emperitosis: an apoptotic cell-in-cell death of immune killer cells inside tumor cells. Cell Death Dis 4:e856

Wang Q, Imamura R, Motani K, Kushiyama H, Nagata S, Suda T (2013b) Pyroptotic cells externalize eat-med and release find-me signals and are efficiently engulfed by macrophages. Int Immunol 25:363–372

Wei YQ, Hang ZB (1989) In situ observation of lymphocyte-tumor cell interaction in human lung carcinoma. Immunol Invest 18:1095–1105

Weissmann A (1889) Essays upon heredity and kindred biological problems. Claderon Press, Oxford

Welin A, Eklund D, Stendahl O, Lerm M (2011) Human macrophages infected with a high burden of ESAT-6-expressing M. tuberculosis undergo caspase-1-and cathepsin B-independent necrosis. PLoS One 6:e20302

Willingham SB, Bergstralh DT, O'Connor W, Morrison AC, Taxman DJ, Duncan JA et al (2007) Microbial pathogen-induced necrotic cell death mediated by the inflammasome components CIAS1/cryopyrin/NLRP3 and ASC. Cell Host Microbe 2:147–159

Wu YH, Kuo WC, Wu YJ, Yang KT, Chen ST, Jiang ST, Gordy C, He YW, Lai MZ (2014) Participation of c-FLIP in NLRP3 and AIM2 inflammasome activation. Cell Death Differ 21:451–461

Xia P, Wang S, Guo Z, Yao X (2008) Emperipolesis, entosis and beyond: dance with fate. Cell Res 18:705–707

Xu J, Liu H, Chen L, Wang S, Zhou L, Yun X, Sun L, Wen Y, Gu J (2012) Hepatitis B virus X protein confers resistance of hepatoma cells to anoikis by up-regulating and activating p21-activated kinase 1. Gastroenterology 143:199–212

Yang YQ, Li JC (2012) Progress of research in cell-in-cell phenomena. Anat Rec (Hoboken) 295:372–377

Yang J, Zheng Z, Yan X, Li X, Liu Z, Ma Z (2013) Integration of autophagy and anoikis resistance in solid tumors. Anat Rec (Hoboken) 296:1501–1508

Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS et al (2014) Regulation of ferroptotic cancer cell death by GPX4. Cell 156:317–331

Zambo V, Simon-Szabo L, Szelenyi P, Kereszturi E, Banhegyi G, Csala M (2013) Lipotoxicity in the liver. World J Hepatol 5:550–557

Zhan M, Zhao H, Han ZC (2004) Signalling mechanisms of anoikis. Histol Histopathol 19:973–983

Zhang Z, Cao L, Li J, Liang X, Liu Y, Liu H, Du J, Qu Z, Cui M, Liu S, Gao L, Ma C et al (2008) Acquisition of anoikis resistance reveals a synoikis-like survival style in BEL7402 hepatoma cells. Cancer Cells 267:106–115

Zhang X, Cheng SL, Bian K, Wang L, Zhang X, Yan B, Jia LT, Zhao J, Gammoh N, Yang AG, Zhang R (2015) MicroRNA-26a promotes anoikis in human hepatocellular carcinoma cells by targeting alpha5 integrin. Oncotarget 6:2277–2289

Zhou Z, Deng H, Yan W, Luo M, Tu W, Xia Y, He J, Han P, Fu Y, Tian D (2014) AEG-1 promotes anoikis resistance and orientation chemotaxis in hepatocellular carcinoma cells. PLoS One 9:e100372

Necrobiology of Liver Cancer: Necrosis and Necroptosis

178

Contents

Abstract

Necrosis is a non-apoptotic form of cell death that comprises a broad spectrum of regressive changes and their causes. Formerly, all forms of necrosis, including that occurring in neoplasms, were regarded as a passive process, ischemic necrosis being a typical examples. Passive necrosis of the tissue in the absence of oxygen or other fuels, or due to physical stress such as heat or freezing, certainly occurs. However, recent findings show that various forms of necrosis are not an uncontrolled, passive, or even chaotic process, but rather a regressive change that is subject to programmed initiation and progression (regulated necrosis). Initiation of regulated necrosis requires a complex cross talk of target cells involving various signaling pathways that regulate cell survival versus non-survival. The signaling platform that regulates orderly initiation and progression of necrosis is the so-called necrosome, a platform that senses cellular ATP depletion and transmits signals of cellular stress to a system of kinases with a death domain. These are the receptor-interacting protein (RIP) serine/threonine kinases, RIP1 and RIP3, which act as execution switches in regulated necrosis. Programmed necrosis is also termed necroptosis, in analogy to apoptosis.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_178

Necrosis: Unregulated Versus Regulated Necrosis

Necrosis, a long known non-apoptotic form of cell and tissue death that represents a broad spectrum of decay patterns also predominating in cancers, has previously been regarded as a "passive," unregulated, or even "chaotic" phenomenon. For example, ischemic necrosis was thought to happen because cells have exhausted their oxygen and fuel resources and then "just die." There are certainly forms of necrosis characterized by passive cell decay, e.g., in situations of massive and abrupt failure of oxygen and/or fuel supply, or due to physical stress such as heat or freezing. However, recent findings clearly show that certain forms of necrosis are not an uncontrolled process, but rather a regressive change that is as well programmed and controlled as apoptosis (regulated necrosis, RN; reviews: Leist and Nicotera 1997; Nicotera et al. 1999; Proskuryakov et al. 2002, 2003; Festjens et al. 2006; Golstein and Kroemer 2007; Vanlangenakker et al. 2008; Proskuryakov and Gabai 2010; Galluzzi et al. 2014).

Morphology of Tumor Necrosis in Liver Cancers

Necrosis of Hepatocellular Carcinoma: Macroscopy

The macroscopic presentation of necrosis in hepatocellular carcinoma (HCC) depends on the extent of the necrosis and cellular/stromal composition of the tumors. On cut surfaces of non-fixed tumors, small necrotic foci appear as whitish speckles or yellowish-white soft spots. Such necroses are mainly seen in neoplasms with a high parenchyma-to-stroma ratio and in poorly differentiated cancers with high cellularity. Multiple spotty necroses may be associated with small hemorrhages. Large necroses, which often occupy central parts of tumors, show a soft mass of grayish-white tissue with an either homogeneous or slightly granular texture. In cellular, stroma-poor (medullary) fresh neoplasms, the center of necrosis may drop off after cutting or part of the necrotic tissue sticks to the knife. Following fixation, the cut surface of large necroses typically shows cracks or slits. The centermost part of necrosis sometimes undergoes liquification, leaving a cyst-like space, but large cysts are unusual in HCCs. Tumors with lower cellularity and higher content in extracellular matrix and stroma usually display a more compact type of necrosis and more often a granular cut surface. In part of neoplasms with a medullary, highly cellular composition (encephaloid liver cancer; Rokitansky 1852), cutting with a knife results in release of viable cells and necrotic cells leaving a creamy matter on the blade (the "cancer juice" or "cancer milk" of old pathology descriptions). Large necroses may undergo massive hemorrhage, sometimes resulting in a lesion that can hardly be distinguished from a hematoma. In HCCs invading the biliary tract, bile can enter the tumor and cause yellow staining of necroses. Rarely, large necroses become infected, resulting in abscess formation in the necrotic tissue. Massive macroscopic necrosis is also found in HCCs invading the portal or hepatic veins and in tumors invading the biliary tract. Necrotic intrabiliary HCC can give rise to so-called intraductal tumor emboli. As liver cancers are highly arterialized, complete interruption of the arterial supply, i.e., due to thrombosis and/or extensive tumor invasion, results in massive ischemia followed by anemic tumor infarction. Marked necrosis of HCCs located close to the hepatic capsule may result in tumor rupture, necrotic tumor tissue with or without gross hemorrhage escaping through capsular gaps into the peritoneal space. In patients with ascites, necrotic tumor fragments are then found floating in the ascitic fluid and can settle in the pelvic Douglas recessus.

Necrosis of Hepatocellular Carcinoma: Histopathology

Histologically, necrosis usually presents the phenotype of coagulation necrosis, with an eosinophilic and slightly granular mass. Remnants of tumor cells may be seen as ill-defined eosinophilic

bodies (ghost cells), with or without chromatin dots. Pycnotic tumor cell nuclei and karyorrhectic structures are found (Figs. 1, 2, 3, and 4). Toward the periphery of tumor nodes, a gradual transition from necrotic cells to viable cells is seen. In case of preserved and perfused tumor vessels, the vessels are surrounded by a rim of viable carcinoma cells, forming a cuff up to about ten cells thick. The former architecture of the tumor is discernible in reticulin stains, where also the tumor vessels are visualized. The macrotrabecular structure of HCCs is often still present in reticulin preparations of necrotic tumors, an important element for diagnosis. Some necroses exhibit dystrophic calcifications.

Cholangiocarcinoma

In contrast to HCCs and metastatic carcinomas, many forms of extrahepatic and intrahepatic cholangiocarcinomas usually do not exhibit

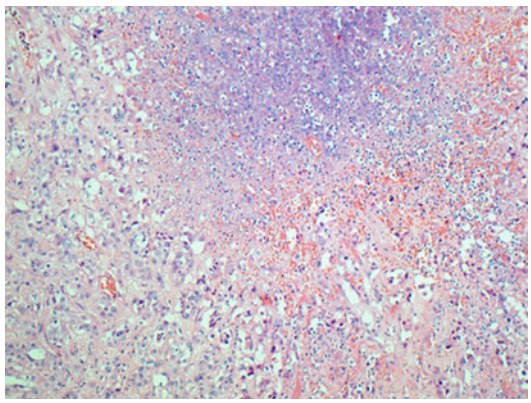

Fig. 1 Fresh hypoxic/ischemic tumor necrosis. The basophilic area (*top half* of figure) contains numerous nuclear debris (karyorrhexis) and pycnotic nuclei (hematoxylin and eosin stain)

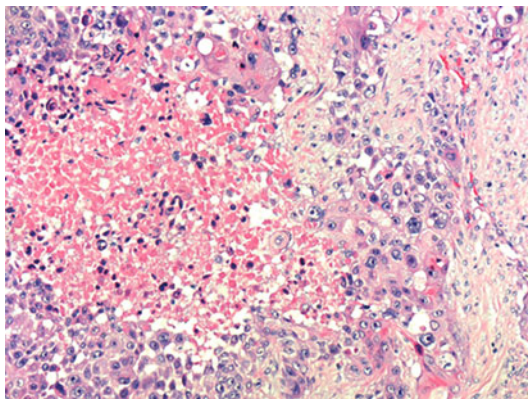

Fig. 2 Ischemic/hypoxic necrosis of hepatic carcinoma. Necrosis (*left half* of figure) is characterized by eosinophilic cell shadows (cells undergoing cytolysis and karyolysis) and accumulation of pycnotic, condensed nuclei, and karyorrhectic debris (hematoxylin and eosin stain)

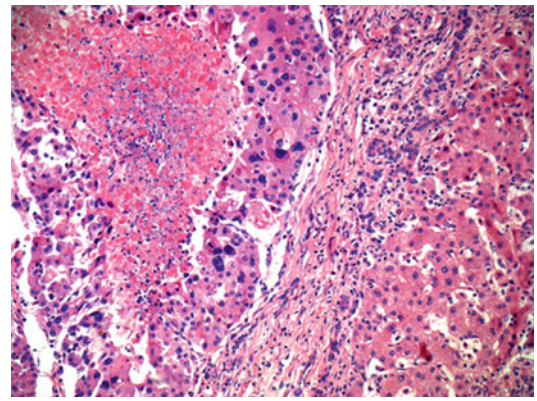

Fig. 3 Hepatocellular carcinoma with hypoxic/ischemic necrosis. Tumor tissue facing perfused blood vessels (*middle* and *left*) remains intact with a perivascular cell layer not exceeding approximately ten cells, while cells beyond this sufficient oxygen diffusion distance underwent necrosis (hematoxylin and eosin stain

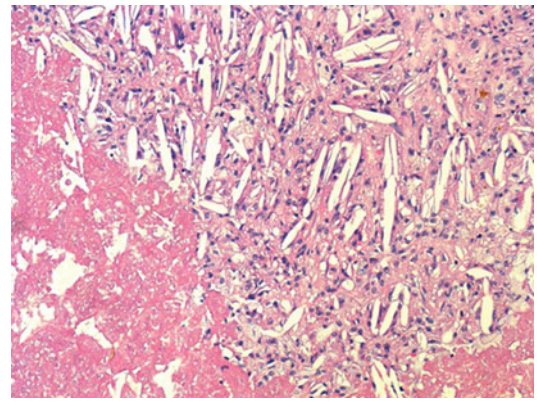

Fig. 4 In older tumor necrosis, cholesterol crystals can be formed from decay of cell membranes with cholesterol release, associated with a macrophage reaction (hematoxylin and eosin stain)

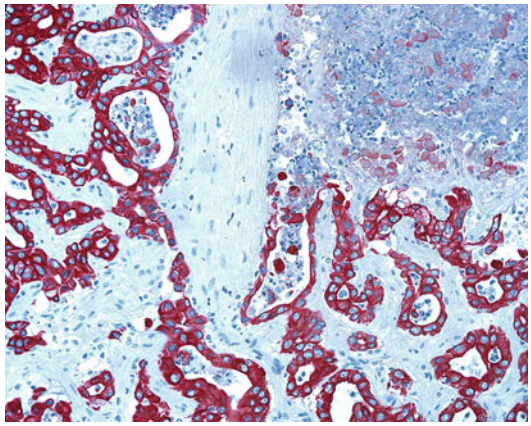

Fig. 5 Cholangiocarcinoma with focal necrosis (*right upper corner*). In this cytokeratin stain, necrotic tumor cells in part still express minor amounts of cytokeratins. There is an abrupt transition from viable to necrotic cancer tissue (CAM5.2 immunostain)

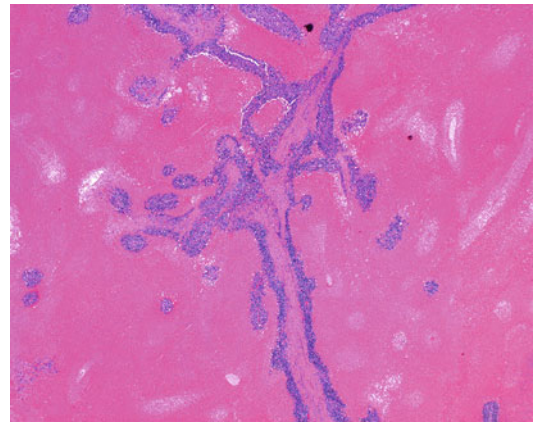

Fig. 6 Small cell undifferentiated carcinoma with hypoxic/ischemic necrosis. Most of the neoplasms consist of an eosinophilic necrotic mass. Preserved tumor cells form perivascular basophilic cuffs with a characteristic width depending on the oxygen diffusion distance (hematoxylin and eosin stain)

large, soft, and friable necroses, predominantly due to the high stromal content. Hilar/perihilar cholangiocarcinomas (Klatskin tumors) are firm tumors that are devoid of mass necrosis, but may show small necrotic foci at macroscopic examination. Larger necroses are eventually encountered in mass-forming intrahepatic cholangiocarcinoma, but are more commonly found in large intraductal tumors. In the latter, and similar to HCC, necrotic parts may detach from the main tumor (tumor amputation), float within the ductal system, and eventually cause obstruction (so-called tumor emboli). Histologically, tumor necrosis ranges from small necrotic foci to large areas with effacement of the tumor structure (Fig. 5). In tumors undergoing ischemic necrosis, amputation of stroma may be seen, with an abrupt transition of cancer cell-containing stroma to acellular areas. In connective tissue stains, the original structure of the stroma may still be discerned.

Liver Metastasis of Carcinomas

Necrosis of carcinoma metastases of the liver mainly depends on tumor type, differentiation/grade, tumor size, vascularization mode/hypoxia, and genomic instability. Massive metastatic necrosis is frequently found in large and poorly differentiated tumors, but also well-differentiated carcinomas can show marked necrosis in case they are large and poorly vascularized. Small metastatic foci often display necrosis when the neoplasms exhibit rapid proliferation associated with genomic instability and abnormal mitotic pathways and poor differentiation. In this situation, subsets of tumor cells can undergo a sudden "crash" visualized as necrosis with numerous shadow cells. Also small metastatic lesions are subject to hypoxia causing ischemic necrosis. Here, a thin rim of preserved cells, often with a thickness of around ten cells, remains as a cuff surrounding a feeding blood vessel, followed by a rather abrupt transition into necrotic tumor tissue (Fig. 6). This phenomenon is caused by sudden failure of oxygen diffusion into a zone beyond a distinct stretch of a few perivascular cells. Large metastases, in particular colorectal carcinomas, show a characteristic form of necrosis. It is characterized by a central zone of complete or almost complete tissue breakdown, with loss of texture, a pale eosinophilic mass with some shadow cells, few nuclear fragments, and traces of tumor vessels. The latter can be shown in more detail by the use of connective tissue stains and specifically reticulin stains. The central tumor necrosis can contain dystrophic calcifications. Long-standing

metastases can undergo cystic change. The lesions may also be infected by bacteria, but purulent inflammation of even abscess formation is unusual in large metastases, because neutrophils cannot infiltrate the necrotic tissue owing to loss of perfused vessels. In case the necrotic metastasis involves bile ducts in the vicinity, bile can enter the necrotic tumor, staining it yellow. The central necrosis blends into a more peripheral zone where some remnants of preserved carcinoma tissue are found. Tubular or cribriform structures may look like "amputated," with a necrotic part facing the tumor center and a viable part facing the tumor periphery. Many necrotic metastases exhibit a viable rim of cancer tissue at the periphery, where tumor blood flow is preserved, but there are also lesions that are apparently completely necrotic. In metastases having been treated with chemoembolization, the necrotic tissue contains visible embolization material, either within damaged blood vessels or freely within tumor tissue.

Necrosis and the Necrosome: Necrosis as a Controlled Process

In the initiation and progression of necrosis, cells involved in this process engage in a complex cross talk based on various signaling pathways that regulate survival versus non-survival. The platform that is in the center of this interactome and the associated signaling pathways is the so-called necrosome, a platform that reacts to intracellular ATP depletion (see below; reviews: Nicotera et al. 1998; Galluzzi et al. 2011). There is evidence that the receptor-interacting protein (RIP) serine/threonine kinases, RIP1 and RIP3 kinases, with a death domain, act as a central switch in initiation of necrosis, while progression is strongly influenced by reactive oxygen species (ROS) and calcium ions (Festjens et al. 2006). In the setting of necrosis, RIP1 and RIP3 are activated by numerous signals, including TNF, TRAIL, oxidative stress, and DNA damage-associated activity of poly-ADP-ribose polymerase (Vandenabeele et al. 2010b; Cho et al. 2011). In TNF-induced necrosis, mixed lineage kinase domain-like (MLKL) is a key RIP3 downstream component, whereby MLKL is recruited to the necrosome through its interaction with RIP3. MLKL is also required for the generation of ROS and a late-phase activation of JNK (Zhao et al. 2012). Activated RIP1 initiates mitochondrial permeability transition (MPT), which in turn results in mitochondrial collapse and the activation of various proteases that act on membranes and organelles, including phospholipases, calpains, and cathepsins, followed by the typical decay of organelles, destruction of the nuclear membrane, and fragmentation of the cell surface membrane (Proskuryakov and Gabai 2010). Normal and cancer cells undergoing necrosis release, during the dying process, numerous signaling substances, including chemokines and cytokines, that can drive a necrosis-associated inflammatory response. A central place in the initiation of this necrosis-associated inflammation is hold by the necrosome, which releases a spectrum of signaling components, specifically RIP1, RIP3, and caspase-8 (review: Wallach et al. 2011).

Secondary Necrosis

In some situations, apoptosis can undergo a transition to a form of necrotic cell death involving the activation of self-hydrolytic enzymes, irreparable damage of cell membranes, and swelling of cells and apoptotic bodies. This process is called secondary necrosis. In vivo, secondary necrosis occurs when massive apoptosis overwhelms scavenging capacity or when scavenger mechanisms are impaired (review: Silva et al. 2008; Silva 2010).

Necroptosis, Necrosome, Necroapoptosis, Aponecrosis, and Necrotaxis

Necroptosis and the Necrosome

In cells lacking the capacity to activate caspase-8 following death receptor binding, cell death does not occur by apoptosis, but rather by a process termed programmed necrosis, or necroptosis

(reviews: Dunai et al. 2011; Lu and Walsh 2012; Wu et al. 2012; Zhou et al. 2012; Fayaz et al. 2014; Giampietri et al. 2014; Linkermann and Green 2014; Murphy and Silke 2014; Van den Berghe et al. 2014; Wei et al. 2014). Necroptosis may represent an isolated element of what is necrosis in its modern concept and is mediated by the necrosome. Apart from its role in the elimination of neoplastic cells, necroptosis is a process active in the regulation of several types of inflammation (Pasparakis and Vandenabeele 2015). The RIP kinase (receptor-interacting protein kinase (RIPK))-containing necrosome is a multiprotein platform that triggers cell death by necroptosis. In principle, necroptosis is a cell death receptor-induced, but caspase-independent regulated type of programmed cell death with morphological resemblance to classical necrosis (Dunai et al. 2011). Necroptosis requires a functional ripoptosome/necrosome in the absence of caspase-8, hence depends on functional RIP1 and RIP3 serine/threonine kinases (RIPK1 and RIPK3; the RIP1-RIP3 necrosome; Lee et al. 2003; Cho et al. 2009; Moriwaki and Chan 2013; Khan et al. 2014; Newton et al. 2014) that are recruited by death receptors (Vandenabeele et al. 2010a; Smith and Yellon 2011) and can be induced by TNF that can activate the critical receptor-interacting protein kinase 3 (RIPK3) in the absence of RIPK1 (Moujalled et al. 2013). In the TNF alpha-induced necrosome, RIP1 is deubiquitinated by the cylindromatosis (CYLD) protein, CYLD thereby controlling RIP1 kinase activity during necrosome assembly (Moquin et al. 2013). A further protein contained in the necrosome is mixed lineage kinase domain-like (MLKL), a pseudokinase required for the necroptosis pathway downstream of RIPK3 (Murphy et al. 2013). Necroptosis caused by RIPK3 requires MLKL which in turn is activated by RIPK3 (Moujalled et al. 2014). The kinases of the RIP1/RIP3 necrosome can form a thioflavine-T- and Congo red-positive beta-amyloid-like signaling complex with a fibrillar core structure (Li et al. 2012). Necroptosis can also be induced by TRAIL (tumor necrosis factor (TNF)-related apoptosis inducing ligand), a well-known apoptosis inducer, via involvement of RIPk1-/RIPK3-dependent PARP-1 (poly-ADP-ribose polymerase-1) activation (Jouan-Lanhouet et al. 2012). The execution of necroptosis requires production of reactive oxygen species (ROS) by the mitochondria. This pathway is linked to RIPK1-dependent phosphorylation of STAT3, which in turn induces interaction with GRIM-19, a subunit of the mitochondrial complex I, with subsequent translocation of STAT3 to the mitochondria, where it induces ROS generation (Shulga and Pastorino 2012). Necroptosis can specifically be inhibited by small molecular inhibitors such as necrostatin-1 (Nec-1; Tischner et al. 2012), suggesting that modulation of necroptosis might be employed in cancer therapy (Yu et al. 2013). Necroptosis is linked to release mechanisms for DAMPs (damage-associated molecular patterns), in that RIP1 interacts with a Toll-like receptor 3-induced adaptor, TICAM-1/TRIF involved in DAMP release (Seya et al. 2012).

Necroapoptosis and Aponecrosis

The term necrapoptosis was chosen to emphasize shared mitochondrial pathways in apoptosis and necrosis, involving the mitochondrial permeability transition (MPT), a process characterized by opening of a high-conductance pore conducting solutes of a molecular mass $<$1,500 Da. The availability of ATP decides whether apoptosis or rather necrosis develop (Nicotera et al. 1998, 1999; Lemasters 1999; Lemsters et al. 1999). Others employed the term aponecrosis to denote this form of cell death intermediate between apoptosis and necrosis (Formigli et al. 2000).

Necrotaxis

Necrotaxis denotes an apparently distinct type of chemotaxis in which positive chemotactic or chemokinetic stimuli are released from necrotic tissue or apoptotic cells (Hu and Barnes 1970; Bessis 1974; Debru 1993). Necrotaxis may play a role in the clearance of necrotic or apoptotic cells and involves the attraction of phagocytes to

dead cells or fragments thereof. There is evidence that necrotic or apoptotic cells and tissue components can also repel phagocytes, a phenomenon termed negative necrotaxis (Ragot 1993).

The Apoptosis-Necroptosis Switch

Which mechanisms decide whether a cell death program switches from apoptosis to necroptosis or other forms of regulated necrosis? When caspase-8 is activated, it drives the process along the apoptosis program and blocks RIPK3-dependent necroptosis. Prolonged and marked activation of TAK1 kinase by TNF induces phosphorylation and activation of RIPK3 leading to regulated necrosis without caspase activation, whereby RIPK1 and RIPK3 promote TAK1 kinase in positive feedforward loop (Morioka et al. 2014). Depletion of RIPK3 or MLKL blocks TNF-driven necroptosis and drives the pathway toward a delayed RIPK1-dependent apoptosis (Remijsen et al. 2014).

References

Bessis M (1974) Necrotaxis. Chemotaxis towards an injured cell. Antibiot Chemother 19:369–381

Cho YS, Challa S, Moquin D, Genga R, Ray TD, Guilford M, Chan FK (2009) Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. Cell 137:1112–1123

Cho Y, McQuade T, Zhang H, Zhang J, Chan FK (2011) RIP1-dependent and independent effects of necrostatin-1 in necrosis and T cell activation. PLoS One 6:e23209

Debru C (1993) A particular form of chemotaxis: necrotaxis. An historical view. Blood Cells 19:5–19

Dunai Z, Bauer PI, Mihalik R (2011) Necroptosis: biochemical, physiological and pathological aspects. Pathol Oncol Res 17:791–800

Fayaz S, Suvanish Kumar V, Rajanikant G (2014) Necroptosis: who knew there were so many interesting ways to die? CNS Neurol Disord Drug Targets 13:42–51

Festjens N, Vanden Berghe T, Vandenabeele P (2006) Necrosis, a well-orchestrated form of cell demise: signalling cascades, important mediators and concomitant immune response. Biochim Biophys Acta 1757:1371–1387

Formigli L, Papucci L, Tani A, Schiavone N, Tempestini A, Orlandini GE, Capaccioli S et al (2000) Aponecrosis: morphological and biochemical exploration of a syncretic process of cell death sharing apoptosis and necrosis. J Cell Physiol 182:41–49

Galluzzi L, Vanden Berghe T, Vanlangenakker N, Buettner S, Eisenberg T, Vandenabeele P et al (2011) Programmed necrosis from molecules to health and disease. Int Rev Cell Mol 289:1–35

Galluzzi L, Kepp O, Krautwald S, Kroemer G, Linkermann A (2014) Molecular mechanisms of regulated necrosis. Semin Cell Dev Biol. doi:10.1016/j.semcdb.2014.02006

Giampietri C, Starace D, Petrungaro S, Filippini A, Ziparo E (2014) Necroptosis: molecular signaling and translational implications. Int J Cell Biol 2014:490275

Golstein P, Kroemer G (2007) Cell death by necrosis: towards a molecular definition. Trends Biochem Sci 32:37–43

Hu CL, Barnes FS (1970) A theory of necrotaxis. Biophys J 10:958–969

Jouan-Lanhouet S, Arshad MI, Piquet-Pellorce C, Martin-Chouly C, Le Moigne-Muller G et al (2012) TRAIL induces necroptosis involving RIPK1/RIPK3-dependent PARP-1 activation. Cell Death Differ 19:2003–2014

Khan N, Lawlor KE, Murphy JM, Vince JE (2014) More to life than death: molecular determinants of necroptotic and non-necroptotic RIP3 kinase signaling. Curr Opin Immunol 26C:76–89

Lee TH, Huang Q, Oikemus S, Shank J, Ventura JJ, Cusson N, Vaillancourt RR et al (2003) The death domain kinase RIP1 is essential for tumor necrosis factor alpha signaling to p38 mitogen-activated protein kinase. Mol Cell Biol 23:8377–8385

Leist M, Nicotera P (1997) The shape of cell death. Biochem Biophys Res Commun 236:1–9

Lemasters JJ (1999) V. Necroapoptosis and the mitochondrial permeability transition: shared pathways to necrosis and apoptosis. Am J Physiol 276:G1–G6

Lemasters JJ, Qian T, Bradham CA, Brenner DA, Cascio WE, Trost LC, Nishimura Y et al (1999) Mitochondrial dysfunction in the pathogenesis of necrotic and apoptotic cell death. J Bioenerg Biomembr 31:305–319

Li J, McQuade T, Siemer AB, Napetschnig J, Morikawa K, Hsiao YS, Damko E, Moquin D et al (2012) The RIP1/RIP3 necrosome forms a functional amyloid signaling complex required for programmed necrosis. Cell 150:339–350

Linkermann A, Green DR (2014) Necroptosis. N Engl J Med 370:455–465

Lu JV, Walsh CM (2012) Programmed necrosis and autophagy in immune function. Immunol Rev 249:205–217

Moquin DM, McQuade T, Chan FK (2013) CYLD deubiquitinates RIP1 in the TNFa-induced necrosome to facilitate kinase activation and programmed necrosis. PLoS One 8:e76841

Morioka S, Broglie P, Omori E, Ikeda Y, Takaesu G, Matsumoto K, Ninomiya-Tsuji J (2014) TAK1 kinase switches cell fate from apoptosis to necrosis following TNF stimulation. J Cell Biol 204:607–623

Moriwaki K, Chan FK (2013) RIP3, a molecular switch for necrosis and inflammation. Genes Dev 27:1640–1649

Moujalled DM, Cook WD, Okamoto T, Murphy J, Lawlor KE, Vince JE, Vaux DL (2013) TNF can activate RIPK3 and cause programmed necrosis in the absence of RIPK1. Cell Death Dis 4:e465

Moujalled DM, Cook WD, Murphy JM, Vaux DL (2014) Necroptosis induced by RIPK3 requires MLKL but not Drp1. Cell Death Dis 5:e1086

Murphy JM, Silke J (2014) Ars moriendi; the art of dying well – new insights into the molecular pathways of necroptotic cell death. EMBO Rep 15:155–164

Murphy JM, Czabotar PE, Hildebrand JM, Lucet IS, Zhang JG, Alvarez-Diaz S, Lewis R et al (2013) The pseudokinase MLKL mediates necroptosis via a molecular switch mechanism. Immunity 39:443–453

Newton K, Dugger DL, Wickliffe KE, Kapoor N, de Almagro MC, Vucic D, Komuves L et al (2014) Activity of protein kinase RIPK3 determines whether cells die by necroptosis or apoptosis. Science 343:1357–1360

Nicotera P, Leist M, Ferrando-May E (1998) Intracellular ATP, a switch in the decision between apoptosis and necrosis. Toxicol Lett 102–103:139–142

Nicotera P, Leist M, Fernando-May E (1999) Apoptosis and necrosis: different execution of the same death. Biochem Soc Symp 66:69–73

Pasparakis M, Vandenabeele P (2015) Necroptosis and its role in inflammation. Nature 217:311–320

Proskuryakov SY, Gabai VL (2010) Mechanisms of tumor cell necrosis. Curr Pharm Des 16:56–68

Proskuryakov SY, Gabai VL, Konoplyannikov AG (2002) Necrosis is an active and controlled form of programmed cell death. Biochemistry (Mosc) 67:387–408

Proskuryakov SY, Konoplyannikov AG, Gabai VL (2003) Necrosis: a specific form of programmed cell death? Exp Cell Res 283:1–16

Ragot R (1993) Negative necrotaxis. Blood Cells 19:81–88

Remijsen Q, Goossens V, Grootjans S, Van den Haute C, Vanlangenakker N, Dondelinger Y et al (2014) Depletion of RIPK3 or MLKL blocks TNF-driven necroptosis and switches towards a delayed RIPK1 kinase-dependent apoptosis. Cell Death Dis 5:e1004

Rokitansky K (1852) Über die Entwickelung der Krebsgerüste mit Hinblick auf das Wesen und die Entwickelung anderer Maschenwerke. SBB Wien Math Nat Klasse 8:391–405

Seya T, Shime H, Takaki H, Azuma M, Oshiumi H, Matsumoto M (2012) TLR3/TICAM-1 signaling in tumor cell RIP3-dependent necroptosis. Oncoimmunology 1:917–923

Shulga N, Pastorino JG (2012) GRIM-19-mediated translocation of STAT3 to mitochondria is necessary for TNF-induced necroptosis. J Cell Sci 125:2995–3003

Silva MT (2010) Secondary necrosis: the natural outcome of the complete apoptotic program. FEBS Lett 584:4491–4499

Silva MT, do Vale A, dos Santos NM (2008) Secondary necrosis in multicellular animals: an outcome of apoptosis with pathogenic implications. Apoptosis 13:463–482

Smith CC, Yellon DM (2011) Necroptosis, necrostatins and tissue injury. J Cell Mol Med 15:1797–1806

Tischner et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22971741

Van den Berghe T, Linkermann A, Jouan-Lanhouet S, Walczak H, Vandenabeele P (2014) Regulated necrosis: the expanding network of non-apoptotic cell death pathways. Nat Rev Mol Cell Biol 15:135–147

Vandenabeele P, Declercq W, Van Herreweghe F, Vanden Berghe T (2010a) The role of the kinases RIP1 and RIP3 in TNF-induced necrosis. Sci Signal 3(115):re4

Vandenabeele P, Galluzzi L, Vanden Berghe T, Kroemer G (2010b) Molecular mechanisms of necroptosis: an ordered cellular explosion. Nat Rev Mol Cell Biol 11:700–714

Vanlangenakker N, Vanden Berghe T, Krysko DV, Festjens N, Vandenabeele P (2008) Molecular mechanisms and pathophysiology of necrotic cell death. Curr Mol Med 8:207–220

Wallach D, Kovalenko A, Kang TB (2011) 'Necrosome'--induced inflammation: must cells die for it? Trends Immunol 32:505–509

Wei B, Yue P, Qingwei L (2014) The molecular mechanism of necroptosis. Yi Chuan 36:519–524

Wu W, Liu P, Li J (2012) Necroptosis; an emerging form of programmed cell death. Crit Rev Oncol Hematol 82:249–258

Yu X, Deng Q, Bode AM, Dong Z, Cao Y (2013) The role of necroptosis, an alternative form of cell death, in cancer therapy. Expert Rev Anticancer Ther 13:883–893

Zhao J, Jitkaew S, Cai Z, Choksi S, Li Q, Luo J, Liu ZG (2012) Mixed lineage kinase domain-like is a key receptor interacting protein 3 downstream component of TNF-induced necrosis. Proc Natl Acad Sci U S A 109:5322–5327

Zhou Z, Han V, Han J (2012) New components of the necroptotic pathway. Protein Cell 3:811–817

Necrobiology of Liver Cancer: Autophagy and Cellular Senescence 179

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_179

Abstract

Autophagy is a process involved in the maintenance of cell and tissue homeostasis, control of protein composition of cells, aging, senescence, and neoplastic transformation. Autophagy induced by oxidative or hypoxic stress, nutrient deprivation, and DNA damage serves to eliminate altered or misfolded proteins, degrade damaged or superfluous organelles, and get rid of pathogens. There are three types of autophagy, i.e., macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy transports cargo to lysosomes through the autophagosome, a membrane-bound vesicle. This pathway can interact with apoptosis and necroptosis in a complex manner. Autophagy is also connected with inflammasome function, inflammation, and immunogenic cell death. There are several specific autophagic pathways involving organelles, including mitophagy, pexophagy, lipophagy, and nucleophagy. Autophagy is closely connected with the mechanisms that induce and regulate senescence, a process by which normal cells cease to divide, perceived as aging mechanisms and a cancer barrier.

Introduction

Definitions

Autophagy (from Greek, "eating of self") is an important process of ordered self-degradation that plays a role in various pathophysiologic reactions, including nutrient deprivation, hypoxia, oxidative stress, and DNA damage. In particular, autophagy serves to eliminate altered, aggregated, or misfolded proteins that might damage the cell, degrade damaged organelles, and get rid of intracellular pathogens (reviews: Gozuacik and Kimchi 2004; Yang et al. 2005; Williams et al. 2006; Dengjel et al. 2008; Galluzzi et al. 2008; Esclatine et al. 2009; Dalby et al. 2010; Glick et al. 2010; Klionsky et al. 2010; Mehrpour et al. 2010; Dengjel et al. 2012; Liu et al. 2013). Autophagy can also regulate distinct forms of cell death, such as necroptosis (Ryter et al. 2014). There are three defined types of autophagy, i.e., macroautophagy, microautophagy, and chaperone-mediated autophagy (Feng et al. 2014). All types share the capacity to proteolytically degrade cell components in lysosomes.

Macroautophagy: The Autophagosomal Pathway

Macroautophagy transports cargo to the lysosome through a membrane-bound vesicle, the autophagosome which fuses with the lysosome to form the autolysosome. The biogenesis of an autophagosome starts with ER-or trans-Golgi-derived membrane component, the phagophore, which can engulf cytoplasmic proteins and organelles to become a cargo-loaden autophagosome. In microautophagy, cargo is directly delivered to the lysosome through a lysosomal invagination. In chaperone-mediated autophagy, targeted proteins are translocated through the lysosomal membrane in a complex with chaperones/heat shock proteins recognized by a lysosomal membrane receptor, LAMP-2A/lysosomal-associated membrane protein 2A (review: Glick et al. 2010). Formation of the critical phagophore as an initial cargo-seeking structure is tightly regulated by several signaling pathways.

Autophagosome Biogenesis

Autophagosome biogenesis requires deformation and induction of curvatures in the membranes. This bending activity is mediated by the Bax-binding protein, Bif-1 (endophilin B1), a protein which forms complexes with beclin 1. Bif-1 interacts with beclin 1 via UVRAG (Takahashi et al. 2007). Bif-1 accumulates in punctate foci where it colocalizes with light chain 3 protein, Atg5, and Atg9. Specifically, Bif-1-positive crescent-shaped vesicles expand by fusing with Atg9-positive membranes to complete autophagosome formation (Takahashi et al. 2009). Macroautophagy is regulated by endoplasmic reticulum stress, in that the unfolded protein response/UPR associated with ER stress

and reticulophagy can induce autophagy (Deegan et al. 2013).

Autophagy: Induction and the Autophagosomal Proteome

Autophagy is induced by numerous proteins (the autophagosomal proteome; Becker et al. 2012), some of which are oncogenes, including TGF-beta, Atg4c, beclin 1, Bif-1, BH3-only proteins, DAPK1, tuberous sclerosis complexes, death-associated protein kinase 1, LKB1, PTEN, and UVRAG (Maiuri et al. 2009; Morselli et al. 2009; Park et al. 2009a,b; Suzuki et al. 2010). The autophagic process is initiated by mTOR phosphorylation of the serine/threonine kinase ULK1 (autophagy-initiating kinase ULK1/Unc-51-like kinase 1; Dunlop and Tee 2013). ULK1 kinase is, however, also an mTOR-independent node in a complex kinase network (Bach et al. 2011). The Beclin-1 (Atg6) complex is an important initiation factor for the initial step of autophagosome formation and is directly targeted by signaling pathways that involve mTOR (Cao and Klionsky 2007; Pattingre et al. 2008). Beclin-1, which is a key regulator of autophagy, acts as a haploinsufficient tumor suppressor. Beclin 1 has several interaction partners. In the human phosphatidylinositol 3/PI(3)-kinase class III complex, beclin 1 directly interacts with Barkor (Beclin 1-associated autophagy-related key regulator), a protein that is required for autophagosome formation (Sun et al. 2008). A further mediator of the class III PI(3)kinase complex is Bif-1 (endophilin B1), a protein that interacts with beclin 1 through UVRAG. In response to nutrient deprivation, Bif-1 localizes to autophagosomes where it colocalizes with Atg5 and the microtubule-associated protein light chain 3 (Takahashi et al. 2007). Beclin 1 forms two distinct PI(3)-kinase complexes with Atg14 and UVRAG (Itakura et al. 2008). Beclin-1 interacts with the PI-3 kinase, Vps34/vesicular protein sorting 34, forming a complex which is selectively involved in autophagy. PtdIns3P synthesized by Vsp34 are crucial components for autophagy induction and accumulate in membrane extensions of the ER, structures called omegasomes. Proteins that interact with this complex in an autophagy-promoting manner are ubiquitin-like proteins (Atg12, Atg8, and Atg16L; Noda et al. 2008), Bif-1, UVRAG, Atg14L, and Ambra, while autophagy inhibitors include Rubicon and Bcl-2. Bif-1 is directly involved in phagophore biogenesis. Induction of autophagy requires the ULK1 protein kinase complex, which co-localizes with omegasomes (Karanasios et al. 2013).

The Lysosomal Degradation Pathway of Autophagy

At the end of any autophagic process is the lysosomal degradation pathway, an attractor for macroautophagic (autophagosomal), microautophagic, and chaperone-dependent autophagic processes (Shen and Mizushima 2014). Autophagic pathways and endosome/lysosome biogenesis are closely linked. Atg5, an autophagosomal protein, is required for the biogenesis of late endosomes and lysosomes in an autophagy-independent manner (Peng et al. 2014). The small GTPase Rab 11 plays an important role in the "docking" of autophagosomes to late endosomal compartments. Rab11 shifts from recycling endosomes to autophagosomes in response to autophagy induction via removing Hook, a negative regulator of endosome maturation, from mature endosomes (Szatmari et al. 2014).

In order to reach their degradation compartment, autophagosomes are transported along microtubule tracks of the cytoskeleton to fuse with late endosomes or lysosomes. As in other vesicular transport systems, the small GTPase Rab7 is implicated in autophagosomal transport and fusion. Autophagosomal membranes harbor the lipid PtdIns3P and phosphatidylethanolamine-conjugated Agt8/LC3/GABARAP family proteins. The FYVE and coiled-coil domain containing 1 (FYCO1) binds to both LC3, PtdIns3P and Rab7, and functions as an adaptor linking autophagosomes to microtubule plus end-directing molecular motors. FYCO1 is selectively recruited to autophagosomal membranes via a mechanism

involving a conformational change upon LC3-LIR interaction to expose the FYVE domain for PtdIns3P. The autophagy flux through lysosomes is regulated by DNA damage-regulated autophagy modulator 1/DRAM1 (Zhang et al. 2013). In the course of necrosis, dying cells release HMGB1, a mobility group box q1 protein with immunostimulatory functions. HMGB1 also plays important intranuclear, cytosolic, and extracellular roles in the regulation of autophagy, in that HMGB1 is Beclin 1-binding protein active in autophagy (Kang et al. 2011a). Autophagy-associated release of HMGB1 protects cancer cells from many chemotherapeutical agents, in that extracellular HMGB1 protects cancer cells from apoptosis through transcriptional upregulation of Mcl-1 (Zhan et al. 2012). On the other hand, the danger signaling protein HMGB1 induces a distinct form of cell death which in cancer cells depends on the presence of mitochondria. HMGB1 induces a rapid depletion of mitochondrial DNA, severe damage to the mitochondrial proteome, and the formation of giant mitochondria (Gdynia et al. 2010).

Autophagy and Apoptosis

Autophagy interacts with apoptosis in a complex manner (Booth et al. 2013). Beclin 1 fails to stimulate apoptosis (Boya and Kromer 2009). The antiapoptotic proteins Bcl2-2 and Bcl-xL negatively regulate autophagy by directly binding to beclin 1 (Luo and Rubinsztein 2010). This interaction involves a Bcl-2 homology 3/BH3 domain in beclin 1 (Levine et al. 2008) and can be abolished by ubiquitination of beclin 1 (Kang et al. 2011b). A critical negative regulator of Fas-mediated apoptosis, the Fap-1 protein phosphatase, is degraded by autophagy, providing a further link between apoptosis and autophagy (Joshi and Ryan 2013). The autophagosomal membrane serves as a platform for DISC-mediated caspase-8 activation (Young et al. 2012). On the autophagosome, caspase-8 aggregation is promoted by the p62/sequestosome-1, an atypical protein kinase C-interacting protein that is involved in various signaling pathways (Huang et al. 2013; Zotti et al. 2014). In the autophagic process, p62 directly interacts with Bcl-2 and disrupts the association between Bcl-2 and beclin 1 (Zhou et al. 2013). By its function in autophagosomal function, the scaffold protein p62 also links autophagy with oxidative stress pathways active in cancer, as this protein directly interacts with the ubiquitin ligase adaptor Kelch-like ECH-associated protein1/KEAP1, which results in constitutive activation of the transcription factor NF-E2-related factor 2/NRF2, two proteins involved in a stress response pathway and that are frequently mutated in cancer (Nezis and Stenmark 2012). KREAP1 itself is degraded by autophagy which thus regulates KEAP1 and redox homeostasis in the liver (Taguchi et al. 2012).

Autophagy-Mediated Necroptosis

Autophagy is linked to apoptosis and necroapoptosis in a complex manner. In particular, autophagy plays something as a "compensatory" role in the elimination of neoplastic cells having become resistant to apoptosis, acquired apoptosis resistance being a major element in the development of chemoresistance in therapeutic settings. Autophagy can modulate apoptotic pathways through the degradation of proapoptotic factor versus antiapoptotic factors. There is, e.g., a JNK-mediated autophagy pathway that induces the degradation of antiapoptotic cIAPs, thereby promoting autophagy-mediated necroptosis (RIP1- and RIP3-dependent necrosis). This pathway is dependent on JNK-mediated phosphorylation of Bcl-2 and Bcl-xL and dissociation of Bcl-2 or Bcl-xL from the autophagy factor, Beclin-1. In addition, this pathway involves formation of the ripoptosome that contributes to necroptosis (He et al. 2014).

Autophagy in Hepatocellular Carcinoma

Autophagy plays an important role in pathways of tumor cell elimination, but this mode of tumor suppression predominantly works in early cancer. In established or advanced tumors, autophagy acts as a cytoprotection mechanism to promote cancer

cell survival (Chen and Karantza-Wadsworth 2009; Chen and Debnath 2010; Dalby et al. 2010; Reyjal et al. 2014). Autophagy has a tumor promoter role by suppressing the p53 response, maintaining mitochondrial function, and promoting metabolic homeostasis (Guo et al. 2013). Autophagy also exerts an influence on cancer cells through its effects on stromal cells and immune cells, mainly tumor-associated macrophages/TAMs, acting against tumor cells. Autophagy in cancer-associated fibroblasts promotes tumor cell survival, mediated by induction of hypoxia-induced factor 1alpha (Martinez-Outschoom et al. 2010). Targeting of nuclear factor-kappaB by autophagy is involved in the polarization and activation of HCC-associated TAMs (Chang et al. 2013). Autophagy is a key factor in innate immunity and regulates the production of macrophages at different developmental stages of these cells (Chen et al. 2014).

Similar to normal cells, Beclin-1 plays an important role in autophagy regulation in HCCs. Beclin-1 levels are lower in HCCs than in nonneoplastic liver, suggesting a downregulation of autophagy in HCCs (Shi et al. 2009; Kotsafti et al. 2012). Autophagy in HCCs is stimulated by TGF-beta, associated with accumulation of autophagosomes in HCC cells, conversion of microtubule-associated protein light chain 3 and enhanced degradation rate of long-lived proteins. The induction of autophagy by TGF-beta occurs significantly earlier than the induction of apoptosis (Kiyono et al. 2009). The finding that p62 protein is increased in HCCs suggests that HCCs are autophagy defective (Bao et al. 2014). In HCCs, the autophagy-related marker LCs (light chain 3) predicts prognosis, in that LC3 expression is related with longer time to recurrence and overall survival (Lee et al. 2013). Autophagy enhances HCC progression by activation mitochondrial beta-oxidation, in that autophagy promotes hypoxia-inducible factor-1alpha-mediated proliferation through the maintenance of intracellular ATP linked to an activated mitochondrial beta-oxidation (Toshima et al. 2014). Autophagy is activated in metastatic colonization of HCC, but not in invasion, migration, and detachment of HCC cells (Peng et al. 2013). In HCC cells, inhibition of the Hedgehog signaling pathway induces autophagy via upregulation of the proapoptotic protein, Bnip3 (Wang et al. 2013). HCC cells exposed to endoplasmic reticulum stress revealed a significant accumulation of autophagosomes and increased conversion of LC3-I to LC3-II as well as an increased autophagic flux (Ma et al. 2013). microRNA-375 inhibits autophagy in HCC cells and reduces the viability of these neoplastic ells under hypoxic conditions (Chang et al. 2012).

Autophagy: Connections with Immunity and Inflammation, and Immunogenic Cell Death/ICD

Introduction

Autophagic pathways are closely linked with certain mechanisms that operate in immunity (Yuk and Jo 2013). Nod-like receptors (NLRs), proteins that are cytoplasmic sensors for microbial molecules (cytoplasmic pattern recognition receptors), interact with autophagy-associated proteins (Carneiro and Travassos 2013). This interaction has a broad range of effects, as the various species of NLRs have different functions. NRLRC5 and CIITA regulate antigen presentation, NLRP1, NLRP3, NLRC1, and NLRC4 act in pathogen/damage sensing, and NLRC3, NLRP6, NLRP12, and NLRX1 suppress or modulate inflammatory responses (Lupfer and Kanneganti 2013).

Inflammasomes

NLRs are components of the inflammasome, large multiprotein platforms and guardians of cell and tissue integrity, sensors of metabolic stress, and critical regulators of immune reactions (Lamkanfi and Dixit 2009; Jin and Flavell 2010; Schroder and Tschopp 2010; Gross et al. 2011; Leemans et al. 2011; Haasken and Sutterwala 2013; Tsuchiya and Hara 2014). The central role of inflammasomes in immunity is underlined by the fact that mutations in NLRP3 activity cause severe autoinflammatory disease (Lawlor and Vince 2014). Inflammasome

assembly depends on several NLR family members such as NALPs (pyrin domain-containing NLRs), NAIP, and IPAF.

Inflammasomes as Mediators of Cell Death

Apart from danger signals derived from infectious agents and cancer cells, the NLRP3 inflammasome is activated by reactive oxygen species released from dysfunctional mitochondria (Tschopp 2011), a further link to cell death pathways. Inflammasomes and their activated inflammatory caspases (caspase-1 and caspase-5) are critical mediators of immunity and inflammatory reaction directed against microorganisms and cells expressing neoantigens, including cancer cells (Martinon and Tschopp 2007; Wen et al. 2013). The canonical pathway in inflammasomes involves activation of caspase-1, which in turn results in the release of interleukins 1beta and -18 in response to danger signals. The noncanonical inflammasome pathway is mediated by caspase-11 and leads to release of interleukins 1beta, -18 and -1alpha, and promotes pyroptosis (Vigano and Mortellaro 2013).

Inflammasomes contain proteins that participate in immune mechanisms linked to cell death, including the adapter molecules ASC, IPAF, and cryopyrin/Nalp3 which regulate the inflammatory caspases, caspase-1, and caspase-5. In inflammasomes, activation of caspase-1 results in cleavage and activation of proinflammatory cytokines (Mariathasan 2007; Martinon et al. 2007). In HCCs, caspase-1 activated by hypoxia induces the release of IL-1beta and IL-18 which in turn promote invasion and metastasis (Yan et al. 2012). On the other hand, inflammasomes mediate pyroptotic and apoptotic cell death, in that active caspase-1 mediates pyroptosis through an unknown mechanism, and activated inflammasomes can recruit procaspase-8, thus initiating apoptosis (Aachoui et al. 2013).

It is expected that damage-sensing NLRs play a role in cancer cells undergoing injury, including liver cancer cells, and pave the track for autophagic cell elimination. Autophagy produces a link between tumor cell death and immunity (immunogenic tumor cell death, ICD) in that damage-associated molecular patterns/DAMPs enhance autophagy (Hou et al. 2013). DAMPs mediate immunogenic features of this form of cell death in their function as pattern recognition receptors that are in part emitted actively by cells undergoing ICD (Krysko et al. 2013). Proteins of the NLRP3 inflammasome, which orchestrates mechanisms of innate immunity and adaptive immune responses, are expressed in HCC cells as a function of tumor progression (Wei et al. 2014) and interact with proteins of the autophagic pathways. Reactive oxygen species escaping from injured mitochondria induce lysosomal damage in an NLRP3-dependent manner (Heid et al. 2013) and may thus modify lysosome-dependent autophagy. As mentioned above, the noncanonical inflammasome pathway related to caspase-11 activation promotes pyroptosis (Vigano and Mortellaro 2013).

Resistance to Apoptosis and Autophagy

Resistance to apoptosis is a key feature of many malignant neoplasms and is a phenomenon involved in cancer progression and treatment failure. Failure of apoptotic cell death can be circumvented by autophagy-related mechanisms that lead to elimination of cancer cells. Injured or stressed cells can release damage-associated molecular patterns/DAMps. Release of DAMP molecules contributes to autophagy induction and hence to cell decay. Autophagy in turn regulates DAMP release and degradation (Hou et al. 2013).

Organellophagy

There are numerous complex autophagic mechanisms that can elicit degradation and controlled elimination of damaged or superfluous organelles and cell nuclei. These processes are summarized under the term organellophagy (Table 1).

Table 1 Types of organellophagy

Type of phagy	Target of phagy
Mitophagy	Mitochondria
Pexophagy	Peroxisomes
Reticulophagy	Endoplasmic reticulum
Ribophagy	Ribosomes
Lipophagy	Lipid droplets (lipid organelles)
Ciliophagy	Cilia and associated structures
Nucleophagy	Nucleus
Nucleolophagy	Nucleolus

Mitophagy

Mitophagy as a Central Feature of Autophagy

In the setting of autophagic processes, mitophagy is a particularly important phenomenon. Mitophagy is the selective autophagic degradation of damaged and/or superfluous mitochondria and is regarded as an essential process for mitochondrial quality and quality control (reviews: Mijaljica et al. 2010a; Novak and Dikic 2011; Rambold and Lippincott-Schwartz 2011; Wang and Klionsky 2011; Hirota et al. 2012; May et al. 2012; Novak 2012; Okamoto and Kondo-Okamoto 2012). Mitochondria with their relatively small genome, their successive cycles of fission and fusion, and their exposition to oxidative stress are prone to damage, requiring a potent mechanism to eliminate "dangerously altered" mitochondria. There is evidence that mitophagy is an instrument not only to sense damaged mitochondria and eliminate them but that also the overall oxygen radical burden is sensed and the signal transmitted in a systematic or episodal removal of mitochondria (review: Gottlieb and Carreira 2010).

Mitophagy is an important mechanism to protect cells from the deleterious effects of damaged mitochondria, in particular apoptosis. Mitophagy can also mitigate an additional catastrophic event. Severe mitochondrial stress can cause the pathologic opening of the mitochondrial permeability transition pore(MPTP), followed by transient but massive release of calcium and radical oxygen species/ROS. This release reaction can trigger other mitochondria to undergo the same crisis, finally resulting in the activation of calcium-dependent proteases such as calpain, lipases (cPLA2), and ROS-activated iPLA2, steps that cause necrosis (reviews: Gottlieb and Carreira 2010). Mitophagy is the major instrument of the cell to regulate mitochondrial number and mass, and there is a regulatory cross talk between mitochondrial function and dysfunction, and mitochondrial abundance (Michel et al. 2011), suggesting the presence of a mitochondrial abundance sensor. Mitophagy belongs to the group of autophagic processes, which also comprise pexophagy, ER-phagy, ribophagy, golgiphagy, and nucleophagy. Autophagy, as discussed in a separate chapter, serves removing of altered proteins and dysfunctional organelles.

Mechanisms of Mitophagy

Injury of mitochondrial DNA, e.g., mtDNA mutations, can result in mitophagy (Gilkerson et al. 2012; de Vries et al. 2012). Mutations in the gene for ATPase type 13A2 (ATP13A2), involved in autosomal-recessive Parkinsonism (Kufor-Rakeb syndrome) are associated with a higher frequency of mtDNA lesions, increased oxygen consumption rates, fragmentation of the mitochondrial network, and mitophagy (Grünewald et al. 2012). Oxygen damage via reactive oxygen species (ROS) as potential mitochondrial damaging agents can normally be neutralized within the mitochondria through enzymatic activity. In case this system is overcharged, mitochondrial damage and mitophagy can occur (Lee et al. 2012). Elimination of mitochondria being overcharged with oxidized proteins via mitophagy is a mechanism suppressing cell damage by mitochondrial oxidative products (Kurihara et al. 2012). But also hypoxia causes mitochondrial injury leading to mitophagy.

PINK1-and Parkin-Mediated Mitophagy

The Parkinson disease-related proteins PINK1 (PTEN-induced kinase 1, a mitochondrially

localized serine/threonine kinase) and Parkin (PARK2, a cytosolically localized E3 ubiquitin ligase) are guardians of mitochondrial fidelity and are essential for targeting mitochondria for mitophagy (Matsuda and Tanaka 2010; Huang et al. 2011; Kane and Youle 2011; Springer and Kahle 2011; Youle and Narendra 2011; Jin and Youle 2012). The mitochondrial turnover of PINK1 and Parkin is tightly controlled. The mitochondrial intramembrane protease PARL cleaves human PINK1 within its conserved membrane anchor. Mature PINK1 is then free to be released into the cytosol or the mitochondrial intermembrane space. In PINK1-dependent mitophagy and following uncoupling of the outer mitochondrial membrane potential, the canonical import of PINK1 and PARL-catalyzed processing is blocked, leading to the accumulation of the PINK1 precursor. Accumulation of PINK1 precursor and its targeting to the outer mitochondrial membrane triggers mitophagy (Meissner et al. 2011). Generally, loss of PINK1 function causes oxidative stress via production of ROS and mitochondrial damage (Cui et al. 2011). Endogenous PINK1 forms a 700 kDa complex with the translocase of the outer membrane (TOM) on depolarized mitochondria. Association of PINK1 with TOM complex allows rapid reimport of PINk1 to rescue depolarized mitochondria from mitophagy (Lazarou et al. 2012). In Parkin-dependent mitophagy, PINK1, which is located in the mitochondrial outer membrane, recruits Parkin from the cytosol to the mitochondria as a first step leading autophagous destruction of the organelle. Complexes containing upstream Atg proteins (autophagy-related proteins), including ULK1 (the mammalian homologue of Agt1), Atg12, Atg14, DFCP1, WIPI-1, and Atg16L1, can associate with depolarized mitochondria. Atg9A and ULK1 structures are also recruited to damaged mitochondria as well as to the autophagosome formation site in the earliest steps of mitophagy, while the autophagosomal LC3 (MT-associated protein 1 light chain 3) family of proteins is involved in later stages of mitophagy (Itakura et al. 2012). LC3 interacts with microtubule-associated protein 1S/MAP1S bridging autophagic components with the microtubular system (Xie et al. 2011). In human endothelial cells, targeted mitochondrial damage upregulated the autophagy factors LC3B, Atg5, and Atg12, and this upregulation resulted in an improved mitochondrial membrane potential, enhanced ATP production, and an antiapoptotic effect (Mai et al. 2012). One of the effectors of the mitophagic cascade, Ulk1, is phosphorylated by AMP-activated protein kinase connecting energy sensing to mitophagy (Egan et al. 2011) and is regulated by the Hsp90-Cdc37 chaperone complex (Joo et al. 2011).

Parkin itself as an ubiquitin E3 ligase ubiquitinates intracellular proteins and via this mechanism induces clearance of cellular molecular debris and of organelles, including mitophagy, whereby ubiquitinylated outer mitochondrial membrane proteins, including mitofusins 1 and 2, are targeted for proteasomal degradation (Gegg et al. 2010; Chan and Chan 2011; Karbowski and Youle 2011; Khandelwal et al. 2011). In the pathway of mitophagy, Parkin binds to Ambra1 (activating molecule in beclin 1-regulated autophagy), a protein that promotes autophagy (Van Humbeeck et al. 2011). PINK1 and Parkin also exert important effects on mitochondrial motility. PINk1 phosphorylates Miro, a component of the primary motor/adaptor complex that anchors kinesin to the mitochondrial surface. The phosphorylation of Miro activates proteasomal degradation of Miro in a Parkin-dependent manner. By thus stopping mitochondria in their tracks, the PINK1/Parkin pathway may quarantine damaged mitochondria prior to their mitophagic clearance (Wang et al. 2011).

Execution of Mitophagic Pathways

Bnip3 (Nip3-like protein X; NIX), an atypical BH3-only protein causing mitochondrial dysfunction and cell death, can under certain circumstances also protect against cell death by inducing mitophagy. Bnip3 activation is a pro-mitophagic signal, and this pathway involves impairment of mitochondrial oxidative phosphorylation and is independent of apoptosis (Thomas et al. 2011). This response requires homodimerization of Bnip3, and clearance of

mitochondria is mediated in part via binding of Bnip3 to the microtubule-associated protein 1 light chain 3 (LC3) on the autophagosome (Hanna et al. 2012). On the other hand, Bnip3 mediated mitophagy is inhibited by activation of the p53-TIGAR axis (Hoshino et al. 2012).

Mdivi (mitochondrial division inhibitor) attenuates mitochondrial division in cells by selectively inhibiting the mitochondrial division dynamin-related protein (Cassidy-Stone et al. 2008). Dynamin-related protein 1 (Drp1) docks at mitochondria, regulating their positioning and activity (Baixauli et al. 2011). Mdivi is also a mitophagy inhibitor that operates via inhibition of Drp1 (Park et al. 2011; Givvimani et al. 2012). FUNDC1, a mitochondrial outer membrane protein, is a receptor for hypoxia-induced mitophagy. Hypoxia leads to dephosphorylation of FUNDC1 and enhances its interaction with LC3 for selective mitophagy (Liu et al. 2012). Following mitophagy, organelle remnants can enter a lysosomal degradation pathway, whereby a distinct system of mitochondria-derived vesicles (MDVs) generates the contact with lysosomes to deliver degradable cargo (Soubannier et al. 2012). BECN1s, a short splice variant of BECN1, function in mitophagy (Cheng et al. 2015).

Other Factors Regulating Mitophagy

The ATM gene mutated in ataxia telangiectasia plays a role in mitochondrial homeostasis. Atm-deficient thymocytes in mice show an altered mitochondrial homeostasis, suggesting that ATM plays a role in regulating mitophagy (Valentin-Vega and Kastan 2012). Melatonin, a highly efficient antioxidant, is involved in the control of mitophagy (Coto-Montes et al. 2012). Mitophagy is also mediated by the C2-domain containing protein, SMURF1 (Orvedahl et al. 2011).

Sequelae of Inhibited Mitophagy

It has been shown that inhibition or blockade of mitophagy leads to the accumulation of damaged, ROS-generating mitochondria, which in turn activate the NLRP3 inflammasome, a pathway positively regulated by reactive oxygen species/ROS. The NLR3P inflammasome acts as a sensor of damaged mitochondria, explaining the frequent association of mitochondrial damage and inflammatory diseases (Zhou et al. 2011).

Mitophagy in Carcinogenic and Hepatocarcinogenic pathways

HBV infection, a major driving force for hepatocarcinogenesis, disrupts mitochondrial dynamics in that it induces mitochondrial fission and mitophagy, two processes that attenuate apoptosis, while perturbation of mitophagy by silencing of Parkin enhances apoptotic signaling (Kim et al. 2013). This is a mechanism that can promote liver cell expansion in the setting of carcinogenic pathways. Generally, mitochondrial dynamics regulated by large GTPase family proteins is functionally linked with apoptosis (Otera and Mihara 2012). Autophagy triggered by oncogenic K-Ras mediates functional loss of mitochondria and mitophagy during cell transformation and early tumorigenesis, and mitophagy in this situation is a process that overcomes the cellular energy deficit triggered by insufficient glucose availability (Kim et al. 2011).

Pexophagy

Pexophagy is defined as the process of specific autophagic degradation and elimination of peroxisomes, organelles which are present in hundreds to thousands in mammalian cells (review: Till et al. 2012). As peroxisomes hold an important position in the metabolome of cells, their number and function is tightly controlled by environmental and genetic conditions. Metabolic situations requiring increasing levels of peroxisome functions lead to peroxisome proliferation and to an augmentation of peroxisomal biomass. Following such metabolic situations with a downregulation of peroxisomal function, superfluous peroxisomes are degraded by autophagy to again reach the baseline level of peroxisome numbers and mass.

In peroxisome autophagy, both macro- and microautophagy are involved (macropexophagy and micropexophagy). In the course of macropexophagy, peroxisomes are individually sequestered by membranes, resulting in pexophagosomes that fuse with degradation vacuoles. In micropexophagy, clusters of peroxisomes are enclosed within vacuolar membrane protrusions, or are integrated into a specific membrane complex, the micropexophagy-specific membrane apparatus/MIPA (Sakai et al. 2006).

In mammalian cells, the following main pathways of peroxisome elimination are recognized: the Lon protease system (Lon is a chaperone-like ATP-dependent protease involved in the degradation of misfolded and unassembled peroxisomal proteins); 15-lipoxygenase-mediated autolysis; and pexophagy. Pexophagy (in a process resembling macropexophagy in yeast) accounts for 70–80 % of peroxisome clearance in mammalian liver (Yokota and Dariush Fahimi 2009). In a hypothetical model of mammalian cell pexophagy, processed and lapidated LC3 (LC3-II) is integrated into the expanding phagophore membrane. LC3 may also mediate the association of the phagophore membrane with cytoskeletal microtubules through the Rab7 effector FYCO1 getting into contact with kinesin. Targeting of the LC3-labeled phagophore membrane to the peroxisome involves p62-mediated detection of ubiquitin motifs on peroxisomal membrane proteins, or by direct binding of LC3 to a distinct peroxisomal protein, Pex14 (review: Till et al. 2012).

Reticulophagy (ER-phagy) and Ribophagy

The homeostasis of the endoplasmic reticulum (ER), in particular its remodeling, is mediated by a distinct reaction called the unfolded protein response (UPR). In the course of a cell's life, numerous components of the cell body, including organelles, undergo a cycle of production and degradation. In cells, activation of UPR induces a distinct type of macroautophagy characterized by the elimination of ER elements, a process called ER-phagy, in analogy to pexophagy or mitophagy (Bernales et al. 2007; Cebollero et al. 2012). Reticulophagy is a specific form of starvation-induced autophagy. ER-phagosomes use membranes derived from ER itself, suggesting that ER can serve as a membrane source for autophagosome biogenesis. ER stress is characterized by a marked expansion of membrane compartments that contain unfolded proteins which may interfere with cell functions and induced cell injury. ER-phagy may serve to eliminate ER compartments with their damaging cargo. ER-phagy might, however, also prepare and deliver modified signaling lipoproteins in cancer cells, signal substances that can become cargo of exosomes.

In the setting of autophagy, the autophagic process can also selectively engulf sub-organellar structures, including ribosomes, a process termed ribophagy (Cebollero et al. 2012). Ribosomes are detectable within autophagosomes of normal mammalian cells and tumor cells, and ribosomal degradation via ribophagy displays distinct dynamics (Kristensen et al. 2008).

Lipophagy

Lipophagy, the process of elimination and degradation of cellular lipid droplets plays an important role in the reversion of hepatic steatosis, and probably also in lipid droplet turnover in steatotic hepatocytes, HCCs, and other lipid-rich liver tumors (Weidberg et al. 2009; Beller et al. 2010; Noguchi et al. 2011; Singh and Cuervo 2012; Christian et al. 2013). Lipophagy is a form of organellophagy because lipid "droplets" are now known to be complex organelles. Lipid droplets are heterogeneous and dynamic organelles with a complex and specific proteome, regulated assembly and maintenance, and controlled turnover (Digel et al. 2010; Hashemi and Goodman 2015). Lipophagy is one pathway to regulate lipid stores in several cell types (Liu and Czaja 2013; Carmona-Gutierrez et al. 2015). Except adipocytes and hepatocytes with macrovesicular steatosis, lipid droplets are small and mobile and interact with other organelles, including lysosomes,

processes mediated by Ras proteins (in particular Rab18), regulators of membrane traffic and caveolin, a membrane protein that provides a functional link between cell surface and lipid droplets (Martin et al. 2005; Murphy et al. 2009). During lipophagy in HCC cells, the small GTPase Rab7 is markedly activated, resulting in trafficking of multivesicular bodies and lysosomes to the cell surface to form a lipophagic synapse (Schroeder et al. 2015). Lipid droplets have been identified as a substrate for macroautophagy, whereby lipid droplets are sequestered in autophagosomes followed by fusion with lysosomes, where droplet constituents are degraded by lysosomal enzymes (Singh et al. 2009; Dong and Czaja 2011; Settembre and Ballabio 2014). In lipophagy, the large GTPase DNM2/dynamin 2 is involved by facilitating the scission of nascent lysosomes from autolysosomal tubules during autophagy (Schulze et al. 2013; Schulze and McNiven 2014). Lysosomes engaged in lipophagic processes can undergo signal exchange with the nucleus, where nutrient-sensing receptors are present to coordinate autophagy (Settembre et al. 2013; Lee et al. 2014).

Ciliophagy

Autophagy possibly regulates the biogenesis and turnover of cilia and associated cytoskeletal structures by a mechanism called ciliophagy. In addition, autophagy is involved in a pathway near the basal body that regulates cilium assembly (Pampliega et al. 2013, reviews: Pierce and Nachury 2013; Wrighton 2013). LC3, a protein of the autophagosomal membrane, interacts with a protein of the centriolar satellite, OFD1 (oral-facial-digital syndrome 1), and removes this protein from the satellite (Tang et al. 2013, 2014). Autophagy can also result in cilium shortening by a mechanism involving histone deacetylase 6 (Cloonan et al. 2014). Such mechanisms affect the sensing capability of cells, as the cilium is a major factor controlling cell polarity and shape, and is a sensor for cell position within a population. Ciliophagy may, therefore, play an important role in cancer.

Nucleophagy

Introduction

In normal and neoplastic cells, processes are active that act to repair nuclear damage through both repair of maintained nuclei and the coordinated removal of damaged nonfunctional nuclear components. Parts of the nucleus or the entire nucleus can be specifically degraded by an autophagic process termed nucleophagy. Degradation of entire nuclei was observed in murine seminal vesicle epithelial cells (Kovacs et al. 2000). In human liver cells, sequestration of mitotic phase chromosomes in autophagosomes was found (Sit et al. 1996). Senescent keratinocytes die through massive degradation of their nuclei (Gosselin et al. 2009). Dying senescent keratinocytes acquired a particular intracellular organization, whereby a cytokeratin network emerged and partitioned the cell into a cortical domain devoid of organelles and a central core domain containing a high number of autophagic vacuoles, mitochondria, and the nucleus. In muscle cell nuclei of patients with laminopathies caused by mutations of the genes encoding A-type lamins and emerin, perinuclear vacuoles are seen, that are sometimes larger than the nucleus. These vacuoles are autophagosomes/autolysosomes containing debris and myelin figures caused by the degradation of damaged or partially extruded nuclei. In the area of nuclear membrane interfacing with autophagosomes, accumulation of nuclear envelope proteins takes place, suggesting that nuclear autophagy/nucleophagy could contribute to the rapid repair of the nuclear membrane (Park et al. 2009a).

Mechanisms of Nucleophagy

In yeast cells, where nucleophagy has been studied in great detail, piecemeal microautophagy of the nucleus or nucleophagy (micronucleophagy) requires a direct interaction of the nuclear membrane with that of the fungal lytic compartment, the vacuole. During yeast micronucleophagy, the nuclear membrane as a dynamic structure

undergoes marked reorganization (Park et al. 2009a; Mijaljica et al. 2010b; Mijaljica and Devenish 2013). In Saccharomyces, starvation stress is followed by nuclear damage, with formation of nucleus-vacuole junctions through interactions between Vas8 in the vacuole membrane and Nvj in the perinuclear ER. Vesicles containing part of the nucleus emanate from these junction sites and finally pinch off into invaginations of the vacuole (Kvam and Goldfarb 2007; Dawaliby and Mayer 2010). This process has been termed piecemeal microautophagy of the nucleus, or PMN, a process that requires a number of ATG genes and the Ygr223c gene known to be involved in macroautophagy in yeast (Kvam and Goldfarb 2007; Krick et al. 2008, 2009; Nair et al. 2010). Micronucleophagy is a mechanism to protect against chromosomal instability (Boya and Codogno 2012).

Nucleophagy in Cancer Cells

Micronuclei, which arise as a result of deficient bipolar chromosome sequestration in cells with cell cycle perturbations, can be removed by autophagy/nucleophagy, detectable by ultrastructural analysis, and the presence of autophagy-associated factors (Rello-Varona et al. 2012). Micronuclei as such are discussed in a separate chapter.

Phagy by Multicellular Components: Angiophagy and Cancerophagy

In angiophagy, endothelial lamellipodia surround thrombotic/embolic material within hours of occlusion. This important mechanism markedly reduces hemodynamic washout and tissue plasminogen activator-mediated fibrinolysis. Within days, the thromboembolic material is completely engulfed by endothelium and extravasated into perivascular space, causing reconstitution of blood flow (Grutzendler et al. 2014). We anticipate that angiophagy in cancer tissue plays a role in the delivery of growth factors and angiogenic factors stored in thrombotic material to cancer tissue. Also circulating signal substances, microRNAs and exosomes may be transported by angiophagic endothelial pockets into the extravascular space of tumor tissue.

Senescence

Cellular senescence denotes a growth-arrest program by which cells prevent uncontrolled cell proliferation and thus limit the lifespan of cell populations. Initiating events of cellular senescence mainly comprise genomic damage, telomere shortening, epigenomic damage, deregulated mitogenic and proliferation-associated signals, and the activation of tumor suppressors (reviews: Sharpless and DePinho 2005; Shay and Wright 2005; d'Adda di Fagagna 2008; Chandeck and Mooi 2010; Campisi 2013; Ivanov et al. 2013; Abdelmohsen and Gorospe 2015; Mar et al. 2015). In cancerogenic pathways, senescence mechanisms are canceled, an effect counteracted by elements of a senescence-messaging secretome that limits the expansion of early neoplastic cells (Schmitt 2003; Dimri 2005; Hornsby 2007; Prieur and Peeper 2008; Kuilman and Pepper 2009; Collado and Serrano 2010; Serrano 2010; Byun et al. 2015; Roos et al. 2016). Normal cells chiefly senescence via the mechanism of replicative senescence. In this process, progressive loss of telomeres associated with DNA double-strand breaks is followed by a DNA damage response (DDR). Part of cancer cells circumvent this senescence reaction by persistent telomerase activity (Xu et al. 2015), whereas other cancer cells are subject to telomere dysfunction and are thus vulnerable to senescence mechanisms. Sensing of intrinsic DNA damage and the subsequent induction of cellular senescence have been implicated as an important barrier against malignant transformation and the development of cancers. On the other hand, senescence is, through the inflammasome platform (see above), associated with inflammation, which in turn promotes cancerogenesis (reviews: Pribluda et al. 2013; Lasry and Ben-Neriah 2015).

Senescence is closely connected with autophagy. Oncogene hyperactivation induces

autophagy to establish a permanent proliferative arrest (Galluzzi et al. 2016). Autophagy affects nuclear and nuclear lamina structure and via these mechanisms exerts an influence on cellular senescence. Loss and elimination of lamin B1, an important component of the nuclear lamina, is a typical feature of senescence (Freund et al. 2012; Dou et al. 2015), and this depletion in senescent cells triggers a large-scale change in gene expression and chromatin landscape (Shah et al. 2013). In senescence, the autophagy-lysosomal pathway causes processing of chromatin contributing to the stability of cellular senescence (Adams 2007; Funayama and Ishikawa 2007; Corpet and Stucki 2014; Ivanov et al. 2013). Autophagy also maintains stemness by preventing senescence (Garcia-Prat et al. 2016).

Neosis: A Pathway to Circumvent Senescence

Neosis is defined as a novel form of cell division which represents a mode of escape of cells from senescence and involved in neoplastic transformation and cancer progression. The process is one of those that are studied to explain several paradoxes concerning current concepts of cancerogenesis (review: Baker and Kramer 2007). Neosis is characterized by polyploidy giant cells which, before they die, give rise to several cells with viable genomes via nuclear budding and asymmetric cytokinesis. It is a parasexual somatic reductive cell division characterized by DNA damage-induced senescence/mitotic crisis and polyploidization; generation of aneuploid daughter cells through nuclear budding; asymmetric cytokinesis and cellularization conferring extended, but limited mitotic life span to the offspring; and is repeated several times to transiently display stem cell properties and eventually neoplastic properties. The most important event of neosis seems to be the generation of mitotically viable daughter genomes after epigenetic modulation from the nonviable polyploidy genome of the so-called neosis mother cell/NMC (Sundaram et al. 2004; Rajaraman et al. 2005, 2006; reviews: Erenpreisa and Cragg 2007; Wheatley 2010). Neosis is a process whereby p53 function-deficient tumor cells undergo self-renewal after genotoxic damage via senescing endopolyploid tumor cells/ETCs. ETCs show autophagic degradation and exhibit extrusion of DNA, and during these conditions, self-renewal transcription factors are activated. ETCs restoring after failed multipolar mitosis undergo subnuclei differentiation, and surviving subnuclei sequester nascent cytoplasm to form subcells. These preformed paradiploid subcells then become released from their linking chromosome bridges through autophagy and begin cell division (neotic ETCs; Erenpreisa et al. 2011). Neosis is thought to play a significant role in carcinogenesis pathways and the development of chemoresistance (Navolanic et al. 2004). Neosis may also operate in syncytia formed in the setting of the formation of unstable syncytia generated by cell fusion between tumor cells and normal cells (Parris 2005). In case acquired genotoxic DNA damage cannot be compensated, it is known that progression through mitosis following DNA damage initiates a p53-and caspase-independent cell death response (Varmark et al. 2009).

Netosis/ETosis: Netting Neutrophils and NETotic Cell Functions That Can Trap Cancer Cells?

In the extracellular space, neutrophils can generate DNA-containing fibrils forming a network, termed neutrophil extracellular traps (NETs; Brinkmann et al. 2010; Remijsen et al. 2011b). This process is termed NETosis or, more recently, ETosis, meaning death with release of extracellular traps/ETs (Guimaraes-Costa et al. 2012). NETs can trap microorganisms (bacteria, fungi), unicellular parasites, and host cells (macrophages, eosinophils, mast cells) followed by their phagocytosis-independent killing while minimizing injury to host cells. NETs can release modified antigens and DNA and play an important role in the regulation of innate immunity and modulation of autoimmunity, specifically in systemic lupus erythematodes (Carmona-Rivera and Kaplan 2014). NET is considered to be the missing link

between cell death and autoimmune disorders (Bouts et al. 2012; Darrah and Andrade 2013; Mesa and Vasquez 2013). Ultrastructurally, NET manifests as fibrillar lattice whereby individual NET fibers consist of DNA filaments and associated globular protein domains, together forming threads with a diameter of 50 nm. These threads can associate to form much thicker and longer elements. In the course of NETosis, neutrophil nuclei lose their shape, and the euchromatin and heterochromatin homogenize, followed by disintegration of the nuclear membrane and granule membranes, so that the NET components can mix (Fuchs et al. 2007). The pathogenesis of NET formation involves a classical step in neutrophil shape change, i.e., activation of protein kinase C by its physiological activator, diacyl glycerols or by phorbol esters, or interleukin-8, causing granule release of release of chromatin to form a compound extracellular network. NET formation also requires both autophagy and superoxide generation (Remijsen et al. 2011a). The mTOR pathway has a pivotal role in NET formation via regulation of autophagy (Itakura and McCarty 2013). NETs contain bacteriocidic proteins bound to DNA (histones, neutrophil elastase), proteins from azurophilic granules (myeloperoxidase, cathepsin G), specific neutrophil granules (lactoferrin), tertiary granules (gelatinase), and DNA that can be delivered to extracellular compartments. The release of these molecules from NETs requires reactive oxygen species/ROS, which trigger the dissociation of neutrophil elastase from a membrane-associated complex into the cytosol, where it activates its proteolytic activity in a myeloperoxidase-dependent manner. Activated neutrophil elastase in the cytosol binds and degrades actin to arrest actin dynamics (Metzler et al. 2014). Aggregated NETs promote the resolution of neutrophil-mediated inflammation by degrading cytokines and chemokines and disrupting neutrophil recruitment and activation (Schauer et al. 2014). The fate of NETs is not yet clarified. However, the extracellular DNA in NETs can associate with proteins, taken up by cells, and stimulate intracellular DNA sensors, including Toll-like receptor 9, to activate DAMPs/pattern recognition molecules (Pisetsky 2012). This is a major pathway linking nuclear components with chromatin-induced immunity (Brinkmann and Zychlinsky 2012).

A special form of NET is intravascular NET, also occurring in the liver and specifically in liver sinusoids and tumor vessels. Intravascular NET is closely associated by thrombosis, and both NET and pathologic thrombosis are regulated by peptidylarginine deiminase 4, an enzyme that mediates chromatin decondensation (Martinod and Wagner 2014). Extracellular histones released from NETs can themselves induce thrombosis and can trigger innate immunity by activating Toll-like receptors and the NLRP3 inflammasome (Allam et al. 2014). Intravascular NET formation is a controlled process in which platelets that have sensed circulating microbes via their TLR4 attach to neutrophils and activate them to generate NETs. This pathway is rapid and does not lead to neutrophil cell death. NETosis associated thrombosis plays a significant role in cancer growth and spread (Demers and Wagner 2014), as it influences homing of cancer cells in thrombotic niches and facilitates spread along platelet- and coagulation factor-containing tracks. NETs can also promote the differentiation and function of fibroblasts (Chrysanthopoulou et al. 2014) and may therefore participate in the generation of a cancer stromal niche.

Roles of Apoptosis and Non-apoptotic Cell Death in Cell Competition: Losers and Winners in Cancerogenesis

In a novel concept of the cellular interactome, termed cell competition, there are winner cells that identify and eliminate viable cells from an expanding cell population without engulfment. According to this concept of "cell war," the demise of loser cells caused by winner cells involves apoptosis of suboptimal or superfluous cells. Killed loser cells are subsequently eliminated by the phagocyte system (Tamori and Deng 2011; Lolo et al. 2012, 2013; Vivarelli et al. 2012). Cell competition may be involved in cellular cooperation in early tumor progression (Krepkin and Costa 2011). The mechanism of cell competition seems to play a role in the

generation of so-called cancerization fields, involving a competition between wild-type cells and mutated preneoplastic or neoplastic cells (Rhiner and Moreno 2009). In the cancerization field, a battle is thought to take place between less well-adapted cells (the losers) and best-adapted cells (winners). For this Darwinian-type model of cancerogenesis, a mechanism of cell-to-cell communication during cell competition has been proposed and termed, the "flower code," due to the involvement of the Drosophila cell membrane protein Flower/Fw conserved in multicellular animals and required to label cells as "winners" or "losers" (Rhiner et al. 2010; Casas-Tinto et al. 2011).

References

Aachoui Y, Sagulenko V, Miao EA, Stacey KJ (2013) Inflammasome-mediated pyroptotic and apoptotic cell death, and defense against infection. Curr Opin Microbiol 16:319–326

Abdelmohsen K, Gorospe M (2015) Noncoding RNA control of cellular senescence. Wiley Interdiscip Rev RNA 6:615–629

Adams PD (2007) remodeling of chromatin structure in senescent cells and its potential impact on tumor suppression and aging. Gene 397:84–93

Allam R, Kumar SV, Darisipudi MN, Anders HJ (2014) Extracellular histones in tissue injury and inflammation. J Mol Med (Berl) 92:465–472

Bach M, Larance M, James DE, Ramm G (2011) The serine/threonine kinase ULK1 is a target of multiple phosphorylation events. Biochem J 440:283–291

Baixauli F, Martin-Cofreces NB, Morlino G, Carrasco YR, Calabia-Linares C, Veiga E et al (2011) The mitochondrial fission factor dynamin-related protein 1 modulates T-cell receptor signalling at the immune synapse. EMBO J 30:1238–1250

Baker SG, Kramer BS (2007) Paradoxes in carcinogenesis: new opportunities for research directions. BMC Cancer 7:171

Bao L, Chandra PK, Moroz K, Zhang X, Thung SN, Wu T, Dash S (2014) Impaired autophagy response in human hepatocellular carcinoma. Exp Mol Pathol 96:149–154

Becker et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22572990

Beller M, Thiel K, Thul PJ, Jäckle H (2010) Lipid droplets: a dynamic organelle moves into focus. FEBS Lett 584:2176–2182

Bernales S, Schluck S, Walter P (2007) ER-phagy: selective autophagy of the endoplasmic reticulum. Autophagy 3:285–287

Booth LA, Tavallai S, Hamed HA, Cruickshanks N, Dent P (2013) The role of cell signalling in the crosstalk between autophagy and apoptosis. Cell Signal 26:549–555

Bouts YM, Wolthuis DF, Dirkx MF, Pieterse E, Simons EM, van Boekel AM, Dieker JW et al (2012) Apoptosis and NET formation in the pathogenesis of SLE. Autoimmunity 45:597–601

Boya P, Codogno P (2012) Micronucleophagy: a new mechanism to protect against chromosomal instability ? Cell Cycle 11:645–656

Boya P, Kroemer G (2009) Beclin 1: a BH3-only protein that fails to induce apoptosis. Oncogene 28:2125–2127

Brinkmann V, Zychlinsky A (2012) Neutrophil extracellular traps is immunity the second function of chromatin ? J Cell Biol 198:773–783

Brinkmann V, Laube B, Abu Abed U, Goosmann C, Zychlinsky A (2010) Neutrophil extracellular traps: how to generate and visualize them. J Vis Exp (36). pii: 1724

Byun HO, Lee YK, Kim JM, Yoon G (2015) From cell senescence to age-related diseases: differential mechanisms of cation of senescence-associated secretory phenotypes. BMB Rep 48:549–558

Campisi J (2013) Aging, cellular senescence, and cancer. Annu Rev Physiol 75:685–705

Cao Y, Klionsky DJ (2007) Physiological functions of Atg6/Beclin 1: a unique autophagy-related protein. Cell Res 17:839–849

Carmona-Gutierrez D, Zimmermann A, Madeo F (2015) A molecular mechanism for lipophagy regulation in the liver. Hepatology. doi:10.1002/hep.27738

Carmona-Rivera C, Kaplan MJ (2014) Detection of SLE antigens in neutrophil extracellular traps (NETs). Methods Mol Biol 1134:151–161

Carneiro LA, Travassos LH (2013) The interplay between NLRs and autophagy in immunity and inflammation. Front Immunol 4:361

Casas-Tinto S, Torres M, Moreno E (2011) The flower code and cancer development. Clin Transl Oncol 13:5–9

Cassidy-Stone A, Chipuk JE, Ingerman E, Song C, Yoo C, Kuwana T, Kurth MJ, Shaw JT et al (2008) Chemical inhibition of the mitochondrial division dynamin reveals its role in Bax/Bak-dependent mitochondrial outer membrane permeabilization. Dev Cell 14:193–204

Cebollero E, Reggiori F, Kraft C (2012) Reticulophagy and ribophagy: regulated degradation of protein production factories. Int J Cell Biol 2012:182834

Chan NC, Chan DC (2011) Parkin uses the UPS to ship off dysfunctional mitochondria. Autophagy 7:771–772

Chandeck C, Mooi WJ (2010) Oncogene-induced cellular senescence. Adv Anat Pathol 17:42–48

Chang Y, Yan W, He X, Zhang L, Li C, Huang H, Nace G, Geller DA, Lin J, Tsung A (2012) miR-375 inhibits autophagy and reduces viability of hepatocellular

carcinoma cells under hypoxic conditions. Gastroenterology 143:177–187
Chang CP, Su YC, Lee PH, Lei HY (2013) Targeting NFKB by autophagy to polarize hepatoma-associated macrophage differentiation. Autophagy 9:619–621
Chen N, Debnath J (2010) Autophagy and tumorigenesis. FEBS Lett 584:1427–1435
Chen N, Karantza-Wadsworth V (2009) Role and regulation of autophagy in cancer. Biochim Biophys Acta 1793:1516–1523
Chen P, Cescon M, Bonaldo P (2014) Autophagy-mediated regulation of macrophages and its applications for cancer. Autophagy 10:192–200
Cheng B, Xu A, Qiao M, Wu Q, Wang W, Mei Y, Wu M (2015) BECN1s, a short splice variant of BECN1, functions in mitophagy. Autophagy 11:2048–2056
Christian P, Sacco J, Adeli K (2013) Autophagy: emerging roles in lipid homeostasis and metabolic control. Biochim Biophys Acta 1831:819–824
Chrysanthopoulou A, Mitroulis I, Apostolidou E, Arelaki S, Mikroulis D, Konstantinidis T et al (2014) Neutrophil extracellular traps promote differentiation and function of fibroblasts. J Pathol. doi:10.1002/path.4359
Cloonan SM, Lam HC, Ryter SW, Choi AM (2014) "Ciliophagy": the consumption of cilia components by autophagy. Autophagy 10:532–534
Collado M, Serrano M (2010) Senescence in tumours: evidence from mice and humans. Nat Rev Cancer 10:51–57
Corpet A, Stucki M (2014) Chromatin maintenance and dynamics in senescence: a spotlight on SAHF formation and the epigenome of senescent cells. Chromosoma 123:423–436
Coto-Montes A, Boga JA, Rosales-Corral S, Fuentes-Broto L, Tan DX, Reiter RJ (2012) Role of melatonin in the regulation of autophagy and mitophagy: a review. Mol Cell Endocrinol 361:12–23
Cui T, Fan C, Gu L, Gao H, Liu Q, Zhang T, Qi Z, Zhao C, Zhao H, Cai Q, Yang H (2011) Silencing of PINK1 induces mitophagy via mitochondrial permeability transition in dopaminergic MN9D cells. Brain Res 1394:1–13
D'Adda di Fagagna F (2008) Living on a break: cellular senescence as a DNA-damage response. Nat Rev Cancer 8:512–522
Dalby KN, Tekedereli I, Lopez-Berestein G, Ozpolat B (2010) Targeting the prodeath and prosurvival functions of autophagy as novel therapeutic strategies in cancer. Autophagy 6:322–329
Darrah E, Andrade F (2013) NETs: the missing link between cell death and systemic autoimmune diseases ? Front Immunol 3:428
Dawaliby R, Mayer A (2010) Microautophagy of the nucleus coincides with a vacuolar diffusion barrier at nuclear-vacuolar junctions. Mol Biol Cell 21:4173–4183
De Vries RL, Gilkerson RW, Przedborski S, Schon EA (2012) Mitophagy in cells with mtDNA mutations: being sick is not enough. Autophagy 8:699–700
Deegan S, Saveljeva S, Gorman AM, Samali A (2013) Stress-induced self-cannibalism: on the regulation of autophagy by endoplasmic reticulum stress. Cell Mol Life Sci 70:2425–2441
Demers M, Wagner DD (2014) NETosis: a new factor in tumor progression and cancer-associated thrombosis. Semin Thromb Hemost 40:277–283
Dengjel J, Kristensen AR, Andersen JS (2008) Ordered bulk degradation via autophagy. Autophagy 4:1057–1059
Dengjel J, Hoyer-Hansen M, Nielsen MO, Eisenberg T, Harder LM, Schandorff S, Farkas T et al (2012). Identification of autophagosome-associated proteins and regulators by quantitative proteomic analysis and genetic screens. Mol Cell Proteome 11. doi:10.1074/mcp.M111.014035
Digel M, Ehehalt R, Füllekrug J (2010) Lipid droplets lighting up: insights from live microscopy. FEBS Lett 584:2168–2175
Dimri GP (2005) What has senescence got to do with cancer ? Cancer Cell 7:505–512
Dong H, Czaja MJ (2011) Regulation of lipid droplets by autophagy. Trends Endorcrinol Metab 22:243–240
Dou Z, Xu C, Donahue G, Shimi T, Pan JA, Zhu J, Ivanov A, Capell BC, Drake AM, Shah PP, Catanzaro JM et al (2015) Autophagy mediates degradation of nuclear lamina. Nature 527:105–109
Dunlop EA, Tee AR (2013) The kinase triad, AMPK, mTORC1 and ULK1, maintains energy and nutrient homoeostasis. Biochem Soc Trans 41:939–943
Egan DF, Shackelford DB, Mihaylova MM, Gerlino S, Kohnz RA, Mair W, Vasquez DS et al (2011) Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. Science 331:456–461
Erenpreisa J, Cragg MS (2007) Cancer: a matter of life cycle ? Cell Biol Int 31:1507–1510
Erenpreisa J, Salmina K, Huna A, Kosmacek EA, Cragg MS, Ianzini F, Anisimov AP (2011) Polyploid tumor cells elicit paradiploid progeny through depolyploidizing divisions and regulated autophagic degradation. Cell Biol Int 35:687–695
Esclatine A, Chaumorcel M, Codogno P (2009) Macroautophagy signaling and regulation. Curr Top Microbiol Immunol 335:33–70
Feng Y, He D, Yao Z, Klionsky DJ (2014) The machinery of macroautophagy. Cell Res 24:24–41
Freund A, Laberge RM, Demaria M, Campisi J (2012) Lamin B1 loss is a senescence-associated biomarker. Mol Biol Cell 23:2066–2075
Fuchs TA, Abed U, Goosmann C, Hurwitz R, Schulze I, Wahn V, Weinrauch Y, Brinkmann V et al (2007) Novel cell death program leads to neutrophil extracellular traps. J Cell Biol 176:231–241
Funayama R, Ishikawa F (2007) Cellular senescence and chromatin structure. Chromosoma 116:431–440
Galluzzi L, Vicencio JM, Kepp O, Tademir E, Majuri MC, Kroemer G (2008) To die or not to die: that is the autophagic question. Curr Mol Med 8:78–91

Galluzzi L, Bravo-San Pedro JM, Kroemer G (2016) Autophagy mediates tumor suppression via cellular senescence. Trends Cell Biol 26:1–3

Garcia-Prat L, Martinez-Vicente M, Perdiguero E, Ortet L, Rodriguez-Ubreva J, Rebollo E, Ruiz-Bonilla V, Gutarra S et al (2016) Autophagy maintains stemness by preventing senescence. Nature 529:37–42

Gdynia G, Keith M, Kopitz J, Bergmann M, Fassl A, Weber AN, George J, Kees T et al (2010) Danger signaling protein HMGB1 induces a distinct form of cell death accompanied by formation of giant mitochondria. Cancer Res 70:8558–8568

Gegg ME, Cooper JM, Chau KY, Rojo M, Schapira AH, Taanman JW (2010) Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. Hum Mol Genet 19:4861–4870

Gilkerson RW, De Vries RL, Lebot P, Wikstrom JD, Torgyekes E, Shirihai OS, Przedborski S et al (2012) Mitochondrial autophagy in cells with mtDNA mutations results from synergistic loss of transmembrane potential and mTORC1 inhibition. Hum Mol Genet 21:978–990

Givvimani S, Munjal C, Tyagi N, Sen U, Metreveli N, Tyagi SC (2012) Mitochondrial division/mitphagy inhibitor (Mdivi) ameliorates pressure overload induced heart failure. PLoS One 7:e32388

Glick D, Barth S, Macleod KF (2010) Autophagy: cellular and molecular mechanisms. J Pathol 221:3–12

Gosselin K, Deruy E, Martien S, Vercamer C, Bouali F, Dujardin T, Slomianny C, Houel-Renault L et al (2009) Senescent keratinocytes die by autophagic programmed cell death. Am J Pathol 174:423–435

Gottlieb RA, Carreira RS (2010) Autophagy in health and disease: V. Mitophagy as way of life. Am J Physiol Cell Physiol 299:C203–C210

Gozuacik D, Kimchi A (2004) Autophagy as a cell death and tumor suppressor mechanism. Oncogene 23:2891–2906

Gross O, Thomas CJ, Guarda G, Tschopp J (2011) The inflammasome: an integrated view. Immunol Rev 243:136–151

Grünewald A, Arns B, Seibler P, Rakovic A, Münchau A, Ramirez A, Sue CM, Klein C (2012) ATP3A2 mutations impair mitochondrial function in fibroblasts from patients with Kufor-Rakeb syndrome. Neurobiol Aging 33(1843):e1–e7

Grutzendler J, Murikinati S, Hiner B, Ji L, Lam CK, Yoo T, Gupta S, Adelman RA et al (2014) Angiophagy prevents early embolus washout but recanalizes microvessels through embolus extravasation. Sci Transl Med 6:226ra31

Guimaraes-Costa AB, Nascimento MT, Wardini AB, Pinto-da-Silva LH, Saraiva EM (2012) ETosis: a microbicidal mechanism beyond cell death. J Parasitol Res 2012:929743

Guo JY, Xia B, White E (2013) Autophagy-mediated tumor promotion. Cell 155:1216–1219

Haasken S, Sutterwala FS (2013) Damage control: management of cellular stress by the NLRP3 inflammasome. Eur J Immunol 43:2003–2005

Hanna et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22505714

Hashemi HF, Goodman JM (2015) The life cycle of lipid droplets. Curr Opin Cell Biol 33C:119–124

He W, Wang Q, Srinivasan B, Xu J, Padilla MT, Li Z, Wang X, Liu Y, Gou X, Shen HM et al (2014) A JNK-mediated autophagy pathway that triggers c-IAP degradation and necroptosis for anticancer chemotherapy. Oncogene 33:3004–3013

Heid ME, Keyel PA, Kamga C, Shiva S, Watkins SC, Salter RD (2013) Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation. J Immunol 191:5230–5238

Hirota Y, Kang D, Kanki T (2012) The physiological role of mitophagy: new insights into phosphorylation events. Int J Cell Biol 2012:354914

Hornsby PJ (2007) Senescence as an anticancer mechanism. J Clin Oncol 25:1852–1857

Hoshino et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22044588

Hou W, Zhang Q, Yan Z, Chen R, Zeh Iii HJ, Kang R, Lotze MT, Tang D (2013) Strange attractors: DAMPs and autophagy link tumor cell death and immunity. Cell Death Dis 4:e966

Huang C, Andres AM, Ratliff EP, Hernandez G, Lee P, Gottlieb RA (2011) Preconditioning involves selective mitophagy mediated by Parkin and p62/SQSTM1. PLoS One 6:e20975

Huang S, Okamoto K, Yu C, Sinicrope FA (2013) p62/sequestosome-1 up-regulation promotes ABT-263-induced caspase-8 aggregation/activation on the autophagosome. J Biol Chem 288:33654–33666

Itakura A, McCarthy OJ (2013) Pivotal role for the mTOR pathway in the formation of neutrophil extracellular traps via regulation of autophagy. Am J Physiol Cell Physiol 305:C348–C354

Itakura E, Kishi C, Inoue K, Mizushima N (2008) Beclin 1 forms two distinct phosphatidylinositol 3-kinase complexes with mammalian Atg14 and UVRAG. Mol Biol Cell 19:5360–5372

Itakura E, Kishi-Itakura C, Koyama-Honda I, Mizushima N (2012) Structures containing Atg9A and the ULK1 complex independently target depolarized mitochondria at initial stages of Parkin-mediated mitophagy. J Cell Sci 125:1488–1499

Ivanov A, Pawlikowski J, Manoharan I, van Tuyn J, Nelson DM, Rai TS, Shah PP, Hewitt G, Korolchuk VI, Passos JF et al (2013) Lysosome-mediated processing of chromatin in senescence. J Cell Biol 202:129–143

Jin C, Flavell RA (2010) Molecular mechanism of NLRP3 inflammasome activation. J Clin Immunol 30:628–631

Jin SM, Youle RJ (2012) PINK1-and parkin-mediated mitophagy at a glance. J Cell Sci 125:795–799

Joo JH, Dorsey FC, Joshi A, Hennessy-Walters KM, Rose KL, McCastlain K, Zhang J et al (2011) Hsp90-Cdc37 chaperone complex regulates Ulk1- and Atg13-mediated mitophagy. Mol Cell 43:572–585

Joshi S, Ryan KM (2013) Autophagy chews Fap to promote apoptosis. Nat Cell Biol 16:23–25

Kane LA, Youle RJ (2011) PINK1 and parkin flag Miro to direct mitochondrial traffic. Cell 147:721–723

Kang R, Livesey KM, Zeh HJ, Lotze MT, Tang D (2011a) Metabolic regulation by HMGB11-mediated autophagy and mitophagy. Autophagy 7:1256–1258

Kang R, Zeh HJ, Lotze MT, Tang D (2011b) The beclin 1 network regulates autophagy and apoptosis. Cell Death Differ 18:571–580

Karanasios et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/24013547

Karbowski M, Youle RJ (2011) Regulating mitochondrial outer membrane proteins by ubiquitination and proteasomal degradation. Curr Opin Cell Biol 23:476–482

Khandelwal PJ, Herman AM, Hoe HS, Rebeck GW, Moussa CE (2011) Parkin mediates beclin-dependent autophagic clearance of defective mitochondria and ubiquitinated Abeta in AD models. Hum Mol Genet 20:2091–2102

Kim JH, Kim HY, Lee YK, Yoon YS, Xu WG, Yoon JK, Choi SE, Ko YG, Kim MJ et al (2011) Involvement of mitophagy in oncogenic K-Ras-induced transformation: overcoming a cellular energy deficit from glucose deficiency. Autophagy 7:1187–1198

Kim SJ, Khan M, Quan J, Till A, Subramani S, Siddiqui A (2013) Hepatitis B virus disrupts mitochondrial dynamics: induces fission and mitophagy to attenuate apoptosis. PLoS Pathog 9:e1003722

Kiyono K, Suzuki HI, Matsuyama H, Morishita Y, Komuro A, Kano MR, Sugimoto K et al (2009) Autophagy is activated by TGF-beta and potentiates TGF-beta-mediated growth inhibition in human hepatocellular carcinoma cells. Cancer Res 69:8844–8852

Klionsky DJ, Codogno P, Cuervo AM, Deretic V, Elazar Z, Fueyo-Margareto J, Gewirtz DA et al (2010) A comprehensive glossary of autophagy-related molecules and processes. Autophagy 6:438–447

Kotsafti A, Farinati F, Cardin R, Cillo U, Nitti U, Bortolami M (2012) Autophagy and apoptosis-related genes in chronic liver disease and hepatocellular carcinoma. BMC Gastroenterol 12:118

Kovacs AL, Rez G, Palfia Z, Kovacs J (2000) Autophagy in the epithelial cells of murine seminal vesicle in vitro. Formation of large sheets of nascent isolation membranes, sequestration of the nucleus and inhibition by wortmannin and 3-ethyladenine. Cell Tissue Res 302:253–261

Krepkin K, Costa J (2011) Defining the role of cooperation in early tumor progression. J Theor Biol 285:36–45

Krick R, Henke S, Tolstrup J, Thumm M (2008) Dissecting the localization and function of Atg18, Atg21 and Ygr223c. Autophagy 4:896–910

Krick R, Mühe Y, Prick T, Bredschneider M, Bremer S, Wenzel D, Eskelinen EL, Thumm M (2009) Piecemeal microautophagy of the nucleus: genetic and morphological traits. Autophagy 5:270–272

Kristensen AR, Schandorff S, Hoyer-Hansen M, Nielsen MO, Jäätelä M, Dengjel J et al (2008) Ordered organelle degradation during starvation-induced autophagy. Mol Cell Proteom 7:2419–2428

Krysko O, Love Aes T, Bachert C, Vandenabeele P, Krysko DV (2013) Many faces of DAMPs in cancer therapy. Cell Death Dis 4:e631

Kuilman T, Peeper DS (2009) Senescence-messaging secretome: SMS-ing cellular stress. Nat Rev Cancer 9:81–94

Kurihara Y, Kanki T, Aoki Y, Hirota Y, Saigusa T, Uchiumi T, Kang D (2012) Mitophagy plays an essential role in reducing mitochondrial production of reactive oxygen species and mutation of mitochondrial DNA by maintaining mitochondrial quantity and quality in yeast. J Biol Chem 287:3265–3272

Kvam E, Goldfarb DS (2007) Nucleus-vacuole junctions and piecemeal microautophagy of the nucleus n S. cerevisiae. Autophagy 3:85–92

Lamkanfi M, Dixit VM (2009) Inflammasomes: guardians of cytosolic sanctity. Immunol Rev 227:95–105

Lasry A, Ben-Neriah Y (2015) Senescence-associated inflammatory responses: aging and cancer perspectives. Trends Immunol 36:217–228

Lawlor KE, Vince JE (2014) Ambiguities in NLRP3 inflammasome regulation: is there a role for mitochondria ? Biochim Biophys Acta 1840:1433–1440

Lazarou M, Jin SM, Kane LA, Youle RJ (2012) Role of PINK1 binding to the TOM complex and alternate intracellular membranes in recruitment and activation of the E3 ligase parkin. Dev Cell 22:320–333

Lee J, Giordano S, Zhang J (2012) Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling. Biochem J 441:523–540

Lee YJ, Ha YJ, Kang YN, Kang KJ, Hwang JS, Chung WJ, Cho KB, Park KS et al (2013) The autophagy-related marker LC3 can predict prognosis in human hepatocellular carcinoma. PLoS One 8:e81540

Lee JM, Wagner M, Xiao R, Kim KH, Feng D, Lazar MA, Moore DD (2014) Nutrient-sensing nuclear receptors coordinate autophagy. Nature 516:112–115

Leemans JC, Cassel SL, Sutterwala FS (2011) Sensing damage by the NLRP3 inflammasome. Immunol Rev 243:152–162

Levine B, Sinha S, Kroemer G (2008) Bcl-2 family members: dual regulators of apoptosis and autophagy. Autophagy 4:600–606

Liu K, Czaja MJ (2013) Regulation of lipid stores and metabolism by lipophagy. Cell Death Differ 20:3–11

Liu L, Feng D, Chen G, Chen M, Zheng Q, Song P, Ma Q, Zhu C, Wang R, Qi W et al (2012) Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol 14:177–185

Liu B, Wen X, Cheng Y (2013) Survival or death: disequilibrating the oncogenic and tumor suppressive autophagy in cancer. Cell Death Dis 4:e892

Lolo FN, Casas-Tinto S, Moreno E (2012) Cell competition time line: winners kill losers, which are extruded and engulfed by hemocytes. Cell Rep 2:526–539

Lolo FN, Casas Tinto S, Moreno E (2013) How winner cells cause the demise of loser cells: cell competition causes apoptosis of suboptimal cells: their dregs are removed by hemocytes, thus preserving tissue homeostasis. Bioessays 35:348–353

Luo S, Rubinsztein DC (2010) Apoptosis blocks Beclin 1-dependent autophagosome synthesis: an effect rescued by Bcl-xL. Cell Death Differ 17:268–277

Lupfer C, Kanneganti TD (2013) Unsolved mysteries in NLR biology. Front Immunol 4:285

Ma T, Li YY, Zhu J, Fan LL, Du WD, Wu CH, Sun GP, Li JB (2013) Enhanced autophagic flux by endoplasmic reticulum stress in human hepatocellular carcinoma cells contributes to the maintenance of cell viability. Oncol Rep 30:433–440

Mai S, Muster B, Bereiter-Hahn J, Jendrach M (2012) Autophagy proteins LC3B, ATG5 and ATG12 participate in quality control after mitochondrial damage and influence lifespan. Autophagy 8:47–62

Maiuri MC, Tasdemir E, Criollo A, Morselli E, Vicencio JM, Carnuccio R, Kroemer G (2009) Control of autophagy by oncogenes and tumor suppressor genes. Cell Death Differ 16:87–93

Mar FA, Debnath J, Stohr BA (2015) Autophagy-independent senescence and genome instability driven by targeted telomere dysfunction. Autophagy 11:527–537

Mariathasan S (2007) ASC, Ipaf and cryopyrin/Nalp3: bona fide intracellular adapters of the caspase-1 inflammasome. Microbes Infect 9:664–671

Martin S, Driessen K, Nixon SJ, Zerial M, Parton RG (2005) Regulated localization of Rab18 to lipid droplets: effects of lipolytic stimulation and inhibition of lipid droplet catabolism. J Biol Chem 280:42325–42335

Martinez-Outschoom UE, Trimmer C, Lin Z, Whitaker-Menezes D, Chiavarina B, Zhou J et al (2010) Autophagy in cancer associated fibroblasts promotes tumor cell survival: role of hypoxia, HIF1 induction and NFkB activation in the tumor stromal microenvironment. Cell Cycle 9:3515–3533

Martinod K, Wagner DD (2014) Thrombosis: tangled up in NETs. Blood 123:2768–2776

Martinon F, Tschopp J (2007) Inflammatory caspases and inflammasomes: master switches of inflammation. Cell Death Differ 14:10–22

Martinon F, Gaide O, Pétrilli V, Mayor A, Tschopp J (2007) NALP inflammasome: a central role in innate immunity. Semin Immunopathol 29:213–229

Matsuda N, Tanaka K (2010) Uncovering the roles of PINK1 and parkin in mitophagy. Autophagy 6:952–954

May AI, Devenish RJ, Prescott M (2012) The many faces of mitochondrial autophagy: making sense of contrasting observations in recent research. Int J Cell Biol 2012:431684

Mehrpour M, Esclatine A, Beau I, Codogno P (2010) Overview of macroautophagy regulation in mammalian cells. Cell Res 20:748–762

Meissner C, Lorenz H, Weihofen A, Selkoe DJ, Lemberg MK (2011) The mitochondrial intramembrane protease PARL cleaves human Pink1 to regulate Pank1 trafficking. J Neurochem 117:856–867

Mesa MA, Vasquez G (2013) NETosis. Autoimmune Dis 2013:651497

Metzler KD, Goosmann C, Lubojemska A, Zychlinsky A, Papayannopoulos V (2014) A myeloperoxidase-containing complex regulates neutrophil elastase release and actin dynamics during NETosis. Cell Rep. doi:10.1016/j.celrep.2014.06.044

Michel S, Wanet A, De Pauw A, Rommelaere G, Arnould T, Renard P (2011) Crosstalk between mitochondrial (dys)function and mitochondrial abundance. J Cell Physiol 227:2297–2310

Mijaljica D, Devenish RJ (2013) Nucleophagy at a glance. J Cell Sci 126:4325–4330

Mijaljica D, Prescott M, Devenish RJ (2010a) Mitophagy and mitoptosis in disease processes. Methods Mol Biol 648:93–106

Mijaljica D, Prescott M, Devenish RJ (2010b) The intricacy of nuclear membrane dynamics during nucleophagy. Nucleus 1:213–223

Morselli E, Galluzzi L, Kepp O, Vicencio JM, Criollo A, Maiuri MC, Kroemer G (2009) Anti-and pro-tumor functions of autophagy. Biochim Biophys Acta 1793:1524–1532

Murphy S, Martin S, Parton RG (2009) Lipid droplet-organelle interactions; sharing the fats. Biochim Biophys Acta 1791:441–447

Nair U, Cao Y, Xie Z, Klionsky DJ (2010) Roles of the lipid-binding motifs of Atg18 and Atg21 in the cytoplasm to vacuole targeting pathway and autophagy. J Biol Chem 285:11476–11488

Navolanic PM, Akula SM, McCubrey JA (2004) Neosis and its potential role in cancer development and chemoresistance. Cancer Biol Ther 3:219–220

Nezis IP, Stenmark H (2012) p62 at the interface of autophagy, oxidative stress signaling, and cancer. Antioxid Redox Signal 17:786–793

Noda T, Fujita N, Yoshimori T (2008) The Ubi brothers reunited. Autophagy 4:540–544

Noguchi Y, Young JD, Aleman JO, Hansen ME, Kelleher JL, Stephanopoulos G (2011) Tracking cellular metabolomics in lipoapoptosis- and steatosis-developing liver cells. Mol Biosyst 7:1409–1419

Novak I (2012) Mitophagy: a complex mechanism of mitochondrial removal. Antioxid Redox Signal 17:794–802

Novak I, Dikic I (2011) Autophagy receptors in developmental clearance of mitochondria. Autophagy 7:301–303

Okamoto K, Kondo-Okamoto N (2012) Mitochondria and autophagy: critical interplay between the two homeostats. Biochim Biophys Acta 1820:595–600

Orvedahl A, Sumpter R, Xiao G, Ng A, Zou Z, Tang Y, Narimatsu M, Gilpin C, Sun Q et al (2011) Image-based genome-wide siRNA screen identifies selective autophagy factors. Nature 480:113–117

Otera H, Mihara K (2012) Mitochondrial dynamics: functional link with apoptosis. Int J Cell Biol 2012:821676

Pampliega O, Orhon I, Patel B, Sridhar S, Diaz-Carretero-A, Beau I, Codogno P, Satir BH et al (2013) Functional interaction between autophagy and ciliogenesis. Nature 502:194–200

Park YE, Hayashi YK, Bonne G, Arimura T, Noguchi S, Nonaka I, Nishino I (2009a) Autophagic degradation of nuclear components in mammalian cells. Autophagy 5:795–804

Park KJ, Lee SH, Lee CH, Jang JY, Chung J, Kwon MH, Kim YS (2009b) Upregulation of Beclin-1 expression and phosphorylation of Bcl-2 and p53 are involved in the JNK-mediated autophagic cell death. Biochem Biophys Res Commun 382:726–729

Park SW, Kim KY, Lindsey JD, Dai Y, Heo H, Nguyen DH, Ellisman MH, Weinreb RN et al (2011) A selective inhibitor of drp1, mdivi-1, increases retinal ganglion cell survival in acute ischemic mouse retina. Invest Ophthalmol Vis Sci 52:2837–2843

Parris GE (2005) Clinically significant cancer evolves from transient mutated and/or aneuploid neoplasia by cell fusion to form unstable syncytia that give rise to ecologically viable parasite species. Med Hypothesis 65:846–850

Pattingre S, Espert L, Biard-Piechaczyk M, Codogno P (2008) Regulation of macroautophagy by mTOR and beclin 1 complexes. Biochimie 90:313–323

Peng YF, Shi YH, Shen YH, Ding ZB, Ke AW, Zhou J, Qiu SJ, Fan J (2013) Promoting colonization in metastatic HCC cells by modulation of autophagy. PLoS One 8: e74407

Peng J, Zhang R, Cui Y, Liu H, Zhao X, Huang L, Hu M, Yuan X, Ma B, Ma X, Takashi U et al (2014) Atg5 regulates late endosome and lysosome biogenesis. Sci China Life Sci 57:59–68

Pierce NW, Nachury MV (2013) Cilia grow by taking a bite out of the cell. Dev Cell 27:126–127

Pisetsky DS (2012) The origin and properties of extracellular DNA: from PAMP to DAMP. Clin Immunol 144:32–40

Pribluda A, Elyada E, Wiener Z, Hamza H, Goldstein RE, Biton M, Burstain I, Morgenstern Y, Brachya G, Billauer H et al (2013) A senescence-inflammatory switch from cancer-inhibitory to cancer-promoting mechanism. Cancer Cell 24:242–256

Prieur A, Peeper DS (2008) Cellular senescence in vivo: a barrier to tumorigenesis. Curr Opin Cell Biol 20:150–155

Rajaraman R, Rajaraman MM, Rajaraman SR, Guernsey DL (2005) Neosis – a paradigm of self-renewal in cancer. Cell Biol Int 29:1084–1097

Rajaraman R, Guernsey DL, Rajaraman MM, Rajaraman SR (2006) Stem cells, senescence, neosis and self-renewal in cancer. Cancer Cell Int 6:25

Rambold AS, Lippincott-Schwartz J (2011) Mechanisms of mitochondria and autophagy crosstalk. Cell Cycle 10:4032–4038

Rello-Varona S, Lissa D, Shen S, Niso-Santano M, Senovilla L, Marino G, Vitale I et al (2012) Autophagic removal of micronuclei. Cell Cycle 11:170–176

Remijsen Q, Vanden Berghe T, Wirawan E, Asselbergh B, Parthoens E, De Rycke R et al (2011a) Neutrophil extracellular trap death requires both autophagy and superoxide generation. Cell Res 21:290–304

Remijsen Q, Kuijpers TW, Wirawan E, Lippens S, Vandenabeele P, Vanden Berghe T (2011b) Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality. Cell Death Differ 18:581–588

Reyjal J, Cormier K, Turcotte S (2014) Autophagy and cell death to target cancer cells: exploiting synthetic lethality as cancer therapies. Adv Exp Med Biol 772:167–188

Rhiner C, Moreno E (2009) Super competition as a possible mechanism to pioneer precancerous fields. Carcinogenesis 30:723–728

Rhiner C, Lopez-Gay JM, Soldini D, Casas-Tinto S, Martin FA, Lombardia L, Moreno E (2010) Flower forms an extracellular code that reveals the fitness of a cell to its neighbors in Drosophila. Dev Cell 18:985–998

Roos WP, Thomas AD, Kaina B (2016) DNA damage and the balance between survival and death in cancer biology. Nat Rev Cancer 16:20–33

Ryter SW, Mizumura K, Choi AM (2014) The impact of autophagy on cell death modalities. Int J Cell Biol 2014:502676

Sakai Y, Oku M, van der Klei IJ, Kiel JA (2006) Pexophagy: autophagy degradation of peroxisomes. Biochim Biophys Acta 1763:1767–1775

Schauer et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24784231

Schmitt CA (2003) Senescence, apoptosis and therapy – cutting the lifelines of cancer. Nat Rev Cancer 3:286–295

Schroder K, Tschopp J (2010) The inflammasomes. Cell 140:821–832

Schroeder B, Schulze RJ, Weller SG, Sletten AC, Casey CA, McNiven MA (2015) The small GTPase Rab7 as a central regulator of hepatocellular lipophagy. Hepatology. doi:10.1002/hep.27667

Schulze RJ, McNiven MA (2014) A well-oiled machine: DNM2/dynamin 2 helps keep hepatocyte lipophagy running smoothly. Autophagy 10(10):388–389

Schulze RJ, Weller SG, Schroeder B, Krueger EW, Chi S, Casey CA, McNiven MA (2013) Lipid droplet breakdown requires dynamin 2 for vesiculation of autolysosomal tubules in hepatocytes. J Cell Biol 203:315–326

Serrano M (2010) Cancer: a lower bar for senescence. Nature 464:363–364

Settembre C, Ballabio A (2014) Lysosome: regulator of lipid degradation pathways. Trends Cell Biol 24:743–750

Settembre C, Fraldi A, Medina DL, Ballabio A (2013) Signals from the lysosome: a control centre for cellular clearance and energy metabolism. Nat Rev Mol Cell Biol 14:283–296

Shah PP, Donahue G, Otte GL, Capell BC, Nelson DM, Cao K, Aggarwala V, Cruickshanks HA, Rai TS, McBryan T et al (2013) Lamin B1 depletion in senescent cells triggers large-scale changes in gene expression and the chromatin landscape. Genes Dev 27:1787–1799

Sharpless NE, DePinho RA (2005) Crime and punishment. Nature 436:636–637

Shay JW, Wright WE (2005) Senescence and immortalization: role of telomeres and telomerase. Carcinogenesis 26:867–874

Shen HM, Mizushima N (2014) At the end of the autophagic road: an emerging understanding of lysosomal functions in autophagy. Trends Biochem Sci 39:61–71

Shi YH, Ding ZB, Zhou J, Qiu SJ, Fan J (2009) Prognostic significance of Beclin 1–dependent apoptotic activity in hepatocellular carcinoma. Autophagy 5:380–382

Singh R, Cuervo AM (2012) Lipophagy: connecting autophagy and lipid metabolism. Int J Cell Biol 2012:282041

Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, Czaja MJ (2009) Autophagy regulates lipid metabolism. Nature 458:1131–1135

Sit KH, Paramanantham R, Bay BH, Chan HL, Wong KP, Thong P et al (1996) Sequestration of mitotic (M-phase) chromosomes in autophagosomes: mitotic programmed cell death in human Chang liver cells induced by an OH* burst from vanadyl(4). Anat Rec 245:1–8

Soubannier et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22226745

Springer W, Kahle PJ (2011) Regulation of PINK1-Parkin-mediated mitophagy. Autophagy 7:266–278

Sun et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/19372752

Sundaram M, Guernsey DL, Rajaraman MM, Rajaraman R (2004) Neosis: a novel type of cell division in cancer. Cancer Biol Ther 3:207–218

Suzuki HI, Kiyono K, Miyazono K (2010) Regulation of autophagy by transforming growth factor-b (TGF-b) signaling. Autophagy 6:645–647

Szatmari Z, Kis V, Lippai M, Hegedus K, Farago T, Lorincz P, Tanaka T, Juhasz G, Sass M (2014) Rab11 facilitates crosstalk between autophagy and endosomal pathway through regulation of Hook localization. Mol Biol Cell 25:522–531

Taguchi K, Fujikawa N, Komatsu M, Ishii T, Unno M, Akakike T, Motohashi H, Yamamoto M (2012) Keap1 degradation by autophagy for the maintenance of redox homeostasis. Proc Natl Acad Sci U S A 109:13561–13566

Takahashi Y, Coppola D, Matsushita N, Cualing HD, Sun M, Sato Y, Liang C, Jung JU et al (2007) Bif-1 interacts with beclin 1 through UVRAG and regulates autophagy and tumorigenesis. Nat Cell Biol 9:1142–1151

Takahashi Y, Meyerkord CL, Wang HG (2009) Bif-1/endophilin B1: a candidate for crescent driving force in autophagy. Cell Death Differ 16:947–955

Tamori Y, Deng WM (2011) Cell competition and its implications for development and cancer. J Genet Genomics 38:483–495

Tang Z, Lin MG, Stowe TR, Chen S, Zhu M, Stearns T, Franco B, Zhong Q (2013) Autophagy promotes primary ciliogenesis by removing OFD1 from centriolar satellites. Nature 502:254–257

Tang Z, Zhu M, Zhong Q (2014) Self-eating to remove cilia roadblock. Autophagy 10:379–381

Thomas RL, Kubli DA, Gustafsson AB (2011) Bnip3-mediated defects in oxidative phosphorylation promote mitophagy. Autophagy 7:775–777

Till A, Lakhani R, Burnett SF, Subramani S (2012) Pexophagy: the selective degradation of peroxisomes. Int J Cell Biol 2012:512721

Toshima T, Shirabe K, Matsumoto Y, Yoshiya S, Ikegami T, Yoshizumi T, Soejima Y et al (2014) Autophagy enhances hepatocellular carcinoma progression by activation of mitochondrial b-oxidation. J Gastroenterol 49:907–916

Tschopp J (2011) Mitochondria: sovereign of inflammation ? Eur J Immunol 41:1196–1202

Tsuchiya K, Hara H (2014) The inflammasome and its regulation. Crit Rev Immunol 34:41–80

Valentin-Vega Y, Kastan MB (2012) A new role for ATM. Regulating mitochondrial function and mitophagy. Autophagy 8:840–841

Van Humbeeck C, Cornelissen T, Hofkens H, Mandemakers W, Gevaert K, De Strooper B, Vandenberghe W (2011) Parkin interacts with ambra1 to induce mitophagy. J Neurosci 31:10249–10261

Varmark H, Sparks CA, Nordberg JJ, Koppetsch BS, Theurkauf WE (2009) DNA damage-induced cell death is enhanced by progression though mitosis. Cell Cycle 8:2952–2964

Vigano E, Mortellaro A (2013) Caspase-11: the driving factor for noncanonical inflammasomes. Eur J Immunol 43:2240–2245

Vivarelli S, Wagstaff L, Piddini E (2012) Cell wars: regulation of cell survival and proliferation by cell competition. Essays Biochem 53:69–82

Wang K, Klionsky DJ (2011) Mitochondria removal and autophagy. Autophagy 7:297–300

Wang X, Winter D, Ashrafi G, Schele J, Wong YL, Selkoe D, Rice S, Steen J, LaVoie MJ et al (2011) PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. Cell 147:893–906

Wang Y, Han C, Lu L, Magliato S, Wu T (2013) Hedgehog signaling pathway regulates autophagy in human hepatocellular carcinoma cells. Hepatology 58:995–1010

Wei Q, Mu K, Li T, Zhang Y, Yang Z, Jia X, Zhao W, Huai W, Guo P, Han L (2014) Deregulation of the NLRP3 inflammasome in hepatic parenchymal cells during liver cancer progression. Lab Invest 94:52–62

Weidberg H, Shvets E, Elazar Z (2009) Lipophagy: selective catabolism designed for lipids. Dev Cell 16:628–630

Wen H, Miao EA, Ting JP (2013) Mechanisms of NOD-like receptor-associated inflammasome activation. Immunity 39:432–441

Wheatley DN (2010) Another decade of advances in research on primary cilia, porosomes and neosis: some passing thoughts at 70. Cell Biol Int 34:335–337

Williams A, Jahreiss L, Sarkar S, Saiki S, Menzies FM, Ravikumar B, Rubinsztein DC (2006) Aggregate-prone proteins are cleared from the cytosol by autophagy: therapeutic implications. Curr Top Dev Biol 76:89–101

Wrighton KH (2013) Cytoskeleton: autophagy and ciliogenesis come together. Nat Rev Mol Cell Biol 14:687

Xie R, Nguyen S, McKeehan K, Wang F, McKeehan WL, Liu L (2011) Microtubule-associated protein 1S (MAP1S) bridges autophagic components with microtubules and mitochondria to affect autophagosomal biogenesis and degradation. J Biol Chem 286:10367–10377

Xu X, Chen W, Miao R, Zhou Y, Wang Z, Zhang L, Wan Y, Dong Y, Qu K, Liu C (2015) miR-34a induces cellular senescence via modulation of telomerase activity in human hepatocellular carcinoma by targeting FoxM1/c-Myc pathway. Oncotarget 6:3988–4004

Yan W, Chang Y, Liang X, Cardinal JS, Huang H, Thorne SH, Monga SP, Geller DA et al (2012) High-mobility group box 1 activates caspase-1 and promotes hepatocellular carcinoma invasiveness and metastasis. Hepatology 55:1863–1875

Yang YP, Liang ZQ, Gu ZL, Qin ZH (2005) Molecular mechanism and regulation of autophagy. Acta Pharmacol Sin 26:1421–1434

Yokota S, Dariush Fahimi H (2009) Degradation of excess peroxisomes in mammalian liver cells by autophagy and other mechanisms. Histochem Cell Biol 131:455–458

Youle RJ, Narendra DP (2011) Mechanisms of mitophagy. Nat Rev Mol Cell Biol 12:9–14

Young MM, Takahashi Y, Khan O, Park S, Hori T, Yun J, Sharma AK, Amin S, Hu CD et al (2012) Autophagosomal membrane serves as platform for intracellular death-inducing signaling complex (iDISC)-mediated caspase-8 activation and apoptosis. J Biol Chem 287:12455–12468

Yuk JM, Jo EK (2013) Crosstalk between autophagy and inflammasomes. Mol Cells 36:393–399

Zhan Z, Li Q, Wu P, YeTseng HY, Zhang L, Zhang XD (2012) Autophagy-mediated HMGB1 release antagonizes apoptosis of gastric cancer cells induced by vincristine via transcriptional regulation of Mcl-1. Autophagy 8:109–121

Zhang XD, Qi L, Wu JC, Qin ZH (2013) DRAM1 regulates autophagy flux through lysosomes. PLoS One 8:e63245

Zhou R, Yazdi AS, Menu P, Tschopp J (2011) A role for mitochondria in NLRP3 inflammasome activation. Nature 469:221–225

Zhou L, Wang HF, Ren HG, Chen D, Gao F, Hu QS, Fu C, Xu RJ, Ying Z, Wang GH (2013) Bcl-2-dependent upregulation of autophagy by sequestosome 1/p62 in vitro. Acta Pharmacol Sin 34:651–656

Zotti T, Scudiero I, Settembre P, Ferravante A, Mazzone P, D'Andrea L, Reale C, Vito P et al (2014) TRAF6-mediated ubiquitination of NEMO requires p62/sequestosome-1. Mol Immunol 58:27–31

Part XXXVI

General Pathology of Hepatobiliary Tumors: Invasion and Metastasis

Mechanisms of Invasion and Metastasis: General Aspects and the Role of Cell Junctions, Adhesion, and Extracellular Matrix

180

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_180

Abstract

Invasion and metastasis of cancer cells involve a complex sequence of events that has been summarized by the use of the term invasion cascade. This concept lists a sequential order of phenomena involved in the complex pathway that cancer cells undertake to invade host tissue and then form metastases. The pathway probably starts with cancer cells leaving a primary lesion by individualization, i.e., being released from a controlling cellular environment. Individualized cancer cells can, due to still unknown mechanisms, acquire a motile phenotype that allows them to migrate through tissues. Morphologically, migrating cancer cells resemble locomoting neutrophils, i.e., being polarized with a leading front and rear end and equipped with a contractile cytoskeleton. Polarized tumor cells may react to chemokinetic and chemotactic stimuli. Migrating tumor cells undergo a continuous shape change and can transverse narrow intercellular spaces. On the other hand, they can acquire a secretory phenotype for diverse species of histolytic enzymes that degrade the extracellular matrix, specifically matrix metalloproteinases. By these mechanisms, cancer cells can invade lymph vessels and blood vessels to be transported to remote regions, where regrowth to metastases can ensue.

Introduction

Invasive Growth and Its Morphology

Local invasion (infiltrative growth) and metastasis are among the most characteristic features of malignant neoplasms and are the main factors causing morbidity and mortality in cancer (reviews: Mareel et al. 2009; Friedl and Alexander 2011; Valastyan and Weinberg 2011). The most important and most common primary liver cancer worldwide, hepatocellular carcinoma (HCC), is characterized by a markedly invasive phenotype, high rates of macrovascular invasion and of local recurrence, and frequent intrahepatic and extrahepatic metastases. Also cholangiocarcinomas are invasive cancers that however differ from HCCs in their spreading pattern, in that they tend to more often invade perineural spaces and metastasize to locoregional lymph nodes. As numerous liver cancers are in an invasive stage at first diagnosis already, an understanding of invasion mechanisms are in the center of interest for current and future therapies (Mareel and Leroy 2003; Leber and Efferth 2009). Specifically, distinct molecular invasion signatures of the neoplasms are expected to be transmitted into specific, and possibly personalized, treatments.

Morphologically, invading cancer cells are capable to leave previously controlled tissue compartments, migrate into adjacent normal tissue, cause tissue destruction (the former "infiltrative-destructive growth" of cancer), and invade lymph and blood vessels (Figs. 1, 2, 3, 4, 5, 6, 7, 8, and 9).

The Invasion Cascade

Conventionally, features of invasion and metastasis are considered to follow a sequence of characteristic steps, the so-called invasion cascade, many of its aspects stemming from animal experimentation findings (Table 1).

This table, which exists in similar forms in numerous works, surmises that we deal with a true sequence of events, i.e., one step in fact

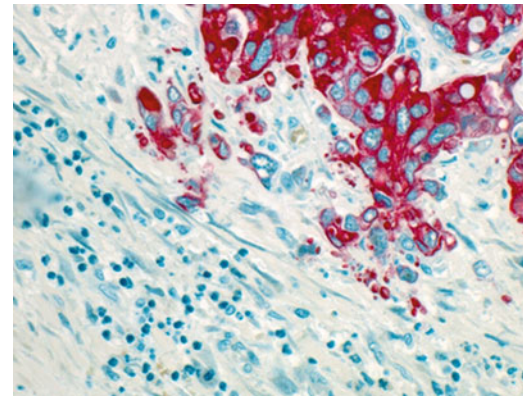

Fig. 1 Poorly differentiated hepatocellular carcinoma, invasion front. Note that neoplastic cells have separated from the cohesive tumor tissue. This cell individualization, caused by defective cell junctions, is an important step in tumor invasion (CAM5.2 immunostain)

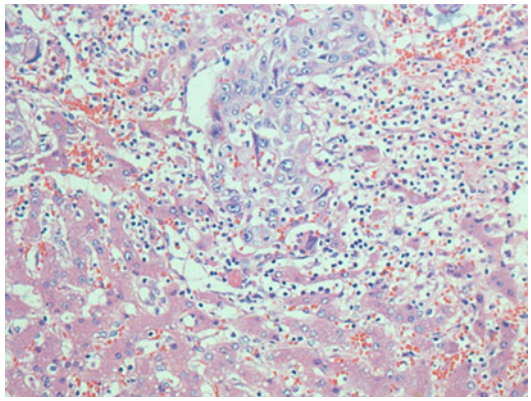

Fig. 2 Invasion of liver tissue by a poorly differentiated cholangiocarcinoma. The tumor shows focal necrosis (*right* part of figure; hematoxylin and eosin stain)

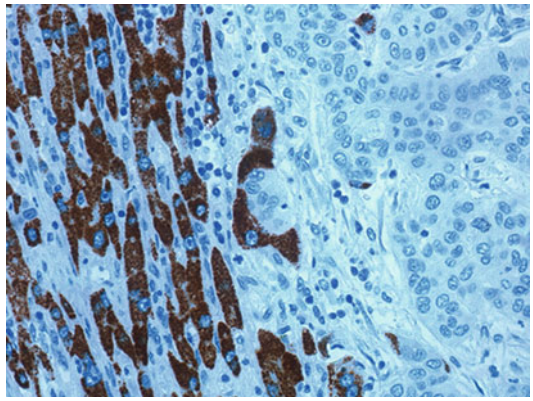

Fig. 3 Interface between hepatocellular carcinoma (*right half*) and invaded liver tissue. A carcinoma nest has infiltrated a hepatocyte plate (center; Hep Par1 immunostain)

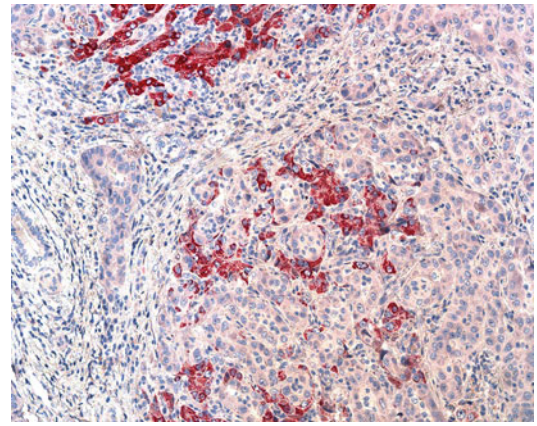

Fig. 4 Marked invasion of lobular hepatic parenchyma by cholangiocarcinoma. The hepatocyte plate architecture is effaced. An interlobular bile duct is seen to the left (Hep Par 1 immunostain)

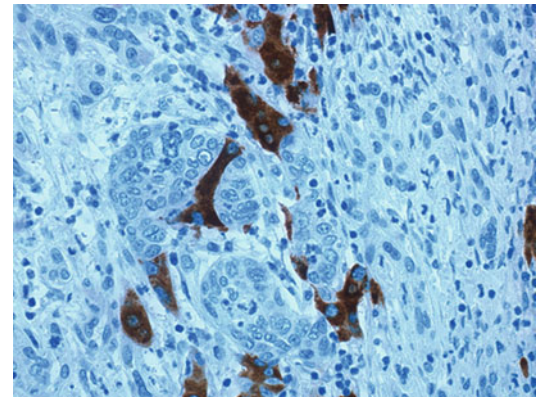

Fig. 5 Poorly differentiated carcinoma has extensively infiltrated liver tissue and caused hepatocyte atrophy. Remnant hepatocytes are trapped within carcinoma cell formations (Hep Par1 immunostain)

following the previous step. This view may help as a learning scheme but markedly misinterprets as to what really takes place in invasion. This is due to the fact that, firstly, a transformed cell becoming an invasive and metastasizing cell does not acquire completely novel features, but rather features that are otherwise found in cells different from the respective cell of origin. For example, the type of motility acquired by carcinoma cells is almost the same as that normally occurring in neutrophils and macrophages, but is not usually present in the epithelial cell of origin. Breaking of tissue barriers is a typical phenomenon for mature blood cells leaving the bone marrow, but is carefully avoided in epithelial linings or other compartment barriers in order to guarantee tissue homeostasis. Hence, invading cancer cells change to behavioral programs that are otherwise reserved for unrelated cells. Secondly, rather than acquiring features necessary for invasion one after another, it seems that cancer cells can acquire these characteristics synchronously, lose them again underway, to regain them afterward, a complex process in part regulated by contact with other cells *en route* or with the extracellular matrix. Thirdly, invading tumor

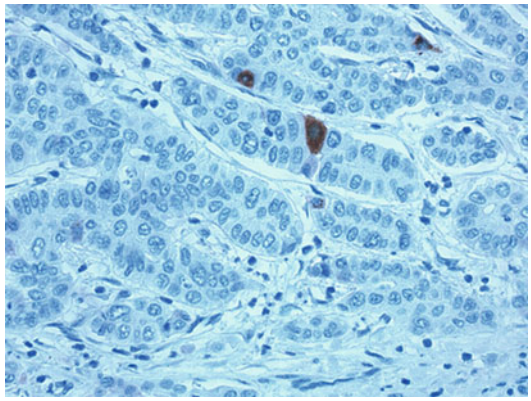

Fig. 6 In advanced parenchymal carcinoma invasion, only very few hepatocytes may be left (in this case, *three dark-brown* cells). In addition, two apoptotic hepatocytes are noted as very small cells with a brown granular cytoplasmic reaction product (Hep Par1 immunostain)

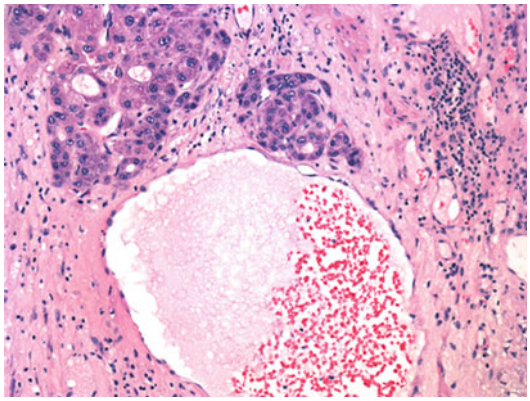

Fig. 7 Invading cholangiocarcinoma cells approaching the intima of dilated liver vein (hematoxylin and eosin stain)

cells keep their capability to proliferate, whereby, however, proliferation strongly depends on the actual status of the cell with respect to invasion. For example, a migrating cell cannot at the same time pass through a division cycle; it has to stop first and resume a nonpolarized phenotype. Conversely, ongoing proliferation will shut down certain mechanisms required for invasion, to resume them after mitosis. It is evident that the study of all these aspects on an invasion platform at the same time is highly difficult, so that certain aspects were and are artificially isolated to become amenable to analysis.

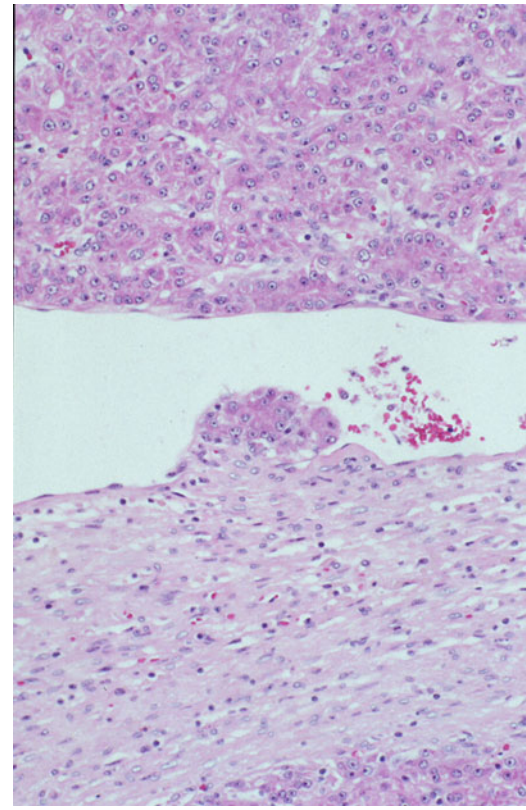

Fig. 8 Venous invasion by hepatocellular carcinoma (hematoxylin and eosin stain)

Intercellular Junctions: Altered Cell Junctions as a Pathway to Tumor Cell Individualization

Introduction

Cell junctions (intercellular bridges) are distinct and conserved structures that control the contacts between adjacent cells, maintain epithelial tissue integrity, create cell polarization, and provide pathways for signal exchange. Cell junctions as multiprotein complexes provide contacts between adjacent cells and between cells and the extracellular matrix. These junctions are a guarantee for the maintenance of tissue geometry, homeostasis, and barrier functions and are the machinery that allows the continuous reconstruction of tissue-specific cell arrangements in the course of cell turnover, where cells are lost and properly

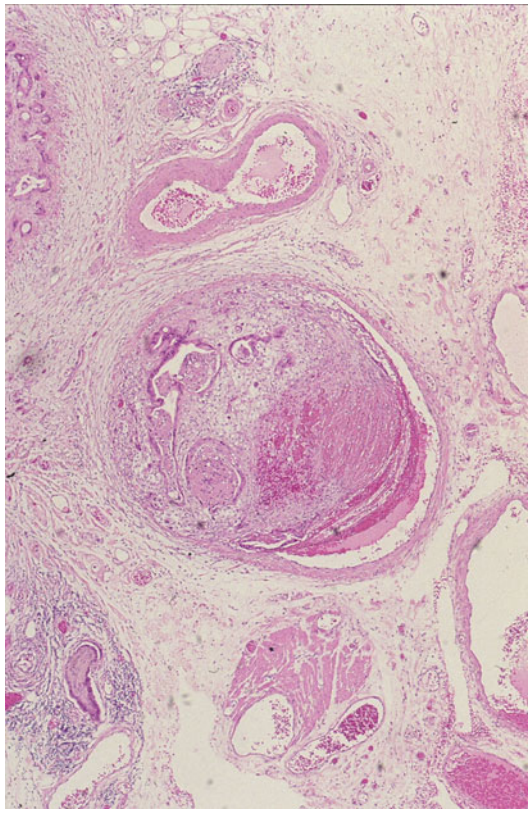

Fig. 9 Invasion of a dilated liver vein by adenocarcinoma, associated with thrombosis (hematoxylin and eosin stain)

Table 1 The invasion cascade of malignant neoplasms: a sequence of distinct steps

Malignant transformation as an initial step
Loss of contact of transformed cells with neighboring non-transformed cells
Individualization of the cancer cell
Exit ("dropout") from the normal tissue niche
Acquisition of novel adhesion features
Acquisition of cell motility and the capability to migrate
Capability to respond to chemokinetic and chemotactic stimuli
Active migration through tissues, whereby normal tissue barriers are no longer respected
Lysis of invaded tissues by use of histolytic enzymes (destructive growth; histolysis)
Recognition of and contact with blood vessels and lymph vessels
Transmigration of vessels (vascular invasion)
Contact with blood stream or lymph stream
Interaction with platelets and leukocytes in the streaming blood
Transport of circulating tumor cells
Homing to and adherence to endothelia at remote sites
Emigration from the blood stream or lymph stream into tissue
Growth of a metastasis

replaced via cell cycling. Cell junctions are highly dynamic microdomains that respond to various signals (McCole 2013). In particular, turnover of cytoskeletal and junction proteins is finely tuned by GTPases of the Rho family, specifically RhoA, Rac1, and Cdc42. Rho GTPases and junctional proteins form a signaling platform or a zonular signalosome which coordinates the functions of diverse cell junctions (Citi et al. 2014). In malignant neoplasms, in which cells leave distinct tissue compartments and destroy tissue barriers, cell junctions are dramatically altered or lost, also leading to failure of homeostatic signaling processes.

Tight Junctions: General Aspects

Tight junctions (TJs; zonula occludens) are occluding junctions that form a paracellular diffusion barrier that occludes epithelial cells from each other and maintains cell polarity. The structures forming circumferential bands are situated in the apical part of the lateral epithelial cell wall. TJs are characterized by a distinct ultrastructure and several specific proteins, including transmembrane barrier proteins (claudins, occludin, junctional adhesion molecule-A (JAM-A)) and peripheral scaffolding proteins which comprise ZOs (Zo-1, ZO-2, ZO-3; zonula occludens family proteins, membrane-associated guanylate kinase homologs), MAGI-1 (membrane-associated guanylate kinase with inverted orientation-1), afadin, PAR3, PAR6, MUPP1, and ZONAB. Claudins are tetraspan transmembrane proteins which undergo differential pathways of oligomerization to form TJs (Koval 2013). Occludin and ZO proteins form a complex that acts as a master regulator of TJ assembly/disassembly (review: Bewley et al. 2013). Scaffolding proteins are linked to actin and microtubules of the cytoskeleton through numerous linking proteins, such as

cingulin, paracingulin, myosins, and protein 4.1 (review: Van Itallie and Anderson 2014). Claudins are critical components of TJS and are present both in hepatocytes and cholangiocytes (Rao and Samak 2013; Van Itallie and Anderson 2013). In normal cholangiocytes, transcription and localization of TJ claudins are regulated by the transcription factor grainyhead-like 2 (Tanimizu and Mitaka 2013). ZO proteins have multiple and complex function that in part exceed TJ biogenesis. ZO-1 and ZO-2 play a central role in the establishment of a belt-like junction with paracellular permselective barrier function (Tsukita et al. 2009). The junctional protein ZO-2 can associate with other transmembrane proteins and transiently targets to the nucleus where it modulates gene expression (Traweger et al. 2013; Gonzalez-Mariscal et al. 2014). An important TJ protein is junctional adhesion protein-A (JAM-A), a protein which interacts with the cell polarity protein PAR-3 (Hirose et al. 2002). JAM-A is localized at primordial, spot-like cell-cell junctions in a non-phosphorylated form. In the course of TJ maturation, JAM-A is phosphorylated by protein kinase C (Ebnet 2013). The linking proteins, cingulin and paracingulin, are effectors of cytoskeleton-junction connections (Citi et al. 2012). Phosphorylated cingulin associates with cytoskeletal microtubules (Yano et al. 2013). Cingulin and paracingulin are also involved in GTPase signaling and therefore participate in the zonular signalosome. Specifically, both proteins control RhoA activation by interacting with RhoA guanidine exchange factors and spatially restrict downregulation of RAC1 activation (Guillemot et al. 2014). Biogenesis of TJs also depends on the zonula adherens (adherens junctions). Specifically, the adherens junction protein PLEKHA7 modulates assembly of TJs through E-cadherin protein complex- and microtubule-dependent mechanisms (Paschoud et al. 2014). The expression and proper localization of tight junction proteins is regulated by numerous factors that are in part deregulated in cancer cells. TJ formation and stability are impeded by tumor necrosis factor receptor-associated factor 4 (TRAF4) through a phosphoinositide-binding protein pathway, favoring cancer cell motility (Rousseau et al. 2014). Occludin localization is modulated by tumor necrosis factor alpha secreted by macrophages (Fletcher et al. 2014). Tight junction protein expression is under the control of microRNAs (review: Cichon et al. 2014). Factors that are involved in hepatocarcinogenesis can affect tight junction function and turnover. For example, HCV envelope structural components alter hepatocyte tight junction protein localization and retain occludin in the endoplasmic reticulum (Benedicto et al. 2008).

Tight Junction Deregulation in Liver Cancer

Biogenesis of TJs is crucial for cell polarity in hepatocytes and the construction of normal liver cell plates (Grosse et al. 2013). In HCC cells, TJs are disorganized, the tight junction networks not being oriented parallel to the canalicular lumen and reduction to structures with a single strand. In some discontinuous junctions, intramembrane particles are aligned to form a discontinuous network. Discontinuities and local proliferation of tight junctions are present. Disruption of tight junctions in HCC is correlated with an invasive phenotype. Vascular endothelial growth factor (VEGF) induces disruption of occludin-delineated tight junctions in HCC cells in a protein kinase C alpha-dependent manner, a mechanism for VEGF-mediated tumor invasion (Schmitt et al. 2004). Claudins as critical components of tight junctions are misexpressed in HCC (Bouchagier et al. 2014). Part of claudins are downregulated in cancers, causing tight junction dysfunction, while other claudins may be upregulated, e.g., claudin-7 (Brokalaki et al. 2012). In HCC, claudin-1 expression promotes epithelial-mesenchymal transition (EMT) and invasion (Stebbing et al. 2013). Claudin-1-mediated EMT proceeds via a c-Abl-ERK signaling pathway (activated c-Abl-Ras-Raf-1-ERK1/2; Suh et al. 2013). Occludin and ZO-1 showed significant downregulation in primary and metastatic HCCs, whereas these proteins were highly expressed in metastatic colorectal carcinoma

(Orban et al. 2008). However, another study demonstrated elevated occludin expression in HCCs (Bouchagier et al. 2014).

Gap Junctions as Communicating Structures

Gap junctions (GJs) are clusters of highly ordered intercellular communicating junctions. They consist of channels that connect the cytoplasm of adjacent cells. GJs keep the cells at a characteristic distance of 2–4 nm, the gap which is absent in tight junctions. Each GJ channel consists of two hemichannels (connexons), each provided by the two respective partner cells. Gap junction connexons are equipped with sets of distinct gap junction proteins, the connexins. Each hemichannel is composed of six connexins arranged like a rosette (connexin hexamer). Hexamers can contain one type of connexin (homologous or homomeric hexamer) or more than one type of connexin (heterologous or heteromeric hexamer). These six connexins encircle a central channel pore which can be open or closed. The pore permits the controlled exchange of signal substance between the partner cells. Apart from being components of connexons, connexins exert functions which affect other types of cell junctions. Connexin 32 can induce tight junction in liver cells via upregulation of the tight junction protein, MAGI-1 (Murata et al. 2005; Kojima et al. 2007).

Gap Junction Deregulation in Liver Cancer

Gap junctions in HCC cells were found only on the lateral plasma membrane and were not observed within the tight junction networks (Swift et al. 1983). Connexins have a central role in the regulation of cell growth control and carcinogenesis (Yamasaki et al. 1999). The expression patterns of connexins differ considerably between normal cells and cancer cells. In HCC cells, connexins 26 and 32 are downregulated, while connexin 43 is upregulated (Ma et al. 2003). Connexin 32 is the major liver gap junctional protein, while the cardiac-type connexin 43 is expressed at very low levels in normal hepatocytes (Oyamada et al. 1990). Expression of connexin 32 gradually decreases as liver disease progresses from cirrhosis to HCC (Nakashima et al. 2004). Experimentally, normal function of connexin 32 suppresses hepatocarcinogenesis (Hokaiwado et al. 2007). The low expression of connexins 26 and 32 in HCC is associated with an invasive phenotype (Sheen et al. 2004), suggesting a pro-invasive effect of gap junction failure. Overexpression of connexin 43 in HCC cells promotes cancer invasion via inhibition of cell-cell communication (Zhang et al. 2007).

Adherens Junctions as Anchoring Devices

Adherens junctions (AJs) form a group of adhering junctions, comprising zonula adherens, fascia adherens, and punctum adherens. All these junctions are anchoring junctions that anchor cells to each other and to the extracellular matrix (Machesky et al. 2008). Apart from adheres junctions, anchoring junctions also comprise desmosomes (maculae adhaerentes) and hemidesmosomes. These adhering junctions connect membrane domains of two cells linked to the respective cytoskeletons. A typical AJ is localized just underneath a tight junction, where it generates a belt-like adhesion (zonula adherens). All AJs share distinct proteins, including cadherins that are connected with the actin cytoskeleton via various anchoring proteins (catenins, vinculin, alpha-actinin; Wickline et al. 2013). AJs, through their link to the cytoskeleton, unify the actin network of adjacent cells to a transcellular cytoskeletal network that is broken in malignant neoplasms in order to individualize cancer cells for invasion.

Deregulation of Adherens Junctions in Liver Cancer

E-cadherin, a major component of adherens junctions, is differentially regulated in HCC cells (see

below). In most of these neoplasms, E-cadherin expression is reduced, while accumulation of cytoplasmic beta-catenin is enhanced (Du et al. 2009). In HCC cells, alterations in beta-catenin expression can be compensated by gamma-catenin expression in adherens junctions (Wickline et al. 2013). In hepatocytes, E-cadherin expression is modulated by the junctional adhesion molecule-A (JAM-A), a tight junction protein (Konopka et al. 2007). Cadherins and junctional proteins play a role in EMT (see below). Tumor-induced upregulation of the EMT-inducing proteins Twist, Snail, and Slug represses the vascular cadherin promoter (Lopez et al. 2009). In cancer cells, maintenance of adherens junctions is regulated by the metastasis suppressor, NM23-H1, the latter therefore being an important factor for the control of cell-cell adhesion and cell migration within the invasion cascade (Boissan et al. 2010). Adherens junctions are stabilized by MAGI1 (membrane-associated guanylate kinase, WW, and PDZ domain containing 1), a protein which therefore counteracts invasion and metastasis. MAGI1 is frequently downregulated in HCC (Zhang et al. 2012).

Focal Adhesions: Crucial Mediators of Cell-Matrix Adhesion

Introduction

Cell-cell and cell-matrix adhesion is a key mechanism to regulate cell homeostasis and the biologic behavior of normal cells and cancer cells (reviews: Reddig and Juliano 2005; Cao et al. 2007; Andl 2010). Numerous types of adhesion complexes and their specific proteins mediate cell and extracellular matrix (ECM) interactions and provide the sensing mechanisms that monitor the mutual relationships between cells and extracellular matrix. In the setting of the invasion cascade, differential expression of diverse adhesion molecules is a major pathway for the spread of tumor cells, as invading cells continuously engage in novel and reversible adhesive contacts with normal cells, partner tumor cells, and constituents of the ECM. Downregulation of certain adhesins in cancer cells contributes to tumor cell individualization, whereas upregulation of other adhesins may increase adhesion to the ECM substratum, e.g., basement membranes of blood vessels. Numerous adhesion molecules have been found to be altered in cancers, in part via differential production of microRNAs which target distinct adhesins.

A prominent role of deranged adhesion processes taking place in cancers is played by focal adhesions (FA), specialized areas on the cell surface where integrin receptors and associated proteins connect the proteins of the extracellular matrix with components of the cellular actin and microtubule cytoskeleton (Palazzo and Gundersen 2002; Wozniak et al. 2004). FA or focal contacts are large protein assembly complexes that spread mechanical force from cell adhesion sites to the cell body, and in particular to the cytoskeleton. FAs are also important mediators of various signaling pathways involved in cell-cell, cell-matrix adhesion, and cell proliferation and differentiation. In this functional network, FA and its specific kinase interacts with the Wnt/beta-catenin signaling pathway (Fonar and Frank 2011). FAs contain numerous proteins, such as actin, tubulin, signaling tyrosine kinases, c-Jun N-terminal kinase (JNK), focal adhesion kinase (FAK), Src kinase, Abl, integrin-linked kinase, phosphatases, actopaxin, and the actin-associated proteins paxillin, talin, vinculin, tensin, and the GTPases dynamin and Rho/Cdc42. These adhesions share part of the protein repertoires also found in podosomes and invadopodia (see below).

In FA, the two paxillin family members paxillin and leupaxin play particularly important roles (Schaller 2001; Chen and Kroog 2010). FAs contain the protein zyxin, which cooperates with caldesmon and Ena/VASP proteins to modulate integrin-dependent cell motility (Hoffman et al. 2006). VASP stands for vasodilator-stimulated phosphoprotein. Ena/VASP homology proteins or EVH proteins are proteins involved in cell motility due to their function as factors associated with actin polymerization and interactions with actin-associated proteins. Ena/VASC proteins are conserved regulators of actin assembly and turnover and are critically involved in cancer cell migration and invasion (Bear and Gertler

2009). In motile cells, Ena/VASP proteins are mainly located to the edge of lamellipodia and at the tips of filopodia. Important interaction partners of VASP are migfilin and several members of the kindlin protein family. The connections of the focal adhesion plaque to the actin cytoskeleton and filamin are mediated by the proteins, migfilin, a LIM-containing protein, and mitogen-inducible gene-2 (Mig-2), whereby migfilin, Mig-2, and filamin constitute a junction between cell-matrix adhesions and the cytoskeleton (Tu et al. 2003; Wu 2005). Via filamin binding, this protein complex is linked to the integrin system (Kiema et al. 2006). Migfilin, a protein with tandem LIM domains, also provides a link between kindlins and the cytoskeleton (Brahme et al. 2013). Kindlins 1 and 2 are actin cytoskeleton-associated proteins mutated in Kindler syndrome (Lai-Cheong et al. 2008). Kindlins play an important role in the regulation of integrin outside-in signaling (Qu et al. 2014; Liao et al. 2015; Ma et al. 2015). A further important Ena/VASP family actin regulator involved in chemotaxis and cell locomotion is Mena, which forms an adhesion-regulated complex with integrin alpha5beta1, a fibronectin receptor with a central role in cell adhesion, fibronectin signaling, and cell motility (Gupton et al. 2012). One Mena isoform is associated with the induction of a mesenchymal-like phenotype in cancer, associated with increased invasion (Di Modugno et al. 2012). The connection between FA and the actin cytoskeleton is mediated by a member of the nebulin family of actin-binding proteins, LIM-nebulette (Lasp-2), which also binds to vinculin and paxillin and enhances cell motility (Bliss et al. 2013). FA turnover is promoted by the cell adhesion system, hyaluronan and hyaluronan receptor/RHAMM, accompanied with an increase in protein tyrosine phosphorylation and an augmented motile cell response (Hall et al. 1994).

Focal Adhesion Kinase

A distinct set of protein kinases is recruited to focal adhesions (Eleniste and Bruzzaniti 2012). The function of focal adhesions is strongly mediated by focal adhesion kinase (FAK, p125), an enzyme also termed PTK2 (protein tyrosine kinase 2), encoded by the PTK2 gene. FAK is a cytoplasmic protein tyrosine kinase that is activated upon its interaction with integrins and is centrally involved in integrin-mediated signaling and regulation of cell adhesion and motility (Cary and Guan 1999; Shen and Guan 2001; Gao et al. 2015). FAK is phosphorylated in response to integrin signaling and growth factor stimulation. Most normal cells express FAK which is concentrated in focal adhesion plaques, but also exists at lower levels in the cytoplasm. FAK phosphorylates and activates several important proteins of focal adhesions, such as paxillin (review: Eleniste and Bruzzaniti 2012). The enzyme also interacts with numerous other proteins, including p53, PTEN, Src, JAK2, TGF-beta, and STAT1. FAK can also phosphorylate proteins involved in cell proliferation, including growth factor receptor-bound protein-7 (Chu et al. 2009).

Deregulation of Focal Adhesion Kinase and Focal Adhesions in Liver Cancer

Focal adhesion kinase (FAK) is deregulated in numerous cancers, in part associated with mislocalization of the kinase in regard to FA (Kornberg 1998; Hauck et al. 2002; Zhao and Guan 2009). The significance of FAK deregulation in cancers is mainly related to its central function in tumor cell motility and invasion (Schlaepfer et al. 2004) and to its interaction with critical transcription factors such as p53 (Golubovskaya and Cance 2007). The FA-associated kinase (FAK) is required for c-Met/beta-catenin-driven hepatocarcinogenesis (Shang et al. 2015) and regulates invasion-associated adhesion of HCC cells. In established HCCs, FAK is often overexpressed and predicts a higher incidence of extrahepatic metastasis, vascular invasion, and poor outcome (Fujii et al. 2004; Itoh et al. 2004; Jan et al. 2009). In part of the tumors, upregulation of the enzyme is correlated with HBV infection and contributes to tumor progression (Cai et al. 2009). The enzyme is involved in invasion and metastasis of HCC via stimulating the activity of matrix metalloproteinases MMP-2 and MMP-9 (Chen et al. 2010).

Upregulated FAK is involved in early events of integrin-mediated adhesion of circulating carcinoma cells and participates in prostaglandin E2-mediated adhesion, migration, and invasion of HCC cells (Bai et al. 2009). In contrast, downregulation of FAK inhibits metastatic cell adhesion in vivo within liver sinusoids (von Sengbusch et al. 2005). Numerous factors have been found to induce FAK activity in liver cancer. A major positive regulator of FAK expression in HCC and thus of tumor cell migration is microRNA-151, located to chromosome 8q24.3 and often amplified in HCC (Luedde 2010). In HCC cells, expression of FAK is promoted by CD147, which also favors actin polymerization and production of gelatinase (Qian et al. 2008). FAK in HCC is also promoted by epimorphin (syntaxin-2), an extracellular protein which is strongly elevated in hepatic stellate cells of the tumor stroma (Jia et al. 2011). Notch1, which is upregulated in many HCCs, stimulates FAK expression in HCC, including the phosphorylated FAK form, associated with enhanced migration and invasion of HCC cells (Hu et al. 2014). Calpain small subunit 1 (Capn4), a major prometastatic factor in HCC, contributes to invasion and metastasis by activation of the FAK-Src pathways. This is brought about by phosphorylation of distinct tyrosine residues of FAK and Src (Dai et al. 2014). Migration of HCC cells is stimulated by expression of the microtubule-associated protein JWA, acting through focal adhesion kinase expression and phosphorylation, RhoA activation, and MMP-2 activity (Wu et al. 2012). The non-receptor tyrosine kinase of the focal adhesion kinase (FAK) family, Pyk2 (proline-rich tyrosine kinase 2), is upregulated in more than 60 % of HCCs and promotes cell motility through induction of EMT (Sun et al. 2011). ACP5 promotes cell motility through modulation of the phosphorylation of focal adhesion kinase and is a factor for aggressiveness in HCCs (Xia et al. 2014). HCC cell migration mediated by focal adhesion kinase/AKT signaling is stimulated by the sonic hedgehog signaling pathway (Chen et al. 2013). The expression pattern of FAK in HCC cells is modulated by the desmosome complex component plectin, a protein that connects cytokeratins and integrin alpha6beta4 in hemidesmosomes anchoring to the extracellular matrix (Cheng et al. 2015). Plectin and its isoforms play an important role in cytoskeleton organization and dynamics. Specifically, plectin is a cross-linker that organizes the stable cytoskeletal meshwork important for maintenance of cell shape (Wiche 1998). The expression of plectin in HCC cells is related to the stability of cytokeratin 18, whereby both plectin and cytokeratin 18 can be downregulated in HCC (Liu et al. 2011b). Plectin deficiency in HCC is associated with tumor cell pleomorphism and abnormal keratin filament bundles (Liu et al. 2007–2008; Liu et al. 2011a). FAK transcription in HCC is also enhanced by a factor involved in short interfering RNA-mediated gene silencing, Argonaute2, frequently upregulated in HCC (Cheng et al. 2013). FAK is also involved in inflammatory pathways that promote liver cancer development and progression. The proinflammatory cytokine tumor necrosis factor alpha (TNF-alpha) activates FAK signaling and via this pathway activates cell migration and invasion (Mon et al. 2006). Activated stellate cells in the stroma of HCCs promote HCC migration and invasion via an activation of the FAK-MMP-9 signaling pathway (Han et al. 2014).

Apart from HCC, FAK is also deregulated in other liver cancers. It is reduced in intrahepatic cholangiocarcinoma, and this downregulation is associated with poor tumor differentiation, an invasive phenotype, and metastasis (Ohta et al. 2006). Expression of FAK is also associated with liver metastasis of colorectal cancer (Lark et al. 2003; Sun et al. 2014). Overexpression of FAK in human colorectal carcinoma liver metastases is a frequent finding and is independent from c-src or c-yes activation (Han et al. 1997). However, there is also evidence that FAK activity is reduced in liver metastases compared with matched primary colorectal cancers (Ayaki et al. 2001).

HCC cells frequently show abnormalities of FA structure and function. In addition to FAK, other components of FA may be abnormal in

liver cancer (Yam et al. 2009). c-Jun N-terminal kinase (JNK), an enzyme located in the focal adhesion plaque, promotes cell migration and invasion in murine HCC cells (Zhang et al. 2011). FA integrity in HCCs is regulated by agrin, a migration-promoting, matrix-sensing protein that is upregulated in HCC (Chakraborty et al. 2015). An integrin beta1-subunit-binding protein is integrin-like kinase which localizes to FA and is involved in cytoskeleton remodeling. Overexpression of this kinase in HCC promotes tumorigenicity and progression (Chan et al. 2011). A member of the focal adhesion protein group, actopaxin, is expressed in part of HCCs and affects tumor progression through modulation of cell migration and invasion (Nikolopoulos and Turner 2000). Actopaxin operates through the focal adhesion proteins ILK, PINCH, paxillin, and Cdc42 and through regulation of EMT (Ng et al. 2013). A focal adhesion protein altered in HCC is vinculin, regulated by CD147 in liver cancer cells. CD147 induces a vinculin expression pattern in FA of HCC cells promoting an invasive phenotype (Liang et al. 2014). HCC cell migration is stimulated by factors interacting with proteins of focal adhesion proteins. Argonaute2 protein, which plays a role in short interfering RNA-mediated gene silencing, upregulates focal adhesion kinase and by this step promotes tumor cell migration, proliferation, and colony formation (Cheng et al. 2013). The LIM domain protein migfilin which mediated links between adhesion plaques and the cytoskeleton is upregulated in HCC cells in vitro and decreases extracellular signal-regulated kinase (ERK) expression which in turn leads to increased invasion (Gkretsi and Bogdanos 2015). Kindlins, important migfilin partners located to FA, are also deregulated in HCC. Kindlin-1 and kindlin-2 are upregulated in HCC, associated with tissue and microvascular invasion, metastatic spread, and aggressive tumor biology (Ge et al. 2015; Ma et al. 2015). In contrast, kindlin-3 has tumor suppressor activities in several cancers (Djaafri et al. 2014). The roles of FA and FAK in tumor cell motility and migration is discussed in a later paragraph in more detail.

Cadherins

Introduction

In HCCs and cholangiocarcinomas, several groups of adhesion molecules are altered in a complex way, whereby these alterations in expression pattern change as a function of tumor progression (Cao et al. 2007). Cadherins (calcium-dependent adhesion molecules) form a large family or superfamily of transmembrane glycoproteins that mediate cell-to-cell adhesion in a calcium-dependent manner. The family includes cadherins proper, protocadherins, desmogleins, desmocollins, and others (Table 2). Cadherins are modified by numerous posttranslational modifications to become functional adhesins.

For cancer cell invasion, deregulation of classical cadherins plays an important role. E-cadherin (epithelial cadherin; CDH1; CAM 120/80; uvomorulin) is a single-pass type-1 classical cadherin which consists of an extracellular domain, a transmembrane domain, and an intracellular domain that binds to catenins, which mediate the connection of the multiprotein complex to the cytoskeleton via alpha-catenin. E-cadherin is expressed at adherens junctions, where it causes clustering of actin-containing cytoskeletal structures. In adherens junctions, the E-cadherin complex interacts with actin regulators, including Arp2/3, Ena/VASP, and WASP family proteins. Due to the composition of this

Table 2 Classification of cadherins (the cadherin superfamily)

Classical cadherins (CDHs)
CDH1 (E-cadherin)
CDH2 (N-cadherin)
CDH3 (P-cadherin)
CDH12 (cadherin 12)
Desmosomal cadherins
Desmogleins (DSG1, DSG2, DSG3, DSG4)
Desmocollins (DSC1, DSC2, DSC3)
Protocadherins (PCDHs)
PCDH1-18
Ungrouped cadherins
T-cadherin, CDHs 4–28

complex, adherens junctions are dynamical structures that are subject to remodeling, both in normal and cancer cells. E-cadherin is an important adhesion molecule acting in the invasion cascade and involved in epithelial-mesenchymal transition/EMT (Osada et al. 1996). It mediates homophilic cell-cell interactions and by this counteracts cell detachment and invasion (Frixen et al. 1991). N-cadherin (CDH2; neural cadherin) is required for gastrulation and the generation of left-right symmetry and mediates presynaptic to postsynaptic adhesion in certain neurons. P-cadherin (CDH3; placental cadherin) is an adhesin that interacts with several molecules, including beta-catenin and plakoglobin.

E-cadherin in Liver Cancer

Epithelial cadherin (E-cadherin) is often lost as a function of tumor progression and a transition to an invasive phenotype, this loss favoring adhesion failure and decomposition of adherens junctions (review: Canel et al. 2013). Loss of E-cadherin expression has complex sequelae that include failure of cell-cell adhesion and disruption of adherens junctions through breakdown of its cytoskeletal links, both causing disconnection of tumor cells from each other, tumor cell individualization, and invasive features (Behrens et al. 1991). Deregulation of E-cadherin in HCC is also a feature of epithelial-mesenchymal transition (Zhai et al. 2014; see below). Genomic alteration in the CDH1 gene encoding E-cadherin causing loss of function of this adhesin has been observed in numerous cancers. Downregulation of E-cadherin in HCCs depends on the tumor grade, expression being less reduced in well-differentiated than in poorly differentiated cancers (Endo et al. 2000). Generally, loss of E-cadherin in HCC confers an invasive phenotype with a more aggressive course (Cho et al. 2008; Hashiguchi et al. 2013; Chen et al. 2014a; Li et al. 2014), probably via loss of intercellular contact which promotes tumor cell individualization, a prerequisite for locomotion and invasion. Levels of E-cadherin were lower in multinodular and extranodular HCC growth types than in the single nodular type (Inayoshi et al. 2003). Fascin-1 expression correlates with repression of E-cadherin expression in HCC cells and augments their invasiveness (Hayashi et al. 2011). Mechanisms to reduce E-cadherin expression comprise somatic and germline mutations and epigenetic modifications of gene expression (review: Schmalhofer et al. 2009). E-cadherin is regulated by the Wnt/beta-catenin signaling cascade and is linked to the functions of the cytoskeleton (Schmalhofer et al. 2009). Reduced expression of E-cadherin was also detected in intrahepatic cholangiocarcinoma and other biliary tract cancers (Settakorn et al. 2005; Németh et al. 2009; Mao et al. 2013). In cholangiocarcinomas, E-cadherin cooperates with decorin-mediated inhibition of growth and migration (Yu et al. 2014) and is repressed by Slug in the setting of epithelial-mesenchymal transition (Zhang et al. 2010). Downregulation of E-cadherin in extrahepatic cholangiocarcinoma is associated with EMT, which favors an invasive growth pattern (Araki et al. 2011). Loss of liver E-cadherin in murine models induced a form of sclerosing cholangitis and hepatic carcinogenesis (Nakagawa et al. 2014). Enhanced expression of E-cadherin in noncancerous liver tissue was associated with recurrence of HCC following curative resection (Minata et al. 2013). Loss of E-cadherin is a feature of epithelial-mesenchymal transition which in turn affects invasion of cancer cells (see below). In fact, part of the effects exerted by E-cadherin in cancer occur in the setting of EMT, with which E-cadherin function is closely integrated (Wang et al. 2012).

N-cadherin in Liver Cancer

In normal liver, neural cadherin/N-cadherin is strongly expressed on cell-cell boundaries of hepatocytes and cholangiocytes. Here, N-cadherin is co-expressed with E-cadherin. Also reactive ductular proliferations express both of these cadherins (Mosnier et al. 2009). In HCCs, expression of N-cadherin varies in several investigations, being upregulated in part of studies (Seo et al. 2008), while others reported reduced

N-cadherin expression in more than 50 % of HCC, associated with poor tumor differentiation, increased migration, invasion, metastasis, and poor outcome (Zhan et al. 2012). In HCC, loss of N-cadherin was associated with concurrent loss of E-cadherin expression and poor outcome after liver resection (Cho et al. 2008; Liu et al. 2015). In cholangiocarcinomas, N-cadherin expression was more common in peripheral tumors than in perihilar ones (Mosnier et al. 2009). N-cadherin as an EMT-related molecule is an independent prognostic factor in extrahepatic cholangiocarcinoma (Nitta et al. 2014).

P-cadherin in Liver Cancer

P-cadherin (CDH3) is a further cadherin superfamily member involved in cancer biology. In HCC, P-cadherin is significantly downregulated compared to normal hepatocytes. In part of tumors, P-cadherin expression is completely lost, and this deregulation is associated with aggressive biology (Bauer et al. 2014). In cholangiocarcinoma cells, P-cadherin is frequently overexpressed and regulates cell migration in an EMT-independent manner (Baek et al. 2010). P-cadherin expression was found in about a third of intrahepatic cholangiocarcinomas and more frequently in extrahepatic cholangiocarcinoma, gallbladder carcinoma, and, most commonly, in dysplastic biliary epithelium, while no expression was seen in normal bile duct epithelia (Riener et al. 2010).

Other Cadherins in Liver Cancer

In diverse human cancers, the atypical cadherin FAT1/giant cadherin acts as an oncogene and tumor suppressor. FAT1 was increased in human HCC tissues. Overexpression of FAT1 is induced by hepatocyte growth factor and hypoxia-inducible factor 1alpha and is correlated with growth and invasion (Valletta et al. 2014). In intrahepatic cholangiocarcinomas, weak cytoplasmic staining for FAT was observed (Settakorn et al. 2005). Liver-intestine cadherin (LI-cadherin), another member of the cadherin superfamily, is expressed in part of biliary intraepithelial lesions (BillN) and the grade of BillN independently correlated with LI-cadherin expression (Inoue et al. 2011). In HCC, protocadherin 9 inhibits EMZ and cell migration via activation of glycogen synthase kinase-3beta of the ceta-catenin signaling pathway (Zhu et al. 2014). Protocadherins also play a role in the biology of extrahepatic cancers and their liver metastasis. Protocadherin 10 suppresses metastasis of colorectal carcinoma (Jao et al. 2014).

Integrins

Introduction

Integrins are heterodimeric adhesion receptors at the cell surface and connect the cytoskeleton with proteins of the ECM. Through their central function in cell-matrix adhesion processes, integrins are important mediators of cancer invasion and spread (Varner and Cheresh 1996; Hayashi 2010; Margadant and Sonnenberg 2010; Ganguly et al. 2013). The integrin family consists of 24 members formed by non-covalently associated alpha- and beta-chains. These heterologous molecules are differentially expressed in various cell systems (Valdembri et al. 2009). Integrin expression is regulated by a complex system of factors, in which TGF-beta signaling has a central place (Hayashi 2010). On the other hand, beta3 integrin enhances TGF-beta signaling, illustrating a close interaction between the two pathways (Feng et al. 2013). Alpha- and beta-subunits possess short cytoplasmic domains that interacts with numerous proteins. For example, the beta-tail of integrins interacts with proteins that display a band 4.1, ezrin, radixin, and moesin (FERM) domain. A protein important for motility and invasion having an integrin-binding FERM domain is myosin X, a factor important for filopodia formation. In adhesion construction and adhesion-mediated signaling pathways, integrins form a complex adhesome that has been compiled in a functional atlas of these molecules (Zaidel-Bar et al. 2007). This integrin adhesome contains a network of 156 components linked together and

modified by several hundred interactions. Apart from mediating adhesion processes, integrins are also active in complex signaling pathways involving a large number of components (the integrin interactome). Integrin signaling includes Src family kinases, Ras proteins, components of the Wnt signaling cascade, Notch, Raf, and caveolae-mediated signaling. Within this network, integrin regulating is in part accomplished by integrin epigenetics, involving DNA and histone modifications (Deb et al. 2012). A central role in cell adhesion and migration is played by alpha3beta1 and alpha6beta4 integrins (review: Giannelli et al 2002). Integrins cooperate with CD44 variants to bind to osteopontin, thereby stimulating cell motility and chemotaxis (Katagiri et al. 1999). Integrins interact with fibronectin. The fibronectin-integrin beta1 signaling pathway is involved in tumor cell migration and is inhibited by the product of a putative cancer gene, SERPINA5 (Jing et al. 2014). The pro-migration function of integrins is blocked by interaction with filamin, which binds to the beta7 integrin tail (Calderwood et al. 2001).

Deregulation of Integrins in Liver Cancer

Various types of integrins are expressed in normal liver and liver neoplasms and are predictors of disease severity (Liu et al. 2002; Jin et al. 2014). Generally, benign hepatocellular tumors, such as hepatocellular adenoma, and well-differentiated HCCs express the same set of integrins as the normal liver, while poorly differentiated HCCs express de novo integrins, such as alpha2-, alpha3-, and alpha6-containing integrins. Similarly, well-differentiated cholangiocarcinomas show an integrin spectrum identical to that of normal cholangiocytes, whereas poorly differentiated cholangiocarcinomas reveal downregulation of integrins (Volpes et al. 1993). Transcription of the alpha3 integrin gene in HCC is upregulated by TGF-beta1 signaling (Katabami et al. 2005). In some HCCs, integrins of the beta2 and beta3 types are downregulated, associated with deletion of collagen triple helix repeat containing 1 (CTHRC1), a protein whose gene is located to chromosome 8q22.3, frequently altered in HCC (Tameda et al. 2014).

Integrins markedly affect tumor cell invasion due to their receptor functions for components of the extracellular matrix, an important scaffold for growth and invasion of cancer cells. Part of integrins are laminin-binding proteins in tumors and via this mechanism strongly affect motility and invasion (Ziober et al. 1996; Belkin and Stepp 2000). Integrin beta-1 is an important molecule to mediate cell-matrix adhesive interactions of HCC cells, and this interaction influences tumor cell migration (Giannelli et al. 2001) and invasive spread (Masumoto et al. 1999; Nejjari et al. 2002; Tian et al. 2005; Mizuno et al. 2008). Integrin alpha6 beta1 is critically involved in the attachment of HCC cells to laminin (Torimura et al. 1999), and these integrin and laminin are coordinately expressed in HCC (Torimura et al. 1997). Integrin alpha5 is expressed in HCC with low metastatic potential, but is absent in highly metastatic HCC (Yao et al. 1997). Beta1 integrin is specifically phosphorylated by TGF-beta1 via Smad2 and Smad-3, a mechanism prompting HCC invasion (Fransvea et al. 2009). Apart from regulating adhesion and invasion of cancer cells, integrins also regulate proliferation and apoptosis (Ozaki et al. 2011). Integrin beta3 has a proapoptotic function in humans HCCs (Wu et al. 2009). In biliary cancers, integrin expression is linked to differentiation patterns. Beta1, beta4, and beta6 integrins are expressed in cholangiolocellular carcinoma, but not in cholangiocarcinoma (Soejima et al. 2014).

Integrins are involved in metastatic spread of cancers within the liver. The prometastatic activity of integrins is modulated by microRNAs. MicroRNA-134 acts as a metastasis suppressor by targeting integrin beta1 in HCC (Zha et al. 2014).

Adhesion Proteins Other Than Integrins and Cadherins

L1 cell adhesion molecule (L1CAM) is overexpressed in HCC, an alteration associated with poor tumor differentiation and advanced

progression (Guo et al. 2012). One of the most important adhesion molecules in epithelial cell-basement membrane interaction is alpha-dystroglycan, serving as a cell surface receptor for several basement membrane proteins, specifically laminin, agrin, and perlecan. The laminin-binding alpha-dystroglycan can act as a tumor suppressor (Bao and Fukuda 2010). Osteopontin secreted adhesive glycoprotein that is important for numerous adhesive processes of cancer cells and for the regulation of EMT. Osteopontin is overexpressed in HCCs, mainly in those with a dispersed growth mode and capsular infiltration (Gotoh et al. 2002), i.e., in tumors with a highly invasive phenotype. Intracellular osteopontin itself is an integral component of the CD44-ezrin/radixin/moesin complex involved in cell migration (Zohar et al. 2000). Agrin is expressed in both HCCs and cholangiocarcinomas (Tatrai et al. 2006) and is, apart from adhesion processes, also involved in angiogenic responses (Batmunkh et al. 2007). Expression of agrin in adherent and motile cells can induce the formation of actin-based filopodia-like protrusions, leading to activation of Cdc42 and Rac1 (Lin et al. 2010). Rac1 expression itself is inhibited in HCCs by TNF-alpha-induced protein 8-like 2, a negative immune regulator and inhibitor of oncogenic Ras (Cao et al. 2013). The adhesin CD24 is involved in various intercellular adhesion processes. The differential expression of CD24 is regulated by NDRG2 (N-myc downstream-regulated gene 2), in that upregulation of NDRG2 results in decreased CD24 expression, cell adhesion, migration, and invasion, while downregulation of NDRG2 is associated with an invasive HCC phenotype (Zheng et al. 2011). Expression of CD44v6 in HCC cells is modulated by overexpression of the A/B hnRNP subfamily member, HnRNP A1, resulting in increased invasion of HCCs (Zhou et al. 2013). CD44 alternative splicing is negatively regulated by a binding protein of PCBP1, THAP11, an essential factor involved in embryonal stem cell pluripotency and cell growth. In HCC cells, THAP11 inhibited CD44v6 expression and cell invasion (Lian et al. 2012). Similar to CD44, CD147/EMMPRIN is involved in adhesion processes and affects cell-ECM interactions in cancer (Hao et al. 2010). Adhesion of epithelial cells along their lateral line is promoted by the immunoglobulin superfamily member, CRTAM (class I-restricted T-cell-associated molecule), a protein related to nectin-like proteins (Garay et al. 2010). Adhesion and migration of HCC cells are positively affected by the regulatory factor SSX2IP (synovial sarcoma, X breakpoint 2 interacting protein), an acute myeloid leukemia-associated antigen. SSX2IP is capable to facilitate HCC metastasis in experimental models (Li et al. 2013).

Extracellular Matrix (ECM) as a Platform Regulating Invasive Processes

Introduction

The extracellular matrix (ECM; intercellular substance) of normal tissues and tumors is a highly complex, noncellular, multimolecular compartment which critically regulates the biology of cells embedded in it (reviews: Wu and Chen 2006; Frantz et al. 2010). Numerous proteins, proteoglycans, and glycosaminoglycans make part of a scaffold produced by stromal cells (mainly myofibroblasts, cancer-associated fibroblasts, immature mesenchymal cells, and stellate cells; Faouzi et al. 1999), but also by tumor cells in the setting of epithelial-mesenchymal transition. Synthesis and secretion of ECM molecules by stromal cells are markedly modulated by signaling performed by leukocytes present in the stroma, in particular tumor-associated macrophages, monocytes, lymphocytes, and neutrophils. Predominant proteins of the ECM include basement membrane proteins, several types of fibrous proteins (mainly collagens), proteoglycans, and glycosaminoglycans (Table 3). Based on its dynamical composition with numerous macromolecules active in signaling and various interacting stromal cells, tumor ECM is a master regulator of carcinogenesis, tumor progression, and metastasis. The ECM is a central structure for numerous signaling pathways, and interacting material for cell receptors, and a storage site for growth factors and other mediators (Quail and Joyce 2013).

Table 3 Constituents of the extracellular matrix (ECM)

Collagens
Fibrillar collagens (types I, II, III, V, XI)
Short-chain (net-forming) collagens (types VIII, X)
Fibril-associated collagens (FACIT) (types IX, XII, XIV)
Anchoring collagen (type VII)
Lace-lake collagen (type VI)
Collagens with transmembrane domains (types XIII, XVII)
Basement membrane collagen (type IV)
Other proteins
Fibronectin
Elastin and associated fibrillins
Tenascins
Proteoglycans
Heparan sulfate proteoglycans
Chondroitin sulfate proteoglycans
Keratan sulfate proteoglycans
Dermatan sulfate proteoglycans
Glycosaminoglycans
Hyaluronic acid (hyaluronan)

Role of Basement Membrane Proteins in Liver Cancers

The basement (BM) as a distinct structure forming an interface with the ECM and providing a scaffold for epithelial, endothelia, muscle, and Schwann cells plays a crucial role in mechanisms of cancer cell spread and invasion.

In normal tissues, the BM consists of two laminae, the basal lamina and the reticular lamina, the latter being attached to the former through type VII collagen anchoring fibrils and fibrillin microfibrils. The basal lamina is itself divided into a layer facing the epithelium or endothelium, the lamina lucida, and the ECM, the lamina densa. The lamina lucida mainly consists of laminins, entactin (nidogen-1), nidogen-2, netrins, agrin, and dystroglycans. Nidogens, netrins, and agrin are laminin-binding proteins. Dystroglycan is part of the dystrophin-glycoprotein complex (DGC) which forms a link that extends from laminin, agrin, and perlecan to alpha-dystroglycan to beta-dystroglycan to dystrophin/utrophin to F-actin. The lamina densa is composed of a network of type IV collagen fibrils coated with the heparan sulfate-rich proteoglycan perlecan. Agrin and perlecan create a collateral linkage to cell surfaces. The reticular lamina is rich in type III collagen.

With its complex composition and intricate contacts with cells and components of the ECM, the BM represents an important signaling platform for numerous cell processes and functions (review: Yurchenco 2011). In the adhesion and invasive process of HCCs and other liver cancers, basement membrane proteins play an active role, expression of laminin genes having a particular significance (Tian et al. 2005; Huang et al. 2008). Laminins form a complex family of proteins where each laminin is a heterotrimer consisting of one each of five alpha, four beta, and three gamma subunits, in vertebrates resulting in 15 laminin species. Laminins bind to a distinct 67 kDa receptor that is expressed in normal cells and cancer cells (Castronovo 1993).

Laminins and type IV collagen have an important effect on tumor cell motility and chemotaxis (Ogata 1998). In HCCs, laminin seems to be produced by sinusoidal-like channels (Donato et al. 1989). Laminin deposition to type IV collagen takes place along sinusoidal vascular channels (capillarization) and is associated with increased tumor cell adhesion and motility mediated by beta1 integrins (Tabarin et al. 1987; Torimura et al. 2001). Several laminin forms have been implicated in HCC invasion, including laminin-4 (LAMA4) and laminin-5 (Huang et al. 2008). In their pro-invasive function, laminins closely interact with the EMC adhesion receptors, integrins. Laminin-1 and laminin-11, which play an important role in motility and invasion, specifically bind to integrins alpha3beta1, alpha6beta1, and alpha6beta4 (Kikkawa et al. 2000). Similar to normal cells, tumor cells can bind to laminin through specific laminin receptors. In HCCs, laminin receptors are differentially expressed and upregulated whereby laminin-binding protein (67 kDa laminin receptor), alpha6 integrin, and beta1 integrin play a central role (Sobel 1993; Ozaki et al. 1998). There is an association between 67 kDa laminin receptor expression and metastasis of HCC (Zheng et al. 1997).

In HCCs this receptor is preferentially expressed in tumors with a high metastatic potential (Zheng et al. 1997). HCC cells strongly adhere, migrate, and spread in the presence of laminin-5 secreted by these neoplasms (Kikkawa et al. 2008; Santamato et al. 2011). This effect of laminin-5 and other laminins in part depends on its interaction with beta1 and beta4 integrins (Torimura et al. 1997; Bergamini et al. 2007). Aberrant expression of laminin gamma2 is correlated with invasion and an aggressive course in extrahepatic cholangiocarcinoma (Liu et al. 2014). In addition to their role as attachment sites for cancer cells, laminins can directly induce distinct alterations of neoplastic cells. For example, laminin-5 together with TGF-beta1 induces epithelial-mesenchymal transition (Giannelli et al. 2005) and via this pathway promotes invasion. In tumor stroma, hepatic stellate cells and myofibroblasts produce laminin-5 and thus stimulate migration of HCC cells (Santamato et al. 2011). Nidogen-2, a laminin-binding protein, is downregulated in HCC. This decreased expression is associated with tumor spread and progression (Cheng et al. 2012). HCC cells also express the BM protein agrin, which interacts with alphaV-type integrins and growth factors (Tatrai et al. 2006). The expression of BM proteins in HCCs varies according to tumor differentiation. In contrast to grade 2–4 HCCs, well-differentiated HCCs show cell cords forming a streak pattern devoid of accompanying reticulin and type IV collagen (Miyao et al. 1999).

Other Proteins of the Extracellular Matrix That Affect Cancer Cell Invasion

Fibronectin is upregulated in HCC and is predominantly present in the subendothelial spaces of sinusoid-like vascular channels and in the stromal ECM of these neoplasms (Isemura et al. 1982; Torimura et al. 1994; Koukoulis et al. 1995; Enjoji et al. 1998). Based on the distinct pericellular arrangement of fibronectin in HCC, it was suggested that this protein is produced by cancer cells themselves (Donato et al. 1989). In HCC stroma, fibronectin deposition is increased or decreased, increased amounts predominantly found in fibrolamellar carcinoma, clear cell HCC, and encapsulated HCC. Augmented fibronectin appears as thin or thick feathery strands in pericellular, periglandular, stromal, or perisinusoidal distribution (Jagirdir et al. 1985). Fibronectin represents a scaffold on which cancer cells can locomote. In the ECM, fibronectin affects tumor cell motility in close cooperation with integrin beta1, an interactome which can be modulated by several stromal factors. For example, SERPINA5, which is encoded by a gene subject to alterations in HCC, inhibits fibronectin-integrin-mediated HCC cell migration (Jing et al. 2014). The pro-invasive effect of fibronectin is promoted by neuropilin-1, which increases fibronectin fibril assembly (Yaqoob et al. 2012). One of the effects of the metastasis suppressor, Nm23-H1 (see below) is its impairment of HCC cell migration on fibronectin scaffolds by modulating glycosylation of integrin beta1 receptors (She et al. 2010). Increased fibronectin expression in tumor microenvironments is stimulated by neuropilin-1, a protein which controls communications between stromal myofibroblasts and soluble fibronectin (Yaqoob et al. 2012). Similar to fibronectin, vitronectin is a protein that is consistently expressed during invasion of HCC (Inuzuka et al. 1992; Chen et al. 2014b). Apart from affecting the invasive behavior of cancer cells, vitronectin expressed in the stroma of hepatic cancers contributes to local immune reactions via the recruitment of lymphocytes in an integrin-dependent manner (Edwards et al. 2006).

A protein that critically affects adhesions of cells in the ECM is tenascin, a glycoprotein which exists in several forms (review: Chiquet-Ehrismann 1993). In normal liver, tenascin is localized along the sinusoidal and other vascular walls, while it is upregulated in inflammatory and fibrotic disorders of the liver and is mainly present in stellate cells (Yamada et al. 1992). In liver cancers, tenascin is predominantly found in cells derived from stellate cells, i.e., myofibroblasts. Tenascin interacts with other proteins that hold a central place in adhesion processes, in particular integrins (Tanaka et al. 2014). Tenascin is upregulated in HCC in comparison with

hepatocytes of cirrhotic livers and is also augmented in small dysplastic liver cells (Zhao et al. 1996). Tenascin is mainly upregulated in fibrous septa and pseudocapsules of HCCs (Yamada et al. 1992). In intrahepatic cholangiocarcinoma, tenascin is expressed in the stroma and suggested to stimulate cancer cell proliferation (Terada and Nakanuma 1994). Tenascin expression in the stroma of these neoplasms was detectable in 68 % of cases, and specifically the presence of tenascin at the invasive front was associated with tumor growth, lymphatic invasion, and lymph node metastasis (Aishima et al. 2003). Tenascin-C also affects the invasive behavior of cancers metastasizing to the liver. In colorectal carcinoma cells, tumor-derived tenascin-C promotes epithelial-mesenchymal transition and via this mechanism favors invasion and spread (Takahashi et al. 2013). The stroma of liver cancers contains various types of interstitial and basement membrane collagens, including type III collagen (Gulubova 1997). These fibrillary proteins provide a scaffold for cell attachment and migration.

Proteoglycans of the Extracellular Matrix

Similar to fibrogenic liver diseases, HCCs with their variably developed stroma show alterations in the content of heparan sulfate-containing proteoglycans (Roskams et al. 1998; Tatrai et al. 2010), a feature that affects the ECM and its invasion-regulating properties. Certain proteoglycans are variably upregulated or downregulated in HCC, e.g., syndecans (Matsumoto et al. 1997). Syndecan-1 and syndecan-4 are involved in HCC cell migration induced by the RANTES/CCL-5 chemokine pathway (Charni et al. 2009). Heparan sulfate expression is also enhanced in the fibromyxoid stroma of intrahepatic cholangiocarcinomas as well as in hepatic colorectal carcinoma metastases (Sabit et al. 2001). Syndecan-3 and perlecan are strongly expressed in stromal vessel walls of liver cancers, and accumulation of perlecan in stroma may play a role as a growth factor reservoir (Roskams et al. 1998).

Glycosaminoglycans of the Extracellular Matrix

Hyaluronan (HA) is an abundant glycosaminoglycan which is important for ECM homeostasis, tissue remodeling, generation of cell-free spaces in tissue, regulation of inflammation, and angiogenesis. HA is also implicated in cell locomotion, both of normal and tumor cells. HA-induced autocrine motility mechanisms are mediated by the HA receptor, RHAMM (receptor for HA-mediated motility). HA is also capable to bind to CD44. HA-RHAMM binding activates a signal cascade that results in protein tyrosine phosphorylation of factors involved in motility and in targeting of focal adhesions (Hall and Turley 1995). Cell locomotion stimulated by TGF-beta1 depends on the HA/RHAMM interaction (Samuel et al. 1993).

References

Aishima S, Taguchi K, Terashi T, Matsuura S, Shirmada M, Tsuneyoshi M (2003) Tenascin expression at the invasive front is associated with poor prognosis in intrahepatic cholangiocarcinoma. Mod Pathol 16:1019–1027

Andl CD (2010) The misregulation of cell adhesion components during tumorigenesis: overview and commentary. J Oncol. doi:10.1155/2010/174715

Araki K, Shimura T, Suzuki H, Tsutsumi S, Wada W, Yajima T, Kobayahi T, Kubo N, Kuwano H (2011) E/N-cadherin switch mediates cancer progression via TGF-β -induced epithelial-to-mesenchymal transition in extrahepatic cholangiocarcinoma. Br J Cancer 105:1885–1893

Ayaki M, Komatsu K, Mukai M, Murata K, Kameyama M, Ishiguro S, Miyoshi J, Tatsuta M, Nakamura H (2001) Reduced expression of focal adhesion kinase in liver metastases compared with matched primary human colorectal adenocarcinomas. Clin Cancer Res 7:3106–3112

Baek S, Lee YW, Yoon S, Baek SY, Kim BS, Oh SO (2010) CDH3/P-cadherin regulates migration of HuCCT1 cholangiocarcinoma cells. Anat Cell Biol 43:110–117

Bai XM, Zhang W, Liu NB, Jiang H, Lou KX, Peng T, Ma J, Zhang L, Zhang H, Leng J (2009) Focal adhesion kinase: important to prostaglandin E2-mediated adhesion, migration and invasion in hepatocellular carcinoma cells. Oncol Rep 21:129–136

Bao X, Fukuda M (2010) A tumor suppressor function of laminin-binding alpha-dystroglycan. Methods Enzymol 479:387–396

Batmunkh E, Tatrai P, Szabo E, Lodi C, Holczbauer A, Paska C, Kupcsulik P, Kiss A et al (2007) Comparison of the expression of agrin, a basement membrane heparan sulfate proteoglycan, in cholangiocarcinoma and hepatocellular carcinoma. Hum Pathol 38:1508–1515

Bauer R, Valletta D, Bauer K, Thasler WE, Hartmann A, Müller M, Reichert TE, Hellerbrand C (2014) Downregulation of P-cadherin expression in hepatocellular carcinoma induces tumorigenicity. Int J Clin Exp Pathol 7:6125–6132

Bear JE, Gertler FB (2009) Ena/VASP: towards resolving a pointed controversy at the barbed end. J Cell Sci 122:1947–1953

Behrens J, Weidner KM, Frixen UH, Schipper JH, Sachs M, Arakaki N, Daikuhara Y, Birchmeier W (1991) The role of E-cadherin and scatter factor in tumor invasion and cell motility. EXS 59:109–126

Belkin AM, Stepp MA (2000) Integrins as receptors for laminins. Microsc Res Tech 51:280–301

Benedicto I, Molina-Jimenez F, Barreiro O, Maldonado-Rodriguez A, Prieto J, Moreno-Otero R, Aldabe R, Lopez-Cabrera M et al (2008) Hepatitis C virus envelope components alter localization of hepatocyte tight junction-associated proteins and promote occludin retention in the endoplasmic reticulum. Hepatology 48:1044–1053

Bergamini C, Sgarra C, Trerotoli P, Lupo L, Azzariti A, Antonaci S, Giannelli G (2007) Laminin-5 stimulates hepatocellular growth through the different function of alpha6beta4 and alpha3beta1 integrins. Hepatology 46:1801–1809

Bewley MC, Tash BR, Tian F, Flanagan JM (2013) A complex affair. Attraction and repulsion make occludin and ZO-1 function! Tissue Barriers 1:e23496

Bliss KT, Chu M, Jones-Weinert CM, Gregorio CC (2013) Investigating lasp-2 in cell adhesion: new binding partners and roles in motility. Mol Biol Cell 24:995–1006

Boissan M, De Wever O, Lizarraga F, Wendum D, Poincloux R, Chignard N, Desbois-Mouthon C et al (2010) Implication of metastasis suppressor NM23-H1 in maintaining adherens junctions and limiting the invasive potential of human cancer cells. Cancer Res 70:7710–7722

Bouchagier KA, Assimakopoulos SF, Karavias DD, Maroulis I, Tzelepi V, Kalofonos H, Karavias DD, Kardamakis D et al (2014) Expression of claudins-1,-4,-5,-7 and occludin in hepatocellular carcinoma and their relation with classic clinicopathological features and patients' survival. In Vivo 28:315–326

Brahme NN, Harburger DS, Kemp-O'Brien K, Stewart R, Raghavan S, Parsons M et al (2013) Kindlin binds migfilin tandem LIM domains and regulates migfilin focal adhesion localization and recruitment dynamics. J Biol Chem 288:35604–35616

Brokalaki EI, Weber F, Sotiropoulos GC, Daoudaki M, Cicinnati VR, Beckebaum S (2012) Claudin-7 expression in hepatocellular carcinoma. Transplant Proc 44:2737–2740

Cai L, Han J, Zhuo X, Xiong Y, Dong J, Li X (2009) Overexpression and significance of focal adhesion kinase in hepatocellular carcinoma and its relationship with HBV infection. Med Oncol 26:409–414

Calderwood DA, Huttenlocher A, Kiosses WB, Rose DM, Woodside DG, Schwartz MA, Ginsberg MH (2001) Increased filamin binding to beta-integrin cytoplasmic domain inhibits cell migration. Nat Cell Biol 3:1060–1068

Canel M, Serrels A, Frame MC, Brunton VG (2013) E-cadherin-integrin crosstalk in cancer invasion and metastasis. J Cell Sci 126:1–9

Cao et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/17880531

Cao X, Zhang L, Shi Y, Sun Y, Dai S, Guo C, Zhu F, Wang Q, Wang J, Wang X et al (2013) Human tumor necrosis factor (TNF)-alpha-induced protein 8-like 2 suppresses hepatocellular carcinoma metastasis through inhibiting Rac1. Mol Cancer 12:149

Castronovo V (1993) Laminin receptors and laminin-binding proteins during tumor invasion and metastasis. Invasion Metastasis 13:1–30

Chakraborty et al. 2015. http://www.ncbi.nlm.nih.gov/pubmed/25630468

Chan et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21347395

Charni et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19632304

Chen PW, Kroog GS (2010) Leupaxin is similar to paxillin in focal adhesion targeting and tyrosine phosphorylation but has distinct roles in cell adhesion and spreading. Cell Adh Migr 4:527–540

Chen JS, Huang XH, Wang Q, Chen XL, Fu XH, Tan HX, Zhang LJ, Li W, Bi J (2010) FAK is involved in invasion and metastasis of hepatocellular carcinoma. Clin Exp Metastasis 27:71–82

Chen YL, Wang TH, Hsu HC, Yuan RH, Jeng YM (2013) Overexpression of CTHRC1 in hepatocellular carcinoma promotes tumor invasion and predicts poor prognosis. PLoS One 8:e70324

Chen J, Zhao J, Ma R, Lin H, Liang X, Cai X (2014a) Prognostic significance of E-cadherin expression in hepatocellular carcinoma: a meta-analysis. PLoS One 9:e103952

Chen RX, Song HY, Dong YY, Hu C, Zheng QD, Xue TC, Liu XH, Zhang Y, Chen J, Ren ZG, Liu YK, Cui JF (2014b) Dynamic expression patterns of differential proteins during early invasion of hepatocellular carcinoma. PLoS One 9:e88543

Cheng ZX, Huang XH, Wang Q, Chen JS, Zhang LJ, Chen XL (2012) Clinical significance of decreased nidogen-2 expression in the tumor tissue and serum of patients with hepatocellular carcinoma. J Surg Oncol 105:71–80

Cheng N, Li Y, Han ZG (2013) Argonaute2 promotes tumor metastasis by way of up-regulating focal adhesion kinase expression in hepatocellular carcinoma. Hepatology 57:1906–1918

Cheng CC, Lai YC, Lai YS, Hsu YH, Chao WT, Sia KC, Tseng YH, Liu YH (2015) Transient knockdown-

mediated deficiency in plectin alters hepatocellular motility in association with activated FAK and RAC-1-GTPase. Cancer Cell Int 15:29
Chiquet-Ehrismann R (1993) Tenascin and other adhesion-modulating proteins in cancer. Semin Cancer Biol 4:301–310
Cho SB, Lee KH, Lee JH, Park SY, Lee WS, Park CH, Kim HS, Choi SK, Rew JS (2008) Expression of E-and N-cadherin and clinicopathology in hepatocellular carcinoma. Pathol Int 58:635–642
Chu PY, Huang LY, Hsu CH, Liang CC, Guan JL, Hung TH, Shen TL (2009) Tyrosine phosphorylation of growth factor receptor-bound protein-7 by focal adhesion kinase in the regulation of cell migration, proliferation, and tumorigenesis. J Biol Chem 284:20215–20226
Cichon C, Sabharwal H, Rüter C, Schmidt MA (2014) MicroRNAs regulate tight junction proteins and modulate epithelial/endothelial barrier functions. Tissue Barriers 2:e944446
Citi S, Pulimeno P, Paschoud S (2012) Cingulin, paracingulin, and PLEKHA7: signaling and cytoskeletal adaptors at the apical junctional complex. Ann N Y Acad Sci 1257:125–132
Citi S, Guerrera D, Spadaro D, Shah J (2014) Epithelial junctions and Rho family GTPases: the zonular signalosome. Small GTPases 5:1–15
Cray LA, Guan JL (1999) Focal adhesion kinase in integrin-mediated signaling. Front Biosci 4:D102–D113
Dai Z, Zhou SL, Zhou ZJ, Bai DS, Xu XY, Fu XT, Chen Q, Zhao YM, Yu L, Yang GH, Wang Z, Wu WZ, Zhou J et al (2014) Capn4 contributes to tumour growth and metastasis of hepatocellular carcinoma by activation of the FAK-Src signalling pathways. J Pathol 234:316–328
Deb M, Sengupta D, Patra SK (2012) Integrin-epigenetics: a system with imperative impact on cancer. Cancer Metastasis Rev 31:221–234
Di Modugno F, Iapicca P, Boudreau A, Mottolese M, Terrenato I, Perracchio L, Carstens RP et al (2012) Splicing program of human MENA produces a previously undescribed isoform associated with invasive, mesenchymal-like breast tumors. Proc Natl Acad Sci U S A 109:19280–19285
Djaafri I, Khayati F, Menashi S, Tost J, Podgorniak MP, Sadoux A, Daunay A, Teixeira L, Soulier J, Idbaih A, Setterblad N et al (2014) A novel tumor suppressor function of Kindlin-3 in solid cancer. Oncotarget 5:8970–8985
Donato MF, Colombo M, Matarazzo M, Paronetto F (1989) Distribution of basement membrane components I human hepatocellular carcinoma. Cancer 63:272–279
Du GS, Wang JM, Lu JX, Li Q, Ma CQ, Du JT, Zou SQ (2009) Expression of P-aPKC-iota, E-cadherin, and beta-catenin related to invasion and metastasis in hepatocellular carcinoma. Ann Surg Oncol 16:1578–1586
Ebnet K (2013) JAM-A and aPKC. A close pair during cell-cell contact maturation and tight junction formation in epithelial cells. Tissue Barriers 1:e22993
Edwards S, Lalor P, Tuncer C, Adams DH (2006) Vitronectin in human hepatic tumours contributes to the recruitment of lymphocytes in an alpha v beta3-independent manner. Br J Cancer 95:1545–1554
Eleniste PP, Bruzzaniti A (2012) Focal adhesion kinases in adhesion structures and disease. J Signal Transduct 2012:296450
Endo K, Ueda K, Ueyama J, Ohta T, Terada T (2000) Immunoreactive E-cadherin, alpha-catenin, beta-catenin, and gamma-catenin proteins in hepatocellular carcinoma: relationships with tumor grade, clinicopathologic parameters, and patients' survival. Hum Pathol 31:558–565
Enjoji M, Sakai H, Nakashima M, Nawata H (1998) Integrins: utility as cell type- and stage-specific markers for hepatocellular carcinoma and cholangiocarcinoma. In Vitro Cell Dev Biol Anim 34:25–27
Faouzi S, Le Bail B, Neaud V, Boussarie L, Saric J, Bioulac-Sage P, Balabaud C, Rosenbaum J (1999) Myofibroblasts are responsible for collagen synthesis in the stroma of human hepatocellular carcinoma: an in vivo in vitro study. J Hepatol 30:275–284
Feng XX, Liu M, Yan W, Zhou ZZ, Xia YJ, Tu W, Li PY, Tian DA (2013) β3 integrin promotes TGF-β1/H2O2/HOCl-mediated induction of metastatic phenotype of hepatocellular carcinoma cells by enhancing TGF-β1 signaling. PLoS One 8:e79857
Fletcher NF, Sutaria R, Jo J, Barnes A, Blahova M, Meredith LW, Cosset FL, Curbishley SM, Adams DH, Bertoletti A et al (2014) Activated macrophages promote hepatitis C virus entry in a tumor necrosis factor-dependent manner. Hepatology 59:1320–1330
Fonar Y, Frank D (2011) FAK and WNT signaling: the meeting of two pathways in cancer and development. Anticancer Agents Med Chem 11:600–606
Fransvea E, Mazzocca A, Antonaci S, Giannelli G (2009) Targeting transforming growth factor (TGF)-betaRI inhibits activation of beta1 integrin and blocks vascular invasion in hepatocellular carcinoma. Hepatology 49:839–850
Frantz C, Stewart KM, Weaver VM (2010) The extracellular matrix at a glance. J Cell Sci 123:4195–4200
Friedl P, Alexander S (2011) Cancer invasion and the microenvironment: plasticity and reciprocity. Cell 147:992–1009
Frixen UH, Behrens J, Sachs M, Eberle G, Voss B, Warda A, Löchner D, Birchmeier W (1991) E-cadherin-mediated cell-cell adhesion prevents invasiveness of human carcinoma cells. J Cell Biol 113:173–185
Fujii T, Koshikawa K, Nomoto S, Okochi O, Kaneko T, Inoue S, Yatabe Y, Takeda S, Nakao A (2004) Focal adhesion kinase is overexpressed in hepatocellular and can be served as an independent prognostic factor. J Hepatol 41:104–111
Ganguly KK, Pal S, Moulik S, Chatterjee A (2013) Integrins and metastasis. Cell Adhes Migr 7:251–261
Gao N, He H, Xiao L, Gao X, Shi H, Wu Q, Xu N, Lei Y, Song X, Hou Y (2015) The effects of focal adhesion

kinase on the mobility, proliferation and apoptosis of Caco2 and SMMC-7721 cells. Med Oncol 32:567
Garay E, Patino-Lopez G, Islas S, Alarcon L, Canche–Pool E, Valle-Rios R, Medina-Contreras O et al (2010) CRTAM: a molecule involved in epithelial cell adhesion. J Cell Biochem 111:111–122
Ge YS, Liu D, Jia WD, Li JS, Ma JL, Yu JH, Xu GL (2015) Kindlin-2: a novel prognostic biomarker for patients with hepatocellular carcinoma. Pathol Res Pract 211:198–202
Giannelli G, Bergamini C, Fransvea E, Marinosci F, Quaranta V, Antonaci S (2001) Human hepatocellular carcinoma (HCC) cells require both alpha3beta1 integrin and matrix metalloproteinases activity for migration and invasion. Lab Invest 81:613–627
Giannelli G, Astigiano S, Antonaci S, Morini M, Barbieri O, Noonan DM, Albini A (2002) Role of the alpha3beta1 and alpha6beta4 integrins in tumor invasion. Clin Exp Metastasis 19:217–223
Giannelli et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/16285438
Gkretsi V, Bogdanos DP (2015) Experimental evidence of Migfilin as a new therapeutic target of hepatocellular carcinoma metastasis. Exp Cell Res. doi:10.1016/j.yexcr.2015.03.002
Golubovskaya VM, Cance WG (2007) Focal adhesion kinase and p53 signaling in cancer cells. Int Rev Cytol 263:103–153
Gonzalez-Mariscal L, Dominguez-Calderon A, Raya-Sandino A, Ortega-Olvera JM, Vargas-Sierra Q, Martinez-Revollar G (2014) Tight junctions and the regulation of gene expression. Semin Cell Dev Biol 36:213–223
Gotoh M, Sakamoto M, Kanetaka K, Chuuma M, Hirohashi S (2002) Overexpression of osteopontin in hepatocellular carcinoma. Pathol Int 52:19–24
Grosse B, Degrouard J, Jaillard D, Cassio D (2013) Build them up and break them down: tight junctions of cell lines expressing typical hepatocyte polarity with a varied repertoire of claudins. Tissue Barriers 1:e25210
Guillemot L, Guerrera D, Spadaro D, Tapla R, Jond L, Citi S (2014) MgcRacGAP interacts with cingulin and paracingulin to regulate Rac1 activation and development of the tight junction barrier during epithelial junction assembly. Mol Biol Cell 25:1995–2005
Gulubova MV (1997) Collagen type III and type IV detection in and around human hepatocellular carcinoma. Gen Diagn Pathol 142:155–163
Guo X, Xiong L, Zou L, Sun T, Zhang J, Li H, Peng R, Zhao J (2012) L1 cell adhesion molecule overexpression in hepatocellular carcinoma associates with advanced tumor progression and poor patient survival. Diagn Pathol 7:96
Gupton SL, Riquelme D, Hughes-Alford SK, Tadros J, Rudina SS, Hynes RO, Lauffenburger D et al (2012) Mena binds a5 integrin directly and modulates a5b1 function. J Cell Biol 198:657–676
Hall CL, Turley EA (1995) Hyaluronan: RHAMM mediated cell locomotion and signaling in tumorigenesis. J Neurooncol 26:221–229
Hall CL, Wang C, Lange LA, Turley EA (1994) Hyaluronan and the hyaluronan receptor RHAMM promote focal adhesion turnover and transient tyrosine kinase activity. J Cell Biol 126:575–588
Han NM, Fleming RY, Curley SA, Gallick GE (1997) Overexpression of ocal adhesion kinase (p125FAK) in human colorectal carcinoma liver metastases: independence from c-src or c-yes activation. Ann Surg Oncol 4:264–268
Han et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24284889
Hao JL, Cozzi PJ, Khatri A, Power CA, Li Y (2010) CD147/EMMPRIN and CD44 are potential therapeutic targets for metastatic prostate cancer. Curr Cancer Drug Targets 10:287–306
Hashiguchi M, Ueno S, Sakoda M, Iino S, Hiwatashi K, Minami K, Ando K, Mataki Y et al (2013) Clinical implication of ZEB-1 and E-cadherin expression in hepatocellular carcinoma (HCC). BMC Cancer 13:572
Hauck CR, Hsia DA, Schlaepfer DD (2002) The focal adhesion kinase-a regulator of cell migration and invasion. IUBMB Life 53:115–119
Hayashi T (2010) Integrins modulate cellular fibrogenesis at multiple levels; regulation of TGF-β signaling. Endocr Metab Immune Disord Drug Targets 10:302–319
Hayashi et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21323792
Hirose T, Izumi Y, Nagashima Y, Tamai-Nagai Y, Kurihara H, Sakai T, Suzuki Y, Yamanaka T, Suzuki A, Mizuno K et al (2002) Involvement of ASIP/PAR-3 in the promotion of epithelial tight junction formation. J Cell Sci 115:2485–2495
Hoffman et al. 2006. http://www.ncbi.nlm.nih.gov/pubmed/16505170
Hokaiwado N, Asamoto M, Futakuchi M, Ogawa K, Takahashi S, Shirai T (2007) Both early and late stages of hepatocarcinogenesis are enhanced in Cx32 dominant negative mutant transgenic rats with disrupted gap junctional intercellular communication. J Membr Biol 218:101–106
Hu YJ, Li HY, Qiu KJ, Li DC, Zhou JH, Hu YH, Zhang FM (2014) Downregulation of Notch1 inhibits the invasion of human hepatocellular carcinoma HepG2 and MHCC97H cells through the regulation of PTEN and FAK. Int J Mol Med 34:1081–1086
Huang X, Ji G, Wu Y, Wan B, Yu L (2008) LAMA4, highly expressed in human hepatocellular carcinoma from Chinese patients, is a novel marker of tumor invasion and metastasis. J Cancer Res Clin Oncol 134:705–714
Inayoshi J, Ichida T, Sugitani S, Tsuboi Y, Genda T, Honma N, Asakura H (2003) Gross appearance of hepatocellular carcinoma reflects E-cadherin expression and risk of early recurrence after surgical treatment. J Gastroenterol Hepatol 18:673–677
Inoue M, Ajioka Y, Wakai T, Takamura M, Korita P, Shirai Y, Hatakeyama K (2011) Liver-intestine cadherin in intraepithelial neoplasia of intrahepatic cholangiocarcinoma. Hepatogastroenterology 58:2045–2051

Inuzuka S, Ueno T, Torimura T, Tamaki S, Sakata R, Sata M, Yoshida H, Tanikawa K (1992) Vitronectin in liver disorders: biochemical and immunohistochemical studies. Hepatology 15:629–636

Isemura M, Yosizawa Z, Kojima N, Ichida F (1982) Fibronectin in human hepatocellular carcinoma. Tohoku J Exp Med 138:441–442

Itoh S, Maeda T, Shimada M, Aishima SI, Shirabe K, Tanaka S, Maehara Y (2004) Role of expression of focal adhesion kinase in progression of hepatocellular carcinoma. Clin Cancer Res 10:2812–2817

Jagirdar J, Ishak KG, Colombo M, Brambilla C, Paronetto F (1985) Fibronectin patterns in hepatocellular carcinoma and its clinical significance. Cancer 56:1643–1648

Jan YJ, Ko BS, Hsu C, Chang TC, Chen SC, Wang J, Liou JY (2009) Overexpressed focal adhesion kinase predicts a higher incidence of extrahepatic metastasis and worse survival in hepatocellular carcinoma. Hum Pathol 40:1384–1390

Jao TM, Tsai MH, Lio HY, Weng WT, Chen CC, Tzeng ST, Chang CY, Lai YC, Yen SJ, Yu SL, Yang YC (2014) Protocadherin 10 suppresses tumorigenesis and metastasis in colorectal cancer and its genetic loss predicts adverse prognosis. Int J Cancer 135:2593–2603

Jia YL, Shi L, Zhou JN, Fu CJ, Chen L, Yuan HF, Wang YF, Yan XL, Xu YC, Zeng Q, Yue W, Pei XT (2011) Epimorphin promotes human hepatocellular carcinoma invasion and metastasis through activation of focal adhesion kinase/extracellular signal-related kinase/matrix metalloproteinase-9 axis. Hepatology 54:1808–1818

Jin Y, Chen JN, Feng ZY, Zhang ZG, Fan WZ, Wang Y, Li JP (2014) OPN and αvβ3 expression are predictors of disease severity and worse prognosis in hepatocellular carcinoma. PLoS One 9:e87930

Jing Y, Jia D, Wong CM, Oi-Lin NI, Zhang Z, Liu L, Wang Q, Zhao F, Li J, Yao M et al (2014) SERPINA5 inhibits tumor cell migration by modulating the fibronectin-integrin b1 signaling pathway in hepatocellular carcinoma. Mol Oncol 8:366–377

Katabami K, Mizuno H, Sano R, Saito Y, Ogura M, Itoh S, Tsuji T (2005) Transforming growth factor-beta1 upregulates transcription of alpha3 integrin gene in hepatocellular carcinoma cells via Ets-transcription factor-binding motif in the promoter region. Clin Exp Metastasis 22:539–548

Katagiri YU, Sleeman J, Fujii H, Herrlich P, Hotta H, Tanaka K, Chikuma S, Yagita H et al (1999) CD44 variants but not CD44s cooperates with beta1-containing integrins to permit cells to bind to osteopontin independently of arginine-glycine-aspartic acid, thereby stimulating cell motility and chemotaxis. Cancer Res 59:219–226

Kiema T, Lad Y, Jiang P, Oxley CL, Baldassarre M, Wegener KL, Campbell ID, Ylänne J, Calderwood DA (2006) The molecular basis of filamin binding to integrins and competition with talin. Mol Cell 21:337–347

Kikkawa Y, Sanzen N, Fujiwara H, Sonnenberg A, Sekiguchi K (2000) Integrin binding specificity of laminin-10/11: laminin-10/11 are recognized by alpha 3 beta 1, alpha 6 beta 1 and alpha 6 beta 4 integrins. J Cell Sci 113:869–876

Kikkawa Y, Sudo R, Kon J, Mizuguchi T, Nomizu M, Hirata K, Mitaka T (2008) Laminin alpha 5 mediates ectopic adhesion of hepatocellular carcinoma hrough integrins and/or Lutheran/basal cell adhesion molecule. Exp Cell Res 314:2579–2590

Kojima T, Murata M, Go M, Spray DC, Sawada N (2007) Connexins induce and maintain tight junctions in epithelial cells. J Membr Biol 217:13–19

Konopka G, Tekiela J, Iverson M, Wells C, Duncan SA (2007) Junctional adhesion molecule-A is critical for the formation of pseudocanaliculi and modulates E-cadherin expression in hepatic cells. J Biol Chem 282:28137–28148

Kornberg LJ (1998) Focal adhesion kinase and its potential involvement in tumor invasion and metastasis. Head Neck 20:745–752

Koukoulis GK, Shen J, Virtanen I, Gould VE (1995) Immunolocalization of cellular fibronectins in the normal liver, cirrhosis, and hepatocellular carcinoma. Ultrastruct Pathol 19:37–43

Koval M (2013) Differential pathways of claudin oligomerization and integration into tight junctions. Tissue Barriers 1:e24518

Lai-Cheong JE, Ussar S, Arita K, Hart IR, McGrath JA (2008) Colocalization of kindlin-1, kindlin-2, and migfilin at keratinocyte focal adhesion and relevance to the pathophysiology of Kindler syndrome. J Invest Dermatol 128:2156–2165

Lark AL, Livasy CA, Calvo B, Caskey L, Moore DT, Yang X, Cance WG (2003) Overexpression of focal adhesion kinase in primary colorectal carcinomas and colorectal liver metastases: immunohistochemistry and real-time PCR analyses. Clin Cancer Res 9:215–222

Leber MF, Efferth T (2009) Molecular principles of cancer invasion and metastasis (review). Int J Oncol 34:881–895

Li P, Lin Y, Zhang Y, Zhu Z, Huo K (2013) SSX2IP promotes metastasis and chemotherapeutic resistance of hepatocellular carcinoma. J Transl Med 11:52

Li Z, Tang M, Ling B, Liu S, Zheng Y, Nie C, Yuan Z, Zhou L, Guo G, Tong A, Wie Y (2014) Increased expression of S100A6 promotes cell proliferation and migration in human hepatocellular carcinoma. J Mol Med (Berl) 92:291–303

Lian WX, Yin RH, Kong XZ, Zhang T, Huang XH, Zheng WW, Yang Y, Zhan YQ et al (2012) THAP11, a novel binding protein of PCBP1, negatively regulates CD44 alternative splicing and cell invasion in a human hepatoma cell line. FEBS Lett 586:1431–1438

Liang Q, Han Q, Huang W, Nan G, Xu BQ, Jiang JL, Chen ZN (2014) Hab18G/CD147 regulates vinculin-mediated focal adhesion and cytoskeleton organization in cultured human hepatocellular carcinoma cells. PLoS One 9:e102496

Liao Z, Kato H, Pandey M, Cantor JM, Ablooglu AJ, Ginsberg MH, Shattil SJ (2015) Interaction of kindlin-2 with integrin β3 promotes outside-in signaling responses by the αVβ3 vitronectin receptor. Blood 125:1995–2004

Lin L, McCroskery S, Ross JM, Chak Y, Neuhuber B, Daniels MP (2010) Induction of filopodia-like protrusions by transmembrane agrin: role of agrin glycosaminoglycan chains and Rho-family GTPases. Exp Cell Res 316:2260–2277

Lin L, Liang H, Wang Y, Yin X, Hu Y, Huang J, Ren T, Xu H, Zheng L, Chen X (2014a) microRNA-141 inhibits cell proliferation and invasion and promotes apoptosis by targeting hepatocyte nuclear factor-3β in hepatocellular carcinoma cells. BMC Cancer 14:879

Lin Y, Lin G, Fang W, Zhu H, Chu K (2014b) Increased expression of annexin A1 predicts poor prognosis in human hepatocellular carcinoma and enhances cell malignant phenotype. Med Oncol 31:327

Liu LX, Jiang HC, Liu ZH, Zhou J, Zhang WH, Zhu AL, Wang XQ, Wu M (2002) Integrin gene expression profiles of human hepatocellular carcinoma. World J Gastroenterol 8:631–637

Liu YH, Ho CC, Cheng CC, Pei RJ, Hsu YH, Yeh KT, Tsai MC, Lai YS (2007–2008) Pleomorphism of cancer cells with the expression of plectin and concept of filament bundles in human hepatocellular carcinoma. Res Coomun Mol Pathol Pharmacol 120–121:43–54

Liu YH, Cheng CC, Ho CC, Chao WT, Pei RJ, Hsu YH, Ho LC, Shiu BH, Lai YS (2011a) Plectin deficiency on cytoskeletal disorganization and transformation of human liver cells in vitro. Med Mol Morphol 44:21–26

Liu YH, Ho CC, Cheng CC, Chao WT, Pei RJ, Hsu YH, Lai YS (2011b) Cytokeratin 18-mediated disorganization of intermediate filaments is induced by degradation of plectin in human liver cells. Biochem Biophys Res Commun 407:575–580

Liu W, Tian F, Jiang P, Zhao X, Guo F, Li X, Wang S (2014) Aberrant expression of laminin g2 correlates with poor prognosis and promotes invasion in extrahepatic cholangiocarcinoma. J Surg Res 186:150–156

Liu YA, Liang BY, Guan Y, You J, Zhu L, Chen XP, Huang ZY (2015) Loss of N-cadherin is associated with loss of E-cadherin expression and poor outcome of liver resection in hepatocellular carcinoma. J Surg Res 194:167–176

Lopez D, Niu G, Huber P, Carter WB (2009) Tumor-induced upregulation of twist, snail, and slug represses the activity of the human VE-cadherin promoter. Arch Biochem Biophys 482:77–82

Luedde T (2010) MicroRNA-151 and its hosting gene FAK (focal adhesion kinase) regulate tumor cell migration and spreading of hepatocellular carcinoma. Hepatology 52:1164–1166

Ma XD, Ma X, Sui YF, Wang WL, Wang CM (2003) Signal transduction of gap junctional genes, connexin32, connexin43 in human hepatocarcinogenesis. World J Gastroenterol 9:946–950

Ma HX, Shu QH, Pan JJ, Liu D, Xu GL, Li JS, Ma JL, Jia WD, Yv JH, Ge YS (2015) Expression of Kindlin-1 in human hepatocellular carcinoma and its prognostic significance. Tumour Biol 36:4235–4241

Machesky L, Jurdic P, Hinz B (2008) Grab, stick, pull and digest: the functional diversity of actin-associated matrix-adhesion structures. EMBO Rep 9:139–143

Mao X, Chen D, Wu J, Li J, Zhou H, Wu Y, Duan X (2013) Differential expression of fascin, E-cadherin and vimentin: proteins associated with survival of cholangiocarcinoma patients. Am J Med Sci 346:261–268

Mareel M, Leroy A (2003) Clinical, cellular, and molecular aspects of cancer invasion. Physiol Rev 83:337–376

Mareel M, Oliveira MJ, Madani I (2009) Cancer invasion and metastasis: interacting ecosystems. Virchows Arch 454:599–622

Margadant C, Sonnenberg A (2010) Integrin-TGF-beta crosstalk in fibrosis, cancer and wound healing. EMBO Rep 11:97–105

Masumoto A, Arao S, Otsuki M (1999) Role of beta1 integrins in adhesion and invasion of hepatocellular carcinoma cells. Hepatology 29:68–74

Matsumoto A, Ono M, Fujimoto Y, Gallo RL, Bernfield M, Kohgo Y (1997) Reduced expression of syndecan-1 in human hepatocellular carcinoma with high metastatic potential. Int J Cancer 74:482–491

McCole DF (2013) Phosphatase regulation of intercellular junctions. Tissue Barriers 1:e26713

Minata M, Kudo M, Harada KH, Ikai I, Nishida N (2013) Expression of E-cadherin and vascular endothelial growth factor in noncancerous liver s associated with recurrence of hepatocellular carcinoma after curative resection. Oncology 84(Suppl 1):88–92

Miyao Y, Ozaki D, Nagao, Kondo Y (1999) Interstitial invasion of well-differentiated hepatocellular carcinoma and subsequent tumor growth. Pathol Int 49:208–213

Mizuno H, Ogura M, Saito Y, Sekine W, Sano G, Gotou T, Oku T, Itoh S, Katabami K, Tsuji T (2008) Changes in adhesive and migratory characteristics of hepatocellular carcinoma (HCC) cells induced by expression of alpha3beta1 integrin. Biochim Biophys Acta 1780:564–570

Mon NN, Ito S, Senga T, Hamaguchi M (2006) FAK signaling in neoplastic disorders: a linkage between inflammation and cancer. Ann N Y Acad Sci 1086:199–212

Mosnier JF, Kandel C, Cazals-Hatem D, Bou-Hanna C, Gournay J, Jarry A, Laboisse CL (2009) N-cadherin serves as diagnostic biomarker in intrahepatic and perihilar cholangiocarcinomas. Mod Pathol 22:182–190

Murata M, Kojima T, Yamamoto T, Go M, Takano K, Chiba H, Tokino T, Sawada N (2005) Tight junction protein MAGI-1 is up-regulated by transfection with connexin 32 in an immortalized mouse hepatic cell line: cDNA microarray analysis. Cell Tissue Res 319:341–347

Nakagawa H, Hikiba Y, Hirata Y, Font-Burgada J, Sakamoto K, Hayakawa Y, Taniguchi K, Umemura A, Kinoshita H et al (2014) Loss of liver E-cadherin induces sclerosing cholangitis and promotes carcinogenesis. Proc Natl Acad Sci U S A 111:1090–1095

Nakashima Y, Ono T, Yamanoi A, El-Assal ON, Kohno H, Nagasue N (2004) Expression of gap junction protein connexin32 in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. J Gastroenterol 39:763–768

Nejjari M, Hafdi Z, Gouyesse G, Fiorentino M, Béatrix O, Dumortier J, Pourreyron C, Barozzi C, D'Errico A, Grigioni WF et al (2002) Expression, regulation, and function of alpha V integrins in hepatocellular carcinoma : an in vivo and in vitro study. Hepatology 36:418–426

Németh Z, Szasz AM, Somoracz A, Tatrai P, Németh J, Gyorffy H, Szijarto A, Kupcsulik P, Kiss A, Schaff Z (2009) Zonula occludens-1, occludin, and E-cadherin protein expression in biliary tract cancers. Pathol Oncol Res 15:533–539

Ng et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23504997

Nikolopoulos SN, Turner CE (2000) Actopaxin, a new focal adhesion protein that binds paxillin LD motifs and actin and regulates cell adhesion. J Cell Biol 151:1435–1448

Nitta T, Mitsuhashi T, Hatanaka Y, Miyamoto M, Oba T, Tsuchikawa T, Suzuki Y, Hatanaka KC, Hirano S, Matsuno Y (2014) Prognosis significance of epithelial-mesenchymal transition-related markers in extrahepatic cholangiocarcinoma: comprehensive immunohistochemical study using a tissue microarray. Br J Cancer 111:1363–1372

Ogata R (1998) Type IV collagen and laminin enhance the motility, adhesion, and proliferation of hepatoma cells. Kurume Med J 45:11–20

Ohta R, Yamashita Y, Taketomi A, Kitagawa D, Kuroda Y, Itoh S, Aishima S, Maehara Y (2006) Reduced expression of focal adhesion kinase in intrahepatic cholangiocarcinoma is associated with poor tumor differentiation. Oncology 71:417–422

Orban E, Szabo E, Lotz G, Kupcsulik P, Paska C, Schaff Z, Kiss A (2008) Different expression of occludin and ZO-1 in primary and metastatic liver tumors. Pathol Oncol Res 14:299–306

Osada T, Sakamoto M, Ino Y, Iwamatsu A, Matsuno Y, Muto T, Hirohashi S (1996) E-cadherin is involved in the intrahepatic metastasis of hepatocellular carcinoma. Hepatology 24:1460–1467

Oyamada M, Krutovskikh VA, Mesnil M, Partensky C, Berger F, Yamasaki H (1990) Aberrant expression of gap junction gene in primary human hepatocellular carcinomas: increased expression of cardiac-type gap junction gene connexin 43. Mol Carcinog 3:273–278

Ozaki I, Yamamoto K, Mizuta T, Kajihara S, Fukushina N, Setoguchi Y, Morito F, Sakai T (1998) Differential expression of laminin receptors in human hepatocellular carcinoma. Gut 43:837–842

Ozaki I, Hamajima H, Matsuhashi S, Mizuta T (2011) Regulation of TGF-β1-induced pro-apoptotic signaling by growth factor receptors and extracellular matrix receptor integrins in the liver. Front Physiol 2:78

Palazzo AF, Gundersen GG (2002) Microtubule-actin cross-talk at focal adhesions. Sci STKE 2002(139): pe31

Paschoud S, Jond L, Guerrera D, Citi S (2014) PLEKHA7 modulates epithelial tight junction barrier function. Tissue Barriers 2:e28755

Qian et al. 2008. http://www.ncbi.nlm.nih.gov/pubmed/18847500

Qu H, Tu Y, Guan JL, Xiao G, Wu C (2014) Kindlin-2 tyrosine phosphorylation and interaction with Src serve as a regulatable switch in the integrin outside-in signaling circuit. J Biol Chem 289:31001–31013

Quail DF, Joyce JA (2013) Microenvironmental regulation of tumor progression and metastasis. Nat Med 19:1423–1437

Rao RK, Samak G (2013) Bile duct epithelial tight junctions and barrier function. Tissue Barriers 1: e25718

Reddig PJ, Juliano RL (2005) Clinging to life: cell to matrix adhesion and cell survival. Cancer Metastasis Rev 24:425–439

Riener MO, Vogetseder A, Pestalozzi BC, Clavien PA, Probst-hensch N, Kristiansen G, Jochum W (2010) Cell adhesion molecules P-cadherin and CD24 are markers for carcinoma and dysplasia in the biliary tract. Hum Pathol 41:1558–1565

Roskams T, De Vos R, David G, Van Damme B, Desmet V (1998) Heparan sulphate proteoglycan expression in human primary liver tumours. J Pathol 185:290–297

Rousseau A, Wilhelm LP, Tomasetto C, Alpy F (2014) The phosphoinositide-binding protein TRAF4 modulates tight junction stability and migration of cancer cells. Tissue Barriers 2:e975597

Sabit H, Tsuneyama K, Shimonishi T, Harada K, Cheng J, Ida H, Saku T, Saito K, Nakanuma Y (2001) Enhanced expression of basement-membrane-type heparan sulfate proteoglycan in tumor fibro-myxoid stroma of intrahepatic cholangiocarcinoma. Pathol Int 51:248–256

Samuel SK, Hurta RA, Spearman MA, Wright JA, Turley EA, Greenberg AH (1993) TGF-beta 1 stimulation of cell locomotion utilizes the hyaluronan receptor RHAMM and hyaluronan. J Cell Biol 123:749–758

Santamato A, Fransvea E, Dituri F, Caligiuri A, Quaranta M, Niimi T, Pinzani M, Antonaci S et al (2011) Hepatic stellate cells stimulate HCC cell migration via laminin-5 production. Clin Sci (Lond) 121:159–168

Schaller MD (2001) Paxillin: a focal adhesion-associated adaptor protein. Oncogene 20:6459–6472

Schlaepfer DD, Mitra SK, Ilic D (2004) Control of motile and invasive cell phenotypes by focal adhesion kinase. Biochim Biophys Acta 1692:77–102

Schmalhofer O, Brabletz S, Brabletz T (2009) E-cadherin, b-catenin, and ZEB1 in malignant progression of cancer. Cancer Metastasis Rev 28:151–166

Schmitt M, Horbach A, Kubitz R, Frilling A, Häussinger D (2004) Disruption of hepatocellular tight junctions by vascular endothelial growth factor (VEGF): a novel mechanism for tumor invasion. J Hepatol 41:274–283

Seo DD, Lee HC, Kim HJ, Min HJ, Kim KM, Lim YS, Chung YH, Lee YS, Suh DJ, Yu E, Chun SY (2008) Neural cadherin overexpression is a predictive marker for early postoperative recurrence in hepatocellular carcinoma patients. J Gastroenterol Hepatol 23:1112–1118

Settakorn J, Kaewpila N, Burns GF, Leong AS (2005) FAT, E-cadherin, beta catenin, HER2/neu, Ki67 immunoexpression, and histological grade in intrahepatic cholangiocarcinoma. J Clin Pathol 58:1249–1254

Shang N, Arteaga M, Zaidi A, Stauffer J, Cotler SJ, Zeleznik-Le NJ, Zhang J, Qiu W (2015) FAK is required for c-Met/β-catenin-driven hepatocarcinogenesis. Hepatology 61:214–226

She S, Xu B, He M, Lan X, Wang Q (2010) Nm23-H1 suppresses hepatocarcinoma cell adhesion and migration on fibronectin by modulating glycosylation of integrin beta1. J Exp Clin Cancer Res 29:93

Sheen IS, Jeng KS, Wang PC, Shih SC, Chang WH, Wang HY, Chen CC, Shyung LR (2004) Are gap junction gene connexins 26, 32 and 43 of prognostic values in hepatocellular carcinoma? A prospective study. World J Gastroenterol 10:2785–2790

Shen TL, Guan JL (2001) Differential regulation of cell migration and cell cycle progression by FAK complexes with Src, PI3K, Grb7 and Grb2 in focal contacts. FEBS Lett 499:176–181

Sobel ME (1993) Differential expression of the 67 kDa laminin receptor in cancer. Semin Cancer Biol 4:311–317

Soejima Y, Inoue M, Takahashi Y, Uozaki H, Sawabe M, Fukusato T (2014) Integrins αvβ6 and α3β1 are downregulated in cholangiolocellular carcinoma but not cholangiocarcinoma. Hepatol Res 44:E320–E334

Stebbing et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23318416

Suh et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23160379

Sun et al. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21533080

Sun C, Zargham R, Shao Q, Gui X, Marcus V, Lazaris A, Salman A, Metrakos P, Qu X, Gao Z (2014) Association of CD98, integrin β1, integrin β3 and Fak with the progression and liver metastases of colorectal cancer. Pathol Res Pract 210:668–674

Swift JG, Mukherjee M, Rowland R (1983) Intercellular junctions in hepatocellular carcinoma. J Submicrosc Cytol 15:799–810

Tabarin A, Bioulac-Sage P, Boussarie L, Balabaud C, de Mascarel A, Grimaud JA (1987) Hepatocellular carcinoma developed on noncirrhotic livers. Sinusoids in hepatocellular carcinoma. Arch Pathol Lab Med 111:174–180

Takahashi Y, Sawada G, Kurashiga J, Matsumura T, Uchi R, Ueo H, Ishibashi M, Takano Y, Akiyoshi S, Iwaya T et al (2013) Tumor-derived tenascin-C promotes the epithelial-mesenchymal transition in colorectal cancer cells. Anticancer Res 33:1927–1943

Tameda M, Sugimoto K, Shiraki K, Yamamoto N, Okamoto R, Usui M, Ito M, Takei Y, Nobori T, Kojima T, Suzuki H et al (2014) Collagen triple helix repeat containing 1 is overexpressed in hepatocellular carcinoma and promotes cell proliferation and motility. Int J Oncol 45:541–548

Tanaka R, Seki Y, Saito Y, Kamiya S, Fujita M, Okutsu H, Iyoda T, Takai T, Owaki T, Yajima H, Taira J, Hayashi R et al (2014) Tenascin-C-derived peptide TNIIIA2 highly enhances cell survival and platelet-derived growth factor (PDGF)-dependent cell proliferation through potentiated and sustained activation of integrin α5β1. J Biol Chem 289:17699–17708

Tanimizu and Mitaka 2013. http://www.ncbi.nlm.nih.gov/pubmed/24665375

Tatrai P, Dudas J, Batmunkh E, Mathé M, Zalatnai A, Schaff Z, Ramadori G, Kovalszky I (2006) Agrin, a novel basement membrane component in human and rat liver, accumulates in cirrhosis and hepatocellular carcinoma. Lab Invest 86:1149–1160

Tatrai P, Egedi K, Somoracz A, van Kuppevelt TH, Ten Dam G, Lyon M, Deakin JA, Kiss A, Schaff Z, Kovalsky I (2010) Quantitative and qualitative alterations of heparan sulfate in fibrogenic liver diseases and hepatocellular cancer. J Histochem Cytochem 58:429–441

Terada T, Nakanuma Y (1994) Expression of tenascin, type IV collagen and laminin during human intrahepatic bile duct development and in intrahepatic cholangiocarcinoma. Histopathology 25:143–150

Tian B, Li Y, Ji XN, Chen J, Xue Q, Ye SL, Liu YK, Tang ZY (2005) Basement membrane proteins play an active role in the invasive process of human hepatocellular carcinoma cells with high metastasis potential. J Cancer Res Clin Oncol 131:80–86

Torimura T, Ueno T, Inuzuka S, Kin M, Ohira H, Kimura Y, Majima Y, Sata M, Abe H, Tanikawa K (1994) The extracellular matrix in hepatocellular carcinoma shows different localization patterns depending on the differentiation and the histological pattern of tumors: immunohistochemical analysis. J Hepatol 21:37–46

Torimura T, Ueno T, Kin M, Inuzuka S, Sugawara H, Tamaki S, Tsuji R, Sujaku K, Sata M, Tanikawa K (1997) Coordinated expression of integrin alpha6beta1 and laminin in hepatocellular carcinoma. Hum Pathol 28:1131–1138

Torimura T, Ueno T, Kin M, Ogata R, Inuzuka S, Sugawara H, Kurotatsu R, Shimada M, Yano H, Kojiro M, Tanikawa K et al (1999) Integrin alpha6beta1 plays a significant role in the attachment of hepatoma cells to laminin. J Hepatol 31:734–740

Torimura T, Ueno T, Kin M, Harad R, Nakamura T, Sakamoto M, Kumashiro R, Yano H et al (2001) Laminin deposition to type IV collagen enhances

haptotaxis, chemokinesis, and adhesion of hepatoma cells through beta1-integrins. J Hepatol 35:245–253
Traweger A, Toepfer S, Wagner RN, Zweimueller-Mayer J, Gehwolf R, Lehner C, Tempfer H, Krizbai I, Wilhelm I et al (2013) Beyond cell-cell junctions. Emerging roles of the tight junction scaffold ZO-2. Tissue Barriers 1:e25039
Tsukita S, Katsuno T, Yamazaki Y, Umeda K, Tamura A, Tsukita S (2009) Roles of ZO-1 and ZO-2 in establishment of the belt-like adherens and tight junctions with paracellular permselective barrier function. Ann N Y Acad Sci 1165:44–52
Tu Y, Wu S, Shi X, Chen K, Wu C (2003) Migfilin and Mig-2 link focal adhesions to filamin and the actin cytoskeleton and function in cell shape modulation. Cell 113:37–47
Valastyan S, Weinberg RA (2011) Tumor metastasis: molecular insights and evolving paradigms. Cell 147:275–292
Valdembri D, Caswell PT, Anderson KI, Schwarz JP, König I, Astanina E, Caccavari F, Normal JC, Humphries MJ et al (2009) Neuropilin-1/GIPC1 signaling regulates alpha5beta1 integrin traffic and function in endothelial cells. PLoS Biol 7:e25
Valletta D, Czech B, Spruss T, Ikenberg K, Wild P, Hartmann A, Weiss TS, Oefner PJ, Müller M, Bosserhoff AK et al (2014) regulation and function of the atypical cadherin FAT1 in hepatocellular carcinoma. Carcinogenesis 35:1407–1415
Van Itallie CM, Anderson JM (2013) Claudin interactions in and out of the tight junction. Tissue Barriers 1:e25247
Van Itallie CM, Anderson JM (2014) Architecture of tight junctions and principles of molecular composition. Semin Cell Dev Biol 36:157–165
Varner JA, Cheresh DA (1996) Integrins and cancer. Curr Opin Cell Biol 8:724–730
Volpes R, van den Oord JJ, Desmet VJ (1993) Integrins as differential cell lineage markers of primary liver tumors. Am J Pathol 142:1483–1492
Von Sengbusch A, Gassmann P, Fisch KM, Enns A, Nicolson GL, Haier J (2005) Focal adhesion kinase regulates metastatic adhesion of carcinoma cells within liver sinusoids. Am J Pathol 166:585–596
Wang et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22052196
Wiche 1998. http://www.ncbi.nlm.nih.gov/pubmed/9701547
Wickline ED, Du Y, Stolz DB, Kahn M, Monga SP (2013) γ-Catenin at adherens junctions: mechanism and biologic implications in hepatocellular cancer after β-catenin knockdown. Neoplasia 15:421–434
Wozniak et al. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15246682
Wu C (2005) Migfilin and its binding partners: from cell biology to human diseases. J Cell Sci 118:659–664
Wu XZ, Chen D (2006) Cell-matrix talks: effects on differentiation of hepatocellular carcinoma. Minerva Gastroenterol Dietol 52:407–413
Wu Y, Zuo J, Ji G, Saiyin H, Liu X, Yin F, Cao N, Wen Y, Li JJ, Yu L (2009) Proapoptotic function of integrin beta(3) in human hepatocellular carcinoma cells. Clin Cancer Res 15:60–69
Wu X, Chen H, Gao Q, Bai J, Wang X, Zhou J, Qiu S, Xu Y, Shi Y, Wang X, Zhou J et al (2012) Downregulation of JWA promotes tumor invasion and predicts poor prognosis in human hepatocellular carcinoma. Mol Carcinog. doi:10.1002/mc.21981
Xia L, Huang W, Tian D, Chen Z, Zhang L, Li Y, Hu H, Liu J, Chen Z, Tang G, Dou J et al (2014) ACP5, a direct transcriptional target of FoxM1, promotes tumor metastasis and indicates poor prognosis in hepatocellular carcinoma. Oncogene 33:1395–1406
Yam JW, Tse EY, Ng IO (2009) Role and significance of focal adhesion proteins in hepatocellular carcinoma. J Gastroenterol Hepatol 24:520–530
Yamada S, Ichida T, Matsuda Y, Miyazaki Y, Hatano T, Hata K, Asakura H, Hirota N, Geerts A, Wisse E (1992) Tenascin expression in human chronic liver disease and in hepatocellular carcinoma. Liver 12:10–16
Yamasaki H, Krutovskikh V, Mesnil M, Tanaka T, Zaidan-Dagli ML, Omori Y (1999) Role of connexin (gap junction) genes in cell growth control and carcinogenesis. C R Acad Sci Ill 322:151–159
Yano T, Matsui T, Tamura A, Uji M, Tsukita S (2013) The association of microtubules with tight junctions is promoted by cingulin phosphorylation by AMPK. J Cell Biol 203:605–614
Yao M, Zhou XD, Zha XL, Shi DR, Fu J, He JY, Lu HF, Tang ZY (1997) Expression of the integrin alpha5 subunit and its mediated cell adhesion in hepatocellular carcinoma. J Cancer Res Clin Oncol 123:435–440
Yaqoob U, Cao S, Shergill U, Jagavelu K, Geng Z, Yin M, de Assuncao TM, Cao Y, Szabolcs A, Thorgeirsson S, Schwartz M et al (2012) Neuropilin-1 simulates tumor growth by increasing fibril assembly in the tumor microenvironment. Cancer Res 72:4047–4059
Yu X, Zou Y, Li Q, Mao Y, Zhu H, Huang G, Ji G, Luo X, Yu C, Zhang X (2014) Decorin-mediated inhibition of cholangiocarcinoma cell growth and migration and promotion of apoptosis are associated with E-cadherin in vitro. Tumour Biol 35:3103–3112
Yurchenco PD (2011) Basement membranes: cell scaffoldings and signaling platforms. Cold Spring Harb Perspect Biol 3:a004911
Zaidel-Bar R, Itzkovitz S, Ma'ayan A, Iyengar R, Geiger B (2007) Functional atlas of the integrin adhesome. Nat Cell Biol 9:858–867
Zha et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24498348
Zhai X, Zhu H, Wang W, Zhang S, Zhang Y, Mao G (2014) Abnormal expression of EMT-related proteins, S100A4, vimentin and E-cadherin, is correlated with clinicopathological features and prognosis in HCC. Med Oncol 31:970
Zhan DQ, Wei S, Liu C, Liang BY, Ji GB, Chen XP, Xiong M, Huang ZY (2012) Reduced N-cadherin expression is associated with metastatic potential and

poor surgical outcomes of hepatocellular carcinoma. J Gastroenterol Hepatol 27:173–180

Zhang D, Kaneda M, Nakahama K, Arii S, Morita I (2007) Connexin 43 expression promotes malignancy of HuH7 hepatocellular carcinoma cells via the inhibition of cell-cell communication. Cancer Lett 252:208–215

Zhang KJ, Wang DS, Zhang SY, Jiao XL, Li CW, Wang XS, Yu QC, Cui HN (2010) The E-cadherin repressor slug and progression of human extrahepatic hilar cholangiocarcinoma. J Exp Clin Cancer Res 29:88

Zhang YH, Wang SQ, Sun CR, Wang M, Wang B, Tang JW (2011) Inhibition of JNK1 expression decreases migration and invasion of mouse hepatocellular carcinoma cell line in vitro. Med Oncol 28:966–972

Zhang G, Liu T, Wang Z (2012) Downregulation of MAGI1 associates with poor prognosis of hepatocellular carcinoma. J Invest Surg 25:93–99

Zhao J, Guan JL (2009) Signal transduction by focal adhesion kinase in cancer. Cancer Metastasis Rev 28:35–49

Zhao M, Laissue JA, Zimmermann A (1996) Tenascin and type IV collagen expression in liver cell dysplasia and in hepatocellular carcinoma. Histol Histopathol 11:323–333

Zheng S, Ruan Y, Wu Z, Tang J (1997) The relationship between 67KD laminin receptor expression and metastasis of hepatocellular carcinoma. J Tongji Med Univ 17:200–202

Zheng J, Li Y, Yang J, Liu Q, Shi M, Zhang R, Shi H, Ren Q, Ma J, Guo H, Tao Y et al (2011) NDRG2 inhibits hepatocellular carcinoma adhesion, migration and invasion by regulating CD24 expression. BMC Cancer 11(251):1–9

Zhou ZJ, Dai Z, Zhou SL, Fu XT, Zhao YM, Shi YH, Zhou J, Fan J (2013) Overexpression of HnRNP A1 promotes tumor invasion through regulating CD44v6 and indicates poor prognosis for hepatocellular carcinoma. Int J Cancer 132:1080–1089

Zhu P, Lv J, Yang Z, Guo L, Zhang L, Li M, Han W, Chen X, Zhuang H, Lu F (2014) Protocadherin 9 inhibits epithelial-mesenchymal transition and cell migration through activating GSK-3β in hepatocellular carcinoma. Biochem Biophys Res Commun 452:567–574

Ziober BL, Lin CS, Kramer RH (1996) Laminin-binding integrins in tumor progression and metastasis. Semin Cancer Biol 7:119–128

Zohar R, Suzuki N, Suzuki K, Arora P, Glogauer M, McCulloch CA, Sodek J (2000) Intracellular osteopontin is an integral component of the CD44-ERM complex involved in cell migration. J Cell Physiol 184:118–130

Mechanisms of Invasion and Metastasis: Cell Migration and Chemotaxis

181

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_181

Abstract

For the acquisition of active motility, cancer cells must undergo a shape change to acquire a polarized phenotype, similar to locomoting leukocytes. Polarity of motile cells is characterized by a leading front and a rear region. Polarity of normal and neoplastic cells depends on a distinct cortical actin skeleton and the generation of various cell junctions. Several cytoskeletal proteins promote polarity in normal and transformed cells, including Hugl-1, radixin, and claudin-1. Cell surface proteins interacting with other cells and matrix transmit signals to the machinery which generates polarity and motility. The motile response of polarized tumor cells is associated with the biogenesis of several types of cell projections, including blebs, pseudopods, lamellipodia, filopodia, and cytonemes. The function of these projections in cell migration critically depends on a complex cytoskeletal machinery. The expression of polarity- and motility-associated proteins in normal and neoplastic cells is subject to epigenetic modifications, specifically to numerous types of microRNAs. Motility and migration are induced by two basic forms of chemical stimulation, i.e., chemokinesis (induced random motility) and chemotaxis (induced directed motility). Several chemokinetic and chemotactic factors have been identified in cancers.

Tumor Cell Polarity: A Prerequisite for Cell Motility and Migration

Introduction

A critical prerequisite for motility-associated shape change is the establishment of a polarized phenotype of cells, characterized by a leading front and a rear region, the latter being devoid of lamellipodia or other cell projections (Keller and Zimmermann 1986; Zimmermann and Keller 1987; Zimmermann et al. 1988; Keller et al. 1991). On the other hand, loss of apicobasal polarity often results in a malignant phenotype in epithelial cells (McCaffrey and Macara 2011), suggesting that distinct types of cell polarity and shape change are required for a motile phenotype. In fact, a severely deranged control of cell polarity is an important feature of epithelial cancers (Halaoui and McCaffey, 2014). Cell polarity depends on an intricate interaction between cell surface molecules and the submembrane actin-containing cytoskeleton, and the microtubular apparatus, components that are critical for the establishment of shape change (Akhshi et al. 2014).

Polarity Proteins

Polarity of epithelial cells depends on a distinct cortical actin cytoskeleton and the development of various cell junctions. The generation and maintenance of a cortical actin network are regulated by spectrins which in turn are regulated by the tumor suppressor protein, Scribble (Elsum et al. 2012; de Vreede et al. 2014; Boeda and Etienne-Manneville 2015). Several proteins promote polarity in normal and transformed epithelial cells, whereby a central role is played by proteins that construct tight junctions (reviews: Kojima et al. 2009; Mariano et al. 2011). Claudins, which are critically important for the maintenance of tight junctions, are overexpressed in several types of cancers (review: Kominsky 2006). Tight junction proteins that strongly affect changes in polarity are the MARVEL proteins (MAL and related proteins for vesicle trafficking and membrane link), specifically tricellulin, occludin, and marvelD3 (Raleigh et al. 2010). A specifically important group of polarity-promoting protein is formed by the conserved PAR (partitioning-defective) proteins that function by generating cortical domains involved in dynamic asymmetries of cells (review: Nance and Zallen 2011). Human ASIP or PAR3 is a cell polarity protein with several isoforms that differ in their functions (Mishima et al. 2002; Hu et al. 2005). ASIP/PAR3/Bazooka is PDZ motif-containing proteins that localize asymmetrically at the cell periphery and mediate polarity and asymmetrical cell division (Fang and Xu 2001). ASIP/PAR3

directly associates with junctional adhesion molecule (JAM) (Ebnet et al. 2001) and promotes epithelial tight junction formation (Hirose et al. 2002). A second PAR protein operating in cell polarity is PAR6, which directly interacts with the morphogen CRB3, a human homologue of the apical transmembrane protein Crumbs (Lemmers et al. 2004). The Crumbs complex affects cell polarity through its regulation of cell junction formation (Médina et al. 2002). Crumbs proteins also interact with Scribble, a scaffold protein involved in cell polarity (Leong et al. 2009). In various epithelial cell types and their neoplastic offspring, Hugl proteins (the human homologues of *Drosophila* lethal giant larva proteins) play a significant role in the establishment of cell polarity. The Hugl-2 polarity protein in part acts via its induction of mesenchymal-epithelial transition (Kashyap et al. 2013). In epithelial cells, induction of polarity is associated with ROCK (Rho-associated kinase)-dependent apical constriction, a process regulated by two proteins, the polarity-regulated protein PAR3 and a FERM domain protein, Willin (Ishiuchi and Takeichi 2011). Willin is a novel 4.1 ezrin, radixin, and moesin (FERM)-containing protein (Gunn-Moore et al. 2005) which activates the Hippo signaling pathway kinases (Angus et al. 2012).

Polarity Changes in Hepatocytes and Invading Liver Carcinoma Cells

Acquisition of polarity changes in HCC cells is expected to involve mechanisms that also play a role in the cells of origin, i.e., hepatocytes and their progenitor cells. Hepatocytes arranged in hepatic cell plates possess a distinct apicobasal polarity which is crucial for their functional embedding between a sinusoidal compartment and the lumen of the canaliculus, which forms a gate to the outer world. The complex metabolic and transport functions of hepatocytes critically depend on this polarity, which is regulated by a distinct set of mechanisms (Hua et al. 2012; Müsch 2014). Apicobasal polarity of parenchymal cells also controls lymphocyte adhesion to hepatocytes and thus affects local immune responses (Reglero-Real et al. 2014) and influences the lateral diffusion of the CD81 HCV receptor (Harris et al. 2013). In normal hepatocytes, radixin, a member of the ezrin-radixin-moesin system that cross-links plasma membrane and the actin cytoskeleton, is required for the maintenance of an apical domain and hence apicobasal polarity (Kojima et al. 2003; Wang et al. 2006). Phosphorylated radixin is mainly localized to the basolateral membrane of liver cells (Suda et al. 2011), thus generating a polarization signal. Radixin phosphorylation also regulates the polarized cellular distribution of the multidrug resistance-associated protein 1/Mrp-1 (Suda et al. 2014). Hepatocyte polarization is linked to cytokinesis, in that polarity proteins are delivered to the site of cell division in a strict order. Daughter cells remain attached for a while through a disk-shaped structure which is a site for targeted exocytosis, the primitive canalicular domain. Oriented or asymmetric cell division will occur at the midpoint of this domain (Slim et al. 2014; Wang et al. 2014). Polarization and repolarization of hepatocytes requires recycling of intracellular constituents and organelles, in particular mitochondria, a process regulated by autophagy (Fu et al. 2013).

It is expected that HCC cells lose this mode of polarity when becoming motile cells, whereas HCC cells that form acinar/pseudoglandular structures resume apicobasal polarity and an apical canaliculus-like domain. The polarity mode of HCC cells is influenced by the expression of several surface proteins, in particular adherens junction and desmosome proteins (Cao et al. 2007). Generally, adherens junctions, tight junctions, and their associated proteins experience a marked redistribution in HCC (Cao et al. 2007). Claudin-1, acting through c-Abl protein kinase Cdelta, is involved in the acquisition of an invasive phenotype in liver cells (Yoon et al. 2010). Downregulation of claudin-10 in HCCs is associated with prolonged survival after surgery, while suppression of this claudin in HCC cells inhibits invasion (Ip et al. 2007). In cholangiocarcinoma, overexpression of claudin-4 is an early alteration and is associated with increased cell migration (Bunthot et al. 2012). PAR3, which plays a role

in normal cell polarity induction, is overexpressed in part of HCC, associated with an invasive phenotype and distant metastases (Jan et al. 2013). Cancer cell polarity is determined by apical proteins that determine polarity, including the Crumb homologue CRB3 (Li et al. 2015a; Mao et al. 2015). Hugl-1, the human homologue of the *Drosophila* lethal giant larvae, is a protein involved in the generation of cell polarity. Aberrant splicing of Hugl-1 in HCCs is associated with disease progression, truncated proteins promoting migration through polarity induction (Lu et al. 2009). LRRC1/LANO, a putative cell polarity regulator, is aberrantly upregulated in part of HCCs and confers a transformed phenotype associated with progression (Li et al. 2013). Planar cell polarity is stimulated by the collagen triple helix repeat containing-1/CTHRC1, a secreted glycoprotein which is overexpressed in HCCs and promotes an invasive phenotype (Chen et al. 2013c). In the signaling pathways affecting polarity and migration of cancer cells, altered functions of protein kinase C play a significant role (Keller et al. 1989; Zimmermann and Keller 1992, 1993; Niggli et al. 1996). The expression of polarity-associated proteins in cancer cells is regulated by microRNAs. In HCC, microRNA-296 controls cell motility by transcriptionally repressing the cell polarity-cell plasticity module, Scribble. Loss of this MiR in HCC causes aberrantly increased and mislocalized Scribble resulting in exaggerated random cell locomotion (Vaira et al. 2012).

Tumor Cell Motility and Migration: Role of Cell Protrusions

Introduction

Tumor cell motility, required for locomotion and migration, is a crucial step in cancer cell invasion. By use of their locomotion machinery, individualized cancer cells having lost their connections with neighboring cells and adhered to substratum can move in response to chemokinetic signals and chemotactic gradients (review: Bradbury et al. 2012). Chemokinesis denotes the phenomenon that normal or tumor cells are motile in a random manner in response to chemical stimuli. In contrast, chemotaxis is defined as a process whereby cells undergo a directional, nonrandom movement in response to chemical stimuli, the chemotactic factors. Positive chemotaxis is a movement toward the source of stimulus and negative chemotaxis a movement away from the stimulus. Initiation of cell motility and active locomotion/migration depends on marked changes in the cytoskeleton, shape change, determination of a front vs. a rear end, and the generation of specialized cell protrusions at the leading edge. These protrusions are blebs, pseudopods, lamellipodia, and filopodia. All these protrusions and their dynamics are regulated by the entire set of cytoskeletal protein networks summarized under the term cytoskeletome (Hall 2009; Klemke et al. 2013). Pseudopodal cell surface specializations play a central role in chemotaxis, chemokinesis, random or directed migration, and extracellular signaling (Insall 2013). A critical role in the initiation of locomotion is the definition a leading edge, which in turn depends on cell polarization and on cellular motility motors. In principle, two motors can drive the leading edge, i.e., actin polymerization and myosin-driven contraction of the cell cortex followed by formation of blebs and various types of pseudopods (Tyson et al. 2014).

Blebs

Blebs are cellular protrusions that are instrumental for cell motility and locomotion, in development, inflammatory reactions, and cancer. Blebs have a significant role in cell migration. The current view is that blebs are driven by hydrostatic pressure generated in the cytoplasm by a contractile action of the actin-myosin cortex of the cell (Paluch and Raz 2013).

Pseudopods

In general, pseudopods (pseudopodia, "false feet") are phylogenetically ancient, transient

protrusions of cells that confer an amoeboid shape. Pseudopods and their variants are crucial structures for motility and locomotion and engulfment of objects that will be phagocytosed. Depending on their shape and the species in which they develop, pseudopods are divided into filopodia and variants thereof, lobopodia, reticulopodia (reticulose pseudopods), and axopodia. Pseudopodial cell protrusions depend on the function of the cytoskeleton and involve the reversible assembly of F-actin subunits and generation of a microtubular network, cytoskeletal machines which in turn depend on a complex regulatory proteome which is altered in cancer cells. Morphogenesis of the various variants of pseudopods starts with the formation of a lamellipodium (see below), whereby the cell projects a membrane bud which is equipped inside with actin filaments forming the leading edge. Into this bud, cytoplasm flows creating the pseudopod. Lamellipodia not only are formed by eukaryotic cells engaged in phagocytosis but are also a feature of locomoting cancer cells.

Lamellipodia

Lamellipodia are flat, sheetlike cellular protrusions centrally involved in cell motility and locomotion. In principle, lamellipodia are an early phase of pseudopod formation. At the base of lamellipodia, unbranched and long F-actin filaments stream into the protrusion, progressing into a complex laterally branched actin network ending at the leading edge of the lamellipodium (Yamaguchi and Condeelis 2007; Bisi et al. 2013; Zimmermann and Falcke 2014). Initiation and orientation of lamellipodia is directed by F-actin bundles via an adhesion-based signaling pathway (Johnson et al. 2015). In their function as motility-promoting structures, lamellipodia adhere to the substratum and the ECM via adhesins, in particular integrins and cadherins. The actin dynamics characterizing lamellipodial turnover depends on cofilin and swiprosin-1, an actin-bundling protein (Kwon et al. 2013). Swiprosin-1 regulates F-actin accessibility to cofilin (Huh et al. 2013). Swiprosin-1 and swiprosin-2 are two homologous calcium-binding adaptor proteins (Dütting et al. 2011). Pseudopodia-induced motility of cancer cells also depends on an actin-binding adaptor protein, alpha-parvin, which is a constituent of pseudopodia/lamellipodia and promotes cancer cell locomotion and metastasis (Ito et al. 2014). The biogenesis of lamellipodia and other forms of cell protrusions is regulated by the Rho GTPases Rac1 and RhoA which are indispensable for protrusion generation and interactions with the extracellular matrix.

In lamellipodia, distinct sets of other regulatory proteins are accumulated, whereby the Arp2/Arp3 complex has a central role. This complex is a seven-subunit protein that operates in the initiation of actin assembly and the generation of actin network treadmilling (Koestler et al. 2013) and is a complex that steers cell migration (Dang et al. 2013). Arp273 itself is controlled by several associated proteins, including N-WASP, Scar/WAVE complexes, and Ena/VASP proteins. Ena/VASP motility-associated proteins are mainly located at the leading edge, where they are involved in the assembly of the actin cytoskeleton. Lamellipodial protrusions are tightly regulated by Ena/VASP proteins, which in turn bind to a distinct ligand, lamellipodin. Lamellipodin is a protein involved in actin polymerization and Ras signaling (Chang et al. 2013). Both lamellipodin and Ena/VASP localize to the tips of lamellipodia and filopodia, but lamellipodin also localizes to dorsal surface ruffles (Michael et al. 2010) and may interact with other actin-associated proteins (Krause et al. 2004). In the lamellipodial edge/tip, lamellipodin interacts with profilin 1, where it binds Ena/VASP and regulates lamellipodin distribution and accumulation (Bae et al. 2010). Lamellipodin cooperates with endophilin and Mena to regulate F-actin-dependent endocytotic processes (Vehlow et al. 2013). Endophilin is an N-BAR protein involved in membrane bending and interacting with plectin (Gallop et al. 2006; Mim et al. 2012; Vannier et al. 2013). In addition, lamellipodin directly binds active Rac, which regulates an interaction between lamellipodin and the Scar/WAVE complex involved in cell migration (Law et al. 2013). Actin turnover in lamellipodia is mediated cofilin, which has a role in breaking

down F-actin and controlling filament turnover (Vitriol et al. 2013). In cancer cells, a distinct kinase interactome regulates lamellipodia and migration, involving activation of myotonic dystrophy kinase-related Cdc42-binding kinase alpha/MRCKalpha by 3-phosphoinositide-dependent kinase 1/PDK1 (Gagliardi et al. 2014). Similar to invadopodia, lamellipodia express certain MMPs. In contrast to invadopodia, lamellipodia display a close association between membrane type 1-MMP (MT1-MMP) and TIMP-2, this co-localization affecting the regulation of MMP activity. The expression of MT1-MMP is associated with the adhesion molecule, CD44, which directly binds to MT1-MMP and promotes its proteolytic activity. While the protrusion of the lamellipodium requires the continuous growth of F-actin filaments toward the leading edge of the cell, microtubules are not essential for lamellipodium formation. However, microtubules are important components for tail retraction (rear retraction) in the setting of a moving/locomoting cell (Ballestrem et al. 2000; Wehrle-Haller and Imhof 2003).

Filopodia

In contrast to lamellipodia, filopodia (also termed microspikes) are rodlike, finger-shaped protrusions that mainly consist of a tight bundle of F-actin filaments (reviews: Faix and Rottner 2006; Gupton and Gertler 2007; Mattila and Lappalainen 2008; Faix et al. 2009; Arjonen et al. 2011; Boer et al. 2015). Filopodia form focal adhesions with the substratum, linking matrix proteins to the cell surface. Filopodia formation depends on non-branched processive actin assembly, in contrast to lamellipodia, and is promoted by the actin-bundling protein, fascin-1, a protein expressed in many malignant neoplasms and involved in migration and invasion (Vignjevic et al. 2006; Tan et al. 2013), fimbrin, and Ena/VASP (Barzik et al. 2014). The actin turnover in filopodia is also critically regulated by the actin-regulatory formin Daam1 (Hoffmann et al. 2014). A strong promoter of filopodia formation is the integrin-binding myosin-X, a protein with a FERM domain and a specific domain binding microtubules. Through the action of myosin-X, integrins are transported to the tips of filopodia. Via this mechanism, filopodia are engaged in integrin-mediated adhesion processes (Arjonen et al. 2011). The actin assembly process depends on the activation of the Rho system of small GTPases, in particular Cdc42 and their downstream effectors. The small GTPase RalA targets filamin, an actin cross-linking protein essential for filopodia genesis (Ohta et al. 1999). The direct regulator of actin polymerization and bundling, Mena (mammalian enabled), is a factor that induces both lamellipodia and filopodia (Lin et al. 2014). Filopodial biogenesis is also regulated by N-WASP, a profiling-binding protein involved in filopodia extension, its actin-depolymerizing activity, and by diaphanous formin and Ena/VASP proteins. The filamin-mediated promotion of filopodia is controlled by a factor that suppresses leading edge protrusion and promotes cell retraction, FilGAP/filamin A-binding Rho GTPase-activating protein (Ohta et al. 2006). Filopodia formation is also induced by the active formins (Mellor 2010), including mDia2/Drf3, which is also involved in biogenesis of lamellipodia.

Filopodia mainly serve as sensor organelles that monitor chemotactic and chemokinetic signals and transfer this sensed information to the motility-active cytoskeletal apparatus. In this sense, filopodia are "antennas" that guide the cells along their migration tract, also in invading cancer cells. Filopodia and their adhesion-promoting features are proinvasive structures in HCC. The filopodial component Mena induces migration and cell spread in HCCs (Lin et al. 2014).

Cytonemes: Spatiotemporal Information Transfer Structures and Pacemakers of Morphogen Gradients

Cytonemes ("cell threads") are a specialized class of highly adhesive, close-ended secretory filopodia and present as ultra-long and thin cell

projections. Typically, cytonemes are around 80 μm in length. Cytonemes are produced by several cell types, including neutrophils (Galkina et al. 2013, 2015) and cancer cells. Cargo located in filopodia such as myosin-X and beta-arrestin is transported into cytonemes, indicating the close relationship between filopodia and cytonemes. These structures serve as a communication system between cells and as a mechanism for spatiotemporal regulations. As cytonemes mediate complex signaling transfers among cells, they were compared to synaptic intercellular connections (Kornberg and Roy 2014; Roy and Kornberg 2015). The paracrine signaling accomplished by cytonemes plays a role in ontogenetic patterning, maintenance of tissue homeostasis, and the generation of morphogenetic fields. Cytonemes disperse morphogen signaling agents across developmental fields (Rogers and Schier 2011; Fairchild and Barna 2014; Kornberg 2014a). An important factor that affects ontogenic and morphogenic signaling is Hedgehog. Hedgehog signaling is known to employ distinct cellular structures for its spatiotemporal distribution. This signaling proceeds from the cilium to the nucleus (Goetz et al. 2009; Nozawa et al. 2013; Kornberg 2014b) and can also use cytonemes as a transport facility (Kornberg 2014b). It might be anticipated that morphogen gradients mediated by cytonemes also operate in neoplasms which mimic ontogenetic processes in a highly aberrant form. The formation of cytonemes is promoted by expression of the stem cell markers Lgr4 and Lgr5 via stabilization of nascent filopodia from an underlying lamellipodia-like network (Snyder et al. 2015).

Membranous Nanotube Connections (Tunneling Nanotubes)

In contrast to close-ended cytonemes as filopodial specializations, certain cells can produce open-ended conduits or cytoplasmic bridges that serve for the transfer of cytoplasmic material and organelles among cells. Such actin-based structures are termed membranous nanotube connections or tunneling nanotubes/TNTs (Gallagher and Benfey 2005; Rustom 2009; Lim and Tang 2012; Austefjord et al. 2014). Phylogenetically, TNTs are closely related to plasmodesmata of plants (Lee 2014). TNTs are generated between normal cells and among tumor cells. Of specific importance are TNTs produced between stem cells, including mesenchymal stem cells, and normal or neoplastic cells (Valente et al. 2015), because this pathway can serve to transmit stem cell information to post-progenitor cells. Intact mitochondria that are transported via TNTs from one cell to the other can restore mitochondrial injury/function failure or transfer normal or altered mitochondrial DNA and affect via this mechanism the biology of target cells (Wang and Gerdes 2015). Restoration of mitochondrial function through TNT-mediated organelle transfer is also accomplished by mesenchymal cells which possess a "native" mitochondrial complement (Las and Shirihai 2014). The transfer of mitochondria through TNTs is mediated by the mitochondrial Rho GTPase, Miro1 (Ahmad et al. 2014; Las and Shirihai 2014). Through TNTs, malignant neoplasms can perform intercellular communication by exchanging organelles and cytoplasmic matter (Lou et al. 2012; Ady et al. 2014). Via TNTs, cancer cells can exchange information with stromal cells, resulting in a complex tumor-stromal cross talk (Thayanithy et al. 2014). This mechanism can affect pathways to invasion and spread.

Tumor Cell Motility and Migration: Shape Change and Motility of Normal and Cancer Cells Are Mediated by Cytoskeletal Proteins (the Cytoskeletome) and Proteins Mediating Cell Surface-Cytoskeleton Connections

Introduction

Motility of normal cells and cancer cells critically depends on shape change, cell polarity, adhesion, and cell motors, which in turn are linked to a functional cytoskeleton and cytoskeleton-cell membrane connections (Wells 2006; Bozzuto et al. 2010). Similar to muscle cells, contractile

force in locomoting cells is provided by the actin-myosin system, a dynamic multiprotein machine that undergoes dramatic changes in cancer cells (Cramer 1999). Cell shape and its changes are also determined by the microtubule component of the cytoskeleton and a connectome linking the cell membrane with the nucleus and various organelles. The position of the nucleus within the cell is critical for polarity changes and the induction of motility. In cancer cells, highly abnormal nuclei with aberrant shapes and massively altered connections with the cytoskeleton markedly affect shape change, polarity, and cell motility. In extreme cases, a polyploid and abnormally shaped nucleus can cause complete failure of a tumor cell to locomote.

Actin Cytoskeleton Formation

Shape change and the acquisition of a motile phenotype critically depend on the generation of a contractile branched actin network, which in its biogenesis and turnover depends on numerous actin-associated factors which control actin monomer polymerization, F-actin stability, microfilament bundling, and the connection of the actin network with other components of the cytoskeleton, the cell membrane, and cell junctions (review: Gross 2013). Assembly and turnover of the actin skeleton is regulated by Rho effectors, i.e., several GTP-Rho-binding proteins (Narumiya et al. 1997), linking the actin machinery with the GTPase signalosome.

The generation of an F-actin cytoskeleton machine depends on numerous actin-binding proteins which promote nucleation and synthesis of F-actin and also regulate capping, severing, shortening, and degradation of F-actin to actin monomers. Important nucleators of actin formation that are altered in liver cancers are members of the formin family, formins being involved in the assembly of cytoskeletal components at cortical sites of the cell (Tanaka 2000). Together with WASP family members, formin coordinates the regulation of cell protrusions in cancer cells (Sarmiento et al. 2008). Formin is operational in cell migration and tumor cell invasion through its promotion of a motile cytoskeletal phenotype. Formin activity is suppressed by the metastasis suppressor, microRNA-335, which is a master regulator of tumor cell migration (Lynch et al. 2013). A formin upregulated in EMT, FHOD1, is expressed at the leading edge of locomoting cells and participates in the cytoskeletal changes occurring in migrating cancer cells (Gardberg et al. 2013). In their function as proteins promoting shape change and an amoeboid motility, formin-related proteins are active in these processes, including members of the diaphanous-related formin family. In normal and tumor cells, the actin-based cytoskeleton is also modulated by the microfilament regulatory protein, Mena, which affects EGF-elicited motility and invasion (Gertler and Condeelis 2011). In particular, the Mena invasive/MenaINV isoform promotes streaming motility and facilitates transendothelial migration. An important F-actin-binding protein that positively affects cell motility is coronin-1C, a member of the coronin family having seven coronin isoforms. Coronin-1 exerts a inhibitory effect on F-actin formation, while coronin-1B is required for cell protrusion formation and cell migration. Coronins also interact with microtubules and are involved in phagocytosis. A group of actin-binding proteins is involved in F-actin severing, including villin, gelsolin, and severin. Gelsolin is a major protein operating in actin filament assembly and disassembly. It is the most potent member of the actin-severing gelsolin-villin superfamily of proteins and is located in the cytoplasm and mitochondria. An important actin-severing protein is villin, a protein which contains multiple gelsolin-like domains and is involved in nucleation, bundling, capping, and severing of actin filaments. The six-repeat part of villin is responsible for calcium-dependent actin severing, whereas the villin headpiece is involved in calcium-independent actin cross-linking and bundling. Another actin-binding protein involved in tumor biology is cortactin. Cortactin can activate cortical actin nucleation and polymerization via its participation in the Arp2/Arp3 complex (Weed and Parsons 2001). Cortactin can also indirectly promote Arp2/Arp3 complex-mediated actin

polymerization by binding to N-WASP. Cortactin is not critically involved in lamellipodium formation, but is an essential molecule for biogenesis of podosomes and invadosomes (Yamaguchi and Condeelis 2007). Other actin-binding proteins which affect motility comprise Spire (a WH2 domain-containing actin nucleator; Baum and Kunda 2005; Chen et al. 2012).

Abnormal Expression and Function of Actin-Binding and Actin-Associated Proteins in Liver Cancer

An important regulator of cancer cell motility and invasion is cofilin, a protein that binds both monomeric and filamentous actin and which is involved in actin turnover through its actin-severing capacity. Cofilin activity depends on its phosphorylation status mediated by LIM kinases in a growth factor-dependent manner. Specifically, cofilin and actin-depolymerizing factor/ADF are inactivated in HCC cells by LIM kinase-1-mediated phosphorylation and reactivated by dephosphorylation by Slingshot-1 and Slingshot-2 protein phosphatases (Bernard 2007; Horita et al. 2008). Activated cofilin participates in the induction of lamellipodia and its overexpression augments tumor cell motility. Cofilin is markedly overexpressed in highly invasive cancers (review: Yamaguchi and Condeelis 2007). Alpha-actinin, which plays an important role in actin turnover, shows high expression levels in HCC cells (Nishiyama et al. 1990). The structure and function of the cytoskeleton is influenced by giant proteins that play an important role in myofibrillogenesis, the obscurins, proteins that modulate cytoskeletal function and intercellular adhesion proteins via their kinase domains (Hu et al. 2013; Perry et al 2013; Ackerman et al. 2014). Obscurin expression prevents EMT, while loss of obscurin activity promotes EMT and an invasive phenotype (Shriver et al. 2014). Downregulation of formin-like 2 is associated with poor prognosis in HCC, because this protein is an inhibitor of cell motility (Liang et al. 2011). Similarly, downregulation of DIAPH3/diaphanous-related formin-3, a noncanonical regulator of metastasis in several cancers located on chromosome 13q, results in tumor aggressiveness and a metastatic phenotype (Hager et al. 2012). Mena increases the activity of RhoA, induces HCC cell motility, and favors metastasis (Lin et al. 2014). Mena deficiency delays tumor progression and decreases metastasis in experimental neoplasms (Roussos et al. 2010). In HCC cells, coronin-1C is overexpressed and favors a motility phenotype, a response correlated with Rac1 activation (Wu et al. 2010; Wang et al. 2013a). Another actin-binding protein involved in regulation of tumor cell invasion is cortactin. Cortactin (the EMS 1 oncogene) has a central place in the actin cytoskeleton, is a Src kinase substrate, and is upregulated in many types of cancers as a result of amplification of chromosome locus 11q13 (Weaver 2008; Kirkbride et al. 2011; MacGrath and Koleske 2012). Cortactin phosphorylated by ERK1/ERK2 is recruited to sites of dynamic actin regulation and is required for carcinoma lamellipodia persistence (Kelley et al. 2010). Part of HCCs show amplification of the cortactin-encoding EMS 1 oncogene (Yuan et al. 2003). In HCC, overexpression of cortactin is correlated with a highly invasive phenotype showing marked vascular invasion and metastasis (Huang et al. 2012; Gang et al. 2013; Zhao et al. 2013). Upregulation of cortactin in HCC is associated with enhanced tumor cell motility (Chuma et al. 2004). Expression of the MPZL1 gene at 1q24.1–24.2 promotes HCC cell migration through Src-mediated phosphorylation of cortactin (Jia et al. 2014; Yeh et al. 2014). The actin-bundling protein, fascin-1, is overexpressed in part of HCCs, associated with downregulation of E-cadherin, dramatically increased tumor cell migration, and poor prognosis (Iguchi et al. 2009; Hayashi et al. 2011; Huang et al. 2012). Among F-actin-severing proteins, villin 1 is expressed in subsets of HCCs, and its expression is correlated with invasion (in particular vascular invasion) and tumor recurrence (Xieraili et al. 2012). Another actin filament-disassembling protein, gelsolin, is overexpressed in HCCs (Megger et al. 2013). In HCC cells, gelsolin binds to p53 protein and promotes the inhibition of p53-induced apoptosis by anchoring p53 in the cytoplasm (An et al. 2011).

In HCC cell lines, the isoforms of gelsolin differ from those of normal cells (Yin et al. 1984). Gelsolin also plays a role in lymphatic metastasis of HCC (Qazi et al. 2011). Secretory gelsolin is highly overexpressed in metastases of colorectal carcinoma (Tsai et al. 2012).

Cytoskeleton and WASP

A central role in organization and reassembly of the actin-based cytoskeleton is played by the Wiskott-Aldrich syndrome protein (WASP) and WASP family verprolin-homologous protein (WAVE) family (reviews: Miki and Takenawa 2003; Kurisu and Takenawa 2009; Helgeson et al. 2014). The WAVE regulatory complex (WRC) regulates cell motility by its capability to promote actin polymerization. The WRC controls actin fibrillogenesis in cooperation with Ena/VASP proteins, this system stimulating Arp2/Arp3 complex-mediated actin assembly (Chen et al. 2014). By its effects on cytoskeleton organization and remodeling, WASP-WAVE systems affects numerous basic cellular mechanisms, including shape change, adhesion, cell positioning, and cell motility. The action of WASP on the actin cytoskeleton is modified by certain WASP-interacting proteins of the verprolin family of proteins, i.e., WIP (WASP-/N-WASP-interacting protein), CR16 (corticoid regulated), and WIRE (Wlp related). WIRE can induce filopodia in cooperation with insulin receptor substrate/IRSp53 (Misra et al. 2010). N-WASP (neural Wiskott-Aldrich syndrome protein), which mediates motility and invasion of cancer cells, is highly expressed in HCCs and its expression is associated with poor prognosis (Jin et al. 2013). N-WASP promotes processive acceleration of actin barbed end assembly (Khanduja and Kuhn 2014). The WAVE2 protein is significantly enhanced in HCC, correlated with tumor multiplicity and an invasive phenotype (Yang et al. 2006). Overexpression of WAVE3 is correlated with increased invasiveness in HCCs (Ji et al. 2015).

Tumor Cell Motility and Migration: Cell Adhesion Mechanisms

Focal Adhesion Proteins as Mediators of Cell Motility and Migration

Several molecules localized to focal adhesions/FAs are critically involved in cell motility via their linking of FA with the cytoskeleton. FAs are situated at the convergence of integrin-mediated adhesion, various signaling pathways, and the actin cytoskeleton (Webb et al. 2003; Wozniak et al. 2004). These proteins mainly include paxillin, vinculin, talin, and actopaxin. A paxillin homologue expressed in FA of fibroblasts is Hic-5, associated with FA kinase and involved in the regulation of growth (Ishino et al. 2000). Paxillin is a focal adhesion adaptor that plays an important role in the connections between cell adhesion and actin cytoskeleton remodeling. Phosphorylation of paxillin required for cell migration is accomplished by c-Jun N-terminal kinase/JNK1 which is an enzyme essential for cell motility (Huang et al. 2003, 2004).

Paxillin positively affects the invasive and metastatic ability of HCC through its promotion of cell locomotion (Li et al. 2005). The differential expression of paxillin and related proteins in tumor FA is regulated by various factors, which are not yet well known. However, the Rho GTPases Rac1 and RhoA control the expression of the two FA components, paxillin and vinculin (Deakin et al. 2012). Hepatocyte growth factor-induced ERK-paxillin signaling in HCC cells is mediated by protein kinase C via phosphorylation of ERK/paxillin (Hu et al. 2013). Paxillin gene mutations do not to play a significant role (Kim et al. 2011). Similarly, altered expressions of the FA protein talin-1 in HCC is associated with an invasive phenotype and aggressive course (Kanamori et al. 2011). Talin-1 expression in HCC is usually lower than that of normal liver (Zhang et al. 2011), and high levels of talin-1 in HCCs were correlated with reduced migration and invasion (Fang et al. 2014). Actopaxin, a member of the focal adhesion proteins, regulates cell locomotion and migration, is frequently overexpressed in HCC, and plays a

role in invasion and metastasis (Ng et al. 2013). In HCC, agrin with its oncogenic role is an important regulator of focal adhesion integrity (Chakraborty et al. 2015).

Integrins, Integrin-Cytoskeleton Linkers, and Integrin-Linked Kinase

As outlined above, integrins are crucial mediators of cell-matrix adhesion and of connections between adhesive cell surfaces and the underlying actin cytoskeleton. Via this configuration, integrin receptors generate a functional bridge between cytoskeleton and the ECM and are thus critical operators for cell locomotion on matrix substrata.

A novel type of adhesion complexes is involved in adhesion of cells to the ECM in an integrin-dependent manner. These complexes (IPP complexes) consist of integrin-linked kinase (ILK), PINCH, and parvin (review: Sepulveda et al. 2005). Integrin-linked kinase/ILK is a central component of cell-matrix adhesions and a key regulator of integrin functions, including those involved in tumor cell migration. ILK interacts with the cytoplasmic domains of integrin beta and beta3 subunits. The ILK kinase domain is required for focal adhesion maturation (Stanchi et al. 2009). ILK forms a ternary complex with two adaptor proteins, PINCH (particularly interesting cysteine- and histidine-rich protein) and parvin, resulting in the formation of an ILK-PINCH-parvin complex. This complex regulates the transmembrane integrin receptor-actin cytoskeleton linkage essential for cell motility (Legate et al. 2006; Qin and Wu 2012; Ghatak et al. 2013). PINCH-1 is a widely expressed focal adhesion protein capable to form complexes with ILK and CH-ILKBP/actopaxin/affixin/alpha-parvin (Wu 2004) and capable to modulate cell shape and cell motility (Fukuda et al. 2003). PINCH and its partner, the tumor suppressor Rsu-1 (Ras suppressor 1), regulate hepatic tumorigenesis and control liver size (Donthamsetty et al. 2013). Affixin (or beta-parvin) is a focal adhesion protein that binds paxillin (Stiegler et al. 2012) and interacts with alpha-actinin and mediates integrin signaling for reorganizing of F-actin (Yamaji et al. 2004). Alpha-parvin is the same as actopaxin and is a paxillin-binding protein required for cancer cell invasion and matrix degradation requiring Rac1 for its activity. In such complexes, ILK is activated by a protein binding to this kinase, the small LIM-only protein LIMD2, a protein that is overexpressed in metastatic cancers and promotes cell motility (Peng et al. 2014). The ILK-PINCH-parvin complex supports integrin alphaIIb beta3 activation (Honda et al. 2013).

Binding to alpha-parvin and localization to focal adhesions of ILK depend on its kinase domain (Fukuda et al. 2009). Due to its binding to ILK, PINCH is recruited to integrin-rich sites in spreading cells (Tu et al. 1999). ILK also binds to kindlin-2, a mechanism that regulates cell adhesion (Fukuda et al. 2014). ILK plays a significant role in tumor cell migration and invasion, through phosphorylation of several intracellular substrates, including protein kinase B (PKB/Akt), glycogen synthase kinase-3 of the Wnt pathway, and myosin light chain (Persad and Dedhar 2003). PINCH-1 enhances the motile features of cancer cells and is suppressed by PINCH-2 by paracrine activity (Park et al. 2014). ILK function is modulated by binding of LIMD2, a member of the LIM domain protein family characterized by shuttling between cytoplasm and nucleus and coupling changes of gene expression to extracellular cues. LIMD2 is overexpressed in metastatic cancers and positively regulates cancer cell motility (Peng et al. 2014). ILK is overexpressed in HCCs and is associated with motility and invasion in these tumors (Chan et al. 2011).

Small GTPase and GTP-Binding Protein Signaling in Tumor Cell Motility

Rho GTPases/Rho effector pathways play a crucial role in liver cancer progression due to their central functions in organizing the cytoskeleton, affecting shape change, and promoting cell motility in various cancers, including HCC (Narumiya et al. 1997; Grise et al. 2009; Wong et al. 2010). An immediate downstream effector of

Rho is Rho-associated kinase (ROCK), an enzyme which acts on cytoskeletal proteins, including MLC2 (myosin light chain2), and deregulated in various cancers. The small GTP-binding protein Rho stimulates the actin-myosin system, causing invasion of cancer cells, whereby Rho is stimulated by 1-oleoyl-lysophosphatidic acid (Yoshioka et al. 1998). Rho kinase 2 is frequently overexpressed in HCC, associated with enhanced tumor cell motility and invasiveness due to activation of cytoskeletal proteins, specifically MLC2 (Wong et al. 2009). MLC2 in turn is modulated by MR-1/myofibrillogenesis regulator 1 in hepatoma cells, enhancing tumor cell locomotion (Ren et al. 2008). ROCK plays a critical role in intrahepatic metastasis of HCC through stimulation of tumor cell migration (Genda et al. 1999). An important member of the Rho GTPase-activating protein family is DLC1/deleted in liver cancer 1. This protein has suppressive activities in tumor development and metastasis. In HCC, DLC1 negatively regulates the Rho/ROCK/MLC pathway (Wong et al. 2008).

Distinct Growth Factors and Genes Acting as Promigration Factors

Hepatocyte Growth Factor and Its Receptor as a Motility and Promigration Factor

Hepatocyte growth factor (HGF) and its receptor c-Met form autocrine and paracrine loops to promote pro-motility cell shape change and migration (Xie et al. 2001). HGF and its receptor c-Met induce formation of lamellipodia, characterizing a polarized cell phenotype required for cell locomotion. Lamellipodia involving actin reassembly at the leading edge of motile cells are a very early step in cell migration. In lamellipodium formation, HGF induces the association between the constitutive complex of betaPIX and GIT1 with WAVE2, thereby facilitating HGF-induced WAVE2 transport required for lamellipodia (Morimura et al. 2009). Cell migration and invasion induced by c-Met is modulated by the Gab1-binding p21-activated kinase 4, Pak4. Interaction of Pak4 with Gab1 results in Gab1 phosphorylation which is essential for the activity of the Gab1 scaffold protein in reorganizing the cytoskeleton (Paliouras et al. 2009).

HGF expression is elevated in the majority of HCCs, and c-Met overexpression plays an important role in HCC cell motility and invasion (Schoedel et al. 2003). HGF as a ligand binds to its receptor, c-Met, which it phosphorylates within a few minutes following receptor binding, to rapidly decline afterward. c-Met receptor kinase-dependent stimulation of p42/p44 mitogen-activated protein kinases is critical for the proteinase-activated receptor-2 (PAR(2))-Met kinase-invasive signaling axis in HCCs (Kaufmann et al. 2009). Tumor cell migration is stimulated by hepatocyte growth factor (HGF) through phosphatidylinositol 3-kinase (Nakanishi et al. 1999). In HCCs, HGF is in part produced by stromal cells, in particular cancer-associated fibroblasts/CAFs (Jia et al. 2013). HBX, a protein of HB virus involved in hepatocarcinogenesis, promotes expression of c-Met by the extracellular signal-regulated kinase/ERK pathway (Xie et al. 2010). c-Met expression in HCC is positively correlated with expression of a protein critically involved in cell adhesion and migration, ezrin (Kang et al. 2010). MicroRNA-198 inhibits HCC cell migration through downregulation of the HGF/c-Met pathway (Tan et al. 2011), whereas microRNA-34a inhibits migration of HCC cells via downregulation of c-Met expression (Li et al. 2009). A similar effect is induced by microRNA-23b (Salvi et al. 2009). HGF-induced motility and invasion in HCC cells is inhibited by heparin, counteracting HGF-induced cell adhesion, and heparin also reduced HGF-induced activation of c-Met and MAP kinase (Ozen et al. 2012). In hilar cholangiocarcinoma, downregulation of Gab1 inhibited cell migration (Sang et al. 2013).

Other Genes and Proteins Promoting Shape Change and Motility in Liver Cancer Cells

Part of invasive features of liver cancers are reflected in chromosomal abnormalities and the

activity of oncogenes and tumor suppressors. A motile phenotype of HCC is induced by a protein encoded by a gene on chromosome 7q21–q22 involved in HCC, PFTAIRE protein kinase 1, a cell division cycle-2 related gene (Pang et al. 2007). A constitutive activation of ERBB3 (erythroblastic leukemia viral oncogene homologue 3)-dependent signaling through the neuregulin1/ERBB3 autocrine loop plays an important role in the regulation of HCC cell motility, migration, and invasion (Hsieh et al. 2011). Cell motility in HCCs is promoted by overexpression of a gene located to the interstitial chromosome 1q21–q22 region, frequently amplified in human cancers. The product is called GEF-H1, a guanine nucleotide exchange factor, and it probably acts through activation of RhoA signaling and modulation of EMT (Cheng et al. 2012). Notch signaling promotes HCC cell migration in conjunction to upregulation of MMPs. The Notch1/COX-2/Snail pathway involving EMT is associated with hypoxia-induced migration and invasion of HCC cells (Yu et al. 2013). Migration of embryonic liver cells and HCC cells is modulated by the homeobox protein, PROX1 (prospero-related homeobox 1). PROX1 directly binds to proximal promoter of the EMT mediator Twist1 gene to repress its transcription, and through this mechanism it reduces cell migration (Chang and Hung 2012). In cancer cells, PROX1 promotes an aggressive behavior through upregulating hypoxia-inducible factor alpha expression, with subsequent induction of EMT (Liu et al. 2013a). CPEB4 (cytoplasmic polyadenylation element-binding protein 4) is a potential tumor suppressor. Its downregulation by microRNA-550a facilitates HCC cell migration and invasion (Tian et al. 2012). Loss of Tg737 in HCCs is associated with cell migration and invasion in a hypoxia-dependent manner, partially through the polycystin-1, IL-8, and TGFbeta1 pathway (You et al. 2012). Tg737 is tumor suppressor gene that encodes a cilia-associated protein involved in the regulation of fetal hepatic progenitor cells and the biology of side population cells in HCCs (Song et al. 2010). As outlined elsewhere in more detail, ECM proteins markedly affect the invasive phenotype of cancer cells. Bone morphogenetic proteins exert a positive influence on HCC cell migration via activation of Smad which interacts with type XVI collagen of the ECM (Maegdefrau and Bosserhoff 2012). HCC cell migration is stimulated by ESM-1/endothelial cell-specific molecule-1, a secretory proteoglycan with a single dermatan sulfate residue. ESM-1 also induces cell cycle arrest by PTEN induction (Kang et al. 2011). Migration of HCC cells is strongly stimulated by Smad signaling activated by bone morphogenetic proteins (BMPs), a process inhibited by the BMP inhibitors chordin and noggin (Maegdefrau and Bosserhoff 2012).

In addition, invasion of HCC cells is stimulated by numerous factors that operate in highly diverse pathways, so that a common denominator of action cannot easily be recognized. HCC cell migration and invasion is suppressed by Dickkopf-1 (Dkk-1; Qin et al. 2007) and Dkk-4, a secreted protein that antagonizes the Wnt/beta-catenin signaling pathway, and is positively regulated by thyroid hormone/T3 acting on a thyroid hormone receptor expressed on tumor cells (Liao et al. 2011). Dkk-4 is downregulated in other gastrointestinal cancers, e.g., colorectal cancer (Baehs et al. 2009). HCC cell migration is stimulated by the glycoprotein stanniocalcin via activation of extracellular signal-regulated kinase 1/2 (ERK1/ERK2) (Wang et al. 2012). Ectopic expression of p16 protein in HCC increases cell migration in vitro and in vivo in a Cdc42-dependent manner, the stimulatory process requiring activity of the Cdc42 GTPase (Chen et al. 2013b). A direct transcriptional target of FOXM1 is tartrate-resistant acid phosphatase 5/ACP5, an enzyme important for osteoclastogenesis and bone resorption. HCC cell migration is induced by nuclear expression of the E3 ubiquitin ligase seven in absentia homologues (SIAH)-1 and (SIAH)-2, in part mediated by the transcription factor FBP-3 (Brauckhoff et al. 2011; Malz et al. 2012). SIAH family proteins are RING-domain proteins making part of ubiquitin ligase complexes that target proteins to proteasomes. SIAHs are involved in functional circuits of Ras, hypoxia-induced pathways, and DNA damage and are also active in a number of signaling pathways in cancer progression (Fang

et al. 2003; Lipkowitz and Weissman 2011). Part of HCC cells express proteinase-activated receptors (PARs), thrombin receptors of a G protein-coupled receptor subfamily. Stimulation of HCC cells with thrombin and PAR-selective peptide promotes migration of these cells (Kaufmann et al. 2007).

Regulation of Cell Motility and Migration by MicroRNAs

An increasing number of microRNAs (MiRs) affect tumor cell locomotion and migration in hepatocellular carcinoma, whereby most of these MiRs have a suppressive effect on tumor cell motility via diverse pathways (Table 1). These MiRs are potential targets of novel therapies.

MicroRNA-7 is reduced in HCC. This is an MiR which inhibits tumor cell migration and metastases via targeting phosphoinositide 3-kinase/Akt signaling pathways (Fang et al. 2012). MicroRNA-9 enhances migration of HCC cells through downregulation of the KLF17 protein expression. KLF17 is a transcription factor that directly acts on the promoter of EMT-associated genes, including ZO-1, vimentin, and fibronectin (Sun et al. 2013), and is downregulated in HCCs (Liu et al. 2013b). MicroRNA-10b, which is overexpressed in HCC, promotes migration of tumor cells through RhoC, uPAR, and metalloproteinases (Liao et al. 2014). This MiR also acts through CADM1 (Li et al. 2012). A second microRNA promoting HCC cell migration via CADM1 is microRNA-1246 (Sun et al. 2014). MicroRNA-17-5p is overexpressed in HCC. This MiR promotes tumor cell locomotion through the p38 mitogen-activated protein kinase-heat shock protein 27 pathway (Yang et al. 2010). MicroRNA-21 regulates migration and invasion of stem cell-like HCC cells via targeting PTEN, RECK, or PDCD4 protein translation (Zhou et al. 2013). STAT3 regulates migration of a stem cell-like subpopulation of HCC cells via microRNA-21 (Zhang et al. 2015a). MicroRNA-23b is a suppressor of HCC cell motility by down-modulation of c-Met and urokinase (Salvi et al. 2009). In HCCs, increased expression of microRNA-26a promotes migration by blocking EZH2 expression (Wang et al. 2015). MicroRNA-26a suppresses HCC cell migration and invasion of human HCC cells by targeting the IL-6-Stat3 pathway. By this pathway, protein levels of IL-6 inversely correlate with microRNA-26a in HCCs (Yang et al. 2013b). MicroRNA-30a, downregulated in HCC, is a suppressor of tumor cell motility and of EMT, through SNAI1 targeting (Liu et al. 2014a). MicroRNA-34a is low in HCCs and is a suppressor

Table 1 MicroRNAs affecting cell migration in hepatocellular carcinoma

MicroRNA (MiR)	Target	Effect[a]
MiR-7	PI3K/Akt signaling	Inhibition
MiR-9	KLF17	Inhibition
MiR-10b	RhoC, uPAR, MMPs, CADM2	Stimulation
MiR-17-5p	p38-MAPK signaling	Stimulation
MiR-21	PTEN, RECK	Inhibition
MiR-23b	c-Met	Inhibition
MiR-26a	EZH2	Stimulation
MiR-30a	SNAI1	Inhibition
MiR-34a	c-Met	Inhibition
MiR-100	Via lamellipodia	Inhibition
MiR-101-3p	Rab5a	Inhibition
MiR-124	ROCK2, EZH2	Inhibition
MiR-125b	Transcriptional activator	Inhibition
MiR-126	?	Inhibition
MiR-133a	MMP-9	Inhibition
MiR-135b	RECK, EVI5	Stimulation
MiR-139	c-Fos	Stimulation
MiR-141	Tiam1	Inhibition
MiR-142-3p	Rac1	Inhibition
MiR-150-5p	MMP-14	Inhibition
MiR-151	RhoGDIA	Stimulation
MiR-181a-5p	c-Met	Inhibition
MiR-193b	CCND1, ETS1	Inhibition
MiR-195	VEGF	Inhibition
MiR-197	KAI1	Inhibition
MiR-198	c-Met	Inhibition
MiR-206	MMP-9	Inhibition
MiR-224	Homeobox D10	Inhibition
MiR-362-5p	CYLD	Inhibition
MiR-424	c-Myb	Inhibition
MiR-433	cAMP response element-binding protein	Inhibition
MiR-525-3p	ZNF395	Stimulation

[a]*Inhibition* inhibition of migration, *stimulation* stimulation of migration

of cell migration by targeting c-Met (Li et al. 2009). Downregulation of microRNA-100 enhances migration and spread of HCC cells, because this MiR suppresses lamellipodium formation (Zhou et al. 2014). Downregulation of microRNA-101-3p by hepatitis B virus promotes migration of HCC cells by targeting Rab5a (Sheng et al. 2014). MicroRNA-124 is reduced in HCC. This MiR directly targets ROCK2 and EZH2 and inhibits EMT and cell migration (Zheng et al. 2012). MicroRNA-125b suppresses migration and invasion of HCC cells by targeting transcriptional coactivator with PDZ-binding motif (Li et al. 2015b). Ectopic expression of microRNA-126 suppresses HCC cell migration, invasion, and colony formation in vitro (Chen et al. 2013a). MicroRNA-133a inhibits tumor cell migration by targeting MMP-9 in HCC, but is downregulated in these neoplasms, favoring a motile phenotype (Chen et al. 2015). In HCC, microRNA-135b promotes tumor cell locomotion by regulating RECK (reversion-inducing cysteine-rich protein with Kazal motifs) and EVI5 (ecotropic viral integration site 5), enhancing cell motility (Li et al. 2015c). Downregulation of microRNA-139 causes depression of c-Fos, promoting cell migration in HCC (Fan et al. 2013). MicroRNA-141, downregulated in HCC, is a potent suppressor of HCC cell migration by targeting the T lymphoma invasion and metastasis 1/Tiam1 gene (Liu et al. 2014). MicroRNA-142-3p suppresses cell migration by targeting Rac1 (Wu et al. 2011). Migration of HCC cells is suppressed by microRNA-144 by targeting E2F transcription factor 3/E2F3 (Cao et al. 2014) and AKT3 (Ma et al. 2015). MicroRNA-150-5p is an inhibitor of HCC cell migration and invasion by targeting matrix metalloproteinase-14 (Li et al. 2014b). Tumor cell migration is facilitated by gain of microRNA-151 through targeting RhoGDIA (Ding et al. 2010). MicroRNA-181a-5p, which suppresses HCC cell motility by directly targeting c-Met, is downregulated in HCC (Korhan et al. 2014). HCCs exhibit decreased expression of microRNA-193b, an MiR that inhibits migration by targeting CCND1 and ETS1 (Xu et al. 2010). Micro RNA-195 abolishes HCC cell migration and proliferation by targeting the TNF-alpha/NF-kappaB pathway (Ding et al. 2013). This microRNA also suppresses angiogenesis and HCC metastasis by inhibiting the expression of VEGF and Cdc42 (Wang et al. 2013b). MicroRNA-197 is increased in HCC and promotes migration of cancer cells by targeting the anti-metastatic protein KAI1/CD82 (Dai et al. 2014). HCCs show downregulation of microRNA-198. This MiR inhibits tumor cell migration by targeting the c-Met pathway (Tan et al. 2011). MicroRNA-206 overexpression in HCC cells inhibits migration of tumor cells via downregulation of MMP-9 (Liu et al. 2014). MicroRNA-224 promotes cell migration and invasion of HCC cells by targeting homeobox D 10 gene involved in MMP-9 signaling (Li et al. 2014a). Further important targets of this MiR are Cdc42, Bcl-2, and MAPK1 (Zhang et al. 2013). MicroRNA-362-5p promotes tumor cell migration and metastasis by targeting CYLD in HCC (Ni et al. 2015). MicroRNA-424 is downregulated in HCC and suppresses cell migration through c-Myb (Yu et al. 2014). MicroRNA-433 inhibits HCC cell migration by repressing expression and function of cAMP response element-binding protein (Yang et al. 2013a). MicroRNA-525-3p enhances migration of HCC cells by targeting zinc finger protein 395/ZNF395 (Pang et al. 2014).

Linking the Signaling of Proliferation and Invasion: The Wnt/Beta-Catenin Signaling Pathway

The Wnt/beta-catenin signaling pathway plays a significant role for the regulation of growth, invasion, and metastasis in numerous cancers studied so far, including HCC (Lee et al. 2014). Beta-catenin expression with its transfer to the nucleus is associated with elevated proliferative activity and higher IL-8 protein levels in HCC cells (Lai et al. 2011). Overexpression of beta-catenin in HCC is enhanced and activated by hypoxia and promotes EMT and expression of MMP-2 (Liu et al. 2010). On the other hand, a subset of HCCs with expression of mutant nuclear beta-catenin was characterized by a noninvasive phenotype and absence of portal venous spread (Mao et al. 2001). In high-metastatic HCC cell lines, the Wnt/beta-catenin signaling pathway was

upregulated, associated with increased expression of c-Myc and cyclin D1, whereas Dickkopf-1/Dkk-1 and Nm23 were downregulated (Qin et al. 2007). However, HCCs with upregulated Dickkopf-1/Dkk-1 show increased cell invasion through Dkk-1 activity in the noncanonical Wnt pathway (Tao et al. 2013). The beta-catenin and mitogen-activated protein kinase pathways are activated by fibroblast growth factor 19 (FGF19), which by this signaling pathway promotes HCC recurrence and a metastatic phenotype (Hyeon et al. 2013). A further protein that interacts with beta-catenin signaling and affects cancer cell growth and invasion is arrest-defective protein1/ARD1, the catalytic subunit of the major N-terminal acetyltransferase. Upregulation of ARD1 is associated with a metastatic phenotype in various cancers, and its autoacetylation stimulates cancer cell proliferation. In the Wnt/beta-catenin pathway, ARD1 acts via acetylation and activation of beta-catenin. In HCCs, ARD1 stimulates microvascular invasion (Shim et al. 2012). Wnt/beta-catenin signaling in HCCs is counteracted by SOX1 (sex-determining region Y-box 1), a transcription factor which acts as a tumor suppressor (Tsao et al. 2012). The proinvasive action of Wnt/beta-catenin signaling in HCC is also counteracted by microRNA-148b which downregulates expression of Wnt1 and beta-catenin (Zhang et al. 2015b). A novel mechanism that antagonizes Wnt signaling is exosomal release of beta-catenin, a mechanism that illustrates the significance of exosomal packaging and release of cytosolic proteins in the modulation of signaling pathways in normal and malignant cells (Chairoungdua et al. 2010).

Chemotaxis and Chemokinesis in Liver Cancer

Introduction

The chemokinetic and chemotactic factors that can elicit a motile response, with either random or directional movements, in liver cancer cells are not yet well characterized. As outlined above, a chemokinetic or chemotactic response depends on polarization, cell shape change, and the production of distinct cellular protrusions, including pseudopods (review: Van Haastert 2010). Polarization of the cell causes the redistribution of membrane receptors for chemokinetic/chemotactic stimuli at front vs. rear ends of the cell, a prerequisite for decision making with respect to locomotion guidance. In the course of chemotaxis, phosphatidylinositol 3,4,5-trisphosphate/PIP3 accumulates at the leading edge of motile cells where it induces the formation of pseudopodia, suggesting that PIP3 is a principal navigator of chemotaxis (Van Haastert and Veltman 2007).

Factors and Signals Affecting Chemokinesis and Chemotaxis in Liver Cancer

In contrast to leukocytes, where chemokinetic and chemotactic factors have been studied in great detail, relatively few factors have so far been identified to act as chemotaxins in cancers. Laminin and type IV collagens present in basement membranes exert a potent chemotactic action on HCC cells, which can express laminin receptors (Ogata 1998). Chemotaxis to laminin via production of pseudopods is mediated by the integrin beta1 receptor subunits, alpha3beta1 and alpha6beta1, in HCC cells (Fu et al. 2004, 2010). Among beta1 integrins, alpha6beta1 integrin is a major cell surface receptor that mediates HCC cell adhesion to type IV collagen and induction of chemotaxis (Fu et al. 2011). The chemokine, monocyte chemoattractant protein-1 (MCP-1), secreted by stromal myofibroblasts promotes migration of human HCC cells in a syndecan-1- and syndecan-4-dependent manner (Dagouassat et al. 2010). This pathway suggests that the stroma of these cancers can itself participate in the promotion of invasion. HCC cells respond with increased motility to elastin and elastin fragments. Chemotaxis to elastin-derived chemoattractants is restricted by laminin, and laminin regulates a tumor cell chemotaxis receptor through the laminin-binding integrin subunit alpha6 (Blood and Zetter 1993). Orientation chemotaxis and adhesion in HCC cells is positively influenced by metadherin (MTDH/astrocyte elevated gene-1

(AEG-1)), which is localized to the perinuclear area (Zhou et al. 2012), and which also induces EMT (Zhu et al. 2011). Cancer cell motility is strongly influenced by integrins. HCC cells predominantly express the integrins alpha1, alpha3, and beta1, while integrins alpha2, alpha5, and alpha6 show intermediate expression levels, and alpha2 has a minor expression only. Integrins mediate the chemotactic response of HCC cells toward laminin (Fu et al. 2004, 2010). Chemokinesis and chemotaxis of HCC cells are induced by chemokines and cytokines. RANTES (a CC chemokine, regulated on activation, normal T cell expressed, and presumably secreted) stimulates directed migration of HCC cells through activation of G protein-coupled receptors, CCR1, CCR3, and CCR5. RANTES binds to glycosaminoglycans of the ECM, which inhibit RANTES-induced migration of HCC cells (Sutton et al. 2007). In cancer cells expressing C-X-C motif chemokine receptor 4/CXCR4, stroma cell-derived factor 1 (C-X-C motif chemokine 12) induces directional locomotion and metastasis (Dillenburg-Pilla et al. 2015). CCR7-related chemotaxis in HCC cells is impaired by the CC chemokine receptor-like 1 (CCRL1) (Shi et al. 2015). Noncanonical Hedgehog signaling contributes to chemotaxis in cholangiocarcinomas via interaction with G protein-coupled receptors (Razumilava et al. 2014). HCC cells can themselves produce chemotactic factors that act on stromal cells, vascular cells, and leukocytes accumulating in stroma. HCC cells can secrete macrophage inflammatory protein-3alpha (MIP-3alpha) which chemotactically recruits endothelial progenitor cells (Shih et al. 2012). On the other hand, tumor endothelial cells can secrete monocyte chemotactic protein-1/MCP-1 which contributes to chemotaxis of HCC cells in a microRNA-21-dependent manner (Shih et al. 2015).

References

Ackerman MA, Shriver M, Perry NA, Hu LY, Kontrogianni-Konstantopoulos A (2014) Obscurins: Goliaths and Davids take over non-muscle tissues. PLoS One 9:e88162

Ady JW, Desir S, Thayanithy V, Vogel RI, Moreira AL, Downey RJ, Fong Y, Manova-Todorova K, Moore MA, Lou E (2014) Intercellular communication in malignant pleural mesothelioma: properties of tunneling nanotubes. Front Physiol 5:400

Ahmad T, Mukherjee S, Pattnaik B, Kumar M, Singh S, Kumar M, Rehman R, Tiwari BK, Jha KA, Barhanpurkar AP et al (2014) Miro1 regulates intercellular mitochondrial transport & enhances mesenchymal stem cell rescue efficacy. EMBO J 33:994–1010

Akhshi TK, Wernike D, Piekny A (2014) Microtubules and actin work together to polarize cells for division and migration. Cytoskeleton (Hoboken) 71:1–23

An JH, Kim JW, Jang SM, Kim CH, Kang EJ, Choi KH (2011) Gelsolin negatively regulates the activity of tumor suppressor p53 through their physical interaction in hepatocarcinoma HepG2 cells. Biochem Biophys Res Commun 412:44–49

Angus L, Moleirnho S, Herron L, Sinha A, Zhang X, Niestrata M, Dholakia K, Prystowsky MB et al (2012) Willin/FRMD6 expression activates the Hippo signaling pathway kinases in mammals and antagonizes oncogenic YAP. Oncogene 31:238–250

Arjonen A, Kaukonen R, Ivaska J (2011) Filopodia and adhesion in cancer cell motility. Cell Adhes Migr 5:421–430

Austefjord MW, Gerdes HH, Wang X (2014) Tunneling nanotubes: diversity in morphology and structure. Commun Integr Biol 7:e27934

Bae YH, Ding Z, Das T, Wells A, Gertler F, Roy P (2010) Profilin1 regulates PI(3,4)P2 and lamellipodin accumulation at the leading edge thus influencing motility of MDA-MB-231 cells. Proc Natl Acad Sci U S A 107:21547–21552

Baehs S, Herbst A, Thieme SE, Perschl C, Behrens A, Scheel S, Jung A, Brabletz T et al (2009) Dickkopf-4 is frequently down-regulated and inhibits growth of colorectal cancer cells. Cancer Lett 276:152–159

Ballestrem C, Wehrle-Haller B, Hinz B, Imhof BA (2000) Actin-dependent lamellipodia formation and microtubule-dependent tail retraction control-directed cell migration. Mol Cell Biol 11:2999–3012

Barzik M, McClain LM, Gupton SL, Gertler FB (2014) Ena/VASP regulates mDia2-initiated filopodial length, dynamics, and function. Mol Biol Cell 25:2604–2619

Baum B, Kunda P (2005) Actin nucleation: spire – actin nucleator in a class of its own. Curr Biol 15: R305–R308

Bernard O (2007) Lim kinases, regulators of actin dynamics. Int J Biochem Cell Biol 39:1071–1076

Bisi S, Disanza A, Malinverno C, Frittoli E, Palamidessi A, Scita G (2013) Membrane and actin dynamics interplay at lamellipodia leading edge. Curr Opin Cell Biol 25:565–573

Blood CH, Zetter BR (1993) Laminin regulates a tumor cell chemotaxis receptor through the laminin-binding integrin subunit alpha 6. Cancer Res 53:2661–2666

Boeda B, Etienne-Manneville S (2015) Spectrin binding motifs regulate Scribble cortical dynamics and polarity function. Elife. doi:10.7554/eLife.04726

Boer EF, Howell ED, Schilling TF, Jette CA, Stewart RA (2015) Fascin1-dependent filopodia are required for directional migration of a subset of neural crest cells. PLoS Genet 11:e1004946

Bozzuto G, Ruggiweri P, Molinari A (2010) Molecular aspects of tumor cell migration and invasion. Ann Iast Super Sanita 46:66–80

Bradbury P, Fabry B, O'Neill GM (2012) Occupy tissue. The movement in cancer metastasis. Cell Adhes Migr 6:424–432

Brauckhoff A, Malz M, Tschaharganeh D, Malek N, Weber A, Riener MO, Soll C, Samarin J et al (2011) Nuclear expression of the ubiquitin ligase seven in absentia homolog (SIAH)-1 induces proliferation and migration of liver cancer cells. J Hepatol 55:1049–1057

Bunthot S, Obchoei S, Kraiklang R, Pirojkul C, Wongkham S, Wongkham C (2012) Overexpression of claudin-4 in cholangiocarcinoma tissues and its possible role in tumor metastasis. Asian Pac J Cancer Prev 13(Suppl):71–76

Cao Y, Chang H, Li L, Cheng RC, Fan XN (2007) Alterations of adhesion molecule expression and cellular polarity in hepatocellular carcinoma. Histopathology 51:528–538

Cao T, Li H, Hu Y, Ma D, Cai X (2014) miR-144 suppresses the proliferation and metastasis of hepatocellular carcinoma by targeting E2F3. Tumour Biol 35:10759–10764

Chairoungdua A, Smith DL, Pochard P, Hull M, Caplan MJ (2010) Exosome release of b-catenin: a novel mechanism that antagonizes Wnt signaling. J Cell Biol 190:1079–1091

Chakraborty S, Lakshmanan M, Swa HL, Chen J, Zhang X, Ong YS, Loo LS, Akincilar SC, Gunaratne J, Tergaonkar V et al (2015) An oncogenic role of Agrin in regulating focal adhesion integrity in hepatocellular carcinoma. Nat Commun 6:6184

Chan J, Ko FC, Yeung YS, Ng IO, Yam JW (2011) Integrin-linked kinase overexpression and its oncogenic role in promoting tumorigenicity of hepatocellular carcinoma. PLoS One 6:e16984

Chang TM, Hung WC (2012) Transcriptional repression of TWIST1 gene by Prospero-related homeobox 1 inhibits invasiveness of hepatocellular carcinoma cells. FEBS Lett 586:3746–3752

Chang YC, Zhang H, Brennan ML, Wu J (2013) Crystal structure of lamellipodin implicates diverse functions in actin polymerization and Ras signaling. Protein Cell 4:211–219

Chen CK, Sawaya MR, Phillips ML, Reisler E, Quinlan ME (2012) Multiple forms of Spire-actin complexes and their functional consequences. J Biol Chem 287:10684–10692

Chen H, Miao R, Fan J, Han Z, Wu J, Qiu G, Tang H, Peng Z (2013a) Decreased expression of miR-126 correlates with metastatic recurrence of hepatocellular carcinoma. Clin Exp Metastasis 30:651–658

Chen YW, Chu HC, Ze-Chiang L, Shiah WJ, Chou CP, Klimstra DS, Lewis BC (2013b) p16 stimulates CDC42-dependent migration of hepatocellular carcinoma cells. PLoS One 8:e69389

Chen YL, Wang TH, Hsu HC, Yuan RH, Jeng YM (2013c) Overexpression of CTHRC1 in hepatocellular carcinoma promotes tumor invasion and predicts poor prognosis. PLoS One 8:e70324

Chen XJ, Squarr AJ, Stephan R, Chen B, Higgins TE, Barry DJ, Martin MC, Rosen MK, Bogdan S, Way M (2014) Ena/VASP proteins cooperate with the WAVE complex to regulate the actin cytoskeleton. Dev Cell 30:569–584

Chen X, Bo L, Zhao X, Chen Q (2015) MicroRNA-133a inhibits cell proliferation, colony formation ability, migration and invasion by targeting matrix metalloproteinase 9 in hepatocellular carcinoma. Mol Med Rep. doi:10.3892/mmr.2015.3232

Cheng IK, Tsang BC, Lai KP, Ching AK, Chan AW, To KF, Lai PB, Wong N (2012) GEF-H1 over-expression in hepatocellular carcinoma promotes cell motility via activation of RhoA signaling. J Pathol. doi:10.1002/path.4084

Chuma et al. (2004) http://www.ncbi.nlm.nih.gov/pubmed/15464244

Cramer LP (1999) Organization and polarity of actin filament networks in cells: implications for the mechanism of myosin-based cell motility. Biochem Soc Symp 65:173–205

Dagouassat M, Suffee N, Hlawaty H, Haddad O, Charni F, Laguillier C, Vassy R, Martin L, Schischmanoff PO, Gattegno L et al (2010) Monocyte chemoattractant protein-1 (MCP-1)/CCL2 secreted by hepatic myofibroblasts promotes migration and invasion of human hepatoma cells. Int J Cancer 126:1095–1108

Dai W, Wang C, Wang F, Wang Y, Shen M, Chen K, Cheng P, Zhang Y, Yang J, Zhu R, Zhang H, Li J, Zheng Y et al (2014) Anti-miR-197 inhibits migration in HCC cells by targeting KAI 1/CD82. Biochem Biophys Res Commun 446:541–548

Dang I, Gorelik R, Sousa-Blin C, Derivery E, Guérin C, Linkner J, Nemethova M, Dumortier JG et al (2013) Inhibitory signaling to the Arp2/3 complex steers cell migration. Nature 503:281–284

De Vreede G, Schoenfled JD, Windler SL, Morrison H, Lu H, Bilder D (2014) The Scribble module regulates retromer-dependent endocytic trafficking during epithelial polarization. Development 141:2796–2802

Deakin NO, Ballestrem C, Turner CE (2012) Paxillin and Hic-5 interaction with vinculin is differentially regulated by Rac1 and RhoA. PLoS One 7:e37990

Dillenburg-Pilla P, Patel V, Mikelis CM, Zarate-Bladés CR, Doçi CL, Amornphimoltham P, Wang Z, Martin D, Leelahavanichkul K et al (2015) SDF-1/CXCL12 induces directional cell migration and spontaneous metastasis via a CXCR4/Gαi/mTORC1 axis. FASEB J 29:1056–1068

Ding J, Huang S, Wu S, Zhao Y, Liang L, Yan M, Ge C, Yao J, Chen T, Wand D, Wang H, Gu J, Yao M, Li J, Tu H et al (2010) Gain of miR-151 on chromosome 8q24.3 facilitates tumour cell migration and spreading

through downregulating RhoGDIA. Nat Cell Biol 12:390–399
Ding J, Huang S, Wang Y, Tian Q, Zha R, Shi H, Wang Q, Ge C, Chen T, Zhao Y et al (2013) Genome-wide screening revealed that miR-195 targets the TNF-a/NF-kB pathway by downregulating IKKa and TAB3 in hepatocellular carcinoma. Hepatology 58:654–666
Donthamsetty S, Have VS, Mars WM, Bowen WC, Orr A, Haynes MM, Wu C, Michalopoulos GK (2013) Role of PINCH and its partner tumor suppressor Rsu-1 in regulating liver size and tumorigenesis. PLoS One 8: e74625
Dütting S, Brachs S, Mielenz D (2011) Fraternal twins – Swiprosin-1/EFhd2 and Swiprosin-2/EFhd1, two homologous EF-hand containing calcium binding adaptor proteins with distinct functions. Cell Commun Signal 9:2
Ebnet K, Suzuki A, Horikoshi Y, Hirose T, Meyer zu Brickwedde MK, Ohno S, Vestweber D (2001) The cell polarity protein ASIP/PAR-3 directly associates with junctional adhesion molecule (JAM). EMBO J 20:3738–3748
Elsum I, Yates L, Humbert PO, Richardson HE (2012) The Scribble-Dlg-Lgl polarity module in development and cancer: from flies to man. Essays Biochem 53:141–168
Fairchild CL, Barna M (2014) Specialized filopodia: at the 'tip' of morphogen transport and vertebrate tissue patterning. Curr Opin Genet Dev 27:67–73
Faix J, Rottner K (2006) The making of filopodia. Curr Opin Cell Biol 18:18–25
Faix J, Breitsprecher D, Stradal TE, Rottner K (2009) Filopodia: complex models for simple rods. Int J Biochem Cell Biol 41:1656–1664
Fan Q, He M, Deng X, Wu WK, Zhao L, Tang J, Wen G, Sun X, Liu Y (2013) Depression of c-Fos caused by microRNA-139 down-regulation contributes to the metastasis of human hepatocellular carcinoma. Cell Biochem Funct 31:319–324
Fang CM, Xu YH (2001) Down-regulated expression of atypical PKC-binding domain deleted asip isoforms in human hepatocellular carcinomas. Cell Res 11:223–229
Fang S, Lorick KL, Jensen JP, Weissman AM (2003) RING finger ubiquitin protein ligases: implications for tumorigenesis, metastasis and for molecular targets in cancer. Semin Cancer Biol 13:5–14
Fang Y, Xue JL, Shen Q, Chen J, Tian L (2012) MicroRNA-7 inhibits tumor growth and metastasis by targeting the phosphoinositide 3-kinase/Akt pathway in hepatocellular carcinoma. Hepatology 55:1852–1862
Fang KP, Zhang JL, Ren YH, Qian YB (2014) Talin-1 correlates with reduced invasion and migration in human hepatocellular carcinoma cells. Asian Pac J Cancer Prev 15:2655–2661
Fu BH, Wu ZZ, Dong C (2004) Integrin beta1 mediates hepatocellular carcinoma cells chemotaxis to laminin. Hepatobiliary Pancreat Dis Int 3:548–551
Fu BH, Wu ZZ, Qin J (2010) Effects of integrins on laminin chemotaxis by hepatocellular carcinoma cells. Mol Biol Rep 37:1665–1670
Fu BH, Wu ZZ, Qin J (2011) Effects of integrin α6β1 on migration of hepatocellular carcinoma cells. Mol Biol Rep 38:3271–3276
Fu D, Lippincott-Schwartz J, Arias IM (2013) Increased mitochondrial fusion and autophagy help isolated hepatocytes repolarize in collagen sandwich cultures. Autophagy 9:2154–2155
Fukuda T, Chen K, Shi X, Wu C (2003) PINCH-1 is an obligate partner of integrin-linked kinase (ILK) functioning in cell shape modulation, motility, and survival. J Biol Chem 278:51324–51333
Fukuda K, Gupta S, Chen K, Wu C, Qin J (2009) The pseudoactive site of ILK is essential for its binding to alpha-Parvin and localization to focal adhesions. Mol Cell 36:819–830
Fukuda K, Bledska K, Yang J, Pererea HD, Plow EF, Qin J (2014) Molecular basis of kindlin-2 binding to integrin-linked kinase pseudokinase for regulating cell adhesion. J Biol Chem 289:28363–28375
Gagliardi PA, di Blasio L, Puliafito A, Seano G, Sessa R, Chianale F, Leung T, Bussolino F, Primo L (2014) PDK1-mediated activation of MRCKα regulates directional cell migration and lamellipodia retraction. J Cell Biol 206:415–434
Galkina SI, Fedorova NV, Stadnichuk VI, Sud'ina GF (2013) Membrane tubulovesicular extensions (cytonemes): secretory and adhesive cellular organelles. Cell Adh Migr 7:174–186
Galkina SI, Fedorova NV, Serebryakova MV, Arifulin EA, Stadnichuk VI, Gaponova TV, Baratova LA, Sud'ina GF (2015) Inhibition of the GTPase dynamin or actin depolymerization initiates outward plasma membrane tubulation/vesiculation (cytoneme formation) in neutrophils. Biol Cell. doi:10.1111/boc.201400063
Gallagher KL, Benfey PN (2005) Not just another hole in the wall: understanding intercellular protein trafficking. Genes Dev 19:189–195
Gallop JL, Jao CC, Kent HM, Butler PJ, Evans PR, Langen R, McMahon HT (2006) Mechanism of endophilin N-BAR domain-mediated membrane curvature. EMBO J 25:2898–2910
Gang Z, Ya-Lin K, Dong-Qing W, Yu L, Li R, Hong-Yi Z (2013) Combining cortactin and CTTN detection with clinicopathologic features increases effectiveness of survival predictions for patients with resectable hepatocellular carcinoma. Clin Lab 59:1343–1352
Gardberg M, Kaipio K, Lehtinen L, Mikkonen P, Heuser VD, Talvinen K, Iljin K, Kampf C et al (2013) FHOD1, a formin upregulated in epithelial-mesenchymal transition, participates in cancer cell migration and invasion. PLoS One 8:e74923
Genda et al. (1999) http://www.ncbi.nlm.nih.gov/pubmed/10498656
Gertler F, Condeelis J (2011) Metastasis: tumor cells becoming MENAcing. Trends Cell Biol 21:81–90

Ghatak S, Morgner J, Wickström SA (2013) ILK: a pseudokinase with a unique function in the integrin-actin linkage. Biochem Soc Trans 41:995–1001

Goetz SC, Ocbina PJ, Anderson KV (2009) The primary cilium as a Hedgehog signal transduction machine. Methods Cell Biol 94:199–222

Grise F, Bidaud A, Moreau V (2009) Rho GTPases in hepatocellular carcinoma. Biochim Biophys Acta 1795:137–151

Gross SR (2013) Actin binding proteins: their ups and downs in metastatic life. Cell Adh Migr 7:199–213

Gunn-Moore FJ, Welsh GI, Herron LR, Brannigan F, Venkateswarlu K, Gillespie S et al (2005) A novel 4.1 ezrin radixin moesin (FERM)-containing, 'Willin'. FEBS Lett 579:5089–5094

Gupton SL, Gertler FB (2007) Filopodia: the fingers that do the walking. Sci STKE 2007(400):re5

Hager MH, Morley S, Bielenberg DR, Gao S, Morello M, Holcomb IN, Liu W, Mouneimne G et al (2012) DIAPH3 governs the cellular transition to the amoeboid tumour phenotype. EMBO Mol Med 4:743–760

Halaoui R, McCaffey L (2014) Rewiring cell polarity signaling in cancer. Oncogene. doi:10.1038/onc.2014.59

Hall A (2009) The cytoskeleton and cancer. Cancer Metastasis Rev 28:5–14

Harris HJ, Clerte C, Farquhar MJ, Goodall M, Hu K, Rassam P, Dosset P, Wilson GK, Balfe P, Ijzendoorn SC, Milhiet PE et al (2013) Hepatoma polarization limits CD81 and hepatitis C virus dynamics. Cell Microbiol 15:430–445

Hayashi Y, Osanai M, Lee GH (2011) Fascin-1 expression correlates with repression of E-cadherin expression in hepatocellular carcinoma cells and augments their invasiveness in combination with matrix metalloproteinases. Cancer Sci 102:1228–1235

Helgeson LA, Prendergast JG, Wagner AR, Rodnick-Smith M, Nolen BJ (2014) Interactions with actin monomers, actin filaments, and Arp2/3 complex define the roles of WASP family proteins and cortactin in coordinately regulating branched actin networks. J Biol Chem 289:28856–28869

Hirose et al. (2002) http://www.ncbi.nlm.nih.gov/pubmed/12045219

Hoffmann AK, Nai X, Linder S (2014) Daam1 is a regulator of filopodia formation and phagocytic uptake of Borrelia burgdorferi by primary human macrophages. FASEB J 28:3075–3089

Honda S, Shirotani-Ikejima H, Tadokoro S, Tomiyama Y, Miyata T (2013) The integrin-linked kinase-PINCH-parvin complex supports integrin aIIbb3 activation. PLoS One 8:e85498

Horita Y, Ohashi K, Mukai M, Inoue M, Mizuno K (2008) Suppression of the invasive capacity of rat ascites hepatoma cells by knockdown of Slingshot or LIM kinase. J Biol Chem 283:6013–6021

Hsieh SY, He JR, Hsu CY, Chen WJ, Bera R, Lin KY, Shih TC, Yu MC, Lin YJ et al (2011) Neuregulin/erythroblastic leukemia viral oncogene homolog 3 autocrine loop contributes to invasion and early recurrence of human hepatoma. Hepatology 53:504–516

Hu Y, Fang C, Xu Y (2005) The effect of isoforms of the cell polarity protein, human ASIP, on the cell cycle and Fas/FasL-mediated apoptosis in human hepatoma cells. Cell Mol Life Sci 62:1974–1983

Hu CT, Cheng CC, Pan SM, Wu JR, Wu WS (2013) PKC mediates fluctuant ERK-paxillin signaling for hepatocyte growth factor-induced migration of hepatoma cell HepG2. Cell Signal 25:1457–1467

Hua M, Zhang W, Li W, Li X, Liu B, Lu X, Zhang H (2012) Molecular mechanisms regulating the establishment of hepatocyte polarity during human hepatic progenitor cell differentiation into a functional hepatocyte-like phenotype. J Cell Sci 125:5800–5810

Huang C, Rajfur Z, Borchers C, Schaller MD, Jacobson K (2003) JNK phosphorylates paxillin and regulates cell migration. Nature 424:219–223

Huang C, Jacobson K, Schaller MD (2004) A role for JNK-paxillin signalling in cell migration. Cell Cycle 3:4–6

Huang X, Ji J, Xue H, Zhang F, Han X, Cai Y, Zhang J, Ji G (2012) Fascin and cortactin expression is correlated with a poor prognosis in hepatocellular carcinoma. Eur J Gastroenterol Hepatol 24:633–639

Huh YH, Kim SH, Chung KH, Oh S, Kwon MS, Choi HW, Rhee S, Ryu JH, Park ZY et al (2013) Swiprosin-1 modulates actin dynamics by regulating the F-actin accessibility to cofilin. Cell Mol Life Sci 70:4841–4854

Hyeon J, Ahn S, Lee JJ, Song DH, Park CK (2013) Expression of fibroblast growth factor 19 is associated with recurrence and poor prognosis of hepatocellular carcinoma. Dig Dis Sci 58:1916–1922

Iguchi T, Aishima S, Umeda K, Sanefuji K, Sugimachi K, Gion T, Taketomi A, Maehara Y, Tsuneyoshi M (2009) Fascin expression in progression and prognosis in hepatocellular carcinoma. J Surg Oncol 100:575–579

Insall R (2013) The interaction between pseudopods and extracellular signalling during chemotaxis and directed migration. Curr Opin Cell Biol 25:526–531

Ip YC, Cheung ST, Lee YT, Ho JC, Fan ST (2007) Inhibition of hepatocellular carcinoma invasion by suppression of claudin-10 in HLE cells. Mol Cancer Ther 6:2858–2867

Ishino K, Kaeyama, Shibanuma M, Nose K (2000) Specific decrease in the level of Hic-5, a focal adhesion protein, during immortalization of mouse embryonic fibroblasts, and its association with focal adhesion kinase. J Cell Biochem 76:411

Ishiuchi T, Takeichi M (2011) Willin and Par3 cooperatively regulate epithelial apical constriction through aPKC-mediated ROCK phosphorylation. Nat Cell Biol 13:860–866

Ito M, Hagiyama M, Mimae T, Inoue T, Kato T, Yoneshige A, Nakanishi J, Kondo T, Okada M, Ito A (2014) α-Parvin, a pseudopodial constituent, promotes cell motility and is associated with lymph node metastasis of lobular breast carcinoma. Breast Cancer Res Treat 144:59–69

Jan YJ, Ko BS, Liu TA, Wu YM, Liang SM, Chen SC, Wang J, Liou JY (2013) Expression of partitioning defective 3 (par-3) for predicting extrahepatic metastasis and survival with hepatocellular carcinoma. Int J Mol Sci 14:1684–1697

Ji Y, Li B, Zhu Z, Guo X, He W, Fan Z, Zhang W (2015) Overexpression of WAVE3 promotes tumor invasiveness and confers an unfavorable prognosis in human hepatocellular carcinoma. Biomed Pharmacother 69:409–415

Jia CC, Wang TT, Liu W, Fu BS, Hua X, Wang GY, Li TJ, Li X, Wu XY, Tai Y et al (2013) Cancer-associated fibroblasts from hepatocellular carcinoma promote malignant cell proliferation by HGF secretion. PLoS One 8:e63243

Jia D, Jing Y, Zhang Z, Liu L, Ding J, Zhao F, Ge C, Wang Q, Chen T, Yao M, Li J, Gu J, He X (2014) Amplification of MPZL1/PZR promotes tumor cell migration Src-mediated phosphorylation of cortactin in hepatocellular carcinoma. Cell Res 24:204–207

Jin KM, Lu M, Liu FF, Gu J, Du XJ, Xing BC (2013) N-WASP is highly expressed in hepatocellular carcinoma and associated with poor prognosis. Surgery 153:518–525

Johnson HE, King SJ, Asokan SB, Rotty JD, Bear JE, Haugh JM (2015) F-actin bundles direct the initiation and orientation of lamellipodia through adhesion-based signaling. J Cell Biol 208:443–455

Kanamori H, Kawakami T, Effendi K, Yamazaki K, Mori T, Ebinuma H, Masugi Y, Du W, Nagasaka K, Ogiwara A et al (2011) Identification by differential tissue proteome analysis of talin-1 as a novel molecular marker of progression of hepatocellular carcinoma. Oncology 80:406–415

Kang YK, Hong SW, Lee H, Kim WH (2010) Prognostic implications of ezrin expression in human hepatocellular carcinoma. Mol Carcinog 49:798–804

Kang YH, Ji NY, Lee CI, Lee HG, Kim JW, Yeom YI, Kim DG, Yoon SK, Kim JW et al (2011) ESM-1 silencing decreased cell survival, migration, and invasion and modulated cell cycle progression in hepatocellular carcinoma. Amino Acids 40:1003–1013

Kashyap A, Zimmerman T, Ergül N, Bosserhoff A, Hartman U, Alla V, Bataille F, Galle PR, Strand S, Strand D (2013) The human Lgll polarity gene, Hugl-2, induces MET and suppresses Snail tumorigenesis. Oncogene 32:1396–1407

Kaufmann R, Rahn S, Pollrich K, Hertel J, Dittmar Y, Hommann M, Henklein P, Biskup C, Westermann M, Hollenberg MD et al (2007) Thrombin-mediated hepatocellular carcinoma cell migration: cooperative action via proteinase-activated receptors 1 and 4. J Cell Physiol 211:699–707

Kaufmann R, Oettel C, Horn A, Halbhuber KJ, Eitner A, Krieg R, Katenkamp K, Henklein P et al (2009) Met receptor tyrosine kinase transactivation is involved in proteinase-activated receptor-2-mediated hepatocellular carcinoma cell invasion. Carcinogenesis 30:1487–1496

Keller HU, Zimmermann A (1986) Shape changes and chemokinesis of Walker 256 carcinosarcoma cells in response to colchicine, vinblastine, nocodazole and taxol. Invasion Metastasis 6:33–43

Keller HU, Zimmermann A, Niggli V (1989) Diacylglycerols and the protein kinase inhibitor H-7 suppress cell polarity and locomotion of Walker 256 carcinosarcoma cells. Int J Cancer 44:934–939

Keller H, Niggli V, Zimmermann A (1991) Diversity of motile responses of human neutrophil granulocytes: functional meaning and cytoskeletal basis. Adv Exp Med Biol 297:23–37

Kelley LC, Hayes KE, Ammer AG, Martin KH, Weed SA (2010) Cortactin phosphorylated by ERK1/2 localizes to sites of dynamic actin regulation and is required for carcinoma lamellipodia persistence. PLoS One 5: e13847

Khanduja N, Kuhn JR (2014) Processive acceleration of actin barbed end assembly by N-WASP. Mol Biol Cell 25:55–65

Kim MS, Yoo NJ, Lee SH (2011) Absence of paxillin gene mutation in lung cancer and other common solid cancers. Tumori 97:211–213

Kirkbride KC, Sung BH, Sinha S, Weaver AM (2011) Cortactin: a multifunctional regulator of cellular invasiveness. Cell Adh Migr 5:187–198

Klemke RL, Jiang X, Choi S, Kelber JA (2013) Proteomic and biochemical methods to study the cytoskeletome. Methods Mol Biol 1046:203–218

Koestler SA, Steffen A, Nemethova M, Winterhoff M, Luo N, Holleboom JM, Krupp J et al (2013) Arp2/3 complex is essential for actin network treadmilling as a well as for targeting of capping protein and cofilin. Mol Biol Cell 24:2861–2875

Kojima H, Nies AT, König J, Hagmann W, Spring H, Uemura M, Fukui H, Keppler D (2003) Changes in the expression and localization of hepatocellular transporters and radixin in primary biliary cirrhosis. J Hepatol 39:693–702

Kojima T, Murata M, Yamamoto T, Lan M, Imamura M, Son S, Takano KI, Yamaguchi H et al (2009) Tight junction proteins and signal transduction pathways in hepatocytes. Histol Histopathol 24:1463–1472

Kominsky SL (2006) Claudins: emerging targets for cancer therapy. Expert Rev Mol Med 8:1–11

Korhan P, Erdal E, Atabey N (2014) MiR-181a-5p is downregulated in hepatocellular carcinoma and suppresses motility, invasion and branching-morphogenesis by directly targeting c-Met. Biochem Biophys Res Commun 450:1304–1312

Kornberg TB (2014a) Cytonemes and the dispersion of morphogens. Wiley Interdisc Rev Dev Biol 3:445–463

Kornberg TB (2014b) The contrasting roles of primary cilia and cytonemes in Hh signaling. Dev Biol 394:1–5

Kornberg TB, Roy S (2014) Cytonemes as specialized signaling filopodia. Development 141:729–736

Krause M, Leslie JD, Stewart M, Lafuente EM, Valderrama F, Jagannathan R, Strasser GA et al (2004) Lamellipodin, an Ena/VASP ligand, is

implicated in the regulation of lamellipodial dynamics. Dev Cell 7:571–583
Kurisu S, Takenawa T (2009) The WASP and WAVE family proteins. Genome Biol 10:226
Kwon MS, Park KR, Kim YD, Na BR, Kim HR, Choi HJ, Piragyte I, Jeon H, Chung KH et al (2013) Swiprosin-1 is a novel actin bundling protein that regulates cell spreading and migration. PLoS One 8:e71626
Lai TY, Su CC, Kuo WW, Yeh YL, Kuo WH, Tsai FJ, Tsai CH, Weng YJ, Huang CY et al (2011) b-catenin plays a key role in metastasis of human hepatocellular carcinoma. Oncol Rep 26:415–422
Las G, Shirihai OS (2014) Miro1: new wheels for transferring mitochondria. EMBO J 33:939–941
Law AL, Vehlow A, Kotini M, Dodgson L, Soong D, Theveneau E, Bodo C, Taylor E et al (2013) Lamellipodin and the Scar/WAVE complex cooperate to promote cell migration in vivo. J Cell Biol 203:673–689
Lee JY (2014) New and old roles of plasmodesmata in immunity and parallels to tunneling nanotubes. Plant Sci 221–222:13–20
Lee JM, Yang J, Newell P, Singh S, Parwani A, Friedman SL, Nejak-Bowen KN et al (2014) Beta-catenin signaling in hepatocellular cancer: implications in inflammation, fibrosis, and proliferation. Cancer Lett 343:90–97
Legate KR, Montanez E, Kudlacek O, Fässler R (2006) ILK, PINCH and parvin: the tIPP of integrin signaling. Nat Rev Mol Cell Biol 7:20–31
Lemmers C, Michel D, Lane-Guermonprez L, Delgrossi MH, Médina E, Arsanto JP, Le Bivic A (2004) CRB3 binds directly to Par6 and regulates the morphogenesis of the tight junctions in mammalian epithelial cells. Mol Biol Cell 15:1324–1333
Leong GR, Goulding KR, Amin N, Richardson HE, Brumby AM (2009) Scribble mutants promote aPKC abd JNK-dependent epithelial neoplasia independently of Crumbs. BMC Biol 7:62
Li HG, Xie DR, Shen XM, Li HH, Zeng H, Zeng YJ (2005) Clinicopathlogical of expression of paxillin, syndecan-1 and EMMPRIN in hepatocellular carcinoma. World J Gastroenterol 11:1445–1451
Li N, Fu H, Tie Y, Hu Z, Kong W, Wu Y, Zheng X (2009) miR-34a inhibits migration and invasion by down-regulation of c-Met expression in human hepatocellular carcinoma cells. Cancer Lett 275:44–53
Li QJ, Zhou L, Yang F, Wang GX, Zheng H, Wang DS, He Y, Dou KF (2012) MicroRNA-10b promotes migration and invasion through CADM1 in human hepatocellular carcinoma cells. Tumour Biol 33:1455–1465
Li Y, Zhou B, Dai J, Liu R, Han ZG (2013) Aberrant upregulation of LRRC1 contributes to human hepatocellular carcinoma. Mol Biol Rep 40:4543–4551
Li Q, Ding C, Chen C, Zhang Z, Xiao H, Xie F, Lei L, Chen Y, Mao B, Jiang M, Li J et al (2014a) miR-224 promotes cell migration and invasion by targeting homeobox D 10 gene in human hepatocellular carcinoma. J Gastroenterol Hepatol 29:835–842
Li T, Xie J, Shen C, Cheng D, Shi Y, Wu Z, Zhan Q, Deng X, Chen H, Shen B, Peng C, Li H, Zhu Z (2014b) miR-150-5p inhibits hepatoma cell migration and invasion by targeting MMP14. PLoS One 9: e15577
Li P, Mao X, Ren Y, Liu P (2015a) Epithelial cell polarity determinant CRB3 in cancer development. Int J Biol Sci 11:31–37
Li J, Fang L, Yu W, Wang Y (2015b) MicroRNA-125b suppresses the migration and invasion of hepatocellular carcinoma cells by targeting transcriptional coactivator with PDZ-binding motif. Oncol Lett 9:1971–1975
Li Y, Xu D, Bao C, Zhang Y, Chen D, Zhao F, Ding J, Liang L, Wang Q, Liu L, Li J, Yao M, Huang S, He X (2015c) MicroRNA-135b, a HSF1 target, promotes tumor invasion and metastasis by regulating RECK and EVI5 in hepatocellular carcinoma. Oncotarget 6:2421–2433
Liang L, Guan J, Zeng Y, Wang J, Li X, Zhang X, Ding Y (2011) Down-regulation of formin-like 2 predicts poor prognosis in hepatocellular carcinoma. Hum Pathol 42:1603–1612
Liao CH, Yeh CT, Huang YH, Wu SM, Chi HC, Tsai MM, Tsai CY, Liao CJ, Tseng YH et al (2011) Dickkopf 4 positively regulated by the thyroid hormone receptor surpasses cell invasion in human hepatoma cells. Hepatology 55:910–920
Liao CG, Kong LM, Zhou P, Yang XL, Huang JG, Zhang HL, Lu N (2014) miR-10b is overexpressed in hepatocellular carcinoma and promotes cell proliferation, migration and invasion through RhoC, uPAR and MMps. J Transl Med 12:234
Lim YS, Tang BL (2012) Intracellular organelle trafficking by membranous nanotube connections: a possible new role in cellular rejuvenation? Cell Commun Adhes 19:39–44
Lin L, Yang XM, Li J, Zhang YL, Qin W, Zhang ZG (2014) Microfilament regulatory protein MENA increases activity of RhoA and promotes metastasis of hepatocellular carcinoma. Exp Cell Res 327:113–122
Lipkowitz S, Weissman AM (2011) RINGs of good and evil: RING finger ubiquitin ligases at the crossroads of tumour suppression and oncogenesis. Nat Rev Cancer 11:629–643
Liu L, Zhu XD, Wang WQ, Shen Y, Qin Y, Ren ZG, Sun HC, Tang ZY (2010) Activation of beta-catenin by hypoxia in hepatocellular carcinoma contributes to enhanced metastatic potential and poor prognosis. Clin Cancer Res 16:2740–2750
Liu Y, Zhang JB, Qin Y, Wang W, Wie L, Teng Y, Guo L, Zhang B, Lin Z, Liu J, Ren ZG et al (2013a) PROX1 promotes hepatocellular carcinoma metastasis via up-regulating hypoxia-inducible factor 1a expression and protein stability. Hepatology 58:692–705
Liu FY, Deng YL, Li Y, Zeng D, Zhou ZZ, Tian DA, Liu M (2013b) Down-regulated KLF17 expression is associated with tumor invasion and poor prognosis in hepatocellular carcinoma. Med Oncol 30:425

Liu Z, Tu K, Liu Q (2014a) Effects of microRNA-30a on migration, invasion and prognosis of hepatocellular carcinoma. FEBS Lett 588:3089–3097

Liu W, Xu C, Wan H, Liu C, Wen C, Lu H, Wan F (2014b) MicroRNA-206 overexpression promotes apoptosis, induces cell cycle arrest and inhibits the migration of human hepatocellular carcinoma HepG2 cells. Int J Mol Med 34:420–428

Liu Y, Ding Y, Huang J, Wang S, Ni W, Guan J, Li Q, Zhang Y, Ding Y, Chen B, Chen B et al (2014c) MiR-141 suppresses the migration and invasion of HCC cells by targeting Tiam1. PLoS One 9:e88393

Lou E, Fujisawa S, Barlas A, Romin Y, Manova-Todorova-K, Moore MA, Subramanian S (2012) Tunnelling nanotubes: a new paradigm for studying intercellular communication and therapeutics in cancer. Commun Integr Biol 5:399–403

Lu X, Feng X, Man X, Yang G, Tang L, Du D, Zhang F, Yuan H, Huang Q, Zhang Z et al (2009) Aberrant splicing of Hugl-1 is associated with hepatocellular carcinoma progression. Clin Cancer Res 15:3287–3296

Lynch J, Meehan MH, Crean J, Copeland J, Stallings RL, Bray IM (2013) Metastasis suppressor microRNA-335 targets the formin family of actin nucleators. PLoS One 8:e78428

Ma Y, She XG, Ming YZ, Wan QQ, Ye QF (2015) MicroRNA-144 suppresses tumorigenesis of hepatocellular carcinoma by targeting AKT3. Mol Med Rep 11:1378–1383

MacGrath SM, Koleske AJ (2012) Cortactin in cell migration and cancer at a glance. J Cell Sci 125:1621–1666

Maegdefrau U, Bosserhoff AK (2012) BMP activated Smad signaling strongly promotes migration and invasion of hepatocellular carcinoma cells. Exp Mol Pathol 92:74–81

Malz M, Aulmann A, Samarin J, Bissinger M, Longerich T, Schmitt S, Schirmacher P et al (2012) Nuclear accumulation of seven in absentia homologue-2 supports motility and proliferation of liver cancer cells. Int J Cancer 131:2016–2026

Mao TL, Chu JS, Jeng YM, Lai PL, Hsu HC (2001) Expression of mutant nuclear beta-catenin correlates with non-invasive hepatocellular carcinoma, absence of portal vein spread, and good prognosis. J Pathol 193:95–101

Mao X, Li P, Ren Y, Li J, Zhou C, Yang J, Liu P (2015) Cell polarity protein CRB3 is an independent favorable prognostic factor for clear cell renal cell carcinoma. Int J Oncol 46:657–666

Mariano C, Sasaki H, Brites D, Brito MA (2011) A look at tricellulin and its role in tight junction formation and maintenance. Eur J Cell Biol 90:787–796

Mattila PK, Lappalainen P (2008) Filopodia: molecular architecture and cellular functions. Nat Rev Mol Cell Biol 9:446–454

McCaffrey LM, Macara IG (2011) Epithelial organization, cell polarity and tumorigenesis. Trends Cell Biol 21:727–735

Médina E, Lemmers C, Lane-Guermonprez L, Le Bivic A (2002) Role of the Crumbs complex in the regulation of junction formation in Drosophila and mammalian epithelial cells. Biol Cell 94:305–313

Megger DA, Bracht T, Kohl M, Ahrens M, Naboulsi W, Weber F, Hoffmann AC, Stephan C, Kuhlmann K, Eisneacher M et al (2013) Proteomic differences between hepatocellular carcinoma and nontumorous liver tissue investigated by a combined gel-based and label-free quantitative proteomics study. Mol Cell Proteomics 12:2006–2020

Mellor H (2010) The role of formins in filopodia formation. Biochim Biophys Acta 1803:191–200

Michael M, Vehlow A, Navarro C, Krause M (2010) C-Abl, lamellipodin, and Ena/VASP proteins cooperate in dorsal ruffling of fibroblasts and axonal morphogenesis. Curr Biol 20:783–791

Miki H, Takenawa T (2003) Regulation of actin dynamics by WASP family proteins. J Biochem 134:309–313

Mim C, Cui H, Gawronski-Salerno JA, Frost A, Lyman E, Voth GA, Unger VM (2012) Structural basis of membrane bending by the N-BAR protein endophilin. Cell 149:137–145

Mishima A, Suzuki A, Enaka M, Hirose T, Mizuno K, Ohnishi T, Mohri H, Ishigatsubo Y, Ohno S (2002) Over-expression of PAR-3 suppresses contact-mediated inhibition of cell migration in MDCK cells. Genes Cells 7:581–596

Misra A, Rajmohan R, Lim RP, Bhattacharyya S, Thanabalu T (2010) The mammalian verprolin, WIRE induces filopodia independent of N-WASP through IRSp53. Exp Cell Res 316:2810–2824

Morimura S, Suzuki K, Takahashi K (2009) BetaPIX and GIT1 regulates HGF-induced lamellipodia formation and WAVE2 transport. Biochem Biophys Res Commun 382:614–619

Müsch A (2014) The unique polarity phenotype of hepatocytes. Exp Cell Res 328:276–283

Nakanishi et al. (1999) http://www.ncbi.nlm.nih.gov/pubmed/10763917

Nance J, Zallen JA (2011) Elaborating polarity: PAR proteins and the cytoskeleton. Development 138:799–809

Narumiya S, Ishizaki T, Watanabe N (1997) Rho effectors and reorganization of actin cytoskeleton. FEBS Lett 410:68–72

Ng L, Poon RT, Yau S, Chow A, Lam C, Li HS, Yau TC, Law WL, Pang R (2013) Suppression of actopaxin impairs hepatocellular carcinoma metastasis through modulation of cell migration and invasion. Hepatology 58:667–679

Ni F, Zhao H, Cui H, Wu Z, Chen L, Hu Z, Guo C, Liu Y, Chen Z, Wang X, Chen D, Wei H, Wang S (2015) MicroRNA-362-5p promotes tumor growth and metastasis by targeting CYLD in hepatocellular carcinoma. Cancer Lett 356:809–818

Niggli V, Zimmermann A, Keller H (1996) Inhibition of protein kinase C-dependent protein phsophorylation correlates with increased polarity and locomotion in

Walker 256 carcinosarcoma cells. Int J Cancer 65:473–478
Nishiyama M, Ozturk M, Frohlich M, Mafune K, Steele G, Wands JR (1990) Expression of human alpha-actinin in human hepatocellular carcinoma. Cancer Res 50:6291–6294
Nozawa YI, Lin C, Chuang PT (2013) Hedgehog signaling from the primary cilium to the nucleus: an emerging picture of ciliary localization, trafficking and transduction. Curr Opin Genet Dev 23:429–437
Ogata R (1998) Type IV collagen and laminin enhance the motility, adhesion, and proliferation of hepatoma cells. Kurume Med J 45:11–20
Ohta Y, Suzuki N, Nakamura S, Hartwig JH, Stossel TP (1999) The small GTPase RalA targets filamin to induce filopodia. Proc Natl Acad Sci U S A 96:2122–2128
Ohta Y, Hartwig JH, Stossel TP (2006) FilGAP, a Rho- and ROCK-regulated GAP for Rac binds filamin A to control actin remodeling. Nat Cell Biol 8:803–814
Ozen E, Gozukizil A, ERdal E, Uren A, Bottaro DP, Tabey N (2012) Heparin inhibits hepatocyte growth factor induced motility and invasion of hepatocellular carcinoma cells through early growth response protein 1. PLoS One 7:e42717
Paliouras GN, Naujokas MA, Park M (2009) Pak4, a novel Gab1 binding partner, modulates cell migration and invasion by the Met receptor. Mol Cell Biol 29:3018–3032
Paluch EK, Raz E (2013) The role and regulation of blebs in cell migration. Curr Opin Cell Biol 25:582–590
Pang EY, Bai AH, To KF, Sy SM, Wong NL, Lai PB, Squire JA, Wong N (2007) Identification of PFTAIRE protein kinase 1, a novel cell division cycle-2 related gene, in the motile phenotype of hepatocellular carcinoma cells. Hepatology 46:436–445
Pang F, Zha R, Zhao Y, Wang Q, Chen D, Zhang Z, Chen T, Yao M, Gu J, He X (2014) MiR-525-3p enhances the migration and invasion of liver cancer cells by downregulating ZNF395. Plosone 9:e90867
Park CH, Rha SY, Ahn JB, Shin SJ, Kwon WS, Kim TS, An S, Kim NK, Yang WI, Chung HC (2014) PINCH-2 presents functional copy number variation and suppresses migration of colon cancer cells by paracrine activity. Int J Cancer. doi:10.1002/ijc.29273
Peng H, Talebzadeh-Farrooji M, Osborne MJ, Prokop JW, McDonald PC, Karar J et al (2014) LIMD2 is a small LIM-only protein overexpressed in metastatic lesions that regulates cell motility and tumor progression by directly binding to and activating the integrin-linked kinase. Cancer Res 74:1390–1403
Perry NA, Ackerman MA, Shriver M, Hu LY, Kontrogianni-Konstantopoulos A (2013) Obscurins: unassuming giants enter the spotlight. IUBMB Life 65:479–486
Persad S, Dedhar S (2003) The role of integrin-linked kinase (ILK) in cancer progression. Cancer Metastasis Rev 22:375–384
Qazi AS, Sun M, Huang Y, Wei Y, Tang J (2011) Subcellular proteomics: determination of specific location and expression levels of lymphatic metastasis associated proteins in hepatocellular carcinoma by subcellular fractionation. Biomed Pharmacother 65:407–416
Qin J, Wu C (2012) ILK: a pseudokinase in the center stage of cell-matrix adhesion and signaling. Curr Opin Cell Biol 24:607–613
Qin X, Zhang H, Zhou X, Wang C, Zhang H, Zhang X, Ye L (2007) Proliferation and migration mediated by Dkk-1/Wnt/beta-catenin cascade in a model of hepatocellular carcinoma cells. Transl Res 150:281–294
Raleigh DR, Marchiando AM, Zhang Y, Shen L, Sasaki H, Wang Y, Long M, Turner JR (2010) Tight junction-associated MARVEL proteins marveld3, tricellulin, and occludin have distinct but overlapping functions. Mol Biol Cell 21:1200–1213
Razumilava N, Gradilone SA, Smoot RL, Mertens JC, Bronk SF, Sirica AE, Gores GJ (2014) Noncanonical Hedgehog signaling contributes to chemotaxis in cholangiocarcinoma. J Hepatol 60:599–605
Reglero-Real N, Alvarez-Varela A, Cernuda-Morollon E, Feito J, Marcos-Ramiro B, Fernandez-Martin L, Gomez-Lechon MJ et al (2014) Apicobasal polarity controls lymphocyte adhesion to hepatic epithelial cells. Cell Rep 8:1879–1893
Ren K, Jin H, Bian C, He H, Liu X, Zhang S, Wang Y, Shao RG (2008) MR-1 modulates proliferation and migration of human hepatoma HepG2 cells through myosin light chains-2 (MLC2)/foacl adhesion kinase (FAK)/Akt signaling pathway. J Biol Chem 283:35598–35605
Rogers KW, Schier AF (2011) Morphogen gradients: from generation to interpretation. Annu Rev Cell Dev Biol 27:377–407
Roussos ET, Wang Y, Wyckoff JB, Sellers RS, Wang W, Li J, Pollard JW, Gertler FB (2010) Mena deficiency delays tumor progression and decreases metastasis in polyoma middle-T transgenic mouse mammary tumors. Breast Cancer Res 12:R101
Roy S, Kornberg TB (2015) Paracrine signaling mediated at cell-cell contacts. Bioessays 37:25–33
Rustom A (2009) Hen or egg?: some thoughts on tunneling nanotubes. Ann N Y Acad Sci 1178:129–136
Salvi A, Sabelli C, Moncini S, Venturin M, Arici B, Riva P, Portolani N, Giulini SM et al (2009) Micro-RNA-23b mediates urokinase and c-met downmodulation and a decreased migration of human hepatocellular carcinoma cells. FEBS J 276:2966–2982
Sang H, Li T, Li H, Liu J (2013) Down-regulation of gab1 inhibits cell proliferation and migration in hilar cholangiocarcinoma. PLoS One 8:e81347
Sarmiento C, Wang W, Dovas A, Yamaguchi H, Sidani M, El-Sibai M, Desmarais V et al (2008) WASP family members and formin protein coordinate regulation of cell protrusions in carcinoma cells. J Cell Biol 180:1245–1260
Schoedel KE, Tyner VZ, Kim TH, Michalopoulos GK, Mars WM (2003) HGF, MET, and matrix-related

proteases in hepatocellular carcinoma, fibrolamellar variant, cirrhotic and normal liver. Mod Pathol 16:14–21

Sepulveda JL, Gkretsi V, Wu C (2005) Assembly and signaling of adhesion complexes. Curr Top Dev Biol 68:183–225

Sheng Y, Li J, Zou C, Wang S, Cao Y, Zhang J, Huang A, Tang H (2014) Downregulation of miR-101-3p by hepatitis B virus promotes proliferation and migration of hepatocellular carcinoma cells by targeting Rab5a. Arch Virol 159:2397–2410

Shi J, Yang L, Wang Z, Wang L, Zhou J, Wang X, Shi G, Ding Z, Ke A, Dai Z, Qiu S, Tang Q, Gao Q, Fan J (2015) CC chemokine receptor-like 1 functions as a tumour suppressor by impairing CCR7-related chemotaxis in hepatocellular carcinoma. J Pathol 235:546–558

Shih YT, Wang MC, Peng HH, Chen TF, Chen L, Chang JY, Chiu JJ (2012) Modulation of chemotactic and pro-inflammatory activities of endothelial progenitor cells by hepatocellular carcinoma. Cell Signal 24:779–793

Shih YT, Wang MC, Zhou J, Peng HH, Lee DY, Chiu JJ (2015) Endothelial progenitors promote hepatocarcinoma intrahepatic metastasis through monocyte chemotactic protein-1 induction of microRNA-21. Gut 64:1132–1147

Shim JH, Chung YH, Kim JA, Lee D, Kim KM, Lim YS, Lee HC, Lee YS, Yu E et al (2012) Clinical implications of arrest-defective protein 1 expression in hepatocellular carcinoma: a novel predictor of microvascular invasion. Dig Dis 30:603–608

Shriver M, Stroka KM, Vitolo MI, Martin S, Huso DL, Konstantopoulos K, Kontrogianni-Konstantopoulos A (2014) Loss of giant obscurins from breast epithelium promotes epithelial-to-mesenchymal transition, tumorigenicity and metastasis. Oncogene. doi:10.1038/onc.2014.358

Slim CL, van Ijzendoorn SC, Lazaro-Diéguez F, Müsch A (2014) The special case of hepatocytes: unique tissue architecture calls for a distinct mode of cell division. Bioarchitecture 4:47–52

Snyder JC, Rochelle LK, Marion S, Lyerly HK, Barak LS, Caron MG (2015) Lgr4 and Lgr5 drive the formation of long actin-rich cytoneme-like membrane protrusions. J Cell Sci 128:1230–1240

Song Z, Li R, You N, Tao K, Dou K (2010) Loss of heterozygosity of the tumor suppressor gene Tg737 in the side population cells of hepatocellularcarcinomas is associated with poor prognosis. Mol Biol Rep 37:4091–4101

Stanchi F, Grashoff C, Nguemeni Yonga CF, Grall D, Fässler R, Van Obberghen-Schilling E (2009) Molecular dissection of the ILK-PINCH-parvin triad reveals a fundamental role for the ILK kinase domain in the late stages of focal-adhesion maturation. J Cell Sci 122:1800–1811

Stiegler AL, Draheim KM, Li X, Chayen NE, Calderwood DA, Boggon TJ (2012) Structural basis for paxillin binding and focal adhesion targeting of b-parvin. J Biol Chem 287:32566–32577

Suda J, Zhu L, Karvar S (2011) Phosphorylation of radixin regulates cell polarity and Mrp-2 distribution in hepatocytes. Am J Physiol Cell Physiol 300:C416–C424

Suda J, Rockey DC, Karvar S (2014) Phosphorylation dynamics of radixin in hypoxia-induced hepatocyte injury. Am J Physiol Gastrointest Liver Physiol. doi:10.1152/ajpgi.00369.2014

Sun Z, Han Q, Zhou N, Wang S, Lu S, Bai C, Zhao RC (2013) MicroRNA-9 enhances migration and invasion through KLF17 in hepatocellular carcinoma. Mol Oncol 7:884–894

Sun Z, Meng C, Wang S, Zhou N, Guan M, Bai C, Lu S, Han Q, Zao RC (2014) MicroRNA-1246 enhances migration and invasion through CADM1 in hepatocellular carcinoma. BMC Cancer 14:616

Sutton A, Friand V, Papy-Garcia D, Dagouassat M, Martin L, Vassy R, Haddad O, Sainte-Catherine O, Kraemer M et al (2007) Glycosaminoglycans and their synthetic mimetics inhibit RANTES-induced migration and invasion of human hepatome cells. Mol Cancer Ther 6:2948–2958

Tan S, Li R, Ding K, Lobie PE, Zhu T (2011) miR-198 inhibits migration and invasion of hepatocellular carcinoma cells by targeting the HGF/c-MET pathway. FEBS Lett 585:2229–2234

Tan VY, Lewis SJ, Adams JC, Martin RM (2013) Association of fascin-1 with mortality, disease progression and metastasis in carcinomas: a systematic review and meta-analysis. BMC Med 11:52

Tanaka K (2000) Formin family proteins in cytoskeletal control. Biochem Biophys Res Commun 267:479–481

Tao YM, Liu Z, Liu HL (2013) Dickkopf-1 (DKK1) promotes invasion and metastasis of hepatocellular carcinoma. Dig Liver Dis 45:251–257

Thayanithy V, Dickson EL, Steer C, Subramanian S, Lou E (2014) Tumor-stromal cross talk: direct cell-to-cell transfer of oncogenic microRNAs via tunneling nanotubes. Transl Res 164:359–365

Tian Q, Liang L, Ding J, Zha R, Shi H, Wang Q, Huang S, Guo W, Ge C, Chen T et al (2012) MicroRNA-550a acts as a pro-metastatic gene and directly targets cytoplasmic polyadenylation element-binding protein 4 in hepatocellular carcinoma. PLoS One 7:e48958

Tsai MH, Wu CC, Peng PH, Liang Y, Hsiao YC, Chien KY, Chen JT, Lin SJ, Tang RP, Hsieh LL, Yu JS (2012) Identification of secretory gelsolin as a plasma biomarker associated with distant organ metastasis of colorectal cancer. J Mol Med (Berl) 90:187–200

Tsao CM, Yan MD, Shih YL, Yu PN, Kuo CC, Lin WC, Li HJ, Lin YW (2012) SOX1 functions as a tumor suppressor by antagonizing the WNT/b-catenin signaling pathway in hepatocellular carcinoma. Hepatology 56:2277–2287

Tu Y, Li F, Goicoechea S, Wu C (1999) The LIM-only protein PINCH directly interacts with integrin-linked kinase and is recruited to integrin-rich sites in spreading cells. Mol Cell Biol 19:2425–2434

Tyson RA, Zatulovskiy E, Kay RR, Bretschneider T (2014) How blebs and pseudopods cooperate during chemotaxis. Proc Natl Acad Sci U S A 111:11703–11708

Vaira V, Faversani A, Dohi T, Montorsi M, Augello C, Gatti S, Altieri DC, Bosari S (2012) miR-296 regulation of a cell polarity-cell plasticity module controls tumor progression. Oncogene 31:27–38

Valente S, Rossi R, Resta L, Pasquinelli G (2015) Exploring the human mesenchymal stem cell tubule communication network through electron microscopy. Ultrastruct Pathol 39:88–94

Van Haastert PJ (2010) Chemotaxis: insights from the extending pseudopod. J Cell Sci 123:3031–3037

Van Haastert PJ, Veltman DM (2007) Chemotaxis: navigating by multiple signaling pathways. Sci STKE 2007:440

Vannier C, Pesty A, San-Roman MJ, Schmidt AA (2013) The Bin/amphiphysin/Rvs (BAR) domain protein endophilin B2 interacts with plectin and controls perinuclear cytoskeletal architecture. J Biol Chem 288:27619–27637

Vehlow A, Soong D, Vizcay-Barrena G, Bodo C, Law AL, Perera U, Krause M (2013) Endophilin, lamellipodin, and Mena cooperate to regulate F-actin-dependent EGF-receptor endocytosis. EMBO J 32:2722–2734

Vignjevic D, Kojima S, Aratyn Y, Danciu O, Svitkina T, Borisy GG (2006) Role of fascin in filopodial protrusion. J Cell Biol 174:863–875

Vitriol EA, Wise AL, Berginski ME, Bamburg JR, Zheng JQ (2013) Instantaneous inactivation of cofilin reveals its function of F-actin disassembly in lamellipodia. Mol Biol Cell 24:2238–2247

Wang X, Gerdes HH (2015) Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells. Cell Death Differ. doi:10.1038/cdd.2014.211

Wang W, Soroka CJ, Mennone A, Rahner C, Harry K, Pypaert M, Boyer JL (2006) Radixin is required to maintain apical canalicular membrane structure and function in rat hepatocytes. Gastroenterology 131:878–884

Wang H, Wu K, Sun Y, Li Y, Wu M, Qiao Q, Wie Y, Han ZG, Cai B (2012) STC2 is upregulated in hepatocellular carcinoma and promotes cell proliferation and migration in vitro. BMB Rep 45:629–634

Wang ZG, Jia MK, Cao H, Bian P, Fang XD (2013a) Knockdown of coronin-1C disrupts Rac1 activation and impairs tumorigenic potential in hepatocellular carcinoma cells. Oncol Rep 29:1066–1072

Wang R, Zhao N, Li S, Fang JH, Chen MX, Yang J, Jia WH, Yuan Y, Zhuang SM (2013b) MicroRNA-195 suppresses angiogenesis and metastasis of hepatocellular carcinoma by inhibiting the expression of VEGF, VAV2 and CDC42. Hepatology 58:642–653

Wang T, Yanger K, Stanger BZ, Cassio D, Bi E (2014) Cytokinesis defines a spatial landmark for hepatocyte polarization and apical lumen formation. J Cell Sci 127:2483–2492

Wang G, Sun Y, He Y, Ji C, Hu B, Sun Y (2015) miR-26a promoted by interferon-alpha inhibits hepatocellular carcinoma proliferation and migration by blocking EZH2. Genet Test Mol Biomarkers 19:30–36

Weaver AM (2008) Cortactin in tumor invasiveness. Cancer Lett 265:157–166

Webb DJ, Brown CM, Horwitz AF (2003) Illuminating adhesion complexes in migrating cells: moving toward a bright future. Curr Opin Cell Biol 15:614–620

Weed SA, Parsons JT (2001) Cortactin: coupling membrane dynamics to cortical actin assembly. Oncogene 20:6418–6434

Wehrle-Haller B, Imhof BA (2003) Actin, microtubules and focal adhesion dynamics during cell migration. Int J Biochem Cell Biol 35:39–50

Wells A (ed) (2006) Cell motility in cancer invasion and metastasis. Series: Cancer metastasis – biology and treatment, vol 8. Spinger, London

Wong CC, Wong CM, Ko FC, Chan LK, Ching YP, Yam JW, Ng IO (2008) Deleted in liver cancer 1 (DLC1) negatively regulates Rho/ROCK/MLC pathway in hepatocellular carcinoma. PLoS One 3:e2779

Wong CC, Wong CM, Tung EK, Man K, Ng IO (2009) Rho-kinase 2 is frequently overexpressed in hepatocellular carcinoma and involved in tumor invasion. Hepatology 49:1583–1594

Wong CC, Wong CM, Au SL, Ng IO (2010) RhoGTPases and Rho-effectors in hepatocelular carcinoma metastasis: ROCK N'Rho move it. Liver Int 30:642–656

Wozniak MA, Modzelewska K, Kwong L, Keely PJ (2004) Focal adhesion regulation of cell behavior. Biochim Biophys Acta 1692:103–119

Wu C (2004) The PINCH-ILK-parvin complexes: assembly, functions and regulation. Biochim Biophys Acta 1692:55–62

Wu L, Peng CW, Hou JX, Zhang YH, Chen C, Chen LD, Li Y (2010) Coronin-1C is a novel biomarker for hepatocellular carcinoma invasive progression identified by proteomics analysis and clinical validation. J Exp Clin Cancer Res 29:17

Wu L, Cai C, Wang X, Liu M, Li X, Tang H (2011) MicroRNA-142-3p, a new regulator of RAC1, suppresses the migration and invasion of hepatocellular carcinoma cells. FEBS Lett 585:1322–1330

Xie Q, Liu KD, Hu MY, Zhou K (2001) SF/HGF-c-Met autocrine and paracrine promote metastasis of hepatocellular carcinoma. World J Gastroenterol 7:816–820

Xie B, Xing R, Chen P, Gou Y, Li S, Xiao J, Dong J (2010) Down-regulation of c-Met expression inhibits human HCC cells growth and invasion by RNA interference. J Surg Res 162:231–238

Xieraili M, Yasen M, Mogushi K, Obulhasim G, Mayinuer A, Aihara A, Tanaka S, Mizushima H, Tanaka H, Arii S (2012) Villin 1 is a predictive factor for the recurrence of high serum alpha-fetoprotein-associated hepatocellular carcinoma after hepatectomy. Cancer Sci 103:1493–1501

Xu C, Liu S, Fu H, Li S, Tie Y, Zhu J, Xing R, Jin Y, Sun Z, Zheng X (2010) MicroRNA-193b regulates proliferation, migration and invasion in human hepatocellular carcinoma cells. Eur J Cancer 46:2828–2836

Yamaguchi H, Condeelis J (2007) Regulation of the actin cytoskeleton in cancer cell migration and invasion. Biochim Biophys Acta 1773:642–652

Yamaji S, Suzuki A, Kanamori H, Mishima W, Yoshimi R, Takasaki H, Takabayashi M et al (2004) Affixin interacts with alpha-actinin and mediates integrin signaling for reorganization of F-actin induced by initial cell-substrate interaction. J Cell Biol 165:539–551

Yang et al. (2006) http://www.ncbi.nlm.nih.gov/pubmed/17020969

Yang F, Yin Y, Wang F, Wang Y, Zhang L, Tang Y, Sun S (2010) miR-17-5p promotes migration of human hepatocellular carcinoma cells through the p38 mitogen-activated protein kinase-heat shock protein 27 pathway. Hepatology 51:1614–1623

Yang Z, Tsuchiya H, Zhang Y, Hartnett ME, Wang L (2013a) MicroRNA-433 inhibits liver cancer cell migration by repressing the protein expression and function of cAMP response element-binding protein. J Biol Chem 288:28893–28899

Yang X, Liang L, Zhang XF, Jia HL, Qin Y, Zhu XC, Gao XM, Qiao P, Zheng Y et al (2013b) MicroRNA-26a suppresses tumor growth and metastasis of human hepatocellular carcinoma by targeting interleukin-6-Stat3 pathway. Hepatology 58:158–170

Yeh YT, Dai HY, Chien CY (2014) Amplification of MPZL1/PZR gene in hepatocellular carcinoma. Hepatobiliary Surg Nutr 3:87–90

Yin HL, Kwiatkowski DJ, Mole JE, Cole FS (1984) Structure and biosynthesis of cytoplasmic and secreted variants of gelsolin. J Biol Chem 259:5271–5276

Yoon CH, Kim MJ, Park MJ, Park IC, Hwang SG, An S, Choi YH, Yoon G, Lee SJ (2010) Claudin-1 acts through c-Abl-protein kinase Cdelta (PKCdelta) signaling and has a causal role in the acquisition of invasive capacity in human liver cells. J Biol Chem 285:226–233

Yoshioka K, Matsumura F, Akedo H, Itoh K (1998) Small GTP-binding protein Rho stimulates the actomyosin system, leading to invasion of tumor cells. J Biol Chem 273:5146–5154

You N, Liu W, Tang L, Zhong X, Ji R, Zhang N, Wang D, He Y, Dou K, Tao K (2012) Tg737 signaling is required for hypoxia-enhanced invasion and migration in hepatoma cells. J Exp Clin Cancer Res 31:75

Yu LX, Zhou L, Li M, Li ZW, Wang DS, Zhang SG (2013) The Notch1/cyclooxygenase-2/Snail/E-cadherin pathway is associated with hypoxia-induced hepatocellular carcinoma cell invasion and migration. Oncol Rep 29:362–370

Yu L, Ding GF, He C, Sun L, Jiang Y, Zhu L (2014) MicroRNA-424 is down-regulated in hepatocellular carcinoma and suppresses cell migration and invasion through c-Myb. PLoS One 9:e91661

Yuan BZ, Zhou X, Zimonjic DB, Durkin ME, Popescu NC (2003) Amplification and overxpression of the EMS 1 oncogene, a possible prognostic marker, in human hepatocellular carcinoma. J Mol Diagn 5:48–53

Zhang JL, Qian YB, Zhu LX, Xiong QR (2011) Talin1, a valuable marker for diagnosis and prognostic assessment of human hepatocellular carcinomas. Asian Pac J Cancer Prev 12:3265–3269

Zhang Y, Takahashi S, Tasaka A, Yoshima T, Ochi H, Chayama K (2013) Involvement of microRNA-224 in cell proliferation, migration, invasion, and anti-apoptosis in hepatocellular carcinoma. J Gastroenterol Hepatol 28:565–575

Zhang N, Duan WD, Leng JJ, Zhou L, Wang X, Xu YZ, Wang XD, Zhang AQ, Dong JH (2015a) STAT3 regulates the migration and invasion of a stem-like subpopulation through microRNA-21 and multiple targets in hepatocellular carcinoma. Oncol Rep 33:1493–1498

Zhang JG, Shi Y, Hong DF, Ong M, Huang D, Wang CY, Zhao G (2015b) MiR-148b suppresses cell proliferation and invasion in hepatocellular carcinoma by targeting WNT1/β-catenin pathway. Sci Rep 5:8087

Zhao G, Huang ZM, Kong YL, Wen DQ, Li Y, Ren L, Zhang HY (2013) Cortactin is a sensitive biomarker relative to the poor prognosis of human hepatocellular carcinoma. World J Surg Oncol 11:74

Zheng F, Liao YJ, Cai MY, Liu YH, Liu TH, Chen SP, Bian XW, Guan XY, Lin MC, Zeng YX, Kung HF, Xie D (2012) The putative tumour suppressor microRNA-124 modulates hepatocellular carcinoma cell aggressiveness by repressing ROCK2 and EZH2. Gut 61:278–289

Zhou Z, Deng H, Yan W, Huang H, Deng Y, Li Y, Tian D (2012) Expression of metadherin/AEG-1 gene is positively related to orientation chemotaxis and adhesion of human hepatocellular carcinoma cell lines of different metastatic potentials. J Huazhong Univ Sci Technol Med Sci 32:353–357

Zhou L, Yang ZX, Song WJ, Li QJ, Yang F, Wang DS, Zhang N, Dou KF (2013) MicroRNA-21 regulates the migration and invasion of a stem-like population in hepatocellular carcinoma. Int J Oncol 43:661–669

Zhou HC, Fang JH, Luo X, Zhang L, Yang J, Zhang C, Zhuang SM (2014) Downregulation of microRNA-100 enhances the ICMT-Rac1 signaling and promotes metastasis of hepatocellular carcinoma cells. Oncotarget 5:12177–12188

Zhu K, Dai Z, Pan Q, Wang Z, Yang GH, Yu L, Ding ZB, Shi GM, Ke AW, Yang XR et al (2011) Metadherin promotes hepatocellular carcinoma metastasis through induction of epithelial-mesenchymal transition. Clin Cancer Res 17:7294–7302

Zimmermann J, Falcke M (2014) Formation of transient lamellipodia. PLoS One 9:e87638

Zimmermann A, Keller HU (1987) Locomotion of tumor cells as an element of invasion and metastasis. Biomed Pharmacother 41:337–344

Zimmermann A, Keller H (1992) Effects of staurosporine, K252a and other structurally related protein kinase inhibitors on shape and locomotion of Walker carcinosarcoma cells. Br J Cancer 66:1077–1082

Zimmermann A, Keller H (1993) Shape changes and chemokinesis of Walker carcinosarcoma cells: effects pf protein kinase inhibitors (HA-1004, polymyxin B, sangivamycin and taxoxifen) and an inhibitor of diacylglycerol kinase (R 59022). Anticancer Res 13:347–354

Zimmermann A, Gehr P, Keller HU (1988) Diacylglycerol-induced shape changes, movements and altered F-actin distribution in human neutrophils. J Cell Sci 90:657–666

Mechanisms of Invasion and Metastasis: Tissue Invasion

182

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_182

Abstract

Invasion of various tissues and vessels depends on distinct cellular structures involved in cell adhesion, initiation of tissue invasion, and degradation of the extracellular matrix (ECM). These structures are generally summarized under the term invadosomes, which in turn comprises the two major types of these specialized structures, i.e., podosomes and invadopodia. Podosomes are matrix-degrading adhesive structures formed by certain normal cells, such as macrophages and endothelial cells, and by invading cancer cells. The generation of podosomes strongly depends on protein kinase C-related signaling pathways. Podosomes can degrade ECM components through the shedding of wide array of proteases, specifically matrix metalloproteinases (MMPs). A special type of podosomes is invadopodia, which mediates basement membrane and tissue invasion of cancer cells. These protrusions are actin-based dynamic structures or "organelles" of transformed cells that are critically required for tumor cell invasion and extravasation. Tumor cells can extend invadopodia through the endothelial lining of vessels to the extravascular space prior to extravasation and metastatic growth.

Tissue Invasion: Invadosomes as Pacemakers of Invasion

Recent findings led to the identification of specialized cellular structures involved in adhesion, initiation of tissue invasion, and matrix degradation. These structures are generally summarized under the term invadosomes, which in turn contains the two major types of these structures, i.e., podosomes and invadopodia (Block et al. 2008). Podosomes and in particular invadosomes are characterized by the production of a wide array of enzymes that serve as histolytic factors that degrade tissues and specifically the extracellular matrix of tumors.

Podosomes

General Aspects

Podosomes ("feet bodies/particles") are matrix-degrading adhesive structures formed by invading normal cells, specifically macrophages, osteoclasts, and dendritic cell (Linder and Aepfelbacher 2003; Linder and Kopp 2005; Stylli et al. 2008; Symons 2008; Gawden-Bone et al. 2010; Murphy and Courtneidge 2011; Starnes et al. 2011; Schachtner et al. 2013). Podosomes or podosome rosettes also play a significant role in endothelial cell biology where they are involved in sprouty angiogenesis (Schlaepfer et al. 2004). Podosomes are induced by factors activating protein kinase C (Tatin et al. 2006), such as diacylglycerols and phorbol esters, and can, following their complete formation and activation, degrade EMC components through the shedding of proteases (Linder 2007). Podosomes are cylindrical cell protrusions located to the outer surface of the cell membrane, measuring up to 2 μm in diameter. Both podosomes and the similar invadopodia are actin-based structures that develop from the ventral cell membrane of cells in contact with a substratum. Podosomes carry the lipid membrane of the cell surface region from which they emerge (Yamaguchi and Oikawa 2010). In locomoting cells, podosomes are situated at the front border (leading edge) between lamellipodia and the lamellum. Podosomes have a central role in migration and invasion of matrix mediated by matrix degradation and therefore are important structures in inflammation and cancer. In contrast to invadopodia, which are small structures, podosomes grow to relatively large structures. Podosomes are usually visualized by phalloidin staining, this toxic cyclopeptide binding to filamentous actin/F-actin. In phalloidin or antibody staining, podosomes appear as isolated punctate structures on the ventral surface of cells. They are often localized behind the leading edge in case of podosomes, while invadopodia are more often clustered under the nucleus. Podosomes consist of a central core structure containing F-actin and actin regulators and a

peripheral ring structure (the podosome ring) showing integrins, vinculin, paxillin, and other proteins (Wernimont et al. 2008). In podosome rings, plectin, alpha-II spectrin, talin, and focal adhesion kinase are present, while these proteins are absent in invadopodia (Takkunen et al. 2010). In the course of the formation of a podosome ring, plectin accumulates at the early ring domain of the cell surface, whereby this deposition requires myosin contractility (Gad et al. 2008). In part of cells, including cancer cells, podosomes are clustered in the form of ringlike arrangements, the podosome rosettes. Rosette formation is strongly stimulated by Src kinases, protein kinase C, Rho family GTPases, ezrin, and certain integrins (review: Murphy and Courtneidge 2011). Formation of podosome rosettes is stimulated by ezrin interacting with cortactin and associated with adhesion of cells to fibronectin (Kocher et al. 2009). Furthermore, phosphorylation of moesin by Jun N-terminal kinase is important for podosome rosette formation (Pan et al. 2013a). Podosome rosette formation is stimulated by focal adhesion kinase (Pan et al. 2011) and by hepatoma-derived growth factor through the activation of the phosphatidylinositol 3-kinase/Akt pathway (Kung et al. 2012). Podosome rosette formation is suppressed by protein tyrosine phosphatase SHP2 (Pan et al. 2013b), and Src-induced rosette formation is inhibited by p53 via the upregulation of caldesmon (Mukhopadhyay et al. 2009).

Biogenesis and Morphogenesis of Podosomes

Podosomes contain a complex set of proteins making part of the actin-based engine, including actin, myosin IIA, the Arp2/3 complex, N-WASP, cortactin, gelsolin, and cofilin. For the generation of podosomes, actin cytoskeleton remodeling through Arp2/3-mediated actin polymerization and dynamic microtubules are required (Linder et al. 2000; Snyder et al. 2011; van den Dries et al. 2013). Rapid and spatially restricted remodeling of the actin cytoskeleton is a crucial step in the initiation of podosome formation. The site of first appearance is a surface microdomain where actin-containing stress fibers and focal adhesions intersect (Kaverina et al. 2003). Certain actin-associated proteins are involved in this process. A central role is played by the Arp2/3 pathway, whereby the Arp2/3 complex promotes actin assembly and competes with caldesmon in this function (Morita et al. 2007). Other actin-associated protein comprises Src-cortactin (Luxenburg et al. 2006; Clark et al. 2007), WASP (Tsuboi 2007), caldesmon, and paxillin (Badowski et al. 2008). Caldesmon has an important role in podosome biogenesis and function. Ectopic expression of caldesmon reduces the number of both podosomes and invadopodia (Yoshio et al. 2007). Furthermore, the actin-mediated morphogenesis of podosomes is modulated by integrins located at the podosome site. Integrin-linked kinase/ILK, located in an area surrounding the actin-rich podosome core, regulates podosome maturation (Griera et al. 2014). WASP (Wiskott-Aldrich syndrome protein) is an adaptor protein critical for podosome formation (Dovas et al. 2009) and operates in conjunction with the WASP-interacting protein/WIP. WIP is responsible for the stability and localization of WASP to sites of actin assembly in podosomes (Chou et al. 2006; Garcia et al. 2012) and is involved in ruffle formation (Banon-Rodriguez et al. 2013). WASP also interacts with the F-BAR domain protein, FBP17, a protein that promotes actin nucleation (Tsujita et al. 2013). Integrins can prevent the Src-induced cell rounding, but cannot impair the formation of podosomes (Huveneers et al. 2008).

It is suggested that an actin-microtubule cross talk in the cytoskeleton is critical for the morphogenesis of podosomes. There is evidence that protrusion of the podosome depends on the activity and function of the microtubule-associated kinesin motor component, KIF1C (Kopp et al. 2006). In early sites of podosome formation, vimentin deposition colocalizes at the stress fiber-focal adhesion interface, and plectin colocalizes with vimentin. Plectin is an important protein in cytoskeleton organization (Wiche 1998). Apart

from well-known members of the actin assembly engine, podosomes also contain other proteins, such as the cytoplasmic scaffold protein Tks5 (synonym: Fish), which accumulates in podosomes under stimulation by Src. The presence of Trk5 in podosomes is required for cell invasion (Courtneidge et al. 2005). In the process of podosome formation, Tks5 recruits AFAP-110, p190RhoGAP, and cortactin, essential for podosome morphogenesis (Crimaldi et al. 2009). The early morphogenesis of podosomes is preceded by the formation of cell surface ruffles at the dorsal surface of cells. Ruffle formation is associated with morphogenesis of podosomes and depends on an interaction between palladin and the receptor tyrosine kinase, Eps8, this interaction promoting assembly of the actin cytoskeleton (Goicoechea et al. 2006). Palladin is a protein that promotes podosome formation and assembly (Goicoechea et al. 2009), but it also regulates cell and ECM interactions via maintenance of a normal actin cytoskeleton architecture (Liu et al. 2007). Podosome size and number are regulated in macrophages by the Rho GTPase effector PAK4, a member of the p21-associated kinase family, and its regulator alphaPIX (PAK-interacting exchange factor), two factors which induce highly localized changes in actin dynamics (Gringel et al. 2006).

Podosome Functions

Podosomes are dynamic mechanosensors that sense torsional tractions underneath the podosome rings, whereby interactions between myosin tension and actin dynamics are essential for podosome regulation (Collin et al. 2008). Podosomes play an important role in the degradation of extracellular proteins. Podosomes express sets of proteases that hydrolyze several proteins and glycoproteins of the ECM. In dendritic cells, protrusive podosomes employ MMP-14 for matrix degradation and endocytosis (Gawden-Bone et al. 2010). Fully developed podosomes operate within a network of stimulatory and inhibiting factors. Podosome-mediated degradation of basement membrane collagen is induced by TGF-beta (Rottiers et al. 2009). Other proteins known to modulate podosome function are the Cdc42 regulators. Cdc42 GTPase-activating protein/CDC42GAP regulates podosome-associated cell motility through mediation of extracellular signal-related kinase/ERK activity (Szczur et al. 2006).

Invadopodia

General Aspects

There are several structures at the cell surface that are specialized in creating distinct intercellular and cell-matrix adhesions. A long-known example is the focal adhesion, which contains clusters of transmembrane integrin receptors which are tethered at one end to the ECM and at the other end to stress fibers of the actin network. A second adhesion structure which is critically involved in cancer invasion is the invadopodia.

Selected References (Gimona and Buccione 2006; Weaver 2006; Yamaguchi et al. 2006; Gimona et al. 2008; Stylli et al. 2008; Albiges-Rizo et al. 2009; Buccione et al. 2009; Saltel et al. 2011; Bravo-Cordero et al. 2012; Klemke 2012; Sibony-Benyamini and Gil-Henn 2012; Yamaguchi 2012; Génot and Gligorijevic 2014; Paz et al. 2014).

Invadopodia mediate basement membrane and tissue invasion of cancer cells and are characterized by the integration of several cytoskeletal processes that involve modulation of contractile forces and mechanotransduction (Lohmer et al. 2014; Tokui et al. 2014). Invadopodia are actin-based protrusions or "organelles" of transformed cells and tumor cells that form distinct cell-matrix adhesion sites. Invadosomes are critically required for cancer cell extravasation. In the course of intravascular spread of tumor cells, these cells can, after homing to distant endothelial surfaces, extend invadopodia through endothelium into the extravascular space prior to their extravasation and metastatic growth (Leong et al. 2014).

Invadopodia share several features with podosomes, but are morphologically different from podosomes, as they have a different structure, occur in larger numbers, and are more active in their capability to degrade matrix (Tolde et al. 2010; Artym et al. 2011). Adhesion rings surround invadopodia, a feature shared with podosomes (Branch et al. 2012). Typical invadopodia are smaller than podosomes and occur in larger numbers per cell. They measure from 0.1 to 0.8 μm in diameter and can reach a length of 2 μm or more. Invadopodia can form clusters around membrane invaginations close to the site of the Golgi complex.

Molecular Composition and Biogenesis of Invadopodia

Similar to podosomes, invadopodia possess a complex microfilament machinery regulating F/G-actin switching mediated by a now impressive number of actin-associated proteins, including N-WASP, cortactin, tensin, formins, Src kinases, the Arp2/3 complex, paxillin, cofilin, and gelsolin (Gimona 2008; Albiges-Rizo et al. 2009). Invadopodia are constructed of an N-WASP-dependent branched actin network and a Rho GTPase Cdc42-based pathway involved in invadopodial-membrane protrusion (Albiges-Rizo et al. 2009). The actin network of invadopodia, which contains cortactin, is regulated by a multimolecular complex containing Src kinase, the formin mDia1, actin, and Spire1, a protein which serves as the connection to Rab3A GTPase (Weaver 2008; Lagal et al. 2014). As an important component of the invadopodial machine, myosin 1e is located to the invadopodial core where it may act as a scaffold, linking the plasma membrane to the actin cytoskeleton (Oudekirk and Krendel 2014). In their interaction with the extracellular matrix, invadopodia are potently induced by dense fibrillar collagen via a kindlin2 serine phosphorylation signaling pathway (Artym et al. 2015). Furthermore, invadopodia are equipped with a complex set of regulatory and signaling proteins (Table 1). In particular, pathways leading to invadopodia formation are linked with a signaling cascade that also critically affects cell proliferation and differentiation, Wnt/beta-catenin signaling. Specifically, the Wnt5a-Ror2 axis is involved in enhanced formation of invadopodia (Endo et al. 2015). Biogenesis of invadopodia is strongly induced by Cdc42, while the adaptor protein is required for the degradative activity of invadosomes (Di Martino et al. 2014). A further

Table 1 Molecular composition of invadopodia

Cytoskeletal components
Actin
N-WASP
ARP2/3
Cortactin
Tensin
Gelsolin
Cofilin
Paxillin
Formin
VASP
Actopaxin
Adhesion-related proteins
Integrins
CD44
Vinculin
Signaling proteins
RhoGTPase/Cdc42
Wnt/beta-catenin signaling
ARF
GTPase-activating proteins
Focal adhesion kinase/FAK
Tyrosine kinases
Src kinases
Protein kinase Cmu
Abl interactor 1
EGFR
ASAP1/AMAP1
Dynamin 2
Tks5/Fish
Matrix-degrading enzymes and associated proteins
Metalloproteinases (mainly MMP-2, MMP-9, and MT1-MMP)
Tissue inhibitors of metalloproteinases/TIMPs
ADAMs
ADAMTS and ADAMTS-like proteins
Serine proteinase (seprase)
Dipeptidyl dipeptidase

protein which markedly promotes formation of invadopodia is the cytoskeletal protein WAVE3, which induces cancer cell invasion and metastasis via induction of MMP-9 and other MMPs (Davuluri et al. 2014). Invadopodia biogenesis depends on diaphanous-related formins (Lizarraga et al. 2009). Paxillin, which plays a role in several steps of invadopodia biogenesis and function, is a focal adhesion-associated, phosphotyrosine-containing protein that possesses several domains for protein-protein interactions. These domains are the necessary docking site for several cytoskeletal proteins, including vinculin and actopaxin, tyrosine kinases and serine/threonine kinases, and GTPase-activating proteins and numerous adaptor proteins (Turner 2000; Schaller 2001; Pignatelli et al. 2012b). Paxillin is associated with the paxillin kinase linker/PKL, a protein regulating directed cell migration (Yu et al. 2009). At sites of ECM degradation, an invasion-related complex constructed of paxillin, cortactin, and protein kinase Cmu associated with invadopodia (Bowden et al. 1999). For the function of the actin-based network, the atypical GTP-binding protein dynamin is required, dynamin being a central modulator of cellular protrusive events (McNiven et al. 2004). In the protruding edge of invadopodia and similar structures, actin-associated proteins are accumulated. The interaction of these proteins is coordinated by a member of the F-BAR family of proteins, CIP4/Cdc42-interacting protein 4, in a Rac1/WAVE1-dependent manner (Saengsawang et al. 2013).

Induction and Regulation of Invadopodia in Cancer Cells

In cancer cells, numerous factors can elicit the biogenesis of invadopodia. A major role is played by a complex interaction of cancer cells with the extracellular matrix (ECM) located to tumor stroma. Invadopodia are strongly induced upon contact of tumor cells with distinct domains of the ECM (review: Hoshino et al. 2013a). This contact promotes the activity of several signaling pathways that induce actin cytoskeleton rearrangement, the recruiting of actin-associated proteins, and the generation of cell protrusions (Destaing et al. 2011; Linder et al. 2011). Similar to lamellipodia and related cell protrusions, formation of invadopodia depends on interactions between focal adhesions and the actin cytoskeleton. Via focal adhesions and integrin receptors, invadopodia interact with proteins in the extracellular matrix/ECM. Among ECM proteoglycans and proteins, hyaluronan interacting proteins RHAMM play a role in invadopodia induction (Gurksy et al. 2012). Generally, adhesion signaling has a central role in invadopodia formation, with the critical involvement of protein kinase C and Src kinases (Destaing et al. 2011). Src signaling to induced invadopodia is a regulated protein involved in cell migration and invasion, TM4SF5/transmembrane 4 L six family member 5 (Jung et al. 2013). Src kinase associates with diaphanous formin-1, actin, and Spire-1 in a complex that contributes to invadopodia biogenesis (Lagal et al. 2014). Invadopodia formation is stimulated by proteins that induce epithelial-mesenchymal transition/EMT, e.g., Twist1 (Eckert et al. 2011) and the focal adhesion protein Hic-5, a paxillin homologue (Pignatelli et al. 2012a), linking EMT with mechanisms that determine tissue invasion. Invadopodia are induced by Src-mediated phosphorylation of ASAP1 (Bharti et al. 2007) and by the activation of Cdc42, e.g., by the stromal cell-derived protein palladin (Goicoechea et al. 2014). Src kinases orchestrate several steps of invadopodia biogenesis in a distinct spatiotemporal pattern (Boateng and Huttenlocher 2012). The latter mechanism illustrates the close interaction between tumor cell and matrix for the induction of invadosomes. Invadopodia are induced by a key regulator of the F/G-actin switch mechanism, Abl interactor 1/Abi 1, which affects invadopodia formation in an Src-dependent manner (Sun et al. 2009). Formation of invadopodia depends on the activity of GTPases, e.g., RhoGTPases, which provide signals to the cytoskeleton through small G proteins of the Rho family (Spuul et al. 2014). Invadopodia contain the Arf GTPase-activating protein ASAP1, whereas ASAP3 is not expressed (Ha et al. 2008). The contact between cancer cells and ECM also

involves a complex mode of pH sensing. Several pH regulators such as V-ATPases and Na(+)/H(+) exchangers are expressed in invadosomes, and these sensors/regulators control the acid microenvironment to provide a milieu for appropriate activation of MMPs and other degradases (Brisson et al. 2012).

A second major pathway that induces invadopodia in cancer cells is epithelial-mesenchymal transition (EMT). Formation of invadopodia is stimulated by EMT taking place upon contact of tumor cells with the extracellular matrix. Apart from its central role in EMT induction, the transcription factor Twist1 is capable to induce invadopodia formation, probably via its transcriptional target, PDGFRalpha (Eckert et al. 2011). Also the EMT-inducing factor TGF-beta induces invadopodia formation via ectopic expression of the focal adhesion protein, Hic-5 (Pignatelli et al. 2012a). In the setting of EMT, podosome-like structures occurring in noninvasive carcinoma cells switch to actin comet-embedded invadopodia containing MMP-1. In the course of this transition, the podosomes become smaller and achieve the shape of numerous invadopodia, structures in which talin is replaced by tensin. Therefore, EMT can induce the production of the potent degrading engine required for cancer invasion (Takkunen et al. 2010). Invadopodia are also induced by a factor involved in the regulation of EMT, CD147/basigin (Grass et al. 2012).

Invadopodia maintenance and function are regulated by integrins, Src tyrosine kinase signaling, cortactin, AMAP/ASAP1, the adaptor protein Tks5/Fish, receptor tyrosine kinases, Rho family GTPases, ARF6, and dynamin 2. Beta1 integrins are required for the formation of competent invadopodia, whereby beta1 integrin interacts with the tyrosine kinase Arg and stimulates Arg-dependent phosphorylation of cortactin (Beaty et al. 2013). Beta1A integrin is a master regulator of podosome and invadopodia organization and function (review: Destaing et al. 2010). ASAP1 is an Arf GTPase-activating protein/GAP containing a BAR domain and is a substrate for Src kinase.

Tissue and Matrix Destruction (Histolysis) as a Major Mechanism of Cancer Invasion

Introduction

Both invadopodia and lamellipodia engage in contacts with the underlying extracellular matrix (ECM) and are then stimulated to secrete matrix metalloproteinases (MMPs; see below; Coussens and Werb 1996; Stamenkovic 2000; Linder 2007; Linder et al. 2011; van Horssen et al. 2013). The contact between invadopodia and ECM is a complex process that involves signals from matrix rigidity and myosin II-FAK/Cas pathways (Alexander et al. 2008). Typical MMPs produced by invadopodia are MMP-2 and MMP-9 and in part of neoplasms also MT1-MMP (Watanabe et al. 2013). Expression and secretion of these enzymes causes pericellular proteolysis in cancer (Sevenich and Joyce 2014). Invadopodia express latent MMP-2 and membrane type 1 MPP at the cell surface, where they are activated (Chen and Wang 1999). ECM degradation by invadopodia is regulated by the action of the phosphoinositide-binding protein, ZF21, a protein that promotes cancer cell migration and invasion (Hoshino et al. 2013b). The function of invadopodia also requires several types of ADAMs, which interact with integrins in invadopodia and cooperate with certain invadopodial adaptor proteins, such as Tks5/Fish. Physiological type I collagen can induce a special type of invadosomes, the linear invadosomes. Linear invadosomes, cortactin- and N-WASP-containing protrusions that can degrade matrix, result through replacement of podosomes or invadopodia upon contact with type I collagen present in collagen-rich ECMs (Juin et al. 2012).

Matrix Metalloproteinases (MMPs): Types and Classification

Matrix metalloproteinases (MMPs) are enzymes that are implicated in remodeling of the extracellular matrix (EMC), including the basement membranes (Deryugina and Quigley 2006; Friedl and Wolf 2009; Shiomi et al. 2010). MMPs are

Table 2 Types of metalloproteases (MMPs) and their substrates

Type of MMP	Substrate(s)
Membrane-bound MMPs	
MT1-MMP (MMP-14)	Collagens I–III, gelatins, aggrecan, laminin
MT2-MMP (MMP-15)	Nidogen, tenascin, aggrecan, perlecan, laminin
MT3-MMP (MMP-16)	Collagen III, gelatins, fibronectin
MT4-MMP (MMP-17)	Gelatins, fibrinogen
MT5-MMP (MMP-24)	Proteoglycans
MT6-MMP (MMP-25)	Collagen IV, gelatins, laminin, fibronectin
MMP-23	Gelatin
GPI-linked MMP	
Secreted MMPs	
MMP-1 (interstitial collagenase)	Collagens I–III, VII, and X, gelatins, proteoglycans
MMP-2 (gelatinase A)	Gelatins, collagens, laminin, fibronectin
MMP-3 (stromelysin-1)	Gelatins, laminin, fibronectin, proteoglycans
MMP-7 (matrilysin-1)	Proteoglycans, gelatins, elastin, tenascin, entactin
MMP-8 (neutrophil collagenase)	Collagens I–III, gelatins, aggrecan
MMP-9 (gelatinase B)	Gelatins, collagens III–V, aggrecan, elastin
MMP-10 (stromelysin-2)	Aggrecan, laminin, fibronectin, collagens III–V
MMP-11 (stromelysin-3)	Fibronectin, laminin, aggrecan, gelatins
MMP-12 (metalloelastase)	Elastin, aggrecan, fibronectin, collagen IV
MMP-13 (collagenase-3)	Collagens I–IV, IX, X, and XIV, aggrecan, tenascin
MMP-19 (RASI-1)	Collagen IV, gelatin, fibronectin, tenascin
MMP-20 (enamelysin)	Amelogenin, aggrecan, gelatin
MMP-21	?
MMP-26 (matrilysin-2)	Gelatin, collagen IV, fibronectin, vitronectin
MMP-27	?
MMP-28 (epilysin)	?

classified as two main types of proteases, i.e., those that are anchored to the cell surface membrane and a second group that is secreted into the extracellular space (Table 2).

General Roles and Regulation of MMPs in Liver Cancer

Generally, MMPs play pleiotropic roles in cancer, exceeding aspects of mere "degradomics" but also including effects on cell adhesion, growth signaling, and other pathways (Kleiner and Stetler-Stevenson 1999; Overall and Dean 2006). The activity of MMPs is regulated and controlled at several levels, such as enzyme activation or inhibition at the cell surface, complex formation, and compartmentalization in various subcellular compartments. Within normal and cancer cells, MMPs can be localized at the cell surface, in the cytosol, and in organelles and the nucleus. The role of intracellular MMPs has not yet been clarified in detail (review: Mannello and Medda 2012). Downregulation of the Notch signaling pathway impairs HCC cell migration (Zhou et al. 2013b) and inhibits HCC cell invasion by inactivating MMP-2 and MMP-9 expression via the extracellular signal-regulated kinases 1 and 2 (ERK1/2) signaling pathways (Zhou et al. 2012), while high levels of Notch1 augment MMP-2 and MMP-9 and promote a highly invasive HCC phenotype. Conversely, sonic hedgehog, a ligand of hedgehog, is frequently expressed in HCC cells and decreases the expression of MMP-9 via the ERK pathway (Lu et al. 2012). High Notch1 expression in HCCs was correlated with tumor size, tumor grade, venous invasion, and the metastatic state (Zhou et al. 2013a). In its inhibitory action on migration and invasion, Notch1 operates by regulating CD44v6, E-cadherin, MMPs, and uPA via the COX-2 and ERK1/2 pathways (Zhou et al. 2013). Downregulation of Notch1 inhibits HCC cell invasion by inactivating the COX2/Snail/E-cadherin pathway involved in EMT (Zhou et al. 2013c). Secretion of multiple MMPs is promoted by HGF via the transcription factor Ets-1 which activates MMP transcription (Ozaki et al. 2003). Secretion of MMPs by stromal cells is stimulated by CD147 (EMMPRIN; basigin), a cell surface glycoprotein that belongs to the immunoglobulin superfamily and is strongly expressed on the surface of many tumor cell types. Basigin exists in several isoforms with differential functions. Basigin stimulates the

secretion of VEGF and hyaluronan, promoting angiogenesis and anchorage-independent growth (Nabeshima et al. 2006). These effects are abolished by depletion of CD147, mainly downregulating MMP-11 and VEGF (Jia et al. 2007). CD147 exerts its pro-metastatic effects also in HCCs (Xu et al. 2007; Zhang et al. 2007c; Jia et al. 2008). In HCC cells, downregulation of CD147 inhibits gelatinase production, interferes with tumor cell adhesion to type IV collagen, and alters cytoskeletal structure (Qian et al. 2008). One basigin isoform, basigin-3, inhibited proliferation of HCC cells and MMP induction (Liao et al. 2011). CD147 interacts with integrin alpha6beta1, stimulating invasion and MMP secretion in HCC cells (Dai et al. 2009). A further protein with which CD147 interacts is annexin, a Ca(2+)- and phospholipid-binding protein subject to phosphorylation by tyrosine kinases and protein kinase C. This interaction promotes migration and MMP-mediated invasion of HCC cells. The pro-invasive and pro-metastatic effect of basigin/CD147 is counteracted by the basigin isoform, basigin-3, in HCC (Liao et al. 2011).

Expression of the Diverse Metalloproteinases in Liver Cancer

Several members of the large MMP family are expressed or overexpressed in HCCs and cholangiocarcinomas and affect the development of a metastatic phenotype (Yamamoto et al. 1999; Bodey et al. 2000; Giannelli et al. 2002; McKenna et al. 2002; Ishii et al. 2003; Ozaki et al. 2003; Matsunaga et al. 2004; Okamoto et al. 2005; Gao et al. 2006; Altadill et al. 2009). Generally, expression of MMPs in cancer cells is augmented by EMT. The EMT factor, Twist1, activates MMPs and by this induces tumor cell invasion (Zhao et al. 2011). Snail, an inducer of EMT, accelerates cancer invasion by an EMT-associated upregulation of MMPs (Miyoshi et al. 2004, 2005). Expression of MMPs increases as a function of increasing stage (Gao et al. 2006). Secretion of MMPs by stromal myofibroblasts is suppressed by TGF-beta1, while the hormone relaxin binding to its cognate receptor, relaxin family peptide receptor 1, upregulates MMPs (Chow et al. 2012).

MMP-1

MMP-1 is involved in both tumor cell invasion and the generation of metastases, also in HCCs (Ogasawara et al. 2005). MMP-1 proteolytically activates protease-activated receptor-1 (PAR-1). In HCCs, the MMP-1/PAR-1 signaling axis is strongly activated and associated with tumor invasion and progression (Liao et al. 2011, 2012). Increased expression of MMP-1 and MMP-2 in HCCs is correlated with tumor differentiation (Ogata et al. 1999). However, other studies arrived at different results. For example, high levels of MMP-1 transcripts were detected in well-differentiated cancer cells of early HCCs, but not in moderately to poorly differentiated HCCs, suggesting an MMP-1-mediated role in early invasive processes, such as destruction of portal tracts (Okazaki et al. 1997).

MMP-2

Expression of MMP-2 is involved in HCC invasion, and its activity is influenced by several genetic variants that modulate the enzyme's effects in the invasive pathway (Wu et al. 2008). Expression of MMP-2 in HCCs is associated with dedifferentiation in HCC (Ogata et al. 1999) and was correlated with intra- and extrahepatic metastases (Liu et al. 2003). Expression of MMP-2 predicted lymph node metastasis in HCCs (Xiang et al. 2011). The secretion of MMP-2 is stimulated by the transcription factor, Snail, which is expressed in HCC cells and mediates EMT. On the other hand, downregulation of Snail in HCC cells is associated with increased expression of the adhesion molecule, E-cadherin, and downregulation of MMP-2 (Chen et al. 2012a). MMP-2 is also upregulated by osteopontin (Chen et al. 2011a,b), through the SDF-1/CXC4 axis (Zhang et al. 2011), via Notch signaling (Zhou et al. 2012), by secreted clusterin (Chen et al. 2012a), Rock2 (Huang et al. 2014), and by sonic hedgehog signaling through focal

adhesion kinase/AKT signaling (Chen et al. 2013a). Osteopontin itself is downregulated by microRNA-181a (Bhattacharyya et al. 2010). The activity of MMP-2 in HCC is strongly controlled by TIMP-2 (Musso et al. 1997; Giannelli et al. 2002). MMP-2 expression is downregulated by microRNA-29b, a microRNA that suppresses angiogenesis, invasion, and metastasis (Fang et al. 2011). As with other MMPs, MMP-2 is regulated by tissue inhibitor of metalloproteinase-2/TIMP-2. Strong expression of TIMP-2 in hilar cholangiocarcinomas is associated with inhibition of cancer invasion and metastasis (Xiao et al. 2004). MMP-2 is also expressed in subsets of gallbladder carcinoma (Karadag et al. 2008).

MMP-3

Expression of MMP-3 is associated with the prognosis of HCV-related HCCs (Okamoto et al. 2010). In HGF-induced invasion of HCC cells, MMP-3 is involved, in that HGF stimulates the secretion of pro-MMP-3 (Monvoisin et al. 2002). Upregulation of MMP-3 in hepatoma cells is associated with a downstream mediation of autocrine motility factor (Yu et al. 2004). MMP-3 is also induced by HBV X protein, which is a known promoter of cell migration (Yu et al. 2005). The pro-metastatic activity of MMP-3 depends on its genetic polymorphism, in that the MMP-3 5A allele was the most prominent MMP-3 enzyme to promote invasion (Okamoto et al. 2010). Expression of MMP-3 in HCC cells is reduced by microRNA-30a-3p (Wang et al. 2014).

MMP-7

Similar to other MMPs, MMP-7 has recently been demonstrated to act in the invasion cascade, also in metastatic HCCs (Gao et al. 2006). In particular, MMP-7 expression is a prognostic factor in cholangiocarcinoma, whereby cholangiocarcinoma cells show strong immunoreactivity for this enzyme (Miwa et al. 2002). Expression of MMP-7 is associated with poor prognosis in patients with intrahepatic cholangiocarcinoma (Hirashita et al. 2012) and is an unfavorable postoperative prognostic factor in perihilar, hilar, and extrahepatic cholangiocarcinomas (Itatsu et al. 2008), and serum MMP-7 seems to be a valuable diagnostic marker in discrimination of cholangiocarcinomas from reactive biliary pathologies (Leelawat et al. 2009). One non-synonymous variant of MMP-7 was found to confer risk of liver cirrhosis in patients with HCC (Hung et al. 2009). MMP-7 engages in a signaling pathway together with beta-catenin. Upregulation of MMP-7 expression by beta-catenin is promoted by DKK1, which is overexpressed in HCCs (Chen et al. 2013b). Similar to sclerostin, DKK1 (Dickkopf-related protein 1) is an antagonist of the Wnt/beta-catenin signaling cascade. DKK1 promotes invasion and metastasis in HCCs, associated with increased RhoA and JNK levels (Tao et al. 2013). In cholangiocarcinomas, DKK1 is related to lymphatic metastasis and an aggressive course (Shi et al. 2013). This phenomenon may be caused by the induction of an invasive phenotype by DKK1. MMP-7 expression is downregulated in HCCs by the tumor suppressor, fibulin-5 (Tu et al. 2014).

MMP-9

MMP-9 has an important role in HCC invasion (Arii et al. 1996; Sun et al. 2005; Nart et al. 2010; Tao et al. 2010; Yeh et al. 2010; Thieringer et al. 2012) and is also involved in invasion of hilar cholangiocarcinoma (Li et al. 2005). Upregulation of MMP-9 is found in a majority of HCCs and is subject to MMP-9 gene polymorphism (El-Samanoudy et al. 2014). Overexpression of MMP-9 mRNA may be associated with the progression of small HCCs with a diameter of <=2 cm (Sakamoto et al. 2000). MMP-9 expression is a significant predictor of recurrence after liver transplantation in HCC patients (Zhang et al. 2006). The MMP family members, MMP-2 and MMP-9, are critical for the invasive potential of numerous malignancies, including HCC. Overexpression of MMP-9 in HCCs is correlated with growth and invasion in

small tumors already (Sakamoto et al. 2000) and is associated with macrovessel invasion in larger tumors (Nart et al. 2010). High expression of MMP-9 was associated with both time to recurrence and overall survival, while high expression of MMP-2 was only correlated with time to recurrence (Chen et al. 2012b). MMP-9 cleaves osteopontin to produce a fragment that is essential for osteopontin-induced invasion of HCC cells (Takafuji et al. 2007). MMP-9 is also expressed in tumor-associated macrophages (TAMs) located at the invasive front of murine HCC (Roderfeld et al. 2010). MMP-9 cooperates with focal adhesion kinase (FAK), whereby this mechanism that is active in HCC cell migration is stimulated by activated hepatic stellate cells (Han et al. 2014). In addition to its role as mediators of histolysis, MMPs may cause other biologic effects, e.g., angiogenesis in cancers (Bergers et al. 2000). In mice, hepatocyte-specific expression of MMP-9 promoted liver tumor development (Thieringer et al. 2012).

The induction and localization of MMP-9 are regulated by several factors. MMP-9 signaling in HCC is promoted by activated hepatic stellate cells (Han et al. 2014), which occur in tumor stroma. MMP-9 activity for mediating invasion is regulated by the calcium-binding protein S100A4 (Zhang et al. 2013) and is strongly regulated by protein kinase C-dependent NF-kappaB activation in HCC cells (Hah and Lee 2003). Trafficking of MMP-9 in invadopodia is regulated by Rab GTPases, specifically Rab40b (Jacob et al. 2013). Induction of MMP-9 expression in HCC is stimulated by interleukin 23 through NF-kappaB induction (Li et al. 2012). Expression of MMP-9 is promoted by the PRL (phosphatase of regenerating liver) phosphatase, a group of distinct protein tyrosine phosphatases. Activation of MMPs is mediated by Twist-induced EMT, whereby specifically MMP-2 and MMP-9 are secreted (Zhao et al. 2011). The activity of MMP-9 and MMP-2 is attenuated by the protein, RECK (reversion-inducing cysteine-rich protein with Kazal motifs), an important regulated metalloproteinase. Downregulating of RECK in cholangiocarcinomas is associated with enhanced MMP-2/MMP-9 activity and a metastatic phenotype (Namwat et al. 2011). HBV viral X protein induces MMP-9 gene expression via activation of ERK and PI-3K/AKT pathway activation (Chung et al. 2004), whereas hepatitis C virus NS3 protein enhances cancer cell invasion by activating MMP-9 activity (Lu et al. 2015). MicroRNA-133a inhibits HCC cell migration and invasion by targeting MMP-9 (Chen et al. 2015). The expression of MMP-9 is inhibited by microRNA-491, which also blocks EMT in HCC (Zhou et al. 2013d). MMP-9 is upregulated in other hepatic and biliary tract cancers, including cholangiocarcinoma. In cholangiocarcinomas, MMP-9 expression is enhanced by downregulation of microRNA-138 (Wang et al. 2013b). MMP-9 expression is enhanced in gallbladder carcinoma (Karadag et al. 2008).

MMP-10

Strong immunoreactivity for MMP-10 was found in HCCs, especially in the extracellular matrix adjacent to blood vessels (Bodey et al. 2000). MMP-10 can be activated by C-terminal-truncated HBV X protein, a process stimulating HCC invasion (Sze et al. 2013).

MMP-11

MMP-11 is strongly expressed in both tumor cells and stromal cells surrounding cancer. There is evidence that MMP-11 is a tumor lymphatic metastasis-associated MMP (Jia et al. 2007). MMP-11 is downregulated by CD147 (basigin), affecting the lymphatic metastasis pattern of HCC in a mouse model (Jia et al. 2007). Expression and secretion of MMP-11, together with VEGF, is inhibited in HCCs by ectopic expression of microRNA-125a (Bi et al. 2012).

MMP-12

Overexpression of MMP-12 was found in 58 % of human HCCs, and its expression was significantly correlated with an invasive phenotype (in particular venous invasion) and poor prognosis in HCC (Ng et al. 2011).

MMP-14

Membrane type 1 MPP (MT1-MMP, MMP-14) promotes invasiveness in HCC cell lines (Murakami et al. 1999), is overexpressed in highly invasive HCCs (Harada et al. 1998), and induces metastases in HCC, but MMP-14 gene polymorphisms also contribute to HCC susceptibility (Chen et al. 2011c). Increased MMP-14 mRNA expression by tumor cells in HCCs may have prognostic significance (Määtä et al. 2000). An aggressive phenotype is observed in HCCs that show atypical localization of MT1-MMP in the tumor cell nuclei (Ip et al. 2007). By its enzymatic activity, it not only degrades extracellular matrix but it also induces a signaling pathway stimulating cell adhesion and proliferation (Ip et al. 2005). MT1-MMP confers a proteolytic activity to invadopodia (see above), particularly upon tumor cell contact with ECM. This activity is regulated by the v-SNARE TI-VAMP/VAMP7 (Steffen et al. 2008). The cell surface level and endocytosis of MMP-14 are also regulated by the planar cell polarity-associated protein, VANGL2, a protein that also induced invadopodium formation (Williams et al. 2012). In tumor cells, endocytosis of MT1-MPP by clathrin- and caveolae-dependent pathways is counteracted by mechanisms stabilizing the enzyme at the cell surface (Poincloux et al. 2009). MT1-MPP is targeted by microRNA-150-5p which inhibits HCC migration and invasion. In metastasizing liver cancers, expression of this MiR is reduced (Li et al. 2014). MT1-MMP can be upregulated by HBV X protein (Ou et al. 2007). Similar to MT1-MMP, also MT3-MMP expression was associated with an invasive phenotype in HCCs (Arai et al. 2007).

Tissue Inhibitors of Metalloproteinases (TIMPs) in Liver Cancer

Tissue inhibitors of metalloproteinases (TIMPs; four members, TIMP-1, TIMP-2, TIMP-3, and TIMP-4) are important regulator proteins that interfere with the activity of certain MMPs. TIMP-1 inhibits MMP-9, while TIMP-2 inhibits MMP-2. Both TIMPs were detected in HCC tumor cells, stromal cells, and endothelial cells, whereby expression signals were stronger for TIMP-1 than for TIMP-2 (Joo et al. 2000; Matsumoto et al. 2004), which is of special interest in the light of the MMP expression patterns in HCCs. In one study, TIMP was preferentially expressed in the capsule of HCCs (Fukuda et al. 1991). Metastatic HCCs showed lower levels of TIMPs (Gao et al. 2006), and HCC tissue expression levels of TIMP-2 were higher in patients without metastases (Giannelli et al. 2002). However, TIMP-1 can create a premetastatic niche in the murine liver through stromal cell-derived factor 1/CXCR4-dependent neutrophil recruitment (Seubert et al. 2015). Expression of TIMPs is heterogeneous and varies considerably among HCC nodules, but there was no clear correlation between the TIMP expression levels, differentiation grade, and invasion, although TIMP expression was also detectable in HCC metastases (Nakatsukasa et al. 1996). In cholangiocarcinoma, expression of TIMP-1 was strong and was associated with the extent of invasion (Nakatsukasa et al. 1996). In cultured cells, expression of TIMP-1 was negatively regulated by the EMT effector, Twist1 (Okamura et al. 2009). In addition to TIMP-1 and TIMP-2, TIMP-3 is involved in the regulation of cancer invasion. Transfection of TIMP-3 in HCC cell lines suppresses invasive capacity (Zhang et al. 2007b). In HBV-associated HCC, TIMP3 can be epigenetically silenced (Lai and Lo 2005).

There are protease inhibitors different from TIMPs. The serine protease inhibitor, clade B, member 1/SERPINB1, is a member of the SERPINB family involved in suppression of migration and invasion in various cancers. SERPINB1 expression in HCCs is correlated with tumor invasion and an aggressive course (Cui et al. 2014).

Metzincin Superfamily Members: ADAMs

A disintegrin and metalloproteinases (ADAMs) or MDCs (metalloprotease-like, disintegrin-like, cysteine-rich proteins) are membrane-bound

metzincins and the adamalysin subfamily. Twenty-two members of ADAM family are known (reviews: Porter et al. 2005; Edwards et al. 2008). ADAMs possess a domain structure similar to that of MMPs, but in contrast to the latter, ADAMs display a cysteine-rich domain, an epidermal growth factor-like repeat domain, and the disintegrin domain, but lack the hemopexin-like domain of MMPs (review: Klein and Bischoff 2011). The main functional activity of ADAM metalloproteases is ectodomain shedding of various receptors, growth factors, Notch, cytokines, and other signaling substances involved in cellular homeostasis ("ADAM sheddases"). For example, ADAM17 is critically involved in post-shedding activation of pro-TNF-alpha and is therefore also termed tumor necrosis factor-alpha convertase or TACE. For several cell membrane signaling proteins, cleave by ADAM sheddases prepares what is called regulated intramembrane proteolysis or RIP, resulting in intracellular domains that can be translocated to the nucleus for the regulation of gene transcription (Edwards et al. 2008).

Various malignant neoplasms express several species of ADAMs, particularly ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17, ADAM19, and ADAM28 (review: Mochizuki and Okada 2007; Duffy et al. 2009). In cancer invasion and spread, the critical function of ADAMs is the metalloproteinase activity of these enzymes (Rocks et al. 2008). Similar to MMPs, the metalloprotease domain is shielded by a pro-domain that involves the cysteine switch mechanism. For activation of the protease, this protecting shield is removed in the trans-Golgi network by the action of proprotein convertases, such as furin (Klein and Bischoff 2011). ADAM8 is overexpressed in HCCs in comparison with normal liver. Expression levels were positively correlated with tumor size, grade, recurrence, and metastasis (Zhang et al. 2013). Downregulation of ADAM10 expression inhibits invasiveness and metastasis of human HCC cells, associated with increased E-cadherin protein levels and a related change in cell migration (Yue et al. 2013). ADAM12 mediates the shedding of the epidermal growth factor receptor (EGFR) ligand, heparin-binding EGF-like growth factor/HB-EGF, in a Notch-dependent manner. Released EB-EGF induces the formation of invadopodia under hypoxic conditions (Diaz et al. 2013). ADAM17 is involved in the cleavage of the ectodomain of numerous transmembrane proteins. ADAM17 is overexpressed in HCC under hypoxic conditions and enhances the phosphorylation of the EGFR (Wang et al. 2013a). ADAM17 is targeted by microRNA-145 which suppresses invasion of HCC cells (Yang et al. 2014). In HCCs, ADAM17 is also regulated by microRNA-122, a tumor suppressor microRNA (Tsai et al. 2009). ADAM28 is implicated in tumor growth and progression in several human cancers (Mochizuki and Okada 2009). It operates through cleavage of the proapoptotic von Willebrand factor. Tumor cells with low expression levels of ADAM28 display a higher rate of apoptosis (Mochizuki et al. 2012).

ADAMTS and ADAMTS-Like Proteins

ADAMTS (a disintegrin and metalloprotease with thrombospondin motifs) are a family of extracellular proteases that is distinguished from ADAM metalloproteases by the presence of multiple copies of thrombospondin 1-like repeats. ADAMTS bind to and process various components of ECM proteins and proteoglycans, including heparin; procollagens I, II, and II; aggrecan; brevican; versican; decorin; fibronectin; and von Willebrand factor. ADAMTS are involved in the regulation of critically important processes such as morphogenesis, angiogenesis, and carcinogenesis. For example, of the at least 20 members in this family, ADAMTS2 is a procollagen N-proteinase; ADAMTS4 and ADAMTS5 are aggrecanases active in the hydrolysis of cartilage aggrecan (review: Tang 2001). Overexpression of ADAMTS1 results in shedding of semaphorin 3C from the ECM, a step that stimulates cell migration (Esselens et al. 2010). The seven ADAMTS-like proteins are proteins that lack proteolytic activity but possess ADAMTS ancillary domains. The proteins have important regulatory roles in the ECM (review: Apte 2009).

Other Proteases Involved in Cancer Invasion and Progression

In invadopodia, few other proteolytic enzymes are expressed, including serine proteinase/seprase, aspartate proteases, threonine proteases, dipeptidyl dipeptidase, and cysteine cathepsins (Jevnikar et al. 2012; Rakashanda et al. 2012). A group of calcium-dependent cysteine proteases is the calpains, enzymes involved in several homeostatic mechanisms. Among the various calpain members, m- and m-calpain are involved in regulating cell migration and invasion. In comparison with normal hepatocytes, these two calpains are elevated in HCC cells and regulate HCC cell migration and invasion (Chen et al. 2013c).

Several types of enzymes active on matrix proteins are produced and secreted by leukocytes infiltrating the tumor stroma. Macrophages express a distinct metalloelastase, a member of the MMP family. Expression of metalloelastase by tumor-associated macrophages in HCC is correlated with angiostatin generation and survival, in that tumors having no metalloelastase expression and hence a reduced angiostatin showed poorer survival (Gorrin Rivas et al. 1998). Human neutrophils produce an elastase that can degrade TIMP-1, a process accelerated by heparin (Nunes et al. 2011).

HCCs can express and secrete various ectopeptidases, including neprilysin (CD10), aminopeptidase N (CD13), and angiotensin-I-converting enzyme (CD143), whereby this expression differs considerably between normal liver and HCCs. In HCCs, neprilysin immunoreactivity is found on canalicular domains, a feature with diagnostic significance (Borscheri et al. 2001). In comparison with normal parenchyma, CD10 is low in HCCs, while CD13 and CD143 were mildly increased. CD13 may be involved in the regulation of cell polarity, whereas CD143 may influence angiogenesis (Rocken et al. 2004).

Thrombin can induce cell migration in HCCs. HCCs express several proteinase-activated receptors (PAR), mainly the thrombin receptors PAR(1), PAR(3), and PAR(4). PAR form a novel G-protein-coupled receptor subfamily. Stimulation of HCC cells in vitro with thrombin increased migration across a collagen barrier (Kaufmann et al. 2007). The urokinase system involves three key components, urokinase-type plasminogen activator (uPA), uPA receptor (uPAR), and plasminogen activator inhibitor type 1 (PAI-1). This system is activated in several tumor types and potently affects tumor invasion and metastasis. Urokinase-type plasminogen activator (uPA) is a key protein in the plasminogen activation system and is critically involved in proteolytic steps in tumor invasion. In human HCCs, uPA and c-met overexpression are coordinated in a complex fashion. Following its binding to its c-met receptor, HGF can upregulate uPA in a dose-dependent manner and by this mechanism augments HCC invasion (Lee et al. 2008). High levels of uPA in HCCs were correlated with macrovessel invasion and metastasis, and in tumors expressing uPA, uPAR, and PAI-1, a more prominent invasion phenotype was observed (Zheng et al. 2000). Overexpression of microRNA-23b in HCC cells leads to uPA and c-met downregulation and to decreased migration (Salvi et al. 2009). Plasmin- and trypsin-mediated activation of MMPs is inhibited by TFPI-2 (tissue factor pathway inhibitor), an extracellular matrix-associated Kunitz-type serine proteinase inhibitor. TFPI-2 inhibits the invasion of HCC cells (Xu et al. 2011).

Non-protease Proteins Involved in ECM Degradation

In the setting of the invasion process, heparan sulfate chains of heparan sulfate proteoglycans located in the ECM are cleaved by the endoglycosidase heparanase. Heparanase is upregulated in HCCs with an invasive-metastatic phenotype (El-Assal et al. 2001; Xiao et al. 2003; Edovitsky et al. 2004; Zhang et al. 2007a). In these neoplasms, heparanase also promotes angiogenesis (Ilan et al. 2006). HCCs also synthesize heparin-degrading sulfatases, sulfatase 1 (SULF1) and sulfatase 2 (SULF2). These two enzymes

desulfatize heparan sulfate proteoglycans localized to cell surface and ECM. SULF1 and SULF2 are differentially expressed in HCCs, in that SULF1 is downregulated in up to a third of HCCs, while SULF2 is upregulated in up to 60 % of primary HCCs, and SULF2 activates MAP kinase and AKT pathways, promoting HCC growth and invasion (Lai et al. 2008).

In the invasion process, several nonstructural proteins of the extracellular matrix play a significant role. These proteins are called matricellular proteins and belong to various protein families. Well-known members include CCN family member cysteine-rich angiogenic inducer 61 (Cyr61/CCN1), CCN6, osteopontin, secreted protein acidic and rich in cysteine (SPARC), angiopoietin-like protein 4 (ANGPTL4), and thrombospondin-1 and thrombospondin-2 (review: Chong et al. 2012).

References

Albiges-Rizo C, Destaing O, Fourcade B, Planus E, Block MR (2009) Actin machinery and mechanosensitivity in invadopodia, podosomes and focal adhesions. J Cell Sci 122:3037–3049

Alexander NR, Branch KM, Parelk A, Clark ES, Iwueke IC, Guelcher SA, Weaver AM (2008) Extracellular matrix rigidity promotes invadopodia activity. Curr Biol 18:1295–1299

Altadill A, Rodriguez M, Gonzalez LO, Junquera S, Corte MD, Gonzalez-Dieguez ML et al (2009) Liver expression of matrix metalloproteases and their inhibitors in hepatocellular carcinoma. Dig Liver Dis 41:740–748

Apte SS (2009) A disintegrin-like and metalloproteinase (reprolysin-type) with thrombospondin type 1 motif (ADAMTS) superfamily: functions and mechanisms. J Biol Chem 284:31493–31497

Arai I, Nagano H, Kondo M, Yamamoto H, Hiraoka N, Sugita Y, Ota H, Yoshioka S et al (2007) Overexpression of MT3-MMP in hepatocellular carcinoma correlates with capsular invasion. Hepatogastroenterology 54:167–171

Arii S, Mise M, Harada T, Furutani M, Ishigami S, Niwano M, Mizumoto M, Fukumoto M et al (1996) Overexpression of matrix metalloproteinase 9 gene in hepatocellular carcinoma with invasive potential. Hepatology 24:316–322

Artym VV, Matsumoto K, Mueller SC, Yamada KM (2011) Dynamic membrane remodeling at invadopodia differentiates invadopodia from podosomes. Eur J Cell Biol 90:172–180

Artym VV, Swatkoski S, Matsumoto K, Campbell CB, Petrie RJ, Dimitriadis EK, Li X, Mueller SC, Bugge TH, Gucek M et al (2015) Dense fibrillar collagen is a potent inducer of invadopodia via a specific signaling network. J Cell Biol 208:331–350

Badowski C, Pawlak G, Grichine A, Chabadel A, Oddou C, Jurdic P, Pfaff M, Albigès-Rizo C et al (2008) Paxillin phosphorylation controls invadopodia /podosomes spatiotemporal organization. Mol Biol Cell 19:633–645

Banon-Rodriguez I, Saez de Guinoa J, Bernardini A, Ragazzini C, Fernandez E, Carrasco YR et al (2013) WIP regulates persistence of cell migration and ruffle formation in both mesenchymal and amoeboid modes of motility. PLoS One 8:e70364

Beaty BT, Sharma VP, Bravo-Cordero JJ, Simpson MA, Eddy RJ, Koleske AJ, Condeelis J (2013) b1 integrin regulates Arg to promote invadopodial maturation and matrix degradation. Mol Biol Cell 24:1661–1675

Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, Tanzawa K, Thorpe P, Itohara S, Werb Z, Hanahan D (2000) Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol 2:737–744

Bharti S, Inoue H, Hirsch DS, Nie Z, Yoon HY, Artym V, Yamada KM, Mueller SC et al (2007) Src-dependent phosphorylation of ASAP1 regulates podosomes. Mol Cell Biol 27:8271–8283

Bhattacharyya SD, Garrison J, Guo H, Mi Z, Markovic J, Kim VM, Kuo PC (2010) Micro-RNA-181a regulates osteopontin-dependent metastatic function in hepatocellular cancer cell lines. Surgery 148:291–297

Bi Q, Tang S, Xia L, Du R, Fan R, Gao L, Jin J, Liang S, Chen Z, Xu G, Nie Y, Wu K et al (2012) Ectopic expression of MiR-125a inhibits the proliferation and metastasis of hepatocellular carcinoma by targeting MMP11 and VEGF. PLoS One 7:e40169

Block MR, Badowski C, Millon-Fremillon A, Bouvard D, Bouin AP, Faurobert E, Gerber-Scokaert D et al (2008) Podosome-type adhesions and focal adhesions, so alike yet so different. Eur J Cell Biol 87:491–506

Boateng LR, Huttenlocher A (2012) Spatiotemporal regulation of Src and its substrates at invadosomes. Eur J Cell Biol 91:878–888

Bodey B, Bodey B, Siegel SE, Kaiser HE (2000) Immunocytochemical detection of MMP-3 and -10 expression in hepatocellular carcinomas. Anticancer Res 20:4585–4590

Borscheri N, Roessner A, Röcken C (2001) Canalicular immunostaining of neprilysin (CD10) as a diagnostic marker for hepatocellular carcinomas. Am J Surg Pathol 25:1297–1303

Bowden ET, Barth M, Thomas D, Glazer RI, Mueller SC (1999) An invasion-related complex of cortactin, paxillin and PKCmu associates with invadopodia at sites of extracellular matrix degradation. Oncogene 18:4440–4449

Branch KM, Hoshino D, Weaver AM (2012) Adhesion rings surround invadopodia and promote maturation. Biol Open 1:711–722

Bravo-Cordero JJ, Hodgson L, Condeelis J (2012) Directed cell invasion and migration during metastasis. Curr Opin Cell Biol 24:277–283

Brisson L, Reshkin SJ, Goré J, Roger S (2012) pH regulators in invadosomal functioning: proton delivery for matrix tasting. Eur J Cell Biol 91:847–860

Buccione R, Caldieri G, Ayala I (2009) Invadopodia: specialized tumor cell structures for the focal degradation of the extracellular matrix. Cancer Metastasis Rev 28:137–149

Chen WT, Wang JY (1999) Specialized surface protrusions of invasive cells, invadopodia and lamellipodia, have differential MT1-MMP, MMP-2, and TIMP-2 localization. Ann NY Acad Sci 878:361–371

Chen RX, Xia YH, Xue TC, Zhang H, Ye SL (2011a) Down-regulation of osteopontin inhibits metastasis of hepatocellular carcinoma cells via a mechanism involving MMP-2 and uPA. Oncol Rep 25:803–808

Chen RX, Xia YH, Xue TC, Ye SL (2011b) Osteopontin promotes hepatocellular carcinoma invasion by up-regulating MMP-2 and uPA expression. Mol Biol Rep 38:3671–3677

Chen TY, Li YC, Liu YF, Tsai CM, Hsieh YH, Lin CW, Yang SF, Weng CJ (2011c) Role of MMP14 gene polymorphisms in susceptibility and pathological development to hepatocellular carcinoma. Ann Surg Oncol 18:2348–2356

Chen D, Wang Y, Zhang K, Jiao X, Yan B, Liang J (2012a) Antisense oligonucleotide against clusterin regulates human hepatocellular carcinoma invasion through transcriptional regulation of matrix metalloproteinase-2 and e-cadherin. Int J Mol Sci 13:10594–10607

Chen R, Cui J, Xu C, Xue T, Guo T, Gao D, Liu Y, Ye S, Ren Z (2012b) The significance of MMP-9 over MMP-2 in HCC invasiveness and recurrence of hepatocellular carcinoma after curative resection. Ann Surg Oncol 19(Suppl 3):S375–S384

Chen JS, Huang XH, Wang Q, Huang JQ, Zhang LJ, Chen XL, Lei J, Cheng ZX (2013a) Sonic hedgehog signaling pathway induces cell migration and invasion through focal adhesion kinase/AKT signaling-mediated activation of matrix metalloproteinase (MMP)-2 and MMP-9 in liver cancer. Carcinogenesis 34:10–19

Chen L, Li M, Li Q, Wang CJ, Xie SQ (2013b) DKK1 promotes hepatocellular carcinoma cell migration and invasion through beta-catenin/MMP7 signaling pathway. Mol Cancer 12:157

Chen B, Tang J, Guo YS, Li Y, Chen ZN, Jiang JL (2013c) Calpains are required for invasive and metastatic potentials of human HCC cells. Cell Biol Int 37:643–652

Chen X, Bo L, Zhao X, Chen Q (2015) MicroRNA-133a inhibits cell proliferation, colony formation ability, migration and invasion by targeting matrix metalloproteinase 9 in hepatocellular carcinoma. Mol Med Rep. doi:10.3892/mmr.2015.3232

Chong HC, Tan CK, Huang RL, Tan NS (2012) Matricellular proteins: a sticky affair with cancers. J Oncol 2012:351089

Chou HC, Anton IM, Holt MR, Curcio C, Lanzardo S, Worth A, Burns S, Thrasher AJ et al (2006) WIP regulates the stability of localization of WASP to podosomes in migrating dendritic cells. Curr Biol 16:2337–2344

Chow BS, Chew EG, Zhao C, Bathgate RA, Hewitson TD, Samuel CS (2012) Relaxin signals through a RXFP1-pERK-nNOS-NO-cGMP-dependent pathway to up-regulate matrix metalloproteinases: the additional involvement of iNOS. PLoS One 7:e42714

Chung TW, Lee YC, Kim CH (2004) Hepatitis B viral HBx induces matrix metalloproteinase-9 gene expression through activation of ERK and Pl-3K/AKT pathways: involvement of invasive potential. FASEB J 18:1123–1125

Clark ES, Whigham AS, Yarbrough WG, Weaver AM (2007) Cortactin is an essential regulator of matrix metalloproteinase secretion and extracellular matrix degradation in invadopodia. Cancer Res 67:4227–4235

Collin O, Na S, Chowdhury F, Hong M, Shin ME, Wang F, Wang N (2008) Self-organized podosomes are dynamic mechanosensors. Curr Biol 18:1288–1294

Courtneidge et al. (2005) http://www.ncbi.nlm.nih.gov/pubmed/16869750

Coussens LM, Werb Z (1996) Matrix metalloproteinases and the development of cancer. Chem Biol 3:895–904

Crimaldi L, Courtneidge SA, Gimona M (2009) Tks5 recruits AFAP-110, p190RhoGAP, and cortactin for podosome formation. Exp Cell Res 315:2581–2592

Cui X, Liu Y, Wan C, Lu C, Cai J, He S, Ni T, Zhu J, Wei L, Zhang Y, Qian H (2014) Decreased expression of SERPINB1 correlates with tumor invasion and poor prognosis in hepatocellular carcinoma. J Mol Histol 45:59–68

Dai JY, Dou KF, Wang CH, Zhao P, Lau WB, Tao L, Wu YM, Tang J, Jiang JL et al (2009) The interaction of HAb18G/CD147 with integrin alpha6beta1 and its implications for the invasion potential of human hepatoma cells. BMC Cancer 9:337

Davuluri G, Augoff K, Schiemann WP, Plow EF, Sossey-Alaoui K (2014) WAVE3-NFkB interplay is essential for the survival and invasion of cancer cells. PLoS One 9:e10627

Deryugina EI, Quigley JP (2006) Matrix metalloproteinases and tumor metastasis. Cancer Metastasis Rev 25:9–34

Destaing O, Planus E, Bouvard D, Oddou C, Badowski C, Bossy V, Raducanu A, Fourcade B et al (2010) b1A integrin is a master regulator of invadosome organization and function. Mol Biol Cell 21:4108–4119

Destaing O, Block MR, Planus E, Albiges-Rizo C (2011) Invadosome regulation by adhesion signaling. Curr Opin Cell Biol 23:597–606

Di Martino J, Paysan L, Gest C, Lagrée V, Juin A, Saltel F, Moreau V (2014) Cdc42 and Tks5: a minimal and universal molecular signature for functional invadosomes. Cell Adh Migr 8:280–292

Diaz B, Yuen A, Iizuka S, Higashiyama S, Courtneidge SA (2013) Notch increases the shedding of HB-EGF by

ADAM12 to potentiate invadopodia formation in hypoxia. J Cell Biol 201:279–292
Dovas A, Gevrey JC, Grossi A, Park H, Abou-Kheir W, Cox D (2009) Regulation of podosome dynamics by WASP phosphorylation: implication in matrix degradation and chemotaxis in macrophages. J Cell Sci 122:3873–3882
Duffy MJ, McKiernan E, O'Donovan N, McGowan PM (2009) Role of ADAMs in cancer formation and progression. Clin Cancer Res 15:1140–1144
Eckert MA, Lwin TM, Chang AT, Kim J, Danis E, Ohno-Machado L, Yang J (2011) Twist1-induced invadopodia formation promotes tumor metastasis. Cancer Cell 19:372–386
Edovitsky E, Elkin M, Zcharia E, Peretz T, Vlodavsky I (2004) Heparanase gene silencing, tumor invasiveness, angiogenesis, and metastasis. J Natl Cancer Inst 96:1219–1230
Edwards DR, Handsley MM, Pennington CJ (2008) The ADAM metalloproteinases. Mol Aspects Med 29:258–289
El-Assal ON, Yamanoi A, Ono T, Kohno H, Nagasue N (2001) The clinicopathological significance of heparanase and basic fibroblast growth factor expressions in hepatocellular carcinoma. Clin Cancer Res 7:1299–1305
El-Samanoudy A, Monir R, Badawy A, Ibrahim L, Farag K, El Baz S, Alenizi D, Alenezy A (2014) Matrix metalloproteinase-9 gene polymorphism in hepatocellular carcinoma patients with hepatitis B and C viruses. Genet Mol Res 13:8025–8034
Endo M, Nishita M, Fujii M, Minami Y (2015) Insight into the role of wnt5a-induced signaling in normal and cancer cells. Int Rev Cell Mol Biol 314:117–148
Esselens C, Malapeira J, Colomé N, Casal C, Rodriguez-Manzaneque JC, Canals F et al (2010) The cleavage of semaphorin 3C induced by ADAMTS1 promotes cell migration. J Biol Chem 285:2463–2473
Fang JH, Zhou HC, Zeng C, Yang J, Liu Y, Huang X, Zhang JP, Guan XY, Zhuang SM (2011) MicroRNA-29b suppresses tumor angiogenesis, invasion and metastases by regulating MMP-2 expression. Hepatology 54:1729–1740
Friedl P, Wolf K (2009) Proteolytic interstitial cell migration: a five-step process. Cancer Metastasis Rev 28:129–135
Fukuda Y, Imoto M, Koyama Y, Miyazawa Y, Nakano I, Hattori M, Urano F, Kodama S et al (1991) Immunohistochemical study on tissue inhibitors of metalloproteinases in normal and pathological human livers. Gastroenterol Jpn 26:37–41
Gad A, Lach S, Crimaldi L, Gimona M (2008) Plectin deposition at podosome rings requires myosin contractility. Cell Motil Cytoskeleton 65:614–625
Gao ZH, Tretiakova MS, Liu WH, Gong C, Farris PD, Hart J (2006) Association of E-cadherin, matrix metalloproteinases, and tissue inhibitors of metalloproteinases with the progression and metastasis of hepatocellular carcinoma. Mod Pathol 19:533–540
Garcia E, Jones GE, Machesky LM, Anton IM (2012) WIP: wasp-interacting proteins at invadopodia and podosomes. Eur J Cell Biol 91:869–877
Gawden-Bone C, Zhou Z, King E, Prescott A, Watts C, Lucocq J (2010) Dendritic cell podosomes are protrusive and invade the extracellular matrix using metalloproteinase MMP-14. J Cell Sci 123:1427–1437
Génot E, Gligorijevic B (2014) Invadosomes in their natural habitat. Eur J Cell Biol 93:367–379
Gianelli G, Bergamini C, Marinosci F, Fransvea E, Quaranta M, Lupo L, Schiraldi O et al (2002) Clinical role of MMP-2/TIMP-2 imbalance in hepatocellular carcinoma. Int J Cancer 97:425–431
Giannelli G, Astigiano S, Antonaci S, Morini M, Barbieri O, Noonan DM, Albini A (2002) Role of the alpha3beta1 and alpha6beta4 integrins in tumor invasion. Clin Exp Metastasis 19:217–223
Gimona M (2008) The microfilament system in the formation of invasive adhesions. Semin Cancer Biol 18:23–34
Gimona M, Buccione R (2006) Adhesions that mediate invasion. Int J Biochem Cell Biol 38:1875–1892
Gimona M, Buccione R, Courtneidge SA, Linder S (2008) Assembly and biological role of podosomes and invadopodia. Curr Opin Cell Biol 20:235–241
Goicoechea S, Arneman D, Disanza A, Garcia-Mata R, Scita G, Otey CA (2006) Palladin binds to Eps8 and enhances the formation of dorsal ruffles and podosomes in vascular smooth muscle cells. J Cell Sci 199:3316–3324
Goicoechea SM, Bednarski B, Garcia-Mata R, Prentice-Dunn H, Kim HJ, Otey CA (2009) Palladin contributes to invasive motility in human breast cancer cells. Oncogene 28:587–598
Goicoechea SM, Garcia-Mata R, Staub J, Valdivia A, Sharek L, McCulloch CG, Hwang RF et al (2014) Palladin promotes invasion of pancreatic cancer cells by enhancing invadopodia formation in cancer-associated fibroblasts. Oncogene 33:1265–1273
Gorrin Rivas MJ, Arii S, Furutani M, Harada T, Mizumoto M, Nishiyama H, Fujita J, Imamura M (1998) Expression of human macrophage metalloelastase gene in hepatocellular carcinoma: correlation with angiostatin generation and its clinical significance. Hepatology 28:986–993
Grass GD, Bratoeva M, Toole BP (2012) Regulation of invadopodia formation and activity by CD147. J Cell Sci 125:777–788
Griera M, Martin-Villar E, Banon-Rodriguez I, Blundell MP, Jones GE, Anton IM, Thrasher AJ et al (2014) Integrin linked kinase (ILK) regulates podosome maturation and stability in dendritic cells. Int J Biochem Cell Biol 50:47–54
Gringel A, Walz D, Rosenberger G, Minden A, Kutsche K, Kopp P, Linder S (2006) PAK4 and alphaPIX determine podosome size and number in macrophages through localized actin regulation. J Cell Physiol 209:568–579
Gurksy LA, Xu X, Labrada LN, Nguyen NT, Xiao L, van Golen KL, Jia X, Farach-Carson MC (2012)

Hyaluronan (HA) interacting proteins RHAMM and hyaluronidase impact prostate cancer cell behavior and invadopodia formation in 3D HA-based hydrogels. PLoS One 7:e50075

Ha VL, Bharti S, Inoue H, Vass WC, Campa F, Nie Z, de Gramont A, Ward Y, Randazzo PA (2008) ASAP3 is a focal adhesion-associated Arf GAP that functions in cell migration and invasion. J Biol Chem 283:14915–14926

Hah N, Lee ST (2003) An absolute role of the PKC-dependent NF-kappaB activation for induction of MMP-9 in hepatocellular carcinoma cells. Biochem Biophys Res Commun 305:428–433

Han S, Han L, Yao Y, Sun H, Zan X, Liu Q (2014) Activated hepatic stellate cells promote hepatocellular carcinoma cell migration and invasion via the activation of FAK-MMP9 signaling. Oncol Rep 31:641–648

Harada T, Arii S, Mise M, Imamura T, Higashitsuji H, Furutani M, Niwano M, Ishigami S et al (1998) Membrane-type matrix metalloproteinase-1 (MT1-MTP) gene is overexpressed in highly invasive hepatocellular carcinomas. J Hepatol 28:231–239

Hirashita T, Iwashita Y, Ohta M, Komori Y, Eguchi H, Yada K, Kitano S (2012) Expression of matrix metalloproteinase-7 is an unfavorable prognostic factor in intrahepatic cholangiocarcinoma. J Gastrointest Surg 16:842–848

Hoshino D, Branch KM, Weaver AM (2013a) Signaling inputs to invadopodia and podosomes. J Cell Sci 126:2979–2989

Hoshino D, Nagano M, Saitoh A, Koshikawa N, Suzuki T, Seiki M (2013b) The phosphoinositide-binding protein ZF21 regulates ECM degradation by invadopodia. PLoS One 8:e50825

Huang D, Du X, Yuan R, Chen L, Liu T, Wen C, Huang M, Li M, Hao L, Shao J (2014) Rock2 promotes the invasion and metastasis of hepatocellular carcinoma by modifying MMP2 ubiquitination and degradation. Biochem Biophys Res Commun 453:49–56

Hung TM, Chang SC, Yu WH, Wang YW, Huang C, Lu SC, Lee PH, Chang MF (2009) A novel nonsynonymous variant of matrix metalloproteinase-7 confers risk of liver cirrhosis. Hepatology 50:1184–1193

Huveneers S, Arslan S, van de Water B, Sonnenberg A, Danen EH (2008) Integrins uncouple Src-induced morphological and oncogenic transformation. J Biol Chem 283:13243–13251

Ilan N, Elkin M, Vlodavsky I (2006) Regulation, function and clinical significance of heparanase in cancer metastasis and angiogenesis. Int J Biochem Cell Biol 38:2018–2039

Ip YC, Cheung ST, Leing KL, Fan ST (2005) Mechanism of metastasis by membrane type 1-matrix metalloproteinase in hepatocellular carcinoma. World J Gastroenterol 11:6269–6276

Ip YC, Cheung ST, Fan ST (2007) Atypical localization of membrane type 1-matrix metalloproteinase in the nucleus is associated with aggressive features of hepatocellular carcinoma. Mol Carcinog 46:225–230

Ishii Y, Nakasato Y, Kobayashi S, Yamazaki Y, Aoki T (2003) A study on angiogenesis-related matrix metalloproteinase networks in primary hepatocellular carcinoma. J Exp Clin Cancer Res 22:461–470

Itatsu K, Zen Y, Yamaguchi J, Ohira S, Ishikawa A, Ikeda H, Sato Y, Harada K, Sasaki M et al (2008) Expression of matrix metalloproteinase 7 is an unfavorable postoperative prognostic factor in cholangiocarcinoma of the perihilar, hilar, and extrahepatic bile ducts. Hum Pathol 39:710–719

Jacob A, Jing J, Lee J, Schedin P, Gilbert SM, Peden AA, Junutula JR, Prekeris R (2013) Rab40b regulates trafficking of MMP2 and MMP9 during invadopodia formation and invasion of breast cancer cells. J Cell Sci 126:4647–4658

Jevnikar Z, Mirkovic B, Fonovic UP, Zidar N, Svajger U, Kos J (2012) Three-dimensional invasion of macrophages is mediated by cysteine cathepsins in protrusive podosomes. Eur J Immunol 42:3429–3441

Jia L, Cao J, Wei W, Wang S, Zuo Y, Zhang J (2007) CD147 depletion down-regulates matrix metalloproteinase-11, vascular endothelial growth factor-A expression and the lymphatic metastasis potential of murine hepatocarcinoma Hca-F cells. Int J Biochem Cell Biol 39:2135–2142

Jia L, Xu H, Zhao Y, Jiang L, Yu J, Zhang J (2008) Expression of CD147 mediates tumor cells invasion and multidrug resistance in hepatocellular carcinoma. Cancer Invest 26:977–983

Joo YE, Seo YH, Lee WS, Kim HS, Choi SK, Rew JS, Park CS, Kim SJ (2000) Expression of tissue inhibitors of metalloproteinases (TIMPs) in hepatocellular carcinoma. Korean J Intern Med 15:171–178

Juin A, Billottet C, Moreau V, Destaing O, Albiges-Rizo C, Rosenbaum J, Génot E et al (2012) Physiological type I collagen organization induces the formation of a novel class of linear invadosomes. Mol Biol Cell 23:297–309

Jung O, Choi YJ, Kwak TK, Kang M, Lee MS, Ryu J, Kim HJ, Lee JW (2013) The COOH-terminus of TM4SF5 in hepatoma cell lines regulates c-Src to form invasive protrusions via EGFR Tyr845 phosphorylation. Biochim Biophys Acta 1833:629–642

Karadag N, Kirimlioglu H, Isik B, Yilmaz S, Kirimlioglu V (2008) Expression of matrix metalloproteinase in gallbladder carcinoma and their significance in carcinogenesis. Appl Immunohistochem Mol Morphol 16:148–152

Kaufmann R, Rahn S, Pollrich K, Hertel J, Dittmar Y, Hommann M, Henklein P, Biskup C et al (2007) Thrombin-mediated hepatocellular carcinoma cell migration: cooperative action via proteinase-activated receptors 1 and 4. J Cell Physiol 211:699–707

Kaverina I, Stradal TE, Gimona M (2003) Podosome formation in cultured A7r5 vascular muscle cells requires Arp2/3-dependent de-novo actin polymerization at discrete microdomains. J Cell Sci 116:4915–4924

Klein T, Bischoff R (2011) Active metalloproteases of the A disintegrin and metalloprotease (ADAM) family: biological function and structure. J Proteome Res 10:1–33

Kleiner DE, Stetler-Stevenson WG (1999) Matrix metalloproteinases and metastasis. Cancer Chemother Pharmacol 43(Suppl):S42–S51

Klemke RL (2012) Trespassing cancer cells: 'fingerprinting' invasive protrusions reveals metastatic culprits. Curr Opin Cell Biol 24:662–669

Kocher HM, Sandle J, Mirza TA, Li NF, Hart IR (2009) Ezrin interacts with cortactin to form podosomal rosettes in pancreatic cancer cells. Gut 58:271–284

Kopp P, Lamers R, Aepfelbacher M, Woehlke G, Rudel T, Machuy N, Steffen W, Linder S (2006) The kinesin KIF1C and microtubule plus ends regulate podosome dynamics in macrophages. Mol Biol Cell 17:2811–2823

Kung ML, Tsai HE, Hu TH, Kuo HM, Liu LF, Chen SC, Lin PR, Ma YL, Wang EM et al (2012) Hepatoma-derived growth factor stimulates podosome rosettes formation in NIH/3T3 cells through the activation of phosphatidylinositol 3-kinase/Akt pathway. Biochem Biophys Res Commun 425:169–176

Lagal V, Abrivard M, Gonzalez V, Perazzi A, Popli S, Verzeroli E, Tardieux I (2014) Spire-1 contributes to the invadosome and its associated invasive properties. J Cell Sci 127:328–340

Lai HJ, Lo SJ (2005) Epigenetic methylation of TIMP-3 may play a role in HBV-associated hepatocellular carcinoma. Chang Gung Med J 28:453–455

Lai JP, Thompson JR, Sandhu DS, Roberts LR (2008) Heparin-degrading sulfatases in hepatocellular carcinoma: roles in pathogenesis and therapy targets. Future Oncol 4:803–814

Lee et al. (2008) http://www.ncbi.nlm.nih.gov/pubmed/17992475

Leelawat K, Sakchinabut S, Narong S, Wannaprasert J (2009) Detection of serum MMP-7 and MMP-9 in cholangiocarcinoma patients: evaluation of diagnostic accuracy. BMC Gastroenterol 9:30

Leong HS, Robertson AE, Stoletov K, Leith SJ, Chin CA, Chien AE, Hague MN, Ablack A, Carmine-Simmen K et al (2014) Invadopodia are required for cancer cell extravasation and are a therapeutic target for metastasis. Cell Rep 8:1558–1570

Li Y, Zhang Y, Zheng Q (2005) Expression of RECK gene and MMP-9 in hilar cholangiocarcinoma and its clinical significance. J Huazhong Univ Sci Technolog Med Sci 25:552–554

Li J, Lau G, Chen L, Yuan YF, Huang J, Luk JM, Xie D, Guan XY (2012) Interleukin 23 promotes hepatocellular carcinoma metastasis via NF-kappa B induced matrix metalloproteinase 9 expression. PLoS One 7: e46264

Li T, Xie J, Shen C, Cheng D, Shi Y, Wu Z, Zhan Q, Deng X, Chen H, Shen B, Peng C, Li H, Zhu Z (2014) miR-150-5p inhibits hepatoma cell migration and invasion by targeting MMP14. PLoS One 9: e15577

Liao CG, Kong LM, Song F, Xing JL, Wang LX, Sun ZJ, Tang H, Yao H, Zhang Y et al (2011) Characterization of basigin isoforms and the inhibitory function of basigin-3 in human hepatocellular carcinoma proliferation and invasion. Mol Cell Biol 31:2591–2604

Liao M, Tong P, Zhao J, Zhang Y, Li Z, Wang J, Feng X, Hu M, Pan Y (2012) Prognostic value of matrix metalloproteinase-1/proteinase-activated receptor-1 signaling axis in hepatocellular carcinoma. Pathol Oncol Res 18:397–403

Linder S (2007) The matrix corroded: podosomes and invadopodia in extracellular matrix degradation. Trends Cell Biol 17:107–117

Linder S, Aepfelbacher M (2003) Podosomes: adhesion hot-spots of invasive cells. Trends Cell Biol 13:376–385

Linder S, Kopp P (2005) Podosomes at a glance. J Cell Sci 118:2079–2082

Linder S, Hüfner K, Wintergerst U, Aepfelbacher M (2000) Microtubule-dependent formation of podosomal adhesion structures in primary human macrophages. J Cell Sci 23:4165–4176

Linder S, Wiesner C, Himmel M (2011) Degrading devices: invadosomes in proteolytic cell invasion. Annu Rev Cell Dev Biol 27:185–211

Liu Z, Yan L, Xiang T, Jiang L, Yang B (2003) Expression of vascular endothelial growth factor and matrix metalloproteinase-2 correlates with the invasion and metastasis of hepatocellular carcinoma. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi 20:249–250

Liu XS, Luo HJ, Yang H, Wang L, Kong H, Jin YE, Wang F, Gu MM, Chen Z, Lu ZY et al (2007) Palladin regulates cell and extracellular matrix interaction through maintaining normal actin cytoskeleton architecture and stabilizing beta1-integrin. J Cell Biochem 100:1288–1300

Lizarraga F, Poincloux R, Romao M, Montagnac G, Le Dez G, Bonne I, Rigaill G, Raposo G et al (2009) Diaphanous-related formins are required for invadopodia formation and invasion of breast tumor cells. Cancer Res 69:2792–2800

Lohmer LL, Kelley LC, Hagedorn EJ, Sherwood DR (2014) Invadopodia and basement membrane invasion in vivo. Cell Adh Migr 8:246–255

Lu JT, Zhao WD, He W, Wei W (2012) Hedgehog signaling pathway mediates invasion and metastasis of hepatocellular carcinoma via ERK pathway. Acta Pharmacol Sin 33:691–700

Lu L, Zhang Q, Wu K, Chen X, Zheng Y, Zhu C, Wu J (2015) Hepatitis C virus NS3 protein enhances cancer cell invasion by activating matrix metalloproteinase-9 and cyclooxygenase-2 through ERK/p38/NK-kB signal cascade. Cancer Lett 356:470–478

Luxenburg C, Parsons JT, Addadi L, Geiger B (2006) Involvement of the Src-cortactin pathway in podosome formation and turnover during polarization of cultures osteoclasts. J Cell Sci 119:4878–4888

Määtä M, Soini Y, Liakka A, Autio-Harmainen H (2000) Differential expression of matrix metalloproteinase

(MMP)-2, MMP-9, and membrane type 1-MMP in hepatocellular and pancreatic adenocarcinoma: implications for tumor progression and clinical prognosis. Clin Cancer Res 6:2726–2734

Mannello F, Medda V (2012) Nuclear localization of matrix metalloproteinases. Prog Histochem Cytochem 47:27–58

Matsumoto E, Nakatsukasa H, Nouso K, Kobayashi Y, Nakamura S, Suzuki M, Takuma Y et al (2004) Increased levels of tissue inhibitor of metalloproteinase-1 in human hepatocellular carcinoma. Liver Int 24:379–383

Matsunaga Y, Koda M, Murawaki Y (2004) Expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in hepatocellular carcinoma tissue, compared with the surrounding non-tumor tissue. Res Commun Mol Pathol Pharmacol 115–116:143–150

McKenna GJ, Chen Y, Smith RM, Meneghetti A, Ong C, McMaster R, Scudamore CH et al (2002) A role of matrix metalloproteinases and tumor host interaction in hepatocellular carcinomas. Am J Surg 183:588–594

McNiven MA, Baldassarre M, Buccione R (2004) The role of dynamin in the assembly and function of podosomes and invadopodia. Front Biosci 9:1944–1953

Miwa S, Miyagawa S, Soeda J, Kawasaki S (2002) Matrix metalloproteinase-7 expression and biologic aggressiveness of cholangiocellular carcinoma. Cancer 94:428–434

Miyoshi A, Kitajima Y, Sumi K, Sato K, Hagiwara A, Koga Y, Miyazaki K (2004) Snail and SIP1 increase cancer invasion by upregulation MMP family in hepatocellular carcinoma cells. Br J Cancer 90:1265–1273

Miyoshi A, Kitajima Y, Kido S, Shimonishi T, Matsuyama S, Kitahara K, Miyazaki K (2005) Snail accelerates cancer invasion by upregulating MMP expression and is associated with poor prognosis of hepatocellular carcinoma. Br J Cancer 92:252–258

Mochizuki S, Okada Y (2007) ADAMs in cancer cell proliferation and progression. Cancer Sci 98:621–628

Mochizuki S, Okada Y (2009) ADAM28 as a target for human cancers. Curr Pharm Des 15:2349–2358

Mochizuki S, Soeijima K, Shimoda M, Abe H, Sasaki A, Okano HJ, Okano H, Okada Y (2012) Effect of ADAM28 on carcinoma cell metastasis by cleavage of von Willebrand factor. J Natl Cancer Inst 104:906–922

Monvoisin et al. (2002) http://www.ncbi.nlm.nih.gov/pubmed/11774258

Morita T, Mayanagi T, Yoshio T, Sobue K (2007) Changes in the balance between caldesmon regulated by p21-activated kinases and the Arp2/3 complex govern podosome formation. J Biol Chem 282:8454–8463

Mukhopadhyay UK, Eves R, Jia L, Mooney P, Mak AS (2009) p53 suppresses Src-induced podosome and rosette formation and cellular invasiveness through the upregulation of caldesmon. Mol Cell Biol 29:3088–3098

Murakami K, Sakukawa R, Ikeda T, Matsuura T, Hasumura S, Nagamori S, Yamada Y et al (1999) Invasiveness of hepatocellular carcinoma cell lines: contribution of membrane-type 1 matrix metalloproteinase. Neoplasia 1:424–430

Murphy DA, Courtneidge SA (2011) The 'ins' and 'outs' of podosomes and invadopodia: characteristics, formation and function. Nat Rev Cell Biol 12:413–416

Musso O, Théret N, Campion JP, Turlin B, Milani S, Grappone C, Clément B (1997) In situ detection of matrix metalloproteinase-2 (MMP2) and the metalloproteinase inhibitor TIMP2 transcripts in human primary hepatocellular carcinoma and in liver metastasis. J Hepatol 26:593–605

Nabeshima K, Iwasaki H, Koga K, Hojo H, Suzumiya J, Kikuchi M (2006) Emmprin (basigin/CD147): matrix metalloproteinase modulator and multifunctional cell recognition molecule that plays a critical role in cancer progression. Pathol Int 56:359–367

Nakatsukasa H, Ashida K, Higashi T, Ohguchi S, Tsuboi S, Hino N, Nouso K, Urabe Y et al (1996) Cellular distribution of transcripts for tissue inhibitor of metalloproteinases 1 and 2 in human hepatocellular carcinomas. Hepatology 24:82–88

Namwat N, Puetkasichonpasutha J, Loilome W, Yongvanit P, Techasen A, Puapairoj A et al (2011) Downregulation of reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) is associated with enhanced expression of matrix metalloproteinases and cholangiocarcinoma metastases. J Gastroenterol 46:664–675

Nart D, Yaman B, Yilmaz F, Zeytunlu M, Karasu Z, Kiliç M (2010) Expression of matrix metalloproteinase-9 in predicting prognosis of hepatocellular carcinoma after liver transplantation. Liver Transpl 16:621–630

Ng KT, Qi X, Kong KL, Cheung BY, Lo CM, Poon RT, Fan ST, Man K (2011) Overexpression of matrix metalloproteinase-12 (MMP-12) correlates with poor prognosis of hepatocellular carcinoma. Eur J Cancer 47:2299–2305

Nunes GL, Simoes A, Dyszy FH, Shida CS, Juliano MA, Juliano L, Gesteira TF et al (2011) Mechanism of heparin acceleration of tissue inhibitor of metalloproteases-1 (TIMP-1) degradation by the human neutrophil elastase. PLoS One 6:e21525

Ogasawara S, Yano H, Momosaki S, Nishida N, Takemoto Y, Kojiro S, Kojiro M (2005) Expression of matrix metalloproteinases (MMPs) in cultured hepatocellular carcinoma (HCC) cells and surgically resected HCC tissues. Oncol Rep 13:1043–1048

Ogata R, Tirmura T, Kin M, Ueno T, Tateishi Y, Kuromatsu R, Shimauchi Y, Sakamoto M et al (1999) Increased expression of membrane type 1 matrix metalloproteinase and matrix metalloproteinase-2 with tumor dedifferentiation in hepatocellular carcinomas. Hum Pathol 30:443–450

Okamoto K, Mandai M, Mimura K, Murakawi Y, Yuasa I (2005) The association of MMP-1, -3 and -9 genotypes with the prognosis of HCV-related hepatocellular

carcinoma patients. Res Commun Mol Pathol Pharmacol 117–118:77–89
Okamoto K, Ishida C, Ikebuchi Y, Mandai M, Mimura K, Murakawi Y, Yuasa I (2010) The genotypes of IL-1 beta and MMP-3 are associated with prognosis of HCV-related hepatocellular carcinoma. Intern Med 49:887–895
Okamura H, Yoshida K, Haneji T (2009) Negative regulation of TIMP1 is mediated by transcription factor TWIST1. Int J Oncol 35:181–186
Okazaki I, Wada N, Nakano M, Saito A, Takasaki K, Doi M, Kameyama K, Otani Y et al (1997) Difference in gene expression for matrix metalloproteinase-1 between early and advanced hepatocellular carcinomas. Hepatology 25:580–584
Ou DP, Tao YM, Tang FQ, Yang LY (2007) The hepatitis B virus X promotes hepatocellular carcinoma metastasis by upregulation of matrix metalloproteinases. Int J Cancer 120:1208–1214
Oudekirk JL, Krendel M (2014) Myosin 1e is a component of the invadosome core that contributes to regulation of invadosome dynamics. Exp Cell Res 322:265–276
Overall CM, Dean RA (2006) Degradomics: systems biology of the protease web. Pleiotropic roles of MMPs in cancer. Cancer Metastasis Rev 25:69–75
Ozaki I, Mizuta T, Zhao G, Zhang H, Yoshimura T, Kawazoe S, Eguchi Y, Yasutake T et al (2003) Induction of multiple matrix metalloproteinase genes in human hepatocellular carcinoma by hepatocyte growth factor via a transcription factor Ets-1. Hepatol Res 27:289–301
Pan YR, Tseng WS, Chang PW, Chen HC (2013a) Phosphorylation of moesin by Jun N-terminal kinase is important for podosome rosette formation in Src-transformed fibroblasts. J Cell Sci 126:5670–5680
Pan YR, Cho KH, Lee HH, Chang ZF, Chen HC (2013b) Protein tyrosine phosphatase SHP2 suppresses podosome rosette formation in Src-transformed fibroblasts. J Cell Sci 126:657–666
Paz H, Pathak N, Yang J (2014) Invading one step at a time : the role of invadopodia in tumor metastasis. Oncogene 33:4193–4202
Pignatelli J, Tumbarello DA, Schmidt RP, Turner CE (2012a) Hic-5 promotes invadopodia formation and invasion during TGF-β-induced epithelial-mesenchymal transition. J Cell Biol 197:421–437
Pignatelli J, LaLonde SE, LaLonde DP, Clarke D, Tunrer CE (2012b) Actopaxin (a-parvin) phosphorylation is required for matrix degradation and cancer cell invasion. J Biol Chem 287:37309–37320
Poincloux R, Lizarraga F, Chavrier P (2009) Matrix invasion by tumour cells: a focus on MT1-MMP trafficking to invadopodia. J Cell Sci 122:3015–3024
Porter S, Clark IM, Kevorkian L, Edwards DR (2005) The ADAMTS metalloproteinases. Biochem J 386:15–27
Qian AR, Zhang W, Cao JP, Yang PF, Gao X, Wang Z, Xu HY, Weng YY, Shang P (2008) Downregulation of CD147 expression alters cytoskeleton architecture and inhibits gelatinase production and SAPK pathway in human hepatocellular carcinoma cells. J Exp Clin Cancer Res 27:50
Rakashanda S, Rana F, Rafiq S, Masood A, Amin S (2012) Role of proteases in cancer: a review. Biotechnol Mol Biol Rev 7:90–101
Rocken C, Carl-McGrath S, Grantzdorffer I, Mantke R, Roessner A, Lendeckel U (2004) Ectopeptidases are differentially expressed in hepatocellular carcinomas. Int J Oncol 24:487–495
Rocks N, Paulissen G, El Hour M, Quesada F, Crahay C, Gueders M, Foidart JM et al (2008) Emerging roles of ADAM and ADAMTS metalloproteinases in cancer. Biochimie 90:369–379
Roderfeld M, Rath T, Lammert F, Dierkes C, Graf J, Roeb E (2010) Innovative immunohistochemistry identifies MMP-9 expressing macrophages at the invasive front of murine HCC. World J Hepatol 2:175–179
Rottiers P, Saltel F, Daubon T, Chaigne-Delalande B, Tridon V, Billottet C, Reuzeau E, Génot E (2009) TGFbeta-induced endothelial podosomes mediate basement membrane collagen degradation in arterial vessels. J Cell Sci 122:4311–4318
Saengsawang W, Taylor KL, Lumbard DC, Mitok K, Price A, Pietila L, Gomez TM, Dent EW (2013) CIP4 coordinates with phospholipids and actin-associated proteins to localize to the protruding edge and produce actin ribs and veils. J Cell Sci 126:2411–2423
Sakamoto Y, Mafune K, Mori M, Shiraishi T, Imamura H, Mori M, Takayama T, Makuuchi M (2000) Overexpression of MMP-9 correlates with growth of small hepatocellular carcinoma. Int J Oncol 17:237–243
Saltel F, Daubon T, Juin A, Ganuza IE, Veillat V, Génot E (2011) Invadosomes: intriguing structures with promise. Eur J Cell Biol 90:100–107
Salvi A, Sabelli C, Moncini S, Venturin M, Arici B, Riva P, Portolani N, Giulini SM et al (2009) Micro-RNA-23b mediates urokinase and c-met downmodulation and a decreased migration of human hepatocellular carcinoma cells. FEBS J 276:2966–2982
Schachtner H, Calaminus SD, Thomas SG, Machesky LM (2013) Podosomes in adhesion, migration, mechanosensing and matrix remodeling. Cytoskeleton (Hoboken) 70:572–589
Schaller MD (2001) Paxillin: a focal adhesion-associated adaptor protein. Oncogene 20:6459–6472
Schlaepfer DD, Mitra SK, Ilic D (2004) Control of motile and invasive cell phenotypes by focal adhesion kinase. Biochim Biophys Acta 1692:77–102
Seubert B, Grünwald B, Kobuch J, Cui H, Schelter F, Schaten S, Siveke JT, Lim NH, Nagase H, Simonavicius N et al (2015) Tissue inhibitor of metalloproteinases (TIMP)-1 creates a premetastatic niche in the liver through SDF-1/CXCR4-dependent neutrophil recruitment in mice. Hepatology 61:238–248
Sevenich L, Joyce JA (2014) Pericellular proteolysis in cancer. Genes Dev 28:2331–2347

Shi RY, Yang XR, Shen QJ, Yang LX, Xu Y, Qiu SJ, Sun YF, Zhang X, Wang Z et al (2013) High expression of Dickkopf-related protein 1 is related to lymphatic metastasis and indicates poor prognosis in intrahepatic cholangiocarcinoma patients after surgery. Cancer 199:993–1003

Shiomi T, Lemaître V, D'Armiento J, Okada Y (2010) Matrix metalloproteinases, a disintegrin and metalloproteinases, and a disintegrin and metalloproteinases with thrombospondin motifs in non-neoplastic disease. Pathol Int 60:477–496

Sibony-Benyamini H, Gil-Henn H (2012) Invadopodia: the leading force. Eur J Cell Biol 91:896–901

Snyder BN, Cho Y, Qian Y, Coad JE, Flynn DC, Cunnick JM (2011) AFAP1L1 is a novel adaptor protein of the AFAP family that interacts with cortactin and localizes to invadosomes. Eur J Cell Biol 90:376–389

Spuul P, Ciufici P, Veillat V, Leclercq A, Daubon T, Kramer I, Génot E (2014) Importance of RhoGTPases in formation, characteristics, and functions of invadosomes. Small GTPases 5:e28195

Stamenkovic I (2000) Matrix metalloproteinases in tumor invasion and metastasis. Semin Cancer Biol 10:415–433

Starnes TW, Cortesio CL, Huttenlocher A (2011) Imaging podosome dynamics and matrix degradation. Methods Mol Biol 769:111–136

Steffen A, Le Dez G, Poincloux R, Recchi C, Nassoy P, Rottner K, Galli T, Chavrier P (2008) MT1-MMP-dependent invasion is regulated by TI-VAMP/VAMP7. Curr Biol 18:926–931

Stylli SS, Kaye AH, Lock P (2008) Invadopodia: at the cutting edge of tumour invasion. J Clin Neurosci 15:725–737

Sun MH, Han XC, Jia MK, Jiang WD, Wang M, Zhang H, Han G, Jiang Y (2005) Expressions of inducible nitric oxide synthase and matrix metalloproteinase-9 and their effects on angiogenesis and progression of hepatocellular carcinoma. World J Gastroenterol 11:5931–5977

Sun X, Li C, Zhuang C, Gilmore WC, Cobos E, Tao Y, Dai Z (2009) Abl interactor 1 regulates Src-Id1-matrix metalloproteinase 9 axis and is required for invadopodia formation, extracellular matrix degradation and tumor growth of human breast cancer cells. Carcinogenesis 30:2109–2116

Symons M (2008) Cell biology: watching the first steps of podosome formation. Curr Biol 18:R925–R927

Szczur K, Xu H, Atkinson S, Zheng Y, Filippi MD (2006) Rho GTPase CDC42 regulates directionality and random movement via distinct MAPK pathways in neutrophils. Blood 108:4205–4213

Sze KM, Chu GK, Lee JM, Ng IO (2013) C-terminal truncated HBx is associated with metastasis and enhances invasiveness via C-Jun/MMP10 activation in hepatocellular carcinoma. Hepatology 57:131–139

Takafuji V, Forgues M, Unsworth E, Goldsmith P, Wang XW (2007) An osteopontin fragment is essential for tumor cell invasion in hepatocellular carcinoma. Oncogene 26:6361–6371

Takkunen M, Hukkanen M, Liljeström M, Grenman R, Virtanen I (2010) Podosome-like structures of non-invasive carcinoma cells are replaced in epithelial-mesenchymal transition by actin comet-embedded invadopodia. J Cell Mol Med 14:1569–1593

Tang BL (2001) ADAMTS: a novel family of extracellular matrix proteases. Int J Biochem Cell Biol 33:33–44

Tao K, Qian N, Tang Y, Ti Z, Song W, Cao D, Dou K (2010) Increased expression of a disintegrin and metalloproteinase-9 in hepatocellular carcinoma: implications for tumor progression and prognosis. Jpn J Clin Oncol 40:645–651

Tao YM, Liu Z, Liu HL (2013) Dickkopf-1 (DKK1) promotes invasion and metastasis of hepatocellular carcinoma. Dig Liver Dis 45:251–257

Tatin F, Varon C, Génot E, Moreau V (2006) A signalling cascade involving PKC, Src and Cdc42 regulates podosome assembly in cultured endothelial cells in response to phorbol ester. J Cell Sci 119:769–781

Thieringer FR, Maass T, Anthon B, Meyer E, Schirmacher P, Longerich T, Galle PR et al (2012) Liver-specific overexpression of matrix metalloproteinase 9 (MMP-9) in transgenic mice accelerates development of hepatocellular carcinoma. Mol Carcinog 51:439–448

Tokui N, Yoneyama MS, Hatakeyama S, Yamamoto H, Koie T, Saitoh H, Yamaya K, Funyu T, Nakamura T, Ohyama C et al (2014) Extravasation during bladder cancer metastasis requires cortactin-mediated invadopodia formation. Mol Med Rep 9:1142–1146

Tolde O, Rösel D, Vesely P, Folk P, Brabek J (2010) The structure of invadopodia in a complex 3D environment. Eur J Cell Biol 89:674–680

Tsai WC, Hsu PW, Lai TC, Chau GY, Lin CW, Chen CM, Lin CD, Liao YL, Wang JL et al (2009) MicroRNA-122, a tumor suppressor microRNA that regulates intrahepatic metastasis of hepatocellular carcinoma. Hepatology 49:1571–1582

Tsuboi S (2007) Requirement for a complex of Wiskott-Aldrich syndrome protein (WASP) with WASP interacting protein in podosome formation in macrophages. J Immunol 178:2987–2995

Tsujita K, Kondo A, Kurisu S, Hasegawa J, Itoh T, Takenawa T (2013) Antagonistic regulation of F-BAR protein assemblies controls actin polymerization during podosome formation. J Cell Sci 126:2267–2278

Tu K, Dou C, Zheng X, Li C, Yang W, Yao Y, Liu Q (2014) Fibulin-5 inhibits hepatocellular carcinoma cell migration and invasion by down-regulating matrix metalloproteinase-7 expression. BMC Cancer 14:938

Turner CE (2000) Paxillin interactions. J Cell Sci 23:4139–4140

van den Dries K, Medders MB, de Keijzer S, Shekhar S, Subramaniam V, Figdor CG et al (2013) Interplay between myosin IIA-mediated contractility and actin

network integrity orchestrates podosome composition and oscillations. Nat Commun 4:1412
Van Horssen R, Buccione R, Willemse M, Cingir S, Wieringa B, Attansio F (2013) Cancer cell metabolism regulates extracellular matrix degradation by invadopodia. Eur J Cell Biol 92:113–121
Wang XJ, Feng CW, Li M (2013a) ADAM17 mediates hypoxia-induced drug resistance in hepatocellular carcinoma cells through activation of EGFR/PI3K/Akt pathway. Mol Cell Biochem 380:57–66
Wang Q, Tang H, Yin S, Dong C (2013b) Downregulation of microRNA-138 enhances the proliferation, migration and invasion of cholangiocarcinoma cells through the upregulation of RhoC/p-ERK/MMP-2/MMP-9. Oncol Rep 29:2046–2052
Wang W, Lin H, Zhou L, Zhu Q, Gao S, Xie H, Liu Z, Xu Z, Wie J, Huang X, Zheng S (2014) MicroRNA-30a-3p inhibits tumor proliferation, invasiveness and metastasis and is downregulated in hepatocellular carcinoma. Eur J Surg Oncol 40:1586–1594
Watanabe A, Hoshino D, Koshikawa N, Seiki M, Suzuki T, Ichikawa K (2013) Critical role of transient activity of MT1-MMP for ECM degradation in invadopodia. PLoS Comput Biol 9:e1003086
Weaver AM (2006) Invadopodia: specialized cell structures for cancer invasion. Clin Exp Metastasis 23:97–105
Weaver AM (2008) Cortactin in tumor invasiveness. Cancer Lett 265:157–166
Wernimont SA, Cortesio CL, Simonson WT, Huttenlocher A (2008) Adhesion ring: a structural comparison between podosomes and the immune synapse. Eur J Cell Biol 87:507–515
Wiche G (1998) Role of plectin in cytoskeleton organization and dynamics. J Cell Sci 111:2477–2486
Williams BB, Mundell N, Dunlap J, Jessen J (2012) The planar cell polarity protein VANGl2 coordinates remodeling of the extracellular matrix. Commun Integr Biol 5:325–328
Wu LM, Zhang F, Xie HY, Xu X, Chen QX, Yin SY, Liu XC, Zhou L, Xu XB, Sun YL et al (2008) MMP2 promoter polymorphism (C-1306T) and risk of recurrence in patients with hepatocellular carcinoma after transplantation. Clin Genet 73:273–278
Xiang ZL, Zeng ZC, Tang ZY, Fan J, Sun HC, Tan YS (2011) Expression of cytokeratin 19 and matrix metalloproteinase 2 predicts lymph node metastasis in hepatocellular carcinoma. Mol Biol Rep 38:3531–3539
Xiao Y, Kleeff J, Shi X, Büchler MW, Friess H (2003) Heparanase expression in hepatocellular carcinoma and the cirrhotic liver. Hepatol Res 26:192–198
Xiao M, Zhou NX, Huang ZQ, Lu YL, Chen LH, Wang DJ, Chang WL (2004) The ratio of MMP-2 and TIMP-2 in hilar cholangiocarcinoma: a semi-quantitative study. Hepatobiliary Pancreat Dis Int 3:599–602
Xu J, Xu HY, Zhang Q, Song F, Jiang JL, Yang XM, Mi L, Wen N, Tian R, Wang L et al (2007) HAb18G/CD147 functions in invasion and metastasis of hepatocellular carcinoma. Mol Cancer Res 5:605–614
Xu Y, Qin X, Zhou J, Tu Z, Bi X, Li W, Fan X, Zhang Y (2011) Tissue factor pathway inhibitor-2 inhibits the growth and invasion of hepatocellular carcinoma cells and is inactivated in human hepatocellular carcinoma. Oncol Lett 2:779–783
Yamaguchi H (2012) Pathological roles of invadopodia in cancer invasion and metastasis. Eur J Cell Biol 91:902–907
Yamaguchi H, Oikawa T (2010) Membrane lipids in invadopodia and podosomes: key structures for cancer invasion and metastasis. Oncotarget 1:320–328
Yamaguchi H, Pixley F, Condeelis J (2006) Invadopodia and podosomes in tumor invasion. Eur J Cell Biol 85:213–218
Yamamoto H, Itoh F, Dachi Y, Fukushima H, Itoh H, Sasaki S, Hinoda Y, Imai K (1999) Messenger RNA expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human hepatocellular carcinoma. Jpn J Clin Oncol 29:58–62
Yang XW, Zhang LJ, Huang XH, Chen LZ, Su Q, Zeng WT, Li W, Wang Q (2014) miR-145 suppresses cell invasion in hepatocellular carcinoma cells: miR-145 targets ADAM17. Hepatol Res 44:551–559
Yeh HC, Lin SM, Chen MF, Pan TL, Wang PW, Yeh CT (2010) Evaluation of serum matrix metalloproteinase (MMP)-9 to MMP-2 ratio as a biomarker in hepatocellular carcinoma. Hepatogastroenterology 57:98–102
Yoshio T, Morita T, Kimura Y, Tsujii M, Hayashi N, Sobue K (2007) Caldesmon suppresses cancer cell invasion by regulating podosome/invadopodium formation. FEBS Lett 581:3777–3782
Yu FL, Liao MH, Lee JW, Shih WL (2004) Induction of hepatoma cells migration by phosphoglucose isomerase/autocrine motility factor through the upregulation of matrix metalloproteinase-3. Biochem Biophys Res Commun 314:76–82
Yu FL, Liu HJ, Lee JW, Liao MH, Shih WL (2005) Hepatitis B virus X protein promotes cell migration by inducing matrix metalloproteinase-3. J Hepatol 42:520–527
Yu JA, Deakin NO, Turner CE (2009) Paxillin-kinase-linker tyrosine phosphorylation regulates directional cell migration. Mol Biol Cell 20:4706–4719
Yue Y, Shao Y, Luo Q, Shi L, Wang Z (2013) Downregulation of ADAM10 HepG2 cells. Biomed Res Int 2013:434561
Zhang Q, Chen X, Zhou J, Zhang L, Zhao Q, Chen G, Xu J, Qian F, Chen Z (2006) CD147, MMP-2, MMP-9 and MVD-CD34 are significant predictors of recurrence after liver transplantation in hepatocellular carcinoma patients. Cancer Biol Ther 5:808–814
Zhang Y, Li L, Wang Y, Zhang J, Wei G, Sun Y, Shen F (2007a) Downregulating the expression of heparanase inhibits the invasion, angiogenesis and metastasis of human hepatocellular carcinoma. Biochem Biophys Res Commun 358:124–129
Zhang H, Wang YS, Han G, Shi Y (2007b) TIMP-3 gene transfection suppresses invasive and metastatic

capacity of human hepatocarcinoma cell line HCC-7721. Hepatobiliary Pancreat Dis Int 6:487–491

Zhang Q, Zhou J, Ku XM, Chen XG, Zhang L, Xu J, Chen GS, Li Q, Qian F, Tian R et al (2007c) Expression of CD147 as a significantly unfavorable prognostic factor in hepatocellular carcinoma. Eur J Cancer Prev 16:196–202

Zhang R, Pan X, Huang Z, Weber GF, Zhang G (2011) Osteopontin enhances the expression and activity of MMP-2 via the SDF-1/CXCR4 axis in hepatocellular carcinoma cell lines. PLoS One 6:e23831

Zhang J, Zhang DL, Jiao XL, Dong Q (2013a) S100A4 regulates migration and invasion in hepatocellular carcinoma HepG2 cells via NF-kB-dependent MMP-9 signal. Eur Rev Med Pharmacol Sci 17:2372–2382

Zhang Y, Tan YF, Jiang C, Zhang K, Zha TZ, Zhang M (2013b) High ADAM8 expression is associated with poor prognosis in patients with hepatocellular carcinoma. Pathol Oncol Res 19:79–88

Zhao XL, Sun T, Chen N, Sun D, Zhao N, Dong XY, Gu Q, Yao Z, Sun BC (2011) Promotion of hepatocellular carcinoma metastasis through matrix metalloproteinase activation by epithelial-mesenchymal transition regulator Twist1. J Cell Mol Med 15:691–700

Zheng Q, Tang ZY, Xue Q, Shi DR, Song HY, Tang HB (2000) Invasion and metastasis of hepatocellular carcinoma in relation to urokinase-type plasminogen activator, its receptor and inhibitor. J Cancer Res Clin Oncol 126:641–646

Zhou L, Wang DS, Li QJ, Sun W, Zhang Y, Dou KF (2012) Downregulation of the Notch signaling pathway inhibits hepatocellular carcinoma cell invasion by inactivation of matrix metalloproteinase-2 and -9 and vascular endothelial growth factor. Oncol Rep 28:874–882

Zhou L, Zhang N, Li QJ, Sun W, Zhang Y, Wang DS, Dou KF (2013a) Associations between high levels of Notch1 expression and high invasion and poor overall survival in hepatocellular carcinoma. Tumour Biol 34:543–553

Zhou L, Zhang N, Song W, You N, Li Q, Sun W, Zhang Y, Wang D, Dou K (2013b) The significance of Notch1 compared with Notch3 in high metastasis and poor overall survival in hepatocellular carcinoma. PLoS One 8:e57382

Zhou L, Wang DS, Li QJ, Sun W, Zhang Y, Dou KF (2013c) The down-regulation of Notch1 inhibits the invasion and migration of hepatocellular carcinoma cells by inactivating the cyclooxygenase-2/snail/E-cadherin pathway in viro. Dig Dis Sci 58:1016–1025

Zhou Y, Li Y, Ye J, Jiang R, Yan H, Yang X, Liu Q, Zhang J (2013d) MicroRNA-491 is involved in metastasis of hepatocellular carcinoma by inhibition of matrix metalloproteinase and epithelial to mesenchymal transition. Liver Int 33:1271–1280

Mechanisms of Invasion and Metastasis: Role of the Stromal Liver Cancer Microenvironment, Epithelial-Mesenchymal Transition, and the Tumor Vascular Bed

183

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_183

Abstract

Progressive growth, invasion, and metastasis of carcinomas depend on the generation, structure, and function of tumor stroma. Several types of stromal cells are in close contact with neoplastic cells, forming a system of interacting elements with important biologic sequelae for both partners. The stroma of carcinomas harbors several types of spindle cells. A major component of stroma are cancer-associated fibroblasts (CAFs) which serve as a guidance substratum for proliferating and migrating cancer cells and also form a niche for cells of the host's immune system. CAFs affect angiogenic pathways and invasion. Liver cancer stroma contains myofibroblasts, derived from hepatic stellate cells, resident fibroblastoid cells, and mesenchymal stem cells. Myofibroblasts are potent regulators of growth and invasion. Spindle cells of tumor stroma produce and secrete various stromal proteins that critically regulate tumor progression, invasion, and metastasis. Stromal cells are also important elements that mediate epithelial-mesenchymal transition (EMT), a mechanism playing a significant role in tumor invasion. EMT is induced by a wide array of distinct factors that are in part expressed by cancer cells. The stroma provides, through its leukocytes, an inflammatory microenvironment affecting the behavior of cancer cells.

Stroma and Stromal Cells Are Critical Mediators of Cancer Cell Invasion

Introduction

The stromal microenvironment and its cell systems play an important role in the promotion of cancer cell invasion and metastasis (reviews: De Wever and Mareel 2003; Mareel and Madani 2006; Albini 2008; Horimoto et al. 2012; Sleeman 2012). Several aspects are treated in more detail in the chapters on hepatic metastases and on tumor stroma. Here, aspects that more specifically relate to invasion pathways are briefly outlined.

Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) form a central cellular component of stroma. These cells may serve as a guidance substratum for migrating cancer cells, but they also provide a niche for dormant tumor cells and leukocytes, in particular monocytes, tumor-associated macrophages/TAMs, lymphocytes, and neutrophils. Furthermore, CAFs affect angiogenic pathways and by this exert an influence of growth and invasion. The biogenesis of CAFs is complex and only partially elucidated. Recruitment of CAFs in cholangiocarcinoma is regulated by platelet-derived growth factor-D and Rho GTPases (Cadamuro et al. 2013). Stromal fibroblasts and myofibroblasts are important effectors of mechanisms involved in cancer cell invasion and metastasis (De Wever and Mareel 2003; De Wever et al. 2008; Hinz 2010; Cirri and Chiarugi 2012).

Myofibroblasts

Myofibroblasts/MFBs in the liver and in the stroma of hepatobiliary tumors originate from three sources, i.e., hepatic stellate cells (HSCs), resident fibroblastoid cells, and circulating mesenchymal stem cells, the latter in part being bone marrow derived. Due to complex interactions, MFBs and cancer-associated fibroblasts (CAFs) affect growth and invasion of HCC cells. Stimulation of stromal cells by epithelial cancer cells results in pro-invasive and pro-metastatic pathways. Spindled stromal cells that express alpha-SMA and have the phenotype of MFBs are associated with low differentiation of HCCs, macrovascular invasion, and metastasis (Yang et al. 2013b). Cancer cells can interact with stromal cells, including myofibroblasts, through cell-to-cell fusion. The mechanisms by which MFBs promote liver cancer invasion are only partially known. Hepatic MFBs can secrete monocyte chemoattractant protein-1/MCP-1, a protein which promotes migration of human HCC cells (Dagouassat et al. 2010). Bone marrow-derived MFBs can be stimulated to secrete metalloproteinases (Lecomte et al. 2012).

Stromal Proteins

An important stromal protein for cancer cell invasion is osteopontin. Osteopontin plays a crucial role as a factor promoting a metastatic phenotype, also in HCCs (Anborgh et al. 2010). Osteopontin is subject to numerous posttranslational modifications, including glycosylation, phosphorylation, proteolytic cleavage, and cross-linking through transglutamination. In addition, the expression pattern of osteopontin is regulated by genetic variation at locus −443 of the osteopontin promoter (Dong et al. 2013). Expression of osteopontin is regulated by the Rac exchange factor Tiam1. Senescence of fibroblasts induces decreased Tiam1 levels and increased osteopontin levels (Liu et al. 2012a), suggesting that activity of senescent fibroblastoid cells and cancer stroma affects migration and invasion via a Tiam1-osteopontin pathway. Tiam1 itself is downregulated by microRNA-141, an effect that suppresses migration and invasion of HCC cells (Liu et al. 2014b). In tumors, osteopontin is produced both by tumor cells and stromal cells, and both of these cells also express osteopontin receptors, giving rise to a complex interactome and a cross-talk between cells involved in a concerted pro-metastatic action (Anborgh et al. 2010). Activated hepatic stellate cells are a source of osteopontin and thus promote HCC invasion and metastasis (Song et al. 2015). Osteopontin upregulates several factors in HCC cells via its binding to osteopontin receptors expressed on these cells, i.e., integrin alpha(V)beta 3 and CD44V6. Via the mechanism of activation of MMP-2 secretion and expression of urokinase-type plasminogen activator (uPA), osteopontin is a key mediator of vasculogenic mimicry in HCC (Liu et al. 2011). Osteopontin is upregulated in well-differentiated HCCs by the transmembrane receptor CXCR7, a mechanism augmenting the risk of extrahepatic metastases (Xue et al. 2013). In stroma, liver cancer cells also interact with diverse proteins and proteoglycans of the extracellular matrix, including basement membrane proteins. Malignant neoplastic cells also interact with elastin, interactions that modulate cancer invasion and spread (Timar et al. 1995; Lapis and Timar 2002). The 67 kDa elastin-laminin receptor plays a role in tumor invasion (Fülöp and Larbi 2002). Elastin fragments resulting from elastin degradation act as matrikines that can promote cell cycle progression and are active as chemotactic agents (Duca et al. 2004).

Epithelial-Mesenchymal Transition (EMT) in Liver Cancer Invasion

Introduction

Epithelial-mesenchymal transition (EMT) plays a central role in the development of the liver (Firrincieli et al. 2010) and is critically involved in pathways of invasion and metastasis of numerous cancers, including HCC (Guarino 2007; Guarino et al. 2007; Van der Zijl et al. 2009; Yilmaz and Christofori 2009; Thomson et al. 2011; Meng and Wu 2012; Zheng et al. 2013) and cholangiocarcinomas (Specht et al. 2013; Gu and Choi 2014). EMT is characterized by loss of epithelial cell markers (E-cadherin and plakoglobin), upregulation of mesenchymal markers (vimentin, N-cadherin), and increase of MMP-2. Several switches that induce EMT have been identified, including the Snail/Slug family of transcription factors, Twist, deltaEF1/ZEB1, SIP1/ZEB2, E12/E47, the TGF-beta/Smad signaling system, the Wnt/beta-catenin signaling system, and p53. EMT is associated with a decreased expression of E-cadherin. A protein that reduces the actin-belt density in the circumferential ring, Tara (Trio-associated repeat of actin), is enriched in cadherin-based adherens junctions and promotes expression of E-cadherin and an epithelial phenotype (Yano et al. 2011). Repression of E-cadherin in cancer cells undergoing EMT is correlated with expression of the actin-bundling protein fascin-1, a protein involved in EMT formation and in invasiveness of HCC cells. Overexpression of fascin-1 dramatically increases the migratory potential of HCC cells, illustrating the important role played by EMT in cancer cell migration.

In the course of EMT, epithelial cancer cells acquire features shared with mesenchymal cells,

in particular stromal cells. It is this alteration that results in the unique phenomenon that carcinomas can generate their own and specific pro-invasive microenvironment, both in primary tumors and at distant sites, the so-called premetastastic niche. EMT can, however, lead to even more complex pathways. EMT induced by inflammatory stimuli, e.g., mediated by tumor-associated lymphocytes, monocytes, and macrophages (see below), can confer to cancer cells and stromal cell-like immune-modulatory properties that affect invasion and metastatic dissemination (Ricciardi et al. 2015). These findings illustrate a high degree of functional and structural plasticity of tumor cells.

Altered Snail Expression in Liver Cancer

An important inducing factor of EMT is Snail1. Through an N-terminal SNAG domain, Snail interacts with several corepressors to suppress distinct target genes, such as the E-cadherin promoter, downregulation of E-cadherin being an important step in EMT (Wang et al. 2013a). In EMT-associated motility signaling, Wnt5a-Ror2 signaling is a critical step (Ren et al. 2011). In HCC cells, Snail expression is enhanced by the action of Notch1, whereby this inductive pathway increases as a function of loss of HCC cell differentiation (Kim and Jung 2014). Macrophage-secreted interleukin-8 is also a factor that enhances Snail expression in HCC and thus promotes EMT (Fu et al. 2015). Ectopic expression of Snail1 in cancer cells promotes EMT, resulting in motile and invasive properties of EMT-cancer cells. Snail upregulates MMP family members in HCC cells (Miyoshi et al. 2004), possibly by its promotion of EMT. By inducing EMT, Snail promotes an invasive phenotype in HCC (Yang et al. 2009). Snail is upregulated by a factor that is associated with poor prognosis in HCC, metastasin, a calcium-binding protein associated with tumor metastasis (Zheng et al. 2013). Snail-induced EMT in HCC is also stimulated by hypoxia-inducible factor-1 alpha, associated with alterations in E-cadherin, N-cadherin, and vimentin expression (Zhang et al. 2013c). Snail signaling promoting EMT is activated by the CXCR2/CXCL5 axis (Zhou et al. 2015). MicroRNA-30a inhibits EMT by suppressing the activity of Snail1/Snail (Kumarswamy et al. 2012). Similarly, microRNA-148a suppresses EMT and metastasis in hepatoma cells via inhibition of Snail signaling (Zhang et al. 2014). Snail1 transcriptionally represses a protein which suppresses HCC migration and invasion, Cezanne2. Cezanne 2 interacts with TNF receptor-associated factor (TRAF) 6 and cleaves polyubiquitin from TRAF6 substrates, and it regulates expression of MMP-2, MMP-9, and ICAM1/interacellular adhesion molecule 1 Xu et al. 2014).

Altered Slug Expression in Liver Cancer

Slug is a transcription factor that promotes EMT, but also promotes invasion, metastasis, and vasculogenic mimicry in HCC (Sun et al. 2013a; Yamada et al. 2014). Slug promotes HCC cell progression by increasing Sox2 and Nanog expression (Zhao et al. 2015). It also transcriptionally regulates CD147 which promotes EMT via TGF-beta signaling (Wu et al. 2011). Slug-induced EMT is stimulated by the Gas6/Axl pathway, which enhances the expression of Slug (Lee et al. 2014c). Its expression is suppressed by microRNA-204, which inhibits EMT in cholangiocarcinoma cells (Qiu et al. 2013). Krüppel-like factor 4, a tumor suppressor in HCCs, can revert EMT by binding to and suppressing the expression of Slug (Lin et al. 2012). On the other hand, Krüppel-like factor 8 (KLF8) is involved in TGF-beta1-induced EMT associated with E-cadherin loss (Zhang et al. 2013b). Slug can induce expression of fascin, an actin-bundling protein involved in shape change and motility (Li et al. 2014). In HCC, Slug expression confers a cancer stem cell phenotype associated with EMT (Sun et al. 2014), and it promotes vasculogenic mimicry (Sun et al. 2013a).

Altered Twist Expression in Liver Cancer

Twist1, a highly conserved transcription factor of the basic helix-loop-helix protein family, is an important inducer of EMT (review: Puisieux et al. 2006). Twist already acts at the level of human mesenchymal stem cells (Isenmann et al. 2009), suggesting that it has central role in basic decision mechanisms of cell lineage determination. Twist1 also favors EMT by regulating other pro-EMT factors, such as Sox5 (Wang et al. 2015). Twist and Snail1 are upregulated by a protein interacting with Smad3, Tribbles homolog 3/TRIB3, a factor that enhances the transcriptional activity of Smad3 via triggering the degradation of Smad ubiquitin regulatory factor 2/Smurf2, resulting in decreased elimination of phosphorylated Smad3 (Hua et al. 2011). For becoming active, Twist1 is phosphorylated by protein kinase B (PKB/Akt), a kinase that is ubiquitously expressed in diverse cell lineages (Vichalkovski et al. 2010). The pro-EMT action of Twist1 depends on Snail2, whereby Twist1 binds on the proximate Snail2 promoter to induce its transcription (Casas et al. 2011). Twist expression is positively correlated with activation of the STAT3 signaling pathway and reduced E-cadherin expression (Zhang et al. 2012).

EMT induced by Twist1 is a potent mechanism for the induction of invasion and metastasis in HCC (Lee et al. 2006; Xu and Chen 2007; Matsuo et al. 2009; Yamada et al. 2014). Twist1 expression promotes migration and invasion of HCC cells via EMT induction (Matsuo et al. 2009), but part of the pro-invasive effect of Twist1 is mediated by induction of angiogenesis (Niu et al. 2007) and of vasculogenic mimicry (Sun et al. 2010, 2011a). In AFP-secreting HCCs, Twist1 is downregulated by microRNA-675, which in turn enhances the proliferative and growth capacities of these neoplasms (Hernandez et al. 2013). Similar to Twist1, also ectopic expression of Twist2 in HCC promotes EMT and invasion via regulation of CD24 (Liu et al. 2014a).

Altered Transforming Growth Factor-Beta (TGF-Beta)/Smad Signaling System in Liver Cancer

It is known for a long time that transforming growth factor beta1/TGF-beta1 overexpression in HCCs is correlated with invasiveness and metastasis of this tumor type (review: Lee et al. 2012). In general, the TGF-beta/Smad pathway is critically involved in the interaction between HCC and its stromal microenvironment (Li et al. 2012a). However, many of the effects of TGF-beta1 on liver cancers and other malignancies are related to its function as an inducer of EMT. TGF-beta is a potent inducer of EMT and through this pathway markedly affects HCC biology and progression (Reichl et al. 2012; Katsuno et al. 2013; Mima et al. 2013). Similar to fibroblast growth factor-2, TGF-beta can induce transdifferentiation of carcinoma cells into fibroblastoid cells that are highly migratory (review: Miyazono et al. 2012). Several factors cooperate with TGF-beta1 in its EMT-promoting activity, including CD44s, the standard isoform of CD44 (Mima et al. 2012), connective tissue-derived growth factor/CTGF, the vitamin D receptor downstream target dermatopontin (Li et al. 2009), and the receptor tyrosine kinase Axl (Reichl et al. 2014). TGF-beta-induced EMT is dependent on Smads, which are known to affect invasion and prognosis of cancer cells (Huang et al. 2012). Smad3 is an important mediator of TGF-beta signaling. In the setting of EMT, Smad3 regulates E-cadherin expression through a microRNA-200 pathway (Ahn et al. 2012). In its induction of EMT, TGF-beta1 cooperates with laminin-5/Ln-5 (Giannelli et al. 2005).

EMT induced by TGF-beta is a major factor for invasion and metastasis of HCCs (Reichl et al. 2012). Several mechanisms cause altered TGF-beta-induced EMT in liver cancers. In liver cancer, including cholangiocarcinoma, Smad proteins promote invasion (Huang et al. 2012), probably due to their role in EMT. High phospho-Smad2 nuclear positivity in HCC cells was associated with upregulation of EMT-associated markers, E-cadherin and vimentin, whereby a

E-cadherin(low)/vimentin(high) phenotype was closely associated with high-grade malignant behavior (Mima et al. 2013). Via regulation of the Smad3-E-cadherin pathway, microRNAs 200a and 200b mediate EMT in HCCs and promote cell migration (Hung et al. 2013). Smad signaling to promote HCC cell migration is also activated by bone morphogenetic proteins (Maegdefrau and Bosserhoff 2012). Induction of EMT in HCCs by TGF-beta1 is also mediated by a downstream effector of TGF-beta1, the transcription factor GLI1 (glioma-associated oncogene 1), via direct upregulation of Snail1 (Zheng et al. 2012). In TGF-beta-induced EMT in HCC, expression of CD147 transcriptionally regulated by Slug plays a role. In this mechanism, CD147 induces the expression of E-cadherin in HCC cells (Ru et al. 2015). TGF-beta II receptor expression was reduced in HCCs, this downregulation being associated with poor differentiation, large vessel invasion, and intrahepatic metastasis (Mamiya et al. 2010). TGF-beta receptor 1 and fibroblast growth factor are targeted by microRNA-140-5p, which by this mechanism suppresses metastasis of HCC (Yang et al. 2013a). The expression of the TGF-beta receptor 2 involved in HCC migration is itself regulated by microRNA-590-5p (Jiang et al. 2012). CTGF expressed in tumor stromal cells induced EMT in HCCs and through this mechanism promotes growth and invasion (Xiu et al. 2012). Laminin-5, which is overexpressed in part of HCCs, cooperates with TGF-beta1 in the induction of EMT (Giannelli et al. 2005). TGF-beta-induced EMT is epigenetically regulated by microRNA-29a in HCC (Kogure et al. 2014). In addition to EMT, TGF-beta1 expression also affects the construction of microvasculature in HCCs (Balzarini et al. 2012) and gives rise to tumor-initiating cells that drive tumor progression (Meindl-Beinker et al. 2012; Wu et al. 2012).

Other Altered Signaling Pathways as EMT-Promoting Mechanisms in Cancer

CD44s is associated with the acquisition of a mesenchymal phenotype in HCC, regulating anchorage-independent capacity (Okabe et al. 2014). EMT is driven by the activation of the Wnt/beta-catenin signaling pathway in HCC (Liu et al. 2010). A factor involved in telomere maintenance and growth of HCCs is sirtuin1 (SIRT1). A partner factor, SIRT2, mediates EMT in HCCs by a signaling pathway based on protein kinase B/glycogen synthase kinase-3beta/beta-catenin (Chen et al. 2013). EMT in cancer cells is induced by chemokines, e.g., CCL18 which is predominantly expressed in monocytes and macrophages (Meng et al. 2015a). In the induction of EMT, p53, which is mutated in a significant fraction of HCCs, plays an important role. Regulation of EMT by p53 protein involves beta-catenin signaling, in that nuclear accumulation of beta-catenin is modulated by p53 (Wang et al. 2013b). Expression of FoxM1 induces EMT and invasion in HCC (Raychaudhun and Park 2011; Meng et al. 2015b), and overexpression of FOXC1 stimulates Snail and EMT (Xia et al. 2013). In its stimulation of EMT, FOXC1 contributes to HCC microvascular invasion (Xu et al. 2012). Induction of EMT in HCCs is promoted by a non-receptor tyrosine kinase of the focal adhesion kinase/FAK family, PYK2 (proline-rich tyrosine kinase 2), which is an inducer of EMT-mediated cell motility (Sun et al. 2011c). In HCC cells, EMT is potently induced by the tight junction component, claudin-1, via the c-Abl/Raf/Ras/ERK signaling pathway (Stebbing et al. 2013; Suh et al. 2013). EMT in HCC is facilitated by the stress-activated protein kinase (APK)-interacting protein 1 (SIN1), a protein which holds a central position in AKT regulation. SIN1-induced EMT is associated with increased venous invasion, tumor number, and prognosis (Xu et al. 2013). Siva1 suppresses EMT and metastasis of tumor cells by inhibiting stathmin and stabilizing microtubules (Li et al. 2011). Siva1 is a specific proapoptotic E3 ubiquitin ligase acting on p53 and the tumor suppressor alternative reading frame/ARF. EMT in HCC cells is also promoted by glypican-3, a membrane-associated heparan sulfate proteoglycan frequently upregulated in HCC (Wu et al. 2015). The sirtuin family

member SIRT1, involved in histone deacetylation, promotes HCC metastasis through induction of EMT (Hao et al. 2014). EMT in metastatic HCC is induced by overexpression of brachyury, which in turn enhances Akt activation by inhibiting PTEN and therefore stabilization of Snail, an EMT inducer (Du et al. 2014). A protein involved with EMT induction, Golgi glycoprotein 73/GP73, is expressed in subsets of HCCs and is negatively correlated with E-cadherin (Sun et al. 2011b; Bao et al. 2013). EMT promoting HCC metastasis is induced by metadherin, which is preferentially expressed in HCC with poor differentiation, satellite formation, microvascular invasion, and lymph node metastasis (Zhu et al. 2011). Cathepsin Z, encoded by a gene located to a locus frequently amplified in HCC, i.e., 20q13.3, induces EMT and an invasive-metastasizing phenotype (Wang et al. 2011). Bone morphogenetic protein-9/BMP-9, a member of the transforming growth factor-beta superfamily, induces EMT in HCC cells, its expression in the tumors paralleling that of the EMT factors Snail and vimentin, while E-cadherin and ZO-1 are downregulated (Li et al. 2013). EMT is induced by tumor-derived secretory clusterin, which is upregulated in these neoplasms as a function of tumor progression (Wang et al. 2012). BTB/POZ domain-containing protein 7 (BTBD7) regulates EMT-associated proteins in HCCs and via this pathway promotes invasion and metastasis (Tao et al. 2013b). EMT in human HCCs is induced by the transcriptional coactivator with PDZ-binding motif/TAZ, one of the nuclear effectors of Hippo-related pathways (Xiao et al. 2014b). BAG3/Bcl2-associated athanogene 3, a co-chaperone of heat-shock protein 70, is overexpressed in HCC tissues and regulates EMT and angiogenesis in these neoplasms (Xiao et al. 2014a). EMT pathways are strongly modulated by factors controlling autophagy, pathways also modulating metastatic colonization of cancer cells (Peng et al. 2013). On the other hand, autophagy suppresses tumorigenesis of HBV-associated HCC via degradation of MiR-224 (Lan et al. 2014).

MicroRNAs as Regulators of EMT in Liver Cancer

MicroRNAs play an important role in cancer invasion and metastasis (review: Aigner 2011). Several species of microRNAs affect EMT in liver cancers and thus migratory and invasive features of these neoplasms.

MicroRNA-9 affects EMT via Krüppel-like factor 7 (KLF17) which in turn regulates vimentin and ZO-1 expression (Sun et al. 2013b). In HCC cells, upregulated microRNA-10a regulates Eph tyrosine kinase receptor A4-mediated EMT (Yan et al. 2013). Overexpression of microRNA-106b activates EMT and via this effect promotes cell migration and metastasis of HCC (Yau et al. 2013). MicroRNA-200 family members are involved in EMT in HCC (Ding et al. 2012). They show decreased expression in poorly differentiated HCCs, associated with decreased expression of E-cadherin, EMT, and enhanced motility (Hung et al. 2013). Epigenetic activation of microRNA-200 family members, which contributes to H19-mediated metastasis suppression in HCCs, promotes EMT, H19 being underexpressed in many HCCs (Zhang et al. 2013a). EMT in HCCs is modulated by microRNA-490-3p through targeting endoplasmic reticulum-Golgi intermediate protein 3/ERGIC3. Overexpression of ERGIC3 by this mechanism promotes EMT, followed by increased growth and cancer cell invasion (Zhang et al. 2013d). MicroRNA-520g, a MiR inducing EMT, cancer cell migration, and invasion by targeting Smad7, is upregulated in HCC (Kan et al. 2015). MicroRNA-612 counteracts the development of EMT in HCCs and thus suppresses the invasion and metastasis cascade (Tao et al. 2013a). MicroRNA-214 targets Twist and by this mechanism counteracts EMT. In intrahepatic cholangiocarcinoma, this MiR is markedly downregulating, favoring EMT and invasion (Li et al. 2012b). MicroRNAs are also involved in the pathways leading to liver metastasis of extrahepatic cancers. Colorectal carcinoma liver metastases display higher levels of microRNA-200c, whereas the invasive front of primary colorectal carcinoma showed decreased expression of

this MiR, suggesting an important role of this MiR in the metastatic pathway linked to epigenetic regulation (Hur et al. 2013).

Certain microRNAs inhibit EMT in liver cancers. MicroRNA-148a suppresses EMT and metastasis of HCC cells by targeting Met/Snail signaling but is downregulated in these cancers (Zhang et al. 2014). Also microRNA-26b inhibits EMT in HCC by targeting the USP9X gene, which in turn affects EMT via Smad4 and the TGF-beta signaling pathway. Again, this anti-invasion MiR is downregulated in HCC cells (Shen et al. 2014). Similarly, the microRNA-122/HNF4alpha/Rho axis negatively regulates EMT and invasion of HCC cells (Wang et al. 2014a). MicroRNA-204 inhibits EMT in intrahepatic cholangiocarcinoma cells by targeting Slug (Qiu et al. 2013).

Modulation of EMT-Mediated Invasion in Liver Cancer by Tumor-Associated Leukocytes and Exsomal Signaling

Leukocytes present in cancer stroma, including tumor-associated macrophages/TAMs and neutrophils, are capable to induce EMT in liver cancers. Alternatively activated (M2) macrophages can promote EMT via Snail and M2-derived CCL22, thereby augmenting invasion in HCC (Yeung et al. 2015). Macrophages located to the HCC stroma induce EMT by secretion of IL-8 via activation of the Snail/JAK2/STAT3 pathway (Fu et al. 2015). Activated macrophages downregulate the expression of E-cadherin in HCC cells and thus promote EMT (Wang et al. 2014b). TAMs can promote cancer stem cell-like properties through TGF-beta1-induced EMT in HCC, associated with the acquisition of a highly invasive phenotype (Fan et al. 2014). Snail, a potent promoter of EMT, positively regulates EMT in part via enhancing the recruitment of macrophages (Hsu et al. 2014). Similarly, Twist1 induces the macrophage chemoattractant CCL2 and through this pathway recruits macrophages (Low-Marchelli et al. 2013). EMT can also be promoted by signals delivered from microvesicular bodies/exosomes produced by leukocytes (review: Vella 2014).

The Vascular Bed in Hepatocellular Carcinoma: Entry Site for Invading Tumor Cells (Angioinvasion)

Invasion of the Microvascular Bed

In HCC, trabecular and acinar formations are separated from each other by intervening sinusoid-like and sometimes dilated vascular channels. These channels do not represent true sinusoids, because they display junctions between endothelial cells, deposition of collagen, and basement membrane-like material in a perivascular space representing an analogue of Disse's space, associated with flattening of tumor cell microvilli, i.e., a change corresponding to sinusoidal capillarization (Livni et al. 1977). Microvascular invasion plays a significant role in pathways leading to tumor progression and metastatic spread in HCCs (Suh et al. 2012). Microvascular invasion of HCC cells is promoted by expression of the transcription factor FOXC1, which induces EMT (Xu et al. 2012). Expression of hepatocyte nuclear factor 1beta/HNF1beta (but not HNF1alpha) in HCCs is associated with increased microvascular invasion and predicts an aggressive course (Shim et al. 2012).

Recently, a novel vascular pattern has been found in HCC and identified as system promoting metastasis. This pattern is characterized by vessels that encapsulate tumor cell clusters, forming cobweb-like networks. The presence of this pattern predicted higher metastasis and recurrence rates of HCC in an EMT-independent manner (Fang et al. 2015).

Invasion of Large Veins of the Liver

Macrovessel invasion is a frequent phenomenon in HCC and characterizes a distinct tumor phenotype associated with younger age, aggressive cancer behavior, and poor liver functional reserve

(Lee et al. 2014b). Large veins, and in particular the portal vein, are invaded directly, i.e., by ingrowth of carcinoma through the vessel wall, followed by formation of a tumor thrombus. However, there is increasing evidence that the frequency and the dimension of macrovascular invasion, above all by HCC, are not only determined by inherent tumor invasion as such,but are rather also regulated by other factors. For example, early-stage venous invasion of HCC followed by metastatic spread is controlled by expression of the metastasis-related microRNA-185 (Zhi et al. 2013). Vascular invasion in HCCs is also associated with expression of the GTP-binding protein Gem, a Ras-related protein (Huang et al. 2014). Such findings illustrate that vascular invasion is more complex than anticipated and will considerably alter our conventional views regarding the pathogenesis of vascular spread.

Invasion of the Lymphatic System and Lymphangiogenesis

The normal liver possesses a complex network of lymphatics with distinct relationships between lymph vessels and other anatomic structures. Intrahepatic lymphatics can be reliably visualized by use of podoplanin staining/D2-40 antibody (Yokomori et al. 2010). Almost 100 % of small intrahepatic portal vein branches are accompanied by lymph vessels, seen in portal tracts, while only 17 % of sublobular/hepatic veins, and 0 % of central veins, were accompanied by lymphatic vessels (Ohashi et al. 2010). Along large septa, lymphatics also reach to the subcapsular region (Yokomori et al. 2012), which affects spread from one lobe to the other. Invasion of lymphatics followed by lymphatic metastasis is clinically more important in cholangiocarcinomas and hepatic metastases than in HCC. In colorectal cancer liver metastasis, intrahepatic lymphatic invasion but not blood vessel invasion was a major prognostic factor (Lupinacci et al. 2014). In such metastases, lymphatic vessel density differed in metastases depending on metastatic sites, suggesting a heterogeneous lymphatic microvascular environment (Kwak et al. 2014). Similar to blood vessels, invasion of lymphatic channels depends on motility, adhesion, and proteolytic features of tumor cells. Due to major differences in vessel wall anatomy and the expression of homing receptors, blood vessel angioinvasion differs considerably from lymphangioinvasion. Lymphatic invasion and metastasis are controlled by complex molecular networks that alter lymphatic endothelia and their interactions with homing and transmigrating tumor cells. Lymphatic endothelia located near tumors change their adhesive properties, a mechanism that facilitates invasion and intralymphatic spread (review: Achen and Stacker 2008).

Lymphatic spread of cancers critically depends on tumor-induced lymphangiogenesis, which depends on the expression of lymphangiogenic growth factors. Similar to blood vessels, lymphatic channels neoformed in tumors are produced both by vasculogenesis and angiogenesis depending on preformed vessels. Bone marrow-derived cells have been implicated as lymphatic endothelial progenitors (Van't Hull et al. 2014). Circulating mononuclear cells that are CD34+VEGFR3+ CD133+ have the capacity to differentiate toward lymphatic endothelial cells (Salven et al. 2003; Tan et al. 2014). Cultured cells with this phenotype can differentiate to cells that express lymphatic-specific markers, such as VE-cadherin, CD51/61, CD105, LYVE-1, and podoplanin (Salven et al. 2003). Lymphangiogenic factors mainly comprise VEGF-C and VEGF-D interacting with the cognate receptor tyrosine kinase VEGF receptor-3/VEGFR-3, which is expressed on lymphatic endothelial cells and is critical for tumor lymphangiogenesis (He et al. 2002; Deng et al. 2015). Expression of VEGFR3 is modulated by neuropilin-2, the receptor of semaphorin-3F/SEMA3F (Ou et al. 2015). Expression of VEGF-C is subject to positive regulation by TGF-beta signaling which in turn is coordinated by the transcription factor, SIX1/sine oculis homeobox homolog1 (Liu et al. 2014d). In addition to these two VEGFs, VEGF-A, hepatocyte growth factor, and platelet-derived growth factor BB have lymphangiogenic activity, and lymphangiogenesis also depends on Wnt/beta-catenin signaling (Ghose et al. 2015). Certain chemokines and their

receptors favor the contact between tumor cells and lymphatics (Achen and Stacker 2008; Lee et al. 2014a).

Local formation of new lymphatic channels affects invasion and progression of liver cancers and cholangiocarcinoma (Karkkainen et al. 2002; Ji 2006; Tobler and Detmar 2006; Da et al. 2008; Das and Skobe 2008; Chen et al. 2010). Interestingly, tumor-associated lymphangiogenesis has a significance not only at the primary tumor site but also in lymph nodes, where primary neoplasms can induce a premetastatic lymphovascular niche prior to the arrival of metastasizing cells (review: Hirakawa 2009). The mechanisms of this niche formation are not yet known, but may be related to lymphatic spread of lymphangiogenic factors and/or transfer of tumor- or macrophage-derived exosomes with pro-lymphatic signal cargo. Tumor-associated lymphangiogenesis is correlated with prognosis after resection of HCCs, correlates with prognosis in intrahepatic cholangiocarcinoma, and reflects lymph node metastasis in hilar cholangiocarcinoma (Thelen et al. 2008, 2009, 2010). Lymphangiogenesis in HCC is associated with distinct expression patterns of VEGFs, in part with polymorphisms of VEGF and VEGFR genes (Scartozzi et al. 2014). VEGF-C, a factor which drives both blood vessel angiogenesis and lymphangiogenesis, is expressed in subsets of HCC, chiefly in poorly differentiated neoplasms. Upregulation of VEGF-C is correlated with larger tumor size, intrahepatic recurrence, and extrahepatic metastasis of HCC (Yamaguchi et al. 2006). On the other hand, certain tumor suppressors act via blocking of VEGF-mediated lymphangiogenesis. Smad4, a tumor suppressor and important downstream effector of TGF-beta signaling, reduces lymphangiogenesis by attenuating VEGF-C production (Liu et al. 2014c). In VEGF-induced lymphangiogenesis, HCCs upregulated the critical receptor VEGFR3. The expression of this receptor can be modulated by factors involved in hepatocarcinogenesis. For example, VEGFR3 is upregulated by the hepatitis B virus X protein (Lian et al. 2007). In hilar cholangiocarcinoma, nerve growth factor-beta overexpression was highly correlated with VEGF-C overexpression and lymphatic spread (Xu et al. 2010). Lymphatic spread of gallbladder carcinoma uses the lymphatic route, with distinct networks of podoplanin-reactive lymph vessels (Wakai et al. 2010). Lymphangiogenesis of gallbladder carcinoma is promoted by TNF-alpha through NF-kappaB-mediated upregulation of VEGF-C (Du et al. 2014). TNF-alpha-mediated lymphangiogenesis acts through the TNF receptor 1 and depends on a modulation of VEGF-C/VEGFR3 signaling (Ji et al. 2014). Intrahepatic lymphatic invasion of metastatic colorectal carcinoma cells is an indicator of aggressive course, recurrence, and poor survival (Korita et al. 2007). In colorectal carcinomas, lymphangiogenesis is mediated by neuropilin-2 via VEGF-C/VEGFR3-independent signaling (Ou et al. 2015).

Podoplanin, a type 1 transmembrane sialomucin-like glycoprotein that is induced by the homeobox gene Prox-1 and detectable by use of the D2-40 antibody, is widely expressed in normal and tumor cells (Raica et al. 2008) and is a marker of lymphangiogenesis in neoplasms. Podoplanin is strongly expressed in epithelioid hemangioendothelioma of the liver (Fujji et al. 2008), but is very rarely detectable in neoplastic cells other liver tumors, while it is strongly expressed in tumor lymphatics. In addition to its role as a lymphatic endothelium marker, podoplanin directly affects tumor biology (Dang et al. 2014). Apart from lymphatic endothelia, podoplanin is expressed in stromal myofibroblasts and cancer-associated fibroblasts/CAFs of tumors (Pula et al. 2013; Shindo et al. 2013). In intrahepatic cholangiocarcinoma, lymphatic spread is related to VEGF-C expression and the presence of D2-40 (podoplanin)-positive myofibroblasts (Aishima et al. 2008), suggesting that these stromal cells affect lymphatic spread. Expression of podoplanin by cancer cells can induce lymphangiogenesis and lymph node metastasis, a response mediated by endothelin-1, villin-1, and tenascin-C (Cuemi et al. 2010).

Angiogenesis as a Requirement for Invasion and Spread

Tumor-induced angiogenesis plays a significant role in invasion and metastatic spread. This issue is discussed in detail in a separate chapter.

The Inflammatory Microenvironment (IME) of Hepatobiliary Carcinoma: A Platform Critically Affecting Invasion and Spread of Cancers

Introduction

An inflammatory milieu (inflammatory microenvironment, IME) has been established as an important component of HCC development, invasion, and progression. IME depends on a complex cross-talk between epithelial cells of the tumor, stromal cells, hepatic fibroblastoid cells and stellate cells, and diverse types of infiltrating leukocytes, including tumor-associated lymphocytes (TILs), natural killer cells, tumor-associated macrophages (TAMs), Tie2-expressing monocytes, myeloid-derived suppressor cells, neutrophils, eosinophils, and dendritic cells. Similar to mechanisms of innate immunity, the most important leukocytes that modulate tumor behavior comprise monocytes/macrophages, neutrophils, and myeloid-derived suppressor cells (Smith and Kang 2013). The effects of stromal leukocytes on cancer cell invasion are in part mediated by secreted chemokines and cytokines.

Tumor-Associated Macrophages (TAMs)

The IME of HCC is critically influenced by the presence of tumor-associated macrophages (TAMs), which have a pivotal role for tumor invasion, progression, and angiogenesis (Shih et al. 2006; Kong et al. 2013; Yeung et al. 2015). TAMs expressing the scavenger receptor CD163 (Fabriek et al. 2005) are obligate partners for cancer cell migration and invasion (review: Condeelis and Pollard 2006). In the stroma of HCC, TAMs occur as two forms, M1 and M2, whereby M2 cells acquire a polarized phenotype and become activated, leading to the production by these cells of cytokines, chemokines, growth factors, TIMP-1, and MMPs, specifically MMP-9 (Capece et al. 2013; Zajac et al. 2013). CD68(+) M1-like macrophages promote HCC cell motility and locomotion via activation of the F-kappaB/focal adhesion kinase signaling pathway (Wang et al. 2014b). Upon contact and interactions with HCC cells, activated TAMs secrete IL-6, a pleotropic cytokine which acts as growth factor for hepatocytes and HCC cells via triggering the downstream signal transducer and activator of transcription 3/STAT-3 and extracellular signal-regulated kinase/ERK pathways, which control several proliferation-associated target genes. Apart from proliferation, TAM-derived IL-6 promotes HCC metastasis and EMT, the latter having an important effect of tumor progression. IL-6 also affects local immune reactions, in that it promotes T memory helper 17 (Th17) cell expansion in HCC (Kuang et al. 2010). M2-polarized TAMs can induce EMT and EMT-associated invasion through TLR4/IL-10 signaling (Liu et al. 2013). Stromal monocytes and macrophages secrete the chemokine CCL18, which promotes EMT and an invasive cancer phenotype (Meng et al. 2015a). TAMs promote progression of HCCs via STAT3 signaling, whereby aggressive and large tumors have higher levels of phosphorylated STAT3 (Mano et al. 2013). TAM contact-induced formation of tumor cell invadopodia is associated with activation of the RhoA GTPase signaling pathway (Roh-Johnson et al. 2014). Apart from the secretion of factors that regulate invasive tumor cell behavior and EMT, TAMs can modulate the expression of distinct proteins in and on cancer cells, a novel interactome that is involved in tumor-stromal cell cross-talk. TAMs can induce the expression of the macrophage-specific receptor CD163 in cancer cells (Maniecki et al. 2012), promoting a tumor cell type capable to migrate and invade.

Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) constitute a heterogeneous cell population contributing to immune tolerance, immunosuppression, tumor escape, and tumor progression (Brandau et al. 2013). These cells form a major group of effector cells in the tumor-related inflammatory microenvironment (Gabrilovich et al. 2007; Dolcetti et al. 2008; Youn and Gabrilovich 2010; Young et al. 2010; Bianchi et al. 2011; Caronni et al. 2015; Keskinov and Shurin 2015). The MDSC macropopulation is characterized by a CD11b+Gr-1+ phenotype, lacking expression of macrophage and dendritic cell markers. Morphologically, MDSCs consist of a mixture of monocytoid and granulocytic cells. In fact, the population consists of two principal types of MDSCs, i.e., cells with a granulocyte-like morphology and immunophenotype (granulocytic MDSCs or GrMDSCs; existing in two subtypes) and monocytic MDSCs/MoMDSCs (Peranzoni et al. 2010; Dumitru et al. 2012; Youn et al. 2012).

Together with regulatory T cells/Tregs, MDSCs have an important role in the progression of HCC, including those related to HBV infection and in the pathogenesis of metastases (Khaled et al. 2013; Solito et al. 2014; Condamine et al. 2015; Kondo and Shimosegawa 2015). MDSCs increase in frequency as a function of tumor growth, and their abundance is inversely correlated with the frequency of CD3+ T cells (Younos et al. 2011). In HCCs and colorectal cancer metastases, MDSCs are recruited by expression of CCL2 and CCL5, the CC chemokine receptor 1/CCR1 (Rodero et al. 2013; Borsig et al. 2014; Hirai et al. 2014), and the action of pyruvate kinase M2/PKM2 (Liu et al. 2015). In cancer, production of MDSCs is driven by the endoplasmic reticulum stress and the release of endoplasmic reticulum disulfide oxidase, ERO1-alpha, which mediates formation of disulfide bonds in collaboration with protein disulfide isomerase. ERO1-alpha promotes recruitment of granulocytic MDSCs via oxidative protein folding (Tanaka et al. 2015). The accumulation of MDSCs in cancer requires microRNA-494 via targeting PTEN (Liu et al. 2012b). MDSCs in cancers and specifically in HCC favor tumor cell invasion and spread through various mechanisms. MDSC infiltration favors angiogenesis/tumor vascularization and by this promotes metastasis (McLean and Buckanovich 2008; Rodero et al. 2013). Tumor-infiltrating MDSCs of the monocytoid type mediate CCR5-dependent recruitment of regulatory T cells (Tregs) in high numbers, cells which favor tumor growth (Schlecker et al. 2012). MDSCs can also act as tumor suppressors. They can produce a cystatin-like protein that inhibits metastasis (Boutté et al. 2011).

Neutrophils (Tumor-Associated Neutrophils, TANs)

As potent microphagocytes, neutrophils frequently accumulate close to necrotic tumor areas, where they are involved in clearance of debris and degraded cells. It was previously thought that this is the exclusive function of these cells in tumors. However, there is now evidence that neutrophils have more complex functions when infiltrating cancers. These granulocytes can, depending on the microenvironment, promote tumor growth and stimulate cancer cell invasion (Dumitru et al. 2013; Mishalian et al. 2013). Through the action of their granule proteins and production of reactive oxygen species/ROS, neutrophils can counteract tumor invasion and progression via tumor cell cytotoxicity and enhancement of antitumoral immune defense. Neutrophils with this activity are termed N1 neutrophils. Factors secreted in tumor stroma, such as TGF-beta and inteferons, induced a distinct polarized type of neutrophil with a different morphology termed N2, a cell type that favors tumor growth and invasion (review: Piccard et al. 2012). Neutrophils home to normal and tumor vessels and are stimulated to leave the intravascular pool via chemokinetic and chemotactic mechanisms, whereby CXCL8 (IL-8) binding to the receptor CXCR1 plays a central role (Bakele et al. 2014). Tumor-associated neutrophils (TANs; CD11b+/Ly6G+), attracted by TGF-beta, differ from normal

neutrophils in that they are hypersegmented, are more cytotoxic to tumor cells, and express higher levels of pro-inflammatory cytokines (Fridlender et al. 2009). In normal tissues and cancer tissues, most normal neutrophils are subject to apoptosis and are therefore short lived (Haslett et al. 1994). In contrast, TANs are long lived due to their expression of antiapoptotic Mcl-1 but less proapoptotic Bax (Wu et al. 2011). The induction of a tumor-associated granulocyte population with a greater survival has an important impact on tumor cell biology. Apoptotic and necrotic neutrophils, also those located to tumor stroma, are cleared via macrophage phagocytosis (Silva 2011). Glucocorticoids induce protein S-dependent phagocytosis of apoptotic neutrophils by macrophages (McColl et al. 2009).

The mechanisms via which neutrophils augment cancer cell invasion are only partially elucidated (Piccard et al. 2012). Neutrophils promote motility of cancer cells via a hyaluronan-mediated TLR4/PI3K activation loop (Wu et al. 2011). The pro-invasion activity of TAMs is strongly linked to expression of proteolytic enzymes. Neutrophils are a major source of MMP-9 in tumors and produce TIMP-free MMP-9 which is also active in angiogenesis (Ardi et al. 2007, 2009; Deryugina et al. 2014). Synthesis of MMP-9 by TANs is upregulated by aldosterone (Gilet et al. 2015). Neutrophil gelatinase is associated with lipocalin-2, a protein overexpressed in numerous cancers and involved in the expression of adhesion proteins involved in invasion, including cadherins (Lippi et al. 2014). TANs express elastase, which not only hydrolyzes elastin but also degrades E-cadherin on cancer cells (Gaida et al. 2012), possibly affecting the induction of EMT. Elastase also cleaves the CXCR1 receptor and by this mechanism modulates reactivity to the attractant, IL-8 (Bakele et al. 2014). Neutrophils can secrete ADAM9, which contributes to ECM protein degradation (Roychaudhuri et al. 2014). Apart from direct pro-invasive features, neutrophils can favor invasion indirectly, e.g., via angiogenesis. Neutrophils have proangiogenic properties via secretion of VEGFs, regulated by various factors. VEGF-A production by neutrophils is increased by aldosterone via PI3K, ERK1/2, and p38 pathways (Walczak et al. 2011). Apart from VEGFs, neutrophils stimulate angiogenesis through MMP-9 and fibroblast growth factor, a mechanism modulated by plasminogen activator inhibitor-1/PAI-1 (Tashiro et al. 2012).

In HCC, intratumoral neutrophil infiltration is promoted by the proangiogenic CXC-type chemokine family member CXCL5, which is overexpressed in part of these neoplasms and induces tumor invasion (Zhou et al. 2012). This chemokine exerts a similar effect in intrahepatic cholangiocarcinoma, where it recruits neutrophils and contributes to recurrence and metastasis (Zhou et al. 2014). In HCC, neutrophils are enriched in the peritumoral stroma, whereby IL-17 is a critical mediator for the recruitment of these cells. Neutrophils in peritumoral HCC stroma are a main source of matrix metalloproteinase-9, where this enzyme fosters invasion and angiogenesis (Kuang et al. 2011). Longevity of TANs in HCC is regulated by expression of the autophagy-specific protein LC3. LC3-reactive TANs exhibit a long-lived phenotype with retained Mcl-1, more intact mitochondria, and a low cleaved caspase-3 level, i.e,. an antiapoptotic phenotype (Li et al. 2015).

Bystanders of Inflammatory Responses: Hepatic Stellate Cells and Other Mesenchymal Cells

Activated hepatic stellate cells (HSCs) have an important position in the fibroinflammatory environment generated in HCC and CC. Activated HSCs play a critical role in fibrogenesis and stromagenesis associated with these two malignancies and participate in the creation of a matrix platform where inflammatory reactions can take place. Within normal liver and the stromal platform, hepatocytes or tumor cells engage in a cross-talk which produces a permissive proangiogenic microenvironment, in part via induction of VEGF-A and MMP-9 expression (Coulouam et al. 2012). The interaction between HSCs and cholangiocarcinoma cells is regulated by the stromal cell-derived factor 1-CXCR4 signaling axis, this pathway affecting the migration

capability of cholangiocarcinoma cells (Gentilini et al. 2012). Mesenchymal stem cells located in an inflammatory microenvironment of HCCs can induce EMT followed by a promotion of tumor progression (Jing et al. 2012).

Effects of Chemokines and Cytokines

Several members of the chemokine family of signaling substances are critical components of cancer-related inflammation and can affect cancer invasion and spread (O'Hayre et al. 2008; Allavena et al. 2011). Motility and invasion of liver cancer cells are modulated by several chemokines, cytokines, and factors regulating leukocyte motility. HCC cell migration is induced by ectopic production of macrophage migration inhibitory factor/MIF, a factor also involved in angiogenesis (Ren et al. 2003). MIF is also a factor that stimulates IL-8 and VEGF production, thus positively affecting angiogenesis (Ren et al. 2003). IL-8, expressed in HCC, itself stimulates HCC cell chemotactic and invasive activities (Kubo et al. 2005). HCC cell migration is strongly stimulated by chemokine ligand 12/CXCL12, which is expressed in these neoplastic cells (Liu et al. 2008). HCC cell migration is stimulated by the CC chemokine RANTES (regulated upon activation, normal T cell expressed and secreted; CCL5), under involvement of focal adhesion kinase, mitogen-activated protein kinase, and Rho kinase. This response depends on an interaction of RANTES with the proteoglycans, syndecan-1 and syndecan-4. CXCL5, a member of the CXC-type chemokine family, contributes to intrahepatic spread and metastasis of intrahepatic cholangiocarcinoma via recruiting intratumoral neutrophils (Zhou et al. 2014). CXCL5 mediates the interaction of cholangiocarcinoma cells with cancer-associated fibroblasts/CAFs of the tumor stroma (Okabe et al. 2012). Cholangiocarcinoma cell invasion is also enhanced by CXCL12, modulated by activation of CXCR4 and its signaling pathways that involve MEK1/2 and Akt (Leelawat et al. 2007). In HCCs, TGF-beta suppresses the expression of microRNA-34a, leading to enhanced production of the chemokine CCL2, which in turn promotes venous metastasis (Yang et al. 2012). The tumor-derived inflammatory chemokine CCL2 can directly activate endothelial cells and together with monocytes facilitate tumor cell extravasation (Borsig et al. 2014). Cytokines released from activated TAMs can induce EMT in cholangiocarcinoma cells (Techasen et al. 2012).

References

Achen MG, Stacker SA (2008) Molecular control of lymphatic metastasis. Ann N Y Acad Sci 1131:225–234

Ahn SM, Cha JY, Kim J, Kim D, Trang HT, Kim YM, Cho YH, Park D, Hong S (2012) Smad3 regulates E-cadherin via miRNA-200 pathway. Oncogene 31:3051–3059

Aigner A (2011) MicroRNAs (miRNAs) in cancer invasion and metastasis: therapeutic approaches based on metastasis-related miRNAs. J Mol Med 89:445–457

Aishima S, Nishihara Y, Iguchi T, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2008) Lymphatic spread is related to VEGF-C expression and D2-40-positive myofibroblasts in intrahepatic cholangiocarcinoma. Mod Pathol 21:256–264

Albini A (2008) Tumor microenvironment, a dangerous society leading to cancer metastasis. From mechanisms to therapy and prevention. Cancer Metastasis Rev 27:3–4

Allavena P, Germano G, Marchesi F, Mantovani A (2011) Chemokines in cancer related inflammation. Exp Cell Res 317:664–673

Anborgh PH, Mutrie JC, Tuck AB, Chambers AF (2010) Role of the metastasis-promoting protein osteopontin in the tumour microenvironment. J Cell Mol Med 14:2037–2044

Ardi et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/18077379

Ardi et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19608737

Bakele M, Lotz-Havla AS, Jakowetz A, Carevic M, Marco V, Munta AC, Gerstin SW, Hartl D (2014) An interactive network of elastase, secretases, and PAR-2 protein regulates CXCR1 receptor surface expression on neutrophils. J Biol Chem 289:20516–20525

Balzarini P, Benetti A, Invernici G, Cristini S, Zicari S, Caruso A, Gatta LB, Berenzi A et al (2012) Transforming growth factor-beta1 induces microvascular abnormalities through a down-modulation of neural cell adhesion molecule in human hepatocellular carcinoma. Lab Invest 92:1297–1309

Bao YX, Cao Q, Yang Y, Mao R, Xiao L, Zhang H, Zhao HR, Wen H (2013) Expression and prognostic significance of Golgi glycoprotein73 (GP73) with epithelial-mesenchymal transition (EMT) related molecules in hepatocellular carcinoma (HCC). Diagn Pathol 8:197

Bianchi G, Borgonovo G, Pistoia V, Raffaghello L (2011) Immunosuppressive cells and tumour microenvironment: focus on mesenchymal stem cells and myeloid derived suppressor cells. Histol Histopathol 26:941–951

Borsig L, Wolf MJ, Roblek M, Lorentzen A, Heikenwalder M (2014) Inflammatory chemokines and metastasis – tracing the accessory. Oncogene 33:3217–3224

Boutté AM, Friedman DB, Bogyo M, Min Y, Yang L, Lin PC (2011) Identification of a myeloid-derived suppressor cell cystatin-like protein that inhibits metastasis. FASEB J 25:2626–2637

Brandau S, Moses K, Lang S (2013) The kinship of neutrophils and granulocytci myeloid-derived suppressor cells in cancer: cousins, siblings or twins? Semin Cancer Biol 23:171–182

Cadamuro M, Nardo G, Indraccolo S, Dall'olmo L, Sambado L, Moserle L, Franceschet I, Colledan M, Massani M et al (2013) Platelet-derived growth factor-D and Rho GTPase regulate recruitment of cancer-associated fibroblasts in cholangiocarcinoma. Hepatology 58:1042–1053

Capece D, Fischietti M, Verzella D, Gaggiano A, Cicciarelli G, Tessitore A, Zazzeroni F et al (2013) The inflammatory microenvironment in hepatocellular carcinoma: a pivotal role for tumor-associated macrophages. Biomed Res Int 2013:187204

Caronni N, Savino B, Bonecchi R (2015) Myeloid cells in cancer-related inflammation. Immunobiology 220:249–253

Casas E, Kim J, Bendesky A, Ohno-Machado L, Wolfe CJ, Yang J (2011) Snail2 is an essential mediator of Twist1-induced epithelial mesenchymal transition and metastasis. Cancer Res 71:245–254

Chen Y, Jiang L, She F, Tang N, Wang X, Li X, Han S, Zhu J (2010) Vascular endothelial growth factor-C promotes the growth and invasion of gallbladder cancer via an autocrine mechanism. Mol Cell Biochem 345:77–89

Chen J, Chan AW, To KF, Chen W, Zhang Z, Ren J, Song C, Cheung YS, Lai PB et al (2013) SIRT2 overexpression in hepatocellular carcinoma mediates epithelial to mesenchymal transition by protein kinase B/glycogen synthase kinase-3b/b-catenin signaling. Hepatology 57:2287–2298

Cirri P, Chiarugi P (2012) Cancer-associated-fibroblasts and tumour cells: a diabolic liaison driving cancer progression. Cancer Metastasis Rev 31:195–208

Condamine T, Ramachandran I, Youn JI, Gabrilovich DI (2015) Regulation of tumor metastasis by myeloid-derived suppressor cells. Annu Rev Med 66:97–110

Condeelis J, Pollard JW (2006) Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 124:263–266

Coulouam C, Corlu A, Glaise D, Guénon I, Thorgeirsson SS, Clément B (2012) Hepatocyte-stellate cell cross-talk in the liver engenders a permissive inflammatory microenvironment that drives progression in hepatocellular carcinoma. Cancer Res 72:2533–2542

Cuemi LN, Hegyi I, Shin JW, Albinger-Hegyi A, Gruber S, Kunstfeld R, Moch H, Detmar M (2010) Tumor lymphangiogenesis and metastasis to lymph nodes induced by cancer cell expression of podoplanin. Am J Pathol 177:1004–1016

Da MX, Wu Z, Tian HW (2008) Tumor lymphangiogenesis and lymphangiogenic growth factors. Arch Med Res 39:365–372

Dagouassat M, Suffee N, Hlawaty H, Haddad O, Charni F, Laguillier C, Vassy R, Martin L, Schischmanoff PO, Gattegno L et al (2010) Monocyte chemoattractant protein-1 (MCP-1)/CCL2 secreted by hepatic myofibroblasts promotes migration and invasion of human hepatoma cells. Int J Cancer 126:1095–1108

Dang Q, Liu J, Li J, Sun Y (2014) Podoplanin: a novel regulator of tumor invasion and metastasis. Med Oncol 31:24

Das S, Skobe M (2008) Lymphatic vessel activation in cancer. Ann N Y Acad Sci 1131:235–241

De Wever O, Mareel M (2003) Role of tissue stroma in cancer cell invasion. J Pathol 200:429–447

De Wever O, Demetter P, Mareel M, Bracke M (2008) Stromal myofibroblasts are drivers of invasive cancer growth. Int J Cancer 123:2220–2238

Deng Y, Zhang X, Simons M (2015) Molecular controls of lymphatic VEGFR3 signaling. Arterioscler Thromb Vasc Biol 35:421–429

Deryugina et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/25379015

Ding W, Dang H, You H, Steinway S, Takahashi Y, Wang HG, Liao J, Stiles B, Albert R, Rountree CB (2012) miR-200b restoration and DNA methyltransferase inhibitor block lung metastasis of mesenchymal-phenotype hepatocellular carcinoma. Oncogenesis 1: e15

Dolcetti L, Marigo I, Mantelli B, Peranzoni E, Zanovello P, Bronte V (2008) Myeloid-derived suppressor cell role in tumor-related inflammation. Cancer Lett 267:216–225

Dong QZ, Zhang XF, Zhao Y, Jia HL, Zhou HJ, Dai C, Sun HJ, Qin Y, Zhang WD et al (2013) Osteopontin promoter polymorphisms at locus -443 significantly affect the metastasis and prognosis of human hepatocellular carcinoma. Hepatology 57:1024–1034

Du R, Wu S, Lv X, Fang H, Wu S, Kang J (2014) Overexpression of brachyury contributes to tumor metastasis by inducing epithelial-mesenchymal transition in hepatocellular carcinoma. J Exp Clin Cancer Res 33:105

Duca L, Floquet N, Alix AJ, Haye B, Debelle L (2004) Elastin as a matrikine. Crit Rev Oncol Hematol 49:235–244

Dumitru CA, Moses K, Trellakis S, Lang S, Brandau S (2012) Neutrophils and granulocytic myeloid-derived suppressor cells: immunophenotyping, cell biology and clinical relevance in human oncology. Cancer Immunol Immunother 61:1155–1167

Dumitru CA, Lang S, Brandau S (2013) Modulation of neutrophil granulocytes in the tumor

microenvironment: mechanisms and consequences for tumor progression. Semin Cancer Biol 23:141–148
Fabriek BO, Dijkstra CD, van den Berg TK (2005) The macrophage scavenger receptor CD163. Immunobiology 210:153–160
Fan QM, Jing YY, Yu GF, Kou XR, Ye F, Gao L, Li R, Zhao QD, Yang Y, Lu ZH, Wei LX (2014) Tumor-associated macrophages promote cancer stem cell-like properties via transforming growth factor-beta1-induced epithelial-mesenchymal transition in hepatocellular carcinoma. Cancer Lett 352:160–168
Fang JH, Zhou HC, Zhang C, Shang LR, Zhang L, Xu J, Zheng L, Yuan Y, Guo RP, Jia WH, Yun JP, Chen MS et al (2015) A novel vascular pattern promotes metastasis of hepatocellular carcinoma in an EMT-independent manner. Hepatology. doi:10.1002/hep.27760
Firrincieli D, Boissan M, Chignard N (2010) Epithelial-mesenchymal transition in the liver. Gastroenterol Clin Biol 34:523–528
Fridlender et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19732719
Fu XT, Dai Z, Song K, Zhang ZJ, Zhou ZJ, Zhou SL, Zhao YM, Xiao YS, Sun QM, Ding ZB, Fan J (2015) Macrophage-secreted IL-8 induces epithelial-mesenchymal transition in hepatocellular carcinoma cells by activating the JAK2/STAT3/Snail pathway. Int J Oncol 46:587–596
Fujji T, Zen Y, Sato Y, Sasaki M, Enomae M, Minato H, Masuda S, Uehara T, Katsuyama T, Nakanuma Y (2008) Podoplanin is a useful diagnostic marker for epithelioid hemangioendothelioma of the liver. Mod Pathol 21:125–130
Fülöp T, Larbi A (2002) Putative role of 67 kDa elastin-laminin receptor in tumor invasion. Semin Cancer Biol 12:219–229
Gabrilovich DI, Bronte V, Chen SH, Colombo MP, Ochoa A, Ostrand-Rosenberg S, Schreiber H (2007) The terminology issue for myeloid-derived suppressor cells. Cancer Res 67:425–426
Gaida et al. 2012. http://www.ncbi.nlm.nih.gov/pubmed/23001948
Gentilini A, Rombouts K, Galastri S, Caligiuri A, Mingarelli E, Mello T, Marra F, Mantero S et al (2012) Role of the stromal-derived factor-1 (SDF-1)-CXCR4 axis in the interaction between hepatic stellate cells and cholangiocarcinoma. J Hepatol 57:813–820
Ghose S, Min Y, Lin PC (2015) δ-catenin activates Rho GTPase, promotes lymphangiogenesis and growth of tumor metastases. PLoS One 10:e116338
Giannelli G, Bergamini C, Fransvea E, Sgarra C, Antonaci S (2005) Laminin-5 with transforming growth factor-beta1 induces epithelial to mesenchymal transition in hepatocellular carcinoma. Gastroenterology 129:1375–1383
Gilet et al. 2015. http://www.ncbi.nlm.nih.gov/pubmed/25449697
Gu MJ, Choi JH (2014) Epithelial-mesenchymal transition phenotypes are associated with patient survival in intrahepatic cholangiocarcinoma. J Clin Pathol 67:229–234
Guarino M (2007) Epithelial-mesenchymal transition and tumour invasion. Int J Biochem Cell Biol 39:2153–2160
Guarino M, Rubino B, Ballabio G (2007) The role of epithelial-mesenchymal transition in cancer pathology. Pathology 39:305–318
Hao C, Zhu P, Yang X, Han Z, Jiang J, Zong C, Zhang X, Liu W, Zhao Q, Fan T, Zhang L, Wei L (2014) Overexpression of SIRT1 promotes metastasis through epithelial-mesenchymal transition in hepatocellular carcinoma. BMC Cancer 14:978
Haslett et al. 1994. http://www.ncbi.nlm.nih.gov/pubmed/7846130
He Y, Kozaki K, Karpanen T, Koshikawa K, Yla-Herrtuala S, Takahashi T, Alitalo K (2002) Suppression of tumor lymphangiogenesis and lymph node metastasis by blocking vascular endothelial growth factor receptor 3 signaling. J Natl Cancer Inst 94:819–825
Hernandez JM, Elahi A, Clark CW, Wang J, Humphries LA, Centeno B, Bloom G, Fuchs BC, Yeatman T, Shibata D (2013) miR-675 mediates downregulation of Twist1 and Rb in AFP-secreting hepatocellular carcinoma. Ann Surg Oncol 20(Suppl 3):S625–S635
Hinz B (2010) The myofibroblasts: paradigm for a mechanically active cell. J Biomech 43:146–155
Hirai H, Fujishita T, Kurimoto K, Miyachi H, Kitano S, Inamoto S, Itatani Y, Saitou M, Maekawa T, Taketo MM (2014) CCR1-mediated accumulation of myeloid cells in the liver microenvironment promoting mouse colon cancer emtastasis. Clin Exp Metastasis 31:977–989
Hirakawa S (2009) From tumor lymphangiogenesis to lymphovascular niche. Cancer Sci 100:983–989
Horimoto Y, Polanska UM, Takahashi Y, Orimo A (2012) Emerging roles of the tumor-associated stroma in promoting tumor metastasis. Cell Adh Migr 6:193–202
Hsu DS, Wang HJ, Tai SK, Chou CH, Hsieh CH, Chiu PH, Chen NJ, Yang MH (2014) Acetylation of snail modulates the cytokinome of cancer cells to enhance the recruitment of macrophages. Cancer Cell 26:534–548
Hua F, Mu R, Liu J, Wang Z, Lin H, Yang H, Chen X, Hu Z (2011) TRB3 interacts with SMAD3 promoting tumor cell migration and invasion. J Cell Sci 124:3235–3246
Huang Q, Liu L, Liu CH, Shao F, Xie F, Zhang CH, Hu SY (2012) Expression of Smad7 in cholangiocarcinoma: prognostic significance and implications for tumor metastasis. Asian Pac J Cancer Prev 13:5161–5165
Huang X, Cong X, Yang D, Ji L, Liu Y, Cui X, Cai J, He S, Zhu C, Ni R, Zhang Y (2014) Identification of Gem as a new candidate prognostic marker in hepatocellular carcinoma. Pathol Res Pract 210:719–725
Hung CS, Liu HH, Liu JJ, Yeh CT, Chang TC, Wu CH, Ho YS, Wei PL, Chang YJ (2013) MicroRNA-200a and -200b mediated hepatocellular carcinoma cell

migration through the epithelial to mesenchymal transition markers. Ann Surg Oncol 20(Suppl 3): S360–S368

Hur K, Toiyama Y, Takahashi M, Balaquer F, Nagasaka T, Koike J, Hemmi H, Koi M, Boland CR, Goel A (2013) MicroRNA-200c modulates epithelial-to-mesenchymal transition (EMT) in human colorectal cancer metastasis. Gut 62:1315–1326

Isenmann S, Arthur A, Zannettino AC, Turner JL, Shi S, Glackin CA, Gronthos S (2009) TWIST family of basic helix-loop-helix transcription factors mediate human mesenchymal stem cell growth and commitment. Stem Cells 27:2457–2468

Ji RC (2006) Lymphatic endothelial cells, tumor lymphangiogenesis and metastasis: new insights into intratumoral and peritumoral lymphatics. Cancer Metastasis 25:677–694

Ji et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/25229256

Jiang X, Xiang G, Wang Y, Zhang L, Yang X, Cao L, Peng H, Xue P, Chen D (2012) Micro-RNA-590-5p regulates proliferation and invasion in human hepatocellular carcinoma cells by targeting TGF-b RII. Mol Cells 33:545–551

Jing Y, Han Z, Liu Y, Sun K, Zhang S, Jiang G, Li R, Gao L, Zhao X, Wu D, Cai X et al (2012) Mesenchymal stem cells in inflammation microenvironment accelerates hepatocellular carcinoma metastasis by inducing epithelial-mesenchymal transition. PLoS One 7: e43272

Kan H, Guo W, Huang Y, Liu D (2015) MicroRNA-520g induces epithelial-mesenchymal transition and promotes metastases of hepatocellular carcinoma by targeting SMAD7. FEBS Lett 589:102–109

Karkkainen MJ, Mäkinen T, Alitalo K (2002) Lymphatic endothelium: a new frontier of metastasis research. Nat Cell Biol 4:E2–E5

Katsuno Y, Lamouille S, Derynck R (2013) TGF-β signaling and epithelial-mesenchymal transition in cancer progression. Curr Opin Oncol 25:76–84

Keskinov AA, Shurin MR (2015) Myeloid regulatory cells in tumor spreading and metastasis. Immunobiology 220:236–242

Khaled YS, Ammori BJ, Elkord E (2013) Myeloid-derived suppressor cells in cancer: recent progress and prospects. Immunol Cell Biol 91:493–502

Kim HS, Jung G (2014) Notch1 increases Snail expression under high reactive oxygen species conditions in hepatocellular carcinoma cells. Free Radic Res 48:806–813

Kogure T, Kondo Y, Kakazu E, Ninomiya M, Kimura O, Shimosegawa T (2014) Involvement of microRNA-29a in epigenetic regulation of transforming growth factor-b-induced epithelial-mesenchymal transition in hepatocellular carcinoma. Hepatol Res 44:907–919

Kondo Y, Shimosegawa T (2015) Significant roles of regulatory T cells and myeloid derived suppressor cells in hepatitis B virus persistent infection and hepatitis B virus-related HCCs. Int J Mol Sci 16:3307–3322

Kong LQ, Zhu XD, Xu HX, Zhang JB, Lu L, Wang WQ, Hang QB, Wu WZ, Wang L et al (2013) The clinical significance of the CD163+ and CD68+ macrophages in patients with hepatocellular carcinoma. PLoS One 8:e59771

Korita PV, Wakai T, Shirai Y, Sakata J, Takizawa K, Cruz PV, Ajioka Y, Hakeyama K (2007) Intrahepatic lymphatic invasion independently predicts poor survival and recurrences after hepatectomy in patients with colorectal carcinoma liver metastases. Ann Surg Oncol 14:3472–3480

Kuang DM, Peng C, Zhao Q, Wu Y, Chen MS, Zheng L (2010) Activated monocytes in peritumoral stroma of hepatocellular carcinoma promote expansion of memory T helper 17 cells. Hepatology 51:154–164

Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L (2011) Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol 54:948–955

Kubo F, Ueno S, Hiwatashi K, Sakoda M, Kawaida K, Nuruki K, Aikou T (2005) Interleukin 8 in human hepatocellular carcinoma correlates with cancer cell invasion of vessels but not with tumor angiogenesis. Ann Surg Oncol 12:800–807

Kumarswamy R, Mudduluru G, Ceppi P, Muppala S, Kozlowski M, Niklinski J, Papotti M et al (2012) MicroRNA-30a inhibits epithelial-to-mesenchymal transition by targeting Snail and is downregulated in non-small cell lung cancer. Int J Cancer 130:2044–2053

Kwak Y, Lee HE, Kim WH, Kim DW, Kang SB, Lee HS (2014) The clinical implication of cancer-associated microvasculature and fibroblast in advanced colorectal cancer patients with synchronous or metachronous metastases. PLoS One 9:e91811

Lan SH, Wu SY, Zuchini R, Lin XZ, Su IJ, Tsai TF, Lin YJ, Wu CT, Liu HS (2014) Autophagy suppresses tumorigenesis of hepatitis B virus-associated hepatocellular carcinoma through degradation of miR-224. Hepatology 59:505–517

Lapis K, Timar J (2002) Role of elastin-matrix interactions in tumor progression. Semin Cancer Biol 12:209–217

Lecomte J, Masset A, Blacher S, Maertens L, Gothot A, Delgaudine M, Bruyère F, Carnet O et al (2012) Bone marrow-derived myofibroblasts are the providers of pro-invasive matrix metalloproteinase 13 in primary tumor. Neoplasia 14:943–951

Lee TK, Poon RT, Yuen AP, Ling MT, Kwok WK, Wang XH, Wong YC, Guan XY et al (2006) Twist overexpression correlates with hepatocellular carcinoma metastasis through induction of epithelial-mesenchymal transition. Clin Cancer Res 12:5369–5376

Lee D, Chung YH, Kim JA, Lee YS, Lee D, Jang MK, Kim KM, Lim YS, Lee HC et al (2012) Transforming growth factor beta 1 overexpression is closely related to invasiveness of hepatocellular carcinoma. Oncology 82:11–18

Lee KM, Danuser R, Stein JV, Graham D, Nibbs RJ, Graham GJ (2014a) The chemokine receptors ACKR2 and CCR2 reciprocally regulate lymphatic vessel density. EMBO J 33:2564–2580

Lee YH, Hsu CY, Huang YH, Hsia CY, Chiou YY, Su CW, Lin HC, Huo TI (2014b) Vascular invasion in hepatocellular carcinoma: prevalence, determinants and prognostic impact. J Clin Gastroenterol 48:734–741

Lee HJ, Jeng YM, Chen YL, Chung L, Yuan RH (2014c) Gas6/Axl pathway promotes tumor invasion through the transcriptional activation of Slug in hepatocellular carcinoma. Carcinogenesis 35:769–775

Leelawat K, Leelawat S, Narong S, Hongeng S (2007) Roles of the MEK1/2 and AKT pathways in CXCL12/CXCR4 induced cholangiocarcinoma cell invasion. World J Gastroenterol 13:1561–1568

Li et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19916908

Li N, Jiang P, Du W, Wu Z, Li C, Qiao M, Yang X, Wu M (2011) Siva1 suppresses epithelial-mesenchymal transition and metastasis of tumor cells by inhibiting stathmin and stabilizing microtubules. Proc Natl Acad Sci U S A 108:12851–12856

Li GC, Ye QH, Dong QZ, Ren N, Jia JL, Qin LX (2012a) TGF beta1 and related-Smads contribute to pulmonary metastasis of hepatocellular carcinoma in mice model. J Exp Clin Cancer Res 31:93

Li QJ, Zhou L, Yang F, Wang GX, Zheng H, Wang DS, He Y, Dou KF (2012b) MicroRNA-10b promotes migration and invasion through CADM1 in human hepatocellular carcinoma cells. Tumour Biol 33:1455–1465

Li B, Han Q, Zhu Y, Yu Y, Wang J, Jiang X (2012c) Down-regulation of miR-214 contributes to intrahepatic cholangiocarcinoma metastasis by targeting Twist. FEBS J 279:2393–2398

Li Q, Gu X, Weng H, Ghafoory S, Liu Y, Feng T, Dzieran J, Li L, Ilkavets I, Kruithof-de Julio M et al (2013) Bone morphogenetic protein-9 induces epithelial to mesenchymal transition in hepatocellular carcinoma cells. Cancer Sci 104:398–408

Li A, Morton JP, Ma Y, Karim SA, Zhou Y, Faller WJ, Woodham EF, Morris HT, Stevenson RP, Juin A, Jamieson NB et al (2014) Fascin is regulated by slug, promotes progression of pancreatic cancer in mice, and is associated with patient outcomes. Gastroenterology 146:1386–1396

Li XF, Chen DP, Ouyang FZ, Chen MM, Wu Y, Kuang DM, Zheng L (2015) Increased autophagy sustains the survival and pro-tumourigenic effects of neutrophils in human hepatocellular carcinoma. J Hepatol 62:131–139

Lian Z, Liu J, Wu M, Wang HY, Arbuhnot P, Kew M, Feitelson MA (2007) Hepatitis B x antigen up-regulates vascular endothelial growth factor receptor 3 in hepatocarcinogenesis. Hepatology 45:1390–1399

Lin ZS, Chu HC, Yen YC, Lewis BC, Chen YW (2012) Krüppel-like factor 4, a tumor suppressor in hepatocellular carcinoma cells reverts epithelial mesenchymal transition by suppressing slug expression. PLoS One 7:e43593

Lippi et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24938019

Liu H, Pan Z, Li A, Fu S, Lei Y, Sun H, Wu M, Zhou W (2008) Roles of chemokine receptor 4 (CXCR4) and chemokine ligand 12 (CXCL12) in metastasis of hepatocellular carcinoma cells. Cell Mol Immunol 5:373–378

Liu L, Zhu XD, Wang WQ, Shen Y, Qin Y, Ren ZG, Sun HC, Tang ZY (2010) Activation of beta-catenin by hypoxia in hepatocellular carcinoma contributes to enhanced metastatic potential and poor prognosis. Clin Cancer Res 16:2740–2750

Liu W, Xu G, Ma J, Jia W, Li J, Che K, Wang W, Hao C, Wang Y, Wang X (2011) Osteopontin as a key mediator for vasculogenic mimicry in hepatocellular carcinoma. Tohoku J Exp Med 22:29–39

Liu J, Xu K, Chase M, Ji Y, Logan JK, Buchsbaum RJ (2012a) Tiam1-regulated osteopontin in senescent fibroblasts contributes to the migration and invasion of associated epithelial cells. J Cell Sci 125:376–386

Liu Y, Lai L, Chen Q, Song Y, Xu S, Ma F, Wang X, Wang J, Yu H, Cao X, Wang Q (2012b) MicroRNA-494 is required for the accumulation and functions of tumor-expanded myeloid-derived suppressor cells via targeting of PTEN. J Immunol 188:5500–5510

Liu CY, Xu JY, Shi XY, Huang W, Ruan TY, Xie P, Ding JL (2013) M2-polarized tumor-associated macrophages promoted epithelial-mesenchymal transition in pancreatic cancer cells, partially through TLR4/IL-10 signaling pathway. Lab Invest 93:844–854

Liu AY, Cai Y, Mao Y, Lin Y, Zheng H, Wu T, Huang Y, Fang X, Lin S, Feng Q, Huang Z, Yang T, Luo Q, Ouyang G (2014a) Twist2 promotes self-renewal of liver cancer stem-like cells by regulating CD24. Carcinogenesis 35:537–545

Liu Y, Ding Y, Huang J, Wang S, Ni W, Guan J, Li Q, Zhang Y, Ding Y, Chen B, Chen B et al (2014b) MiR-141 suppresses the migration and invasion of HCC cells by targeting Tiam1. PLoS One 9:e88393

Liu Y, Sheng J, Dai D, Liu T, Qi F (2014c) Smad4 acts as tumor suppressor by antagonizing lymphangio-genesis in colorectal cancer. Pathol Res Pract. doi:10.1016/j.prp.2014.09.008

Liu D, Li L, Zhang XX, Wan DY, Xi BX, Hu Z, Ding WC, Zhu D, Wang XL, Wang W, Feng ZH, Wang H, Ma D et al (2014d) SIX1 promotes tumorl lymphangiogenesis by coordinating TGFβ signals that increase expression of VEGF-C. Cancer Res 74:5597–5607

Liu WR, Tian MX, Yang LX, Lin YL, Jin L, Ding ZB, Shen YH, Peng YF, Gao DM, Zhou J, Qiu SJ, Dai Z, He R et al (2015) PKM2 promotes metastasis by recruiting myeloid-derived suppressor cells and indicates poor prognosis for hepatocellular carcinoma. Oncotarget 6:846–861

Livni N, Behar A, Brautbar N (1977) Ultrastructure of hepatocellular carcinoma in a cirrhotic liver. Isr J Med Sci 13:590–599

Low-Marchelli JM, Ardi VC, Vizcarra EA, van Rooijen N, Quigley JP, Yang J (2013) Twist1 induces CCL2 and recruits macrophages to promote angiogenesis. Cancer Res 73:662–671

Lupinacci RM, Mello ES, Pinheiro RS, Marques G, Coelho FF, Kruger JA, Perini MV, Herman P (2014) Intrahepatic lymphatic invasion but not vascular invasion is a major prognostic factor after resection of colorectal cancer liver metastases. World J Surg 38:2089–2096

Maegdefrau U, Bosserhoff AK (2012) BMP activated Smad signaling strongly promotes migration and invasion of hepatocellular carcinoma cells. Exp Mol Pathol 92:74–81

Mamiya T, Yamazaki K, Masugi Y, Mori T, Effendi K, Du W, Hibi T, Tanabe M, Ueda M et al (2010) Reduced transforming growth factor-beta receptor II expression in hepatocellular carcinoma correlates with intrahepatic metastasis. Lab Invest 90:1339–1345

Maniecki MB, Etzerodt A, Ulhoi BP, Steiniche T, Borre M, Dyrskjot L, Orntoft TF, Moesrup SK, Moller HJ (2012) Tumor-promoting macrophages induce the expression of the macrophage-specific receptor CD163 in malignant cells. Int J Cancer 131:2320–2331

Mano Y, Aishima S, Fujita N, Tanaka Y, Kubo Y, Motomura T, Taketomi A, Shirabe K et al (2013) Tumor-associated macrophage promotes tumor progression via STAT3 signaling in hepatocellular carcinoma. Pathobiology 80:146–154

Mareel M, Madani I (2006) Tumour-associated host cells participating at invasion and metastasis: targets for therapy? Acta Chir Belg 106:635–640

Matsuo N, Shiraha H, Fujikawa T, Takaoka N, Ueda N, Tanaka S, Nishina S, Nakanishi Y et al (2009) Twist expression promotes migration and invasion in hepatocellular carcinoma. BMC Cancer 9:240

McColl et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19597001

McLean K, Buckanovich RJ (2008) Myeloid cells functioning in tumor vascularization as a novel therapeutic target. Transl Res 151:59–67

Meindl-Beinker NM, Matsuzaki K, Dooley S (2012) TGF-b signaling in onset and progression of hepatocellular carcinoma. Dig Dis 30:514–523

Meng F, Wu G (2012) The rejuvenated scenario of epithelial-mesenchymal transition (EMT) and cancer metastasis. Cancer Metastasis Rev 31:455–467

Meng F, Li W, Li C, Gao Z, Guo K, Song S (2015a) CCL18 promotes epithelial-mesenchymal transition, invasion and migration of pancreatic cancer cells in pancreatic ductal adenocarcinoma. Int J Oncol 46:1109–1120

Meng FD, Wei JC, Qu K, Wang ZX, Wu QF, Tai MH, Liu HC, Zhang RY, Liu C (2015b) FoxM1 overexpression promotes epithelial-mesenchymal transition and metastasis of hepatocellular carcinoma. World J Gastroenterol 21:196–213

Mima K, Okabe H, Ishimoto T, Hayashi H, Nakagawa S, Kuroki H, Watanabe M, Beppu T et al (2012) CD44s regulates the TGF-b-mediated mesenchymal phenotype and is associated with poor prognosis in patients with hepatocellular carcinoma. Cancer Res 72:3414–3423

Mima K, Hayashi H, Kuroki H, Nakagawa S, Okabe H, Chikamoto A, Watanabe M et al (2013) Epithelial-mesenchymal transition expression profiles as a prognostic factor for disease-free survival in hepatocellular carcinoma: clinical significance of transforming growth factor-b signaling. Oncol Lett 5:149–154

Mishalian I, Bayuh R, Levy L, Zolotarov L, Michaeli J, Fridlender ZG (2013) Tumor-associated neutrophils (TAN) develop pro-tumorigenic properties during tumor progression. Cancer Imunol Immunother 62:1745–1756

Miyazono K, Ehata S, Koinuma D (2012) Tumor-promoting functions of transforming growth factor-β in progression of cancer. Ups J Med Sci 117:143–152

Miyoshi A, Kitajima Y, Umi K, Sato K, Hagiwara A, Koga Y, Miyzaki K (2004) Snail and SIP1 increase cancer invasion by upregulating MMP family in hepatocellular carcinoma cells. Br J Cancer 90:1265–1273

Niu RF, Zhang L, Xi GM, Wei XY, Yang Y, Shi YR, Hao XS (2007) Up-regulation of twist induces angiogenesis and correlates with metastasis in hepatocellular carcinoma. J Exp Clin Cancer Res 26:385–394

O'Hayre M, Salanga CL, Handel TM, Allen SJ (2008) Chemokines and cancer: migration, intracellular signalling and intercellular communication in the microenvironment. Biochem J 409:635–649

Ohashi M, Wakai T, Korita PV, Ajioka Y, Shirai Y, Hatakeyama K (2010) Histological evaluation of intracapsular venous invasion for discrimination between portal and hepatic venous invasion in hepatocellular carcinoma. J Gastroenterol Hepatol 25:143–149

Okabe H, Beppu T, Ueda M, Hayashi H, Ishiko T, Masuda T, Otao R, Horlad H, Mima K et al (2012) Identification of CXCL5/ENA-78 as a factor involved in the interaction between cholangiocarcinoma cells and cancer-associated fibroblasts. Int J Cancer 131:2234–2241

Okabe H, Ishimoto T, Mima K, Nakagawa S, Hayashi H, Kuroki H, Imai K, Nitta H, Saito S, Hashimoto D, Chikamoto A et al (2014) CD44s signals the acquisition of the mesenchymal phenotype required for anchorage-independent cell survival in hepatocellular carcinoma. Br J Cancer 110:958–966

Ou JJ, Wei X, Peng Y, Zha L, Zhou RB, Shi H, Zhou Q, Liang HJ (2015) Neuropilin-2- mediates lymphangiogenesis of colorectal carcinoma via a VEGF/VEGFR3 independent signaling. Cancer Lett 358:200–209

Peng YF, Shi YH, Shen YH, Ding ZB, Ke AW, Zhou J, Qiu SJ, Fan J (2013) Promoting colonization in metastatic HCC cells by modulation of autophagy. PLoS One 8:e74407

Peranzoni E, Zilio S, Marigo I, Dolcetti L, Zanovello P, Mandruzzato S, Bronte V (2010) myeloid-derived suppressor cell heterogeneity and subset definition. Curr Opin Immunol 22:238–244

Piccard H, Muschel RJ, Opdenakker G (2012) On the dual roles and polarized phenotypes of neutrophils in tumor development and progression. Crit Rev Oncol Hematol 82:296–309

Puisieux A, Valsesia-Wittmann S, Ansieau S (2006) A twist survival and cancer progression. Br J Cancer 94:13–17

Pula B, Witkiewicz W, Dziegiel P, Podhorska-Okolow M (2013) Significance of podoplanin expression in cancer-associated fibroblasts: a comprehensive review. Int J Oncol 42:1849–1857

Qiu YH, Wei YP, Shen NJ, Wang ZC, Kan T, Yu WL, Yi B, Zhang YJ (2013) miR-204 inhibits epithelial to mesenchymal transition by targeting Slug in intrahepatic cholangiocarcinoma cells. Cell Physiol Biochem 32:1331–1341

Raica M, Cimpean AM, Ribatti D (2008) The role of podoplanin in tumor progression and metastasis. Anticancer Res 28:2997–3006

Raychaudhun P, Park HJ (2011) FoxM1: a master regulator of tumor metastasis. Cancer Res 71:4329–4333

Reichl P, Haider C, Grubinger M, Mikulits W (2012) TGF-b in epithelial to mesenchymal transition and metastasis of liver carcinoma. Curr Pharm Des 18:4135–4147

Reichl P, Dengler M, van Zijl F, Huber M, Führlinger G, Reichel C, Sieghart W, Peck-Radosavljevic M, Grubinger M, Mikulits W (2014) Axl activates autocrine transforming growth factor- βsignaling in hepatocellular carcinoma. Hepatology. doi:10.1002/hep.27492

Ren Y, Tsui HT, Poon RTP, Ng IOL, Li Z, Chen Y, Jiang G, Lau C, Yu WC, Bacher M et al (2003) Macrophage migration inhibitory factor: roles in regulating tumor cell migration and expression of angiogenic factors in hepatocellular carcinoma. Int J Cancer 107:22–29

Ren D, Minami Y, Nishita M (2011) Critical role of Wnt5a-Ror2 signaling in motility and invasiveness of carcinoma cells following Snail-mediated epithelial-mesenchymal transition. Genes Cells 16:304–315

Ricciardi M, Zanotto M, Malpeli G, Bassi G, Perbellini O, Chilosi M, Bifari F, Krampera M (2015) Epithelial-to-mesenchymal transition (EMT) induced by inflammatory priming elicits mesenchymal stromal cell-like immune-modulatory properties in cancer cells. Br J Cancer. doi:10.1038/bjc.2015.29

Rodero MP, Auvynet C, Poupel L, Cmbadière B, Combadière C (2013) Control of both myeloid cell infiltration and angiogenesis by CCR1 promotes liver cancer metastasis development in mice. Neoplasia 15:641–648

Roh-Johnson M, Bravo-Cordero JJ, Patsialou A, Sharma VP, Guo P, Liu H, Hodgson L et al (2014) Macrophage contact induces RhoA GTPase signaling to trigger tumor cell intravasation. Oncogene 33:4203–4212

Roychaudhuri R, Hergrueter AH, Polverino F, Laucho-Contreras ME, Gupta K, Borregaard N, Owen CA (2014) ADAM9 is a novel product of poylmorphonuclear neutrophils: regulation of expression and contributins to extracellular matrix protein degaradtion during acute lung injury. J Immunol 193:2469–2482

Ru NY, Wu J, Chen ZN, Bian H (2015) Hab18G/CD147 is involved in TGF-β-induced epithelial-mesenchymal transition and hepatocellular carcinoma invasion. Cell Biol Int 39:44–51

Salven P, Mustjoki S, Alitalo R, Alitalo K, Rafii S (2003) VEGFR-3 and CD133 identify a population of CD34+ lymphatic/vascular endothelial precursor cells. Blood 101:168–172

Scartozzi M, Faloppi L, Svegliati Baroni G, Loretelli C, Piscaglia F, Iavarone M, Toniutto P, Fava G, De Minicis S, Mandolesi A et al (2014) VEGF and VEGFR genotyping in the prediction of clinical outcome for HCC patients receiving sorafenib: the ALICE-1 study. Int J Cancer 135:1247–1256

Schlecker E, Stojanovic A, Eisen C, Quack C, Falk CS, Umansky V, Cerwenka A (2012) Tumor-infiltrating monocytic myeloid-derived suppressor cells mediate CCR5-dependent recruitment of regulatory T cells favoring tumor growth. J Immunol 189:5602–5611

Shen G, Lin Y, Yang X, Zhang J, Xu Z, Jia H (2014) MicroRNA-26b inhibits epithelial-mesenchymal transition in hepatocellular carcinoma by targeting USP9X. BMC Cancer 14:393

Shih JY, Yuang A, Chen JJW, Yang PC (2006) Tumor-associated macrophage: its role in cancer invasion and metastasis. J Cancer Mol 2:101–106

Shim JH, Chung YH, Kim JA, Lee D, Kim KM, Lim YS, Lee HC, Lee YS, Yu E et al (2012) Clinical implications of arrest-defective protein 1 expression in hepatocellular carcinoma: a novel predictor of microvascular invasion. Dig Dis 30:603–608

Shindo K, Aishima S, Ohuchida K, Fujiwara K, Fujino M, Mizuuchi Y, Hattori M, Mizumoto K, Tanaka M, Oda Y (2013) Podoplanin expression in cancer-associated fibroblasts enhances tumor progression of invasive ductal carcinoma of the pancreas. Mol Cancer 12:168

Silva 2011. http://www.ncbi.nlm.nih.gov/pubmed/21169518

Sleeman JP (2012) The metastatic niche and stromal progression. Cancer Metastasis Rev 31:429–440

Smith HA, Kang Y (2013) The metastasis-promoting roles of tumor-associated immune cells. J Mol Med (Berl) 91:411–429

Solito S, Marigo I, Pinton L, Damuzzo V, Mandruzzato S, Bronte V (2014) Myeloid-derived suppressor cell heteroegenity in human cancers. Ann N Y Acad Sci 1319:47–65

Song J, Ge Z, Yang X, Luo Q, Wang C, You H, Ge T, Deng Y, Lin H, Cui Y, Chu W, Yao M, Zhang Z, Gu J, Fan J et al (2015) Hepatic stellate cells activated by acidic tumor microenvironment promote the metastasis

of hepatocellular carcinoma via osteopontin. Cancer Lett 356:713–720
Specht S, Isse K, Nozaki I, Lunz JG, Demetris AJ (2013) SPRR2A expression in cholangiocarcinoma increases local tumor invasiveness but prevents metastasis. Clin Exp Metastasis 30:877–890
Stebbing J, Filipovic A, Giamas G (2013) Claudin-1 as a promoter of EMT in hepatocellular carcinoma. Oncogene 32:4871–4872
Suh YJ, Kim MJ, Choi JY, Park MS, Kim KW (2012) Preoperative prediction of the microvascular invasion of hepatocellular carcinoma with diffusion-weighted imaging. Liver Transpl 18:1171–1178
Suh Y, Yoon CH, Kim RK, Lim EJ, Oh YS, Hwang SG, An S, Yoon G, Gye MC et al (2013) Claudin-1 induces epithelial-mesenchymal transition through activation of the c-Abl-ERK signaling pathway in human liver cells. Oncogene 32:4873–4882
Sun T, Zhao N, Zhao XL, Gu Q, Zhang SW, Che N, Wang XH, Du J, Liu YX, Sun BC (2010) Expression and functional significance of Twist1 in hepatocellular carcinoma: its role in vasculogenic mimicry. Hepatology 51:545–556
Sun T, Sun BC, Zhao XL, Zhao N, Dong XY, Che N, Yao Z, Ma YM, Gu Q, Zong WK et al (2011a) Promotion of tumor cell metastasis and vasculogenic mimicry by way of transcription coactivation by Bcl-2 and Twist1: a study of hepatocellular carcinoma. Hepatology 54:1690–1706
Sun Y, Yang H, Mao Y, Xu H, Zhang J, Li G, Lu X, Sang X, Zhao H, Zhong S, Huang J et al (2011b) Increased Golgi protein 73 expression in hepatocellular carcinoma tissue correlates with tumor aggression but not survival. J Gastroenterol Hepatol 26:1207–1212
Sun CK, Ng KT, Lim ZX, Cheng Q, Lo CM, Poon RT, Man K, Wong N, Fan ST (2011c) Proline-rich tyrosine kinase 2 (Pyk2) promotes cell motility of hepatocellular carcinoma through induction of epithelial to mesenchymal transition. PLoS One 6:e18878
Sun D, Sun B, Liu T, Zhao X, Che N, Gu Q, Dong X, Yao Z, Li R, Li J, Chi J, Sun R (2013a) Slug promoted vasculogenic mimicry in hepatocellular carcinoma. J Cell Mol Med 17:1038–1047
Sun Z, Han Q, Zhou N, Wang S, Lu S, Bai C, Zhao RC (2013b) MicroRNA-9 enhances migration and invasion through KLF17 in hepatocellular carcinoma. Mol Oncol 7:884–894
Sun Y, Song GD, Sun N, Chen JQ, Yang SS (2014) Slug overexpression induces stemness and promotes hepatocellular carcinoma cell invasion and metastasis. Oncol Lett 7:1936–1940
Tan YZ, Wang HJ, Zhang MH, Quan Z, Li T, He QZ (2014) CD34+ VEGFR3+ progenitor cells have a potential to differentiate towards lymphatic endothelial cells. J Cell Mol Med 18:422–433
Tanaka T, Kajiwara T, Torigoe T, Okamoto Y, Sato N, Tamura Y (2015) Cancer-associated oxidoreductase ERO1-α drives the production of tumor-promoting myeloid-derived suppressor cells via oxidative protein folding. J Immunol 194:2004–2010
Tao ZH, Wan JL, Zeng LY, Xie L, Sun HC, Qin LX, Wang L, Zhou J, Ren ZG et al (2013a) miR-612 suppresses the invasive-metastatic cascade in hepatocellular carcinoma. J Exp Med 210:789–803
Tao YM, Huang JL, Zeng S, Zhang S, Fan XG, Wang ZM, Yang HX, Yuan XH et al (2013b) BTB/POZ domain-containing protein 7: epithelial-mesenchymal transition promoter and prognostic biomarker of hepatocellular carcinoma. Hepatology 57:2326–2337
Tashiro Y, Nishida C, Sato-Kusubata K, Ohki-Koizumi M, Ishihara M, Sato A, Gritli I, Komiyama H, Sato Y, Dan T et al (2012) Inhibition of PAI-1 induces neutrophil-driven neoangiogenesis and promotes tissue regeneration via production of angiocrine factors in mice. Blood 119:6382–6393
Techasen A, Loilome W, Namwat N, Dokduang H, Jongthawin J, Yongvanit P (2012) Cytokines released from activated human macrophages induce epithelial mesenchymal transition markers of cholangiocarcinoma cells. Asian Pac J Cancer Prev 13 (Suppl):115–118
Thelen A, Scholz A, Benckert C, Weichert W, Dietz E, Wiedenmann B, Neuhaus P, Jonas S (2008) Tumor-associated lymphangiogenesis correlates with lymph node metastases and prognosis in hilar cholangiocarcinoma. Ann Surg Oncol 15:791–799
Thelen A, Jonas S, Benckert C, Weichert W, Schott E, Bötcher C, Dietz E, Wiedenmann B, Neuhaus P, Scholz A (2009) Tumor-associated lymphangiogenesis correlates with prognosis after resection of human hepatocellular carcinoma. Ann Surg Oncol 16:1222–1230
Thelen A, Scholz A, Weichert W, Wiedenmann B, Neuhaus P, Gessner R, Benckert C, Jonas S (2010) Tumor-associated angiogenesis and lymphangiogenesis correlate with progression of intrahepatic cholangiocarcinoma. Am J Gastroenterol 105:1123–1132
Thomson S, Petti F, Sujka-Kwok I, Mercado P, Bean J, Monaghan M, Seymour SL et al (2011) A systems view of epithelial-mesenchymal transition signaling states. Clin Exp Metastasis 28:137–155
Timar J, Diczhazi C, Ladanyi A, Raso E, Hornebeck W, Robert L, Lapis K (1995) Interaction of tumour cells with elastin and the metastatic phenotype. Ciba Found Symp 192:321–335
Tobler NE, Detmar M (2006) Tumor and lymph node lymphangiogenesis – impact on cancer metastasis. J Leukoc Biol 80:691–696
Van der Zijl F, Zulehner G, Petz M, Schneller D, Kornauth C, Hau M, Machat G, Grubinger M et al (2009) Epithelial-mesenchymal transition in hepatocellular carcinoma. Future Oncol 5:1169–1179
Van't Hull EF, Bron S, Henry L, Ifticene-Treboux A, Turrini R, Coukos G, Delaloye JF, Doucey MA (2014) Bone marrow-derived cells are implicated as a source of lymphatic endothelial progenitors in human breast cancer. Oncoimmunology 3:e29080

Vella LJ (2014) The emerging role of exosomes in epithelial-mesenchymal-transition in cancer. Front Oncol 4:361

Vichalkovski A, Gresko E, Hess D, Restuccia DF, Hemmings BA (2010) PKB/AKT phosphorylation of the transcription factor Twist-1 at Ser42 inhibits p53 activity in response to DNA damage. Oncogene 29:3554–3565

Wakai T, Shirai Y, Sakata J, Nagahashi M, Ajioka Y, Hatakeyama K (2010) Mode of hepatic spread from gallbladder carcinoma: an immunohistochemical analysis of 42 hepatectomized specimens. Am J Surg Pathol 34:65–74

Walczak C, Gaignier F, Gilet A, Zou F, Thornton SN, Ropars A (2011) Aldosterone increases VEGF-A production in human neutrophils through PI3K, ERK1/2 and p38 pathways. Biochim Biophys Acta 1813:2125–2132

Wang J, Chen L, Li Y, Guan XY (2011) Overexpression of cathepsin Z contributes to tumor metastasis by inducing epithelial-mesenchymal transition in hepatocellular carcinoma. PLoS One 6:e24967

Wang C, Jiang K, Kang X, Gao D, Sun C, Li Y, Sun L, Zhang S, Liu X, Wu W, Yang P et al (2012) Tumor-derived secretory clusterin induces epithelial-mesenchymal transition and facilitates hepatocellular carcinoma metastasis. Int J Biochem Cell Biol 44:2308–2320

Wang Y, Shi J, Chai K, Ying X, Zhou BP (2013a) The role of Snail in EMT and tumorigenesis. Curr Cancer Drug Targets 13:963–972

Wang Z, Jiang Y, Guan D, Li J, Yin H, Pan Y, Xie D, Chen Y (2013b) Critical roles of p53 in epithelial-mesenchymal transition and metastasis of hepatocellular carcinoma cells. PLoS One 8:e72846

Wang SC, Lin XL, Li J, Zhang TT, Wang HY, Shi JW, Yang S, Zhao WT, Xie RY, Wei F, Qin YJ, Chen L et al (2014a) MicroRNA-122 triggers mesenchymal-epithelial transition and suppresses hepatocellular carcinoma cell motility and invasion by targeting RhoA. PLoS One 9:e101330

Wang H, Wang X, Li X, Fan Y, Li G, Guo C, Zhu F, Zhang L, Shi Y (2014b) CD68(+)HLA-DR(+) M1-like macrophages promote motility in HCC cells via NF-kB/FAK pathway. Cancer Lett 345:91–99

Wang X, Wang H, Li G, Song Y, Wang S, Zhu F, Guo C, Zhang L, Shi Y (2014c) Activated macrophages down-regulate expressin of E-cadherin in hepatocellular carcinoma cells via NF-kB/Slug pathway. Tumour Biol 35:8893–8901

Wang D, Han S, Wang X, Peng R, Li X (2015) SOX5 promotes epithelial-mesenchymal transition and cell invasion via regulation of Twist1 in hepatocellular carcinoma. Med Oncol 32:461

Wu J, Ru NY, Zhang Y, Li Y, Wie D, Ren Z, Huang XF, Chen ZN, Bian H (2011) Hab18G/CD147 promotes epithelial-mesenchymal transition through TGF-β signaling and is transcriptionally regulated by Slug. Oncogene 30:4410–4427

Wu K, Ding J, Chen C, Sun W, Ning BF, Wen W, Huang L, Han T, Yang W, Wang C et al (2012) Hepatic transforming growth factor beta gives rise to tumor-initiating cells and promotes liver cancer development. Hepatology 56:2255–2267

Wu Y, Liu H, Weng H, Zhang X, Li P, Fan CL, Li B, Dong PL, Li L, Dooley S, Ding HG (2015) Glypican-3 promotes epithelial-mesenchymal transition of hepatocellular carcinoma cells through ERK signaling pathway. Int J Oncol 46:1275–1285

Xia L, Huang W, Tian D, Zhu H, Qi X, Chen Z, Zhang Y, Hu H, Fan D, Nie Y, Wu K (2013) Overexpression of forkhead box C1 promotes tumor metastasis and indicates poor prognosis in hepatocellular carcinoma. Hepatology 57:610–624

Xiao H, Cheng S, Tong R, Lv Z, Ding C, Du C, Xie H, Zhou L, Wu J, Zheng S (2014a) BAG3 regulates epithelial-mesenchymal transition and angiogenesis in human hepatocellular carcinoma. Lab Invest 94:252–261

Xiao H, Jiang N, Zhou B, Liu Q, Du C (2014b) TAZ regulates cell proliferation and epithelial-mesenchymal transition of human hepatocellular carcinoma. Cancer Sci. doi:10.1111/cas.12587

Xiu M, Liu YH, Brigstock DR, He FH, Zhang RJ, Gao RP (2012) Connective tissue growth factor is overexpressed in human hepatocellular carcinoma and promotes cell invasion and growth. World J Gastroenterol 18:7070–7078

Xu J, Chen X (2007) Expression of twist gene in primary liver cancer. J Huazhong Univ Sci Technol Med Sci 27:668–670

Xu LB, Liu C, Gao GQ, Yu XH, Zhang R, Wang J (2010) Nerve growth factor-beta expression is associated with lymph node metastasis and nerve infiltration in human hilar cholangiocarcinoma. World J Surg 34:1039–1045

Xu ZY, Ding SM, Zhou L, Xie HY, Chen KJ, Zhang W, Xing CY, Guo HJ, Zheng SS (2012) FOXC1 contributes to microvascular invasion in primary hepatocellular carcinoma via regulating epithelial-mesenchymal transition. Int J Biol Sci 8:1130–1141

Xu J, Li X, Yang H, Chang R, Kong C, Yang L (2013) SIN1 promotes invasion and metastasis of hepatocellular carcinoma by facilitating epithelial-mesenchymal transition. Cancer 119:2247–2257

Xu Z, Pei L, Wang L, Zhang F, Hu X, Gui Y (2014) Snail1-dependent transcriptional repression of Cezanne2 in hepatocellular carcinoma. Oncogene 33:2836–2845

Xue TC, Chen RX, Ren ZG, Zou JH, Tang ZY, Ye SL (2013) Transmembrane receptor CXCR7 increases the risk of extrahepatic metastasis of relatively well-differentiated hepatocellular carcinoma through upregulation of osteopontin. Oncol Rep 30:105–110

Yamada S, Okumura N, Wei L, Fuchs BC, Fujii T, Sugimoto S, Nomoto S, Takeda SS, Tanabe KK, Kodera Y (2014) Epithelial to mesenchymal transition is associated with shorter disease-free survival in hepatocellular carcinoma. Ann Surg Oncol 21:3882–3890

Yamaguchi R, Yano H, Nakashima O, Akiba J, Nishida N, Kurogi M, Kojiro M (2006) Expression of vascular endothelial growth factor-C in human hepatocellular carcinoma. J Gastroenterol Hepatol 21:152–160

Yan Y, Luo YC, Wan HY, Wang J, Zhang PP, Liu M, Li X, Li S, Tang H (2013) MicroRNA-10a is involved in the metastatic process by regulating Eph tyrosine kinase receptor A4-mediated epithelial-mesenchymal transition and adhesion in hepatoma cells. Hepatology 57:667–677

Yang MH, Chen CL, Chau GY, Chiou SH, Su CW, Chou TY, Peng WL, Wu JC (2009) Comprehensive analysis of the independent effect of twist and snail in promoting metastasis of hepatocellular carcinoma. Hepatology 50:1464–1474

Yang P, Li QJ, Feng Y, Zhang Y, Markowitz GJ, Ning S, Deng Y, Zhao J, Jiang S et al (2012) TGF-b-miR-34a-CCL22 signaling-induced Treg cell recruitment promotes venous metastases of HBV-positive hepatocellular carcinoma. Cancer Cell 22:291–303

Yang H, Fang F, Chang R, Yang L (2013a) MicroRNA-140-5p suppresses tumor growth and metastasis by targeting TGFBR1 and FGF9 in hepatocellular carcinoma. Hepatology 58:205–217

Yang XY, Zhang D, Zou QF, Fan F, Shen F (2013b) Association of tumor-associated fibroblasts with progression of hepatocellular carcinoma. Med Oncol 30:593

Yano T, Yamazaki Y, Adachi M, Okawa K, Fort P, Uji M, Tsukita S, Tsukita S (2011) Tara up-regulates E-cadherin transcription by binding to the Trio RhoGEF and inhibiting Rac signaling. J Cell Biol 193:319–332

Yau WL, Lam CS, Ng L, Chow AK, Chan ST, Chan JY, Wo JY, Ng KT, Man K et al (2013) Over-expression of miR-106b promotes cell migration and metastasis in hepatocellular carcinoma by activating epithelial-mesenchymal transition process. PLoS One 8: e57882

Yeung OW, Lo C, Ling C, Qi X, Geng W, Li C, Ng KT, Forbes SJ, Guan X, Poon RT, Fan S, Man K (2015) Alternatively activated (M2) macrophages promote tumour growth and invasiveness in hepatocellular carcinoma. J Hepatol 62:607–616

Yilmaz M, Christofori G (2009) EMT, the cytoskeleton, and cancer cell invasion. Cancer Metastasis Rev 28:15–33

Yokomori H, Oda M, Kaneko F, Kawachi S, Tanabe M, Yoshimura K, Kitagawa Y, Hibit T (2010) Lymphatic marker podoplanin/D2-40 in human advanced cirrhotic liver – re-evalauations of microlymphatic abnormalities. BMC Gastroenterol 10:131

Yokomori H, Oda M, Yoshimura K, Takahasi Y, Hibi T (2012) Microlymphatic vessels in human liver subcapsular regions. Hepatogastroenterology 59:2

Youn JI, Gabrilovich DI (2010) The biology of myeloid-derived suppressor cells: the blessing and the curse of morphological and functional heterogeneity. Eur J Immunol 40:2969–2975

Youn JI, Collazo M, Shalova IN, Biswas SK, Gabrilovich DI (2012) Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. J Leukoc Biol 91:167–181

Young PP, Ardestani S, Li B (2010) Myeloid cells in cancer progression: unique subtypes and their roles in tuor growth, vascularity, and host immune suppression. Cancer Microenviron 4:1–11

Younos I, Donkor M, Hoke T, Dafferner A, Samson H, Westphal S, Talmadge J (2011) Tumor-and organ-dependent infiltration by myeloid-derived suppressor cells. Int Immunopharmacol 11:816–826

Zajac E, Schweighofer B, Kupriyanova TA, Juncker-Jensen A, Minder P, Quigley JP, Deryugina EI (2013) Angiogenic capacity of M1-and M2-polarized macrophages is determined by the levels of TIMP-1 complexed with their secreted proMMP-9. Blood 122:4054–4067

Zhang CH, Xu GL, Jia WD, Li JS, Ma JL, Ren WH, Ge YS, Yu JH, Liu WB, Wang W (2012) Activation of STAT3 signal pathway correlates with twist and E-cadherin expression in hepatocellular carcinoma and their clinical significance. J Surg Res 174:120–129

Zhang L, Yang F, Yuan JH, Yuan SX, Zhou WP, Huo XS, Xu D, Bi HS, Wang F et al (2013a) Epigenetic activation of the MiR-200 family contributes to H19-mediated metastasis suppression in hepatocellular carcinoma. Carcinogenesis 34:577–586

Zhang H, Liu L, Wang Y, Zhao G, Xie R, Liu C, Xiao X, Wu K, Nie Y, Zhang H, Fan D (2013b) KLF8 involves in TGF-beta-induced EMT and promotes invasion and migration in gastric cancer cells. J Cancer Res Clin Oncol 139:1033–1042

Zhang L, Huang G, Li X, Zhang Y, Jiang Y, Shen J, Liu J, Wang Q, Zhu J, Feng X et al (2013c) Hypoxia induces epithelial-mesenchymal transition via activation of SNAI1 by hypoxia-inducible factor-1a in hepatocellular carcinoma. BMC Cancer 13:108

Zhang LY, Liu M, Li X, Tang H (2013d) miR-490-3p modulates cell growth and epithelial to mesenchymal transition of hepatocellular carcinoma cells by targeting endoplasmic reticulum-Golgi intermediate compartment protein 3 (ERGIC3). J Biol Chem 288:4035–4047

Zhang JP, Zeng C, Xu L, Gong J, Fang JH, Zhuang SM (2014) MicroRNA-148a suppresses the epithelial-mesenchymal transition and metastasis of hepatoma cells by targeting Met/Snail signaling. Oncogene 33:4069–4076

Zhao X, Sun B, Sun D, Liu T, Che N, Gu Q, Dong X, Li R, Liu Y, Li J (2015) Slug promotes hepatocellular cancer cell progression by increasing sox2 and nanog expression. Oncol Rep 33:149–156

Zheng X, Vittar NB, Gai X, Fernandez-Barrena MG, Moser CD, Hu C, Almada LL et al (2012) The transcription factor GLI1 mediates TGFb1 driven EMT in hepatocellular carcinoma via a SNAI1-dependent mechanism. PLoS One 7:e49581

Zheng X, Gai X, Wu Z, Liu Q, Yao Y (2013) Metastasin leads to poor prognosis of hepatocellular carcinoma

through partly inducing EMT. Oncol Rep 29:1811–1818

Zhi Q, Zhu J, Guo X, He S, Xue X, Zhou J, Hu B, Li H, Chen S, Zhao H, Kuang Y (2013) Metastasis-related miR-185 is a potential prognostic biomarker for hepatocellular carcinoma in early stage. Biomed Pharmacother 67:393–398

Zhou SL, Dai Z, Zhou ZJ, Wang XY, Yang GH, Wang Z, Huang XW, Fan J, Zhou J (2012) Overexpression of CXCL5 mediates neutrophil infiltration and indicates poor prognosis for hepatocellular carcinoma. Hepatology 56:2242–2254

Zhou SL, Dai Z, Zhou ZJ, Chen Q, Wang Z, Xiao YS, Hu ZQ, Huang XY, Yang GH et al (2014) CXCL5 contributes to tumour metastasis and recurrence of intrahepatic cholangiocarcinoma by recruiting infiltrative intratumoral neutrophils. Carcinogenesis 35:597–605

Zhou SL, Zhou ZJ, Hu ZQ, Li X, Huang XW, Wang Z, Fan J, Dai Z, Zhou J (2015) CXCR2/CXCL5 axis contributes to epithelial-mesenchymal transition of HCC cells through activating PI3K/Akt/GSK-3β/Snail signaling. Cancer Lett 358:124–135

Zhu K, Dai Z, Pan Q, Wang Z, Yang GH, Yu L, Ding ZB, Shi GM, Ke AW, Yang XR et al (2011) Metadherin promotes hepatocellular carcinoma metastasis through induction of epithelial-mesenchymal transition. Clin Cancer Res 17:7294–7302

Mechanisms of Invasion and Metastasis: Prometastatic and Antimetastatic Factors

184

Contents

Abstract

Metastatic spread of cancer cells is a highly complex process which depends on inherent features of tumors, including the expression of prometastatic genes and metastasis suppressors, characteristics of invasion, factors of angioarchitecture and angiogenesis, and remote homing mechanisms. Tumors, including hepatobiliary cancers, can express diverse prometastatic proteins, such as metastatin-1, MTA1, FOXQ1, NDRG1, and MACC1. Hepatocellular carcinoma (HCC) shows downregulation of distinct metastasis suppressors. One major member is KAI1 (CD82), a tetraspanin. Non-metastasizing tumors exhibit normal levels of KAI1, whereas metastasizing variants show low levels of KAI1 expression. Further metastasis suppressors downregulated in liver cancers comprise Nm23-H1, MTSS1, and HTPAP. The ability to produce metastasis in hepatobiliary cancers is also strongly associated with the expression of a growing number of microRNAs that have a wide array of target proteins involved in metastatic spread. Cellular informations involved in the regulation of metastasis are in part exchanged among tumor cells and stromal cell partner through exosomes and other vehicles that transfer signal cargo.

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_184

Introduction

Metastatic spread of cancer cells is a highly complex process that depends on inherent features of tumors (expression of so-called prometastatic genes and metastasis suppressors), invasion characteristics, architecture of the vascular and lymphatic systems, and remote homing mechanisms. In diffuse HCC, in which the liver is studded with minute and usually uniformly shaped and sized nodules, the multiple small and seemingly synchronous metastases are thought to result from widespread intrahepatic spread through the portal venous system, involving both liver lobes (Okuda et al. 1981). However, intrahepatic vascular spread through the portal venous system is not a passive process but rather depends on the expression of tumor-specific factors that facilitate vascular invasion and tumor cell homing. Extrahepatic metastasis of liver cancers is critically influenced by circulating tumor cells that, by distinct homing mechanisms and the generation of premetastatic niches, are associated with dissemination and implantation of cancer cells at distant sites (review: Jacob et al. 2007).

Prometastatic Genes and Their Products

S100A4 or metastatin-1 is a metastasis-associated protein, which also plays a role in HCCs, where it is associated with tumor differentiation, invasion, and recurrence (Cui et al. 2006; Liu et al. 2013). S100A4 participates in an S100A4-microRNA-155-SOCS1-MMP-9 axis pathway in HCCs, whereby S100A4 can be secreted by liver cancer-associated mesenchymal stem cells (Yan et al. 2013). It physically and functionally interacts with Smad3, a mediator of the TGF-beta signaling pathway. Through this pathway, S100A4 increases cancer cell invasion ability induced by TGF-beta (Matsuura et al. 2010). S100A4 regulates migration and invasion in HCC cells through NF-kappaB-dependent MMP-9 signaling (Zhang et al. 2013). Nuclear expression of S100A4 increases cholangiocarcinoma invasiveness and metastasis, in part by inducing release of MMP-9 (Fabris et al. 2011). A further metastasis-associated gene in HCC is MTA1, expressed in about 40 % of HCCs (Hamatsu et al. 2003). Overexpression of the FOXQ1 oncogene is strongly linked to an aggressive and metastasizing phenotype of HCC (Wang et al. 2013a), through transactivation of ZEB2 and versican V1 expression (Xia et al. 2014), while FOXC2 contributes to invasion and metastasis of extrahepatic cholangiocarcinomas (Watanabe et al. 2013). Aggressive HCCs conferring poor prognosis more often and more strongly express N-myc downstream-regulated gene 1/NDRG1, a multifunctional protein associated with carcinogenesis; NDRG1 modulates the expression of genes associated with transmembrane transporter activity, activity of chemoattractants, cell adhesion, and proliferation (Cheng et al. 2011). Another member of the NDGR family, NDGR2, is associated with tumor suppression as is a protein highly responsive to various stresses. Hyperthermia-induced NDRG2 upregulation inhibits invasion and spread of HCC through suppression of ERK1/ERK2 signaling (Guo et al. 2013). Upregulation of metastasis-associated in colon cancer 1 (MACC1) is associated with metastasis of various malignancies in humans. MACC1 is highly expressed in HCCs and is localized in the tumor cell nuclei. This expression is associated with cell migration and increased expression of MMP-2 and MMP-9 (Gao et al. 2013). MACC1 in HBV-associated HCCs is associated with enhanced tumor progression and poor outcome (Qu et al. 2012). MACC1 also affects proliferation and apoptosis in HCCs (Yang et al. 2013a). Overexpression of the T-lymphoma invasion and metastasis 1 (Tiam1) protein, a metastasis-related factor, correlates with HCC metastasis and poor prognosis (Huang et al. 2013). Ectopic expression of COTE1 (FAM189B; family with sequence similarity 189, member B), a putative oncogene, promotes cellular invasion and metastasis of HCCs, acting by associating with WW domain oxidoreductase (WWOX), a known tumor suppressor (Zhang et al. 2012).

Metastasis Suppressors

Several genes and their products that promote or inhibit metastasis have been identified. Downregulation of the tetraspanin, KAI1 (CD82), expression is associated with formation of metastasis and disease progression in HCC (Guo et al. 1998). KAI1 is a widely expressed tetraspanin that is a regulator of behavior of numerous cancer types, including HCC (Jackson et al. 2005; Liu and Zhang 2006; Yang et al. 2008; Malik et al. 2009; Kim et al. 2010; Romanska and Berditchevski 2011; Tsai and Weissman 2011). Whereas in nonmetastatic HCC cancer cells exhibit KAI1 mRNA signals similar to normal control cells, HCC cells from metastatic tumors exhibited only faint KAI1 signals (Guo et al. 1998, 2009). Similarly, the expression rate of KAI1 in HCC cells as determined by RT-PCR was higher in tumor without intrahepatic metastases than in those with metastases (Sun et al. 1998). The activity of the KAI1 metastasis suppressor is regulated by its palmitoylation, this step being necessary for integrity and activity of the tetraspanin (Zhou et al. 2004). KAI1 inhibits the protrusion and retraction phenomena in cell movements by attenuating actin organization in the submembrane cytoskeleton (Bari et al. 2011; Liu et al. 2012a). KAI1 suppresses hepatocyte growth factor-induced migration of HCC cells in vitro via upregulation of Sprouty2 (Mu et al. 2008) and regulates the maturation of integrin beta1 to become functional on the cell surface (Jee et al. 2007). Sprouty2 (SPRY2) is an intracellular regulator of receptor tyrosine kinase signaling involved in the control of cell growth and differentiation. Tetraspanins such as CD82/KAI1 also form a network that modulates the surface expression of MMP-1 (Schröder et al. 2013). CD82/KAI1 also affects HCC biology, including invasive pathways, by its interference with the Wnt signaling pathway. It inhibits canonical Wnt signaling by controlling the cellular distribution of beta-catenin in carcinoma cells (Chigita et al. 2012). For its action as a metastasis suppressor, the COOH-terminal region of KAI1 is essential. The protein VANGL1, a further member of the tetraspanin family, also termed KITENIN (KaI1 COOH-terminal interacting tetraspanin), selectively interacts with KAI1 and enhances metastasis in cancer via promoting tumor cell adhesion and invasion (Lee et al. 2004; Rowe and Jackson 2006). KITENIN is also associated with activation of AP-1 target genes in HCCs through MAP kinase cascade signaling, resulting in the upregulation of MMP-1 and MMP-3 (Cho et al. 2011). Further metastasis suppressors include Nm23-H1, MTSS1, and HTPAP. The metastasis-associated gene Nm23-H1 encodes an 18 kDa nucleoside diphosphate kinase, and its expression is associated with pro-oncogenic effects (Lee et al. 2012) but a low-metastasis phenotype, while its decreased expression in HCCs is associated with tumor metastasis (Fujimoto et al. 1998; Shimada et al. 1998). Nm23-H1 and Nm23-H2 isoforms are highly expressed in HCCs, but mainly Nm23-H1 predicted intrahepatic metastasis (Iizuka et al. 1995). Wild-type p53 upregulates the expression of Nm23-H1, while mutant p53 does not (Chen et al. 2003). Nm23-H1 maintains adherens junctions and via this mechanism limits the invasive potential of cancer cells (Boissan et al. 2010). Metastasis suppressor 1 (MTSS1) is downregulated by microRNA-182, a microRNA significantly upregulated in HCCs, and depression of MTSS1 favors metastasis (Wang et al. 2012). A potent suppressor of HCC metastasis is phosphatidic acid phosphatase (PAP) and its co-regulated factors, the pro-inflammatory genes IL-8 and TLR2 (Ren et al. 2011).

MicroRNAs Associated with Metastasis of Liver Cancer

A number of microRNAs have been identified to directly or indirectly affect metastasis and metastatic patterns in liver cancer (Budhu et al. 2008; Table 1).

MicroRNA-26a, which is expressed at low levels in aggressive HCCs, suppresses metastasis by targeting interleukin-6-STAT3 signaling pathways (Yang et al. 2013b). MicroRNA-30d

Table 1 Prometastatic microRNAs in hepatocellular carcinoma

MicroRNA (MiR)	Target
MiR-26a	IL-6-STAT3 signaling
MiR-30d	Galphai2
MiR-29b	Matrix metalloproteinase-2
MiR-100	ICMT-Rac1 signaling
MiR-126	?
MiR-134	Integrin-beta1
MiR-135a	Metastasis suppressor-1
MiR-137	AKT2
MiR-139	Rho-kinase 2
MiR-140-5p	TGF-beta receptor
MiR-143	Fibronectin
MiR-146a	VEGF
MiR-151	RhoGDIA
MiR-181a	Tumor suppressor WIF-1
MiR-182	Metastasis suppressor 1
MiR-195	VEGF
MiR-214	Fibroblast growth factor receptor 1
MiR-331-3p	Protein phosphatase
MiR-372	ATAD2 oncogene
MiR-503	Rho guanine nucleotide exchange factor
	19
MiR-550a	Polyadenylation element-binding protein
	4

promotes HCC invasion and metastasis by targeting Galphai2 (Yao et al. 2010). MicroRNA-29b directly targets matrix metalloproteinase-2 in HCCs and through this mechanism suppresses invasion, angiogenesis, and metastatic spread (Fang et al. 2011). Tumor progression and a metastatic phenotype in HCC patients are correlated with downregulation of microRNA-100 (Chen et al. 2013). Downregulation of microRNA-100 in HCCs enhances metastasis through stimulation of the ICMT (isoprenylcysteine carboxyl methyltransferase)-Rac1 (Ras-related C3 botulinum toxin substrate 1) signaling pathway (Zhou et al. 2014a). In HCCs, microRNA-126 is downregulated. This is associated metastatic recurrence, as microRNA-126 inhibits HCC cell migration, invasion, and angiogenesis (Du et al. 2014). MicroRNA-134 operates as a potent metastasis suppressor by targeting the key mediator of tumor cell adhesion and migration, integrin beta1 (Zha et al. 2014). MicroRNA-135a contributes to metastatic spread of HCC by inducing portal vein tumor thrombus formation. The functional target of this microRNA is metastasis suppressor 1 (Liu et al. 2012b). Suppression of tumor growth and metastasis in HCC by microRNA-137 is mediated by targeting AKT2 (Liu et al. 2014). MicroRNA-139, downregulated in HCC, is a potent metastasis suppressor through targeting Rho-kinase 2 (Wong et al. 2011). Targeting TGF-beta receptor 1 and fibroblast growth factor 9 is the mechanism whereby microRNA-140-5p suppresses HCC metastasis (Yang et al. 2013c). MicroRNA-143, which is upregulated in HCCs, is transcribed by the action of NF-kappaB and promotes metastasis by repressing the expression of fibronectin (Zhang et al. 2009). MicroRNA-146a, exhibiting low expression in HCC, suppresses cancer metastasis through targeting VEGF (Zhang et al. 2015). This MiR also enhances angiogenic activity of endothelial cells in HCC by promoting PDGFRA expression (Zhu et al. 2013). Another MiR that acts in metastasis suppression via targeting of VEGF is microRNA-195 (Wang et al. 2013b). Angiogenesis and angiogenesis-related metastasis are also suppressed by microRNA-122, a tumor suppressor in HCCs (Tsai et al. 2009). Gain of microRNA-151 facilitates tumor cell migration in HCC through downregulation of RhoGDIA (Ding et al. 2010). MicroRNA-181a promotes tumor growth and metastasis of colorectal carcinoma by targeting the tumor suppressor WIF-1 (Ji et al. 2014). In HCCs, microRNA-182 is overexpressed. This MiR downregulates the metastasis suppressor 1 and thus contributes to metastasis (Wang et al. 2012). Downregulation of microRNA-214 and overexpression of fibroblast growth factor receptor 1 contribute to HCC metastasis (Wang et al. 2013c). MicroRNA-331-3p promotes metastasis of HCC by targeting PH domain and leucine-rich repeat protein phosphatase, an enzyme involved in EMT (Chang et al. 2014). The highly expressed oncogene ATAD2, which promotes metastasis, can be downregulated by microRNA-372 (Wu et al. 2014). MicroRNA-503, downregulated in HCC, inhibits HCC metastasis through targeting of Rho guanine nucleotide

exchanger factor 19 (Zhou et al. 2014b). MicroRNA-550a promotes HCC metastasis by directly targeting cytoplasmic polyadenylation element-binding protein 4 (Tian et al. 2012). Part of microRNAs affect HCC metastasis through their effects on epithelial-mesenchymal transition.

Subcellular Transfer of Proinvasive and Prometastatic Information Among Cancer Cells: Exosomes and Other Vehicles of an Invasive Phenotype

Introduction

Informational molecules that exchange a proinvasive and prometastatic message between target cells are carried by specialized vehicles, comprising exosomes (exosomic vesicles, itinerant exosomes), argosomes, cytonemes, and tunneling nanotubes (Lakkaraju and Rodriguez-Boulan 2008; Morello et al. 2013; Raposo and Stoorvogel 2013; Minciacchi et al. 2015). Exosomes transporting and spreading oncogenic signals and cancer genes are called large oncosomes and play a significant role for the functions of the cellular interactome in cancer (Rak and Guha 2012; Rak 2013). Oncosomes can mediate intercellular transfer of functional microRNAs (Morello et al. 2013) and other important regulating molecules.

Exosomes, Argosomes, and Multivesicular Bodies

Exosomes derive from multivesicular bodies originating from endosomal sorting complexes required for intracellular transports, i.e., ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III, all multimeric protein complexes acting as an endosomal sorting complex/ESCRT (Colombo et al. 2013). Following ubiquitination, the ESCRT engine can be utilized to generate multivesicular bodies, but formation of multivesicles can also be driven by the later exosome cargo itself in a ubiquitin-independent manner (review: Lakkaraju and Rodriguez-Boulan 2008). Multivesicular bodies engage in contact with distinct cell surface domains, in particular with cholesterol- and sphingolipid-rich microdomains termed lipid rafts. From these domains, exosomes emerge and are loaded with lipid raft proteins, such as GPI-anchored proteins and tetraspanins. Exosomes are released both constitutively and in a regulated manner (Lakkaraju and Rodriguez-Boulan 2008). Exosomes in principle contain the protein, RNA, and DNA components of the cells from which they originate. By use of their cargo, exosomes can influence numerous biological processes, including the establishment of short-distance morphogen gradients, the generation of planar polarity, the capability for locomotion, the cell-cell and cell-matrix adhesion, and the expression of matrix-degrading enzymes. By these mechanisms, exosomes can transfer an invasive phenotype among target cells. Argosomes are a specialized form of exosomes that transport Wingless-associated information and organelles and are transported from cell to cell by the exocytic fusion of microvesicular bodies that contain Wingless.

Tunneling Nanotubes

Information between cells can also occur through subsets of F-actin-based transient tubular connections termed tunneling nanotubes (review: Abounit and Zurzolo 2012). Tunneling nanotubes are specialized tubular conduits than can transport cargo from one cell to the other. Connections of neighboring cells can also be mediated by filopodial bridges or cytonemes, structures which enable ligand-receptor-mediated transfer of cell surface-associated cargoes among cells (Sherer and Mothes 2008). Cytonemes are actin-based close-ended filopodial bridge structures that can connect neighboring cells by fusion of filopodia-like protrusions and induce flux-limited spreading of information (Lim and Tang 2012; Verbeni et al. 2013). Cytoneme-mediated cell-to-cell signaling plays a significant role in development, cancerogenesis, and establishment of an invasive phenotype (Gradilla and Guerrero 2013).

References

Abounit S, Zurzolo C (2012) Wiring through tunneling nanotubes – from electrical signals to organelle transfer. J Cell Sci 125:1089–1098

Bari R, Guo Q, Xia B, Zhang YH, Giesert EE, Levy S, Zheng JJ, Zhang XA (2011) Tetraspanins regulate the protrusive activities of cell membrane. Biochem Biophys Res Commun 415:619–626

Boissan M, De Wever O, Lizarraga F, Wendum D, Poincloux R, Chignard N, Desbois-Mouthon C et al (2010) Implication of metastasis suppressor NM23-H1 in maintaining adherens junctions and limiting the invasive potential of human cancer cells. Cancer Res 70:7710–7722

Budhu A, Jia HL, Forgues M, Liu CG, Goldstein D, Lam A, Zanetti KA, Ye QH, Qin LX, Croce CM, Tang ZY et al (2008) Identification of metastasis-related microRNAs in hepatocellular carcinoma. Hepatology 47:897–907

Chang RM, Yang H, Fang F, Xu JF, Yang LY (2014) MicroRNA-331-3p promotes proliferation and metastasis of hepatocellular carcinoma by targeting PH domain and leucine-rich repeat protein phosphatase. Hepatology 60:1251–1263

Chen SL, Wu YS, Shieh HY, Yen CC, Shen JJ, Lin KH (2003) P53 is a regulator for the metastasis suppressor gene Nm23-H1. Mol Carcinog 36:204–214

Chen P, Zhao X, Mal L (2013) Downregulation of microRNA-100 correlates with tumor progression and poor prognosis in hepatocellular carcinoma. Mol Cell Biochem 383:49–58

Cheng J, Xie HY, Xu X, Wu J, Wei X, Su R, Zhang W, Lv Z, Zheng S, Zhou L (2011) NDRG1 is a biomarker for metastasis, recurrence and of poor prognosis in hepatocellular carcinoma. Cancer Lett 310:35–45

Chigita S, Sugiura T, Abe M, Kobayashi Y, Shimoda M, Onoda M, Shirasuna K (2012) CD82 inhibits canonical Wnt signaling by controlling the cellular distribution of b-catenin in carcinoma cells. Int J Oncol 41:2021–2028

Cho SB, Park YL, Park SJ, Park SY, Lee WS, Park CH, Choi SK, Heo YH, Koh YS et al (2011) KITENIN is associated with activation of AP-1 target genes via MAPK cascades signaling in human hepatocellular carcinoma progression. Oncol Res 19:115–123

Colombo M, Moita C, van Niel G, Kowal J, Vigneron J, Benaroch P, Manel N, Moita LF et al (2013) Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. J Cell Sci 126:553–5565

Cui JF, Liu YK, Zhang LJ, Shen HL, Song HY, Dai Z, Yu YL, Zhang Y, Sun RX et al (2006) Identification of metastasis candidate proteins among HCC cell lines by comparative proteome and biological function analysis of S100A4 in metastasis in vitro. Proteomics 6:5953–5961

Ding J, Huang S, Wu S, Zhao Y, Liang L, Yan M, Ge C, Yao J, Chen T, Wand D, Wang H, Gu J, Yao M, Li J, Tu H et al (2010) Gain of miR-151 on chromosome 8q24.3 facilitates tumour cell migration and spreading through downregulating RhoGDIA. Nat Cell Biol 12:390–399

Du C, Lv Z, Cao L, Ding C, Gyabaah OA, Xie H, Zhou L, Wu J, Zheng S (2014) MiR-126-3p suppresses tumor metastasis and angiogenesis of hepatocellular carcinoma by targeting LRP6 and PIK3R2. J Transl Med 12:259

Fabris L, Cadamuro M, Moserle L, Dziura J, Cong X, Sambado L, Nardo G, Sonzogni A et al (2011) Nuclear expression of S100A4 calcium-binding protein increases cholangiocarcinoma invasiveness and metastasization. Hepatology 54:890–899

Fang JH, Zhou HC, Zeng C, Yang J, Liu Y, Huang X, Zhang JP, Guan XY, Zhuang SM (2011) MicroRNA-29b suppresses tumor angiogenesis, invasion and metastases by regulating MMP-2 expression. Hepatology 54:1729–1740

Fujimoto Y, Ohtake T, Nishimori H, Ikuta K, Ohhira M, Ono M, Kohgo Y (1998) Reduced expression and rare genomic alteration of nm23-H1 in human hepatocellular carcinoma and hepatoma cell lines. J Gastroenterol 33:368–375

Gao J, Ding F, Liu Q, Yao Y (2013) Knockdown of MACC1 expression suppressed hepatocellular carcinoma cell migration and invasion and inhibited expression of MMP2 and MMP9. Mol Cell Biochem 376:21–32

Gradilla AC, Guerrero I (2013) Cytoneme-mediated cell-to-cell signaling during development. Cell Tissue Res 352:59–66

Guo XZ, Friess H, Di Mola FF, Heinicke JM, Abou-Shady-M, Graber HU, Baer HU et al (1998) KAI1, a new metastasis suppressor gene, is reduced in metastatic hepatocellular carcinoma. Hepatology 28:1481–1488

Guo C, Liu QG, Zhang L, Song T, Yang X (2009) Expression and clinical significance of p53, JunB and KAI1/CD82 in human hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 8:389–396

Guo Y, Ma J, Wu L, Wang Q, Li X, Li X, Zhang Y, Zhang J, Yao L, Zhang J, Liu W (2013) Hyperthermia-induced NDRG2 upregulation inhibits the invasion of human hepatocellular carcinoma via suppressing ERK1/2 signaling pathway. PLoS One 8:e61079

Hamatsu T, Rikimaru T, Yamashita Y, Aishima S, Tanaka S, Shirabe K, Shimada M et al (2003) The role of MTA1 gene expression in human hepatocellular carcinoma. Oncol Rep 10:599–604

Huang J, Ye X, Guan J, Chen B, Li Q, Zheng X, Liu L, Wang S, Ding Y, Ding Y, Chen L (2013) Tiam1 is associated with hepatocellular carcinoma metastasis. Int J Cancer 132:90–100

Iizuka N, Oka M, Noma T, Nakazawa A, Hirose K, Suzuki T (1995) NM23-H1 and NM23-H2 messenger RNA abundance in human hepatocellular carcinoma. Cancer Res 55:652–657

Jackson P, Marreros A, Russell PJ (2005) KAI1 tetraspanin and metastasis suppressor. Int J Biochem Cell Biol 37:530–534

Jacob et al. 2007. http://www.ncbi.nlm.nih.gov/pubmed/18067413

Jee BK, Lee JY, Lim Y, Lee KH, Jo YH (2007) Effect of KAI1/CD82 on the beta1 integrin maturation in highly migratory carcinoma cells. Biochem Biophys Res Commun 359:703–708

Ji D, Chen Z, Li M, Zhan T, Yao Y, Zhang Z, Xi J, Yan L, Gu J (2014) MicroRNA-181a promotes tumor growth and liver metastasis in colorectal cancer by targeting the tumor suppressor WIF-1. Mol Cancer 13:86

Kim B, Boo K, Lee JS, Kim KI, Kim WH, Cho HJ, Park YB, Kim HS, Baek SH (2010) Identification of the KAI1 metastasis suppressor gene as a hypoxia target gene. Biochem Biophys Res Commun 393:179–184

Lakkaraju A, Rodriguez-Boulan E (2008) Itinerant exosomes: emerging roles in cell and tissue polarity. Trends Cell Biol 18:199–209

Lee JH, Park SR, Chay KO, Seo YW, Kook H, Ahn KY, Kim YJ, Kim KK (2004) KAI1 COOH-terminal interacting tetraspanin (KITENIN), a member of the tetraspanin family, interacts with KAI1, a tumor metastasis suppressor, and enhances metastasis of cancer. Cancer Res 64:4235–4243

Lee MJ, Xu DY, Li H, Yu GR, Leem SH, Chu IS, Kim IH, Kim DG (2012) Pro-oncogenic potential of NM23-H2 in hepatocellular carcinoma. Exp Mol Med 44:214–224

Lim YS, Tang BL (2012) Intracellular organelle trafficking by membranous nanotube connections: a possible new role in cellular rejuvenation? Cell Commun Adhes 19:39–44

Liu WM, Zhang XA (2006) KAI1/CD82, a tumor metastasis suppressor. Cancer Lett 240:183–194

Liu WM, Zhang F, Moshiach S, Zhou B, Huang C, Srinivasan K, Khurana S, Zheng Y et al (2012a) Tetraspanin CD82 inhibits protrusion and retraction in cell movement by attenuating the plasma membrane-dependent actin organization. PLoS One 7:e51797

Liu S, Guo W, Shi J, Li N, Xu X, Xue J, Fu X, Chu K, Lu C, Zhao J, Xie D, Wu M, Cheng S, Liu S (2012b) MicroRNA-135a contributes to the development of portal vein tumor thrombus by promoting metastasis in hepatocellular carcinoma. J Hepatol 56:389–396

Liu Z, Liu H, Pan H, Du Q, Liang J (2013) Clinicopathological significance of S100A4 expression in human hepatocellular carcinoma. J Int Med Res 41:457–462

Liu LL, Lu SX, Li M, Li LZ, Fu J, Hu W, Yang YZ, Luo RZ, Zhang CZ, Yun JP (2014) FoxD3-regulated microRNA-137 suppresses tumour growth and metastasis in human hepatocellular carcinoma by targeting AKT2. Oncotarget 5:5113–5124

Malik FA, Sanders AJ, Jiang WG (2009) KAI-1/CD82, the molecule and clinical implication in cancer and cancer metastasis. Histol Histopathol 24:519–530

Matsuura I, Lai CY, Chiang KN (2010) Functional interaction between Smad3 and S100A4 (metastatin-1) for TGF-b-mediated cancer cell invasiveness. Biochem J 426:327–335

Minciacchi VR, Freeman MR, Di Vizio D (2015) Extracellular vesicles in cancer: exosomes, microvesicles and the emerging role of large oncosomes. Semin Cell Dev Biol 40:41–51

Morello M, Minciacchi VR, de Candia P, Yang J, Posadas E, Kim H, Griffiths D, Bhowmick N et al (2013) Large oncosomes mediate intercellular transfer of functional microRNA. Cell Cycle 12:3526–3536

Mu Z, Wang H, Zhang J, Li Q, Wang L, Guo X (2008) KAI1/CD82 suppresses hepatocyte growth factor-induced migration of hepatoma cells via upregulation of Sprouty2. Sci China C Life Sci 51:648–654

Okuda K, Noguchi T, Kubo Y, Shimokawa Y, Kojiro M, Nakashima T (1981) A clinical and pathological study of diffuse type hepatocellular carcinoma. Liver 1:280–289

Qu JH, Chang XJ, Lu YY, Bai WL, Chen Y, Zhou L, Zeng Z, Wang CP, An LJ et al (2012) Overexpression of metastasis-associated in colon cancer 1 predicts a poor outcome of hepatitis B virus-related hepatocellular carcinoma. World J Gastroenterol 18:2995–3003

Rak J (2013) Extracellular vesicles – biomarkers and effectors of the cellular interactome in cancer. Front Pharmacol 4:21

Rak J, Guha A (2012) Extracellular vesicles – vehicles that spread cancer genes. Bioessays 34:489–497

Raposo G, Stoorvogel W (2013) Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 200:373–383

Ren N, Wu JC, Dong QZ, Sun HJ, Jia HL, Li GC, Sun BS, Dai C, Shi J, Wei JW et al (2011) Association of specific genotypes in metastatic suppressor HTPAP with tumor metastasis and clinical prognosis in hepatocellular carcinoma. Cancer Res 71:3278–3286

Romanska HM, Berditchevski F (2011) Tetraspanins in human epithelial malignancies. J Pathol 223:4–14

Rowe A, Jackson P (2006) Expression of KITENIN, a KAI1/CD82 binding protein and metastasis enhancer, in bladder cancer cell lines: relationship to KAI1/CD82 levels and invasive behaviour. Oncol Rep 16:1267–1272

Schröder HM, Hoffmann SC, Hecker M, Korff T, Ludwig T (2013) The tetraspanin network modulates MT1-MMP cell surface trafficking. Int J Biochem Cell Biol 45:1133–1144

Sherer NM, Mothes W (2008) Cytonemes and tunneling nanotubes in cell-cell communication and viral pathogenesis. Trends Cell Biol 18:414–420

Shimada M, Taguchi K, Hasegawa H, Gion T, Shirabe K, Tsuneyoshi M, Sugimachi K (1998) Nm23-H1 expression in intrahepatic or extrahepatic metastases of hepatocellular carcinoma. Liver 18:337–342

Sun HC, Tang ZY, Zhou G, Li XM (1998) KAI1 gene expression in hepatocellular carcinoma and its relationship with intrahepatic metastases. J Exp Clin Cancer Res 17:307–311

Tian Q, Liang L, Ding J, Zha R, Shi H, Wang Q, Huang S, Guo W, Ge C, Chen T et al (2012) MicroRNA-550a acts as a pro-metastatic gene and directly targets

cytoplasmic polyadenylation element-binding protein 4 in hepatocellular carcinoma. PLoS One 7:e48958
Tsai YC, Weissman AM (2011) Dissecting the diverse functions of the metastasis suppressor CD82/KAI1. FEBS Lett 585:3166–3176
Tsai WC, Hsu PW, Lai TC, Chau GY, Lin CW, Chen CM, Lin CD, Liao YL, Wang JL et al (2009) MicroRNA-122, a tumor suppressor microRNA that regulates intrahepatic metastasis of hepatocellular carcinoma. Hepatology 49:1571–1582
Verbeni M, Sanchez O, Mollica E, Siegl-Cachedenier I, Carleton A, Guerrero I, Ruiz I, Alataba A et al (2013) Morphogenetic action through flux-limited spreading. Phys Life Rev 10:457–475
Wang J, Li J, Shen J, Wang C, Yang L, Zhang X (2012) MicroRNA-182 downregulates metastasis suppressor 1 and contributes to metastasis of hepatocellular carcinoma. BMC Cancer 12:227
Wang W, He S, Ji J, Huang J, Zhang S, Zhang Y (2013a) The prognostic significance of FOXQ1 oncogene overexpression in human hepatocellular carcinoma. Pathol Res Pract 209:353–358
Wang R, Zhao N, Li S, Fang JH, Chen MX, Yang J, Jia WH, Yuan Y, Zhuang SM (2013b) MicroRNA-195 suppresses angiogenesis and metastasis of hepatocellular carcinoma by inhibiting the expression of VEGF, VAV2 and CDC42. Hepatology 58:642–653
Wang J, Li J, Wang X, Zheng C, Ma W (2013c) Downregulation of microRNA-214 and overexpression of FGFR-1 contribute to hepatocellular carcinoma metastasis. Biochem Biophys Res Commun 439:47–53
Watanabe A, Suzuki H, Yokobori T, Altan B, Kubo N, Araki K, Wada S, Mochida Y et al (2013) Forkhead box protein C2 contributes to invasion and metastasis of extrahepatic cholangiocarcinoma, resulting in a poor prognosis. Cancer Sci 104:1427–1432
Wong CC, Wong CM, Tung EK, Au SL, Lee JM, Poon RT, Man K, Ng IO (2011) The microRNA miR-139 suppresses metastasis and progression of hepatocellular carcinoma by down-regulating Rho-kinase 2. Gastroenterology 140:322–331
Wu G, Liu H, He H, Wang Y, Lu X, Yu Y, Xia S, Meng X, Liu Y (2014) miR-372 down-regulates the oncogene ATAD2 to influence hepatocellular carcinoma proliferation and metastasis. BMC Cancer 14:107
Xia L, Huang W, Tian D, Zhang L, Qi X, Chen Z, Shang X, Nie Y, Wu K (2014) FoxQ1 promotes hepatocellular carcinoma metastasis by transactivating ZEB2 and VersicanV1 expression. Hepatology 59:958–973
Yan XL, Jia YL, Chen L, Zeng Q, Zhou JN, Fu CJ, Chen HX, Yuan HF, Li ZW et al (2013) Hepatocellular carcinoma-associated mesenchymal stem cells promote hepatocarcinoma progression: role of the S100A4-miR155-SOCS1-MMP9 axis. Hepatology 57:2274–2286
Yang JM, Peng ZH, Si SH, Liu WW, Luo YH, Ye ZY (2008) KAI1 gene suppresses invasion and metastasis of hepatocellular carcinoma MHCC97-H cells in vitro and in animal models. Liver Int 28:132–139
Yang YP, Qu JH, Chang XJ, Lu YY, Bai WL, Dong Z, Wang H, An LJ, Xu ZX et al (2013a) High intratumoral metastasis-associated in colon cancer-1 expression predicts poor outcomes of cryoablation therapy for advanced hepatocellular carcinoma. J Transl Med 11:41
Yang X, Liang L, Zhang XF, Jia HL, Qin Y, Zhu XC, Gao XM, Qiao P, Zheng Y et al (2013b) MicroRNA-26a suppresses tumor growth and metastasis of human hepatocellular carcinoma by targeting interleukin-6-Stat3 pathway. Hepatology 58:158–170
Yang H, Fang F, Chang R, Yang L (2013c) MicroRNA-140-5p suppresses tumor growth and metastasis by targeting TGFBR1 and FGF9 in hepatocellular carcinoma. Hepatology 58:205–217
Yao J, Liang L, Huang S, Ding J, Tan N, Zhao Y, Yan M, Ge C, Zhang Z, Chen T, Wan D, Yao M, Li J, Gu J, He X (2010) MicroRNA-30d promotes tumor invasion and metastasis by targeting Galphai2 in hepatocellular carcinoma. Hepatology 51:846–856
Zha R, Guo W, Zhang Z, Qiu Z, Wang Q, Ding J, Huang S, Chen T, Gu J, Yao M et al (2014) Genome-wide screening identified that miR-134 acts as a metastasis suppressor by targeting integrin b1 in hepatocellular carcinoma. PLoS One 9:e87665
Zhang X, Liu S, Hu T, Liu S, He Y, Sun S (2009) Up-regulated microRNA-143 transcribed by nuclear factor kappa B enhances hepatocarcinoma metastasis by repressing fibronectin expression. Hepatology 50:490–499
Zhang H, Huang CJ, Tian Y, Wang YP, Han ZG, Li XC (2012) Ectopic overexpression of COTE1 promotes cellular invasion of hepatocellular carcinoma. Asian Pac J Cancer Prev 13:5799–5804
Zhang J, Zhang DL, Jiao XL, Dong Q (2013) S100A4 regulates migration and invasion in hepatocellular carcinoma HepG2 cells via NF-kB-dependent MMP-9 signal. Eur Rev Med Pharmacol Sci 17:2372–2382
Zhang Z, Zhang Y, Sun XX, Ma X, Chen ZN (2015) microRNA-146a inhibits cancer metastasis by downregulating VEGF through dual pathways in hepatocellular carcinoma. Mol Cancer 14:5
Zhou B, Liu L, Reddivari M, Zhang XA (2004) The palmitoylation of metastasis suppressor KAI1/CD82 is important for its motility- and invasiveness-inhibitory activity. Cancer Res 64:7455–7463
Zhou HC, Fang JH, Luo X, Zhang L, Yang J, Zhang C, Zhuang SM (2014a) Downregulation of microRNA-100 enhances the ICMT-Rac1 signaling and promotes metastasis of hepatocellular carcinoma cells. Oncotarget 5:12177–12188
Zhou J, Tao Y, Peng C, Gu P, Wang W (2014b) miR-503 regulates metastatic function through Rho guanine nucleotide exchanger factor 19 in hepatocellular carcinoma. J Surg Res 188:129–136
Zhu K, Pan Q, Zhang X, Kong LQ, Fan J, Dai Z, Wang L, Yang XR, Hu J, Wan JL, Zhao YM, Tao ZH, Chai ZT et al (2013) MiR-146a enhances angiogenic activity of endothelial cells in hepatocellular carcinoma by promoting PDGFRA expression. Carcinogenesis 34:2071–2079

Part XXXVII

General Pathology of Hepatobiliary Tumors: Tumor Stroma

Tumor Stroma, Desmoplasia, and Stromagenesis

185

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_185

Abstract

Tumor stroma forms a distinct microenvironment that critically regulates the development and behavior of malignant neoplasms, including hepatobiliary cancers. The formation of stroma is a complex process and a decisive pathogenic mechanism for cancer growth, differentiation, invasion, and metastatic spread. Hepatic neoplasms show striking coevolution of cancerous cells and their associated stromal microenvironment, including components of the extracellular matrix. Tumor stroma provides the proliferating cancer cell population with nutrients, oxygen, and growth factors that are stored in this microenvironment. Stroma is also the cell system that initiates and regulates tumor angiogenesis. The cell systems that mediate all these complex functions include mesenchymal stem cells as a major source of stromal spindle cells, hepatic stellate cells, cancer-associated fibroblasts, myofibroblasts, endothelial cells and their progenitors, and a large number of various leukocytes. Mesenchymal stem cells as a source of stromal cells and cells of premetastatic niches in part originate from extrahepatic sites, mainly blood and bone marrow. Stromal leukocytes provide a distinct inflammatory microenvironment for cancer that mediates growth control and provides chemokines and cytokines involved in invasion and spread. Inflammatory stromal cells comprise tumor-associated macrophages, lymphocytes, myeloid suppressor cells, and granulocytes.

Introduction: Stroma as a Specific Tumor Microenvironment That Is Critical for Growth, Invasion, and Metastasis

Generally, stroma forms a tumor microenvironment that critically regulates the development and behavior of malignant epithelial neoplasms, including hepatocellular carcinoma (HCC), cholangiocarcinomas (CCs), and carcinoma metastases (Li et al. 2007; Wu et al. 2012; Hernandez-Gea et al. 2013; Quail and Joyce 2013; Wang and Chen 2013; Lee and Campbell 2014).

In this context, biogenesis of tumor stroma ("stromatogenesis"; Sivridis et al. 2004) is a decisive pathogenic mechanism in cancer progression. Hepatic tumors show coevolution of their cancerous cells and the associated stromal microenvironment, including components of the extracellular matrix (ECM; Fang et al. 2013). The tumor stroma has a central role in providing the proliferating cancer cell populations with oxygen and nutrients, via the stroma-associated microvasculature. The stroma is also an important depot and outlet structure for various growth factors and signaling substances. In addition, stromal cells can express gene signatures that affect tumor growth, differentiation, apoptosis, and angiogenesis (Gao et al. 2011).

In regard to the amount of stroma formation, HCCs and CCs differ considerably, as many CCs, and in particular the desmoplastic hilar/perihilar CCs, typically develop a rich stroma, while most HCCs are characterized by a relatively poor stroma. However, there is evidence that there is an important phenotypic overlap between HCC and CC, suggesting a continuous liver cancer spectrum. For example, the rare scirrhous HCC expresses progenitor cell markers, shows expression of core epithelial-mesenchymal transition-related genes, and seems to have traits intermediate between HCC and CC (Seok et al. 2012).

Morphology of Cancer Stroma

General Features

The stroma of carcinomas is currently regarded as a "reactive" tissue induced by the malignant epithelial tissue. However, this view might change in the future, as there is evidence that malignant cells interact with their apparently benign partners in a complex way that also includes the production of epithelial-stromal cell hybrids through cell-to-cell fusion. Via exchange of genetic information, either by cell contact or through exosomes (see below),

stromal cells might receive oncogenic information that originally characterized the malignant epithelial lineage. In contrast, the spindle cell tissue of sarcomas is a malignant neoplastic tissue per se; therefore, it should not be termed a stroma. In carcinomas, including hepatocellular carcinoma and cholangiocarcinoma, the amount of stroma varies widely, ranging from a minor component to tumors predominantly consisting of stroma. This variability in stroma formation was found to be a striking feature in the old cancer pathology literature and had led to carcinoma terminologies based on the relation between epithelial and stroma, i.e., carcinoma solidum simplex (about equal amounts of epithelia and stroma), carcinoma solidum scirrhosum (stroma is clearly the predominant component; scirrhous carcinoma), and carcinoma solidum medullare (epithelia predominating, with poor stroma; medullary carcinoma). These different proportions of stroma versus epithelia are manifest in the gross presentation of the tumors, scirrhous carcinomas being firm and sclerosed; medullary carcinomas soft and friable, like marrow (hence the term medullary); and simplex-type carcinomas being somewhere between these two extremes.

Stroma of Hepatocellular Carcinoma

In ordinary HCCs, the stroma is characterized as often delicate strands of fibroblastoid tissue interposed between tumor cell plates and acinar structures. However, these neoplasms often display intervening sinusoid-like, sometimes dilated, vascular channels that are not, or barely, accompanied by a spindle cell stroma. Ordinary HCCs regularly show stromal sheaths around tumor arteries and, less prominently, tumor-draining veins. Larger amounts of spindle cell stroma consisting of cancer-associated fibroblasts/CAFs and myofibroblasts/MFBs are found in HCCs producing significant tumor capsules. The spindle cells located within the stroma cytomorphologically either present as elements that closely resemble fibroblasts, i.e., cells with an amphophilic to slightly eosinophilic and sometimes even basophilic cytoplasm (depending on the ribosome content reflecting protein synthesis), and elongated nuclei with blunt ends, or as cells resembling smooth muscle cells in the case of MFBs. The fibroblastoid stromal cells may be difficult to distinguish from activated, elongated histiocytes/macrophages (tumor-associated macrophages; TAMs). Less common variants of HCCs, in particular sclerosing HCC, scirrhous HCC, and fibrolamellar HCC, exhibit a marked stromal development with deposition of large amounts of extracellular matrix proteins, glycoproteins, and proteoglycans. In areas of recent stroma formation, the spindle cell cellularity is usually high, and the ECM can show a slight basophilia, while older stroma parts display a reduced cellularity, inactively looking spindle cells, and larger amount of ECM fibrils, sometimes with van Gieson-positive coarse collagen bundles.

Stroma of Cholangiocarcinoma

In comparison with ordinary HCC, most cholangiocarcinomas, and particularly the hilar/perihilar region, are characterized by rich stroma development, often with marked desmoplasia. Desmoplasia is, e.g., a hallmark of Klatskin tumors that are macroscopically highly sclerosed, firm, or even stony hard neoplasms. A variable but sometimes marked stroma formation is also observed in several types of carcinomas metastatic to the liver. In many situations, the amount and composition of stroma in metastatic lesions reflect the stroma pattern of the primary tumor, but this is not always the case. In the course of a change in differentiation, stromagenesis may be downregulated, resulting in hypercellular tumors with poor stroma, unlike the primary lesion. On the other hand, carcinomas with minor stroma formation may show a marked desmoplasia in their metastases. The amount of stroma formed in metastases is not only linked to features inherent to the tumor, but also depends on the microenvironment of the metastatic site and the recruitability of stromal cells from the local metastatic niche.

Stroma of Hepatic Metastases

The morphology of the stroma of hepatic metastases varies markedly as a function of the tumor type involved. There are desmoplastic cancers that show a stromal reaction in liver metastases very similar to that of the primary tumor, e.g., carcinomas of the breast, stomach, and pancreas. On the other hand, there are tumors which downregulate stroma in their hepatic metastases. Whereas colorectal carcinoma shows a well-developed stroma in primary lesions, large liver metastases either show marked desmoplasia or exhibit a stromal reaction only in the center, often camouflaged by extensive necrosis. In many cases, the stromal pattern most representative for the entire situation is that actually found in the region of the invasion front.

Secondary Alterations of Tumor Stroma

Tumor stroma can undergo secondary alterations. In the course of desmoplasia and increasing deposition of collagen, stromal sclerosis and hyalinosis can develop, visualized as an eosinophilic fibrotic tissue of low cellularity. In sclerotic stroma, the fibrillary texture of collagen bundles is still recognizable, also in van Gieson's stain, while in stromal hyalinosis, a more or less homogeneous eosinophilic and hypocellular mass with only minor fibrillary texture is seen. In its original meaning, "hyaline" as a purely descriptive term denotes a more transparent or even "glassy" feature of tissues (Greek ualinoz, transparent). There are rare hepatobiliary tumors that show marked hyaline change of their stroma. One prominent example is hepatobiliary cystadenoma with hyaline stroma (Cacciaguerra et al. 1996; Beasley 1998). Hepatic cancers, but mainly cholangiocarcinomas, can show myxoid change of the stroma, characterized by a prominent accumulation of proteoglycans and glycosaminoglycans in the ECM, shown as basophilic or amphophilic areas staining with alkaline alcian blue, sometimes with a fine microcystic or vesicular structure. Myxoid vesicles can coalesce to larger myxoid cysts, not to be confounded with accumulations of extracellular mucin in mucinous/colloid carcinomas.

Stroma can show fresh or old hemorrhage, associated with hemosiderosis or other forms of deposition of stainable iron. Rarely, stainable iron is present as incrustation of stromal matrix fibers. Degradation of blood and/or of necrotic tumor cells leads to release of cholesterol and its esters, visualized as cholesterol clefts and eventually a foreign body reaction to crystals (cholesterol granulomas). Mucin released from carcinomas may produce mucin clefts in stroma or large mucin accumulations that cause dissection of stroma, sometimes with formation of mucin granulomas made up of mucin-ingesting, PAS- and alcian blue-positive macrophages/histiocytes (mucinophages). Stroma can also contain bile released from HCC cells or from damaged bile ducts invaded or surrounded by cancer. In case of tumor infection, the stroma can contain numerous leukocytes or even undergo purulent inflammation with abscess formation. Mainly sclerosed stroma can develop focal calcifications, either in the form of granular basophilic, von Kossa-positive deposits, sickle-shaped mineralizations, or, much less commonly, psammoma body formation. Rarely, stroma can undergo metaplastic changes, such as formation of bone (osseous metaplasia) or adipose tissue, probably related to the presence of multipotent mesenchymal stem cells in the stroma. Chemotherapy and/or radiotherapy can induce nuclear atypia and multinuclearity of stromal cells.

Function of Stroma in Liver Cancers and Hepatic Metastases

Stroma in Hepatocellular Carcinoma

Although histologically not prominent in many ordinary HCCs, development of a stromal microenvironment is a constant feature in these neoplasms and plays a significant role in tumor biology (Tu et al. 2014). There are small groups of HCC with a prominent desmoplastic stroma, including sclerosing HCC and fibrolamellar HCC.

The stromal microenvironment markedly influences HCC progression both in its primary tumors and its metastases (Wang and Chen 2013).

Stroma in Cholangiocarcinoma

Similar to HCC, stroma development (desmoplasia) in cholangiocarcinomas (CCs) plays a central for tumor growth, invasion, and progression (Lee and Campbell 2014; Sirica and Gores 2014). In contrast to ordinary HCC, desmoplasia is more developed in CCs and is, e.g., for hilar CCs, a morphological hallmark. Molecular profiling of CC stroma resulted in the identification of distinct stromal proteins that affect the behavior of cancer cells. In intrahepatic CC, several stromal ECM and non-ECM proteins are upregulated including collagen 4A1, laminin gamma 2, TGF-beta2, tenascin, osteopontin, and periostin. Stromal osteopontin expression is associated with an invasive tumor phenotype and predicts poor prognosis (Sulpice et al. 2013).

Stroma in Liver Metastasis

The development of tumor stroma is a central mechanism for metastasis of diverse extrahepatic cancers, in particular colorectal carcinoma (reviews: Joyce and Pollard 2009; Conti and Thomas 2011; Quail and Joyce 2013; Urech 2014). The development of an abundant stroma in primary tumors affects the probability of metastatic disease. In colorectal carcinomas, production of a rich desmoplastic stroma is associated with a shorter time interval between diagnosis of primary tumor and diagnosis of liver metastasis in comparison with tumors with poor stroma or a pushing morphology (Nyström et al. 2012). Stromal fibroblasts and other spindle cells in hepatic metastases are induced by carcinoma cells and mainly originate from resident fibroblasts (Mueller et al. 2007). In the metastatic stromal niche, epithelial tumor cells and their mesenchymal partners, which in part originate from bone marrow-derived cells, undergo a complex and dynamic crosstalk driven by stromal cell factors, cytokine-cytokine receptor networks, and ongoing genetic and epigenetic alterations of cancer cells (Sleeman 2012). Through these pathways, the metastatic stromal niche acquires a characteristic molecular composition that exerts trophic effects on tumor cells and favors growth and further spread of metastatic cells (Descot and Oskarsson 2013). This molecular pro-metastatic signature can be propagated by circulating tumor cells and stromal mesenchymal cells to induce so-called premetastatic niches. Such niches may originate both from primary tumors and metastases and are one major mechanism for the generation of re-metastases from already established metastases. Stromal cells and their mesenchymal stem cell precursors express distinct secretomes of factors that modulate tumor cell behavior (Zimmerlin et al. 2013).

Stromal Cells

Introduction

In the liver, stromal biogenesis is closely linked to the complex hepatic set of non-parenchymal cells (Table 1; reviews: Bouwens et al. 1992; Cortez et al. 2014). Stromal leukocytes (lymphoid and plasma cells, macrophages, dendritic cells, and myeloid suppressor cells) are discussed in a separate chapter.

Table 1 Types of cells located in tumor stoma

Mesenchymal stem cells (MSCs)
Hepatic stellate cells (HSCs)
Myofibroblasts (MFBs)
Cancer-associated fibroblasts (CAFs)
Endothelial cells, endothelial progenitors, and other microvessel cells
Tumor-associated macrophages (TAMs)
Tumor-associated neutrophils (TANs)
Myeloid-derived suppressor cells
Dendritic cells
Lymphocytes and plasma cells
Mast cells
Eosinophils

Mesenchymal Stem Cells as a Source of Tumor Stromal Cells

Mesenchymal stem cells (MSCs) derived from extrahepatic sites, and specifically from bone marrow and blood, can home to the liver and give rise to hepatic differentiated cells, including hepatocytes (Aurich et al. 2009). MSCs can also home in the stroma of hepatic malignancies and play a role in tumor development and progression (reviews: Cuiffo and Karnoub 2012; Kidd et al. 2012; Barcellos-de-Souza et al. 2013; Hernanda et al. 2013, 2014; Sun et al. 2014). Subsequent to homing, migration of stem cell-derived mesenchymal cells toward cancer cells is directly simulated by motility factors secreted by HCC cells (Garcia et al. 2011). In the prospective stromal niche, primed MSCs fated to become connective tissue cells can differentiate into stromal cells, including CAFs and a subset of myofibroblasts/MFBs (Zhu et al. 2014). An obligate intermediate stage of differentiation from MSC to mature CAFs is an enigmatic mesenchymal progenitor termed fibrocyte (review: Bellini and Mattoli 2007). Fibrocytes (telocytes), which in their relationship with MSCs are derived from hematopoietic stem cells, circulate in the blood and are recruited to connective tissue remodeling sites as CD34+ cells, including inflammatory tissue fibrosis, wound healing, and tumor stroma (Zhang et al. 2013b). CD34+ fibrocytes constitute a tissue reserve of fibroblastoid stromal and connective tissue cells (Diaz-Flores et al. 2014). In the pathway leading from MSCs to CAFs, differential expression of CD44 plays a role, in that CD44 attenuation in MSCs limited their expression of CAF markers (Spaeth et al. 2013). MSCs have an effect on growth, differentiation, and invasion of cancer cells. The migration and homing behavior of MSCs is in itself modulated by HCC cells (Garcia et al. 2011).

Hepatic Stellate Cells as a Source of Stromal Cells: General Aspects

Hepatic stellate cells (HSCs) are a subpopulation of pericytes with a broad spectrum of functions (Tsukamoto et al. 2012). Apart from their central role as cells differentiating into myofibroblasts and mediating hepatic fibrosis (see below), HSCs play vital roles in several other hepatic physiological and pathological pathways, including regeneration, damage repair, carcinogenesis, and cancer invasion and metastasis (Ju et al. 2009a; Kang et al. 2011). In cancer stroma, HSCs often accompany CAFs, with which they interact (Carloni et al. 2014). HSCs also interact with quiescent and regenerating hepatocytes in a complex fashion and are activated by adherent hepatocytes (Mabuchi et al. 2004). Activation of HSCs within tumor stroma depends on a complex network of factors that includes growth factors and the tumor suppressor menin encoded by the MEN1 gene (Zindy et al. 2006). HSCs can migrate into hepatic tumor stroma where they interact with carcinoma cells.

Hepatic Stellate Cells in Hepatocellular Carcinoma

As a source of the most important stromal cells, MFBs, HSCs are critically involved in development and progression of liver cancers (Rombouts and Carloni 2013; Yu et al. 2013; Coulouam and Clément 2014). Peritumorally activated HSCs predict an aggressive phenotype in HCCs, with poor clinical outcome (Ju et al. 2009a; Sun et al. 2013). This is mainly due to promotion of tumor growth and invasion by these cells. HSCs in contact with HCC cells induce proliferation and migration of these tumor cells, via activation of NF-kappaB- and extracellular-regulated kinase (ERK)-mediated pathways (Amann et al. 2009) and crosstalk mediated by TGF-beta (Gupta et al. 2014; Yoshida et al. 2014). Activated HSCs can promote HCC migration and invasion also through activation of the FAK-MMP-9 signaling pathway (Han et al. 2014). HSCs stimulate HCC cell migration via production of laminin-5 (Santamato et al. 2011). Deposition of laminin-5 in HCCs induces EMT (Giannelli et al. 2005) and is associated with a more invasive and metastatic phenotype (Giannelli et al. 2003). In tumor stroma, HSCs express the triggering receptor

expressed in myeloid cells/TREM-1, a transmembrane receptor. Secretion of TREM-1 by HSCs augments the migratory behavior of HCC cells and is associated with tumor aggressiveness (Liao et al. 2012). HSCs can secrete stromal cell-derived factor-1 (SDF-1) which as part of the SDF-1-CXCR4 signaling axis can induce epithelial-mesenchymal transition (EMT), which in turn promotes tumor cell migration and invasion (Li et al. 2014). HSCs in HCC stroma are also capable to promote tumor angiogenesis through VEGF secreted by these cells (Lin et al. 2014). Activated HSCs in HCC can promote metastasis through secretion of osteopontin which enhances the invasive and migratory features of HCC cells (Song et al. 2015). On the other hand, HCC cells modulate the function and survival of HSCs, e.g., via glypican-3 which regulates HSC viability through hedgehog signaling (Magistri et al. 2014). Glypican-3 overexpressed in HCCs modulates fibroblast growth factor-2 and bone morphogenetic protein-7 signaling (Midorikawa et al. 2003). The function of HSCs and their effects on tumor cells are also influenced by the status of the tumor-bearing liver. HSCs from steatotic rodent livers stimulated growth of HCC metastases to a greater degree than HSCs from normal livers, suggesting that liver steatosis provides a pro-metastatic microenvironment (Mikuriya et al. 2015).

Hepatic Stellate Cells in Cholangiocarcinoma

The presence of HSCs and their MFB offspring is related to progression in cholangiocarcinomas/CC (Okabe et al. 2009). This is in part due to the general pro-growth and pro-invasive role of tumor stroma, of which HSCs and MFBs are major components. In CCs, stromal HSCs can secrete stroma-derived factor-1 and generate an SDF-1-CXCR4 axis that promotes cell migration (Gentilini et al. 2012). This axis also operates in the induction of EMT in intrahepatic CC (Okamoto et al. 2012). HSCs in CC also stimulate migration and invasion through the establishment of hedgehog signaling between cancer cells and stromal cells (Kim et al. 2014).

Liver Metastases

HSCs play a role in the induction of premetastatic niches. In early phases of liver metastasis formation, cancer cell clusters forming micrometastasis are associated with an organized network of HSCs and laminin deposits. These HSCs are involved in cancer cell recruitment to the niche and angiogenesis, transforming an avascular primordial niche into a vascularized metastasis (Eveno et al. 2014).

Myofibroblasts: Introduction

The myofibroblast (MFB) is a modulated fibroblast that has acquired the capacity to express alpha-smooth muscle actin (alpha-SMA), an isoform of actin that characterizes vascular smooth muscle cells. Apart from alpha-SMA, endosialin (tem1) is a marker for tumor-associated MFBs (Christian et al. 2008). Tem1 is a binding partner of the metastasis-related protein Mac-2 BP/90K (Becker et al. 2008). In the liver, most MFBs derive from hepatic stellate cells (HSCs) through a distinct transdifferentiation mode induced by paracrine signals produced by tumor cells or cells in the tumor microenvironment. HSC-MFB transdifferentiation (HSC activation) depends on cell surface receptor activation, signal transduction, membrane-to-signal transfer, gene transcription, and epigenetic regulation (review: Kang et al. 2015). A subset of MFBs also originates from a fibroblast-MFB transition, a step that can be inhibited by relaxin through a notch-1-mediated inhibition of TGF-beta/Smad3 signaling (Sassoli et al. 2013). A third group of MFBs derives from PDGF-responsive peribiliary fibrogenic cells distinct from HSCs and from portal mesenchymal cells/portal fibroblasts (Kinnman et al. 2003; Lemoinne et al. 2013; Wells 2014). Portal myofibroblasts play a role in vascular remodeling underlying liver cirrhosis (Lemoinne et al. 2014). HSCs and MFBs can also develop via mesothelial-mesenchymal

transition (Li et al. 2013b). Differentiation along a MFB lineage goes in parallel with the expression of palladin by these cells, whereby overexpression of palladin promotes an invasive phenotype to tumors (Brentnall et al. 2012). Similar to hepatic stellate cells, MFBs display contractility in stroma, regulated by relaxin via inactivating RhoA/Rho-associated protein kinase (Huang et al. 2011). Relaxin also inhibits the differentiation of MFBs (Samuel et al. 2009).

MFBs have an important role in connective tissue remodeling and are central to the biologic effects of tumor stroma (reviews: Chau et al. 1992; Desmoulière et al. 2004). In particular, stromal MFBs influence progression of HCCs, CCs, and carcinoma metastases and thus display prognostic effects (Ooi 1999; Sirica 2011; Liao et al. 2013; Slany et al. 2013). MFBs form a major cellular component of stroma in HCCs (Schmitt-Gräff et al. 1991; Enzan et al. 1994). MFBs are also an important stromal cell population of cholangiocarcinomas (Terada et al. 1996; Sirica 2011). In these neoplasms, myofibroblasts promote progression through activation of epidermal growth factor (EGF) receptor expression. Stromal MFBs produce heparin-binding EGF which induces EGFR activation, disruption of adherens junctions, and migratory/invasive behavior in cholangiocarcinoma cells (Clapéron et al. 2013). MFBs also produce periostin in the stroma, a TGF-beta-inducible protein that closely interacts with type I collagen, tenascin, and integrin surface receptors to promote focal adhesion kinase activation and invasion (Sirica et al. 2014). In colorectal carcinomas, the abundance of stromal MFBs markedly influences tumor progression and metastasis (Tsujino et al. 2007).

Functions of Myofibroblasts in Tumor Stroma

Both in chronic fibrous hepatopathies and cancer stromal development, MFBs play a central role. In certain situations, most of stromal cells of desmoplastic carcinomas have the features of MFBs, which exert a decisive influence on cancer cell growth, migration, invasion, and metastasis (review: Otranto et al. 2012). MFBs are responsible to synthesize and secrete many or most of the proteins detectable in the extracellular matrix (ECM) of tissues, including tumor stroma. MFBs in stroma show transcripts of collagens typically found in tumor stroma, i.e., type III, type IV, and VI collagens and less type I and type V collagens (Gulubova 1997; Faouzi et al. 1999). The effective collagen deposition by MFBs is inhibited by relaxin, a hormone which also decreases these cells' differentiation (Williams et al. 2001). MFBs exert an influence on stromal vascular function and angiogenesis (Fausther and Dranoff 2014). MFBs can synthesize endothelin-1, which modulates hepatic stellate cell function by promoting their contraction in the setting of stromal remodeling. Endothelin-1 synthesis by MFBs is a step stimulated by ECM fibronectin via a Src/ERK-regulated signaling pathway (Zhan et al. 2009).

Myofibroblasts in Tumor Capsule/ Pseudocapsule Formation

MFBs with their function as potent producers of extracellular matrix are critically involved in the generation of tumor capsules (tumor encapsulation; Kojima et al. 1999), a phenomenon that influences tumor progression and spread (Lockwood et al. 2003). MFBs are the main cells responsible for collagen production and deposition within tumor capsules surrounding HCCs (Ooi et al. 1997; Bridle et al. 2001).

Cancer-Associated Fibroblasts (CAFs)

In addition to myofibroblasts, several other spindle cell lineages have been identified in cancer stroma, including a metabolically active subset of cells termed cancer-associated fibroblasts (CAFs).

Selected References: Orimo and Weinberg 2006; Anderberg and Pietras 2009; Gonda et al. 2010; Pietras and Östman 2010; Räsänen and Vaheri 2010; Xing et al. 2010; Xouri and

Christian 2010; Cirri and Chiarugi 2011, 2012; Li et al. 2012; Tripathi et al. 2012; Madar et al. 2013; Marsh et al. 2013; De Wever et al. 2014; Kharaishvili et al. 2014; Öhlund et al. 2014; Paulsson and Micke 2014.

The term, CAF, denotes cell populations that are not yet well defined, and some authors classified CAFs as myofibroblasts (MFBs). In fact, there is some overlap between CAFs and MFBs. CAFs are detectable in both HCCs and CCs (Sirica et al. 2011) and also form an important cell lineage in the stroma of metastatic cancers. CAFs form a heterogeneous cell population that can originate from several cell types, including "normal" resident fibroblasts, precursors of MFBs, preadipocytes, immature reticulum cell-like cells, pericytes, vascular smooth muscle cells or their progenitors, and mesenchymal stem cells (MSCs) derived from bone marrow (Orimo and Weinberg 2006; Bagley et al. 2009; Räsänen and Vaheri 2010). Mesenchymal cells are recruited to HCC by the action of autocrine motility factor produced by HCC cells (Bayo et al. 2014), suggesting that tumor cells themselves can generate a cellular complement of their stroma. There is also evidence that CAFs derive from epithelial cells via epithelial-mesenchymal transition/EMT. Markers of CAF comprise vimentin, fibroblast-specific protein 1, and platelet-derived growth factor receptor alpha/beta. In addition, at least 12 new proteins have been detected in CAFs (Bozoky et al. 2013), suggesting that CAFs are more than just activated normal fibroblasts. One subset of CAFs expresses fibroblast activation protein/FAP (an atypical serine protease; Hamson et al. 2014), a protein involved in stroma-induced cancer invasion (Wang et al. 2013). Among these FAP-positive cells, a population coexpresses the pan-leukocyte marker CD45, suggesting that these cells are variant of tumor-associated macrophages (TAMs) (Tchou et al. 2014). Part of CAFs express CD44, a functional molecule supporting the stemness of cancer cells in the tumor-associated microenvironment (Kinugasa et al. 2014). Fibroblast-specific protein 1 (FSP1) regulates cell cycle progression and cytoskeletal integrity in stromal cells, but it also identifies an inflammatory subpopulation of macrophages in the liver (Österreicher et al. 2011).

In tumor stroma, mesenchymal stem cells can be transformed into CAFs by a myeloid zinc finger 1 (MZF1)-TGF-beta1-dependent pathway mediated by osteopontin (Weber et al. 2014). CAF development may also be related to EMT as the pro-EMT protein Twist1 is an important regulator of CAFs (Lee et al. 2015). The transcriptional regulator heat shock factor 1 (HSF1) is frequently activated in CAFs, in which it drives a transcriptional program involving stromal-derived factor 1 (SDF-1) and TGF-beta (Scherz-Shouval et al. 2014). In CAFs derived from normal, "standard" fibroblasts, the switch to CAFs is regulated by the action of distinct microRNAs (Aprelikova and Green 2012), such as microRNA-31, microRNA-155, and microRNA-214 in ovarian cancer (Mitra et al. 2012). The turnover of stromal CAFs is regulated by apoptosis. As activated cells, CAFs are primed for cell death. Platelet-derived growth factor primes CAFs for apoptosis through Puma-mediated Bak activation (Rizvi et al. 2014).

CAFs and epithelial cancer cells form a cooperating cell system that critically affects the structure and function of cancer microenvironments in organs and tissues (Bhattacharya et al. 2012b). Through their secretome (Al-Toub et al. 2013; De Boeck et al. 2013), CAFs have numerous effects on critical mechanisms of cancer cell behavior, including proliferation, migration, invasion, and spread. CAFs can, in contact with carcinoma cells, inhibit cell proliferation and apoptosis (Berdiel-Acer et al. 2011), in part through TGF-beta signaling (Calon et al. 2014). CAFs induce EMT of cancer cells through paracrine TGF-beta signaling (Yu et al. 2014). The metastasis-associated protein S100A4 induces a network of inflammatory cytokines that activate stromal cells to acquire protumorigenic properties (Bettum et al. 2014). Downregulation of microRNA-148a in CAFs results in WNT10B-mediated stimulation of tumor cell motility (Aprelikova et al. 2013). CAFs can secrete factors that promote cancer cell invasion and metastasis. Inactivation of the retinoblastoma (Rb) protein in

CAFs promotes epithelial cell invasion (Pickard et al. 2012). Elevated expression of platelet-derived growth factor (PDGF) by CAFs is associated with increased migration invasion and metastasis, a PDGF effect mediated by the secretion of the glycoprotein, stanniocalcin-1 (STC1) (Peña et al. 2013). Stromal cells are a source of matrix metalloproteinases (MMPs), including MMP-2 (Longerich et al. 2004).

CAFs modulate tumor stroma in a paracrine fashion (Karagiannis et al. 2012), whereby they secrete plasminogen activators, matrix metalloproteinases, growth factors, and cytokines. Activation of plasminogen to plasmin, mediated by urokinase-type plasminogen activator and tissue plasminogen activator, is an important step in tumor cell growth and invasion induction (review: Räsänen and Vaheri 2010). CAFs show upregulation of genes related to growth and progression of HCCs, such as CCL2, CCL26, IL6, and LOXL2 genes (Lin et al. 2012; Lin and Chuang 2013). The proliferation of stromal fibroblasts is promoted by TGF-beta, overexpressed in HCCs (Yamazaki et al. 2011). Human primary fibroblasts expressing the ING protein, ING4, show a secretory phenotype that promotes tumor cell proliferation (Moreno et al. 2014). CAFs, similar to normal fibroblasts, are capable to migrate, collective migration being enhanced by overexpression of the tight junction-associated proteins claudin-11 and occludin (Karagiannis et al. 2014). CAFs can also be stimulated to develop invadopodia, e.g., following stimulation with palladin. Via invadopodia, palladin-stimulated CAFs can remodel the microenvironment of the extracellular matrix and promote invasion of cancer cells (Brentnall 2012; Goicoechea et al. 2014). CAFs produce and secrete a small leucine-rich proteoglycan, asporin, which is involved in cancer progression (Satoyoshi et al. 2014). The cancer niche component periostin is produced by CAFs, supporting cancer growth through ERK signaling (Kikuchi et al. 2014). Through their interaction with diverse immune and inflammatory cells, CAFs can modulate the immunologic niche in tumor stroma (Harper and Sainson 2014) and engage in close interactions with tumor-associated macrophages (TAMs) (Chiarugi 2013). CAFs and their humoral mediators provide a complex network of regulatory signals that modulate recruiting and function of inflammatory cells in stroma (review: Servais and Erez 2013).

A further effect on tumor invasion exerted by CAFs is their modulation of interstitial flow. Interstitial fluid flow promotes tumor cell invasion by modulating CAF-tumor cell interactions. In experimental models, interstitial flow drove TGF-beta1- and collagenase-dependent fibroblast migration (Shieh et al. 2011), probably mediated by chemotactic factors distributed by flow.

CAFs play an important role in tumor progression (Östman and Augsten 2009) and can secrete several factors that affect tumor biology. For example, they can show upregulation of the TGF-beta/BMP family member, GDF15/MIC-1, in tumor stroma, followed by increased tumor migration and invasion (Bruzzese et al. 2014). CAFs can secrete CXCL14, a potent protumorigenic factor (Augsten et al. 2014), and produce podoplanin, a protein associated with an aggressive phenotype of colorectal cancer (Yamanashi et al. 2009). These cells also produce the glycoprotein stanniocalcin-1 which is a mediator of metastasis by PDGF receptor function in colorectal cancers (Peña et al. 2013). CAFs accumulating in the stroma of colorectal carcinoma metastases promote proliferation of cancer cells and show a distinct expression profile of numerous upregulated genes (Nakagawa et al. 2004).

Stromal Leukocytes: Tumor-Associated Macrophages (TAMs)

As described in the chapter on immune reactions directed against hepatocellular carcinoma, tumor-associated macrophages (TAMs) are located in stroma and engage in complex interactions with stromal fibroblasts and other stromal cells. CAFs and other spindled stromal cells possess a signaling instrumentarium that can recruit various immune cells and cells involved in inflammatory reactions (Raz and Erez 2013), including TAMs. In their interaction with CAFs and myofibroblasts, TAMs generate a distinct microenvironment with

growth-promoting or suppressive features (Dutsch-Wicherek and Kazmierczak 2013). TAMs also promote tumor invasion by their activity as matrix-degrading cells (Madsen and Bugge 2013). TAMs can promote cancer stem cell-like properties in HCC cells through EMT induced by TGF-beta1. The acquisition of this phenotype favors the acquisition of an invasive and aggressive tumor biology (Fan et al. 2014). Another immune cell population that forms an interactome with CAFs is tumor-infiltrating lymphocytes rich in regulatory T cells (Tregs). Tregs suppress the generation of CAFs via promoting CAF cell cycle arrest at the G2/M transition (Fu et al. 2013). TAMs can affect the recruitment of Tregs, but activated monocytes in HCC stroma also promote the expansion of proinflammatory memory T helper 17 cells (Kuang et al. 2010).

Stromal Leukocytes: Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) are bone-marrow-derived cells that play an important role in the regulation of tumor immunity, but they also modulate tumor growth and invasion (Caronni et al. 2015; Keskinov and Shurin 2015). MDSCs home to tumor stroma and interact with cancer cells in this microenvironment. Together with regulatory T cells (Treg), a category of tumor-associated lymphocytes, MDSCs are key components of the so-called immunosuppressive tumor microenvironment (TME). TME is associated with pathways that downregulate tumor immunity and promote tumor immune evasion by inhibiting T-cell responses (Khaled et al. 2013). MDSCs expand in growing tumors and cause T-cell dysfunction favoring tumor progression (Lindau et al. 2013). Specifically, a distinct population of MDSCs CD14(+)HLA-DR(-/low) is present in HCCs and can induce CD4(+)CD25(+)Foxp3(+) T cells/Tregs in these cancers (Arihara et al. 2013). In HBV-associated HCCs, MDSCs affect the induction and function of Tregs and thereby modulate tumor progression, but also modify the mode of persistent HBV infection (Kondo and Shimosegawa 2015). MDSCs inhibit natural killer (NK) cells in HCC patients via the NKp30 receptor located on NK cells (Hoechst et al. 2009). Infiltration of HCC tissue by MDSCs is enhanced by IL-17A produced by gamma/delta T cells in a CXCL5-/CXCR2-dependent manner, whereby CXCL5 is produced by tumor cells. This pathway is a mechanism by which stromal IL-17A can modulate tumor growth via immune modulation (Ma et al. 2014). Recruitment of MDSCs is also promoted by pyruvate kinase M2 (PKM2), a member of the pyruvate kinase family expressed in HCC (Liu et al. 2015).

Stromal Leukocytes: Tumor-Associated Neutrophils (TANs)

Neutrophils are attracted to tumor tissues to become a distinct stromal cell population termed tumor-associated neutrophils (TANs). TANs enter the tumor microcirculation where they roll on and attach to the endothelium, perform transmigration, and actively invade the tumor as highly motile, polarized cells. Here, they fulfill various functions, including phagocytosis of tumor cell debris, toxic oxidative damage to normal and neoplastic cells, promotion of tumor cell growth, induction of cancer cell invasion, and induction of metastasis (Houghton 2010). The pro-growth and pro-invasion effects of TANs are relatively new features that have formerly been neglected. The toxic versus tumor-promoting features of TANs are considered to be future treatment targets (Gregory and Houghton 2011). TANs exert these effects through the secretion of cytokines, chemokines, growth-promoting molecules, and matrix metalloproteinases (reviews: Houghton 2010; Galdiero et al. 2013). Homing of TANs into tumor stroma varies considerably among diverse cancer types, but several cancers are capable to recruit large numbers of TANs. In contrast to resting neutrophils, which have a survival time of hours to few days, neutrophils activated in inflammation and in tumors have a longevity that is increased severalfold (review: Kolaczkowska and Kubes 2013). As neutrophils undergo necrosis and apoptosis in tissues, they

must be continuously replaced by new cells entering tumor vessel networks. TANs are attracted to liver cancers through several mechanisms. Chemokinesis and positive chemotaxis can be induced by products of necrotic or apoptotic tumor cells. However, stroma can also contain specific chemoattractants active for TNAs. In intrahepatic cholangiocarcinoma, the CXC-type chemokine CXCL5 exerts a direct chemoattractant effect on neutrophils via a PIK3-Akt signaling pathway (Zhou et al. 2014).

TANs can directly influence the invasive behavior of cancer cells (Imai et al. 2005). They promote motility of these cells through a hyaluronan-mediated pathway involving the hyaluronan receptor TLR4 and PI3K (Wu et al. 2011). One subset of neutrophils is engaged in angiogenesis (Kuang et al. 2011). VEGF-A recruits a proangiogenic, MMP-9-delivering population of neutrophils that induces angiogenesis (Christoffersson et al. 2012). The cells are an important source of matrix metalloproteinases (MMPs) in stroma and can secrete pro-MMP-9, similar to but more potently than tumor-associated macrophages (TAMs). TAN-derived activated MMP-9 plays a major role in tumor angiogenesis. In TANs, pro-MMP-9 is a pre-stored cargo that can rapidly be released, whereas TAMs require time to differentiate, change into a M2 phenotype, produce pro-MMP, and shut down TIMP-1 expression (Deryugina et al. 2014). But also in TANs, release of proangiogenic MMP-9 is associated with downregulation of TIMP-1, thus providing non-inhibited, fully active MMP (Bekes et al. 2011). Neutrophil infiltration in HCCs is associated with increased levels of the CXC chemokine receptor CXCR6, which contributes to a proinflammatory tumor microenvironment (Gao et al. 2012).

Tumor necrosis, a common alteration in both primary liver cancers, and in particular HCC, and metastases, markedly affects tumor infiltration by TANs. Sterile inflammation in tumors followed by cell death/necrosis is induced by damage-associated molecular patterns (DAMPs). One critical component of DAMPs in normal and neoplastic tissues is high-mobility group box 1 (HMGB1), a nuclear nonhistone protein released to the extracellular space as a response to various stimuli (Kostova et al. 2010). In epithelial cell populations, HMGB1 (amphoterin) and its receptor RAGE (receptor for advanced glycation end products) play an important role in necrosis and necrosis-associated inflammation, including inflammatory responses in cancer (Sims et al. 2010). HMGB1 triggers the recruitment of neutrophils, a central mechanism for neutrophil accumulation in necrotic tissues (Huebener et al. 2015). HMGB1, which is loosely bound to chromatin, is released from necrotic cells, but not apoptotic cells (Lotze and DeMarco 2003). Necrosis-associated stimulation of the HMGB1-RAGE system and associated neutrophil reactions affect the biology of liver cancers. Activation of the HMGB1-RAGE system induces NF-kappaB activation in HCCs, associated with enhanced tumor cell migration and invasion (Chen et al. 2014). RAGE is overexpressed in HCC, and activation of the RAGE receptor signaling in HCCs stimulates cell proliferation (Yaser et al. 2012) and enhances the angiogenic potential of these neoplasms through upregulation of VEGF expression (Takino et al. 2012). These effects are associated with poor prognosis in HCC patients (Ito et al. 2014).

Neutrophils also effect homeostasis in normal and neoplastic tissues due to their distinct modes of survival and death. The survival of neutrophils differs between normal tissues and tumors. TANs in HCC show increased autophagy with enhanced functional LC3 protein and autophagosomes, associated with a long-lived phenotype with more intact mitochondria and low cleaved caspase-3 (Li et al. 2015). However during inflammation, including inflammatory responses taking place in tumor stroma, neutrophils undergo apoptosis after a certain time. Neutrophils possess components of both extrinsic and intrinsic apoptotic pathways (Geering and Simon 2011). Early apoptotic neutrophils and TANs are cleared by macrophages, while late apoptotic neutrophils/TANs provoke proinflammatory reactions including secretion of tumor necrosis factor-alpha.

Neutrophils also undergo a distinct mode of cell death called NETosis characterized by the

formation of neutrophil extracellular traps (NETs) containing diverse nuclear proteins and peptides that affect microorganisms, normal cells, and cancer cells (Vorobjeva and Pinegin 2014). Neutrophils also undergo a distinct form of necrosis, termed secondary necrosis. Phagocytosis of secondary necrotic neutrophils by macrophages results in a proinflammatory pathway characterized by release of macrophage inflammatory protein-2 (MIP-2) which in turn promotes neutrophil infiltration.

The presence and number of TANs in liver cancers is associated with biology of disease, and their high number in HCCs is a poor prognostic factor (Li et al. 2011). In HCCs, the neutrophil-lymphocyte ratio has prognostic significance (meta-analysis: Xiao et al. 2014). That TANs have a significant influence on liver cancer growth and invasion is underlined by the observation that the presence of increased numbers of neutrophils in cholangiocarcinoma is associated with worse patient survival. In particular, neutrophils correlated with the presence of vascular invasion in these tumors (Gu et al. 2012). Neutrophils also affect metastatic pathways. Circulating neutrophils are associated with distant metastasis in a number of carcinomas. TANs can promote cancer cell adhesion and arrest in sinusoidal vessels. Neutrophils can themselves adhere to arrested cancer cells and may facilitate interactions between cancer cells, blood vessel cells, and stromal cells (Spicer et al. 2012).

Stromal Leukocytes: Tissue Mast Cells

In carcinomas, the stroma can contain tissue mast cells in variable numbers (Aaltomaa et al. 1993; Jing et al. 1993). This phenomenon is also found in HCCs and cholangiocarcinomas (Terada and Matsunaga 2000; Grizzi et al. 2003). Mast cells play a role in production and turnover of various connective tissues (Hartveit 1993). In the stroma of intrahepatic cholangiocarcinomas, the density of mast cells was significantly higher than that of portal tracts of normal livers, and mast cell densities of these cancers were higher than those in HCCs (Terada and Matsunaga 2000), what might reflect the stronger desmoplastic reaction of cholangiocarcinomas in comparison with HCCs. High densities of peritumoral mast cells were positively correlated with early HCC recurrence and poorer outcome (Ju et al. 2009b), while another study failed to show any significant correlation between mast cell density and stage or grade of HCCs (Grizzi et al. 2003).

Stromal Microvasculature, Endothelial Cells, and Endothelial Progenitors

Effects of Stroma on Vasculogenesis and Angiogenesis

In its function as a main supportive cell and matrix system for cancer cell growth and spread, the stroma provides a reactive (nonneoplastic) microvascular system (stromal microvasculature, SMV) for the energy requirements of the neoplastic cells. This microvascular system is driven by angiogenesis and vasculogenesis and functions through a complex interaction between cancer cells and stromal cells. The production and turnover of ECM is closely linked with remodeling of the stromal vascular system. The endothelial cells of SMV differ in several respects from normal, preexisting endothelial systems of the liver. The proteoglycan, agrin, is selectively deposited in microvessels of HCCs and is a marker for blood vessels growing in malignant hepatic neoplasms (Tatrai et al. 2009). In comparison with HCCs, cholangiocarcinomas showed a higher expression level of agrin, suggesting a differential function of agrin in tumor-induced neoangiogenesis (Batmunkh et al. 2007). Sinusoid-like vascular channels of HCCs accumulate, in the setting of their capillarization, the basement membrane protein matrilin 2 (Szabo et al. 2008). Stromal cells can themselves promote stromal and tumor angiogenesis. Stromal cells also alter endothelial cell-ECM interactions and cause differential expression of factors affecting angiogenesis, such as the matricellular protein thrombospondin 2 (TSP2) (Calabro et al. 2014). CAFs can express podoplanin (Pula et al. 2013b), and this expression correlates with VEGF-C expression,

suggesting that stromal podoplanin is involved in tumor lymphangiogenesis (Pula et al. 2013a).

Tumor stroma also modulates the development and function of pericytes, cells that mediate blood vessel maturation and limit tumor cell metastasis (Raza et al. 2010). Recruitment of pericytes to stroma is regulated by platelet-derived growth factor-B (PDGF-B), while endothelial PDGF-B retention is indispensable for integration of pericytes into vessel walls (Jain and Booth 2003). Overexpression of PDGF-BB decreases growth of colorectal carcinomas, an effect associated with increased coverage of endothelial cell tubes and a blunted angiogenesis (McCarty et al. 2007).

Endothelial Cells and Endothelial Progenitors in Tumor Stroma

Endothelial cells and their progenitors circulate in the blood of highly vascularized liver cancers in higher numbers. Endothelial progenitor cells can home to stroma and stromal vascular channels, undergo maturation to endothelial cells, and integrate into newly formed vessels (Ganss 2006). The tumor stroma and its ECM exert a proangiogenic effect on these homing cells and participate in maturing and branching of tumor vessels. As liver cancer progression strongly depends on angiogenesis, the priming of endothelial progenitors has an impact on tumor biology. Apart from their role of cells providing for angiogenesis, endothelial cells located in the tumor stroma have additional functions. Through paracrine regulation, endothelial cells affect the migratory and invasive behavior of cancer cells, both stimulatory and inhibitory. For example, expression of perlecan by endothelial cells can suppress cancer cell invasiveness (Franses et al. 2011). Endothelial progenitor cells can secrete monocyte chemotactic protein-1 (MCP-1), which in turn contributes to chemotaxis of HCC cells by inducing microRNA-21 biogenesis and favors intrahepatic HCC metastasis (Shih et al. 2015). Through endothelial-mesenchymal transition (EndoMT), endothelial cells can contribute to the emergence of stromal cells (Medici and Kalluri 2012).

Stromal Extracellular Matrix (ECM)

Introduction

The ECM is a highly dynamic compartment that plays a central role in the biology of HCCs, CCs, and other malignancies (Wu et al. 2006; Duncan 2013). The tumor ECM shows a turnover that is mediated by the controlled release and activation of numerous hydrolases and the peptide hormone, relaxin, a member of the insulin superfamily critically involved in ECM remodeling and the sinusoidal microcirculation. Relaxin binds to a receptor expressed by connective tissue cells, including stromal cells, relaxin family peptide receptor-1 (RXFP1).

ECM Proteins, Proteoglycans, and Glycosaminoglycans: General Aspects

There is a group of ECM molecules preferentially overexpressed in the ECM of hepatobiliary malignancies (Table 2).

Basement Membrane Proteins

Many tumors are rich in several proteins that are constituents of basement membrane (BM),

Table 2 Proteins and proteoglycans of tumor ECM

Proteins
Basement membrane proteins
Collagens and collagen-associated proteins
Fibronectin
Vitronectin
Tenascins
Matrilins
Microfibrils and fibrillins
Elastin
Thrombospondins
Heparan sulfate proteoglycans
Basement membrane-type heparan sulfate proteoglycans
Syndecans
Perlecan
Biglycan
Lumican
Fibromodulin
Versican

including laminins, type IV collagen, agrin, and nidogen (Hashmi and Marinkovich 2011). BM proteins form a critical set of ECM proteins and glycoproteins that mediate cell adhesion, cell motility, and invasive features. One specifically important group of BM proteins is the laminins which hold a central position in the tumor invasion cascade (reviews: Aumailley 2013; Simon-Assmann 2013). Laminins constitute a group of at least 16 isoforms of alpha/beta/gamma heterotrimers constructed from five alpha, three beta, and three gamma chains. Critical receptors for laminins in several cell systems are integrins of several classes.

HCCs express distinct combinations of integrins (Volpes et al. 1993; Ozaki et al. 1998) and are thus capable to interact with ECM and specifically BM laminins in various ways. There are distinct patterns of laminin expression in the various types of hepatic tumors (Grigioni et al. 1987). Extracellular laminin expression is already detectable in nodular preneoplastic hepatic lesions, and the amount of laminin gradually increases in the course of hepatic carcinogenesis (Albrechtsen et al. 1988). Laminins can markedly modulate the differentiation status of HCC cells. For example, they modulate cytoskeletal proteins, in that laminins induce the expression of cytokeratin 19 in HCC cells and hence modify the biologic behavior (Su et al. 2003). Expression of laminin alpha 4 in HCCs is an important factor mediating invasion and metastasis (Huang et al. 2008). Laminin alpha 5 promotes ectopic adhesion of HCC cells through integrins and/or Lutheran/basal cell adhesion molecule (Kikkawa et al. 2008). Laminin-5 is expressed in almost all intrahepatic CCs, but was absent in scirrhous HCC (Okamura et al. 2005). Expression of type IV collagen, a BM component, decreased in HCCs as a function of a lower differentiation grade (Zhao et al. 1996), and this decrease is probably a function of the disruption of the BM structures in the course of tumor progression (Patriarca et al. 1993). When detectable, type IV collagen is usually observed at the level of sinusoid-like vascular channels (Grigioni et al. 1987). Nidogen-2 is an ubiquitous BM protein that is significantly decreased in HCCs. This downregulation is associated with tumor progression parameters (Cheng et al. 2012).

Abnormal expression of basement membrane proteins in stroma is also found in cholangiocarcinomas. Intrahepatic cholangiocarcinomas aberrantly express laminin gamma 2 chain, predominantly in the intraductal and periductal infiltrating cancer types, and most strongly in the region of the invasive front, suggesting a role of this laminin in tumor invasion and progression (Aishima et al. 2004).

Fibronectin

Fibronectin is an important ECM protein that exerts several biologic functions, including the mediation of adhesion processes. Fibronectin is expressed in a majority of moderately to well-differentiated HCCs, together with other ECM components, but is absent in poorly differentiated neoplasms (Szendröi and Lapis 1985). Fibronectin and laminins are usually found in a peritrabecular or periacinar expression in HCCs (Donato et al. 1989), and in the perivascular space (Torimura et al. 1994), and are expressed in greater amounts in peritumoral capsules (Grigioni et al. 1990).

Tenascins

Tenascins are ECM glycoproteins which in a pleiotropic manner affect cell proliferation, differentiation, adhesion, and motility. There are four members of the tenascin protein family, i.e., C, R, W, and X. Tenascin-C and tenascin-W inhibit cell spreading through binding to fibronectin, while tenascin-R and tenascin-X also display anti-adhesive properties. Tenascin-W is a marker for activated tumor stroma (Degen et al. 2007). Tenascin is usually expressed in CCs (Terada and Nakanuma 1994) and is less expressed in stroma-rich variants of HCCs (Okamura et al. 2005), but tenascin expression is generally stronger in HCCs than in cirrhotic nodules (Zhao et al. 1996). In HCCs, tenascin prevails in capsular tissue and in septa, but is poorly expressed in the wall of

sinusoid-like vessels (Yamada et al. 1992). In intrahepatic CCs, tenascin expression at the invasive front is associated with poor prognosis (Aishima et al. 2003).

Matrilins

Matrilins form a small family of proteins with currently four members and characteristic von Willebrand factor A domains and epidermal growth factor-like domains. Matrilin 1 (cartilage matrix protein) is mainly expressed in cartilage, while matrilins 2 and 4 are widely distributed in ECMs (review: Deak et al. 1999). Matrilin 2 is strongly expressed in HCCs, but mainly in its capillarized tumor vessels (Szabo et al. 2008).

Microfibrils and Fibrillins

The ECM contains a distinct group of fibrils termed microfibrils, mainly consisting of fibrillins. Fibrillin-1, the main component, multimerizes into bead-like structures that can self-assemble to microfibrils (Baldwin et al. 2014). Initiation and maturation of microfibrils are controlled by several factors, e.g., fibronectin, which interacts with fibrillin-1. Fibrillin-rich microfibrils are involved in developmental and morphogenetic processes of many tissues and affect ECM turnover through modulation of TGF-beta/bone morphogenetic protein signaling (Massam-Wu et al. 2010). Fibrillins form an intricate ECM network implicated in storage and release of growth factors. In normal liver tissue, fibrillin-1 and elastin co-localize in vessel walls and portal tract connective tissue, while fibrillin-1 alone is expressed along sinusoids and at the limiting plate and close to bile duct basement membranes. In HCCs, fibrillin-1 is present between neoplastic hepatocytes and between stromal cells and is associated with fibronectin (Dubuisson et al. 2001; Kinsey et al. 2008). Microfibrils are associated with distinct glycoproteins, the MAGPs (microfibril-associated glycoproteins). Mammalian cells express two MAGPs, MAGP1 and MAGP2 (Segade 2009).

Elastin

An ECM fibril that is involved in the regulation of cancer cell behavior is elastin, an important matrikine, but less information is available regarding cellular interactions of this complex fibril system (Lapis and Timar 2002; Rodgers and Weiss 2005). Elastin fibrils are present in the normal liver and are expressed in tumor stroma (Lapis and Timar 2002). Elastin peptides (matrikines as degradation products of elastin) present in the ECM can stimulate receptor signaling, cell cycle progression, and chemotaxis, can induce release of proteases from stromal cells, and may act as invasion enhancers for tumor cells (Yusa et al. 1989; Uemura and Okamoto 1997). Certain cancer cells can synthesize elastin and express lysyl oxidase, possibly affecting angiogenic responses (Lapis and Timar 2002). Hepatocellular carcinomas and cholangiocarcinomas express several members of the thrombospondin family of proteins, including cartilage oligomeric matrix protein (COMP Xiao et al. 2004).

Proteoglycans

Basement membranes and other components of the ECM contain a distinct set of proteoglycans. Heparan sulfate proteoglycans play a specifically important role in processes that regulate adhesion between cancer cells and these cells with the ECM (review: Roskams et al. 1998). Many cancer cells, including HCC and CC cells, can synthesize syndecans, in particular syndecan-1. A second important ECM proteoglycan is perlecan, which is a multifunctional molecule affecting numerous biological processes (review: Knox and Whitelock 2006). Stromal cells of cholangiocarcinomas can synthesize basement membrane-type heparan sulfate proteoglycans, MFBs being the main source of these EMC molecules (Sabit et al. 2001). The basement membrane protein, matrilin-2, is produced in the course of capillarization of sinusoid-like vascular channels in HCCs and cirrhosis (Szabo et al. 2008). Proteoglycans are not only located to the ECM, but they are also components inherent to cell surface,

including those of neoplastic cells. One important group is the glypicans (GPC), of which six families are known (GPC1–GPC6). An important GPC of HCCs is glypican-3, which also is a potent diagnostic marker. GPCs are linked to the cell surface membrane by a glycosylphosphatidylinositol anchor (review: Filmus 2001).

ECM proteins, proteoglycans, and glycosaminoglycans are effectors and modifiers of cancer cell growth, differentiation, and invasion.

Syndecans are known to affect various functions of cancer cells. They can bind a variety of ECM ligands and play a role in the regulation and modulation of tumor cell proliferation, cell-cell adhesion, cell-matrix adhesion, and invasion (review: Carey 1997). High expression of syndecan-1, together with paxillin, in HCCs is associated with increased differentiation and decreased invasion and metastasis of this neoplasm (Li et al. 2005), whereas reduced syndecan-1 expression in HCCs characterized tumors with a high metastatic potential (Matsumoto et al. 1997).

In human HCCs, elevated levels of glycosaminoglycans and altered sulfation patterns of chondroitin sulfate were associated with the differentiation status of HCCs. In the course of decreasing differentiation of HCCs, chondroitin sulfates, nonsulfated and disulfated chondroitin sulfate disaccharide units, and low-molecular glycosaminoglycans progressively increased, while the expression of heparan sulfate decreased (Lv et al. 2007). Stromal cell-derived growth factor-1 is associated with the heparan sulfate proteoglycan, syndecan-4, which is located at the HCC cell membrane; this association is promoting cell growth (Sutton et al. 2007).

Mechanisms Promoting Tumor Stroma Formation

Humoral Factors

Stroma formation is regulated by TGF-beta isoforms (beta1–beta3), whereby TGF-betas are produced by both tumor cells (HCC and CC) and stromal cells, indicating a complex auto-paracrine regulation network (Abou-Shady et al. 1999; Meindl-Beinker et al. 2012). Connective tissue growth factor (CTGF) produced by HCC cells is associated with increased stromagenesis in xenografts (Mazzocca et al. 2010). In CCs, platelet-derived growth factor (PDGF) and Rho GTPases regulate the recruitment of cancer-associated fibroblasts (Cadamuro et al. 2013).

Stroma and Epithelial-Mesenchymal Transition (EMT) and Mesenchymal-Epithelial Transition (MET)

Epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) have an important function in cancer biology, specifically for invasion and metastatic spread, and both mechanisms are forms of epithelial-mesenchymal plasticity or EMP. EMT and MET are functional circuits in the normal liver and in inflammatory liver disease and are important mechanisms in cancer invasion and progression (reviews: Micalizzi et al. 2010; Jing et al. 2011). EMT and MET not only fundamentally alter the metabolome of cells but also change the orientation and intrinsic shape features of cells involved, e.g., cell polarity (Royer and Lu 2011), an effect that has a great impact on all mechanisms that generate an invasive phenotype. In the normal adult liver, EMT is induced by TGF-beta via upregulation of Snail1, whereby the action of TGF-beta is regulated by the microRNA-200 (Schliekelman et al. 2011). Several other factors are inducers or modulators of EMT and MET, including Twist, Snail1, FoxM, FoxQ1, Slug, metadherin, block of proliferation1 (BOP1), RUNX3, RANKL, vimentin expression, the collagen receptor discoidin domain receptor 2, VEGFR1, the ZEB1/ZEB2 protein axis, CD15, the Cas family protein NEDD9, and SerpinB3 (Kong et al. 2011a). Overall, EMT and MET are promoted by the activation of a multifactor transcriptional network (Venkov et al. 2011). In HCCs, EMT is induced by high expression of microRNA-191 (He et al. 2011). In tumors, including HCCs and CCs, EMT is also influenced by the action of distinct stromal cell populations, e.g., myeloid-derived suppressor

cells (Toh et al. 2011) and cancer stem cells (Kong et al. 2011b). Cancer stem or progenitor cells represent a transitioning cell population between hepatic epithelial cells and stromal cells (Deng et al. 2011).

EMT is associated with hepatic tumor stromal biology in a complex fashion (Mikulits 2009; Kim et al. 2010; Marijon et al. 2011). The stromal microenvironment of tumors significantly affects both EMT and MET (Ding et al. 2013). HCC cell-stroma crosstalk guides EMT at the tumor edge via pathways involving TGF-beta and platelet-derived growth factor (van Zijl et al. 2009). In HCC, loss of the adhesion molecule, E-cadherin, is a key molecular event in EMT regulated by inhibitory transcription factors such as Twist and epigenetic mechanisms. In these neoplasms, EMT-associated downregulation of E-cadherin is also accomplished by a corepressor binding to several transcription factors, C-terminal-binding protein 1, a factor upregulated in HCCs (Zhang et al. 2013a). Epithelial-to-fibroblast conversion in HCCs is associated with distinct cytoskeletal changes that affect E-cadherin expression (Murata et al. 2009).

EMT taking place at the cancer cell-stroma interface forms a platform that markedly influences the growth and invasion behavior of cancer cells. Switching of the cytoskeletal and polarity phenotype of epithelial cells undergoing EMT modulates their motility behavior and, in the case of tumor cells, their metastatic capacity (Wells et al. 2011). The EMT regulator Twist1, a protein modulating E-cadherin expression, activates matrix metalloproteinases in HCCs and via this pathway promotes tissue invasion (Zhao et al. 2011). EMT is promoted by the ECM protein periostin, produced by both HCCs and CCs (Morra and Moch 2011). In HCCs, EMT and EMT-associated growth are also regulated by the expression of osteopontin (Bhattacharya et al. 2012a). There are subtypes of HCC in which EMT-associated features differ from those of ordinary HCCs. For example, B-viral HCCs with high expression of CD133, a stem cell marker, showed upregulation of EMT and of invasion-associated genes (Na et al. 2011). In the stroma, where mesenchymal stem cells settle after homing, these cells may undergo fusion with cancer cells, e.g., cells of HCCs (Li et al. 2013a), a process that might participate in mechanisms for EMT.

Metabolic Functions of Stroma, Humoral Factors, and Mechanisms of Stromal Signaling

Stromal cells and cancer cells form a complex interacting cell system (the stromal interactome) that is characterized by humoral network regulating the relationships between the cells in "paracrine cooperativity" (Luciani et al. 2011). MFBs of tumor stroma secrete factors that promote proliferation of HCC cells. Conversely, HCC cell in vitro induces the proliferation of MFBs (Nhieu et al. 1998), suggesting the presence of mutually active growth augmentation loop. The chemokine, stromal cell-derived factor-1 (SDF-1), is produced by stromal cells, but also HCC cells in an autocrine loop, SDF-1 interacts with the G protein-coupled receptor, chemokine receptor (C-X-C motif) 4, reorganizes the HCC cell cytoskeleton, induces tyrosine phosphorylation of focal adhesion kinase, and activates matrix metalloproteinase-9, thus stimulating cell growth, migration, and invasion (Sutton et al. 2007). Stromal MFBs promote HCC cell migration through secretion of monocyte chemoattractant protein-1 (MCP-1) (Dagouassat et al. 2010) and increase the invasiveness of HCC cells through the secretion of hepatocyte growth factor (Neaud et al. 1999). Stromal cells of HCCs produce fibroblast growth factors 1 and 2 which may promote tumor angiogenesis (Chow et al. 1998). In CCs, MFBs secrete platelet-derived growth factor BB, promoting hedgehog survival signaling (Fingas et al. 2011). The crosstalk between stromal cells and CC cells was found to be mediated by platelet-derived growth factor D (Berasain and Avila 2013). Stromal spindle cells can express podoplanin, a protein that induces stromal lymphangiogenesis important for lymphatic cancer spread (Kitano et al. 2010).

Stromal Cell Exosomes and Other Communication Systems in Stroma

As outlined in more detail in the chapter on liver metastasis, there are several types of subcellular structures that are capable to load information molecules, such as signal substances and noncoding RNAs, and transfer this cargo to other cells. These vehicles mainly include exosomes and oncosomes, both acting as "signalosomes" (Masyuk et al. 2013; Nazarenko et al. 2013). Exosomes are small membrane vesicles derived from endosomal multivesicular structures (Bobrie et al. 2011). Via TGF-beta expressed at the exosomal surface, exosomes can activate fibroblasts and stimulate the differentiation of myofibroblasts from fibroblasts (Webber et al. 2014). As exosomes can produce adenosine from ATP, they play a role in adenosine-mediated signaling processes (Clayton et al. 2011). Exosomes can carry molecules that operate in target cell selection for cancer cells, e.g., tetraspanins that select certain endothelial surfaces (Rana et al. 2012). Microvesicles are also derived from endothelial cells and carry in this case distinct carcinoembryonic antigen-related cell adhesion molecule (CEACAM), a factor that influences other stromal cells, in particular T cells (Muturi et al. 2013).

In cancers, exosomes and related cargo carriers are released by both carcinoma cells and stromal cells. Tumor cell-derived microvesicles can interact with stromal mesenchymal cells, modulate the composition and function of the microenvironment, and by this affect tumor invasion (Haga et al. 2015). In tumor stroma, CAFs can produce exosomes that are then taken up by epithelial cancer cells, a process that may modulate the growth, invasion, and metastatic modes of cancer cells. Exosomes – or oncosomes in this case – provide for a system of crosstalk between stromal cells and cancer cells, and for the programming of premetastatic niches, in part by delivering microRNAs (Morello et al. 2013; Rana et al. 2013). Apart from exosomal vesicles that can fuse with target cells to deliver their information cargo, exchange of information in stroma also takes place through direct cell-cell fusion (Howcroft et al. 2011).

Stroma as a Sensing Cell System Controlling Tumor Prosperity

The tumor stroma is an apparatus that senses critical alterations of the tumor's metabolome, including hypoxia and oxidative stress. CAFs and other stromal cells differ in their metabolism from epithelial cancer cells, but can engage in metabolic coupling, providing fuel to cancer cells, including amino acids, ketones, and lactate (Hart 2011). CAFs can undergo anaerobic glycolysis and release lactate to "feed" adjacent cancer cells, a mechanism driving mitochondriogenesis in the neoplastic cells. This stromal-epithelial lactate shuttle is therefore suggested to play an important role in the steering of tumor cell adaptation to critical metabolic stress (Whitaker-Menezes et al. 2011). Also stromal CAFs can transfer energy and biomass to anabolic cancer cells (Martinez-Outschoom et al. 2014; Miles and Sikes 2014), suggesting a stroma cell-cancer cell feeding circuit. There is evidence that oncogenes can induce the development of such metabolic symbiotic circuits (Lisanti et al. 2013). Reactive oxygen species produced in tumor stroma can be used by stromal cells for the generation of signaling within the microenvironment. CAFs exploit reactive oxygen species via a proinflammatory signature leading to stemness and EMT (Giannoni et al. 2011). CAFs interacting with cancer cells produce high levels of the chemokines CCL2 (chemokine C-C motif ligand 2) and subsequently enhance endogenous reactive oxygen production (Li et al. 2014).

Industasis

Introduction

Classical views regarding the spread and growth of cancer have it that malignant neoplastic cells are capable to leave a primary tumor,

individualize, invade the adjacent normal tissues, and dislocate to remote areas, where they may home and restart growth to form metastases. In fact, it is long known that cells of both metastasizing and non-metastasizing cancer circulate in the blood of patients (Ashworth 1869; Butler and Gullino 1975). In addition to cancer cells, nonmalignant cells can also enter into the efferent blood of organs and tissues, e.g., through injury or surgical interventions (Raa et al. 2005). These so-called stray cells may get into physical contact with disseminated cancer cells or incipient tumor cells and exert an influence on them in regard to their future biology. Specifically, stray cells may alter local signaling networks, modulate Darwinian type of competitions between cells of the target niche (Tubiana 2009), generate novel cell-cell communications via junctional complexes (Trosko and Ruch 1998; Trosko and Chang 2001), or exchange genetic material with spread cancer cells and precancerous cells, including components of the mitochondrial genome (Ralph et al. 2010).

Nemosis

Nemosis (from the Greek goddess of retribution, Nemesis) denotes a process of cell death that was originally termed programmed necrosis. Nemosis occurs through cell-to-cell contact of diploid fibroblasts which become activated through this contact leading to programmed cell death associated with cytoskeleton degradation (Bizik et al. 2004; Vaheri et al. 2009). In contrast to cancer cells, normal fibroblasts do not grow to form multicellular, spheroid-like aggregates, but rather grow in the form of layers on substratum. If forced to form clusters, contact among fibroblasts in these clusters results in an activated associated form of "retributional" cell death, probably as a control mechanism counteracting abnormal growth patterns. Nemosis is more close to a variant of necrosis than apoptosis. In the course of nemosis, involved cells release numerous signal substances, growth factors, and inflammation mediators. Therefore, nemosis plays a significant role in the transmission of the fibroblast activation status into the microenvironment, the nemotic factor release generating a novel signaling network suitable to reorganize and reassemble the cellular system involved. By the nemotic response, the mesenchymal cells can induce inflammation, epithelial cell proliferation (Peura et al. 2009), and angiogenesis (Enzerink et al. 2010).

There are certain differences in fibroblast/stromal cell nemosis between non-transformed cells and cancer cells (Räsänen et al. 2009). As cancer-associated fibroblasts (CAFs) and other stromal cells are continuously activated in the stroma of carcinomas, nemosis is expected to take place in stroma. Generally, CAFs are more strongly activated to upregulate inflammatory mediators and to express alpha-SMA than normal fibroblasts in the setting of nemosis (Räsänen et al. 2009). Fibroblast clustering in tumors followed by nemosis is associated with the increased production of hepatocyte growth factor by these cells, causing spread and invasion of cancer cells (Kankuri et al. 2005). Stromal fibroblast nemosis also induces angiogenic responses of endothelial cells (Enzerink et al. 2010). The interaction between epithelial cells and fibroblasts has a strong impact in nemosis. Whereas normal epithelial cells inhibit fibroblast nemosis, cancerous epithelia promote a nemotic response (Räsänen et al. 2008). But also normal fibroblasts and stromal cells can affect malignant cells via nemosis. For example, fibroblast nemosis arrests growth and induces differentiation of human leukemia cells (Kankuri et al. 2008).

References

Aaltomaa S, Lipponen P, Papinaho S, Kosma VM (1993) Mast cells in breast cancer. Anticancer Res 13:785–788

Abou-Shady M, Baer HU, Friess H, Berberat P, Zimmermann A, Graber H, Gold LI et al (1999) Transforming growth factor betas and their signaling receptors in human hepatocellular carcinoma. Am J Surg 177:209–215

Aishima S, Taguchi K, Terashi T, Matsuura S, Shimada M, Tsuneyoshi M (2003) Tenascin expression at the invasive front is associated with poor prognosis in intrahepatic cholangiocarcinoma. Mod Pathol 16:1019–1027

Aishima S, Matsuura S, Terashi T, Taguchi K, Shimada M, Maehara Y, Tsuneyoshi M (2004) Aberrant expression of laminin gamma 2 chain and its prognostic significance in intrahepatic cholangiocarcinoma according to growth morphology. Mod Pathol 17:938–945

Albrechtsen R, Wewer UM, Thorgeirsson SS (1988) Do novo deposition of laminin-positive basement membrane in vitro by normal hepatocytes and during hepatocarcinogenesis. Hepatology 8:538–546

Al-toub M, Almusa A, Amajed M, Al-Nbaheen M, Kassem M, Aldahmash A, Alajez NM (2013) Pleiotropic effects of cancer cells' secreted factors on human stromal (mesenchymal) stem cells. Stem Cell Res Ther 4:114

Amann T, Bataille F, Spruss T, Mühlbauer M, Gäbele E, Schölmerich J, Kiefer P, Bosserhoff AK et al (2009) Activated hepatic stellate cells promote tumorigenicity of hepatocellular carcinoma. Cancer Sci 100: 646–653

Anderberg C, Pietras K (2009) On the origin of cancer-associated fibroblasts. Cell Cycle 8:1461–1462

Aprelikova O, Green JE (2012) MicroRNA regulation in cancer-associated fibroblasts. Cancer Immunol Immunother 61:231–237

Aprelikova O, Palla J, Hibler B, Yu X, Greer YE, Yi M, Stephens R, Maxwell GL, Jazaeri A et al (2013) Silencing of miR-148a in cancer-associated fibroblasts results in WNT10B-mediated stimulation of tumor cell motility. Oncogene 32:3246–3253

Arihara F, Mizukoshi E, Kitahara M, Takata Y, Arai K, Yamashita T, Nakamoto Y, Kaneko S (2013) Increase in CD14+HLA-DR-/low myeloid-derived suppressor cells in hepatocellular carcinoma patients and its impact on prognosis. Cancer Immunol Immunother 62:1421–1430

Ashworth TR (1869) A case of cancer in which cells similar to those in the tumors were seen in the blood after death. Aust Med J 14:146

Augsten M, Sjöberg E, Frings O, Vorrink SU, Frijhoff J, Olsson E, Borg A, Östman A (2014) Cancer-associated fibroblasts expressing CXCL14 rely upon NOS1-derived nitric oxide signaling for their tumor-supporting properties. Cancer Res 74:2999–3010

Aumailley M (2013) The laminin family. Cell Adhes Migr 7:48–55

Aurich H, Sgodda M, Kaltwasser P, Vetter M, Weise A, Liehr T, Brulport M, Hengstler JG et al (2009) Hepatocyte differentiation of mesenchymal stem cells from human adipose tissue in vitro promotes hepatic integration in vivo. Gut 58:570–581

Bagley RG, Weber W, Rouleau C, Yao M, Honma N, Kataoka S, Ishida I, Roberts BL, Teicher BA (2009) Human mesenchymal stem cells from bone marrow express tumor endothelial and stromal markers. Int J Oncol 34:619–627

Baldwin AK, Cain SA, Lennon R, Godwin A, Merry CL, Kielty CM (2014) Epithelial-mesenchymal status influences how cells deposit fibrillin microfibrils. J Cell Sci 127:158–171

Barcellos-de-Souza P, Gori V, Bambi F, Chiarugi P (2013) Tumor microenvironment: bone marrow-mesenchymal stem cells as key players. Biochim Biophys Acta 1836:321–335

Batmunkh E, Tatrai P, Szabo E, Lodi C, Holczbauer A, Paska C, Kupcsulik P, Kiss A et al (2007) Comparison of the expression of agrin, a basement membrane heparan sulfate proteoglycan, in cholangiocarcinoma and hepatocellular carcinoma. Hum Pathol 38:1508–1515

Bayo J, Fiore E, Aquino JB, Malvicini M, Rizzo M, Peixoto E, Andriani O, Alaniz L, Piccioni F, Bolontrade M, Podhajcer O et al (2014) Increased migration of human mesenchymal stromal cells by autocrine motility factor (AMF) resulted in enhanced recruitment towards hepatocellular carcinoma. PLoS ONE 9, e95171

Beasley SW (1998) Hepatobiliary cystadenoma with hyaline stroma. Pediatr Surg Int 13:462

Becker R, Lenter MC, Vollkommer T, Boos AM, Pfaff D, Augustin HG, Christian S (2008) Tumor stroma marker endosialin (Tem1) is a binding partner of metastasis-related protein Mac-2 BP/90K. FASEB J 22:3059–3067

Bekes EM, Schweighofer B, Kupriyanova TA, Zajac E, Ardi VC, Quigley JP, Deryugina EI (2011) Tumor-recruited neutrophils and neutrophil TIMP-free MMP-9 regulate coordinately the levels of tumor angiogenesis and efficiency of malignant cell intravasation. Am J Pathol 179:1455–1470

Bellini A, Mattoli S (2007) The role of the fibrocyte, a bone marrow-derived mesenchymal progenitor, in reactive and reparative fibroses. Lab Invest 87:858–870

Berasain C, Avila MA (2013) Platelet-derived growth factor D: a new player in the complex cross-talk between cholangiocarcinoma cells and cancer-associated fibroblasts. Hepatology 58:853–855

Berdiel-Acer M, Bohem ME, Lopez-Doriga A, Vidal A, Salazar R, Martinez-Inieasta M et al (2011) Hepatic carcinoma-associated fibroblasts promote an adaptive response in colorectal cancer cells that inhibit proliferation and apoptosis: nonresistant cells die by nonapoptotic cell death. Neoplasia 13:931–946

Bettum IJ, Vasiliauskaite K, Nygaard V, Clancy T, Pettersen SJ, Tenstad E, Maelandsmo GM et al (2014) Metastasis-associated protein S100A4 induces a network of inflammatory cytokines that activate stromal cells to acquire pro-tumorigenic properties. Cancer Lett 344:28–39

Bhattacharya SD, Mi Z, Kim VM, Guo H, Talbot LJ, Kuo PC (2012a) Osteopontin regulates epithelial mesenchymal transition-associated growth of hepatocellular cancer in a mouse xenograft model. Ann Surg 255:319–325

Bhattacharya SD, Mi Z, Talbot LJ, Guo H, Kuo PC (2012b) Human mesenchymal stem cell and epithelial hepatic carcinoma cell lines in admixture: concurrent stimulation of cancer-associated fibroblasts and epithelial-to-mesenchymal transition markers. Surgery 152: 449–454

Bizik J, Kankuri E, Ristimäki A, Taieb A, Vapaatalo H, Lubitz W, Vaheri A (2004) Cell-cell contacts trigger programmed necrosis and induce cyclooxygenase-2 expression. Cell Death Differ 11:183–195

Bobrie A, Colombo M, Raposo G, Théry C (2011) Exosome secretion: molecular mechanisms and roles in immune responses. Traffic 12:1659–1668

Bouwens L, De Bleser P, Vanderkerken K, Geerts B, Wisse E (1992) Liver cell heterogeneity: functions of non-parenchymal cells. Enzyme 46:155–168

Bozoky B, Savchenko A, Csermely P, Korcsmaros T, Dul Z, Pontén F, Szekely L, Klein G (2013) Novel signatures of cancer-associated fibroblasts. Int J Cancer 133:286–293

Brentnall TA (2012) Arousal of cancer-associated stromal fibroblasts: palladin-activated fibroblasts promoter tumor invasion. Cell Adhes Migr 6:488–494

Brentnall TA, Lai LA, Coleman J, Bronner MP, Pan S, Chen R (2012) Arousal of cancer-associated stroma: overexpression of palladin activates fibroblasts to promote tumor invasion. PLoS ONE 7, e30219

Bridle KR, Crawford DH, Powell LW, Ramm GA (2001) Role of myofibroblasts in tumour encapsulation of hepatocellular carcinoma in haemochromatosis. Liver 21:96–104

Bruzzese F, Hägglöf C, Leone A, Sjöberg E, Roca MS, Kiflemariam S, Sjöblom T, Hammarsten P, Egevad L, Bergh A et al (2014) Local and systemic protumorigenic effects of cancer-associated fibroblast-derived GDF15. Cancer Res 74:3408–3417

Butler TP, Gullino PM (1975) Quantitation of cell shedding into efferent blood of mammary adenocarcinoma. Cancer Res 35:512–516

Cacciaguerra S, Lucenti A, Vasta G, Gangarossa S, Milone P, Rizzo L, Farggetta F et al (1996) Hepatobiliary cystadenoma with hyaline stroma: a pediatric case associated with multiple hemangiomas. Pediatr Surg Int 11:380–383

Cadamuro M, Nardo G, Indraccolo S, Dall'Olmo L, Sambado L, Moserle L, Franceschet I et al (2013) Platelet-derived growth factor-D and Rho GTPases regulate recruitment of cancer-associated fibroblasts in cholangiocarcinoma. Hepatology 58:1042–1053

Calabro NE, Kristofik NJ, Kyriakides TR (2014) Thrombospondin-2 and extracellular matrix assembly. Biochim Biophys Acta 1840:2396–2402

Calon A, Tauriello DV, Batlle E (2014) TGF-beta in CAF-mediated tumor growth and metastasis. Semin Cancer Biol 25:15–22

Carey DJ (1997) Syndecans: multifunctional cell-surface co-receptors. Biochem J 327:1–16

Carloni V, Luong TV, Rombouts K (2014) Hepatic stellate cells and extracellular matrix in hepatocellular carcinoma: more complicated than ever. Liver Int 34:834–843

Caronni N, Savino B, Bonecchi R (2015) Myeloid cells in cancer-related inflammation. Immunobiology 220: 249–253

Chau KY, Lily MA, Wu PC, Yau WL (1992) Myofibroblasts in hepatitis B related cirrhosis and hepatocellular carcinoma. J Clin Pathol 45:446–448

Chen RC, Yi PP, Zhou RR, Xiao MF, Huang ZB, Tang DL, Huang Y, Fan XG (2014) The role of HMGB1-RAGE axis in migration and invasion of hepatocellular carcinoma cell lines. Mol Cell Biochem 390:271–280

Cheng ZX, Huang XH, Wang Q, Chen JS, Zhang LJ, Chen XL (2012) Clinical significance of decreased nidogen-2 expression in the tumor tissue and serum of patients with hepatocellular carcinoma. J Surg Oncol 105:71–80

Chiarugi P (2013) Cancer-associated fibroblasts and macrophages: friendly conspirators for malignancy. Oncoimmunology 2, e25563

Chow NH, Cheng KS, Lin PW, Chan SH, Su WC, Sun YN, Lin XZ (1998) Expression of fibroblast growth factor-1 and fibroblast growth factor-2 in normal liver and hepatocellular carcinoma. Dig Dis Sci 43:2261–2266

Christian S, Winkler R, Helfrich I, Boos AM, Besemfelder E, Schadendorf D, Augustin HG (2008) Endosialin (Tem1) is a marker of tumor-associated myofibroblasts and tumor vessel-associated mural cells. Am J Pathol 172:486–494

Christoffersson G, Vagesjö E, Vandooren J, Lidén M, Massena S, Reinert RB, Brissova M, Powers AC, Opdenakker G et al (2012) VEGF-A recruits a proangiogenic MMP-9-delivering neutrophil subset that induces angiogenesis in transplanted hypoxic tissue. Blood 120:4653–4662

Cirri P, Chiarugi P (2011) Cancer associated fibroblasts: the dark side of the coin. Am J Cancer Res 1:482–497

Cirri P, Chiarugi P (2012) Cancer-associated-fibroblasts and tumour cells: a diabolic liaison driving cancer progression. Cancer Metastasis Rev 31:195–208

Clapéron A, Mergey M, Aoudjehane L, H-Bouldoires TH, Wendum D, Prignon A, Merabtene F, Firrincieli D et al (2013) Hepatic myofibroblasts promote the progression of human cholangiocarcinoma through activation of epidermal growth factor receptor. Hepatology 58:2001–2011

Clayton A, Al-Taei S, Webber J, Mason MD, Tabi Z (2011) Cancer exosomes express CD39 and CD73, which suppress T cells through adenosine production. J Immunol 187:676–683

Conti J, Thomas G (2011) The role of tumour stroma in colorectal cancer invasion and metastasis. Cancers 3:2160–2168

Cortez E, Roswall P, Pietras K (2014) Functional subsets of mesenchymal cell types in the tumor microenvironment. Semin Cancer Biol 25:3–9

Coulouam C, Clément B (2014) Stellate cells and the development of liver cancer: therapeutic potential of targeting the stroma. J Hepatol 60:1306–1309

Cuiffo BG, Karnoub AE (2012) Mesenchymal stem cells in tumor development. Emerging roles and concepts. Cell Adhes Migr 6:220–230

Dagouassat M, Suffee N, Hlawaty H, Haddad O, Charni F, Laguillier C, Vassy R, Martin L et al (2010) Monocyte chemoattractant protein-1 (MCP-1)/CCL2 secreted by hepatic myofibroblasts promotes migration and invasion of human hepatoma cells. Int J Cancer 126:1095–1108

De Boeck A, Hendrix A, Maynard D, Van Bockstal M, Daniels A, Pauwels P, Gespach C et al (2013) Differential secretome analysis of cancer-associated fibroblasts and bone-marrow-derived precursors to identify microenvironmental regulators of colon cancer progression. Proteomics 13:379–388

De Wever O, Van Bockstal M, Mareel M, Hendrix A, Bracke M (2014) Carcinoma-associated fibroblasts provide operational flexibility in metastasis. Semin Cancer Biol 25:33–46

Deak F, Wagener R, Kiss I, Paulsson M (1999) The matrilins: a novel family of oligomeric extracellular matrix proteins. Matrix Biol 18:55–64

Degen M, Brellier F, Kain R, Ruiz C, Terraciano L, Orend G, Chiquet-Ehrismann R (2007) Tenascin-W is a novel marker for activated tumor stroma in low-grade human breast cancer and influences cell behavior. Cancer Res 67:9169–9179

Deng H, Wang HF, Gao YB, Jin XL, Xiao JC (2011) Hepatic progenitor cell represents a transitioning cell population between liver epithelium and stroma. Med Hypotheses 76:809–812

Deryugina EI, Zajac E, Juncker-Jensen A, Kupriyanova TA, Welter L, Quigley JP (2014) Tissue-infiltrating neutrophils constitute the major in vivo source of angiogenesis-inducing MMP-9 in the tumor microenvironment. Neoplasia 16:771–788

Descot A, Oskarsson T (2013) The molecular composition of the metastatic niche. Exp Cell Res 319:1679–1686

Desmoulière A, Guyot C, Gabbiani G (2004) The stroma reaction myofibroblast: a key player in the control of tumor cell behavior. Int J Dev Biol 48:509–517

Diaz-Flores L, Gutiérrez R, Garcia MP, Saez FJ, Diaz-Flores L, Valladares F, Madrid JF (2014) CD34+ stromal cells/fibroblasts/fibrocytes/telocytes as a tissue reserve and a principal source of mesenchymal cells. Location, morphology, function and role in pathology. Histol Histopathol 29:831–870

Ding S, Zhang W, Xu Z, Xie H, Guo H, Chen K, Song P, Gu Y, Xiao F, Zhou L, Zheng S (2013) Induction of an EMT-like transformation and MET in vitro. J Transl Med 11:164

Donato MF, Colombo M, Matarazzo M, Paronetto F (1989) Distribution of basement membrane components in human hepatocellular carcinoma. Cancer 63:272–279

Dubuisson L, Lepreux S, Bioulac-Sage P, Balabaud C, Costa AM, Rosenbaum J, Desmoulière A (2001) Expression and cellular localization of fibrillin-1 in normal and pathological human liver. J Hepatol 34:514–522

Duncan MB (2013) Extracellular matrix transcriptome dynamics in hepatocellular carcinoma. Matrix Biol 32:393–398

Dutsch-Wicherek M, Kazmierczak W (2013) Creation of a suppressive microenvironment by macrophages and cancer-associated fibroblasts. Front Biosci (Landmark Ed) 18:1003–1016

Enzan H, Himeno H, Iwamura S, Onishi S, Saibara T, Yamamoto Y, Hara H (1994) Alpha-smooth muscle actin-positive perisinusoidal stromal cells in human hepatocellular carcinoma. Hepatology 19:895–903

Enzerink A, Rantanen V, Vaheri A (2010) Fibroblast nemesis induces angiogenic responses of endothelial cells. Exp Cell Res 316:826–835

Eveno C, Hainaud P, Rampanou A, Bonnin P, Bakhouche S, Dupuy E, Contretres J, Pocard M (2014) Proof of prometastatic niche induction by hepatic stellate cells. J Surg Res. doi:10.1016/j.jss.2014.11.005

Fan QM, Jing YY, Yu GF, Kou XR, Ye F, Gao L, Li R, Zhao QD, Yang Y, Lu ZH, Wei LX (2014) Tumor-associated macrophages promote cancer stem cell-like properties via transforming growth factor-beta1-induced epithelial-mesenchymal transition in hepatocellular carcinoma. Cancer Lett 352:160–168

Fang M, Peng CW, Yuan JP, Zhang ZL, Pang DW, Li Y (2013) Coevolution of the tumor microenvironment revealed by quantum dot-based multiplexed imaging of hepatocellular carcinoma. Future Oncol 9:1029–1037

Faouzi S, Le Bail B, Neaud V, Boussarie L, Saric J, Bioulac-Sage P, Balabaud C, Rosenbaum J (1999) Myofibroblasts are responsible for collagen synthesis in the stroma of human hepatocellular carcinoma: an in vivo and in vitro study. J Hepatol 30:275–284

Fausther M, Dranoff JA (2014) Beyond scar formation: portal myofibroblast-mediated angiogenesis in the fibrotic liver. Hepatology. doi:10.1002/hep.27653

Filmus J (2001) Glypicans in growth control and cancer. Glycobiology 11:19R–23R

Fingas CD, Bronk SF, Werneburg NW, Mott JL, Guicciardi ME, Cazanave SC, Mertens JC et al (2011) Myofibroblast-derived PDGF-BB promotes Hedgehog survival signaling in cholangiocarcinoma cells. Hepatology 54:2076–2088

Franses JW, Baker AB, Chitalia VC, Edelman ER (2011) Stromal endothelial cells directly influence cancer progression. Sci Transl Med 3:66ra5

Fu Z, Zuo Y, Li D, Xu W, Li D, Chen H, Zheng S (2013) The crosstalk: tumor-infiltrating lymphocytes rich in regulatory T cells suppressed cancer-associated fibroblasts. Acta Oncol 52:1760–1770

Galdiero MR, Bonavita E, Barajon I, Garlanda C, Mantovani A, Jaillon S (2013) Tumor-associated macrophages and neutrophils in cancer. Immunobiology 218:1402–1410

Ganss R (2006) Tumor stroma fosters neovascularization by recruitment of progenitor cells into the tumor bed. J Cell Mol Med 10:857–865

Gao Q, Wang XY, Qiu SJ, Zhou J, Shi YH, Zhang BH, Fan J (2011) Tumor stroma reaction-related gene signature predicts clinical outcome in human hepatocellular carcinoma. Cancer Sci 102:1522–1531

Gao Q, Zhao YJ, Wang XY, Qiu SJ, Shi YH, Su J, Yi Y, Shi JY, Shi GM, Ding ZB, Xiao YS, Zhao ZH, Zhou J et al (2012) CXCR6 upregulation contributes to a proinflammatory tumor microenvironment that drives metastasis and poor patient outcomes in hepatocellular carcinoma. Cancer Res 72:3546–3556

Garcia MG, Bayo J, Bolontrade MF, Sganga L, Malvicini M, Alaniz L, Aquino JB et al (2011) Hepatocellular carcinoma cells and their fibrotic microenvironment modulate bone marrow-derived mesenchymal stromal cell migration in vitro and in vivo. Mol Pharm 8:1538–1548

Geering B, Simon HU (2011) Peculiarities of cell death mechanisms in neutrophils. Cell Death Differ 18:1457–1469

Gentilini A, Rombouts K, Galastri S, Caligiuri A, Mingarelli E, Mello T, Marra F, Mantero S, Roncalli M et al (2012) Role of the stromal-derived factor-1 (SDF-1)-CXCR4 axis in the interaction between hepatic stellate cells and cholangiocarcinoma. J Hepatol 57:813–820

Giannelli G, Fransvea E, Bergamini C, Marinosci F, Antonaci S (2003) Laminin-5 chains are expressed differentially in metastatic and nonmetastatic hepatocellular carcinoma. Clin Cancer Res 9:3684–3691

Giannelli G, Bergamini C, Fransvea E, Sgarra C, Antonaci S (2005) Laminin-5 with transforming growth factor-beta1 induces epithelial to mesenchymal transition in hepatocellular carcinoma. Gastroenterology 129:1375–1383

Giannoni E, Bianchini F, Calorini L, Chiarugi P (2011) Cancer associated fibroblasts exploit reactive oxygen species through a proinflammatory signature leading to epithelial mesenchymal transition and stemness. Antioxid Redox Signal 14:2361–2371

Goicoechea SM, Garcia-Mata R, Staub J, Valdivia A, Sharek L, McCulloch CG, Hwang RF et al (2014) Palladin promotes invasion of pancreatic cancer cells by enhancing invadopodia formation in cancer-associated fibroblasts. Oncogene 33:1265–1273

Gonda TA, Varro A, Wang TC, Tycko B (2010) Molecular biology of cancer-associated fibroblasts: can these cells be targeted in anti-cancer therapy ? Semin Cell Dev Biol 21:2–10

Gregory AD, Houghton AM (2011) Tumor-associated neutrophils: new targets for cancer therapy. Cancer Res 71:2411–2416

Grigioni WF, D'Errico A, Mancini AM, Biagini G, Gozzetti G, Mazziotti A, Garbisa S (1987) Hepatocellular carcinoma: expression of basement membrane glycoproteins. An immunohistochemical approach. J Pathol 152:325–332

Grigioni WF, D'Errico A, Biagini G, Mazziotti A, Bolondi L, Liotta LA, Mancini AM et al (1990) The capsule surrounding primary liver tumors: wherefrom its prognostic significance. Int J Cancer 45:637–643

Grizzi F, Franceschini B, Chiriva-Internati M, Liu Y, Hermonat PL, Dioguardi N (2003) Mast cells and human hepatocellular carcinoma. World J Gastroenterol 9:1469–1473

Gu FM, Gao Q, Shi GM, Zhang X, Wang J, Jiang JH, Wang XY, Shi YH, Ding ZB, Fan J, Zhou J (2012) Intratumoral IL-17+ cells and neutrophils show strong prognostic significance in intrahepatic cholangiocarcinoma. Ann Surg Oncol 19:2506–2514

Gulubova MV (1997) Collagen type III and type IV detection in and around human hepatocellular carcinoma. Gen Diagn Pathol 142:155–163

Gupta DK, Singh N, Sahu DK (2014) TGF-β mediated crosstalk between malignant hepatocyte and tumor microenvironment in hepatocellular carcinoma. Cancer Growth Metastasis 7:1–8

Haga H, Yan IK, Takahashi K, Wood J, Zubair A, Patel T (2015) Tumour cell-derived extracellular vesicles interact with mesenchymal stem cells to modulate the microenvironment and enhance cholangiocarcinoma growth. J Extracell Vesicles 4:24900

Hamson EJ, Keane FM, Tholen S, Schilling O, Gorrell MD (2014) Understanding fibroblast activation protein (FAP): substrates, activities, expression and targeting for cancer therapy. Proteomics Clin Appl 8:454–463

Han S, Han L, Yao Y, Sun H, Zan X, Liu Q (2014) Activated hepatic stellate cells promote hepatocellular carcinoma cell migration and invasion via the activation of FAK-MMP9 signaling. Oncol Rep 31:641–648

Harper J, Sainson RC (2014) Regulation of the anti-tumour response by cancer associated fibroblasts. Semin Cancer Biol 25:69–77

Hart I (2011) Eating for two: how stromal fibroblasts might nurture adjacent carcinoma cells. Cell Cycle 10:2829–2830

Hartveit F (1993) Mast cell association with collagen fibres in human breast stroma. Eur J Morphol 31:209–218

Hashmi S, Marinkovich MP (2011) Molecular organization of the basement membrane zone. Clin Dermatol 29:398–411

He Y, Cui Y, Wang W, Gu J, Guo S, Ma K, Luo X (2011) Hypomethylation of the hsa-miR-191 locus causes high expression of hsa-mir-191 and promotes the epithelial-mesenchymal transition in hepatocellular carcinoma. Neoplasia 13:841–853

Hernanda PY, Pedroza-Gonzalez A, van der Laan LJ, Bröker ME, Hoogduijn MJ, Ijzermans JN, Bruno MJ, Janssen HL et al (2013) Tumor promotion through the mesenchymal stem cell compartment in human hepatocellular carcinoma. Carcinogenesis 34:2330–2340

Hernanda PY, Pedroza-Gonzalez A, Sprengers D, Peppelenbosch MP, Pan Q (2014) Multipotent mesenchymal stromal cells in liver cancer: implications for tumor biology and therapy. Biochim Biophys Acta 1846:439–445

Hernandez-Gea V, Toffanin S, Friedman SL, Llovet JM (2013) Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma. Gastroenterology 144:512–527

Hoechst B, Voigtlaender T, Ormandy L, Gamrekelashvili J, Zhao F, Wedemeyer H, Lehner F, Manns MP, Greten TF et al (2009) Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. Hepatology 50:799–807

Houghton AM (2010) The paradox of tumor-associated neutrophils: fueling tumor growth with cytotoxic substances. Cell Cycle 9:1732–1737

Howcroft TK, Zhang HG, Dhodapkar M, Mohla S (2011) Vesicle transfer and cell fusion: emerging concepts of cell-cell communication in the tumor microenvironment. Cancer Biol Ther 12:159–164

Huang X, Ji G, Wu Y, Wan B, Yu L (2008) LAMA4, highly expressed in human hepatocellular carcinoma from Chinese patients, is a novel marker of tumor invasion and metastasis. J Cancer Res Clin Oncol 134:705–714

Huang X, Gai Y, Yang N, Lu B, Samuel CS, Thannickal VJ, Zhou Y (2011) Relaxin regulates myofibroblast contractility and protects against lung fibrosis. Am J Pathol 179:2751–2765

Huebener P, Pradere JP, Hernandez C, Gwak GY, Caviglia JM, Mu X, Loike JD, Jenkins RE, Antine DJ, Schwabe RF (2015) The HMGB1/RAGE axis triggers neutrophil-mediated injury amplification following necrosis. J Clin Invest 125:539–550

Imai Y, Kubota Y, Yamamoto S, Tsuji K, Shimatani M, Shibatani N, Takamido S, Matsushita M, Okazaki K (2005) Neutrophils enhance invasion activity of human cholangiocellular carcinoma and hepatocellular carcinoma cells: an in vitro study. J Gastroenterol Hepatol 20:287–293

Ito R, Ishii Y, Wakiyama S, Shiba H, Fujioka S, Misawa T, Ishida Y, Hano H, Yanaga K (2014) Prognostic significance of receptor for advanced glycation and products expression in hepatocellular carcinoma after hepatectomy. J Surg Res 192:503–508

Jain RK, Booth MF (2003) What brings pericytes to tumor vessels ? J Clin Invest 112:1134–1136

Jing Y, Xue RM, Zhang ZY, Yao HW, Dong ZL (1993) Distribution and histochemical characteristics of mast cells in stroma of the cervix squamous cell carcinoma. Chin Med J (Engl) 106:698–702

Jing Y, Han Z, Zhang S, Liu Y, Wei L (2011) Epithelial-mesenchymal transition in tumor microenvironment. Cell Biosci 1:29

Joyce JA, Pollard JW (2009) Microenvironment regulation of metastasis. Nat Rev Cancer 9:239–252

Ju MJ, Qiu SJ, Fan J, Xiao YS, Gao Q, Zhou J, Li YW, Tang ZY (2009a) Peritumoral activated hepatic stellate cells predict poor clinical outcome in hepatocellular carcinoma after curative resection. Am J Clin Pathol 131:498–510

Ju MJ, Qiu SJ, Gao Q, Fan J, Cai MY, Li YW, Tang ZY (2009b) Combination of peritumoral mast cells and T-regulatory cells predicts prognosis of hepatocellular carcinoma. Cancer Sci 100:1267–1274

Kang N, Gores GJ, Shah VH (2011) Hepatic stellate cells: partners in crime for liver metastases? Hepatology 54:707–713

Kang N, Shah VH, Urrutia R (2015) Membrane-to-nucleus signals and epigenetic mechanisms for myofibroblastic activation and desmoplastic stroma: potential therapeutic targets for liver metastasis? Mol Cancer Res. 13:604–612

Kankuri E, Cholujova D, Comajova M, Vaheri A, Bizik J (2005) Induction of hepatocyte growth factor/ scatter factor by fibroblast clustering directly promotes tumor cell invasiveness. Cancer Res 65:9914–9922

Kankuri E, Babusikova O, Hlubinova K, Salmenprä P, Boccaccio C, Lubitz W, Harjula A et al (2008) Fibroblast nemesis arrests growth and induces differentiation of human leukemia cells. Int J Cancer 122:1243–1252

Karagiannis GS, Poutahidis T, Erdman SE, Kirsch R, Riddell RH, Diamandis EP (2012) Cancer-associated fibroblasts drive the progression of metastasis through both paracrine and mechanical pressure on cancer tissue. Mol Cancer Res 10:1403–1418

Karagiannis GS, Schaeffer DF, Cho CK, Musrap N, Saraon P, Batruch I, Grin A, Mitrovic B et al (2014) Collective migration of cancer-associated fibroblasts is enhanced by overexpression of tight junction-associated proteins claudin-11 and occluding. Mol Oncol 8:178–195

Kharaishvili G, Simkova D, Bouchalova K, Gachechiladze M, Narsia N, Bouchal J (2014) The role of cancer-associated fibroblasts, solid stress and other microenvironmental factors in tumor progression and therapy resistance. Cancer Cell Int 14:41

Keskinov AA, Shurin MR (2015) Myeloid regulatory cells in tumor spreading and metastasis. Immunobiology 220:236–242

Khaled YS, Ammori BJ, Elkord E (2013) Myeloid-derived suppressor cells in cancer: recent progress and prospects. Immunol Cell Biol 91:493–502

Kidd S, Spaeth E, Watson K, Burks J, Lu H, Klopp A, Andreeff M, Marini FC (2012) Origins of the tumor microenvironment: quantitative assessment of adipose-derived and bone marrow-derived stroma. PLoS ONE 7:e30563

Kikkawa Y, Sudo R, Kon J, Mizuguchi T, Nomizu M, Hirata K, Mitaka T (2008) Laminin alpha 5 mediates ectopic adhesion of hepatocellular carcinoma through integrins and/or Lutheran/basal cell adhesion molecule. Exp Cell Res 314:2579–2590

Kikuchi Y, Kunita A, Iwata C, Komura D, Nishiyama T, Shimazu K, Takeshita K, Shibahara J et al (2014) The niche component periostin is produced by cancer-associated fibroblasts, supporting growth of gastric cancer through ERK activation. Am J Pathol 184:859–870

Kim J, Hong SJ, Park JY, Park JH, Yu YS, Park YS, Lim EK, Choi KY, Lee EK et al (2010) Epithelial-mesenchymal transition gene signature to predict clinical outcome of hepatocellular carcinoma. Cancer Sci 101:1521–1528

Kim Y, Kim MO, Shin JS, Park SH, Kim SB, Kim J, Park SC, Han CJ, Ryu JK, Yoon YB, Kim YT (2014)

Hedgehog signaling between cancer cells and hepatic stellate cells in promoting cholangiocarcinoma. Ann Surg Oncol 21:2684–2698

Kinnman N, Francoz C, Barbu V, Wendum D, Rey C, Hultcrantz R, Poupon R, Housset C (2003) The myofibroblastic conversion of peribiliary fibrogenic cells distinct from hepatic stellate cells is stimulated by platelet-derived growth factor during liver fibrogenesis. Lab Invest 83:163–173

Kinsey R, Williamson MR, Chaudhry S, Mellody KT, McGovern A, Takahashi S, Shuttleworth CA et al (2008) Fibrillin-1 microfibril deposition is dependent on fibronectin assembly. J Cell Sci 121:2696–2704

Kinugasa Y, Matsui T, Takakura N (2014) CD44 expressed on cancer-associated fibroblasts is a functional molecule supporting the stemness and drug resistance of malignant cancer cells in the tumor microenvironment. Stem Cells 32:145–156

Kitano H, Kageyama SI, Hewitt SM, Hayashi R, Doki Y, Ozaki Y, Fujino S, Takikita M et al (2010) Podoplanin expression in cancerous stroma induces lymphangiogenesis and predicts lymphatic spread and patient survival. Arch Pathol Lab Med 134:1520–1527

Knox SM, Whitelock JM (2006) Perlecan : how does one molecule do so many things ? Cell Mol Life Sci 63:2435–2445

Kojima A, Kaneda K, Ueda M, Maki A, Takabayashi A, Fukushima S, Sakurai M, Nagai R et al (1999) Induction of smooth muscle cells in the fibrous capsule of human hepatocellular carcinoma but not in the septa of hepatic cirrhosis. Virchows Arch 434:413–422

Kolaczkowska E, Kubes P (2013) Neutrophils recruitment and function in health and inflammation. Nat Rev 13:159–175

Kondo Y, Shimosegawa T (2015) Significant roles of regulatory T cells and myeloid derived suppressor cells in hepatitis B virus persistent infection and hepatitis B virus-related HCCs. Int J Mol Sci 16:3307–3322

Kong C, Wang C, Wang L, Ma M, Niu C, Sun X, Du J, Dong Z, Zhu S, Lu J, Huang B (2011a) NEDD9 is a positive regulator of epithelial-mesenchymal transition and promotes invasion in aggressive breast cancer. PLoS ONE 6:e22666

Kong D, Li Y, Wang Z, Sarkar FH (2011b) Cancer stem cells and epithelial-to-mesenchymal transition (EMT)-phenotypic cells: are they cousins of twins? Cancers (Basel) 3:716–729

Kostova N, Zlateva S, Ugrinova I, Pasheva E (2010) The expression of HMGB1 protein and its receptor RAGE in human malignant tumors. Mol Cell Biochem 337:251–258

Kuang DM, Peng C, Zhao Q, Wu Y, Chen MS, Zheng L (2010) Activated monocytes in peritumoral stroma of hepatocellular carcinoma promote expansion of memory T helper 17 cells. Hepatology 51:154–164

Kuang DM, Thao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L (2011) Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol 54:948–955

Lapis K, Timar J (2002) Role of elastin-matrix interactions in tumor progression. Semin Cancer Biol 12:209–217

Lee JI, Campbell JS (2014) Role of desmoplasia in cholangiocarcinoma and hepatocellular carcinoma. J Hepatol 61:432–434

Lee KW, Yeo SY, Sung CO, Kim SH (2015) Twist1 is a key regulator of cancer-associated fibroblasts. Cancer Res 75:73–85

Lemoinne S, Cadoret A, El Mourabit H, Thabut D, Housset C (2013) Origins and functions of liver myofibroblasts. Biochim Biophys Acta 1832:948–954

Lemoinne S, Cadoret A, Rautou PE, El Mourabit H, Ratziu V, Corpechot C, Rey C, Bosselut N, Barbu V et al (2014) Portal myofibroblasts promote vascular remodeling underlying cirrhosis formation through the release of microparticles. Hepatology. doi:10.1002/hep.27318

Li HG, Xie DR, Shen XM, Li HH, Zeng H, Zeng YJ (2005) Clinicopathological significance of expression of paxillin, syndecan-1 and EMMPRIN in hepatocellular carcinoma. World J Gastroenterol 11:1445–1451

Li H, Fan X, Houghton J (2007) Tumor microenvironment: the role of the tumor stroma in cancer. J Cell Biochem 101:805–815

Li YW, Qiu SJ, Fan J, Zhou J, Gao Q, Xiao YS, Xu YF (2011) Intratumoral neutrophils: a poor prognostic factor for hepatocellular carcinoma following resection. J Hepatol 54:497–505

Li J, Chen L, Qin Z (2012) Multifaceted tumor stromal fibroblasts. Cancer Microenviron 5:187–193

Li GC, Ye QH, Dong QZ, Ren N, Jia HL, Qin LX (2013a) Mesenchymal stem cells seldomly fuse with hepatocellular carcinoma cells and are mainly distributed in the tumor stroma in mouse models. Oncol Rep 29:713–719

Li Y, Wang J, Asahina K (2013b) Mesothelial cells give rise to hepatic stellate cells and myofibroblasts via mesothelial-mesenchymal transition in liver injury. Proc Natl Acad Sci U S A 110:2324–2329

Li X, Li P, Chang Y, Xu Q, Wu Z, Ma Q, Wang Z (2014) The SDF-1/CXCR4 axis induces epithelial-mesenchymal transition in hepatocellular carcinoma. Mol Cell Bochem 392:77–84

Li XF, Chen DP, Ouyang FZ, Chen MM, Wu Y, Kuang DM, Zheng L (2015) Increased autophagy sustains the survival and pro-tumourigenic effects of neutrophils in human hepatocellular carcinoma. J Hepatol 62:131–139

Liao R, Sun TW, Yi Y, Wu H, Li YW, Wang JX, Zhou J, Shi YH, Cheng YF, Qiu SJ et al (2012) Expression of TREM-1 in hepatic stellate cells and prognostic value in hepatitis B-related hepatocellular carcinoma. Cancer Sci 103:984–992

Liao R, Wu H, Yi Y, Wang JX, Cai XY, He HW, Cheng YF, Zhou J, Fan J, Sun J et al (2013) Clinical significance and gene expression study of human hepatic stellate cells in HBV related-hepatocellular carcinoma. J Exp Clin Cancer Res 32:22

Lin ZY, Chuang WL (2013) Hepatocellular carcinoma cells cause different responses in expressions of cancer-promoting genes in different cancer-associated fibroblasts. Kaohsiung J Med Sci 29:312–318

Lin ZY, Chuang YH, Chuang WL (2012) Cancer-associated fibroblasts up-regulate CCL2, CCL26, IL6, and LOXL2 genes related to promotion of cancer progression in hepatocellular carcinoma cells. Biomed Pharmacother 66:525–529

Lin N, Chen Z, Lu Y, Li Y, Hu K, Xu R (2014) Role of activated hepatic stellate cells in proliferation and metastasis of hepatocellular carcinoma. Hepatol Res. doi:10.1111/hepr.12356

Lindau D, Gielen P, Kroesen M, Wesseling P, Adema GJ (2013) The immunosuppressive tumour network: myeloid-derived suppressor cells, regulatory T cells and natural killer T cells. Immunology 138:105–115

Lisanti MP, Martinez-Outschoo UE, Sotgia F (2013) Oncogenes induce the cancer-associated fibroblast phenotype: metabolic symbiosis and "fibroblast addiction" are new therapeutic targets for drug discovery. Cell Cycle 12:2723–2732

Liu WR, Tian MX, Yang LX, Lin YL, Jin L, Ding ZB, Shen YH, Peng YF, Gao DM, Zhou J, Qiu SJ, Dai Z, He R et al (2015) PKM2 promotes metastasis by recruiting myeloid-derived suppressor cells and indicates poor prognosis for hepatocellular carcinoma. Oncotarget 6:846–861

Lockwood DS, Yeadon TM, Clouston AD, Crawford DG, Fawcett J, Callaghan SA et al (2003) Tumor progression in hepatocellular carcinoma: relationship with tumor stroma and parenchymal disease. J Gastroenterol Hepatol 18:666–672

Longerich T, Breuhahn K, Odenthal M, Petmecky K, Schirmacher P (2004) Factors of transforming growth factor beta signalling are co-regulated in human hepatocellular carcinoma. Virchows Arch 445:589–596

Lotze MT, DeMarco RA (2003) Dealing with death: HMGB1 as a novel target for cancer therapy. Curr Opin Investig Drugs 4:1405–1409

Luciani MG, Seok J, Sayeed A, Champion S, Goodson WH, Jeffrey SS, Xiao W et al (2011) Distinctive responsiveness to stromal signaling accompanies histologic grade programming of cancer cells. PLoS ONE 6:e20016

Lv H, Yu G, Sun L, Zhang Z, Zhao X, Chai W (2007) Elevate level of glycosaminoglycans and altered pattern of chondroitin sulfate are associated with differentiation status and histological type of human primary hepatic carcinoma. Oncology 72:347–356

Ma S, Cheng Q, Cai Y, Gong H, Wu Y, Yu X, Shi L, Wu D, Dong C, Liu H (2014) IL-17A produced by γδ T cells promotes tumor growth in hepatocellular carcinoma. Cancer Res 74:1969–1982

Mabuchi A, Mullaney I, Sheard PW, Hessian PA, Mallard BL, Tawadrous MN, Zimmermann A, Senoo H, Wheatley AM (2004) Role of hepatic stellate cell/hepatocyte interaction and activation of hepatic stellate cells in the early phase of liver regeneration in the rat. J Hepatol 40:910–916

Madar S, Goldstein I, Rotter V (2013) 'Cancer associated fibroblasts' – more than meets the eye. Trends Mol Med 19:447–453

Madsen DH, Bugge TH (2013) Imaging collagen degradation in vivo highlights a key role for M2-polarized macrophages in extracellular matrix degradation. Oncoimmunology 12:e27127

Magistri P, Leonard SY, Tang CM, Chan JC, Lee TE, Sicklick JK (2014) The glypican 3 hepatocellular carcinoma marker regulates human hepatic stellate cells via Hedgehog signaling. J Surg Res 187:377–385

Marijon H, Dokmak S, Paradis V, Zappa M, Bieche I, Bouattour M, Raymond E, Faivre S (2011) Epithelial-mesenchymal transition and acquired resistance to sunitinib in a patient with hepatocellular carcinoma. J Hepatol 54:1073–1078

Marsh T, Pietras K, McAllister SS (2013) Fibroblasts as architects of cancer pathogenesis. Biochim Biophys Acta 1832:1070–1078

Martinez-Outschoom UE, Lisanti MP, Sotgia F (2014) Catabolic cancer-associated fibroblasts transfer energy and biomass to anabolic cancer cells, fueling tumor growth. Semin Cancer Biol 25:47–60

Massam-Wu T, Chiu M, Choudhury R, Chaudhry SS, Baldwin AK, McGovern A, Baldock C et al (2010) Assembly of fibrillin microfibrils governs extracellular deposition of latent TGF beta. J Cell Sci 123:3006–3018

Masyuk AI, Masyuk TV, Larusso NF (2013) Exosomes in the pathogenesis, diagnostics and therapeutics of liver diseases. J Hepatol 59:621–625

Matsumoto A, Ono M, Fujimoto Y, Gallo RL, Bernfield M, Kohgo Y (1997) Reduced expression of syndecan-1 in human hepatocellular carcinoma with high metastatic potential. Int J Cancer 74:482–491

Mazzocca A, Fransvea E, Dituri F, Lupo L, Antonaci S, Giannelli G (2010) Down-regulation of connective tissue growth factor by inhibition of transforming growth factor beta blocks the tumor-stroma cross-talk and tumor progression in hepatocellular carcinoma. Hepatology 51:523–534

McCarty MF, Somcio RJ, Stoeltzing O, Wey J, Fan F, Liu W, Bucana C, Ellis LM (2007) Overexpression of PDGF-BB decreases colorectal and pancreatic cancer growth by increasing tumor pericyte content. J Clin Invest 117:2114–2122

Medici D, Kalluri R (2012) Endothelial-mesenchymal transition and its contribution to the emergence of stem cell phenotype. Semin Cancer Biol 22:379–384

Meindl-Beinker NM, Matsuzaki K, Dooley S (2012) TGF-b signaling in onset and progression of hepatocellular carcinoma. Dig Dis 30:514–523

Micalizzi DS, Farabaugh SM, Ford HL (2010) Epithelial-mesenchymal transition in cancer: parallels between normal development and tumor progression. J Mammary Gland Biol Neoplasia 15:117–134

Midorikawa Y, Ishikawa S, Iwanari H, Imamura T, Sakamoto H, Miyazono K, Kodama T, Makuuchi M, Aburatani H (2003) Glypican-3, overexpressed in hepatocellular carcinoma, modulates FGF2 and BMP-7 signaling. Int J Cancer 103:455–465

Mikulits W (2009) Epithelial to mesenchymal transition in hepatocellular carcinoma. Future Oncol 5:1169–1179

Mikuriya Y, Tashiro H, Kuroda S, Nambu J, Kobayashi T, Amano H, Tanaka Y, Ohdan H (2015) Fatty liver creates a pro-metastatic microenvironment for hepatocellular carcinoma through activation of hepatic stellate cells. Int J Cancer 136:E3–E13

Miles FL, Sikes RA (2014) Insidious changes in stromal matrix fuel cancer progression. Mol Cancer Res 12:297–312

Mitra AK, Zillhardt M, Hua Y, Tiwari P, Murmann AE, Peter ME, Lengyel E (2012) MicroRNAs reprogram normal fibroblasts into cancer-associated fibroblasts in ovarian cancer. Cancer Discov 2:1100–1108

Morello M, Minciacchi VR, de Candia P, Yang J, Posadas E, Kim H, Griffiths D, Bhowmick N et al (2013) Large oncosomes mediate intercellular transfer of functional microRNA. Cell Cycle 12:3526–3536

Moreno A, Soleto I, Garcia-Sanz P, Moreno-Bueno G, Palmero I (2014) ING4 regulates a secretory phenotype in primary fibroblasts with dual effects on cell proliferation and tumor growth. Oncogene 33:1945–1953

Morra L, Moch H (2011) Periostin expression and epithelial-mesenchymal transition in cancer: a review and an update. Virchows Arch 459:465–475

Mueller L, Goumas FA, Affeldt M, Sandtner S, Gehling UM, Brilloff S, Walter J, Karnatz N, Lamszus K, Rogiers X et al (2007) Stromal fibroblasts in colorectal liver metastases originate from resident fibroblasts and generate an inflammatory microenvironment. Am J Pathol 171:1608–1618

Murata K, Suzuki H, Okano H, Oyamada T, Yasuda Y, Sakamoto A (2009) Cytoskeletal changes during epithelial-to-fibroblastoid conversion as a crucial mechanism of des-gamma-carboxy prothrombin production in hepatocellular carcinoma. Int J Oncol 35:1005–1014

Muturi HT, Dreesen JD, Nilewski E, Jastrow H, Giebel B, Ergun S, Singer BB (2013) Tumor and endothelial cell-derived microvesicles carry distinct CEACAMs and influence T-cell behavior. PLoS ONE 8:e74654

Na DC, Lee JE, Yoo JE, Oh BK, Choi GH, Park YN (2011) Invasion and EMT-associated genes are up-regulated in B viral hepatocellular carcinoma with high expression of CD133-human and cell culture study. Exp Mol Pathol 90:66–73

Nakagawa H, Liyanarachchi S, Davuluri RV, Auer H, Martin EW, de la Chapelle A, Frankel WL (2004) Role of cancer-associated stromal fibroblasts in metastatic colon cancer to the liver and their expression profiles. Oncogene 23:7366–7377

Nazarenko I, Rupp AK, Altevogt P (2013) Exosomes as a potential tool for a specific delivery of functional molecules. Methods Mol Biol 1049:495–511

Neaud V, Faouzi S, Guirouilh J, Monvoisin A, Rosenbaum J (1999) Hepatocyte growth factor secreted by human liver myofibroblasts increases invasiveness of hepatocellular carcinoma cells. Curr Top Pathol 93:195–203

Nhieu JT, Brochériou I, Préaux AM, Mallat A, Cherqui D, Zafrani ES, Mavier P (1998) Myofibroblasts and hepatocellular carcinoma: an in vivo and in vitro study. J Hepatol 29:120–128

Nyström H, Naredi P, Berglund A, Palmqvist R, Tavelin B, Sund M (2012) Liver-metastatic potential of colorectal cancer is related to the stromal composition of the tumour. Anticancer Res 32:5183–5191

Öhlund D, Elyada E, Tuveson D (2014) Fibroblast heterogeneity in the cancer wound. J Exp Med 211:1503–1523

Okabe H, Beppu T, Hayashi H, Horino K, Masuda T, Komori H, Ishikawa S, Watanabe M et al (2009) Hepatic stellate cells may relate to progression of intrahepatic cholangiocarcinoma. Ann Surg Oncol 16:2555–2564

Okamoto K, Tajima H, Nakanuma S, Sakai S, Makino I, Kinoshita J, Hayashi H, Nakamura K, Oyama K et al (2012) Angiotensin II enhances epithelial-to-mesenchymal transition through the interaction between activated hepatic stellate cells and the stromal cell-derived factor-1/CXCR4 axis in intrahepatic cholangiocarcinoma. Int J Oncol 41:573–582

Okamura N, Yoshida M, Shibuya A, Sugiura H, Okayasu I, Ohbu M (2005) Cellular and stromal characteristics in the scirrhous hepatocellular carcinoma: comparison with hepatocellular carcinomas and intrahepatic cholangiocarcinomas. Pathol Int 55:724–731

Ooi LL (1999) 3rd Yahya Cohen lecture: the role of the myofibroblast-like cell in hepatocellular carcinoma – host defense? Ann Acad Med Singap 28:342–346

Ooi LP, Crawford DH, Gotley DC, Clouston AD, Strong RW, Gobe GC, Halliday JW et al (1997) Evidence that "myofibroblast-like" cells are the cellular source of capsular collagen in hepatocellular carcinoma. J Hepatol 26:798–807

Orimo A, Weinberg RA (2006) Stromal fibroblasts in cancer: a novel tumor-promoting cell type. Cell Cycle 5:1597–1601

Österreicher CH, Penz-Österreicher M, Grivennikov SI, Guma M, Koltsova EK, Datz C et al (2011) Fibroblast-specific protein 1 identifies an inflammatory subpopulation of macrophages in the liver. Proc Natl Acad Sci U S A 108:308–313

Östman A, Augsten M (2009) Cancer-associated fibroblasts and tumor growth – bystanders turning into key players. Curr Opin Genet Dev 19:67–73

Otranto M, Sarrazy V, Bonté F, Hinz B, Gabbiani G, Desmouliere A (2012) The role of the myofibroblast in tumor stroma remodeling. Cell Adhes Migr 6:203–219

Ozaki I, Yamamoto K, Mizuta T, Kajihara S, Fukushima N, Setoguchi Y, Morito F, Sakai T (1998) Differential expression of laminin receptors in human hepatocellular carcinoma. Gut 43:837–842

Patriarca C, Roncalli M, Gambacorta M, Cominotti M, Coggi G, Viale G (1993) Patterns of integrin common chain beta 1 and collagen IV immunoreactivity in hepatocellular carcinoma. Correlations with tumour growth rate, grade and size. J Pathol 171:5–11

Paulsson J, Micke P (2014) Prognostic relevance of cancer associated fibroblasts in human cancer. Semin Cancer Biol 25:61–68

Peña C, Céspedes MV, Lindh MB, Kiflemariam S, Mezheyeuski A, Edqvist PH, Hägglöf C et al (2013) STC1 expression by cancer-associated fibroblasts drives metastasis of colorectal cancer. Cancer Res 73:1287–1297

Peura M, Bizik J, Salemperä P, Noro A, Korhonen M, Pätilä T, Vento A, Vaheri A et al (2009) Bone marrow mesenchymal stem cells undergo nemosis and induce keratinocyte wound healing utilizing the HGF (cMet/PI3K pathway. Wound Repair Regen 17:569–577

Pickard A, Cichon AC, Barry A, Kieran D, Patel D, Hamilton P, Salto-Tellez M, James J et al (2012) Inactivation of Rb in stromal fibroblasts promotes epithelial cell invasion. EMBO J 31:3092–3103

Pietras and Őstman 2010. http://www.ncbi.nlm.nih.gov/pubmed/20211171

Pula B, Wojnar A, Witkiewicz W, Dziegiel P, Podhosrska-Okolow M (2013a) Podoplanin expression in cancer-associated fibroblasts correlates with VEGF-C expression in cancer cells of invasive ductal breast carcinoma. Neoplasma 60:516–524

Pula B, Witkiewicz W, Dziegiel P, Podhorska-Okolow M (2013b) Significance of podoplanin expression in cancer-associated fibroblasts: a comprehensive review. Int J Oncol 42:1849–1857

Quail DF, Joyce JA (2013) Microenvironmental regulation of tumor progression and metastasis. Nat Med 19:1423–1437

Raa ST, Oosterling SJ, van der Kaaij NP, van den Tol MP, Beelen TH, Meijer S et al (2005) Surgery promotes implantation of disseminated tumor cells, but does not increase growth of tumor cell clusters. J Surg Oncol 92:124–129

Ralph SJ, Rodriguez-Enriquez S, Neuzil J, Saavedra E, Moreno-Sanchez R (2010) The causes of cancer revisited: "mitochondrial malignancy" and ROS-induced oncogenic transformation – why mitochondria are targets for cancer therapy. Mol Asp Med 31:145–170

Rana S, Yue S, Stadel D, Zöller M (2012) Toward tailored exosomes: the exosomal tetraspanin web contributes to target cell selection. Int J Biochem Cell Biol 44:1574–1584

Rana S, Malinowska K, Zöller M (2013) Exosomal tumor microRNA modulates premetastatic organ cells. Neoplasia 15:281–295

Räsänen K, Vaheri A (2010) Activation of fibroblasts in cancer stroma. Exp Cell Res 316:2713–2722

Räsänen K, Salmenperä P, Baumann M, Virtanen I, Vaheri A (2008) Nemosis of fibroblasts is inhibited by benign HaCaT keratinocytes but promoted by malignant HaCaT cells. Mol Oncol 2:340–348

Räsänen K, Virtanen I, Salmenperä P, Grenman R, Vaheri A (2009) Differences in the nemosis response of normal and cancer-associated fibroblasts from patients with oral squamous cell carcinoma. PLoS ONE 4, e6879

Raz Y, Erez N (2013) An inflammatory vicious cycle: fibroblasts and immune cell recruitment in cancer. Exp Cell Res 319:1596–1603

Raza A, Franklin MJ, Dudek AZ (2010) Pericytes and vessel maturation during angiogenesis and metastasis. Am J Hematol 85:593–598

Rizvi S, Mertens JC, Bronk SF, Hirsova P, Dai H, Roberts LR, Kaufmann SH, Gores GJ (2014) Platelet-derived growth factor primes cancer-associated fibroblasts for apoptosis. J Biol Chem 289:22835–22849

Rodgers UR, Weiss AS (2005) Cellular interactions with elastin. Pathol Biol (Paris) 53:390–398

Rombouts K, Carloni V (2013) The fibrotic microenvironment as a heterogeneity facet of hepatocellular carcinoma. Fibrogenesis Tissue Repair 6:17

Roskams T, De Vos R, David G, Van Damme B, Desmet V (1998) Heparan sulphate proteoglycan expression in human primary liver tumours. J Pathol 185:290–297

Royer C, Lu X (2011) Epithelial cell polarity: a major gatekeeper against cancer? Cell Death Differ 18:1470–1477

Sabit H, Tsuneyama K, Shimonishi T, Harada K, Cheng J, Ida H, Saku T, Saito K, Nakanuma Y (2001) Enhanced expression of basement-membrane-type heparan sulfate proteoglycan in tumor fibro-myxoid stroma of intrahepatic cholangiocarcinoma. Pathol Int 51:248–256

Samuel CS, Mookerjee I, Halls ML, Summers RJ, Chew E, Bathgate RA, Tregear GW et al (2009) Investigations into the inhibitory effects of relaxin on renal myofibroblast differentiation. Ann NY Acad Sci 1160:294–299

Santamato A, Fransvea E, Dituri F, Caligiuri A, Quaranta M, Niimi T, Pinzani M, Antonaci S, Giannelli G (2011) Hepatic stellate cells stimulate HCC cell migration via laminin-5 production. Clin Sci (Lond) 121:159–168

Sassoli C, Chellini F, Pini A, Tani A, Nistri S, Nosi D, Zecchi-Orlandini S, Bani D, Formigli L (2013) Relaxin prevents cardiac fibroblast-myofibroblast transition via notch-1-mediated inhibition of TGF-b/Smad3 signaling. PLoS ONE 8, e63896

Satoyoshi R, Kuriyama S, Aiba N, Yashiro M, Tanaka M (2014) Asporin activates coordinated invasion of scirrhous gastric cancer and cancer-associated fibroblasts. Oncogene. doi:10.1038/onc.2013.584

Scherz-Shouval R, Santagata S, Mendillo ML, Sholl LM, Ben-Aharon I, Beck AH, Dias-Santagata D, Koeva M

et al (2014) The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. Cell 158:564–578
Schliekelman MJ, Gibbons DL, Faca VM, Creighton CJ, Rizvi ZH, Zhang Q, Wong CH et al (2011) Targets of the tumor suppressor miR-200 in regulation of the epithelial-mesenchymal transition in cancer. Cancer Res 71:7670–7682
Schmitt-Gräff A, Krüger S, Bochard F, Gabbiani G, Denk H (1991) Modulation of alpha smooth muscle actin and desmin expression in perisinusoidal cells of normal and diseased human livers. Am J Pathol 138:1233–1242
Segade F (2009) Functional evolution of the microfibril-associated glycoproteins. Gene 439:43–54
Seok JY, Na DC, Woo HG, Roncalli M, Kwon SM, Yoo JE, Ahn EY, Kim GI, Choi JS et al (2012) A fibrous stromal component in hepatocellular carcinoma reveals a cholangiocarcinoma-like gene expression trait and epithelial-mesenchymal transition. Hepatology 55:1776–1786
Servais C, Erez N (2013) From sentinel cells to inflammatory culprits: cancer-associated fibroblasts in tumour-related inflammation. J Pathol 229:198–207
Shieh AC, Rozansky HA, Hinz B, Swartz MA (2011) Tumor cell invasion is promoted by interstitial flow-induced matrix priming by stromal fibroblasts. Cancer Res 71:790–800
Shih YT, Wang MC, Zhou J, Peng HH, Lee DY, Chiu JJ (2015) Endothelial progenitors promote hepatocarcinoma intrahepatic metastasis through monocyte chemotactic protein-1 induction of microRNA-21. Gut 64:1132–1147
Simon-Assmann 2013. http://www.ncbi.nlm.nih.gov/pubmed/23263365
Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ (2010) HMGB1 and RAGE in inflammation and cancer. Annu Rev Immunol 28:367–388
Sirica AE (2011) The role of cancer-associated myofibroblasts in intrahepatic cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 9:44–54
Sirica AE, Gores GJ (2014) Desmoplastic stroma and cholangiocarcinoma: clinical implications and therapeutic targeting. Hepatology 59:2397–2402
Sirica AE, Campbell DJ, Dumur CI (2011) Cancer-associated fibroblasts in intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol 27:276–284
Sirica AE, Almenara JA, Li C (2014) Periostin in intrahepatic cholangiocarcinoma: pathobiological insights and clinical implications. Exp Mol Pathol 97:515–524
Sivridis E, Giatromanolaki A, Koukourakis MI (2004) "Stromatogenesis" and tumor progression. Int J Surg Pathol 12:1–9
Slany A, Haudek-Prinz V, Zwicki H, Stättner S, Grasl-Kraupp B, Gerner C (2013) Myofibroblasts are important contributors to human hepatocellular carcinoma: evidence for tumor promotion by proteome profiling. Electrophoresis 34:3315–3325
Sleeman JP (2012) The metastatic niche and stromal progression. Cancer Metastasis Rev 31:429–440
Spaeth EL, Labaff AM, Toole BP, Klopp A, Andreeff M, Marini FC (2013) Mesenchymal CD44 expression contributes to the acquisition of an activated fibroblast phenotype via TWIST activation in the tumor microenvironment. Cancer Res 73:5347–5359
Spicer JD, McDonald B, Cools-Lartigue JJ, Chow SC, Giannias B, Kubes P, Ferri LE (2012) Neutrophils promote liver metastasis via Mac-1-mediated interactions with circulating tumor cells. Cancer Res 72:3919–3927
Song et al. 2015. http://www.ncbi.nlm.nih.gov/pubmed/25449435
Su Q, Fu Y, Liu YF, Zhang W, Liu J, Wang CM (2003) Laminin induces the expression of cytokeratin 19 in hepatocellular carcinoma cells growing in culture. World J Gastroenterol 9:921–929
Sulpice L, Rayar M, Desille M, Turlin B, Fautrel A, Boucher E, Llamas-Gutierrez F, Meunier B, Boudjema K et al (2013) Molecular profiling of stroma identifies osteopontin as an independent predictor of poor prognosis in intrahepatic cholangiocarcinoma. Hepatology 58:1992–2000
Sun B, Zhang X, Cheng X, Zhang Y, Chen L, Shi L, Liu Z, Qian H, Wu M, Yin Z (2013) Intratumoral hepatic stellate cells as a poor prognostic marker and a new treatment target for hepatocellular carcinoma. PLoS ONE 8, e80212
Sun Z, Wang S, Zhao RC (2014) The roles of mesenchymal stem cells in tumor inflammatory microenvironment. J Hematol Oncol 7:14
Sutton A, Friand V, Brulé-Donnegger S, Chaigneau T, Ziol M, Sainte-Catherine O, Poiré A et al (2007) Stromal cell-derived factor-1/chemokine (C-X-C motif) ligand 12 stimulates human hepatoma cell growth, migration, and invasion. Mol Cancer Res 5:21–33
Szabo E, Korpos E, Batmunkh E, Lotz G, Holczbauer A, Kovalszky I, Deak F, Kiss I et al (2008) Expression of matrilin-2 in liver cirrhosis and hepatocellular carcinoma. Pathol Oncol Res 14:15–22
Szendröi M, Lapis K (1985) Distribution of fibronectin and laminin in human liver tumors. J Cancer Res Clin Oncol 109:60–64
Takino J, Yamagishi S, Takeuchi M (2012) Glycer-AGEs-RAGE signaling enhances the angiogenic potential of hepatocellular carcinoma by upregulating VEGF expression. World J Gastroenterol 18:1781–1788
Tatrai P, Somoracz A, Batmunkh E, Schirmacher P, Kiss A, Schaff Z, Nagy P, Kovalszky I (2009) Agrin and CD34 immunohistochemistry for the discrimination of benign versus malignant hepatocellular lesions. Am J Surg Pathol 33:874–885
Tchou J, Zhang PJ, Bi Y, Satija C, Marjumadar R, Stephen TL, Lo A, Chen H, Mies C et al (2014) Fibroblast activation protein expression by stromal cells and tumor-associated macrophages in human breast cancer. Hum Pathol 45:1553–1554

Terada T, Matsunaga Y (2000) Increased mast cells in hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Hepatol 33:961–966

Terada T, Nakanuma Y (1994) Expression of tenascin, type IV collagen and laminin during human intrahepatic bile duct development and in intrahepatic cholangiocarcinoma. Histopathology 25:143–150

Terada T, Makimoto K, Terayama N, Suzuki Y, Nakanuma Y (1996) Alpha-smooth muscle actin-positive stromal cells in cholangiocarcinomas, hepatocellular carcinomas and metastatic liver carcinomas. J Hepatol 24:706–712

Toh B, Wang X, Keeble J, Sim WJ, Khoo K, Wong WC, Kato M, Prevost-Blondel A et al (2011) Mesenchymal transition and dissemination of cancer cells is driven by myeloid-derived suppressor cells infiltrating the primary tumor. PLoS ONE 9, e1001162

Torimura T, Ueno T, Inuzuka S, Kin M, Ohira H, Kimura Y, Majima Y, Sata M, Abe H et al (1994) The extracellular matrix in hepatocellular carcinoma shows different localization patterns depending on the differentiation and the histological pattern of tumors: immunohistochemical analysis. J Hepatol 21:37–46

Tripathi M, Billet S, Bhowmick NA (2012) Understanding the role of stromal fibroblasts in cancer progression. Cell Adhes Migr 6:231–235

Trosko JE, Chang CC (2001) Mechanism of up-regulated gap junctional intercellular communication during chemoprevention and chemotherapy of cancer. Mutat Res 480–481:219–229

Trosko JE, Ruch RJ (1998) Cell-cell communication in carcinogenesis. Front Biosci 3:d208–d236

Tsujino T, Seshimo I, Yamamoto H, Ngan CY, Ezumi K, Takemasa I, Ikeda M, Sekimoto M, Matsuura N, Monden M (2007) Stromal myofibroblasts predict disease recurrence for colorectal cancer. Clin Cancer Res 13:2082–2090

Tsukamoto H, Zhu NL, Wang J, Asahina K, Machida K (2012) Morphogens and hepatic stellate cell fate regulation in chronic liver disease. J Gastroenterol Hepatol 27(Suppl 2):94–98

Tu T, Budzinska MA, Maczurek AE, Cheng R, Di Bartolomeo A, Warner FJ, McCaughan GW, McLennan SV et al (2014) Novel aspects of the liver microenvironment in hepatocellular carcinoma pathogenesis and development. Int J Mol Sci 15:9422–9458

Tubiana M (2009) Prevention of cancer and the dose-effect relationship: the carcinogenic effects of ionizing radiations (in French). Cancer Radiother 13:238–258

Uemura Y, Okamoto K (1997) Elastin-derived peptide induces monocyte chemotaxis by increasing intracellular cyclic GMP level and activating cyclic GMP dependent protein kinase. Biochem Mol Biol Int 41:1085–1092

Urech C (2014) Identification of tumor-stroma interactions crucial for the establishment of liver metastasis. Thesis 6148, Federal Polytechnical School, Lausanne

Vaheri A, Enzerink A, Räsänen K, Salmenprä P (2009) Nemosis, a novel way of fibroblast activation, in inflammation and cancer. Exp Cell Res 315:1633–1638

Van Zijl F, Mair M, Csiszar A, Schneller D, Zulehner G, Huber H, Eferl R, Beug H et al (2009) Hepatic tumor-stroma crosstalk guides epithelial to mesenchymal transition at the tumor edge. Oncogene 28:4022–4033

Venkov C, Plieth D, Ni T, Karmaker A, Bian A, George AL, Neilson EG (2011) Transcriptional networks in epithelial-mesenchymal transition. PLoS ONE 6: e25354

Volpes R, van den Oord JJ, Desmet VJ (1993) Integrins as differential cell lineage markers of primary liver tumors. Am J Pathol 142:1483–1492

Vorobjeva NV, Pinegin BV (2014) Neutrophil extracellular traps: mechanisms of formation and role in health and disease. Biochemistry (Mosc) 79:1286–1296

Wang H, Chen L (2013) Tumor microenvironment and hepatocellular carcinoma metastasis. J Gastroenterol Hepatol 28(Suppl 1):43–48

Wang RF, Zhang LH, Shan LH, Sun WG, Chai CC, Wu HM, Ibla JC, Wang LF et al (2013) Effects of the fibroblast activation protein on the invasion and migration of gastric cancer. Exp Mol Pathol. pii: S0014-4800(13)00125-1

Webber JP, Spary LK, Sanders AJ, Chowdhury R, Jiang WG, Steadman R, Wymant J et al (2014) Differentiation of tumour-promoting stromal myofibroblasts by cancer exosomes. Oncogene. doi:10.1038/onc.2013.560

Weber CE, Kothari AN, Wai PY, Li NY, Driver J, Zapf MA, Franzen CA, Gupta GN, Osipo C, Zlobin A et al (2014) Osteopontin mediates an MZF1-TGF-β1-dependent transformation of mesenchymal stem cells into cancer-associated fibroblasts in breast cancer. Oncogene. doi:10.1038/onc.2014.410

Wells RG (2014) The portal fibroblast: not just a poor man's stellate cell. Gastroenterology 147:41–47

Wells A, Chao YL, Grahovac J, Wu Q, Lauffenburger DA (2011) Epithelial and mesenchymal phenotypic switchings modulate cell motility in metastasis. Front Biosci 16:815–837

Whitaker-Menezes D, Martinez-Outschoom UE, Lin Z, Ertel A, Flomenberg N, Witkiewicz AK et al (2011) Evidence for a stromal-epithelial "lactate-shuttle" in human tumors: MCT4 is a marker of oxidative stress in cancer-associated fibroblasts. Cell Cycle 10:1772–1783

Williams EJ, Benyon RC, Trim N, Hadwin R, Grove BH, Arthur MJ, Unemori EN et al (2001) Relaxin inhibits effective collagen deposition by cultured hepatic stellate cells and decreases rat liver fibrosis in vivo. Gut 49:577–583

Wu XZ, Chen D, Xie GR (2006) Extracellular matrix remodeling in hepatocellular carcinoma: effects of soil on seed ? Med Hypotheses 66:1115–1120

Wu Y, Zhao Q, Peng C, Sun L, Li XF, Kuang DM (2011) Neutrophils promote motility of cancer cells via a hyaluronan-mediated TLR4/PI3K activation loop. J Pathol 225:438–447

Wu SD, Ma YS, Fang Y, Liu LL, Fu D, Shen XZ (2012) Role of the microenvironment in hepatocellular carcinoma development and progression. Cancer Treat Rev 38:218–225

Xiao Y, Kleeff J, Guo J, Gazdhar A, Liao Q, Di cesare PE, Büchler MW, Friess H (2004) Cartilage oligomeric matrix protein expression in hepatocellular carcinoma and the cirrhotic liver. J Gastroenterol Hepatol 19:296–302

Xiao WK, Chen D, Li SQ, Fu SJ, Peng BG, Liang LJ (2014) Prognostic significance of neutrophil-lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. BMC Cancer 14:117

Xing F, Saidou J, Watabe K (2010) Cancer associated fibroblasts (CAFs) in tumor microenvironment. Front Biosci 15:166–179

Xouri G, Christian S (2010) Origin and function of tumor stroma fibroblasts. Semin Cell Dev Biol 21:40–46

Yamada S, Ichida T, Matsuda Y, Miyazaki Y, Hatano T, Hata K, Asakura H, Hirota N et al (1992) Tenascin expression in human chronic liver disease and in hepatocellular carcinoma. Liver 12:10–16

Yamanashi T, Nakanishi Y, Fujii G, Akishima-Fukasawa Y, Moriya Y, Kanai Y, Watanabe M, Hirohashi S (2009) Podoplanin expression identified in stromal fibroblasts as a favorable prognostic marker in patients with colorectal carcinoma. Oncology 77:53–62

Yamazaki K, Masugi Y, Sakamoto M (2011) Molecular pathogenesis of hepatocellular carcinoma: altering transforming growth factor-b signaling in hepatocarcinogenesis. Dig Dis 29:284–288

Yaser AM, Huang Y, Zhou RR, Hu GS, Xiao MF, Huang ZB, Duan CJ, Tian W, Tang DL, Fan XG (2012) The role of receptor for advanced glycation end products (RAGE) in the proliferation of hepatocellular carcinoma. Int J Mol Sci 13:5982–5997

Yoshida K, Murata M, Yamaguchi T, Matsuzaki K (2014) TGF-β/Smad signaling during hepatic fibrocarcinogenesis (review). Int J Oncol 45:1363–1371

Yu G, Jing Y, YeGao L, Fan Q, Yang Y, Zhao Q, Li R, Wu M, Wei L (2013) Hepatic stellate cells secreted hepatocyte growth factor contributes to the chemoresistance of hepatocellular carcinoma. PLoS ONE 8:e73312

Yu Y, Xiao CH, Tan LD, Wang QS, Li XQ, Feng YM (2014) Cancer-associated fibroblasts induce epithelial-mesenchymal transition of breast cancer cells through paracrine TGF-b signalling. Br J Cancer 110:724–732

Yusa T, Blood CH, Zetter BR (1989) Tumor cell interactions with elastin: implications for pulmonary metastasis. Am Rev Respir Dis 140:1458–1462

Zhan S, Chan CC, Serdar B, Rockey DC (2009) Fibronectin stimulates endothelin-1 synthesis in rat hepatic myofibroblasts via a Src/ERK-regulated signaling pathway. Gastroenterology 136:2345–2355

Zhang XL, Huang CX, Zhang J, Inoue A, Zeng SE, Xiao SJ (2013a) CtBP1 is involved in epithelial-mesenchymal transition and is a potential therapeutic target for hepatocellular carcinoma. Oncol Rep 30:809–814

Zhang H, Maric I, Diprima MJ, Khan J, Orentas RJ, Kaplan RN, Mackall CL (2013b) Fibrocytes represent a novel MDSC subset circulating in patients with metastatic cancer. Blood 122:1105–1113

Zhao M, Laissue JA, Zimmermann A (1996) Tenascin and type IV collagen expression in liver cell dysplasia and in hepatocellular carcinoma. Histol Histopathol 11:323–333

Zhao XL, Sun T, Che N, Sun D, Zhao N, Dong XY, Gu Q, Yao Z, Sun BC (2011) Promotion of hepatocellular carcinoma metastasis through matrix metalloproteinase activation by epithelial-mesenchymal transition regulator Twist1. J Cell Mol Med 15:691–700

Zhou SL, Dai Z, Zhou ZJ, Chen Q, Wang Z, Xiao YS, Hu ZQ, Huang XY, Yang GH, Shi YH, Qiu SJ, Fan J, Zhou J (2014) CXCL5 contributes to tumor metastasis and recurrence of intrahepatic cholangiocarcinoma by recruiting infiltrative intratumoral neutrophils. Carcinogenesis 35:597–605

Zhu L, Cheng X, Ding Y, Shi J, Jin H, Wang H, Wu Y, Ye J, Lu Y, Wang TC, Yang CS et al (2014) Bone marrow-derived myofibroblasts promote colon tumorigenesis through the IL-6/JAK2/STAT3 pathway. Cancer Lett 343:80–89

Zimmerlin L, Park TS, Zambidis ET, Donneberg VS, Donnenberg AD (2013) Mesenchymal stem cell secretome and regenerative therapy after cancer. Biochimie 95:2235–2245

Zindy PJ, L'Helgoualc'h A, Bonnier D, Le Béchec A, Bourd-Boitin K, Zhang CX, Musso O et al (2006) Upregulation of the tumor suppressor gene menin in hepatocellular carcinomas and its significance in fibrogenesis. Hepatology 44:1296–1307

Part XXXVIII

General Pathology of Hepatobiliary Tumors: Angiogenesis

Angiogenesis in Liver Cancer 186

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_186

Abstract

Angiogenesis, the formation of new tumor vessels, is a critical mechanism for the development and progression of hepatobiliary cancers, which are often highly vascular tumors. In contrast to normal tissues, tumor vessels frequently form highly atypical branching patterns, with irregular diameters and abrupt changes from large to small diameters. This abnormal vasculature of malignant neoplasms serves as an important diagnostic element in modern tumor imaging. The principal cells mediating angiogenesis in neoplasms are tumor endothelial cells, and auxiliary cells involved in tumor angiogenesis include perivascular cells, stromal cells, tumor-associated monocytes and macrophages, and other leukocytes. Initiation and progression of angiogenesis, which requires a vigorous proliferative response of tumor endothelial cells and their precursors, involves the action of numerous angiogenic factors. Similar to normal tissues, the main factors comprise vascular endothelial growth factors, angiopoietins, basic fibroblast growth factor, platelet-derived endothelial growth factor, endoglin, and ephrin. Hepatobiliary cancers also express several anti-angiogenic factors. Tumor angiogenesis is markedly modulated by factors secreted by stromal leukocytes and by epigenetic mechanisms, mainly numerous microRNAs expressed by tumor cells and stromal cells.

Introduction

Angiogenesis is a complex process that involves a multicomponent network of pro-and anti-angiogenic factors and holds a central position in tumor growth and progression (review: Semela and Dufour 2004). In most cancers, angiogenic and anti-angiogenic factors are produced and released by cancer cells, while others have their origin in endothelial cells and several types of myeloid cells located in the tumor stroma. Basically, angiogenesis in liver cancers proceeds along the same pathways as in the normal liver and specifically in liver regeneration, with some remarkable differences. Under induction and guidance by distinct secreted factors, resting endothelial cells in the tumor bed are activated to migrate, proliferate, and form new vessel structures. In the course of this process, endothelial cells of preexisting vessels individualize by loss of intercellular contact and decay of basement membranes, followed by invasion of new angiogenic territories via secreted proteases. Proteolytic degradation of extracellular matrix also releases angiogenic factors that are stored in matrix compartments. In the setting of sprouting vasculogenesis and formation of new vascular tubes, basement membranes are formed, sometimes incomplete in tumors, and the new tumor vessels undergo maturation and are stabilized by distinct factors and supportive pericytes. This entire process goes in parallel with tumor growth and is constantly adapted to new vascularization demands by an intricate regulatory system, forming a multicomponent interactome between cancer cells, vascular cells, stromal cells, and homing leukocytes. In dormant neoplasms, angiogenesis is switched off or is active at a low level, while vascularized, rapidly growing cancers activate numerous genes involved in the angiogenic response. The transition to an aggressive phenotype with high vascularity has been termed angiogenic switch, transforming a dormant neoplasm into an invasive and spreading cancer and representing a rate-limiting step for tumor progression. The angiogenic switch is based on the upregulation of numerous angiogenic factors and a downregulation of anti-angiogenic factors (Pang and Poon 2006; Almog et al. 2009; Baeriswyl and Christofori 2009; Moserle et al. 2009; Almog 2013; Benzekry et al. 2014). In the present chapter, main aspects of angiogenesis are presented for two main liver cancers, hepatocellular carcinoma and cholangiocarcinoma, followed by a short survey on general aspects of angiogenesis and lymphangiogenesis.

Angiogenesis in Hepatocellular Carcinoma: Morphology and Cell Systems

Introduction

Angiogenesis is a critical mechanism for the development and progression of hepatocellular carcinomas (HCCs), which are often highly vascular tumors. In humans, the earliest steps of angiogenesis in HCCs are not well known, as very small or incipient HCC lesions are difficult to study in this respect. It is assumed that the first lesions that consist of collections of few cells may be devoid of an own vascular system, whereas neovascularization is certainly present in small HCCs. Generally, growing HCCs are characterized by arterialization of the vascular supply and capillarization of sinusoidal channels (Pang and Poon 2006; Yang and Poon 2008; Muto et al. 2015).

Morphology of Angiogenesis in Liver Cancers

The morphology and biology of tumor vessels produced in the setting of tumor angiogenesis differs in several respects from normal blood vessels (Ribatti et al. 2007; Hida et al. 2011). Tumor vessels exhibit an abnormal branching pattern and have irregular diameters, sometimes with abrupt changes from large to small diameters instead of a gradual transition. Tumor vessels can form highly atypical arrays, with densely placed larger vessels and an increase in microvessel density. These patterns are under constant dynamic change, due to ongoing angiogenesis, loss of newly formed vessels by tumor-induced destruction, angiophagy, thrombosis and necrosis, and vessel repair. The abnormal vasculature of tumors serves as an important diagnostic element in modern tumor imaging. Endothelial cells in tumor micro-and macrovessels form heterogeneous populations (Hida et al. 2013) and differ in several respects from those in normal tissues. In particular, tumor vessels also display a distinct molecular heterogeneity (Aird 2009).

Histologically, tumor vessels often have an incomplete basement membrane; show an irregular endothelial lining interspersed with tumor cells, homing leukocytes, and adherent platelets; are incompletely covered by supporting pericytes; and are leaky. Many tumor vessels show a lining of both fully developed endothelial cells and focally thin, flat, and fragile (attenuated) endothelial cells lacking expression of typical lineage markers, resulting in mosaic vessels (di Tomaso et al. 2005). The ratio of intact vs. attenuated endothelial cells may have an impact on tumor cell emigration and homing of immune cells. Part of the tumor vasculature is specialized and fit for selective cell transfer. Some tumors contain high endothelial venules that serve for trafficking of immune cells, in particular T and B lymphocytes (Bellone and Calcinotto 2013; Martinet et al. 2011, 2013). Within the vessel lining, tumor cells can interdigitate with endothelial cells. The contribution of cancer cells to the lining of mosaic tumor vessels can be significant and may reach 25 % of the luminal surface in certain neoplasms (Chang et al. 2000). Part of endothelial cells forming new tumor vessels are tumor cell derived, suggesting that tumor vessels in angiogenesis are not always genetically stable (Pezzolo et al. 2007). In addition, tumor cells of certain neoplasms can themselves form vessel-like blood-containing spaces, called vasculogenic mimicry. HCCs are typically arterialized and contain high densities of arterioles. The hypervascularity seen in certain HCCs by the use of angiography or modern MRI techniques is mainly due to the production of intratumoral arterioles. The density of alpha-SMA-reactive arterioles is higher in moderately and poorly differentiated tumors than in well-differentiated tumors and is correlated with proliferative activity of cancer cells (Morinaga et al. 2001).

Biology of Angiogenic Cells in Hepatocellular Carcinoma

The principal cells mediating angiogenesis in tumors are tumor endothelial cells/TECs, but

auxiliary cells include perivascular cells, stromal cells (including myofibroblasts and CAFs), tumor-associated monocytes and macrophages, and other leukocytes. Normal endothelial cells form a rather stable and quiescent cell population with a slow turnover time (months to years) and a proliferation fraction of 0.01 % or less. Upon initiation of the angiogenic switch, numerous preexisting endothelial cells undergo transition from G0 to S phase of the cell cycle, leading to a dramatic increase of the proliferation fraction associated with upregulation of endothelial cell surface markers. TECs form a heterogeneous population of endothelial cells that differ more or less from normal endothelial cells as a function of tumor type and cancer progression (review: Hida et al. 2013). TECs arise from normal preexisting endothelial cells or from circulating progenitor cells (see below), but not from tumor-initiating cells/TICs (Ghanekar et al. 2013). Normal endothelial cells and TECs may not maintain their lineage status, but can transform into mesenchymal cells of the stroma, a phenomenon termed endothelial-to-mesenchymal transition/EndoMT and a mechanism that downregulates microvessels (Ten Dijke et al. 2012). This process probably plays a role in the dynamic evolution of tumor microenvironment and pro-metastatic niches. The proliferative activity of endothelial cells in HCCs was higher in peripheral parts of tumors than in central parts (Imura et al. 2004). TECs in HCC manifest increased angiogenesis capability and augmented resistance to apoptosis (Xiong et al. 2009). Whereas sinusoidal endothelia in the normal liver are not reactive for the progenitor cell marker CD34, CD34 is strongly and diffusely expressed in sinusoid-like vascular channels of advanced HCCs, while CD34 positivity is irregular and focal (Ruck et al. 1995; Cui et al. 1996; Kimura et al. 1998). A switch in endothelial cells to CD34 positivity already takes place in dysplastic nodules, the former adenomatous hyperplasia (Kimura et al. 1998). Intratumoral capillary endothelial cells in HCCs express an adipokine receptor, T-cadherin, reactivity being stronger and diffuse in poorly differentiated tumors and only focal in well-differentiated HCCs (Adachi et al. 2006).

Proliferation of TECs promoted by angiogenic factors parallels other marked changes in TEC biology. Activated TECs become motile cells reacting to chemokinetic and chemotactic stimuli. This motility is required for the placing of tip cells in vascular sprouting (see below) and migration of TECs into the tumor bed. Invasion of tissue by TECs is associated with the breakdown of the surrounding basement membrane and extracellular matrix, basement membranes later being reconstituted, at least in part, during tumor vessel maturation (Baluk et al. 2003, review: Semela and Dufour 2004). By an interacting cell network that also includes blood-borne cells such as macrophages, proteolytic enzymes are secreted, including matrix metalloproteinases/MMPs, tissue plasminogen activator, and cathepsins, whereby the secretion of these enzymes is partially controlled by angiogenic factors produced by tumor cells, stromal cells, and myeloid cells. Important sources for MMPs, in particular MMP-9/gelatinase B, are cancer-associated fibroblasts/CAFs (Vandooren et al. 2013; Farina and Mackay 2014; Taguchi et al. 2014). Proteases expressed during angiogenesis also serve to liberate growth factors. For example, MMP-9 plays a major role in releasing VEGF sequestered in the extracellular matrix (Bergers et al. 2000).

Endothelial Progenitor Cells as Mediators of Vasculogenesis in Hepatocellular Carcinoma

In numerous neoplasms, endothelial progenitor cells are operational in tumor vascularization. Similar to normal tissues, these progenitors derive, at least in part, from circulating CD133(+)CD34(+) stem cells that are capable to home the tumors, in particular to incipient stroma and pro-metastatic niches (reviews: Ribatti 2004; Patenaude et al. 2010). For tumor vasculogenesis in HCC, endothelial progenitor cells (EPCs; CD133+) have been proposed to play an important role (Nolan et al. 2007; Ping and Bian 2011; Moschetta et al. 2014), albeit other authors did not find a contribution of EPCs to tumor endothelium (Wickersheim et al. 2009). EPCs can, in certain

tumors, populate new blood vessels that emerged from local endothelial cells, giving rise to complex mosaic patterns (Chen et al. 2014b). In HCCs, higher circulating levels of EPCs were observed in patients with advanced unresectable tumors as compared to patients with resectable tumors (Ho et al. 2006). Part of EPCs mediating angiogenesis in HCC originate from bone marrow-derived endothelial precursors (Yu et al. 2007a; Sun et al. 2012; Yoder 2012; Zhu et al. 2012b; Carrion et al. 2013), and also multipotent adult progenitor cells/MAPCs contribute to HCC neovasculature (Barajas et al. 2007). Part of EPCs express the lineage markers, CD133, CD34, and VEGFR2 (Ho et al. 2006). An EPC contribution may occur at an early stage and throughout the entire process of HCC growth (Zhu et al. 2012a). Circulating EPCs are elevated in patients with liver cirrhosis and/or HCC (Sieghart et al. 2009). These cells belong to two major phenotypes, i.e., myeloid-derived EPCs (colony-forming unit-endothelial cells, CFU-ECs) and outgrowth EPCs (endothelial colony-forming cells, ECFCs). Priming, mobilization, recruitment, and homing of EPCs are a multistep event that requires regulation by several factors, including adhesion molecules, angiogenic factors, interacting tumor cells, stromal cells, and a hypoxic microenvironment. Cancer cells interact with EPCs in a complex manner and modify the biologic behavior of these cells. HCC cells induce chemotaxis, migration, and an invasive phenotype in CFU-ECs via secretion of macrophage inflammatory protein-3alpha which binds to the CCR6 receptor on CFU-ECs, but HCC cells do not induce chemotactic migration in ECFCs (Shih et al. 2012a).

The upregulation of angiogenic factors in HCC causes recruitment of endothelial progenitor cells into microvessels, both in the tumor itself, but also in peritumoral cirrhotic tissue, which forms a highly angiogenic area (Yu et al. 2010b). In fact, normal and cirrhotic liver surrounding HCCs are an important source of angiogenic cells, suggesting that HCCs are embedded in an angiogenic "hot-spot area." Hypoxic and angiogenic peritumoral liver tissue forms a niche of endothelial progenitor cells (Yu et al. 2010a).

Angiogenic Factors in Hepatocellular Carcinoma

Vascular Endothelial Growth Factors

An important proangiogenic factor in tumors is vascular endothelial growth factor (VEGF), which interacts with specific receptors on endothelial cells. HCC cells express VEGF, and the VEGF receptors are upregulated in HCCs in comparison with normal liver tissue (Shimoda et al. 1999; McMahon 2000; Shimamura et al. 2000; Mitsuhashi et al. 2003; Moon et al. 2003; Deli et al. 2005; Ribatti et al. 2006; Sharma et al. 2013; Zhang et al. 2014). In patients with cancer, angiogenic factors are produced, taken up, stored, and transported by platelets (Walsh et al. 2014), resulting in net platelet angiogenic activity/NPAA which, in certain tumors, correlated with progression and prognosis (Yao et al. 2014).

Apart from tumor cells, also hepatic stellate cells may express VEGF, possibly in the setting of autocrine/paracrine loops. Increased VEGF expression is already present in early steps of hepatocarcinogenesis (Park et al. 2000). In advanced HCC, increased VEGF expression is more frequently found in hypervascular tumors and those with poor differentiation and is associated with tumor progression (Torimura et al. 1998). Both VEGFR1 (Flt-1) and VEGFR2 (Flk-1) are expressed in subsets of HCCs, whereby four categories of tumors were proposed, i.e., receptor double negative, Flt-1 single positive, Flk-1 single positive, and receptor double positive. Poorly differentiated HCCs were either receptor double negative or double positive (Amaoka et al. 2006). Expression of VEGFR1 correlated with the endothelial CD31 expression pattern (Dhar et al. 2002). Part of HCCs also express a VEGF involved in lymphangiogenesis, VEGF-C, expression being detectable more often in large tumors and those with intrahepatic recurrence and extrahepatic metastases. VEGF-C was also found in HCC cells forming tumor casts in portal and hepatic veins (Yamaguchi et al. 2006). VEGFs and VEGFRs are subject to therapies with receptor kinase inhibitors, such as sorafenib and

sunitinib (Adnane et al. 2006; Takahashi 2011; Johnson et al. 2013; Kim and Abou-Alfa 2014; Scartozzi et al. 2014) and cabozantinib (blockade of VEGFR2 and MET; Xiang et al. 2014), or humanized monoclonal antibody against VEGF-A, bevacizumab. The mechanisms leading to upregulation of angiogenic factors, including VEGFs, in HCC are only partially elucidated. VEGF expression in HCC is promoted by ATPase inhibitory factor 1 (IF1), a factor highly expressed in large and aggressive tumors, via activating NF-kB signaling. Via this pathway, IF1 also upregulates Snail followed by active epithelial-mesenchymal transition (Song et al. 2014).

Angiopoietins

Angiopoietin-1 (Ang1) and its antagonist angiopoietin-2 (Ang2) regulate the Tie2 receptor (vascular endothelial receptor of tyrosine kinase) and are expressed in various tumors (Yu 2005; Bach et al. 2007). Both Ang1 and Ang2 are expressed in HCCs, the factors being present in tumor cells and stromal cells, including hepatic stellate cells and myofibroblasts, while the Tie2 receptor is expressed in endothelial cells, hepatic stellate cells, and smooth muscle cells (Torimura et al. 2004). In HCC, Ang2 is predominantly expressed on cancer cells themselves, while Ang1 is mainly present in stromal and endothelial cells (Bupathi et al. 2014). In contrast to the normal liver, Ang2 is more often expressed, and its expression level is higher in hypervascular tumors and those with poor differentiation, suggesting a reversal of Ang1 and Ang2 expression (Mitsuhashi et al. 2003; Zhang et al. 2006). Ang2 expression is correlated with expression of the Tie2 receptor in tumor vessels (Sugimachi et al. 2003) and closely associated with tumor angiogenesis and microvessel density (Chen et al. 2001; Wada et al. 2006). The production of Ang1 and Ang2 is correlated with HCC vascularity, indicating that the factors play a role in HCC angiogenesis (Torimura et al. 2004). Ectopic expression of Ang2 promotes rapid progression of HCC, supporting an important role of this factor in HCC neovascularization (Tanaka et al. 2003; Zhang et al. 2006). Upregulation of Ang2 in HCC was associated with poor overall survival (Miyahara et al. 2013). In hepatocyte lineages, Ang2 expression is promoted by the HBV X protein (Sanz-Cameno et al. 2006). HCC tissue expresses significantly lower levels of angiopoietin-like protein 4/ANGPTL4 than non-tumor liver tissue, via an epigenetic downregulation mechanism. This downregulation is associated with advanced stage (Ng et al. 2014).

Basic Fibroblast Growth Factor

Basic fibroblast growth factor/bFGF is an angiogenic factor in HCC (Nomura et al. 2013). In tumors expressing bFGF, the proliferative activity of tumor endothelial cells (PCNA labeling) was significantly higher than that in bFGF-negative HCCs (Imura et al. 2004). FGF8, FGF17, and FGF18 are involved in autocrine and paracrine signaling in HCC and promote angiogenesis (Gauglhofer et al. 2011).

Platelet-Derived Endothelial Cell Growth Factor

Platelet-derived endothelial cell growth factor (PD-ECGF; thymidine phosphorylase) is an angiogenic factor that is expressed in malignancies. Expression of PD-ECGF was detected in about 50 % of HCCs, with immunostaining of both cytoplasm and nuclei. In addition to HCC cells, reactivity is also present in stromal cells and tumor-infiltrating lymphocytes. Reactivity for PD-ECGF was associated with elevated tumor microvessel density and higher grade (Guo et al. 2001).

Endoglin and Ephrin

Endoglin (CD105) is a cell surface glycoprotein involved in the development of blood vessels and vascular repair (Duff et al. 2003; van Laake et al. 2006). Endoglin is a receptor for TGF-beta1 and TGF-beta3 and modulates TGF-beta signaling via interacting with

TGF-betaR1 and/or TGF-betaR2. Endoglin is expressed in HCCs, restricted to endothelial cells of capillary vessels and sinusoid-like channels (Dhar et al. 2002; Minhajat et al. 2006; Yu et al. 2007b). CD105 microvessel density was positively associated with expression intensity of VEGF (Yao et al. 2007). Lower CD105 microvessel density was associated with larger and more aggressive tumors (Ho et al. 2005). In livers harboring HCC, diffuse endoglin reactivity was also noted in microvessels of adjacent nonneoplastic liver tissue, mainly in sinusoidal endothelial cells (Yu et al. 2007b), and this reactivity was associated with early tumor recurrence (Ho et al. 2005). CD105 is detectable as a belt-like reactivity in peritumoral tissue in HCC patients (Nakamura 2009). Ephrins and their receptors are involved in tumor angiogenesis. Ephrin-A1 affects several signaling pathways depending on MAP/ERK and PI3K and has an integral role in angiogenesis and vasculogenesis. Ephrin-B2 regulates VEGFR2 function in neoplasms (Hainaud et al. 2006; Sawamiphak et al. 2010). Several ephrin types can be expressed in HCCs. The expression of ephrin-B1 was significantly higher in these cancers than in normal liver tissue, and ephrin-B1-positive tumors had a higher vascular density and a more rapid progression (Sawai et al. 2003). Ephrin-A1 is preferentially expressed in AFP-producing HCC cells, expression in HCCs being higher than in the cirrhotic or normal liver tissue (Iida et al. 2005). Ephrin-A1 is upregulated by hypoxia in cancer cells (Song et al. 2013).

Cytokines and Chemokines

Chemokines (CC, CXC, C, and CX3C) are involved in several important aspects of cancer biology, including chemokinesis and chemotaxis, proliferation, apoptosis, and modulation of angiogenesis (Kiefer and Siekmann 2011; Bosisio et al. 2014). The angiogenic effect of certain cytokines and chemokines in HCC and other hepatic malignancies is also recognizable in hepatic inflammatory disorders where immunologic effector cells are the source of these factors, e.g., in HCV infection (Hassan et al. 2014). Seven ELR-positive CXC chemokines promote migration and proliferation of endothelial cells and are potent angiogenic substances, also in tumors. Three members of the CC chemokine family, CCL2, CCL11, and CCL16, can also induce neovascularization. Several CXC ligands (CXCL 4,9,10 and 11) cause an angiostatic effect via binding to a common receptor, CXCR3 (Dias et al. 2001; Salcedo and Oppenheim 2003; Keeley et al. 2011; Kiefer and Siekmann 2011; Santoni et al. 2014). Proangiogenic chemokines can elicit an angiogenic response in HCC (Keeley et al. 2011). The chemokine IL-8 (CXCL8), which is produced by macrophages and stored in endothelial cell vesicles, is expressed in part of HCCs and related to angiogenesis in these neoplasms (Nomura et al. 2013). An important role is played by CXCR3, a receptor for at last five CXCL chemokines (Billottet et al. 2013). A further chemokine that is involved in angiogenesis is stromal cell-derived factor-1, a protein that exclusively binds to the CXCR4 receptor and regulates endothelial cell branching morphogenesis (Salvucci et al. 2002). CXCR7 stimulates HCC angiogenesis through activation of the MAPK signaling pathway (Lin et al. 2014). Stromal cell-derived factor-1 produced by platelets is involved in the recruitment of progenitor cells to vascular compartments (Stellos and Gawaz 2007).

Thrombospondin and Vasohibins

Thrombospondin 1/THBS1 is a matricellular protein that can modulate angiogenesis and in many situations acts in an angiostatic manner in nonneoplastic cell systems (Lawler 2002). In principle, THBS1 acts as a molecular facilitator that promotes a union among several other factors, such as cytokines, membrane receptors, and proteases, allowing cross talk between receptor clusters (review: Chen et al. 2000). THBS1 binds to its receptor on microvascular endothelium, CD36, necessary for anti-angiogenic activity and acting through inhibition of VEGFR2 signaling (Simantov and Silverstein 2003; Chu et al. 2013; Klenotic et al. 2013). In HCCs, THBS1 is expressed in both tumor cells and stromal cells and acts as an

angiogenesis modulating factor that promotes invasion and progression (Poon et al. 2004).

Vasohibin-1 is an endothelium-derived negative feedback regulator of angiogenesis that is induced by FGF-2 and VEGF-A. Vasohibin-1 expression in tumor vessel endothelial cells regulates tumor angiogenesis (Hosaka et al. 2009; Ito et al. 2013), but the effects of vasohibin-1 on tumor endothelia is complex and depends on the status of target vessels. In HCC, vasohibin-1 expression is correlated with neovascularization (Murakami et al. 2014). Patients with vasohibin-1-expressing HCCs had a significantly reduced overall survival (Wang et al. 2012). Vasohibin-2 as a proangiogenic factor is highly expressed in part of HCC and promotes angiogenesis in these tumors (Xue et al. 2013). Its expression is a function of differentiation, and this factor also modulates chemoresistance (Li et al. 2014). Vasohibin expressed by HCC cells augments the angiogenic response through induction of epithelial-mesenchymal transition/EMT, whereby vasohibin-2 is induced by microRNA-200 (Xue et al. 2014).

Angiogenic Factors with Complex or Not Well-Studied Functions

Neuropilin-1, which plays a role in arteriogenesis in normal and cancerous tissues, is expressed in HCC and peritumoral tissue (Zhuang et al. 2014). Platelet-derived growth factor/PDGF and its receptors are involved in HCC angiogenesis. The expression of PDGFRA in HCC vessels is induced by microRNA-146a (Zhu et al. 2013). Prostaglandins produced in HCC via the action of the cyclooxygenase/COX system positively affects angiogenesis (Cervello and Montalto 2006; Zhao et al. 2006). Angiogenin (ribonuclease 5) belonging to the vertebrate RNase superfamily was identified as tumor angiogenic factor, but is now known to be a factor that generally stimulates proliferation and survival. Angiogenin stimulates ribosomal RNA transcription (Sheng et al. 2014). The embryonic morphogen Nodal is expressed in subsets of HCC and is associated with angiogenesis and an aggressive cancer phenotype (Chen et al. 2014a). Twist, a bHLH transcription factor promoting epithelial-mesenchymal transition/EMT, is expressed in part of HCCs and is associated with an elevated tumor microvessel density (Che et al. 2011). Upregulation of Twist in HCC is correlated with intrahepatic and extrahepatic metastasis and poor prognosis (Niu et al. 2007). HCCs express protein phosphatase of regenerating liver 3/PRL-3 as a metastasis-associated phosphatase. PRL-3 promotes angiogenesis in these neoplasms (Zhao et al. 2008). A factor involved in epithelial-mesenchymal transition, BAG3 (Bcl2-associated athanogene 3; a co-chaperone of Hsp70), is expressed in HCC and augments invasion and angiogenesis via VEGF induction (Xiao et al. 2014). Several types of microRNAs target angiogenic and anti-angiogenic factors and thus influence tumor angiogenesis (Pecot et al. 2013). HCCs express acylglycerol kinase (AGK), a factor associated with an aggressive phenotype and increased tumor angiogenesis (Cui et al. 2014). In several tumors, including HCC, angiogenesis is promoted by activation of NF-kappaB signaling. Golgi phosphoprotein 3 (GOLPH3) is frequently upregulated in HCC, and its expression is correlated with clinical stage, survival, and promotion of angiogenesis. This effect is mediated by NF-kappaB signaling and promotion of K63-linked polyubiquitination of TNF receptor-associated factor 2/TRAF2, receptor-interacting protein/RIP, and NF-kappaB essential modulator/NEMO as activators of NF-kappaB (Dai et al. 2015). In HCC, angiogenesis and metastatic spread are stimulated by ATPase inhibitory factor 1/IF1, via upregulation of Snail1 and increased transcription of VEGF (Song et al. 2014).

Angiogenic Factors and Biology of Disease in Hepatocellular Carcinoma

Angiogenesis induced by various angiogenic factors strongly affects growth and progression of HCC. Silencing of VEGF not only abolishes angiogenesis, but also inhibits growth of HCCs (Wu et al. 2013). HCCs with high Ang2 expression were associated with a shorter survival time than those with low Ang2 expression (Mitsuhashi

et al. 2003). The expression patterns of angiogenic factors in HCCs are associated or correlated with biology of disease. Increased serum VEGF in patients with HCC was correlated with tumor recurrence, disease-free survival, and overall survival (Chao et al. 2003). However, only part of angiogenic factors can serve as predictors of outcome. For example, VEGF-A and VEGF-C could not predict recurrence in HCC patients (Ho et al. 2007).

Inhibitors of Angiogenesis in Hepatocellular Carcinoma

Endostatin, a 20 kDa C-terminal fragment of collagen XVIII, is an endogenous inhibitor of angiogenesis that exists in *a short and long* form. Endostatin targets both tumor blood vessels and lymphatic vessels and is, therefore, also an inhibitor of lymphangiogenesis (Zhuo et al. 2010, 2011). HCC cells can express *the long* form in contrast to cholangiocarcinoma cells that express *the short* form. *The long* form seems to be specific to the hepatocyte lineage, while the *short* form is also produced by stromal cells in liver cancer, including myofibroblasts (Musso et al. 2001). In HCC, increased endostatin expression correlated with elevated VEGF levels and poor prognosis (Hu et al. 2005). Angiostatin inhibits angiogenesis when expressed in HCCs (Soff 2003; Tao et al. 2004). Angiostatin expression in HCC results in decreased microvessel density (Kim et al. 2004). An angiogenesis inhibitor in tumors is angioarrestin, a protein related to angiopoietins. Angioarrestin inhibits VEGF-induced endothelial cell proliferation, adhesion, migration, and tubular network formation (Dhanabal et al. 2002; Dhanabal et al. 2005). Generation of angioarrestin in HCC requires expression of human macrophage metalloelastase/HME as a processing enzyme (Gorrin Rivas et al. 1998). Expression of VEGF in HCC is suppressed by the tumor suppressor XAF1 (X-linked inhibitor of apoptosis/XIAP-associated factor 1), whereby most HCCs showed a downregulation of XAF1 (Zhu et al. 2014a). Angiogenesis can be inhibited by downregulation of angiogenic factors. In HCC, microRNA-26a inhibits angiogenesis by reducing a VEGF-A pathway (Chai et al. 2013) and by targeting the HGF/cMet pathway (Yang et al. 2014; Greenhill 2014). MicroRNA-29b antagonizes angiogenesis by targeting and downregulating MMP-2 expression (Fang et al. 2011a), microRNA-503 targets VEGF-A and FGF2 and via this mechanism inhibits angiogenesis (Zhou et al. 2013), and microRNA-223 antagonizes angiogenesis by targeting beta1 integrin and preventing growth factor signaling (Shi et al. 2013).

Induction and Driving Forces of Angiogenesis in Hepatocellular Carcinoma

Hypoxia and Hypoxia-Inducible Factors

Hypoxia promotes the progression of liver cancers via affecting cell proliferation and invasion, but tumor hypoxia is also a strong driving force for angiogenesis in many malignancies, including HCCs (Kim et al. 2002; Hirota and Semenza 2006; Ji 2014; Wilson et al. 2014). The local oxygenation status in tumors is monitored by oxygen sensors, of which hypoxia-inducible factors (HIFs) and their hydroxylating dioxygenases are the prominent members (review: Verma 2006). For angiogenesis, hypoxia acts through upregulation of VEGF gene expression, via increased VEGF gene transcription and an increase in VEGF mRNA stability (von Marschall et al. 2001). VEGF expression in HCC is tightly regulated by HIF-1alpha, a transcription factor that upregulates angiogenic factors under hypoxia (Wu et al. 2014). HIF-1 plays an important role in the progression and angiogenesis of HCC (Luo et al. 2014). In experimental HCC cells, plasminogen activator inhibitor 1/PAI-1 is a HIF-2alpha target gene. HIF-2alpha increases PAI-1 to decrease local concentrations of active plasmin, thereby supporting angiogenesis (Geis et al. 2014). HBV X protein, a protein involved in hepatocarcinogenesis, increases the expression of VEGF via stabilizing HIF-1alpha, active HIF-1alpha upregulating VEGF (Moon

et al. 2004). In contrast to VEGF, hypoxia does not upregulate Ang1 and Ang2 in HCC (Torimura et al. 2004). HCV core protein induces hypoxia-inducible factor 1alpha-mediated VEGF expression in HCC cells (Zhu et al. 2014b). Apart from VEGF-mediated pathways, HIF-1alpha also affects invasive features of HCC. For example, it promotes transcription of the chemotactic peptide CXCL6 in HCC cells, inducing chemotactic migration of HCC cells (Tian et al. 2014). Hypoxia induces the secretion of platelet-derived growth factor-BB by HCCs, which in turn increases the secretion of VEGF-A by activated hepatic stellate cells (Lu et al. 2015). Hypoxia-induced angiogenesis is regulated by distinct microRNAs which are upregulated under hypoxic conditions, above all in tumors (Madanecki et al. 2013). Hypoxia-responsive microRNAs target the argonaute 1 protein leading to desuppression of VEGF and promotion of angiogenesis (Chen et al. 2013). Hypoxia-related mechanisms are also operational in tumor lymphangiogenesis (Ji 2014).

Factors Not Driven by Hypoxia

Apart from hypoxia, other factors can induce angiogenic factors. Early steps of vasculogensis and angiogenesis in tumors mainly involve the generation of endothelial tubes, which in the course of further expansion of the vessel network undergo maturation, including arterialization which depends on smooth cell production. Tumor arteriogenesis in HCC is induced by the apelin/APJ signaling system, a multifunctional pathway involved in endotheliogenesis and the generation of smooth muscle cells (Muto et al. 2014). A strong promoter of angiogenic factor expression in HCC is macrophage migration inhibitory factor/MIF, which increases VEGF and IL-8 in these neoplasms and induces angiogenesis in HCC (Ren et al. 2003; Hira et al. 2005). Distinct expression patterns of matrix metalloproteinases affect angiogenic responses in HCC (Ishii et al. 2003). TNF-like weak inducer of apoptosis/TWEAK, a TNF family member expressed by HCC cells, modulates tumor-associated angiogenesis via induction of IL-8 and MCP-1 in endothelial cells (Kawakita et al. 2004).

Epigenetic Mechanisms in Liver Cancer Angiogenesis

MicroRNAs as Regulators of Angiogenesis in Cancer

Intracellular and extracellular microRNAs/MiRs play a significant role in both normal angiogenesis/vasculogenesis and tumor angiogenesis, as these MiRs critically affect numerous signaling pathways in endothelial cells (Finn and Searles 2012). Deregulation of microRNAs is an important mechanism that modulates angiogenesis in primary cancers and metastatic disease (Gramantieri et al. 2008; Png et al. 2011; Geng et al. 2014; Zeng et al. 2014; Zhou et al. 2014; Dang and Myers 2015). Promotion of tumor angiogenesis depends on differential expression of miR-296 and miR-378 (Bonauer et al. 2010). The potent angiogenic factors, VEGF-A and fibroblast growth factor 2, are downregulated by microRNA-503 which targets these factors (Zhou et al. 2013). miR-93 promotes tumor angiogenesis by targeting integrin-beta8 (Fang et al. 2011b). MicroRNA-26a suppresses angiogenesis in HCC by targeting the hepatocyte growth factor-cMet signaling pathway, resulting in VEGF-A downregulation. This miR is reduced in part of HCCs, associated with enhanced angiogenesis (Greenhill 2014; Yang et al. 2014). MicroRNA-29b suppresses the ability of HCC cells to promote capillary tube formation via downregulating matrix metalloproteinase-2 expression. In HCC, miR-29b expression is low, associated with aggressive tumor biology (Fang et al. 2011a). Downregulation of microRNA-214 in human HCC contributes to tumor hypervascularity through activation of hepatoma-derived growth factor paracrine pathway for tumor angiogenesis (Shih et al. 2012b). The endothelial cell-specific microRNA-302c suppresses HCC growth through metadherin-mediated inhibition of endothelial-mesenchymal transition/EndMT (Zhu et al. 2014c).

Epigenetic Pathways in Tumor Angiogenesis Other Than MicroRNAs

In addition to microRNAs, epigenetic alterations in tumor angiogenesis include histone modifications and chromatin modifiers. Cancers subject to hypoxia exhibit upregulation of hypoxia-inducible factor (HIF) alpha which plays an important role as inducer of VEGF signaling. The actions of HIF-alpha strongly depend on epigenetic modifications including acetylation mediated by histone acetyltransferases and histone deacetylation mediated by histone deacetylases (Ellis et al. 2009). Expression of cell adhesion molecules, e.g., intercellular adhesion molecule-1/ICAM-1 in endothelial cells is modulated by histone modifications. ICAM-1 downregulation in tumor endothelial cells is associated with ICAM-1 promoter histone 3 deacetylation and loss of histone H3 methylation, resulting in ICAM-1 silencing (Hellebrekers et al. 2006). Histone modifications operate in the transcription control of vascular endothelial growth factor receptor 3 involved in tumor lymphangiogenesis (Hertel et al. 2014). In cancers, angiogenesis-induced metastasis is also regulated by epigenetic histone modifications (Sahin et al. 2010). Yin Yang 1/YY1 is a member of the polycomb family involved in epigenetic mechanisms. YY1 acts as a positive regulator of angiogenesis by interacting with the VEGF-A signaling system. Binding of YY1 to VEGF-A is required to maintain steady-state VEGF-A expression. Hypoxia, a frequent and critical alteration in cancers, impairs YY1 binding to VEGF-A, downregulates YY1 and Dicer, and changes posttranscriptional VEGF-A regulation via accumulation of primiRNA200b/c instead of mature miR (Infante et al. 2015).

Tumor Exosomes (TEXs)

Exosomes are microvesicular structures that are derived from endosomes and released from numerous normal and cancer cells. Exosomes are among the most efficient mediators of intercellular communication and signaling and play a critical role in tissue patterning, regeneration, carcinogenesis, and tumor progression (Dignat-George and Boulanger 2011; Martinez and Andriantsitohaina 2011). Exosomes can contain proangiogenic factors and are released by tumor cells and endothelial cells of tumor vessels. A further source of exosomal proangiogenic factors are macrophages, neutrophils, and myeloid-derived suppressor cells located to the tumor stroma (Yang et al. 2011; Burke et al. 2014). Tumor exosomes (TEXs) as potent nanoscale messengers communicate with tumor cells themselves, stromal cells, endothelial cells, and circulating cells. As outlined in more detail in a later paragraph, cargo transported by microvesicles/exosomes is involved in the transfer of proangiogenic signals in cancers, including liver cancer (Kahlert and Kalluri 2013). The exosomal cargo in angiogenesis consists of angiogenic factors, cell adhesion molecules, and Notch ligands (Muturi et al. 2013; Sharghi-Namini et al. 2014). Signal components and growth factors carried and released by exosomes can induce endothelial cell proliferation and tube formation in a paracrine manner (Hood et al. 2009; Taverna et al. 2012). Transport and release of the Notch ligand Delta-like 4 by exosomes mediates development of tip cells and suppression of endothelial stalk cells in vascular sprouting (Sharghi-Namini et al. 2014). Exosomal TGF-beta1 induces the differentiation of tumor-promoting stromal myofibroblasts (Webber et al. 2014), whereas exosomes derived from mesenchymal stem cells can suppress angiogenesis by downregulating VEGF expression (Lee et al. 2013). Exosomes produced by myeloid-derived suppressor cells/MDSC transport and deliver cargo that transforms macrophages into tumor-promoting and proangiogenic M2 macrophages (Burke et al. 2014). Microvesicle-delivery of microRNA-150 promotes secretion of VEGF by M2-type TAMs (Liu et al. 2013). Exosomes involved in angiogenesis are promoted by hypoxia (Salomon et al. 2013), and endothelial cells require microRNA-214 to secrete exosomes that induce angiogenesis (van Balkom et al. 2013). In cancer

angiogenesis, release and transfer of exosomes is mediated by sortilin/neurotensin receptor-3 in a complex (TES complex) involving two tyrosine kinase receptors, TrkB and EGFR (Wilson et al. 2014), and by WNT5A, a component of Wnt signaling pathways (Ekström et al. 2014). Exosomes are one pathway by which hypoxia can drive angiogenesis, as exosomes are preferentially released from hypoxic tumor cells (Tadokoro et al. 2013). Part of proangiogenic effects of exosomal cargo is mediated by exosomal microRNAs (Zhang et al. 2015a). Exosomes may serve as a reservoir of anti-apoptotic microRNAs (Yu et al. 2015), a potential mechanism to favor endothelial cell survival.

Exosomes also carry a secretome that facilitates the emergence of epithelial-mesenchymal transition/EMT which in turn promotes invasion and angiogenesis of cancers (Greening et al. 2015). MicroRNAs carried by TEX are capable to induce premetastatic niches and proinflammatory niches that are programmed for later tumor angiogenesis (Rana et al. 2013). Premetastatic niche angiogenesis proceeds directly through binding and uptake of TEX by cells of the niche microenvironment, or indirectly through TEX taken up by bone marrow-derived, circulating stromal cell progenitors, endothelial cell progenitors, and mesenchymal stem cells primed to become stromal or vascular cells (Thuma and Zöller 2014). Exosomes released from pluripotent mesenchymal stem cells promote angiogenesis (Zhang et al. 2015b). Exosomal components may induce the differentiation of stromal tumor-promoting myofibroblasts and thus favor a proangiogenic microenvironment (Webber et al. 2015). On the other hand, cargo of exosomes can contribute to a cancer-associated immunosuppressive microenvironment, causing impairment of proangiogenic actions of monocytes and macrophages (Taylor and Gercel-Taylor 2011). Apart from complete nucleated cells, platelets can release microvesicles that promote tumor angiogenesis through the induction of CD41-MAPK kinase signaling pathways and upregulation of MMP-9 (Janowska-Wieczorek et al. 2005).

Tumor Angiogenesis: Roles of Tumor-Associated Macrophages (TAMs), Tie2-Expressing Monocytes (TEMs), Myeloid-Derived Suppressor Cells, Lymphocytes, Neutrophils, and Stromal Cells

Introduction

Several types of immune-related myeloid cells are involved in angiogenesis. They include circulating monocytes, Tie2-expressing monocytes (TEMs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and neutrophils (reviews: Schmieder et al. 2012; Chambers et al. 2013). Among these cell types, TAMs seem to play the most important role for tumor angiogenesis, but their Tie2-expressing monocyte precursors are also important for the initiation of tumor angiogenesis in HCC (De Palma et al. 2007, 2013; Guo et al. 2013; Matsubara et al. 2013).

TEMs and TAMs as Driving Forces in HCC Angiogenesis

The stroma of liver cancers contains various numbers of immune system cells acting as proinflammatory and proangiogenic elements, specifically TEMs, TAMs, and tumor-associated lymphocytes (Stockmann et al. 2014). These cells in part originate from circulating, bone marrow-derived cells, from locally proliferating cells, and stem/progenitor cells that home to the stromal niche. The homing mechanisms that cause accumulation of these cells within tumors are only partially elucidated. Tumor endothelium releases Ang2 and further facilitates recruitment of Tie2-positive monocytes into tumors (Riabov et al. 2014). In HCC, the presence of TEMs and TAMs is associated with angiogenesis (Matsubara et al. 2013). In the inflammatory microenvironment of HCC, TAMs acquire an M2-polarized phenotype and are associated with angiogenesis and increased microvessel density (Capece et al. 2013; Fujita et al. 2014) and can exert angiogenic functions by secreting proangiogenic factors

and matrix metalloproteinases. TAMs as alternative M2 cells modulate angiogenesis through secretion of the cytokine IL-1, which initiates and propagates inflammation and induces angiogenesis via proangiogenic inflammatory mediators (Carmi et al. 2009, 2013; Voronov et al. 2014). Also IL-8 is involved in tumor angiogenesis (Medina et al. 2011). TAMs secrete TNFalpha which coordinates inflammation and angiogenesis in HCC (Hammam et al. 2013). TNFalpha that targets to neoangiogenic vessels enhances lymphocyte infiltration in tumors (Calcinotto et al. 2012). Tie2 signaling cooperates with TNFalpha in promoting the proinflammatory activation of macrophages (Garcia et al. 2014). Interaction of TAMs with tumor cells increases the secretion of EMMPRIN (CD147, basigin) by tumor cells. EMMPRIN promotes the expression of VEGF and matrix metalloproteinases in endothelial cells and induces angiogenesis (Amit-Cohen et al. 2013). In their angiogenic function, TAMs are subject to regulatory pathways, including Toll-like receptor signaling (Belmont et al. 2014).

Tie2-expressing monocytes/TEMs are a diagnostic marker for HCC, and their presence in stroma correlates with tumor angiogenesis (Buonaguro 2014; Dapas et al. 2014; Germano and Daniele 2014). Tie2-expressing monocytes promote tumor angiogenesis in a paracrine manner (De Palma and Naldini 2009; Ribatti 2009). In the normal liver substance, these monocytes with a vigorous angiogenic potential are selectively induced by liver resection and accumulate near the site of liver regeneration (Schauer et al. 2014). The proangiogenic activity of Tie2-expressing monocytes is regulated by hypoxia and Ang2 (Lewis et al. 2007), whereby this depends on Ang2-regulated angiogenesis gene expression in monocytes (Coffelt et al. 2010). Differentiation of Tie2-expressing monocytes is induced by macrophage colony-stimulating factor (Forget et al. 2014).

Tumor-Associated Lymphocytes (TALs)

The network of angiogenesis-associated myeloid cells is modulated by other immune cells, including tumor-associated lymphocytes (TALs). Tumor-infiltrating regulatory T cells (TREGs) in cancers are positively correlated with angiogenesis, probably by generating immune tolerance units in the tumor microenvironment (Ning et al. 2012). On the other hand, angiogenic factors modulate immune reactions (Ohm and Carbone 2001), in part through affecting the function of monocytes/macrophages, including TAMs, and of other myeloid cells. Ang2 can stimulate Tie2-expressing monocytes to suppress T cell activation and to induce expansion of regulatory T cell (TREG) expansion (Coffelt et al. 2011). VEGF affects dendritic cell maturation and by this exerts and influences on local immune reactions (Oyama et al. 1998). Placental growth factor downregulates T helper immune responses through modulation of dendritic cell function (Lin et al. 2007).

Tumor-Associated Neutrophils (TANs)

In patients with cancer, heterogeneous populations of circulating neutrophils have been identified. One subset is formed by low-density neutrophils (LDNs) that accumulate continuously with cancer progression. LDNs display impaired neutrophil function and immunosuppressive properties, in contrast to mature, high-density neutrophils/HDNs. LDNs consist of two populations, i.e., cells that are derived from HDNs in a TGF-beta-dependent manner and immature myeloid-derived suppressor cells/MDSCs (see next paragraph), illustrating the overlap between TANs and one subset of MDSCs (granulocytic MDSCs; Dumitru et al. 2012; Pillay et al. 2013; Sagiv et al. 2015). Tumor-associated neutrophils (TANs) represent a distinct subpopulation of neutrophils that home to compartments within tumor stroma and in part within carcinoma epithelial formations (Dumitru et al. 2013). Similar to normal mature neutrophils, circulating neutrophils that will become TANs can adhere to microvascular endothelium via the action of cellular adhesion molecules/CAMs (Jain et al. 1996). On the other hand, tumor angiogenesis can reduce endothelial adhesion molecule

expression, thereby modulating neutrophil homing (Dirkx et al. 2003). TANs secrete various cytokines, part of which are proinflammatory and proangiogenic factors (Tecchio et al. 2013), and are a major source of proangiogenic matrix metalloproteinases (Deryugina et al. 2014). TANs also positively affect angiogenesis via integrin alphaMbeta2 (Soloviev et al. 2014). Neutrophils, chief mediators of acute and chronic inflammation, are enriched in peritumoral stroma of HCCs via IL-17-mediated recruitment. TANs can promote tumor angiogenesis via secretion of neutrophil-derived cytokines such as fibroblast growth factor-2, angiopoietin-1, and IL-17 (Tecchio and Cassatella 2014). Neutrophils also promote angiogenesis in HCCs through secretion of matrix metalloproteinase-9 (Kuang et al. 2011). Neutrophils in tumors can also contribute to lymphangiogenesis via increasing VEGF-A bioavailability and secretion of VEGF-D (Tan et al. 2013). Apart from neutrophils, eosinophils, which respond to hypoxia, can promote angiogenesis (Nissim Ben Efraim and Levi-Schaffer 2014).

Tumor-Associated Myeloid-Derived Suppressor Cells (TAMDSCs)

Myeloid-derived suppressor cells (MDSCs; immature myeloid cells; myeloid suppressor cells) are a heterogeneous class of bone marrow-derived cells that have a marked potential to suppress immune responses via induction of deficient T cell function (Monu and Frey 2012). Two major types of MDSCs are distinguished, i.e., granulocytic MDSCs and monocytic MDSCs. Granulocytic MDSCs share many features with neutrophils, including their capability to induce angiogenesis (Brandau et al. 2013). MDSCs associated with tumors (tumor-associated MDSCs; TAMDSCs) exhibit additional functions, specifically, they can promote tumor progression, mainly through their proinvasive, proinflammatory, and proangiogenic actions (Ye et al. 2010; Condamine et al. 2015). Soluble mediators produced by inflammatory cells in tumor-associated, MDSC-induced stromal inflammation can positively affect tumor angiogenesis (Caronni et al. 2015). There is evidence that a subset of MDSCs can directly promote angiogenesis in tumors (myeloid angiogenic cells, MACs; Chambers et al. 2013). Homing of MDSCs to cancer tissue and specifically to carcinoma stroma is a complex and poorly understood process. IL-18 promotes the differentiation of bone marrow-derived progenitor cells into monocytic MDSCs (Lim et al. 2014). MicroRNA-494, upregulated by TGF-beta1, is required for the accumulation and function of tumor-expanded MDSCs through targeting of PTEN (Liu et al. 2012).

Stromal Inflammation Promotes Tumor Angiogenesis (Inflammation-Induced Angiogenesis)

Inflammatory processes are a critical component of tumor progression, and part of this component consists of inflammation-induced angiogenesis. Inflammation-associated angiogenesis is promoted by CCL2-dependent monocytes (Ehling et al. 2014) and neutrophils. Via binding to the Tie2 receptor on macrophages, Ang1 can switch macrophages to a proinflammatory phenotype (Seok et al. 2013), which in turn can exert novel functions in the tumor stroma, such as MMP secretion and production of chemokines and cytokines acting on tumor cells.

Stromal Cells as Pacemakers of Tumor Angiogenesis

In addition to immune cells/leukocytes homing to tumor stroma, stromal cells themselves affect tumor angiogenesis and lymphangiogenesis. Hepatic stellate cells/HSCs have angiogenic features in liver cancer and are themselves stimulated by HCC cells (Sancho-Bru et al. 2010). HSCs are capable to secrete VEGF-A upon stimulation by factors produced by HCC cells, including PDGF-BB (Lu et al. 2015). Generation and maintenance of integrity of tumor microvessels is influenced by perivascular alpha-SMA-positive stromal cells/myofibroblasts, originating from HSCs. Low densities of these cells in HCCs are associated with poor microvessel integrity (Wang et al. 2013).

Subsets of cancer-associated fibroblasts (CAFs) are podoplanin-positive and involved in angiogenesis and lymphangiogenesis (Pula et al. 2013). VEGFs and their receptors are also expressed on subsets of hepatic progenitor cells, VEGF being involved in the expansion of the progenitor cell niche in liver disease (Franchitto et al. 2013).

Angiogenesis in Cholangiocarcinomas

Angiogenesis plays a significant role in cholangiocarcinoma, and both tumor-associated angiogenesis and lymphangiogenesis are correlated with tumor progression (Möbius et al. 2007; Thelen et al. 2010). Several angiogenic factors expressed in other tumors also promote angiogenesis in cholangiocarcinomas (Glaser et al. 2010). In intrahepatic cholangiocarcinomas (IHC), both angiogenesis and lymphangiogenesis are induced. In these cancers, a high microvessel density (MVD) is associated with advanced primary stage and recurrence, while a high lymph vessel density was correlated with nodal spread and recurrence (Thelen et al. 2010).

VEGFs and other angiogenic factors are expressed in cholangiocarcinomas, sometimes in correlation with microvessel density (Möbius et al. 2007; Cherry-Bohannan et al. 2012). Among 33 cholangiocarcinomas, 75.6 % were VEGF positive, 36 % were positive for Ang1, 57.6 % for Ang2, and 45.5 % for thrombospondin-1, whereby VEGF and Ang2 expression was associated with higher microvessel density levels (Tang et al. 2006). In regard to VEGF expression, there are certain differences between intra-and extrahepatic cholangiocarcinomas (Wiggers et al. 2014). In extrahepatic cholangiocarcinoma, VEGF expression was an independent negative predictor of prognosis (Hida et al. 1999). The neovasculature in cholangiocarcinomas can release Ang2 into circulation, providing a novel candidate for tumor monitoring (Voigtländer et al. 2014). Tumor angiogenesis also plays a role in gallbladder cancer development and progression (Okita et al. 1998), but did not affect prognosis (Sugawara et al. 1999). In gallbladder carcinoma, HIF-1alpha- and HIF-2alpha-induced VEGF expression was correlated with angiogenesis (Giatromanolaki et al. 2006), and thrombospondin-1 expression was associated with angiogenesis in these cancers (Harino et al. 2008). VEGFs are also overexpressed in hepatic progenitor cells located to ductular reaction (Franchitto et al. 2013). Similar to HCCs, tumor-associated, alternatively activated macrophages modulate angiogenesis in that they can secrete VEGF-A and MMP-2 in these neoplasms (Hasita et al. 2010).

As in HCC, angiogenesis is counteracted by several factors, whereby the sensors monitoring the balance between angiogenesis and anti-angiogenesis have not been clarified. Endothelin-1 binding to endothelin receptors ET(A) and ET (B) expressed in cholangiocarcinoma cells decreases the expression of VEGF-A, VEGF-C, EGFR-2, and VEGFR-3 in these neoplasms (Fava et al. 2009). In cholangiocarcinomas, angiogenesis is inhibited by microRNA-101 through targeting of VEGF (Zhang et al. 2013).

Angiogenesis in Benign Nodular Hepatocyte Lesions

Focal nodular hyperplasia (FNH) is a mass-forming lesion in part caused by an abnormal vascularization and focally deranged hepatic blood flow. In FNH, Ang1 is significantly upregulated, whereas Ang2 is downregulated, with a markedly increased Ang1/Ang2 ratio, much higher than in HCC, suggesting an Ang switch. As also the Tie2 receptor is expressed in FNH, the Ang1/Tie2 system may be involved in angiogenesis in this lesion, specifically in the generation of dystrophic and hyperplastic blood vessels (Paradis et al. 2003).

Lymphangiogenesis in Liver Cancers

Introduction

The lymph vessel system and lymphangiogenesis play a central role in progression and spread of cancers, including HCC and CC (Thelen et al. 2009). The principal mechanisms of

lymphangiogenesis in tumors resemble those in angiogenesis, but several other signaling pathways are involved, and tumors possess distinct lymphatic vessel subtypes (reviews: Al-Rawi et al. 2005; Witte et al. 2006; Sundar and Ganesan 2007; Cao et al. 2013; Chung and Iwakiri 2013; Stacker et al. 2014). Lymphangiogenesis in tumors depends on proliferation and migration of lymphatic endothelial cells (LECs), processes activated by several signals, including VEGF-C, VEGFR-3, and PDGFRbeta (Chen et al. 2012). In tumors, the cellular source of VEGF-C and VEGF-D for inducing lymphangiogenesis has been identified to be a subset of macrophages located in the stroma and expressing large amounts of these two factors (Schoppmann et al. 2002). VEGFR-3 signaling is critically involved in early phases of metastasis (Matsumoto et al. 2013). PDGFRbeta is a key mediator of tumor lymphatic vessel formation and acts downstream of Prox1 (Miyazaki et al. 2014). The proinflammatory cytokine, IL-6, promotes tumor lymphangiogenesis through VEGF-C induction in tumor cells, a process modulated by Src (Huang et al. 2014). Lymphatic cell migration, protection from apoptosis, and stimulation of lymph channel formation in tumors are promoted by apelin, the ligand of the G-protein-coupled APJ receptor (Berta et al. 2014; Yu et al. 2014). Lymphangiogenesis in tumors is also promoted by stromal cancer-associated fibroblasts/CAFs upon stimulation with the chemokine CXCL14 (Augsten et al. 2014) and is regulated by the neuropilin/semaphorin signaling system (Migliozzi et al. 2014). It was suggested that cancer cells themselves, or distinct subsets thereof, are capable of producing factors that promote lymphangiogenesis. On the other hand, this process is probably also stimulated by cancer stem cells (Li and Li 2014) and various cell types located to the tumor stroma, including immune cells.

Relatively few factors are known to inhibit lymphangiogenesis in tumors. Paralemmin-1 is a filopodia-and cell spine-inducing protein belonging to the paralemmin protein family, other members being paralemmin-2 and palmdelphin (Hu et al. 2001, 2005; Arstikaitis et al. 2008). Paralemmin-1 is expressed in LECs, represses LEC migration, and delays the formation of tubelike structures of LECs (Albrecht et al. 2013). Bone morphogenetic protein-9 inhibits lymphatic vessel formation through activin receptor-like kinase 1 during cancer progression (Yoshimatsu et al. 2013). The cytokine IL-27 inhibits proliferation of LECs by STAT1-regulated gene expression (Nielsen et al. 2013). MicroRNA-26a can induce endothelial cell cycle arrest and inhibit migration by targeting BMP/SMAD1 signaling (Icli et al. 2013). Lymphangiogenesis in cancers is closely related to metastatic spread. Newly formed lymphatic vessels in and around tumors not only increase lymph flow and its transport of cellular cargo, but lymphatic endothelial cells control tumor cell entry and exit from the lymphatic channels, and interact with immune cells (see below; Podgrabisnka and Skobe 2014).

Lymphangiogenesis and Lymphatic Spread in Hepatocellular Carcinoma

In HCCs, VEGF-C expression is higher in larger tumors and those of moderate or poor differentiation and is also detectable in large venous tumor casts, suggesting VEGF-C expression to be related to tumor progression (Yamaguchi et al. 2006).

Lymphangiogenesis and Lymphatic Spread in Cholangiocarcinomas

In intrahepatic cholangiocarcinomas, a higher lymphatic vessel density was present in the periphery and peritumoral area of poorly differentiated tumors, and lymphatic invasion predominated in these two areas. Lymphatic invasion was correlated with VEGF-C expression (Aishima et al. 2008).

Role of Lymphatic Vessels Other Than Tumor Cell Transport

There is increasing evidence that lymphatic vessels in and around tumors not only act as a physical route for tumor cell spread, but also form

important components of the cancer cell microenvironment and the pro-metastatic niche. Lymphatic endothelial cells exert immunomodulatory functions and regulate adaptive immunity (Card et al. 2014). Mechanisms involved comprise T cell suppression, inhibition of dendritic cell maturation, induction of T cell tolerance, and transendothelial antigen transport (review: Swartz 2014). Lymphatic vessel endothelium cells (LECs) induce peripheral tolerance by direct presentation to CD8(+) T cells and activation of these cells, and by deletion induced via programmed cell death-1 (PD-1) ligand 1 (Tewait et al. 2012). LECs interact with dendritic cells and regulate their homing and activation (Russo et al. 2013). On the other hand, LEC function in tumors and associated lymph nodes is modulated by immune effector cells and their chemokines/cytokines (Kataru et al. 2014). Lymphatic vessels serve as conduits for immunologic effector cells, and LECs control the homing and exit of immune cells. Tumor-associated macrophages/TAMs induce lymphangiogenesis via interaction with tumor cells and secretion of VEGF-C and VEGF-A (Ding et al. 2014). Tumor-derived interleukin-1 promotes lymphangiogenesis and M2-type macrophages that promote a metastatic microenvironment (Watari et al. 2014). Lymphangiogenesis is enhanced by podoplanin-positive monocytes (PPMs) and platelets (Watson et al. 2014), in that PPMs express VEGFR3 and proangiogenic transcription factors and interact with platelets expressing the podoplanin receptor, CLEC-2. Upon this interaction, platelets secrete the lymphangiogenic cytokine, interleukin-1beta (Hur et al. 2014).

References

Adachi Y, Takeuchi T, Sonobe H, Ohtsuki Y (2006) An adiponectin receptor, T-cadherin, was selectively expressed in intratumoral capillary endothelial cells in hepatocellular carcinoma: possible cross talk between T-cadherin and FGF-2 pathways. Virchows Arch 448:311–318

Adnane L, Trail PA, Taylor I, Wilhelm SM (2006) Sorafenib (BAY 43–9006, Nexavar), a dual-action inhibitor that targets RAF/MEK/ERK pathway in tumor cells and tyrosine kinases VEGFR/PDGFR in tumor vasculature. Methods Enzymol 407:597–612

Aird WC (2009) Molecular heterogeneity of tumor endothelium. Cell Tissue Res 335:271–281

Aishima S, Nishihara Y, Iguchi T, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M (2008) Lymphatic spread is related to VEGF-C expression and D2-40-positive myofibroblasts in intrahepatic cholangiocarcinoma. Mod Pathol 21:256–264

Albrecht I, Bieri R, Leu A, Granacher P, Hagmann J, Kilimann MW, Christofori G (2013) Paralemmin-1 is expressed in lymphatic endothelial cells and modulates cell migration, cell maturation and tumor lymphangiogenesis. Angiogenesis 16:795–807

Almog N (2013) Genes and regulatory pathways involved in persistence of dormant micro-tumors. Adv Exp Med Biol 734:3–17

Almog N, Ma L, Raychowdhury R, Schwager C, Erber R, Short S, Hlatky L, Vajkoczy P et al (2009) Transcriptional switch of dormant tumors to fast-growing angiogenic phenotype. Cancer Res 69:836–844

Al-Rawi MAA, Mansel RE, Jiang WG (2005) Lymphangiogenesis and its role in cancer. Histol Histopathol 20:283–298

Amaoka N, Saio M, Nonaka K, Imai H, Tomita H, Sakashita F, Takahashi T, Sugiyama Y et al (2006) Expression of vascular endothelial growth factor receptors is closely related to the histologic grade of hepatocellular carcinoma. Oncol Rep 16:3–10

Amit-Cohen BC, Rahat MM, Rahat MA (2013) Tumor cell-macrophage interactions angiogenesis through secretion of EMMPRIN. Front Physiol 4:178

Arstikaitis P, Gauthier-Campbell C, Carolina Gutierrez Herrera R, Huang K, Levinson JN et al (2008) Paralemmin-1, a modulator of filopodia induction is required for spine maturation. Mol Biol Cell 19:2026–2038

Augsten M, Sjöberg E, Frings O, Vorrink SU, Frijhoff J, Olsson E, Borg A, Östeman A (2014) Cancer-associated fibroblasts expressing CXCL14 rely upon NOS1-derived nitric oxide signaling for their tumor-supporting properties. Cancer Res 74: 2999–3010

Bach F, Uddin FJ, Burke D (2007) Angiopoietins in malignancy. Eur J Surg Oncol 33:7–15

Baeriswyl V, Christofori G (2009) The angiogenic switch in carcinogenesis. Semin Cancer Biol 19:329–337

Baluk P, Morikawa S, Haskell A, Mancuso M, McDonald DM (2003) Abnormalities of basement membrane on blood vessels and endothelial sprouts in tumors. Am J Pathol 163:1801–1815

Barajas M, Franchi F, Clavel C, Aranguren XL, Kramer MG, Abizanda G, Merino J et al (2007) Multipotent adult progenitor cells (MAPC) contribute to hepatocarcinoma neovasculature. Biochem Biophys Res Commun 364:92–99

Bellone M, Calcinotto A (2013) Ways to enhance lymphocyte trafficking into tumors and fitness of tumor infiltrating lymphocytes. Front Oncol 3:231

Belmont L, Rabbe N, Antoine M, Cathelin D, Guignabert C, Kurie J, Cadranel J, Wislez M (2014) Expression of TLR9 in tumor-infiltrating mononuclear cells enhances angiogenesis and is associated with a worse survival in lung cancer. Int J Cancer 134:765–777

Benzekry S, Gandolfi A, Hahnfeldt P (2014) Global dormancy of metastases due to systemic inhibition of angiogenesis. PLoS ONE 9, e84249

Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, Tanzawa K, Thorpe P et al (2000) Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol 2:737–744

Berta J, Hoda MA, Laszlo V, Rozsas A, Garay T, Torok S, Grusch M, Berger W, Paku S et al (2014) Apelin promotes lymphangiogenesis and lymph node metastasis. Oncotarget 5:4426–4437

Billottet C, Quemener C, Bikfalvi A (2013) CXCR3, a double-edged sword in tumor progression and angiogenesis. Biochim Biophys Acta 1836:287–295

Bonauer et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20415654

Bosisio D, Salvi V, Gagiostro V, Sozzani S (2014) Angiogenic and antiangiogenic chemokines. Chem Immunol Allergy 99:89–104

Brandau S, Moses K, Lang S (2013) The kinship of neutrophils and granulocytic myeloid-derived suppressor cells in cancer: cousins, siblings or twins? Semin Cancer Biol 23:171–182

Buonaguro L (2014) TIE-2-expressing monocytes: a possible cellular diagnostic and prognostic biomarker for hepatocellular carcinoma. Hepatobiliary Surg Nutr 3:419–420

Bupathi M, Kaseb A, Janku F (2014) Angiopoietin-2 as a therapeutic target in hepatocellular carcinoma treatment: current perspectives. Oncol Targets Ther 7:1927–1932

Burke M, Choksawangkarn W, Edwards N, Ostrand-Rosenberg S, Fenselau C (2014) Exosomes from myloid-derived suppressor cells carry biologically active proteins. J Proteome Res 13:836–843

Calcinotto A, Grioni M, Jachetti E, Curnis F, Mondino A, Parmiani G, Corti A, Bellone M (2012) Targeting TNF-α to neoangiogenic vessels enhances lymphocyte infiltration in tumors and increases the therapeutic potential of immunotherapy. J Immunol 188:2687–2694

Cao Z, Shang B, Zhang G, Miele L, Sarkar FH, Wang Z, Zhou Q (2013) Tumor cell-mediated neovascularization and lymphangiogenesis contrive tumor progression and cancer metastasis. Biochim Biophys Acta 1836:273–286

Capece D, Fischietti M, Verzella D, Gaggiano A, Cicciarelli G, Tessitore A, Zazzeroni F et al (2013) The inflammatory microenvironment in hepatocellular carcinoma: a pivotal role for tumor-associated macrophages. Biomed Res Int 2013:187204

Card CM, Yu SS, Swartz MA (2014) Emerging roles of lymphatic endothelium in regulating adaptive immunity. J Clin Invest 124:943–952

Carmi Y, Voronov E, Dotan S, Lahat N, Rahat MA, Fogel M, Huszar M, White MR, Dinarello CA, Apte RN (2009) The role of macrophage-derived IL-1 in induction and maintenance of angiogenesis. J Immunol 183:4705–4714

Carmi Y, Dotan S, Rider P, Kaplanov I, White MR, Baron R, Abutbul S, Huszar M, Dinarello CA, Apte RN, Voronov E (2013) The role of IL-1β in the early tumor cell-induced angiogenic response. J Immunol 190:3500–3509

Caronni N, Savino B, Bonecchi R (2015) Myeloid cells in cancer-related inflammation. Immunobiology 220:249–253

Carrion B, Kong YP, Kaigler D, Outnam AJ (2013) Bone marrow-derived mesenchymal stem cells enhance angiogenesis via their α6β1 integrin receptor. Exp Cell Res 319:2964–2976

Cervello M, Montalto G (2006) Cyclooxygenases in hepatocellular carcinoma. World J Gastroenterol 12:5113–5121

Chai ZT, Kong J, Zhu XD, Zhang YY, Lu L, Zhou JM, Wang LR, Zhang KZ, Zhang QB et al (2013) MicroRNA-26a inhibits angiogenesis by down-regulating VEGFA through the PIK3C2/Akt/HIF-1α pathway in hepatocellular carcinoma. PLoS ONE 8, e77957

Chambers SE, O'Neill CL, O'Doherty TM, Medina RJ, Stitt AW (2013) The role of immune-related myeloid cells in angiogenesis. Immunobiology 218:1370–1375

Chang YS, di Tomaso E, McDonald DM, Jones R, Jain RK, Munn LL (2000) Mosaic blood vessels in tumors: frequency of cancer cells in contact with flowing blood. Proc Natl Acad Sci U S A 97:14608–14613

Chao Y, Li CP, Chau GY, Chen CP, King KL, Lui WY, Yen SH, Chang FY et al (2003) Prognostic significance of vascular endothelial growth factor, basic fibroblast growth factor, and angiogenin in patients with resectable hepatocellular carcinoma after surgery. Ann Surg Oncol 10:355–362

Che N, Zhao XL, Sun T, Zhao XM, Gu Q, Dong XY, Zhao N, Liu YR, Yao Z, Sun BC (2011) The role of Twist1 in hepatocellular carcinoma angiogenesis: a clinical study. Hum Pathol 42:840–847

Chen H, Herndon ME, Lawler J (2000) The cell biology of thrombospondin-1. Matrix Biol 19:597–614

Chen L, Yang Z, Wang G, Wang C (2001) Expression of angiopoietin-2 gene and its receptor Tie2 in hepatocellular carcinoma. J Tongji Med Univ 21:228–230

Chen JC, Chang YW, Hong CC, Yu YH, Su JL (2012) The role of the VEGF-C/VEGFRs axis in tumor progression and therapy. Int J Mol Sci 14:88–107

Chen et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23426184

Chen J, Liu WB, Jia WD, Xu GL, Ma JL, Ren Y, Chen H, Sun SN, Huang M, Li JS (2014a) Embryonic morphogen nodal is associated with progression and poor prognosis of hepatocellular carcinoma. PLoS ONE 9, e85840

Chen X, Fang J, Wang S, Liu H, Du X, Chen J, Li X, Yang Y, Zhang B, Zhang W (2014b) A new mosaic pattern in glioma vascularization: exogenous endothelial progenitor cells integrating into the vessels containing tumor-derived endothelial cells. Oncotarget 5:1955–1968

Cherry-Bohannan J, Baker K, Francis H (2012) VEGF and cholangiocarcinoma: feeding the tumor. Transl Gastrointest Cancer 1:95–102

Chu LY, Ramakrishnan DP, Silverstein RL (2013) Thrombospondin-1 modulates VEGF signaling via CD36 by recruiting SHP-1 to VEGFR2 complex in microvascular endothelial cells. Blood 122:1822–1832

Chung C, Iwakiri Y (2013) The lymphatic vascular system in liver diseases: its role in ascites formation. Clin Mol Hepatol 19:99–104

Coffelt SB, Tal AO, Scholz A, De Palma M, Patel S, Urbich C, Biswas SK, Murdoch C et al (2010) Angiopoietin-2 regulates gene expression in TIE2-expressing monocytes and augments their inherent proangiogenic functions. Cancer Res 70:5270–5280

Coffelt SB, Chen YY, Muthana M, Welford AF, Tal AO, Scholz A, Plate KH, Reiss Y et al (2011) Angiopoietin 2 stimulates TIE2-expressing monocytes to suppress T cell activation and to promote regulatory T cell expansion. J Immunol 186:4183–4190

Condamine T, Ramachandran I, Youn JI, Gabrilovich DI (2015) Regulation of tumor metastasis by myeloid-derived suppressor cells. Annu Rev Med 66:97–110

Cui S, Hano H, Sakata A, Harada T, Liu T, Takai S, Ushigome S (1996) Enhanced CD34 expression of sinusoid-like vascular endothelial cells in hepatocellular carcinoma. Pathol Int 46:751–756

Cui Y, Lin C, Wu Z, Liu A, Zhang X, Zhu J, Wu G, Wu J, Li M, Li J, Song L (2014) AGK enhances angiogenesis and inhibits apoptosis via activation of the NF-kB signaling pathway in hepatocellular carcinoma. Oncotarget 5:12057–12069

Dai T, Zhang D, Cai M, Wang C, Wu Z, Ying Z, Wu J, Li M, Xie D, Li J, Song L (2015) Golgi phosphoprotein 3 (GOLPH3) promotes hepatocellular carcinoma cell aggressiveness by activating the NF-kB pathway. J Pathol 235:490–501

Dang K, Myers KA (2015) The role of hypoxia-induced miR-210 in cancer progression. Int J Mol Sci 16:6353–6372

Dapas B, Grassi M, Grassi G (2014) Can TIE-2 expressing monocytes represent a novel marker for hepatocellular carcinoma? Hepatobiliary Surg Nutr 3:175–178

De Palma M, Naldini L (2009) Tie2-expressing monocytes (TEMs): novel targets and vehicles of anticancer therapy ? Biochim Biophys Acta 1796:5–10

De Palma M, Murdoch C, Venneri MA, Naldini L, Lewis CE (2007) Tie2-expressing monocytes: regulation of tumor angiogenesis and therapeutic implications. Trends Immunol 28:519–524

De Palma M, Coukos G, Semela D (2013) TIE2-expressing monocytes: a novel cellular biomarker for hepatocellular carcinoma ? Hepatology 57:1294–1296

Deli G, Jin CH, Mu R, Yang S, Liang Y, Chen D, Makuuchi M (2005) Immunohistochemical assessment of angiogenesis in hepatocellular carcinoma and surrounding cirrhotic liver tissues. World J Gastroenterol 11:960–963

Deryugina EI, Zajac E, Juncker-Jensen A, Kupriyanova TA, Welter L, Quigley JP (2014) Tissue-infiltrating neutrophils constitute the major in vivo source of angiogenesis-inducing MMP-9 in the tumor microenvironment. Neoplasia 16:771–788

Dhanabal et al. 2002. http://www.ncbi.nlm.nih.gov/pubmed/15950186

Dhanabal et al. 2005. http://www.ncbi.nlm.nih.gov/pubmed/12097297

Dhar DK, Naora H, Yamanoi A, Ono T, Kohno H, Otani H, Nagasue N (2002) Requisite role for VEGF receptors in angiogenesis of hepatocellular carcinoma: a comparison with angiopoietin/Tie pathway. Anticancer Res 22:379–386

Di Tomaso E, Capen D, Haskell A, Hart J, Logie JJ, Jain RK, McDonald DM, Jones R et al (2005) Mosaic tumor vessels: cellular basis and ultrastructure of focal regions lacking endothelial cell markers. Cancer Res 65:5740–5749

Dias S, Choy M, Rafii S (2001) The role of CXC chemokines in the regulation of tumor angiogenesis. Cancer Invest 19:732–738

Dignat-George F, Boulanger CM (2011) The many faces of endothelial microparticles. Arterioscler Thromb Vasc Biol 31:27–33

Ding H, Cai J, Mao M, Fang Y, Huang Z, Jia J, Li T, Xu L, Wang J, Zhou J, Yang Q et al (2014) Tumor-associated macrophages induce lymphangiogenesis in cervical cancer via interaction with tumor cells. APMIS 122:1059–1069

Dirkx AE, ude Egbrink MG, Kuijpers MJ, vander Niet ST, Heijnen VV, Bouma-ter Steege JC, Wagstaff J, Griffioen AW (2003) Tumor angiogenesis modulates leukocyte-vessel wall interactions in vivo by reducing endothelial adhesion molecule expression. Cancer Res 63:2322–2329

Duff et al. 2003. http://www.ncbi.nlm.nih.gov/pubmed/12773481

Dumitru CA, Moses K, Trellakis S, Lang S, Brandau S (2012) Neutrophils and granulocytic myeloid-derived suppressor cells: immunophenotyping, cell biology and clinical relevance in human oncology. Cancer Immunol Immunother 61:1155–1167

Dumitru CA, Lang S, Brandau S (2013) Modulation of neutrophil granulocytes in the tumor microenvironment: mechanisms and consequences for tumor progression. Semin Cancer Biol 23:141–148

Ehling J, Bartneck M, Wei X, Gremse F, Fech V, Möckel D, Baeck C, Hittatiya K, Eulberg D et al (2014) CCL2-dependent infiltrating macrophages promote angiogenesis in progressive liver fibrosis. Gut 63:1960–1971

Ekström EJ, Bergenfelz C, von Bülow V, Serifler F, Carlemalm E, Jönsson G, Andersson T (2014) WNT5A induces release of exosomes containing

pro-angiogenic and immunosuppressive factors from malignant melanoma cells. Mol Cancer 13:88
Ellis L, Hammers H, Pili R (2009) Targeting tumor angiogenesis with histone deacetylase inhibitors. Cancer Lett 280:145–153
Fang JH, Zhou HC, Zeng C, Yang J, Liu Y, Huang X, Zhang JP, Guan XY, Zhuang SM (2011a) MicroRNA-29b suppresses tumor angiogenesis, invasion, and metastasis by regulating matrix metalloproteinase 2 expression. Hepatology 54:1729–1740
Fang L, Deng Z, Shatseva T, Yang J, Peng C, Du WW, Yee AJ, Ang LC, He C, Shan SW, Yang BB (2011b) MicroRNA miR-93 promotes tumor growth and angiogenesis by targeting integrin-β8. Oncogene 30:806–821
Farina AR, Mackay AR (2014) Gelatinase B/MMP-9 in tumour pathogenesis and progression. Cancers (Basel) 6:240–296
Fava G, Demorrow S, Gaudio E, Franchitto A, Onori P, Carpino G, Glaser S, Francis H et al (2009) Endothelin inhibits cholangiocarcinoma growth by a decrease in the vascular endothelial growth factor expression. Liver Int 29:1031–1042
Finn NA, Searles CD (2012) Intracellular and extracellular miRNAs in regulation of angiogenesis signaling. Curr Angiogenesis 4:299–307
Forget et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24892425
Franchitto A, Onori P, Renzi A, Carpino G, Mancinelli R, Alvaro D, Gaudio E (2013) Expression of vascular endothelial growth factors and their receptors by hepatic progenitor cells in human liver diseases. Hepatobiliary Surg Nutr 2:68–77
Fujita N, Nishie A, Aishima S, Kubo Y, Asayama Y, Ishigami K, Kakihara D, Ushijima Y et al (2014) Role of tumor-associated macrophages in the angiogenesis of well-differentiated hepatocellular carcinoma: pathological-radiological correlation. Oncol Rep 31:2499–2505
Garcia S, Krausz S, Ambarus CA, Fernandez BM, Hartkamp LM, van Es IE, Hamann J et al (2014) Tie2 signaling cooperates with TNF to promote the pro-inflammatory activation of human macrophages independently of macrophage functional phenotype. PLoS ONE 9, e82088
Gauglhofer C, Sagmeister S, Schrottmaier W, Fischer C, Rodgarkia-Dara C, Mohr T, Stättner S et al (2011) Up-regulation of the fibroblast growth factor 8 subfamily in human hepatocellular carcinoma for cell survival and neoangiogenesis. Hepatology 53:854–864
Geis T, Döring C, Popp R, Grossmann N, Fleming I, Hansmann M, Dehne N, Brüne B (2014) HIF-2alpha-dependent PAI-1 induction contributes to angiogenesis in hepatocellular carcinoma. Exp Cell Res. pii:S0014-4827(14)00521-7
Geng L, Chaudhuri A, Talmon G, Wisecarver JL, Are C, Brattain M, Wang J (2014) MicroRNA-192 suppresses liver metastasis of colon cancer. Oncogene 33:5332–5340
Germano D, Daniele B (2014) TIE2-expressing monocytes as a diagnostic marker for hepatocellular carcinoma correlates with angiogenesis. Hepatobiliary Surg Nutr 3:166–167
Ghanekar A, Ahmed S, Chen K, Adeyi O (2013) Endothelial cells do not arise from tumor-initiating cells in human hepatocellular carcinoma. BMC Cancer 13:485
Giatromanolaki A, Sivridis E, Simopoulos C, Polychronidis A, Gatter KC, Harris AL et al (2006) Hypoxia inducible factors 1alpha and 2alpha are associated with VEGF expression and angiogenesis in gallbladder carcinomas. J Surg Oncol 94:242–247
Glaser SS, Gaudio E, Alpini G (2010) Vascular factors, angiogenesis and biliary tract disease. Curr Opin Gastroenterol 26:246–250
Gorrin Rivas MJ, Arii S, Furutani M, Harada T, Mizumoto M, Nishiyama H, Fujita J et al (1998) Expression of human macrophage metalloelastase gene in hepatocellular carcinoma: correlation with angiostatin generation and its clinical significance. Hepatology 28:986–993
Gramantieri L, Fornari F, Callegari E, Sabbioni S, Lanza G, Croce CM, Bolondi L, Negrini M (2008) MicroRNA involvement in hepatocellular carcinoma. J Cell Mol Med 12:2189–2204
Greenhill C (2014) Hepatocellular carcinoma: new insight into angiogenesis in hepatocellular carcinoma – involvement of microRNA-26a. Nat Rev Gastroenterol Hepatol 11:3
Greening DW, Gopal SK, Mathias RA, Liu L, Sheng J, Zhu HJ, Simpson RJ (2015) Emerging roles of exosomes during epithelial-mesenchymal transition and cancer progression. Semin Cell Dev Biol. pii: S1084-9521(15)00035-X
Guo L, Kuroda N, Toi M, Miyazaki E, Hayashi Y, Enzan H, Jin Y (2001) Increased expression of platelet-derived endothelial cell growth factor in human hepatocellular carcinomas correlated with high Edmondson grades and portal vein tumor thrombosis. Oncol Rep 8:871–876
Guo C, Buranych A, Sarkar D, Fisher PB, Wang XY (2013) The role of tumor-associated macrophages in tumor vascularization. Vasc Cell 5:20
Hainaud P, Contrerès JO, Villemain A, Liu LX, Plouet J, Tobelem G, Dupuy E (2006) The role of the vascular endothelial growth factor-delta-like 4 ligand/Notch4-ephrin B2 cascade in tumor vessel remodeling and endothelial cell functions. Cancer Res 66:8501–8510
Hammam O, Mahmoud O, Zahran M, Sayed A, Salama R, Hosny K, Farghly A (2013) A possible role for TNF-α in coordinating inflammation and angiogenesis in chronic liver disease and hepatocellular carcinoma. Gastrointest Cancer Res 6:107–114
Harino Y, Imura S, Kanemura H, Morine Y, Fujii M, Ikegami T, Uehara H, Shimada M (2008) Role of tumor angiogenesis in gallbladder carcinoma: with

special reference to thymidine phosphorylase. Int J Clin Oncol 13:452–457
Hasita et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20545696
Hassan M, Selimovic D, El-Khattouti A, Soell M, Ghozlan H, Haikel Y, Abdelkader O, Megahed M (2014) Hepatitis C virus-mediated angiogenesis: molecular mechanisms and therapeutic strategies. World J Gastroenterol 20:15467–15475
Hellebrekers DM, Catsermans K, Viré E, Dings RP, Hoebers NT, Mayo KH, Oude Egbrink MG, Molema G, Fuks F et al (2006) Epigenetic regulation of tumor endothelial cell anergy: silencing of intercellular adhesion molecule-1 by histone modifications. Cancer Res 66:10770–10771
Hertel J, Hirche C, Wissmann C, Ebert MP, Höcker M (2014) Transcription of the vascular endothelial growth factor receptor-3 (VEGFR3) gene is regulated by the zinc finger proteins Sp1 and Sp3 and is under epigenetic control: transcription of vascular endothelial growth factor receptor 3. Cell Oncol (Dord) 37:131–145
Hida Y, Morita T, Fujita M, Miyasaka Y, Horita S, Fujioka Y, Nagashima K, Katoh H (1999) Vascular endothelial growth factor expression is an independent negative predictor in extrahepatic biliary tract carcinomas. Anticancer Res 19:2257–2260
Hida K, Kawamoto T, Ohga N, Akiyama K, Hida Y, Shindoh M (2011) Altered angiogenesis in the tumor microenvironment. Pathol Int 61:630–637
Hida K, Ohga N, Akiyama K, Maishi N, Hida Y (2013) Heterogeneity of tumor endothelial cells. Cancer Sci 104:1391–1395
Hira E, Ono T, Dhar DK, El-Assal ON, Hishikawa Y, Yamanoi A, Nagasue N (2005) Overexpression of macrophage migration inhibitory factor induces angiogenesis and deteriorates prognosis after radical resection for hepatocellular carcinoma. Cancer 103:588–598
Hirota K, Semenza GL (2006) Regulation of angiogenesis by hypoxia-inducible factor 1. Crit Rev Oncol Hematol 59:15–26
Ho JW, Poon RT, Sun CK, Xue WC, Fan ST (2005) Clinicopathological and prognostic implications of endoglin (CD105) expression in hepatocellular carcinoma and its adjacent non-tumorous liver. World J Gastroenterol 11:176–181
Ho JW, Pang RW, Lau C, Sun CK, Yu WC, Fan ST, Poon RT (2006) Significance of circulating endothelial progenitor cells in hepatocellular carcinoma. Hepatology 44:836–843
Ho MC, Chen CN, Lee H, Hsieh FJ, Shun CT, Chang CL, Lai YT, Lee PH (2007) Placenta growth factor not vascular endothelial growth factor A or C can predict the early recurrence after radical resection of hepatocellular carcinoma. Cancer Lett 250:237–249
Hood JL, Pan H, Lanza GM, Wickline SA (2009) Consortium for translational research in advanced imaging and nanomedicine (C-TRAIN). Lab Invest 89:1317–1328
Hosaka T, Kimura H, Heishi T, Suzuki Y, Miyashita H, Ohta H, Sonoda H, Moriya T et al (2009) Vasohibin-1 expression in endothelium of tumor blood vessels regulates angiogenesis. Am J Pathol 175:430–439
Hu B, Copeland NG, Gilbert DJ, Jenkins NA, Kilimann MW (2001) The paralemmin protein family: identification of paralemmin-2, an isoform differentially spliced to AKAP2/AKAP-KL, and of palmdelphin, a more distant cytosolic relative. Biochem Biophys Res Commun 285:1369–1376
Hu TH, Huang CC, Wu CL, Lin PR, Liu SY, Lin JW, Chuang JH, Tai MH (2005a) Increased endostatin/collagen XVIII expression correlates with elevated VEGF level and poor prognosis in hepatocellular carcinoma. Mod Pathol 18:663–672
Hu B, Petrasch-Parwez E, Laue MM, Kilimann MW (2005b) Molecular characterization and immunohistochemical localization of palmdelphin, a cytosolic isoform of the paralemmin protein family implicated in membrane dynamics. Eur J Cell Biol 84:853–866
Huang YH, Yang HY, Hsu YF, Chiu PT, Ou G, Hsu MJ (2014) Src contributes to IL-6-induced vascular endothelial growth factor-C expression in lymphatic endothelial cells. Angiogenesis 17:407–418
Hur J, Jang JH, Oh IY, Choi JI, Yun JY, Kim J, Choi YE, Ko SB, Kang JA, Lee SE et al (2014) Human podoplanin-positive monocytes and platelets enhance lymphangiogenesis through the activation of the podoplanin/CLEC-2 axis. Mol Ther 22:1518–1529.–
Icli B, Wara AK, Moslehi J, Sun X, Plovie E, Cahill M, Marchini JF, Schissler A, Padera RF et al (2013) MicroRNA-26a regulates pathological and physiological angiogenesis by targeting BMP/SMAD1 signaling. Circ Res 113:1231–1241
Iida H, Honda M, Kawai HF, Yamashita T, Shirota Y, Wang BC, Miao H, Kaneko S (2005) Ephrin-A1 expression contributes to the malignant characteristics of {alpha}-fetoprotein producing hepatocellular carcinoma. Gut 54:843–851
Imura S, Miyake H, Izumi K, Tashiro S, Uehara H (2004) Correlation of vascular endothelial cell proliferation with microvessel density and expression of vascular endothelial growth factor and basic fibroblast growth factor in hepatocellular carcinoma. J Med Invest 51:202–209
Infante T, Mancini FP, Lanza A, Soricelli A, de Nigris F, Napoli C (2015) Polycomb YY1 is a critical interface between epigenetic code and miRNA machinery after exposure to hypoxia in malignancy. Biochim Biophys Acta 1853:975–986
Ishii Y, Nakasato Y, Kobayashi S, Yamazaki Y, Aoki T (2003) A study on angiogenesis-related matrix metalloproteinase networks in primary hepatocellular carcinoma. J Exp Clin Cancer Res 22:461–470
Ito S, Miyashita H, Suzuki Y, Kobayashi M, Satomi S, Sato Y (2013) Enhanced cancer metastasis in mice deficient in vasohibin-1 gene. PLoS ONE 8, e73931
Jain RK, Koenig GC, Dellian M, Fukumura D, Munn LL, Melder RJ (1996) Leukocyte-endothelial adhesion and

angiogenesis in tumors. Cancer Metastasis Rev 15:195–204
Janowska-Wieczorek A, Wysoczynski M, Kijowski J, Marquez-Curtis L, Machalinski B, Ratajczak J, Ratajczak MZ (2005) Microvesicles derived from activated platelets induce metastasis and angiogenesis in lung cancer. Int J Cancer 113:752–760
Ji RC (2014) Hypoxia and lymphangiogenesis in tumor microenvironment and metastasis. Cancer Lett 346:6–16
Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH et al (2013) Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 31:3517–3524
Kahlert C, Kalluri R (2013) Exosomes in tumor microenvironment influence cancer progression and metastasis. J Mol Med (Berl) 91:431–437
Kataru RP, Lee YG, Koh GY (2014) Interactions of immune cells and lymphatic vessels. Adv Anat Embryol Cell Biol 214:107–118
Kawakita T, Shiraki K, Yamanaka Y, Yamaguchi Y, Saitou Y, Enokimura N, Yamamoto N et al (2004) Functional expression of TWEAK in human hepatocellular carcinoma: possible implication in cell proliferation and tumor angiogenesis. Biochem Biophys Res Commun 318:726–733
Keeley EC, Mehrad B, Strieter RM (2011) Chemokines as mediators of tumor angiogenesis and neovascularization. Exp Cell Res 317:685–690
Kiefer F, Siekmann AF (2011) The role of chemokines and their receptors in angiogenesis. Cell Mol Life Sci 68:2811–2830
Kim S, Abou-Alfa GK (2014) The role of tyrosine kinase inhibitors in hepatocellular carcinoma. Clin Adv Hematol Oncol 12:36–41
Kim KR, Moon HE, Kim KW (2002) Hypoxia-induced angiogenesis in human hepatocellular carcinoma. J Mol Med 80:703–714
Kim S, Park HS, Son HJ, Moon WS (2004) The role of angiostatin, vascular endothelial growth factor, matrix metalloproteinase 9 and 12 in the angiogenesis of hepatocellular carcinoma (in Korean). Kor J Hepatol 10:62–72
Kimura H, Nakajima T, Kagawa K, Deguchi T, Kakusui M, Katagishi T, Okanoue T et al (1998) Angiogenesis in hepatocellular carcinoma as evaluated by CD34 immunohistochemistry. Liver 18:14–19
Klenotic PA, Page RC, Li W, Amick J, Misra S, Silverstein RL (2013) Molecular basis of antiangiogenic thrombospondin-1 type 1 repeat domain interactions with Cd36. Arterioscler Thromb Vasc Biol 33:1655–1662
Korpelainen EI, Karkkainen M, Gunji Y, Vikkula M, Alitalo K (1999) Endothelial receptor tyrosine kinases activate the STAT signaling pathway: mutant TIE-2 causing venous malformations signals a distinct STAT activation response. Oncogene 18:1–8
Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, Yin XY, Zheng L (2011) Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol 54:948–955
Lawler 2002. http://www.ncbi.nlm.nih.gov/pubmed/12003665
Lee JK, Park SR, Jung BK, Jeon YK, Lee YS, Kim MK, Kim YG, Jang JY, Kim CW (2013) Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. PLoS ONE 8, e84256
Lewis CE, De Palma M, Naldini L (2007) Tie2-expressing monocytes and tumor angiogenesis: regulation by hypoxia and angiopoietin-2. Cancer Res 67:8429–8432
Li S, Li Q (2014) Cancer stem cells and tumor metastasis (review). Int J Oncol 44:1806–1812
Li Z, Tu M, Han B, Gu Y, Xue X, Sun J, Ge Q, Miao Y, Qian Z, Gao W (2014) Vasohibin 2 decreases the cisplatin sensitivity of hepatocarcinoma cell line by downregulating p53. PLoS ONE 9, e90358
Lim HX, Hong HJ, Cho D, Kim TS (2014) IL-18 enhances immunosuppressive responses by promoting differentiation into monocytic myeloid-derived suppressor cells. J Immunol 193:5453–5460
Lin YL, Liang YC, Chiang BL (2007) Placental growth factor down-regulates type 1 T helper immune response by modulating the function of dendritic cells. J Leukoc Biol 82:1473–1480
Lin L, Han MM, Wang F, Xu LL, Yu HX, Yang PY (2014) CXCR7 stimulates MAPK signaling to regulate hepatocellular carcinoma progression. Cell Death Dis 5, e1488
Liu Y, Lai L, Chen Q, Song Y, Xu S, Ma F, Wang X, Wang J, Yu H, Cao X, Wang Q (2012) MicroRNA-494 required for the accumulation and functions of tumor-expanded myeloid-derived suppressor cells via targeting of PTEN. Immunol 188:5500–5510
Liu Y, Zhao L, Li D, Yin Y, Zhang CY, Li J, Zhang Y (2013) Microvesicle-delivery miR-150 promotes tumorigenesis by up-regulating VEGF, and the neutralization of miR-150 attenuate tumor development. Protein Cell 4:932–941
Lu Y, Lin N, Chen Z, Xu R (2015) Hypoxia-induced secretion of platelet-derived growth factor-BB by hepatocellular carcinoma cells increases activated hepatic stellate cell proliferation, migration and expression of vascular endothelial growth factor-A. Mol Med Rep 11:691–697
Luo D, Wang Z, Wu J, Jiang C, Wu J (2014) The role of hypoxia inducible factor-1 in hepatocellular carcinoma. Biomed Res Int 2014:409272
Madanecki et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23124858
Martinet L, Garrido I, Filleron T, Le Guellec S, Bellard E, Fournie JJ, Rochaix P, Girard JP (2011) Human solid tumors contain high endothelial venules: association with T-and B-lymphocyte infiltration and favorable prognosis in breast cancer. Cancer Res 71:5678–5687

Martinet L, Filleron T, Le Guellec S, Rochaix P, Garrido I, Girard JP (2013) High endothelial venule blood vessels for tumor-infiltrating lymphocytes are associated with lymphotoxin β-producing dendritic cells in human breast cancer. J Immunol 191:2001–2008

Martinez MC, Andriantsitohaina R (2011) Microparticles in angiogenesis: therapeutic potential. Circ Res 109:110–119

Matsubara T, Kanto T, Kuroda S, Yoshio S, Higashitani K, Kakita N, Miyazaki M, Sakakibara M et al (2013) TIE-2 expressing monocytes as a diagnostic marker for hepatocellular carcinoma correlates with angiogenesis. Hepatology 57:1416–1425

Matsumoto M, Roufail S, Inder R, Caesar C, Karnezis T, Shayan R, Farnsworth RH et al (2013) Signaling for lymphangiogenesis via VEGFR-3 is required for the early events of metastasis. Clin Exp Metastasis 30:819–832

McMahon G (2000) VEGF receptor signaling in tumor angiogenesis. Oncologist 5(suppl 1):3–10

Medina RJ, O'Neill CL, O'Doherty TM, Knott H, Guduric-Fuchs J, Gardiner TA, Stitt AW (2011) Myeloid angiogenic cells act as alternative M2 macrophages an modulate angiogenesis through interleukin-8. Mol Med 17:1045–1055

Miayahara K, Nouso K, Morimoto Y, Takeuchi Y, Hagihara H, Kuwaki K, Onishi H et al (2013) Pro-angiogenic cytokines for prediction of outcomes in patients with advanced hepatocellular carcinoma. Br J Cancer 109:2072–2078

Migliozzi MT, Mucka P, Bielenberg DR (2014) Lymphangiogenesis and metastasis-A closer look at the neuropilin/semaphorin3 axis. Microvasc Res. doi:10.1016/j.mcr.2014.07.006

Minhajat R, Mori D, Yamasaki F, Sugita Y, Satoh T, Tokunaga O (2006) Organ-specific endoglin (CD105) expression in the angiogenesis of human cancers. Pathol Int 56:717–723

Mitsuhashi N, Shimizu H, Ohtsuka M, Wakabayashi Y, Ito H, Kimura F, Yoshidome H et al (2003) Angiopoietins and Tie-2 expression in angiogenesis and proliferation of human hepatocellular carcinoma. Hepatology 37:1105–1113

Miyazaki H, Yoshimatsu Y, Akatsu Y, Mishima K, Fukayama M, Atabe T, Miyazono K (2014) Expression of platelet-derived growth factor receptor β is maintained by Prox1 in lymphatic endothelial cells and is required for tumor lymphangiogenesis. Cancer Sci 105:1116–1123

Möbius C, Demuth C, Aigner T, Wiedmann M, Wittekind C, Mössner J, Hauss J, Witzigmann H (2007) Evaluation of VEGF A expression and microvascular density as prognostic factors in extrahepatic cholangiocarcinoma. Eur J Surg Oncol 33:1025–1029

Monu NR, Frey AB (2012) Myeloid-derived suppressor cells and anti-tumor T cells: a complex relationship. Immunol Invest 41:595–613

Moon WS, Rhyu KH, Kang MJ, Lee DG, Yu HC, Yeum JH, Koh GY, Tarnawski AS (2003) Overexpression of VEGF and angiopoietin 2: a key to high vascularity of hepatocellular carcinoma? Mod Pathol 16:552–557

Moon EJ, Jeong CH, Jeong JW, Kim KR, Yu DY, Murakami S, Kim CW, Kim KW (2004) Hepatitis B virus X protein induces angiogenesis by stabilizing hypoxia-inducible factor-1alpha. FASEB J 18:382–384

Morinaga S, Imada T, Shimizu A, Akaike M, Sugimasa Y, Takemiya S, Takanashi Y (2001) Angiogenesis in hepatocellular carcinoma as evaluated by alpha smooth muscle actin immunohistochemistry. Hepato-Gastroenterology 48:224–228

Moschetta M, Mishima Y, Sahin I, Manier S, Göavey S, Vacca A, Roccaro AM, Ghobrial IM (2014) Role of endothelial progenitor cells in cancer progression. Biochim Biophys Acta 1846:26–39

Moserle et al. 2009. http://www.ncbi.nlm.nih.gov/pubmed/19925406

Murakami K, Kasajima A, Kawagishi N, Sekiguchi S, Fujishima F, Watanabe M, Sato Y et al (2014) The prognostic significance of vasohibin 1-associated angiogenesis in patients with hepatocellular carcinoma. Hum Pathol 45:589–597

Musso O, Theret N, Heljasvaara R, Rehn M, Turlin B, Campion JP, Pihlajaniemi T et al (2001) Tumor hepatocytes and basement membrane-producing cells specifically express two different forms of the endostatin precursor, collagen XVIII, in human liver cancers. Hepatology 33:868–876

Muto J, Shirabe K, Yoshizumi T, Ikegami T, Aishima S, Ishigami K, Yonemitsu Y, Ikeda T, Soejima Y, Maehara Y (2014) The apelin-APJ system induces tumor arteriogenesis in hepatocellular carcinoma. Anticancer Res 34:5313–5320

Muto J, Shirabe K, Sugimachi K, Maehara Y (2015) Review of angiogenesis in hepatocellular carcinoma. Hepatol Res. doi:10.1111/hepr

Muturi HT, Dreesen JD, Nilewski E, Jastrow H, Giebel B, Ergun S, Singer BB (2013) Tumor and endothelial cell-derived microvesicles carry distinct CEACAMs and influence T-cell behavior. PLoS ONE 8:e74654

Nakamura T (2009) Changes in expression of bile canalicular CD10 and sinusoidal CD105 (endoglin) in peritumoral hepatic tissue. Tumori 95:495–500

Ng KT, Xu A, Cheng Q, Guo DY, Lim ZX, Sun CK, Fung JH, Poon RT, Fan ST, Lo CM, Man K (2014) Clinical relevance and therapeutic potential of angiopoietin-like protein 4 in hepatocellular carcinoma. Mol Cancer 13:196

Nielsen SR, Hammer T, Gibson J, Pepper MS, Nisato RE, Dissing S, Tritsaris K (2013) IL-27 inhibits lymphatic endothelial cell proliferation by STAT1-regulated gene expression. Mirocirculation 20:555–564

Ning H, Shao QQ, Ding KJ, Gao DX, Lu QL, Cao QW, Niu ZH, Fu Q, Zhang CH et al (2012) Tumor-infiltrating regulatory T cells are positively correlated with angiogenic status in renal cell carcinoma. Chin Med J (Engl) 125:2120–2125

Nissim Ben Efrain AH, Levi-Schaffer F (2014) Roles of eosinophils in the modulation of angiogenesis. Chem Immunol Allergy 99:138–154

Niu RF, Zhang L, Xi GM, Wie XY, Yang Y, Shi YR, Hao XS (2007) Up-regulation of Twist induces angiogenesis and correlates with metastasis in hepatocellular carcinoma. J Exp Clin Cancer Res 26:385–394

Nolan DJ, Ciarrocchi A, Mellick AS, Jaggi JS, Bambino K, Gupta S, Heikamp E, McDevitt MR et al (2007) Bone marrow-derived endothelial progenitor cells are a major determinant of nascent tumor neovascularization. Genes Dev 21:1546–1558

Nomura T, Morishita A, Jian G, Mimura S, Kato K, Nomura K, Tani J, Miyoshi H, Yoneyama H et al (2013) Expression of angiogenic factors in hepatocarcinogenesis: identification by antibody arrays. Oncol Rep 30:2476–2480

Ohm JE, Carbone DP (2001) VEGF as a mediator of tumor-associated immunodeficiency. Immunol Res 23:263–272

Okita S, Kondoh S, Shiraishi K, Kaino S, Hatano S, Okita K (1998) Expression of vascular endothelial growth factor correlates with tumor progression in gallbladder cancer. Int J Oncol 12:1013–1018

Oyama T, Ran S, Ishida T, Nadaf S, Kerr L, Carbone DP, Gabrilovich DI (1998) Vascular endothelial growth factor affects dendritic cell maturation through the inhibition of nuclear factor-kappa B activation in hemopoietic progenitor cells. J Immunol 160:1224–1232

Pang and Poon 2006. http://www.ncbi.nlm.nih.gov/pubmed/16564617

Paradis V, Bieche I, Dargere D, Laurendeau I, Nectoux J, Degott C, Belghiti J, Vidaud M et al (2003) A quantitative gene expression study suggests a role for angiopoietins in focal nodular hyperplasia. Gastroenterology 124:651–659

Park YN, Kim YB, Yang KM, Park C (2000) Increased expression of vascular endothelial growth factor and angiogenesis in the early stage of multistep hepatocarcinogenesis. Arch Pathol Lab Med 124:1061–1065

Patenaude A, Parker J, Karsan A (2010) Involvement of endothelial progenitor cells in tumor vascularization. Microvasc Res 79:217–223

Pecot CV, Rupaimoole R, Yang D, Akbani R, Ivan C, Lu C, Wu S, Han HD, Shah MY et al (2013) Tumour angiogenesis regulation by the miR-200 family. Nat Commun 4:2427

Pezzolo A, Parodi F, Corrias MV, Cinti R, Gambini C, Pistoia V (2007) Tumor origin of endothelial cells in human neuroblastoma. J Clin Oncol 25:376–383

Pillay J, Tak T, Kamp VM, Koenderman L (2013) Immune suppression by neutrophils and granulocytic myeloid-derived suppressor cells: similarities and differences. Cell Mol Life Sci 70:3813–3827

Ping YF, Bian XW (2011) Concise review: contribution of cancer stem cells to neovascularization. Stem Cells 29:888–894

Png KJ, Halberg N, Yoshida M, Tavazoie SF (2011) A microRNA regulon that mediates endothelial recruitment and metastasis by cancer cells. Nature 481:190–194

Podgrabinska S, Skobe M (2014) Role of lymphatic vasculature in regional and distant metastases. Microvasc Res 95C:58–52

Poon RT, Chung KK, Cheung ST, Lau CP, Tong SW, Leung KL, Yu WC, Tuszynski GP et al (2004) Clinical significance of thrombospondin 1 expression in hepatocellular carcinoma. Clin Cancer Res 10:4150–4157

Pula B, Witkiewicz W, Dziegiel P, Podhorska-Okolow M (2013) Significance of podoplanin expression in cancer-associated fibroblasts: a comprehensive review. Int J Oncol 42:1849–1857

Rana S, Malinowska K, Zöller M (2013) Exosomal tumor microRNA modulates premetastatic organ cells. Neoplasia 15:281–295

Ren Y, Tsui HT, Poon RT, Ng IO, Li Z, Chen Y, Jiang G, Lau C, Yu WC, Bacher M et al (2003) Macrophage migration inhibitory factor: roles in regulating tumor cell migration and expression of angiogenic factors in hepatocellular carcinoma. Int J Cancer 107:22–29

Riabov V, Gudima A, Wang N, Mickley A, Orekhov A, Kzhyshkowska J (2014) Role of tumor associated macrophages in tumor angiogenesis and lymphangiogenesis. Front Physiol 5:75

Ribatti D (2004) The involvement of endothelial progenitor cells in tumor angiogenesis. J Cell Mol Med 8:294–300

Ribatti D (2009) The paracrine role of Tie-2-expressing monocytes in tumor angiogenesis. Stem Cells Dev 18:703–706

Ribatti D, Vacca A, Nico B, Sansonno D, Dammacco F (2006) Angiogenesis and anti-angiogenesis in hepatocellular carcinoma. Cancer Treat Rev 32:437–444

Ribatti D, Nico B, Crivellato E, Vacca A (2007) The structure of the vascular network of tumors. Cancer Lett 248:18–23

Ruck P, Xiao JC, Kaiserling E (1995) Immunoreactivity of sinusoids in hepatocellular carcinoma: an immunohistochemical study using lectin UEA-1 and antibodies against endothelial markers, including CD34. Arch Pathol Lab Med 119:173–178

Russo E, Nitschké M, Halin C (2013) Dendritic cell interactions with lymphatic endothelium. Lymphat Res Biol 11:172–182

Sagiv JY, Michaeli J, Assi S, Mishalian I, Kisos H, Levy L, Damti P, Lumbroso D, Polyansky L, Sionov RV, Ariel A et al (2015) Phenotypic diversity and plasticity in circulating neutrophil subpopulations in cancer. Cell Rep 10:562–573

Sahin M, Sahin E, Gümüslü S, Erdogan A, Gültekin M (2010) DNA methylation or histone modification status in metastasis and angiogenesis-related genes: a new hypothesis on usage of DNMT inhibitors and S-adenosylmethionine for genome stability. Cancer Metastasis Rev 29:655–676

Salcedo R, Oppenheim JJ (2003) Role of chemokines in angiogenesis: CXCL12/SDF-1 and CXCR4 interaction,

a key regulator of endothelial cell responses. Microcirculation 10:359–370
Salomon C, Ryan J, Sobrevia L, Kobayashi M, Ashman K, Mitchell M, Rice GE (2013) Exosomal signaling during hypoxia mediates microvascular endothelial cell migration and vasculogenesis. PLoS ONE 8, e68451
Salvucci O, Yao L, Villalba S, Sajewicz A, Pittaluga S, Tosato G (2002) regulation of endothelial cell branching morphogenesis by endogenous chemokine stromal-derived factor-1. Blood 99:2703–2711
Sancho-Bru P, Juez E, Moreno M, Khurdayan V, Morales-Ruiz M, Colmenero J, Arroyo V et al (2010) Hepatocarcinoma cells stimulate the growth, migration and expression of proangiogenic genes in human hepatic stellate cells. Liver Int 30:31–41
Santoni M, Bracarda S, Nabissi M, Massari F, Conti A, Bria E, Tortora G, Santoni G et al (2014) CXC and CC chemokines as angiogenic modulators in nonhaematological tumors. Biomed Res Int 2014:768758
Sanz-Cameno P, Martin-Vilchez S, Lara-Pezzi E, Borque MJ, Salmeron J, Munoz de Rueda P et al (2006) Hepatitis B virus promotes angiopoietin-2 expression in liver tissue: role of HBV x protein. Am J Pathol 169:1215–1222
Sawai Y, Tamura S, Fukui K, Ito N, Imanaka K, Saeki A, Sakuda S, Kiso S, Matsuzawa Y (2003) Expression of ephrin-B1 in hepatocellular carcinoma: possible involvement in neovascularization. J Hepatol 39:991–996
Sawamiphak S, Seidel S, Essmann CL, Wilkinson GA, Pitulescu ME, Acker T, Acker-Palmer A (2010) Ephrin-B2 regulates VEGFR2 function in developmental and tumour angiogenesis. Nature 465:487–491
Scartozzi M, Faloppi L, Svegliati Baroni G, Loretelli C, Piscaglia F, Iavarone M, Toniutto P et al (2014) VEGF and VEGFR genotyping in the prediction of clinical outcome for HCC patients receiving sorafenib: the ALICE-1 study. Int J Cancer 135:1247–1256
Schauer D, Starlinger P, Zajc P, Alidzanovic L, Maier T, Buchberger E, Pop L, Gruenberger B, Brostjan C (2014) Monocytes with angiogenic potential are selectively induced by liver resection and accumulate near the site of liver regeneration. BMC Immunol 15:50
Schmieder A, Michel J, Schönhaar K, Goerdt S, Schledzewski K (2012) Differentiation and gene expression profile of tumor-associated macrophages. Semin Cancer Biol 22:289–297
Schoppmann SF, Birner P, Stöckl J, Kalt R, Ullrich R, Caucig C, Kriehuber E, Nagy K et al (2002) Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis. Am J Pathol 161:947–956
Semela D, Dufour JF (2004) Angiogenesis and hepatocellular carcinoma. J Hepatol 41:864–880
Seok et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23686433
Sharghi-Namini S, Tan E, Ong LL, Ge R, Asada HH (2014) DII4-containing exosomes induce capillary sprout retraction in a 3D microenvironment. Sci Rep 4:4031
Sharma BK, Srinivasan R, Kapil S, Singla B, Chawla YK, Chakraborti A, Saini N, Duseja A et al (2013) Angiogenic and anti-angiogenic factor gene transcript level quantitation by quantitative real time PCR in patients with hepatocellular carcinoma. Mol Biol Rep 40:5843–5852
Sheng J, Yu W, Gao X, Xu Z, Hu GF (2014) Angiogenin stimulates ribosomal RNA transcription by epigenetic activation of the ribosomal DNA promoter. J Cell Physiol 229:521–529
Shi L, Fisslthaler B, Zippel N, Frömel T, Hu J, Elgheznawy A, Heide H, Popp R, Fleming I (2013) MicroRNAs-223 antagonises angiogenesis by targeting β1 integrin and preventing growth factor signaling in endothelial cells. Circ Res 113:1320–1330
Shih YT, Wang MC, Peng HH, Chen TF, Chen L, Chang JY, Chiu JJ (2012a) Modulation of chemotactic and pro-inflammatory activities of endothelial progenitor cells by hepatocellular carcinoma. Cell Signal 24:779–793
Shih TC, Tien YJ, Wen CJ, Yeh TS, Yu MC, Huang CH, Lee YS, Yen TC, Hsieh SY (2012b) MicroRNA-214 downregulation contributes to tumor angiogenesis by inducing secretion of the hepatoma-derived growth factor in human hepatoma. J Hepatol 57:584–591
Shimamura T, Saito S, Morita K, Kitamura T, Morimoto M, Kiba T, Namata K, Tanaka K et al (2000) Detection of vascular endothelial growth factor and its receptor expression in human hepatocellular carcinoma biopsy specimens. J Gastroenterol Hepatol 15:640–646
Shimoda K, Mori M, Shibuta K, Banner BF, Barnard GF (1999) Vascular endothelial growth factor/vascular permeability factor mRNA expression in patients with chronic hepatitis C and hepatocellular carcinoma. Int J Oncol 14:353–359
Sieghart W, Fellner S, Reiberger T, Ulbrich G, Ferlitsch A, Wacheck V, Peck-Radosavljevic M (2009) Differential role of circulating endothelial progenitor cells in cirrhotic patients with or without hepatocellular carcinoma. Dig Liver Dis 41:902–906
Simantov R, Silverstein RL (2003) CD36: a critical anti-angiogenic receptor. Front Biosci 8:s874–s882
Soff G (2003) Angiostatin and hepatocellular carcinoma. Hepatology 37:505–506
Soloviev DA, Hazen SL, Szpak D, Bledzka KM, Ballantyne CM, Plow EF, Pluskota E (2014) Dual role of the leukocyte integrin αMβ2 in angiogenesis. J Immunol 193:4712–4721
Song Y, Zhao XP, Song K, Shang ZJ (2013) Ephrin-A1 is up-regulated by hypoxia in cancer cells and promotes angiogenesis of HUVECs through a coordinated crosstalk with eNOS. PLoS ONE 8, e74464
Song R, Song H, Liang Y, Yin D, Zhang H, Zheng T, Wang J, Lu Z, Song X, Pei T et al (2014) Reciprocal

activation between ATPase inhibitory factor 1 abd NF-kB drives hepatocellular carcinoma angiogenesis and metastasis. Hepatology 60:1659–1673
Stacker SA, Williams SP, Karnezis T, Shayan R, Fox SB, Achen MG (2014) Lymphangiogenesis and lymphatic vessel remodeling in cancer. Nat Rev Cancer 14:159–172
Stellos K, Gawaz M (2007) Platelets and stromal cell-derived factor-1 in progenitor cell recruitment. Semin Thromb Hemost 33:159–164
Stockmann C, Schadendorf D, Klose R, Helfrich I (2014) The impact of the immune system on tumor: angiogenesis and vascular remodeling. Front Oncol 4:69
Sugawara Y, Makuuchi M, Harihara Y, Noie T, Inoue K, Kubota K, Takayama T (1999) Tumor angiogenesis in gallbladder carcinoma. Hepato-Gastroenterology 46:1682–1686
Sugimachi K, Tanaka S, Taguchi K, Aishima S, Shimada M, Tsuneyoshi M (2003) Angiopoietin switching regulates angiogenesis and progression of human hepatocellular carcinoma. J Clin Pathol 56:854–860
Sun XT, Yuan XW, Zhu HT, Deng ZM, Yu DC, Zhou X, Ding YT (2012) Endothelial precursor cells promote angiogenesis in hepatocellular carcinoma. World J Gastroenterol 18:4925–4933
Sundar SS, Ganesan TS (2007) Role of lymphangiogenesis in cancer. J Clin Oncol 25:4298–4307
Swartz MA (2014) Immunomodulatory roles of lymphatic vessels in cancer progression. Cancer Immunol Res 2:701–707
Tadokoro H, Umezu T, Ohyashiki K, Hirano T, Ohyashiki JH (2013) Exosomes derived from hypoxic leukemia cells enhance tube formation in endothelial cells. J Biol Chem 288:34343–34351
Taguchi A, Kawana K, Tomio K, Yamashita A, Isobe Y, Nagasaka K, Koga K, Inoue T et al (2014) Matrix metalloproteinase (MMP)-9 in cancer associated fibroblasts (CAFs) is suppressed by omega-3 polyunsaturated fatty acids in vitro and in vivo. PLoS ONE 9, e89605
Takahashi S (2011) Vascular endothelial growth factor (VEGF), VEGF receptors and their inhibitors for antiangiogenic tumor therapy. Biol Pharm Bull 34:1785–1788
Tan et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/24113869
Tanaka S, Sugimachi K, Yamashita Y, Shirabe K, Shimada M, Wands JR, Sugimachi K (2003) Angiogenic switch as a molecular target of malignant tumors. J Gastroenterol 38(suppl 15):93–97
Tang D, Nagano H, Yamamoto H, Wada H, Nakamura M, Kondo M, Ota H, Yoshioka S et al (2006) Angiogenesis in cholangiocellular carcinoma: expression of vascular endothelial growth factor, angiopoietin-1/2, thrombospondin-1 and clinicopathological significance. Oncol Rep 15:525–532
Tao KS, Dou KF, Wu XA (2004) Expression of angiostatin cDNA in human hepatocellular carcinoma cell line SMMC-7721 and its effect on implanted carcinoma in nude mice. World J Gastroenterol 10:1421–1424
Taverna S, Flugy A, Saieva L, Kohn EC, Santoro A, Meraviglia S, De Leo G, Alessandro R (2012) Role of exosomes released by chronic myelogenous leukemia cells in angiogenesis. Int J Cancer 130:2033–2043
Taylor DD, Gercel-Taylor C (2011) Exosomes/microvesicles: mediators of cancer-associated immunosuppressive microenvironments. Semin Immunopathol 33:441–454
Tecchio C, Cassatella MA (2014) Neutrophil-derived cytokines involved in physiological and pathological angiogenesis. Chem Immunol Allergy 99:123–137
Tecchio C, Scapini P, Pizzolo G, Cassatella MA (2013) On the cytokines produced by human neutrophils in tumors. Semin Cancer Biol 23:159–170
Ten Dijke P, Egorova AD, Goumans MJ, Poelmann RE, Hierck BP (2012) TGF-β1 signaling in endothelial-to-mesenchymal transition: the role of shear stress and primary cilia. Sci Signal 5:pt2
Tewait EF, Cohen JN, Rouhani SJ, Guidi CJ, Qiao H, Fahl SP, Conaway MR, Bender TP et al (2012) Lymphatic endothelial cells induce tolerance via PD-L1 and lack of costimulation leading to high-level PD-1 expression on CD8 T cells. Blood 120:4772–4782
Thelen A, Jonas S, Benckert C, Weichert W, Schott E, Bötcher C, Dietz E, Wiedenmann B, Neuhaus P, Scholz A (2009) Tumor-associated lymphangiogenesis correlates with prognosis after resection of human hepatocellular carcinoma. Ann Surg Oncol 16:1222–1230
Thelen A, Scholz A, Weichert W, Wiedenmann B, Neuhaus P, Gessner R, Benckert C et al (2010) Tumor-associated angiogenesis and lymphangiogenesis correlate with progression of intrahepatic cholangiocarcinoma. Am J Gastroenterol 105:1123–1132
Thuma F, Zöller M (2014) Outsmart tumor exosomes to steal the cancer initiating cell its niche. Semin Cancer Biol 28:39–50
Tian H, Huang P, Zhao Z, Tang W, Xia J (2014) HIF-1α plays a role in the chemotactic migration of hepatocarcinoma cells through the modulation of CXCL expression. Cell Physiol Biochem 34:1536–1546
Torimura T, Sata M, Uena T, Kin M, Tsuji R, Suzaku K, Hashimoto O, Sugawara H et al (1998) Increased expression of vascular endothelial growth factor is associated with tumor progression in hepatocellular carcinoma. Hum Pathol 29:986–991
Torimura T, Ueno T, Kin M, Harada R, Taniguchi E, Nakamura T, Sakata R, Hashimoto O et al (2004) Overexpression of angiopoietin-1 and angiopoietin-2 in hepatocellular carcinoma. J Hepatol 40:799–807
Van Balkom et al. 2013. http://www.ncbi.nlm.nih.gov/pubmed/23532734
Vandooren J, Van den Steen PE, Opdenakker G (2013) Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9): the next decade. Crit Rev Biochem Mol Biol 48:222–272

Van Laake et al. 2006. http://www.ncbi.nlm.nih.gov/pubmed/17088457

Verma A (2006) Oxygen-sensing in tumors. Curr Opin Clin Nutr Metab Care 9:366–378

Voigtländer T, David S, Thamm K, Schlué J, Metzger J, Manns MP, Lankisch TO (2014) Angiopoietin-2 and biliary diseases: elevated serum, but not bile levels are associated with cholangiocarcinoma. PLoS ONE 9, e97046

Von Marschall Z, Cramer T, Hocker M, Finkenzeller G, Wiedenmann B, Rosewicz S (2001) Dual mechanism of vascular endothelial growth factor upregulation by hypoxia in human hepatocellular carcinoma. Gut 48:87–96

Voronov E, Carmi Y, Apte RN (2014) The role of IL-1 tumor-mediated angiogenesis. Front Physiol 5:114

Wada H, Nagano H, Yamamoto H, Yang Y, Kondo M, Ota H, Nakamura M, Yoshioka S et al (2006) Expression pattern of angiogenic factors and prognosis after hepatic resection in hepatocellular carcinoma: importance of angiopoietin-2 and hypoxia-induced factor-1 alpha. Liver Int 26:414–423

Walsh TG, Metharom P, Berndt MC (2014) The functional role of platelets in the regulation of angiogenesis. Platelets 15:1–13

Wang Q, Tian X, Zhang C, Wang Q (2012) Upregulation of vasohibin-1 expression with angiogenesis and poor prognosis of hepatocellular carcinoma after curative surgery. Med Oncol 29:2727–2736

Wang WQ, Liu L, Xu HX, Luo GP, Chen T, Wu CT, Xu YF, Xu J, Liu C, Zhang B et al (2013) Intratumoral α-SMA enhances the prognostic potency of CD34 associated with maintenance of microvessel integrity in hepatocellular carcinoma and pancreatic cancer. PLoS ONE 8, e71189

Watari K, Shibata T, Kawahara A, Sata K, Nabeshima H, Shinoda A, Abe H, Azuma K et al (2014) Tumor-derived interleukin-1 promotes lymphangiogenesis and lymph node metastasis through M2-type macrophages. PLoS ONE 9, e99568

Watson SP, Lowe K, Finney BA (2014) Platelets in lymph vessel development and integrity. Adv Anat Embryol Cell Biol 214:93–105

Webber JP, Spary LK, Sanders AJ, Chowdhury R, Jiang WG, Steadman R, Wymant J et al (2014) Differentiation of tumour-promoting stromal myofibroblasts by cancer exosomes. Oncogene. doi:10.1038/onc.2013.560

Webber et al. 2015. http://www.ncbi.nlm.nih.gov/pubmed/25662446

Wickersheim A, Kerber M, de Miguel LS, Plate KH, Machein MR (2009) Endothelial progenitor cells do not contribute to tumor endothelium in primary and metastatic tumors. Int J Cancer 125:1771–1777

Wiggers JK, Ruys AT, Groot Koerkamp B, Beuers U, Ten Kate FJ, van Gulik TM (2014) Differences in immunohistochemical biomarkers between intra-and extrahepatic cholangiocarcinoma: a systematic review and meta-analysis. J Gastroenterol Hepatol 29:1582–1594

Wilson CM, Naves T, Vincent F, Melloni B, Bonnaud F, Lalloué F, Jauberteau MO (2014a) Sortilin mediates the release and transfer of exosomes in concert with two tyrosine kinase receptors. J Cell Sci. pii:jcs. 149336

Wilson GK, Tennant DA, McKeating JA (2014a) Hypoxia inducible factors in liver disease and hepatocellular carcinoma: current understanding and future directions. J Hepatol 61:1397–1406

Witte MH, Jones K, Wilting J, Dictor M, Selg M, McHale M, Geshenwald JE, Jackson DG (2006) Structure function relationships in the lymphatic system and implications for cancer biology. Cancer Metastasis Rev 25:159–184

Wu YY, Chen L, Wang GL, Zhang YX, Zhou JM, He S, Qin J, Zhu YY (2013) Inhibition of hepatocellular carcinoma growth and angiogenesis by dual silencing of NET-1 and VEGF. J Mol Histol 44:433–445

Wu L, Fu Z, Zhou S, Gong J, Liu CA, Qiao Z, Li S (2014) HIF-1α and HIF-2α: siblings in promoting angiogenesis of residual hepatocellular carcinoma after high-intensity focused ultrasound ablation. PLoS ONE 9, e88913

Xiang Q, Chen W, Ren M, Wang J, Zhang H, Deng DY, Zhang L, Shang C, Chen Y (2014) Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. Clin Cancer Res 20:2959–2970

Xiao H, Cheng S, Tong R, Lv Z, Ding C, Du C, Xie H, Zhou L, Wu J, Zheng S (2014) BAG3 regulates epithelial-mesenchymal transition and angiogenesis in human hepatocellular carcinoma. Lab Invest 94:252–261

Xiong YQ, Sun HC, Zhang W, Zhu XD, Zhuang PY, Zhang JB, Wang L, Wu WZ et al (2009) Human hepatocellular carcinoma tumor-derived endothelial cells manifest increased angiogenesis capability and drug resistance compared with normal endothelial cells. Clin Cancer Res 15:4838–4846

Xue X, Gao W, Sun B, Xu Y, Han B, Wang F, Zhang Y, Sun J, Wei J, Lu Z, Zhu Y et al (2013) Vasohibin 2 is transcriptionally activated and promotes angiogenesis in hepatocellular carcinoma. Oncogene 32:1724–1734

Xue X, Zhang Y, Zhi Q, Tu M, Xu Y, Sun J, Wei J, Lu Z, Miao Y, Gao W (2014) MiR200-upregulated vasohibin 2 promotes malignant transformation of tumors by inducing epithelial-mesenchymal transition in hepatocellular carcinoma. Cell Commun Signal 12:62

Yamaguchi R, Yano H, Nakashima O, Akiba J, Nishida N, Kurogi M, Kojiro M (2006) Expression of vascular endothelial growth factor-C in human hepatocellular carcinoma. J Gastroenterol Hepatol 21:152–160

Yang ZF, Poon RT (2008) Vascular changes in hepatocellular carcinoma. Anat Rec (Hoboken) 291:721–734

Yang M, Chen J, Su F, Yu B, Su F, Lin L, Huang JD, Song E (2011) Microvesicles secreted by macrophages shuttle invasion-potentiating microRNAs into breast cancer cells. Mol Cancer 10:117

Yang X, Zhang XF, Lu X, Jia HL, Liang L, Dong QZ, Ye QH, Qin LX (2014) MicroRNA-26a suppresses

angiogenesis in human hepatocellular carcinoma by targeting HGF-cmet pathway. Hepatology 59:1874–1885

Yao Y, Pan Y, Chen J, Sun X, Qiu Y, Ding Y (2007) Endoglin (CD105) expression in angiogenesis of primary hepatocellular carcinomas: analysis using tissue microarrays and comparisons with CD34 and VEGF. Ann Clin Lab Sci 37:39–48

Yao L, Dong H, Luo Y, Du J, Hu W (2014) Net platelet angiogenic activity (NPAA) correlates with progression and prognosis of non-small cell lung cancer. PLoS ONE 9, e96206

Ye XZ, Yu SC, Bian XW (2010) Contribution of myeloid-derived suppressor cells to tumor-induced immune suppression, angiogenesis, invasion and metastasis. J Genet Genom 37:423–430

Yoder 2012. http://www.ncbi.nlm.nih.gov/pubmed/22762017

Yoshimatsu Y, Lee YG, Akatsu Y, Taguchi L, Suzuki HI, Cunha SI, Maruyama K et al (2013) Bone morphogenetic protein-9 inhibits lymphatic vessel formation via activin receptor-like kinase 1 during development and cancer progression. Proc Natl Acad Sci U S A 110:18940–18945

Yu Q (2005) The dynamic roles of angiopoietins in tumor angiogenesis. Future Oncol 1:475–484

Yu D, Sun X, Qiu Y, Zhou J, Wu Y, Zhuang L, Chen J, Ding Y (2007a) Identification and clinical significance of mobilized endothelial progenitor cells in tumor vasculogenesis of hepatocellular carcinoma. Clin Cancer Res 13:3814–3824

Yu D, Zhuang L, Sun X, Chen J, Yao Y, Meng K, Ding Y (2007b) Particular distribution and expression pattern of endoglin (CD105) in the liver of patients with hepatocellular carcinoma. BMC Cancer 7:122

Yu DC, Chen J, Sun XT, Zhuang LY, Jiang CP, Ding YT (2010a) Mechanism of endothelial progenitor cell recruitment into neo-vessels in adjacent non-tumor tissues in hepatocellular carcinoma. BMC Cancer 10:435

Yu DC, Chen J, Ding YT (2010b) Hypoxic and highly angiogenic non-tumor tissues surrounding hepatocellular carcinoma: the 'niche' of endothelial progenitor cells. Int J Mol Sci 11:2901–2909

Yu et al. 2014. http://www.ncbi.nlm.nih.gov/pubmed/24055369

Yu B, Kim HW, Gong M, Wang J, Millard RW, Wang Y, Ashraf M, Xu M (2015) Exosomes secreted from GATA-4 overexpressing mesenchymal stem cells serve as a reservoir of anti-apoptotic microRNAs for cardioprotection. Int J Cardiol 182:349–360

Zeng W, van den Berg A, Huitema S, Gouw AS, Molema G, de Jong KP (2014) Correlation of microRNA-16, microRNA-21 and microRNA-101 expression with cyclooxygenase-2 expression and angiogenic factors in cirrhotic and noncirrhotic human hepatocellular carcinoma. PLoS ONE 9, e95826

Zhang ZL, Liu ZS, Sun Q (2006) Expression of angiopoietins, Tie2 and vascular endothelial growth factor in angiogenesis and progression of hepatocellular carcinoma. World J Gastroenterol 12:4241–4245

Zhang J, Han C, Zhu H, Song K, Wu T (2013) miR-101 inhibits cholangiocarcinoma angiogenesis through targeting vascular endothelial growth factor (VEGF). Am J Pathol 182:1629–1639

Zhang W, Zhao CG, Sun HY, Zheng WE, Chen H (2014) Expression characteristics of KAI1 and vascular endothelial growth factor and their diagnostic values for hepatocellular carcinoma. Gut Liver. doi:10.5009/gnl13331

Zhang J, Li S, Li L, Li M, Guo C, Yao J, Mi S (2015a) Exosome and exosomal microRNA: trafficking, sorting, and function. Genomics Proteomics Bioinforma 13:17–24

Zhang J, Guan J, Niu X, Hu G, Guo S, Li Q, Xie Z, Zhang C, Wang Y (2015b) Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. J Transl Med 13:49

Zhao QT, Yue SQ, Cui Z, Wang Q, Cui X, Zhai HH, Zhang LH, Dou KF (2006) Potential involvement of the cyclooxygenase-2 pathway in hepatocellular carcinoma-associated angiogenesis. Life Sci 80:484–492

Zhao WB, Li Y, Liu X, Zhang LY, Wang X (2008) Evaluation of PRL-3 expression, and its correlation with angiogenesis and invasion in hepatocellular carcinoma. Int J Mol Med 22:187–192

Zhou B, Ma R, Si W, Li S, Xu Y, Tu X, Wang Q (2013) MicroRNA-503 targets FGF2 and VEGFA and inhibits tumor angiogenesis and growth. Cancer Lett 333:159–169

Zhou JJ, Zheng S, Sun LF, Zheng L (2014) MicroRNA regulation network in colorectal cancer metastasis. World J Biol Chem 5:301–307

Zhu H, Shao Q, Sun X, Deng Z, Yuan X, Yu D, Zhou X, Ding Y (2012a) The mobilization, recruitment and contribution of bone marrow-derived endothelial progenitor cells to the tumor neovascularization occur at an early stage and throughout the entire process of hepatocellular carcinoma growth. Oncol Rep 28:1217–1224

Zhu H, Shao Q, Sun X, Deng Z, Yuan X, Zhou X, Ding Y (2012b) Bone marrow cells: important role on neovascularization of hepatocellular carcinoma. J Gastroenterol Hepatol 27:1241–1251

Zhu K, Pan Q, Zhang X, Kong LQ, Fan J, Dai Z, Wang L, Yang XR, Hu J, Wan JL et al (2013) MiR-146a enhances angiogenic activity of endothelial cells in hepatocellular carcinoma by promoting PDGFRA expression. Carcinogenesis 34:2071–2079

Zhu LM, Shi DM, Dai Q, Cheng XJ, Yao WY, Sun PH, Ding Y, Qiao MM, Wu YL et al (2014a) Tumor suppressor XAF1 induces apoptosis, inhibits angiogenesis and inhibits tumor growth in hepatocellular carcinoma. Oncotarget 5:5403–5415

Zhu C, Liu X, Wang S, Yan X, Tang Z, Wu K, Li Y, Liu F (2014b) Hepatitis C virus core protein induces hypoxia-inducible factor 1α-mediated vascular endothelial growth factor expression in Huh7.5.1 cells. Mol Med Rep 9:2010–2014

Zhu K, Pan Q, Jia LQ, Dai Z, Ke AW, Zeng HY, Tang ZY, Fan J, Zhou J (2014c) MiR-302c inhibits tumor growth of hepatocellular carcinoma by suppressing the endothelial-mesenchymal transition of endothelial cells. Sci Rep 4:5524

Zhuang PY, Wang JD, Tang ZH, Zhou XP, Yang Y, Quan ZW, Liu YB, Shen J (2014) Peritumoral neuropilin-1 and VEGF receptor-2 expression increases time to recurrence in hepatocellular carcinoma patients undergoing curative hepatectomy. Oncotarget 5:11121–11132

Zhuo W, Luo C, Wang X, Song X, Fu Y, Luo Y (2010) Endostatin inhibits tumour lymphangiogenesis and lymphatic metastasis via cell surface nucleolin on lymphangiogenic endothelial cells. J Pathol 222:249–260

Zhuo W, Chen Y, Song X, Luo Y (2011) Endostatin specifically targets both tumor blood vessels and lymphatic vessels. Front Med 5:336–340

Angiogenesis in Liver Cancer: General Aspects and Cellular Sources of Normal Angiogenesis

187

Contents

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_187

Abstract

Morphogenesis and biogenesis of new blood vessels comprise two major mechanisms, vasculogenesis and angiogenesis. Vasculogenesis denotes the de novo formation of blood vessels from progenitor cells or stem cells that home to tissues and accomplish the development of the vascular system during ontogenesis. In contrast, angiogenesis is defined as the sprouting of new blood vessels from differentiated endothelial cells present in preexistent vessels. Angiogenesis is the form of blood vessel neoformation occurring in cancers. It involves a sprouting process involving endothelial cell commitment (priming), migration, proliferation and vascular tube morphogenesis (sprouting angiogenesis), and intussusceptive microvascular growth, in which existing vessel lumina are separated and reconstructed. This complex sequence of events is regulated by an array of distinct proangiogenic factors, antiangiogenic factors, and vessel maturation factors. The remodeling of newly formed vessel networks requires tightly controlled apoptotic processes. Similar angiogenic modes, but with involvement of different angiogenic factors, operate in lymphangiogenesis.

Vasculogenesis and Angiogenesis

Definitions

Vasculogenesis denotes the de novo formation of blood vessels from progenitor cells or stem cells ("angioblasts") that home to tissues and accomplish the development of the vascular system during ontogenesis. In contrast, angiogenesis is defined as the sprouting of new vessels from differentiated endothelial cells (ECs) present in preexisting vessels.

Vascular Stem Cells in Vasculogenesis

The concept of vasculogenesis requires the availability of precursor or progenitor cells with stem cell features, either recruited from the local vasculogenic mesoderm or derived from remote cellular sources such as the bone marrow (Xu 2005; Kim et al. 2014). Cells with such characteristics are termed angioblasts or hemangioblasts (Eichmann et al. 2002; Rose et al. 2015). Locally committed hemangioblasts originating in the mesoderm operate during ontogenesis, and the offspring of stem cells is capable to home to target sites. It was, e.g., demonstrated that endothelial cells selected from differentiating mouse embryonic stem cells incorporate at sites of neovascularization (Marchetti et al. 2002). Following ontogenesis, connective tissues are the source of mesenchymal stem cells that can also give rise to vascular cells (Murray et al. 2014). Vascular stem cells show a characteristic spectrum of markers, including CD133(+), CD34(+), Soxq0, Sox17, and S100beta (Tang et al. 2012). The generation and priming of vascular stem cells, including mesenchymal stem cells, are subject to regulation mediated by several species of microRNAs (Xing et al. 2014).

Conversely, in the adult organism, cells from other sources, and in particular those derived from the bone marrow, play a significant role. The bone marrow harbors stem cells or stem-like cells, including mesenchymal stem cells and hemopoetic stem cells, which can be committed to several lineages, including the hemangioblast, a phenomenon called stem cell plasticity (Poulsom et al. 2002). Part of these proangiogenic progenitor cells are nestin-positive mesenchymal stem cells (Pacini and Petrini 2014). In the context of vascular morphogenesis, stem cell plasticity would infer that progenitor cells located outside the vascular cell compartment proper can home to preexisting vascular structures and either become a local stem cell in the new niche or be directly committed to enter a vascular cell, and in particular an endothelial cell, lineage, with so-called transdifferentiation. Currently, it is difficult to analyze which of these mechanisms is involved, requiring the tracing of a single cell (Poulsom et al. 2002) in order to test the potential somatic site of engraftment. Furthermore, several aspects of the concept of bone marrow-derived stem cells

with or without plasticity have recently been reappraised or criticized. The existence of bone marrow-derived, circulating precursor cells for endothelia has been suggested many years ago, based on the study of Barr bodies (Williams and Alvarez 1969). That circulating endothelial precursors play a role in the reconstitution of blood vessels has now been confirmed (Asahara et al. 1999; Takahashi et al. 1999; Lin et al. 2000; Nishikawa 2001; Rafii et al. 2002a; Hirschi and Goodell 2002). Endothelial cells can differentiate and expand from CD133(+) bone marrow cells, a subset of CD34(+) hematopoietic progenitors (Quirici et al. 2001; Ahn et al. 2010; Borlongan et al. 2011), but also multipotent adult progenitor cells (MAPC) with a CD34(−) phenotype and copurifying with mesenchymal stem cells from postnatal human bone marrow can give rise to cells with an angioblast phenotype (Reyes et al. 2002). The question as to the extent of the replacement of vascular endothelial cell by circulating stem cells under normal conditions (i.e., the so-called maintenance vasculogenesis) has not conclusively been settled, although several studies support this phenomenon (Gunsilius et al. 2000), also in the liver (Gao et al. 2001). There is evidence that such progenitor cells are operational mainly in situations of vascular damage, i.e., under non-maintenance conditions (Sinclair 1972; Tomita et al. 1999; Lagaaij et al. 2001). The homing to and incorporation into vessels of bone marrow-derived endothelial progenitors may depend on the local expression of distinct factors, in particular stem cell-active cytokines, in the target tissue. It has been shown that vascular endothelial growth factor increases the engraftment of such cells into the vasculature of newborn murine recipients (Young et al. 2002) and that mobilization and recruitment can be promoted by adenoviral vectors expressing angiogenic factors (Rafii et al. 2002b). The recruitment and translocation of stem and progenitor cells in and from the bone marrow require the shedding of soluble Kit ligand (sKitL) via the action of matrix metalloproteinase-9 (MMP-9), as based on experiments with MMP-9-deficient mice (Heissig et al. 2002).

Angiogenesis: The Principal Vascularization Mode in Cancers

Angiogenesis is the form of blood vessel neoformation that occurs both during development and adult life, and it characterizes most of the vessel neoformation occurring in cancers. In normal tissues, angiogenesis is involved in the remodeling, distinct structuring, and expansion of primordial networks generated by vasculogenesis. In principle, angiogenesis is based on two pathways, (1) a sprouting process involving endothelial cell commitment (priming), migration, proliferation, and vascular tube morphogenesis (sprouting angiogenesis) and (2) intussusceptive microvascular growth (IMG, intussusceptive angiogenesis), in which existing vessel lumina are separated and reconstructed by insertion or interposition of distinct tissue pillars or intervascular tissue structures and by in situ loop formation. In more detail, sprouting angiogenesis denotes the process whereby a new blood vessel branch (the sprout) develops from a preexisting vessel. Generation of a new sprout requires the presence of a distinct guiding cell which acts as a pacemaker for the new branch and determines the axis of growth. This cell is the tip cell, a motile endothelial cell localized at the tip of the new sprout. Behind tip cells, endothelial stalk cells proliferate and form the new microvessel lumen. Following VEGF signaling, the delta-like 4/Notch signaling system controls the selection of tip cells which are the guides for sprouting angiogenesis (Jakobsson et al. 2009), a process counteracted by synaptojanin-2 (Adam et al. 2013). The interactions between VEGFs and Notch have a key role in vascular patterning and in the pathways where endothelial cells compete for the tip cell position (Jakobsson et al. 2009, 2010). Tip cells express a set of distinct genes and secrete endothelial-specific molecule 1, Ang2, and apelin which bind on cognate receptors on endothelial stalk cells (del Toro et al. 2010), supporting the role of tip cells as sprouting organizers. Recruiting of new formed endothelial cells to the sprout requires, apart from cell proliferation, endothelial cell motility and

migration, a process that is critical for pattern formation during vasculogenesis (review: Czirok 2013). Migration of endothelial cells in the sprouting process is inhibited the receptor tyrosine kinase modulator, sprouty4 (Gong et al. 2013). The sprouting process also shares features with epithelial-mesenchymal transition/EMT, in that sprouting endothelial cells express the EMT-inducers, Slug and Snail (Welch-Reardon et al. 2014). Subsequent to sprouting, the new vascular sprouts require lumen formation, a process called tubulogenesis and regulated by an endothelial cell lumen signaling complex or proteins, involving MT1-MMP, collagen-binding integrin alpha2beta1, junction adhesion molecules(JAMs B and C), polarity proteins Par3 and Par6b, and the Rho GTPase Cdc42-GTP (Stratman et al. 2009; Sacharidou et al. 2012). In a first step, a network of proteolytically generated vascular guidance tunnels is produced, followed by flow-induced remodeling and arteriovenous endothelial cell sorting and differentiation (Davis et al. 2011).

Blood Vessel Maturation and Organ-Specific Vascular Morphogenesis

Following vasculogenesis and angiogenesis, further steps in the generation of a functional vascular system involve vessel maturation (recruitment of pericytes, extracellular matrix assembly, generation of smooth muscle cells, pruning of neovasculature), acquisition of vessel identity, organotypic differentiation, and assembly of vessels into networks according to distinct patterning modes. Vascular morphogenesis is closely linked to mechanisms involved in the production of intricate branching patterns in order to serve the specific needs of a given tissue or organ and to maximize the vascular surface/contact area. Patterning modes resulting in distinct vascular networks may also operate in tumor angiogenesis. So far, relatively little is known as to whether branching and pattern formation are mainly intrinsic mechanisms working via self-organized endothelial cells or whether extrinsic tissue elements are involved as well.

Perivascular Cells

Pericytes, which exist in several subtypes, are a distinct form of vascular mural cells mainly supporting venules, capillaries, and sinusoids. Together with smooth muscle cells, pericytes are critically involved in stabilizing endothelial cell-to-cell contacts and may influence vessel-type-specific differences of the endothelial phenotype (Kurzen et al. 2002). They have also been implicated in angiogenesis. Recruitment of supporting pericytes is thought to be essential for the modulation of endothelial sprout growth, vessel maturation, stability, and survival (D'Amore 1992). The vascularization switch that results in pericyte recruitment depends on a Notch1 pathway (Guichet et al. 2015). Pericytes limit the proliferative response of endothelial cells (Hirschi et al. 1998) and play a role in vascular pruning and vessel remodeling (Nguyen and D'Amore 2001), survival of blood vessels (Chatterjee and Naik 2012), and production of extracellular matrix proteins in vessels (Birbrair et al. 2014). In experiments using the chorioallantoic membrane (CAM), it surfaced that small CAM vessels exhibited ramified alpha-smooth muscle actin-negative cells with delicate desmin staining indicating the presence of pericytes, and these cells were also recruited into experimental tumor nodules during tumor angiogenesis (Kurz et al. 2002). During angiogenesis, pericytes may act as some sort of switch permitting vessel enlargement and branching: in early VEGF-induced angiogenesis, detachment of pericytes from microvessels ensues, followed by extensive vessel enlargement and generation of mother vessels, the latter subsequently differentiating along several lines into mature, pericyte-coated or myocyte-coated vessels of varying types (Sundberg et al. 2002). Several factors are involved in the recruitment of pericytes. In the embryo (but not in the adult), PDGF is involved in pericyte function (Lindahl et al. 1998). Rat pericyte-like cells respond

in vitro to TGF-beta1 (Asashima et al. 2002), and TGF-beta mediates the differentiation to pericytes (Darland and D'Amore 2001) Furthermore, it has recently been demonstrated that pericytes markedly and stably express angiopoietin-1, but not angiopoietin-2, Tie-1, or Tie-2, suggesting that the role of angiopoietin-1 in vessel maturation can be extended to vessel maturation after the phase of angiogenesis in adult tissues (Sundberg et al. 2002). Pericytes can originate from plutipotent stem cells (Orlova et al. 2014).

Vascular Smooth Muscle Cells

The maturation and the acquisition of functional capacity of blood vessels larger than capillaries and sinusoids require the production of vascular smooth muscle cells (VSMCs), specialized vascular mural cells that participate in a complex interactome with endothelial cells, pericytes, and adventitial cells. VSMCs and pericytes are critical cells for the stabilization of immature endothelial tubes. VSMCs proliferating in, and homing to, endothelial tubes migrate from the media toward the intimal layer. Similar to endothelial cells, VSMCs can originate from stem cells (Hirschi and Majesky 2004; Klein et al. 2010; Cheung and Sinha 2011; Kennedy et al. 2014; Marchand et al. 2014). Circulating CD14(+) bone marrow-derived mononuclear cells can acquire a spindle-shaped phenotype and then express VSMC-specific markers in reponse to PDGF-BB (circulating smooth muscle progenitor cells). Lineage markers include alpha-SMA, desmin, smooth muscle calponin, and myosin light chain kinase (Hegner et al. 2005). However, part of these CD14(+) progenitors become cells that co-express CD68, being "SMC-like macrophages" that are involved in inflammatory vascular reactions (Iwata et al. 2010; Daniel and Sedding 2011). The differentiation of stem cells toward a VSMC lineage is regulated by several factors, including PI3K/Akt/mTOR signaling (Hegner et al. 2009). Vascular progenitors can be primed to generate two lineages, i.e., concurrent generation of functional VSMCs and endothelial cells (Marchand et al. 2014). Apart from circulating progenitor cells, also nestin(+) tissue-resident multipotent stem cells can contribute to VSMC production (Klein et al. 2014). Vascular wall-resident CD44(+) multipotent stem cells give rise to VSMCs and pericytes (Klein et al. 2011), suggesting a lineage relationship between these two cell types.

Arteriogenesis

Arteriogenesis critically depends on a switch that decides the fate of a tip cell-driven endothelial tube to become equiped with smooth muscle cells, generates an adventitia, and synthesizes various elastin-containing lamellae. This complex sequence of events is induced and regulated by several factors. The determination of the arterial phenotype is controlled by various proteins, including ephrinB2, neuropilin-1, connexin-40 (CX40), apelin, and Alk-1. Neuropilin-1, a coreceptor for VEGF164 (Kawasaki et al. 1999), is preferentially expressed in chick arteries (Moyon et al. 2001), and CX40, a gap junction protein, is specifically expressed in murine dorsal aorta and smaller arteries during ontogenesis. Apelin, the ligand of G-protein-coupled APJ receptor, is a a widely distributed peptide with various functions in the cardiovascular system (Yu et al. 2014a). It is involved in blood vessel generation and maturation and affects both early steps of endothelial cell production and shaping and late steps of vessel maturation (Kidoya and Takakura 2012). Apelin is strongly expressed in vascular endothelial cells and labels sprouting vasculogenesis, both in normal tissues and tumors (Liu et al. 2015). Apelin also provided a link between perivascular adipose cells and endothelial angiogenic processes, in that, e.g., apelin production is augmented by hypoxia in adipose cells, thus creating an angiogenic regulation platform (Kunduzova et al. 2008). In arteries, the apelin/AJP system is expressed in endothelial cells and smooth muscle cells but is also present in periadventital adipocytes (Kostopoulos et al. 2014). Various apelin forms exert differential

function in arterial vessels. Apelin-13 regulates potassium channels in arterial smooth muscle cells (Modgil et al. 2013) and promotes smooth muscle cell proliferation via a Jagged-1/Notch3 signaling pathway (Li et al. 2013c).

Arterial differentiation occurs in association with peripheral, sensory nerves, and VEGF164 and VEGF120 are sufficient to promote expression of arterial markers in isolated embryonic endothelial cells in vitro (Mukouyama et al. 2002). Probably, these VEGF isoforms represent a permissive signal for determinants such as ephrinB2. In fact, mutant mice lacking the the 164 and 120, but not the 188, isoforms of VEGF exhibit a defect in ephrinB2 expression in vessels in vivo (Stalmans et al. 2002). Observations using the murine limb skin suggest that peripheral nerves are the source of VEGF isoforms, thus promoting blood vessel association and arterial differentiation (Mukouama et al. 2002). These authors showed that mutations eliminating peripheral sensory nerves or Schwann cells prevent proper arteriogenesis and that, in vitro, sensory neurons or Schwann cells can induce arterial marker expression (ephrinB2, neuropilin1, connexin40) in embryonal endothelial cells, VEGF 164/120 being necessary and sufficient for this specific induction. Nerves by themselves are growth stimulated by neutrotrophic factors expressed by blood vessels, including NGF, NT3, and BDNF, the latter also being a survival factor for endothelial cells (Scarisbrick et al. 1993; Francis et al. 1999; Donovan et al. 2000).

Angiogenesis: Angiogenic and Antiangiogenic Factors

Introduction

Angiogenesis critically depends on a balance between pro-and antiangiogenic factors. Biochemically, proangiogenic factors form a very heterogeneous group of molecules (Table 1) with various cellular sources and highly different mechanisms of action. Angiogenesis and antiangiogenesis are chiefly mediated by core groups of relatively few factors, while a host of other factors modulate angiogenic responses or have supplementary functions.

Table 1 Proangiogenic factors

Vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs)
Angiopoietins
Angiopoietin-like proteins (Angptls)
Fibroblast growth factors
Placenta growth factor
Platelet-derived endothelial cell growth factor
Cytokines
Endoglin
Ephrins
Thrombomodulin
Angiomotins
Platelet-derived growth factor
Transforming growth factor-beta
Tumor necrosis factor-alpha
Hepatocyte growth factor
Leptin
Platelet endothelial cell adhesion molecule-1
Granulocyte colony-stimulating factor
Wt1 tumor suppressor
Nitric oxide

Vascular Endothelial Growth Factors

Vascular endothelial growth factors (VEGFs) control the development of the vascular system and the growth and function of blood vessels and lymphatic vessels in the adult organism (vasculogenesis and angiogenesis). VEGFs comprise five related members of homodimeric proteins, i.e., VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor (PIGF). These five types of VEGFs are subject to further diversification through alternative splicing (VEGF-Axxxb) and posttranslational changes, such as proteolytic processing, steps that modulate the binding features to VEGF receptors, heparin sulfate and neuropilins. Several VEGFs are regulated by hypoxia and hypoxia-inducible factors (HIFs), a mechanism that is of great importance in hypoxic malignancies (review: Koch et al. 2011). VEGFs interact with three related tyrosine kinase VEGF receptors (VEGFRs),

i.e., VEGFR1, VEGFR2, and VEGFR3. The angiogenic effects of the VEGF family members are chiefly mediated by the receptor VEGFR2, while the function of VEGFR1, which is expressed in endothelial and non-endothelial cells, is less well known, although two VEGFs, VEGF-B and PIGF, exclusively bind to this receptor (review: Cao 2009). VEGF-A signaling plays a crucial role in ontogenesis through promotion of vasculogenesis and angiogenesis. It regulates proliferation and migration of endothelial cells, vascular permeability, and the selection of tip cells and stalk cells in sprouting angiogenesis and regulates organ homeostatis in adults (review: Matsumoto and Ema 2014). Conversely, VEGF-C and VEGF-D hold a central place in lymphangiogenesis (see below). Placenta growth factor (PlGF) is a member of the VEGF family that exclusively binds to VEGFR1. It is angiogenic under certain circumstances, affects vessel permeability (leakiness), is active in monocyte chemotaxis, and potentiates the activity of VEGF, participating in autocrine and paracrine regulation of angiogenesis (Yonekura et al. 1999). PIGF can activate monocytes and has arteriogenic properties through this mechanism (Pipp et al. 2003). By displacing VEGF from VEGFR-2/Flt1, which may be a non-signaling reservoir for VEGF, PlGF delivers VEGF to promote Flk-1-mediated signaling (Park et al. 1994). The somewhat controversial data relating to angiogenic activities of PlGF have been clarified by the observation that PlGF-1 acts as a natural antagonist of VEGF when both factors are synthesized in the same cell populations, via the formation of functionally inactive heterodimers (Eriksson et al. 2002). It is well known that endothelial cell lineages of various vascular systems are diverse and organ/tissue specific with respect to several features, although the response to key angiogenic factors is ubiquitous. These differences may, at least in part, depend on the vessels' microenvironment (Aird et al. 1997), and recent observations have demonstrated a peptide vascular address system (Ruoslahti and Rajotte 2000). Novel findings relevant to organ-specific angiogenic functions include the identification of endocrine-gland-derived VEGF (EG-VEGF), which is the human homolog of black mamba venom protein A or mamba intestinal toxin 1 (LeCouter et al. 2001). It may be expected that other such cell-or tissue-specific factors, including those for the liver vascular bed, will be detected, permitting an additional system of signal refinement (LeCouter et al. 2002). Several factors regulate the activity of VEGFs. The expression of VEGFs is regulated by microRNAs. MicroRNA-329 targets a coreceptor of VEGFR2, CD146, and through this mechanism suppresses angiogenesis (Wang et al. 2013). Fibroblast growth factor receptor substrate 2 (FRS2alpha) regulates VEGF-A- and VEGF-C-dependent activation of receptor kinase signaling (Chen et al. 2014a).

Angiopoietins and Related Proteins

Angiopoietins (Angs) form a family of four members (Ang1 to Ang4) and are potent inducers of angiogenesis (Thomas and Augustin 2009). Ang1–4 are ligands of the Tie2 tyrosine kinase receptor, while Tie1 is an orphan receptor which can heterodimerize with Tie2 and thus modulates Tie2 signaling (Fagiani and Christofori 2013; Barton et al. 2014). The most prominent Ang members in angiogenesis are Ang1 and Ang2. Ang1 regulates blood vessel maturation, mediates endothelial cell migration, adhesion, and survival, and also controls the stability of newly formed vessels. Specifically, Ang1 reduces number and size of endothelial gaps in venules, thus descreasing plasma leakage and stabilizing the vessels (Baffert et al. 2006). The action of Ang1 on endothelial cells depends on the relative levels of the Tie2 and the inhibitory coreceptor Tie1. Ang2 has a complex functional pattern. It disrupts connections between endothelium channels and their perivascular cells, inducing vessel cell apoptosis and vessel regression, but in cooperation with VEGF, it promotes neovascularization. In the presence of VEGF-A, Ang2 can promote vascular sprouting, while it induces vascular regression in the absence of VEGF-A (review: Fagiani and Christofori 2013). Ang2 is also involved in remodeling and stabilization of lymphatic vessels (review: Wu and Liu 2010).

The inhibitory Tie1 is cleaved and hence inactivated by VEGF, cytokines, and changes in shear stress. Cleavage of Tie1 enables Tie2 to mediate the angiogenic action of the ligand, Ang1 (review Singh et al. 2011). Ang3 (mouse) and Ang4 (human) are interspecies orthologs. Ang3 is tethered on cell surfaces through heparan sulfate proteoglycans (Xu et al. 2004). Ang4 is a third protein binding to the Tie2 receptor (Valenzuela et al. 1999). Both Ang3 and Ang4 phosphorylate the Tie2 receptor, but only Ang4 induces migration and survival in endothelial cells. Ang2 plays an essential role in liver regeneration, as it is expressed in a dynamically regulated and phase-specific manner in emerging sinusoidal endothelial cells, a cell system that serves as a pacemaker in lobule expansion. Ang2 expression is present in a later angiogenic phase of liver regeneration and controls sinusoidal VEGFR2 expression (Hu et al. 2014). A group of proteins that are structurally similar to angiopoietins are the angiopoietin-like proteins (Angptls/ALPs), encoded by eight genes (Angptls 1–8; Santulli 2014). These proteins, having a host of synonyms, form orphan ligands and have complex functions in angiogenesis and metabolism (Arca et al. 2013; Aoi et al. 2014). Angptl2 positively regulates endothelial cell colony and vascular lumen formation through its effects on cell migration (Richardson et al. 2014).

Fibroblast Growth Factors

Fibroblast growth factors (FGFs) belong to a family with more than 20 members, of which acidic FGF (aFGF) and basic FGF (bFGF) have been described in greatest detail. bFGF has a strong angiogenic capacity, and both endothelial cells produce bFGF in an autocrine manner and tumor cells release bFGF in a paracrine fashion (review: Pang and Poon 2006). FGF signaling plays a central role in both vascular formation and maintenance and is integrated in a complex regulation network (Murakami and Sakurai 2012). bFGF binds to endothelial cells via the tyrosine kinase receptors FGFR1 and FGFR2 and through heparin sulfate proteoglycans and integrins.

Endoglin

Endoglin (CD105) is a cell surface glycoprotein and member of the TGF-beta receptor complex that operates in the development of blood vessels and vascular repair (Duff et al. 2003; van Laake et al. 2006). Endoglin expression is modulated by TGF-beta and Smad3 through a distinct promoter site and is associated with betaglycan and the formation of higher order complexes with TGF-beta signaling receptors.

Ephrins

Ephrins are a family of proteins that bind the Eph/erythropoietin-producing hepatocellular receptor tyrosine kinase family. Ephrins and their Eph receptor are differentially expressed in several cell systems, including vascular endothelial cells and leukocytes. For ephrin signaling, distinct Eph receptor clusters are required (Janes et al. 2012). The known ephrins differ in their capacity to promote angiogenesis. Ephrin-B2 controls VEGF-induced angiogenesis and lymphangiogenesis via promoting the internalization of VEGFR3 (Wang et al. 2010). Ephrins and ephrin receptors also play a role in arterial versus venous phenotype decision making, in that ephrin-B2 marks the endothelium of artery precursors and EphB4 the endothelium of venous precursors (Wang et al. 1998).

Thrombomodulin

Soluble thrombomodulin is an example of a factor that maintains an angiogenic response by presenting endothelial cell loss. It is a paracrine anti-apoptotic factor for vascular endothelial cells (Chao et al. 2014). Thrombomodulin is a membrane-bound anticoagulant expressed on endothelial cells. In the course of endothelial cell

stress, thrombomodulin is released as a soluble form (Martin et al. 2013).

Neuropilin-Semaphorin Signaling System

Through a connection with VEGFs, the neuropilin-semaphorin signaling system is linked to angiogenesis and lymphangiogenesis, also in tumors (Chaudhary et al. 2014). Neuropilins are the coreceptors for class 3 semaphorins and some members of the VEGF family (Sakurai et al. 2012; Bussolino et al. 2014; Zachary 2014). Neuropilin-1 and neuropilin-2 receptors form complexes with type A plexins, which serve as signaling receptors for specific class-3 semaphorins (SEMA3). Neuropilin-2 is transcriptionally regulated by GATA-binding protein 2 (GATA2) and LIM domain only 2 (Lmo 2). Through this pathway, neuropilin-2 regulates VEGF-induced angiogenesis and lymphangiogenesis (Coma et al. 2013). Semaphorin-3A and semaphorin-3F, secreted by several tumors, cooperate to repel endothelial cells, inhibit migration, and promote their apoptosis (Guttmann-Raviv et al. 2007). Also semaphorin-3B is an angiogenesis inhibitor that is inactivated by pro-protein convertases (-Varshavsky et al. 2008). Inhibition of endothelial cell motility/migration by class 3 semaphorins works through collapse of the actin cytoskeleton via neuropilins and plexins (Gaur et al. 2009). Neuropilin-1 is upregulated in HCC and is involved in vascular remodeling (Bergé et al. 2011). In tumors, semaphorin-3F serves as an inhibitor angiogenesis (Kessler et al. 2004).

Angiogenic Factors Acting Through the Cytoskeleton and Tight Junctions and Endothelial Cell Motility

p80-angiomotin promotes angiogenesis via its simulatory action on endothelial cell migration and regulation of endothelial cell-cell junctions (Bratt et al. 2005). A splice isoform of angiomotin is p130-angiomotin, a protein that associates with actin and controls endothelial cell shape (Ernkvist et al. 2006). p80-angiomotin interacts with the protein angiomotin-like 1, a protein involved in actin cytoskeleton-based processes (Gagné et al. 2009). Angiomotin also participates in a tight junction-associated complex containing merlin, Patj, and Pals1, mediating merlin-induced regulation of mitogenic signaling and tumor suppression (Yi et al. 2011). Migration and proliferation of endothelial cells during angiogenesis also requires angiomotin-like 2, a tight junction protein which promotes MAPK/ERK activation via c-Src (Wang et al. 2011). Generally, angiomotin family proteins are activators of the LATS2 kinase tumor suppressor which is part of the Hippo signaling pathway that promotes contact inhibition of tumor cell growth by phosphorylating and inhibiting the transcriptional coactivator YAP (Paramasivam et al. 2011; Oka et al. 2012). Endothelial motility is also regulated by the cytoskeleton-associated protein, epithelial protein lost in neoplasm (EPLINalpha), an actin-regulating protein that has antiangiogenic properties (Sanders et al. 2010).

Signal Pathways as Angiogenic Factors

Transforming growth factor-beta (TGF-β) has been reported to play an important role in inducing angiogenesis, mainly in cancers (Pepper 1997a), modulated by the action of angiotensin II and its type 1 receptor, AT1R (Miyajima et al. 2002). Also integrins are involved in angiogenesis (Hynes 2002). A major regulator of tumor angiogenesis is the Wilms tumor suppressor Wt1, expressed in various cancers (Wagner et al. 2014). Wt1 promotes endothelial cell proliferation and migration via activation of the ETS-1 transcription factor (Wagner et al. 2008). Prostaglandins can induce the proliferation of endothelial cells in vitro and in vivo (Form and Auerbach 1983), mainly mediated by the induction of VEGF (Majima et al. 2000). Kinins, potent vasoactive peptides generated from high molecular kininogen via activation of the intrinsic coagulation/kallikrein system, can promote prostaglandin release and induce vascular cell proliferation. Kininogens, a substrate for kallikrein, are present

in vascular smooth muscle cells (Okamoto et al. 1998), and tissue kallikreins (kallikrein-like proteases) are also active in vessel walls (Saed et al. 1990). This question has been studied in more detail by the use of a rat model, the kininogen-deficient Brown Norway Katholiek rat. These mutant rats lack the capacity for kinin generation, related to their inability to secrete relevant kininogen moieties from the liver. Angiogenesis is significantly suppressed in these animals, suggesting that endogenous kinin generated from the tissue kallikrein-kinin system may enhance angiogenesis in several situations (Hayashi et al. 2002), probably via B1 and B2 receptor signaling.

Angiogenesis: The Role of Matrix Metalloproteinases

One important role of microvascular endothelial cells is to actively remodel the extracellular matrix (ECM), including basement membranes. On the other hand, the ECM exerts an impact on the layout of the microvasular system, including the generation of typical vascular networks. Proliferating and migrating endothelial cells must be enabled to grow along ECM components, involving attachment mechanisms and matricolytic capacities (Pepper 1997b). In this remodeling process, metalloproteinases (MMPs) play a significant role. Synthesis, secretion, and ectivation of MMPs go in parallel with the migratory and invasive behavior of endothelial cells, but the mechanisms involved in the regulation of vessel-associated MMPs are only partially clarified. Recently, it has been elucidated that strain exerted by hemodynamic forces (blood pressure, vessel wall tension, and shear stress), known to be strong stimuli for vascular morphogenesis, can act via the MMP cascade (Haas et al. 2000). Levels of Egr-1, a zinc finger immediate-early response transcription factor, are increased upon endothelial cell shear stress, and this Egr-1 response is mediated by the extracellular signal-related kinase 1/2 mitogen-activated protein kinase pathway (Schwachtgen et al. 1998). Egr-1 is known to be an important activator for several ECM genes playing a role in vascular morphogenesis, including PDGF A and B, TGF-beta, and MMPs, and putative nucleotide recognition elements for Egr-1 appear in the promoters of MT1-MMP (Haas et al. 1999). By the use of rat microvascular endothelial cells, it surfaced that cyclic strain upregulates the Egr-1-mediated expression of MT1-MMP, thus supporting the view that hemodynamic parameters exert a regulating role in vascular morphogenesis (Yamaguchi et al. 2002).

Hypoxia-Induced Angiogenesis: Oxygen Sensing and Hypoxia-Related Pathways

Hypoxia and oxygen sensing play a central role in pathways leading to angiogenesis (Fraisl et al. 2009). Hypoxia-inducible factor-1 (HIF-1) is a transcriptional complex controlling homeostatic responses to tissue oxygen availability and acting as an oxygen sensor. An αβ heterodimeric complex, HIF-1α, is the oxygen-regulated subunit of HIF-1. While HIF-1α is stable in hypoxia, oxygen presence targets it to the proteasomal degradation pathway via the ubiquitination complex pVHL, the protein of the von Hippel-Lindau (VHL) tumor suppressor gene and a component of an E3 ubiquitin ligase complex. The E3 ligase complex involved in HIF-1α capture (VCB E3 ligase) consists of pVHL, elongins B and C, Cul (cullin)2, and Rbx1. Capture is regulated by hydroxylation of specific prolyl residues in two functionally independent regions of HIF-1α, this hydroxylation being accomplished by a group of 2-oxoglutarate-dependent nonheme dioxygenases, and there is a single, conserved hydroxyproline-binding pocket in pVHL (Hon et al. 2002).

Antiangiogenesis

Antiangiogenic Factors

The process of angiogenesis depends on a delicate balance between the effects of pro-and antiangiogenic factors. Numerous molecules counteracting angiogenesis have been identified (Table 2).

Table 2 Antiangiogenic (angiostatic) factors

Thrombospondin-1
Endostatin
Angiostatin
Angiomotins
Fibstatin
Vasohibin
Decorin
Angioarrestin (angiopoietin-like protein 1)
Properdistatin
Interleukin-12
Tissue inhibitor of metalloproteinase 1, 2
Macrophage metalloelastase
Interferons
Parathyroid hormone-related peptide

The Thrombospondin Family

The thrombospondin (TSP) family consists of five glycoproteins with various functions. Thrombospondins 1–5 form two subgroups. Subgroup A contains the homotrimers thrombospondins 1 and 2, while subgroup B consists of the homopentameric thrombospondins 3, 4, and 5. TSP1 and TSP2 are secreted ECM proteins of the matricellular protein group, i.e., proteins without a primary structural role in the ECM but rather a modulator function. TSP1 and TSP2 have several functions, including antiangiogenesis (Lawler 2000, 2002; Qin et al. 2014), and exert their effects through CD36, CD47, and integrins. CD36 and beta1 integrin receptors associate with VEGFR2 and form a platform regulating angiogenesis, the thrombospondin interactome (Lawler and Lawler 2012; Resovi et al. 2014). TSP1 activates latent TGF-beta1 and is a potent chemotactic factor for neutrophils and monocytes (Mansfield and Suchard 1993, 1994). Double-TSP1/TSP2-null mice in comparison with the single-null mice exhibited an apparent phenotype representing the sum of the anomalies seen in single-null mice, but double knockouts displayed a hypovascular repair tissue in wound healing, similar to TSP1-null mice, and different from TSP2-null mice, which exhibit a hypervascular healing response, suggesting a predominating role of TSP1 in repair neovascularization and differential spatial and temporal expression patterns of TSP1 and TSP2 (Agah et al. 2002).

Endostatin

Endostatin, a 20 kDa COOH-terminal fragment of collagen type XVIII, is a potent antiangiogen (O'Reilly et al. 1997; Fu et al. 2009). It blocks in vitro endothelial cell migration, promotes cell cycle arrest, and induces apoptosis (Dhanabal et al. 1999), but it also affects non-endothelial cells, e.g., renal branching morphogenesis and tubulogenesis (Karumanchi et al. 2001), the latter phenomenon also showing up in the clinical situation of Knobloch syndrome, where a truncated collagen type XVIII lacking the endostatin fragment occasionally produces abnormal renal collecting ducts (Sertie et al. 2000). In the setting of antiangiogenesis, endostatin has nucleolin as its receptor (Shi et al. 2007). The pathways of endostatin signaling have only partially been elucidated so far, but impinging of the Wnt signal pathway is involved. In *Xenopus* embryogenesis, endostatin at high levels suppresses Wnt-dependent transcription and stimulates proteasome-mediated degradation of beta-catenin in a Siah 1 protein-independent manner, and the endostatin-induced inhibition of endothelial cell migration and S phase entry is rescued by the downstream transcriptional activator, (TCF)-VP16 (Hanai et al. 2002). The role of endostatin as an antiangiogenic factor has also been demonstrated in the C3(1)/SV 40 transgenic murine model of tumor angiogenesis inhibition (Yokoyama et al. 2000; Calvo et al. 2002) and in antiangiogenic therapy employing a recombinant adenovirus to elevate systemic endostatin levels (Feldman et al. 2000).

Angiostatin

Angiostatin is a potent inhibitor of angiogenesis. It binds to and inhibits the cell surface protein p80-angiomotin, a proangiogenic scaffold protein that increases motility and migration of endothelial cells through its phosphorylation-dependent

action of the actin cytoskeleton (Dai et al. 2013). Angiomotins belong to the motin family of proteins, which also contains angiomotin-like A and angiomotin-like 2 (Bratt et al. 2002; Chan et al. 2013; Moleirinho et al. 2014). Angiostatin inhibits endothelial MMP-2 and MMP-14 expression in a hypoxia-dependent manner (Radziwon-Balicka et al. 2013). Apart from endothelial cell, angiostatin also inhibits the activation and migration of neutrophils (Aulakh et al. 2014).

Fibstatin

Fibstatin, an antiangiogenic factor, is an extracellular FGF-2-binding polypeptide with fibronectin domains (Bossard et al. 2004). Fibstatin cooperates with CXCL4L1 to inhibit angiogenesis and lymphangiogenesis (Prats et al. 2013).

Vasohibins

Vasohibins form a protein family that inhibit migration, proliferation, and network formation by endothelial cells and downregulate angiogenesis in vivo (Watanabe et al. 2004; Sato and Sonoda 2007). Vasohibin is induced by VEGF, suggesting a regulatory loop for angiogenesis versus angiostasis (Shimizu et al. 2005).

Decorin and Other Antiangiogenic Factors

Decorin, a small leucine-rich proteoglycan of the extracellular matrix, inhibits angiogenesis through induction of an autophagic program for endothelial cells resulting in endothelial cell depletion (Neill et al. 2013). By the use of a homology-based gene mining approach, an angiopoietin-related cDNA identical to angiopoietin-like protein 1 has been isolated and the gene product shown to be an antiangiogenic protein, termed angioarrestin (Dhanabal et al. 2002, 2005). The recombinant protein was found to block several steps in the angiogenic cascade, including endothelial cell proliferation, migration, tubular network formation, and adhesion to ECM proteins. A further angiogenesis inhibitor is parathyroid hormone-related peptide or a ten-amino-acid peptide from its N terminus, inhibiting endothelial cell migration in vitro and angiogenesis in vivo by activating endothelial cell protein kinase A (Bakre et al. 2002).

MicroRNAs as Regulators of Angiogenesis and Vasculogenesis: The Critical Roles of AngiomiRs

Several endothelial cell functions and angiogenic pathways are critically regulated by microRNAs (miRs), such as miR-27a/b, miR-126, the miR-17-92 cluster, miR-200b, and miR-93 (Urbich et al. 2008, 2012; van Solingen et al. 2009; Bonauer et al. 2010; Yao et al. 2015). Proangiogenic miRs are termed AngiomRs. Part of miRs involved in angiogenesis are induced by angiogenic stimuli, including hypoxia. Hypoxia is a strong inducer of angiogenesis and in part acts via increased endothelial expression of proangiogenic miRs (Madanecki et al. 2013). Hypoxia-responsive miRs target argonaute 1, which anchors the miR-induced silencing complex (miRISC) to promote angiogenesis (Chen et al. 2013). MiRs are also involved in the regulation of angiogenic progenitor cells, which exploit distinct miR modalities (Chang et al. 2014). AngiomiR-126 expression affects circulating CD34(+) mononuclear cells to have proangiogenic features (Mocharla et al. 2013). MiR-126 modulates angiogenic growth of endothelial progenitors circulating in blood (Goerke et al. 2015). The angiogenesis-regulating potential of mesenchymal stem cells, which can give rise to endothelial progenitors, is inhibited by miR-494 (Chen et al. 2015). Certain miRs directly interact with angiogenic factors. MiR-199b modulates vascular cell fate by targeting the Notch ligand Jagged1 and enhancing vascular endothelial growth factor (VEGF) signaling (Chen et al. 2014b). MiRs are involved in a late step of angiogenesis, i.e., blood vessel stabilization. This process is promoted by miR-143/145, a microRNA that is transferred from smooth muscle

cells to endothelial cells by the action of TGF-beta (Climent et al. 2015). Factors critically active in miR synthesis by themselves affect angiogenesis, e.g., Dicer and Drosha, which promote endothelial miR expression (Kuehbacher et al. 2007). Apart from proangiogenic actions of miRs, certain miRs counteract angiogenesis or are true antiangiogenic factors. Members of the miR-17-92 cluster exhibit a cell-intrinsic antiangiogenic function in endothelial cells (Doebele et al. 2010). MiRs are also involved in pathways leading to the release of exosomes by endothelial cells. For example, endothelial cells require miR-214 to produce progangiogenic exosomes (van Balkom et al. 2013).

The exchange of proangiogenic miRs in angiogenic tissue areas is complex and involves several cell types. Macrophages are active in the transfer of miRs and can traffick signals among cells of their vicinity (Ismail et al. 2013).

Role of Macrophages, Tie2-Expressing Angiogenic Monocytes, Other Leukocytes, and Stromal Cells in Angiogenesis

Monocytes, Macrophages, and Myeloid-Derived Suppressor Cells as Proangiogenic Cells in Normal Tissues

There is increasing evidence that monocytes, macrophages, and myeloid-derived suppressor cells play an important role in angiogenesis. The role of these cell systems in angiogenssis has been elucidated by studying vascular recovery in irradiated tumor microenvironments, a situation where also a contribution of bone marrow-derived monocytoid cells can be observed (Russell and Brown 2013). Immune cells such as monocytes and macrophages can secrete several angiogenic and lymphangiogenic factors (David Dong et al. 2009; Jaipersad et al. 2014; Loffredo et al. 2014). A main execution pathway is mediated by macrophage-derived chemokines, in particular members of the CXC and CC chemokine families that are potent inducers of angiogenesis, while a group of CXC chemokines are angiostatic (Owen and Mohamadzadeh 2013). Macrophages can commit endothelium-derived progenitor cells to angiogenesis (Zordan et al. 2014). Subsets of monocytes/macrophages express Tie2 and are therefore capable to respond to angiopoietins. Monocytes with angiogenic features are recruited to the operational site via LRP1/LDL receptor-related protein, an endocytic and cell-signaling receptor regulating cell migration (Staudt et al. 2013). A large reservoir of monocytes with angiogenic properties is the expanding adipose tissue compartment (Navarro et al. 2014). Macrophage colony-stimulating factor increases Tie2-expressing monocyte differentiation and angiogenic function (Forget et al. 2014). Ang1 stimulates monocytes/macrophages followed by TNF-alpha expression and a proinflammatory action, suggesting that Ang1 transforms macrophages toward a proinflammatory phenotype (Seok et al. 2013). Angiopoietin-2 (Ang2) regulates gene expression in Tie2-expressing monocytes, increasing their proangiogenic capacity (Coffelt et al. 2010). There are subsets of leukocytes that can exert antiangiogenic functions. A subpopulation of monocytes are myeloid calcifying cells, procalcific cells expressing osteocalcin. These cells overexpress thrombospondin-1 and inhibit angiogenesis (Menegazzo et al. 2013). Macrophage-derived factors inducing or modulating angiogenesis in normal tissues and tumors are delivered either by secretion into the pericellular fluid or from the cargo of exosomes/microvesicles. MicroRNA-150 which promotes capillary tube formation is transferred from monocytes to endothelial cells by microvesicles (Li et al. 2013b).

Stromal Cells: Role in Angiogenesis and Partners of Endothelial to Mesenchymal Transition (EndoMT)

Cells of the tumor stroma can affect angiogenesis and antiangiogenesis. An important role is played by cancer-associated fibroblasts (CAFs), myofibroblasts, and hepatic stellate cells, all of which can interact with endothelial cells and

their progenitor cells. Tumor-activated hepatic stellate cells can exert a proangiogenic role via hypoxic induction of VEGF in these cells (Olaso et al. 2003). There is also evidence that connective tissue cells or stromal cells can become a source of endothelial cells. Multipotency factors such as Okt4 and Klf4 can convert fibroblasts to functional endothelial cells (Li et al. 2013a). On the other hand, endothelial cells can be converted to mesenchymal cells, a process termed endothelial to mesenchymal transition (EndoMT/EndMT) (Rieder et al. 2011; Lin et al. 2012; Piera-Velazquez and Jimenez 2012). EndoMT is induced by TGF-beta mediated by microRNA-21 (Kumarswamy et al. 2012). EndoMT may be involved in the acquisition of stem cell characteristics, because conversion of endothelial cells can result in several mesenchymal lineages, including fibroblasts, mural cells, osteoblasts, chondrocytes, and adipocytes (Medici and Kalluri 2012).

Exosomes and Microvesicles in Angiogenesis

Exosomes derived from myeloid-derived suppressor cells, macrophages, and T lymphocytes carry active proteins and miRs that modulate angiogenesis (Ribeiro et al. 2013; Burke et al. 2014). Exosomal cargo can also induce apoptosis and autophagy (Baixauli et al. 2014). Exosomes can carry active matrix metalloproteinase-1 and via this pathway promote angiogenesis (Hakulinen et al. 2008). Exosomal constituents can also positively affect endothelial cell growth and angiogenesis by promoting cell survival, e.g., via the transport and release of survivin (Khan et al. 2015). Exosomes containing Delta-like 4 (Dll4), a membrane-bound Notch ligand, induce capillary sprout retraction by regulating stalk cell and tip cell biology (Sharghi-Namini et al. 2014). Apart from leukocytes, CD34(+) progenitor cells primed to become endothelial cells release exosomes that exert paracrine proangiogenic activities (Sahoo et al. 2011). The transfer of angiogenic exosomes from cell sources to target cells is complex and is not a passive process. Sortilin, a multifaceted receptor also termed neurotensin receptor 3, mediates the release and transfer of exosomes through assembly of a tyrosine kinase receptor complex (the TES complex) found in exosomes and characterized by the linkage of the two tyrosine kinase receptors TrkB and EGFR with sortilin (Wilson et al. 2014). Part of exosomal cargos mediating angiogenesis are microRNAs (miRs). Exosomes released under hypoxic condition can contain miR-135b which regulates cell-to-endothelial-cell communications in angiogenesis (Fan 2014). Exosomes can also carry mitochondrial DNA (Guescini et al. 2010) which may modulate angiogenesis by its proinflammatory actions.

General Aspects of Lymphangiogenesis

In contrast to blood vessels, the lymphatic vascular system is not a closed- but an open-ended and one-way transit system, which has an impact on ontogenic mechanisms of lymphangiogenesis. According to Sabin's model (the centrifugal model), primitive lymph sacs take their origin from endothelial cells budding from early venous vessels, the peripheral lymphatic system then spreading from these primordial sacs by sprouting (Sabin 1904). On the other hand, lymph vessel cells may arise independently from peripheral mesenchyme surrounding the lymph sacs (the centripetal model; Kampmeier 1969). In particular (and similar to blood vessel morphogenesis) it has been proposed that cells of lymphatics derive from stem-like precursor cells, the so-called lymphangioblasts, shown to contribute to centripetal lymphangiogenesis in chimeric quail-chick embryos (Schneider et al. 1999; Wilting et al. 2000a, b). There is evidence that bone marrow-derived mesenchymal stem cells drive lymphangiogenesis (Maertens et al. 2014). Lymphangioblasts are also present in the avian chorioallantoic membrane and express a lymphangiogenic switch gene, Prox1 (Papoutsi et al. 2001). In the setting of normal lymph vessel development, lymphangioblasts or lymphatic

endothelial cell (LEC) precursors upregulate lymphatic vessel endothelial hyaluronan receptor-1 (LYVE1), followed by induction of the transcription factor SOX18. SOX18 promotes Prox1 expression, the first marker of LEC priming. The future LECs retain VEGFR3, defining VEGFR3+ abd CD34+ lymphatic progenitor cells (Tan et al. 2014). The progenitor cells express neuropilin-2, rendering these cells capable to respond to VEGF-C signaling coming from adjacent mesenchymal cells. LECs expand under the induction of VEGF-C and also VEGF-D (Tammela and Alitalo 2010).

Novel and in particular molecular aspects of lymphangiogenesis have been reviewed, particularly with respect to tumor lymphangiogenesis (Witte et al. 2001; Partanen and Paavonen 2001; Alitalo and Carmeliet 2002; Stacker et al. 2002; Jussila and Alitalo 2002; Achen and Stacker 2006; Ji 2006; Karpanen and Alitalo 2008; Tammela and Alitalo 2010). Major achievements in our knowledge on critical factors and their signaling pathways in lymphangiogenesis are related to transgenic mouse models, including VEGF-C transgenic mice, soluble VEGFR-3 transgenic mice, mice with enhanced VEGF-C and VEGF-D activity, Ang2 knockout mice, and Prox1 null mice. Apart from these "classical" mediators of lymphangiogenesis, other factors are involved, including Notch signaling, bone morphogenetic proteins, Ras, mitogen-activated protein kinase, PI3 kinase pathway, calcineurin signaling, and endothelin-1 (Rosano et al. 2013; Caprara et al. 2014; Coso et al. 2014; Zheng et al. 2014b). The complexity of lymphangiogenesis is underlined by the finding that cells other than LECs are involved in the process, including macrophages and neutrophils. In inflammatory lymphangiogenesis, neutrophils contribute to lymphatic vessel formation via secreting VEGF-D and increasing bioavailability of VEGF-A (Tan et al. 2013).

Among the members of the VEGF family, two are critically implicated in lymphangiogenesis, i.e., VEGF-C and VEGF-D. VEGF-C regulates the growth of lymphatic vessels and is produced as a preprotein, which is proteolytically cleaved, the processed forms (homodimers of the VEGF homology domains) having sequentially increased affinity for VEGFR2 and VEGFR3 (Joukov et al. 1997). The signals of VEGF-C, acting on blood vessel endothelia via VEGFR-2 and on lymphatic vessels via VEGFR-3, promote the migration and proliferation of the respective endothelial cells and induce vascular permeability (review: Stacker et al. 2002). The expression of VEGF-C does not appear to be regulated by hypoxia (Enholm et al. 1997) but rather by proinflammatory cytokines (Ristimaki et al. 1998). In mouse embryos, a paracrine expression pattern is observed between VEGF-C and VEGFR-3 at sites of the first detectable lymphatic sprouts, suggesting a critical role of VEGF-C in early phases of lymph vessel development (Kukk et al. 1996; Lohela et al. 2009). The overexpression of VEGF-C in the skin of VEGF-C transgenic mice results in lymphatic vessel hyperplasia (Jeltsch et al. 1997), and VEGFR-3 signaling alone is sufficient for this effect, based on experiments with a mutant VEGF-C exclusively binding to VEGFR-3 (Veikkola et al. 2001). However, VEGF-C exerts its specific actions on lymphatics only when cells are already primed for a lymphatic endothelial lineage because, in the chorioallantoic membrane model, VEGF-C will promote angiogenesis in phases where lymphatic vessel cells are not yet present (Oh et al. 1997). For its activity, VEGF-C requires proteolytic cleavage by ADAMTS-3, a step stimulated by collagen-and calcium-binding epidermal growth factor domains 1 (CCBE1), mutated in Hennekam lymphangiectasia-lymphedema syndrome (Jeltsch et al. 2014). The cleaved, mature form of VEGF-C can bind to VEGFR-2 and has an increased affinity for VEGFR-3. Receptor dimerization determines which type of vessel formation ensues: Binding of dimeric VEGF-C stimulates receptor dimerization, whereby VEGFR-3/VEGFR-3 homodimers promote lymphangiogenesis, while VEGFR-2/VEGFR-3 heterodimers promote (hem)angiogenesis. Internalization of the VEGFR3 receptor is modulated by the Slit2/Robo4 pathway (Yu et al. 2014b). Apart from VEGF-C, VEGF-

D is a potent pro-lymphangiogenic molecule that depends in its function on a SOXF-mediated transcriptional network (Duong et al. 2014). The expression of VEGFR-3, mutations of which have been linked to human hereditary lymphedema, becomes restricted chiefly to developing lymphatic vessels after midgestation. The binding sites of VEGF and VEGF-C in mouse embryos overlap in early ontogenesis, later to diverge to target blood and lymph vessel systems, respectively, in parallel with lymphangiogenesis (Lymboussaki et al. 1999). The VEGF/VEGFR system acting in lymphangiogenesis is inhibited by several mechanisms. Tumor lymphangiogenesis can be suppressed by blocking VEGFR-3 signaling (He et al. 2002). The MMP family member, ADAMTS1, inhibits lymphangiogenesis by attenuating phosphorylation of the LEC-specific VEGF receptor (Inagaki et al. 2014). Blockade of the VEGFR-3 signal pathway also inhibits fibroblast growth factor-2-induced lymphangiogenesis (Kubo et al. 2002).

Apart from certain forms of VEGF, angiopoietins are also involved in lymphangiogenesis. Deficiency of angiopoietin-2 causes abnormal lymphatic vessels, while induced overexpression in animals promotes lymphatic hyperplasia. The main function of angiopoietin-2 in lymphatic vessels is the regulation of interendothelial cell-cell junctions (Zheng et al. 2014a). An important role in the fating of early endothelial cells to become lymphatic endothelia is played by the homeobox gene, Prox1. In the mouse, Prox1 is expressed in a subpopulation of endothelial cells that, after budding from early veins, gives rise to lymphatics. In Prox1-null mice, budding and sprouting of lymphatic cells are not affected in a first phase, but are prematurely arrested, and these mice are then devoid of lymphatic vasculature (Wigle and Oliver 1999). In experiments with Prox1-null mice, budding and migration of endothelial cells from the cardinal vein are no longer polarized, following a random path, and these cells switch in differentiation to a blood vessel phenotype (Wigle et al. 2002), suggesting that Prox1 is a key gene maintaining budding and sprouting of future lymphatic endothelia and hence determining a lymphatic fate.

References

Achen MG, Stacker SA (2006) Tumor lymphangiogenesis and metastatic spread – new players begin to emerge. Int J Cancer 119:1755–1760

Adam MG, Berger C, Feldner A, Yang WJ, Wüstehube-Lausch J, Herberich SE et al (2013) Synaptojanin-2 binding protein stabilizes the Notch ligands DLL1 and DLL4 and inhibits sprouting angiogenesis. Circ Res 113:1206–1218

Agah A, Kyriakides TR, Lawler J, Bornstein P (2002) The lack of thrombospondin-1 (TSP1) dictates the course of wound healing in double-TSP1/TSP2-null mice. Am J Pathol 161:831–839

Ahn JB, Rha SY, Shin SJ, Jeung HC, Kim TS, Zhang X, Park KH, Noh SH, Roh JK, Chung HC et al (2010) Circulating endothelial progenitor cells (EPC) for tumor vasculogenesis in gastric cancer patients. Cancer Lett 288:124–132

Aird WC, Edelberg JM, Weiler-Guettler H, Simmons WW, Smith TW, Rosenberg RD (1997) Vascular bed-specific expression of an endothelial cell gene is programmed by the tissue microenvironment. J Cell Biol 138:1117–1124

Alitalo K, Carmeliet P (2002) Molecular mechanisms of lymphangiogenesis in health and disease. Cancer Cell 1:219–227

Aoi J, Endo M, Kadomatsu T, Miyata K, Ogata A, Horiguchi H, Masuda T, Fukushima S et al (2014) Angiopoietin-like protein 2 accelerates carcinogenesis by activating chronic inflammation and oxidative stress. Mol Cancer Res 12:239–249

Arca M, Minicocci I, Maranghi M (2013) The angiopoietin-like protein 3: a hepatokine with expanding role in metabolism. Curr Opin Lipidol 24:313–320

Asahara T, Masuda H, Takahashi T et al (1999) Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological conditions. Circ Res 85:221–228

Asashima T, Iizasa H, Terasaki T, Hosoya K, Tetsuka K, Ueda M, Obinata M, Nakashima E (2002) Newly developed rat brain pericyte cell line, TR-PCT1, responds to transforming growth factor-beta1 and beta-glycerophosphate. Eur J Cell Biol 81:145–152

Aulakh GK, Balachandran Y, Liu L, Singh B (2014) Angiostatin inhibits activation and migration of neutrophils. Cell Tissue Res 355:375–396

Baffert F, Le T, Thurston G, McDonald DM (2006) Angiopoietin-1 decreases plasma leakage by reducing number and size of endothelial gaps in venules. Am J Physiol Heart Circ Physiol 290:H107–H118

Baixauli F, Lopez-Otin C, Mittelbrunn M (2014) Exosomes and autophagy: coordinated mechanisms for the maintenance of cellular fitness. Front Immunol 5:403

Bakre MM, Zhu Y, Yin H, Burton DW, Terkeltaub R, Deftos LJ, Varner JA (2002) Parathyroid hormone-related peptide is a naturally occurring protein kinase

A-dependent angiogenesis inhibitor. Nat Med 8:995–1003
Barton WA, Dalton AC, Seegar TC, Himanen JP, Nikolov DB (2014) Tie2 and Eph receptor tyrosine kinase activation and signaling. Cold Spring Harb Perspect Biol 6 (3), pii: a009142
Bergé M, Allanic D, Bonnin P, de Montrion C, Richard J, Suc M, Boivin JF, Contrerès JO et al (2011) Neuropilin-1 is upregulated in hepatocellular carcinoma and contributes to tumour growth and vascular remodeling. J Hepatol 55:866–875
Birbrair A, Zhang T, Flies DC, Mannava S, Smith T, Wang ZM, Messi ML, Mintz A, Delbono O (2014) Type-1 pericytes accumulate after tissue injury and produce collagen in an organ-dependent manner. Stem Cell Res Ther 5:122
Bonauer A, Boon RA, Dimmeler S (2010) Vascular microRNAs. Curr Drug Targets 11:943–949
Borlongan CV, Glover LE, Taijiri N, Kaneko Y, Freeman TB (2011) The great migration of bone marrow-derived stem cells toward the ischemic brain: therapeutic implications for stroke and other neurological disorders. Prog Neurobiol 95:213–228
Bossard C, Van den Berghe L, Laurell H, Castano C, Cerutti M, Prats AC, Prats H (2004) Antiangiogenic properties of fibstatin, an extracellular FGF-2-binding polypeptide. Cancer Res 64:7507–7512
Bratt A, Wilson WJ, Troyanovsky B, Aase K, Kessler R, Van Meir EG, Holmgren L (2002) Angiomotin belongs to a novel protein family with conserved coiled-coil and PDZ binding domains. Gene 298:69–77
Bratt A, Birot O, Sinha I, Veitonmäki N, Aase K, Ernkvist M, Holmgren L (2005) Angiomotin regulates endothelial cell-cell junctions and cell motility. J Biol Chem 280:34859–34869
Burke M, Choksawangkarn W, Edwards N, Ostrand-Rosenberg S, Fenselau C (2014) Exosomes from myeloid-derived suppressor cells carry biologically active proteins. J Proteome Res 13:836–843
Bussolino F, Giraudo E, Serini G (2014) Class 3 semaphorin in angiogenesis and lymphangiogenesis. Chem Immunol Allergy 99:71–88
Calvo A, Yokoyama Y, Smith LE, Ali I, Shih S-C, Feldman AL, Libutti SK, Ramakrishnan S, Green JE (2002) Inhibition of the mammary carcinoma angiogenic switch in C3(1)/SV40 transgenic mice by a mutated form of human endostatin. Int J Cancer 101:224–234
Cao Y (2009) Positive and negative modulation of angiogenesis by VEGFR1 ligands. Sci Signal 2:re1
Caprara V, Scappa S, Garrafa E, Di Castro V, Rosano L, Bagnato A, Spinella F (2014) Endothelin-1 regulates hypoxia-inducible factor-1α and -2α stability through prolyl hydroxylase domain 2 inhibition in human lymphatic endothelial cells. Life Sci 118:185–190
Chan SW, Lim CJ, Guo F, Tan I, Leung T, Hong W (2013) Actin-binding and cell proliferation activities of angiomotin family members are regulated by Hippo pathway-mediated phosphorylation. J Biol Chem 288:37296–37307
Chang TY, Huang TS, Wang HW, Chang SJ, Lo HH, Chiu YL, Wang YL, Hsiao CD, Tsai CH, Chan CH, You RI et al (2014) miRNome traits analysis on endothelial lineage cells discloses biomarker potential circulating microRNAs which affect progenitor activities. BMC Genomics 15:802
Chao TH, Tsai WC, Chen JY, Liu PY, Chung HC, Tseng SY, Kuo CH, Shi GY et al (2014) Soluble thrombomodulin is a paracrine anti-apoptotic factor for vascular endothelial protection. Int J Cardiol 172:340–349
Chatterjee S, Naik UP (2012) Pericyte-endothelial cell interaction. A survival mechanism for the tumor vasculature. Cell Adhes Migr 6:157–159
Chaudhary B, Khaled YS, Ammori BJ, Elkord E (2014) Neuropilin 1: function and therapeutic potential in cancer. Cancer Immunol Immunother 63:81–99
Chen Z, Lai TC, Jan YH, Lin FM, Wang WC, Xiao H, Wang YT, Sun W, Cui X et al (2013) Hypoxia-responsive miRNAs target argonaute 1 to promote angiogenesis. J Clin Invest 123:1057–1067
Chen PY, Qin L, Zhuang ZW, Tellides G, Lax I, Schlessinger J, Simons M (2014a) The docking protein FRS2 is a critical regulator of VEGF receptors signaling. Proc Natl Acad Sci U S A 111:5514–5519
Chen T, Margariti A, Kelaini S, Cochrane A, Guha ST, Hu Y, Stitt AW, Zhang L, Xu Q (2014b) MicroRNA-199b modulates vascular cell fate during iPS cell differentiation by targeting the notch ligand jagged1 and enhancing VEGF signaling. Stem Cells. doi:10.1002/stem.1930
Chen S, Zhao G, Miao H, Tang R, Song Y, Hu Y, Wang Z, Hou Y (2015) MicroRNA-494 inhibits the growth and angiogenesis-regulating potential of mesenchymal stem cells. FEBS Lett 589:710–717
Cheung C, Sinha S (2011) Human embryonic stem cell-derived vascular smooth muscle cells in therapeutic neovascularisation. J Mol Cell Cardiol 51:651–664
Climent M, Quintavalle M, Miragoli M, Chen J, Condorelli G, Elia L (2015) TGFβ triggers miR-143/145 transfer from smooth muscle cells to endothelial cells, thereby modulating vessel stabilization. Circ Res 116:1753–1764
Coffelt SB, Tal AO, Scholz A, De Palma M, Patel S, Urbich C, Biswas SK, Murdoch C et al (2010) Angiopoietin-2 regulates gene expression in TIE2-expressing monocytes and augments their inherent proangiogenic functions. Cancer Res 70:5270–5280
Coma S, Allard-Ratick M, Akino T, van Meeteren LA, Mammato A, Klagsbrun M (2013) GATA2 and Lmo2 control angiogenesis and lymphangiogenesis via direct transcriptional regulation of neuropilin-2. Angiogenesis 16:939–952
Coso S, Bovay E, Petrova TV (2014) Pressing the right buttons: signaling in lymphangiogenesis. Blood 123:2614–2624
Czirok A (2013) Endothelial cell motility, coordination and pattern formation during vasculogenesis. Wiley Interdiscip Rev Syst Biol Med 5:587–602

D'Amore PA (1992) Capillary growth: a two-cell system. Semin Cancer Biol 3:49–56
Dai X, She P, Chi F, Feng Y, Liu H, Jin D, Zhao Y, Guo X, Jiang D, Guan KL, Zhong TP et al (2013) Phosphorylation of angiomotin by Lats1/2kinases inhibits F-actin binding, cell migration, and angiogenesis. J Biol Chem 288:34041–34051
Daniel JM, Sedding DG (2011) Circulating smooth muscle progenitor cells in arterial remodeling. J Mol Cell Cardiol 50:273–279
Darland DC, D'Amore PA (2001) TGF beta is required for the formation of capillary-like structures in three-dimensional cocultures of 10T1/2 and endothelial cells. Angiogenesis 4:11–20
David Dong ZM, Aplin AC, Nicosia RF (2009) Regulation of angiogenesis by macrophages, dendritic cells, and circulating myelomonocytic cells. Curr Pharm Des 15:365–379
Davis GE, Stratman AN, Sacharidou A, Koh W (2011) Molecular basis for endothelial lumen formation and tubulogenesis during vasculogenesis and angiogenic sprouting. Int Rev Cell Mol Biol 288:101–165
del Toro R, Prahst C, Mathivet T, Siegfried G, Kaminker JS, Larrivee B, Bréant C et al (2010) Identification and functional analysis of endothelial tip cell-enriched genes. Blood 116:4025–4033
Dhanabal M, Volk R, Ramchandran R, Simons M, Sukhatme VP (1999) Cloning, expression, and in vitro activity of human endostatin. Biochem Biophys Res Commun 258:345–352
Dhanabal M, LaRochelle WJ, Jeffers M, Herrmann J, Rastelli L, McDonald WF, Chillakuru RA, Yang M, Bo et al (2002) Angioarrestin: an antiangiogenic protein with tumor-inhibiting properties. Cancer Res 62:3834–3841
Dhanabal M, Jeffers M, LaRochelle WJ, Lichenstein HS (2005) Angioarrestin: a unique angiopoietin-related protein with anti-angiogenic properties. Biochem Biophys Res Commun 333:308–315
Doebele et al. 2010. http://www.ncbi.nlm.nih.gov/pubmed/20299512
Donovan MJ, Lin MI, Wiegn P, Ringstedt T, Kraemer R, Hahn R, Wang S, Ibanez CF, Rafii S, Hempstead BL (2000) Brain derived neurotrophic factor is an endothelial cell survival factor required for intramyocardial vessel stabilization. Development 127:4531–4540
Duff SE, Li C, Garland JM, Kumar S (2003) CD105 is important for angiogenesis: evidence and potential applications. FASEB J 17:984–992
Duong T, Koltowska K, Pichol-Thievend C, Le Guen L, Fontaine F, Smith KA, Truong V et al (2014) VEGFD regulates blood vascular development by modulating SOX18 activity. Blood 123:1102–1112
Eichmann A, Pardanaud L, Yuan L, Moyon D (2002) Vasculogenesis and the search for the hemangioblast. J Hematother Stem Cell Res 11:207–214
Enholm et al. 1997. http://www.ncbi.nlm.nih.gov/pubmed/9188862
Eriksson A, Cao R, Pawliuk R, Berg SM, Tsang M, Zhou D, Fleet C, Tritsaris K, Dissing S, Leboulch P, Cao Y (2002) Placenta growth factor-1 antagonizes VEGF-induced angiogenesis and tumor growth by the formation of functionally inactive PlGF-1/VEGF heterodimers. Cancer Cell 1:99–108
Ernkvist M, Aase K, Ukomadu C, Wohlschlegel J, Blackman R, Veitonmäki N, Dutta A et al (2006) p130-angiomotin associates to actin and controls endothelial cell shape. FEBS J 273:2000–2011
Fagiani E, Christofori G (2013) Angiopoietins in angiogenesis. Cancer Lett 328:18–26
Fan GC (2014) Hypoxic exosomes promote angiogenesis. Blood 124:3669–3670
Feldman AL, Restifo NP, Alexander HR, Bartlett DL, Hwu P, Seth P, Libutti SK (2000) Antiangiogenic gene therapy of cancer utilizing a recombinant adenovirus to elevate systemic endostatin levels in mice. Cancer Res 60:1503–1506
Forget MA, Voorhees JL, Cole SL, Dakhlallah D, Patterson IL, Gross AC, Moldovan L et al (2014) Macrophage colony-stimulating factor augments Tie2-expressing monocyte differentiation, angiogenic function, and recruitment in a mouse model of breast cancer. PLoS One 9:e98623
Form DM, Auerbach R (1983) PGE2 and angiogenesis. Prog Soc Exp Biol Med 172:214–218
Fraisl P, Mazzone M, Schmidt T, Carmellet P (2009) Regulation of angiogenesis by oxygen and metabolism. Dev Cell 16:167–179
Francis N, Farinas I, Brennan C, Rivas-Plata K, Backus C, Reichardt L, Landis S (1999) NT-3, like NGF, is required for survival of sympathetic neurons, but not their precursors. Dev Biol 210:411–427
Fu Y, Tang H, Huang Y, Song N, Luo Y (2009) Unraveling the mysteries of endostatin. IUBMB Life 61:613–626
Gagné V, Moreau J, Plourde M, Lapointe M, Lord M, Gagnon E, Fernandes MJ (2009) Human angiomotin-like 1 associates with an angiomotin protein complex through its coiled-coil domain and induces the remodeling of the actin cytoskeleton. Cell Motil Cytoskeleton 66:754–768
Gao Z-H, McAlister V, Williams G (2001) Repopulation of liver endothelium by bone marrow-derived cells. Lancet 357:932–933
Gaur P, Bielenberg DR, Samuel S, Bose D, Zhou Y, Gray MJ, Dallas NA, Fan F et al (2009) Role of class 3 semaphorins and their receptors in tumor growth and angiogenesis. Clin Cancer Res 15:6763–6770
Goerke et al. 2015. http://www.ncbi.nlm.nih.gov/pubmed/25473802
Gong Y, Yang X, He Q, Gower L, Prudovsky I, Vary CP, Brooks PC, Friesel RE (2013) Sprouty4 regulates endothelial cell migration via modulating integrin α3 stability through c-Src. Angiogenesis 16:861–875
Guescini M, Genedani S, Stocchi V, Agnati LF (2010) Astrocytes and glioblastoma cells release exosomes carrying mtDNA. J Neural Transm 117:1–4

Guichet PO, Guelfi S, Teigell M, Hoppe L, Bakalara N, Bauchet L, Duffau H, Lamszus K, Rothhut B, Hugnot JP (2015) Notch1 stimulation induces a vascularization switch with pericyte-like cell differentiation of glioblastoma stem cells. Stem Cells 33:21–34

Gunsilius E, Duba H-C, Petzer AL, Kalher CM, Grunewald K, Stockhammer G, Gabl C, Dirnhofer S, Calusen J, Gastl G (2000) Evidence from a leukaemia model for maintenance of vascular endothelium by bone marrow-derived endothelial cells. Lancet 355:1688–1691

Guttmann-Raviv N, Shraga-Heled N, Varshavsky A, Guimaraes-Sternberg C, Kessler O et al (2007) Sempahorin-3A and semphorin-3F work together to repel endothelial cells and to inhibit their survival by induction of apoptosis. J Biol Chem 282:26294–26305

Haas TL, Stitelman D, Davis SJ, Apte SS, Madri JA (1999) Egr-1 mediates extracellular matrix-driven transcription of membrane type 1 matrix metalloproteinase in endothelium. J Biol Chem 274:22679–22685

Haas TL, Milkiewicz M, Davis SJ, Zhou AL, Egginton S, Brown MD, Madri JA, Hudlicka O (2000) Matrix metalloproteinase activity is required for activity-induced angiogenesis in rat skeletal muscle. Am J Physiol Heart Circ Physiol 279:H1540–H1547

Hakulinen J, Sankkila L, Sugiyama N, Lehri K, Keski-Oja J (2008) Secretion of active membrane type 1 matrix metalloproteinase (MMP-14) into extracellular space in microvesicular exosomes. J Cell Biochem 105:1211–1218

Hanai J-I, Gloy J, Karumanchi SA, Kale S, Tang J, Hu G, Chan B, Ramchandran R, Jha V, Sukhatme VP, Sokol S (2002) Endostatin is a potential inhibitor of Wnt signaling. J Cell Biol 158:529–539

Hayashi I, Amano H, Yoshida S, Kamata K, Kamata M, Inukai M, Fujita T, Kumagai Y, Furudate S, Majima M (2002) Suppressed angiogenesis in kininogen-deficiencies. Lab Invest 82:871–880

He Y, Kozaki K, Karpanen T, Koshikawa K, Yla-Herttuala S, Takahashi T, Alitalo K (2002) Suppression of tumor lymphangiogenesis and lymph node metastasis by blocking vascular endothelial growth factor receptor 3 signaling. J Natl Cancer Inst 94:819–825

Hegner B, Weber M, Dragun D, Schulze-Lohoff E (2005) Differential regulation of smooth muscle markers in human bone marrow-derived mesenchymal stem cells. J Hypertens 23:1191–1202

Hegner B, Lange M, Kusch A, Essin K, Sezer O, Schulze-Lohoff E, Luft FC, Gollasch M, Dragun D (2009) mTOR regulates vascular smooth muscle cell differentiation from human bone marrow-derived mesenchymal progenitors. Arterioscler Thromb Vasc Biol 29:232–238

Heissig B, Hattori K, Dias S, Friedrich M, Ferris B, Hackett NR, Crysta RG, Besmer P, Lyden D, Moore MA, Werb Z, Rafii S (2002) Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand. Cell 109:625–637

Hirschi KK, Goodell MA (2002) Hematopoietic, vascular and cardiac fates of bone marrow-derived stem cells. Gene Ther 9:648–652

Hirschi KK, Majesky MW (2004) Smooth muscle stem cells. Anat Rec A: Discov Mol Cell Evol Biol 276:22–33

Hirschi KK, Rohovsky SA, D'Amore PA (1998) PDGF, TGF-beta, and heterotypic cell-cell interactions mediate endothelial cell-induced recruitment of 10T1 /2 cells and their differentiation to a smooth muscle fate. J Cell Biol 141:805–814

Hon W-C, Wilson MI, Harlos K, Claridge TDW, Schofield CJ, Pugh CW, Maxwell PH, Ratcliffe PJ, Stuart DI, Jones Y (2002) Structural basis for the recognition of hydroxyproline in HIF-1 alpha by pVHL. Nature 417:975–978

Hu J, Srivastava K, Wieland M, Runge A, Mogler C, Besemfelder E, Terhardt D, Vogel MJ et al (2014) Endothelial cell-derived angioppietin-2 controls liver regeneration as a spatiotemporal rheostat. Science 343:416–419

Hynes RO (2002) A reevaluation of integrins as regulators of angiogenesis. Nat Med 8:918–921

Inagaki J, Takahashi K, Ogawa H, Asano K, Faruk Hatipoglu O, Cilek MZ, Obika M et al (2014) ADAMTS1 inhibits lymphangiogenesis by attenuating phosphorylation of the lymphatic endothelial cell-specific VEGF receptor. Exp Cell Res 323:263–275

Ismail N, Wang Y, Dakhlallah D, Moldovan L, Agarwal K, Batte K, Shah P, Wisler J, Eubank TD, Tridandapani S et al (2013) Macrophage microvesicles induce macrophage differentiation and miR-223 transfer. Blood 121:984–995

Iwata H, Manabe I, Fujiu K, Yamamoto T, Takeda N, Eguchi K, Furuya A, Kuro-o M, Sata M, Nagai R (2010) Bone marrow-derived cells contribute to vascular inflammation but do not differentiate into smooth muscle cell lineages. Circulation 122:2048–2057

Jaipersad AS, Lip GY, Silverman S, Shantsila E (2014) The role of monocytes in angiogenesis and atherosclerosis. J Am Coll Cardiol 63:1–11

Jakobsson L, Bentley K, Gerhardt H (2009) VEGFRs and Notch: a dynamic collaboration in vascular patterning. Biochem Soc Trans 37:1233–1236

Jakobsson L, Franco CA, Bentley K, Collins RT, Ponsioen B, Aspalter IM, Rosewell I et al (2010) Endothelial cells dynamically compete for the tip cell position during angiogenic sprouting. Nat Cell Biol 12:943–953

Janes PW, Nievergall E, Lackmann M (2012) Concepts and consequences of Eph receptor clustering. Semin Cell Dev Biol 23:43–50

Jeltsch M, Kaipainen A, Joukov V, Meng X, Lakso M, Rauvala H, Swartz M, Fukumura D, Jain RK, Alitalo K (1997) Hyperplasia of lymphatic vessels in VEGF-C transgenic mice. Science 276:1423–1425

Jeltsch M, Jha SK, Tvorogov D, Anisimov A, Leppänen VM, Holopainen T, Kivelä R et al (2014) CCBE1 enhances lymphangiogenesis via a disintegrin and metalloprotease with thrombospondin motifs-3-mediated vascular endothelial growth factor-C activation. Circulation 129:1962–1971

Ji RC (2006) Lymphatic endothelial cells, tumor lymphangiogenesis and metastasis: new insights into intratumoral and peritumoral lymphatics. Cancer Metastasis Rev 25:677–694

Joukov V, Sorsa T, Kumar V, Jeltsch M, Claesson-Welsh L, Cao Y, Saksela O, Kalkkinen N, Alitalo K (1997) Proteolytic processing regulates receptor specificity and activity of VEGF-C. EMBO J 16:3898–3911

Jussila L, Alitalo K (2002) Vascular growth factors and lymphangiogenesis. Physiol Rev 82:673–700

Kampmeier OF (ed) (1969) Evolution and comparative morphology of the lymphatic system. Charles C. Thomas, Springfield

Karpanen T, Alitalo K (2008) Molecular biology and pathology of lymphangiogenesis. Annu Rev Mech Dis 3:367–397

Karumanchi SA, Jha V, Ramchandran R, Karihaloo A, Tsiokas L, Chan B, Dhanabal M, Hanai JI, Ventkataraman G, Shriver Z et al (2001) Cell surface glypicans are low-affinity endostatin receptors. Mol Cell 7:811–822

Kawasaki T, Kitsukawa T, Bekku Y, Matsuda Y, Sanbo M, Yagi T, Fujisawa H (1999) A requirement for neuropilin-1 in embryonic vessel formation. Development 126:4895–4902

Kennedy E, Mooney CJ, Hakimjavadi R, Fitzpatrick E, Guha S, Collins LE, Loscher CE, Morrow D, Redmond EM et al (2014) Adult vascular smooth muscle cells in culture express neural stem cell markers typical of resident multipotent vascular stem cells. Cell Tissue Res 358:203–216

Kessler O, Shraga-Heled N, Lange T, Gutmann-Raviv N, Sabo E, Baruch L, Machluf M, Neufeld G (2004) Semaphorin-3F is an inhibitor of tumor angiogenesis. Cancer Res 64:1008–1015

Khan S, Bennit HF, Wall NR (2015) The emerging role of exosomes in survivin secretion. Histol Histopathol 30:43–50

Kidoya H, Takakura N (2012) Biology of the apelin-APJ axis in vascular formation. J Biochem 152:125–131

Kim SW, Houge M, Brown M, Davis ME, Yoon YS (2014) Cultured human bone marrow-derived CD31(+) cells are effective for cardiac and vascular repair through enhanced angiogenic, adhesion, and anti-inflammatory effects. J Am Coll Cardiol 64:1681–1694

Klein D, Hohn HP, Kleff V, Tilki D, Ergün S (2010) Vascular wall-resident stem cells. Histol Histopathol 25:681–689

Klein D, Weisshardt P, Kleff V, Jastrow H, Jakob HG, Ergün S (2011) Vascular wall-resident CD44+ multipotent stem cell give rise to pericytes and smooth muscle cells and contribute to new vessel maturation. PLoS One 6:e20540

Klein D, Meissner N, Kleff V, Jastrow H, Yamaguchi M, Ergün S, Jendrossek V (2014) Nestin(+) tissue-resident multipotent stem cells contribute to tumor progression by differentiating into pericytes and smooth muscle cells resulting in blood vessel remodeling. Front Oncol 4:169

Koch S, Tugues S, Li X, Gualandi L, Claesson-Welsh L (2011) Signal transduction by vascular endothelial growth factor receptors. Biochem J 437:169–183

Kostopoulos CG, Spioglou SG, Varakis JN, Apostolakis E, Papadaki HH (2014) Adiponectin/T-cadherin and apelin/APJ expression in human arteries and periadventitial fat: implication of local adipokine signaling in atherosclerosis ? Cardiovasc Pathol 23:131–138

Kubo H, Cao R, Brakenhielm E, Makinen T, Cao Y, Alitalo K (2002) Blockade of vascular endothelial growth factor receptor-3 signaling inhibits fibroblast growth factor-2-induced lymphangiogenesis in mouse cornea. Proc Natl Acad Sci U S A 99:8868–8873

Kuehbacher A, Urbich C, Zeiher AM, Dimmeler S (2007) Role of Dicer and Drosha for endothelial microRNA expression and angiogenesis. Circ Res 101:59–68

Kukk E, Lymboussaki A, Taira S, Kaipainen A, Jeltsch M, Joukov V, Alitalo K (1996) VEGF-C receptor binding and pattern of expression with VEGFR-3 suggests a role in lymphatic vascular development. Development 122:3829–3837

Kumarswamy R, Volkmann I, Jazbutyte V, Dangwal S, Park DH, Thum T (2012) Transforming growth factor-beta-induced endothelial-to-mesenchymal transition is partly mediated by microRNA-21. Arterioscler Thromb Vasc Biol 32:361–369

Kunduzova O, Alet N, Delesque-Touchard N, Millet L, Catsan-Laurell I, Muller C, Dray C, Schaeffer P, Herault JP et al (2008) Apelin/APJ signaling system: a potential link between adipose tissue and endothelial angiogenic processes. FASEB J 22:4146–4153

Kurz H, Lauer D, Papoutsi M, Christ B, Wilting J (2002) Pericytes in experimental MDA-MB231 tumor angiogenesis. Histochem Cell Biol 117:527–534

Kurzen H, Manns S, Dandekar G, Schmidt T, Pratzel S, Kraling BM (2002) Tightening of endothelial cell contacts: a physiologic response to cocultures with smooth-muscle-like 10T1 / 2 cells. J Invest Dermatol 119:143–153

Lagaaij E, Cramer-Knijnenburg G, van Kemenade F, van Es L, Bruijn J, van Krieken J (2001) Endothelial cell chimerism after renal transplantation and vascular rejection. Lancet 357:33–37

Lawler J (2000) The functions of thrombospondin-1 and -2. Curr Opin Cell Biol 12:634–640

Lawler J (2002) Thrombospondin-1 as an endogenous inhibitor of angiogenesis and tumor growth. J Cell Mol Med 6:1–12

Lawler PR, Lawler J (2012) Molecular basis for the regulation of angiogenesis by thrombospondin-1 and -2. Cold Spring Harb Perpsect Med 2:a006627

LeCouter J, Kowalski J, Foster J, Hass P, Zhang Z, Dillard -Telm L, Frantz G, Rangell L et al (2001) Identification of an angiogenic mitogen selective for endocrine gland endothelium. Nature 412:877–884

LeCouter J, Lin R, Ferrara N (2002) Endocrine gland-derived VEGF and the emerging hypothesis of organ-specific regulation of angiogenesis. Nat Med 8:913–917

Li J, Huang NF, Zou J, Laurent TJ, Lee JC, Okogbaa J, Cooke JP, Ding S (2013a) Conversion of human fibroblasts to functional endothelial cells by defined factors. Arterioscler Thromb Vasc Biol 33:1366–1375

Li J, Zhang Y, Liu Y, Dai X, Li W, Cai X, Yin Y, Wang Q, Xue Y, Wang C, Li D, Hou D et al (2013b) Microvesicle-mediated transfer of microRNA-150 from monocytes to endothelial cells promotes angiogenesis. J Biol Chem 288:23586–23596

Li L, Li L, Xie F, Zhang Z, Guo Y, Tang G, Lv D, Lu Q, Chen L, Li J (2013c) Jagged-1/Notch3 transduction pathway is involved in apelin-13-induced vascular smooth muscle cells proliferation. Acta Biochim Biophys Sin (Shanghai) 45:875–881

Lin Y, Weisdorf D, Solovey A, Hebbel R (2000) Origin of circulating endothelial cells and endothelial outgrowth from blood. J Clin Invest 105:71–77

Lin F, Wang N, Zhang TC (2012) The role of endothelial-mesenchymal transition in development and pathological process. IUBMB Life 64:717–723

Lindahl P, Hellstrom M, Kalen M, Betsholtz C (1998) Endothelial-perivascular cell signaling in vascular development: lessons from knockout mice. Curr Opin Lipidol 9:407–411

Liu Q, Hu T, He L, Huang X, Tian X, Zhang H, He L, Pu W, Zhang L, Sun H, Fang J, Yu Y, Duan S, Hu C, Hui L et al (2015) Genetic targeting of sprouting angiogenesis using Apln-CreER. Nat Commun 6:6020

Loffredo S, Staiano RI, Granata F, Genovese A, Marone G (2014) Immune cells as a source and target of angiogenic and lymphangiogenic factors. Chem Immunol Allergy 99:15–36

Lohela M, Bry M, Tammela T, Alitalo K (2009) VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. Curr Opin Cell Biol 21:154–165

Lymboussaki A, Olofsson B, Eriksson U, Alitalo K (1999) Vascular endothelial growth factor (VEGF) and VEGF-C show overlapping binding sites in embryonic endothelia and distinct sites in differentiated adult endothelia. Circ Res 85:992–999

Madanecki P, Kapoor N, Bebok Z, Ochocka R, Collawan JF, Bartoszewski R (2013) Regulation of angiogenesis by hypoxia: the role of microRNA. Cell Mol Biol Lett 18:47–57

Maertens L, Erpicum C, Detry B, Blacher S, Lenoir B, Carnet O, Péqueux C, Cataldo D, Lecomte J, Paupert J et al (2014) Bone marrow-derived mesenchymal stem cells drive lymphangiogenesis. PLoS One 9:e106976

Majima M, Hayashi I, Muramatsu M, Katada J, Yamashina S, Katori M (2000) Cyclo-oxygenase-2 enhances basic fibroblast growth factor-induced angiogenesis through induction of vascular endothelial growth factor in rat sponge implants. Br J Pharmacol 130:641–649

Mansfield PJ, Suchard SJ (1993) Thrombospondin promotes both chemotaxis and haptotaxis in neutrophil-like Hl-60 cells. J Immunol 150:1959–1970

Mansfield PJ, Suchard SJ (1994) Thrombospondin promotes chemotaxis and haptotaxis of human peripheral blood monocytes. J Immunol 153:4219–4229

Marchand M, Anderson EK, Phadnis SM, Longaker MT, Cooke JP, Chen B, Reijo Pera RA (2014) Concurrent generation of functional smooth muscle cells and endothelial cells via a vascular progenitor. Stem Cells Transl Med 3:91–97

Marchetti S, Gimond C, Iljin K, Bourcier C, Alitalo K, Pouyssegur J, Pages G (2002) Endothelial cells genetically selected from differentiating mouse embryonic stem cells incorporate at sites of neovascularization in vivo. J Cell Sci 115:2075–2085

Martin FA, Murphy RP, Cummins PM (2013) Thrombomodulin and the vascular endothelium: insights into functional, regulatory, and therapeutic aspects. Am J Physiol Heart Circ Physiol 304: H1585–H1597

Matsumoto K, Ema M (2014) Roles of VEGF-A signalling in development, regeneration, and tumours. J Biochem 156:1–10

Medici D, Kalluri R (2012) Endothelial-mesenchymal transition and its contribution to the emergence of stem cell phenotype. Semin Cancer Biol 22:379–384

Menegazzo L, Albiero M, Millioni R, Tolin S, Arrigoni G, Poncina N, Tessari P, Avogaro A et al (2013) Circulating myeloid calcifying cells have antiangiogenic activity via thrombospondin-1 overexpression. FASEB J 27:4355–4365

Miyajima A, Kosaka T, Asano T, Asano T, Seta K, Kawai T, Hayakawa M (2002) Angiotensin II type 1 antagonist prevents pulmonary metastasis of murine renal cancer by inhibiting tumor angiogenesis. Cancer Res 62:4176–4179

Mocharla P, Briand S, Giannotti G, Dörries C, Jakob P, Paneni F, Lüscher T, Landmesser U (2013) AngiomiR-126 expression and secretion from circulating CD34(+) and CD14(+) PBMCs: role for proangiogenic effects and alterations in type 2 diabetics. Blood 121:226–236

Modgil A, Guo L, O'Rourke ST, Sun C (2013) Apelin-13 inhibits large-conductance Ca2+-activated K+ channels in cerebral artery smooth muscle cells via a PI3-kinase dependent mechanism. PLoS One 8:e83051

Moleirinho S, Guarrant W, Kissil JL (2014) The angiomotins – from discovery to function. FEBS Lett 588:2693–2703

Moyon D, Pardanaud L, Yuan L, Breant C, Eichmann A (2001) Plasticity of endothelial cells during arterial-venous differentiation in the avian embryo. Development 128:3359–3370

Mukouama Y-S, Shin D, Britsch S, Taniguchi M, Anderson DJ (2002) Sensory nerves determine the pattern of

arterial differentiation and blood vessel branching in the skin. Cell 109:693–705

Murakami M, Sakurai T (2012) Role of fibroblast growth factor signaling in vascular formation and maintenance: orchestrating signaling networks as an integrated system. Wiley Interdiscip Rev Syst Biol Med 4:615–629

Murray IR, West CC, Hardy WR, James AW, Park TS, Nguyen A, Tawonsawatruk T, Lazzari L, Soo C et al (2014) Natural history of mesenchymal stem cells, from vessel walls to culture vessels. Cell Mol Life Sci 71:1353–1374

Navarro A, Marin S, Riol N, Carbonell-Uberos F, Miñana MD (2014) Human adipose tissue-resident monocytes exhibit an endothelial-like phenotype and display angiogenic properties. Stem Cell Res Ther 5:50

Neill T, Torres A, Buraschi S, Iozzo RV (2013) Decorin has an appetite for endothelial cell autophagy. Autophagy 9:10

Nguyen LL, D'Amore PA (2001) Cellular interactions in vascular growth and differentiation. Int Rev Cytol 204:1–48

Nishikawa SI (2001) A complex linkage in the developmental pathway of endothelial and hematopoietic cells. Curr Opin Biol 13:673–678

O'Reilly MS, Boehm T, Shing Y, Fukai N, Vasios G, Lane WS, Flynn E, Birkhead JR, Olsen BR, Folkman J (1997) Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. Cell 88:277–285

Oh SJ, Jeltsch MM, Birkenhager R, McCarthy JE, Weich HA, Christ B, Alitalo K, Wilting J (1997) VEGF and VEGF-C: specific induction of angiogenesis and lymphangiogenesis in the differentiated avian chorioallantoic membrane. Dev Biol 188:96–109

Oka T, Schmitt AP, Sudol M (2012) Opposing roles of angiomotin-like-1 and zona occludens-2 on pro-apoptotic function of YAP. Oncogene 31:128–134

Okamoto H, Yayama K, Shibata H, Nagaoka M, Takano M (1998) Kininogen expression by rat vascular smooth muscle cells: stimulation by lipopolysaccharide and angiotensin II. Biochem Biophys Acta 1404:329–337

Olaso E, Salado C, Egilegor E, Gutierrez V, Santisteban A, Sancho-Bru P, Friedman SL, Vidal-Vanaclocha F (2003) Proangiogenic role of tumor-activated hepatic stellate cells in experimental melanoma metastasis. Hepatology 37:674–685

Orlova VV, van den Hil FE, Petrus-Reurer S, Drabsch Y, Ten Dijke P, Mummery CL (2014) Generation, expansion and functional analysis of endothelial cells and pericytes derived from human pluripotent stem cells. Nat Protoc 9:1514–1531

Owen JL, Mohamadzadeh M (2013) Macrophages and chemokines as mediators of angiogenesis. Front Physiol 4:159

Pacini S, Petrini I (2014) Are MSCs angiogenic cells ? New insights on human nestin-positive bone marrow-derived multipotent cells. Front Cell Dev Biol 2:20

Pang R, Poon RTP (2006) Angiogenesis and antiangiogenic therapy in hepatocellular carcinoma. Cancer Lett 242:151–167

Papoutsi M, Tomarev SI, Eichmann A, Prols F, Christ B, Wilting J (2001) Endogenous origin of the lymphatics in the avian chorioallantoic membrane. Dev Dyn 222:238–251

Paramasivam M, Sarkeshik A, Ytes JR, Fernandes MJ, McCollum D (2011) Angiomotin family proteins are novel activators of the LATS2 kinase tumor suppressor. Mol Biol Cell 22:3725–3733

Park JE, Chen HH, Winer J, Houck KA, Ferrara N (1994) Placenta growth factor. Potentiation of vascular endothelial growth factor bioactivity, in vitro and in vivo, and high affinity binding to Flt-1 but not to Flk-1/KDR. J Biol Chem 269:25646–25654

Partanen TA, Paavonen K (2001) Lymphatic versus blood vascular endothelial growth factors and receptors in humans. Microsc Res Technol 55:108–121

Pepper MS (1997a) Transforming growth factor-beta: vasculogenesis, angiogenesis, and vessel wall integrity. Cytokine Growth Factor Rev 8:21–43

Pepper MS (1997b) Manipulating angiogenesis: from basic science to the bedside. Arterioscler Thromb Vasc Biol 17:605–619

Piera-Velazquez S, Jimenez SA (2012) Molecular mechanisms of endothelial to mesenchymal cell transition (EndoMT) in experimentally fibrotic diseases. Fibrogenesis Tissue Repair 5(Suppl 1):S7

Pipp F, Heil M, Issbrücker K, Ziegelhoeffer T, Martin S, van den Heuvel J, Weich H et al (2003) VEGFR-1-selective VEGF homologue PIGF is arteriogenic: evidence for a monocyte-mediated mechanism. Circ Res 92:378–385

Poulsom R, Alison MR, Forbes SJ, Wright NA (2002) Adult stem cell plasticity. J Pathol 197:441–456

Prats AC, Van den Berghe L, Rayssac A, Ainaoui N, Morfoisse F, Pujol F, Legonidec S et al (2013) CXCL4L1-fibstatin cooperation inhibits tumor angiogenesis, lymphangiogenesis and metastasis. Microvasc Res 89:25–33

Qin Q, Qian J, Ge L, Shen L, Jia J, Jin J, Ge J (2014) Effect and mechanism of thrombospondin-1 on the angiogenesis potential in human endothelial progenitor cells: an in vitro study. PLoS One 9:e88213

Quirici N, Soligo D, Caneva L, Servida F, Bossolasco P, Deliliers GL (2001) Differentiation and expansion of endothelial cells from human bone marrow CD133 (+) cells. Br J Haematol 115:186–194

Radziwon-Balicka A, Ramer C, Moncada de la Rosa C, Zielnik-Drabik B, Jurasz P (2013) Angiostatin inhibits endothelial MMP-2 and MMP-14 expression: a hypoxia specific mechanism in action. Vasc Pharmacol 58:280–291

Rafii S, Meeus S, Dias S, Hattori K, Heissig B, Shmelkov S, Rafii D, Lyden D (2002a) Contribution of marrow-derived progenitors to vascular and cardiac regeneration. Semin Cell Dev Biol 13:61–67

Rafii S, Heissig B, Hattori K (2002b) Efficient mobilization and recruitment of marrow-derived endothelial and hematopoietic stem cells by adenoviral vectors expressing angiogenic factors. Gene Ther 9:631–641

Resovi A, Pinessi D, Chiorino G, Taraboletti G (2014) Current understanding of the thrombospondin-1 interactome. Matrix Biol 37:83–91

Reyes M, Dudek A, Jahagirdar B, Koodie L, Marker PH, Verfaillie CM (2002) Origin of endothelial progenitors in human postnatal bone marrow. J Clin Invest 109:337–346

Ribeiro MF, Zhu H, Millard RW, Fan GC (2013) Exosomes function in pro-and anti-angiogenesis. Curr Angiogenes 2:54–59

Richardson MR, Robbins EP, Vemula S, Critser PJ, Whittington C, Voytik-Harbin SL et al (2014) Angiopoietin-like protein 2 regulates endothelial colony forming cell vasculogenesis. Angiogenesis 17:675–683

Rieder F, Kessler SP, West GA, Bhilocha S, de la Motte C, Sadler TM, Gopalan B et al (2011) Inflammation-induced endothelial-to-mesenchymal transition: a novel mechanism of intestinal fibrosis. Am J Pathol 179:2660–2673

Ristimaki A, Narko K, Enholm B, Joukov V, Alitalo K (1998) Proinflammatory cytokines regulate expression of the lymphatic endothelial mitogen vascular endothelial growth factor-C. J Biol Chem 273:8413–8418

Rosano L, Spinella F, Bagnato A (2013) Endothelin 1 in cancer: biological implications and therapeutic opportunities. Nat Rev Cancer 13:637–651

Rose JA, Erzurum S, Asosingh K (2015) Biology and flow cytometry of proangiogenic hematopoietic progenitors cells. Cytometry A 87:5–19

Ruoslahti E, Rajotte D (2000) An address system in the vasculature of normal tissues and tumors. Annu Rev Immunol 18:813–827

Russell JS, Brown JM (2013) The irradiated tumor microenvironment: role of tumor-associated macrophages in vascular recovery. Front Physiol 4:157

Sabin FR (1904) On the development of the superficial lymphatics in the skin of the pig. Am J Anat 9:43–91

Sacharidou A, Stratman AN, Davis GE (2012) Molecular mechanisms controlling vascular lumen formation in three-dimensional extracellular matrices. Cells Tissues Organs 195:122–143

Saed GM, Carretero OA, MacDonald RJ, Scicli AG (1990) Kallikrein messenger RNA in rat arteries and veins. Circ Res 67:510–516

Sahoo S, Klychko E, Thorne T, Misener S, Schultz KM, Millay M, Ito A, Liu T, Kamide C, Agrawal H, Perlman H et al (2011) Exosomes from human CD34(+) stem cells mediate their proangiogenic paracrine activity. Circ Res 109:724–728

Sakurai A, Doçi CL, Gutkind JS (2012) Semaphorin signaling in angiogenesis, lymphangiogenesis and cancer. Cell Res 22:23–32

Sanders AJ, Ye L, Mason MD, Jiang WG (2010) The impact of EPLINα (epithelial protein lost in neoplasm) on endothelial cells, angiogenesis and tumorigenesis. Angiogenesis 13:317–326

Santulli G (2014) Angiopoietin-like proteins: a comprehensive look. Front Endocrinol (Lausanne) 5:4

Sato Y, Sonoda H (2007) The vasohibin family: a negative regulatory system of angiogenesis genetically programmed in endothelial cells. Arterioscler Thromb Vasc Biol 27:37–41

Scarisbrick IA, Jones EG, Isackson PJ (1993) Coexpression of mRNAs for NGF, BDNF, and NT-3 in the cardiovascular system of the pre-and postnatal rat. J Neurosci 13:875–893

Schneider M, Othman-Hassan K, Christ B, Wilting J (1999) Lymphangioblasts in the avian wing bud. Dev Dyn 216:311–319

Schwachtgen JL, Houston P, Campbell C, Sukhatme V, Braddock M (1998) Fluid shear stress activation of egr-1 transcription in cultured human endothelial and epithelial cells is mediated via the extracellular signal-related kinase1/2 mitogen-activated protein kinase pathway. J Clin Invest 101:2540–2549

Seok SH, Heo JI, Hwang JH, Na YR, Yun JH, Lee EH, Park JW, Cho CH (2013) Angiopoiein-1 elicits pro-inflammatory responses in monocytes and differentiating macrophages. Mol Cells 35:550–556

Sertie AL, Sossi V, Camargo AA, Zatz M, Brahe C, Passos-Bueno MR (2000) Collagen XVIII, containing an endogenous inhibitor of angiogenesis and tumor growth, plays a critical role in the maintenance of retinal structure and in neural tube closure (Knobloch syndrome). Hum Mol Genet 9:2051–2058

Sharghi-Namini S, Tan E, Ong LL, Ge R, Asada HH (2014) DII4-containing exosomes induce capillary sprout retraction in a 3D microenvironment. Sci Rep 4:4031

Shi H, Huang Y, Zhou H, Song X, Yuan S, Fu Y, Luo Y (2007) Nucleolin is a receptor that mediates antiangiogenic and antitumor activity of endostatin. Blood 110:2899–2906

Shimizu K, Watanabe K, Yamashita H, Abe M, Yoshimtasu H, Ohta H, Sonoda H, Sato Y (2005) Gene regulation of a novel angiogenesis inhibitor, vasohibin, in endothelial cells. Biochem Biophys Res Commun 327:700–706

Sinclair R (1972) Origin of endothelium in human renal allografts. Br Med J 4:15–16

Singh H, Tahir TA, Alawo DO, Issa E, Brindle NP (2011) Molecular control of angiopoietin signalling. Biochem Soc Trans 39:1592–1596

Stacker SA, Achen MG, Jussila L, Baldwin ME, Alitalo K (2002) Lymphangiogenesis and cancer metastasis. Nat Rev Cancer 2:573–583

Stalmans I, Ng YS, Rohan R, Fruttiger M, Bouche A, Yuce A, Fujisawa H, Hermans B et al (2002) Arteriolar and venular patterning in retinas of mice selectively expressing VEGF isoforms. J Clin Invest 109:327–336

Staudt ND, Jo M, Hu J, Bristow JM, Pizzo DP, Gaultier A, VandenBerg SR, Gonias SL (2013) Myeloid cell receptor LRP1/CD91 regulates monocyte recruitment and angiogenesis in tumors. Cancer Res 73:3902–3912

Stratman AN, Saunders WB, Sacharidou A, Koh W, Fisher KE, Zawieja DC, Davis MJ et al (2009) Endothelial cell lumen and vascular guidance tunnel formation requires

MT1-MMP-dependent proteolysis in 3-dimensional collagen matrices. Blood 114:237–247

Sundberg C, Kowanetz M, Brown LF, Detmar M, Dvorak HF (2002) Stable expression of angiopoietin-1 and other markers by cultured pericytes: phenotypic similarities to a subpopulation of cells in maturing vessels during later stages of angiogenesis in vivo. Lab Invest 82:387–401

Takahashi T, Kalka C, Masuda H et al (1999) Ischemia-and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. Nat Med 5:434–438

Tammela T, Alitalo K (2010) Lymphangiogenesis: molecular mechanisms and future promise. Cell 140:460–476

Tan KW, Chong SZ, Wong FH, Evrard M, Tan SM, Keeble J, Kemeny DM, Ng LG et al (2013) Neutrophils contribute to inflammatory lymphangiogenesis by increasing VEGF-A bioavailability and secreting VEGF-D. Blood 122:3666–3677

Tan YZ, Wang HJ, Zhang MH, Quan Z, Li T, He QZ (2014) CD34+ VEGFR-3+ progenitor cells have a potential to differentiate towards lymphatic endothelial cells. J Cell Mol Med 18:422–433

Tang Z, Wang A, Yuan F, Yan Z, Liu B, Chu JS, Helms JA, Li S (2012) Differentiation of multipotent vascular stem cells contributes to vascular diseases. Nat Commun 3:875

Thomas M, Augustin HG (2009) The role of the angiopoietins in vascular morphogenesis. Angiogenesis 12:125–137

Tomita S, Li R, Weisel R, Mickle DA, Kim EJ, Sakai T, Jia ZQ (1999) Autologous transplantation of bone marrow cells improves damaged heart function. Circulation 100:II 247–II 256

Urbich C, Kuehbacher A, Dimmeler S (2008) Role of microRNAs in vascular diseases, inflammation, and angiogenesis. Cardiovasc Res 79:581–588

Urbich C, Kaluza D, Frömel T, Knau A, Bennewitz K, Boon RA, Bonauer A, Doebele C, Boeckel JN, Hergenreider E et al (2012) MicroRNA-27a/b controls endothelial cell repulsion and angiogenesis by targeting semaphorin 6A. Blood 119:1607–1616

Valenzuela DM, Griffiths JA, Rojas J, Aldrich TH, Jones PF, Zhou H, McClain J, Copeland NG, Gilbert DJ, Jenkins NA et al (1999) Angiopoietins 3 and 4: diverging gene counterparts in mice and humans. Proc Natl Acad Sci U S A 96:1904–1909

Van Balkom BW, de Jong OG, Smits M, Brummelman J, den Ouden K, de Bree PM et al (2013) Endothelial cells require miR-214 to secrete exosomes that suppress senescence and induce angiogenesis in human and mouse endothelial cells. Blood 121:3997–4006

van Laake LW, van den Driesche S, Post S, Feijen A, Jansen MA, Driessens MH et al (2006) Endoglin has a crucial role in blood cell-mediated vascular repair. Circulation 114:2288–2297

Van Solingen C, Seghers L, Bijkerk R, Duijs JM, Roeten MK, van Oeveren-Rietdijk AM, Baelde HJ, Monge M, Vos JB et al (2009) Antagomir-mediated silencing of endothelial cell specific microRNA-126 impairs ischemia-induced angiogenesis. J Cell Mol Med 13:1577–1585

Varshavsky A, Kessler O, Abramovitch S, Kigel B, Zaffryar S, Akiri G, Neufeld G (2008) Semaphorin-3B is an angiogenesis inhibitor that is inactivated by furin-like pro-protein convertases. Cancer Res 68:6922–6931

Veikkola T, Jussila L, Makinen T, Karpanen T, Jeltsch M, Petrova TV, Kubo H, Thurston G et al (2001) Signalling via vascular endothelial growth factor receptor-3 is sufficient for lymphangiogenesis in transgenic mice. EMBO J 20:1223–1231

Wagner N, Michiels JF, Schedl A, Wagner KD (2008) The Wilms' tumour suppressor WT1 is involved in endothelial cell proliferation and migration: expression in tumour vessels in vivo. Oncogene 27:3662–3672

Wagner KD, Cherfils-Vicini J, Hosen N, Hohenstein P, Gilson E, Hastie ND, Michiels JF, Wagner N (2014) The Wilms' tumour suppressor Wt1 is a major regulator of tumour angiogenesis and progression. Nat Commun 5:5852

Wang HU, Chen Z, Anderson DJ (1998) Molecular distinction and angiogenic interaction between embryonic arteries and veins revealed by ephrin-B2 and its receptor Eph-B4. Cell 93:741–753

Wang Y, Nakayama M, Pitulescu ME, Schmidt TS, Bochenek ML, Sasakibara A, Adams S et al (2010) Ephrin-B2 controls VEGF-induced angiogenesis and lymphangiogenesis. Nature 465:483–486

Wang Y, Li Z, Xu P, Huang L, Tong J, Huang H, Meng A (2011) Angiomotin-like2 (amotl2) is required for migration and proliferation of endothelial cells during angiogenesis. J Biol Chem 286:41095–41104

Wang P, Luo Y, Duan H, Xing S, Zhang J, Lu D, Feng J, Yang D, Song L, Yan X (2013) MicroRNA 329 suppresses angiogenesis by targeting CD146. Mol Cell Biol 33:3689–3699

Watanabe K, Hasegawa Y, Yamashita H, Shimizu K, Ding Y, Abe M, Ohta H, Imagawa K et al (2004) Vasohibin as an as an endothelium-derived negative feedback regulator of angiogenesis. J Clin Invest 114:898–907

Welch-Reardon KM, Ehsan SM, Wang K, Wu N, Newman AC, Romero-Lopez M, Fong AH et al (2014) Angiogenic sprouting is regulated by endothelial cell expression of Slug. J Cell Sci 127:2017–2018

Wigle JT, Oliver G (1999) Prox1 function is required for the development of the murine lymphatic system. Cell 98:769–778

Wigle JT, Harvey N, Detmar M, Lagutina I, Grosveld G, Gunn MD, Jackson DG, Oliver G (2002) An essential role for Prox1 in the induction of the lymphatic endothelial cell phenotype. EMBO J 21:1505–1513

Williams G, Alvarez C (1969) Host repopulation of the endothelium in allografts of kidneys and aorta. Surg Forum 20:293–294

Wilson CM, Naves T, Vincent F, Melloni B, Bonnaud F, Lalloué F, Jauberteau MO (2014) Sortilin mediates the

release and transfer of exosomes in concert with two tyrosine kinase receptors. J Cell Sci 127:3983–3997
Wilting J, Papoutsi M, Schneider M, Christ B (2000a) The lymphatic endothelium of the avian wing is of somitic origin. Dev Dyn 217:271–278
Wilting J, Schneider M, Papoutsi M, Alitalo K, Christ B (2000b) An avian model for studies of embryonic lymphangiogenesis. Lymphology 33:81–94
Witte MH, Bernas MJ, Martin CP, Witte CL (2001) Lymphangiogenesis and lymphangiodysplasia: from molecular to clinical lymphology. Microsc Res Technol 55:122–145
Wu X, Liu N (2010) The role of Ang/Tie signaling in lymphangiogenesis. Lymphology 43:59–72
Xing Y, Hou J, Guo T, Zheng S, Zhou C, Huang H, Chen Y, Sun K, Zhong T, Wang J, Li H, Wang T (2014) MicroRNA-378 promotes mesenchymal stem cells survival and vascularization under hypoxic-ischemic condition in vitro. Stem Cell Res Ther 5:130
Xu QB (2005) Endothelial progenitor cells in angiogenesis. Sheng Li Xue Bao 57:1–6
Xu Y, Liu YJ, Yu Q (2004) Angiopoietin-3 is tethered on the cell surface via heparan sulfate proteoglycans. J Biol Chem 279:41179–41188
Yamaguchi S, Yamaguchi M, Yatsuyanagi E, Yun S-S, Nakajima N, Madri JA, Sumpio BE (2002) Cyclic strain stimulates early growth response gene product 1-mediated expression of membrane type 1 matrix metalloproteinase in endothelium. Lab Invest 82:949–956
Yao P, Eswarappa SM, Fox PL (2015) Translational control mechanisms in angiogenesis and vascular biology. Curr Atheroscler Rep 17:506
Yi C, Troutman S, Fera D, Stemmer-Rachamimov A, Avila JL, Christian N, Persson NL et al (2011) A tight junction-associated Merlin-angiomotin complex mediates Merlin's regulation of mitogenic signaling and tumor suppressive functions. Cancer Cell 19:527–540
Yokoyama Y, Green JE, Sukhatme VP, Ramakrishnan S (2000) Effect of endostatin on spontaneous tumorigenesis of mammary adenocarcinoma in a transgenic mouse model. Cancer Res 60:4362–4365
Yonekura H, Sakurai S, Liu X, Migita H, Wang H, Yamagishi S, Nomura M, Abedin MJ, Unoki H, Yamamoto Y, Yamamoto H (1999) Placenta growth factor and vascular endothelial growth factor B and C expression in microvascular endothelial cells and pericytes. Implication in autocrine and paracrine regulation of angiogenesis. J Biol Chem 274:35172–35178
Young PP, Hofling AA, Sands MS (2002) VEGF increases engraftment of bone marrow-derived endothelial progenitor cells (EPCs) into vasculature of newborn murine recipients. Proc Natl Acad Sci U S A 99:11951–11956
Yu XH, Tang ZB, Liu LJ, Qian H, Tang SL, Zhang DW, Tian GP, Tang CK (2014a) Apelin and its receptor APJ in cardiovascular diseases. Clin Chim Acta 428:1–8
Yu J, Zhang X, Kuzontkoski PM, Jiang S, Zhu W, Li DY, Groopman JE (2014b) Slit2N and Robo4 regulate lymphangiogenesis through the VEGF-C/VEGFR-3 pathway. Cell Commun Sign 12:25
Zachary I (2014) Neuropilins: role in signalling, angiogenesis and disease. Chem Immunol Allergy 99:37–70
Zheng W, Nurmi H, Appak S, Sabine A, Bovay E, Korhonen EA, Orsenigo F, Lohela M et al (2014a) Angiopoietin 2 regulates the transformation and integrity of lymphatic endothelial cell junctions. Genes Dev 28:1592–1603
Zheng W, Aspelunf A, Alitalo K (2014b) Lymphangiogenic factors, mechanisms, and applications. J Clin Invest 124:878–887
Zordan P, Rigamonti E, Freudenberg K, Conti V, Azzoni E, Rovere-Querini P, Brunelli S (2014) Macrophages commit postnatal endothelium-derived progenitors to angiogenesis and restrict endothelial to mesenchymal transition during muscle regeneration. Cell Death Dis 5:e1031

Part XXXIX

Staging of Liver Cancer

Staging of Hepatocellular Carcinoma, Hepatoblastoma, and Cholangiocarcinomas

188

Contents

Abstract

Staging of hepatocellular carcinoma (HCC) and other hepatobiliary cancers is critical for optimal treatment and a complex task that depends on multiple factors, such as tumor extent at diagnosis and liver function. In recent years, several staging systems have been developed that have markedly improved the methods to arrive at optimal risk stratification procedures and the formulation of novel treatment approaches. However, still no single staging system is successfully applicable to any patient with hepatobiliary cancer. Apart from HCC, intricate and highly reproducible staging systems have been developed for extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, and hepatoblastoma.

Staging of Hepatocellular Carcinoma

Introduction

Staging of HCC is critical for guiding optimal treatment and a complex task that depends on multiple factors, including tumor extent at diagnosis and liver function. This has led to a situation in which no single staging system is successfully applicable to any patient with HCC (Burns and Greene 2005; Pons et al. 2005; Vauthey et al. 2010; Maida et al. 2014). For example, the AJCC/UICC system is suitable for predicting outcome following resection or transplantation,

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6_188

while the Barcelona Clinic Liver Cancer scheme is useful in the assessment of patients with advanced, unresectable HCC.

Staging Systems

Several staging systems and classifications for HCC have been proposed and established (Tables 1 and 2).

The most often used staging systems for HCC include the Okuda staging classification (Okuda et al. 1985), CLIP (the Cancer of the Liver Italian Program, a primary staging system for HCC; No authors 1998; modification, Huo et al. 2006), GRETCH system (Chevret et al. 1999), Barcelona Clinic Liver Cancer staging classification (BCLC; Llovet et al. 1999), Chinese University Prognostic Index (CUPI; Leung et al. 2002), Vauthey staging system (Vauthey et al. 2002), Japanese Integrated Staging (JIS; Kudo et al. 2003; modified: Nanashima et al. 2006), SLiDe score (Omagari et al. 2004), Tokyo score (Tateishi et al. 2005), American Joint Committee on Cancer (AJCC) TNM system (seventh edition, TNM-7; Sobin et al. 2009a, b; Edge et al. 2010), Taipei Integrated Scoring system (Hsu et al. 2010), and Hong Kong Liver Cancer staging system (Yau et al. 2014).

Table 1 Staging systems and classifications for hepatocellular carcinoma: overview

Okuda staging classification
CLIP score (Cancer of the Liver Italian Program score)
GRETCH
BCLC (Barcelona Clinic Liver Cancer) staging classification
CUPI (Chinese University Prognostic Index)
Vauthey staging system
Japanese staging system and JIS (Japan Integrated Staging) score
SLiDe score
Tokyo score
AJCC/UICC
Taipei Integrated Scoring system
Hong Kong Liver Cancer staging system

The Okuda classification was widely used and includes parameters related to the liver functional status (albumin, bilirubin, ascites) and to tumor stage, i.e., more or less than 50 % of liver area involved. End-stage patients are Okuda stage III. CLIP contains a combination of four variables that provide a seven-stage classification.

BCLC B denotes intermediate stage of HCC in the BCLC staging system, a highly heterogeneous patient group whereby patients present with varying tumor burden and liver function, often treated with transarterial chemoembolization (TACE). Due to the inherent difficulties to characterize intermediate-stage HCCs, an expert panel has proposed four substages, B1–B4, to better describe and stratify these tumors (Bolondi et al. 2012). The French GRETCH system combines five variables (portal invasion, AFP, bilirubin, alkaline phosphatase, and the Karnofsky health status) that stratify patients into three stages. The Vauthey staging encompasses a simplified staging relying on the TNM system with a simplified T classification; in addition, it incorporates the presence and degree of fibrosis on liver biopsy. The JIS score is based on the Liver Cancer Study Group of Japan (LCSGJ) and combines Child-Pugh grade (grade A, score 0; grade B, score 1; grade C, score 2) and TNM staging by the LCSGJ criteria (stage I, score 0; stage II, score 1; stage III, score 2; stage IV, score 3). The SLiDe scoring system is a combined approach based on stage (S), liver damage (Li), and des-gamma-carboxyprothrombin (De), whereby stage and liver damage are used as in the revised fourth edition of the Japanese staging system edited by the Liver Cancer Study Group of Japan. The AJCC/UICC TNM-7 (seventh edition; Table) staging system is particularly suitable for classifying early HCC (Cheng et al. 2011). A modified TNM-7 has been proposed for patients undergoing hepatectomy, based on the observation of no difference between pT3a and pT4, but pT3b patients having a worse outcome than those with pT4. The authors proposed to combine current pT3a and pT4 together as a new pT3 and to change pT3b to a new pT4 (Huang et al. 2013).

Table 2 Criteria and parameters of HCC staging systems (selection)

Okuda staging classification		
Positive features		
Tumor involving >50 % of the liver		
Ascites		
Albumin <3 g/dl		
Bilirubin >3 mg/dl		
Stage I		No positive features
Stage II		One or two positive features
Stage III		Three or four positive features
CLIP score		Score
Child-Pugh stage		
A		0
B		1
C		2
Tumor morphology		
Uninodular and extension = <50 %		0
Multinodular and extension = <50 %		1
Massive or extension >50 %		2
Alpha-fetoprotein (ng/dl)		
<400		0
= >400		1
Portal vein thrombosis		
No		0
Yes		1
BCLC		
Stage A (early HCC)		
A1 PST 0	Single tumor	No portal hypertension, normal bilirubin
A2 PST 0	Single tumor	Portal hypertension, normal bilirubin
A3 PST 0	Single tumor	Portal hypertension, abnormal bilirubin
A4 PST 0	Three tumors, all <3 cm	Child-Pugh A-B
Stage B (intermediate HCC)		
PST 0	Large multinodular	Child-Pugh A-B
Stage C (advanced HCC)		
PST 1–2	Vascular invasion or extrahepatic spread	Child-Pugh A-B
Stage D (end-stage HCC)		
PST 3–4	Any	Child-Pugh C
PST: performance status test		

(*continued*)

Table 2 (continued)

CUPI	Score
TNM stage	
I and II	−3
IIIa and IIIb	−1
IVa and IVb	0
Asymptomatic disease on presentation	−4
Ascites	3
Alpha-fetoprotein = >500 ng/ml	2
Total bilirubin (micromol/l)	
<34	0
34–51	3
= >52	4
Alkaline phosphatase = >200 units/l	3
Risk groups: low, score <1; intermediate, score 2–7; high, score >8	
Vauthey staging system	
sT1	Single tumor without vascular invasion
sT2	Single tumor with vascular invasion or multiple tumors, none >5 cm
sT3	Multiple tumors, any >5 cm or tumor (s) involving major branch of hepatic vein(s)
F0	Grade 0–4 fibrosis (no fibrosis to moderate fibrosis)
F1	Grade 5–6 (severe fibrosis or cirrhosis)
Stage I	sT1 N0 M0
Stage II	sT2 N0 M0
Stage IIIA	sT3 N0 M0
Stage IIIB	Any sT N1 M0
Stage IV	Any sT, any N M1
Japanese staging system/JIS score	
Japanese staging system	
T criteria	Single tumor, <2 cm, no vascular involvement
T1	Agrees with all three criteria
T2	Agrees with two of three criteria
T3	Agrees with one of three criteria
T4	Agrees with no criteria
Stage I	T1 N0 M0
Stage II	T2 N0 M0

(*continued*)

Table 2 (continued)

Stage III		T3 N0 M0	
Stage IVA		T4 N0 M0 or any T N1 M0	
Stage IVB		Any T N0–1 M1	
Japan Integrated Staging (JIS) score			
Stage I		0	
Stage II		1	
Stage III		2	
Stage IV		3	
Child-Pugh A		0	
Child-Pugh B		1	
Child-Pugh C		2	
AJCC/UICC TNM staging system (seventh edition, TNM-7)			
Primary tumor (T)			
TX		Primary tumor cannot be assessed	
T0		No evidence of primary tumor	
T1		Solitary tumor without vascular invasion	
T2		Solitary tumor with vascular invasion or multiple tumors, none >5 cm	
T3a		Multiple tumors more than 5 cm	
T3b		Single tumor or multiple tumors of any size involving a major of portal vein or hepatic vein	
T4		Tumors with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum	
Regional lymph nodes (N)			
NX		Regional lymph nodes cannot be assessed	
N0		No regional lymph node metastasis	
N1		Regional lymph node metastasis	
Distant metastases (M)			
M0		No distant metastasis	
M1		Distant metastasis	
Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

On the other hand, another study found no survival difference between patients with T3a and T3b tumors nor between those with T3b and T4 tumors, while tumor multiplicity, bilobar disease, tumor size >5 cm, and microvascular invasion were potent prognosticators (Chan et al. 2013). The Taipei Integrated Scoring system is based on the calculated total tumor volume and specifically showed prognostic ability when used in combination with Child-Turcotte-Pugh and AFP levels (Hsu et al. 2010). The Hong Kong Liver Cancer staging system includes patient performance status, Child-Pugh grade, tumor status (size, number of nodules, presence of intrahepatic vascular invasion), and presence of extrahepatic vascular invasion or metastasis.

Prognostic Value of Staging Systems

The various staging systems have been analyzed in comparative investigations in regard to their prognostic value (Kudo et al. 2004; Huang et al. 2005; Marrero et al. 2005; Cillo et al. 2006; Kee et al. 2007; Minagawa et al. 2007; Chun and Ahn 2011; Maida et al. 2014; Zhang et al. 2014). In a cohort of US patients of any stage, the BCLC revealed the best independent predictive power for survival when compared with TNM, CLIP, CUPI, JIS, GRETCH, and Okuda (Marrero et al. 2005), and a similar conclusion was drawn by Kim and coworkers (2012). In a comparative analysis of the prognostic values, the seventh AJCC staging system (TNM-7 system) revealed better prognostic power than the sixth for patients with HCC but not better than that of the BCLC system, the AJCC system being capable to adequately stratify early HCC cases, but having lower prognostic power in advanced-stage HCC (Minagawa et al. 2007; Chun et al. 2011; Chan et al. 2013). By comparing the JIS system, TNM sixth edition system, LCSGJ criteria, CLIP, Advanced Liver Cancer Prognostic System (ALCPS), GRETCH scoring, CUPI, Okuda scoring system, Tokyo scoring system, and BCLC, ALCPS, CLIP, and CUPI were the preferred scoring systems for the prediction of overall survival and 3-month

survival in patients with advanced HCC (Li et al. 2013). Distinct HCC stages are associated with varying frequencies of extrahepatic metastases (EHM). For the modified AJCC/UICC stages T1, T2, T3, and T4, the frequencies of EHM in 314 newly diagnosed HCCs were 0 %, 7.6 %, 25.0 %, and 27.0 %, respectively (Yi et al. 2013).

Molecular Staging Systems

In addition to staging systems based on morphologic parameters, tumor classifications referring to distinct molecular features of HCC are currently developed. Molecular signatures will be employed to refine stratification of HCC stages so far defined in order to improve treatments, including the future generation of personalized therapies. By integrating plasma insulin-like growth factor-1 (IGF-1) concentration into the CLIP score (a strategy called I-CLIP), an improved stratification of patients with unresectable HCC could be obtained (Kaseb et al. 2011a, b). The Glasgow Prognostic Score is an inflammation-based prognostic score (inflammation-based index, IBI) that can serve as an independent marker for poor prognosis in patients with HCC in various stages of disease (Pinato et al. 2012; Kinoshita et al. 2013). Combined determination of AFP mRNA and vascular endothelial growth factor (VEGF) proved to be prognostically accurate for discriminating risk of death (ROC) and survival probability estimated by Cox analysis (Vitale et al. 2011).

Staging of Hepatoblastoma and Pediatric Hepatocellular Carcinoma

The TNM staging system is not widely used for hepatoblastomas. In North America, the Children's Oncology Group staging system is widely employed. It is based on postoperative evaluation and hence relies less on imaging findings (Table 3).

Table 3 Children's Oncology Group staging of liver cancer

Stage I	Tumor completely resected
Stage II	Tumor grossly resected with microscopic residual disease
Stage III	Tumor unresectable or resected with gross residual disease
	Nodal involvement
	Tumor spill
	Gross residual intrahepatic disease
Stage IV	Distant metastases

Table 4 Liver sections as defined by the PRETEXT system

Left lateral section:	Liver segments 2 and 3
Left medial section:	Liver segments 4a and 4b
Right anterior section:	Liver segments 5 and 8
Right posterior section:	Liver segments 6 and 7

In contrast, the pretreatment extent of tumor system or PRETEXT system is based on imaging findings. The PRETEXT system was designed by the International Childhood Liver Tumor Strategy Group (SIOPEL) for risk stratification of pediatric liver tumors (Aronson et al. 2005; Roebuck et al. 2006, 2007a, b; Meyers et al. 2007, 2009; McCarville and Roebuck 2012). PRETEXT staging is based on Couinaud's system of liver segmentation. In the system, the liver segments are grouped into four *sections* (Table 4). In the original PRETEXT system, the caudate lobe (segment 1) was ignored.

In addition to liver segment involvement, PRETEXT also assesses involvement of the inferior vena cava (IVC) or hepatic veins (designated V), involvement of the portal vein (designated P), extrahepatic abdominal disease (designated E), and distant metastases (designated M). The original system is compiled in Table 5.

PRETEXT, which showed to have a good prognostic value in infants and children with hepatoblastoma, is employed to describe tumor extent before any therapy. Analysis of data and of experience has uncovered certain limitations of this system. A revised PRETEXT system has been proposed (2005 PRETEXT; Roebuck et al. 2007a; Table 6).

Table 5 PRETEXT staging system (original version)

Stage	Definition
PRETEXT I	One section involved, three adjoining sections free
PRETEXT II	One or two sections involved, two adjoining sections free
PRETEXT III	Two or three sections involved, no two adjoining sections free
PRETEXT IV	All four sections involved
V+	Involvement of the IVC and/or all three hepatic veins
P+	Involvement of the main portal vein and/or both left and right portal vein branches
E+	Extrahepatic disease in the abdomen
M+	Distant metastases

The changes are specified as follows: involvement of the caudate lobe at diagnosis is coded as C1, irrespective of the PRETEXT group. As imaging techniques are more performant, biopsy proof of involvement is not necessary in all situations. In the 2005 revision, patients with direct extension of tumor through the diaphragm (a rare event) are coded as E1 without biopsy proof. Peritoneal tumor nodules are assumed to be metastases and are coded as E2. All other patients should be coded as E0. Patients with ascites are coded as E0a, E1a, or E2a. Abdominal lymph node metastases, previously coded as E+, are now coded as N. Tumor focality (F) denotes the presence of a solitary vs. more nodules. Patients with one hepatic tumor nodule are coded as F0, while all those with more than one nodule are coded as F1, regardless of tumor size or PRETEXT stage. Patients with tumor rupture are coded as H1. Patients with no evidence of tumor rupture or hemorrhage, and those with only subcapsular or biopsy-related bleeding, are coded as H0. Patients with no lymph node metastases are N0, those with nodal metastases limited to the abdomen (caudal to the diaphragm and cranial to the inguinal ligament) are N1, and those with extraabdominal nodal metastases are N2. In regard to portal vein involvement, the original version did not specify what "involvement" means. Involvement based on imaging means complete venous obstruction or circumferential encasement. In the revised version, P1 means

Table 6 2005 PRETEXT staging: additional criteria (Roebuck et al. 2007a)

C:	
Caudate lobe involvement	C1, tumor involving the caudate lobe
	C0, all other patients
E:	
Extrahepatic abdominal disease	E0, no evidence of extrahepatic abdominal disease (except M or N)
	E1, direct extension of tumor into adjacent organs or diaphragm
	E2, peritoneal nodules
F:	
Tumor focality	F0, patient with solitary tumor
	F1, patient with two or more discrete tumors
H:	
Tumor rupture or intraperitoneal hemorrhage	H1, imaging and clinical findings of intraperitoneal hemorrhage
	H0, all other patients
M:	
Distant metastases	M0, no metastases
	M1, any metastases (except E and N)
N:	
Lymph node metastases	N0, no nodal metastases
	N1, abdominal lymph node metastases only
	N2, extraabdominal lymph node metastases (with or without abdominal lymph node metastasis)
P:	
Portal vein involvement	P0, no involvement of the portal vein or its left or right branches
	P1, involvement of either the left or the right branch of the portal vein
	P2, involvement of the main portal vein
V:	
Involvement of the IVC and/or hepatic veins	V0, no involvement of the hepatic veins or inferior vena cava (IVC)
	V1, involvement of one hepatic vein but not the IVC
	V2, involvement of two hepatic veins but not the IVC
	V3, involvement of all three hepatic veins and/or the IVC

evidence of involvement of one major branch of the portal vein, and P2 (= original P+) is involvement of the main portal vein, its bifurcation, or both of its main branches, as well as those with cavernous transformation. Detection of portal vein invasion is coded as with the suffix "a" (e.g., P2a). For inferior vena cava and hepatic veins, the original V + has been defined in more detail, in analogy to the portal vein. V1 and V2 indicate involvement of one or two main hepatic veins, respectively, while V3 means involvement of either the IVC or all three of hepatic veins. As in the portal vein, invasion is coded with the suffix "a."

Together with serum AFP levels, PRETEXT is useful for risk stratification of hepatoblastomas. High-risk patients are those with any of the following: serum AFP less than 100 mg/l, PRETEXT IV, and additional PRETEXT criteria (E1, E1a, E2, E2a, H1, M1 (any site), N1, N2, P2, P2a, V3, V3a). All other patients are standard risk (Roebuck et al. 2007a).

Staging of Hilar/Perihilar Cholangiocarcinoma (Klatskin Tumor)

Preoperative evaluation of the tumor extension (staging) is important in order to judge resectability, extent of surgery, and prognostication of outcome. Most staging systems refer to invasive tumors that have reached a certain extension. Early carcinoma of the extrahepatic ducts was defined as being carcinoma confined to within the mucosa and fibromuscular layer (Tsunoda et al. 1989), but with the exception of carcinoma in situ, the concept of early cancer in its various manifestations does not make part of staging systems.

Several methods have been proposed to stage tumor extension, with a varying spectrum of impact. Following the Bismuth-Corlette classification, several staging systems have been proposed and updated or reviewed (Hiriart et al. 2011). Currently, the new editions of UICC and the American Joint Committee on Cancer (AJCC) staging, the Japanese Society of Biliary Surgery (JSBS) classification, and the modified Memorial Sloan Kettering Cancer Center (MSKCC) classification are used worldwide for PHC staging. These systems not only refer to tumor extent but also to local biological factors (reviews: Kim 2005; Nishio et al. 2005; Chung et al. 2008; Hasebe et al. 2008; Blechacz et al. 2011; DeOliveira et al. 2011; Juntermanns et al. 2013; Koerkamp et al. 2014). Alternative staging systems have recently been proposed (DeOliveira et al. 2011). Aspects of the new staging systems have been commented and reviewed (Hiriart et al. 2011; Nagino 2011). The Bismuth-Corlette classification has been employed to define the longitudinal tumor extension in PHC, whereas the T-staging system of the AJCC defines lateral tumor extension, and resectability of PHC can be evaluated by means of the Blumgart T-staging system combined with the AJCC T-stage system.

Classification and Staging Based on Longitudinal Extension

Hilar/perihilar carcinomas have been classified according to their anatomical location and extension with respect to their relation to the confluence and the longitudinal tumor extension (the Bismuth-Corlette classification; Bismuth and Corlette 1975). The Bismuth-Corlette type I cancer is defined by a lesion confined below the main confluence of right and left hepatic ducts. Bismuth-Corlette type I tumors extend to the confluence of the right and left hepatic ducts. Type IIIa is a tumor that extends to the bifurcation of the right hepatic duct, and a type IIIb tumor extends to the bifurcation of the left hepatic duct (Bengmark et al. 1988). Type IV tumors extend to the bifurcation of both the right and left hepatic ducts. The Bismuth-Corlette classification provides an anatomical classification of the tumor which is a widely used preoperative standard to assess PHC, but has been shown to have low accuracy in cases of PHC undergoing resection, and it is not indicative of survival (Chung et al. 2008; Paul et al. 2011). There is a relationship between longitudinal growth extension and histological type of tumor. The common sclerosing (desmoplastic)

variant of PHC tends to be circumscript, while exophytically growing, and in particular papillary, carcinomas tend to show long-range mucosal spread.

Classification and Staging Based on Lateral Extension

The principal staging system describing lateral extension of tumors and their invasion of duct-associated soft tissues is the TNM staging system, as specified in the seventh edition of the UICC manual (Sobin et al. 2009a; Table 7).

There are some differences between the sixth and the seventh editions of the UICC/AJCC classifications for PHC. Specifically, the seventh edition improved separation of patients with intermediate-stage tumors compared with the sixth edition (Juntermanns et al. 2013). Similar to the Bismuth-Corlette system, there is a relationship between the T stage and the predominant growth pattern and tumor differentiation. In T1 tumors, exophytically growing, polypoid, and papillary carcinomas are overrepresented. In contrast, T2 tumors, which grow through the duct wall, typically exhibit a nodular invasive mass encasing the duct and showing periductal tumor infiltrates. It may be problematic to distinguish T1 and T2 tumors, because the determination of the border of the bile duct may be difficult, even histologically. The outer border of the bile duct is defined by the outer smooth muscle layer, but the distribution of smooth muscle bundles varies along the bile duct, with only few and scattered myocyte bundles in the proximal-most parts of extrahepatic ducts and a continuous sheath in the distal-most part (Hong et al. 2000). In addition, nodular-sclerosing forms of PHC elicit a cellular stromal reaction (desmoplasia) in the invasive part of the tumor, often effacing the anatomo-histologic features of the involved duct (review: Chung et al. 2008). In T3 and T4 tumors, gross vascular invasion makes part of the phenotype. As specified in Chung et al. (2008), vascular involvement on cross-sectional imaging is present if vascular occlusion, ipsilateral hepatic atrophy, stenosis or contour deformity, or tumor contact

Table 7 UICC staging of extrahepatic cholangiocarcinoma (seventh edition, 2009)

***Primary tumor* (*T*)**			
TX		Primary tumor cannot be assessed	
T0		No evidence of primary tumor	
Tis		Tumor in situ	
T1		Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue	
T2a		Tumor invades beyond the wall of the bile duct to surrounding adipose tissue	
T2b		Tumor invades adjacent hepatic parenchyma	
T3		Tumor invades unilateral branches of the portal vein or hepatic artery	
T4		Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery, or the second-order biliary radicles bilaterally, or unilateral second-order biliary radicles with contralateral portal vein or hepatic artery involvement	
***Regional lymph nodes* (*N*)**			
NX		Regional lymph nodes cannot be assessed	
N0		No regional lymph node metastasis	
N1		Regional lymph node metastasis including nodes along the cystic duct, common bile duct, common hepatic artery, and portal vein	
***Distant metastasis* (*M*)**			
MX		Distant metastasis cannot be assessed	
M0		No distant metastasis	
M1		Distant metastasis	
Stage grouping			
Group staging	Tumor staging	Nodal staging	Metastasis staging
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a, b	N0	M0
Stage IIIa	T3	N0	M0
Stage IIIb	T1-3	N1	M0
Stage IVa	T4	Any N	M0
Stage IVb	T1–4	Any N	M1

where more than 50 % of the perimeter of the vessel is detected are observed. In order to improve preoperative T staging, several propositions have been published.

Staging System Developed to Evaluate Resectability

The preoperative clinical T-staging system of Blumgart (Blumgart preoperative staging), defined by the radial/lateral and longitudinal tumor extent, accurately predicts resectability of PHC (Jarnagin 2000; Jarnagin et al. 2001; Matsuo et al. 2012; Table 8). In other words, the system evaluates the longitudinal and lateral spread patterns based on the Bismuth-Corlette and TNM staging systems (Chung et al. 2008). In this staging system, T3 cancers correspond to Bismuth-Corlette type IV or bilateral or main portal vein invasion, or Bismuth-Corlette type III cancers with contralateral portal vein invasion or hepatic atrophy are considered poor candidates for surgery.

Staging of Lymph Node Involvement

The TNM system of the sixth edition of the AJCC manual is simple and specifies with the code N1 that regional (locoregional) lymph node metastasis is present (see the table above). Regional lymph nodes are hilar, celiac, periduodenal, peripancreatic, and superior mesenteric nodes. A detailed lymph node numbering system has been developed by the Japanese Research Society for Gastric Cancer (Nishi et al. 1998). An alternative regional lymph node group system has been proposed by Kitagawa et al. (2001; Table 9).

Table 8 Blumgart preoperative staging (Jarnagin et al. 2001)

T-stage criteria	
T1	Tumor involving biliary confluence +/− unilateral extension to second-order biliary radicles
T2	Tumor involving biliary confluence +/− unilateral extension to second-order biliary radicles and ipsilateral portal vein involvement +/− ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + bilateral extension to second-order biliary radicles, or unilateral extension to second-order biliary radicles with contralateral portal vein involvement, or unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy, or main or bilateral portal venous involvement

Staging of Extrahepatic Cholangiocarcinomas

The American Joint Committee on Cancer (AJCC) has designated a TNM staging system for extrahepatic bile duct cancer that is widely used (*AJCC Cancer Staging Manual*, seventh edition; Edge et al. 2010). T3 and T4 tumors differ in regard to the organ that is invaded, invasion of the pancreas being defined as T3, and that of the duodenum as T4 tumor in the T classification of the American Joint Committee on Cancer (AJCC). Stages defined by the TNM classification apply to all primary carcinomas arising in the extrahepatic bile duct or in the cystic duct and do not apply to intrahepatic cholangiocarcinomas, sarcomas, or carcinoid tumors. The AJCC TNM

Table 9 Definition of regional lymph node groups (According to Kitagawa et al. 2001, and the classification by the Japanese Society of Biliary Surgery)

TNM classification	Kitagawa system
N1	N1
Hilar	Pericholedochal (numbers 12 h, 12c, 12b)
Cystic duct	
Pericholedochal	
N2	N2
Periportal	Periportal (numbers 12p, 12a)
Periduodenal	Common hepatic (numbers 8a, 8p)
Peripancreatic	Posterior pancreaticoduodenal (number 13a)
Celiac	Celiac (number 9)
Superior mesenteric	Superior mesenteric (number 14)

Numbers in brackets indicate lymph node groups according to the classification of the Japanese Society of Biliary Surgery

Table 10 AJCC Staging of distal bile duct carcinoma: primary tumor (Edge et al. 2010)

TX	Primary tumor be assessed
T0	No evidence of primary tumor
Tis	Tumor in situ
T1	Tumor confined to the bile duct histologically
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery

Table 11 AJCC classification of lymph node involvement (Edge et al. 2010)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

system applying to distal extrahepatic cholangiocarcinomas is shown in Table 10.

Assessment of pT2 and pT3 varies somewhat as a function of the anatomical compartment involved. The extrahepatic biliary tract histology varies along its length, in that there is little smooth muscle in the wall of proximal duct parts compared to distal duct parts, rendering the assessment of invasion depth difficult in some situations. It has been proposed to measure the maximum invasion depth from the surface epithelium (basement membrane) to the deepest point of tumor invasion. The current pT3 stage of distal extrahepatic bile duct carcinomas can be subdivided into superficial (pT3a) and deep pancreatic invasion (pT3b). In the TNM system, special cases can further be defined by certain prefixes and suffixes. The suffix "m" denotes the presence of multiple primary tumors in a single site and is recorded in parentheses (pT(m)NM). The prefix "y" indicates those cases in which classification takes place during or after initial multimodality therapy. For example, the cTNM or pTNM is identified by a "y" prefix. ycTNM and ypTNM thus categorize the extent of tumor actually present at the time of that examination. The prefix "r" denotes a recurrent tumor when staged after a documented disease-free interval. The prefix "a" indicates the stage determined at autopsy (aTNM) (Washington et al. 2010).

Carcinomas with invasion confined to within the mucosa and fibromuscular layer have been defined as early carcinoma (Tsunoda et al. 1989). In a study of 95 patients, survival rates for patients with pT3 and pT4 were similar, and duodenal invasion was present in 39 % of the patients with pancreatic invasion, whereas pancreatic invasion was observed in 86 % of those with duodenal invasion, suggesting that T classifications should undergo further stratification procedures (Ebata et al. 2007).

For lymph node involved in patients with CDBD, available classifications mainly include the AJCC system (Table 11) and the system of the Japanese Society of Biliary Surgery (Tables 12, 13 and 14).

The AJCC staging system for distant metastasis is shown in Table 15.

AJCC stage/prognostic groups are compiled in Table 16.

Staging of Intrahepatic Cholangiocarcinoma (ICC)

Stage classification (staging) of ICC is a rather complex and evolving matter that has been discussed in several publications (Adam and Benjamin 1992; Blechacz et al. 2009, 2011; Nathan et al. 2009; Kokudo and Arita 2010; Uenishi et al. 2014). Historically, the same classification has been applied and validated in the West for hepatocellular carcinoma (HCC) and ICC (UICC/AJCC; Sobin and Wittekin 1997; Vauthey et al. 2002), while two TNM staging systems had been specifically developed in Japan for HCC and ICC (Okabayashi et al. 2001; the Liver Cancer Study Group of Japan 1997; Yamasaki 2003; Tables 17 and 18). The past Western staging systems for cholangiocarcinoma, including the sixth edition of AJCC, which were based on HCC therefore also referred to tumor size as a prognostic factor. In ICC, tumor size as a prognosticator is controversial, as part of the studies found a prognostic effect (Weber et al. 2001; Endo et al. 2008; Shen

Table 12 Nomenclature and numerical classification of lymph nodes and lymph node groups General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract (Japanese Society of Biliary Surgery 1997)

Number 8, nodes along the common hepatic artery
Number 9, nodes around the celiac artery
Number 10, nodes at the splenic hilum
Number 11, nodes along the splenic artery
Number 12, nodes in the hepatoduodenal ligament
12a, nodes along the hepatic artery
12b, nodes along the bile duct
12c, nodes around the cystic duct
12p, nodes posterior to the portal vein
12abp1, nodes along the superior hepatoduodenal ligament
12abp2, nodes along the inferior hepatoduodenal ligament
Number 13, posterior pancreaticoduodenal nodes
13a, above the papilla of Vater
13b, below the papilla of Vater
Number 14, nodes around the superior mesenteric artery
14a, nodes at the origin of the superior mesenteric artery
14b, nodes at the origin of the inferior pancreaticoduodenal artery
14c, nodes at the origin of the middle colic artery
14d, nodes at the origin of the jejunal arteries
Number 15, nodes along the middle colic artery
Number 16, para-aortic nodes
16a1, nodes around the aortic hiatus of the diaphragm
16a2, nodes from the superior margin of the celiac trunk to the inferior margin of the left renal artery
16b1, nodes from the inferior margin of the left renal artery to the superior margin of the inferior mesenteric artery
16b2, nodes from the superior margin of the inferior mesenteric artery to the aortic bifurcation
Number 17, anterior pancreaticoduodenal nodes
17a, above the papilla of Vater
17b, below the papilla of Vater

Table 13 Nodal involvement for middle (mid-region) CDBD (CDBD-M): classification according to the Japanese Society of Biliary Surgery (1997)

n0, no evidence of regional lymph node involvement
n1, nodal involvement in the primary lymph node group close to the tumor (lymph node numbers 12b and 12c)
n2, lymph node metastasis in the secondary lymph node group (lymph node numbers 8, 12a, 12p, and 13a)
n3, lymph node metastasis in the third group (lymph node numbers 9, 13b, 14, 16a, 16b, and 17)
n4, lymph node metastasis in the fourth group

Table 14 Nodal involvement for distal CDBD (CDBD-D): classification according to the Japanese Society of Biliary Surgery (1997)

n0, no evidence of regional lymph node involvement
n1, nodal involvement in a primary lymph node group close to the tumors (lymph node numbers 12b2 and 13a)
n2, lymph node metastasis in the secondary lymph node group (lymph node numbers 8, 12 except 12b2, and 13b)
n3, lymph node metastasis in the third group (lymph node numbers 9, 13b, 14, 16a2, 16b1, and 17)
n4, lymph node metastasis in the fourth group (beyond the third group)

Table 15 AJCC classification for distant metastasis in distal cholangiocarcinoma (Edge et al. 2010)

M0	No distant metastasis
M1	Distant metastasis

Table 16 AJCC anatomic stage/prognostic groups (stage groupings) (Edge et al. 2010)

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

et al. 2009), while other investigations did no demonstrate a prognostic effect of tumor size (Choi et al. 2009; Uchiyama et al. 2011). In the seventh edition of the American Joint Committee on Cancer (AJCC) staging manual, a novel staging specific for ICC was proposed (Edge 2009; Table 19). This new staging system is largely based on data found in the Surveillance, Epidemiology, and End Results (SEER) program on numerous patients having undergone cancer-directed surgery for ICC (Nathan et al. 2009). Nathan and coworkers demonstrated that the sixth edition of the AJCC system staging was

Table 17 Liver Cancer Study Group of Japan staging system for ICC

T factor:			
T1		Meets requirements (see below)	
T2		Meets two of the three requirements	
T3		Meets one of the three requirements	
T4		Meets none of the three requirements	
Three requirements:			
Number of tumors:		Solitary	
Size of tumor:		2 cm or less	
Negative invasion:		Portal vein, hepatic vein, serosal membrane	
N factor:			
N1		No metastasis to lymph node	
N2		Metastasis to any lymph nodes	
M factor:			
M0		No distant metastasis	
M1		Positive distant metastasis	
Stages (Yamasaki 2003)			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Or any T	N1	M0
Stage IVB	Any T	Any N	M1

Table 18 Lymph node groups in ICC by tumor location (Liver Cancer Study Group of Japan)

Tumor location		
Groups or locoregional lymph nodes		
N1	N2	N3
Right lobe	Hepatoduodenal ligament	Along left gastric artery
Distant lymph nodes		
		Along common hepatic artery
		Along celiac artery
		Posterior surface of pancreatic head
Left lobe	Right cardiac region	Along left gastric artery
Distant lymph nodes		
	Lesser gastric curvature	Along common hepatic artery
	Hepatoduodenal ligament	Along celiac artery
		Posterior surface of pancreatic head

Table 19 AJCC/UICC staging system for intrahepatic cholangiocarcinoma (seventh edition)

TNM stage	
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors 5 cm or less
T3	Multiple tumors more than 5 cm or tumor involving major branch of the portal or hepatic veins
T4	Tumors with invasion of adjacent organs other than the gallbladder or tumors with perforation of visceral peritoneum
N0	No regional lymph node metastases
N1	Regional lymph node metastases
M0	No distant metastases
M1	Distant metastases
UICC stage	
I	T1N0M0
II	T2N0M0
IIIA	T3N0M0
IIIB	T4N0M0
IIIC	AnyTN1M0
IV	AnyTAnyNM1

unable to distinguish prognostically T2 from T3 tumors. In their study it also surfaced that tumor number and vascular invasion were significant prognostic markers, and the lymph node status had prognostic values. The novel seventh edition of the AJCC staging system has, among others, the advantage that it is simpler than the sixth edition system and focuses on multiple tumors, vascular invasion, and lymph node metastasis (review: Nathan and Pawlik 2010).

In this seventh edition, the TNM classification of ICC is separated from that for hepatocellular carcinoma. This novel staging system has been intended to replace the two Western and ideally also the two Eastern staging systems currently in use (Ribero et al. 2011), but its clinical relevance strongly depends on performing routine lymphadenectomy at the time of surgery for ICC (Farges et al. 2011).

Based on some inconsistencies, some modifications of the TNM staging system have been proposed. ICC with multiple tumors was classified as pT4 disease; periductal invasion was excluded from

determinant of the T categories; and metastasis to gastrohepatic lymph nodes was treated as distant metastasis (Igami et al. 2011). Serosal invasion is not a T factor, because it has been found that serosal invasion in patients with MF-ICC has no impact on survival of patients after hepatic resection (Uenishi et al. 2005). For MF-ICC, a specific staging system was formulated. Stage I disease was defined as a solitary tumor without vascular invasion; stage II disease was defined as a solitary tumor with vascular invasion; stage IIIA disease was defined as multiple tumors with or without vascular invasion; stage IIIB disease was defined as any tumor with regional lymph node metastasis; and stage IV disease was defined as any tumor with distant metastases. It turned out that these MF-ICC staging categories were suitable for predicting biology of disease and treatment response (Okabayashi et al. 2001). There is increasing evidence that current staging systems have to be adapted to the main growth pattern types of ICC, as general ICC staging systems may not be suitable to properly stratify each type (e.g., MF-ICC) in the same way (Okabayashi et al. 2001; Uenishi et al. 2014). In a recent investigation performed to identify predictors of outcome in MF-ICC, tumor size, tumor number, and vascular invasion were independently associated with survival after curative resection, whereas periductal invasion and serosal invasion were not (Uenishi et al. 2014).

References

Adam A, Benjamin IS (1992) The staging of cholangiocarcinoma. Clin Radiol 46:299–303

Aronson DC, Schnater M, Staalman CR, Weverling GJ, Plaschkes J, Perilongo G et al (2005) Predictive value of the pretreatment extent of disease system in hepatoblastoma: results from the International Society of pediatric Oncology Liver Tumor Study Group SIOPEL-1 study. J Clin Oncol 23:1245–1252

Bengmark S, Ekberg H, Evander A, Klofver-Stahl B, Tranberg KG (1988) Major liver resection for hilar cholangiocarcinoma. Ann Surg 207:120–125

Bismuth H, Corlette MB (1975) Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet 140:170–178

Blechacz BR, Sanchez W, Gores GJ (2009) A conceptual proposal for staging ductal cholangiocarcinoma. Curr Opin Gastroenterol 25:238–239

Blechacz B, Komuta M, Roskams T, Gores GJ (2011) Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 8:512–522

Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL et al (2012) Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 32:348–359

Burns JM, Greene FL (2005) Controversies in staging of hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 12:456–462

Chan AC, Fan ST, Poon RT, Cheung TT, Chok KS, Chan SC, Lo CM (2013) Evaluation of the seventh edition of the American Joint Committee on cancer tumour-node-metastasis (TNM) staging system for patients undergoing curative resection of hepatocellular carcinoma: implications for the development of a refined staging system. HPB (Oxford) 15:439–448

Cheng CH, Lee CF, Wu TH, Chan KM, Chou HS, Wu TJ, Yu MC, Chen TC, Lee WC et al (2011) Evaluation of the new AJCC staging system for resectable hepatocellular carcinoma. World J Surg Oncol 9:114

Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C (1999) A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinoma Hépatocellulaire. J Hepatol 31:133–141

Choi SB, Kim KS, Choi JY, Park SW, Choi JS, Lee WJ, Chung JB (2009) The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. Ann Surg Oncol 16:3048–3056

Chun YH, Ahn SH (2011) Prognostic value of the 7th edition of the AJCC staging system as a clinical staging system in patients with hepatocellular carcinoma. Eur J Cancer 47:2568–2575

Chun JM, Kwon HJ, Sohn J, Kim SG, Park JY, Bae HI, Yun YK, Hwang YJ (2011) Prognostic factors after early recurrence in patients who underwent curative resection for hepatocellular carcinoma. J Surg Oncol 103:148–151

Chung YE, Kim MJ, Park YN, Lee YH, Choi JY (2008) Staging of extrahepatic cholangiocarcinoma. Eur Radiol 18:2182–2195

Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, Neri D, Boccagni P et al (2006) Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 44:723–731

DeOliveira ML, Schulick RD, Nimura Y, Rosen C, Gores G, Neuhaus P, Clavien PA (2011) New staging system and a registry for perihilar cholangiocarcinoma. Hepatology 53:1363–1371

Ebata T, Nagino M, Nishio H, Igami T, Yokoyama Y, Nimura Y (2007) Pancreatic and duodenal invasion in distal bile duct cancer: paradox in the tumor classification of the American Joint Committee on Cancer. World J Surg 31:2008–2015

Edge SB (2009) American Joint Committee on Cancer: AJCC cancer staging manual, 7th edn. Springer, New York

Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds) (2010) AJCC cancer staging manual, 7th edn. Springer, New York

Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, D'Angelica M, DeMatteo RP et al (2008) Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 248:84–96

Farges O, Fuks D, Le Treut YP, Azoulay D, Laurent A, Bachellier P, Nuzzo G, Belghiti J et al (2011) AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma: by the AFC-IHCC-2009 study group. Cancer 117:2170–2177

Hasebe T, Konishi M, Iwasaki M, Nakagohri T, Takahashi SI, Gotohda N, Kinoshita T, Ochiai A (2008) Primary tumor/vessel tumor/nodal tumor classification of extrahepatic bile duct carcinoma. Hum Pathol 39:37–48

Hiriart JB, Laurent C, Blanc JF (2011) Perihilar cholangiocarcinoma, the need for a new staging system. Clin Res Hepatol Gastroenterol 35:697–698

Hong SM, Kang GH, Lee HY, Ro JY (2000) Smooth muscle distribution in the extrahepatic bile duct: histologic and immunohistochemical studies of 122 cases. Am J Surg Pathol 24:660–667

Hsu CY, Huang YH, Hsia CY, Su CW, Lin HC, Loong CC, Chiou YY, Chiang JH et al (2010) A new prognostic model for hepatocellular carcinoma based on total tumor volume: the Taipei Integrated Scoring System. J Hepatol 53:108–117

Huang YH, Chen CH, Chang TT, Chen SC, Wang SY, Lee HS, Lin PW, Huang GT et al (2005) Evaluation of predictive value of CLIP, Okuda, TNM and JIS staging systems for hepatocellular carcinoma patients undergoing surgery. J Gastroenterol Hepatol 20:765–771

Huang J, Zhang Y, Peng Z, Gao H, Xu L, Jiao LR, Chen M (2013) A modified TNM-7 staging system to better predict the survival in patients with hepatocellular carcinoma after hepatectomy. J Cancer Res Clin Oncol 139:1709–1719

Huo TI, Huang YH, Lin HC, Wu JC, Chiang JH, Lee PC, Chang FY, Lee SD (2006) Proposal of a modified Cancer of the Liver Italian Program staging system based on the model for end-stage liver disease for patients with hepatocellular carcinoma undergoing loco-regional therapy. Am J Gastroenterol 101:975–982

Igami T, Ebata T, Yokoyama Y, Sugawara G, Takahashi Y, Nagino M (2011) Staging of peripheral-type intrahepatic cholangiocarcinoma: appraisal of the new TNM classification and its modifications. World J Surg 35:2501–2509

Japanese Society of Biliary Surgery (1997) General rules for surgical and pathological studies on cancer of biliary tract, 4th edn. Kanehara, Tokyo

Jarnagin WR (2000) Cholangiocarcinoma of the extrahepatic bile ducts. Semin Surg Oncol 19:156–176

Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS et al (2001) Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 234:507–519

Juntermanns B, Sotiropoulos GC, Radunz S, Reis H, Heuer M, Baba HA, Canbay A et al (2013) Comparison of the sixth and the seventh editions of the UICC classification for perihilar cholangiocarcinoma. Ann Surg Oncol 20:277–284

Kaseb AO, Morris JS, Hassan MM, Siddiqui AM, Lin E, Xiao L, Abdalla EK, Vauthey JN et al (2011a) Clinical and prognostic implications of plasma insulin-like growth factor-1 and vascular endothelial growth factor in patients with hepatocellular carcinoma. J Clin Oncol 29:3892–3899

Kaseb AO, Abbruzzese JL, Vauthey JN, Aloia TA, Abdalla EK, Hassan MM, Lin E et al (2011b) I-CLIP: improved stratification of advanced hepatocellular carcinoma patients by integrating plasma IGF-1 into CLIP score. Oncology 80:373–381

Kee KM, Wang JH, Lee CM, Chen CL, Changchien CS, Hu TH, Cheng YF, Hsu HC et al (2007) Validation of clinical AJCC/UICC TNM staging system for hepatocellular carcinoma: analysis of 5,613 cases from a medical center in southern Taiwan. Int J Cancer 120:2650–2655

Kim HJ (2005) TNM staging of hilar cholangiocarcinoma (in Korean). Korean J Gastroenterol 46:20–27

Kim BK, Kim SU, Park JY, Kim do Y, Ahn SH, Park MS, Kim EH, Seong J, Lee do Y et al (2012) Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single centre experience from long-term clinical outcomes of 1717 treatment-naïve patients with hepatocellular carcinoma. Liver Int 32:1120–1127

Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, Fushiya N, Koike K, Nishino H et al (2013) The Glasgow Prognostic Score, an inflammation based prognostic score, predicts survival in patients with hepatocellular carcinoma. BMC Cancer 13:52

Kitagawa Y, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Nimura Y (2001) Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection. Ann Surg 233:385–392

Koerkamp BG, Wiggers JK, Allen PJ, Busch OR, D'Angelica MI, DeMatteo RP, Fong Y et al (2014) American Joint Committee on Cancer staging for resected perihilar cholangiocarcinoma: a comparison of the 6th and 7th editions. HPB (Oxford) 16:1074–1082

Kokudo N, Arita J (2010) Staging for intrahepatic cholangiocarcinoma. Liver Int 30:931–933

Kudo M, Chung H, Osaki Y (2003) Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging

system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 38:207–215
Kudo M, Chung H, Haji S, Osaki Y, Oka H, Seki T, Kasugai H, Sasaki Y, Matsunaga T (2004) Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. Hepatology 40:1396–1405
Leung TW, Tang AM, Zee B, Lau WY, Lai PB, Leung KL, Lau JT, Yu SC, Johnson PJ (2002) Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. Cancer 94:1760–1769
Li X, Dong M, Lin Q, Chen ZH, Ma XK, Xing YF, Wan XB, Wen JY, Wei L, Chen J et al (2013) Comparison of current staging systems for advanced hepatocellular carcinoma not amendable to locoregional therapy as inclusion criteria for clinical trials. Asia Pac J Clin Oncol 9:86–92
Liver Cancer Study Group of Japan (1997) Clinical and surgical findings. In: Liver Cancer Study Group of Japan (ed) Classification of primary liver cancer. First English edition. Kanehara Shuppan, Toyko, pp 1–22
Llovet JM, Bru C, Bruix J (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19:329–338
Maida M, Orlando E, Camma C, Cabibbo G (2014) Staging systems of hepatocellular carcinoma: a review of literature. World J Gastroenterol 20:4141–4150
Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, Lok AS (2005) Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Hepatology 41:707–716
Matsuo K, Rocha FG, Ito K, D'Angelica MI, Allen PJ, Fong Y, Dematteo RP, Gonen M et al (2012) The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. J Am Coll Surg 215:343–355
McCarville MB, Roebuck DJ (2012) Diagnosis and staging of hepatoblastoma: imaging aspects. Pediatr Blood Cancer 59:793–799
Meyers RL, Katzenstein HM, Malogolowkin MH (2007) Predictive value of staging systems in hepatoblastoma. J Clin Oncol 25:737
Meyers RL, Rowland JR, Krailo M, Chen Z, Katzenstein HM, Malogolowkin MH (2009) Predictive power of pretreatment prognostic factors in children with hepatoblastoma: a report from the Children's Oncology Group. Pediatr Blood Cancer 53:1016–1022
Minagawa M, Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M (2007) Staging of hepatocellular carcinoma. Assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg 245:909–922
Nagino M (2011) Perihilar cholangiocarcinoma: a much needed but imperfect new staging system. Nat Rev Gastroenterol Hepatol 8:252–253
Nanashima et al. (2006) http://www.ncbi.nlm.nih.gov/pubmed/16699859
Nathan H, Pawlik TM (2010) Staging of intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol 26:269–273
Nathan H, Aloia TA, Vauthey JN, Abdalla EK, Zhu AX, Schulick RD, Choti MA et al (2009) A proposed staging system for intrahepatic cholangiocarcinoma. Ann Surg Oncol 16:14–22
Nishi M, Omori Y, Miwa K (1998) Japanese Research Society for Gastric Cancer (JRSGC): Japanese classification of gastric carcinoma. Kanehara, Tokyo
Nishio H, Nagino M, Oda K, Ebata T, Arai T, Nimura Y (2005) TNM classification for perihilar cholangiocarcinoma: comparison between 5th and 6th editions of the AJCC/UICC staging system. Langenbecks Arch Surg 390:319–327
No authors (1998) A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 28:751–755
Okabayashi T, Yamamoto J, Kosuge T, Shimada K, Yamasaki S, Takayama T, Makuuchi M (2001) A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. Cancer 92:2374–2383
Okuda K, Ohtsuki T, Obata H, Tamimatsu M, Okazaki N, Hasegawa H et al (1985) Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 56:918–928
Omagari K, Honda S, Kadokawa Y, Isomoto H, Takeshima F, Hayashida K, Mizuta Y et al (2004) preliminary analysis of a newly proposed prognostic scoring system (SLiDe score) for hepatocellular carcinoma. J Gastroenterol Hepatol 19:805–811
Paul A, Kaiser GM, Molmenti EP, Schroeder T, Venadakis S, Oezcelik A, Baba HA et al (2011) Klatskin tumors and the accuracy of the Bismuth-Corlette classification. Am Surg 77:1695–1699
Pinato DJ, Stebbing J, Ishizuka M, Khan SA, Wasan HS, North BV, Kubota K, Sharma R (2012) A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). J Hepatol 57:1013–1020
Pons F, Varela M, Llovet JM (2005) Staging systems in hepatocellular carcinoma. HPB (Oxford) 7:35–41
Ribero D, Nuzzo G, Amisano M, Tomatis M, Guglielmi A, Giulini SM, Aldrighetti L et al (2011) Comparison of the prognostic accuracy of the sixth and seventh editions of the TNM classification for intrahepatic cholangiocarcinoma. HPB (Oxford) 13:198–205
Roebuck DJ, Olsen O, Pariente D (2006) Radiological staging in children with hepatoblastoma. Pediatr Radiol 36:176–182
Roebuck DJ, Aronson D, Clapuyt P, Czauderna P, de Ville de Goyet J, Gauthier F et al (2007a) 2005 PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. Pediatr Radiol 37:123–132

Roebuck DJ, Sebire NJ, Pariente D (2007b) Assessment of extrahepatic abdominal extension in primary malignant liver tumours of childhood. Pediatr Radiol 37:1096–1100

Shen WF, Zhong W, Xu F, Kan T, Geng L, Xie F, Sui CJ, Yang JM (2009) Clinicopathological and prognostic analysis of 429 patients with intrahepatic cholangiocarcinoma. World J Gastroenterol 15:5976–5982

Sobin LH, Wittekin C (1997) UICC TNM classification of malignant tumors, 5th edn. Wiley-Liss, New York

Sobin LH, Gospodarowicz MK, Wittekind C (2009a) International union against cancer (UICC) TNM classification of malignant tumours, 7th edn. Wiley, New York

Sobin LH, Gospodarowicz MK, Wittekind C (eds) (2009b) TNM classification of malignant tumours, 7th edn. UICC, International Union against Cancer, Wiley-Blackwell, Oxford

Tateishi R, Yoshida H, Shiina S, Imamura H, Hasegawa K, Teratani T, Obi S, Sato S et al (2005) Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. Gut 54:419–425

Tsunoda T, Eto T, Koga M, Tomioka T, Motoshima K, Yamaguchi T, Izawa K, Tsuchiya R (1989) Early carcinoma of the extrahepatic bile duct. Jpn J Surg 19:691–698

Uchiyama K, Yamamoto M, Yamaue H, Ariizumi S, Aoki T, Kokudo N, Ebata T, Nagino M et al (2011) Impact of nodal involvement on surgical outcomes of intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Surg 18:443–452

Uenishi T, Yamazaki O, Yamamoto T, Hirohashi K, Tanaka H, Tanaka S, Hai S, Kubo S (2005) Serosal invasion in TNM staging of mass-forming intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 12:479–483

Uenishi T, Ariizumi S, Aoki T, Ebata T, Ohtsuka M, Tanaka E, Yoshida H, Imura S et al (2014) Proposal of a new staging system for mass-forming intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci 21:499–508

Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, Curley SA, Ellis LM et al (2002) Simplified staging for hepatocellular carcinoma. J Clin Oncol 20:1527–1536

Vauthey JN, Dixon E, Abdalla EK, Helton WS, Pawlik TM, Taouli B, Brouquet A et al (2010) Pretreatment assessment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford) 12:289–299

Vitale et al. (2011) http://www.ncbi.nlm.nih.gov/pubmed/21912636

Washington MK, Berlin J, Branton PA, Burgart LJ, Carter DK, Compton CC, Fitzgibbons PL et al (2010) Protocol for the examination of specimens from patients with carcinoma of the distal extrahepatic bile ducts. Arch Pathol Lab Med 134:e8–e13

Weber SM, Jarnagin WR, Klimstra D, DeMatteo RP, Fong Y, Blumgart LH (2001) Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. J Am Coll Surg 193:384–391

Yamasaki S (2003) Intrahepatic cholangiocarcinoma: macroscopic type and stage classification. J Hepatobiliary Pancreat Surg 10:288–291

Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT (2014) Development of Hong Kong Liver Cancer Staging System with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 146:1691–1700

Yi J, Gwak GY, Sinn DH, Kim YJ, Kim HN, Choi MS, Lee JH, Koh KC, Paik SW, Yoo BC (2013) Screening for extrahepatic metastases by additional staging modalities is required for hepatocellular carcinoma patients beyond modified UICC stage T1. Hepatogastroenterology 60:328–332

Zhang JF, Shu ZJ, Xie CY, Li Q, Jin XH, Gu W, Jiang FJ, Ling CQ (2014) Prognosis of unresectable hepatocellular carcinoma: comparison of seven staging systems (TNM, Okuda, BCLC, CLIP, CUOPI, JIS, CIS) in a Chinese cohort. PLoS One 9:e88182

Index

A. Zimmermann, *Tumors and Tumor-Like Lesions of the Hepatobiliary Tract*,
DOI 10.1007/978-3-319-26956-6

C

Q

R